IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

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ABSTRACT BOOK

IASLC 2022 World Conference on Lung Cancer

August 6-9, 2022 | Vienna, Austria

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This abstract is under embargo until August 8 at 10:30 Vienna, Austria Time, CEST.

PL03 PLENARY 3: PRESIDENTIAL SYMPOSIUM - TOP RATED ABSTRACTS,
MONDAY, AUGUST 8, 2022 - 08:30–10:20

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N.K. Altorki[1], X. Wang[2,3], D. Kozono[4], C. Watt[4], R. Landreneau[5], D. Wigle[6], J. Port[1], D.R. Jones[7], M. Conti[8], A.S. Ashrafi[9], R. Keenan[10], T. Bauer[11], L.J. Kohman[12], T.E. Stinchcombe[13], E. Vokes[14]

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PL03 PLENARY 3: PRESIDENTIAL SYMPOSIUM - TOP RATED ABSTRACTS,
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H. Wakelee[1], N. Altorki[2], E. Felip[3], E. Vallieres[4], I.O. Vynnychenko[5], A. Akopov[6], A. Martinez-Marti[3], A. Chella[7], I. Bondarenko[8], S. Sugawara[9], Y. Fan[10], H. Kenmotsu[11], Y-M. Chen[12], Y. Deng[13], F. Wu[14], V. McNally[15], E. Bennett[13], B.J. Gitlitz[13], C. Zhou[16]

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PL03 PLENARY 3: PRESIDENTIAL SYMPOSIUM - TOP RATED ABSTRACTS,
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PL03.12 Progression Free Survival and Overall Survival in NADIM II Study

M. Provencio[1], R. Serna[1], E. Nadal[2], J.L. Glez Larriba[3], A. Martínez-Martí[4], R. Bernabé[5], J. Bosch-Barrera[6], C. Garcia Benito[7], V. Calvo[1], A. Insa[8], S. Ponce[9], N. Reguart[10], J. De Castro[11], B. Massutí[12], R. Palmero[2], C. Aguado de la Rosa[3], J. Mosquera[13], M. Cobo[14], A. Aguilar[15], G. López Vivanco[16], C. Camps[17], F. Hernando Trancho[3], R. López Castro[18], T. Moran[19], I. Barneto[20], D. Rodríguez-Abreu[21], A. Romero[1]

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Oral Abstract Sessions

OA01 REAL WORLD DATA TO GUIDE OUR DAILY NEEDS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

OA01.03 Lung Cancer in Victoria: Association Between Stage-Specific Receipt of Guideline-Concordant Treatment and Survival

S. Tissera[1], B. Billah[1], N. Karim[1], M. Brand[1], S. Smith[1], J. Zalcberg[1], R. Stirling[2]

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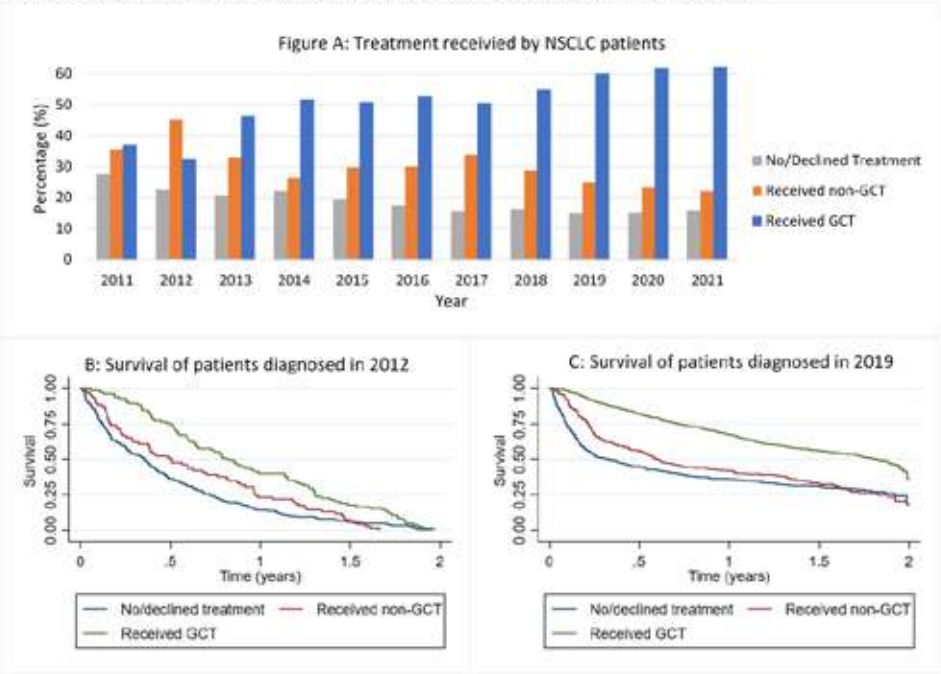
Introduction: In Victoria, the second most populous Australian state (population 6.6 million), lung cancer contributed to 9% of new cancers diagnosed, 18.6% of all cancer deaths in 2020 and suffered the lowest survival rate of 17.4% amongst all cancers. Clinical practice guidelines for the treatment of non-small cell lung cancer (NSCLC) by localised, locally-advanced and advanced-stage cancer have been developed to improve evidence-based management and treatment. Provision of guideline-concordant treatment (GCT) is likely to lead to an improvement in patient survival. To date, there is little evidence confirming the degree to which NSCLC patients receive stage-specific GCT and whether patient and clinical characteristics affect receiving stage-specific GCT. We sought to explore the level of provision of stage-specific GCT to patients with NSCLC, the impact on 1- and 2-year survival and assess the overall provision of GCT since the commencement data collection by the Victorian Lung Cancer Registry (VLCR).

Methods: This is a prospective cohort study conducted in Melbourne, Victoria, using data collected by the VLCR between July 2011 and November 2021. The VLCR is a clinical quality registry developed to improve the quality of care provided to lung cancer patients in Victoria. Data collection is ongoing. Differences in stage-specific GCT were explored between patients diagnosed in 2011 till the current date. A multivariable COX regression model was developed to estimate likelihood for receipt of GCT. Survival analyses were performed using Kaplan-Meier estimates of survival.

Results: The number of patients receiving stage-specific GCT increased over time (Figure 1A and 1B). GCT was received by 37.1% of patients diagnosed in 2012 and 61.9% of patients diagnosed in 2019. Patients were less likely to receive GCT if they were aged 60 years and over, lived in rural Victoria, had advanced-stage cancer, current/ex-smokers, experienced weight loss and had an ECOG score ≥2. One and two-year survival over time since the VLCR commenced data collection, improved for patients treated with stage-specific GCT (Figure 1C and 1D).

Conclusions: The proportion of patients receiving stage-specific GCT increased from 2011 to 2021. Survival for 1 and 2-years of patients receiving stage-specific GCT was significantly higher than for patients receiving non-GCT or no treatment. The proportion of patients receiving GCT may be a useful measure of appropriateness and quality of care delivered to patients with NSCLC. Delays in referral, diagnosis and treatment time need to be further investigated as they may also have an impact on survival.

Figure 1: Panel graph for treatment and survival of patients since commencing of VLCR



Keywords: NSCLC, Guideline concordant treatment, Clinical quality registry

OA01 REAL WORLD DATA TO GUIDE OUR DAILY NEEDS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

OA01.04 Persisting Gaps in Optimal Care of Stage III Non-Small Cell Lung Cancer: An Australian Patterns of Care Analysis

K.L. Woodford[1,2], K. Koo[1,3,4], J. Reynolds[4], R.G. Stirling[5,6], S.V. Harden[3,4], M. Brand[4], S. Senthi[1,2]

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Introduction: Wide variation exists globally in the treatment and outcomes of stage III non-small cell lung cancer (NSCLC) patients. We conducted an up-to-date patterns of care analysis in the state of Victoria, Australia, with a particular focus on the proportion of patients receiving treatment with radical intent, treatment trends over time and survival.

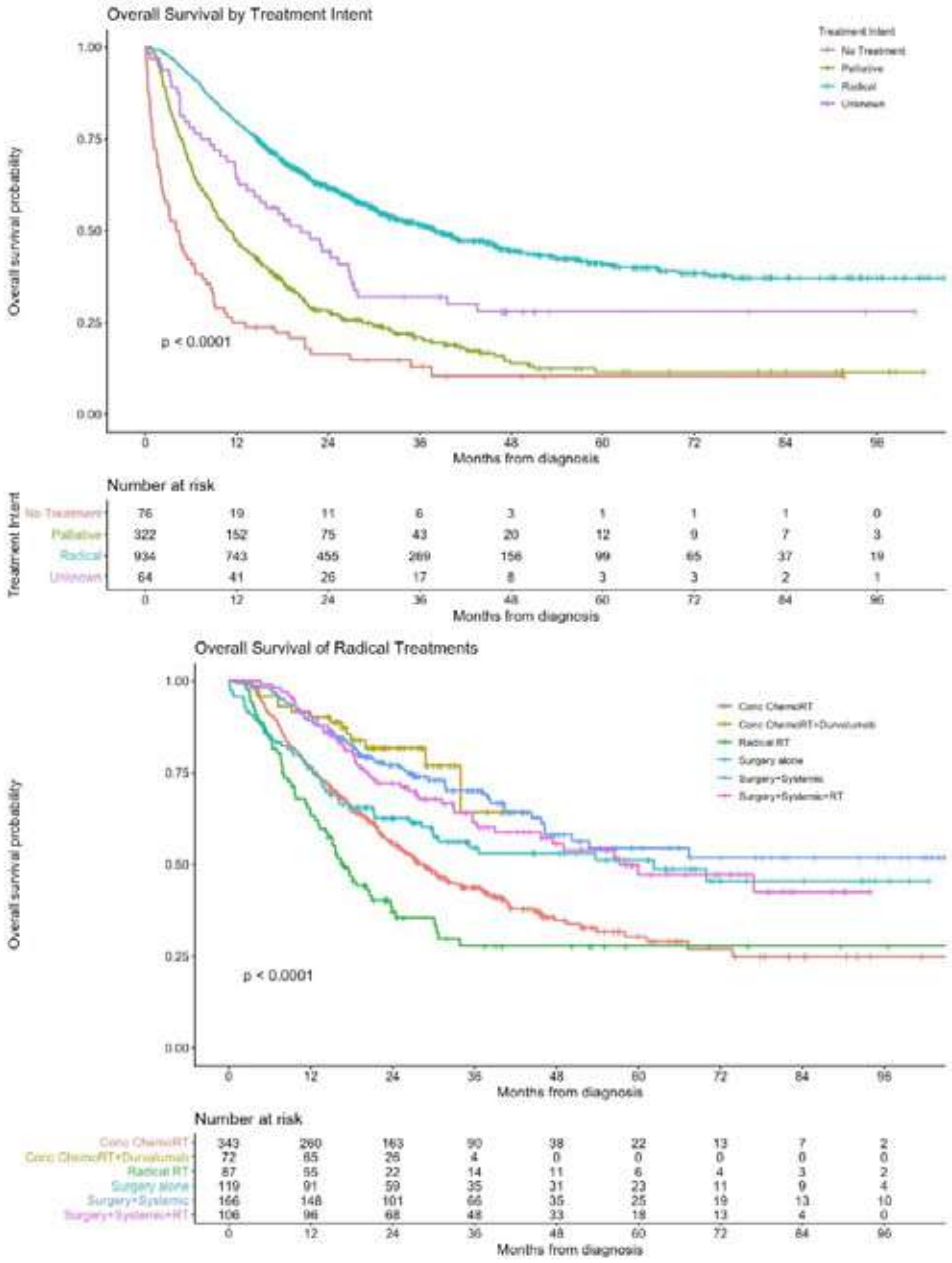
Methods: Stage III NSCLC patients were identified in the Victorian Lung Cancer Registry and categorised by treatment received and treatment intent. Logistic regression was used to explore factors predictive of receipt of radical treatment and the treatment trends over time. Cox regression was used to explore variables associated with overall survival (OS). Covariates evaluated included age, sex, ECOG performance status, smoking status, year of diagnosis, Australian born, Aboriginal or Torres Strait Islander status, socioeconomic status, rurality, public/private status of notifying institution and multidisciplinary meeting discussion.

Results: A total of 1,396 patients were diagnosed between 2012-2019 and received treatment with radical intent 67%, palliative intent 23%, unknown intent 5% and no treatment 5%. Radical intent treatment was less likely if patients were >75 years, ECOG >/=1, had T3-4 or N3 disease or resided rurally. The proportion of patients receiving radical, palliative and no treatment remained unchanged over time. Surgery use decreased over time, while concurrent chemoradiotherapy and immunotherapy use increased. Median OS was 38.0 months, 11.1 months and 4.4 months following radical treatment, palliative treatment or no treatment respectively (p<0.001). On multivariate analysis, age, ECOG, smoking status, T-stage, N-stage, socioeconomic status and radical treatment were associated with survival. Chemoradiotherapy followed by durvalumab produces similar survival outcomes to that of surgical combinations within first 3 years from diagnosis.

Conclusions: Almost a third of stage III NSCLC patients still do not receive radical treatment. Strategies to facilitate radical treatment and better support decision making between increasing multimodality options are required.

Treatments delivered by disease stage (n=1396)

	Stage IIIA (n=772) n (%)			Stage IIIB (n=491) n (%)			Stage IIIC (n=133) n (%)			All Stage III (n=1396) n (%)		
	Radical	Palliative	Unknown	Radical	Palliative	Unknown	Radical	Palliative	Unknown	Radical	Palliative	Unknown
Single modality												
Surgery alone	94 (12.2)	-	-	24 (4.9)	-	-	1 (0.8)	-	-	119 (8.5)	-	-
Systemic therapy alone	-	41 (5.3)	-	-	55 (11.2)	-	-	21 (15.8)	-	-	117 (8.4)	-
RT alone	57 (7.4)	59 (7.6)	12 (1.6)	20 (4.1)	60 (12.2)	10 (2.0)	10 (7.5)	26 (19.5)	3 (2.3)	87 (6.2)	145 (10.4)	25 (1.8)
Multimodality												
Surgery+Systemic	133 (17.2)	-	-	33 (6.7)	-	-	0 (0)	-	-	166 (11.9)	-	-
Surgery+RT	25 (3.2)	-	-	4 (0.8)	-	-	0 (0)	-	-	29 (2.1)	-	-
Concurrent ChemoRT	204 (26.4)	11 (1.4)	19 (2.5)	169 (34.4)	19 (3.9)	14 (2.9)	42 (31.6)	3 (2.3)	0 (0)	415 (29.7)	33 (2.4)	33 (2.4)
Sequential ChemoRT	4 (0.5)	7 (0.9)	2 (0.3)	7 (1.4)	11 (2.2)	3 (0.6)	1 (0.8)	9 (6.8)	1 (0.8)	12 (0.9)	27 (1.9)	6 (0.4)
Surgery+Systemic+RT	70 (9.1)	-	-	33 (6.7)	-	-	3 (2.3)	-	-	106 (7.6)	-	-
Total	587 (76.0)	118 (15.3)	33 (4.3)	290 (59.1)	145 (29.5)	27 (5.5)	57 (42.9)	59 (44.4)	4 (3.0)	934 (66.9)	322 (23.1)	64 (4.6)
No treatment	34 (4.4)			29 (5.9)			13 (9.8)			76 (5.4)		



Kaplan Meier survival curves by treatment intent (top) and by radical treatment type (bottom).

Keywords: Stage III NSCLC, Patterns of Cae, Elderly

OA01 REAL WORLD DATA TO GUIDE OUR DAILY NEEDS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

OA01.05 Socio-economic Inequalities in NSCLC Treatment During the Era of Tumour Biomarker Guided Therapy: A Population-based Study

R.P. Norris[1], R. Dew[2], A. Todd[1], A. Greystoke[3], L. Sharp[1]

[1]Newcastle University, Newcastle/GB, [2]Sunderland University, Sunderland/GB, [3]Newcastle upon Tyne Hospitals, Newcastle/GB

Introduction: Novel anti-cancer treatments targeting tumour biology and/or the immune system have improved non-small cell lung cancer (NSCLC) outcomes. Socio-economic treatment inequalities are well documented with more "traditional" lung cancer treatment modalities such as chemotherapy, radiotherapy and surgery, but it is not known if these inequalities are also seen with novel therapies. This population-based study took advantage of comprehensive national databases within a publicly funded healthcare system (the UK) to investigate this by determining the association of deprivation with targeted therapy and immunotherapy utilisation in NSCLC.

Methods: NSCLC cases, diagnosed between 01/01/2012 - 31/12/2017 and sourced from the English population-based national cancer registration database and linked Systemic Anti-Cancer Therapy (SACT) database, were analysed. Novel systemic anti-cancer therapy utilisation was dichotomised for each patient, based on SACT drug data. Multivariable logistic regression examined the likelihood of utilisation of any of these drugs by deprivation category of area of residence at diagnosis (measured by quintiles of the income domain of the Index of Multiple Deprivation). Sub-group analyses (restricting to stage IV and adenocarcinomas or non-squamous histology) were performed. A further exploratory analysis evaluated utilisation by deprivation for targeted treatments (EGFR and ALK), biologics (anti-angiogenics) and immunotherapy. Models were adjusted for the following (where appropriate) covariates: age, sex, diagnosis year, ethnicity, rural/urban indicator, stage, multiple tumours, comorbidities and histology.

Results: 195,387 NSCLC cases were analysed. Significant treatment inequalities by deprivation in novel anti-cancer therapies were observed (Figure 1). Patients living in the most deprived areas were almost half as likely to utilise any novel therapy (multivariable odds ratio (mvOR) 0.54 [95% CI] 0.50, 0.58) compared to patients living in the most affluent areas. This result was mirrored in all sub-group and exploratory analyses, though associations were stronger with targeted therapy (mvOR) 0.40 [95% CI] 0.36, 0.44) than immunotherapy (mvOR) 0.58 [95% CI] 0.53, 0.64) utilisation.

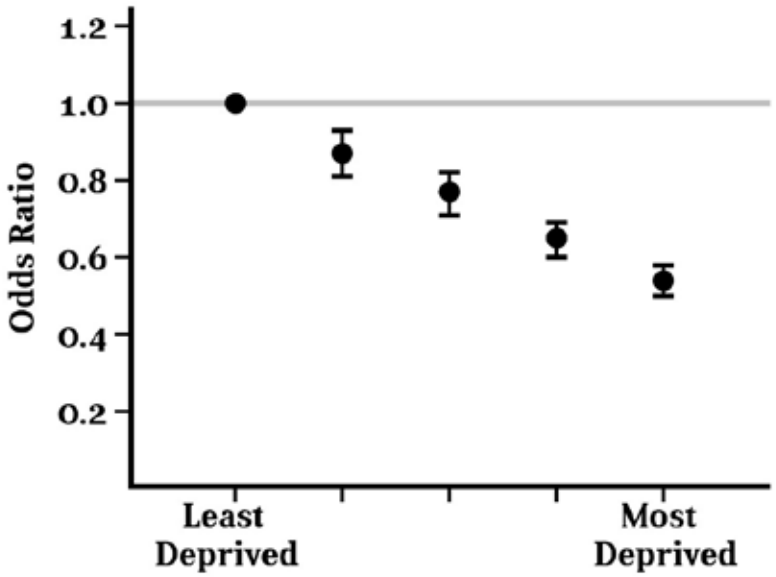


Figure 1. Multivariable model of novel therapy utilisation by deprivation, adjusted for: sex, age, diagnosis year, ethnicity, rural/urban indicator, stage, comorbidities & histology.

Conclusions: Socio-economic status is an important factor in NSCLC novel treatment utilisation, even in the UK National Health Service where treatment is free at the point of delivery, tumour biology is known, and therapies biomarker guided. As novel therapies are increasingly integrated into prescribing guidelines, attention is needed to address inequalities. Further work exploring why such treatment inequalities persist will help the promise of stratified NSCLC treatment to improve outcomes for all to be fully realised.

Keywords: Novel anti-cancer therapies, Socio-economic Inequalities, NSCLC

OA01 REAL WORLD DATA TO GUIDE OUR DAILY NEEDS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

OA01.06 Project PEER: A Longitudinal Real-World Study to Understand the Experience of Patients with Lung Cancer and Their Caregivers

U. Basu Roy[1], A-M. Baird[2], G. Kersey[1], S. Wing[3], B. King-Kallimanis[1]
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Introduction: The lung cancer treatment landscape has substantially changed in the last decade with novel treatment options available for subsets of lung cancer. With these treatment advances, many patients receive multiple lines of therapies, including clinical trials as a potential option. Our current knowledge of how patients are diagnosed, and how they access and experience treatments is limited to clinical trials and single-institution studies. Project PEER (Understanding the lung cancer **P**atient **E**xperi**E**nce in the **R**eal-world setting), a collaborative endeavor between LUNGevity Foundation and FDA-OCE (Oncology Centers of Excellence), aims to systematically understand how lung cancer patients feel and function during treatment and whether this experience is affected by their specific diagnosis and treatment options. PEER also includes a specific module on the caregiver experience.

Methods: The research team comprising of LUNGevity staff, a PRO expert from the FDA, and an expert from LuCE conceptualized the study and developed comprehensive surveys to:1. Catalog the diagnostic and treatment journey of patients, and 2. Collect real-world patient-experience data across different domains using validated PRO instruments used in lung clinical trials. Surveys were pilot-tested through cognitive debriefing with US and international patients and caregivers, and integrated input from thoracic oncologists. A patient or a caregiver completes one baseline and 11 monthly surveys for a follow-up of 12 months. The study was approved by the New England IRB and deployed using the EmpiraMed online PROTM portal. Analyses were carried out using Stata.

Results:

Conclusions: To our knowledge, this is the first all-comers international real-world longitudinal study aimed at understanding how patients are diagnosed with and are living with lung cancer.

Keywords: RWD (Real World Data), Patient-reported outcomes (PRO), Health disparities

OA02 FROM LOCALLY ADVANCED TO UNRESECTABLE NSCLC: IMPROVEMENT OF MULTIMODALITY TREATMENT, SUNDAY, AUGUST 7, 2022 - 12:00–13:00

OA02.03 Tumor Bulk-RNA Seq Identifies Patients at High Risk of Progression in Non-complete Pathological Responders from NADIM Trial

M. Casarrubios[1], A. Cruz-Bermúdez[1], B. Sierra-Rodero[1], C. Martinez[1], E. Nadal[2], V. Calvo[1], A. Insa[3], M.d.R. García- Campelo[4], C. Gonzalez Ojea[5], M. Dómine[6], M. Majem[7], D. Rodríguez-Abreu[8], A. Martínez-Martí[9], J. De Castro Carpeño[10], M. Cobo[11], G. López-Vivanco[12], E. Del Barco[13], R. Bernabé[14], B. Massutí[15], M. Provencio[1]

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OA02 FROM LOCALLY ADVANCED TO UNRESECTABLE NSCLC: IMPROVEMENT OF MULTIMODALITY TREATMENT, SUNDAY, AUGUST 7, 2022 - 12:00–13:00

OA02.04 Multimodal Management of T4 N2 Non-small-cell Lung Cancer with Additional Ipsilateral Pulmonary Nodules

A. Kumar[1], S. Kumar[2], A. Potter[2], S. Gilja[1], D. Liou[3], C-F.J. Yang[2,4]

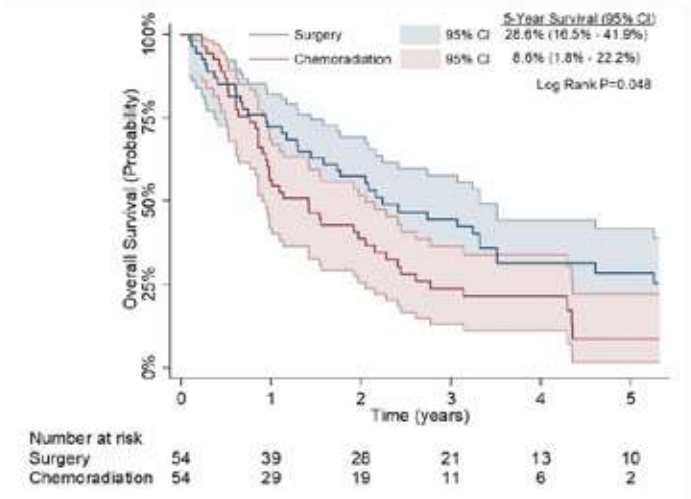
[1]Icahn School of Medicine at Mount Sinai, New York/NY/USA, [2]Massachusetts General Hospital, Boston/MA/USA, [3]Stanford University Medical Center, Stanford/CA/USA, [4]Wentworth Douglass Hospital, Dover/NH/USA

Introduction: The optimal treatment strategy for T4 NSCLC that presents as a primary tumor with additional pulmonary nodules in an ipsilateral lobe is not well characterized. While current National Comprehensive Cancer Network (NCCN) guidelines suggest surgical resection for N0 or N1 disease, the recommended treatment for N2 disease is chemoradiation therapy without surgery. Few studies with limited sample sizes, however, have assessed the use of surgery for patients with T4, N2 (Stage IIIB) NSCLC. This study evaluated long-term survival of patients with T4, N2 NSCLC who received multimodal therapy including surgery as compared with patients who received chemoradiation alone.

Methods: Patients with T4, N2, M0 NSCLC presenting as a primary tumor with additional ipsilateral pulmonary nodule(s) ("T4-Add") in the National Cancer Database (NCDB) from 2010-2015 were included. Long-term survival was evaluated and compared between patients who underwent surgical resection of the primary tumor and those who received concurrent chemoradiation therapy, using Kaplan-Meier analysis, Cox proportional hazards modeling, and propensity score matching on 13 common prognostic variables including comorbidities.

Results: Of the 534 patients who were diagnosed with T4-Add, N2, M0 NSCLC and satisfied the study's inclusion criteria, 166 (31.1%) received surgery and 368 (68.9%) received chemoradiation. In unadjusted analysis, surgery was associated with better 5-year overall survival than chemoradiation (34.9% [27.1-42.8] vs 21.0% [16.4-26.0], p<0.001). After multivariable-adjusted Cox proportional hazards modeling, surgery continued to be associated with better long-term survival than chemoradiation (HR: 1.46, 95% CI: 1.02-2.08, p=0.038). A propensity score-matched analysis was conducted that yielded 54 patients who received surgery and 54 patients who received chemoradiation. In this analysis, patients who received surgery had better 5-year overall survival than patients who received chemoradiation (Figure 1).

Figure 1. Overall Survival of Patients with Clinical T4, N2, M0 NSCLC (with Additional Pulmonary Nodules in an Ipsilateral Lobe) who underwent Chemoradiation vs Multimodality Therapy Including Surgery: Propensity Score-Matched Analysis



Conclusions: This national analysis of patients with T4, N2 NSCLC presenting as a primary tumor with additional nodules suggests that surgery as part of multimodal therapy may confer a survival benefit compared to chemoradiation alone. These findings support the further evaluation of surgery as part of multimodal therapy in prospective, randomized trials for carefully selected patients with T4-add, N2 disease.

Keywords: Multimodal therapy, Additional Nodules, T4 NSCLC

OA02 FROM LOCALLY ADVANCED TO UNRESECTABLE NSCLC: IMPROVEMENT OF MULTIMODALITY TREATMENT, SUNDAY, AUGUST 7, 2022 - 12:00–13:00

OA02.05 Sugemalimab vs Placebo after cCRT or sCRT in pts with Unresectable Stage III NSCLC: Final PFS Analysis of a Phase 3 Study

Y-L. Wu[1], Q. Zhou[2], M. Chen[3], Y. Pan[1], O. Jian[4], D. Hu[5], Q. Lin[6], G. Wu[7], J. Cui[8], J. Chang[9], Y. Cheng[10], C. Huang[11], A. Liu[12], N. Yang[13], Y. Gong[14], C. Zhu[15], Z. Ma[16], J. Fang[17], G. Chen[18], J. Zhao[19], A. Shi[20], Y. Lin[21], G. Li[22], Y. Liu[23], D. Wang[24], R. Wu[25], X. Xu[26], J. Shi[27], Z. Liu[28], J. Wang[29], J. Yang[29]

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OA03 MOLECULAR TARGETED TREATMENTS,
SUNDAY, AUGUST 7, 2022 - 14:30–15:40

OA03.03 Sotorasib in Combination with RMC-4630, a SHP2 Inhibitor, in KRAS p.G12C-Mutated NSCLC and Other Solid Tumors

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Introduction: Sotorasib, a specific and irreversible KRASG^{12}C inhibitor, has demonstrated clinical activity as monotherapy in *KRAS* p.G12C-mutated solid tumors. Genomic alterations of receptor tyrosine kinase (RTK) were identified as a common putative resistance mechanism to sotorasib in the CodeBreaK100 Ph1/2 trial, highlighting the potential role for combining sotorasib with upstream RTK signaling inhibitors. In mouse xenograft models, combining sotorasib with a SHP2 inhibitor (SHP2i) impaired RTK signaling to RAS and enhanced anti-tumor efficacy. Herein, we report the first safety and efficacy data for sotorasib combined with RMC-4630, a small molecule SHP2i.

Methods: In dose exploration of the CodeBreaK101 phase 1b master study, patients with *KRAS* p.G12C-mutated NSCLC, CRC, or other solid tumors were treated with sotorasib (960 mg QD) and RMC-4630, with escalating dose levels of 100 mg, 140 mg, or 200 mg at days 1 and 2 or days 1 and 4 every 7 days. The primary endpoint was safety/tolerability; secondary endpoints included objective response rate per RECIST 1.1 and pharmacokinetics.

Results: As of January 17, 2022, 21 patients (11-NSCLC, 6-CRC, and 4-other solid tumors) who had received a median of 2 prior lines of therapy (range, 1-6) were enrolled; 10 patients (48%) had received prior KRASG^{12}C inhibitor therapy (8-sotorasib, 2-adagrasib). Dose escalation was completed without any grade ≥ 4 treatment-related adverse events (TRAEs). TRAEs of any grade occurred in 71% of patients; the most common were peripheral and localized edema (33%), diarrhea (29%), and fatigue (14%). Grade 3 TRAEs occurred in 6 (29%) patients (diarrhea [2 patients]; ascites, AST increase, colitis, dyspnea, hypertension, pleural effusion [1 patient each]). Two patients had TRAEs leading to discontinuation of RMC-4630 (1-diarrhea and 1-ascites) and one patient had a TRAE leading to discontinuation of both RMC-4630 and sotorasib (AST increased). Of the 11 NSCLC patients enrolled, 3 (27%) had a confirmed partial response (PR) with 2 responses ongoing at data cutoff, and 7 (64%) had disease control. Of the 4 KRASG^{12}C inhibitor-naïve patients with NSCLC who received the highest two doses of RMC-4630 in combination with sotorasib, 3 (75%) had a confirmed PR and 4 (100%) had disease control. One patient, whose NSCLC had progressed on prior sotorasib, achieved an unconfirmed PR at 24 weeks with progressive disease at 30 weeks; one patient with ovarian cancer had a confirmed PR with an 81% reduction in tumor burden; 5 of 6 patients with CRC achieved disease control including one patient achieving a 26% reduction in tumor burden. Pharmacokinetic analysis demonstrated that average sotorasib and RMC-4630 exposures were consistent with distributions observed in monotherapy studies, with no clinically meaningful drug-drug interactions noted.

Conclusions: The combination of sotorasib with RMC-4630 was safe and tolerable in patients with *KRAS* p.G12C-mutated solid tumors. Promising clinical activity was observed in *KRAS* p.G12C-mutated NSCLC patients, most notably in those KRASG^{12}C inhibitor-naïve. Dose expansion is underway to further define efficacy and safety in both KRASG^{12}C inhibitor-naïve and KRASG^{12}C inhibitor-exposed NSCLC patients.

Keywords: sotorasib, SHP2 inhibitor, NSCLC

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OA03.04 Phase I A Study to Evaluate GDC-6036 Monotherapy in Patients with Non-small Cell Lung Cancer (NSCLC) with KRAS G12C Mutation

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Introduction: *KRAS G12C* is one of the most common oncogenic mutations in NSCLC. GDC-6036 is an oral, highly potent, and selective KRAS G12C inhibitor with robust tumor growth inhibition in multiple pre-clinical models. An open-label, Phase I dose-escalation/expansion study of GDC-6036 as monotherapy and in combination with other anticancer therapies is underway for patients (pts) with locally advanced or metastatic solid tumors harboring a *KRAS G12C* mutation. Data from GDC-6036 monotherapy in pts with NSCLC are presented herein.

Methods: This study (NCT04449874) assessed the safety (NCI-CTCAE v5), pharmacokinetics (PK), and preliminary anti-tumor activity (RECIST v1.1) of GDC-6036 administered daily (QD) orally at 50, 100, 200, and 400 mg in 21-day cycles until intolerable toxicity or disease progression. Pts with NSCLC that progressed after ≥ 1 prior line of therapy (or not suitable for standard of care therapy) enrolled in the dose-escalation (including backfill) cohorts and in the dose-expansion at 400 mg. *KRAS G12C* mutation status was determined with local tests or central blood-based next-generation sequencing. Target engagement was assessed with targeted 2D-LC-MS/MS from tumor biopsies at Cycle 1 Day 10-16 at trough exposure.

Results: As of 29 Oct 2021, 37 pts with NSCLC were enrolled (27 pts in the dose-escalation [6 pts at 50 mg, 5 pts at 100 mg, 10 pts at 200 mg, and 6 pts at 400 mg] and 10 pts in the dose-expansion at 400 mg). No dose-limiting toxicities were reported in the dose-escalation arm (across all solid tumors). Among NSCLC patients, the median time on study treatment was 3.5 months (range: 0-9.7 months) and median cumulative dose intensity was 99%. Seventeen pts (46%) had discontinued study treatment (12 due to disease progression [11 due to RECIST progression, 1 symptomatic deterioration], 3 due to physician's decision, 1 due to withdrawal of consent, and 1 due to an adverse event [AE] of diarrhea). The most frequent GDC-6036-related AEs reported in ≥ 20% of pts were nausea, vomiting, diarrhea, and fatigue. GDC-6036-related Grade 3 AEs in ≥ 2 (5%) pts were ALT or AST increase, and diarrhea; no GDC-6036-related Grade 4-5 AEs were reported. AEs were manageable with supportive measures. Thirteen (35%) pts required a dose modification (interruption, reduction, or withdrawal) for GDC-6036-related AEs. Across all solid tumor patients, the mean half-life for GDC-6036 ranged from 13- 17 hours at doses of 50- 400 mg. The unconfirmed overall response rate (ORR) in pts with NSCLC was 43% (15/37 pts), while the confirmed ORR was 37% (13/37 pts) across dose levels. Approximately 90% or higher target engagement was achieved at multiple dose levels in pts with NSCLC.

Conclusions: GDC-6036 exhibits encouraging clinical activity and high target engagement levels across dose levels in NSCLC with a *KRAS G12C* mutation. This study has also demonstrated a wide therapeutic range for GDC-6036 (50- 400 mg), an acceptable safety profile with manageable and reversible AEs, and a PK profile compatible with once-daily dosing. Data from an expanded cohort will be presented at the conference.

Keywords: KRAS, GDC-6036, NSCLC

OA03 MOLECULAR TARGETED TREATMENTS,
SUNDAY, AUGUST 7, 2022 - 14:30–15:40

OA03.05 Tepotinib in Patients with MET Exon 14 (METex14) Skipping NSCLC: Primary Analysis of the Confirmatory VISION Cohort C

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Introduction: Tepotinib is an oral, once daily, highly selective, potent MET inhibitor approved for *MET* exon 14 (*MET*ex14) skipping NSCLC based mainly on Cohort A of the multi-cohort Phase II VISION study. We report primary analysis (>9-months' follow-up) of the independent confirmatory Cohort C; data cut-off February 20, 2022.

Methods: Patients with advanced *MET*ex14 skipping NSCLC, by liquid and/or tissue biopsy (TBx), enrolled in Cohort A (primary analyses) and C (confirmatory analyses), received tepotinib 500 mg (450 mg active moiety) once daily. Primary endpoint was objective response by IRC (RECIST v1.1). Pre-planned exploratory analysis of brain lesions was conducted by IRC using RANO-BM criteria.

Results: Patients in Cohort C (N=161) had a median age of 71.0 years (range 42-91), 46.6% were male, 54.0% were white, 42.2% were Asian, 43.5% had smoking history, 75.2% had adenocarcinoma histology, 74.5% had ECOG PS 1, and 59.0% were treatment-naïve (1L). In Cohort C, ORR was 54.7% (46.6, 62.5) with mDOR of 20.8 months (12.6, ne) and mPFS of 13.8 months (10.4, ne). Efficacy was robust and durable across therapy lines (**Table**). In Cohort C, *MET*ex14 skipping was detected by TBx in 120/161 patients (T+; 74.5%). In 1L T+ patients (n=69), ORR was 62.3% (95% CI: 49.8, 73.7) with mDOR ne (10.4, ne) and mPFS of 15.9 months (10.8, ne). Previously treated (2L+) T+ patients (n=51) had an ORR of 51.0% (36.6, 65.2) with mDOR of 12.6 months (4.3, ne) and mPFS of 13.8 months (6.9, ne). Across Cohorts A+C, 43 patients with brain metastases were evaluable by RANO-BM (1L, n=23; 2L+, n=20); 30 (69.8%) received prior brain radiotherapy or surgery. Intracranial (i) disease control rate was 88.4% (74.9, 96.1) with iPFS of 20.9 months (5.7, ne), and in patients with target lesions only (n=15), iORR was 66.7% (38.4, 88.2) with iDOR ne (0.9, ne). In Cohorts A+C, treatment-related adverse events (TRAEs) occurred in 91.7% of patients (Grade ≥3 34.2%); including (≥15%) peripheral edema (any grade/Grade ≥3: 66.5/10.9%), nausea (23.3/0.6%), hypoalbuminemia (23.0/3.2%), diarrhea (22.4/0.3%), and increased blood creatinine (21.7/0.6%). Permanent discontinuation due to TRAEs occurred in 14.7% of patients.

Conclusions: In VISION - the largest clinical trial of a MET inhibitor in *MET*ex14 skipping NSCLC - Cohort C primary analysis provided independent confirmation for robust and durable efficacy of tepotinib, with comparable or improved outcomes across endpoints compared to Cohort A. Efficacy was particularly durable in 1L T+ patients and promising intracranial activity was observed.

Line of therapy	Cohort	ORR, % (95% CI)	mDOR, months (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
1L	C (n=95)	60.0 (49.4, 69.9)	ne (13.4, ne)	15.9 (10.4, ne)	21.1 (12.7, ne)
	A (n=69)	50.7 (38.4, 63.0)	46.4 (7.2, ne)	10.3 (8.0, 15.3)	19.1 (9.9, 25.9)
	A+C (n=164)	56.1 (48.1, 63.8)	46.4 (13.8, ne)	12.6 (9.6, 17.7)	19.1 (13.7, 23.7)
1L T+	C (n=69)	62.3 (49.8, 73.7)	ne (10.4, ne)	15.9 (10.8, ne)	22.7 (12.7, ne)
	A (n=42)	47.6 (32.0, 63.6)	46.4 (7.6, ne)	15.3 (8.2, ne)	29.7 (13.5, ne)
	A+C (n=111)	56.8 (47.0, 66.1)	46.4 (13.4, ne)	15.3 (11.3, ne)	25.9 (17.5, 36.6)
2L+	C (n=66)	47.0 (34.6, 59.7)	12.6 (5.1, ne)	12.1 (6.9, ne)	18.8 (13.5, ne)
	A (n=83)	43.4 (32.5, 54.7)	12.4 (8.4, 18.5)	10.9 (8.2, 12.7)	19.8 (15.0, 22.3)
	A+C (n=149)	45.0 (36.8, 53.3)	12.4 (9.5, 18.5)	11.0 (8.2, 13.7)	19.6 (15.2, 22.3)
2L+ T+	C (n=51)	51.0 (36.6, 65.2)	12.6 (4.3, ne)	13.8 (6.9, ne)	19.6 (14.6, ne)
	A (n=46)	47.8 (32.9, 63.1)	12.4 (7.0, 18.0)	11.0 (8.2, 16.8)	20.8 (14.3, 27.2)
	A+C (n=97)	49.5 (39.2, 59.8)	10.2 (8.3, 18.0)	11.5 (8.2, 16.8)	20.4 (17.0, 26.8)
Overall	A+C (n=313)	50.8 (45.1, 56.5)	18.0 (12.4, ne)	11.2 (9.5, 13.8)	19.3 (15.8, 22.3)

1L, first line; 2L+, second-or-later line; CI, confidence interval; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ne, not estimable; ORR, objective response rate; T+, *MET*ex14 skipping positive in tissue biopsy.

Keywords: MET inhibitor, Tepotinib, MET exon 14 skipping

OA03 MOLECULAR TARGETED TREATMENTS,
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OA03.06 CodeBreaK 100/101: First Report of Safety/Efficacy of Sotorasib in Combination with Pembrolizumab or Atezolizumab in Advanced KRAS p.G12C NSCLC

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OA03.07 Safety and Efficacy of D-1553 in Patients with KRAS G12C Mutated Non-Small Cell Lung Cancer: A Phase 1 Trial

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Introduction: KRAS G12C mutation acts as a key oncogenic driver occurring in approximately 15% of non-small cell lung cancer (NSCLC). An activating KRAS mutation (for example, G12C mutation) results in KRAS protein accumulated in the GTP-bound, active form, which is believed to drive the abnormal growth of cancer cells in multiple tumor types. D-1553 is an orally bioavailable inhibitor of KRAS G12C that selectively and irreversibly binds KRAS G12C mutated protein in an inactive GDP-bound state.

Methods: A phase 1, open-label, multicenter study (NCT05383898) is conducted to evaluate the safety, pharmacokinetics (PK) and efficacy of D-1553 in patients with advanced or metastatic NSCLC harboring KRAS G12C mutation who progressed after receiving standard therapy. Oral daily (QD) doses of 600, 800 and 1200 mg, and twice daily (BID) doses of 400 and 600 mg were assessed in dose escalation cohorts in a 3+3 design; 600 mg BID was assessed in dose expansion cohort. The endpoints included safety, PK parameters, objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and duration of response (DOR), evaluated according to RECIST 1.1.

Results: As of May 9, 2022, a total of 79 patients with NSCLC (70 [88.6%] male, median age 65 [range: 30-86]) were enrolled. Patients received a median of 2 (range: 1-7) prior lines of systemic anticancer therapy, with 42 patients (53.2%) receiving ≥ 2 prior lines. At the data cutoff on May 9, 2022, median follow-up time was 21.7 weeks (range: 3-47). Of all 79 patients, 53 patients (67.1%) were still on treatment. No DLT has been reported. MTD was not reached. 68 pts (86.1%) had treatment-related adverse events (TRAEs), most of which were grade 1-2. The most common (≥ 20%) TRAEs were AST increased, ALT increased, gamma-glutamyltransferase increased, bilirubin conjugated increased and anemia. No grade 5 TRAE has been reported. Among 73 patients at all dose levels evaluable for tumor response, 29 patients had partial response (PR) and 38 had stable disease (SD); ORR and DCR were 39.7% (29/73) and 91.8% (67/73), respectively. Among 3 patients with measurable CNS metastasis at baseline, one PR and two SD were achieved in brain lesions. Median DOR was not reached, but among 29 responders there were 25 (86.2%) patients still ongoing with 14 patients having DOR ≥ 12 weeks. For PFS, 57 (78.1%) subjects have not reached an event. More details of DOR and PFS will be reported at the meeting.

Conclusions: D-1553 was well tolerated, with promising antitumor activity in heavily pretreated KRAS G12C mutant-NSCLC patients. The study is ongoing, and more results will be presented at the meeting.

Keywords: Non-small cell lung cancer, KRAS G12C mutation, Small molecular inhibitor

OA04 MESOTHELIOMA UNDER THE LOOKING GLASS,
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OA04.03 Multi-omic Analysis of Malignant Pleural Mesothelioma PDXs Reveal Pathway Alterations and Therapeutic Targets

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Introduction: Despite recent treatment advances, malignant pleural mesothelioma (MPM) is an aggressive, recalcitrant malignancy. Currently, histologic subtype (epithelioid/non-epithelioid/biphasic) is the primary prognostic factor; other potential biomarkers to guide therapeutic strategies remain elusive. Even with multimodality therapies, recurrence is high in early-stage disease. In the unresectable/metastatic setting, there are only two FDA-approved regimens, both in the first-line setting: cisplatin/pemetrexed and ipilimumab/nivolumab. Unfortunately, most who respond to first-line treatment experience disease progression within a year. Therapeutic and diagnostic advances in DPM are hindered by a paucity of well-annotated preclinical models which can faithfully recapitulate the complex genomic interplay of the disease.

Methods: We established a library of patient-derived xenografts (PDX) from patients with DPM. We performed multi-omic analyses on available PDX and patient samples to deconvolute the mutational landscapes, global expression profiles, and molecular subtypes. Targeted next-generation sequencing (NGS; MSK-IMPACT), immunohistochemistry, and histologic subtyping were performed on all available samples. RNA-sequencing was performed on all available PDX samples. Clinical outcomes and treatment history were annotated for all patients. Platinum-doublet progression-free survival (PFS) was determined from the start of chemotherapy until radiographic/clinical progression and grouped into < or ≥ 6 months.

Results: The mutational landscapes of PDX models strongly correlated with paired tumor samples. There were some differences in *CDKN2A/B* mutations and relative enrichment of *NF2* with fewer *BAP1* alterations, the significance of which is being investigated. When compared by histological subtype, we observed an upregulation of genes involved in NOTCH and EMT signaling in the epithelioid models. Models derived from patients with shorter overall survival or poor response to platinum doublet had higher expression of WNT/ß-catenin signaling, hedgehog pathway, and epithelial-mesenchymal transition signaling as well as downregulation of immune-activation pathways, including type I and II interferon signaling and inflammatory response pathways.

Conclusions: This library of MPM PDXs, the largest to date, effectively mimics human disease and provides unprecedented insight into the genomic, transcriptomic, and protein landscape of MPM. These PDX models will inform future clinical investigations and provide an important new preclinical resource.

Keywords: mesothelioma, PDX, biomarker

OA04 MESOTHELIOMA UNDER THE LOOKING GLASS,
SUNDAY, AUGUST 7, 2022 - 14:30–15:30

OA04.04 Association of Novel microRNAs with Diagnosis and Histology of Malignant Pleural Mesothelioma

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Introduction: Achieving an accurate diagnosis of malignant pleural mesothelioma (MPM) can be quite difficult and time consuming, with the differentiation of MPM from pleural metastases of other cancers being particularly challenging. The availability of tissue-specific biomarkers could prove very helpful in this context. Through a recent analysis of the TCGA-MESO small RNA sequencing data previously undetected microRNAs have been identified, which showed significantly higher expression than in sequencing data from primary lung cancers. A signature of 10 of these microRNAs was able to distinguish MPM from lung cancer with high accuracy (Martinez VD et al, AJRCM 2019: 61(2)). In the present study, we evaluate the expression of these microRNAs in MPM tissue as well as pleural biopsies from benign inflammatory reactions and metastases of other cancers using an alternative detection approach (two-tailed RT-qPCR).

Methods: We used diagnostic chemo-naïve biopsies from 32 MPM patients and 14 non-MPM cases who were treated at the University Hospital Zurich between 1999 and 2021. For 23 of our MPM cases microRNA expression was also assessed in the matching post-chemotherapy specimen. The non-MPM cases consisted of 8 patients with benign inflammatory reaction or plaques, 3 patients with metastasis due to lung adenocarcinoma and 3 patients with pleural metastases of other primaries. RNA was extracted from FFPE specimens and the 10 novel candidates as well as RNU48 as endogenous reference gene were detected by RT-qPCR. Independent or paired samples t-test was used to evaluate statistical significance of observed expression differences.

Results: In this extended patient series, we could confirm our initial findings reported at WCLC 2021 regarding significantly higher expression of four of the novel mpm-microRNAs in chemo-naïve MPM tumours as compared to non-MPM controls. Specifically, we found significantly higher levels for mpm-miR-136 (6.1-fold, $p<0.001$), mpm-miR-72 (4-fold, $p=0.011$), mpm-miR-18 (4.3-fold, $p>0.001$), and mpm-miR-58 (5.6-fold, $p>0.001$). Furthermore, in the diagnostic, chemo-naïve specimens we could observe a trend towards higher expression in biphasic tumors (N=6) as compared to epithelioid tumours (N=26), which reached statistical significance for mpm-miR-136 (relative expression: 30.72 vs 10.28, $p=0.043$). In post-chemotherapy samples, this expression difference between epithelioid and non-epithelioid tumours could not be observed. When comparing chemo-naïve and chemo-treated tumour specimens small expression differences with slightly higher levels before chemotherapy were not statistically significant. Of the three non-MPM cases that showed levels of all four microRNAs comparable to those in MPM tumours, two were pleural metastases of lung adenocarcinomas.

Conclusions: Findings from this extended patient series confirm the potential diagnostic value of novel mesothelioma-specific microRNAs in MPM. While chemotherapy does not appear to alter levels of these microRNAs, higher expression levels in biphasic tumours suggest an association between expression and histological subtype. The finding of higher expression in pleural metastases of lung cancer cases requires further investigations. Based on our present data, analyses in additional samples, including primary lung cancer cases is warranted and currently underway.

Keywords: malignant pleural mesothelioma, microRNAs, biomarkers

OA04 MESOTHELIOMA UNDER THE LOOKING GLASS,
SUNDAY, AUGUST 7, 2022 - 14:30–15:30

OA04.05 MESOMICS Project: Using Whole-Genome Sequencing Data to Fill the Gaps in Malignant Pleural Mesothelioma Molecular Studies

L. Mangiante[1,2], N. Alcala[1,2], A. Di Genova[1,2], A. Sexton-Oates[1,2], N. Le Stang[3], S. Boyault[4], C. Cuenin[5], F. Damiola[3], C. Voegele[1], M. Mesobank[6], D. Jean[7], S. Lantuejoul[3], A. Ghantous[5], H. Hernandez-Vargas[8], C. Caux[9], N. Girard[10], N. Lopez-Bigas[11], L.B. Alexandrov[12], F. Galateau Salle[3], M. Foll[1,13], L. Fernandez-Cuesta[1,13]

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Introduction: Malignant Pleural Mesothelioma (MPM) is an aggressive cancer with rising incidence and challenging clinical management. The current WHO classification distinguishes three major histological types with prognostic value: epithelioid (MME), biphasic (MMB), and sarcomatoid (MMS). In the past decade, knowledge on the molecular profile of MPM has rapidly expanded, owing to cohorts combining whole-exome sequencing, transcriptomic, and epigenomic data. As a result, the preponderent hypothesis is that MPM inter-patient heterogeneity is sufficiently explained by a simple histopathological classification, with phenotypes ranging from MME to MMS. Nevertheless, the full extent of MPM phenotypes, and the mechanisms by which these phenotypes evolved are poorly understood. This might be due to the fact that the genomic complexity of these tumors requires more high-resolution data including whole-genome sequencing, multi-omic analyses, and cancer evolution frameworks, to effectively link genotypes to phenotypes.

Methods: We have designed the MESOMICS study (http://rarecancersgenomics.com/mesomics/) to uncover the main sources of molecular variation explaining MPM inter-tumoral heterogeneity, and to identify the underlying biological functions. We combined a novel cohort of 120 MPMs corresponding to the largest series of whole-genome sequencing data and integrating transcriptomic and epigenomic data. Using detailed clinical, epidemiological, and morphological annotations and multi-omic factor analysis, we first tested whether the current histopathological classification explained most of the inter-patient molecular heterogeneity of the disease. In addition, we used these unique datasets and performed task specialization analyses to elucidate the link between genotype and phenotype in mesothelioma. Finally, we used two independent replication MPM cohorts and data from MPM cell line models to confirm our findings and translate them to a functional validation.

Results: We demonstrate that MPM molecular heterogeneity arises from four continuous axes of variation: ploidy, tumor cell morphology, adaptive immune response, and CpG island methylator profile. Furthermore, we prove that the current histopathological classification only explains a fraction of the molecular heterogeneity of the disease, while ploidy, adaptive immune response, and CpG island methylation are as important. These axes of variation are delimited by extreme phenotypes that, in the case of the interdependent tumor cell morphology and adapted immune response, reflect tumor specialization. The ploidy axis underscores MPMs with whole-genome doubling and near-haploid profiles at each extremity while the CpG island methylator axis reveals a continuum of methylation level in the CpG islands. Finally, by mapping the genomic landscape of 120 MPMs along the tumor cell morphology and adapted immune response axes, we discovered tumors specialized in the Cell division and Tumor-immune-interaction tasks, as well as an acinar morphology profile. All these extreme phenotypes present different genomic events and survival rates.

Conclusions: These findings unearth the interplay between MPM functional biology and its genomic history, set the bases for a new morpho-molecular classification, and provide insights into the variations observed in the clinical behavior of MPM patients. This work is currently under second round of revision in Nature Genetics. This work has been funded by the French National Cancer Institute (INCa, PRT-K 2016-039), Ligue Nationale contre le Cancer (LNCC 2017 and 2020), and by France Génomique National.

Keywords: Malignant Pleural Mesothelioma, Inter-tumoral Heterogeneity, Genome

OA04 MESOTHELIOMA UNDER THE LOOKING GLASS,
SUNDAY, AUGUST 7, 2022 - 14:30–15:30

OA04.06 PEMbrolizumab Plus Lenvatinib In Second And Third Line Malignant Pleural MEsotheLiomA Patients: A Single Arm Phase II Study (PEMMELA)

L-A.H. Douma, C.J. de Gooijer, V.v.d. Noort, F. Lalezari, J.F. de Vries, M. Vermeulen, B. Schilder, I. Smesseim, P. Baas, J.A. Burgers

Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam/NL

Introduction: There is a need for effective second line treatment in patients with recurrent malignant pleural mesothelioma (MPM). Pembrolizumab, a PD-1 receptor blocker, has shown a response rate up to 20% as monotherapy. Lenvatinib, a multiple tyrosine kinase inhibitor with mostly vascular endothelial growth factor receptor (VEGFR) blocking properties, has synergistic interactions with PD-1 blocking in other tumors. We aimed to evaluate clinical activity and toxicity of pembrolizumab plus lenvatinib in patients with recurrent MPM.

Methods: PEMMELA was a prospective single-center, single-arm, open-label, investigator-initiated phase 2 trial of pembrolizumab (200 mg once every three weeks intravenously) plus lenvatinib (20 mg orally once daily) in patients with MPM who progressed after chemotherapy. Main eligibility criteria were age 18 years or older, histologically proven MPM, Eastern Cooperative Oncology Group PS 0-1 and presence of measurable disease according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1. Treatment continued up to two years or until unacceptable toxicity or disease progression evaluated by CT-scan every six weeks. The primary endpoint was objective response rate (ORR; proportion of patients with complete response (CR), or partial response (PR)) assessed by the local investigator according to mRECIST, taking into account the immunotherapy related rules for response evaluation of iRECIST. Secondary endpoints included safety of treatment combination, disease control rate (DCR) at 3 and 6 months as well as ORR and progression free survival (PFS) determined by an independent radiologist. The study is registered with ClinicalTrials.gov, NCT04287829.

Results: Between March 05, 2021 and January 31, 2022, 38 eligible patients were included. At data cutoff (31 March 2022), 22 of 38 patients had reached PR as best overall response (58%, 95% CI: 41-74%, p<0.0001), of which 15 patients had confirmed PR (39.5%, 95% CI: 24-57%, p=0.07). 3 of 7 unconfirmed PR patients can still reach confirmed PR. 26 patients developed grade 3-4 treatment-related adverse events (AE's). The most common grade 3 treatment-related AE's were hypertension (24%) and anorexia (18%). There were 3 grade 4 events: myositis, hyponatremia, and increased gamma-GT. There were 14 treatment-related serious adverse events in 10 patients. 76% of all patients required at least one dose reduction or permanent discontinuation of lenvatinib due to toxicity.

Conclusions: This study met its primary endpoint, showing promising clinical activity of pembrolizumab plus lenvatinib in patients with recurrent MPM who progressed after chemotherapy, with remarkable but no unexpected toxicity.

Keywords: Malignant pleural mesothelioma, pembrolizumab, lenvatinib

OA05 THE GRANULARITY OF LUNG CANCER SCREENING IMPLEMENTATION,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

OA05.03 Incidence, Timing, and Survival of Second Primary Lung Cancer in Patients in the National Lung Screening Trial

A. Potter[1], M. Pan[1], C. Mathey-Andrews[1], C. Haridas[1], P.A. Ugalde[2], L.W. Martin[3], C-F.J. Yang[1]

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This abstract is under embargo until August 7 at 10:10 Vienna, Austria Time, CEST.

OA05 THE GRANULARITY OF LUNG CANCER SCREENING IMPLEMENTATION,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

OA05.04 A Comparison of Stage- and Histology-Specific CT Sensitivity in the NELSON Trial and the NLST

K. de Nijs[1], K. ten Haaf[1], C.M. van der Aalst[1], M. Oudkerk[2,3], H.J. de Koning[1]

[1]Erasmus University Medical Center, Rotterdam/NL, [2]University Medical Center Groningen, Groningen/NL, [3]iDNA (institute for DiagNostic Accuracy), Groningen/NL

This abstract is under embargo until August 7 at 10:10 Vienna, Austria Time, CEST.

OA05 THE GRANULARITY OF LUNG CANCER SCREENING IMPLEMENTATION,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

OA05.05 China Lung Cancer Screening (CLUS) Version 1.0: Mortality, Survival and Incidence Rates with Long-Term Follow-up

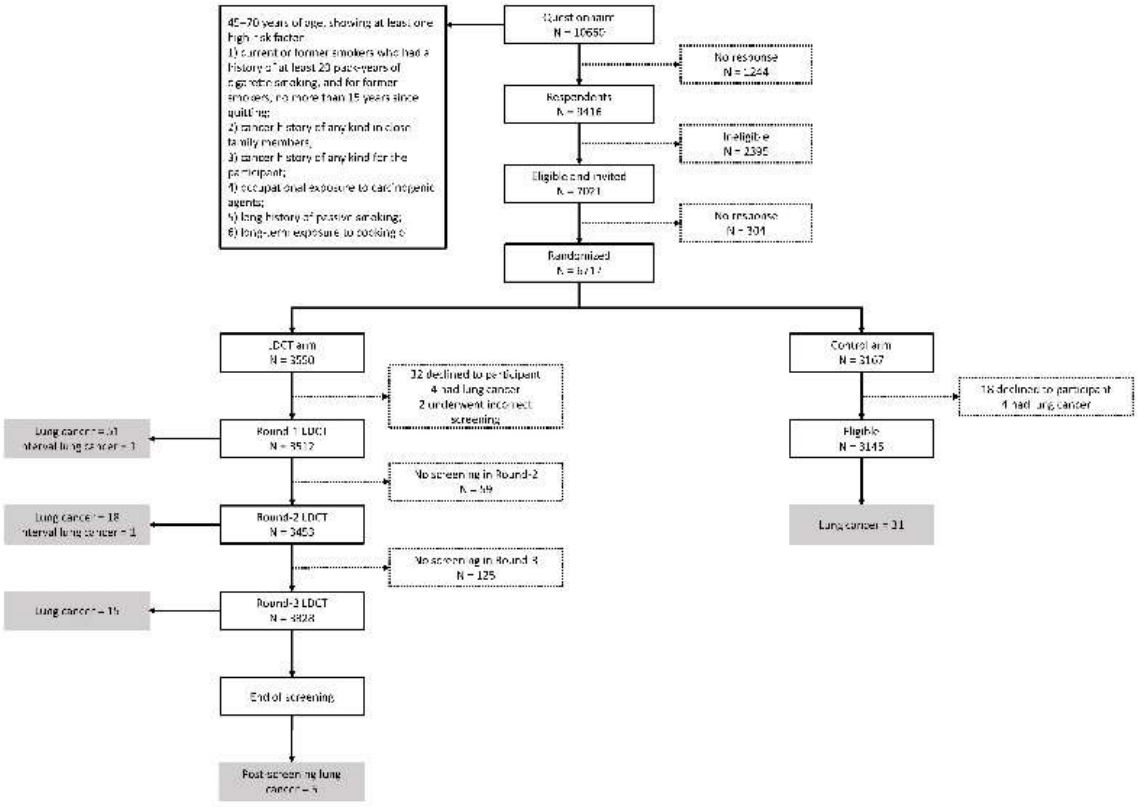
F. Qian, Y. Zhang, J. Teng, H. Wang, Y. Lou, W. Zhang, H. Zhong, B. Han
Shanghai Chest Hospital, Shanghai/CN

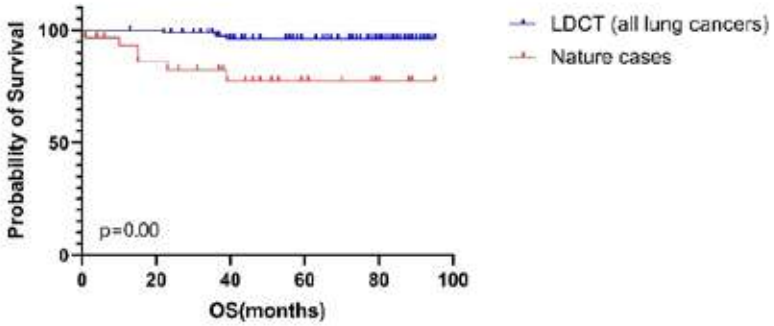
Introduction: Low-dose computed tomography (LDCT) is recommended for lung cancer screening. However, criteria of high-risk population, screening interval, screening rounds remain uncertain. This study provides results of three-round biennial screenings in China.

Methods: From November 2013 to November 2014, 6657 eligible participants with high-risk factors of lung cancer were randomly assigned to three-round biennial screenings or a control group. Data were collected on cases of lung cancer and deaths from lung cancer that occurred through February 28, 2022.

Results: In all, 86 and 31 lung cancers were diagnosed in the LDCT and control arms, respectively. Screening-detected lung cancers were found in 79 of the 3512 participants (2.24%). Early-stage lung cancer was found in 91.9% (with LDCT arm) versus 41.9% (with control arm). Lung cancer related deaths were observed in 3.5% (with LDCT arm) versus 22.6% (with control arm). Compared to standard care, LDCT led to a 19.1% decrease in lung cancer related mortality. 5-year overall survival of LDCT and control arms were 68.6% and 30.0%, respectively.

Conclusions: Biennial screening showed low interval cancer rate. This study provides insights about the non-smoking related risk factors of lung cancer in the Chinese population.





Clinical characteristics, stage and histologic features of lung cancers diagnosed				
	LDCT (N = 3512)			Nature cases (N = 3145)
	Screening-detected	Non-Screening-detected	All	
Lung cancers (No.)	79	7	86	31
Age			61.03±5.72	62.42±5.54
Gender				
Male	29	4	33	16
Female	50	3	53	15
Stage				
AIS	9	0	9	2
IA	64	5	69	13
IB	10	0	10	0
IIA	0	0	0	2
IIB	1	0	1	2
IIIA	1	1	2	4
IIIB	1	0	1	0
IV	1	1	2	9
Limited	1	0	1	1
Histologic features				
Adenocarcinoma	73	6	79	27
Squamous-cell carcinoma	3	1	4	3
Large-cell carcinoma	1	0	1	0
Adenosquamous carcinoma	1	0	1	0
Small cell lung cancer	0	0	0	1
Complex small cell lung cancer	1	0	1	0
Mortality of lung cancer	2	1	3	7

Keywords: Screening, Early-stage

OA05 THE GRANULARITY OF LUNG CANCER SCREENING IMPLEMENTATION,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

OA05.06 Early Diagnosis of Lung Cancer Among Younger vs. Older Adults: Widening Disparities in the Era of Lung Cancer Screening

A. Potter, P. Senthil, A. Mansur, C. Mathey-Andrews, H. Auchincloss, C-F.J. Yang
Massachusetts General Hospital, Boston/MA/USA

This abstract is under embargo until August 7 at 10:10 Vienna, Austria Time, CEST.

OA06 IMPACT OF COVID-19 ON CANCER MANAGEMENT AND PROTECTION FROM VACCINES,
MONDAY, AUGUST 8, 2022 - 11:00–12:10

OA06.03 Serological Response to SARS-CoV-2 Vaccination in Patients Lung Cancer: A Mount Sinai-Led Prospective Matched Controlled Study

P.C. Mack[1], J.C. Gomez[1], A. Rodilla[1], J.M. Carreño[2], C-Y. Hsu[3], C.D. Rolfo[1], N. Meshulami[1], A. Moore[4], R. Brody[5], J.C. King[6], J. Treatman[1], S. Lee[1], A. Raskin[2], K. Srivastava[2], C.R. Gleason[2], J. Tcheou[2], D. Bielak[2], R. Acharya[6], D.E. Gerber[7], N. Rohs[1], C.I. Henschke[8], D.F. Yankelevitz[8], V. Simon[2,5,9,10], J.D. Minna[7], P.A. Bunn Jr[11], A. García- Sastre[2,5,9,10,12], F. Krammer[2,5], Y. Shyr[3], F.R. Hirsch[1,5]

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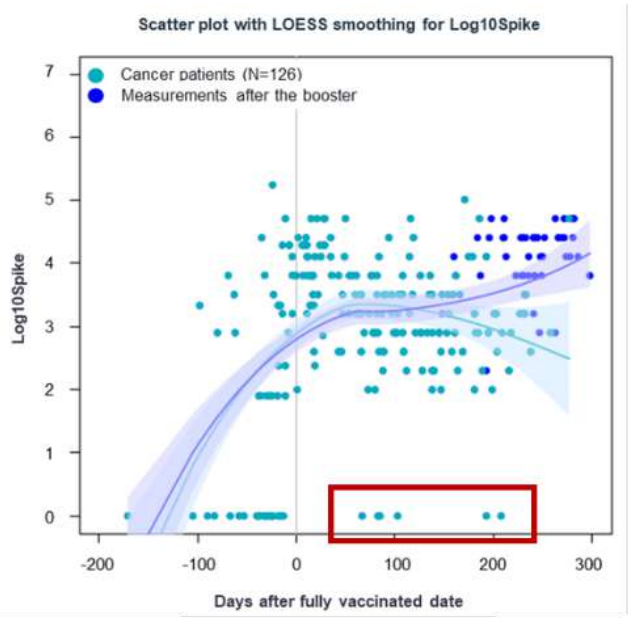
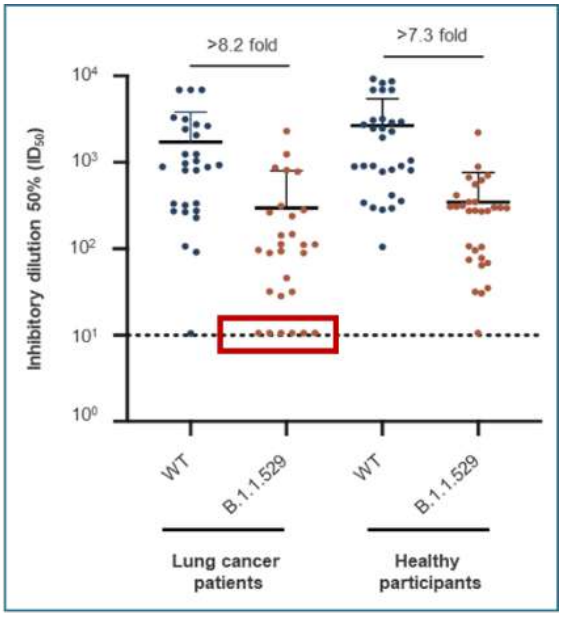
Introduction: Since the onset of the COVID-19 pandemic, patients with lung cancer (LC) are at increased risk of severe outcomes from SARS-CoV-2 infection, prompting efforts to encourage LC patient vaccination. There remains a significant knowledge gap in how LC patient demographics and clinical features impact on the response to SARS-CoV-2 vaccines or infection. Understanding these patient- and cancer-specific factors is essential to providing optimal care.

Methods: This ongoing IRB-approved NCI U54/SeroNet-sponsored study, designed to accrue a prospective longitudinal cohort of LC patients, was initiated January 2021 at the Mount Sinai Hospital, NY. The study enrolled LC patients of any stage, histology, SARS-CoV-2 exposure/vaccination or cancer treatment. Demographic, epidemiological, clinical data, and blood specimens for participating patients were collected at the time of enrollment, 3 and 6 months thereafter. Presence of IgG Ab against the SARS-CoV-2 Spike protein was quantitated using a validated enzyme-linked immunosorbent assay (ELISA) established at Mount Sinai. Neutralizing antibody titers (NAbT) against ancestral SARS-CoV-2 and Omicron were quantified in a post-booster subset. For comparison, 114 age-matched cancer-free participants were recruited as controls.

Results: Overall, 176 LC patients were recruited (January to December 2021), of which a subset of 114 had two doses of mRNA vaccine (66% PfizerBNT162b2; 34% Moderna1273). Controls were well-matched for age and ethnicity. Analysis of anti-SPIKE Ab titers showed that the vast majority of LC patients mounted a similar response to controls following vaccination - with the exception that 5% of patients presented titers of zero ($p<0.0001$). Maintenance of titers over time was significantly lower in LC patients than controls ($p=0.0018$), significantly more intra-patient variance in titers within the cancer group ($p=0.002$). No relationships were observed by age or smoking status, but treatment effects could not be ruled out as a possible contributor to zero titer cases. Additionally, 35% of patients received a booster (third dose) vaccination, showing significant enhancement of their Ab titers ($p<0.001$). After their booster, both controls and patients had significantly diminished NAbT against Omicron compared to ancestral variant after the booster, and a sizable proportion of LC patients (21%) had no detectable NAbT against Omicron compared to 3% of controls.

Conclusions: Overall, the majority of LC patients mounted a humoral response comparable to that of healthy controls. A small but significant subset of patients failed to mount an Ab response to vaccination, only partially rescued by booster shots. Additionally, post-booster Omicron neutralizing activity was compromised in a subset of LC patients.





Keywords: SARS-CoV-2, Antibody titers, lung cancer

OA06 IMPACT OF COVID-19 ON CANCER MANAGEMENT AND PROTECTION FROM VACCINES,
MONDAY, AUGUST 8, 2022 - 11:00–12:10

OA06.04 Immune Response after SARS-CoV-2 Vaccination in Lung Cancer Patients. Update of the Covid Lung Vaccine Cohort

A. Hernandez[1], L. Notario[1], B. Quirant[2], E. Felip[1], M. Boigues[3], M. Saigí[1], M. Cucurull[1], P. Torres[1], M.J. Martinez[1], R. Gomez Castella[1], M. Rodriguez Esteban[1], M. Benitez Martin[1], E. Carcereny[1], M. Domenech[1], A. Estival[4], A. Pous[1], A. López-Paradís[1], M. Romeo[1], T. Moran[5]

[1]Catalan Institute of Oncology-Badalona, Badalona/ES, [2]Hospital Universitari Germans Trias i Pujol, Badalona/ES, [3]Hospital Universitari Germans Trias i Pujol; Autonomous University of Barcelona, Badalona/ES, [4]Hospital Insular de Gran Canaria, Gran Canaria/ES, [5]Catalan Institute of Oncology-Badalona; Autonomous University of Barcelona, Badalona/ES

Introduction: Lung cancer (LC) patients (p) represent a subgroup of p in whom the infection by SARS-CoV-2 could attained higher rates of morbidity and mortality. Therefore, those p were recommended to receive SARS-CoV-2 vaccines (V) once they were approved. However, little was known regarding the degree of immunity after vaccination, potential interactions with oncology treatments and V-adverse events (AE) in this population. More uncertainty involved the need for a third (3) dose (D) of the V in this population or its efficacy in controlling the Omicron variant, which ousted Delta variant by the end of 2021 in Spain. The aim of this prospective study is to evaluate the immune response to the SARS-CoV-2 V in LCp. Secondary objectives include V-related AE, V impact on survival, immune response, toxicity and survival outcomes in p>75 y, (re)infection after V, complications and mortality.

Methods: LCp who receive the V against SARS-COV-2 were candidates to participate in this study. A pre-V quantitative IgG spike determination was performed to identify p with previous infection, but asymptomatic course. After V, IgG have been repeated at 3-6, 7-9, and 12 months since the first (1) D. V-related AEs, serological results, clinical data, and survival have been collected.

Results: From 3/31-5/15, 2021 126 p have participated in the study. 61.9% were male, median age was 66 y (46- 83), 88.1% were NSCLC, 76% had stage IV at diagnosis. Systemic therapy included *EGFR/ALK/ROS1/RET/MET* oral inhibitors *(*19.9%), immunotherapy (IT) (41.8%), IT-chemotherapy (CT) (14.1%) and CT (19.9%). 9p were not receiving active therapy. 9 p had COVID symptomatic infection prior any dose of the V, with positive baseline IgG in 6p. No vaccine-related AE were reported in this group. 4 additional p had positive baseline IgG. Out of 126 p, 94.3% received MODERNA® on behalf of the Hospital Vaccination Program for 1 and 2 D. 97p (77%) received MODERNA® as third (3)D according to National Health Care guidelines. AES with 1-2D were generally mild and included local pain (35%), asthenia (6%) and myalgia (4%). These were slightly more frequent in p>75, especially after 2D (42%, 15%, 42%). More frequent AE after 3D included pain (20.6%), asthenia (6.2%) and myalgia (7.2%). Pain after 3D occurred in 21.1% of p>75. All but 1p developed IgG after 1-2D. Median IgG levels were 2228.9 UI/mL (9,91-8169) at 3-6 months (m), which were sustained at 7-9 m [2335.8 UI/mL, (87-3696)]. All p>75 seroconverted. 9 infections occurred after V during the sixth wave of pandemic (all a/paucisymptomatic with no admissions). 4 out of these 9 p had received 3D, 2 of them were reinfections. 32 deaths were reported in this cohort, with no COVID-related deaths

Conclusions: • SARS-COV-2 V are safe irrespective of systemic therapy in our cohort of LCp.• AE and efficacy were similar regardless the age groups.• Most of the p developed immunity after 2D, which was maintained over time.• Rates of infection were low but more frequent with the Omicron variant and with milder clinical course after V.

Keywords: SARS-CoV-2, Vaccine, Lung Cancer

OA06 IMPACT OF COVID-19 ON CANCER MANAGEMENT AND PROTECTION FROM VACCINES,
MONDAY, AUGUST 8, 2022 - 11:00–12:10

OA06.05 Impact of COVID-19 Pandemic on Proportion and Treatment Patterns for Stage I Non-small Cell Lung Cancer in the Netherlands

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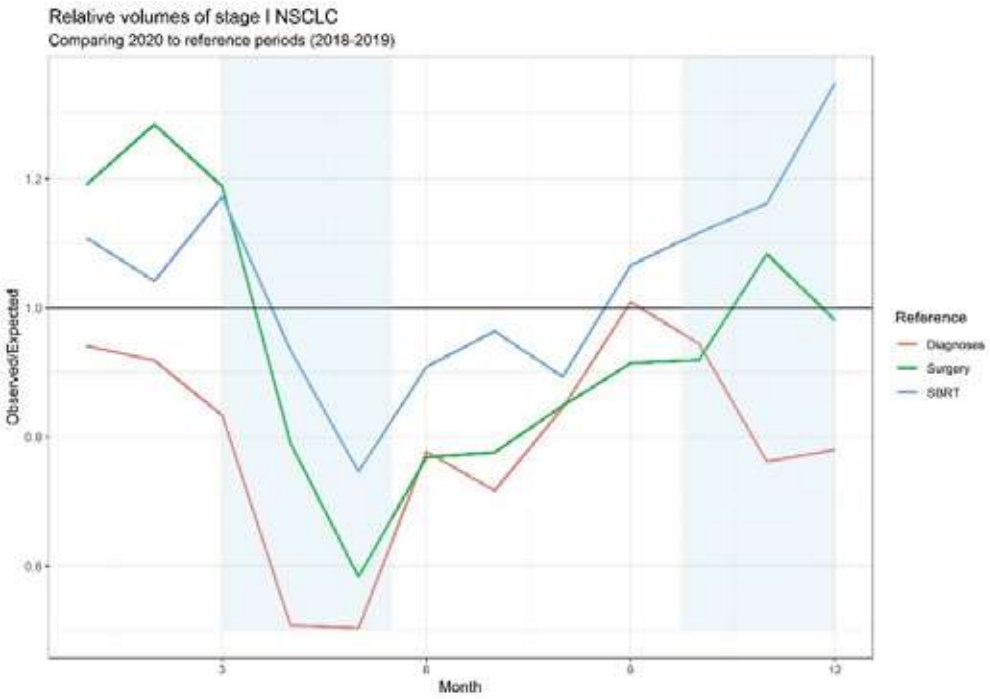
Introduction: COVID-19 has profoundly changed healthcare practice worldwide. Due to scarcity of resources, overflowing health care facilities and fear of infection, treatment and referral patterns changed. This study aims to investigate the impact of the COVID-19 pandemic on treatment patterns for stage I Non-Small Cell Lung Cancer (NSCLC) in the Netherlands.

Methods: All patients treated for clinical stage I NSCLC from 2018 to 2020 that were registered in the Dutch Lung Cancer Audit in the Netherlands were included in this study. Primary outcome was defined as number of patients diagnosed with stage I NSCLC and their respective treatment (SBRT or surgery). In 2020 this was related to three periods based on COVID-19 hospital admission rates: 'First wave', 'Interim period' and 'Second wave'. Data from stage I NSCLC patients from 2018 and 2019 were used as reference period. Secondary outcomes were defined as patient characteristics, hospital stay, ICU admission, postoperative complications and 30-day mortality for surgery patients. For patients treated with SBRT patient characteristics, acute toxicity and 90 day mortality were analyzed. Secondary outcomes were compared with 2018 and 2019.

Results: In total, 7422 patients with cTNM stage I NSCLC were analyzed. During 2020, the annual number of stage I NSCLC diagnoses decreased by 21% compared to 2018-2019 (mean 2664 vs. 2094). Especially during the first COVID wave, the observed number of diagnoses was lower than expected. Subsequently, surgeries and SBRT treatments decreased sharply during the first wave. However, during the interim period and second wave, SBRT treatments recovered more than the number of surgeries. In 2020, a smaller portion of stage I NSCLC patients was treated with surgery compared to reference years (38% vs. 40%, p=0.04). More comorbidity (Charlson Comorbidity Index) was observed among surgical patients in 2020. Treatment delays did not increase during 2020. Median hospital and ICU stay were shorter in 2020 compared with 2018-2019 (4 vs. 5 days, p<0.05; 1 vs 2 days, p<0.05, respectively). Postoperative complications and 30-day mortality did not significantly differ. For SBRT patients in 2020, there were no significant differences in patient characteristics, toxicity and 90-day mortality compared with reference years.

Conclusions: During the COVID-19 pandemic less patients were diagnosed with Stage I NSCLC. There was a significant change in treatment pattern from surgery to SBRT. Early outcomes were not affected by this shift. Postoperative complications, acute toxicity, 30-day and 90-day mortality remained low and time to treatment did not increase.



Keywords: Covid-19, Non Small Cell Lung Cancer, Treatment patterns

OA06 IMPACT OF COVID-19 ON CANCER MANAGEMENT AND PROTECTION FROM VACCINES,
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OA06.06 Impact of Systemic Anti-cancer Treatments on Outcomes of COVID-19 in Patients with Thoracic Cancers: CCC19 Registry Analysis

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Introduction: Patients with thoracic cancers (TC) have one of the highest rates of mortality among patients with cancer and COVID-19. Data evaluating the impact of recent anti-cancer therapies on COVID-19 outcomes in patients with TC are confined to small heterogenous retrospective studies, with limited follow-up data. We analyzed data from the COVID-19 and Cancer Consortium (CCC19) (NCT04354701) to examine the impact of recent systemic therapies on the clinical outcomes of COVID-19 in patients with TC.

Methods: The CCC19 registry was queried for adult patients with TC and lab-confirmed SARS-CoV-2 infection. Only patients with data quality scores of 0-4 were included in the analysis. The primary outcome was 30-day all-cause mortality. Secondary outcomes were need for oxygen supplementation, hospitalization, ICU admission, and mechanical ventilation. The outcomes were further stratified by demographics, smoking history, ECOG PS (0, 1, >2), cancer status (remission, responding/stable, progressing) and type of systemic treatment <3 months prior to COVID-19 (chemotherapy with or without immunotherapy, chemotherapy plus radiation, immunotherapy alone or targeted therapy).

Results: From January 2020 to December 2021, 900 patients with thoracic cancer met the inclusion criteria. The median age was 70 years (IQR 62-77), 53% were female, 79% were former or current tobacco users, 56% of patients had ECOG PS of 0 or 1, and 34% of patients had active but stable or responding cancer. Fifty-three percent (N=477) of patients received at least one anti-cancer systemic therapy <3 months prior to COVID-19 diagnosis. Chemotherapy with or without immunotherapy was the most prevalent treatment exposure (51%; N=242). After a median follow-up of 70 days (IQR 28-180), 30-day all-cause mortality was similar in patients who received any systemic cancer treatment versus no cancer treatment (23% and 22% respectively). Patients treated with immunotherapy and targeted therapy had the lowest mortality (15% and 18% respectively), the majority of whom were treated with palliative intent. Similar trends were also noted with secondary outcomes (Table 1).

Conclusions: We report one of the largest studies evaluating the clinical outcomes of COVID-19 in the context of recent systemic anti-cancer treatments for TC. While continued caution is required when utilizing systemic treatments, delays in treatment may not be justified. The study provides reassuring data that patients receiving immunotherapy or targeted therapy even in the context of palliative treatment appear to have a lower risk for all-cause COVID-19 mortality. Further analysis exploring the prognostic factors associated with poor outcomes in patients with chemoradiation is planned.

Table 1						
Characteristics	**All patients (N = 900)**	**Chemotherapy +/- immunotherapy (N = 242)**	**Immunotherapy alone (N = 94)**	**Chemotherapy and radiation (N=66)**	**Targeted therapy (N=114)**	**No cancer treatment (N = 423)**
Age [Median (IQR)]	70 (62-77)	66 (59-73)	70 (62-75)	69 (62-73)	64 (56-74)	72 (65-80)
Female	480 (53%)	56%	46%	52%	65%	53%
Current or Former smoker	713 (79%)	79%	91%	82%	47%	83%
ECOG performance status prior to infection						
0	183 (20%)	19%	19%	18%	25%	21%
1	321 (36%)	42%	53%	38%	42%	28%
2 or more	204 (23%)	26%	22%	26%	18%	21%
Cancer Status						
Remission/No evidence of disease	258 (29%)	<5%	5%	9%	6%	52%
Active, stable/ responding	302 (34%)	43%	69%	39%	53%	17%
Active, progressing	217 (24%)	38%	19%	38%	32%	17%
Treatment intent						
Curative	196 (22%)	34%	28%	52%	20%	11%
Palliative	313 (35%)	60%	67%	42%	73%	7%
Outcomes						
30-day all-cause mortality	204 (23%)	26%	15%	33%	18%	22%
Supplemental oxygen	503 (56%)	58%	48%	62%	49%	56%
Hospitalization within 30 days	571 (63%)	64%	51%	71%	61%	64%
ICU admission	173 (19%)	22%	18%	27%	18%	17%
Received mechanical ventilation	97 (11%)	12%	9%	17%	12%	9%
Follow up time, days [Median (IQR)]	70 (28-180)	53 (18-135)	70 (30-180)	90 (13-180)	90 (28-180)	80 (30-180)

Keywords: COVID-19, Immunotherpay, Thoracic Cancers

OA06 IMPACT OF COVID-19 ON CANCER MANAGEMENT AND PROTECTION FROM VACCINES,
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OA06.07 Stereotactic Ablative Radiotherapy Before Resection to Avoid Delay for Early-Stage LunG Cancer or OligomEts

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Introduction: The COVID-19 pandemic led to worldwide barriers to access to operating rooms; some multidisciplinary thoracic oncology teams pivoted to a paradigm of stereotactic ablative radiotherapy (SABR) as a bridge to provide radical-intent treatment combining immediate SABR followed by planned surgery when surgical resource constraints ameliorated. This pragmatic approach, termed SABR-BRIDGE, was instituted with prospective data collection at four institutions (3 Canada, 1 USA); herein we present the surgical and pathological results from this approach.

Methods: Eligible participants had early-stage presumed or biopsy-proven lung malignancy that would otherwise be surgically-resected. SABR was delivered using standard institutional guidelines with one of three fractionation regimens: 30-34 Gy /1 fraction, 45-55 Gy/3-5 fractions, or 60 Gy/8 fractions. Surgery was recommended at a minimum of 3 months following SABR with standardized pathologic assessment of resected tissue. A pathological complete response (pCR) was defined as absence of viable cancer, and a major pathologic response (MPR) was defined as ≤10% viable tissue.

Results: Seventy-five participants were enrolled, of which 72 received SABR. Following SABR, 26 patients underwent resection, while 46 did not; reasons for not undergoing surgery included metastasis (n=2), non-cancer death (n=1), awaiting lung surgery (n=13) and patient choice given favorable post-SABR imaging response (n=30). Of 26 patients who underwent resection, 62% had a pre-treatment biopsy. The most common SABR regimens were 34 Gy /1 fraction (31%) and 48 Gy in 3-4 fractions (31%). SABR was well-tolerated, with two grade 1 toxicities (pain, 7.7%), and one grade 3 pneumonitis (3.8%). Median time-to-surgery was 4.5 months from SABR completion (range:2-17.5 months). Most had minimally-invasive surgery (n=19, 73%) with 4 patients (15%) requiring conversion to thoracotomy, and 3 (12%) had planned open operation. Surgery was reported as being more difficult because of SABR in 38% (n=10). There were two intraoperative complications (7.7%, pulmonary artery injury), and 8 patients with post-operative complications (31%, all grade 2, most commonly air leaks [n=5]). The amount of residual primary tumor ranged from 0% to 90%. Thirteen (50%) had pCR while 19 (73%) had MPR. Rates of pCR were higher in patients operated upon at earlier time points (75% if within 3 months, 50% if 3-6 months, and 33% if ≥6 months). Rates of pCR were higher in patients without pre-treatment tissue diagnosis (91% versus 20% in those without and with tissue diagnosis, respectively). In 31% (n=8) of patients, nodal disease was discovered on resection, with half being N2 (4/26=15%).

Conclusions: The SABR-BRIDGE approach allowed for delivery of treatment with minimal upstaging during a period of operating room closure & high risk for patients. Surgery was well-tolerated. However, most patients who received SABR did not proceed to surgery, limiting precise estimates of pCR rates. However, the reported pCR rate is consistent with previous phase II trial data.

Keywords: lung surgery, SBRT, Multi-modal therapy

OA07 IS THERE STILL A ROLE FOR CHEMOTHERAPY ALONE IN THE MANAGEMENT OF NSCLC?,
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OA07.03 Association Between Genetic Variation in the ATP-binding Cassette Transporter ABCC10 and nab-PTX Treatment in Japanese Cohort

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Introduction: ABCC10 is an ATP-binding cassette transporter, which is shown to be involved in the extracellular transport of taxanes. We has reported that differences in rs2125739, one of the single nucleotide polymorphism in ABCC10, affect the cytotoxic effects of docetaxel in lung cancer cell lines and the occurrence of docetaxel side effects in clinical practice. The present study elucidated whether rs2125739 affects the cytotoxicity of paclitaxel (PTX) in lung cancer cell lines. The investigation was conducted for determining the effect of rs2125739 on the efficacy and side effects of nanoparticle albumin-bound PTX (nab-PTX) in clinical practice.

Methods: We analyzed the rs2125739 in 18 non-small cell lung cancer (NSCLC) cell lines and HeLa cells as well as in HeLa cells genome-edited using clustered regularly interspaced short palindromic repeats-CRISPR associated protein 9. The cell lines were diluted to 50 cells/μl and seeded on plates, and then after 2 h, stepwise 10-fold dilutions of PTX were added. Further, the cells were incubated at 37°C for 72 h, and cell viability was determined using the MTS [3-(4,5-dimethylthiazol-2-yl)-5(3-carboxymethniphenol)-2-(4-sulfophenyl)-2H-tetrazolium] assay. Then, 77 blood samples that were collected from patients with NSCLC and treated with carboplatin plus nab-PTX were analyzed for genetic variation (ABCC10 [rs2125739], ABCB1 [C1236T, C3435T, G2677 T/A], ABCC2 [rs12762549], SLCO1B3 [rs11045585]). Clinical outcomes were evaluated among these genotype groups.

Results: In 18 NSCLC cell lines (10 cell lines carried the T/T variant, four carried the T/C variant, and four carried the C/C variant), the 50% inhibitory concentration (IC50) of the T/T group was significantly higher than that of the combined T/C and C/C group (T/T group: 8.76 nM vs. T/C and C/C group: 4.36 nM; P = 0.0085). In HeLa cells (T/T) and genome-edited HeLa cells (T/C, C/C), HeLa cells had a higher IC50 than that of genome-edited HeLa cells (T/T: 3.14 nM vs. T/C: 2.75 nM vs. C/C: 1.48 nM; P < 0.001). Of the 77 NSCLC patients, 70 were men and 7 were women. The median age was 69 years, and 69 patients had a history of smoking. Histological types were squamous cell carcinoma in 33 cases and non-squamous cell carcinoma in 44 cases. The clinical-stage was IIIA in four cases, IIIB in 12 cases, and IV in 61 cases. The genotype of rs2125739 was T/T in 57 cases and T/C in 20 cases. There were no significant differences between the T/T and T/C groups in terms of response rate (35.1% vs. 25.0%; P = 0.58), median progression-free survival (115 days vs. 121 days; P = 0.73), and median overall survival (383 days vs. 345 days; P = 0.553). However, the genotype of rs2125739 was associated with grade 3/4 neutropenia (T/T group: 63.2% vs. T/C group: 30.0%; P = 0.018). Other genetic variations were not associated with the clinical efficacy and side effects.

Conclusions: Our results indicate that rs2125739 is associated with neutropenia in the nab-PTX treatment. The confirmation of rs2125739 may allow for the use of granulocyte colony-stimulating factor and the reduction of anticancer drugs before the occurrence of severe neutropenia.

Keywords: ATP-binding cassette transporter, Paclitaxel, Neutropenia

OA07 IS THERE STILL A ROLE FOR CHEMOTHERAPY ALONE IN THE MANAGEMENT OF NSCLC?,
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OA07.04 Overall Survival in Patients with Advanced NSCLC Receiving Taxane-Containing Regimen After Exposure to Immunotherapy and Platinum-Doublet

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Introduction: For decades, docetaxel has been the standard salvage chemotherapy for patients with advanced non-small cell lung cancer (aNSCLC) after progression on platinum-doublet chemotherapy. Standard first-line therapy has evolved to incorporate early use of immunotherapy with PD-(L)1 inhibitors. The impact of immunotherapy on the efficacy of subsequent chemotherapy remains unclear. This real-world study aimed to assess overall survival (OS) of patients with aNSCLC treated with taxane-containing regimen after immunotherapy and platinum-doublet chemotherapy.

Methods: This study used the nationwide (US only), electronic health record-derived, de-identified Flatiron Health database containing information from patients with aNSCLC diagnosed after 1-Jan-2011. Patients were selected if they initiated a taxane-containing regimen before 30-Jul-2020 following exposure to one unique prior PD-(L)1 inhibitor and platinum-doublet chemotherapy, either sequentially or concurrently for aNSCLC, with an ECOG performance status of 0-1 at initiation of taxane. Patients who had actionable biomarkers, received only one dose of PD-(L)1 inhibitor, or with inadequate renal, hepatic or hematological functions according to lab values at the initiation of taxane-containing regimen were excluded. Data cutoff was 30-Jul-2021. Kaplan-Meier method was used to estimate OS.

Results: Of 467 eligible patients, 166 (35.5%) patients initiated a taxane monotherapy (docetaxel, paclitaxel or nab-paclitaxel) and 301 (64.5%) patients initiated a taxane-containing combination (taxane combo). Overall, median age was 66.7 years, 268 (57.4%) were male and 446 (95.5%) had nonsquamous histology; 366 (78.4%) were initially diagnosed at stage IV. PD-L1 expression was ≥50%, 1-49%, <1%, and unknown for 93 (19.9%), 99 (21.2%), 128 (27.4%) and 147 (31.5%) patients, respectively. The majority of patients received one or two prior lines of therapy for aNSCLC (39.6% and 49.7%, respectively) with pembrolizumab being the most frequently used PD-(L)1 inhibitor (61.7%), followed by nivolumab (36.8%) and atezolizumab (1.5%). Overall, median OS was 8.9 months (95% confidence interval [CI], 8.0-9.6), with 12- and 24-month OS rates of 37.5% (95%CI, 33.0-41.9) and 14.7% (95%CI, 11.3-18.5). Median OS was 9.0 months (95%CI, 8.1-11.2) and 8.4 months (95%CI, 7.5-9.6) in taxane monotherapy and taxane combo cohorts, respectively.

Conclusions: OS estimates in this real-world sample of patients receiving taxane-containing regimen after exposure to PD-(L)1 inhibitor and platinum-doublet are similar to historical data in patients with prior exposure to platinum-doublet before availability of immunotherapy.

Keywords: taxane, IO-exposed, real-world

OA07 IS THERE STILL A ROLE FOR CHEMOTHERAPY ALONE IN THE MANAGEMENT OF NSCLC?,
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OA07.05 Gemcitabine Plus Platinum Chemotherapy Re-challenge in Metastatic Pulmonary Lymphoepithelioma-like Carcinoma

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Introduction: Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subtype of non-small cell lung cancer. While first line treatment for stage IV disease with gemcitabine plus either cisplatin (GP) or carboplatin (GC) is more established with encouraging objective response rate, there is no consensual subsequent treatment strategy upon progression. In view of their potent efficacy in the first line setting, re-challenge gemcitabine-platinum is considered a reasonable option, but efficacy data is currently lacking.

Methods: All consecutive patients with pulmonary LELC in 2010 - 2019 treated in a tertiary institution were reviewed. Due caution was exercised to exclude co-existence of nasopharyngeal carcinoma (NPC), due to the high histological similarity between pulmonary LELC and NPC. Patients who previously received GP or GC as first line systemic treatment with no progression of disease during treatment were included. Treatment response was monitored by clinical history, physical examination and imaging. Progression-free survival (PFS2) and overall survival (OS2), counting from the start of gemcitabine-platinum re-challenge, were estimated by the Kaplan-Meier method. Clinical predictors for PFS2 and OS2 and were analyzed using log-rank test and the Cox proportional hazard model.

Results: 140 LELC patients were identified; 59 patients received GP or GC as first line treatment for their metastatic disease. 17 patients subsequently received re-challenge gemcitabine-platinum upon progression and satisfied the inclusion criteria (7 male, 10 female). Median age was 58.1 years old (range, 52.2 - 77.7). 16 patients (94.1%) had ECOG performance score of 0-1, and 11 patients (64.7%) were never-smokers. 8 and 9 patients received first line chemotherapy GP and GC respectively. Median number of first line chemotherapy cycles received was 6 (range 4-6); all patients achieved partial response. Median chemotherapy-free interval from last administration of first line chemotherapy was 8.0 months (range, 1.0 - 51.8). 16 patients subsequently received GC, and 1 received GP upon re-challenge. Median cycles of re-challenge chemotherapy were 4 (range, 1 - 6). Overall response rate was 47.1%, disease control rate was 94.1%. With a median follow-up of 15.4 months (range, 4.0 - 91.9), the median PFS2 and OS2 from time of re-challenge were 6.5 months (95% CI, 3.7 - 9.3) and 21.9 months (95% CI, 11.6 - 32.2) respectively. Safety profile was satisfactory; while 76.5% of patients required dose reduction and 41.2% had grade 3 adverse events (all hematological), only 1 patient required treatment termination due to intolerance, and no treatment induced mortality was noted. On subgroup analysis, patients who experienced more than 12 months of chemotherapy free interval before gemcitabine-platinum re-challenge is correlated with higher rate of partial response (83.3% vs 27.3%, p=0.049). Presence of liver metastases is a significant adverse prognosticator of PFS2 (HR 5.11, 95% CI 1.12 - 21.8, p=0.027).

Conclusions: Re-challenge gemcitabine-platinum doublet for previously sensitive metastatic pulmonary LELC is a feasible treatment strategy, especially for patients with durable response from 1st line chemotherapy with more than 12 months of chemotherapy free interval before progression. Despite the frequent need of dose reduction, clinical benefit was observed in majority of patients.

Keywords: Lymphoepithelioma-like Carcinoma, Palliative Chemotherapy, Gemcitabine Platinum

OA07 IS THERE STILL A ROLE FOR CHEMOTHERAPY ALONE IN THE MANAGEMENT OF NSCLC?,
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OA07.06 Second Line Treatment Outcomes After Progression on Immunotherapy Plus Chemotherapy (IO-CT) In Advanced Non-small Cell Lung Cancer (aNSCLC)

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Introduction: The combination of IO-CT has become the standard of care for patients with aNSCLC with a low or intermediate programmed death-ligand 1 (PD-L1) expression (<50%), and an option for patients with high PDL1 (≥50%) expression. There are no data available on the subsequent line (L2) outcomes after IO-CT. We aimed to assess the outcomes of various L2 treatments after IO-CT in aNSCLC.

Methods: Retrospective international study including patients who progressed under a first line IO-CT regimen. Data were extracted from medical records. Patients treated with a targeted therapy in L2 were excluded. Primary endpoint was overall survival (OS-L2) defined as the time between L2 start and death. Secondary endpoints were progression free survival (PFS-L2), objective response rate (ORR). IO-CT primary resistance was defined as PFS under IO-CT < 3 months; IO-CT response was defined as PFS-L1 > 6 months.

Results: We included 125 patients. Mean age was 62 years, 32% female, mainly smokers (91%); 75% had adenocarcinoma histology, and 13% high PD-L1. As L2, 49 patients (39%) received taxane monotherapy (T-mono), 19 (15%) taxane plus anti-angiogenic (T-AA), 11 (9%) platinum-based chemotherapy, 17 (14%) other chemotherapies, and 29 (23%) other drugs. Baseline L2 characteristics were well balanced between the treatment groups. After a median (m) follow-up of 8.3 months, mOS-L2 was 6.4 months (95%CI:4.8-12.9) in the T-mono, not reached - NR (3.5-NR) in the T-AA, 14.6 months (11.6-NR) in the platinum-based chemotherapy, and 7.7 months (3.7-NR) in the other chemotherapy groups, p=0.2. mPFS-L2 was longer in the platinum-based group compared with the other treatment groups (p=0.04, **Table**). ORR was 20% overall, 19% in the T-mono, 10% in the T-AA, none in the platinum-based chemotherapy, and 13% in the other chemotherapies groups, p=0.57, **Table.** In the IO-CT primary resistant population (n=21), mOS-L2 was not reached in the platinum-based chemotherapy, while it was 4.8, 5.2 and 6.7 months in the T-mono, T-AA and other chemotherapy groups, respectively (**Table**). In the IO-CT responder population (n= 65), longer PFS was observed in the platinum-based chemotherapy group (**Table 1**). According to PD-L1 status, there was a numerically longer OS-L2 for patients with high PD-L1 (10.1 months vs 8.3 and 6.7 months for intermediate and low PD-L1 groups, p=0.8). The same tendency was observed for PFS-L2.

	Overall survival, months Median (95%CI)	Progression free survival, months Median (95%CI)	Objective response rate
Overall population (n=125)	7.7 (5.7-12.7)	3.0 (2.6-3.7)	19.7%
- Taxane monotherapy	6.4 (4.8-12.9)	2.30 (1.7-3.1)	19.4%
- Taxane plus anti-angiogenic	NR (3.5-NR)	3.0 (1.9-NR)	10%
- Platinum-based chemo	14.6 (11.6-NR)	5.8 (5.1-NR)	0%
- Other chemotherapies	6.73 (5.1-12.7)	3.1 (1.6-4.9)	12.5%
Primary resistance to IO-CT population (n=21)	4.8 (2.1-NR)	1.7 (1.4-4.7)	8.3%
- Taxane monotherapy	4.8 (2.4-NR)	2.3 (1.4-NR)	12.5%
- Taxane plus anti-angiogenic	5.2 (1.7-NR)	1.7 (1.5-NR)	0%
- Platinum-based chemo	NR (NR-NR)	NR (NR-NR)	0%
- Other chemotherapies	6.7 (NR-NR)	1.2 (1.2-NR)	0%
Responder to IO-CT population (n=65)	12.7 (7.7-NR)	4.5 2.96 6.04	29%
- Taxane monotherapy	7.6 (5.7-NR)	3.12 (2.0-12.9)	28.6%
- Taxane plus anti-angiogenic	NR (NR-NR)	1.9 (1.9-NR)	0%
- Platinum-based chemo	17.6 (11.6-NR)	5.8 (5.1-NR)	0%
- Other chemotherapies	12.6 (8.1-NR)	4.7 (2.9-NR)	0%

Conclusions: Second line treatment after IO-CT provides modest outcomes in patients with aNSCLC. The T-AA and platinum-based groups experienced better outcomes in the overall population.

Keywords: NSCLC, second line, immuno-chemotherapy

OA08 MULTIDISCIPLINARY CARE OF THE LUNG CANCER PATIENT,
MONDAY, AUGUST 8, 2022 - 11:00–12:00

OA08.03 Do in Screening - Calf Circumference and Muscle Strength is Predictive of Outcomes in Lung Cancer Treatment

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Introduction: Low muscle mass is highly found in lung cancer and is known to contribute to a higher occurrence of treatment toxicity, worse physical functioning, quality of life and mortality. Muscle mass(MM) assessment methods referred to as computed tomography are expensive, not always available and not easy to use in clinical practice. The aim of this study was to investigate whether measurement of MM using a simple, low-cost measure such as calf circumference (CC) and handgrip strength (HGS) at diagnosis is predictive of oncologic outcomes in lung cancer patients.

Methods: This is a prospective, observational, clinical study, approved by the ethics committee at a chest tumor treatment center in Rio de Janeiro, Brazil. Data were collected at the first nutritional consultation between January and December 2019 and consisted of nutritional risk screening using patient-generated subjective global assessment (PG-SGA), height, body weight, weight loss (WL), CC, HGS measured through a hand dynamometer. The cutoff points adopted for CC were age-adjusted. Survival curves were generated by Kaplan-Meier analysis to assess the association between low MM combined with low handgrip strength and 3-year mortality.

Results: Fifty lung cancer patients were included, where 62% were female, 94% were elderly, 88% had non-small cell lung cancer, 88% were diagnosed with stage III and IV disease, and 64% were smokers. 62% of patients experienced WL while 36% had WL greater than 5% of body weight, a measure of cachexia. In the assessment of CC, an easy-to-use MM indicator, and now with cut-off values also for the adult population, in our sample 44% of patients had values below the cut-off point, indicating low MM. In the evaluation of dynamometry, 34% of the individuals who presented low muscular strength. In the assessment of overall survival, patients with low MM and low strength had significantly lower survival at 349 days versus 1247 for those with parameters above the defined cut-off points, Log rank (p<0.000), Breslow (p<0.000) and Tarone-Ware (p<0.000). Despite the sample size limitation, our results found significant differences that can be reversed by nutritional and multimodal interventions.

Conclusions: Low MM using a simple, easy and accessible measure such as WC combined HGS was a predictor of negative outcomes in the treatment of lung cancer and can no longer be overlooked. The recovery of MM can be reversed with nutritional and multimodal interventions as long as they are detected early, which can improve the outcomes of these patients.

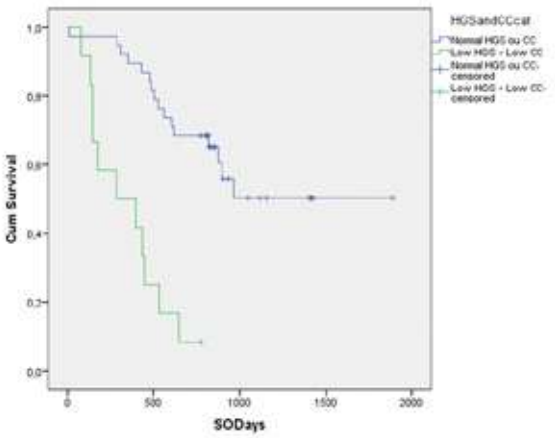

Figure 1: Kaplan-Meier curve of the association of low calf circumference and low handgrip strength and 3-year overall survival in lung cancer patients; HGS, handgrip strength; CC, Calf Circumference; SO Survival Overall;

Keywords: Lung Cancer, Low muscle mass, handgrip strength

OA08 MULTIDISCIPLINARY CARE OF THE LUNG CANCER PATIENT,
MONDAY, AUGUST 8, 2022 - 11:00–12:00

OA08.04 The Impact of Video-fluoroscopic Swallow Assessment on Dysphagia Management in Lung Cancer

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Introduction: Oropharyngeal dysphagia can occur in lung cancer due to neck node disease, laryngeal nerve compression and subsequent vocal cord palsy, deconditioning and comorbidities. Dysphagia can cause adverse outcomes such as aspiration pneumonia, malnutrition and worse quality of life. Videofluoroscopy (VFS) is used by Speech & Language Therapists (SLTs) to evaluate oropharyngeal swallowing anatomy and physiology. It enables SLTs to identify silent aspiration, which is undetectable in standard clinical assessment and study the impact of variables on swallowing such as bolus texture and size, position and manoeuvres. At Guy's and St Thomas' Trust there is dedicated SLT input for lung cancer patients. This evaluation aims to establish whether VFS is a valuable tool in this patient group and its impact on swallow safety and oral intake.

Methods: A retrospective review of medical notes and VFS reports was completed. Inclusion criteria were patients receiving treatment for primary lung cancer at Guy's Cancer Centre who had a VFS at Guy's Hospital from January 2020-December 2021. Data collected included: disease pathology, location and staging, GRBAS score and VFS outcomes; Penetration-Aspiration Score (PAS) and Functional Oral Intake Scale (FOIS) score to capture recommended oral intake, plus other recommendations e.g. onward referral.

Results: 17 studies on 15 patients (11m, 4f, 38-86yrs) were completed. 13 had metastatic disease and 13 had neck and/or mediastinal node disease. 14 also presented with dysphonia. VFS led to changes in management in 94% (n=16) studies. In the remaining case, the study was used to reassure a concerned patient. Silent aspiration and/or aspiration not ejected from the airway was identified in 65% VFS (PAS:7/8,n=11). Of these severe cases; a strategy was implemented to minimise aspiration in 64% (n=7), oral intake was increased in 55% (n=6) and maintained in 27% (n=3). In 1 case enteral feeding was advised (FOIS:2) and in another full oral diet continued with modifications (FOIS:5). Less severe impairment was identified in 35% (PAS:1-3,n=6). Median FOIS pre-assessment was 5 and post-assessment was 6. Other recommendations included: ENT referral (70%,n=12 highlighted reduced vocal cord movement), swallow rehabilitation (30%,n=5), oesophageal investigations (18%,n=3), feeding tube removal (5%,n=1) and urgent management of tracheoesophageal fistula (5%,n=1).

Conclusions: Silent aspiration was common in a cohort of lung cancer patients and yet VFS enabled continuation of oral intake for all but one patient. VFS also frequently allowed identification of strategies for increased or maintained oral intake with improved swallow safety. A high proportion of patients referred for VFS had nodal disease with close proximity to the recurrent laryngeal nerve and/or swallowing anatomy. Most patients also presented with dysphonia which can be caused by laryngeal nerve impairment. Limitations include the small sample size, including only patients referred to SLT at one site. The high rate of silent aspiration identified may indicate that there are patients with dysphagia unknown to SLT, as symptoms are not always clear. An important role for VFS has been identified and further study is indicated to investigate the clinical profile of patients more likely to aspirate to support early identification and management.

Keywords: Dysphagia, Video-fluoroscopy, Lung Cancer

OA08 MULTIDISCIPLINARY CARE OF THE LUNG CANCER PATIENT,
MONDAY, AUGUST 8, 2022 - 11:00–12:00

OA08.05 A Quality Improvement Project Determining if Dietitian Input with the UHS Lung Oncology Team Improved Patient Outcomes

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Introduction: Unintentional weight loss is common in lung cancer, with 40-60% of patients presenting with this at diagnosis. Weight loss and depleted nutritional status have been identified as negative prognostic variables for survival and directly impact the effectiveness of cancer treatments. The Lung Oncology team at the University Hospital Southampton (UHS) received external funding from Bionical Solutions and AstraZeneca for a part time oncology Dietitian to join the team in treating this patient group. The aim was to determine if specialist Dietitian input improves patients' nutritional outcomes in those diagnosed with Stage III Non-Small Cell Lung Carcinomas (NSCLC) undergoing radical treatment.

Methods: Over 12 months (February 2021-February 2022) all patients with stage III NSCLC received specialist Dietitian input during their radiotherapy treatment. Non-patient identifiable data was collected, which included; whether patients were enterally fed, admission rates and reason, and their weights at the start, middle, end and 2 weeks post radiotherapy. This data was compared to previously collected data in 2018 with the same patient group. No ethical approval was required.

Results: A total of 50 patient data sets and 11 feedback questionnaires were collected over 11 months. Between the start and end of radiotherapy, patients experienced; 2.1% overall average weight loss, 64% experienced <3.0% unintentional weight loss and 0% experienced >9.6% unintentional weight loss. In 2021 patients reached their lowest weight earlier at 70% of their way through radiotherapy compared with 86% in 2018. Patients maximum unintentional weight loss was 3.2% in 2021 compared with 4.4% in 2018. This is likely due to closer monitoring and dietitian input in 2021. Admission rates were higher in 2021 (n=13, 26%) compared to 2018 (n=5, 18.5%). However, this may be due to changes to patients' radiotherapy treatment plans in 2021 due to the covid pandemic, resulting in more intense treatments. Patients requiring nasogastric (NGT) feeding increased from 0 in 2018 to 6 in 2021. This is likely due to increased awareness of the importance of nutritional support attributable to dietetic involvement in the multidisciplinary team. All patients who completed the feedback questionnaire found dietetic consultations useful and were able to follow most, or all dietary advice. 91% felt well supported during their treatment with dietetic input. Final Outcomes: Patients experienced reduced weight loss during treatment with Dietitian input compared to 2018 data where there was minimal dietetic input. Increased number of patients required NGTs compared to 2018, therefore Dietitian input is required in this area of oncology. Most patients felt well supported receiving dietetic input during treatment. Increased admission rates compared to 2018, however more nutrition support related admissions in 2021.

Conclusions: Overall, patients lost less weight during treatment with Dietitian involvement in their care which is a positive factor in the prognostic outcomes. In addition, most patients felt seeing a Dietitian during treatment improved their experience and felt well supported. The final outcomes support the British Dietetic Associations' recommendation that there is a dedicated dietetic service for lung cancer patients', and they are seen by a Dietitian during their treatment.

Keywords: Dietitian involvement, Reduced weight loss, Improved patient outcomes

OA08 MULTIDISCIPLINARY CARE OF THE LUNG CANCER PATIENT,
MONDAY, AUGUST 8, 2022 - 11:00–12:00

OA08.06 Implementation of a Nurse-led Geriatric Oncology Assessment Model in the Lung Cancer Care Pathway

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[1]*Austin Hospital, Melbourne/AU*

Introduction: The incidence of lung cancer increases with age. The comprehensive geriatric assessment (CGA) identifies patients at high risk of adverse outcomes and has shown to improve health-related outcomes, quality of life and reduction in health service use. However, the uptake is hampered by limitations in both time and resources. We evaluated the implementation of a nurse-led model of geriatric oncology assessment for elderly patients (≥ 65 years) with newly diagnosed lung cancer.

Methods: Eligible patients with newly diagnosed lung cancer were identified from the lung cancer clinic referral system. A clinical nurse undertook an hour long face-to-face assessment incorporating six validated tools: G8, the distress thermometer, timed up and go, mini-cog, hospital anxiety and depression scale, and ELFI (The Elderly Functional Index). Individual cases were discussed by a multidisciplinary team comprising nursing staff, geriatrician and oncologist and referrals for further CGA were made where appropriate. Assessments and recommendations were made available to the treating oncologist prior to the patient's initial oncology appointment. Patients were followed up every three weeks after the baseline assessment to determine the impact of these assessments on oncological treatment plans, treatment completion rates and healthcare utilization.

Results: At interim analysis, a total of 38 patients were identified as eligible with 18 patients undergoing nurse-led assessments. Twenty patients did not undergo assessment due to late scheduling of outpatient appointments (n=14), and being admitted to the inpatient area (n=6). The mean age of patients was 79 (range 65 - 87) years, majority male 14 (78%), current or ex-smokers 15 (83%) and of good performance status (ECOG ≤ 1) 12 (67%). All patients had one or more comorbidities. Most patients presented with metastatic disease 12 (67%). The average score for the G8 was 12 (SD 3), the distress thermometer 3 (SD 2), timed up and go 14 seconds (SD 6), mini-cog 4 (SD 1), hospital anxiety and depression scale 7 (SD 4) and 6.5 (SD 4) respectively, and ELFI 57 (SD 16). Six patients were referred for a full CGA for low G8 score (n=4), risk of falls (n=3), and polypharmacy (n=3). The most common impairments identified during nurse-led assessments leading to allied health referrals were psychosocial and mobility issues. Findings from the assessments led to changes in oncological management in nine (50%) patients.

Conclusions: A nurse-led geriatric assessment model is feasible and sustainable way to integrate geriatric assessments into routine oncological care. Impact of this model on treatment completion rates and health service utilization is being analyzed.

Keywords: Geriatric assessment, Lung cancer, Nursing

OA09 PRECISION IMMUNOTHERAPY VIA MODULATION OF THE TUMOR MICROENVIRONMENT,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

OA09.03 Single Cell Analyses Reveal Effects of Immunosenescence Cells in Neoadjuvant Immunotherapy of Lung Squamous cell Carcinoma Patients

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Introduction: Immunosenescence can reduce the immune system's ability to destroy cancer cells and effectively respond to pathogens, thereby increasing susceptibility to cancer development and proliferation. Previous studies have shown that T cell senescence might be one of the important features of immunosenescence mechanism, but lack of single cell evidences. This study aimed to investigate the associations between immunosenescence cells and treatment responses of Lung squamous cell cancer (LUSC) patients who received neoadjuvant immunotherapy.

Methods: Six patients underwent neoadjuvant immunotherapy before surgery were included in this study. All the 6 patients received the combination therapy of PD-1 immunocheckpoint inhibitor Pembrolizumab and chemotherapy. Tumor responses to neoadjuvant therapy for the patients were evaluated. Among them, four patients were major Pathologic Response (MPR), and the other two were non-MPR. PBMC samples before and after treatment were collected and single-cell RNA and T cell receptor (TCR) sequencing were performed. Single cell sequencing data were processed by dimension reduction and clustering using *Seurat*. Immunosenescence associated cell subset was extracted according to the canonical cell markers (CD8+, CD28-, CD57+, KLRG1+). We then identified differentially expressed genes (DEGs) between this immunosenescence cell subsets and other CD8+T cells, followed by Gene Set Enrichment Analysis (GSEA). The cell proportions between MPR patients and non-MPR patients were examined by Chi-squared tests. TCR sequences were analyzed to study antigen specificities for this immunosenescence subset.

Results: From a total of 45,504 cells, immunosenescence associated cell subset was identified. GSEA results based on the differentially expressed genes in the immunosenescence subset revealed that this cell subset was negatively correlated with RNA binding and ribosome-related pathways, which may affect protein synthesis and may be associated with immunosenescence. We found that there were more immunosenescence cells in the non-MPR patients than MPR patients ($P<0.01$), and the number of immunosenescence cells were enriched after neoadjuvant immunotherapy($P<0.01$). Immunomic analysis suggested that the number of TCR clonetypes was uneven among patients with different neoadjuvant therapy outcomes (MPR and non-MPR). More specifically, non-MPR patients had lower TCR Shannon's index diversity than non-MPR patients. We further explored the TCR clonotypes within non-MPR patients, one common TCR clonotype (TRBV19-TRBJ2-2) was identified in all the non-MPR patients, which might imply TRBV19-TRBJ2-2 clonotype was associated with a specific function in immunosenescence. Immunosenescence may profoundly impact T lymphocytes and lead to reduced TCR repertoire diversity, thus result in poor treatment outcomes, and this is consistent with our preliminary observation.

Conclusions: We studied the immunosenescence cells in neoadjuvant immunotherapy settings of LUSC patients using single cell RNA sequencing. We found that immunosenescence cells were more enriched in non-MPR patients than that in MPR patients, and non-MPR patients had lower TCR diversity than MPR patients. The preliminary results implied immunosenescence T cells played roles in different neoadjuvant outcomes, and help to further understand associations with tumor microenvironment in LUSC patients.

Keywords: single cell, immunosenescence cell, neoadjuvant immunotherapy

OA09 PRECISION IMMUNOTHERAPY VIA MODULATION OF THE TUMOR MICROENVIRONMENT,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

OA09.04 Spatial Mapping and Clinical Significance of the LAG-3/FGL1 Pathway in Non-small Cell Lung Cancer Using High-Dimensional Tissue Imaging

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Introduction: Fibrinogen-like protein (FGL1) is a recently described ligand of the immune inhibitory T-cell receptor LAG-3 and participates in tumor immune evasion. FGL1 is predominantly produced in the (normal) liver and can also be locally upregulated in the tumor microenvironment of aggressive malignancies including non-small cell lung cancer (NSCLC). Multiple clinical trials are currently evaluating the therapeutic role of targeting LAG-3 using monoclonal antibodies. However, the expression pattern, biological context and clinical significance of the LAG-3/FGL1 pathway in NSCLC remain poorly understood.

Methods: We analyzed the LAG-3/FGL1 pathway and associated immune contexture in 119 primary NSCLCs from 2 independent cohorts represented in tissue microarrays using Imaging Mass Cytometry (IMC). The first cohort (Cohort#1, YTMA423) included baseline biopsy samples from 57 cases treated with standard non-immunotherapy. The second collection (Cohort #2, YTMA471) included pre-treatment specimens from 62 cases treated with PD-1 axis blockers. The IMC panel included simultaneous and spatially resolved measurement of 37 tumor- and immune-cell markers (LAG-3, FGL1, DNA1, DNA2, Histone3, cytokeratin, vimentin, PD-L1, PD-L2, VISTA, CD47, ß2M, CD56, CD8, CD4, CD25, CD27, CD20, CD68, CD45RO, CD45RA, EOMES, TOX1/2, TCF-1/7, TIM-3, CD137, PD1, FOXP3, TBET, GZB, Ki-67, DC-lamp, CD68, CC3, ARG1, HIF1α, and Carbonic-Anhydrase9). Single-cell segmentation of the stained slides was performed and association of LAG-3 and FGL1 with the tumor immune contexture and treatment-specific outcomes were established.

Results: High FGL1 protein expression was detected in 18.4% of cases across the cohorts and the signal was more prominent in tumor-cells than in non-tumor/immune cells. Elevated FGL1 expression in cytokeratin-positive cancer cells was associated with high local LAG-3 expression on CD8+ tumor infiltrating lymphocytes (TILs). In addition, cases with elevated FGL1 shown a distinct CD8+ and CD4+ TIL profile as compared with cases with low FGL1 expression characterized by altered levels of CD45RO, TCF-1/7, TIM-3, FOXP3 and hypoxia markers. Elevated levels of FGL1 were associated with worse overall survival in cases treated with PD-1 axis blockers, but no difference was seen in cases treated with standard non-immunotherapy.

Conclusions: The LAG-3/FGL1 axis is expressed in ~20% of primary NSCLCs and associated with a distinct T-cell immune contexture. Elevated levels of FGL1 occur predominantly in tumor-cells and are associated with worse outcome in patients treated with PD-1 axis blockers. Our results suggest a dominant role of the LAG-3/FGL1 pathway in a subset of lung malignancies and a possible biomarker role. Additional studies are ongoing including analysis of integrated multi-marker profiles and spatial features.

Keywords: NSCLC, Immunotherapy, Biomarkers

OA09 PRECISION IMMUNOTHERAPY VIA MODULATION OF THE TUMOR MICROENVIRONMENT,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

OA09.05 Neoadjuvant IL-15-PDL1 Antibody Promotes T cell Memory and Decreases Metastatic Recurrence in Resectable NSCLC

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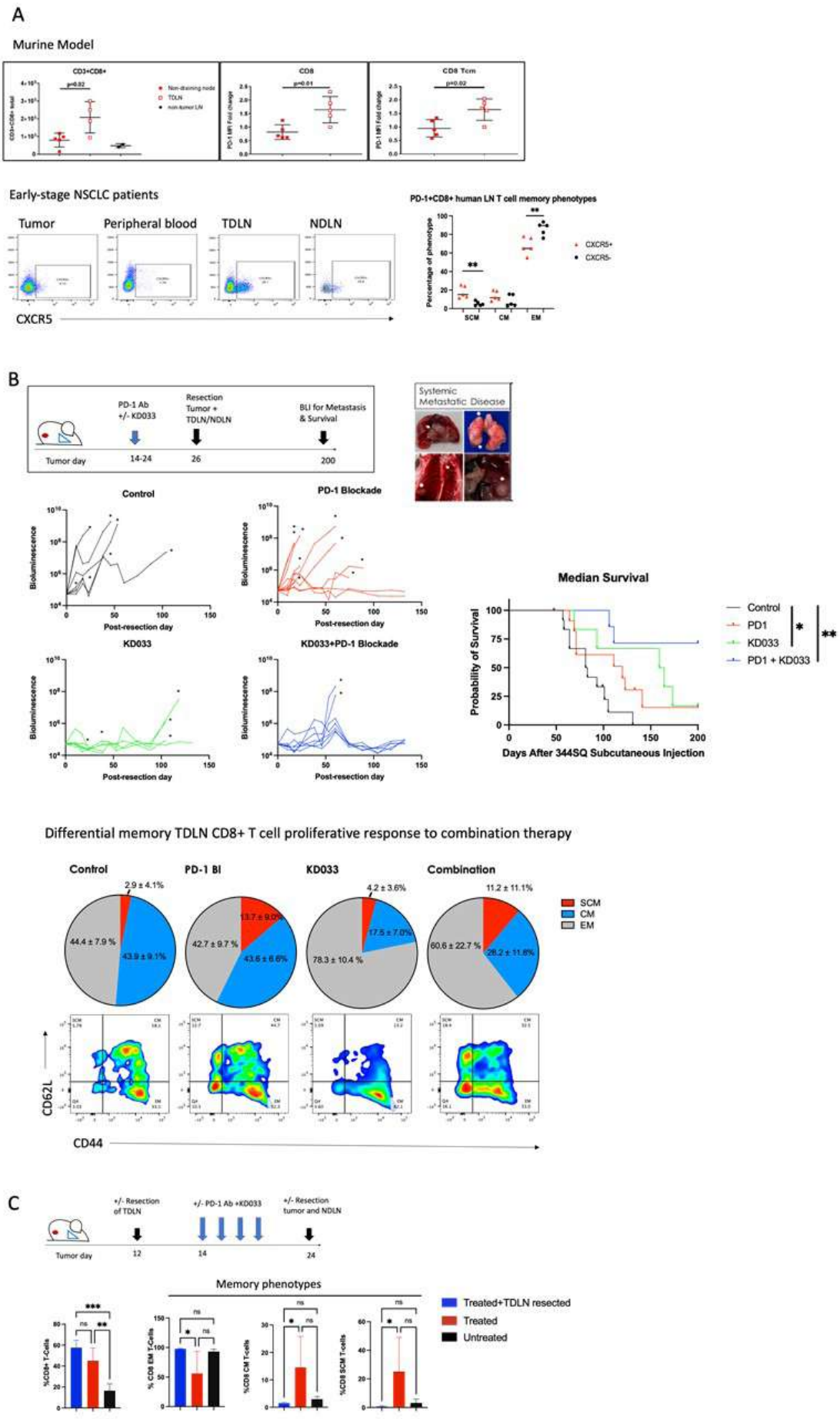
Introduction: Identifying mechanisms of long-term responses to immune checkpoint inhibition (ICI) is key to developing new therapies for resectable non-small cell lung cancer (NSCLC). Herein we explore the effects of ICI therapy in an immunocompetent murine model of lung adenocarcinoma that displays delayed systemic recurrence after tumor resection. We *hypothesized* that targeting the immune repertoire of the tumor draining lymph node (TDLN) with a memory inducing IL-15-PDL1 bispecific antibody (KD033) would establish immunosurveillance and decrease metastatic recurrence.

Methods: We utilized an immunocompetent murine model of highly metastatic lung adenocarcinoma (344SQ) after resection of tumor, TDLN, and non-draining lymph nodes (NDLN). Using bioluminescent imaging (BLI) and flow cytometric analysis (FACS) we monitored T-cell kinetics and anti-tumor activity after administration of anti-PD1 antibody and/or KD033, a fusion antibody combining a high affinity anti- PD-L1 IgG1 antibody with an IL15Rα sushi binding domain. Tumor/TDLN and NDLN T cells were characterized for CD62L/CD44/CXCR5 memory phenotypes. In parallel, we analyzed resected tumor, TDLN and NDLN from early-stage NSCLC patients.

Results: TDLN from murine models and early-stage patients maintain a robust PD-1 + CXCR5+ CD8 T cell memory phenotypes not significantly found in the primary tumor, NDLN and peripheral blood (Fig. 1A). Neoadjuvant treatment with PD-1 axis blockade alone had a heterogenous response, with robust proliferation of T-cell central and “stem cell like” memory populations (CM & SCM) at the TDLN and a subsequent decrease in metastatic recurrence in 30% of mice. Combination therapy with IL-15 agonist (KD033) potentiated diverse PD-1+ CD8 effector memory (EM) population in the TDLN and subsequent response at the primary tumor as well as displayed superior protection against metastatic recurrence up to 200 days compared to PD-1 inhibition or KD033 alone (median survival undetermined vs. 120d, 161d respectively $p<0.05$, Fig. 1B). Removal of TDLN prior to neoadjuvant combination therapy did not significantly affect the antitumor efficacy, or CD8 T cell infiltration at the primary tumor. However, removal of the TDLN prior to therapy decreased a population of SCM and CM CD8 T cells found in the primary tumor and altered systemic memory subpopulations in the NDLN ($p<0.05$, Fig. 1C).

Conclusions: Our data suggests that an Il-15/anti-PD1 neoadjuvant treatment strategy maintains an optimal response to metastatic recurrence. Promoting T-cell memory in the TDLN through IL-15-based immunomodulation may increase immunosurveillance and thus improve overall survival providing a rationale for an upcoming neoadjuvant clinical trial.



Keywords: Lung Cancer, Immunotherapy

OA09 PRECISION IMMUNOTHERAPY VIA MODULATION OF THE TUMOR MICROENVIRONMENT,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

OA09.06 Vascular Leakage Promotes Immunosuppression and is Associated with Reduced Patient Survival in Non-Small Cell Lung Cancer

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Introduction: Vascular hyperpermeability (leakage) facilitates tumor progression, metastasis, and limited delivery of therapeutics by fostering a hypoxic tumor microenvironment. Recently, pharmacological inhibition of vascular leakage enhanced tumor infiltration and activity of cytotoxic (CD8+) T-cells when used in combination with anti-PD1 blockade. However, the influence of vascular leakage on the tumor immune contexture and prognostic implications in human cancer patients remains to be investigated.

Methods: Post-surgical FFPE tissue microarrays from 327 NSCLC patients (Uppsala, 2006-2010) were stained with fibrinogen to detect areas of vascular leakage (Fig. 1) and stratify patients into Low (LL) or High (HL) leakage groups. For immune characterizations, imaging mass cytometry was performed using an immune-oncology panel consisting of 18 metal-conjugated antibodies.

Results: HL patients constituted ~20% of the NSCLC cohort. Patients in the high leakage group were significantly older (70.2±0.6 vs. 67.4±0.8, $p<0.05$) and had higher vascular density (+32%, $p<0.05$) compared to low leakage patients, HL patients presented with significantly worse 5-year overall survival (OS) rate (HR: 0.618, 95% CI: 0.42-0.91, $p= 0.015$) and progression-free survival (PFS, HR: 0.616, 95% CI:0.39-0.97, $p=0.038$). Multivariate analysis showed that the effect vascular leakage on OS and PFS were independent of clinico-pathological variables, vascular density and adjuvant chemotherapy. The HL tumor microenvironment (TME) was characterized by a higher proportion of CD8+ ($p<0.05$), CD20+ ($p<0.001$) and CD4+ ($p<0.05$) cells. However, A 90% reduction in the proportion of GranzymeBHigh immune cells coupled with a tendency for higher tumor PD-L1 expression ($p=0.08$) was evident in HL patients ($p<0.05$) indicating reduced activation. Furthermore, neighbourhood analyses revealed an increased interaction between regulatory T-cell (Treg) and both B-cells and CD8+ T-cells, in HL patients.

Conclusions: Vascular leakage promotes an immunosuppressive TME involving the upregulation of PD-L1 and increased Treg interaction with effector immune cells, which may contribute to reduced patient survival.

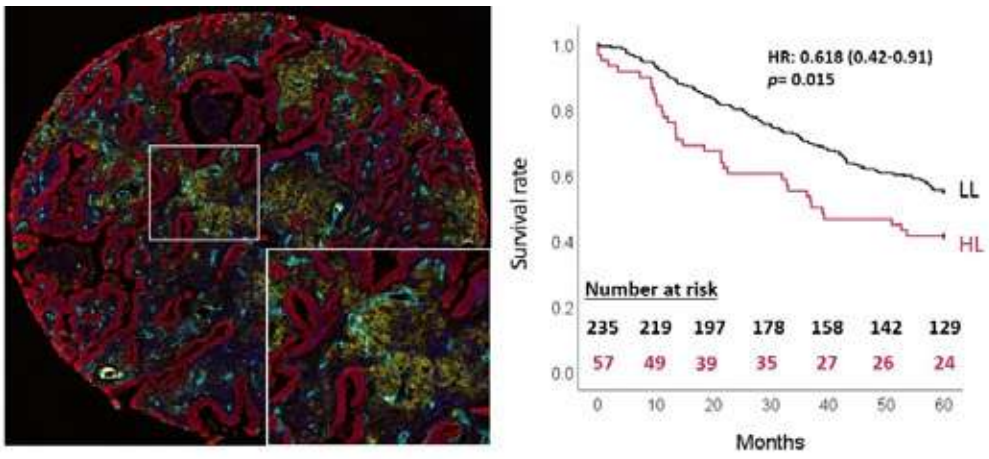

Fig. 1: (Left) Representative image depicting detection of leakage areas in human NSCLC patients. (Right) Kaplan-Meier survival curve illustrating reduced 5-year survival rates amongst patients in the high (HL) group compared to the low (LL) leakage group.

Keywords: Vascular leakage, Survival, Immune contexture

OA10 STRATEGIES TO INTEGRATE SMOKING CESSATION AND CANCER CARE,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

OA10.03 A Randomized Trial of Telephone-Based Smoking Cessation Treatment in the Lung Cancer Screening Setting

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Introduction: Lung cancer mortality is reduced via low-dose CT screening and treatment of early-stage disease. Evidence-based smoking cessation treatment delivered in the lung cancer screening setting can further reduce mortality. We report the quit rates, the short-term cost per quit, and long-term cost effectiveness of a trial of telephone counseling and nicotine replacement for individuals who smoke and were undergoing lung screening at 8 US screening facilities.

Methods: We conducted a cessation trial in the US National Cancer Institute's SCALE collaboration (Smoking Cessation At Lung Examination). Eligible patients (N=818) aged 50-80 were randomized to Intensive vs. Minimal arms (8 vs. 3 sessions of telephone counseling and 8 vs. 2 weeks of nicotine replacement therapy (NRT), respectively). Self-reported and biochemically verified 7-day abstinence rates were assessed 3- and 6-months post-randomization. Logistic regression analyses evaluated the overall and subgroup effects of the study arms. The cost-effectiveness analysis used the University of Michigan's established Cancer Intervention Surveillance and Modeling Network (CISNET) lung cancer model. The model used micro-costing to estimate costs per 6-month bio-verified quit rates together with national registry and cost data to project the lifetime incremental cost-effectiveness of the 8- or 3-session counseling in conjunction with lung screening vs. screening alone from a societal perspective. Costs (2021 dollars) and effects (life-years gained, quality-adjusted life-years saved [QALYs]) were discounted at 3%. Sensitivity analyses tested the effects of varying intervention quit rates, costs, and screening eligibility criteria.

Results: Participants reported 48.0 (SD=17.2) pack years and 51.6% were not ready to quit in <30 days. Self-reported 3-month quit rates were significantly higher in the Intensive vs. Minimal arm (14.3% vs. 7.9%, OR=2.00 [1.26,3.18]). Bio-verified abstinence was also higher in the Intensive vs. Minimal arm (9.1% vs. 3.9%, OR=2.70 [1.44, 5.08]), although the absolute rates were lower than self-report. Compared to Minimal counseling, moderation analyses indicated that Intensive counseling was more effective among those with greater nicotine dependence (OR=3.47 [1.55,7.76]), normal screening results (OR=2.58 [1.32,5.03]), high engagement in counseling (OR=3.03 [1.50,6.14]), and greater NRT use (OR=2.81 [1.39,5.68]). At 6-months, abstinence rates were not significantly different between arms (OR=1.2 [0.68, 2.11]). The delivery costs of Intensive and Minimal telephone counseling were $380.23 and $144.93 per person, respectively. The 8 weeks of counseling had higher costs per quit than 3 weeks ($5,325 vs. $2,432). When projected over a lifetime horizon, both counseling approaches cost less and saved more lives than the screening alone strategy. The incremental cost per QALY for 8- vs. 3-weeks of counseling was $3,085. The conclusions were robust over a range of quit rates, costs and eligibility criteria, assuming non-relapse.

Conclusions: Delivering an 8-week telephone counseling and NRT intervention in conjunction with lung screening is an effective strategy to increase short-term smoking cessation and is cost-effective. Even with modest quit rates, integrating cessation treatment into lung screening programs may result in a large public health impact on tobacco-related mortality at reasonable costs.

Keywords: smoking cessation, lung cancer screening, cost-effectiveness

OA10 STRATEGIES TO INTEGRATE SMOKING CESSATION AND CANCER CARE,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

OA10.04 Opt-out Outperforms Opt-in Smoking Cessation Treatment One-month Post Randomization

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Introduction: Lung cancer risk is reduced by 30-50% within 5 years of quitting smoking. Yet, smoking cessation interventions remain suboptimal even during cancer care. The way smoking cessation is currently offered to patients who smoke, which requires them to opt-in to smoking cessation treatment is inefficient and leaves those who are not ready to quit behind. To test the opt-out approach in which the patients are offered treatment except they refuse, we used the modified Zelen's design (delayed consent until one-month post-randomization) to recruit patients at all levels of motivation into a pragmatic trial of Opt-in versus Opt-out smoking cessation treatment.

Methods: The study was conducted in an academic medical center with an established tobacco treatment service. Counselor screened patients for eligibility at hospital bedside, conducted baseline assessment, randomized patients to study arm (adaptive randomization assigned 64% to Opt-out and 36% to Opt-in), and provided opt-out or opt-in care as randomized. Patients in opt-out arm received inpatient NRT, inpatient counseling/treatment planning, a two-week medication starter kit, scripts for post-discharge medications, and four outpatient counseling calls. Patients could opt out of any or all elements of care. Opt-in patients willing to quit were offered each element of treatment described above. Opt-in patients unwilling to quit received brief "5R" based counseling. Primary outcome (biochemically verified smoking abstinence) was assessed at one month follow up.

Results: Most (74%) of 1,000 randomized patients consented and enrolled at one-month follow up. One hundred and twenty-seven (12.7%) refused consent and 132 (13.2%) could not be reached. There were baseline characteristic differences between those who consented and were enrolled (n=741) and those who were not enrolled (n=259). Cohen's d effect size differences between those who consented/enrolled (n=741) and those who were not enrolled (n=259) were negligible (<0.2) for age, gender, race/ethnicity, and most forms of insurance. The effect size was small for Medicaid (0.36), and other public insurance (0.48). After excluding those unreached at 1 month (12.7%), there were medium Cohen's d effect size differences between those who consented to participate (n=741) and those who explicitly refused (n=127) with respect to age (0.55) and self-pay or no insurance (0.51). There were small to negligible effect size differences with respect to sex, race/ethnicity, and other forms of health insurance. Verified quit rates for Opt-out vs Opt-in were 22% vs 16% at month one follow up.

Conclusions: The pragmatic trial reduces the pitfalls associated with conventional clinical trials in which informed consent precedes randomization. The modified Zelen's design resulted in successful enrollment of most participants who were initially randomized into the trial. Opt-out care increased the reach of evidence-based treatment smokers and achieved better one-month quit rates. Future studies should examine long-term abstinence rates.

Keywords: Smoking Cessation, Behavioral Treatment, Modified Zelen's Design

OA10 STRATEGIES TO INTEGRATE SMOKING CESSATION AND CANCER CARE,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

OA10.05 Integrating Smoking Cessation into LDCT Lung Cancer Screening. Results of the Ontario, Canada, Pilot

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Introduction: Screening for lung cancer (LC) using low-dose computed tomography (LDCT) in high-risk individuals reduces LC mortality. In June 2017, Ontario Health (Cancer Care Ontario) initiated a screening Pilot that included a smoking cessation (SC) intervention to inform the implementation of a provincial organized lung screening program.

Methods: Three hospital sites were selected that met requirements (>150 thoracic resections/year; dedicated thoracic service; commitment to provide on-site smoking cessation services by trained personnel). The Pilot utilized targeted recruitment strategies, eligibility determined by the $PLCOm2012_{noRace}$ risk prediction model, an opt out referral of current smokers to cessation services and navigators providing end-to-end support.

Results: When the Pilot closed on August 31, 2019, 7,768 individuals had been recruited to the Pilot and 7,329 (94.3%) were risk assessed. Of those risk assessed, 4,944 (67.5%) were eligible for screening and 4,463 (60.9%) were current smokers. Individuals were primarily recruited to the Pilot through family physicians (69.9%); media (8.8%) and nurse practitioners (5.3%). Of the 4,463 current smokers at risk assessment, 80.6% accepted referral to some form of SC service: 3,314 (69.8%) accepted referral to an in-hospital SC program, 431 (9.7%) used telephone quit lines and 50 (1.1%) accepted referral to other programs. Only 4.4% reported that they intended not to quit and 8.5% were not interested in participating in a SC program. Of the 4,451 individuals who had a baseline LDCT scan, 3,063 (68.8%) were current smokers and 2,736 (89.3%) attended in-hospital smoking cessation counselling on the day of the LDCT screening appointment. Program intensity varied by site: Site A utilized the Ottawa Model for Smoking Cessation with a 12-week program and a 6-month follow-up; Site B offered four in-person sessions (baseline + follow up at 3 and 8 weeks and 6 months; Site C offered 3 options: referral back to primary care provider, or community pharmacist or a 1.5-hour hospital-based group educational session. 1,689 individuals had a 12-month follow-up LDCT scan with complete data. The overall quit rate (30-day abstinence) at one-year was 15.5% (95% CI:13.4-17.7%) varying across sites from 10.5% to 20.0%, with the highest rate at Site A. Of those who had not quit smoking at the annual follow-up, there were consistent improvements in heaviness of smoking index ($p< 0.001$), number of quit attempts ($p< 0.001$) and average number of cigarettes smoked per day ($p< 0.001$). At one year, 6.3% of those who were not current smokers at baseline had resumed smoking. 92.7% of respondents to a participant experience survey were highly satisfied with the hospital SC program and counselling received but suggested improvements included provision of free smoking cessation medication (NRT), more face-to-face counselling, group classes and lower parking costs.

Conclusions: Based on learnings from the Pilot, the provincial *Ontario Lung Screening Program* (started April 1, 2021) includes recruitment through primary care providers and self-referral, assessment of eligibility by trained navigators, in-hospital smoking cessation support, an opt out approach to referral to cessation services and intensive smoking cessation interventions to the extent possible.

Keywords: smoking cessation, LDCT screening, opt out referral

OA10 STRATEGIES TO INTEGRATE SMOKING CESSATION AND CANCER CARE,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

OA10.06 An Unconventional Financial Incentive Based Feasibility Trial for Smoking Cessation

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Introduction: Financial incentive-based smoking cessation trials increased cessation rates from 6% to 16.3%. We adjusted our trial to address two major concerns regarding nicotine addiction. First, the constancy of nicotine withdrawal needs to be counteracted by a frequently given financial reward to offset cravings. Therefore, we increased the reward interval to weekly/biweekly. Second, commitment contracts produced favorable quitting rates but were not widely accepted. We created an experimental group that employs delayed rewards to mimic commitment contracts without their objectionable aspects.

Methods: This four-month randomized, single blinded trial compared two financial strategies for smoking cessation. Enrolled subjects were referred to the smoking cessation program and then returned weekly for 12 weeks and then bi-weekly for 4 weeks where they were tested for evidence of smoking by exhaled Carbon Monoxide (COex). COex ≤ 6PPM confirmed smoking abstinence and awarded each subject a $40 incentive. Subjects were randomized into two groups; the Reward Group immediately received the $40 however, the Banked-Money Group had the money deposited in a 'bank account' they could only access if they completed the four-month trial. During the first 3 months, subjects were allowed two positive smoking tests before the third disqualified them. During the last month they were disqualified with a single positive smoking test. If disqualified, the Reward Group subjects keep the money accrued so far whereas the Banked-Money lose all the money in the 'bank account'. Upon successful completion of the study the Banked-Group subjects receive all the money in the 'bank account'.

Results: All 36 subjects were enrolled between June and October, 2021. Three subjects withdrew from the trial post randomization due to job relocation, dissatisfaction with group assignment and unwillingness to continue participation in the trial. One subject enrolled in hospice, thus precluding further participation. Seven subjects signed the informed consent, however did not complete the next steps to start the study. 25 subjects (69.44%) set a quit date and started the trial. The mean age was 63.3 years (34 to 79), COex on enrolment was 16.6 PPM (4 to 68) and packs per year (PPY) was 39.8 (1.75 to 159). Using the Fagerstrom Nicotine Dependence Test, 41.7% had very high nicotine dependence and 25% had high dependence. 75% of subjects endorsed a previous traumatic event with 37% of them having a score favoring PTSD. 13.9% subjects had severe anxiety and 5.5% subjects had severe depression. 58.3% subjects reported significant sleep disturbance. Eleven subjects (30.6%) successfully completed the four-month trial and quit smoking.

Conclusions: Our pilot study shows the feasibility to enroll subjects for a high intensity smoking cessation study using financial incentives, demonstrated a higher quit rate than previous studies and identified baseline intervenable characteristics to design future studies to further improve smoking cessation rates.

Keywords: Smoking, Cessation, Financial

OA11 OPTIMAL PATIENT SELECTION FOR LOCAL THERAPY IN STAGE IV NSCLC,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

OA11.03 Nonregional Lymph Nodes as the Only Metastatic Site in Stage IV Non-Small Cell Lung Cancer: A Marker of Better Prognosis

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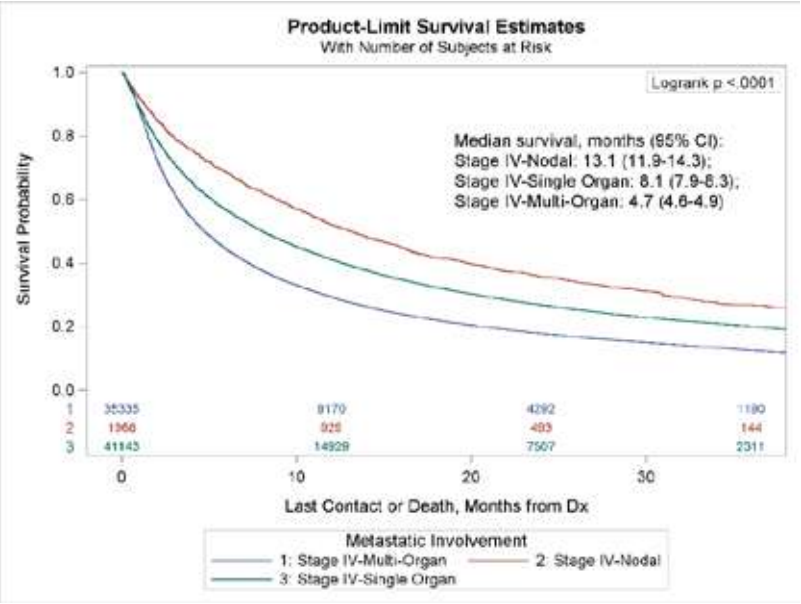
Introduction: Metastatic involvement of nonregional lymph nodes is currently a stage IV determinant (M1b) for non-small cell lung cancer (NSCLC). However, the management and outcome of patients whose distant disease is limited to nonregional lymph nodes is unknown.

Methods: The National Cancer Database was queried to identify patients >18 years of age who were diagnosed with stage IV NSCLC between 2016 and 2018. Unadjusted Kaplan-Meier analysis was performed to analyze survival of stage IV patients whose distant disease was: limited to nonregional lymph nodes (stage IV-nodal), limited to a single visceral organ excluding distant lymph nodes (stage IV-single organ), and multi-organ metastases (stage IV-multi-organ). Kaplan-Meier analysis was also performed after a propensity score matching procedure to adjust for sociodemographic variables.

Results: In total, 113,756 patients met inclusion criteria, including 58,712 with stage IV-single organ, 52,153 with stage IV-multi-organ, and 2,891 with stage IV-nodal disease. The median age was 67 years (interquartile range: 60-75), and 46.5% of patients were female. Sociodemographic characteristics were similar among the three metastatic groups. Patients with stage IV-nodal disease were more likely than patients with single- or multi-organ metastases to present with squamous cell carcinoma; they were also more likely to receive immunotherapy and chemotherapy, but less likely to receive radiation therapy (**Table 1**). The prognosis of stage IV NSCLC varied by pattern of organ involvement, with stage IV-nodal exhibiting the best survival (3-year survival of 27.4%), followed by stage IV-single organ (20.5%), and stage IV-multi-organ (13.0%; **Figure 1**). These findings remained significant for the propensity score-matched cohorts.

Conclusions: Stage IV NSCLC patients presenting with only distant lymph node metastases may have a significant survival advantage compared to other stage IV patients, which can help guide shared decision-making and may support revision of the M1 stage subclassifications.



Management of Stage IV NSCLC Patients				
	Stage IV-Nodal, n (col %); n=2891	**Stage IV-Single Organ, n (col %); n=58712**	**Stage IV-Multi-Organ, n (col %); n=52153**	**Chi-squared p-value**
No Treatment	597 (20.7)	15282 (26.0)	11139 (21.4)	<0.0001
Any Surgery	49 (1.7)	2171 (3.7)	505 (1.0)	<0.0001
Any Chemotherapy	1748 (60.5)	28732 (48.9)	26491 (50.8)	<0.0001
Any Radiation	806 (27.9)	23305 (39.7)	26352 (50.5)	<0.0001
Any Immunotherapy	847 (29.3)	13439 (22.9)	13128 (25.2)	<0.0001
Missing	136 (4.7)	2881 (4.9)	2362 (4.5)	-

Keywords: Non-Small Cell Lung Cancer, Distant Lymph Node Metastases, Stage IV Prognosis

OA11 OPTIMAL PATIENT SELECTION FOR LOCAL THERAPY IN STAGE IV NSCLC,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

OA11.04 The Factors Associated with Reduced Risk of Progression in Patients with Oligometastatic NSCLC Treated with Local Ablative Radiotherapy

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Introduction: We aimed to investigate which subset of patients with oligometastatic lung adenocarcinoma would benefit from local ablative radiotherapy (LART).

Methods: 274 patients diagnosed with stage IV non-small cell lung cancer (NSCLC), with three or fewer metastases at the timing of LART were enrolled. Histology other than adenocarcinoma (n=56), patients who did not undergo systemic therapy (n=23) at the time of RT, who had uncontrolled brain metastases (n=20) were excluded. Thus a total of 175 patients were included. Among these patients, some patients received LART as 1st line treatment and were defined as the oligometastasis group. The rest of the patients received LART when presented with oligoprogression in spite of other treatments. We classified these patients as the olioprogression group. Single-fraction cumulative doses ≥ 12 Gy, 3-fraction doses ≥ 24 Gy, 5-fraction doses ≥ 30 Gy were regarded as LART. The primary end point was progression-free survival (PFS); secondary end point was overall survival (OS).

Results: In the oligometastasis group (N=53), 25 patients (47.2%) presented with EGFR mutation, 4 patients (7.5%) with ALK positive status and 9 patients (17.0%) with ROS1. 37 patients (69.8%) had single metastatic lesion, 12 patients (22.6%) had two lesions. Bone metastasis was the most commonly treated site (63.0%) followed by lung (27.8%). Among these patients, 38 patients (71.7%) received LART to all sites of gross disease, and we defined it as all metastatic site RT. The median follow-up time was 20.2 months (range, 0.3-109.7 months). During this follow-up period, 1-year PFS was 39.9% and 3-year PFS was 22.4%. In a Cox multivariate model, EGFR and ALK positive status were independently correlated with improved PFS (hazard ratio (HR), 0.24; 95% confidence interval (CI), 0.11-0.56, HR, 0.04; 95% CI, 0.01-0.37, respectively). All metastatic site RT independently correlated with PFS (HR 0.39; 95% CI, 0.18-0.86). In patients who were administered with Tyrosine kinase inhibitor (TKI) at the time of RT (N=23) and treated with all metastatic site RT, 1-yr PFS was 86.7%, while that of the patients who were not treated with all site RT was 37.5% (p=0.029). In the oligoprogression group (N=122), 62 patients (50.8%) were treated with TKI, 45 patients (36.9%) with cytotoxic chemotherapy (CTx) for 1st line systemic therapy. At the time of LART, 50 patients (41.0%) were undergoing TKI and 43 patients (35.2%) immunotherapy. 67.2% of the patients (N=82) maintained the CTx regimen after LART. The median duration prolonged was 5.8 months. In the subset of patients who were treated with TKI at the time of LART, the median duration prolonged was 11.1 months.

Conclusions: EGFR positive and ALK positive status are associated with improved PFS in patients with oligometastatic lung adenocarcinoma. For oligometastatic patients, early all site RT might improve PFS, especially for those who are receiving TKI. In patients who presented with oligoprogression, LART could delay the the timing of CTx regimen change.

Keywords: oligometastasis, local ablative radiotherapy, all site radiotherapy

OA11 OPTIMAL PATIENT SELECTION FOR LOCAL THERAPY IN STAGE IV NSCLC,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

OA11.05 Treatment Strategies Based on Different Oligoprogressive Patterns After Immunotherapy Resistance in Advanced NSCLC

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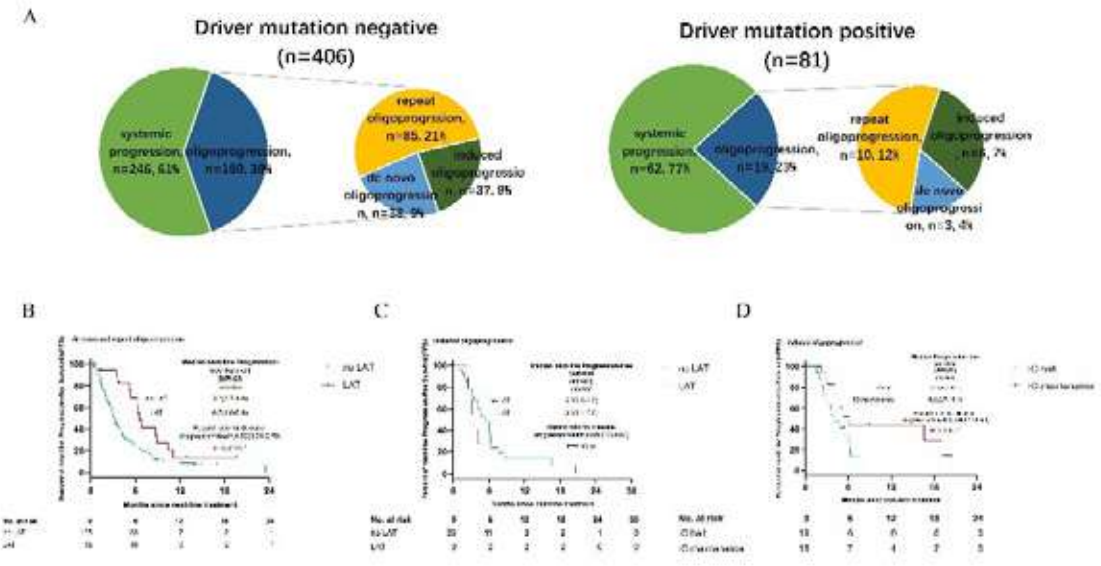
Introduction: Oligoprogressive disease is recognized as the overall umbrella term, however, a small number of metastases on imaging can represent different clinical scenarios. This study aims to explore the optimal treatment regimens after immunotherapy resistance in advanced NSCLC, especially in personalized therapies for patients with distinct oligoprogressive patterns.

Methods: On the basis of the EORTC consensus, patients with cancer progression were divided into four patterns, de-novo oligoprogression, repeat oligoprogression, induced oligoprogression and systemic progression. Patients with advanced NSCLC who received immunotherapy initiated between Jan 2016 and Jul 2021 at Shanghai Chest Hospital were identified and examined by clinical and radiographic features. The progression patterns and next-line progression-free survival (nPFS), overall survival (OS) were investigated stratified by treatment strategies. nPFS and OS were calculated using the Kaplan-Meier method, and differences were assessed by the stratified log-rank test.

Results: A total of 612 patients were included. 487 patients developed disease progression in the overall population, 37% (n=179) developed oligoprogression and 63% (n=308) developed systemic progression. 41 (8%) patients had de-novo oligoprogression, 95 (20%) patients had repeat oligoprogression and 43 (9%) patients had induced oligoprogression. The incidence of oligoprogression was higher in driver mutation negative cohort versus driver mutation positive cohort (39% vs 23%; P=0.0066, Figure A). After IO treatment resistance, patients with de-novo and repeat oligoprogression had substantial survival advantages from local ablative therapy (LAT). The median nPFS was significantly prolonged compared with no LAT group (6.8 vs 3.3 months; P=0.01, Figure B). Patients with induced oligoprogression could not benefit from LAT by contrast with no LAT group (nPFS, 3.6 vs 5.3 months; P=0.35; OS, 36.6 vs 45.4 months; P=0.87, Figure C) but from IO maintenance treatment (nPFS, 6.1 vs 4.1 months; P=0.03; OS, 45.4 vs 32.3 months; P=0.03, Figure D).

Conclusions: Patients with de-novo and repeat oligoprogression have survival advantages from local therapy. But for those induced oligoprogression patients, IO maintenance alone instead of combination with LAT may be the optimal treatment regimen.



Keywords: non-small cell lung cancer, oligoprogression, immunotherapy

OA11 OPTIMAL PATIENT SELECTION FOR LOCAL THERAPY IN STAGE IV NSCLC,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

OA11.06 Sequencing of ctDNA Revealed Radiotherapeutic Efficacy and Prognosis in Non-small Cell Lung Cancer Patients with Brain Metastasis

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Introduction: Brain metastasis is a leading cause for advanced non-small cell lung cancer (NSCLC) mortality. Derived from necrosis, apoptosis and secretion of tumor cells, circulating tumor DNA (ctDNA) is widely distributed in various body fluids including peripheral blood and cerebrospinal fluid (CSF), and has been utilized in NSCLC with brain metastases. In this study, we aimed to explore ctDNA through liquid biopsy before and after radiotherapy of NSCLC brain metastases.

Methods: Thirty NSCLC patients with brain metastases receiving brain radiotherapy were enrolled in this study. Cerebrospinal fluid (CSF) and peripheral blood were collected at baseline, 24 hours (T0) and 28 days (T28) after treatment. ctDNA sequences were identified by high-throughput sequencing in both compartments.

Results: At baseline, distinct genomic patterns were observed between blood and CSF liquid biopsy, identical mutations shared by paired blood and CSF emerged in only nine patients (30%). No significant changes were found in mutation allele frequency (AF) and overlap mutations between blood and CSF throughout the treatment. ctDNA AF in blood may related to extracranial response. Blood-ctDNA clearance at T28 was significantly associated with better overall survival (OS, HR = 4.027, p = 0.028) and progression-free survival (PFS, HR = 4.176, p = 0.024). The predictive effects of these markers were independent of other clinical factors in multivariate Cox analysis.

Conclusions: CSF and peripheral blood were independent compartments in ctDNA genomic signatures. The decrease of ctDNA in peripheral blood could predict a favorable clinical outcome for NSCLC patients with brain metastases

Keywords: ctDNA, non-small cell lung cancer, brain metastasis

OA12 NOVEL AND COMBINATION STRATEGIES FOR SCLC,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

OA12.03 Phase 2 Study Analysis of Talazoparib (TALA) Plus Temozolomide (TMZ) for Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

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Introduction: TALA exhibits cytotoxic effects by inhibiting poly (ADP-ribose) polymerase (PARP) proteins 1 and 2 in addition to "trapping" PARP on DNA. TMZ has been shown to increase antitumor response when combined with TALA in SCLC models (Wainberg AACR 2016). TALA plus TMZ as second-line therapy for ES-SCLC may improve disease-related outcomes.

Methods: This is a phase 2, open-label, single-arm study of the safety and efficacy of TALA plus TMZ in patients with ES-SCLC, relapsed or refractory to a first-line platinum-based regimen. Participants receive TALA 0.75 mg (or 0.5 mg if creatinine clearance < 60 mL/min) po daily on 28-day cycles with TMZ 37.5 mg/m2 po on days 1-5. The primary endpoint is objective response rate (ORR) based on RECIST 1.1 criteria, versus a historical control of 15% ORR in second-line topotecan, with the null hypothesis rejected for 8 or more confirmed responses among 28 evaluable subjects (29% ORR). Secondary endpoints include progression-free survival, overall survival, duration of response, and time to response. Exploratory endpoints include biomarker studies such as status of DNA damage response genes (DDR) and patient reported outcomes. A Simon two-stage design was utilized to reach a total accrual of 28 evaluable patients.

Results: Thirty-one subjects were enrolled, of which 3 were non-evaluable due to ineligibility (1) or early withdrawal of consent prior to first disease assessment (2). Eleven of 28 evaluable subjects (39.3%) achieved a confirmed partial response. The ORR was similar among platinum-refractory (3/6), -resistant (4/9), and -sensitive subgroups (4/13). The median time to response was 1.8 months (m), duration of response 5.8 m, progression free survival 4.5 m, and overall survival 11.9 m. Adverse events (AEs) were manageable, with grade ≥ 3 AEs being thrombocytopenia (61.3%), anemia (54.8%), neutropenia (41.9%), and atypical pneumonia (3.2%), which responded well to dose-hold or dose-reduction and transfusion or growth factor support as needed. Cell free DNA and tissue analysis demonstrated no germline DDR mutations among the trial subjects, but somatic DDR mutations at baseline and acquired during treatment were common. Three subjects remain on study treatment.

Conclusions: The study exceeded its target response rate. This is the second trial to demonstrate a benefit of PARP inhibition with low-dose TMZ in SCLC (see Farago Cancer Discovery 2019). A phase 3 study is appropriate to confirm the benefit of this approach compared to currently approved options.

Keywords: Phase 2, Relapsed or refractory ES-SCLC, DNA damage repair inhibitor

OA12 NOVEL AND COMBINATION STRATEGIES FOR SCLC,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

OA12.04 Efficacy of Nivolumab and Temozolomide in Extensive Stage Small Cell Lung Cancer after Chemo-Immunotherapy: A Phase 2 Trial

D.H. Owen, L. Wei, B. Benner, C. Pilcher, G. Christenson, S. Ferguson, M. Jukich, V. Sukrithan, B. Konda, M. Shah, H. Savardekar, E. Schwarz, R.O. Norman, R. Wesolowski, W.E. Carson, J. Kaufman, A. Alahmadi, R. Memmott, P. Shields, K. He, E.M. Bertino, C.J. Presley, D.P. Carbone, C. Verschraegen, G.A. Otterson

The Ohio State University, Columbus/OH/USA

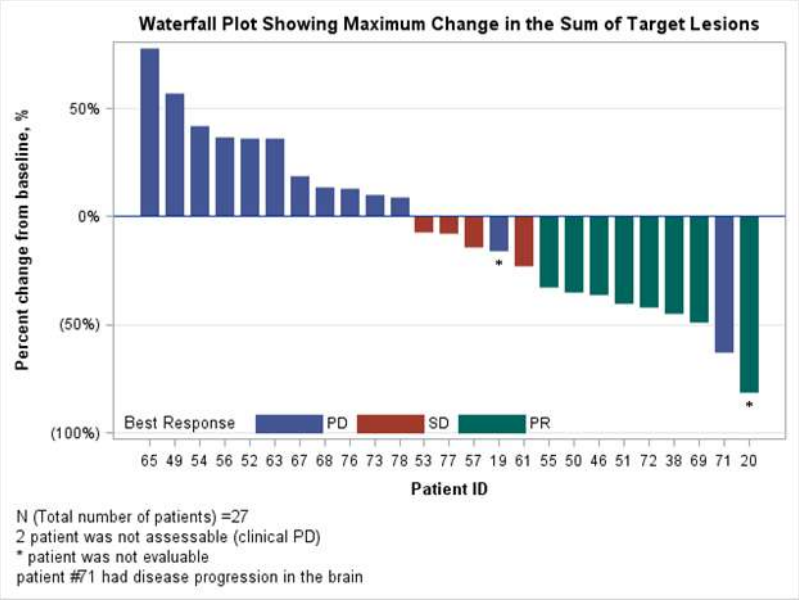
Introduction: Treatment options are limited in patients with extensive stage small cell lung cancer (ES-SCLC) after progression on first line chemo-immunotherapy (CIT). Temozolomide (TEM) is active in ES-SCLC and has been shown to have immunomodulatory impact in patients with advanced cancers, however data are unavailable in patients after CIT. We present the final analysis of a phase 2 trial of combination nivolumab and TEM in patients with ES-SCLC as 2nd or 3rd line after progression on CIT.

Methods: NCT03728361 is a non-randomized, multi-cohort, single-institution, open-label phase 2 study of nivolumab and TEM in patients with ES-SCLC and neuroendocrine tumors (reported separately). Eligible patients with ES-SCLC experienced disease progression after CIT and brain metastases were permitted. Treatment consisted of nivolumab 480 mg IV and TEM 150 mg/m2 for 5 days of a 28 day cycle. The primary endpoint was best overall response rate (BOR) by RECIST v1.1. Progression free survival (PFS) and overall survival (OS) were assessed by the method of Kaplan-Meier. Adverse events were graded using CTCAE v5.

Results: 27 patients were accrued including 11 (41%) with platinum resistant disease and 10 (37%) with brain metastases (mCNS, Table 1); 25 patients who progressed after CIT were eligible for primary endpoint analysis. Responses occurred in 7/25 patients with prior CIT (28%, 95% CI: 12, 49%) and 8/27 (30%) patients overall (Figure 1), meeting predefined efficacy criteria. mPFS was 2.4 months (95% CI: 1.9, 3.4); mOS was 6.3 months (95% CI: 3.7, 9.8, Table 1). OS was not associated with line of therapy or mCNS. mOS for patients with mCNS was 9 months (95% CI: 2.0, 11.4). Toxicities were similar to CIT strategies.

Conclusions: Nivolumab and TEM showed promising efficacy after first-line CIT in patients with ES-SCLC as 2nd and 3rd line of therapy and in patients with brain metastases.

Patient Characteristics and Survival			
Patient Characteristics (N=27)			
Age	Median (range)	65 (56-78)	
Sex	Male	17 (63%)	
	Female	10 (37%)	
ECOG	0-1	26 (96%)	
	2	1 (4%)	
Platinum resistant	Yes	11 (41%)	
	No	16 (59%)	
Smoking history	Yes	27 (100%)	
Brain Metastasis	Yes	10 (37%)	
	No	17 (63%)	
Survival Analysis	Median (months)	95% CI	p value
Progression Free Survival:			
All pts (n=27)	2.4	1.9, 3.4	
2nd Line of therapy	2.0	0.5, 7.5	p=0.907
>2nd Line of therapy	2.6	1.9, 3.3	
No brain metastases	2.1	1.9, 3.5	p=0.537
Brain metastases	3.3	1.7, 3.7	
Overall Survival:			
All pts (n=27)	6.3	3.7, 9.8	
2nd Line of therapy	6.9	0.5, 10.4	p=0.628
>2nd Line of therapy	5.8	3.7, 9.2	
No brain metastases	5.2	3.1, 9.2	p=0.231
Brain metastases present	9.0	2.0, 11.4	



Keywords: small cell lung cancer; SCLC, immunotherapy, immune checkpoint inhibitor

OA12 NOVEL AND COMBINATION STRATEGIES FOR SCLC,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

OA12.05 Phase 1 Updated Exploration and First Expansion Data for DLL3-targeted T-cell Engager Tarlatamab in Small Cell Lung Cancer

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Introduction: Delta-like ligand 3 (DLL3) is overexpressed in most small cell lung cancer (SCLC). Tarlatamab (AMG 757), a half-life extended bispecific T cell engager (HLE BiTE®) molecule, binds DLL3 and CD3 leading to T cell-mediated tumor lysis. Interim phase 1 dose exploration data in SCLC (NCT03319940) show preliminary evidence for tarlatamab efficacy with an acceptable safety profile. Here we report for the first time safety, response, and survival for the combined dose exploration and expansion cohorts.

Methods: Tarlatamab (0.003-100.0 mg) was administered intravenously every two weeks ± step dosing in patients with SCLC that progressed after ≥1 platinum-based regimen. Antitumor activity was assessed using modified RECIST 1.1. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier methods. Tumor DLL3 expression was assessed by immunohistochemistry (IHC). T-cell activation and cytokine profiles were evaluated in serum samples.

Results: As of 13 January 2022, 102 patients had received ≥1 dose tarlatamab in the dose exploration and expansion cohorts with a median follow-up time of 6.3 months (range, 0.2-25.7). Median age was 63 years (range, 32-80), ECOG PS was 0-1 in 99%, median prior lines were 2.0 (range, 1-6); 21.6% were platinum refractory, 49% had prior PD-1/PD-L1. DLL3 was positive by IHC (≥1%) in 96% (93/97) of available samples. Median treatment duration was 9.3 weeks (range, 0.1-77.3).Treatment-related AEs (TRAEs) of any grade occurred in 93 patients (91.2%): grade ≥ 3 (31.4%), grade ≥ 4 (7.8%), and grade 5 (1.0%; pneumonitis in one patient). Cytokine release syndrome (CRS) was generally grade 1; treatment-related grade ≥2 CRS occurred in 12 patients (11.8%) and grade 3 in one patient (1.0%). Grade ≥ 2 treatment-related neurologic events occurred in 17 patients (16.7%) and grade 3 in 7 patients (6.9%). No grade 4/5 CRS or neurologic events occurred. Treatment-related grade ≥ 3 neutropenia occurred in 8 patients (7.8%) and grade 4 in 3 patients (2.9%); no febrile neutropenia occurred. Three patients (2.9%) discontinued tarlatamab due to TRAEs (CRS, encephalopathy, and pneumonitis). Overall confirmed and unconfirmed objective response rate (ORR) was 24.0% (95% CI: 15.8, 33.7); confirmed responses occurred in 18.8% (95% CI: 11.5, 28.0) including 2 complete responses (CRs) and 16 partial responses (PRs). Among confirmed responders, median time to response was 1.79 months (range, 1.15-7.43) and median duration of response was 12.3 months (95% CI: 5.6, 14.8). Disease control rate (stable disease/CR/PR) was 51% (95% CI: 40.6, 61.4). Median PFS was 3.5 months (95% CI: 2.1, 4.6) and median OS was 12.3 months (95% CI: 7.2, NE). Updated pharmacokinetics and pharmacodynamics results will be presented. (*Note: DOR/PFS/OS were calculated in all patients with 6 months follow-up after first dose [n=85]; ORR in those with ≥ 9 weeks [n=96]*)

Conclusions: Tarlatamab has an expected and manageable safety profile and delivers promising efficacy with excellent response durability amongst confirmed responders in this heavily pretreated SCLC population. The PFS/OS compares well to other therapies currently available for relapsed SCLC. A phase 2 study of tarlatamab in 3L+ SCLC (NCT05060016) is enrolling based on these results.

Keywords: immunotherapy, BiTE, DLL3

OA12 NOVEL AND COMBINATION STRATEGIES FOR SCLC,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

OA12.06 First-Line Pembrolizumab or Placebo Combined with Etoposide and Platinum for ES-SCLC: KEYNOTE-604 Long-Term Follow-Up Results

C.M. Rudin[1], H.R. Kim[2], A. Navarro[3], M. Gottfried[4], S. Peters[5], T. Csőszi[6], P.K. Cheema[7], D. Rodriguez-Abreu[8], M. Wollner[9], G. Czyżewicz[10], J.C-H. Yang[11], J. Mazieres[12], F.J. Orlandi[13], A. Luft[14], M. Gümüş[15], T. Kato[16], G.P. Kalemkerian[17], W. Fu[18], B. Zhao[18], H. El-Osta[18], M.M. Awad[19]

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This abstract is under embargo until August 9 at 10:10 Vienna, Austria Time, CEST.

OA13 EVOLVING EPIDEMIOLOGY OF LUNG CANCER BEYOND TOBACCO,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

OA13.03 Evaluation of Outdoor Air Pollution Exposure (PM2.5) In Female Non-smoking Lung Cancer Patients

R.L. Myers[1], M.C. Tammemagi[2], M. Brauer[3], S. Atkar-Khattra[4], A. Dy Buncio[4], J. Yee[5], B. Melosky[1], S. Lam[1]

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This abstract is under embargo until August 9 at 10:10 Vienna, Austria Time, CEST.

OA13 EVOLVING EPIDEMIOLOGY OF LUNG CANCER BEYOND TOBACCO,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

OA13.04 Prevalence of Molecular Alterations in NSCLC and Estimated Indoor Radon in Europe: RADON EUROPE Study

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Introduction: There are geographical differences in the prevalence of driver oncogenic alterations in non-small cell lung cancer (NSCLC) around the world, potentially related to genetic and/or environmental factors. Radon is the leading cause of lung cancer in nonsmokers, in whom molecular driver alterations occur most commonly. We previously reported a potential correlation between the prevalence of certain drivers alterations in NSCLC and estimated radon risk in France (Mezquita et al, WCLC 2018). Here, we explore the correlation between estimated indoor radon exposure and the prevalence of driver alterations in NSCLC across European countries.

Methods: Retrospective analysis of NSCLC molecular data and radon data reported from all European countries was performed. Demographic data were collected from the World´s Health Organization Global Cancer Observatory. Radon exposure data, including estimated mean and proportion (%) of dwellings with concentrations higher than 200Bq/m3 and 400Bq/m3 by country were collected from the European Commission Report 2005. The prevalence of NSCLC molecular alterations (*EGFR*, *ALK,* and others) by country were obtained from PubMed original articles published with a sample size greater than 100 patients. We studied the correlation between molecular alterations and radon data available by country.

Results: In this preliminary analysis, a total of 21 European countries had data available and were included. The estimated annual indoor radon mean was 78.5 Bq/m3, range 10 (Iceland) - 184 Bq/m3 (Serbia). Five countries had mean levels above 100 Bq/m3 (Serbia, Sweden, Finland, Czech Republic, Albania), and six countries had >1% (high) of dwellings with concentrations > 400 Bq/m3, particularly Finland, Czech Republic and Austria (>3%). In 159,818 and 111,746 NSCLC cases evaluated for *EGFR* and *ALK*, respectively, the median prevalence of *EGFR* and *ALK* alterations was 10% (n=16.461; range 6.3%-32%) and 4% (n=4.470, range 1.4%-15.8%). In countries with mean radon exposure >100 Bq/m3, median *EGFR* and *ALK* prevalence was 10% and 5% respectively compared to 11% and 4% in those countries with <100 Bq/m3. We observed a positive correlation between *ALK*-fusion prevalence and the percentage of dwellings with >400 Bq/m3 (r=0.54, p=0.02), and a trend for the percentage of dwellings > 200 Bq/m3 (r=0.39, p=0.1). No correlation was found between *EGFR* and radon exposure.

Conclusions: In this ecologic study, the prevalence of *ALK* fusion in NSCLC was higher in those European countries with higher percentage of dwellings with radon levels above 400 Bq/m3. The role of radon in NSCLC harboring oncogenic drivers needs to be further explored.

Keywords: Radon, Molecular alterations, NSCLC

OA13 EVOLVING EPIDEMIOLOGY OF LUNG CANCER BEYOND TOBACCO,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

OA13.05 Lung Cancer Risk Prediction Nomogram in Chinese Female Non-smokers

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Henan Cancer Hospital, Zhengzhou/CN

This abstract is under embargo until August 9 at 10:45 Vienna, Austria Time, CEST.

OA13 EVOLVING EPIDEMIOLOGY OF LUNG CANCER BEYOND TOBACCO,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

OA13.06 Changing Patterns of Lung Cancer Histology in an Asbestos Exposed Population

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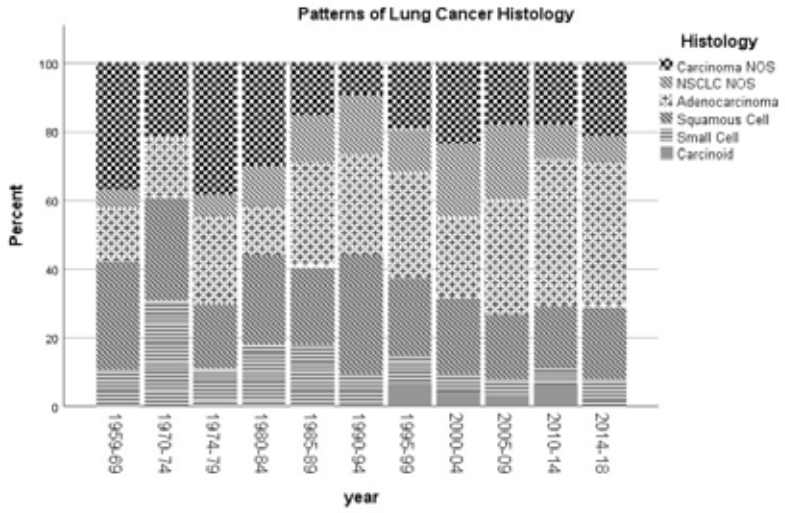
Introduction: Asbestos is a widely recognised lung carcinogen. Exposure to both asbestos and cigarette smoke has a synergistic effect on the risk of developing lung cancer. It is not known if the histology of asbestos-related lung cancer has changed over time, as has been observed with non-asbestos-related lung cancer.

Methods: The study cohort is derived from the Wittenoom (crocidolite) miners and ex-residents cohorts, and the Western Australian Asbestos Review Program (ARP), with a predominant mixed fibre, mixed occupation population. Follow up of all participants included tobacco exposure histories and asbestos exposure estimates. Incident cases of lung cancer were determined from linkage to the Western Australian Cancer Registry and the National Cancer Clearing House. Lung cancer was identified using ICD-10 categories C33.9-C34.9.

Results: There were 14,318 asbestos-exposed subjects identified. The majority were men (11,182 (78.1%)) and 2,436 (17.0%) were never-smokers. Between 1955 and 2018, there were 715 (4.9%) cases of lung cancer. Most cases were diagnosed in men (86.9%), with a median age of 67.4 (IQR 60.5-75.0) years. Wittenoom workers comprised 505 (70.6%) of lung cancer cases, ex-residents 121 (16.9%) and others 89 (12.4%). 16 (2.2%) of the lung cancer cohort identified as never-smokers, and 452 (68.2%) were either current or former smokers. Non-small cell lung cancer accounted for 478 (66.9%) lung cancer cases, small cell 68 (9.5%) cases and carcinoma not otherwise specified 146 (20.4%) cases. Histological subtypes changed significantly over time. Comparing pre-1980 vs. post 2010, the proportion of adenocarcinoma increased (20.5% vs. 42.7%, p<0.0001), whilst the rates of squamous cell carcinoma (26.5% vs. 19.1%, p<0.0001) and small cell lung cancer (16.7% vs. 6.1%, p<0.0001) decreased. Overall median survival across the lung cancer cases was 158 (IQR 52-483) days.

Conclusions: In our cohort of asbestos exposed individuals, 1:20 developed lung cancer. The cohort demonstrated similar histological patterns and temporal change compared to other populations without a history of asbestos exposure. The recent fall in squamous cell carcinoma and small cell lung cancer is likely a reflection of falling smoking rates.

Figure 1. Change in proportions of histological subtypes of lung cancer across 5-year periods, from 1959 to 2018.



Keywords: Lung Cancer, Epidemiology, Asbestos Exposure

OA14 NEW TECHNIQUES TO IMPROVE OUTCOME IN EARLY STAGE NSCLC PATIENTS TREATED WITH SURGERY OR RADIOTHERAPY,
TUESDAY, AUGUST 9, 2022 - 12:00–13:00

OA14.04 Chest Wall Toxicity after Individualized Stereotactic Ablative Radiotherapy for Lung Tumors

B. Lau[1], Y.F. Wu[1], J. Fu[1], S. Cui[1], D. Pham[1], H. Gee[2], L. Skinner[1], H. Shirato[3], H. Taguchi[3], A. Chin[1], M. Gensheimer[1], M. Diehn[1], B. Loo[1], L. Vitzthum[1]

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Introduction: Chest wall toxicity (CWT), comprising chest wall (CW) pain and radiation-induced rib fracture, is a common adverse effect of lung stereotactic ablative radiotherapy (SABR) for treatments near the CW. However, there is currently no clear consensus on dosimetric constraints or fractionation schemes (single versus multiple) to mitigate this toxicity. The goal of this analysis is to identify predictive dosimetric parameters for CWT and to compare outcomes for patients undergoing single- vs. multi-fraction SABR.

Methods: From 2011 to 2018, 217 patients (some patients were enrolled multiple times) were enrolled in a phase II individualized lung tumor SABR (iSABR) clinical trial (NCT01463423) that personalized dose and fractionation schemes (mostly 25 Gy in 1 fraction or 40-50 Gy in 4 fractions) based on tumor volume and location. We analyzed a subset of 187 patients (200 lung SABR treatments) who received SABR to a single tumor in one course. Patients were excluded for treatment to multiple tumors in a single course. Per protocol, treatments were performed using a highly conformal technique with sharp dose gradients toward the chest wall. Dosimetric, simulation CT, and treatment plan parameters were evaluated as potential predictors for CWT in tumors near the CW using univariate logistic regression and chi-squared analyses.

Results: Of the 200 lung SABR treatments, 138 were for tumors near the CW (defined as the CW receiving at least 65% of the prescription dose). Of these, 108 (78%) had overlap of the planning target volumes (PTV) with the CW. Thirty-eight patients (19.1%) developed CWT, of which 31 (15.6%) were grade 1, 7 (3.5%) were grade 2, and none were grade 3+. The rate of CWT was significantly higher in patients with a PTV overlapping the CW compared to those that were not (27% vs. 12%, p=0.02). The ratio of maximum CW dose to the prescription dose was a predictor of CWT (p=0.02). There was no difference in rate of CWT between 25 Gy/1 fraction and 40-50 Gy/4 fraction regimens (25% vs. 17%, p=0.24). This continued to hold true when looking at grade 2 toxicities only (p=0.25). There were no associations between CWT and 1-fraction CW V18 (p=0.12), 4-fraction CW V30 (p=0.76), 4-fraction CW V33.6 (p=0.81), or PTV volume (p=0.48).

Conclusions: For thoracic tumors near the CW, treatment with the iSABR protocol is safe without grade 3+ CWT. Overlap of the PTV with the CW and a higher ratio of maximum CW dose to the prescription dose are dosimetric predictors of mild grade 1-2 CWT. Although there are power limitations given the low event rate, there was not a statistically significant difference in the rate of CWT between 1-fraction 25 Gy SABR and 4-fraction 40-50 Gy SABR to tumors near the CW.

Keywords: SABR/SBRT, Chest Wall Toxicity, Dosimetric Parameters

OA14 NEW TECHNIQUES TO IMPROVE OUTCOME IN EARLY STAGE NSCLC PATIENTS TREATED WITH SURGERY OR RADIOTHERAPY,
TUESDAY, AUGUST 9, 2022 - 12:00–13:00

OA14.05 Intraoperative Molecular Imaging Guided Resection of CEACAM5+ Lung Tumors: First In-Human SGM-101 Lung Cancer Surgical Trial

F. Azari[1], R.P.J. Meijer[2], G.T. Kennedy[1], A. Chang[1], B. Nadeem[1], A. Din[1], I. Marfatia[1], F. CAILLER[3], A. Pèlegrin[4], A.L. Vahrmeijer[2], S. Singhal[1]

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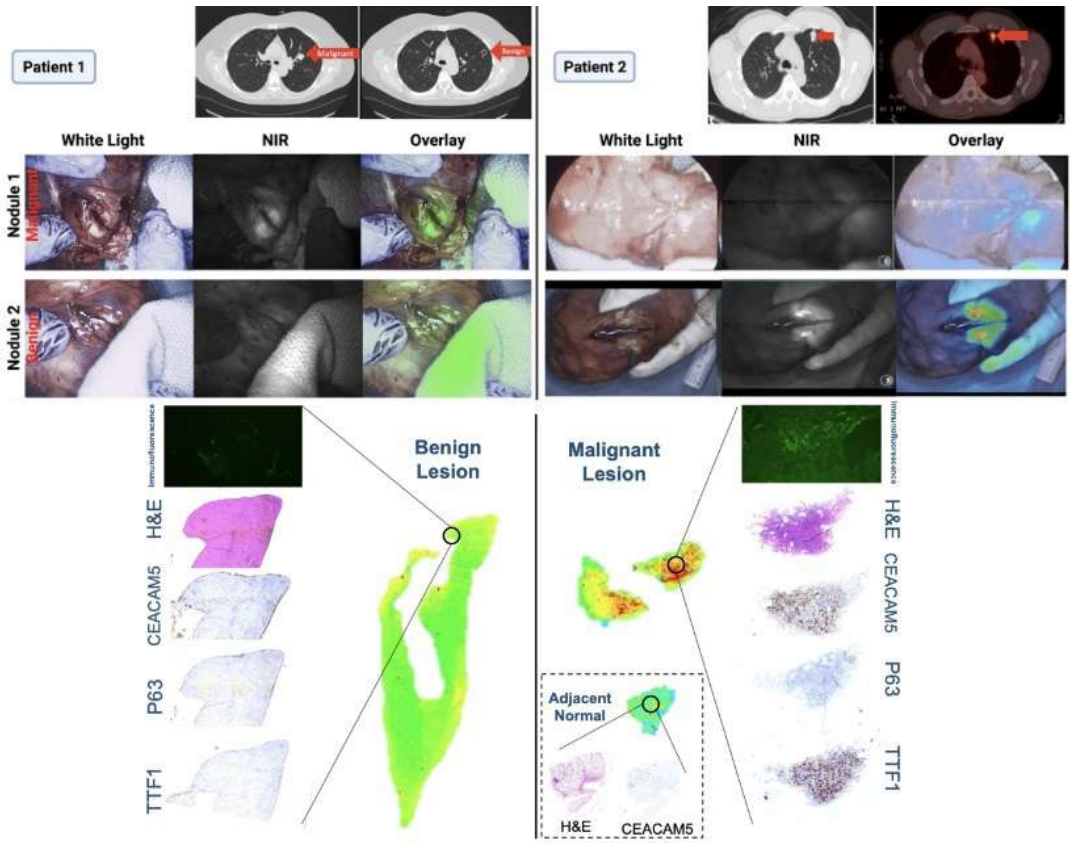
Introduction: Surgical management of NSCLC has multiple challenges including localization of sub-centimeter nodules, assessment of margin adequacy, and detection of occult lesions. Intraoperative molecular imaging (IMI) has emerged as a potential solution that addresses these surgical dilemmas. The purpose of our study (NCT04315467) was to evaluate the suitability of SGM-101, a CEACAM5 antibody targeted NIR fluorochrome, for molecular imaging guided lung cancer resections, as the glycoprotein is expressed in >80% of adenocarcinomas.

Methods: This is a proof-of-principle, non-randomized, open label trial of SGM-101 in lung cancer. Patients were divided into two arms. Patients with known CEACAM5+ gastrointestinal tumors with suspicion for lung metastasis were selected as proof-of principle positive control. Investigative arm included patients with lung nodules suspicious for primary lung malignancy. SGM-101 (10 mg) was infused up to 5 days prior to index operation and imaged using Quest Artemis NIR camera systems. In-situ, ex-vivo, and immunofluorescence microscopic SGM-101 localization was compared to final histopathologic diagnosis and IHC expression for TTF-1, CEA, CK 5/6, P63, and Ki-67.

Results: Prospective analysis of institutional cohort demonstrated 85% CEACAM5 expression in 33 NSCLC surgical patients with 4.67x predominance in adenocarcinomas ($p<0.05$). Subsequently, 10 patients (5 per arm) with 14 total concerning lesions were enrolled in the study. Median age was 66 (IQR: 58-69) with average lesion size of 0.91 [0.9-2] cm. Median serum CEA levels in the overall cohort were 3.0 ng/mL, specifically 5.11 ng/ml in metastasis group and 3.0±1.23 ng/mL in primary lung nodule group ($p<0.05$). SGM-101 localized to all CEACAM5+ malignant nodules (5/5) in the control group with mean TBR of 3.11±0.31 ($p<0.01$). In primary lung nodule group, SGM-101 identified all malignant nodules (4/7) and none of the benign lesions (3/7) fluoresced ($p<0.05$). Across both arms, mean TBR was 2.44±0.22 in malignant lesions and 1.1 in benign lesions ($p<0.05$). In malignant lesions, SGM-101 localized in areas of high CEACAM5 and TTF-1 IHC staining ($p<0.05$). SGM-101 identified all malignant lesions in both cohorts. Two non-fluorescent lesions were found to be benign. There was no SGM-101 related complications.

Conclusions: Our first in-human proof of principle clinical trial demonstrated SGM-101 localization to CEACAM5+ tumors with detection of real-time NIR fluorescence in-situ, ex-vivo, and on immunofluorescence microscopy. SGM-101 is a safe, receptor specific, and feasible IMI fluorochrome which should be further evaluated in randomized clinical trials.



Keywords: Intraoperative Molecular Imaging, CEACAM5, Fluorescence Guided Lung Cancer Surgery

OA14 NEW TECHNIQUES TO IMPROVE OUTCOME IN EARLY STAGE NSCLC PATIENTS TREATED WITH SURGERY OR RADIOTHERAPY,
TUESDAY, AUGUST 9, 2022 - 12:00–13:00

OA14.06 T-Cell Dynamics in Response to Neoadjuvant Atezolizumab in Early NSCLC by Antigen Response and T-Cell Receptor Sequencing

F. Oezkan[1,2,3,4,5], S. Hilz[6], J. Grindheim[6], A. Wallace[6], M. Seweryn[1,7], A. Reuben[8], J. Zhang[8], D.H. Owen[1,9], A. Nicholas[6], M. Yadav[6], D. Nagarkar[6], P. de Almeida[10], P. Ebert[10], E. Osborne[10], A. Johnson[6], J.M. Lee[11], P. Bunn[12], B.E. Johnson[13], J. Chaft[14], M.G. Kris[14], V.W. Rusch[14], K. Schulze[6], D.J. Kwiatkowski[15], I.I. Wistuba[8], D.P. Carbone[1,9]

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Introduction: The Phase II LCMC3 (NCT02927301) trial of neoadjuvant atezolizumab in early-stage NSCLC (primary efficacy population [patients with surgery, excluding EGFR/ALK alterations]) showed a 20% (29/143) major pathologic response (MPR, ≤10% viable tumor) rate. LCMC3 incorporated numerous biomarker analyses. We explored the impact of treatment on T-cell dynamics in the tumor and peripheral blood in association with pathologic response.

Methods: T-cell receptor ß-chain (TCR) sequencing using immunoSEQ® technology (Adaptive Biotechnologies) and Multiplex Identification of T-Cell Receptor Antigen (MIRA®, Adaptive Biotechnologies) specificity were performed on treatment-naive (pre-treatment) and post-atezolizumab (post-treatment) peripheral blood and tumor tissue. Clonality (Simpson), richness (downsampled) and T-cell fraction were computed for each sample, and for pre- vs post-treatment paired samples. Differential abundance analysis of paired samples was used to identify individual T-cell clone expansion post-treatment. *P*-values were unadjusted for multiple comparisons. In performing MIRA, T cells from pre-treatment, post-treatment or combined pre-and post-treatment samples were exposed to transgenes encoding tumor-specific neoantigens (median, 80 chosen/patient; range, 21-80) to identify TCRs responding to ≥1 tumor-specific antigen (MIRA+ TCRs).

Results: 134/143 patients (94%) had TCR sequencing performed on ≥1 sample type. Of these, 113 (84%) and 87 (65%) had paired pre- and post-treatment samples from the periphery or tumor, respectively; 80 (60%) had both pairs. In the tumor, T-cell clonality increased in patients with both nonsquamous (NSQ; n=80) and squamous (SQ; n=49) histology (*P*<0.01), and richness decreased (NSQ, *P*=0.05; SQ, *P*=0.03) following treatment. Clonality increased regardless of PD-L1 expression in patients with NSQ, and only with TPS<50% in SQ. In the periphery, clonality increased (*P*=0.01) and richness decreased (*P*=0.02) in SQ only. Pathologic response was associated with pre-treatment T-cell fraction (NSQ only, r=0.55, *P*<0.01), higher post-treatment clonality in the tumor (NSQ+SQ combined, r=0.26, *P*<0.01) and post-treatment T-cell fraction (NSQ+SQ combined, r=0.32; *P*<0.01). The change for pre- to post-treatment clonality showed a weak but significant positive correlation with response (NSQ+SQ combined, r=0.22; *P*=0.05). 60% (range, 10%-90%) of clones that expanded in the tumor were present in pre-treatment tumor samples. 24/30 (80%) MIRA-profiled patients had ≥1 MIRA+ TCR identified (recognizing a median [range] of 6% [1%-21%] of neoantigens tested). More MIRA+ TCRs were identified in post-treatment (n=3) MIRA samples than pre-treatment (n=10) samples (median [range], 40 [6-57] vs 6.5 [0-13], *P*=0.06; the remaining 17 patients were from combined timepoints). There was no difference between responders and non-responders in MIRA+ TCR numbers (median [range], 8.5 [0-57] vs 2 [0-100] for MPR=No [n=12] vs MPR=Yes [n=5]; *P*=0.84); notably, the patient with 100 MIRA+ TCRs (for 16/78 neoantigens tested) was the only complete responder (100% pathologic response) profiled with MIRA.

Conclusions: Neoadjuvant atezolizumab in early-stage NSCLC increased specific T-cell clone expansion in the tumor compared with pre-treatment, which was associated with better pathologic response. Higher pre-treatment T-cell fraction was associated with response in the NSQ subtype. The number of tumor antigen-specific T-cell clones alone post treatment did not differentiate pathologic responders from non-responders. Understanding T-cell dynamics of atezolizumab response, including tumor subtype-specific differences, may inform future neoantigen prediction and development of novel therapeutic concepts.

Keywords: T cell receptor sequencing, Early stage NSCLC, Neoadjuvant atezolizumab

OA15 PATIENT SELECTION IN ADVANCED NSCLC IMMUNOTHERAPY,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

OA15.03 Avelumab vs Chemotherapy for First-line Treatment of Advanced PD-L1+ NSCLC: Primary Analysis from JAVELIN Lung 100

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Introduction: Avelumab is an anti-PD-L1 antibody that has shown antitumor activity and an acceptable safety profile in patients with non-small cell lung cancer (NSCLC). We report results from the phase 3 JAVELIN Lung 100 trial, which compared first-line (1L) avelumab monotherapy (2 dose schedules) vs platinum-based doublet chemotherapy in patients with previously untreated PD-L1+ advanced NSCLC.

Methods: JAVELIN Lung 100 (NCT02576574) was an open-label, multicenter, phase 3 trial that enrolled adult patients with previously untreated metastatic or recurrent stage IV PD-L1+ (PD-L1 expression on ≥1% of tumor cells determined by Dako PD-L1 IHC 73-10 pharmDx) and EGFR/ALK-wild-type NSCLC. Patients were initially randomized 1:1 to receive avelumab 10 mg/kg every 2 weeks (Q2W) or platinum-based doublet chemotherapy every 3 weeks (Q3W) intravenously, stratified by histology. Following a protocol amendment based on pharmacokinetics/exposure analyses, patients were randomized 1:2:2 to receive avelumab 10 mg/kg Q2W, platinum-based doublet chemotherapy Q3W, or avelumab 10 mg/kg weekly (QW) for 12 weeks and Q2W thereafter, stratified by histology and PD-L1 expression cutoffs (high, ≥80%; moderate, ≥50%; and any, ≥1% of tumor cells). Primary endpoints were overall survival (OS) and progression-free survival (PFS) per independent review committee (IRC) in patients with high-expression PD-L1+ tumors (≥80% of tumor cells).

Results: 1,214 patients with PD-L1+ tumors (≥1% of tumor cells) were randomized to the avelumab Q2W (n=366), chemotherapy (n=526), or avelumab QW (n=322) arms. At data cutoff (October 2021), median follow-up was >41 months in all arms. No statistically significant difference in OS or PFS was observed between each of the avelumab arms and the chemotherapy arm (**Table**). Among patients with high-expression PD-L1+ tumors, 5.3% and 20.2 % of patients in the avelumab Q2W and QW arms vs 30.6% of patients in the chemotherapy arm received poststudy anti-PD-(L)1 treatment. Among all treated patients in the avelumab Q2W, avelumab QW, and chemotherapy arms, treatment-emergent adverse events (TEAEs) occurred in 95.8%, 96.9%, and 96.8%, including grade ≥3 TEAEs in 60.1%, 56.9%, and 64.8%, respectively.

Conclusions: JAVELIN Lung 100 did not meet its primary objective of demonstrating superior OS or PFS by IRC with 1L avelumab (Q2W or QW) vs platinum-based doublet chemotherapy in patients with high-expression PD-L1+ tumors. The safety profile of avelumab was consistent with that observed in previous studies of avelumab monotherapy.

Table				
PD-L1 expression cutoff (73-10 assay)	**≥80% of tumor cells (high-expression PD-L1+ population)**			
Treatment arm	**Avelumab Q2W(n=151)**	**Chemotherapy Q3W (n=216)**	**Avelumab QW (n=130)**	**Chemotherapy Q3W (n=129)**
OS, median (95% CI), months	20.1 (15.0-24.3)	14.9 (11.8-18.6)	19.3 (14.0-28.1)	15.3 (11.6-19.1)
Stratified HR for OS (95% CI)	0.85 (0.67-1.09)		0.79 (0.59-1.07)	
1-sided p value	0.1032*		0.0630*	
PFS by IRC, median (95% CI), months	8.4 (5.4-12.6)	5.6 (5.4-6.8)	7.5 (4.2-11.1)	5.6 (5.0-6.8)
HR for PFS (95% CI)	0.71 (0.54-0.93)		0.72 (0.52-0.98)	
1-sided p value	0.0070*		0.0196*	
*Did not meet predefined significance thresholds.				

Keywords: avelumab, NSCLC, first–line

OA15 PATIENT SELECTION IN ADVANCED NSCLC IMMUNOTHERAPY,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

OA15.04 Association Between KRAS/STK11/KEAP1 Mutations and Outcomes in POSEIDON: Durvalumab ± Tremelimumab + Chemotherapy in mNSCLC

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This abstract is under embargo until August 9 at 10:10 Vienna, Austria Time, CEST.

OA15 PATIENT SELECTION IN ADVANCED NSCLC IMMUNOTHERAPY,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

OA15.05 HUDSON: An Open-Label, Multi-Drug, Biomarker-Directed Phase 2 Study in NSCLC Patients Who Progressed on Anti-PD-(L)1 Therapy

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Introduction: HUDSON (NCT03334617) is a multi-arm umbrella trial for patients with advanced non-small-cell lung cancer (NSCLC) previously treated with platinum-doublet chemotherapy and anti-PD-(L)1 immunotherapy (separately or in combination) who had disease progression on prior anti-PD-(L)1 therapy. The study evaluates the efficacy, safety, and tolerability of multiple treatment combinations tailored by molecular alteration, with the goal of overcoming resistance to PD-(L)1 blockade. Here we present mature efficacy and safety results for the initial combinations - durvalumab plus: olaparib (PARP inhibitor; Module 1), danvatirsen (STAT3 inhibitor; Module 2), ceralasertib (ATR inhibitor; Module 3), and oleclumab (anti-CD73 antibody; Module 5).

Methods: Based on tumor molecular profile, patients were enrolled into either a biomarker-matched (Group A) or a biomarker-non-matched (Group B) cohort. Patients in Group B were further subdivided by primary or acquired resistance to prior anti-PD-(L)1 therapy, defined respectively as progression ≤24 weeks of starting treatment or >24 weeks after starting treatment. Assessment of overall response rate (ORR; primary endpoint), progression-free survival (PFS), and overall survival (OS) was used to decide whether to expand each initial cohort size from 20 to 40 patients. Safety was continuously monitored.

Results: Between January 26, 2018, and April 14, 2021, 255 patients were enrolled and treated with durvalumab plus olaparib (n=87), danvatirsen (n=45), ceralasertib (n=66; accrual ongoing to Group A cohort, data reported for n=21), or oleclumab (n=57). Baseline demographics and disease characteristics were generally balanced across treatment groups (Table); 41.4%, 44.4%, 50.0%, and 43.9% of patients in the respective groups had received ≥3 prior regimens, and 19.5%, 13.3%, 24.2%, and 21.1% had received ≥2 prior platinum-based therapies. ORR and 12-week/24-week disease control rates were numerically highest, and median PFS and OS numerically longest (Table), with durvalumab plus ceralasertib; within this module, efficacy appeared greatest in the biomarker-matched cohort. The majority of patients reported treatment-related adverse events (TRAEs); rates of grade ≥3 TRAEs and discontinuation due to TRAEs were numerically lower with durvalumab plus ceralasertib or oleclumab than with the other regimens (Table). The most common TRAEs were nausea, reported in 42.5%, 2.2%, 51.5%, and 7.0% of patients in the respective treatment groups, anemia (25.3%, 8.9%, 21.2%, 3.5%), fatigue (20.7%, 13.3%, 16.7%, 14.0%), decreased appetite (9.2%, 4.4%, 22.7%, 7.0%), diarrhea (12.6%, 11.1%, 15.2%, 12.3%), and vomiting (20.7%, 4.4%, 28.8%, 1.8%).

Conclusions: Durvalumab plus ceralasertib demonstrated a promising efficacy signal, with a tolerable safety profile, in patients with advanced/metastatic NSCLC following failure of anti-PD-1/PD-L1-containing immunotherapy and ≥1 platinum-doublet regimen.

	Durvalumab plus											
	Olaparib				Danvatirsen		Ceralasertib			Oleclumab		
Baseline characteristics	**n=87**				**n=45**		**n=66**			**n=57**		
Median age, years	63				65		64			64		
Male, %	57.5				51.1		65.2			52.6		
Adenocarcinoma /	71.3 /				68.9 /		66.7 /			66.7 /		
Squamous cell carcinoma /	20.7 /				26.7 /		25.8 /			22.8 /		
Other histology, %	8.0				4.4		7.5			10.5		
≥3 metastatic sites, %	52.9				13.3		54.5			40.4		
PD-L1 positive (≥1%) / negative / unknown, %	25.3 / 31.0 / 43.7				46.7 / 24.4 / 28.9		39.4 / 33.3 / 27.3			54.4 / 22.8 / 22.8		
Efficacy by Group and cohort	**A HRRm n=21**	**A LKB1 n=21**	**B PRI n=22**	**B ACQ n=23**	**B PRI n=23**	**B ACQ n=22**	**A ATM n=21**	**B PRI n=20**	**B ACQ n=25**	**A CD73h n=23**	**B PRI n=9**	**B ACQ n=25**
ORR (all PRs), %	9.5	4.8	0	4.3	0	0	28.6	15.0	8.0	0	0	4.0
SD ≥35 days,* %	42.9	23.8	59.1	56.5	47.8	63.6	47.6	45.0	64.0	34.8	22.2	56.0
12-week disease control rate, %	38.1	9.5	45.5	52.2	13.0	40.9	71.4	55.0	56.0	30.4	11.1	36.0
24-week disease control rate, %	19.0	9.5	13.6	26.1	0	27.3	57.1	40.0	32.0	8.7	11.1	24.0
Median PFS, months	2.79	1.41	3.38	4.17	1.68	3.09	8.41	4.86	4.63	1.61	1.41	2.69
Median OS, months	9.63	5.75	7.16	15.51	6.01	11.20	22.80†	11.79	19.06	10.97	7.06	12.78
Safety and tolerability	**n=87**				**n=45**		**n=66**			**n=57**		
Median treatment duration,‡ months	3.68				2.76		7.33			2.86		
Any TRAE, %	77.0				73.3		78.8			59.6		
Any grade ≥3 TRAE, %	34.5				37.8		22.7			15.8		
TRAE resulting in discontinuation, %	9.2				15.6		7.6			5.3		
Death due to AEs (none due to TRAEs), %	1.1				6.7		3.0			1.8		

*≥40 days for durvalumab plus danvatirsen or ceralasertib. †Data are still accruing; this median value for OS may change. ‡Median duration of durvalumab treatment. ACQ, acquired resistance; AE, adverse event; CD73h, high expression of CD73 biomarker-matched cohort; HRRm, homologous recombination repair mutated biomarker-matched cohort; LKB1, aberration in LKB1/STK11 biomarker-matched cohort; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRI, primary resistance; SD, stable disease; TRAE, treatment-related adverse event

Keywords: Anti-PD-(L)1 resistance, Platform trial, Combination therapy

OA15 PATIENT SELECTION IN ADVANCED NSCLC IMMUNOTHERAPY,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

OA15.06 Pooled Analysis of Outcomes with Second-Course Pembrolizumab Across 5 Phase 3 Studies of Non-Small-Cell Lung Cancer

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Introduction: Pembrolizumab as monotherapy and in combination with chemotherapy substantially prolongs OS and PFS compared with chemotherapy alone in patients with advanced or metastatic NSCLC without *EGFR/ALK* alterations. In the clinical trial setting, patients whose disease progressed after completing 35 cycles (~2 years) of pembrolizumab were eligible to receive a second course of pembrolizumab. We present outcomes from an exploratory pooled analysis of patients who began second-course pembrolizumab monotherapy.

Methods: This analysis pooled patients with advanced or metastatic NSCLC treated with pembrolizumab monotherapy (**cohort 1**) in the KEYNOTE-024, KEYNOTE-042, and KEYNOTE-598 studies, and pembrolizumab plus chemotherapy (**cohort 2**) in the KEYNOTE-189 and KEYNOTE-407 studies (global studies, NCT02142738, 02220894, 03302234, 02578680, 02775435; extension studies, NCT03850444, 03950674, 03875092). Patients included in this analysis received second-course pembrolizumab (up to 17 cycles) following PD after either completing 35 cycles of pembrolizumab (with/without chemotherapy) with SD or better or stopping pembrolizumab before 35 cycles due to CR. Efficacy was analyzed in the ITT population and safety in the as-treated population.

Results: In cohort 1, among 148 patients who completed 35 cycles of pembrolizumab and experienced PD, 58 patients received second-course pembrolizumab and were included in this analysis. Cohort 2 included 16 of 55 patients who completed 35 cycles of pembrolizumab (as part of pembrolizumab plus chemotherapy), experienced PD, and received second-course pembrolizumab. 18/58 patients (31%) in cohort 1 and 7/16 (44%) in cohort 2 had squamous histology, and 47/58 (81%) and 7/16 (44%), respectively, had PD-L1 TPS ≥50%. Median (range) time from stopping first-course pembrolizumab to starting second course was 11.7 (3.8-35.6) months in cohort 1 and 6.3 (0.9-18.2) months in cohort 2. Median duration on second course was 8.3 months in cohort 1 and 7.6 months in cohort 2, with an estimated 62% and 59%, respectively, remaining on second course at 6 months. ORR by investigator review during second-course pembrolizumab was 19% in cohort 1 and 6% in cohort 2 (**Table**). 14 patients (24%) in cohort 1 and 4 (25%) in cohort 2 experienced treatment-related AEs on or after second course, of which 3 (5%) and 1 (6%) were grade 3-4, respectively; none were grade 5.

Conclusions: A second course of pembrolizumab monotherapy was feasible, associated with antitumor activity and clinically meaningful benefit, with manageable safety in patients with advanced or metastatic NSCLC who experienced PD after completing first-course pembrolizumab with/without chemotherapy. These data support pembrolizumab retreatment upon PD.

Table		
	Cohort 1	**Cohort 2**
	Pembrolizumab Monotherapy	**Pembrolizumab + Chemotherapy**
	n = 58	**n = 16**
OS, median (95% CI), moa	27.5 (21.7-NR)	NR (NR-NR)
6-mo OS rate, % (95% CI)	*85.4 (72.9-92.4)*	*86.2 (55.0-96.4)*
PFS,a,b median (95% CI), mo	8.2 (5.3-14.0)	7.7 (1.8-NR)
6-mo PFSb rate, % (95% CI)	*59.6 (45.0-71.5)*	*58.3 (27.0-80.1)*
ORR,b % (95% CI)	19.0 (9.9-31.4)	6.3 (0.2-30.2)
SD, n (%)	31 (53.4)	7 (43.8)
DCR, n (%)	42 (72.4)	8 (50.0)
DCR, disease control rate (CR + PR + SD); NR, not reached; SD, stable disease.		
[a]From start of second-course pembrolizumab.		
[b]By investigator review per RECIST v1.1.		

Keywords: pembrolizumab, retreatment, non–small-cell lung cancer

Mini Oral Abstract Sessions

MA01 MOLECULAR SUBTYPES AND PROGNOSTIC FACTORS FOR SCLC AND NEUROENDOCRINE TUMORS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA01.03 Exploiting DNA Methylation for Classification of SCLC Subtypes from Liquid Biopsies Using a Robust Machine Learning Approach

S. Heeke, C.M. Gay, M.R. Estecio, A. Stewart, H. Tran, B. Zhang, X. Tang, M.G. Raso, K. Concannon, L. Guimaraes De Sousa, W.E. Lewis, K. Kondo, M.B. Nilsson, Y. Xi, L. Diao, Q. Wang, J. Zhang, J. Wang, I.I. Wistuba, L.A. Byers, J.V. Heymach
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Introduction: Small cell lung cancer (SCLC) is a highly aggressive cancer with limited treatment options and a generally poor prognosis that has not appreciably changed despite recently approved therapies. Importantly, therapeutic options for SCLC patients have been focused on unselected populations as SCLC was thought to be a relatively homogenous malignancy in the past. Recently, our group and others identified four major distinct subgroups of SCLC (Gay CM et al. Cancer Cell 2021). Three of the four subtypes are defined by the predominant expression of a specific transcription factor, ASCL1 (SCLC-A), NEUROD1 (SCLC-N) and POU2F3 (SCLC-P) while the fourth subtype is defined by an inflamed phenotype (SCLC-I). We demonstrated that these subgroups are associated with distinct therapeutic vulnerabilities. For example, in the phase III IMpower133 trial which assessed the addition of atezolizumab to platinum-etoposide chemotherapy, the SCLC-I subtype had the highest benefit of the addition to immunotherapy (Gay CM. et al. Cancer Cell. 2021). Consequently, we hypothesized that patients would benefit from a subtype-specific treatment approach. Therefore, the development of robust and practical selective biomarkers to define those subtypes in a clinical context is urgently needed. We have previously reported on a DNA methylation-based classifier (SCLC-DMC) with 98% accuracy (AACR 2022). Here we extend our initial findings by translating our initial classifier in a liquid biopsy assay (SCLC-cfDMC) with high accuracy across multiple cohorts of plasma samples to enable personalized treatments in SCLC based on liquid biopsies.

Methods: We used reduced representation bisulfite sequencing (RRBS) with a protocol that we have specifically amended for the use of fragmented DNA from FFPE and cfDNA samples in order to analyze > 100 samples across different clinical cohorts of predominantly extensive-stage SCLC patients. Based on our initial SCLC-DMC we used consensus classification by combining 2000 extreme-gradient boosting machine learning models in order to classify samples based on their overlap in prediction with samples with >50% consensus being classified into the respective subtype.

Results: By applying our SCLC-DMC on additional cohorts we could confirm the >90% accuracy compared to our initial classification using RNAseq. While the tissue-trained SCLC-DMC performed well on the plasma samples with >80% accuracy, we could adapt the algorithm by maintaining the same DNA methylation sites and increased the classification accuracy to >90%, a significant and clinically relevant improvement. Importantly, we could demonstrate that clinical outcome with our DNA methylation based classification is not different to classification based on our RNA-based approach (SCLC-A HR (95%CI) RNA vs SCLC-DMC = 1.57 (0.84-2.95); SCLC-N = 0.93 (0.4-2.15)) highlighting that DNA methylation-based classification can enable clinically relevant subtyping in SCLC.

Conclusions: SCLC subtyping has paved the way to enable personalized treatments but robust classification in clinical trials needs to be established. Here we demonstrate that DNA methylation can provide accurate classification of SCLC in clinical samples. Additionally, we highlight that this approach can be used in a liquid biopsy setting dramatically expanding access to such a classification system to enable subtype-specific clinical trials in SCLC.

Keywords: SCLC, Liquid Biopsy, DNA methylation

MA01 MOLECULAR SUBTYPES AND PROGNOSTIC FACTORS FOR SCLC AND NEUROENDOCRINE TUMORS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA01.04 Molecular Subtypes of Surgically Resected Small Cell Lung Cancer: Expression Pattern and Prognostic Relevance

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Introduction: Although our knowledge of small cell lung cancer (SCLC) molecular subtypes has grown significantly over the recent years, translating this information into clinics has been less effective. This may in part be due to the unique nature of SCLC where most patients present at an inoperable stage, and diagnostic biopsies do not provide enough material for profiling studies that can also address tumor heterogeneity. Therefore, the tissue distribution and prognostic relevance of subtype-specific proteins (ASCL1, NEUROD1, POU2F3, YAP1) are largely unexplored in SCLC.

Methods: Expression of subtype-specific transcription factors and P53 and RB1 proteins were measured by immunohistochemistry (IHC) in 386 surgically resected SCLC samples. Correlations between subtype-specific proteins and in vitro efficacy of various therapeutic agents were investigated by proteomics and cell viability assays in 26 human SCLC cell lines.

Results: Besides SCLC-A (ASCL1-dominant), SCLC-AN (combined ASCL1/NEUROD1), SCLC-N (NEUROD1-dominant) and SCLC-P (POU2F3-dominant), IHC and cluster analyses identified a quadruple-negative SCLC subtype (SCLC-QN). No unique YAP1-subtype was found. The highest overall survival rates were associated with non-neuroendocrine (SCLC-P and SCLC-QN) whereas the lowest with neuroendocrine (SCLC-A, SCLC-N, SCLC-AN) subtypes. In univariate analyses, high ASCL1 and POU2F3 expression was associated with poor and good prognosis, respectively. Notably, high ASCL1 expression remained an independent negative prognosticator in a multivariate model as well. High POU2F3 and YAP1 protein abundances correlated with sensitivity and resistance to standard-of-care chemotherapeutics, respectively. Specific correlation patterns were also found between the efficacy of targeted agents and subtype-specific protein abundances.

Conclusions: This is the first study on a large cohort of surgically resected specimens investigating the clinicopathological relevance of SCLC molecular subtypes. Differential expression of ASCL1, NEUROD1 and POU2F3 defines SCLC subtypes. No YAP1-subtype can be distinguished by IHC. ASCL1 and POU2F3 expressions have prognostic significance. Proteomic and cell viability assays of human SCLC cell lines reveal distinct vulnerability profiles defined by transcription regulators.

Keywords: small cell lung cancer, molecular subtypes, prognosis

MA01 MOLECULAR SUBTYPES AND PROGNOSTIC FACTORS FOR SCLC AND NEUROENDOCRINE TUMORS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA01.05 Immuno-microenvironment (TIME) Heterogeneity of Small Cell Lung Cancer (SCLC) Stratified by Molecular Subtypes

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Introduction: Small cell lung cancer (SCLC) is a highlyaggressive and refractory lung cancer. Most patients respond to first-linechemotherapy but relapse rapidly, resulting in a relatively poor prognosis. Inthe past few years, immunotherapy, especially the immune checkpoint inhibitorsrepresented by PD-L1 inhibitors, has made initial progress in SCLC. Butdifferent patients respond differently to treatment, and it is necessary todetermine which part of patients benefit the most.

Methods: 81 samples from George et al were involved inthe study. Molecular subtypes (SCLC-A/N/P/Y) were determined of each case by calculatingthe z-score of ASCL1, NEROUD1, POU2F3, YAP1. The ImmuneScore, calculated by Estimatepackage on R software, the abundance of immunocytes, estimated by CIBERSORTx, andimmune checkpoint genes were compared among four subtypes. Differentiallyexpressed factors were further verified by 48 resected Formalin-Fixed andParaffin-Embedded (FFPE) SCLC tissues on mRNA (Nanostring nCounter platform)and protein (Nanostring digital spatial profiling, DSP and immunohistochemistry,IHC) levels based on z-score calculated by mRNA data. Kruskal–Wallis and Wilcoxwere performed by R software (4.1.2 version) to make overall comparisons andpairwise comparisons.

Results: 81 cases were assigned into SCLC-A (n=33,40.7%), SCLC-N (n=16,19.8%), SCLC-P (n=10,12.3%)and SCLC-Y (n=22,27.2%) group. ImmueScore of SCLC-P/Y was higher than SCLC-A/N (p=0.08). CIBERSORTxresults indicated SCLC-P had a higher absolute abundance CD8+ T cells (p=0.026),and a higher absolute abundance of memory B cells, plasma cells, T cells memoryactivated, T cells follicular and M2 macrophages than SCLC-A or SCLC-N subtypes.Monocytes had a higher expression on SCLC-Y (p=0.022). And T cells CD4 memory restinghad a higher expression on SCLC-Y than SCLC-A subtype. While B cells naive ofSCLC-N was higher than SCLC-Y. Besides, there is a tendency for high expressionof PD-1 in SCLC-P (p=0.29). The RNA data of 48clinical cases found that in the four groups of SCLC-A (n=22,45.8%), N(n=11,22.9%), P(n=4,8.3%), and Y(n=11,22.9%), and the mainimmunological markers (CD4, CD8) and immune checkpoints (PD-1, PD-L1) of the SCLC-Psubtype were shown high expression tendency. At the protein level, DSP dataalso showed that the main immunological markers (CD4, CD8) and immunecheckpoints (PD-1, PD-L1) were highly expressed in the SCLC-P, and representativeIHC staining slides also confirmed that.

Conclusions: Our experimental analysis confirmsheterogeneity of immune microenvironment among different subtypes of SCLC,which may provide an explanation for the different benefits of immunotherapy inpatients. Compared with other subtypes, the P subtype has the highest level ofimmune cells, and shows the characteristics of high T cell expression, and highimmune checkpoints expression of PD-1 and PD-L1, indicating that the SCLC-P subtypeis more likely to have a specific response to immunotherapy.

Keywords: small cell lung cancer, Immuno-microenvironment (TIME), molecular subtypes

MA01 MOLECULAR SUBTYPES AND PROGNOSTIC FACTORS FOR SCLC AND NEUROENDOCRINE TUMORS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA01.07 From Molecular to Histological Characterization of Lung Carcinoids via Computer Vision and Spatial Genomics

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Introduction: Lung neuroendocrine tumors (LNETs) are rare cancers subdivided into low-grade (typical) and intermediate-grade (atypical) carcinoids. Atypical carcinoids are more aggressive, with a 4- to 6-fold increased risk of developing metastatic disease and to relapse within the first 10 years after surgical treatment. We performed the first comprehensive molecular characterization of lung carcinoids and identified 3 robust molecular clusters; A1, A2 and B (Alcala, Nature Com., 2019; Gabriel, Gigascience, 2020). These clinically relevant groups have different prognosis: carcinoids B have a 10-year overall survival of 60% versus ~80% for groups A1 and A2. This study revealed the existence of supra-carcinoids, highly infiltrated and aggressive specimens with carcinoid-like morphology and a molecular profile of large cell neuroendocrine carcinoma (LCNEC). These molecular groups only partially matched the current histopathological classification and aggressive carcinoids cannot be identified by current diagnostic tools, requiring complex multi-omics analyses. Deep learning (DL) algorithms have shown utility for cancer diagnosis and prognosis (Tran, Genome Med. 2021). Hence, we have implemented DL techniques to discriminate histological features associated with aggressive cases. Spatial proteomics helps us to assess the spatial immune profile of molecular groups, including supra-carcinoids. Reconciling the histological and molecular classification of lung carcinoids is key to facilitating their diagnosis and thus improving the clinical management of patients.

Methods: We generated and assembled an unprecedented histopathology image database of >650 LNET patients. Hematoxylin and eosin (H&E) stained whole slide images (WSI) were used to train an unsupervised anomaly detection algorithm. This class of DL algorithms, meets our specific need to work without any prior knowledge of what an anomaly is, allowing us to locate the discriminating region of aggressive carcinoids (Mathian, ECCV 2022). To refine the characterization of the identified regions, we trained DL algorithms to estimate the proliferation index, tumour-infiltrated lymphocytes and mitotic cells at the WSI scale, rather than on predefined regions of interest, as is usually the case in routine diagnosis. To link molecular and morphological features, we performed spatial proteomic profiling of a panel immune genes in a series of well-represented molecular groups.

Results: Subtle histological features discriminating molecular groups were extracted via our anomaly detection model, yielding the first molecular features specific to group B. Correlation of these morphological features with hotspot regions detected on WSI immunohistochemistry facilitated their interpretation. For the spatial quantification of immune protein expression, we have so far observed that while for many carcinoids it is difficult to find areas of high immune infiltration, those with such areas also generally have a molecular profile more similar to LCNECs.

Conclusions: The identification of histological features specific to aggressive s carcinoids would represent a major advance for diagnosis and clinical decision making in LNETs, as it would allow the translation of molecular classification into the clinical setting without the need to generate costly and complex to analyse molecular data. Furthermore, identification of the immune profile of supra-carcinoids will initiate our understanding of the potential evolution between low- and high-grade lung neuroendocrine neoplasms.

Keywords: lung carcinoids, deep-learning, histopathology

MA01 MOLECULAR SUBTYPES AND PROGNOSTIC FACTORS FOR SCLC AND NEUROENDOCRINE TUMORS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA01.08 Impact of [18F]FDG PET/CT-derived Metabolic Parameters on Outcomes in Extensive-stage SCLC

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Introduction: Small-cell lung cancer (SCLC) is a highly aggressive neuroendocrine lung cancer, accounting for 10-15% of all lung cancers, commonly classified in limited stage (LS-SCLC) and extensive stage (ES-SCLC). Despite the introduction of chemoimmunotherapy as new standard first-line therapy for ES-SCLC, the benefit of addition of the programmed-death ligand 1 (PD-L1) inhibitors is limited to a subset of patients, suggesting the importance of identifying predictive biomarkers of response. [18F]FDG-PET/CT is commonly used for the staging and therapeutic planning of SCLC patients. Metabolic parameters derived from [18F]FDG-PET could predict patient outcomes by measuring the extension of metabolically active tumor (metabolic tumor volume [MTV]) or its metabolic heterogeneity (total lesion glycolysis [TLG]).

Methods: We retrospectively collected patients with pathologically confirmed diagnosis of SCLC, who had undergone an [18F]FDG PET/CT scan within 30 days before the start of first-line treatment for ES-SCLC (platinum-etoposide in 76 patients, PE plus PD-L1 inhibitor in 5 patients, carboplatin plus paclitaxel in 4 patients and carboplatin monotherapy in 1 patient). We calculated metabolic parameters, MTV and TLG, by summing each single lesion's MTV and TLG respectively. The primary endpoint of the study was overall survival (OS), defined as the time from [18F]FDG PET/CT scan acquisition to death from any cause.

Results: A total of 86 patients with ES-SCLC were included (median age 68 years, 45% female). Patients with hyponatremia, hypoalbuminemia and elevated LDH levels were associated with greater number of lesions, greater total MTV, and higher total TLG at [18F]FDG-PET/CT/CT scan. At a median follow-up of 20.9 months, the median OS was 11.1 months, and was longer among patients with Na+ ≥135 mEq/L (11.4 vs 4.0 months; p=0.003), with normal albumin levels (11.5 vs 4.4 months, p=0.004), in those with normal LDH levels (11.9 vs 6.3 months; p=0.03) and without bone metastases (14.2 vs 6.8 months; p=0.01). The median PFS was 6.2 months and was shorter in patients with brain metastases (4.7 vs 6.5 months, p=0.01). After correcting for potential confounding factors, total MTV was independently associated with OS (HR: 1.003 [95%CI: 1.002 - 1.006]; p<0.001) and PFS (HR: 1.003 [95%CI: 1.0002 - 1.005]; p=0.034), while SUVmax was independently associated with PFS (HR: 1.04 [95%CI 1.02 - 1.07]; p<0.001). Using a total MTV cut-off of 245.7 cm3 calculated by ROC curve analysis to predict survival at 6 months, low total MTV (<245.7 cm3) was associated with longer OS (11.9 vs 4.8 months, p<0.001) and longer PFS (7.1 vs 4.7 months, p=0.003). After correcting for confounding factors, total MTV <245.7 cm3 was independently associated with the risk of death (HR: 7.15 [95%CI: 2.48 - 20.63]; p<0.001) but not with the risk of progression.

Conclusions: Our preliminary data showed that total MTV could provide prognostic information in patients with ES-SCLC, suggesting a potential role as stratification factor in clinical trials.

Keywords: FDG-PET, Prognostic factor, ES-SCLC

MA01 MOLECULAR SUBTYPES AND PROGNOSTIC FACTORS FOR SCLC AND NEUROENDOCRINE TUMORS,
SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA01.09 Characterising Aggressive Pulmonary Carcinoids Through Integrative Omics Analysis Within the lungNENomics Project

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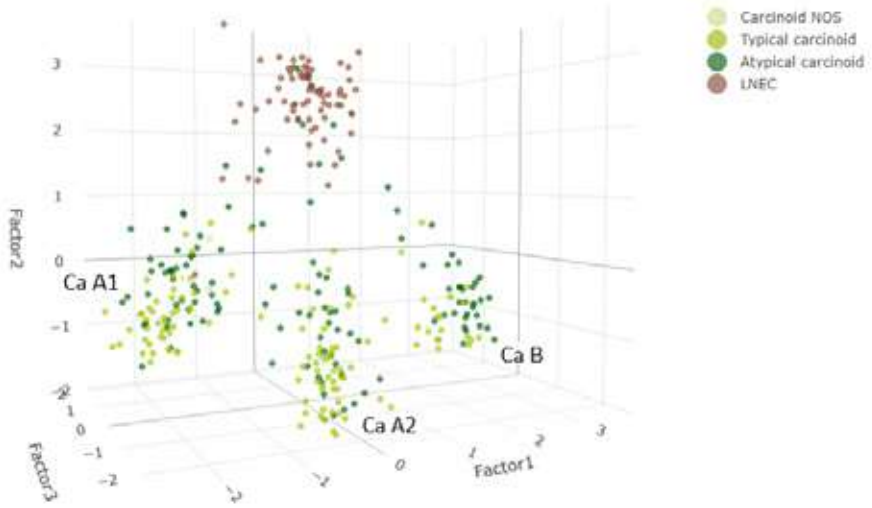
Introduction: Typical and atypical carcinoids are well differentiated lung neuroendocrine tumours (LNETs) that belong to the group of lung neuroendocrine neoplasms, which also include highly aggressive lung neuroendocrine carcinomas (LNECs). Although carcinoids show relatively good prognosis in comparison to carcinomas, metastatic disease and relapse do occur. In a previous study we introduced the concept of molecular groups of carcinoids: A (further separated into A1 and A2) and B, which did not clearly correspond to individual histological types. Additionally, we identified six tumours, termed supra-carcinoids, that displayed genuine carcinoid-like morphology, but had clinical and molecular characteristics of LNECs. In comparison to carcinoid A, overall survival rates were lower for the more aggressive carcinoid B and supra-carcinoid tumours. As yet, little is known about the underlying biology or developmental origins of these two groups of aggressive carcinoids, hampering efforts to identify predictive markers and suitable therapeutic options.

Methods: To address these questions we aim to perform comprehensive multi-omic molecular, morphological and clinical characterisation of LNETs. We have generated WGS, RNA sequencing, and DNA methylation array data from a new cohort of 205 LNET patients, enriched for the very rare atypical type. These data have been combined with previously published LNET and LNEC data to perform integrative analysis using multi-omics factor analysis (MOFA), resulting in a molecular map of lung neuroendocrine neoplasms for exploration. Subsequently, we applied the Pareto optimum theory over the map to identify specialised tumour profiles resulting from natural selection for cancer tasks.

Results: Through the integration of multi-omic data with MOFA we obtained five axes (factors) of variation. Visualising the first three factors results in a tetrahedron, with each vertex corresponding to a previously proposed molecular group (Figure 1). Each was characterised by specific clinical and genomic features, as well as cancer-task specialisation, with enrichment for older males with MEN1 alterations and chromosome 11 loss in the more aggressive carcinoid B. Factor 2 separated the high grade LNEC from LNET, and was strongly associated with overall survival and level of neutrophil infiltration. Along Factor 2 are a subset of carcinoids within the LNEC group (supra-carcinoids), whilst others appeared to straddle the carcinoid/carcinoma boundary, suggesting potential progression from an indolent to a more aggressive phenotype through the acquisition of molecular alterations and changes in microenvironment.

Conclusions: Through this work we have identified molecular and morphological characteristics of aggressive pulmonary carcinoids, which may assist in the clinical management of this rare disease.



Keywords: pulmonary carcinoid, molecular characterisation, genomics

MA02 MOLECULAR UNDERPINNINGS OF LUNG CANCER HISTOLOGICAL DIFFERENTIATION AND TARGETED THERAPEUTICS, SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA02.03 The Evolution of Lung Neuroendocrine Tumors

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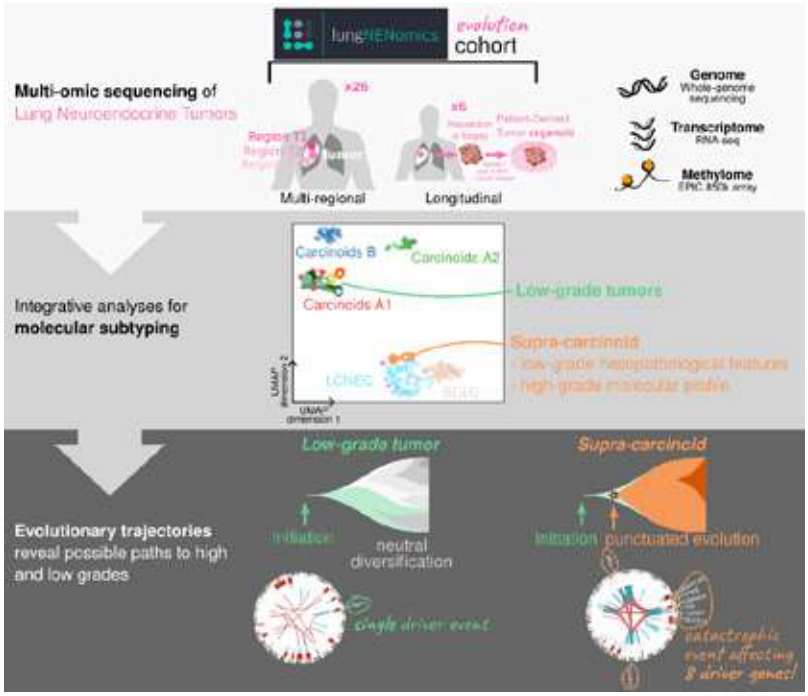
Introduction: In the context of the *lungNENomics* project, we have generated comprehensive molecular profiles of the rare and understudied lung neuroendocrine tumors (LNETs). We revealed three molecular groups of LNETs that challenge the current WHO classification: low-aggressive groups A1 and A2, and the more aggressive group B. Additionally, we revealed the existence of a subgroup of very aggressive LNETs, that we named supra-carcinoids, with the histopathological features of LNETs but the molecular and clinical characteristics of the higher-grade large-cell neuroendocrine carcinoma. Nevertheless, how tumors from each molecular group originate, and how some tumors evolve toward more aggressive phenotypes remains a mystery.

Methods: We combined a unique cohort of 26 tumors with surgically resected pieces from multiple-regions (total of *n*=71 regions) with state-of-the art organoid models to dissect intra-tumor heterogeneity in LNETs and reconstruct the timeline of evolution of LNETs. To do so, we performed multi-omic sequencing (RNA-seq, whole-genome, EPIC methylation arrays) of all tumor regions and called all types of genomic alterations (small variants, copy number variants, structural variants). We then inferred the evolutionary trajectory of each tumor from the distribution of variant allelic fractions and copy number variant calls. We finally integrated genomic data with expression and methylation data to assign the different regions to the known molecular profiles of LNETs.



Results: We find that evolutionary trajectories can strongly vary across LNETs. Low-grade, A1-group tumors can be initiated by as little as a single driver alteration, followed by the slow accumulation of neutral (non-driver) alterations under the influence of weak age-related endogenic mutational processes. At the other end of the spectrum, supra-carcinoids can evolve following catastrophic chromosomal events such as chromothripsis that simultaneously affect multiple cancer genes, in a textbook example of punctated evolution, fueled by more diverse mutational processes spanning small variants and large structural rearrangements. An organoid model of supra-carcinoid further allows the longitudinal study of evolution and reveals fast turnover of intra-tumor diversity due to recurrent selective sweeps.

Conclusions: We provide the first dive into the evolution of the rare lung neuroendocrine tumors and highlight pathways to increased aggressiveness. Patient-derived tumor organoid models developed across all LNET grades further promise to allow testing hypotheses regarding the initiation and progression of these tumors.

This work is funded by the Worldwide Cancer Research (2020 Grant Round), NET Research Foundation (2019 Investigator Award), and Institut National du Cancer (INCa PRT-K-2017).

Fernandez-Cuesta and Foll jointly supervised this work.

Keywords: cancer evolution, neuroendocrine tumors, organoids

MA02 MOLECULAR UNDERPINNINGS OF LUNG CANCER HISTOLOGICAL DIFFERENTIATION AND TARGETED THERAPEUTICS, SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA02.04 Molecular Drivers and Therapeutic Targets for Neuroendocrine Transformation in Lung Cancer

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Introduction: Histological transformation from lung adenocarcinoma (LUAD) to an aggressive neuroendocrine (NE) derivative resembling small cell carcinoma (SCLC) is a signature example of lineage plasticity in cancer. NE transformation is the primary mechanism of acquired resistance in up to 14% of *EGFR*-mutant LUADs. Despite this high prevalence, little is known about the molecular alterations occurring during NE transformation in human tumors. The high prevalence, together with the fact that transformed SCLC has a notably poor prognosis, make in-depth understanding of NE transformation in lung cancer highly clinically relevant and a critical need. A paucity of well-annotated paired pre- and post-transformation clinical samples has been a major hurdle in defining the genetic and epigenetic landscape of NE transformation, a problem we have addressed and successfully overcome in the current study.

Methods: In this study we performed multi-omic (genomic, transcriptomic, epigenomic and proteomic) characterization of NE transformation in combined LUAD/SCLC histology (n=22); pre-transformation LUADs (n=5) and post-transformation SCLCs (n=3); never-transformed LUADs (n=15); and *de novo* SCLCs (n=18) clinical specimens. To identify therapeutic targets that can delay and/or reverse NE transformation, we performed pharmacological inhibition studies in *EGFR*-mutant patient-derived xenograft (PDX) model. Finally, we performed single-cell RNA sequencing of clinical samples to identify subtype switching during NE transformation.

Results: Our results suggest that NE transformation is primarily driven by transcriptional reprogramming rather than mutational events and indicate that the resulting SCLC retains transcriptomic and methylation profiles of their previous LUAD state. Interestingly, chromosome 3p arm loss was identified to be a novel predictive biomarker for NE transformation. Gene expression and epigenetic profiling showed upregulation of key lineage determining transcription factors like FOXN4, ONECUT2, and POU3F2 during NE transformation. Furthermore, we observed a concurrent suppression of NOTCH signaling, innate immunity; and antigen presentation throughout the process of NE transformation. We also observed a consistent upregulation of WNT signaling and PI3K/AKT signaling in NE-transformed samples. Single-cell RNA sequencing confirmed immunosuppression and upregulation transcription factors like ASCL1 as early events of NE transformation. Pharmacologic inhibition of AKT in combination with osimertinib prevented relapse and NE transformation in an EGFR-mutant patient-derived xenograft model, and inhibition of AKT signaling re-sensitized resistant LUAD tumors to osimertinib.

Conclusions: In this study, we report the first comprehensive multi-omic (genomic, transcriptomic, epigenomic, and proteomic) characterization of lung adenocarcinoma to small cell lung cancer transformation in a large cohort of clinical samples. We provide novel insights into molecular drivers and potential therapeutic vulnerabilities of this neuroendocrine transformation in lung cancer. Furthermore, our study supports the role of targeting the AKT signaling pathway in delaying neuroendocrine relapse in *EGFR*-mutant lung adenocarcinoma.

Keywords: lineage plasticity, biomarkers, therapeutic resistance

MA02 MOLECULAR UNDERPINNINGS OF LUNG CANCER HISTOLOGICAL DIFFERENTIATION AND TARGETED THERAPEUTICS, SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA02.05 Dynamic Mutation Profiles of SCLC Transformation in NSCLC Patients Harboring Concurrent EGFR/TP53/RB1 Mutations

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Introduction: Small cell lung cancer (SCLC) transformation remains one of the unsettled resistant mechanisms for lung adenocarcinoma (LUAD), of which co-occurring TP53 and RB1 mutations defined a subgroup of patients with increased risk of SCLC transformation. Our study aimed to uncover genomic features and identify clinically high-risk patients of SCLC-transformed LUAD with EGFR/TP53/RB1 alterations.

Methods: The study was performed in 58 LUAD patients harboring concurrent mutations in EGFR/TP53/RB1. Capture-based targeted sequencing covering 76 genes related to LUAD were performed at baseline and after SCLC transformation to obtain genomic profiles. A decision tree integrating clinical and genomic features was constructed to predict SCLC transformation.

Results: Of 58 patients, 30 were pathologically confirmed as SCLC-transformed LUAD while 28 remained LUAD. In addition to TP53 and RB1, we also identified alterations in PIK3CA (12%), PTEN (12%), and copy number variations (CNVs) in CCNE1 (10%), IL7R (10%), MET (10%), MYC (10%) and TERT (10%). Comparable mutation counts were observed between SCLC transformed group and control group but EGFR 19del mutation and CNVs were more frequently presented in transformed group ($p<0.05$). Patients with SCLC transformation were diagnosed with LUAD at younger age than control group ($p<0.05$). The overall median time to SCLC transformation was 27.43 months. In transformed group, less mutation count at LUAD diagnosis was independently associated with less time to transformation ($p<0.05$). The presence of PTEN mutation was also associated with less time to transformation ($p<0.05$) while CNVs in IL7R and TERT were associated with longer time to transformation ($p<0.05$). From baseline to SCLC transformation, the overall trends of mutation counts tended to increase in transformed group but decrease in control group ($p<0.001$). The second sequencing after SCLC transformation observed that gain of CNVs in genes including PIK3CA, AKT1 and MYC was the key factor underlying increased mutation counts. In addition, EGFR mutations featured by absence of CNVs occurred more frequently in transformed group than control ($p<0.05$). A decision-tree based model was constructed to predict SCLC transformation using CNV≥2, age≤56.5 years and positive EGFR 19del mutation with sensitivity of 76% and specificity of 71%.

Conclusions: In LUAD patients with concurrent EGFR/TP53/RB1 mutations, SCLC transformed patients showed different mutation profiles featured by gain of CNVs. The combination of clinical and molecular features might be used to predict SCLC transformation of LUAD.

Keywords: EGFR/TP53/RB1, CNV gain, decision tree

MA02.07 Aurora A Kinase Inhibition with VIC-1911Potentiates KRASG12C Inhibitor and Overcomes Resistance to Sotorasib in Lung Cancer

J.W. Lee, S. Kim, S. Cruz-Gomez, C. Yang, B. Burtness

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Introduction: Direct KRASG^{12}C inhibitors have shown promising clinical activity in cancers bearing *KRAS^{G12C}* mutation and sotorasib, in particular, is approved for the treatment of these patients. While intrinsic and acquired resistance to this drug limits its utility, the mechanisms underlying such resistance remain to be elucidated. Aurora A Kinase (AURKA) has been considered as a key druggable KRAS effector and mediates adaptive resistance to direct KRASG^{12}C inhibitors. We have previously demonstrated synergistic antitumor effects when the mitotic cell regulator WEE1 is inhibited in combination with AURKA inhibition and explored this strategy to prevent or overcome sotorasib resistance.

Methods: We examined the correlation between AURKA expression and outcome of lung cancer patients using caBIG, GEO and TCGA databases. Cell-based experiments and preclinical animal studies were conducted to demonstrate a novel combination of the selective AURKA inhibitor VIC-1911 and sotorasib in *KRAS^{G12C}*-mutated lung cancer cells intrinsically resistant to sotorasib, along with a combination of VIC-1911 and WEE1 inhibitor adavosertib in mutant KRAS(G12C) lung cancer cells with acquired resistance to the inhibitor.

Results: Using Cooperative screening, Loewe plotting and clonogenic survival assays, combination treatment with VIC-1911 and sotorasib showed profound synergistic antitumor effect on *KRAS^{G12C}*-mutated lung cancer cells harboring intrinsic resistance to sotorasib compared to sotorasib-sensitive cells (Loewe synergy scores: NCI-H1792=16.03; HCC44=14.37; NCI-H358=1.48). Notably, addition of VIC-1911 dramatically inhibited sotorasib-mediated rebound of ERK1/2 phosphorylation in cells after 96 hours drug exposure, indicating AURKA inhibition delays adaptive resistance to sotorasib. Further, sequestered non-quiescent cells which resume proliferation after sotorasib treatment showed significant AURKA expression and their reactivation was reversed by VIC-1911. Consistent with our findings in *in vitro*, concomitant inhibition of AURKA and KRAS(G12C) resulted in a stronger antitumor effect *in vivo* compared to sotorasib monotherapy. We also demonstrated synergistic antitumor effects of combined inhibition with AURKA and WEE1 across *KRAS/TP53*-mutated *in vitro* and *in vivo* models. Synergy was further confirmed in assays of cell cycle distribution, mitotic catastrophe, and apoptosis induction. In addition, we established *KRAS^{G12C}*-mutated human lung cancer cell lines with acquired resistance to sotorasib through escalated incremental dosing. Interestingly, the combination of AURKA and WEE1 inhibition synergistically induced greater cell death in NCI-H358 lung carcinoma cells harboring acquired resistance to sotorasib, as compared to VIC-1911/sotorasib combination.

Conclusions: Our findings link AURKA activation to both intrinsic and acquired resistance to sotorasib in *KRAS^{G12C}*-mutated lung cancer and show antitumor activity for AURKA inhibition in these settings. The combination of AURKA inhibition with sotorasib may be a promising therapeutic approach in lung cancer with intrinsic resistance to direct KRASG^{12}C inhibitors, while the combination of AURKA and WEE1 inhibition merits exploration in acquired resistance to these agents.

Keywords: Aurora kinase A, Sotorasib, KRAS

MA02 MOLECULAR UNDERPINNINGS OF LUNG CANCER HISTOLOGICAL DIFFERENTIATION AND TARGETED THERAPEUTICS, SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA02.08 Trametinib Inhibition of MEK1 2 Upregulates PD-L1 Expression in KRAS-Mutant NSCLC Through ID1 Downregulation

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Introduction: Anti-PD-1/PD-L1 immunotherapy significantly improves NSCLC patients' survival. However, these treatments efficacy is highly dependent on a high PD-L1 tumor expression. We previously reported the role of *Id1* in *KRAS* mutant NSCLC and the efficacy of a combined blockade of PD-1 and *Id1* in a KRAS-mutant NSCLC mouse model, as a new therapeutic approach (Baraibar, Cancers 2020). Trametinib is an oral MEK1/2 inhibitor, which acts downstream of *KRAS*. Trametinib is FDA-approved for metastatic melanoma and NSCLC treatment in patients with $BRAF V^{600}E$ mutations. We aimed to evaluate trametinib to block *Id1* expression and enhance anti-PD-1/PD-L1 treatment efficacy through PD-L1 overexpression.

Methods: To demonstrate that the inhibition of MEK1/2 reduces *Id1* expression, human *KRAS*-mutant (H1792, H2009, H2122, H358, HCC44) as well as *KRAS* wild-type (H1568, H1993) cell lines and *KRAS*-mutant murine cell lines (LLC, KLA, CMT-167) were used. Cells were treated with trametinib at different concentrations (10 nM-500 nM) and time points (24H-72H). *Id1* expression was measured by qPCR and western blot. Specific shRNA against *Id1* was used to compare *Id1* silenced tumor cells with cells treated with trametinib. Syngeneic subcutaneous tumors were generated using LLC cells (*Id1* wild-type or *Id1* silenced) in C57BL6J and in *Id1*-deficient mice treated with PBS or with daily trametinib 0.5 mg/Kg. PD-L1 expression was measured by flow-cytometry in *Id1*-silenced and wild-type cells after trametinib and IFN-γ exposure. To demonstrate that PD-L1 expression increase after MEK1/2 inhibition is dependent on Id1 inhibition, we generated *Id1*-overexpressing cells and trametinib-resistant cell lines.

Results: *In vitro* experiments with human and murine NSCLC cell lines treated with trametinib revealed that MEK1/2 inhibition significantly reduces *Id1* expression in *KRAS* mutant and *KRAS* wild-type NSCLC cell lines. The comparison between cells treated with trametinib and *Id1*-silenced cells showed the same effect reducing EMT markers and FOSL1 pathway in murine cell lines. *In vivo* experiments performed in C57BL6J and in *Id1*-deficient mice showed no significant differences in tumor growth between *Id1* knock-out and in *Id1* wild-type mice treated with trametinib. IHC analysis of those tumor samples showed reduced *Id1* levels. As *Id1* plays a key role in PD-L1 regulation, we measured PD-L1 expression in H1792, H2009, H2030, H358, LLC, KLA, CMT-167 cell lines treated with trametinib. Flow-cytometry analysis revealed that MEK1/2 inhibition significantly increased PD-L1 expression in tumor cells surface and correlated with *Id1* inhibition. To validate that PD-L1 upregulation, through MEK1/2 inhibition, was dependent on *Id1* downregulation, we generated *Id1* overexpressing cells and trametinib-resistant cells. Flow-cytometry experiments showed *Id1* overexpressing cells did not respond to MEK1/2 inhibition with unchanged PD-L1 expression, whereas, trametinib-resistant cells did not show *Id1* inhibition with sustained PD-L1 expression. Final data of the therapeutic efficacy of trametinib and anti-PD-1 combination therapy in in vivo models will be also presented.

Conclusions: Pharmacological inhibition of MEK1/2 though Trametinib significantly decreased *Id1* expression *in vitro* and *in vivo*, replicating a specific shRNA against *Id1*. PD-L1 upregulation induced by *Id1* blockade after trametinib treatment in *KRAS*-mutant NSCLC cell lines, could be used as a novel therapeutic strategy to sensitize NSCLC to anti-PD-1/PD-L1 immunotherapy.

Keywords: mek1 2, PD-L1, id1

MA02 MOLECULAR UNDERPINNINGS OF LUNG CANCER HISTOLOGICAL DIFFERENTIATION AND TARGETED THERAPEUTICS, SUNDAY, AUGUST 7, 2022 - 10:45–11:45

MA02.09 Impact of Baseline Clinicopathologic and Genomic Features on Outcomes to KRAS G12C Inhibitors in Patients with NSCLC

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Introduction: For patients with KRASG^{12}C-mutant non-small cell lung cancer (NSCLC), baseline factors that influence efficacy of KRASG^{12}C inhibitors (G12Ci) are largely unknown. We sought to identify clinicopathological and genomic characteristics associated with outcome to these inhibitors.

Methods: Among patients at the Dana-Farber Cancer Institute with NSCLC who received a G12Ci as monotherapy, baseline clinicopathological and genomic characteristics were correlated with objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Genomic alteration pathogenicity was assessed using OncoKB, COSMIC, and Poly-phen2.

Results: We identified 68 patients who received a G12Ci (median age 67 years, 65% female). Of these, 18 (27%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, 28 (41%) had history of brain metastases prior of G12Ci start, of which 12 (43%) were untreated before G12Ci start. The PD-L1 tumor proportion score (TPS) was <1%, 1-49%, and ≥50%, in 19 (32%), 24 (40%), and 17 (28%) cases, respectively. Overall, the objective response rate (ORR) was 47% (30/64), the median PFS (mPFS) was 5.8 months, and the median OS (mOS) was 11.1 months. The mPFS and mOS progressively decreased with worsening ECOG PS (mPFS for ECOG PS 0, 1, ≥2 was: 13.8 vs 5.9 vs 2.5 months, respectively, p=0.003; mOS was: not reached vs 13.0 vs 3.4 months, respectively, p<0.001). Compared to treatment in the ≥2nd line setting (N=57), 1st-line treatment (N=11) was associated with a higher ORR (90% [N=9/10] vs 39% [N=21/54], p=0.011), but no difference in mPFS (16.6 vs 3.9 months, p=0.06) or mOS (not reached vs 9.8 months, p=0.10). Co-occurring genomic alterations included *STK11* mutation (mut) in 17 cases (27%), *KEAP1* mut in 10 (21%), *TP53* mut in 25 (39%), *SMARCA4* mut in 5 (10%), and *KRAS* copy gain in 10 (18%). There was no statistically significant difference in ORR in *STK11* wild-type (wt) vs mut (52% vs 38%), in *KEAP1* wt vs mut (51% vs 33%), in *TP53* wt vs mut (49% vs 46%), or in *SMARCA4* wt vs mut (50% vs 20%). There was no difference in mPFS or mOS in *STK11* wt compared to mut (mPFS: 5.8 vs 10.1 months, p=0.30; mOS 13.0 vs 5.6 months, p=0.20) or in *KEAP1* wt compared to mut (mPFS: 5.9 vs 3.4 months, p=0.40; mOS 11.1 vs 7.8 months, p=0.60). After correcting for confounding factors, ECOG PS 2 was independently associated with PFS (HR: 4.52 [95%CI: 1.63-12.56], p=0.004) and OS (HR: 15.06 [95%CI: 1.65-137.48], p=0.016), treatment line was associated with PFS (HR: 4.31 [95%CI: 1.44-12.84], p=0.009), and *SMARCA4* mut was independently associated with OS (HR: 6.48 [95%CI: 1.87-22.51], p=0.003).

Conclusions: Baseline clinicopathological characteristics may help predict outcome to G12Ci in patients with KRASG^{12}C-mutant NSCLC. Larger series are needed to better investigate the impact of subgroups defined by co-occurring mutations.

Keywords: KRAS G12C, KRAS inhibitors, Predictive factors

MA03 PREDICTING OUTCOMES IN PATIENTS WITH EARLY DISEASE NSCLC,
SUNDAY, AUGUST 7, 2022 - 12:00–13:00

MA03.03 Predicting Occult Lymph Node Metastasis in Patients with Clinical Stage IA Non-small Cell Lung Cancer: A Prospective Cohort Study

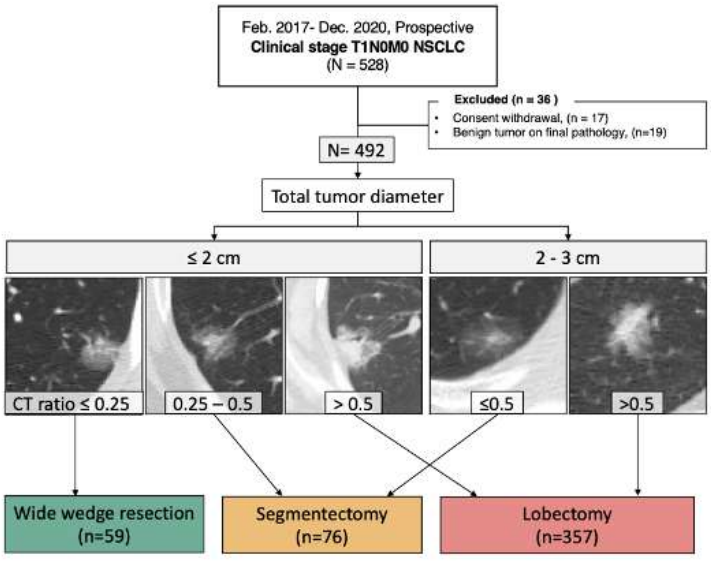
J. Lee, H.Y. Lee, Y.J. Jeon, S. Shin, J.H. CHo, Y.S. Choi, J. Kim, J.I. Zo, Y.M. Shim, H.K. Kim
Samsung Medical Center, Seoul/KR

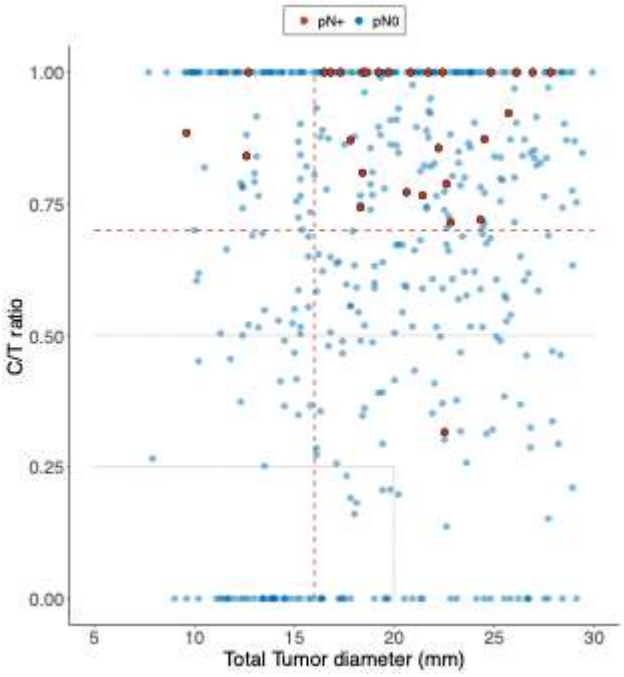
Introduction: Nodules with GGO components have been known as indolent tumors with a low risk of node metastasis, while occult lymph node metastasis (OLNM) is observed in 15-20% even in clinical stage I non-small cell lung cancer (NSCLC) with radiologically solid nodules. We aimed to evaluate predictive factors for occult lymph node metastasis (OLNM) in clinical stage IA NSCLC patients using a prospective observational cohort (OREX-1A: Optimal Extent of Pulmonary Resection in Clinical Stage IA Non-Small Cell Lung Cancer (NCT03066297)).

Methods: In February 2017, we developed our institutional decision-making algorithm to guide the optimal extent of resection in clinical stage IA NSCLC based on total tumor diameter (TD) and consolidation-to-tumor ratio (CTR): TD ≤ 2 cm with CTR ≤ 0.25 for wide wedge resection; either TD ≤ 2 with CTR 0.25-0.5 or TD 2-3 with CTR ≤ 0.5 for segmentectomy; and any TD with CTR > 0.5 for lobectomy. A dedicated radiology specialist measured the radiologic features in all the enrolled cases. The primary outcome was nodal upstaging. Receiver operating characteristic curve analysis and logistic regression were performed to determine the optimal cut-off value for predicting OLNM.

Results: Among the enrolled 492 patients, wide wedge resection, segmentectomy, and lobectomy were planned in 59 (12%), 76 (15%), and 357 (73%) patients, with median CTR 0.9 (interquartile range, 0.7-1.0), 0.3 (0.1-0.4), and 0 (0-0) and total removed lymph nodes of 17(13-23), 12(5-16), and 4(3-8), respectively. Overall algorithm compliance rate was 80.3%. The prevalence of OLNM was 6.0%(n=29) (pN1, n=11; pN2, n=18). Optimal cut-off value for OLNM is 0.74 for CTR, 14.85mm for solid diameter (SD), and 16.45mm for TD. Adjusted odd ratios for CTR, SD, and TD were 32.38 (95% confidence interval, 2.89-698.72), 1.18 (1.05-1.37), and 1.02 (0.95-1.10).

Conclusions: CTR predicted OLNM better than TD or SD in clinical stage IA NSCLC.





Keywords: CT ratio, subsolid nodule, NSCLC

MA03 PREDICTING OUTCOMES IN PATIENTS WITH EARLY DISEASE NSCLC,
SUNDAY, AUGUST 7, 2022 - 12:00–13:00

MA03.04 An Integrated Deep Learning Method to Predict Lung Cancer Recurrence Risk for Resected Stage IA NSCLC

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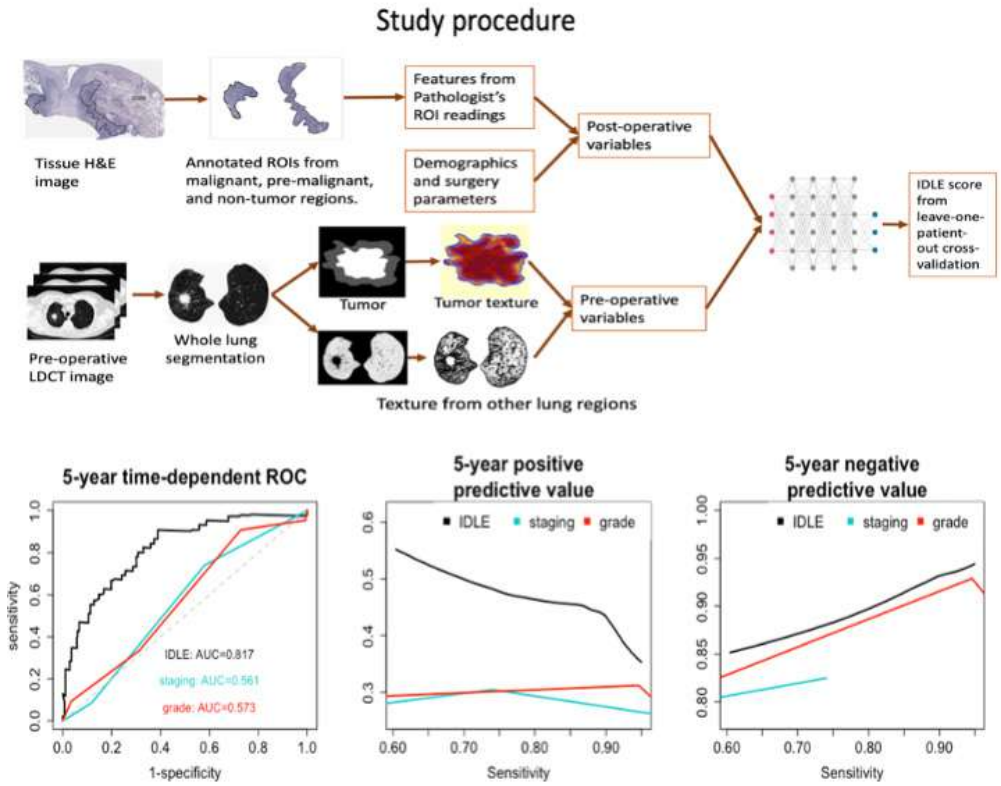
[1]Johns Hopkins University, Baltimore/MD/USA, [2]University of Colorado, Baltimore/CO/USA, [3]University of British Columbia, Vancouver/BC/CA, [4]BC Cancer Research Institute, Vancouver/BC/CA

Introduction: Prognostic risk factors for completely resected stage IA NSCLCs have advanced minimally over recent decades. Although several biomarkers have been found to be associated with tumor recurrence, their added value to traditional TNM staging are unclear.

Methods: Surgical specimens and pre-operative low-dose CT (LDCT) images from 182 stage IA patients in the National Lung Screening Trial were analyzed. Radiomics features and other image features were extracted from 1,076 pathologist-annotated regions-of-interest (total 477 H&E slides) and patient's pre-operative LDCT images. We integrated these features with surgical parameters, patient demographics, and medical history to produce an integrated deep learning evaluation (IDLE) score to predict progression free survival. Added values of IDLE to TNM staging and tumor grade were evaluated through area under the ROC curve (AUC) and independent association with tumor recurrence. We decode the deep learning network's black-box to identify top risk factors and synergies between global and local tumor features, and how they are associated with tumor recurrence or progression.

Results: The 5-year time-dependent AUC of IDLE2 was 0.817±0.037 as compared to AUC=0.561±0.042 and 0.573±0.044 from TNM staging and tumor grade respectively. IDLE2 gave uniformly higher 5-year positive-predictive-value and negative-predictive-value than both TNM staging and tumor grade under the same sensitivity levels. IDLE2 score was significantly associated with tumor recurrence ($p<0.0001$) after adjusting for TNM staging and tumor grade. Increased prediction accuracy within the deep learning black-box was primarily due to synergy between CT image features and pathological features.

Conclusions: Integrating diverse prognostic variables from LDCT images and tissue H&E images through deep learning can more accurately identify aggressive stage IA NSCLC cancers than TNM staging and tumor grade. Strong synergy between tumor's global features and localized histologic features suggests integrating information from different platforms is more important than adding features from platforms with overlapping information.



Keywords: Artificial intelligence and machine learning, Early diagnosis, Cancer recurrence prediction

MA03 PREDICTING OUTCOMES IN PATIENTS WITH EARLY DISEASE NSCLC,
SUNDAY, AUGUST 7, 2022 - 12:00–13:00

MA03.05 EGFR mutation Is Not a Risk Factor for Postoperative Recurrence of Lung Adenocarcinoma on Long Follow-up of a Multi-Institutional Cohort

Y. Matsumura[1], K. Hayasaka[2], T. Ohira[1], S. Shiono[3], J. Abe[4], H. Suzuki[1], Y. Okada[2]

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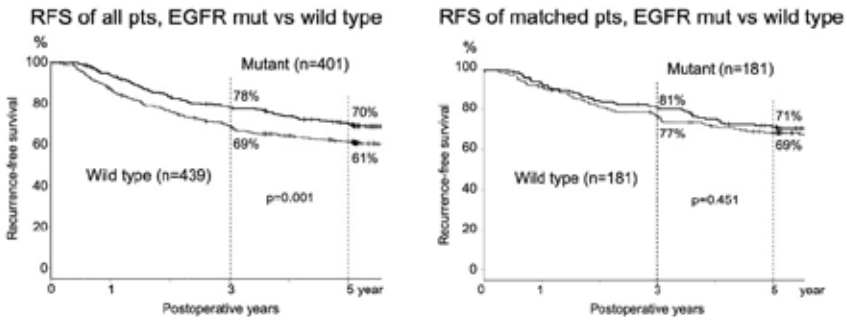
Introduction: ADAURA trial demonstrated efficacy of 3rd-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as postoperative adjuvant chemotherapy for resected lung adenocarcinoma (ADC) harboring EGFR mutations. However, it is still unclear whether EGFR mutation itself is a risk factor of postoperative recurrence. Therefore, we conducted the multi-institutional observation study to compare recurrence-free survival (RFS) and overall survival (OS) according to EGFR mutation status.

Methods: We collected the medical records of 840 consecutive patients who underwent surgical resection for lung ADC between 2005 and 2012 at four participating institutions. EGFR mutation status of all specimen were examined, and RFS and OS due to their EGFR mutation status were compared. In addition, after matching the patients' institution, age, gender, smoking history, pathological stage (pStage), and adjuvant treatment between EGFR mutant and wild type, we also compared RFS and OS of both groups.

Results: Among the enrolled 840 patients, there were 401 (48%) EGFR mutants. Some clinicopathological factors, such as gender, smoking history and pathological stage (pStage) of EGFR mutant (M group) were significantly different from those of EGFR wild type (W group). Median follow-up period was 85 months (0-191). The 3/5-year RFSs of M and W group were 78/70% and 69/61%, respectively, and their survival curves were significantly different (p<0.001). The 3/5-year OSs of both groups were 92/85% and 85/75%, respectively, whose survival curves were also significantly different (p<0.001). In the multivariate analysis of RFS and OS, however, EGFR mutation status was not an independent predictor of prognosis. In the matched-pair analysis, the patients were allocated into two cohorts (n = 181 each) with EGFR mutation (mM group) or wild type (mW group), both of which had identical characteristics as follows: institution, median age (68 years), men (85, 47%), ever smokers (77, 43%), and pStage (IA, 108, 60%; IB, 48, 27%; II, 14, 8%; III, 11, 6%). The 3/5-year RFS of mM and mW groups were 81/71% and 77/69%, respectively and their survival curves were not significantly different (p = 0.451). The 3/5-year OS of mM and mW group were 93/84% and 90/81%, respectively and their survival curves were not significantly different, either (p = 0.453).

Conclusions: Long follow-up of pair-matched patients reveals that an EGFR mutation was not a significant risk factor for recurrence of surgically resected lung ADC.



Keywords: Lung adenocarcinoma, epidermal growth factor receptor mutation, risk factor of postoperative recurrence

MA03 PREDICTING OUTCOMES IN PATIENTS WITH EARLY DISEASE NSCLC,
SUNDAY, AUGUST 7, 2022 - 12:00–13:00

MA03.07 Accurate Intraoperative Diagnosis of Spread Through Air Spaces (STAS) Using a Cryo Embedding Medium Inflation Method

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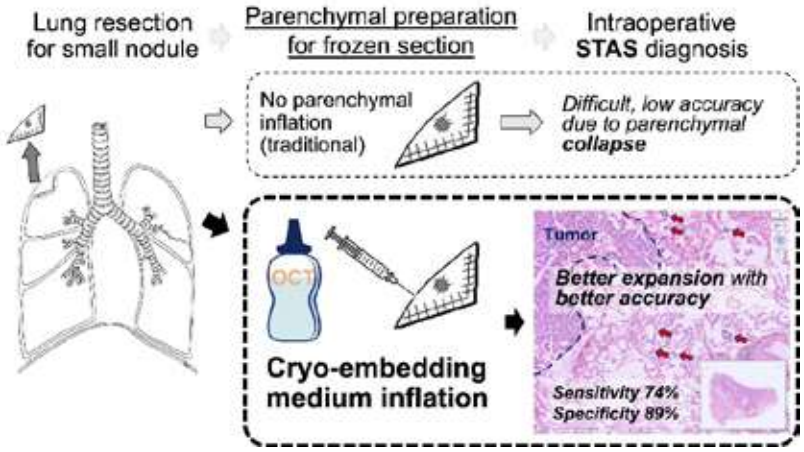
Introduction: STAS is associated with a worse prognosis, especially in patients undergoing sublobar resection (Eguchi, Travis, Adusumilli et al. *J Thorac Oncol* 2019). Intraoperative diagnosis of STAS may help surgical decision-making for the extent of resection (e.g., lobectomy vs. sublobar resection). However, the reported accuracy of STAS diagnosis using frozen section slides has been low. We hypothesized that the low accuracy was associated with the collapsed parenchyma surrounding the tumor. We aimed to investigate the diagnostic performance of STAS using frozen section slides prepared by cryo-embedding-medium inflation methods.

Methods: We prospectively investigated 113 consecutive patients who underwent lung resection for small-sized lung lesions without a preoperative diagnosis in our institution in 2021. Diluted cryo-embedding medium (Tissue-Tek O.C.T. Compound, Sakura Finetek, USA) with saline (1:1 dilution) was gently injected into the lung parenchyma of the resected specimen until the lung swelled sufficiently. Five-μm-thick frozen section slides with hematoxylin-eosin staining were prepared in a standard manner using a cryostat. Three pathologists were assigned to determine STAS status using FS slides (FS_STAS): positive, negative, and unable-to-evaluate. Thirty-seven patients with unable-to-evaluate were excluded from the following analyses. The three pathologists also evaluated STAS diagnosis using permanent slides (Dx_STAS) blindly to the FS_STAS results. FS_STAS was compared with Dx_STAS (golden standard) to assess the diagnostic performance of frozen sections to detect STAS intraoperatively.

Results: In 76 included patients (57 primary lung cancers and 19 metastatic tumors), Dx-STAS was positive in 29 patients (38%). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FS_STAS were 69%, 89%, 80%, 82%, and 82% in total 76 patients: 74%, 89%, 78%, 87%, and 84% in 57 patients with primary lung cancers (Figure 1).

Conclusions: Our cryo-embedding-medium inflation method helps obtain frozen section slides with sufficiently expanded lung parenchyma, increasing the accuracy of intraoperative STAS diagnosis.



Keywords: STAS, frozen section, sublobar resection

MA03 PREDICTING OUTCOMES IN PATIENTS WITH EARLY DISEASE NSCLC,
SUNDAY, AUGUST 7, 2022 - 12:00–13:00

MA03.08 Survival Impact of Benchmarking Lung Cancer Surgeons' Performance by Quality Metrics

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[1]University of Memphis, Memphis/TN/USA, [2]Baptist Cancer Center, Memphis/TN/USA, [3]NEA Baptist Hospital, Jonesboro/AR/USA, [4]Baptist Memorial Hospital Memphis, Memphis/TN/USA

Introduction: The oncologic quality of curative-intent resection influences lung cancer survival. We categorized surgeon performance quality as a driver of lung cancer survival.

Methods: In the US population-based Mid-South Quality of Surgical Resection cohort, we used pre-intervention baseline data (24 surgeons, 1130 resections) to derive three performance cut-points for survival-impactful quality metrics: resection with positive margins, non-examination of lymph nodes (pNX), non-examination of mediastinal lymph nodes (pNXmed), wedge resection. For each metric, surgeons below the 25th percentile were considered low (score of 1), 25th to 75th percentile moderate (2), and above 75th percentile high (3) performers. We aggregated scores for each metric, and using tertiles, created three surgeon performance tiers: Tier 1 (4-6, low); Tier 2 (7-9, intermediate); Tier 3 (10-12, high). After excluding surgeons with ≤15 resections, and neoadjuvant cases, we compared the survival of patients in surgeon tiers using Cox proportional hazard models and used multinomial logistic regression to determine possible predictors of aggregate surgeon tiers.

Results: From 2009-2021, 39 eligible surgeons performed 4082 resections: 17 (44%) surgeons (2580 resections [65%]) were in Tier 3; 15 (39%) surgeons (977 resections [25%]) were Tier 2, and 7 (18%) surgeons (402 resections [10%]) were Tier 1. Resections by Tier 1 and Tier 2 surgeons had significantly worse outcomes than Tier 3, with incomplete mitigation by patient-level adjustments (Table, Figure). Surgeon's use of a lymph node specimen collection kit was the only significant predictor of surgeon tier. The odds of being in Tier 3 were 2.04 (95% CI, 1.11, 3.73) and 1.48 (1.11, 1.98) times the odds of being in Tier 1 or Tier 2, respectively, for every 10% increase in surgeon's use of the kit.

Conclusions: Readily quantifiable quality metrics can categorize surgeons into survival-impactful performance tiers. The extent of use of a lymph node collection kit influenced surgeon performance.

Figure. Kaplan-Meier plot and Log-rank test for overall survival across three tiers of surgeon performance.

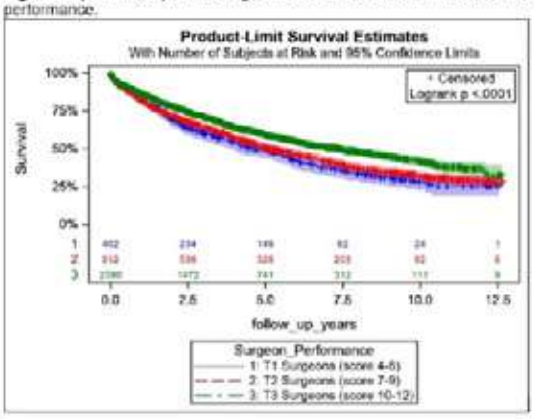

Table. Crude and adjusted hazard ratios (HR; with 95% confidence intervals) of Tier 1 and Tier 2 surgeons compared to Tier 3 surgeons across surgical quality metrics.

Quality Metric (and respective number [%] of surgeons for each tier)	Crude HR	HR[1]	HR[2]	HR[3]
Positive margins				
Tier 1 (8 [20.5%]) v Tier 3 (13 [33%]; ref)	**1.54 (1.33, 1.78)**	**1.55 (1.35, 1.78)**	**1.24 (1.04, 1.49)**	**1.24 (1.03, 1.51)**
Tier 2 (18 [46.2%]) v Tier 3 (ref)	1.1 (0.9, 1.36)	1.06 (0.87, 1.31)	1.03 (0.89, 1.19)	1.03 (0.89, 1.2)
No mediastinal sampling				
Tier 1 (10 [25.6]) v Tier 3 (20 [51.3])	**1.3 (1.07, 1.57)**	**1.33 (1.1, 1.61)**	**1.15 (1.01, 1.32)**	**1.17 (1.02, 1.34)**
Tier 2 (9 [23.1]) v Tier 3	**1.27 (1.08, 1.5)**	1.22 (1.06, 1.42)	1.09 (0.94, 1.27)	1.11 (0.97, 1.27)
pNx				
Tier 1 (8 [20.5]) v Tier 3 (18 [46.5])	**1.36 (1.11, 1.66)**	**1.4 (1.14, 1.71)**	1.18 (0.99, 1.42)	1.21 (0.98, 1.48)
Tier 2 (13 [33.3]) v Tier 3	**1.29 (1.09, 1.52)**	**1.28 (1.11, 1.49)**	**1.12 (1, 1.26)**	**1.13 (1.02, 1.26)**
Wedge resections				
Tier 1 (8 [20.5]) v Tier 3 (16 [41])	**1.47 (1.24, 1.75)**	**1.49 (1.26, 1.76)**	1.2 (0.98, 1.46)	1.21 (0.98, 1.5)
Tier 2 (15 [38.5]) v Tier 3	**1.37 (1.21, 1.54)**	**1.32 (1.18, 1.48)**	**1.17 (1.03, 1.32)**	**1.17 (1.05, 1.32)**
Aggregate score[4]				
Tier 1 (7 [18]) v Tier 3 (17 [43.6])	**1.42 (1.16, 1.74)**	**1.47 (1.2, 1.79)**	1.2 (0.98, 1.46)	1.22 (0.99, 1.51)
Tier 2 (15 [38.5]) v Tier 3	**1.3 (1.11, 1.52)**	**1.28 (1.12, 1.48)**	**1.12 (1, 1.25)**	**1.13 (1.03, 1.24)**

[1]adjusted for clinical stage; [2] adjusted for clinical stage, patient age, number of comorbidities, sex, race, insurance, histology, pet CT, extent of surgery, surgical technique, and invasive staging; [3] adjusted for same variables + proportion of kit use; [4] Aggregate score is the sum of scores for negative margins, pNXmed, pNX, and wedge resections.

Keywords: surgical resection, NSCLC, quality

MA03 PREDICTING OUTCOMES IN PATIENTS WITH EARLY DISEASE NSCLC,
SUNDAY, AUGUST 7, 2022 - 12:00–13:00

MA03.09 Real-World Acute Toxicity and 90-day Mortality in Patients with Stage I Non-Small Cell Lung Cancer Treated with Stereotactic Body Radiotherapy

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Introduction: Stereotactic body radiotherapy (SBRT) has firmly established its role in the management of stage I non-small cell lung cancer (NSCLC). Results from trials are difficult to generalize to the entire patient population in the real world. In addition, in contrast to trials, real-world data provides increased statistical power to study rare outcomes and their predictors. The primary aim of this nationwide study was to determine the real-world incidence of acute toxicity and 90-day mortality in patients treated with SBRT for stage I NSCLC. A secondary aim was to develop prediction models for acute toxicity and 90-day mortality.

Methods: Data was retrieved from the Dutch Lung Cancer Audit for Radiotherapy (DLCA-R). All 19 Radiation Oncology departments participated nationally. Patients with primary cT1-2aN0M0 (stage I) NSCLC who underwent SBRT with curative intent between 2017 and 2020 were included. Acute toxicity was defined as radiation-pneumonitis grade ≥2 or other non-hematologic toxicity grade ≥3 within 90 days after the start of SBRT. Univariable and multivariable logistic regression analyses were used to create prediction models for acute toxicity and 90-day mortality separately. Redundant variables were eliminated with a backward stepwise approach based on Akaike's information criterion.

Results: A total of 5,285 patients were included. Patients had a mean age of 73.0 (±6.0) years and 1,146 (21.7%) were older than 80 years. The majority was male (51.5%), had a WHO performance score of 0-1 (69.3%), and a cT1a-b tumor (65.2%) that was mostly located in an upper lobe (64.7%). Histopathologic proof of NSCLC was obtained in 34.1% of patients. Acute toxicity was observed in 218 (4.1%) of patients and 90-day mortality in 88 (1.7%) of patients. Age 70-80 years (but not >80 years), worse WHO performance score, lower FEV1, higher cT-stage, absence of histopathologic proof, and a higher mean lung dose were independently predictive of acute toxicity in the final model (c-statistic 0.70; Table 1). A prediction model for 90-day mortality is under construction.

Conclusions: To the best of our knowledge, this nationwide study represents the largest real-world series of patients with stage I NSCLC with availability of acute toxicity and mortality data after SBRT. Acute toxicity and 90-day mortality rates were low. Age >80 years was not related to a higher risk of acute toxicity. A pretreatment prediction model for acute toxicity was created with a satisfactory model performance, which could aid in identifying patients at increased risk.

Table 1: Univariable and multivariable logistic regression analyses for acute toxicity.

Characteristic	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age, years (categorical)				
≤70	Ref		Ref	
70-80	1.29 (0.95-1.76)	0.110	1.28 (0.93-1.76)	0.138
>80	0.93 (0.62-1.38)	0.723	0.87 (0.57-1.33)	0.515
Age, years (linear)	1.00 (0.99-1.02)	0.669	-	-
Male gender	1.09 (0.83-1.43)	0.536	-	-
WHO performance status				
0	Ref		Ref	
1	1.37 (0.91-2.11)	0.143	1.14 (0.73-1.77)	0.567
≥2	2.67 (1.77-4.13)	<0.001*	1.83 (1.15-2.93)	0.011*
Co-morbidities ((CCI)				
0	Ref		-	-
1	1.62 (0.78-3.91)	0.235		
≥2	1.70 (0.84-4.07)	0.183		
Smoking at diagnosis	0.71 (0.44-1.10)	0.134	-	-
Weight loss >5%	0.97 (0.48-1.78)	0.929	-	-
Log(FEV1), % of predicted	0.40 (0.23-0.69)	<0.001*	0.30 (0.13-0.69)	0.008*
Log(DLCO), % of predicted	0.22 (0.10-0.46)	<0.001*	-	-
Histopathologic confirmation	0.58 (0.42-0.79)	<0.001*	0.61 (0.43-0.86)	0.006*
Tumor location				
Upper lobe	Ref		Ref	
Middle or lower lobe	1.51 (1.13-2.01)	0.005*	1.47 (1.08-2.02)	0.015*
Tumor lateralization				
Left lung	Ref		-	-
Right lung	0.99 (0.74-1.32)	0.949		
Clinical T-stage				
cT1a	Ref		Ref	
cT1b	1.72 (1.11-2.76)	0.019*	1.62 (1.02-2.57)	0.042*
cT1c	2.36 (1.49-3.87)	<0.001*	2.14 (1.27-3.61)	0.004*
cT2a	2.34 (1.38-4.02)	0.002*	2.15 (1.17-3.96)	0.014*
Log(GTV), mL	1.46 (1.16-1.83)	0.001*	-	-
Tumor BED10, Gy	1.00 (0.99-1.01)	0.793	-	-
Log(MLD3), Gy	2.41 (1.56-3.77)	<0.001*	1.43 (0.80-2.59)	0.239
Log(Lung V20Gy), %	1.61 (1.16-2.26)	0.005*	-	-
Year of treatment				
2017	Ref		-	-
2018	0.73 (0.50-1.07)	0.108		
2019	0.60 (0.41-0.88)	0.009*		
2020	0.66 (0.45-0.96)	0.030*		

*: Statistically significant (p<0.05). BED10: Biologically effective dose (α/β=10). CCI: Charlson co-morbidity index. CI: Confidence interval. DLCO: Diffusion capacity for carbon monoxide. FEV1: Forced expiratory volume during the first second. GTV: Gross tumor volume. MLD3: Mean lung dose (α/β=3). OR: Odds ratio. V20Gy: Percentage of volume receiving ≥20 Gy.

Keywords: Non-small cell lung cancer, Stereotactic radiotherapy, Toxicity and mortality

MA04 PULMONOLOGY, RADIOLOGY, AND STAGING,
SUNDAY, AUGUST 7, 2022 - 14:30–15:30

MA04.03 Reconsidering T Classification for T3/T4 Non-small Cell Lung Cancer with Additional Nodule(s)

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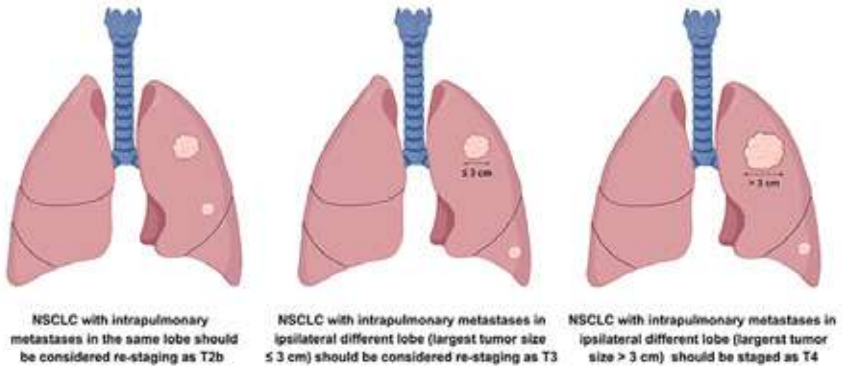
Introduction: Non-small cell lung cancer (NSCLC) with additional nodule(s) located in the same lobe or ipsilateral different lobe were designated as T3 and T4, respectively, which was merely defined by anatomical location of additional nodule(s), regardless of other prognostic factors.

Methods: A total of 4,711 patients with T1-4, N0-2, M0 NSCLC undergoing complete resection were identified between 2009 to 2014, including 145 patients with additional nodule(s) in the same lobe (T3-Add) and 174 patients with additional tumor nodule(s) in ipsilateral different lobe (T4-Add). Overall survival (OS) was compared using multivariable Cox regression models and propensity score matching analysis (PSM).

Results: T3-Add patients had better OS than T3 patients (T3-Add versus [*vs.*] T3, hazard ratio [HR], 0.693; 95% confidence interval [CI], 0.526-0.912; $p = 0.009$) and comparable OS with T2b patients (T3-Add *vs.* T2b, HR, 0.949; 95% CI, 0.724-1.245; $p = 0.703$) through multivariable Cox analysis, and further validated by PSM. T4-Add patients carried a wide spectrum of prognosis, and the largest diameter of single tumor (> 3cm *vs.* ≤ 3 cm, HR, 1.701; 95% CI, 1.166-2.482; $p = 0.006$) was screened out as the most effective indicator for distinguishing prognosis. T4-Add (≤ 3 cm) patients had better OS than T4 patients (T4-Add [≤ 3 cm] *vs.* T4, HR, 0.629; 95% CI, 0.455-0.869; $p = 0.005$) and comparable OS with T3 patients (T4-Add [≤ 3 cm] *vs.* T3, HR, 0.830; 95% CI, 0.610-1.129; $p = 0.119$). And T4-Add (> 3 cm) patients had comparable OS with T4 patients.

Conclusions: NSCLC patients with additional nodule(s) in the same lobe (T3-Add) and ipsilateral different lobe (T4-Add, maximum tumor diameter ≤ 3 cm) should be further validated and considered restaging as T2b and T3 in the forthcoming 9th TNM staging system.



Keywords: Non-small cell lung cancer, Restaging, Additional nodule

MA04 PULMONOLOGY, RADIOLOGY, AND STAGING,
SUNDAY, AUGUST 7, 2022 - 14:30–15:30

MA04.05 T3 Defining Features Influence Long Term Survival after Resection of T3N0M0 NSCLC

P.A. Ugalde Figueroa[1], E. Marques[2], V. J. Cilento[3], D.J. Giroux[3], K. K. Nishimura[3], P. Bertoglio[4], C-F.J. Yang[5], W. Fang[6], Y. Tae Kim[7], H. Asamura[8]

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Introduction: Despite improvements from the 7th edition, the T3 category in the 8th edition TNM staging system is still heterogeneous. We evaluated long-term survival in patients with non-small cell lung cancer (NSCLC) classified as T3N0M0 by different T3 tumor features to identify ways to improve the prognostic utility of the classification.

Methods: The IASLC database was queried for patients who underwent primary surgical resection of T3N0M0 NSCLC. The primary outcome examined was overall survival (OS) stratified by individual T3 features and completeness of resection.

Results: Of the 1448 patients with T3N0M0 tumors, 1187 (82.0%) had a single feature dictating classification as T3. T3 tumors with chest wall infiltration (CWI) or parietal pleura infiltration (PPI) had the highest rates of incomplete resection (9.8% and 8.4% respectively), and those classified as T3 by size >5 but ≤ 7 cm had the lowest rate of incomplete resection (2.9%). The individual T3-defining features were associated with significant differences in OS (p=0.005) (Figure 1). When tumors with similar survival and complete resection rates were grouped, patients with T3 tumors characterized by size or by the presence of a separate nodule (SN) in the same lobe had better OS 5 years after resection than patients with tumors characterized by CWI or PPI (Size/SN 60% vs CWI/PPI 53%, p=0.017) (Figure 2).

Conclusions: Significant differences in 5-year OS were associated with the size, SN, PPI, and CWI T3-defining features. Subdividing T3N0M0 tumors or more generally considering the presence of CWI or PPI when delineating stage IIB from stage IIA may increase the prognostic accuracy of tumor staging.

Figure 1. Overall survival after resection (complete or incomplete) of a T3N0M0 tumor by individual T3-defining feature. CWI, chest wall invasion; PPI, parietal pleura infiltration.

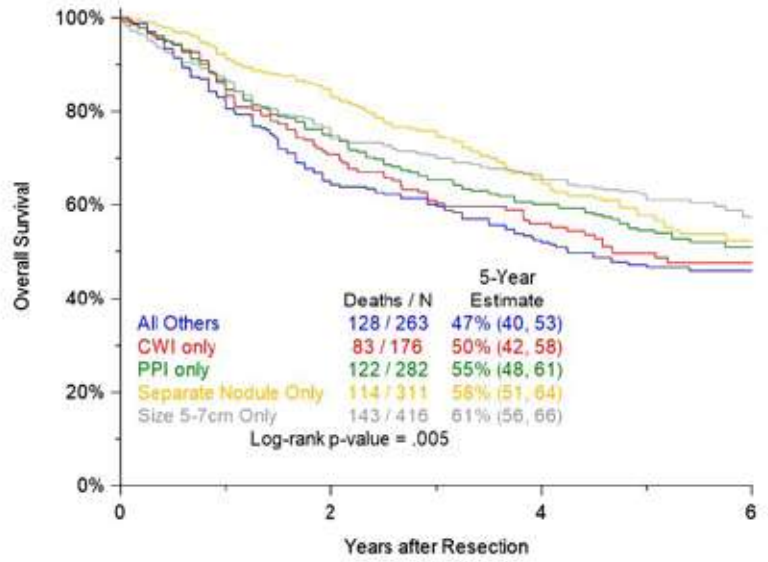
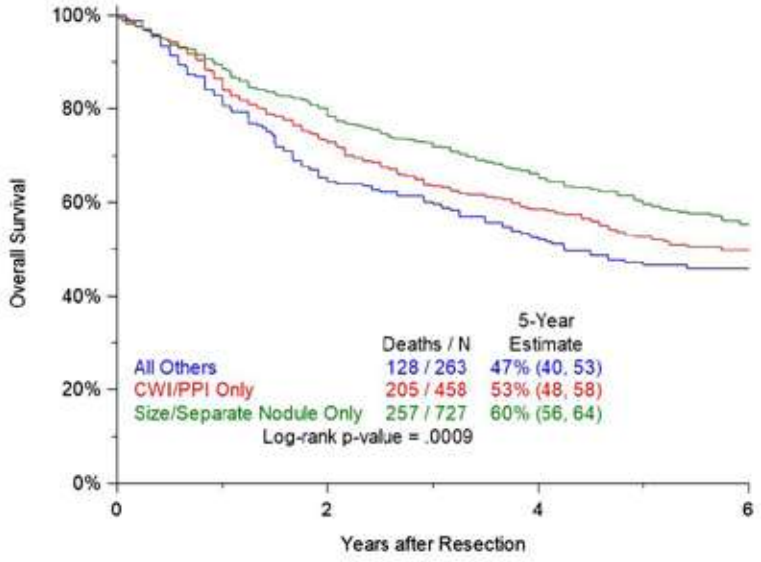


Figure 2. Overall survival after resection (complete or incomplete) of a T3N0M0 tumor. Patients with similar T3-defining features were grouped for analysis (size or separate nodule versus chest wall invasion (CWI) or parietal pleura infiltration (PPI) versus all others).



Keywords: Non-small Cell Lung Cancer, T3 features, staging

MA04 PULMONOLOGY, RADIOLOGY, AND STAGING,
SUNDAY, AUGUST 7, 2022 - 14:30–15:30

MA04.04 The Ground-Glass Component Status Combined with the Clinical T Descriptor Predicts Prognosis and Genomic Alterations in NSCLC

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Introduction: This single-institution retrospective study investigated whether adding the ground-glass component status from high-resolution computed tomography (HRCT) to the T descriptor of the TNM classification serves as a better predictive factor for prognosis in non-small cell lung cancer (NSCLC). In addition, we asked whether the ground-glass component status is related to genetic markers of the cancer.

Methods: We included patients (N=1164) who underwent surgery for cTisN0M0 or cT1N0M0 NSCLC between 2013 and 2016. Clinical T classification was further subdivided into solid or subsolid according to the presence of a ground-glass component.

Results: Of all patients, 585 (50.3%) were female, 514 (44.2%) were patients who had never smoked and 1013 (87.0%) had adenocarcinoma. On HRCT, we found 548 patients with subsolid nodules, including pure ground-glass nodules (n=148) and part-solid nodules (n=400), and 616 patients with solid nodules. Five-year OS rates were 98.1% (95% CI: 96.3-99.0) for patients with subsolid nodules (n=548) and 86.1% (95% CI: 82.8-88.8) for those with solid nodules (n=616). There were significant differences in OS between patients with subsolid nodules versus those with solid nodules (p<0.01, log-rank test). Five-year overall survival rates were 99.5% for Tis and T1mi (n=204), 98.6% for T1a_subsolid (n=126), 94.5% for T1a_solid (n=38), 97.4% for T1b_subsolid (n=165), 85.4% for T1b_solid (n=298), 93.1% for T1c_subsolid (n=54), and 85.7% for T1c_solid (n=279). Multivariate analysis of the ground-glass component and clinical T descriptor found that the absence of a ground-glass component was a worse prognostic factor for overall survival (hazard ratio, 3.69; 95% CI: 1.86-7.33; p=0.01). We subsequently grouped the 7 categories (i.e., Tis&T1mi, T1a_subsolid, T1a_solid, T1b_subsolid, T1b_solid, T1c_subsolid, and T1c_solid) into groups reflecting prognosis in terms of OS. Group 1 included the Tis and T1mi categories, which had only 1 death from another disease and no recurrence. Group 2 included the T1a_solid, T1a_subsolid, T1b_subsolid, and T1c_subsolid categories, which had a good prognosis, and Group 3 included the T1b_solid and T1c_solid categories, which had a poor prognosis. Five-year OS rates were 99.5% (95% CI: 96.5-99.9) for Group 1, 96.9% (95% CI: 94.2-98.3) for Group 2, and 85.5% (95% CI: 82.1-88.4) for Group 3. A significant difference in OS was observed between groups (p<0.01, log-rank test). These results demonstrated that the ground-glass component status is a key determinant for prognosis among patients with lesions with a solid component diameter of >1 cm. RNA sequencing (n=193) revealed that the frequency of EGFR alterations (71.1% and 53.6%, p=0.01) and tumor mutation burden (median, 1.36 mut/Mb and 1.74 mut/Mb, p=0.02) were significantly different between subsolid nodules (n=83) and solid nodules (n=110), respectively.

Conclusions: The ground-glass component status is an independent prognostic factor in NSCLC and also reflects molecular markers of the cancer, and should be incorporated into the clinical T descriptor in the next revision of the TNM classification.

Keywords: ground-glass component, genomic alteration, TNM classification

MA04 PULMONOLOGY, RADIOLOGY, AND STAGING,
SUNDAY, AUGUST 7, 2022 - 14:30–15:30

MA04.07 A Controlled Study of Pathological T- staging and Imaging T-staging of NSCLC Based on Artificial Intelligence

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Introduction: The incidence of non-small cell lung cancer (NSCLC) currently ranks first in lung cancer, and accurate staging is the key to its prognosis. Multi-slice computed tomography (MSCT) is the preferred method for evaluating lung cancer staging, prognosis and efficacy. By measuring the maximum diameter of the tumor, more accurate preoperative imaging and clinical T staging can be made. In recent years, the rapid development of artificial intelligence (AI) has brought a lot of convenience to physicians in the automatic detection, measurement and risk assessment of pulmonary nodules. Compared with traditional manual measurement methods, it can more sensitively detect tumor growth changes and more It has the advantage of repeatability. To explore the value of AI in clinical T staging of lung adenocarcinoma, and to provide accurate T staging for selecting appropriate treatment options.

Methods: Clinical data were collected from 103 patients with surgically pathologically confirmed peripheral NSCLC, all of whom underwent MDCT scans preoperatively. TNM staging was performed on chest CT according to the latest Union for International Cancer Control (UICC) lung cancer staging criteria in 2017. Two methods, manual measurement by radiologist and automatic measurement of the maximum diameter of the lesion by AI, were used for preliminary assessment of preoperative T staging and compared with postoperative pathological results to compare the accuracy of the two methods for T staging of NSCLC and compare the accuracy of AI quantitative measurement with manual measurement by radiologist and gross pathological measurement The difference in the maximum diameter of the tumour.

Results: Taking surgical and pathological staging as the "gold standard", there was no significant difference between the two measurement methods in T1-T2 staging (P>0.05). The overall coincidence rate of radiologist CT-T staging was 69.90% (72/103), the overall coincidence rate of AI CT-T staging was 83. 49% (86/103), the two methods were in good agreement with the pathological T staging (Kappa = 0.56, 0.79), and the CT-T staging analyzed by AI was better than the radiologists' CT-T staging and the pathological T staging. The staging comparison rate is higher. There was no significant difference in the CT-T staging results of different density nodules in NSCLC between the two methods (P>0. 05)

Conclusions: The CT-T staging automatically measured by AI and manually measured by radiologists are more consistent with the pathological T staging, and the CT-T staging analyzed by AI has a higher coincidence rate with the pathological T staging, with better repeatability and high stability. It has important guiding significance for the preoperative T staging of peripheral NSCLC, which is conducive to the precise selection of surgical treatment plans and improves the prognosis of patients.

Keywords: NSCLC, Artificial intelligence, MDCT

MA04 PULMONOLOGY, RADIOLOGY, AND STAGING,
SUNDAY, AUGUST 7, 2022 - 14:30–15:30

MA04.08 Navigation Bronchoscopy Mediated Sentinel Lymph Node Procedure: an Explorative Study in Ex-vivo Lung Cancer Specimens

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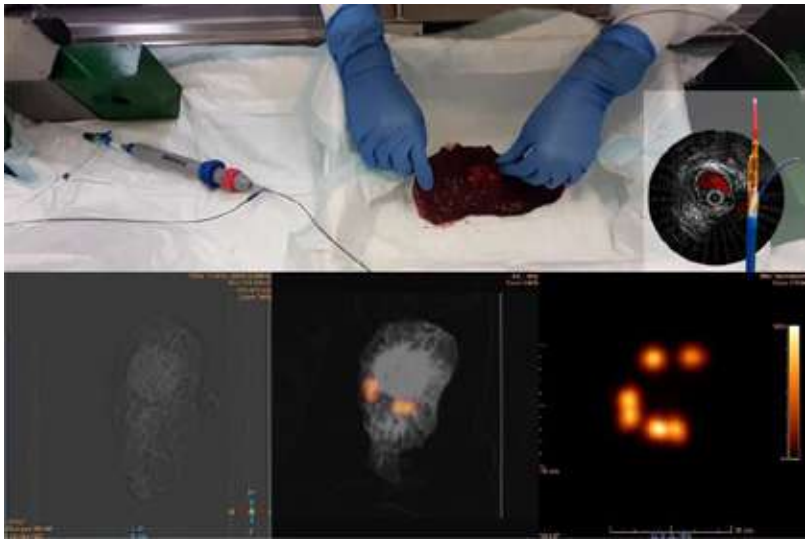
Radboudumc, Nijmegen/NL

Introduction: When early-stage lung cancer is diagnosed, the treatment of choice is surgical resection of the affected lobe or segment with complete lymph nodal resection, or stereotactic ablative radiotherapy. Despite curative intent, recurrence rates of 9.4% to 28.3% are reported. The implementation of a sentinel lymph node (SLN) procedure could possibly enhance staging accuracy by identifying nodes that are most likely to contain metastasis and help select patients for sublobar resections. A condition for a successful SLN procedure is diffusion of a tracer into at least one or more lymph nodes near the tumor. We investigated the feasibility of a navigation bronchoscopy mediated SLN procedure by performing multiple endobronchial injections of a tracer in human ex-vivo lung cancer specimens.

Methods: Ten specimens were acquired of patients who underwent lung surgery. Specimens were assigned to either peri- or intratumoral injections of ^{99}mTc-ICG-nanocolloid (GE Healthcare, USA) using a dose escalation protocol. An intravascular catheter that incorporates radial ultrasound (US) visualization, and a curved, 25.5G needle was used for injection (Philips B.V., the Netherlands). We aimed to determine feasibility of multi-depot injection in and around different tumour types. Unsuccessful injections were defined by visible leakage of the tracer or inability to inject due to high intratumoral pressure. Additionally, a SPECT/CT-scan was performed to assess tracer visibility and retention before routine pathological assessment.

Results: Of ten specimens, eight were solid tumours and two were ground glass opacities (GGOs). Follow-up revealed seven adenocarcinomas, two squamous cell carcinomas and one benign lesion. The median tumor size was 30 mm (range 16-64 mm). In two GGOs and three solid tumours, intratumoral US-guided injections were successful in 100% (7/7) and 64.3% (9/14) respectively. In five solid tumours, all performed peritumoral US-guided injections were successful (22/22). However, the peritumoral region itself proved to be difficult to reach in two more centrally located tumours, where repositioning or an intratumoral injection was needed to adequately cover all tumour regions. An average of 4 injections (range, 3-6 injections) with an average total volume and radioactivity of 0.7 ml (range, 0.3-1.2 ml) and 89.5 MBq (range, 35.4-188.0 MBq) respectively, were performed. 77.7% (33/43) of all injected radioactive depots could be individually identified on SPECT/CT-images (see Figure).

Conclusions: Performing a minimal invasive SLN procedure by endobronchial US-guided tracer injection seems best feasible when depots are peritumorally injected. Further research will determine the in-vivo applicability, lymphatic tracer-drainage for SLN detection and its added clinical value.



Keywords: Navigation Bronchoscopy, Sentinel Lymph Node Procedure, Ex-vivo

MA04 PULMONOLOGY, RADIOLOGY, AND STAGING,
SUNDAY, AUGUST 7, 2022 - 14:30–15:30

MA04.09 The Incidence and Predictors of Unsuspected Brain Metastases in Patients with Stage IA NSCLC

C.A. Mathey-Andrews[1], M.S. Zaidi[1], A. Potter[1], L. Backhus[2], C-F.J. Yang[1]

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Introduction: Pretreatment evaluation for brain metastases with brain MRI is not routinely recommended for patients diagnosed with clinical T1N0 non-small cell lung cancer (NSCLC). However, the incidence of brain metastases in this patient population is not well known. In this study, we used two large U.S. clinical databases to examine the incidence and predictors of brain metastases among patients with stage IA NSCLC.

Methods: Patients in the National Cancer Database (NCDB) and National Lung Screening Trial (NLST) with clinical T1N0 NSCLC were identified. The NCDB is a national clinical registry with prospective data acquired by certified tumor registrars and includes over 70% of cancer diagnoses annually in the U.S. The NLST is a randomized multicenter trial comparing radiographic screening approaches for lung cancer among older current and former smokers and contains data for 1,971 biopsy-confirmed lung cancers. The incidence of brain metastases among patients meeting inclusion criteria was first evaluated in the NCDB and separately evaluated in the NLST. Patients reported to have additional metastases to the liver, lung, or bone were excluded from this analysis. In the NCDB cohort only, variables associated with an increased likelihood of brain metastases were assessed using multivariable logistic regression.

Results: Of the 131,338 patients in the NCDB and 618 patients in the NLST diagnosed with clinical T1N0 tumors, the incidence of brain metastases at diagnosis was 1.9% (n=2,531) and 2.6% (n=16), respectively. In multivariable-adjusted analysis of the NCDB cohort, grade was the variable most strongly associated with brain metastases; patients with undifferentiated tumors had 14 times the odds of having a brain metastasis compared to patients with well-differentiated tumors (OR 14.4, [8.64-23.97], p<0.001). Among patients in the NCDB with undifferentiated adenocarcinomas, the incidence of brain metastasis at diagnosis was 4.3%, even greater than the 4.1% incidence of brain metastasis among patients with T2 tumors, for whom screening brain MRI is routinely recommended in the U.S. Other variables associated with increased odds of brain metastases included adenocarcinoma histology and tumor size (Table 1). Right lower lobe tumor location was associated with decreased likelihood of having a brain metastasis (Table 1).

Conclusions: We found that the incidence of brain metastases in patients with small lung cancers (T1 N0 NSCLC) is not negligible and was 1.9% in the NCDB and 2.6% in the NLST. Pretreatment evaluation with brain MRI may be warranted in patients with small, node-negative tumors, especially for patients with poorly and undifferentiated adenocarcinomas.

Brain Metastasis	*Odds Ratio*	*P-value*	*95% Confidence Interval*
Age	0.96	<0.00	0.96-0.97
Sex (ref= male)	0.93	0.32	0.81-1.07
Race (ref= white)	1.03	0.66	0.91-1.16
Clinical T Stage (ref=T1a)			
T1b	0.78	0.20	0.54-1.13
T1c	0.89	0.67	0.53-1.51
Tumor size	1.07	<0.00	1.04-1.10
Tumor location (ref= right upper lobe)			
Right middle lobe	0.74	0.09	0.52-1.05
Right lower lobe	0.70	<0.00	0.56-0.88
Left upper lobe	1.06	0.51	0.90-1.24
Left lower lobe	0.96	0.69	0.77-1.19
Adenocarcinoma histology (ref= non-adenocarcinoma)	2.62	<0.00	2.23-3.07
Grade (ref= well differentiated)			
Moderately differentiated	2.20	<0.00	1.64-2.96
Poorly differentiated	8.15	<0.00	6.14-10.82
Undifferentiated/anaplastic	14.39	<0.00	8.64-23.97

Table 1. Predictors of brain metastasis at diagnosis among patients in the National Cancer Database with stage I NSCLC.

Keywords: NSCLC, Brain metastasis, Brain MRI

MA05 IMMUNE LANDSCAPE AND MOLECULAR PROFILING OF LUNG CANCER,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

MA05.03 Utilization of Genomic Mutation Signature to Predict the Immunotherapy Response in Non-small Cell Lung Cancer

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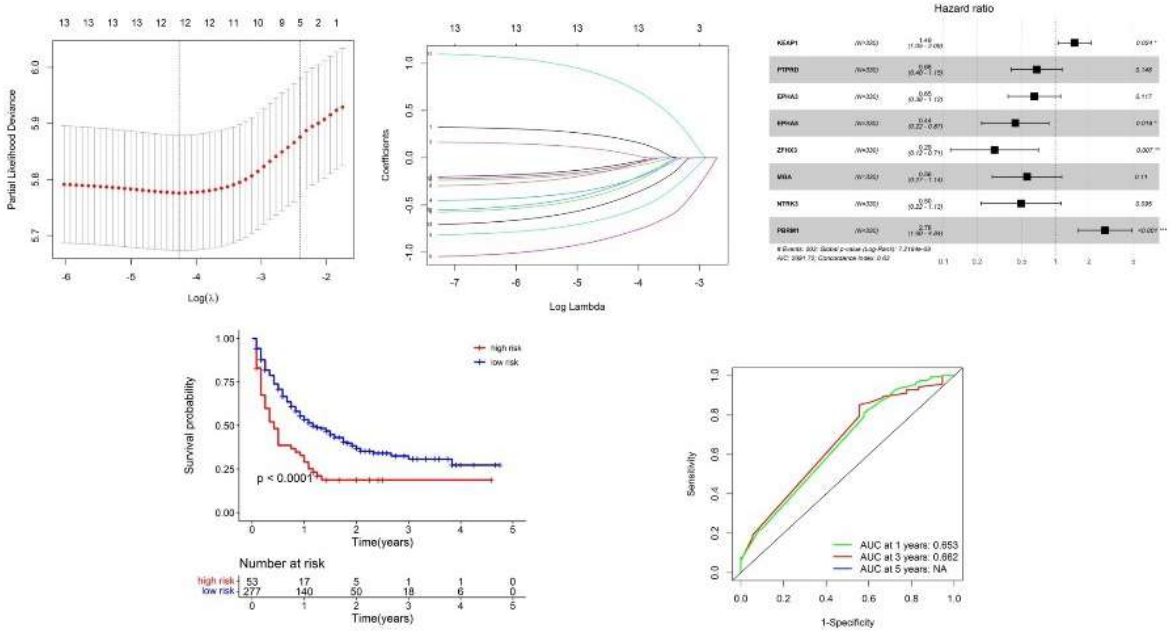
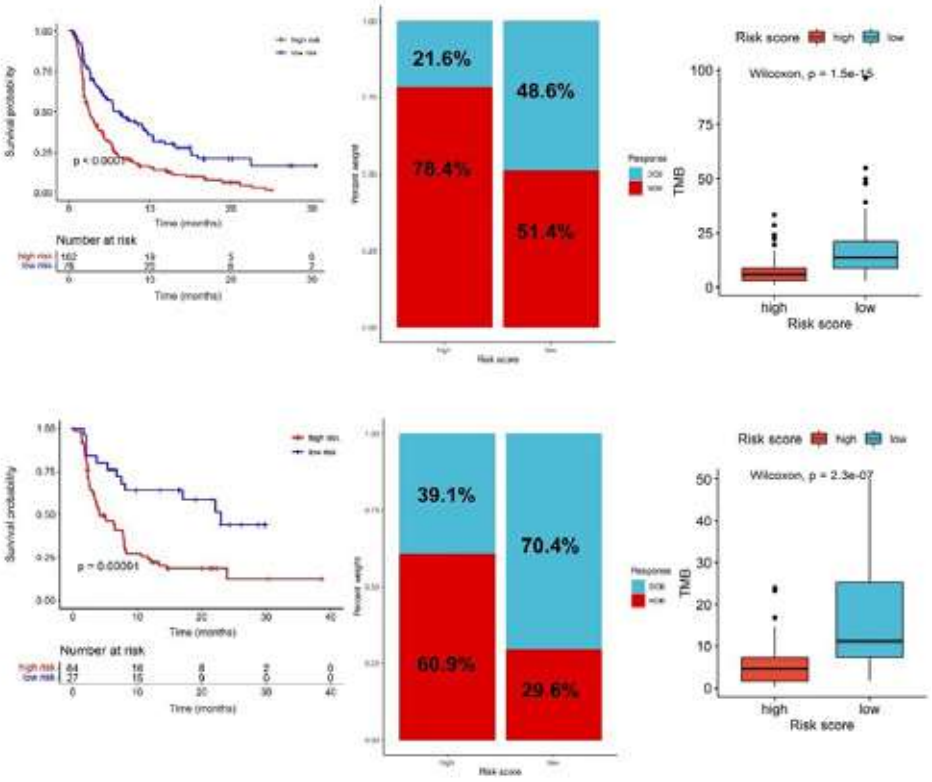
Introduction: Immune checkpoint inhibitors (ICIs) have facilitated more effective clinical therapy in non-small cell lung cancer (NSCLC). And the prediction of the immunotherapy response is an urgent issue in clinical practice. Thus, we investigated the genomic mutation signature associated with immunotherapy response and developed a gene mutation-based risk model to better predict the clinical outcomes of immunotherapy in NSCLC.

Methods: The genomic mutation profile of 330 NSCLC patients which received immunotherapy were collected from the Memorial Sloan Kettering (MSK) Cancer Center cohort. And two validation cohorts including 240 and 91 NSCLC patients after immunotherapy were gathered from cBioPortal database. We selected genes with high mutation frequency and genes related with prognosis status (P<0.05) using Cox regression analysis. Based on these genes, we conducted LASSO regression to establish prediction model. According to the computational formula, we calculated the risk score for samples. Then, patients were classified into high risk and low risk groups based on the optimum cutoff value. Prognosis difference between two groups were analyzed with Kaplan-Meier method.

Results: We developed a genomic classifier consisting of six decisive prognosis-related genes to calculate the risk score for NSCLC patients:Risk score = (0.395 × KEAP1) - (0.384 × PTPRD) −(0.433 × EPHA3)−(0.827×EPHA5)−(1.253×ZFHX3) − (0.584× MGA) - (0.703 × NTRK3) + (1.023×PBRM1). In three cohorts, high-risk patients has lower TMB and worse immunotherapy response according to this prediction model. The Kaplan-Meier analysis showed risk scores were negatively correlated with survival probabilities (P<0.001).

Conclusions: In our study, a gene mutation-based risk model has been developed and proved to be a a powerful genomic classifier in NSCLC, which can provide better prediction of immunotherapy response and may serve as a potential indicator guiding immunotherapy treatment decisions.





Keywords: Immunotherapy, non-small cell lung cancer, Genomic Mutation Signature

MA05 IMMUNE LANDSCAPE AND MOLECULAR PROFILING OF LUNG CANCER,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

MA05.04 Multiplex Phenotyping Reveals Spatial Immune Patterns in NSCLC

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Introduction: Accumulating evidence suggests that the presence of immune cells in the tumor environment determines prognosis and response to therapy. However, most studies rely on single markers, with a focus on T-cells, disregarding spatial cell neighboring. In the present study we provide a comprehensive characterization of immune cell infiltration patterns and an analysis of the mutational and clinicopathological background of non-small cell lung cancer (NSCLC) with respect to spatial immune phenotypes.

Methods: We established a fluorescence-based multiplexed immunohistochemical method in combination with a multispectral imaging system to quantify immune infiltrates in human lung cancer tissue. Tissue microarrays of a NSCLC cohort of 300 operated patients were stained by three panels, with antibodies against 13 immune markers (CD4, CD8, CD20, FoxP3, CD3, NKp46, CD56, CD68, CD163, CD1a, CD208, CD123, CD15), defining 13 immune cell types: CD4 effector cells (CD4-Eff), CD4 regulatory cells (CD4-Treg), CD8 effector cells (CD8-Eff), CD8 regulatory cells (CD8-Treg), B cells (B-cells), NK-cells (NK-cells), NKT-cells (NKT-cells), M1-macrophages (M1), CD163+myeloid cells (CD163), M2-macrophages (M2), immature dendritic cells (iDC), mature dendritic cells (mDC) and plasmacytoid dendritic cells (pDC). Cell densities and cell distances were calculated and used in association analysis.

Results: Overall, immune cells showed a coordinated infiltration with a general higher dominance in the stroma. Immune cell densities were not associated with histological subtypes or estimated tumor mutational burden. Immune cells within tumor cell nests were most often CD4 and CD8 effector cells together with M1 macrophages. Unsupervised hierarchical cluster analysis revealed a group of tumors with abundant NK and NKT cell infiltration, associated with CD4 and CD8 regulatory T-cells, but not with CD4 or CD8 effector cells. EGFR mutated cases showed a higher amount of intra-tumoral iDCs (FDR adjusted p-value = 0.03) while p53 mutated cases showed a lower infiltration of this cell type in the stroma (FDR adjusted p-value = 0.03). Cox regression analysis adjusted for stage, performance status (PS), and age indicated that CD4-Eff, CD4-Treg CD8-Treg, B-cells, and pDC were associated with longer survival (FDR adjusted p-value <0.05). When the distances of immune cells to each other were included in the density analysis (density/distances adjusted for PS, age, stage) the vicinity of CD4-Treg cells to B-cells, CD4-Eff, CD8-Eff and CD8-Treg cells had a positive impact on patient outcome. Also, density/distance ratios of CD4-Eff and CD8-Eff as well as CD4-Eff and CD8-Treg were associated with prolonged patient survival.

Conclusions: Our extended characterization of lung cancer tissue demonstrated the presence of tumors with abundant NK and NKT cell infiltration, not associated with effector cells suggesting a different mechanism of immunogenicity. We showed that certain immune cell subsets have increased tendency to invade tumor nests, potentially reflecting their anti-tumor activity. Finally, our findings suggest that the spatial information is a crucial component in the quantitative description of immune cells and should be considered to improve the accuracy of predictive biomarkers in NSCLC.

Keywords: Immuno-oncology, Prognosis, Tumor-infiltrating lymphocytes

MA05 IMMUNE LANDSCAPE AND MOLECULAR PROFILING OF LUNG CANCER,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

MA05.05 Analysis of CREBBP as a Potential Biomarker for Immune Checkpoint Therapy in Solid Tumors and Its Correlation with Immune Microenvironment

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Introduction: The *CREBBP* gene provides instructions for making CREB binding protein, is ubiquitously expressed and is involved in the transcriptional coactivation of many different transcription factors. Previous mechanism research on the *CREBBP* gene revealed that *CREBBP* is correlated with tumor occurrence and the efficacy of immune checkpoint inhibitors (ICIs) through directly regulating DNA damage response (DDR) pathway, but few clinical studies have proven this theory.

Methods: Next generation sequencing (NGS) data from an independent cohorts (the MSKCC study cohort) of 1661 patients and Chinese clinical dataset (panel on 381/733-gene) of 14855 patients with pan-cancer, were analyzed to explore the association between *CREBBP* mutations and immune biomarkers. TMB was defined as the total number of somatic non-synonymous mutations in coding region. MSI was evaluated by NGS of 500 known MSI loci. PD-L1 expression was evaluated using immunohistochemistry (Dako 22C3). Patients from three independent cohorts (OAK study cohort, POPLAR study cohort and MSKCC study cohort) were used to analyze the correlation between *CREBBP* mutations and the efficacy of immune checkpoint blockade immunotherapies (ICIs). Estimation of immune filtration cells scores were conducted via TIMER2.0 (http://timer.cistrome.org/) using TCGA-SKCM cohort.

Results: In the MSKCC cohort, there were 99 (59.6%) patients harboured CREBBP mutation (CREBBPmut), slightly more than the Chinese cohort (48.54%, 721/14855). For the TMB, both MSKCC (median, 24.18 Muts/Mb vs 6.26 Muts/Mb, P <0.0001) and Chinese (median, 39.08 Muts/Mb vs 8.47 Muts/Mb, P <0.0001) cohort were associated with higher TMB than the wild-type (CREBBPwt). Supplemental analysis of MSI in the Chinese cohort showed significant differences between the CREBBPmut and CREBBPwt groups (P <0.0001), as well as PD-L1 levels (P =0.0019). In terms of prognostic effect with ICIs therapy, CREBBP mutations were significantlyassociated with the overall survival (OS) of bladder (median, 15 months vs NR;HR = 0.42; 95% CI, 0.21-0.88; P = 0.017), colorectal (median, 43 months vs 13months; HR = 0.23; 95% CI, 0.07-0.75; P = 0.0085) and non-small cell lung(median, 4.8 months vs 13.5 months; HR = 2.04; 95% CI, 1.33-3.13; P = 0.00084)cancers. Interestingly, CREBBPmut in NSCLC was inversely associated with ICIs efficacy, as opposed to other solid tumors. However, there was no difference in PD-L1 expression between the two groups (P =0.53). Exploring the correlation between CREBBP and immune microenvironment, it was found that CD4+ T cell and NK cell infiltration was significantly higher in bladder (P = 0.022; P = 0.042) and colorectal (P = 0.031; P<0.001) patients with CREBBPmut, but significantly lower in NSCLC (P = 0.042; P = 0.043). That may be the reason for the opposite prognosis.

Conclusions: The results showed that the *CREBBP* had a high correlation in solid tumors with TMB, MSI and PD-L1. The *CREBBP* might a potential biomarker for ICIs therapy, and the immune microenvironment may be a factor affecting it.

Keywords: CREBBP, ICIs, Immune microenvironment

MA05 IMMUNE LANDSCAPE AND MOLECULAR PROFILING OF LUNG CANCER,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

MA05.07 Intertumoral Molecular Heterogeneity of Non-small Cell Lung Cancer with MET Exon 14 Skipping

Y. Han[1], S. Chen[1], C. Xiang[1], L. Guo[1], L. Zhu[1], J. Shao[1], T. Hu[2], J. Wang[2], C. Zhu[2]
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This abstract is under embargo until August 7 at 10:10 Vienna, Austria Time, CEST.

MA05 IMMUNE LANDSCAPE AND MOLECULAR PROFILING OF LUNG CANCER,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

MA05.08 MET Exon 14 Skipping Mutation in Non-Small Cell Lung Cancer (NSCLC) by Specific Mutation, Histology, and Smoking History

J. Marks[1], J. Yin[2], B. Halmos[3], L. Bazhenova[4], S.S. Ramalingam[5], M.E. Marmarelis[6], J. Xiu[2], P. Walker[2], M. Oberley[2], P.C. Ma[7], S.V. Liu[1]

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Introduction: MET exon 14 skipping mutations (METex14) are a heterogeneous family of oncogenic mutations (mt) found in NSCLC that can be effectively treated with approved targeted agents. While more commonly found in lung adenocarcinoma, METex14 is also known to occur in squamous NSCLC and in patients with a smoking history, unlike many other actionable drivers. We evaluated the association of histology and smoking history with the mutational landscape among patients with NSCLC harboring METex14 mutations.

Methods: NSCLC tissue samples were analyzed with DNA-based next-generation sequencing (NGS; 592 genes, NextSeq) or whole-exome sequencing (NovaSeq), RNA-based whole transcriptome sequencing (WTS, NovaSeq), and immunohistochemistry (IHC) at Caris Life Sciences (Phoenix, AZ). PD-L1 expression utilized the 22C3 clone (Dako); TMB-high was defined as ≥ 10 mt/Mb. Wilcoxon or Fisher's exact were used to determine statistical significance (p without and q with multi comparison correction). Immune cell fraction (QuanTiseq) and pathway analysis (ssGSEA) were informed by WTS analysis.

Results: In a cohort of 440 NSCLC samples harboring METex14, 147 distinct mutations were identified with more than 11 protein changes. The most common METex14 mutations were D1028H (8.4%), D1028N (7.0%), c.3082+2T>C (5.7%), D1028Y (5.2%), and c.3082+1G>A (4.5%). Co-mutations in TP53 were common (43.9%) but varied by specific mutation, with TP53 co-mutations in 53.9% of c.3082+3A>T but only 21.1% of c.3082+1G>T. Overall, 8.6% were TMB-high. PD-L1 ≥1% was present in 82.2% of METex14 patients but varied by mutation type, with a median PD-L1 tumor proportion score (TPS) of 97.5% in c.3082+1G>C and 0% in c.3082+3A>G ($q<0.05$). Forty-nine cases (11.1%) had squamous histology, 381 (86.6%) had non-squamous histology, and 10 (0.2%) had adenosquamous histology. Co-mutations in TP53 were more frequent in squamous METex14 (90.4%) than non-squamous (60.7%). Squamous METex14 NSCLC had numerically shorter survival than non-squamous (mOS 336 vs. 1106 days, HR 1.22, $p=0.47$). Smoking status was available for 93 METex14 cases: 79 (84.9%) were smokers, and 14 (15.1%) were non-smokers. HLA-G (TPM) mRNA expression was significantly upregulated in non-smokers compared to smokers (0.31 vs. 0.09 TPM, $q<0.05$). There were no other significant differences in co-mutations or activation of signaling pathways by smoking status after controlling for other variables.

Conclusions: Within METex14 NSCLC, there is significant variability, with heterogeneity in co-mutations, TMB, and PD-L1 expression across distinct METex14 mutations. METex14 occurs in both squamous and non-squamous NSCLC, but there are differences in co-mutations and outcomes by histology. HLA-G mRNA expression is lower in smokers compared to non-smokers. The impact of these differences on treatment, with either targeted therapy or immunotherapy, warrants further investigation.

Keywords: MET exon 14 skipping, NSCLC, NGS

MA05 IMMUNE LANDSCAPE AND MOLECULAR PROFILING OF LUNG CANCER,
SUNDAY, AUGUST 7, 2022 - 15:45–16:45

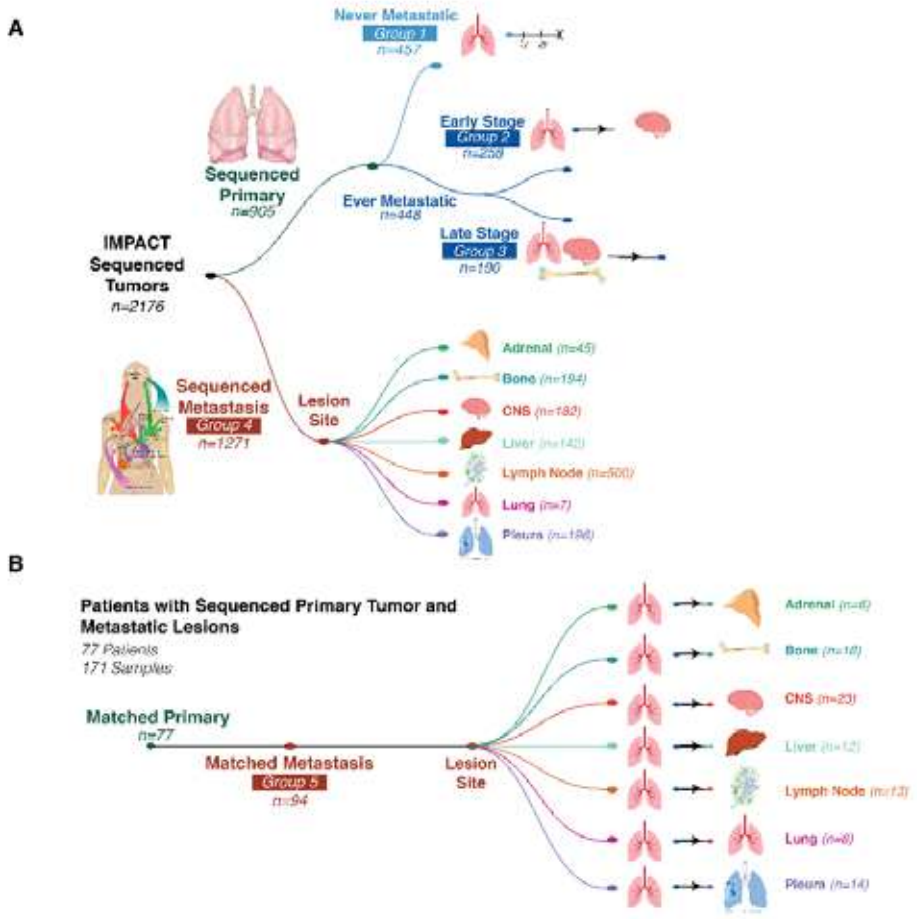
MA05.09 Genomic Mapping of Metastatic Organotropism: Analysis of 2326 Primary and Organ-Specific Metastases in Lung Adenocarcinoma

H. Lengel

Memorial Sloan Kettering Cancer Center, New York/NY/USA

Introduction: Lung adenocarcinoma (LUAD) preferentially metastasizes to specific organ sites, a process known as organotropism. To expand upon pan-cancer analyses that have analyzed genomic features associated with metastasis, we performed an integrative analysis of clinicopathologic and genomic data from a large series of patients treated at a single institution to identify features associated with LUAD metastasis and organotropism.

Methods: We examined 2326 LUAD specimens with clinicopathologic annotation and genomic data from broad-panel next-generation sequencing. Metastatic history was mapped to 7 common organ sites including the adrenal glands, bone, central nervous system (CNS), liver, lung, lymph nodes (LN), and pleura. 905 primary tumor samples and 1271 metastatic lesions were divided into four groups based upon sample type and timing of metastasis. Comparisons were performed between ever-metastatic and never-metastatic primary tumors, primary tumors with metastasis to different organ sites, metastatic samples from different sites, and between primaries and metastases. A separate analysis of matched samples from 77 primary tumors and 94 metastases was also performed. Univariate and multivariate models were used to investigate clinicopathologic and genomic differences between groups.



Results: We identified clinicopathologic and genomic features associated with ever-metastatic tumors including 4 genes (*EGFR, MYC, SMARCA4,* and *TP53*) which were also associated with metastasis-free survival (MFS). Of the features associated with ever-metastatic tumors, younger age, male sex, *TP53* alterations, and *ERBB2* alterations were also associated with greater

metastatic burden. In our analysis of site-specific metastasis, we identified *SMARCA4* and *TP53* alterations as associated with organotropism to the bone and LN, respectively. In a subsequent analysis of time to metastasis we identified unique temporal features such as *CDKN2A* alterations and HIPPO pathway alterations with shorter time to bone and CNS metastases, respectively. We identified greater mutational burden (TMB) and increased chromosomal instability in metastatic lesions when compared to primary tumors. Finally, in our analysis of matched samples, we catalogued somatic alterations that were shared or private to either the primary or the metastatic specimen and found private alterations in metastatic samples were frequently copy-number alterations or fusions that were not actionable.

Conclusions: In the largest analysis to date of the genomic and clinicopathologic determinants of LUAD metastasis and metastatic organotropism, we have highlighted features associated with the development of metastases, metastatic dissemination, and metastasis-free survival. Our data shows an overall trend towards greater mutational burden and more chromosomal instability in metastases than primary tumors, but without a corresponding increase in therapeutically actionable targets.

Keywords: Lung Adenocarcinoma, Metastasis, Genomics

MA06 RESECTABLE AND UNRESECTABLE LOCALLY ADVANCED LUNG CANCER,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA06.03 Pre-treatment ctDNA Levels Significantly Predicts of OS and PFS in NADIM II Trial

A. Romero[1], R. Serna[1], E. Nadal[2], J.L. Glez Larriba[3], A. Martínez-Martí[4], R. Bernabé[5], J. Bosch-Barrera[6], A. Garrido Fernandez[7], V. Calvo[1], A. Insa[8], S. Ponce[9], N. Reguart[10], J. De Castro[11], B. Massutí[12], R. Palmero[2], C. Aguado de la Rosa[3], J. Mosquera[13], M. Cobo[14], A. Aguilar[15], G. López Vivanco[16], C. Camps[17], F. Hernando Trancho[3], R. Lopez Castro[18], T. Moran[19], I. Barneto[20], D. Rodríguez-Abreu[21], A. Cruz[1], M. Provencio[1]

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Introduction: Neoadjuvant nivolumab plus chemotherapy has recently received approval for early-stage non-small cell lung cancer. Prognostic factors capable to discriminate between patients at high- or low-risk of progression and death can be useful to tailor subsequent treatment.

Methods: NADIM II (NCT03838159) is an open-label, randomized, two-arm, phase II, multi-center clinical trial. Patients with resectable clinical stage IIIA (per AJCC 7th ed) NSCLC, ECOG PS 0-1, and no known EGFR/ALK alterations were randomized to receive Nivolumab (NIVO) 360mg + Paclitaxel 200mg/m^2 + Carboplatin AUC5 for 3 cycles every 21 days (+/- 3 days) as neoadjuvant treatment followed by surgery, or Paclitaxel 200mg/m^2 + Carboplatin AUC5 for 3 cycles every 21 days (+/- 3 days) followed by surgery. Patients with R0 resection confirmed by pathological evaluation initiated adjuvant administration of NIVO (480 mg Q4W) within the 3rd to 8th week (+ 7 days) from surgery and for 6 months. The circulating tumor DNA (ctDNA), from the pre-treatment plasma sample, was analyzed with the TruSight Oncology ctDNA next-generation sequencing (NGS) assay.

Results: Median follow up time was 21.2 (15.1-25.6) months**.** Baseline ctDNA was detected in 52 of 54 (91.4%) of the pre-treatment plasma samples and were significantly associated with tumor size (maximum diameter ≥ 70mm) (P=0.006). Pre-treatment ctDNA levels were significantly associated with progression free survival (PFS) and overall survival (OS) and regardless of the cutoff used (table 1). Using a cutoff of <5% mutant allele frequency (MAF), patients with low ctDNA levels), at baseline, had significantly improved PFS and OS than patients with high ctDNA levels (HR: 0.19; 95%CI: 0.07-0.52; P=0.013 and HR: 0.13; 95%CI: 0.04-0.45; P=0.001, for PFS and OS, respectively).

Conclusions: Baseline ctDNA clearly identified patients at high risk of progression and death and may be used to tailor subsequent treatments accordingly.

Cutoff	PFS	OS		
HR (95% CI)	**p.value**	**HR (95% CI)**	**p.value**	
MAF4	0.24 (0.089-0.67)	0.006	0.15 (0.042-0.53)	0.0032
MAF4.5	0.19 (0.068-0.52)	0.0013	0.13 (0.036-0.45)	0.0014
MAF5	0.19 (0.068-0.52)	0.0013	0.13 (0.036-0.45)	0.0014
MAF5.5	0.29 (0.094-0.9)	0.033	0.26 (0.067-1)	0.055
MAF6	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF6.5	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF7	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF7.5	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF8	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF8.5	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF9	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF9.5	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF10	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF15	0.18 (0.023-1.5)	0.11	0.15 (0.019-1.2)	0.08

Table 1. Hazard ratio and 95% CI for PFS and OS according to ctDNA levels at baseline

Keywords: ctDNA levels, overall survival prediction, neoadjuvant CH-IO

MA06 RESECTABLE AND UNRESECTABLE LOCALLY ADVANCED LUNG CANCER,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA06.04 Phase II Study of Durvalumab Plus Concurrent Radiotherapy in Unresectable Locally Advanced NSCLC: DOLPHIN Study (WJOG11619L)

M. Tachihara[1], K. Tsujino[2], M. Shimokawa[3], T. Ishihara[1], H. Hayashi[4], Y. Sato[5], T. Kurata[6], S. Sugawara[7], Y. Shiraishi[8], S. Teraoka[9], K. Azuma[10], H. Daga[11], M. Yamaguchi[12], T. Kodaira[13], M. satouchi[2], N. Yamamoto[9], K. Nakagawa[4]

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This abstract is under embargo until August 8 at 12:15 Vienna, Austria Time, CEST.

MA06 RESECTABLE AND UNRESECTABLE LOCALLY ADVANCED LUNG CANCER,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA06.05 Consolidation Nivolumab and Ipilimumab or Nivolumab Alone Following Concurrent Chemoradiation for Patients with Unresectable Stage III NSCLC

G.A. Durm[1], H. Mamdani[2], S. Althouse[3], S. Jabbour[4], A. Ganti[5], S. Jalal[1], J. Chesney[6], J. Naidoo[7], B. Hrinczenko[8], M.J. Fidler[9], T. Leal[10], L. Feldman[11], N. Fujioka[12], N. Hanna[1]

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This abstract is under embargo until August 8 at 12:15 Vienna, Austria Time, CEST.

MA06 RESECTABLE AND UNRESECTABLE LOCALLY ADVANCED LUNG CANCER,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA06.07 Molecular Typing of pN2 Lung Adenocarcinoma: A Retrospective Study Based on Transcriptome Sequencing

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Introduction: In the eighth edition of the pathological N2 (pN2) descriptor of lung adenocarcinoma (LUAD) was recommended to be subdivided into three categories (pN2a1, pN2a2, and pN2b) according to their prognostic heterogeneity. However, the study on the biomolecular characteristics that lead to the prognostic heterogeneity of this disease was limited.

Methods: The pN2 stage patients with LUAD from the The Cancer Genome Atlas (TCGA) database were enrolled for analysis, all patients were classified into different molecular types by consistent clustering. The analysis of disease-free survival (DFS), overall survival (OS), differential genes, biology, and cell infiltration in the immune microenvironment was performed. All findings were validated in GSE68465 dataset.

Results: We divided pN2 patients with LUAD into two categories: N2-A and N2-B, survival analysis showed that DFS (30.2 months vs 8.2 months, P=0.016) and OS (46.0 months vs 15.9 months, P=0.003) of N2-A patients were significantly better than those of N2-B patients, multivariate analysis confirmed that molecular classification was an independent factor affecting the prognosis of pN2 stage LUAD. Notable, further analysis showed that the DFS (P=0.523) and OS (P=0.250) of pN2-A patients were not even different from those of pN1 patients. We also found that compared with pN2-A stage patients, pN2-B stage patients had a higher frequency of canonical oncogenic pathways mutations, more immunosuppression, and a higher proliferation rate and classic carcinogenic molecular events. Moreover, we established a gene prediction model based on LUAD pN2 molecular classification of 24 genes, and the predictive effect of this model was reasonable. Finally, the above-mentioned meaningful results were basically confirmed in the GES68645 database.

Conclusions: Our results provided that molecular classification model based on gene signature for pN2 stage LUAD confirmed the underlying reasons for the heterogeneity of this type of disease, and was expected to be a powerful supplement to pN2 substaging and guide individualized treatment.

Keywords: lung adenocarcinoma, pN2 stage, molecular classification

MA06 RESECTABLE AND UNRESECTABLE LOCALLY ADVANCED LUNG CANCER,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA06.08 Long-term Survival and Competing Risks of Death in the ESPATUE Randomized Phase-III Trial in Stage III NSCLC

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Introduction: An increasing number of stage III non-small-cell lung cancer (NSCLC) patients experience long-term survival (LTS). New treatment principles of checkpoint inhibitor (CPI)-immunotherapy have specific impact on LTS in all LC stages. Therefore, we need to reassess randomized phase-III trial datasets looking at optimum local treatment. We have already reported randomized phase-III ESPATUE-trial results looking at definitive surgery versus definitive boost-radiochemotherapy following complex induction (Eberhardt et al, J Clin Oncol 2015). Here, we update 5- and 10-yrs-LTS-data and report competing risk of deaths for the different Tx-strategies.

Methods: Complete trial design in potentially resectable stage-III NSCLC including induction with chemotherapy and concurrent chemoradiotherapy has been published (Eberhardt et al, JCO 2015). Here, we update LTS based on follow-up until 1/2022 for all pts still alive including recent surveillance/follow-up visits. JMP 15.2 was used for survival functions. For survival comparison between both arms log-rank-test was used. SAS 9.4 was used for a competing risk of deaths analysis over the whole period of follow-up until 1/2022. LTS data of both arms are presented with percentages(%) and confidence intervals(CI). Comparison between arms was performed with the Gray-test.

Results: From 1/2004 until 1/2013 246 patients enrolled to the trial in selected centers in Germany and the Netherlands. Following induction 161 pts potentially resectable were randomized to definitive RTx/CTx-boost(arm A;n=80) or surgery(arm B;n=81). At last follow-up(1/2022) 37 of 246 pts were still alive, median follow-up of patients still alive was 129 months(range 76-204), pts alive 15/80 arm A, 16/81 arm B. Overall survival(OS,%,CI) following randomization: 5-y-OS: A (43.8(32.7-54.2)) B (43.2(32.3-53.6)); 10-y-OS: A (28.3(18.8-38.5)) B (29.9(20.2-40.3));p=0.70 log-rank. Progression-free survival(PFS,%,CI) following randomization: 5-y-PFS: A (30.0(20.4-40.2) B (29.2(19.7-39.4)); 10-y-PFS: A (23.3(14.6-33.1)) B (19.8(11.8-29.4));p=0.94 log-rank. Competing-risk-of-deaths in both arms summarized in Table 1: Deaths-from-First-Lung-Cancer(DfFLC);Treatment-Related-Deaths(TRD); Deaths from Comorbidity(DfCMB);Deaths from Second Cancer without Lung Cancer(DfSCwLC); Deaths from Second Lung Cancer(DfSLC).

Conclusions: LTS-rates in stage III show encouraging 5-y-OS and 10-y-OS and -PFS results and no significant differences between surgery and radiochemotherapy as definitive Local-Tx(B vs A). A detailed competing-risk-of-deaths-analysis shows, that there are no clear signals for relevant differences between both arms in DfFLC, TRD, DfCMB, DfSCwLC, and DfSLC. DfCMB and DfSLC turn out to be major long-term-risks of patients in these stages. These important phase-III data may serve as baseline information to compare with those in future protocols including CPI-immunotherapy. DfSLC may potentially be decreased by prospective LC-screening. DfCMB is mainly related to cardiovascular/vascular events. pulmonary events and infections/septicemia.

Table 1. Competing Risks of Deaths					
	A:10-yrs	**A:15-yrs**	**B:10-yrs**	**B:15-yrs**	**p Gray-test**
DfFLC%,CI	50.1 (38.6 - 60.5)	50.1 (38.6 - 60.5)	44.4 (33.3 - 55.0)	44.4 (33.3 - 55.0)	0.3733
TRD%,CI	2.5 (0.5 - 7.9)	2.5 (0.5 - 7.9)	6.2 (2.3 - 12.9)	6.2 (2.3 - 12.9)	0.2568
DfCMB%,CI	10.2 (4.7 -18.3)	20.8 (10.7 - 33.2)	10.0 (4.6-17.8)	16.3 (8.3 - 26.8)	0.9068
DfSCwLC%,CI	1.3 (0.1 - 6.1)	1.3 (0.1 - 6.1)	1.2 (0.1- 6.0)	3.6 (0.5 - 11.9)	0.9609
DfSLC%,CI	7.7 (3.1 - 15.1)	13.0 (5.4 - 24.0)	8.3 (3.3 - 16.2)	13.0 (5.8 - 23.2)	0.8631

Keywords: Stage III, Non-small-cell lung cancer, Long-term Survival and Competing Risks

MA06 RESECTABLE AND UNRESECTABLE LOCALLY ADVANCED LUNG CANCER,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA06.09 Deep Learning for Predicting MPR to Neoadjuvant Immunotherapy in NSCLC

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Introduction: A significant percentage of non-small cell lung cancer (NSCLC) patients could not achieve major pathologic response (MPR) through the neoadjuvant immunotherapy. This study, based on multicenter cohorts, purposes to utilize CT images to construct and validate a deep learning model for predicting MPR of NSCLC patients treated by neoadjuvant immunotherapy.

Methods: Patients undergoing curative surgery after neoadjuvant chemoimmunotherapy for NSCLC at Shanghai Pulmonary Hospital, Ningbo Hwa Mei Hospital, The First Affiliated Hospital of Nanchang University and Sir Run Run Shaw Hospital from January 2019 to December 2021 were included. The baseline characteristics and chest CT images within 2 weeks before neoadjuvant administration were retrospectively collected. Patients in Shanghai Pulmonary Hospital were divided into a training cohort and an inter-validation cohort at a ratio of 7 to 3, and patients at other centers were all grouped into the exter-validation cohort.

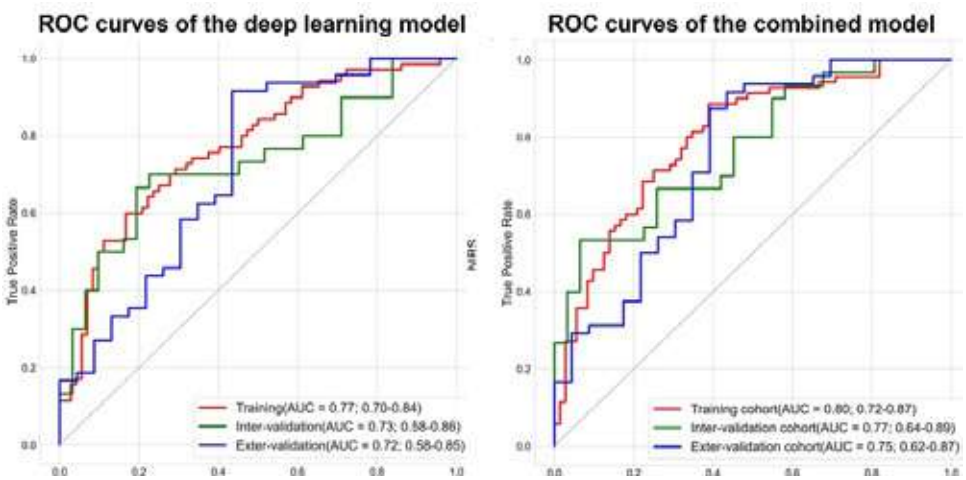
Results: A total of 274 patients were included, 142, 61 and 71 patients were divided into the training cohort, inter-validation cohort and exter-validation cohort, respectively. Most patients (n = 148, 54.0%) were evaluated as MPR and pathological complete response was achieved in 29.9% (n = 82) patients. The area under the curve (AUC) of the deep learning model to distinguish MPR was 0.73 (95% CI: 0.58 - 0.86) and 0.72 (95% CI: 0.58 - 0.85) in the inter-validation cohort and the exter-validation cohort, respectively. After integrating clinical characteristics into the deep learning model. The combined model achieved satisfactory performance in the inter-validation cohort (AUC: 0.77, 95% CI: 0.64 - 0.89) and the exter-validation cohort (AUC: 0.75, 95% CI: 0.62 - 0.87),

Conclusions: This is the first study to investigate the predictive value of deep learning for neoadjuvant immunotherapeutic efficacy in NSCLC. The proposed deep learning model can effectively predict MPR of NSCLC patients treated with neoadjuvant immunotherapy.

Table 1. Clinicopathological characteristics of all included patients

Characteristics	Entire cohort (n = 274)	Internal cohort (n = 203)		Exter-validation cohort (n = 71)	P value*
		Training cohort (n = 142)	Inter-validation cohort (n = 61)		
Age, Mean ± SD, years	62.1 ± 8.7	61.4 ± 9.3	61.8 ± 8.6	63.6 ± 7.3	0.379
< 65	151 (55.1)	79 (55.6)	35 (57.4)	37 (52.1)	
≥65	123 (44.9)	63 (44.4)	26 (42.6)	34 (47.9)	
Gender					0.071
Female	32 (11.7)	21 (14.8)	8 (13.1)	3 (4.2)	
Male	242 (88.3)	121 (85.2)	53 (86.9)	68 (95.8)	
Smoking status					0.234
Never smoked	145 (52.9)	82 (57.7)	28 (45.9)	35 (49.3)	
Smoker	129 (47.1)	60 (42.3)	33 (54.1)	36 (50.7)	
Pretreatment T stage					0.107
T1	41 (15.0)	22 (15.5)	9 (14.8)	10 (14.1)	
T2	109 (39.8)	60 (42.3)	19 (31.1)	30 (42.3)	
T3	64 (23.4)	33 (23.2)	11 (18.0)	20 (28.2)	
T4	60 (21.9)	27 (19.0)	22 (36.1)	11 (15.5)	
Pretreatment N stage					<0.001
N0	52 (19.0)	15 (10.6)	10 (16.4)	27 (38.0)	
N1	49 (17.9)	29 (20.4)	6 (9.8)	14 (19.7)	
N2	173 (63.1)	98 (69.0)	45 (73.8)	30 (42.3)	
Pretreatment TNM stage					<0.001
I	13 (4.7)	2 (1.4)	0	11 (15.5)	
II	36 (13.1)	15 (10.6)	5 (8.2)	16 (22.5)	
III	225 (82.1)	125 (88.0)	56 (91.8)	44 (62.0)	
Histology					0.020
SCC	170 (62.0)	80 (56.3)	35 (57.4)	55 (77.5)	
ADC	82 (29.9)	48 (33.8)	19 (31.1)	15 (21.1)	
Others	22 (8.0)	14 (9.9)	7 (11.5)	1 (1.4)	
Surgical procedure					0.665
Lobectomy	223 (81.4)	115 (81.0)	51 (83.6)	57 (80.3)	
Bilobectomy	31 (11.3)	16 (11.3)	8 (13.1)	7 (9.9)	
Pneumonectomy	20 (7.3)	11 (7.7)	2 (3.3)	7 (9.9)	
Pathological N stage					0.878
N0	179 (65.3)	90 (63.4)	43 (70.5)	46 (64.8)	
N1	34 (12.4)	19 (13.4)	7 (11.5)	8 (11.3)	
N2	61 (22.3)	33 (23.2)	11 (18.0)	17 (23.9)	
N downstage in pretreatment N2 disease					0.581
N2 to N0	105 (60.7)	59 (60.2)	31 (68.9)	15 (50.0)	
N2 to N1	25 (14.5)	15 (15.3)	5 (11.1)	5 (16.7)	
N2	43 (24.9)	24 (24.5)	9 (20.0)	10 (33.3)	
Response					0.112
MPR	148 (54.0)	70 (49.3)	30 (49.2)	48 (67.4)	
pCR	82 (29.9)	40 (28.1)	17 (27.9)	25 (35.2)	
Non-MPR	126 (46.0)	72 (50.7)	31 (50.8)	23 (32.4)	

*, comparisons were conducted between the internal cohort and external cohort; SD, standard deviation; MPR, major pathologic response; pCR, pathologic complete response; SCC, squamous cell carcinoma; ADC, adenocarcinoma



Keywords: Neoadjuvant immunotherapy, Deep learning, Non-small cell lung cancer

MA07 OVERCOMING RESISTANCE TO EGFR INHIBITORS,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA07.03 Real-world Landscape of EGFR C797X Mutation as a Resistance Mechanism to Osimertinib in Non-small Cell Lung Cancer

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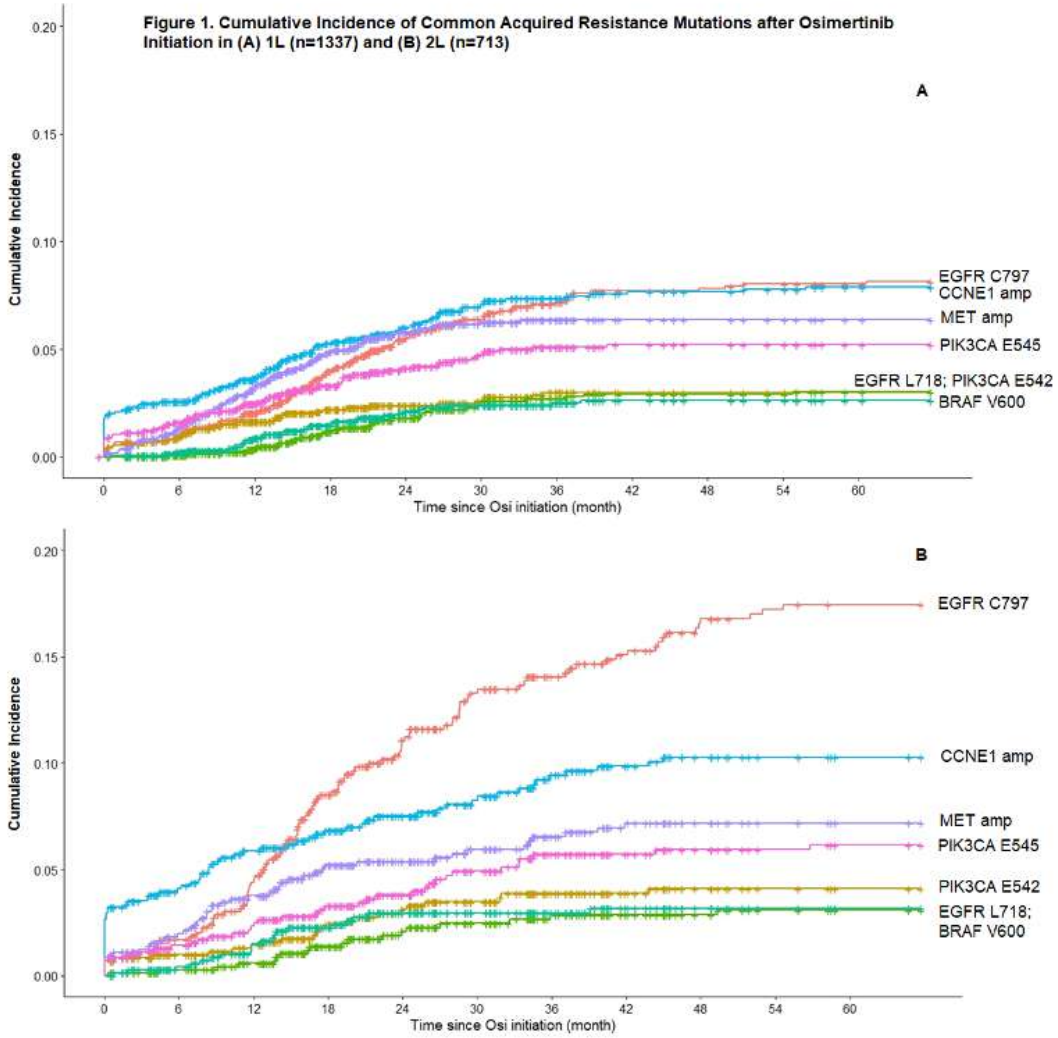
Introduction: The third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib has dramatically improved clinical outcomes for patients (pts) with EGFR-mutant (EGFRm) non-small cell lung cancer (NSCLC). Unfortunately, resistance develops after osimertinib, with EGFR C797X mutations as one of the major mechanisms. We utilized the Guardant INFORM real-world clinical-genomic database to assess the real-world detection rate and biomarker co-occurrence landscape of EGFR C797X and other resistance drivers in EGFRm NSCLC.

Methods: This retrospective observational study was conducted in a nationally representative clinical-genomic database of 174,000+ advanced stage cancer pts with comprehensive ctDNA results between 7/2014 and 6/2021 and associated clinical information from administrative claims. Adult patients with metastatic NSCLC with activating EGFR mutations detected by Guardant360 (G360) liquid biopsy test were included.

Results: Among 71,430 NSCLC pts, 9,306 pts had EGFR exon 19 deletion or L858R, with 1337 documented as treated with osimertinib first line (1L) and 713 second line (2L). In pts treated with 1L osimertinib, off-target amplification in MET and CCNE1 were the most common early resistance mechanisms in the first year after starting osimertinib, but then became more infrequent, while on-target mutations in EGFR C797X increased substantially over time and were the most common mutation documented in patients after 12 months on osimertinib. Median time to MET and CCNE1 amplification and EGFR C797X detection was 10.5, 9.1, and 16.8 months respectively.

Five years after osimertinib initiation in 1L, the cumulative incidence of MET and CCNE1 amplification and EGFR C797X mutations was 6.4%, 7.9%, 8.0%, with EGFR C797X cumulative incidence exceeding MET and CCNE1 amplification after 38 months (Figure 1A). Five years after osimertinib initiation in the 2L setting, this was heightened, with the cumulative incidence of MET and CCNE1 amplification and EGFR C797X mutations being 7.2%, 10.3%, 17.5% with EGFR C797X cumulative incidence exceeding MET and CCNE1 amplification after 19 months (Figure 1B). The cumulative incidence for C797X was higher in a subset analysis of patients who had discontinued osimertinib within a month of G360 (proxy for progression).

Conclusions: EGFR C797X is the most common acquired on-target or off-target resistance mutation after both 1L and 2L osimertinib treatment at 8.0% and 17.5% respectively, overtaking early off-target amplification in MET and CCNE1 after the first year of osimertinib. The study results demonstrate the need for the development of next-generation EGFR TKI to target C797X-driven resistance for patients with EGFRm NSCLC.



Keywords: TKI, EGFR-mutant, NSCLC

MA07 OVERCOMING RESISTANCE TO EGFR INHIBITORS,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA07.04 Amivantamab and Lazertinib in Combination with Platinum-Based Chemotherapy in Relapsed/Refractory EGFR-mutant NSCLC

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Introduction: Platinum-based chemotherapy is the current standard of care for patients with non-small cell lung cancer (NSCLC) whose disease progresses on osimertinib. However, osimertinib-relapsed disease may still be sensitive to EGFR and/or MET inhibition, as demonstrated by the antitumor activity observed with amivantamab and lazertinib in this setting (Cho *Ann Oncol* 2020; 31:S813; 1258O). Combining platinum-based chemotherapy with targeted inhibition of EGFR/MET signaling through the action of amivantamab and lazertinib may lead to improved outcomes in EGFR tyrosine kinase inhibitor (TKI)-relapsed/refractory disease.

Methods: The LACP (lazertinib, amivantamab, carboplatin, pemetrexed) cohort of the CHRYSALIS-2 study (NCT04077463) enrolled patients with EGFR-mutant NSCLC whose disease progressed on or after treatment with an EGFR TKI as last line of therapy (maximum of 3 prior lines). Patients received 1400 mg (1750 mg for bodyweight ≥80 kg) intravenous amivantamab weekly (21-day cycle) for the first 4 doses (first dose is split) up to cycle 2 day 1 and then 1750 mg (2100 mg for bodyweight ≥80 kg) every 3 weeks thereafter, in combination with 240 mg oral lazertinib daily, and 500 mg/m^2 pemetrexed with carboplatin (AUC5). Carboplatin treatment was stopped after 4 cycles. Adverse events were graded using CTCAE, v.5. Response in patients who had at least 1 postbaseline disease assessment will be assessed by the investigator per RECIST v1.1.

Results: Enrolled patients have received a median of 2 (range, 1-3) prior lines of therapy, including osimertinib (n=14), gefitinib (n=3), and afatinib (n=3). To date, at a minimum follow-up of 3 months, best responses include 10 patients with confirmed partial response, 7 with stable disease, and 3 with progressive disease. The most common treatment-emergent adverse events were infusion related reaction (73.3%), neutropenia (66.7%), rash (46.7%), thrombocytopenia (40.0%), fatigue and nausea (33.3% each). Of the 5 participants discontinued from treatment, 2 were because of chemotherapy-related serious adverse events and 3 were because of progressed disease.

Conclusions: Amivantamab in combination with lazertinib and chemotherapy yielded high overall response rates in patients who progressed on EGFR TKIs as prior line of therapy. The safety profile of the LACP regimen was consistent with the individual agents, with no evidence of new safety signals or additive toxicity.

Keywords: amivantamab, lazertinib, platinum-based chemotherapy

MA07 OVERCOMING RESISTANCE TO EGFR INHIBITORS,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA07.05 Phase 1b/2 Study of Combined HER Inhibition in Refractory EGFR-mutated Metastatic Non-small Cell Lung Cancer (NSCLC)

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Introduction: Patients with metastatic EGFR-mutated NSCLC who have progressed on osimertinib have limited treatment options. Dual EGFR blockade with HER2 blockade has been shown to have complete and long-term reversal of osimertinib resistance in preclinical models.

Methods: This is a single-arm, multi-center, open-label phase 1b/2 study to identify the recommended phase 2 dose (RP2D), safety, tolerability, and preliminary efficacy of the combination of osimertinib, necitumumab, and trastuzumab (ONT) in adults with histologically confirmed, metastatic NSCLC with an activating and sensitizing EGFR mutation who have progressed on osimertinib. Study participants receive osimertinib orally daily in conjunction with necitumumab and trastuzumab intravenously every other week. A 3+3 dose-escalation design is used to determine the RP2D of osimertinib and necitumumab (table 1). Patient reported outcomes (PRO-CTCAE) data and quality of life (FACT-L) data are collected prospectively. Efficacy is assessed as objective response rate (ORR) based on RECIST 1.1 criteria. Analyses include all patients who receive at least one dose of study treatment.

Results: As of February 1, 2022, 11 participants (median age = 64; range = 54-82) were enrolled and treated. Dose levels 1 and 2 had no dose-limiting toxicities, and the maximum dose—level 3—is being expanded. In all participants, the most common adverse events seen at any dose regardless of causality and grade include acneiform rash (73%), headache (55%), nausea (45%), dry skin (36%), diarrhea (27%), fatigue (27%), oral mucositis (27%), and vomiting (27%). Grade 3 treatment-related toxicities are acneiform rash (36%), diarrhea (9%), and hypertension (9%). There were no grade 4 or 5 adverse events or treatment-related deaths. The proportion of evaluable participants achieving partial response or stable disease was 62.5% (5/8). One participant with an EGFR p.L861Q mutation achieved a partial response (56% tumor shrinkage, ongoing at 5.5 months), and both participants treated at the highest dose level have had a numerical reduction in tumor size (27% in a participant with an EGFR exon 19 deletion and 16% in a participant with an EGFR p.L858R mutation).

Conclusions: ONT toxicities are manageable, and the combination has promising preliminary efficacy in EGFR-mutated metastatic NSCLC patients. The trial will continue to enroll.

Dose level	Osimertinib (mg)	Necitumumab (mg)	Trastuzumab (mg/kg)
-1	40 qd	400 q2w	6, followed by 4 q2w
1	40 qd	600 q2w	6, followed by 4 q2w
2	80 qd	600 q2w	6, followed by 4 q2w
3	80 qd	800 q2w	6, followed by 4 q2w

Table 1. Dose levels of osimertinib, necitumumab, and trastuzumab.

Keywords: Phase 1b/2, EGFR-mutated NSCLC

MA07 OVERCOMING RESISTANCE TO EGFR INHIBITORS,
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MA07.07 Clinical/Molecular Profile of Patients with Non-small Cell Lung Cancer (NSCLC) with Incidental Pathogenic Germline Variants Detected in cfDNA

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Introduction: Preliminary evidence highlighted inherited predisposition to lung cancer (LC) related to certain pathogenic germline variant (PGV) in cancer-predisposing genes. Liquid biopsy is able to identify incidental PGV (iPGV) in patients with non-small cell lung cancer (NSCLC), but so far, the frequency and the clinical/molecular profile of patients with NSCLC and PGV is unknown. Here, we report the iPGV detected in cfDNA and the clinical/molecular profile of carriers with advanced (a) NSCLC.

Methods: Genomic results were retrospectively queried from patients with aNSCLC who had Guardant360 testing in routine clinical care from 10/2020-12/2021. iPGVs were defined as non-synonymous/non-VUS in selected genes known to increase lifetime cancer risk (**Table1**) with variant allele frequency (VAF) >30% and pathogenicity defined by a proprietary bioinformatics pipeline. Clinical factors were extracted from test requisition forms. The driver group included somatic mutations (m) in *EGFR/KRAS/BRAF/MET/HER2*, fusions (f) in *ALK/ROS1/RET/NTRK1-3* and amplifications (a) in *HER2/MET*.

Results: Out of 31126, 721 patients had iPGV; 54% were female, with median age of 64; 80% had adenocarcinoma histology. Among them, 92% had iPGVs identified in the homologous recombination repair (HRR) pathway, 3% in mismatch repair (MMR) pathway and 5% *EGFR* iPGVs (T790M). *ATM* was the most common iPGV identified, with the splice-site alterations as the predominant variants.The characteristics of these patients are summarized in **Table 1.**In patients with iPGV in the HRR-pathway, the median age was 69, with similar female/male rate, except for *FANCA/RAD51D* (frequent in females). Up to 62% of cases had one somatic driver alteration; with *KRAS*m/*EGFR*m being the most common.In patients with iPGV in the MMR-pathway, the median age was 74; mainly observed in males except for *MSH6*. The somatic alterations were *KRAS*m/*BRAF*m.In *EGFR T790M*-iPGV population, with a median age of 62, was mainly observed in females; all cases had somatic *EGFR*m.No relevant clinical differences were observed between the iPGVs-population vs. the overall-population. In contrast, the somatic driver alterations in iPGVs-carriers were variable, particularly high in *ATM/CHEK2* in the HRR-pathway, in *MLH1/MSH2* in the MMR pathway, and in all *gEGFR* cases.

Conclusions: In this large cohort, cfDNA identified iPGVs involving *HRR/MMR/EGFR* pathways, with no relevant differences in the clinical profile in NSCLC. However, the somatic molecular profile seems to be different, with higher proportion of driver alterations. Somatic *KRAS*m was enriched in the HRR/MMR pathways; somatic *EGFR*m in the *gEGFR* pathway. The molecular profile could provide relevant information to establish the criteria for genetic testing in NSCLC.

	Homologous Recombination Repair (HRR) pathway							*Mismatch Repair (MMR) pathway*				*EGFR Pathway*
	ATM, *(N=266)*	***BRCA1*** *(N=101)*	***BRCA2*** *(N= 220)*	***CHEK2*** *(N=13)*	***FANCA*** *(N=39)*	***PALB2*** *(N=23)*	***RAD51D*** *(N=4)*	***MLH1*** *(N=3)*	***MSH2*** *(N=1)*	***MSH6*** *(N=13)*	***PMS2*** *(N=5)*	***EGFR*** *(N=33)*
Age Median, range	69 (30-94)	66 (40-84)	69 (22-100)	69 (56-81)	71 (60-89)	66 (44-81)	64 (50-78)	87 (57-98)	68	74 (44-85)	77 (53-81)	62 (46-77)
Gender Female Male	145 (55%) 121 (45%)	47 (47%) 54 (54%)	117 (53%) 103 (47%)	6 (46%) 7 (54%)	25 (64%) 14 (36%)	10 (43%) 13 (57%)	3 (75%) 1 (25%)	1 (33%) 2 (66%)	1 (100%)	9 (69%) 4 (31%)	1 (20%) 4 (80%)	22 (67%) 11 (33%)
Histology Adeno Squamous NOS	228 (86%) 24 (9%) 14 (5%)	74 (73%) 24 (24%) 3 (3%)	174 (79%) 33 (15%) 13 (6%)	11 (84%) 1 (8%) 1 (8%)	31 (79%) 6 (15%) 2 (5%)	14 (61%) 9 (39%) 0	4 (100%) 0 0	3 (100%) 0 0	1(100%) 0 0	9 (69%) 2 (15%) 2 (15%)	3 (60%) 1 (20%) 1 (20%)	29 (88%) 1 (3%) 3 (9%)
Molecular profile (somatic) Main Driver alterations	*KRAS* (36%) *EGFR* (10%) *BRAF* (4%)	*KRAS* (13%) *EGFR* (7%) *BRAF* (4%)	*KRAS* (13%) *EGFR* (15%) MET (8%)	*KRAS* (31%) *BRAF* (15%) MET (15%)	*KRAS* (21%) *EGFR* (5%) *ALK* (5%)	*KRAS* (26%) *ERBB2* (4%) *ALK* (4%)	*KRAS* (25%)	*KRAS* (33%) *BRAF* (33%)	*KRAS* (100%)	*KRAS* (38%) *BRAF* (8%)	*KRAS* (20%)	*EGFR* (100%)
Driver Group	56% (150/266)	27% (27/101)	42% (93/220)	62% (8/13)	38% (15/39)	39% (9/23)	25% (1/4)	67% (2/3)	100% (1/1)	54% (7/13)	20% (1/5)	64% (21/33)
Most common iPGVs	-Splice alt. (19%)	- Splice alt. (13%)	-S1982fs (4%)	- R117G (38%)	- Splice alt (26%)	- Splice alt (17%)	- R232* (50%) - R300* (50%)	- All unique	-A636P (100%)	- All unique	- P246fs (60%)	- T790M (97%)

Keywords: Germline pathogenic alterations, Driver oncogenic alterations, NSCLC

MA07 OVERCOMING RESISTANCE TO EGFR INHIBITORS,
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MA07.08 JIN-A02, a Highly Effective 4th Generation EGFR-TKI, Targeting EGFR C797S Triple Mutation in NSCLC

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Introduction: Among non-small cell lung cancer (NSCLC) gene mutations, epidermal growth factor receptor (EGFR) mutations are the most common and occur in approximately 50% of Asian NSCLC.[1]) Although EGFR-targeted therapeutics have been widely used for the treatment of EGFR-mutant lung cancer, acquired resistance invariably develops after 12-18 months in patients.[2]) EGFR C797S mutation, located within the tyrosine kinase domain, was recently reported to be a potential mechanism of resistance to irreversible EGFR inhibitors. There are no approved targeted therapies for EGFR C797S mutation, addressing the unmet clinical need. JIN-A02 is a novel, orally available, fourth-generation EGFR tyrosine kinase inhibitor (TKI) targeting C797S mutation and has demonstrated potent anti-tumor activity in preclinical models of double- or triple-mutant EGFR (ex19del/T790M or ex19del/T790M/C797S).

Methods: To test the inhibitory activity of JIN-A02, Ba/F3 cell lines overexpressing human EGFR mutants or human EGFR wild-type (WT) and patient-derived cell (PDC) lines harboring EGFR mutations were used. For *In vivo* efficacy test, triple-mutant (Ex19del/T790M/C797S or L858R/T790M/C797S) EGFR tumors were xenografted in mice models.

Results: JIN-A02 strongly inhibited cellular activity in Ba/F3 cells engineering to express the mutants ex19del/T790M/C797S (IC_{50}=51.0 nM) and L858R/T790M/C797S (IC_{50}=49.2 nM). It showed comparable potency to osimertinib in both double mutants (IC_{50}=12.3 for ex19del/T790M, IC_{50}=5.3 nM for L858R/T790M) and single mutants (IC_{50}=3.2 nM for ex19del, IC_{50}=9.1 nM for L858R). In addition, JIN-A02 was effective in cells harboring rare EGFR mutations (IC_{50}=102 nM for ex19del/T790M/L718Q, IC_{50}=62.1 nM for L858R/T790M/L718Q). JIN-A02 demonstrated a significant efficacy in PDC model. JIN-A02 inhibited EGFR ex19del/T790M/C797S more profoundly than osimertinib in YU-1097 cells, a PDC harboring the EGFR ex19del/T790M/C797S mutation (IC_{50}=61.5 nM for JIN-A02 vs. IC_{50}=3360 nM for osimertinib), while largely sparing EGFR WT activity in the EGFR WT A549 cell (IC_{50}=742.4 nM). In the Ba/F3 cells harboring ex19del/T790M/C797S xenograft mouse models, JIN-A02 significantly inhibited tumor growth at 50 mg/kg and 60 mg/kg daily repeated dosing groups (tumor growth inhibition (TGI=91.7% and 95.7%, respectively). In the YU-1097 PDC xenograft model, repeat oral dosing of JIN-A02 for 39 days at 50 mg/kg led to significant tumor regression (TGI=132.9%) whereas the tumor growth of mice treated with osimertinib (25 mg/kg once daily) was unaffected (TGI=51.7%). Antitumor efficacy was occurred at 10 mg/kg and 50 mg/kg in a dose-dependent manner. No significant toxicity was observed in all treated groups.

Conclusions: These preclinical studies demonstrated that JIN-A02 is a potential best-in-class fourth-generation EGFR TKI with high potency and selectivity. JIN-A02 showed robust activities against EGFR C797S mutation including single and double EGFR mutations. It was also effective against L718Q, for which there are currently no treatment alternatives. JIN-A02 is expected to provide a therapeutic opportunity for patients who progressed upon previous EGFR TKI, and a future first-in-human trial is planned for testing clinical efficacy and safety.

Keywords: 4th Generation EGFR-TKI, non-small cell lung cancer (NSCLC), C797S

MA07 OVERCOMING RESISTANCE TO EGFR INHIBITORS,
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MA07.09 BBT-176, a 4th generation EGFR TKI, for Progressed NSCLC after EGFR TKI Therapy: PK, Safety and Efficacy from Phase 1 Study

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Introduction: EGFR TKIs are the standard of care for *EGFR* mutated, advanced-stage NSCLC. Various mechanisms contribute to their resistance, among which a tertiary point mutation in the C797 residue of EGFR is the most well-known. Currently, there is no approved drug for NSCLC in patients harboring the *EGFR* C797S resistance mutation. BBT-176, a reversible, ATP-competitive inhibitor was developed to target such complex *EGFR* mutations and was shown to exhibit low nanomolar IC_{50} values in cell and animal efficacy models.

Methods: A phase 1 study was designed to determine the PK parameters, safety profile, recommended phase 2 dose (RP2D) and to explore efficacy. Patients harboring an *EGFR* mutation who were previously treated with at least one EGFR TKI were enrolled and tested by imaging study and underwent Guardant liquid biopsy every 6 weeks. BBT-176 was orally administered once daily continuously from 20 mg to 600 mg until progressive disease or intolerability. Bayesian linear regression model was employed to guide dose escalation. Intra-patient dose escalation to the next dose level was allowed.

Results: As of March 10, 2022, a total of 18 patients were treated with BBT-176. A triple mutant *EGFR* gene (exon 19 del/T790M/C797S or L858R/T790M/C797S) was detected in the blood of five patients. Drug exposure was apparently dose-proportional and within the therapeutic range with QD dosing. Common treatment-related adverse events (TRAEs) were nausea (n=5), vomiting (n=3), diarrhea (n=3), rash (n=4), pruritus (n=2), amylase increase (n=2), and lipase increase (n=2). No dose-limiting toxicity or discontinuation of treatment due to TRAE was reported so far. Reduction in *EGFR* mutation allelic frequency was observed in three patients, including non-classical exon 19 deletion and T790M. These changes were correlated with tumor shrinkage in two of the patients. Two patients harboring triple mutations of exon 19 del/T790M/C797S showed radiological improvements in both target and non-target lesions. Clinical outcomes in representative patients are summarized in the table.

Conclusions: Continuous daily dosing of BBT-176 was well-tolerated with manageable toxicities. The effectiveness of BBT-176 may be further enhanced by molecular selection of the patients and dynamic monitoring with liquid biopsy. Further exploration at RP2D is planned (NCT04820023).

Clinical outcomes of representative patients					
Dose	**Age/Gender/Race**	***EGFR* allelic frequency at baseline**	***EGFR* allelic frequency at nadir**	**Target lesion size change by RECIST**	**Investigator's Assessment of Overall Response**
160→ 320 mg	43/F/Asian	L747_K754delinsSPQ (30.6%)	L747_K754delinsSPQ (4.1%)	-30.3%	PR
320 mg	39/M/Asian	E746_A750del (39.7%), T790M (13.8%)	E746_A750del (25.7%), T790M (9.7%)	0.0%	SD
320 mg	52/F/Asian	E746_A750del (1.7%), T790M (0.4%), C797S* (0.5%) * in cis relation with T790M	E746_A750del (3.0%), T790M (1.5%), C797S (1.4%) From the second follow-up. All values increased from baseline, with no nadir	-12.1%	SD
480 mg	67/F/Asian	L858R (0.08%)	L858R (0.04%)	-11.8%	SD
480 mg	54/M/Asian	E746_A750del (56.8%), T790M (37.0%), L792H* (34.6%), C797S** (2.9%) *,** mutually exclusive and in cis relation with T790M	Not available at the time of submission	-26.3%	SD

Keywords: non-small cell lung cancer, EGFR, resistance

MA08 PATIENT ADVOCACY AND PATIENT PREFERENCES,
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MA08.03 Breathe Anew: Designing and Testing the Feasibility of a Novel Intervention for Lung Cancer Survivorship

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Introduction: Lung cancer survivors often suffer from chronic pain, anxiety, depression, fatigue, and dyspnea, and research in survivorship care has been lacking. We designed and tested the feasibility of Breathe Anew (BA), a multidisciplinary survivorship intervention comprising of physical rehabilitation using wearable technology; symptom management through mindfulness-based cognitive therapy (MBCT); and radiological surveillance. The first part of this study had been presented at the 2020 World Conference on Lung Cancer.

Methods: Patients who underwent resection for NSCLC at one academic site from 01/2019 to 07/2021 were postoperatively enrolled in this single-arm, feasibility trial. Participants were provided with a wearable activity tracker (Fitbit) and an education session on aerobic, deep breathing, and mindfulness exercises. Daily step goals were set by increasing the participants' baseline step count by 10% each week until 3-months. The first 25 participants were provided with an in-person group MBCT immersion session at 3-months, while the second with a guided mindfulness app (Headspace) for the study duration. EQ-5D-5L was completed at baseline and 3-months. Primary outcome was compliance with the intervention, while secondary included recruitment rate, differences in health-related quality of life, and patient-reported satisfaction. Continuous variables were compared using Student's t-test ($p<0.05$).

Results: Of the 92 patients screened, 67.39% (62/92) were eligible, and 80.65% (50/62) enrolled. Of the 30 ineligible, 86.67% (26/30) did not own a smart device. Median age was 66 (44-85) and 58% (29/50) were women. Participants spent a median of 85 days (79-90) on trial and wore their Fitbits for 79.89% ± 29.19% of days. The mean baseline daily step count for this cohort was 2,458 ± 2,101 steps, and daily step goals were achieved in 74.06% ± 26.15% of days. For the mindfulness component, 44.00% (11/25) attended the in-person group session, while 56.00% (14/25) used Headspace. Routine radiological surveillance appointments were attended by 100% (40/40) of the participants who required it. Significant improvement was seen in the overall health component of the EQ-5D-5L from before to after the intervention (64.69 ± 23.68 vs. 78.14 ± 14.03; p=0.0003). Overall, 100% (50/50) recommended BA for future patients, and 96.00% (48/50) stated they will buy their own Fitbits and continue with this BA lifestyle.

Conclusions: A postoperative survivorship intervention for lung cancer survivors is feasible based on the encouraging recruitment rate, and compliance rates with the physical rehabilitation and radiological surveillance components of the intervention. However, the MBCT component needs to be modified to improve compliance. BA also seems to motivate the participants in this feasibility study to improve their quality of life and continue with a healthy lifestyle post-intervention. This study therefore provides impetus for a large prospective comparative trial.

Keywords: Lung Cancer, Survivorship Program, Multidisciplinary

MA08 PATIENT ADVOCACY AND PATIENT PREFERENCES,
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MA08.04 Initial Steps in Creating a Patient-Centric Addendum to Clinical Trial Informed Consent Forms

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This abstract is under embargo until August 9 at 10:10 Vienna, Austria Time, CEST.

MA08 PATIENT ADVOCACY AND PATIENT PREFERENCES,
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MA08.05 Advancing Education and Advocacy for the Small Cell Lung Cancer Community

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Introduction: Small Cell Lung Cancer (SCLC) accounts for approximately 15% of lung cancer diagnoses and has historically had a poor prognosis coupled with limited educational and support resources directly targeting this population. GO2 Foundation for Lung Cancer developed a SCLC Initiative to reach, build, and learn from the SCLC community - an underserved patient group that has proven challenging to identify and engage in an on-going, consistent way. The goals were to increase SCLC awareness and education in patients and caregivers, improve small cell clinical trial knowledge and accrual, and to begin to build a connected SCLC community.

Methods: To inform the initiative, a focus group was held with healthcare providers and input was regularly solicited from patients and caregivers through a focus group, an online survey, and ongoing phone interviews. In the initial year of the project, the SCLC educational brochure was updated and two new one-page education materials were created (one for limited stage and one for extensive stage) that were requested by the healthcare provider focus group. Improved clinical trial knowledge, SCLC community development, and overall understanding of SCLC was facilitated by development of a new website landing page (www.go2foundation.org/smallcell), ten SCLC focused blog/news articles, and two online educational/support events.

Results: In 2021, 93 patients/caregivers affected by SCLC contacted the GO2 Foundation toll-free HelpLine with 53% of tickets being generated in the last quarter, indicating ongoing significant growth after launch in May 2021. Requests for LungMATCH treatment and clinical trial navigation increased proportionately with 8.9% of participants having SCLC in 2021, compared to 5.6% in 2020. Over 2000 of each of the new one-page materials and over 1800 of the updated brochures were ordered by healthcare providers. The time spent on SCLC landing page was nearly 3 minutes, higher than the website average. In addition, the December 2021 online educational support event ranked in the top three most attended online events for the year, despite small cell being a less common diagnosis.

Conclusions: Specific, focused outreach to the community of people with SCLC and their loved ones increased the uptake of education and support services. Utilizing healthcare provider input to inform resources was an important component. With dedicated effort, awareness and access to resources and support in specific underserved subsets of the lung cancer community can be improved. The SCLC Initiative is continuing to expand in 2022 with additional education and outreach efforts.

Keywords: Small Cell Lung Cancer, Advocacy, Education

MA08 PATIENT ADVOCACY AND PATIENT PREFERENCES,
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MA08.07 Understanding Lung Cancer Patients' Preferences in Speaking to Their Treatment Team: Insights from a Global Patient Experience Survey

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Introduction: The Global Lung Cancer Coalition (GLCC) is a partnership of 42 patient organisations across 30 nations dedicated to improving outcomes for lung cancer patients. During the COVID-19 pandemic, many lung cancer patients were offered virtual (telephone or video) consultations alongside or instead of face-to-face appointments. Reasons included protecting patients from exposure to the virus, saving travel time, and freeing-up clinical time. As health systems explore the potential of hybrid systems of telemedicine post-COVID-19, the GLCC wanted to understand patients' preferences for speaking to their treatment team and how they felt about virtual consultations.

Methods: In its third annual online patient survey, the GLCC included questions to ask how patients would like to be able to contact their treatment team in different situations. In total, the survey received 555 responses from patients across 21 countries.

Results: The findings show that globally, the majority of responding patients would prefer to see their treatment team in person when: finding out their diagnosis (91%, 406/444); having their first consultation (94%, 412/438); having regular check-ups (78%, 349/450); and there is a change to their treatment (84%, 374/444). However, if they are worried about something, many patients would also be willing to have a telephone consultation (32%, 146/452). Figure 1 highlights that patients in almost all countries favoured telephone over video consultations in all situations. However, video consultations were preferred over telephone consultations by patients in the USA for regular check-ups, and in Taiwan if there is a change to treatment.

Figure 1: Patients' responses when asked about their preferences in speaking to their treatment team in a range of situations.

How would you like to have a conversation with the treatment team in the following situations?		Finding out the diagnosis				The first consultation				Regular check ups				If there is a change to treatment				If I'm worried about something			
		Video	Telephone	Face-to-face	Not sure	Video	Telephone	Face-to-face	Not sure	Video	Telephone	Face-to-face	Not sure	Video	Telephone	Face-to-face	Not sure	Video	Telephone	Face-to-face	Not sure
Australia	%	0	0	100	0	0	0	100	0	11	33	56	0	0	13	88	0	0	44	56	0
	n	0	0	9	0	0	0	9	0	1	3	5	0	0	1	7	0	0	4	5	0
Brazil	%	6	0	88	6	0	0	100	0	0	0	100	0	0	6	94	0	13	19	69	0
	n	1	0	14	1	0	0	16	0	0	0	16	0	0	1	15	0	2	3	11	0
Bulgaria	%	0	100	0	0	0	100	0	0	0	100	0	0	0	100	0	0	0	100	0	0
	n	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0
Canada	%	0	12	85	0	4	4	92	0	12	23	62	0	12	23	62	0	8	35	54	0
	n	0	3	22	0	1	1	24	0	3	6	16	0	3	6	16	0	2	9	14	0
Denmark	%	0	9	91	0	0	3	97	0	9	26	66	0	3	12	82	3	3	37	60	0
	n	0	3	30	0	0	1	33	0	3	9	23	0	1	4	27	1	1	13	21	0
Ireland	%	0	0	100	0	0	0	100	0	10	20	70	0	10	10	80	0	0	40	60	0
	n	0	0	10	0	0	0	10	0	1	2	7	0	1	1	8	0	0	4	6	0
Italy	%	1	4	93	2	2	0	95	3	4	7	90	0	2	12	84	2	2	38	53	2
	n	1	4	98	2	2	0	97	3	4	7	95	0	2	13	89	2	2	41	57	2
Netherlands	%	0	3	97	0	0	3	97	0	9	19	71	0	3	3	94	0	0	30	67	3
	n	0	1	32	0	0	1	32	0	3	6	23	0	1	1	30	0	0	10	22	1
Portugal	%	0	0	100	0	0	0	100	0	0	0	12	0	0	0	100	0	0	31	69	0
	n	0	0	12	0	0	0	12	0	0	0	0	0	0	0	12	0	0	4	9	0
Spain	%	2	2	91	4	0	7	89	5	12	12	74	2	0	4	94	2	12	24	64	0
	n	1	1	43	2	0	3	39	2	6	6	37	1	0	2	46	1	6	12	32	0
Taiwan	%	6	7	85	2	4	8	89	2	4	9	83	4	11	6	83	0	6	21	70	4
	n	3	4	46	1	2	4	47	0	2	5	45	2	6	3	44	0	3	11	37	2
UK	%	2	3	95	0	2	2	97	0	11	19	70	0	6	13	81	0	11	36	48	5
	n	1	2	59	0	1	1	60	0	7	12	45	0	4	8	51	0	7	23	31	3
USA	%	3	7	83	7	3	0	90	7	21	7	69	3	3	3	83	10	3	31	59	7
	n	1	2	24	2	1	0	26	2	6	2	20	1	1	1	24	3	1	9	17	2
Mexico*	%	0	0	100	0	0	0	100	0	0	0	100	0	0	0	100	0	0	0	100	0
	n	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0
Greece*	%	0	0	100	0	0	0	100	0	0	0	100	0	0	100	0	0	0	0	100	0
	n	0	0	1	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	1	0
Germany*	%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	n	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
India*	%	0	0	100	0	0	0	100	0	100	0	0	0	0	0	100	0	100	0	0	0
	n	0	0	1	0	0	0	1	0	1	0	0	0	0	0	1	0	1	0	0	0
Isle of Man*	%	0	0	100	0	0	0	100	0	0	0	100	0	0	0	100	0	0	0	100	0
	n	0	0	0	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0
New Zealand*	%	0	0	100	0	0	0	100	0	100	0	0	0	100	0	0	0	0	100	0	0
	n	0	0	1	0	0	0	1	0	1	0	0	0	1	0	0	0	0	1	0	0
Sweden*	%	0	0	100	0	0	0	100	0	0	0	100	0	0	0	100	0	0	50	50	0
	n	0	0	2	0	0	0	2	0	0	0	2	0	0	0	2	0	0	1	1	0

*Responded to a general survey in 2022 which was open to patients from around the world that did not have a national survey
Some countries' results include less than five responses and therefore the percentages may seem larger than others with more responses

Conclusions: The findings highlight the importance of treatment teams seeking to understand patients' preferred methods of contact. Support will be needed for treatment teams and for patients if health systems are to successfully transition to a hybrid model of virtual and in-person appointments. This includes treatment teams and patients having appropriate settings and IT in which to conduct virtual consultations. Patients should be asked whether virtual consultations are working for them, since preferences may change with their experience of technology.

Keywords: advocacy, virtual consultations, COVID-19

MA08 PATIENT ADVOCACY AND PATIENT PREFERENCES,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA08.08 Impact of Lung Cancer on Quality of Life - A European Perspective

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Introduction: With improved outcomes, there is a need to identify and understand quality of life issues in the lung cancer community. In this context, it is important to capture the experiences of both people living with lung cancer and those in a caregiving capacity. Integration of supportive care within health care systems is essential, therefore it is paramount that needs are clearly recognized and understood.

Methods: An in-depth literature review was undertaken, from which two online surveys were designed. One specifically examining the needs of those living with lung cancer and the other relating to the needs of those in a caregiving capacity. Surveys were translated into 15 languages, were active for a period of 6 weeks and delivered using the SurveyMonkey platform. A quality control check of the data was performed and the data from different language versions were integrated together using SurveyMonkey analytic tools. Open questions were translated into English, aggregated, and standardized into a single curated data set. Sixteen interviews were also conducted with people impacted by lung cancer.

Results: For people impacted by lung cancer (n=515 respondents): 91% experienced some limitation in daily activities, with severe limitations experienced by 1 in 4 participants, which was linked to fatigue (71%), breathlessness (43%) and emotional issues (39%). Fatigue (45%), weight changes (32%), sleep disturbances (29%), digestive disorders (28.5%) and sexual issues (25%) impacted wellbeing the most. Significantly, 27% of participants felt overwhelmed by the side effects they experienced, with 53% not feeling equipped to self-manage symptoms and side effects. A quarter felt that they had little to no involvement in their healthcare decisions, and 1 in 5 felt that their opinion was never or rarely considered. Only 9% had fully discussed their preferences regarding end-of-life-care decisions with their healthcare team. For people in a caregiving capacity (n=285 respondents): 89% acknowledged some limitations in daily life, which mostly related to their own emotional concerns (63%), treatment requirements (54%) and caregiving responsibilities (49%). Eight in 10 were directly involved in treatment decisions and 32% stated they were the primary decision-maker. Most participants felt stress while providing care and experienced some difficulties in balancing caregiving with other responsibilities and their own care. For example: 82% reported some physical health deterioration since they started caregiving, with 37% acknowledging that they had not attended all their own medical appointments. For those still actively caregiving (n=127), half confirmed that they discussed end-of-life care with their loved one. However, 50% considered that they had not discussed it enough, and a further 9.5% had not talked about end-of-life, even though they would have preferred to.

Conclusions: Significant unmet needs were identified by people impacted by lung cancer. Health care systems must ensure access to supports to help with the impact of this disease, which should include the development of care plans and educational programs to support improved quality of life. There is also a need to raise awareness and develop communication supports concerning end-of-life care.

Keywords: Quality of life, Europe, Unmet needs

MA08 PATIENT ADVOCACY AND PATIENT PREFERENCES,
MONDAY, AUGUST 8, 2022 - 12:15–13:15

MA08.09 The Role of Social Media as a Platform for Patient-Led Support Groups

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Introduction: In the past ten years, many lung cancer social media communities have been established. These communities have become increasingly popular forums for communication and connection amongst those affected by lung cancer. Social media-based groups are not bound by the same geography and time constraints as in-person support groups. Each group sets their own rules and conditions for membership and discussion. The Canadian Lung Cancer Advocacy - Breathe Hope Facebook group ("Breathe Hope") was established in 2018 by and for Canadian lung cancer patients and caregivers. As of March 2nd, 2022 it has 279 members. This study was conducted in order to understand: (i) the role of social media in the evolution of the support group model; and (ii) what motivates patients and caregivers to participate in social media-based support groups.

Methods: A quantitative survey of Breathe Hope members was fielded from February 20 to 27, 2022.

Results: Seventy-seven people responded representing 27.6% of the members. The top motivators for joining were rated as joining a community with lived experience (66.2%) and access to lung cancer information (64.9%). After becoming members, the benefits of belonging were similar: "I am more informed about lung cancer" (81.8%); "I have joined a community that understands me" (50.6%); and "I feel less isolated" (33.8%). Close to half (44.2%) participate in the group on a daily basis. In contrast, 41.6% indicated that they only read posts in the group and do not create their own posts nor make comments. What motivates members to participate in Breathe Hope was a little different but consistent: the open safe environment (55.8%); [being able to express and read] true feelings/patient reflections (53.2%), and [that it is an] encouraging [environment] (51.9%). When asked about difficult aspects of being part of the social media group, [the] constant reminder of lung cancer (63.6%), end of life care discussions (55.8%), and loss of friends (41.6%) were most commonly reported. Comparing their comfort in Breathe Hope to in-person support groups, members expressed more comfort in discussing trouble coping with having lung cancer, fear of cancer coming back, fear of death/dying, and feeling apart from family and friends within Breathe Hope.

Conclusions: Social media groups are playing an important role in creating a safe, non-judgmental environment for patients and caregivers to connect and share, and are evolving the definition of a traditional patient support group and patient group. We know that the stigma associated with lung cancer leads many to feel reluctant to share their diagnosis and experience. The impact of feeling "less isolated" cannot be underestimated, especially given the absence of a face-to-face connection within these groups, and even more so in the context of the pandemic. As approaches to patient collaboration progress, the value and role of patient-driven, social media-based communities need to be recognized and incorporated into comprehensive strategies to address ongoing gaps in lung cancer education, awareness, support, research, and advocacy.

Keywords: Patient Advocacy, Social Media, Support Groups

MA09.03 Response of Palliative Radiotherapy in Bone Metastases of Lung Cancer - Results of Prospective Longitudnal Study from India

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Introduction: To objectively report the outcomes of uncomplicated bone metastases (BM) in patients of lung cancer (LC) treated with radiotherapy (RT) and observe the pattern and durability of pain response with the change in their quality of life (QOL).

Methods: Patients with histologically proven LC with radiologically confirmed BM were enrolled in this IRB approved, prospective observational study from June 2020 till Oct 2021. Majority received palliative RT to the painful BM using conventional RT. Primary endpoint was to evaluate pain response at 2 and 4 weeks and secondary endpoint was pain response at 3 and 6 months. Pain scores were documented using the Numeric Pain Rating Scale and the opioid analgesics were converted into Oral Morphine Equivalent Dose (OMED). The pain response was assessed as per updated International BM Consensus response criteria. Pain progression-free survival (PFS) was measured from the date of baseline pain assessment till date of pain progression or death. QOL were recorded using EORTC QLQ-C30 and BM22.

Results: A total of 125 consecutive patients were accrued. Majority were NSCLC (95%), males (67%), and non-smokers (66%). Majority had lytic lesions (82%) and in axial skeleton (77%). Driver mutation was identified in 47% and were started on TKIs. Seventy percent were treated with conventional RT using single posterior portals. Most common dose fractionation was 8Gy in single fraction. At baseline, mean pain score was 5.5 (SD +/- 2.46) with mean OMED of 17.5 mg/day (SD+/-18.8). After RT, CR and PR rates at 2 weeks (total n=86) and 4 weeks (total n=85) were 9% and 19% and 37% and 48%, respectively. CR and PR rates at 3 months (total n=67) and 6 months (total n=47) were 36% and 38% and 42% and 32%, respectively. ORR (CR+PR) at 3 and 6 months was 78% and 70%. The Indeterminate response rate (IRR) at 2 weeks, 4 weeks, 3 and 6 months were 45%, 27%, 21% and 25% while rate of pain progression (PP) was 8%, 6%, 1.5% and 4%, respectively. Opioid requirement significantly decreased to mean OMED of 11 (+/-15.2) and 6 mg/day (+/-11.6) at 3 and 6 months, respectively. Median duration of pain response was significantly higher in mutation positive cohort (7.8 vs 4 months, p=0.003). Re-irradiation rate was 13.6% and median time was 4.4 weeks. The pain PFS was 82% and 69% at 3 and 6 months, respectively. RT was well tolerated with no grade II or more acute or late toxicities. QOL improved significantly at 3 months with respect to pain, emotional functioning, fatigue, insomnia, and global health scores. Both symptom and function domains of BM22 also showed statistically significant improvement in mean absolute scores at 3 months in 60% patients.

Conclusions: Excellent and durable overall response rates with significant improvement in their QOL were achieved with conventional radiotherapy in this prospective study of uncomplicated BM in lung cancer patients. It is imperative to identify who required re-irradiation and possibly a more conformal, high dose radiotherapy, especially in driver mutation positive patients.

Keywords: Bone metastases, Palliative Radiotherapy, Lung cancer

MA09 PALLIATIVE RADIOTHERAPY: THE CHANGING LANDSCAPE WITH IMMUNOTHERAPY AND TARGETED THERAPIES, MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA09.04 First-line PD-1 Inhibitors and Chemotherapy Combined with or without Radiotherapy in Advanced Non-small-cell Lung Cancer

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Introduction: Immunochemotherapy has become a standard first-line regimen for advanced non-small-cell lung cancer (NSCLC). Several studies showed the synergistic effects of immunotherapy and radiotherapy on local and abscopal tumour control. But the data of first-line immunochemotherapy combined with radiotherapy for the advanced NSCLC is still scarce.

Methods: Patients with advanced NSCLC receiving first-line PD-1 inhibitors immunotherapy plus chemotherapy in a single center were retrospectively analyzed in this study. They were divided into two groups according to whether they had received radiotherapy. The efficacy and safety of first-line immunochemotherapy combined with radiotherapy (ICRT group) and immunochemotherapy alone (ICT group) were investigated.

Results: A total of 135 patients were included; 65 patients received PD-1 inhibitors plus chemotherapy and radiotherapy, while other 70 patients were treated with immunochemotherapy alone. The median interval time between radiotherapy and PD-1 inhibitors immunotherapy was 5 days (range, 0-96 days). Patients in the ICRT group achieved significant longer progression-free survival (PFS, median 16.5 vs 10.4 months, *P*=0.043) and overall survival (OS, median not reached vs 21.0 months, *P*=0.030) compared with those in the ICT group. The addition of radiotherapy was the only prognostic factor for PFS (HR=0.617, 95%CI: 0.385-0.989, *P*=0.045) and OS (HR=0.512, 95%CI: 0.277-0.947, *P*=0.033) by univariate Cox regression analysis. Patients were well tolerated and the overall incidence of adverse events was similar between the ICRT group and ICT group. One patient in ICRT group stopped immunotherapy because of severe immune-associated pneumonia. 3.1% of grade 3-4 radiation-related adverse events were observed.

Conclusions: Adding radiotherapy to first-line PD-1 inhibitors immunotherapy and chemotherapy improved outcomes of patients with advanced NSCLC and showed acceptable toxicity. Additional prospective studies exploring the first-line combination of immunochemotherapy and radiotherapy are warranted.

Keywords: Immunotherapy, Radiotherapy, Non-small-cell lung cancer

MA09 PALLIATIVE RADIOTHERAPY: THE CHANGING LANDSCAPE WITH IMMUNOTHERAPY AND TARGETED THERAPIES, MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA09.05 Increased PD-L1 Tracer Uptake in Recently-irradiated Lesions in NSCLC: Preliminary Results of a Phase 0 Trial (ImmunoPET) of a Novel PET Tracer

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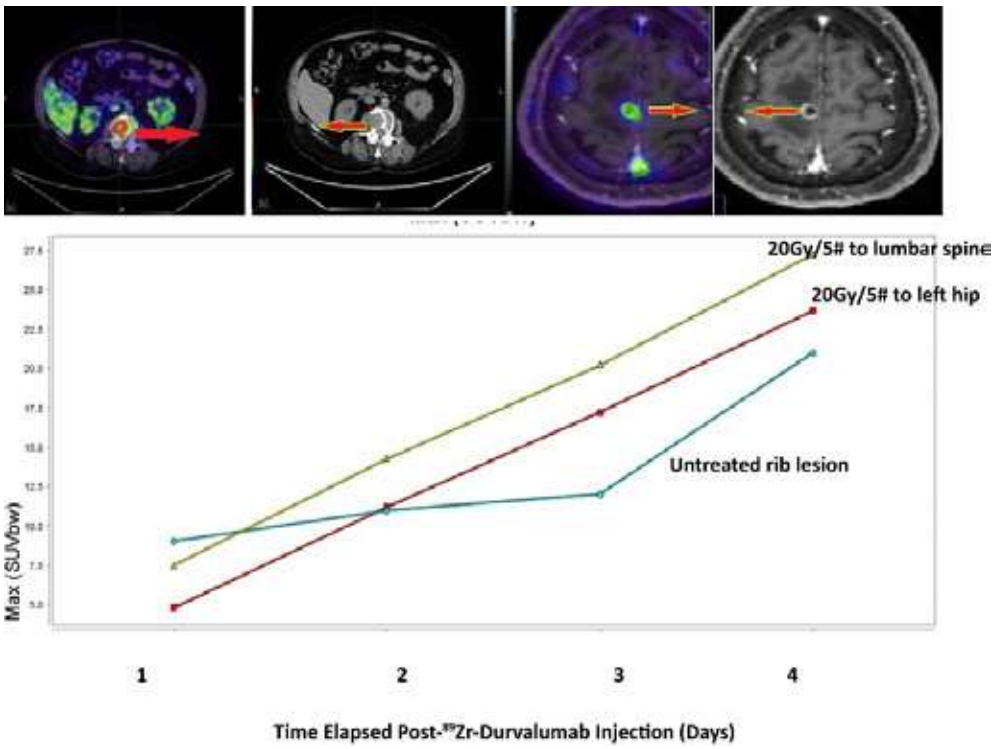
Introduction: A clinical trial was initiated to investigate the safety and optimum scanning protocol for a novel first-time-in human imaging agent, comprising the anti-PD-L1 monoclonal antibody durvalumab linked to the positron-emitting isotope ^{89}Zr using a desferrioxamine-squaramide ester in patients with NSCLC.

Methods: After the administration of the DFO-Sq-durvalumab tracer, PET imaging was specified for immediately after tracer injection, on day 1, and on approximately days 3 and 5. Scans were analysed both visually and semi-quantitatively.

Results: Four patients have been recruited to date to this ongoing ImmunoPET clinical trial. Eligible patients have advanced NSCLC with PD-L1 >25% on pre-enrolment biopsies. Three patients had recently received palliative radiotherapy (20-40 Gy) to all or some of their known disease sites as determined by FDG-PET or MRI, including brain metastases treated with SRS. In patients with FDG-avid tumour lesions apparent on baseline FDG-PET scans, all known disease sites showed ^{89}Zr-durvalumab uptake. There was significant heterogeneity within and between lesions. In one patient, who received palliative radiotherapy before PD-L1 imaging, to some but not all radiologically apparent lesions, including stereotactic radiosurgery to brain metastases, more rapid ^{89}Zr tracer uptake was seen in irradiated lesions compared to non-irradiated lesions (see figure). In a patient with an activating EGFR mutation who had attained a complete metabolic response on FDG-PET to osimertinib, no tumour related ^{89}Zr uptake was observed, thereby serving as a negative control. There was no significant bone marrow uptake of tracer and the tracer showed favourable tumour to background ratios at known tumour sites. One patient experienced a transient infusion reaction related to tracer administration.

Conclusions: A novel ^{89}Zr-DFO-Sq-durvalumab PET tracer imaged all known sites of disease in patients with PD-L1 positive NSCLC who had FDG-avid tumour lesions, including brain metastases. PD-L1 PET scans showed significant heterogeneity within and between tumour lesions. Recently irradiated tumours appeared to show more rapid tracer uptake than non-irradiated lesions, suggesting that radiation treatment may modulate PD-L1 in patients with cancer. These preliminary results suggest that this tracer is suitable for use in a planned clinical trial in stage III patients treated with curative-intent chemoradiation.



Keywords: Positron emission tomography, Radiation Therapy, Immunotherapy

MA09 PALLIATIVE RADIOTHERAPY: THE CHANGING LANDSCAPE WITH IMMUNOTHERAPY AND TARGETED THERAPIES, MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA09.07 Understanding Outcomes of Patients with Metastatic Non-Small Cell Lung Carcinoma Undergoing Whole Brain vs Stereotactic Radiotherapy

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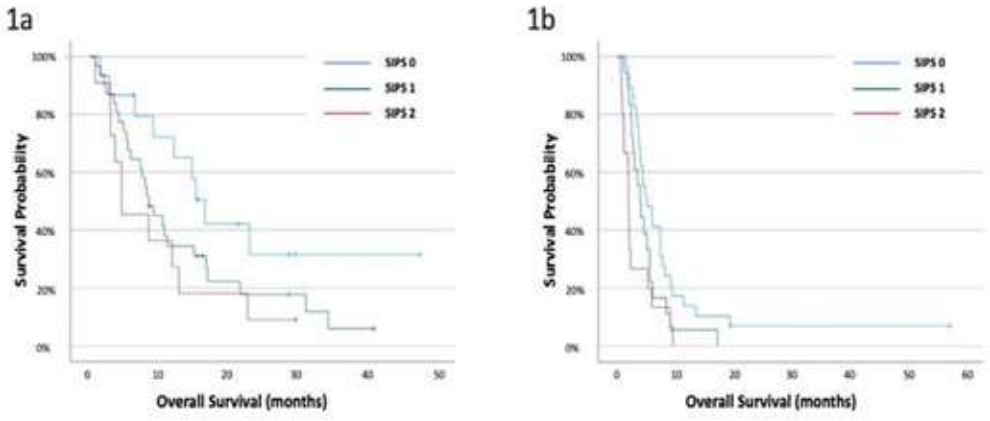
Introduction: Brain metastases occur in 10-20% of patients with non-small cell lung cancer (NSCLC). Management options include surgical resection, stereotactic radio-surgery (SRS), whole brain radiotherapy (WBRT), systemic therapy or best supportive care. At the Edinburgh Cancer Centre (ECC), the choice of treatment modalities is decided after multidisciplinary team discussion. To better understand variations in outcome, we evaluated the prognostic significance of the Scottish Inflammatory Prognostic Score (SIPS), a biomarker of systemic inflammation, in patients with NSCLC with brain metastases undergoing radiotherapy treatments.

Methods: All patients with NSCLC receiving radiotherapy-based treatment for brain metastases between 01/2016-03/2021 at ECC were identified. Clinicopathological data was gathered from electronic patient records. SIPS, assigning 1 point each for albumin <35g/L and neutrophil count >7.5X10^9/L to give a 3-tier categorical score, was calculated for each patient at the time of diagnosis of brain metastases. The relationship between SIPS and overall survival (OS) was examined.

Results: Data was available for 118 patients. 66% started radiotherapy treatment within 3 months of diagnosis of brain metastases. Median OS from date of radiotherapy treatment was 8.1 (IQR 2.8-17.1) months. 56 (47%) patients were treated with SRS and 62 (53%) with WBRT. Patients treated with SRS had more favourable survival than those treated with WBRT (10.4 months (IQR 4.6-21.5) v 3.9 months (IQR 2.0-7.2) (p<0.001). SIPS predicted survival in all patients (HR1.43 (95%CI 1.10-1.86) p=0.008). SIPS predicted survival in patients treated with SRS (HR1.60 (95%CI 1.04-2.47) p=0.034), stratifying survival from 4.5 (SIPS2), 8.5 (SIPS1) to 16.5 (SIPS0) months (Figure 1a). SIPS was also predictive of survival in patients treated with WRBT (HR 1.63 (95%CI 1.19-2.52) p=0.003), stratifying survival from 1.8 (SIPS2), 3.8 (SIPS1) to 5.0 (SIPS0) months (Figure 1b).

Conclusions: Patients with NSCLC metastatic brain lesions have poor outcomes. Patients treated with SRS have better outcomes than those treated with WBRT. This likely reflects selection for treatment at our institution, with SRS limited to patients with small, oligometastic, brain metastases, controlled systemic disease and of suitable ECOG performance status. For the first time we demonstrate that SIPS, a biomarker of systemic inflammation, predicts survival for patients with NSCLC receiving SRS or WBRT for brain metastases. In particular, we identify a small, but significant, group of patients we high systemic inflammation (i.e. SIPS2) who derive limited clinical benefits from these treatments. The SIPS may be an additional factor to consider when selecting treatment modalities for this group of patients.



Keywords: Brain metastases, Stereotactic Radiotherapy, Prognostic score

MA09.08 Radiotherapy Improves Outcomes to Immunotherapy in Patients with Stage III and IV NSCLC

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Introduction: Radiotherapy might augment systemic antitumoral responses to immunotherapy. We did a retrospective analysis to infer whether radiotherapy improves outcomes to immunotherapy in patients with stage III or IV non-small-cell lung cancer.

Methods: This retrospective study conducted at Enze Medical Center enrolled 259 patients with histopathology confirmed NSCLC and from December 1,2018 to December 31, 2021. These patients with stage III and IV non-small-cell lung cancer (NSCLC) were suitable for immunotherapy (Sintilimab). Some patients received radiotherapy at a specific and appropriate time point. Radiotherapy includes conventional radiotherapy (64.8Gy/30 fractions,and 54Gy/25 fractions) and stereotactic body radiotherapy (SBRT: 50Gy/5 fractions,60Gy/ 8 fractions). The endpoints were progression-free survival (PFS), and overall survival (OS).

Results: 259 patients were included in the retrospective analysis, 140 of whom had been only immunotherapy and 119 who had been immunotherapy plus radiotherapy. Baseline variables did not differ between treatment groups, including gender and age and smoking status and TNM stage and number of metastases and ECOG grade and histology. Median progression-free survival was all 6.00 months (95%CI 5.03-6.97), and immunotherapy alone 5.00 months (4.38-5.62) versus immunotherapy plus radiotherapy 9.00 months (95% CI 5.95-12.05; p<0.001) Figure 1A. Median overall survival was all 20.00 months (95%CI 15.27-24.73), and immunotherapy alone 16.00 months (95%CI 12.59-19.42) versus immunotherapy plus radiotherapy 30.00 months (95%CI 20.75-39.25; p=0·027) Figure 1B. A univariate analysis, ECOG=0, male, radiotherapy were associated with a significantly better progression free survival (P=0.03; P=0.002; P<0.001). A multivariate analysis, radiotherapy and ECOG=0 were independent prognostic factor with a significantly better progression free survival (HR 1.89 95%CI 1.41-2,54,P<0.001;HR 1.55 95%CI 1.16-2.07, P=0.003). A univariate analysis, ECOG=0, female, Stage III, squamous carcinoma and non-metastase were associated with a significantly better overall survival (P=0.002, P=0.036, P=0.002, P=0.025, P=0.01). A multivariate analysis, non-metastase was an independent prognostic factor with a significantly better overall survival (HR 2,42 95%CI 1.29-4.54, P=0.02). However, radiotherapy was a tendency factor with a better overall survival (HR 1.42 95%CI 0.95-2.14, p=0.09).

Conclusions: Adding radiotherapy in immunotherapy was significantly associated with a better outcome in patients with non-small-cell lung cancer.

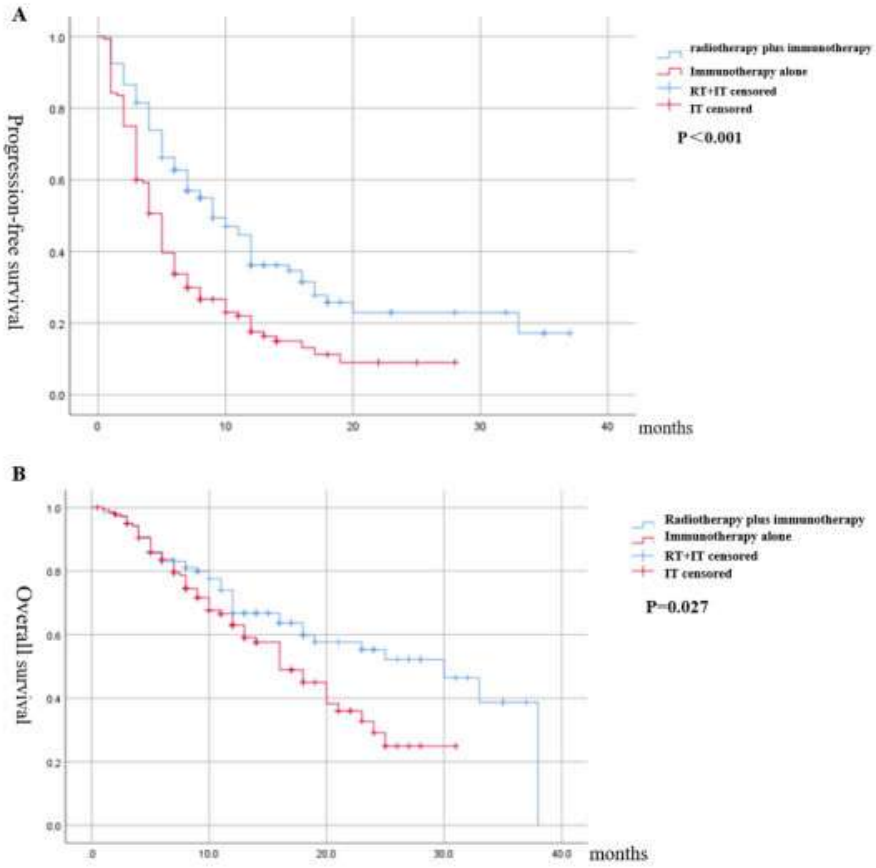

Figure 1: Kaplan-Meier analysis of progression-free survival (A) and overall survival (B)

Keywords: Radiotherapy, Immunotherapy, Non-small cell lung cancer

MA09 PALLIATIVE RADIOTHERAPY: THE CHANGING LANDSCAPE WITH IMMUNOTHERAPY AND TARGETED THERAPIES, MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA09.09 Perilesional Edema and Size of Brain Metastases as Prognostic and Predictive Factors to Local Therapy in Advanced Non-small-Cell Lung Cancer

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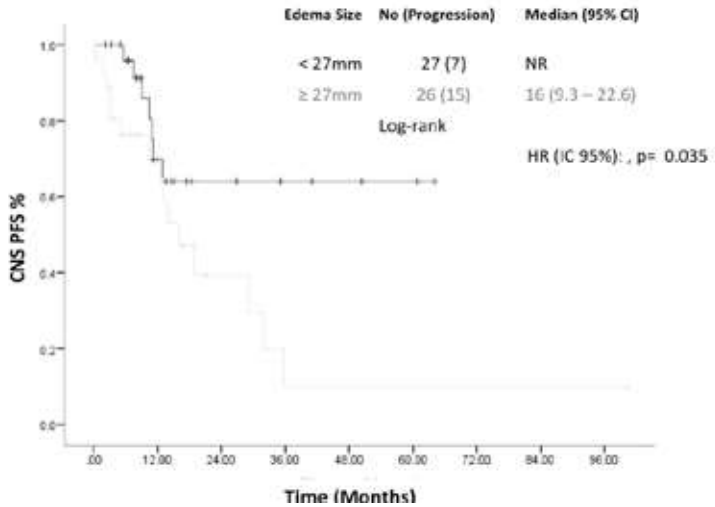
Introduction: Perilesional edema (PLE) associated with brain metastases (BMs) has been related to high morbidity and mortality in advanced non-small cell lung cancer (NSCLC) patients. Scarce evidence exists about the predictive usefulness of PLE and local therapy. This study aimed to evaluate the extent of PLE and BMs size as predictive and prognostic factors to local treatment.

Methods: This retrospective cohort study included 106 patients with a confirmed NSCLC diagnosis, central nervous system (CNS) disease, and CNS measurable disease from January 2010-December 2021. BMs were assessed by magnetic resonance image (MRI) at diagnosis. For those patients with less than three BMs, the sum of the maximum diameter in millimeters of each lesion [assessed on a gadolinium-enhanced T1 sequence] and the sum of the PLE in millimeters [assessed in a fluid-attenuated inversion recovery sequence (FLAIR)] were considered to calculate the average for each dimension. The three most representative lesions were chosen for patients with three or more BMs. Intracranial response (ICR), CNS control rate (DCR), and CNS progression-free survival (PFS) were assessed after radiosurgery (SRS) or whole-brain radiation (WBRT).

Results: The median age was 57.2 ± 12.8 years, 55% were males, lung adenocarcinomas (83%), and moderately or poorly differentiated tumors (80%). An EGFR mutant tumor was observed in 28.3% and treated with first or second-generation EGFR-TKIs. BMs were detected at diagnosis in 67%, multiple lesions observed in 73.6%, and ≥4 lesions in 38.7%. The mean BMs size was 19.2 ± 11.7 and mean associated PLE was 27.1 ± 28.5. Approximately 92.5% receive local therapy, WBRT (86%), and SRS (7.5%), of which sixty-six patients have an evaluable response. ICR was 62.1%, and CNS DCR was 86.4%. The mean PLE (27mm) was set as the cut-off point to associate with responses and survival. PLE >27mm at diagnosis was associated with a poor CNS DCR, [56.7% vs. 72.4%; p=0.049] and a shorter CNS PFS, non- reached vs. 16 months [95% CI (9.3-22.6); p: 0.035] compared with those patients with a lesser PLE extension **Fig.1**. In the multivariate analysis, a PLE (>27mm) remained significant for CNS PFS after adjustment for age, sex, and number of BMs.

Conclusions: An increased PLE associated with brain metastases in advanced NSCLC was predictive of a poorer intracranial disease control rate and related with a shorter CNS progression-free survival. This study warrants further prospective analyses assessing the predictive and prognostic role of PLE at baseline in NSCLC patients.

Figure 1. CNS progression-free survival according to PLE dimensions



Keywords: brain metastases, radiotherapy, perilesional edema

MA10 UPDATES IN THYMOMA,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA10.03 Is Thoracoscopic Thymectomy Safe and Oncologically Sound in Large Thymic Tumors?

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Introduction: Thoracoscopic thymectomy is being increasingly preferred for non-thymoma Myasthenia Gravis and smaller thymic tumors, however its safety and feasibility in large thymic tumors is yet to be established.

Methods: A retrospective analysis of a prospectively maintained database of surgeries performed for thymic pathologies in a Thoracic surgical unit at a Referral Cancer center was done. Thoracoscopic thymectomies (Video assisted (VATS) and robot assisted(RATS)) performed between 2005 and 2020 were included in the study with a follow up of 1 year. Thymectomies done as part of non-thymic surgeries, minimal access surgery converted to open surgery and diagnostic biopsies were excluded. Data pertaining to demographics, peri operative outcomes, staging, histology, adjuvant therapy and follow up were collected from electronic patient records and analyzed using SPSS 26.0

Results: A total of 227 thymectomies were performed during the said period with 34.4% (n=78) of them being performed thoracoscopic with a conversion rate of 4.8% (n=4). The mean age of the population was 49.7 years with nearly equal sex distribution (M:F-41:37). 2/3 of the procedures were VATS (n=52) and 30% (n=24) were RATS. Mean operating time was 167 min with a mean blood loss of 165 ml. Median time to removal of ICDs was 3 days with a median time to discharge of 4 days. Major complications (CD≥III) were noted in only 5.2% (N=4). 30-day post operative mortality was nil. 80% of the tumors were ≥5cm with a mean size of 6.6cm(Range:2.5-17.8cm). Thymoma AB was the most common histology in our group (n=23). A margin negative resection was achieved in 87.3% of the population and all margin positive resections were seen in tumors greater than 5cm. **Intra-operative capsule rupture was exclusively noted in tumors ≥8cm**. **ROC showed a cut off tumor size of 6.4cm predicting post op margin positivity with 80% sensitivity (AUC- 0.67)**. At the end of 1 year, the entire cohort was alive with a 10.2% (n=8) recurrence. Neuroendocrine carcinoma was associated with a 66% margin positivity and 100% recurrence within 1 year.

Conclusions: Conclusion: Thoracoscopic thymectomies can be safely performed adhering to sound oncological principles in thymomas lesser than 8cms. Thoracoscopic resection for high grade thymic cancers should be undertaken with extreme caution. Large collaborative studies with longer follow up are needed to aid in establishing standard of care

Keywords: Thymectomy, VATS, RATS

MA10 UPDATES IN THYMOMA,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA10.04 Long-term Follow-up Study of Thymic Epithelial Tumors. Report of the Updated Nation-wide Database in Japan

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Introduction: International Thymic Malignancy Interest Group (ITMIG) and IASLC started the global database project in the 2010's, and finally, established a large-scale database of more than 10,000 patients. TNM-based staging system proposed by IASLC Staging and prognostic factor Committee Thymic domain (SPFC-TD) was approved by UICC version 8 in 2016. Japanese Association for Research of the Thymus (JART) established Japanese nation-wide database of approximately 3000 cases in 2013 and contributed to IASLC Staging project. Currently, a project of updating the previous database of IASLS SPFC-TD is going on for UICC TNM version 9, and JART also updated the previous database. We reviewed the clinical characteristics and long-term outcome using the updated database.

Methods: JART office asked the directors of the 34 institute which joined the previous database, and the final outcome was updated in 2021.

Results: The updated JART database held 2872 patients undergoing surgery between 1991 and 2010. All the patients had pathological diagnosis of WHO classification. There were 2492 thymomas (WHO Type A: 208, Type AB: 705, Type B1: 598, Type B2 653, Type B3 328), 314 thymic carcinomas (TC), and 66 neuroendocrine carcinomas (NEC). 1362 patients were male, and 1510 patients were female. The age distributed from 13 to 88 years and the average was 56.9. The number of patients according to pathological Masaoka stage was 1011, 1019, 452, 183, and 157 in stage I, II, III, IVA and IVB, respectively (unknown in 54). Those according to pathological stage by UICC TNM version 7 was 2073, 50, 365, 39, 219, and 62 in stage I, II, IIIA, IIIB, IVA and IVB, respectively (unknown in 64). The final outcome was alive in 2385 patients and dead in 477 patients (unknown in 10 patients). The cause of death was tumor in 218 patients and other disease in 248 (unknown in 11 patients). Survival was calculated by tumor-specific survival because nearly half of the death causes were non-tumor death. 10-year survival rate according to WHO hisotological type was 99%, 99%, 93%, 95%, 87%, 58% and 63% in Type A, AB, B1, B2, B3, NC and NEC, respectively. 10-year survival rate according to Masaoka stage was 99%, 98%, 81%, 68%, and 49% in stage I, II, III, IVA and IVB, respectively. 10-year survival rate according to UICC TNM stage was 99%, 77%, 84%, 66%, 63%, and 49% in stage I, II, IIIA, IIIB, IVA and IVB, respectively.By multivariable analysis, WHO pathological type, distant metastasis, nodal metastasis, tumor size, invasion to the pericardium, macroscopic completeness of resection, association with myasthenia gravis, association with PRCA were independent prognostic factors while age, gender, pleural metastasis, intrapericardial metastasis, invasion to the lung, invasion to the thoracic wall, invasion to the great vessels, invasion to the phrenic nerve, and association with Good's syndrome were not.

Conclusions: Updated JART database confirmed utility of both Masaoka stage and TNM-based stage. Tumor size was revealed to be an independent prognostic factor, and including the tumor size in T factor is expected to be considered in the future version.

Keywords: Thymoma, Thymic carcinoma, Thymic neuroendocrine tumor

MA10 UPDATES IN THYMOMA,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA10.05 High Levels of CD47 Expression in Thymic Epithelial Tumors

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Introduction: CD47 is a tumor marker that inhibits phagocytosis thereby providing tumor cells with a means of escape from immune surveillance and elimination. Anti-CD47 therapy is a promising new immunotherapy across numerous tumor types but have not been tested in thymic epithelial tumors (TETs; thymomas and thymic carcinomas). TETs are rare tumors which are difficult to treat, especially with PD-1/PD-L1 checkpoint inhibitors, due to the excessive rates of immune-related adverse effects. This study investigated the levels of CD47 expression in TETs to explore the possibility of anti-CD47 therapies.

Methods: A total of 67 thymic tumors (64 thymomas and 3 thymic carcinomas) and 14 benign thymus controls, and their clinical data were included. Samples with an average of 3 cores each were stained for CD47 expression (rabbit monoclonal antibody SP279, Abcam, USA) and scored for both intensity and H-score (intensity multiplied by the percentage of tumor involved). Intensity was defined as: 0 = none, 1 = weak, 2 = moderate, and 3 = strong. H-scores ranged from 0 to 300. Samples with an intensity score below 2 or an H-score below 150 were considered CD47low, while the rest were CD47high. Multivariate regression and survival analyses were performed (Prism v9, Graphpad; R v4).

Results: CD47 expression was more frequently present in TETs than in normal thymic tissue (by H-score: 91% vs 64.3%; by intensity: 82.1% vs 57.1%). The level of expression was on average 16-fold higher in TETs (mean H-score 75.0 vs 4.6, p = 0.003; mean intensity score 1.4 vs 0.6, p = 0.004).Univariate analyses showed that among tumors, higher CD47 expression was correlated with a lower stage (p = 0.032) and more complete resection (p = 0.058). A multivariate analysis taking into account these factors showed that CD47 expression by both H-score and intensity were each highly correlated with WHO histology subtype (p = 0.0005; p = 0.0017 respectively) and paraneoplastic syndromes (p = 0.0014). Tumors which were CD47high, when compared to CD47low, were frequently associated with a lower grade WHO subtype and the absence of a paraneoplastic syndrome (12.0% vs 52.4%). The most frequent subtype in CD47high was AB (61.5% vs 13.7%) and the least frequent was B2 (0% vs 37.3%). Tumors with the highest grade (subtype C, thymic carcinomas) were exclusively CD47low. CD47 expression did not correlate with overall survival.

Conclusions: In contrast to normal thymus, TETs had significantly higher levels of CD47 expression. Tumor samples with relatively higher CD47 expression were associated with a less aggressive histology and stage, and with a lower frequency of paraneoplastic syndromes. This is the first study to explore CD47 expression in thymic cancers, and lends support for ongoing investigation of anti-CD47 macrophage checkpoint inhibitor therapy in these tumors.

Keywords: CD47, thymoma, thymic carcinoma

MA10 UPDATES IN THYMOMA,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA10.07 Phase II Trial of Sunitinib in Patients with Type B3 Thymoma or Thymic Carcinoma in Second and Further Lines - STYLE Trial (NCT03449173)

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Introduction: Thymic malignancies are rare tumors with few therapeutic options. According to the limited literature data, drugs targeting VEGF, KIT or PDGF, including sunitinib, might be efficacious in thymic epithelial tumors. Here we report results from our clinical trial aiming to assess the activity and safety of sunitinib in patients with advanced or recurrent type B3 thymomas (T) or thymic carcinoma (TC).

Methods: This was a multicentric phase II trial involving 5 Italian Centers (INT, Milan; Ospedali Riuniti, Ancona; AOUP, Pisa; ICH, Rozzano; IOV, Padova). Patients with advanced type B3 T or TC, treated with at least one prior platinum-based chemotherapy, were eligible. Patients were enrolled in two cohorts (T or TC histology) and analyzed separately according to two Simon two-stages design (H0: p < 5%, H1: p > 25%, alpha=5% one-sided, power=85%, stage 1: 12 patients, stage 2: 23 patients). Sunitinib was administered 50 mg daily for 4-weeks, followed by a 2-week rest period, until disease progression or unacceptable toxicity. The primary endpoint was Objective Response Rate (ORR), according to RECIST criteria V1.1. Secondary endpoints were Progression Free Survival (PFS), Overall Survival (OS), Disease Control Rate (DCR) and safety.

Results: From March 2017 to January 2022, 12 in T cohort and 32 patients in TC cohort were enrolled. Median (m) age was 53.8 years (Q1-Q3: 45.4-61.6), 70.5% were male. Three T patients had myasthenia gravis. Thirty-two patients (80%) had stage IVB disease, ECOG PS was 0 in 32 (74.4%) and 1 in 10 (23.3%) patients. The most frequent metastatic sites were lymph nodes (54.5%), pleura (50%), liver (47.7%) and lung (45.5%). At stage 1 an ORR of 0% (90% CI 0.0%-22.1%) in T and 16.7% (90% CI 3.1%-43.8%) in TC, were observed with 2 TC patients achieving Partial Response (PR). Based on these results, enrollment continued only in the TC cohort. At the final analysis on 23 TC patients, ORR was 21.7% (90% CI 9.0%-40.4%), with 1 Complete Response (CR), and 4 PR. In the intention to treat analysis on 12 T and 32 TC patients, the median follow up was 55.5 and 29.8 months, respectively. DCR was 91.7% (95% CI 61.5%-99.8%) in T and 89.3% (95% CI 71.8%-97.7%) in TC. mPFS was 7.7 months (95% CI 2.4-45.5) in T and 8.9 months (95% CI 5.3-11.1) in TC, mOS was 47.9 months (95% CI 4.5-NR) in T and 27.8 months (95% CI 13.2-53.2) in TC. As for safety profile, 18 (40.9%) patients experienced at least one treatment-related G3-G4 adverse event, and 4 (9.1%) patients discontinued sunitinib for adverse event**.**

Conclusions: Our trial confirms activity of sunitinib in thymic carcinoma. Considering the rarity of this pathology, sunitinib should be a valid therapeutic option in TC patients after progression to standard chemotherapy. No responses were seen in T cohort. However, DCR rate was high suggesting a potential role of sunitinib in the treatment of B3 thymomas. Further studies are needed to better clarify its role in B3 thymoma and to better identify responsive patients.

Keywords: Thymoma, Thymic Carcinoma, Sunitinib

MA10 UPDATES IN THYMOMA,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA10.08 Activated Pathways of Myastenia Gravis in Thymic Epithelial (TETs)

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Introduction: TETs are rare malignancies of the anterior mediastinum. Clinical behavior varies from mild thymoma (T) A to aggressive thymic carcinoma (TC). Up to 30% of patients will develop associated autoimmune disorders (AIDs), mainly myasthenia gravis (MG). The biology of TETs and its relation with the development of AIDs is poorly understood. We aimed to characterize the main cancer activation pathways of MG in TETs.

Methods: We selected a representative balanced set of Ts and TCs to analyze 24 main cancer activation pathways using gene expression through the HTG Oncology biomarkers panel (2562 genes) and HTG autoimmune biomarker panel (2003 genes). Tumor representative paraffin-embedded blocks were macrodissected. Then, we merged data with published TCGA atlas project molecular information (profiles with >30% tumor cellularity were kept). We analyzed epidemiologic, clinical and pathological characteristics of patients with TET's and correlated with genes expression based on cancer Hallmarks.

Survival analyses were performed with the survival package using a Cox model. Association of clusters with clinical annotations was assessed using a X^2 test.

Results: 314 pts were included in the cohort, including 120 from TCGA. Median age at diagnosis was 52 (10-84). 51.6% were women. 84/314 (26.7%) reported MG, mostly in T B2 (11,4%) and B3 (8%) but none for TC. AB was the most frequent T subtype (n=70, 22.3%), followed by B2, B1, B3, A and TC. RNA expression analysis identified 3 main clusters, distribution of MG prevalence among clusters was: cluster 1 (8/108 patients), cluster 2 (43/68 patients) and cluster 3 (32/135 patients) (Persons's X2 = 67.556, p<0.0001).

Tumors from patients reporting MG shown suppressed pathways of angiogenesis (gene ratio= 0.52; p<0.0025), epithelial to mesenchymal transition (EMT) hallmarks (gene ratio= 0.56; p<0.01), extracellular matrix degradation (gene ratio= 0.4; p<0.04) and organization (gene ratio= 0.55; p<0.01), cell adhesion (gene ratio= 0.3; p<0.01), cell motility (gene ratio= 0.5; p<0.03) and tyrosine kinases receptor signaling (gene ratio= 0.3; p<0.01). MG was associated with activated oxidative metabolic pathway (gene ratio= 0.3; p<0.04). No differences were found in pathways related to immunity (immune regulation, inflammatory response, immune suppression).

Gene expression for MG were similar to T subtypes with better prognostic (A, AB, B1). Of note, T AB and B1 reported suppression of interferon ɣ and α routes. T B2 showed suppression of matrix organization pathway. Otherwise, T B3 presented suppression of pluripotential cell regulation and TC had EMT and NFkb activated pathways, meaning the biological aggressiveness of these two subtypes.

Conclusions: TET with MG have suppressed invasion and metastatic pathways, but no AIDs specific activation pathways were found. The analysis shows new acknowledge of MG activation pathways in TETs.

Keywords: thymoma, myastenia gravis, molecular characterisation

MA10 UPDATES IN THYMOMA,
MONDAY, AUGUST 8, 2022 - 14:45–15:45

MA10.09 Outcomes of Induction Therapy Followed by Surgical Resection for Advanced Thymic Tumor

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Introduction: The aim of this study is to investigate outcomes of induction therapy subsequent surgical resection for advanced thymic epithelial tumor (TET)

Methods: Between 2007 and 2020, seventy patients who underwent induction treatment followed by thymectomy for clinical stage III/IV TET were identified and reviewed retrospectively.

Results: Of the 70 patients, histologic type was thymic carcinoma in 42 (60%) and thymoma in 28 (40%) patients. Clinical staging were IIIA/IIIB/IVA/IVB=17/8/26/19 and pathologic staging were I/II/IIIA/IIIB/IVA/IVB=5/1/21/6/21/16. Nodal metastasis was identified in 16 patients (22.9%), thymic carcinoma was significantly associated with nodal metastasis (OR=6.5, 95% CI=1.35-31.39). Complete resection was achieved in 39 patients (55.7%), patients with pathologic stage I-III are more likely to have R0 resection compare to those with stage IV disease (81.8 vs. 32.4%, p<0.001). With a median follow-up of 37.0 months, 5-year overall survival (OS) and progression free survival (PFS) was 62.6% and 39.5%, respectively. Patient who achieved complete resection had significantly better OS and PFS compared to those with incomplete resection (OS= 86.4% vs. 52.5%, p=0.004; PFS=56.6% vs. 19.6%, p<0.001). Nodal metastasis was significantly related to poorer OS and PFS, 5-year OS by nodal metastasis was 34.1 and 87.4% (p<0.001) and PFS was 12.5% vs 86.8% (p=0.002), respectively. In the multivariate analysis, nodal metastasis was independent prognostic factor for OS (adjusted HR=5.91, 95% CI=1.84-19.0) and PFS (adjusted HR=2.37, 95% CI=1.08-5.22), while R0 resection only provide prognostic significance for PFS (adjust HR=4.39 (95% CI=1.94-9.95).

Conclusions: Patients with advanced TET showed relatively favorable long-term survival after induction therapy and subsequent surgery, completeness of resection and nodal metastasis were significant prognostic factor.

Keywords: Thymic epithelial tumor, induction therapy, surgery

MA11 OPTIMIZATION OF TECHNOLOGIES FOR LUNG CANCER SCREENING: POPULATION SELECTION AND NODULE HANDLING,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

MA11.03 Updated Cost-Effectiveness Analysis of Lung Cancer Screening for Australia, Capturing Differences in the Impact of NELSON and NLST Outcomes

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Introduction: An Australian risk-based lung cancer screening program using low-dose computerised tomography is moving towards implementation. Cost-effectiveness in the Australian setting is yet to be confirmed against a background of increasing systemic therapy costs over the last 5 years.

Methods: We estimated cost-effectiveness of lung screening in Australia by applying the screening parameters and outcomes observed in either the National Lung Screening Trial (NLST) or the NEderlands-Leuvens Longkanker Screenings ONderzoek (NELSON) to Australian data on lung cancer mortality, survival, health-system costs, and historical smoking trends using a deterministic, multi-cohort model. The proportion of the population eligible was estimated from an Australian, population-based cohort study (45 and Up Study, 2006-2009). Incremental cost-effectiveness ratios (ICERs) were calculated for a life-time horizon.

Results: Based on NELSON parameters and outcomes, the ICER for lung screening in Australia was $39,250 (95%CI $18,150-108,300) per quality-adjusted life-year (QALY) gained; lower than estimates based on NLST (ICER=$76,300, 95%CI $41,750-236,500). In probabilistic sensitivity analyses, lung screening was cost-effective in 15%/60% of NELSON-like simulations, assuming a willingness-to-pay threshold of $30,000/$50,000 per QALY gained respectively, compared to 0.5%/6.7% for the NLST. Of all factors, ICERs were most sensitive to the screening-related lung cancer mortality benefit (20% in NLST; 24% in NELSON) and assumptions regarding the duration of benefit over time. Overall, ICERs were more sensitive to the cost of screening than the cost of lung cancer treatment, even after quadrupling the 2006-2016 healthcare costs of stage IV disease.

Conclusions: Lung screening could be cost-effective in Australia, contingent on translating trial-like lung cancer mortality benefits to the Australian clinical setting. Key indicators of implementation success, such as participation and adherence rates, should be the focus of future economic evaluations.

Keywords: early detection, screening, cost-effectiveness

MA11 OPTIMIZATION OF TECHNOLOGIES FOR LUNG CANCER SCREENING: POPULATION SELECTION AND NODULE HANDLING,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

MA11.04 Genetic Variants of HUNT Lung Cancer Model Improve Lung Cancer Risk Assessment Over Clinical Models

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Introduction: The increasing incidence and high mortality rate of lung cancer calls for methods for early diagnostic. Early diagnosis is key for effective treatment and thereby increasing survival. The validated HUNT Lung Cancer Model (HUNT-LCM) predicts individual 6-year risk of lung cancer in large cohorts of ever smokers with a C-index 0.879 and AUC of 0.87 based on eight clinical variables (sex, age, BMI, pack-years, smoking intensity (cigarettes per day), quit time, daily cough and daily indoors smoke exposure). We aimed to improve performance of the HUNT model by integrating the eight clinical variables with genetic variables.

Methods: A novel prediction model, named HUNT-Lung-SNP, was fit by combining the eight clinical variables of the original HUNT-LCM with 22 SNPs highly associated with lung cancer risk, previously identified in literature. The model was fit using the HUNT2 population study which includes data of ever-smokers (n=30746, median follow-up 15.26 years) where 160 individuals were diagnosed with lung cancer within six years (median time to event 3.04 years). The model was validated externally in another population-based cohort, the Tromsø Study (n=3074, median follow-up 25.01 years for controls and median time to event 4.13 years for cases).

Results: The clinical-polygenic model HUNT-Lung-SNP showed improved predictive power: c-index 0.88 (95% CI 0.86-0.9) versus 0.849 (95% CI 0.824-0.873, p-value < 0.01); and AUC within six years of 0.875 (95% CI 0.854-0.896) versus 0.844 (95% CI 0.820-0.869, p-value = 0.064). The HUNT-Lung-SNP also had a significant increase in cancer detection rate compared to the NLST, NELSON and 2021 USPSTF criteria, namely ≈300%, 250% and 50% respectively. In terms of numbers needed to screen to identify one lung cancer case (NNS), the HUNT-Lung-SNP performed significantly better than the aforementioned criteria with NNS of 24 vs 43 (NLST), 24 vs 47 (NELSON) and 40 vs 52 (2021 USPSTF), p-value < 0.01 for all comparisons. The model was successfully validated in the external Tromsø-cohort with a C-index of 0.924 (95% CI 0.892-0.955) and AUC within six years 0.926 (95% CI 0.891-0.955).

Conclusions: Combining genetic information with clinical variables can improve the predictive value of current models of lung cancer risk prediction significantly. The clinical-polygenic HUNT-Lung-SNP model may be used to identify subjects of very high lung cancer risk and exclude people with a true low risk from lung cancer screening studies. This novel integrated clinical-polygenic model needs further validation in order to evaluate clinical implementation.

Keywords: Polygenic model, Lung cancer screening, Biomarkers

MA11 OPTIMIZATION OF TECHNOLOGIES FOR LUNG CANCER SCREENING: POPULATION SELECTION AND NODULE HANDLING,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

MA11.05 The Blood Proteome of Imminent Lung Cancer

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Introduction: Lung screening with low-dose CT reduces lung cancer mortality, as demonstrated by several large, randomized trials. However, imprecise selection criteria for CT can lead to overdiagnosis, as well as many false positive and false negative results. Current screening programs use either categorical or risk-model based eligibility criteria based on age and smoking history. Our team has previously shown that incorporating blood measurements of cancer-related protein biomarkers to traditional smoking-based prediction models can improve their discriminatory performance. In this project we sought to identify novel circulating proteins indicative of imminent lung cancer using a state-of-the-arts proteomics platform.

Methods: Based on pre-diagnostic samples from six prospective cohorts (USA, Europe, Singapore, Australia), we measured circulating levels of 1,162 proteins using the Olink Proteomics platform on 731 case-control pairs. Cases and controls were matched on sex, smoking status, age, and date of inclusion. Lung cancer cases were diagnosed at most 3 years after their blood draw. Odds ratios for incident lung cancer were estimated per standard deviation increment in relative protein concentrations (OR_{std}) using conditional logistic regression. We implemented a resampling algorithm that split the data into discovery (70%) and replication (30%) sets 500 times, and we identified proteins with consistent associations (i.e. found in at least 50% of the resamples) across samples as robust markers of imminent lung cancer.

Results: We found 67 proteins associated with lung cancer risk after accounting for multiple comparisons, 36 of which were deemed robust markers of imminent lung cancer following the resampling analysis. The robust markers had a wide range of biological functions, and included growth factors, chemokines cytokines and interleukins, tumor necrosis factors, and we found that 8 out of 10 hallmarks of cancer were represented amongst the robust markers, including 'proliferative signaling' (n=15), tumor-promoting inflammation (n=14), activation invasion and metastasis (n=12), angiogenesis (n=7), escaping programmed cell death (n=4), deregulating cellular energetics (n=3), evading suppression of growth (n=1), and avoiding immune destruction (n=1). We confirmed several known tumor markers such as CA-125/MUC-16 (OR_{std}: 1.46, 95%CI: 1.30-1.65) and CEACAM5/CEA (OR_{std}: 2.43, 95%CI: 2.04-2.89), but most of the identified robust markers were novel. Most of the robust markers were stably associated with lung cancer risk across relevant strata (former vs current smokers, female vs male, and across cohorts) and histological subtypes (Adenocarcinoma vs Squamous Cell Carcinoma). Multiple proteins (n=19) displayed stronger risk associations in blood drawn closer to diagnosis. Accounting for smoking parameters did not attenuate the risk association estimates, suggesting that the identified robust markers indicate imminent lung cancer rather than smoking history.

Conclusions: After assessing 1,162 circulating proteins prior to lung cancer diagnosis, we identified 36 robust markers of imminent lung cancer with a wide range of functions in carcinogenesis. This study provides a first expansive view of the blood proteome in the years leading up to lung cancer diagnosis and can serve as a reference for investigations seeking to identify early protein markers of lung cancer.

Keywords: Protein biomarkers, Early diagnosis, pre diagnostic blood samples

MA11 OPTIMIZATION OF TECHNOLOGIES FOR LUNG CANCER SCREENING: POPULATION SELECTION AND NODULE HANDLING,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

MA11.07 The ELIC Distributed Database and Computation Environment for Analyses of Lung Cancer Screening LDCTs Across the World

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Introduction: The rapid adoption of LDCT lung cancer screening throughout the world has resulted in a significant number of published reports providing important local findings from lung cancer screening studies. While these reports provide regional study/program performance information, a global resource to facilitate radiomics and AI research is currently not available. We report here on the recently deployed Early Lung Imaging Confederation (ELIC) database and computation infrastructure currently running on the AWS cloud and illustrates how this resource can be used for AI research.

Methods: A total of 510 low dose CT lung cancer screening participants, each with two CT screening imaging time points and demographic data, were obtained from screening performed in Gdansk, Milan, Ishikawa, Perth, Porto Alegre, and Vancouver. Each site was asked to provide 100 cases including 25 with screen detected lung cancer prior to treatment, 50 with non-malignant lung nodules, and 25 without lung nodules. The scans and associated metadata were anonymized, standardized, and placed at a regional ELIC cloud server for analysis. Case demographics and semi-automated volume size change for subsolid lung nodules >= 6.0 mm in diameter was calculated using the Accumetra open-source Lesion Sizing Toolkit lung nodule volume segmentation algorithm (ACM-LSTK).

Results: Demographic and lung cancer subtype characteristics of globally distributed ELIC cases are summarized in **Table 1**. The number of cases from Porto Alegre was lower than other sites and the percentage of lung cancer cases was higher because they only recently started providing cases to ELIC and their first cases were all lung cancers. The number of pack-years of smoking for cases from the Ishikawa site was lower than other sites. We quantitatively measured change in volume of benign and malignant nodules. We found that for benign subsolid nodules with < 300 mm^3 the mean and coefficient of variation for semi-automated automated volume change was 9.3 mm^3, 5.35 COV and for malignant nodules was 313.9 mm^3, 0.91, respectively. For benign subsolid nodules >= 300 mm^3 the mean and COV was -75.4 mm^3, -6.68 and for malignant nodules was 471.3 mm^3, 1.57, respectively.

Conclusions: This study illustrates the ease and utility of conducting automated quantitative analyses of screening LDCTs across globally distributed screening populations. The ELIC environment has great potential for understanding variations and differences in screening populations, for validation of AI algorithms and to serve as a valuable resource for learning and testing.

ELIC case characteristics by site												
										Lung Cancer Subtype		
Site	**# Cases**	**Age**	**% Female**	**% Past Smoker**	**Pack Years**	**Mean Rad. Diam.**	**% Cancer Cases**	**% Adeno.**	**% Squamous Cell**	**% Large Cell**	**% Small Cell**	**% Other**
Gdansk	100	62.1 +- 6.8	45.0 %	34.0 %	47.8 +- 24.9	9.3 mm	23.0 %	56.5 %	13.0 %	0.0 %	17.4 %	13.0 %
Milan	100	59.4 +- 6.2	28.0 %	28.0 %	45.2 +- 20.6	8.3 mm	25.0 %	84.0 %	12.0 %	4.0 %	0.0 %	0.0 %
Ishikawa	100	55.0 +- 7.0	42.0 %	28.0 %	14.0 +- 20.8	7.2 mm	25.0 %	96.0 %	0.0 %	4.0 %	0.0 %	0.0 %
Perth	92	65.2 +- 6.1	50.0 %	46.7 %	49.5 +- 22.3	8.7 mm	15.2 %	71.4 %	14.3 %	0.0 %	0.0 %	14.3 %
Porto Alegre	18	68.4 +- 9.8	61.1 %	50.0 %	39.2 +- 37.7	14.3 mm	100.0 %	0.0 %	0.0 %	0.0 %	0.0 %	0.0 %
Vancouver	100	65.7 +- 6.0	39.0 %	56.0 %	44.1 +- 15.8	7.3 mm	25.0 %	84.0 %	12.0 %	0.0 %	4.0 %	0.0 %

Keywords: LDCT, lung cancer screening, Federated database

MA11 OPTIMIZATION OF TECHNOLOGIES FOR LUNG CANCER SCREENING: POPULATION SELECTION AND NODULE HANDLING,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

MA11.08 Value of Computer Aided Diagnosis on Radiologists' Workflow and Recommendation for Reporting Lung Cancer Screening LDCT

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Introduction: In lung cancer screening, the utility of using a Computer Aided Diagnostic tool (CAD) has not been tested in a prospective randomized clinical study. We aim to evaluate whether CAD would change the next step recommendation and how the use of CAD would influence the radiologist's reporting time.

Methods: In the Vancouver site of the International Lung Screening Trial, the baseline CT scans were randomized to Radiologist reading-first (RAD-1st), or CAD reading-first (CAD-1st) arm. In Rad-1st arm, a chest radiologist read the CT alone, manually measured the nodules, documented nodule findings (i.e., manual reading), and then turned on CAD annotations to accept, reject or add nodule(s) for final reporting (i.e., combined reading). The manual reading and final reporting times were documented separately. In the CAD-1st arm, the CAD annotations were displayed first, the radiologist accepted, rejected or added nodule(s) and then generate the report. In the RAD-1st arm, the PanCan nodule malignancy risk score (N Engl J Med 2013; 369:908-17) was automatically generated by the CAD on nodules based on the combined reading. The PanCan nodule risk score for nodules found by manual reading was also calculated. Differences in triaging participants into biennial/annual follow-up (FU) CT (Group 1), early recall CT in 3 months (Group 2) or diagnostic work-up referral (Group 3) were compared between the manual reading versus the combined reading. The radiologist's reading time was also compared between CAD-1st and Rad-1st arms.

Results: Between August 2016 and December 2019, a total of 2053 ever smokers between the age of 55 to 80 years who met the USPSTF 2013 screening criteria or those with a PLCOm2012 6-years lung cancer risk >1.5% were enrolled in the study. Seventy (3.4%) cancers were diagnosed after a minimum of 2-years of follow-up; 48/70 cancers were in Rad-1st arm. All malignant nodules were successfully detected by both radiologist and CAD. In 42/48 cancers, the management recommendation using the PanCan nodule malignancy risk score was consistent between manual and combined reading. In 6/48 cancer cases, using CAD after manual reading prompted a shorter FU interval in 5 cases (FU changed from 12 to 3 months in 3 cancers; FU changed from 3 months to diagnostic workup in 2 cancers). In one 11.5mm GGN that was later found to be an adenocarcinoma, adding CAD changed the management from diagnostic work-up to a 3-month FU CT, which retrospectively seemed more appropriate. Radiologist's reading time was significantly shortened by using CAD concurrently in all 3 groups (reading time for CAD-1st arm versus Rad-1st arm: in Group1: 4.3± 2.4 vs. 5.5±2.9 min; in Group2: 7.6±4.6 vs. 9.3± 4.6 min; in Group3: 7.9±3.9 vs. 12.3± 7.7 min, all $p<0.05$).

Conclusions: Use of CAD improved accuracy of reporting and management recommendation. Reading concurrently with CAD saved the radiologist's reading time. These features are important regarding the clinical implementation of CAD in a screening program.

Keywords: Computer Aided Diagnosis, Lung Cancer Screening, LDCT

MA11 OPTIMIZATION OF TECHNOLOGIES FOR LUNG CANCER SCREENING: POPULATION SELECTION AND NODULE HANDLING,
MONDAY, AUGUST 8, 2022 - 16:00–17:00

MA11.09 Artificial Intelligence in Lung Cancer Screening: Accuracy and Predictive Value

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Introduction: To investigate the performance of an Artificial Intelligence (AI) powered radiology platform in detecting solid pulmonary nodules on Low Dose Computed Tomography (LDCT) chest scans when compared against expert radiologists and to assess LungRADSTM categories agreement between software and radiologists.

Methods: Consecutive cohort with real-life data, which evaluated 790 LDCT of patients participating in a lung cancer screening program. All LDCT were reviewed by an experienced team of thoracic radiology. An AI algorithm was used, independently and anonymously, blind to CT results, to analyze the same set of LDCT. The LungRADSTM classification system was used for both groups and reported findings were compared, considering the expert analysis as the gold standard.

Results: AI group software showed high sensitivity and negative predictive value (97.8%), but low specificity and positive predictive value (56.1%), with an overall accuracy of 81.1%. A significant number of subsolid nodules were missed by the AI group; however, none of them were greater than 8 mm (LungRADSTM 4).

Conclusions: The AI software demonstrated high negative predictive value and relatively low positive predictive value. The device seems to be an important adjunct through the navigation team can prioritize exams with clinically significant nodules.

Diagnostic performance and agreement (negative vs positive CT)

	Botkin AI											
	Negative (LungRADS 1 and 2)		**Positive (LungRADS 3 and 4)**		**Total**		**Kappa**	**Sensitivity**	**Specificity**	**AUC ROC**	**PPV**	**NPV**
Radiogist	N	%	N	%	N	%	**(IC 95%)**	**(IC 95%)**	**(IC 95%)**	**(IC 95%)**	**(IC 95%)**	**(IC 95%)**
Negative (LungRADS 1 and 2)	496	63,7	136	17,5	632	81,1	0,535	92,5	78,5	0,855	50	97,8
Positive (LungRADS 3 and 4)	**11**	1,4	136	17,5	147	**18,9**	(0,474; 0,596)	(87; 96,2)	(75,1; 81,6)	(0,828; 0,882)	(43,9; 56,1)	(96,2; 98,9)
Total	**507**	**65,1**	**272**	**34,9**	**779**	**100**						

Lung-RADSTM categories in diagnosed lung cancer cases

Patient	**LungRADSTM Radiologist**	**LungRADSTM Botkin**	**Diagnosis**	**Staging**
1	4A	4B	Invasive squamous cell carcinoma	pT1a pN0
2	4B	4B	Adenocarcinoma of the lung	pT1a pN0
3	4B	4A	Adenocarcinoma of the lung	pT1a pN0
4	4B	4B	Adenocarcinoma of the lung	pT1a pN0
5	4A	4A	Squamous cell carcinoma	pT1a pN0
6	4X	4B	Non-small cell lung cancer	ypT1a ypN0
7	4B	4B	Invasive adenocarcinoma of the lung	pT2a pN0
8	4A	4A	Adenocarcinoma of the lung	pT1a pN0
9	3	3	Carcinoid tumor	

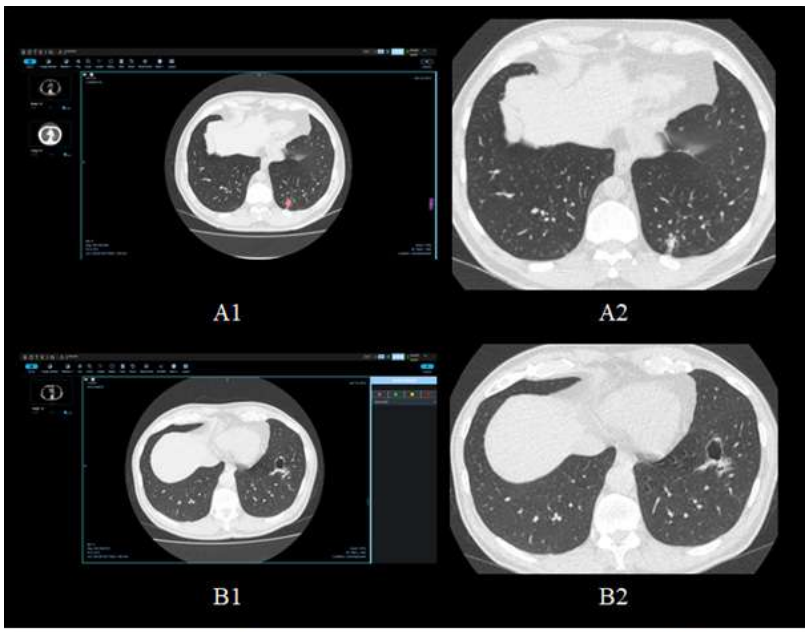

Figure 1. A1 Image from the AI software, pulmonary nodule classified as LungRADS 4A. A2. Radiologist analysis of the same pulmonary nodule, classified as LungRADS 4A. B1. Image from the AI software, pulmonary nodule classified as LungRADS 1. B2. Radiologist analysis of the same pulmonary nodule, classified as LungRADS 4A.

Keywords: lung cancer, screening, artificial intelligence

MA12 PATHOLOGY: TUMOUR DIAGNOSTICS,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

MA12.03 Mechanims of Immune Evasion in Patients With KRAS-Mutant Lung Adenocarcinoma: A Role of MAPK Pathway Activation

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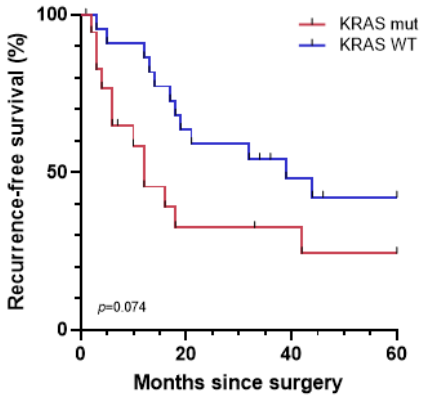
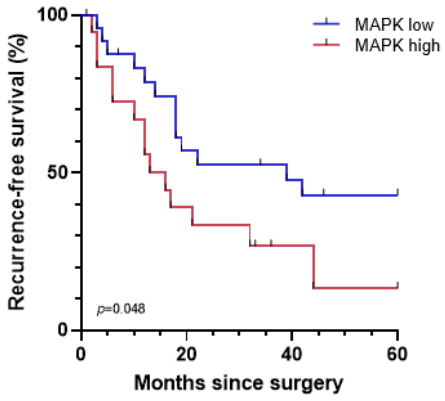
Introduction: There is emerging evidence of modulatory ability of (in)activated oncogenic pathways in shaping antitumor immune responses. Synergistic superior efficacy of novel KRAS-G12C inhibitor AMG510 with anti-programmed cell death1 (PD-1) immune checkpoint blockade has been demonstrated to reverse the immunosuppressive tumor microenvironment. We hypothesized that activation of RAS signaling pathway, and not necessarily KRAS mutation status, induces a distinct immune evasion pattern.

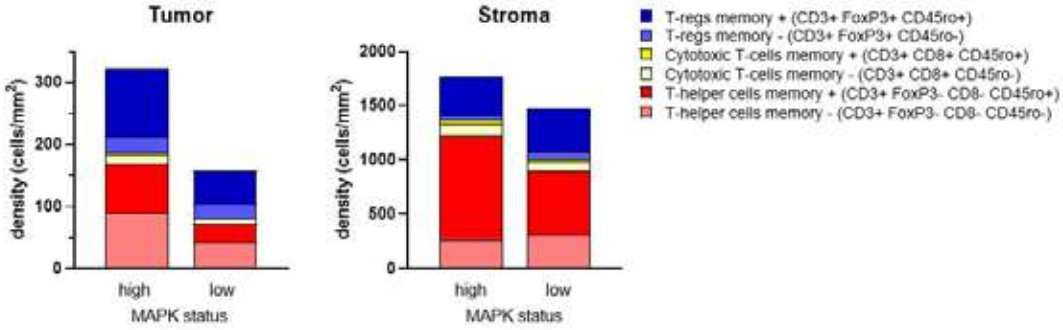
Methods: Sixty-four clinically annotated surgically resected LADC were analyzed using two multiplex immunohistochemistry panels and scanned with Vectra® Polaris™ Multispectral Imaging System to gain quantitative insight into lymphocyte (CD3, FoxP3, CD20, CD45ro, CD8) and myeloid cell (HLA-DR, CD83, CD68, CD14, CD163) composition. A subset of 21 patients was profiled with liquid chromatography tandem-mass spectrometry (LC-MS/MS-based proteomics). Granulocyte neutrophils and immunohistochemistry (IHC) for PD-(L)1, MAPK and p-ERK were semiquantitatively assessed.

Results: Median follow-up period was 34 months (IQR: 19-60). Thirty-four out of 64 patients (53%) had high MAPK pathway activation and had significantly shorter recurrence-free survival (RFS) as compared to those with low MAPK activation [Figure 1]. Interestingly, MAPK activation was not always associated with KRAS mutation (14/26 KRASMut, 20/38 wildtype). Unbiased gene-set enrichment analysis of proteomics was performed for MAPK-high versus MAPK-low patients. Multiplex immunohistochemistry showed increased infiltration of M2 macrophages around the tumors of MAPK-high cases compared with MAPK-low cases. Of these, only MAPK-high tumors were strongly infiltrated by T-helper (CD3+ FoxP3- CD8-) and T-regulatory (CD3+ FoxP3+) cells [Figure 2].

Conclusions: MAPK pathway activation was associated with poor RFS in curatively treated LADC patients. The coordinated infiltration of T-helper and T-regulatory cells, M2 macrophage border and exclusion of cytotoxic T-cells in MAPK-high tumors might contribute to its underlying immune-suppressed state. Our data open the possibility of novel combination therapies, including RAS inhibitors and different immune checkpoint blockers, outside the KRAS-mutant group.







Keywords: MAPK, KRAS, LADC

MA12 PATHOLOGY: TUMOUR DIAGNOSTICS,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

MA12.04 SAKK 16/14: CD8 T Cell Positioning Correlates with Survivalin Stage IIIA(N2) NSCLC After Neoadjuvant Immunotherapy

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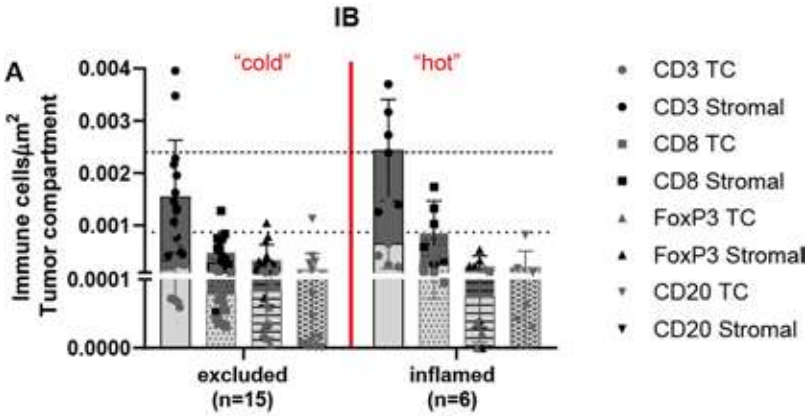
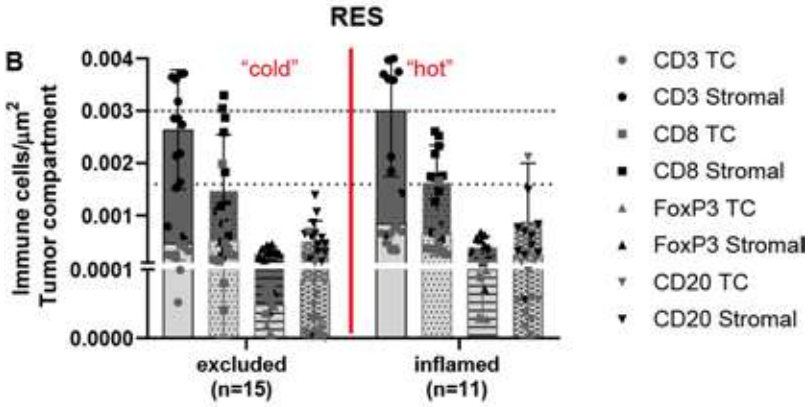
Introduction: Spatial distribution of immune cells within the tumor immune microenvironment (TIME) influences response to immunotherapy in many malignancies, but its role in neoadjuvant immunotherapy in non-small cell lung cancer (NSCLC) is not clearly established. To address this knowledge gap, we performed digital pathology analysis of tumor tissue obtained from patients with stage IIIA(N2) NSCLC undergoing neoadjuvant chemotherapy with three cycles of cisplatin/docetaxel followed by treatment with the PD-L1 antibody durvalumab in the single-arm phase II trial SAKK 16/14.

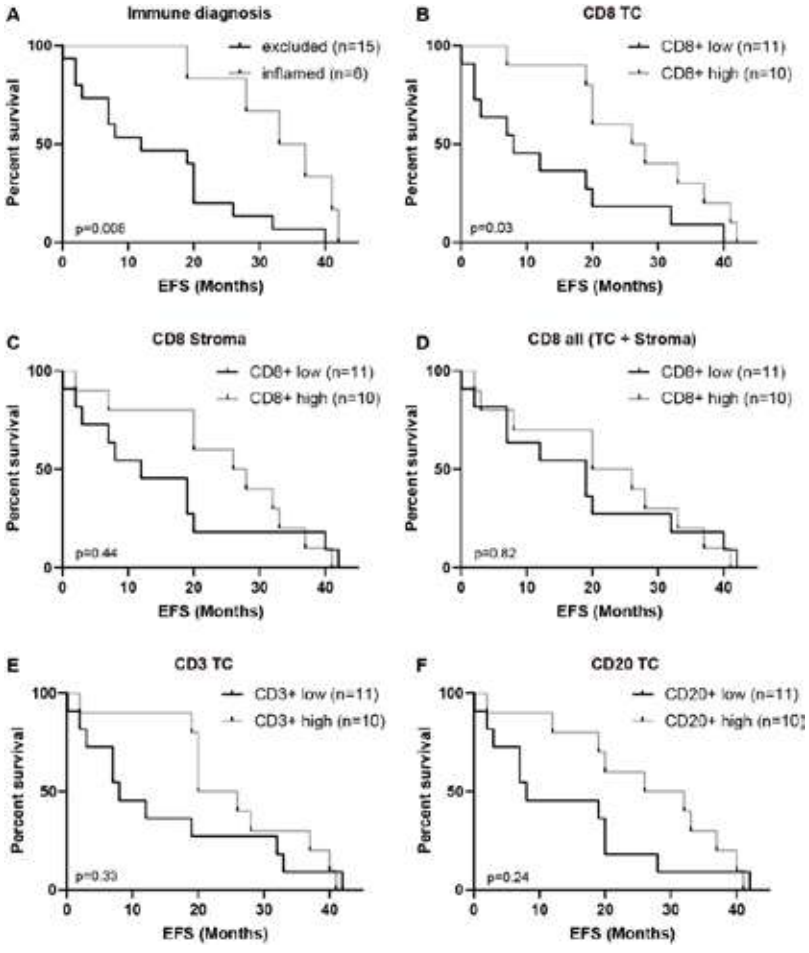
Methods: Formalin-fixed paraffin-embedded tissue specimens of 21 initial biopsies (IB) and 38 resection specimens (RES) were obtained from patients enrolled in the trial SAKK 16/14. Tissue was immunostained for CD3, CD8, CD20 and FoxP3. Digitalized slides were annotated for invasive cancer. A machine-learning classifier was trained to localize and quantify marker-positive immune cell densities within the epithelial and stromal compartments. Also, the TIME for each specimen was classified as excluded (“cold tumor”) or inflamed (“hot tumor”) by pathologist consensus. Event-free survival (EFS) was analyzed by Mann-Whitney-Wilcox test.

Results: The infiltration densities of CD3 T cells, CD8 T cells, CD20 B cells and Foxp3 T cells in IB (Fig. 1A) and RES (Fig. 1B) were comparable in hot and cold tumors. Stratification of tumors based on their immune cell positioning (excluded or inflamed phenotype) in the IB strongly correlated with EFS (p=0.008, Fig. 2A). This association was driven by CD8 T cell infiltration in the tumor (Fig. 2B), but not for the stromal compartment (Fig. 2C) or total T cell content (Fig. 2D) as assessed by digital pathology, with similar trends observed for CD3 T cells (Fig. 2E) and CD20 B cells (Fig. 2F).

Conclusions: Immune phenotyping of the tumor and spatial distribution of CD8 T cells correlates with EFS in the SAKK16/14 cohort.







Keywords: neoadjuvant immunotherapy, CD8 T cells, spatial distribution

MA12 PATHOLOGY: TUMOUR DIAGNOSTICS,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

MA12.05 Economic Impact of Delaying Care with Single-Gene Testing Versus Next-Generation Sequencing in Non-small Cell Lung Cancer

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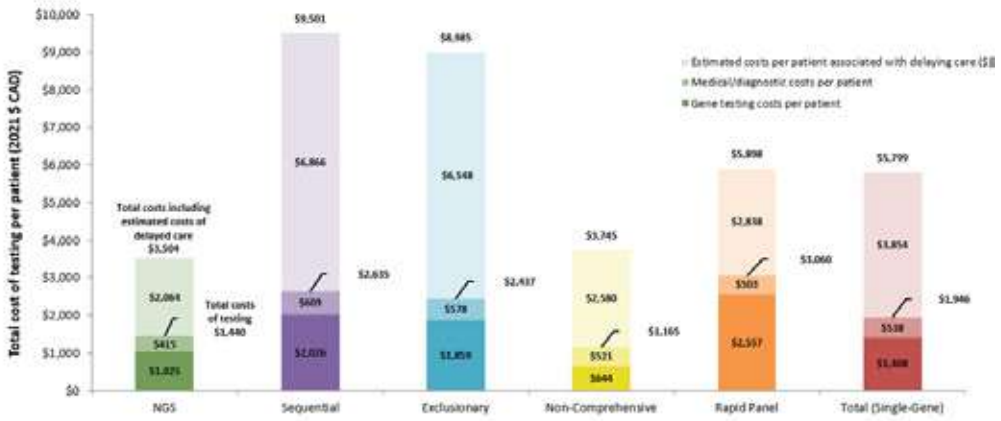
Introduction: By reducing delays in identifying a broad list of genomic alterations in non-small cell lung cancer (NSCLC), next-generation sequencing (NGS) testing has been found to be cost-effective in the United States compared to single-gene testing strategies. However, evidence is limited in Canada. This study assessed total costs of testing (including estimated costs of delaying care) associated with NGS versus single-gene testing strategies among patients with metastatic NSCLC (mNSCLC) from a Canadian public payer perspective.

Methods: A decision tree model considered testing for genomic alterations (EGFR, ALK, ROS1, BRAF, KRAS, MET, HER2, RET, NRG1, NRAS, NTRK1/2/3) among patients with newly diagnosed mNSCLC using liquid or tissue biopsy NGS tests, or single-gene testing including sequential tests, exclusionary mutation (KRAS) followed by sequential tests, non-comprehensive (EGFR, ALK, ROS1) sequential tests, or rapid panel tests. The genetic testing sequence followed Canadian clinical guideline recommendations. Inputs included prevalence of mNSCLC, proportion of patients using each testing strategy (50% NGS [95% tissue, 5% liquid], 5% sequential, 10% exclusionary, 25% non-comprehensive, 10% rapid panel), proportion of patients who tested positive for each genomic alteration, rebiopsy rates, time to test results, testing and medical costs, and estimated costs associated with delaying care based on literature, public data, and expert opinion. The proportion of patients testing positive for genomic alterations with approved targeted therapies, including the time to initiation and total costs were calculated for NGS, each individual single-gene testing strategy, and all single-gene testing strategies combined.

Results: The proportion of patients testing positive for a genomic alteration with an approved targeted therapy was 38.0% for NGS and 26.1% for single-gene testing (sequential=32.1%, exclusionary=29.3%, non-comprehensive=20.3%, rapid panel=34.4%). Estimated mean time to appropriate targeted therapy initiation was 5.1 weeks for NGS and 9.5 weeks for single-gene testing (sequential=16.9 weeks, exclusionary=16.1 weeks, non-comprehensive=6.4 weeks, rapid panel=7.0 weeks). Mean per patient costs, including costs associated with delaying care, were $3,504 for NGS and $5,799 for single-gene testing (sequential=$9,501, exclusionary=$8,985, non-comprehensive=$3,745, rapid panel=$5,898). Increasing the proportion of patients using NGS to 70% resulted in plan-level savings of $159,934, assuming a hypothetical plan of 1,000,000 members (including 382 with mNSCLC), translating to potential savings of $6,079,091 in a pan-Canadian context.

Conclusions: In this Canadian decision tree model, NGS testing for patients with mNSCLC resulted in a higher proportion of patients with an identified mutation, shorter time to appropriate targeted therapy initiation, and lower total testing costs per patient compared to single-gene testing strategies.



Keywords: non-small cell lung cancer, economic model, next-generation sequencing

MA12 PATHOLOGY: TUMOUR DIAGNOSTICS,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

MA12.07 Defining Morphologic Features of Invasion in Pulmonarynon-Mucinousadenocarcinoma with Lepidic Growth

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Introduction: Recognizing invasion in pulmonary adenocarcinomas is important since, in the 8th edition of UICC/AJCC TNM classification system, the primary tumor T stage is determined based on presence and size of the invasive components. The aim of this study was to identify histological features in tumors with lepidic growth pattern that may be used to establish criteria for distinguishing invasive from non-invasive areas.

Methods: A Delphi approach was used with two rounds of blinded anonymized analysis of resected non-mucinous lung adenocarcinoma cases with presumed invasive and non-invasive components including a subset of cases with known outcomes. This was followed by one round of reviewer de-anonymized and unblinded review of cases with known outcomes. A digital pathology platform was used for measuring total tumor size and invasive tumor size. Validation of the proposed criteria was performed on a set of 43 static images.

Results: The mean coefficient of variation for measuring total tumor size and tumor invasive size was 6.9% (range 1.7-22.3%) and 54% (range 14.7-155%), respectively, with substantial variations in interpretation of the size and location of invasion among pathologists. A panel of 10 pathologists reviewed the results including unblinded re-evaluation of the images focused on cases with known outcome, and discussion of histologic features with a high likelihood of invasive behavior. Following the presentation of the results and further discussion among members at large of the IASLC Pathology Committee, extensive epithelial proliferation (EEP) in areas of collapsed lepidic growth pattern is recognized as a feature likely to be associated with invasive growth. EEP is characterized by multilayered luminal epithelial cell growth, usually with high grade cytological features in several alveolar spaces. A stepwise feature-driven algorithm to improve interobserver variation in the interpretation of invasion in lung adenocarcinoma is proposed.

Conclusions: Collapsed alveoli and transition zones with EEP were identified by the Delphi process as morphologic features that were a source of interobserver variability. Defining collapse and EEP are proposed to improve reproducibility of invasion measurement.

Keywords: invasion pathology, non-mucinous adenocarcinoma, iatrogenic collapse

MA12 PATHOLOGY: TUMOUR DIAGNOSTICS,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

MA12.08 Pagetoid Growth of Squamous Cell Carcinoma with a Subsolid Component

T. Radonic[1], F. Filipello[2], H. Blaauwgeers[3], A. Grefte[4], E. Thunnissen[1]

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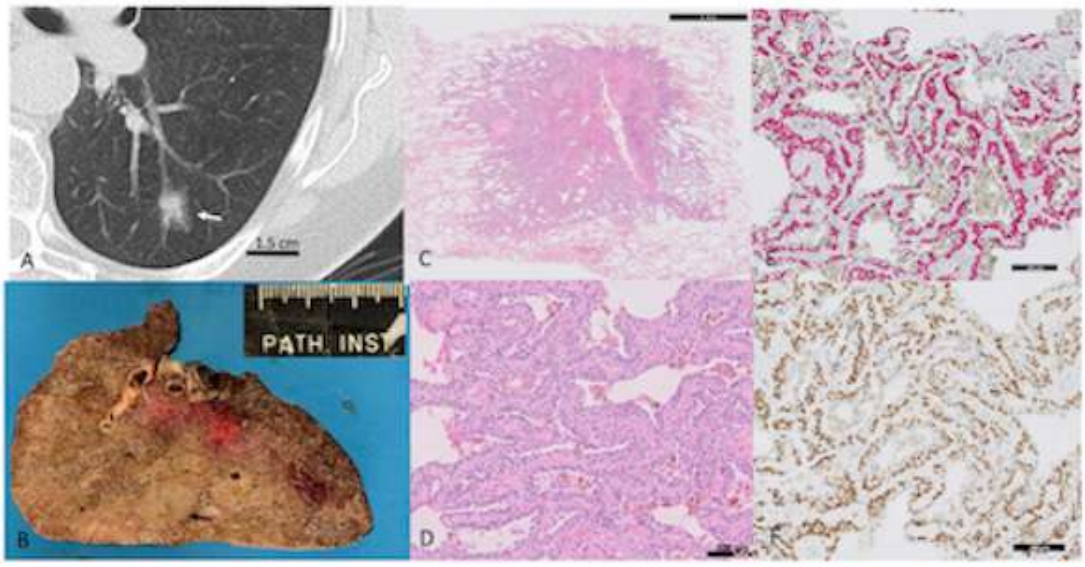
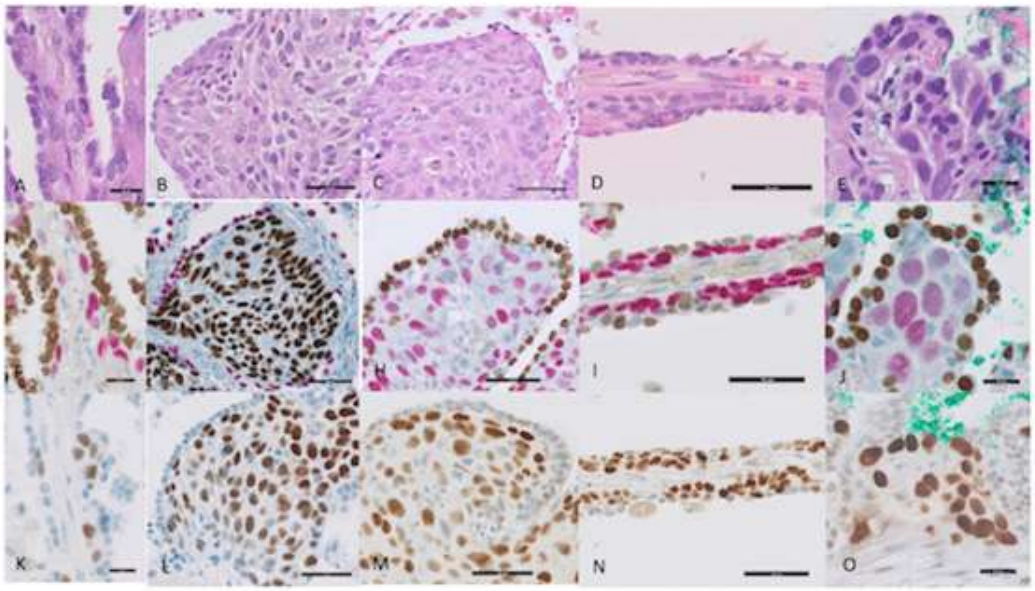
Introduction: Squamous cell carcinoma (SCC) is a solid, frequently central tumor. In recent years, an increase of peripheral type SCC was reported, accounting for up to 55% of SCC and characterized by alveolar filling growth pattern. We describe a novel growth of SCC.

Methods: Histology of a retrospective case series of 11 resections and 1 biopsy with SCC with pagetoid growth is described together with radiological correlation.

Results: All 12 resected SCC showed in histology, beside a central invasive component, growth of tumor cells alongside bronchioles and a subtotal (n=5) or partial (n=7) lepidic growth pattern under the pre-existing respiratory and alveolar epithelium, respectively [Figure 1,2]. Figure 1 shows radiology (A), gross image (B), haematoxylin and eosin (HE) 2X (C), HE 10X (D), p40(red)/TTF1(brown) (E) and p53 (F) of peripheral lung carcinoma with extensive pagetoid growth.The double stain for p40/TTF1 revealed p40+/TTF1- in the tumor cells and p40-/TTF1+ in the pre-existing epithelial cells. Immunohistochemistry for p53 demonstrated strong nuclear staining in the tumor cells and a wild type pattern in TTF1+ cells. Collagen IV staining was continuous under the tumor cells, suggestive of a not-invasive growth pattern: so called “Pagetoid spread”. On CT-scan the tumor presented as part solid nodule with a peripheral ground glass component. Figure 2 shows five cases with subtotal pagetoid SCC at 40x magnification (A-E). For each case HE, double stain TTF1/p40 and p53 immunohistochemistry are shown (F-O). The growth of atypical cells under the bland pulmonary epithelium is well appreciable. Double stain TTF1 (brown)/p40 (red) (F,H-J) and TTF1 (red)/p40 (brown) (G) highlights this growth pattern. Tumor cells show strong nuclear p53 positivity (K-O).

Conclusions: SCC can spread in a pagetoid manner along bronchiolar and alveolar walls and has a corresponding peripheral ground glass radiological pattern. The prognostic significance is still to be determined.





Keywords: Squamous Cell Carcinoma, Pagetoid Growth

MA12 PATHOLOGY: TUMOUR DIAGNOSTICS,
TUESDAY, AUGUST 9, 2022 - 10:45–11:45

MA12.09 Frequency and Detectability of Uncommon EGFR Mutations in NSCLC

H.M. O'Sullivan[1], S. MacMahon[2], W. Cui[1,3], C. Milner-Watts[1], N. Tokaca[1], J. Bhosle[1], M. Davidson[1], A. Minchom[1], N. Yousaf[1], M. O'Brien[1,4], S. Popat[1,4,5]

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Introduction: Although commonly excluded from large clinical trials, studies have demonstrated uncommon *EGFR* mutations are sensitive to *EGFR* tyrosine kinase inhibitors (TKIs). Variant identification is essential to identify these patients who may benefit from targeted therapy. Detection of uncommon *EGFR* alterations can be challenging due to the limited coverage of frequently used real-time polymerase chain reaction (PCR) assays. We describe the frequency of uncommon *EGFR* mutations detected at our institution by next generation sequencing (NGS) and the ability of commonly used PCR assays to identify these alterations.

Methods: NSCLC samples that underwent NGS at the clinical genomic lab at the Royal Marsden Hospital were assessed to identify cases with *EGFR* mutations in exons 18-21. Uncommon mutations were defined as *EGFR* mutations in exons 18-21, excluding exon 19 deletions, L858R, T790M and exon 20 insertions. The proportion of uncommon mutations identifiable by cobas® and Idylla™ PCR assays was evaluated using the manufacturer-provided coverage information.

Results: We identified 1463 NSCLC patients who had successful analysis of *EGFR* exons 18-21 by NGS between February 2020 and September 2021. *EGFR* alterations were detected in 21% (303/1463) of cases. Exon 19 deletions, L858R, and exon 20 insertions were reported in 46% (139/303), 32% (96/303), and 8% (25/303) of cases, respectively. Uncommon *EGFR* mutations were detected in 14% (43/303) of cases, including 27 single and 16 compound mutations. Exon 18 G719X was the most prevalent uncommon alteration, present in 7% of cases (22/303), as a single alteration in 9 cases and compound in 13. Exon 20 S768I was found in 13 cases (12/13 were compound), and Exon 21 L861Q was present in 5 cases (1/5 were compound). Cobas® and Idylla™ PCR tests would have missed an uncommon *EGFR* mutation in 12/43 (28%) cases (Table 1).

Conclusions: Due to the limited coverage of PCR assays, 28% of uncommon *EGFR* cases may be missed. NGS-based genetic testing can substantially improve the identification of these mutations, facilitating the prescription of *EGFR* TKIs to these patients.

Table 1 Uncommon *EGFR* Mutations and Detectability by PCR

Uncommon *EGFR* Mutation detected by Next Generation Sequencing	No of cases N=43	Detectable by cobas® / Idylla™
Single Mutations		
Exon 18 G719X	9	Yes
Exon 18 deletion	3	No
Exon 18 K714N	1	No
Exon 19 insertion	2	No
Exon 20 S768I	1	Yes
Exon 20 G779F	3	No
Exon 20 G796S	1	No
Exon 20 L798F	1	No
Exon 21 L861Q	5	Yes
Exon 21 L861R	1	No
Compound Mutations		
Exon 18 G719X, Exon 20 S768I	10	Yes
Exon 18 G719C, Exon 18 E709V	1	Yes*
Exon 18 G724S, Exon 20 S768I	1	Yes*
Exon 18 G719A + Exon 18 E709K	1	Yes*
Exon 18 G719C, Exon 21 L861Q	1	Yes
Exon 20 H773L, Exon 20 V774M	1	No
Exon 20 S768I, Exon 20 V774M	1	Yes*

*Only one alteration detectable

Keywords: EGFR, Next Generation Sequencing, PCR

MA13 UPDATE ON ROS1 INHIBITORS AND NEW PATHWAYS,
TUESDAY, AUGUST 9, 2022 - 12:00–13:00

MA13.03 Integrated Efficacy and Safety of Brigatinib Following Alectinib Treatment in the ALTA-2 and J-ALTA Studies

S-H.I. Ou[1], M. Nishio[2], T. Yoshida[3], T. Kumagai[4], M-J. Ahn[5], T. Mok[6], K. Kudou[7], T. Asato[7], H. Yang[8], P. Zhang[8], N. Yamamoto[4], E.S. Kim[9]

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Introduction: Alectinib, an anaplastic lymphoma kinase (ALK) inhibitor, is a standard-of-care option for patients with *ALK*-positive (*ALK*+) non-small cell lung cancer (NSCLC). However, most patients eventually develop disease progression on alectinib. Although subsequent ALK inhibitor therapy is beneficial in these patients, few trials have evaluated ALK inhibitors in patients with NSCLC following progression on alectinib. We present integrated efficacy and safety results from two phase 2 studies of brigatinib treatment in patients with *ALK*+ NSCLC with disease progression on alectinib.

Methods: ALTA-2 (NCT03535740) and J-ALTA (NCT03410108) were open-label, single-arm, multicenter studies in patients with advanced or metastatic *ALK*+ NSCLC. Patients in ALTA-2 had disease progression on alectinib or ceritinib. Patients in the main cohort of the refractory expansion part of J-ALTA, conducted in Japan, had progressed on alectinib. Prior crizotinib and stable or asymptomatic brain metastases were allowed in both studies. Patients in both studies received brigatinib 180 mg QD with a 7-day lead-in at 90 mg QD. The primary endpoint in ALTA-2 and the J-ALTA main cohort was confirmed objective response rate (ORR) as assessed by a blinded independent review committee (BIRC). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Integrated efficacy and safety data for patients from ALTA-2 and the J-ALTA main cohort who progressed on alectinib are presented here.

Results: There were 133 patients in the analysis (ALTA-2 post-alectinib, n=86; J-ALTA main cohort, n=47). Median follow-up for the integrated population was 11.1 months (data cut-off: ALTA-2, 30 September 2020; J-ALTA, 22 January 2020), with treatment ongoing in 34 (25.6%) patients. Most (79.7%) patients were aged <65 years, 49.6% had baseline brain metastases, and 98.5% had stage IV disease at study entry. The majority of patients (57.9%) received alectinib as the only prior ALK inhibitor, 42.1% received both crizotinib and alectinib, and 30.8% had received prior chemotherapy for metastatic disease; 18.0% had received all 3 therapies. Most (72.2%) patients had complete responses (CR) or partial responses (PR) to prior alectinib. With brigatinib treatment, confirmed ORR was 30.8% (95% CI, 23.1-39.4), with 1 CR and 40 PR, and median DOR was 9.2 months (95% CI, 5.5-not estimable); median PFS was 5.2 months (95% CI, 3.7-7.3) by BIRC, and median OS was not reached as of this analysis. In patients with BIRC-assessed baseline brain metastases, confirmed intracranial ORR by BIRC was 13.6% (95% CI, 6.4-24.3), with 6 CR and 3 PR. Grade ≥3 treatment-emergent adverse events (AEs) were reported in 66.2% of patients; most common were increased blood creatine phosphokinase (11.3%), hypertension (10.5%), increased lipase (7.5%), and pneumonia (5.3%). Any grade interstitial lung disease/pneumonitis was reported in 8 (6.0%) of patients, 2 (1.5%) with early onset. Discontinuations due to AEs occurred in 12% of patients.

Conclusions: Brigatinib treatment demonstrated clinically meaningful efficacy in this integrated analysis of patients with advanced or metastatic *ALK*+ NSCLC who progressed on prior alectinib in the ALTA-2 or J-ALTA trials. Safety results were consistent with the known profile for brigatinib, with no new safety findings observed.

Keywords: NSCLC, ALK-positive, brigatinib

MA13 UPDATE ON ROS1 INHIBITORS AND NEW PATHWAYS,
TUESDAY, AUGUST 9, 2022 - 12:00–13:00

MA13.04 Entrectinib in Patients with ROS1 Fusion-Positive (ROS1-fp) NSCLC: Updated Efficacy and Safety Analysis

Y. Fan[1], A. Drilon[2], C-H. Chiu[3], D.W. Bowles[4], H.H.F. Loong[5], S. Siena[6,7], K. Goto[8], M. Krzakowski[9], M-J. Ahn[10], H. Murakami[11], R. Dziadziuszko[12], H. Zeuner[13], B. Pitcher[14], D. Cheick[15], M.G. Krebs[16]

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Introduction: *ROS1* gene rearrangements can lead to constitutively active fusion proteins that are targetable oncogenic drivers in NSCLC. Entrectinib, a potent *ROS1* tyrosine kinase inhibitor (TKI), has demonstrated efficacy and CNS activity in patients with *ROS1*-fp NSCLC from the integrated analysis of the phase I/II studies STARTRK-1 (NCT02097810), STARTRK2 (NCT02568267) and ALKA-372-001 (EudraCT 2012-000148-8): objective response rate (ORR) was 67% (n=108/161; data cutoff: May 1, 2019; median duration of survival follow-up: 15.8 months). We present updated data from this ongoing analysis.

Methods: Adults with locally advanced/metastatic *ROS1*-fp NSCLC who received ≥1 dose of entrectinib and had ≥12 months of follow-up from first post-treatment initiation tumor assessment, were included in the efficacy analysis. The safety-evaluable population comprised all patients who received ≥1 dose of entrectinib. Tumor assessments (by blinded independent central review [BICR] per RECIST v1.1) were performed at the end of cycle 1 (Week 4) and then every 8 weeks. Primary endpoints: ORR and duration of response (DoR). Secondary endpoints included progressionfree survival (PFS), overall survival (OS), intracranial (IC)ORR, ICDoR, IC-PFS and safety. Efficacy endpoints were assessed by BICR. Enrolment cutoff: July 2, 2020; data cutoff: August 2, 2021.

Results: The efficacy-evaluable population comprised 172 patients with *ROS1*-fp NSCLC who were ROS1 TKI-naïve; median duration of survival follow-up: 37.8 months. Median age was 54.5 years (range 20-86); 61 patients (35%) were current/former smokers; 40 patients (23%) had received ≥2 prior lines of therapy; 60 patients (35%) had investigator-assessed baseline CNS metastases. Entrectinib demonstrated efficacy in patients with *ROS1*-fp NSCLC with and without investigator-assessed baseline CNS metastases (**Table**). In patients with BICR-assessed baseline CNS metastases (n=51), median IC-ORR was 49% (25/51; 95% CI 34.8-63.4); median IC-DoR was 12.9 months (95% CI 7.6-22.5); median IC-PFS was 12.0 months (95% CI 6.7-15.6). In patients who received entrectinib as first-line treatment (n=67; exploratory analyses; **Table**), ORR was 69% (95% CI 56.2-79.4), median DoR was 35.6 months (95% CI 13.9-38.8); median PFS was 17.7 months (95% CI 11.8-39.4). In the safety-evaluable population (N=247), most treatment-related adverse events (TRAEs) were Grade 1/2 (54%); 1 patient (<1%) died due to a TRAE. TRAEs leading to dose interruption, reduction and discontinuation occurred in 36%, 35% and 7% of patients, respectively.

Conclusions: In this updated analysis with longer follow-up and a larger patient population, entrectinib continues to demonstrate overall and intracranial efficacy, and a manageable safety profile in patients with *ROS1*-fp NSCLC.

	***ROS1* fusion-positive NSCLC**			
	Overall efficacy-evaluable population (N=172)	**Baseline CNS metastases* (n=60)**	**No baseline CNS metastases* (n=112)**	**First-line cohort (n=67)**
ORR, n (%) [95% CI]	116 (67.4) [59.9-74.4]	38 (63.3) [49.9-75.4]	78 (69.6) [60.2-78.0]	46 (68.7) [56.2-79.4]
Best overall response, n (%)				
CR	23 (13.4)	4 (6.7)	19 (17.0)	10 (14.9)
PR	93 (54.1)	34 (56.7)	59 (52.7)	36 (53.7)
SD	16 (9.3)	6 (10.0)	10 (8.9)	7 (10.4)
PD	16 (9.3)	8 (13.3)	8 (7.1)	5 (7.5)
Non CR/PD	10 (5.8)	2 (3.3)	8 (7.1)	6 (9.0)
Missing/unevaluable	14 (8.1)	6 (10.0)	8 (7.1)	3 (4.5)
Median time-to-event, months (95% CI)				
DoR	20.4 (14.8-34.8)	14.6 (11.0-20.4)	28.6 (14.9-38.6)	35.6 (13.9-38.8)
PFS	16.8 (12.2-22.4)	11.8 (7.2-15.7)	25.2 (15.7-36.6)	17.7 (11.8-39.4)
OS	44.1 (40.1-NE)	28.3 (17.0-44.6)	NE (41.8-NE)	NA

*Investigator-assessed CNS metastases; CI, confidence interval; CR, complete response; NA, not available; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease

Keywords: ROS1 fusions, NSCLC, Entrectinib

MA13 UPDATE ON ROS1 INHIBITORS AND NEW PATHWAYS,
TUESDAY, AUGUST 9, 2022 - 12:00–13:00

MA13.05 TA0953/HM06, a Novel RET-specific Inhibitor Effective in Extracranial and CNS Disease Models of NSCLC with RETfusions

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Introduction: *RET* kinase fusions act as oncogenic drivers in approximately 2% of NSCLC patients. Two RET-selective kinase inhibitors, selpercatinib and pralsetinib, have proven effective at reducing tumor burden, and are FDA-approved. However, the emergence of resistance to these drugs, and brain metastasis, remain serious clinical challenges. TAS0953/HM06 is a new pharmacologically advanced RET-specific inhibitor that is structurally different from other RET inhibitors, has superior brain penetration kinetics compared to selpercatinib and pralsetinib, and retains activity in the setting of RET G810 (solvent front) mutations. Here we examined the efficacy of TAS0953/HM06 in NSCLC preclinical models representing extracranial and CNS disease.

Methods: We established unique patient-derived xenograft (PDX) and cell line models with RET fusions from treatment naïve or RET multi-kinase inhibitor refractory NSCLC patient samples. Disease models were characterized by the MSK-IMPACT large panel DNA NGS assay. A CNS disease model was established by injecting into the brain of mice, a NSCLC cell line (ECLC5) that allows non-invasive monitoring of tumor growth via bioluminescence imaging. Protein phosphorylation and expression were analyzed by western blotting. Enzymatic assays were used to assess caspase activity.

Results: TAS0953/HM06 was more effective than RET multi-kinase inhibitors (cabozantinib, RXDX105, vandetanib), and equipotent to selpercatinib and pralsetinib, at inhibiting growth of patient-derived (8) and isogenic (2) cell lines harboring different RET fusions (IC_{50}<0.1μM). In contrast, growth of non-tumor cells and RET fusion-negative tumor cells remained largely unaffected by TAS0953/HM06 (IC_{50}>5μM). Growth inhibition of RET-fusion-driven cell lines was accompanied by a substantial loss of phosphorylation of RET and downstream effectors (MAPK, PI3K, MTOR pathways), and downregulation of cyclin D1. Treatment of several RET fusion-driven cell lines induced expression of apoptosis activators and stimulated caspase 3/7 activity by 3-5 fold above basal. Oral administration of TAS0953/HM06 (50 mg/kg, BID or 100 mg/kg QD) to five NSCLC PDX models resulted in substantial reduction in tumor growth. TAS0953/HM06 was as effective as selpercatinib (10-30 mg/kg BID) and pralsetinib (15-30 mg/kg BID) at reducing growth of PDX models. TAS0953/HM06 (50 mg/kg BID) was superior to selpercatinib (10 mg/kg BID, p=0.0002; 25 mg/kg BID, p<0.0001) at inhibiting growth of ECLC5 brain xenograft tumors and increasing survival (selpercatinib 10 mg/kg BID, p=0.0012, selpercatinib 25 mg/kg BID, p=0.001, Log-rank test).

Conclusions: Our data show that TAS0953/HM06 is effective at inhibiting growth *in vitro* and *in vivo* of preclinical models driven by RET fusions. TAS0953/HM06 was more effective than selpercatinib at decreasing CNS disease and extending survival, at a dose that produced comparable suppression of tumor growth in extracranial disease models. TAS0953/HM06 represents a promising new therapeutic option for patients with RET fusions including those with brain metastasis and those resistant to first-generation selective RET inhibitors. We hypothesize that TAS0953/HM06 may produce a longer duration of response compared to selpercatinib and pralsetinib by preventing the outgrowth of tumor cells with acquired resistance mutations such as RET G810R/S, and by reducing CNS disease. TAS0953/HM06 is currently being evaluated in a phase 1/ 2 clinical trial for patients with solid tumors driven by *RET* alterations (NCT04683250).

Keywords: RET fusion, TAS0953/HM06, small molecule kinase inhibitor

MA13 UPDATE ON ROS1 INHIBITORS AND NEW PATHWAYS,
TUESDAY, AUGUST 9, 2022 - 12:00–13:00

MA13.07 TROPION-Lung02: Initial Results for Datopotamab Deruxtecan Plus Pembrolizumab and Platinum Chemotherapy in Advanced NSCLC

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Introduction: Most patients with advanced/metastatic NSCLC experience disease progression within 8-10 months of starting frontline therapy, highlighting the need for novel therapies. Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed antibody-drug conjugate (ADC) that demonstrated encouraging efficacy and a manageable safety profile as monotherapy in patients with relapsed/refractory advanced/metastatic NSCLC (NCT03401385; objective response rate [ORR] of 28% with 6 mg/kg and median response duration of 10.5 months). In addition, DXd ADCs plus anti-PD-1 yielded greater preclinical tumor regression than either agent alone. Here we report initial safety and efficacy results of Dato-DXd combined with pembrolizumab ± platinum chemotherapy in patients with NSCLC.

Methods: TROPION-Lung02 (NCT04526691) is a phase 1b, global, dose-escalation and expansion study evaluating 6 cohorts of ≈20 patients each (Table). Patients in cohort expansion must not have received prior therapy for advanced/metastatic NSCLC, unless otherwise noted below. The primary objective is to assess tolerability and safety. Secondary objectives are to evaluate efficacy, pharmacokinetics, and antidrug antibodies.

Table

Cohort[a]	Dato-DXd, mg/kg[b]	Pembrolizumab, mg[b]	Platinum therapy[b]
1[c]	4	200	–
2[c]	6	200	–
3	4	200	Carboplatin AUC 5
4	6	200	Carboplatin AUC 5
5	4	200	Cisplatin 75 mg/m^2
6	6	200	Cisplatin 75 mg/m^2

[a] Prior treatments are permitted for patients enrolled during the safety run-in of each cohort (n=3-6).
[b] All agents are given every 21 days.
[c] Patients in dose expansion in cohorts 1 and 2 may have received 1 line of prior platinum-based systemic chemotherapy.

Results: As of the January 2022 data cutoff, 60 patients were treated. The median age was 64 years. 35% of patients had PD-L1 (assessed locally) expression of <1%, and 25% each had PD-L1 expression of 1% to 49% or ≥50% (PD-L1 status was unknown in the remaining 15%). Median treatment duration was 2.7 months, with 67% of patients still receiving treatment. Treatment discontinuations due to adverse events occurred in 10% of patients; Dato-DXd dose reduction occurred in 20% of patients. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 43% of patients. The most frequent TEAEs of any grade were stomatitis (42%), nausea (38%), and fatigue (27%). No cases of adjudicated treatment-related interstitial lung disease have been identified. All combinations were considered tolerable and transitioned to dose expansion. In 46 response-evaluable patients across cohorts, the ORR was 39% (9 confirmed partial responses [PRs] and 9 ongoing PRs, pending confirmation), and the disease control rate (DCR) was 82.6%. In 16 response-evaluable first-line patients, the ORR was 69% (5 confirmed PRs and 6 ongoing PRs, pending confirmation), and the DCR was 100%. Updated results, including by PD-L1 expression, from a May 2022 data cutoff will be presented during the meeting.

Conclusions: Dato-DXd with pembrolizumab, ± platinum chemotherapy, demonstrates a tolerable safety profile and has notable activity in frontline and relapsed/refractory settings. To our knowledge, this is the first reported clinical experience of a TROP2 ADC in combination with checkpoint inhibitors and platinum chemotherapy in NSCLC.

Keywords: Dato-DXd, NSCLC, Pembrolizumab

MA13 UPDATE ON ROS1 INHIBITORS AND NEW PATHWAYS,
TUESDAY, AUGUST 9, 2022 - 12:00–13:00

MA13.08 A Phase 1 Trial of Sapanisertib and Telaglenastat (CB-839) in Patients with Advanced NSCLC (NCI 10327): Results from Dose Escalation

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Introduction: Prior work presented by us identified, in both pre-clinical models and in a phase 2 clinical trial of sapanisertib (NCT02417701), that lung squamous cell carcinomas (LUSC) harboring NRF2 activating mutations are sensitive to treatment with the TORC1/2 inhibitor sapanisertib. Further preclinical data suggests that suppression of glycolysis by sapanisertib is potentiated by targeting glutaminolysis that helps fuel the Krebs cycle, which is actionable via co-treatment of NRF2 activated NSCLC with sapanisertib and the glutaminase inhibitor telaglenastat (CB-839), leading to synergistic anti-tumor activity. This phase 1 study was designed to assess safety and preliminary activity of sapanisertib and telaglenastat in advanced NSCLC, with a focus on different NRF2 activating genotypes.

Methods: The phase 1 dose finding portion of this study used the queue-based variation of the 3+3 dose escalation scheme with the primary endpoint of identifying the recommended expansion dose (RED). Key eligibility for dose escalation: stage IV or recurrent/metastatic NSCLC that progressed on or after platinum-based chemotherapy and/or PD-(L)1 immune checkpoint inhibitor, PS=0-2, measurable disease by RECIST 1.1., adequate organ function, fasting blood glucose ≤ 130, HbA1c ≤ 8.0% and fasting triglycerides ≤ 300 mg/dL. No NRF2-pathway mutation requirements (i.e. KEAP1 or NFE2L2 mutations) for eligibility in dose escalation. Toxicity graded (G) by CTCAE v5. Response assessment by RECIST 1.1 every 2 cycles (each cycle 28 days). Starting dose level (DL1) was sapanisertib 2 mg PO daily and telaglenastat 800 mg PO bid. DL2 was sapanisertib 3 mg PO daily and telaglenastat 800 mg PO bid.

Results: In total, 13 patients enrolled onto the dose finding portion of study (10 at DL1 and 3 at DL2). Patient characteristics: median age 65, 4 male/9 female, 3 (23%) PS=0 and 10 (77%) PS=1, 6 (46%) LUSC and 7 (54%) LUAD, 13/13 (100%) prior chemotherapy and 8/13 (62%) prior immunotherapy. 1/3 patients experienced a DLT at DL2 (G3 anorexia) and 1/10 pts experienced a DLT at DL1 (G3 anorexia/G3 nausea/vomiting). Other G3 AEs that may be related to study drugs include pruritis and rash in 1 patient at DL2, G3 lymphocyte count decrease in 1 patient at DL1, and anorexia of any grade (3/3) 100% at DL2 and (2/10) 20% at DL1. Hyperglycemia was observed in 4/13 patients (all <G3) and hypertriglyceridemia in 3/13 patients (all <G3). Of the 8 patients evaluable for response (1 PR/4 SD/3 PD), 5 patients had tumor shrinkage including a patient with KRAS/KEAP1 mutant LUAD (SD) and 1 patient with LUSC harboring an NFE2L2 mutation (PR) at DL2.

Conclusions: The RED for sapanisertib + telaglenastat is DL1 (sapanisertib 2mg po qd, telaglenastat 800mg po bid). The majority of evaluable patients had tumor shrinkage including a PR in a patient with LUSC harboring an NFE2L2 mutation. Sapanisertib and telaglenastat is safe and tolerable at the RED. We now plan patient enrollment onto 1 of 4 expansion cohorts (n = 14 per cohort): (1) LUSC harboring NFE2L2 or (2) KEAP1 mutations, or (3) LUAD harboring KRAS/(KEAP1 or NFE2L2) co-alterations, or (4) LUSC wild type for NFE2L2 and KEAP1 (NCT04250545).

Keywords: NRF2 pathway, Squamous Lung cancer, targeted therapy

MA13 UPDATE ON ROS1 INHIBITORS AND NEW PATHWAYS,
TUESDAY, AUGUST 9, 2022 - 12:00–13:00

MA13.09 Time from Immune Checkpoint Inhibitor to Sotorasib Use Correlates with Risk of Hepatotoxicity in Non-small Cell Lung Cancer

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Introduction: Sotorasib was FDA approved in May 2021 for adult patients with KRAS G12C mutated, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy. Low rates (<10%) of grade 3 or higher hepatotoxicity were reported with sotorasib in the phase II registration study. Risk factors for development of hepatotoxicity have not been formally studied. We evaluated the risk factors for hepatotoxicity after use of sotorasib in KRAS mutated NSCLC.

Methods: Retrospective chart review of NSCLC patients with KRAS G12C mutation who were treated with sotorasib between 06/01/21 and 12/31/21 across all Mayo Clinic sites.

Results: Thirty-two patients received sotorasib as standard of care treatment. Median duration of treatment was 95 days (range, 18-172). Grade 3 or higher hepatoxicity was seen in 31%(10/32) patients. Median time to grade 3 toxicity was 49 days (range, 27-123). Baseline demographics were comparable between patients who developed ≥grade 3 hepatotoxicity versus those who did not except time from prior immune check point inhibitor (ICI) (Table 1). Improvement in liver tests was observed in all patients after stopping sotorasib, and it was restarted at lower dose in 8 patients. Despite dose reduction, hepatotoxicity requiring interruption of sotorasib occurred in 5 patients.

Twenty-eight of 32 patients had received prior ICI. Median time since prior ICI was 69 days(range, 4-542). Rates of ≥grade 3 hepatoxicity were 75% (3/4), 64% (7/11) and 0% (0/13) for patients who received ICI within 30 days, 31-90 days and >90 days (figure 1). None of the 4 patients without prior ICI exposure developed hepatoxicity.

Conclusions: One-third of patients developed sotorasib induced ≥grade 3 hepatotoxicity. Risk of hepatotoxicity was higher in patients who received sotorasib within 90 days of ICI treatment. This may have implications for sequencing and timing of these 2 modalities.

Table 1. Baseline demographics

Grade >=3 hepatotoxicity	No (N=22)	Yes (N=10)	Total (N=32)	p value
Age at diagnosis, years, median (range)	67 (43- 77)	69 (49- 81)	68(43- 81)	0.405
Male gender, n (%)	6 (27.3%)	3 (30.0%)	9 (28.1%)	0.874
Smoking in pack years, median (range)	30 (7-60)	28 (3-60)	30 (3-60)	0.500
Histology, n (%)				0.354
Adenocarcinoma	18 (81.8%)	10 (100.0%)	28 (87.5%)	
NSCLC NOS	1 (4.5%)	0 (0.0%)	1 (3.1%)	
Squamous	3 (13.6%)	0 (0.0%)	3 (9.4%)	
Duration of sotorasib treatment, days, median (range)	82.5 (7.0, 264.0)	131.5 (31.0, 254.0)	95.0 (7.0, 264.0)	0.309
Prior ICI use, n (%)	18 (81.8%)	10 (100.0%)	28 (87.5%)	0.149
Time from prior ICI to sotorasib initiation, days, median (range)	131.0 (15.0, 542.0)	39.0 (4.0, 70.0)	68.5 (4.0, 542.0)	0.001

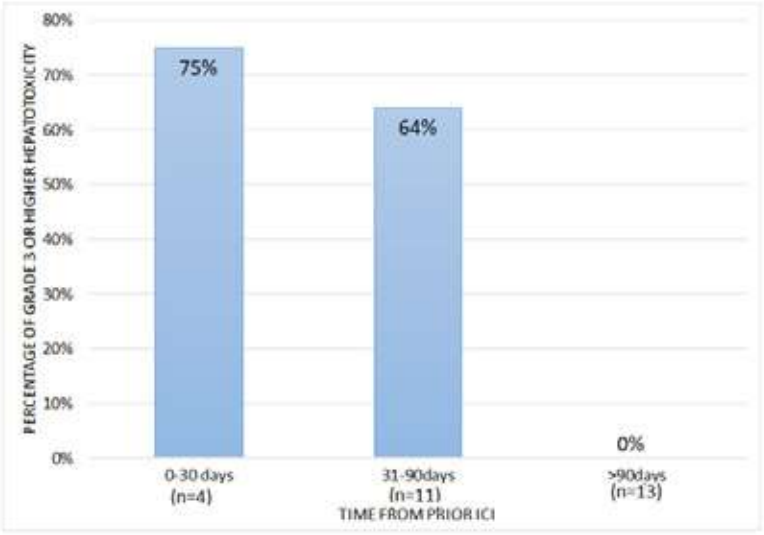

Figure 1. Rate of grade 3 or higher hepatoxicity in patients who received prior ICI

Keywords: Sotorasib, hepatotoxicity, Immune checkpoint inhibitor

MA14 PALLIATIVE AND SUPPORTIVE CARE - THE FORGOTTEN TRADE,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

MA14.03 Effect of Mirtazapine on Energy Intake in Patients with Anorexia Associated with NSCLC

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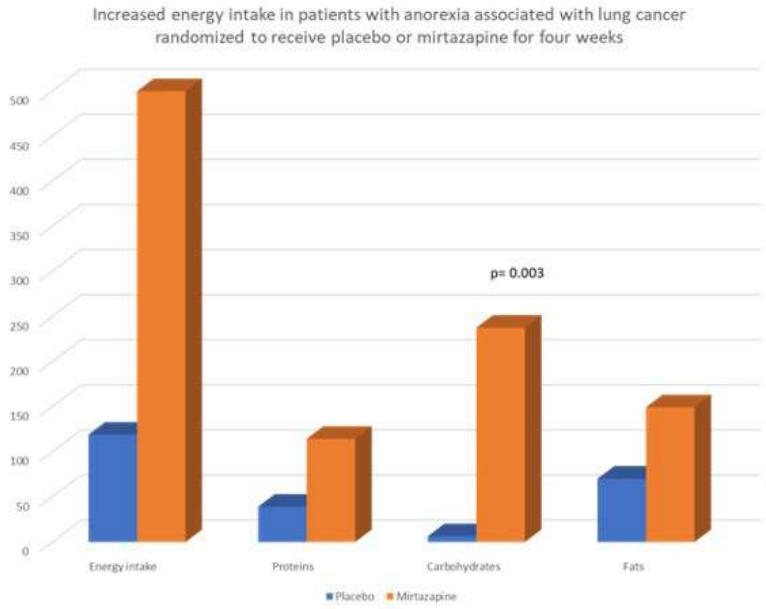
Introduction: Anorexia (lack of appetite), is a phenomenon which promotes malnutrition from insufficient food consumption; anorexia represents a widespread issue in patients with lung cancer, driving negative outcomes and hampering survival. Currently there is no standard therapy to improve cancer-related anorexia. This study sought to evaluate the effect of mirtazapine *vs.* placebo on nutritional parameters in patients with NSCLC diagnosed with anorexia.

Methods: Randomized, placebo-controlled clinical trial to evaluate the effect of supplementation with mirtazapine *vs.* placebo in terms of energy intake thorough 4 and 8 weeks in NSCLC patients diagnosed with anorexia using the validated Spanish version of the Anorexia Cachexia Scale (ACS). Patients were randomized 1:1 to receive 15 mg of mirtazapine or placebo for 2 weeks followed by a dose escalation to 30 mg until week 8. Dietary parameters were evaluated at baseline, 4 weeks and 8 weeks with a 24 hour dietary recall, and energy quantification based on the Mexican system of nutritional equivalents.

Results: A total of 65 patients met the inclusion criteria and were randomized to placebo group (n=32) or the mirtazapine group (n=33). The mean age was 63.5 ± 11.1, 37 (56.9%) were female and 28 (43.1%) were male. Baseline characteristics including sex, age, performance status, weight, body composition and ACS score were similar between study groups. Appetite was significantly increased in both study groups at 4 weeks post-intervention, no significant differences were identified at this study point (p=0.824). The percentage of energy requirement was significantly improved in the mirtazapine group compared with those who received placebo (34.9% vs. 8.8% p= 0.001). Energy consumption increase was greater in patients receiving mirtazapine as well (500 kcal *vs.* 119 kcal; p=0.001). This increase was reflected in protein (28.6gr *vs.* 9.8gr, p=0.011) and carbohydrate (59.4gr *vs.* 1.6gr, p= 0.003) intake. For the 8-week evaluation, patients in the mirtazapine showed a significant improvement in energy intake, percentage of requirement, proteins and fat from their baseline evaluation. Fats were also significantly improved among patients receiving mirtazapine *vs.* placebo (17.9 gr *vs.* 0.4 gr; p=0.009).

Conclusions: Patients with cancer-related anorexia can improve nutritional intake with the addition of mirtazapine, which promotes energy consumption reflected in diverse macronutrients.



Keywords: Anorexia, Mirtazapine, Malnutrition

MA14 PALLIATIVE AND SUPPORTIVE CARE - THE FORGOTTEN TRADE,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

MA14.04 Sexual Health Assessment in Women with Lung Cancer (SHAWL) Study

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This abstract is under embargo until August 9 at 10:10 Vienna, Austria Time, CEST.

MA14 PALLIATIVE AND SUPPORTIVE CARE - THE FORGOTTEN TRADE,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

MA14.05 A Double-blind Phase III Trial of Denosumab Biosimilar QL1206 vs Denosumab in Bone Metastatic Tumor: Lung Cancer Cohort Data

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Introduction: In the multicenter, randomized, double-blind phase III study (NCT04550949), QL1206 (the first biosimilar denosumab) demonstrated similar efficacy, safety, and PK characteristics to denosumab in solid tumor patients with bone metastases. Here we reported the data from lung cancer cohort analysis.

Methods: Bone metastatic solid tumor patients aged 18-80 years, with ECOG performance status of 0-2 were randomly assigned 1:1 to receive subcutaneous QL1206 or denosumab (120 mg Q4W, both), stratified by tumor types, previous skeletal-related event, and current systemic anti-tumor therapy. Primary efficacy endpoint was the percentage changes from baseline to week 13 in urinary N-telopeptide/creatinine ratio (uNTX/uCr); Clinical equivalence would be confirmed if the two-sided 90% confidence intervals (CI) of the least-squares mean (LSM) difference of natural log-transformed ratio of week 13 uNTX/uCr to baseline calculated by analysis of covariance were within the margins of ±0.135. However, the equivalence testing was conducted only in the overall study population but not in subgroups. Skeletal-related event (SRE), adverse events (AE), and immunogenicity (IG) were also assessed.

Results: In the full analysis set, totally, 717 patients were included and there were 199 and 198 lung cancer patients in the QL1206 and denosumab groups, respectively. The median percentage changes at week 13 in uNTX/uCr were -78.0% for QL1206 and -76.9%for denosumab. LSM of natural log-transformed ratio of week 13 uNTX/uCr to baseline were -1.327 (standard error 0.159) and -1.303 (0.156) in the two groups. The LSM difference between the two groups was -0.024 (0.072; 90% CI -0.144 to 0.095; P =0.7364). At data cutoff, the SRE rate was 6.0% (12/199) for QL1206 and 5.1% (10/198) for denosumab. In the safety set, treatment-emergent AE occurred in 196 (98.5%) of 199 patients in the QL1206 group and 194 (97.5%) of 199 in the denosumab group. The proportions of positive anti-drug antibody (8/190 [4.2%] vs 12/193 [6.2%]) and neutralizing antibody (2/190 [1.1%] vs 3/193 [1.6%]) were similar between the two groups.

Conclusions: The first biosimilar denosumab QL1206 showed similar clinical efficacy, acceptable safety, and IG to denosumab in lung cancer patients. QL1206 is a new option for bone metastatic lung cancer patients.

Keywords: QL1206, Denosumab, Bone metastasis

MA14 PALLIATIVE AND SUPPORTIVE CARE - THE FORGOTTEN TRADE,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

MA14.07 The Use of Medical Cannabis Concomitantly with Immune-Check Point Inhibitors (ICI) in Non Small Cell Lung Cancer (NSCLC): A Sigh of Relief?

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Introduction: In recent years, the use of medical cannabis rapidly increased among cancer patients in Israel. Yet, cannabinoid receptors are abundantly expressed on immune cells and modulate their activity. It is abundantly being use by metastatic NSCLC patients, shortly following diagnosis and is taken in parallel to first line treatment with ICI. Recent studies suggested that the use of cannabis may reduce the efficacy of ICI. However, these studies were biased by the heterogeneity of patients and the increased use of cannabis specifically in highly symptomatic patients with high disease burden.

Methods: We first tested the interaction anti-PD-1 antibody and Δ−9-tetrahydrocannabinol (THC) in a preclinical model consisting of CT26 tumor-bearing mice, and examined the effects on tumor size, T-cell infiltrates, and mice survival. Mice were euthanized when tumor volume reached above 700 mm^3. Next, we conducted a retrospective study of NSCLC patients, treated at a tertiary center, and included all consecutive patients treated with a single agent pembrolizumab as a first line treatment for advanced disease and evaluated clinical outcome and response to treatment.

Results: Studies using the CT26 mice cancer model, indicated a potential beneficial effect for the combination an anti-PD-1 antibody and THC with a median overall survival (OS) of the mice receiving no treatment, THC, anti-PD-1 antibody or their combination being 21 days, 24, 31 days and 54 days, respectively ($p<0.05$). Data of 201 NSCLC cancer patients who received first-line single agent pembrolizumab for metastatic disease, 102 (50.7%) patients received cannabis and 99 (49.3%) were cannabis naïve was analyzed. Their median age was 68 for the cannabis treated group and 74 for the cannabis naïve ($p=0.003$), 34 (34.3%) in the cannabis treated group and 62 (60.8%) for the cannabis naïve were women ($p=0.002$). Similar distribution of histology, smoking status and PDL1 expression was noted between the groups. The efficacy of pembrolizumab, as determined by time to progression (TTP) was similar for cannabis-naïve and cannabis-treated patients (6.1 vs. 4.8 months, respectively, $p=0.386$), while OS was higher, though not statistically significant, in the cannabis-naïve group (54 vs. 23.3 months, respectively $p=0.08$).

Conclusions: Both preclinical and clinical data suggest no deleterious effect of cannabis on the activity of pembrolizumab as first line monotherapy for advanced NSCLC. The differences in OS can be most likely by attributed to higher disease burden and more symptomatic disease in the cannabis-treated group. While additional validation is required, these data provide somewhat reassuring data regarding the absence of a deleterious effect of cannabis in this clinical setting.

Keywords: Immunotherapy, NSCLC, Cannabis

MA14 PALLIATIVE AND SUPPORTIVE CARE - THE FORGOTTEN TRADE,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

MA14.08 Longitudinal Symptoms and Health Utility Scores (HUS) in Patients Receiving PD-1 Inhibitors for Metastatic NSCLC

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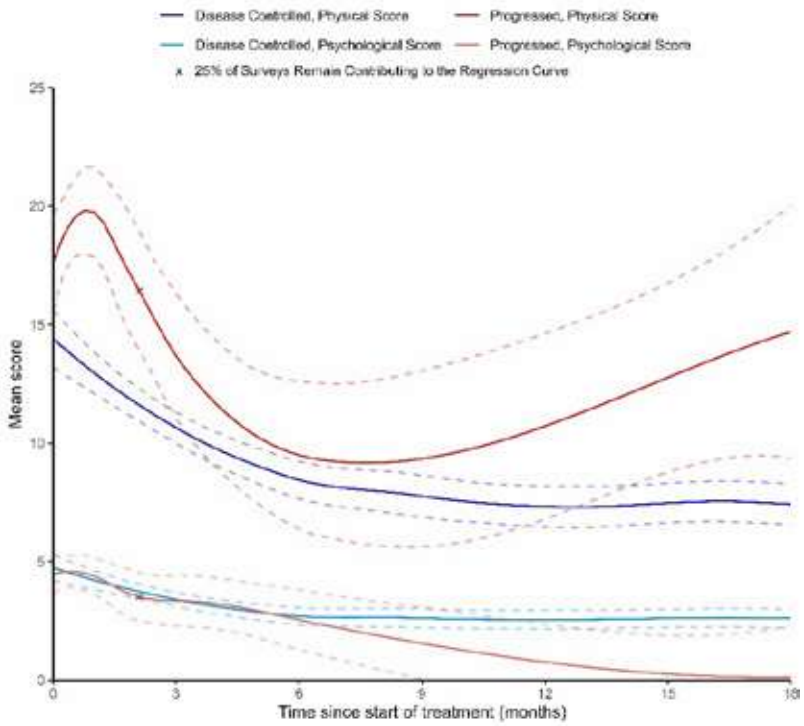
Introduction: The use of PD-1 inhibitors has dramatically prolonged survival in patients with metastatic NSCLC. Quality of life was better compared to chemotherapy in prospective trials. However, the symptom trajectory over time is not well described, especially for patients who remain on treatment long term. Therefore, we sought to characterize the symptom burden longitudinally in a large population-based sample.

Methods: We reviewed all patients who received single agent PD-1 inhibitor for metastatic NSCLC and completed at least one quality of life questionnaire at the Princess Margaret Cancer Centre between 2013 and 2020. Validated questionnaires used were Edmonton Symptom Response Assessment, (scale of 0-10, 10 being the worst), and the European Quality of Life 5 Dimensions (EQ-5D) derived health utility scores (HUS) (0-1, 0 between the worst). Mean scores on treatment were compared to baseline using T-tests. Longitudinal trends in scores were plotted using locally weighted polynomial least squares regression.

Results: We identified 1740 number of encounters representing 227 individual patients, with a median number of 4 encounters (IQR 2-9) per patient. 91% of patients had ECOG 0-1. The median duration of treatment was 3.7 months (IQR 1.4-8.4) and median line of treatment was 2 (1-11). At baseline, the mean combined physical symptom score was 16.6 with component means: tiredness (4.2), shortness of breath (3.4), pain (3.0), drowsiness (2.8), appetite (2.4) and nausea (1.0). The combined psychologic score was 4.9 with component means: anxiety (2.6) and depression (2.2). The pattern of change in symptoms differed by treatment response, with patients who had progressive disease demonstrating an initial increase in symptoms before stopping treatment (Figure 1). Pairwise comparisons demonstrate an improvement in mean physical symptoms for patients who remain on therapy at 6 months (-4.5, p=0.10) and 12 months (-5.1, p=0.04). A similar trend to benefit was seen even among patients treated second line or beyond (mean 6-month change -7.2, p=0.09). Psychologic symptoms remain similar throughout. A subset of 114 patients also completed 484 EQ-5D surveys with a mean baseline HUS of 0.7. Mean HUS was maintained at 6 months (0.9) and 12-months (0.9) in patients with at least stable disease.

Conclusions: Patients with metastatic NSCLC have a high symptom burden at baseline with tiredness, shortness of breath and pain being the most common symptoms. Patients with disease control who remain on immunotherapy long term had significant improvements in physical symptom burden compared to baseline and maintained HUS overtime.



Keywords: Health utility, Quality of life, Immunotherapy

MA14 PALLIATIVE AND SUPPORTIVE CARE - THE FORGOTTEN TRADE,
TUESDAY, AUGUST 9, 2022 - 14:30–15:30

MA14.09 Lower Paraspinous Muscle Index at First Thoracentesis is Associated with Poor Survival in Non-Small Cell Lung Cancer

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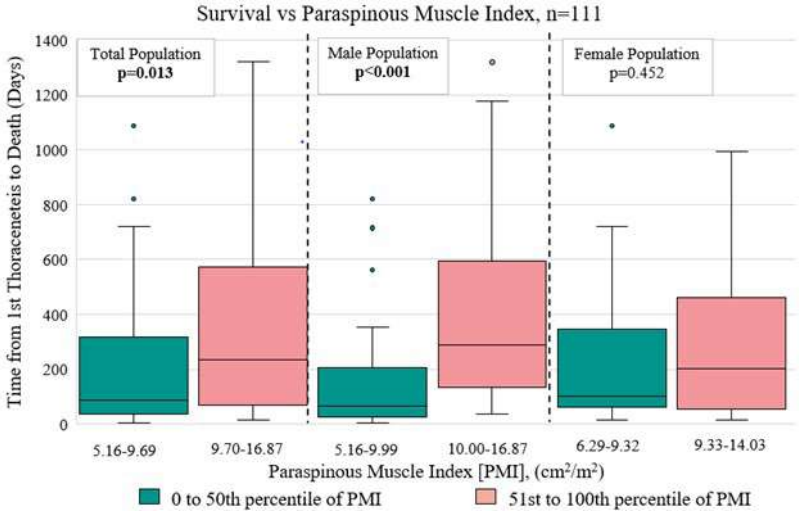
Swedish Cancer Institute, Seattle/WA/USA

Introduction: Malignant pleural effusions (MPEs) are common and associated with a poor prognosis. Current MPE prognostic tools can be difficult to utilize, such as the LENT score which requires laboratory testing and multiple calculations. Paraspinous muscle cross sectional area measured on computed tomography (CT) has shown to be associated with survival following thoracic surgery and as a prognostic indicator in non-small cell lung cancer (NSCLC). Additionally, the use of paraspinous muscle index (PMI) and other muscle indices have been associated with survival in diabetes and smokers. Our aim was to assess the relationship between PMI and survival in NSCLC patients with MPE.

Methods: We reviewed 148 MPE from NSCLC patients managed with a tunneled pleural catheter (TPC) from 01/01/2008-02/29/2020. Twenty-one patients were excluded for no CT scan or having a scan more than 45 days from the first thoracentesis, and 16 patients were excluded for lack of death record. Thus, 111 patients were included in the analysis. Paraspinous measurements (muscle area at 12th thoracic vertebrae) on CT within 45 days of first thoracentesis were recorded by two independent researchers and averaged. PMI was calculated by dividing paraspinous muscle area and height^2 (cm^2/m^2). Mann Whitney U tests were performed to assess the relationship between survival and PMI.

Results: Median age at first thoracentesis was 70 years (interquartile range [IQR]: 62-80). Median BMI was 24 (IQR: 20-27) and ECOG score was 1 (IQR: 1-2). Fifty-four percent (60/111) were female. The median paraspinous muscle area was 26 cm^2 (IQR: 23-31) and PMI was 9.7 cm^2/m^2 (IQR: 8.1-11.1). The 1st and 2nd quartiles of PMI (5.16-9.68) had a median survival of 88 days (IQR: 37-308) compared to the 3rd and 4th quartiles of PMI (9.69-16.87) with a median survival of 233 days (IQR: 69-557), p=0.013. A similar survival association was identified in the male population but not the female population (Figure 1).

Conclusions: A lower PMI was associated with poor median survival in NSCLC patients with MPE. The association was not present in a female population. PMI potentially represents a readily available, convenient tool to aid in prognostication of survival in NSCLC patients with MPE. Additional research is needed to explore the associations between PMI and outcomes in NSCLC patients with MPE.



Keywords: prognostic, muscle, effusion

Poster Presentation List

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Posters

P1.01 EARLY DETECTION AND SCREENING - BIOMARKERS,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.01-01 Comparison Between Protein and Autoantibody Biomarkers for the Early Detection of Lung Cancer

X. Feng[1], W.Y-Y. Wu[2], J. Onwuka[1], K. Alcala[1], K. Smith-Byrne[3], H. Zahed[1], F. Guida[1], J-M. Yuan[4], R. Wang[4], R.L. Milne[5], J. Bassett[5], A. Langhammer[6], K. Hveem[6], V.L. Stevens[7], Y. Wang[8], P. Brennan[1], B. Melin[2], M. Johansson[2], H.A. Robbins[1], M. Johansson[1]

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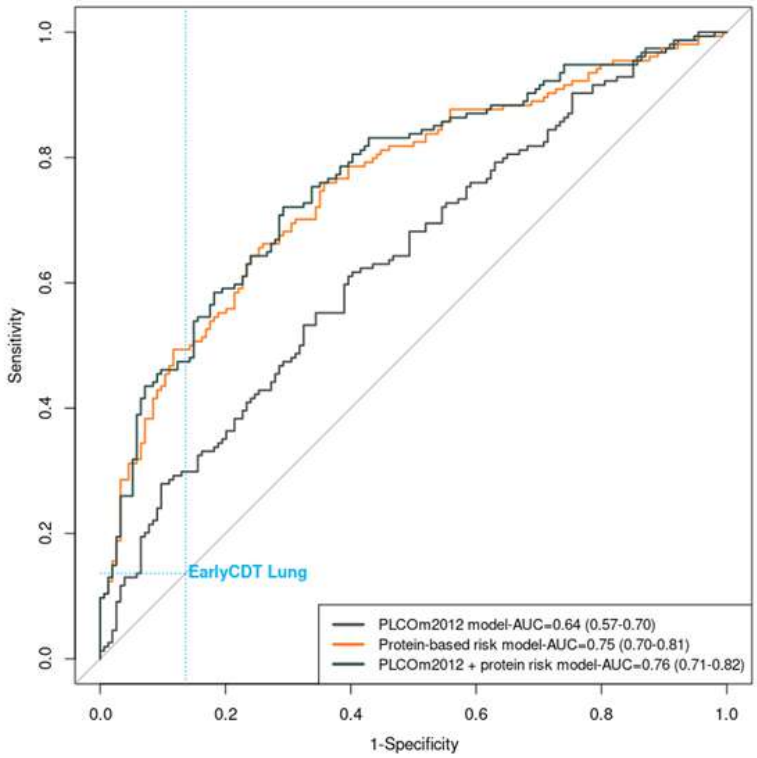
Introduction: The autoantibody-based EarlyCDT®-Lung test is advertised as a pre-screening test that can be used to identify individuals at high risk of lung cancer who may benefit from LDCT screening. The test is increasingly used to inform eligibility for lung cancer screening in practice, but data from the general population on its ability to predict incident lung cancer is limited. We aimed to evaluate the performance of the EarlyCDT®-Lung test for predicting incident lung cancer in the general population, and compare it with a preliminary protein-based risk model.

Methods: The study was conducted in the Lung Cancer Cohort Consortium (LC3). We used 470 case-control pairs nested in four cohorts to train a protein-based risk model and 154 case-control pairs nested from two cohorts to evaluate the protein-based risk model and the EarlyCDT®-Lung test. The blood samples for lung cancer cases were collected at most 3 years prior to diagnosis. EarlyCDT®-Lung test autoantibodies were measured using kits provided by the manufacturer and 302 proteins were measured using the Olink Proteomics platform. We used lasso-penalized logistic regression to select proteins and logistic regression to fit the protein-based risk model. The sensitivity and specificity of the EarlyCDT®-Lung test was evaluated and compared with that of the protein-based risk model. Receiver Operating Characteristic (ROC) curves were used to compare the discriminative performance of the protein-based model with a smoking-based risk model (PLCOm2012).

Results: The EarlyCDT®-Lung test had a sensitivity of 14% (95% CI: 8.2%-19%) and a specificity of 86% (95% CI: 81%-92%) for incident lung cancer overall. The sensitivity for the protein-based risk model was estimated at 49% (95% CI: 41%-57%, *p-difference*: 4×10^{-10}) at the same specificity as the EarlyCDT®-Lung test of 0.86. The AUC for the protein-based risk model in the validation set was 0.75 (95% CI: 0.70-0.81) compared to 0.64 (95% CI: 0.57-0.70) for the PLCOm2012 model (*p-difference*: 0.001).

Conclusions: The EarlyCDT®-Lung test had low sensitivity in identifying lung cancer cases in the general population based on blood drawn at most three years prior to diagnosis. In contrast, the risk discriminative performance of a protein-based risk model was notably better than the EarlyCDT-Lung test, as well as in comparison with the well-established PLCOm2012 smoking history-based risk prediction model. The potential of circulating proteins to inform eligibility for lung cancer screening warrant further evaluation in large-scale studies.



Keywords: Autoantibodies, Protein, Lung cancer

P1.02 EARLY DETECTION AND SCREENING - IMPLEMENTATION,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.02-02 Current Status, Challenges and Perspectives of Lung Cancer Screening in Low- and Middle-Income Countries

M. Cavic[1], A. Kerpel-Fronius[2], L. Viola[3], L. Ventura[4], L. Jiang[5], R. Sales dos Santos[6], D. Yang[7], C. Koegelenberg[8], J. Zulueta[9], C. Henschke[9], E. Kazerooni[10], M. Tammemägi[11], J. Field[12], M. Wynes[13], H. Balata[14,15], D. Yankelevitz[16], G. Sozzi[17], S. Lam[18], R. Huber[19]

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This abstract is under embargo until August 7 at 10:10 Vienna, Austria Time, CEST.

P1.02 EARLY DETECTION AND SCREENING - IMPLEMENTATION,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.02-03 Budget Impact Analysis of Volume CT Lung Cancer Screening Based on NELSON Study Outcomes in Europe

X. Pan[1,2], E. Dvortsin[1], J. Aerts[3], D.R. Baldwin[4], H.J.M. Groen[5], D. Ramaker[1], R. Velikanova[2], M. Oudkerk[1,5], M.J. Postma[2]

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This abstract is under embargo until August 7 at 17:00 Vienna, Austria Time, CEST.

P1.02 EARLY DETECTION AND SCREENING - IMPLEMENTATION,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.02-04 Spatial Access to Lung Screening in British Columbia, Canada

J. Simkin[1,2], E. Khoo[1], M. Darvishian[1], J. Sam[1], P. Bhatti[1,2], S. Lam[1,2], R. Woods[1,3]

[1]BC Cancer, Vancouver/BC/CA, [2]University of British Columbia, Vancouver/BC/CA, [3]Simon Fraser University, Burnaby/BC/CA

Introduction: As British Columbia (BC), the western-most province in Canada, prepares for lung cancer screening implementation, accessibility to screening services needs to be carefully considered. We examined travel times to potential screening sites among previously diagnosed lung cancer cases in BC, which serve as a proxy for a screen-eligible population.

Methods: Incident lung cancers (N=12,688) from 2015-2019 were identified through the BC Cancer Registry. The Open Source Routing Machine was used to calculate vehicle travel time from residential postal code at diagnosis to the nearest screening site (n=36). Relationships between travel time, urbanization, and the Statistics Canada's Canadian Index of Multiple Deprivation (CIMD; composed of sociodemographic and economic indicators) including its individual components, were assessed using chi-square tests.

Results: Median travel time to the nearest screening site was 11.7 minutes (interquartile range 6.2-23.2 minutes). Most cases were within 20 minutes of a screening site (69.8%; N=8,856). Urbanization was significantly associated with drive time ($p<0.001$). Most cases with ≤20-minute travel times lived in Metropolitan and Urban areas (93.5%, N=8,281). Most cases with ≥60-minute travel times lived in rural and remote areas (99.4%, N=1,008). Drive times were also associated with sex, ethno-cultural composition, situational vulnerability, economic dependency, and residential instability. For example, increased situational vulnerability was associated with longer drive times ($p<0.001$). The percentage of cases with drive times ≥60 minutes among the least deprived group was 4.7% versus 44.4% in the most deprived group. The percentage of cases with drive times ≤20 minutes among the least deprived group was 18.1% versus 22.0% in the most deprived group.

Conclusions: While most lung cancer cases lived within 20 minutes of a potential screening site, populations at risk in rural and remote regions may face more challenges accessing sites due to increased travel times. Our results demonstrated that drive times also increased with increasing deprivation across some sociodemographic and economic measures, highlighting populations that may require further support. These findings can inform the implementation of lung screening programs to ensure equal accessibility across population groups.

Keywords: Screening, Equity, GIS

P1.03 EARLY DETECTION AND SCREENING - PULMONARY NODULE,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.03-01 Do We Follow Incidental Lung Nodules Appropriately? A Retrospective Study

J.K. Pannu[1], G. Venious[2], R. Gallagher[1], A. Shaver[1], R. Cloyes[1], E. Josan[1], E. Donnelly[1], M. King[1], M. Knopp[1], R. Merritt[1], P. Kneuertz[1], D. D'souza[1], C. Ghattas[1], A. Revelo[1], N. Pastis[1], T. Sowers[1], C. Eastep[1], M. Ottersbach[1], M. Malinky[1], R. Reinbolt[1], M. Wert[1], J. Horowitz[1], D. Carbone[1]

[1]The Ohio State University Medical Center, Columbus/OH/USA, [2]Indiana University, Indianapolins/IN/USA

Introduction: Incidental pulmonary nodules (IPN) are common on computerized tomography (CT) scans and appropriate follow-up per Fleischner guidelines, 2017 is recommended. Indeterminate pulmonary nodules (8-20 mm, ages 40-89) can have a prevalence of malignancy of up to 25%. The rates of appropriate follow-up of IPN are low, presenting a missed opportunity for early lung cancer detection. We studied follow-up of incidental pulmonary nodules found on CT scans of chest, abdomen, and neck from January 1, 2018, to December 31, 2018 at our tertiary hospital system and the factors that influence the same.

Methods: We conducted a retrospective cohort study to investigate factors influencing appropriate follow-up of incidental lung nodules. Patients over 35 years of age who had an IPN detected on CT of their chest, neck or abdomen between January 1, 2018 to December 31, 2018 were included and followed for two years for disease progression. Patients who received appropriate follow-up per Fleischner 2017 guidelines were compared to those who did not. Patients with active malignancies, known lung nodules, and nodules that did not meet the criteria for follow-up per guidelines at the time of detection were excluded. We compared patient demographics, lung nodule characteristics, malignancy risk prediction scores (by Mayo Clinic model), and follow-up patterns between the two groups.

Results: We retracted 127,765 mentions of lung nodules from radiology reports of all CT chests, abdomen, and pelvis from six different scanners under the same tertiary hospital system. Total 696 truly incidental lung nodules meeting criteria for follow-up were found after removing false positives, duplicates, and studies meeting exclusion criteria. Only 301 (43.2%) completed appropriate follow-up per guidelines. The odds of inappropriate follow-up were significantly higher for CT abdomen (OR 1.98, p=0.001) and CT neck (OR 2.61, p = 0.016) compared to chest CT. Nodules with larger size (OR 0.33, p<0.001), multiplicity (OR 0.55, p=0.010), spiculation (75% less odds, p<0.001), upper lobe location (30% lower odds, p=0.018) and radiographic emphysema (29% odds, p=0.04) were less likely of not being followed appropriately than others. Patients with a family history of lung cancer (43% lower odds, p=0.011) and high-risk lung nodules (by mayo clinic model score) were less likely to be not followed per guidelines(69% lower odds than low risk, p<0.001). IPNs detected in emergency room scans seemed more likely to miss the appropriate follow-up, although not statistically significant (OR 1.3, p = 0.100). We found no significant difference based on race or gender. Interestingly, reporting the lung nodule in the impression section of the radiology report had 45% lower odds of not getting appropriate follow up (p=0.004). The groups remained significant in multivariate regression even after adjusting for risk, solid nodule size, speculation and family history.

Conclusions: The rate of appropriate follow-up for IPNs remains low. Hospitals should consider dedicating resources towards structured programs and systematic processes to address local disparities and prevent missed opportunities for early lung cancer detection. We identified key factors linked to not getting an appropriate follow-up in our study.

Keywords: Lung nodule, incidental, early lung cancer detection

P1.04 EARLY DETECTION AND SCREENING - RISK STRATIFICATION,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.04-01 Risk Stratification for Personalised Screening Intervals: Performance of PLCOm2012NoRace at Second Round of Manchester LHC

P. Bradley[1], H. Balata[2], A. Alonso[2], R. Booton[2], P.A. Crosbie[1]

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Introduction: There is a lack of consensus regarding optimal lung cancer screening (LCS) intervals. Shorter intervals are more likely to detect early stage (curable) cancers at the cost of increased low-dose computed tomography (LDCT) resource, financial costs, and more invasive tests. Annual screening is recommended in the USA, whilst biennial screening is recommended in England's Targeted Lung Health Check (TLHC) programme for those with an entirely negative baseline scan. Risk prediction models (RPMs) for lung cancer risk are used to determine screening eligibility. It is hypothesized that RPMs may also inform personalized screening intervals. In this study, we investigate the potential use of a RPM ($PLCO_{m2012NoRace}$) to stratify screening intensity through analysis of the Manchester Lung Health Checks (MLHC) annual results.

Methods: The expanded MLHC programme commenced in 2019, having been successfully piloted between 2016-2019. Residents, age 55-80, who had ever smoked are invited to a free LHC. Those at higher risk ($PLCO_{m2012NoRace}$ ≥1.5%) are offered annual LDCT screening. Lung cancers diagnosed from the second round of screening, either from the initial second round scan (T0+12) or from the 3-month surveillance scan (T0+15), were included in this analysis describing incidence at different putative risk thresholds.

Results: A total of 3,491 individuals participated in the second round of screening. Median age was 67y (IQR 61-72), 47% were female, 41% current smokers and median $PLCO_{m2012NoRace}$ score was 3.4% (IQR 2.2-6.2). Lung cancer incidence in the second round was 1.4% (n=49/3,491 LDCTs), compared with a prevalence of 2.1% (n=95/4,471 LDCTs) at the baseline round. Detection rates at different $PLCO_{m2012NoRace}$ thresholds are shown in Table 1. Annual incidence was significantly associated with increasing baseline $PLCO_{m2012NoRace}$ score, increasing to 3.5% in those with a risk score of ≥10% (Chi-sq p=0.014).

Table 1. LDCT screens performed and lung cancers detected in second round of NEM LHC programme.

$PLCO_{m2012NoRace}$ threshold	**≥1.5%**	**≥2%**	**≥3%**	**≥4%**	**≥6%**	**≥10%**
2nd round LDCTs performed, n	3,491	2,834	2,023	1,517	921	401
2nd round lung cancer detected, n	49	42	38	30	23	14
2nd round LC incidence, as % screened	1.4%	1.5%	1.9%	2.0%	2.5%	3.5%
NNS per LC detected, n	71	67	53	51	40	29

Conclusions: A significant proportion of MLHC participants were diagnosed with lung cancer in the first annual incidence round of screening. The number needed to screen (NNS) to detect one lung cancer was 71. Incidence rates were directly associated with increasing baseline $PLCO_{m2012NoRace}$ scores, increasing to 3.5% (NNS 29) in those with a baseline $PLCO_{m2012NoRace}$ of ≥10%. Further work is required to establish the most efficient and cost-effective screening intervals. However, our data suggest that RPMs could support a personalised screening interval strategy.

Keywords: Lung cancer screening, Risk prediction, Early detection

P1.04 EARLY DETECTION AND SCREENING - RISK STRATIFICATION,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.04-02 Optimizing Screening Frequency and Interval Using a Deep Learning Algorithm

S. Lam[1], J. Mayo[2], R. Myers[1], J. Yee[2], S. Atkar-Khattra[1], J. English[1], R. Yuan[1], M. Wu[1], P. Huang[3]

[1]BC Cancer Research Institute & University of British Columbia, Vancouver/BC/CA, [2]Vancouver General Hospital & University of British Columbia, Vancouver/BC/CA, [3]John Hopkins University, Balitmore/MD/USA

Introduction: A key issue in lung screening is how to identify low-risk individuals who could safely undergo the next scheduled screening CT in 2 years instead of annually and the small proportion of participants who may benefit from more frequent screening for biologically aggressive tumours. In the International Lung Screening Trial (ILST), after the baseline LDCT, participants were triaged to biennial or annual repeat screening, early recall CT scan in 3 months or diagnostic work-up referral based on lung cancer risk (Ann Am Thorac Soc. 2020;17(4):503-512). Subsequent management recommendations were based on nodule volume (for new nodules) and volume doubling time (VDT) for pre-existing nodules using the EU-NELSON protocol. The objective of this study is to determine whether we can optimize the screening interval after two or more LDCTs using a deep learning risk prediction tool.

Methods: From 2,145 participants enrolled in the Vancouver arm of ILST, we included those who had at least 2 LDCTs taken ≥3 months apart and had ≥ 12 months of follow-up after the second LDCT. Deep learning scores (DeepLR) (Lancet Digital Health 2019;1(7):e353-e362) were generated using the following input variables: age at the most recent scan, sex, smoking duration, pack-years, age quit smoking, family history of lung cancer, emphysema, days between the last two scans, and nodule parameters (new or pre-existing, location, attenuation, spiculation, average diameter, growth defined as VDT ≤400 days and increase in density). The implication of using DeepLR for recommending the next step was compared with the EU-NELSON protocol.

Results: The distribution of the 1,437 participants in each of the next step recommendation categories after the first two (T1, T2) or the last two LDCTs are shown in Figure 1. There were 45 lung cancers, 71% of them were Stage IA NSCLC. The key findings for the alternative strategy of using DeepLR instead of the EU-NELSON protocol which does not have a biennial repeat screening provision are: (1) Instead of 1,312 participants (91.3%) had annual screening, 696/1,437 (48.4%) could have biennial screening with no development of lung cancer. (2) Of the 45 lung cancers, 15.6% could be diagnosed earlier using DeepLR.

Conclusions: Our results suggest the DeepLR algorithm may optimize the screening LDCT intervals by catching lung cancers earlier among high-risk individuals and reducing the frequency of LDCTs in low-risk individuals. The findings serve as the basis to design a prospective randomized study to compare DeepLR versus volumetric screening protocols.

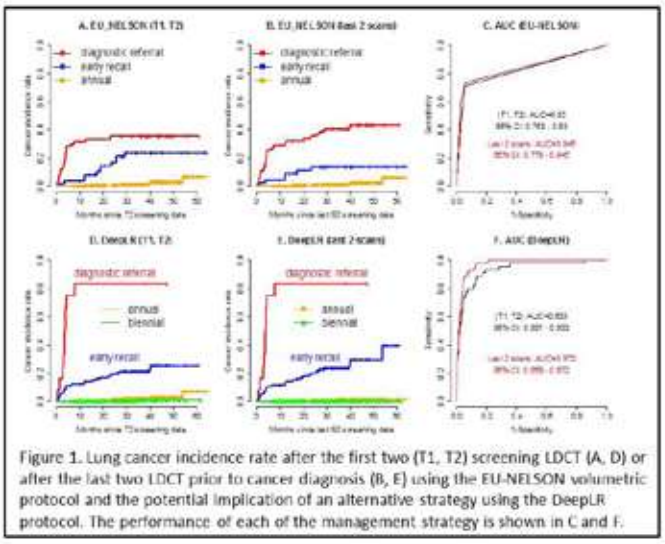

Figure 1. Lung cancer incidence rate after the first two (T1, T2) screening LDCT (A, D) or after the last two LDCT prior to cancer diagnosis (B, E) using the EU-NELSON volumetric protocol and the potential implication of an alternative strategy using the DeepLR protocol. The performance of each of the management strategy is shown in C and F.

Keywords: Screening Interval, Deep Learning Algorithm

P1.04 EARLY DETECTION AND SCREENING - RISK STRATIFICATION,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.04-03 Independent Validation of the Maisonneuve Lung Cancer Risk Model to Optimize Screening Interval in High-risk Individuals

P. Maisonneuve[1], M. Casiraghi[2], R. Bertolotti[3], C. Rampinelli[4], P. Muriana[5], L. Spaggiari[2], G. Veronesi[6]

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Introduction: Lung cancer screening represents a valid tool to reduce lung cancer mortality in high-risk individuals due to the ability to detect early lung cancer in a phase where curable treatments have best choice of success. Different risk models have been developed and validated to identify the best target population taking into consideration different epidemiological variables, but few have focused on the identification of the best screening interval for a particular individual. The aim of this study it to validate in a subset of the COSMOS II study, the risk model built by Maisonneuve et al. on COSMOS I participants that unify epidemiological data with radiological findings at baseline LDCT.

Methods: We analyzed results of 3107 high-risk individuals (62.3% males, 76.8% current smokers, median 43 pack-years) enrolled in a single institution between 2012 and 2015 and followed for 4 years based on our risk model. Subjects with a calculated probability to develop lung cancer lower than 0.6% (low risk) after baseline were allocated to biennial interval CT scan, those with a risk higher or equal than 0.6% (high risk) were allocated to annual screening interval.

Results: At baseline CT, 55 subjects (1.8%) were identified with lung cancer, 1339 (44.9%) of the remaining subjects were classified at high-risk and 1713 (55.1%) at low-risk. In the high-risk group 44 lung cancers were detected from year 2 to 5 (3.3% of individuals), in the low risk group detection rate was 11/1713 equal to 0.6%. Only 1 low-risk subject was identified with cancer at first biennial screening. Cancer/CT ratio was 1/155 for the low risk and 1/31 for the high risk.

Conclusions: Our model is able to discriminate high and low risk individuals in the population of ever smoker optimizing the screening interval, avoiding useless radiation exposure and saving cost. People at low risk after baseline CT can safely undergo biennial CT scan. These data have important health policy consequences when planning large-scale screening programs.

Table 1: Detection rate of screening lung cancers in two risk groups after baseline according to Maisonneuve model

	Subjects at baseline	Lung cancer during screening period				
		2nd year	3rd year	4th year	5th year	Total
Recall/annual CT	1339	15	9	8	12	44
Biennial CT	1713	-	1	5*	5	11

*199 low-risk subjects had new radiological findings at first biennial screening, were re-classified at high-risk and re-scheduled to annual screening.

Keywords: Low-dose CT, Lung Cancer, Screening

P1.05 EARLY STAGE NON-SMALL CELL - BIOMARKERS,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.05-01 Phase II Study of ctDNA Directed Consolidation Durvalumab After Induction and Concurrent Durvalumab with SABR for Stage I NSCLC

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Introduction: Following Stereotactic Ablative Body Radiotherapy (SABR) for T1-2 N0 M0 non-small cell lung carcinoma (NSCLC), the estimated overall relapse rate at 3 years is 29%, with rates of failure by location of approximately 8% local, 12% regional, and 18% distant. SABR can induce mixed immunologic effects: ablation can prime antitumor immunity, but it can also upregulate tumor cell expression of PD-L1. Checkpoint inhibitor (CI) monotherapy is active in early NSCLC in the neoadjuvant setting. Anecdotal reports of SABR delivered concurrently with CI describe abscopal response in various advanced tumor histologies, including NSCLC. Consolidation Durvalumab following chemoradiotherapy for stage III NSCLC nearly halved the rate of distant failure. Predicting which patients may benefit from consolidation CI is challenging. The presence of residual circulating tumor DNA (ctDNA) following definitive treatment for NSCLC (Molecular Residual Disease or MRD) portends a high risk of relapse and may predict a benefit for extended CI. The intent of this study is to determine whether disease control in early NSCLC achieved by SABR can be augmented by safely combining it with a PD-L1 inhibitor, Durvalumab. Moreover, the study will assess whether patients likeliest to benefit from extended Durvalumab treatment can be predicted prospectively by assaying for MRD after initial treatment.

Methods: We hypothesize that combining SABR and Durvalumab using a ctDNA-directed approach in patients with T1-2 N0 M0 NSCLC reduces the overall relapse rate at 18 months by 50% compared with historical controls treated with SABR alone, from 19.3% to 9.7%. Subjects with biopsy-proven T1-T2 N0 M0 NSCLC who are not undergoing surgical resection are eligible. Subjects will receive four cycles of q4w Durvalumab, concurrent with SABR at cycle 2. Subjects will be assessed at baseline using the AVENIO assay on tumor biopsy material, then reassessed for MRD following cycle 4 with a tumor-informed AVENIO assay on blood for ctDNA. AVENIO is a proprietary ctDNA assay using the CAPP-Seq detection method. At MRD assessment, subjects with no detectable ctDNA will receive no further therapy; subjects with detectable ctDNA will be randomized to receive either no further therapy or 8 additional cycles of Durvalumab. (see Schema) Efficacy and safety will be evaluated, with special attention to patterns of relapse, pneumonitis and immune-related toxicity. Exploratory analyses will assess the predictive value of MRD assessment, and of biomarkers in tumor genome, blood, and gut microbiome.

Results: Enrolment beginning Q2 2022

SCION. SABR and Checkpoint Inhibition Of NSCLC (NCT04944173)

Conclusions:

Keywords: Early Stage Non-Small Cell Lung Cancer, Immunotherapy, Stereotactic Radiotherapy

P1.05 EARLY STAGE NON-SMALL CELL - BIOMARKERS,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.05-02 Mutations in CREBBP are Associated with Local Failure after Lung Stereotactic Body Radiation Therapy

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Introduction: Lung stereotactic body radiation therapy (SBRT) can achieve high rates of local control for primary and metastatic lung tumors. However, local failures after SBRT still occur, and there is a need to identify predictors of failure. We used next-generation sequencing to test the hypothesis that particular genetic mutations may be predictive of local control.

Methods: We updated a retrospective database of patients treated with lung SBRT at our institution for primary or metastatic tumors. Patients included in this analysis received a minimum biologically effective dose (BED) of 80 Gy (alpha/beta=10) and underwent next-generation tumor sequencing utilizing an FDA-approved targeted panel of at least 341 genes. Patient and tumor characteristics, radiation dose, and all genetic alterations identified by the panel were collected. The primary endpoint was local control (LC), assessed on follow-up CT or PET-CT imaging. We limited candidate genes to those with at least 5% incidence of alteration in this cohort and utilized a p-value cutoff of ≤0.001 for candidate genes to account for multiple testing. Univariate and multivariate Cox proportional hazards analysis was then performed.

Results: We identified 298 lesions in 264 patients treated between 2015 and 2020, with a median follow-up of 29.8 months for survivors. Lesions received SBRT to a median BED of 100 Gy (range 80-151 Gy). Primary tumor histology included 204 lung (68%), 30 soft tissue sarcoma (10%), 24 colorectal (8%), and 40 other (13%). For the entire cohort, 12- and 24-month cumulative LC rates were 92.0% (95% CI 88.8 - 95.4) and 77.2% (71.7 - 83.1), respectively. Overall, we identified 36 mutations occurring with ≥5% frequency (≥15 times). Tumor size (HR 1.2, p=0.021), colorectal histology (HR 2.2, p=0.02), and mutations in CREBBP (CREB-binding protein, HR 3.5, p<0.001) were found on univariate analysis to be significantly associated with LC. Mutations in RMB10, NKX2-1, and TP53 were also negatively associated with LC (p<0.05) but above a p-value cutoff of p=0.001. The 18 CREBBP-mutated tumors were treated to a median BED of 100 Gy, with respective 12- and 24-month LC of 65.3% (95% CI 42.6 - 100.0) and 37.3% (95% CI 17.3 - 80.7). On multivariate analysis, tumor size (p=0.018), colorectal histology (p=0.015), and CREBBP mutation (p=0.009) remained significantly associated with local control, whereas BED was not (p=0.20).

Conclusions: This analysis identified mutations in CREBBP as independently associated with higher risk of local failure after lung SBRT. CREBBP is a ubiquitously expressed protein that regulates gene expression via its acetyltransferase activity and its role in chromatin remodeling as a protein scaffold. Further study is needed to validate these findings and to investigate whether treatment strategies such as dose intensification, radio-sensitization, or alternative local therapies could be superior to SBRT monotherapy for local control of CREBBP-mutated lung tumors.

Keywords: stereotactic body radiation therapy, ablative, next-generation sequencing

P1.06 EARLY STAGE NON-SMALL CELL - SYSTEMIC THERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.06-01 Adjuvant Osimertinib vs Placebo in Completely Resected Stage IA2-IA3 EGFR-mutated NSCLC: The ADAURA2 Phase III Study

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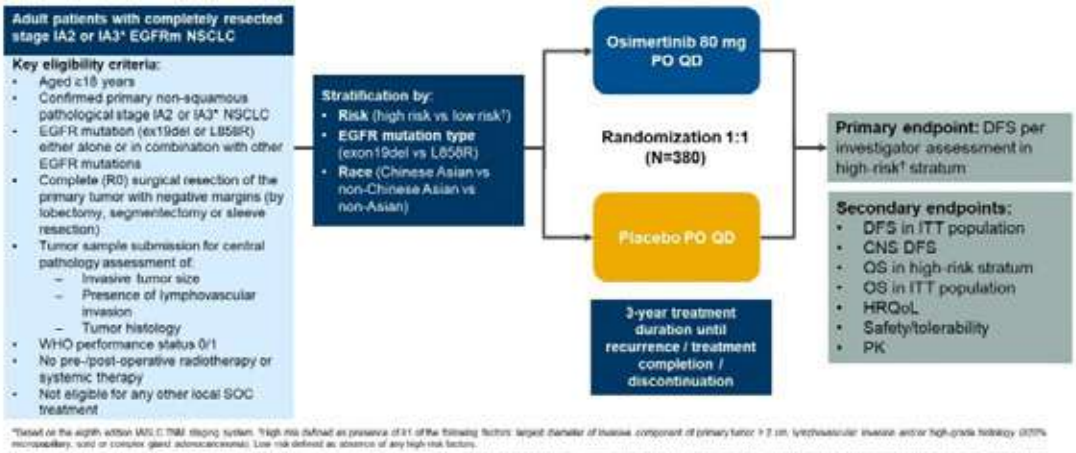
Introduction: Management of patients with stage IA epidermal growth factor receptor (EGFR)-mutated nonsmall cell lung cancer (NSCLC) is currently restricted to observation following complete tumor resection. No widely approved systemic adjuvant therapy has demonstrated a disease-free survival (DFS) or overall survival (OS) benefit in this setting. Approximately 25-30% of patients with stage IA NSCLC will have recurrent disease within 5 years, often involving distant metastases. Osimertinib is a third-generation, central nervous system (CNS)-active EGFR-tyrosine kinase inhibitor (TKI) selective for EGFR-TKI sensitizing and EGFR T790M resistance mutations. Based on results from the Phase III ADAURA study (NCT02511106), adjuvant osimertinib is the first targeted therapy approved for patients with stage IB-IIIA resected NSCLC, after a statistically significant improvement in DFS versus placebo was demonstrated (HR=0.20, 99.12% CI: 0.14-0.30; p<0.001). ADAURA2 (NCT05120349) is a global, randomized, double-blind Phase III study assessing the efficacy and safety of osimertinib compared with placebo as adjuvant therapy for patients with stage IA2-IA3 EGFRmutated NSCLC following complete tumor resection.

Methods: Eligible patients will be aged ≥18 years with histologically confirmed primary nonsquamous stage IA2-IA3 NSCLC harboring EGFR exon 19 deletion (ex19del) or L858R mutations, either alone or in combination with other EGFR mutations. Patients must have recovered from complete surgical resection (R0) of the primary NSCLC by lobectomy/segmentectomy/sleeve resection, be between 4-12 weeks after surgery at the time of randomization, and have a World Health Organization performance status of 0/1. Patients with mixed small cell and non-small cell histologies; incomplete (R1/R2) resection, or who underwent pneumonectomy/wedge resection; and/or received any other type of anticancer therapy for NSCLC, are excluded. Approximately 380 patients will be randomized 1:1 to receive oral osimertinib 80 mg or placebo once daily, for 3 years or until disease recurrence/discontinuation. Patients will be stratified by risk (highrisk [defined as having any of the following pathologic factors: invasive component of tumor diameter >2cm, lymphovascular invasion, high-grade histology] vs low-risk [no high-risk features]), race (Chinese Asian/non-Chinese Asian/non-Asian), and EGFR mutation type (ex19del/L858R). Patients experiencing Grade 1/2 interstitial lung disease or pneumonitis may continue (Grade 1) or restart (if Grade 2 symptoms resolve within 4 weeks of interruption) study treatment. Primary endpoint: DFS per investigator assessment in the high-risk stratum; secondary endpoints include DFS in the overall population, CNS DFS, OS, HRQoL, safety/tolerability. The study is currently recruiting; interim analysis of the primary endpoint is expected August 2027, with final completion in November 2032.



Keywords: Osimertinib, Stage IA2/IA3 NSCLC, DFS

P1.07 EPIDEMIOLOGY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.07-01 Early Detection Plus Timely Surgery Remains the Standard despite Advances in Immunotherapy

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Introduction: Lung cancer mortality has declined over time, at a faster rate than lung cancer incidence, likely because of multiple factors including changes in smoking behavior, novel therapies, and early detection, which shifts diagnosis towards earlier stages. Because of limited resources, it is important to quantify the contribution of early detection versus novel therapies in improving lung cancer survival.

Methods: Non-small cell lung cancer (NSCLC) patients were queried from the Surveillance, Epidemiology, and End Results (SEER)-Medicare data, and split into 2 cohorts: (1) stage IV patients diagnosed in 2015, who received either immunotherapy or chemotherapy (n=1,499); (2) stage I-III patients diagnosed in 2010-2012 (n=15,817), before the approval of any immunotherapy. Multivariable Cox-proportional hazards models were performed to assess the independent association of receipt of immunotherapy vs no immunotherapy (cohort 1) or diagnosis at stage I/II vs. stage III (cohort 2) with overall survival. Differences in median survival between the groups in each cohort were calculated, and used to simulate additional person years survival per 100,000 diagnoses based on what percent of the higher risk group switches to the lower risk group.

Results: In cohort 1, those with immunotherapy had significantly better overall survival than those without (Adjusted Hazard Ratio (HRadj): 0.71, 95% Confidence Interval (CI): 0.62-0.82), as did those diagnosed at stage I/II versus stage III (HRadj: 0.36, 95% CI: 0.35-0.36). In cohort 1, those with immunotherapy had a 5.6 month longer survival than those without. In cohort 2, stage I/II patients had an average survival benefit of 34 months, compared to stage III. If 100% of those without immunotherapy received immunotherapy, there would be a gain of 46,667 person years survival per 100,000 diagnoses; a switch of only 25% from stage III to stage I/II would correspond to 70,833 person years survival per 100,000 diagnoses (Table 1).

Conclusions: Earlier stage at diagnosis can substantially modify life expectancy by almost 3 years. Comparatively, gains from immunotherapy are modest and translate to fewer person years of survival gained on a population level, even assuming the best case scenario of all stage IV patients responding well to immunotherapy. Especially given the relative affordability of early detection screenings, every effort should be made to increase screening availability and resources should be directed towards early diagnosis.

Table 1: Simulation of years of life gained in case of stage shift (from III to I-II), and in case of immunotherapy treatment in stage IV NSCLC

Stage IV patients treated with immunotherapy (%)	Average years of survival gained x person	Person years of survival gained x 100,000 diagnoses
100	0.47	46,667
75	0.47	35,000
50	0.47	23,333
25	0.47	11,667
10	0.47	4,667
Stage III patients diagnosed at Stage I-II (%)	**Average years of survival gained x person**	**Person years of survival gained x 100,000 diagnoses**
100	2.83	283,333
75	2.83	212,500
50	2.83	141,667
25	2.83	70,833
10	2.83	28,333

Keywords: Immunotherapy, Lung cancer, Early detection

P1.07 EPIDEMIOLOGY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.07-02 Personal and Family HiStory of CANcer in Patients with Non-small Cell Lung Cancer: Preliminary Data of the SCAN Study

J.C. Laguna[1], L. Gonzalez-Aguado[1], E. Auclin[2], J. Torres-Jiménez[3], V. Albarrán-Artahona[1], B. Pastor[1], T. Gorría[1], L. Moreno[1], M. Potrony[1], R. Reyes[1], D. Martínez[1], O. Castillo[4], N. Viñolas[1,4], L. Gaba[1,4], B. Adamo[1,4], A. Arcocha[1], J.A. Puig-Butillé[1], A. Prat[1,4], C. Teixidó[1,4], N. Reguart[1,4], L. Mezquita[1,4]

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Introduction: Emerging evidence indicates that lung cancer can be associated with individual predisposition to cancer, however there are very limited data regarding the clinical and molecular profile of lung tumors in patients with family history of cancer. We aimed to describe the prevalence of family history of cancer and the profile of patients/tumor associated in a cohort of patients with non-small cell lung cancer (NSCLC).

Methods: Prospective study of 400 patients with all-stages NSCLC treated at Hospital Clinic (Spain) between 10/2020-01/2022 (ongoing). After signature of the informed-consent form, patients had a personal interview to collect personal/family history of cancer (three-generation pedigree), demographic data, and exposure to environmental/occupational carcinogens. Clinical and molecular data was collected from medical records. Data was registered in an electronic case report form (redcap). Here, we studied the personal/family history in the overall population and in the driver population (including somatic mutations (m) in *EGFR/KRAS/BRAF/MET/ERBB2*, fusions (f) in *ALK/ROS1/RET/NTRK1-3* and amplifications (a) in *ERBB2/MET*).

Results: To date, 202 patients were enrolled. Of the first 156 patients, the median age was of 68 years (39-91), 62% were male, 87% smokers; 77% had stage IV disease and adenocarcinoma was the most common histology (70%). Among the 131 patients with available molecular profile, 60% had a somatic driver alteration (18 *EGFRm*, 40 *KRASm*, 8 *BRAFm*, 6 *METm*, 7 *ALKf*). 85% of patients have ≥1 familiar with cancer, particularly in first-degree relatives (56%), with lung cancer as the most frequent (19%), followed by breast (12%). In this preliminary dataset, no relevant differences were identified in cancer family history according to gender, smoking and histology. In the driver population, 88% of patients have ≥1 relative with cancer, particularly in first-degree (57%); among first degree relatives, lung cancer was the most frequent (23%), followed by colorectal (11%). By molecular group, the highest % was observed in *KRASm* population (90%). In the non-driver population, family history was also observed in 82% (56% in first-degree relatives), specially lung tumors (23%). 35% of patients had personal history of another cancer, particularly lung cancer (16%), followed by breast (15%). No significant differences were observed between male/female population. In the driver population, 41% of patients had a personal history of cancer, principally breast cancer (23%), followed by a second lung tumor (15%). By molecular subtype, the highest % was observed in *KRASm* population (45%) vs. no cases in *METm*.

Conclusions: Our preliminary data showed high prevalence of family/personal cancer history in patients with NSCLC, specially lung cancer. It appears that prevalence could be different for each molecular subtype; this study is currently ongoing to explore this findings in a larger cohort. More detailed data regarding the clinical/molecular profile will be presented in the meeting.

Keywords: family history, non-small cell lung cancer, personal cancer history

P1.08 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.08-01 Updated Costs and Survival Expectations for Stage IV Lung Cancer in Australia

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Introduction: New therapies have transformed the standard of care for advanced lung cancer. Due to the pace of change, often existing data on lung cancer no longer reflect current practices. As health system planning and economic evaluations rely on the availability of relevant data, there is a need for up-to-date estimates on costs and survival expectations for stage IV lung cancer.

Methods: We developed a discrete event simulation of stage IV lung cancer treatment for the Australian setting. The model simulated treatment for histological and molecular subpopulations based on a clinician-specified treatment algorithm. Model inputs included published treatment utilisation rates, treatment-specific progression-free survival curves from clinical trials, and healthcare costs. Healthcare costs included published reimbursement fees for antineoplastics, and linked hospital records (Admitted Patient Data Collection/Emergency Department Data Collection) and health care claims (Medicare Benefits Schedule/ Pharmaceutical Benefits Scheme) of participants in a prospective Australian cohort study (45 and Up Study, 2006-2016, n=267,153). Uncertainty intervals were generated with probabilistic sensitivity analyses. Survival predictions were validated against real-world studies.

Results: Under contemporary care, mean costs at 10 years were predicted to have risen to AU$111,000 (95% uncertainty interval [UI]: $102,000-$120,000). Despite the arrival of novel therapies, prognosis remained poor due to low rates of treatment utilisation (5-year survival: 5%, UI: 4-7%). 10-year costs and survival outcomes were highest for patients with ALK-rearranged NSCLC, ROS1-rearranged NSCLC, and EGFR-positive NSCLC but remained low for SCLC. Costs were sensitive to assumptions about treatment rates and drug prices. The model performed well in validation, replicating real-world survival outcomes based on reported treatment patterns.

Conclusions: Treatment costs for stage IV lung cancer have dramatically increased in recent years. The estimates produced in this study will be useful for budget planning and the re-evaluation of lung cancer control strategies in Australia.

Keywords: immunotherapy, cost, health economics

P1.09 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - SUPPORT TO PATIENTS AND STAFF, SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.09-01 The Lung Cancer Patient Experience and Care Pathway: A Multi-Country Survey

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Introduction: There is growing evidence that outcomes of cancer patients are impacted not only by treatments, but also by quality of clinical care and supportive resources. For a better understanding of differences in the patient care pathway and unmet patient support needs, we conducted a global survey of lung cancer (LC) patients.

Methods: A questionnaire was developed covering 4 domains: Socio-demographic and medical profile; Treatment experience; Disease impact; Information and services utilized. A panel of LC patient advocates from 4 countries were consulted on the questionnaire design. Cognitive testing was conducted with LC patients in 3 countries to test the questionnaire. Respondents ≥18 years old living in Canada, China, France, Germany, Italy, Japan, Spain, the UK, or the USA who self-identified as patients diagnosed with LC were recruited to complete the online questionnaire via an online patient platform or local recruiter.

Results: 1000 LC patients completed the online questionnaire between October 14, 2021 and January 31, 2022. Participant distribution by region was 21.5% Asia, 49.5% Europe, and 29% North America; and by type was 47% NSCLC, 32% SCLC, 6% another LC type, and 15% unknown. Besides the high participation rate of SCLC patients, there was a high proportion of early-stage LC 55.5% vs 31.5% locally advanced, 10.6% advanced, and 2.4% unknown. The median age of diagnosis reflects a relatively young population of ~51 yrs; the median time to diagnosis was ~2 yrs; 56% were male. Patients reported pulmonologists / respiratory specialists (P/RS) as the key physician type to diagnose LC at 53%, then primary care physicans / general practitioners (PCP/GP) at 21% and medical oncologists (MO) at 17%. The main person influencing their treatment choice were P/RS 53%, then MO 44% and PCP/GP 28%. P/RS were the main person 45% with whom patients spoke to about how the disease / treatment affects their quality of life (QoL), then MO 42% and the patient's spouse / partner 38%. The top reasons patients report choosing a treatment are to live longer 54% or control the cancer 53%. However, QoL is also an important consideration with 44% citing QoL improvements as a factor for choosing a treatment. Likewise, 33% of patients report impact on daily life and 29% overall QoL as reasons for hesitating to start a treatment. Patients reported that a LC diagnosis impacted many areas of their daily lives. 50% of patients' employment status was impacted - reduced employment or interrupted employment due to sick leave / early retirement. 48% reported mental well-being as one of the main difficulties in their daily life, and 64% have received psychological support or would like to.

Conclusions: The 1000 LC patient survey findings highlight that both medical factors and external factors impact LC patients' experiences and outcomes. Physicians have a significant role in influencing patient decisions, and discussing their QoL considerations. How LC affects patients' daily lives regarding employment and mental well-being, should not be underestimated and requires ongoing focused efforts.

Keywords: Survey, Patient experience, Care experience

P1.09 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - SUPPORT TO PATIENTS AND STAFF, SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.09-02 Real-world Clinical Characteristics and Treatment Patterns of METExon 14 Skipping Mutation in Advanced/Metastatic NSCLC

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Introduction: *MET* exon 14 skipping mutation (*METex14*) is an uncommon genomic alteration occurring in ~3%-4% of patients with non-small cell lung cancer (NSCLC). The clinical characteristics of patients with *METex14* NSCLC are poorly understood due to limited evidence in real-world (RW) setting. Here, we compare the clinical characteristics and treatment patterns of patients with advanced/metastatic NSCLC harboring *METex14* mutation and *MET* wild type (*METwt*) from a RW database.

Methods: This retrospective cohort study used RW data from US electronic health record-derived de-identified nationwide Flatiron Health-Foundation Medicine clinico-genomic database. Adult patients (≥18yrs) with documented diagnosis of advanced/metastatic NSCLC with *METex14* or *METwt* based on next-generation sequencing, who received ≥1 line of systemic treatment and follow-up for >90 days, were included. Patients treated with capmatinib or tepotinib were excluded. The index date was defined as the date of start of first-line (1L) treatment.

Results: Of 5300 eligible patients with advanced/metastatic NSCLC between Jan 2011 and Dec 2020, 138 (2.6%) had *METex14* and 5162 (97.4%) had *METwt*. Patients in *METex14* cohort were older than those in *METwt* (median age, 75.0 yrs vs 68.0 yrs; *P* <.0001), majority were female (59.4% vs 46.6%), and non-squamous cell carcinoma was identified as the most frequent histologic subtype (83.3% vs 69.3%; *P* =.0001). The proportion of patients with history of smoking were considerably lower in *METex14* than *METwt* (64.5% vs 91.2%; *P* <.0001). No significant differences were observed between the two cohorts in parameters such as ECOG performance status and sites of metastasis such as brain (21.0% vs 18.4%) and liver (9.4% vs 12.2%). Notably, the expression of PD-L1 ≥50% was significantly higher in patients with *METex14* compared with *METwt* (27.5% vs 13.0%; *P* <.0001), whereas prevalence of 'high' tumor mutation burden (TMB-H, 10 mutations/Mb) was comparatively lower in patients with *METex14* versus *METwt* (5.1% vs 13.3%; *P* <.0001). In both cohorts, chemotherapy was the most common 1L treatment followed by immunotherapy (IO). Multikinase inhibitors *(MKis)* were used as 1L treatment in 16 (11.6%) patients with *METex14* NSCLC, as 2L in 17(12.3%), and as 3L in 10 (7.2%) patients (**Table 1**).

Conclusions: The clinical characteristics of *METex14* cohort were distinct from *METwt* NSCLC; *METex14* patients were typically older, female, had non-squamous subtype, and higher PD-L1 ≥50% with lower TMB-H levels. Prognosis of *METex14* needs to be investigated within this population, future analysis needs to compare clinical outcomes between *METex14 and METwt* cohorts.

Table 1. Treatment patterns

	1L		2L		3L	
Therapy, %	*METex14*	*METwt*	*METex14*	*METwt*	*METex14*	*METwt*
IO alone	21.0	18.3	15.2	19.5	3.6	5.9
IO + chemotherapy	15.2	25.0	2.9	4.7	2.2	1.3
MKis#	11.6	0.3	12.3	0.2	7.2	0.1
Chemotherapy (alone or combination)	44.2	49.3	15.2	17.3	5.1	11.4
Other	8.0	7.1	9.4	10.2	6.5	6.1
No subsequent therapy*	-	-	44.9	48.1	75.4	75.2

*includes patients with no 2L or no 2L/3L; #MKis includes carbozantinib and crizotinib

Keywords: NSCLC, METex14, real-world

P1.09 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - SUPPORT TO PATIENTS AND STAFF, SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.09-03 Multidisciplinary Thoracic Tumors Board Survey in Spain

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Introduction: Increasing complexity in diagnosis and management of lung cancer requires collaboration of multiple specialists. In Spain there are few Cancer Centers. Medical Oncology is in the center of cancer care covering academic and community hospitals but other resources like Thoracic Surgery, Nuclear Medicine and Radiotherapy are limited to larger centers. Spanish Lung Cancer Group/Grupo Español Cáncer Pulmón performed a survey to describe current structure, network and standard operational procedures (SOPs) of Thoracic Tumor Boards (TTB) in the country.

Methods: Between April-June 2021, 92 hospitals with different complexity level (< 300 beds, 301-500 beds and > 500 beds) distributed at different regions in Spain answered an online survey. The survey covered different items about facilities' characteristics, access to diagnostic techniques, biomarkers and NGS access and operational organization.

Results: -Overall facilities: Pneumology, Radiology, Pathology and Medical Oncology Units in 100% of centers, Radiotherapy in 75%, Nuclear Medicine in 63%, Molecular Diagnostic Unit 61% and Thoracic Surgery in 59%. Fast diagnostic pathways in 90%. - Molecular diagnosis: NGS access 53%. Liquid biopsy 72% (65% in house). Biomarkers reflex ordered by pathologist 59%.- Significant differences were found between Academic and Community centers for: EBUS disposal (60 vs 98%), NGS access (36 vs 68%), mediastinoscopy facilities (32 vs 100%), SBRT (32 vs 98%), clinical trials recruitment rate (12 vs 55%), timelines control (16 vs 35%)- Tumor Board Coordinator: medical oncologist 49%, pneumologist 37%, thoracic surgeon 11%. Members of MTB: mean 7 different specialties. Weekly meetings in 96% of centers. Mixed format (presential and virtual) in 36%. Specific case manager in 39%. Molecular biologist 19%. Palliative Care 12%.- Mean patients per session: 10. All new cases presented in 65%. Stage distribution: St I-II (16%), St III (42%), St IV (42%). Discussion before and after surgery in 67%.

- Timeline evaluation recorded in 24%. Mean time from decision to treatment: 3.7 week (w) for surgery, 2.6 w for radiotherapy and 1.4 w for systemic treatment. - Reference guidelines used: ESMO 72%, SEOM (Spanish Medical Oncology Society) 65%, NCCN 61%

- SOPs in 69%, Continuous Medical Education activity 39%.

Conclusions: Multidisciplinary Thoracic Tumors Boards are implemented at every center of Spanish Lung Cancer Group but differs according complexity level of the center. Facilities and access to diagnostic tools and therapeutic options show significant differences especially for EBUS, NGS and SBRT. Timelines recording from initial symptom to diagnosis and treatment and outcomes metrics need to be implemented more widely. Specific case managers could be a key tool for improvement. Virtually meetings for tumor boards are feasible and increase the TTB networking could be useful to preserve equity for lung cancer patients.

Keywords: Thoracic Tumors Board, Molecular diagnosis, Lung Cancer Network

P1.10 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - CHEMORADIOTHERAPY AND RADIOTHERAPY, SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.10-01 Phase 3 Study of Durvalumab Combined with Oleclumab or Monalizumab in Patients with Unresectable Stage III NSCLC (PACIFIC-9)

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Introduction: Based on the findings of the PACIFIC trial, durvalumab as consolidation therapy is the standard-of-care for patients with unresectable Stage III NSCLC and no disease progression following chemoradiotherapy (CRT; the PACIFIC regimen). However, further improvements in outcomes are needed for this population and, to build upon the backbone of PD-L1 inhibition with durvalumab, immunotherapy combinations including anti-TIGIT, anti-CD73, and anti-NKG2a mAbs are now being explored. Two potential candidates, oleclumab and monalizumab, have demonstrated encouraging clinical activity in a phase 2 study when combined with durvalumab in this setting. Oleclumab (MEDI9447) is a human IgG1-lambda mAb that inhibits the function of CD73, to reduce extracellular adenosine production and thus promote antitumour immunity. Monalizumab (IPH2201) is a first-in-class, humanised, IgG4 mAb that prevents NKG2A from binding to HLA-E, which reduces inhibition of natural killer and CD8+ T cells. The combination of each of these molecules with durvalumab consolidation therapy was evaluated in the phase 2 COAST study (NCT03822351). In COAST (n=189), patients receiving combination therapy reported numerically higher objective response rates (durvalumab plus oleclumab: 30.0%; durvalumab plus monalizumab: 35.5%; durvalumab monotherapy: 17.9%) and prolonged progression-free survival versus durvalumab alone, with no new/significant safety signals. Thus, the combination of oleclumab or monalizumab with consolidative durvalumab warrants further evaluation in a phase 3 trial.

Methods: PACIFIC-9 (NCT05221840) is a phase 3, double-blind, placebo-controlled, randomised, international study. Eligible patients (age ≥18 years) must have EGFR/ALK wild-type unresectable Stage III NSCLC, a WHO performance status of 0/1, documented PD-L1 status, and must not have progressed following ≥2 cycles of definitive, platinum-based concurrent CRT. Patients (N≈999) will be randomised (1:1:1) to receive up to 12 months of treatment (in 28-day cycles) with durvalumab plus either oleclumab (Arm A); monalizumab (Arm B); or placebo (Arm C). The primary endpoint is progression-free survival (RECIST v1.1) by blinded independent central review (BICR). Overall survival is a key secondary endpoint. Other secondary endpoints include objective response rate and duration of response (RECIST v1.1; BICR), patient-reported outcomes, PD-L1 expression on tumor cells relative to efficacy outcomes, and safety/tolerability. Enrolment in PACIFIC-9 is ongoing.

Keywords: durvalumab, oleclumab, monalizumab

P1.10 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - CHEMORADIOTHERAPY AND RADIOTHERAPY, SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.10-02 ImmunoPET: A Phase 0/1 Study Characterising PD-L1 with 89Zr-Durvalumab (MEDI4736) PET/CT in Stage III NSCLC Patients Receiving Chemoradiation

M. MacManus[1], S. Rudd[2], P. Roselt[1], C. Wichmann[3], J. Callahan[1], T. John[1], A. Scott[3], P. Donnelly[2], G. Hanna[1], F. Hegi-Johnson[1]

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Introduction: ImmunoPET is a multicentre, single arm, phase 0-1 study investigating the use of ^{89}Zr-durvalumab PET/CT to interrogate the expression of PD-L1 in patients with NSCLC, in preparation for large clinical trials. We describe novel processes for automated production of zirconium-labelled Immune-PET tracers, validation processes and imaging credentialing for a multicentre trial of ^{89}Zr-durvalumab (^{89}Zr-durva) to characterize PD-L1 upregulation during the treatment of locally advanced non-small cell lung cancer (NSCLC) patients receiving radical chemoradiotherapy.

Methods: The Phase 0 study will recruit 5 PD-L1+ patients with metastatic NSCLC. Patients will receive 60MBq/70kg ^{89}Zr-durvalumab up to a maximum of 74 MBq, with scan acquisition at day 0, 1, 3 or 5 ± 1 day. Data on 1) Percentage of injected ^{89}Zr-durvalumab dose found in organs of interest 2) Absorbed organ doses (μSv/MBq of administered ^{89}Zr-durvalumab) and 3) Whole-body dose expressed as mSv/100MBq of administered dose will be collected to characterize biodistribution. The Phase 1 study will recruit 20 patients undergoing concurrent chemoradiotherapy for Stage III NSCLC. Patients will have ^{89}Zr-durvalumab and FDG-PET/CT before, during and after chemoradiation (see Figure). In order to establish the feasibility of ^{89}Zr-durvalumab PET/CT for larger multicentre trials we will collect both imaging and toxicity data. Feasibility will be deemed to have been met if more than 80% of patients are able to complete all trial requirements with no significant toxicity.

Results: Clinical quality ^{89}Zr-durvalumab is produced through a novel procedure utilizing customized iPhase MultiSyn automated synthesizer and disposable cassette kits. Batches of clinical grade DFOSq-durvalumab conjugate and buffer reagent kits were prepared centrally, validated, and distributed to participating sites under controlled conditions. Quality control of ^{89}Zr-durvalumab included assessment of specific activity (273-357 MBq/mg), radiochemical purity (>99%), protein integrity (>96%), immunoreactive fraction (>75%), pH, sterility, and endotoxin levels as well as preclinical imaging and biodistribution studies in PD-L1 positive models to confirm tumour targeting. All participating sites are certified for PET scanner validation for imaging of ^{89}Zr-durvalumab by the Australian Radiopharmaceutical Trials Network (ARTnet).

Conclusions: Despite the rapid development of Immune-PET tracers, the large multicentre trials to establish the clinical validity of Immune-PET tracers as biomarkers remain elusive. Cost, expertise, and the labour-intensive workflow of novel tracer production are formidable obstacles. Our fully automated approach ensures standardized production of ^{89}Zr-durvalumab when the final radiolabelling is performed at different sites, thus reducing the burden on staff and facilitating the consistent PET tracer production required to perform a multicenter trial.

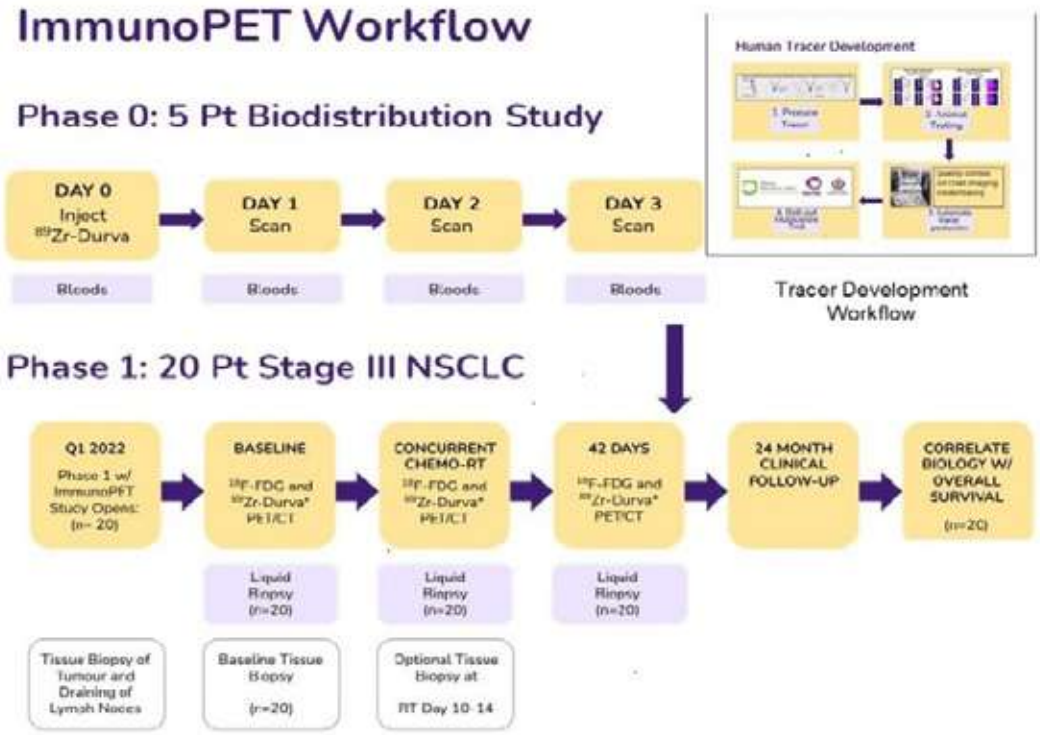

Figure 1: Clinical Workflow and Technical Development for the Phase 0/Phase 1 Trial

Keywords: Non-small cell lung cancer, PET Imaging, Immunotherapy

P1.10 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - CHEMORADIOTHERAPY AND RADIOTHERAPY, SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.10-03 A Deep Learning Auto-Segmentation Tool for Cardiac Substructures in 4D Radiotherapy Planning for Locally Advanced Lung Cancer

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Introduction: Radiation dose to the heart correlates negatively with survival in locally advanced lung cancer. Emerging data suggest that dose-sparing of several key cardiac substructures is prognostically beneficial in conventional fractionation lung cancer radiotherapy. The cardiac substructures are challenging to contour on planning CT scans, due to geometry complexity, limited intracardiac soft tissue definition and cardiorespiratory motion artefact. To this end, a neural network was trained from n=240 radiotherapy 3D-CT plans to generate 12 cardiac substructures based on the Feng cardiac atlas (Haq et al, phiRO 2020). As 4D-CT is now the standard-of-care radiotherapy planning modality in lung cancer, validation of the tool in 4D-CT is required. Herein, geometry, dosimetry and clinical acceptability metrics were tested for this tool's performance in the 4D-CT setting.

Methods: The average scan from the 4D-CT dataset of 20 patients completing radical radiotherapy for lung cancer 2015-2020 at a tertiary centre were used for manual and automated cardiac substructure segmentation. All manual delineations were completed by a radiation oncologist and subsequently verified by a senior radiation oncologist and cardiologist. Scans were imported into MATLAB v2020b for auto-segmentation. Manual and automated substructures were geometrically compared by percentage volume difference (VD), centroid shift (CS), Dice similarity coefficient (DSC), and 95% percentile Hausdorff distance (HD95). The mean dose and maximum dose (D_{max}) of the automated substructures were also compared against the corresponding manual dose. The two senior clinicians qualitatively assessed the performance of the auto-segmentation tool's output.

Results: Geometric comparison of the automated and manual segmentations exhibited high levels of similarity as measured by VD, CS, HD95 and DSC (**Figure 1**), and were consistent with the original 3D-CT paper. There was a trend for lower performance on the pulmonary artery (large VD, low DSC) and higher performance on the right ventricle (small CS, high DSC, low HD95). Differences in mean and maximum doses to substructures were generally small for all substructures, for both mean dose (median -0.02Gy, range -1.64-0.32Gy) and D_{max} (median 0.00Gy, range -2.20-0.85Gy). Virtually all cases (99.4%) were deemed to be appropriate for clinical use without further editing by two senior clinicians.

Conclusions: Cardiac substructure auto-segmentation using a deep-learning based tool was feasible on the average 4D-CT scan, the current standard-of-care radiotherapy planning modality in lung cancer. Auto-segmentation tools could increase the practical feasibility of routine cardiac substructure delineation and enable centres to undertake large clinical studies investigating cardiac radiation effects.

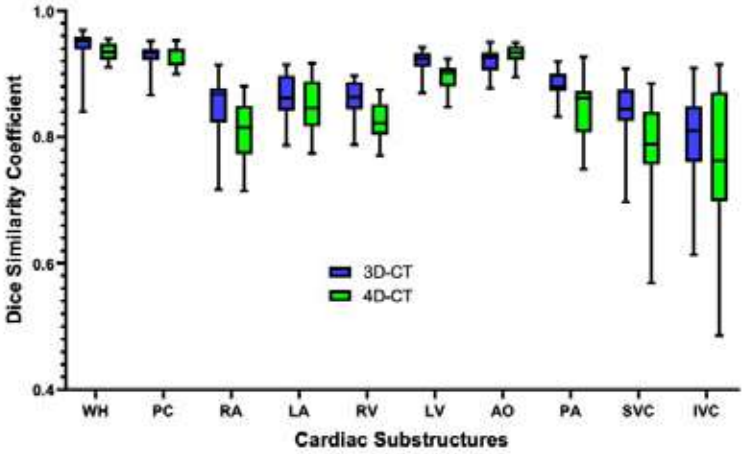

Figure 1. A box plot comparing performance of the deep learning-based auto-segmentation tool in 4D-CT against 3D-CT *(Haq et al 2020)* by Dice Similarity Co-efficient *(WH = whole heart; PC = pericardium; RA = right atrium; RV = right ventricle; LA = left atrium; LV = left ventricle; PA = pulmonary artery; SVC = superior vena cava; IVC = inferior vena cava; AO = aorta)*

Keywords: Radiation Cardiotoxicity, Auto-segmentation, Locally advanced lung cancer

P1.10 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - CHEMORADIOTHERAPY AND RADIOTHERAPY, SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.10-04 Impact of Radiation Dose to the Immune Cells in Unresectable or Stage III Non-Small Cell Lung Cancer in the Durvalumab Era

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Emory Winship Cancer Institute, Atlanta/GA/USA

Introduction: Previous studies have demonstrated that higher radiation doses to the immune cells correlated with worse disease control and overall survival (OS) in patients with locally advanced non-small cell lung cancer (NSCLC). However, these studies were conducted in patient cohorts treated prior to the PACIFIC trial, which established a new standard of care of consolidative durvalumab after chemoradiation. This study examines the prognostic impact of the estimated radiation dose to the immune cells (EDIC) in the era of consolidative durvalumab.

Methods: This single-institution, multi-center study included consecutive patients with unresectable stage II or III NSCLC treated between 2017 and 2021 with concurrent chemoradiation followed by at least one cycle of durvalumab. EDIC was calculated per Jin et al. (PMID: 34944813), as a function of mean heart, lung, and integral body dose. Associations between EDIC, analyzed as both a continuous and categorical (≤6 Gy vs. >6 Gy) variable, with OS, progression-free survival (PFS), and locoregional control (LRC), were assessed using the Kaplan-Meier method and univariate and multivariate Cox proportional hazards.

Results: 100 patients were identified for analysis with a median follow-up of 16.8 months. 88% of patients received weekly carboplatin and paclitaxel, and most were treated with either intensity-modulated radiation therapy (82%) or intensity-modulated proton therapy (12%). The median radiation dose was 60 Gy (range: 56-70 Gy) with 54% receiving an EDIC >6 Gy. Patients in the EDIC >6 Gy group had a significantly greater percentage of stage IIIB or IIIC disease (76.0% vs. 32.6%; p<0.001) and larger gross tumor volumes (median 170cc vs. 42cc; p<0.001). No differences were observed between groups in the rates of early durvalumab discontinuation from toxicity (24.1% vs. 15.2%; p=0.27). Among the 56 patients for whom PD-L1 status was available, 22 of 31 (71%) in the EDIC >6 Gy group had PD-L1 TPS ≥1% compared to 15 of 25 patients (60%) in the EDIC ≤6 Gy group (p=0.24).

Median OS was significantly shorter among EDIC >6 Gy group (29.6 months vs. not reached; p<0.001). After accounting for stage and gross tumor volume among other covariates, EDIC >6 Gy correlated with worse OS (HR: 4.15, 95% CI: 1.52-11.33; p=0.006), PFS (HR: 3.79; 95% CI: 1.80-8.0; p<0.001), and LRC (HR: 2.66, 95% CI: 1.15-6.18; p=0.023). When analyzed as a continuous variable, higher EDIC was again associated with worse OS (HR: 1.34; 95% CI: 1.16-1.57; p<0.001), PFS (HR: 1.52; 95% CI: 1.29-1.79; p<0.001), and LRC (HR: 1.34, 95% CI: 1.13-1.60; p=0.007).

Conclusions: In the era of immunotherapy, EDIC is an independent predictor of OS and PFS in locally advanced NSCLC. These data warrant investigation into radiation planning techniques and modalities to reduce dose to the immune system to improve outcomes for this patient population.

Keywords: non-small cell lung cancer, chemoradiation, immunotherapy

P1.11 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - NEOADJUVANT AND ADJUVANT THERAPY, SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.11-01 Cobolimab with Dostarlimab and Docetaxel in Patients with Advanced Non-small Cell Lung Cancer (NSCLC): COSTAR Lung

H.R. Kim[1], C. Gridelli[2], D. Kapur[3], A. Tufman[4], E. Felip[5], V. Velcheti[6], Y.J. Kim[7], T.O. Goetze[8], P. Garrido Lopez[9], R. Corre[10], K. Penkov[11], R. Anjum[12], B. Di Pace[13], W. Liu[12], T. Borgovan[12], D. Ledger[14], J. Carver[13], A. Waszak[12], A. Dhar[13], S. Novello[15]

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Introduction: TIM-3 and PD-1 are markers of T-cell exhaustion co-expressed on tumor-infiltrating T cells (CD4+, CD8+) and antigen presenting cells in lung cancer. TIM-3 expression has also been associated with poor overall survival (OS) outcomes in NSCLC.

In the Phase 1 AMBER study (NCT02817633), cobolimab (GSK4069889, a TIM-3 inhibitor) plus dostarlimab (a PD-1 inhibitor) showed clinical responses with an acceptable safety profile in patients with heavily pretreated, PD-1/PD-L1 relapsed/refractory, advanced or metastatic NSCLC.

COSTAR Lung (NCT04655976) aims to compare the efficacy and safety of cobolimab plus dostarlimab and standard of care chemotherapy (CT, docetaxel; Arm A) to dostarlimab plus docetaxel (Arm B) to docetaxel alone (Arm C) in patients with PD-1/PD-L1 relapsed/refractory NSCLC.

Methods: This is an ongoing global, multicenter, parallel-group treatment, randomized, Phase 2, open-label, 3-arm study, with the potential for a Phase 3 expansion. Eligible patients will be ≥18 years old, with pathologically confirmed advanced/metastatic NSCLC (squamous or non-squamous) who have received ≤2 prior lines of therapy that include an anti-PD-1/PD-L1 therapy plus platinum-based CT only. Additional inclusion criteria are documented radiological disease progression on prior therapy, confirmed PD-L1 status, absence of sensitizing *EGFR*, *ALK,* or *ROS-1* mutations, and ECOG PS 0-1.

Patients will be randomized 2:2:1 to Arm A, Arm B, or Arm C. Patients will receive cobolimab (300 mg IV), dostarlimab (500 mg IV), and/or docetaxel (75 mg/m^2 IV) Q3W. Cobolimab and dostarlimab treatment will continue until disease progression, unacceptable toxicity, patient withdrawal, investigator's decision, or death. Docetaxel treatment will continue for ≥4 cycles or until unacceptable toxicity or disease progression.

The primary endpoint is OS for Arms A or B vs C. Secondary endpoints include OS for Arm A vs B and investigator-assessed confirmed objective response rate (ORR); progression-free survival (PFS) and duration of response (RECIST v1.1); quality of life assessments; safety; and tolerability. Exploratory endpoints include investigator-assessed confirmed ORR and PFS (iRECIST), pharmacokinetics, biomarkers of response, and patient-reported efficacy and tolerability.

Approximately 250 patients will be randomized to the Phase 2 portion with an interim analysis planned after at least 18 weeks of follow-up. An additional 500 patients (n=200 each in Arms A-B and n=100 in Arm C) may be included in the Phase 3 portion.

Funding: GSK (213410). Editorial support provided by Fishawack Indicia Ltd., UK, part of Fishawack Health, and funded by GSK.

P1.11 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - NEOADJUVANT AND ADJUVANT THERAPY, SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.11-02 Combined Regimen of Anlotinib and Trametinib for NSCLC Patients Harbouring Pan-KRAS Mutation without KRASG12C

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Introduction: KRAS mutation accountsthe one of the most frequent alterations in non-small cell lung cancer (NSCLC).For 40 years, the KRAS mutations had been considered undruggable until theadvent of inhibitors targeting $KRAS^{G12C}$, but it just coveredabout 13% of NSCLC. The strategy of approximately 20% of NSCLC harboring other KRASmutation types including $KRAS^{G12F}$, $KRAS^{G12D}$,$KRAS^{Q61H}$, $KRAS^{G12V}$ and $KRAS^{G12A}$is still considered elusive.

Methods: Herewe evaluated a novelty combination strategy of MEK inhibitor-trametinib andmulti-targeted TKI-anlotinib for pan-KRAS mutant NSCLC harboring $KRAS^{G12F}$,$KRAS^{G12D}$, $KRAS^{Q61H}$, $KRAS^{G12V}$and $KRAS^{G12A}$, as well as $KRAS^{G12C}$. A serialof *in vitro* and *in vivo* experiments were performed to examine thesynergistic effect of the combined regime oftrametinib plus anlotinib. Furthermore, a phase I clinical trial (NCT04967079)was performed to explore the potential clinical value of the combined regimen forthe NSCLC patients harbouring pan-KRAS mutation without $KRAS^{G12C}$.

Results: In preclinical,co-blocking of MEK pathway and anlotinib-covered targets via the combinationstrategy demonstrated its clinical translational potential for the pan-*KRAS*mutant NSCLC. Clinically, our results of clinical trial provided the primaryresults that 6 of 10 NSCLC (harboring the mutation of $KRAS^{G12F}$,$KRAS^{G12D}$, $KRAS^{Q61H}$, $KRAS^{G12V}$,$KRAS^{G12A}$, respectively) had remarkably responses afterreceiving at least 1 cycle of combination treatment.

Conclusions: Collectively, this studyindicated the potential of the novelty combination of anlotinib and trametinibin a strategy against the NSCLC patients harbouring pan-KRAS mutation without$KRAS^{G12C}$.

Keywords: Targeted Therapy and Immunotherapy Combination, Immunogenic Cell Death, Tumour Microenvironment Remodeling

P1.12 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.12-01 Lung Cancer Screening in the COVID-19 Era: Understanding Program-Level Impact

L.K. Lutzow[1], A. Ciupek[2], A. Criswell[2], L. Fine[2], G.X. Ma[3], J.C. King[2], C.P. Erkmen[1]

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Introduction: Lung Cancer Screening (LCS) via Low Dose Computed Tomography (LDCT) reduces lung cancer mortality, yet utilization has remained low even before the onset of the COVID-19 pandemic and the resulting disruption to screening (Aberle et al., 2011; de Koning et al., 2020; Jemal, 2017). The impact of COVID-19 on specific LCS program components and how this has led to differences in LCS uptake is unknown. Understanding program-level barriers experienced in the context of COVID-19 will help guide resource allocation and inform optimization of LCS in the future.

Methods: The GO2 Foundation for Lung Cancer conducts an annual, retrospective survey of United States (US) LCS programs meeting comprehensive screening standards designated as Screening Centers of Excellence in Lung Cancer Screening (SCOE). Our academic lung center partnered with the GO2 Foundation to add additional questions related to delivering LCS in the context of COVID-19. We conducted descriptive statistical analysis of survey results from 2021, reflecting the 2020 screening year, to understand LCS program demographics and self-reported perception of LCS program components most affected by COVID-19.

Results: Ninety-nine programs completed the survey with 61% representing multi-site centers. Programs represented a broad US sample with the Southern, Northern, Midwestern, and Western regions representing 33%, 28%, 25%, and 13% of respondents, respectively. Together, community hospital-affiliated programs including both teaching and non-teaching sites, represented 67% of respondents while academic medical centers represented 10% of respondents. Programs reported a median of 868 patients (Range 0 - 7,930; SD 1267) screened in 2020. Components most commonly cited as being somewhat or significantly compromised by the COVID-19 pandemic were patient recruitment (85%), in-person consultation (79%), patient education (71%), access to radiology services (67%), and smoking cessation (60%). Coordination of care and timely reporting of results were felt to be unaffected by COVID-19 by 71% and 85% of respondents. Sixty-two percent of respondents felt the use of telemedicine had been improved somewhat or significantly.

Conclusions: Our findings suggest some of the most critical components of screening, those associated with recruitment, maintaining optimal patient communication, access to CT services, and smoking cessation efforts, were most vulnerable to compromise. Our findings also suggest that once patients had completed the LDCT scan, screening workflows were relatively unaffected. These findings underscore the role telemedicine can play in the delivery of LCS within the context of COVID-19 when in-person visits are placed on hiatus. More research is needed to fully understand and optimize the use of telehealth visits to conduct patient recruitment, education, and smoking cessation efforts. The importance of the ongoing participation in this survey effort cannot be overstated as it establishes a longitudinal understanding of real-world LCS challenges, particularly in the context of COVID-19, and helps guide targeted solutions to optimize the future of LCS.

Keywords: Lung Cancer Screening, Covid-19, Patient Education

P1.12 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.12-02 The Impact of COVID-19 on Quality of Care for Lung Cancer - Analyses of Prospective Clinical Data from The EnRICH Cohort

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Introduction: The COVID-19 pandemic has impacted healthcare systems worldwide, causing substantial changes to routine healthcare delivery such as a shift to virtual-health consultations, and postponed or cancelled planned-procedures. Simultaneously, patients have changed their healthcare-seeking behaviours.

In New South Wales (NSW), Australia's most populous State, there were sizeable declines in a wide range of healthcare activities from March-June 2020 compared with the same period in 2019, prior to the emergence of COVID-19. Of note, were decreases of 22.1% in primary care face-to-face consultations, 13.9% in emergency department visits, and 32.6% in public-hospital planned surgical activity.

There is a need to understand how these changes in healthcare delivery have affected quality-of-care and outcomes for lung cancer.

The EnRICH program, a prospective clinical cohort of over 2000 consecutive patients diagnosed with lung cancer between 2016 and 2021 in regional and metropolitan hospitals across the State, is ideally placed to examine the impact of COVID-19 on quality-of-care for lung cancer in NSW.

The EnRICH dataset includes comprehensive patient, diagnostic, treatment, and outcome data, mapped against evidence-based clinical-quality-indicators (QIs).

Methods: Sample: Pre-COVID cohort, n=1144 patients diagnosed 8 September 2016 to 10 March 2020; post-COVID cohort, n=849 patients diagnosed 11 March 2020 (date COVID-19 declared global pandemic by World Health Organisation) to 29 October 2021.

Data collection: Clinical data are extracted from medical records longitudinally. This analysis reports data collected to 12-months post-diagnosis.

Statistical methods: Patient characteristics and performance against QIs were compared between pre- and post-COVID-19 cohorts using Wilcoxon rank sum and chi-square tests. One-year survival was compared using Kaplan-Meier estimates.

Results: Patient and disease characteristics were similar in the pre- versus post-COVID-19 cohorts (median age 70; 55%v53% male; 88%v80% NSCLC, 42%v40% stage IV). Fewer patients received a diagnosis within 28-days of presentation with symptoms in the post-COVID-19 cohort (80%v75%; p=0.01) (Table1). The proportion of stage III patients discussed by a multidisciplinary team (MDT) and the proportion of those with advanced disease promptly referred to palliative care improved post-COVID-19. There was no significant difference in the proportion of patients commencing treatment within 28-days of diagnosis. One-year survival did not differ (70%v71%; p~0.54).

Table 1. Performance against quality indicators pre- and post-COVID-19

ALL PATIENTS	Pre-COVID-19 N=1144[1]	Post-COVID-19 N=849[1]	p value[2]
Diagnostic Quality Indicators			
Proportion diagnosed within 28 days of first presentation	910 (80%)	582 (75%)	0.01
Proportion with a pathological diagnosis within 28 days of first presentation	668 (61%)	419 (56%)	0.078
Proportion of Stage III patients reviewed by MDT	341 (54%)	277 (60%)	0.037
Proportion of Stage IV patients with molecular testing	343 (96%)	220 (97%)	0.4
Treatment Quality Indicators			
Proportion of Stage I-III patients commencing curative treatment with 28 days of diagnosis	129 (24%)	101 (27%)	0.2
Proportion of Stage IV patients commencing systemic treatment with 28 days of diagnosis	87 (21%)	75 (26%)	0.14
Proportion of Stage IV patients referred to palliative care within 8 weeks of diagnosis	146 (48%)	108 (60%)	0.014
Outcome Quality Indicators			
1-year survival[3]	70% (67, 73)[4]	71% (68, 75)[5]	~0.54

[1]n (%) [2]Pearson''s Chi-squared test [3]Kaplan Meier estimates (95% CI) [4] Median follow-up 3.1 years [5] Median follow-up 1.2 years

Conclusions: After the emergence of COVID-19, performance changed against several QIs. Of concern, fewer patients received a lung cancer diagnosis within 28-days, however, to date, there has been no impact on survival. Whether the observed variations are due to changes in routine healthcare delivery or changes in patient healthcare-seeking behaviour requires further investigation.

Keywords: Quality of care, Impact of COVID-19

P1.12 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.12-03 Computed Tomography-based Artificial Intelligence System in the Diagnosis of COVID-19

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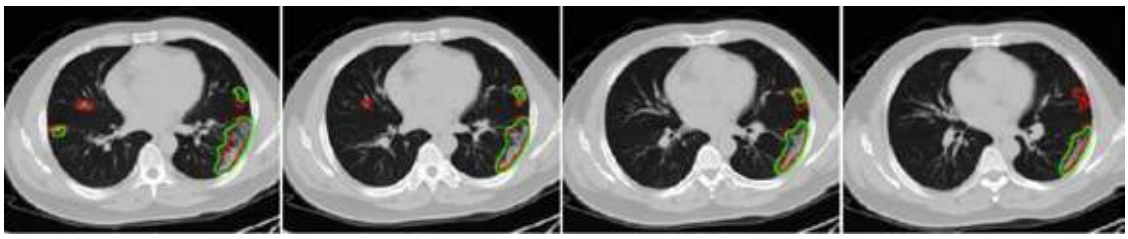
Introduction: Thorax computed tomography (CT) is the main imaging method in the diagnosis of Coronavirus disease 2019 (COVID-19) which requires an experienced radiologist, workforce and time for the interpretation of radiologic findings. In this study, it was aimed to evaluate the results of the computed tomography-based artificial intelligence (AI) system in the diagnosis of COVID-19.

Methods: Ten thousand cases of pneumonia (COVID-19/non-COVID-19 pneumonia) or non-pneumonic lung pathologies were detected with CT. After completing machine learning with these patients' images, an AI diagnosis platform was provided by a medical technology company originating from the People's Republic of China (*Dr.Turing AI-assisted diagnosis platform Huiying Medical Technology Co., Ltd.*). Thorax CT of 30 patients (Test set 1) who were operated for lung adenocarcinoma with subsolid radiological appearance and 32 COVID-19 positive patients (Test set 2) in our center between 2011-2020 was uploaded to the platform and the diagnostic success of the platform was tested.

Results: Automatic contour marking (automatic segmentation) of the images of the test sets was successfully achieved [Dice score=0.9 (0-1)] by the platform (Figure 1**:** Lung window sections of thorax CT of a COVID-19 positive patient. The segmentation performed by the radiologist (red marking) and automatic segmentation (green marking) overlaps to a large extent.)In the ROC analysis, the area under the curve [area under curve=AUC (0.5-1)] of test sets 1 and 2 were found to be 0.94 and 1, respectively. With AI, test set 1 and 2 could be differentiated by 100%.

Conclusions: During extraordinary processes such as the COVID-19 pandemic, there is a need for fast, cost-effective, non-invasive diagnostic tools with a high specification that protect healthcare workers from possible contamination, and neither PCR test nor thorax CT could meet these needs. AI can be successfully used in the diagnosis of COVID-19, as demonstrated in our study. Experiences gained from AI studies will be important in terms of being prepared for possible future pandemics.



Keywords: COVID-19, Artificial Intelligence, Machine Learning

P1.12 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.12-04 The FLARE Score and Circulating Neutrophils are Associated with Poor Covid-19 Outcomes in Patients with Thoracic Cancers

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Introduction: Inflammation and neutrophils play a central role in severe Covid-19 disease. In previous data, we showed that the FLARE score, combining both tumor and Covid-19-induced proinflammatory status (proinflam-status), predicts early mortality in cancer patients (pts) with Covid-19 infection. We aim to assess the impact of this score in a cohort of only thoracic cancers (TC) and to characterize the immunophenotype (IF) of circulating neutrophils.

Methods: Multicenter retrospective cohort (RC) of pts with TC and Covid-19 infection across 14 international centers. Circulating inflammatory markers were collected at two timepoints: baseline (-15 to -45d before Covid-19 diagnosis) and Covid-19 diagnosis. Tumor-induced proinflam-status was defined by high dNLR (neutrophils/(leucocytes-neutrophils)>3) at baseline. Covid-19-induced proinflam-status was defined by +100% increase of dNLR between both timepoints.We built the FLARE score combining both Tumor and Infection-induced inflammation: **T+/I+ (poor)**, if both proinflam-status; **T+/I- (T-only)**, if inflammation was only due to tumor; **T-/I+ (I-only)**, if inflammation was only due to Covid; **T-/I- (favorable)**, if there was no proinflam-status.The IF of circulating neutrophils by flow cytometry was determined in a unicenter prospective cohort (PC) of pts with TC during Covid-19 infection and in healthy volunteers (HV). Primary endpoint was 30-day mortality.

Results: 134 pts were enrolled in the RC with a median follow-up of 96 days (95%CI 86-108). Median age was 67 (range 41-88), 66% were male and 75% had baseline PS <1. 78% had active disease, 4% advanced stage and 58% were under systemic therapy. dNLR was high in 31% at baseline vs 57.6% at Covid-19 diagnosis. The median dNLR increase between both timepoints was +59% (IQR:0-54%); 43% had +100% increase of dNLR.Pts distribution and mortality across FLARE groups are shown in Table 1. Overall mortality rate was 36%.Thirteen pts were enrolled in the PC. Median circulating neutrophils were higher in pts with TC (n=7, 75.5% [IQR:71.9-78.7%]) vs HV (n=6, 35.8% [IQR:25.6-21%]), and particularly higher in pts with TC and severe Covid-19 infection (n=2, 87.1% [IQR:82.9-91.3%]. A more comprehensive characterization of the IF of circulating neutrophils, including Lox1/CD62/CD64, will be presented at the meeting.

Conclusions: The FLARE score, combining tumor and Covid-19-induced proinflam-status, can identify patients at higher risk for mortality. A better characterization of circulating neutrophils may help us to improve the prediction of Covid-19 outcomes in pts with cancer.

Table 1

	Distribution	30-day mortality	
FLARE T+/I+	5% (n=5)	60%	p=0.004
FLARE T+/I-	27% (n=28)	48%	
FLARE T-/I+	38% (n=40)	42%	
FLARE T-/I-	30% (n=31)	30%	

Keywords: Covid-19, Neutrophils, Inflammation

P1.12 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.12-05 Prediction of Clinically Significant Pathological Upstaging in Resected Lung Cancer: Insight from COVID-19 Pandemic (1st Wave)

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Introduction: We aim to investigate clinicopathological characteristics of our surgical lung cancer population presenting during the 1st wave of pandemic, describe the key service parameters, and to identify pathological upstaging compared to a pre-pandemic cohort.

Methods: This is part of an ongoing observational study including all primary lung cancer patients who underwent resection at our centre. Data were collected as part of an institutional lung cancer database. COVID vulnerability status was derived from Department of Health (UK) guidelines. Clinically significant pathological upstaging was defined as migration between clinical and pathological final TNM stage, either major (between stages) or minor (between substages except IA). Logistic regression was employed to identify independent predictors of upstaging, and a 3-tier risk stratification system was developed.

Results: We included 242 cases from 1st wave and 456 cases from a 2019 cohort. Radiological lesion size, nodal status, Maximum Standard Unit Value (SUVmax) and histological risk group were independent predictors of upstaging. The 3-tier system stratified such risk into low (8.3%), intermediate (26.1%) and high (48.4%), with AUC of 0.683. There was 20.4% reduction in caseload, and significant drop in all-purpose frozen section usage. No significant difference was seen regarding patients classified as clinically extremely vulnerable (CEV), clinically vulnerable (CV) as well as multimorbidity. No significant changes were observed for surgical waiting time, histological subtypes, final pathological stage, R0 resection or clinically significant upstaging (30.1% vs 30.2%), but there was minor impact on pathology reporting times.

Conclusions: We present a practical and accessible tool in predicting clinically significant pathological upstaging, with implications on patient prioritisation and transition towards risk-based management of lung cancer in post-COVID era. Furthermore surgical caseload decreased during the 1st wave of pandemic with no significant impact on clinicopathological characteristics, service parameters and risk of pathological upstaging. This could be due to delayed effect.

Figure 1 Patient Characteristics and Key Service Parameters

Variable		2019	COVID-19 1st Wave	P
Total number of cases		**456**	**242**	-
Age, median (range)		**69 (19-90)**	**70 (30-87)**	0.294
	>65 years	301 (66.0%)	167 (69.0%)	0.422
Sex, female (%)		243 (53.3%)	139 (57.4%)	0.295
Procedure				
	Wedge resection	51 (11.2%)	33 (13.6%)	**0.014**
	Segmentectomy	17 (3.7%)	21 (8.7%)	(Wedge/segmentec
	Lobectomy/Bi-lobectomy	371 (81.4%)	183 (75.6%)	tomy
	Pneumonectomy	11 (2.4%)	0 (0%)	vs others)
	Chest wall resection	6 (1.3%)	5 (2.1%)	
Neoadjuvant therapy		14 (3.1%)	5 (2.1%)	0.438
COVID-19 clinically extremely vulnerable		**29 (6.4%)**	**25 (10.3%)**	0.062
	Respiratory	27 (93.1%)	14 (56.0%)	0.078
COVID-19 clinically vulnerable		**342 (75.0%)**	**184 (76.0%)**	0.763
	Respiratory	156 (45.6%)	82 (44.6%)	0.818
Multimorbidity (>1 organ system involved)				
Clinically extremely vulnerable		18 (3.9%)	13 (5.4%)	0.456
Clinically vulnerable		102 (22.4%)	58 (24.0%)	0.687
Time from referral to surgery, median (range)		32 days (4-224)	31 days (6-163)	0.828
Time from surgery to final report (with diagnostic IHC), median (range)		9 days (3-87)	10 days (3-92)	**0.004**
RCPath 7-day target (80%)		334 (73.2%)	167 (69.0%)	0.237
RCPath 10-day target (90%)		438 (96.1%)	220 (90.9%)	**0.005**
Usage of frozen section (all purposes)		123 (27.0%)	40 (16.5%)	**0.002**
Tumour types				
	Non-mucinous adenocarcinoma	256 (56.1%)	112 (46.3%)	
	Mucinous adenocarcinoma (IMA/MMA)	48 (10.5%)	32 (13.2%)	
	Squamous cell carcinoma	64 (14.0%)	49 (20.2%)	0.125
	Adenosquamous cell carcinoma	3 (0.7%)	3 (1.2%)	(all types)
	Pleomorphic carcinoma	12 (2.6%)	5 (2.1%)	
	Neuroendocrine neoplasms	70 (15.4%)	36 (14.9%)	
	Large cell carcinoma	3 (0.7%)	5 (2.0%)	
Pathological final TNM stage				
	0	8 (1.8%)	5 (2.1%)	0.774
	I	296 (64.9%)	158 (65.3%)	0.921
	II	61 (13.4%)	45 (18.6%)	0.068
	III	73 (16.0%)	28 (11.6%)	0.113
	IV	18 (3.9%)	6 (2.5%)	0.311
Resection status				
	R0	208 (45.6%)	104 (43.0%)	0.746
	R0 (un)	224 (49.1%)	123 (50.8%)	
	R1/2	24 (5.3%)	15 (6.2%)	
Pathological upstaging				
	Major + Minor	112 (30.2%)	62 (30.1%)	0.982
	Major	64 (17.3%)	36 (17.5%)	0.945
	Minor	48 (12.9%)	26 (12.6%)	0.913

Figure 2 Prediction of Clinically Significant Pathological Upstaging

Variable		Score
Size of primary lesion		
	≤10mm	0
	11-30mm	2
	31-50mm	2
	51-70mm	2
	>70mm	0
Clinical nodal status		
	N0	0
	N+	-2
SUVmax		
	Very Low: ≤2.5 (any size)	0
	Low: 2.6-5.0 (for ≤50mm) or 2.6-10.0 (>50mm)	1
	Intermediate: 5.1-10.0 (for ≤50mm), 10.1-20.0 (>50mm)	1
	High: >10.0 (for ≤50mm) or >20.0 (>50mm)	2
Tumour risk group		
	Low risk	0
	Intermediate risk	1
	High risk	2

Total score	% patients	% upstaging
0	11/577 (1.9%)	1/11 (9.1%)
1	19/577 (3.3%)	1/19 (5.3%)
2	79/577 (13.7%)	7/79 (8.9%)
3	135/577 (23.4%)	28/135 (20.7%)
4	141/577 (24.4%)	44/141 (31.2%)
5	133/577 (23.1%)	60/133 (45.1%)
6	59/577 (10.2%)	33/59 (55.9%)

Score group	% patients	% upstaging
0-2	109/577 (18.9%)	9/109 (8.3%)
3-4	276/577 (47.8%)	72/276 (26.1%)
5-6	192/577 (33.3%)	93/192 (48.4%)

Total score: Area under curve (AUC) = **0.703** (95% CI 0.658-0.748, P<0.001)
Score group: Area under curve (AUC) = **0.683** (95% CI 0.637-0.729, P<0.001)

Keywords: Lung cancer, Pathological upstaging, COVID-19

P1.13 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.13-01 Preoperative Chemotherapy Induces Epithelial-Mesenchymal Transition Which Reduces Survival After Surgery for Mesothelioma

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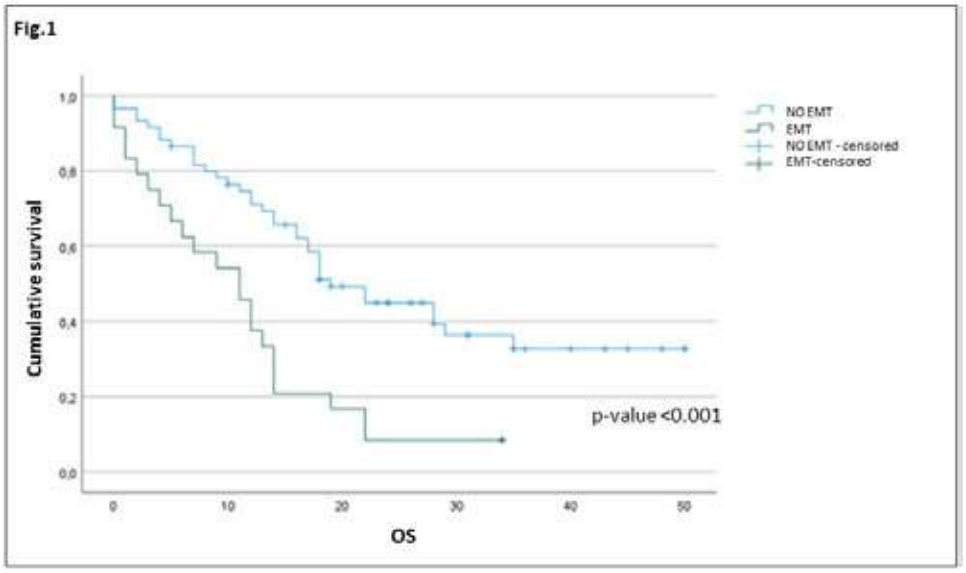
Introduction: Epithelial-mesenchymal transition (EMT) may increase the malignant potential of tumours and may be induced by chemotherapy agents including platinum and pemetrexed (cis/pem). Non-epithelial malignant pleural mesothelioma (MPM) has a significantly poorer survival than epithelial MPM. We aimed to evaluate whether EMT occurred in MPM after induction cis/pem and whether this reduced survival.

Methods: We analyzed the perioperative course of 127 patients (106M:21F, median age: 68.0 (IQR:63.0-73.0)) who underwent pleurectomy/decortication (PD) for MPM in a single institution over a 5-year period. Preoperative histology showed epithelial in 88% and non-epithelial in 12%. Neoadjuvant chemotherapy was given in 91 patients whilst 36 had upfront surgery followed by adjuvant chemotherapy. At a median follow up of 17 months (IQR: 11.0-28.0), 50 (39%) patients are still alive.

Results: Post-resectional histology showed epithelial in 72% and non-epithelial in 28%. In patients who underwent neoadjuvant chemotherapy, EMT was observed in 24 of 94 (28.6%) patients and it was significantly associated with the use of neoadjuvant chemotherapy (p=0.006-Fisher Exact). On the contrary, in patients who underwent upfront surgery, in the interval between the diagnostic procedure and PD, only one case of EMT has been discovered (p= 0.127-Fisher Exact). EMT was not associated with either the method of biopsy: VATS 61% vs 59%, LATS 19% vs 33%, Percutaneous 19% vs 8%, p= 0.188 or the extent of disease: maximum tumour thickness 16(5-35) mm vs 13(3-66) mm, p=0.135. Overall survival was significantly reduced in those patients who received neoadjuvant chemotherapy and exhibited EMT compared to those who did not: 11 (95% CI 6.2 - 15.8) months vs 19 (95% CI 14.2 -23.8) months, p<0.001. In addition to this, overall survival was significantly reduced in those whose post-resectional histology contained less than 80% epithelial component: 12 (95% CI 8.7-15.3) months vs 18 (95%CI 13.6-22.4) months, p=0.07. On the contrary, there was no difference in overall survival, as yet, between those who received neoadjuvant chemotherapy and those who had upfront surgery: 16 (95%CI 12.5-19.5) months vs 30 (95% CI 11.6 - 48.4) months, p=0.2.

Conclusions: The risk of epithelial-mesenchymal transition and the consequence of decreased survival should be acknowledged when deciding on the initial treatment modality in otherwise resectable mesothelioma. Further comparative research between neoadjuvant and adjuvant chemotherapy in early-stage epithelial disease is awaited.



Keywords: Malignant Pleural Mesothelioma, Epithelial-mesenchymal transition, Surgery

P1.13 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.13-02 Quantitative Assessment Using MR in Malignant Pleural Mesothelioma

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Introduction: Quantitative assessment is currently being explored as a means of enhancing the accuracy of clinical staging in malignant pleural mesothelioma (MPM). Tumor volume, pleural thickness and diaphragmatic thickness measurements have been shown to be prognostic in recent studies (*J Natl Cancer Inst. 2018 Mar 1;110(3):258-264, J Thorac Oncol.2016 Dec: 11(12):2089-2099; Eur Respir J. 2017 Mar 15;49(3*): 1601428) and could potentially provide a reproducible quantitative component of the 'T' descriptor for TNM staging. MR assessment offers better resolution and less interobservor variability when compared CT (Radiol Cardiothoracic Imaging 2(2):e190066). We compared prognostic performance head-to-head among proposed quantitative metrics using MR in a single institutional MPM cohort.

Methods: Quantitative assessment was undertaken for all patients with MPM referred for surgical evaluation between 2009-2014 who underwent MRI using an IRB-approved optimized protocol. CT scans within 15 days of the MRI were also assessed. Survival analyses were performed for the subset who underwent complete surgical resection. Quantitative assessment included CT and MR derived volume and unidimensional measurements of the pleura, fissures, and diaphragm along multiple planes measured on MR. The best (as assessed by the "*exponential scaling*" criterion) categorization into 2, 3 or 4 classes of each of the linear measurements vs. overall survival was evaluated and internally cross validated on a randomly selected training dataset (1/3 of the observations) using a recursive binary splitting algorithm (CART, R package *rpart*). The predictive ability (C-statistic) of each split measurement was then ascertained and internally cross validated on the remaining validation dataset, using a univariable Cox model. Kaplan-Meier estimators were plotted.

Results: Among 695 patients with MPM evaluated 2009-2014, the study cohort comprised 349 who had MR imaging using optimized parameters on protocol. Median age was 68 (range 30-90), 273 (78%) were men, and 203 (58%) had epithelioid subtype tumors. Table 1 shows the ranking of the measurements by C-statistic value for the 256 patients who underwent complete resection.

Table 1: Ranking of the Quantitative parameters by C statistic in univariable analysis.

Variable	C statistic
Diaphragm total (anterior+ middle +posterior measurement)	0.6093
Diaphragm average (Davg)	0.6062
Fissural Maximal thickness (Fmax)	0.6047
Diaphragm Maximal Thickness (Dmax)	0.5933
MRVolume cm3	0.5912
Maximal thickness Middle Lateral pleura	0.5887
Maximal thickness posterior diaphragm	0.5863
Maximal thickness lower posterior pleura	0.5747
Maximal thickness upper posterior pleura	0.5732
Total Posterior thickness maximal	0.5677
Average Pleural thickness measurement	0.5637
Maximal thickness Lower medial pleura	0.5633
Maximal thickness middle posterior pleura	0.5618
VolCTcm3	0.5607
Maximal thickness middle oof the Diaphragm	0.5605
Maximal thickness Upper posterior Pleura	0.5582
Maximal thickness Middle medial pleura	0.5531
Maximal thickness Middle posterior pleura	0.5522
Maximal thickness Upper medial pleura	0.5463
Maximal thickness Lower posterior pleura	0.5293
Maximal thickness Lower lateral pleura	0.5276
Diaphram anterior maximal thickness	0.5266
Pleural thickness Upper lateral	0.4757

Conclusions: Quantitative MR derived metrics have the potential to augment 'T' classification of MPM. Linear measurements have similar promise as volume in predicting prognosis using MR. Multivariable analyses using combinations of linear measurements will be presented at the meeting.

Keywords: Malignant Pleural mesothelioma,, Staging, Quantitative

P1.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.14-01 Transcriptomic Analysis of Malignant Pleural Mesothelioma (MPM) Reveals Insights for Basic Research and Preclinical Testing

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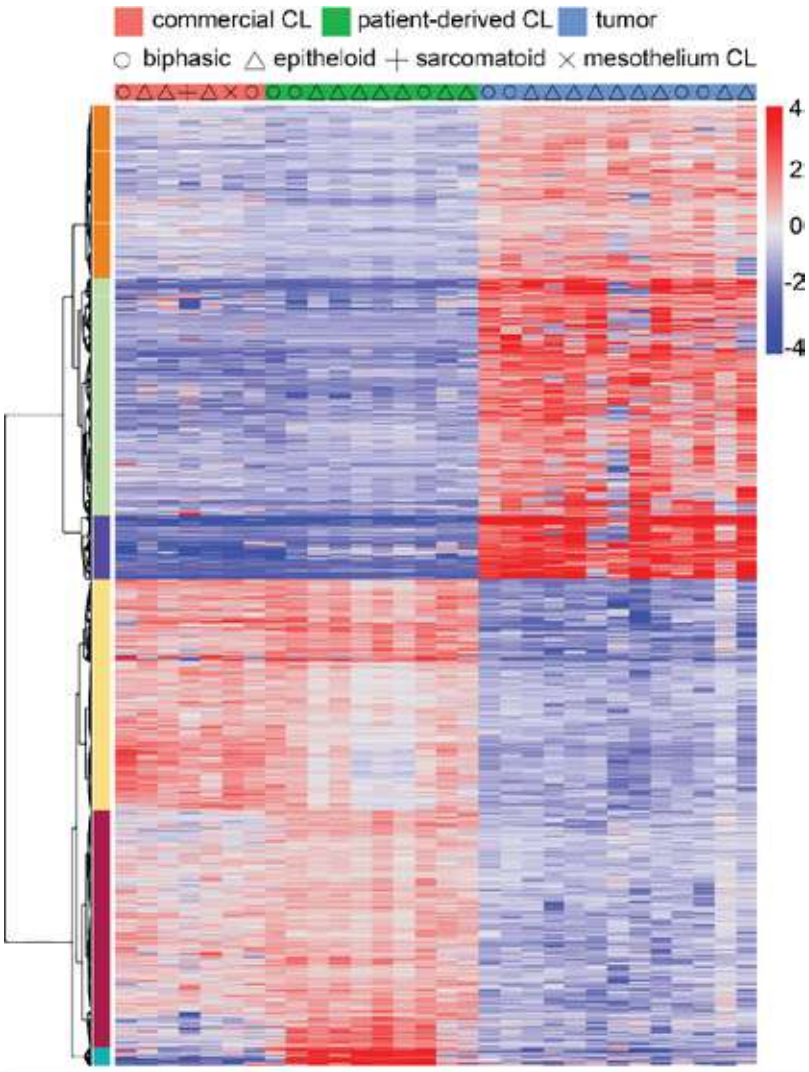
Introduction: Cell lines are extensively used to study cancer biology. However, the use of highly passaged commercial cell lines has to be questioned, as they do not closely resemble the originating tumor. Studies investigating transcriptomic changes have been performed in various cancer types indicating significant differences between commercial cell lines and patient-derived, low-passage-number cell lines when compared to the originating tumor material. However, this analysis has never been performed on MPM. To understand the reliability of preclinical models for MPM studies, we have performed whole transcriptome analysis of fresh frozen MPM tumors and compared them to cell lines generated from these tumors as well as commercial cell lines.

Methods: Patient-derived cell lines were generated from digested fresh tumors and FibrOut™ medium supplement was used to prevent overgrowth of fibroblastic cells. After 10 passages, cell lines were evaluated for remaining contaminations by microscopy and RNA was isolated. Tumors were digested enzymatically and cancer cells isolated by negative MACS sorting for TER119, CD45 and CD31. Sequencing libraries were prepared from 18 fresh frozen tumor samples, the corresponding 10 patient-derived cell lines and 7 commercial cell lines. Whole mRNA sequencing was performed using the SmartSeq2-Picelli protocol due to the low mRNA input of the human samples.

Results: Differential gene expression analysis revealed that in hierarchical clustering, patient derived cell lines cluster closer to the fresh tumors. Gene Ontology (GO) terms related to translation, regulation of transcription, cell cycle, NF-κB signaling and regulation of canonical WNT signaling were upregulated in all cell lines compared to cells isolated from fresh tumors. GO terms related to reregulation of transcription, RNA splicing, mRNA processing, cell-cell signaling, immune response and cytokine-mediated signaling were upregulated in tumors compared to cell lines. Further analysis revealed that canonical WNT signaling genes were significantly differently regulated between commercial cell lines and fresh tumors: WNT-agonists WNT2, WNT2B, and CCN4, WNT-antagonists FRZB, SERPINF1 and SFRP2/4, WNT-receptors FZD8 and LGR5 and CCND2 were significantly underrepresented in commercial cell lines. The expression of canonical WNT-pathway genes was conserved in patient derived cell lines.

Conclusions: Our results show, that the transcriptome of tumors correlates to a higher degree with patient-derived cell lines rather than commercial cell lines. These results are of major relevance for the scientific community in regard of using cell lines and, depending on the biological question, an appropriate model, resembling the pathway of interest has to be chosen to avoid miss-leading results.



Cluster 1	antigen processing and presentation, protein transport, actin filament organization, vesicle-mediated transport
Cluster 2	regulation of transcription, chromatin organization, mRNA transcription, RNA splicing, mRNA processing
Cluster 3	translation, ATP biosynthetic process, regulation of mRNA stability, NF-kappaB signalling, Wnt signalling, tumor necrosisfactor mediated signaling
Cluster 4	cell-cell signalling, positive regulation of transcription, immune response, cell differentiation
Cluster 5	angiogenesis
Cluster 6	inflammatory response, positive regulation of apoptotic cell clearance, positive regulation of cell death

Keywords: Malignant Pleural Mesothelioma, Patient-Derived Cell Lines, Transcriptomic Profiling

P1.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.14-02 Implantable Cytokine Factories for Eradication of Malignant Pleural Mesothelioma (MPM) Tumors in Mice

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Introduction: Interleukin-2 (IL-2) is a potent immunostimulatory cytokine that has been approved for various cancer treatments. Unfortunately, widespread clinical use of IL-2 therapy is dampened by the short serum half-life and the severe toxicities associated with high dose systemic administration. To overcome these limitations, we developed a clinically translatable cytokine delivery platform (cytokine factories) composed of genetically modified epithelial cells encapsulated in biocompatible polymers. These modified cells are able to continuously produce IL-2 from within the polymers and allow for controlled and predictable cytokine dosing *in vivo*.

Methods: Mouse Studies: For IP tumor models of AB1-Fluc; 100,000 cells suspended in HBSS were injected in the IP space of Balb/C mice (n=7-8). Cytokine factories were implanted 7 days post tumor injection.Rat Studies: RPE-hIL2 cytokine factories were administered to the pleural cavity of Sprague Dawley rats (n=20). Complete blood count and blood chemistry analysis were performed 1, 7, or 30 days after administration.IVIS Imaging: Mice were injected in the IP space with D-luciferin (300 µg/mL, PerkinElmer). Photographs and luminescent images were acquired 10 minutes after injection.Cytof: Infiltrating Immune Cell Composition (CyTOF): Peritoneal fluid was homogenized into single-cell suspensions and stained with an optimized antibody panel. Stained cells were analyzed on a mass cytometer (CyTOF3TM, Fluidigm®).

Results: Local administration of IL-2-based cytokine factories (RPE-mIL2) caused increased T cell activation, conversion of M2-like macrophages to an M1-like phenotype, and reduction of tumor burden by 70% when delivered as a monotherapy to mice with mesothelioma tumors. Notably, when administered in combination with anti-PD1 therapy, RPE-mIL2 led to increased cDC cells and subsequent eradication of these highly aggressive tumors in 7/7 treated mice. In addition, this combination treatment afforded 4/4 rechallenged mice protection from tumor recurrence. Further, we utilized antibodies against CD4 and CD8 to evaluate which T cell subset was required for anti-tumor efficacy with our platform. We found that mice depleted of CD8+ T cells were unable to elicit a sufficient anti-tumor response after treatment suggesting that CD8+ T cells are essential for IL-2-based immunotherapy. Finally, to validate the translatability of this platform, we evaluated the safety profile and feasibility of dosing in the pleural cavity of healthy rats. Significantly, this platform was well tolerated in the pleural cavity for 30 days without evidence of significant toxicity in all animals.

Conclusions: Our findings demonstrate the safety and efficacy of cytokine factories in preclinical animal models and provide rationale for future clinical testing for the treatment of metastatic peritoneal and pleural cancers in humans.

Keywords: IL-2, Mesothelioma, Immunotherapy

P1.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.14-03 Characterization of Tumor Immune Microenvironment and Its Prognostic Value in Patients with Surgically Resected Thymic Epithelial Tumors

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Introduction: Limited treatment strategies exist for thymic epithelial tumors (TET) patients, and immunotherapy may become a promising therapy for these patients. However, investigation of tumor microenvironment in TET was still insufficient. Herein, we investigated characteristics of tumor microenvironment and evaluated prognostic value of characteristics in TET patients.

Methods: 209 patients, including 184 thymomas and 25 thymic carcinomas, at Shanghai Pulmonary Hospital between January 2015 and December 2017 were reviewed. The expression of seven immune features were using immunohistochemistry. Then, least absolute shrinkage and selection operator method (LASSO) Cox regression and nomogram model were used to construct an immunological score and predictive model for recurrence, respectively.

Results: Expression of multiple immune markers were greater in thymic carcinomas than they were in thymomas. Based on expression of PD-$1_{\text{invasive margin (IM)}}$, PD-$L1_{\text{tumor center (TC)}}$, PARP-$1_{IM}$, $CD272_{IM}$, $CD272_{TC}$ and $CD8_{IM}$, immunological score was constructed. TET patients with higher immunological score had significantly worse prognosis (RFS, $P < 0.001$; OS, $P < 0.001$). Multivariable analysis confirmed immunological score (high score *vs.* low score: HR, 3.470, $P = 0.018$) was an independent prognostic factor. Histology type, T stage, and immunological score were used for developing a nomogram model which was proved to be of superior predictive value than single factor.

Conclusions: Thymic carcinomas and thymomas showed distinct tumor microenvironment based on immune markers' expression difference. The immunological score was significantly associated with prognosis, indicating the significance of evaluating TET tumor microenvironment. The nomogram model, which combined histology type, T stage, and immunological score, could predict recurrence effectively.

Keywords: thymic epithelial tumors, tumor environment, immunological score

P1.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.14-04 Silencing ADAR1 Abrogates Mesothelioma Tumorigenicity

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Introduction: Adenosine deaminase for double-stranded RNA 1 (ADAR1) is proposed to be an important protein in promoting cancer development and growth. In melanoma and colon cancer models, inhibition of ADAR1 by shRNA leads to improved response to immune therapy in murine models and delayed tumor growth. In addition, tumor-derived type I interferon (IFN) primes cancer cells for susceptibility to immune checkpoint therapies following ADAR1 loss. ADAR1 is highly expressed in malignant mesothelioma, and is hypothesized to play a role in preventing response to PD-L1 targeted therapy. Silencing of ADAR1 in mesothelioma cells may increase sensitivity to immune checkpoint inhibitors and lead to impaired tumor growth.

Methods: Mesothelioma cells 2461, 2561 (human), 40L and AB12 (murine) were used. ADAR1 was silenced with targeted siRNA or by CRISPR deletion. ADAR1 silencing was confirmed by both western blotting and DNA sequencing. Following treatment of mesothelioma cells with IFNbeta ADAR1 induction was assayed by western blotting. IFNbeta secretion following ADAR1 silencing was detected by ELISA. ADAR1 silenced murine mesothelioma cells were implanted in genetically appropriate both athymic and immune competent mice. Tumor formation was assayed 3 times weekly.

Results: Following treatment of mesothelioma cells with IFNbeta the p150 isoform of ADAR1 was induced in both human and murine mesothelioma cells, consistent with known functions and previously described behavior of ADAR1 in non-mesothelial cells. Silencing of ADAR1 with siRNA blunted this response. Following silencing of ADAR1 a concomitant decrease of IFNbeta secretion in supernatants was observed. CRISPR was used to delete the p110 and the p150 isoforms of ADAR1 in both the 40L (C57Bl/B6) and AB12 (BALB/c) murine mesothelioma cell lines, as well in the human cell lines H2461 and H2561. The parental and ADAR1 deleted (ADAR1KO) murine mesothelioma cells were used to raise xenografts in genetically appropriate mice. In 20 of 20 mice, no tumors (0 of 20 mice with ADAR1KO cells formed tumors) arose on the flanks with ADAR1KO cells, while mesothelioma tumors appropriately appeared on the contralateral flanks of the same mice when injected with parental 40L cells (20 of 20 parental 40L cells formed tumors). Similar results were seen following the implantation of the ADAR1KO cells in C57/B6nude (athymic) mice (1 of 5 mice with ADAR1KO cells formed tumors; 5 of 5 contralateral parental 40L cells formed tumors), demonstrating the lack of tumor formation was unlikely dependent on an intact T cell response. Tumorigenicity of ADAR1KO mesothelioma cells was not restored with concurrent use of an extracellular matrix (Matrigel) with no tumors being formed using this approach in neither immune competent nor athymic mice. To identify pathways involved in the reversal of tumorigenicity NanoString studies of interferon response signature genes are planned, as well as profiling of DNA damage response (DDR) pathways and sensors of DNA damage and replication.

Conclusions: ADAR1 deletion or inactivation is a strong signal in mesothelioma cells reversing the tumorigenic phenotype. The loss of tumorigenicity is unlikely to be dependent on T cell related responses, but the precise mechanisms remain under active investigation.

Keywords: ADAR1, Mesothelioma, interferon

P1.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.14-05 TROP2 Expression and SN38 Antitumor Activity in Malignant Pleural Mesothelioma Cells

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Introduction: Malignant pleural mesothelioma (MPM) is a rare disease with a grim prognosis. Despite the fact that immune checkpoint inhibitors were recently approved as a potential first line therapy beside platinum based chemotherapy a large portion of patients are not responding or acquire resistance following treatment. Irinotecan (CPT-11) is a topoisomerase I inhibitor that is an approved drug in several cancer types. Its active metabolite, SN38 has a 100-1000 fold stronger cytotoxicity. It can be efficiently delivered in antibody - drug conjugates as sacituzumab govitecan where it is attached to the trophoblast cell-surface antigen 2 (TROP-2). Sacituzumab govitecan was recently approved as treatment for pretreated metastatic triple-negative breast cancer. In order to explore preclinically the potential of this treatment, we investigated the epxression of TROP2 in MPM as well as determined the sensitivity of mesothelioma cells to SN38.

Methods: We established a novel cell line panel of 15 cell lines derived from pleural effusion samples of 14 MPM patients and in addition we used two international cell lines. TROP2 protein expression was determined by RT-QPCR, immunoblot, flow cytometry and immunohistochemistry in our cell lines and in the corresponding tumor tissues. SN38 and irinotecan sensitivity was determined by cell viability, cell cycle and PARP cleavage measurements. A selected DNA repair gene expression analysis was performed on the NanoString platform.

Results: Six from the 17 investigated MPM cell models express TROP2 protein. Abundance of TROP2 varied among cell lines and showed high intratumoral heterogeneity, however, TROP2 was present on the cell surface in all positive cell lines. Importantly, TROP2 is not expressed in the healthy pleura and in mesothelial cells. We found that 10 of the 17 cell lines was sensitive to SN38 treatment and five of these showed low nanomolar sensitivity. Gene expression analysis revealed that SN38 sensitivity correlated with higher AURKA gene expression. TROP2 expression did not correlate with SN38 sensitivity nevertheless, two highly sensitive cell lines expressed TROP2. Mechanistically, SN38 treatment induced S-phase and G2/M arrest in MPM cells and in sensitive cell lines induced apoptotic cell death already at very low concentrations.

Conclusions: We demonstrated that TROP2 expression is present in certain MPM tumor cells and MPM cells are highly sensitive to SN38 treatment. These results suggest that the antibody drug conjugate sacituzumab govitecan could be a potential approach in TROP2 positive MPM tumors. Furthermore, the correlation of Aurora kinase A expression with SN38 sensitivity indicates that Aurora kinase A - a negative prognostic factor in malignant mesothelioma - might be a predictor for sensitivity.

Keywords: mesothelioma, TROP2, antibody-drug conjugate

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-01 Differential Diagnosis of Pneumonitis in Metastatic NSCLC (Non-Small Cell Lung Cancer) Patients Receiving Immunotherapy With Radiomics

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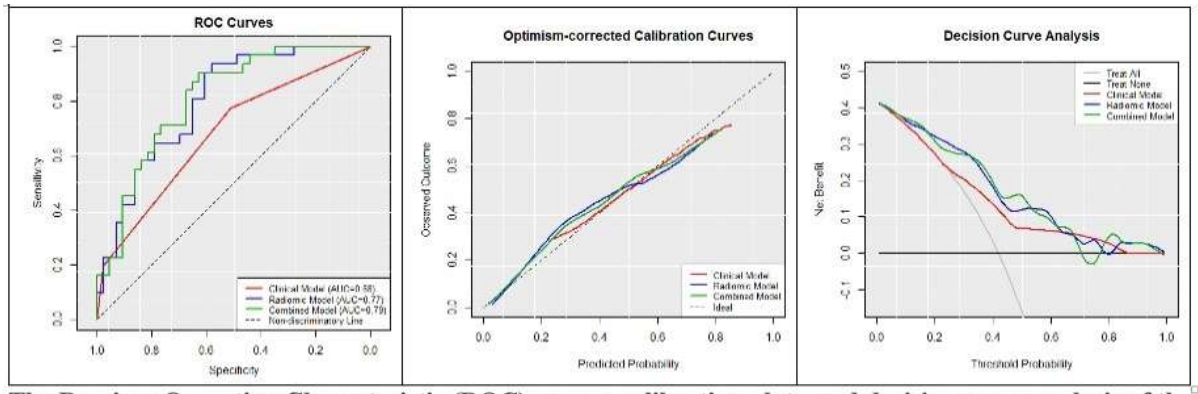
Introduction: Immunotherapy-induced pneumonitis (IIP) is a rare side effect but decreases patients' quality of life and often leads to permanent Immunotherapy (ICI) cessation. The diagnostic challenge is the overlapping clinical manifestations of IIP and Other types of Pneumonitis (OP), such as infectious pneumonitis. A wrong diagnosis may lead to inappropriate toxic treatment (high-dose steroids) or needless cessation of ICI. We developed a combined radiomic and clinic model to support a better differential diagnosis.

Methods: A clinical trial (NCT03305380) recruited 626 stage IV NSCLC patients receiving anti-PD(L)1 medications as the I/II-line treatment from six centers in NL/BE. Radiomic features were extracted from Computed Tomography (CT) images at the time of dyspnea from: A) the segmented lungs (auto-contouring with deep learning), and B) spherical/cubical regions surrounding the center of the inflammation indicated by the radiologists (semi-automated segmentation). Together with presumptive clinical risk factors they were used to build three models: clinical, radiomic, and combined. ROC (Receiver operating characteristic curve) analysis was performed using bootstrap for optimism-corrected results. To evaluate the clinical gain in using the model, the Decision Curve Analysis (DCA) was performed.

Results: A total of n=31 IIP and n=42 OP events were detected. The clinical model included the following variables associated with IIP: Presence of cardiopulmonary comorbidities (yes/no) and line of ICI treatment. Many of the combinations of the radiomic models included three wavelet texture features measuring both grey-level heterogeneity/complexity and one statistical feature measuring the maximum intensities in the frequency space. All the final combined models included one clinical factor (presence of cardiac comorbidities) and two wavelet radiomic features. The best combined model reached an AUC of 0.78 and a negative predictive value of 90%, higher than the radiomic- and clinical-only models. DCAs showed a net benefit for both low-risk and high-risk patients. All the semi-automated approaches led to better results and overall benefit in the DCA, showing the importance of introducing clinical knowledge in model design.

Conclusions: Our proof-of-concept combined model, when prospectively validated can aid in the differential diagnosis of IIP and OP in metastatic NSCLC patients receiving ICI, but the same concept can also be extended to adjuvant ICI for earlier stages.



The Receiver Operating Characteristic (ROC) curves, calibration plots, and decision curve analysis of the clinical, radiomic, and combined models based on a sphere centered at the region of highest inflammation.

Keywords: immunotherapy, prediction modelling, toxicities

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-02 Plasma microRNAs Modulation in Advanced NSCLC Patients Receiving Single Agent Immune Checkpoint Inhibitors

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Introduction: Advanced NSCLC patients showing long-lasting response to immune checkpoint inhibitors (ICI) have been especially observed among patients with PD-L1≥50%. However, patient selection based on PD-L1 is still suboptimal and additional markers to better personalize therapy are needed. It is becoming clear that tumor-intrinsic, -extrinsic and host related factors may improve response to ICIs. MicroRNAs (miRNAs) are epigenetic regulators, targeting messenger RNAs to induce its translational repression. They can be released by cells within circulating microvesicles so they are easily measurable in body fluids. We have previously identify 24 lung cancer related miRNAs, whose plasma variation of the ratios reflects the switch towards an immunosuppressive profile of circulating immune cells such as neutrophils, T-lymphocytes and macrophages. Here, by analyzing baseline and longitudinally collected plasma samples, we aimed to investigate whether specific circulating miRNA features are associated with clinical outcomes in NSCLC patients treated with single agent ICIs.

Methods: From July 2015 until June 2020, we collected clinico-pathological information and plasma samples (at baseline, at the time of best response and every year upon disease progression) of advanced NSCLC patients undergoing ICI monotherapy at our Institution and enrolled in the Apollo trial. The miRNA profile was prospectively assessed on available plasma samples. Progression free survival (PFS), estimated according to RECIST 1.1 criteria, and overall survival (OS) were considered as outcomes to estimate multivariate Cox models, assessed by C-index. For features selection procedure, penalized regressions were fitted. To further investigate the associations between single selected miRNA and the outcome, univariate analyses were evaluated.

Results: During the 5 years of the project, 211 advanced NSCLC patients receiving single agent ICI and with available plasma samples at baseline were enrolled. Median age was 67 (IQR: 13), 80 patients (38%) were female, and 29 (14%) were never smokers. For 78 (37%) patients, single agent ICI was administered as first line and 65 patients (31%) were high (≥50%) PD-L1 expressors. In the overall population, median PFS and OS were 2.96 (95%CI: 2.43; 3.81) and 9.24 (95%CI: 8.09; 12.8) months, respectively. For PFS, the multivariate model showed a C-index of 0.62 (95%CI: 0.58; 0.67) and, considering baseline samples, at the univariate level, 7 of 11 selected features were significantly associated with PFS. Similar results were obtained for OS, where the 5 selected miRNAs were all significant at the univariate level and in the multivariate model a C-index of 0.64 (95%CI: 0.60; 0.69) was observed. In details, 3 miRNA ratios were in common between the two models: miR-126-3p/miR-15b, miR-145-5p/miR-21-5p and miR-145-5p/miR-221-3p. None of these miRNAs features was associated with other clinical variables, including PD-L1 expression. For 82 out of the 91 (90%) patients with responsive or stable disease, longitudinal plasma samples were further analyzed. Using these samples we will evaluate the longitudinal modulation of miRNAs and their impact on patients' outcome.

Conclusions: Circulating miRNA features at baseline and during treatment may be an easily evaluable tool to help clinicians in selecting patients and monitoring response to single agent ICI in advanced NSCLC.

Keywords: NSCLC, Immune checkpoint inhibitors, microRNAs

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-03 Clinical Outcomes Among Patients with Non-small Cell Lung Cancer Who Discontinued Immune Checkpoint Inhibitors Due to Toxicity

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Introduction: The onset of immune-related adverse events (irAEs) often necessitates discontinuation of immune checkpoint inhibitor (ICI) in patients with non-small cell lung cancer (NSCLC), but the clinicopathologic characteristics and outcomes in this population are largely unknown.

Methods: Clinicopathologic data at the Dana-Farber Cancer Institute were abstracted from patients with advanced NSCLC who received ICI monotherapy which was permanently discontinued due to irAEs. Type and grade of irAEs were recorded according to Common Terminology Criteria for Adverse Events version 5. Event-time distributions were estimated using Kaplan-Meier methodology. Log-rank tests were used to test for differences in event-time distributions, and Cox proportional hazards models were fitted to obtain estimates of hazard ratios. “Early” and “late” subgroups were defined as discontinuation of ICI treatment in <3 months vs ≥3 months after ICI initiation, respectively.

Results: Among 1038 patients with advanced NSCLC treated with ICI, 120 (11.5%) discontinued treatment due to irAEs. The median duration of ICI treatment before discontinuation for irAEs was 4.7 months [interquartile range (IQR) 0.99-10.10], and the median time to first irAE onset was 2.9 months (IQR 1.09-7.66). Forty-eight (40%) patients discontinued within 3 months of ICI initiation (early subgroup), and 72 (60%) discontinued after 3 months (late subgroup). Patients with early vs late ICI discontinuation due to irAEs were similar in terms of age, sex, smoking status, histologic subtype, PD-L1 expression, and tumor mutational burden. The most common irAE that led to ICI discontinuation was pneumonitis in the early subgroup (22.9%) and gastrointestinal toxicity in the late subgroup (26.3%). Considering the grade of irAEs that led to ICI discontinuation, 28 (58%) patients in the early subgroup and 22 (31%) patients in the late subgroup discontinued for grade 3-4 irAEs. At a median follow up of 31.2 months, among 112 (93%) patients without disease progression at the time of ICI discontinuation for irAEs, the post discontinuation median progression-free survival (mPFS) was 12.0 months, and the post discontinuation median overall survival (mOS) was 32.4 months. The post discontinuation mPFS was significantly shorter in the early subgroup when compared to the late subgroup [5.3 vs 14.7 months, HR 0.43 (95%CI 0.27-0.70), p<0.0001]. Similarly, the post discontinuation mOS was shorter in the early subgroup when compared to the late subgroup [19.8 months vs not reached, [HR 0.42 (95%CI 0.24-0.70), p<0.0001]. Comparing patients who did (N=97, 80%) or did not (N=23, 20%) receive systemic corticosteroids for irAEs management, there was no difference in mPFS (15.8 vs 23.9 months, HR 1.23 (95%CI 0.67-2.25), p=0.5) or mOS (30.4 months vs not reached, HR 1.47 (95%CI 0.65-3.20), p=0.4) assessed from the time of immunotherapy initiation.

Conclusions: Among patients treated with ICIs, irAEs leading to ICI discontinuation occurred in 11.5% of cases, with gastrointestinal and pulmonary irAEs representing the most common reasons for treatment discontinuation. The post discontinuation median PFS and OS were significantly shorter in patients who discontinued treatment within 3 months of ICI initiation.

Keywords: immune-related adverse events, immune checkpoint inhibitors, discontinuation

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-04 Dynamic Profiling of Blood Immunophenotypes and Radiomic Features to Predict Immunotherapy Response in Advanced Non-small Cell Lung Cancer

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Introduction: Up to date, no predictive biomarkers can robustly identify patients with non-small cell lung cancer (NSCLC) who will benefit from immune checkpoint inhibitors (ICIs). Thus, we sought to non-invasively decode tumor-immune interactions implicated in ICI response by exploring the dynamic of blood immune-inflammatory markers and radiomic features in a cohort of advanced NSCLC treated with ICIs.

Methods: On 58 stage IV NSCLC patients undergoing ICI-based therapy, blood immune-phenotyping data and CT-derived radiomic features (RFs) were acquired at baseline (T0) and at first disease assessment (T1). In detail, we performed a flow-cytometric analysis of circulating CD3+, CD8+, CD4+, NK, NKT and Tregs as their expression of functional molecules (PD-1, Granzyme B [GnzB], Perforin [Perf]) and proliferative index (Ki67). Overall, 851 RFs were extracted from T0 and T1 CT scans through a dedicated software (SlicerRadiomics). Time/treatment-dependent changes in blood parameters were expressed as percentage delta variation (Δ% = [T1 value - T0 value/T0 value]*100), while delta-RFs were computed as follows: (T1-T0)/T0. Primary endpoint was disease response per RECIST. CR/PR or SD ≥ 6 months defined clinical benefit (CB), while SD < 6 months or PD non-responders (NR).

Results: From October 2020 to August 2021, 58 advanced NSCLC patients candidate to receive ICI-based therapy were enrolled. Median age was 69 years (range: 41-88) and 80% underwent first-line ICIs (mostly consisting of pembrolizumab + platinum-based chemotherapy). According to disease response, 32 patients (55%) belonged to CB, while the remaining 26 (45%) were NR. Focusing on blood immune descriptors, we observed a significant increase in the overall number (n/μL) of CD3+, CD8+ and NK cells in CB, with a marked proliferative burst (Ki67+) of CD8+ lymphocytes carrying cytotoxic molecules (GnzB+, Perf+). Specifically, mean delta variations of NK, CD8+Ki67+ and CD8+GnZ+Perf+ phenotypes were, respectively, +22%, +170% and +65% in CB compared to -20%, -0.4% and -41% in NR ($p<0.05$, U-Mann Whitney test). Furthermore, the kinetic and extent of Treg (CD4+CD25+FOXP3high) counteraction, likely triggered by the expanding (Ki67+) and activated (GnZ+/Perf+) pool of effector T lymphocytes, appeared more pronounced in CB patients, reaching a mean Δ% variation of +375%. Delta-RFs were subjected to feature pre-processing, including redundant features elimination (Spearman correlation, cut-off=0.99) and Z-score standardization, and the remaining 657 features were correlated to ICI efficacy. We interestingly identified 11 delta-RFs differentially regulated in CB *vs* NR ($p<0.05$, U-Mann Whitney test). Subsequently, Principal Component Analysis (PCA) was computed to extract the main sources of variation from radiomic data, and principal components (PCs) were correlated with circulating delta-immune parameters (Pearson test). A noteworthy trend towards positive correlation was observed between PCs 21-22 (mostly contributing RFs: wavelet-LLH_firstorder_Mean and wavelet-HLL_firstorder_Maximum, respectively) and proliferating cytotoxic T phenotypes. Conversely, PC12 (mostly contributing RF: wavelet-HLL_firstorder_Skewness) negatively correlated with the same subsets of immune cells.

Conclusions: Our results suggest that tracking the evolution of blood immune-inflammatory and radiomic profiles may provide a more faithful portray of tumor-host interactions following ICIs, potentially representing a step toward the achievement of individualized decision support in advanced NSCLC patients.

Keywords: Non-small cell lung cancer, Immunotherapy, Immunophenotypes

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-05 Nintedanib in Combination with Nivolumab in Pretreated Patients with Advanced Adenocarcinoma of the Lung (AIO-TRK-0117 Phase IB/II Trial)

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Introduction: Nivolumab and Nintedanib (in combination with docetaxel) are both established 2nd-line treatments in non-squamous NSCLC. The NintNivo trial was conducted to explore the therapeutic potential of the combination of immune checkpoint inhibition (Nivolumab) and anti-angiogenesis (Nintedanib) in advanced treatment lines of NSCLC with adenocarcinoma histology. We hypothesized that the combination of both substances increases efficacy in the 2nd/3rd-line setting and may even restore tumor response with IO refractory patients progressing after IO + platinum-based front-line treatment.

Methods: In this multi-center, open-label, single arm, phase Ib trial patients with advanced or metastatic non-squamous NSCLC of adenocarcinoma histology after failure of first- or second-line therapy with platinum-based chemotherapy with or without an approved checkpoint inhibitor were treated with Nintedanib and Nivolumab. Following a safety run-in phase conducted as a conventional 3 + 3 dose finding approach, patients continued in an expansion phase to receive the recommended phase 2 dose (RP2D) of the combination therapy determined as Nintedanib 200 mg BID and Nivolumab 240 mg Q2W. The primary endpoints were safety and tolerability as determined by frequency and severity of adverse events as well as progression-free survival (PFS) after 6 and 9 months. Secondary endpoints included objective response rate (ORR), PFS, OS, time to progression (TTP), duration of response (DoR), time to response (TTR) as well as safety in terms of AEs, serious AEs (SAEs) and treatment-emergent AEs (TEAEs).

Results: Since no dose-limiting toxicities (DLT) occurred in the safety run-in phase, a total of 53 patients (pts) with median age of 64 years (range 36 - 84 years) received the RP2D of Nivolumab at 240 mg Q2W and Nintedanib at 200 mg BID. The majority of enrolled patients received one line of prior platinum-based CTx (with or without additional IO) and 15.1% received 2 lines of prior therapy according to current treatment algorithms. Preliminary results revealed an ORR of 11.3% (95% CI, 4.3% to 23.0%) with all cases being partial remissions. 30.2% of patients had stable disease as their best overall response. The PFS rate at six, nine months and median PFS was 24.5% (95% CI, 14.0% to 36.6%),10.5% (95% CI 4.0% to 20.8%) and 2.5 months respectively. The 1-year overall survival (OS) rate was 53% and median OS was 12.5 months. AEs causally related to study treatment were recorded in 86.8 % of trial subjects. The most frequent AEs were diarrhea (52.8% of pts), nausea (43.4% of pts), fatigue (24.5% of pts), weight loss (20.8% of pts), GGT increase (18.9% of pts), dyspnea (17.0 % of pts), and headache (13.2% of pts). Grade 3+ events causally related to study medication (N=34) were observed in 38.8% (n=19) of patients. Two grade 5 events were observed, both of which were unrelated to study medication.

Conclusions: Our preliminary results confirm the feasibility of the combination of nivolumab+nintedanib together with clinical efficacy in pretreated patients with advanced adenocarcinoma of the lung after chemotherapy +/- immunotherapy. Further analyses including translational investigations are planned to identify benefitting patients.

Keywords: Progression Immunotherapy, Antiangiogenic Treatment, Adenocarcinoma

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-06 Immune-Checkpoint Inhibitors-Related Colitis in Advanced Non-small Cell Lung Cancer Patients: A Real-World Analysis

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Introduction: Immunotherapy has radically changed outcome of patients with advanced non-small cell lung cancer (aNSCLC). Despite generally well tolerated, Immune-Checkpoint inhibitors (ICIs) can induce a specific pattern of adverse events (AEs), immune-related AEs (irAEs). Aim of this project is to collect real-world data (RWD) about ir-colitis, focusing on clinical management and histological features.

Methods: We retrospectively collected aNSCLC patients treated with ICIs as single agent or in combination with chemotherapy from August 2015 to December 2021. Thus, we analyzed clinical data of patients developing symptoms consistent with ir-colitis. A blinded revision of colonic biopsies was performed. Pathological features were depicted and categorized through a colitis severity score (1-3 points).

Results: At data cut-off, 554 patients received ICIs: 464 in monotherapy, 90 in combination with chemotherapy. 84 (15.2%) patients developed any grade diarrhea: 65 out of 464 (14.0%) with single agent ICIs, 19 out of 90 (21.1%) with combination treatment. In 80 cases (14.4% of the study population) diarrhea was judged treatment-related (Grade[G]1=61.2%, G2=31.3%, G3=7.5%). According to clinical practice, 52 (65%) patients discontinued ICIs. Of them, 26(50%) resumed treatment after symptoms resolution experiencing diarrhea recurrence in 14 cases. 55 out of 80 ir-cases (68.8%) required steroid treatment, 38 (47.5%) for more than 8 weeks (median duration of steroid was 105 days, range 7-932) and 8 (10%) required hospitalization. Since May 2021, symptomatic patients were discussed with highly specialized gastroenterology team and 18 (22.5%) were managed and followed-up by the team. Since then, a higher rate of colonoscopy was performed (N=13/18, 72.2% versus N=14/62, 22.6%, p<0.001) and a lower rate of hospitalization was registered (N=1/18, 5.5% versus N=7/62, 11.3%, p<0.001). 27(33.8%) patients underwent an endoscopy and multiple colon biopsies. Notably, 9 out of 27 (33.3%) had macroscopic lesions. Microscopic features from colonic biopsies from 25 patients, revised by two blinded pathologists, are summarized in Table 1. All patients presented a lymphomonocytic infiltrate and the majority showed intraepithelial lymphocytes. No case formally complied criteria for lymphocytic colitis. Median duration of symptoms in patients with collagenous colitis (N=4,16%) was 200 days versus 51 in non-collagenous colitis (N=21, 84%; p=0.009).

Conclusions: RWD on ir-colitis underlined high prevalence of microscopic colitis among patients undergoing endoscopy. Collagenous colitis were associated with longer symptoms duration notwithstanding steroids administration according to clinical practice. Multidisciplinary management has potential to improve toxicity outcome. Further analyses are ongoing to investigate the role of immune-infiltrate in colitis biopsies.

Microscopic features from colonic biopsies.

Variable	*N*	(%)
Number of cases	25	(100.0)
Crypt atrophy/loss		
Present	12	(48.0)
Absent	13	(52.0)
Crypt distorsion		
Present	15	(60.0)
Absent	10	(40.0)
Mucin Depletion		
Present	20	(80.0)
Absent	5	(20.0)

Variable	*N*	(%)
Apoptotic bodies		
Present	19	(76.0)
Absent	6	(24.0)
Lamina propria expansion		
Present	21	(84.0)
Absent	4	(16.0)
Collagenous band		
Absent	16	(64.0)
Focal	5	(20.0)
Extensive	4	(16.0)
Intraepithelial lymphocytes		
Absent	1	(4.0)
0-2/100 enterocytes	11	(44.0)
3-20/100 enterocytes	13	(52.0)
>20/100 enterocytes	0	(0.0)
Lymphomonocytic infiltrate		
Absent	0	(0.0)
Mild	8	(32.0)
Moderate	17	(68.0)
Heavy	0	(0.0)
Granulocyte infiltrate		
Absent	13	(52.0)
Mild	11	(44.0)
Moderate	1	(4.0)
Heavy	0	(0.0)
Cryptitis		
Absent	20	(80.0)
Not focally present	3	(12.0)
Focally present	2	(8.0)
Crypt abscess		
Present	2	(8.0)
Absent	23	(82.0)
Subepithelial macrophages		
Present	6	(24.0)
Absent	19	(76.0)
Superficial erosion/ulceration		
Present	5	(20.0)
Absent	20	(80.0)
Ischemic colitis-like		
Present	6	(24.0)
Absent	19	(76.0)
Paneth metaplasia		
Present	7	(28.0)
Absent	18	(72.0)
Global score		
1	9	(36.0)
2	9	(36.0)
3	7	(28.0)

Keywords: Immune-checkpoint inhibitors, colitis, immune-related adverse events

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-07 Phase II Study of Pembrolizumab and Itacitinib for First Line Treatment of Metastatic NSCLC Expressing PD-L1

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Introduction: Adaptive resistance to immunotherapy in metastatic non-small cell lung cancer (mNSCLC) remains a challenge. Preclinical work suggests that constitutive interferon signaling promotes resistance to immune checkpoint blockade and blocking JAK1/2 later during the course of immunotherapy can potentially reverse this resistance. We present a phase II clinical trial of pembrolizumab and 6 weeks of itacitinib (INCB039110**;** JAK1 inhibitor) in mNSCLC patients with PDL expression ≥50% as first line therapy.

Methods: Patients with mNSCLC who were treatment-naïve and ECOG PS 0-1 received pembrolizumab (200mg every 21 days). Itacitinib 200mg daily po was started Cycle 3 Day 1 of pembrolizumab and continued for 6 weeks. Primary endpoints were: 1) overall response rate (ORR) determined by RECIST 1.1 partial (PR) and complete responses at 12 weeks 2) toxicity of pembrolizumab and itacitinib by CTCAE v5.0. Secondary clinical objectives included progression free survival (PFS), and overall survival (OS). Paired blood and tissue samples were collected for several translational and exploratory objectives.

Results: Of 31 patients screened, 23 were enrolled between 10/16/2018 and 3/4/2021 and received at least 1 cycle of pembrolizumab: 56.5% female, median age 62 years (range, 41-78), 87% with smoking history, 78% adenocarcinoma, 22% squamous, 9/23 with PD-L1 ≥90%). 20 patients completed 12 weeks of treatment, 3 patients stopped the trial due to pembrolizumab toxicity (1), CNS progression after pembrolizumab (1) and patient decision (1). At 12 weeks ORR was 62% (13 PR, 7 stable disease, 1 progressive disease) (Figure 1). One grade 5 pneumonitis was observed after 12 weeks of treatment. There were no grade 4 events. Grade 3 events possibly related to study treatment before itacitinib included: diarrhea (2/23, 9%), nervous system disorder (9%), and hypokalemia (4%); and after itacitinib included: diarrhea (1/20, 5%), nervous system disorder (5%), and skin disorder (5%). In all 23 patients, with median follow up of 27 months, median PFS was 23.4 months. OS rate at 12 months was 83%.

Conclusions: Treatment-naïve pts with mNSCLC and PD-L1 expression ≥50% treated with pembrolizumab and a brief course of JAK inhibition starting at week 6 of treatment resulted in an ORR of 62% at 12 weeks and mPFS of 23.4 months. This novel combination was well tolerated. Interferon signaling modulation through JAK1 inhibition may help prevent resistance to anti-PD1 therapy and should be studied further in a randomized trial.

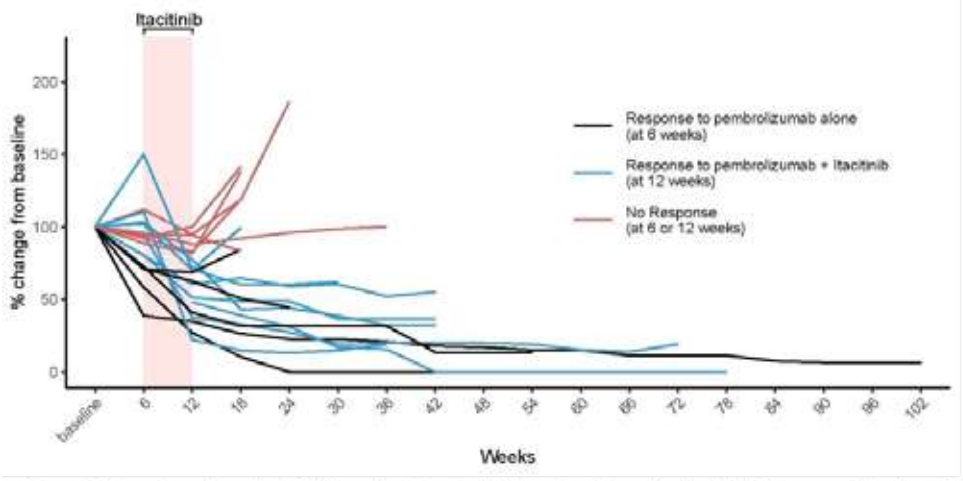

Figure 1: Change from baseline (100) in patients treated with pembrolizumab + itacitinib. Response defined as ≥29% decrease in tumor size from baseline. 2 patients without complete 6-week imaging were excluded.

Keywords: Immunotherapy, JAK, pembrolizumab

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-08 Phase 1: IMU-201 (PD1-Vaxx), a B-Cell Immunotherapy as Monotherapy or in Combination with Atezolizumab, in Adults with Non-Small Cell Lung Cancer

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Introduction: Therapies with monoclonal antibodies targeting PD-1 and its ligands are associated with remarkable outcomes and have revolutionized cancer treatment (Honey 2017). However, patients treated with PD-1/PD-L1 blockade may develop "a primary or secondary resistance" to therapy (Sharma, HuLieskovan et al. 2017).Contrary to monoclonal antibodies, chimeric B-cell cancer vaccines have the advantage of producing polyclonal B-cell antibodies that can potentially induce memory B- and T-cell responses, while reducing immune evasion and suppression. The hypothesis is that a polyclonal induced Bcell antibody response will be more effective or as effective with improved safety over current monoclonal antibody therapy.IMU-201 (PD1-Vaxx) is being developed using an active immunization approach to treat cancers that overexpress PD-L1 by inducing the production of anti-PD-1 antibodies with a peptide epitope designed to stimulate polyclonal antibodies against PD-1 (Kaumaya et al. 2020).

Methods: The IMPRINTER study is an ongoing open-label dose escalation study of IMU-201 as monotherapy (Phase 1) or in combination with atezolizumab (Phase 1b) for patients with PD-L1 expressing non-small cell lung cancer (NSCLC). All patients enrolled in Phase 1 of the study must have previously received an immune checkpoint inhibitor and experienced disease progression.The primary objective is to evaluate the safety and tolerability of IMU-201 and identify the optimal biological dose (OBD). The secondary objective is to evaluate the efficacy of IMU-201 as monotherapy and in combination with atezolizumab. Humoral and cellular immunogenicity data will be evaluated, including IMU-201 and PD-1 specific antibodies (IgG, IgM), vaccine-specific cytokine levels, and regulatory and effector T and B cells.IMU-201 is administered by intramuscular (IM) injection on Day 1, Day 15, and Day 29. Dose-limiting toxicity (DLT) assessment is completed after 29 days on treatment. Tumor progression is evaluated according to RECIST 1.1 at Day 43 then every 42 days until progression or withdrawal.

Results: In Phase 1, four patients were enrolled into each of the three cohorts at 10 µg/dose, 50 µg/dose and 100 µg/dose IMU-201 with no DLTs observed. In the 10 µg/dose cohort, one patient achieved CR and one patient SD; in the 50 µg/dose cohort, four patients achieved SD; and in the 100 µg/dose cohort, one patient achieved PR and two patients achieved SD. Within the 100 µg/dose cohort, one patient experienced an immune related pneumonitis after two IMU-201 administrations and discontinued from study treatment.

Conclusions: IMU-201 had no observed DLT and demonstrated preliminary signs of efficacy. The study will therefore move into Phase 1b with IMU-201 being assessed in combination with atezolizumab.

Keywords: PD1-Vaxx, B-cell Immunotherapy, Non-Small Cell Lung Cancer

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-09 First-line Atezolizumab plus Bevacizumab for Metastatic High-Intermediate TMB in Non-squamous NSCLC. The TELMA Study

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Introduction: Atezolizumab has been approved as first-line monotherapy in PD-L1-selected NSCLC patients. In addition, there is a growing body of evidence that suggests pro-angiogenic factors can modulate the immune response and may serve as mechanisms of escape. Therefore, the combination of cancer immunotherapy with antiangiogenic agents makes sense in this setting. As well as PD-L1, tumor mutational burden (TMB) has recently emerged as a promising biomarker for immune checkpoint inhibitor (ICI) patient stratification, though more evidence is needed.

Methods: We conducted a single-arm phase II study to investigate the clinical benefits of adding Bev 15 mg/kg to Atez 1200 mg/body in first-line for patients with intermediate-high TBM≥10 mutation/megabase (mut/meg). Both agents were administered on day 1 q3wk until disease progression. Patients were eligible if they had pathologically confirmed advanced non-Sq NSCLC without any EGFR/ALK/ROS1, STK 11, or MDM2 alterations; had ECOG performance status 0-1; and TBM≥10mut/meg. The primary endpoint was PFS at one year. The sample size was 36, assuming PFS at 12 months (m) was 40%, alpha 0.05, 90% statistical power, one-sided. The statistical test for survival probability was assumed to be based on the non-parametric estimate of survival distribution. Secondary endpoints were overall response rate (ORR), duration of response (DoR), overall survival (OS), and safety. Other objectives included determination of TMB and its association with all four types of genomic alteration (Indels, mutation, CNV, rearrangement) in 324 tumor-related genes, MSI, and determination by FoundationOne CDx™ (F1CDx).

Results: From May 2019 to January 2021, we screened 307 p who had been assessed for eligibility. Two hundred and sixty-six (266) were negative: 151 TMB<10, 39 TMB≥10 but with other non-eligible criteria met. Forty-one (41) p (the intention-to-treat population, ITT) were enrolled from 13 institutions. Seventy-four percent (74%) were male with a mean age of 63 (SD: 8.3); 36 (94%) had a history of smoking. PFS at 12m was 55% (37.5-69.9). Median PFS was 13.8m (95% CI, 8.6-19.5). OS at 12m was 71% (95% CI, 52.9%-83.5%). ORR was 39.5% (15 p with PR). DoR (p50) was 11m (5-16.7m). Data maturity at 12 m was 92%. Only one patient (3%) had diarrhea. Grade 4 toxicity was observed. Grade 5 toxicity was not observed.

Conclusions: These positive results support the combination of Atez+Bev as a potential treatment option for non-Sq NSCLC with TBM≥10. This is the first trial to evaluate the combination of Bev and TBM≥10mut/Mb excluding other alterations with very good results, even superior to other ICI+chemotherapy combinations.

Keywords: Non-squamous NSCLC, TMB, First line Atezolizumab plus Bevacizumab

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-10 Chronic Obstructive Pulmonary Disease Patients Receiving Immunotherapy for Lung Cancer: A Population-Based Study in Canada

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Introduction: Outside of clinical trial eligibility criteria, there is limited data to guide the selection of patients with non-small cell lung cancer (NSCLC) for immune checkpoint inhibitor (ICI) therapy. Chronic obstructive pulmonary disease (COPD) and lung cancer are associated, independent of smoking history, with a common background of chronic inflammation. Previous studies have demonstrated that COPD is a negative prognostic marker for NSCLC, but the clinical benefit of ICI in patients with NSCLC and COPD is unknown.

Methods: A population-level administrative data analysis of Ontario patients in Canada was performed through the Institute of Clinical Evaluative Sciences (ICES) Data Analytic Services. All patients with NSCLC diagnosed between Jan 2010 and Dec 2020 and treated with immune-checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab) were included. Demographics, comorbidity and marginalization scores, and COPD status were extracted along with outcome information. Overall survival (OS) was estimated using the Kaplan-Meier method and compared between patients with or without COPD using Cox proportional hazards regression. The frequency of patients requiring hospitalization and duration of treatment was also estimated and compared using the chi-square and Wilcoxon rank-sum test.

Results: 73331 NSCLC patients were identified, of which 4.5% (n = 3285) patients received ICI. COPD patients were less likely to receive immunotherapy (3.8% vs. 5.1%, p < 0.001). Among those receiving an ICI, 41% (n = 1362) of patients had a diagnosis of COPD prior to NSCLC diagnosis. Median (95% CI) OS was 17.3 (16.6 to 18.2) months for patients with COPD and 16.9 (16.2 to 17.8) for patients with no known COPD, which was not significantly different in univariate (hazard ratio = 0.96, 95% CI = 0.89 to 1.04, p = 0.35) or multivariate analysis (HR = 0.96, 95% CI = 0.89 to 1.05, p = 0.40). The 5-year survival was also similar between both groups (6.7% vs. 6.5%). The rate of hospitalization within 6 months (18.4% vs 18.0%, p = 0.82) and the duration of immunotherapy treatment (median = 80 vs 71 days p = 0.23) did not differ for the COPD vs. non-COPD groups.

Conclusions: Despite an expectation of frailty, our data suggest that NSCLC patients with COPD receiving ICI maintained similar durations of treatment and similar rates of hospitalization, with no significant difference in survival time, compared with those without COPD. While a treatment selection bias cannot be excluded in this non-randomized dataset, our data suggest that a diagnosis of COPD itself should not be considered a contraindication to immune checkpoint inhibitor use in NSCLC.

Keywords: COPD, metastatic lung cancer, immune checkpoint inhibitor

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-11 Durvalumab + Olaparib vs Durvalumab Alone as Maintenance Therapy in Metastatic NSCLC: Outcomes from the Phase 2 ORION Study

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Introduction: Immunotherapy alone or combined with chemotherapy (CT) has transformed first-line treatment of metastatic NSCLC. Nevertheless, median PFS typically remains <1 year in clinical studies, highlighting the need for novel treatment strategies. Increased DNA damage triggered through poly (ADP-ribose) polymerase (PARP) inhibition may modify tumour immunogenicity, sensitising tumours to immunotherapy. ORION evaluates the efficacy and safety of durvalumab (D; PD-L1 inhibitor) plus olaparib (O; PARP inhibitor) as maintenance therapy.

Methods: ORION (NCT03775486) is a Phase 2, randomised, multicentre, double-blind, international study. Patients with metastatic NSCLC (without activating *EGFR*m/*ALK* fusions) and ECOG PS 0/1 were enrolled to receive first-line D (1500mg IV; Q3W) with investigator's choice of platinum-based CT for 4 cycles (initial-therapy phase). Patients without progression (RECIST-v1.1) were then randomised (1:1) to D (1500mg; Q4W) plus O (300mg; orally; BID) or placebo (P), until progression (maintenance phase). Randomisation was stratified by objective response during initial therapy (CR/PR vs SD) and histology (squamous vs non-squamous). The primary endpoint was investigator-assessed PFS (ITT; RECIST-v1.1). Secondary endpoints included OS (ITT), PFS in patients with homologous-recombination-repair gene mutations (HRRm), and safety. PFS by PD-L1 status was exploratory.

Results: Between January-2019 and February-2020, 269/401 patients who received initial D+CT were randomised to maintenance D+O (134) or D+P (135); baseline characteristics were generally well balanced. As of 11 January 2021 (median follow-up duration in censored patients: 9.6 months), median PFS was 7.2 months (95% CI: 5.3-7.9) with D+O versus 5.3 months (3.7-5.8) with D+P (HR: 0.76; 95% CI: 0.57-1.02; p=0.074). OS was immature. Safety findings were consistent with the known profiles of D and O. Anaemia was the most common AE with D+O (26.1%; vs 8.2% with D+P). Incidence of grade 3/4 AEs (34.3% vs 17.9%), serious AEs (18.7% vs 14.2%), and AEs leading to treatment discontinuation (10.4% vs 4.5%) was numerically higher with D+O versus D+P; grade 5 AEs occurred in 3.7% versus 5.2%, respectively. 96.7% of randomised patients were HRRm-evaluable (10.8% of whom had HRRm), and 69.5% were PD-L1-evaluable. The Table shows PFS in HRR and PD-L1 subgroups.

Conclusions: Maintenance D+O did not significantly improve PFS versus D monotherapy. Within the small HRRm subgroup, no improved activity for D+O was observed. Aligned with ITT findings, HRs favoured D+O across PD-L1 levels <50% (HRs: 0.51-0.76); in the ≥50% subgroup, median PFS was numerically higher versus the <50% subgroups regardless of treatment, and the HR for D+O versus D+P was 1.03. Small subgroup sizes preclude definitive conclusions.

PFS (measured from randomisation) by subgroup			
Subgroup	**D+O Median PFS, months (95% CI)**	**D+P Median PFS, months (95% CI)**	**HR (95% CI)***
All patients	(n=134) 7.2 (5.3–7.9)	(n=135) 5.3 (3.7–5.8)	0.76 (0.57–1.02)
HRR status†			
Mutant	(n=11) 3.9 (1.8–7.5)	(n=17) 4.7 (2.1–NE)	1.58 (0.63–4.00)
Wildtype	(n=119) 7.4 (5.5–9.3)	(n=113) 5.2 (3.6–5.6)	0.64 (0.47–0.88)
PD-L1 expression level‡			
<1%	(n=40) 5.6 (2.8–7.8)	(n=45) 4.8 (2.1–6.6)	0.76 (0.46–1.26)
1–49%	(n=34) 5.8 (3.9–9.1)	(n=25) 3.7 (2.4–4.5)	0.51 (0.28–0.92)
≥50%	(n=24) 10.1 (3.7–NE)	(n=19) 9.0 (3.7–13.9)	1.03 (0.47–2.32)
Unknown	(n=36) 7.9 (3.8–NE)	(n=46) 5.6 (3.4–9.5)	0.71 (0.38–1.27)

*HR <1 favours D+O vs D+P. †260 patients were HRRm-evaluable; 181 were tested using the FoundationOne tissue-based assay and 81 (who had failed tissue-based testing) underwent sequencing of ctDNA using the GuardantOMNI assay; 9 patients had unknown HRR status (D+O n=4, D+P n=5); the analysis presented here is exploratory as re-analysis was performed in the patients previously missing tissue-based data. ‡187 patients were PD-L1-evaluable; all were tested using the VENTANA PD-L1 (SP263) assay.

ctDNA, circulating tumour DNA; NE, not estimable.

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-12 Patient-reported Outcomes of Cemiplimab versus Chemotherapy in Advanced NSCLC: PD-L1 Level Subgroups in EMPOWER-Lung 1

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Introduction: Previously reported subgroup analysis of EMPOWER-Lung 1 (NCT03088540), a randomised 1:1 open-label Phase 3 study, showed incremental improvements in overall survival and progression-free survival with cemiplimab monotherapy (CEMI, n=283) versus platinum-doublet chemotherapy (CHEMO, n=280) as programmed cell death-ligand 1 (PD-L1) expression increased from ≥50% to ≥90% (overall survival with PD-L1 ≥50% to ≤60%: hazard ratio [HR] 0.77, 95% confidence interval [CI, 0.49, 1.23]; with PD-L1 >60% to <90%: HR 0.47, 95% CI [0.27, 0.80]; with PD-L1 ≥90%: HR 0.46, 95% CI [0.25, 0.85]) in patients with advanced non-small cell lung cancer (NSCLC) with PD-L1 ≥50%. Post hoc exploratory analyses were conducted to evaluate patient-reported outcomes (PROs) across three PD-L1 level subgroups 1) ≥50% to ≤60%, 2) >60% to <90%, and 3) ≥90%.

Methods: PROs were assessed at baseline and Day 1 of each treatment cycle for the first 6 cycles, and then on Day 1 of every third cycle using the European Organization for Research and Treatment of Cancer Quality of Life-Core 30 (QLQ-C30) and Lung Cancer module (QLQ-LC13) questionnaires. Higher scores indicate better functioning, and global health status (GHS)/quality of life (QoL), or worse symptom severity. Mixed-model repeated-measures analyses were performed to compare overall change from baseline scores between the two treatment arms, while controlling for baseline characteristics. Time to definitive clinically meaningful deterioration (TTD) based on a 10-point threshold was analysed using a stratified log-rank test and a Cox proportional hazards model.

Results: Baseline PRO scores were broadly similar between treatment arms. A statistically significant overall change from baseline in GHS/QoL favouring CEMI versus CHEMO was observed across some PD-L1 ≥50% subgroups (PD-L1 >60% to <90%: 6.78, 95% CI [2.20, 11.36], *P*=0.004; PD-L1 ≥90%: 5.67, 95% CI [1.37, 9.96], *P*=0.010). CEMI also resulted in statistically significant favourable difference across all PD-L1 ≥50% subgroups in overall change from baseline in physical functioning; symptoms of fatigue, nausea/vomiting, and appetite loss per the QLQ-C30; and symptoms of peripheral neuropathy and alopecia per QLQ-LC13. There was a statistically significant delay in TTD in GHS/QoL across ≥90% PD-L1 subgroup, favouring CEMI (HR 0.42, 95% CI [0.20, 0.86], *P*=0.015). Statistically significant delay in TTD favouring CEMI was observed in both PD-L1 subgroups of >60% to <90% and ≥90%, in physical functioning, social functioning, appetite loss (per QLQ-C30), and dyspnoea (per QLQ-LC13). Statistically significant delay in TTD favouring CEMI was observed across all three PD-L1 ≥50% subgroups for symptoms of peripheral neuropathy and alopecia per the QLQ-LC13. When comparing between arms, no analyses yielded statistically significant PRO results favouring CHEMO for any QLQ-C30 or QLQ-LC13 scale.

Conclusions: In this post-hoc analysis, patients with advanced NSCLC across multiple PD-L1 ≥50% subgroups, CEMI resulted in significant overall improvement and delayed TTD in GHS/QoL and multiple patient-reported cancer-related and lung cancer-specific functions and symptoms. Positive PRO results further support the favourable benefit-risk profile of CEMI monotherapy versus CHEMO in advanced NSCLC across all the subgroups with PD-L1 ≥50%.

Keywords: non-small cell lung cancer, patient-reported outcomes, cemiplimab

P1.15 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.15-13 Immune Escape Mechanisms Mediated by B-Catenin in Non-small Cell Lung Cancer

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Introduction: Tumor intrinsic immune escape mechanisms have attracted attention as a mechanism of resistance to immune checkpoint inhibitors. We have previously reported that lung cancers overexpressing b-catenin have a poor prognosis due to low infiltration of antigen-presenting cells and lymphocytes into the tumor. Although mechanisms of resistance to immune checkpoint inhibitors by b-catenin have been reported in other cancers, it was not clear whether similar mechanisms exist in non-small cell lung cancer. In this study, we aimed to clarify the relationship between b-catenin expression and therapeutic efficacy of immune checkpoint inhibitors.

Methods: We analyzed the relationship between b-catenin expression and therapeutic effect by immunohistochemistry in 50 non-small cell lung cancer patients treated with anti-PD-1 antibody monotherapy at our department. Gene expression analysis was also performed by microarray, and RT-PCR was performed using lung cancer cell lines in vitro.

Results: Ten (20%) b-catenin-positive patients had a poorer prognosis than the negative patients in both PFS (HR 0.37, P=0.02) and OS (HR 0.31, P<0.01) with anti-PD-1 antibody monotherapy compared with the negative patients. The positive rates of CD8-positive and CD11c-positive cell infiltration into the tumor epithelium were significantly lower in the b-catenin-positive group (20% and 30%) compared to 65% and 80% in the b-catenin-negative group, respectively. On microarray, b-catenin-positive cases had lower expression of *IFNG*, *CD8A*, *CD103*, *BATF3* and *CCL4* than b-catenin-negative cases. In vitro, the b-catenin-positive cell line LK-2 had higher expression of *ATF3* and suppressed expression of *CCL4* compared to the negative RERF-LC-A1 cell line. The addition of carboplatin and paclitaxel increased the expression of *CCL4*.

Conclusions: Non-small cell lung cancer patients overexpressing b-catenin showed poor response to treatment with anti-PD-1 antibody, so-called cold tumors. In non-small cell lung cancer, overexpression of b-catenin downregulates *CCL4* expression via *ATF3*, suggesting the existence of an immune escape mechanism that suppresses tumor infiltration by antigen-presenting cells. This immune escape mechanism could be at least temporarily lifted by the combination of chemotherapy.

Keywords: non-small cell lung cancer, beta catenin, immune checkpoint inhibitors

P1.16 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.16-01 Amivantamab and Lazertinib in Treatment-Naive EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)

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Introduction: The CHRYSALIS study (NCT02609776) is an ongoing Phase 1 trial evaluating the combination of amivantamab (ami) and lazertinib (laz) in patients with epidermal growth factor receptor (EGFR)-mutant (EGFRm) NSCLC. As previously reported, all 20 patients in the treatment-naive cohort who received ami + laz achieved a partial response (overall response rate of 100.0% [95% CI, 83.2-100.0]) after a median follow-up of 7 months (Cho *Ann Oncol* 2021; 31:S813; 1258O). Herein, we present updated results from this treatment-naive cohort.

Methods: The treatment-naive cohort enrolled patients who had NSCLC characterized by either EGFR exon 19 deletion (ex19del) or L858R activating mutations. Patients received 1050 mg IV ami (1400 mg, ≥80 kg) and 240 mg oral laz. Response was assessed by the investigator per RECIST v1.1. Circulating tumor DNA (ctDNA) analysis (Guardant 360) was performed on plasma samples collected prior to initiation of ami + laz therapy and again at cycle 3 day 1 (C3D1).

Results: Of the 20 patients in the treatment-naive cohort (median 62.5 years of age, 55.0% women, all Asian), 11 had EGFR ex19del and 9 had L858R NSCLC. As of Nov 2021, with a median follow-up of 22.3 months (range, 4.2-25.3), the median duration of response (mDOR) and median progression-free survival (mPFS) were not reached. At the time of data cutoff, 14 patients (70.0%) are progression-free and remain on therapy, including 9 of 11 (81.8%) with EGFR ex19del and 5 of 9 (55.6%) with L858R. Two additional patients with L858R remain on treatment after recent progression. The safety profile of ami + laz was consistent with previous reports, and no new safety signals were identified. Treatment-related adverse events (TRAE) of grade ≥3 severity occurred in 5 patients (25%). TRAEs leading to dose reduction of either ami or laz occurred in 7 patients, most commonly due to rash (n=4). One patient had TRAE of interstitial lung disease which led to treatment discontinuation. Baseline ctDNA analysis was performed on 18 of 20 patients; 15 of 18 patients had detectable EGFR activating mutations. Co-occurring somatic alterations included TP53 (n=10 patients), EGFR amplification (n=1), MET amplification (n=1), and JAK2 V617F (n=1); no correlation was observed between co-occurring alterations and response. At C3D1, activating EGFR mutations were not detected in any of the 15 patients with baseline positive ctDNA.

Conclusions: At a median follow-up of 22.3 months, mDOR and mPFS have not been reached in treatment-naive patients who were treated with ami + laz, with 70.0% of patients progression-free and ongoing treatment. Clearance of activating EGFR mutations in plasma was observed in all patients who had detectable ctDNA at baseline. The ongoing phase 3 MARIPOSA study (NCT04487080) is investigating ami + laz versus osimertinib as front-line therapy in EGFRm NSCLC.

Keywords: Amivantamab, Lazertinib, Treatment-naive

P1.16 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.16-02 Clinical Utility of ctDNA in Advanced NSCLC at Diagnosis or Where Insufficient Tissue Was Available, Based on the ESMO ESCAT Scale

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Introduction: Comprehensive genomic profiling (CGP) by next generation sequencing (NGS) of ctDNA can identify a wide spectrum of genomic alterations that range from driver oncogenic alterations with FDA/EMA approved targeted therapies for routine use, to other alterations with lack of evidence for actionability. We aimed to assess the clinical utility of NGS based ctDNA genomic profiling, based on the ESMO scale for clinical actionability of molecular targets (ESCAT), in a large prospective cohort of advanced NSCLC patients.

Methods: Advanced NSCLC patients were prospectively enrolled between Nov2015-May2021 in Gustave Roussy and Hospital Clinic of Barcelona. Blood samples were collected at different time points: at diagnosis, under therapy, or at progressive disease (PD), and analyzed by InVisionFirst®-Lung. Clinical data were extracted from medical records. We evaluated the detection of driver genomic alterations (GA) in ctDNA and the clinical utility for accessing targeted therapies (TT) according to ESCAT: a) *tier 1* ready for routine use (e.g. *EGFR* sensitizing mutation (m), b) *tier2* investigational (e.g. *MET* amplification *(amp)*), and c) *tier3 (*e.g. *KRAS nonG12C).*

Results: Of 992 samples collected from 615 patients, we report here the treatment-naïve cohort N=211 patients (n=56 with insufficient tissue for molecular profiling): 103 (49%) were females, 67 (32%) nonsmokers, with median age of 65 (28-88) and 137 (65%) had adenocarcinoma histology.Overall, ≥1 ctDNA GA was found in 74% patients (154/208; 3 failed). Based on ESCAT: 29% of ctDNA positive cases (44/154) carried an ESCAT tier1 GA (25 *EGFRm*, 1 *ALKr*, 1 *ROS1r*, 14 *BRAFV600Em, 3 METm*), 19% tier2 (18 *KRASG12C*m, 6 *EBBR2*m, 3 *EGFRex20*m, 2 *MET*amp) and 19% tier3 (27 *KRASnonG12Cm*, 2 *BRAFnonV600*m, *1 FGFR1amp*). The clinical utility of ctDNA for TT in routine clinical practice was 21% (44/208). However, the clinical utility was 50% (103/208), including GAs giving access to investigational targeted therapies with preliminary clinical benefit reported. Of patients with tier1 (n=33) and tier2 (n=2) variants, who received TT, there was an objective response rate (ORR) of 89% (17/19 evaluable) and 50% (1/2 evaluable), respectively.Molecular analysis was performed exclusively in liquid biopsy in 56 patients (26%) who had insufficient tissue for analysis; in this cohort: 27 (48%) were females, 14 (25%) nonsmokers, with median age of 67 (28-86) and 36 (64%) adenocarcinoma histology.71% had ≥1 GAs (39/55; 1 failed): 15% (6/39) were ESCAT tier1 (5 *EGFRm* ex19/21, 1 *ROS1r*), 31% tier2 (12/39; 8 *KRASG12C*m, 3 *EBBR2*m, 1 *MET*amp) and 13% tier3 (4 *KRASm*, *1 FGFR1amp*).The detection of ctDNA to inform on the use of TT in routine clinical practice was impactful in 11% cases (6/55), but rose to 33% (18/55) when considering investigational TT. Five patients from tier1 received TT; ORR will be reported in the meeting.

Conclusions: In this cohort, 21% of unselected patients with advanced NSCLC had clinically actionable alterations used to guide TT in routine practice, including the cases with insufficient tissue for molecular testing. This rose to 50% when considering clinically informative GAs from tier2, where investigational targeted therapies may be considered.

Keywords: ctDNA, NSCLC, clinical utility

P1.16 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.16-03 Managing Cardiotoxicity in Metastatic Non-Small Cell Lung Cancer Patients Treated with Tyrosine Kinase Inhibitors (TKIs)

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Introduction: Current guidelines for prevention and monitoring cardiac dysfunction in patients with cancer state that there is insufficient evidence to support surveillance strategies for TKIs alone. Furthermore, risk stratification for baseline and frequency of monitoring remains unclear for various products. This study evaluates the current practice of screening and monitoring for cardiotoxicity in patients treated for non-small cell lung cancer (NSCLC) with TKIs and the adherence rate to the standards of care. An additional objective was to develop an institutional guideline to ensure patients were appropriately monitored throughout their therapy.

Methods: A single-center retrospective study of 113 patients with metastatic NSCLC who received TKIs at a large academic-community cancer center was performed. The current practice for screening and monitoring for cardiotoxicity and the adherence rate to the suggested standards recommended by the prescribing information of each drug were analyzed. Total incidence of cardiotoxicity was also evaluated. Descriptive statistics were calculated for all demographic variables and clinical outcome endpoints. Incidence of cardiotoxic adverse events were reported as percentages and a chi-square test to evaluate outcomes with and without adherence to the standards of care was performed. A literature review was conducted for guideline development.

Results: A total of 113 metastatic NSCLC patients were identified with the majority of patients taking osimertinib (67.3%) at baseline. Significant comorbidities at baseline included hypertension (47.8%), obesity (15.9%), diabetes (15%), and coronary artery disease (11.5%). Total adherence rate for screening and monitoring for cardiotoxicity as recommended by the prescribing information for all agents was 54%. A chi-square test of independence was performed to examine the relation between adherence and cardiotoxicity. The relation between these variables was insignificant (p=0.89). Cardiotoxicity occurred in 46 (40.7%) patients, presenting most frequently as hypertension and bradycardia. Decreased left ventricular ejection fraction (LVEF) ≥ 10% or to < 50% occurred in 6 (7.9%) patients on osimertinib; however, only 12 (15.8%) patients were able to be assessed due to lack of baseline data. QTc interval prolongation occurred in 2 (33.3%) patients on afatinib, 1 (20%) patient on crizotinib, and 1 (1.3%) patient on osimertinib. Three (3.9%) patients on osimertinib were diagnosed with atrial fibrillation. Forty-nine (43.4%) patients were on at least one high-risk QT prolonging agent at baseline with the majority taking ondansetron as needed for nausea and vomiting.

Conclusions: Our results showed higher rates of decreased LVEF and similar rates of QTc prolongation with osimertinib compared to prior studies. The increased rate of hypertension observed may be associated with the high rate of uncontrolled blood pressure at baseline. Low adherence rates to the recommendations provided by prescribing information may contribute to increased risk of cardiac dysfunction. An institutional guideline for patients with NSCLC on TKI therapy has been developed. The major components highlighted in the guideline include baseline and subsequent monitoring requirements, recommended dose adjustments, dose reduction schedules, and preferred antiemetics for patients at risk for QT prolongation. Appropriate patient management centered on cardiovascular risk factors and collaboration in cardio-oncology may mitigate overall cardiotoxic events.

Keywords: EBUS, NSCLC, next generation sequencing

P1.16 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS,
SUNDAY, AUGUST 7, 2022 - 17:00–19:00

P1.16-04 Phase 3 EVOKE-01 Study of Sacituzumab Govitecan vs Docetaxel in NSCLC After Prior Platinum and Checkpoint Inhibitors

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Introduction: Single-agent chemotherapy, such as docetaxel, is the standard of care in patients with metastatic NSCLC who progressed on platinum-based therapy and checkpoint inhibitors. However, docetaxel is associated with poor survival (median overall survival [OS] of <1 year); thus, novel agents are needed to further improve outcomes in this setting. Sacituzumab govitecan (SG) is an antibodydrug conjugate composed of an anti-Trop2 antibody coupled to the cytotoxic SN38 payload via a proprietary, hydrolyzable linker. In a single-arm expansion of the phase 1/2 IMMU-132-01 basket study of advanced epithelial cancers (NCT01631552), SG demonstrated an objective response rate (ORR) of 17% and median OS of 9.5 months, with a manageable safety profile in 54 patients with metastatic NSCLC who had multiple prior therapies (Heist RS, et al. *J Clin Oncol*. 2017). EVOKE-01 randomized phase 3 study was designed to further evaluate SG in patients with metastatic NSCLC.

Methods: EVOKE-01 (NCT05089734) is an open-label, global, multicenter, randomized, phase 3 study comparing the efficacy and safety of SG vs docetaxel in patients with metastatic NSCLC. Key eligibility criteria include age ≥18 years, pathologically documented stage IV NSCLC at time of study entry, and progression after platinum-based chemotherapy and anti-PD(L)1 therapy given either in combination or sequentially. Patients with EGFR, ALK, or other known actionable genomic alterations must have also received treatment with ≥1 approved appropriate TKI. Other inclusion criteria are ECOG performance status 0-1 and adequate hematologic, hepatic, and renal function. Patients with prior treatment with topoisomerase inhibitors are excluded. Patients are randomized 1:1 to receive intravenous SG (10 mg/kg on day 1 and 8) or docetaxel (75 mg/m^2 on day 1) in 21-day cycles until progressive disease or unacceptable toxicity. Stratification is based on predominant histology (squamous vs nonsquamous), best response to prior immune therapy (PD/SD vs CR/PR), and prior therapy for actionable genomic alteration (yes vs no). The primary endpoint is OS. Key secondary endpoints include progression-free survival, ORR, duration of response, and disease control rate, as assessed by investigator RECIST v1.1, mean change from baseline in NSCLC-SAQ total score and shortness of breath, and safety. This study plans to enroll ~520 patients globally and is open for recruitment.

Keywords: antibody-drug conjugate, immune checkpoint inhibitors, phase III clinical trial

P2.01 METASTATIC NON-SMALL CELL LUNG CANCER - OLIGOMETASTATIC DISEASE,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.01-01 Association Between Clinical Outcomes and Local Treatment in Stage IV Non-small Cell Lung Cancer Patients with Single Extrathoracic Metastasis

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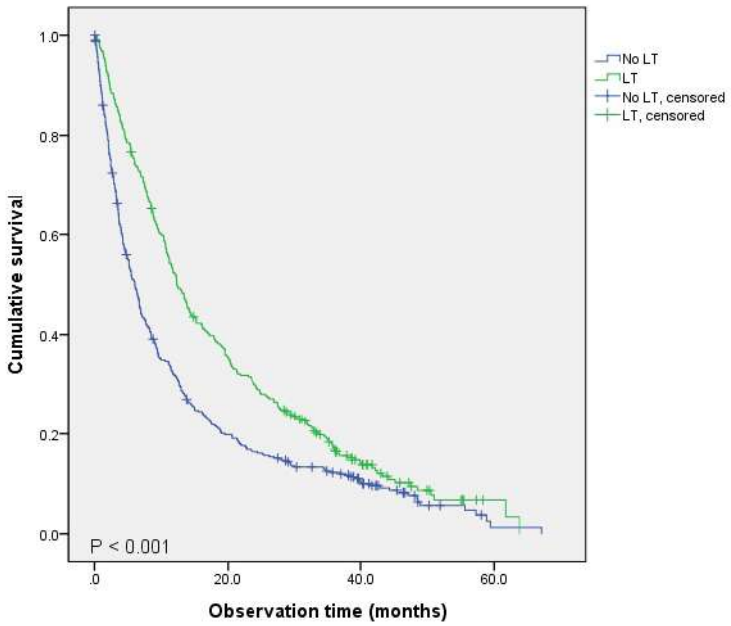
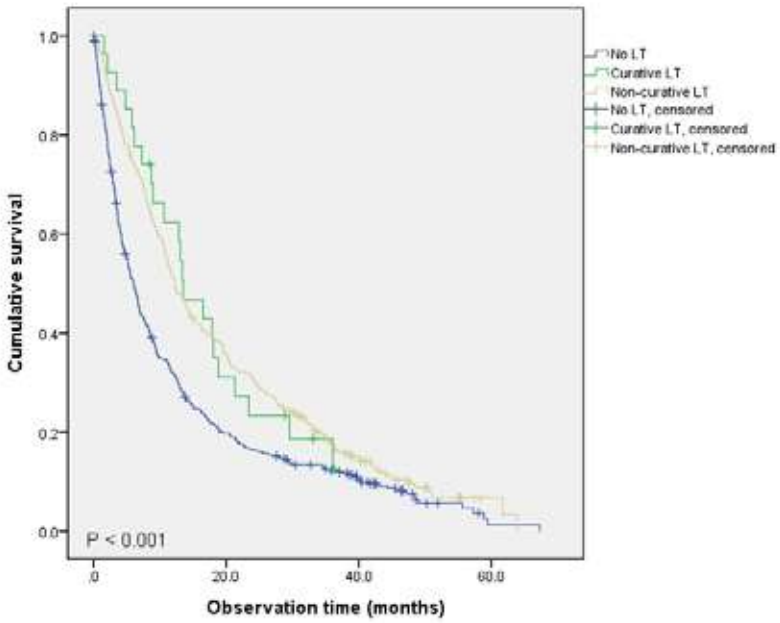
Introduction: Local treatment (LT) such as radiotherapy and metastasectomy on metastatic sites may improve outcomes in oligometastatic NSCLC patients, but more data are necessary to support LT in oligometastatic diseases. Patients with single extrathoracic metastatic lesion are more likely to benefit from local therapy. In this study, we evaluated the impact of LT in NSCLC patients with a single extrathoracic metastatic lesion.

Methods: Data were obtained from the Korean Association for Lung Cancer Registry (KALC-R), a database created using a retrospective sampling survey by the Korean Central Cancer Registry (KCCR) and the Lung Cancer Registration Committee.

Results: A total of 787 NSCLC patients with a single extrathoracic metastatic lesion were evaluated. In the multivariate analysis for OS, age, female sex, poor performance score, squamous histologic subtype, LT, and initial treatment modality showed significant associations. Regarding LT, groups that underwent curative LT showed significantly associated with better OS compared to groups that did not undergo LT (P=0.011, HR 0.448, 95% CI: 0.242-0.829). In the multivariate analysis of patients who underwent LT, poor performance score, initial treatment modality, and T stage were independently associated with poor OS. Compared to the T1 stage, T3 stage showed an HR of 2.470 (95% CI: 1.309-4.663; P=0.005) and T4 stage showed an HR of 2.063 (95% CI: 1.093-3.904; P=0.026).

Conclusions: In NSCLC with a single extrathoracic metastatic lesion, LT, especially for curative purposes, has an independent association with OS. Moreover, among the patients who received LT, factors such as T stage, poor performance score, and initial treatment modality were significantly associated with OS.





Keywords: oligometastasis, radiotherapy, non-small cell lung cancer

P2.01 METASTATIC NON-SMALL CELL LUNG CANCER - OLIGOMETASTATIC DISEASE,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.01-02 Delivery of Concurrent Extracranial Stereotactic Body Radiotherapy with Osimertinib for Oligoprogressive EGFR Mutated Stage IV NSCLC

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Introduction: Osimertinib is a third generation Tyrosine Kinase Inhibitor (TKI) and is considered first line therapy for patients with metastatic Epidermal Growth Factor Receptor (EGFR) NSCLC with exon 19 deletion or exon 21 L858R. Osimertinib has demonstrated improved progression free survival (PFS) and overall survival (OS) compared to first generation TKI's. However, during the course of their disease many patients develop oligoprogressive disease (OPD): <=3 metastatic lesions with otherwise controlled systemic disease. In our institution, SBRT is often recommended in these scenarios in an attempt to extend time to a new systemic agent. We herein, report our outcomes with this novel approach.

Methods: Patients receiving Osimertinib for EGFR positive Stage IV NSCLC receiving SBRT for OPD were identified in our IRB-approved registry. Outcomes included local control (LC), time to progression (radiographic and time to new systemic agent), OS and treatment-related toxicity were determined.

Results: Of a total 69 patients with metastatic EGFR positive NSCLC (with exon 19 deletion or exon 21 L858R) NSCLC in our registry, 18 patients received extracranial SBRT at the time of oligoprogression (median age 65 at time of SBRT, 50% female). Prior to Osimertinib, 5 patients (27.7%) were treated with first/second generation TKI and 3 (16.7%) with chemotherapy. Median time from start of Osimertinib to SBRT was 31.9 weeks. Dose fractionation schemas included 45-54Gy in 3 fractions, 48Gy in 4 fractions, 40-50 Gy in 5 fractions, 60 Gy in 8 fractions. In total, 26 lesions were treated of which: lung (n=19), adrenal (4), spine (1), liver (1), rib (1). At median of 10.8-month follow-up from SBRT, LC was achieved in 88.9% of treated lesions, PFS of 27.7% and OS of 88.8%. 10 patients (55.5%) progressed with first sites including 8 distantly and 2 who progressed both distantly and locally. 6 patients (33.33%) received another course of salvage SBRT. Of those who progressed, median time to radiographic progression after SBRT was 5.333 months and the median time to systemic treatment change was 7.61 months. At a median follow up of 6.8 months, 8 patients (44.44%) showed no evidence of radiographic progression. Treatment with SBRT was well tolerated with no grade 3-5 toxicity.

Conclusions: Our initial experience suggests that SBRT for OPD in EGFR mutated Stage IV NSCLC patients while on Osimertinib appears to be safe and may lengthen time until need for systemic therapy change. Further prospective study into this novel approach is warranted.

Keywords: Oligoprogression, SBRT, Osimertinib

P2.02 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE CHEMOTHERAPY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.02-01 Value of Albumin-to-Globulin Ratio for Survival Prediction in Advanced Stage Non-Small Cell Lung Cancer Treated with Chemotherapy

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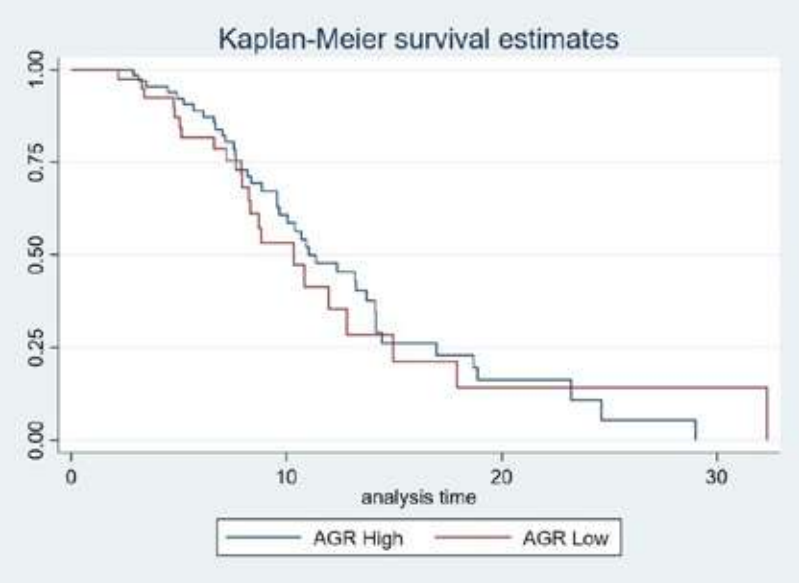
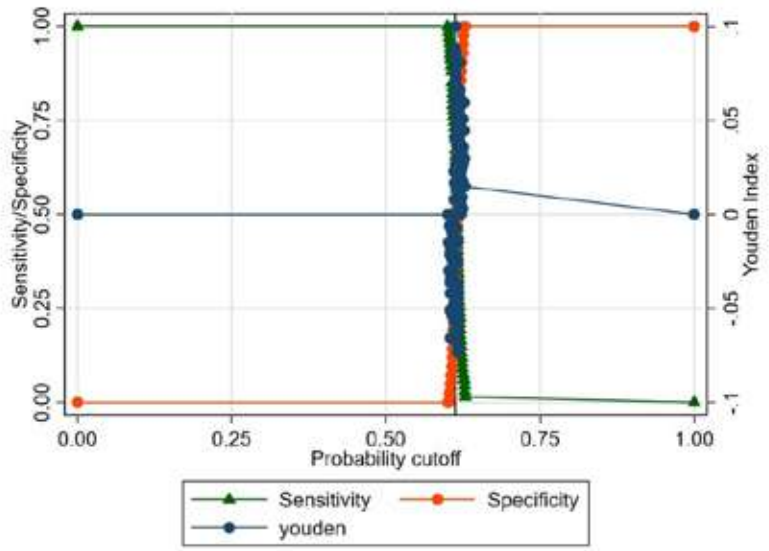
Introduction: According to previous data, pretreatment albumin-to-globulin ratio (AGR) was a simplified biomarker that was an independent prognostic factor in lung cancer, but there are no data on the use of AGR as a prognostic factor in metastatic non-small cell lung cancer (NSCLC) treated with chemotherapy. The aim of this study was to determine whether AGR can be used as a prognostic factor under these conditions.

Methods: Data from 109 patients who had received complete first-line chemotherapy were analyzed. Estimate the optimal cutoff point of AGR using the Youden 's index. A multivariate complex survival analysis was used to explore independent prognostic factors including AGR and clinical factors, i.e., gender, elderly patients, ECOG performance status (ECOG PS), tumor grading, anemia (hemoglobin< 12 g/dL), initial brain metastases at diagnosis. The correlation between AGR and short-term survival was assessed by regression analysis.

Results: The median overall survival (mOS) was 10.9 months. The optimal cutoff point of AGR was 1 according to the Youden's index. The mOS of patients with a low AGR (less than 1) was shorter than patients with a high AGR (greater than or equal to 1) (10.3 months versus 11.0 months). A multivariate flexible parametric proportional-hazards model with restricted cubic splines (RCS) revealed that poorer ECOG PS was a single strong independent prognostic factor for poor survival in patients receiving chemotherapy. The relationship between low AGR and short-term survival, defined as survival shorter than mOS, was analyzed using univariate and multivariate regression analyzes, it was found that low AGR associated with short-term survival (clude odds ratio 2.68, 95%CI 1.03-6.94, P=0.04) (adjusted odds ratio 2.59, 95%CI 0.98-6.83, P=0.05).

Conclusions: The low AGR, which is measured in routine clinical practice, was associated with short survival in metastatic NSCLC treated with chemotherapy and had a tendency to be a simplifying prognostic factor.





Keywords: Albumin-to-Globulin Ratio, Prognostic factor, Advanced stage non-small cell lung cancer

P2.02 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE CHEMOTHERAPY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.02-02 A Phase 2 Study of MLN4924 (Pevonedistat) in Combination with Carboplatin and Paclitaxel in Advanced NSCLC Previously Treated with Immunotherapy

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Introduction: Development of combination strategies to overcome resistance in previously treated patients is an area of unmet need in advanced non-small cell lung cancer (NSCLC). The neddylation pathway represents a promising therapeutic target by which to restore efficacy of cytotoxic chemotherapy. Upregulation of this pathway, which is a sub-component of the ubiquitin-proteosome system and plays a role in protein degradation, has been observed in NSCLC, with higher expression associated with poorer overall survival. Pevonedistat (MLN4924), a first-in-class small molecule NEDD8-activating enzyme (NAE) inhibitor, inhibits neddylation which in turn affects proteosome function and leads to cell death. The combination of carboplatin/paclitaxel/pevonedistat has been investigated in the phase I setting in solid tumors. Consistent with preclinical studies reporting synergy between pevonedistat and platinum-based chemotherapy, the objective responses in patients resistant to prior platinum suggest the potential reversal of resistance.

Methods: This is a phase 2, single arm, multicenter study of pevonedistat 20mg/m2 IV Days (D) 1, 3, 5 + carboplatin (AUC=5) D1 and paclitaxel 175mg/m2 D1 every 21 days in patients with advanced NSCLC conducted through the NCI Experimental Therapeutics Clinical Trials Network (ETCTN). Eligible patients must have had progression on or after platinum-based chemotherapy and checkpoint inhibitor therapy. After 4 cycles, pts were able to continue on a) carboplatin, paclitaxel, pevonedistat; b) carboplatin, pevonedistat; or c) observation. The primary endpoint was overall response rate (ORR) per RECIST 1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. Correlative studies to assess circulating tumor cells (CTCs) for DNA damage repair pathway alterations (γH2AX induction), PD-L1, and HLA were performed at baseline, cycle 3, and progression.

Results: From 4/2020 to 7/2021, 28 patients were enrolled, of whom 25 were eligible and treated. Three patients were enrolled but did not start treatment. The median age was 64 years and 56% were male/44% female. Most patients had nonsquamous histology (88%). 40% had received 1 prior line of systemic therapy; 60% had received ≥ 2 prior lines. The most common prior checkpoint inhibitor was pembrolizumab (64%); four patients received > 1 prior checkpoint inhibitor. ORR was 24% (95% CI: 0.11-43%), stable disease: 56%, PD: 12%, not assessed: 8%. Secondary endpoints PFS, OS, safety will be reported. Out of 25 patients anticipated to be sampled at 3 time points each, only 37 total samples were successfully evaluated for CTC yH2AX, PD-L1 and HLA I, due either to C3 timepoints not being reached or delayed/missing shipments. Lower CTC numbers were detected in samples from responding patients, with a cohort-wide decrease over time reflecting those with time on therapy having lower numbers of CTCs. yH2AX foci were detected in 6/30 samples with detectable CTCs, not reaching high enough detection levels to evaluate clinical utility. Cohort-wide decrease in HLA I over time but increase in PD-L1 may reflect accumulation of resistant clones (HLA I-/PD-L1+).

Conclusions: In patients with NSCLC who have had progression on prior platinum and checkpoint inhibitor therapy, pevonedistat/carboplatin/paclitaxel led to promising activity and the study met its primary endpoint. Safety data will be reported (NCT03965689).

Keywords: Non-small cell lung cancer, Pevonedistat, Chemotherapy

P2.02-03 A Phase II Study of Metformin with Pemetrexed/Carboplatin in Patients with Metastatic Non-Squamous Non-Small Cell Lung Cancer

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Introduction: There is a subset of NSCLC patients ineligible for benefit from TKIs/Immunotherapy (e.g. STK11 mutation conferring resistance to Immunotherapy). Besides, many patients cannot afford these therapies. Metformin has anticancer properties acting both on glycolytic metabolism and tumor microenvironment. In vitro studies suggest synergism between metformin and pemetrexed. STK11 deficient cell lines are more sensitive to metformin. Clinical studies combining metformin with chemotherapy are limited by small sample size. We conducted an exploratory phase-2 clinical trial of metformin with pemetrexed/carboplatin in advanced non-squamous NSCLC.

Methods: This was a single center, open label, single arm phase 2 clinical trial with a Simon's two stage design. The null hypothesis was that the combination would not improve the 6-month PFS rate by 15%, from 50%. Treatment-naive, non-diabetic patients aged 18-75 years with NSCLC (adenocarcinoma/not-otherwise-specified) with stage IV disease having ECOG PS 0-2 with unmutated EGFR/ALK and without brain metastasis or with asymptomatic brain metastases were treated with pemetrexed-carboplatin chemotherapy and metformin for six months. The primary outcome was 6-month progression free survival (PFS) rate. Secondary outcomes were safety, overall survival (OS), overall response rate (ORR), proportion of STK 11 mutation and effect of STK 11 mutation on 6-month PFS rate. PFS and OS were estimated using the Kaplan-Meier method. Targeted sequencing was attempted for available tissue specimens.

Results: The first interim analysis was performed after enrollment of 26 patients for the first stage (before the target accrual of first stage was reached) due to slow accrual, in view of COVID pandemic. The study was terminated after first stage for futility. The median age of patients in the study was 52 years (range, 30 to 68) and 18 patients (69.0%) were males. Half of the patients had ECOG-PS 2. Brain metastases were present in eight (31%) patients and among these four (50%) were symptomatic at presentation. The median follow-up time was 25 months. The median PFS was four months. 6-month PFS rate was 28% (95% CI - 0.12 to 0.46). Of the 25 evaluable patients, five (20%) had a partial response, and eight (32%) had stable disease; 13 (52%) of the patients had disease control. The median OS was 16 months. During combined therapy, 14 (54%) and 3 (11%) patients had any grade and grade 3 anemia respectively. One patient had grade 3 neutropenia. Among non-hematological toxicities, gastrointestinal toxicities (nausea, vomiting and diarrhea) were the most common. No grade 4 toxicities were reported. There were no treatment discontinuations, however treatment delay due to grade three toxicities was present in two patients. Dose modification for Metformin was required in four patients. Targeted Sequencing was possible in nine cases. Two of these patients had STK11 mutation and an associated bad outcome (PFS < 2 months).

Conclusions: We could not demonstrate the benefit of combination of Metformin with pemetrexed-carboplatin in terms of improvement in 6-month PFS rate. The addition of metformin to pemetrexed-carboplatin has an acceptable safety profile. Future trials should test metformin in specific subsets (STK11 mutated) and in combination with immunotherapy and TKIs.

Keywords: Metformin, NSCLC, STK11

P2.03 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE RADIOTHERAPY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.03-01 Initial Biodistribution Data of ImmunoPET A Phase 0/1 Study Characterising PD-L1 with 89 Zr-Durvalumab (MEDI4736) PET/CT

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Introduction: ImmunoPET is a multicentre, single arm, phase 0-1 study investigating the use of ^{89}Zr-durvalumab PET/CT to interrogate the expression of PD-L1 in patients with NSCLC. We present the initial biodistribution data, which is being used to establish the safety and scan timepoints for a multicentre study in Stage III patients.

Methods: The Phase 0 study is recruiting 5 PD-L1+ patients with metastatic NSCLC, who receive 60MBq/70kg ^{89}Zr-durvalumab up to a maximum of 74 MBq, with scans at day 0, 1, 3 or 5±1 day. Baseline FDG PET/CT is also performed 7 days prior to injection of ^{89}Zr-durvalumab. Data on 1) Percentage of injected ^{89}Zr-durvalumab dose found in organs of interest (%ID) 2) Absorbed organ doses (μSv/MBq of administered ^{89}Zr-durvalumab) and 3) Whole-body dose expressed as mSv/100MBq of administered dose from our initial 2 patients are presented here.

Results: 4 patients have been recruited to the Phase 0 study, with no significant toxicity observed after tracer injection. 1 patient had a transient infusion reaction, developing tachypnoea that resolved within 1 hour after dexamethasone and anthistamines. ^{89}Zr-durvalumab uptake increases from Day 0 to 5 post-injection in accordance with the long half-life of durvalumab (Figure 1). Normal biodistribution is characterized at 5 days by high levels of whole body retention (mean 84%), low kidney uptake (mean 0.795 and 0.785 %ID for right and left kidney respectively), and rapidly diminishing circulation in blood pool (mean 3.95 at Day 5). A small diminishment in bone uptake from 12.05 to 10.3 %ID is also observed over 5 days.

Conclusions: Initial biodistribution data suggests that the optimal scan timepoint is Day 5. Favourable avidity is observed in PD-L1 positive metastatic lesions in comparison to normal organs with minimal toxicity, supporting the evaluation of this tracer in a planned, multicentre trial in Stage III NSCLC patients.

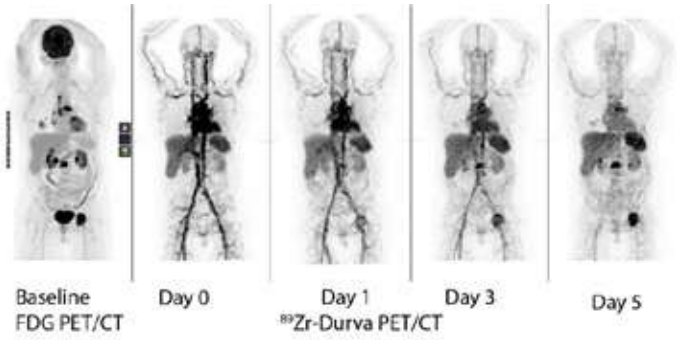

Figure 1: FDG-PET CT (far left) demonstrates metastatic lesions in the lumbar spine, ribs, right pelvis and mediastinum. Day 0-5 89Zr-durvalumab imaging demonstrates increasing uptake in tumour sites with decreasing blood pool, reduced bone marrow and stable liver and spleen uptake.

	2 hour scan			24 hour scan			72 hour scan			Day 5 scan		
Patient	**1**	**2**	**Mean**	**1**	**2**	**Mean**	**1**	**2**	**Mean**	**1**	**2**	**Mean**
Tumor Site 1 - SUVmax	6.6	2.9	4.75	17	5.5	11.25	33	5.5	19.25	37	7.3	22.15
Tumor Site 2 - SUVmax	6.8	7.6	7.2	12	14	13	17	15	16	24	18	21
Blood pool SUVmean	17	13	15	10	6.9	8.45	9	4.2	6.6	6.2	1.7	3.95
Whole Body Retention (%ID)	100	88	94	97	86	91.5	98	79	88.5	92	76	84
Bone %ID	11	13.1	12.05	11	11	11	11	10	10.5	11	9.6	10.3
Liver %ID	13	14	13.5	13	14	13.5	14	14	14	13	19	16
Spleen %ID	1.9	3	2.45	1.9	2.7	2.3	2.4	2.4	2.4	2.2	2.7	2.45
RT Kidney %ID	0.8	0.89	0.845	0.7	0.9	0.8	0.94	0.7	0.82	0.94	0.65	0.795
LT Kidney %ID	0.9	0.88	0.89	0.8	1	0.9	0.94	0.7	0.82	0.97	0.6	0.785

Table 1: Initial analysis of biodistribution data within the first 5 days.

Keywords: Non Small Cell Lung Cancer, PET imaging, Immunotherapy

P2.04 NURSING AND ALLIED HEALTH PROFESSIONALS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.04-01 Lung Cancer Patient Experience Survey from Twelfth Central and Eastern Europe Countries

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Introduction: Croatian Coalition of Associations in Healthcare distribute an online Cancer Patient Experience Survey with aim to identify areas that need to be addressed. Initiative was supported by national patient's oncology associations from twelfth Central and Eastern Europe countries.

Methods: Sixty-nine item online survey was translated on native language participating countries. Only registered members (subjects with confirmed cancer diagnosis) of the national patient oncology associations in each participating country were allowed to access and complete the online questionnaire (n=16,458). Data were collected between Oct. 2018 to Feb. 2019. In this abstract will be presented data of lung cancer patients (n=2,034).

Results: from lung cancer sample: in nine countries (range 12% to 65%) patients reported that delivery of bad news was done on sensitively way. In ten countries (range from 5% to 38%) patients were definitely explained possible side effects of treatment(s) (short term and long term) on understandable way and in ten countries (range from 5% to 35%) were offered practical advice and support in dealing with the side effects of oncology treatment(s). In nine countries more than half (range from 53% to 71%) participants confirmed that they didn't received enough care and support from health or social services (for example, district nurses, home helps, psychological support) during their cancer care. Lung cancer patients were asked to rate their overall cancer care (with "0" being the lowest, and "10" the highest score) in all countries patients that rated their care positively (7 or higher) was in range from 4% to 45%.

Conclusions: This study adds to the current understanding of cancer patient experience in Central and Eastern European countries and based on obtain data there is a large room for improvement. Effective communication skills in healthcare sector are essential for patient experience and essential for the overall quality and safety care. Based on this study we do believe that every structured investment of resources can bring beneficial effects on patient outcomes such as patient satisfaction, well-being, and quality of life and that are aspects that should not be ignored.

Keywords: Lung cancer, Patients experience

P2.04 NURSING AND ALLIED HEALTH PROFESSIONALS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.04-02 Psychosocial Burdens in Cancer Caregivership, an Updated Overview

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Introduction: Carers of cancer patients have a larger hardship than caregivers of older persons and a burden equivalent to caregivers of dementia patients. While carers' health has been demonstrated to worsen as a result of their caregiving for cancer patients, the psychological determinants of long-term health deterioration are less well understood.

Methods: The physical and sleep burdens, psychosocial and spiritual burdens, long-term and quality-of-life-related burdens, financial burden, bereavement burden, and caregiver guilt will all be discussed in our presentation, based on the most recent available data.

Results: Because depression is a long-term problem for this population, all of these findings suggest that cancer caregiver programs should include information on how to manage caregiver-related distress in the early survivorship phase, as well as how to best identify and recruit effective social programs to improve caregivers' personal and social resources in early survivorship. Furthermore, the diverse aspects of cancer care as well as the psychological elements of persons participating in cancer care at various phases of survivorship are crucial to increasing care effectiveness and optimizing the quality of life of survivors and caregivers.

Conclusions: Because informal caregivers play such an important role in cancer care, cancer policy is increasingly focusing on and recognizing the importance of providing effective and appropriate support to informal caregivers in managing the impact of their caregiving responsibilities on their regular jobs or other caregiving responsibilities.

Acknowledgement: Research funded by the Executive Unit for the Financing of Higher Education, Research, Development and Innovation (UEFISCDI)Registration number: PN-III-P1-1.1-TE-2019-0097

Keywords: cancer caregiver, psycho-social, distress

P2.04 NURSING AND ALLIED HEALTH PROFESSIONALS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.04-03 Perceptions and Knowledge of Electronic Smoking Devices among Patients with Solid Tumors and their Care-Givers

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Introduction: Smoking is the most important risk factor for solid tumors development. Cigarette smoke is responsible for 85% of lung cancer-related deaths. Approximately 1 over 4 Italians are active smokers, while 18% are former smokers. The spread of electronic smoking devices (ESDs) such as e-cigarettes and the so-called “heat-not-burn” (HnB), claimed by the tobacco industry as less toxic and potentially useful for quitting traditional smoking, poses new challenges for public health authorities, especially when dealing with the E-cigarette or vaping use-associated lung injury (EVALI) epidemic. However, public awareness on risk of ESDs is variable and few data are available from patients affected by cancer and their care-givers.

Methods: A survey about smoking habits, nicotine dependence and ESDs knowledge has been administered to patients affected by solid tumors treated at S.Luigi Gonzaga Hospital (Orbassano, Italy). The questionnaire was administered by the nursing staff who offered support in filling out the form. The same questionnaire was also administered to care-givers. Results were analysed using frequency distribution. The Fagerström Test for Nicotine Dependence (FTND) was used to assess nicotine dependence in active smokers.

Results: From June to September 2021, 80 subjects were recruited (62 patients; 77.5%), and 97.5% completed the questionnaire. 51% of participants were males, 56% aged 56-75 years-old, and 74% had a middle or high school degree. 44% were former smokers, 15% were active smokers (30% with high or very high nicotine dependence according to FTND. Most patients were affected by lung (35%) and prostate (24%) tumors. 20% of participants have tried E-cigs and 40% were daily users. 39% knew at least one type of ESD, but only 12% had some knowledge about their components. 53% and 58% of participants did not have any opinion about E-cigs and HnB potential harms, respectively. Notably, 41% did not think that ESDs could be useful for quitting traditional smoking, while 28% did. 51% reported that ESDs could push never smokers to traditional smoking.

Conclusions: Both oncological patients and their care-givers showed fair knowledge of ESDs. However, most of them do not have any perception of their potential harms. Interestingly, half of participants report some fears about the potential role of ESDs as a bridge to tobacco smoke. These results may be useful for designing awareness campaign on ESDs harms for oncological patients and their care-givers where nursing role will be pivotal.

Keywords: electronic smoking devices, solid tumors, perceptions and knowledge

P2.04 NURSING AND ALLIED HEALTH PROFESSIONALS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.04-05 Is Opioid Use in the Management of Stage III Non-Small Cell Lung Cancer Patients Necessary?

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Introduction: In 2019, 70,000 people in the United States overdosed on opioids, with thousands more dependent on these highly addictive substances.[1] With the recognition of the opioid epidemic, physicians have been turning to alternative pain medications to address cancer pain and treatment-related side effects. There are little data, however, to guide care teams on how to best manage treatment-related pain in curative stages of Non-Small Cell Lung Cancer (NSCLC).[2,3]

Methods: In this retrospective chart review, 85 patients with unresectable stage III NSCLC treated within our multi-site clinical practice were evaluated between October 2017 and December 2021. Patients were included if they were undergoing radiation therapy with concurrent chemotherapy and had medication logs available for review. Fifty-six patients met inclusion criteria. Each patient's medication log was examined and all prescriptions or self-reported over-the-counter use of analgesics or analgesia analogues were recorded, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), dexamethasone, and proton pump inhibitors (PPIs).

Results: Of the 56 patients, 11 patients (19.6%) were on oxycodone or morphine only; 8 patients (14.3%) were on ibuprofen, acetaminophen, or tramadol with or without a PPI; 4 patients (7.1%) were on a PPI and gabapentin; 12 patients (21.4%) were on either a PPI and dexamethasone, a PPI alone, or a PPI and Magic Mouthwash/Carafate; 3 patients (5.4%) were on dexamethasone only; and 18 patients (32.1%) were on no recorded analgesics. In total, 45 of the 56 patients (80.4%) were not on any opioid medications.

Conclusions: Most patients with unresectable stage III NSCLC undergoing chemoradiation were able to manage their pain without the use of opioids by relying on adjuncts such as NSAIDs, PPIs, and steroids. Future studies should examine pain management regimens in a randomized control trial to better assess the efficacy of non-opioid pain medications.

Observed pain regimens in Stage III NSCLC patients undergoing definitive chemoradiation

Pain Regimen	Number of Patients	Percentage
Oxycodone or morphine	11	19.6%
Ibuprofen, acetaminophen, or tramadol with or without a PPI	8	14.3%
PPI and gabapentin	4	7.1%
PPI and steroids, PPI alone, or PPI and Magic Mouthwash	12	21.4%
Steroids only	3	5.4%
No medication	18	32.1%

Keywords: NSCLC, Chemoradiation, Opioids

P2.05 PALLIATIVE AND SUPPORTIVE CARE,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.05-01 The Effect of Treadmill Training on Cardiopulmonary, Health-related Quality of Life in Lung Cancer with Lobectomy

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Introduction: Patients with lung cancer are often deconditioned and may have poor cardiopulmonary fitness (CPF). Lung resection surgery further reduces the CPF. To our knowledge, only four studies have assessed the exercise capacity after lung resection surgery using cardiopulmonary exercise test (CPET) and prescribed exercise intensity according to the measured VO_2max. However, these studies used a cycle ergometer or combined exercise with resistance training. There has been no study to apply only treadmill training for pulmonary rehabilitation, the implementation of which was based on CPET-measured VO_2max. Therefore, we aimed to evaluate how CPET-based treadmill training could affect the cardiopulmonary function, psychological function, and HRQoL in patients with lung cancer who underwent lobectomy.

Methods: This prospective, single-group, controlled before and after study was designed to determine the effectiveness of treadmill training in patients with lung cancer who underwent lobectomy. Four weeks after discharge, the cardiovascular function of the participants was assessed using the CPET and 6MWD tests. In addition, questionnaires on the physical function using the Korean Activity Scale/Index (KASI), psychological function for assessment of depression using Patient Health Questionnaire (PHQ-9), for assessment anxiety using Generalized Anxiety Disorder Screener (GAD-7), for assessment fatigue using Fatigue Severity Scale (FSS), for assessment sleep problem using Pittsburgh Sleep Quality Index-Korean version (PSQI-K), and for assessment of HRQoL using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer (EORTC QLQ-LC13), and Functional Assessment of Cancer Therapy-General (FACT-G) were conducted. After the successful completion of the baseline assessments, all the participants were scheduled for immediate supervised treadmill training. After a period of 12 weeks, all the assessments were performed again.

Results: Significant changes were observed in the VO_2max, 6MWD, and KASI from baseline to postintervention. The mean VO_2max and 6MWD increased by 5.3 mL/kg/min and 71.2 m, respectively, and the mean KASI increased by 22.7 points (P<0.01). The PHQ-9, GAD-7, and PSQI-K showed significant improvements after treadmill training. The mean PHQ-9, GAD-7, and PSQI-K scores decreased by 3.5, 1.6, and 2.2 points (P<0.01), respectively. In the HRQoL, significant changes were observed in the EORTC and FACT-G physical and FACT-G emotional domains. The mean of the EORTC and FACT-G physical domain decreased by 3.7 and 3.6 points, respectively (P<0.01). The emotional domain of FACT-G decreased 2 points after treadmill training and showed a statistically significant improvement(p=0.033).

Conclusions: In conclusion, this pilot study provided evidence that individualized tailored treadmill training is effective in improving the cardiopulmonary function and psychological aspects, such as anxiety, depression, and HRQoL, in lung cancer patients who underwent lobectomy.

Keywords: lung cancer, treadmill training, quality of life

P2.06 PATHOLOGY - TUMOUR DIAGNOSTICS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.06-01 Skip Hilar Lymph Node Metastasis in Non-Small Cell Lung Cancer Has Similar Survival to N0 Disease: Need for a Change in the pN Sub-classification?

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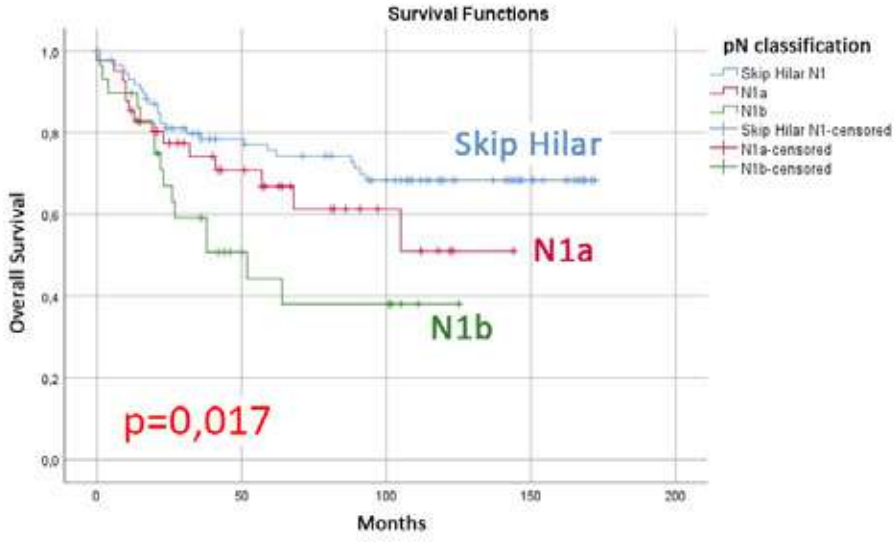
Introduction: Previous edition of TNM lung cancer staging system divided N1 disease into two subgroups: N1a and N1b. Our study aimed to investigate the survival difference between patients with hilar lymph node metastasis only (skip metastasis) and other N1a patients.

Methods: Patients with NSCLC who were operated between February 2003 and February 2019 were retrospectively analyzed. Patients who have oligometastases or neoadjuvant treatment were excluded. A total of 629 patients were investigated in terms of lymph node metastasis status. Overall survival (OS) of skip hilar was compared to N0 and other N1 patients. Kaplan Meier was used for the analysis with 95% confidence intervals.

Results: There were 470 patients with N0 disease. Patients with N1 disease (n=159) were divided into three groups. Group 1 has 89 skip hilar lymph node metastasis, Group 2 has 41 patients with N1a disease without the skip hilar metastasis and Group 3 has 29 patients with N1b disease. OS of the patients with skip hilar lymph node metastasis was 129 months (95% Confidence Interval: 114-143 months) similar to N0 patients with an OS of 133 months (95% Confidence Interval: 125-142 months) (p=0,013). This was statistically significantly better than N1a and N1b patients (p=0.017). The OS of Group 2 was 95 months (95% Confidence Interval: 75-115 months) and Group 3 was 65 months (95% Confidence Interval: 44-84 months).



Conclusions: Skip hilar lymph node metastasis has a similar survival to N0 disease and is significantly better than non-skip N1 disease. Therefore we are suggesting a change in pN sub-classification for the 9th edition of TNM staging studies. We suggest that patients with skip hilar lymph node metastasis should be staged as pN1a1. The mechanism behind this prognostic advantage and verification of our findings need further studies with larger patient series.

Keywords: pN sub-classification, N1 disease, lymph node metastasis

P2.07 PATHOLOGY - TUMOUR GENOMICS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.07-01 Deep-Learning Based Prediction of c-MET Status from Digitized H&E-Stained Non-Small Cell Lung Cancer Tissue Samples

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Introduction: Genetic profiling of non-small cell lung cancer (NSCLC) tissue has identified alterations in a number of genes, including *c-MET*. Dysregulation of c-MET, a receptor tyrosine kinase mesenchymal epithelial transition factor, is associated with worse prognosis. Therapeutics targeting c-MET such as the antibody drug conjugate (ADC) Telisotuzimab vedotin (Teliso-V) may be of benefit. Currently, immunohistochemical staining of tissue is used to determine whether c-MET protein is overexpressed. Here we report development of a machine learning (ML)-powered method that identifies features of the tumor microenvironment (TME) as predictors of c-MET overexpression status (positive vs. negative) directly from hematoxylin and eosin (H&E)-stained NSCLC samples.

Methods: Convolutional neural networks (CNNs), previously trained to characterize the NSCLC TME (Diao JA et al., *Nat Commun* 2021), were applied to H&E sections from a Phase 2 clinical trial (NCT03539536) and commercial sources. Digitized slides were split into training, validation, and test sets. The c-MET status was determined from pathologist scoring: cases with >= 25% c-MET positive tumor cells at 3+ intensity were labeled positive and all other cases were labeled negative. Quantitative characterizations of the TME were extracted from images to produce spatially resolved human interpretable features (HIFs) based on CNN predictions. HIFs were correlated with c-MET status using univariate logistic regression and grouped using agglomerative clustering with Pearson-R^2. The false discovery rate was corrected with the Benjamini-Hochberg and Empirical Brown's method. Multivariate logistic regression with Elastic Net regularization was used to predict c-MET status from HIFs. Further, we developed a graph neural network (GNN) model to predict c-MET status using a 5-fold cross validation strategy to select the optimal network hyperparameters.

Results: In the clinical dataset (n= 400), c-MET positive cases were significantly associated with a cluster of related HIFs that describe elevated immune cell densities, specifically lymphocytes, in tumor epithelium (e.g. c-MET positive was significantly associated with the density of lymphocytes within the cancer epithelium [p= 0.009], but not in stroma [p= 0.483]). We also independently confirmed this association on the commercial dataset (n= 82, p= 0.003). To assess whether these associations can be used to predict patient c-MET status, we fit a multivariate logistic regression model based on HIFs (AUROC was 0.62, Accuracy 0.37). In comparison, the GNN showed an improved performance in predicting c-MET when applied to the test dataset of primary and metastatic samples with an AUROC of 0.65 (Sensitivity: 0.87; Specificity: 0.43; Accuracy: 0.75).

Conclusions: In this work, we reviewed complimentary AI-based models for the prediction of c-MET overexpression status from H&E NSCLC samples. Using the HIF and GNN approaches, we were able to further understand the relationship between the TME and c-MET overexpression status as well as identify patients whose tumor overexpressed c-MET. This work serves as a basis to further explore the utility of this approach as a screening tool for patient selection for c-MET targeting therapies.

Keywords: c-Met, targeted therapy, NSCLC

P2.07 PATHOLOGY - TUMOUR GENOMICS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.07-02 RET Fusion Testing with FISH and Real-Time PCR: a Comparison with RNA-Based Next-Generation Sequencing in RET Positive NSCLC

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Introduction: Although next-generation sequencing (NGS) is now the gold-standard for lung cancer biomarker testing, single-gene assays are still used for different reasons. Therefore, we were intrigued by the perfomance of commonly used fluorescence *in situ* hybridization (FISH) and real-time PCR assays in a cohort of *RET* fusion-positive non-small cell lung carcinoma (NSCLC) patients.

Methods: Physicians across 16 hospitals contributed to identify patients with *RET* fusion-positive NSCLC as part of routine clinical care. All tumors underwent targeted RNA-based NGS (Oncomine Comprehensive Assay v3), break-apart *RET* FISH with two different assays (Vysis and ZytoVision), and RNA real-time PCR (AmoyDx Multi-Gene Mutations Detection Kit). The material available for all tumors had been formalin-fixed and paraffin-embedded. Only cases with enough tissue available for all four methodologies were included. All assays were perfomed and interpreted according to the manufacturer´s recommendations and/or by using previously described criteria. The NGS result was used as the gold-standard.

Results: Analyses by the four assays was succesful in all 35 tumors. Signet ring cells, psammomatous calcifications and nuclear pleomorphism were frequently observed (in 37%, 34% and 37% of tumors, respectively), with a frequent overlap between those features (data not shown). The most common *RET* partners were *KIF5B* (27/35, 77%), followed by *CCDC6* (6/35, 17%). Other fusions included *NCOA4* (1/35, 3%) and *AKAP13* (1/35, 3%). Thirty-three out of the 35 (94%) NGS-positive samples were real-time PCR-positive or FISH-positive. However, there was no overlap in the two false-negative results by either approach. The two *RET* fusions not identified with real-time PCR were *AKAP13(35)-RET(12)* and *KIF5B(24)-RET(9)*. The number of positive tumor cells with both FISH assays was very high in those two cases (82% and 92% for Vysis; 60% and 94% for ZytoVision). Regarding FISH-positive cases (94%), the overall results were very similar for both probes (85% of tumors showed a typical split pattern and the remaining 15% a predominant single 3' signal pattern). Interestingly, the number of cases with narrow split FISH signals (>1 but ≤2 signal diameter) was higher with one of the probes (21% for Vysis *versus* 36% for ZytoVision). Surprisingly, the two FISH-negative samples (6%) contained the frequent *KIF5B(15)-RET(12)* variant. They showed very subtle split (≤1 signal diameter) images with both FISH probes.

Conclusions: Nuclear plemorphism is an underrecognized histological feature of *RET* fusion-positive NSCLCs. If NGS is not perfomed, orthogonal testing should be considered after a negative *RET* single-test result. The likelihood of a false-negative outcome with a real-time PCR assay is influenced by the molecular epidemiology of *RET* fusions in a given population. In addition, a novel observation is that FISH false-negative results can occur with the most frequent *RET* fusion partner. Although two commonly used *RET* FISH assays appear to be interchangeable, there might be probe-specific interpretation challenges.
Funding: this study was mainly funded by Lilly. We also thank ISCIII (Project INGENIO [PMP21/00107] and the Next Generation EU funds; Fondos FEDER and Plan Estatal I+D+I 2008-2011 [PI11/02866] and 2013-2016 [PI14-01176 y PI17-01001]) and the iLUNG Program (B2017/BMD-3884), Comunidad de Madrid.

Keywords: Non-small cell carcinoma, RET fusions, Next generation sequencing

P2.08 PATIENT ADVOCACY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.08-01 Real-world Barriers to Clinical Trial Enrollment as Reported by U.S. Lung Cancer Patients and Community Cancer Centers

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Introduction: Only 6% to 8% of U.S. cancer patients participate in a clinical trial despite NCCN guidelines recommending trial consideration for all patients as part of a high-quality standard of care. To better understand health system and patient level factors impacting trial enrollment we looked at real-world clinical data from a network of community cancer centers and patient reported data from a personalized trial navigation program.

Methods: A retrospective analysis of clinical trial enrollment patterns and factors impacting enrollment was carried out utilizing two real-world data sources. The first was from an annual (2020) survey of GO2 Foundation for Lung Cancer's (GO2) Centers of Excellence (COE) - a network of U.S. based community health care facilities that diagnose and treat lung cancer. Data was collected from 26 COEs. The second was data from people who received clinical trial navigation through GO2's LungMATCH program (in which a navigator provides patient education and a personalized list of trial matches to participants) in 2020 and 2021. Outcomes data were able to be collected from 56 program participants.

Results: COEs reported the percentage of their lung cancer patients reviewed for the possibility of clinical trial participation, with a median of 75%. COEs then reported the portion of the patients reviewed for possibility of trial participation that were also referred to a specific trial, with a median of 10%. Lastly, COEs reported the portion of patients that were both reviewed for possibility of trial participation and referred to a specific trial that ended up enrolling, with a median of 16%. When asked to report the primary reason for patients not enrolling, 12/26 COEs (46%) reported lack of an appropriate local trial and 7/26 (27%) reported patient level factors (low trial awareness/understanding or refusal to participate). When asked to indicate top drivers that could enhance enrollment 10/26 COEs (38%) indicated increasing the number of local trials and 6/26 COEs (23%) indicated patient awareness/education initiatives. 29% of LungMATCH participants had not previously discussed trials with a provider. 95% of participants went on to discuss trials with a provider after participating in LungMATCH and 62% of those then contacted a specific trial. 11% of participants overall enrolled in a trial. The top reason participants reported not contacting a trial was having a stable condition on treatment (45%) and the top reason reported for not enrolling on a trial they contacted was not meeting eligibility criteria (55%). 54% of participants who did not enroll went on standard therapeutic care and none enrolled on another trial.

Conclusions: Patients and a broad range of healthcare providers (COE network members) report lack of appropriate local trials and ineligibility for available trials as key contributing factors to low clinical trial enrollment. Efforts to increase local trial availability and access alongside facilitating remote access to distant trials could be instrumental to increasing enrollment. Patient-centric clinical trial education and navigation may also increase clinical trial enrollment as indicated by COEs and supported by observed high rates of trial discussions after participation in LungMATCH.

Keywords: clinical trials, real-world data, patient-reported data

P2.08 PATIENT ADVOCACY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.08-02 Burning the Candle at Both Ends-Sleep Quality Before and After Chemotherapy in Lung Cancer Patients - A Systematic Review and Meta-Analysis

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Introduction: Lung cancer (LC) is the leading cause of cancer-related deaths worldwide. Although sleep affects both biological and psychological functioning and quality of life, it is a largely under-reported problem in LC. Furthermore, systemic chemotherapy is a standard of care for most people with advanced stage disease, yet research on the impact of chemotherapy for LC on sleep quality is inconsistent. Understanding sleep quality before and after chemotherapy for LC is important for future intervention research and resource allocations to improve patient quality of life. We conducted a systematic review with two aims: *1)* To determine the prevalence and severity of sleep disturbance in LC patients; and, *2)* Does sleep quality differ before and after chemotherapy treatment in LC patients.

Methods: Using PRISMA guidelines, we systematically searched MEDLINE, Embase, Ovid, PubMed, SCOPUS, and Web of Science databases from inception to August 2021 as well as reference lists from key articles. All articles that investigated the impact of chemotherapy compared with no treatment (baseline) on sleep and all articles that reported sleep at baseline prior to any treatment were included in the systematic review. The study was registered in the Prospective Register of Systematic Reviews Prospero (CRD42021223918).

Results: From 3,747 article titles and abstracts, a total of 40 studies involving 6,395 LC patients from 15 countries were included in this analysis. Due to the large heterogeneity and reporting of the data, only 30 studies were included in the meta-analysis. At baseline, prior to any treatment, moderate to severe sleep disturbance was highlighted in 18 of 40 (45%) studies. Following chemotherapy, sleep quality improved in 7 of 19 (37%) studies, remained stable/unchanged in 5 of 19 (26%) studies and worsened in 7 of 19 (37%) studies. Meta-analysis of studies at baseline prior to chemotherapy demonstrated QLQ-C30 Insomnia scores (0-100 scale; k = 13) were M [95% CI] = 33.3; [30.4, 36.1], below the threshold score of 50 indicative of clinically significant symptoms. In contrast, baseline PSQI scores (0-28; k = 10) were M [95% CI] = 9.0 [7.1, 10.9] exceeding the threshold (M > 5) indicative of clinically significant moderate-severe sleep disturbances. Both the QLQ-C30 Insomnia and PSQI meta-analyses had significant heterogeneity (I^2= 82% and 99%, respectively). Sleep quality after the initiation of chemotherapy was significantly better on the QLQ-C30 Insomnia score (k = 5; M [95% CI] = 23.3 [18.3, 28.2], $p < 0.05$, I^2 = 52%), 10 points lower compared to baseline studies, indicating a modest clinically significant improvement. In contrast, PSQI scores were (k = 7; M [95% CI] 9.7 [7.1, 12.3], $p > 0.05$, I^2 = 99%), a non-significant, 0.7-point worse score compared to baseline.

Conclusions: Poor sleep quality is common in LC patients, prior to any treatment. Current literature is insufficient to quantify the effect of chemotherapy on sleep quality in LC. Differences emerged between the single-item QLQ-C30 Insomnia score and multi-item PSQI. Larger, prospective studies with comprehensive sleep quality assessments are needed to examine the relationship of chemotherapy on sleep quality in LC patients.

Keywords: Chemotherapy, Sleep Quality, Quality of Life

P2.08 PATIENT ADVOCACY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.08-03 Patient Reported Lung Cancer Care Team Satisfaction and Treatment Dynamics, Based on the Online MyHealthTeams Survey

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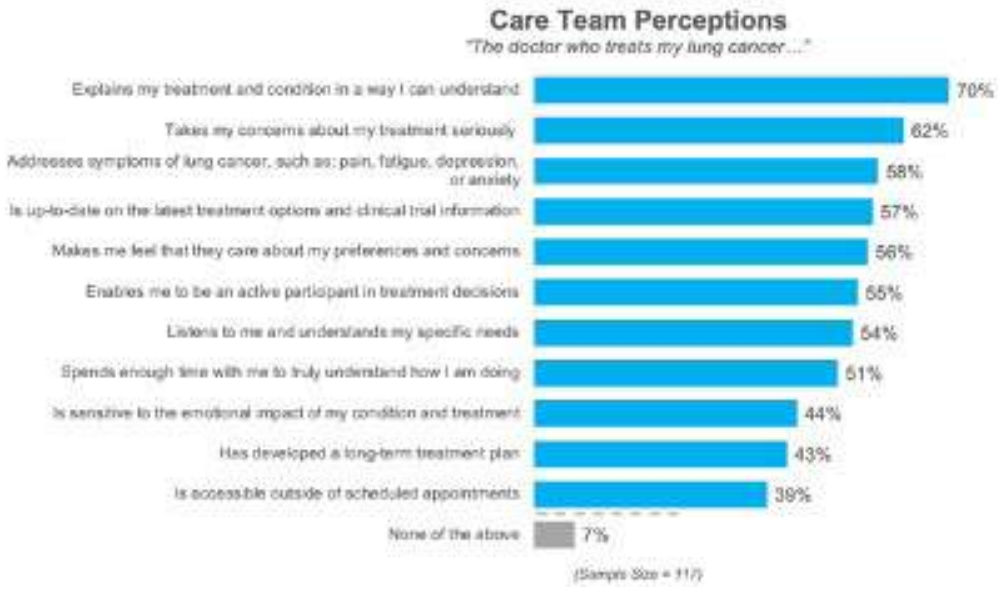
Introduction: Understanding lung cancer (LC) patient satisfaction with their doctors and the drivers of this satisfaction are crucial to improving doctor-patient interactions, helping patients get on the right treatment path to help slow progression and improving health outcomes overall.

Methods: An online survey about LC patient experience was conducted between November 18, 2021-December 6, 2021 among members of the social network MyLungCancerTeam, aged ≥21 years and reporting a LC diagnosis. In total, 117 patients were included in this research.

Results: More than 3 in 4 LC patients surveyed are satisfied with their care team (78%). More than two-thirds feel that their care team is able to explain their treatment and condition in a way they can understand (70%); however, more than 2 in 5 are unsure of what their specific lung cancer diagnosis is (43%). The majority feel that HCPs take their concerns about treatment seriously (62%), address symptoms of lung cancer (58%), and enable patients to be active participants in treatment decisions (55%). Approximately half feel that HCPs spend enough time with them to understand how they are doing (51%); less than half feel HCPs are sensitive to the emotional impact of their condition and treatment (44%) and have developed a long-term treatment plan (43%). Some disparities also exist on the basis of education. More highly educated (HE) patients are significantly more likely than less educated (LE) patients (HE vs. LE) to report that the doctor who treats their lung cancer: takes concerns about their treatment seriously (74% vs. 55%), makes them feel that they care about patient preferences and concerns (70% vs. 48%), and is sensitive to the emotional impact of their condition and treatment (59% vs. 35%). Additionally, HE are more than 2x as likely to receive biomarker testing than LE (46% vs. 18%).

Conclusions: Understanding the strengths and weaknesses of current communication strategies can help physicians improve relationships with their lung cancer patients. Furthermore, in identifying education-based treatment disparities that exist within the lung cancer patient population, HCPs can help to address these issues and create better health outcomes by improving health equity.



Keywords: HCP relationship, Patient education, Patient communication

P2.08 PATIENT ADVOCACY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.08-04 Patient Reported Impact of Lung Cancer Symptoms and Treatment on Mental Health and Quality of Life, Based on the Online MyHealthTeams Survey

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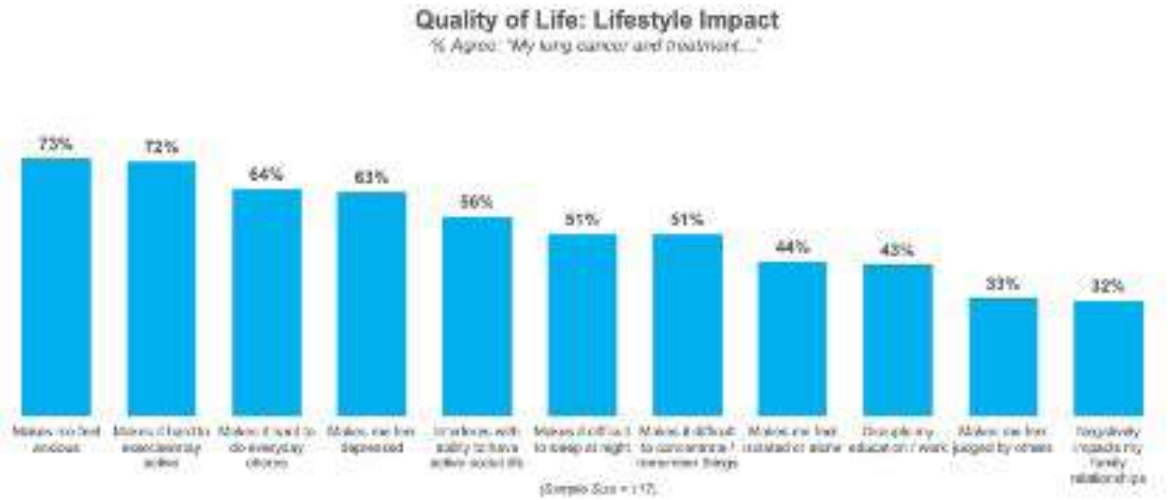
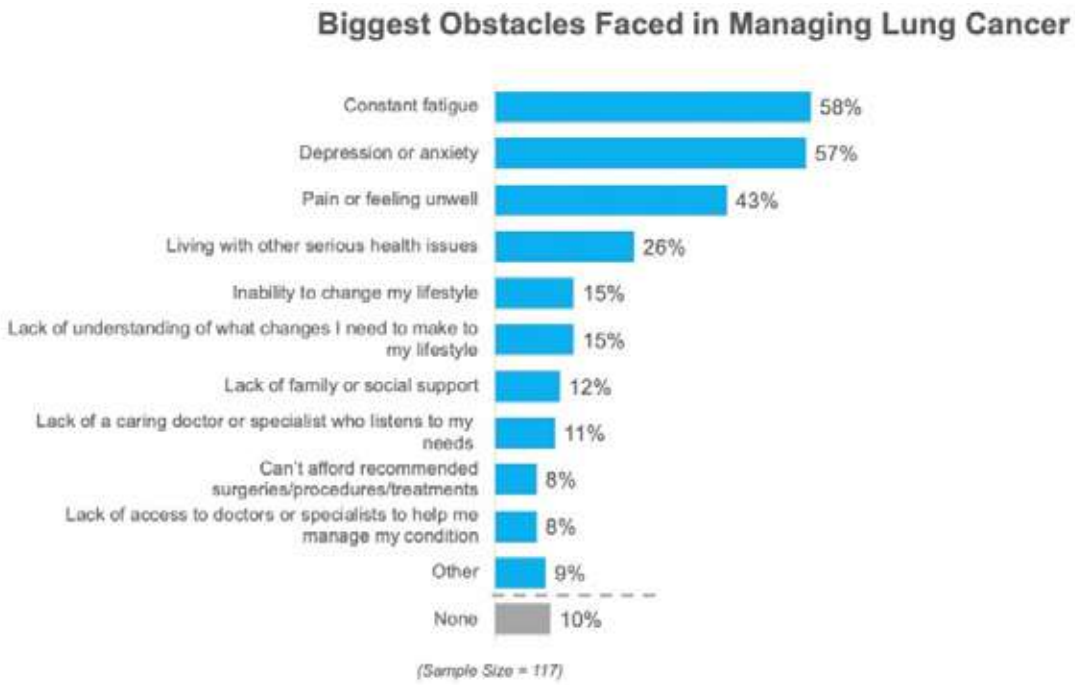
Introduction: Research was undertaken to better understand how people living with lung cancer (LC) describe its holistic impact on their lives, including work, challenges with relationships, and its toll on mental health.

Methods: An online survey about LC patient experience was conducted November 18, 2021-December 6, 2021 among members of the social network MyLungCancerTeam, aged ≥21 years and reporting a LC diagnosis. In total, 117 patients were included in this research.

Results: Of the respondents, 71% were female, 29% male, aged 51-86 years old, and all from the US. Living with the symptoms of LC has a detrimental impact on the quality of life of patients, particularly on mental health. The majority of patients feel that lung cancer makes them feel anxious (73%) and depressed (63%). These negative mental health experiences have made living with lung cancer more challenging - with 57% citing depression or anxiety as a top obstacle in managing lung cancer. Patients reported that constant fatigue (58%) was experienced, which contributes to making it hard for patients to exercise/stay active (72%) and complete everyday chores (64%).The research illustrated distinct differences based on gender. For example, female patients are nearly twice as likely to feel judged by others (39%) due to having lung cancer as compared to men (21%). As a result, female patients were significantly more likely to cite lack of family/social support as a top obstacle (17%) than male patients were (0%).

Conclusions: Understanding the impact that lung cancer has on the physical and emotional aspects of patients' wellbeing can help doctors provide a more holistic approach to treating their lung cancer patients. These findings show the value of the patient voice in addressing challenges that they face and can educate HCPs on unmet needs of LC patients.





Keywords: Patient quality of life, Mental health, Symptoms

P2.08 PATIENT ADVOCACY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.08-05 Lung Cancer Patients' Willingness to Attend a Screening Appointment or Lung Health Check: Insights from a Global Patient Experience Survey

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Introduction: Lung health checks or screening programmes are a key measure to detecting the disease earlier, when treatment is most likely to be successful, and thus reducing the huge burden currently imposed on the individuals affected, their families, the country, and the healthcare system as a whole.

The Global Lung Cancer Coalition (GLCC), a partnership of 42 patient organisations across 30 nations, states in its patient charter that all patients have the right to witness the widespread implementation of well structured, evidence-based programmes of early diagnosis, including screening. With few countries currently offering screening programmes, the GLCC wanted to understand if patients would be willing to attend an appointment if it was available and they were invited.

Methods: In the GLCC's third annual survey, the steering group included questions on the availability of screening in their country, including a question asking patients if they would attend a lung health check or screening programme if invited. The survey received 555 responses from patients across 21 countries.

Results: The majority of responding patients (85%, 449/526) said they would attend a screening appointment or lung health check if they were invited. The number of patients willing to attend ranged from 100% in Spain and Ireland to 63% in the USA. One in ten patients (54/526) said they were unsure if they would attend a screening appointment, and almost one in 20 (4%, 23/526) stated that they would not attend. Patients in Italy (17%, 22/129), Taiwan (17%, 12/71) and the USA (37%, 10/27) most frequently selected these options, although the proportions are lower than those stating that they would attend a screening appointment. Figure 1 shows a breakdown of responses by country.

Figure 1: Patient responses when asked if they would attend a lung health check or screening appointment if invited.

If you were invited to attend a lung health check or screening appointment, would you attend?		Yes – I would attend	No – I wouldn't attend	I'm not sure
Australia	%	90	0	10
	n	9	0	1
Brazil	%	83	6	11
	n	15	1	2
Bulgaria	%	100	0	0
	n	2	0	0
Canada	%	88	8	4
	n	22	2	1
Denmark	%	81	0	19
	n	34	0	8
Ireland	%	100	0	0
	n	10	0	0
Italy	%	83	5	12
	n	107	6	16
Netherlands	%	80	11	9
	n	35	5	4
Portugal	%	82	0	18
	n	14	0	3
Spain	%	100	0	0
	n	54	0	0
Taiwan	%	83	6	11
	n	59	4	8
UK	%	91	4	4
	n	62	3	3
USA	%	63	7	30
	n	17	2	8
Germany*	%	100	0	0
	n	1	0	0
Greece*	%	100	0	0
	n	1	0	0
India*	%	100	0	0
	n	1	0	0
Isle of Man*	%	100	0	0
	n	1	0	0
Mexico*	%	100	0	0
	n	1	0	0
New Zealand*	%	100	0	0
	n	1	0	0
Sweden*	%	100	0	0
	n	3	0	0

*Responded to a general survey in 2022 which was open to patients from around the world that did not have a national survey
Some countries' results include less than five responses and therefore the percentages may seem larger than others with more responses

Conclusions: Lung health checks or screening programmes are available in very few countries worldwide, despite the increasing number of people being diagnosed every year. The findings from this survey demonstrate that the majority of patients would have been willing to attend a screening appointment to detect their lung cancer earlier if it had been available and they had been invited. As stated in the GLCC patient charter, in countries where lung cancer screening programmes are not available, governments should look to implement pilots as a matter of urgency, as evidence suggests that screening programmes support earlier detection and diagnosis and better patient outcomes.

Keywords: advocacy, screening, COVID-19

P2.08 PATIENT ADVOCACY,
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P2.08-06 Patient Involvement in Decision-Making around Their Treatment and Care: Findings from a Global Patient Experience Survey

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Introduction: Two years in, COVID-19 continues to impact healthcare systems and the treatment and care all patients receive, including those living with lung cancer. The Global Lung Cancer Coalition (GLCC) is a partnership of 42 patient organisations across 30 nations dedicated to improving outcomes for lung cancer patients. The GLCC used its third annual global patient experience survey to explore whether the pandemic had affected the extent to which patients are able to be involved in decision-making around their treatment and care.

Methods: Among several topics in the survey, the GLCC's multi-national steering group of patients, advocates, and clinicians included a question to ask about the extent to which patients felt involved in decisions about their treatment and care when talking to their treatment team. The survey received 555 responses from lung cancer patients across 21 countries.

Results: Globally, almost half (48%, 258/533) of patients responding to the 2022 survey said they did not feel fully involved in decisions about their treatment and care, with almost one in ten (9%, 48/533) noting that they were not involved but would like to have been. This is a smaller proportion than in the 2021 survey, where 59% (755/1287) of responding patients stated that they did not feel fully involved in decision-making.

The national data in Figure 1 highlights variation in the extent to which patients felt involved in decision-making. In both years, the country with the highest proportion of respondents feeling fully involved in decisions was the Netherlands (76% in 2022 and 75% in 2021).

Figure 1: When talking to your treatment team, did you feel involved in the decisions about your treatment and care? 2022 and 2021 survey responses.

When talking to your treatment team, did you feel involved in the decisions about your treatment and care? Please choose the option that best describes you.		2022						2021					
		Yes, I've been fully involved	Yes, I've been involved mostly	Yes, I've been involved sometimes	No, but I would like to be involved	No, but I didn't want to be involved	No, but my caregiver was involved	Yes, I've been fully involved	Yes, I've been involved mostly	Yes, I've been involved sometimes	No, but I would like to be involved	No, but I didn't want to be involved	No, but my caregiver was involved
Australia	%	20	50	10	0	20	0	60	30	0	10	0	0
	n	2	5	1	0	2	0	6	3	0	1	0	0
Brazil	%	33	56	6	0	0	6	61	14	7	7	4	7
	n	6	10	1	0	0	1	34	8	4	4	2	4
Bulgaria	%	0	0	50	50	0	0	0	0	100	0	0	0
	n	0	0	1	1	0	0	0	0	1	0	0	0
Canada	%	48	26	22	4	0	0	49	27	12	12	0	0
	n	13	7	6	1	0	0	24	13	6	6	0	0
Denmark	%	69	19	5	7	0	0	47	24	9	14	2	5
	n	29	8	2	3	0	0	31	16	6	9	1	3
Ireland	%	36	36	18	0	0	9	42	17	21	21	0	0
	n	4	4	2	0	0	1	10	4	5	5	0	0
Italy	%	41	27	17	9	2	4	34	26	15	17	4	4
	n	52	35	22	11	3	5	36	27	16	18	4	4
Netherlands	%	76	17	5	2	0	0	75	13	5	6	1	1
	n	31	7	2	1	0	0	131	22	9	11	1	2
Portugal	%	63	0	25	6	6	0	54	29	8	8	0	0
	n	10	0	4	1	1	0	13	7	2	2	0	0
Spain	%	33	22	18	20	4	4	40	19	26	12	2	2
	n	18	12	10	11	2	2	17	8	11	5	1	1
Taiwan	%	64	15	10	8	1	1	57	21	7	6	2	4
	n	47	11	7	6	1	1	305	113	54	34	10	20
UK	%	53	30	6	9	3	0	48	32	19	7	2	2
	n	37	21	4	6	2	0	26	17	10	4	1	1
USA	%	73	7	7	13	0	0	66	18	11	5	0	1
	n	22	2	2	4	0	0	87	24	14	6	0	1
Mexico*	%	0	0	100	0	0	0	33	17	33	0	0	17
	n	0	0	1	0	0	0	2	1	2	0	0	1
Greece*	%	0	0	100	0	0	0	0	0	100	0	0	0
	n	0	0	1	0	0	0	0	0	1	0	0	0
Germany*	%	0	0	0	100	0	0	-	-	-	-	-	-
	n	0	0	0	1	0	0	-	-	-	-	-	-
India*	%	0	0	100	0	0	0	-	-	-	-	-	-
	n	0	0	1	0	0	0	-	-	-	-	-	-
Isle of Man*	%	100	0	0	0	0	0	-	-	-	-	-	-
	n	1	0	0	0	0	0	-	-	-	-	-	-
New Zealand*	%	100	0	0	0	0	0	-	-	-	-	-	-
	n	1	0	0	0	0	0	-	-	-	-	-	-
Sweden*	%	33	0	0	67	0	0	0	100	0	0	0	0
	n	1	0	0	2	0	0	0	1	0	0	0	0

*Responded to a general survey in 2022 which was open to patients from around the world that did not have a national survey
Some countries' results include less than five responses and therefore the percentages may seem larger than others with more responses

Conclusions: The GLCC's patient charter highlights that every patient should have informed self-determination, which includes involvement in decision-making. This survey highlights the importance of treatment teams asking, and supporting, lung cancer patients to be as involved in decisions around their treatment and care as they wish to be. In all countries, there is scope to increase the extent to which patients feel involved in decision-making. Research is needed to identify best practice from countries where larger proportions of respondents felt fully involved in decision-making.

Keywords: patient involvement, decision making, COVID-19

P2.08 PATIENT ADVOCACY,
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P2.08-07 The Campaign to End Lung Cancer Stigma: The ACS National Lung Cancer Roundtable Efforts to Confront and Extinguish Lung Cancer Stigma

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Introduction: Lung cancer stigma is common across the lung cancer care continuum and has a significant psychosocial impact on individuals diagnosed with lung cancer and their families. From hampering efforts to support lung cancer risk reduction to impeding biomarker testing post-diagnosis or restricting access to optimal treatment and survivorship, lung cancer stigma plays a pernicious role, contributing to suboptimal delivery of care and outcomes. Recognizing the need for coordinated and comprehensive efforts to eliminate lung cancer stigma, the American Cancer Society National Lung Cancer Roundtable's (NLCRT) Survivorship, Stigma, and Nihilism Task Group developed and launched a national initiative, the *Campaign to End Lung Cancer Stigma*.

Methods: In February 2020, a Lung Cancer Stigma Summit was held with key stakeholders (n=65) representing patient advocates, clinicians, researchers, advocacy organizations, professional societies, government agencies, and industry partners (n= 42 organizations). The summit created the foundation for a community-engaged transdisciplinary initiative to address lung cancer stigma. Over the course of 2020 and 2021, a rigorous strategic planning process identified three central themes, four primary goals, one cross-cutting consideration, and was followed by an intervention development blueprint.

Results: The summit's strategic plan adopted three core themes to guide efforts to end lung cancer stigma: *urgency*, *empathy*, and *optimism*. These themes support four visionary goals and are linked with specific multi-level interventions. The four goals and corresponding projects include: **1. Reframing Lung Cancer (cross-cutting):** Media and messaging *Current Supporting Project(s):* National media campaign (in progress) **2. Improving Survivorship:** Enhance optimal lung cancer control and care (e.g., normalize screening, expand biomarker testing and clinical trials, support survivor well-being, etc.) *Current Supporting Project(s):* Support development of lung cancer survivorship care consensus guidelines or best practices (under development) **3. Enhancing Understanding and Empathy**: Multi-level educational efforts *Current Supporting Project(s):* Health System Stigma Assessment Kit (in progress) and professional training materials & collateral (adaptable to lay and clinical stakeholders across lung cancer continuum) (in progress) **4. Amplifying and Expanding Research:** Lung cancer research portfolio evaluation *Current Supporting Project(s):* (under development)These four goals also address the complicated relationship between lung cancer and tobacco. Ongoing work focuses on building, refining, and testing destigmatizing interventions as well as securing support from NLCRT members and state-based organizations to disseminate these interventions broadly.

Conclusions: There have been ground-breaking strides in lung cancer early detection, diagnosis, and treatment that are rapidly changing the lung cancer landscape. Although these clinical innovations have infused hope and opportunity across the lung cancer continuum, individuals at high-risk and those diagnosed with lung cancer still experience disconcerting challenges linked to pervasive lung cancer stigma. This national initiative has great potential to eliminate stigma's prevalence and adverse effects. The ACS-NLCRT is committed to the execution of this framework as an enduring, national, multi-organizational initiative from finalizing development and testing of interventions, preparation for broad implementation, and ongoing measurement and evaluation of the effort to eliminate stigma from our communities and health services. Additionally, it is desirable to gain greater understanding of intersectional stigma and cross-cultural considerations, and support international collaboration.

Keywords: Lung Cancer Stigma, Advocacy, National Lung Cancer Roundtable

P2.08 PATIENT ADVOCACY,
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P2.08-08 Where Have All the Lung Cancer Support Groups Gone?

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Introduction: In-person support groups are effective in addressing the greater unmet physical and emotional needs and high rates of distress experienced by those diagnosed with lung cancer. Due to the stigma, disease-specific groups are preferred but can be challenging to start and maintain. As a result, there are never enough active groups in the United States to meet the support needs of the community. When the pandemic hit, groups across the world stopped meeting in person, cutting off vital support. To date, lung cancer groups in the United Kingdom, typically run by RNs, have yet to restart. What happens when it is no longer safe for lung cancer groups to meet? Do they fold completely or does innovation increase access, and allow more people to connect than ever before?

Methods: A 48 question online survey was open to the 85 lung cancer group facilitators of the National Lung Cancer Support Group Network between January to June of 2021. To assess the pandemic impact on their groups, facilitators were asked about the group's status; if and how they might have adapted; and to share tips and guidance for those starting and maintaining virtual lung cancer groups.

Results: Of the 44 responses, 35 groups continued to actively meet, either virtually or by telephone. Twenty eight had pivoted to using Zoom and, regardless of platform, most did not require participants to join on camera. While some group members struggled with technology, overall the switch to virtual groups increased access to lung cancer support. Only six of the groups required participants to reside in the area of the group, with the vast majority expanded to welcome participants from a broader region, including an entire state or from anywhere in the United States. Facilitators shared what was gained and lost from making the switch to virtual meetings and indicated "patience" as the quality most needed to make the shift work.

Conclusions: Our prior research showed that lung cancer support groups in the United States are run by a more diverse group of facilitators compared with those in the United Kingdom and Australia. Having groups facilitated by a wide range of healthcare professionals, as well as lung cancer survivors and lay people, likely acted as a protective factor for US group survival.

Keywords: Survivorship, Support

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P2.08-09 Adaptation of Empathic Communication Skills Training for Oncology Care Providers to Reduce Lung Cancer Stigma

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Introduction: Stigma is commonly experienced by individuals diagnosed with lung cancer, particularly in discussions about smoking during clinical encounters with their oncology care providers (OCPs). Building upon prior work developing and pilot testing an Empathic Communication Skills (ECS) training module targeting lung cancer patients, this study sought feedback from key stakeholders about the ECS training module in preparation of launching a virtually-delivered, multi-site clinical trial to test the implementation and effectiveness of the evidence-based ECS training module to reduce lung cancer stigma.

Methods: Key stakeholders (n=21) representing clinicians, researchers, and patient advocates working in the area of lung cancer and stigma were invited to a daylong hybrid (onsite and virtual) immersive demonstration of the ECS training module. The overall goal of the ECS module is to enhance OCPs' recognition of and responsiveness to opportunities to provide empathy to their lung cancer patients by communicating understanding, alleviating stigma and distress, and providing support. The training includes a 45-minute didactic presentation summarizing the literature on stigma experienced by people with lung cancer, negative consequences of this stigma, and communicating empathically as a clinician-level strategy to reduce lung cancer stigma. The presentation includes brief video clips of OCPs demonstrating exemplary empathic communication skills. Immediately after the large group presentation, stakeholders participated in 90-minute experiential role plays in small groups, co-facilitated by two trainers with expertise in tobacco treatment and cancer-focused communication skills. Stakeholders then provided detailed group feedback and specific recommendations for improving the effectiveness and acceptability of the training module. Guided by a well-established framework (Stirman et al, 2013) for adaptation of evidence-based interventions, deductive thematic content analysis was conducted to code focus group responses into 12 distinct *a priori* content modification themes.

Results: Content refinement was suggested in 8 of the 12 content modification themes: tailoring/tweaking/refining (e.g., tailoring the role play scenarios to be more diverse and representative of the local context of the participating cancer care institution), adding elements (e.g., smart phrases for difficult clinical encounters), removing elements (e.g., details about communication skills not relevant to lung cancer stigma), shortening/condensing content (e.g., background rationale for the intervention), lengthening/extending (e.g., activities to engage OCPs in rethinking communication with patients), substituting elements (e.g., replacing the demonstration videos with a more interactive smart phrases activity), re-ordering elements (e.g., start with lung cancer stigma instead of communication skills), and repeating elements (e.g., bringing smart phrases into role plays). There were no stakeholder suggestions that were coded as integrating another framework, integrating another treatment, loosening structure, or departing from the intervention content modification themes.

Conclusions: Stakeholder engagement and feedback on the ECS training module to reduce lung cancer stigma influenced intervention content modification in several intervention adaptation domains. Using a structured format for refining evidence-based interventions can facilitate efforts to guide modifications needed to make this promising ECS training module more effective in promoting de-stigmatizing discussions about tobacco use and relevant to diverse patient populations encountered in real-world clinical settings.

Keywords: Stigma, Smoking, Communication

P2.09 PULMONOLOGY, RADIOLOGY, AND STAGING,
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P2.09-01 MRI-based Radiomic Signature to Predict Pathologic High-grade Pattern in Lung Adenocarcinoma

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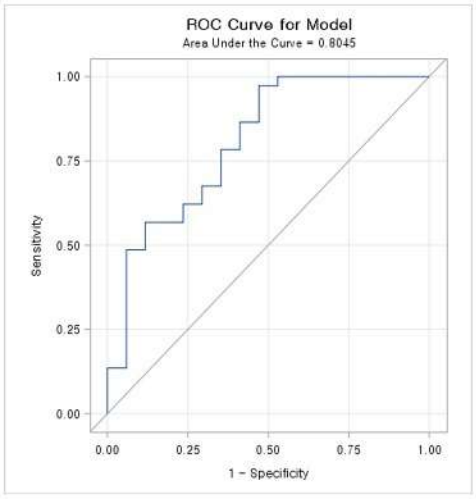
Introduction: While curative resection is the established treatment in N0 early lung adenocarcinoma patients, recurrence have been reported to be more than 30% and one of the risk factors can be attributed to micropapillary and solid pattern in histology, both being high-grade patterns associated with adverse outcome. Also, incorporation of high-grade pattern in lung adenocarcinoma grading system yields good correlation with prognosis. In this regard, our study focuses on developing the first prediction model to find quantitative MRI features of micropapillary or solid pattern (MPsol) in lung adenocarcinoma by radiomics approach.

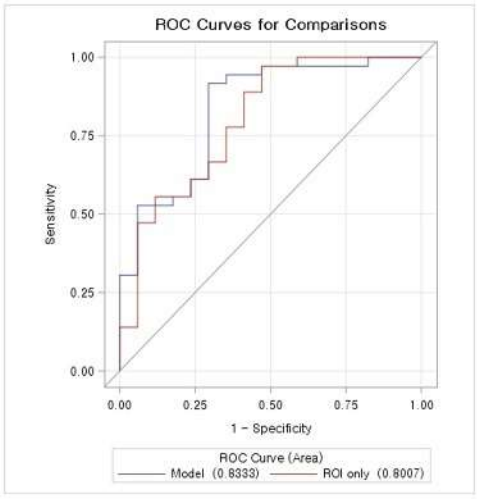
Methods: Among clinical T1N0 lung cancer patients who are curative surgical candidates from August 2018 to January 2020 (n=616), patients showing high-risk features in computed tomography (CT) and FDG PET/CT were selected: purely solid lesions with either SUV max greater than 5 or definite irregular or poorly defined border. From the two regions of interest (ROI) of T1 and T2 sequence axial images on MRI, 77 radiomics features were extracted and mean ADC value was measured on DWI. The least absolute shrinkage and selection operator (LASSO) method was used for feature selection and prediction modeling. Internal validation was run by out-of-back method after bootstrapping. Univariate analysis was run for clinical information including nodal staging and gender to see association with MPsol.

Results: In 72 patients who underwent surgery after MRI examination, 55 cases were confirmed as adenocarcinoma of the lung. Performance of prediction model using 5 radiomics features finally selected by LASSO was good with AUC value 0.8045 (95% CI 0.67 - 0.9389) in the test set and 0.7142 (95% CI 0.4449 - 0.9609) in the validation set. Upon adding clinical variables, prediction model showed improved performance compared with the original model by Delong's test (AUC value 0.8333 versus 0.8007). (Figure 1)

Conclusions: Considering ongoing effort to incorporate high-grade patterns for early lung adenocarcinoma, a radiomics approach using MRI can offer additional information for predicting MPsol preoperatively, thus helping establish better surgical and medical treatment plan.



Prediction performance based on radiomics features extracted from both T1 and T2 weighted images



Prediction performance based on radiomics features extracted from both T1 and T2 weighted images plus clinical variables

Keywords: Lung adenocarcinoma, MRI, High-grade pattern

P2.09 PULMONOLOGY, RADIOLOGY, AND STAGING,
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P2.09-02 Clinical Nodal (cN) Category Is Independently Prognostic for Overall Survival in Unresectable Advanced/Metastatic Lung Cancer

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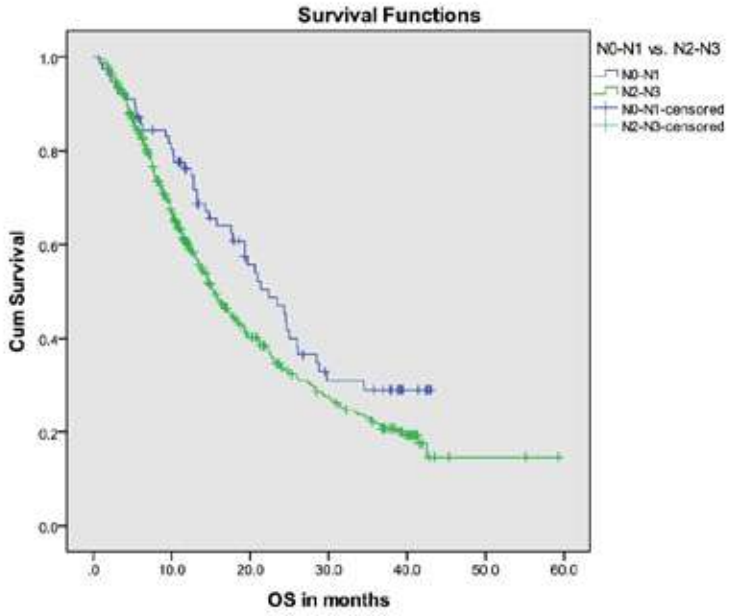
Introduction: TNM stage is a well-established prognostic factor for overall survival(OS) in lung cancer(LC). Clinical and pathological nodal (cN, pN) categories were assessed in 7th and 8th editions of IASLC TNM staging system. Data submission for IASLC 9th TNM edition database (involving patients diagnosed between 2011-19) has just been completed. This single-centre analysis is focused on prognostic role of clinical nodal(cN) categories in a cohort of unresected advanced LC from this database.

Methods: The cohort was comprised of all LC cases entered from a tertiary-care referral centre participating in the IASLC TNM staging project (9th edition database). Prognostic variables assessed included age, gender, smoking status, ECOG performance status(PS), body mass index(BMI), histology and T, N and M categories (all by 8th edition). Median OS was calculated by Kaplan-Meier method, group differences analyzed by log rank test and prognostic factors assessed by Cox regression analysis(CRA).

Results: Of 506 cases entered, analysis was limited to 466 unresected advanced/metastatic LC cases. Majority were males (77.3%), current/ex-smokers (72.8%) and had ECOG-PS=0-1 (58.2%), normal/high BMI≥18.5 (76.2%), T4 (73.6%) and M1 disease (65.2%). Distribution of histology was 52.4% non-squamous (95% adenocarcinoma), 30.5% squamous and 17.2% small-cell and of cN categories: 16.7% N0-N1, 32.4% N2 and 50.9% N3. Median age was 60 (IQR=53-67) years. Median OS was 16.6 months (95% CI=14.5-18.7). OS based on key variable subgroups is shown in Table. On multivariate CRA, predictors of better OS were female gender [HR=0.69 (95% CI=0.52-0.93; p=0.016)], non-squamous NSCLC histology [HR=0.69 (95% CI=0.52-0.91; p=0.008)] and cN0-N1 category [HR=0.70 (95% CI=0.50-0.96; p=0.026)] while ECOG-PS≥2 [HR=1.83 (95% CI=1.45-2.32; p<0.001)] and extra-thoracic metastasis [HR=1.35 (95% CI=1.06-1.73; p=0.016)] were associated with worse OS.

Conclusions: cN0-N1 category was independently associated with better OS in this cohort analysis from 9th TNM database. Accurate determination of N categories is relevant even in unresected advanced LC.



Overall survival based on key variable groups				
Variable	**OS VarGrp1* (in months)*** Represented as median (95% confidence intervals)	**OS VarGrp2* (in months)*** Represented as median (95% confidence intervals)	**OS VarGrp3* (in months)*** Represented as median (95% confidence intervals)	**p value**
Age	18.1 (14.7 – 21.5) For <65 years	13.3 (10.7 – 15.9) For ≥65 years		**0.024**
Gender	15.2 (13.0 – 17.4) For males	24.8 (18.5 – 31.1) For females		**0.006**
Smoking Status	22.5 (17.8 – 27.2) For non-smokers	14.6 (12.2 – 17.0) For current/ former smokers		**0.015**
	22.5 (17.8 – 27.2) For non-smokers	15.5 (12.2 – 18.8) For former smokers	13.9 (11.9 – 15.9) For current smokers	**0.048**
Body mass index (BMI)	12.1 (10.2 – 14.0) For BMI <18.5	19.0 (16.2 – 21.8) For BMI=18.5 to <23.0	18.7 (12.9 – 24.5) For BMI ≥23.0	**0.025**
	12.1 (10.2 – 14.0) For BMI <18.5	18.7 (15.6 – 21.8) For BMI ≥18.5		**0.010**
ECOG PS	22.7 (20.7 – 24.7) For PS 0	19.3 (14.9 – 23.7) For PS 1	12.0 (9.3 – 14.7) For PS ≥2	**<0.001**
	21.2 (18.0 – 24.4) For PS 0 to 1	12.0 (9.3 – 14.7) For PS ≥2		**<0.001**
Histology	13.0 (10.0 – 16.0) For Squamous NSCLC	21.3 (17.8 – 24.8) For Non-squamous NSCLC	11.4 (8.3 – 14.5) For SCLC	**0.003**
NSCLC Histology	13.0 (10.0 – 16.0) For Squamous	21.3 (17.8 – 24.8) For Non-squamous		**0.003**
T Category	19.0 (14.6 – 23.4) For T1-T2	19.2 (14.3 – 24.1) For T3	15.7 (13.1 – 18.3) For T4	0.472
	19.0 (16.0 – 22.0) For T1-T3	15.7 (13.1 – 18.3) For T4		0.349
N Category	22.4 (17.5 – 27.3) For N0-N1	16.3 (11.5 – 21.1) For N2	15.2 (13.2 – 17.2) For N3	0.084
	22.4 (17.5 – 27.3) For N0-N1	15.4 (13.4 – 17.4) For N2-N3		**0.035**
M Category	19.3 (15.8 – 22.8) For M0	16.6 (12.2 – 21.0) For M1a-M1b	14.2 (10.5 – 17.9) For M1c	**0.038**
	18.1 (15.4 – 20.8) For M0-M1a	15.3 (12.2 – 18.4) For M1b-M1c		**0.022**
TNM Stage	19.3 (15.8 – 22.8) For ≤IIIC	15.7 (13.3 – 18.1) For IV		0.185

Keywords: Overall Survival, Nodal Status, 9th TNM database

P2.09 PULMONOLOGY, RADIOLOGY, AND STAGING,
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P2.09-03 A Radiomics Approach Using Baseline CT Can Predict Response to 1st-Line Pembrolizumab in Advanced NSCLC with High PD-L1

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Introduction: Clinical trials showed both pembrolizumab alone (KN024), and pembrolizumab/platinum doublet chemotherapy (PDC) (KN189/407) are superior to PDC in 1st-line setting for advanced NSCLC without EGFR/ALK aberration. In PDL1≥50% subset across 3 trials, objective response rate (ORR) with pembrolizumab in KN024 was 45%, compared to 60% with pembrolizumab/PDP in KN189/407 with comparable 12 months overall survival (OS). Recent 5-year survival data from KN024 showed 32% of patients were alive at 5 years, most of whom were "responders". The clinical question is: Can we distinguish this 45% of patients who are best treated with pembrolizumab, and who needs additional PDC? Currently, no biomarkers or clinicopathological features can distinguish this population. The objective of this study is to test whether a machine learning (ML) model trained on the radiomic features of lung tumors at baseline CT scan can predict response to pembrolizumab in advance NSCLC with PDL1≥50%, and thereby can help clinician to choose the first-line treatment for this cohort.

Methods: The study included 98 patients with advanced NSCLC. All had CT at baseline and 9-12 weeks after receiving 1st-line pembrolizumab (58% female, 73±6 yo, 69 EX-/25 Current-smokers/4 non-smokers; pack-years: 40±26; ECOG range: 0-4). Two radiologists assessed treatment response to pembrolizumab using the RECIST standard definitions (n=60, "disease control" vs. n=38, "progression"). We used a radiomic feature extraction pipeline for each lung tumor using up to 5 adjacent axial CT slices containing the tumor. Sequential forward feature selection was used to identify up to 10 key features from shape, texture, and intensity features generated from 3 discrete tumor masks (tumor core, core plus edge parenchymal transition pixels, and a ring around the lesion capturing parenchymal tissue). We leveraged a 5-fold cross validated ML model (Linear Discriminate Analysis, LDA), trained on these selected radiomic features, together with clinical factors (i.e., demographics, smoking, ECOG, and disease burden) to classify treatment response.

Results: The LDA model including lung tumor radiomic features from baseline CT and clinical factors demonstrates the best classification performance compared to those only included either clinical or radiomics features (Figure 1. AUC: 0.92 vs 0.77 and 0.88, respectively).

Conclusions: A Machine Learning model using radiomic features derived from lung tumor on the CT images prior to treatment initiation, can predict treatment response to 1st line single-agent pembrolizumab in advanced NSCLC patients with high PD-L1 expression. This AI tool has a potential to become an important decision-making tool to guide therapy.

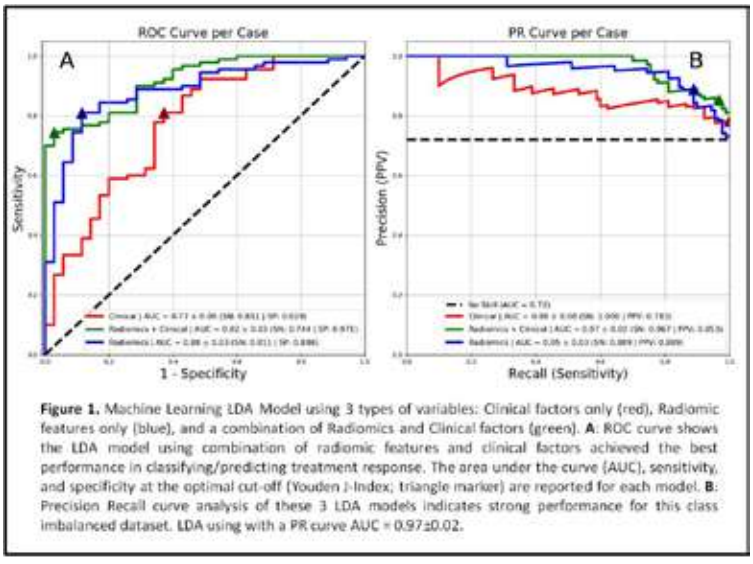

Figure 1. Machine Learning LDA Model using 3 types of variables: Clinical factors only (red), Radiomic features only (blue), and a combination of Radiomics and Clinical factors (green). **A**: ROC curve shows the LDA model using combination of radiomic features and clinical factors achieved the best performance in classifying/predicting treatment response. The area under the curve (AUC), sensitivity, and specificity at the optimal cut-off (Youden J-Index; triangle marker) are reported for each model. **B**: Precision Recall curve analysis of these 3 LDA models indicates strong performance for this class imbalanced dataset. LDA using with a PR curve AUC = 0.97±0.02.

Keywords: Artificial Intelligence, PDL1, immunotherapy

P2.10 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.10-01 Transcriptional Diversity of Emerging Cell Populations in Refractory Small Cell Lung Cancer Biopsies and Xenografts

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Introduction: Small cell lung cancer (SCLC) is a high-grade neuroendocrine lung carcinoma notable for early dissemination and rapid, albeit transient, responses to standard of care (SOC) treatment [platinum-based chemotherapy plus immune checkpoint blockade (ICB)] that are rapidly undone by refractory relapses. Using single cell profiling, we previously demonstrated that a major factor regulating resistance is an increase in plasticity and transcriptional intratumoral heterogeneity (ITH) in response to treatment. We hypothesize that characterization of cellular populations associated with relapse and their inherent resistance mechanism(s) provides an opportunity to develop therapeutic strategies to prevent or reverse resistance, before more widespread clinical relapse and ITH takes hold.

Methods: To better define the biology inherent in relapsed SCLC, we have established a library of >40 xenograft models derived from circulating tumor cells and core needle biopsies from treatment-naïve and -relapsed patients covering all molecular subtypes (SCLC-A/N/P/I). We performed single-cell RNAseq of xenograft models treated with platinum chemotherapy until resistance developed, as well as of biopsies from extensive stage SCLC patients collected following relapse to SOC. Cancer cells from xenografts and biopsies were analyzed by clustering individually and classified based on cycling status to identify senescence-like dormancy inherent to drug-tolerant persister cell populations (cycling=non-persisters; non-cycling=persister cells).

Results: Cluster analyses revealed one cluster in all xenografts treated with cisplatin until relapse and in relapsed patient biopsies associated with an increased epithelial to mesenchymal transition (EMT) signature. This EMT-associated cluster from each biopsy, presumably a population emerging following relapse, also demonstrated an absence of SCLC subtype markers (e.g., *ASCL1, NEUROD1, POU2F3*) and neuroendocrine (NE) genes (e.g., *INSM1*) together with an enrichment of non-NE (e.g., *REST*) and EMT genes (e.g., *AXL*, *VIM*). Interestingly, when cell cycling status was taken into account, the emerging clusters consisted of both persister and non-persister cells; however, GSEA analysis comparing these two cell populations revealed an enrichment in EMT, as well as inflammatory response pathways predominantly in the persister cells, and E2F targets and DNA repair pathways in the non-persister cells. Accordingly, NE genes, therapeutic targets (e.g., *TOP1/2A, AURKA/B, BCL2, PARP1, CHEK1*), and biomarkers of response (e.g., *SLFN11* and *CDH1)* were elevated in non-persister cells; however, some genes associated with resistance (e.g., *EZH2, NFIB*) were also enriched in this population. Consistent with the GSEA analysis, persister cells similarly demonstrate an enrichment in genes associated with common resistance mechanisms, including EMT and loss of NE phenotype (e.g., *ZFP36L1*), as well as increased inflammatory genes (e.g. HLA family), similar to the SCLC-Inflamed (SCLC-I) subtype.

Conclusions: These data suggest that unique cell populations within a relapsed tumor, identified through clustering or characterized by cell cycle status, may be vulnerable to distinct therapeutics. Persister cell populations may be more sensitive to ICB and/or AXL inhibition, while non-persisters may be more responsive to platinum chemotherapy or DNA repair targeted therapies. Clinically, these data underscore the importance of identifying therapeutics in the frontline or maintenance setting, prior to relapse, that suppress transcriptional diversity and the emergence of unique cellular subsets following treatment resistance.

Keywords: resistance, intratumoral heterogeneity, persister cells

P2.10 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS,
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P2.10-02 EMERGE 402: Preliminary Real-world Characteristics and Safety of Lurbinectedin in Patients with Small-cell Lung Cancer

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Introduction: Lurbinectedin, a selective inhibitor of oncogenic transcription, received accelerated approval in June 2020 from the US FDA as monotherapy (3.2 mg/m^2 by 1-hour IV infusion every 3 weeks) for the treatment of adults with metastatic small-cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. Approval was based on overall response (35.2%) and median duration of response (5.3 months) from a phase 2 study. The ongoing EMERGE 402 study is assessing the effectiveness, safety, and health-related quality of life of patients with SCLC who were prescribed lurbinectedin in the real-world setting.

Methods: EMERGE 402 is a prospective, observational, multicenter, phase 4 study enrolling patients with SCLC who progressed on or after ≥1 prior platinum-based chemotherapy regimen, with or without immunotherapy. Patients are assessed for enrollment after a physician prescribes lurbinectedin (per US prescribing information).

Results: Between 06/28/2021 and 01/24/2022 (data cutoff), 26 patients were enrolled (**Table**). The median age was 62.5 years; 21 (81%) patients had a baseline ECOG performance status ≤2. All patients received prior platinum-etoposide chemotherapy; 81% also received prior immunotherapy. Eleven (42%) patients had platinum-sensitive disease (chemotherapy-free interval [CTFI] ≥90 days: n=11 [42%]; CTFI ≥180 days: n=6 [23%]). CNS involvement was reported in 6 (23%) patients. All patients received lurbinectedin as monotherapy: 11 (42%) as second-line therapy and 15 (58%) as third/later-line therapy. Patients received a median of 2 (range: 1, 3) and 4 (3, 5) second-line and third/later-line lurbinectedin cycles, respectively, with treatment ongoing for 15 (58%) patients at the data cutoff date. There have been no dose delays; 3 (12%) patients required a dose reduction. Granulocyte-colony stimulating factor (G-CSF) was administered in 11 (42%) patients, of whom 10 received G-CSF as primary prophylaxis. Treatment-related adverse events (AEs) of any grade were observed in 4 (15%) patients and included neutropenia (n=2 [8%]), anemia (n=1 [4%]), and decreased platelet count (n=1 [4%]). Serious AEs were reported in 5 (19%) patients.

Conclusions: The ongoing EMERGE 402 study is enrolling a broader SCLC population (58% with ≥2 prior therapy lines; 81% with prior immunotherapy) than the phase 2 study that supported approval of lurbinectedin monotherapy. The observed real-world safety profile of lurbinectedin is generally consistent with the phase 2 study, with no new safety signals. EMERGE 402 continues to enroll patients to further assess the effectiveness and safety of lurbinectedin, and updated data analyzing a larger sample size will be reported at the meeting.

Table. Demographic and Clinical Characteristics of Patients Enrolled in EMERGE 402 (as of 01/24/2022)

	Total (N=26)
Line of lurbinectedin therapy, n (%)	
Second-line	11 (42)
Third- or later line	15 (58)
Age	
Median (range), years	62.5 (44, 87)
≥65 years, n (%)	12 (46)
Sex, n (%)	
Female	12 (46)
Male	14 (54)
Race, n (%)	
White	18 (69)
Black or African American	5 (19)
American Indian or Alaska Native	1 (4)
Declined to state	2 (8)
ECOG performance status at baseline, n (%)	
0	3 (12)
1	14 (54)
2	4 (15)
Missing	5 (19)
Stage at initial diagnosis, n (%)	
Extensive stage	19 (73)
Limited stage	7 (27)
CTFI, n (%)	
<30 days	4 (15)
≥30 to <90 days	5 (19)
≥90 to <180 days	5 (19)
≥180 days	6 (23)
Not reported	6 (23)
Prior therapy, n (%)	
Systemic therapy only	9 (35)
Systemic therapy and radiotherapy	17 (65)
First-line systemic therapy regimen, n (%)	
Platinum-etoposide chemotherapy only	9 (35)
Platinum-etoposide chemotherapy + immunotherapy	17 (65)
Sites of involvement other than lung, n (%)	
Liver	17 (65)
Bones	10 (38)
Distant nodes	8 (31)
Brain	6 (23)

ECOG, Eastern Cooperative Oncology Group; CTFI, chemotherapy-free interval.

Keywords: Lurbinectedin, Real-world Evidence, Small Cell Lung Cancer

P2.10 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.10-03 High-dose Thoracic Radiotherapy Improves the Overall Survival of Oligo-Metastatic Extensive-Stage Small Cell Lung Cancer

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Introduction: The CREST trial reported consolidative thoracic radiotherapy (TRT) of 30 Gy in 10 fractions provided a 10% 2-year overall survival (OS) benefit in extensive-stage small cell lung cancer (ES-SCLC) with residual intrathoracic disease after standard chemotherapy. A secondary analysis of the CREST trial data indicated that more intensive TRT should be investigated. But follow-up studies regarding this topic were scarce. Therefore, we evaluated the efficacy of high-dose TRT in ES-SCLC patients from our institution.

Methods: 165 patients with ES-SCLC admitted to our institution from December, 2012 to September, 2020 were enrolled, median follow-up was 15 months. Ninety patients received high-dose TRT (TRT group), 75 patients did not receive TRT (no TRT group). The TRT dose ranged from 45 to 66 Gy at 1.8 to 2.0 Gy per fraction, with a median dose of 52Gy. Subgroup analysis were performed in oligo-metastasis (defined as 3 or less metastatic lesions in 2 or fewer organs) and non-liver metastatic patients. Baseline characteristics were compared using the x2 test. Survival between groups were compared using log-rank analysis, event risk factors were analyzed with univariate and multivariate cox regression. Propensity score matching (PSM) was performed as 1:1 match in the two subgroups.

Results: In the entire cohort, the median OS was 15 months, TRT-group had better OS [HR0.662,95%CI (0.479-0.915), p=0.012] and PFS [HR0.781,95%CI (0.551-1.107), p=0.0003]. Further sub-cohort analysis, TRT significantly improved OS (p=0.023) and PFS(p=0.026) in patients with oligo-metastases. This trend persisted after PSM. On the other hand, TRT did not significantly improve OS in non-oligo metastatic sub-cohort (p=0.662). In non-liver metastatic sub-cohort, it seemed that patients could benefit from TRT in OS(p=0.063) and PFS (p=0.010). but this trend disappeared after PSM (OS p=0.291,PFS p=0.574). There were also no significant difference in liver metastatic sub-cohort (OS p=0.990, PFS p=0.067).

Conclusions: High-dose TRT improved OS in ES-SCLC. This phenomenon mainly applied to patients with oligo-metastases.

Keywords: Extensive-Stage Small Cell Lung Cancer, High-dose thoracic radiotherapy, Overall Survival

P2.10 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.10-04 Immunologic Subtype of Small Cell Lung Carcinoma Dictates Susceptibility to NK Cell-Mediated Cytotoxicity

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Introduction: Small cell lung carcinoma (SCLC) comprises approximately 15% of all lung cancer cases and SCLC patients initially respond to cytotoxic chemotherapy, but resistance inevitably emerges. Despite recent incorporation of immune checkpoint blockade (ICB) into first line treatment, predictive biomarkers of response remain lacking and patients with SCLC continue to have a poor prognosis with limited treatment options. Notably, recent transcriptomic profiling of SCLC cell lines and patient samples has indicated significant inter-tumoral and intra-tumoral heterogeneity. We recently characterized the immunologic heterogeneity of SCLC, demonstrating that neuroendocrine SCLC subpopulations (70% of SCLC) downregulate MHC I, whereas non-neuroendocrine SCLC subpopulations (15% of SCLC) exhibit increased innate immune signaling and robust upregulation of MHC I antigen presentation. Since neuroendocrine SCLC displays a striking MHC I repression, we predict that these cells might be vulnerable to NK cell attack. Here, we interrogate the susceptibility of immunologically distinct SCLC subtypes to NK cell-mediated cytotoxicity.

Methods: We first characterized the NK cell ligand expression on isogenic MHC I low and high SCLC cell lines derived from the NCI-H69 cell line, as well additional MHC I low and high cell lines (CORL47, H196) by flow cytometry. We then examined their sensitivity to primary human NK cells using 2D cytotoxicity assays. Additionally, we developed a 3-dimensional (3D) microphysiological tumor microenvironment (TME) model of SCLC in which tumor spheroids are embedded in a microvascular network comprised of endothelial cells and lung fibroblasts. We also used this novel microfluidic model of the TME to examine MHC I-low and high SCLC sensitivity to NK cell attack.

Results: We found that neuroendocrine SCLC subpopulations generally express increased levels of NK-activating ligands and downregulate major NK inhibitory molecules, and vice versa for non-neuroendocrine SCLC populations. MHC I low neuroendocrine SCLC cells were exquisitely vulnerable to primary NK cells in our 2D and 3D models/assays, whereas MHC I-high SCLC was resistant to NK cell-mediated killing, which could be reversed by knockout of beta-2 microglobulin.

Conclusions: Distinct immunologic subtypes of SCLC display differential susceptibility to NK cell-mediated cytotoxicity. Resistance to NK cell cytotoxicity in non-neuroendocrine SCLC is likely mediated by expression of MHC I, a major NK cell inhibitory ligand. Thus, MHC I expression by SCLC may serve as a valuable biomarker for sensitivity or resistance to different immune cell subsets present within the TME.

Keywords: Small cell lung cancer, Natural killer cell, MHC Class I

P2.10 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS,
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P2.10-05 Circulating CD3+CD56+ Cells as a Biomarker for Immunotherapy in SCLC

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IRCCS Istituto Tumori Giovanni Paolo II, BARI/IT

Introduction: Concerning small-cell lung cancer (SCLC), the addition of immune checkpoint inhibitors to first-line chemotherapy represents the first significant improvement of systemic therapy in several decades. However, only a small proportion of patients with SCLC benefit from immune checkpoint inhibitors. In contrast, biomarkers that predict efficacy of immunotherapy are not well characterized in SCLC. In this observational cohort study, we performed a basal assessment of circulating immune cells, evaluating the association with progression free survival (PFS) and overall survival (OS) in patients treated with IMpower 133 schedule.

Methods: We built an observational cohort study by recruiting prospectively patients with extensive SCLC treated with IMpower 133 schedule. Peripheral blood samples were collected at baseline, the day 1 pre-dose of the first cycle, and immediately processed for flow cytometer evaluation. Follow up continued until patients died or until the final update in February 2022. Data regarding circulting immune cells were dichotomized according to median values. Univariate COX regression and kaplan-meier were performed.

Results: Starting from September 2020, 30 patients were enrolled in the study, all treated with platinum-based chemotherapy plus atezolizumab. A higher level of CD3+CD56+ cells was significantly correlated with longer OS (HR 0.26, 95% CI, 0.07 - 0.92, *p*=0.036, Tab 1), with a median OS not reached versus a median OS of 8 months for the group with low level of CD3+CD56+ cells (*p*=0.025, Figure 1). Moreover, regarding PFS, a trend towards significance was also reported (HR 0.41, 95% CI, 0.16 - 1.05, *p*=0.063, Tab 1), with a median PFS of 11 months in the higher level of CD3+CD56+ cells group versus 4 months in the low-level one (*p*=0.063, Figure 1).

Conclusions: The baseline level of CD3+CD56+ cells, could be a candidate as biomarkers for immunotherapy efficacy in SCLC. Large samples size studies are needed to confirm these data.

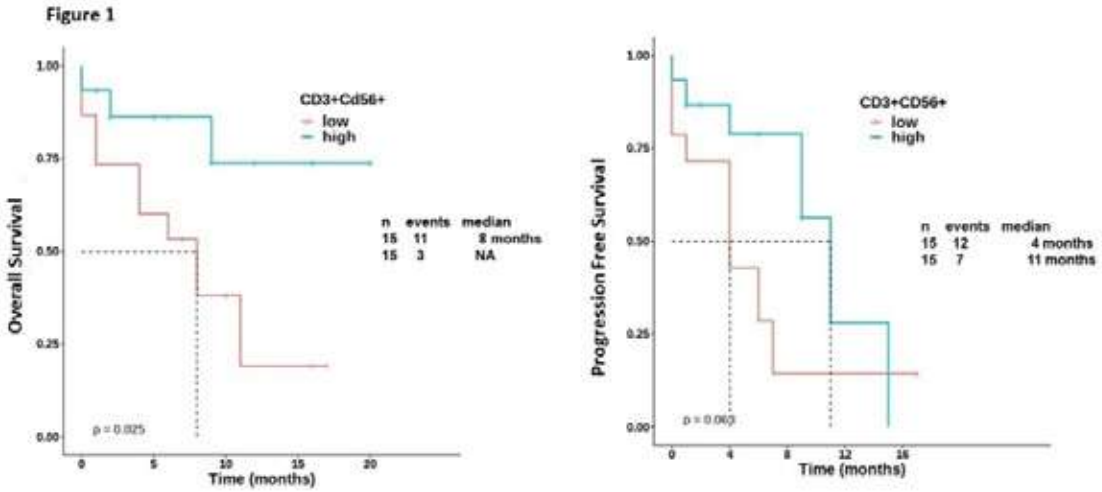

TABLE 1 : UNIVARIATE COX REGRESSION CONCERNING CIRCULATING IMMUNE CELLS AND OUTCOME OF SCLC PATIENTS						
Type of immune cells	**OS**			**PFS**		
	Number of patients	Hazard ratio (95% CI)	*P*	Number of patients	Hazard ratio (95% CI)	*P*
CD3+	30	1.37 (0.46-4.06)	0.57	29	1.75 (0.66-4.66)	0.26
CD4+	30	0.59 (0.20-1.78)	0.35	29	0.79 (0.32-1.99)	0.62
CD3+CD56+	**30**	**0.26 (0.07-0.92)**	**0.036**	**29**	**0.41 (0.07-1.05)**	**0.063**
CD3-CD56+	30	0.51 (0.18-1.51)	0.23	29	0.56 (0.22-1.42)	0.22
Treg/lymphocytes	29	0.71 (0.24-2.11)	0.53	28	0.74 (0.29-1.88)	0.52
Treg/CD3+	29	0.86 (0.29-2.57)	0.79	28	0.70 (0.28-1.76)	0.45
CD19+	30	1.69 (0.57-5.05)	0.35	29	1.23 (0.49-3.06)	0.66
CD3+CD8+	30	1.61 (0.53-4.83)	0.40	29	1.32 (0.53-3.31)	0.55

Keywords: Circulating CD3+CD56+ cells, Biomarker, Immunotherapy

P2.11 TOBACCO CONTROL AND RISK REDUCTION,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.11-01 Awareness of Lung Cancer Risk Factors in Palestine: Current Situation and Future Directions

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Introduction: Poor awareness of lung cancer (LC) risk factors may contribute to late presentation, which leads to poor survival outcomes. This study aimed to evaluate the awareness of LC risk factors among Palestinians and identify the factors associated with good awareness.

Methods: This was a national cross-sectional study conducted in Palestine from July 2019 to March 2020. Participants were recruited using convenience sampling from hospitals, primary healthcare centers, and public spaces located in 11 governorates. A translated-into-Arabic version of the validated LC awareness measure was used to assess recognition of 10 LC risk factors. One point was given for each correctly recognized risk factor. The awareness level was determined by the number of LC risk factors recognized: poor (0 to 3), fair (4 to 7), and good awareness (8 to 10).

Results: Of 5174 approached, 4817 participants completed the questionnaire (response rate= 93.1%). A total of 4762 questionnaires were included in the analysis, 2742 from the West Bank and Jerusalem (WBJ) and 2020 from the Gaza Strip. Participants from the WBJ were more likely to be older, have higher monthly income but lower education, and suffer from more chronic diseases.

Smoking-related risk factors were more often recognized than other LC risk factors. The most recognized risk factors were ‘smoking cigarettes’ (n=4466, 93.8%) and ‘smoking shisha [waterpipes]’ (n=4337, 91.1%). The least recognized risk factors were ‘having a close relative with LC’ (n=2084, 43.8%) and ‘having had treatment for any cancer in the past’ (n=2368, 49.7%) (Table 1). A total of 2381 participants (50.0%) displayed good awareness of LC risk factors. Participants from the WBJ and the Gaza Strip had a similar likelihood to display good awareness (50.6% vs. 49.1%). Being ≥45 years old, having higher education and monthly income, knowing someone with cancer, and visiting hospitals and primary healthcare centers were all associated with an increase in the likelihood of displaying good awareness.

Table 1: Recognition of lung cancer risk factors.				
Factor	**Total (n= 4762) n (%)**	**Gaza Strip (n= 2020) n (%)**	**WBJ (n= 2742) n (%)**	**p-value**
Smoking-related risk factors				
Smoking cigarettes	4466 (93.8)	1892 (93.7)	2574 (93.9)	0.77
Smoking shisha	4337 (91.1)	1822 (90.2)	2515 (91.7)	0.07
Exposure to another person's cigarette smoke	3867 (81.2)	1621 (80.2)	2246 (81.9)	0.15
Other risk factors				
Air pollution	3838 (80.6)	1543 (76.4)	2295 (83.7)	<0.001
Exposure to chemicals (e.g., asbestos)	3802 (79.8)	1582 (78.3)	2220 (81.0)	0.024
Exposure to radiation	3788 (79.6)	1598 (79.1)	2190 (79.9)	0.52
Having a previous history of lung disease (e.g., COPD)	3216 (67.5)	1382 (68.4)	1834 (66.9)	0.27
Having a previous history of cancer such as head and neck cancer	2778 (58.3)	1165 (57.7)	1613 (58.8)	0.43
Having had treatment for any cancer in the past	2368 (49.7)	1020 (50.5)	1348 (49.2)	0.36
Having a close relative with lung cancer	2084 (43.8)	832 (41.2)	1252 (45.7)	0.002

Conclusions: Half of study participants displayed good awareness of LC risk factors. Effective implementation of tobacco control policies is essential, along with educational initiatives to increase public awareness of the risk of smoking and other LC risk factors.

Keywords: lung cancer, risk factors, awareness

P2.11 TOBACCO CONTROL AND RISK REDUCTION,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.11-02 New Assay for Smoking Status based on 3D Imaging of Pulmonary Macrophages

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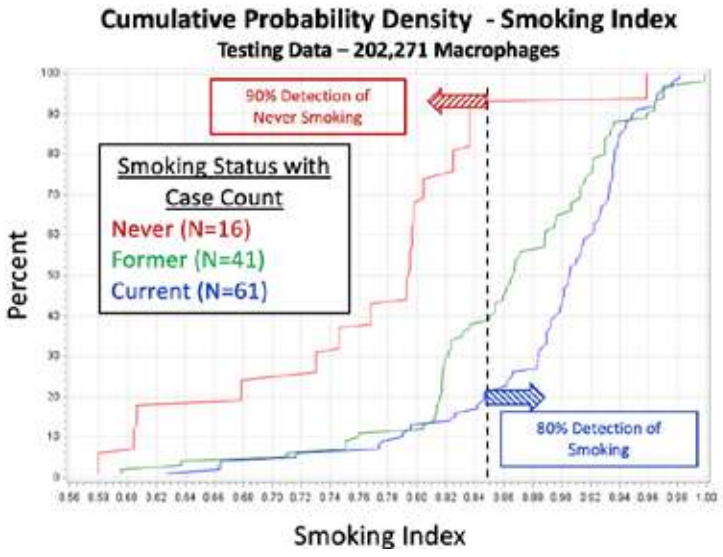
Introduction: The Cell-CT™ platform images cells in 3D with isometric, sub-micron resolution and measures orientation invariant 3D features in each cell. The Cell-CT is being used to identify abnormal pulmonary epithelial cells in sputum to indicate early-stage lung cancer. Sputum also contains pulmonary macrophages that ingest inhaled contaminants from smoking. We hypothesize that the Cell-CT with machine learning would discover subtle phenotypic characteristics in macrophages to differentiate current and never smokers. Using sputum from patients without lung cancer and cells identified by the macrophage detection classifier, we developed a second classifier to produce the smoking index to discriminate macrophages from current and non-smoking patients.

Methods: Using a supervised learning approach, we trained the macrophage detection classifier with 503 cell features based on 3D imaged cells and cytologically identified macrophages (N=5,320) and non-macrophage cells (N=12,067). Focusing on sputum from 58 smoking and 10 non-smoking patients without lung cancer, we identified 10,116 macrophages. Cell-CT feature data from these cells was used to train a second classifier using smoking status as ground truth to produce the smoking index probability for each cell. The smoking index is the median of the smoking index probability for all macrophages in each case. The smoking index was tested by identifying 202,271 macrophages from 61 current, 41 former, and 16 never smokers without lung cancer.

Results: 1. The macrophage detection classifier identifies cytology confirmed macrophages with 99% specificity.

2. The smoking index identifies smokers and never smokers with 80% and 90% sensitivity, respectively. The figure shows the cumulative probability functions of the smoking index for testing data for never (red), former (green), and current (blue) smokers. Consider a threshold of 0.85: 80% of the smoking population has an index above, while 90% of the never smokers have an index below this threshold, demonstrating the robust accuracy of the smoking index.



Conclusions: This analysis demonstrates the efficacy of 3D cell analysis to characterize subtle changes in macrophage morphology to assess smoking status. The study also suggests a partial regression of macrophage status toward the never-smoking state following smoking cessation. This assay is fully automated and does not require human cytology interpretation. With further clinical studies, it may be possible to gauge the effect of smoking and monitor smoking cessation based on the smoking index.

Keywords: Smoking, 3D Cell Imaging, Artificial Intelligence

P2.11 TOBACCO CONTROL AND RISK REDUCTION,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.11-03 Smoking Prevention Intervention With School Classes in University Hospital by Thoracic Surgeon und Pulmonologist

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Introduction: Smoking prevention in schoolchildren to inform and prevent smoking initiation has been widely studied, however the potential effect of interventions provided in a hospital setting is unknown. An intervention program named “Schoolchildren smoking prevention in the hospital” was developed in which the health aspects of smoking and its individual consequences were presented in an interactive informational event provided by a thoracic surgeon and a pulmonologist. We aimed to assess the feasibility and the short-term effect of smoking-related knowledge improvement in schoolchildren in a hospital setting.

Methods: Scholars of 45 classes in the Canton of Zurich in Switzerland filled in an anonymous 5-item questionnaire with questions on general knowledge about smoking and included in this prospective observational cohort study. The primary endpoint was to compare the knowledge improvement by interpretation of answers before-and-after the smoking prevention intervention. Additionally, the performance of children was compared after setting up an overall score and specific subgroups according to gender and school-level.

Results: Between Jan 2010, and Oct 2019, schoolchildren aged 10 to 16 years participated in this intervention programme and completed the questionnaire before (N=1270) and after (N=1264) the intervention. The amount of correctly answered questions increased from 40% (±20) before to 81% (±17), p< 0·0001 after the educational session.

Conclusions: An intervention program on health effects of smoking provided by lung specialists in the hospital is feasible, well received and leads to a substantial increase of knowledge and hopefully can be further explored in the development of smoking prevention programs for schoolchildren.

Keywords: smoking prevention, global health, school children

P2.12 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.12-01 Intratumoral Conventional Type 1 Dendritic Cells (cDC1s) Predict Response to Immunotherapy in Human Non-small Cell Lung Cancer (NSCLC)

A. Porciuncula[1], B. Henick[2], N. Gianino[1], J. Zugazagoitia[1], I. Vathiotis[1], N. Gavrielatou[1], S. Zacharek[3], D.L. Rimm[1], K.A. Schalper[1]
[1]Yale University, New Haven/CT/USA, [2]Columbia University, New York/NY/USA, [3]Moderna, Cambridge/MA/USA

Introduction: Conventional type 1 dendritic cells (cDC1s) mediate antigen cross-presentation to cytotoxic T-lymphocytes and participate in adaptive anti-tumor immune responses. The abundance, tumor tissue distribution and clinical significance of cDC1s in human lung cancer remain poorly understood. In this study, we spatially mapped cDC1s and other DC subsets in human non-small cell lung cancer (NSCLC) and studied their contribution to tumor immune infiltration and treatment-specific outcomes.

Methods: Five retrospective cohorts of patients with NSCLC represented in tissue microarray format treated either with immune checkpoint blockers (2 cohorts, N=185) or standard non-immunotherapy (3 cohorts, N=551) were analyzed by multiplexed quantitative immunofluorescence (QIF) panels including tumor and immune cell markers. A sixth cohort included lung adenocarcinomas with annotated KRAS and EGFR mutational status (N=128). Co-expression of HLA-DR, CD11c and XCR1 was used to identify cDC1s and measure them across different tumor tissue compartments using fluorescence co-localization strategies. The association between cDC1 density and spatial patterns in baseline NSCLCs, clinicopathologic/molecular variables and treatment-specific outcomes were studied.

Results: cDC1s comprised ~3% of cells within the tumor microenvironment. The density of cDC1s was significantly higher in lung adenocarcinomas harboring activating KRAS mutations than in tumors with EGFR variants or those lacking mutations in both oncogenic drivers. No significant association between cDC1 levels and major clinicopathologic variables was identified. Increased cDC1 density within the tumor-cell compartment showed positive association with markers of productive local adaptive immune response and T-cell regulation such as CD4, CD8, FOXP3, PD-1, TIM-3, LAG-3, MHC-I and ß2M (Spearman's R, $p<0.05$). In patients treated with immune checkpoint blockers (mostly PD-1 axis blockade), elevated density of cDC1s within the tumor-cell area was significantly associated with durable clinical benefit defined as response or stable disease lasting ≥6 months, and this was significant in two independent cohorts ($p=0.028$ and $p=0.033$, respectively). A similar association was seen between cDC1 density and overall survival. However, no consistent association with outcomes was observed after measuring cDC1s in the stromal-cell compartment, considering other non-cDC1 subsets, or in cases treated with standard of care non-immunotherapy.

Conclusions: cDC1s constitute a small fraction of immune cells in the tumor microenvironment of human NSCLC and are associated with productive local adaptive immune responses and oncogenic KRAS mutations in lung adenocarcinomas. Despite their relatively low abundance, cDC1s located within the tumor-cell nests are predictive of better outcome after immune checkpoint blockers.

Keywords: Non-small cell lung cancer (NSCLC), Immunotherapy, Conventional type 1 dendritic cells

P2.12 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.12-02 Immune-Cell Distribution Between Tumor Edge and Center Affects Lung Cancer Aggressiveness - Multiplex Immunofluorescence

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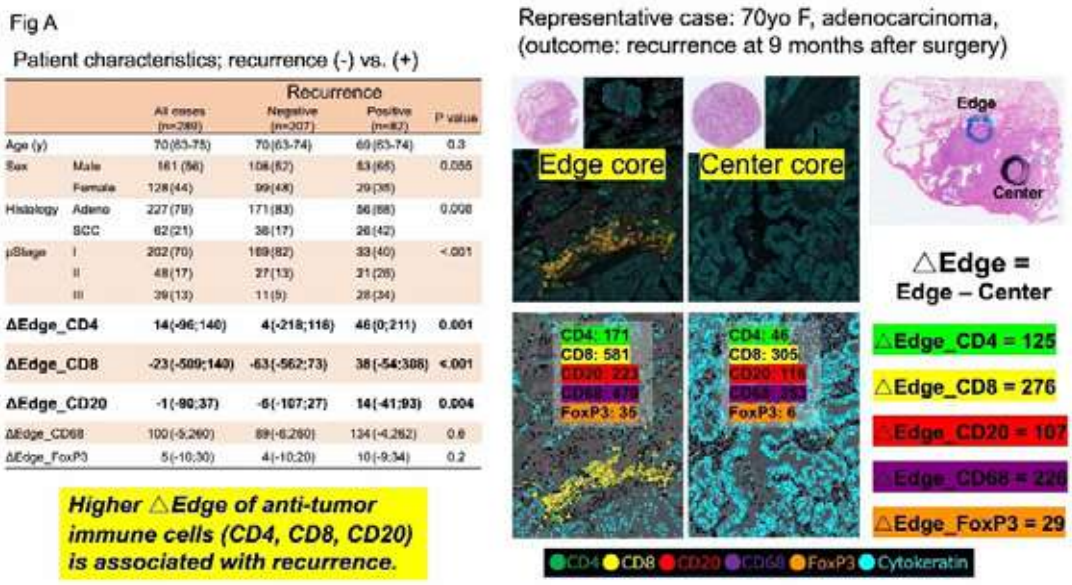
Shinshu University School of Medicine, Matsumoto/JP

Introduction: Spread through air spaces (STAS) is a form of invasion wherein tumor cells extend beyond the tumor edge, associated with a worse prognosis (Eguchi, Travis, Adusumilli et al. *J Thorac Oncol* 2019). The tumor microenvironment affects tumor aggressiveness. We hypothesized that the distribution of immune cells (edge vs. center) was associated with the formation/prognostic impact of STAS and lung cancer prognosis.

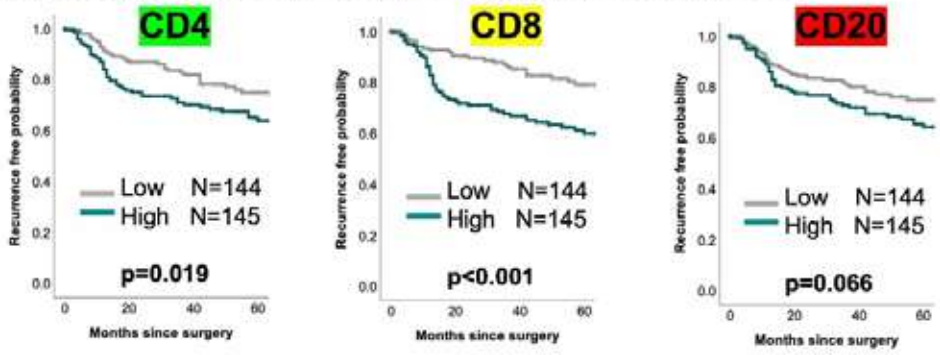
Methods: We retrospectively investigated 289 patients who underwent curative-intent lung resection 2013-2017 (227 adenocarcinomas and 62 squamous cell carcinomas). We developed a tissue microarray with two 3-mm cores both from the edge and center in each tumor. All tissue-microarray slides were stained by a multiplex immunofluorescence panel, comprising CD4, CD8, CD20, CD68, FoxP3, cytokeratin, and DAPI, followed by image acquisition (Vectra) and cell phenotyping (inForm). We defined ΔEdge as the difference in the number of immune cells between edge and center cores (ΔEdge = edge - center) (high ΔEdge value represents more immune cells in the tumor edge than those in the center). ΔEdge values were compared using logistic analysis. Recurrence-free probability (RFP) was evaluated using the Cox hazard model and Kaplan-Meier methods with the log-rank test.

Results: Our significant findings were 1) elevated ΔEdge of anti-tumor immune cells (CD4, CD8, CD20) were associated with recurrence (Figures A1-B1), 2) multivariable analysis for recurrence in stage I patients revealed high ΔEdge of CD8+ T cells and the presence of STAS as independent risk factors for recurrence (Figure B2), and 3) patients with STAS were associated with a higher risk of recurrence only when ΔEdge of FoxP3 was high but not low (Figure B3).

Conclusions: Tumors protecting themselves from anti-tumor immune-cell infiltration are associated with a worse prognosis regardless of pathological prognosticators, including STAS. The prognostic impact of STAS depends on the peripheral distribution of FoxP3+ regulatory T-cell infiltration.



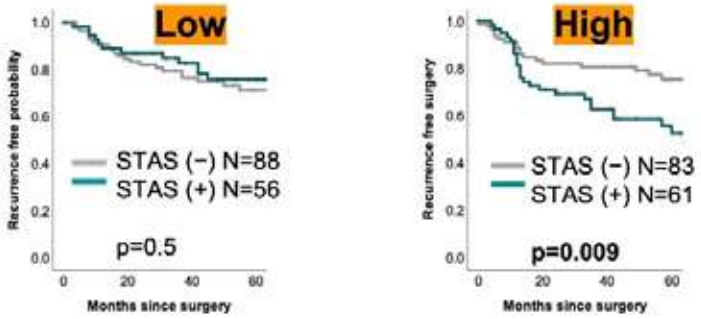
B-1) RFP: **High vs. Low ΔEdge** of anti-tumor immune cells



B-2) Multivariable analysis for recurrence (stage I, final model)

	HR (95% confidence interval)	P value
SCC (vs. adenocarcinoma)	3.70 (1.63-8.41)	**0.002**
STAS positive (vs. negative)	2.38 (1.13-5.00)	**0.022**
High ΔEdge_CD8 (vs. low)	2.44 (1.18-5.02)	**0.016**

B-3) RFP: **STAS (+) vs. (-)** by **ΔEdge_FoxP3** status



Keywords: STAS, Tumor microenvironment, FoxP3

P2.12 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.12-03 External Validation of a Novel CT-Based Prognostic Radiomic Signature in Patients with Metastatic NSCLC in SWOG S0819 Phase III Randomized Trial

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[1]NewYork-Presbyterian, Columbia University Irving Medical Center, New York/NY/USA, [2]Memorial Sloan Kettering Cancer Center, New York/NY/USA, [3]UC Davis Comprehensive Cancer Center, Sacramento/CA/USA, [4]Smilow Cancer Hospital Care Center, North Haven/CT/USA, [5]Fred Hutchinson Cancer Research Center, Seattle/WA/USA

Introduction: There is an unmet need in elucidating effective correlative biomarkers for individualized selection of therapeutic regimens in patients with a diagnosis of advanced NSCLC. Recent innovations in artificial intelligence (AI) can enhance the role of CT imaging by taking advantage of previously unutilized information through the ability to identify imaging biomarkers through quantitative analysis that is objective, reproducible, and rapidly obtainable. Our group has previously leveraged this approach by applying AI in patients with NSCLC treated with nivolumab in CheckMate017, CheckMate026, and CheckMate063. In this cohort, we identified a radiomics signature (NivoSig) that was correlated with overall survival (OS). In the current analysis, we sought to validate NivoSig in a separate cohort of patients with distinct systemic therapy regimens who were enrolled in a large randomized trial.

Methods: We retrospectively analyzed CT images and associated clinical metadata for patients enrolled on SWOG S0819 [NCT00946712]. Participants (n=1,229) had a diagnosis of advanced NSCLC and were randomized to treatment with chemotherapy (carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab) alone (n=607) or the same chemotherapy regimen in combination with cetuximab (n=622). All participants were included as an external validation set for NivoSig. From CT images, the volume of measurable tumor lesions was semi-automatically segmented and seven radiomic variables depicting tumor phenotype were extracted. The radiomic signature used a predefined and locked combination of these imaging variables to output a continuous value, ranging from 0 to 1 (from most to least favorable estimated OS); patients were categorized as low- vs. high-risk groups as previously determined. Cox regression and the log-rank test was used to validate the NivoSig risk-groupings with OS. Survival distributions were estimated via Kaplan-Meier. Radiomic features between risk groups were compared using a t-test.

Results: The primary publication reported no difference in OS (Hazard ratio (HR)=0.93[95CI: 0.83-1.04], P=0.22) and data in this analysis were consistent (HR=0.94[95CI: 0.84-1.06], P=0.315). Patients with high-risk prognostic NivoSig had a 50% increased risk of death compared to low-risk NivoSig (HR=1.50 [95CI: 1.33-1.69], P<0.0001), and shorter median survival (n=697, 12.3 months [95CI: 11.1-13.3]) vs. high-risk NivoSig (n=532, 8.4 months [95CI: 7.48-8.98]).In addition, comparison of NivoSig's individual radiomic features stratified high-risk (n=532) vs. low-risk (n=697) patients as follows (mean(SD), P-value): A) distinct tumor texture in two radiomics components, laws boundary and spatial correlation (P<0.001 for both); B) higher overall tumor volume (157.3(202.2) vs. 53(51.5) cm^3, P<0.001); C) higher liver tumor volume (20.4(88.3) vs. 0(0.4) cm^3, P<0.001); D) higher mediastinal lymph node tumor volume (25.2(40.2) vs. 10.9(15) cm^3, P<0.001); E) higher axillary lymph node tumor volume (2.2(32.6) vs. 0(0) cm^3, P=0.078); and F) higher number of target lesions (6.18(3.71) vs. 3.97(2.29) cm^3, P<0.001).

Conclusions: NivoSig is a novel AI-guided radiomics signature previously derived in patients treated with immunotherapy. In this analysis we found that it was generalizable to patients in a large, randomized trial receiving a distinct treatment approach without immunotherapy. In addition, individual AI-generated radiomic features stratified high- vs. low-risk patients with respect to OS. Future directions will incorporate these features to better elucidate mechanisms of resistance.

Keywords: NSCLC, Artificial Intelligence, Radiomics

P2.12 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.12-04 The Role of Serum Proteomic Signature in Predicting Survival in PD-L1 Low Non-small Cell Lung Cancer Receiving Immune Checkpoint Inhibitor (ICI)

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Introduction: The VeriStrat test is a blood-based proteomic test derived from machine learning which uses MALDI-ToF mass spectrometry based signature. Results from this test have shown prognostic utility in different stages, histologies, and treatment types for patients with non-small-cell lung cancer (NSCLC). Recently, the VeriStrat test has also shown prognostic utility in patients receiving ICI treatment. Meanwhile, the role of biomarker is not established among lung cancer patients with low PD-L1 expression, for whom the effect of ICI treatment is limited.

Methods: This is a retrospective study that includes 61 patients with advanced-stage NSCLC who received ICI monotherapy or in combination with chemotherapy with PD-L1 <50%. Patients underwent VeriStrat testing from 2016 to 2021. Spectra from blood samples were evaluated to assign patients into the VeriStrat 'Good' (VS-G) or VeriStrat 'Poor' (VS-P) groups. OS and PFS were calculated with log-rank test for the first ICI containing regimen that each patient received.

Results: Among 61 patients, 32 patients had low PD-L1 expression (1-49%) and 29 patients had negative expression (< 1%). And 32 patients had ICI in combination with chemotherapy and 29 patients had ICI monotherapy as the first ICI containing treatment.

Compared to the VS-P group, patients in VS-G group demonstrated better PFS (mPFS of 7 vs. 4 months, HR 0.54; 95%CI, 0.25 - 1.17; P=0.05) and OS (mOS 14 vs. 9 months, HR 0.55; 95%CI 0.27 - 1.16; P=0.06.) Among patients with negative PD-L1 expression, the VS-G group demonstrated significantly longer PFS in comparison to VS-P group (median PFS 10 vs. 3.5 months, HR 0.38; 95%CI 0.14-1.00; P=0.01) with no significant difference in OS (P=0.17). Among patients with low PD-L1 expression level, superior OS was observed in VS-G group compared to VS-P group (mPFS 13 vs. 5 months, HR 0.27; 95%CI 0.05-1.34; P=0.003) with no significant difference in PFS (P=0.22). For patients who received ICI monotherapy, better OS was observed in VS-G group compared to the VS-P group (mOS 20 vs. 7 months, HR 0.30; 95%CI 0.07 - 1.19; P=0.006) with equivalent PFS (P=0.28). There was no significant difference in OS (P=0.49) and PFS (P=0.15) among patients who received ICI and chemotherapy combination.

Conclusions: Our results demonstrate that the blood-based proteomic test result is predictive of PFS and OS in NSCLC with low or negative PC-L1 treated with ICIs. Patients whose VeriStrat status was Good had better PFS and OS compared to the patients whose VeriStrat status was Poor.

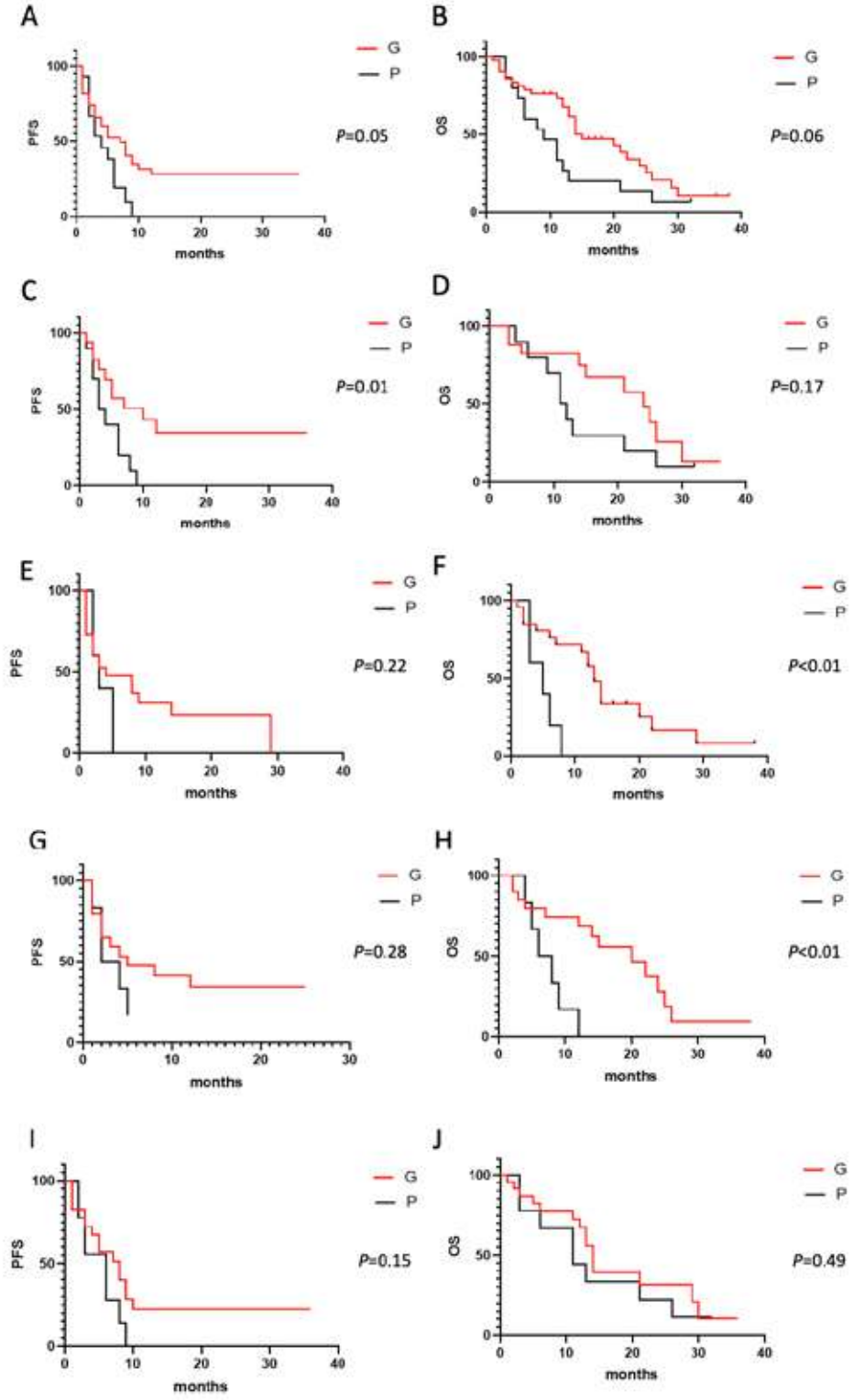

Figure 1. Kaplan-Meier survival curves for progression free survival and overall survival: in all patients (A,B); patients with PD-L1 <1% (C,D), patients with 1%≤ PD-L1 <50% (E,F), patients with ICI only regimen (G,H), and patients with ICI and chemotherapy combination (I,J)

Keywords: biomarker, NSCLC, immunotherapy

P2.12 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.12-05 Cancer and Atopy: Parallel Drivers? IL-4 Blockade Synergizes with PD-L1 Blockade to Reverse Type-2Mediated Immunosuppression

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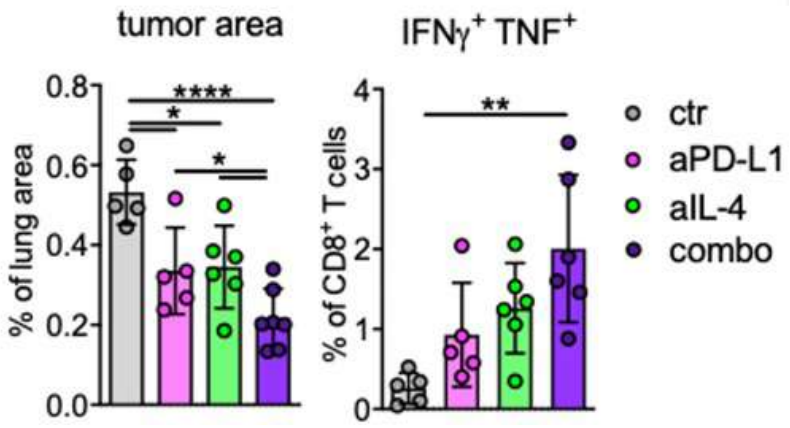
Introduction: Type-2 cytokines, such as IL-4, alter macrophage immunogenicity *in vitro* leading to the M1/M2 paradigm, however, the role of IL-4 *in-vivo* in cancer remains unclear. Using high dimensional immune profiling of human NSCLC lesions we previously described several functionally distinct populations of macrophages, and a tumor-enriched dendritic cell program of concomitant immunosuppression and activation which we termed the mregDC, and we identified analogous cells in a murine model of lung cancer (Maier *et al, Nature* 2020, Casanova-Acebes *et al, Nature,* 2021, Leader *et al, Cancer Cell* 2021).

Methods: We used scRNAseq and CITEseq to identify that immunosuppressive tumor-infiltrating myeloid cells subsets express an IL-4 responsive transcriptional program upon tumor antigen uptake, suggesting a role of Type-2 immunity in establishing an immunopermissive intratumoral milieu. To probe the role of IL-4 signaling on tumor growth, we subsequently blocked this cytokine *in vivo* in tumor bearing mice and investigated potential synergy with PD-L1 blockade in multiple preclinical models.

Results: In a krasG^{12}Dp53-/- lung cancer model we found that IL-4 blockade reduced lung tumor burden, and synergizes with PD-L1 blockade; diminished tumor growth corresponded to an increase in cytotoxic CD8+ T cells (*figure*). We recapitulated this synergistic anti-tumor effect of dual IL-4/PD-L1 blockade in multiple other cancer models. Notably, using the B16-F10 tumor line engrafted at different tissue sites, we found that IL-4 blockade reduced tumor burden within the lung, but had no effect on tumor growth in subcutaneous tissue, suggesting there may exist context-dependent interactions between the tissue microenvironment and tissue-resident immune cells.

Conclusions: We have demonstrated in both humans and mice a strong Type-2 immune program in intra-tumoral myeloid cells, induced upon tumor antigen uptake, with a pronounced IL-4 responsive transcriptional program that coincides with an immunosuppressive transcriptional profile. Here we report new data demonstrating that IL-4 blockade augments antitumor immunity and synergizes with PD-L1 blockade in multiple pre-clinical models, likely in a context dependent manner. Based on these findings in both human and mice of a strong Type-2 myeloid signature, we are now exploring the role of IL-4 blockade in lung cancer patients using dupilumab, an anti-IL-4Ralpha antibody widely used for treatment of atopic diseases. In patients with NSCLC whose disease has progressed on PD-(L)1 therapies, checkpoint blockade is continued and dupilumab is added to see whether clinical response to immunotherapy can be rescued. Recruitment to this trial is ongoing and results will be presented at a later time (NCT05013450).



Keywords: Type-2 immunity, Immunotherapy, Mechanisms of resistance

P2.13 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.13-01 Low EV miR-30c Levels as Biomarker of Increased Tumor Autophagy and Chemoradiotherapy Resistance in Locally Advanced NSCLC

D. de Miguel Perez[1,2,3], F.G. Ortega[2], R. Guerrero Tejada[4], C.B. Peterson[5], A. Russo[6], M. Gunasekaran[7], A.F. Cardona[8], C.I. Bayarri Lara[9], A. Garcia-Diaz[2], F.R. Hirsch[1], J.A. Lorente[2,3], J. Exposito Hernandez[4], M.J. Serrano[2,10], C. Rolfo[1]

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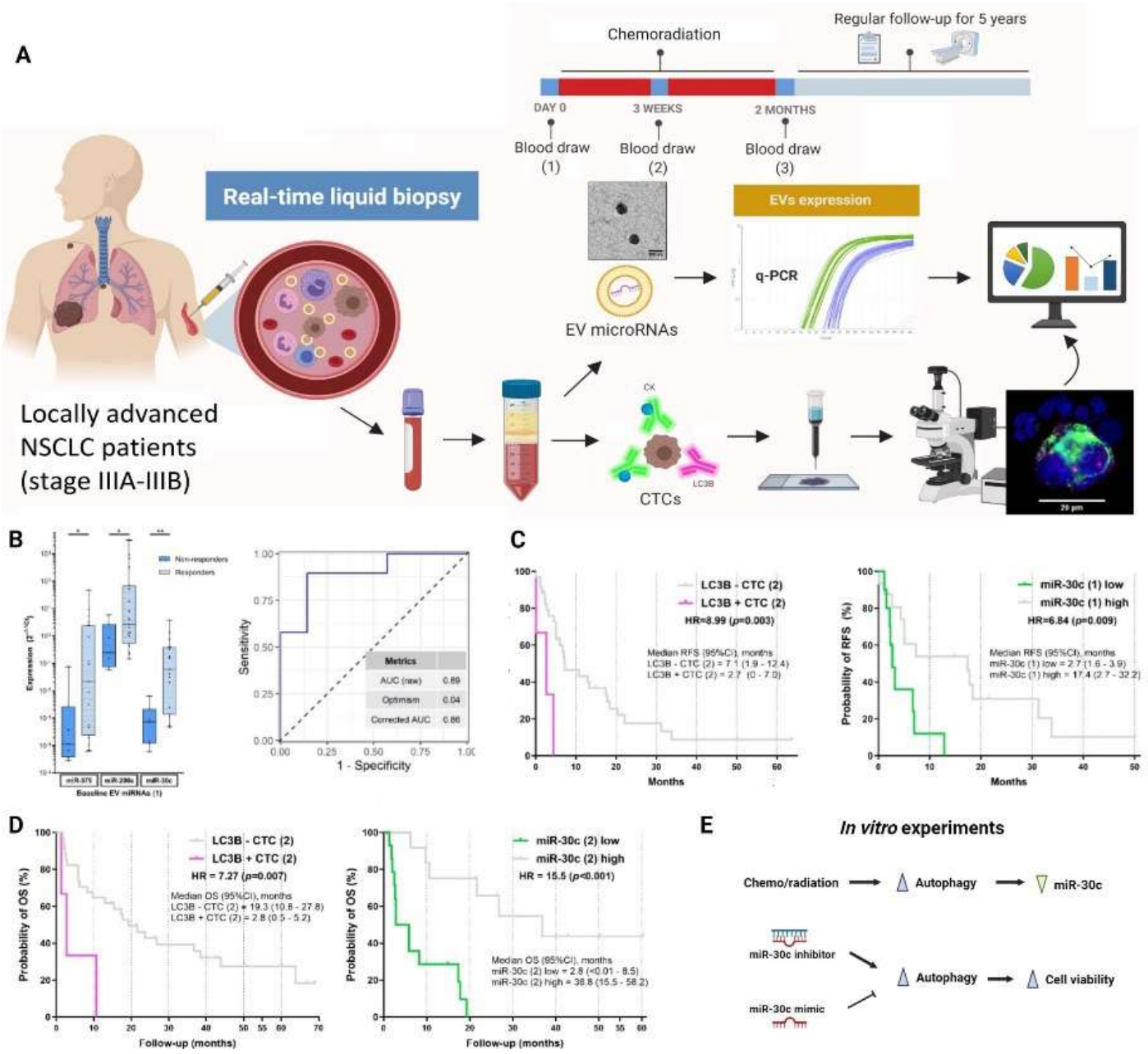
Introduction: Chemoradiation is the standard treatment for patients with unresectable locally advanced non-small cell lung carcinoma (LA-NSCLC), however, treatment resistance is commonly developed and the prognosis still poor, since no reliable biomarkers are available for patient stratification. In this context, autophagy up-regulation has been postulated as a mechanism of resistance to chemoradiation and we presented, at the IASLC 2020 Lung Cancer Hot Topic: Liquid Biopsy and the AACR: Radiation Science and Medicine 2021, autophagy in circulating tumor cells (CTCs) and levels of specific extracellular vesicle (EV) miRNAs can be correlated and evaluated as promising minimally invasive predictive biomarkers. Here, we aim to further investigate the mechanism by which these EV-associated miRNAs are involved in the activation of autophagy and the development of chemoradiation resistance in advanced NSCLC patients.

Methods: Prospective blood samples from 38 LA-NSCLC patients were collected before, during and after chemoradiotherapy (Figure 1A). CTCs were immunomagnetically isolated and characterized for the expression of the autophagic marker LC3B. EVs were isolated by differential centrifugation and expression levels of a panel of specific EV-miRNAs were determined. Chemoradiation *in vitro* models were performed in A549 and H1975 cell lines where autophagy, viability, and miR-30c levels where analyzed under all treatments and after the transfection with miR-30c mimic or inhibitor.

Results: Non-responders showed lower pretreatment levels of EV-miR-375, miR-200c, miR-30c creating a predictive model with an area under the curve of 86% (Figure 1B). During treatment, decrease of these EV miRNAs levels were correlated with an increase of autophagic CTCs. Moreover, low EV miR-30c and presence of autophagic-CTCs were also independent predictive biomarkers for shorter relapse-free survival (Figure 1C) and overall survival (Figure 1D). Then, *in vitro* models showed that chemoradiation promoted autophagy and reduced levels of miR-30c. When a miR-30c mimic was added, treatment-induced autophagy was inhibited and cellular viability was decreased, contrary to the activation of autophagy and increase of viability observed with the miR-30c inhibitor (Figure 1E).

Conclusions: This study describes, for the first time, that EV-miRNAs, in particular miR-30c, are involved in the regulation of autophagy as a mechanism of resistance to chemoradiotherapy observed also by the presence of autophagic-CTCs. Thus, we promising propose the use of EV miR-30c and autophagic CTCs as biomarkers for the stratification and monitoring of stage III NSCLC patients undergoing chemoradiation, who could also potentially benefit from novel combinatorial therapies with autophagy inhibitors.



Keywords: Chemoradiotherapy, Extracellular vesicles, Autophagy

P2.13 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.13-02 Dynamic Tracking of Bespoke Circulating Tumour DNA During Multi-Modality Therapy for Locally Advanced NSCLC (LA-NSCLC)

K.L.M. Chua[1], A. Tan[1], S. Saw[1], G. Lai[1], W.L. Tan[1], A. Jain[1], T. Rajasekaran[1], B. Chia[1], Y. Li[1], K.W. Fong[1], T.R. Siow[1], Q.S. Ng[1], A. Thiagarajan[1], R. Kanesvaran[1], W.L. Ng[1], S.P. Yap[1], E. Kalashnikova[2], A. Aleshin[2], A.J. Skanderup[3], W-T. Lim[1], C. Yip[1], S.H. Tan[1], D.S.W. Tan[1], M-K. Ang[1]

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Introduction: LA-NSCLC is intrinsically heterogeneous, with distinct molecular and phenotypic subtypes. Curative treatment includes surgery, chemo-radiotherapy, and more recently immunotherapy and tyrosine kinase inhibitors. Yet half of all patients relapse within the first year, highlighting the need for reliable biomarkers to guide risk stratification strategies. Circulating tumour DNA (ctDNA) has emerged as a non-invasive method to detect and track minimal/molecular residual disease.

Methods: In this prospective, observational study conducted between 11/2019-1/2022, 46 patients were screened, of which 30 met the eligibility criteria for inclusion. The cohort included patients with Stage-III (N=27) and oligometastatic Stage-IV (N=3) NSCLC, who were planned for radical local therapy (LT). 27 patients received planned LT: radiotherapy (RT; N=22), surgery (S; N=2) and both (RT-S; N=3). Of these, 16 received further maintenance therapy (MT). The remaining 3/30 patients received chemo/TKI only due to disease progression or physician considerations. Plasma samples (N=112) were prospectively collected at pre-determined longitudinal timepoints: pre-induction, pre-, during- and post-LT, during-MT and during-surveillance. Whole exome sequencing of biopsy/resected tissue and matched normal DNA was used to design personalized, tumour-informed ctDNA assays (SignateraTM) to track 16 single-nucleotide variants in plasma samples. The relationship between longitudinally tracked ctDNA levels and treatment failure (TF) at any local/distant site, detected by radiographic imaging was evaluated by Fisher's exact test. Time-to-failure (TTF) was estimated using the Kaplan-Meier method.

Results: In this cohort, tumour subtypes included, adenocarcinoma (EGFR-mutated: 26.7%, EGFR-wildtype: 43.3%) and squamous cell (SCC)/other subtypes (30.0%). At baseline, ctDNA was detected in all patients, with significant heterogeneity across subtypes (median MTM/mL: 3.1[EGFR-mutated] *vs* 8.7[EGFR-wildtype] *vs* 243.3[SCC/others], P=0.03). At the time of reporting, 29 patients had evaluable outcomes. Following LT, imaging responses were CR (2/26, 7.7%), PR (18/26, 69.2%), SD (3/26, 11.5%) and PD (3/26, 11.5%**)**. At the post-LT timepoint, 24 patients had ctDNA samples available and 14 (58.3%) achieved ctDNA clearance. TF was observed in 13 (44.8%) patients and significantly associated with a serial increase in ctDNA (P<0.001); two patients developed solitary sub-cm brain metastasis and remained undetected by ctDNA. Another two patients demonstrated increasing ctDNA and had indeterminate imaging findings. Of the 16 patients who had MT, 4 experienced a ctDNA rise. Interestingly, TTF for these patients was significantly shorter compared to those without ctDNA increase (3.4mo[rise] *vs* 11.2mo[no rise], P=0.02). In the longitudinal setting, 27 patients had serial timepoints available, of which 19 (70.4%) achieved ctDNA clearance; 7/19 (36.8%) subsequently developed TF. TTF was significantly longer for patients who achieved clearance compared to patients with detectable nadir levels throughout treatment (12.3mo[undetectable] *vs* 3.1mo[detectable]; P<0.001).

Conclusions: Here, we demonstrate the clinical feasibility of deploying a personalized, tumour-informed ctDNA assay in LA-NSCLC. Detectable ctDNA nadir levels throughout therapy identified patients at high risk of early relapse, providing a rationale for treatment intensification. Our data suggests that dynamic tracking of ctDNA levels functions as a reliable biomarker of response at various phases of multi-modality therapy, providing a potential window into developing patient-specific combinatorial approaches. Prospective biomarker stratified studies are needed to assess the clinical utility of these ctDNA assays.

Keywords: circulating tumour DNA, locally advanced, oligometastates

P2.13 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.13-03 Plasma Profiling Unveils Transcriptional Signatures Associated with Resistance to Osimertinib in Non-Small Cell Lung Cancer

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Introduction: Targeted therapy with tyrosine kinases inhibitors (TKIs) against epidermal growth factor receptor (EGFR) is part of routine clinical practice for EGFR mutant advanced non-small cell lung cancer (NSCLC) patients. These patients eventually develop resistance, frequently accompanied by a gatekeeper mutation, T790M. Osimertinib is a third-generation EGFR TKI displaying potency to the T790M resistance mutation. Here we aimed to analyze if exosomal RNAs, isolated from longitudinally sampled plasma of osimertinib-treated EGFR T790M NSCLC patients, could provide biomarkers of acquired resistance to osimertinib.

Methods: Plasma was collected at baseline and progression of disease from 20 patients treated with osimertinib in the multicenter phase II study TKI in Relapsed EGFR-Mutated non-small cell lung cancer patients (TREM). Plasma was centrifuged at 16,000g followed by exosomal RNA extraction using Qiagen exoRNeasy kit. RNA was subjected to transcriptomics analysis with Clariom D.

Results: Transcriptome profiling revealed differential expression (log2(fold-change)>0.25, false discovery rate (FDR) p<0.15, and p(interaction) > 0.05) of 128 transcripts. We applied network enrichment analysis (NEA) at the pathway level in a large collection of functional gene sets. This overall enrichment analysis revealed alterations in pathways related to EGFR and PI3K as well as to syndecan and glypican pathways (NEA FDR<3*10-[10]). When applied to the 40 individual, sample-specific gene sets, the NEA detected 16 immune-related gene sets (FDR<0.25, p(interaction) > 0.05 and NEA z-score exceeding 3 in at least one sample.

Conclusions: Our study demonstrates the ability of plasma-derived exosomal RNA to characterize molecular phenotypes of emerging osimertinib resistance. Furthermore, it highlights the involvement of multiple RNA species in shaping the transcriptome landscape of osimertinib-refractory NSCLC patients.

Keywords: Non-small cell lung cancer, exosomal RNA, osimertinib

P2.14 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.14-01 Clinical Utility of Reflex to Tissue-based Comprehensive Genomic Profiling (CGP) After Negative Liquid Biopsy (LBx) in NSCLC

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Introduction: Identification of genomic driver alterations can assist patients with NSCLC to the most efficacious treatment selection. CGP of circulating tumor DNA (ctDNA) has emerged as a compelling option for identifying these alterations given availability of FDA-approved multi-gene NGS panels. However, LBx approaches can have imperfect sensitivity for detecting driver alterations under certain circumstances, and the FDA labels recommend a reflex to tissue biopsy (TBx) testing to confirm negative LBx. We sought to use real-world (rw) evidence to quantify the utility of confirmatory TBx testing after negative LBx.

Methods: This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine advanced NSCLC clinico-genomic database (FH-FMI CGDB). The de-identified data originated from approximately 280 US cancer clinics (~800 sites of care). The analysis was limited to patients with advanced NSCLC (aNSCLC) receiving any LBx multi-gene NGS followed by a tissue CGP (F1/F1CDx). LBx "negative" was based on either F1L/F1LCDx results or abstracted results from other NGS-panels demonstrating negative status of 5 common NSCLC driver alterations: *KRAS/EGFR* mutations, *BRAF* V600E and *ALK/ROS1* rearrangements. Fisher's exact tests were used to assess categorical differences observed between groups. Kaplan-Meier curves were used to assess rwPFS and rwOS.

Results: Of 1,221 LBx sent prior to 1st-line therapy (1L) in patients with aNSCLC, 437 (36%) were positive for one of the 5 common driver alterations. Amongst patients with negative LBx, 410 (226 G360, 51 F1L/F1LCDx, 133 other) received follow up TBx testing. Of these, 133 patients (32%) were positive on TBx for driver alterations in one or more of the 5 genes: 64 *KRAS* (25 G12C), 34 *EGFR*, 21 *ALK*, 11 *ROS1*, 3 *BRAF* V600E. An additional 45 patients (11%; 43% in total) were positive for one or more newer NSCLC NCCN driver alterations: 20 *MET* exon14, 9 *MET* amp, 10*ERBB2* mutation, 6 *RET* rearrangements. Focusing on 358 patients with TBx after negative LBx (median 3.4 weeks from LBx to TBx report), 179 (50%) had TBx CGP prior to 1L. TBx CGP prior to 1L was associated with lower likelihood of receiving a chemo containing regimen (107/179, 60% vs 146/179, 82%) and a higher likelihood of receiving matched targeted therapy (36/179, 20% vs 10/179, 6%). The 36 patients that received TBx-matched targeted therapy had median real-world PFS of 20 months (95% CI: 10.5 - NA) and prolonged rwOS (median not reached).

Conclusions: Reflex to TBx CGP identified an NCCN driver alteration in 43% of patients with aNSCLC and a prior negative LBx for 5 common driver alterations. These results support the IASLC Consensus Statement recommending reflex to tissue testing after negative LBx, an approach that can enable guideline-adherent treatment and ensure access to standard of care targeted therapy to improve clinical outcomes. Future research is ongoing to refine which patients benefit most from TBx reflex testing, and whether patients with elevated ctDNA tumor fraction on LBx can be spared confirmatory TBx.

P2.14-02 TP53 Mutations Affect Sensitivity to Lorlatinib in ROS1 Positive NSCLC: Final Results of the PFROST Trial

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Introduction: In crizotinib-refractory *ROS1+* non small-cell lung cancer NSCLC, lorlatinib showed intracranial and systemic activity especially in absence of acquired *ROS1* mutations. Other molecular events potentially affecting sensitivity to lorlatinib remain to be explored. In the prospective PFROST trial, which evaluated lorlatinib at crizotinib failure, response rate (RR) was >40%; median progression-free survival (PFS) and overall survival (OS) were 8.9 months and not reached, respectively. Here, we present final results of the trial focusing on the role of molecular events in modulating activity of lorlatinib.

Methods: In the PFROST trial, tissue or plasma samples collected at baseline and at lorlatinib failure were analyzed with NEOSelect and NEOliquid, two NGS assays covering 39 cancer-related genes. In the study, all patients received lorlatinib 100 mg once daily orally until disease progression. Clinical outcomes were analyzed according to molecular characteristics, long-term survival and impact of brain metastases (BM).

Results: At data cut-off (February 2022), with a median follow-up of 36.0 months, in the whole population (N=22) median PFS and OS were 8.9 months (95% CI: 2.2-15.6) and 30.4 months (95% CI: 10.6-50.2), respectively. Among patients with baseline BM (N=15), median PFS and OS were 8.5 months (95% CI: 4.3-12.7) and 30.4 months (95% CI: 0-62.4), respectively. In patients without BM (N=7), median PFS and OS were 12.6 months (95% CI: 0-41.9) and 34.2 months (95% CI: 13.6-54.8), respectively. In patients with BM, extracranial failure was the main pattern of relapse (72%) during lorlatinib therapy. All but one patient had baseline tissue or plasma samples for NGS analyses. Mutations in *TP53* gene were detected in 11 (52.3%) patients, including 4 cases with concomitant *ROS1* mutation (N=2, G2032R; N=1, V2054A; N=1, S1861I). Co-altered ROS1+/TP53+ individuals were mainly females (54.5%), never smokers (54.5%), with median age of 57 years and PS of 1 (63.6%). In this subgroup, RR was 27.3%, median PFS was 8.5 months (95% CI: 0.8-16.2) and median OS was 14.6 months (95% CI: 0-31.1), respectively. In contrast, in ROS1+/TP53- patients, RR was 50%, median PFS was 26.3 months (HR: 2.30, 95% CI: 0.78-6.75) and median OS was 30.7 months (HR: 2.75, 95% CI: 0.84-8.96).

Conclusions: In our trial, presence of *TP53* mutations identified a subset of *ROS1+* individuals at high risk of progression and death. Different and/or more aggressive strategies should be investigated in this specific population.

Keywords: ROS1 NSCLC, TP53, LORLATINIB

P2.14 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.14-03 Restored Ubiquitination and Degradation of Exon 14 Skipped MET with Proteolysis Targeting Chimeras

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Introduction: Hepatocyte growth factor receptor, more commonly referred to as MET, is a known oncogenic driver in multiple malignancies. Recently the tyrosine kinase inhibitors capmatinib and tepotinib have been approved by the United States Food and Drug Administration for the treatment of patients with non-small cell lung cancers that harbor *MET* exon 14 skipping mutations. Mutations that affect the donor or acceptor splice sites of *MET* exon 14 pre-mRNA can lead to skipping of exon 14 during splicing and an mRNA product where exons 13 and 15 are fused. Subsequent translation results in a shortened MET protein without its juxtamembrane domain. This juxtamembrane domain includes a degron that is recognized by the E3 ubiquitin-protein ligase Cbl. In the absence of the MET degron recognized by Cbl, MET is not readily ubiquitinated, thus prolonging its half-life by avoiding proteasomal degradation, and drives downstream signaling and oncogenicity. Protein degradation with protein targeting chimeras (PROTACs) represents a novel strategy to inhibit and eliminate oncogenic targets. PROTACs are heterobifunctional molecules that link two protein-binding molecules: one that recognizes a target, and the other that recruits an E3 ubiquitin-protein ligase. Thus, PROTACs can recruit E3 ubiquitin-protein ligases to ubiquitinate their targets and mark them for degradation by the proteasome. We hypothesized that a MET-targeting PROTAC could restore ubiquitination of MET with exon 14 skipping mutations and promote its degradation.

Methods: Multiple MET-targeting PROTACs were synthesized with a known MET kinase inhibitor, linkers of varying lengths, and two different E3-ligase recruiters. We screened these PROTACs for their potential to degrade MET using HEK293T cells that had been transfected with MET exon 14 skipping - GFP plasmids. The top candidates were then tested in cell lines with *MET* exon 14 skipping or amplification, a xenograft with *MET* exon 14 skipping and a 3D patient-derived micro-cancer model with a *PTPRZ1-MET* fusion. Western blots, proteomics, immunohistochemistry and cell viability were used to assess MET degradation and cytotoxicity.

Results: PROTAC 48-284 resulted in the most potent degradation of GFP-tagged MET with exon 14 skipping. This degradation was confirmed by mass spectrometry and Western blots with increasing degradation over 8 hours of exposure, and an expected hook effect with doses above 1.0 µM due to saturation of the target and E3 ligase. Short interval treatment of the UW21 xenograft model with *MET* exon 14 skipping resulted in ubiquitination of MET confirmed by Western blot and degradation of MET confirmed by immunohistochemistry. Finally, 48-284 was tested in a 3D micro-cancer model with a *PTPRZ1-MET* fusion with an IC_{50} of 0.08 µM.

Conclusions: MET-targeting PROTACs can restore the ubiquitination of MET that is lost with exon 14 skipping mutations and may represent a novel therapeutic approach against multiple types of MET altered cancers.

Keywords: MET, non-small cell lung cancer, Proteolysis Targeting Chimera (PROTAC)

P2.14 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.14-04 Re-Definition of Lung Adenocarcinoma Transcriptional Subtypes Using Integrative Bioinformatics Approaches

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Introduction: Lung adenocarcinoma (LUAD) is both clinically and genetically heterogeneous. Current diagnostic practices based on histological and molecular characteristics do not completely recapitulate this heterogeneity, leading to unsuccessful treatment performance and lack of alternative therapeutic targets. In this context, transcriptional profiling has emerged as a promising tool for further patient stratification and treatment guidance. However, intrinsic technical and analytical limitations have hindered the use of expression signatures in the clinical setting. For instance, gene expression measures at individual gene levels are subjected to multiple sources of variability. In this context, measures of the global activation of transcriptional pathways would be more robust to stochastic variations of single genes and to differences between platforms. In this regard, we sought to develop a robust personalized medicine computational biology framework for LUAD patients based on signature-based transcriptional tumor profiling.

Methods: The activity of 50 hallmark molecular pathways in 4,576 LUAD patients from 56 gene expression datasets was inferred using Gene Set Variation Analysis. LUAD molecular subtypes were defined based on the joint behavior of the studied pathways. Once LUAD transcriptional subtypes were defined, we integrated data from different pharmacogenomic datasets to infer the best treatment approach for each transcriptional subgroup. First, we classified LUAD cell lines according to the primary tumor's classification. Using pairwise comparisons between groups, we identified those treatments that were consistently more effective in every specific cluster compared to the rest.

Results: Seven molecular subtypes were defined for LUAD based on the activity of the studied signaling pathways: AD1 (17%), AD2 (19%), AD3 (10%), AD4 (13%), AD5 (21%), AD6 (17%), AD7 (3%). While the classification seems to be strongly guided by the expression of cell-cycle and immune system related genes, other more specific pathways also contribute to further refine the identified groups, conferring each of the subtypes their particular transcriptional footprint. AD1, AD4 and AD5, characterized by lower cell cycle-related pathways expression, were associated with better overall survival compared to AD2, AD3, AD6 and AD7, which show higher cell cycle-related pathways expression. Regarding genomic alterations, AD2 and AD6 were found to be associated with higher genomic instability and were enriched for TP53 mutations, higher copy number alteration rates and increased homologous recombination deficiency. Finally, the integration of publicly available pharmacogenomic data suggested potentially different pharmacologic interventions for the subtypes. For instance, AD2 seems to be more sensitive for drugs targeting cell cycle and DNA repair pathways, which is consistent with the high proliferative nature of this cluster of LUAD

Conclusions: After integrating data from more than 4,500 tumors, we have defined a robust classification of seven LUAD subtypes based on the differential expression of landmark cancer pathways. These subtypes differ in survival outcomes and molecular characteristics. Our classification may pave the way for novel and more precise therapeutic strategies beyond current DNA-based targeted therapies, especially in patients not harboring actionable genomic alterations.

Keywords: Lung adenocarcinoma, Transcriptomics, Precision medicine

P2.15 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES,
MONDAY, AUGUST 8, 2022 - 17:15–19:15

P2.15-01 Digital Pathology Uncovers Multi-Omic Hallmarks of Lung Cancer in Histopathology Images

M. Guramare, S.A. Javed, N. Agrawal, M. Griffin, J. Abel, M. Montalto, A.H. Beck, V. Mountain, I. Wapinski, M. Resnick, C. Biddle-Snead, J.R. Conway

PathAI, Inc., Boston/MA/USA

This abstract is under embargo until August 8 at 17:15 Vienna, Austria Time, CEST.

ePoster Presentation List

EP01.01 – EP01.07	**Early Detection and Screening**
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EP03.01	**Epidemiology**
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EP05.01 – EP05.03	**Locally Advanced Non-small Cell Lung Cancer**
EP06.01	**Management of Lung Cancer in the Era of COVID-19**
EP07.01 – EP07.03	**Mesothelioma, Thymoma, and Other Thoracic Malignancies**
EP08.01 – EP08.05	**Metastatic Non-small Cell Lung Cancer**
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ePosters

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-001 Circulating Tumor Cells-Based Radiobiological Model Improves the Indeterminate Pulmonary Solid Nodules Diagnosis

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Introduction: Accurate risk stratification of indeterminate lung solid nodules (IPSNs) is still critical to decrease the rate of unnecessary invasive procedures. Hence, our study was aimed to develop and validate an integrated model by combining clinical variables, circulating tumor cells (CTCs) and radiomics features for improving the management of IPSNs.

Methods: The integrated model was trained on 364 IPSNs, and validated in an internal set (*Validation I*, n=155), an independent external set (*Validation II*, n=82). The performance of the integrated model was estimated by applying receiver operating curve (ROC) analysis in the comparison with single CTC test prediction, radiomics model and Mayo clinical model. We tested the integrated model in different nodules size and intermediate risk IPSNs. Specific performance metrics, including sensitivity, specificity, positive predictive value, negative predictive value, and accurancy at the threshold of 0.5 or higher, of each approach were calculated. Net reclassification index (NRI) was applied to quantify the additional benefit derived from the integrated model.

Results: The integrated model provided an area under ROC (AUC) of 0.83, 0.76 in *Validation I* and *II*, outperforming CTCs (0.70, p=0.001; 0.68, p=0.128), Mayo clinical model (0.68, p<0.001; 0.55, p=0.007) and radiomics model (0.72, p=0.002; 0.67, p=0.050) in both two validation sets. Robust performance with high sensitivity up to 98% maintained in IPSNs with different solid size and intermediate risk probability, as well. Besides, performance of the integrated model was comparable with PET-CT examination (p=0.308) on the participants with established PET-CT records. NRI demonstrated the integrated model provided net reclassification of at least 10% on the external validation set compared with single CTCs test.

Conclusions: The integrated model could complement conventional risk models to improve the diagnosis of IPSNs, which was no inferior to PET-CT and potentially help to reduce unnecessary invasive procedures.

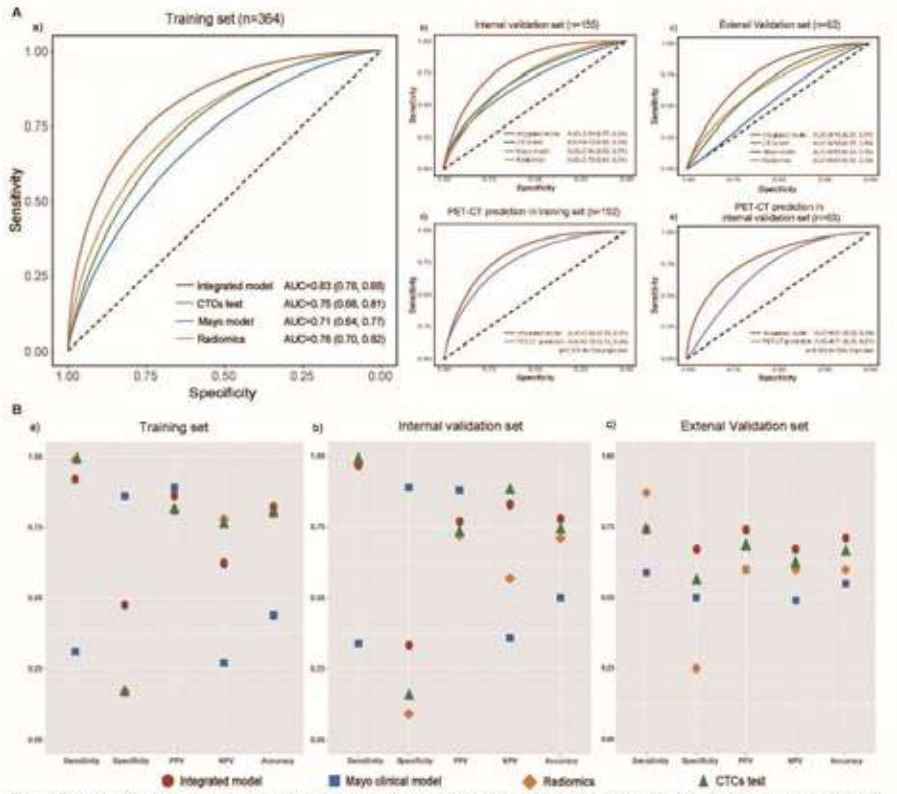

Figure 1. Diagnostic performance of the integrated model. A, receiver operating curves for integrated model, and other three models alone in training (a), internal validation (b), and external validation set (c); A(d-e), the comparison of integrated model with PET-CT for participants with the examination performed. B, illustration for performance metrics of models in training (a), internal validation (b), and external validation set (c). PPV, positive predictive value; NPV, negative predictive value. CTCs, circulating tumor cells; PET-CT, positron emission tomography/computed tomography.

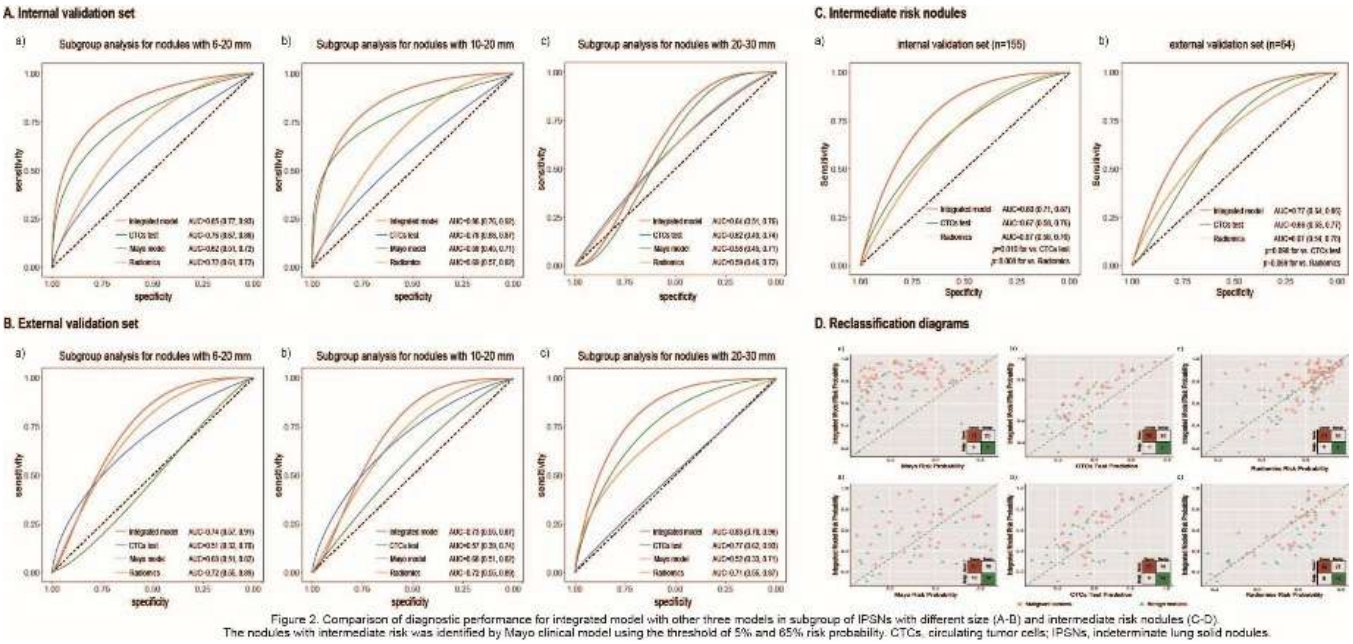

Figure 2. Comparison of diagnostic performance for integrated model with other three models in subgroup of IPSNs with different size (A-B) and intermediate risk nodules (C-D). The nodules with intermediate risk was identified by Mayo clinical model using the threshold of 5% and 65% risk probability. CTCs, circulating tumor cells; IPSNs, indeterminate lung solid nodules.

Keywords: Indeterminate pulmonary nodules diagnosis, circulating tumor cells, radiomics model

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-002 Challenges in the Use of NLST Image Data for Quantitative Algorithm Development

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Introduction: One of the products of the National Lung Screening Trial (NLST) is a public database of all the CT images performed during the trial. With 73,118 studies and 203,099 image series, this is the largest publicly available database of chest CT images and is being used for the development and testing of quantitative algorithms, such as lung nodule measurement, detection, and diagnosis. However, the NLST screened participants with CT between 2002 and 2006; these scans are 15-20 years old. Minimum quality guidelines for scan acquisition and reconstruction have been developed by the Quantitative Imaging Biomarker Alliance (QIBA) of the Radiological Society of North America for tasks related to quantitative measurements in the context of LDCT. We examined how often these scans met those standards.

Methods: We downloaded all available NLST images from the Cancer Imaging Archive, excluding localizer or topogram images, or incomplete series. We analyzed the DICOM header information of the remaining series to extract the scanner and protocol information. As a measure of modern quantitative image standards, we determined the proportion of scans meeting protocol recommendations of QIBA Small Nodule Committee.

Results: 70486 CT image series containing < 20 images were excluded. Of the remaining 132613 CT series, 10321 (7.8%) were acquired with a slice thickness (ST) <= 1.25 mm, the current QIBA Small Lung Nodule recommendation. Table 1 shows that in ST <= 1.25 mm group, the 10 most frequent combinations account for 97.8% (10098/10321) of the CT series. After eliminating scans with edge-enhancing kernels (4185) and from scanners in which spatial warping has been identified (4649), only 1487 meet QIBA eligibility criteria.

There were 4447 CT images series for NLST participants with lung cancer, of which only 399 CT image series in 139 participants were acquired with ST <= 1.25 mm.

Conclusions: With advances in image processing, quantitation, and artificial intelligence (AI), there is a need for high quality image databases for software development for automation and standardization of screening CT image analysis. The NLST CT images have been made openly available for this purpose, but over 95% of the images do not meet the image acquisition and reconstruction quality standards required for optimizing algorithm performance. New databases and distribution approaches are necessary for progression of software development; various organizations, including the IASLC and Medical Imaging and Data Resource Center, are now in the process of developing newer databases that will be made available.

Table 1. Top 10 most frequent scanner/slice thickness/kernel combinations for scans <= 1.25 mm slice thickness. QIBA? = Protocol meets QIBA Small Nodule Profile recommendation

Manufacturer	Model	Slice Thickness	Kernel	QIBA?	Count
GE	LightSpeed Ultra	1.25	Bone	N	2137
GE	LightSpeed Ultra	1.25	Standard	Y	1975
GE	LightSpeed Pro 16	1.25	Standard	Y	1310
GE	LightSpeed Pro 16	1.25	Bone	N	1232
GE	LightSpeed 16	1.25	Standard	Y	899
Siemens	Sensation 16	1.0	B30f	Y	811
Siemens	Sensation 16	1.0	B80f	N	809
Siemens	Sensation 16	1.0	B50f	Y	489
GE	LightSpeed QX/i	1.25	Standard	Y	265
GE	HiSpeed QX/i	1.25	Standard	Y	171
				TOTAL	10098

Keywords: NLST, Algorithm evaluation, image databases

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-003 DELFI-L101: Development of a Blood-Based Assay That Evaluates Cell-Free DNA Fragmentation Patterns to Detect Lung Cancer

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Introduction: Uptake of lung cancer screening is low worldwide, including in the US despite established recommendations and national reimbursement for eligible persons. Studies show that screening by low-dose computed tomography (LDCT) can reduce mortality, but the benefits of screening are challenged by barriers that include access to screening, costs, and harms like false-positives and radiation exposure. A tool that can separate the screening-eligible population into groups with higher and lower risk of lung cancer could allow more judicious use of LDCT screening. DELFI is a novel, blood-based technology that evaluates fragmentation patterns of cfDNA using supervised machine learning to distinguish individuals with cancer from those without cancer.

Methods: The DELFI-L101 is an ongoing case-control observational study (NCT04825834) prospectively enrolling at >40 academic and community sites. Eligibility criteria include: age ≥50 years, current or previous smoking history, and smoking history of ≥20 pack-years. Individuals are excluded if they had cancer treatment in the prior year or a history of hematologic malignancies or myelodysplasia. Cases are individuals with pathologically confirmed cancers (group A - lung cancer, group C - cancer other than lung). Controls are those without lung cancer (group B) as determined by CT scan completed within 12 months before or 6 weeks after enrollment (Lung-RADS category 1 or 2 findings). Cases and controls can be enrolled from any participating site. Total enrollment is estimated to be ~2500 participants across the three groups. Blood samples are collected at enrollment and banked as plasma for subsequent DELFI analyses, which involves cfDNA isolation from plasma, followed by low-coverage, whole-genome, next-generation sequencing, and machine learning methods. Clinical data (medical history, demographics, and diagnostic, surgery, imaging, and pathology reports, and/or other diagnostic information) are collected at enrollment and at 12 months post-enrollment. The primary objective is to train and test a classifier for the detection of lung cancer using the DELFI technology with other biomarkers and clinical features. Secondary objectives include the evaluation of classifiers to distinguish lung cancer from other cancers, modeling benefits and harms using performance estimates of these classifiers, and description of the analytical performance (eg, repeatability and reproducibility) of the DELFI technology and classifiers. The primary endpoint is the accuracy of lung cancer detection as measured by sensitivity, specificity, and the area under the receiver operating characteristic curve. Secondary endpoints include accuracy of tissue of origin classification, and adverse events associated with blood sample collection. The training and performance characterization of a DELFI classifier will further the development of an affordable, accessible, blood-based cancer detection tool that could personalize risk estimates for lung cancer. The ability to separate individuals with higher vs lower risk of lung cancer may address the barriers to wider use of LDCT screening.

Keywords: cfDNA, fragmentation profile, lung cancer

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-004 The Correlation Between Exhaled Volatile Organic Compounds Using Breath Analyzer and Interleukin-23 (IL-23) in Lung Cancer

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Introduction: Interleukin-23 has been known as a pro-inflammatory cytokine in the development and progression of tumor cells. The development and progression of the tumor itself has been associated with the development of various gasses on the exhaled breath, especially the composition of its Volatile Organic Compounds (VOC). This study aimed to find the correlation between IL-23 and various gasses, especially the VOC.

Methods: A cross-sectional study was carried out recruiting 80 participants consist of 38 lung cancer patients and 42 healthy subjects. All participants were asked to exhale their breath into a 500 ml sample bag with a special valve. The sample was immediately analyzed. The concentration of Oxygen (O_2), Ozone (O_3), Total Volatile Organic Compound (TVOC), Carbon Dioxide (CO_2), Ethanol (C_2H_5OH), Particulate matter 1.0 ($PM_{1.0}$), Formaldehydes (CH_2O), Toluene (C_7H_8), Acetone (C_3H_6O), Ammonia (NH_3), Ammonium (NH_4), Hexane (C_6H_{14}), Nitrogen Dioxide (NO_2), Carbon Monoxide (CO), Methane (CH_4) and Sulfur Dioxide (SO_2) were recorded. All the subjects were tested for IL-23 by using the ELISA assay. The data was evaluated by using the Kruskal Wallis test, Heat Map analysis, and Pair-Wise analysis.

Results: The study has been revealed that the correlation between IL-23 and exhaled gas compounds was weak (r^2 <0.5 with p value <0.05). However, the presence of IL-23 was found in the development of lung cancer. As the result, the VOC level was increased behind the IL-23. In the further analysis, higher IL-23 populations were observed on stage 4 lung cancer than control. Furthermore, the statistical approaches on the exhaled breath content found different between health participant and participant with lung cancer especially for TVOC (p <0.05), Toluene (p <0.05), Ethanol (p <0.05), Acetone (p <0.05), and Hexane (p <0.05).

Conclusions: IL-23 has weak correlation with the exhaled breath contents, especially volatile organic compounds.

Keywords: IL-23, Volatile Organic Compound, Lung Cancer

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-005 Increased Levels of mRNAs and miRNAs Associated with Imminent and Advanced Lung Cancer

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Introduction: Lung cancer (LC) incidence and mortality are still increasing globally, and results from screening studies show that earlier LC detection is a promising approach to reduce LC mortality. Circulating mRNAs and miRNAs in peripheral blood of LC patients represent a source of potentially useful biomarkers, but it is unclear if their expression in blood samples taken years prior to LC diagnosis can predict future development of LC. Expression blood profiling is minimally invasive for the patient and could serve as an important tool in identifying individuals with increased LC risk who may benefit from participating in LC screening or be an additional tool to increase sensitivity and specificity in LC screening programs.

Methods: Using RNA-Seq data, we compared expression of >60,000 mRNAs and >1,600 miRNAs in peripheral blood samples taken at LC diagnosis in confirmed LC cases (n=128) and in individuals with suspected but negative LC diagnostic evaluation (n=62). Differentially expressed mRNAs and miRNAs were identified using linear models (*limma*) combined with *voom* transformation. According to selected criteria, 14 candidate mRNAs and nine candidate miRNAs were identified in the diagnostic cohort. Their expression was evaluated in up to three independent prospective cohorts using blood samples taken up to eight years prior to LC diagnosis and their matched controls (n=163 cases and 184 controls for mRNA data, and n=360 cases and 375 controls for miRNA data). We assessed associations of the candidate mRNAs and miRNAs with LC in the prospective cohorts for case-control comparisons as well as in relation to time to diagnosis using mixed models (*lmer*) and generalized additive models (*gam*), respectively.

Results: Three mRNAs (*ANXA3*, *ARG1* and *HP*) and three miRNAs (miR-320b, miR-320c, and miR-320d) were considered the most promising candidates in the diagnostic cohort. High expression of these candidates was associated with poor survival, especially in late-stage LC cases. Notably, in the prospective cohorts, two miRNA candidates (miR-320c and miR-320d) demonstrated a strong association with developing LC disease, with high expression up to two years prior to LC diagnosis. On the other hand, mRNA candidates demonstrated overall weak associations with LC in the prospective cohorts.

Conclusions: We applied a novel approach to identify potential biomarkers for LC in peripheral blood with mRNA and miRNA expression profiling using both diagnostic and prospective design in one study. Our analyses indicate that elevated levels of two miRNAs (miR-320c and miR-320d) can be detected in peripheral blood up to two years prior to LC diagnosis and seem to be the most promising candidate markers of imminent and advanced lung cancer. Thus, they can be used as early markers for risk of LC disease, but screening intervals should then be less than two years.

Keywords: diagnostic and pre-diagnostic markers, peripheral blood, miRNA

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-006 Sensitive Detection of Lung Cancer Using a Multiomic Plasma Cell-Free DNA Sequencing Assay

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Introduction: Cancer detection at early stages expands therapeutic options and improves treatment efficacy. Existing cancer screening methods, however, are often invasive and have limited accuracy, subjecting patients to unnecessary follow-up procedures. Detection of plasma circulating tumor DNA (ctDNA) is a reliable method for detecting cancer, but sensitivity can be limited. Methylation signatures in cell-free DNA (cfDNA) can enhance cancer detection by providing cancer-specific epigenetic information. In addition, cfDNA from tumor cells are relatively shorter than cfDNA from normal cells, and this difference can be measured as a tumor-specific signal. We describe a novel combinatorial amplicon-based next-generation sequencing (NGS) test measuring ctDNA abundance, cfDNA fragmentation profiles and cfDNA methylation, for sensitive cancer detection.

Methods: Plasma cfDNA from 254 individuals (91 normal controls and 163 lung cancers; 37.4% early-stage) were included in the study. To capture cancer-specific cfDNA methylation signatures, a 100-amplicon panel targeting differentially methylated regions, which was selected based on publicly available data, was used in an NGS assay incorporating molecular barcoding for error-suppression. ctDNA somatic mutations and cfDNA fragment sizes were profiled in a combined 32-gene cancer hotspot panel integrating amplicons of varying lengths. For each sample, cfDNA fragmentation profile was independently assessed from the sequencing alignment files by calculating a “fragment size ratio” of the combined coverages of short amplicons vs. coverages of long amplicons. A combination of cfDNA parameters, including ctDNA abundance, cfDNA fragment size ratio and cfDNA methylation profiles were used to train an ensemble of logistic regression models for lung cancer detection.

Results: ctDNA was detected in 114 (69.9%) of the cancer samples. cfDNA fragment size ratio (median 1.24 vs 1.06) was higher in cancer samples compared to normal samples, and increased with cancer stage. With the multi-modal cfDNA approach, at 95% specificity, the average 3-fold cross-validation sensitivity of overall cancer detection was 85.0% (95% CI: 84.5%-85.4%). Sensitivity increased with cancer stage and was 69.5% (95% CI: 68.6%-70.4%) and 94.2% (95% CI: 94.0%-94.5%) for early-stage and advanced lung cancers, respectively. Compared to ctDNA detection alone, the combinatorial approach correctly detected 14.3% additional cancer samples.

Conclusions: We report the sensitive and accurate detection of lung cancers using a liquid biopsy assay combining cfDNA methylation signatures, cfDNA fragment sizes and ctDNA detection. Despite small sample sizes, this study shows that multiple molecular and physical properties of cfDNA representing distinct cancer-specific signals can together augment the non-invasive detection of cancer. Further validation is ongoing in larger cohorts, combined with cfRNA and plasma protein profiling, for greater sensitivity of early cancer detection towards a total liquid biopsy approach.

Keywords: Early detection, Liquid biopsy, Plasma cell-free DNA

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-007 Incorporating cfDNA Detection to CT Scan Assessment in Post-Surgical Lung Cancer Patients

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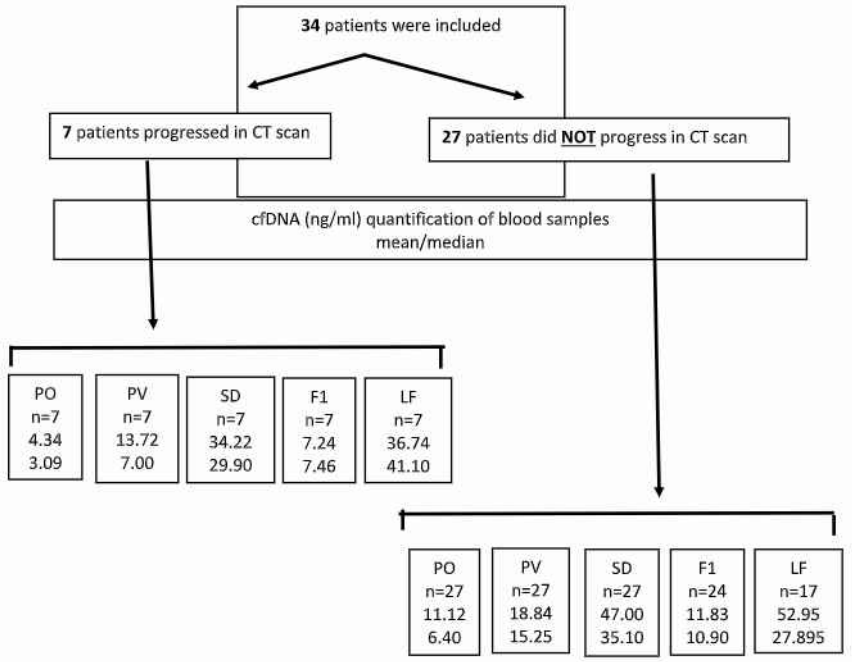
Introduction: Liquid biopsies based on plasma cell-free tumour deoxyribonucleic acid (cfDNA) has shown to be promising in monitoring lung cancer evolution. The expression of cfDNA across time and its relationship with lung cancer progression through imageology, allows us to weigh how useful cfDNA could be in monitoring surgically resectable lung cancer. Our aim is to evaluate the role of incorporating cfDNA detection to CT scan assessment in post-surgical early-stage lung cancer patients as well as assess its usefulness in detecting residual postsurgical cfDNA.

Methods: A cohort of 34 patients with early-stage lung cancer were included. All patients had five blood samples at the preoperative stage, from the pulmonary vein, at surgical discharge, at first follow-up, and at last follow-up. All blood samples were evaluated for cfDNA expression.

Results: From a total of 34 patients, seven patients showed imageology progression. Twenty-seven patients did not. These seven patients also presented higher median cfDNA values at last follow-up when compared to cfDNA values at surgical discharge, in opposition to the 27 patients as shown in table 1. As also observed patients with tumors bigger than 3 cm, with more than 1 poor prognostic factors (PPF) and histological adenocarcinomas were the clinicopathological features favoring progression. The absolute values of cfDNA quantification show that the meantime to molecular relapse was 343.86 days [94; 504] and the meantime for CT progression was 647 days [150; 959]. Before imageology progression, molecular evidence shows metabolic cancer activity with gradual increase of cfDNA, to values superior to those quantified at SD time point.

Conclusions: Our findings suggest a prognostic role of combining early cfDNA detection in conjunction with CT scan assessment in a post-surgical context. Early clearance of cfDNA is associated to better survival outcomes. cfDNA relapse is quantified and mensurable oncological disease is later confirmed by CT scan.

Figure 1. Evaluation of CT progression (n=34).



CT scan	cfDNA (median)				
	PO	PV	SD	F1	LF
PROGRESSION n=7	3.09	7.0	29.9	7.46	41.1
NO PROGRESSION n=27	6.4	15.25	35.1	10.9	27.895

Table 1. cfDNA expression at five time-points according to imageology progression.

Keywords: molecular relapse, CT scan assessment, resectable lung cancer

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-008 Expression of PD-L1 mRNA and Its Epigenetic Regulators: MicroRNA-17, -93 and -142 in Early Stages NSCLC Patients' Plasma

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Introduction: One of the leading treatment options for advanced non-small cell lung cancer (NSCLC) patients is immunotherapy based on immune checkpoint inhibitors, including programmed death ligand 1 (PD-L1) inhibitors. PD-L1 molecule expressed on tumor cells causes PD-1+ tumor infiltrating lymphocytes (TILs) exhaustion and thus escape from immune surveillance. Blockade of the PD-1/PD-L1 pathway by monoclonal antibodies enables restoration of the anti-tumor response. PD-L1 expression is regulated by epigenetic factors, e.g.: microRNAs (miRNAs). The aim of presented study was to evaluate the expression of PD-L1 mRNA and its regulators: microRNA-17, microRNA-93 and microRNA-142 in plasma from patients with early stages of NSCLC.

Methods: The study was carried out (as a master's thesis) on 50 individuals (18 controls and 32 patients with NSCLC). Total RNA with microRNA fraction was extracted from plasma and quantitative PCR with reverse transcription was conducted afterwards. The expression was evaluated with the use of 2-ΔCt method. Statistical analysis was conducted with the use of Statistica 13.3 program.

Results: The PD-L1 mRNA expression was detected in 40% individuals with NSCLC, whereas it was not detected in the healthy individuals at all. It was found that microRNA-17 and microRNA-142 expression is negatively correlated with tumor size. Also, it was demonstrated that the expression of these molecules is significantly higher in healthy controls when compared with lung cancer patients. ROC analysis showed that sensitivity and specificity values in distinguishing the cancer patients from the healthy controls with all tested microRNAs have reached high values.

Conclusions: Presumably, PD-L1 mRNA appears in the plasma along with the tumor occurrence, and its expression increases as the disease progresses. The tested microRNAs constitute potential non-invasive biomarkers to detect tumors impossible to observe in low-sensitive imaging tests. Moreover, these tests do not require the patient's hospitalization, which is extremely important in the era of Covid-19 virus pandemic. It could be a starting point of research on diagnostic potential of analyzed molecules.

The findings are the result of research conducted as part of a master's thesis which was awarded first prize in the Faculty Thesis Competition at the Medical University of Lublin.

Keywords: non-small cell lung cancer, microRNA, PD-L1

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-009 Common MicroRNAs in Pre-diagnostic Serum Associated with Lung Cancer in Two Cohorts up to Eight Years Before Diagnosis: A HUNT Study

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Introduction: Blood biomarkers for early detection of lung cancer are in demand. There are few studies of the full microRNome in serum of asymptomatic subjects that later develop lung cancer. Here we perform next-generation sequencing on blood from a non-cancer, ever-smokers population up to eight years before diagnosis to discover and validate novel biomarkers.

Methods: Two large prospective population health studies, HUNT2 and HUNT3, 98 737 subjects in total were initially considered. Inclusion criteria for cases were current or former smoker, no known cancer at study entrance, and 0-8 years from blood sampling to lung cancer diagnosis. An equal number of adenocarcinoma, squamous cell carcinoma and small-cell lung carcinoma were selected. Each future lung cancer case had one control matched to sex, age at entrance into the study, pack-years and smoking cessation time as well as similar risk score according to the HUNT Lung Cancer model. Finally, 240 and 72 serum samples were includable in the discovery (HUNT2) and validation (HUNT3) set, respectively and analysed by next-generation sequencing. The validated serum microRNAs were also tested in two pre-diagnostic plasma datasets collected from participants as part of the prospective population studies NOWAK, Sweden (n=195) and NSHDS, Norway (n=187) and sequenced by the same technology.

Results: The raw number of microRNAs detected in the HUNT2 was 1615 and in HUNT3 566. When all cases were contrasted against all controls, nine unique microRNAs were discovered and validated in the serum pre-diagnostic dataset, all with AUC > 0.60. Three microRNAs were associated with non-small cell metastatic, namely miR-1306-5p, miR-185-5p, miR-191-3p, with mean AUC of 0.65 (discovery) and 0.76 (validation set). When these three miRNAs are analysed as a signature, their combined AUC reaches 0.75 (discovery) and 0.90 (validation). These results could not be validated in the plasma samples.

Conclusions: There were a few significantly differential expressed microRNAs in serum up to eight years before diagnosis. These promising microRNAs alone, or in concert, serve as early diagnostic or prognostic lung cancer biomarkers. These findings need to be explored and validated in a larger prospective serum dataset.

Keywords: pre-diagnostic serum biomarkers, early diagnosis, microRNA sequencing

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-010 Graphene Based Activity Sensors Detect All Stages of Lung Cancer Using an Evolutionary Machine Learning Algorithm Approach

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Introduction: Lung cancer presents predominantly with advanced disease. The low dose computed tomography (LDCT) screening tool has been poorly implemented. Biomarker studies frequently lack the performance to significantly inform detection in the earliest stages. We describe a biomarker analysis that demonstrates clear performance improvement over traditional regression analysis tools with performance that could support LDCT.

Methods: Hawkeye has developed a graphene based activity sensor sensitive to sub-picomolar concentrations of protease enzymes. The sensors produce a signal detectable on standard fluorescent plate readers when the fluorescent dye (tetrakis (4-carboxyphenyl) porphyrin (TCPP)-peptide conjugate attached to a graphene backbone is cleaved by active protease enzymes in a serum sample. 256 serum samples from patients with pathologically confirmed lung cancer, a variety of benign lung conditions, or healthy controls were evaluated with a panel of 19 different peptide sensors. Fluorescence was measured in triplicate assay wells, with assay and serum background measurements after 90 minutes incubation on a VarioSkan Lux. The relationship between protease activity and disease status was evaluated using standard logistic regression tools for multivariate analysis and a novel machine learning approach, called “Emerge”, for model generation based on an evolutionary selection of Turing machines.

Results: Our study examined 256 subjects, 35% with lung cancer distributed 29%, 26%, 24%, 21% across stages I-IV respectively. 20% of the non-lung cancer samples represented co-moribund conditions such as COPD, bronchitis, asthma and other benign conditions. A logistic regression model was derived with a 50:50 stratified allocation to maintain the lung cancer to non-lung cancer ratio in both sets. The Training set produced an AUC of 0.9573. The model applied to the Validation set (n=128) produced an AUC=0.7843. Targeting a sensitivity of >95% in the Training set, we observed a sensitivity of 0.79 (CI: 0.648-0.886) and specificity of 0.65 (CI: 0.541-0.751) in the Validation set. “Emerge” calculations involved separating the data into thirds for Training, Testing and Validation cohorts. Modeling produced 7 algorithms which were voted up to a binary output for presence or absence of lung cancer. For the entire dataset, the sensitivity was indexed at 96.6% (CI 90.5%-99.3%) and specificity was 82.0% (CI 75.4% - 87.5%). Importantly, for the Validation set (n=84), the sensitivity was measured at 96.6% (CI 82.2%-99.9%) and specificity was 81.8% (CI 69.1% - 90.9%).

Conclusions: Traditional regression analysis focuses on linear, non-overlapping relationships between biomarkers. We compared logistic regression tools to a machine learning evolutionary approach. Random Turing machines are mutated and selected for fitness over many generations. This builds robust mathematical voting models with higher accuracy and reproducibility. In this analysis, the Validation set performance was much closer to the Training set performance, indicating a feature selection that better captured biological complexity. We are assembling larger cohorts to validate an analysis algorithm with diagnostic performance for the detection of early stage lung cancer.

Keywords: Protease enzyme, activity biosensor, early detection

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-011 Utility of Arm-level cfDNA Fragment Size Distribution in the Early Detection of Lung Cancer and Pan Cancer

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Introduction: Lung cancer has the highest incidence and mortality worldwide. Early detection of lung cancer is critical for improving the prognosis of patients. cfDNA fragmentomics has shown a potential in the detection of lung cancer; however, existing predictive models lack of extensive cross-study validation, and the robustness and generalizability of the features and models should be tested and improved.

Methods: The local lung cancer cohort consisted of 56 patients with lung cancer (93% stage I) and 106 healthy volunteers. The 162 subjects were divided into a training cohort (n=110) and a temporal validation cohort (n=52). The samples were subjected to whole-genome sequencing. Two types of cfDNA fragment features were extracted: window-level fragment size summary (WINDOW-FSS), which summarizes the fragment size distribution as short fragment (100-150bp) and total fragment coverage at 5MB window level, and commonly used in previous studies, and our newly-developed arm-level fragment size distribution (ARM-FSD), which separately calculates the coverage of fragments with 5bp as a stepat arm level and retains the size distribution information basically. In addition, the derived PCA components and autoencoder deep features were also extracted and used to construct machine learning models for lung cancer prediction. The performance of the models was validated by the temporal validation cohort and two independent external on-line cohorts (n=142 and 19 respectively). The value of the two types of features in the detection of pan cancer was assessed by an on-line pan-cancer cohort (n=460) as training and validated by another on-line pan-cancer cohort (n=58), an on-line liver cancer cohort (n=122) as well as the local lung cancer cohort (n=162).

Results: For lung cancer detection, the elastic network logistic regression model (GLM) based on the autoencoder deep features of ARM-FSD achieved the highest cross validation AUC (0.999±0.001, average AUC ± standard deviation) in the training cohort and validated by the temporal validation cohort (AUC=0.997). The model was further validated by two on-line lung cancer cohorts (AUC=0.97 and 0.87, respectively). GLM model based on WINDOW-FSS also showed predictive value in the local cohort with a cross validation AUC of 0.89±0.02 and temporal validation AUC of 0.98. However, it was inferior to the ARM-FSD in external validation by the on-line cohorts (AUC=0.86 and 0.76, respectively). For pan-cancer detection, although both WINDOW-FSS and ARM-FSD based models showed good predictive power in the internal cross validation (AUC=0.91±0.004 and 0.93±0.002 for ARM-FSD and WINDOW-FSS), only ARM-FSD based model could be well validated by two on-line cohorts and the local lung cancer cohort (AUC=0.88 for on-line pan cancer cohort; AUC=0.87 for on-line liver cancer cohort; AUC=0.98 for the local lung cancer cohort). In pan-cancer validation, except pancreatic cancer, the ARM-FSD based model obtained >0.90 AUC in all other cancer types. On the contrary, the highest AUC of WINDOW-FSS based models in the on-line pan cancer and local lung cancer validation was only 0.75 and 0.63 respectively.

Conclusions: Our newly-developed ARM-FSD is a robust and generalized biomarker, and has a potential in the early detection of lung cancer and pan cancer.

EP01.01 EARLY DETECTION AND SCREENING - BIOMARKERS

EP01.01-012 Clinical and Molecular Features of Chinese Early-stage Multiple Primary Lung Cancer Patients

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Introduction: The incidence of early-stage multiple primary lung cancer (MPLC) has been increasing in recent years, while the ideal strategy for its diagnosis and treatment remains controversial. Moreover, the difference between MPLC and intrapulmonary metastasis (IM) in patients with lung cancer is vital but controversial.

Methods: Using commercial NGS assays, we retrospectively analyzed clinical and genetic data of MPLC patients from January 2019 to May 2021. A total of 94 selected surgical specimens were obtained from 41 patients who had more than one tumor with IA1 to IIB stage, were subjected to targeted multigene panel sequencing.

Results: The MPLC patients included 31 women and 10 men. The median age were all 59 years. A total of 5 MPLC patients were current smokers or pre-morbid smokers,and most patients were never-smokers. 33 patients (80.49%) had two lesions, four patients (9.75%) had three lesions, and four patients (9.75%) had more than three lesions. And every patient, multiple tumors were located on the same side. A total of thirty-six patients (88%) showed inconsistent driver mutations, and five MPLC patients (12%) shared single identical *EGFR/BRAF/TP53* hotspot mutations in the early stage. In MPLC patients, high frequency mutations included *EGFR* (63%), *TP53*(12%), *BRAF* (12%), *KRAS* (10%), *ERBB2* (4%), *PIK3CA* (3%) and *MET* (3%). Compared with those independent primary lung cancers patients, significantly more genomic mutations in *BRAF* ($P = 0.0285$) and significantly fewer mutations in *TP53* ($P = 0.0295$) were identified in early-stage MPLC.

Conclusions: This small study demonstrated the relative higher frequency of *BRAF* and fewer frequency *TP53* mutations in early-stage MPLC patients. Therefore, the molecular difference between MPLC and independent primary lung cancers may be helpful to study the mechanism of MPLC pathogenesis.

Keywords: Driver mutations, Multiple primary lung cancers, NGS

EP01.02 EARLY DETECTION AND SCREENING - DISSEMINATION

EP01.02-001 Citizens' Perspective on Combination Screening for Lung Cancer, COPD and CVD

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Introduction: The benefits of screening depend directly on the number of targeted individuals willing to participate. This study aimed to inform policymakers by determining the expected willingness of potential lung cancer screenees to participate in low-dose chest CT (LDCT) screening. Chest LDCT also allows evaluation of early stages of chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD). We studied whether screening for combinations of lung cancer with COPD and/or CVD (the Big-3 diseases) would influence willingness to participate. Furthermore, the relative importance of amendable barriers to participation was assessed to advise policymakers.

Methods: An online survey was designed using pairwise comparisons, as implemented in the analytic hierarchy process (AHP). Eligible respondents were current and former smokers aged 50-75 without a history of lung cancer. The survey consisted of three parts. Firstly, demographics and respondents' smoking history were asked for. Secondly, respondents had to rank eight predefined criteria in order of importance when deciding to participate in a screening program, followed by pairwise comparisons of these criteria. The predefined criteria were *location of screening, waiting time, immediate feedback on the scan, the number of screenings per 5 year period, benefits of screening, missed cases, follow-up tests* and *diseases screened for.* Lastly, information on the benefits and risks of LDCT screening for each of the Big-3 diseases were provided, followed by questions about the respondent's willingness to participate in screening for lung cancer, lung cancer with COPD, lung cancer with CVD or all Big-3 diseases simultaneously. The respondent's response to lung cancer screening was provided as a reference point for the disease combinations.

Results: The survey was filled in by 1,459 respondents from the Netherlands, Germany, France and Italy. Overall, the mean willingness to participate in lung cancer screening was 71.2%. Adding either COPD or CVD screening did not substantially change the willingness to participate. However, adding both COPD and CVD screening, as a combined Big-3 screening program, resulted in a willingness to participate of 73.4% (P=0.00636). On average, current smokers reported a higher willingness to participate compared to former smokers for all disease combinations (e.g. 73.0% vs 69.0% for lung cancer screening). The most important criteria related to willingness to participate in screening were 1) the number of cases missed during screening and 2) the frequency of screening (except for the Netherlands: waiting time for results).

Conclusions: Overall, combined screening for the Big-3 resulted in the highest willingness to participate, but differences between screening for different diseases and between subgroups were small. These small observed differences should be extrapolated to determine the long term impact (i.e. health benefits and costs) of screening. The willingness to participate observed in this study population is substantially higher than participation in US lung cancer screening (14%) and is larger than the previously reported minimum participation of 40% for a cost-effective lung cancer screening program. High diagnostic sensitivity (i.e. few missed cases) and screening frequency (i.e. achieving health benefits with a low screening frequency) were the most important decision criteria for screenees.

Keywords: Combination screening, Preference study, Screening participation

EP01.02 EARLY DETECTION AND SCREENING - DISSEMINATION

EP01.02-002 Awareness of Palestinians about Lung Cancer Symptoms: A National Cross-sectional Study

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Introduction: The majority of lung cancer(LC) cases are diagnosed at an advanced stage. Poor awareness of LC symptoms is a contributor to late diagnosis. This study aimed to assess the awareness of LC symptoms among Palestinians and to examine the factors associated with displaying good awareness.

Methods: Participants were recruited from hospitals, primary healthcare centers, and public spaces using convenience sampling. A translated-into-Arabic version of the validated LC awareness measure was used to assess recognition of 14 LC symptoms. One point was given for each recognized symptom. The total score was calculated and categorized based on the number of symptoms recognized: poor(0-4), fair(5-9), and good(10-14). Multivariable logistic regression was used to examine the association between participant characteristics and having good awareness. The multivariable analysis adjusted for age-group, gender, education, monthly income, occupation, residence, marital status, any chronic disease, knowing someone with cancer, smoking history, and site of data collection.

Results: Of 5174 potential participants approached, 4817 completed the questionnaire (response rate=93.1%) and 4762 were included in the final analysis. Of these, 2742(56.9%) were from the West Bank and Jerusalem(WBJ) and 2020(43.1%) were from the Gaza Strip. Participants from the WBJ were older, had higher monthly income but lower education, and suffered from more chronic diseases. The most recognized respiratory LC symptom was 'worsening in an existing cough'(n=3884, 81.6%) while the least recognized was 'a cough that does not go away for two or three weeks'(n=2951, 62.0%). The most recognized non-respiratory LC symptom was 'persistent tiredness or lack of energy'(n=3205, 67.3%) while the least recognized was 'persistent shoulder pain'(n=1170,24.6%). A total of 2466 participants(51.8%) displayed good awareness of LC symptoms. Participants from both the Gaza Strip and the WBJ had similar likelihoods to have good awareness levels. Factors associated with a higher likelihood to display good awareness included female gender, having post-secondary education, being employed, knowing someone with cancer, and visiting hospitals and primary healthcare centers (attached image).

Conclusions: About half of the study participants displayed a good level of awareness of LC symptoms. Further improvement in public awareness of LC symptoms by educational interventions might reduce LC mortality by promoting early diagnosis.

Bivariable and multivariable logistic regression analyzing factors associated with having a good awareness of lung cancer symptoms.

Characteristic	Good awareness			
	COR (95% CI)	P	AOR (95% CI)*	P
Age group				
18 to 44	Ref	Ref	Ref	Ref
45 or older	1.01 (0.88-1.15)	0.91	1.06 (0.90-1.24)	0.52
Gender				
Male	Ref	Ref	Ref	Ref
Female	1.27 (1.14-1.43)	<0.001	1.30 (1.10-1.53)	0.002
Educational level				
Secondary or below	Ref	Ref	Ref	Ref
Post-secondary	1.45 (1.29-1.62)	<0.001	1.49 (1.31-1.70)	<0.001
Occupation				
Unemployed/housewife	Ref	Ref	Ref	Ref
Employed	1.01 (0.89-1.14)	0.88	1.22 (1.04-1.43)	0.015
Retired	1.15 (0.78-1.69)	0.48	1.25 (0.82-1.90)	0.30
Student	1.05 (0.86-1.28)	0.64	1.17 (0.92-1.48)	0.21
Monthly income				
< 1450 NIS	Ref	Ref	Ref	Ref
≥ 1450 NIS	1.18 (1.04-1.33)	0.010	1.18 (1.00-1.40)	0.052
Marital status				
Single	Ref	Ref	Ref	Ref
Married	1.05 (0.93-1.19)	0.44	0.94 (0.81-1.10)	0.44
Divorced/Widowed	0.97 (0.71-1.34)	0.86	0.96 (0.67-1.36)	0.80
Residency				
Gaza Strip	Ref	Ref	Ref	Ref
WBJ	1.08 (.97-1.22)	0.18	0.99 (0.85-1.16)	0.92
Having a chronic disease				
No	Ref	Ref	Ref	Ref
Yes	1.01 (.88-1.16)	0.91	1.0 (.85-1.18)	0.98
Knowing someone with cancer				
No	Ref	Ref	Ref	Ref
Yes	1.28 (1.14-1.43)	<0.001	1.41 (1.25-1.59)	<0.001
Ever smoked cigarettes and/or shisha				
No	Ref	Ref	Ref	Ref
Yes	0.84 (0.74-0.95)	0.005	0.94 (0.80-1.09)	0.40
Site of data collection				
Public Spaces	Ref	Ref	Ref	Ref
Hospitals	1.58 (1.38-1.80)	<0.001	1.80 (1.57-2.07)	<0.001
Primary healthcare centers	1.90 (1.64-2.20)	<0.001	2.20 (1.87-2.59)	<0.001

COR= crude odds ratio, AOR= adjusted odds ratio, CI= confidence interval, WBJ= West Bank and Jerusalem.

*Adjusted for age-group, gender, educational level, occupation, monthly income, marital status, residency, having a chronic disease, knowing someone with cancer, smoking history, and site of data collection.

Keywords: Lung Cancer Symptoms, Early Presentation, Educational Interventions

EP01.02 EARLY DETECTION AND SCREENING - DISSEMINATION

EP01.02-003 Lung Cancer Screening: A Systematic Review of Knowledge Translation Interventions

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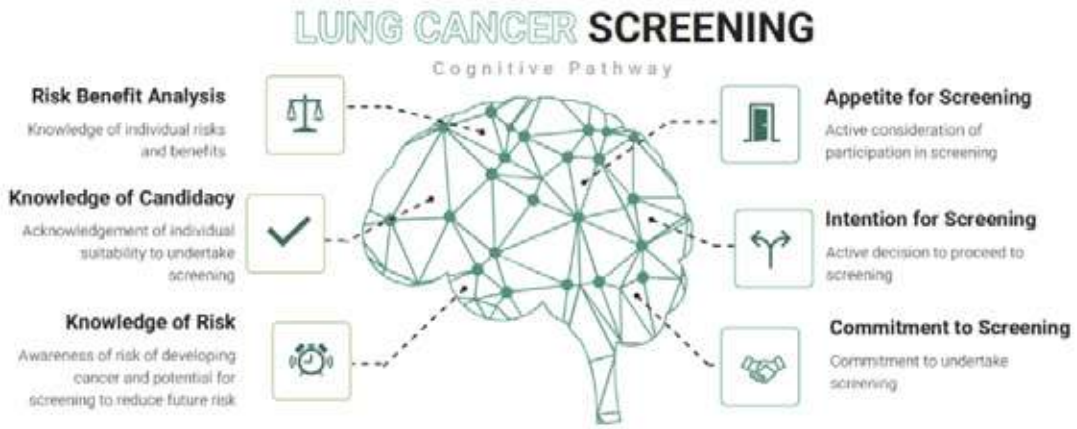
Introduction: There is good evidence that low dose CT scan (LDCT) lung cancer screening (LCS) improves outcomes including mortality in clinical trials, but it is unclear whether this evidence is being implemented effectively into practice. Little is known about the extent and effectiveness of knowledge translation (KT) and dissemination and implementation science in the translation of lung cancer screening trial results into effective programmes. This systematic review attempts to address how knowledge translation (KT) strategies have been used to improve knowledge, screening behaviour, and participation in LCS programmes.

Methods: A PICO framework was designed to identify eligible articles. The study was registered in PROSPERO. Literature searches were performed for studies incorporating KT strategies in relation to LCS. Searches were performed in MEDLINE, EMBASE, CINAHL, Cochrane, Web of SCIENCE and Scopus. These searches were imported into Covidence reference management software for selection and consensus by 2 reviewers. Included articles had to include a KT intervention intended to facilitate participation in screening, improve intention to screen, or increase screening uptake. Studies with comparator groups, or "before and after" studies, were included.

Results: 1160 studies were identified for title and abstract review after removal of duplicates. After applying inclusion and exclusion criteria, 112 were identified for full text review and from these 24 were selected for data extraction. Studies were identified from USA (20), Canada (1), UK (2) and Japan (1) and were published between years 2014 and 2021. KT interventions were various including staff training and patient education (classes, print, web-based and video), shared decision making tools, forms (online and paper), reminders and triggers, data presentation modalities, and materials targeting specific populations. In relation to a defined KT intervention, there were 5 studies that addressed knowledge based endpoints to facilitate screening participation; 8 studies that addressed intention to screen endpoints; and 11 studies that addressed actual LDCT uptake. Of these 11 studies, 4 demonstrated a positive effect on lung cancer screening rates after the KT intervention; 3 showed no effect; and 4 had no comparator.

Conclusions: This systematic review identified several studies that addressed the utilisation and effectiveness of various KT interventions in the context of LCS. Most of these were low level evidence. Randomised controlled trials that measured actual screening rates as an outcome were lacking. It is important that KT interventions are explored through high quality studies in order to optimise the implementation of LCS programmes and participation with them.



Keywords: Lung cancer screening, Knowledge translation, Low dose CT scan

EP01.02 EARLY DETECTION AND SCREENING - DISSEMINATION

EP01.02-004 Education Messages and Strategies About Lung Cancer Screening: A Systematic Review

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Introduction: International lung cancer screening trials, using low-dose computed tomography, have demonstrated clinical effectiveness in reducing lung cancer mortality. This systematic review aims to synthesise key messages and strategies that might be successful in increasing awareness and knowledge of lung cancer screening, and ultimately uptake of screening.

Methods: Studies were identified via relevant database searches up to January 2022. Two authors evaluated the eligibility of studies with verification from the study team, extracted and crosschecked data, and assessed quality.

Results: Of 3205 titles identified, 116 full texts were reviewed and 22 met inclusion criteria. Twenty studies were conducted in the United States, all having taken place since the 2013 United States Preventive Services Task Force recommendation supporting implementation of lung cancer screening programs. Study findings were heterogenous making comparisons difficult, but some key messages such as information about lung cancer screening recommendations (n=8), benefits and harms of screening (n=6), cost of screening/insurance coverage (n=6) and eligibility criteria (n=5) were repeated across studies. Limited information was provided across the studies about how potential participants could best access resources or be given cues to action such as how to talk to their doctor about whether they should screen.

Conclusions: Some key messages were repeated across studies, but there is a need to further test those strategies that appear to be most effective in attracting participants to take part in screening. The learnings from awareness strategies implemented in other cancer screening programs could also be used to enhance knowledge about the purpose, and the benefits and harms of screening. International guidelines which draw on international successes of how best to inform potential participants and increase awareness and knowledge of lung cancer screening would be beneficial, for other countries to develop locally appropriate messaging and strategies for testing.

Keywords: lung cancer screening, education

EP01.02 EARLY DETECTION AND SCREENING - DISSEMINATION

EP01.02-005 Exploring Individuals' Views on Invitation to Lung Cancer Screening: Developing a Tailored Approach

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Introduction: Lung cancer outcomes in the UK are poor with 70% of patients first presenting to specialist care with advanced disease and treatment at this stage having little effect on mortality. To improve outcomes, earlier diagnosis is essential, and a promising approach is Low Dose Computer Tomography screening (LS). Despite the efficacy of LS, there is evidence that those most at risk of lung cancer are the least likely to attend screening. Effective methods to encourage high-risk people into screening programmes are needed. This project focuses on developing tailored invites to LS with potential screening participants (PSP) and their family members (FM).

Methods: Smokers and ex-smokers aged between 50 and 75 years were invited via adverts placed in community-based settings and social media, to take part in semi-structured interviews. FMs were also invited to take part in a separate interview. Experian Mosaic Public Sector Groups (MPSG) data are identified through the postal code and their preferred methods of contact. These groups are also at varying risk of lung cancer and there is therefore a potential method for tailoring invites. Qualitative interviews explored current health screening invitations, knowledge of and barriers to LS attendance and the role of FMs in encouragement to attend LS. Interviews were conducted via telephone, audio-recorded, transcribed verbatim and analysed using the framework approach.

Results: Fifty interviews were completed with smokers and ex-smokers (n=39; 27 women, mean age 57yrs) and family members (n=11; 8 women, mean age 51yrs). The proportion of people with high risk associated MPSG was 31%, intermediate risk 9% and low risk 60%. Preliminary findings indicate that health screening is seen as an important part of preventive health care, but that lung screening itself is relatively unheard of. Many participants had personal experience of lung cancer, which was seen to be a disease with poor prognosis. In terms of developing invitations to LS, a pre-invite (promotional stage) involving greater advertising of LS and the demographics at which it is aimed was needed to both reassure people and to prepare the way for the invitation. Data suggests the tone should be positive, and content should emphasise the 'routine' nature of screening, which may increase engagement. Images were discouraged with participants suggesting that images aimed at smokers were often used to scare and shock. Participants suggested invites should discuss the range of lung diseases identifiable through screening and the benefits to identifying these early. Importantly, participants advocated positive stories of lung cancer are needed in invitation materials to reassure about prognosis of the disease. Thus far we have not analysed for differences according to MPSG.Findings highlighted that FMs often played a key role in health issues including encouraging smoking cessation and supporting relatives through health screening programmes, including a potential LS programme.

Conclusions: Invitation to LS needs careful consideration to ensure that it serves to reassure eligible individuals and prepare them for the process, where a staged approach, positive framing and engagement of FM was encouraged.

Keywords: Lung screening, qualitative, cancer

EP01.02 EARLY DETECTION AND SCREENING - DISSEMINATION

EP01.02-006 Excuse Me? Patient Perceptions of Lung Cancer Screening Results

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Introduction: Low-Dose Computed Tomography (LDCT) is safe and effective screening method improving lung cancer outcomes. Individuals at risk are less interested in screening indicating a disconnect between patient perceptions, beliefs, and willingness to follow recommendations. Additionally, patients undergoing LDCT may have difficulty interpreting results, especially in underserved communities where health literacy can be limited, affecting compliance with further testing and treatment. Our goal was to determine how patients in an underserved area interpret LDCT results, recommendations for subsequent testing, and what factors influence these interpretations.

Methods: From 8/2020 to 7/2021, we surveyed patients two weeks after undergoing LDCT at Charleston Area Medical Center in West Virginia. We asked about LDCT results, their cancer risk based on results, when additional testing was recommended, and items assessing their attitudes and beliefs about lung cancer. Demographics and Lung-RADS Score (LRADS) were obtained from records. SAS Version 9.4 was used for analyzing frequencies, chi-square, and Fisher's exact tests. Psychometrics were divided into fear/shame, locus of control, and fatalism/stigma components by exploratory factor analysis with a 0.45 factor loading cutoff. Internal consistency was validated with Cronbach's alpha.

Results: Of 1500 surveys, 505 (33.7%) were returned with average age of 64.7 years, 50.9% female, 52.5% current smokers, and 77.0% with government insurance. Of psychometric components, only fear/shame demonstrated internal consistency (α=0.72). As LDCT malignancy risk increased, patient's interpretation of results were less accurate (84.8% LRADS-1, 51.3% LRADS-2, 27.3% LRADS-3, and 6.7% LRADS-4,p<0.001). Patients reporting their LDCT showed possible cancer more often agreed with fear/shame statements (3.01 vs 2.26,p=0.02). Patients with higher risk scans (LRADS-3 and LRADS-4) were more likely to be unclear about results (14.3% vs 4.0%,p=0.002). For those unable to remember results, patients were more often male (72.7% vs 27.3%,p=0.02). No differences were noted by insurance or smoking status. Over half of patients correctly correlated their results with cancer risk with 58.2% of LRADS-1 and LRADS-2 assessing low to no risk, and 60.9% of LRADS-3 and LRADS-4 assessing medium to high risk (p=0.01). Unfortunately, 39.1% of LRADS-3 and LRADS-4 patients reported risk was low to none. Patients reporting high risk more often agreed with fear/shame statements (2.85 vs 3.08,p=0.04). Current smokers more often perceived their malignancy risk higher than former smokers (51.0% vs 34.7%,p=0.004). The vast majority of patients understood subsequent recommendations with 83.1% of LRADS-1 and LRADS-2 patients acknowledging imaging at one year, and 95.1% of LRADS-3 and LRADS-4 in ≤6 months.

Conclusions: Lung cancer screening is a relatively new recommendation with poor utilization in West Virginia influenced by public awareness and health literacy. Affecting lung cancer mortality relies on performing LDCTs, completing further testing, and undergoing treatment if needed. This study demonstrates patients may lack understanding of LDCTs revealing higher risk nodules. Individuals acknowledging higher risk demonstrate fear of diagnosis and treatment, are more likely to currently smoke, and are ashamed smoking places them at risk. These are important factors when communicating results and plan as patients with potential malignant findings might not understand the significance and may be fearful of subsequent steps.

Keywords: lung cancer screening, interpretation, patient perceptions

EP01.02 EARLY DETECTION AND SCREENING - DISSEMINATION

EP01.02-007 It's Not How You Start, It's How You Finish: Patient Motivators to Follow Low-Dose Screening Recommendations

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Introduction: Low-Dose CT (LDCT) for lung cancer screening (LCS) is recommended for ages 50-80 with 20 pack-years smoking history that currently smoke or have quit within 15 years. Although LCS decreases lung cancer mortality 20-25%, recent US screening rates are only 6.5%. Furthermore, adherence to follow-up is suboptimal outside of studies due to provider, patient, and system barriers. Our goal was to explore patients' motivating factors and deterrents to LDCT follow-up in an underserved population.

Methods: From 8/2020 to 7/2021, we surveyed patients two weeks after undergoing LDCT at Charleston Area Medical Center in West Virginia. We inquired about smoking status, cessation plans, familiarity of screening and lung cancer, their intention to follow recommendations, and items assessing their attitudes and beliefs about lung cancer. Demographics and Lung-RADS Score (LRADS) were obtained from records. SAS Version 9.4 was used for analysis examining frequencies, chi-square, and Fisher's exact tests. Psychometrics were divided into fear/shame, locus of control, and fatalism/stigma components by exploratory factor analysis with a 0.45 factor loading cutoff. Internal consistency was validated with Cronbach's alpha.

Results: Of 1500 surveys, 505 (33.7%) were returned with average respondent age of 64.7 years, 50.9% female, 52.5% current smokers, and 77.0% with government insurance. Of psychometric components, only fear/shame demonstrated internal consistency (α=0.724). Of respondents, 87.9% stated that getting a LDCT was their physician's idea, 48.7% knew someone that died from lung cancer while only 32.1% knew someone that had a LDCT. Of current smokers, 48.3% intended to quit smoking, and another 34.0% to decrease. This was not correlated with sex, LRADS score, patient's interpretation of results or risk, or fear/shame psychometrics. The vast majority of patients (92.7%) stated they were very or extremely likely to follow recommendations. Patients likely to follow recommendations more frequently knew someone that died with lung cancer (50.4% vs 33.3%,p=0.05), and had government insurance (78.5% vs 58.3%,p<0.01). Likelihood did not correlate with sex, smoking status, if LDCT was their idea, knowing someone with LCS or lung cancer, or with interpretation of their LDCT results and risk. Those not likely to follow recommendations cited reasons of cutting down smoking (53.1% vs 25.7%,p=0.003), feeling fine (56.7% vs 23.3%,p<0.001), not feeling they needed screening (37.9% vs 9.6%,p<0.0001), concerns about radiation exposure (18.8% vs 5.8%,p=0.007), and busy schedules (10.0% vs 3.1%,p=0.007). They were also more likely to disagree with fear/shame statements (3.43 vs 2.92,p=0.03).

Conclusions: Lung cancer mortality is improved by LCS, however real-world implementation has proven to be challenging. It is important to understand patient factors that affect low adoption. Although many patients know someone that died with lung cancer, much less know someone undergoing LCS and willingness to follow-up is affected by similar personal connections. Those with misconception of risks and symptoms of early lung cancer, denial of fear for diagnosis and treatment, and concerns of insurance coverage and radiation exposure are at high risk of not following recommendations. Advocacy and promotion efforts may be more effective by educating on risks, symptoms, and mortality of lung cancer by highlighting personal connections.

Keywords: lung cancer screening, motivation, patient perceptions

EP01.02-008 Pocket Nodules, An Innovative Patient Education Tool to Explain Lung Nodules

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Introduction: Annually, thousands of patients are told they have a pulmonary nodule within the context of lung cancer screening or as an incidental finding. Many nodules are discovered during lung cancer screening with LDCT and benign, posing a low risk of cancer. Despite the low risk of malignancy, lung nodules are a common cause of emotional distress among patients. To improve patient's understanding, decrease distress for a lung nodule finding and engage patients in recommended follow up lung screening, Pocket Nodules is designed to enhance the discussion of pulmonary nodules during the Lung Cancer Screening Shared Decision Making consult. The patient education tool is designed to be visually engaging, easy to understand and support patient engagement in lung screening.

Methods: Preliminary Data: A prototype 3D printed lung nodule model representing lung nodules of increasing diameter and of varying physical features was piloted at the Maine Medical Center Thoracic Oncology Clinic. The 3D model was employed during the Shared Decision Making conversation to address the significance of nodule size, appearance and malignancy risk. The effectiveness of the educational tool was assessed using a 5-question patient survey containing 4 quantitative questions and 1 qualitative question.

Results:

Thirty one patient surveys were completed at the end of consult. Preliminary data indicated the nodule was widely perceived as helpful to increasing understanding of lung nodules, including the significance of size and appearance. The average score for helpfulness in overall nodule understanding was 9.4, out of 10 with 10 being extremely helpful (Figure 1)

Conclusions:

A goal is to corroborate pilot survey results of Pocket Nodules in a scientific manner by inviting sites internationally to engage in use of Pocket Nodules to further validate the use of an innovative, experiential learning tool to engage patients and support lung cancer screening retention around the world.

On a scale from 1 to 10:

1. How helpful was the nodule model to your understanding of lung nodules?

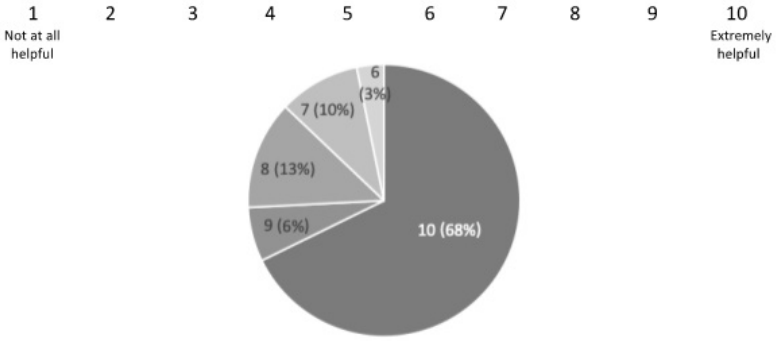

Figure 1: Number and percent of respondents (n=31) who indicated how helpful the 3D educational tool was in their overall understanding of lung nodules.

Keywords: Pocket Nodule Patient Education Tool, Lung Nodule visual engagement tool, Reduced Anxiety

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-001 Māori Perspectives on a Potential Lung Cancer Screening Programme Aotearoa NZ: An Indigenous People's Perspective

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Introduction: Lungcancer is a significant health issue for Māori, indigenous people of AotearoaNZ, and has been found to be the greatest contributor to the absolute inequityin mortality for Māori compared to NZ European. Internationally, lung cancerscreening trials have demonstrated a 20-26% reduction in lung cancer mortality. A pilot lung cancer screening trial acrossAuckland city has commenced as an intervention to accelerate Māori health gainthrough early detection and treatment. The aim of this survey was to understandthe attitudes and beliefs of Māori toward a lung cancer screening programme.

Methods: Across-sectional survey design recruiting Māori aged 50-80 years who werecurrent or former regular smokers. Whānau (family) support people were alsorecruited to complete a similar survey. Convenience and snowball sampling wasused across locations in Auckland and Northland. Analysis was undertaken usingdescriptive statistics plus Chi-squared and z-tests for comparing groups.

Results: The sample were 54% female, relativelyequally spread across the 50-59 (38%) and 60-69 (44%) age groups, had a widerange of educational qualifications, and 36% were current smokers.The most common preferences for decidingabout whether to participate in lung health check that includes screening forlung cancer were to "Follow your doctor's recommendations on this" (35%), "Begiven the pros and cons of screening and make the decision yourself (or maybealso with family/whānau)" (30%), and "A shared decision with your doctor/nursehelping you decide" (24%). The most preferred sources of invites to the screeningprogramme were: "Screening programme" (37%), "General Practitioner" (33%), and "No preference" 30%. Almost half ofparticipants (46%) had a 'health champion' in their whānau that they talk to(or who takes the lead) when health related things happen. Factors most likelyto increase attendance were "My desire to find any lung cancer early" (76%),"The reassurance that I/my whanau would get if the scan showed no cancer" (63%)and "Fear that they might find cancer" (22%). Factors most likely to reduce attendancewere other responsibilities (16%), cost (15%), staff making judgements based onsmoking history (15%), transport/timing of appointments (14%), and worry aboutradiation (14%). Factors that would make participants more comfortable withhaving a smoking cessation component within the screening programme were"Ensuring that there is no judgement on smoking from health professionals"(46%), "Free quit services" (38%), "Feeling OK to say no to smoking cessationhelp" (36%), "Being given medicines to help quit" (32%), "Choice of support"(26%), and "Quit help at screening location" (25%).

Conclusions: Resultsare encouraging in terms of the high proportion of the sample who would bewilling to attend a screening programme. The survey identified equipoise inpreferred invitation method between central and primary care based invitation;from this finding we have designed an invitation trial. There were numerousother factors identified that may create enablers or barriers to actualattendance, including: health champions, addressing fears/concerns, deliveringinformation through preferred channels, options for practical barriers, andensuring the smoking cessation component is carefully delivered, free andnon-stigmatising.

Keywords: screening, equity, indigenous health

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-002 Implementation of the International Lung Screen Trial (ILST) in Catalonia: A Cost Analysis Study

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Introduction: NLST and NELSON lung cancer screening (LCS) clinical trials with LDCT reduce mortality by >20%, as more early stages are diagnosed. With this stage migration, global treatment costs can be cut.

Objectives: To perform a healthcare-provider cost analysis comparing the LCS according to the ILST protocol costs, with the expected reduction in treatment costs of NSCLC patients due to stage migration treated at the Catalan public health system.

Methods: The Germans Trias Hospital is participating in the ILST. A cost analysis was based on the following variables: costs of the LCS and the usual care diagnosis, treatments and radiological follow-up based on the standard retail price; reference staging for the LCS obtained from NELSON and NLST (mean: I 63%,II 9%,III 17%,IV 11%); stage distribution (I 14%,II 6%,III 13%,IV 67%), lung cancer detection rate and need of smoking cessation program in our site. Costs were adjusted to survival according to the 8th TNM. Complications, 2nd line treatments and other minor costs were not computed.

Results: The observed detection rate in our site was 2.44% (2 stage IA patients out of 82 patients screened). In our sample, 54% of patients required smoking cessation. The baseline LCS cost is 787€ per participant and 1,012€ if smoking cessation is included. With these data, savings would offset the LCS cost by 160%-206% (mean 183%)

Conclusions: Baseline LCS costs per patient according to the ILST protocol are low. In the Catalan public health system, a short term mean benefit of 83% of the estimated total cost of LCS program would be achieved based on stage migration.*Funded by*: ACMCiB, BRN, Fundació Ramon Pla, MINECO, Lung Ambition Alliance, ISCIII

Keywords: COST ANALYSIS, SCREENING

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-003 AI Detection of Emphysema in an Ultra-Low Dose CT Lung Cancer Screening Program

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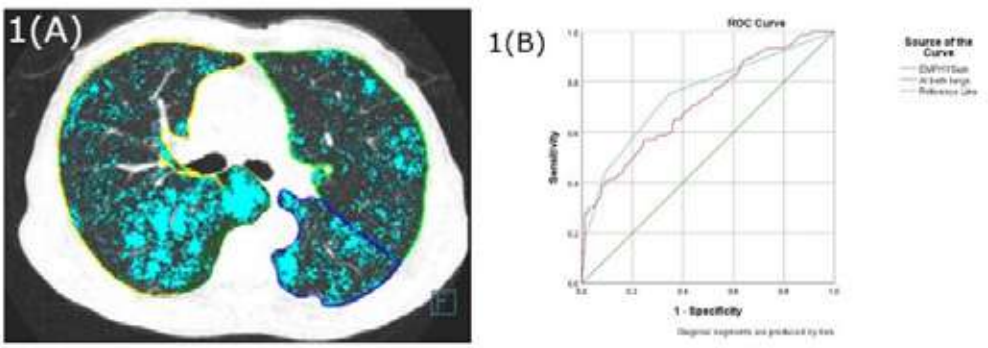
Introduction: Emphysema is a significant independent risk factor for lung cancer (LC) and may be diagnosed for the first time during a LC screen using low dose CT (LDCT) scan. The role of artificial intelligence (AI) in the detection of lung nodules is clear, but its use in the detection of emphysema at ultra-low radiation dose CT (uLDCT) has not been explored. This study explores the ability of AI to detect emphysema as part of a LC screening program (the Asbestos Review Program).

Methods: Participants underwent uLDCT and lung function testing between June and December 2018. COPD was defined based on spirometry (FEV_1 <80% predicted and FEV_1/FVC ratio <0.7). uLDCTs were reported by one of two radiologists using synoptic scoring with grading of emphysema and fibrosis. 158 cases with radiologist defined emphysema score of ≥1 were randomly selected, and 150 cases with no emphysema or fibrosis served as controls. SIEMENS AI Rad software provided a total emphysema score for both lungs.

Results: Of 308 participants, median (IQR) age was 75 years (65 - 79), 249 (81%) were male, and 218 (71%) were current or former smokers. Mean (SD) percent predicted FEV_1 was 86.26 (20.44); FEV1/FVC ratio 0.69 (0.11), DLCO 23.94 (2.95). 94 (31%) had fibrosis. Mean (SD) radiologist emphysema score was 2.94 (4.2) and AI score 4.82 (5.56). Mean radiation dose was 0.19 mSv. Radiologist scores were strongly correlated with AI scores for emphysema (0.335, p<0.001). For participants with fibrosis, mean (SD) emphysema scores were higher by both AI and radiologist (6.9 ± 6.8 and 5.9 ± 4.57), as compared to patients without fibrosis (3.91 ± 4.65 and 1.63 ± 3.26 respectively). Radiologist scores had stronger correlation with measures of airflow obstruction such as FEV_1 (coefficient -0.251, p<0.001) and FEV_1/FVC ratio (-0.397, p<0.001) as compared to AI scores (FEV_1 -0.26, p= 0.496; FEV_1/FVC ratio -0.331, p<0.001). In the subgroup containing participants without fibrosis, both radiologist and AI scores correlated less strongly with FEV_1/FVC ratio (-0.345, p<0.001 and -0.267, p<0.001, respectively). Using spirometrically defined COPD as the standard, the area under the curve for radiologist-scored emphysema was 0.751 and for AI 0.718, see Figure 1.

Conclusions: AI can be used to detect emphysema using uLDCT, although radiologist scores perform marginally better. The presence of fibrosis influences both scoring methods. With refinement, the automated scoring of emphysema as part of lung cancer screening may help modify individual risk assessment.

Figure 1. (A) ultra-LDCT (0.15mSv) with AI-detected emphysema. (B) ROC curve depicting the sensitivity and specificity of AI and Radiologists (EMPHY Sum) in detecting emphysema with uLDCT scans.



Keywords: Lung Cancer Screening, Artificial Intelligence, Emphysema

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-004 Should We Screen for Lung Cancer? A 10-Country Analysis Identifying Key Decision-Making Factors

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Introduction: Early detection, including early diagnosis and screening, is critical for improving the prognosis of lung cancer. Supported by extensive clinical evidence including NLST and NELSON trials, screening using low-dose computed tomography (LDCT) can effectively reduce lung cancer mortality. However, implementation of formal lung cancer programmes remains limited across the world. This study investigates how governments make decisions on the implementation of formal lung cancer screening programmes and identifies key factors that impact the decision.

Methods: This study reviews decisions in Australia, Canada, Croatia, France, Germany, Japan, South Korea, Switzerland, the UK, and the US. Materials used for case study development include academic articles, governmental documents, NGO publications and media reports. We distilled critical factors in the decision-making process which were validated through workshops with local experts within MSD and a roundtable including academics, policy advisors and representatives from patient and clinical communities.

Results: Our research identified formal programmes in Canada, Croatia, Japan, South Korea, and the US. Australia, Germany, and the UK are on the path to formally implementing a programme. France and Switzerland decided against a programme. Key decision-making factors identified are 1) recognizing lung cancer disease burden and the value of early detection, 2) strong clinical data showing mortality reduction and benefit-risk analysis relevant to the local context, 3) cost-effectiveness data and budget impact estimates which are in line with local thresholds 4) demonstration of local feasibility and 5) an integrated decision-making process involving all stakeholders (Table 1). The relative importance of the factors may vary in different local contexts.

Conclusions: The set of factors identified in this paper can help policymakers and advocates address knowledge gaps and evaluate opportunities of a lung cancer screening programme and therefore make informed decisions to best improve lung cancer outcomes.

Decision-making factors of lung cancer screening implementation	
Decision-making factor	**Indicators**
Recognition of the disease burden of lung cancer and the value of early detection	1.Integration of lung cancer screening in national cancer plans 2.Major lung initiatives spearheaded by key political figures
Strong clinical data showing mortality reduction and benefit-risk analysis relevant to the local context	3.Acceptance of clinical evidence supporting LDCT screening 4.Concerns over inconclusive effectiveness evidence on LDCT screening in the non-smoker population 5.Comfort level of the benefit-risk ratio associated with false positive, overdiagnosis, radiation exposure, etc.
Cost-effectiveness data and budget impact estimate, despite variations across health systems	6.Country-specific cost-effectiveness analysis 7.Long-term budget impact for financial planning
Local feasibility demonstration	8.Local pilots to understand whether the desired results can be achieved or upscaled 9.Integration with existing services, e.g., annual health check-ups and smoking cessation
A clear and integrated decision-making mechanism involving all relevant stakeholders	10.Clear decision owner and decision-making chain 11.Channels for the scientific community and civil societies to advise and participate in decision-making 12.Consideration of health equity and vulnerable communities

Keywords: lung cancer screening, early detection, health policy

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-005 Current status of High-risk Smokers Participating in Population-based National Lung Cancer Screening Program in Korea

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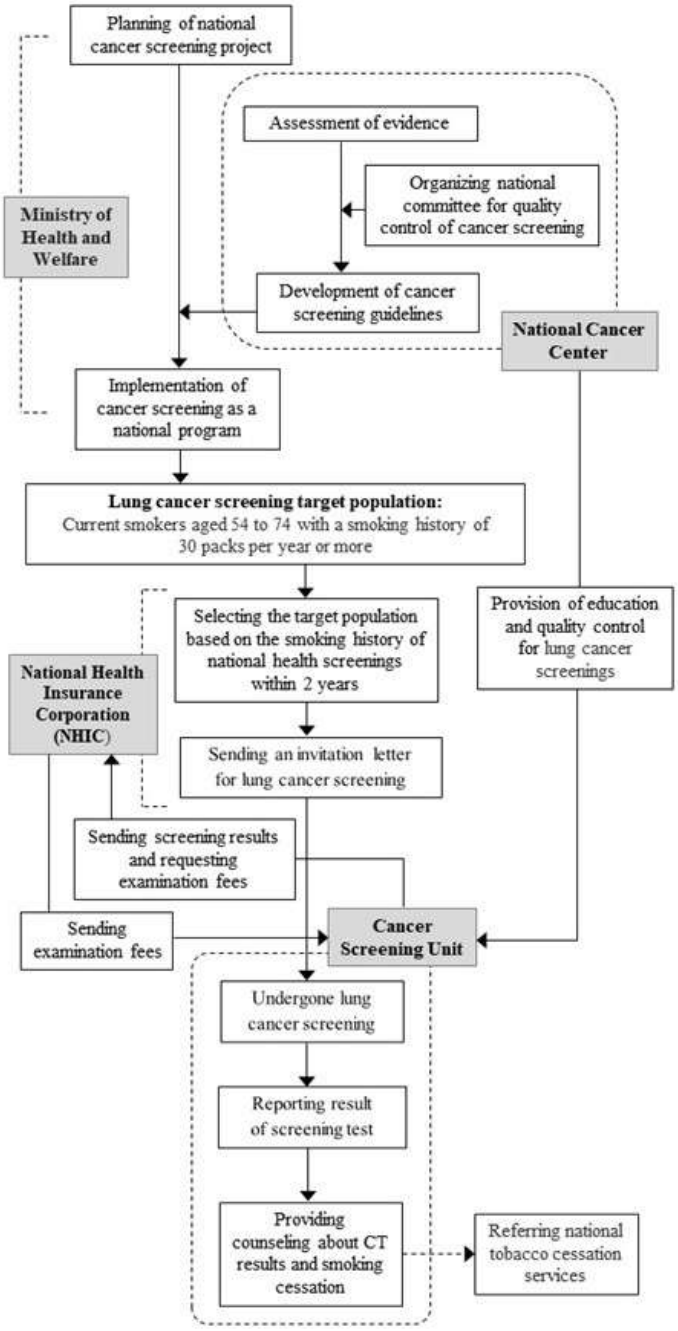
Introduction: Following assessment of the effectiveness and feasibility based on the results from a two-year population-based nationwide prospective multi-center trial, the Korean government implemented a national lung cancer screening program using low-dose computed tomography (LDCT) for high-risk smokers in 2019.

Methods: National Health Insurance Corporation selected high risk targets who are current smokers aged 54 to 74 years with 30 packs per year or more smoking history on the basis of national health-screening database. (Figure 1). Those eligible were offered lung cancer screening by invitation letters in every two years. Screening units provide LDCT using radiation less than 3mGy by at least 16-row multi-detector CT scanners. Screening results were reported by Lung Imaging Reporting and Data System (Lung-RADS). The examinee received results by mail or e-mail; after then, counseling on results and mandatory smoking cessation counselling were provided by certified doctors. National Cancer Center monitored participation rates, post-counseling rates and statistics of screening result for quality control. Screening positive rate is defined as proportion of Lung-RADS category 3 and 4 nodules.

Results: The participation rate gradually increased from 24.8% among 332,244 eligible targets in 2019, 25.9% in 2020, to 38.7% among 310,260 targets in 2021, however, the proportion of examinees who participated in post-counseling decreased from 46.3% in 2019 to 32.7% in 2021 due to the COVID-19 pandemic (Figure 2). The positive rates slightly decreased from 9.2% in 2019 to 8.7% in 2021. The variation in positive rates of screening units showed a tendency to decrease (in 2019, the 1st quartile was 4.3%, and the 3rd quartile was 12.9%; and in 2021, 5.2% and 12.5% respectively).

Conclusions: National lung cancer screening program has been implemented successfully in Korea with controlling screening positive rates not so high. Controlling false negatives and strengthening post-screening management including smoking cessation counselling needs to improve.



Keywords: National Lung Cancer Screening, Quality control

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-006 Potential Drivers of Lung Cancer Screening Participation in Australia: A Qualitative Study to Inform Future Implementation

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Introduction: Lung cancer is the leading cause of cancer death worldwide. Significant reductions in lung cancer mortality among screening in high-risk individuals has been demonstrated. Yet, participation in lung cancer screening trials and real-world programs is low, with many people at high-risk opting out of baseline screening after registering interest. Challenges in implementation include that potential participants are often 'hard to reach' and tobacco smoking, the single biggest risk factor for lung cancer, is a highly stigmatised behaviour. We aimed to identify the potential drivers of participation and declining to participate in lung cancer screening, to inform future implementation.

Methods: Semi-structured telephone interviews were conducted with individuals at high-risk of lung cancer who were eligible for screening and who had either participated (screeners) or declined to participate (decliners) in the International Lung Screening Trial from two Australian sites. Interview guide development was informed by the Precaution Adoption Process Model. Interviews were audio-recorded, transcribed and analysed using the COM-B model of behaviour to explore capability, opportunity and motivation related to screening behaviour.

Results: Thirty-nine participants were interviewed (25 screeners; 14 decliners). Motivation to participate in screening was high in both groups driven by the lived experience of lung cancer and a belief that screening is valuable. Decliners in our study, unlike their screening counterparts, reported challenges in capability including practical barriers of everyday, knowledge and understanding, and self-efficacy. Decliners also reported challenges related to physical and social opportunity, in particular location as a barrier and family support to attend screening.

Conclusions: Our findings suggest that motivation alone may not suffice in changing behaviour related to screening participation unless capability and opportunity are also considered. Rather than strategies to increase participant motivation, our findings suggest that strategies which focus on the practical barriers of capability and opportunity may better enhance screening participation. These may include: supporting the unique concerns of individuals through clinician education; lessening geographic barriers to screening through use of mobile scanners; reducing the financial impact on low-income participants through travel and accommodation assistance; addressing the importance of social support in decision making; reducing the social stigma related to smoking and lung cancer. Interventions that connect an individual with a lung cancer screening program will enable participation of those who stand to benefit most and will be crucial for successful implementation of an organised lung cancer screening program. These learnings are relevant both in the Australian setting and internationally.

Keywords: lung cancer screening, screening participation, implementation

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-007 Lung Cancer Screening Use Among Screening-Eligible Adults with Disability in the United States: Evidence From Population-Based Data

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Introduction: Lung cancer continues to be the leading cause of cancer-related death in the United States (US). Annual screening with low-dose computed tomography is shown to detect lung cancer earlier and significantly decrease mortality. Yet, lung cancer screening use among adults with disability is understudied. This study estimated the prevalence of disability and investigated the association between disability status and lung cancer screening utilization among adults at increased risk for lung cancer in the US.

Methods: Cross-sectional data from the 2020 Behavioral Risk Factor Surveillance System (BRFSS), Lung Cancer Screening module were used. This is a population-based, nationally representative sample from 5 US states (Delaware, Maine, New Jersey, North Dakota, South Dakota). We included adults aged 50-79 years old who were eligible for lung cancer screening based on the US Preventive Service Task Force criteria. The outcome was self-reported lung cancer screening use in the past 12 months. The key independent variable was disability status that was measured using the six-item set of questions used in the American Community Survey. The six items assessed the following disability types: hearing, vision, cognition, mobility, self-care, and independent living. We categorized disability into three groups: no disability, 1-2 disabilities, and 3 or more disabilities. We conducted descriptive statistics, including frequencies and weighted percentages with corresponding 95% confidence intervals (CI). We report estimated adjusted odds ratios (OR) and 95% CI using weighted multivariable logistic regression model adjusted for self-reported socio-demographic factors (age, sex, race, income, education, marital status), metropolitan residency, cancer history (other than lung cancer), having health insurance coverage and health care provider. All analyses were weighted to account for BRFSS's complex survey design.

Results: Overall our sample included 1,522 adults, representing 265,896 adults. About 43.0% were women and 57.0% men, 63.7% were between 60-79 years old, 1.6% self-identified as non-Hispanic American Indian/Alaskan Native, 4.8% non-Hispanic Black, 5.6% Hispanic, 86% non-Hispanic White, and 2.0% as other non-Hispanic race. Over half (59.0%) had a high school or lower level of education, 26% were in the lowest-income tier (<$25000 annual household income), 13.0% did not have a health care provider and 9.7% did not have health insurance coverage. Approximately, 54.0% were current smokers and 46.0% were former smokers with mean pack-years smoking of 43.6 (SE 0.93). Overall, 31.4% had any disability. About, 69.0% had no disability, 22.0% had 1-2 disabilities and 9.0% had 3 and more disabilities. Mobility was the most prevalent disability type (25.3%), followed by hearing (12.0%), cognition (11.6%), lack of independent living (10.4%), vision (6.7%) and self-care (6.4%). A total of 20.3% received lung cancer screening in the past 12 months. Compared with adults without disability, those with 3 and more disabilities had a significantly higher odds of receiving lung cancer screening (OR 2.34, 95% CI 1.14-4.80, p=0.021), adjusted for all other factors.

Conclusions: This study suggests that disability is associated with a greater likelihood of receiving lung cancer screening in the past year. More research is needed to understand the benefits of lung cancer screening among adults with disability.

Keywords: Early detection, Screening, Disability

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-008 Lung Cancer Screening Patients Experiences and Satisfaction: Quantitative and Qualitative Findings From a Survey Study

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Introduction: In 2015, H. Lee Moffitt Cancer Center & Research Institute (MCC) launched a lung cancer screening program for high-risk individuals based on National Comprehensive Cancer Network guidelines. To identify successes and barriers of this program from the patient perspective, we conducted a survey study to measure patient experiences and satisfaction with lung cancer screening.

Methods: In August 2020, a survey and cover letter were mailed to 576 patients who completed one or more lung cancer screenings at MCC. In addition to demographics, smoking history, and impact of the COVID-19 pandemic to get screened, the survey included 34 quantitative questions using a 5-point Likert scale and six open-ended questions. The quantitative questions measured patient satisfaction and experiences across 6 domains: appointment process, clinical staff interactions, communication, visit with the provider, screening results, cost, and clinic facility/overall satisfaction. Results were quantified using descriptive statistics. The six open-ended items elicited barriers and facilitators related to returning for screening, experiences with other cancer screenings, positive and negative experiences with the low-dose computed tomography (LDCT) visit, and suggestions for improving the process of LDCT screening visits. Content analysis using the constant comparison method was applied to the text and coded based on the *a priori* codes of the open-ended questions.

Results: Among the 212 patients (37% completion rate) who completed the survey, 97.6% were white, 48.6% were female, and the mean age was 69 years. In the communication domain, 81.1% “strongly agreed/agreed” that the lung cancer screening process was clearly explained, 92.5% “strongly agreed/agreed” that the potential harms and limitations were clearly explained and 76.9% “strongly agreed/agreed” that the process for follow-up screening was clearly explained. For the provider questions, 71.7% “strongly agreed/agreed” that the provider was willing to listen carefully and 68.4% “strongly agreed/agreed” that the instructions were easy to understand. For results and costs, 78.3% “strongly agreed/agreed” the screening results were clearly explained and 70.8% “strongly agreed/agreed” that the cost of the screening was justified. Regarding overall satisfaction, 88.2% “strongly agreed/agreed” they would recommend lung cancer screening at MCC. Patients who had Medicare insurance or paid out-of-pocket had higher agreement about helpfulness of the staff who assisted them with billing or insurance compared to patients who had private insurance coverage (79.4% Medicare coverage, 60.0% private, and 75.0% self-pay: P-value=0.025). In the qualitative findings, respondents provided generally positive comments about their lung cancer screening experience. Negative comments were related to desire for more information about results, long wait times for results, and billing issues.

Conclusions: This study provided insights about patient experiences and satisfaction with lung cancer screening which are important, given the low uptake of this life-saving modality. Ongoing patient-centered feedback may improve the lung cancer screening experience and increase follow-up screening rates.

Keywords: survey, screening, patient satisfaction

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-009 Cost-effectiveness of Lung Cancer Screening in New Zealand Varies by Ethnicity

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Introduction: In many countries, including New Zealand, lung cancer causes disproportionate health loss to indigenous populations such as Māori. Screening by low dose CT scan (LDCT) has emerged as a promising intervention to reduce lung cancer mortality among high-risk populations but reported incremental cost-effectiveness ratios (ICERs) have varied widely. Furthermore, these analyses rarely examine cost-effectiveness or impacts on health inequalities for indigenous populations.

Methods: A Markov macrosimulation model estimated health-adjusted life-years (HALYs), costs and cost-effectiveness of biennial LDCT screening from ages 55-74 years for Māori and non-Māori male and female current smokers and ex-smokers (within 15 years of quitting) with 30+ pack-years of tobacco exposure, compared with usual care. Input parameters came from literature and NZ-linked health datasets. Where possible parameters were drawn from the findings of the NELSON LDCT screening trial. Scenario analysis tested sensitivity to the model parameters.

Results:

Costs*, net costs, HALYs gained and ICERs by sex and ethnicity for biennial LDCT screening					
	Total	**Māori**	**Non-Māori**	**Female**	**Male**
Intervention cost ($m)	56 (47-65)	7.6 (6.4-8.8)	48 (41-48)		
Net cost ($m)	86 (71-103)	15 (11-18)	72 (60-85)	46 (38-55)	40 (33-47)
HALYs gained	3230 (2320-4310)	670 (480-900)	2550 (1770-3300)	1800 (1300-2410)	1310 (939-1760)
HALYs per capita				0.070 (0.051-0.094)	0.054 (0.039-0.072)
ICER ($000s/HALY)	28.1 (22.4-35.0)	22.4 (18.0-26.9)	29.6 (23.5-37.0)	25.9 (20.7-32.2)	31.2 (24.8-38.9)

LDCT screening for lung cancer would be cost-effective in all groups. Cost-effectiveness would be higher in Māori and females compared with non-Māori and males. At a population level LDCT screening in NZ would lead to greater HALY gains for Māori than non-Māori and therefore reduce absolute health inequalities, although

Conclusions: Cost-effectiveness models for lung cancer screening should obtain ethnic-specific estimates as these can vary substantially and reveal the impact on ethnic health inequalities. Interventions that reduce population health inequalities should be prioritised over those that do not.

Keywords: Screening, Cost-effectiveness, Equity

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-010 China Lung Cancer Screening Study (CLUS) Version 2.0: Study Design and Baseline Screening Results

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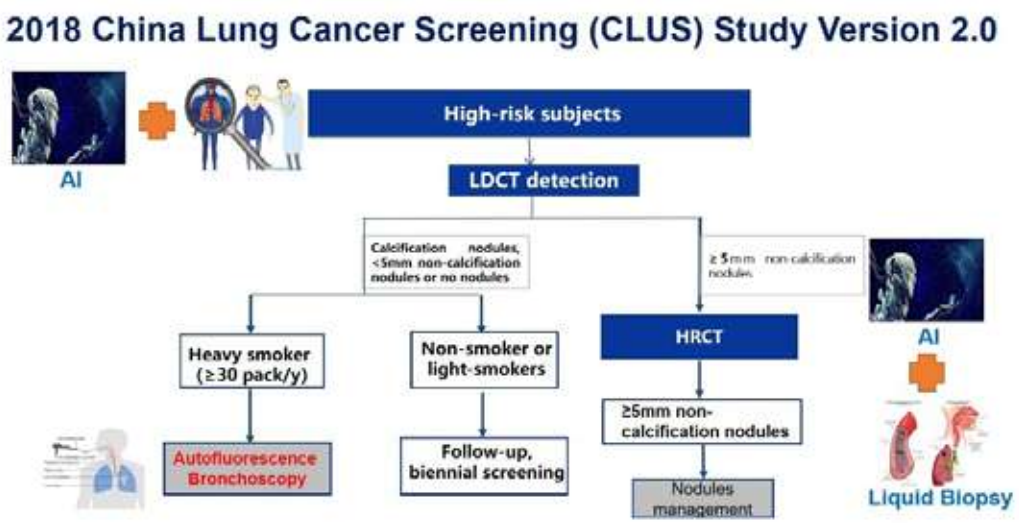
Introduction: In 2013, our team performed **China Lung Cancer Screening (CLUS)** study version 1.0 which was published in Lung Cancer**.** The key finding showed that LDCT led to a 74.1% increase in detecting early-stage lung cancer compared to usual care. The present study was conducted from 2018 to validate the efficacy of LDCT in detecting early stage lung cancer and explore new techniques for lung cancer screening (NCT03975504).

Methods: From 2018-2019, eligible participants with high-risk factors of lung cancer were enrolled to take LDCT detection. Any non-calcified nodules or masses with longest diameters of ≥5mm identified on LDCT images were considered as positive. Artificial intelligence was used in screening high-risk populations and imaging diagnostics. Liquid Biopsy biomarkers were explored in distinguishing positive lung nodules between malignant and benign. Participants who were heavy smokers (over 30 pack/y) were recommended to take the Autofluorescence Bronchoscopy (AFB) detection even their LDCT images were negative.

Results: A total of 5265 eligible high-risk participants were enrolled into the study after questionnaire inquiries, and 4491 participants (85.3%) underwent LDCT detection. A positive screening result was observed in 498 participants (11.1%), and 82 participants (1.83%) were highly suspected as lung cancer after multidisciplinary discussion. Up to October 2020, 62 patients were diagnosed by operation or biopsy, including 57 lung cancer (stage 0: 5, stage I: 47, stage II to IV: 5), 2 mediastinal tumor, 3 benign nodules. Early-stage lung cancer was found in 91.2%.

Conclusions: LDCT screening could detect more early stage lung cancer patients. New techniques will improve the implementation of LDCT Screening.



Keywords: lung cancer screening, Artificial intelligence, Liquid Biopsy biomarkers

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-011 Clinical Features and Surgical Outcomes of Young Patients with Ground Glass Opacity Featured Lung Adenocarcinoma

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Introduction: In recent years, with the popularity of low-dose computed tomography (LDCT) and the pandemic of COVID-19 (many young people suspected of having COVID-19 infection also routinely undergo LDCT examination), more and more ground glass opacity (GGO) featured lung adenocarcinoma have been diagnosed in young patients. Many studies have proved that the prognosis of GGO featured lung adenocarcinoma is excellent, the 5-year OS is close to 100%, but lack of attention has been paid to the clinical features and prognosis of GGO featured lung adenocarcinoma in young patients.Thus, our study aims to investigate the clinical characteristics and surgical outcome presenting as GGO featured lung adenocarcinoma in young patients.

Methods: Patients aging from 15 to 40 who were diagnosed as lung adenocarcinoma and underwent video assisted thoracoscopic surgery (VATS) were reviewed from January 2017 to December 2018. According to radiological appearance of the patient's lesions, they were divided into a GGO group and a solid nodule (SN) group. The pathological types, nodules size, surgical methods were analyzed, and the clinical characteristics and prognosis were evaluated between these patients.

Results: A total of 165 patients were included, of which 133 were in the GGO group and 32 in the SN group. Both the GGO group and the SN group had a higher proportion of females and non-smokers. Compared with patients (15.63%) in the SN group, there are more patients (27.8%) under the age of 30 in the GGO group. Pathological findings showed a predominance of pre-invasive lesions in the GGO group, although 16.5% of lesions were invasive adenocarcinoma, whereas in the SN group, 96.9% were invasive adenocarcinoma. Compared to the GGO group, the SN group showed significantly worse histological characteristics and prognosis. After a median follow-up time of 41.2±7.2 months (32-56), the 3-year RFS (100%) and OS (100%) of the GGO group were significantly higher than those (93.42% and 96.88%) in the SN group.

Conclusions: Young patients with GGO featured lung adenocarcinoma are mainly female and non-smokers. The vast majority of these patients were early-stage with extremely good prognosis after surgery. Further studies are required to better understand the molecular mechanisms causing younger patients to develop GGO featured lung adenocarcinoma and also identify potential targets to develop new treatment options.

Keywords: Ground glass opacity, Lung adenocarcinoma, Young patients

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-012 Acceptability and Feasibility of Lung Cancer Screening in Australia: The View of Key Stakeholders

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Introduction: Lung cancer is the number one cause of cancer death worldwide. International trials have demonstrated that targeted screening using low dose computed tomography (LDCT) is effective in significantly reducing lung cancer mortality and detecting cancers at an early stage. Implementation of screening in the high-risk population presents complex challenges that need to be clearly understood prior to policy change. The aim of this study was to elicit stakeholders' (health care providers, policymakers) views about barriers and enablers for potential implementation of lung cancer screening in the Australian setting.

Methods: We conducted 24 focus groups and two interviews in 2021, mostly using the Zoom platform, with 84 health professionals from multiple disciplines (including primary care, oncology, respiratory medicine, nursing and allied health), as well as researchers and managers and policy makers in current cancer screening programs. The focus group process included a structured presentation about the disease and lung cancer screening. Participants took part in facilitated discussions for about one hour. The focus group content was recorded, transcribed and analysed thematically.

Results: The large majority of participants considered lung cancer screening to be feasible and acceptable but identified a wide range of challenges to implementation. Challenges included participant factors such as encouraging participation from priority groups (those at high-risk), whilst ensuring that access and equity issues were carefully considered in designing a screening program. Health system factors included workforce resources, physical infrastructure (e.g. access to CT scanners) and establishing a quality assurance program. Participants strongly advocated for developing awareness and education campaigns that engaged participants and health professionals, as well as streamlined referral processes for initial entry into a program and follow-up scans. Smoking cessation was also perceived to be an essential program component. Practical considerations, such as using mobile vans, were also emphasised by participants, reflecting concerns about the diverse geographical spread of the Australian population, and addressing equitable access for Aboriginal and Torres Strait Islander communities, who are disproportionately impacted by lung cancer.

Conclusions: Key stakeholders readily identified the complex challenges that need to be addressed to ensure the acceptability and feasibility of lung cancer screening. Although these findings are particularly relevant to Australia in light of the Government's early scoping of a potential national lung cancer screening program, they are also highly relevant internationally.

Keywords: lung cancer screening, acceptability, early detection

EP01.03 EARLY DETECTION AND SCREENING - IMPLEMENTATION

EP01.03-013 A Pilot Study of Lung Cancer Screening with Low Dose CT in Georgia (One Centre Experience and Preliminary Data)

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Introduction: Lung cancer is one of the leading causes of mortality in both men and women worldwide, as well as in our country, Georgia. According to the data from the population registry of cancer in Georgia (2015-2017) lung cancer was the most prevalent type of cancer among men, 60% of cases were diagnosed at stage IV. The majority of lung cancer cases are associated with smoking. According to the 2016 results of the non-communicable disease risk factors STEPwise approach to surveillance (STEPS), almost one-third of Georgia's population (31.1%) smokes. We decided to launch the pilot study of lung cancer screening with low-dose CT in the risk group population.

Methods: Between June 1, 2021, and June 30, 2021, Todua Clinic offered the Georgian population LDCT for screening of lung cancer in high-risk patients. The eligibility criteria included risk factors: tobacco smoking (>20 packs year), former heavy smoking, age>55 years. The patients applied online and fill in the online questionnaire. A total of 241 patients registered, two were excluded due to the history of cancer in anamnesis (one with breast cancer and one with lung cancer). The low dose chest CT was performed on state of the art scanner Siemens SomatomGoTop, with contiguous thin (1 mm thickness) sections and high spatial frequency (sharp) filter, displayed in lung window. Axial sections were reconstructed in coronal and sagittal series. The low dose technique was applied according to the body habitus. The images were interpreted by five radiologists with more than 5 years of experience. The results were interpreted and categorized according to LUNG RADS version 1.1. The further stratification and decision about screening frequency was made by the multidisciplinary team.

Results: The majority of patients (82.4%) fell in Category 1, with no lung nodules and 4 of them with specific benign calcifications, while 15 patients (6.3 %) fell in category 2. The biennial screening was suggested for these groups. In 12 patients (5.0 %) category 3 nodules were discovered and 6-12 months interval CT was suggested, taking into account their risk factors, such as tobacco smoking and age, as well as their sex and family history. 8 patients (3.35%) had findings categorized as 4A/4B/4X). 5 of them were diagnosed with lung cancer: 3 cases were stage IV disease (two with metastasis to the contralateral lung and one with unsuspected metastasis to the lumbar vertebrae), they proceeded to systemic treatment, 2 patients were diagnosed with stage I-II disease with radical treatment intensions (surgical treatment was planned). 3 patients had suspicious findings, categorized as 4A, needing closer to follow up (3 months) or PET-CT.7 patients of the screened individuals (3.0%) were identified with pathology other than lung cancer needing further workup.

Conclusions: The preliminary data from our pilot study show that low dose chest CT can be used for screening lung cancer in an asymptomatic high-risk population group. Further results and better recruitment of the population is needed to prove the reduction of mortality and cost-effectiveness of this approach in Georgia.

Keywords: lung cancer screening Georgia, LMIC lung cancer screening, approaches to lung cancer screening

EP01.04 EARLY DETECTION AND SCREENING - IMPLEMENTATION QUALITY CONTROL

EP01.04-001 A Programmatic Approach to Improve Efficiency in Lung Cancer Screening

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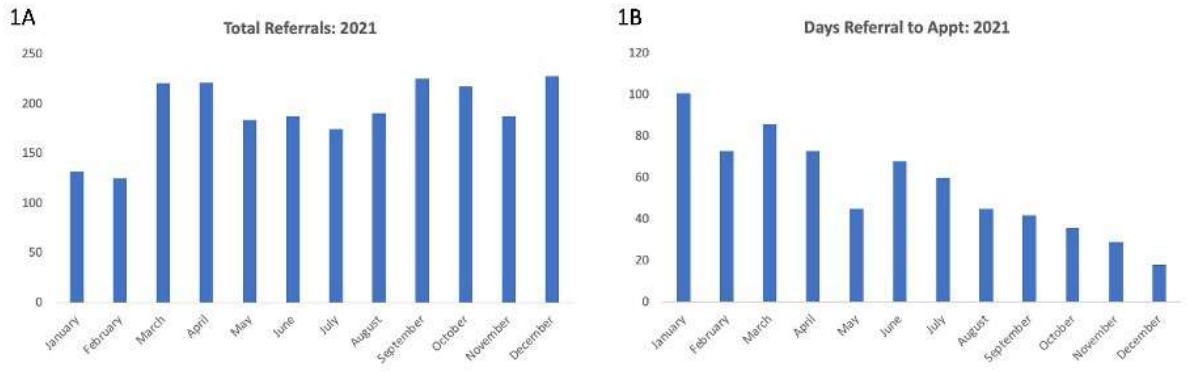
Introduction: Largely as a result of the COVID pandemic, our lung cancer screening (LCS) program was underperforming entering 2021. The program serves a majority minority, socio-economically disadvantaged community. Loss of personnel and reallocated resources, allied to pandemic focus, led to decreased referrals and excessive time from referral to low dose computed tomography (LDCT) appointments. Here we describe our programmatic approach to improve LCS metrics.

Methods: LCS transitioned from a Department of Radiology program into a Cancer Center-administered collaborative effort under surgical oncology and radiology leadership. Outreach efforts were reinitiated. To facilitate referrals from our primary care network, the cancer service line created a practical guide, "6 Steps to Lung Cancer Screening", directly linked to an e-referral mechanism in our EMR. Monthly review and quality assurance meetings were held with a multidisciplinary team, specifically focused on program volume and on addressing delays to LDCT appointments. An additional Nurse Practitioner was brought in to enhance the existing LCS Nurse Navigator and Cancer Center staff were utilized to contact and schedule patients and to perform data compilation and analysis.

Results: In 2020, LCS referrals had decreased 13% from 2019. In Q1/2021, the median monthly number of LCS referrals was 132 which increased steadily by quarter to 218 in Q4/2021 (p=0.16, Figure 1A). In January 2021, the average time from LCS referral to LDCT appointment was 101 days. Despite the increasing number of referrals through 2021, we were able to decrease the time to appointment from a median of 86 days in Q1/2021 to a median of 29 days in Q4/2021 (p=0.02, Figure 1B). By December 2021, the average time from LCS referral to LDCT appointment was just 18 days. Our LCS referral population was predominantly non-white (76%). Among them, 7.4% of patients with LDCT scans were found to have Lung RADS 3 or 4 nodules. All of these patients were referred to a newly created high-risk lung nodule clinic for management and follow up.

Conclusions: We employed a multidisciplinary team approach to improve inefficiencies in our LCS program. The resources, support, and leadership of the health care system's Cancer Center were crucial to this multi-pronged initiative. The decreased time from LCS referral to LDCT facilitates our ability to handle the anticipated growth in referral volume. This has been shown to enhance engagement with LCS and to improved annual screening compliance, translating to earlier detection of lung cancer and to improved patient outcomes.



Keywords: Lung cancer screening, Adherence, Disparity

EP01.04 EARLY DETECTION AND SCREENING - IMPLEMENTATION QUALITY CONTROL

EP01.04-002 The Impact of Enforcing a Structure in Lung Cancer Screening Strategy on the Effectiveness and Efficiency of the Screening Program

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Introduction: In 2021, the US Preventive Services Task Force (USPSTF) recommended annual lung cancer screening for individuals aged 50-80 years, who have at least 20 pack-year smoking history and currently smoke or have quit smoking within 15 years. The USPSTF strategy is practical and easy to implement, but suboptimal in terms of effectiveness and efficiency. Recently, the ENGAGE decision-analytic screening framework has been developed offering dynamic personalized lung cancer screening schedules that maximize individuals' expected quality-adjusted life years (QALY). The ENGAGE strategy is (analytically) optimal but has no structure and thus its implementation is challenging. In this work, we assess the impact of imposing a structure into screening on the effectiveness and efficiency of the overall screening program by comparing the 2021 USPSTF strategy and 4 alternative structured strategies that allow a single switch in screening frequency against ENGAGE's strategy.

Methods: We evaluated the performance of 6 strategies: ENGAGE; 2021 USPSTF; Strategy 3: screen annually until age 60 biennially thereafter; Strategy 4: screen biennially until age 60 annually thereafter; Strategy 5: screen annually until age 64 biennially thereafter; Strategy 6: screen biennially until age 64 annually thereafter. All structured strategies screened the USPSTF-eligible population between ages 50-80 years. Primary outcomes included mortality reduction and screening exams per death avoided. Secondary outcomes included QALYs gained from screening, number of individuals ever-screened, and false-positives. All outcomes were sex-, smoking status- (former vs current) and smoking intensity-specific (light, moderate, heavy). The robustness of our conclusion was assessed through sensitivity analyses on key model assumptions.

Results: The ENGAGE-strategy recommends screening for all current smokers and former heavy smokers, with more frequent screening recommended for women (vs men) and heavy (vs light) smokers. The impact of enforcing a structure into screening on the effectiveness of the overall program was not clinically significant. Albeit being statistically significant, differences in QALY gained were modest (0-16 days gained more with ENGAGE vs. structured strategies). The 2021 USPSTF recommendation achieved the highest mortality reduction for current moderate smokers and male heavy smokers; structured strategies yielded lower mortality reduction compared to ENGAGE for the remaining groups. Imposing a structure into screening however significantly affected the efficiency of the overall program. Structured strategies required 1.2-5 times more screening exams to avert one lung cancer death as compared to ENGAGE. Strategies that initially screen individuals biennially until age 60 or 65 and annually thereafter yielded comparable mortality reduction to 2021 USPSTF strategy while being more efficient. Enforcing a structure into screening increased the number of individuals ever-screened and yielded higher false-positive rates. The impact of enforcing a structure into screening on the screening program's performance was sensitive to the disutility associated with screening and indeterminate findings.

Conclusions: Imposing a structure into the screening strategy significantly affects the efficiency of the program and has modest impact on its effectiveness. Strategies that start with biennial screening until age 60 or 65 years and transition to annual screening thereafter until age 80 are more efficient than the 2021 USPSTF strategy and warrant further consideration.

Keywords: screening, low-dose CT, ENGAGE

EP01.04 EARLY DETECTION AND SCREENING - IMPLEMENTATION QUALITY CONTROL

EP01.04-003 Effectiveness of Cloud-based Computer Aided Quality Control System in Korean National Lung Cancer Screening

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Introduction: Korean national lung cancer screening program (KNLCS) targeting high-risk smoking population using low-dose CT (LDCT) was implemented in 2019. A cloud-based quality control system (CQCS) using computer aided detection program (CAD) was used to assist radiologists in detection, measurement and categorization of lung nodules in LDCT. From 2021, Artificial Intelligence (AI)-based CAD has been launched as a developed version of CQCS. This study aimed to evaluate the effectiveness of CQCS on positive rate and inter-observer variability in KNLCS on national level.

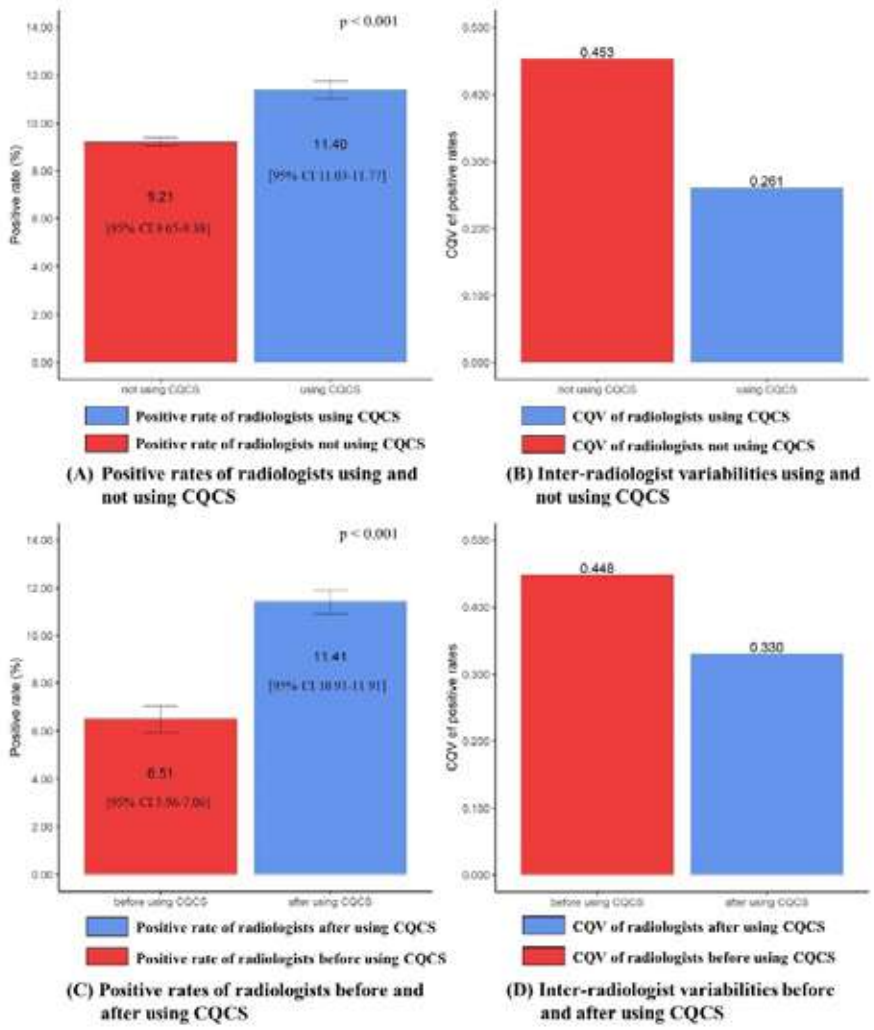
Methods: Among 302 screening units in KNLCS, 48 screening units are using CQCS. 61 radiologists using CQCS interpreted 28,677 (18.7%) LDCTs obtained from KNLCS from 2019 to 2021. The other 516 radiologists not using CQCS evaluated 124,515 (81.3%) LDCT screenings. This study compared the quality index measured between groups of radiologists using and not using CQCS and before and after using CQCS from 2019 to 2021. Also, we compared the quality index measured before and after the implementation of AI-based CQCS on registered units in 2021. The main quality index was evaluated by positive rates (the proportion of nodules classified as Lung-RADS category 3 and 4) and their variabilities across radiologists in screening units. Coefficient of quartile variation (CQV) of positive rates was used to calculate variabilities ($\theta_{CQV}=(\theta_3-\theta_1)/(\theta_1+\theta_3)$).

Results: In CQCS, positive rates were higher by 2.19% (11.40% vs. 9.21%; p<.001) (Figure 1(A)) and variability of the positive rates was lower by 0.192 (CQV, 0.261 vs. 0.453) (Figure 1(B)).

When positive rates were compared before and after using CQCS, the positive rates were increased by 4.90% (11.41% vs. 6.51%; p<.001) (Figure 1(C)) and the variability (CQV) was decreased from 0.448 to 0.330 (Figure 1(D)) after utilization of CQCS among 29 radiologists.

After adopting AI-based CAD program in CQCS, the positive rates were increased by 1.75% (11.71% vs. 9.96%; p=.044) and the variability (CQV) was increased from 0.233 to 0.272 for 35 radiologists.

Conclusions: The CQCS showed effectiveness in assisting in lung nodule detection and lowering variabilities of screening results across radiologists and screening units. Further studies on a quality control strategy in relation to newly implemented AI-based CAD are required.



Keywords: Lung Cancer, Screening, Artificial Intelligence

EP01.04 EARLY DETECTION AND SCREENING - IMPLEMENTATION QUALITY CONTROL

EP01.04-004 Overcoming the Barriers to Lung Cancer Screening using a Systemwide Approach

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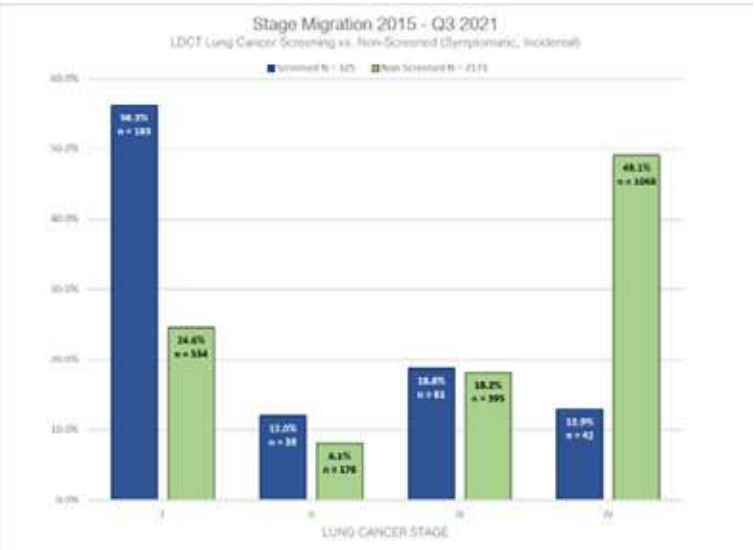
Introduction: The lung cancer screening program (LCSP) at St. Elizabeth Healthcare (SEHC), a 1,191 bed Northern Kentucky community hospital system, began in 2013. Over 22,000 low-dose CT lung cancer screens have been performed. From 2015 through 3Q 2021, 2,498 lung cancers were diagnosed systemwide. ASPIRED, a Screening Program with Impactful Results from Early Detection, reviews that experience. 325 (13.0%) were diagnosed by screening and 2,173 (87.0%) were non-screened. The non-screened cohort was queried to determine how many additional individuals could have been screened, as per 2015 CMS criteria, identifying barriers and failures to meet eligibility.

Methods: Our QlickSense database extracted the lung cancer patients from CPDMS (Cancer Patient Data and Management System) and identified and categorized them separately as screened or non-screened populations. Stage distribution was compared in screened and non-screened groups. Non-screened patients were all queried by CMS 2015 criteria. Those meeting age criteria with any smoking history were further queried for screening eligibility, accessing the EMR smoking history and audit trail, determining if enough information was available to substantiate screening eligibility.

Results: The screened and non-screened patients were accounted for in the stage migration chart (figure 1), documenting a clear shift to early stage among screened lung cancer patients. 722 (33.2%) of the non-screened patients were outside of the screening age criteria. Of the remaining 1,451 patients, 1,380 (95.1%) had *any* history of smoking cigarettes. Of the 2,173 non-screened lung cancer patients, we determined that 690 (31.8%) met screening criteria as documented in discreet EMR fields. A query of the smoking history audit trail further determined an additional 278 (12.8% of non-screened) patients would have met screening criteria had the smoking history been more complete, maintained, and documented accurately in the EMR discreet fields. 113 patients were undeterminable from the history available.

Conclusions: There are innumerable barriers to successful lung cancer screening. 49.3% of the SEHC eligible patients attributed to primary care providers were screened in 2021. This was seen consistently across all 41 sites within the SEHC System. Despite this level of success, this study highlights that there is still a sizeable pool of additional individuals (968) that could have been screened. We aspire to improve the capture of eligible individuals through improved education, communication, smoking history accuracy, and improved adherence utilizing the EMR system, other tools, and outreaches. This focus on the non-screened pool of patients that meet eligibility criteria will enhance the impact on our community.



Keywords: stage shift, lung cancer screening opportunity, St. Elizabeth Healthcare

EP01.04 EARLY DETECTION AND SCREENING - IMPLEMENTATION QUALITY CONTROL

EP01.04-005 Quantitative Characteristics in Global CT Lung Cancer Screening Populations Using the ELIC Distributed Database and Computation Environment

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Introduction: High resolution CT lung scans contain large amounts of potentially relevant information to evaluate the prospective risk of developing lung cancer. Significant relationships between presence of emphysema and lung cancer risk have been observed, particularly when analyzing high-quality, high-resolution CT scans. A systematic quantitative analysis of lung structure, considering both the shape and density of lungs and lobes of screening detected lung cancer patients and lung cancer free screening participants has the potential to provide insight into promising quantitative lung cancer risk biomarkers. In this report the Early Lung Imaging Confederation (ELIC) database and computation infrastructure was used to analyze cancer and non-cancer cases obtained from six globally distributed low dose CT lung cancer screening populations.

Methods: A total of 443 low dose CT (LDCT) lung cancer screening participants were analyzed in the ELIC cloud-based environment. The cases were obtained from Gdansk, Milan, Ishikawa, Perth, Porto Alegre, and Vancouver screening sites and each case consisted of two CT lung screening imaging time points and demographic data. One hundred cases were requested from each site such that 25% had a screen detected lung cancer, 50% had non-malignant lung nodules, and 25% did not contain lung nodules. A fully automated deep learning AI algorithm was used to obtain the lung and lobe boundaries including the lobe distribution of the lung cancer cases. Using these AI generated boundaries on data from the two sites that used between 1.0 and 1.25 mm slice thickness and used a non-highly edge enhancing reconstruction kernel, the volume, Hounsfield Unit (HU) mean, HU standard deviation, and HU median was calculated for each lung and lobe on the first time point for each case. In addition, the Low Attenuating Volume (LAV) at - 950 HU and the Perc15 quantitative metrics were analyzed.

Results: The distribution of screen detected lung cancers for all cancer cases was 35.2% RUL, 5.6% RML, 18.5% RLL, 24.1% LUL, and 16.7% LLL. Analysis of lung shape metrics indicated that HU standard deviation had the highest lung cancer classification capability. Lung and lobe HU standard deviations were found to be 7.0% and 5.2% lower than non-cancer cases for the Milan and Gdansk datasets, respectively. The lower attenuation may potentially be due to the destruction of lung tissue associated with emphysema.

Conclusions: This preliminary quantitative CT lung cancer screening study has shown the potential for AI-based quantitative lung lobe segmentation and HU standard deviation analysis to help distinguish between early lung cancers and benign cases. Further analyses using the ELIC distributed database and computing infrastructure will help determine the utility and resilience of these and other quantitative lung measures across globally distributed CT lung cancer screening populations.

Keywords: LDCT, lung cancer screening, emphysema

EP01.04-006 Clinical Scores, Biomarkers and It Tools in Lung Cancer Screening - Can an Integrated Approach Overcome Current Challenges?

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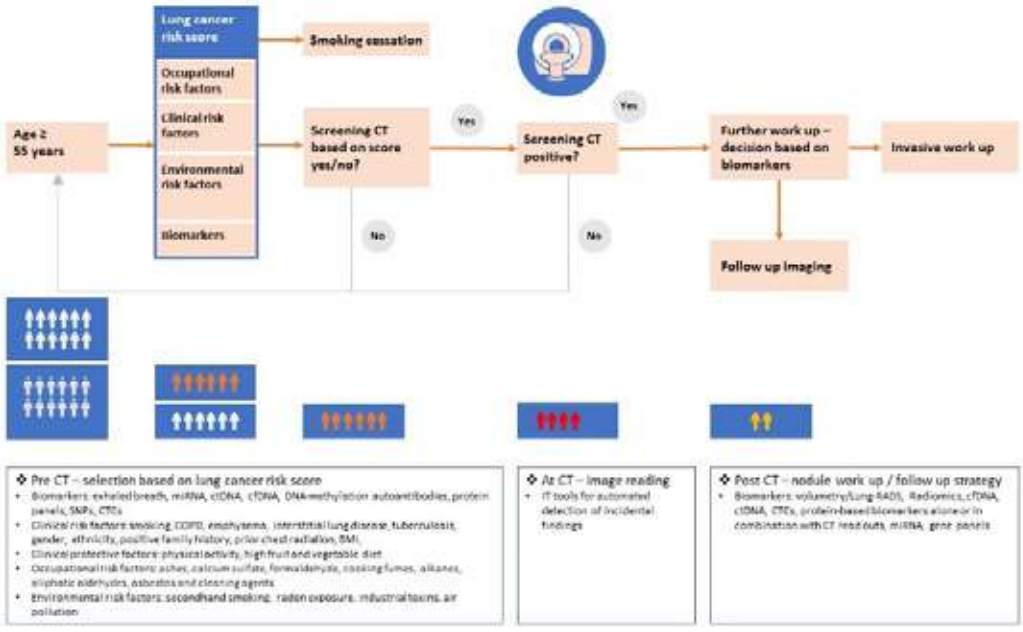
Introduction: Lung cancer (LC) is the leading cause of cancer related mortality. One reason is that still more than two thirds of patients are diagnosed with advanced disease. Cigarette smoking is the most important risk factor (RF). Recent LC screening studies demonstrated that annual low dose chest CT (LDCT) screening can reduce LC related mortality. Challenges still exist with LDCT based LC screening like optimal selection of individuals for LC screening programs, personalization of screening intervals, specification of individualized follow up intervals for nodule management or the detection of incidental findings

Methods: Narrative review

Results: Most screening programs like the national program in the US select participants based on age and smoking habits but these eligibility criteria seem to miss around half of LC cases. Consequently, more precise definition of an individual's baseline risk is required. Aside from smoking habits and age, respective risk models could include factors like gender or ethnicity, comorbidities like COPD, occupational factors, environmental factors or specific biomarkers (Figure). Current national screening programs do recommend annual screening. However, recent evidence suggest that based on a baseline risk, screening intervals could be individualized. Such baseline risk could be defined by a combination of the result of initial LDCT plus clinical, occupational and environmental RFs plus biomarkers (Figure). In case of indeterminate lung nodules combinations of nodule volume and biomarkers could aid the decision to conduct a biopsy or further follow up and guide the selection of follow up intervals. Overall, risk stratification/screening personalization based on clinical (including occupational and environmental RFs) scores or combinations of clinical and biomarker scores might help to increase the efficacy of a LC screening program, reduce the number of required serial CT scans and with that lessen radiation exposure and ultimately reduce the costs of a screening program. LC screening programs in addition to LC detection harbor the chance to discover formerly undiagnosed nonmalignant diseases such as COPD, aortic aneurysms, or coronary artery disease (CAD). Reading of LDCT can be enhanced by IT tools to detect such incidental findings, e.g. CAD with high sensitivity and specificity

Conclusions: We discuss an integrated screening approach consisting of clinical RFs and biomarkers to improve risk stratification pre-CT and post-CT as well as IT tools to increase the yield of imaging information. In this educational poster we summarize the existing evidence to stimulate further research and model development to enhance future and existing LC screening programs.



Keywords: Lung Cancer Screening, Personalization, Risk scores

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-001 Radiomics to Increase the Effectiveness of Lung Cancer Screening Programs. Radiolung Preliminary Results

A. Rosell[1], S. Baeza[1], S. Garcia-Reina[1], J.I. Mate[1], I. Guasch[1], I. Nogueira[1], G. Torres[2], C. Sanchez-Ramos[2], D. Gil[2]
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Introduction: Main lung cancer screening clinical trials demonstrated a 20-25% mortality reduction but rendered 19.7-27.3% false-positive nodules in the chest CT. Radiomics can provide discriminatory capacity beyond what is perceived by the naked eye.

Methods: GoalEstablish a radiomic signature of pulmonary nodules (PN) to distinguish malignancy from benignity. PatientsProspective observational study with PNs studied and resected according to usual clinical practice.Method

CT images are sent to the Computer Vision Center, and the nodules segmented. Gray Level Co-occurrence Matrix radiomic based texture features that significatively correlate with malignancy are extracted. These variables are used to train a neural network with an architecture optimized according to the diagnosis of the nodule.

The model has been trained with 8 benign PNs and 43 malignant PNs from our hospital, and subsequently validated with 6 benign and 21 malignant PNs from our hospital and from a public database.

Results: Results51 PNs of 22.68mm (range 3-45mm), 32 men, mean age 69 years, 41 smokers or ex-smokers were analyzed. The pathological results were: 32 (62.7%) ADK, 7 (13.7%) SCC, 3 (5.8%) NSCLC, 1 (1.9%) carcinoid; 2 (3.9%) nonspecific necrosis, 6 (11.7%) benign tumors. The diagnostic accuracy of our hybrid system is 96.30%, 100% sensitivity, specificity of 83.3%.

Conclusions: ConclusionsIn our sample, the application of a hybrid radiomic system achieves high diagnostic accuracy(96.3%) to detect malignant nodules on chest CT. External validation in a lung cancer screening program is needed.

Funded by: ACMCiB, BRN, Fundació Ramon Pla, Lung Ambition Alliance

Keywords: RADIOMICS, PULMONARY NODULE, SCREENING

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-002 Role of the Lung Cancer Screening MDT in the Manchester Lung Health Check Programme

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Introduction: Low-dose CT (LDCT) screening for lung cancer has been shown to reduce lung cancer mortality and its implementation is currently being examined and considered across multiple countries. In the United Kingdom (UK), the Targeted Lung Health Checks (TLHC) program has initiated small-scale screening programs across several regions of the country. A significant challenge to implementation is the increased demand for quality-assured radiology reporting, as stipulated by the TLHC service protocols, in order to maximize screening efficacy and reduce potential harm to participants from false-positive and false-negative results. In this analysis, we describe outcomes from the first six months of case discussions at the Manchester Lung Health Checks screening Multidisciplinary Team meeting(MDT).

Methods: The expanded Manchester Lung Health Check screening program was initiated in 2019, having been successfully piloted between 2016-2019. Ever-smokers, aged 55-80, are invited to a free community-based LHC. Those at higher risk of lung cancer ($PLCO_{m2012NoRACE}$≥1.5%) are invited to annual LDCT screening. Scans are initially analyzed through a computer-aided detection software before being formally reported by an external thoracic radiology reporting company. LDCT results are categorized as either 'Negative', 'Indeterminate' (requiring close surveillance or clinical review), or 'Positive' (requiring assessment for malignancy) as per TLHC reporting protocols. In Manchester, all Indeterminate and Positive screening results are triaged and then discussed in a weekly lung cancer screening MDT, attended by the program's responsible clinicians, responsible radiologists, and specialist nurses, before confirming final screening outcomes for individual participants. When applicable, previous radiology imaging is reviewed as a comparator. This analysis describes initial screening LDCT and subsequent MDT outcomes for all cases discussed at the Manchester screening MDT between August 2021, when the MDT was first established, and February 2022.

Results: A total of 358 cases were reviewed at the screening MDT in the analyzed time period, including 58 positive and 300 indeterminate results. Of the 58 positive results discussed, 53.4% (n=31) were downgraded from requiring immediate investigation for malignancy (positive) to requiring surveillance imaging only (indeterminate). Seven of the 31 downgraded cases have already had their surveillance imaging performed from which no cancers have been diagnosed to date. Of the 300 indeterminate results, 25.3% (n=76) were downgraded from requiring a 3-month surveillance scan (indeterminate) to an interval 2-year LDCT scan (negative). However, 3% (n=9) cases were upgraded from requiring a short-term surveillance scan (indeterminate) to a positive outcome and investigated immediately for malignancy, four of which have been subsequently diagnosed with lung cancer. Overall, initial screening LDCT outcomes were altered in a third (32.4%; n=116) of cases discussed at the screening MDT.

Conclusions: A lung cancer screening MDT, where all indeterminate and positive screening outcomes are reviewed, plays an important role in providing prospective quality assurance of initial radiology reporting to maximize screening efficacy, reduce unnecessary harm and optimise the use of limited resources. A limitation of our analysis is that long-term clinical outcomes are not yet available for participants discussed at the MDT.

Keywords: Lung Cancer Screening, Screening MDT, Targeted Lung Health Check

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-003 Changes of Repeated Lung Cancer Screening Results and Affected Factors; Analysis of Korean National Lung Cancer Screening Program

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Introduction: Korean national lung cancer screening program (KNLCS) from 2019 provides screening test to high-risk smokers (30 pack-year or more) between the ages of 54-74 with low-dose computed tomography (LDCT) every two years. According to the results of lung cancer screening modeling studies, repeated screening is more beneficial than a single screening. This study aimed to investigate changes of repeated screening compared to initial screening, and to analyze affected factors to the changes.

Methods: This study analyzed lung cancer screening results in national cancer center data base which includes about 50% of KNLCS. In 2019, 50,666 examinees participated to lung cancer screening, and in 2021, 57,578 participated. A total of 12,802 subjects were screened in both 2019 and 2021. Based on Lung RADS, categories 1 to 2 represent negative screening results, and categories 3 to 4 define as positive results. In this study, frequency analysis and multiple logistic analysis was performed for determination of factors associated with changes in LDCT results to positive among the examinees whose results were negative in initial screening. In logistic model, predictors included age, sex, past medical history (cancer, pulmonary disease), family history of cancer, number of pulmonary nodules and other findings on first CT scan.

Results: Of the total 12,802 subjects, 11,723 (91.6%) showed a negative result in 2019. Among those 11,723 participants, 709 (6.0%) changed from negative to positive results in 2021, and 11,014 (94.0%) did not change. Of the 1,079 people who had a positive result in 2019, 880 (81.6%) changed to a negative result in 2021, and 199 (18.4%) had no change. In multiple logistic analysis, the elderly group showed a significant association with the change of CT result from negative to positive (65-69 [adjusted OR [aOR] 1.43; 95% CI 1.41-1.80] and 70-74 [aOR 1.51; 95% CI 1.14-2.00]). The number of lung nodules on the first scan (1-2 nodules [aOR 1.72; 95% CI 1.46-2.03] and 3 or more [aOR 2.21; 95% CI 1.72-2.86]) and the presence of interstitial lung disease (aOR 1.60; 95% CI 1.10-2.33) showed the change of CT result from negative to positive showed a significant association.

Conclusions: For high-risk smokers, negative results in lung cancer screening can be changed to positive in follow up study. Therefore, repeated screening should be strongly recommended for the target population, especially those with relevant factors. Also compared reading between initial and repeated screening can decrease false positive results.

Changes of repeated lung cancer screening results with low-dose computed tomography, 2019-2021 (N=12)

Results of 1st CT scan (2019)	Total (N, (%))	Results of 2nd CT scan (2021)	
		Negative*	Positive**
Negative	11,723 (91.6%)	11,014 (94.0%)	709 (6.0%)
Positive	1,079 (8.4%)	880 (81.6%)	199 (18.4%)

Keywords: lung cancer, repeated screening, affected factors

EP01.05-004 Trial in Progress: An Observational Study for Management of Lung Nodules across Latin America (DOuBLED Study)

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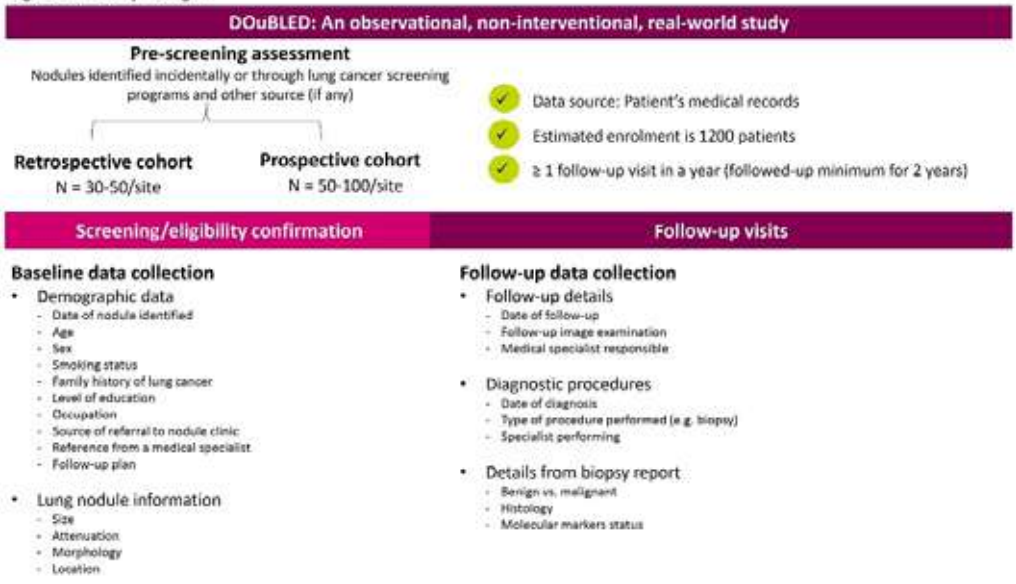
Introduction: Early diagnosis of lung cancer (LC) in the asymptomatic stage through screening programs and/or incidental pulmonary nodule identification and follow-up aids in identifying potentially curable tumours, thus improving survival. However, several gaps exist in early detection of LC, especially in low- and middle-income countries, mainly driven by socioeconomic and infrastructural factors (limited number of specialised human resources and technical capacity). Even if a lung nodule is identified, the pathway towards a definitive diagnosis is often unorganised and redundant, resulting in loss to follow up and a missed opportunity to early diagnosis. Additionally, high rates of granulomatous disease may affect the follow-up and diagnosis of suspicious nodules. This study aims to characterise the lung nodule journey at different hospitals across Latin America (LATAM), with an objective of creating nodule clinics that can replicate the knowledge acquired and serve as reference institutions and also working models that can be implemented in other regions.

Methods: This non-interventional, observational study (NCT05091437) is currently capturing retrospective and prospective data of lung nodule journey from 21 institutions across 9 LATAM countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Panama and Perú). Adult patients (aged ≥ 35 years) with a solid or subsolid (part solid, pure ground glass) lung nodule identified in imaging exams as part of routine clinical practice prior to 30 days of informed consent given (prospective cohort), or between March 2020 and the site initiation visit date (retrospective cohort) will be included. The primary objective is to describe the lung nodule journey from the time of nodule identification through its final diagnosis, staging and treatment decision. Secondary objectives are to determine the medical specialties involved in the lung nodule journey, the medical specialist who first identified the lung nodule and any referral patterns, healthcare resource utilization across the nodule journey (number of hospital visits and medical tests and access to HCPs), time from nodule identification until a final diagnosis and treatment decision and specialties involved in the decision-making. Exploratory objectives include identification of differences among patient journey across institutions and countries. Baseline and follow-up data will be collected (Figure 1). Data will be analysed using descriptive statistics. Continuous data will be reported as mean and standard deviation, while categorical data as count and percentage. Enrolment began in December 2021 across 4 sites and last patient visit planned in December 2024. An interim analysis is planned with the first 450 patients (retrospective cohort).

Figure 1. Study Design



Keywords: Pulmonary Nodules, Lung cancer, Early diagnosis

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-005 The Accuracy of Baseline Low-dose CT Lung Cancer Screening: A Systematic Review and Meta-analysis

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Introduction: Screening using low-dose computed tomography (LDCT) is a more effective approach and has the potential to detect the lung cancer more accurately. We aimed to conduct a meta-analysis to estimate the accuracy from population-based screening studies primarily assessing baseline LDCT screening for lung cancer.

Methods: MEDLINE, EMBASE, and Web of Science were searched for articles published until April 30, 2021. According to the inclusion and exclusion criteria, the data of true positive, false positive, false negative and true negative in screening test were extracted. Quality Assessment of Diagnostic Accuracy Studies-2 was used to evaluate the quality of literature. A bivariate random effects model was used to estimate pooled sensitivity and specificity. The area under the curve (AUC) was calculated by using HSROC analysis. Heterogeneity between studies was measured by the Higgins I^2 statistic, and publication bias was evaluated by a Deeks' funnel plot and linear regression test.

Results: A total of 47 studies with 145437 individuals were identified for the final qualitative synthesis, most of them were from Europe and America (38 studies), 8 from Asia, and 1 from Oceania. The recruitment period was 1992-2018, and most of the subjects were 40-75 years old. The analysis showed that the AUC of lung cancer screening by LDCT was 0.97 (95% CI=0.95-0.98), and the overall sensitivity and specificity were 0.97 (95% CI=0.94-0.98) and 0.86 (95% CI=0.81-0.89). Funnel plot and test results showed there was no significant publication bias among the included studies.

Conclusions: Baseline LDCT has high sensitivity and specificity as a screening technique for lung cancer. However, long-term follow-up of the whole study population (including those with a negative baseline screen) should be performed to enhance the accuracy of those measurements.

Keywords: Lung cancer, LDCT, Screening

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-006 Influenza Season Influence on Incidence and Outcome of Nodules in the NELSON Trial

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Introduction: We investigated whether incidence and outcome of new lung nodules was influenced by the influenza season in a LDCT lung cancer screening trial population.

Methods: Participants from the NELSON trial with ≥1 new nodule detected in screening rounds two and three were included. The influenza season (winter) was classified as 1st October to 31st March, and was compared to the hay-fever season (summer) 1st April to 30th September. Nodule outcome was reported as resolving, persisting, requiring immediate referral or requiring no additional screen. Additionally, all new nodules which were linked to lung cancers were reported as matched cancers in the dataset. Seasonal variance was tested using Chi-square Goodness-of-fit test, after correction for unequal distribution of incidence screening scans and new nodules detected across the seasons.

Results: In the 7,156 LDCT scans performed during screening rounds two and three (4029[56%] in winter versus 3127[44%] in summer), a total of 981 new nodules were reported for 613 participants. Of these new nodules, 597 (61%) were detected during winter which, after correction for seasonal distribution of incidence screening scans, was significantly more than the 384 (39%) detected during summer (*p=0.002*). Similarly, there were significantly more participants with ≥1 new nodule in winter compared to summer (373 [61%] versus 240 [39%] respectively, *p<0.001*). When looking at outcomes of the largest new nodule per participant, after correction for seasonal distribution of new nodules (373 in winter versus 240 in summer), no significant difference was found in the number of resolving nodules (191/373 in winter versus 140/240 in summer, *p=0.219*), persisting nodules (126/373 in winter versus 77/240 in summer, *p=0.562*), immediate referrals (49/373 in winter versus 21/240 in summer, *p=0.123*), or matched cancers (29/373 in winter versus 15/240 in summer, *p=0.504*). Furthermore, no variation was seen in new nodule type, size, or location per season.

Conclusions: Incidence of lung nodules on LDCT thorax scans in a lung cancer screening population is higher during the influenza season. However, resolution of new nodules and number of matched cancers appears comparable in both winter and summer. Hence, this study does not clarify whether seasonal respiratory illnesses are directly related to this increased incidence. Further investigation into seasonal incidence and outcome of baseline nodules in this population could help elucidate the cause of the higher incidence of nodules during the influenza months.

Keywords: LDCT, Lung cancer screening, New nodules

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-007 Radiomics Based Machine Learning Model for Sub-cm Lung Nodule Malignancy Diagnosis in the PanCan Screening Study

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Introduction: Lung cancers detected by Low Dose Computed Tomography (LDCT) screening programs have been shown to improve patient mortality rates. As lung cancer is the number one cancer killer in Canada, there is a need for developing tools to assist physicians in identifying potential cancerous lung nodules during screening studies. These tools are especially desirable for notoriously difficult-to-classify small, sub-cm nodules (<8mm solid component) as these cases tend to have very little pixel-based information. Compounded by the large number of small objects often detected during screening programs, the implementation of CADx tools for cost-effective screening prediction is in high demand. We posit that one can train a machine learning model to classify sub-cm nodules as malignant or benign with radiomic features to greatly speed up nodule assessment speeds and allow for the implementation early cancer treatment for protocols during baseline LDCT screening scans.

Methods: Data for this study is drawn from a subset of the Pan Canadian Screening Study (PanCan) LDCT lung volume dataset. We identified a sub-cohort of cancer patients from this dataset that matched the LungRADS 4A category or lower (<8mm solid nodule component). We then size, smoking status, and sex matched benign nodules to malignant nodules at a rate of 4:1. An Otsu-based thresholding CT Volume segmentation program and 2D radiomic feature extraction pipeline generated a CT-based feature set. Each feature was calculated from 3 discrete nodule segmentation masks (core, core plus edge transitionary perimeter pixels, and a ring of parenchymal tissue surrounding the nodule). We implemented a feature selection algorithm to identify up to 10 discriminating radiomic features. In this study, we trained a GroupK-fold cross validation Linear Discriminate Analysis (LDA) model on this reduced feature set to classify sub-cm nodules as malignant or benign.

Results: From 2537 patients in the PanCan set, a sub-cohort of 373 patients (55% male; 63±5 yrs; pack years: 56±23) with 515 sub-cm nodules (107 clinically confirmed cancer; 408 benign, 5 year follow up) detected at baseline. From the nodule bounding boxes, axial images were extracted to generate CT images (N=5765) and 3 discrete ROIs (nodule core, core+edge, ring) were generated for each available axial slice of the nodule. Radiomic features (shape, texture, intensity) were calculated from these ROIs. Sequential forward feature selection identified the 10 most highly discriminating features; a majority of features coming from the ring ROIs. ROC analysis was performed on the 5 fold cross validated LDA model resulted in an accuracy of 75.3% [SN: 0.693, SP: 0.786] (AUC: 0.80) for our patient dataset. Given our class label imbalance, we performed precision-recall analysis to identify sources of class bias (PR AUC vs No-skill AUC: 0.57 vs 0.22).

Conclusions: This radiomics-based CADx model showed an ability to predict cancerous vs benign nodules up to 48 months before clinical confirmation of malignancy. A predominant number of ring features were identified as discriminating features. This demonstrates that morphological phenomenon in the parenchyma around the nodule can be attributed to cancerous nodule development.

Keywords: LDCT Screening, radiomics, machine learning

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-008 Pre-Trial Validation of a Risk Prediction Model for Pulmonary Nodules Trained on a Nested Case-Control Study with No External Cohort

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Introduction: Prior to testing in a clinical trial, a biomarker for diagnostic risk prediction requires validation through a nested case-control study design to avoid verification and other biases and split or independent samples to avoid overfitting bias. When the focus within this paradigm is on building a risk prediction model, standard metrics include discrimination, measured by the area under the ROC curve (AUC) and calibration measured by the accuracy of absolute risk estimates using calibration curves, intercept, and slope. Because of case-control sampling, the model's intercept may not accurately reflect the prevalence of the outcome in the biomarker's intended target population. The model's discrimination, however, will generally be unaffected. Assessment of calibration is further complicated when no external representative population is available. Following previous work by Prentice and Pyke (1997) and Huang and Pepe (2008), recommendations from Steyerberg et al. (2001) and Steyerberg (2018), and guidelines from Moons et al. (2019), we describe an approach for validation of a radiomic risk prediction model for indeterminate pulmonary nodules at risk of lung cancer developed in a nested case-control setting with no available external validation cohort.

Methods: A combination of bootstrap sampling nested within repeated k-fold cross-validation is used to: 1) recalibrate the model to reflect prevalence in the clinical population of interest, and 2) provide an approximation to the sampling variance for the calibration slope, assuming a properly recalibrated intercept. We illustrate the approach using data from a model for Indeterminate Pulmonary Nodule (IPN) classification based upon radiomic features developed and internally validated on a nested case-control set of 737 patients with incidental and screening discovered lung nodules, of which 461 (63%) were malignant, but whose intended population cancer prevalence is 33%.

Results: A logistic regression model including 10 quantitative radiomic features was used to build a prediction model. Model recalibration to a prevalence of 0.33 was applied using a Bayes (recalibration) factor {(0.33/0.67)/(0.63/0.37)} and 3-fold cross-validation (2/3 for training and 1/3 for testing) repeated 3 times was applied in combination with 200 bootstrap samples of size 100, each with approximately 0.33 prevalence of cancer. The estimated mean and 95% nonparametric bootstrap confidence interval for the recalibrated intercept were -0.038 (-0.098, 0.032) and for the calibration slope were 0.985 (0.924, 1.048). AUC was estimated to be 0.758 (0.749, 0.766). In contrast to the calibration without the Bayes factor adjustment, the calibration intercept was -1.244 (-1.297, -1.198).

Conclusions: The results indicate the radiomics model was recalibrated to a prevalence of 0.33 with a calibration slope close to 1.0, suggesting a model that can predict well outside of the sample in a population with similar case-mix and prevalence. In summary, using state of the art statistical resampling tools, calibration of a risk prediction model can be effectively assessed using a nested case-control study even when no external validation cohort is available. This serves to expedite liquid and radiomic biomarker implementation pipelines for early detection, given limited validation cohorts

Keywords: calibration, recalibration, resampling methods

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-009 Simulation-Based Sample Size Estimation for an Early Detection of Lung Cancer Clinical Utility Trial in Indeterminate Pulmonary Nodules

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Introduction: Indeterminate pulmonary nodules (IPN) are a common clinical challenge worldwide. Current management can result in delayed diagnosis and unnecessary invasive procedures, two important indicators of clinical utility (CU). Improved risk stratification using a combination of biomarkers and CT imaging was recently published, mandating a randomized clinical trial to assess its CU. Essential trial design considerations include prevalence of cancer and variation in diagnostic practices across sites. Here, we describe an approach to estimate the sample size for a randomized Phase IIb trial measuring CU of a validated combined risk prediction score (CBM; blood biomarker + radiomics + Mayo risk score). We rely on simulation due to limitations of existing standard sample size software.

Methods: Data on time to diagnosis (TTD) and invasive procedures (INV) for intermediate risk IPN (10% ≤ risk ≤ 70%) from two US clinical sites (Vanderbilt University Medical Center, University of Colorado Anschutz Medical Campus) were used to design a site-stratified two-arm trial. Improvements in CU under CBM (shorter TTD in cancers, fewer INV among benign) were assumed to result from correct reclassification compared to Mayo model risk estimates alone. Incorrect reclassification was assumed to lead to longer TTD in cancers, and to additional invasive procedures for benign disease. In each of 1000 simulations, for totals of intermediate risk IPN patients varying from 500 to 1000 randomized to SOC vs. CBM (1:1 allocation), stratified by site (1:1 allocation), we randomly generated numbers of patients with lung cancer or benign disease assuming a 33% prevalence of lung cancer. TTD for lung cancer patients were randomly generated from a piecewise exponential distribution truncated at 2 years of follow-up (Site 1: median (days) under Mayo = 47, CBM = 21; Site 2: median under Mayo = 101, CBM = 43). TTD was compared using a site-stratified Peto-Peto modified Gehan-Wilcoxon test to detect early differences. Proportions with INV (any vs. none) in patients with benign disease were compared using a site-stratified Mantel-Haenszel chi-square test, with data generated from a binomial distribution (proportion with INV, Site 1: Mayo = 0.85, CBM = 0.61; Site 2: Mayo = 0.42, CBM = 0.39). Numbers of test rejections, at a significance level $\alpha = 0.10$, were monitored separately for each test. We identified the total sample size that achieved power (# rejections/1000 trials) of at least 0.80 for each utility outcome. We implemented the algorithm using R software.

Results: We determined that a total of at least 560 patients is needed to achieve a minimum of 80% power for testing each of the utility outcomes based on the observed site-specific practice patterns.

Conclusions: When testing multiple outcomes in separate patient groups within a randomized trial for clinical utility, simulation studies facilitate customized sample size estimation. Input parameters can be obtained using site-specific preliminary observational data from the population(s) of interest.

Keywords: Multicenter Clinical Trial, Clinical Utility Trial, Sample Size Estimate

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-011 Radiologic Features of Nodules Attached to the Mediastinal or Diaphragmatic Pleura

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Introduction: Pulmonary nodules less than 10 mm, which attached to the fissural or costal pleura with specific features (triangular, oval, lentiform shapes and smooth margins) on baseline or annual repeat rounds of screening, can be followed in one year rather than having more immediate workup. The purpose of this study is to identify specific features showed above that distinguish benign from malignant mediastinal pleura attached noncalcified nodules (**MP**-NCNs) and diaphragmatic pleura attached noncalcified nodules (**DP**-NCNs).

Methods: Two separate dedicated databases were used in this study, one is a prospective lung cancer treatment cohort at Mount Sinai Health System enrolled in the Initiative for Early Lung Cancer Research on Treatment (IELCART) between 2016 and 2021 and the other one is a prospective lung cancer screening cohort enrolled in the International Early Lung Cancer Action Program(I-ELCAP) which including 76 participating institutions between 1992 and 2019. We reviewed all malignant nodules in both databases, which included 416 patients with 416 malignant nodules (ILCART) and 1045 patients with 1121 malignant nodules (I-ELCAP). We classified nodules attached to the mediastinal pleura (0 mm distance from nodule to pleura) as MP-NCNs and attached to the diaphragmatic pleura (0 mm distance) as DP-NCNs. Documented on each MP-NCN and DP-NCN were size (average diameter of length and width), location, shape (triangular, lentiform/oval/semi-circular, polygonal, round, or irregular), margin (smooth or non-smooth), type of attachment to the mediastinal or diaphragmatic pleura (broad or narrow), emphysema and fibrosis within 10 mm radius of each nodule.

Results: In **IELCART** database, among 416 malignant nodules, we identified 73 solid **MP**-NCN (4 were attached to both mediastinum and hilum) and 9 solid **DP**-NCN, all 3.0-30.0mm in average diameter. Among the 73 MP-NCNs, 13 (17.8%) were less than 10.0 mm, 36 (49.3%) were between 10.0 mm to 20.0mm, 24 (32.9%) were between 20.0 mm to 30.0 mm. Of the 9 DP-NCNs, 1 (11.1%) was less than 10.0 mm, 2 (22.2%) were between 10.0 mm to 20.0mm, and 6 (66.7%) were between 20.0 mm to 30.0 mm. None of the solid malignant MP-NCNs nor solid malignant DP-NCNs, 30.0 mm or less, in IELCART had an oval, lentiform, semi-circular or triangular shape and smooth margin.In **I-ELCAP** database, among 1121 malignant nodules, we identified 85 solid malignant **MP**-NCN (12 attached to both mediastinum and hilum) and 5 with solid malignant **DP**-NCN, all 3.0-30.0mm in average diameter. Among the 85 MP-NCNs, 27 (31.8%) were less than 10.0 mm, 33 (38.8%) were between 10.0 mm to 20.0mm, 25 (29.4%) were between 20.0 mm to 30.0 mm. Of the 5 solid malignant DP-NCNs, 3 (60%) was less than 10.0 mm, 2 (40%) were between 10.0 mm to 20.0mm. None of the solid malignant MP-NCNs nor solid malignant DP-NCNs, 30.0 mm or less, in I-ELCAP had an oval, lentiform, semi-circular or triangular shape and smooth margin.

Conclusions: None of the solid malignant MP-NCNs nor solid malignant DP-NCNs 30.0 mm or less in average diameter had a triangular or lentiform/oval/semi-circular shape with smooth margin, regardless of tumor size and type of pleural attachment.

Keywords: mediastinal pleura attached noncalcified nodules, diaphragmatic pleura attached noncalcified nodules, Lung cancer screening

EP01.05 EARLY DETECTION AND SCREENING - PULMONARY NODULE

EP01.05-010 Using a Pattern Submodel Approach to Predict Lung Cancer in High-Risk Lung Nodule Clinics

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Introduction: Appropriate risk-stratification of indeterminate pulmonary nodules (IPN) is necessary to direct diagnostic evaluation. Validated models for high-risk IPN are poorly calibrated and do not allow for missing data in clinical use. We sought to expand the Thoracic Research Evaluation and Treatment (TREAT) model into a more generalized, robust model for lung cancer prediction, the TREAT 2.0. A prior version of this abstract, "The TREAT Model 2.0: Predicting Lung Cancer in Patients Seeking Care in High-Risk Clinics," has been presented. Several significant changes to the model development have been made.

Methods: Patients with IPN's from six sites (n=1401) were used to recalibrate the TREAT model. Six retrospectively collected datasets were divided into 3 clinical subgroups which represent the location of clinical presentation: patients who presented to pulmonary nodule clinic (n=374), outpatient thoracic surgery clinic (n=553) and for surgical resection (n=474). This location of clinical presentation variable was included as a predictor to account for varying prevalence of cancer, along with other clinical factors such as age, smoking pack years, and size of the nodule. A novel approach to missing data in prediction modeling, the pattern submodel (PS), was used to develop the TREAT 2.0 model. The PS approach essentially divides the data into "missing patterns" and fits the model in each subset. This approach is conceptually simple, has minimal computation time compared to multiple imputation, and leverages the information contained in the presence of missingness to strengthen the predictive ability of the model. A wide range of flexible prediction models was developed and considered. The final TREAT 2.0 model allowed for non-linear and high-order interaction terms and utilized a relaxed lasso logistic regression model, minimizing the chance of model overfitting. The discriminative ability and calibration of the TREAT 2.0 model were estimated using repeated cross-validation in each missing pattern and compared to the original TREAT, Mayo Clinic and Herder models.

Results: Lung cancer prevalence varied by clinical subgroup: pulmonary nodule clinic 42%; thoracic surgery clinic 73%; and surgical resection cohort 90%. Two-thirds of patients had missing data; nodule growth and FDG-PET avidity were most frequently missing. The mean area under the received operating curve (AUC) across missing patterns for TREAT 2.0 was 0.85, compared to the original TREAT (AUC = 0.81), Herder (AUC = 0.73), and Mayo Clinic (AUC = 0.72) models. The calibration curves for each model indicate that TREAT 2.0 has improved calibration.

Conclusions: The TREAT 2.0 model has an improved ability to distinguish between benign and cancerous nodules and shows potential for improved calibration for predicting the risk of lung cancer in high-risk IPN compared to the Mayo or Herder models. While we performed rigorous internal validation of the models, external validation of both the discriminative ability and calibration of thee model are still needed. The TREAT 2.0 model performs well in the presence of missing data and leverages information contained in the missingness. Nodule calculators such as TREAT 2.0 that account for varied lung cancer prevalence may improve generalizability and increase use in clinical practice.

Keywords: Lung Cancer Risk, Risk Prediction Model, Missing Data

EP01.06 EARLY DETECTION AND SCREENING - RISK STRATIFICATION

EP01.06-001 Lung Cancer after First Primary Breast Cancer: Risk Factors and Results of Treatment

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Introduction: Patients with breast cancer have a relatively favorable long-term prognosis compared with other malignancies. The increase in survival puts these patients at risk of developing other primary tumors, including lung cancer. We hereby present our experience in this setting, reporting characteristics and results of patients who underwent surgery for second primary lung cancer after first primary breast cancer.

Methods: Between 2011 and March 2021, 91 consecutive patients with a first primary breast cancer underwent surgery for non-small cell lung cancer (NSCLC). Resection was lobectomy in 59 cases, sublobar in 31 and pneumonectomy in 1. Patients were divided into 2 groups according to the latency of occurrence of lung cancer: more than 5 years (late, group A) or within 5 years (early, group B) after breast cancer. Data regarding breast carcinoma including histology, hormonal status, treatment received, and data on lung carcinoma including fertility at onset, histology, stage, treatment received, and cancer-specific and disease-free survival were retrospectively analyzed.

Results: Females were 97.8% (n=89). All the resections were complete (R0). No postoperative mortality occurred. Lung cancer histology was adenocarcinoma in 75 cases (82.4%). Lung cancer pathologic stage was I in 67 cases, IIA in 1 case, IIB in 15 cases and IIIA in 8. At risk analysis, Progesterone Receptors-Positive (PR+) breast cancer and Estrogen Receptors-Positive (ER+) breast cancer were associated with a delayed occurrence of NSCLC (PR+: group A=76.7% vs group B=23.3%, OR 3.18, p=0.015; ER+: group A=78.3% vs group B=21.7%, OR 3,2, p=0.027), as well as fertility (group A=63.6% vs group B=36.4%, OR 3.15, p=0.049). Previous radiation therapy (RT) for breast cancer was associated with an early onset (group A=32% vs group B=68%, OR 0.205, p=0.001). Mean follow-up was 38.1 months (range 6-122). No death due to breast cancer was observed during follow-up. Five-year cancer-specific survival (CSS) was 94.5%, while 5-year disease-free survival (DFS) was 84.6%. Five-year CSS and DFS were significantly affected by the lung cancer stage (CSS: stage <IIB=98.5% vs stage ≥IIB=82.6%, p=0.001; DFS: stage <IIB=92.6% vs stage ≥IIB=60.9%, p<0.001).

Conclusions: Survival of patients undergoing surgery for NSCLC after breast cancer is mainly affected by the stage of lung cancer. The hormonal behavior as well as a previous RT can influence the time of occurrence of NSCLC. A lung cancer screening program after breast cancer might increase survival.

Keywords: lung cancer, surgery, breast cancer

EP01.06 EARLY DETECTION AND SCREENING - RISK STRATIFICATION

EP01.06-002 Impact of Immediate AI Enabled Patient Triage to Chest CT on the Lung Cancer Pathway: LungIMPACT

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Introduction: In England, 30% of patients die within 90 days of diagnosis and late diagnosis is strongly implicated in comparatively poor survival shown by the International Cancer Benchmarking Partnership. UK guidance recommends the chest radiograph (CXR) for initial investigation of certain red-flag symptoms but CXRs are done for many indications and may pick up lung cancer as an incidental finding. Thus, the National Optimal Lung Cancer Pathway (NOLCP) was developed to address, amongst other issues, a rapid process from progress from abnormal CXR to CT and clinic. Resource is often allocated to fast track reports for patients referred via an urgent cancer pathway, because the NOLCP mandates a progression from suspicious CXR to CT within 72 hours, but preferably on the same day. This reduces delays experienced by patients including those referred via other routes. Longer pathways can worsen outcomes in both early and late-stage disease and increase anxiety. In the National Cancer Experience Survey, a quarter of patients report deterioration in their condition during diagnostic workup. Figure 1 illustrates the NOLCP.

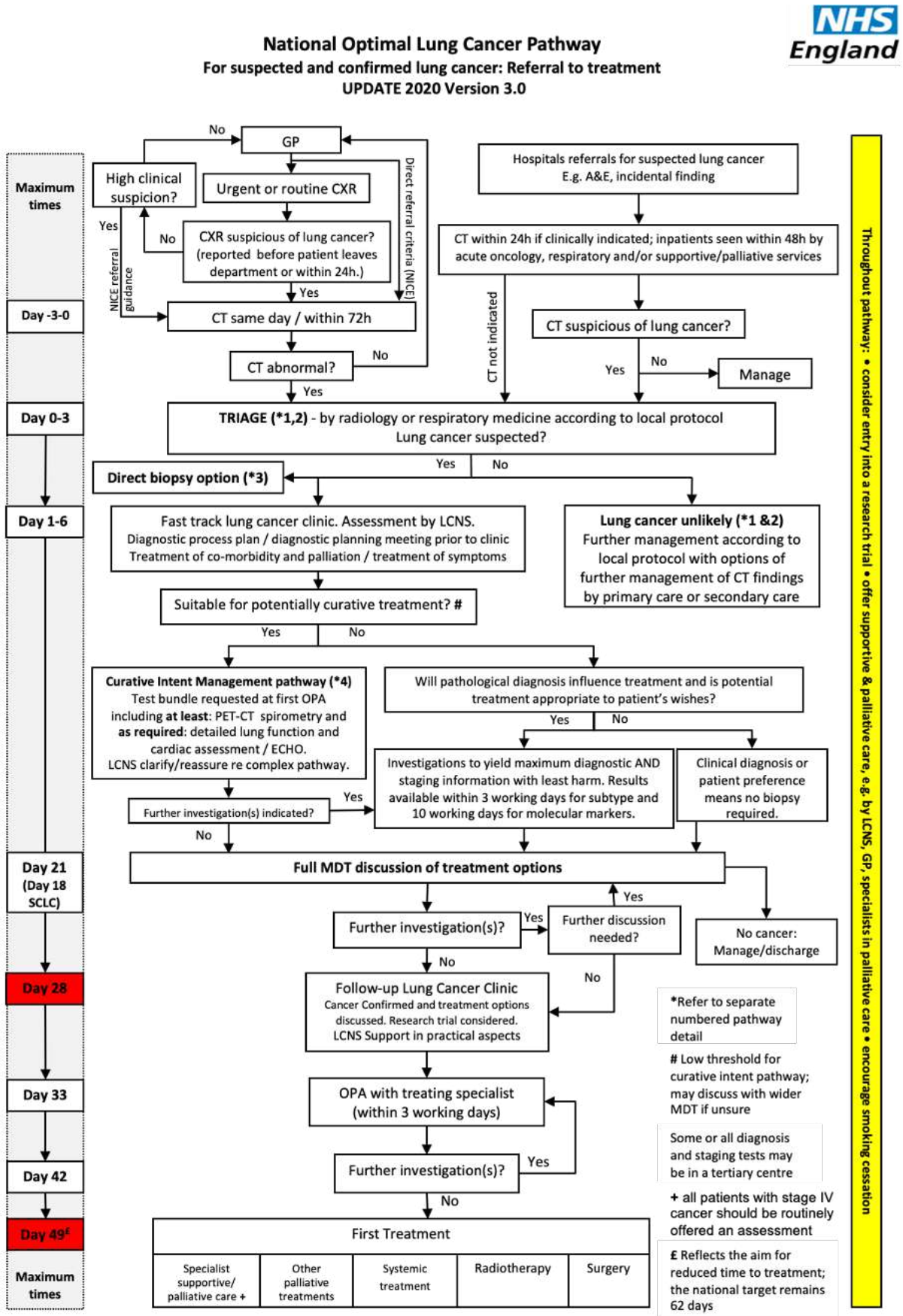
If best case implementation of the NOLCP is to be achieved, all imaging investigations are performed in one diagnostic episode but pivotal is immediate recognition of the suspicious CXR. In the UK, there is a shortage of radiologists and radiographers which makes this implementation a challenge. Artificial intelligence applied here may assist in flagging suspicious CXRs enabling a direct to CT pathway.

qXR is a class II CE approved medical device that detects and localizes the presence of lung nodules on a CXR. qXR is intended to support consultant radiologists and reporting radiographers for clinical decision making.

Methods: The study will be a multi-center, prospective, randomized controlled trial, with block randomisation of radiology sessions to those with and without AI assistance. Seven centres will participate with 150,000 CXRs. Primary outcome: • difference in time (in whole days) to lung cancer diagnosis. Secondary outcomes:• Measurement of accuracy of qXR using independent expert arbitration between discordant qXR/human report for false positive/negative decisions• The difference in number of urgent referrals to respiratory medicine (2WW) with a non-cancer diagnosis• Health economic evaluation of AI chest X-ray triage• Accuracy of qXR alone in triage to CT and the factors needed to ensure no inappropriate CTs• Proportion of qXR-classified malignant nodules which turned out to be biopsy confirmed cases.

Results: This is a planned study

Conclusions: This is a planned study



Keywords: Chest radiograph, Artificial intelligence, Rapid Diagnosis Pathway

EP01.06 EARLY DETECTION AND SCREENING - RISK STRATIFICATION

EP01.06-003 Female Asian Nonsmoker Screening Study (FANSS): Exploring Lung Cancer Screening in a High Risk Population

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Introduction: Lung cancer is the leading cause of cancer death in Asian Americans and unfortunately the majority are diagnosed at advanced or late stages. In Asia, approximately 60 to 80% of female lung cancer patients are never smokers. Patients with early-stage lung cancer have higher cure and survival rates, supporting the premise of lung cancer screening programs. However, lung cancer screening in the United States has been focused on current or former smokers. Recent data presented from the TALENT study, a lung cancer screening study for nonsmokers conducted in Taiwan, reported a lung cancer detection rate of 2.6%. The expansion of lung cancer screening guidelines to other high-risk populations warrants further attention. The FANSS study is an ongoing study investigating the use of LDCT Chest scans in Asian female nonsmokers to evaluate the feasibility of a lung cancer screening program in this population.

Methods: Key eligibility criteria includes women ages 40-74 years old; never smokers or less than 100 cigarettes of lifetime exposure; and identify as from Asian descent, defined as having reported ancestry or race from the continent of Asia. Participants with history of lung cancer; treatment of any cancer within the past five years; and present symptoms suggestive of current lung cancer are not eligible. Eligible participants will proceed to have a LDCT Chest screening exam with a result reported by a radiologist approved to read lung cancer screening scans. Results of this screening test will be discussed with the participant and further recommendations will be given. Negative results will proceed to have a repeat annual LDCT for two additional years. Positive results will be recommended to have further diagnostic workup and possible treatment. In addition, blood draw collection for a plasma-based assay by Delfi Diagnostics will be sent at baseline, years 1 and 2. A questionnaire containing questions regarding ethnicity, environmental exposures including secondhand smoke exposure, and World Trade Center dust exposure will be given to the participant at the initial visit after informed consent has been obtained. The primary objective is to create a database and biorepository of Asian female never smokers who undergo LDCT Chest scans to evaluate the feasibility of a lung cancer screening program for this population. Secondary objectives are to estimate the rate of lung cancer cases detected; to summarize the distribution of lung cancer stages among detected cases; and to estimate the percentage of incidental findings of coronary artery disease and thyroid nodules. Recruitment is ongoing in New York City with plans for expansion of sites to Southern California and other major cities in the United States. (NCT05164757)

Keywords: lung cancer screening, nonsmoker, early detection

EP01.06 EARLY DETECTION AND SCREENING - RISK STRATIFICATION

EP01.06-004 Eliciting Quantitative Smoking History by the Use of Natural Language Processing

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Introduction: To develop a generalizable method for extracting quantitative smoking history (pack years smoked and time from cessation or quit time) in order to facilitate cohort identification for Low Dose CT Scanning (LDCT) for early detection of lung cancer.

Methods: A sample of 2307 adult patients were randomly selected from the Multiparameter Intelligent Monitoring in Critical Care (MIMIC-III) database. Unstructured data was drawn from clinician notes via Natural Language Processing (NLP) using named entity recognition (NER) and our proprietary information extraction to identify two main clinical criteria for each smoking patient: 1) pack years smoked and 2) time from quit date (if applicable). We explored combinations of NER models including rules-based, machine learning, or hybrid models. We then translated the USPSTF guidelines into a rules-based decision tree. The inclusion criteria for selection included age between 50 and 80, > 20 pack year smoking history and, if quit, having done so in the previous 15 years. The structured data was obtained by SQL queries of the diagnosis tables using the ICD-9 codes in use at that time.

Results: Results The structured data revealed 263 (11.4%) 'Ever Smokers' (current plus past use). None of these patients had quantitation of their smoking history and 2044 (88.6) had no smoking information in the diagnosis tables; consequently, a cohort of patients eligible for LDCT could not be determined. The NLP review disclosed that 899 of the 2044 (44%) patients with no data had a clear smoking history and 36 of the 263 'Ever' smokers (13.7%) had no notes to confirm the diagnosis. Review of the unstructured data (primarily physician notes) by NLP disclosed 902 (39.1%) 'Ever' smokers of whom 388 were active smokers and 564 former smokers. Eight hundred thirty-eight patients (36.7%) had no smoking data recorded. Of the active smokers, 266 had smoked greater than 20 pack years and 155 of the former smokers had quit in the prior 15 years resulting in 421 patients eligible for LDCT based on smoking history. When the age criteria for LDCT were applied to this group 52 were found to be eligible for LDCT using the USPSTF criteria. The accuracy of the smoking criteria was 80.4% and the eligibility criteria 93.5% as determined by clinician review.

Conclusions: Unstructured data, obtained by NLP, can accurately identify a cohort that meets the USPSTF guidelines and can be expanded to include other inclusion and exclusion criteria. Structured data derived from ICD-9 codes is unable to develop a cohort of patients eligible for LDCT. Accurate identification of a cohort of eligible patients in a healthcare organization's patient population using data from the EHR, or the data warehouses derived therefrom, would significantly enhance the numbers of patients potentially eligible for LDCT and reduce the current reliance on social marketing campaigns and the need to individually solicit patients for their quantitative smoking history during unrelated patient visits.

Keywords: Natural Language Processing, Low Dose CT Scan, Lung cancer early detection

EP01.06 EARLY DETECTION AND SCREENING - RISK STRATIFICATION

EP01.06-005 Assessment of Cardiovascular Risk in the Non Screening Radically Treated Lung Cancer Cohort

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Introduction: Cardiovascular disease causes increased mortality in all patients with lung cancer irrespective of age and sex.[1] Furthermore, during systemic anti-cancer therapy (SACT) or surgical intervention they experience increased risk of cardiovascular morbidity and mortality.[2] Analysis of lung cancer mortality data showed that 11.4% of deaths had cardiovascular co-morbidities - this was the most prevalent non-respiratory factor.[3] Lung cancer screening has identified a cohort of individuals at high risk of cardiovascular disease[4], yet formal cardiovascular risk assessment is not done routinely in patients treated for lung cancer. We evaluated cardiovascular risk, using the QRISK®3 algorithm[5], and statin uptake in radically treated patients.

Methods: Our retrospective cohort study identified 66 patients who had been treated radically for lung cancer and met the exclusion criteria between 01.01.2021 and 31.12.2021. Patients who were over 85 or had a confirmed diagnosis of cardiovascular disease were excluded, as were patients who had died less than 12 months from treatment. QRISK®3 score was calculated and assessed whether they were on a statin.

Results: During the observation period, 59/66 (89.4%) patients had a QRISK®3 greater than >10%. In this patient group 14/59 (23.7%) were on statin therapy and 45/59 (76.3%) patient were not on any statins. The average QRISK®3 for those on statin therapy was 29.59% (range 3.2 - 57.2%, n=15) whereas for those who were not on statin therapy was 23.9% (range 1.2 -47.9%, n=51).

Conclusions: Screening for cardiovascular risk in patients undergoing radical lung cancer therapy is an effective way in identifying those who may benefit from primary prevention. Commencing patients who are appropriate for statin therapy may reduce their cardiovascular risk. Addressing cardiovascular risk should be considered in post-treatment follow-up clinics.

Keywords: cardiovascular risk radical lung cancer therapy, QRISK3 QRISK statin screening primary prevention, co-morbidity mortality

EP01.06-006 Impact of Low Dose CT Screening on Cause of Death in Different Socio-Economic Groups

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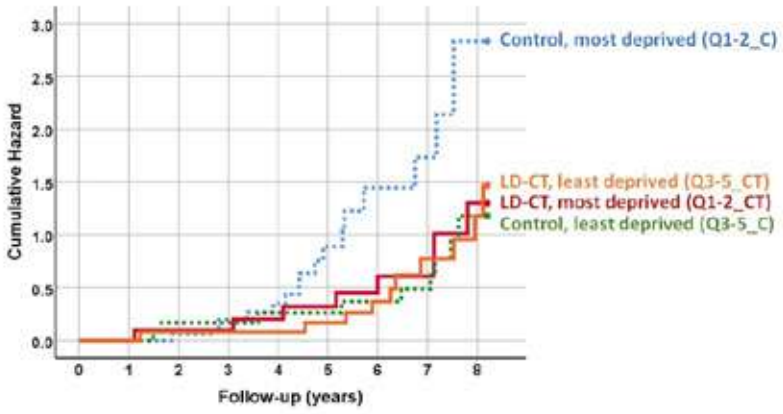
Introduction: Lower socioeconomic status, as measured by the Index of Multiple Deprivation (IMD), is associated with higher rates of smoking-related disease mortality, and with poor uptake in cancer screening. The UKLS low-dose-CT (LD-CT) screening trial for lung cancer was consistent with a lung cancer mortality benefit for CT screening [Field, *et al*. (2021) Lung cancer mortality reduction by LDCT screening: UKLS randomised trial results and international meta-analysis. Lancet Regional Health Europe, doi.org/10.1016/j.lanepe.2021.100179]. We previously reported that risk-based selection increases the proportion of lower socioeconomic groups in LD-CT screening and there is a significant benefit in lung cancer survival in both lower and upper IMD quintiles [Davies, *et al*. (2022) Impact of risk-based low dose CT screening on different socio-economic groups. Lung Cancer Vol 165 Supplement 1 p520]. Here we explore the impact of LD-CT screening on other causes of death.

Methods: IMD quintiles were defined according to UK-wide data, with the deprived group defined as the lower 2 quintiles (Q1-2) and the less deprived as Q3-5. Data on lung cancer diagnosis was obtained from NCRAS cancer registry (median follow-up 7.5 years) and deaths from the Office of National Statistics (median follow-up 8.2years). Follow-up was calculated from date of randomisation and underlying cause of death noted.

Results: Both lower IMD quintiles [HR 0.53 (95% CI 0.31-0.92), log-rank P=0.02] and upper quintiles [HR 0.31 (95% CI 0.15-0.64), log-rank P=0.0008] benefitted significantly from LD-CT screening for survival from lung cancer, in keeping with the stage-shift seen across all quintiles[2]. Whilst LD-CT resulted in similar drops in lung cancer as a cause of death in both quintile groups (Q1-2 by 19%, Q3-5 by 20%), there was a bigger impact on deaths due to COPD and emphysema in Q1-2 (34%) than in Q3-5 (-4%). Time to death due to COPD or emphysema was notably shorter in the more deprived quintiles when no LD-CT was performed (Figure 1), but with LD-CT the rates were the same as for the higher quintiles, where death from COPD is less common. The impact of LD-CT on deaths from heart disease was also less in Q3-5 (13%) than Q1-2 (30%).

Conclusions: LD-CT screening had a significant impact on the rates of death from other smoking-related diseases, notably COPD and emphysema. Future research is required to confirm these finding and related factors, including improved smoking cessation, medical awareness and engagement, and improved diagnosis via the LD-CT scan.

Figure 1 COPD and emphysema specific mortality, stratified by LDCT and IMD (P=0.043)



Keywords: Screening, Socioeconomic, COPD

EP01.06 EARLY DETECTION AND SCREENING - RISK STRATIFICATION

EP01.06-007 The Impact of Modified Screening Eligibility Criteria on Race and Sex Disparities in Lung Cancer Screening

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Introduction: Low Dose CT screening (LDCT) redistributes lung cancer to earlier stage at diagnosis and reduces mortality. However, established screening criteria underestimate risk in women and racial minorities, inadvertently exacerbating access disparities. Using a cohort of patients enrolled into an incidental lung nodule program (LNP), we evaluated the impact of criteria modifications on rates of LDCT eligibility and lung cancer detection by race and sex.

Methods: From 2015, we enrolled patients into a prospective LNP observational cohort within a community-based healthcare system in the mid-south USA. The LNP used natural language processing to capture patients flagged by radiologists as having potentially malignant lesions. Dedicated navigators and physicians in the LNP used Fleischner Society guidelines to triage patients into risk strata for subsequent management. We classified patients using US Preventive Services Task Force (USPSTF) 2013 LDCT eligibility criteria (55-80 years old, >=30 pack-years of smoking, and <=15 years since cessation (USPSTF2013) and 2021 criteria (50-80 years old, >=20 pack-years of smoking, and <=15 years since cessation (USPSTF2021). We also expanded cessation duration to <=25 (USPSTF2021-CD25), the pack-years of smoking to >=10 (USPSTF2021-PY10), and then both (USPSTF2021-CD25-PY10). We report summary statistics and comparisons across groups using the chi-square test or Analysis of Variance.

Results: 18,086 patients had nodules identified from 2015-2021: median age 64 years (Interquartile range: 52-73); 57% female; 67% White, 29% Black, and 3% other; 12% met USPSTF2013 criteria; 15% USPSTF2021; 17% USPSTF2021-CD25; 17% USPSTF2021-PY10; and 19% USPSTF2021-CD25-PY10. Eligible patients were 48% female with USPSTF2013. The additional eligible patients with USPSTF2021 were more frequently female (55%, p-value=0.0029); and this increase was sustained, with expanded eligibility criteria (53-57%, Table 1). Eligible patients were 17% black with USPSTF2013. The additional eligible patients with USPSTF2021 were more frequently black (28%, p-value< 0.0001); and this increase was sustained, with expanded eligibility criteria (25-32%, Table 1). We identified a total of 954 (5.3%) persons with lung cancer, including 18% of those eligible by USPSTF13, and 9-11% of the additional individuals eligible with expanded eligibility criteria. USPSTF2021-CD25-PY10 increased the total lung cancers identified by 34% over USPSTF2013. These additional individuals with lung cancer were 56% female and 29% black.

Conclusions: USPSTF2021 criteria reduced well-documented disparities in lung cancer screening eligibility. Expanding the quit duration and smoking intensity eligibility criteria beyond USPSTF2021 maintained the reduction in disparities and continued to yield a high percentage of cancers identified per person screened.

	Total Eligible	Additional Eligible Beyond USPSTF2013			
Demographic Characteristics	**USPSTF2013**	**USPSTF2021**	**USPSTF2021-CD25**	**USPSTF2021-PY10**	**USPSTF2021-CD25-PY10**
	N = 2119	**N = 656**	**N = 909**	**N = 1019**	**N = 1340**
Lung Cancer(n, %)	379(18)	62(10)	102(11)	88(9)	130(10)
Age					
Median (Q1-Q3)	67(61 - 72)	59(53 - 67)	64(54 - 71)	60(53 - 68)	63(54 - 71)
Sex (n, %)					
Female	1026(48)	362(55)	481(53)	585(57)	746(56)
Male	1093(52)	294(45)	428(47)	434(43)	594(44)
Race (n, %)					
White	1726(82)	460(70)	662(73)	666(65)	917(68)
Black	357(17)	183(28)	231(25)	328(32)	394(29)
Other/Unk/Not Reported	36(2)	13(2)	16(2)	24(2)	28(2)
Risk Characteristics					
Smoking Status (n, %)					
Active Smoker	1458(69)	516(79)	516(57)	776(76)	776(58)
Former Smoker	661(31)	140(21)	393(43)	243(24)	564(42)
Pack years					
Median (Q1-Q3)	50(40 - 68)	25(21 - 30)	26.5(23 - 40)	20(15 - 26)	22.5(16 - 30)
Quit Duration (Years)					
Median (Q1-Q3)	7(3 - 10)	6(3 - 10)	17(8 - 21)	5(3 - 10)	16(7 - 20)

Keywords: low dose CT screening, early detection, disparities

EP01.06 EARLY DETECTION AND SCREENING - RISK STRATIFICATION

EP01.06-008 Low Dose CT Screening in Asian Female-Never-Smokers is as Efficacious as in Asian Male-Ever-Smokers. A Systemic Review and Meta-Analysis

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Introduction: Lung cancer in never-smokers is a significant global cancer burden. We performed this systematic review and meta-analysis to compare efficacy of low-dose computed tomography (LDCT) lung cancer screening among never-smokers versus ever-smokers.

Methods: LDCT lung cancer screening studies that simultaneously included both ever-smokers and never-smoker participants up to April 30, 2021 were searched via Pubmed and Scopus. Primary outcome measure was relative risk (RR) of lung cancer diagnosed between never-smokers and ever-smokers in overall and by sex.

Results: Fourteen studies were included (141,376 ever-smokers, 109,486 never-smokers, 1973 lung cancer cases diagnosed). Thirteen studies were conducted in Asia. Proportional meta-analysis (metaprop) of cumulative incidence of lung cancer diagnosed among overall ever-smokers and never-smokers was 1.02% (95%CI: 0.77% - 1.30%) and 0.88% (95%CI: 0.61% - 1.19%), respectively. The incidence was highest in female never-smokers [1.55% (95%CI 0.78-2.55%), followed by male ever-smokers [0.73% (95%CI: 0.27% - 1.39%), male never-smokers [0.50% (95%CI: 0.17% - 0.99%), and female ever-smokers [0.05% (95%CI: 0.00% - 0.38%).

The RR of lung cancer diagnosed between ever-smokers versus never-smokers was 1.21 (95%CI: 0.86 - 1.72) for overall, 1.54 (95%: 1.15-2.06) for male, and 0.97 (95%CI: 0.61 - 1.55) for female. Importantly, RR of lung cancer diagnosed among female never-smokers versus male ever-smokers was 1.28 (95%CI: 0.7 - 2.34), 0.98 (95%CI: 0.62 - 1.55) versus all high-risk smokers (≥30 pack-years), and 1.85 (95%CI: 1.41-2.44) versus male never-smokers.

Proportional meta-analysis showed significantly more lung cancers diagnosed at first scan [95.4% (95%CI: 84.9% - 100.0%) versus 70.1% (95%CI: 53.6% - 84.4%), P = 0.009 for between-group heterogeneity], and at early stage (0-1) [89.7% (95%CI 81.0% - 96.1%) versus 75.4% (95%CI: 62.7% - 86.5%), P = 0.020 for between-group heterogeneity] among never-smokers versus ever-smokers, respectively. The RR of incidence of lung cancer detected at the baseline scan was similar among never-smokers over ever-smokers (RR = 0.88, 95%CI: 0.56-1.40). Most importantly, the RR for lung cancer mortality and 5-year overall mortality were significantly reduced 77% and 89% among lung cancer cases diagnosed among never-smokers compared to ever-smokers, [RR = 0.23; 95%CI: 0.11-0.47, and RR = 0.11 (95%CI 0.04 - 0.26)], respectively.

Conclusions: The RR of lung cancer diagnosed among female never-smokers was similar to among ever-smokers (male, female, and overall high-risk smoking group) in Asia. Mortality from the lung cancer cases diagnosed among never smokers was significantly reduced compared to those in ever-smokers.

Keywords: LUNG CANCER, LDCT SCREENING, NEVER-SMOKERS

EP01.06 EARLY DETECTION AND SCREENING - RISK STRATIFICATION

EP01.06-009 Frequency of Lung Adenocarcinoma in Patients with Growing Nonsolid and Part-Solid Nodules with Solid Component ≤5 mm

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Introduction: The 2011 Classification of adenocarcinoma of the lung added terms “preinvasive” terminology for pathological diagnosis of resection specimens; Atypical adenomatous hyperplasia (AAH), Adenocarcinoma in situ (AIS) which on CT usually present as nonsolid nodules and minimally invasive adenocarcinoma, which at CT usually present as nonsolid nodules but may have a solid component of up to 5 mm. Previous studies has reported that subsolid nodule have a high likelihood of pathological diagnosis of malignancy varying between 83.6% -100%. However, frequency of primary lung adenocarcinoma in growing nonsolid nodules and part-solid nodules with small solid component ≤5 mm has not been well established. Our purpose is to investigate the frequency of primary lung adenocarcinoma in growing nonsolid nodules and part-solid nodules with small solid component ≤5 mm.

Methods: We reviewed all prospectively collected patients who had undergone transthoracic CT-guided biopsy at Icahn School of Medicine between 2012 and 2021 and had subsequently undergone lung resection for the biopsied nodule. We focused on those who had a nonsolid or part-solid nodule with solid component up to 5 mm and showed growth based on increase in size and/or attenuation compared with a prior scan in the images prior to biopsy and the time to first identify the nodule in CT and biopsy.

Results: Among 75 patients meeting the criteria, there were 20 nonsolid nodules (mean diameter 15 mm, range 7-30 mm) and 55 part-solid nodules with solid component ≤5 mm (mean diameter 15 mm, range 7-51 mm). Median follow up time to assess growth for nonsolid and part-solid nodules was 20.5 months, and 12 months, respectively. Of the 20 patients with NSN, 17 cases had pathological diagnosis of primary pulmonary adenocarcinoma (2 AIS, 7 MIA, and 8 invasive adenocarcinoma), 3 were benign (1 patchy lymphocytic inflammation, 1 nodular lymphoid hyperplasia, and 1 lymphocytic interstitial pneumonia). The first 2 cases presented as subcentrimeter in diameter, smooth border, oval shape, pleural attached and the third case presented as a 3.1 cm in diameter, smooth border, and irregular shape. The frequency of pulmonary adenocarcinoma in participants with growing NSN overall was 85% (17/20), 77.8% (7/9) for follow up of 12 months or less, and 90.9% (10/11) for follow up nodule growth for more than 1 year. Of the 55 patients with PSN with solid component ≤5 mm, all cases (100%) had pathological diagnosis of cancer; 54 primary pulmonary adenocarcinoma (6 MIA, 48 invasive adenocarcinoma) and 1 (1.8%) extranodal marginal zone lymphoma.

Conclusions: The frequency of pulmonary adenocarcinoma in patients with growing nonsolid nodule, and part-solid with solid component ≤5 mm are high, particularly when the solid component ≤5 mm. This is an important consideration when considering next step in management.

Keywords: Growing nonsolid nodule, Growing part-solid nodule, Lung adenocarcinoma

EP01.07 EARLY DETECTION AND SCREENING - WORK UP

EP01.07-001 Surveillance with FDG PET/CT after Completion of Therapy for NSCLC: A Status Update on Inclusion in the SUPE_R Trial

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Introduction: Even after completion of curative treatment for non-small cell lung cancer (NSCLC), patients have a high risk of recurrence and consequently, active surveillance is recommended. The SUPE_R trial is an ongoing trial, designed to explore whether surveillance with F-18 fluoro-deoxy-glucose positron emission tomography/computed tomography (FDG PET/CT) and cell-free tumor DNA sequencing (ctDNA) can improve recurrence detection and increase the number of treatable relapses.

Methods: Patients diagnosed with NSCLC who are candidates for curative therapy, are recruited prior to therapy to obtain a baseline blood sample for ctDNA analysis (part 1). After successful completion of curative treatment verified at the first post-treatment surveillance CT scan, patients are randomized to either continue standard surveillance or surveillance with FDG PET/CT replacing CT every 6 months, for two years or until recurrence (part 2). Baseline characteristics were recorded for all patients, as well as reasons for dropout or exclusion of patients not randomized for part 2.

Table 1: Baseline characteristics of patients included in part 1

Characteristic	Not randomized (N = 492)	Randomized (N = 431)
Gender - no (%)		
Female	245 (51)	173 (40)
Male	239 (49)	258 (60)
Age		
18-50 years	9 (2)	8 (2)
50-70 years	199 (43)	223 (52)
> 70 years	255 (55)	200 (46)
Pack Years		
0	24 (6)	39 (9)
1-30	139 (34)	155 (36)
>30	248 (60)	233 (55)
Performance Status		
0-1	377 (67)	337 (73)
2-4	182 (33)	122 (27)
Baseline Imaging		
FDG PET/CT	356 (87)	355 (93)
CT	54 (13)	25 (7)
TNM Stage		
I	194 (48)	247 (65)
II	91 (22)	63 (17)
III	123 (30)	68 (18)
Histology		
Adenocarcinoma	258 (63)	257 (71)
Squamous cell carcinoma	127 (31)	93 (26)
Other	26 (6)	14 (4)
PD-L1 Status		
<1%	113 (34)	112 (39)
1-50%	110 (33)	95 (33)
>50%	112 (33)	79 (28)

Baseline characteristics of patients included in part 1 of the SUPE_R trial. Patients are grouped by whether they were randomized for inclusion in part 2 of the trial.

Results: Patient enrollment started in 2018 and the inclusion goal of 750 randomized patients was met in November 2021. As of February 2022, 40.4% (n = 303) of randomized patients have completed the intervention. 923 patients were enrolled in part 1 (table 1). 492 (53.3%) patients included in part 1 were not randomized for part 2. This was most frequently due to dropout before screening for part 2 (n = 203, 41.3%), refusal to participate in part 2 (n = 118, 12.8%), exclusion due to unmet inclusion criteria for part 2 (n = 97, 10.5%) or progressive disease (n = 62, 6.7%). Twenty-two patients missed screening for part 2 due to Covid-19. 319 patients were included in part 2 without prior inclusion in part 1. The proportion of patients not randomized for part 2 was higher for patients with advanced disease at diagnosis (stage III) compared to patients with localized disease (stage I-II, 64.7 vs 47.8%, $p < 0.001$), which is partially explained by a higher risk of death (6.3 vs 2.2%, $p = 0.008$) and disease progression (9.5 vs 5.5%, $p = 0.063$) in these patients.

Conclusions: Enrollment in the SUPE_R trial was recently completed after 3 years of patient recruitment. Half of patients included in part 1 were not randomized for part 2 and the proportion of patients not randomized was higher for patients with more advanced disease at diagnosis. Whether this will affect the outcome of the SUPE_R trial remains to be explored.

Keywords: Surveillance, PET/CT, ctDNA

EP01.07 EARLY DETECTION AND SCREENING - WORK UP

EP01.07-002 Objectives and Design of the ACR Lung Cancer Screening CT Incidental Findings - Quick Reference Guide

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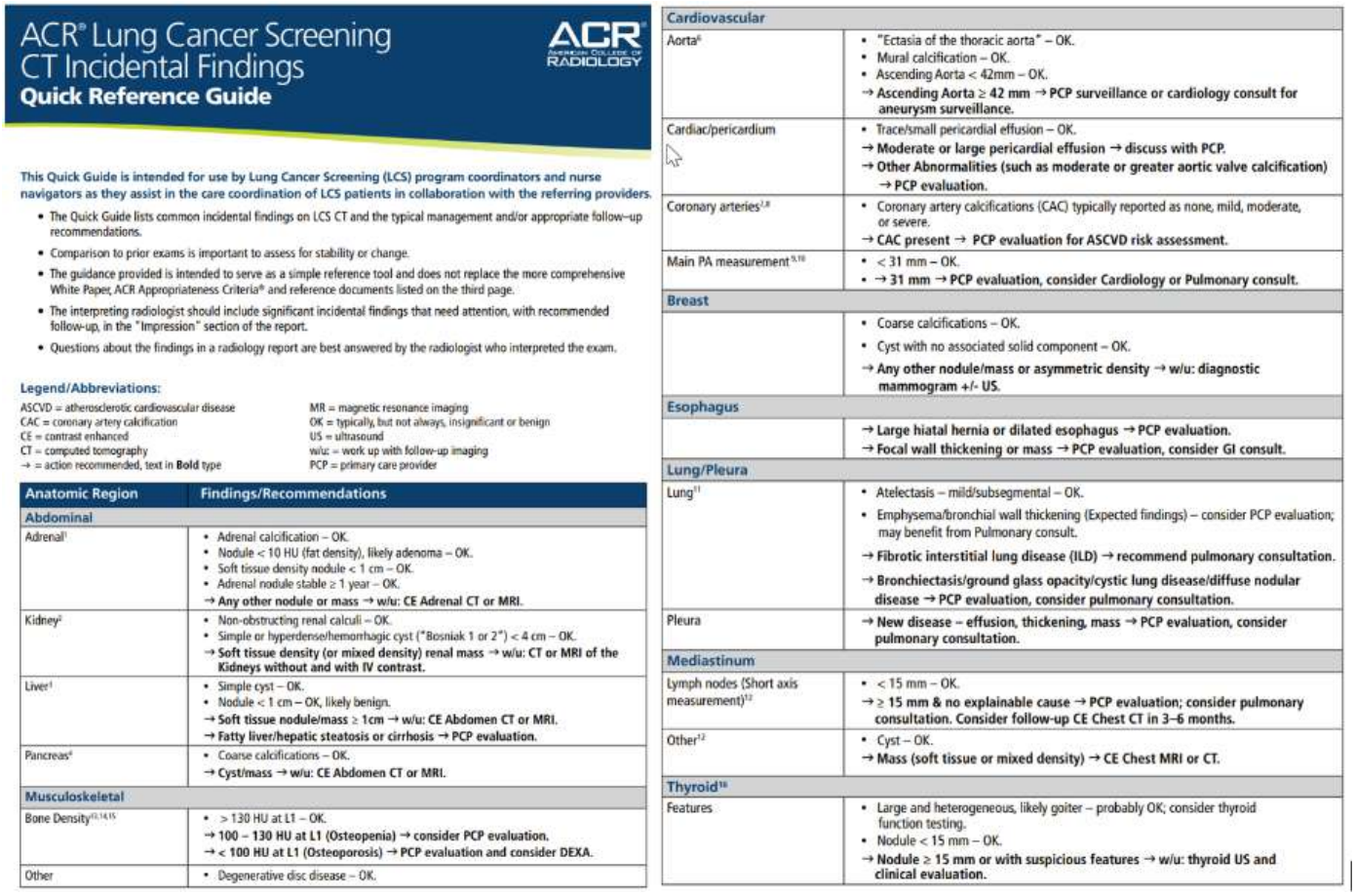
Introduction: The U.S. Preventive Services Task Force (USPSTF) 2021 Guidelines assigned a B grade to low dose computed lung cancer screening (LDCT LCS) for high-risk individuals meeting specified criteria. The longitudinal axis of chest CT encompasses many organs and organ systems. The opportunity for discovering incidental findings (IF) is substantially greater than that of breast, colorectal, cervical, and prostate cancer screening. Many such findings are actionable, indicating a need for further investigation and evaluation. Accountability for timely and appropriate disposition or follow-up ultimately resides with the ordering provider, often a primary care provider (PCP). The advent of Electronic Medical Records and patient portals affords patients immediate access to their imaging reports. Scrutiny of these results may raise concerns among both screenees and providers about the relevance of various IF. Recommendations and communication of these findings may be suggested by radiologists or communicated directly through the assistance of lung cancer screening program (LCSP) navigators or coordinators. The development of a standardized reference guide for navigators, coordinators, allied health professionals, and providers is both desirable and clinically necessary.

Methods: This reference guide was developed and revised by a team of radiologists, pulmonologists, PCPs, navigators, and coordinators, employing white papers and subject matter experts to assess the relevance and applicability of the discovery of incidental and potentially actionable findings to LDCT LCS. Input regarding the design and utility of the guide was received from 40 participants at 32 institutions across the United States, through surveys and feedback, and incorporated into the final draft. Emphasis was placed on conciseness, and ease of understanding.

Results: Seven anatomic regions, including 15 discrete organs and metrics, were deemed to be within the field of view obtained by LDCT LCS. Recommendations and levels of action were suggested for each organ/system, limiting the guide to one page (front/back). This guide proposes typical management/follow-up and is intended as a helpful reference tool for the most commonly encountered incidental findings. It is not intended to be an exhaustive list of all possible findings.

Conclusions: While comprehensive, this guide is purposefully concise, addressing clinically relevant and commonly encountered incidental findings on LDCT LCS. The ACR Quick Reference Guide to Lung Cancer Incidental Findings is anticipated to prove useful for LSCP navigators, ordering providers, and allied healthcare professionals involved in managing the care continuum of LCS, addressing commonly encountered incidental findings and determining the appropriate course of action, with relevant recommendations.



ACR® Lung Cancer Screening CT Incidental Findings
Quick Reference Guide

This Quick Guide is intended for use by Lung Cancer Screening (LCS) program coordinators and nurse navigators as they assist in the care coordination of LCS patients in collaboration with the referring providers.

- The Quick Guide lists common incidental findings on LCS CT and the typical management and/or appropriate follow-up recommendations.
- Comparison to prior exams is important to assess for stability or change.
- The guidance provided is intended to serve as a simple reference tool and does not replace the more comprehensive White Paper, ACR Appropriateness Criteria® and reference documents listed on the third page.
- The interpreting radiologist should include significant incidental findings that need attention, with recommended follow-up, in the "Impression" section of the report.
- Questions about the findings in a radiology report are best answered by the radiologist who interpreted the exam.

Legend/Abbreviations:

ASCVD = atherosclerotic cardiovascular disease
CAC = coronary artery calcification
CE = contrast enhanced
CT = computed tomography
→ = action recommended, text in **Bold** type
MR = magnetic resonance imaging
OK = typically, but not always, insignificant or benign
US = ultrasound
w/u: = work up with follow-up imaging
PCP = primary care provider

Anatomic Region	Findings/Recommendations
Abdominal	
Adrenal[1]	• Adrenal calcification – OK. • Nodule < 10 HU (fat density), likely adenoma – OK. • Soft tissue density nodule < 1 cm – OK. • Adrenal nodule stable ≥ 1 year – OK. → **Any other nodule or mass → w/u: CE Adrenal CT or MRI.**
Kidney[2]	• Non-obstructing renal calculi – OK. • Simple or hyperdense/hemorrhagic cyst ("Bosniak 1 or 2") < 4 cm – OK. → **Soft tissue density (or mixed density) renal mass → w/u: CT or MRI of the Kidneys without and with IV contrast.**
Liver[1]	• Simple cyst – OK. • Nodule < 1 cm – OK, likely benign. → **Soft tissue nodule/mass ≥ 1cm → w/u: CE Abdomen CT or MRI.** → **Fatty liver/hepatic steatosis or cirrhosis → PCP evaluation.**
Pancreas[4]	• Coarse calcifications – OK. → **Cyst/mass → w/u: CE Abdomen CT or MRI.**
Musculoskeletal	
Bone Density[13,14,15]	• > 130 HU at L1 – OK. → **100 – 130 HU at L1 (Osteopenia) → consider PCP evaluation.** → **< 100 HU at L1 (Osteoporosis) → PCP evaluation and consider DEXA.**
Other	• Degenerative disc disease – OK.
Cardiovascular	
Aorta[6]	• "Ectasia of the thoracic aorta" – OK. • Mural calcification – OK. • Ascending Aorta < 42mm – OK. → **Ascending Aorta ≥ 42 mm → PCP surveillance or cardiology consult for aneurysm surveillance.**
Cardiac/pericardium	• Trace/small pericardial effusion – OK. → **Moderate or large pericardial effusion → discuss with PCP.** → **Other Abnormalities (such as moderate or greater aortic valve calcification) → PCP evaluation.**
Coronary arteries[7,8]	• Coronary artery calcifications (CAC) typically reported as none, mild, moderate, or severe. → **CAC present → PCP evaluation for ASCVD risk assessment.**
Main PA measurement[9,10]	• < 31 mm – OK. • → **31 mm → PCP evaluation, consider Cardiology or Pulmonary consult.**
Breast	
	• Coarse calcifications – OK. • Cyst with no associated solid component – OK. → **Any other nodule/mass or asymmetric density → w/u: diagnostic mammogram +/- US.**
Esophagus	
	→ **Large hiatal hernia or dilated esophagus → PCP evaluation.** → **Focal wall thickening or mass → PCP evaluation, consider GI consult.**
Lung/Pleura	
Lung[11]	• Atelectasis – mild/subsegmental – OK. • Emphysema/bronchial wall thickening (Expected findings) – consider PCP evaluation; may benefit from Pulmonary consult. → **Fibrotic interstitial lung disease (ILD) → recommend pulmonary consultation.** → **Bronchiectasis/ground glass opacity/cystic lung disease/diffuse nodular disease → PCP evaluation, consider pulmonary consultation.**
Pleura	→ **New disease – effusion, thickening, mass → PCP evaluation, consider pulmonary consultation.**
Mediastinum	
Lymph nodes (Short axis measurement)[12]	• < 15 mm – OK. → **≥ 15 mm & no explainable cause → PCP evaluation; consider pulmonary consultation. Consider follow-up CE Chest CT in 3–6 months.**
Other[12]	• Cyst – OK. → **Mass (soft tissue or mixed density) → CE Chest MRI or CT.**
Thyroid[16]	
Features	• Large and heterogeneous, likely goiter – probably OK; consider thyroid function testing. • Nodule < 15 mm – OK. → **Nodule ≥ 15 mm or with suspicious features → w/u: thyroid US and clinical evaluation.**

Keywords: incidental findings, lung cancer screening, American College of Radiology (ACR)

EP01.07 EARLY DETECTION AND SCREENING - WORK UP

EP01.07-003 Accuracy of Cytological Diagnosis for Malignant Nodule in Participants with Nonsolid Nodules and Part-Solid Nodules with Solid Component≤5 mm

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Introduction: Nonsolid and part-solid nodule with small solid components are the most common radiologic manifestations of preinvasive and minimally invasive lung cancers. However, other benign lesions can also manifest in this manner and choice of further work-up for the lesions often includes percutaneous needle biopsy. Our purpose is to investigate accuracy of cytological diagnosis for malignant nodule in participants with non-solid nodules and part-solid nodules with solid component ≤5 mm.

Methods: We reviewed all patients who had undergone transthoracic CT-guided biopsy at Icahn School of Medicine between 2012 and 2021 and subsequently undergone lung resection for the biopsied nodule. We focused on those who had nonsolid nodule or part-solid nodule with solid component ≤5 mm.

Results: Among 80 patients, there were 21 nonsolid nodules (mean diameter 15 mm, range 7-30 mm) Of these, 18 had final pathological diagnosis of primary pulmonary adenocarcinoma, and 3 had benign diagnosis. Cytological diagnosis was malignant (n=11) suspicious for malignancy (n=6) and atypical (n=1), respectively. Of the 3 benign cases, cytological results of suspicious for malignant for 1, and atypical for 2. The diagnostic accuracy of cytological diagnosis of malignant or suspicious for malignancy in the NSNs was = 90.5% (19/21) with PPV = 94.4% (17/18), NPV = 66.7% (2/3), sensitivity = 94.4% (17/18), and specificity = 66.7% (2/3).

Of the 59 part-solid nodules with solid component ≤5 mm (mean diameter 15 mm, range 7-51 mm), 57 cases had pathological diagnosis of cancer (56 primary pulmonary invasive adenocarcinoma, and 1 lymphoma). Cytological diagnosis was malignant (n=35), suspicious for malignancy (n=12), atypical (n=6), benign (n=1) and nondiagnostic (n=3) Of the 2 benign cases, cytological results of suspicious for malignant for 1 and atypical for 1 The diagnostic accuracy of cytological diagnosis of malignant or suspicious for malignancy in the PSN with solid component ≤5 mm was 81.4% (48/59) with PPV = 97.9% (47/48), NPV=9.1% (1/11), sensitivity = 82.5% (47/57), and specificity = 50% (1/2).

Conclusions: Accuracy of cytological diagnosis for malignant nodule in participants with nonsolid nodules and part-solid nodules with solid component ≤5 mm was substantial. Overall prevalence of malignancy among nonsolid and part-solid nodules with small solid component sent for biopsy was high. The accuracy of percutaneous needle biopsy was 90.5%, and 81.4%, respectively.

Keywords: Nonsolid and part-solid nodule, Percutaneous needle lung biopsy, Accuracy of cytological diagnosis

EP01.07-004 FDG-PET-CT for Staging Screen Detected Lung Cancer

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Introduction: As lung cancer screening programs develop globally, concern for increasing downstream investigations and cost remain. Flurodeoxyglucose positron emission tomography computed tomography (FDG-PET-CT) is routinely conducted for pre-operative staging, however its utility in screen detected lung cancer is unclear. PET-CT increases the wait time from tissue diagnosis to surgery as well as adds cost. We hypothesize for screen detected early-stage lung cancer (cT1a), PET-CT will not significantly change peri-operative management beyond clinical staging with traditional CT and linear endobronchial ultrasound staging (EBUS).

Methods: This is a retrospective analysis of prospectively collected pathologically confirmed screen detected lung cancer patients from three screening studies, in Vancouver, with PET-CT prior to treatment. The screening eligibility criteria were: age 45-75 and ≥30 pack-years, or age 50 - 80 years with $aPLCO_{m2012}$ risk score of >1.5% over 6 years or ≥30 pack-years and smoked within 15 years. The 8th edition of TNM classification was used for staging.

Results: Of the 130 patients, 54 also had linear EBUS biopsy. 107/130 (82%) were pStage I/II (Table 1). There was good agreement between PET-CT and final pathology stage with a Kappa of.83 and with even better agreement between EBUS and final pathology stage (k=.93). Compared to the pathological stage, CT-PET over-staged nodal involvement in 8.5% of cases and under-staged 7.7% of cases (Table 2). EBUS did not over-stage any mediastinal lymph nodes, but under-staged 3.8% cases with extra-thoracic metatases alone. There were no false negative nodal biopsies. None of the cancers presented with part-solid or non-solid nodule had nodal or distant metastasis.

Conclusions: PET-CT provides useful staging information for screen detected lung cancers >1cm (1A1) but not for smaller tumors or tumors presented as part-solid or non-solid nodules. EBUS bronchoscopy plays a role in pre-operative assessment.

Table 1
Patient characteristics of screen detected cancers

Participants	130
Age, y, median (range)	65.5 (48-80)
Male/females (%)	48.5% / 51.5%
Former Smokers (%)	57.7%
Smoking pack-years, median (range)	48 (18-113)
EBUS	54 (42%)
Histology (total n= 130)	
MIA (%)	7 (5.4%) (INCLUDED 1 AIS)
Invasive Adenocarcinoma (%)	91 (70%)
Squamous Cell (%), n	19 (14.6%)
Large Cell (%), n	2 (1.5%)
Small Cell (%), n	4 (3.1%)
Other (%), n	7 (5.4%)
SUV_{max}, g/ml, median (range)	3.3 (0 - 34.2)
Tumor Size, mm, median (range)	19 (6 - 90)
Tumor Size cT1 (%) cT2 (%), n cT3 (%), n cT4 (%), n	 114 (87.7%) 11 (8.5%) 2 (1.5%) 3 (2.3%)
Radiographic Appearance (total n= 130)	
Solid (%)	75.4%, n = 98
Ground glass component (%)	10.8%, n = 14
Part-Solid (%)	13.8%, n= 18
Solid nodule with Positive N1/N2/Nodes	23
Part-solid nodule with Positive N1/N2/Nodes	0
Non-solid nodules with Positive N1/N2/Nodes	0
Tumor Location (total n = 130)	
Upper lobe (%)	65.4%, n = 85
Lower lobe (%)	34.6%, n = 45

Table 2. Concordance between CT-PET clinical stage versus final Pathologic Stage

	Pathologic Stage										
CT/PET Stage	**1A1**	**1A2**	**1A3**	**1B**	**2A**	**2B**	**3A**	**3B**	**3C**	**4A**	**4B**	**Total**
1A1	21	4	2	1								28
1A2	4	33	4	2		3	1			1		48
1A3	1	3	11	1	1	2						19
1B				3			1					4
2A					1							1
2B	2		1	1		3	1					8
3A					1	1	6					8
3B		1					2	3				6
3C								1				1
4A										2	1	3
4B										1	3	4
Total	**28**	**41**	**18**	**8**	**3**	**9**	**11**	**4**		**4**	**4**	**130**

Keywords: FDG-PET-CT, Screen detected lung cancer, staging

EP01.07 EARLY DETECTION AND SCREENING - WORK UP

EP01.07-005 Combined Diffusion-Weighted Imaging and Dynamic Contrast-Enhanced MRI for Diagnosing Indeterminate Pulmonary Nodules

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Introduction: Investigate the value of diffusion-weighted imaging (DWI) combined with dynamic contrast-enhanced (DCE)-MRI in the diagnosis of indeterminate pulmonary nodules (IPNs) and their subgroups.

Methods: One hundred twenty-three IPNs (median diameter: 15.78 mm; 46.34% solid nodules and 53.66% subsolid nodules) were identified retrospectively. The diagnostic performance was estimated by analyses of ROC curves, after which the sensitivity, specificity, positive predictive value, and negative predictive value were calculated. IPN subgroups were also analyzed. Among patients examined with DWI, DCE-MRI and positron emission tomography-computed tomography (PET-CT), the diagnostic performance of DWI and DCE-MRI was compared with that of PET-CT.

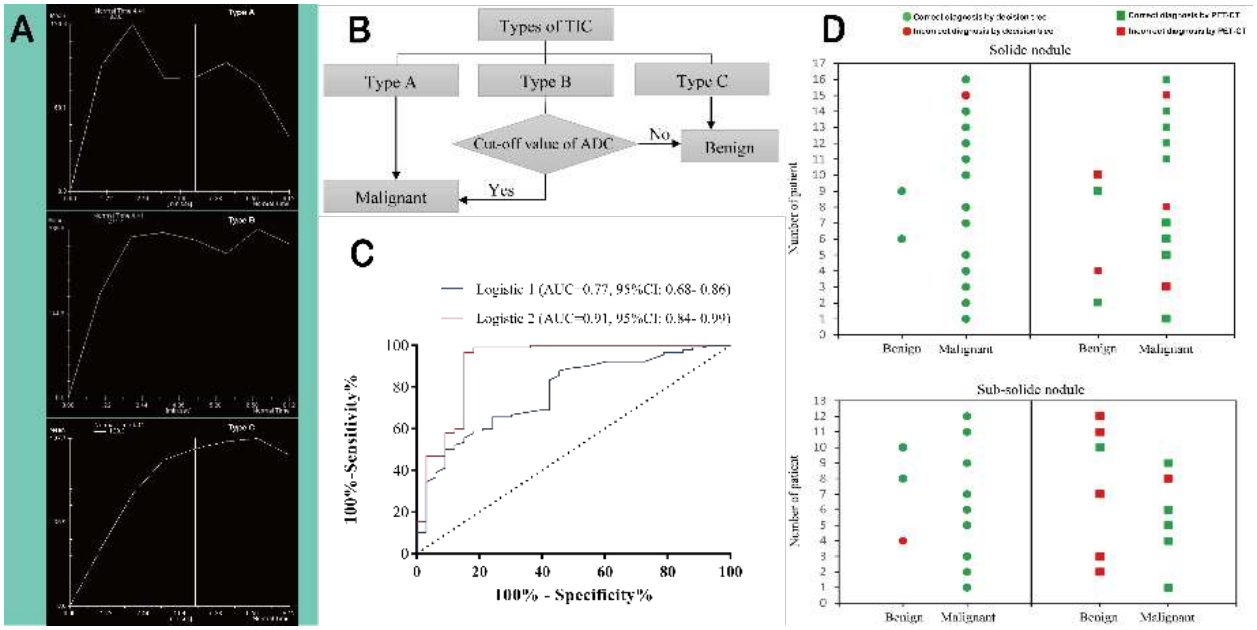
Results: The ADC of malignant pulmonary nodules (MPNs) was significantly lower ($p < 0.001$) than that of benign pulmonary nodules (BPNs). The distribution of three types (Fig A) of time-intensity curve (TIC) was significantly ($p < 0.001$) different between BPNs and MPNs. Combining the apparent diffusion coefficient (ADC) and TIC using a "decision tree" (Fig B) revealed powerful performance in the diagnosis of all IPNs (sensitivity = 0.933, specificity = 0.848) and in different subgroups (sensitivity and specificity of 1.000 and 0.800 in solid IPNs, and 0.948 and 0.875 in subsolid IPNs, respectively). Analyses of ROC curves with logistic models revealed the incremental diagnositic value of MRI parameters on the basis of CT (As shown in Fig C, where logistic 1 is based on clinical features and CT, and logistic 2 is based on ADC and TIC). Twenty-eight patients underwent DWI, DCE-MRI, and PET-CT. More false-diagnoses occurred using PET-CT compared with those using DWI and DCE-MRI (Fig D).

Conclusions: Combination of DWI and DCE-MRI was useful in the diagnosis of solid and subsolid IPNs and could play a part in management of pulmonary nodules.

Diagnostic performance of decision tree (DT) in IPN and its subgroups

	Sen (95% CI)	Spe (95% CI)	Acc (95% CI)	PPV (95% CI)	NPV (95% CI)
All IPNs	0.933(0.882-0.987)	0.848(0.670-0.950)	0.911(0.860-0.961)	0.944(0.896-0.992)	0.824(0.650-0.930)
Solid IPNs	1.000(0.890-1.000)	0.800(0.640-0.950)	0.912(0.839-0.986)	0.865(0.750-0.970)	1.000(0.830-1.000)
Subsolid IPNs	0.948(0.891-1.000)	0.875(0.470-1.000)	0.939(0.882-0.997)	0.982(0.947-1.000)	0.700(0.350-0.930)

Sen, sensitivity; Spe, specificity; Acc, accuracy; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; IPNs, indeterminate pulmonary nodules; Subsolid IPNs, partial solid and pure ground glass opacities IPNs.



Keywords: Pulmonary nodule, Magnetic Resonance Imaging, Positron Emission Tomography Computed Tomography

EP01.07 EARLY DETECTION AND SCREENING - WORK UP

EP01.07-006 Incidence and Resource Burden for the Management of CT Detected Ground Glass Opacities at a Tertiary Lung Cancer Service in the UK

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Introduction: The increased use of computer tomography (CT) for lung cancer screening and evaluation of other intrathoracic disease has led to greater awareness of ground glass opacity (GGO) lesions. We aim to evaluate the incidence of GGOs identified on CT at a tertiary lung cancer service in the UK to determine any trends and to quantify impact on time and resources.

Methods: We retrospectively identified patients reported with GGOs and discussed during MDT meetings held from 2017 to 2019 between the Royal Free and the Royal Brompton Hospitals. Data were collected, their demographics were reported, and annual incidence as well as further analyses on their management were calculated.

Results: 3,731 patients were discussed at MDT meetings from 2017-2019. 53% were male, the mean age (SD) of the cohort was 68 years and 11% (401 patients) had GGOs identified on CT scans. GGO incidence showed an increasing trend between 2017 and 2019 at a frequency of 95 (8%), 141 (11%), 165 (13%) respectively. These 401 were filtered using an exclusion criterion to leave 259 individual patients; 110 were duplicate patients being rediscussed, 17 were being primarily followed up for separate solid nodules and 15 had a part-solid component on diagnosis. Of these, 148 (54%) were discharged from the MDT over a 2-5 year follow up period, 24 (9%) were deceased in the follow up period, and 31 (11%) were not followed up due to logistical reasons; the rest remain under follow up.The “burden” is best quantified on number of MDT meetings per patient, number of CT scans, and further interventions. Median number of MDTs per patient was 2 (1-3) and scans performed was 3 (2-4); the median time interval between scans was 2.9 months (1.0-6.0) and follow-up time was 8.7 months (2.0-24.1). 74 (27%) patients received a PET scan, and 40 patients (15%) had biopsies performed, of which 29 were biopsy proven pre-cancerous lesions or adenocarcinoma. 24 (9%) went on to have surgical intervention in our study period.

Conclusions: We report an increasing trend in the identification and presentation of patients with GGOs in MDT. The combination of follow up with existing guidelines, MDT discussions, biopsy and surgery represents a significant burden in the present and increasing burden for the future. There is a need for more effective pathways than those currently stipulated by existing national and international guidelines to better manage this burden.

Keywords: Ground glass opacity, lung cancer, GGO

EP02.01-001 Plasma Cell-Free DNA as a Point-of-Care Wellbeing Biomarker for Early-Stage Non-Small Cell Lung Cancer Patients

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Introduction: Lung cancer is the worldwide leading cause of cancer-related death. Thoracic Surgical lung cancer patients often possess smoking associated comorbidities including coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD). The Charlson Comorbidity Index (CCI) is currently used to quantify wellbeing and risk of postoperative complications. An objective biomarker surrogate for wellbeing such as circulating cell-free DNA (cfDNA) could aide in perioperative risk estimation and monitoring. The objective of this pilot study is to examine the association between pre-lung cancer surgery plasma cfDNA concentration and CCI in order to provide evidence for clinical utility as a point of care wellbeing biomarker.

Methods: Clinical variables and pre-thoracic surgery 30mL whole blood samples were prospectively collected in adults with operative early-stage lung cancer. CCI was tabulated and plasma processed to establish cfDNA plasma concentration (ng/mL). Box plots were constructed for ng/mL ctDNA by CCI. A multiple linear regression model was developed to predict cfDNA dependant on CCI score, adjusted for independent variables identified a priori to be of clinical relevance including age, sex, smoking status, pT stage and SUVmax. A p>0.05 was considered statistically significant.

Results: Among 55 study participants (Table 1), pre-thoracic surgery plasma cfDNA yield was significantly different between CCI categories (p=0.004), (Figure 1). We further observed a significantly higher cfDNA per ml/plasma concentration for those with a very high CCI>=5 compared to those with CCI less than five (p=0.002). This is clinically important finding, as patients with CCI>=5 are at highest risk of post-surgery adverse events.

Conclusions: Plasma cfDNA concentration was associated with elevated CCI score prior to thoracic surgery for early-stage lung cancer. This preliminary observation suggests that plasma cfDNA could serve as a point of care biomarker for lung cancer patient wellbeing.

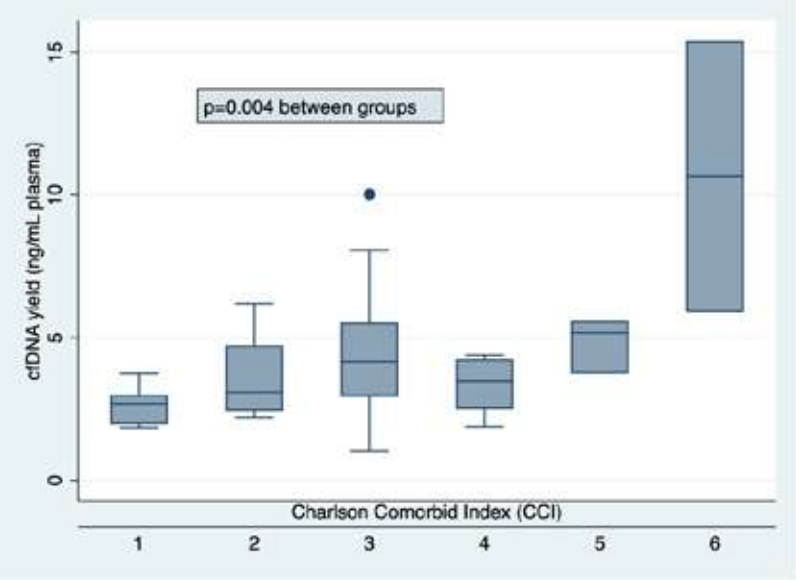

Figure 1. Plasma cell free DNA yield by Charlson Comorbidity Index.
This figure depicts boxplots for plasma cell-free DNA yield (ng cfDNA/mL plasma) stratified by Charlson Comorbidity Index (CCI) Score. Between CCI groups there is a significantly different cfDNA yield observed (p=0.004).

Table 1. Characteristics of Study Participants				
	Total	**CCI < 5**	**CCI ≥ 5**	**P value**
Characteristic	**n=55**	**n=50**	**n=5**	**-**
Age (years), mean (±SD)	68 (±11)	68 (±11.2)	75 (±4.9)	0.169
Female Sex - no. (%)	34 (62)	32 (64)	3 (60)	1.0
Never smoker - no. (%)	22 (40.7)	20 (40)	2 (40)	1.0
Pre-op cfDNA yield (ng/mL plasma)	4 (±2.3)	4 (±1.8)	7 (±4.6)	0.002

Keywords: Lung Cancer, Biomarkers, Thoracic Surgery

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-002 Development of Circulating and Tissue Biomarkers Predicting Immune Phenotype and Response to Immunotherapy in NSCLC

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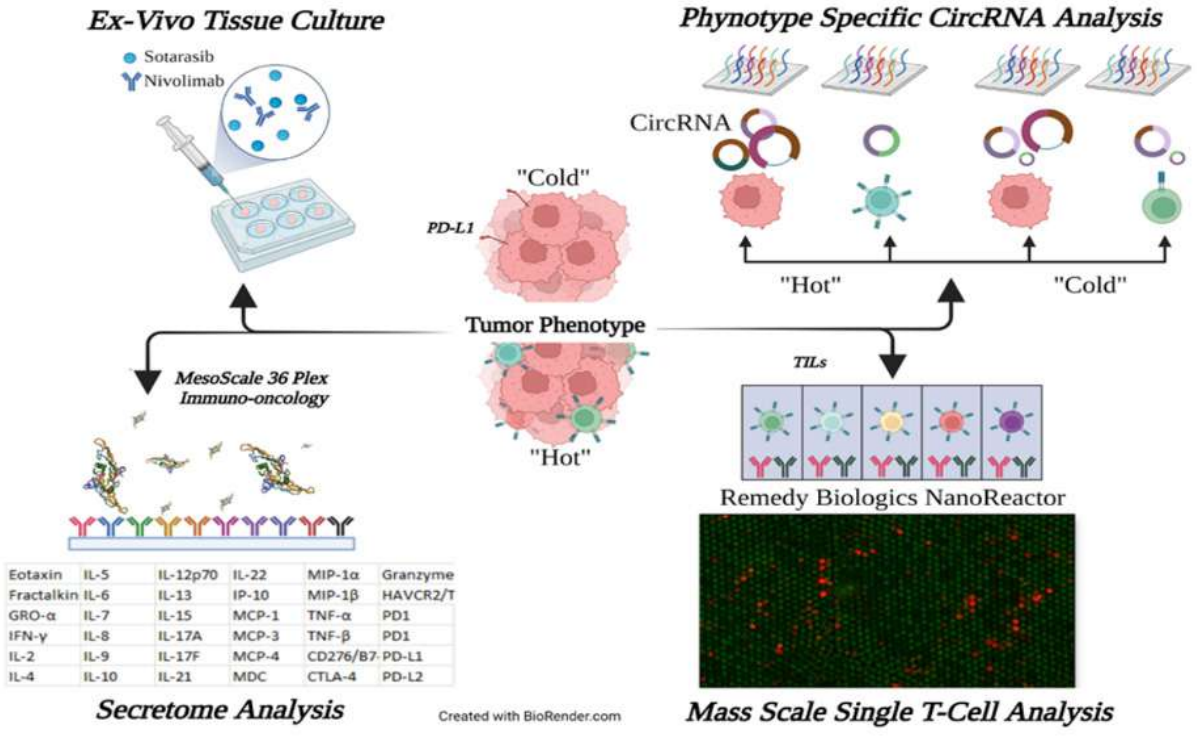
Introduction: Approximately 20-50% of advanced NSCLC patients respond to immunotherapy and show prolonged survival. For patients that fail to respond or those who develop drug resistance there is an unmet clinical need for predictive biomarkers that can stratify patients into groups that will benefit from immunotherapy alone or in combination with targeted therapies. Tumor Infiltrating Lymphocytes (TILs) evaluation can distinguish three dominant immune phenotypes: immune-inflamed (Hot), immune-excluded, and immune-desert (Cold), which can correlate with response to Immune Checkpoint Inhibitors (ICIs).

Methods: A 20 patient cohort with Non-Small Cell Lung Cancer (NSCLC) is assessed by IHC to differentiate "Hot" and "Cold" tumor phenotype using CD4+, CD8+ T cells count and PD-L1 expression. Whole exome sequencing (WES) of tumor mutation burden (TMB), microarray analysis of circular RNAs (circRNAs) within tumor cell and TILs, and digital droplet PCR (ddPCR) of immune checkpoint associated circRNAs genes (B7H3, BTN3A1, BTN3A3, IAP, TIM3, Nectin1, SIRPA etc.) are used to identify novel predictive biomarkers of tumor phenotype. Immunomodulatory effects of Nivolumab alone or in combination with Sotorasib (in KRAS G12C mutant tumours) on the secretome are evaluated in conditioned media from cultured NSCLC explants using a Meso Scale Discovery 36-plex immuno-oncology assay. Finally, individual neoantigen matched TILs are isolated from all treated and untreated explants using a mass scale single cell analysis platform from Remedy Biologics to investigate T-cell activation.

Results: Differentially expressed circRNAs in the tumor & TILs between "hot" and "cold" cohorts are identified. Immunomodulatory effects of Nivolumab alone or in combination with Sotorasib on the secretome are correlated to T-cell activation data from the Remedy Biologics nanoreactor.

Conclusions: This project delivers multi-omic data integration to identify predictive biomarkers of response to immunotherapy.



Keywords: CircRNA, Tumor Immune-Phenotype, T-Cells

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-003 Predictive Role of Novel Grading System on Adjuvant Chemotherapy in Early Resected Lung Adenocarcinoma Based on EGFR Mutation Status

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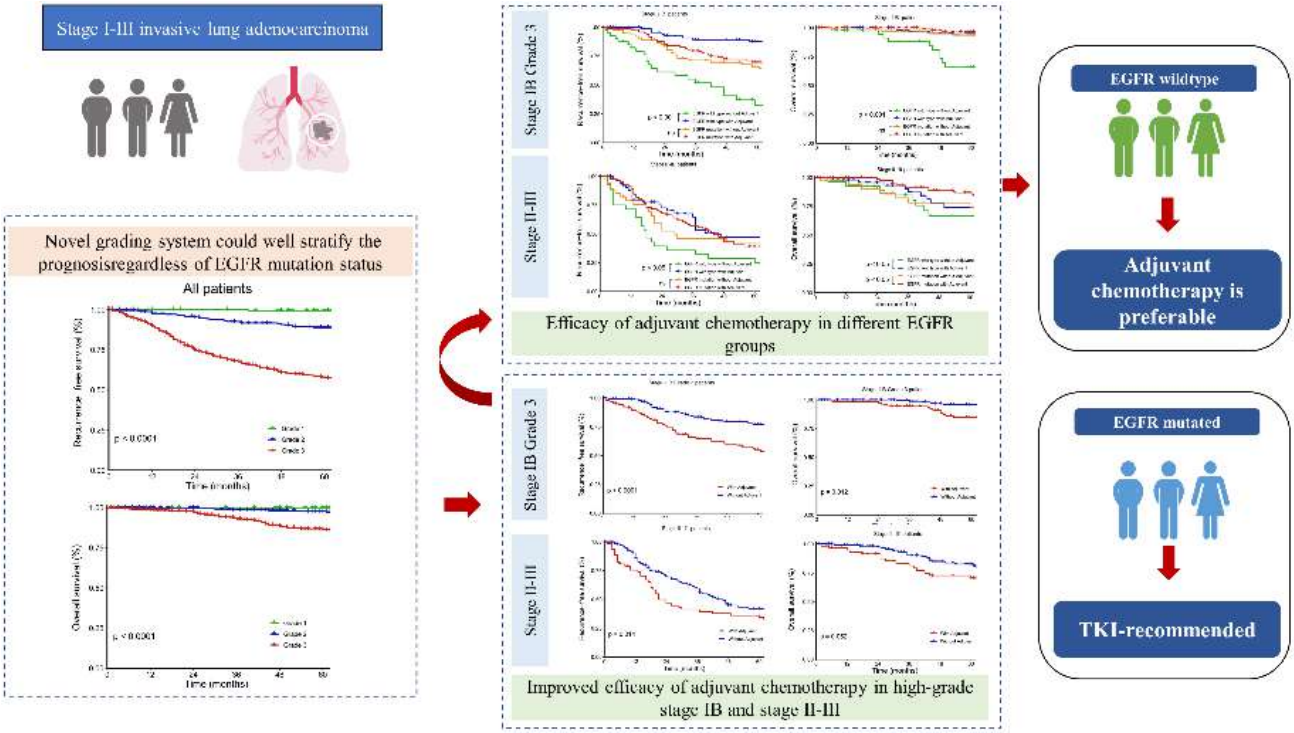
Introduction: The aim of the study was to investigate the relationship between the novel grading system and EGFR mutation, as well as their joint influence on prognosis and efficacy of adjuvant chemotherapy.

Methods: From Jan. 2014 to Aug. 2015, 1073 patients who underwent complete resection and EGFR mutation analysis in Shanghai Pulmonary Hospital were included in our study. The prognostic significance of the novel grading system and EGFR mutation was investigated via the Kaplan-Meier method and Cox regression models. Furthermore, the efficacy of adjuvant chemotherapy was evaluated based on distinct histologic grading and EGFR mutation status in different pathological stages.

Results: Of all 1073 cases, 190, 262, and 540 were stratified into grade I, II, III lung adenocarcinoma, respectively. EGFR mutation was more frequently detected in Grade I- II patients. Survival analysis indicated that the novel grading system could well stratify the prognosis regardless of EGFR mutation status. As for stage IB patients with Grade III adenocarcinoma, those with EGFR wild-type mutations were associated with significantly better survival with adjuvant chemotherapy, while those with positive mutations were not. Similarly, survival benefits were associated with adjuvant chemotherapy only in patients with negative EGFR mutations for stage II-III lung adenocarcinoma.

Conclusions: The novel grading system was a significant prognostic factor in both EGFR-mutated and wild-type patients. High-grade histologic subtypes and EGFR mutation status should be considered simultaneously when evaluating patients with early resected lung adenocarcinoma for adjuvant chemotherapy.



Keywords: Novel grading system, EGFR mutation, Lung adenocarcinoma

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-004 Application of a Genomic Assay for Risk Stratification of Resected NSCLC in a Community Cancer Center Setting, a Pilot Study

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Introduction: 30 to 50% of patients with resected, early stage, non-small cell lung cancer (NSCLC) will recur within 5 years of surgery. DetermaRx, a 14-gene molecular assay can be used to better risk stratify patients with stage I-IIA non-squamous NSCLC who may benefit from adjuvant chemotherapy. This assay more accurately identifies patients at high-risk for recurrence than the current National Comprehensive Cancer Network (NCCN) criteria for early-stage NSCLC. In a prospective validation study, DetermaRx high-risk patients who were treated with adjuvant chemotherapy had a 91.7% 5-year disease-free survival (DFS) compared to 48.9% for the same molecular high-risk patients who did not receive adjuvant treatment. The purpose of this pilot study was to evaluate the applicability of this genomic assay in the management of patients with early-stage, non-squamous NSCLC after complete surgical resection in a community setting.

Methods: We retrospectively reviewed 28 patients with resected, stage I-IIA non-squamous NSCLC who had surgical resection at any of the two main healthcare systems (Kettering Health and Premier Health) in Dayton, Ohio from January 1, 2019, to December 31, 2021. We performed a 14-gene molecular stratification test (DetermaRXTM, Oncocyte) on each surgical specimen and analyzed the concordance between molecular risk and NCCN risk stratification.

Results: Of the 28 patients, 17 patients (60.7%) were stratified as high-risk by the 14-gene assay. Of the 17 patients with molecular high-risk, 7 patients (41.2%) were deemed at low recurrence risk by the NCCN criteria. Of 14 patients without any NCCN high risk feature, 7 (50%) were found to be at high recurrence risk by molecular genomic assay. In subgroup analysis, 11 patients were stage IA2, and more than one-fourth of them had a high-risk feature by molecular assay (36.4%) and by the NCCN criteria (27.3%). However, among 7 patients with tumors between 2-3 cm in size (stage IA3), 71.4% of them were molecular high-risk, but only 28.6% of them had NCCN high-risk features. Stage IB (N=6) and IIA patients (N=4) had comparable risk stratification profiles by the molecular assay and NCCN high-risk stratification (83.3% vs 100% and 75.0% vs 75.0%, respectively).

Conclusions: In our cohort of resected, early-stage NSCLC patients, a 14-gene molecular risk stratification test identified a higher number of stage IA patients at high-risk for recurrence compared to the traditional NCCN criteria. 50% of patients without any NCCN risk factors were found to be high risk by molecular assay. Although adjuvant chemotherapy for patients with NSCLC stage IA is not currently recommended by oncology guidelines, utilizing molecular risk profiling may be considered to accurately identify patients with stage IA at increased recurrence risk who could benefit from adjuvant chemotherapy. The recurrence rate in our study was 7.1%, all of them in patients with stage I NSCLC with high molecular risk. However, due to the limited number of patients in our cohort and the relatively short follow up, firm conclusions cannot be drawn. Additional and prospective studies, particularly in the molecular high risk, stage IA subset of patients are recommended.

Keywords: 14-gene molecular risk stratification test, Stage I-IIA non-squamous NSCLC

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-005 The Efficacy of Platinum-Based Chemotherapy as Adjuvant Therapy in EGFR Mutant Lung Adenocarcinoma

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Introduction: The ADAURA trial reported that osimertinib improved disease-free survival (DFS) compared with placebo as an adjuvant chemotherapy for stage II-IIIA EGFR mutant lung cancer. Currently, platinum-based adjuvant chemotherapy is the standard adjuvant therapy for patients with and without EGFR mutations. This study aimed to evaluate the efficacy of platinum-based adjuvant chemotherapy in stage II-IIIA EGFR mutant lung adenocarcinoma.

Methods: A total of 251 patients who underwent complete resection between January 2008 and December 2018 were retrospectively evaluated for the efficacy of platinum-based adjuvant chemotherapy for overall survival (OS) and relapse-free survival (RFS) in patients with or without EGFR mutation. Multivariable analysis was also performed using age, sex, performance status (PS), smoking index, respiratory function, Charlson comorbidity index (CCI), Clavien-Dindo classification, pathological stage, platinum-based adjuvant chemotherapy, and pathological factors as prognostic factors.

Results: The median age was 69 (range, 40-91) years, 159 (63.3%) were male, and 90 (35.9%) were EGFR mutant. 31 EGFR mutants (34.4%) and 49 EGFR wild-types (30.4%) received platinum-based adjuvant chemotherapy. EGFR wild-types showed an improvement in OS and RFS with platinum-based chemotherapy, while EGFR mutants showed no significant difference in OS and RFS between the two groups. Multivariable analysis for RFS showed that PS and platinum-based adjuvant chemotherapy remained as prognostic factors in EGFR wild-types. In contrast, in EGFR mutants, PS, CCI and pathological stage were prognostic factors, but platinum-based adjuvant chemotherapy was not. In the multivariable analysis for OS, the prognostic factor for EGFR wild types was PS, and that for mutants was lymphatic invasion. There was a trend toward improved prognosis, although not significant, for OS in EGFR wild-type patients with platinum-based adjuvant therapy.

Conclusions: Platinum-based adjuvant chemotherapy may be less effective in EGFR mutant lung adenocarcinoma.

Keywords: EGFR mutation, Adjuvant chemotherapy, Platinum-based chemotherapy

EP02.01-006 Advances in the Treatment of Postoperative Recurrence of Non-Small Cell Lung Cancer and Their Real-World Impact on Survival

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Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo/JP

Introduction: We investigated the impact of tyrosine kinase inhibitors (TKIs) and immunotherapy on survival after postoperative recurrence of non-small cell lung cancer (NSCLC).

Methods: This single-center retrospective study included patients with NSCLC who underwent lobectomy or more with pR0 between 2008-2018 (N=2254). Follow-up was continued until June 2021 (median 5.1 years). Survival trends, prognostic factors, and the impact of TKIs/immunotherapy were analyzed by Joinpoint and Cox regression.

Results: In 443 (19.7%) postoperative recurrences, median time to recurrence was 1.1 years; median age, 68 (range 28-88) years; female, 183 (41.3%); EGFR mutation (EGFR+), 191 (43.1%) / ALK rearrangement (ALK+), 13 (2.9%) / not detected or unknown (ND), 239 (54.0%). In multivariate analysis, age (HR 1.33, 95%CI 1.15-1.53), time to recurrence (HR 0.66, 95%CI 0.56-0.77), adenocarcinoma (HR 0.57, 95%CI 0.42-0.76), symptomatic recurrence (HR 2.04, 95%CI 1.46-2.86), use of EGFR-TKI (HR 0.65, 95%CI 0.48-0.87), use of ALK-TKI (HR 0.28, 95%CI 0.09-0.90), and use of immunotherapy (HR 0.45, 95%CI 0.29-0.70) were significant prognostic factors. Survival was significantly better in the EGFR+/ALK+ group than in the ND group (median, 4.7 vs. 2.1 years, p<0.01; Fig.1). From 2010-2018, 2-year survival after recurrence improved significantly (annual percentage change [APC] 4.2, 95%CI 1.5-7.0). In subset analyses, neither change in 2-year survival nor TKI use was significant over time in the EGFR+/ALK+ group, but the ND group experienced a significant improvement in 2-year survival (APC 13.5, 95%CI 5.4-22.2) during the period and increasing trend in immunotherapy use (APC 23.0, 95%CI -5.9 to 60) after 2013 (Fig.2).

Conclusions: Survival after postoperative recurrence of NSCLC has improved significantly since 2010. Use of immunotherapy in patients without driver mutations might have contributed to that improvement. Prognosis in patients with driver mutations remains favorable with the TKIs introduced before the study period.

Fig. 1 **Overall survival after postoperative recurrence of NSCLC stratified by mutation status**

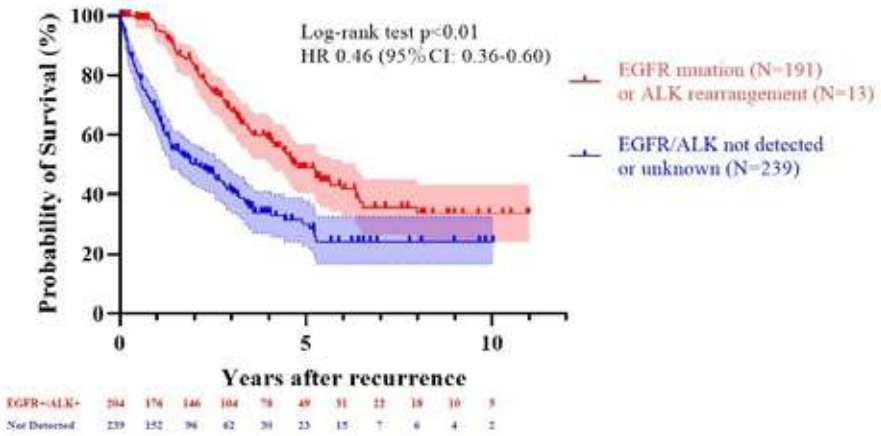
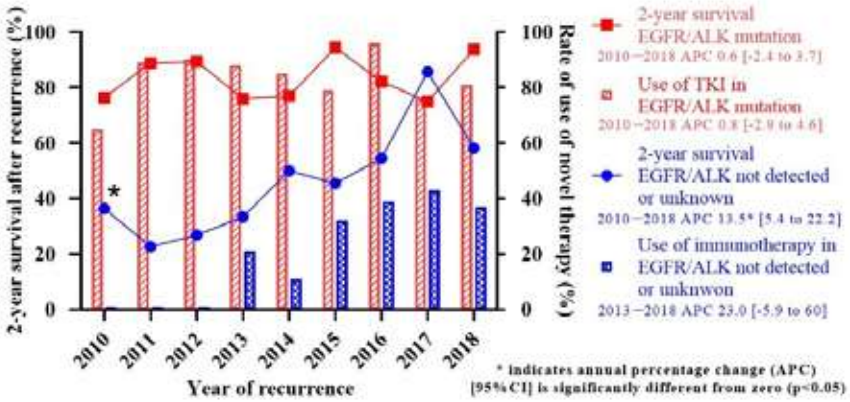


Figure 2. Trends in 2-year overall survival after postoperative recurrence of NSCLC and use of novel therapies for recurrence



Keywords: postoperative recurrence, Survival trend, immunotherapy

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-007 Clinicopathologic and Prognostic Features of Early Resected Lung Adenocarcinoma Characterized with Uncommon EGFR Mutation

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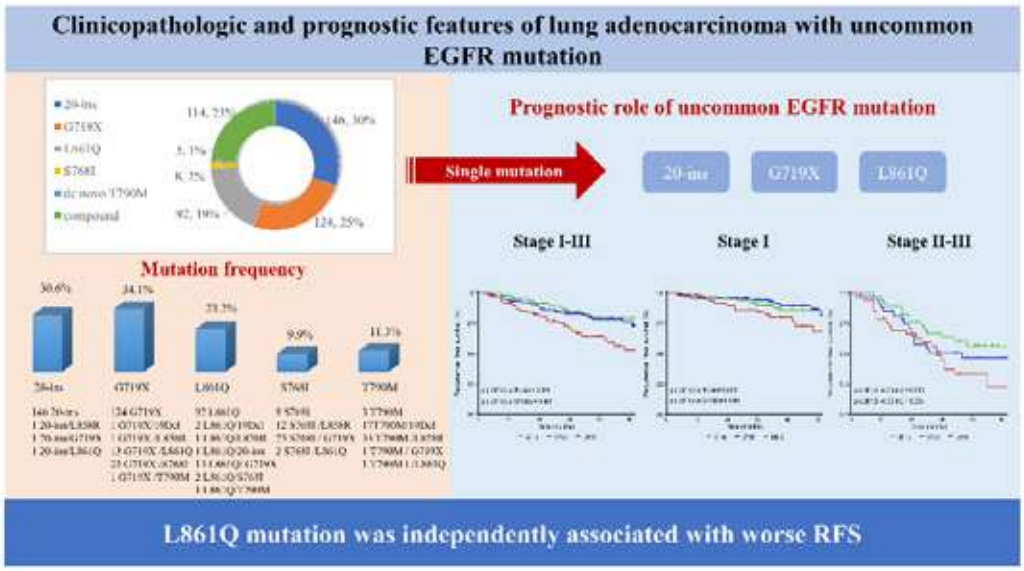
Introduction: The aim of the study was to investigate the clinicopathologic characteristics and the prognostic role of uncommon EGFR mutations in early resected lung adenocarcinoma.

Methods: From 2014 to 2017, 511 resected invasive lung adenocarcinomas with uncommon EGFR mutations were retrospectively reviewed, among which tumors with 19Del/L858R (n=13) or concurrent KRAS (n=2), ALK (n=6), BRAF (n=1), and ROS1 (n=2) mutations were excluded. Clinicopathologic characteristics of patients were displayed based on different EGFR mutation status and subtypes., The prognostic role of uncommon EGFR mutations and effect of adjuvant chemotherapy was assessed according to distinct single mutation subtypes and different pathological stages

Results: A total of 487 patients were ultimately included in our study, among which 373 single mutations and 114 compound mutations were detected. In our cohorts, the mutation frequency of 20-insertion, G719X, L861Q, S768I and de novo T790M were 30.6%, 34.1%, 23.2%, 9.9%, and 11.3%, respectively. Compared with common EGFR mutations, uncommon mutations were closely associated with male and smokers. Survival analysis showed that the L861Q mutation was associated with significantly worse survival in the entire cohorts but not in stage II-III patients. Multivariate analysis revealed that L861Q mutation was an independent risk factor for recurrence-free survival (RFS). Additionally, our results indicated that adjuvant chemotherapy could not bring benefits for lung adenocarcinoma with uncommon EGFR mutations.

Conclusions: L861Q mutation was independently associated with worse RFS in lung adenocarcinoma with uncommon EGFR mutations, which was not associated with improved efficacy of adjuvant chemotherapy.



Keywords: uncommon EGFR mutation, lung adenocarcinoma, prognosis

EP02.01-008 Clinicopathological Features of Rare but Targetable Mutations in Surgically Resected Lung Carcinomas

M. Zacharias[1], S. Konjic[1], G. Absenger[1], M.J. Hochmair[2], H. Fabikan[3], C. Weinlinger[3], O. Illini[2], P.J. Jost[1], V. Schlintl[1], R. Wurm[1], J. Lindenmann[1], M. Fediuk[1], L. Brcic[1], A. Terbuch[1]

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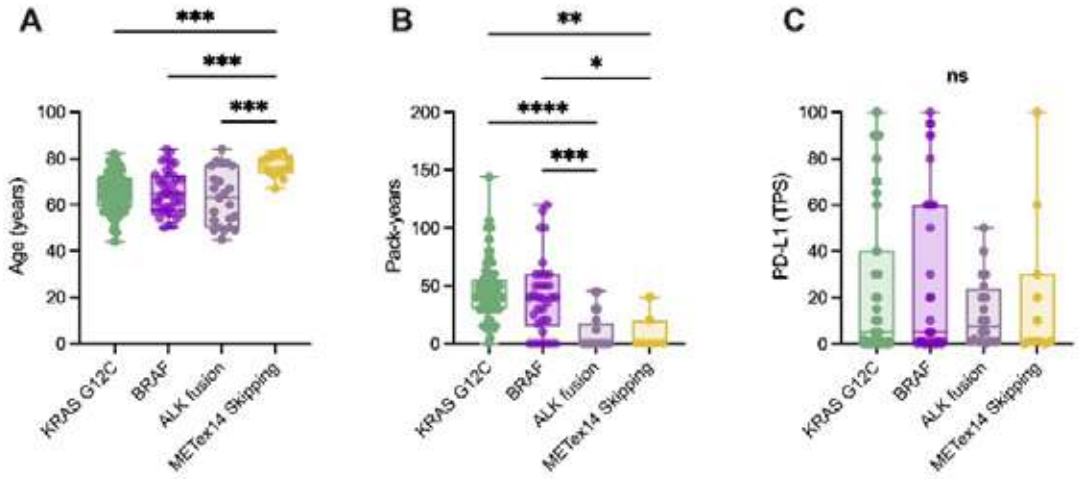
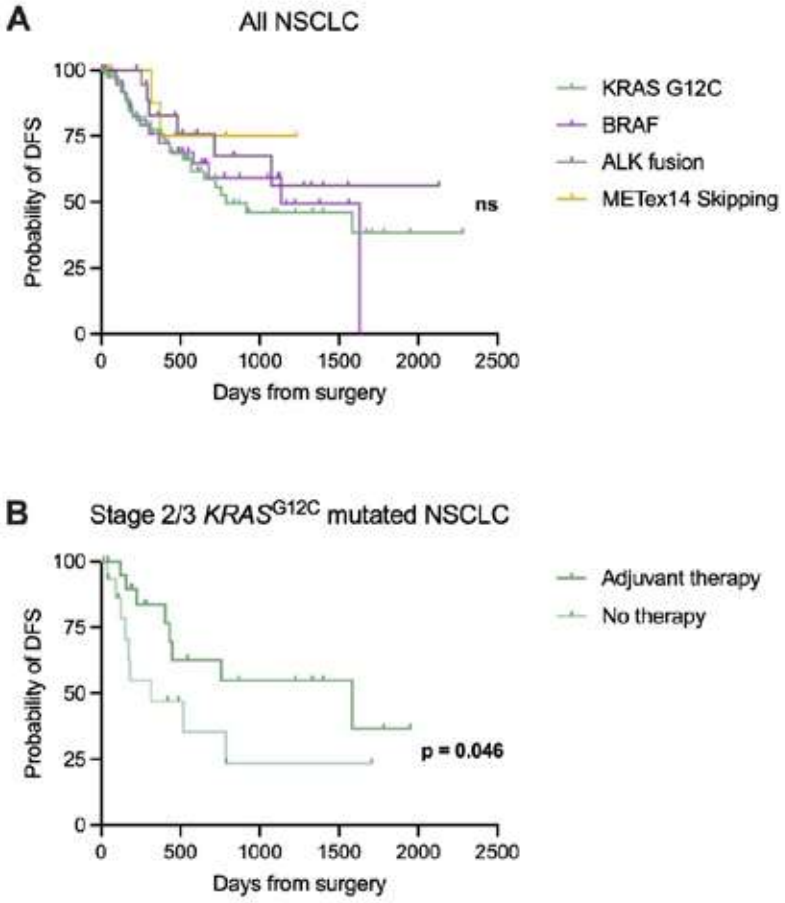
Introduction: Targeted therapies have revolutionized the treatment of lung carcinomas harboring specific mutations. The most common and well-studied gene in this context is *EGFR*, however, the landscape of targetable alterations expands rapidly. While many studies characterizing these rarer mutations have focused on the metastatic setting, data on early-stage lung carcinoma is scarce.

Methods: We investigated clinicopathological features, including disease-free survival (DFS), in patients with surgically resected lung carcinomas harboring *KRAS*G[12]C, *BRAF*, *ALK* or *MET*ex14 skipping alterations. All lung cancer patients of two academic centers who underwent resection between 2015 and 2021 were included; patients with definitive radiotherapy were excluded. DFS was compared between groups using the Gehan-Breslow-Wilcoxon test. Clinical metadata (age, pack-years, PD-L1 status) were compared between mutation groups using the Kruskal-Wallis test.

Results: 84 *KRAS*G[12]C, 37 *BRAF*, 21 *ALK* and 13 *MET*ex14 skipping alteration cases were identified. Significant differences between mutation groups were found in age distribution and smoking behavior, but not PD-L1 status (Figure 1). No significant differences in DFS could be detected between mutation groups (Figure 2A), however, the lowest median DFS was found in the *KRAS*G[12]Cgroup (785 days). Within the *KRAS*G[12]C group, adjuvant therapy was associated with a significantly better DFS compared to no therapy (Median DFS 1582 days vs 315 days; p=0.046; Figure 2B).

Conclusions: With the exception of activating *EGFR* mutations, patients with early-stage lung carcinoma are usually treated regardless of the underlying driver mutation. However, options for targeted therapy expand rapidly and might soon also include rarer mutations. A better characterization of the respective mutation groups is therefore urgently needed. Among other findings, our study highlights the benefit of adjuvant therapy in *KRAS*G[12]C mutated early-stage lung carcinomas, with possible implications for future patient stratification.





Keywords: Early-Stage Lung Cancer, Targeted Therapy, KRAS G12C

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-009 PD-L1 Expression in Biopsies and Surgical Specimens of Lung Cancer: Impact of Biopsy Methods and Neoadjuvant Therapy

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Introduction: PD-L1 testing in lung cancer patients is performed mainly on biopsy specimens. However, it is questionable whether the small amount of tissue may represent the PD-L1 expression. Furthermore, it is hypothesized that PD-L1 expression on tumour cells may vary due to chemotherapy or immunotherapy. To evaluate the accuracy of PD-L1 testing in biopsy specimens, we conducted this study aiming to compare the PD-L1 expression on tumour cells of specimens acquired by various diagnostic biopsy techniques and surgical specimens with consideration of the neoadjuvant therapy.

Methods: Patients with the diagnosis of lung cancer assessed by biopsy (endobronchial biopsy, endobronchial ultrasound guided tranbronchial needle aspiration (EBUS-TBNA), tranbronchial biopsy (TBB), brush cytology or computed tomography guided biopsy) who underwent surgical resection in 2019-2020 at the Medical University of Vienna were enrolled in this retrospective study. The database queried for this study included the pathological, bronchosopic, radiological, oncological, and surgical reports.

Results: A total of 113 patients (60% male, mean age 65 ± 9 years) with lung cancer of whom PD-L1 expression on tumour cells were available in biopsy specimens and corresponding surgical specimens were enrolled in this study. CT-guided biopsy was performed in 36% and bronchoscopy in 64% of patients (endobronchial biopsy (n=29), EBUS-TBNA (n=12), TBB (n=33) and/or brush cytology (n=31)). Mean PD-L1 expression in 114 biopsy specimens and surgical specimens was 27.9 ± 32.6% and 21.9 ± 28.6% respectively. Quantitative comparison revealed a significant correlation (r=0.58) of PD-L1 expression on tumour cells ($p<0.001$). TPS was found to be ≥50% and <50% in 68% (78/114) and 32% (36/114) diagnostic biopsies, respectively, and 22% (25/114) and 78% (89/114) in surgical specimens, respectively. In 89 cases, there was a concordance in PD-L1 testing with a cut-off value of ≥50% between biopsy and surgical specimen resulting in a concordance rate of 78%. The overall agreement was found to moderate with a Cohen´s Kappa of 0.45. For all bronchoscopic techniques except for TBB as well as for CT-guided transthoracic biopsy, a statistically significant correlation of PD-L1 expression on tumour cells between the biopsies and surgical specimens were found. Correlation of PD-L1-expression on tumour cells between biopsy and surgical specimens was significant in the subgroup of patients undergoing neoadjuvant treatment ($p<0.001$) and for patient without neoadjuvant treatment ($p<0.001$).

Conclusions: This study found a statistically significant correlation for PD-L1 expression on tumour cells between biopsy and surgical specimen, but of uncertain clinical relevance. Particular the use of a cut-off value of ≥50% PD-L1 TPS resulted only in a moderate agreement. Therefore, the interpretation of biopsy-based PD-L1 status should be considered with caution when deciding therapeutic approach for a patient

Keywords: lung cancer, PD-L1 expression, Biopsy

EP02.01-010 Preoperative PET-SUVmax and Volume Based PET Metrics of the Tumor Fail to Predict Nodal Upstaging in Early-Stage Lung Cancer

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Introduction: Accurate nodal staging is of utmost importance in treatment planning for lung cancer. Integrated FDG-PET/CT is part of the routine staging in lung cancer, however, data concerning the predictive value of preoperative PET-SUVmax and other volume based PET metrics of the primary tumor on nodal upstaging are still limited. For this reason, we aimed to assess the impact of preoperative tumor SUVmax and other volume based PET parameters on nodal upstaging in early-stage lung adenocarcinoma and squamous cell carcinoma.

Methods: 500 patients with pT1-T2/cN0 lung cancer underwent primary resection with curative intent at a single center from January 2016 to November 2018. Patients with histologically confirmed adenocarcinoma and squamous cell carcinoma with PET-CTs available were retrospectively included in this study. Data of 171 patients were analyzed for the association of preoperative PET-SUVmax and volume based PET metrics of the primary tumor with clinicopathological variables and with nodal upstaging. Of note, volume based PET parameters included total lesion glycolysis (TLG), metabolic tumor volume (MTV), TLG @2.5, MTV@ 2.5, MTV40% and SUVmean in MTV.

Results: Higher preoperative PET SUVmax values of the primary tumor associated with squamous cell carcinoma and larger tumors. Increased preoperative C-reactive protein levels (<1mg/dL), but not lactate dehydrogenase activity, white blood cell count, gender or age correlated significantly with high preoperative PET-SUVmax values. The overall nodal upstaging rate in our cohort was 14 %. N1 upstaging was observed in 15 Patients (8.8%) and N2 upstaging in 9 patients (5.3%). 7 patients with a T1 tumor and 17 patients with a T2 tumor showed nodal upstaging. No significant difference was found in histology type SUVmax or volume based PET parameters for cases with or without nodal upstaging. Only MTV 40% and MTV @2,5 showed a tendency with nodal upstaging.

Conclusions: Higher SUV max values were found in patients with squamous cell carcinoma and T2 tumors. Beyond tumor size no PET parameters were found to be predictive for nodal upstaging.

Keywords: early-stage lung cancer, FDG-PET-CT, nodal upstaging

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-011 Immune-related Histologic Phenotype in Pretreatment Tumor Biopsy Predicts Efficacy of Neoadjuvant Anti-PD-1 Treatment in Squamous Lung Cancer

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Introduction: The neoadjuvant platform affords a valuable resource for understanding the responses to therapy and carrying out reverse translation. We aimed to develop a pretreatment histologic scoring system to predict the efficacy of neoadjuvant immunotherapy.

Methods: 140 NSCLC cases were evaluated in this study. Initially, surgical specimens from 31 squamous cell lung cancer patients with neoadjuvant anti-PD-1 therapy and eligible paired pretreatment biopsies were used for pathologic evaluation after neoadjuvant immunotherapy and develop the pretreatment scoring system. Immune-related histologic phenotype assessment criteria (irHPC) was developed based on the pathologic features identified after neoadjuvant treatment. Three trained pathologists independently scored the hematoxylin-eosin (HE) slides of the pretreatment tumor biopsies according to irHPC. The follow-up was from March 7, 2018, to December 31, 2021, mainly focusing on disease free survival (DFS) and overall survival (OS). Secondarily, 109 biopsies of lung squamous cell carcinoma were evaluated to explore the relationship between eosinophils and PD-L1 expression.

Results: Superior 2-year DFS rates were observed in patients who achieved MPR (MPR vs. Non-MPR: 92.9% vs. 78.6%). Whether necrosis was included in the calculation of percent of residual viable tumor (%RVT) or not had almost no effect on the consistency of pathologic assessment and the histological response grouping. The inter-pathologist variability of assessing %RVT with immune-activated phenotype was not statistically significant (P=0.480). Four immune-related features of pretreatment biopsies were included for calculating the predictive score. The trained pathologist accurately predicted most cases according to irHPC. For inter-observer reproducibility using “2 points” as the cut-off point, the overall percent agreement was 77.8%. The reliability between pathologists for a binary tumor evaluation showed “moderate” agreement (κ=0.54). Patients with score≥2 points tended to have a better 2-year DFS rate compared to those with score<2 points (85.7% vs. 71.4%).

Conclusions: The irHPC scoring system reflecting the preexisting immune response could be used to predict the pathologic response of neoadjuvant immunotherapy, possibly further predict the long-term prognosis, but still needs larger trails to verify.

Keywords: Neoadjuvant, Biopsy, Predict

EP02.01-012 PD-L1 Expression Predicts Prognosis in Completely Resected NSCLC Patients with an EGFR Mutation

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Introduction: Several studies have demonstrated that the high expression of programmed death-ligand-1 (PD-L1) can predict the low overall response rate (ORR) rates in advanced non-small cell lung cancer patients (NSCLCs) with epidermal growth factor receptor (*EGFR*) mutation treated with TKI therapy. But the role of PD-L1 expression in the completely resected NSCLCs with *EGFR* mutation is still controversial.

Methods: Completely resected patients with pathological stage IB-III NSCLC from 2008 to 2018 in Guangdong Provincial People's Hospital were screened. The status of *EGFR* mutation and PD-L1 expression were collected. High PD-L1 expression was defined as tumor proportional score (TPS) ≥ 50 %. PD-L1 expression was defined as TPS ≥1 %.

Results: 146 patients with *EGFR* mutations and data of PD-L1 expression were eligible. The mean age was 61 years old, and 58.2% of patients were female. Among 122 patients with known disease-free survival (DFS) status, the median DFS was 31 months, and the median follow-up time was 34 months. The median DFS of patients with PD-L1 expression (n=37) was shorter than those with no PD-L1 expression (n=85) (21 vs 43months, *P*=0.011; HR=1.6, 95%CI:0.86-3.0, *P*=0.135). Patients with high PD-L1 expression (n=7) also had shorter median DFS (21 vs 34months, *P*=0.0039; HR=5.49, 95%CI:1.83-16.5, *P*=0.002). In the 54 adjuvant targeted therapy patients, patients with expression of PD-L1 (n=13) had shorter median DFS (25 vs 34 months, *P*=0.75; HR=1.2, 95%CI:0.47-3.2, *P*=0.668). The median DFS was also shorter in patients with high expression of PD-L1(n=2) (3 vs 31 months, *P*=0.5; HR=11.2, 95%CI:0.94-134.2, *P*=0.056). As for 47 patients treated with no adjuvant therapy or ones except target therapy, the median DFS was also shorter in patients with expression of PD-L1(n=14) (21 vs 34 months, *P*=0.25; HR=1.89, 95%CI:0.82-4.4, *P*=0.136) and high expression of PD-L1(n=4) (21 vs 33 months, *P*=0.057; HR=3.13, 95%CI:0.99-9.9, *P*=0.052).

Conclusions: PD-L1 high expression was associated with poor DFS in completely resected NSCLCs with *EGFR* mutation, especially in those treated with adjuvant targeted therapy.

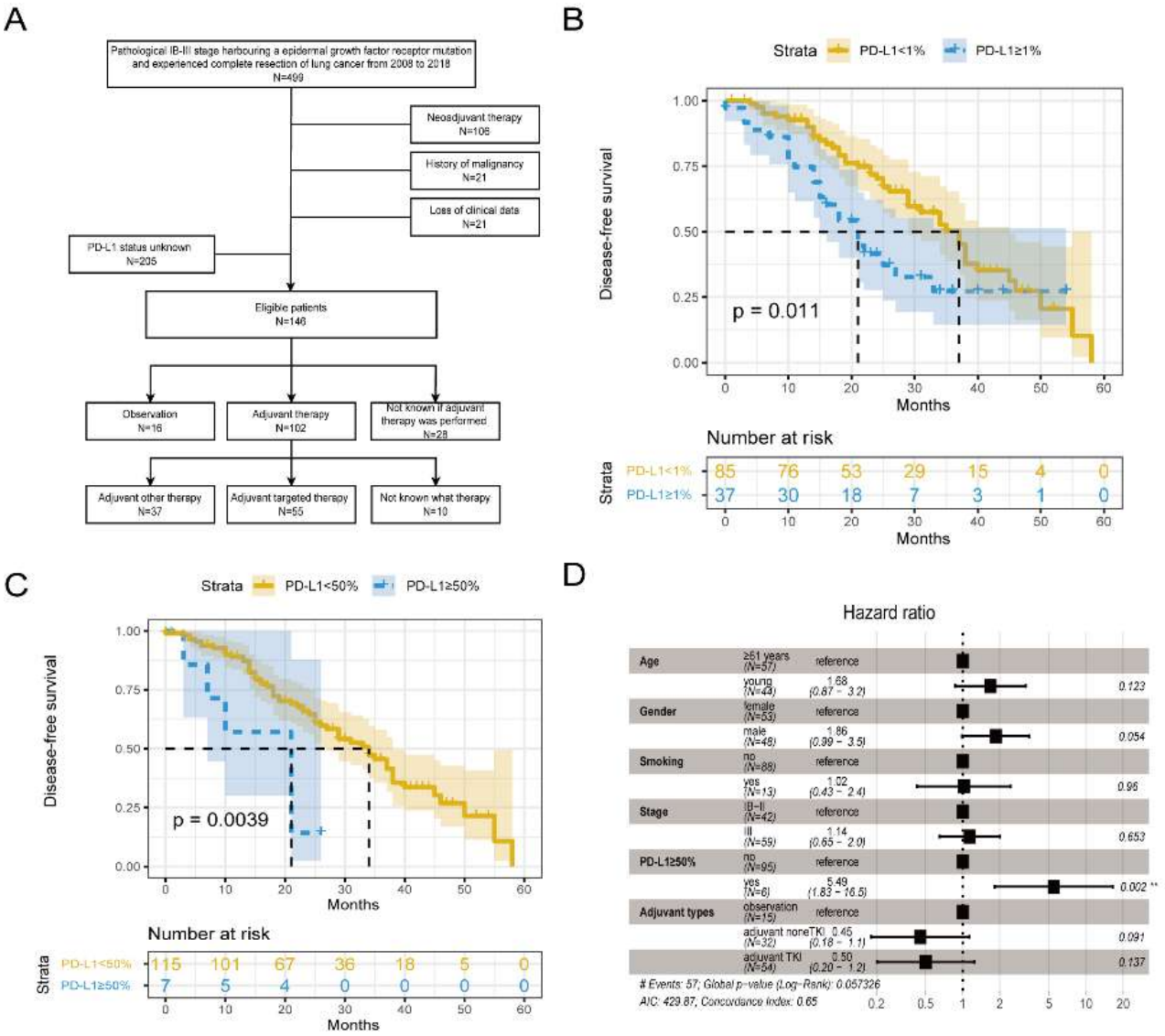

Figure 1. Our study (A) depicted the association between PD-L1 expression (B) or PD-L1 high expression (C, D) and DFS in the completely resected *EGFR* mutation NSCLC patients.

Keywords: EGFR mutated, NSCLC, Programmed death ligand 1

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-013 Real World Treatment Patterns, Prevalence and Outcomes in Patients with KRAS Mutated Non Small Cell Lung Cancer in Southwestern Ontario

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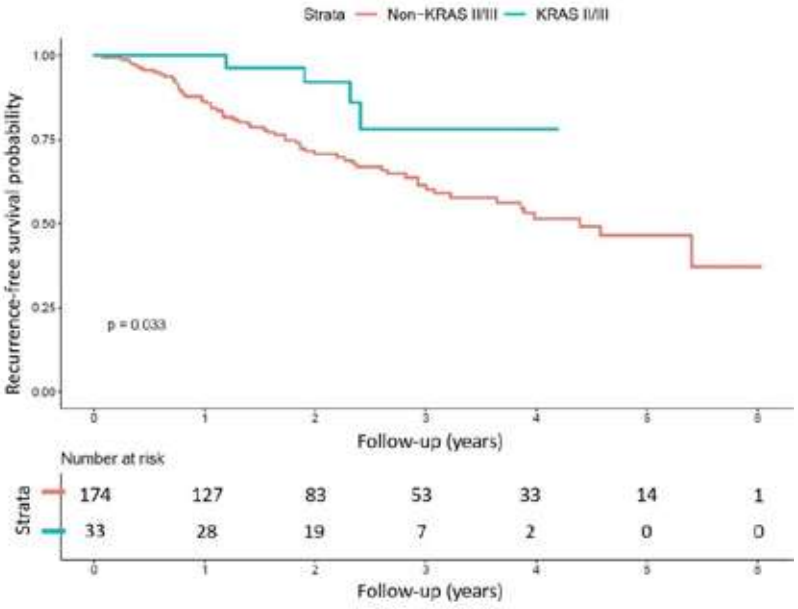
Introduction: Among patients(pts) with resectable Non-Small-Cell-Lung-Cancer(NSCLC), survival outcomes, despite standard of care adjuvant therapies, remains suboptimal. Pts with advanced KRAS mutated(KRASm) tumors benefit from molecularly-directed KRAS inhibitors. Efforts to improve outcomes using molecularly-targeted therapies are underway in the early-stage setting. The objective of this study was to evaluate the prevalence/distribution and outcomes of pts with resected(stage I- III) KRASm NSCLC in the real world setting in Southwestern Ontario.

Methods: Retrospective chart review of all adult pts with stage I-III NSCLC, resected from 1/1/2016-30/6/2020, at the London Health Sciences Center(regional center for Southwestern Ontario), following institutional Research Ethics Board approval. Data on KRASm status, clinico-demographics and outcomes were collected. Overall survival(OS) and Recurrence free survival(RFS) were evaluated using Kaplan-Meier curves and Cox proportional hazards models

Results: Of 356 stage I-III pts who underwent curative resection and whose tumors had KRAS reflex testing, 42 pts(12%) were KRASm. Of these, 3 and 2 patients were stage IA and IIIB, respectively. Among pts with KRASm, median age was 70 years; 54.8% were female; 92.9% KRASm and 82.2% KRASwt were current/former smokers. In the KRASm population, 21.4% presented with stage I, 35.7% stage II, and 42.8% stage III. In the KRAS wild-type(KRASwt) population, 36.6% presented with stage I, 35.6% stage II, and 19.7% stage III. 40.5% KRASm and 22.9% KRASwt received adjuvant chemotherapy. Differences in stage distribution and adjuvant therapy between both groups was statistically significant(p-value 0.0005, 0.02 respectively). Median follow-up time was 2.33 years. When compared to KRASwt, OS for KRASm at 3 years was higher, though not statistically significant(80.7% vs. 76.2%; HR-all-cause mortality 0.57,CI[0.23, 1.41];p-value 0.21). When compared to KRASwt, RFS for the KRASm at 2.4 years was 74.1% vs 71.9% (HR-recurrence 0.61 [0.28,1.32];p-value 0.22)(Figure 1). For stage II & III, RFS at 2.4 years was statistically significant(78.2% vs. 65.9%,HR-recurrence 0.35,CI [0.13,0.96];p-value 0.04). This difference remained statistically significant(HR 0.32,CI[0.12,0.90];p-value 0.03) when adjusted for age, sex, smoking status, adjuvant therapy and completeness of resection.

Conclusions: Among patients in Southwestern Ontario with resected stage I-III NSCLC, KRASm was associated with improved RFS in more advanced stages. This difference remained significant after adjustment for adjuvant therapy and completeness of resection. It is possible that KRAS in this population may serve as a prognostic factor. However, the exact mechanism behind this remains to be elucidated. These data may provide context to emerging clinical trials and an opportunity to explore novel targeted therapeutics for this population.



Keywords: Non small cell lung cancer, KRAS, resection

EP02.01-014 Prognostic Classification of Early-Stage Lung Cancer Using Preoperative Prealbumin and D-dimer Levels

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Introduction: The relationship between the level of inflammatory indicators and the development and progression of lung cancer have been reported. However, few studies have compared the prognostic impact of various inflammatory markers in patients with early-stage lung cancer. Therefore, this study aimed to explore the preoperative blood test markers that are strongly associated with long-term prognosis in patients with early-stage lung cancer.

Methods: We retrospectively examined patients with lung cancer who underwent surgery from 2011 to 2018. The impact of 12 preoperative blood test values on the overall and recurrence-free survival was compared, and a prognostic classification using blood test markers was established. The prognostic impact of the classification was evaluated by multivariable Cox proportional hazard model analysis, including age, sex, surgical procedure, smoking index, tumor size, respiratory function, comorbidity, and histology.

Results: A total of 1,742 patients were included in this study. The abnormal prealbumin and D-dimer levels were independent associated factors for overall and recurrence-free survival among blood test values. The patients were divided into three groups according to prealbumin and D-dimer levels: group A with normal levels of both, group B with abnormal levels of one, and group C with abnormal levels of both. The significant difference in overall survival ($p < 0.001$) and recurrence-free survival ($p < 0.001$) after surgery was found between the three groups. Multivariable analysis showed that groups B and C were independently associated with poor overall survival (hazard ratio: 1.48, $p = 0.004$) and recurrence-free survival (hazard ratio: 1.36, $p = 0.007$).

Conclusions: Prognostic classification using prealbumin and D-dimer levels was significantly associated with the long-term prognosis of patients with clinical stage I lung cancer.

FIGURE 1.

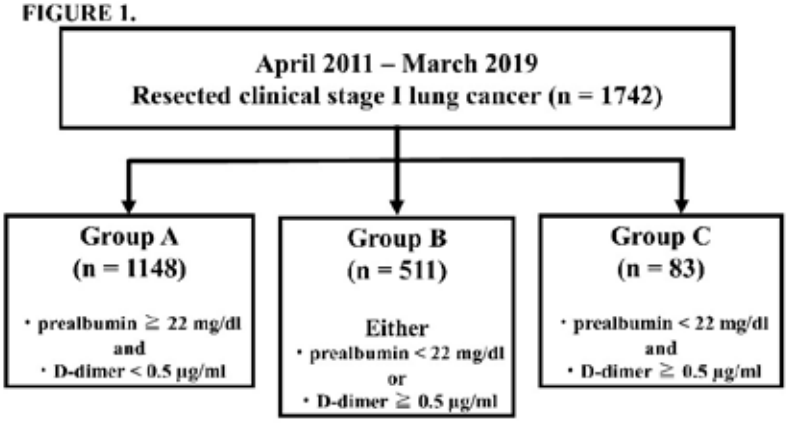
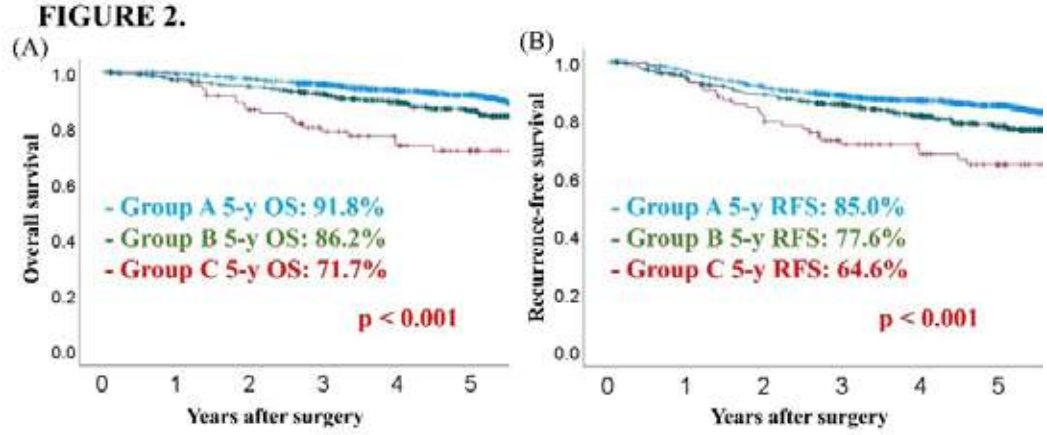


FIGURE 2.



Patients at risk						
Group A	1148	1126	1082	980	796	613
Group B	551	480	459	408	320	235
Group C	83	82	70	53	43	31

Patients at risk						
Group A	1148	1097	1017	908	737	567
Group B	551	468	431	378	295	218
Group C	83	78	66	50	41	31

Keywords: Early-stage lung cancer, prealbumin, D-dimer

EP02.01-015 Computer-Aided Volumetry by Multidetector Computed Tomography is Efficient for Prognostic Prediction of Early-Stage Solid Lung Cancers

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Introduction: On the basis of computed tomography (CT) findings, published recommendations for the clinical care of pulmonary nodules differentiate between solid and subsolid nodules, and solid nodules have a significantly worse prognosis than subsolid nodules, even if the nodules are subcentimeter in size. The prognosis of patients with subsolid nodules is predicted by solid size of the tumor. However, there are almost no established criteria for assessing the prognostic relevance of solid tumors on CT. In this study, we investigated the association between three-dimensional (3D) volumetry value on CT scan and the postoperative prognosis in patients with early-stage solid lung adenocarcinoma.

Methods: Ninety patients with pathological Stage I lung adenocarcinoma appearing solid nodule on thin-section CT who underwent complete resection between 2008 and 2012 were analyzed. To investigate the correlation with postoperative disease-free survival (DFS), eligible patients' clinical information, pathologic reports and preoperative multidetector CT were reviewed. Two oncologists (including radiologist) determined the tumor size on the two-dimensional axial image (2DS), the 3D tumor volume (3DV), and the 3D solid volume between 0 and 199 HU on multiplanar reconstructed images (3DSV). The correlations between the recurrence and clinicopathological characteristics, 2DS, 3DV, and 3DSV were analyzed by using a Cox proportional hazards model.

Results: The median follow-up period was 67 months. The recurrence was found in 26 patients (28.9%). The mean 2DS was 22 mm in non-recurrent patients and 25 mm in recurrent patients. The mean 3DSVs were 5724 mm^3 and 9250 mm^3, respectively. 3DSV (P = 0.019) was significantly different between non-recurrent and recurrent patients, although 2DS, serum CEA level and SUVmax on FDG PET/CT were not. The DFS curves stratified by 3DSV-derived diameter more accurately classified postoperative survival than ones stratified by 2DS (log-rank test for 2DS: P =0.696, 3DSV: P = 0.015, Figure). The multivariate analysis indicated that significant predictive factors for DFS were 3DSV (hazard ratio, 2.24; 95% CI, 1.21 to 4.15), pleural invasion (hazard ratio, 1.85; 95% CI, 1.06 to 3.21) and EGFR mutation (hazard ratio, 2.47; 95% CI, 1.12 to 5.43).

Conclusions: The assessment of 3DSV predicted the postoperative prognosis in patients with early-stage solid lung adenocarcinoma more accurately than those of 2DS, 3DV, serum CEA level and SUVmax on FDG PET/CT.

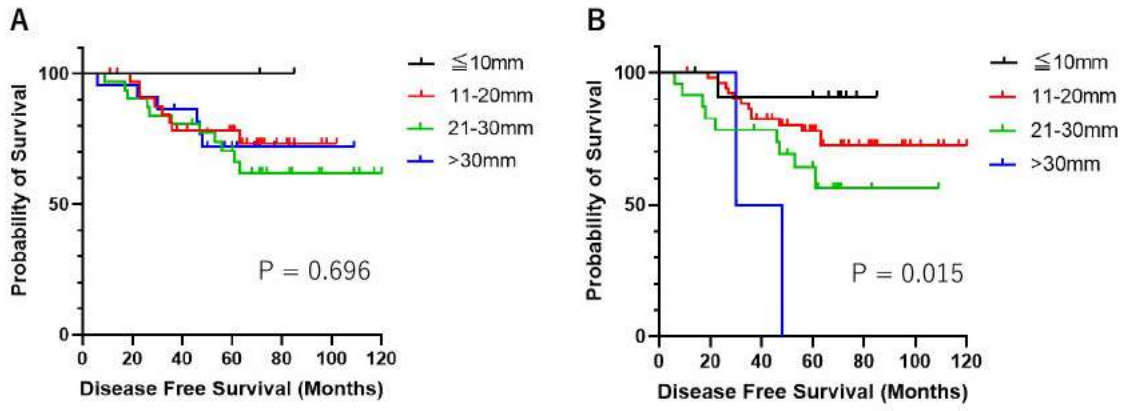

Figure. Disease free survival curves stratified by 2DS (A) and 3DSV-derived diameter (B) in Stage I solid lung adenocarcinoma

Keywords: Solid lung adenocarcinoma, Prognostic prediction, Computer-aided volumetry

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-016 Molecular Alterations and Clinical Prognostic Factors in Resectable Non-Small Lung Cancer

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Introduction: EGFR-TKI and immunotherapy have been recently approved for adjuvant treatment in resectable NSCLC. Limited reports of both molecular and clinical characteristics as prognostic factors have been found. We aimed to explore prevalence EGFR mutation (*EGFRm*), PDL-1 expression and clinical correlations as the prognostic factors in this population.

Methods: Electronic medical record was reviewed of resectable NSCLC stage I-III whom diagnosed in Ramathibodi hospital during 2015-2020. Realtime-PCR by Super-ARMs kit was used for *EGFR* testing (exon 18-21, 42 mutations). Tissue microarray for immunohistochemistry staining (IHC) was used for *ALK* fusion and PDL-1 expression (SP263 and 22C3) testing. Categorical variables were compared using Chi-squared test or Fisher's exact test. Univariate and multivariate analysis were performed by the Cox proportional hazard. *P*-value of less than 0.05 was considered statistical significance. Stata version 17 was used for all analysis.

Results: Total 441 patients were included, 3-year recurrent free survival (RFS) was 71% (95%CI 67-76%) and 3-year overall survival was 92% (95%CI 89-94%). Prevalence of *EGFRm* was 57.8%, ALK fusion was 1.9%, and PDL-1-positive by SP263 was 20.5%. The agreement of SP263 and 22C3 Ab was 93.4% (Kappa 0.78). Most common *EGFRm* were *Del19* (43%) and *L858R* (41%), followed by combined mutations (9.9%) and uncommon mutations (5.7%). Prevalence of *EGFRm* patients were 59.6%, 69.6%, 40%, 49%, 57.5%, and 45.5% in stage IA, IB, IIA, IIB, IIIA, and IIIB, respectively. There was no significant difference of recurrence-free survival (RFS) by *EGFRm*. However, RFS was significantly lower in PDL-1-positive patients compared to PDL-1-negative patients (HR 1.75, 95%CI;1.03-2.98, P=0.036). Dual positive of *EGFRm* and PDL-1 had significantly worst RFS compared with either double negative patients (HR 2.21 95%CI 1.09-4.48 P = 0.027) or *EGFRm* and PDL-1-negative patients. Furthermore, *EGFRm* patients had significantly higher of 3-year overall survival (OS) rate compare to *EGFR*-WT patients (HR=0.31, 95%CI 0.16-0.57, *P*<0.001). Sixty-two out of 192 (32%) *EGFRm* patients had recurrent disease and 46 of them received EGFR TKIs which probably affected the OS. Multivariable analysis showed higher CEA at cutoff 3.8 ng/ml, pT4, pN1/pN2 and margin were significantly poor prognostic factors for predicting RFS in all population, which was similar to *EGFRm* population except T-stage. While only pathological stage was significantly poor prognostic factor for PDL-1-positive patients. The predictive score of all patients, EGFRm and PDL-1-positive populations will be reported at the congress.

Conclusions: In resectable lung cancer, *EGFRm* prevalence, types of *EGFRm,* and PDL-1-positive prevalence were similar to advanced stage NSCLC. There was no *EGFRm* prevalence difference in each stage of disease (I-III). The OS was significantly longer in *EGFRm* patients which might be the effect of EGFR TKIs treatment in the recurrent patients. *EGFRm* and PDL-1 expression were proved in this research as the important prognostic factors for resectable NSCLC. Adjuvant EGFR-TKI treatment may play important role in both *EGFRm* and PDL-1-positive patients in developing countries as well as adjuvant immunotherapy should be considered in PDL-1-positive patients. The validation study of predictive score for resectable lung cancer is under investigated in larger cohort.

Keywords: Resectable lung cancer, EGFR mutation, prognostic factors

EP02.01-017 The Role of Adjuvant Chemotherapy for Stage II/III Lung Adenocarcinoma Based on Epidermal Growth Factor Receptor Mutation Status

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Introduction: The effect of adjuvant chemotherapy for tumors with epidermal growth factor receptor (EGFR) mutation has not been fully elucidated. The aim of this study was to evaluate the role and effect of adjuvant chemotherapy based on EGFR mutation status in patients with stage II/III lung adenocarcinoma.

Methods: Between 2010 and 2016, 362 patients with stage II/III (8th edition) lung adenocarcinoma who underwent lobectomy with nodal dissection were identified. We calculated propensity scores to adjust for confounding variables associated with the application of adjuvant chemotherapy. The variables included age, sex, smoking status, adenocarcinoma subtype, stage, and EGFR mutation status. Cumulative incidence of recurrence (CIR), which accounted for death without recurrence as a competing event, adjusting the propensity score was compared between patients who received adjuvant chemotherapy and those who did not in patients with stage II/III lung adenocarcinoma with or without/unknown EGFR mutation.

Results: Of 257 patients without/unknown EGFR mutation, 135 (52.5%) received adjuvant chemotherapy and 122 (47.5%) did not. In 91 pairs of patients who were propensity score-matched, the 5-year CIR was significantly lower in those who underwent adjuvant chemotherapy (43.2%) than in those who did not (55.5%; P = 0.016). Propensity score adjusted multivariable analysis revealed that adjuvant chemotherapy was an independent prognostic factor for CIR (hazard ratio, 0.671; P = 0.040). Of 105 patients with EGFR mutation, 59 (56.2%) received adjuvant chemotherapy and 46 (43.8%) did not. In 25 pairs of propensity score-matched patients, there was no significant difference in the 5-year CIR between those who underwent adjuvant chemotherapy (58.3%) and those who did not (60.7%; P = 0.948). Propensity score adjusted multivariable analysis revealed that adjuvant chemotherapy was not an independent prognostic factor for CIR (hazard ratio, 0.861; P = 0.590).

Conclusions: The effect of adjuvant chemotherapy for stage II/III lung adenocarcinoma varied by EGFR mutation status. EGFR mutation should be tested in patients with stage II/III lung adenocarcinoma to decide the application of adjuvant chemotherapy. Patients with EGFR mutation may not benefit from adjuvant chemotherapy.

Propensity score-adjusted multivariable analysis for cumulative incidence of recurrence				
		Hazard ratio	**95% CI**	**P-value**
EGFR mutation negative/unknown	Adjuvant chemotherapy	0.671	0.459-0.981	0.040
EGFR mutation positive	Adjuvant chemotherapy	0.861	0.500-1.481	0.590

Keywords: EGFR mutation, Adjuvant chemotherapy, Lung adenocarcinoma

EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS

EP02.01-018 EGFR Mutations Promote Lung Adenocarcinoma From Adenocarcinoma in Situ to Minimally Invasive Carcinoma to Invasive Adenocarcinoma

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Introduction: The differences in gene alterations among the three lung adenocarcinoma (LUAD) stages of adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IAC) are unclear, and few studies have evaluated EGFR mutations for their prognosis.

Methods: Using a single-center high-volume database, patients with a single malignant pulmonary nodule (≤3.0 cm) and postoperative pathology confirmed as pN0 stage were retrospectively analyzed, we investigated the impact of EGFR mutation status on LUAD ranging from AIS to MIA and then to IAC, and asesed the effect of EGFR mutation status on disease-free survival (DFS) and overall survival (OS) in patients with LUAD.

Results: Among the 762 LUAD cases, 136 were AIS, 131 were MIA, and 495 were IAC (pT1N0M0), EGFR mutations were identifiied in 361 patients (47.4%). Notably, EGFR mutation rate in AIS was 33.1%, which was much lower than 51.1% in MIA and 50.3% in IAC, P=0.001. Further analysis showed that EGFR mutations were more prevalent in women (P=0.001), non-smokers (P<0.001), and tumors greater than 2cm in diameter (P=0.004). A total of 21 patients with recurrence and metastasis were all IAC, without AIS and IAC. For patients diagnosed as IAC, we found that patients with EGFR mutations had longer DFS compared to EGFR wild-type patients, and we found the same results in OS.

Conclusions: Increased frequency of EGFR mutations mediates the progression of LUAD from glandular precursor lesions to IAC. EGFR mutation is a predictor of better prognosis in LUAD patients diagnoses as pT1N0M0.

Keywords: EGFR mutations, adenocarcinoma in situ, lung adenocarcinoma

EP02.02 EARLY STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY

EP02.02-001 Genome-wide Analysis and Dynamic Changes of Human Non-small Cell Lung Carcinoma Cells After Radiation

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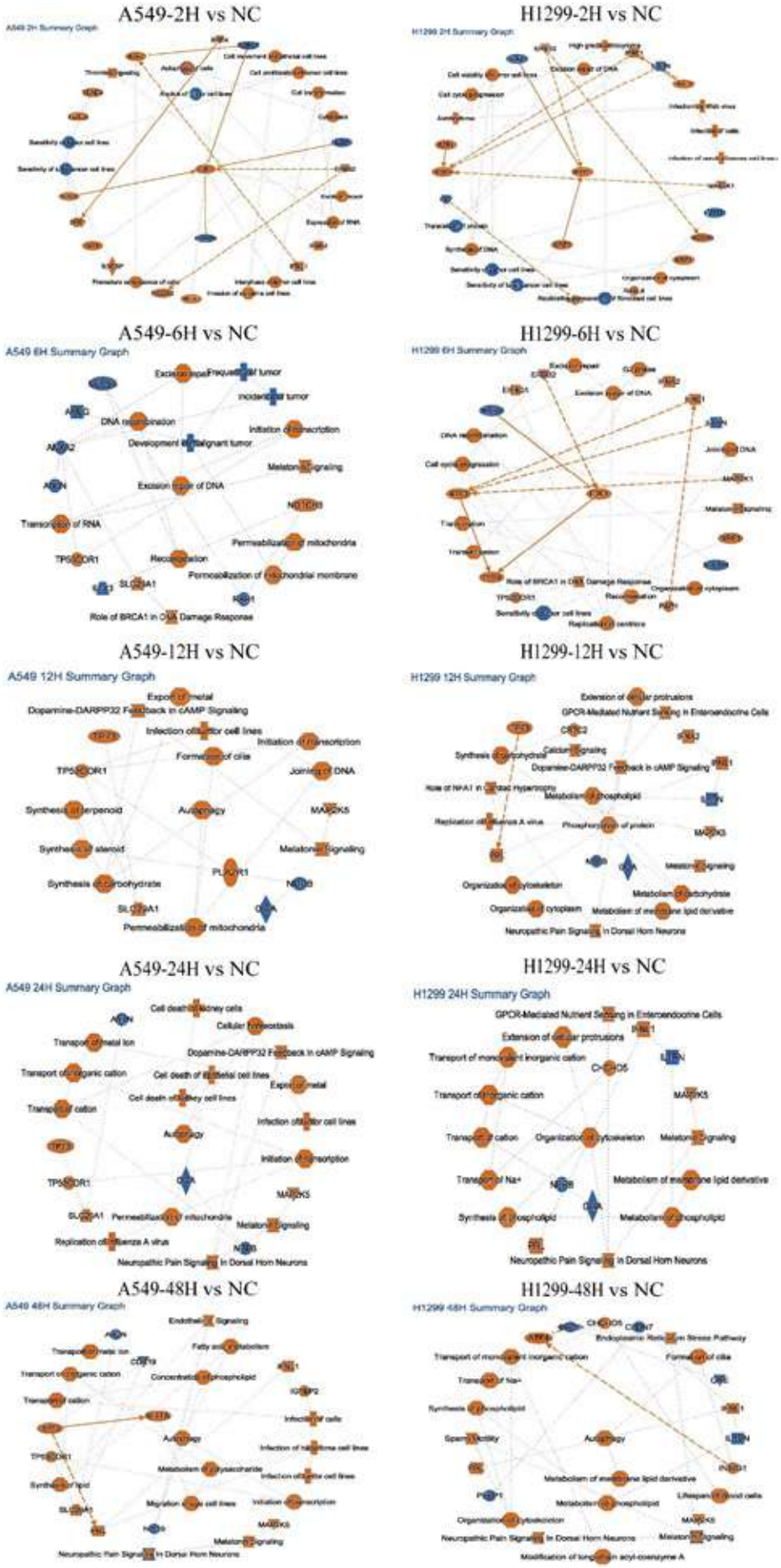
Introduction: Non-small cell lung cancer is malignant tumor.Precision radiotherapy has progressed rapidly.

Methods: A549 and H1299 were irradiated with 10Gy X-ray, and the cells were treated at different times (2, 6, 12, 24, 48 h), and the whole transcriptome sequence was performed together with the unlitated cells. Then, through a series of bioinformatics methods, the difference analysis of multiple points and angles is carried out. The stem algorithm was used to screen out the differential genes related to time change, and the differential mRNA, miRNA, circRNA, and lncRNA were analyzed, and GO and KEGG were analyzed to obtain the enriched functions and pathways. Functional analysis of differential mRNAs, disease correlation analysis, causal pathway correlation analysis, and multi-time point differential effect analysis were carried out with Ingenuity Pathway Analysis software. Subsequently, cell cycle changes at different times were detected by cell cycle experiments, and CCNB1 was detected by qPCR and Western blot experiments.

Results: The results showed that there was no intersection of RNA in various time periods after radiotherapy, indicating that the genome of lung adenocarcinoma was in a significant dynamic change within 48 hours after radiation. The differential RNA related to time change was analyzed for ceRNA to obtain network. MiR-219-1-3p is located in the core of the ceRNA. The first 30 mRNAs with obvious enrichment were found to include glucose metabolism and insulin pathways. The results of IPA pathway software showed that the gene set function of lung adenocarcinoma in the early stage of radiation was centered on the regulation of cell cycle-related transcription factor E2F1, and autophagy was mainly in the later stage, and the toxicity pathway analysis showed that 10Gy radiation was toxic to kidney and liver. We conducted cell cycle experiments and found that the G2/M stage cell cycle block of lung adenocarcinoma was the most severe at 24 hours after radiation, and the corresponding PCR and WB experiments showed the cell cycle-related protein CCNB1 whose content is highest at 24 h after radiation.

Conclusions: Through the effect of short-range and high-dose radiation on non-small cell lung cancer, this study found the key molecules, network regulation, disease pathways (such as CREB Signaling in Neurons) that affect NSCLC from the perspectives of genomics and timing. Toxic pathways (such as kidney and liver-related pathways) provide high-throughput data for basic experiments, which can provide basic data for radiotherapy and guidance and basis for clinical combination treatment options.



Keywords: radiation, non-small cell lung cancer, whole transcriptome sequencing

EP02.02 EARLY STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY

EP02.02-002 Increased Utilization of Stereotactic Body Radiotherapy Has Decreased Treatment Disparities for Early-Stage NSCLC

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EP02.02-003 Mean Lung Dose Correlates with Volume of Radiation-Induced Lung Injury in Patients Treated with SABR for Lung Cancer

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Introduction: Stereotactic ablative body radiotherapy (SABR) is the standard of care for patients with early-stage lung cancer who are unable to undergo surgery. Although SABR is generally well-tolerated, radiation-induced lung injury (RILI) can occur in up to 58% of treated patients, which can be difficult to distinguish from local recurrence in follow-up imaging. Predictive markers that identify patients at greater risk of RILI may aid in the interpretation of post-treatment imaging. In this retrospective study, we investigated whether dosimetric data correlate with the relative volume of post-treatment RILI.

Methods: Included patients had consented to participate in a study investigating biomarkers in patients receiving SABR for early-stage lung cancer, with both histologically and radiologically diagnosed disease included. 21 patients underwent SABR, receiving 54 - 60Gy over 3 - 8 fractions. The 4-month post-treatment scans of all 21 patients and the 12-month post-treatment scans of 18 patients were imported into *Eclipse* radiotherapy planning software. Areas of lung damage volume were outlined by a senior clinical oncology trainee and reviewed by a consultant radiologist. The *relative volume of lung damage* was calculated by dividing the total lung damage volume by the total volume of the treated lung. The *prescribed dose, planned treatment volume, maximum lung dose* and *mean lung dose* delivered to the treated lung were obtained from the radiotherapy plans and dose volume histograms. Regression analyses were carried out with the planning data as the input variables and *relative volume of lung damage* as the output.

Results: On the 4-month follow-up CT scans, the amount of *relative volume of lung damage* ranged from 0.02% to 12.04%, with a median of 0.49%. On the 12-month follow-up scans, *relative volume of lung damage* ranged from 0.03% to 5.17%, with a median of 1.13%. From regression analyses, *mean lung dose* most strongly correlated with *relative volume of lung damage* visible on the 4-month and 12-months scans with $R^2 = 0.3301$ ($P = 0.0064$) and $R^2 = 0.3342$ ($P = 0.012$) respectively (Figure 1).

Conclusions: Mean lung dose correlates with the relative volume of radiation induced lung injury visible on post-treatment CT at 3-4 months and 12 months after SABR for lung cancer. Further work will help establish whether dosimetric data can be used to predict the degree of expected lung injury and aid with the interpretation of post-treatment imaging by identifying patients at higher risk of radiation-induced lung injury.

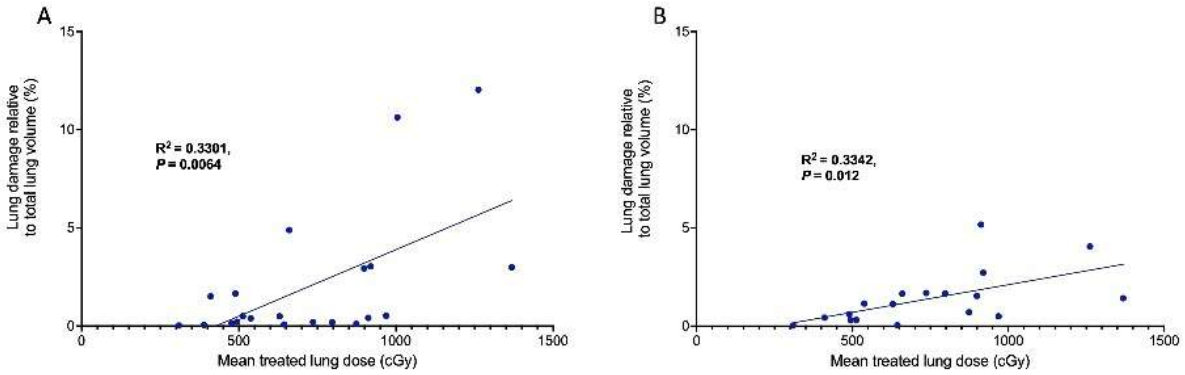

Figure 1: Scatter plot demonstrating the mean treated lung dose as per treatment planning dose volume histograms against relative volume of radiation-induced lung injury at **(A)** 3 – 4 months post-treatment and **(B)** 1 year post-treatment.

Keywords: Stereotactic ablative body radiotherapy, Early-stage lung cancer, Radiation induced lung injury

EP02.02 EARLY STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY

EP02.02-004 Clinical Outcomes Following Photon-Based and Proton-Based Stereotactic Body Radiation Therapy for Early Stage Lung Cancer

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Introduction: To report clinical outcomes of photon-SBRT and proton-SBRT in early stage lung cancer patients who are unfit for surgery.

Methods: Between 2010 and 2019, 210 cT1-2N0M0 lung cancer patients underwent SBRT: 172 by photon-SBRT; and 38 by proton-SBRT, respectively. Proton-SBRT started clinical application since 2017, which was allocated more frequently to patients with underlying lung disease and/or poor pulmonary function test (PFT) results (Table 1). Under the same target delineation policy, 60 Gy (or GyRBE) in 4 consecutive fractions were prescribed to all patients. We compared oncologic outcomes and morbidities following each treatment modality.

Results: Oncologic outcomes at 3 years were not different between arms (Table 2): LFFS (90.3% vs. 84.1%, p=0.648); PFS (63.9% vs. 60.0%, p=0.894); CSS (77.0% vs. 84.7%, p=0.655); and OS (65.6% vs. 71.4%, p=0.977), respectively. Though insignificant, toxicity profiles were, more or less, favorable following proton-SBRT (Table 2): overall (31.4% vs. 21.1%, p=0.206); pulmonary (16.9% vs. 15.8%, p=0.873); chest wall (12.2% vs. 5.3%, p=0.265); skin (4.1% vs. 0.0%, p=0.355), respectively.

Conclusions: Considering similar toxicity profiles and oncologic outcomes, proton-SBRT could be regarded as reasonable alternative to photon-SBRT especially in patients with high risk of pulmonary toxicity.

Table 1. Underlying lung disease status and pre-SBRT PFT of patients

	2010-2016	2017-2019		P value
	Photon-SBRT (N=81)	Photon-SBRT (N=91)	Proton-SBRT (N=38)	
COPD	22 (27.2%)	42 (46.2%)	26 (68.4%)	0.034
ILD	9 (11.1%)	10 (11.0%)	6 (15.8%)	0.559
Median FEV1 (%)	79.5 (64.0~98.0)	78 (63.0~90.0)	68 (58.0~79.0)	0.025
Median DLCO (%)	79 (63.5~93.5)	66 (55.0~80.5)	51 (38.0~61.0)	<0.001

Table 2. Oncologic outcomes and toxicities of photon-SBRT and proton-SBRT.

	Photon-SBRT (N=172)	Proton-SBRT (N=38)	P value
Oncologic outcomes			
LFFS			0.716
1-year	98.70%	100.00%	
3-year	91.00%	85.10%	
PFS			0.499
1-year	87.30%	86.50%	
3-year	64.00%	58.30%	
CSS			0.895
1-year	96.30%	97.20%	
3-year	81.70%	85.10%	
OS			0.750
1-year	91.20%	92.10%	
3-year	69.80%	72.20%	
Toxic events			
Overall	54 (31.4%)	8 (21.1%)	0.206
Pulmonary	29 (16.9%)	6 (15.8%)	0.873
Chest wall	21 (12.2%)	2 (5.3%)	0.265
Skin	7 (4.1%)	0 (0.0%)	0.355

Keywords: SBRT, Photon, Proton

EP02.02-005 Changes in PFT Parameters and Correlation with Symptomatic Pulmonary Toxicity Following SBRT For Early Stage Lung Cancer

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Introduction: To report changes in pulmonary function test (PFT) following stereotactic body radiation therapy (SBRT) for early stage lung cancer patients.

Methods: Between 2010 and 2019, 210 patients with cT1-2N0M0 lung cancer underwent SBRT of 60 Gy (or 60 GyRBE) in 4 consecutive fractions either by photon or proton, among who baseline and ≥2 post-SBRT PFTs obtained within two years were available in 46. RTOG PFT toxicity scale, reflecting changes of PFT parameters from baseline values, were comparatively evaluated in relation with pulmonary toxicity.

Results: Included patients generally had poor baseline PFT: FEV1 of 1.9 L; predicted FEV1 of 68.9%; predicted FVC of 83.1%; and predicted DLCO of 57.5%, respectively. Significant decreases in post-SBRT FEV1 (-5.31%, p=0.028) and predicted FVC (-4.80%, p=0.025) occurred in 1.5 years and predicted DLCO (-8.58%, p=0.032) did in 2 years, respectively. Grade ≥2 pulmonary toxicity was observed in ten patients (22.2%), and serial changes of PFT values and its relation with pulmonary toxicity are summarized in Table 1 and Figure 1. In the binary logistic regression analyses, significant PFT changes in relation with pulmonary toxicity included 1-year predicted FEV1 (OR 0.916, p=0.044), and 1.5-year FEV1 (OR 0.933, p=0.040), predicted FEV1 (OR 0.937, p=0.050) and predicted FVC (OR 0.925, p=0.044), respectively.

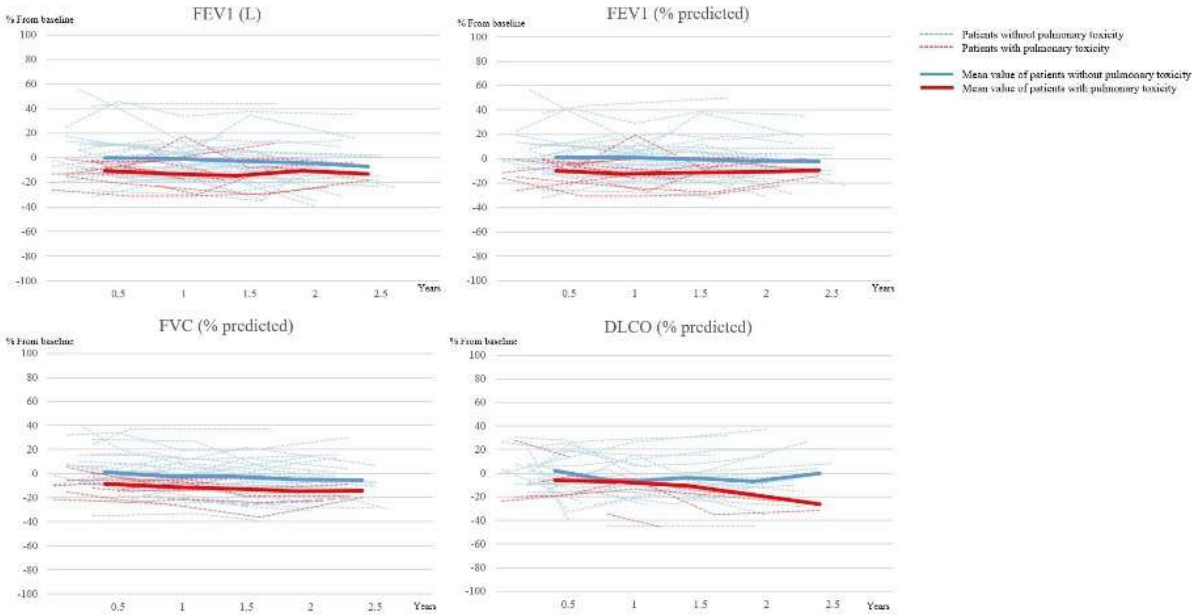
Conclusions: Post-SBRT decrease in PFT parameters began apparently in 1.5 to 2-years following SBRT, and PFT changes seemed co-related to symptomatic pulmonary toxicity.

Table 1. Serial post-SBRT PFT changes and RTOG PFT toxicity

PFT change	Baseline		0.5-year			1-year			1.5-year			2-year			After 2-year		
	N	Nominal	N	% from baseline	P value	N	% from baseline	P value	N	% from baseline	P value	N	% from baseline	P value	N	% from baseline	P value
FEV1 (L)	46	1.91 ± 0.61	35	-2.07 ± 18.52	0.512	40	-2.90 ± 17.44	0.299	39	-5.31 ± 14.56	0.028	32	-5.39 ± 19.39	0.126	31	-8.18 ± 15.56	0.006
FEV1 (% predicted)	46	68.91 ± 21.48	35	-0.99 ± 17.72	0.744	40	-1.59 ± 16.75	0.553	39	-3.06 ± 14.19	0.186	32	-3.62 ± 20.01	0.315	31	-3.18 ± 14.86	0.174
FVC (% predicted)	46	83.11 ± 20.02	35	-0.75 ± 16.27	0.789	40	-4.29 ± 14.77	0.074	39	-4.80 ± 12.81	0.025	32	-6.57 ± 17.08	0.037	31	-6.99 ± 14.32	0.011
DLCO(% predicted)	46	57.46 ± 18.43	26	0.60 ± 15.51	0.846	29	-7.46 ± 19.86	0.053	22	-5.42 ± 16.17	0.13	22	-8.58 ± 17.49	0.032	17	-4.67 ± 21.01	0.373

PFT toxicity	Any time		0.5-year			1-year			1.5-year			2-year			After 2-year		
	N	Grade 2	N	Grade 1	Grade 2	N	Grade 1	Grade 2	N	Grade 1	Grade 2	N	Grade 1	Grade 2	N	Grade 1	Grade 2
FEV1 (L)	46	9 (20.0%)	35	8 (22.9%)	4 (11.4%)	40	16 (40.0%)	1 (2.5%)	39	11 (28.2%)	5 (12.8%)	32	9 (28.1%)	4 (12.5%)	31	11 (35.5%)	3 (9.7%)
FEV1 (% predicted)	46	9 (20.0%)	35	6 (17.1%)	4 (11.4%)	40	12 (30.0%)	1 (2.5%)	39	8 (20.5%)	3 (7.7%)	32	9 (28.1%)	4 (12.5%)	31	6 (19.4%)	2 (6.5%)
FVC (% predicted)	46	6 (13.3%)	35	5 (14.3%)	1 (2.9%)	40	14 (35.0%)	1 (2.5%)	39	10 (25.6%)	2 (5.1%)	32	10 (31.3%)	5 (15.6%)	31	10 (32.3%)	3 (9.7%)
DLCO(% predicted)	37	12 (32.4%)	26	6 (23.1%)	0 (0.0%)	29	7 (24.1%)	7 (24.1%)	22	4 (18.2%)	3 (13.6%)	22	10 (45.5%)	2 (9.1%)	17	3 (17.6%)	3 (17.6%)

Figure 1. post-SBRT change of PFT parameters



Keywords: SBRT, pulmonary function test, pulmonary toxicity

EP02.02 EARLY STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY

EP02.02-006 Differing Doses: The Effects of Radiation Dose Calculation Algorithms on Local Control in Early-Stage Lung Cancer

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Introduction: Stereotactic body radiation therapy (SBRT) is an established treatment option for stage I non-small cell lung cancer (NSCLC). Dose calculation for SBRT in lung tissue is highly complex due to significant density heterogeneity in both the target tissue and beam path. Dose calculation algorithms employed clinically, including Pencil Beam Convolution (PBC), convolution-superposition Anisotropic Analytical Algorithm (AAA), and Acuros XB (AXB), have varying levels of accuracy when compared with the gold standard, Monte Carlo. These differences may be clinically significant in patients, particularly in the lung. Their impact on cancer outcomes is not well elucidated. We analyzed the magnitude of dose calculation differences between PBC, AAA, and AXB in patients receiving SBRT for lung cancer and their impacts on local tumor control.

Methods: As part of an IRB-approved study, data were collected on all patients treated with SBRT at our institution for early-stage NSCLC between 2007 and 2018. Patients with <6 months follow-up were excluded. Clinical patient and tumor characteristics were collected along with treatment details and patterns of failure. All PBC and AAA plans were recalculated using AXB, and a subset of plans were recalculated with Monte Carlo to validate the accuracy of AXB. Dosimetric data including mean dose to the planning target volume (PTV), the near maximum dose (the minimum dose received by the hottest 1% of the PTV, PTV D1%), the minimum dose received by 99% of the PTV (PTV D99%), internal target volume (ITV) D1%, ITV D99%, and volume of the PTV receiving 100% of the prescription dose (PTV V100%) were collected for PBC, AAA, and AXB plans. Given the variety of fractionation schedules, doses for all patients were normalized to BED using an alpha/beta ratio of 10 Gy. Death without failure was treated as a competing risk.

Results: During the time interval, 126 patients were eligible and analyzed. Dose statistics from AXB were comparable with Monte Carlo. When AAA was used, multivariable linear regression revealed an expected difference from AXB in mean PTV dose for 15X, 10X, and 6X beam energy of -9.1%, -5.9%, and -3.6% respectively. AAA overestimated PTV mean dose relative to AXB by 0.8% per 500cc increase in total lung volume likely due to increased beam path through lung. Median follow-up was 26 months. Of the 126 patients analyzed, 15 experienced local failure. On univariate analysis, decreases in calculated PTV D1 and ITV D1 between AXB and the original plan were associated with significant increases in local failure (p=0.04 and 0.022 respectively). On multivariable analysis controlling for PTV volume, the relationship with ITV D1 remained significant (p=0.038) with a trend towards significance for PTV D1 (p=0.057).

Conclusions: This comparison of dose calculation algorithms in a cohort of early-stage NSCLC patients revealed significant decreases in dose for every metric collected due to overestimation by initial PBC/AAA calculation. The magnitude of decrease in calculated PTV D1 and ITV D1 was associated with statistically significant inferior rates of local control. Improvements in dose calculation algorithms may lead to improved clinical outcomes for these patients.

Keywords: Early stage lung cancer, Stereotactic body radiation therapy, Dose calculation algorithms

EP02.02 EARLY STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY

EP02.02-007 Correlation between Biological Equivalent Dose and Radiological Changes after Lung Stereotactic Ablative Radiation Therapy

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Introduction: Stereotactic ablative radiation therapy (SABR) is the standard of care for inoperable early-stage NSCLC offering excellent local control. Although the related probability of grade ≥2 toxicities is low, 60-100% of the patients present radiological toxicities. Even though these changes may not lead to direct clinical consequences, some are associated with future clinical toxicities and long-term patient management challenges. In this study, we evaluated radiological changes after SABR and correlated them with the received Biological Equivalent Dose (BED).

Methods: We retrospectively analyzed CT scans of 50 patients treated with SABR between 2017 and 2021. An experienced radiologist evaluated the radiation-related changes 6 months and 2 years after SABR. The presence/absence of organizing pneumonia-like changes and bronchiectasis, the extension of consolidation pattern, and the percentage of the affected lung (in 25% steps) were recorded. Dose-volume histograms of the lung were transformed to BED (considering an alfa/beta of 3). Clinical parameters such as age, smoking habits, and other pathologies were registered. Correlations were evaluated using Pearson (for quantitative variables), Chi-Square test (qualitative variables), or Anova analysis (other cases) and considered statistically significant for $p<0.05$.

Results: In the 6 months follow-up scans we observed a positive and statistically significant correlation between lung BEDs higher than 300Gy and the presence oforganizing pneumonia-like changes. The degree of lung affectation also correlated with BEDs higher than 320Gy. We found a positive and statistically significant correlation between the 2-year prevalence and/or increase of these radiological changes with BEDs greater than 300Gy. All our patients that received a BED dose greater than 300Gy to a volume greater or equal than 30cc showed radiological changes at 6 months that increased or remained in the 2 years follow-up scan. This BED corresponds to 16 Gy in 3 fractions, 12Gy in 5 fractions, or 9Gy in 8 fractions, which are within the expected dose values for SABR treatments. We found no statistically significant correlation between radiological changes and the clinical parameters we took into consideration, except for the patients with chronic obstructive pulmonary disease which showed a lower risk of consolidation and organizing pneumonia-like changes patterns only in the 6 months scan.

Conclusions: There seems to be a clear correlation between BEDs higher than 300GyBED and radiological changes in the lung parenchyma both short and long term. If confirmed in an independent patient cohort, these findings could lead to the first radiotherapy dose constraints for grade I pulmonary toxicity.

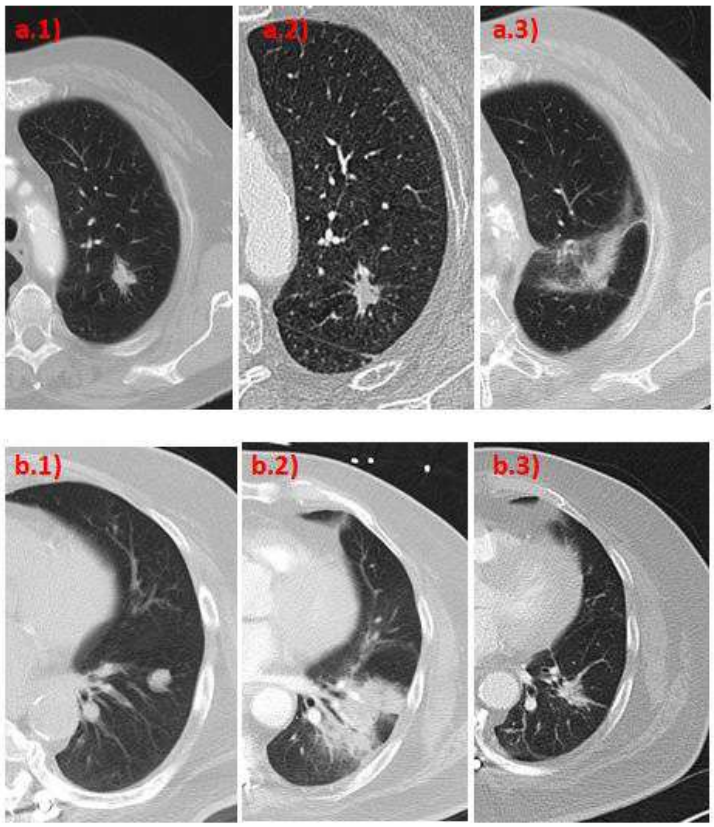

Figure1. Axial CT images a.1) Pre-treatment a.2) 6 months and a.3) 2 years follow-up CT scans for the same patient. This patient received V300GyBED=31cc in a left upper lobe pulmonary nodule, and late changes in the parenchyma can be seen with organizing pneumonia-like changes. b.1) Pre-treatment CT scan b.2) 6 months and b.3) 2 years follow-up CT scan for the same patient. This patient received V300GyBED=0cc in a left lower lobe pulmonary nodule, showing late changes with a consolidation pattern at 6 months follow up CT, with radiological improvement at 2 years.

Keywords: Biological Equivalent Dose, Toxicity, Stereotactic Ablative Radiation Therapy

EP02.02 EARLY STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY

EP02.02-008 Transbronchial Microwave Ablation of Lung Nodules - Good Safety Profile and Promising Mid-Term Results

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Introduction: Microwave ablation of lung nodules provides a faster, larger and more predictable ablation zone than its predecessor radiofrequency energy, while bronchoscopic ablation has theoretical advantage of less pleural-based complications than percutaneous approach. The combination of bronchoscopic approach and microwave ablation is a novel approach in local treatment of lung nodules. Its safety and mid-term results are presented here.

Methods: Ninety lung nodules in 73 patients who underwent electromagnetic navigation bronchoscopy microwave ablation in hybrid operating room from March 2019 to February 2022 were retrospectively reviewed. Patients either refused surgery or had significantly high surgical risks. Eligible lung nodules were either proven lung cancers, metastases, or radiologically suspicious. Feasibility, safety and mid-term control rate of the technique were assessed.

Results: Mean maximal diameter of lung nodules was 15.3mm (range 6-29mm), and bronchus sign was positive in 43% of them. Technical success rate was 100%, although 24 nodules required double ablation and 2 required triple ablation for adequate coverage. Mean minimal ablation margin was 5.4mm. There was no significant heat sink effect. Mean hospital stay was 1.57 days, 70 cases (78%) and 86 cases (96%) were discharged by post-ablation day 1 and 3 respectively. Complications included mild pain which did not require hospitalization (11.1%), pneumothorax requiring drainage (5.6%), post-ablation reaction (3.3%), pleural effusion (2.2%) and hemoptysis (1.1%). For the 42 nodules which had completed 1-year follow up computer tomography scan, 3 had complete response, 27 had partial response, 9 had stable disease, and only 3 (7.1%) had progressive disease at ablation site. Median follow up for all cases is 18 months, of which 4 cases had ablation site recurrence, and 2 had recurrence within same lobe but distant to ablation site. Average progression-free interval was 6.7 months for the locally recurred cases. Risk factors for recurrence include larger solid nodules and intra-operative atelectasis which affect image quality and margin determination.

Conclusions: Transbronchial microwave ablation is a safe and novel ablative technique for early stage lung cancers, lung metastases or highly suspicious lung nodules in selected cases, and has an encouraging mid-term local control rate. Important selection criteria include anatomical considerations and disease factors.

Keywords: Microwave ablation, Electromagnetic navigation bronchoscopy, lung cancer

EP02.02 EARLY STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY

EP02.02-009 Stereotactic Body Radiotherapy for Primary and Metastatic Lung Cancer, Cyberknife-M6 Experience

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Introduction: It was aimed to evaluate the efficacy, local control and survival in patients with inoperable primary or metastatic lung cancer who underwent stereotactic body radiotherapy (SBRT) using the Cyberknife-M6 (CK-M6) with lung optimized treatment (LOT) module.

Methods: Ethics committee (no: 2018-7/6) and scientific research project (OUAP (T) 2019/1) approval were obtained. 23 lesions of 21 patients were treated between April 2019 to December 2020 at our department. The patients were immobilized in the supine position by wearing a Synchrony vest, with the hands at their sides. A planning 4D-CT was obtained in a free breathing modality. The gross target volumes was created both on the full-inhale and full-exhale phases and internal target volume (ITV) was created. By taking an image of patients on the treatment device, tracking modality was selected according to the visibility of the target. Zero-View tracking was applied in 10 patients, 1-View in 10 patients, 2-View in 1 patients. 3 to 5 mm margin added for planning target volume (PTV) according to tracking method. Median ITV and PTV was 9,38 (2-52,34) and 20,27 (9,25-82,7) cc, respectively. An InCise2 multileaf collimator optimized by the Monte Carlo algoritm was used in all patients. A pair of the orthogonal kV X-ray imaging systems were used for simultaneous target tracking. Median prescribed dose was 48 Gy in 4 fractions (30-54 Gy in 3-6 fractions) administered consecutively or every other day. Prescription isodose covering 95% of PTV was 82,5% (77,4-99,3). Median conformity and homogeneity index was 1,17 (1,02-1,77) and 1,22 (1,09-1,29), respectively. Median BED10 was 100 Gy (53,62-151,2) and median beam on time was 26 minutes (12-42).

Results: Patients were evaluated on January 2022. The median follow-up was 21 months (2-33). The median age was 68 (53-80) and 40% of the cases were adenocarcinoma. Two patients diagnosed with radiologically. Median lesion size was 13 mm (9-27). SBRT was applied to 13 primary tumors, 3 lung metastases and 7 lymph nodes. At initial evaluation, complete, partial and stable response was found 30%, 65% and 5%, respectively. During the follow-up, 3 patients locally recurred at a median of 11 months (9-14). The median and one-year local recurrence free survival was 22 months, and 89%. Acute and late grade 1-2 pulmonary complications was seen in 10 patients in a median of 7 months (2-13). While the cause of death in 6 cases was existent cardiac morbidity, covid19 pneumonia, lung infection (2) and progression (2), it was unknown in 1 patient. The median and one-year survival was 23 months and 95%.

Conclusions: LOT module of the CK-M6 Xsight lung tracking system allows for the application of fiducial-free motion management strategies. The advantage of our study is that the most appropriate tracking modality can be selected prospectively before treatment. In our study, excellent local control with a median survival of 23 months for primary and metastatic lung cancer. With a median treatment time 26 minutes, noninvasive CK-M6 based SBRT was efficient, safe and comfortable treatment in lung cancer.

Keywords: lung cancer, Cyberknife-M6, stereotactic body radiotherapy

EP02.02 EARLY STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY

EP02.02-010 Histology Impacts Time-to-Treatment on Lung SBRT Outcomes

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Introduction: Time-to-treatment (TTT) is considered an indicator of quality care that has been postulated to affect lung cancer outcomes. The process by which an early stage medically inoperable lung cancer patient (pt) is deemed appropriate for lung stereotactic body radiation therapy (SBRT) typically involves a multi-disciplinary assessment over extended time. This study analyzed a large single institution registry to explore the impact of TTT on SBRT outcomes.

Methods: From an IRB-approved lung SBRT registry, we identified 1573 pts treated definitively for early stage lung cancer between 2003 and 2020. TTT was defined as elapsed months between date of diagnosis (date of biopsy or date of PET CT in cases of radiographic diagnosis) and SBRT start date. Fine-Gray's Test was employed to evaluate the effect of TTT on local control (LC) and freedom from disease progression (FFP), and the long rank test was used for overall survival (OS). Cumulative incidence rates with death as competing event were calculated for LC and FFP. Actuarial analysis as used to calculate OS rates

Results: Median follow-up was 22.9 months. Median age at SBRT start in years was 74.5 (range 35-98), median KPS was 80 (range 40-100), 52.3% of pts were female and 84.0% were white. Median tumor size and median PET SUV max were 2.2 cm (range 0.4-10.5) and 7.5 (range 0.8-56), respectively; 88.3% of pts were stage I. Of 75.7% pts with biopsies, 30.6% were adenocarcinomas (AC), 27.8% had squamous carcinoma (SqC). Median SBRT dose was 50 Gy in 5 fractions (40.5% cases). The 2-year rates of LC, FFP and OS for all pts were 6.5%, 76.3%, and 62.6%, respectively. Median TTT was 1.7 months (range 0.2-18.1). Using a cut-off of 1.5 months to compare patients receiving upfront vs delayed treatment, there was no difference in LC (p=0.5644), FFP (p=0.1976) or OS (p=0.3018) between the two groups. Of 1038 pts with histologic diagnosis, TTT was associated with OS but not LC or FFP for SqC pts (p=0.0422), and with no AC outcomes. An association of TTT with FFP for pts aged 70-79 (p=0.0302) was seen but otherwise no significant differences were noted in TTT outcomes for pts stratified by T stage, age in decades or KPS. Pt and tumor characteristics were balanced between cut-off cohorts.

Conclusions: Although TTT per se was not associated with altered lung SBRT outcomes in this cohort of nearly 1600 early stage inoperable lung cancer pts, increasing TTT was found to have a negative association with OS for SqC pts on subset analysis. Previous studies have suggested impaired LC for SqC with SBRT although this was not seen in either of the TTT cut-off cohorts. Further work is warranted to determine how TTT may affect SBRT outcomes in the SqC population.

Keywords: time to treatment, lung sbrt, histology

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-001 The Role of Completion Lobectomy Following Sublobar Resection in Patients with T1 Non-Small Cell Lung Cancer

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Introduction: Although lobar resection is the standard approach for surgical resection, it has been shown that sublobar resections can also be performed in select patients. In our study, we aimed to analyze the survival of the patients with T1N0-1-2M0 who underwent completion lobectomy following sublobar resection.

Methods: Between January 2003 and August 2021, 233 patients with T1 NSCLC who were operated on in our clinic were retrospectively analyzed. There were 30 patients(12.9%) who had completion lobectomy (Group 1), whereas 23 patients(9.9%), 10(4.3%) and 70(30.0%) underwent wedge, and segmentectomy(Group 3), and lobectomy(Group 4) respectively. The groups were analyzed in terms of demographic characteristics, laboratory values, tumor characteristics, lymph node removed, N status, perineural invasion, lymphatic invasion, vascular invasion, presence of STAS, postoperative hospitalization day, amount of drainage, need for intensive care hospitalization, complications and survival.

Results: The mean survival of all analyzed patients was 147 months. At least one complication occurred in 4 patients (13.3%) who underwent completion lobectomy. There was no statistical significance in terms of tumor diameter and lymph node metastasis (i.e.N0, N1 and N2) between groupsa. There was also no statistically significant difference between the survivals of patients who had completion lobectomy and wedge resection(p=0.606). No statistically significant difference was found in terms of survival of patients who underwent completion lobectomy(79 months) and segmentectomy(76 months)(p=0.502). The survival of patients who underwent lobectomy (148 months) was higher than that of cases who had wedge resection (136 months) (p=0.029) and the patients who underwent segmentectomy(76 months). (p=0.023).

Conclusions: Since the mean survival rate is worse in patients with T1 NSCLC who underwent wedge resection and segmentectomy compared to the patients who underwent lobectomy, completion lobectomy is safe and should be performed in patients with T1 tumor undergoing sublobar resections

Keywords: sublobar resection, completion lobectomy, T1 lung cancer

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-002 Impact of Society and National Guidelines on Patient Selection for Lung Cancer Surgery in the UK from 2008 to 2013

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Introduction: Whilst guidelines are issued in abundance, little work has been undertaken to evaluate impact of their recommendations on acceptability by clinicians and to evaluate any change in practice. Of particular interest in this time frame in the UK, the simultaneous introduction of an opposing recommendation between professional society (BTS/SCTS) and national (NICE) guidelines on surgery for N2 disease, providing a unique opportunity to ascertain the practice of clinicians in the presence of direct conflicting clinical recommendation. The aims of this work are to determine the impact on patient selection for surgery three years before and after the introduction of 2010 BTS and 2011 NICE clinical practice guidelines items for consensus recommendation of patient selection for surgery by more permissive lung function parameters and conflicting recommendation on N2 stage.

Methods: We conducted a retrospective analysis of prospectively collected data by the National Lung Cancer Audit comprising all patients diagnosed with lung cancer between 2008 to 2013 within England and Wales. The project was approved by the Health Research Authority (HRA) as a service evaluation (IRAS ID 295021; REC reference 21/PR/0204). Surgical resections of any other chest cancer (sarcoma, mesothelioma, thymoma) and were excluded. Categorical data was summarised as frequency (%), continuous data was summarised as mean (SD). Linear and logistic regression analyses were used with each year as an independent categorical outcome to determine global and year specific changes in FEV1 and proportions with N2 undergoing surgery respectively. Statistical analyses and non-parametric test for trend (inbuilt Stata function) were conducted using Stata 16 (College Station, Texas, USA).

Results: From January 2008 to December 2013, 167,192 patients with primary lung cancers were included. The proportion of patients undergoing surgery for lung cancer increased from 9.5% in 2008 to 20.5% in 2013 ($p < 0.001$) as the number of thoracic surgeons in the UK increased from 40 to 81 in the corresponding timeframe.Mean FEV1 of surgical patients increased from 76% in 2008 to 81% in 2013 ($p < 0.001$). Of the patients undergoing surgery, the proportion of patients with N2 disease across the 6-year interval was broadly consistent between 8 to 11% without any evidence of trend ($P = 0.125$).

Conclusions: Within 3 years of publication of new recommendations for more permissive surgery in UK clinical guidelines, we did not observe any overall change in selection based that could be attributed to lower levels of lung function. Although surgical operations increased, the resection rates were more likely reflective of greater access to surgery by an increasing number of surgeons rather than any impact of guideline recommendations

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-003 Survival of Patients with Interstitial Lung Disease Who Undergoing Lung Cancer Surgery: A Propensity Score Matching Study

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Introduction: Patients with ILD may have a poor prognosis after lung cancer surgery due to respiratory complications and increased recurrence rate due to limited resection. Few studies have investigated the prognosis after surgery by matching variables with patients without ILD.

Methods: Medical records of patients who underwent lung cancer surgery between 2010 and 2020 at a referral hospital in South Korea were reviewed. ILD patients were determined by preoperative CT findings. Through propensity score matching using age, sex, smoking status, clinical stage, surgical procedure and pathological diagnosis as matched variables, clinical outcomes of patients with and without ILD were compared.

Results: Of the total 1629 patients, 113 patients (6.9%) with ILD were identified. Among them, 104 patients were matched through propensity score matching. Before matching, patients with ILD had a higher mean age, a higher proportion of men, and higher rates of sublobectomy and squamous cell carcinoma than patients without ILD. After matching, there was no statistically significant difference in postoperative complications and mortality rates between the control and ILD group. The 5-year survival rate was significantly lower in ILD group (66%) than in control group (78.8%; p=0.007). In comparison according to ILD subtype for ILD group, postoperative mortality rate was higher in the IPF group (10.9%) than in the non-IPF group (0%) with marginal statistical significance (p=0.05). IPF showed a worse survival curve than the control group (p=0.004), but the difference in survival curve between IPF and non-IPF showed no statistical significance (p=0.196; Figure 1). Multivariable Cox analysis demonstrated that IPF, higher clinical stage, and recurrence were found to be independent prognostic factors related to mortality (Table 1).

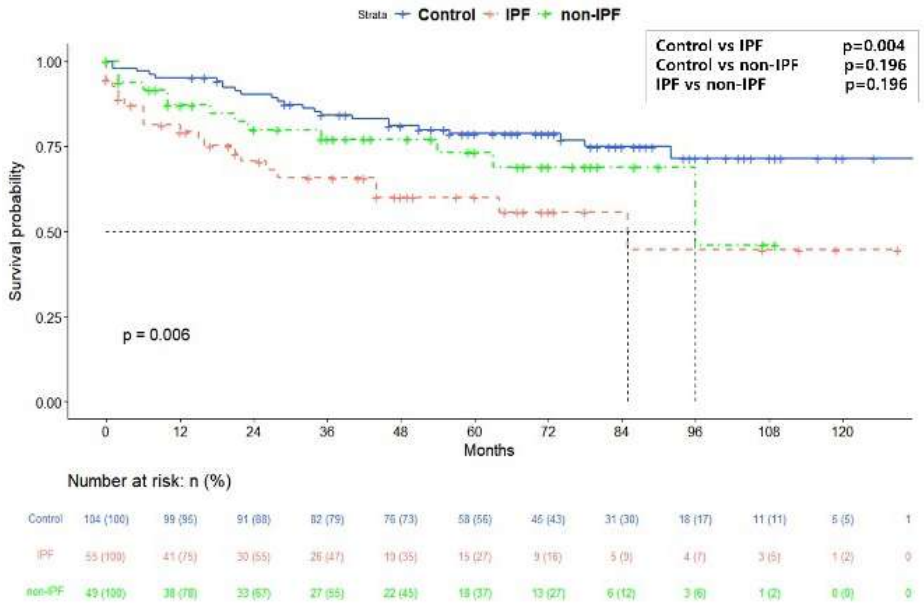

Figure 1. The Kaplan-Meier survival curve of the patients according to the ILD subtype: control vs IPF vs non-IPF.

Variables	Univariable HR	95%CI	p-value	Multivariable HR	95%CI	p-value
ILD (vs control)						
IPF	2.56	1.42-4.62	0.002	2.52	1.39-4.57	0.002
non-IPF	1.54	0.78-3.02	0.215	1.61	0.79-3.29	0.191
Sex, male (vs female)	2.02	0.81-5.05	0.134			
Age, years	1.05	1.02-1.09	0.003	1.06	1.02-1.10	0.001
Smoking index, pack-years	1	0.99-1.02	0.941			
BMI, kg/m2	0.95	0.87-1.04	0.238			
%FEV1	1	1.00-1.00	0.082			
%FVC	0.98	0.96-0.99	0.013			
%DLco	0.98	0.97-0.99	0.001			
ILD-GAP stage (vs control)						
stage I II	1.63	0.93-2.84	0.087			
stage III	9.96	4.37-22.70	<0.001			
Tumor location, RLL+LLL (vs the others)	1.19	0.71-1.99	0.520			
Clinical stage (vs stage I)						
II	2.21	1.17-4.17	0.015	2.13	1.06-4.30	0.035
III+IV	2.88	1.38-6.01	0.005	3.17	1.50-6.68	0.002
Surgical procedure (vs sublobar resection)						
Lobectomy	1.11	0.58-2.15	0.748			
Pneumonectomy	2.2	0.28-17.19	0.451			
Incision, VATS (vs open)	0.38	0.20-0.72	0.003	0.60	0.30-1.20	0.148
Hospital stay	1.01	1.01-1.02	<0.001	1.01	1.01-1.02	<0.001
Postop complication	1.61	0.96-2.70	0.073			
Recurrence	2.56	1.29-5.07	0.007	2.67	1.33-5.39	0.006

Table 1. Cox proportional hazard regression analysis for mortality after pulmonary resection for lung cancer in patients with or without ILD (total n =208, propensity score-matched population).

Conclusions: Long-term prognosis after surgery for lung cancer in patients with ILD was worse than in patients without ILD. ILD subtypes were found to be independently associated with prognosis after surgery.

Keywords: ILD, Lung cancer surgery, Prognosis

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-004 Association Between Sarcopenia and Outcomes of Lung Cancer Surgery in Old-Age Patients: Interim Analysis of Prospective Cohort Study

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Introduction: According to some retrospective studies, sarcopenia has previously been shown to be a predictor of poor surgical results and long-term outcomes in patients with lung cancer. However, the evidence is limited due to the lack of standardized measurements of sarcopenia and small retrospective studies. Herein, we conducted large prospective cohort study to investigate the association between sarcopenia and outcomes of lung cancer patients who undergoing curative surgical resection.

Methods: This cohort planned to recruit 400 patients over the age of 70 who received curative lung resection for lung cancer from April 2021. Sarcopenia was evaluated using the Asian Working Group's sarcopenia criteria, which were released in 2019. Bioelectrical impedance analysis, handgrip strength, and the 6-meter walk test were used to evaluate appendicular skeletal muscle mass, muscular strength, and physical performance, respectively. The relationship between sarcopenia and early surgical outcomes was investigated.

Results: Until February 2022, 154 patients were included in this cohort. Among those, 148 patients were fully evaluated for sarcopenia. Twenty-seven patients (18.2%) corresponded to low muscle mass, 71 patients (48.0%) corresponded to low hand grip strength, and 53 patients (35.8%) corresponded to low gait speed. Total 27 patients (18.2%) were diagnosed with sarcopenia. Complication occurred in 37 patients (25.0%) (33 in normal patients (25.6%) and 4 in sarcopenia patients (21.1%)), and there was no significant difference (p = 0.670). There was no in-hospital mortality in both groups. Length of stay was not different between two groups (p = 0.415). Multivariable analysis showed no significant predictor for complication.

Conclusions: Lung cancer surgery could be safely performed in elderly sarcopenia patients, as most surgical procedures were performed by minimally invasive surgery with enhanced recovery after surgery protocol. Effect of sarcopenia on lung cancer outcome should be assessed for long-term prognosis.

Table 1. Clinical characteristics and postoperative outcome in sarcopenia patients

Variables	Normal patients (n = 129)	Sarcopenia (n = 19)	P value
Age	74.0 (72.0 - 76.0)	76.0 (72.5 - 80.5)	0.111
Gender (male)	84 (65.1%)	14 (73.7%)	0.461
Body Mass Index	24.8 (22.2 - 26.4)	22.6 (21.3 -24.0)	0.002
Clinical TNM stage			0.148
Stage I	104 (80.6%)	11 (57.9%)	
Stage II	12 (9.3%)	6 (31.6%)	
Stage III	13 (10.1%)	2 (10.5%)	
Type of surgery			0.604
Minimally invasive surgery	114 (88.4%)	16 (84.2%)	
Thoracotomy	15 (11.6%)	3 (15.8%)	
Surgical extent			
Wedge resection	10 (7.8%)	2 (10.5%)	
Segmentectomy	28 (21.7%)	2 (10.5%)	
Lobectomy/Bilobectomy	89 (69.0%)	15 (78.9%)	
Pneumonectomy	2 (1.6%)	0 (0.0%)	
Complication rate	33 (25.6%)	4 (21.1%)	0.670
Prolonged air leakage	16 (12.4%)	1 (5.3%)	0.373
Pneumonia	8 (6.2%)	2 (10.5%)	0.144
Rhythm disturbance	6 (4.7%)	2 (10.5%)	0.273

Chylothorax	6 (4.7%)	0 (0.0%)	0.351
In-hospital mortality	0 (0.0%)	0 (0.0%)	
Length of stay days	5.0 (3.0 -7.0)	4.0 (3.0-7.5)	0.415

Table 2. Multivariable Analysis of Postoperative Complication rate; using Logistic Regression

	Primary Predictor Variables Analysis	
Variables	**Odds Ratio (95% confidential interval)**	**P value**
Age	0.942 (0.833 - 1.065)	0.342
Gender (male)	6.104 (0.801- 46.503)	0.081
Body Mass Index	0.922 (0.802- 1.059)	0.252
Sarcopenia	0.536 (0.131 - 2.205)	0.388
Smoking (never smoker)	1.183 (0.209 - 6.705)	0.849
Clinical TNM stage (reference = stage I)		
Stage II	1.082 (0.277- 4.224)	0.909
Stage III	3.972 (0.970 - 16.274)	0.055
Minimally invasive surgery	0.392 (0.117 - 1.320)	0.131
Surgical extent (reference = lobectomy)		
Wedge resection	2.381 (0.481 - 11.787)	0.288
Segmentectomy	1.689 (0.589 - 4.840)	0.330
Pneumonectomy	0.355 (0.014 - 8.880)	0.528
FEV1 (% predicted)	1.007 (0.986 - 1.028)	0.515
DLCO (% predicted)	1.003 (0.980 - 1.027)	0.769

Keywords: Sarcopenia, Lung cancer, Surgery

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-005 Perioperative Factors That Predict or Are Associated with Prolonged Air Leaks After Robotic-Assisted Pulmonary Lobectomy

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Introduction: Prolonged air leaks (PAL) lasting longer than 5 days after pulmonary resection complicate the postoperative course, prolong hospital lengths of stay (LOS), and increase costs. We analyzed pre- and peri-operative factors and postoperative (postop) complications associated with PAL in patients who underwent robotic-assisted video-thoracoscopic (RAVT) pulmonary lobectomy.

Methods: We retrospectively analyzed consecutive patients who underwent RAVT pulmonary lobectomy from September 2010 to May 2021. Chi-Square (x^2) test, Fisher's exact test, Wilcoxon rank sum test, and logistic regression were used to examine relationships between PAL and patient demographics, intraoperative and postop complications, and perioperative outcomes, with $p \leq 0.05$ as significant.

Results: Of 699 patients examined, 159 (22.8%) experienced PAL. Statistical analysis between PAL and non-PAL patients revealed significant differences in age, body mass index (BMI), smoking history (pack-years), pre-op COPD, pleural adhesions present during operation, operative time (skin-to-skin), postop effusion or empyema, postop subcutaneous emphysema, postop pneumonia, postop atrial fibrillation (a-fib), other postop arrhythmia, chest tube duration, and hospital length of stay (LOS), (see Table).

Conclusions: Higher mean age in PAL patients suggests that age-associated lung healing issues may predispose to PAL. PAL patients have greater smoking history and more preoperative COPD. Lower BMI in PAL patients suggests that malnutrition may predispose to PAL. Longer operative time, possibly related to presence of pleural adhesions, predispose patients to PAL. Increased occurrence of postop effusion or empyema, pneumonia, subcutaneous emphysema, a-fib, and other arrhythmias indicate probable association of PAL with other complications. Increased chest tube duration and hospital LOS highlight contributions of PAL to increased healthcare costs.

Variables	Patients with PAL >5d (n=159)	Patients without PAL >5d (n=540)	*p-value*
Age*, yr	70.5 ± 0.6	67.6 ± 0.5	0.0013
Gender, Male	79 (49.7%)	228 (42.2%)	0.0956
Gender, Female	80 (50.3%)	312 (57.8%)	
BMI*, kg/m^2	26.9 ± 0.4	28.8 ± 0.3	0.0149
Smoking History*, Pack-Years	39.4 ± 2.5	33.2 ± 1.4	0.0318
Pre-op COPD, n(%)	54 (34.0%)	95 (17.6%)	<.0001
Laterality (Right), n(%)	104 (65.4%)	313 (58.0%)	0.0605
Laterality (Left), n(%)	45 (28.3%)	197 (36.5%)	
Pathology Tumor Size*, cm	3.3 ± 0.2	3.2 ± 0.1	0.4524
Pleural Adhesions at Surgery, n(%)	108 (67.9%)	245 (45.4%)	<.0001
S-t-S Operative Time**, min	194 (157, 234)	168 (139.5, 206)	0.0011
Estimated Blood Loss**, mL	175 (100, 300)	122.5 (50, 250)	0.1167
Post-op A-fib, n(%)	40 (25.2%)	89 (16.5%)	0.0122
Post-op Other Arrhythmia, n(%)	46 (28.9%)	93 (17.2%)	0.0011
Post-op SubQ Emphysema, n(%)	89 (56.0%)	130 (24.1%)	<.0001
Post-op Effusion or Empyema, n(%)	13 (8.2%)	19 (3.5%)	0.0135
Post-op Pneumonia, n(%)	18 (11.3%)	27 (5.0%)	0.004
Chest Tube Duration**, days	11 (7, 16)	3 (2, 4)	<.0001
Hospital LOS**, days	8 (7, 12)	4 (3, 5)	<.0001
30-Day Mortality, n(%)	7 (4.4%)	5 (0.9%)	0.008

*Mean ± SEM; **Median (Q1, Q3); PAL = prolonged air leak; BMI = body mass index, Pre-op = preoperative; COPD = chronic obstructive pulmonary disease; S-t-S = skin-to-skin; Post-op = postoperative; A-fib = atrial fibrillation; SubQ = subcutaneous; LOS = length of stay; SEM = standard error of the mean; (Q1, Q3) = quartile-1 value and quartile-3 value.

Keywords: prolonged air leak, robotic surgery, pulmonary lobectomy

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-006 Oncological Outcome And Surgical Instruments in VATS Lobectomy For Early Stage Lung Cancer

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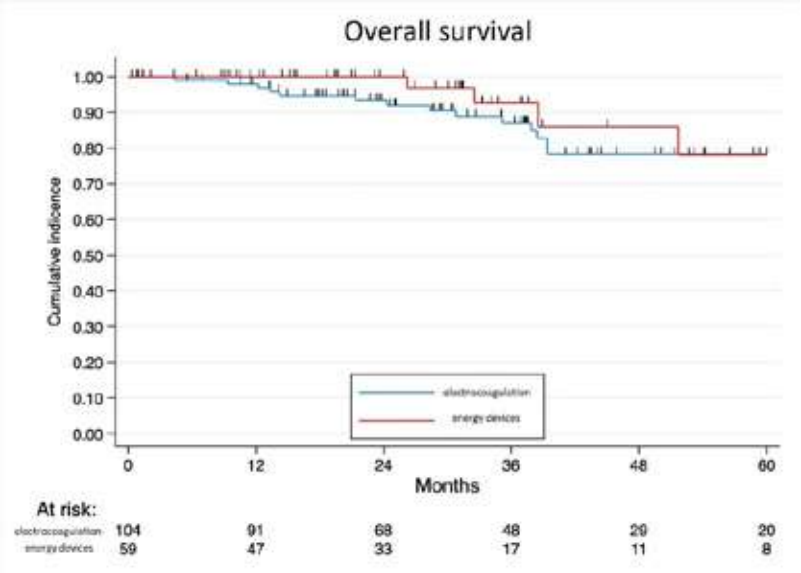
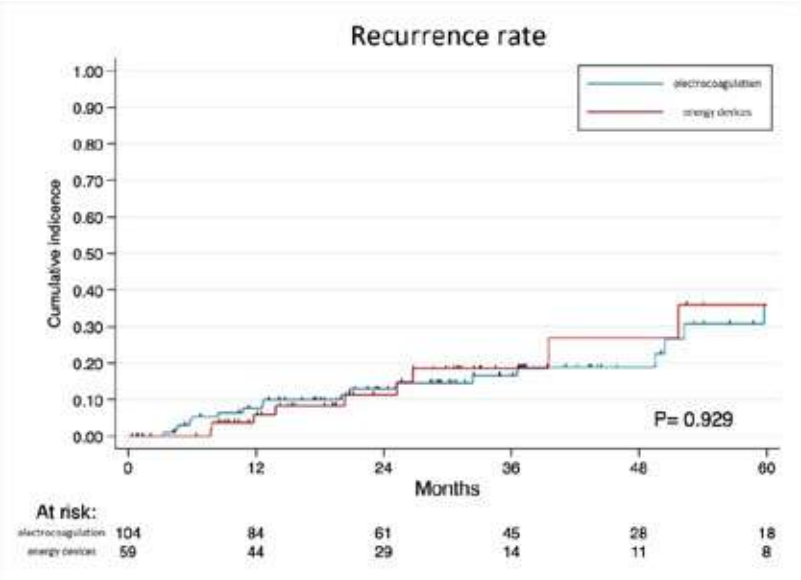
Introduction: Lung lobectomy with lymphadenectomy is the standard treatment for resectable lung cancer. Surgical treatment with video-assisted thoracic surgery (VATS) for early-stage lung cancer is becoming increasingly adopted. Surgical instrumentation may influence the completeness of resection and lymphadenectomy, therefore affecting postoperative staging and oncological outcomes. New instruments that deliver different types of energy are used in surgery to conduct tissue dissection. The aim of our study was to compare the effect on overall survival and recurrence-free survival of intraoperative use of different surgical instruments in patients who underwent VATS lobectomy for lung cancer.

Methods: We retrospectively reviewed 187 consecutive patients who underwent VATS lobectomy with systematic lymphadenectomy for stage I or II lung cancer. Postoperative follow up was conducted; 24 (12.8%) patients were lost at follow up. The remaining 163 patients were divided into two groups, according to the type of instruments used intraoperatively for tissue dissection: the “energy device” group (59 patients), and the standard electrocoagulation group (104 patients). Overall survival and recurrence rate were analyzed for both groups.

Results: The mean follow-up time was 34.1 months. There were no statistically significant differences in overall survival and recurrence rate between the two analyzed groups.

Conclusions: Adoption of different surgical instruments does not appear to influence overall survival and recurrence-free survival in patients with stage I or II lung cancer treated with VATS lobectomy and lymphadenectomy.





Keywords: Lobectomy, VATS, Surgical Instruments

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-008 Combined Robotic Assisted Thoracic Surgery (CRATS)

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Introduction: Robotic assisted thoracic surgery (RATS) is an effective treatment for early stage lung cancer and for diagnosis of small lung nodules. The Ion robotic bronchoscopy system allows for more accurate biopsy and dye marking of smaller peripheral lung nodules. We have combined these two robot systems along with endobronchial ultrasound (EBUS) to create a single anesthesia procedure for the diagnosis, staging and resection of suspicious lung nodules: Combined Robotic Assisted Thoracic Surgery (CRATS).

Methods: We present a retrospective review of CRATS cases performed at Medstar Georgetown University Hospital. Operable patients who were referred to our Thoracic Oncology program for evaluation of small lung nodules 7mm - 3.0cm and who had no obviously enlarged mediastinal lymph nodes on PET/CT scan were included. Patients underwent general anesthesia with Ion robot bronchoscopy with transbronchial needle needle aspiration (TBNA), brushing, and transbronchial biopsies (TBBX) of the nodule. 0.05-0.1cc of indocarmine green (ICG) dye was inserted in the nodule using a 23 gauge TBNA needle. EBUS TBNA was performed to stage the mediastinum. Once the nodes were confirmed to be normal, the patient underwent resection of the nodule.

Results: 13 CRATS cases were performed between November 11, 2021 and February 28, 2022. 11 Cases had Ion robot bronchoscopy guided TBNA, brush and TBBX along with EBUS TBNA and ICG dye marking. 1 Case of oligometastatic sarcoma and 1 previously biopsied GGO included ICG dye marking only followed by resection. All cases underwent single anesthesia procedure with Robotic resection of the target lesion. (2 segmentectomies and 11 lobectomies) Intraoperative pathology review of EBUS TBNA lymph nodes (ROSE) proved normal lymph nodes in all patients. Ion guided lung nodule biopsies were diagnostic in 9/11 patients. Final pathology confirmed 7 cases of stage IA NSCLC, 1 stage IIB (T3N0 satellite nodule in same lobe) typical carcinoid, 1 stage IIB (T3N0 satellite nodule in the same lobe) NSCLC, 1 hamartoma and 1 benign granuloma. CRATS was the definitive treatment for 12/13 patients. The patient with stage IIB NSCLC was recommended to have adjuvant chemotherapy.

Conclusions: CRATS can be performed in a single anesthesia setting. EBUS TBNA allows for contralateral mediastinal staging. Ion robot bronchoscopy can assist in intraoperative diagnosis to guide resection. ICG dye marking can help localize nodules for robotic resection. In a well selected patient population, CRATS may shorten the time from CT imaging to definitive treatment.

Keywords: CRATS (Combined Robotic Assisted Thoracic Surgery), Ion robotic bronchoscopy, ICG dye marking

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-007 Seeds of Gold. Triple Contrast Marking in Hybrid Operative Room for All-in One Diagnostic and Therapeutic Precision Surgery

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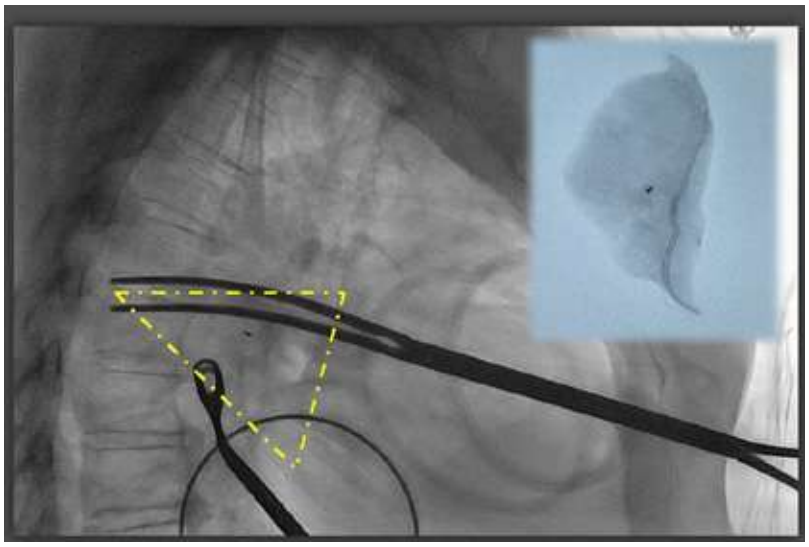
Introduction: The minimally invasive management of small lung lesions represents a quite challenging task for thoracic surgeons. As a matter of fact, video-assisted thoracic surgery (VATS) wedge resection could usually require conversion to thoracotomy when pulmonary lesions cannot be identified. Hybrid operating rooms (H-OR) can serve as a helpful tool in providing real-time lesion imaging and targeting, allowing the preoperative placement of different marking techniques to help locate non-palpable nodules. Our aim is to assess the efficacy of our triple contrast technique based on the simultaneous use of three different marking systems, including gold seed Biomarc - Vigeo S.r.l.), methylene blue (Methylthioninium Chloride - Bioindustria L.I.M.), and indocyanine green (-ICG- Verdye - Diagnostic Green Gmbh) to help locate non-palpable lung lesion.

Methods: Nine patients with non-palpable lung lesions requiring VATS wedge resection underwent lesional targeting in the H-OR with at least the technique, including gold seed, methylene blue, and ICG marking. Lesions were considered non-palpable due to sizing, radiological subsolid aspect, or location. All of the patients were placed in lateral decubitus position, and the lesion was then identified using intraoperative targeting (Philips Allura Xper FD 20). The correct intralesional needle positioning and gold seed positioning were verified using intraoperative fluoroscopy in a multidisciplinary setting, including interventional radiologists and technicians. Before surgery, 5 out of 9 patients underwent a preoperative lung lesion biopsy in H-OR to obtain a preliminary pathological report.

Results: The gold seed marking was visualized correctly in all of the patients except for one in which it was dislocated. Methylene blue was visible in 7 patients; in 2 patients, it appeared to be non-visible, while in 2 patients blue-lake effect was observed. The ICG n was not visualized in 3 patients. Minimally invasive wedge resections were then performed in all nine patients included in the study. They were sent for a frozen section pathological report resulting in lung adenocarcinoma diagnosis in 6 patients who underwent VATS lobectomy. Three patients were diagnosed with inflammatory lung lesions. In 80 % of the cases, the preoperative core biopsy was coherent with the final pathologic report.

Conclusions: Our experience confirms that the hybrid operating room can represent a suitable tool in helping locate hard-to-find lung lesions if a VATS resection is planned. A multiple marking approach, using different techniques, seems advisable to maximize the lung lesions detecting rate by direct vision, therefore reducing the VATS conversion rate.



Keywords: lung cancer, Hybrid Operative Room, VATS

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-009 Real-world Disease-Free Survival as a Predictor of Overall Survival in Resected Early-Stage Non-Small Cell Lung Cancer

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Introduction: Intermediate endpoints (e.g., disease-free survival [DFS]) have shown very good correlation with overall survival (OS) in early-stage non-small cell lung cancer (NSCLC) clinical trials. Yet limited studies quantified the clinical and economic burden of disease recurrence in this population in the real-world. This study aims to assess the association between real-world DFS (rwDFS) and OS and estimate the clinical and economic burden associated with recurrence among patients with resected early-stage NSCLC.

Methods: This retrospective, observational study used the linked SEER-Medicare database (2007-2019) to identify patients with newly diagnosed stage IB (tumor size>4cm)-IIIA NSCLC who received primary surgery before 2015 with or without adjuvant chemotherapy and did not receive neo-adjuvant chemotherapy or adjuvant radiation therapy. rwDFS was defined as time from primary surgery to first recurrence (diagnosis of metastatic disease, additional surgery, radiation therapy, or systemic treatment for advanced or metastatic NSCLC) or death, whichever occured first. OS was defined as time from primary surgery to death. Correlation between rwDFS and OS was assessed using the normal scores rank correlation. Median OS was compared between patients with and without recurrence at 1, 3 and 5-year landmarks post-surgery; hazard ratios were estimated using Cox models adjusted for disease stage, histology type, age at surgery, gender, race, adjuvant chemotherapy status, and comorbidities. All-cause and NSCLC-related healthcare resource utilization and costs will be compared between patients with and without recurrence using generalized linear models.

Results: 1,748 patients with early-stage NSCLC post-primary surgery (1,187 with recurrence and 561 without) met the eligibility criteria (median follow-up from surgery to death or end of data: 55.1 months). The mean age at primary surgery was 73.8 years; 47.9% were male, 83.6% were white and 40.5% received adjuvant chemotherapy. A higher proportion of stage IB NSCLC (29.8% vs. 18.0%) and a lower proportion of stage IIIA NSCLC (15.9% vs. 29.7%) were observed among patients without recurrence than those with recurrence. The estimated normal scores rank correlation demonstrated a statistically significant correlation between rwDFS and OS (0.57; 95% CI: 0.53-0.61; P<0.001). Patients with recurrence had significantly shorter OS than those without recurrence at each landmark post-surgery. Specifically, the median OS for patients with recurrence were 2.67, 3.52, and 3.71 years as compared to 6.76, 6.50, and 5.72 years for patients without recurrence at 1-year, 3-year, and 5-year landmarks (P<0.001 at each landmark). Adjusted Cox models indicated that patients with recurrence had 2.1-2.4 times increased risk of death as compared to those without.

Conclusions: In an era preceding the availability of immunotherapy in early-stage NSCLC, we observed a positive correlation between rwDFS and OS, and recurrence following resection is significantly associated with a shorter OS among patients with early-stage NSCLC. Additional analyses on clinical and economic burden associated with recurrence among the study population are ongoing and will be presented.

Keywords: real-world disease-free survival, non-small cell lung cancer, real-world overall survival

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-010 Intrapulmonary and Hilar Lymph Node Dissection Performed by the Surgical Team: Impact on Pathological Stage of NSCLC

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Introduction: Lymph node assessment improves staging and results in better overall survival in surgically treated lung cancer patients. Routinely, the hilar and intrapulmonary lymph nodes are collected by the pathologist in surgical specimens after surgical treatment of lung cancer. Our hypothesis is that the dissection and identification of hilar and intrapulmonary lymph nodes performed by the surgeon results in greater lymph node sampling than the same dissection performed by pathologist.

Objectives: Compare the change from clinical to pathological lymph node stage in patients who had both hilar and intrapulmonary lymph nodes from the surgical specimen dissected by the surgeon compared to the same dissection performed by the pathologist.

Methods: Prospective cohort clinical study. Lymph node dissection in the surgical specimen performed by the surgeon (intervention group) was compared with historical data for the years 2019 and 2020, when the same lymph node dissection was performed by the pathologist (control group). Inclusion criteria were as follows: non-small cell lung cancer patients submitted to lobectomy, bilobectomy or pneumonectomy and mediastinal/hilar lymphadenectomy. The groups were matched using the following variables: age, histological type, anesthetic risk classification (ASA), clinical staging, invasive staging of the mediastinum, and surgical approach. The primary endpoints were: total number of hilar and intrapulmonary (N1) lymph nodes, number of stations(N1) sampled, number of affected N1 lymph nodes, and change from clinical to pathological stage

Results: After the propensity score, 34 patients were included in the intervention group and 96 patients were included in the control group. There was a statistically significant difference when comparing the total number of dissected N1 lymph nodes ($p < 0.01$) and number of stations(N1) sampled ($p < 0.01$). There is no statistically significant difference when comparing the number of compromised N1 stations ($p=0.148$) and the total number of lymph nodes ($p=0.69$). The comparison between the groups regarding the change of staging to more advanced stages (upstage), occurred in 3 (8.8%) of the patients in the intervention group and 5 (7,8%) of the patients in the control group. This comparison between groups revealed a statistically significant difference with ($p= 0.048$) in favor of the dissection performed in the intervention group.

Conclusions: The dissection of the surgical specimen by the surgeons led to a greater number of dissected lymph nodes and lymph node stations. We also observed that the specimen lymph node dissection by the surgeon was associated with a higher rate of nodal upstaging

Groups		N°	Median	Minimum	Maximum	p
Total Number of Lymph Nodes	Intervention	34	14,00	5	43	0,69
	Control	68	10,00	4	38	
Number of Stations (N1) Sampled	Intervention	34	4,00	1	5	0,00
	Control	68	2,00	0	3	
Total Number of Hilar and Intrapulmonary (N1) Lymph Nodes	Intervention	34	4,00	0	11	0,01
	Control	68	1,00	0	7	
Number of Affected N1 Lymph Nodes	Intervention	34	0,50	0	6	0,148
	Control	68	0,50	0	4	

Figure 2 – Number of Lymph Nodes

Keywords: Lung cancer, lymphadenectomy, N1 lymph nodes

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-011 Timeliness of Surgery for Early-Stage Lung Cancer: Perspectives from Surgeons and Patients

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Introduction: Surgical resection remains the gold standard for treatment of early-stage lung cancer. There has been extensive research on the association between time to treatment initiation (TTI) and survival for lung cancer, with most studies finding a negative association including a recent systematic review. Nevertheless, there is no widely accepted standard for the appropriate TTI for patients undergoing surgical resection for early-stage lung cancer, though different guidelines exist, ranging from 2-8 weeks. While the sources of delay from the provider has been explored in the literature, there is limited research on appropriate TTI from the perspective of either the patient or the surgeon. The perspective of timeliness of treatment, from a provider and patient-side, has yet to be explored.

Our study seeks to evaluate the perceptions of both the surgeons and patients considered to be a safe TTI by evaluating delayed TTI from the patient perspective.

Methods: We interviewed 104 participants enrolled in the Mount Sinai Initiative for Early Lung Cancer Research on Treatment (IELCART) study who had curative surgical resection from 2016-2021. These interviews were conducted from June to December 2021, at least six months after treatment, to give enough time for recovery. TTI was defined as the time in days from histologic diagnosis of lung cancer to curative surgical resection. We performed a qualitative investigation to explore the patient's assessment of the timeliness of the lung cancer treatment and identify factors which may have led to TTI delays, including personal factors, health history, and exposures. In-person patient interviews were conducted which allowed for an open-ended discussion of the patient's concerns. Fifteen IELCART-participating surgeons completed a survey assessing their perceptions on appropriate TTI for clinical stage I lung cancers. The surgeon perceptions on appropriate TTI were compared to the actual TTI on the 104 participants who received surgery to assess timeliness.

Results: Of 104 participants, 89 (85.6%) identified their TTI as "timely", and 15 (14.4%) patients identified their TTI as "untimely." The median TTI of timely group was 40 days, compared to 71 days for the untimely group. The median days from suspicious CT scan to surgery of the timely group was 70 days, compared to 130 days for the untimely group. From the surgeon perspective, the median amount of time a patient could safely wait was 8 weeks or 56 days. This aligns with the untimely group's time from suspicious CT scan to surgery all greater-than-or-equal-to 59 days.

Conclusions: Participants who perceived their TTI as untimely had significantly higher days to surgery than those who perceived it as timely. Many participants who felt that their TTI was timely exceeded the recommended TTI from a surgeon perspective. Patient factors and causes for delay that result in a longer TTI should be further explored for intervention.

Keywords: lung cancer, delays, timeliness of care

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-012 Peri-operative and Oncologic Outcomes after Robotic-Assisted Segmentectomy at a NCI-designated Cancer Center

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Introduction: Lung-sparing procedures have increased over the years to treat non-small cell lung cancer (NSCLC). Our study reports the perioperative and long-term outcomes of patients who underwent robotic-assisted segmentectomy at a NCI-designated cancer center and aims to show associations between preoperative PET-scan standard update value (SUV) to tumor stage, differentiation, and recurrence patterns.

Methods: We retrospectively analyzed 166 consecutive patients who underwent a robotic-assisted segmentectomy at a single institution from 2010 to 2021. Among this, 121 robotic-assisted segmentectomies were performed for NSCLC. A total of 102 patients were evaluated with a PET-CT scan. The clinical, surgical, and pathologic profiles and perioperative outcomes were summarized by descriptive statistics. Numerical variables were described as median and interquartile range. Categorical variables were described as count and proportion. Chi-square or Fisher's exact test were used for association. The main outcomes of interest were over-all survival (OS) and recurrence-free survival (RFS). Kaplan-Meier curves were also constructed to visualize the over-all survival and recurrence-free survival of these patients, which were also stratified according to tumor histology, pathologic stage, and standard uptake value. Log-rank test for equality of survival curves was done to determine significant differences between groups.

Results: The median operative duration was 168.5 minutes, while median estimated blood loss was 50 mL. Conversion rate to thoracotomy in this cohort was 3.9% (4/102). Intraoperative complications occurred in 2.9% (3/102). Median hospital length of stay was 3 days. Median chest tube duration was 3 days, but 4.9% (5/102) of patients were sent home with a chest tube. The most common post-operative complications were atrial fibrillation (8.8%, 9/102), persistent air leak (7.84%, 8/102), pneumonia (4.9%, 5/102), and hypoxia (4.9%, 5/102). Thirty-day mortality rate was 0.0%. Recurrence for this cohort was at 28.4% (29/102). Time to recurrence was 353 days, while time to mortality was 505 days. The NSCLC patients were divided into 2 groups: low SUV (<5, n=55) and high SUV (≥5, n=47). There were statistically significant associations between SUV and tumor histology (p=0.019), tumor grade (p=0.002), lymphovascular invasion (p=0.029), viscero-pleural invasion (p=0.008), recurrence (p<0.001) and site of recurrence (p=0.047). Pathologic stage was not associated with preoperative SUV in this cohort of patients. KM survival analysis showed significant difference in the curves for OS (log rank p value 0.0204) and RFS (log rank p value 0.0034).

Conclusions: Robotic-assisted segmentectomy for NSCLC appears to have reasonable perioperative and oncologic outcomes. Furthermore, we demonstrate here the prognostic implication of SUV.

Table 1. Association of SUV with the following pathologic factors among primary lung cancer patients who underwent robotic segmentectomy.

Factor	SUV < 5 n = 55 *n (%)*	SUV ≥ 5 n = 47 *n (%)*	p-value
Tumor histology			0.019
Adenocarcinoma	42 (64.62%)	23 (35.38%)	
Squamous	9 (36.00%)	16 (64.00%)	
Carcinoid/Neuroendocrine	4 (36.36%)	7 (63.64%)	
Other Lung Cancers	0	1 (100.0%)	
Tumor grade			0.002
Well differentiated	19 (76.00%)	6 (24.00%)	
Moderately differentiated	29 (58.00%)	21 (42.00%)	
Poorly differentiated	7 (28.00%)	18 (72.00%)	
Pathologic stage			0.233
I	48 (58.54%)	34 (41.46%)	
II	5 (38.46%)	8 (61.54%)	
III	2 (33.33%)	4 (66.67%)	
IV	0	1 (100.0%)	
Lymph-vascular space invasion			0.029
With	3 (25.00%)	9 (75.00%)	
Without	52 (58.43%)	37 (41.57%)	
Viscero-pleural invasion			0.008
With	7 (30.43%)	16 (69.57%)	
Without	48 (61.54%)	30 (38.46%)	
Recurrence			<0.001
With	7 (24.14%)	22 (75.86%)	
Without	48 (65.75%)	25 (34.25%)	
Site of recurrence			0.047
Nodal	0	4 (100.0%)	
Pleural	1 (50.00%)	1 (50.00%)	
Local	5 (50.00%)	5 (50.00%)	
Distant	1 (7.69%)	12 (92.31%)	

Keywords: robotic segmentectomy, preoperative SUV, recurrence

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-013 Should Visceral Pleural Invasion Be Prognostic Factor in Early-Stage Lung Adenocarcinoma with Tumor Size 3cm or Less?

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Introduction: The presence of visceral pleural invasion (VPI) in adenocarcinoma 5cm or less in size means stage T2 regardless of tumor size. However, it is controversial whether VPI is a poor prognostic factor in patients with stage IA adenocarcinoma. The purpose of this study was to investigate the prognostic significance of VPI in early lung adenocarcinoma with tumor size 3 cm or less.

Methods: We retrospectively reviewed 283 curative intended NSCLC patients surgically and selected patients with pathologic N0 and lung invasive adenocarcinoma sized 3 cm or less. Invasive adenocarcinoma was classified into 4 predominant subtypes: lepidic, acinar, papillary, and solid. The Kaplan-Meier method was used for disease-free survival (DFS), overall survival (OS), and univariate analysis for clinical characteristics. The multivariate analysis was performed by the Cox regression hazard model.

Results: The number of early-stage (pathologic N0) lung adenocarcinoma with tumor size 3cm or less was 101 patients. Median follow up was 65.7 months. VPI was 24 (23.8%) cases. Patients with VPI were not inferior in DFS and OS compared to those without VPI. However, DFS and OS in patients with solid predominant were worse than those with non-solid predominant, respectively (p=0.003, p=0.046). In a Cox proportional hazard model, solid predominant increased the risk of recurrence by 3.3-fold (95% confidence interval = 1.44-7.67, p=0.005).

Conclusions: VPI was **not** a significant predictor of poor prognosis. Solid subtype was a better significant factor in evaluating the prognosis than VPI in early-stage lung adenocarcinoma with tumor size 3cm or less. Although further research is needed, solid subtype has the potential to be an important determinant of TMN staging system in early-stage lung adenocarcinoma.

Keywords: early lung cancer, Solid, visceral pleura

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-014 Pulmonary Segmentectomy via Minimally Invasive Open Surgery: An Analysis From a Japanese High-Volume Hospital

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Introduction: Based on the results of the JCOG0802 trial and due to the recent increase in the frequency of detection of small-sized lung cancers, the role of segmentectomy will be more important than ever. Therefore, standard parameters in terms of various perioperative findings are necessary to evaluate the feasibility of segmentectomy. To date, there have been few studies with a large number of patients who underwent segmentectomy via a minimally invasive approach. To establish a standard index of perioperative outcomes of segmentectomy in the era of minimally invasive surgery, we evaluated the perioperative outcomes of minimally invasive open surgery (MIOS) segmentectomy at a Japanese high-volume hospital.

Methods: Between 2014 and 2021, 5436 patients who underwent pulmonary resection at National Cancer Center Hospital, Tokyo, Japan. Among them, 1244 (22.9%) patients with segmentectomy through MIOS were included in this study. MIOS was performed with direct vision and thoracoscopic vision through a 2-cm port and a muscle-sparing mini-thoracotomy (incision, 5-8 cm in the fourth or fifth intercostal space at the anterior or posterior axillary line) (Jpn J Clin Oncol 2021;51:1649-1655). Regarding surgical procedures for segmentectomy, target segmental pulmonary arteries, veins and bronchi were divided using either ligation or a surgical stapler. To dissect the lung parenchyma along an intersegmental plane, a surgical stapler was also usually used. We evaluated the perioperative findings and surgical outcomes.

Results: The patients consisted of 582 (46.8%) men and 662 (53.2%) women with a median age of 70 years (interquartile range [IQR]: 61-76 years). Segmentectomy was performed in 1076 patients (86.5%) with lung cancer, 109 (8.8%) with metastatic tumor, and 59 (4.7%) with benign pulmonary lesion. Regarding the laterality of segmentectomy, right-side segmentectomy was performed in 625 (50.2%) patients and left-side segmentectomy was performed in 619 (49.8%). The number of segmentectomies performed between 2014 and 2017 was 413. In contrast, the number of segmentectomies performed between 2018 and 2021 was 831. The median operative time was 106 min (IQR: 92-120 min) and the median blood loss was 14 ml (IQR: 9-29 ml). The median number of stapler cartridges was 9 (IQR: 8-10). Fibrin sealants were used in 123 (9.9%) patients. The median length of the post-operative hospital stay was 3 days (IQR: 3-4 days). The morbidity rate was 7.1%. Prolonged air leakage was the most frequent postoperative complication and was observed in 32 (2.6%) patients. Only one patient died within 30 days from cerebral infarction and the 30-day mortality rate was 0.08%.

Conclusions: The frequency of segmentectomy in pulmonary resection has increased over the past few years. The perioperative findings and surgical outcomes of pulmonary segmentectomy via MIOS at our hospital seem to be favorable. These results could represent reasonable parameters for minimally invasive segmentectomy.

Keywords: Lung Cancer, Surgery, Segmentectomy

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-015 Fully Robotic Arm Robot Assisted Lung Surgery Exploration

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Introduction: Da Vinci robots have been approved for clinical use for more than 20 years. Subsequently, full-robot three-arm three-hole lobectomy and five-hole lobectomy appeared successively. These methods need to replace mechanical arm repeatedly, which seriously affects the surgical fluency. With the accumulation of surgical experience, four-hole (three-arm robot + assistant hole) lobectomy/segmentectomy is commonly used in recent years. This method does not need instruments replacement, but it needs to add an experienced assistant. Our purpose was to explore a robot lobectomy/segmentectomy without frequent intraoperative instrument replacement and an experienced assistant.

Methods: This operation is four-hole, but without an experienced assistant. The incision and the robotic arm were as follows: 1.Anterior axillary incision of the 4th rib is 3 cm, No.4 robotic arm with Maryland Biolar Forceps; 2.Anterior axillary incision of the 7th rib is 1cm, No.3 robotic arm with Permanent Cautery Hook; 3.Midaxillary line incision of the 8th rib is 1cm, No.2 robotic arm with lens; 4.After axillary line incision of the 8th rib is 1cm, No.1 robotic arm with Cadiere Forceps. The most critical step of this method is twining high-tension knot as follows: 1. to let the wire passes through tissue structure; 2. to hold both ends of the wire; 3. to rotate the mechanical arm; 4. to wrap both ends of the wire around the arm for 3 circles respectively; 5. to pull the wire knot tight. The function of twining is to strengthen the ligation force of the wire knot. The firmness of ligation is mainly determined by the surgeon's experience judgement, who would observe the shape changes of blood vessels, ligation wires and knots through a mirror magnified 10 times. All the steps of intrathoracic surgery are performed by the surgeon on the robot operating table.

Results: Fully robotic arm robot assisted lung surgery were accomplished in 21 patients(7 males, 14 females) from March 2021 to March 2022, including 13 lung lobectomy, which included each type of lobectomy and 8 lung segments/combined lung segments. Most patients were non-small cell carcinoma (20/21[95%]), and one patient was a typical carcinoid. Every patient underwent an R0 resection. No one needed to transfer to thoracotomy.The median chest tube duration was 4.0 days (range, 2-10 days), and the median length of stay after surgery was 6.0 days (range, 3-11 days). The median operative time was 286 minutes (range, 168-422 minutes). The average blood loss was 30ml(range, 10-100ml). There was no bronchial leakage, postoperative bleeding and other serious complications for all cases.

Conclusions: We successfully explored a robot lobectomy/segmentectomy without frequent intraoperative instrument replacement and an experienced assistant, fully robotic arm robot assisted lung surgery. There are several advantages for this method: 1. No assistant is needed, saving the human resources; 2. Ligation with mechanical arm is simple and easy to handle the structures, which saving one-time high-value consumables and reducing surgical costs; 3. It is easier to realize remote operation with this method, which making remote surgery more feasible.

Keywords: Fully robotic arm robot assisted lung surgery, No assistant, twining high-tension knot

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-016 Dynamics of Recurrence After Curative Resection of Non-small Cell Lung Cancer

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Introduction: The surveillance strategy after surgery for lung cancer should be adjusted according to the risk of recurrence. This study examined trends of hazard rate of postoperative recurrence of non-small cell lung cancer (NSCLC) by stage.

Methods: We reviewed the records of 1,987 patients who underwent curative resection for NSCLC between 2007 and 2012. Postoperative recurrence, development of second primary lung cancer, and survival status were analyzed to evaluate the hazard rate curves.

Results: Recurrence-free survival (RFS) rates at 5 years postoperatively were 87.8%, 54.7%, and 33.4% in patients with stage I, II, and III disease, respectively. The hazard rate for RFS was consistently low (<0.005) in stage I patients for 5 years postoperatively. The hazard rate for RFS in stage II patients showed a peak of 0.016 at 12.4 months postoperatively, followed by a gradual decrease. The hazard rate for RFS in stage III patients had a higher peak of 0.029 at 13.7 months postoperatively, which was also followed by a gradual decrease (**Figure 1**). The hazard rate for development of second primary lung cancer exceeded that of recurrence of first primary lung cancer after 72 months postoperatively (**Figure 2**).

Conclusions: The RFS hazard rate curves were markedly different according to the stage. Short-term surveillance might be unnecessary for patients with stage I NSCLC but should be considered in those with stage II or III disease. Screening for secondary primary lung cancer rather than surveillance for recurrence might be beneficial after more than 6 years postoperatively.

Figure 1.

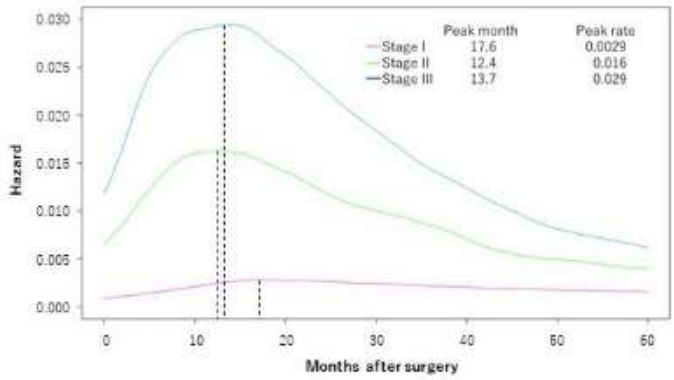
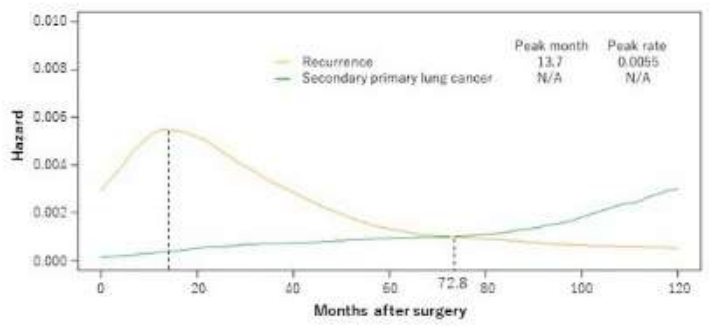


Figure 2.



Keywords: hazard function, non-small cell lung cancer, recurrence

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-017 Novel Intraoperative CT-Guided Marking Using O-Arm in Video-Assisted Thoracoscopic Surgery

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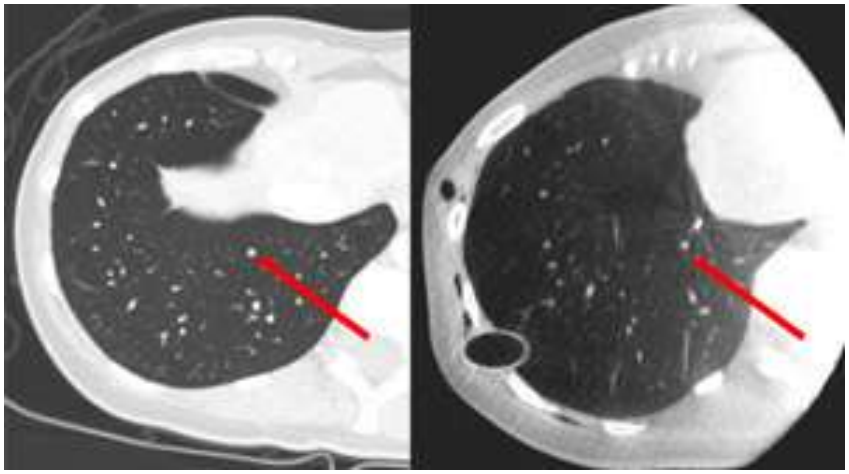
Introduction: With the increased frequency of detection of small lung tumors, there has been similar increase in limited surgery, such as wedge resection. Conventional percutaneous marking methods are simple and accurate, and are widely used. Although rare, cases of complications of air embolism have been reported, so there is difficulty in performing these marking methods. To identify such small lung tumors, we use a CT-guided intraoperative marking method using the O-arm surgical imaging system. We retrospectively investigated its usefulness.

Methods: Of 1043 cases of thoracic surgery performed at our department between May 2017 and June 2021, O-arm marking was used in 30 cases (2.9%), totaling39 lesions. Tumor location was predicted preoperatively based on 3D-CT and anatomical positioning. Visceral pleura near the tumor was marked with a metal clip, and the O-arm was brought to the surgical site. CT was taken after the tumor side lung was fully re-expanded and clamped. After confirming the tumor and the clip locations, the clip is repositioned as necessary and marked in the same way. If the marking was successful, the clips were used as markers when performing lung resection.

Results: Marking was successful in all cases. The average number of targets was 1.3, the average number of O-arm insertions was 1.3, and the average total number of marking clips was 2.6. In all cases, we checked the specimens and if the tumor was palpable, the resection margin was also checked. No intraoperative or postoperative complications were observed in any patients.

Conclusions: O-arm marking is especially helpful for peripheral non-palpable tumors, and it does not require special preparations or techniques, so determination of whether to use the O-arm or not can be decided after insertion of the thoracoscope. If the O-arm is available, this technique is a non-invasive, simple and practical method that could be widely used in clinical practice with low dose of radiation.



Keywords: intraoperative CT-guided marking, O-arm, minimally-invasive thoracic surgery

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-018 Intermittent Chest Tube Clamping Shortens Chest Tube Duration After Lung Cancer Surgery: An Open-label, Randomized Controlled Trial

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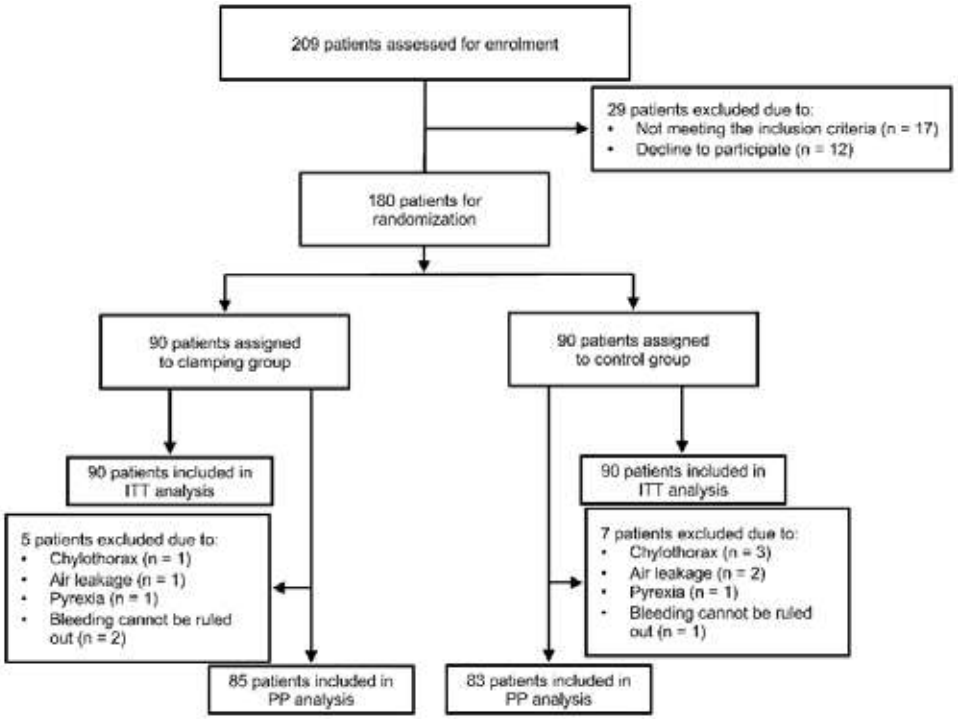
Introduction: Our previous retrospective study proved the safety and effectiveness of chest tube clamping in terms of shortening chest tube duration. This study sought to determine if intermittent chest tube clamping decreases chest tube duration and total drainage volume after lung cancer surgery in patients without air leak.

Methods: In this single-center, open-label, randomized controlled trial, all the patients were managed with gravity drainage (water seal only, without suction) during the first 12-24 h (depending on the time of surgery completion) after surgery. Once the re-expansion of the lung was confirmed via radiography the morning of postoperative day 1 (POD 1) and no air leak was detected, the patients were randomly assigned (1:1) to intermittent chest tube clamping (the clamping group) or continuous gravity drainage (the control group). Patients in the clamping group would experience 30 minutes of de-clamping every 24 hours. The primary outcome was the duration of chest tube drainage. This trial is registered with ClinicalTrials.Gov (NCT03379350).

Results: One hundred and eighty consecutive patients were randomly assigned to the clamping group (n=90) or the control group (n=90). In the intention-to-treat analysis, the chest tube drainage duration was significantly shorter {2 [2, 3] vs. 3 [2, 3] days; P=0.009}, and total drainage volume was much less (516.73±410.9 vs. 657.8±448.2 mL; P=0.029) in the clamping group than the control group. In the per-protocol analysis, the chest tube drainage duration was significantly shorter {2 [2, 3] vs. 3 [2, 3] days; P=0.007}, and total drainage volume was much less (437.8±213.9 vs. 604.8±352.8 mL; P=0.001) in the clamping group than the control group. Further, the clamping group showed a major improvement in plasma albumin declination at discharge compared to the control group (7.7±2.9 vs. 9.0±5.2 g/L; P=0.040).

Conclusions: Our study indicates that chest tube clamping decreased the duration of chest tube drainage and drainage volume without causing adverse effects. Chest tube clamping also slowed the decline of plasma albumin after the major pulmonary resection. Its wider application will facilitate recovery after surgery.



Keywords: lung cancer, surgery, chest tube clamping

EP02.03-019 T3 Non Small Cell Lung Cancer with Satellite Nodules: A Multicentric Analysis

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Introduction: Current Non-Small Cell Lung Cancer (NSCLC) TNM defines T3 tumors not only based on their size (between 5 and 7 cm), but also on a series of descriptors such as infiltration of adjacent structures or the presence of satellite nodules within the same lobe. The aim of this study was to assess the features of different T3 with satellite nodules (SN) NSCLC and to verify their impact on Overall Survival (OS).

Methods: We retrospectively collect clinical and pathological data of all T3 SN NSCLC operated on between 2005 and 2020 in two high-volume thoracic surgery divisions. We excluded from our analysis patients who received systemic treatments in the previous three years, those with a pathological N3 involvement or stage IV, and patients with incomplete pathological or follow up information. We evaluate the impact on OS of total size of the tumor (the sum of the major diameter of all nodules), of the diameter of the largest and smallest nodule and the number of nodules.

Results: A total of 56 patients were included in the study. Among them, 35 (62.5%) were male and 39 (69.7%) had a smoking history. On preoperative CT scan the presence of satellite nodules was seen in only 28 patients (50.0%). On preoperative imaging the mean total size of the nodules (the sum of the diameter of all the nodules) were 41.9 mm. Lobectomy was performed in most patients (42, 75.0%) and in 39 cases (69.6%) an open technique was used. 35 patients (62.5%) were pN0; 13 (23.2%) pN1 and 8 (14.3%) pN2. Pathology report showed the presence of 2 nodules in 43 patients (76.8%); 3 nodules in 8 cases (14.3%), while in 5 cases (8.9%) multiple nodules were found in the same lobe. The mean total diameter of the nodules was 43.9 mm ± 21.7mm; the mean largest nodule measured 31.1 mm ± 15.5 mm, while the mean smallest nodule measured 10.7mm±9.4mm. Median OS in the cohort was 111 months (95% CI 83.2-138.9). Clinical total size of the lung nodules and size of the smallest nodule did not significantly impact on OS (p=0.108 and p=0.267 respectively), while clinical size of the largest nodule did (p=0.035). Pathological total size of the nodules and pathological size of the largest nodule have a significant impact on OS (p= 0.001, HR 1.038; CI 95% 1.014-1.061 and p= 0.007, HR 1.038; CI 95% 1.010-1.066, respectively). Moreover, patients with multiple nodules had a significant worse survival compared to those with 2 or 3 nodules (p<0.001); multiple nodules confirmed their negative impact on OS also in the N0 subgroup (p<0.001).

Conclusions: The total size of T3 NS NSCLC is a prognostic factor for OS in our cohort of patients. Moreover, the presence of multiple nodules is as a clear negative prognostic factor that might require a more careful postoperative management even in pN0 patients and might be considered for possible upstaging.

Keywords: Non-Small Cell Lung cancer, satellite nodules, survival

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-020 Patient Outcomes Following Salvage Lung Cancer Surgery Post Definitive Chemotherapy or Radiation

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Introduction: Definitive chemoradiaotherapy (dCRT) is an option for patients with lung cancer who are medically inoperable or have unresectable locally advanced disease. The local recurrence rate after dCRT is 30% and the prognosis is poor. Salvage surgery, or surgical resection of recurrent disease following dCRT, is one therapeutic option, however, optimal therapy for locoregional recurrences or residual disease is controversial. The purpose of this study was to determine the efficacy of salvage lung resection.

Methods: This is a single centre retrospective database review. Patients eligible for the study received definitive chemotherapy, radiation therapy or both followed by salvage pulmonary resection for local recurrence or residual disease. Patient characteristics and outcomes were examined.

Results: Sixteen patients (11 male, 5 female) out of 201 that met the inclusion criteria treated between January 2017 and August 2020 were identified with a median follow-up time of 21 months (Q1, Q3 8-37.5). The median patient age was 68. All 16 patients received radiation, 7 of whom received less than 59 Gy and 9 received greater than 59 Gy. The rationale for dCRT varied as 6 patients had disease considered to be unresectable, 5 patients were originally considered to be medically inoperable, 4 patients had a preference for non-surgical management initially, and 1 patient pursued dCRT due to uncertainty of surgical options due to the COVID-19 pandemic. The median time from radiotherapy to surgery was 22 months (Q1, Q3 14.25-27.5). The extent of salvage resections differed as 5 patients had wedge resections, 4 had lobectomies, and 5 patients had more than one lobe resected. No pneumonectomies were preformed. Two resections were aborted in the operating room due to upstaging at the time of resection. The final pathology was 9 adenocarcinomas, 5 squamous cell carcinomas, 1 adenosquamous carcinoma and 1 non-malignant (nodular fibroblastic scarring with surrounding focal organizing pneumonia). Median procedure time was 3h10.5m. Adhesions were noted in 12 cases (75%). Ninety-day mortality was 0%. Overall survival at most recent follow-up was 75% (12 patients).

Conclusions: Salvage pulmonary resection after dCRT can be performed with low morbidity and mortality rates and is a good option for treatment of recurrent or residual disease after dCRT.

Keywords: Early stage lung cancer treatment, Salvage pulmonary resection, Definitive chemoradiaotherapy

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-021 Uncertain Resection for Localized cN0M0 Non Small Cell-Lung Cancer: The Crucial Prognosis of Suboptimal Lymph Node Assessment

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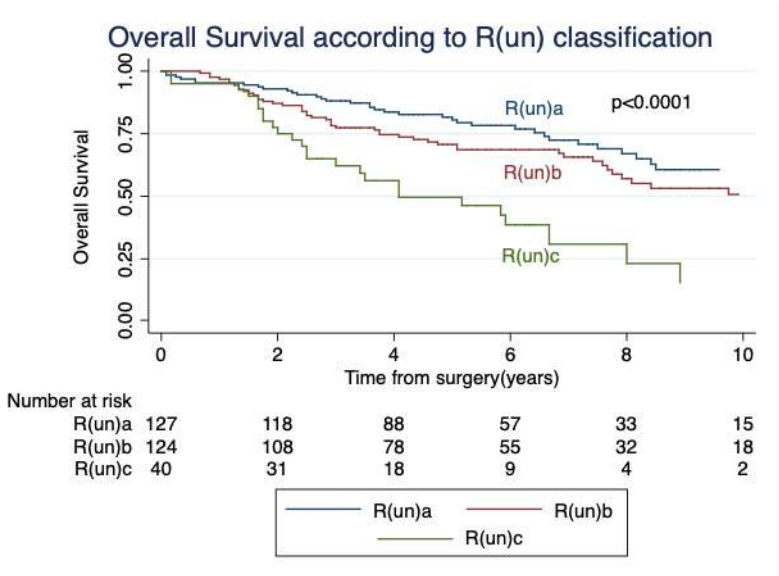
Introduction: Surgery remains the gold standard in the treatment of early stages of lung cancer.To achieve longer overall survival, complete resection of the tumor and careful lymphadenectomy are essential. The concept of uncertain resection R(un) was defined in 2005 by IASLC to highlight inadequate and limited resections and focused on intraoperative lymph node assessment. Although complete lymphadenectomy is recommended even in cN0M0 patients, the effect of R(un) in these patients has never been studied.

Methods: We include cN0M0 patients who underwent an anatomical lung resection for NSCLC from 2008 to 2018 at Toulouse University Hospital. We retrospectively reclassified tumours according to IASLC R-status based on pathologist reports.
The primary outcome was overall patient survival according to the R classification system. Secondary outcomes were to determine whether uncertain resection was an independent factor in mortality, to highlight heterogenity of R(un) to perform subcategorization predicting survival.

Results: Of the 1108 cN0M0 patients, we identified 732 (66.1%) R0 patients, 291 (26.2%) R(un) patients, and 85 (7.7%) R1 patients. There was a significant difference in survival according to R status (p<0.0001).The impact of complete resection was confirmed in the adjusted models, with an adjusted hazard ratio of 1.26 (95% CI: 1.01-1.59) between R0 and R(un) patients and 2.41 (95% CI: 1.76-3.30) between R0 and R1 patients.We found substantial heterogeneity among R(un) patients with significantly different survival according to the R(un) definition criteria.Therefore, we defined 3 new subgroups of R(un) to discriminate between populations of homogeneous survival. R(un)c included all patients with lymph node involvement of the highest mediastinal node. R(un)b included patients with less than 3 mediastinal lymph node sites examined or no station 7 nodes examined. All other R(un) patients who did not meet the above criteria were classified as R(un)a.

Conclusions: Our study demonstrated the validity of the IASLC R classification in cN0M0 patients. By demonstrating the heterogeneity of R(un)patients, we proposed the creation of subcategories to highlight the critical problem of suboptimal lymph node assessment.



Keywords: Early Stage NSCLC, Surgery, Resection

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-022 Evolution of Lung Cancer Resection Quality: A Prospective Staggered Implementation Quality Improvement Study

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Introduction: Suboptimal lymph node (LN) evaluation is a major cause of survival disparities after curative-intent lung cancer resection. We evaluated institution-level evolution of surgical quality with implementation of a corrective intervention with a LN specimen collection kit.

Methods: We stratified curative-intent lung cancer resections in the 14-hospital Mid-South Quality of Surgical Resection cohort, a prospective population-based staggered implementation of the kit, by: 1.) institution implementation status; 2.) kit use within implementing institutions. We measured poor-quality metrics- non-examination of LNs (pNX), non-examination of mediastinal LNs (pNXmed)- and a good quality metric- the American College of Surgeons Operative Standard 5.8 (ACS_OS 5.8), which requires negative margins, examination of ≥1 N1 and ≥3 mediastinal LN stations. With non-implementing institutions for reference, we compared the odds of attaining good and bad quality metrics adjusting for patient sociodemographic and clinical characteristics.

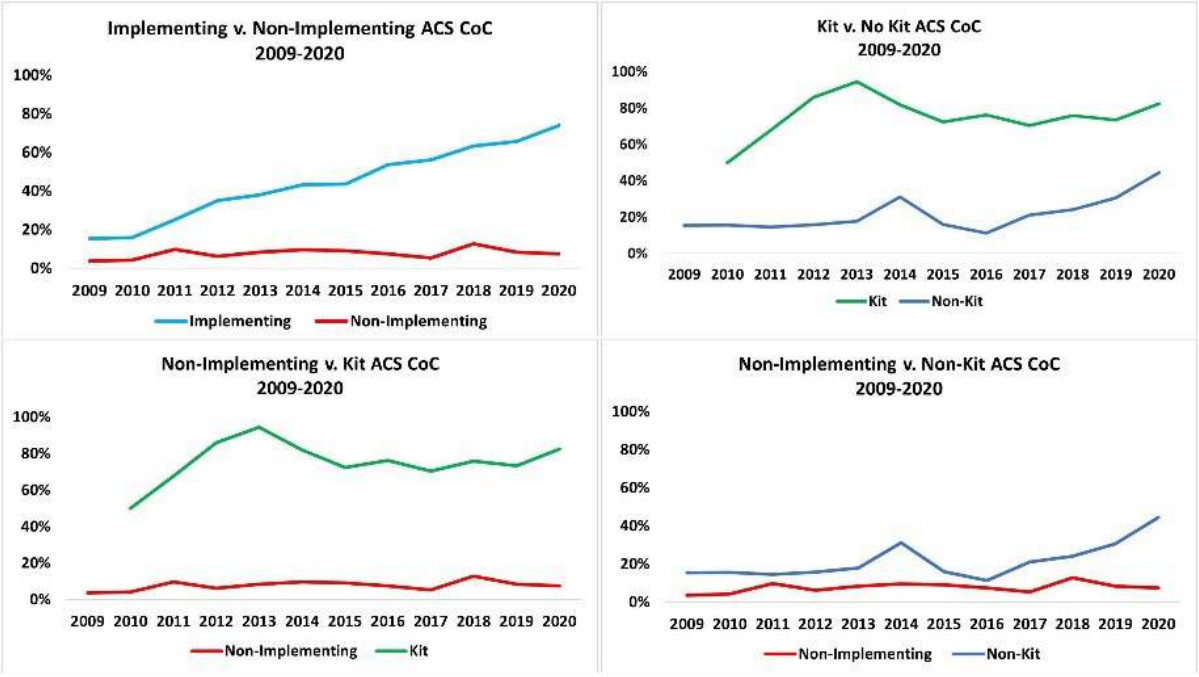
Results: From 2009-2020, 11 hospitals in implementation phase had 4,008 resections (1,686 [42%] kit, 2,322 [58%] non-kit resections); 3 institutions in the non-implementing phase had 958 resections. Quality metrics differed significantly according to implementation status and use of the kit (Implementing versus Non-implementing versus kit versus non-kit; p-value): pNX (6.4% v 10% v 0% v 11%; - p 0.0002), pNXmed (19% v 31% 2.6% 30%; p<0.0001), and ACS_OS 5.8 (42% v 8% v 76% v 18%; p<0.0001). Odds Ratios differed significantly by institution and kit category (Table). Implementing institutions evolved with sequentially improving rates of attainment of ACS_OS 5.8, non-implementing institutions did not (Figure panel 1); improvement in implementing institutions was mostly attributable to kit cases (Figure panels 2, 3); non-kit cases in implementing institutions were similar to cases in non-implementing institutions (Figure panel 4).

Conclusions: Surgery with a LN collection kit improves the institution-level quality of curative-intent surgical resection for NSCLC. Routine use of such kits should be encouraged for curative-intent resections.

Table. Rates of attainment of metrics of poor quality and good quality, according to institutional category and kit exposure. Crude and adjusted OR, with P-value

Odds Ratio (OR) 95% (CI) p value	Implementing v. Non-Implementing	Kit v. Non-Kit	Non-Implementing v. Kit	Non-Implementing v. Non-Kit
Unadjusted OR				
No LN Examination	0.63 (0.49-0.8) <0.0001	0.01 (0-0.03) <0.0001	0.005 (<0.001-0.039) <0.0001	1.136 (0.89-1.46) 0.3157
No Mediastinal LN Examination	0.54 (0.46-0.64) <0.0001	0.06 (0.05-0.09) <0.0001	0.064 (0.05-0.09) 0.7	1.03 (0.88-1.22) 0.7
ACS CoC Standard 5.8	8.82 (6.9-11.27) <0.0001	14.11 (12.1-16.45) <0.0001	37.5 (28.9-48.79) <0.0001	2.66 (2.05-3.45) <0.0001
Adjusted OR				
No LN Examination	0.58 (0.41-0.83) 0.0023	0.01 (0-0.06) <0.0001	0.01 (0-0.05) <0.0001	0.9 (0.63-1.28) 0.5424
No Mediastinal LN Examination	0.56 (0.46-0.67) <0.0001	0.08 (0.06-0.11) <0.0001	0.08 (0.05-0.11) <0.0001	0.99 (0.82-1.19) 0.3961
ACS CoC Standard 5.8	7.03 (5.43-9.09) <0.0001	11.72 (9.96-13.79) <0.0001	26.88 (20.42-35.39) <0.0001	2.3 (1.75-3.01) <0.0001

Covariates in adjusted Odds Ratios: age, sex, patient comorbidities, use of pre-operative PET-CT and invasive nodal staging tests, histology, extent of resection, surgical technique, and tumor size.



Keywords: Lung cancer surgery quality, lymph node collection kit, survival outcomes

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-023 Decreasing Time to Definitive Therapy with MIDAS: Minimally Invasive Diagnosis and Surgery

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Main Line Health System, Wynnewood/PA/USA

Introduction: Earlier detection and expeditious intervention will improve survival for patients with NSCLC. Lung screening and lung nodule programs identify patients for whom lung biopsy is appropriate. Robotic navigational bronchoscopy is a platform providing access to the entire lung and is uniquely capable of reaching nodules and GGO in the periphery making it an effective adjunct to early detection pathways. Patients diagnosed with NSCLC are referred for definitive therapy. We are evaluating the safety and efficacy of coupling Ion navigational bronchoscopy with minimally invasive surgical resection during a single episode of anesthesia; **MIDAS** (Minimally Invasive Diagnosis and Surgery) may become the new paradigm for lung nodule management.

Methods: Patients were entered into a prospective registry beginning August 2020. Patients with risk factors or nodule characteristics favoring malignancy were offered MIDAS. Ion navigational bronchoscopy with rEBUS and 2D/3D fluoroscopy was performed. Tissue was collected with needle aspiration for onsite cytopathology and biopsy forceps for frozen section analysis. Localization was performed with indocyanine green (ICG); firefly illumination was utilized during robotic resections. EBUS was performed prior to resection for clinically suspicious nodes. Surgery was accomplished with da Vinci Xi robot (49) or VATS (2). Complete nodal staging was performed in all lung cancer cases. All records were reviewed.

Results: Ion navigational bronchoscopy was performed on 203 patients. Diagnosis was achieved in 90%. Resection was performed on 76 patients for proven or suspected malignancy; 51 patients had **MIDAS** (Ion and resection during single episode of anesthesia). ICG localization was used in 18 procedures. Patient characteristics for MIDAS cohort were: mean age 69.6 yo (34 -84); 36 female and 15 male; mean FEV1 1.85 (0.93 - 3.05) Nodules were biopsied in all lobes: RUL 22, RML 1, RLL 11, LUL 9, LLL 8. Nodule size was 3 mm - 44 mm (mean 15 mm). Resections included: lobectomy 21, segmentectomy 6, and sub lobar 24. Pathology confirmed malignancy in 42 patients (82%). NSCLC represented 86% of the malignant diagnoses: Stage 1 (33), Stage 2 (3) Stage 3 (2). The 2 patients with mediastinal nodes had single station microscopic disease. Six patients had metastasis from other solid tumors: colorectal (3), anal (1), leiomyosarcoma (1), esophageal (1). Nine lesions were benign granulomatous disease. There were no ICU admissions and mortality was zero. There were no procedural complications in the MIDAS cohort; pneumothorax rate for all Ion procedures was 1.5% (3).

Conclusions: Minimally invasive diagnosis and surgery (**MIDAS**) during single episode of anesthesia is safe and enthusiastically embraced by patients; 96% elected to have the procedure. The combined procedure does not add morbidity or influence hospital course. This innovative approach eliminates the stressful and often prolonged interval between diagnosis and therapy. MIDAS dramatically decreases the time to definitive treatment by resection at time of diagnosis. The ability to reach, diagnose, localize, and resect small, peripheral solid and/or ground glass lesions in a compressed timeline may facilitate the shift in management of NSCLC to earlier stages and contribute to enhanced long-term patient outcomes.

Keywords: minimally invasive surgery, navigational bronchoscopy, early detection

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-024 Clinical and Prognostic Impact of Pleural Adhesions during Lung Cancer Surgery

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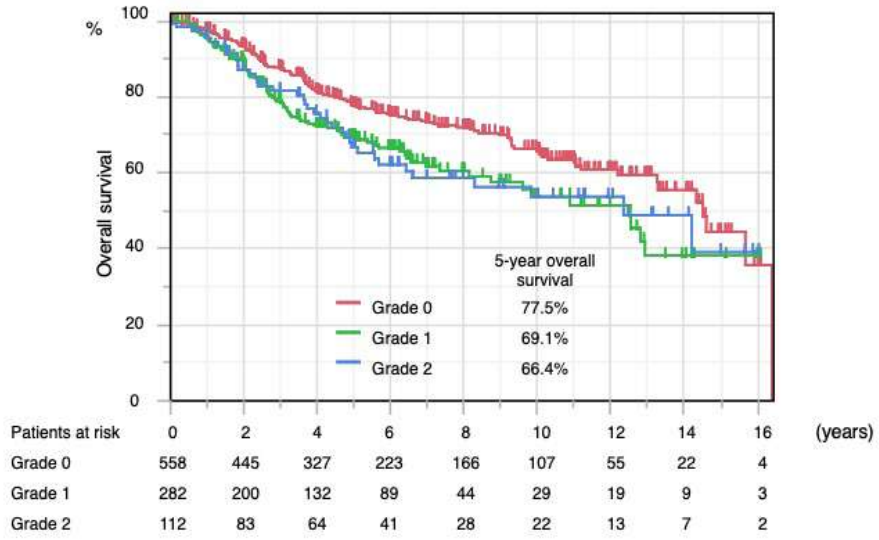
Introduction: Pleural adhesions complicate lung cancer surgery. Specifically, pleural adhesiolysis is associated with increased operative time and excess blood loss. The clinical and prognostic impact of plural adhesions in lung cancer surgery, however, has not been established. The aim of this study was to determine whether pleural adhesions had a clinical and prognostic impact on patients who underwent lung cancer surgery.

Methods: This was a retrospective study using our prospectively-collected institutional database, which was established in May 2004. From May 2004 to March 2021, 1089 consecutive patients underwent lobectomy with complete resection for lung cancer. After excluding patients with multiple lung cancers, preoperative treatment, extended resection, or early lung cancer within the hilum, we evaluated 952 patients. Our surgical approach was a thoracoscope-assisted, hybrid-style lobectomy. We defined adhesion grade based on the extent of adhesions as follows: no adhesions, grade 0 (G0; n = 558); slight adhesions, grade 1 (G1; n = 282); and adhesions involving > 1 one lobe, grade 2 (G2; n = 112). We compared clinical outcomes and prognosis based on the surgical adhesion grade.

Results: The distribution of adhesion grades among males was 54.7%, 66.7%, and 77.7% for G0, G1, and G2 adhesions, respectively (p<0.01). G0, G1, and G2 adhesions had the following associations, respectively: median age (69, 71, and 73 years); median smoking index (253, 520, and 710); proportion of clinical stage II and III patients (21.1%, 24.1%, and 34.9%); mean operative time (153, 158, and 204 min); median blood loss (25, 27, and 89 g); frequency of patients requiring a blood transfusion (1.4%, 0.3%, and 3.6%); frequency of postoperative complications (17.2%, 24.1%, and 21.4%); and 5-year overall survival (77.5%, 69.1%, and 66.4%). Patients with G0 adhesions tended to have a significantly longer survival than patients with adhesions (p<0.01).

Conclusions: Pleural adhesion grade was associated with male gender, higher age, higher smoking index, and advanced cancer stage. Although pleural adhesions were not associated with postoperative complications, patients without pleural adhesions had a longer overall survival than patients with adhesions.



Keywords: Surgery, Lung cancer, Pleural adhesion

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-025 Long-Term Oncological Outcomes and Risk Factors of Recurrence After Segmentectomy for Primary Lung Cancer

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Introduction: High-resolution computed tomography (CT) scan detected small-sized lung cancers. Among these tumors, tumors with ground glass nodule (GGN) have shown pathologically minimally invasive carcinoma based on Japan Clinical Oncology Group (JCOG) 0201 trial. In recent years, the number of patients undergo segmentectomy for these early-stage lung cancer or in the elderly patients. However, there are few reports that have evaluated the long-term outcomes over 10 years after segmentectomy. The objective of this study was to investigate the long-term prognosis and evaluated risk factors of recurrence after segmentectomy.

Methods: In this study, we investigated the short- and long-term outcomes of patients underwent segmentectomy for primary lung cancer performed from 2008 to 2012 excluding incomplete resection cases. The median follow-up period was 104 months. Survival and recurrence free survival curves were analyzed using the Kaplan-Meier methods. Univariate and multivariate analyses were used to identify significant factors that predicted recurrence in patients who underwent segmentectomy. A p value of less than 0.05 was considered significant.

Results: Among 1207 patients who underwent pulmonary resection for lung cancer, 180 (15 %) underwent segmentectomy. These patients comprised 104 women and 76 men, with a median age of 67 years (range 27-88 years). The histological types were adenocarcinoma in 164 patients, squamous cell carcinoma in 11, AAH in 3, small cell carcinoma in 1, and typical carcinoid in 1. The median tumor size was 15 mm (range 5-65 mm). Operation was performed with a median time of 156 min (range 61-315 min), blood loss 15 ml (range 2-520 ml). The median postoperative hospital stay was 5 days (range 3-183 days). Nineteen patients (11%) had complications of Clavien-Dindo classification IIIa or higher. Thirty days mortality was 0%. The pathological stages were stage 0 in 4, stage IA1 in 65, stage IA2 in 80, stage IA3 in 17, stage IB in 8, stage IIB in 2, and stage IIIA in 4. A total of 11 patients (6.1%) had recurrence, local recurrence in 4 (2.2%), local and distant recurrence in 3 (1.7%), and distant recurrence in 4 (2.2%). Local recurrences included ipsilateral hilar and mediastinal lymph node in 3, intrapulmonary metastasis in 1, and resection margin in 1. Ten patients had recurrence within 5 years, and one had recurrence beyond 5 years. The surgical procedures with recurrences were left superior segmentectomy in 5, right S6 in 3, right S2 in 2, right S8 in 1. The 5-year recurrence-free survival rate and survival rate were 88.8% and 91.6%, respectively. The 10-year recurrence-free survival rate and survival rate were 79.4% and 81.9%, respectively. On multivariate analysis, the variables associated with recurrence were pure solid tumor (Odds Ratio, 23.9; 95% confidence interval 2.80-203; $p<0.01$), tumor maximum diameter more than 20 mm (Odds Ratio, 4.44; 95% confidence interval 1.05-18.8; $p=0.04$).

Conclusions: The short and long-term outcomes of segmentectomy at our institution were feasible. Most cases had relapsed within 5 years after segmentectomy. The risk factors of recurrence were pure solid tumor, the diameter of tumor larger than 20 mm.

Keywords: Lung cancer, Segmentectomy, Recurrence

EP02.03-026 Is Ratio of Surgical Margin to Nodule Size a Prognostic Factor in Stage 1 Adenocarcinoma?

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Introduction: The most common non-anatomical resection is wedge resection for the patients with comorbidities and limited pulmonary function. We investigated, the ratio of surgical margin to nodule size (SM/NS) as a prognostic factor.

Methods: Data of 94 patients operated for adenocarcinoma between June 2004 and September 2021 were analyzed retrospectively. Wedge resection was performed to patients because of comorbid diseases and limited respiratory reserve. All of the cases were clinical stage 1.

Results: Sixty-four (68.1%) of the patients were male. The mean age was 65.04±9.9 (36-83) years. Recurrence was observed in 16 (17%) patients and 17 patients (18.1%) died. Median Disease Free Survival(DFS) was 15±13.4 (3-58) months (Figure 1a). Median Overall Survival(OS) was 35±45.5 (3-181) months (Figure 1b). The 5-year DFS was 80%, and the 5-year OS was 78%. OS in females was longer (p<0.036) (Figure 1c).

In ROC curve analysis, the cut-off value for the SM/NS in terms of both DFS and OS was calculated as 0.8 (p<0.05) (Table 1).There was a significant difference between T1a and T1c patients in terms of DFS with the p value of 0.032 (Figure 1d). Also there were significant differences between T1a and T1b patients and T1a and T1c patients in terms of OS with the p values of 0.037 and 0.035, respectively (Figure 1e).

Conclusions: We observed that if wedge resection is performed with a larger safe margin, survival will be better in tumors smaller than 1 cm. If we have to perform wedge resection for lung adenocarcinoma with various reasons, we should take into account that providing a SM/NS ratio bigger than 0.8 significantly prolongs the survival rather than a constant distance like 1 cm recommended previously.

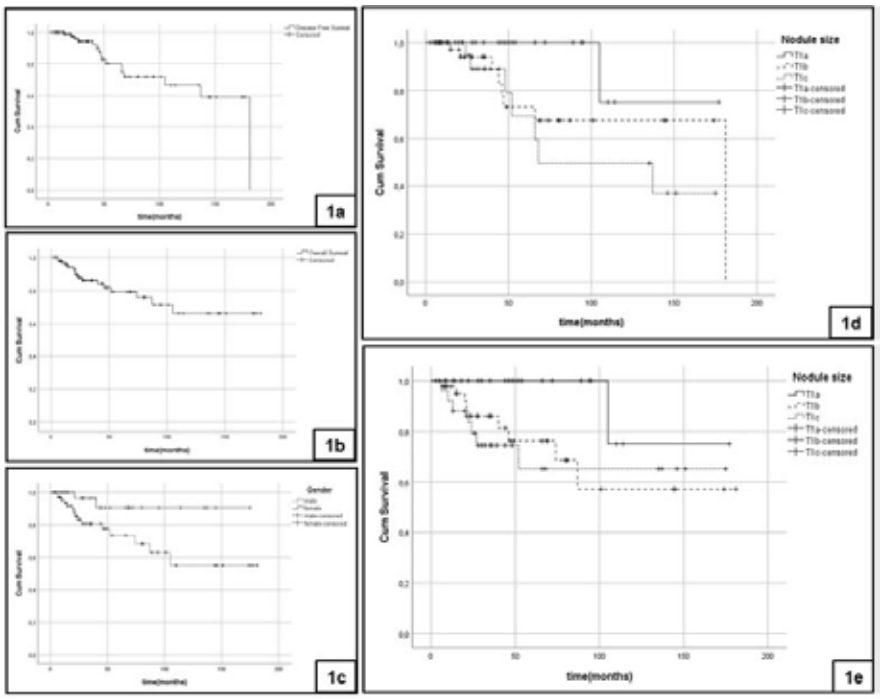

Fig. 1a: Disease free survival
Fig. 1b: Overall survival
Fig. 1c: OS according to gender
Fig. 1d: DFS according to nodule size
Fig. 1e: OS according to nodule size

Table 1				
	Mean DFS	***p***	**Mean OS**	***p***
Gender (n)				
Male (64)	140.7	0.529	123.1	0.036
Female (30)	123.8	0.529	161.4	0.036
Age (n)				
≥65 (45)	120.0	0.285	129.8	0.683
<65 (49)	146.5	0.285	141.7	0.683
Nodule size (n)				
T1a (26)	159.0	0.073	159.0	0.037
T1b (43)	136.0	0.032	125.5	0.035
T1c (25)	107.9	0.365	123.4	0.684
Surgical margin/nodule size				
<0.8 (58)	119.7	0.023	124.5	0.017
≥0.8 (36)	156.6	0.023	152.7	0.017

Keywords: Surgical Margin, Nodule Size, Adenocarsinoma

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-027 After Surgery Factors Affecting Relapse in Early Stage Non Small Cell Lung Cancer

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Introduction: While curative surgical resection is sufficient for early-stage non-small cell lung Cancer (NSCLC)(stage I-II), adjuvant systemic treatment is applied in advanced stage patients. Determining the high recurrence risk patients after surgery may help in the formation of treatment strategies. The aim of this study is to determine the surgical and pathological factors that affect the risk of recurrence after surgery for early-stage NSCLC.

Methods: Between January 2014 and August 2021, 212 patients with Stage I-IIA NSCLC who underwent curative surgery in our clinic were analyzed.Surgical procedures, age, gender, malignancy stages, tumor dimensions, histopathological diagnosis and features were recorded. The relationships between these values with recurrence and survival time were analyzed.

Results: 155(73.1%) of the patients were male, 57(26.9%) were female and the mean age of all patients was 62.82±10.07 (32-86). According to the eighth staging system, 204(96.2%) of the patients were identified as Stage I and 8(3.8%) as Stage IIA. 166(78.3%) of cases were diagnosed as adenocarcinoma(AC) and 46(21.7%) as squamous cell carcinoma(SqCC).While 20(9.4%) of the cases had recurrence after the surgical treatment, mortality occurred in 36(17%) patients during follow up. The mean survival time of the patients was determined as 71.01±1.76 (2-82±24.52)/month.The survival time was determined as 30.97±4.65 (4-63)/month in patients with relapse; and determined as 75.34±1.36 (2-82)/month in patients without relapse(p=<0.001). Recurrence was observed in 12(7.2%) patients histopathologically diagnosed with AC and in 8(17.4%) patients with SqCC. The recurrence rate was found to be higher in patients diagnosed with SqCC (p=0.037)(Table1). When the recurrence rates are evaluated according to histopathological sub-characteristics, recurrence was observed in 9(26.5%) of 34 patients with STAS and 11(6.2%) of 178 patients without STAS(p=<0.001).Although the recurrence rate was higher in patients with lymphovascular, vascular or visceral pleural involvement compared to the other group, the difference was not statistically significant. When patients with a diagnosis of AC were examined according to their histopathological subtypes, recurrence was observed in 7(23.3%) of 30 patients with STAS and 5(3.7%) of 136 patients without STAS(p= <0.001).Although recurrence was observed in 2(50%) of 4 patients with SqCC diagnosed with STAS and 6(14.3%) of 42 patients without STAS, the difference was not statistically significant(p=0.072).

Conclusions: It should be kept in mind that more recurrences may develop in patients with diagnosis of SqCC, and the presence of STAS may be a risk factor for recurrence. In cases with a high recurrence risk, complementary surgery or systematic treatments can be applied.

Table 1: Recurrence relation with histopathological factors in NSCLC

		Recurrence(%)		P value
		Yes	No	
Histopathological Diagnosis	AC	12(%7,2)	154	0,037
	SqCC	8(%17,4)	38	
Lymphovascular Involvement	Yes	6(%18,2)	27	0,061
	No	14(%7,8)	165	
Vascular Involvement	Yes	5(%19,2)	21	0,068
	No	15(%8,1)	171	
Visceral Pleural Involvement	Yes	4(%7,5)	49	
	No	16(%10,1)	143	0,0587
STAS	Yes	9(%26,5)	25	<0,001
	No	11(%6,2)	167	

Keywords: Non-small cell lung cancer, Recurrence, Survival

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-028 Pathologic Risk Factors for Recurrence in Early Stage Invasive Lung Adenocarcinoma with Tumor Spread through Air Spaces

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Introduction: Tumor spread through air spaces (STAS) is a newly adopted pathologic pattern of invasion of cancer cell nests spreading into air spaces in the lung parenchyma adjacent to the border of the main tumor and well-known risk factor of recurrence. The aim of this study was to evaluate relevant pathologic risk factors in early stage lung adenocarcinoma containing tumor spread through air spaces (STAS) treated with surgical intervention.

Methods: Medical records of patients who underwent surgical resections for stage I (AJCC 8th edition) lung adenocarcinomas between 2012 and 2020 in our institutes were reviewed retrospectively. Patients who had invasive component less than 5mm (adenocarcinoma in situ and minimally invasive adenocarcinoma) or larger than 2cm and without STAS were excluded in this study. Pathologic risk factors for recurrence in enrolled patients were investigated.

Results: Among 201 patients who had invasive adenocarcinoma less than 2cm in size, 50 cases (24.9%) represent STAS and included in this study. The mean follow-up periods were 38.3 (±22.14, ranging 7.2 to 94.3) months and that of ages were 66.4 (±9.57, ranging 48 to 85). Recurrence rates were 8.7% (4 patients, 1 woman and 3 men). Three patients were died during follow-up periods and no one died due to lung cancer progression (Two because of cancer progression of other organs and one heart failure). The largest distance of STAS from tumor edge showed statistical significance (Odd ratio 2.8, 95% confidential interval 1.29 to 5.87 p=0.016), and patients with STAS more than 10 alveolar distances revealed statistical significance as recurrence risk factors in univariable analysis while other pathologic features including micropapillary patterns and invasive ratio were not. In multivariate analysis, only the largest distance from tumor edge showed statistical significance. 5-year recurrence free survival rates of patients with the largest distance of STAS from tumor edge less than 2mm were 96.3% and that of patients with larger than 2mm were 62.5%.

Conclusions: The presence of STAS and distance from the edge of tumor was important risk factors for recurrence in patients with early stage invasive lung adenocarcinoma treated with surgery.

Keywords: adenocarcinoma, recurrence, surgery

EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY

EP02.03-029 Prognostic Factors in Curative Intent Stage I lung Adenocarcinoma: Hospital's Cancer Registry Based Analysis

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Introduction: Radiotherapy or surgery, associated with hospital specialization status (HSS) may increase the overall survival rate (OS) in patients diagnosed with lung cancer. However, many patients do not adhere to surgery due to comorbidities and personal preferences. In addition, the long time between diagnosis and treatment and qualification of the HSS may be altering the evolution of patients with lung adenocarcinoma (Adn). The aim was to evaluate prognostic factors in patients with lung cancer Adn, clinical stage I (CS), diagnosed in the State of São Paulo, Brazil.

Methods: A retrospective hospital-based cohort study was conduced with 681 patients, both sexes, over 18 years of age and diagnosed with Adn lung in SC IA/IB, undergoing radiotherapy or surgery between Jan/2000 and Dec/2015. The variables analyzed were sex, age, education, health system (public or private), CI at diagnosis, period of diagnosis (2000-2005; 2006-2010; 2011-2015), type of treatment, time between the first care and diagnosis in months (Up to 1 > 1 to 2, ≥2), time between diagnosis and treatment (Up to 1 > 1 to 2, ≥2) and HSS: High Complexity Centers in Oncology (HCCO) - hospitals with conditions techniques, physical facilities, equipment and human resources suitable for highly complex specialized assistance; Partial Hospital Complexity Centers in Oncology (PHCCO) are hospitals with similar infrastructures and specialization of HCCO, however the diagnosis and treatment are done only for most common cancers. Multivariate Cox regression analysis was applied to assess the risk of death. The second model was performed using propensity score technique. Balancing variables were sex, age group, treatment and education (including absentees) considering HSS as dependent variable. The matching was performed by logistic regression with the Nearest Neighbors algorithm.

Results: The OS rate was 58.1% for five years. In the conventional multiple Cox regression analysis, patients who underwent radiotherapy alone had nearly three times more risk of death than those who underwent surgery alone (aHR=3,44; IC95% 2,45-4,82). Patients treated in NHCCO hospitals have a higher the risk of death (aHR=1,49 [IC95% 1,10-2,03]) when compared to patients treated in HCCO; patients > 60 years old and male sex showed higher risk of death. The multivariate regression analysis using propensity score technique showed that patients treated in NHCCO hospitals have a higher risk of death (aHR=1,80 [IC95% 1,26-2,56]), and those that had time between diagnosis and treatment > 2 months (aHR=2,00; [IC95% 1,33-3,00). As protective factor, patients diagnosed between 2011-2015 have a lower the risk of death when compared to those diagnosed between 2000-2005 (HR = 0.60; [IC95% 0,38-0,94]).

Conclusions: In our study the risk of death in patients with lung Adn were the delay between diagnosis and treatment and to be treated in NHCCO hospitals. Regarding protective factor, patients diagnosed after 2010 showed lower risk of death.

Keywords: Adenocarcinoma, Overall survival, Prognostic factors

EP02.04 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY

EP02.04-001 Alectinib as Neoadjuvant Treatment in Surgically Resectable Stage III ALK-Positive NSCLC: ALNEO Phase II Trial (GOIRC-01-2020)

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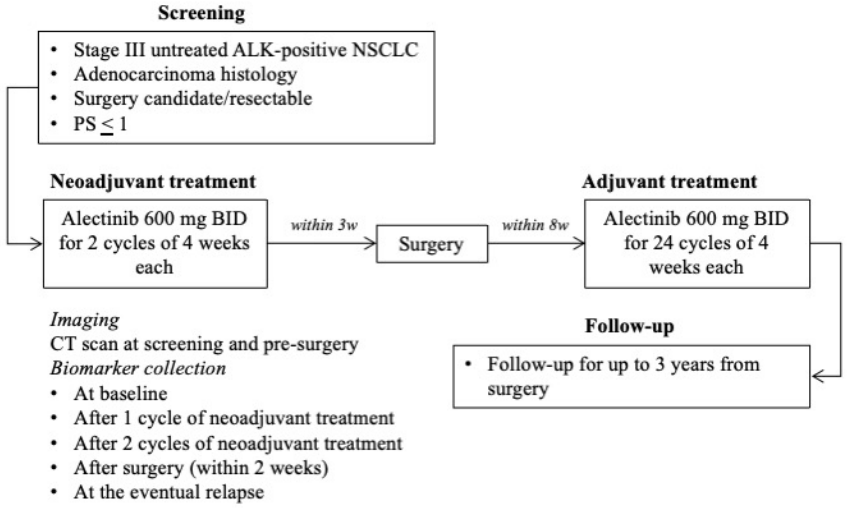
Introduction: Stage III Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous group of tumors with a wide spectrum of clinical presentations and no single definitive therapeutic approach. The role of neoadjuvant anaplastic lymphoma kinase (ALK)-tyrosine kinase inhibitors in stage III ALK-positive non-small cell lung cancer (NSCLC) is still unclear and poorly explored. We designed a phase II, open-label, single-arm, multicenter study aimed at investigating alectinib in potentially resectable locally advanced stage III ALK-positive NSCLC patients (ALNEO trial, EUDRACT number 2020-003432-25).

Methods: Treatment-naïve patients with potentially resectable stage III ALK+ NSCLC (any T with N2, T4N0-1) will be registered to receive neoadjuvant oral alectinib 600 mg twice daily for 2 cycles of 4 weeks each (8 weeks totally). If no progressive disease will be documented following the neoadjuvant phase, candidates will undergo surgery with radical intent within 3 weeks (± 1 week). After a maximum of 8 weeks from definitive surgery, patients will receive adjuvant alectinib 600 mg twice daily for 24 cycles (96 weeks) (Figure 1). The primary endpoint is major pathological response (MPR), defined as ≤ 10% residual viable tumor cells histologically detected in the resected primary tumor and all resected lymph nodes after surgery. Secondary endpoints include pathological complete response, objective response, event-free survival, disease-free survival, overall survival, adverse events. According to the Simon's two stage mini-max design, the null hypothesis that the MPR rate is ≤ 20% will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 4 or fewer MPR in these 18 patients, the study will be stopped early for futility. Otherwise, 15 additional patients will be accrued for a total of 33. The null hypothesis will be rejected if 11 or more MPR are observed in 33 patients. This design yields a type I error rate of 0.05 and power of 0.80 when the true MPR rate is 40%.



Results: ALNEO study started on May 20, 2021 and is planned to recruit 33 subjects in 20 national Italian Centers. To date, 20 Centers are active and 10 patients have been accrued.

Conclusions: ALNEO study will assess the activity and safety of alectinib as neoadjuvant treatment in surgically resectable stage III ALK-positive NSCLC.

Keywords: Neoadjuvant alectinib, Adjuvant alectinib, ALK-TKI

EP02.04 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY

EP02.04-002 Synergy of Local Treatment with Pulsed Electric Fields and Anti-PD1 Checkpoint Blockade

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Introduction: Pulsed Electric Fields (PEFs) are a focal ablation treatment that induces cell death without damaging the extracellular matrix, sparing sensitive structures. Its mechanism induces inflammatory signaling and affords viable antigen presentation within the tumor microenvironment. This preclinical study determines the immunogenic impact of PEF and whether its inclusion with anti-PD1 is beneficial.

Methods: Balb/c mice were bilaterally inoculated with 2x105 EMT-6 cells. PEF energy (AliyaTM System, Galvanize TherapeuticsTM, GTI-00018 investigational device) was delivered to tumors (5mm diameter) in the PEF group through a single needle. For combinatorial studies mice were distributed into 4 groups: IgG controls, anti-PD1-only, PEF-only, and anti-PD1 + PEF. PEF dosing targeted 80% of tumor volume. High mobility group box protein 1 (HMGB1) was quantified with ELISA 8 days after PEF, from serum collected 24-hours prior to and 24-hours post-treatment. T-cell immune infiltrate was evaluated with flow cytometry 10 days post-PEF. Tumor size was monitored 3 times a week to evaluate tumor response on a cohort. The anti-PD1 dosing was 200µg given once a week starting on PEF treatment day. Serum was also used for cytokine analysis.

Results: HMGB1, a damage-associated molecular pattern, was significantly elevated in the serum from pre- to post-treatment in the PEF group only. PEF treatment significantly increased infiltrating CD4+ and CD8+ T cells compared to No Treatment Control (NTC). This is consistent with tumor response, where 36% of treated tumors were eliminated 18 days after PEF versus 0% of NTC tumors. Combinatorial therapy improved survival outcomes in comparison to PEF or anti-PD1 monotherapy, producing 85% complete response compared to 18% and 10%, respectively. Heatmap review of expression of 24 cytokines pre- and post-treatment confirms that anti-PD1 and PEF appear to have synergistic effects on 14 inflammatory mediators, especially at Day 3. Additional differential effects were noted by Day 10 suggesting a shift to a more pro-inflammatory state.

Conclusions: PEF therapy delivered to a solid EMT-6 tumor model produces immunogenic cell death via HMGB1, which is correlated with the observed increases in T cell infiltration in the tumors. Furthermore, combination of PEF with anti-PD1 in this mouse model produces a synergistic immunostimulatory cytokine profile.

Data Table

PEF Tumor	PEF + anti-PD1 Tumor
Increase Infiltrating $CD4^+$ T cells	Upregulation of 14 Cytokines in serum at Day 3 vs PEF, anti-PD1 and Control
Increase Infiltrating $CD8^+$ T cells	Upregulation of 3 Cytokines in serum at Day 10 vs PEF, anti-PD1 and Control
HMGB1 Release	Down Regulation of 3 Cytokines in serum at Day 10 vs PEF, anti-PD1 and Control
36% Tumors Resolved	85% Complete Response at Day 60 Post treatment vs 18% for PEF and 10% for anti-PD1 monotherapy

EP02.04 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY

EP02.04-003 A Retrospective Comparison of Survival Outcomes in EGFR-mutated, NSCLC Patients on Osimertinib +/- Brain Metastases

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Introduction: Intracranial disease progression is a significant complication in patients with EGFR-positive non-small cell lung cancer (NSCLC) that can impact performance status, quality of life, and treatment options for patients. There is an increased need of oral tyrosine kinase inhibitors with central nervous system (CNS) activity in treating this population to prolong survival. Osimertinib is an oral tyrosine kinase inhibitor (TKI) which has demonstrated penetration of the blood brain barrier and effective treatment of intracranial metastases in some patients. The purpose of this study was to compare survival outcomes of patients with and without brain metastases who had first-line Osimertinib treatment in Alberta.

Methods: A retrospective study was completed to review all EGFR-positive NSCLC patients with brain metastases in Alberta, Canada treated with Osimertinib as a first-line treatment for advanced or metastatic disease between July 2018 to January 2021. Demographic, clinical, treatment and outcome details were extracted from the Glans-Look Lung Cancer Research Database. Patients were stratified according to the absence (BrMet-) or presence (BrMet+) of brain metastases at the time of Osimertinib. The primary outcome was median overall survival (mOS) between treatment groups. Secondary outcomes were median time to treatment failure (mTTF) and objective response rate (ORR). Both univariate (Kaplan Meier) and multivariate (Cox) curves were used to determine survival outcomes and compared with the log-rank test.

Results: Of the 77 patients were identified: 77% were BrMet- at Osimertinib initiation. BrMet- and BrMet+ did not differ significantly in any clinical or demographic features. The BrMet- group were more likely to be age 70+ years (54% vs. 16%, p=0.004) at diagnosis and less likely to have distant metastatic disease at Osimertinib initiation (54% vs. 100%, p<0.001). 61% of the BrMet+ group underwent brain radiation. Outcome measures, including mTTF, mPFS, and mOS did not differ significantly between the brain metastases and non-brain metastases groups. BrMet- and BrMet+ groups (mTTF: 17.8 vs. 22.1 months, log-rank p=0.53; mPFS: 15.1 vs. 16.2 months, log-rank p=0.58; mOS: not reached vs. 18.5 months, log-rank p=0.58), nor did, clinical response to Osimertinib (ORR: 46% vs. 50%, p=0.77; DCR: 83% vs. 88%, p=0.66). A multivariate model accounting for sex, age, and patient performance status, distant metastatic disease and brain metastases revealed ECOG ≥ 2 to be an independent factor for poor survival outcomes [HR: 6.9, p<0.001].

Conclusions: In both the BrMet- and BrMet+ groups, ECOG (independent of the presence or absence of intracranial disease), was the most predictive of OS. Surprisingly, there were no significant differences in treatment response or outcome between patients with or without brain metastases at the time of their treatment Osimertinib in the first-line setting, although it is noteworthy that over half of the BrMet+ group had brain RT at some point during treatment. These results demonstrated two findings. One is that 40% of patients with brain metastases have shown adequate intracranial and extracranial control of their disease on Osimertinib alone, although RT may still be indicated for some patients, and secondly, that poor performance status may indicate survival outcomes in this population.

Keywords: Non-small cell lung cancer, Targeted Therapies, Brain Metastases

EP02.04 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY

EP02.04-004 Time to Surgery After Neoadjuvant Immunotherapy: Not a Day Too Soon

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Introduction: The timing of surgery after neoadjuvant cytotoxic therapy for non-small cell lung cancer (NSCLC) is based on the time required for recovery of bone marrow function and the patient's performance status. By convention, surgical resection has been performed 3-4 weeks after preoperative chemotherapy and 4-8 weeks after preoperative chemoradiation. It is unclear whether these empirically defined time delays to surgery are also applicable to the timing of surgical resection after neoadjuvant immunotherapy. Here we report the association between the timing of surgical resection and pathological response after neoadjuvant immunotherapy using durvalumab with or without focal stereotactic radiation (8Gyx3).

Methods: Between January 2017 and September 2020, 60 patients with NSCLC clinical stages I-IIIA were randomly assigned to receive two three-weekly cycles of neoadjuvant durvalumab (D) alone or the same therapy combined with sub-ablative focal stereotactic radiation (8Gyx3) delivered concurrently with the first cycle of D. Major pathological response (MPR) was the primary endpoint. Surgical resection was planned 1-6 weeks after the last cycle of durvalumab. The planned surgical resection was performed in 26 patients in each arm. Transcriptomic profiling was performed on 32 pre and 46 post-treatment samples. Based on the median time to surgical resection (16 days), two groups were created; Group A (16 days or less) and Group B (>16 days).

Results: Twenty-seven patients were operated a median of 13 days after the last D cycle (Group A) and 25 after a median of 22 days (Group B). Baseline demographic, clinical and molecular characteristics including PD-L1 expression, EGFR mutations and gene expression profiles in pretreatment samples were similar between the two groups. Nine patients had a MPR in each group including a complete pathological response in 3/9 patients in Group A and 5/9 patients in Group B (Table 1). There was also no difference between the two groups in the depth of pathological response. Finally, there was no difference in immune gene expression profiles of resected tumors between the two groups.

Conclusions: Lung resection after neoadjuvant durvalumab with or without sub-ablative focal stereotactic radiation can be performed as early as two weeks after the end of neoadjuvant therapy without compromising the rate of MPR or the depth of pathological response.

Table 1

Pathologic Characteristics	**Group 1 N=27**	**Group 2 N=25**	***p*-value**
Median time to surgery from dose 2			
Days, IQR	13 (11-15)	22 (19-27.5)	<0.001
Min-Max days	7-16	17-93	--
Pathologic Stage			
Stage 0	3 (11.1%)	5 (20.0%)	0.109
Stage I	11 (40.7%)	6 (24.0%)	
Stage II	4 (14.8%)	2 (8.0%)	
Stage III	6 (22.2%)	12 (48.0%)	
Stage IV	3 (11.1%)	0	
Pathologic Nodal Status			
pN0	15 (55.6%)	11 (44.0%)	0.206
pN1	8 (29.6%)	5 (20.0%)	
pN2	4 (14.8%)	9 (36.0%)	
Pathologic Response			
None	18 (66.7%)	16 (64.0%)	0.624
Major	6 (22.2%)	4 (16.0%)	
Complete	3 (11.1%)	5 (20.0%)	
Percent Cancer Cells Killed			
Median, IQR	70% (40.0-99.0)	75% (27.5-99.5)	0.883

Keywords: Lung Cancer, Immunotherapy

EP02.04 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY

EP02.04-005 Phase II NAUTIKA1 Study of Targeted Therapies in Stage II-III NSCLC: Preliminary Data of Neoadjuvant Alectinib for ALK+ NSCLC

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Introduction: Targeted therapies for patients with NSCLC with molecular alterations, including alectinib (a preferred first-line treatment for patients with advanced anaplastic lymphoma kinase [*ALK+*] NSCLC), are being explored in the adjuvant setting in clinical trials. However, the role of targeted treatments as neoadjuvant therapy for patients with resectable NSCLC remains unclear. NAUTIKA1 (NCT04302025) is an ongoing, phase II umbrella trial investigating the efficacy and safety of targeted therapies as neo(adjuvant) treatment in patients with resectable NSCLC with molecular alterations, including *ALK*, *ROS1*, *NTRK*, *BRAF* V600, and *RET*. Here, we present preliminary data from the *ALK+* cohort in the neoadjuvant setting.

Methods: Adult patients (≥18 years old) with resectable stage II, IIIA or select IIIB (T3N2 only; per AJCC 8th edition) *ALK+* NSCLC with an Eastern Cooperative Oncology Group Performance Status of 0/1 were enrolled. Patients were treated with alectinib 600mg twice daily (BID) for 8 weeks as neoadjuvant treatment followed by surgery. In the post-surgery surveillance period, patients received up to four cycles of platinum-based chemotherapy followed by alectinib 600mg BID as adjuvant therapy. The primary endpoint of NAUTIKA1 is major pathologic response (≤10% residual viable tumor cells); secondary endpoints include investigator-assessed radiographic response, pathologic complete response, disease-free survival, event-free survival, overall survival, and safety. For this preliminary analysis, preliminary response, surgical outcomes, and safety data for the neoadjuvant period were assessed.

Results: The first five patients with *ALK+* NSCLC who have undergone neoadjuvant treatment and surgery were included in this analysis (data as of 22 February 2022). All patients completed at least 8 weeks of neoadjuvant treatment (median treatment duration: 8.14 weeks [range: 8.0-8.7]), had surgery during the defined protocol window (Day 57 [+10 days]), and had a complete resection (R0 resection rate: 100%) without delays or major complications; patient characteristics and further surgical outcomes data are presented in the **Table**. No patients had radiographic evidence of disease progression pre-surgery and no downstaging was observed. Adverse events (AEs) reported during alectinib neoadjuvant treatment were mostly Grade 1/2 (n=34/35; 97.1%); one Grade 3 AE (increased creatine phosphokinase [CPK]) was resolved upon dose reduction. None of the AEs leading to dose reduction during neoadjuvant treatment (increased CPK [n=1; Grade 3]; gastroesophageal reflux disease [n=1; Grade 2]) led to treatment discontinuation.

Conclusions: In this preliminary analysis from the *ALK+* cohort of NAUTIKA1, alectinib was well tolerated in patients with *ALK+* NSCLC and is considered feasible for neoadjuvant treatment.

	ALK+ cohort (N=5)
Patient characteristics	
Age (years), median (range)	52.0 (41-75)
Sex, n Female / Male	3 / 2
Race, n White / Unknown	4 / 1
Smoking history, n Former / Never	2 / 3
ECOG PS at baseline, n 0 / 1	4 / 1
Clinical staging (AJCC 8th edition), n Stage IIA / IIB / IIIA	1 / 1 / 3
Surgery outcomes	
Time from first neoadjuvant treatment dose to surgery (days), median (range)	61 (56-67)
Time from last neoadjuvant treatment to surgery (days), median (range)	1 (1-11)
Surgery performed out of the window defined in the protocol, n	0
Surgery type, n Minimally invasive surgery / Open approach	4 / 1
Unplanned surgery conversion, n	1
Surgery approach, n Robotically assisted VATS / Thoracotomy / VATS	2 / 1 / 2
Complete resection, n	5
Extent of resection, n Left upper lobectomy / Right lower lobectomy / Right upper lobectomy	2 / 2 / 1
Duration of surgery (minutes), median (range)	245 (104-386)
Time in hospital (days), median (range)	6 (3-8)
Intraoperative events	
Intraoperative complications / injury, n	0
Estimated blood loss (mL), median (range)	100 (20-650)
Intraoperative fibrosis, n	2
Intraoperative lymphadenopathy, n	2
Type of lymphadenopathy, n Both N1 and N2 / N1 only	1 / 1
Severity of lymphadenopathy, n Grade 0 (<1 cm) / Grade 1 (1-<2 cm) / Grade 2 (2-3 cm)	3 / 1 / 1
Peripheral adhesions, n	2
Hilar adhesions, n	2
Severity of hilar adhesions, n Grade 1 (mild fibrosis) / Grade 2 (moderate fibrosis)	1 / 1

AJCC, American Joint Committee on Cancer; ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; VATS, video-assisted thoracoscopic surgery

Keywords: Neoadjuvant, NSCLC, Alectinib

EP02.04 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY

EP02.04-006 Adjuvant Chemotherapy in Non-Small Cell Lung Cancer (NSCLC) Patients Treated with Preoperative Chemotherapy

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Introduction: A portion of NSCLC patients receive adjuvant chemotherapy after neoadjuvant treatment followed by curative surgery. This study aims to utilize National Cancer Database (NCDB) to determine its impact on survival.

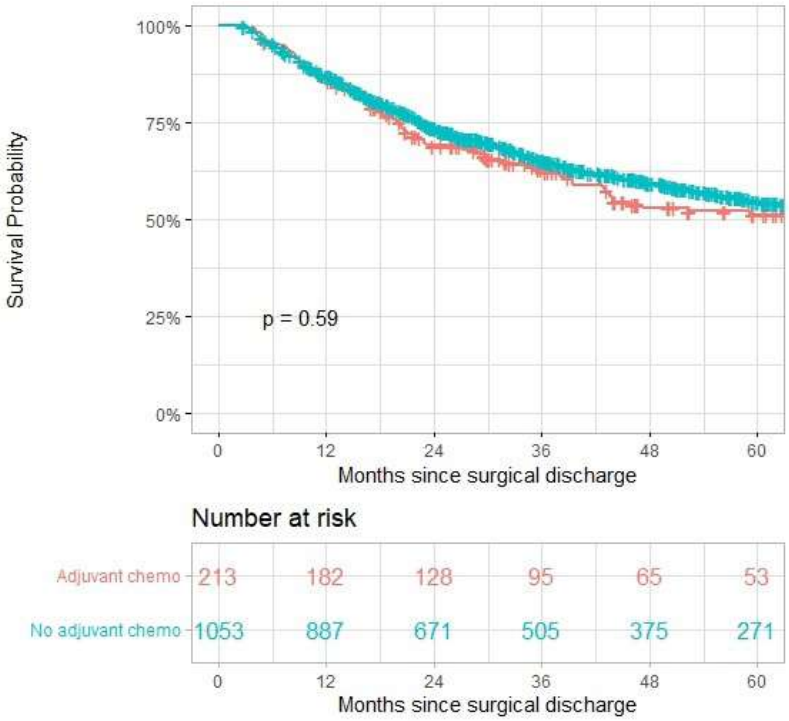
Methods: Patients with histologically confirmed clinical stage II-III NSCLC who have received preoperative chemotherapy and R0 curative surgery were identified in the NCDB between 2006 and 2017. Patients who have developed metastasis at the time of surgery, received any perioperative radiotherapy or single agent chemotherapy, or died within 90 days of surgery, were excluded. Neoadjuvant chemosensitivity is categorized as ypT0N0, downstaged (pTNM < cTNM, excluding ypT0N0), and not downstaged (pTNM ≥ cTNM). Logistic regression was used to evaluate associations between chemosensitivity and demographic and clinicopathological factors. Log-rank was used for survival analysis and adjusted by cox regression for age, gender, race, year of diagnosis, academic center, insurance, comorbidity, histology, clinical stage, and neoadjuvant chemosensitivity.

Results: A total of 1266 patients were included, of whom 213 (16.8%) received adjuvant, while the rest received neoadjuvant chemotherapy only. Younger age and more chemoresistant disease are independently associated with the use of adjuvant chemotherapy(Table), while gender, race, years of diagnosis, treatment at academic center, histology, and clinical TNM stage were not. Five-year overall survival (OS) rate is 54.7% and 51.2%, respectively (log-rank p = 0.59). There is no interaction of preoperative chemosensitivity and postoperative survival benefit from adjuvant chemotherapy.

Conclusions: Among NSCLC treated with neoadjuvant chemotherapy, those without clear response to neoadjuvant treatment are more likely to have received adjuvant chemotherapy. However it does not appear to improve outcomes of NSCLC. More novel agent is needed in this field.

Logistic regression model of significant variables associated with use of adjuvant chemotherapy

Characteristic	Odds Ratio	95% CI	p-value
Age	0.98	0.96-0.99	0.006
Preoperative Chemosensitivity		<0.001	<0.001
Not Downstaged	-		
Downstaged	0.56	0.40 - 0.78	
ypT0N0	0.40	0.19 - 0.78	



Keywords: Neoadjuvant chemotherapy, Adjuvant chemotherapy, Chemosensitivity

EP02.04 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY

EP02.04-007 Phase 2 Trial of Neoadjuvant KRASG12C Directed Therapy with Adagrasib (MRTX849) with or Without Nivolumab in Resectable NSCLC (Neo-KAN)

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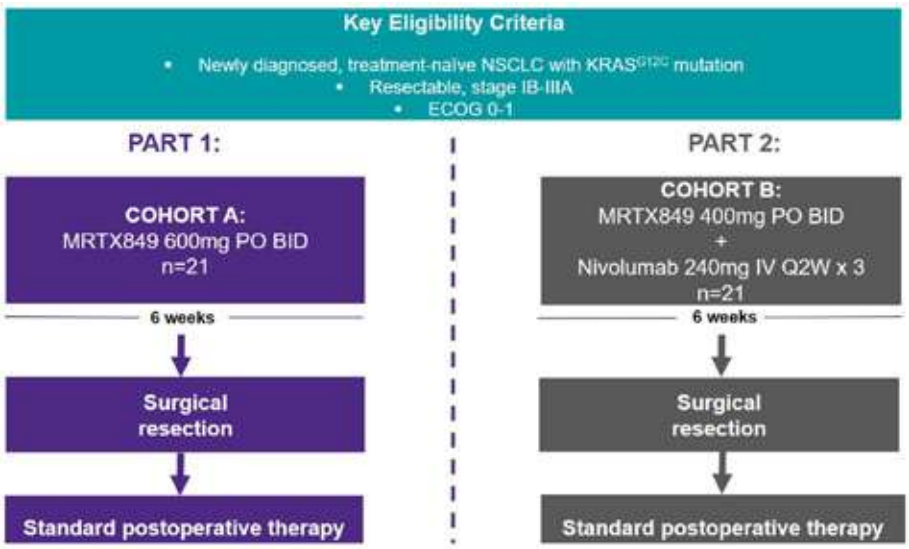
Introduction: The majority of patients with resectable non-small cell lung cancer (NSCLC) experience relapse following surgery despite standard of care systemic therapies. These patients are in critical need of new treatment approaches, and neoadjuvant systemic therapy provides an opportunity to improve rates of cure. The *KRAS^{G12C}* mutation is present in more than 13% of NSCLC tumors. Novel inhibitors of KRASG^{12}C have shown promise in advanced NSCLC, including adagrasib (MRTX849), with 43% confirmed objective response rate and 80% disease control rate. Furthermore, emerging data suggests that adagrasib reconditions the tumor microenvironment to enhance anti-tumor immune activity, and combination treatment with anti-PD-1 therapy was found to augment rates of durable response in pre-clinical studies. Use of targeted therapy in the neoadjuvant setting offers potential benefits over adjuvant therapy, including pathologic treatment response assessment, earlier treatment of micrometastatic disease, limited duration of drug exposure, as well as the opportunity to implement surgical prehabilitation programs to improve surgical outcomes and safety. The association between pathologic complete response (pCR) and event-free survival has been demonstrated in NSCLC clinical trials. The aim of this study is to assess the efficacy and safety of neoadjuvant adagrasib alone and in combination with nivolumab in resectable NSCLC with a *KRAS^{G12C}* mutation.

Methods: This is a prospective, open-label, multicenter, phase 2 trial to assess the efficacy and safety of neoadjuvant adagrasib with and without nivolumab. Adult patients with newly diagnosed, resectable stage IB-IIIA NSCLC (AJCC 8th edition; tumor ≥3 cm and/or N1-2) harboring a *KRAS^{G12C}* mutation are eligible. Up to 42 patients will be sequentially enrolled to receive adagrasib 600 mg twice daily for 42 days (Cohort A) or adagrasib 400 mg twice daily for 42 days concurrent with nivolumab 240 mg every 2 weeks for 3 doses (Cohort B). Patients then proceed to surgery within two weeks of the end of the neoadjuvant regimen (3-14 days), followed by standard postoperative treatment at the discretion of their treating oncologist. The primary endpoints are safety and feasibility as well as pCR rate in each cohort. Our hypothesis for pCR is that treatment in either cohort will achieve a pCR rate of ≥20%. Secondary endpoints include major pathologic response rate, surgical outcomes, event-free survival, and overall survival. Detailed correlative studies to characterize molecular and immunologic features associated with response will include multiplex immunohistochemistry, T-cell receptor sequencing, MANAFEST, and whole exome sequencing of tissue specimens, as well as plasma circulating tumor DNA analysis.



Keywords: Neoadjuvant therapy, Immunotherapy, KRAS targeted therapy

EP02.04 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY

EP02.04-008 Efficacy and Safety of Neoadjuvant Chemoimmunotherapy in Resectable Non-small Cell Lung Cancer (NSCLC): A Systematic Review and Meta-analysis

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Introduction: Clinical trials have investigated the benefit of combining chemotherapy and immune checkpoint inhibitors (ICIs) in resectable non-small cell lung cancer (NSCLC) patients has been investigated. Our aim is to synthesize the evidence of efficacy and safety of neoadjuvant chemoimmunotherapy treatment in a systematic review.

Methods: We have conducted a search on PubMed, EMBASE, and CENTRAL. Our inclusion criteria contained clinical trials of stage I-IIIA NSCLC patients who underwent any combination of ICIs and chemotherapy. Primary outcomes were major pathological response (MPR) and pathological complete response (pCR), and the secondary outcomes were overall survival (OS) at 24 months and the adverse events rate to represent safety. A meta-analysis was conducted for MPR and pCR, in addition to a meta-regression model to investigate the effect of PD-L1 expression, tumor mutational burden (TMB), N stage (8th AJCC), tumor size and tumor histology on MPR. PD-L1+ patients were defined to have a tumor proportion score of more or equal to 1%.

Results: We included 9 phase II clinical trials and 1 phase III trial, all consisting of 471 patients. Trials have administered neoadjuvant chemotherapy agents like carboplatin (N = 6 studies), cisplatin (N = 5), nab-paclitaxel (N = 4), pemetrexed (N = 2), and others, either as a double- or a triple-agent regimen. ICIs used were anti-PD-1 (N = 5), anti-PD-L1 (N = 3), or anti-CTLA-4 agents (N = 2). Meta-analysis of 447 patients from 9 trials resulted in a pooled MPR of 49.2% (95% CI: 34.8 to 63.7%) with a high heterogeneity (I^2 = 87%, p < 0.01). Pooling the pCR from 10 trials including 471 patients results in a value of 27.5% (95% CI: 17.2 to 38.2%) with a significant heterogeneity (I^2 = 80%, p < 0.01). We have also found a significant association between MPR and being PD-L1+ (odds ratio = 3.82, 95% CI: 1.55 to 9.58 p < 0.005) via meta-regression. However, this effect diminished in the multiple meta-regression that included age, tumor histology, in addition to PD-L1 status. Achieving a pCR was not correlated by none of those factors. Determining the effect of tumor size, T stage, or TMB on MPR or pCR was not possible due to underreported data. Three trials containing 137 patients reported a 24-month OS of 84.4% (95% CI: 77.6 to 90.2%) with a low heterogeneity (I^2 = 11%, p = 0.33). The most common grade 3/4 AEs from the neoadjuvant treatment were neutropenia (7.2%), diarrhea (3.2%), fatigue (3.0%), and anemia (2.1%). The most common any-grade AEs were fatigue (43.9%), alopecia (38.4%), diarrhea (31.6%), anemia (23.8%) and neutropenia (17.0%).

Conclusions: The addition of ICIs to chemotherapy in neoadjuvant settings is an effective and feasible option. Survival outcomes and pathological response are favorable to these of neoadjuvant immunotherapy alone. We recommend further investigation of the effect of tumor size and TMB on MPE and pCR for better selection of treatment candidates.

Keywords: NSCLC, Chemoimmunotherapy, Neoadjuvant

EP02.04 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY

EP02.04-009 Real World Survival Outcome Analysis of Adjuvant Therapies in Non-EGFR, Non-ALK Early Stage Resected NSCLC

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Introduction: Multiple clinical trials and meta-analyses have demonstrated the benefit of adjuvant chemotherapy for patients with early-stage resected NSCLC. Using a real-world registry of patients with early-stage NSCLC, we evaluated the effects of adjuvant chemotherapy, adjuvant radiation, and adjuvant chemoradiation on overall survival (OS).

Methods: We conducted a retrospective analysis of patients with early-stage NSCLC (IB-IIIA; years 2014-2019) who had undergone surgical resection from the Princess Margaret All-stage Cancer Outcome Repository for NSCLC (ACORN database). Excluded were patients who had received neoadjuvant therapies, or those with EGFR or ALK mutations. OS was assessed via Cox proportional hazards models using all outcomes data, and explored when data were truncated at various annual increments. The associations between either adjuvant chemotherapy alone and 5-year OS or any adjuvant chemotherapy (with or without adjuvant radiation) and at 1-5 year OS, while controlling for age, sex, stage at diagnosis, and smoking history, were assessed. Adjusted Hazard Ratios (aHR) with 95% confidence intervals were reported for each analysis.

Results: Among 326 patients with non-EGFR, non-ALK, resected NSCLC, the median age was 68.8 years, 46.6% were female, and 12.6% were never-smokers. Adenocarcinoma represented 64.4% of cases. Stage IB=33.7%; Stage IIA=15.6%; Stage IIB=23.3%; Stage IIIA=27.3%. 22.1% of patients received adjuvant chemotherapy alone, 9.2% received adjuvant radiation alone, and 20.2% received adjuvant chemotherapy and radiation, with adjuvant therapies administered more often to later stages. Stage IIIA diagnosis was associated with the lowest OS (HR: 4.00; 95%CI:2.12-7.57), followed by Stage IIB (HR: 2.08; 95%CI:1.05-4.11). At 1 year truncation, adjuvant chemotherapy (with or without radiation) demonstrated an OS benefit compared to surgical resection alone (aHR 0.37; 95%CI:0.15-0.90). A similar survival benefit was observed at 2 year follow-up (aHR 0.51; 95%CI:0.27-0.97). There was a trend towards decreasing OS benefit at 3 years (aHR: 0.66; 95%CI:0.37-1.17), 4 years (aHR 0.80; 95%CI:0.46-1.39), and 5 years (aHR 0.79; 95%CI:0.46-1.36), suggesting that OS benefit becomes diluted as death from non-NSCLC causes accumulate. Though no longer significant at 5 years, the aHR is numerically similar to that of the benefit of adjuvant chemotherapy as reported in the LACE Consortium. Secondary analysis of the effect of adjuvant chemotherapy alone revealed a significant OS benefit (aHR 0.35; 95%CI:0.15-0.80). In contrast, the presence of any adjuvant radiation was globally associated with a reduction in OS (HR: 1.99; 95%CI:1.00-3.93), likely due to use of radiation alone in poorer performance status patients and in patients with positive margins or stage III N2 disease.

Conclusions: Whereas the use of adjuvant radiation, a surrogate for more advanced tumours, was associated with worse outcomes, as expected, it is reassuring that in the contemporary setting, patients who received adjuvant chemotherapy (alone or with radiation) derived similar benefit in non-EGFR, non-ALK Stage IB-IIIA resected NSCLC.

Keywords: NSCLC, adjuvant therapy, overall survival

EP02.04-010 Clinical Outcomes After Neoadjuvant Tislelizumab plus Chemotherapy in Resectable Stage IIIA-B NSCLC: A Retrospective Study

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Introduction: Tislelizumab combined with chemotherapy was approved for first-line treatment of advanced squamous cell lung carcinoma and non-squamous non-small cell lung carcinoma in China. This study aimed to evaluate the efficacy of neoadjuvant Tislelizumab plus chemotherapy in resectable stage IIIA-B NSCLC in a real-world setting.

Methods: We retrospectively collected medical data of patients (pts) with resectable IIIA-B (AJCC8th) NSCLC who received neoadjuvant tislelizumab combined with chemotherapy and who successfully underwent surgery between Feb 2020 and Jan2022 at First Affiliated Hospital, Guangzhou Medical University. The primary endpoints were the downstaging rate and major pathological response rate (MPR); the secondary endpoints were surgical outcomes, including feasibility and safety outcomes etc.

Results: 19pts were eligible for inclusion with the median age was 57years (range 45-78),94.74%male and 63.16% squamous cell lung carcinoma. Neoadjuvant therapy options included tislelizumab plus (Alb)paclitaxel/ pemetrexed and carboplatin; All pts received 2-4cycles neoadjuvant therapy except1 had 5 cycles and 1 had 1cycle; the downstage rate was 78.95% (95% CI: 54.43, 93.95) [a]; The major pathological response and pathological complete response were78.95% (95%CI: 54.43, 93.95) and 52.63% (95%CI: 28.86, 75.55), respectively; R0 surgery rate was 100% ;the median surgery interval was 35.5 (range 7-55)* days. After a postoperative follow-up with median 10.5 (range 3-21) months, 19 pts were alive and recurrence-free. Besides two cases of mild pruritus, no other immune-related AE was reported.

Conclusions: Neoadjuvant tislelizumab combined with chemotherapy may be a valid treatment for resectable stage IIIA-B NSCLC in pathological remission and tumor downstage, does not affect the feasibility of surgery.

Table 1. Surgical outcomes

Impact on surgery	
Surgery VATS, n(%)	19 (100%)
surgery interval(day), median (min, max)*	35.5 (7-55)
Surgery time (min), median (min, max)	175 (100-535)
Estimated blood loss(ml), median (min, max)	20 (10-400)
Hospital stays (day), median (min, max)	7 (4-13)

* Interval day from last neoadjuvant to surgery [a] the evolution of cTNM cancer staging in each patient between baseline and preoperative evaluations after neoadjuvant ICI therapy

Keywords: Resectable Stage IIIA-B NSCLC, Neoadjuvant Tislelizumab plus Chemotherapy, Clinical Benefit and Surgical Outcomes

EP03.01 EPIDEMIOLOGY

EP03.01-001 Is Airflow Limitation a CausalFactor for Lung Squamous Cell Carcinoma? Evidence from Mendelian RandomizationAnalysis

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Introduction: Observational studies showed associations of smoking, airflow limitation, with lung squamous cell carcinoma. However, it remains unclear whether airflow limitation is a causal factor for lung squamous cell carcinoma.

Methods: Genetic summary data were obtained from large genome-wide association studies (GWAS). The two-sample Mendelian Randomization (MR) analysis was performed to assess the association of airflow limitation (i.e., FEV_1/FVC < 0.7), smoking behavior with lung squamous cell carcinoma. A multivariable MR method was used to determine whether airflow limitation is an independent causal factor for lung squamous cell carcinoma after controlling the effects of smoking.

Results: In the two-sample MR analysis, genetic predisposition towards airflow limitation [Inverse Variance-Weighted (IVW) method Odds Ratio (OR) = 4.83, 95% Confidence Interval (CI) 1.55 to 15.06, P = 0.060], age of smoking initiation (IVW method OR = -2.29, 95%CI -3.48 to -0.91, P < 0.001), cigarettes smoked per day (IVW method OR = 1.13, 95%CI 0.72 to 1.53, P < 0.001), ex-smoking (IVW method OR = 0.47, 95%CI 0.31 to 0.69, P < 0.001), current smoking status (IVW method OR = 13.08, 95%CI 2.53 to 67.84, P = 0.002), pack years of smoking (MR-Egger method OR = 5.37, 95%CI 3.69 to 7.04, P < 0.001) were associated with lung squamous cell carcinoma. In the multivariable MR analysis, the causal effect of airflow limitation was still observed on lung squamous cell carcinoma (OR = 2.97, 95% CI 1.09 to 8.04, P = 0.032 adjusted for age of smoking initiation and cigarettes smoked per day; OR = 3.24, 95% CI 1.09 to 9.58, P = 0.033 adjusted for ex-smoking, current smoking status, and pack-years of smoking; OR = 2.91, 95% CI 1.01 to 8.41, P = 0.049 adjusted for 5 smoking behaviors mentioned above).

Conclusions: Our MR analysis demonstrated that airflow limitation is likely to be an independent predictor of lung squamous cell carcinoma.

Keywords: Lung squamous cell carcinoma, Airflow limitation, Causal effect

EP03.01 EPIDEMIOLOGY

EP03.01-002 Co-occurring Mutations, Smoking Status and Prognosis of Early-stage Resected NSCLCs with EGFR Mutations

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Introduction: Co-occurring pathological mutations in non-small cell lung cancer (NSCLC) may account for clinical heterogeneity not explained by the single driver mutation model. The prognostic significance of various co-mutations and adjuvant treatment modalities has been explored in early-stage NSCLC, but there has not been a focus on the impact of smoking and EGFR co-mutations in early-stage NSCLC. This study aims to characterize the frequency of co-mutations in EGFR-mutated (EGFRm) early-stage resected NSCLC; to describe relationships between smoking history and co-mutation status; and to determine whether prognosis differs by co-mutation status and smoking status among patients with EGFRm NSCLC.

Methods: In this retrospective cohort, patients diagnosed with EGFRm early-stage (IB-IIIA) NSCLC, surgically resected between 2014-2019 (Princess Margaret Cancer Centre, Toronto, Canada) were analyzed. Presence of co-mutations was tested via next-generation sequencing (Illumina TruSight Tumor 15 Panel). Excluded were patients with multiple primaries, receiving adjuvant targeted therapy or neo-adjuvant chemotherapy, or with unknown smoking status. Descriptive statistics were generated using Chi-square tests; odds ratios were produced from multivariable logistic regression. Prognosis was assessed using log-rank tests and Cox proportional hazards regression adjusted for stage.

Results: Of 104 patients with resected EGFRm NSCLC, 83(80%) had no co-mutation; 21(20%) had at least one co-mutation: TP53 (n=19), KRAS (n=2), BRAF (n=1). EGFR exon-19 deletion was present in 38 (37%), L858R in 43 (41%), both exon-19 and L858R in 1 (1%). Included patients were diagnosed at stage IB (n=47;45%), stage II (n=25;24%) and stage IIIA (n=32;31%). Median age was 73.4 years (IQR 50.2-94.4) with no co-mutations, compared to 70.2 years (IQR 53.1-88.2) in the co-mutated group. In total, 74 (71%) were never-smokers and 30 (29%) were ever-smokers (current or former). Among never-smokers, 16 NSCLCs had co-mutations while 58 were EGFR-only.

Proportions of patients with co-mutation among never-smokers and ever-smokers were not significantly different (p=0.76). Ever-smokers had numerically (but not statistically significant) higher odds of co-mutation compared to never-smokers (OR=1.38; 95%CI=0.52-3.58), adjusted for age, sex, morphology and stage.

Overall survival (OS) did not differ between EGFR-only and EGFR co-mutated groups (p=0.2). Individuals with EGFR co-mutated disease had a hazard ratio (HR) of 1.85 (95%CI=0.65-5.32) compared to the EGFR-only group, adjusted for stage. Among never-smokers, those with co-mutations had lower OS compared to never-smokers with EGFR-only (logrank p=0.04). The median survival in the EGFR co-mutated group was 3.94 years but was not reached in the EGFR-only group; the adjusted HR was 2.64 (95%CI=0.85-8.21).

Disease-free survival (DFS) did not differ statistically between patients with co-mutated disease and EGFR-only (p=0.5): median DFS in the co-mutated group was 2.52 years, compared to 4.08 years for the EGFR only group, with an adjusted HR of 1.21 (95%CI=0.61-2.38). DFS did not differ significantly by co-mutation status in never-smokers (logrank p=1.0; stage-adjusted HR 0.94, 95%CI=0.41-2.19).

Conclusions: In this cohort, co-mutation rates in early-EGFRm NSCLC were not significantly different by smoking status. Numerically, never-smokers with co-mutations had worse overall survival than patients with only EGFRm NSCLC. Co-mutations in early-EGFRm NSCLC may negatively influence survival outcomes, similar to accumulated evidence in late-stage EGFRm NSCLC.

Keywords: EGFR, co-mutation, early-stage

EP03.01 EPIDEMIOLOGY

EP03.01-003 Clinical Features and Molecular Profile of Advanced Non-small Cell Lung Cancer in Latin America: LATINO Lung (LACOG 0116)

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Introduction: With raising incidence rates, non-small cell lung carcinoma (NSCLC) is the leading cause of death and a major health problem in Latin America. The region faces several challenges to deliver optimal care related to delay in diagnosis, lack of access to biomarker testing and limited access to novel therapies. LATINO Lung is a large observational study describing the current situation of advanced NSCLC in Latin America. We present the first results of patient's characteristics and diagnostic profiles.

Methods: LATINO Lung (LACOG 0116) is an observational prospective and retrospective cohort study which included patients with histologically or cytologically proven advanced NSCLC, distant relapse or de novo metastatic disease, diagnosed between June 2018 to August 2021 in 21 research sites in Latin America. Data were collected from medical charts including patient demographics and clinicopathological features, treatment patterns and outcomes with a follow-up period of up to 3 years. (ClinicalTrials.gov identifier: NCT04227457)

Results: Among 21 participating sites, a total of 727 patients were included, 11 (1.5%) from Argentina, 597 (82.1%) from Brazil, 16 (2.2%) from Colombia and 103 (14.2%) from Mexico. Median age at advanced NSCLC diagnosis was 64.8 years (IQR 57.9 - 72.3), 53.5% (N=389) were white, 69.3% (N=504) were current or former smokers, and 433 (59.6%) had the public healthcare system coverage. Most frequent symptoms at diagnosis were cough in 32.2%(N=234), chest pain 13.9% (N=101), and dyspnea 13.8% (N=100). Median time from first symptom to diagnostic biopsy was 3.3 months (IQR 1.6-6.1). The majority (N=400, 55%) had ECOG PS 0-1, 57.3% (N=419) had adenocarcinoma histology, 87.8% (N=638) were diagnosed with de novo metastatic NSCLC, and 22.7% (N=165) had brain metastasis at diagnosis of advanced disease. Among patients with adenocarcinoma, 79.5% (N=333) had molecular test performed, from 295 patients tested for EGFR, 39.3% (N=116) had EGFR mutation and from 231 patients evaluated for ALK, 12.1% (N=28) had ALK-positive tumors. PD-L1 testing was performed in 50.4% (N=367) of patients, 41.4% (N=152) were PD-L1 negative (< 1%), 31.6% (N=116) had PD-L1 1-49% and 20.2% (N=74) had PD-L1 ≥ 50%.

Conclusions: Patients with advanced NSCLC in Latin America are diagnosed within 3.3 months of the first symptom, the majority have a smoking history although the 30% of non-smokers seems higher than other regions in the West. Importantly, half of the patients presents with a good PS and adenocarcinoma is the most frequent histology. Our results show that molecular testing is performed in 80% of adenocarcinomas in clinical practice and that EGFR mutation and ALK positive tumors are frequent. PD-L1 expression seems similar to other reports. LATINO Lung is one of the largest cohort studies of advanced NSCLC in Latin America and will generate important information on Real World clinical management and will inform critical challenges and public health policies in the region.

Keywords: advanced NSCLC, Latin America, Molecular profile

EP03.01 EPIDEMIOLOGY

EP03.01-004 Impact of Covid-19 Pandemic in Lung Cancer Patients in Albania

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Introduction: Lung cancer is the most common cancer malignancy worldwide. With the spread of the coronavirus disease 2019 (COVID-19) globally, it is important to investigate the impact of Covid-19 in the diagnosis of lung cancer. In Albania, the first case of Covid-19 was reported in Tirana on 8 March 2020

Methods: The aim of this study was to explore how covid -19 pandemic, affected the diagnosis of lung cancer patients.It was retrospective cohort study of newly diagnosed lung cancer patients confirmed by biopsy, according to demographic,clinical, histological characteristics during 2019 and 2020, in the biggest center of lung diseases,in our country.

Results: The total number of lung cancer patients was 377 (2019) and 172 (2020).Male to female ratio was equal 4:1(2019 m/f:296/41;2020:156/16).Median age (2019) was 65,9 years and 63,8 years (2020).60% were NSCLC (2019), 75% NCCL(2020).

Conclusions: Lung cancer diagnosis has been affected during the COVID-19 pandemic. Diagnoses of lung cancer dropped off significantly during the pandemic, 45% less in 2020 compare to 2019, due to prioritization of healthcare toward Covid-19 patients. This study is still ongoing and further data will be collected to better understand the total impact of the COVID-19 pandemic on lung cancer patient population.

	Sqm	Adnca	Small cell	other	Total
2019	148	79	61	49	377
2020	84	45	28	15	172

Keywords: lung, cancer, Covid-19

EP03.01 EPIDEMIOLOGY

EP03.01-005 Clinicopathological Features of ROS1-rearranged Adenocarcinomas: A Single Institutional Experience Spanning Four Years From India

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Introduction: ROS1-rearranged (ROS1-R) adenocarcinomas represent a relatively uncommon but therapeutically targetable molecular subgroup of non-small cell lung carcinomas. Western literature estimates their prevalence at <1% of all non-squamous adenocarcinomas while the prevalence in Asian countries is slightly higher. Here, we present the clinicopathological features of ROS1-R adenocarcinomas diagnosed over the last 4 years from a tertiary care institution in India.

Methods: Study was of combined retrospective (2018-2019) and prospective (2020-2021) design. All patients presenting with advanced stage non-squamous non-small cell lung carcinoma with adequate tumor tissue were routinely subject to epidermal growth factor receptor (EGFR) mutations by qPCR and anaplastic lymphoma kinase (ALK) and ROS1 rearrangement testing by immunohistochemistry supplemented by fluorescence-in-situ hybridisation, wherever required. Immunohistochemistry for ROS1 was performed manually using the D4D6 clone (Cell signalling Technology) and FISH was performed for confirmation of rearrangement in all ROS1-IHC positive cases using either ROS1 single gene probe (CytoTest) or dual ALK/ROS1 FlexISH probe (ZytoVision). Clinical details including follow-up were retrieved from clinical records.

Results: During the 4 year duration, a total of 1463 tumor samples from patients diagnosed as primary lung adenocarcinoma or non-small cell carcinoma (favour adenocarcinoma or not otherwise specified) were subject to predictive biomarker analysis for EGFR mutations with EGFR mutations identified in 508 samples (35% prevalance). Of these, ROS1 IHC was also performed in 723 samples. Diffuse or focal moderate to strong intensity cytoplasmic staining in tumor cells for ROS1 was observed in 64 samples (9%). Of these, 21 samples harboured concurrent EGFR mutations and 10 samples tested positive for ALK-rearrangement. ROS1 FISH confirmed ROS1-R in 13 patients. ROS1-R was not identified in any of the EGFR mutant or ALK-R tumors that were ROS1-IHC positive. The median age of the patients at diagnosis was 44 years (22-71) with male:female ratio of 6:7. Majority (n=9) were never-smokers. All except two presented with metastatic disease, most commonly to bone (n=8), liver (n=2), contralateral lung (n=1), brain (n=1), adrenal (n=1), chest wall (n=1) and thyroid (n=1). Histopathology showed solid pattern adenocarcinoma in majority patients. Nine patients received conventional chemotherapy, four received crizotinib/ceritinib and one received immunotherapy. The median follow-up duration was 8 months, with two patients on chemotherapy dead within 3 months. The median PFS on the patients on TKI was 23 weeks with no deaths reported. One patient diagnosed in 2014 was alive on date and on immunotherapy.

Conclusions: ROS1 rearranged adenocarcinomas accounted for ~1.8% (13/723) of non-small cell lung adenocarcinomas tested in our cohort. Female gender preponderance, younger age at presentation and frequent bony metastases including an unusual presentation as a thyroid mass with occult lung primary were observed. Prospective screening with immunohistochemistry followed by confirmation with FISH is easily implementable to identify ROS1 rearranged adenocarcinomas in routine practice. Non-specific ROS1 immunopositivity is not uncommon in EGFR mutant and ALK-R adenocarcinomas.

Keywords: ROS1, India, FISH

EP03.01 EPIDEMIOLOGY

EP03.01-006 Familial Aggregation in Non-small Cell Lung Cancer - An Observational Study

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Introduction: Lung cancer is typically considered as tobacco related disease, however familial aggregation has also been observed indicating towards possible genetic predisposition. A small proportion of lung cancer patients may also carry a known pathogenic germline variant in hereditary cancer related genes. Ethnic variations in genetic predispositions are known highlighting need of regional data. There is lack of data about familial aggregation in lung cancer from Indian subcontinent. In this study, we aim to evaluate patterns of familial aggregation and its correlation with clinico-pathological and molecular characteristics in Indian non-small cell lung cancer (NSCLC) patients.

Methods: We conducted a single-center observational study to estimate the proportion and pattern of familial aggregation in patients with NSCLC. This study included patients with NSCLC, aged 18 years, who attended our lung cancer clinic between August 2020 to January 2021. We conducted an in-person interview and constructed a three-generation pedigree for each patient. Demographic data and clinicopathological information pertaining to histopathology and molecular subtypes were recorded from the case files of the patients. Significant family history was defined as the presence of at least 1 affected first-degree relative (FDR) and/or 2 affected second-degree relatives (SDR)s.

Results: A total of 270 patients were enrolled. The median age was 55 years (26-82). Males accounted for 68.5% and 46.8% were smokers. Adenocarcinoma was the most common histology (67.4%) followed by squamous cell carcinoma (25.9%). Metastatic disease was present in 75% of patients at diagnosis. Significant family history was present in 50 patients (22.72%). Familial aggregation was observed with both tobacco-related as well and non-tobacco-related malignancies with the most common being carcinoma head and neck (15), followed by breast (7) and lung (8). Tobacco-related malignancies accounted for 61% of all malignancies in affected relatives. On multivariate analysis, we observed that those with a significant family history of malignancy were more likely to be females(p=0.035), and less likely to have a driver mutation (p=0.002).

Association of various clinicopathological factors with a family history on univariate analysis

	Significant family history(n=50)	No significant family history(n=220)	P-value
Median age (in years)	55	55	0.480
Age group <40 years 41-60 years >60 years	5(10%) 23(46%) 22(44%)	27(12.3%) 125(56.8%) 68(30.9%)	0.062
Males Females	28(56%) 22(44%)	157(71%) 63(29%)	0.035
Smokers Non-smokers	19(38%) 31(62%)	110(50%) 110 (50%)	0.125
Adenocarcinoma	38(76%)	144(65.5%)	0.151
Squamous cell carcinoma	10(20%)	60(27.3%)	0.289
Stage at diagnosis Metastatic Non-metastatic	39(78%) 11(22%)	164(74.5%) 56(25.5%)	0.610
Driver mutation (EGFR/ALK/ROS1) (n=190) Present Absent	n=40 15(37.5%) 25(62.5%)	n=150 96(64%) 54(36%)	0.003

Conclusions: Familial aggregation is common in Indian NSCLC patients. It is more frequent in females and driver mutation-negative lung cancer patients with aggregation of tobacco-related malignancies like head and neck cancers and lung cancer over non-tobacco-related cancers in families. This probably might indicate a common genetic susceptibility gene responsible for tobacco related carcinogenesis or an effect of common environmental exposures responsible for familial clustering. Further studies evaluating genetic susceptibility in NSCLC are warranted and may have implications on screening and treatment.

Keywords: Familial Aggregation, Non-small cell lung cancer, Familial Clustering

EP03.01 EPIDEMIOLOGY

EP03.01-007 Comprehensive Genomic Profile of Advanced Lung Cancer in a Region with the Worst Human Development Index in Brazil

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Introduction: Brazil is a developing country of continental dimensions, and the northeast region has the lowest human development index in the country. Lung cancer is an important cause of death, and there is a lack of data on the genetic profile in this region. We aimed to study the comprehensive genomic profile of non-small cell lung cancer (NSCLC) tested in a reference center in northeast Brazil.

Methods: we retrospectively analyzed the results of a next-generation sequencing (NGS) test performed on patients diagnosed with NSCLC in our service from May to December 2021. We described the molecular profile of the tumor samples and also the carachteristics of these patients.

Results: We analyzed data from 53 patients, and about 55% of them were male. Their median age was 71 years old. Smokers or former smokers accounted for 43%. Programmed cell death ligand 1 (PD-L1) expression was analyzed by TPS (tumor proportion score); it was negative (<1%) in 51% of the cases and only 11% had a high expression (≥50%). At the moment of diagnosis, 54% of the patients were metastatic. The most commom mutation was TP53, detected in 54% of tumor samples. The most frequent druggable drive mutations were in EGFR, ERBB2, ALK and ROS1, found respectively in 38%, 9%, 9% and 5% of the patients. TP53 was also the most common comutated gene, found in 45% patients with other mutations. TP53 alterations were observed most commonly in association with EGFR mutations. Tumor mutational burden (TMB) analysis was available in 86% of the cases; 41% of all patients had a low TMB (1-5 mutations/Mb) and only 5% had a high TMB (≥ 20 mutations/Mb).

Conclusions: this analysis showed that patients of our service had similar molecular tumor profile as previoulsy reported in other studies: EGFR alteration as one of the main drive mutations, TP53 alterations as being the most common comutated gene, and most of the patients with low TMB. Also, our data about PD-L1 expression are in agreement with the results of a brazilian study previously publisehd. Knowing the molecular tumor profile of the patients with NSCLC is essential, and more studies are necessary in this poor region of Brazil, to better understand this population genomic profile, allowing physicians to individualize the treatment and offer the best option for each case. Contribuiting to a faster diagnosis, in our service the NGS is performed as a reflex molecular testing requested by our pathologists, after a diagnosis of squamous cell carcinoma in non-smokers or adenocarcinoma.

Keywords: genomic profile, non-small cell lung cancer, NGS

EP03.01 EPIDEMIOLOGY

EP03.01-008 Shift in Lung Cancer Stage at Diagnosis during the COVID-19 Pandemic in New York City

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Introduction: New York City was the first place in the US to record a COVID-19 case on March 1, 2020, and soon became the epicenter of the pandemic. Because of the large number of hospitalized patients, Governor Cuomo imposed a halt on all elective care from March 22 to June 8, 2020. Such action resulted in delayed cancer screening rates, care and treatment. However, no study has quantified the effect of the "pause" on cancer stage at diagnosis, one of the best indicators of cancer prognosis. We analyze here data from the Mount Sinai Heath System cancer registry; we chose lung cancer as an example of a condition where early diagnosis can dramatically modify survival.

Methods: Lung cancer cases diagnosed between January 1, 2018 and February 28, 2021 (n=1884) at the Mount Sinai Health System were identified from Mount Sinai's cancer registry, based on ICD-10 codes of C34.x. Only analytic cases (00-22) were included, based on Commission on Cancer guidelines. For multi-tumor or multi-hospital cases, unique patients were identified by selecting the earliest date of diagnosis. The ratio of the number of monthly cases in 2020-2021 over the average number of monthly cases in 2018 and 2019 was calculated. The percent of monthly diagnoses with early (0/I/II), late (III/IV) and unknown stage over the total number of monthly diagnoses was examined and was compared to the average percent in 2018 and 2019 from the same month.

Results: The number of diagnoses sharply dropped in March 2020, reaching a minimum in April (78% lower than pre-pandemic averages), and returned to near pre-pandemic levels by July 2020, began to decline again in January and February 2021 (35% lower than pre-pandemic averages) (Figure 1a). Stages 0/I/II dropped to 21.9% of total in May 2020, while stage III/IV hit 75% in April 2020. Early stage diagnoses dropped again to 23.5% of total, while late stages increased to 64.7% of total in February 2021 (Figure 1b). The percent of stage III/IV diagnoses in April of 2020 was 1.79 times greater than the pre-pandemic average, the percent of stage 0/I/II diagnoses was 50% lower. The percent of stage 0/I/II cases increased between August 2020 and January 2021, but in February 2021 it was 50% lower than pre-pandemic levels, and the percent of stage III/IV diagnoses was 1.3 times greater than pre-pandemic levels (Figure 1c).

Conclusions: This descriptive analysis suggests an immediate negative impact on lung cancer diagnoses of COVID-19 restrictions, which affected screening, early detection, and drastically reduced any patient's contact with the health system that would have prompted an early lung cancer diagnosis. The increase in late stage diagnoses during pandemic surges may reflect the fact that only sick patients with symptoms, and acute events that require immediate care were seeking hospital attention. The data suggests that we will likely observe an increase in lung cancer mortality in the next few months and years, as consequence of stage shift at diagnosis associated with the COVID-19 pandemic.

Keywords: Lung cancer, Covid-19, Stage shift

EP03.01 EPIDEMIOLOGY

EP03.01-009 BrainMets-Cross-Sectional Study To Identify The Presence Of Brain Metastasis At Diagnosis Of Advanced NSCLC EGFRm in Portuguese Patients

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Introduction: Lung cancer is associated with rising disease burden, most in advanced stages with brain as the predominant metastatic site. Patients with EGFR mutations are more susceptible to develop brain metastasis (BM) than EGFRwt. BM predicts poor prognosis often leading to changes in treatment. We aimed to understand this clinical context that requires deeper scientific investigation.

Methods: BRAINMETS was a multicentric, cross-sectional, interventional study to estimate the presence of BM in NSCLC patients (stage III unresectable or stage IV) in EGFRm NSCLC Patients at the time of diagnosis. Patients with previous primary brain tumors or other malignancies and prior systemic anti-cancer treatment were excluded. MRI assessment was performed within 7 days after inclusion, except those with previous MRI or diagnosis of BM with CT-scan. Descriptive analysis were conducted with results reported as frequencies and medians.

Results: A total of 73 patients were enrolled. Demographics and clinical characteristics of overall population and subgroups according to BM are presented in Figure 1 and Table 1, respectively. Brain imaging data at first visit was available for 58.9% (n=43) patients (MRI, 67.4%; CT scan 32.6%) and BM were detected in 46.5% (n=20). From the overall study population, 41.1% (n=30) of patients were positive for BM. In patients without neurological symptoms 33.3% (n=20/60) were positive for BM while in patients with neurological symptoms, 76.9% (n=10/13) presented BM. Among female patients 50% (n=26/52) were positive for BM, whereas only 19% (n=4/21) of men were positive.

Conclusions: BRAINMETS showed a high prevalence of BM in patients without neurological symptoms, a fact that sustains the need to perform brain imaging at diagnosis. The discrepancy between gender needs to be further validated in order to sustain this observation and further analysis should be conducted to assess the possible role of gender in BM development.

Figure 1 - Overall patients' demographics and clinical characteristics at baseline.

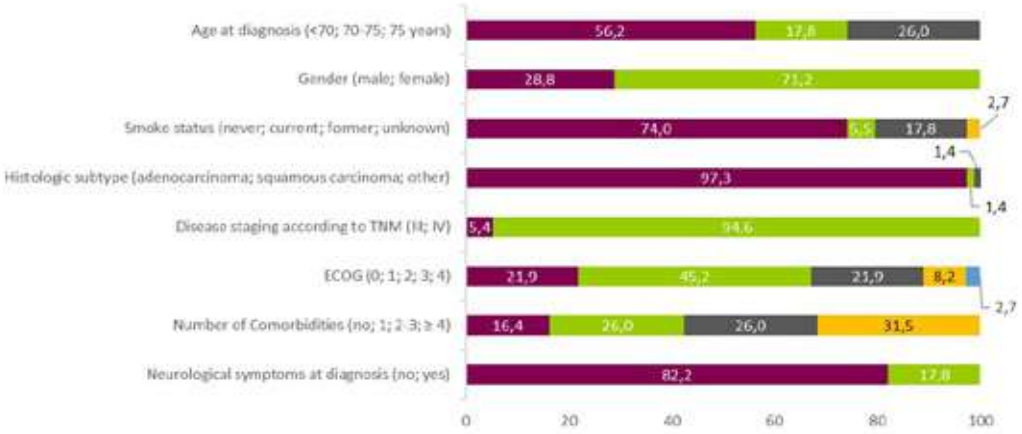

Table 1 - Disease characteristics for patients without brain metastasis and with brain metastasis.

	BM result: Negative		BM result: Positive		p-Value
Demographics (N)	43		30 41.1%, 95%CI=(30.8%;51.3%)		
Age					0,643
<70	24	55,8%	17	56,7%	
70-75	9	20,9%	4	13,3%	
>75	10	23,3%	9	30,0%	
Gender					0,015
Female	26	60,5%	26	86,7%	
Male	17	39,5%	4	13,3%	
Smoking Status					0,666
Current	3	7,0%	1	3,3%	
Former	6	14,0%	7	23,3%	
Never	33	76,7%	21	70,0%	
Unknown	1	2,3%	1	3,3%	
Disease Characteristics					
Histology Type Primary Tumour					0,656
Adenocarcinoma	42	97,7%	29	96,7%	
Squamous cell carcinoma	1	2,3%	0	0,0%	
Other: Poorly differentiated non-small cell carcinoma	0	0,0%	1	3,3%	
Mutations					NA*
Exon 18	0	0,0%	1	3,3%	
Exon 18 Glu709Lys and exon 18 Gly719Ala	1	2,3%	0	0,0%	
Exon 18 G719 variant	1	2,3%	0	0,0%	
Exon 19 Deletion	26	60,5%	15	50,0%	
Exon 19 Deletion and Exon 20 Insertions	0	0,0%	1	3,3%	
Exon 20 Insertions	0	0,0%	0	0,0%	
Exon 20 T790M	0	0,0%	1	3,3%	
Exon 21 L858R	15	34,8%	10	33,3%	
Exon 21 L858R and Exon20 S768I	0	0,0%	1	3,3%	
Exon 21 L858R and Exon 20 T790M	0	0,0%	1	3,3%	
Imaging assessment prior to 1st visit					0,260
No	20	46,5%	10	33,3%	
Yes	23	53,5%	20	66,7%	
Neurological Symptoms					0,004
No	40	93,0%	20	66,7%	
Yes	3	7,0%	10	33,3%	

*NA: Not available

Keywords: Brain Metastasis, EGFRm, advanced NSCLC

EP03.01 EPIDEMIOLOGY

EP03.01-010 Clinicopathological Characteristics of Non-Small Cell Lung Cancer patients in the United Arab Emirates and Correlation with Their Outcomes

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Introduction: Lung cancer is relatively uncommon in the United Arab Emirates (UAE) compared to the rest of the world, ranking the 6th most common cancer. Nevertheless, it is the 2nd leading cause of cancer-related mortality. The main objective of this study was to determine the clinicopathological characteristics of Non-Small Cell Lung Cancer (NSCLC) patients treated at the largest cancer centre in the UAE and correlate these characteristics with their outcome.

Methods: A retrospective review of consecutive NSCLC patients treated at Tawam hospital from January 2016 to December 2020 was conducted. Data were extracted from Electronic Health Records which include patients' demographics, tumour pathological and molecular features, staging, treatments used and overall survival (OS) outcomes. Descriptive and inferential statistical methods were used in analysing the data.

Results: 280 patients with NSCLC were enrolled in this study. The median age of the patients was 60 years (25 - 93), most of them were males (72.1%) and of Arab ethnic origin (66.4%). Almost half of the patients had never smoked (48.2%). The most common pathology was non-squamous carcinoma (78.2%) and most of the patients had stage 4 disease at diagnosis (75.7%). EGFR mutations were detected in 64 (34%) out of 188 patients tested. ALK rearrangements were tested in 180 patients and 27 (15%) were positive. ROS-1 rearrangement was detected only in 3 patients (2.5 %) from 120 patients tested. PD-L1 expression was tested in 198 patients, out of which 139 patients tested positive (70%), and 80 of them (57.5 %) had PD-L1 expression of > 50% The median OS for stage 4 patients was 34M (95% CI, 21M to 45M). Women had much better median OS than men (44M vs 27M respectively). Patients with non-squamous pathology had a longer median OS than squamous (40M vs. 17M respectively). EGFR mutated NSCLC patients had a median OS of 42M compared to 22M for EGFR wild NSCLC. PD-L1 positive NSCLC patients had better outcome than PD-L1 negative group (30M vs 21M respectively)

Conclusions: Our results are consistent with the previously published studies with most NSCLC patients presented with advanced stage and non-squamous pathology. Interestingly, compared to previous literature, we found a higher incidence of EGFR and ALK genetic alterations and better survival across all subgroups, particularly in women, non-squamous pathology, EGFR-mutated and PD-L1 positive patients

Keywords: NSCLC, UAE, Tawam Hospital

EP03.01 EPIDEMIOLOGY

EP03.01-011 Prevalence of KRASMutations in Treatment-naïve Non-small Cell Lung Cancer Patients in Hong Kong

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Introduction: There are limited studies on the prevalence of *KRAS* and *KRAS* G12C mutations in Chinese NSCLC patients in mainland China, reporting from a range of 7.5% to 9.8% *KRAS* mutations and 2.1% to 4.3% *KRAS* G12C mutation in NSCLC patients. In addition to genetic factors, the difference in environmental and lifestyle factors may potentially affect the prevalence of *KRAS* and *KRAS* G12C mutations therefore the aim of this study is to examine the prevalence in Hong Kong NSCLC patients.

Methods: Data from treatment-naïve NSCLC patients with a record of molecular testing by a molecular diagnostics laboratory, Hong Kong Molecular Pathology Diagnostic Centre (HKMPDC), was used. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples were collected and *KRAS* mutations were detected using Sanger sequencing.

Results: A total of 2,120 cases, collected from Jan 2012 till Oct 2021, were analysed in this study. 205 out of 2,120 cases were screened to have *KRAS* mutations, accounting for a total of 9.67% *KRAS* mutations. 99 cases (4.67%) were found to be *KRAS* G12C and 106 cases (5.00%) were other *KRAS* mutations (non-G12C).

Conclusions: This is the first report on the prevalence of *KRAS* mutations in Hong Kong NSCLC patients from a single centre. Similar prevalence of *KRAS* and *KRAS* G12C mutations were found in Hong Kong NSCLC patients compared to studies from Chinese patients recruited in mainland China. This pilot study laid the foundations for estimating potential NSCLC patients who can benefit from emerging KRAS medications and further investigation is warranted for the overview of Hong Kong landscape.

Keywords: KRAS G12C, NSCLC, prevalence

EP03.01 EPIDEMIOLOGY

EP03.01-012 Characterization of Lung Cancer in Patients with High Familial Aggregation of Cancer: Preliminary Data From the SCAN Study

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Introduction: In patients with lung cancer, familial aggregation of cancer has been described. However, the clinical/molecular profile of lung tumors associated has not been characterized. We aimed to describe the profile of patient/tumor in patients with non-small cell lung cancer (NSCLC) and high-familial aggregation of cancer.

Methods: The SCAN study is a prospective study of patients with NSCLC treated at Hospital Clinic between 10/2020-01/2022 (ongoing). All patients had a personal interview to collect personal/family history of cancer (three-generation pedigree), demographic data and exposure to environmental/occupational carcinogens. Clinical/molecular data of the tumors were collected from medical records. We considered high-familial aggregation of cancer in case of ≥1 of these criteria:a) ≥ 4 relatives with cancer on the same family branch;b) ≥3 first/second-degree relatives with cancer (≥1 younger than 60 years old)c) ≥2 first-degree relatives with cancer (≥1 younger than 55 years old).

Results: To date, 202 patients were enrolled. Of the first 156 patients included, 29 had high-familial aggregation criteria (18%). Among them, median age was 64, 45% were female, 72% smokers, 41% had stage IV disease at diagnosis, 72% with adenocarcinoma histology. Amidst 21 patients with molecular profile available, 62% had a somatic driver alteration (7 *KRASm*, 3 *EGFRm*, 2 *BRAFm*, 1 *METm*). Most of patients with high-familial aggregation had personal history of a second-cancer (52%). In females: breast (44%) and lung cancer (33%) were the most common. In males: hematological/bladder cancer were the most frequent (22%) followed by kidney/colorectal/prostate/melanoma (11%). In 10% of cases, ≥2 tumors were seen in the same patient. One case had 4 tumors. Personal history of a second-lung cancer was observed in 10% (all non-smokers). Molecular profile was available in 3 cases: 2 were *EGFRm*. One case had 3 lung tumors. In families with high familial aggregation, the most common tumors were lung cancer (20%/14%/17% in first/second/third-degree relatives), gastric (20%/12%/17% in first/second/third-degree relatives respectively) and breast cancer (10%/10%/13% in first/second/third-degree relatives respectively). Out of 29 patients, 8 were studied at Genetic Counseling Unit (GCU) and a genetic study was performed in 5. The 80% analyzed were carriers of a pathogenic germline variant (1*PALB2*/1*MLH1*/1*APC*/1*CDKN2A*).

Conclusions: In this preliminary cohort, 18% of unselected patients with NSCLC had high familial aggregation of cancer, particularly lung cancer. Unfortunately, this population is not currently studied in GCU's. In the small number of cases studied, the rate of PGV detected is high. Specific criteria for genetic testing should be identified for patients with lung cancer.

Keywords: family history, non-small cell lung cancer, familial cancer aggregation

EP03.01 EPIDEMIOLOGY

EP03.01-013 Improving the Risk Estimation for Second Primary Lung Cancer after Lung Cancer by Taking Histologic Subtype into Account

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Introduction: Previous research has shown that lung cancer (LC) survivors are at increased risk for developing a second primary cancer (SPC) compared to the general population. While this risk is particularly high for smoking-related SPCs, the published standardized incidence ratio (SIR) for lung cancer after lung cancer are unexpectedly low (e.g. 0.83 and 2.06 for males and females in Germany [1]; 1.47 for both sexes in the UK [2]; 1.62 for both sexes in the United States [3]). These SIRs might be underestimated due to the histology-dependent documentation of SPC with the same location as the first cancer and differing definitions of SPC between International Agency for Research on Cancer (IARC) and US Surveillance, Epidemiology, and End Results (SEER) Program.This study aims to improve the estimation of SIR for second primary lung cancer (SPLC) in LC survivors by using histology-specific reference rates for estimating the expected number of SPLC.

Methods: We use data of 146,726 LC survivors from Germany (German Cancer Registry; IARC definition of SPC) and 282,479 LC survivors from the United States (SEER database; SEER definition of SPC) diagnosed between 2002 and 2013. We calculate sex-specific SIRs for second LC based on age-, sex-, region- and period-specific reference rates and compare results for 1) using general references rates for LC provided by the cancer registries with 2) using histology-specific reference rates excluding same LC subtype. We grouped histologic subtype of LC into adenocarcinoma, small-cell carcinoma, squamous cell carcinoma, carcinoid, other NSCLC, and unspecified.

Results: We observed 9750 cases of SPLC in this analysis cohort. The incidence rate was 1906.5 cases per 100,000 person-years for German males, 1438.8 for females and 2931.6 for US males and 2569.5 for females, respectively. We could confirm the comparably low SIR for SPLC after LC when disregarding the histologic subtype (using approach 1). Only 5.1% of patients in Germany, but 47.9% of patients in the US had a SPLC of the same histologic subtype as the first cancer, confirming differing registration practices of multiple primaries. For Germany, SIRs for SPLC after LC differ greatly depending on whether histology-specific reference rates are used or not. For the US, those differences were much smaller.

Conclusions: We showed that when analyzing cancer registry data for the risk of SPLC after LC, an underestimation of SIRs might be reduced by using histology-specific reference rates. This approach appears to improve SIR estimations especially for cancer registries that use the IARC definition of multiple primaries.

Keywords: Second primary lung cancer, Standardized incidence ratio, Cancer registry data

EP03.01 EPIDEMIOLOGY

EP03.01-014 Results From the BEWELL Study: Black Raspberry Nectar for the Prevention of Lung Cancer (NCT04267874)

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Introduction: Lung cancer is a leading cause of cancer deaths. Therefore, prevention strategies are greatly needed, especially in high-risk populations. Dietary interventions can affect disease risk via changes to the microbiome. Black raspberries are a rich source of polyphenols which have attenuated inflammation in preclinical and clinical studies. The BEWELL Study is a placebo-controlled, randomized, cross-over pilot trial that examined the impact of a phytochemical-rich black raspberry (BRB) nectar on markers of chronic inflammation and the microbiome (Trials in Progress, WCLC 2021). We now report the main outome results which are to: 1) measure changes in blood inflammatory cytokines (e.g. CRP, IL-6), and 2) measure changes in the relative abundances of diverse gut microbes.

Methods: Individuals aged 55-77 with 30+ pack-year smoking histories were recruited from the OSU Lung Cancer Screening Clinic and social media. In this 10-week cross-over trial, participants were randomized to consume a 2x80 mL BRB nectar or placebo beverage daily for 4 weeks each, with a 2-week washout period. The specifically designed BRB nectar contained 8%-lyophilized BRB powder suspended in water with pectin and citric acid, while the taste- and texture-matched placebo lacked dietary polyphenols abundant in BRB. Urine, stool and blood were collected before and after each 4-week dietary intervention period. Additional measures included diet compliance, medical history, food frequency and physical activity questionnaires. Plasma cytokines were assessed at each timepoint. Gut microbiome samples were collected in DNAgenotek devices and metagenomic whole genome shotgun sequencing was performed.

Results: A total of 96 individuals consented, 62 initiated the study and 33 completed all study visits. Of these, 73% were former smokers (24/33), with mean age of 65 years (range 58-76 years). Overall adherence (% nectar/placebo consumed) was 97%. After 4 weeks of BRB nectar, individuals showed a lower plasma CRP (paired t-test p-value= 0.06) but not after 4 weeks of placebo (paired t-test p-value= 0.84). Post-BRB, participants had higher relative abundance of the phylum Firmicutes (Wilcoxon signed-rank (p-value= 0.03), which was not observed after placebo. The change in Firmicutes was driven by increased relative abundances of Clostridia (p-value 0.02) in the genera *Ruminococcus* (*R. bicirculans* and *R. lactaris*, p-values= 0.04 and 0.03, respectively), Eubacterium (*E. eligens*, *E. ramulus*, and *E. rectale*, p-values= 0.005, 0.03, and 0.03, respectively), and Lachnospira (*L. pectinoschiza*, p-value= 0.02).

Conclusions: The BEWELL Study successfully implemented a 10-week dietary intervention in high-risk long-time smokers. After the intervention, but not after placebo, plasma CRP was lower, suggesting decreased systemic inflammation and reduced lung cancer risk. In addition, several gut microbes in the phylum Firmicutes exhibited an increase in relative abundance. These microbes have been associated with health outcomes in many contexts, most recently in promoting improved response to immune checkpoint inhibitors (ICIs). These novel results suggest that the BRB dietary intervention is a viable method of reducing lung cancer risk and may promote response to ICIs in the context of active treatment. Future research is warranted to further investigate the role of BRB phytochemicals and response to ICIs for lung cancer prevention and treatment.

Keywords: Lung Cancer, Diet Intervention, Smokers

EP03.01 EPIDEMIOLOGY

EP03.01-015 Disease-Free Survival and Clinical Characteristics in Early-Stage NSCLC Patients From a Danish Cohort

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Introduction: New and targeted treatment options in early-stage non-small cell lung cancer (NSCLC) patients have the potential to increase survival, but further characterization is needed to improve patient selection. Here, we present real-world patient characteristics, survival data, and disease-free survival (DFS) patterns of early-stage NSCLC patients treated in the county of Aarhus, Denmark.

Methods: Stage IB-III NSCLC patients diagnosed between 2010 and 2018 in Aarhus County were included and followed-up until August 2021 (median follow-up 1.58 years). Planned treatment intention and patient characteristics at diagnosis, including EGFR and PD-L1 status, were recorded. Data were linked to socioeconomic position and vital status from the national registries. Surgery (yes/no), stereotactic radiotherapy (yes/no) and occurrence of central nervous system (CNS) metastases were evaluated during follow-up. DFS and overall survival (OS) were estimated using time-to-event methods.

Results: A total of 1443 stage IB-III NSCLC patients were included in the study cohort, of which 610 (42.3%) had been tested for EGFR and 58 (9.5%) had an EGFR mutation (EGFRm+) (Table 1). Surgery was performed in 67.5% of stage IB patients, 70.3% of stage II and 38.3% patients with stage III. Stereotactic radiotherapy was given to 29.1% of stage IB, 14.4% of stage II and just 4.4% of stage III patients that were either ineligible for surgery or progressed with oligometastasis following surgery. Occurrence of CNS metastases increased in patients with stage II and III (8.2% and 8%) compared to stage IB (<4%). A higher proportion of EGFRm+ patients was observed in stage IB (19.7%) compared to stage II (8.2 %) and III (6.4%). PD-L1 expression levels were similar across stages. In the study cohort the median DFS from diagnosis in patients receiving surgery was 37.8 months (32.6-51.1 months) compared to 13.7 months (12,2-15,48 months) for those not receiving surgery. Interestingly, 444 (30.8 %) patients out of 1443 patients did not have disease progression(in 5 years after diagnosis and their survival was comparable to an age and socioeconomic matched background population.

Conclusions: Real-world data on stage IB-III NSCLC patients showed that patients who received surgery had a median DFS of 37.8 months from diagnosis. Additionally, our preliminary observations suggest that curative intended therapy was successful for the early-stage NSCLC patients who did not have disease progression within 5 years from diagnosis.

Table 1:
Patient characteristics of EGFR tested patients by stage, N=610

		IB	II	III(A+B)
	n (%)	117 (19.2)	195 (32.0)	298 (49.0)
Median age (IQR)	Years	73 (66-77)	70 (65-46)	70 (63-75)
Sex	Male	52 (44.4)	93 (47.7)	127 (42.6)
	Female	65 (55.6)	102 (52.3)	171 (57.4)
EGFR status	EGFRm+	23 (19.7)	16 (8.2)	19 (6.4)
	WT	94 (80.3)	174 (91.8)	279 (93.6)
Histology	Adenocarcinoma	109 (93.2)	161 (82.6)	254 (85.2)
	Other	8 (6.8)	34 (17.4)	44 (14.8)
CNS metastasis		<5 (4.3)	16 (8.2)	24 (8.0)
Surgery	Yes	79 (67.5)	137 (70.3)	114 (38.3)
	No	38 (32.5)	58 (29.7)	184 (61.7)
Stereotactic RT	Yes	34 (29.1)	28 (14.4)	13 (4.4)
	No	83 (70.9)	167 (85.6)	285 (95.6)
PD-L1 TC level	<1	30 (48.4)	52 (44.8)	70 (38.9)
	1-49	18 (29.0)	33 (28.4)	46 (25.6)
	>50	14 (22.6)	31 (26.7)	64 (35.6)

EGFR, Epidermal Growth Factor Receptor; WT, Wild Type; CNS, Central Nervous System; RT, Radiotherapy; PD-L1, Programmed Death-Ligand 1.

Keywords: NSCLC, Early Stage, EGFR mutation

EP03.01 EPIDEMIOLOGY

EP03.01-016 The Canadian Small Cell Lung Cancer Database (CASCADE): Results from a Multi-Institutional Real-World Evidence Collaboration

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Introduction: Small cell lung cancer (SCLC) is an aggressive malignancy representing 15% of lung cancers. Good evidence exists to guide upfront treatment, however upon relapse there is only modest prospective evidence available to guide management. Clinical trials are challenging due to the aggressive natural history, urgency to begin therapy, high incidence of brain metastases, and frequent comorbidities in the affected patient population. Therefore, extrapolation of clinical trial results to the general population is troublesome. Real-world evidence (RWE) can play a significant role in identifying whether therapies studied in a controlled trial have equal impact for patients seen in routine practice, inform treatment in settings where evidence is limited, and support regulatory approvals of new therapies. We have initiated a collaborative Canadian SCLC database (CASCADE), including data from multiple sites in order to generate robust RWE.

Methods: CASCADE is a multi-institutional RWE database of patients with SCLC involving 8 Canadian academic institutions: BC Cancer, Tom Baker Cancer Centre, CancerCare Manitoba, Princess Margaret Cancer Centre (PMCC), Cancer Centre of Southeastern Ontario, the Ottawa Hospital Cancer Centre (TOHCC), Jewish General Hospital, and the QEII Cancer Centre. Housed on the REDCap system, CASCADE contains over 150 variables covering baseline demographics, staging information, treatment details, and outcomes for patients with SCLC. We performed a descriptive analysis with data from the first 3 centers, with a primary outcome of overall survival (OS) from the date of diagnosis. Data harmonization is underway for additional the CASCADE sites.

Results: A total of 1925 patients were included across 3 sites (1048 BC Cancer, 671 TOHCC, 206 PMCC). Baseline characteristics include: median age at diagnosis 68, 84 (5%) year of diagnosis 2010 or earlier / 1132 (59%) 2011-2015 / 709 (37%) 2016-2020, 52% female, 58% current / 39% former smoking history, 47% ECOG performance status 0-1/ 42% ECOG >=2. There were 698 (36%) patients with limited stage (LS) disease, and 1225 (64%) with extensive stage (ES). TNM staging included 103 (5%) stage I / 80 (4%) II / 572 (30%) III / 1159 (60%) IV. Twenty-six percent of ES patients had baseline brain metastases. For those with data available, staging investigations included a PET scan for 473/870 (54%), and brain imaging in 809/870 (549 [63%] MRI, 260 [30%] CT). Among 698 patients with LS-SCLC, 588 (84%) received thoracic radiotherapy (490 curative, 97 palliative), 280 (41%) prophylactic cranial irradiation (PCI), and 625 (90%) systemic therapy. For 1225 patients with ES-SCLC, 507 (42%) received thoracic radiotherapy (41 concurrent, 187 consolidative, 273 palliative), 120 (10%) PCI, and 940 (77%) systemic therapy. Median follow-up was 26.3 months (m). Overall survival in the entire patient population was 9.5m (95% confidence interval [CI] 9.0-10.0m). By stage, median OS was 19.8m (95%CI 18.0-22.0m) for LS-SCLC and 6.5m (95% CI 6.0-7.0m) for ES-SCLC.

Conclusions: CASCADE represents one of the largest RWE databases for SCLC. With ongoing data collection and harmonization, CASCADE will capture detailed clinical information about patients with SCLC treated in the real-world and has the potential to contribute to multiple clinical, research, and regulatory questions.

Keywords: small cell lung cancer, real-world evidence, epidemiology

EP03.01 EPIDEMIOLOGY

EP03.01-017 Epidemiology of Lung Cancer in Northern Serbia During the Past Ten Years

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Introduction: Lung cancer (LC) incidence and mortality in Serbia are among the highest in Europe. Changes in LC types by gender have been observed during the last decades, but there are limited data in our country for more accurate analysis. Institute for Pulmonary Diseases of Vojvodina (IPBV) is the health care institution specialized for diagnosis and diagnosis and treatment of pulmonary diseases covering the health management of 1.8 million inhabitants. Since 2009 data of all diagnosed LC patient from Northern Serbian region are entered in IPBVs LC registry (LCR). The aim of this research was to describe changes in demographic characteristics, smoking habits and LC types over the ten-year period.

Methods: Data were harvested using the institutional LCR (age, gander, LC type, stage of the disease, ECOG PS and smoking habits) at the time of LC diagnosis. Observed period was ten years (2011-2020).

Results: Out of total 12.055 LC patients included in our analysis 8.390 (69.6%) were males and 3.665 (30.4%) females. Majority of patient were diagnosed in Stage III/IV 9.725 (80.7%) and in ECOG PS 1 9.360 (77.6%). Early stage of LC (1A) was more often among females (5,3% vs. 3,1%), (p=0.000). During observed period increased number of newly diagnosed LC patients was observed in each following year. This increasement was more prone in female than in male. The average age of LC patients was 64.21 years (25-94 year); 65.56 (64,56±8,455) for males and 63 years for females (63,43±9,035) without major differences during observed period. Majority of LC type in total was NSCLC 77.0% (40,5% adenocarcinoma; 29.5% squamous cell carcinoma), followed by SCLC 15.4% and other carcinoma types 7.6%. Adenocarcinoma (49.9% vs 38.4%) and carcinoid tumors (1.1% vs 0.4%) were more often in females, while squamous cell carcinoma (38.4% vs 19.0%) were more often diagnosed in males (p=0.000). Over the observed period decline in representation of adenocarcinoma and SCLC was observed in female and male as well as of squamous carcinoma in male and increase in representation of neuroendocrine large cell carcinoma in both female and male. Smoking history data showed 61.9% of smokers, 26.7% ex-smokers, and 9.1% never-smokers. Statistically significant difference was observed in gender between never-smoker female and male population (18,3% vs 5,1%) (p=0.000). In females increasement of ex-smokers (from 13.1% in 2011 to 21.1% in 2020) and smokers (57.8% to 65.7%) was observed as well as increasement of never-smokers in males (3.0% to 6.5%).

Conclusions: Number of newly diagnosed LC patients in Northern Serbia during past decade increases over years and this increasement was more prone in female population. Majority of LC patients are still diagnosed in late Stage of the disease with limited treatment option. Maintained high incidence of smokers and the growing of smoking habit among women is alarming. This data indicates an urgent public health measures to decrease high smoking prevalence and to improve early detection of lung cancer.Screening LC program started in 2020

Keywords: Epidemiology, Lung cancer

EP04.01-001 Prevalence And Outcomes of EGFR Exon 20 Insertion Mutation In NSCLC: Princess Margaret Cancer Center Experience

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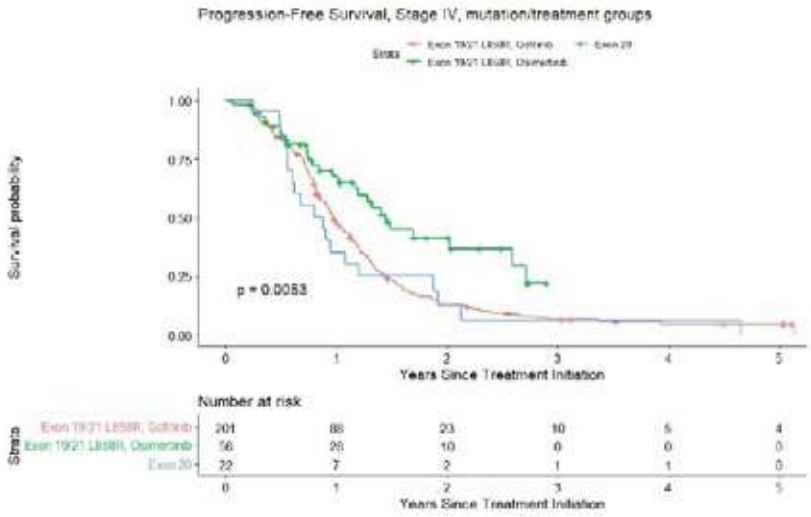
Introduction: The majority of data on the prevalence and outcome of patients with EGFR exon 20 insertion has been derived from studies in Asian population. Real-world data from Canada has been sparse.

Methods: Retrospective chart review was performed to identify patients with stage-IV EGFR-mutated (EGFRm) NSCLC from an existing database diagnosed and treated at Princess Margaret Cancer Centre, Toronto, Canada between 2014-2018. For survival analysis, additional patients were added based on clinician review, diagnosed between 2013-2019. Kaplan-Meier estimators and log-rank tests were used to compare overall (OS) and progression-free survival (PFS) in patients with EGFR exon 20 and classical sensitizing mutations

Results: Among 236 patients with EGFRm stage IV NSCLC, 11 (4.7%) had exon 20 insertion. The estimated prevalence among all metastatic NSCLC patients was 1.5%. An additional 74 patients were included for survival analysis (total n=29 with EGFR exon 20 insertion). Among patients with EGFR exon 20 insertion, median age was 65.8 (22.5-88.3) years and 62% were female; these were similar to our EGFR classical (sensitizing) cohort. Compared to EGFR classical mutations, patients with exon 20 insertion were more often Caucasian [66% in exon 20 vs 25% in classical, p<0.001] but had similar rates of smoking [41% in exon 20 vs 30%; p=0.21]. Within the exon 20 group considering first systemic therapy, 15 (52%) patients received chemotherapy, 3 (10%) patients received combination chemoimmunotherapy, 2 (7%) received afatinib and 1 (3%) received gefitinib; 3 (10%) received only palliative radiation. Median PFS for patients with EGFR exon 20 insertion was 10.5 (7.3-22.6) months], while for those with classical EGFR mutations treated with gefitinib was 11.8 (10.8-13.6) months, and for those with classical EGFR mutations who received first-line osimertinib was 17.4 months (14.1-not reached, NR; p=0.005; figure). Median OS for patients with EGFR exon 20 insertion was 30.8 (20.9-59.2) months; in comparison, median OS for patients with classical EGFR mutations who received osimertinib in first-line was 44.5 (24.4-NR) months, while those who received osimertinib in second or subsequent line was 40.7 (35.4-61.7) months, and for patients with EGFR classical mutations who never received osimertinib, 23.6 (20.9-29.5) months (p<0.0001).

Conclusions: In our cohort, prevalence of EGFR exon 20 insertion was similar to previously published literature. Outcomes of patients remain inferior to those with classical alterations treated with the current standard-of-care osimertinib. There is an urgent need for new effective drugs that improve outcomes for this rare molecular alteration.



Keywords: exon 20 insertion, non small cell lung cancer, real world data

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-002 Costs of Locoregional and Metastatic Recurrences in Patients with Resectable Stage II-III NSCLC in Spain

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Introduction: The Spanish Society of Medical Oncology (SEOM) estimates 30,948 new lung cancer cases in Spain for 2022, and around 85% of lung cancers are non-small cell lung cancer (NSCLC). More than half of patients with resecable stage II-III NSCLC experience disease recurrence within 5 years of treatment, so the economic burden of relapse is expected to be high. The objective of this analysis was to estimate the cost of disease recurrence (both locoregional and metastatic) after appropriate treatment of early-stage NSCLC (eNSCLC) in Spain.

Methods: A two-round consensus panel of 8 Spanish clinical experts (4 oncologists and 4 hospital pharmacists) was conducted. In the first round, experts were asked to complete a questionnaire describing patient's flow, treatment pathways, use of healthcare resources and work leave in patients with NSCLC (both squamous and non-squamous) who relapse after curative intended treatment. After that, a second round was carried out to share the answers, aiming to reduce their variability and reach a common consensus. Then, a decision-tree model was developed to estimate the cost of a recurrence after appropriate treatment of early-stage NSCLC from both the Spanish National Health System (NHS) and societal perspectives. Direct costs included treatment cost for each line and related adverse events, and healthcare resources costs (surgery, radiotherapy, follow-up visits, hospitalizations, tests, etc.). Indirect costs were estimated using the human-capital approach. Unit costs were obtained from national databases and expressed in euros of 2022. Uncertainties were explored through a univariate sensitivity analysis which also provided a range to the mean values.

Results: Among a 100-patients cohort experiencing a relapse, 45 would have a locoregional relapse (of which 36 would eventually progress to metastasis, so 9 patients would be considered in remission) and 55 a metastatic relapse. Patients experiencing metastatic relapse received up to 4 lines of treatment (fourth-line is reached by 3.5% and 11.5% of squamous and non-squamous patients, respectively). Mean (range) total costs of the 100-patients cohort experiencing relapse is €10,049,194 (€7,411,491 - €13,192,023), of which €9,336,782 (€7,025,209 - €12,009,073) correspond to direct costs, while €712,412 (€386,282 - €1,182,950) correspond to indirect costs. The average cost per patient who experiences a locoregional relapse is €24,260 (€19,658 direct costs, €4,602 indirect costs), while the average cost a patient with metastasis who receives up to 4 lines of treatment is €126,833 (€117,328 direct, €9,505 indirect), with the first-line being the main item (accounting for 70% and 52% of the average direct and indirect costs of a metastatic relapse, respectively).

Conclusions: Based on the results of this analysis, the costs of recurrences in resectable stage II-III NSCLC are high and increase considerably in the setting of metastatic relapse. Pharmacological treatment of first-line metastatic disease (specifically, adenocarcinoma histology) represents the greatest impact in terms of costs due to the number of novel therapies in these settings, which represent a higher cost to the NHS. **New treatment options that further reduce the risk of recurrence are needed.**

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-003 Is It Time for a New Paradigm in Care of Young Cancer Patients? A Retrospective Study

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Introduction: advances in treatment of lung cancer (LC) over the past two decades, with target agents (tyrosine-kinase inhibitors, TKI) and immunotherapy (IO) have contributed to improve survival in patients with metastatic non-small cell lung cancer (NSCLC). About 40% of LC patients seek the emergency department at least once during the course of the disease and 63% of these visits lead to hospital admission. Of all intensive care unit (ICU) admissions among patients with solid cancers, 27% refer to LC patients. When these patients need intensive care support, physicians have a hard time deciding the level of investment (to admit to an ICU or not), especially with young patients. We aim to analyze overall survival in young patients and their different subgroups to better understand the outcome of the disease in these patients and in an attempt to help modify the ICU admission criteria.

Methods: retrospective study of patients with NSCLC aged <50 years followed in the Multidisciplinary Unit of a tertiary hospital from November/2016 to September/2021. Demographic, clinical and tumor characteristics were analyzed, as well as global survival (OSm-time between diagnosis and death/last hospital visit).

Results: identified 44 patients, one with 2 synchronous lung neoplasms. They had a median age of 45, 52% were male (n=23) and 75% had history of smoking (n=33). At diagnosis, 84.1% had an ECOG≤1 (n=37) and 68% were in stage IV (n=30). About 75% (n=34) were adenocarcinomas and in 28.9% the expression of PD-L1 was ≥50% (n=13). In 15 neoplasms no molecular changes were identified; in three were identified 2 concomitant oncogenic drivers and in one 3 concomitant oncogenic drivers, making a total of 35 oncogenic drivers in 29 patients. According to the available target therapies, they would be available in 69.0% of patients (n=20). The OSm was 11.2 months (minimum-1.3 months, maximum-59.1 months). In the non-metastatic stages (I-III) the OSm was 24 months; in the metastatic stage (IV) it was 9.2 months, but for those who received any treatment it was 20 months (n=22). Taking into account the first line treatment, the OSm of patients treated with TKI (n=7) was 39 months, with immunotherapy (n=5) it was 48 months and of those treated with chemotherapy (n=10) was 7.3 months.

Conclusions: although LC patients are generally perceived to have worse ICU outcomes compared to patients with other malignancies, some studies suggest that mortality rates are similar. With the new therapeutical options, we have reached a sustained increase in the overall survival, including in the advanced stages (in our study, nearly 2 years within those who received any treatment, 3-4 years if they were treated with TKI/IO). This reveals the importance of systematic molecular characterization of the tumor and of the development of targeted therapies and reinforces that there is a group of patients that responds in a sustained way to IO. We believe that nowadays ICU admission should not be refused to LC patients based solely on diagnosis and/or stage. The decision is complex and must involve pulmonologists/oncologists, intensivists and also the patient.

Keywords: NSCLC, OS

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-004 Interim Feedback on Pilot Public Facing Website for Cancer Clinical Trial Patient-Reported Symptom Data: Project Patient Voice

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Introduction: Patient experience data is rarely included in oncology drug labeling. Over the last 10 years, there have been only 13 oncology drug product labels where this data was included. Project Patient Voice (PPV) is a pilot website developed by the US FDA Oncology Center of Excellence to show patient-reported symptom data from select cancer clinical trials of approved products. PPV is intended to be reviewed by patients and caregivers alongside their healthcare providers (HCPs) when discussing treatment. PPV currently includes AURA3, a phase III study comparing TAGRISSO versus platinum-based chemotherapy in patients with treatment-refractory EGFR-positive NSCLC. LUNGevity conducted patient focus groups (FG) and HCP one-on-one interviews to obtain feedback on PPV to identify potential areas for improvement as well as feasibility of use.

Methods: Qualitative data collection included two patient FGs. Patient FGs included those previously or currently treated for NSCLC (one with those currently or previously treated with tyrosine kinase inhibitors; one with those treated with doublet chemotherapy). HCP interviews included oncologists and nurse practitioners who treated at least 10 advanced-stage NSCLC patients in the past year. Transcripts were coded to identify key themes.

Results: Sixteen participants (8 patients; 8 HCPs) provided feedback on PPV. Both patients and HCPs had favorable first impressions of the website, mentioning that the information was comprehensive, “well organized”, and “easy to understand”. Patients found the pie charts describing the worst response given for a specific symptom over the first 24-weeks of treatment were the most understandable element. They also liked that information “unfolded” by clicking to learn more (e.g., specific symptoms in the table expand to show additional information), thereby offering the choice of the amount of information viewed. Both patients and HCPs perceived the table summarizing symptom frequency for all symptoms to be burdensome. Patients suggested the ability to sort symptoms in the table based on their preference (e.g., alphabetical). HCPs suggested initially presenting three to four of the most common symptoms due to the amount of information patients are given when initiating their treatment. The results for the less common symptoms could then be “unfolded” for those interested. Also, both patients and HCPs felt a video walk-through could be helpful as an additional resource on how PPV should be used.

Conclusions: The concept and usefulness of PPV was well supported by patients and HCPs. Patients appreciated how this could become a reliable “go-to” source of information on patient-reported symptoms. HCPs were open to using a resource like PPV to help patients with treatment decisions, as well as navigating symptomatic side effects during treatment. Feedback from patients and HCPs confirms PPVs feasibility of practical use and may be considered as the FDA expands the PPV pilot website.

Keywords: Patient-reported outcomes, Clinical trials, NSCLC

EP04.01-005 Lung Cancer Diagnosis Following Emergency Admission: Diagnostic and Therapeutic Pathways and Outcomes Within an Italian Cancer Center

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Introduction: Lung cancer diagnosis following emergency admission accounts for 5.3-34.5% of lung cancer diagnoses, with poor survival rates. Most studies focused on factors predictive of this route to diagnosis, with less data about subsequent diagnostic and therapeutic approach to these patients.

Methods: We reviewed data of patients with lung cancer diagnosis following emergency admission from 6 wards of a comprehensive cancer center in Genoa (Italy). Primary endpoint was overall survival (OS); secondary endpoints were probability of starting first-line therapy and probability of oncogene-addiction.

Results: 94.4% of patients underwent systemic staging, and only 83.9% underwent biopsy; 89.5% received molecular characterization; 66.2% received first-line therapy. Median OS for the overall population was 3.9 months (95% CI 2.0-5.8). At univariate analysis advanced stage (p<0.001), age >73 years (p<0.001), Charlson comorbidity index >4 (p=0.002) were associated with shorter OS. In advanced non-small-cell lung cancer subgroup, factors associated with longer OS were: target mutations for first-line treatment (p<0.001); starting a first-line therapy (p<0.001), irrispectively of treatment regimen of choice (as reported in table).

Starting a first-line therapy, according to regimen of choice					
Treatment regimen of choice based on histo-molecular features	**Treated patients; n (%)**	**Treated patients; OS (months)**	**Untreated patients; n (%)**	**Untreated patients; OS (months)**	
Chemotherapy or chemotherapy + immunotherapy	19 (59.5)	5.3 (95% CI: 2.0-8.5)	13 (40.5)	1.8 (95% CI: 0.9-2.9)	p<0.001
Immunotherapy alone	12 (54.5)	12.7 (95% CI: 0.0-26.8)	10 (45.5)	1.3 (95% CI: 1.0-1.6)	p<0.001
Target therapy	14 (100)	23.3 (95% CI: not evaluable)	0 (0)	Not applicable	

At multivariate analysis, favorable prognostic factors were: target mutations for first-line treatment (p=0.018); initiation of therapy (p<0.001). Factors significantly associated with likelihood of starting therapy were age (p=0.0092) and target mutations for first-line treatment (p=0.0183); no clinical factors predictive of oncogene-addiction were found.

Conclusions: Lung cancer diagnosis following emergency admission is associated with extremely poor outcomes, but patients with oncogene-addicted disease have acceptable OS and high likelihood of starting treatment, similarly to outpatients who receive diagnosis of lung cancer. Further studies are needed to define viable strategies to obtain molecular diagnostics earlier, or factors predictive of oncogene-addiction, in order to identify among these patients those worthy of an aggressive approach.

Keywords: emergency, diagnosis, oncogene-addicted

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-006 A Systematic Review (SR) of Cost-effectiveness Analysis (CEA) of ALK Inhibitors (iALK) in Advance Non-small Cell Lung Cancer (NSCLC)

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Introduction: The availability of second (2nd) and third (3rd) generation iALK for NSCLC increased rapidly in the last years. This scenario is associated with an improved in health outcomes, nonetheless the financial burden have become an issue. CEA provides outputs to ease the decision-making process when there is a lack of head-to-head comparison trials of high price drugs as iALK.

Methods: Following PRISMA guidelines, a SR of fully published CEA from 2015 to 2022 evaluating 2nd and 3rd generation iALK used for NSCLC was performed. The main objectives were to address CEA quality using QHES score ; methodology ; preferred perspective, time horizon and threshold ; funding and its relationship with the recommendation made.

Results: Fourteen studies fulfilled the inclusion criteria, 71% analyzed iALK at first line. No studies reporting 3rd generation iALK at first line were found. QHES score was above 75% in selected studies. The main comparison was alectinib vs. crizotinib followed by ceritinib vs.crizotinib. The preferred model was partitioned survival followed by Markov model. Regarding threshold, 6 studies use WHO definition, being 5 performed from a Chinese healthcare system perspective. The remaining were done from the U.S.A. (4), Europe (4), and Canada (1) perspective. Lifetime was selected as the most frequent time horizon. Effectiveness of data was derived from randomized controlled trials. Indirect comparison methods were used when head-to-head trials were not available. All studies reported outcomes in ICER/QALY. Conflicts of interest were not disclosed only in 1 study, of the remaining 13, 30% presented positive COI. All studies performed a sensitive analysis. The main model driver was iALK cost (10;71.42%). The main funding source was the private for-profit sector (9; 64 %). Considering the 9 studies reporting favorable conclusions, 8 were funded by private for-profit sector. All studies funding by government agencies (4) reported negative outcomes.

Conclusions: This review showed how the cost-effectiveness thresholds varied among countries and provided an overview of the available cost-effectiveness findings for stakeholders. Setting thresholds and negotiate drug prices should be prioritized to improve patients access to innovative This review showed how the cost-effectiveness thresholds varied among countries and provided an overview of the available cost-effectiveness findings for stakeholders. Setting thresholds and negotiate drug prices should be prioritized to improve patients access to innovative drugs, as iALK, in timely manner. iALK, in timely manner.

Keywords: ALK, cost-effectiveness

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-007 Impact of Precision Medicine Methods on First-Line Therapies in Metastatic Non-Small Cell Lung Cancer

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Introduction: While next-generation sequencing (NGS) has transformed advanced NSCLC treatment, protocols for testing vary widely. In our hospital system, Northwestern Medicine, the standard for NGS testing at Northwestern Memorial, the main 894-bed academic hospital, is an in-house reflex panel of 50 mutations and fusions sent at NSCLC diagnosis independent of histology or stage. At affiliate hospitals, there are no set protocols so testing is sent out to private vendors. We conducted a retrospective review of patients with de novo metastatic NSCLC to evaluate frequency of NGS testing between these two hospital settings.

Methods: We queried the Northwestern Medicine Enterprise Data Warehouse for patients with newly diagnosed lung cancer in 2019 and 2020 at Northwestern Memorial Hospital (NMH) and two Affiliated Hospitals - Central DuPage Hospital (CDH) and Delnor Hospital. This yielded 864 patients. Inclusion criteria for analysis: 1) de novo metastatic NSCLC with diagnostic evaluation at NMH, CDH or Delnor. Statistical significance was evaluated using 2-sample test for equality of proportions.

Results: 191 patients with stage IV NSCLC met inclusion criteria - 85 at NMH, 106 at CDH + Delnor. 22.4% (19/85) at NMH and 20.8% (22/106) at CDH and Delnor were never-smokers. Median age 70 years - 68 at NMH, 71 at CDH + Delnor. 56% of patients were female. Racial distribution - 74.9% White, 11.5% Black, 7.3% Asian or Native/Pacific Islander, 6.8% declined/other, 4.2% Hispanic/Latino. 89.5% (171/191) of patients had NGS testing at diagnosis - 95% (81/85) at NMH, 84.5% (90/106) at CDH + Delnor (p = 0.009). 94.2% (161/171) had testing for more than EGFR, ALK, and ROS1 - 100% at NMH, 88.9% (80/90) at CDH + Delnor. 29.6% (24/81) of patients at NMH and 21.1% (19/90) at CDH + Delnor (p = 0.10) had targetable mutations for first-line therapy; specific mutations shown in Table 1. 77.4% (148/191) of patients received systemic therapy - 83.5% (71/85) at NMH, 72.6% (77/106) at CDH + Delnor. 31.0% (22/71) at Northwestern received first-line targeted therapies compared with 20.8% (16/77) at CDH + Delnor (p = 0.08).

Conclusions: NGS testing rates were significantly higher at Northwestern than at CDH and Delnor, highlighting the impact of reflex testing. A trend was seen toward higher rates of targetable mutations and first-line targeted therapies with reflex testing. Rates of NGS testing among all sites exceeded those in prior cohort studies (50-70%). Our work demonstrates the importance of reflexive NGS testing in advanced NSCLC diagnosis.

Table 1: Specific mutations seen at each hospital.

NMH (n = 24)	CDH + Delnor (n = 19)
EGFR L858R (7) EGFR deletion 19 (5) MET (4) ALK (3) EGFR – other (2) - Osimertinib-sensitive exon 20 - L861Q ROS (1) NTRK3 (1) BRAF V600E (1)	EGFR deletion 19 (11) EGFR L858R (4) ALK (2) EGFR – other (1) - L861Q BRAF V600E (1) MET (1)

Keywords: NGS

EP04.01-008 Factors Impacting Time from Biopsy to Initiation of Treatment for Advanced NSCLC at an Academic Hospital and Affiliate Hospitals

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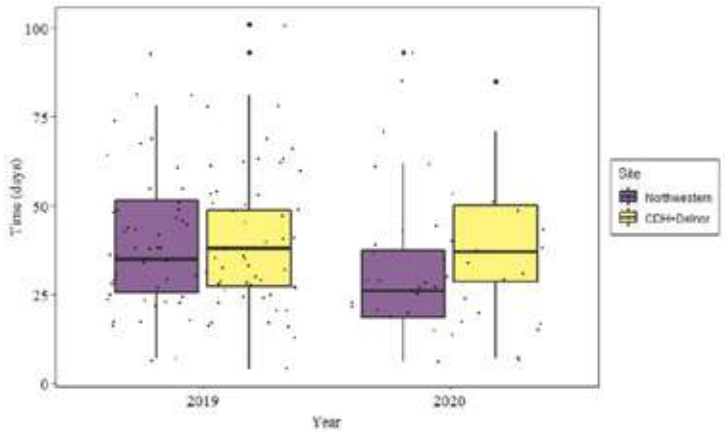
Introduction: Delays in initiation of treatment for advanced cancers are associated with poorer outcomes. In advanced NSCLC, one factor impacting time of treatment initiation is next-generation sequencing (NGS) testing. In our hospital system, Northwestern Medicine, the standard for NGS testing at Northwestern Memorial, the 894-bed academic hospital, is in-house reflex testing on all histologies and stages for a 50-gene panel of mutations and fusions. At affiliate hospitals, there is no set protocol so testing is sent to private vendors. The purpose of this study was to compare time from biopsy to treatment between the academic center and two affiliate hospitals evaluating for impact of NGS testing, radiation therapy, repeat biopsies, and the COVID-19 pandemic.

Methods: We queried the Northwestern Medicine Enterprise Data Warehouse for patients with a new diagnosis of lung cancer between January 1, 2019 and December 31, 2020 at Northwestern Memorial Hospital (NMH), Central DuPage Hospital (CDH), and Delnor Hospital. This yielded a total of 864 patients - 623 (72.1%) diagnosed in 2019 and 241 (27.9%) diagnosed in 2020. Inclusion criteria for analysis: new diagnosis of stage IV NSCLC with diagnostic evaluation conducted at one of the three aforementioned hospitals.

Results: 191 patients with stage IV NSCLC met inclusion criteria, 68.6% (131/191) diagnosed in 2019 and 31.4% (60/191) diagnosed in 2020. 148/191 patients received systemic therapy, 102 diagnosed in 2019 (44 NMH / 58 CDH and Delnor), and 46 diagnosed in 2020 (27 NMH / 19 CDH + Delnor). 59/148 patients had radiation prior to systemic therapy (29 NMH, 30 CDH + Delnor), and 20/148 required repeat biopsy (10 NMH, 10 CDH + Delnor). Median time from first biopsy to treatment was 30 days at Northwestern and 37 days at CDH + Delnor overall; in 2019, these times were 35 days at Northwestern and 38 days at CDH + Delnor, and in 2020, these times were 26 days at Northwestern and 37 days at CDH + Delnor (Figure 1).

Figure 1: Boxplot of time from biopsy to first treatment by year and site



Each plot displays the minimum time from biopsy to first treatment, first quartile, median, third quartile, and maximum. We saw a decrease in time from biopsy to first treatment for patients at Northwestern from 2019 to 2020, but not at CDH + Delnor from 2019 to 2020.

Conclusions: Time from biopsy to treatment decreased between 2019 and 2020 at Northwestern but not at CDH + Delnor, and was shorter overall at Northwestern compared with CDH + Delnor. Radiation therapy and need for repeat biopsy did not differ between the two sites, suggesting that reflex NGS may be associated with faster turnaround times. Fewer patients presented with lung cancer in 2020 than 2019, highlighting the impact of the COVID pandemic on cancer care.

Keywords: NGS, Time to treatment

EP04.01-009 Performance Indicators of Lung Cancer MDT at a Regional Center: Disagreements Between Trust and NLCA Data

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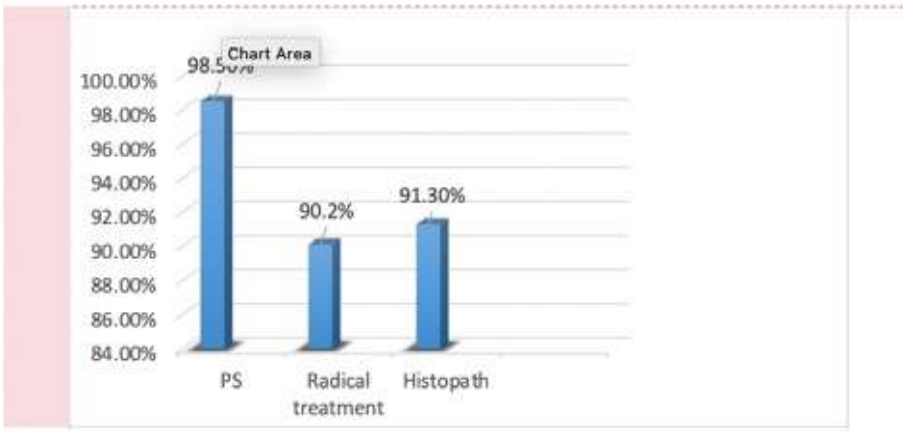
Introduction: • The NLCA has developed a set of Quality Performance Indicators that Trusts providing high quality lung cancer care could be expected to deliver. These require high levels of data completeness to provide meaningful performance indicators such as surgical resection or radical intent treatment for patients to assist Lead Clinicians & Trusts to understand service disparities and maintain quality assurance.• Based on the NCLA 2020 report for patients seen in 2018, we conducted an audit to clarify reasons for not attaining compliance with expected key performance indicators following the merger of two large acute Trusts in 2017• For the affected KPI's, the National Audit recommends that the following benchmarks should be achieved by each trust: 1. PS recorded >90% 2. Radical treatment proportion (surgery/ curative intent radiotherapy) in stage I/II, PS 0-2, NSCLC >80 % 3. Proportion of patients with histopathological confirmation PS 0-1, stage I-II > 90%

Methods: • We conducted a retrospective analysis of the MDT database between 01/01/2018 and 31/12/18 to identify all the cases coded C34-ICD-10• For PS, 3 cohorts were identified where PS was recorded in MDT, where PS was recorded in clinic letters, and those without PS. We merged the cohorts where PS was recorded into one set. Staging data was clarified from the MDT database according to TNMv7.• For path confirmation, we applied a filter to PS data, selecting PS 0-1 & stage I-II. 3 cohorts were identified; Pre treatment, post treatment and radiological.• For radical intent treatment, PS data was filtered for PS 0-2 & stage I-II. 3 cohorts were identified; surgery, radiotherapy and other modalities.

Results: See image

Conclusions: • Following MDT and casenote review, we ascertained that all of the required information was available in the majority of cases. Minor gaps in the MDT database could be identified in out-patient attendance documents.• Overall, our data demonstrated, reassuringly, that the regional centre was successfully achieving the key performance indicators of the NCLA 2020 audit. However, it is disappointing that this is only recognized post-submission to the audit and that a prolonged manual audit is required to address potential quality assurance issues.• Recommendation: To develop a real-time digital dashboard from Trust MDT record to highlight data discrepancies & potential poor performance ahead of national reporting requirements, to facilitate targeted data entry and timely resolution of performance issues.

Results:



Keywords: Lung cancer services, Lung Cancer Audit, Performance of regional center

EP04.01-010 Addressing Barriers to Lung Cancer Care for Diverse Populations through Patient Navigation: The University of Miami Experience

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Introduction: Patients with lung cancer face unique challenges in managing their care, and interventions aimed at improving access to timely diagnosis and treatment are urgently needed. Patient navigation programs have been developed to address barriers to care (e.g., financial, logistical, and communication) across the cancer care continuum. We aimed to evaluate a patient navigation program to identify and address barriers to lung cancer care at the time of diagnosis in a university-based system serving a diverse population.

Methods: From February 2021 to January 2022, new patients aged >18 years with a suspicion or diagnosis of lung cancer were enrolled consecutively. A patient navigator interviewed the patients over the phone and assisted patients with scheduling, paperwork, results, transportation, and other barriers to care prior to their first appointment. The primary outcome was the proportion of patients who reported more than one barrier to care at the time of diagnosis and completed referrals to address those barriers. Demographic characteristics, stage at diagnosis and type of barrier identified were analyzed.

Results: Five-hundred and forty-six new patients with lung cancer (median age 66, range 23 to 97) participated in this study. Eighteen percent of patients (100/546) identified >1 barrier to cancer care. The majority of the patients who reported a barrier were women (51%), Hispanics (62%) and had Stage IV disease (62%). The most common barriers were language/need for interpreter (n=33), followed by financial burden/health insurance (n=30), and technological barriers (n=23). Technological barriers were related to technical issues with setting up telehealth in all cases, and more commonly reported by older patients (age 65+). Physical needs (n=12) and transportation issues (n=2) were less common in this cohort. There were 58 referrals generated by the patient navigators to the social work department to address these barriers.

Conclusions: Utilizing a patient navigation program to address barriers to cancer care is important in increasing access to lung cancer care and can lead to early referrals to supportive services. Language barriers and technical issues related to telemedicine were pertinent barriers for Hispanics. Implementing a patient navigation program to meet the needs of diverse populations is important to develop more equitable care for patients with lung cancer.

Keywords: patient navigation, barriers to care, lung cancer

EP04.01-011 Diagnostic Approach and Treatment of Lung Cancer Patients in Portugal: Portuguese Lung Cancer Study Group Survey

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Introduction: In Portugal, in 2020, 5415 new lung cancer patients were diagnosed and 4797 deaths were caused by lung cancer. Lung cancer ranks third in terms of cancer incidence and is the leading cause of cancer mortality. Early diagnosis, complete and fast patient assessment and staging, multidisciplinary approach, access to personalized medicine, new treatment options and research are essential to improve survival and quality of life. Access to clinical trials is critical for this improvement.The aim of this study is to assess the techniques available to the diagnostic work-up, treatments, the waiting time and the needs perceived by physicians.

Methods: The Portuguese Lung Cancer Study Group launched a survey in order to study the diagnostic approach and treatment of lung cancer patients in Portugal. An online survey with 47 questions was sent to all Portuguese hospitals that treat lung cancer, referring to the pre-COVID-19 pandemic experience.

Results: Responses from 31 Portuguese hospitals were collected, between May and September 2020. Availability to bronchoscopy, image-guided transthoracic needle biopsy (TNB), endobronchial ultrasound- transbronchial needle aspiration (EBUS-TNBA), PET/CT, molecular biology testing is presented in table I.

In 58% (n=18) the molecular biology test was performed as a “reflex test”. About 68% (n=21) of hospitals used next generation sequencing. Two hospitals (7%) reported not having access to liquid biopsies.Video-assisted thoracoscopic surgery was the main surgical technique (61%; n=19). The waiting time for the first radiation oncology consultation was less than 15 days in 71% (n=26). About 61% (n=19) of hospitals had clinical trials. A wide majority of doctors (77%) would like to have more clinical trials. In 71% (n=22) of the hospitals, it was possible to refer patients to Palliative Care receiving systemic anticancer therapy.

Table I- Access and waiting time to diagnostic and staging tools.

Diagnostic test	Availability	Performed at the own hospital	Delay <15 days	Delay 15-30 days	Delay>30 days
Bronchoscopy	100% (n=31)		100% (n=31)		
TNB	100% (n=31)	83.9% (n=26)	77.4% (n=24)	16.1% (n=5)	6.5% (n=2)
EBUS-TBNA	100% (n=31)	35.5% (n=11)	58.1% (n=18)	22.6% (n=7)	19.4% (n=6)
PET/CT	96.7% (n=30)	22.6% (n=7)	51.6% (n=16)	41.9%(n=13)	3.2% (n=1)
Molecular biology test	100% (n=31)		45.2%(n=14)	48.4(n=15)	6,5% (n=2)

Conclusions: Despite the limitations of the methods, this study allowed us to deepen our knowledge about the work-up technologies and treatments available for lung cancer patients in Portugal. It has also identified future opportunities, such as increasing accessibility to some diagnostic tools and clinical trials.

Keywords: Diagnosis and treatment approach, Lung Cancer in Portugal, Health Services Research - Portugal

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-012 Sex and Age-Related Guideline-Adherence Disparities in Non-Small-Cell Lung Cancer Treatment Patterns: Real-World Data

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Introduction: Age-related disparities in lung cancer treatment have been observed with elderly patients being less likely to receive guideline-adherent treatment despite reported benefit. However, studies on the effect of sex in treatment disparity are few. Therefore, we aimed to address this knowledge gap by examining sex and age-related treatment patterns in non-small-cell lung cancer (NSCLC).

Methods: The study was a retrospective population-based observational study. Patients with NSCLC who had their first treatment at the Vaasa Central Hospital between 01.01.2016 and 31.12.2020 were eligible. Patient characteristics including gender, stage at diagnosis, histopathology, BMI, and smoking status were obtained from patient records. The primary outcome was guideline adherence, which was defined according to most recent national and international guidelines. Undertreatment was defined as patients with PS 0-2 not receiving treatment of adequate intensity for each NSCLC-stage defined by guidelines. The risk ratios (RR) for undertreatment in men and women in younger (<75 year olds) and older adults (≥75 year olds) were calculated.

Results: A total of 321 patients with NSCLC were eligible with 209 (65.1%) of them being male and 112 (34.9%) being female. The amount of undertreatment increased with age. In the older adults, 29.1% of men and 37.0% of women were undertreated, as opposed to 26.0% of men and 12.1% of women in younger adults. Overall and in the older adults there was no significant difference between sexes. However, the risk of undertreatment was significantly higher in younger men (RR: 2.15, 95% CI 1.05 - 4.39) compared to younger women.

Conclusions: Our results suggest that sex and age-related disparities may be prevalent in NSCLC treatment patterns. Further studies on patient-related factors affecting treatment choice are being conducted.

Table 1. Characteristics of eligible patients

	Men n=209	Women n=112	p-value
Median age in full years (IQR)	73 (67, 78)	73 (68, 79)	0.860[a]
Median BMI (IQR)	25.8 (23.0, 27.8)	24.8 (22.3, 28.9)	0.972[b]
Stage at diagnosis			
I-II	48 (23.0)	26 (23.2)	0.925[c]
III	43 (20.6)	21 (18.8)	
IV	118 (56.5)	65 (58.0)	
Histopathology			
Adenocarcinoma	119 (56.9)	70 (62.5)	0.272[c]
Squamous cell carcinoma	64 (30.6)	25 (22.3)	
Other NSCLC and unknown histopathology	26 (12.4)	17 (15.2)	
Smoking history			
Current	90 (43.1)	37 (33.0)	<0.001[c]
Former	105 (50.2)	45 (40.2)	
Never	14 (6.7)	30 (26.8)	
Performance status			
0-2	165 (78.9)	85 (75.9)	0.530[c]
3-4	44 (21.1)	27 (24.1)	

[a]Independent Samples Test, 2-sided [b]Mann-Whitney U, 2-tailed [c]Pearson Chi-Square test, 2-sided

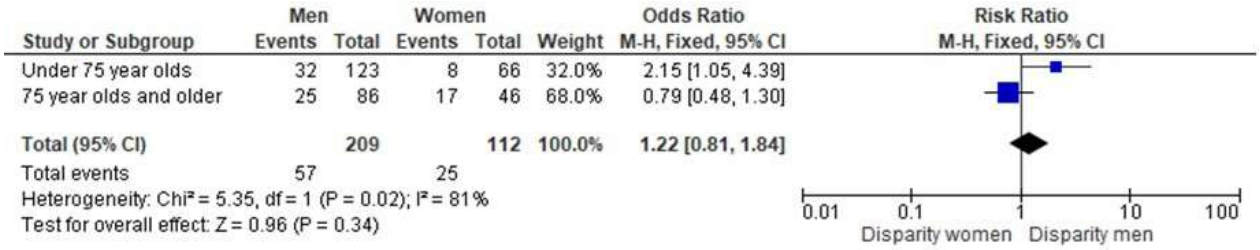

Figure 1. Risk ratio for undertreatment in younger and older men and women.

Keywords: guideline adherence, health disparities, sex

EP04.01-013 Frailty Index Predicts Treatment Outcomes in Older Adults with Lung Cancer

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Introduction: Frailty is prevalent in older adults with lung cancer, and it has been associated with adverse treatment-related outcomes. Measurement of baseline frailty using a multi-domain frailty index (FI) has been incorporated into routine practice for older adults with lung cancer at our institution. The FI is advantageous as it provides a granular measure of frailty, and the multi-domain assessment may identify specific vulnerabilities or areas for therapeutic intervention. The aims of this study were to determine whether baseline FI was associated with treatment completion and adverse outcomes.

Methods: This retrospective cohort study examined the treatment outcomes of 127 patients aged 65 and older with lung cancer who were referred for consideration of systemic therapy of any type between January 2019 and July 2021. The FI assessments were completed by a specialist geriatric oncology nurse prior to first specialist oncologist appointments.

Results: The median age was 73 years (IQR 71-78), and the majority were male (57%). Half of the patients (n=64, 50%) were categorised as a frail (FI > 0.25) and the median FI (IQR) was 0.26 (0.18-0.32). There were no significant differences between the fit and frail cohorts in terms of age, sex, or stage of disease. While ECOG performance status was positively correlated with the FI, a significant proportion of patients (n=29, 34%) with good performance status (ECOG 0-1) were frail. Those who completed treatment were the least frail (FI median[IQR]: 0.21[0.13-0.29]), compared with those who had incomplete treatment (FI median[IQR]: 0.26[0.20-0.30]) or no treatment planned (FI median[IQR]: 0.30[0.25-0.41]). In multivariable ordinal regression, FI was associated with treatment completion. Each 0.10 increase in FI was associated with an increased likelihood of not commencing or not completing systemic therapy, OR 1.82 (95% CI 1.21-2.73; p =.004). Increasing FI was also associated with treatment-related toxicity (adjusted OR 1.91, 95% CI 1.01-3.61; p =.047), and unplanned hospital admissions (adjusted OR 2.15, 95% CI 1.18-3.92; p =.012). In univariable analysis, FI was associated with survival. Frail patients (FI > 0.25) had an increased risk of mortality in Kaplan Meier estimates (HR 3.81, 95% CI 1.92-7.56; p <.001). Age was not a significant predictor of treatment completion, toxicities, or survival.

Conclusions: Baseline FI is a granular measure that can help to identify frailer older adults with lung cancer who may benefit from additional supports or treatment modifications, and also those who are less frail and more likely to tolerate their proposed therapies.

Keywords: Frailty, Geriatric oncology, Geriatric assessment

EP04.01-014 Adherence to Treatment Recommendations From Multidisciplinary Tumor Boards

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Introduction: Lung cancer centers are responsible for coordinating the care of lung cancer patients in a region and to diagnose and treat them according to the latest evidence-based knowledge. In the tumor board an individual treatment plan is discussed and treatment recommendations are given. Therefore, we investigate: 1.) how are the recommendations from tumor boards being adhered to; 2.) which factors determine the adherence of tumor board recommendations and 3.) what is the relationship between the adherence of tumor board recommendations and patient outcomes in terms of OS?

Methods: Data from 1784 newly-diagnosed patients with lung cancer discussed in tumor boards in one certified lung cancer center in Northern Germany between 2014 and 2018 were documented and evaluated according to the adherence to tumor board recommendations. An analysis of 418 cases analyzed will be presented. Data was analyzed descriptively.

Results: Median age of the 418 patients was 67 years (26-91yrs) and 64.5% (n=270/418) of them were male. Most of the patients had an ECOG of 0 or 1 (81%, n=338/418) and 87.3% of them were current or ex heavy smoker (n=365/418). In 84% (n=352/418) of patients, the treatment recommendations from the multidisciplinary tumor boards were completely adhered to. There were different reasons for non-adherence, e.g. patient's wish, patient characteristics and death before starting therapy. The median OS for the 418 patients was 13 months. Patients with a complete adherence to the multidisciplinary tumor board recommendation had an OS of 16 months (n=354) compared to 3 months (n=39) for patients with a partial adherence compared to 3 months (n=24) for patients with a non-adherent treatment ($p<0.000$).

Conclusions: Preliminary results give a hint to the fact that patients with an adherent treatment after first diagnosis had a longer overall survival than patients with another therapy. More cases will be presented at the meeting using a multivariate analysis which includes patient characteristics and healthcare organizations that took over further treatment as predictors.

Keywords: lung cancer, NSCLC, SCLC

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-015 Lung Cancer after Solid Organ Transplantation - A Claims Data Analysis

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Introduction: After solid organ transplantation (SOT), patients are treated with immunosuppressive drugs to avoid acute and chronic rejection of the transplanted organ. Immunosuppression has been linked to a higher incidence of cancers of all types, and cancer therapy of patients with a SOT can be difficult. The aim of this analysis was to determine differences in therapy and outcomes of lung cancer patients with a prior SOT.

Methods: We used claims of 36272 German lung cancer patients diagnosed in 2015 and 2016, and identified patients who had a SOT prior to their lung cancer diagnosis. Our dataset included information on inpatient and outpatient hospitalizations, doctor visits, and drug prescriptions, including costs, ICD codes, and procedural codes from the two years prior to the lung cancer diagnosis to the 3 years following it. We compared patient characteristics, therapy, costs, and survival between patients with and without transplantation as well as stratified by transplanted organ using means with standard deviation and t-test for numeric variables, and absolute and relative frequencies with Chi^2-test for categorical variables. We used Kaplan-Meier curves with Log Rank-test to compare survival.

Results: In total, 85 patients (0.2%) had undergone a SOT prior to being diagnosed with lung cancer. Patients with transplantation were significantly younger (64.8 vs. 69.2 years, p-value <0.0001) and had a higher comorbidity burden (mean Charlson score 4.4 vs. 2.7, p-value < 0.0001) compared to patients without transplantation. Around 60% of tumors were metastasized at diagnosis or after 3 months in both groups, and survival did not differ significantly overall and stratified by metastases. Additionally, we did not find significant differences in the relative frequency of tumor treatments including surgery, radiotherapy and chemotherapy. In this cohort one patient with transplantation (1.1%) received therapy with a checkpoint inhibitor compared to 1.7% of patients without transplantation. Overall costs, and costs for inpatient hospital stays as well as doctor visits were significantly higher for patients with transplantation. Forty-eight patients (56.5%) had received a kidney, 20 (23.5%) a liver, 12 (14.1%) a heart, and 5 (5.9%) received a lung transplant. Metastatic status did not differ significantly by transplanted organ, however, no patient with a lung transplant had distant metastases. Overall therapy did not differ significantly according to transplanted organ. Only 8.3% of patients with a heart transplant received surgery, whereas 40% of patients with a lung transplant did. Immunosuppression with prednisolone was discontinued for 73.3% of patients after diagnosis of lung cancer. Costs did not differ significantly stratified by transplanted organ.

Conclusions: Lung cancer emerges at a younger age in patients with immunosuppression, and advanced disease at diagnosis does not differ between patients with and without transplantation. In patients with lung transplantation, lung cancer seemed to be detected at an earlier stage. Clinical attention to new symptoms and screening measures in SOT recipients might help improve lung cancer detection and survival in this high-risk setting.

Keywords: solid organ transplant, thoracic malignancy, claims data

EP04.01-016 First Comprehensive Lung Cancer Long-Term Survivorship Analysis - Late Toxicities and Overall Survival

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Introduction: More and more patients with lung cancer experience long-term survival (LTS) following multimodality treatment (Tx) protocols. Benefits of LTS have to be critically weighted against long-term toxicities, comorbidity related events and life quality (QoL) in these patient groups. Therefore, we designed a Comprehensive Lung Cancer Long-term Survivorship Program (CLTSP) in patients sequentially showing up for follow-up and surveillance visits after at least 36 months from initial diagnosis.

Methods: Patients planned for follow-up and surveillance (FUPaS) were consented to participate in a comprehensive survivorship investigational program including restaging imaging including brain-MRI, organ function tests, laboratory investigations, and detailed QoL and symptom control analysis including several neurocognitive function tests. Long-term toxicity was classified according to CTCAE4.0 and RTOG-EORTC Late Toxicity criteria. QoL tests were QLQ-C30, FACT-L, and FACT-B. Neurocognitive function tests included trail-making tests, Grooved-pegboard-test, Nürnberger- and Regensburgertest- subscales and imaging analysis evaluated by Fazekas criteria in brain-MRI. Further long-term surveillance and event analysis was carried out following the initial survivorship program until 1/2022. Data were listed according to their probability in the whole CLTSP population and LTS was determined with the Kaplan-Maier method.

Results: From 7/2012 until 10/2013 patients sequentially showing up for FUPaS visits were consented to participate in the investigational CLTSP. 51 pts were accrued after already LTS >36 months, 84% >5 years. At the time of inclusion patients had a median survival since diagnosis of 85 months (range 38-225). Patient characteristics: 32 men, 19 women; age (median; range) 64, 37-77; NSCLC 48, SCLC 3; stages UICC8 IB 4 IIA 4 IIB 5 IIIA 26 IIIB 5 IIIC 3 IVA 3 IVB 1; stage III 67%; histopathology SCC 19, ADC 23 LCC 1 NOS 2 P-NET 1 SCLC 3. Smoking status med 32 packyrs (0-113), treatment CTx 96%, cisplatin 90%, RTx 80% S 82%; Late toxicities detected in the SSP: majority of pts without relevant late toxicities in investigations (CTCAE4.0): cardiac 2°(EF) 4, lung (COPD) IV 3 III 5 II 16 I 4; renal (GFR) 2° 4, 1° 0; endocrine (cortisol) 2° 1, 1° 5; PNP 2° 1, 1° 15, 0° 35. EORTC-QLQ-C30-functional scales (F)(%): Physical-F 74.1, Role-F 72.8, Emotional-F 79.9, Cognitive-F 79.9, Social-F 73.8. EORTC-symptoms with moderate relevance were dyspnoe, fatigue and sleeplessness. Fact-L subscales: physical 23/28, social 22.6/28, emotional 22.8/28, functional 20.6/28. Ability to work (including at home) was evaluated very good in 30.6%, moderate 28.6%, pretty much 20.4%, relatively poor 16.3%, not at all 4.1%. LTS (until 1/2022) median 203 months; 10-yrs-OS-rate 86.3%, 15-yrs-OS-rate 62.9%; overall events 25/51.

Conclusions: Even aggressive multimodality Tx aiming at LTS leads to a relatively moderate late morbidity in LTS > 3 years. Especially, cardiac, lung, renal, and endocrine functions showed no clinically relevant impairment over initial comorbidities. QoL-data and symptom control scores were also only moderately influenced based on the background of initial known comorbidities in our population. Our selected group of LTS patients showed excellent and encouraging LTS. This investigation represents the first reported comprehensive SSP-analysis in LTS-LC with extended long-term surveillance data available for all patients.

Keywords: Lung Cancer, Survivorship, Toxicity and Surveillance

EP04.01-017 Cost-Effectiveness of Atezolizumab for Adjuvant Treatment of Patients with Stage II-IIIA PD-L1+ Non-small Cell Lung Cancer

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Introduction: Chemotherapy was the historical standard of care for adjuvant treatment of early-stage resectable NSCLC. Atezolizumab demonstrated a significant disease-free survival (DFS) benefit versus best supportive care (BSC) as adjuvant treatment following resection and platinum-based chemotherapy for adults with stage II-IIIA (AJCC 7th edition) NSCLC and PD-L1 expression on ≥1% of tumor cells (PD-L1+). This regimen was FDA-approved based on the randomized, open-label, phase 3 IMpower010 clinical trial (NCT02486718). Understanding the economic impact of therapeutic innovations is essential to prioritizing healthcare resources. This study evaluated the cost-effectiveness of atezolizumab vs BSC in this setting from a US commercial payer perspective.

Methods: A Markov model was developed where patients with DFS can progress to locoregional, first- or second-line metastatic recurrence and death. Starting age for all patients was 61 years. A lifetime time horizon and 3% discount rate were used. Treatment duration, DFS and other clinical inputs were derived from IMpower010 (data cutoff: 21 January 2021). Other clinical inputs, utilities and costs were derived from the literature and the IMpower150 (NCT02366143), IMpower110 (NCT02409342) and OAK (NCT02008227) trials. Unpublished clinical inputs were validated with a clinical expert. Sensitivity analyses were performed to test the robustness of model results and identify influential parameters.

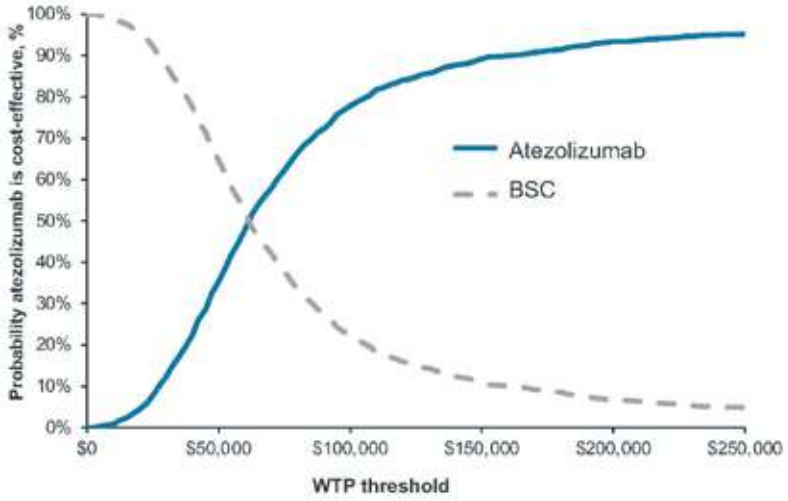
Results: In the base case, atezolizumab was cost-effective at $61,454 per quality-adjusted life-year (QALY), below the willingness-to-pay (WTP) threshold of $150,000. Atezolizumab was cost-effective in 89% of iterations at $150,000 WTP. Atezolizumab drug costs were partially offset by savings from longer time in DFS and fewer recurrences. Results were most sensitive to choice of DFS distribution, duration of treatment effect and time to immunotherapy rechallenge after recurrence.

Conclusions: Atezolizumab is cost-effective vs BSC as part of adjuvant treatment for patients with early stage, resected PD-L1+ NSCLC, supporting utilization of this regimen as the new standard of care in this setting.

Base case model results			
	Atezolizumab (intervention)	**BSC (comparator)**	**Absolute difference**
DFS	$131,179.61	$941.49	$130,238.12
Locoregional recurrence (curative)	$7,666.68	$8,838.79	-$1,172.11
Locoregional recurrence (palliative)	$1,826.87	$3,156.90	-$1,330.03
Metastatic recurrence (1L)	$54,154.64	$77,888.86	-$23,734.22
Metastatic recurrence (2L)	$71,501.69	$101,228.50	-$29,726.81
Total costs	**$292,491.84**	**$227,671.57**	**$64,820.27**
Total LYs	9.27	7.87	1.41
Total QALYs	**6.83**	**5.78**	**1.06**
Cost per LY	Atezolizumab vs BSC: $46,070		
Cost per QALY (ICER)	**Atezolizumab vs BSC: $61,454**		

LY, LIFE-YEAR; QALY, quality-adjusted life-year.

Figure. Cost-effectiveness acceptability curve



Keywords: non-small cell lung cancer, atezolizumab, cost-effectiveness

EP04.01-019 Into the Wild: Assessing Acute Care for Lung Cancer Patients, A Cohort Study to Improve Cancer Care at Emergency Department

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Introduction: Lung cancer (LC) patients are a risk population for Emergency Department (ED) consultation, but information on unplanned care patterns is limited. Optimizing outpatient care requires understanding the acute care needs of our patients.

Methods: We conducted a retrospective study selecting all LC patients treated at the Medical Oncology Department of Puerta de Hierro University Hospital (PHUH) between 2016 and 2020. Data cutoff: June 30, 2021. Our objective was to evaluate the risk ED visit, risk of admission and compliance with the recommended attention time according to the Manchester Triage System (MTS): 0, 10, 60, 120 and 240 minutes for immediate, very urgent, urgent, standard and non-urgent visits, respectively.

Results: Between 2016 and 2020, 821 LC patients were evaluated in the Medical Oncology Department at PHUH. 621 patients (82.9%) needed an emergency consultation, median follow-up of 37.1 months, with 71% of patients attending ED in the first year after diagnosis. There were 2681 ED visits (median: 2 visits per patient; IQR: 1 - 4). Multivariate analysis showed an increased risk of ED consultation for locally advanced patients, HR 1.41 (95% CI: 1.06 - 1.89; p=0.02), and for metastatic patients, HR 1.84. (95% CI: 1.39 - 2.44; p<0.001); compared to local disease. There was also an increase for ECOG 2 vs 0, HR 1.37 (95% CI: 1.04 - 1.80, p=0.027). No association with age, sex, or histology was observed. 42% of ED visits required hospital admission and an association was observed between the extent of the disease and admission, p=0.006, with 35.8%, 39.7% and 45% admissions for local, locally advanced and metastatic respectively. ED visits were classified with the MTS: 0.3% immediate, 12.8% very urgent, 64.9% urgent, 21.6% standard, and 0.4% non-urgent. 91.5% of ED visits were attended within the recommended time for each level of the MTS, showing good compliance with unplanned acute care for LC patients.

Conclusions: Our study shows that ED visits are a frequent event in LC, with 82.9% of patients attending at least once, 71% in the first year after diagnosis. Advanced disease is associated with an increased risk of ED, HR 1.84, and an increased risk of admission. It is necessary to know the patterns of health care to balance resources and needs. The emergency times allow an evaluation of the quality. According to the MTS reference, 91.5% of our patients are treated in less time than recommended, guaranteeing the quality of acute care.

Cummulative Incidence and risk of Emergency Department consultation			
Cumulative incidence (and 95%CI)	**Local disease**	**Locally advanced**	**Metastatic**
3 months	38% (0.28 – 0.47)	38% (0.31 – 0.44)	55% (0.50 – 0.59)
6 months	44% (0.34 – 0.53)	54% (0.46 – 0.61)	67% (0.62 – 0.71)
9 months	48% (0.38 – 0.58)	66% (0.59 – 0.73)	73% (0.69 – 0.77)
12 months	50% (0.40 – 0.60)	70% (0.63 – 0.76)	76% (0.72 – 0.80)
Risk of ED visit: HR (95%CI)	Reference	1.41 (1.06 – 1.89)	1.84 (1.39 – 2.44)

Keywords: Emergency Cancer Care, Patterns of care, Real World Data

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-018 Medical Oncology and Radiation Oncology Consultation in Non-small Cell Lung Cancer (NSCLC). A Population-Based Study Using Administrative Data

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Introduction: Therapeutic advances in non-small cell lung cancer (NSCLC) have shifted treatment away from chemotherapy towards immunotherapy (IO), monoclonal antibody and tyrosine kinase inhibitor (TKI) therapy. Most studies focusing on access to specialist care and lung cancer treatment were conducted before novel therapeutic strategies in NSCLC. This study aimed to better understand and inform referral practices for patients with NSCLC in Ontario.

Methods: A retrospective population-based study using linked administrative health care data was conducted between 2010 and 2019. The study cohort was defined as patients, aged 18 years of age or older, with a stage I to IV NSCLC diagnosis in Ontario. Primary outcome: medical oncology or radiation oncology consultation (MOROC) within 120 days of diagnosis. Prognostic factors for MOROC and receipt of treatment were identified using logistic regression.

Results: 73,849 patients were diagnosed with NSCLC with 61.3% and 50.9% receiving a MOROC respectively. Median time to consultation was 24 days (interquartile range [IQR] 13-49 days). As the stage increased, MOROC was more likely (odds ratio [OR] 6.07, 95% CI 5.78-6.38). As distance to the nearest cancer center increased MOROC was less likely (OR 0.72, 95% CI 0.67-0.78). Stage III NSCLC and patients aged 40-44 years were more likely to receive treatment OR 4.09 (95%CI 3.82-4.38) and OR 3.28 (95% CI 2.51-4.28) respectively.

Conclusions: Even in a universal health care system, socioeconomic factors impact a patient's access to specialist care. Given newer, more effective therapeutic options for NSCLC, access to specialist care must be equitable.

Keywords: non-small cell lung cancer, access, Canada

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-020 Impact of Next-Generation Sequencing on Treatment Choice Among Patients with Metastatic NSCLC from the CHUM University Center

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Introduction: Early identification of actionable mutations with precise molecular testing, such as Next-Generation Sequencing (NGS), has changed the management of patients with metastatic lung cancer. We report real-world data showing how NGS has become an essential tool in determining each patient's molecular profile and allowing the individualization of cancer treatment.

Methods: We retrospectively reviewed the Université de Montréal Health Center's (CHUM) oncology database for patients with NSCLC who undergone NGS analysis from July 2014 to April 2019. Patients were referred for NGS at physician's discretion if they had metastatic NSCLC (mNSCLC) after testing negative for EGFR (exon 19 and 21) and ALK rearrangement. We report patients molecular profiling characteristics, overall-survival (OS), survival from date of metastatic diagnosis (rwOS) as well as the impact on treatment choice, including tyrosine-kinase inhibitors (TKI).

Results: We included 87 patients, among them 40 patients had an actionable mutation (AM), 44 had a non-actionable mutation (NAM) and 3 had no identified mutation. For analysis purposes, we included the 3 patients without mutations to the NAM group. Both groups (AM vs NAM) were balanced with respect to baseline characteristics except for positive smoking status (58% AM vs 91% NAM $p < 0.01$). An average of 2.9 mutations were found per patient. EGFR (exons 18 to 21) was found in 11 patients, ALK variant of unknown significance (VUS) in 3, BRCA in 8, BRAF in 8, ROS1 in 2, MET in 7, HER2 in 6, and NUTM1 in 1. Thirteen patients of the AM group had a VUS. TP53 co-mutation was positive for 35 (40%) patients and KRAS mutation was found in 30 (34%) patients, of which 55% had the G12c mutation. Median time from mNSCLC diagnosis and NGS results were of 120 days. The median time between mNSCLC diagnosis and initiation of treatment was 47 days. Twenty-one patients in the AM group received TKIs with 27% receiving as first-line treatment, 16% in second-line, and 16% in third-line. Of these patients, 8% were directed to palliative care and 65% received chemo-immunotherapy as first-line treatment. While not statistically significant, in part due to small sample size, the 5y OS favoured the AM group vs NAM group (41.4% vs 35.8%, $p=0.313$) with a mOS of 53 months vs 34 months. The median rwOS for patients with AM receiving TKIs vs no TKIs was 31 vs 17 months, with a 5y rwOS of 17.6% vs 26.4% ($p=0.857$). The 5y OS was statistically significant for TP53 status, favouring TP53 negative patients, 54 vs 24 months ($p < 0.01$).

Conclusions: Our study showed that 47% of patients had an actionable mutation found on NGS that was not identified by reflex testing for EGFR and ALK. This modified the course of treatment for 53% of patients who benefited from TKIs. However, the significant delay in actionable mutation identification prevented many patients from receiving targeted therapy. This suggests that early molecular profiling with NGS, ideally done routinely at diagnosis of mNSCLC, is essential in order to personalize patients' treatments.

Keywords: Next-Generation Sequencing (NGS), Metastatic NSCLC, quality of care

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-022 Real-world Evidence of Durvalumab for Stage III NSCLC: Survival Outcomes and Patterns of Care Post-progression

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Introduction: Lung cancer is the leading cause of cancer-related death worldwide. In locally advanced NSCLC, there were few therapeutic options other than concomitant chemoradiation until immunotherapy consolidation with durvalumab has shown improved overall survival (OS) and became a standard of care. There is paucity of real-world evidence (RWE) on effectiveness of durvalumab, especially in Brazil, and limited studies have assessed treatment patterns after completion/discontinuation of durvalumab.

Methods: Retrospective observational study with de-identified data from patients diagnosed with stage III NSCLC who had received durvalumab until February 2022 in the largest private community oncology practice in Brazil. Patient-level information was extracted from an integrated multicenter database that combines structured longitudinal data from electronic health records (EHRs) with elements from unstructured sources using technology-based abstraction techniques by trained curators. Primary endpoint was median OS, and secondary endpoints were time to treatment discontinuation (TTD) and post-progression exposure.

Results: This study included 158 patients with median follow-up was 13 months. Median OS was 32 months with 12- and 24-month OS rates of 85% and 69%, respectively. Only 20 patients (13%) completed 1 year of durvalumab while 112 (71%) discontinued planned treatment after a median TTD of 7 months. Overall, 36 patients (23%) received post-progression therapy, most frequently chemotherapy (45%, exclusively in patients that discontinued durvalumab prematurely), followed by immunotherapy +/- chemotherapy combination (33%, mostly in patients that completed durvalumab) and tyrosine kinase inhibitors (22%). Median TTD of the treatment offered post-durvalumab was 4 months.

Conclusions: Our RWE on consolidation treatment with durvalumab for stage III NSCLC has shown survival outcomes comparable with randomized clinical trial data, despite the shorter median follow-up. Post durvalumab patterns of care differ according to whether patients have completed or not consolidation regimen, with limited effectiveness of existing rescue treatments.

Keywords: Durvalumab, Real World Evidence, Non-Small Cell Lung Cancer

EP04.01-021 Cancer Clinical Quality Registries: A Systematic Review of the Utilisation and Effectiveness of Knowledge Translation Interventions

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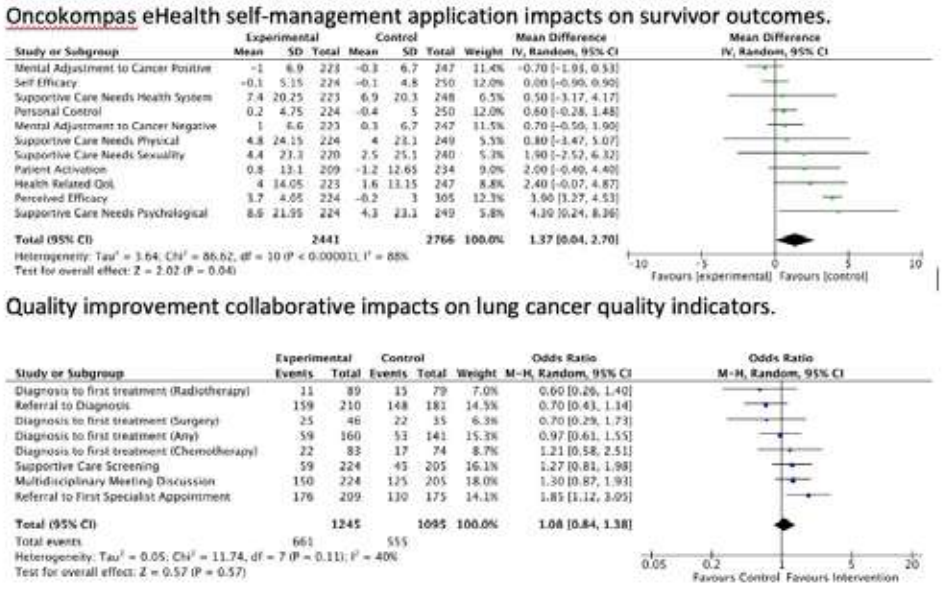
Introduction: Clinical quality registries (CQRs) are essential to support quality improvement in cancer, leading to interventions that improve outcomes. Knowledge translation (KT) strategies bridge the gap between clinical evidence and implementation of solutions. This study is a systematic review of KT strategies utilised, and the effectiveness of them, in the context of cancer CQRs.

Methods: A PICO framework was designed to identify eligible articles. The study was registered in Prospero. Literature searches were performed for studies incorporating KT strategies in relation to CQRs in MEDLINE, Embase, Cochrane, CINAHL, PsycInfo, Web of Science, Scopus and ProQuest. The results were imported into Covidence software for selection by 2 reviewers. Consensus was achieved by discussion between the reviewers and a third reviewer in event of conflicts. Gap analysis was performed using the "Knowledge to Action framework". Two studies had data available for meta-analysis, which was conducted in Review Manager (Cochrane Collaboration, Oxford, UK).

Results: 1496 studies were identified for screening. After applying inclusion and exclusion criteria, 37 were identified from title and abstract review, and only 10 were accepted after full text review. These included reports from UK, USA, Netherlands and Australia (4 regarding lung cancer, 2 breast cancer, and 1 colorectal cancer, and 3 multiple cancers). 5 studies used national registries, 5 state based registries or local databases. Knowledge gap analysis showed that identified studies utilised monitoring and evaluation of data outcomes routinely, consistent with the registry primary function. However identified studies demonstrated minimal exploration of application of these data. These include sustaining knowledge use, approaches to assessment of barriers, adapting knowledge to the local context, and selecting, tailoring or implementing interventions. The meta-analysis of 2 studies showed positive effects of the KT intervention on several domains. One study using a web based behavioural intervention technology showed overall positive effects for patient activation and 10 secondary measures (mean difference of reported measures 1.37 (0.04-2.70), p=0.04). The other study using a quality improvement collaborative showed an increased likelihood of meeting performance standards with odds ratio 1.08 (0.84-1.38), p=0.57).

Conclusions: There was only limited evidence in the literature of utilisation and effectiveness of KT strategies in the context of cancer CQRs, or formal dissemination and implementation strategies to improve decision making in healthcare for cancer. The studies identified mainly reported on monitoring and evaluation. A greater focus on KT strategies is necessary in order to effectively implement interventions resulting from analysis of registry data.



Keywords: cancer quality registries, knowledge translation, quality improvement

EP04.01-023 Development of an Australia and New Zealand Lung Cancer Clinical Quality Registry (ANZLCR)

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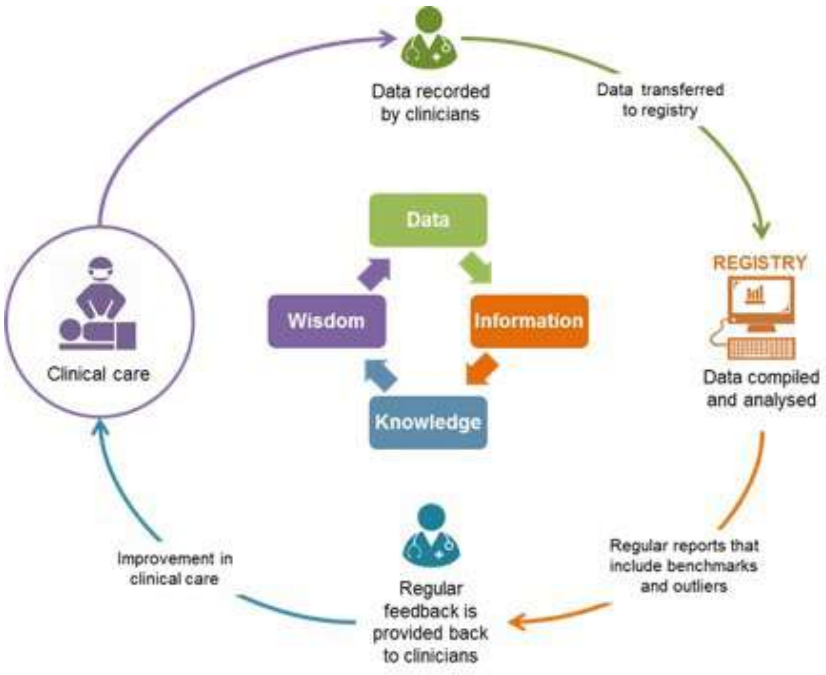
Introduction: Lung cancer is the leading cause of cancer mortality and comprises the largest national cancer disease burden in Australia and New Zealand. Local and regional reports identify substantial evidence-practice gaps with unwarranted variation from best practice, and variation in processes and outcomes of care between treating centres. The ANZLCR will monitor the safety, quality, and effectiveness of lung cancer care by collecting, analysing, and reporting key quality indicators of lung cancer management.

Methods: Patient participants will include all adults > 18 years of age with a new diagnosis of non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), thymoma or mesothelioma.

Methods and analysis: The ANZLCR will register clinical and tissue confirmed diagnoses, using an opt-out consent strategy, mapping the patient pathway from diagnosis through to survivorship or death. Data captured will address key patient, disease, diagnostic and treatment processes and outcomes reported as Clinical Quality Indicators (CQI). A Delphi process will be undertaken to confirm national consensus on lung cancer CQI. Electronic data collection will be facilitated by local data collectors engaging hospital coded ICD-10 data from the EMR. Data linkage will be developed with local, state and federal bodies to enhance data completeness and accuracy. Data will be stored and maintained in a secure web-based data platform, with central data cleaning, risk adjustment, and reporting overseen by a registry management team. National governance will be convened with consumer, patient and carer, governance, administration, health policy bodies, university, and healthcare worker representation. The registry will deliver risk-adjusted, benchmarked reports of clinical performance and outcomes, providing rolling national reporting to enable clinicians, patients and carers, consumers, researchers, health service administrators, government, and policy makers to inform clinical practice and health service decision making in a learning health system.

Results: The ANZLCR has received national ethics approval from Alfred Health Human Research Ethics Committee (HREC) under the National Mutual Acceptance (NMA) scheme (HREC/16/Alfred/84). Data will be routinely reported back to participating site stakeholders illustrating their performance against the measures of agreed best practice.

Conclusions: The ANZLCR will provide risk adjusted, benchmarked, quality indicator reports providing a framework within which it is possible to compare institutional performance with peer and state average outcomes for reported measures. The report may help identify opportunities for improvement within an institution and reflect improvements already undertaken within institutions. Future development will target measures of value, burden and patient reported outcomes.



Keywords: Clinical Quality Registry, Quality Improvement, Perfomance indicator

EP04.01-024 Influence of Lung Diagnostic Assessment Program on Health Resource Utilization in Lung Cancer in Southeastern Ontario, Canada

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Introduction: Lung cancer (LC) is the leading cause of cancer-related mortality and is associated with high socioeconomic impact. The Lung Diagnostic Assessment Program (LDAP) in Southeastern (SE) Ontario, Canada is a rapid assessment clinic that provides efficient and guideline-recommended care for patients undergoing evaluation for suspected LC. We evaluate the influence of LDAP management on health resource utilization (HRU) in the diagnostic phase of suspected LC in SE Ontario.

Methods: A population-based retrospective cohort study was conducted using data obtained from the LDAP database from January 2017 to December 2019. We linked our LDAP database to Ontario Cancer Registry which identified patients with newly diagnosed LC and to identify patients that received care through the LDAP. Data collected included patient and disease characteristics, as well as the number of imaging studies, biopsies, and hospital admissions during the diagnostic phase of LC, defined as the time from first abnormal imaging suspicious for LC to first LC treatment. We compared HRU for those patients receiving care through the LDAP compared to those diagnosed through non-LDAP pathways. Data are presented descriptively as means and N (percent).

Results: A total of 1741 patients with LC were identified; 818 (47.0%) were managed through LDAP while 923 (53.0%) were in the non-LDAP cohort. The average number of hospital admissions per patient in the diagnostic phase was lower in the overall LDAP cohort and lower for every stage of disease. The average number of biopsies per patient was similar but the use of invasive mediastinal staging was higher in the LDAP cohort, a difference seen in all stages of disease, but most pronounced for Stage II. The average number of imaging studies per patient was lower in the overall LDAP cohort, and lower for every stage of disease.

Regarding LC staging imaging, a higher proportion of LDAP patients underwent PET-CT, especially in limited stage disease. A higher proportion of LDAP patients underwent brain imaging, including those with Stage I disease where brain imaging is not guideline-recommended, suggesting overuse of this test. However, a lower proportion of LDAP patients underwent bone scans for limited stage LC. Data shown in Table (1).

Conclusions: LDAP management was associated with fewer hospital admissions and more guideline-appropriate HRU in the diagnostic phase of LC. However, there remain opportunities to optimize HRU in LC care, particularly in terms of reducing unnecessary brain imaging for patients with Stage I disease.

Table 1: Health Resource Utilization in the Diagnostic Phase of Lung Cancer

	LDAP cohort (N = 818)	non-LDAP cohort (N = 923)
Average # Hospital Admissions/ Patient		
Stage I	0.58	0.75
Stage II	0.69	0.86
Stage III	0.45	0.64
Stage IV	0.50	1.05
Unknown Stage	0.66	0.89
Overall	0.55	0.90
Average # Biopsy Procedures/ Patient		
Stage I	0.99	1.24
Stage II	1.59	1.73
Stage III	1.41	1.57
Stage IV	1.30	1.18
Unknown Stage	1.26	0.89
Overall	1.25	1.19

Invasive Mediastinal Stating (EBUS or Mediastinoscopy), n (%)		
Stage I	41 (17.2%)	18 (12.7%)
Stage II	43 (63.2%)	17 (44.7%)
Stage III	92 (60.1%)	57 (50.0%)
Stage IV	67 (25.4%)	38 (9.4%)
Unknown Stage	29 (30.2%)	12 (5.4%)
Overall	271 (33.1%)	142 (15.4%)
Average # Imaging Studies/ Patient		
Stage I	3.06	3.67
Stage II	3.62	4.62
Stage III	3.42	4.14
Stage IV	3.31	4.15
Unknown Stage	3.77	4.53
Overall	3.34	4.18
Brain Imaging (CT or MRI Head), n (%)		
Stage I	143 (60.1%)	68 (47.9%)
Stage II	59 (86.8%)	26 (68.4%)
Stage III	134 (87.6%)	86 (75.4%)
Stage IV	231 (87.5%)	284 (70.3%)
Unknown Stage	66 (68.8%)	86 (38.4%)
Overall	632 (77.3%)	550 (59.5%)
PET-CT, n (%)		
Stage I	211 (88.7%)	97 (68.3%)
Stage II	62 (91.2%)	28 (73.7%)
Stage III	109 (71.2%)	71 (62.3%)
Stage IV	87 (33.0%)	50 (12.4%)
Unknown Stage	60 (62.5%)	32 (14.3%)
Overall	529 (64.7%)	278 (30.1%)
Bone Scan, n (%)		
Stage I	13 (5.5%)	23 (16.2%)
Stage II	3 (4.4%)	9 (23.7%)
Stage III	28 (18.3%)	29 (25.4%)
Stage IV	109 (41.3%)	175 (43.3%)
Unknown Stage	17 (17.7%)	44 (19.6%)
Overall	169 (20.7%)	280 (30.3%)
CT abdo/pelvis, n (%)		
Stage I	63 (26.5%)	53 (37.3%)
Stage II	19 (27.9%)	20 (52.6%)
Stage III	76 (49.7%)	63 (55.3%)
Stage IV	149 (56.4%)	290 (71.8%)
Unknown Stage	46 (47.9%)	114 (50.9%)
Overall	353 (43.2%)	540 (58.4%)

Keywords: Diagnostic Phase of Lung Cancer, Health Resource Utilization, Health Economics

EP04.01 GLOBAL HEALTH, HEALTH SERVICES RESEARCH, AND HEALTH ECONOMICS - COST ISSUES

EP04.01-025 Implementation of Electronic Patient Reported Outcomes in Routine Cancer Care

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Introduction: To realize the broader benefits of electronic patient-reported outcome measures (ePROMs) in routine care, we used the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework to inform the translation of a clinically effective ePROM system (hereafter referred to as the PRM system) into practice. The study aimed to evaluate the processes and success of implementing the PRM system in the routine care of patients diagnosed with lung cancer.

Methods: A controlled before-and-after mixed-methods study was undertaken. Data sources included a self-report questionnaire and interviews with healthcare providers, electronic health record data for PRMs patients and historical controls and field notes. Descriptive statistics, logistic regression modelling, negative binomial models, generalized estimating equations and repeated measures ANOVA were used to analyze quantitative data. Qualitative data was thematically analyzed.

Results: A total of 48/79 eligible people diagnosed with lung cancer completed 90 assessments during the 5-month implementation period (RE-AIM reach). Every assessment breached the pre-defined threshold and care coordinators reviewed and actioned 95.6% of breaches, resulting in 146 referrals to allied health services, most frequently for social work (25.3%), dietetics (18.5%), physiotherapy (18.5%) and occupational therapy (17.1%). PRMs patients had significantly fewer visits to the cancer assessment unit for problematic symptoms (M = 0.23 vs M = 0.43; p = 0.035), and were significantly more likely to be offered referrals (71% vs 29%, p <.0001) than historical controls (RE-AIM effect). There was no change in the level of organizational readiness for change at follow-up, though this was already high at baseline; but significantly more staff reported improved confidence when asking patients to complete assessments (64.7% at baseline vs 88.2% at follow-up, p = 0.0046), and when describing the assessment tool to patients (64.7% at baseline vs 76.47% at follow-up, p = 0.0018) (RE-AIM adoption). A total of 78 staff received PRM system training, and 95.6% of the PRM system alerts were actioned (RE-AIM implementation); and all lung cancer care coordinators were engaged with the PRM system beyond the end of the study period (RE-AIM maintenance).

Conclusions: This study demonstrates the potential of the PRM system in enhancing the routine care of lung cancer patients, through leveraging the capabilities of automated web-based care options.

Keywords: Patient reported outcomes, Lung cancer, Supportive care

EP04.01-026 Cone-Beam CT Guided Navigation Bronchoscopy: A Cost-Effective Modality for the Diagnosis of Pulmonary Nodules

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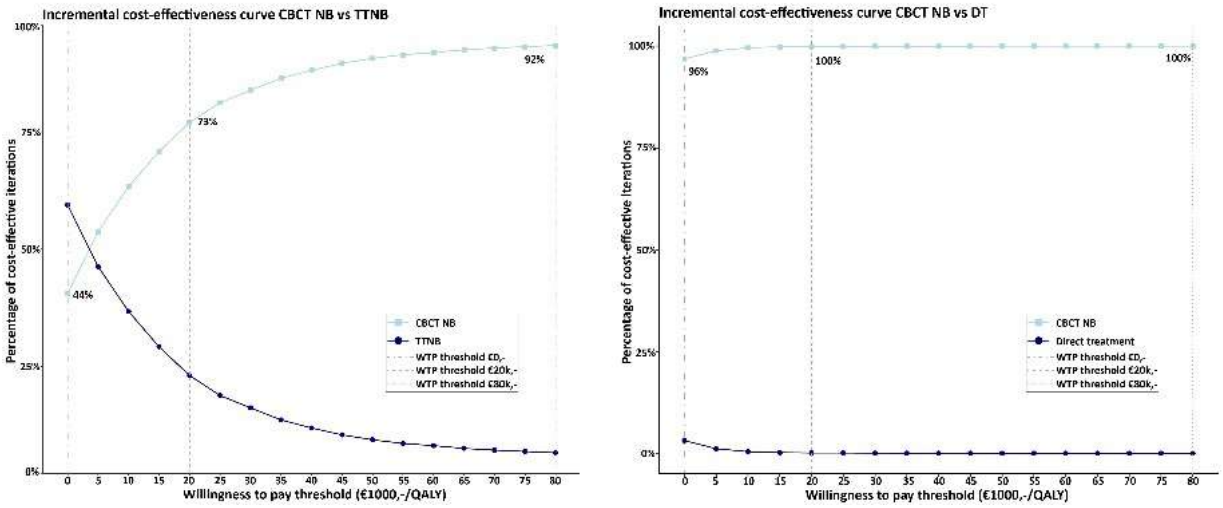
Introduction: With the rising incidence of lung cancer and the anticipated implementation of lung cancer screening programs, the need for minimal invasive diagnostic procedures for small pulmonary nodules (PN) will increase. Cone-beam CT guided navigation bronchoscopy (CBCT-NB) is a novel diagnostic technique which utilizes CBCT to navigate towards and accurately sample small peripheral PN. CT guided transthoracic biopsy (TTNB) is currently the most widely available method of minimal invasive biopsy. It has high diagnostic accuracy, but also high complication rates (~25%). Alternatively, patients are often referred for treatment without pathology proof. CBCT-NB can be a minimal invasive alternative with a low complication rate of ~2-3%, but the potential cost-effectiveness of CBCT-NB has not been evaluated to date. This model-based cost-effectiveness study aims to determine if CBCT-NB is a cost-effective diagnostic procedure in patients with a peripheral PN.

Methods: Two decision analytical models were developed to compare the long-term costs, survival and quality of life. In the first model, CBCT-NB was compared to CT guided TTNB in patients for whom TTNB is suitable. In the second model, CBCT-NB was compared to direct treatment (without pathology proven lung cancer) in TTNB ineligible patients. Input data were gathered in-house, from literature and expert opinion. Effects were expressed in quality adjusted life years (QALYs). A probabilistic sensitivity analysis was performed to assess uncertainty. A distribution was modelled around each parameter to adequately simulate the uncertainty of the model. 5,000 iterations were performed, choosing a different value for every parameter from within these distributions, resulting in 5000 possible outcomes. A deterministic sensitivity analysis was performed to test the relative importance of individual parameters.

Results: CBCT-NB is cost-effective when compared to TTNB (model 1) with an incremental cost-effectiveness ratio (ICER) of €16,190/QALY. CBCT-NB dominated in the direct treatment strategy (model 2) in regard to both costs and effects (-€1316 and +0.103 QALY). Figure 1 shows the percentage of cost-effective iterations in favor of CBCT-NB from the probabilistic sensitivity analysis for different willingness to pay thresholds. In the comparison between CBCT-NB and TTNB, the deterministic sensitivity analysis showed that the diagnostic properties and costs of both procedures have a large impact on the outcome. The minimal required diagnostic accuracy for CBCT-NB to be cost-effective was ~90% vs TTNB and ~65% vs direct treatment.

Figure 1: Incremental cost-effectiveness curves



Conclusions: CBCT-NB seems a cost-effective procedure when compared to both TTNB and a direct treatment strategy in patients with an intermediate risk pulmonary nodule.

Keywords: Navigation bronchoscopy, Early Stage Lung Cancer, Health Technology Assesment

EP04.01-027 Pain and Interventions in Stage IV Non-Small Cell Lung Cancer: A Province-Wide Analysis

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Introduction: Pain is a common symptom in advanced lung cancer. The objective of this cohort study was to examine the utilization and factors associated with interventions for pain in stage IV non-small cell lung cancer (NSCLC).

Methods: Using health services administrative data, a population-based cohort study in Ontario, Canada was conducted of patients diagnosed with stage IV NSCLC from January 2007 to September 2018. Patient characteristics assessed included age, sex, rural residence, income quintile and comorbidity burden. The primary outcome was moderate to severe pain defined by an Edmonton Symptom Assessment System (ESAS) score ≥4. Interventions for pain included palliative care referral, radiation therapy, nerve block and prescription of opiates. The latter was only evaluated in patients ≥65 years, through the Ontario Drug Benefit (ODB) program. The association between patient characteristics and intervention use was estimated using multivariable modified Poisson regression models.

Results: The study cohort included 13,159 patients with stage IV NSCLC, of which 68.5% (n=9,008) reported at least 1 high ESAS pain score. Most patients were managed with a palliative care assessment (85.4%), and the most common therapeutic intervention was radiation therapy (73.2%). For patients ≥65 years of age, 59.6% received an opiate prescription. The use of nerve block was relatively uncommon (0.8%). Patients with high pain scores were more likely to receive palliative assessment (88.1% vs. 79.6%; p<0.001) or radiation therapy (77.1% vs. 64.8%; p<0.001). However, for patients who reported high pain, 4.3% did not receive any intervention for pain (palliative assessment, radiation therapy or nerve block). Older patients (age ≥ 70) who reported high pain were less likely to receive radiation therapy. Patients with greater comorbidity burden and high pain were less likely to receive palliative care and radiation therapy. In addition, patients with high pain from a rural or non-major urban residence were also less likely to receive palliative care. For patients ≥65 years of age with high pain, there was no significant association between patient characteristics and opiate prescription.

Conclusions: Patient-reported moderate to severe pain was common in stage IV NSCLC. Most patients received intervention for pain including palliative care or radiation therapy. Factors associated with interventions for high pain in metastatic lung cancer were described in this study which will help to inform symptom management in this population, particularly in the 4.3% of patients where there is an unmet need.

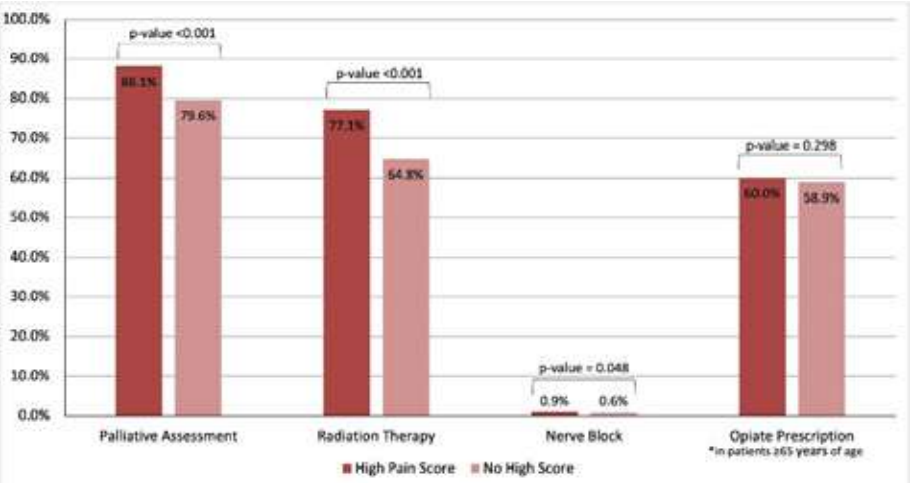

Figure 1. Intervention use stratified by patient-reported pain score

Keywords: non-small cell lung cancer, pain, quality of life

EP04.01-029 Reduction of ER Visits of Lung Cancer Patients Through Care Interventions in Day-To-Day Clinical Service: Experience of a Thoracic Unit in México

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Introduction: Cancer patients seek Emergency Room (ER) attention due to several clinical concerns, including symptoms associated with their cancer diagnosis or side effects of cancer treatment. Potential risk factors to attend ER include disease´s stage, systematic treatment effects, advanced age and socioeconomic status. The most common symptoms reported for ER presentation were pain, respiratory symptoms including dyspnoea, nausea, vomiting and disease progression. Lung cancer patients have reported the highest ER utilization. Preventive care interventions can reduce those unnecessary ER visits for lung cancer patients.The aim of this study was to assess the impact of preventive care interventions during outpatient clinics to avoid unnecessary ER visits of advanced non-small cell lung cancer (NSCLC) patients.

Methods: Patients and their primary caregivers in preventive care intervention were instructed, during clinical visits, on how to better manage the side effects of the treatment at home including care coordination strategies during outpatient systemic therapy treatment. Medical records of 176 patients with advanced lung cancer who visited ER between January 2011 and December 2021 were reviewed and splitted into two categories: group A (patients without preventive intervention) and group B (patients with preventive intervention). For each group, the number of ER visits (1yr period, the symptoms prompting the visit, and the proportion of cancer-related issues, were identified.

Results: A total of 176 advanced lung cancer patients were reported between 2011 and 2021. The average age of the patient was 64 years, and 50% of patients were male. In the same period of time, a total of 310 ER visits occurred. Cancer-related symptoms that lead to ER attention were Dyspnea (28 %), followed by pain (19%), gastrointestinal symptom (14%), fever (8%) and neurologic (5%). Cancer-unrelated issues ending in ER visits were mainly infections (21 %), followed by fever (19%), pain (16%), and gastrointestinal (9%). The analysis of Group A versus Group B revealed that the proportion of ER visits were reduced significantly by 44% in group B ($p<0.05$). Overall, the proportion of ER cancer-related visits were higher in group A.

Conclusions: In conclusion, our study showed that preventive care interventions can reduce unnecessary ER visits among lung cancer patients and the proportion of cancer- related complaints. However, further studies should be conducted.

Keywords: Lung Cancer, Emergency Room, Prevention

EP04.02-001 Sex as a Potential Independent Prognostic Factor in Non-Small Cell Lung Cancer Survival

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Introduction: This is an update of an abstract entitled "The impact of sex on non-small cell lung cancer survival in Canada" that was presented at WCLC 2021. The leading cause of cancer-related death in Canada is lung cancer, with non-small cell lung cancer (NSCLC) accounting for the majority of lung cancer cases. Studies from other countries have demonstrated differences in NSCLC survival by sex, even after accounting for other factors. There has yet to be a robust analysis of the role of sex in NSCLC survival in the Canadian context. Here we evaluate the impact of sex on survival among a population-based Canadian cohort of lung cancer patients.

Methods: A retrospective cohort study was completed using real-world data from the Glans-Look Lung Cancer Research database (GLR). The GLR contains demographic, clinical, pathological, treatment, and outcome data for all individuals diagnosed with NSCLC in Alberta, Canada, between 2010 and 2017. Descriptive statistics were used to characterize the cohort, and basic survival analyses were completed using Kaplan-Meier estimates with log rank tests. Univariable and multivariable analyses were performed with Cox proportional hazards models. Overall survival (OS) was defined as time from diagnosis to death from any cause.

Results: The cohort included 10,849 patients, of whom 80.66% were deceased at end of follow-up. 49.20% of the cohort was female, and median age was 70.40 years (IQR 62.84-77.46). The stage at diagnosis distribution was 18.19% stage I, 10.04% stage II, 17.02% stage III, and 53.38% stage IV. Adenocarcinoma and squamous cell carcinoma represented 51.82% and 22.44% of histological subtypes, respectively. Median OS was 11.10 months (95% CI 10.77-11.50) for the total cohort, 9.33 months (95% CI 8.83-9.87) for males, and 13.57 months (95% CI 12.90-14.40) for females. Significant differences in OS were found when stratified by sex and stage or subtype ($p < 0.01$). In univariate analysis, male sex had a hazard ratio (HR) of 1.32 (95% CI 1.26-1.37). Multivariable analysis also indicated that male sex had an increased hazard of death compared to female sex (HR 1.28, 95% CI 1.23-1.34).

Conclusions: In this population-based Canadian cohort, females with NSCLC tended to have longer survival than males with NSCLC, independent from the effect of differences in stage, histology, and treatment. These results are similar to those seen in other western countries, and further research is needed in the consideration of sex as an independent prognostic factor for NSCLC survival.

Multivariable Cox proportional hazards model of sex in survival in the GLR		
Characteristic	**Strata**	**HR (95% CI)**
Sex	Female	Ref (1.0)
	Male	1.28 (1.23-1.34)
Age	-	1.00 (0.99-1.00)
Stage	I	Ref (1.0)
	II	1.67 (1.51-1.85)
	III	2.39 (2.20-2.60)
	IV	4.93 (4.58-5.32)
Subtype	Adenocarcinoma	Ref (1.0)
	Squamous Cell Carcinoma	1.14 (1.08-1.21)
	Other	1.10 (1.04-1.16)
Surgery	No	Ref (1.0)
	Yes	0.36 (0.33-0.40)
Radiation	No	Ref (1.0)
	Yes	0.89 (0.85-0.94)
Systemic Therapy	No	Ref (1.0)
	Yes	0.44 (0.42-0.47)

Keywords: sex, survival, prognosis

EP04.02-002 International Consensus on Actions to Improve Lung Cancer Survival: Delphi Method in the International Cancer Benchmarking Partnership

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Introduction: The ICBP is a global partnership of clinicians, academics, data experts and policymakers. It is the first of its kind seeking not only to quantify international variation in cancer survival, incidence and mortality in high-income countries, but also, to explore factors that might influence observed variations. ICBP research demonstrates that international variation in lung cancer survival persists, particularly within early stage disease. There is a current lack of published international consensus on critical contributing components to variation in outcomes and the steps needed to optimise lung cancer services to improve the quality of options for and equitable access to treatment, and ultimately improve survival.

Methods: Semi-structured interviews were conducted with 9 key informants from ICBP countries. An international clinical network representing 6 ICBP countries (Australia, Canada, Denmark, Ireland, New Zealand & the UK) was established to share local clinical insights and examples of best practice. Using a modified Delphi consensus model, network members suggested and rated recommendations to optimise the management of lung cancer. Calls to action were developed via Delphi voting as the most crucial recommendations, with Good Practice Points included to support their implementation.

Results: Five Calls to Action and thirteen Good Practice Points applicable to high income, comparable countries were developed and achieved 100% consensus. Calls to Action include (1) Implement cost-effective, clinically efficacious, and equitable lung cancer screening initiatives; (2) Ensure diagnosis of lung cancer within 30 days of referral; (3) Develop Thoracic Centres of Excellence; (4) Undertake an international audit of lung cancer care; and (5) Recognise improvements in lung cancer care and outcomes as a priority in cancer policy. Calls to Action should be interpreted as key priorities to inform policy not only across the ICBP countries, but in similar high-income countries globally. It is recognised that different countries will have differing resource, capacity, funding, and population-based needs and should action these recommendations accordingly to their local settings

Conclusions: The recommendations presented are the voice of an expert international lung cancer clinical network, and signpost key considerations for policymakers in countries within the ICBP but also in other comparable high-income countries. These define a roadmap to help align and focus efforts in improving outcomes and management of lung cancer patients globally.

Keywords: Health policy, Lung cancer, Public health

EP04.02-003 Improving Supportive Care for Patients with Thoracic Cancer

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Introduction: Improving lung cancer care among Veterans is a priority within the Veterans Affairs due to higher rates of lung cancer incidence, morbidity, and mortality among Veterans compared to non-veterans. Unaddressed symptom burden is common among Veterans with lung cancer due to many factors. These factors include complex comorbidities and psychosocial challenges, including concurrent smoking related illness such as cardiac disease and diabetes and limited social support networks. Additionally, complications from social determinants of health can obstruct successful discussions of symptom-burden between Veterans and their clinical care teams and can limit compliance with recommended symptom management strategies. To overcome these barriers, in collaboration with a Veteran and Family Advisory Board, we conducted a randomized controlled trial to test the effectiveness of a lay volunteer-led proactive symptom assessment and symptom education intervention. The objective was to determine if the intervention improved clinician documentation (defined as clinician documentation of patient-reported symptoms that required intervention by the nurse practitioner) from baseline to 6-months post-enrollment compared to usual care. Secondary outcomes included change in patient activation (defined as patients' willingness and ability to take independent actions to manage their health), health-related quality of life (HrQOL), and symptom-burden.

Methods: Patients were randomized into the lay volunteer proactive symptom assessment intervention with usual cancer care (intervention group) or usual cancer care alone (control group). We conducted electronic health record review to assess primary cancer-clinician symptom documentation of Veterans' symptoms that were identified as moderate-to-severe at baseline and 6-months using the Edmonton Symptom Assessment Scale assessments. We also administered patient surveys with validated assessments to assess patient activation, HrQOL and symptom burden both at baseline (time of enrollment) and 6-months post-enrollment. We used regression models to evaluate differences in our primary and secondary outcomes.

Results: 60 Veterans were consented and randomized into the study (29 control; 31 intervention). There were no differences in demographic or clinical factors across groups. The median age was 70 years (range 56-85), 95% were male (95%), 10% identified their ethnicity as Latino or Hispanic, 70% identified their race as White, 53% were married and 48% had a 2-year or 4-year college degree. The majority (54%) had at least 3 comorbidities (54%), were diagnosed with stage 3 or 4 (62%) and receiving systemic treatment with chemotherapy and/or radiation (77%). At 6-months post-enrollment as compared to baseline, the intervention group had greater improvements in symptom documentation (56% from 12.5% vs. 29% from 43%, p=0.01), greater improvements in patient activation (p<0.001), HrQOL (<0.001), and lower symptom burden (p<0.001) than control group participants.

Conclusions: Integration of proactive symptom assessment by lay volunteers has a significant and meaningful effect on symptom documentation, patient activation, quality of life, and reducing symptom burden among Veterans with lung cancer.

Keywords: Symptom management, Acute care use, Veterans

EP04.02-004 The Patient Impact of Liquid Biopsy - Health-Related Quality of Life in Patients Undergoing Liquid Biopsy for Advanced Non-Small Cell Lung Cancer

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Introduction: Liquid biopsy (LB) with plasma cell-free DNA (cfDNA) next-generation sequencing (NGS) leads to more complete molecular profiling with faster turnaround time than tumor tissue (TT) profiling alone and may be cost-effective. The impact of comprehensive LB testing at diagnosis or progression on patient's quality of life (QOL) in advanced NSCLC has not been previously reported. In this prospective multicentre Canadian study using LB to guide treatment, we tested the hypothesis that by identifying more candidates for targeted therapy, patient-reported QOL outcomes would be improved.

Methods: Six Canadian centres enrolled 210 patients, 150 patients with treatment naïve advanced non-squamous NSCLC (Cohort 1, C1) and 60 with acquired resistance to targeted therapy (Cohort 2, C2; NCT03576937). LB testing was conducted at a central lab with an FDA-approved comprehensive cfDNA NGS test; standard-of-care TT profiling was conducted at each local academic centre. All patients completed the EQ-5D-5L at baseline and 3 months post study enrolment. A subset of patients at a single centre also reported willingness-to-pay (WTP) for LB using a structured questionnaire. Changes in EQ-5D visual analogue scores (VAS), Canadian health utility values and WTP data are presented.

Results: Global QOL data by VAS were available for all patients at baseline and 78% at 3 months. For treatment naïve patients, the mean baseline VAS was 62.4 and 68.2 at 3 months (mean Δ+3.7, SD 21.4). In patients progressing on targeted therapy, mean baseline VAS was 70.5 and 67.2 at 3 months (mean Δ-5.0, SD 18.4).

Treatment naïve patients who received targeted therapy had improved global QOL compared to those receiving non-targeted therapy (mean Δ+7.4 versus -1.5, p=0.04). Among patients receiving non-targeted therapy, QOL at 3 months appeared to decrease with chemotherapy (mean Δ-6.4), improve for those receiving checkpoint inhibitor monotherapy (mean Δ+6.1) and was similar among those receiving chemo-immunotherapy (mean Δ+2.0).

Patients with treatable alterations detected by LB or LB+TT had improved QOL (LB +8.2, LB+TT +7.4, TT only +3.9) compared to those without alterations detected (mean Δ-3.9). Patient-reported health utility scores were numerically higher for those receiving targeted therapy compared to non-targeted therapy but not significantly different.

Of 75 patients (54 C1, 20 C2) that reported WTP in the context of a universal funded public system, 2 indicated they would not undergo LB testing if additional payment was required. The median WTP was $400 CAD (IQR $100-$1000). Patients believed a reasonable price (RP) for self-payment for LB was $100 CAD (median; IQR $0-$400). There were no significant differences in WTP or RP among treatment naïve versus pre-treated patients nor by age, sex, ethnicity or smoking status.

Conclusions: Comprehensive liquid biopsy testing at diagnosis leads to more patients accessing first-line targeted therapy, which in turn results in better patient QOL compared to those receiving non-targeted therapy. Patients in a publicly funded health system were willing to pay for testing. Detection of actionable alterations by LB improved QOL in our study and should be incorporated into routine molecular testing for advanced lung cancer patients.

Keywords: liquid biopsy, quality of life, targeted therapy

EP04.02-005 First Comprehensive Lung Cancer Long-Term Survivorship Program - Late Toxicities and Overall Survival

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Introduction: More and more patients with lung cancer experience long-term survival (LTS) following multimodality treatment (Tx) protocols. Benefits of LTS have to be critically weighted against long-term toxicities, comorbidity related events and life quality (QoL) in these patient groups. Therefore, we designed a Comprehensive Lung Cancer Long-term Survivorship Program (CLTSP) in patients sequentially returning for follow-up and surveillance visits after at least 36 months from initial diagnosis.

Methods: Patients planned for follow-up and surveillance (FUPaS) were consented to participate in a comprehensive survivorship investigational program including restaging imaging including brain-MRI, organ function tests, laboratory results, and detailed QoL and symptom control analysis including several neurocognitive function tests. Long-term toxicity was classified according to CTCAE4.0 and RTOG-EORTC Late Toxicity criteria. QoL tests were QLQ 30, FACT-L, and FACT-B. Neurocognitive function tests included trail-making tests, Grooved-pegboard-test, Nürnberger- and Regensburger-test-subscales and imaging analysis evaluated by Fazekas criteria in brain-MRI. Further long-term surveillance and event analysis was carried out following the initial survivorship program until 1/2022. Data were listed according to their probability in the whole CLTSP population and LTS was determined with the Kaplan-Maier method.

Results: From 7/2012 until 10/2013 patients sequentially returning for FUPaS visits were consented to participate in the investigational CLTSP. 51 pts were accrued after minimum LTS >36 months, 84% > 5 years. At the time of inclusion patients had a median survival since diagnosis of 85 months (range 38-225). Patient characteristics: 32 men, 19 women; age (median; range) 64, 37-77; NSCLC 48, SCLC 3; stages UICC8 IB 4 IIA 4 IIB 5 IIIA 26 IIIB 5 IIIC 3 IVA 3 IVB 1; stage III 67%; histopathology SCC 19, ADC 23 LCC 1 NOS 2 P-NET 1 SCLC 3. Smoking status med 32 packyrs (0-113), treatment CTx 96%, cisplatin 90%, RTx 80% S 82%; Late toxicities detected in the SSP: majority of pts without relevant late toxicities (CTCAE4.0): cardiac 2°(EF) 4, lung (COPD) IV 3 III 5 II 16 I 4; renal (GFR) 2° 4, 1°0; endocrine (cortisol) 2° 1 1° 5; PNP 2° 1, 1° 15, 0° 35. EORTC-QLQ30-functional scales (F)(%): Physical-F 74.1, Role-F 72.8, Emotional-F 79.9, Cognitive-F 79.9, Social-F 73.8. EORTC-symptoms with moderate relevance were dyspnea, fatigue and sleeplessness. Fact-L subscales: physical 23/28, social 22.6/28, emotional 22.8/28, functional 20.6/28. Ability to work (including at home) was very good in 30.6%, moderate 28.6%, pretty much 20.4%, relatively poor 16.3%, not at all 4.1%. LTS (until 1/2022) median 203 months; 10-yrs-OS-rate 86.3%, 15-yrs-OS-rate 62.9%; overall events 25/51.

Conclusions: Even aggressive multimodality Tx aiming at LTS leads to a relatively moderate late morbidity in LTS > 3 years. Especially, cardiac, lung, renal, and endocrine functions showed no clinically relevant impairment over initial comorbidities. QoL-data and symptom control scores were also only moderately influenced based on the background of initial known comorbidities in our population. Our selected group of LTS patients showed excellent and encouraging LTS. These are results from the first reported comprehensive SSP in LTS-LC with extended long-term surveillance data available for all patients.

Keywords: Lung Cancer, Survivorship, Toxicity and Surveillance

EP04.02-006 Burn-Out Syndrome: Neglected Syndrome Among Health Care Professionals Managing Lung Cancer Patients

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Introduction: Although high prevalence in healthcare professionals (HCP) and its dependence on work related stressors is shown in many researches and can lead to serious consequences on individual and organizational levels Burn-out syndrome (BS) is still neglected. The aim of this study was to examine the prevalence of BS among healthcare professionals (HCP) treating Lung cancer (LC) patients, its correlation to psychological distress and determination of significant job related stressors.

Methods: This study was conducted among HPC treating LCP at the Institute for Pulmonary Diseases of Vojvodina, Serbia. Data was anonymously collected using the Questionnaire on socio-demographic characteristics, Maslach burnout inventory (MBI), General health questionnaire (GHQ-12) and Questionnaire on predicted job stressors made by investigator.

Results: Out of total of 41 included HCP majority were female (70.7%), nurses (58.5%), treating LCP for 6-15 years (39.0%). High Emotional Exhaustion (EE) was detected in 56.1%, high Depersonalization (DP) in 29.3% and low Personal accomplishment (PA) in 36.6% of respondents. Observed prevalence of BS in total interviewed HCP was 24.4%. All observed BS was in nurses and none in physicians (p=0.002). Severe psychological distress was found in 12.0% and mild in 48.8% of respondents. Correlation between BOS and distress was significant at the 0.01 level. For majority the most significant stressors were: inadequate salary (90.2%), number of staff (87.8%), work overload (78.0%) and number of patients (75.6%). One third of HPC (29.3%) consider change of working place and 19.5% change of profession.

Conclusions: Prevalence of EE and DP domain of BS in HCP caring for LCP is high. BS significantly correlates with level of psychological distress and is more prevalent among nurses. The need for determination of job stressor and actions in order to prevent BS is beyond doubt. Improvement of recognition and overcoming stress factors should be one of the priorities of all healthcare institutions.

Keywords: Burn-out syndrome, work related stress, general health

EP04.02-007 First Comprehensive Lung Cancer Long-Term Survivorship Program- Competing Risks

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Introduction: More and more patients with lung cancer (LC) experience long-term survival (LTS) following multimodality treatment (Tx) protocols. Patients in these LTS cohorts have high risks of developing second cancers (SC), especially second-lung cancer (SLC) or comorbidity-related events. In our Comprehensive Lung Cancer Long-term Survivorship Program (CLTSP) (see abstract Exner JP et al), we investigated and followed a cohort of patients sequentially returning for follow-up and surveillance (FUPaS) visits after a minimum of 36 months from initial diagnosis.

Methods: Patients planned for FUPaS were consented to participate to a CLTSP with restaging imaging including brain-MRI, organ function tests, laboratory results, and extensive QoL and symptom control analysis including several neurocognitive function tests. Further consented long-term surveillance and events analysis was carried out until 1/2022. Data were listed according to their probability in the whole CLTSP cohort and LTS was determined by the method of Kaplan-Maier. We calculated overall survival (OS) and progression-free survival (PFS). Furthermore, we analyzed cumulative incidence of SC and SLC in this cohort up to 1/2022. Statistical package JMP was employed for survival analysis and cumulative incidence functions. Statistical package R was used for competing risk of death analysis over the whole period of follow-up.

Results: From 7/2012 until 10/2013 patients sequentially returning for FUPaS visits were consented to participate in the investigational CLTSP. 51 pts consented after a minimum LTS of > 36 months, 84% > 5 years. At the time of inclusion pts had a median survival since diagnosis of 85 months (range 38-225). Pts characteristics: 32 men, 19 women; age (median) 37-77 (64); NSCLC 48, SCLC 3; stages UICC8 IB 4 IIA 4 IIB 5 IIIA 26 IIIB 5 IIIC 3 IVA 3 IVB 1; stage III 67%; histopathology SCC 19 ADC 23 LCC 1 NOS 2 P-NET 1 SCLC 3. Smoking status med 32 packyears (0-113), treatment CTx 96% cisplatin 90% thoracic-RTx 80% Surgery 82%. Long-term OS (until 1/2022) of all patients: median OS 203 months, 10-yrs-OS-rate 86.3 %, 15-yrs-OS-rate 62.9 %, events: 25/51. Long-term PFS: median 140 months, 10-yrs-PFS-rate 58.8%, 15-yrs-PFS-rate 36.2%, events 38/51. Cumulative rate of SC including LC: 23/51 events; 10-yrs-SC-rate 25% (18.7-31.3), 15-yrs-SC-rate 42.7% (35.1-50.3) 20-yrs-SC-rate 52.8% (43.8-61.8). Cumulative rate of SLC: events 15/51; 10-yrs-SLC-rate 18.0% (12.6-23.4), 15-yrs-SLC-rate 28.4% (21.5-35.3), 20-yrs-SLC-rate 34.4% (25.9-42.9). Competing-risk analysis: Death of disease (progression) 10-yrs-DoD-rate 2.0% (0.2-9.2) 15-yrs-DoD-rate 4.6% (0.8-14.0) 20-yrs-DoD-rate 7.7% (1.9-19.3); Death from SC: 10-yrs-DoSC-rate 7.8% (2.5-17.3) 15-yrs-DoSC-rate 18.1 % (8.8-30.1) 20-yrs-DoSC-rate 27.7% (14.8-42.2) Death from Comorbidities 10-yrs-DoCMB-rate 3.9% (0.7-12.0) 15-yrs-DoCMB-rate 14.4% (6.2-25.9) 20-yrs-DoCMB-rate 17.8% (7.9-30.7).

Conclusions: Patients with LTS (over 3 years) have only a low risk to die from progression of their first LC. The two most clinically relevant risks are deaths from a SC or deaths from complications of major comorbidities (heart, lung, infections). The highest risk lies in the development of SLC based on the underlying long-term smoking history in the majority of these patients. A relevant amount of these SLC can potentially be diagnosed early and treated again.

EP05.01 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - CHEMORADIOTHERAPY AND RADIOTHERAPY

EP05.01-001 Hispanic Patients with Unresectable Stage III NSCLC under PACIFIC Protocol: Evidence of Interior Outcomes and Health Inequity

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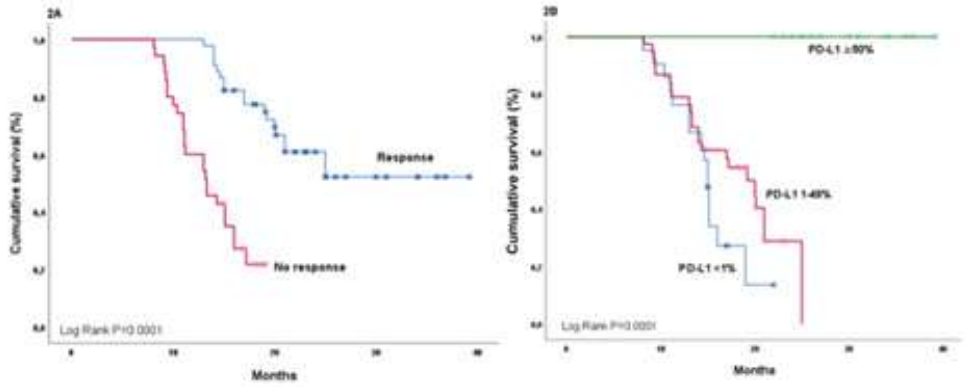
Introduction: The PACIFIC trial changed the treatment for patients with locally advanced (LA) non-small cell lung cancer (NSCLC) improving the survival outcomes. However, many populations such as Hispanics are under-represented, which has been found to have different outcomes with immunotherapy. We designed this study, in order to compare the rate disparity between outcomes and safety of concurrent chemoradiation (cCRT) followed by durvalumab in two patient cohorts with LA stage III NSCLC, one Non-White Hispanics (NWH) and one Latin-American.

Methods: A multicenter retrospective study was performed, including 80 Hispanic and 45 NWH LA stage III NSCLC patients treated with cCRT followed by durvalumab. Three main outcomes were analyzed: Overall survival (OS), Progression-free survival (PFS), and safety; and compared between them and with the PACIFIC trial populations outcomes. The efficacy-effectiveness gap was assessed using an efficacy-effectiveness (EE) factor. In both cohorts, results of PDL-1 testing were recorded, and the main outcomes were compared according to PD-1 expression levels (≥50%,1-49%, <1%).

Results: For the population (N=125), the overall response rate (ORR) was 57.6% (N=72), and 18.4% (N=25) achieved stable disease. OS was 26.3 months (95%CI 23.9-28.6), and PFS was 20.5 months (95%CI 18.0-23.0). PFS by ethnicity showed a median for the Hispanic population of 19.4 months (95%CI 16.4-22.5) and 21.2 months (95%CI 17.2-23.3; p=0.76) for the NHW group. OS by race showed a significant difference in favor of the NHW group, with a median OS of 27.7 months (95%CI 24.6-30.9) vs. 20.0 months (95%CI 16.4-23.5) for Hispanics. (P=0.032). Unadjusted 12 and 24-month OS was 86.6% (95%CI 79.9-88.0) and 46.6% (95%CI 40.2-48.3) for NHW compared to 82.5% (95%CI 77.1-84.2) and 17.5% (95 %CI 15.6-24.5) in Hispanics. NHWs had an EE factor of 0.78 and Hispanics had 0.58, showing a reduction in survival versus NHWs and PACIFIC of 20% and 42%, respectively. HR for the OS among NHWs and Hispanics was 1.53 (95%CI 1.12-1.71; P=0.052) and 2.31 (95%CI 1.76-2.49; P=0.004). Fifty-six patients (44.8%) had some degree of pneumonitis due to cCRT plus durvalumab. There was no difference in the proportion of pneumonitis according to race (P=0.95), and the severity of pneumonitis was not different between Hispanics and NHWs (P=0.41).

Conclusions: Among patients with stage III NSCLC, NHW has better survival outcomes when compared to Hispanics, with an OS that seems to favor the NHW population and with an EE factor that shows a shorter survival in Hispanics compared with NHW and with the PACIFIC trial group.

Figure 1. Overall survival among Hispanics according to response (2A) and PD-L1 expression (2B).



Keywords: Durvalumab, Stage III NSCLC, Hispanic pupulation

EP05.01-002 Real World Treatment Patterns and Outcomes among Unresectable Stage III Non-Small Cell Lung Cancer Patients Initiating Chemoradiotherapy

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Introduction: Concurrent platinum-based chemoradiation therapy (cCRT) with or without durvalumab consolidation for 12 months is the current standard of care for patients with unresectable stage III Non-Small Cell Lung Cancer (NSCLC). This study characterized the real-world treatment utilization patterns and associated outcomes after approval of durvalumab for this indication.

Methods: This retrospective cohort study used The US Oncology Network's iKnowMed (iKM) electronic health record (EHR) data (structured data) and included adults diagnosed with unresectable stage III NSCLC initiating cCRT between 01-Nov-2017 to 31-Oct-2019. The data cut-off date was 30-Apr-2021. Unresectable were defined as patients without evidence of surgery since their stage III diagnosis. cCRT included concurrent treatment with platinum-based chemotherapy and radiation therapy (+/-14 days). The index date was defined as the date of initiation of cCRT (chemotherapy initiation date). Descriptive statistics were used to describe demographic, patient, and clinical characteristics, and treatment patterns. Kaplan-Meier analysis was performed to examine real-world overall survival (rwOS).

Results: Of 959 unresectable stage III NSCLC patients who initiated cCRT, 43.0% (n = 412) received durvalumab post cCRT (cCRT+durvalumab) and 57.0% (n = 547) did not (cCRT alone). The median duration of follow-up was 15.7 months (range: 0.1, 42.0). The median age for the overall/cCRT+durvalumab/cCRT alone cohort was 70.3/68.9/71.2 years; 55.6/53.9/56.9% were male; 73.4/74.3/72.8% were white; 53.3/53.9/52.8% were non-squamous histology; 61.7/66.7/58.0% had ECOG PS 0-1; 11.6/9.5/13.2 % had ECOG PS 2+; and 52.7/51.9/53.2%had stage IIIA at diagnosis respectively. At durvalumab initiation, 64.1% had ECOG PS of 0-1; 10.9% had ECOG 2-4 and 94.7% had ≤2 comorbidities. The most common chemotherapy was carboplatin+paclitaxel (overall, 86.4%; cCRT+durvalumab, 87.6%; and cCRT alone, 85.6%) followed by cisplatin+etoposide (overall, 7.8%; cCRT+durvalumab, 8.5%; and cCRT alone, 7.3%). Overall, 37.5% patients died, including 29.6% among those who received cCRT+durvalumab and 43.5% among cCRT alone. The median rwOS from index was 34.1 months (95% CI: 30.4, NR) for overall cohort, not reached (NR) (95% CI: 39.0, NR) for cCRT+durvalumab and 21.3 months (95% CI: 17.0, 25.8) for cCRT alone (table 1).

Conclusions: Carboplatin+paclitaxel was commonly utilized chemotherapy regimen among stage III NSCLC patients who initiated cCRT. A large proportion of patients do not receive durvalumab as consolidation therapy in real world. Further follow-up is required to adequately characterize patient outcomes for this cohort.

Table 1: Treatment characteristics and Real-world Outcomes among Stage III NSCLC patients			
Table 1	**Overall (n = 959)**	**Patients treated with durvalumab post cCRT (n= 412) ****	**Patients treated with cCRT alone (n= 547) ****
Treatment characteristics			
Duration of therapy, months, median (range)			
cCRT	1.2 (0.0, 12.9)	1.4 (0.0, 5.3)	1.2 (0.0, 12.9)
durvalumab	6.9 (1.2, 21.1)	6.9 (1.2, 21.1)	NA
Time between the last dose of cCRT and initiation of durvalumab, median, (range) months	NA	1.5 (0.3,7.1)	
Chemotherapy regimens of cCRT (n, %)			
Carboplatin + Paclitaxel	829 (86.4)	361 (87.6)	468 (85.6)
Cisplatin + Etoposide	75 (7.8)	35 (8.5)	40 (7.3)
Cisplatin + Pemetrexed	18 (1.9)	9 (2.2)	9 (1.6)
Others	37 (3.9)	7 (1.7)	24 (5.5)
Real-world Overall Survival*			
Events (%)	360 (37.5)	122 (29.6)	238 (43.5)
Median (95% CI) months	34.1 (30.4, NR)	NR (39.0, NR)	21.3 (17.0, 25.8)
OS probabilities, % (95% CI)			
6 months	81.2 (78.5, 83.6)	92.4 (89.4, 94.6)	72.0 (67.7, 75.8)
12 months	71.3 (68.2, 74.2)	82.8 (78.7, 86.2)	61.7 (57.1, 66.0)
18 months	64 (60.6, 67.2)	75.8 (71.1, 79.8)	54.0 (49.2, 58.6)

Abbreviations: cCRT: concurrent chemoradiation therapy, CI: confidence interval, OS: overall survival, NR: Not Reached, NA: Not Applicable *OS is defined as the interval between the index treatment and the date of death (any cause) as documented in the Limited Access Death Master File (LADMF) and/or the iKM EHR database **The two exposure groups (cCRT + / - durvalumab) are presented descriptively and should not be compared. To receive durvalumab patients are required to not progress after cCRT and hence a potential for immortal time bias.

Keywords: unresectable Stage III NSCLC, chemoradiation therapy, durvalumab

EP05.01-003 First Real-World Data on Unresectable Stage III NSCLC Patients Treated with Durvalumab after Chemoradiotherapy in Asia Area

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Introduction: The PACIFIC trial demonstrated the survival benefit of durvalumab as consolidation therapy in patients with unresectable stage III non-small cell lung cancer (NSCLC) after concurrent chemoradiotherapy (cCRT). However, it is necessary to assess the effectiveness of durvalumab consolidation using real-world data.

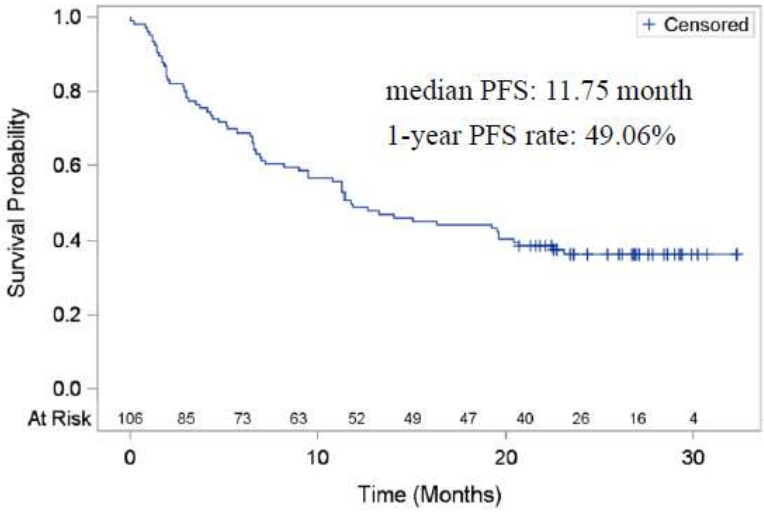
Methods: A retrospective study was conducted in 106 patients diagnosed with unresectable stage III NSCLC and treated with CRT followed by durvalumab in Taiwan. Primary outcome was progression-free survival (PFS)

Results: Table 1 presented baseline characteristics. 87 (83.65%) patients initiated durvalumab consolidation > 42 days after radiotherapy. The median PFS was 11.75 months (95% CI: 8.20, 19.60). The PFS rate was 49.06% at 12 months and 44.34% at 18 months (Figure 1). Respiratory adverse events (20.75 %), particularly pneumonitis were the most common in the full analysis set (Table 2).

Conclusions: Delayed initiation of durvalumab was noted in the majority of patients in this real-world data. Furthermore, 12 (11.43 %) patients were epidermal growth factor receptor mutation positive, which was higher than PACIFIC trial (6.09 %). Whether the slightly shorter PFS (compared with the median PFS of 16.9 months in PACIFIC trial) is related to the delayed initiation of durvalumab requires further investigation.

Baseline characteristics of subjects		
Variable, n (%)		**Full analysis set (N=106)**
Age (years)	Median (range)	62.5 (31-87)
Sex	Male	77 (72.64)
	Female	29 (27.36)
Performance status	ECOG score (0, 1)	90 (84.91)
Comorbidities	No	43 (40.57)
	Yes	63 (59.43)
Smoking status	Never	30 (28.30)
	Current/former	74 (69.81)
	Not a vailable	2 (1.89)
Stage III status	De novo	102 (96.23)
	Relapse	4 (3.77)
Disease stage*	IIIa	29 (27.36)
	IIIb	51 (48.11)
	IIIc	21 (19.81)
Histologics ubtype	Squamous	35 (33.02)
	Non Squamous	71 (66.98)
PACIFIC like cohort	Yes	10 (9.43)
	No	96 (90.57)
Initiation of Durvalumab relative to end of radiotherapy	1-42 d ays	17 (16.35)
	>42 days	87 (83.65)
PDL1 expression level	≥1 %	39 (37.14)
	< 1 %	13 (12.38)
	Unknown	54 (50.94)
EGFR status	Positive	12 (11.43)
	Negative	43 (40.95)
	Unknown	51 (48.11)

A bbreviations: ECOG, Eastern Cooperative Oncology Group ; PD L1, programmed death ligand 1 ; EGFR, epidermal growth factor receptor*Four patients were diagnosed at disease stage <III.



Adverse events of special interest with durvalumab			
Frequency, n (%)	**Full analysis set (N=106)**	**Starting durvalumab 42 days after radiotherapy (N=17)**	**Starting durvalumab >42 days after radiotherapy (N=87)**
Pneumonitis	22 (20.75)	7 (41.18)	14 (16.09)
Endocrine disorders	9 (8.49)	0	9 (10.34)
Rash	6 (5.66)	2 (11.76)	4 (4.6)
Dermatitis	2 (1.89)	0	2 (2.3)
Hepatitis	3 (2.83)	1 (5.88)	2 (2.3)
Blood creatinine increased	2 (1.89)	1 (5.88)	1 (1.15)
Transaminases increased	2 (1.89)	0	2 (2.3)
Diarrhea	1 (0.94)	0	1 (1.15)
Radiation fibrosis lung	1 (0.94)	0	1 (1.15)

Keywords: PACIFIC, Locally advanced, unresectable

EP05.01-004 Induction Chemoimmunotherapy before Definitive Chemoradiotherapy for Large-Volume Unresectable Locally Advanced NSCLC

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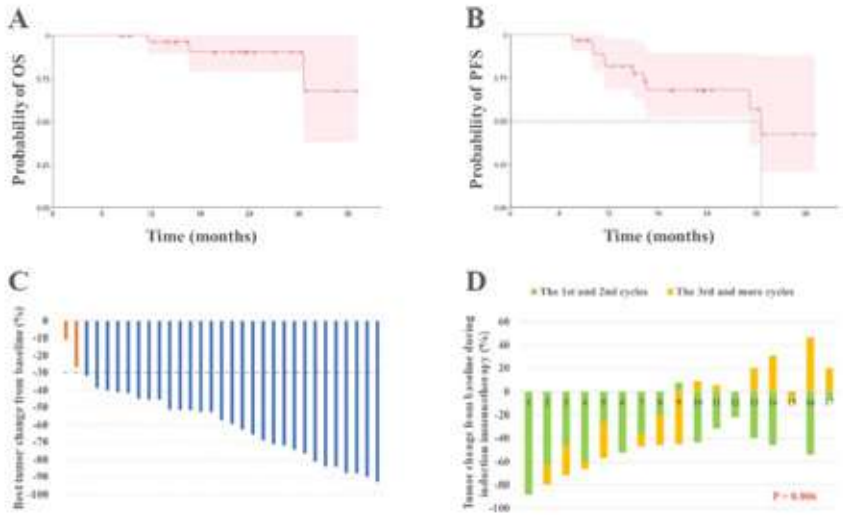
Introduction: Although outcomes of locally advanced non-small-cell lung cancer (LA-NSCLC) have been greatly improved since the practice-changing results from the PACIFIC trial, treatments for large-volume LA-NSCLC remain challenging. We investigated induction chemoimmunotherapy and definitive chemoradiotherapy (CRT) for unresectable LA-NSCLC patient subgroups with larger tumor bulk, aiming to improve survival by optimizing patient selection and individualizing combination treatments.

Methods: Unresectable stage III NSCLC patients with large tumor bulk (defined as primary tumor ≥ 5cm in greatest dimension or regionally involved lymph nodes ≥ 2cm in shortest diameter) who underwent induction chemotherapy and PD-1 inhibitors before concurrent or sequential CRT between November 2018 to August 2021 were retrospectively identified. One- and 2-year overall-survival (OS) and progression-free-survival (PFS) rates were assessed from the start of induction treatment. We simulated radiotherapy planning (60Gy in 2Gy fractions) on CT images before and after 2-cycle induction immunotherapy to analyze changes of dosimetric parameters, including gross tumor volume of primary tumor (GTVp), GTV of lymph nodes (GTVn), and planning target volume (PTV).

Results: Thirty-one patients were included, with 20 (64%) diagnosed at stage IIIB and 7 (23%) at IIIC. Median follow-up was 19.9 months. The 1-year OS and PFS rates were 96.3% and 81.5%, and the 2-year OS and PFS rates were 80.0% and 46.7%, respectively. Median OS was not reached, and median PFS was 30.6 months (95%CI, 29.2-NA, **Figure 1A and B**). The objective response rates of induction chemoimmunotherapy and induction treatment plus CRT were 54.8% and 93.5% (**Figure 1C**), respectively. Twenty-three (74.2%) patients achieved the best response at a median of 42 days after radiotherapy. Despite median 4 cycles of immunotherapy, lesions significantly shrank after the first 2 cycles than after more cycles (36.9% versus 2.3%, P=0.006, **Figure 1D**). Seven (22.6%) patients experienced grade 2 pneumonitis and one (3.2%) with grade 3. No grade 4 or 5 toxicity. Simulated radiotherapy plans indicated GTVp, GTVn, and PTV after the first 2-cycle immunotherapy significantly (P<0.001) decreased by 35.7 cm^3 (45.0% reduction), 10.7 cm^3 (39.1% reduction), and 84.5 cm^3 (25.1% reduction), respectively. The mean lung dose, lung V5, V20 and V30 significantly reduced by 1.2 Gy (8.0% reduction, P<0.001), 4.6% (8.1% reduction, P<0.001), 1.8% (7.7% reduction, P=0.002) and 1.6% (9.8% reduction, P=0.002), respectively.

Conclusions: Two cycles of induction chemoimmunotherapy followed by definitive CRT for large-volume LA-NSCLC is feasible, with promising tumor control and significant target volume reduction. Further investigations on this novel regimen and optimal patient selection are warranted.



Keywords: Immunotherapy, Non-small-cell lung cancer, Chemoradiotherapy

EP05.01-005 Impact of Antibiotic Use Before Definitive Concurrent Chemoradiation in Patients with Locally Advanced Non Small Cell Lung Cancer

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Introduction: The study evaluated whether antibiotic treatment before chemoradiotherapy influenced outcomes in patients with locally advanced non-small cell lung cancer (LA-NSCLC).

Methods: The records of LA-NSCLC patients treated with chemoradiotherapy between 2010 and 2017 at West China Hospital were retrospectively examined together with their antibiotic use (antibiotic type, duration of treatment, and time between discontinuation and chemoradiotherapy). The influence of antibiotics on progression-free survival (PFS) and overall survival (OS) was evaluated with Kaplan-Meier curves and univariate and multivariate Cox regression.

Results: Of 522 patients, 176 had received intravenous broad-spectrum antibiotics in the month before chemoradiotherapy. Antibiotic use was linked to both reduced PFS (7.9 vs. 13.4 mo, $p<0.001$) and OS (20.4 vs. 25.3 mo, $p=0.049$). Multivariate regression demonstrated that antibiotic treatment was an unfavorable independent prognostic factor for LA-NSCLC patients that received chemoradiotherapy (HR, 1.234; 95% CI, 1.019-1.494; $p=0.031$). Prognosis was also influenced by the antibiotic type, length of treatment, and interval between discontinuation and start of chemoradiotherapy initiation. ß-lactamase inhibitors were found to be the most harmful (median OS for ß-lactamase inhibitors /Fluoroquinolones / Cephalosporins:16.5/19.9/25.9 mo, p=0.045). Cutoff values for interval and duration calculated by the X-tile procedure showed that intervals of 7-16 days or durations ≤6 days did not significantly affect OS relative to untreated patients (intervals: $p=0.9$, duration: $p=0.93$).

Conclusions: Antibiotic treatment for longer than six days, especially with ß-lactamase inhibitors, was associated with poor prognosis. Furthermore, delaying chemoradiotherapy for 7-16 days after antibiotic discontinuation may reduce these negative effects.

Keywords: Non-small cell lung cancer, Antibiotic treatment, chemoradiotherapy

EP05.01-006 Population Kinetic Assessment of Chemoradiation for Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Progression-free survival (PFS) curves generally approximate first order kinetics. PFS curve exponential decay nonlinear regression analysis (EDNLRA) provides useful insights. Chemoradiation is standard therapy in locally advanced NSCLC. Durvalumab improves PFS.

Methods: Using PubMed, we identified trials published from 2010 to February 2022 using chemoradiation for locally advanced NSCLC. We used GraphPad Prism 7 for EDNLRA of digitized PFS curves. We excluded curves derived from fewer than 50 patients and curves that were less than 25 months long. We also excluded data from 3 outliers, although their inclusion would not alter our conclusions.

Results: Across 54 evaluable curves, there was a median (range) of 96 (50-829) patients per curve, with curve length a median (range) of 60 (26-150) months. On 1-phase-decay EDNLRA, PFS half-life was a median (range) of 13.8 (7.2-25.9) months. Of the 54 curves, 53 fit 2-phase-decay EDNLRA models and demonstrated a rightward inflection on log-linear plots. Curve 2-phase decay indicated presence of a rapidly progressing subpopulation and a separate potentially cured subpopulation. The rapidly progressing subpopulation accounted for a median (range) of 86% (27%-95%) of the entire population, meaning that there was a potentially cured subpopulation of 14%. PFS half-life was 9.3 (4.0-15.7) months for the rapidly progressing subpopulation and was 3.4×10^{15} (35 to 6.1×10^{15}) months for the potentially cured subpopulation. (Since the half-life of the potentially cured subpopulation was generally much longer than the duration of follow-up, 95% confidence intervals for this half-life were very wide for most curves. Since PFS is impacted by death from any cause, we conclude that this overestimates the true PFS half-life for the favorable group). For patients who remained progression-free at different follow-up time points, EDNLRA data permitted estimation of the proportion who were still destined to eventually relapse. Of those still progression-free at 12, 24, 36, 48, 60 and 120 months, respectively, the estimated proportion destined to eventually relapse was 35%, 14%, 6%, 2%, 1% and 0.01%. Conversely, of those still progression-free at 36 and 60 months, respectively, 94% and 99% are probably cured. In the PACIFIC trial, the proportion of patients in the subpopulation with good outcome increased from 43% on the placebo arm to 74% on the durvalumab arm. PFS half-lives in the rapidly progressing subpopulation were similar on the durvalumab and placebo arms. This is in keeping with immune checkpoint inhibitors having either no effect or else a marked beneficial effect on different patients, as also seen in metastatic disease. PFS half-life in the favorable subpopulation was 61 months on the durvalumab arm vs 97 months on the placebo arm. This suggests that the durvalumab arm may eventually demonstrate 3-phase decay with longer follow-up (a rapidly progressing subpopulation, a subpopulation cured by chemoradiation and an intermediary subpopulation that is not cured but has prolonged control with durvalumab).

Conclusions: Population kinetic assessments of PFS curves for patients with locally advanced NSCLC offer potentially useful biological and statistical insights.

Keywords: chemoradiation, non-small cell lung cancer, population kinetics

EP05.01-007 CONCORDE - A Phase Ib Platform Study of Novel Agents in COmbinatioN with COnventional RaDiothErapy in Non-small Cell Lung Cancer (NSCLC)

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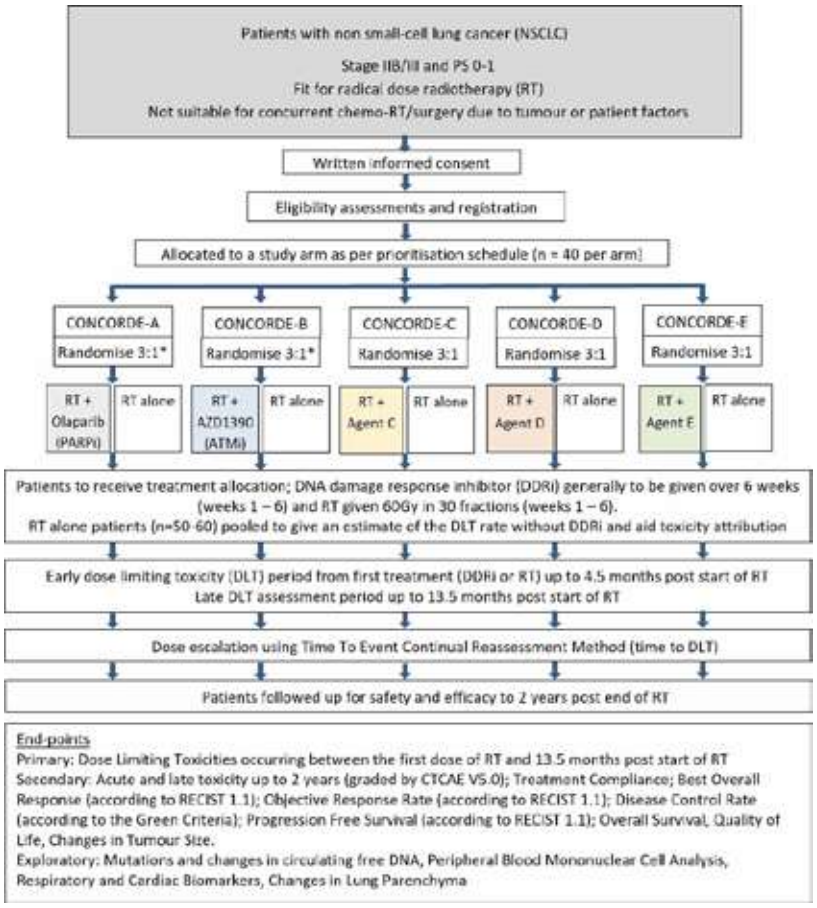
Introduction: The CONCORDE study is sponsored by the University of Leeds and funded by Cancer Research UK and AstraZeneca. It is an innovative, hypothesis-driven open-label, randomised, phase Ib, multi-institution, platform study for patients with NSCLC receiving radical radiotherapy (RT). It aims to assess five DNA damage response inhibitors (DDRi) with participants randomised to receive one agent in combination with RT or RT alone. Two of the arms will also deliver Durvalumab and DDRi consolidation. CONCORDE adopts a Bayesian adaptive model-based approach to dose escalation. An estimated 210 patients will be recruited from 13 centres across the UK, including 30 patients in each experimental arm and approximately RT alone 50-60. The estimated total duration of trial: 6 years.

Methods: Key eligibility: Stage IIB/IIIA/B/C NSCLC, medically inoperable and not suitable for concurrent chemo-radiotherapy, ECOG PS 0-1. Patients will be treated with radical RT given at a dose of 60Gy/30# delivered over 6 weeks. As per Figure 1, they will be allocated to one of 5 study arms as per prioritisation schedule (n=40 per arm). Within that arm they will be randomised to RT with or without DDRi (randomised 3:1). The primary endpoint is to assess the safety and determine the recommend phase II dose (RP2D) of each DDRi. The RP2D will be the dose level at which it is estimated 25% of subjects will experience dose limiting toxicity during and up to 13.5 months following RT.



Results: Trial arms A (PARPi) and B12 (ATMi) are open to recruitment in 6 centres and 14 patients have been recruited (as of 15/03/2022).

Conclusions: Conclusion: Further arms and centres to open soon. Correlative studies aiming to identify biomarkers of toxicity and response to combination therapy, and the impact of treatment on the immune system are in development. For further information go to: https://clinicaltrials.gov/ct2/show/NCT04550104 Trials unit contact: ctru_concorde@leeds.ac.uk

Keywords: Radiotherapy, DNA damage response inhibitors, Phase 1b trial

EP05.01-008 The Scottish Inflammatory Prognostic Score Predicts Survival in Non-Small Cell Lung Cancer Treated with Chemoradiotherapy

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Introduction: Scores assessing inflammatory status such as the modified Glasgow Prognostic Score (mGPS) can prognosticate outcomes in cancer. The mGPS combines albumin and C-Reactive Protein (CRP) to stratify outcomes of patients with cancer. However, non-small cell lung cancer (NSCLC) patients do not routinely have CRP measured as part of their diagnostic pathway. We have shown that the Scottish Inflammatory Prognostic Score (SIPS), assigning 1 point each for albumin <35g/L and neutrophil count >7.5X109/L to give a 3-tier categorical score, predicts outcomes for cohorts of patients with stage III or IV NSCLC. In this study we wanted to understand whether SIPS reflected overall tumour volume.

Methods: We identified all patients who received chemoradiotherapy for stage III NSCLC at the Edinburgh Cancer Centre between November 2012 and December 2020. We determined overall survival as the date from initiating treatment to date of death or censorship (30/11 2021). Pre-treatment serum albumin and neutrophil count were recorded. Gross tumour volume (GTV) was calculated using Eclipse radiotherapy planning software. When 4-D planning scans were utilised, an average of GTV0 and GTV50 was calculated. We standardised tumour volume by dividing the cohort into 3 equal groups based on tumour volume.

Results: 295 patients were identified. SIPS stratified survival from 17.5months (SIPS 2) to 26.6 months (SIPS 1) to 48.2 months (SIPS 0) (p=0.0015) (Figure 1a). GTV stratified survival from 21.0 months (third-tertile (128.0-1601.5cm3)) to 33.1 months (second-tertile (55.4-128.0 cm3)) to 52.3 months (first-tertile (6.8-55.1cm3)) (p=<0.001) (Figure 1b). Median GTV was significantly lower in patients with SIPS0 compared to those with SIPS1 or 2 (56.98cm3 vs 105.7cm3 or 146.1 cm3 respectively (p<0.001)). The proportion of SIPS0/1/2 patients in each GTV subgroup were: first-tertile 65.3%/30.6%/4.1%, second-tertile 49.0%/ 31.6%/19.4%, third-tertile 22.4%/51.0%/27.6%.

There was no consistent significant relationship between survival and SIPS in each GTV tertile. However, there was a trend to poorer survival in patients with the highest levels of systemic inflammation. For example, in the second-tertile patients with SIPS2 had poorer survival than those with SIPS0 and 1 (17.5 months vs 38.8 months, p=0.0019)(Figure 1c)

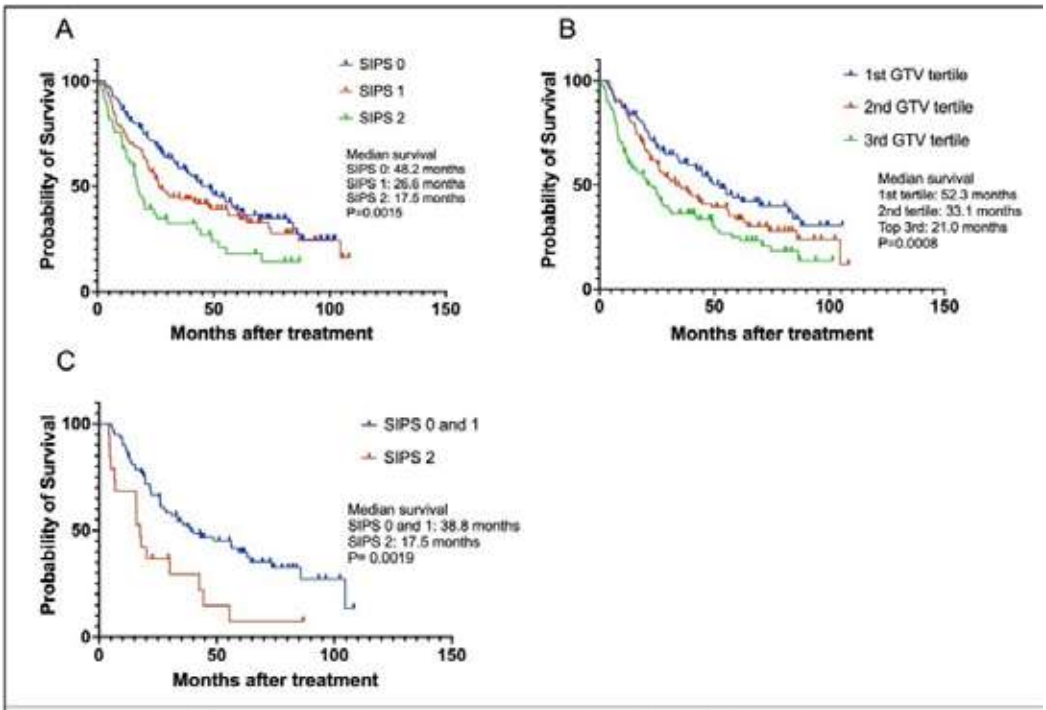

Figure 1: Kaplain-Meier (KM) curve demonstrating overall survival in **(A)** SIPS0, 1 and 2 groups, **(B)** between GTV tertiles, **(C)** between SIPS0-1 vs 2 in middle GTV tertile group.

Conclusions: Both the SIPS and GTV similarly prognosticate outcome in patients with stage III NSCLC treated with chemoradiotherapy. There is evidence of a relationship between inflammatory status and tumour volume, but it is likely more complex than a simple linear correlation. How this relates to survival outcomes is less clear. We advocate further work to define this relationship and its clinical utility.

Keywords: non-small cell lung (NSCLC), prognostic biomarker, systemic inflammation

EP05.01-009 A Clinical Outcome Comparison of IMRT and VMAT in Stage II and III NSCLC Irradiated with Radical Intent

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Introduction: Volumetric Modulated Arc Therapy(VMAT) has an improved delivery efficiency over fixed-field Intensity Modulated Radiotherapy(IMRT). In 2019 IMRT was replaced with VMAT using two arcs at our department for NSCLC patients treated with radical intent. Our hypothesis was that with the introduction of VMAT the incidence of acute toxicity did not increase. All patients received image-guided treatment utilizing daily cone beam CT.

Methods: All patients receiving treatment between 2017 until 2022 at out institute with radical intent for (primary or recurrent) stage II and III NSCLC were analyzed. Radiotherapy (RT) was either given alone or combined with concurrent (cCRT) or sequential chemotherapy (seqCRT). Patients were irradiated with various regimens: hypofractionated radiotherapy (24 fractions of 2.75 Gy up to 70 Gy (EQD210) to the primary tumor and 60 Gy (EQD210) to the involved lymph nodes), 17 fractions of 3 Gy (EQD210=55 Gy) or 30 fractions up to 60 Gy. Most cCRT patients received daily low-dose Cisplatin (6 mg/m2). Others were given concurrent or sequential Cisplatin (75mg/m2 d1) with Etoposide (100mg/m2 d1-3, Q31-days) or 3-weekly Cisplatin or Carboplatin (75mg/m2 d1) with Vinorelbine (60mg/m2, d2+8, Q21-days) and Pemetrexed. Since 2018 adjuvant immunotherapy was administered in some hospitals within an 'expanded access program'. From 2019 on, the adjuvant immunotherapy became standard of care in patients without disease progression after cCRT. Acute non-hematological toxicity (< 3 months after the end of the irradiation) and 90-days mortality was retrieved from the Dutch Lung Cancer Audit-Radiotherapy registration.

Results: A total of 828 patients with stage II and III NSCLC were irradiated between 2017-2022 449 with IMRT and 379 with VMAT. Patient's characteristics are shown in Table 1. Both treatments had similar stage, and performance status distribution. The incidence of acute grade ≥3 non hematological toxicity or grade ≥2 radiation pneumonitis was 7% for IMRT (95% CI:4.7%-9.5%) and 7% for VMAT (95% CI:4.8%-10.0%). The 90-day mortality was 6% and 4% for IMRT and VMAT respectively.

Conclusions: Acute non-hematological toxicity and 90-days mortality were comparable between VMAT and IMRT treated patients with stage II and III NSCLC treated with radiotherapy alone, cCRT or seqCRT.

Table 1: Patients with stage II and III NSCLC treated between 2017 and 2022 with IMRT or VMAT

	IMRT n=449		VMAT n=379	
Gender: male	236	48%	190	50%
female	213	52%	189	50%
Treatment:				
RT alone	146	33%	108	28%
cCRT	246	55%	227	60%
seqCRT	57	13%	44	12%
Stage: IIA	8	2%	1	1%
IIB	58	13%	47	12%
IIIA	153	34%	143	38%
IIIB	178	40%	138	36%
IIIC	52	11%	50	13%
WHO: 0	115	26%	120	32%
1	232	52%	187	49%
2	72	16%	47	12%
3	8	2%	6	2%
unknown	22	4%	19	5%
Histology proven NSCLC	243	54%	207	55%
Cytology proven NSCLC	172	38%	150	40%
unknown	34	8%	22	5%
Grade ≥3 toxicity and RP grade ≥2	31	7%	26	7%
90 day mortality	27	6%	15	4%

Keywords: VMAT, IMRT, NSCLC

EP05.01-010 External Validation of Two Prediction Models for Severe Radiation-induced Lymphopenia during Concurrent Chemoradiotherapy for Lung Cancer

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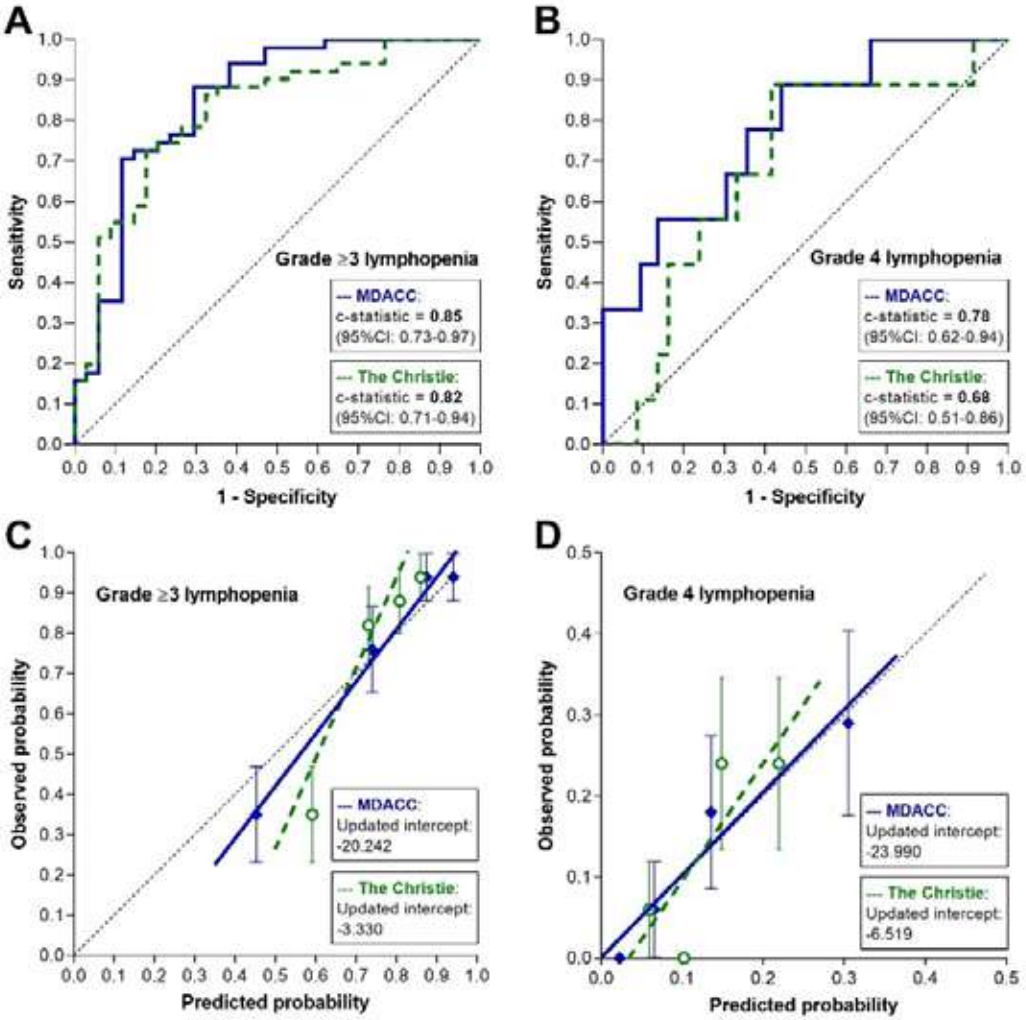
Introduction: Severe radiation-induced lymphopenia in patients undergoing chemoradiotherapy (CRT) for non-small cell lung cancer (NSCLC) is associated with detrimental survival outcomes and decreased efficacy of subsequent immunotherapy. This impact provides a strong incentive to identify patients at high risk who could benefit from lymphopenia-mitigating strategies. At The Christie, a prediction model for grade ≥3 lymphopenia was developed in lung cancer patients. At MDACC, a model for grade 4 lymphopenia was developed in esophageal cancer patients. The aim of this study was to validate both models for predicting grade ≥3 and grade 4 lymphopenia during concurrent CRT in patients with stage III NSCLC.

Methods: Consecutive patients who underwent concurrent CRT for stage III NSCLC at our comprehensive cancer center between 2019 and 2020 were included. Mildly hypofractionated radiotherapy was administered (24x2.75 Gy to primary tumor and 24x2.42 Gy to involved lymph nodes). Chemotherapy consisted of daily low-dose cisplatin. The primary outcomes of grade ≥3 and grade 4 lymphopenia were defined as absolute lymphocyte count (ALC) nadirs during CRT of <0.5 and <0.2 K/mL, respectively. Predictors of the Christie model included age, baseline ALC, mean heart and lung doses, and thoracic vertebrae V20Gy. Predictors of the MDACC model were age, baseline ALC, and PTV in interaction with BMI. The prediction models' performance was assessed in terms of discrimination and calibration.

Results: A group of 68 patients was studied in which 51 patients (75%) developed grade ≥3 lymphopenia during CRT, with grade 4 lymphopenia in 9 patients (13%). For prediction of grade ≥3 lymphopenia, application of the Christie and MDACC models yielded c-statistics of 0.82 (95%CI: 0.71-0.94) and 0.85 (95%CI: 0.73-0.97), respectively (Figure 1A). For prediction of grade 4 lymphopenia, the Christie and MDACC models yielded c-statistics of 0.68 (95%CI: 0.51-0.86) and 0.78 (95%CI: 0.62-0.94), respectively (Figure 1B). Calibration (adjusted for the a-priori risk) demonstrated moderate agreement between the observed and predicted risk for grade ≥3 and grade 4 lymphopenia using the Christie model. Good calibration was found using the MDACC model for both grade ≥3 and grade 4 risk predictions (Figure 1C-1D).

Conclusions: The MDACC prediction model for severe radiation-induced lymphopenia demonstrated superior external performance in the setting of concurrent CRT in patients with stage III NSCLC as compared with the Christie prediction model. As such, the prediction model may aid in identifying thoracic cancer patients at high risk for severe lymphopenia.



Keywords: Non-small cell lung cancer, Radiotherapy, Lymphopenia

EP05.01-011 Real World Outcomes of Durvalumab After Chemoradiotherapy in Unresectable Advanced Non-Small Cell Lung Cancer: The Mayo Clinic Experience

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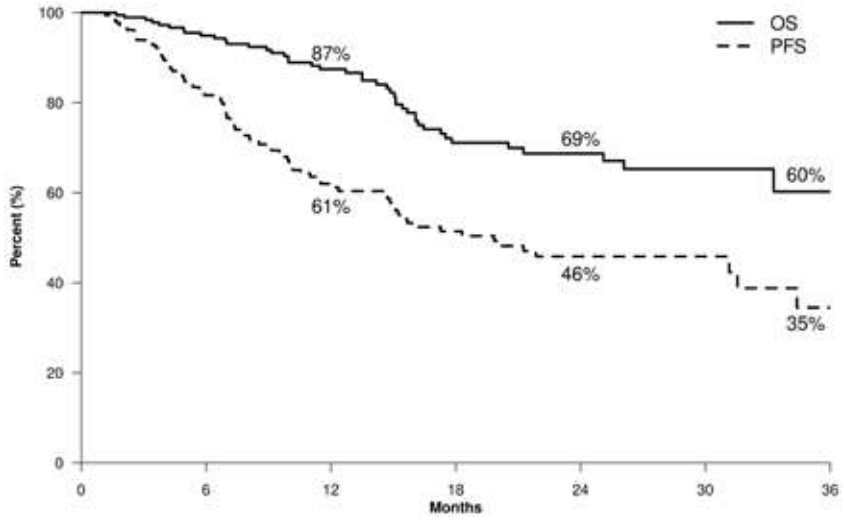
Introduction: Concurrent chemoradiation followed by durvalumab has become the standard of care in patients with unresectable, locally advanced NSCLC based on the PACIFIC trial. Real life data of this practice are emerging, but few data are available on outcomes of patients with progression of disease after this treatment.

Methods: We performed a retrospective study of patients treated at all Mayo Clinic sites from January 2018 to October 2020. We assessed OS, PFS, immune related adverse events (IRAEs), effects of the number of chemotherapy/durvalumab cycles on outcomes, time from first progression to objective tumour progression on next-line treatment or death from any cause (PFS-2) and sites of progression.

Results: We evaluated a total of 190 patients, 49% men and 51% women. The median age was 67 years (range, 41- 90 years) and 13% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 2. At a median follow-up of 14.8 months, OS and PFS results are shown in figure 1. In our cohort, the 24-months OS was 68.7% (95% CI 60, 78) and PFS 45.6% (95% CI 37, 56). The most common adverse event (AE) of any cause (all grades) was pneumonitis (29%). Common IRAEs were hypothyroidism (12%), colitis (4%) and rash (3%). The most common distant metastatic disease sites at first progression were brain (28%), bone (24%), and lung (20%). For the 66 patients who had disease progression after/during durvalumab, PFS-2 was 32% at 12 months. In patients after first progression, PFS-2 at 12 months for local only recurrent disease was 23% vs 36% for distant only metastasis. Patients completing all cycles of concurrent chemotherapy with radiation compared to those who did not, had no difference in progression (HR 0.81, 95% CI 0.5,1.4; p=0.42). ECOG performance status 2 was associated with increased risk in both progression (HR 2.36, CI 95% 1, 5; p=0.01) and death (HR 5.11, CI 2-12; p=0.001). Expression of PD-L1 1-49% and PD-L1 >50%, when compared to PD-L1 0% were associated with statistically significant lower risk for death (p=0.004 and p=0.028, respectively).

Conclusions: PFS and OS result at 12 months was comparable to those previously reported in the PACIFIC Trial. Events of pneumonitis were similar to those seen in the PACIFIC trial. The patterns of disease progression suggest that patients with locoregional recurrence had worse PFS-2 than those with distant metastasis. Performance status and PD-L1 expression were associated with OS.

Figure 1. Kaplan Meier curves for overall survival (OS) and progression-free survival (PFS)



Keywords: Locally advanced NSCLC, PACIFIC TRIAL, Durvalumab

EP05.01-012 Avoiding Cardiac Toxicity in Lung Cancer Radiotherapy (ACcoLade) Trial - Initial Results

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Introduction: Increasing cardiac radiation dose is associated with worse survival and cardiac events following thoracic radiotherapy however, the mechanism of injury is unknown. High sensitivity cardiac troponin I (hsTnI) and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) are established blood biomarkers of cardiac injury. Cardiac CT (CCT) is a non-invasive method of assessing coronary artery disease and echocardiography assesses cardiac structure and function. We present initial results of a prospective cohort study of cardiac blood and imaging biomarkers in patients undergoing lung cancer radiotherapy.

Methods: Eligible patients had a histological or clinical diagnosis of stage 1-3 lung cancer and received curative-intent radiotherapy (total dose >45Gy). Blood samples were collected at three timepoints: prior to, at the end of and four months after radiotherapy (± 14 days). A subset of patients underwent CCT and echocardiography before starting and four months after the end of radiotherapy (± 14 days). The heart was contoured to include all 4 chambers and the pericardial sac. Coronary arteries were contoured using the atlas by Duane et al. Coronary artery and heart mean doses were converted to biologically equivalent dose using an α/ß ratio of 3 Gy^{-1}. Significance of changes in hsTnI, NT pro-BNP, coronary artery calcium score (CACS) and left ventricular ejection fraction (LVEF) between different timepoints were tested using Kruksal-Wallis.

Results: Initial results from 38 patients who had both cardiac imaging and blood biomarkers were available for analysis. Median age was 68.5 years (range, 52.8-85.4 years), 18 (47.4%) were male and 25 (65.7%) had stage 3 disease. Only 4 patients (10.5%) were not taking cardiac medications at the time of radiotherapy. Five patients (13%) had a cardiac event; 3 occurred before radiotherapy.

Figure 1 shows hsTnI was significantly different between the 3 timepoints (p=0.0012). Median hsTnI was 3ng/ml at baseline, rose to 5ng/ml at the end of radiotherapy and then fell to pre-radiotherapy levels 4 months later. There was no change in NT pro-BNP. There was no correlation between MHD or dose to coronary arteries and change in hsTnI. Median pre-radiotherapy CACS was 371 (0-3478) and median LVEF was 63% (38.9%-73.9%). There was no significant change in CACS or LVEF following radiotherapy.

Conclusions: The study patients had high CACS prior to radiotherapy. There was a significant but temporary increase in hsTnI during radiotherapy and 13% of patients had a cardiac event. Patients undergoing thoracic radiotherapy may benefit from cardiology assessment prior to treatment.

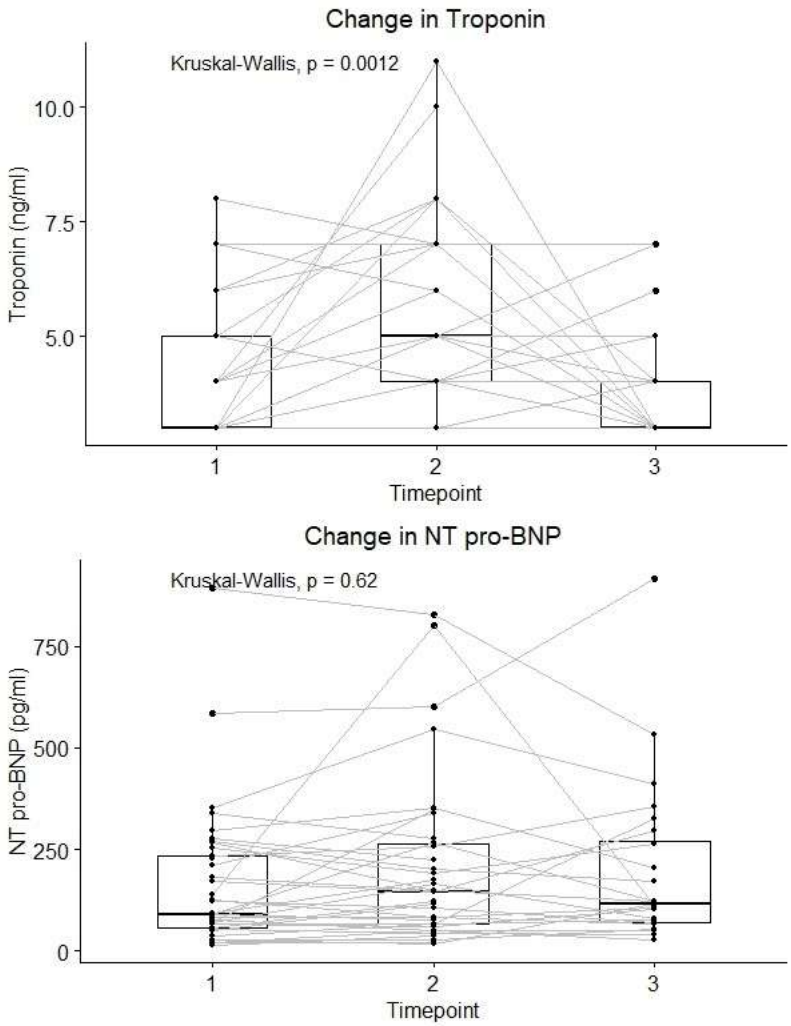

Figure 1 Change in high sensitivity troponin I and NT pro-BNP from baseline to end of and 4 months after thoracic radiotherapy

Keywords: Radiotherapy, Cardio-oncology, Toxicity biomarkers

EP05.01-013 Increased C-reactive Protein after Chemoradiotherapy and Immunotherapy in Locally Advanced Non-small Lung Cancer Indicates Worse Survival

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Introduction: Adjuvant durvalumab after chemoradiotherapy (ChRT) in PD-L1 positive tumours is standard radical treatment for fit patients with locally advanced non-small cell lung cancer (LA-NSCLC). Many studies showed that immune response based on neutrophil-to-lymphocyte ratio (NLR), serum C-reactive protein (CRP) values and the use of antibiotic treatment before and during immunotherapy (IT) can predict survival in metastatic NSCLC patients, but rare data are published for LA-NSCLC.

Methods: We retrospectively reviewed medical records of patients diagnosed with LA-NSCLC receiving definitive ChRT and IT at the Institute of Oncology Ljubljana from December 2017 to December 2020. Baseline, during and post-treatment NLR, CRP and the usage of antibiotics were collected from our medical database. Overall survival was calculated from the start of the ChRT to death from any cause or last follow up 15th February 2022. The Cox proportional hazards model was used to assess the association between OS and NLR, CRP and antibiotic usage. All tests were two tailed. A p-value less than 0.05 was considered statistically significant.

Results: A total of 85 patients were included in our analyses. After the median follow up time of 36 months the median overall survival (mOS) time was not reached. Three-year survival rate was 59.3%. NLR ratio either before, during or after treatment was not predictive for survival. In univariate analysis increased CRP with the value of more than 6 times upper limit of normal (6XULN) before ChRT (p=0.047) and before IT significantly predicted worse survival (p=0.009). Also, if increased value after IT was above ULN, mOS was 36 months vs. not reached for those with normal CRP (p=0.005). For patients with CRP 6XULN after IT mOS was 21 months vs. not reached (p<0.001). The use of antibiotics during therapy showed increased trend toward worse survival (p=0.067). In multivariate analyses, only CRP 6XULN at the end of treatment significantly predicted worse survival (p=0.021, CI 0.16-0.86).

Conclusions: In our analyses of patients with LA-NSCLC treated with radical ChTRT and adjuvant IT, only increased CRP value predicted worse survival, while antibiotic use showed trend for worse survival. Further analyses are warranted.

Keywords: C-reactive protein, chemoradioimmunotherapy, LA-NSCLC

EP05.01-014 Circulating Tumor DNA to Identify Genomic Biomarkers of Radiation Sensitivity in Locally Advanced Non-Small Cell Lung Cancer

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Introduction: Despite our increasing understanding of the genomic heterogeneity of non-small cell lung cancer (NSCLC), patients with locally advanced inoperable disease are treated with the same dose of radiation therapy (RT). Tissue-based analyses have identified likely biomarkers of RT response. We evaluated the feasibility of prospective molecular profiling with liquid biopsy ctDNA testing to identify genomic markers of RT sensitivity and resistance.

Methods: This prospective clinical cohort consists of patients with inoperable locally advanced NSCLC (*n*=29). Our institutional next-generation sequencing liquid biopsy assay MSK-ACCESS was used for profiling, which includes 129 genes and paired white blood cell sequencing. OncoKB was utilized to classify alterations. Likely oncogenic alterations in *KEAP1*, *NFE2L2*, *STK11*, and *PIK3CA* were classified as markers of RT resistance. Likely oncogenic alterations in the DNA Damage Repair (DDR) pathway including *ATM*, *ATR*, *BRCA1/2*, *ARID1A*, *MLH1*, and other DDR alterations were classified as markers of RT sensitivity. Distant and locoregional disease recurrence was evaluated from time of chemoradiation (CRT) completion.

Results: We completed prospective ctDNA testing with MSK-ACCESS among 29 patients with inoperable locally advanced NSCLC: 14% (*n*=4) had stage II disease and 86% (*n*=25) had stage III disease. Seventeen of the 25 patients with stage III disease received durvalumab. The median RT dose was 60 Gy (range: 55 - 66 Gy). The median follow-up from the completion of RT was 11 months (range: 0-16 months). Overall, 24% of patients (*n*=7) patients had disease progression including isolated locoregional (*n*=1), distant (*n*=3) or both locoregional and distant progression (*n*=3). One patient had a marker of RT resistance detected in plasma ctDNA (*KEAP1* Q282*) and developed locoregional and distant recurrence 6 months after definitive CRT. Markers of RT sensitivity were detected in 3 patients including *ARID1A* Q1127*, *ARID1A* X1367_splice, and *MLH1* X226_splice alterations, none of whom had a local recurrence. Two of these patients were disease-free at last follow-up (4 and 14 months after CRT), and one patient had distant disease progression 13 months after CRT.

Conclusions: We demonstrate the feasibility of prospective profiling with liquid biopsy to identify genomic markers of RT response including somatic mutations associated with RT sensitivity and resistance. This data may inform future evaluations of personalized, genomically-guided thoracic RT for lung cancer.

Keywords: Liquid biopsy, ctDNA, Radiation sensitivity

EP05.01-015 Validate Radiomics Features and XGBoost Model in Radiation Pneumonitis (RP) Prediction in Patients with Primary Lung Cancer: A MultiCenter Study

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Introduction: Radiomics features of pre-radiotherapy planning CT scans have been reported to have a potential to predict radiation pneumonitis (RP), with evidence largely from Western countries and or single Institutions. The purpose of this study was to 1) validate the significance of pre-radiotherapy planning CT radiomics-specific RP prediction in a China multicenter database, and 2) explore the performance boost of extreme gradients (XGBoost) in Chinese patients with primary lung cancer for identifying RP grade 2 and above.

Methods: Study population included a total of 505 patients from 4 centers (43, 198, 187, and 77 patients from Center #1, #2, #3, and #4 respectively). Patients must have total lung delineated or radiotherapy pneumonitis diagnosed and graded, and extractable radiographic features. Pretreatment plan CT is the average CT of 4D-CT for HKUH center, TZ center and SZCH center and Deep-Inspiration Breath-hold CT for ZD center because the center uses respiratory gating system. The primary endpoint was defined as grade 2 and above RP using the CTCAE5.0 criteria. The criteria adopted by center#2 was slightly different from others. Radiomics features were extracted from total lungs minus GTV volumes from planning CTs (which were same among all centers except #4) using the python package PyRadiomics. Signficant radiomics features are used for modeling by the use of XGBoost method. Data from one center (#1) was used for training, and the remaining for validation (#2, #3, #4). The predictive power of the model was assessed using the area under the receiver operating characteristic curve (AUC).

Results: A total of 405 patients met the study entrance criteria (43, 114, 175, 73 from each hospital). Eighty-four (20.7%) of 405 patients developed RP grade 2 and above. Among 107 radiomics features extracted, 70 features were significantly different (p value ≤ 0.05) between patients with RP2 and without RP2, including 15 first-order, 16 gray level co-occurrence matrix (GLCM), 7 gray level dependence matrix (GLDM),10 gray level run length matrix (GLRLM), 11 gray level size zone matrix (GLSZM), 3 neighbouring gray tone difference matrix (NGTDM) and 8 shape features. These significant radiomics features were used for model building. The AUC for the training dataset center (#1 center) was 0.763 [95% CI 0.684 - 0.837], and the AUC for the validation datasets of #2 center was 0.661[95% CI 0.507 - 0.806], for #4 center with 0.545 [95% CI 0.430 - 0.658] with difference breathing phase of the CT scan for planning, and 0.611 [95% CI 0.333 - 0.898] for #3 center with different RP diagnostic criteria.

Conclusions: This study validated the significance of radiomics features on predicting grade 2 and above RP in primary lung cancer in multi-center Chinese patients. However, model accuracy is limited and heterogeneous from center to center, poorer of the centers with either different diagnosis criteria or different simulation CT. Future study will need look into the detail of breathing phase, diagnostic criteria and dosimetric information before we can establish a more accurate model. Further biological data are also need to be included for further improvement.

Keywords: radiation pneumonitis, radiomics

EP05.01-016 Radiation Recall Pneumonitis (RRP) Induced by Immune Checkpoint Inhibitors (ICIs) after Thoracic Radiotherapy for Lung Cancer

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Introduction: Radiation recall pneumonitis (RRP) describes inflammatory reactions at previously irradiated fields of pulmonary tissue after exposure to certain systemic agents. Immune checkpoint inhibitors (ICIs) have been reported as potential causal agents of RRP in lung cancer. Yet, the general characteristics and risk factors of ICI-related RRP remain unclear. This study investigates the incidence, characteristics, and risk factors of RRP induced by ICIs after thoracic radiotherapy in patients with lung cancer.

Methods: Patients with lung cancer who received ICIs and had a history of lung irradiation at our institution from Jan 2016 to July 2021 were retrospectively reviewed. RRP was identified by inflammatory reactions at previously irradiated fields on chest computed tomography after ICI administration and more than 6 months after thoracic radiotherapy. Clinical and dosimetric data were analyzed to identify potential risk factors for RRP. Toxicity grading was per common terminology criteria for adverse events (CTCAE) Vol. 5.0. Comparison between patients with or without RRP was assessed using the Chi-squared test (or Fisher's exact test) for qualitative risk factors and the Mann-Whitney test for quantitative risk factors. The receiver operating characteristic analyses were performed to identify optimal cut points for quantitative variables.

Results: A total of 196 patients with lung cancer who received ICIs after thoracic radiotherapy were identified. The median follow-up time was 18.0 months (interquartile range, 12.5-28.7 months), and the median interval between the completion of radiotherapy and the initiation of ICIs was 78 days (range, 0-1240 days). RRP occurred in 14 patients (7.1%) and the incidences of grade≥2 and grade≥3 RRP were 1.5% and 0.5%, respectively. The median interval between the end of radiotherapy and RRP was 271 days (range, 188-630 days) and the median interval between the initiation of ICIs and RRP was 147 days (range, 49-588 days). No relationship was identified between the time to onset of RRP from ICI or TRT and its severity. There were 4 RRP patients had a history of radiation therapy and one RRP patient had concurrent checkpoint inhibitor pneumonitis. Patients with grade≥2 RRP received glucocorticoid treatment and all patients recovered from RRP. Three patients with grade≥2 RRP and 1 patient with grade 1 RRP terminated the ICI treatment. Univariate analysis indicated that the mean lung dose (13.2 Gy vs. 11.1 Gy, *P*=0.038), the volume more than 5Gy (V5, 47% vs. 38.7%, P=0.0124) and the volume more than 20Gy (V20, 23% vs. 18.8%, P=0.03) of previous thoracic radiotherapy were significantly higher among patients with RRP than those without. ROC analyses found the optimal cutoffs of dosimetric parameters that predicted RRP, which corresponded to MLD > 12.9 Gy, V5 > 46.3%, V20 > 16.7%. Further, the history of chronic pulmonary diseases (50% vs. 23.6%, P=0.05) was marginally significant to predict the development of RRP. Smoking history, female sex, age, lower lobe irradiation, types of ICI therapy (monotherapy vs. combination therapy; PD-1 inhibitors vs. PD-L1 inhibitors), Prior radiation therapy and interval between TRT and ICI were not associated with the occurrence of RRP.

Conclusions: In our population of lung cancer patients who received ICIs after thoracic radiotherapy, the occurrence of RRP was acceptable and manageable. Dosimetric parameters (i.e., V5, V20, and MLD) may help predict the development of RRP.We

Keywords: radiation recall pneumonitis, immune checkpoint inhibitors, radiotherapy

EP05.01-017 Exploring the Benefits of Adaptive Radiotherapy in NSCLC-patients

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Introduction: Locally advanced NSCLC (LA-NSCLC) is treated with the same chemoradiotherapy strategy irrespective if the histology is adenocarcinomas (AC) or squamous cell carcinomas (SCC). However, they differ in terms of pattern of failure with AC being more prone to distant failure (D) and SCC more prone to loco-regional failure (LR). Recent study [1] has shown improved overall survival (OS) and progression free survival (PFS) using adaptive radiotherapy (ART). This study investigates if patients with different histology experience different benefits of ART.

[1] Møller et. al., Survival benefits for non-small cell lung cancer patients treated with adaptive radiotherapy. Radiother Oncol. 2022 Feb 2;168:234-240. doi: 10.1016/j.radonc.2022.01.039. Epub ahead of print. PMID: 35121030.

Methods: ART was implemented in the treatment of LA-NSCLC patients at a single institution in April 2013. 184 (100 AC and 84 SCC) consecutive patients prior and 255 (156 AC and 99 SCC) consecutive patients after implementation of ART were retrospectively reviewed. Baseline characteristics (chemotherapy, age, performance status, stage), administration of immunotherapy for recurrences and radiotherapy parameters (mean heart dose (MHD), mean lung dose (MLD) and GTV-volume) were collected. Patients were divided in 2 groups by AC/SCC and overall survival in each group was analyzed with multivariate cox regression. Kaplan-Meier curves were plotted for four groups by pre-ART/ART and AC/SCC and compared using log-rank test.

Results: Median follow-up for the combined cohort was 24 months. Treatment and patient-characteristics were similar for all groups but patients in the ART-group received more chemotherapy ($p<0.01$) and had lower MLD and MHD. Multivariate cox regression of OS for AC showed significant correlation between OS and GTV-volume (HR=1.0027 pr. mL increase, $p=0.02$), while cox regression for SCC showed significant correlation with GTV-volume (HR=1.003 pr. mL increase, $p>0.01$), chemotherapy (HR=0.64, $p=0.02$), MLD (HR=1.06 pr. Gy, $p=0.02$) and performance status HR=0.65, $p=0.02$). ART was borderline significant for SCC (HR=0.69, $p=0.05$). No correlation with MHD or immunotherapy treatment was seen for neither histology. Figure 1 shows significantly different Kaplan-Meier survival plots for the four groups. The impact of ART on SCC increased 2-year OS from 31% to 54.5%, while OS was unchanged for AC

Conclusions: The improved precision of radiotherapy combined with lower normal tissue doses increases OS, but the impact seems to be histology dependent. ART primarily leads to an improved overall survival for patients with SCC.

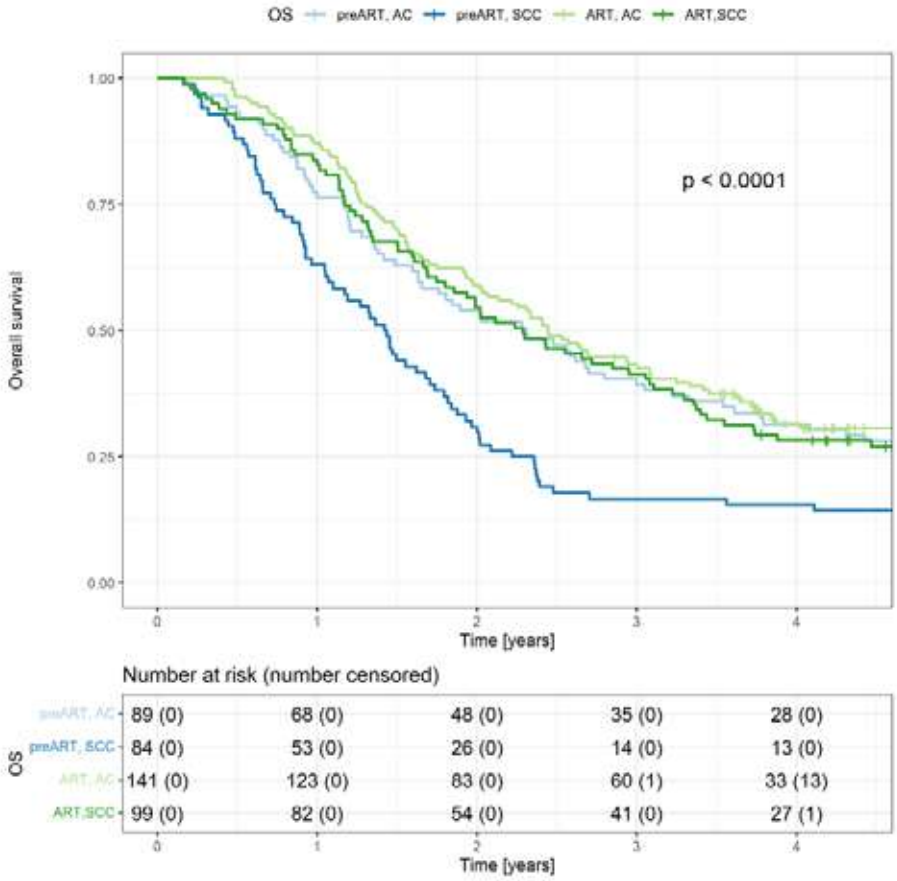

Fig. 1. Over-all survival for patients divided by histopathology (AC=adenocarcinomas, SCC=squamous cell carcinomas) before (pre-ART) and after (ART) the implementation of ART.

Keywords: NSCLC, Adaptive Radiotherapy, Overall survival

EP05.01-018 Chemoradiotherapy Followed by Durvalumab in Unresectable Locally Advanced NSCLC- A Single Institution Experience in Croatia

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Introduction: The PACIFIC trial demonstrated significant improvement in progression-free survival and overall survival of patients with unresectable locally advanced NSCLC treated with durvalumab consolidation after concurrent chemoradiotherapy and changed the standard of care of this subset of NSCLC patients.We here present the real world data and outcomes of our patients diagnosed with unresectable locally advanced NSCLC and treated with concurrent or sequential chemoradiotherapy, followed by consolidation durvalumab.

Methods: We retrospectively analyzed the data of 42 patients treated for unresectable LA NSCLC between February 2018 and Septembre 2020 in University Hospital Centre Zagreb, Croatia (Department of Pulmonary Diseases). Patient data were collected from medical data base. The cutoff date for data collection was February 2022.

Results: Our investigation included 42 patients. There were 33 male (79%) and 9 female patients (21%), aged 47-74 years (mean age 62.6 y). 22 patients (52.3%) were diagnosed with squamous and 20 (47.6%) with non-squamous NSCLC, with PD-L1 expression >50% in 19 (45.2%), 1-49% in 17 (40.5%), negative in 1 (2.4%) and unknown in 5 (11.9%) patients.Patients were treated with concurrent (n 35; 83.3%) or sequential chemoradiotherapy (n 7; 16.7%), followed by durvalumab at the dose of 10 mg/kg every 2 weeks for up to 12 months, as consolidation therapy. Median time to drug administration was 45 days (9-131 d) from the date of radiation therapy completion.Altogether 21 (50%) patients completed planned 12 month durvalumab treatment, 14 patients (33.3%) had disease progression during durvalumab and in 7 (16.6%) patients durvalumab was discontinued earlier because of the adverse events.Adverse events that led to durvalumab cessation were reccurent pneumonitis (n5), reccurent hepatitis (n1) and grade 4 myocarditis with total AV block (n1).The most common adverse event was pneumonitis (n 17), followed by thyroid function disorders (n8), dermatitis (n4), hepatitis (n 3), pruritus (n1) and myocarditis with total AV conduction interruption (n1). Most adverse events were CTC grade 1-2 (91.2%; n 31). The mPFS for the whole cohort was 24.1 months (95% CI 6.03 - 42.16). Female patients had a siginificantly longer PF time (17.2 months vs NR). Surprisingly, disease stage and the nodal status did not influence PFS, nor did tumor histology (Squamous vs non-squamous 14.9 months vs NR). Patients with PDL1 >= 50% had singificantly longer PFS (8.13 months vs NR).A significant PFS benefit was observed among patients who underwent concurrent chemoradiotehrapy, compared to those who were treated sequentially (NR vs 5.1 months).Patients who experienced side effects which caused treatment delay or cessation did not have a shorter PFS (17.2 months vs NR). The mOS for the whole cohort was not reached.

Conclusions: Our data support the survival benefit and safety of durvalumab consolidation in patients with locally advanced NSCLC in the real- life setting. Further observations are needed to define other possible factors that contribute durvalumab benefit, taking into account the diversity of this NSCLC subgroup.

Keywords: durvalumab, locally advanced NSCLC, chemoradiotherapy

EP05.01-019 4D CT Ventilation Image-Guided Lung Functional Avoidance Radiotherapy: A Single-Arm Prospective Pilot Clinical Trial

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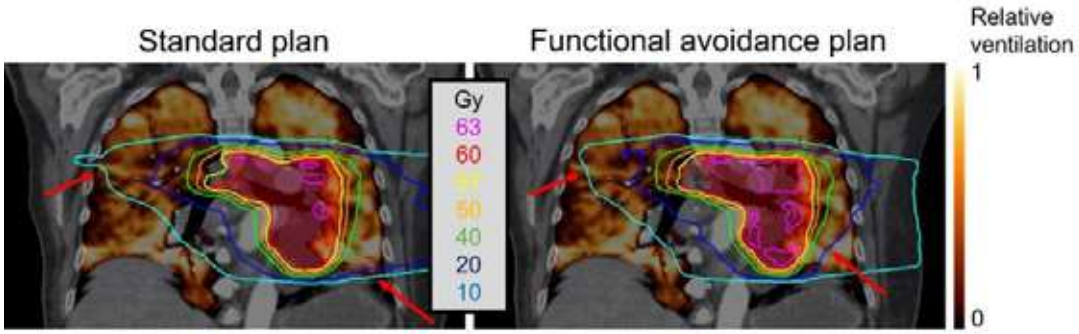
Introduction: Thoracic radiotherapy is limited by substantial toxicities, including radiation pneumonitis which is potentially fatal. Functional avoidance radiotherapy that preferentially avoids irradiating normal (ventilated or perfused) lung regions has shown potential to reduce pneumonitis. The primary objective of this single-arm prospective pilot clinical trial (NCT02308709) was to assess the safety and feasibility of functional avoidance radiotherapy with 4-dimensional (4D) computed tomography (CT) ventilation imaging, which only requires a standard-of-care 4D CT scan and image processing/analysis. We hypothesized that functional avoidance radiotherapy could be safely administered.

Methods: Patients with primary lung cancer or metastatic disease to the lungs to receive either conventionally fractionated radiotherapy (CFRT) or stereotactic body radiotherapy (SBRT) were eligible. All patients underwent a 4D CT scan, which was used for ventilation computation through deformable image registration and image analysis. Each patient required clinically-approved standard treatment plans (the lungs were considered uniformly functional) and functional avoidance plans with intensity-modulated radiotherapy. The primary endpoint was the rate of grade ≥3 toxicities that occurred ≤12 months after treatment. Dose-volume metrics were compared between the two plans using the Wilcoxon signed-rank test.

Results: Between May 2015 and November 2019, 34 patients were enrolled: 25 patients with stage II-III non-small cell lung cancer (NSCLC) to receive CFRT with concurrent chemotherapy and 9 patients with stage I-II NSCLC to receive SBRT. One patient died before treatment. Of 33 evaluable patients, 32 patients received full dose (CFRT 60 Gy in 2 Gy fractions; SBRT 54-55 Gy in 3-5 fractions) and one patient chose to discontinue CFRT due to grade 4 esophagitis. The overall rate of grade ≥3 toxicities was 12.1% (n=4; 16.7% for CFRT and 0% for SBRT). One and three patients had grade 3 pneumonitis and grade ≥3 esophagitis, respectively. Compared with the standard plans, functional avoidance plans significantly (P <0.01) reduced the functional mean lung dose by 0.9 Gy (relative reduction 5.2%) for CFRT and by 0.9 Gy (9.6%) for SBRT without compromising target coverage or adherence to standard constraints of organs at risk (OARs). Figure shows a comparison of isodose distributions between the standard and functional avoidance plans of a representative case who received CFRT.

Conclusions: This study demonstrated the safety and feasibility of 4D CT ventilation image-guided functional avoidance radiotherapy that significantly reduced dose to ventilated lung regions without compromising target coverage or adherence to standard OAR constraints, providing evidence to support a larger-scale randomized phase 3 clinical trial.



Keywords: Radiotherapy, Pulmonary functional imaging, Radiation pneumonitis

EP05.01-020 Unanticipated Radiation Re-planning for Stage III Non-small Cell Lung Cancer

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Introduction: Technological advancements in the planning process have facilitated more efficient complex radiotherapy (RT) adaptation in cancers where changes in motion and anatomy during treatment may occur, such as in stage III non-small cell lung cancer (NSCLC). The primary objective of this study was to identify factors associated with unanticipated RT re-planning in Stage III NSCLC. Secondary objectives were to examine survival and cumulative incidence of local, regional and distant recurrence.

Methods: In this single-institution ethics-board approved study, all stage III NSCLC patients from January 1, 2016, to December 31, 2019, treated with radical intent RT were analyzed. Descriptive statistics were performed, including the frequency of RT re-planning and reason for re-planning. Logistic regression analysis was used to identify predictive factors associated with re-planning. Variables significant on univariate modelling, with a P value < 0.05, were selected for multivariate modelling. Overall survival was determined using the Kaplan-Meier method. Cumulative incidence of local, regional, and distant recurrence was determined using the competing risk method.

Results: There were 144 patients with Stage III NSCLC meeting study criteria, of which 18% (n=26) required re-planning. The most common reason for re-planning was due to volume changes (target shift or enlargement) on cone beam computed tomography (CBCT) (n=20, 77%), followed by failure to meet planning constraints (n=6, 23%). On univariate analysis, patients with a larger superior -inferior (SI) dimension of the primary and nodal planning target volume (PTV) was associated with a higher incidence of re-planning [Odds ratio (OR) 1.17, 95% CI 1.03-1.35 p = 0.02). Larger PTV (primary and nodal) was also associated with higher incidence of re-planning on univariate analysis [(OR) 2.48, 95% CI 1.21-5.38, p= 0.02). On multivariable analysis, only larger PTV (primary and nodal) were statistically predictive of re-planning. The actuarial median OS was 36.3 months (95% CI 27.7-66.5). The cumulative incidence for local, regional, and distant recurrence at 2 years were 18% (95% CI 12-25%), 19% (95% CI 13-26%), and 38% (95% CI 30-46%), respectively.

Conclusions: A larger SI dimension of the PTV, as well as larger PTV are associated with a higher odds ratio of re-planning. Survival and recurrence outcomes for this group of patients are similar to the outcomes reported in the literature.

Keywords: Stage 3 Non Small Cell Lung cancer, Unanticipated re planning, Oncology outcomes

EP05.01-021 Radiation Dose to Cardiac Substructures and the Incidence of Cardiac Events in Patients with Stage III NSCLC Receiving CCRT

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Introduction: Cardiac toxicities after radiation therapy (RT) in lung cancer patients (pts) have been increasingly recognized as an important factor in clinical outcomes. Here we investigated the impact of radiation doses to the heart and cardiac substructures (left atrium (LA), left ventricle (LV), right atrium (RA) and right ventricle (RV)) on the incidence of cardiac events following completion of concurrent chemoradiotherapy (CCRT).

Methods: We conducted a retrospective study of pts with stage III NSCLC treated with CCRT from 2010 to 2016. The primary endpoint was post-CCRT occurrence of a cardiac event, defined as myocardial infarction, stroke/TIA, heart failure with echo diagnosis of EF <50%, any arrhythmia, including atrial fibrillation (A fib) or atrial flutter (A flutter) or ventricular tachycardia (V tach). RT dose ranged from 60-66 Gy. Cardiac events were identified from the electronic medical records by 2 independent volunteers and adjudicated by 2 cardiologists for accuracy. Cardiac substructures were contoured by 2 volunteers and reviewed by 2 independent radiation oncologists. Radiation dose parameters were extracted from each treatment plan; doses to the cardiac substructures were calculated. The association between a pt's individual risk factors and % of cardiac structures receiving RT dose, and the occurrence of a cardiac event was analyzed using logistic regression, and odds ratios (OR) were estimated.

Results: Of the 201 pts included in this study, 88(43%) experienced a cardiac event as defined above, with 53(60%) of the latter having arrhythmias. Median follow up was 18 mo. Pts with prior history of cardiovascular disease (CVD) (vs none OR 2.67, p=0.001), higher BMI (OR 1.04, p=0.047), male gender (OR 2.46, p=0.002), or prior hypertension (HT) (OR 2.88, p<0.001) had significantly greater probability of a cardiac event after CCRT. In addition, pts had significantly greater risk of a cardiac event if ≥1.8% LA received 60 Gy (OR 2.11, p=0.013) or any % LA received 70 Gy (OR 2.5, p=0.029). Similarly, pts had significantly greater risk if ≥3% RV received 30 Gy (OR 2, p=0.024), ≥1.5% RV received 35 Gy (OR 2.2, p=0.009), or ≥2.25 % RV received either 40 Gy (OR 2.44, p=0.018) or 45 Gy (OR 3.5, p=0.0093).

Conclusions: Cardiac events, especially arrhythmias, occurring after definitive chemoradiation among pts with stage III NSCLC can be common (as high as 43%), especially in pts with prior history of CVD or HT, or having male gender. Even when dose constraints for total heart are adhered to, RT dose to LA and RV structures could play a significant role in the development of new cardiac events.

Keywords: cardiac toxicity, lung cancer, radiotherapy

EP05.01-022 Evaluation of the Management of Stage III NSCLC at Mohamed IV Center for Cancer Treatment Casablanca

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Introduction: Stage III in the NSCLC should be separated into stages IIIA, IIIB and IIIC according to the 8th edition of the TNM classification. Subgroup N2 remains the most controversial. In our study, we evaluated the management of NSCLC in our oncology center.

Methods: This is a descriptive retrospective study of 123 patients collected at Mohamed IV Center for Cancer Treatment Casablanca, over a period of 2 years from 01/01/2018 to 31/12/2019. The data collection was done using a form duly filled in from the patients' files followed in consultation.

Results: The average age of our patients was 61 years with extremes ranging from 43 to 77 years. A clear male predominance was noted with a sex ratio of 23. 94.4% of our patients were smokers. The time to treatment was less than 6 months in 61.8% of cases, between 6 and 12 months in 30%, and more than a year in 8.2%. In our series, diagnostic biopsies were performed during bronchoscopy in 51.2% of cases, by transparietal biopsy in 32.5% of cases, by mediastinoscopy and EBUS in 6.5% and 3.2% of cases respectively, and on surgical specimen in 8.9% of cases. The anatomopathological study supplemented by an immunohistochemical study showed adenocarcinoma in 48% of cases, epidermoid carcinoma in 34% of cases and poorly differentiated carcinoma in 18% of cases, genomic complement was performed only in 9% of our patients. 90% of the cases benefited from a complete check-up including a brain scan in 93.5% of the cases, MRI in 30% of the cases and CT scan in 63.5% of the cases, the PET scan was performed in 49% of the cases. This assessment allowed us to classify our patients according to the 8th TNM classification as stage IIIB in 62.6% of cases, stage IIIA in 27.6% of cases and stage IIIC in 9.8% of cases. All the files were discussed in multidisciplinary meeting, and surgical management was decided only in 26% of the cases and after VAMLA in one patient. 68% of our patients received neoadjuvant chemotherapy and 45% received chemoradiotherapy concomitant and only 11.3% received surgery followed by adjuvant chemotherapy. Adjuvant radiotherapy was performed in only one patient who had an R1 resection. Progression was noted in 30.9% of cases, including brain progression, and radiological stability in 13% of cases. The complete response was achieved in only 3.2% of cases. Thus, an alteration of the performance status before or during neoadjuvant chemotherapy was noted in 17% of patients, and 21% of patients lost sight of the SP before any treatment.

Conclusions: The therapeutic strategy for NSCLC is decided in multidisciplinary meetings within an experienced team for all cases; but only a minority of the decisions are made given the delays in treatment and the rapid alteration of the patient's performance status, imposing the personalization of the treatment taking into account the co-morbidities of each patient

Keywords: Management, NSCLC, Stage III

EP05.01-023 Feasibility of Functional Lung Avoidance using Ga-68 4D Ventilation Perfusion PET/CT: The HI-FIVE Trial

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Introduction: Functional lung avoidance (FLA) radiation therapy spares regions of functional lung with an aim of reducing toxicity. We present results of a prospective trial of FLA using Ga-68 PET/CT to image both ventilation (V) and perfusion (Q). The primary objective of this single arm interventional trial (NCT03569072, protocol doi:10.1136/bmjopen-2020-042465) was to test the feasibility of achieving FLA whilst increasing dose to the primary tumour.

Methods: Planning 4D V/Q PET/CT images were used to define functional lung volumes using previously published methods using the intersection of highly perfused and ventilated lung. Volumetric Modulated Arc Therapy (VMAT) optimisation was performed to a) deliver 60Gy in 30 fractions to the primary and nodal planning target volume b) deliver a simultaneous integrated boost to the primary tumour to 69Gy in 30 fractions and c) reduce heart dose d) reduce functional lung dose. Comparison plans based on standard anatomical lung constraints were generated for each patient and were required to be clinically acceptable and comparable to functional plans (<5% difference between non-functional lung dose metrics). Criteria for feasibility were assessed for each patient and was considered met if all following criteria were achieved on functional plans when compared to anatomical plans: (A) Reduction in mean functional lung dose of ≥2 Gy (fMLD) and functional lung volume receiving 20 Gy (fV20) of ≥4%; (B) Mean heart dose ≤30 Gy and relative heart volume receiving 50 Gy <25%. Feasibility was defined as ≥15 of 20 patients achieving stated goals. Secondary endpoints are yet to be analysed and will be reported separately.

Results: 19 of a planned 20 patients were recruited, one of whom withdrew consent. 18 patients underwent chemoradiation with functional lung sparing radiation therapy, 10 of which received consolidation immunotherapy. 14 of 18 patients were alive at the end of the study follow up period of 12 months with 10 patients free from recurrent disease. Of the 18 patients, 15 met criteria for feasibility. The mean functional lung dose reduced by (mean, range) 12% (-8% - 37%), the functional V20 Gy reduced by 17% (-13% - 42%). Two patients had increased mean functional lung dose in the FLA plan.

Conclusions: This trial met its predefined feasibility endpoint which suggests the development of a randomised trial will be both feasible and acceptable to patients. The majority of the patients treated with FLA experienced significant reductions in fV20 and fMLD. A large trial involving randomisation to radiation therapy with either an anatomical or a functional treatment is required to assess if these dosimetric gains translate into lower rates of toxicity.

Keywords: Locally Advanced Non-small Cell Lung Cancer, Volumetric Modulated Arc Therapy, Functional lung avoidance

EP05.01-024 Real-life Management of Stage III NSCLC Patients in Italy: The BE-PACIFIC Observational Study

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Introduction: Stage III locally advanced non-small cell lung cancer (NSCLC) includes a heterogeneous group of patients with diverse disease presentation, biological portrait and prognosis. Given its complexity, optimal management of patients requires tailored approach through a multidisciplinary team (MDT) decision-making process. According to the PACIFIC trial [NCT02125461] results, the evolving treatment paradigm in the setting of unresectable disease includes the programmed death-ligand 1 (PD-L1) inhibitor durvalumab as beneficial consolidation immunotherapy following chemoradiation. Here we report the final results from the 'Italian oBsErvational study on Patient mAnagement strategies in real-world Clinical practIce For patIents with loCally advanced (stage III) NSCLC' (BE-PACIFIC), aimed at describing diagnostic work-up and treatment of stage III NSCLC according to the Italian standard clinical practice, and outcomes during observation.

Methods: The BE-PACIFIC study is an observational multicenter retrospective prospective cohort study, involving both a primary data collection and secondary use of data. Adult patients diagnosed with stage III NSCLC were included by 40 sites and followed-up for 12 months after diagnostic process completion.

Results: A total of 296 eligible patients were considered in this analysis. Baseline characteristics are reported in Table.

BE-PACIFIC study: demographic and clinical characteristics at stage III NSCLC diagnosis (baseline)		
Age (years), median (25th-75th percentiles)		68.0 (62.5-72.0)
Males, n (%)		219 (74.0%)
Caucasians, n (%)		290 (98.0%)
Known smoker, n (%)*		257 (90.8%)
Presence of comorbidities/history of relevant medical conditions, n (%)*		243 (82.4%)
Presence of NSCLC symptoms, n (%)		149 (50.3%)
ECOG-PS, n (%)*	0	174 (60.4%)
	1-2	114 (39.6%)
Tumor histology, n (%)	Adenocarcinoma	164 (55.4%)
	Squamous cell carcinoma	115 (38.9%)
Tumor descriptor, n (%)*	T1	32 (11.0%)
	T2	54 (18.5%)
	T3	90 (30.8%)
	T4	116 (39.7%)
Node descriptor, n (%)*	N0	19 (6.5%)
	N1	37 (12.6%)
	N2	187 (63.6%)
	N3	51 (17.3%)
Tumor stage**, n (%)*	IIIA	117 (40.2%)
	IIIB	149 (51.2%)
	IIIC	25 (8.6%)

ECOG-PS = Eastern Cooperative Oncology Group - Performance Status. *Percentages computed out of the number of eligible patients with available data. **Tumor stage assessment according to the 8th lung cancer TNM classification and clinical staging system.

The median (25th-75th Percentiles) duration of the diagnostic process was 30.4 (21.0-60.9) days, with 144 (48.6%) patients completing the work-up in a single cancer center. MDT was involved in the treatment plan definition of 88.7% (n/N=260/293) patients with available data, with participation of oncologists, radiation oncologists, radiologists, pneumologists, surgeons and pathologists in ≥50% of cases. PD-L1 level was initially tested in 196 patients, with ≥1% of tumor cells expressing PD-L1 in 133 (67.9%) patients. PD-L1 level was tested later during observation in 59 additional patients. Sixty patients had tumor resection, mostly associated with neoadjuvant (27, 45.0%) or adjuvant (21, 35.0%) treatment. Chemoradiation was used in 165 (69.9%) of 236 non-resected patients, followed by durvalumab in 79 cases. Overall, 82 (27.7%) patients underwent durvalumab, 70.7% of whom had ongoing treatment at end of observation. An overall response to durvalumab was shown in 17 of 71 evaluable patients (23.9%). Disease progression or death occurred in 153 (51.7%) patients during observation, regardless of treatment.

Conclusions: According to the BE-PACIFIC final results, the MDT was largely involved in stage III NSCLC management, with at least 75% of patients completing the diagnostic process within 2 months. Consolidation durvalumab was used in 48% of non-resected patients treated with chemoradiation, with favorable retention in treatment and response, consistently with the PACIFIC trial findings.

Keywords: locally advanced non-small cell lung cancer, Patient Management, Real World Evidence

EP05.01-025 Planned Interim Analysis of a Phase II Trial of Concurrent Durvalumab and Radiation Therapy for Locally Advanced Lung Cancer

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Introduction: The current standard of care for newly diagnosed inoperable locally advanced non-small cell lung cancer (LA-NSCLC) is concurrent chemoradiation therapy (cCRT) followed by consolidative durvalumab. However, up to 50% of patients are not candidates for cCRT and thus treated with sequential CRT or RT alone, a setting in which immunotherapy is not approved. We launched an investigator-initiated trial to study the safety and outcomes of concurrent and consolidative durvalumab and RT without chemotherapy in patients who are not candidates for cCRT. Here, we report the results of a pre-planned interim analysis.

Methods: This is a single-arm, open label phase II study. Patients with LA-NSCLC, not selected by PD-L1 expression status, were treated with definitive conventionally fractionated RT (60 Gy in 30 fractions). Concurrent durvalumab 1500mg q4weeks was initiated within 7 days of RT start and continued for up to 13 cycles, until disease progression or unacceptable toxicity. The primary objective was progression-free survival (PFS). A pre-planned interim analysis at 50% enrollment (27 patients) was performed, with descriptive statistics on patient characteristics, interim PFS, overall survival (OS), and toxicity. An early stopping safety rule required ≤6 out of the first 18 patients to experience grade ≥3 treatment-related toxicity within 12 weeks from the end of RT. No efficacy or futility tests were planned for interim analysis, as the study was only powered for these endpoints with full enrollment.

Results: Between 08/2019 and 10/2021, 27 patients were treated per protocol. At the time of the interim analysis, the median follow-up was 12 months (range: 3.3 to 27.7). Median age at diagnosis was 82 years; ECOG status was 0, 1 or 2 for 1, 22 and 4 patients, respectively. Fifteen patients had adenocarcinoma, 8 squamous cell carcinoma, and 4 NSCLC not otherwise specified. Two patients presented with stage IIB, 17 with IIIA, 6 with IIIB and 2 with IIIC NSCLC. PD-L1 expression was available for 21 patients and >1% in 11 and >50% in 5 patients. Median tumor mutation burden was 10.5 mutations/megabase (available for 16 patients, range 0.8 to 18.9). All but 4 patients received 60 Gy in 30 fractions; the median number of durvalumab cycles was 9 (range: 2 to 13). One-year PFS and OS were 51.8% and 74.7%, respectively. Median PFS was not reached, and median OS was 22.8 months. No early stopping safety rule was met. Three treatment-related serious adverse events were observed in the first 27 patients, including one patient with grade 3 pneumonitis possibly related to RT and durvalumab that improved with corticosteroid treatment, 1 patient with grade 3 pneumonia and pulmonary embolism possibly related to durvalumab, and 1 patient with grade 5 pneumonitis probably related to RT and durvalumab.

Conclusions: This is the first report on concurrent and consolidative durvalumab and RT without chemotherapy in an elderly and frail patient population with LA-NSCLC. No early stopping safety rule was met. One patient experienced grade 5 pneumonitis. Preliminary PFS and OS appear superior to historical results of sequential CRT or RT alone.

Keywords: Concurrent durvalumab, Radiation therapy, Non-small cell lung cancer

EP05.01-026 Carboplatin Dose Calculations for Patients with Lung Cancer: Significant Dose Differences Found Depending on Dosing Equation

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Introduction: Carboplatin is the backbone cytotoxic agent of most chemotherapy regimens for lung cancer. The dosing of carboplatin is complicated due to its narrow therapeutic index and its relationship to renal function. Higher doses or increased exposure to carboplatin increases the risk of myelosuppression, hepatotoxicity, and nephrotoxicity, while reduced exposure to carboplatin may lead to underdosing and therapeutic failure. Carboplatin dose is calculated for each patient based on their estimated glomerular filtration rate (eGFR), which is a surrogate indicator of renal function. The Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations reportedly have higher accuracy in calculating eGFR. However, medical oncologists have been reluctant to implement these new equations. Despite its shortcomings, the Cockcroft-Gault (CG) formula is still used globally to estimate renal function and carboplatin dosage in patients with cancer.

Methods: A retrospective study was designed using data from 96 patients with lung cancer treated at the Sunshine Coast Hospital and Health Service, QLD, Australia. The unprocessed data included patient demographics, treatment pathway, eGFR, carboplatin dose, adjusted dose, dose calculation parameters, and the number of the treatment cycles. eGFR values were calculated for each patient using different formulae (i.e., CG, MDRD, CKD-EPI^{2009}, and CKD-EPI^{2021}). The per cent dose change by substituting CG with any of the other three equations was calculated. Key patient characteristics were identified by categorising patients based on their susceptibility to dose change with the implementation of different eGFR equations. Clinical evidence was provided by establishing a link between ad-hoc dose reductions and hypothetical carboplatin dosages estimated by each eGFR equation.

Results: (i) MDRD and CKD-EPI equations resulted in comparable carboplatin dosages. CG doses diverged markedly with up to 17% of the patients receiving a carboplatin dose that was at least 20% higher than a non-CG formula would have predicted, and 20% received a dose that was at least 20% lower than a non-CG formula would have predicted. **(ii)** This accounted for almost one-third of the whole patient cohort with a sub-optimal carboplatin dose using CG-based eGFR values. **(iii)** The CG formula overestimated kidney function in patients with a higher bodyweight and body surface area (BSA) while underestimating it in patients with a lower bodyweight and BSA. **(iv)** CKD-EPI predicted lower doses for patients whose CG-derived carboplatin dose was later reduced following clinical assessment prior to infusion. **(v)** Approximately 20mg-90mg carboplatin dose difference was detected between the two versions of the CKD-EPI equations (i.e., 2009 and 2021) depending on the patient characteristics.

Conclusions: We have confirmed significant differences in carboplatin dosing depending on the equation used in our modern patient population and suggest that use of CKD-EPI provides the most clinically appropriate carboplatin dosing and should be implemented as the new standard of care internationally. Further work with a larger and more diverse population will hopefully confirm and establish a new standard of care for carboplatin dosing globally.

Keywords: Carboplatin, eGFR, Toxicity

EP05.01-027 Uncertain Resection of pN2 NSCLC Patients-survival Analysis of Postoperative Radiotherapy and Driver Gene Mutations

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Introduction: The role of postoperative radiotherapy (PORT) in uncertain resection of pN2 non-small cell lung cancer (NSCLC) with highest mediastinal lymph node positive has not been determined. We aim to evaluate the effect of PORT and driver gene mutation status (DGMS) on survival in such patients.

Methods: The clinical factors, treatment and survival of 140 selected patients were recorded. Patients were grouped according to whether they received PORT and their DGMS. Locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS) of each group were evaluated by Kaplan-Meier analyses. COX regression was used to evaluate the effects of various factors on DFS and OS.

Results: Of 140 patients, mean age was 58 years. Thirty-four patients (24.3%) received PORT, and forty (28.6%) had positive driver gene mutation status (DGp). PORT significantly prolonged LRFS (p=0.002), DFS (p=0.019) and OS (p=0.02), but not DMFS (p=0.062). By subgroup analysis, in patients with negative driver gene mutation status (DGn), those receiving PORT had notably longer LRFS (HR, 0.465; 95% CI, 0.271-0.798; p=0.022) and DFS (HR, 0.516; 95% CI, 0.308-0.867; p=0.033), but not DMFS (HR, 0.557; 95% CI, 0.329-0.943; p=0.060) or OS (HR, 0.652; 95% CI, 0.357-1.192; p=0.215), compared to those not receiving PORT. Cox analysis showed that the number of positive lymph nodes (PLNs) and administration of PORT were independent prognostic factors of DFS, and pathology, PLNs, and DGMS may be prognostic factors of OS (all p <0.05).

Conclusions: Postoperative radiotherapy may improve locoregional recurrence-free and disease-free survival in patients with pN2 NSCLC with positive highest mediastinal lymph nodes, while driver gene mutation status impacted OS significantly. Only patients with positive driver gene mutations experienced significant overall survival benefits from postoperative radiotherapy. A further prospective study is warranted for use in clinical practice.

Keywords: non-small cell lung cancer, postoperative radiotherapy, driver gene mutation status

EP05.01-028 Thoracic Radiotherapy of Baseline Severe Pulmonary Dysfunction NSCLC Patients and Predictive Analysis for Acute Radiation Pneumonitis

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Introduction: Currently, there is no standard treatment for lung cancer patients with deteriorated pulmonary function. In this study, we aimed to assess the efficacy of thoracic radiotherapy for unresectable non-small cell lung cancer (NSCLC) with baseline severe pulmonary dysfunction and severe acute radiation pneumonitis (SARP).

Methods: A total of 170 patients were categorized into two groups: a radiotherapy group and a non-radiotherapy group, followed by analyzing the clinical variables and prognosis rates of patients in both groups. In the radiotherapy group, the dose-volume histogram and the occurrence of SARP were evaluated. The endpoints were overall survival (OS) and the occurrence of SARP. A Cox regression was used to evaluate the impact of various factors on OS. Each SARP factor's predictive value was assessed using logistic regression, receiver operating characteristic curve (ROC), and Kaplan-Meier analyses.

Results: The average OS in the radiotherapy group was 21.6 months (95% CI 19.5-23.7 months), while in the non-radiotherapy group, it was 8.9 months (95% CI 6.5-11.4 months) (HR: 0.481, 95% CI 0.344-0.673, p< 0.001). Cox analysis revealed that chemotherapy (HR: 0.221, 95% CI 0.149-0.329, p<0.001) and radiotherapy (HR: 0.589, 95% CI 0.399-0.869, p=0.008) are independent prognostic factors for the current cohort. The data obtained from the patient undergoing radiotherapy suggested that the ipsilateral lung V_{10} (ilV_{10}) was an independent predictor of SARP. Furthermore, the area under the curve (AUC) of ilV_{10} was recorded as 0.785, validated by the ROC curve. The ilV_{10}-high group had a higher chance of SARP than the ilV_{10}-low group (HR: 5.33, 95% CI 1.99-14.29, p=0.003).

Conclusions: Our findings indicated that thoracic radiotherapy provided clinical benefits to inoperable NSCLC patients with severe pulmonary dysfunction and that ilV_{10} (> 50.7%) may be involved in the prediction of risk for SARP in these patients.

Keywords: Severe pulmonary dysfunction, Thoracic radiotherapy, Severe acute radiation pneumonitis

EP05.01-029 Association between DNA Repair Gene Pathway SNPs and Tumour Response in NSCLC Patients Receiving Radiotherapy: A Meta-Analysis

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Introduction: Tumour response to radiotherapy is affected by genetic variations in the DNA repair gene pathway. Previous studies have been inconsistent in conclusion. This study aimed at examining the effect of SNPs on tumour response of NSCLC patients receiving radiotherapy.

Methods: We performed a systematic review of relevant studies published on or before 12 October 2021 on PubMed, Scopus, Embase, and Web of Science databases. Studies with genotyping data of NSCLC patients receiving radiotherapy were included. Conference abstracts, reviews, non-English articles, and studies on radiotherapy used as a neoadjuvant therapy were excluded. Quality assessment was performed using the Newcastle-Ottawa Scale (NOS) by two independent reviewers. We calculated the pooled odds ratios and the 95% confidence intervals to evaluate the association between each DNA repair gene pathway polymorphism and tumour response in NSCLC patients receiving radiotherapy. The allelic, dominant, recessive, homozygous and heterozygous genotype models were used to assess the association.

Results: 706 studies were initially obtained after database searching and de-duplication. Only 6 studies (1429 patients) were eligible for the systematic review. The median follow-up time ranged from 1 month to 24.9 months. Under the allelic model, the C allele of XRCC1 rs25487 was significantly associated with a reduced odds of tumour nonresponse (stable disease plus progressive disease) compared to the T allele (odds ratio: 0.52, 95% CI: 0.30, 0.91, p-value: 0.02, I-square: 61%, total number of patients: 584). Other SNPs were found to have no significant associations with tumour response.

Conclusions: This systematic review and meta-analysis showed that the XRCC1 rs25487 SNP is significantly associated with tumour response in NSCLC patients receiving radiotherapy. This meta-analysis is limited by a small number of studies on the topic. Further cohort studies covering a combination of DNA repair gene polymorphisms with a greater sample size are needed.

Keywords: tumour response, DNA repair gene pathway, single-nucleotide polymorphism

EP05.01-030 CRISP: First Real-World Evidence of NSCLC Stage I, II and III in Germany - AIO-TRK-0315

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Introduction: CRISP (Clinical Research platform Into molecular testing, treatment and outcome of (non-)Small cell lung carcinoma Patients) is a non-interventional, prospective, multi-center clinical research platform whose aim is to understand current treatment reality of patients with lung cancer in Germany. Here we present data of patients diagnosed with early-stage NSCLC (IIIB/C only if treated with curative intent), including first outcome data in routine-care.

Methods: Since August 2018 106 sites in Germany have recruited almost 1400 patients diagnosed with NSCLC stage I, II or III (recruitment of stage I possible from December 2020). Detailed patient and tumor characteristics, treatment strategies, outcome and PRO data are collected and analyzed. Here we present data on the first 810 patients followed until 30 June 2021.

Results: 26% of patients were diagnosed with pretherapeutic stage II (5% stage IIA, 21% stage IIB), and 66% with stage III disease (32% stage IIIA, 34% stage IIIB/C). For 6% of tumors the exact stage could not be determined at diagnosis. In total, 52% of the tumors were adenocarcinomas. Median age at diagnosis was 66 years, 38% were women, 62% men, 83% of the patients had an ECOG 0/1. 80% of the patients presented with comorbidities; 47% had a Charlson comorbidity index of 0. 25% of the patients were current smokers; 44%, heavy ex-smokers (>10 pack years or quit less than 15 years prior to diagnosis), and 9% were never-smokers. The most common treatment strategy for patients with clinical stage II-tumors with at least one year follow-up (n=188) was surgery (84%, n=157) followed by adjuvant chemotherapy (CTx) (75%, n=140). The 2-year relapse-free survival (RFS) rate was 77% and the 2-year overall survival (OS) rate was 90%. For patients with clinical stage IIIA tumors (n=236) the most frequent treatment strategy was surgery (53%, n=124) followed by adjuvant CTx (37%, n=88). The 2-year RFS rate was 52%, and the 2-year OS rate was 79%. 27% (n=64) of the patients with stage IIIA received definitive radiochemotherapy (RTCTx). For patients with stage IIIB/C tumors (n=249) the most frequent treatment was definitive RTCTx (n=131, 53%); 26% (n=64) started with CTx, and 18% (n=44) had initial surgery (followed mostly by CTx, n=36, 15%). The median progression-free survival (PFS) for patients with RTCTx was 10.4 months (stage IIIA) and 9.2 months (stage IIIB/C). The median OS was 21.5 and 22.9 months for patients with stage IIIA and IIIB/C, respectively. 80% (n=131) of patients with a non-resectable stage III tumor who received RTCTx (n=164) were tested for PD-L1 expression. 80 patients had positive PD-L1 expression, which corresponds to 49% of all patients and 62% of tested patients. Taken together, 44 out of 68 durvalumab-eligible patients (best response CR/PR/SD) received consolidation therapy with durvalumab.

Conclusions: CRISP presents comprehensive current real-life data of patients with NSCLC in stage II or III covering all treatment settings in Germany. With a longer recruitment time data on patients with stage I will be analyzed.

Keywords: CRISP, early-stage NSCLC, NSCLC stage I, II or III

EP05.01-031 Lysimachia Capillipes Capilliposide C Enhances the Radiosensitivity of Lung Cancer by Promoting ERRFI1 via Inhibiting Phosphorylation of STAT3

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Introduction: Lysimachia capillipes capilliposide C (LC-C), an extract from traditional medicinal plant LC Hemsl, has demonstrated multiple anti-cancer effects in several types of cancer. In our previous study, LC-C has been shown to sensitize ionizing radiation-resistant lung cancer cells to radiotherapy in vitro and in vivo, and the radiosensitization effects of LC-C correlated to the level of ErbB receptor feedback inhibitor 1 (ERRFI1) expression. The purpose of this study is to investigate the detailed mechanism of LC-C in upregulating the expression of ERRFI1.

Methods: Non-small cell lung cancer (NSCLC) cell line A549/H1299 was initially irradiated with a total dose of 80Gy (2 Gy/Fx, 2-3 Fx/week) to generate radiation-resistant lung cancer cell line A549-IR/H1299-IR. Western blotting and RT-PCR were used to detect ERRFI1 and STAT3 expression in lung cancer cells exposed to LC-C, STAT3 inhibitor and STAT3 activator. Luciferase reporter assay was used to detect transcriptional activity of ERRFI1 promoter. Flow cytometry was performed to determine the cell cycle distribution, immunofluorescence assay was used to detect the expression of DNA damage biomarker γ-H2AX, and colony formation assay was applicated to examine the radiosensitivity in A549-IR/H1299-IR cells treated with radiation in combine with LC-C alone or with STAT3 activator.

Results: We confirmed that LC-C reduced the phosphorylation level of STAT3 (Tyr705) and promoted the expression of ERRFI1 in A549-IR/H1299-IR cells. After being exposed to stattic, a STAT3 inhibitor, the mRNA and protein expressions of ERRFI1 were upregulated; meanwhile, after being exposed to IL-6, a STAT3 activator, the expression of ERRFI1 was downregulated. Next, we found that LC-C enhanced the transcriptional activity of ERRFI1 promoter, and the transcriptional activity of ERRFI1 promoter was also enhanced by stattic and reduced by IL-6. We also demonstrated that IL-6 could significantly attenuated the effect of LC-C on the expression and promoter transcription activity of ERRFI1. Additional investigations revealed that LC-C effectively inhibited IR-induced DNA damage repair, induced G2/M checkpoint and significantly increased the radiosensitivity of A549-IR/H1299-IR cells, while IL-6 attenuated these function of LC-C.

Conclusions: Our results demonstrate that the phosphorylation of STAT3 plays a pivotal role in the regulating of ERRFI1 expression and radiosensitivity in lung cancer treated with LC-C. Phosphorylated STAT3 affects ERRFI1 expression through regulating the transcriptional activity of ERRFI1 promoter. These findings will help us to understand the molecular mechanisms of LC-C on the regulation of ERRFI1 in lung cancer treated with radiation therapy, and provide a rationale for the combination treatment of LC-C and radiotherapy.

Keywords: Lysimachia capillipes capilliposide C, ErbB receptor feedback inhibitor 1, STAT3

EP05.01-032 The Incidence of Brain Metastasis and Radiation Pneumonitis with Durvalumab After Chemoradiotherapy in Unresectable Stage III NSCLC

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Introduction: PACIFIC trial has manifested a lower incidence of new brain metastasis in the durvalumab group than in the placebo group of patients with unresectable stage III NSCLC. Nevertheless, there are few studies mainly focusing on the effect of durvalumab on brain progression. Patients who receive radiotherapy (RT) may have adverse effects like symptomatic RP (radiation pneumonitis) which could be a life-threatening when combined with drug induced pneumonitis. Because many clinicians hesitate to start durvalumab after concurrent CCRT. The aim of this study is to evaluate the effects of durvalumab on brain metastasis and RP with real world data.

Methods: Patients diagnosed with stage III, unresectable NSCLC were included in the analysis. We collected data from 6 Affiliated Hospitals for comparison between CCRT group and CCRT followed by Durvalumab (CCRT+D) group. Unlike the PACIFIC trial, induction chemotherapy (CT) was excluded to eliminate the effect of prior effect of treatment, and the CT regimen was limited to paclitaxel and carboplatin (PC). The primary endpoints were the incidence rate of brain metastasis and the RP after CCRT started. We tried to focus on RP, and eliminated other pneumonitis or pneumonia caused by other possible factors. Cumulative incidence rates were calculated.

Results: A total of 115 patients, 60 patients in the CCRT group and 55 patients in the CCRT-D group were evaluated. Baseline patient demographics and disease characteristics were broadly well balanced. Median follow-up time was 16.3 months and 12.2 months for each group. The incidence of brain metastasis in the CCRT group was 11.67%, and that of the CCRT+D group was 9.09%. Cumulative incidence rate between the CCRT group and the CCRT+D group was significantly different (p=0.012). Even though, The CCRT+D group had earlier occurrence of brain metastasis, it had shorter duration and lower incidence rate of brain progression than the CCRT group. The first brain progression occurred at 5.3 months for the CCRT group and at 3.3 months for the CCRT+D group. The last episode of brain metastasis was at 18.3 months and at 9.5 months, respectively. RP appeared similar between two groups, which was not statistically significant. There were no significant differences among grade 1/2, 3, and 4 RP. There were no grade 5 events. Durvalumab improved OS compared to the CCRT only group. (p=0.0005) Median OS was 19.4 months in the CCRT group, while it was not reached in the CCRT+D group. Durvaluab significantly prolonged PFS. Median PFS was 7.77 months with CCRT group, and 11.3 months with CCRT+D group.

Conclusions: Durvalumab seemed to suppress brain metastasis progression than the CCRT only group. Symptomatic RP more frequently occurred in the durvalumab group. OS and PFS were improved by using durvalumab. Longer follow-up duration is required to confirm the brain progression and CNS activity in the durvalumab.

Keywords: Durvalumab, Brain metastasis, Radiation pneumonitis

EP05.01-033 Stimulation CT-Based Radiomics Predict Radiation Pneumonitis after Chemoradiotherapy in Locally Advanced NSCLC

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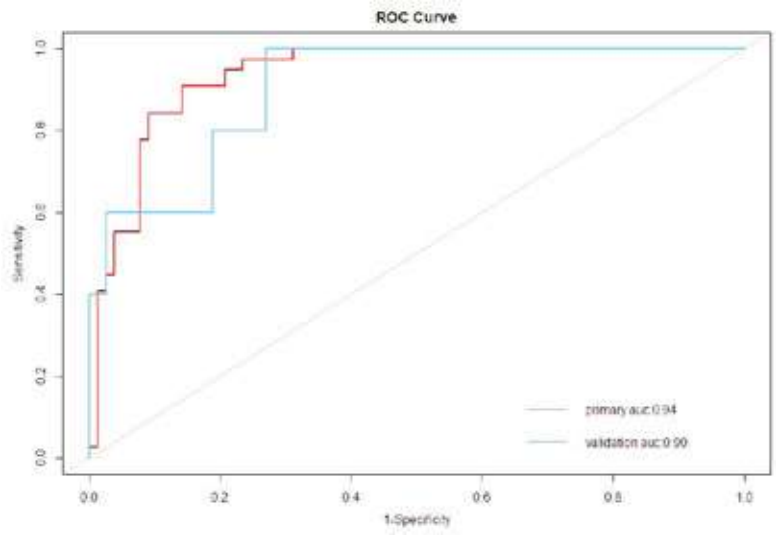
Introduction: This study aimed to establish machine learning model using radiomics features with region of interest (ROI) in treatment planning computed tomography (CT) images to predict symptomatic radiation pneumonitis(RP) (grad≥2) in patients with locally advance non-small cell lung cancer(NSCLC).

Methods: At our institute, a retrospective study was conducted on 134 NSCLC patients (24 patients RP≥2) who treated with chemoradiotherapy in Locally advanced non-small cell lung cancer from January 2014 to October 2017. We defined total lung(TL)-PTV in planning CT as ROI. A total of 944 radiomics features were extracted form ROI. According to the radio of 7:3, the data is randomly divided into primary cohort and validation cohort. Since our study data is unbalanced data, the oversampling method is used to balance the data. The t-test and least absolute shrinkage selection operator (LASSO) was applied to selection radiomics features and build mode. The receiver operating characteristic (ROC) curve was used to evaluate the prediction capacity of the model. calibration curves and decision curves were used to demonstrate the discriminatory and clinical benefit radiomics, respectively.

Results: The best predictors for symptomatic RP were the combination 20 radiomics features (2 shape features and 18 texture features), achieving an area under the curve (AUC) of 0.94 (95% confidence interval [CI],0.89-0.97) (accuracy,77%) in the primary cohort, and in the validation cohort, the AUC was 0.90 (95%CI, 0.78-1) (accuracy,78%) (Figure 1). Calibration curves indicate a favorable consistency between the radiomics model prediction and the actual outcomes. The decision curve exhibits satisfactory clinical utility.

Conclusions: The radiomics model based on treatment planning CT is a potentially valuable tool for predicting RP. Adding a external validation cohort is what we need to work on in the future.



Keywords: Radiation pneumonitis, Radiomics, Prediction model

EP05.01-036 Role of Nanoparticle Polymeric Micellar Paclitaxel in Reducing Toxicity and Enhancing Efficacy in Non-small Cell Lung Cancer

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Introduction: Nanoparticle polymeric micellar paclitaxel (Pm-Pac) has been demonstrated to have an *ex post facto* safety profile and efficacy in advanced non-small cell lung cancer (NSCLC) patients. However, the histopathologic toxicity assessment of Pm-Pac in mammalian animals and whether Pm-Pac could prolong overall survival (OS) for specific advanced NSCLC patients are still unknown. The purpose of this study is to understand the underlying role of Pm-Pac in reducing the toxicity and enhancing the efficacy in NSCLC via a retrospectively analysis of clinical (NCT02667743) and a series of animal experiments.

Methods: In the present study, firstly, we retrospectively analyzed the Pm-Pac-induced antitumor effect and safety profiling in advanced NSCLC patients. Next, we evaluated the anti-tumor efficacy of Pm-Pac upon the A549 cell line and an A549-derived xenograft tumor model. Lastly, we examined the Pm-Pac-induced toxicity in healthy rats and healthy dogs.

Results: We provided the first evidence that nanoparticle Pm-Pac potentially prolonged OS with a favorable safety profile in the NSCLC patients without pleural metastasis. Evaluation of the objective reaction suggested that Pm-Pac has better therapeutic efficacy than Sb-Pac in both a xenograft tumor model and advanced NSCLC patients without increased toxicity. Assessment of mammalian animals indicated that 3-fold to 4-fold doses of Pm-Pac induced short-term toxicity similar to 1-fold Sb-Pac-induced toxicity in healthy rats and dogs. The long-term toxicity of Pm-Pac was dyszoospermia/atrophy of the testis and epididymis.

Conclusions: Collectively, this study demonstrates that nanoparticle Pm-Pac could decrease the paclitaxel-induced toxicity and enhance the paclitaxel-induced anti-tumor efficacy in NSCLC and provides a novel perspective on the development of nanomedicine to investigate chemotherapeutic efficacy and toxicity.

Keywords: Nanomedicine, Polymeric micellar paclitaxel, NSCLC

EP05.02 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - NEOADJUVANT AND ADJUVANT THERAPY

EP05.02-001 Early Treatment Failure Of Consolidation Durvalumab for Unresectable Stage III NSCLC: A Real-World Canadian Cohort

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Introduction: The use of consolidative durvalumab following concurrent chemoradiotherapy in unresectable Stage III NSCLC patients has contributed to improvement in patient outcome; however, some patients experience early treatment failure on durvalumab, characterized by primary drug resistance or toxicity requiring durvalumab termination. With clinical characteristics associated with early treatment failure on immunotherapy not well explored, this study investigated this phenomenon and endeavored to identify predictors associated with resistance or toxicity on durvalumab.

Methods: Alberta patients with a diagnosed 2018-2020 with unresectable Stage III NSCLC, having received consolidation durvalumab following ≥2 cycles of platinum-doublet chemotherapy and concurrent definitive radiotherapy, without progression and suitable for immunotherapy treatment, were identified. Demographic, clinical, treatment and outcome details were extracted from the Glans-Look Lung Cancer Research Database. Patients were grouped according to response to durvalumab: 'Early-failure' were those with progressive disease as best treatment response, or those with non-evaluable disease due to durvalumab discontinuation prior to treatment response assessment. 'Responders' were defined as those achieving a best response of stable disease or higher. Univariate and multivariate methods compared the Early-Failure and Responder groups and identified factors predictive of early durvalumab failure while controlling for confounders.

Results: 94 patients were identified: 53% female, 89% ever-smokers, 91% ECOG<2, 69% overweight/obese, 48% recorded as experiencing an immune-related adverse event (irAE), 54% PD-L1 positive, 31% age > 70 years at diagnosis, 6% with detected oncodriver (83% EGFR-mutant, 17% ROS1-rearranged), 23% receiving additional post-durvalumab systemic therapy, and median overall survival of 36.7 months. 75% of the cohort were Responders, and the remaining 25% meeting the criteria to be categorized as Early-failure: 78% by virtue of progressive disease present at first response evaluation, and the remainder discontinuing durvalumab due to toxicity (13%) or patient decline/death (9%). Early-failure and Responders were similar in relation to demographic and clinical characteristics with the exception that when compared to Responders, Early-failures reported a significantly lower rate of mild irAE characterized primarily as skin rash or endocrine-related (0% vs. 38%, p<0.001), a higher rate of post-durvalumab systemic therapy (52% vs. 14%, p<0.001) and a significantly shorter survival time (13.1 month vs. not reached, log-rank p<0.001). Additional systemic therapy in the Early-failure cohort failed to salvage outcome, with no significant difference in survival between those with and without additional post-durvalumab systemic therapy (18.1 vs. 11.6 months, log-rank p=0.61). Multivariate analysis revealed a history of smoking decreased the odds of experiencing Early-failure on durvalumab [OR: 0.09, p=0.02]

Conclusions: This study found 25% of patients in a real-world clinical setting failed to achieve clinical disease control on durvalumab, mostly by virtue of primary durvalumab resistance. Demographic and clinical features fail to distinguish those at risk of early failure on durvalumab, suggesting other underlying and not routinely assessed features of the tumour microenvironment may be placing patients at risk of early failure and poor outcome. Future investigation to identify other factors associated with response to durvalumab appears crucial, particularly in the finding of this study that additional post-durvalumab systemic therapy appears to be limited in meaningfully impacting patient prognosis.

Keywords: durvalumab, locally advanced NSCLC, treatment failure

EP05.02-002 Who Benefits More of Durvalumab after Chemoradiotherapy (CRT) in Real-World Patients with Locally Advanced Non-Small-Cell Lung Cancer (NSCLC)?

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Introduction: Durvalumab received EMA approval as consolidation therapy (CT) for unresectable stage III NSCLC with PD-L1 ≥1% and who did not have progression after CRT. Our objective was to analyze in real clinical practice the effectiveness of durvalumab and explore the clinical factors that may be associated with the benefit from CT.

Methods: Retrospective study was made at Hospital of Leon (Spain), including 37 patients with locally advanced NSCLC treated with durvalumab after CRT treatment between March 2018 and october 2021 (40.5% patients were included in the durvalumab early access program). The neutrophil-to-lymphocyte ratio (NLR) could identified after CRT as a factor that may be benefit from durvalumab.

Results: Median age was 67 years (range 46-82 years). 40.5% of patients were ≥70 years old. 78.4% were male and 51.4% smokers. 54% had non-squamous histology. PD-L1 expression was <1% in 5% and not available in 8% patients. 2.7% ROS1 rearrangements, 5.4% KRAS mutations and not available in 43.2% patients. Stage IIIA, IIIB, IIIC disease were 24.3%, 54.1% and 21.6%, respectively. Median time from end of CRT to onset durvalumab was 44 days (range 13-120 days). Overall median CT duration was 214.8 days (range 69-399 days) with a median of 14 infusions (range 6-27 infusions). With a median follow up of 19.7 months (range 1.4-34.9 months); 67.6% had stopped CT: 37.8% due to completing treatment, 16.2% disease progression, 10.8% adverse event and 2.7% due to COVID19 infection. Median real-world progression-free survival (rwPFS) was 17 months (95% CI, 11-23). Median real-world overall survival (rwOS) was 29.9 months (95% CI, 23.3-36.6). %rwOS at 6, 18 and 24 months were 100%, 86.9% and 74.5%, respectively. For patients with post-CRT NLR not exceeding the cohort median value of 6, receipt of durvalumab was associated with an improvement in rwOS (median not reached vs 25.7 months; p=0.025). 56.8% patients had any grade of radiation pneumonitis (median time from CRT start: 119 days [range 36-241 days]). Of these, 19% patients developed worsening of radiation pneumonitis with durvalumab. 54,1% developed immune-mediated toxicity, mostly G1-2 (85.1%).

Conclusions: Our results demonstrate the effectiveness of durvalumab consolidation in this patients population in a real-life setting. We identified low NLR after CRT as a potentially predictive factor for the benefit of CT in locally advanced NSCLC.

Keywords: DURVALUMAB, PACIFIC, REAL WORLD DATA

EP05.02-003 Durvalumab after Chemoradiotherapy (CRT) in Unresectable Stage III NSCLC. Comparative Study of Two Cohorts in the Real-World Setting

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Introduction: Durvalumab is the new standard of care for unresectable locally advanced NSCLC, with PD-L1 >1% and who did not have progression after CRT treatment in the European Union. Our study compares the effectiveness and the frequency of radiation pneumonitis in patients treated with concurrent CRT with or without durvalumab consolidation during the same period in real clinical practice.

Methods: A single-center retrospective study. 71 treated patients with unresectable stage III NSCLC were included between March 2018 and December 2021, 37 with CRT followed by durvalumab and 34 with CRT alone. Real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) were calculated since the date of the end CRT. Propensity score matching (PSM) 1:1 was used to account for differences in baseline characteristics.

Results: Median age was 67 years (range 46-82). 25.4% of the patients were ≥75 years old. 78.9% were men and 53.5% former smokers. 54.9% had squamous histology and 28%, 51% and 21% stage IIIA, IIIB and IIIC disease, respectively. The most used scheme was carboplatin-paclitaxel (43.7%), receiving induction chemotherapy in up to 54.9% of patients. 73.2% received between 60-66 Gy doses of radiotherapy. Median time from end of CRT to onset durvalumab was 44 days (range 13-120) with a median of 14 infusions (range 6-27). Of the 34 patients without durvalumab treatment, the expression PD-L1 <1% (58.8%) was the most frequent cause for rejecting consolidation therapy. After PSM analysis, patients distributions were well balanced. With a median follow-up of 19.7 months (range 1.4-36.6); median rw-PFS was 9.3 months (95% CI, 5-13.5) without durvalumab and 17 months (95% CI, 11-22.9) with durvalumab (p=0.013). Median rw-OS was 19.3 months (95% CI, 3.8-34.8) without durvalumab and 29.9 months (95% CI, 23.3-36.6) with durvalumab (p=0.241) with a rw-OS% at 6, 18 and 24 months of 90%, 62% and 49% vs 100%, 86% and 74%, respectively. The rate of radiation pneumonitis was more frequent with durvalumab consolidation (56.8% against 44.1%), (p=0.346), especially within 3 months after CRT. G3 pneumonitis was only observed in the consolidation therapy.

Conclusions: Our results demonstrate the effectiveness of durvalumab consolidation after CRT in real-world patients with unresectable stage III NSCLC. Further sample and longer follow-up are required to obtain more accurate results. Active surveillance and appropriate management for radiation pneumonitis are needed, in especially in candidates for consolidation treatment.

Keywords: DURVALUMAB, PACIFIC, REAL WORLD DATA

EP05.02-004 Could Fifty Percent Tumor Viability Be a Good Prognostic Factor?

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Introduction: Pathological response is an indicator of prognosis in patients with non-small cell lung cancer after neoadjuvant chemotherapy if the tumor viability is below 10%. We aimed to investigate the effects of up to 50% tumor viability on overall survival in pathological examinations after lung surgery.

Methods: From April 2006 to January 2022, 105 consecutive patients with anatomic lung resection after neoadjuvant therapy for non-small cell lung cancer in our clinic were retrospectively screened. Demographic, operative, pathological and survival data of the patients were recorded. All pathology reports were scanned one by one and viable tumor rates were recorded where possible and the survival analysis was performed according to tumor viability.

Results: Of 105 patients, 48 (45.7%) received chemotherapy, 40 (38%) chemoradiotherapy, and 17 (16.2%) received chemoimmunotherapy. Neoadjuvant treatment was decided for 54.5% of the patients because of N2, and other patients were given due to various locally advanced disease. 51.5% of the patients were diagnosed with adenocarcinoma. A maximum of 50% vitality was observed in 69.9% of the 83 patients whose vitality data were available. When survival analysis was performed according to 50% tumor viability, it was observed that 2-year and 5-year survivals were better in the patient group with 50% or less tumor viability, although it was not statistically significant. The 2-year survival was 85% vs. 75.7%, and the 5-year survival was 78.9% vs. 56.7% in favor of the group with viability is below 50%.

Conclusions: Tumor viability of 10% or less is known as a good prognostic factor in lung cancers after neoadjuvant therapy. Whereas, in our series, although it did not reach statistical significance, it was revealed that the viability that increased up to 50% was a relatively good prognostic factor. In order to clarify this issue, multicenter studies are needed in homogeneous patient groups.

Keywords: Neoadjuvant therapy, tumor viability, lung cancer

EP05.02-005 Is Immunotherapy Safer Than Radiotherapy in Combination with Chemotherapy in Neoadjuvant Therapy?

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Introduction: Surgery in locally advanced lung cancer can be performed safely with neoadjuvant treatment preparation. Perioperative and postoperative characteristics and survival data of patients differ with changing parameters in neoadjuvant treatment modalities. We aimed to analyze the pathological response, complication and survival data with different combinations of neoadjuvant therapy.

Methods: The data of 105 consecutive patients who underwent lung resection after neoadjuvant therapy for non-small cell lung cancer in our clinic between 2006-2022 were retrospectively reviewed. Neoadjuvant treatment modalities and demographic, operative, pathological and survival data were analyzed

Results: In the neoadjuvant treatment protocol, 48 (45.7%) of the patients chemotherapy only, while the combination of chemotherapy and radiotherapy was applied to 40 (38.1%) patients, and chemotherapy and immunotherapy was applied to 17 (16.2%) patients. According to the treatment modality applied, the major pathological response rate was 21.1% in the patients who received only chemotherapy, while it was 64.1% in the chemo-radiotherapy group and 64.7% in the chemo-immunotherapy group. When the major complication data were analyzed in the patient groups, it was 12.9% in the chemo-radiotherapy group, while no major complication was observed in the chemo-immunotherapy group. When the 2-year survival data of the patients were examined, it was 81.3% in the chemotherapy group, 67.5% in the patients who received chemo-radiotherapy, and 100% in the chemo-immunotherapy group.

Conclusions: Since the combination of immunotherapy and chemotherapy has been used in neoadjuvant therapy in our center for the last 2 years, our survival data are short-term follow-up. However, when both operative morbidity and mortality results and survival time are examined; We believe that adding immunotherapy to chemotherapy instead of radiotherapy provides almost equal major pathological response in patients, while providing safer follow-up and possibly longer survival time.

Keywords: immunotherapy, chemoradiotherapy, Neoadjuvant treatment

EP05.02-006 Neoadjuvant DS-8201 for Stage III Non-small Cell Lung Cancer with HER2 20ins

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Introduction: Stage III-N2 non-small cell lung cancer (NSCLC) represents a highly heterogeneous disease and requires multimodality management. Neoadjuvant therapy is indicated when upfront surgery is difficult with the aim of tumor shrinkage. Trastuzumab deruxtecan (i.e., DS-8201) is an emerging antibody-drug conjugate (ADC) which four topoisomerase I inhibitors are linked to a HER2-targeting antibody. Prior study has shown a 55% objective response rate (ORR) in previous treated metastatic HER2-mutant NSCLC with durable effect. However, the efficacy and safety of DS-8201 in early and localized advanced NSCLC patients has been not investigated.

Methods: Here we report a stage IIIA3 NSCLC patient with *HER2 20ins* who received 3 cycles of neoadjuvant DS-8201 (345mg q3w) followed by R0 surgical resection. PET/CT and brain MR were done before and after treatment. Radiologic response was assessed by 2 independent physicians (HHZ, WZZ) based on RECIST, 1.1 version. Pathologic response was evaluated and reviewed by 2 independent pathologists (LXY, CL). Side effects and surgical outcomes were documented.

Results: A 58-year-old female, never-smoker, who was diagnosed with stage IIIA (cT1cN2M0) lung adenocarcinoma, presented to our hospital with no tumor-related symptom, (ECOG) PS is 0. Pre-treatment PET/CT revealed a solid nodule in left upper lobe and ipsilateral bulky lymph nodes including lower paratracheal, subaortic and hilar lymph nodes with increased glucose intake. Considering the status of potentially resectable and lack of optimal treatment for HER2 mutant NSCLC, multidisciplinary board suggested DS-8201 treatment followed by localized intervention. Partial response was obtained after 3 cycles of treatment. Heterogeneous response was observed between primary and metastatic lesions with 25% shrinkage in primary tumor in contrast to 65% in metastatic lymph nodes. Left upper lobectomy with systemic lymph node dissection was performed 3 weeks after the last dose of DS-8201. Complete resection (R0) was achieved. The surgery has last for 100 minutes with 20ml intraoperative blood loss. Neither extensive chest wall adhesion, fibrosis nor neovascular formation was found during surgery. Patient was discharged 3 days after surgery without incidence of postoperative complication. Systemic pathologic evaluation has demonstrated an 80% of residual viable tumor cells. Resected lymph nodes except a lower tracheal lymph node were negative for cancer cells. Grade 1 drug-related adverse events occurred during treatment including nausea, vomiting and alopecia. Immunohistochemistry (IHC) test indicated infiltration of CD4 (10%), CD8 (10%), CD20 (10%), CD163 (30%), CD38 (10%) cells. IHC showed a low expression of HER2 protein (IHC 1+) and negative PD-L1(22C3) (TPS<1%) in tumor cells. Peripheral blood analysis indicated that treatment induced T cell repertoire diversification.

Conclusions: DS-8201 has demonstrated an anticancer activity in localized advanced NSCLC with minimal side effects and without delay of surgery. DS-8201 could produce effect regardless of HER-2 protein expression. This case has provided an insight into the potential usage of ADC in a neoadjuvant setting.

Keywords: Antibody-Drug Conjugate (ADC), Neoadjuvant, HER2 mutant

EP05.02-008 Phase II Trial of Neoadjuvant Icotinib Plus Chemotherapy for Stage II-IIIB EGFR-mutant Non-small-Cell Lung Cancer

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Introduction: Icotinib is a novel and selective epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKI) for oral usage. Adjuvant therapy with icotinib has been confirmed to be associated with the improvement of DFS among patients with EGFR-mutant non-small-cell lung cancer (NSCLC) in several studies. However, the clinical benefit of neoadjuvant icotinib combined with chemotherapy for EGFR-mutant NSCLC remains unknown. This is the first trial evaluating the efficacy and safety of icotinib plus chemotherapy as neoadjuvant therapy for patients with stage II-IIIB EGFR-mutant NSCLC.

Methods: This is a prospective, open-label, single-arm, phase II study (NCT05104788). Treatment-naïve patients aged 18-75 years were eligible for this trial if they were histologically or cytologically documented to have resectable stage II-IIIB lung adenocarcinoma within 60 days prior to study enrollment. Patients are also required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1, EGFR-mutant (exon 19-deletion or exon 21-L858R point mutation), adequate organ and bone marrow function, and at least one measurable lesion. Recruitment started on October 25, 2021 and is foreseen to end on December 1, 2023. An estimated 27 patients will be enrolled. Eligible patients will be given 8 weeks of oral icotinib (125 mg thrice daily) in combination with 2 cycles (3 weeks/cycle) of concurrent chemotherapy (pemetrexed [500 mg/m^2 on Day 1] plus carboplatin [area under the curve=5 on Day 1] or cisplatin [75 mg/m^2 on Day 1]] until disease progression or unacceptable toxicity. The primary endpoint is major pathological response (MPR). Secondary endpoints include pathological complete response (pCR), overall survival (OS), disease free survival (DFS), objective response rate (ORR), disease control rate (DCR), R0 resection rate, and adverse events (AEs). The ORR is assessed according to Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. The AEs are graded according to the Common Terminology Criteria Adverse Events version 5.0 (CTCAE 5.0). Exploratory endpoints include changes of plasma EGFR-mutation copy number, as well as detecting potential resistance-associated genes by analyzing paired pre- and post-neoadjuvant treatment samples.

Results: None.

Conclusions: The results of this phase II study are expected to provide a promising treatment option for patients with stage II-IIIB EGFR-mutant NSCLC.

Keywords: neoadjuvant therapy, icotinib, non-small-cell lung cancer

EP05.02-007 Impact Of Fibrinogen Levels and mGPS on Survival of Stage III/N2 NSCLC Patients Treated with Neoadjuvant Therapy and Radical Surgery

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Introduction: The prognostic value of pretreatment and preoperative fibrinogen plasma levels and the modified Glasgow prognostic score (mGPS) in stage III/N2 non-small cell lung cancer (NSCLC) patients who receive neoadjuvant treatment followed by radical surgery is yet unclear.

Methods: Fibrinogen levels and mGPS of 84 patients with initial stage III/N2 NSCLC, who received neoadjuvant therapy followed by complete surgical resection from 2002 to 2013 were retrospectively analyzed and correlated with clinical parameters and overall survival. Fibrinogen levels and mGPS were reviewed at time of diagnosis and after neoadjuvant treatment at time of surgery. Data were analyzed using log-rank and Cox regression analysis adjusted for clinical and pathological factors.

Results: Median serum fibrinogen level after neoadjuvant treatment was 439 mg/dL (IQR 158 mg/dL). Elevated fibrinogen levels (>400mg/dL) after neoadjuvant treatment were significantly associated with poorer OS (28.2 months vs. 60.9 months, HR 0.562, p=0.048). Importantly, a decrease in fibrinogen levels after neoadjuvant treatment (n=34) was found to be an independent predictor for favorable OS in multivariate analysis (HR 0.994, p=0.025). Out of 80 patients, 55, 19 and 6 patients had a mGPS of 0, 1 and 2, respectively. Moreover, elevated mGPS after neoadjuvant treatment (mGPS 1-2) conferred a non-significant trend for poorer OS compared to mGPS 0 (28.2 vs. 46.5 months, HR 0.587, p=0.066).

Conclusions: Elevated fibrinogen levels after neoadjuvant therapy prior to surgery in stage III/N2 NSCLC patients conferred significant disadvantage for OS. A decrease in fibrinogen levels after neoadjuvant therapy was found to be a predictor for superior OS in this retrospective patient cohort.

Keywords: Non-small-cell lung cancer, Fibrinogen, mGPS

EP05.02-009 Aumolertinib Versus Erlotinib/Chemotherapy for Neoadjuvant Treatment of Stage IIIA EGFR-mutant NSCLC (ANSWER)

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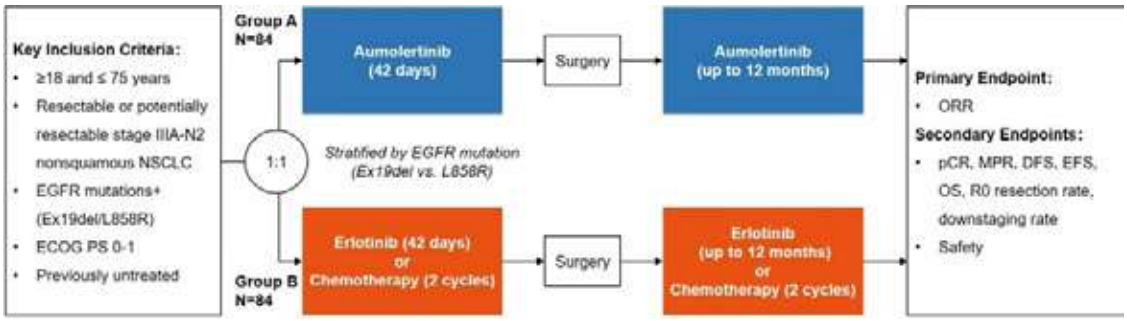
Introduction: For stage IIIA-N2 EGFR-mutant NSCLC, there have been several randomized controlled studies comparing various EGFR-TKI targeted therapy versus chemotherapy as neoadjuvant therapy. However, the role of third-generation EGFR-TKIs in neoadjuvant settings remains inconclusive. Aumolertinib (formerly almonertinib; HS-10296) is a novel, third-generation EGFR-TKI approved in China to treat EGFR-mutant NSCLC. The ANSWER study (NCT04455594) will assess the efficacy and safety of aumolertinib compared with erlotinib or platinum doublet chemotherapy (pemetrexed plus carboplatin or cisplatin) as neoadjuvant therapy in resectable patients with EGFR-mutant stage IIIA NSCLC.

Methods: This is a multicenter, open-label, randomized, controlled trial. Previously untreated, histologically documented resectable or potentially resectable stage IIIA-N2 nonsquamous NSCLC patients harboring sensitive EGFR mutations are eligible for this study. Approximately 168 patients will be randomized (1:1) to aumolertinib group (group A) or erlotinib or chemotherapy group (group B), stratified by EGFR mutation (Ex19del vs. L858R). Patients in group A will receive oral aumolertinib 110 mg/d (neoadjuvant therapy, 42 days; adjuvant therapy, up to 12 months) and those in group B will receive erlotinib 150 mg/d (neoadjuvant therapy, 42 days; adjuvant therapy, up to 12 months) or pemetrexed 500 mg/m2 plus carboplatin AUC=5 or cis-platinum 75mg/m2 (neoadjuvant therapy, 2 cycles; adjuvant therapy, 2 cycles). The primary endpoint is objective response rate (ORR). Secondary endpoints include pathological complete response (pCR), major pathological response (MPR), disease-free survival (DFS), event-free survival (EFS), overall survival (OS), R0 resection rate, downstaging rate, and safety. Adverse effects are graded per CTCAE v.4.0. The first patient had been enrolled in September 2021.



Keywords: aumolertinib, stage IIIA NSCLC, neoadjuvant

EP05.02-010 Robotic-Assisted Thoracic Surgery Following Neoadjuvant Chemoimmunotherapy in Patients with Stage III Non-small Cell Lung Cancer

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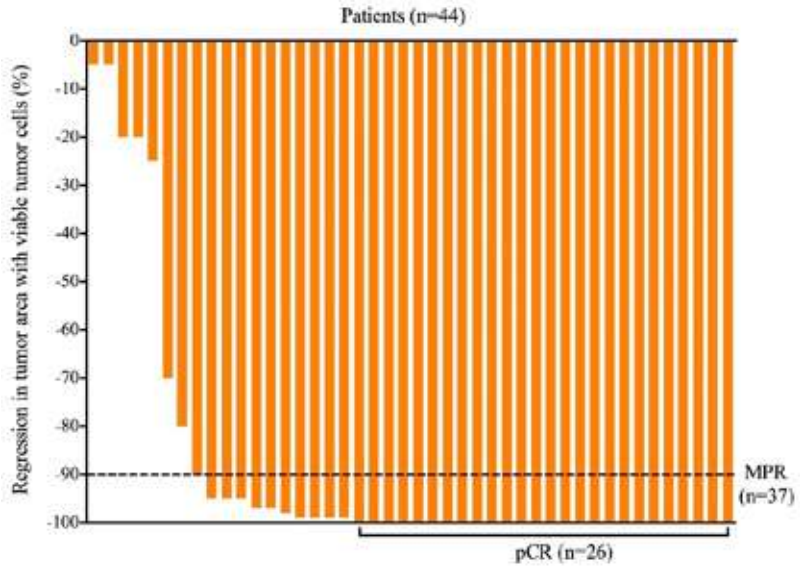
Introduction: Stage III non-small cell lung cancer (NSCLC) is a heterogeneous group of diseases. For this subset of patients, clinical management is still under debate and prognosis remains poor so far. In the present study, we aimed to evaluate the feasibility and safety of robotic-assisted thoracic surgery after neoadjuvant chemoimmunotherapy in stage III NSCLC.

Methods: A real-world prospective cohort study was performed in a single-center setting from April 2021 to December 2021. Patients who were diagnosed with resectable or potentially resectable stage IIIA-B NSCLC and received neoadjuvant chemoimmunotherapy followed by robotic-assisted thoracic surgery were enrolled. Pathological response to neoadjuvant chemoimmunotherapy, treatment-related adverse events and surgical outcomes of these patients were evaluated.

Results: A total of 44 patients who underwent robotic-assisted thoracic surgery after 3 doses of neoadjuvant chemoimmunotherapy were included in this study. Of these, 37 of 44 (84.1%) patients had major pathological response, and 26 (59.1%) had pathological complete response based on pathological examination of surgical specimen. Eight patients (18.2%) suffered grade 3 treatment related adverse events, including neutropenia (n=4), increased aminotransferases (n=3), anemia (n=1) and cutaneous capillary endothelial proliferation (n=1). Robotic-assisted thoracic surgery was performed subsequently, and R0 resection was achieved in all patients. Only 2 (4.5%) patient required conversion to thoracotomy. Surgical complications occurred to 5 (11.4%) patients, including air leak (n=3), chylothorax (n=2) and surgical site infection (n=1). There was no re-surgery or postoperative mortality within 90 days.

Conclusions: Neoadjuvant chemoimmunotherapy showed high pathological remission rate in stage III NSCLC. Robotic-assisted thoracic surgery following neoadjuvant chemoimmunotherapy was not associated with unexpected perioperative morbidity or mortality, and may be a promising therapeutic option in stage III NSCLC. These results need further confirmation by more large-scale clinical trials.



Baseline characteristics, pathological responses and perioperative outcomes of patients	
Characteristics	**Median (IQR) and n (%)**
Age, yrs	61.5 (54-65)
Male	33 (75.0)
Smoking history	
Non-smoker	11 (25.0)
Former or current smoker	33 (75.0)
ECOG PS score	
0	27 (61.4)
1	14 (31.8)
2	3 (6.8)
FEV1% predicted	85% (75-90%)
Clinical stage	
IIIA	27 (61.4)
IIIB	17 (38.6)
Histological subtypes	
Squamous cell carcinoma	33 (75.0)
Adenocarcinoma	10 (22.7)
Others	1 (2.3)
Immune checkpoint inhibitor types	
Nivolumab	20 (45.5)
Camrelizumab	8 (18.2)
Toripalimab	6 (13.6)
Tislelizumab	4 (9.1)
Sintinimab	4 (9.1)
Pembrolizumab	2 (4.5)
Pathological response	
MPR	37 (84.1)
pCR	26 (59.1)
R0 resection	44 (100)
Incidence of surgical delay	0
Extent of resection	
Lobectomy	39 (88.6)
Sleeve lobectomy	2 (4.5)
Bilobectomy	2 (4.5)
Pneumonectomy	1 (2.3)
Surgical time (min)	191 (150-235)
Estimated blood loss (mL)	100 (50-150)
Conversion to thoracotomy	2 (4.5)
Intraoperative transfusion	3 (6.8)
Re-surgery	0
Surgical complications	5 (11.4)
Air leak	3 (6.8)
Chylothorax	2 (4.5)
Surgical site infection	1 (2.3)
Chest tube duration (days)	6 (4-8)
ostoperative length of stay (days)	6.5 (5-8)
Postoperative 90-day mortality	0

Keywords: non-small cell lung cancer, neoadjuvant therapy, robotic-assisted thoracic surgery

EP05.02-011 Phase II Trial of Neoadjuvant Tislelizumab with Chemotherapy for Resectable Stage IIB-III Non-small Cell Lung Cancer

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Introduction: Preoperative immunotherapy has been shown to be promising in treating resectable NSCLC. The current study aimed to investigate the activity and safety of neoadjuvant chemoimmunotherapy with PD-1 inhibitor, tislelizumab, for resectable stage IIB-III NSCLC in Asian population.

Methods: This was an open-label, multicenter, single-arm phase 2 trial done at 3 hospitals in China. Eligible patients recruited were aged 18 years or older with histologically confirmed AJCC-defined stage IIB-III NSCLC deemed surgically resectable. Patients received 3~4 cycles of neoadjuvant treatment with intravenous tislelizumab (200mg), carboplatin (area under curve 5), and pemetrexed (500 mg/m^2 for adenocarcinoma) or nab-paclitaxel (260mg/m^2 for others) on day 1 of each 21-day cycle. Surgical resection was performed 4-6 weeks afterward. The primary end point was the incidence of treatment-related adverse events (TRAEs; within 90 d after first dose of tislelizumab plus chemotherapy or 30 d after operation). The major pathological response (MPR), defined as less than 10% residual tumor remaining at the time of surgery, and disease-free survival were also assessed in modified intention-to-treat population. Molecular markers, including PD-L1 expression, TMB, etc. on efficacy and adverse reactions of such chemoimmunotherapy were explored in tissue, blood and stool samples. This study is registered with ClinicalTrials.gov, NCT05244837.

Results: Between December 2020 and December 2021, 37 patients (median age:63, IQR:45-77; female:6 16.2%) were enrolled, of whom 33 (89.2%) had stage III disease, and received neoadjuvant treatment. Twenty-nine (78.4%) patients had squamous cell lung cancer. During neoadjuvant treatment period, a total of 34 patients (91.9%) experienced neoadjuvant TRAEs. The most common TRAEs were alopecia (n=23;62.2%), anemia (n=16;43.2%), rash (n =18; 48.6%) and increased ALT/AST (n =10; 27.0%). Most of the TRAEs were grade 1or 2. One patient (2.7%) experienced severe TRAE of grade 3 increased ALT/AST and decreased white blood cell count. No grade 4 or 5 TRAEs was observed. Among 37 enrolled patients, 27 (73.0%) patients had received surgical resection, of whom 26 (96.0%) achieved R0 resection. Twenty-two of those 27 patients (81.5%) had an MPR, including 13 (13/27, 48.1%) with a pathological complete response (pCR).

Conclusions: Tislelizumab plus platinum-based doublet chemotherapy yields a high MPR rate, manageable treatment-related toxicity, and feasible surgical resection in stage IIB-III NSCLC. Ongoing analysis of predictive biomarker on efficacy and adverse reactions will be available at the meeting.

Keywords: Neoadjuvant treatment, Chemoimmunotherapy, Tislelizumab

EP05.02-012 Chemoradiotherapy versus Chemotherapy in Neoadjuvant Settings for Stage III-N2M0 Non-Small Cell Lung Cancer (NSCLC) Patients

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Introduction: Patients with stage III non-small cell lung cancer (NSCLC), especially with ipsilateral lymph node involvement (N2) represent marked heterogeneity. The standard of care for stage III-N2 NSCLC is induction therapy as part of a multimodal treatment regimen. The purpose of this study is to assess how the addition of radiotherapy to neoadjuvant chemotherapy affects survival outcomes.

Methods: Using ICD-O-3 histologic type coding on the Surveillance, Epidemiology, and End Results (SEER) database, we identified all adult NSCLC patients diagnosed between 2004 and 2015. Patients with stage III-N2 NSCLC, of any T stage, and with no known distant metastasis (M0) were eligible. Patients who received neoadjuvant chemoradiotherapy (CRT) or neoadjuvant chemotherapy (CT) comprised our sub-cohorts. Overall survival (OS) and cancer-specific survival (CSS) were our primary outcomes. In both univariate and multivariate analyses, the Cox proportional hazards model was applied to assess the effect of each treatment modality on OS and CSS. Age, sex, marital status, T stage, resected lymph node status, tumor histology, primary site, laterality, and surgical procedure were all adjusted for in the multivariate analysis. To create weighted samples based on study covariates, we applied inverse probability treatment weighting (IPTW).

Results: Our study analyzed 1175 patients, of whom 799 (68.0%) received neoadjuvant CRT and 376 (32.0%) received neoadjuvant CT. The sample median age was 63 (IQR:56-69). T2 (N=561, 47.7%) was the most common stage, followed by T4 (N=243, 20.7%), T1 (N=228, 19.4%), and T3 (N=143, 12.2%). Non-squamous cell carcinoma was the most prevalent tumor histology occurring in 773 (65.8%) of the patients. The most common primary tumor site (N =788, 67.1%) was the upper lobe. 917 (78.0%) patients underwent lobectomy, 184 (15.7%) patients underwent pneumonectomy, and 69 (5.9%) patients underwent sub-lobar resection. In neoadjuvant settings, adding radiotherapy to chemotherapy resulted in a slightly higher median OS compared to chemotherapy alone (51 vs. 47 months, respectively), as well as a higher median CSS (75 vs. 59 months, respectively). These results, nonetheless, were not statistically significant for OS or CSS (HR = 1.08, 95% CI: 0.91-1.28 and HR = 1.04, 95% CI: 0.89-1.21, respectively). Age, T3-T4 stage, non-squamous histology, lower lobe primary site, positive resected lymph nodes, and pneumonectomy were all significant independent predictors of poorer OS and CSS after adjustment. For OS and CSS, IPTW analysis revealed no significant survival benefit with CRT patients (HR = 1.15, 95% CI: 0.95-1.40 and HR = 1.12, 95% CI: 0.90-1.39).

Conclusions: The addition of radiotherapy to neoadjuvant chemotherapy did not yield significant survival outcomes. Several prognostic factors should be considered when determining the optimal multimodal treatment option and sequence for patients with stage III-N2M0 NSCLC.

Keywords: Neoadjuvant, Locally Advanced, NSCLC

EP05.02 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - NEOADJUVANT AND ADJUVANT THERAPY

EP05.02-013 Immune-Related Adverse Effects and Durvalumab Treatment Patterns in VHA Patients with Unresectable Stage III NSCLC

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Introduction: Immune checkpoint inhibitors (ICIs) such as durvalumab can cause immune-related adverse effects (irAEs) that may result in treatment interruptions (TI) and/or treatment discontinuations (TD). This study aimed to describe relationships between irAEs and durvalumab treatment patterns (TI, TD, and duration of therapy [DoT]) in patients with unresectable stage III non-small cell lung cancer (NSCLC).

Methods: Patients with unresectable stage III NSCLC who received durvalumab following chemoradiotherapy at any Veterans Health Administration (VHA) facility from January 1, 2017 to June 30, 2020 with a minimum follow up of 12 months were included in this analysis. Patients were followed from their date of durvalumab initiation through the earliest of their last VHA visit, loss to follow up, death, or the end of the study. Patients were excluded if durvalumab therapy was ongoing at the end of the study period because the full durvalumab treatment course could not be determined. Data abstractors reviewed charts for patient characteristics, pre-specified irAEs of any grade as assessed by treating physicians (pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, dermatologic toxicities, other), and durvalumab TI (>28 days between durvalumab doses), TD, and DoT. Nominal logistic regression was used to assess relationships between irAEs and TI or TD, with adjustments for patient age, sex, Charlson comorbidity score, and priority group (a VHA marker of socioeconomic status), with results reported using adjusted odds ratios (aOR) and 95% confidence intervals (95%CI). DoT was reported using medians and interquartile ranges (IQR).

Results: 935 patients met the study criteria. irAEs were reported more frequently in patients who experienced a TI vs No-TI (43% vs 32%, aOR 1.58, 95%CI 1.05-2.37, p=0.03) or TD vs No-TD (38% vs 29%, aOR 1.55, 95%CI 1.09-2.21, p=0.01). In particular, pneumonitis was reported more frequently in patients who experienced a TD (20% vs 2%, aOR 11.6, 95%CI 4.6-29.2, p<0.01). The median [IQR] DoT among patients with irAEs was 8.0 months [2.6-11.7], comparable to the median DoT among those without an irAE (9.5 months [3.3-11.9]). Patients with pneumonitis had a median DoT of 3.3 months [1.4-7.8] vs 10.2 months [3.7-11.9] among those without pneumonitis.

Conclusions: This study demonstrated that patients treated with durvalumab who experience an irAE may also have a greater likelihood of treatment interruption and/or treatment discontinuation. Specifically, patients who develop pneumonitis may be at a higher risk of treatment discontinuation. Patients with and without irAEs tend to have a similar durvalumab durations of therapy, though patients with pneumonitis had a shorter durations of therapy than those without pneumonitis. These findings underscore the importance of early identification and management of irAEs.

EP05.02-014 Neoadjuvant Toripalimab Combination in Patients with Stage IIB-IIIB NSCLC: A Single-Arm, Phase 2 Trial (Renaissance Study)

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Introduction: PD-1 inhibitors have displayed potential anti-tumor activities in non-small cell lung cancer (NSCLC). Here we conducted a single center, prospective study to investigate the efficacy and safety of neoadjuvant toripalimab (the first PD-1 inhibitor from china) plus double platinum-based chemotherapy for stage IIB-IIIB NSCLC.

Methods: Study eligibility involved stage IIB-IIIB, wildtype EGFR/ALK NSCLC pts with ECOG PS 0-1 status. Pts received 2-4 cycles of toripalimab (240mg, q3w) plus cisplatin-based chemotherapy. All pts were assessed by imaging/surgical indication after the second cycle of treatment. Pts who cannot undergo surgery will be reassessed after another 1-2 cycles of neoadjuvant therapy. Primary endpoints were major pathological response (MPR), complete pathological response (pCR). Secondary endpoints were objective response rate (ORR), R0 resection rate and safety. Clinical trial information: NCT04606303.

Results: A total of 53 eligible pts (median age: 62, IQR: 45-76; female: 5, 9.4%; squamous cell carcinoma: 42, 79.2%) were enrolled and received 2-4 cycles neoadjuvant treatment since Mar 2021. Disease distribution in stage IIB, IIIA and IIIB consisted of 15, 30 and 8 pts, respectively. 15 pts were in the preoperative stage or unsuitable for surgery. 39 pts underwent resection (median interval between neoadjuvant treatment and surgery: 67 days, IQR: 39-113). 25 pts (25/39, 64.1%) achieved MPR, including 20 pts (20/39, 51.3%) with pCR. R0 resection was achieved in all 39 pts (100%). 29 pts underwent surgery with cN2/N1 at baseline (29/31, 93.5%) achieved nodal downstaging. 49 pts finished the treatment schedule and radiological reassessment, ORR was 85.7% (42/49). Grade 1-2 TRAEs were reported in 46 pts (46/49, 93.9%). Grade 3-4 TRAEs were reported in 15 pts (15/49, 30.6%). Of the pts who underwent surgery, 3 pts (3/39, 7.7%) experienced grade 2-3 irAE (enteritis or rash) and received glucocorticoid therapy. Interestingly, all these 3 pts achieved pCR, and the median interval between neoadjuvant treatment and surgery was 56 days (IQR: 56-70). Compared with all pts underwent surgery, there were no treatment-related surgical delay and additional surgery difficulty for these 3 pts. It may suggest that pts who experienced grade 2-3 irAEs have a better pCR rate (100% vs 47.2%). Of the pts who were preparing or unsuitable for surgery, 2 pts experienced grade 2-3 irAE (enteritis or pneumonia) and received glucocorticoid therapy, 1 had partial response (PR) after neoadjuvant treatment and maintained stable disease (SD) after 10 months of observation, another had clinical complete response (cCR) after neoadjuvant treatment. Of all 5 pts who experienced irAEs and received glucocorticoid therapy, the median onset time of irAE was 12 days (IQR: 7-54), the median duration time of glucocorticoid therapy was 12 days (IQR: 7-79).

Conclusions: Neoadjuvant toripalimab plus platinum-based doublet is a promising, tolerable and effective treatment for pts with stage IIB-IIIB NSCLC. Interestingly, a potential correlation between grade 2-3 irAE and the efficacy of neoadjuvant toripalimab combination was observed. And we are looking forward to a more complete and solid correlation.

Keywords: Neoadjuvant, PD-1 inhibitor, NSCLC

EP05.02-015 Neoadjuvant Prehabilitation Therapy for Locally Advanced Non-small-Cell Lung Cancer: Optimizing Outcomes throughout the Trajectory of Care

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Introduction: Prehabilitation is well established for improving outcomes in cancer surgery. Combining prehabilitation with neoadjuvant treatments may provide an opportunity to rapidly initiate cancer-directed therapy while improving functional status in preparation for local consolidation. In this proof-of-concept study, we analyzed non-small-cell lung cancer patients who underwent simultaneous prehabilitation and neoadjuvant therapy.

Methods: We retrospectively analyzed all patients who underwent neoadjuvant treatment for non-small-cell lung cancer followed by curative intent surgery between 2015-2021. Patients who were screened for the prehabilitation program were identified. Screening included assessment of physical performance, nutritional status and signs for anxiety and depression.

Results: We identified a total of 141 patients who underwent neoadjuvant therapy. Twenty patients were screened to undergo a prehabilitation program. Four patients did not complete the exercise program (1 surgical intervention too soon, 1 drop-out out after first session and 2 patients were deemed fit without intervention). Postoperative median length of stay was 2 days (range 1-18). Patients improved their 6-minute-walk test despite undergoing neoadjuvant treatment by a mean of 33 meters (± 50, p=0.1). Self-reported functional status (DASI) showed significant improvement by a mean of 10 points (±11, p=0.03) and HADS-anxiety-score was significantly reduced after the prehabilitation program by a mean of 1.5 points (±1, p=0.005).

Conclusions: Neoadjuvant prehabilitation therapy is feasible and associated with encouraging results. The performance of all measures remains a logistic challenge. With multimodal strategies for lung cancer treatment becoming key to optimal outcomes, neoadjuvant prehabilitation therapy is a concept worthy of prospective multi-center evaluation.

Keywords: Prehabilitation, neoadjuvant therapy, exercise program

EP05.02-016 Aumolertinib after Adjuvant Chemotherapy/Radiotherapy in Stage pIIIA-N2 Non-Small-Cell Lung Cancer with EGFR Mutation

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Introduction: Several trials such as the ADJUVANT, ADAURA, EVAN, EVIDENCE, and SELECT have been confirmed that epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) targeting adjuvant therapy provides a dramatic response to patients with EGFR-mutation non-small cell lung cancer (NSCLC). Especially compared with stage II, patients with pIIIA-N2 may be the precise population for the clinical benefit of adjuvant targeted therapy. A number of multi-center, large-sample retrospective studies have evaluated that adjuvant chemotherapy/radiotherapy can also improve the local control rate and survival rate of pIIIA-N2 NSCLC. However, the role of the adjuvant chemotherapy/radiotherapy followed by sequential EGFR-TKI maintenance therapy in improving the survival of pIIIA-N2 NSCLC patients with EGFR-sensitive mutations is not clear. Aumolertinib is a novel third-generation EGFR-TKI with proved efficiency and safety for untreated NSCLC patients with EGFR sensitizing mutations. This study aims to investigate the efficacy of aumolertinib as a maintenance therapy after adjuvant chemotherapy/radiotherapy for stage pIIIA-N2 NSCLC patients with EGFR mutation.

Methods: Approximately 102 untreated Chinese pIIIA-N2 NSCLC postoperative patients with EGFR mutations (exon 19 deletion or L858R) will be enrolled in this study. After surgery followed by adjuvant chemotherapy/radiotherapy, eligible patients were randomized equally, using simple randomization, to either the aumolertinib(110 mg QD) for 24 months or observation arm. Treatment assignment cannot be masked given its open-label design.Chemotherapy: Pemetrexed (500 mg/m2 on day 1) plus carboplatin (25 mg/m2 on days 1 and 8; cis/vin) once every 3 weeks for four cycles for non-squamous cell cancer; Paclitaxel(135-175 mg/m2 on day 1) plus carboplatin (25 mg/m2 on days 1 and 8; cis/vin) once every 3 weeks for four cycles for squamous cell cancer. Radiation: 3-Dimensional Conformal Radiotherapy(3DCRT) or Intensity Modulated Radiation Therapy (IMRT). Image guided, 1.8-2.0 Gy*1F was recommended, large residual lesions will be treated with a local dose (≤DT 50-54Gy/15F).The primary end point was disease-free survival (DFS) of two years. Secondary endpoints are adverse events of grade 3-4 or higher, rate of long term adverse events, DFS, overall survival. ClinicalTrials.gov Identifier: ChiCTR2200057150.

Keywords: NSCLC, adjuvant chemotherapy/radiotherapy, Aumolertinib

EP05.02-017 Prognostic Factors Following Induction Therapy for N2 Lung Cancer

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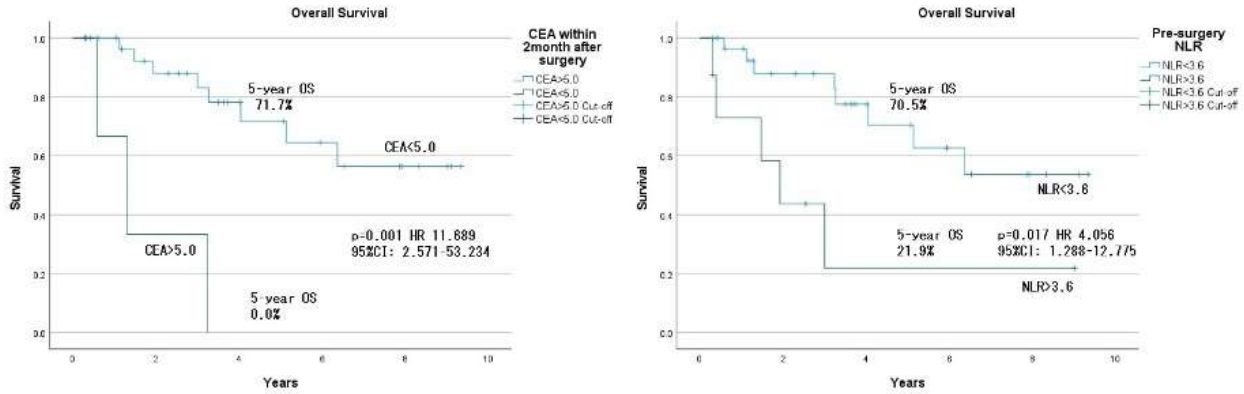
Introduction: Treatment for non-small cell lung cancer in patients with N2 lymph node metastasis is controversial. Our facility performs induction therapy (chemotherapy ± radiation) for N2 lung cancer or surgery when not PD. Cases with induction therapy for N2 lung cancer were examined.

Methods: Forty-three patients who underwent induction therapy from January 2011 to December 2020 were included, with prognosis surveyed in February 2022. Prognostic factors examined included inflammatory indexes and tumor markers (GPS, mGPS, NLR, PLR, PI, PNI, CEA). Survival rate was calculated using the Kaplan-Meier method and comparisons between groups were performed using the log-rank method. P <0.05 was considered to be significant.

Results: There were 40 males and 3 females, and average age was 66.3 years. Treatment was chemo-radiotherapy in 24, chemotherapy in eight, chemotherapy + VEGF inhibitor in six, and EGFR-TKI in five patients. Thirty-seven underwent surgery (CR 1, PR 18, SD 18), while six did not (PD 4, interstitial pneumonia 1, refusal 1). Surgical procedures were lobectomy in 34 (bronchial plasty 9, pulmonary artery plasty 1, left atrial resection 1, superior vena cava resection 2), middle and lower lobectomy in two, and pneumonectomy in one. Ef3, EF2, EF1, and EF0 were noted in seven, 17, 12, and one, respectively. Perioperative complications occurred in 21. There were no surgical deaths. The average observation period was 1157 days, with postoperative recurrence noted in 19, survival in 24, and death in 13 (cancer 6, other disease 7). Univariate analysis revealed pre-surgery NLR <3.6 [p=0.017, HR 4.056 (95%CI: 1.288-12.775)] and CEA <5.0 within two months after surgery [p=0.001 HR 11.689 (95%CI: 2.571-53.234)] to be significant factors, while multivariate analysis showed the same results. The five-year overall survival rate for presurgical NLR <3.6 and ≥3.6 was 70.5% and 21.9%, respectively, while that for postsurgical (within two months) CEA <5.0 and ≥5.0 was 71.7% and 0 0%, respectively.

Conclusions: Analyses of results of treatment for N2 lung cancer patients and prognostic factors showed that presurgical NLR <3.6 and CEA <5.0 within two months after surgery were associated with better prognosis.



Keywords: Lung Cancer, Adjuvant Therapy, Prognostic factor

EP05.02-019 Transitioning to Neoadjuvant Therapy for Resectable Non-Small Cell Lung Cancer: Surgical Outcomes in a Regionalized Pulmonary Oncology Network

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Introduction: Neoadjuvant therapy (NAT) allows pre-operative tumor downstaging and evaluation of pathological response. Clinical trials have demonstrated benefit of using NAT in the context of locally advanced non-small cell cancer (NSCLC). However, NAT is not commonly employed around the world and data are lacking as to how to establish a NAT program for locally advanced resectable NSCLC. The aim of this study is to evaluate the evolution in care patterns for patients with resectable locally advanced NSCLC within a regionalized pulmonary oncology academic network and to assess the impact of transition towards a large-scale NAT program.

Methods: Patients with proven clinical stage II-III NSCLC who underwent surgery at a University based unit from 2015-20 were identified from a prospectively maintained institutional thoracic cancer registry, supplemented by retrospective review of patients' charts. Demographic, clinical and pathological variables were gathered. Peri-operative outcomes were compared between patients who received NAT to those treated by upfront surgery (S). Prospectively collected surgical complications data were classified according to validated severity grading system (modified Clavien-Dindo). Chi-square and Fischer exact test were used to compare categorical data and independent T-test to compare numerical data. Logistic regression analyses were performed to assess risk factors for developing post-operative complication.

Results: A total of 3,533 patients with NSCLC were assessed for eligibility. 434 met inclusion criteria; 110 (25.3%) NAT and 324 (74.7%) S. Post-operative complication occurred in 249 patients (57.4%). No differences in number of minor (grade I-II) and major (grade III-V) post-operative complications was observed between groups (P=.127). Postoperative mortality was 0.9% (n=1) and 1.5% (n=5) in the NAT and S respectively. Median length of stay (days) was similar; NAT=4 (1-94) and S=5 (1-73) (P=.647). Readmission frequency was similar; 7 (6.4%) NAT and 34 (10.4%) S (P=.258). Multivariable regression demonstrated that Neoadjuvant-treated patients were no more likely as those who underwent upfront surgery to suffer from post-operative complication (aOR=1.36, 95% CI= 0.76-2.43). Higher post-operative complication was observed in older patients (>65y.o.) (aOR=2.32, 95% CI=1.17-4.61), current smokers (aOR=2.04, 95% CI=1.04-4.02), diagnosed in 2017 (aOR=2.61, 95% CI=1.26-5.40) and those that underwent open surgery (aOR=1.67, 95% CI=1.03-2.70). An increase from 10% to 44% in neoadjuvant administration was noted during this 5-year period. A rise in neoadjuvant regimen diversity was observed over the years with advances in targeted therapies and immunotherapies, and reduced use for pre-operative radiation.

Conclusions: No significant differences in perioperative outcomes were observed in patients undergoing neoadjuvant therapy for clinical stage II and III NSCLC, as compared to those who underwent upfront surgery. This study illustrates a progressive transition towards neoadjuvant therapy amongst operable NSCLC patients which is safe and feasible from a surgical perspective. Further analysis of long-term outcomes will be done to determine if neoadjuvant is as effective as adjuvant therapy, the current standard of care.

Keywords: Neoadjuvant therapy, Non-small cell lung cancer (NSCLC), Thoracic surgery

EP05.02-020 IL-9Stimulates Anti-tumor Immune Response and Facilitates Checkpoint Blockade in Lung Cancer

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Introduction: Lung cancer continues to be the most common cause of cancer-related mortality. There was mounting evidence that interleukin-9 (IL-9) was associated with cancer. Its function in lung cancer, however, is still debatable. The goal of this study was to elucidate the role of IL-9 in lung cancer and the mechanisms involved using murine lung carcinoma models.

Methods: Murine lung carcinoma cell lines (Lewis lung carcinoma (LLC) and CMT167) were used. IL-9 receptor (IL-9R) expression was evaluated by Western blot CMT167 cells were transduced with lentivirus carrying IL-9R shRNA to knock down the expression of IL-9R.MTT assay was used to assess cytotoxicity with treatment. Two syngeneic murine lung cancer models were established by subcutaneous inoculation of 5 x 10^5 LLC or CMT167 cells into the right flank of wildtype C57BL/6J immunocompetent mice. Tumor-bearing mice were randomized to receive treatment with IL-9 (50 ng/mouse, alternate day) ± murine anti-programmed cell death protein 1 (anti-PD-1) or control until reaching humane endpoints whereby tumors were harvested. Flow cytometry was utilized to analyze tumor-infiltrating immune cells and major histocompatibility complex (MHC)-I expression. The mRNA expression of chemokines in tumors was determined using quantitative polymerase chain reaction (qPCR). Signaling proteins associated with IL-9 were detected by Western blot.

Results: IL-9R expression was detected in CMT167 cells, but not in LLC cells. IL-9 was not cytotoxic in both LLC and CMT167 cells. In LLC tumor-bearing mice, tumor growth or intratumoral T cells were not affected by IL-9 treatment. However, IL-9 significantly decreased CMT167 tumor growth and enhanced T cell infiltration, which were absent in IL-9R knockdown CMT167 tumors. Upon depletion with murine CD8 neutralizing antibody, CD8+ T lymphocytes were identified as the key effector in driving IL-9-induced tumor suppression in the CMT167 mouse model. Upon IL-9 treatment in CMT167 tumor-bearing mice, there was no change in mRNA expression of chemokines (CXCL9, CXCL10, and CXCL11) involved in T cell recruitment, but significant upregulation of the components of murine MHC-I (H-2K and B2m). *In vitro*, IL-9 could also enhance interferon (IFN)-γ induced MHC-I expression on CMT167 cells, with upregulated ERK1/2 but no change in STAT1 and Akt. Simultaneously, PD-1 and PD-L1 expression on CD8+ T cells and CMT167 cells were upregulated. The combination of IL-9 and anti-PD-1 antibody was synergistic in CMT167 mouse model resulting in further tumor suppression and enhanced CD8+ T cell infiltration.

Conclusions: IL-9/IL-9R interaction in CMT167 murine lung carcinoma enhanced tumoral MHC-I expression through activated ERK1/2 pathway, facilitating CD8+ T cell infiltration and tumor suppression, which could potentially synergize with anti-PD-1.

Keywords: Lung cancer, IL-9, MHC-I

EP05.02-021 An Updated Analysis of Toripalimab and Platinum-Doublet Chemotherapy as Neoadjuvant Therapy for Potentially Resectable NSCLC

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Introduction: We initiated a prospective, single-arm, phase II study to explore the efficacy, safety, and feasibility of neoadjuvant toripalimab plus platinum-doublet chemotherapy in treatment-naive patients with potentially resectable non-small cell lung cancer (NSCLC). The preliminary results of the study have been presented in 2021 WCLC poster 15.02. Here we report updated data (ClinicalTrials.gov: NCT04144608).

Methods: The study enrolled patients with non-driver gene mutation stage IIIA-IIIB potentially resectable NSCLC. All patients received 2-4 cycles of toripalimab (240 mg d1), nab-paclitaxel (260 mg/m^2 d1) (non-squamous cell carcinoma: pemetrexed 500 mg/m^2 d1) and carboplatin (AUC 5 d1) or cisplatin (75 mg/m^2 d1) before surgery, every 3 weeks. Preoperative imaging evaluation and surgical indication evaluation were performed within 3-5 weeks after completion of neoadjuvant therapy. Within 30 days after surgery, another 2 cycles of adjuvant toripalimab plus chemotherapy were administered, followed by toripalimab monotherapy for 13 cycles (240 mg, Q3W). The primary endpoint was R0 resection rate. Pathologic complete responses (pCR), major pathologic responses (MPR), disease free survival (DFS), and safety were set as secondary endpoints.

Results: As of March 15, 2022, a total of 40 patients with stage III potentially resectable NSCLC were screened, and 7 patients were still receiving neoadjuvant therapy. Among 33 evaluable patients, 3 did not meet surgical criteria, and 30 (90.9%) met surgical criteria including 4 who refused surgery due to financial factors and personal needs. R0 resection was achieved in all 26 patients who underwent surgery. The actual operation rate was 78.8% (26/33), the MPR was 57.7% (15/26), and the pCR was 42.3% (11/26). In evaluable patients, the median age was 58, 12.1% were females and 18.2% were non-smokers. 87.9% patients (29/33) had squamous cell lung cancer, and 45.5% (15/33) patients were identified with stage IIIB disease. In surgical population, the median duration of follow-up was 16 months (range: 3-28), and the 1 and 2-year DFS rates were 89.4 % and 72.9%. No new unexpected adverse events were observed.

Conclusions: The updated results further demonstrate that neoadjuvant toripalimab combination is highly efficient and well-tolerated in potentially resectable NSCLC. And more importantly, an improvement in survival can be expected.

Keywords: Neoadjuvant, Toripalimab, Potentially Resectable NSCLC

EP05.02-022 Thoracic Radiotherapy May Increase the Risk of Treatment-induced Pneumonitis after Immune Checkpoint Inhibitors: A Meta-Analysis

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Introduction: Thoracic radiotherapy (TRT) combined with immune checkpoint inhibitors (ICIs) has shown promising results. However, it remains unclear whether TRT would increase the risk of lung toxicity after treatment of immune checkpoint inhibitor. This study aimed to compare the risk of treatment-related pneumonitis (TRP) between patients treated with TRT combined with immunotherapy and those with ICIs or TRT alone.

Methods: This is a meta-analysis conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Two researchers independently conducted the platform searches on PubMed, Embase, Cochrane Library, and Web of Science up to Dec. 31th, 2021. Cancer patients treated with ICIs and TRT, and with report of radiation or immune checkpoint inhibitor associated pneumonitis were eligible for this study. The pooled average rate of pneumonitis was estimated along with corresponding 95% confidence interval (CI). The odds ratio (OR) was computed using the random-effects model after checking the heterogeneity across studies using the Cochran Q chi-square test and the I2 statistics. Data analyses were performed using R version 4.1.1, meta, and metafor packages.

Results: A total of 29 studies, including 3260 patients, were eligible. The pooled rate of any grade of TRP were 22% (95% CI: 14-32%) in patients treated with ICIs and TRT, which is significantly higher compared to the ICIs or TRT group (OR: 1.47, 95% CI: 1.17-2.00, p=0.002).In the subgroup analysis, patients with lung cancer had a significantly higher risk of TRP than that of other types of cancer after ICIs (25% 95% CI: 0.16-0.35 vs. 7% 95% CI: 0.04-0.12; p=0.04). Patients received concurrent TRT did not significantly increase the risk of TRP comparing to those treated with sequential TRT and ICIs.

Conclusions: This study demonstrates that TRT significantly increased the risk of grade>2 TRP in patients treated with sequential or concurrent ICIs, especially in patients with lung cancer.

Keywords: pneumonitis, radiotherapy, immune-checkpoint inhibitor

EP05.03-001 Impact of Neoadjuvant Chemo/radiotherapy Followed by Surgical Resection on T4N0-1 Non-Small Cell Lung Cancer

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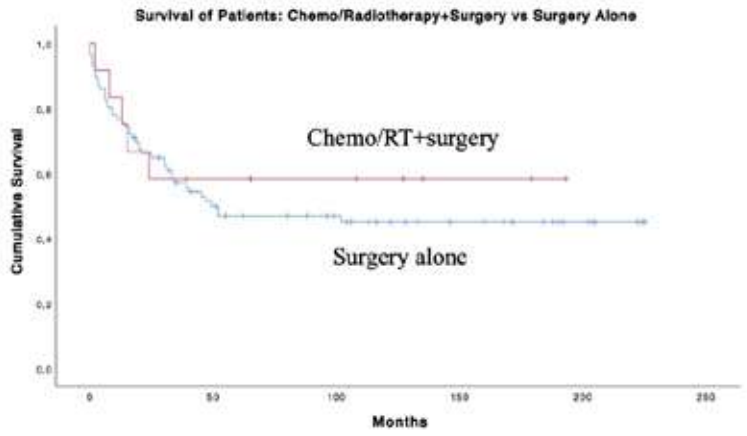
Introduction: Despite many improvements in thoracic surgery and oncology, the best treatment strategy for T4 non-small cell lung cancer(NSCLC) is yet to be identified. However, select patients without N2/N3 disease have been shown to be benefited from surgical resection. We aim to determine the impact of neoadjuvant chemotherapy and/or high-dose radiation therapy on survival in patients with T4N0-1 non-small cell lung cancer.

Methods: Between January 2002 and December 2020, 107 patients with T4 who were operated for NSCLC in our clinic were analyzed. There were 9 patients(8.3%) with T4N2 whereas 65 patients were N0 (60.2%), 33 patients were N1 (30.6%) according to surgical-pathologic evaluation. The patients with T4N2 disease were excluded from the study. Eighty-six patients (87.8%) received neoadjuvant high-dose (59-64 cGy) radiation therapy and/or chemotherapy before resection (Neoadjuvant+Surgery group). Twelve(12.2%) patients underwent surgical resection without receiving induction chemo/radiotherapy(Surgery group). Patients were followed up for a mean of 66.8 (11-220) months. Survival of the Neoadjuvant+Surgery and Surgery groups was compared using both log-rank test and Cox proportional hazards models.

Results: The postoperative 90-day mortality occurred in 6 patients (6.1%). The 5-year, 10-year, and median survivals were 58.3%, 58.3%, and 117 months[95% confidence interval: 67.3-168.2 months], respectively, in the neoadjuvant therapy+surgery group versus 46.9%, 45.0%%, and 136.2 months[95% confidence interval: 90.9-136.2 months], respectively, in the Surgery group. Subjects in the Surgery group had an increased risk of death (hazard ratio, 1.309; 95% confidence interval, 0.519-3.302; p=0.567) compared with the neoadjuvant+surgery group. After adjustment for potential confounding variables of gender, age, tumor size, nodal involvement in the(N0 or N1) neoadjuvant+surgery group, there was no statistically significant difference in terms of survival (hazard ratio, 1.26; 95% confidence interval, 0.49-3.21, p=0.631) compared with the surgery-alone group. In addition, N1 disease was not found to be independent prognostic factor (hazard ratio, 1.26; 95% confidence interval, 0.49-3.21, p=0.631)

Conclusions: Aggressive treatment of T4N0 NSCLC with neoadjuvant chemotherapy and/or radiotherapy did not seem to prolong survival. In addition, N1 was not found to be a significantly significant prognosticator. These results should be evaluated in a prospective multicenter trial.



Keywords: non-small cell lung cancer, T4, neoadjuvdnt therapy

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-002 Pulmonary Artery Reconstruction for Lung Cancer with N1 Vessel Infiltration: Is It Justified?

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Introduction: Pulmonary artery (PA) can be infiltrated by primary lung cancer or by a metastatic N1 lymph node with extracapsular extension. Lobectomy associated with PA reconstruction has been reported to be a valid option in both situations. However, up to now, no study has been conducted in order to compare results from patients undergoing reconstructive surgery for primary lung cancer PA infiltration with those undergoing PA reconstructions for metastatic single N1 infiltration. Hereby, we report our experience in this setting.

Methods: Between 2018 and June 2021, 30 consecutive clinical single-N1 NSCLC patients underwent lobectomy associated with PA reconstruction for N1 lymph node direct infiltration (n=16), group A or for primary lung cancer direct vessel infiltration (n=14), group B. Eight patients had received induction chemotherapy before surgery. PA reconstruction was: patch in 18 cases (porcine pericardial patch in 13 and autologous pulmonary vein patch in 5), end-to-end after PA sleeve resection in 11, and porcine pericardial conduit in 1. Bronchoplasty was associated in 9 cases.

Results: All the resections were complete (R0). Tirthy-day mortality rate was 3%. Major complication rate was 10%. No technical complications occurred. Pathologic stage was IIB in 10 cases, IIIA in 17 cases and IIIB (ypT3N2) in 3 cases. Patients who have undergone induction chemotherapy and/or bronchoplasty were equally distributed within the two groups (p=ns). Adjuvant treatments were given to 89.6% of patients. Three-year overall survival (OS) and disease-free survival (DFS) were 55.2% and 37.9% respectively. The comparison of survival curves related to the PA infiltration pattern (group A vs group B) showed no statistically significant difference in terms of OS (53.3% vs. 57.1%, p=0.88) and DFS (33.3% vs. 42.9%; p=0.54) between the two groups. Pathologic N2 occult lymph node metastases (p=0.05) and lymphovascular invasion (LVI, p<0.001) have been identified as independent negative prognostic factors for recurrence.

Conclusions: Lobectomy with PA reconstruction for NSCLC is a safe and effective surgical treatment, which allows for satisfactory oncologic results even in the case of N1 disease. The pattern of PA infiltration does not influence survival. Occult pN2 disease and LVI are associated with a worse outcome.

Keywords: pulmonary artery reconstruction, non-small cell lung cancer, surgery

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-003 Superior Sulcus (Pancoast) Tumors: A 11-Year Single-Centre Experience

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Introduction: The term Pancoast tumors (PT) encompasses any tumor located on the lung apex with extension into vital structures in the thoracic inlet, leading to the development of the characteristic clinical syndrome. The main goal of this study was to analyze the response to surgical-multimodal treatment and the outcome of patients with PT.

Methods: A retrospective cohort single center study was performed of patients with superior sulcus non-small cell lung carcinomas who underwent surgery between January of 2011 and February of 2022. Statistical analysis was performed with IBM SPSS® v27.

Results: 11 patients were identified with PT. 1 patient was excluded due to the diagnosis of breast cancer metastasis. Mean age was 53,6 (6,6) years, with male predominance (80,0%). All patients were smokers with a median of 37,5 pack-years. Most frequently observed symptoms at presentation were pain (80,0%) and paresthesia (40%) in the ipsilateral upper limb. At diagnosis, 2 tumors were stage II and 8 were stage III (8th TNM classification). Histopathology showed 8 were adenocarcinomas and 2 were sarcomatoid carcinomas. 9 patients were treated with neoadjuvant chemoradiotherapy and, 1 patient received neoadjuvant chemotherapy. Surgical approach was a Paulson incision. 8 patients received lung lobectomy with *en-bloc resection* comprising the chest wall (80,0%) and the brachial plexus (30,0%). In 2 patients, the need for vascular resection was anticipated and an arterial bypass was performed previously. In 1 patient, the surgical procedure was aborted because surgical findings rendered it inadvisable. Mean pleural drainage time was 5,8 (2,6) days and mean hospital stay was 7,6 (3,0) days. There was 1 postoperatively death (10,0%) and no other major complications. Surgical histopathology showed non-invaded surgical margins (R0) were achieved in 8 patients. 2 tumors were stage I (22,2%), 2 tumors were stage II (22,2%), 2 tumors were stage III (22,2%) and 1 tumor was stage IV (11,1%). 2 patients achieved full tumoral remission (22,2%) and the patient submitted to exploratory thoracotomy presented full metabolic remission after definitive chemoradiotherapy. Following surgery, the most frequent complaint was paresthesia (40,0%). In 2 patients, complete clinical resolution of deficits was achieved. Mean follow-up time after surgery was 32,3 (42,8) months. 1 patient relapsed locally 5 months and 1 patient had distant metastization 4 months, after the surgical procedure. Mean disease-free survival was 83,9 (CI95% 42,1-125,8) months. 3-month disease-free survival rate was 88,9% and 1-year and 5-year disease-free survival rates were equal, corresponding to 63,5%. After the first-year follow-up, no disease progression events were detected in our sample of patients. Mean overall survival was 115,7 (CI95% 89,3-142,1) months. At 3-month, 1-year and 5-years, overall survival was equivalent, correlating to 88,9%.

Conclusions: The survival curves for PT in our institution are superior to current literature and although the selective eligibility criteria for surgical treatment and limited patient number should be considered, results exhibit a positive outcome. A multidisciplinary approach is essential to attain the best outcome possible. Significant improvements have been reported recently in understanding the biology and treatment response of PT, but still further research is required.

Keywords: Superior sulcus tumors, Pancoast, Surgery

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-004 Risk Prediction of Multiple-station N2 Metastasis in Patients with Clinical Single-station N2 Non-small Cell Lung Cancer

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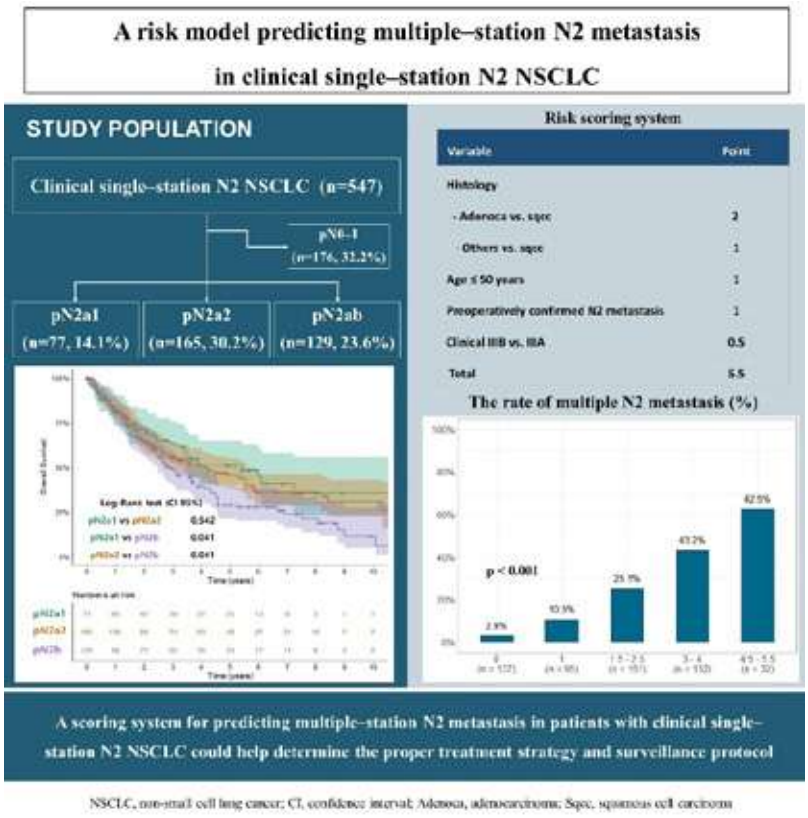
Introduction: Although the standard treatment for patients with N2 non-small-cell lung cancer (NSCLC) is definitive chemoradiation, several studies have demonstrated that minimal N2 disease, such as single-station N2 disease (N2 disease limited to a single mediastinal station), is a favorable prognostic indicator of resected N2 NSCLC. The objective of this study is to investigate long-term survival outcomes and develop a risk model for multiple-station N2 metastasis in patients with clinical single-station N2 NSCLC.

Methods: From 2006 to 2008, 547 patients who underwent upfront surgery for clinical single-station N2 NSCLC were analyzed. Based on the findings of the multivariable analysis using preoperative clinical variables, a risk model for predicting multiple-station N2 metastasis was developed.

Results: Among patients with clinical single-station N2 NSCLC (n=547), preoperative N2 node biopsy was performed in 125 (22.9%) patients. There were 118 (21.6%), 58 (10.6%), and 371 (67.8%) patients with pathologically N0 (pN0), pN1, and pN2 disease. When patients with pN2 NSCLC (n=371) were divided based on subdivided pN descriptors, there were 77 (20.8%), 165 (44.5%), and 129 (34.7%) patients with pN2a1 (single-station N2 without N1 involvement), pN2a2 (single-station N2 with N1 involvement), and pN2b (multiple-station N2). The 5-year overall survival rate of patients with pN2a1 (51.2%) and pN2a2 (45.8%) were significantly higher than those with pN2b (29.0%) (all $p = 0.041$). According to the risk model, histologic type ($p < 0.001$), age ≤ 50 years ($p < 0.001$), preoperatively confirmed N2 metastasis ($p < 0.001$), and clinical stage IIIB (vs. IIIA) ($p = 0.003$) were independent risk factors for multiple-station N2 metastasis in patients with clinical single-station N2 NSCLC. The risk scoring system based on this model showed a good discriminant ability for pN2b disease (area under the receiver operating characteristic curve: 0.779)

Conclusions: In patients with clinical single-station N2 NSCLC, those with pN2b had significantly worse prognosis than those with pN2a1 and pN2a2. Our risk scoring system for predicting pN2b has good discriminant ability in patients with clinical single-station N2 NSCLC.



NSCLC, non-small cell lung cancer; CI, confidence interval; Adenoca, adenocarcinoma; Sqcc, squamous cell carcinoma

Keywords: Multiple–station N2 Metastasis, Clinical Single–station N2, Non-small Cell Lung Cancer

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-005 Clinical Impact of Histologic Type in Patients with Surgically Resected Stage II and III Non-small Cell Lung Cancer

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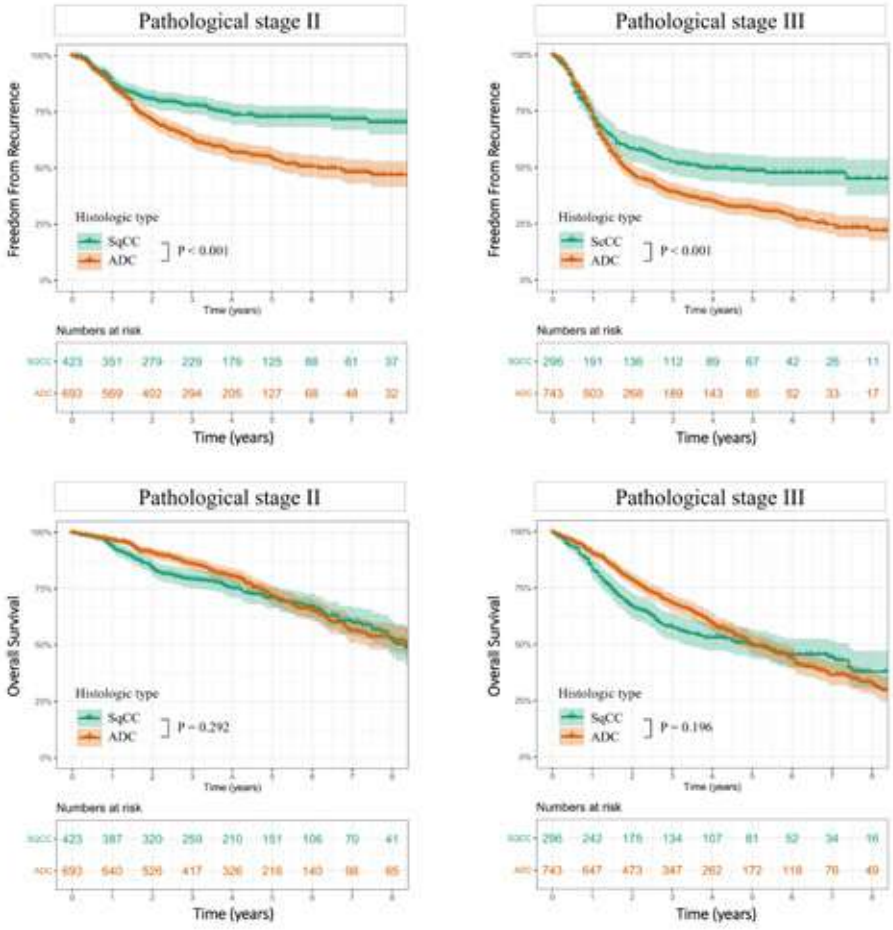
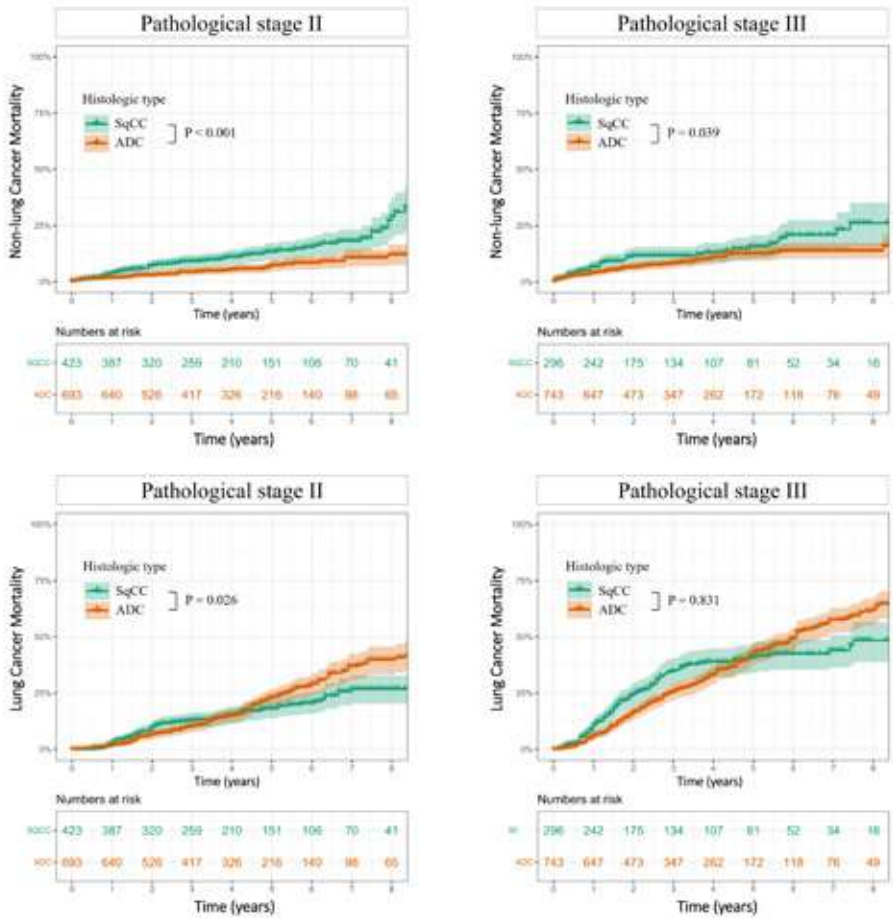
Introduction: This study aimed to investigate the clinical impact of histology on survival and recurrence outcomes of patients with stage II and III non-small cell lung cancer (NSCLC).

Methods: From 200 to 2018, 2155 patients who underwent complete resection for stage II and III NSCLC were enrolled. The primary was the time to recurrence and overall death. The secondary outcome was the time to death from lung cancer and non-lung cancer.

Results: Among 2155 consecutive adult patients, there were 1,436 patients (66.6%) with adenocarcinoma (ADC) and 719 patients (33.4%) with squamous cell carcinoma (SqCC). For freedom from recurrence, patients with SqCC had better outcome than those with ADC, both in stage II (p<0.001) and III (p<0.001). For overall survival, although ADC showed slightly better survival outcome until 5 years than SqCC, there was no significant difference between them (p=0.292 for stage II and 0.196 for stage III). Patients with SqCC had increased risk of non-lung cancer death in both stage II (p<0.001) and III (p=0.039). The time from lung cancer recurrence to death was shorter in patients with SqCC than those with ADC in both stage II (median 13 vs. 37 months, p<0.001) and III (11 vs. 26 months, p <0.001).

Conclusions: In stage II and III NSCLC, patients with ADC have higher risk of recurrence than those with SqCC, without differences in overall survival. These results are due to the significant difference in non-lung cancer mortality and recurrence-to-death time between the two histologic types.





Keywords: Histology, Prgonosis, Non-small cell lung cancer

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-006 Real-World Treatment Pathways In Stage III Non-Small Cell Lung Cancer in Portugal (PICTuRE): An Interim Analysis Of Surgical Patients

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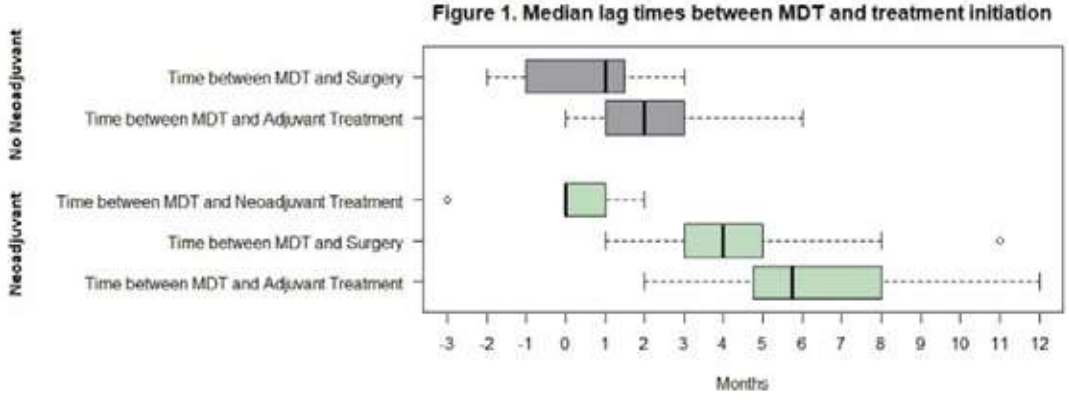
Introduction: Stage III NSCLC presents as heterogenous and questions regarding treatment remain unanswered. We aimed to portray stage III NSCLC in Portugal, focusing patients undergoing surgery.

Methods: PICTuRE is a multicentric, retrospective study with data from medical records. Eligible patients were adults with stage III NSCLC diagnosed in 2018 followed until disease progression, death, loss of follow-up or end of study. Descriptive and survival analyses were conducted.

Results: In PICTuRE 287 patients were included of which 19.8% (n=57) underwent surgery. Surgical patients' mean age was 65±9, mostly men (56.1%), 78.6% current/former smokers, 70.2% had adenocarcinoma histology, 80.7% stage IIIA and 19.3% stage IIIB, all with ECOG 0-1. All patients were submitted to non-invasive staging, while only 63.2% were submitted to minimally invasive/invasive staging methods (i.e. EBUS/mediastinoscopy). Median lag times between MDT and treatment initiation are represented in Figure 1. Neoadjuvant treatment was performed in 21 patients, mostly stage IIIA (71.4%). Pathologic response to neoadjuvant treatment was poorly reported (<25%). Most common surgery modality was lobectomy (75.4%), with 73.7% R0 and 14.0% R1/R2. Operative mortality and morbidity were 3.5% and 21.1%, respectively. Adjuvant treatment was performed in 82.5% patients (n=47: chemotherapy 34.0%; radiotherapy 12.8% and chemoradiotherapy 53.2%), mostly stage IIIA (80.9%). Survival analysis are depicted in Table1. A significant difference between mDFS in No-neoadjuvant+Adjuvant vs. No-neoadjuvant+No-adjuvant was observed. Although there were no statistical differences in mOS, clinical differences were observed between mOS in Stage IIIA-N2 vs. Stage IIIA-noN2.

Conclusions: PICTuRE reveals NSCLC-Stage III complexity: staging is yet not consensual (a relevant proportion of patients were not staged with minimally invasive/invasive methods); outcomes in surgical patients can be further improved (no statistical significance were observed between most groups). As so, future guidelines should be designed, considering the implementation of efficient multidisciplinary teams targeting optimal median times for diagnosis, staging and treatment initiation in Portugal.

Figure 1. Median lag times between MDT and treatment initiation



o observation classified as a potencial outlier using the interquartile range (IQR=P75-P25) criterion.
*IQR criterion: all observations outside of the interval [P25-1.5*IQR; P75+1.5*IQR], will be considered as potential outliers.*

Table 1. Surgical population' outcomes

	Disease Free Survival				Overall Survival		
	N	Number of Events	Median DFS (months)	p-Value	Number of Events	Median OS (months)	p-Value
Overall	57	29	25.0 (18.0-NA)		24	NA	
Stage IIIB	11	3	37.0 (37.0-NA)	0.11	3	NA	0.32
Stage IIIA	46	26	24.0 (15.0-NA)		21	37.0 (28.0-NA)	
Stage IIIA-noN2	19	11	25.0 (15.0-NA)	0.88	6	NA	0.08
Stage IIIA-N2	27	15	24.0 (15.0-NA)		15	33.0 (20.0-NA)	
No neoadjuvant	36	21	24.0 (15.0-NA)	0.21	16	NA	0.47
Neoadjuvant	21	8	37.0 (25.0-NA)		8	37.0 (33.0-NA)	
No adjuvant	8	4	7.0 (4.0-NA)	0.23	4	22.0 (5.0-NA)	0.44
Adjuvant*	47	25	30.0 (18.0-NA)		19	NA	
Adjuvant RT	6	5	21.5 (14.0-NA)	0.53	4	35.5 (33.0-NA)	0.79
Adjuvant CT	16	7	38.0 (15.0-NA)		6	NA	
Adjuvant CRT	25	13	27.5 (21.0-NA)		9	NA	
Neoadjuvant + Adjuvant	14	7	37.0 (18.0 – NA)	0.66	5	37.0 (33.0-NA)	0.69
Neoadjuvant + No adjuvant	5	1	NR		2	NR	
No neoadjuvant + Adjuvant	33	18	25.0 (15.0-NA)	<0.0001	14	NA	0.10
No neoadjuvant + No adjuvant	3	3	NR		2	NR	

DFS, disease-free survival (time from diagnosis until progression); OS, Overall survival; NA: not achieved; NR: not reported;
**adjuvant treatment was unknown for 2 patients;*

Keywords: NSCLC locally advanced, Surgery, Real Word Evidence

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-007 Comparison of Surgical Methods in Patients Receiving Neoadjuvant Treatment; Thoracoscopy vs. Thoracotomy

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Introduction: Detecting lung cancer at an early stage has become easier due to the developing diagnostic methods, the treatment modalities of patients with locally advanced stages differ. It is desired that minimally invasive methods can be used to provide local control and to perform surgery on these patients with treatment methods such as neoadjuvant chemotherapy (CT), radiotherapy (RT) and immunotherapy (ImT). In our study, we compared thoracotomy and thoracoscopic method in patients who had advanced stage non-small cell surgery who received neoadjuvant therapy.

Methods: 110 patients who received neoadjuvant treatment and were operated between 2004 and 2020 were included. Patients who did not undergo resection after neoadjuvant therapy and cases that underwent non-anatomical resection were excluded from the study. They were divided into two groups as thoracotomy thoracoscopy. Demographic characteristics, post-op complications, need for additional surgical intervention, amount of drainage, air leak duration, tumor diameter, number of lymph nodes dissected, hospitalization period and survival were evaluated.

Results: Of 110 patients operated after neoadjuvant therapy, 59 (53.63%) of them underwent thoracoscopic resection, and 51 (46.36%) with thoracotomy. As neoadjuvant treatment protocols, CT in 54 cases (49.1%), KT + RT in 39 cases (35.45%), KT + ImT in 9 (8.2%), ImT in 6 (5.5%), and 2 KT + RT + ImT (1.8%) The mean age of the patients who underwent thoracoscopy was 63.02, versus the patients who underwent resection by thoracotomy was 59.94. The mean hospitalization day of the patients who underwent thoracoscopy was 5.76, it was calculated as 8.98 days in thoracotomy group. The duration of air leakage during hospitalization was 1.30 days in patients who underwent thoracoscopy, while it was 2.85 days in thoracotomy group. A statistically significant difference was found in favor of the patients who underwent thoracoscopy in both hospital stay and air leak period ($p<0.004$). While major complications (ARDS, Emboli, etc.) developed in the post-operative period in 9 patients (17.64%) who underwent thoracotomy resection, major complications were observed in only 1 (1.69%) of the patients who underwent thoracoscopy. Post-operative hemorrhage, prolonged air leak, etc. were observed in 6 (11.7%) of the cases who underwent thoracotomy and in 1 (1.69%) of the cases who underwent thoracoscopy. Additional surgical intervention was required for such reasons. A statistically significant difference was found in terms of both major complication rates and the need for additional intervention in the postoperative period ($p<0.009$). There was no statistically significant difference between the number of lymph nodes removed in resections and lymph node stations dissected between the two groups. As of January 2022, a statistically significant difference was observed in terms of survival in patients who underwent thoracoscopy compared to those who underwent thoracotomy ($p<0.005$).

Conclusions: The chance of surgery after neoadjuvant therapy should definitely be considered in advanced stage non-small cell lung cancer. We believe that thoracoscopic anatomic resections should be preferred in cases suitable for surgery, without compromising oncological principles, due to shorter hospital stay and less post-operative complications.

Keywords: Neoadjuvant therapy, thoracoscopy, thoracotomy

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-008 Surgery after First-Line Alectinib for (Locally) Advanced ALK-rearranged NSCLC: Pathological Response and Peri-Operative Results

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Introduction: The role of surgery after 1rst-line alectinib for is largely unexplored. We aimed to describe the pathological features and surgical early-outcomes of patients undergoing salvage surgery in this framework

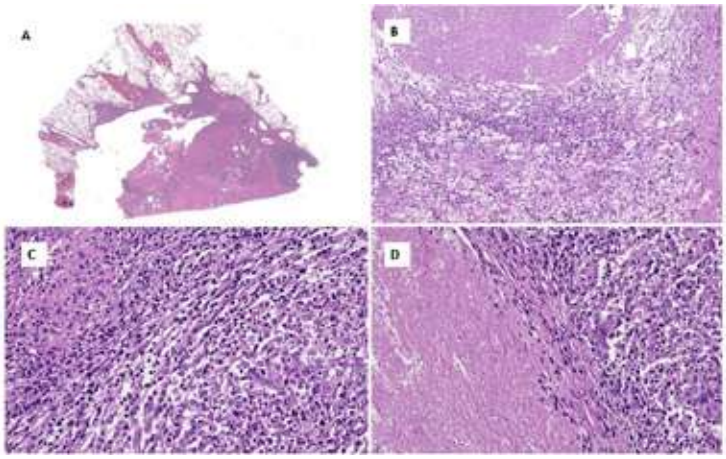
Methods: We retrospectively collected and analyzed multicentric data (from 6 Oncological Centers) of 9 patients treated with alectinib for Stage III-IV non-small cell lung cancer (NSCLC) who underwent anatomical surgical resection from 01/2020 to 12/2021. All the patients were treatment naive and received alectinib at a starting dose of 600 mg twice daily. Surgery was proposed only after discussion at local multidisciplinary tumor board. The primary endpoints were pathological response and surgical feasibility (technical intra-operative complications, post-operative outcomes).

Results: Alectinib was received for a mean of 229 days before surgery (42-415 days) and was generally interrupted one week before surgery (range: 0-32 days) with no patient experienced grade 4 toxicity (see Table 1). All patients received an R0 resection with surgery consisting mostly of lobectomy in 7 cases with bilobectomy and (left) pneumonectomy in one case each. Intra-operative difficulties were described in 6 cases (67%), mostly due to perivascular fibrosis or thickening of mediastinal lymph nodal tissues. Major and minor complications occurred in 0 and 3 cases (33%), respectively. A pathological complete response and major pathological response (defined as 0% and <10% viable tumor cells, respectively) were observed in 55% and 88%, respectively (see Table 2 and Figure 1). Despite the follow-up was inconsistent to drawn any conclusion, we observed only one tumor recurrence (brain metastases 9 months after surgery) in the only patient who did not received alectinib after surgery

Conclusions: Despite some technical intra-operative difficulties, salvage surgery was safe and feasible after alectinib for (locally) advanced NSCLC and an impressive pathological response may be often obtained in the surgical specimens.

Clinical characteristics, Surgical Notes and Pathological Features of the study group

Patient No.	Sex/ Age	Tumor Acquisition	cTNM	Type of ALK rearrenge-ment	Duration of Alectinib Therapy (days)	Interruption before surgery (days)	Surgical Approach	Surgical resection (surgical time in minutes)	Surgical difficulties	Post-operative Compli-cation	RECIST v 1.1	Tumor Shrink-age	pTNM	PCR	% viable cells	% necro-sis	% stroma	MPR	Post-operative treatment	Overall Survival (months)	Time for relapse (Site)
1	M / 66	CT-GUIDED FNAB	cT3N2Mo	EML4-ALK trans-location	214	6	Thoracotomy	225	Perivascular fibrosis	Prolonged air leak	PR	95,0%	pT0N0M0	Yes	<1%	40%	60%	Yes	Alectinib	11	-
2	M / 72	ENDOSCOPIC-TBNA	cT4N2M0	EML4-ALK trans-location	194	6	Thoracotomy	192	Perivascular fibrosis	Chylothorax	PR	90,0%	pT0N0M0	Yes	<1%	50%	50%	Yes	Alectinib	9	-
3	M / 71	ENDOSCOPIC-TBNA	c T3N2M0	EML4-ALK trans-location	308	5	Thoracotomy	240	Perivascular fibrosis	-	PR	95,0%	pT0N0M0	Yes	<1%	20%	80%	Yes	-	15	9 (Brain)
4	M / 56	EBUS-TBNA	cT4N2M0	EML4-ALK trans-location	42	3	Vats	260	-	-	CR	100,0%	pT0N0M0	Yes	<1%	20%	80%	Yes	Alectinib	2	-
5	F / 49	EBUS-TBNA	cT2N2M0	EML4-ALK trans-location	254	32	Thoracotomy	152	Difficult mediastinal nodal dissection	-	PR	25,0%	pT3N2M0	No	40%	20%	40%	No	Alectinib	1	-
6	M / 41	EBUS-TBNA	cT1cN2M1	2p23-ALK rearrange-ment	415	0	Robot	159	-	Anemia	PR	75,0%	pT1a(m) N0M0	No	2%	0%	98%	Yes	Lorlatinib	15	-
7	M / 60	EBUS-TBNA	cT3N2M0	2p23-ALK rearrange-ment	178	2	Vats	177	-	-	PR	95,0%	pT0N0M0	Yes	0%	2%	98%	Yes	Alectinib	3	-
8	F / 55	EBUS-TBNA	cT4N2M1	2p23-ALK rearrange-ment	292	3	Vats	292	Perivascular fibrosis	-	PR	90,0%	pT2N0M0	No	<10%	80%	10%	Yes	Alectinib	3	-
9	M / 64	EBUS-TBNA	cT2bN2M1	EML4-ALK trans-location	170	6	Thoracotomy	170	Perivascular fibrosis and difficult mediastinal nodal dissection	-	PR	47,60%	pT1bN2M0	No	<10%	30%	60%	Yes	Alectinib	2	-



Keywords: alectinib, lung surgery, ALK-rearrangement

EP05.03-009 Prognostic Impact of Tumor Volume Doubling Time for Resected Squamous Cell Carcinoma of the Lung

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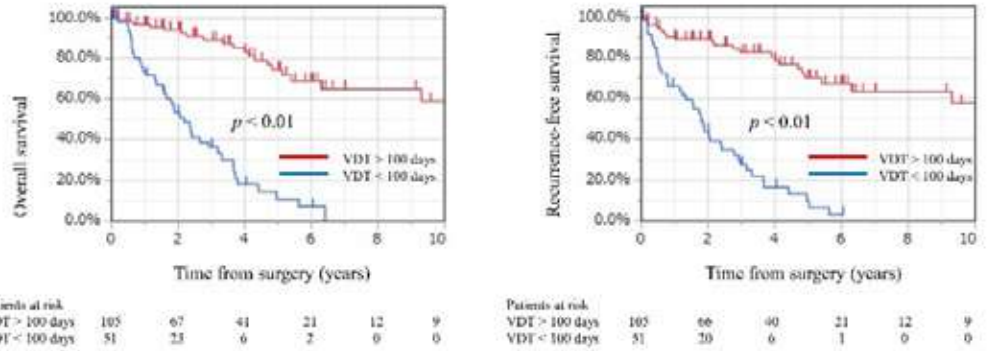
Introduction: This study aimed to investigate whether tumor volume doubling time (VDT) could be a prognostic factor in resected squamous cell carcinoma of the lung.

Methods: Overall, 233 patients who underwent an anatomic pulmonary resection for squamous cell carcinoma between January 2006 and April 2020 were retrospectively reviewed. Patients were excluded if they had no interval of computed tomography (CT) date between lung nodule detection and preoperation ≤1 month, had undergone induction therapy, or had undergone wedge resection or pneumonectomy. After exclusion, a total of 156 patients were analyzed. VDT was calculated as [VDT (days) = $(T_2 - T_1) \times \log 2/(\log V_2 - \log V_1)$]. T_2 was the date of the last CT prior to surgery; T_1 was the date of the first CT detection of the lung nodule. V_2 and V_1 were the volumes of the tumors at T_2 and T_1, respectively. The volumes were measured as follows: (tumor volume, cm^3) = $1/6 \times \pi \times X \times Y^2$, where X refers to the diameter in the long-axis direction [cm], and Y refers to the diameter in the short-axis direction [cm] on axial CT images.

Results: This study included 140 males and 16 females with a median age of 76 years (range 52-86 years). The median VDT was 163 days. Univariable analysis identified tumor diameter on CT (>3.0 cm) and VDT (<100 days) as significant prognostic factors for overall survival (OS). Multivariable analysis identified tumor diameter on CT (>3.0 cm; Hazard ratio (HR) = 1.75, $p = 0.04$) and VDT (<100 days; HR = 7.24, $p < 0.01$) as significantly independent prognostic factors for OS. Univariable analysis identified standardized uptake value (SUV) max of the tumor (>15), tumor diameter on CT (>3.0 cm), and VDT (<100 days) as significant prognostic factors for recurrence-free survival (RFS). Multivariable analysis identified only VDT (<100 days; HR = 6.15, $p < 0.01$) as a significantly independent prognostic factor for RFS. The 5-year OS was 74.5% in the group with long VDT (>100 days) and 10.9% in the group with short VDT (<100 days) ($p < 0.01$). The 5-year RFS years was 70.0% in the group with long VDT (>100 days) and 6.7% in the group with short VDT (<100 days) ($p < 0.01$) (Figure).

Conclusions: VDT could affect a significant prognostic impact for resected squamous cell carcinoma of the lung.

Figure. The overall survival and recurrence-free survival curves for all the eligible patients divided by the long tumor volume doubling time (>100 days) and short tumor volume doubling time (<100 days).



Keywords: squamous cell carcinoma, tumor volume doubling time, prognostic factor

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-010 Extended Resection of Non-small Cell Lung Cancer with Superior Vena Cava Involvement: A Systematic Review and Meta-analysis

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Introduction: Lung cancer is the most common cause of cancer deaths worldwide. Rarely, non-small cell lung cancer (NSCLC) invades the mediastinum, especially the superior vena cava (SVC), where surgery is not usually offered. However, advances in surgery allow for careful selection of candidates who might benefit from it. Nevertheless, no systematic review and meta-analysis has evaluated this treatment strategy's short and long-term outcomes; thus, results remain elusive.

Methods: We conducted a systematic search on PubMed, EMBASE, Scopus to retrieve studies on extended resection of NSCLC with SVC involvement. Our primary outcome was survival data represented by 1-, 3-, 5-, and 10-year overall survival (OS). Our secondary outcome was 30-day operative mortality. A mixed-effects meta-regression model was applied to investigate the effect of tumor histology, pathological N stage, type of surgical procedure, and achieving a complete resection on 5-year OS.

Results: We have included nine observational studies involving 341 patients. Patients' median/mean age ranged from 57 to 64 years. From the reported data, most patients were males (83%), 50% had a squamous cell carcinoma histology, 57% had a pathological N0-1 disease, and 39% had N2 disease. Pneumonectomy was performed in 49% of patients, lobectomy in 48%, and sublobar resection in 3%. As for perioperative therapies, 20% of patients underwent neoadjuvant therapy, and 37% underwent postoperative adjuvant therapy. Among 341 patients, 74% achieved complete resection (R0). Meta-analysis of 315 patients from 7 studies resulted in a pooled 5-year OS rate of 24.8% (95% CI: 16.9 to 33.6%), with moderate heterogeneity (I^2 = 61%, p = 0.02). We carried out a sensitivity analysis by removing a study that reported a 0% survival rate, resulting in a pooled 5-year OS of 26.8% (95% CI: 21.8 to 32.1%) with low heterogeneity (I^2 = 22%, p = 0.27), which represented 302 patients. Three-year OS was reported by 5 studies that contained 196 patients, pooled 3-year OS was 30.8% (95% CI: 16.0 to 47.8%, I^2 = 75%, p < 0.01). Two studies reported 10-year OS rates of 23.1% and 35.4%. Operative mortality rates ranged from 4.7% to 13.3% in six studies. We have found that the percentage of patients with N2 stage disease is associated with lower 5-year OS across studies (OR = 0.54, 95% CI: 0.31 to 0.94, p = 0.03). Patients with complete resection were more likely to have a higher 5-year OS, but with borderline significance (OR = 2.32, 95% CI: 0.90 to 5.98, p = 0.08).

Conclusions: Extended resection for NSCLC invading the SVC is worth being performed. It is associated with better survival rates with an acceptable morbidity and mortality rate.

Keywords: NSCLC, Superior vena cava, Locally advanced

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-011 Bilateral Orthotopic Lung Transplantation for a Patient with Advanced Invasive Mucinous Adenocarcinoma

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Introduction: Invasive mucinous adenocarcinoma (IMA) is a rare type of lung cancer associated with poor prognosis since systemic chemo- and immunotherapies are generally ineffective and lack of actionable genomic alterations often preclude targeted therapy. While organ transplantation is excluded in patients with solid malignancies, we hypothesized that tumor extirpation through bilateral lung transplantation in a patient with lack of systemic metastasis could be a life-saving treatment in medically refractory IMA.

Methods: case report

Results: A 53-year-old man diagnosed with bilateral diffuse IMA (Stage IIIA T4N0M0, well-differentiated, PD-L1 TPS <1%) revealed lack of actionable mutations with tumor mutation burden of 1.6 and mutation variants of unknown significance on next-generation sequencing (NGS) of tissue biopsy and serum. Additionally, extrathoracic disease was absent on brain MRI and whole-body PET CT imaging.

Despite three standard of care treatments [5 cycles of carboplatin/pemetrexed/pembrolizumab (3 weeks/cycle), 6 cycles of docetaxel/ramucirumab (3 weeks/cycle), and 2 cycles of vinorelbine and gemcitabine (3 weeks/cycle)], and a clinical trial with EZH2 inhibitor, cancer continued to progress.

While hospice care was discussed, consideration was given to bilateral orthotopic lung transplantation (BOLT) given the lack of systemic and nodal metastasis. Evaluation process for transplant was started. In the meantime, the patient was started on lenvatinib 20 mg daily in combination with ipilimumab and nivolumab which corresponded with clinical improvement.

Then medical conditions deteriorated with development of respiratory failure, spontaneous bronchopleural fistula necessitating tube thoracostomy, and pneumonia with sepsis. The patient was admitted to ICU, and BOLT was performed using cardiopulmonary bypass after a cumulative waitlist time of 17 days. Complete cancer extirpation and mediastinal lymph node dissection were accomplished without complications. At 6 months following transplantation, the patient is breathing on room air, with forced expiratory volume in 1 second > 80% predicted, and reports independence for activities of daily living. At 1 and 3 months, the minimal residual disease was absent using an assay utilizing circulating tumor DNA based on 16 somatic variants selected from whole-genome sequencing of primary cancer sample and matched normal tissue. Additionally, repeat chest imaging and lung biopsies after six months from surgery indicated a lack of recurrent disease.

Conclusions: BOLT was successfully performed in a patient with medically refractory and terminally-advanced IMA with no detectable recurrence at 6 months despite the use of immunosuppression. The benefit of BOLT in carefully selected patients with IMA without systemic metastasis should be further investigated in prospective studies.

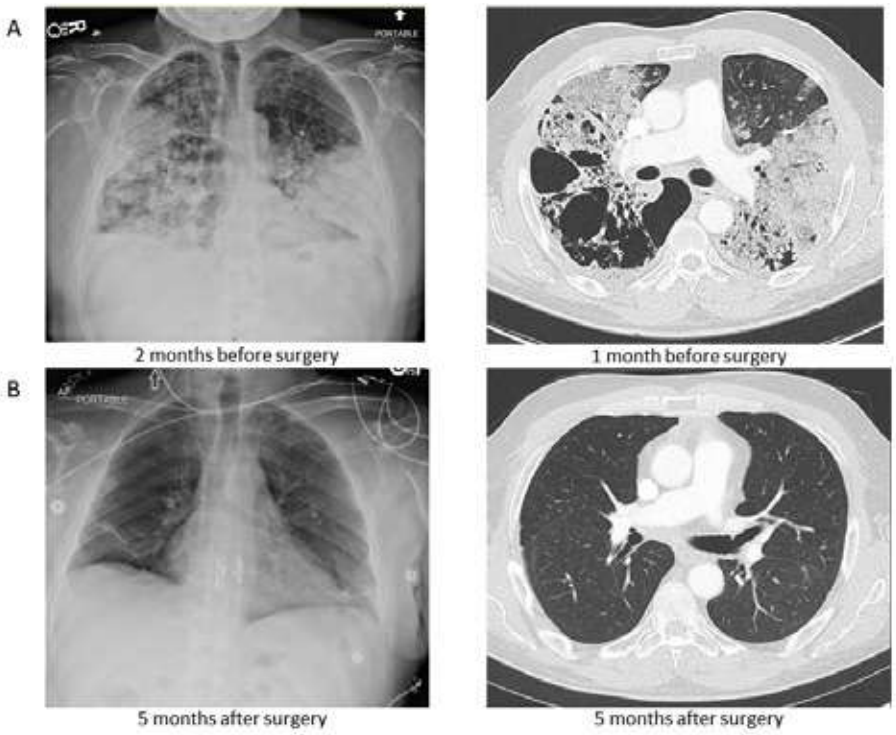

Figure 1. Chest X ray and CT scan before (A) and after (B) lung transplantation

Keywords: invasive mucinous adenocarcinoma, Bilateral orthotopic lung transplantation, minimal residual disease

EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY

EP05.03-012 Deep Learning-based Classifier to Predict Intensified Locoregional Approach Need in Stage III Non-Small Cell Lung Cancer

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Introduction: The prognosis varies greatly in stage III non-small-cell lung cancer (NSCLC) patients after complete resection. Patients in this stage have a high risk of disease recurrence even after receiving postoperative chemotherapy. Locoregional recurrence (LRR) is one of the major patterns of failure after surgery. Current methods of staging could not predict the risk of LRR for patients accurately. This study aimed to develop a deep learning-based classifier to predict the risk of LRR in stage III NSCLC patients using preoperative thoracic computed tomography (CT) images.

Methods: We enrolled 588 patients who were diagnosed as completely resected pathologic stage T1-3N2M0 NSCLC and did not receive postoperative radiotherapy. Patients were randomly divided into a training set, validation set, and independent testing set (4:1:2). The training set and validation set were collectively referred to as the development set. Significant clinical prognostic factors for LRR were identified by univariate Cox proportional hazard (CPH) regression with a P value less than 0.1. Afterward, we proposed a novel multi-scale and multi-task attention neural network (MSTA-net) to predict the LRR risk of patients using preoperative CT images. The network was trained in an end-to-end manner in the training set and tuned in the validation set. When the training process was finished, the MSTA-net would output a deep learning prediction score (DL-score). Furthermore, a hybrid model incorporating the DL-score and clinical factors with multivariable CPH regression was constructed in the development set and independently validated in the testing set. The discriminative ability of the model was evaluated with the concordance index (C-index) and hazard ratio (HR).

Results: Smoking history, clinical N category, tumor size, involved N2 stations, skip N2 and the ratio of positive lymph nodes were identified as significant prognostic factors. The CT-based DL-score can effectively predict the risk of LRR for patients in the development set (C-index: 0.747, 95% confidence interval [CI]: 0.645-0.828) and independent testing set (C-index: 0.663, 95% CI: 0.500-0.794). Moreover, integrating the DL-score with clinical factors can significantly improve the predictive value compared to the clinical model in the development set (C-index: 0.748, 95% CI: 0.646-0.829 versus C-index: 0.621, 95% CI: 0.514-0.717; P < 0.001) and testing set (C-index: 0.677, 95% CI: 0.515-0.806 versus C-index: 0.611, 95% CI: 0.449-0.751; P = 0.036). Furthermore, the hybrid mode can significantly stratify patients into high-risk and low-risk subgroup of LRR in the development set (HR: 4.355, 95% CI: 3.058-6.203; P < 0.001), which was validated in the testing set (HR: 2.449, 95% CI: 1.442-4.158; P < 0.001).

Conclusions: The deep learning-based classifier could predict the individual risk of LRR in patients with stage III NSCLC and help physicians to identify a subtype of patients who probably need an intensified locoregional approach.

Keywords: stage III non-small cell lung cancer, locoregional recurrence, deep Learning-based classifier

EP06.01-001 The Longitudinal Impact of COVID-19 on the Diagnosis and Treatment of Lung Cancer at a Canadian Academic Centre: A Retrospective Chart Review

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Introduction: The COVID-19 pandemic presented many challenges to the delivery of healthcare, especially for those with lung disease.Our group recently reported that the rate of new lung cancer diagnoses declined by 35% during the first year of the COVID-19 pandemic (year 2020). The objective of the present study is to evaluate the changes in new lung cancer (LC) diagnoses during the 2 years of the pandemic compared to the pre-pandemic era, and its subsequent effect on survival of lung cancer patients.

Methods: This is a retrospective chart review study including patients diagnosed with lung cancer between March 1st 2019 and February 28th 2022 at the Peter Brojde Lung Cancer Centre at the Jewish General Hospital, Montreal. We compared 3 cohorts: Cohort 1 (C1): March 1, 2019 to February 29, 2020 (pre-COVID). Cohort 2 (C2): March 1, 2020 to February 28, 2021 (1st year of COVID). Cohort 3 (C3): March 1, 2021 to February 28, 2022 (2nd year of COVID; reporting for 11 months).

Results: A total of 404 patients were diagnosed with lung cancer throughout the three-year study: 130 in C1, 103 in C2 and 171 in C3. Using C1 as a baseline, we found that new diagnoses of LC declined by 21% in C2, and rose by 32% in C3. The incidence of metastatic lung cancer increased by 41% in 2021 compared to 2019 (96 cases vs 68 cases) and by 63% compared to 2020 (96 cases vs 59 cases). Of the 59 metastatic LC patients diagnosed in 2020, 31 (52%) died, whereas 28/68 (41%) died in 2019. The median survival for metastatic LC in the first year of the pandemic decreased compared to pre-COVID year (14.5 vs 8.7 months) (Table 1). Statistical significance has not been reached as follow-up time was not long enough for year 2020 (p=0.58).

Conclusions: The present study represents interim data of our ongoing effort to evaluate the effect of the COVID-19 pandemic on our lung cancer patients. The pandemic has led to a significant decline in LC diagnoses in the first year, and a subsequent increase in diagnoses during the 2nd year. Unfortunately, these changes resulted in a trend towards decreased survival for our metastatic LC patients. The final survival analysis will require longer follow-ups and this data will be presented at the meeting.

Table 1. Median survival for Stage 4 lung cancer

Group	N	MedianSurvival (months)	Standard Error	95% Confidence Interval
Cohort1	68	14.47	3.23	8.15-20.79
Cohort2	96	8.73	4.90	0.00-18.34
Total	164	13.10	2.57	8.06-18.14

Keywords: COVID-19, Retrospective, Survival

EP06.01 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19

EP06.01-002 Cancer Care in a Time of COVID: Lung Cancer Patient's Experience of Telehealth and Connectedness

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Introduction: As health care systems have raced to prepare for, and manage, the SARS-CoV-2 (COVID19) pandemic, we have seen a reorganization of how health care is delivered. Delivery of cancer care has been affected globally. New Zealand (NZ) entered their highest restriction level in March 2020, essentially locking down the country for all but essential services for a period of five weeks. Reprioritization of healthcare services began. Auckland Regional Cancer and Blood Service, which provides oncology services for a population of approximately 1.72 million quickly implemented pathways to protect vulnerable patients. This included a shift from on-site clinic visits to telehealth. The current literature suggests that while telehealth offers an alternative approach to care delivery, there are a number of factors for consideration. Virtual assessments may offer a reduction in patient related costs such as petrol, travel, time off work, and childcare. In addition, some patients have reported that a virtual assessment is less stressful than attending a face to face consultation. Clinicians have identified convenience and flexibility with virtual consultations, and expressed the addition of tools such as email and texting could facilitate assessments in the cases of patients who were too anxious to attend face to face consultations. However, the research raises concerns regarding telehealth, including the potential for increased clinical risk and future uptake of services. Challenges related to technology, including familiarity of use, access to internet and data, and confidentiality are all ongoing concerns for services planning virtual assessments and remote care delivery.

Methods: 30 patients with lung cancer were recruited. Data was collected using a qualitative exploratory design with semi-structured interviews. Transcripts were thematically coded using NVivo software.

Results: Five key themes were identified. 1) Maintaining resilience: participants acknowledged they were self-reliant prior to their diagnosis, and that the sense of their own internal capabilities was a source of comfort for them.2) Importance of pre-established relationships with healthcare professionals: the sense of connection established prior to the telehealth consultation supported participants to engage with healthcare professionals. The need for connectedness was amplified by a sense of isolation. 3) Seeking help: participants sought help from services that they perceived as being "expert".4) Convenience: factors such as costs and saving time were highlighted.5) Preferences for consultation type: majority of participants identified physical and emotional comfort being in their own space. For a small number of patients, continuing a face to face assessment was important due to expectation based on previous experience.

Conclusions: The use of telehealth was supported during the management of COVID-19. Connectedness and convenience were key to the level of comfort and confidence for patients with lung cancer using telehealth during 'lockdown'.

Keywords: COVID-19, lung cancer, resilience

EP06.01 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19

EP06.01-003 Impact of COVID-19 on Lung Cancer Patients; The Patients' Perspective

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Introduction: Delays and disruptions in cancer care throughout the COVID19 pandemic have created additional stressors for cancer patients. Following the second wave of the COVID19 pandemic in Alberta, we surveyed a convenience sample of cancer patients undergoing treatment at the Tom Baker Cancer Centre in Calgary, Alberta, Canada to evaluate the effect of the pandemic on patients' treatment decision-making, and cancer care experiences.

Methods: A-24 item patient survey was constructed based on the results from literature review, existing instruments and iterative feedback from medical oncologists, nurses, and a patient volunteer. The survey included items measuring patients' health concerns, delays/cancellations in treatments, attitudes towards vaccination, and virtual care. Between January to March 2021, 161 patients with different types of cancer were accrued, of which 54 had lung cancer. Patient and treatment-related factors were collected from review of the electronic medical record. Descriptive statistics were utilized to describe the cohort and survey responses.

Results: Fifty-four (n=54) patients with lung cancer completed the survey. The median age of patients was 71.5 years (46-84 years), 59% (n=32) were female, and 69% (n=37) of the patients had non-small cell lung cancer. Among surveyed patients 9% (n=5) had surgery, 46% (n=25) had radiation therapy, 59% (n=32) had chemotherapy, 39% (n=21) had immunotherapy and 7% (n=4) were treated with targeted therapy. 85% (n=46) of the patients were stage IV and thus treated with palliative intent therapy. Our survey showed that 57% (n=31) of the patients agreed or strongly agreed that they were at increased risk of contracting COVID19, and 52% (n=28) were afraid of dying from COVID19. Similarly, 48% (n=26) felt uncomfortable or anxious thinking about COVID19, 9% (n=5) had trouble sleeping, 9% (n=5) reported their hands felt clammy, and 5% (n=3) experienced palpitations. Despite patients' fears of COVID19, none reported their concerns impacting their decision-making around cancer treatment. In our survey, 56% (n=30) had undergone COVID19 testing, but only two tested positive: one had to delay palliative treatment, while the other curative-intent patient had no changes in the treatment plan. Regarding the COVID19 vaccine, 70% (n=38) patients were willing to get vaccinated, whereas 9% (n=5) patients were not comfortable with getting the COVID19 vaccine; 20% of the patients were uncertain if they would proceed with vaccination against COVID19. About 69% (n=37) of patients reported changing from in-person clinic assessments to virtual care; all were satisfied with their appointments. Similarly, 94% (n=51) reported being very comfortable with the measures taken by the healthcare team to minimize the risk of COVID19 during their in-person appointments.

Conclusions: Our survey highlights that despite a high degree of concern about COVID19 among lung cancer patients on active therapy, their treatment decisions were seemingly not affected by their fears/anxiety. Our patients were satisfied with the transition to virtual care during the pandemic. The interaction between oncologists and patients should be persistent and augmented with effective platforms for continuous and improved health outcomes.

Keywords: COVID19, lung cancer, treatment decisions

EP06.01-004 Lung Cancer Resection During the Covid-19 Pandemic: A Single Centre Study

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Introduction: During the Covid-19 pandemic, less invasive alternatives to surgery were recommended to minimise the risk of patient exposure to the virus. Therefore, this study aimed to assess the impact of covid-19 on lung cancer resections.

Methods: We retrospectively analysed lung resections between March 2019 and May 2021. Eligibility criteria included patients with confirmed non-small cell lung cancer. We divided the patients into Group A (lung cancer resection between March 2019 and February 2020 and Group B (lung cancer resection between March 2020 and May 2021. The WHO declared Covid-19 a pandemic on 11th March 2020. The outcome measures were (1) the number of lung resections, (2) the completed waiting period and (3) Survival between the two groups

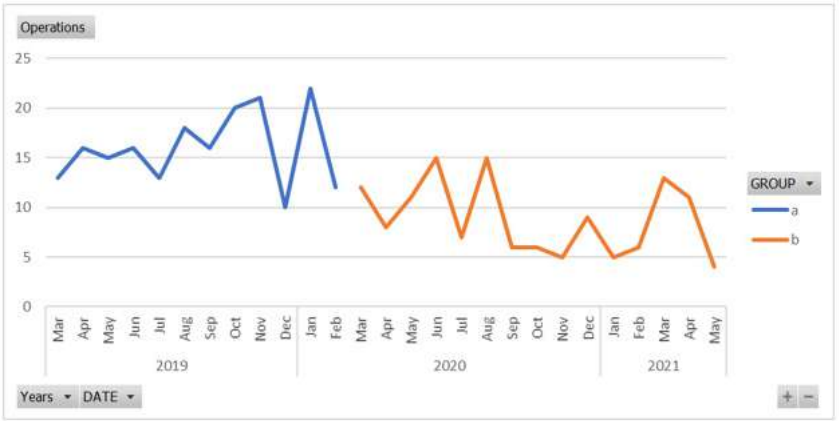
Results: In Group A, 192 (78.7%) were for primary lung cancer, while in Group B, 133 (71%) were for primary lung cancer ($p<0.05$).

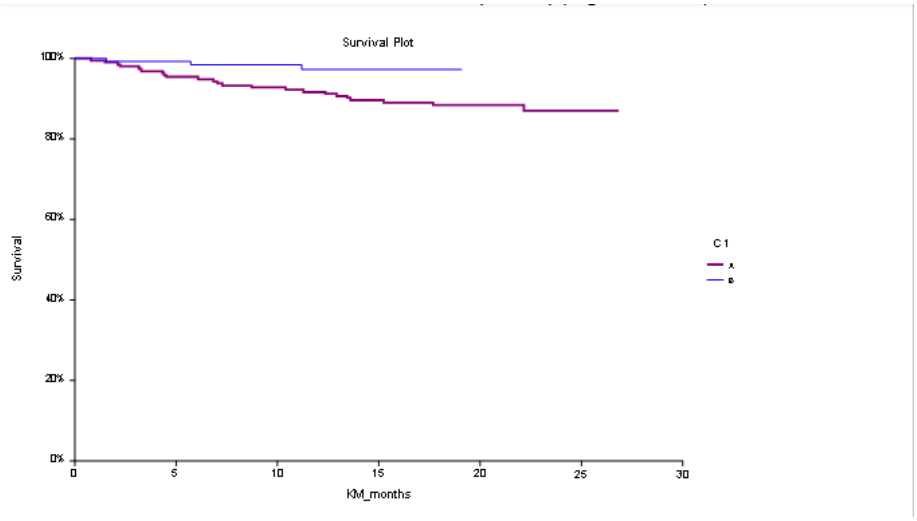
The mean completed waiting period for Group A patients was 71.85±60 days (median 58 days; R 5-449 days), while the mean completed waiting period in Group B patients was 45.2±34 days (median 38 days; R 4-213 days) ($p<0.0001$).

The mean survival times for Group A & B were 17.8 and 18.7 months, respectively (Logrank = 0.015). In Group A, survival at 30-days, 90 days and 1-year was 99.48%, 98% and 91.67%) respectively. In Group B, survival was 100%, 99.25%, and 97.1% at 30-days, 90 days, and 1-year

Conclusions: We found a 30.7% decrease in the lung cancer resection volume. Also, the completed waiting times for lung cancer resection decreased by 26.51 days during the study period. Early survival was better in Group B patients than Group A. Recoded staging figures reflected higher pathological stages in the latter group (p=0.04). Additionally, subgroup analysis showed that we operated on more stage-1 lung cancers in Group B vs Group A (63.4% vs 54.2%).

Figure 1: Operations done between 2019 and 2021





Keywords: Lung cancer resection, Covid-19, Survival

EP06.01 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19

EP06.01-005 COVID-19 and Post-COVID Outcomes in Lung Cancer Patients: Experience from an Indian Cancer Center

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Introduction: Patients with lung cancer appear to be at higher risk of COVID-19 related complications and mortality. There is limited data on COVID-19 outcomes in lung cancer patients, particularly from India. Studies have rarely included post-COVID morbidity and mortality in cancer patients.

Methods: In this single center study, a prospectively maintained database of lung cancer patients who were diagnosed with COVID-19 infection between May 1, 2020 and November 30, 2021 was used to assess the outcomes, and to identify the factors associated with mortality and intensive care unit (ICU) admission. 30-day post-COVID mortality was assessed in patients who recovered.

Results: A total of 54 lung cancer patients with COVID-19 were identified (mean [SD] age, 61.8 [8.5] years; 20.4% women, 79.6% men), of whom 74.1% had advanced stage disease. Recent treatment (within 30 day preceding COVID-19 diagnosis) was received by 77.8% of the patients (53.7% with systemic chemotherapy, 23.8% with tyrosine kinase inhibitors, and 5.6% with immune-checkpoint inhibitors). Patients requiring hospitalization and ICU admission were 59.3% and 16.7% respectively. In-hospital mortality during the same admission was 24.1%. Total mortality including the 30-day post discharge period was 40.7%, while in 18.5% patients there was no further follow up after discharge from hospital. Cancer progression was detected in 11.1% of patients and 29.6% had performance status (PS) decline making them ineligible for further systemic anticancer therapy. Among various factors tested only progressive disease (PD) in the last response evaluation preceding COVID-19 diagnosis was associated with mortality (p=0.005).

Conclusions: Lung cancer patients with COVID-19 infection had a high rate of complications and mortality. Patients with progressive lung cancer diagnosed with COVID 19 were at higher risk of death. Mortality, cancer progression, and PS decline were also high in this group of patients in a 30-day period following COVID-19 recovery.

Keywords: COVID-19, Lung Cancer, Mortality

EP06.01 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19

EP06.01-006 Multidisciplinary Team during the COVID-19 Pandemic: The BE-PACIFIC Italian Observational Study Analysis

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Introduction: COVID-19 pandemic outbreak in Italy started in February 2020 in Codogno (LO) and rapidly spread to most of the country. National and local regulators soon implemented emergency measures, including a generalized lockdown and reorganization of health institutions in response to the pandemic. BE-PACIFIC (Italian oBsErvational study on Patient mAnagement strategies in real-world Clinical practice For patIents with loCally advanced (stage III) NSCLC) is a multicenter observational retro-prospective cohort study designed to describe the management of patients with stage III NSCLC in the Italian real-life setting. Study includes patients with confirmed diagnosis of Stage III NSCLC at enrolment or within the prior 6 months. A total of 296 eligible patients were analysed between July 2020 and July 2021 in 40 participating Italian sites.

Methods: A subject-level analysis was performed on 296 eligible patients' diagnostic procedures, treatment strategy and tumor resection. A site-level analysis was performed on 40 participating sites, in order to explore the COVID-19 pandemic impact on NSCLC diagnosis, treatment practice, including multidisciplinary team (MDT) management. Site-level data were collected through survey to physicians involved in the MDT to describe different scenarios encountered during the pandemic: most acute lockdown phase and time of loosening of COVID-19 health restrictions in Italy (between 1st and 30th sept 2021).

Results: A total of 222 patients were diagnosed and included before the first COVID-19 lockdown imposed on 10 march 2020, 74 patients completed the diagnostic process during the pandemic outbreak. During the pandemic, 26 sites (65%) declared impact on diagnosis and patient management: 55% declared changes in follow-up contacts modalities, 45% delays in radiological evaluations, 40% reported decreased number of diagnostic evaluations performed, 33% reported a decreased number of NSCLC diagnosis. MDT survey was completed by 39 sites. During the most acute phase of the pandemic, 5 sites (12.8%) reported absence or temporary absence of MDT meetings, 22 sites (56.4%) reported reduced MDT activity with respect to pre-COVID-19 outbreak, 12 sites (30.8%) reported regular MTD activity. Changes in MDT modalities and schedule persisted in 7 sites (18%) after the most acute phase of the pandemic (September 2021). Patients' diagnostic process suffered reduced healthcare professionals presence: -28% of pathologist involvement, -23% of molecular biologist, -14% nuclear medicine physician, -13% of radiation oncologist, -11% of surgeon, -10% of pneumologist. Delayed surgery procedures were reported for 13 sites (32.5%); 5 sites (12.5%) reported delayed start of treatments. Sites reported changes in treatment type (13%) and schedule (18%), including minimization of hospital access, reduction of prescribed therapy dose and altered fractionation of radiotherapy.

Conclusions: MDT meeting activity changed in most participating sites during the acute phases of the pandemic, with potential impact on patient journey. Site-level data collected after the acute phase suggest that changes in MDT composition and schedule might not be reverted to pre-pandemic status in the short term. Pandemic seems to have impacted the diagnostic and monitoring processes more (65%) than the cancer treatment practice (45%) of participating sites.

Keywords: COVID-19, Stage III NSCLC, Multidisciplinary Team

EP06.01-007 Fate of Pneumonectomy Patients During Covid-19 Pandemic

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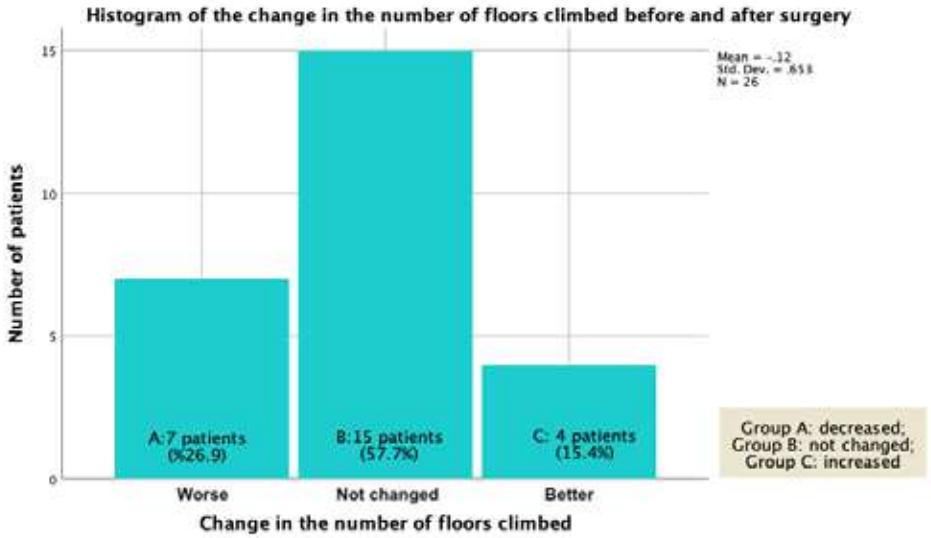
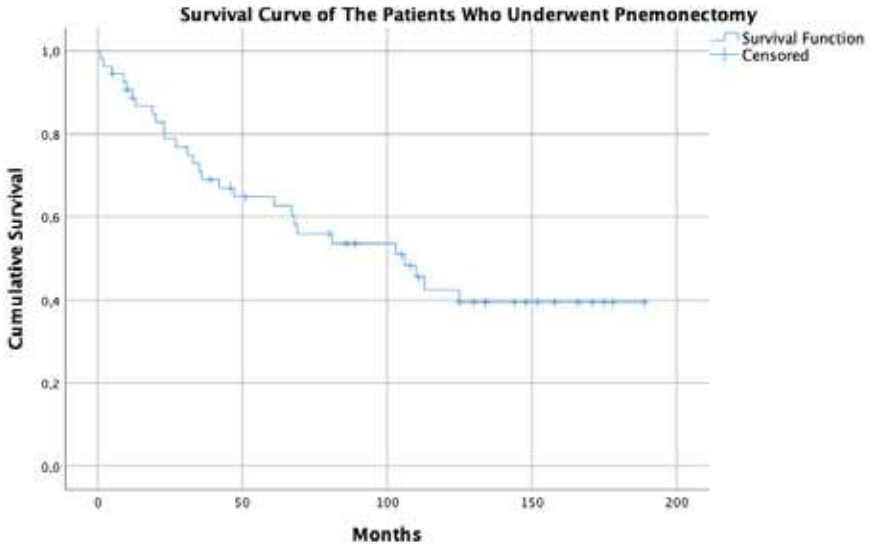
Introduction: The best treatment modality for lung cancer patients relies on survival estimates to weigh risks and benefits of treatments. However, patients who had pneumonectomy may have inherent oncologic or physiologic survival challanges. We aimed to analyzed the physiologic and survivability consequences of COVID-19 in these patients.

Methods: A total of 111 of 898 patients(12.3%) who underwent resection in our clinic between 2001-2021 underwent pneumonectomy. Data of 70 patients were completed and the remaining 41 patients were excluded from the study for various reasons. The patients' survival, daily physical activities, comparison of preoperative and postoperative physical activity, and the general condition of those who had COVID-19 were questioned.

Results: Sixty-seven patients were male (95.7%), three patients were female (4.3%). Forty patients (57.14%) had left pneumonectomy whereas 30 patients (42.85%) had right pneumonectomy. While 26 people (37.1%) were alive, 44 patients (62.9%) died. Four patients were suffered from COVID-19 infection and two of them died. Mortality was 50.0% whereas 1 (3.8%) and 2 (7.7%) patients had had extremely poorer and poorer physical activity compared to those of before pneumonectomy respectively, 9 patients (34.6%), 10 (38.5%) and 4 (15.4%) had same, better and extremely better physical activity compared to those of prior to pneumonectomy respectively. Estimated survival of all patients was 106 months (at the (95% confidence interval [CI]:58.69-153.30 months). The median survival of patients with right pneumonectomy was 103 months (95% CI:56.0-150.0 months) whereas it was 110 months (95% CI:45.5-174.5 months) in patients who had left pneumonectomy (p=0.859).

Conclusions: The mortality due to Covid-19 was very high following pneumonectomy although the prevalence of COVID-19 seemed low in those patients. The physical activity was found to be worsened in small fraction of patients after pneumonectomy. Pneumonectomy seems safe and not debilitating in select patients even in Covid-19 era.





Keywords: Covid-19, Pneumonectomy, Quality of Life

EP06.01 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19

EP06.01-008 COVID-Protected Pathways for Image Guided Lung Cancer Intervention During the COVID-19 Pandemic: A Cohort Study

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Introduction: The COVID-19 pandemic has driven the development of novel patient flow pathways to separate patients with suspected COVID-19 infection admitted to hospital from elective surgical and interventional radiology patients.

In this single centre study we compare the experience of COVID-protected and mixed-cohort pathways at a tertiary referral hospital for elective CT-guided lung biopsy and ablation during the COVID-19 pandemic. In particular to assess the risk of developing COVID-19 post-procedure in both pathways.

Methods: A total of 123 patients were admitted for elective thoracic intervention from April 2020 to August 2021.

From September 2020 to August 2021 patients admitted for elective thoracic intervention were treated at the main site of a tertiary referral hospital (Site 1). Site 1 also received patients nationally for extracorporeal membrane oxygenation (ECMO) and invasive ventilation in the treatment of COVID-19 pneumonia. Shared imaging, theatre, and hallway facilities were used by both groups.

From April 2020 to August 2020 patients admitted for elective thoracic intervention were treated at a COVID-protected hospital (Site 2). No patients with suspected or confirmed COVID-19 were treated at Site 2.

Demographic and admission data was retrospectively collected. Patients were surveyed retrospectively for clinical and laboratory signs of COVID-19 infection up to 30 days post-procedure.

Results: At the mixed cohort site (Site 1), 2 patients (2.4%) tested positive for COVID-19 at 10 and 14 days post-procedure. One patient encountered a COVID-positive contact at a social gathering prior to developing symptoms. Both patients recovered at home with supportive therapy.

At the COVID-protected site (Site 2) there were no COVID-19 positive cases within 30 days of undergoing elective lung biopsy or ablation.

Demographic and post-operative data for both cohorts is provided in table 1.

Conclusions: A mixed-site method for infection control, where there is partial mixing of COVID-19 and elective patients represents a pragmatic approach to the management of elective procedures during the COVID-19 pandemic or similar illnesses.

Table 1: Demographic and Postoperative data for COVID-Protected and Mixed-Pathway Cohorts

	Site 1: Mixed-Pathway Cohort (August 2020 to August 2021)	Site 2: COVID-Protected Cohort (April to August 2020)
Number of Patients	85	38
Mean Age (Range)	62 (20-88)	68 (38-90)
Sex (M/F)	40 : 45	18 : 20
Postoperative ICU Admission	0	1
Mean Days in Hospital	1.8	0.7
Number of Confirmed COVID-19 Cases 30 Days Post-Procedure	2	0

Keywords: Infection Control, Patient Flow, Lung Biopsy

EP06.01-009 Maintaining Thoracic Services During COVID-19 - A Single Centre Experience

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Introduction: In March 2020 the COVID19 pandemic erupted resulting in significant burden on critical care capacity and profound disruption on lung cancer surgery.Despite the reduction in capacity, staff, and resources, we agreed locally to try and maintain full surgical services for lung cancer by adapting the surgical pathway to one less resource intense without compromising patient safety.

Methods: We conducted a retrospective review of thoracic surgery patients from 16th March 2020 to 1st May 2020 which coincided with the first COVID19 peak (Group A). We compared activity, outcomes, peri-operative course, and histology with a group of patients operated on during the same period in 2019 (Group B).

Results: 53 patients in Group A were compared to the 69 patients in Group B.There was no significant different in pulmonary function, mortality, mechanical ventilation, length of inter-costal drain or hospital stay between each group. There was less use of high dependency care in Group A (57% Vs 75%) and more patients in Group A (72%) were part of the Lung Cancer Pathway compared to Group B (59%) (TABLE 1). Malignant histology was confirmed in 64% of Group A compared to 34% of Group B. Two-week post-operative outpatient follow up in Group A, did not identify any patients with symptoms consistent of, or with a confirmation test for COVID19. There were differences in confirmation of malignant histology, tumour size and usage of high dependency care between the groups for patients on the Lung Cancer Pathway (TABLE 2).After 2-year follow up, 85% of Group A and 88% of Group B remain alive.

Conclusions: Despite previously unfaced challenges, with careful peri-operative planning we were able to maintain thoracic cancer services and minimise the use of Critical Care resources without increasing complications. During this time tumours were larger in nature and histology was universally malignant.

Thoracic Surgery Operative Data Comparison for COVID19 Era (Group A) and 2019 Cohort (Group B)			
	Group A n=53	**Group B n=69**	**p Value**
Age Median (Range)	62 (18-84) years	61 (17-87) years	0.78
Male / Female	53% / 47%	64% / 36%	0.53
FEV1% Median (Range)	80 (36-131) %	79 (37-123) %	0.85
TLCO% Median (Range)	77 (25-123) %	80 (33-103) %	0.82
Cancer Pathway n(%)	38 (72%)	41 (59%)	0.51
Mortality n(%)	1 (1.8%)	0 (0%)	0.26
Mechanical Ventilation	1 (1.8%)	1 (1.5%)	0.85
Drains Duration Median (Range)	2 (1-14) days	3 (1-21) days	0.35
Hospital Stay Median (Range)	3 (0-15) days	3 (0-15) days	0.81
Cancer Diagnosis n(%)	34 (64%)	22 (32%)	0.003
High Dependency Usage n(%)	30 (57%)	52 (75%)	0.32

Lung Cancer Surgery Operative Data Comparison for COVID19 Era (Group A) and 2019 Cohort (Group B)			
	Group A n=38	**Group B n=41**	**p Value**
Tumour Size Median (Range)	2.4 (0.7-16) cm	1.7 (0.5-11) cm	0.12
Drains Duration Median (Range)	2 (1-7) days	3 (1-8) days	0.43
Hospital Stay Median (Range)	3 (1-10) days	3 (1-11) days	0.87
Cancer Diagnosis n(%)	34 (89%)	22 (54%)	0.15
High Dependency Usage n(%)	22 (58%)	31 (76%)	0.45

Keywords: Lung Cancer, Uniportal VATs, COVID19

EP06.01 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19

EP06.01-010 Clinical Outcomes after Hypo Fractionated Radiotherapy for Locally Advanced Non-Small Cell Lung Cancer During The Covid-19 Pandemic In Morocco

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Introduction: Patients treated with curative-intent lung radiotherapy are in the group at highest risk of severe complications and death from COVID-19. There is an urgent need to reduce the risks associated with multiple hospital visits and their anti-cancer treatment. The aim of this preliminary retrospective report is to present outcomes of patients treated by Hypo fractionated radiotherapy for locally advanced non-small cell lung cancer during the covid-19 pandemic in the Greater Casablanca Region, Morocco.

Methods: All adult inoperable or unresectable patients with a clinical and radiological diagnosis of locally advanced non-small cell lung cancer treated in our department by Hypo fractionated radiotherapy (55 Gy in 20 fractions over 4 weeks) by using the 3-dimensional conformal (RT) technique with or without chemotherapy were retrospectively analysed, during the COVID-19 Pandemic between 2nd April 2020 and 2nd April 2021. All cases were discussed at the multidisciplinary tumor board (MDT) and referred for Hypo-IGRT. Primary endpoint was the local control, local progression-free survival (PFS), metastasis free survival and toxicity rates were also analysed and reported.

Results: 100 patients Were included and treated by Hypo fractionated radiotherapy. Median age was 60 years (range: 40 -83 years); mean follow-up time was 15 months (range: 6-24 months). Partial response was seen in 70.8% of patients, and stable disease was seen in 29.2% while there was neither complete. The results of mean local control, overall survival and metastasis free survival are in progress. Satisfactory symptom relief was found after RT, but severe acute dysphagia and radiation dermatitis (more than grade 3) were not observed.

Conclusions: The COVID-19 pandemic resulted in changes to patient treatment in line with national recommendations. The main change was an increase in hypofractionation. This analysis aims to report the outcomes of patients treated during the pandemic in order to assess the effect of radiotherapy and chemotherapy adaptations on survival and toxicity for these patients.

Keywords: Hypo Fractionated Radiotherapy, Lung Cancer, Covid-19

EP06.01 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19

EP06.01-011 COVID-19 Impact in Thoracic Surgery: a Comparison Between Public and Private Care in a Single-Center Facility

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Introduction: Due to restrictions caused by the COVID-19 pandemic, elective procedures were canceled or postponed. This study aims to compare the epidemiological profile of cases from Brazilian's Public Healthcare System (SUS) and Private Healthcare (PH) in a teaching single-center facility between 2019 and 2021.

Methods: Data were gathered from patients who underwent lung resection (LR) by PUCRS's Sao Lucas Hospital Thoracic Surgery team between 2019 and 2021. Data were obtained by retrospective review of electronic charts in March 2022. A retrospective analysis was made.

Results: There were 212 procedures performed, being 80 in 2019, 66 in 2020 and 66 in 2021. In 2019, there were 45 (56.2%), in 2020, 43 (65.1%), and in 2021, 34 (51,5%) LR on SUS. Lobectomies on SUS in 2019 were 19 (42.2%), in 2020, 13 (30.2%), and in 2021, 17; on PH were 19 (54.2%) in 2019, 12 (52.1%) in 2020, and 18 in 2021. On SUS, in 2019 were performed 41 (91%) open thoracic surgeries and in 2020, there were 33 (76%); on PH, in 2019 video-assisted thoracic surgery (VATS) was done in 24 (68.5%) patients, 17 (73.9%) in 2020 and 29 (75%) in 2021. Procedures for oncological disease (primary or metastatic) on SUS in 2019 were performed in 27 (60%) patients, 23 (53.4%) in 2020, and 13 (44,8%) in 2021; on PH, in 2019, there were 23 (65.5%) patients, in 2020 were 15 (65.2%), and 16 (55,2%) in 2021. On SUS there were 24 women in 2019 (53%) and in 2020 (55%); on PH, there were 23 (65%) men in 2019 and 13 (56%) in 2020. The mean age of patients on SUS was 59, and 66 on PH. Clinical staging (CS) for primary lung cancer on SUS in 2019 was 12 (50%) CS I, 8 CS II, 3 CS III, and 1 CS IV; in 2020 was 8 (47%) CS I, 6 CS II, and 3 CS III. On PH, in 2019, there were 12 (66.6%) CS I, 4 CSII, and 2 CS IV; in 2020, 11 (84.6%) CS I and 2 CS II.

Conclusions: We found maintenance in the numbers of procedures in 2020 and 2021, but a global reduction in the number of LR on SUS, mainly because the pandemic became worst in its second year, leading to the closure of surgery centers. And a reduction of 17.5% in the number of LR in 2020, compared with 2019. Lobectomies lowered 36.8% on PH and 31.5% on SUS between 2019 and 2020. Albeit there was a reduction in general incidence, LR for oncological reasons predominated. In 2021 it represented 82,8%, with 44,8% on SUS, and 52,2% on PH. There was a higher average age on PH. Open thoracic surgery was most frequent on SUS due to limitations on offered equipment, while VATS predominated on PH (difference: 44.5%). The predominant CS remained equal on both healthcare systems, CS I, which indicates maintenance of early-stage diagnoses. Nevertheless, the overall incidence has diminished (33.33% [SUS] and 8.3% [PH]), a probable reflection of the pandemic.

Keywords: COVID-19, Thoracic Surgery, Lung Cancer

EP06.01 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19

EP06.01-012 Impact of COVID-19 on the Stage of Lung Cancer Diagnosis at the Mohamed VI Center for Cancer Treatment in Morocco

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Introduction: Lung cancer is a public health problem because it is the leading cause of death. And the coronavirus (COVID-19) pandemic has led to a sharp drop in referrals to oncology services. A delay in the diagnostic process could have an impact on the diagnostic stage. We will study the impact of the COVID-19 pandemic on the diagnostic stage in our center.

Methods: the retrospective study was carried out in the radiotherapy department between January 2019 and 2020. We included all patients with a usable file. We used the KHI2 test to determine the impacts of the covid periods on the management parameters of our patients (variables) and the impacts with a value of $p \leq 0.05$ were considered significant. The data were analyzed using SPSS 16.

Results: We included 953 patients. Eighty-nine percent (89%) of patients were male. The median age was 63 years (the interquartile range was 13 years). The proportion of patients with stage IV lung cancer has increased significantly (2019: II=11, III=201, IV=291; 2020: II=7, III=105, IV=338; p= 0.0001) and that of those sent to palliative care for symptomatic treatment was also significant (2019: 190 and 2020: 204; p=0.018).

Conclusions: The proportion of patients with lung cancers at a metastatic stage has increased during the COVID-19 pandemic with a large number of patients who will not be able to receive specific treatment.

Keywords: impact, COVID-19, lung cancer

EP06.01-013 Differences of Oncology Treatment for Lung Cancer Patients in Pandemic COVID-19 Year: Our Clinical Experience

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Introduction: It is estimated that in North Macedonia delays in diagnosis due to COVID-19 pandemic, could result in significant reductions in the number of potentially curative stages in lung cancer patients.

Methods: The aim of this study was to evaluate patient characteristics and treatment strategy of lung cancer patients treated at the University Clinic of Radiotherapy and Oncology (UCRO), during the pre-pandemic year (from 1 of March 2019 to the end of February 2020) compared to pandemic year (from 1 of March 2020 to the end of February 2021). We analyzed eligible patients in the course of these two years according to the patient characteristics and treatment strategies.

Results: We have record increasing in number of undefined lung cancer patients without any pathological or histological conformation (11% pandemic year compared to 7 % in the previous year), and increased number of stage III and IV NSCLC patients in pandemic year 449 (87%) patients of NSCLC, in comparison to the pre-pandemic year 403 (74%). We have found decreasing number of stage II NSCLC patients in pandemic year 82 (13%) compared to 141 (26%) patients in pre-pandemic year and reporting decreasing number of operated patients with NSCLC from 218 to the 123 in the pandemic group. But we have to report increasing number of early stage IA and stage IB patients total 16, treated only by surgery.

Conclusions: The strict screening and admittance criteria instilled by hospitals during the pandemic might have improved oncology treatment course of the lung cancer patients.

Keywords: COVID-19, lung cancer, pandemic year

EP06.01-014 Lung Resections After COVID: Short-term Outcomes

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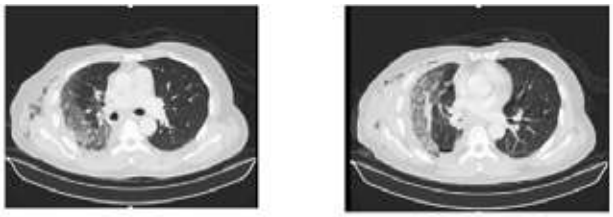
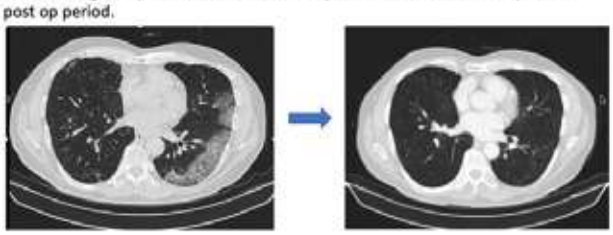
Introduction: The coronavirus pandemic has had a major impact on patients undergoing elective cancer surgery. According to data from COVIDsurg collaborative, patients operated within seven weeks after diagnosis of COVID 19 fared worse than those operated later. However, there is scant data regarding outcomes after lung resections. These surgeries involve handling of the pulmonary parenchyma previously affected by COVID and could worsen post-operative outcomes.

Methods: This is a retrospective study. Information was obtained from a prospectively maintained database and electronic medical records. Patients were divided into post-COVID and non-COVID groups. Demographics, co-morbidities, surgery type and immediate post-operative outcomes were analysed. All patients undergoing major anatomical lung resections from 15/04/2020 to 31/12/2021 were included.

Results: Overall, 184 lung resections were performed during the study period. 26 (14.1%) had tested positive for COVID-19. Majority of patients 25/26 (96.1%) had only mild infection. The average time between diagnosis and surgery for the entire group was 16.1 weeks. In the post-COVID group, 4/26(15.4%) patients developed significant post-operative complications (Clavien-Dindo 3a and above) including 2 deaths. In the non-COVID group, 31/127 (24.4%) developed significant complications. There was no significant difference between the two groups with respect to post-operative complications. Three patients who underwent lung resection developed an exaggerated post-COVID immune flare up clinically akin to ARDS:

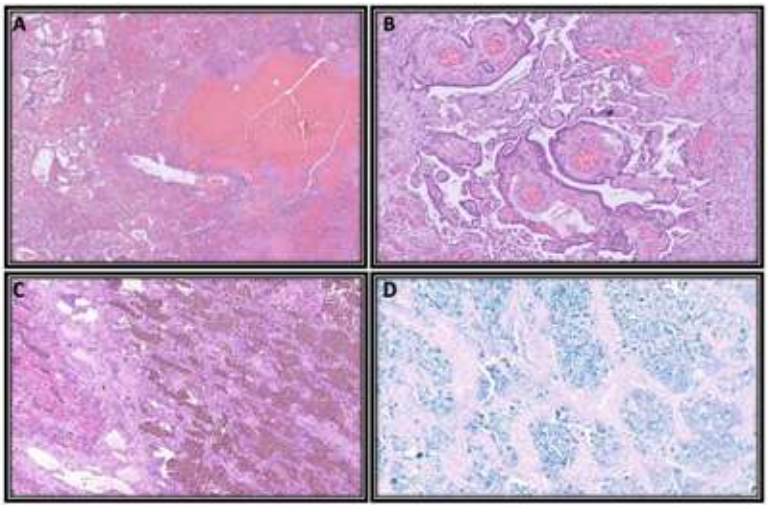


CT scan images of patients who died due to post covid immune flare up in the post op period.



Before and after CT scan images of a patient who had a covid flare up in the post op period, responded to steroids and survived.

In the post-operative period: 1 responded to steroids and 2 died. Histopathological examination of the resected lung specimens in patients who died, revealed increased vascularity, micro-abscess formation placental transmogrification:



Conclusions: It is reasonably safe for patients to undergo major thoracic surgery >7 weeks after COVID infection. The complication rate is similar to non-COVID patients. Post-covid sequelae in the form of immune mediated lung changes can complicate the post operative course in a few patients and is unpredictable. Identifying these patients pre-operatively still remains a challenge.

Keywords: Lobectomy, Lung Cancer, post-Covid

EP06.01 MANAGEMENT OF LUNG CANCER IN THE ERA OF COVID-19

EP06.01-015 Will Virtual Care Stand the Test of Time; One Site's Perspective on the Continuity of Virtual Care Post-Pandemic

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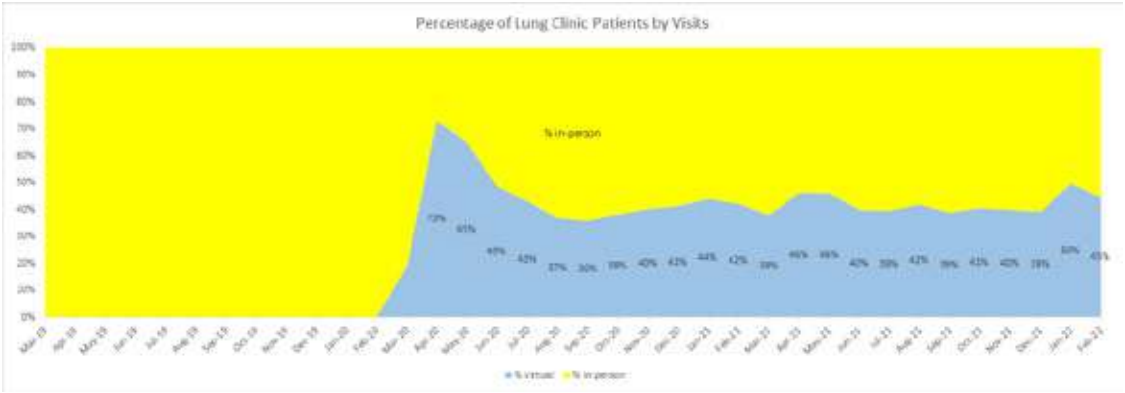
Introduction: Since the declaration of the COVID-19 pandemic in March 2020, the healthcare field has undergone innumerable changes. Both patients and health care providers (HCP) alike had to adapt to new precautionary measures, while simultaneously addressing ongoing health concerns. Hence, a shift was seen in which many conventional in-person patient appointments were changed into virtual appointments. The aim of this abstract is to analyze patient appointments from March 2019 to February 2022 by the mode in which it was provided.

Methods: The total number of visits occurring at Princess Margaret Cancer Center ambulatory thoracic oncology clinic was collected from March 2019 to February 2022. The compiled results were organized by mode of encounter and converted to graph format. The "In-Person" category accounts for traditional patient consults that had been conducted by having patients physically attend the clinic. This includes appointments for new patients and follow-up patient consults for medical, radiation, and surgical oncology. All patient consults that were conducted remotely, where the patient was not physically present within the clinic, are grouped into the "Virtual" category. These appointments were conducted through various media platforms; phone calls, Microsoft Teams, Ontario Telemedicine Network, and telehealth meetings.

Results: There is an initial peak in virtual appointments seen at the start of the pandemic, occurring from April 2020 to May 2020. During this time, virtual appointments accounted for more than 65% of appointments. After this, the use of virtual appointments has continued to persist (with virtual appointments accounting for 36% to 50% of consults during the period from June 2020 to February 2022). This occurs despite external changes related to COVID-19, including the introduction of the COVID-19 vaccine, and the fluctuating number of COVID-19 cases.



Conclusions: Although this does not definitively conclude that virtual care will persist after the pandemic has concluded, there is strong evidence to suggest that health care may no longer be limited to in-person settings. With the integration of virtual care, the disadvantages of remote patient care must be considered, primarily the inability to complete a physical assessment. Given these disadvantages, HCP must recognize these limitations and methodically select appropriate situations for utilizing virtual care. There is a growing need to further develop innovative ways to support HCP in providing quality patient care in a virtual platform through research, development, and education.

Keywords: COVID-19, Virtual Care

EP06.01-016 Nationwide Activity of Lung Cancer Surgery Before and During the COVID-19 Pandemic

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Introduction: COVID-19 pandemic has considerably affected patients' access to healthcare, including management of cancer patients. Although for early-stage lung cancer surgical treatment is the preferred management option, availability of operating theatres and hospital beds has been reduced during the pandemic. In Estonia, the absolute number of newly diagnosed lung cancer cases per year has remained stable during last decades. However, the number of lung cancer operations has been steadily increasing, with thoracoscopic approach (VATS) applied more often.The aim of the current study was to compare the amount of lung cancer operations performed before and during the first years of the COVID-19 pandemic to evaluate its impact on cancer surgery.

Methods: All patients in Estonia who underwent a lung cancer operation with radical intent during 2018-2021 were included. Data were obtained from all hospitals performing lung cancer surgery. Operations performed before the beginning of the COVID-19 pandemic (years 2018-2019) were considered baseline and compared to operations performed during the first years of the pandemic (2020-2021).

Results: Study results are presented in the following table.

	2018–2019	2020–2021
Number of operations/patients	427/426	447/443
Male/female	291/135	285/158
Mean age	69.7	69.5
Patient status:		
ECOG 0-1	374	415
ECOG 2-3	39	27
Unknown	13	1
Surgical access:		
Thoracotomy	129	108
VATS (conversion to thoracotomy)	298 (38)	339 (26)
Extent of surgery:		
Lobectomy	318	319
incl sleeve lobectomy	18	30
Pneumonectomy	21	24
incl sleeve pneumonectomy	1	3
Segmentectomy	48	71
Wedge resection	36	30
Probatory surgery	1	3
Postoperative in-hospital mortality (%)	8 (1.9%)	8 (1.8%)
Cancer stage:		
0 (Tis)	1	4
I	254	259
II	80	85
III	82	91
IV	10	8
Cancer morphology:		
Adenocarcinoma	208	234
Squamous cell cancer	132	137
Small cell cancer	10	11
Carcinoid tumor	31	30
Other	46	38

Comparing the two study periods, the number of surgically treated female lung cancer patients increased, yet other demographic characteristics of study patients, cancer stage and distribution of morphological types did not considerably differ in the two study periods. The overall number of lung cancer operations increased, with more operations performed by VATS in the second study period. Also, the number of more technically demanding operations increased (e.g. segmentectomies and bronchial sleeve resections, incl. few cases of sleeve lobectomies performed by VATS).

Conclusions: Considering the stable number of yearly diagnosed lung cancer, we can conclude that the COVID-19 pandemic has not had a considerable impact on the amount and evolution of surgical treatment of lung cancer in Estonia, as the number of operations performed even continued to increase, as did the proportion of operations performed by VATS.

Keywords: Lung cancer, Surgery, Covid-19

EP06.01-017 Clinical Impact of SARS-CoV2 Pandemic in the Diagnosis of Early-Stage Thoracic Tumours

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H. U. Puerta de Hierro Majadahonda, Majadahonda/ES

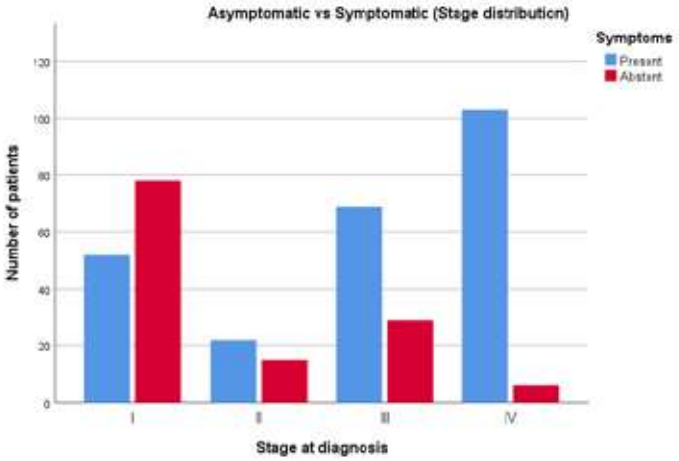
Introduction: Cancer healthcare has been affected by Coronavirus disease 2019 (COVID-19) pandemic, interfering the normal function of oncology units and increasing diagnostic delay. Nevertheless, the rising incidence of respiratory infections led to an increase in medical consultations and chest imaging explorations. The aim of the study was to assess whether the increase in medical evaluations in the context of the pandemic led to an increase in the detection of early-stage thoracic tumours.

Methods: We performed a retrospective single-institution study, collecting data from patients diagnosed with thoracic tumours between March, 1, 2020 and December, 31, 2021. We analysed their demographic and clinical data, symptoms at diagnosis and those who were diagnosed due to SARS-CoV-2 infection.

Results: A total of 378 patients were analysed**.** Main results are shown in Table-1. Only 5.3% of newly diagnosed thoracic tumours were related to a suspected or confirmed SARS-CoV-2 infection. However, these patients were not diagnosed at earlier stages (p = 0.414). When we evaluated symptoms at diagnosis, we found that asymptomatic patients presented in earlier stages (p <0.000, Figure-1), being the majority incidental findings during the follow-up of oncological and non-oncological pathologies. Regarding symptomatic patients, most presented as locally advanced or metastatic diseases and no changes have been observed in the pattern of presentation compared to studies prior to the pandemic.

	Total (N = 378)
Sex	Male: 256 (67.7%) Female: 122 (32.3%)
Age	67.0 (21.0-87.0)
Smoking habit	Never smoker: 42 (11.1%) Former smoker: 189 (50.0%) Current smoker: 137 (36.2%) Unknown: 10 (2.7%)
Stage at diagnosis	I: 130 (34.4%) II: 37 (9.8%) III: 98 (25.9%) IV: 109 (28.8%) Unknown: 4 (1.1%)
Histology	Adenocarcinoma: 192 (50.8%) Squamous carcinoma: 92 (24.3%) Small cell carcinoma: 39 (10.3%) Adenosquamous: 2 (0.5%) Large cell carcinoma: 3 (0.8%) Neuroendocrine large cell carcinoma: 11 (2.9%) Sarcomatoid: 1 (0.3%) NOS: 12 (3.2%) Carcinoid: 16 (4.2%) Mesothelioma: 2 (0.5%) Others: 8 (1.6%)
Symptoms reported at diagnosis	Asymptomatic: 131 (34.7%) Anorexia: 23 (6.1%) Asthenia: 34 (9.0%) Dyspnoea: 66 (17.5%) Pain: 64 (16.9%) Haemoptysis: 27 (7.1%) Weight loss: 57 (15.1%) Cough: 65 (17.2%) Others: 60 (15.9%)
Diagnosis due to SARS-CoV-2 suspicion/disease	20 (5.3%)
Causes of diagnosis in asymptomatic patients	Follow-up of a non-oncological pathology: 56.6% Follow-up of another tumour: 17.5% Preoperative study: 7.0% Extension study of another tumour: 6.3% Rutinary revision: 6.3% Symptoms not related with thoracic cancer: 6.3%

Conclusions: COVID-19 pandemic did not seem to increase thoracic tumours diagnosis in our study. Lung cancer diagnosed in patients due to SARS-CoV-2 infection was not detected in earlier stages. Clinical presentation was similar to previous reported outside COVID-19 pandemic. Nevertheless, we find that asymptomatic patients diagnosed incidentally presented more frequently in localized stages in comparison with symptomatic patients.



Keywords: COVID19, Lung Cancer, Diagnosis

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-001 Molecular Profiling Predicts Outcomes in Patients with Resected Malignant Pleural Mesothelioma

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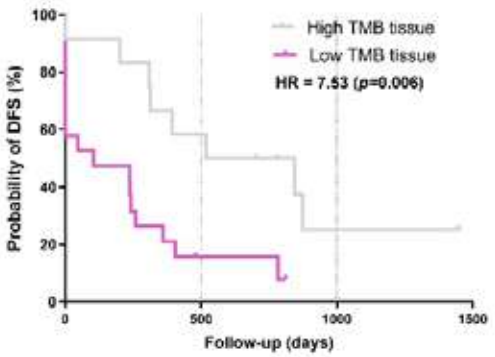
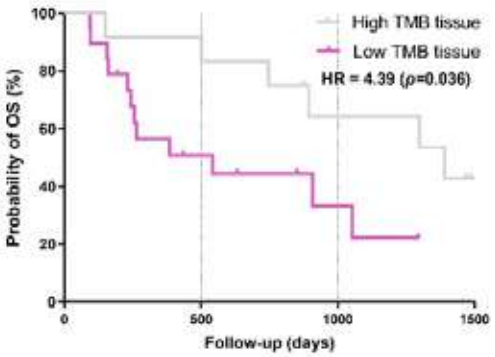
Introduction: Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer that rarely develop distant metastasis but often invade surrounding areas. Due to the limited therapeutic options available, the prognosis of these patients is poor, particularly in those with sarcomatoid histology. Moreover, trimodality treatment of resectable MPM is still controversial with high heterogeneity of clinical outcomes among resected patients and the lack of predictive biomarkers. Genomic studies have showed that MPM tumors are characterized by poor mutational landscapes characterized by minute mutations, rather than driver mutations, that are often missed in comparative genomic hybridization and next-generation sequencing studies. Thus, we aimed to further characterize the genetic background of these tumors and to identify predictive biomarkers in these MPM patients.

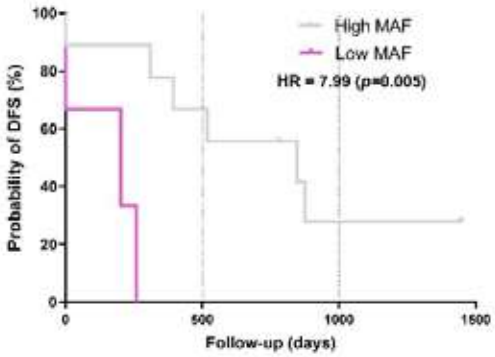
Methods: We retrospectively analyzed pleural-based tumor samples and plasma samples (3mL) from patients with stage IB-IIIB resected MPM from the National Mesothelioma Virtual Registry and Tissue Bank (NMVB) collected under informed consent and IRB approval. Analysis of 409 cancer related genes was performed on MPM tumors and blood samples by targeted next-generation sequencing (NGS) with the Oncomine TML assay. Tissue and blood tumor mutation burden (TMB) was calculated. Median minor allele frequency (MAF) from somatic mutations was calculated by comparing tissue MAF>50% NGS data with corresponding plasma specimens.

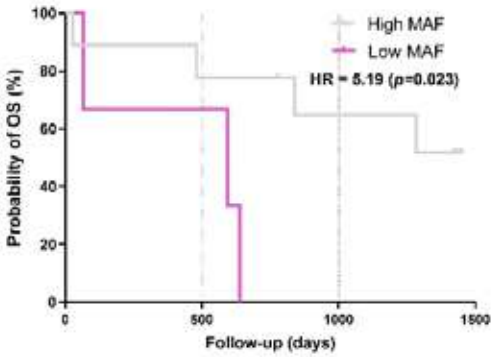
Results: We analyzed tissue samples from 31 MPM patients and matching blood samples in 12 of them. Median of 25 and 21 mutations were found in the tissue and blood, respectively. *BAP1* mutations were found in 9 (29%) of patients with 1 (3.2%) found germline. None of these mutations were associated with the outcome. Interestingly, we found higher tissue TMB (>9), higher median MAF (>7), and higher blood TMB (>6), were associated with better disease-free survival (DFS) and/or overall survival (OS) (Figure 1). Then, we observed that tissue *ITGB2* (p=0.049) and *LIFR* (p=0.043) mutations were present in patients with shorter DFS and *EPHB1* (p=0.026), *LRP1B* (p=0.049), *MARK4* (p=0.025), *PKHD1* (p=0.020) mutations were present in those with longer OS.

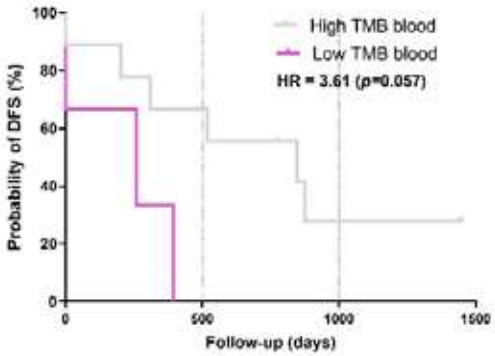
Conclusions: Our results showed that tissue and blood TMB, MAF, and specific tissue mutations were associated to the outcome of MPM patients and could be used as predictive biomarkers. Despite the limitations of this preliminary data, this study opens the door for the application of molecular profiling to identify longer survivors in patients resected MPM.











Keywords: Mesothelioma, Gene mutations, Biomarkers

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-002 Surgery in Stage I-III Malignant Pleural Mesothelioma: A Surveillance, Epidemiology, and End Results (SEER)- Medicare Analysis 1995-2015

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Introduction: Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy with very poor prognosis. Histology (epithelioid, biphasic and sarcomatoid) has important prognostic implications. Although radical surgery (RS) has been recommended in resectable epithelioid MPM patients, whether RS is associated with improved overall survival (OS) is inconclusive due to lack of data from randomized clinical trials, and the optimal treatment paradigm remains unclear.

Methods: We extracted stage I-III MPM patients from the Surveillance, Epidemiology, and End Results (SEER)-Medicare 1995-2015. Multivariable Cox proportional hazard regression models were used to calculate the OS and mesothelioma specific survival associated with different treatment modalities (non-RS, RS alone vs multimodality), overall and stratified by histology and several key clinical features.

Results: Overall, 20.6% of 1,293 patients underwent multimodality therapy. 81% of MPM patients were male. The median OS (mOS) was 10.4 months in the overall cohort. After adjusting for confounders, we found that RS alone could significantly increase the mortality, especially in sarcomatoid MPM patients (HR_{adj}=2.35, 95%CI: 1.43-3.86) (Figure 1). Multimodality conferred survival advantages in epithelioid disease (HR_{adj}=0.70, 95%CI: 0.56-0.88) even among those who were aged > 70 years (HR=0.66, 95%CI: 0.51-0.85) or male (HR_{adj}=0.73; 95%CI: 0.57-0.93), which were historically considered as poor prognostic factors (Figure 2).

Conclusions: Our study indicates that RS-alone should not be recommended for patients with stage I-III MPM patients, especially sarcomatoid disease. Multimodality is the preferred treatment paradigm, particularly for patients with epithelioid, even in the presence of certain high-risk clinical features. Multimodality treatment incorporating RS may be considered in early-stage biphasic disease. Careful patient selection and multidisciplinary evaluation of MPM patients are essential in making surgical decisions. Prospective randomized clinical trials are needed to clarify the role of RS and the impact of histology on the prognosis of MPM patients.

Figure 1. Overall survival in RS alone versus non-RS treatment, by histology and clinical features

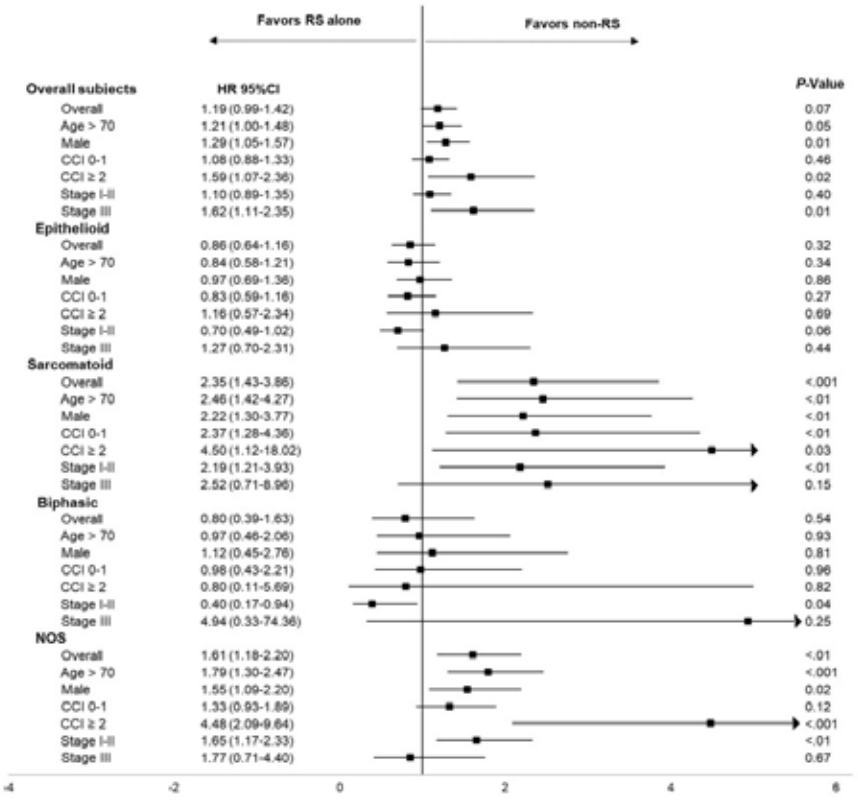
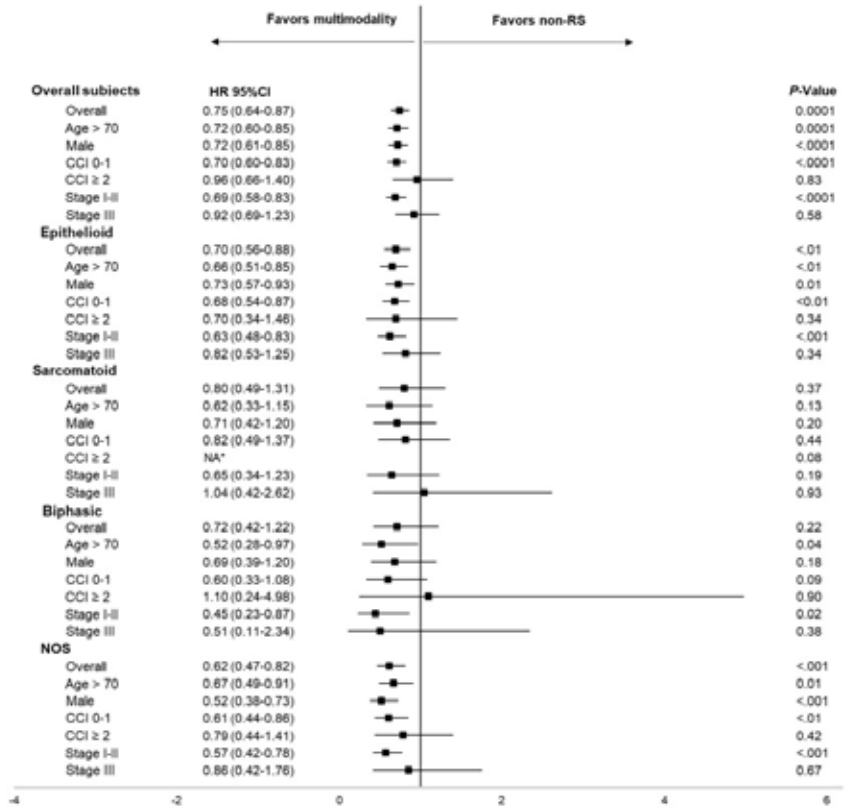


Figure 2. Overall survival in multimodality versus non-RS treatment, by histology and clinical features



Keywords: malignant pleural mesothelioma, radical surgery, SEER-Medicare

EP07.01-003 Metadata-Oriented Data Engineering Approach for Integration of Medical Data: A Pilot Study

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Introduction: Data Mining (DM) applications may benefit from artificial intelligence (AI) approaches that aim to reveal valuable information from data. The quantity and quality of data are important to receive accurate and reliable information. In recent years, research on the development of computer software programs under the title of metadata has been carried out to reach reliable data. In this study, it is aimed to evaluate the applicability of metadata-oriented data engineering methods in a relatively small medical dataset.

Methods: 43 different data tables were prepared by different researchers on different dates. In total, 262 patients diagnosed with thymoma and treated between 2010 and 2020 in Ankara University Faculty of Medicine Department of Thoracic Surgery, were used. To create a single data frame, in addition to the functions embedded in the Python programming language, NumPy numerical processing and Pandas data processing libraries were used to create a software that allowed us to develop a holistic new data frame free of any contradictions. With the help of this software, we were able to detect not only missing and incorrect data, examples of which are shown in Table 1, and outlier analysis, but also merge/deduplicate horizontal and vertical data.

Results: 43 data tables, created at different times, by different sources, containing repetitive or different data, were processed through the software developed using NumPy/Pandas libraries in Python, to create a holistic data frame that can be used in AI-supported data analytics studies to be made later on.

Conclusions: Successful integration of data from all different sources in health services is important for all stakeholders in the health system. However, traditional data processing methods are insufficient, especially for the process of Big Data and then for Data Mining. With the software developed in this study, it was predicted that metadata sets, that can be used in AI-assisted data analytics studies and may be helpful to the different researchers, can be developed with multidisciplinary studies. The software created is planned to be evaluated by our team in larger datasets, especially in lung cancer, but it is also needed that the software should be tested by other researchers.

Table 1. Examples of detected erroneous data and outliers

Error Type	Patient ID	Biopsy or Surgery Date	Gender	Age	Symptoms	Last Control Date	Recurrence Free Survival (Months)	Survival Control Date	Survival Status	Survival Time (Months)
Incorrect Survival Status	1403	09-08-2005	0	73	1	13-12-2006	16,4	30-09-2018	0	160
	1403	09-08-2005	0	73	1	13-12-2006	16,4	05-01-2020	1	175,4
Incorrect Gender	36451	01-09-2005	1	61		07-11-2013	99,6	31-10-2014	1	111,566667
	36451	01-09-2005	0	61		07-11-2013	99,6	31-10-2014	1	111,566667
Incorrect Age	55517	18-07-2017	0	43	0	27-09-2021	51,1	04-10-2021	0	51,3
	55517	18-07-2017	0	433	0	17-04-2018	9,1	26-09-2018	0	14,5

Keywords: Data engineering, Data mining, Metadata

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-004 Long Survivor Epithelioid Pleural Mesotheliomas Are Characterized by Tertiary Lymphoid Structures: An Update to the MATCH Study

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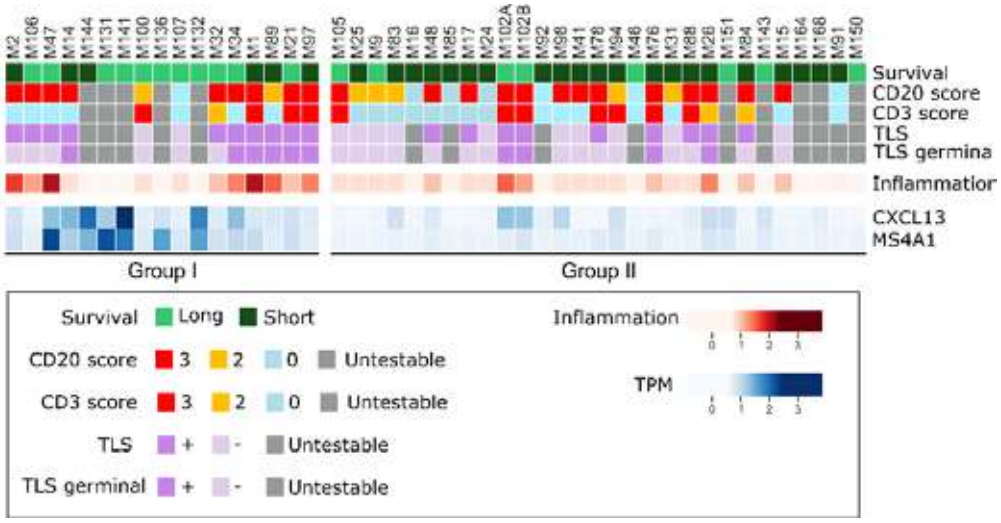
Introduction: In a previous poster presentation at the EACR 2021 (poster n. EACR21v0229), we presented transcriptomic data showing that long survivor epithelioids pleural mesothelioma (PM) patients had a higher B lymphocytes fraction in comparison to shorter survivors. Here we present an update focusing on long survivors in this study.

Methods: Among the previously analyzed 69 biopsies from the MATCH study that underwent transcriptional profiling, we selected the cases for which formalin fixed paraffin embedded slides were appropriate for immuno-histopathological revision. CD20 and CD3 markers were tested together with the morphological assessment to identify tertiary lymphoid structures (TLS). Immuno-histopathological evaluation was then integrated with transcriptomic analysis.

Results: Focusing on epithelioid PM, we found two distinct transcriptional groups: Group I that was significantly enriched in long survivors with a higher fraction of B cells and Group II that was enriched in short survivors characterized by macrophages and neutrophils (p<0.03). We revised the pathological samples and tested with immunohistochemistry 12 out of 17 (70%) from Group I, 24 out of 29 (82%) from Group II. We confirmed the presence of B cells in Group I through CD20 evaluation. Moreover, morphological assessment showed that TLS are present in in 10 out of 12 slides (83%) in Group I, whereas in Group II TLS were identified in 9 out of 24 (37%). Furthermore, transcriptomic expression of CXCL13, a known marker of TLS, was coherently higher in Group I as well as that of MS4A1 gene encoding for CD20 marker providing overlap between omics and immuno-histopathological data.

Conclusions: The immunohistochemistry analysis confirmed our previous results suggesting a higher B cell infiltration in long survivor epithelioid MP. Although this series is small, the presence of TLS might be prognostic. This evidence could suggest a direct role of the immune system in modulating the aggressiveness of the disease. How this could be exploited for selecting the optimal candidate for immunotherapy has still to be defined.



Keywords: mesothelioma, long survivor, Terziary Lymphoid Structures

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-005 Second Primary Cancers in a Population-Based Mesothelioma Registry

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Introduction: The etiology of malignant pleural mesothelioma (MPM) is mainly related to asbestos exposure. Genetic predisposition may play a role, and familial clustering of MPM has been reported. Second primary cancers (SPCs) have been proposed as a possible indicator for genetic clustering and/or shared mechanisms of carcinogenesis. We aimed to investigate the occurrence of SPCs in Lombardy Mesothelioma Registry (about 10 million inhabitants), Northern Italy.

Methods: Demographic and disease characteristics of all MPM incident in Lombardy from 2000 to 2018 were extracted. Patients with and without SPCs were compared. Median survival time (ST) of the two groups was calculated.

Results: 6682 MPM patients were included in the analysis. Median age at diagnosis was 72 years (range 24-99) in 4399 males (M) and 75 years (range 27-102) in 2283 females (F). Previous asbestos exposure was reported in 65.9% of patients; ever-smokers were 55.4%. Among MPM with histological confirmation (n=5371), the histological type was epithelioid in 3965 (73.8%), sarcomatoid in 454 (8.4%) and biphasic in 723 (13.5%) cases. Median ST of the whole population was 10.9 months (95% CI: 10.4-11.2), without differences by gender. A SPC was reported in 979 (14.6%) of patients: 668 (15.2%) M and 311 (13.6%) F. Of note, 117 patients (84 M) had more than one SPC. Among M, the most frequent SPCs were prostate cancer (292 patients), colorectal cancer (88), bladder cancer (75), cutaneous basalioma (64), renal cancer (40) and melanoma (27). Among F, the most frequent SPCs were breast cancer (147 patients), cutaneous basalioma (31), cancer of the uterus (30), colorectal cancer (23), melanoma (19), renal cancer (8) and bladder cancer (5). Overall, asbestos-related SPCs were reported in 56 patients, with 33 cases of larynx cancer, 17 of lung cancer, and 6 of ovary cancer.Prevalence of asbestos exposure in SCPs group was 64.2%, and 51.5% had a previous smoking history. Histology of patients with SPCs was available in 759 patients, and was epithelioid in 589 (77.6%), sarcomatoid in 50 (6.5%) and biphasic in 86 (11.3%) cases.Median ST was 10.8 months (95% CI: 9.5-11.7) in patients with SPC, and 10.9 months (95% CI: 10.4-11.2) in the non-SPCs group. When the ST analysis was splitted for histology, no difference between PSCs and non-PSC groups was observed with the epithelioid subtype. In patients with non-epithelioid phenotype, median ST among SPCs and non-SPCs groups was 5.7 months (95% IC 5.1-7.3) and 7.6 months (95% IC 7.1-8.4), respectively.

Conclusions: In a large population-based MPM Registry, SPCs were common (14.6%). The presence of SPCs did not influence patient survival. Asbestos-related SPCs were reported in a minority of cases. The frequent occurrence of prostate and breast cancers could be related to their high global incidence; however, a genetic predisposition cannot be excluded.

Keywords: mesothelioma, second primary cancers, epidemiology

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-006 Clinicopathologic Determinants of Survival in Thoracic NUT Carcinoma (TNUT): Analysis of a Pooled Database

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Introduction: NUT carcinoma is a poorly differentiated squamous cancer characterized by the translocation of nuclear protein in testis gene that is mostly fused with bromodomain and extra-terminal family proteins. NUT carcinoma is a rare and aggressive cancer that tends to involve midline structures, frequently the head and neck (H&N) areas and thoracic (T) cavity. Several studies reported on a small mixed NUT samples from different sites. The characteristics and optimal management of thoracic NUT carcinoma (TNUT) are unclear. We conducted this pooled database analysis to delineate key disease characteristics and clinicopathologic determinants of survival in TNUT.

Methods: To study the demographic characteristics, molecular and immunohistochemical signatures, therapeutic interventions, survival, and prognostic factors, we compiled a pooled database of 141 cases. Kaplan-Meier survival curves were constructed. Cox proportional-hazards model and Log-rank tests were used to assess the influence of demographic and clinicopathologic factors on overall survival (OS).

Results: A total of 141 patients with confirmed TNUT were identified. The median age was 33 years with peak incidence between ages 28 and 41 years. There was a slight male predominance with M:F ratio of 1.2. Lung was the most common site of origin followed by the mediastinum and thymus respectively. The majority had BRD4-NUT fusion and presented with metastatic disease. The median OS of the group was 5 months which is worse than H&N-NUT. The median duration of symptoms prior to diagnosis was 1 month. Compared to no treatment, surgery (S), chemotherapy (C), chemoradiotherapy (CRT), C+S, and CRT+S were statistically superior with a median OS of 0.8, 1, 4.5, 6, 8, and 16 months respectively ($p<0.0001$). Metastatic disease was detrimental to OS and so was BRD3-fusion, but the latter did not reach significance. Check point inhibitors (CPI) as well as BRD inhibitors positively impacted OS, but the latter did not reach significance. OS was not impacted by age, sex, or thoracic location.

Conclusions: This study presents the largest cohort of patients with T-NUT. It demonstrates that T-NUT has a poorer prognosis. Aggressive multimodality treatment approaches including CPI are associated with better OS.

Keywords: NUT midline carcinoma, Thoracic carcinoma, nuclear protein in testis (NUT) protein

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-007 Is Extended Resection for Tracheo Bronchial Adenoid Cystic Carcinoma Warranted ?

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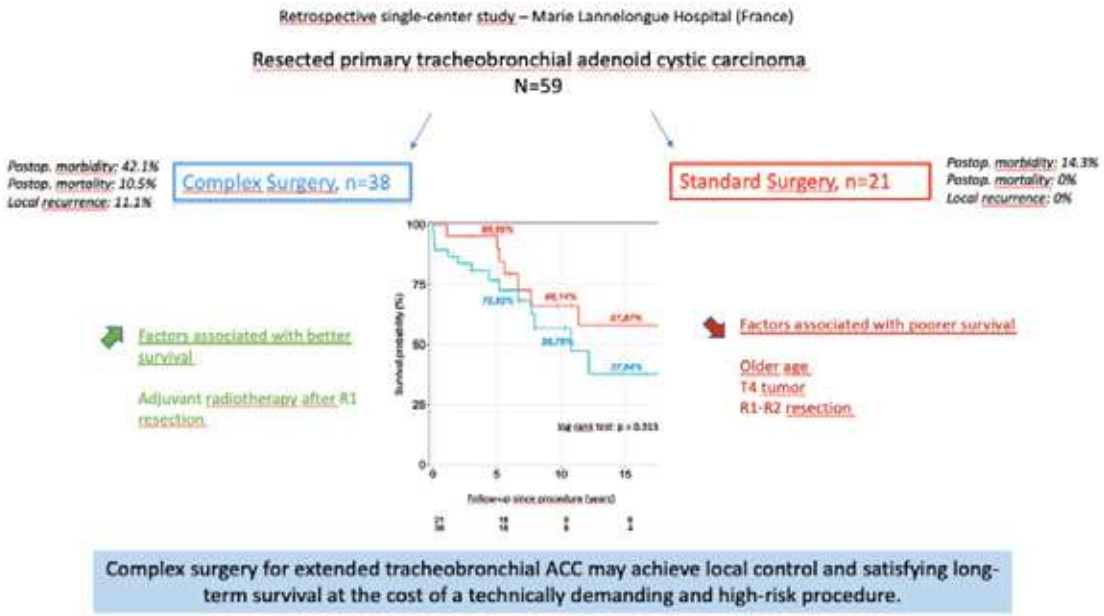
Introduction: Tracheobronchial adenoid cystic carcinoma (TBACC) is a rare, slow-growing, malignancy whose considerable propensity for local extension may require complex airway resection to achieve tumor-free (R0) margins. The objective of this study was to assess whether our experience supports complex airway resection for TBACC.

Methods: Consecutive patients who underwent curative resection for TBACC at our institution in 1970-2019 were included retrospectively and classified as having had complex or standard resection. Complex resection included total tracheal replacement, associated esophageal resection, pneumonectomy, total laryngectomy with tracheal resection and carinal resection. Standard resection included tracheal resection, bronchoplastic resection, lobectomy, bilobectomy. We obtained data from medical records, referring physicians, patients, relatives, and public death records. The TNM classification used is from Bhattacharyya, Boston, 2004.

Results: Of 59 included patients, 38 had complex and 21 standard resection. All 4 (6.8%) patients who died postoperatively had had complex resection. Postoperative morbidity was 32.2% overall and was significantly higher after complex resection (*P=0,043)*. Overall 5- and 10-year survival rates were 81.5% and 60.2%, with no significant between-group differences (*P*=0.31). By both univariate and multivariate analysis, age, T4 tumor and R1-R2 resection were associated with poorer survival (*P*<0.05). In the subgroup with R1 resection, survival was significantly better when adjuvant radiotherapy was given (*P*<0.05).

Conclusions: Complex resection for extended TBACC may achieve local control and satisfying long-term survival. However, this demanding procedure is associated with high postoperative morbidity and mortality rates. Because adjuvant radiotherapy improved outcomes after R1 resection, expected outcomes after R0 resection must be compared to those after R1 resection plus radiotherapy, according to the operative risk.



Keywords: trachea, carcinoma, surgery

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-008 Perturbation of Warburg Effect by Dichloroacetate and Niclosamide in Malignant Pleural Mesothelioma in Vitro and in Vivo

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Introduction: Inhaling asbestos fibers is the commonest cause of malignant pleural mesothelioma (MPM). Although the use of asbestos has been strictly regulated, the incidence of MPM is still elevating because a long lag time in malignant transformation. In 2004, the United States Food and Drug Administration approved a combination of cisplatin with pemetrexed for treatment of unresectable MPM. However, extremely poor overall prognosis is observed. As such, development of novel treatment is urgently needed. The tumor suppressive effect of dichloroacetate (DCA) or niclosamide (Nic) has been shown in different cancer types. The objective of this study is to disclose the combination effect of DCA and Nic in MPM.

Methods: The combination effect of DCA and Nic was studied using a panel of MPM cell lines (H28, MSTO-211H, H226, H2052, H2452). Cell viability was monitored by MTT assay. Glycolysis, oxidative phosphorylation, glycogen, citrate and succinate concentrations were determined by corresponding ELIZA. Apoptosis, mitochondrial transmembrane potential, cell cycle analysis, hydrogen peroxide and superoxide were investigated by flow cytometry. Cell migration and colony formation were investigated by transwell migration and colony formation assays respectively. The in vivo effect was confirmed by 211H and H226 nude mice xenograft models.

Results: Cell viability was reduced synergistically by DCA/Nic combination in all cell lines. Perturbation of glycolysis and/or oxidative phosphorylation by DCA and/or Nic resulting in downregulation of glycogen, citrate and succinate. DCA and/or Nic increased apoptosis, mitochondrial transmembrane depolarization, G2/M arrest and reactive oxygen species (hydrogen peroxide and superoxide). Moreover, DCA and/or Nic suppressed cell migration and colony formation. Furthermore, a better initial tumor suppressive effect was induced by DCA/Nic when compared with single drug in both 211H and H226 xenograft models. In 211H xenografts, DCA and DCA/Nic increased median survival. DCA, Nic and DCA/Nic increased intratumoral glycogen, citrate and succinate levels. At the same time, Bcl-2 as well as PARP were downregulated by Nic and DCA/Nic as well as DCA/Nic respectively. In H226 xenografts, DCA/Nic increased median survival of mice when compared with single treatment. Intratumoral glycogen, citrate and succinate levels were declined by Nic and DCA/Nic. Suppression of Bcl-2 (by Nic and DCA/Nic), CDK2 (by DCA/Nic), beta-catenin (by DCA/Nic), PCNA (by Nic and DCA/Nic) and Akt (by DCA/Nic) were observed. Single drug and/or combination induced perturbation of Warburg effect as well as activation of apoptosis, and inhibition of migration and proliferation in vivo.

Conclusions: Dichloroacetate and/or niclosamide showed tumor suppressive effect in MPM in in vitro and in vivo which was partially mediated by perturbation of glycolysis/oxidative phosphorylation, apoptosis as well as suppression of migration and proliferation. Acknowledgment: This research was supported by Hong Kong Pneumoconiosis Compensation Fund Board.

Keywords: Mesothelioma, Dichloroacetate and niclosamide, Warburg effect

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-009 Solitary Fibrous Tumors of the Pleura, Clinical and Surgical Dilemma. Single-Center Experience

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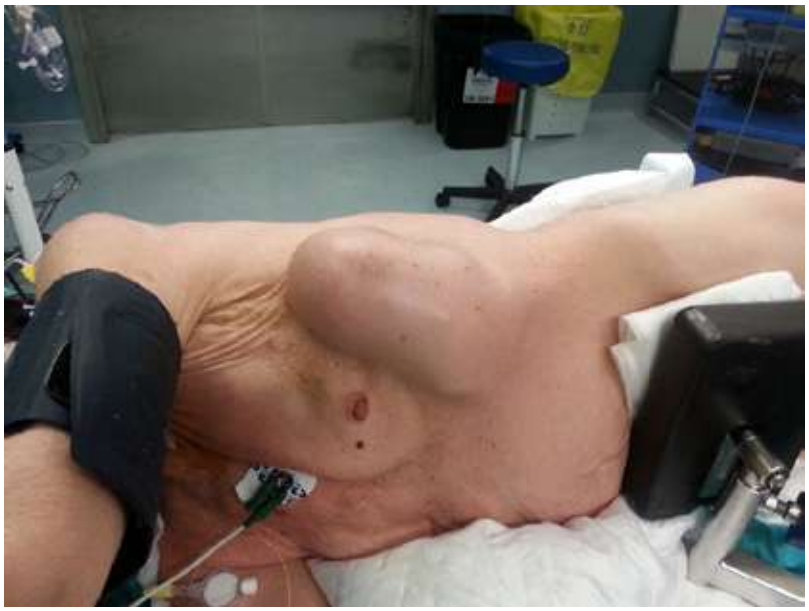
Introduction: Solitary fibrous tumor of the pleura (SFTP), is a rare benign pleural-based tumor that accounts for <5% of all tumors involving the pleura. Usually presents in the 6th to 7th decades. Approximately 80% of pleural fibromas arise from the visceral pleura.We report 9 cases of solitary fibrous tumor of the pleura, more than half of them was giant. Histology and immunohistochemistry were classical of a solitary fibrous tumor.

Methods: The initial evaluation and diagnosis, tumor classification, surgical treatment, results of therapy, and long-term prognosis are reviewed, based on a selective review of the literature beginning from 1980. Between 2009 and 2021, the 9 patients: 4 men and 5 women; median age 61 years (48-76 years), 30% had symptoms. All patients had complete en bloc resection with wedge lung excision (n=5), lobectomy (n=1), pneumonectomy (n=1), chest wall resection (n=1) - case of relapse (Fig. 1), diaphragm resection (n=1). The tumors were pedunculated (n=5) or sessile (n=4). Definitive histologic examination showed benign tumors (BSFTP) in all patients. Tumor recurrence was in 1 case - 5,5 years after previous pneumonectomy.

Results: Complete en bloc surgical resection is the preferred treatment of benign and malignant varieties of the tumor. The pedunculated tumors attached to the visceral pleura can be effectively treated with a wedge resection of lung. Sessile tumors arising on the lung require a larger lung resection. Sessile tumors on the chest wall require wide local excision, often with chest wall resection because of their propensity for local recurrence. Adjuvant therapy remains controversial in SFTP. The majority of tumours tend to be benign and slow growing. Malignant tumours are uncommon but have been reported. Surgical resection is the treatment of choice. There can be recurrence in a small proportion (8%) of cases, most of which do not recur again following re-excision.

Conclusions: Benign SFTP has a high cure rate and an 8% local recurrence rate that is usually amenable to curative re-excision. Malignant SFTP, especially the more common sessile type, has a 63% recurrence rate even with complete resection. The majority of patients with recurrent disease die of the tumor within 2 years. Nevertheless, the overall long-term cure rate for all patients is 88% to 92%. Complete en bloc resection of SFTP provides good long-term survival. Tumor recurrence is the main risk factor for death and may occur in mSFTP despite en bloc resection and requires multimodal treatment and close follow-up.



Keywords: Chest Tumors, Pleural mass, Surgery

EP07.01-010 Results of Multimodal Treatment in Patients with Malignant Pleural Mesothelioma Undergoing Pleurectomy/Decortication

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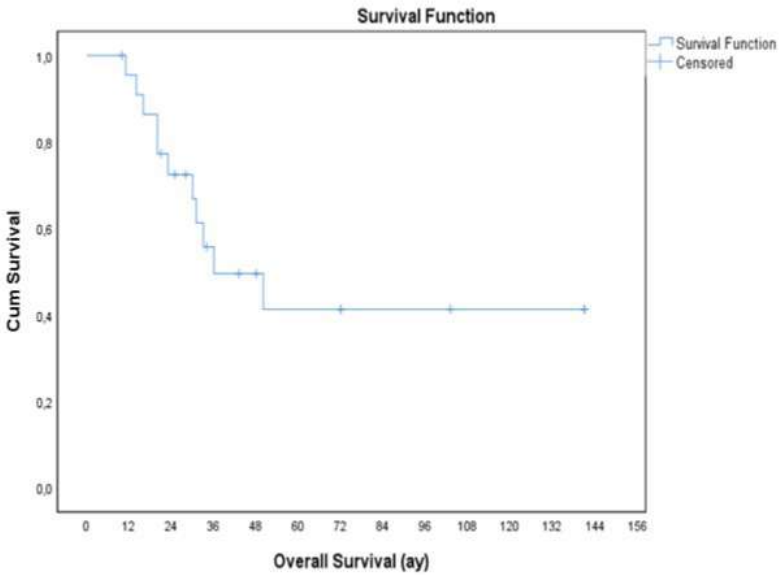
Ankara University Faculty of Medicine, Ankara/TR

Introduction: Malignant pleural mesothelioma (MPM) is a cancer type with poor prognosis and no effective treatment. On the other hand, it is known that the multimodal treatment approach including cytoreductive surgery (±neoadjuvant treatment+surgery+adjuvant treatment) provides a survival advantage. In this study, it was aimed to present the survival results of patients who have received multimodal treatment for MPM and underwent pleurectomy/decortication (P/D) as a surgical method.

Methods: Among 28 patients who underwent cytoreductive surgery for MPM in Ankara University Faculty of Medicine, Department of Thoracic Surgery between 2009 and 2021, 23 patients who received multimodal treatment and underwent P/D were evaluated retrospectively for survival analysis. The patients were divided into 2 groups: Group 1 (n=8)= neoadjuvant treatment+surgery+adjuvant treatment, Group 2 (n=15)=surgery+adjuvant treatment. Relationships between clinicopathological factors, multimodal treatment pattern and overall survival rates were investigated. SPSS version 23.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Kaplan-Meier method was used to calculate median survival and log-rank test was used to compare results. Statistical significance was accepted as p value <0.05 within the 95% confidence level.

Results: The number of females and males were 14/9, respectively, and the mean age was 58.7 years (50-69). The mean follow-up time of all patients was 43.5 months. The 2 and 5 year survival rates of all patients were 72% and 43%, respectively, and the 5 year median survival time was 36 months (Figure 1).The 2-year survival rate was not statistically different between the Group 1 and Group 2 (%70/%71, p=0.89).

Conclusions: The main problem in MPM is that the survival rate is very low. Today, it is known that better survival rate can be achieved with multimodal treatment. P/D is an acceptable method to achieve macroscopic complete resection in MPM surgery. P/D is a surgery that can have low morbidity and mortality after neoadjuvant treatment or as first-line treatment, and also has satisfactory survival results. It is possible to achieve better survival ratios by integrating targeted treatment or immunotherapy methods that block immune checkpoints to multimodal treatment.



Keywords: malignant pleural mesothelioma, pleurectomy, multimodal treatment

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-011 Integrating PD-L1 Expression to the CALGB Prognostic Scoring System in Malignant Pleural Mesothelioma

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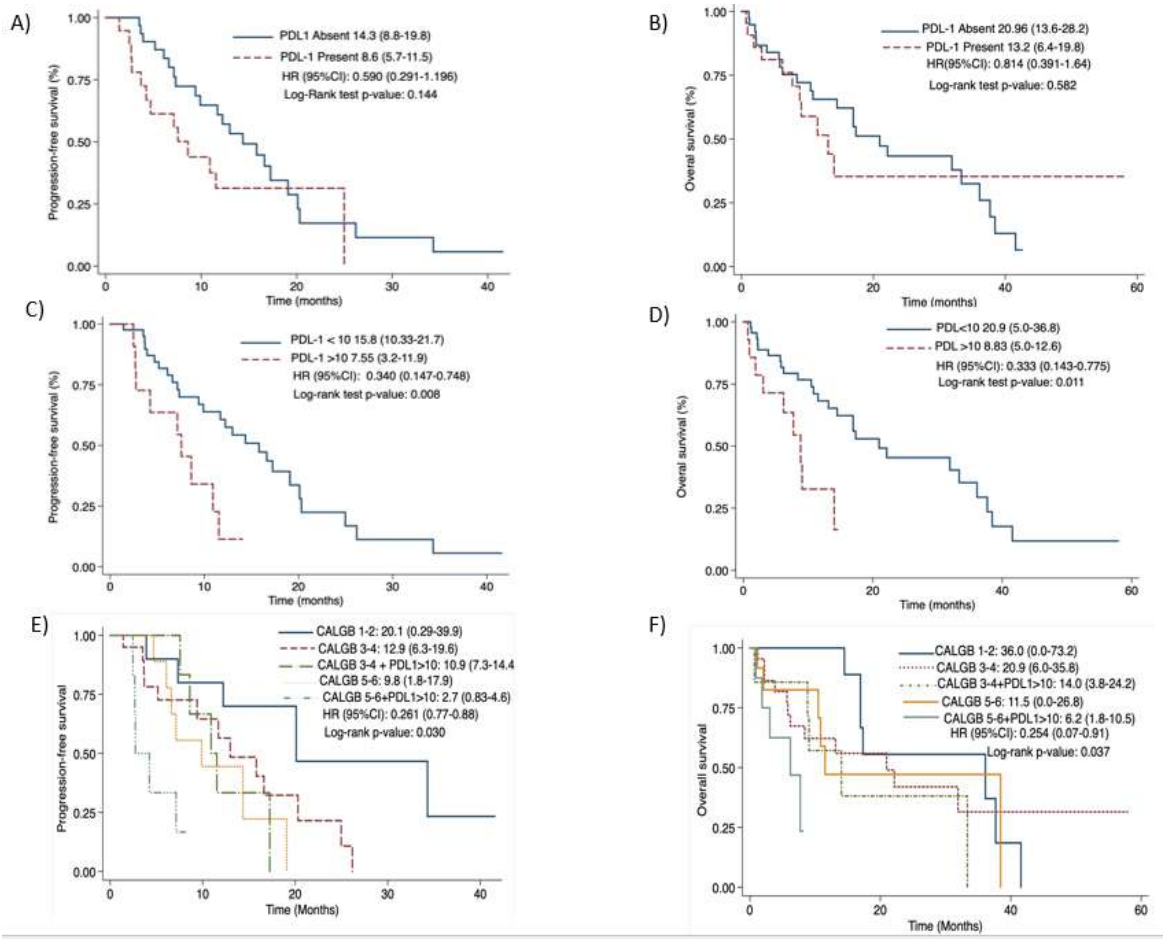
Introduction: Programmed death ligand-1 (PD-L1) expression is a predictive biomarker guiding treatment decisions with immunotherapy in lung cancer patients, but its role in malignant pleural mesothelioma (MPM) is unclear. However, evidence suggests that higher PDL-1 expression correlates with worse survival outcomes. The Cancer and Leukemia Group B (CALGB) prognostic scoring system is widely used to define prognosis in MPM. This study aims to assess the prognostic value of PDL-1 expression integrating it into the CALGB scoring system.

Methods: This retrospective cohort study evaluated samples with a confirmed locally advanced and metastatic MPM diagnosis between January 10, 2009, and December 31, 2019. PD-L1 tumor proportional score (TPS) was determined at diagnosis by a trained pathologist using the SP263 clone (Ventana, OptiView DAB IHC) in formalin-fixed paraffin-embedded (FFPE) tumor tissue specimens. PD-L1 expression cut-off points of interest were PD-L1 positive (TPS≥1%) and high-PD-L1 expression (TPS≥10%). Clinical variables of interest were associated with PDL-1 expression and PDL-1 expression cut-off points with survival outcomes.

Results: A total of 73 patients were included; mean age was 63.1 years, predominantly males (69.9%) and epithelioid histology (84.9%). Approximately 28% percent of patients had positive PDL-1 expression, and 23.3% had a high PDL-1 expression, defined as TPS ≥10%. An increased PD-L1 expression (TPS≥10%) was associated with worse progression-free survival (PFS) than patients with a low PDL-1 expression (TPS<10) [7.6 vs. 15.8 months; HR 2.17, 95% CI (0.89 - 5.27); p= 0.088]. A high PD-L1 expression also was associated with overall survival (OS), demonstrating a worse prognosis for patients with a higher PD-L1 expression [8.8 vs. 20.9 months; HR 2.44, 95% CI (1.01-5.93); p=0.048]. CALGB scores were distributed as follows: scoring 1-2 (17.8%), scoring 3-4 (45.2%) and scoring 5-6 (37%). Those patients scoring 1-2 did not have cases with a high-PD-L1 expression. In contrast, the highest number of cases (TPS≥10%) was observed in the group scoring 5-6. Multivariate analysis confirmed PDL-1 expression as an independent factor for PFS and OS in patients with MPM and a CALGB score of 5 to 6.

Conclusions: PD-L1 expression had prognostic implications in the current study. Patients with a high PD-L1 expression were significantly associated with lower survival outcomes in advanced MPM. Moreover, PD-L1 expression was a significant prognostic factor regardless of the CALGB validated scoring system. This study warrants prospective evidence for integrating PDL-1 expression into the CALGB scoring system.



Keywords: pleural mesothelioma, PD-L1 expression, CALGB prognostic scoring system

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-012 Ipilimumab and Nivolumab in Pretreated Patients with Malignant Pleural Mesothelioma

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Introduction: Combination immunotherapy with ipilimumab and nivolumab is a promising treatment option for patients with malignant pleural mesothelioma (MPM), but with still limited access and real-world data.

Methods: Ipilimumab (1mg/kg/6weeks) + Nivolumab (3mg/kg/2weeks) (I+N) treatment has been started in 13 patients diagnosed with non-resectable MPM, epithelial subtype, in our department, after progression on regular chemotherapy regimens. Data at cutoff point (28/2/2022) are being presented.

Results: Immunotherapy has been introduced in 2nd (7 pts, 54%) or 3rd line (6pts, 46%), with a median patient age of 69.7 years (46.3 - 80.9). Only one female and twelve male patients have been involved in this treatment. Until data cutoff, 3 cycles (2-4) of ipilimumab and 7 cycles (5-11) of nivolumab have been applied, with a median treatment time of 15.9 weeks (10.43-26). During that time 4 patients experienced disease progression, with an mPFS of 20.3 weeks. No deaths were reported. Current data suggest no PFS difference between patients who started I+N treatment in second line and those who started it in 3rd line (Chi square 2.307, p =0.129), but rapid disease progression on first-line therapy may indicate poorer disease response to immunotherapy (Chi-square 8.287, p=0.04). Data maturity is to be awaited to confirm or refute these results. Side effects in our patients were negligible, perhaps unexpectedly given the experience with dual immunotherapy to date. One case of grade 2 mucositis/gingivitis was observed, requiring only a 7-day treatment delay and symptomatic therapy. In another patient a grade 1-2 hyperthyroidism has been under evaluation at the time of date cutoff, requiring no treatment delay. No grade 3 or higher side effects have been observed to date.

Conclusions: Ipilimumab and nivolumab combination immunotherapy seems to be a well-tolerable treatment option for pre-treated patients with malignant pleural mesothelioma. The results so far are promising and hopefully mature results will continue to reflect a good response.

Keywords: mesothelioma, nivolumab, ipilimumab

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-013 Physical Function, Symptom Burden, and Quality of Life in Patients with Malignant Pleural Mesothelioma

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Introduction: There is insufficient prospective data on the factors that may impair the quality of life (QoL) of patients with malignant pleural mesothelioma (MPM). We investigated the associations between physical function, symptom burden, and QoL in order to identify key factors that may be targeted for supportive care interventions.

Methods: This was a prospective, cohort study of MPM patients enrolled consecutively at a single center. Baseline metrics were obtained at the first visit and repeated every 3 months for up to 5 visits. Symptom and QoL metrics were assessed via the EORTC QLQ-C30 questionnaire. Lower extremity function was measured with the Short Physical Performance Battery (SPPB), which includes balance, gait, and chair stand tests. Spearman rank correlation was used to examine baseline relationships between physical function and symptom and QoL measures. Univariate and multivariate Cox proportional hazards models were used to calculate hazard ratios for all-cause mortality.

Results: Seventy-six patients were enrolled between May 2019 and March 2020. Median age was 70 (range 41-89); 70% were male; 92% were White (non-Hispanic); 76.3% had epithelioid histology. The prevalence of baseline symptoms were: fatigue (80.3%), dyspnea (72.4%), insomnia (63.2%), pain (58.7%), constipation (39.5%), appetite loss (36.8%), nausea (23.7%), and diarrhea (17.1%). The mean EORTC global health status/QoL score was 67.2 (SD 19.7), mean EORTC summary score was 78.3 (SD 15.4), and mean SPPB score was 10.7 (SD 1.5). Total SPPB score was significantly correlated with global health status/QoL, summary health, fatigue, dyspnea, and appetite loss ($r \geq |.35|$, $p<.01$), but not with pain or insomnia. These correlations were preserved with chair stand performance, but QoL and symptom associations with balance and gait speed were weaker and generally not statistically significant. At time of data analysis, 33 patients (43.4%) were deceased. Decreased survival was associated with baseline severity of fatigue (HR 1.30 per 10-point increase in symptom score, 95% CI 1.12-1.51), dyspnea (HR 1.28, 95% CI 1.11-1.47), and appetite loss (HR 1.27, 95% CI 1.12-1.45). A higher total SPPB score was associated with better survival (HR 0.76, 95% CI 0.61-0.95), while among SPPB components, only chair stand performance was significantly associated with survival (HR 0.67, 95% CI 0.49-0.91).

Conclusions: This study confirms the high symptom burden of patients with MPM, with fatigue, dyspnea, insomnia and pain affecting more than half of patients. Our findings additionally show that lower extremity function, specifically measured by ability to perform chair stands, is significantly associated with symptom burden and QoL and may have prognostic significance for MPM patients. Lower extremity function may be a modifiable factor that supportive care interventions can target to improve QoL for patients.

Keywords: malignant pleural mesothelioma, quality of life, physical function

EP07.01-014 Mesothelioma-Associated Fibroblasts Enhance Mesothelioma Aggressiveness and Modulate Drug Response

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Introduction: Malignant pleural mesothelioma (MPM) is an aggressive malignancy, which arises from the pleural linings of the chest wall. Although it is less common than breast, lung or prostate cancer, MPM is almost always fatal, owing to rapid local spreading, limited therapeutic options and frequent recurrence after treatment. Unlike the majority of cancers, MPM rarely exhibits gain-of-function mutations in oncogenes and is rather characterized by inactivating alterations of tumor suppressor genes. Its highly malignant nature in absence of oncogenic driver mutations indicates an extrinsic supply of tumor-stimulating signals by cancer-associated cells of the tumor microenvironment. Cancer-associated fibroblasts (CAFs) represent the most abundant cell type in the tumor stroma of various cancers and have been shown to regulate many aspects of tumor progression, including proliferation, migration or therapy resistance. However, respective data for MPM is still very limited, and the role of patient-derived mesothelioma-associated fibroblasts (MAFs) in particular has not been studied so far. Here, we focus on MAFs and their impact on malignant behavior of MPM.

Methods: We isolated fibroblastoid cell populations from surgical specimens of MPM patients and characterized them on the DNA, RNA and protein level. We analyzed their genomes for amplifications and deletions by array-based comparative genomic hybridization, examined gene expression of common CAF markers using expression microarrays and quantitative real-time PCR, and analyzed proteomes and secretomes via LC-MS. To study MAF effects on MPM aggressiveness, we retrovirally introduced GFP into the genome of tumor cells and monitored them in 2D and 3D co-culture models with both cell types embedded in a collagen matrix. We investigated the influence of MAFs on tumor cell growth, migration and the response to various therapeutics including cisplatin and small molecule inhibitors relevant for MPM.

Results: The fibroblasts isolated from MPM samples exhibit a characteristic elongated cell shape and possess normal genomes without gene copy number aberrations typical for MPM cells. They express multiple CAF markers such as alpha-smooth muscle actin or fibroblast activation protein, and lack expression of MPM markers, like mesothelin confirming them as MAFs. Also, MAFs exhibit proteome and secretome profiles clearly distinct from normal lung fibroblasts with particularly strong differences in the fraction of actively secreted proteins. The presence of MAFs in 2D and 3D co-culture approaches significantly enhanced proliferation of tumor cells, with particularly strong effects in the 3D model. MAFs also significantly stimulated migration of MPM cells and strongly influenced the response to inhibitors of tumor-associated pathways. Surprisingly, the presence of MAFs resulted in an increased rather than a decreased cisplatin sensitivity of tumor cells.

Conclusions: In this study, we established and thoroughly characterized primary mesothelioma-associated fibroblasts as a new experimental platform for MPM research. We found a strong impact of MAFs on several aspects of MPM aggressiveness including tumor cell growth, migration and therapy response indicating a substantial role of MAFs in driving MPM progression.

Keywords: cancer-associated fibroblasts, 3D co-culture, pathway inhibitor response

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-015 Multimodality Imaging for Characterization, Classification, and Staging of Malignant Pleural Mesothelioma, Focusing on MR Imaging

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Introduction: Malignant pleural mesothelioma (MPM) is the most common primary malignancy of the pleura and the prognosis for MPM patients is still dismal despite the progress of treatment. Early diagnosis at a potentially curative stage is crucial to prolong patient survival and reduce morbidity and mortality. Here, we review the imaging findings of surgically confirmed MPM cases at preoperative CT and MR imaging.

Methods: This retrospective study included patients who underwent surgery for MPM between 1989 and 2021 at our tertiary care hospital. Patients' clinicopathological characteristics were collected from electronic medical records. Their preoperative chest CT and MR findings were analyzed by two thoracic radiologists as follows: location (right vs. left), pleural effusion, nodule (diameter ≤ 3.0 cm), mass (diameter > 3 cm), pleural or fissural thickening, chest wall involvement including malignant seeding along the tracts of biopsy needles or chest tubes. The maximum standardized uptake values (SUVmax) were obtained from the PET/CT report.

Results: Out of a total of 62 patients (median age, 58 years; range, 19 - 83; 45 men), 30 patients underwent excisional biopsy and 32 patients were treated with pleuropneumonectomy for MPM. Preoperative chest CT, MRI, and PET/CT were performed in 62, 33, and 43 patients, respectively. Epithelioid mesothelioma was most common pathologic subtype (34/62 [54.8%]), followed by biphasic (8/62 [12.9%]), sarcomatoid (4/62 [6.5%]), and desmoplastic subtypes (3/62 [4.8%]). The right hemithorax was involved more often than the left (34 [54.8%] vs. 26 [41.9%]) and there were two cases (3.2%) with isolated pericardial involvement. Pleural effusion was observed in the majority of patients (90.3% [56/62]) and it was the only finding in 5 patients (8.1%). Nodule and mass were observed in 44 (71.0%) and 17 patients (27.4%), respectively, and both were shown in 13 patients (21.0%). Pleural of fissural thickening was observed in 44 patients (71.0%). Chest wall involvement was observed in 18 patients (29.0%). SUVmax was available in 25 patients and their median SUVmax was 5.8 (range, 1.1 - 18.1). Findings to suggest asbestosis or asbestos-related pleural disease were not detected in any patient.

Conclusions: CT remains the primary imaging modality used to evaluate MPM and effectively demonstrates the extent of the primary tumor, intrathoracic lymphadenopathy, and extrathoracic spread. Thoracic MR imaging is complementary to CT for identifying invasion of the chest wall, mediastinum, and diaphragm. PET/CT is useful for demonstrating intrathoracic and extrathoracic lymphadenopathy and metastatic disease.

Keywords: mesothelioma, Compute tomography, Magnetic Resonance Imaging

EP07.01-016 Role of Neoadjuvant Chemotherapy in Thymic Tumors

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Introduction: Thymomas, although rare remain the most frequently encountered primary tumor of the anterior mediastinum comprising about 50% of all masses in the region. Surgical resection, via thymectomy, remains the mainstay treatment modality conventionally. In locally advanced and borderline resectable tumors, neoadjuvant chemotherapy may be utilized. Therefore, questions of efficacy and safety of the NACT arise.

Methods: Data from 25 patients (10 NACT vs 15 primary surgery) who had undergone tumor resection (January 2015-October 2021) collected from electronic medical records at the King Hussein Cancer Center. CT scan was used to delineate clinical staging, tumor size and to detect post therapeutic variations in tumor burden. The response evaluation criteria in solid tumors (RECIST) was used to classify effect of neoadjuvant chemotherapy (NACT) on tumor burden as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Pathological response was determined by measuring the percentage of necrotic tissue.

Results: The majority of patients were male. mean age 46.28 +-15.31 at diagnosis. Distribution among stages was similar; stage I (4; 16%), stage II (7; 28%), stage III (7; 28%), stage IV (7; 28%). Patients who received NACT were evenly distributed among stage III and IV accounting for 71.4% each. Eleven patients underwent VATS tumor resection; one of them is in the NACT group (10%). Negative resection margins in 96% ; 24 patients. Patients received 3-6 cycles platinum based NACT. A single patient who received definitive radiation and 12 cycles of chemotherapy outside our center developed chemotherapy induced heart failure and died immediately postoperatively. No other patients reported severe toxicity. The mean change in tumor volume and maximum diameter was 165 cm3 (p=0.079) and 1.53 +- 1.49 cm (p <0.01) respectively. Tumor diameter stratified according to stage showed a variation of 2.0+- 1.6 cm in stage IVa (p= 0.02) and 1+-1.35 cm in stage III (p= 0.08), respectively. The effect of NACT on tumor burden based on RECIST criteria was minimal as 80% (n=8) of patients had SD and the remaining 2 patients had PR and PD. Based on pathological findings, the average necrotic portion of the tumor was 39.5%.; 23% in stage III and 56% in stage IVa (p=0.152). The overall survival rate is 91.2%, mean survival was 115 months (4-125). Recurrence occurred in 28% (n=7). NACT group had a higher risk for recurrence (5; 50%) with a mean survival of 43.8 months in comparison to 59.6 months in those who did not receive induction therapy.

Conclusions: The exact role of induction chemotherapy in locally advanced thymoma patients theoretically to increase the chance of R0 resection still remains controversial. Though our study group number is small but we found that radiographic and histolopathological effect of NACT on thymic tumors is minimal with the greatest variation in tumor burden is in Stage IVa. However, regardless of stage, NACT was not found to significantly improve oncological outcomes compared to upfront surgery. To further demonstrate the impact of induction chemotherapy, we recommend multicentric collaborative studies.

Keywords: thymoma, neoadjuvant chemotherapy, upfront surgery

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-017 Malignant Fibrous Solitary Tumour of the Pleura Is Not All the Same: Evaluation of Risk Stratification Models in a Large Single Centre Series

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Introduction: Malignant solitary fibrous tumours of the pleura (mSFTP) are extremely rare diseases (<5% of all pleural neoplasms) with unpredictable behaviour. Surgery remains the standard of care for these tumours, however, estimating prognosis and planning follow-up remains challenging. Several risk stratification models have been proposed, but a classification with diagnostic and prognostic potential has not been yet well standardised. The aim of this study is to analyse the clinicopathological data of mSFTP to investigate their prognostic features and to compare the performance of three risk stratification models proposed in the literature.

Methods: Observational retrospective cohort study on all proven cases of mSFTP surgically resected with radical intent, between 2000 and 2019 in a single centre. Demographic, surgical and pathological data were examined. All patients were risk-stratified by using three prediction models: modified Demicco, De Perrot and Tapias. Overall survival(OS) and disease-free survival(DFS) were analysed

Results: There were 21 men and 13 women (median age, 67 years, range, 23-83 years). Twenty-one patients (62%) were symptomatic. Pathological and surgical details are described in table 1. Median follow-up was 111 months (range, 6-258 months). 5-year OS and DFS were 81.2% and 77.4%, respectively. Nine patients (26.5%) experimented recurrences. At univariate analysis the presence of calcification(p=0.000), necrosis(p=0.002), nuclear atypia (p=0.033); non administration of adjuvant treatment (p=0.050) and relapse/disease progression (p=0.006) were independent prognostic factor of worse OS. Radicality of resection (p=0.005); tumour dimension (p=0.013), the presence of necrosis (p=0.041) and nuclear atypia (p=0.004) and high expression of Ki67 (p=0.032) were independent prognostic factor of worse DFS. Analysing the three risk stratification systems, Tapias score has been revealed the best model to predict both OS (p=0.007) and DFS (p=0.008) in mSFTP.

Conclusions: Using the risk stratification model proposed by Tapias, patients with the highest risk of recurrence could be identified at the time of surgery to establish a more frequent imaging surveillance and longer follow-up.The role of adjuvant treatment for mSFTP has not been established yet, but further analysis on patients with high risk of recurrence, stratified according risk models, along with biomolecular panels may tailored future post-surgical therapies

Table 1 Surgical procedures, tumour characteristics and risk stratification	
Surgical procedures	
• Exeresis	14 (41.2%)
• Wedge resection	12 (35.3%)
• Lobectomy	6 (17.6%)
• Pneumonectomy	2 (5.9%)
Surgical approach:	Open: 31 (91.2%) Minimally invasive: 3 (8.8%)
Radicality:	R0: 31 (91.2%) R1: 2 (5.9%) R2: 1 (2.9%)
Pleural pattern	
• Parietal	4 (11.8%)
• Visceral	28 (82.4%)
• Inverted (intrapulmonary)	2 (5.9%)
Growth pattern	
• Nonpedunculated	23 (67.6%)
• Pedunculated	11 (32.4%)
Mitosis >4/10HPF	23 (67.6%)
Necrosis or haemorrhagic areas	28 (82.4%)
Inercellularity	23 (67.6%)
De Perrot	
• Stage 2	11 (32.4%)
• Stage 3	23 (67.6%)
• Stage 4	0
Modified Demicco	
• Low	10 (29.4)
• Moderate	9 (26.5%)
• High	15 (44.1%)
Tapias	
• Low	14 (41.2%)
• high	20 (58.8%)

Keywords: malignant solitary fibrous tumour, surgery, risk assessment

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-018 Phase III Randomized Trial on Surgery, Chemo and Pleural Radiation (IMPRINT) for Resectable Pleural Mesothelioma (NRG LU-006)

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Introduction: Pleurectomy/Decortication (P/D) has become a common lung-sparing surgical approach for MPM. Chemotherapy may be delivered in the neoadjuvant or adjuvant setting. Adjuvant hemithoracic IMPRINT was developed at Memorial Sloan Kettering Cancer Center and found safe in a multi-institutional phase II study, with promising survival outcomes. CTEP approved a phase III randomized cooperative group trial (NRG LU-006) to evaluate the efficacy of this lung-sparing trimodality treatment approach for resectable MPM.

Methods: Patients with newly diagnosed MPM amenable to P/D are enrolled and undergo upfront P/D followed by adjuvant platinum/pemetrexed chemotherapy (preferred approach) or neoadjuvant chemotherapy followed by P/D. Patients are stratified by epithelioid vs. biphasic histologic subtype, achievement of a macroscopic complete resection (R0/1 vs. R2), and center patient volume (≤10 vs. >10 P/Ds per year). Within 8 weeks after completion of the second modality, patients are randomized 1:1 to undergo hemithoracic IMPRINT vs. no further therapy. All IMPRINT contours and treatment plans are centrally reviewed. A contouring atlas and treatment planning constraints for target structures and organs at risk, including acceptable and unacceptable variations and deviations, were developed. Photon and proton therapy are permitted.The primary endpoint of the study is overall survival. Secondary endpoints include local failure-free, distant-metastases free and progression-free survival, treatment-related toxicities (CTCAE v5.0) and change in quality-of-life (EORTC QLQ-C30 mean score changes at 9 months post randomization). Exploratory objectives include correlation of clinical/radiographic staging with pathologic stage, immunologic and pathologic biomarkers as predictors of response, the rate of R0/R1 vs. R2 resections, and EORTC QLQ-C30 and LC13 symptom scores changes over time. As of 02/2022, 20 sites have been approved and 43 sites are pending approval to open the study. Treatment planning guidelines and helpful hints for photon and proton therapy will be presented. Eight patients have been accrued, and the target accrual is 150 patients.

Results: N/A

Conclusions: NRG LU-006 is open to accrual. This is the first NRG Oncology randomized phase III trial on malignant pleural mesothelioma and evaluates the use of IMPRINT following lung-sparing P/D and chemotherapy. Treatment planning aspects and current status will be presented.

Keywords: Pleural mesothelioma, Pleural radiation, NRG LU-006

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-019 Multiinstitutional Patterns of Use and Compliance with Tumor Treating Fields for Patients with Unresectable Malignant Pleural Mesothelioma

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Introduction: Given the significant lack of effective therapies for malignant pleural mesothelioma (MPM), Tumor Treating Fields (TTFields) was made available for use under an FDA-approved Humanitarian Device Exemption (HDE) protocol in 2019. In the phase 2 STELLAR study, a 68% median device usage rate (16.3 hours/day) was reported for MPM patients treated with TTFields along with platinum-based chemotherapy in the first 3 months. However, there is no reported real-world usage rate of TTFields for unresectable MPM to date and patterns of use may differ in clinical practice. The objective of this study was to evaluate the usage rates and duration with TTFields with MPM patients, outside the initial trial results.

Methods: Patients with histologically-confirmed unresectable MPM were enrolled onto FDA-required HDE protocols at 14 institutions from September 2019 to March 2022. All patients were treated with a regimen of continuous TTFields (150 kHz) therapy. Usage patterns and rates were analyzed from the device output data. For comparison of categorical and continuous variables, Chi square test or Wilcoxon signed-rank test were used.

Results: 33 patients with unresectable MPM were included. The median number of TTFields usage days was 72 (range: 6-649 days) and the combined treatment duration was 160 months for all patients. A low usage rate defined as less than 6 hours/day (25% of daily duration) was observed in 34 (21.2%) of the total 160 months. Four (12.1%) patients discontinued the treatment by the first month. The median number of 4-week TTFields cycles was 3 (range 1-23 cycles). The median TTFields device usage in the first 3 months was 12 hours/day (range: 1.9-21.6 hours), representing 50% (range: 8%-90%) of the potential daily duration. Nineteen (57.5%) patients chose to discontinue TTFields after 3 months. The median TTFields usage after 3 months decreased to 9.1 h/day (range: 3.1- 17 h), representing 38% (range: 13%-71%) of the daily duration and was lower than usage in the first 3 months ($p=0.01$). The overall usage was 10.3 h/day (range: 1.9-21.4 h) which was 43% (range: 8%-89%) of daily duration during all treatment courses. Three (9.1%) patients had a compliance rate over 75% (manufacturer suggested usage) and 4 (12.1%) patients had a usage rate over 68% (median compliance rate in the STELLAR study). Six (18.2%) patients had a usage under the low usage rate. Significant differences were observed in usage across months with the highest percentage of usage observed in first treatment month with 56% (range: 8%-90%) and lowest percentage of usage in last treatment month with 32% (range: 1%-74%) ($p<0.05$). We observed self-discontinuation in 23 (69.7%) patients, mostly in first three months.

Conclusions: This study is the first multicenter analysis of real-world TTFields usage - an emerging treatment approach for several solid tumor malignancies - based on usage patterns for MPM patients in clinical practice. We observed that this treatment combination is a feasible treatment strategy for appropriately selected patients. Ultimately, use patterns correlated with clinical characteristics and disease control rates will be necessary to determine the optimal threshold compliance rates for MPM disease control.

Keywords: mesothelioma, TTFields, compliance

EP07.01-020 Pulmonary MALT Lymphoma: Detailed CT Findings

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Introduction: Pulmonary mucosa associated lymphoid tissue (MALT) lymphoma is a rare and malignant neoplasm affecting the lung. Its CT characteristics have been described in previous studies but due to their nonspecific and heterogeneous description, radiological diagnosis is still largely difficult, often being mistaken as lung primary adenocarcinomas or sarcoidosis. We performed an analysis to describe the detailed chest CT findings with pulmonary MALT lymphoma, with emphasis on the presence of extrapulmonary involvement.

Methods: From January 2011 to December 2021, 43 patients (23 men; mean age, 57.7 years ± 13.2) with pathology-confirmed pulmonary MALT lymphoma and available chest CT immediately prior to pathology confirmation were selected for this study. Chest CT scans were reviewed for various findings, including "galaxy sign" described in sarcoidosis, by two radiologists who reached a conclusion by consensus. Patients were classified as those with pulmonary involvement only (group 1) and those with pulmonary and extrapulmonary involvement (group 2), and CT findings were compared between group 1 and group 2 using Mann-Whitney U test.

Results: Of total 43 patients, 29 patients (67.4%) presented as multiple lung lesions; 33 (76.7%) patients showed nodule or mass, 15 (34.8%) patients showed consolidation, and 4 (9.3%) patients showed both nodule/mass and consolidation on CT, with bronchocentric distribution of lesions in 32 patients (74.4%). Other CT findings were GGO component (21 patients, 48.8%), air-bronchogram (39 patients, 90.7%), perilesional spicules (34 patients, 79.7%), and "galaxy sign" (17 patients, 39.5%). GGO component was associated with intralesional interstitial thickening in 95.2%. All patients in group 2 demonstrated multiple lung lesions (p=0.031) and more patients in group 2 showed "galaxy sign" (75.0% vs. 31.4%, p=0.025). 27 out of 43 patients (62.8%) were not correctly diagnosed before pathology confirmation, but majority of patients in group 2 (87.5%) were correctly diagnosed before pathology confirmation (p=0.005).

Conclusions: Pulmonary MALT lymphoma should be considered in multifocal bronchocentric nodules or masses with air-bronchogram and perilesional spicules; GGO with intralesional interstitial thickening and "galaxy sign" may also be seen.

CT findings in patients with pulmonary MALT lymphoma

CT characteristics	Total (n=43)	Pulmonary involvement only (n=35)	Pulmonary and extrapulmonary involvement (n=8)	*p* value
Single vs. multiple Single multiple	14 (32.6)29 (67.4)	14 (40.0)21 (60.0)	08 (100.0)	0.031
Nodule or mass	33 (76.7)	26 (74.3)	7 (87.5)	0.430
Consolidation	15 (34.8)	12 (34.3)	3 (37.5)	0.865
GGO component	21 (48.8)	17 (48.6)	4 (50.0)	0.943
Bronchocentric distribution	32 (74.4)	26 (74.3)	6 (75.0)	0.967
Air-bronchogram	39 (90.7)	31 (88.6)	8 (100.0)	0.321
Perilesional spicules	34 (79.1)	27 (77.1)	7 (87.5)	0.521
Separate interlobular septal thickening	5 (11.6)	5 (14.3)	0	0.261
Galaxy sign	17 (39.5)	11 (31.4)	6 (75.0)	0.025
Intralesional cavity	10 (23.3)	7 (20.0)	3 (37.5)	0.296
Lymphadenopathy (> 1cm)	6 (14.0)	4 (11.4)	2 (25.0)	0.323

Keywords: lymphoma, mucosa associated lymphoid tissue, CT

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-021 Clinical and Biochemical Profiling of Pleural Mesothelioma Patients Treated with Immunotherapy

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Introduction: Pleural mesothelioma (PM) is a rare and very deadly disease for which there is the necessity to predict treatment's response and to estimate the overall prognosis. For decades, the only approved treatment for PM has been platinum-based chemotherapy with pemetrexed. Recently the combination of ipilimumab plus nivolumab (I-N) and nivolumab monotherapy (N) have demonstrated a survival benefit in these patients (pts). Nevertheless, any predictive factors of response to immune checkpoint inhibitors (IO) have been identified yet. The aim of this study is to evaluate the clinical value of inflammation-based biomarkers in PM during IO.

Methods: From October 2017 to February 2022, we retrospectively collected data of pts with unresectable PM and ECOG PS 0 - 2 that received I-N or N monotherapy in second/third line or the combination of platinum-based chemotherapy with IO (pembrolizumab (P) or atezolizumab (A)) (CT - IO) in first line. We analyzed data to evaluate the impact of PS (0-1 vs 2), BMI (≤25 vs >25), baseline CRP-to-albumin ratio (CAR cutoff 7.5), neutrophil-to-lymphocyte ratio (NLR cutoff 5), lymphocyte-to-monocyte ratio (LMR cutoff 7.4) values and Glasgow Prognostic Score (GPS), evaluating CRP >10.0 mg/l and low albumine ≤3.5 g/dL, and defined as GPS 0 no alterations, 1 CRP or albumin altered, GPS 2 both altered, (GPS 0 vs 1-2) on overall response rate (ORR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS). The thresholds for NLR, LMR and CAR were based on data available in literature. The impact of these variables on PFS and OS was evaluated through Pairwise comparisons using Log-Rank test whereas Fisher's exact test was performed for DCR and ORR.

Results: Among 30 pts enrolled, 22 (73%) received IO treatment (11 I-N and 11 N) and 8 (27%) received (CT - IO). Median follow up was 12.5 months (mo), median OS was 25.4 mo and median PFS was 8.4 mo. We found that DCR and ORR were associated with PS 1 ($p<0.001$ and 0.03), CAR ≤7.5 ($p<0.01$ and 0.03), GPS 0 ($p<0.001$ and <0.01) and NLR≤5 ($p<0.003$ but not statistically significant in ORR $p=0.09$). In survival analyses, better PFS was associated with PS 0-1 (9.7 vs 1.4 mo, $p<0.0001$), NLR ≤5 (15.5 vs 4.4, $p<0.0001$) while was showed a better OS in PS 0-1 (NR vs 2.1 $p<0.0001$), CAR ≤7.5 (NR vs 10.5 $p=0.016$), NLR ≤5 (NR vs 9.4, $p=0.0016$) and GPS 0 (NR vs 0.5 $p=0.025$). None other associations were found.

Conclusions: Our data suggest an association between inflammatory biomarkers and prognosis in patients with PM treated with IO or CT-IO. If validated prospectively, these easy-to-measure biomarkers could be used to predict IO efficacy in PM patients.

Keywords: Pleural mesothelioma, Immunotherapy, Biomarkers

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-022 Analysis of Second Surgery for Recurrence in Malignant Pleural Mesothelioma (MPM) Patients (P)

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Introduction: MPM is a highly aggressive pleural tumor associated with asbestos exposure and with limited survival despite systemic therapy. Recently immunotherapy have demonstrated survival benefit in first line. Currently there is no universally accepted surgical therapy for MPM and it remains unclear whether cytoreductive surgery prolongs survival. Some reports on selected patients demonstrated that, at the progressive disease, second round surgery is an effective strategy with minimal morbidity and promising survival rates. The objective of this study is to characterize the role of surgical procedures for recurrence on survival in p diagnosed with MPM at our institution.

Methods: We review 200 MPM p diagnosed at Vall d´Hebron University Hospital between November 2002 and April 2021. Associations between clinical variables and outcome were assessed with Cox regression models and survival data were calculated by the Kaplan-Meier method.

Results: Patient's characteristics: median age 68 years (y) (45-88 y), males: 70%, performance status (PS)1: 69%, asbestos exposure: 75%, epithelioid subtype: 81%. First line chemotherapy was offered to 85% of p and 19 p were treated in clinical trials in first line. Median survival (OS) in overall population was 21.3 m (95%CI18.8-23.9). Epithelioid histology, PS 0 and treatment with cisplatin vs carboplatin were associated with significant improvements in OS. Surgical treatment was performed in 102 p (79 p talc pleurodesis, 19 p pleural decortication and 4 patients extrapleural pneumonectomy). Among these patients, 7 p received second surgery (5 p debulking or partial pleurectomy and 2 p talc pleurodesis) and histology was epithelioid in 6 p and biphasic in 1 p. Median OS for p receiving some surgical procedure was 23.2 m vs 18.8 m for p without surgery (HR0.68, 95%CI 0.49-0.95). The median time between the first and second surgery was 21 m. OS of patients receiving second surgery was 39.1 m vs 21.1 m for p without second surgery (HR0.42, CI95% 0.15-1.13). The median survival after second surgical procedure was 15 m (2.9-NA).

Conclusions: Currently, studies of surgery in MPM have not provided a clear benefit on OS. In our series, second surgery was an acceptable option for selected MPM p. Randomized trials are necessary to measure the efficacy of surgery in MPM

Keywords: malignant pleural mesothelioma, surgery, prognosis

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-023 Family History of Cancer in a Series of Malignant Pleural Mesothelioma (MPM) Patients (P)

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Introduction: MPM is a highly aggressive pleural tumor associated with asbestos exposure and with limited survival despite systemic therapy. Recently immunotherapy have demonstrated survival benefit. Studies of familial aggregation of MPM have identified *BAP-1* as a tumour suppressor gene involved in the increased risk of mesothelioma. The objective of this study is to explore familial history of cancer in p diagnosed with MPM at our institution.

Methods: We review 200 MPM p diagnosed at Vall d´Hebron University Hospital between November 2002 and April 2021. Associations between clinical variables and outcome were assessed with Cox regression models and survival data were calculated by the Kaplan-Meier method.

Results: Patient's characteristics: median age 68 years (y) (45-88 y), males: 70%, performance status (PS)1: 69%, asbestos exposure: 75%, epithelioid subtype: 81%. First line chemotherapy was offered to 85% of p and 19 p were treated in clinical trials in first line. Median survival (OS) in overall population was 21.3 m (95%CI18.8-23.9). Epithelioid histology, PS 0 and treatment with cisplatin vs carboplatin were associated with significant improvements in OS. Familial history was recorded in142 p and 41 p presented familial history of other cancers. Among the 41 patients with familial history of cancer median age was 64 years, 25 p were male, 34 p had asbestos exposure and 33 p presented epithelioid histology. The most common familiar tumor antecedent was lung carcinoma (15 cases), followed by breast (10 cases), colon (6 cases) and hepatocarcinoma (5 cases). None of the p presented relatives with *BAP1-1* related tumors. In our series 24 p presented only one relative with history of cancer, 12 patients presented 2 relatives with cancer and 5 p had 3 or more relatives with cancer. Among the 41p con familial history only 2 p were evaluated in a counselling genetic unit and in one case germline alteration was detected (*BRCA2*). The median OS of p with familial history was 25 m vs 22.3 m p without familial history (95%CI0.63-1.52, HR 0.98)

Conclusions: In our series, 29% of p with MPM presented familial history of cancer and only 2 p were evaluated in counselling genetic unit. Further studies on larger series of MPM and family history of cancer could help in monitoring of family members for the purpose of early detection.

Keywords: malignant pleural mesothelioma, genetic counselling, BRCA2

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-025 Survival Advantage of Pulmonary Metastasectomy in Advanced Melanoma Patients: A Population-Based Study

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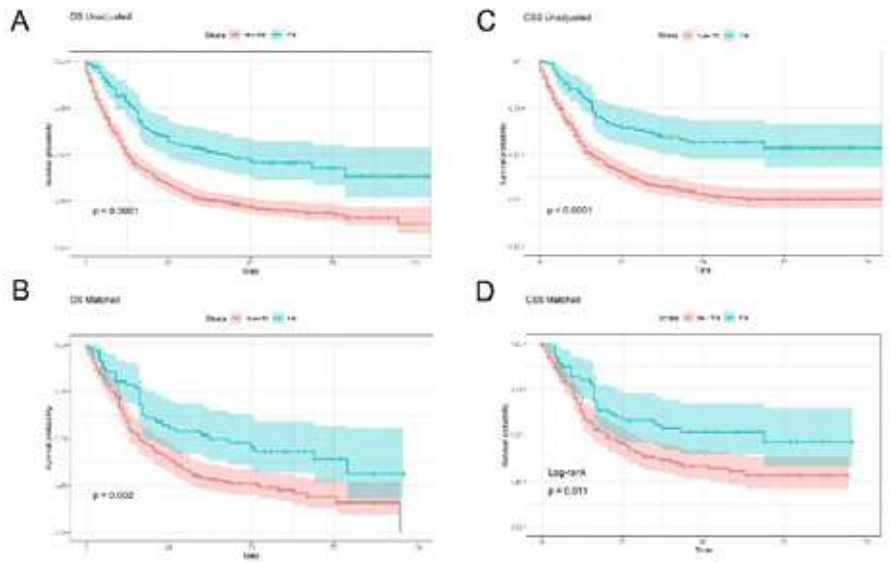
Introduction: The lungs are a common site for metastasis for many cancer types. In advanced melanoma patients, the performance of pulmonary metastasectomy (PM) requires more evidence. Our aim is to study the survival effect of PM in advanced melanoma patients.

Methods: We have extracted all adult patients diagnosed with advanced melanoma with lung metastasis (7th AJCC Stage M1b) in the period of 2010 to 2015 using the Surveillance, Epidemiology, and End Results (SEER) database. Patients with any extrathoracic metastases were excluded. Primary outcomes were overall survival (OS) and cancer-specific survival (CSS) in months. We employed Kaplan-Meier plots to analyze survival outcomes. A multivariate Cox proportional hazards model was used to adjust for covariates such as age, sex, marital status, surgery of the primary tumor, undergoing chemotherapy, and radiotherapy. To further eliminate the nonrandomization bias, we carried out an inverse probability treatment weighted (IPTW) analysis to estimate the effect of PM on OS and CSS.

Results: Our query included 520 patients, of which 18.8% (n=98) of patients have undergone PM and 81.2% (n=422) did not. Median (IQR) age was 71 (61-80) years. Most patients had an N0-1 disease (58.1%, n=302). T0 stage was found in 34.4% of patients (n=179). A portion of patients had a primary surgical resection (41.7%), 26.2% and 12.3% have undergone chemotherapy and radiotherapy, respectively. A higher median OS was found in patients who underwent PM than ones who did not (43.0 months, 95% CI: 25.0-not reached vs. 13 months, 95% CI: 11-16). The median CSS in PM group patients was not reached (95% CI: 43.0-not reached), while it was 16 months (95% CI: 13-21) in non-PM patients. Older age, being never married, and not undergoing primary surgical resection, were all significant independent prognostic factors for worse OS and CSS, while sex, and receipt of chemotherapy and/or radiotherapy did not affect survival outcomes. PM group patients had a statistically significant survival advantage than non-PM patients, for both OS and CSS (HR = 0.50, 95% CI: 0.37-0.67 and HR = 0.45, 95% CI: 0.32-0.63, respectively). As for IPTW analysis, OS was still significantly higher in PM patients (HR = 0.42, 95% CI: 0.30-0.59), in addition to CSS (HR = 0.38, 95% CI: 0.26-0.57).

Conclusions: PM could provide survival benefits in a multimodality treatment plan for certain advanced melanoma patients who had lung metastasis only. These patients should receive a carefully individualized management to enhance their survival chances.



Keywords: Metastasectomy, Oligometastases, Melanoma

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-024 Preclinical Investigation of Immune Checkpoint Blockade and Anti-Angiogenic Therapy in Malignant Pleural Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) is a fatal cancer type that affects the membranes lining the lungs and is causally associated with asbestos exposure. Despite the effectiveness of conventional anti-cancer treatment, its prognosis remains very poor. We previously demonstrated a significant survival benefit for PD-L1 blockade in preclinical models of MPM. Data from preclinical studies in other tumour models show that anti-PD-L1 and anti-angiogenic therapy can enhance each other's efficacy, thereby supporting the investigation of combined blockade of PD-L1 and VEGFR2 in MPM.

Methods: The AE17 C57BL/6 mesothelioma mouse model was used to identify a good dose for anti-VEGFR2 and to investigate the effect of combined treatment with anti-PD-L1 in the concomitant, adjuvant, and neo-adjuvant settings. Tumour cells were injected subcutaneously. Treatment was given intraperitoneally every third day for a total of 3 doses (q3dx3). In the adjuvant and neo-adjuvant groups, the start of the second treatment was delayed by 5 days. Tumour growth and survival were monitored over time.

Results: Dose titration of anti-VEGFR2 revealed statistically significant tumour growth delay and survival benefit compared to PBS for all doses tested (100, 200, 400, 800μg). The highest concentration (800μg) also differed significantly from the other doses in terms of tumour growth. We therefore selected 800μg anti-VEGFR2 for combination with anti-PD-L1. Results from our preclinical evaluation of the concomitant combination therapy indicated a significant tumour growth delay and survival benefit for both anti-PD-L1 monotherapy and its combination with anti-VEGFR2. However, no significant differences were observed between these two treatments. Therefore, we conducted additional experiments to evaluate the potential of different treatment schedules (concomitant, adjuvant, neo-adjuvant) compared to monotherapy and PBS control. Results from all treatment groups indicated a significant tumour growth delay, and a survival benefit was observed for the concomitant and neo-adjuvant groups, but not the adjuvant group.

Conclusions: *In vivo* investigation of combined anti-PD-L1 and anti-VEGFR2 therapy revealed significant effects for the concomitant administration of both antibodies as well as in the neo-adjuvant setting. However, in order to identify the best combined immunotherapeutic strategy, verification of these data in our second MPM mouse model is still ongoing. Future work will look into the impact of anti-VEGFR2 on the tumour microenvironment and vasculature.

Keywords: Malignant pleural mesothelioma, Immune checkpoint blockade, Anti-angiogenesis

EP07.01 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - CLINICAL

EP07.01-026 Primary Pulmonary Ewing´S Sarcoma: Post Hoc Analysis From Two International Multicenter Prospective Randomized Trials

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Introduction: Primary pulmonary sarcoma accounts for 1% of all pulmonary malignant tumors. Ewing's sarcoma (ES) is an aggressive cancer with an incidence of 1 per 1,000,000. It is most commonly diagnosed in the second decade of life. It usually derives from bony structures of the axial skeleton, pelvis and femur but can occur in every localization. Pulmonary ES is extremely rare with less than 40 cases reported mostly as case reports. Here we aimed to gain better understanding of primary pulmonary ES in describing patients treated within two international multicenter prospective randomized ES trials.

Methods: Data from patients with primary pulmonary ES were retrieved from database of the EURO-E.W.I.N.G.99 (ClinicalTrials.gov identifier: NCT00020566) and EWING-2008 (ClinicalTrials.gov identifier: NCT00987636) trials. Patient and treatment characteristics were analyzed.

Results: Out of 2969 patients with ES, 13 (0.4%) had primary pulmonary ES. Median age at diagnosis was 35 years (3 to 66). Seven (53%) patients had metastases at time of diagnosis. All patients underwent multiagent chemotherapy consisting of vincristine, ifosfamide, actinomycin D, etoposide (VIDE) and vincristine, actinomycin D, ifosfamide/cyclofosfamide (VAI/VAC). Twelve (92%) patients had biopsy prior to multimodal treatment, while one (8%) had upfront surgery. Ten (77%) patients underwent surgical resection. Type of lung resection were wedge (n=2, 20%), wedge plus pleurectomy/decortication (n=1, 10%), lobectomy (n=3, 30%), intrapericardial pneumonectomy (n=1, 10%) and extrapleural pneumonectomy (n=3, 30%). Six (46%) patients underwent extended resection including pericardium, diaphragm, chest wall and atrium. R0 resection was achieved in n=5 (50%) patients. Postoperative Radiotherapy was performed in 8 (80%) patients. Mean follow-up was 33 months (±26). Overall, 5-year survival for the whole cohort was 40%. 5-year survival for patients who underwent R0 resection was 80%.

Conclusions: Primary pulmonary ES is extremely rare and often presents with metastatic or locally advanced disease. R0 resection within multimodality treatment offers good long-term survival.

Keywords: Ewing Sarcoma, Multimodality Treatment, Primary pulmonary sarcoma

EP07.02 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL

EP07.02-001 Evaluation of FGF18 as a Contributing Factor in Malignant Pleural Mesothelioma Growth and Its Role as a Potential Biomarker

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Introduction: Malignant pleural mesothelioma (MPM) is an aggressive malignancy originating from the mesothelial lining of the pleural cavity. Despite the numerous advances in treatment approaches in recent years, the prognosis remains poor with a median overall survival time (OS) ranging from 10 to 22 months. Therefore, the identification of novel non-invasive biomarkers is urgently needed in order to identify patients with a better prognosis and to make the best personalized therapeutic decision. In our previously published study, we were able to show that fibroblast growth factor 18 (FGF18) is overexpressed in MPM tissue specimens. Also, in pleural mesothelioma cell lines, FGF18 showed very high gene expression levels when compared to most other FGF family members. The objective of this study is to further explore the effects of FGF18 on MPM cells to evaluate FGF18 as a contributing factor in MPM cell growth and migration as well its role as a potential plasma biomarker.

Methods: FGF18 gene expression was analyzed by quantitative real-time reverse transcription PCR (qRT-PCR) and in silico. Cell lines overexpressing FGF18 were generated by retroviral transduction and cell behavior was investigated by clonogenic growth and transwell assays. Plasma was collected from 40 MPM patients at the time of diagnosis or before surgical resection. Samples from 40 healthy participants and from 6 patients with non-malignant pleural diseases served as controls. Circulating FGF18 was measured by enzyme-linked immunosorbent assay and correlated to clinicopathological parameters and survival.

Results: Forced overexpression of FGF18 resulted in reduced cell growth but increased migration in one of two cell models with low to moderate endogenous FGF18 expression investigated. Circulating FGF18 was significantly lower in patients with MPM and pleuritis/fibrosis (P=0.004) when compared to healthy controls (P<0.001). Non-epithelioid histology showed a slight, however not significant, tendency towards higher plasma FGF 18 levels (P=0.205) when compared to epithelioid morphology. Median OS for the entire cohort was 622 days. Overall, no significant association of circulating FGF18 with OS of MPM patients could be observed (median survival 725 versus 567 d, HR 1.177, 95% CI 0.537-2.580, P=0.685 in the low and high FGF18 groups, respectively). Epithelioid histology held a prognostic value in the univariate analysis (P=0.027), it was not, however, found to be an independent prognostic factor in our cohort on multivariate analysis (P=0.123).

Conclusions: Our findings on cell growth and migration suggest that FGF18 can influence the behavior of a subset of MPM cells. Despite high expression in MPM cell lines and in tissue, FGF18 could not be connected to prognosis.

Keywords: mesothelioma, biomarker, FGF18

EP07.02 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL

EP07.02-002 Investigating the Role of MicroRNAs in Cell Growth and Cisplatin-Sensitivity of Malignant Pleural Mesothelioma

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Introduction: In recent years, in vitro studies, including our own, have shown that re-expression of tumour suppressive microRNAs can alter malignant pleural mesothelioma (MPM) cell line growth, and that dysregulation of microRNAs might contribute to the intrinsic resistance towards the standard therapeutic regimen of platinum/pemetrexed. Since our screening for predictive biomarkers has revealed several candidates, we have recently decided to expand our studies from the three previously analysed microRNAs to a systematic evaluation of a larger number of predictive and prognostic biomarker candidates.

Methods: The MPM cell lines MSTO-211H (biphasic origin), H28, Meso-1, Mero-82 (all epithelioid origin) and the non-malignant transformed cell line MeT-5A are revers transfected with 1 and 5nM of synthetic microRNA mimics (Shanghai GenePharma) for a total of currently 15 candidates. Growth of transfected cells is assessed using a SYBR Green assay every 24h from 48-120h post transfection. In addition, the colony forming ability of cells is assessed 5-7 days post transfection. The migratory potential of the cells is evaluated using scratch wound healing assays, with photos taken at 3h, 6h and 24h post transfection. Lastly, to evaluate sensitivity to cisplatin and pemetrexed, 24h post transfection cells are subjected to increasing concentration of the respective drug for 5 days, at which time point the IC50 value is determined.

Results: Of the 15 candidates identified as potential biomarkers in our previous studies, in addition to miR-30a, miR-221-3p and miR-380-5p on which we reported previously, an additional 4 new candidates showed growth inhibition at varying degrees in all MPM cell lines. The most pronounced effects were observed for miR-210, which reduced cell growth at 120h to 30-50% of mock transfected cells, and for miR-625-3p, which resulted in a reduction to 35-65%. Growth of non-malignant MeT-5A cells remained largely unaffected. In addition, transfection with mimics of miR-222 and miR-19b, resulted in reduction of cell growth to 60-80% of mock transfected cells. Furthermore, for miR-210 and miR-625-3p, we also observed a strong decrease in colony forming ability to 5-35% of the control in MSTO-211H, H28, and Meso-1. In Mero-82, the reduction in colony forming ability was lower, but still reached 50% of the control. The wound healing capacity was however not consistently altered by re-expression of these 4 microRNAs. Finally, miR-625-3p and miR-19b were also able to sensitise cells to cisplatin, with the strongest effect observed in MSTO-211H for miR-19b (IC50 from 7.5µM reduced to 0.7µM), and in Mero-82 for miR-625-3p (IC50 from 3.75µM reduced to 0.8µM). Evaluation of the response to pemetrexed and the cisplatin/pemetrexed doublet is currently underway.

Conclusions: Similar to our previous findings, we could show that additional prognostic and predictive microRNA candidates also hold therapeutic potential in MPM, as they were able to reduce MPM cell growth and colony forming ability in vitro. Based on the currently available data, further evaluation of these candidates is warranted. In the next steps, we will also evaluate the effect of simultaneous re-expression of several candidates and investigate the effect of microRNA re-expression on their target genes and downstream signaling pathways.

Keywords: malignant pleural mesothelioma, microRNAs, chemoresistance

EP07.02 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL

EP07.02-003 Characterization of the Extracellular Vesicle-Derived Transcriptome in Malignant Pleural Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) is usually detected at an advanced stage. Several studies have shown a link between RNA (i.e. mRNA, lncRNA, miRNA) detected in extracellular vesicles (EVs) and disease prognosis and progression, putting a special focus on EVs' role in cancer. In this study, we characterize the transcriptome of EVs isolated from tumor cells from MPM patients to gain first insights into the RNA components of the MPM secretome.

Methods: Primary cell cultures of tumor cells isolated from pleural effusion of 4 MPM patients were established. EVs from cell culture supernatants were extracted using Qiagen Exoeasy Maxi kit followed by RNA extraction using the mirVana PARIS and RNA sequencing (single-end, 101 bp). Reads were trimmed and filtered using Trimmomatic and mapped on the GRCh38 reference genome using STAR. Gene counts were calculated using Kallisto and normalized using cpm.default function from edgeR package. Survival analysis was performed using the survminer package on the TCGA-MESO dataset. CircRNA was identified using an in-house script and CIRI2. Extravesicular RNAs were compared against the Vesiclepedia database.

Results: In EVs isolated from 4 primary MPM lines, we obtained between 30-47 million high quality reads (Phred>30) which were processed and mapped on the reference genome: the average mapping rate was 68% with the majority of reads mapping to multiple loci (17.5% uniquely mapped reads on average). Given the high proportion of multi-mapped reads, we used Kallisto to count gene expression. We detected a total of 14,800 RNAs expressed in all samples, including 12,543 protein coding genes, 2,011 lncRNAs, 3 miRNAs, 25 snoRNAs and 43 snRNAs. We compared the identified genes against records from Vesiclepedia database: 2,085 protein coding RNAs were previously found in EVs (in normal, glioblastoma, melanoma and Ewing sarcoma samples). None of the miRNAs (MIR663B, MIR3648-1, MIR3648-2) were reported in Vesiclepedia, but were mentioned in literature. Exosomal MIR663B promotes proliferation and epithelial-to-mesenchymal transformation (EMT) in cervical and bladder cancers while MIR3648 promotes proliferation in prostate cancer. Additionally, we found that higher expression of transcription factor ZFHX3 is associated with worse survival of TCGA-MESO patients (Cox p-value<0.05). Based on the mean expression of genes across samples, we searched for enriched pathways. The top enriched ones were TNFA signaling via NFKB, P53 and EMT. Finally, we identified 5 circRNAs in MPM EVs of which circMYO10 was previously shown to promote proliferation and progression in osteosarcoma.

Conclusions: Our preliminary study has shown that MPM tumor cells secrete EVs containing diverse RNA species as a cargo. These RNAs might serve as circulating biomarker candidates. In further steps, we will focus on identification of novel mRNAs and miRNAs and extend the analysis with additional samples and datasets.

Keywords: malignant pleural mesothelioma, transcriptome, bioinformatics

EP07.02 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL

EP07.02-004 Endogenous Retrovirus Expression and Type I Interferon Signaling in Human Mesothelioma

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Introduction: Pleural mesothelioma (PM) is a rapidly fatal tumor. The Cancer Genome Atlas (TCGA) investigation of PM revealed that patients with activated type-I interferon (IFN) pathway have a better clinical outcome. We recently demonstrated that the expression of endogenous retroviruses (ERV) due to promoter demethylation contributes to dsRNA formation and activation of type-I IFN signaling in an experimental mouse model of mesothelioma development. The aim of this study is to investigate ERV and type-I IFN activation in human PM.

Methods: ERV's expression was determined from TCGA and Bueno's cohorts RNA-seq data, as well as mesothelial precursors RNA-seq data as non-tumor control. ERV's expression was confirmed by qPCR. Methylation of genomic DNA was assessed after treatment with sodium bisulfite followed by quantitative methylation specific PCR. DNA demethylation was induced in human mesothelial cells by demethylating agent 5-Aza-2'-deoxycytidine (5-Aza-CdR) treatment. To block the type-I IFN signaling, cells were treated with JAK inhibitor Ruxolitinib or with small interfering RNA to down-regulate mitochondrial antiviral signaling (MAVS). IFN stimulated genes (ISGs) expression upon 5-Aza-CdR or Ruxolitinib treatment was determined by qPCR and Western Blot (WB). Flow cytometry using J2 antibody in the presence or absence of RNase III digestion and J2 pull-down were used to verify the presence of dsRNA.

Results: Long-terminal-repeats (LTR) represent the most abundant transposable elements (TE) upregulated in PM patients datasets compared to mesothelial precursors. 86% and 57% of LTR represent more than two fold upregulated TE in TCGA dataset and Bueno dataset, respectively. Within LTR, we identified three representative ERVs which are specifically enriched in PM and we further analyzed the most abundant one, "hMesoERV-1". We confirmed that that its expression was lower in normal compared to tumor tissue and in mesothelial cells compared to mesothelioma cells. The presence of dsRNA was detected by flow cytometry and we verified that "hMesoERV-1" is part of the dsRNA by J2 pull-down. The levels of "hMesoERV-1" were significantly increased by 5-Aza-CdR treatment in mesothelial cells. We determined that 5-Aza-CdR induced "hMesoERV-1" promoter demethylation. hMesoERV-1 promoter was more demethylated in mesothelioma tissue compared to non-tumor tissue. 5-Aza-CdR treatment of mesothelial cells was also accompanied by increased levels of ISGs. Basal ISGs expression was higher in mesothelioma cells with intact IFNB1 gene compared to mesothelial cells and it was significantly decreased by treatment with Ruxolitinib or MAVS silencing. Furthermore, we found that ISGs expression was higher in the tumor tissue with high expression levels of "hMesoERV-1", High expression of "hMesoERV-1" was associated with longer overall survival.

Conclusions: Immunotherapy has been recently approved as first-line treatment for unresectable PM and best response is predicted in tumors with an activated basal immune response. We may provide tools for patients' stratification if tumor tissue is available.

Keywords: Mesothelioma, Endogenous Retrovirus, Type-1 Inteferon

EP07.02 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL

EP07.02-005 Multicenter Clinical Analysis, Gene Expression Profiling and Correlation Analysis of Immune Cell Infiltration in Pleural Mesothelioma

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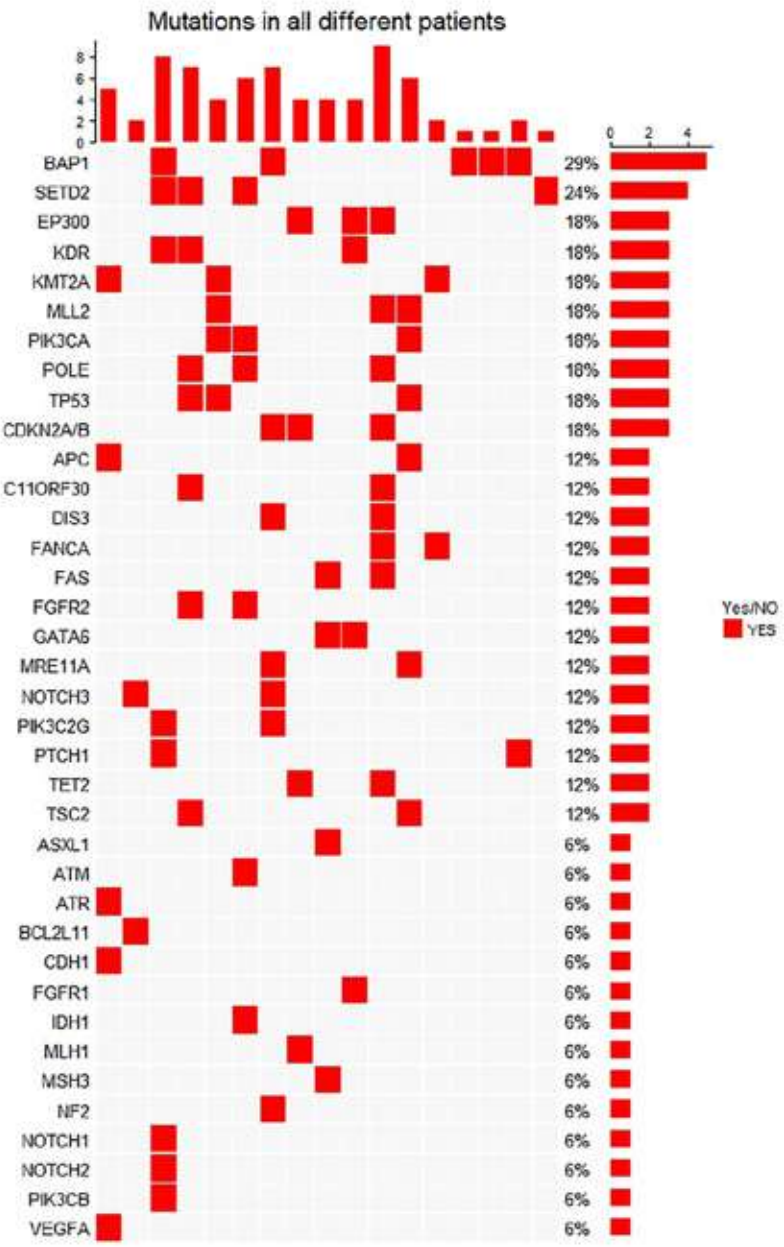
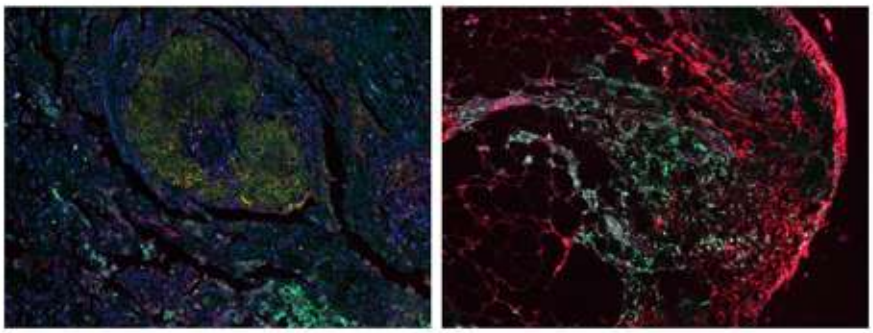
Introduction: Malignant pleural mesothelioma (MPM) is a rare malignant tumor. There are big differences between Eastern and Western populations. At present, there are few research data on the eastern population for pleural mesothelioma. This study aims to study the clinicopathological data, gene expression profile and tumor immune microenvironment of MPM patients from multicenters of Eastern populations.

Methods: A comprehensive analysis of clinicopathological characteristics and immunotherapy was performed by retrospectively collecting 30 patients with MPM from multiple centers. Among them, the paraffin sections of 17 patients were detected by panel-NGS, and the genes with higher mutation frequency were selected. Subsequently, public database and multiplex immunohistochemistry was used in 20 MPM patients to verify the correlation between these genes and various immune cells.

Results: There are slightly more males than females in patients with pleural mesothelioma in China. Epithelial type is the main type, and the positive expression rate of calbindin, Wilms tumor gene 1 and pinpodin is high. The mutation rate of BRCA1 associated protein 1 (BAP1) gene detection was 64.7%. The efficacy of immunotherapy alone or combined chemotherapy was considerable (2 PR, 11 SD). Furthermore, we identified potential target genes BAP1, SETD2, PI3KCA and BCL2L11 in MPM patients through public databases combined with real-world analysis. Mutations of these genes are associated with abnormal expression of PD-L1, CD11b, CD8, LAG3, CD163 and TIGIT. In addition, we also found that the expressions of PD-L1 and TIGIT were significantly increased in mesothelioma tissue compared with normal pleural tissue and the expressions of CD11b and LAG3 were significantly decreased ($P<0.05$).

Conclusions: We performed a multicenter analysis of clinicopathological characteristics and a series of potential immune-related genes of MPM were identified. In addition, we also initially explored the immune microenvironment of MPM. However, large sample studies were need to validate our results.





Keywords: Malignant pleural mesothelioma, Gene expression profile, Immune microenvironment

EP07.02 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - PRECLINICAL

EP07.02-006 Tumor Immune Microenvironment Related Makers are Overexpressed and Served as Favourable Prognostic Factors in Resectable ESCC

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Introduction: Previous studies have shown that the expression of tumor immune microenvironment (TIME) related makers is closely related to tumor prognosis. However, there are rare studies to explore the prognostic value of related biomarkers in patients with resectable esophageal squamous cell carcinoma (ESCC). Therefore, we conducted a retrospective study to investigate the relationship of PD-L1, CD8, LAG3, TIGIT, TIM3, and CD163 expression and the clinicopathological features in resectable ESCC patients.

Methods: We used multiple immunofluorescence histochemistry techniques to evaluate the surgical specimens of 89 patients with complete resection of ESSC. Real-time RT-PCR was used to detect mRNA expression of TIGIT in 5 ESCC cell lines compared with the normal esophageal epithelial cell line. The expression of TIGIT in pan-cancers was analyzed in TCGA/cBioportal/The Human Protein Atlas project database.

Results: The PD-L1, CD8, LAG3, TIGIT, TIM3, and CD163 were highly expressed in 20, 46, 20, 40, 16, and 37 ESCC cases. The high expression of these five biomarkers (PD-L1, CD8, LAG3, TIGIT, and CD163) was favourable prognostic factor for overall survival. High expression of PD-L1 and CD163 were also significantly correlated with an improvement of disease-free survival (PD-L1: P = 0.002, CD163: P = 0.027). Interestingly, TIGIT was also overexpressed in ESCC cell lines. Furthermore, we reconfirmed TIGIT high expression in ESCC by fluorescence co-localization. We further validated TIGIT was overexpressed in many cancers especially in the squamous carcinoma subtype in the public database.

Conclusions: In summary, the high expression of TIME related makers including TIGIT can be a good prognostic predictor for resectable ESCC. Notably, unlike previous studies, TIGIT is not only expressed in T cells or NK cells, but also highly expressed in ESCC cell lines and tumor tissue. Further studies to explore the biological function and mechanism of TIGIT in tumor cells, especially squamous cell carcinoma cells are urgently needed.

Keywords: esophageal squamous cell carcinoma (ESCC), immune microenvironment, biomakers

EP07.03 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - THYMOMA

EP07.03-001 Comparison of Treatment Outcomes in Neoadjuvant Chemotherapy and Chemo-radiotherapy for Thymoma and Thymic Carcinoma

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Introduction: Thymomas and thymic carcinoma are rare disease and completeness of resection has consistently been shown to be a critical factor for determining prognosis. Neoadjuvant chemotherapy has been adopted widely to achieve complete resection, and recently there is an attempt to addition of radiotherapy. The aim of our study was to verify whether neoadjuvant concurrent chemoradiotherapy (CCRT) offers an advantage in resectability and toxicity in comparison with neoadjuvant chemotherapy.

Methods: We retrospectively reviewed 69 patients who received neoadjuvant chemotherapy or CCRT between Jan, 2010 and March, 2021 at our institution. Of the total patients, 33 (48%) patients were thymoma and 36 (52%) patients were thymic carcinoma. In this study, we evaluated the resectability with negative resection margin and toxicity between neoadjuvant chemotherapy and CCRT in locally advanced thymoma and thymic carcinoma patient. In addition, we compared impact of radiographic response rate and downstaging rate of based on neoadjuvant treatment.

Results: Among all patients in this study, 20 (29%) and 49 (71%) were clinical stage III and IV, respectively. There were no significant differences in negative resection margin rate (13.6% vs 19.0%, P = 0.844) and radiographic response rate (31.8% vs 27.7%, P = 0.821) between the CCRT and chemotherapy group. However, CCRT group shown significant different in rate of tumor downstaging, especially about T stage (tumor downstaging: 77.3% vs 40.4%, P = 0.009, T-downstaging: 86.4% vs 31.9%, P < 0.001). Grade III neutropenia was lower in neoadjuvant CCRT patient (4.5% vs 29.8%, P = 0.040) and other toxicity was not shown significant difference.

Conclusions: Neoadjuvant CCRT and chemotherapy shown no significant difference in resection margin status, but CCRT group shown higher rate of tumor downstaging and less toxicity.

Table 1. Resection margin status

34(	Neoadj.CTx (N=47)	Neoadj. CCRT (N=22)	p
Resection margin			0.844
RM negative	34(81.0%)	19(86.4%)	
RM positive	8(19.0%)	3(13.6%)	

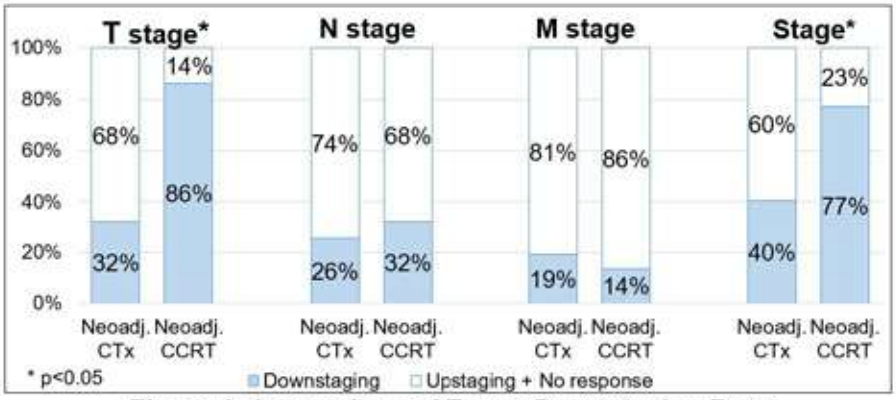

Figure 1. Comparison of Tumor Downstaging Rate

Keywords: Neoadjuvant chemo-radiotherapy of thymic carcinoma, Comparison of chemotherapy and chemo-radiotherapy, neoadjuvant therapy of thymic carcinoma

EP07.03 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - THYMOMA

EP07.03-002 Combined Classifications for Thymoma and Thymic Carcinoma From a 10 years CHUM University Hospital Real-world Experience

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Introduction: Despite thymomas and thymic carcinomas being rare mediastinal tumors, WHO histologic and modified Masaoka surgical classifications translate to different predictive staging.

Methods: In this single-center, retrospective study using SARDO oncologic database, patients diagnosed with thymoma or thymic carcinoma between 2008 and 2018 at the Montreal University hospital center (CHUM), were reviewed. Inclusion criteria were patients receiving oncologic treatments at CHUM and being followed for at least 1 year. We tried to combine the modified Masaoka (I, II, III, IV) and the WHO (AB, B1-2-3, Carcinoma) staging classifications in our population in order to have better prognostic factors and a better multidisciplinary treatment approach.

Results: Over a period of 10 years, 66 patients were identified using our inclusion criteria: 52 thymomas and 14 thymic carcinomas. 22 thymomas were associated with paraneoplastic syndromes such as myasthenia gravis (n=19) and Good syndrome (n=3). Amongst the AB thymomas, 45% were stage I (n=9) and 55% were stage II (n=11). The B thymomas (B1 n=8, B2 n=16 and B3 n=8) had a wider range of stages with 28% stage I (n=9), 44% were stage II (n=14), 6% were stage III (n=2) and 22% stage IV (n=7) at diagnostic. The thymic carcinomas C were diagnosed 14% at stage I (n=2), 21% at stage II (n=3), 7% at stage III (n=1) and 57% at stage IV (n=8) at diagnosis. The 5y OS of AB thymomas was 93% and of B thymomas was 97% compared to only 80% for thymic carcinoma C. When looking by modified Masaoka staging, the 5y OS was 95% for stage I, 95% for stage II, 100% for stage III and 79% for stage IV. Combining this data gave us a 38% risk of death for stage IV thymic carcinoma C, only 11% risk of death for stage I thymoma B and 18% for stage II thymoma AB. The 5y OS for stage IV thymic carcinoma was 56%. The resection rate was 90% for the stage I thymoma AB and 100% for stage I thymoma B and thymic carcinoma. No neoadjuvant treatment was given for stage I, but 20% received adjuvant treatment, including one with positive margins. For stage II, the resection rate was 100% for thymomas AB with no neoadjuvant treatment but 9% of positive margins, 93% for thymomas B without neoadjuvant treatment but 38% of positive margins and 100% for thymic carcinomas with 66% neoadjuvant treatment and all negative margins. In stage III, all patients were resected, but 50% with positive margins with no neoadjuvant treatment. In stage IV, the resection rate was 100% for thymomas B and 75% for thymic carcinomas. Despite 40% of neoadjuvant chemo, 71% of thymomas B had positive surgical margins and 50% of thymic carcinomas whereas 83% had received neoadjuvant chemotherapy.

Conclusions: Our single center results demonstrate that combination of WHO and modified Masaoka staging classifications improve predictive value. In addition, neo-adjuvant therapy was associated with reduced positive margins for stage II disease. These results warrant validation in larger cohorts.

Keywords: thymomas, thymic carcinomas, modified Masaoka staging classification, Neoadjuvant treatment

EP07.03 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - THYMOMA

EP07.03-003 First Line Combination of Toripalimab and Chemotherapy in Advanced Thymic Carcinoma: A Single-Center, Prospective, Single-Arm, Phase II Trial

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Introduction: Thymic epithelial tumors (TETs) are rare primary tumours of the mediastinum, derived from the thymic epithelium, which are classified as Thymomas (Ts) and thymic carcinomas (TCs). Platinum-based chemotherapy is the standard of care (SOC) for patients with advanced TCs, but the efficacy is limited. Toripalimab is a novel PD-1 inhibitor. We initiated a phase II, prospective trial to explore the activity, safety and feasibility of toripalimab plus SOC as first line treatment in advanced thymic carcinoma.

Methods: Key inclusion criteria: patients aged ≥18 years, ECOG≤2, Histologically or cytologically confirmed Masaoka stage III or IV TC, without prior system anticancer therapy after diagnosed with this disease, adequate organ function. Eligible patients will receive toripalimab (240mg, d1) in combination with paclitaxel (175mg/m2, d1) and carboplatin (AUC=5, d1), q3w, for 6 cycles. Afterwards, Toripalimab (240mg, d1, q4w) maintenance therapy would be given continuously until disease progression, intolerable toxicity, or withdrawal by the patients' request. Primary end point: Progression-free survival (PFS). Secondary end points: objective response rate (ORR), duration of response (DOR), Disease control rate (DCR), overall survival (OS), time to response (TTR) and safety. This study is registered with chinadrugtrials.org.cn, ChiCTR2000039155.

Results: From Dec. 2020 to Jun. 2021, 5 patients were enrolled. Median age was 46 years (range: 37-61) and 60.0% were male. 3 (60%) patients were still on treatment (toripalimab maintenance) at the time of analysis. For 5 patients, 3 (60.0%) partial responses, 2 (40.0%) stable diseases were observed. The ORR was 40.0% (2/5) and DCR was 100.0% (5/5). At the time of data cutoff, the median PFS and OS were not reached. Treatment-related adverse event (TRAE) of any-grade occurred in 5 patients. Grade 3-4 TRAE occurred in 2 patients: 1 with grade 3 myelosuppression and 1 with grade 4 myelosuppression. No new safety signals were observed and no TRAEs leading to treatment discontinuation or death.

Conclusions: Toripalimab combined with chemotherapy is efficient and well tolerated as first line therapy for advanced TCs patients. This study is ongoing, and more data will be released. And we look forward to demonstrating that Toripalimab combination becomes a new SOC for such rare tumors.

Keywords: Thymic Carcinoma, Toripalimab, PD-1 inhibitor

EP07.03 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - THYMOMA

EP07.03-004 Efficacy of Thoracic Radiotherapy for Local Progression in Advanced Thymic Carcinoma

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Introduction: Advanced thymic carcinoma is a rare epithelial tumor of the thymus with a poor prognosis. Local advance is crucial in many patients due to the anatomical adjacent large vessels, bronchus, and heart. Thoracic radiotherapy is the main modality for the treatment of local progression. We analyzed the efficacy of radiotherapy to anti-mediastinal region in patients with advanced and recurrent thymic carcinoma.

Methods: We retrospectively reviewed the data of patients with diagnosis of advanced and recurrent thymic carcinoma and treated by thoracic radiotherapy for local control at our hospital between June 2005 and October 2021. Progression free survival (PFS) and Overall survival (OS) were calculated from the start of thoracic radiotherapy.

Results: A total of 46 patients received chemotherapy and radiotherapy to mediastinal region. We focused on 14 patients who only had local progression which had any of the following lesions: pleural or pericardial dissemination, mediastinal lymph node metastases, or vessel invasion. Median of age was 62 years (range: 25-75) and all the patients were ECOG-PS 0-1. 78.6% of patients were males and 85.7% of histology were squamous cell carcinoma. The median follow-up time was 41 months. 13 patients had Masaoka stage IV diseases at a diagnosis and 1 patient had local recurrence after surgery. All 14 patients had 7.1% stage II, 14.3% stage III, and 78.6% stage IV diseases before radiotherapy. The median total dose of radiotherapy was 60 Gy (range: 40-66), and 12 patients received first-line carboplatin plus paclitaxel before radiotherapy. The median PFS was 12.6 months (95%CI: 6.41-30.6); median OS was not reached (95%CI: 33.9-not reached); median duration of the local control (with or without progression in other sites) after radiotherapy was not reached (95%CI: 12.6-not reached).

Conclusions: Our study found that thoracic radiotherapy in advanced thymic carcinoma could obtain good local control and eventually lead to good survival.

Keywords: advanced thymic carcinoma, thoracic radiotherapy, local control

EP07.03-005 MesoGraph: Graph Neural Networks for Weakly Supervised Cellular Profiling in the Subtyping of Malignant Mesothelioma Images

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Introduction: Malignant mesothelioma is typically subtyped into Epithelioid (E), Sarcomatoid (S), and Biphasic (B) according to the proportions of epithelioid and sarcomatoid tumor cells present. Identification of the subtype informs treatment and can improve patient outcome, however this subtyping has a high level of variability between pathologists.

A novel dual-task Graph Neural Network (GNN) architecture is developed to learn a model capable of scoring regions of tissue down to cellular resolution. The ability to quantitatively score tissue on how much sarcomatoid component is present, and overlay cell-level instance scores, will help pathologists assess a sample more quickly and consistently.

Methods: The dataset used is a collection of 4 H&E stained biopsy Tissue Micro-arrays (TMAs) scanned using Hamamatsu Nanozoomer-S360 at 20×. After removal of damaged/incomplete cores, we use 243 cores, of which 155 are E, 64 B, and 24 S. Only core-level labels are available. We represent each TMA core as a cell graph, segmenting cells and extracting features as illustrated in Fig. 1 and learning a GNN model in a weakly supervised Multiple Instance Learning setting, using the core labels to learn a cell-level scoring. The mean of the cell-level scores is used to predict the subtype of a core.

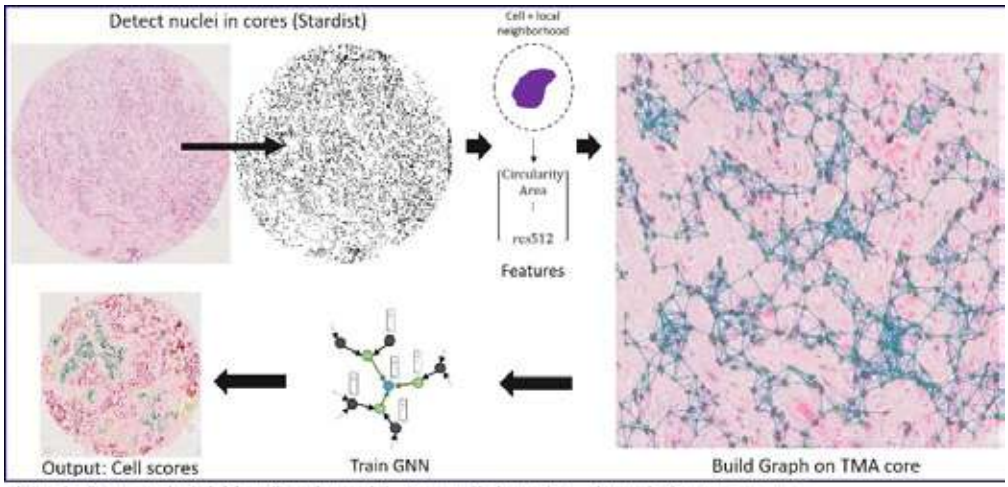

Fig. 1. Steps to build MesoGraph model, from cell detection, through feature extraction and graph construction, to model training

Results: For performance evaluation we employ a hold-one-out cross-validation strategy over slides. We acheive an AUROC of 0.908 +/- 0.011 on the subtyping task. Our model outputs can be visualised in an interactive GUI, as can be seen in Fig. 2.

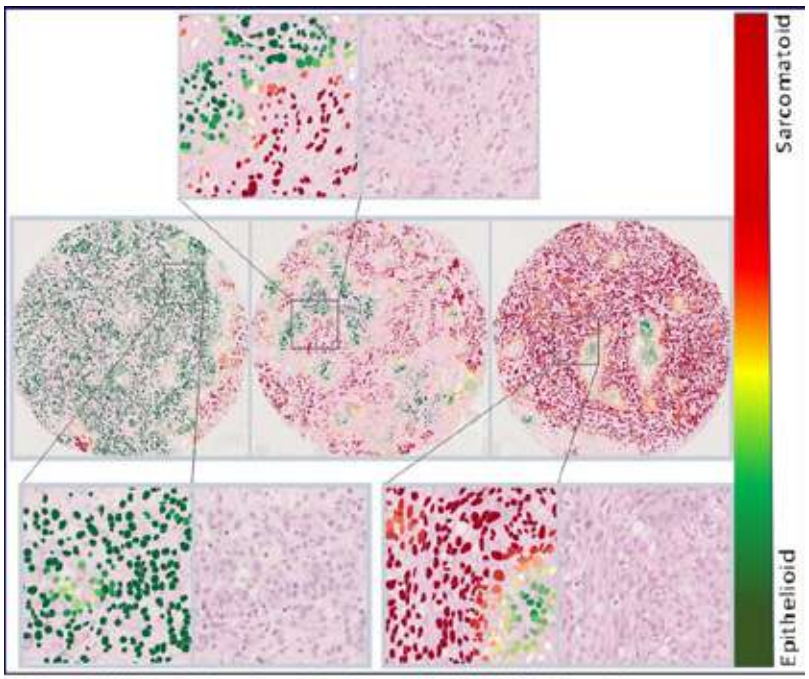

Fig. 2. Model visualisation. From left to right, an Epithelioid, Biphasic and Sarcomatoid core, together with zoomed regions showing cell morphology

Conclusions: We have developed a model capable of learning a cell-level indication of sarcomatoid and epithelioid regions of a TMA core. This approach could help pathologists to subtype a core more accurately, consistantly and efficiently, and paves the way to move from categorical subtypes towards a more fine-grained characterisation matching the underlying continuous biological expression of tissue on the E-S spectrum.

Keywords: Mesothelioma Subtyping, Graph Neural Networks, Multiple Instance Learning

EP07.03 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - THYMOMA

EP07.03-006 Feasibility of TTFields with Pemetrexed and Platinum-Based Chemotherapy for Unresectable Malignant Pleural Mesothelioma: Real-World Data

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Introduction: Management of malignant pleural mesothelioma (MPM) is challenging as patients frequently present with unresectable advanced disease and the response rates with systemic therapy alone remain low. Tumor Treating Fields (TTFields) is an antimitotic locoregional treatment comprising of low-intensity, alternating electric fields delivered through a portable medical device to the chest. Given the paucity of effective therapies for MPM, TTFields treatment was made available for use under an FDA-approved Humanitarian Device Exemption (HDE) protocol in 2019, but no real-world data beyond the initial trial have been published to date. The objectives of this study were to evaluate the implementation, compliance rates, clinical outcomes, and treatment-related toxicities associated with TTFields in combination with pemetrexed plus platinum-based chemotherapy in patients with unresectable MPM, outside the initial trial results.

Methods: Consecutive patients with histologically confirmed unresectable, locally-advanced or metastatic, MPM were enrolled onto a FDA-required HDE protocol at a single tertiary care institution from 2019 to 2021. All patients were treated with a protocol-defined regimen of continuous TTFields (150 kHz) and pemetrexed plus platinum-based chemotherapy. Compliance rates were computed from the device output data and treatment-related toxicity was evaluated using CTCAE v4 criteria.

Results: Five patients with unresectable MPM (4 epitheliod and 1 sarcomatoid) were enrolled. The median age was 69 years (range: 64-84 years) and 60% were male. Two patients received palliative radiotherapy prior to TTFields treatment (30 Gy/10 fractions and 30 Gy/5 fractions). The median number of pemetrexed and platinum-based chemotherapy cycles was 5 (range 2-6) during TTFields treatment; all patients were treated with the carboplatin and pemetrexed combination. None of the 5 patients developed any Grade 4+ chemotherapy-related adverse effects. The median number of 4-week TTFields cycles was 5 (range: 2-7 cycles). Median compliance with TTFields in the first 3 months was 12.5 hours per day (range: 5-16.8 hours), representing 52% (21%-70%) of the potential daily duration. The median compliance with TTFields after 3 months decreased to 8.9 hours per day (range: 6.2-11.5 hours), representing 37% (26%-48%) of the potential daily duration. The median follow-up was 5.4 months (range: 1.1-20.9 months). Treatment-related dermatitis was the only side effect associated with TTFields treatment and was reported as grade 1-2 in all patients; no patient had grade3+ device-related toxicities. Four (80%) patients were alive at the time of analysis. To date, one patient had a distant progression in a gastrohepatic lymph node after 6 cycles of TTFields, the remaining 4/5 (80%) patients continue to have stable disease, and 2/5 (40%) continue to use the device. The 6-month and 1-year progression-free survivals were 80% and 53%, respectively.

Conclusions: This study represents the first results of the real-world implementation of TTFields for MPM. In comparison to the initial clinical trial, initial compliance rates were lower, although skin-related adverse events appeared similar. Further initiatives and guidelines should be developed to manage treatment-related dermatitis and improve treatment compliance.

Keywords: mesothelioma, TTFields, side effects

EP07.03 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC MALIGNANCIES - THYMOMA

EP07.03-007 Clinicopathological Analyses for Predicting Recurrence After Complete Resection of Thymoma

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Introduction: The purpose of this study is to evaluate the prognosis of patients with completely resected thymoma and to identify clinicopathological predictors of recurrence.

Methods: We retrospectively reviewed clinicopathological data of consecutive 96 patients who underwent complete resection of thymoma from 2003 to 2016 and were followed 5 years or longer. Clinicopathological features of patients who developed postoperative thymoma recurrence were compared with those without recurrence, and predictors of recurrence were identified using a univariate analysis.

Results: The median age was 55 (range, 21 to 74) at surgery, and 42 (44%) were men. 88 patients (82%) were p-stage I and 8 patients (8%) were p-stage III (TNM classification 8th edition), no patients were p-stage II nor IV. During the follow-up, a total of 7 patients developed recurrence, and the pattern of recurrence included pleural dissemination in 4, mediastinal lymph node in one, mediastinum in one, and distant (lung) metastasis in one. The median time to recurrence was 4.0 years (range, 1.2-9.0). The pathological tumor diameter was longer in recurrence group than in non-recurrence group (7.0 cm vs. 3.9 cm,$p<0.001$). All tumors in recurrence group were 3cm or larger (range, 3.0-16.5). In recurrence group, p-stage was also higher than non-recurrence group (p-stage III-IV: 43% vs. 6%, $p=0.01$). Among 7 patients who had tumors larger than 3 cm and p-stage III, 3 (43%) patients developed recurrence. Type of resection (thymomectomy or thymectomy) and WHO histological classification were not different between 2 groups. In 7 patients with recurrence, one patient died of thymoma progression 1.5 years after surgery and one patient died of other disease 10 years after surgery, but the remaining 5 patients were alive without disease by resection of recurrent lesion (n = 3) and radiotherapy (n = 2). The median post-recurrence survival of the 7 patients was 4.7 years (0.2-9.0) and the 5-year overall survival of all 96 patients was 97.9%.

Conclusions: In patients with completely resected thymoma, pathological tumor in addition to p-Stage could be useful for predicting recurrence.

Keywords: thymoma recurrence, complete resection, surgery

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-001 Update Analysis of Sintilimab with Two Cycles Chemotherapy for Untreated Advanced Squamous Non-small-Cell Lung Cancer

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Introduction: Most sq-NSCLC patients were aged, heavy somkers, with multiple comorbidities who were considered badly-tolerated to chemotherapy. We designed this multi-center, single arm, phase II study of sintilimab plus two cycles nab-paclitaxel / carboplatin in treatment naïve advanced squamous NSCLC patients, aimed to maximize the antitumor activities with less toxicity.

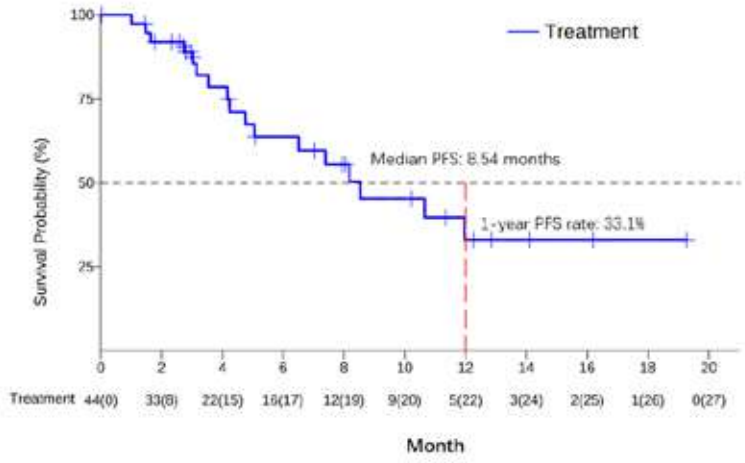
Methods: Eligible patients will receive sintilimab (200mg, IV) with nab-paclitaxel and carboplatin on day 1 every 3 weeks for 2 cycles. Patients without disease progression (PD) will receive sintilimab (200mg, Q3W) until PD, intolerable toxicity, death, or for up to 2 years. Primary end point is progression free survival (PFS). Secondary end points are objective response rate (ORR), duration of response (DOR), disease control rate (DCR), overall survival (OS) and safety.

Results: 44 patients were enrolled and treated from May 2020 to Feb 2022. Most patients were stage IV (33/44). Median age was 65 years. Median follow-up was 4.21 months (range 0.03, 19.25) until Feb 28 2022. Median PFS was 8.54 months (95% CI: 4.76 mo - NA), and the 1-year PFS rate was 33.1% (95% CI: 17.7%, 61.5%) (Picture 1). ORR was 75.7% (28/37) and DCR was 97.3%(36/37)among 37 evaluable patients. Median time to response was 1.49 months (range 1.48 mo, 1.51 mo), and median DOR was not reached. OS was immature. Until data cutoff, 36 patients (81.8%) experienced treatment emergent adverse events (TEAEs), among which 10 (22.7%) were Grade 3-4, 2 (4.5%) were Grade 5 considered not treatment related. Potential immune-related AE occurred in 34 patients (77.3%), including 5 (11.4%) grade 3-4 irAEs. No grade 5 irAEs were observed (Table 1).

Conclusions: Sintilimab combined with two cycles nab-paclitaxel / carboplatin showed encouraging PFS and manageable safety profile as first line therapy for advanced squamous NSCLC. Enrollment continues until 50 patients per protocol designed.

Safety Summary	Sinti + chemo
Any TEAEs	36 (81.8%)
Grade 3-4 TEAEs	10 (22.7%)
Serious AEs	8 (18.2%)
TEAEs led to death	2 (4.5%)
TEAEs led to any treatment discontinuation	4 (9.1%)
Immune related AEs	34 (77.3%)
Grade 3-4 irAEs	5 (11.4%)
Grade 5 irAEs	0
≥ 10% TEAEs	
Anemia	34.09%
ALT Increased	25.00%
Albumin Reduction	15.91%
Hyperthyroidism	15.91%
GGT Increased	15.91%
AST Increased	15.91%
Leukocyte Decreased	13.64%
Fatigue	11.36%
Platelets Decreased	11.36%

Picture 1. PFS of Sintilimab combined with two cycles nab-paclitaxel / carboplatin.



Keywords: PD-1, squamous NSCLC, Immunotherapy

EP08.01-002 Real-World Survival Outcomes of Patients with High PD-L1 Advanced NSCLC Who Received Chemo-Immunotherapy vs Immunotherapy

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Introduction: Randomised studies have demonstrated superior overall survival (OS) of pembrolizumab, both alone and in combination with chemotherapy over chemotherapy alone in patients with programmed cell death ligand 1 (PD-L1) ≥50% advanced non-small cell lung cancer (NSCLC). We reviewed the real-world outcomes of patients who received pembrolizumab-chemotherapy combination versus pembrolizumab alone.

Methods: This Australian-based retrospective cohort study used data from 3 hospitals in Sydney. Eligible patients had advanced NSCLC with PD-L1 ≥50%, diagnosed between January 2016 and July 2021 and received first-line pembrolizumab-chemotherapy or pembrolizumab alone. Patients with an EGFR/ALK/ROS1 sensitising mutation were excluded. Cox proportional-hazards model and Kaplan-Meier methods were used to estimate OS and progression-free survival (PFS). Multivariate analyses were performed to test for prognostic factors.

Results: Of the 111 eligible patients (19 squamous, 92 non-squamous), 25 received pembrolizumab-chemotherapy and 86 received pembrolizumab alone. There were 85 males and 26 females across both groups combined. Median (range) age at diagnosis was 64.8 years (34.8-79.4) for the pembrolizumab-chemotherapy group and 70.9 years (44.8-87.1) for the pembrolizumab alone group. After a median follow up of 15.7 months, median (95% CI) OS was not reached in the pembrolizumab-chemotherapy group versus 15.6 (9.5-21.7) months in the pembrolizumab alone group (HR OS 0.57, 95% CI 0.28-1.16, p=0.12). Median PFS was 12.4 (6.5-18.3) versus 9.5 (6.3-12.6) months in pembrolizumab-chemotherapy vs pembrolizumab alone groups respectively (HR PFS 0.62, CI 0.32-1.18, p=0.18). Objective response rate (ORR) was higher in the pembrolizumab-chemotherapy group (60% vs 30.3%). Younger patients who received pembrolizumab-chemotherapy had longer OS. There were more hospitalisations in the pembrolizumab-chemotherapy group vs pembrolizumab alone group, 28% vs 18.6%, but immune-related adverse events were similar (32% vs 32.6%).

Conclusions: In patients with PD-L1≥50% advanced NSCLC, addition of chemotherapy to first-line pembrolizumab yielded a higher ORR with no additional benefit in PFS or OS. Whilst improved OS was observed in younger patients who received combination treatment, the higher rates of hospitalisations should warrant caution.

Keywords: NSCLC, PD-L1 high, Immunotherapy

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-003 Efficacy of Immune Checkpoint Inhibitors in Pulmonary Sarcomatoid Carcinoma, A Multicenter Retrospective Study

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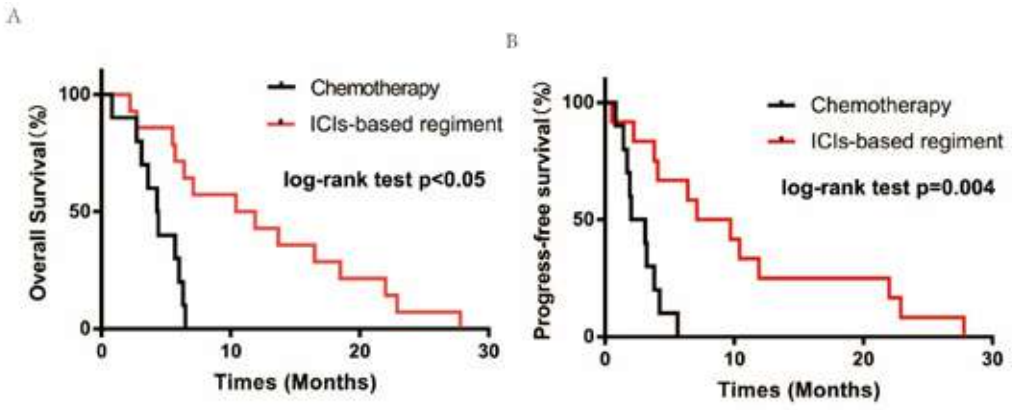
Introduction: Pulmonary sarcomatoid carcinoma (PSC) is a rare NSCLC subtype with a poor prognosis. Platinum-based chemotherapy often has limited efficacy for advanced PSC. However, some cases have suggested that immunotherapy may be effective for PSC.This study aimed to retrospectively assess the efficacy of Immune Checkpoint Inhibitors (ICIs) in PSC.

Methods: We retrospectively evaluated PSC patients treated with ICI-based regiments or chemotherapy between April 2016 to December 2021 at the Second Affiliated Hospital of Nanchang University and other two centers in Jiangxi, China. Cases were identified from the pathological diagnosis, baseline demographic, treatment data and outcomes were obtained, and the primary endpoints were overall survival (OS)and progression-free Survival(PFS).

Results: A total of 95 patients with PSC were diagnosed during this period, of which 12 patients and 14 patients were treated with chemotherapy and ICIs, respectively. The median age was 64 years (range 40-90) with a majority of them being males (86.32%) and smokers (62.11%). The clinical stage was stage III in 31.58 %, and stage IV in 52.63 %. 70.82% patients had higher PD-L1 expression. In ICI group, 34.6 % patients were assessed programmed death ligand 1 (PD-L1), of which 66.7 % patients PD-L1≥50%. Median PFS was 8.4 months (95% CI, 3.8 to 22) in the ICIs group and 2.55 months (95% CI, 1.4 to 4.2) in the chemotherapy group. Median OS was 11.15 months (95% CI, 5.5 to 22) in the ICIs group and 4.35 months (95% CI, 2.7 to 6.3) in the chemotherapy group.

Conclusions: Patients with PSC exhibited a trend of prolonged OS and PFS under ICI treatment. We are now conducting a prospective phase II clinical study of Tislelizumab combined with Anlotinib in the treatment of advanced PSC, early data showed a preliminarily promising efficacy and acceptable tolerability. We will release further data in the later stage.

Table 1. Charctristics of patients	
	Number (%)
Age (years)	40-90
Gender	
male	82 (86.32%)
female	13 (13.68%)
PS score	
<2	69(72.63%)
≥2	26(27.36%)
Smoking	
No	36 (37.89%)
Yes	59 (62.11%)
Ki-67(%)	
≤30	31(32.6%)
>30	64(67.4%)
PD-L1	
<50	7(29.18%)
≥50	17(70.82%)
TNM Stage	
I	9 (9.47%)
II	6 (6.32%)
III	30 (31.58%)
IV	50 (52.63%)
Brain metastases	
Without	90 (94.74%)
With	5 (5.26%)
Bone metastases	
Without	76 (80.00%)
With	19 (20.00%)
Liver metastases	
Without	81 (85.26%)
With	14 (14.74%)
Adrenal gland metastases	
Without	81 (85.26%)
With	14 (14.74%)
Treatment of 1 line	
Surgery	23 (38.98%)
TKIs	10 (16.95%)
Chemotherapy	12 (20.34%)
ICIs-based regiment	14 (23.73%)



Keywords: Pulmonary sarcomatoid carcinoma, Immune checkpoint inhibitors, Overall survival

EP08.01-004 Pattern of Subsequent Treatment and Outcomes in Relapsed PD-L1 high NSCLC Pre-treated with Pembrolizumab

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Introduction: In the absence of prospective studies to determine the best subsequent treatment after failure of first-line (1L) pembrolizumab in biomarker negative NSCLC, platinum doublet chemotherapy based on KEYNOTE-024 trial is preferred (ESMO guideline). This study examines the systemic treatment patterns and survival outcomes among immune checkpoint inhibitor (ICI) pretreated real-world NSCLC patients.

Methods: A retrospective analysis of the Glans-Look Lung Cancer Research database was performed. Non-small cell lung cancer (NSCLC) patients (EGFR, ALK and ROS1 negative) who received 1L pembrolizumab ±chemotherapy between 2017-2020 and developed progressive disease (PD) were included. A change to new systemic regimen was defined as second-line (2L) and no 2L refers no systemic treatment after PD. Descriptive (Fisher's Exact) and Kaplan-Meier survival statistics (Log-Rank test) were performed.

Results: 140 patients with PD after pembrolizumab ±chemotherapy were analysed. The median age (range) was 68 (45-87) yrs. 39 (30%) had ECOG status >1 at the time of starting 1L, 116 (83%) had advanced stage (III or IV) disease, 136 (97%) had non-squamous histology. 89 (64%) had 1L pembrolizumab of these, 88 expressed high PD-L1. At PD, 33 (24%) received a 2L. 15 (11%) continued the same ICI beyond PD for ≥12 weeks of these, 5 had 2L. The median time to treatment discontinuation was ~4 vs 10 months in the 2L group compared to patients continuing same ICI, (p=0.04). At data cut-off (December 15, 2021) and median follow-up of 26 months, 88% of no 2L (85/97), 70% of 2L (23/33) and 30% (3/10) of those continuing ICI had died (p<0.01). Median post-progression survival (pOS) was 12 months with 2L. Table 1 shows post-PD treatment details and outcomes for pembrolizumab or pembrolizumab +chemotherapy pretreated group. All 2L after pembrolizumab +chemotherapy was single chemotherapy, (5 docetaxel and 3 vinorelbine). Among the PD-L1 high group, platinum doublet was the most common 2L regimen (84%). pOS was 14 months vs not reached (NR) with 2L-platinum doublet compared to continuing ICI treatment, (p=0.02). Median overall survival (OS) from starting 1L was 24 months vs NR (p=0.02) in the 2L-platinum doublet compared to continuing ICI treatment cohort.

Table 1: NSCLC patients who received first-line (1L) pembrolizumab ±chemotherapy and developed progressive disease (PD) N=140

Treatment pattern post PD	ICI contd.	2L initiated	No Systemic
Proportion (%)	Systemic treatment for PD in Pembrolizumab pretreated n=89		
n	7	25	57
Median Age at 1L, years	72	68	69
ECOG status >1	2 (29)	3 (12)	20 (35)
PD-L1 high	7 (100)	25 (100)	56 (98)
TNM (at 1L) M0	1 (14)	4 (16)	7 (12)
M1a	1 (14)	6 (24)	9 (16)
M1b	4 (57)	9 (36)	22 (39)
M1c	1 (14)	6 (24)	19 (33)
Received radiotherapy	5 (71)	19 (76)	41 (72)
Treatment Outcomes, median month			
Time to discontinuation	12.9	4.4	-
Post-progression Survival	Not reached	13.5	0.5
Proportion (%)	Systemic treatment for PD in Pembro+chemotherapy pretreated n=51		
N	3	8	40
Median Age at 1L, years	72	62	68
ECOG status >1	0 (0)	2 (25)	12 (30)
PD-L1 low	2 (67)	6 (75)	15 (38)
PD-L1 negative	1 (33)	2 (25)	25 (63)
Received radiotherapy	3 (100)	6 (75)	25 (63)
Treatment Outcomes, median month			
Time to discontinuation	9.1	1.8	-
Post-progression Survival	12.4	10.6	2.0

2L= second-line, TNM= American Joint Committee Cancer Tumor Node Metastasis 8th edition stage M-status, ICI= immune checkpoint inhibitor, NSCLC= non-small cell lung cancer

Conclusions: Although overall 2L rate was low (24%), regimen choice beyond PD was largely in concordance with recommendations for both pre-treated pembrolizumab and pembrolizumab +chemotherapy patients. Among PD-L1 high patients, longer pOS and OS associated with continuing pembrolizumab versus 2L-platinum doublet for PD suggests pembrolizumab as an effective option or having better benefit than pembrolizumab +chemotherapy

Keywords: Non-Small Cell Lung Cancer, Immunotherapy beyond progression, survival outcomes

EP08.01-005 A Multicenter Prospective Observational Study of Atezolizumab in Unresectable Advanced or Metastatic NSCLC in Japan: J-TAIL

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Introduction: Atezolizumab monotherapy has been shown to prolong the overall survival of patients with metastatic non-small-cell lung cancer (NSCLC), who had been previously treated, indicating manageable toxicity. The J-TAIL study aimed to evaluate the long-term effectiveness and safety of atezolizumab monotherapy in patients with unresectable advanced or recurrent NSCLC under real-world settings in Japan. In addition, blood-based biomarker studies were conducted as exploratory research.

Methods: Patients with unresectable advanced or metastatic NSCLC scheduled to be initiated with atezolizumab monotherapy as ≥2nd-line treatment were eligible for this multicenter, non-interventional, non-blinded, single-arm observational study. Patients were prospectively enrolled from August 2018 to October 2019 at 169 sites in Japan. The primary endpoint was the overall survival (OS) rate at 18 months. Secondary endpoints included median OS, progression-free survival (PFS), and objective response rate (ORR), which were assessed by the investigators according to Response Evaluation Criteria in Solid Tumors v.1.1. The safety endpoints were the incidence of any adverse events (AEs) and immune-related AEs (irAEs) according to the grade based on National Cancer Institute Common Terminology Criteria for Adverse Events v.4.0. As exploratory research, pre- and post-treatment blood samples were analyzed to identify candidate biomarkers associated with the effectiveness and safety of atezolizumab.

Results: A total of 1,039 patients were enrolled. Among them, 1,002 were included in the safety analysis set, and 1,000 were included in the full analysis set (FAS). The median follow-up was 11.5 months (interquartile range, 4.3-20.3). Among the FAS, the median age was 71 years (range, 34-93) with 28.9% ≥75 years, 12.0% with ECOG PS ≥2, 18.9% with brain metastases, 2.0% with a history of autoimmune disease, and 21.9% had received prior immune checkpoint inhibitors (ICIs) at the baseline. Patients who received atezolizumab monotherapy in ≥4th-line treatment accounted for 35.5%. The median duration of atezolizumab treatment in the FAS was 2.4 months (range, 0-28.9). The OS rate at 18 months was 41.1% (95% confidence interval [CI], 38.0-44.3). The ORR was 8.8% (95% CI, 7.0-10.6), the median PFS was 2.1 months (95% CI, 2.1-2.3), and the median OS was 13.0 months (95% CI, 12.2-15.1) in the FAS. The incidences of any AEs and irAEs were 43.9% and 19.0%, respectively. Treatment-related irAEs, irAEs of grade 3-4, and irAEs leading to discontinuation were observed in 18.2%, 7.0%, and 5.8%, respectively. The median OS in the subgroup of patients who had received prior ICIs was 10.3 months (95% CI, 8.1-12.2), although the patients might have discontinued the ICIs for any reasons due to toxicity or disease progression. Regardless of the time between the atezolizumab initiation and the irAE onset, patients who developed grade 1-2 irAEs tended to have numerically more prolonged survival (median OS, not reached).

Conclusions: The J-TAIL study confirmed that the effectiveness and safety of atezolizumab monotherapy as ≥2nd-line treatment were comparable to the pivotal phase III study of the OAK study in Japanese patients with previously treated NSCLC in real-world settings, including elderly patients with poor PS, who had received intensive pre-treatment.

Keywords: PD-L1 inhibitor, Real-world data, Observational study

EP08.01-006 Using Real World Data to Build Effective Predictive Machine Learining Models for NSCLC Patients Treated with Immune-Based Therapy

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Introduction: So far, Programmed Death-Ligand 1 (PD-L1) represents the only approved predictive biomarker of response to immunotherapy (IO) in advanced non-small cell lung cancer (NSCLC), but its predictive power is insufficient. For this purpose, artificial intelligence (AI) methods are being increasingly investigated to generate predictive models applicable in clinical practice. In this study, we try to develop a model able to predict activity and efficacy of IO in patients with advanced NSCLC using AI methods.

Methods: We prospectively collected real world data from patients receiving immune-checkpoint inhibitors (ICIs) either as single agent or in combination with chemotherapy for advanced NSCLC at "Fondazione IRCCS Istituto Nazionale Tumori" (Milan). Aiming to generate a model of efficacy prediction, we investigated the association of clinical variables with different outcomes: Disease Control Rate (DCR), Objective Response Rate (ORR), and 6-months Overall Survival (OS6). A Bayesian Ridge regression was iteratively for imputation of the missing value of input features (PD-L1, NLR, pack-year). A 90%-10% randomic split for the training/test datasets have been performed to evaluate the final performance on an independent dataset. On the resulting training dataset, we optimized the hyper-parameters and selected the model, among Support Vector Machine (SVM), Logistic Regression (LR), a Feed-Forward shallow Neural Network (FFNN) and the CatBoost algorithm, were selected using a 10-fold cross-validation approach. Finally, we run the SHAP algorithm, an Explainable trustworthy AI (XAI) procedure, to evaluate the importance of the features used in the model and to explain the algorithms.

Results: Of 480 patients were included in the study 407 received immunotherapy and 73 the combination of chemotherapy and immunotherapy. Manual feature selection was used and 29 features were included in the final model (clinical, lab analysis and radiological information). The CatBoost model resulted to be the best performing one, in terms of accuracy, over the 432 patients of the training dataset by the cross-validation procedure. On the 48 patients present in the test set, the performance in terms of accuracy (ACC) and Area Under the ROC Curve (AUC) were, ACC = 88%, AUC = 85% for DCR, ACC = 81%, AUC = 70% for ORR, and ACC = 79%, AUC = 78% for OS6. SHAP XAI showed that the most important features influencing models performance (for DCR, ORR and OS6) were: performance status, PD-L1, LDH, NLR line of IO, BMI.

Conclusions: A promising path to improve the prediction of IO response in patients with advanced NSCLC consists in the application of AI techniques, and more specifically ML ones, to the available data. Although PD-L1 is an imperfect response biomarker, it has been shown to play an important role in determining the performance of the founded models. With the aim of implementing precision medicine, the use of real-world data, easily collected in daily clinical practice and analyzed through AI techniques, can represent an exciting field of investigation.

Keywords: NSCLC, Machine Learning, Immunotherapy

EP08.01-007 Real-World Outcomes of Patients with Advanced Lung Adenocarcinoma Treated with First-Line Chemo-Immunotherapy in Italy

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Introduction: This study sought to evaluate the real-world clinical outcomes of chemo-immunotherapy (CT-IT) with cis/carboplatin, pemetrexed and pembrolizumab for the first-line (1L) treatment of advanced lung adenocarcinoma (LUAC) patients in Italy.

Methods: This is a retrospective-prospective study including patients diagnosed with advanced LUAC who received 1L CT-IT from September 4th, 2018 in 42 Italian Centers.

Results: 642 patients were enrolled at the time of data cut-off (January 31st, 2022). Patients' characteristics are shown in Table 1. Median treatment duration was 7.6 months (95% Confidence Interval [CI], 6.7-8.6). 447 (69.6%) patients completed the induction phase with all three drugs; 451 (70.2%) patients started the maintenance phase. Overall response rate (ORR) was 42.7% (95% CI, 38.8-46.6) in the overall population. ORR was 39.7% (95% CI, 34.2-45.3) in PD-L1 < 1%, 45.7% (95% CI, 39.5-52.0) in PD-L1 1-49% and 34.5% (95% CI, 17.9-54.3) in PD-L1 ≥ 50%, respectively. 269 (41.9%) patients experienced progression of disease (PD) and the most frequent site of PD was lung (25.9%). After a median follow-up for surviving patients of 10.2 months (95% CI, 9.1-11.5), median progression-free survival was 10.1 months (95% CI, 8.7-11.5) and median overall survival was 15.2 months (95% CI, 13.4-20.4). 246 (38.3%) patients discontinued one or more drugs. The most frequently discontinued drug was pemetrexed (n=218, 33.9%), and the most common reason for pemetrexed discontinuation was toxicity (n=99, 15.4%). Adverse events (AEs) of grade 3 (G3) or higher occurred in 85 (13.2%) patients and most common ≥ G3 AE was neutropenia (8.2%) (Table 2).

Conclusions: Our findings support the effectiveness and safety of 1L CT-IT in advanced LUAC patients. Our results were in line with the KEYNOTE-189 registration study.

Table 1: Patients' Baseline Characteristics	
Patients' Baseline Characteristics (n=642)	
Type of Cohort - no. (%)	
Retrospective Prospective	442 (68.9) 200 (31.1)
Age	
Median (range) - years	66 (27-85)
Sex - no. (%)	
Male Female	412 (64.2) 230 (35.8)
BMI	
Median (kg/m2)	24.8
Smoking status - no. (%)	
Never Past Current Unknown	83 (12.9) 310 (48.3) 242 (37.7) 7 (1.1)
ECOG Performance Status - no. (%)	
0 1 2 3 Unknown	270 (42.1) 311 (48.4) 54 (8.4) 1 (0.2) 6 (0.9)
Sites of distant metastasis - no. (%)	
Brain Bone Liver ≥ 4 sites	153 (23.8) 243 (37.9) 79 (12.3) 280 (43.6)
Molecular alterations - no. (%)	
ROS1 rearrangement BRAF V600E mutation KRAS mutation • G12C • Non-G12C	7 (1.1) 6 (0.9) 238 (37.1%) 87 (13.6) 151 (23.5)
PD-L1 tumor proportion score - no. (%)	
< 1% ≥ 1% • 1-49% • ≥ 50% Could not be evaluated	315 (49.1) 287 (44.7) 258 (40.2) 29 (4.5) 40 (6.2)

Table 2: Adverse Events. *note: missing data on grade of toxicities are present			
Adverse Event	**At least 1 of any grade (%)**	**Grade 1-2 (%)**	**Grade ≥ 3 (%)**
Overall	**427 (66.5)***	**339 (52.8)**	**85 (13.2)**
Haematologic (n=223, 34.7%)			
• Anemia	153 (23.8)	114 (17.8)	39 (6.1)
• Thrombocytopenia	54 (8.4)	36 (5.6)	18 (2.8)
• Leukopenia	16 (2.5)	10 (1.6)	6 (0.9)
• Neutropenia	102 (15.9)	49 (7.6)	53 (8.2)
• Febrile neutropenia	9 (1.4)	-	9 (1.4)
Gastrointestinal (n=176, 27.4%)			
• Vomiting	37 (5.8)*	34 (5.3)	2 (0.3)
• Abdominal pain	5 (0.8)	5 (0.78)	-
• Diarrhea	67 (10.4)*	58 (9.0)	8 (1.3)
• Colitis	6 (0.9)	6 (0.9)	-
• Gastritis	4 (0.6)	4 (0.6)	-
• Nausea	100 (15.6)*	88 (13.7)	9 (1.4)
• Stipsis	32 (5.0)	31 (4.8)	1 (0.2)
Pulmonary (n=20, 3.1%)			
• Dyspnea	6 (0.9)	6 (0.9)	-
• Autoimmune pneumonitis	15 (2.3)	8 (1.3)	7 (1.1)
Haepatic (n=120, 18.7%)			
• Bilirubin increase	7 (1.1)	7 (1.1)	-
• GOT increase	69 (10.8)	63 (9.8)	6 (0.9)
• GPT increase	88 (13.7)	75 (11.7)	13 (2.0)
• GGT increase	26 (4.1)	21 (3.2)	5 (0.8)
• Autoimmune haepatitis	2 (0.3)	-	2 (0.3)
Neurological (n=10, 1.6%)			
• Paresthesia	10 (1.6)*	9 (1.4)	-
Cutaneous (n=121, 18.9%)			
• Pruritus	22 (3.4)	22 (3.4)	-
• Rash	46 (7.2)	45 (7.0)	1 (0.2)
• Erysipelas	7 (1.1)	4 (0.6)	3 (0.5)
• Mucositis	54 (8.4)	49 (7.6)	5 (0.8)
• Aedema	18 (2.8)	17 (2.7)	1 (0.2)
Renal (n=54, 8.4%)			
• Creatinine increase	54 (8.4)	46 (7.2)	8 (1.3)
Endocrine (n=34, 5.3%)			
• Hypothyroidism	17 (2.7)	17 (2.7)	-
• Hyperthyroidism	19 (3.0)	18 (2.8)	1 (0.2)
Ocular (n=41, 6.4%)			
• Congiuntivitis	30 (4.7)*	29 (4.5)	-
• Xerophtalmia	5 (0.8)	5 (0.8)	-
• Hyperlacrimation	10 (1.6)	10 (1.6)	-
Other (n=175, 27.3%)			
• Fatigue	123 (19.2)*	106 (16.5)	15 (2.3)
• Musculoskeletal pain	13 (2.0)	13 (2.0)	-
• Fever	21 (3.3)	21 (3.3)	-
• Chills	1 (0.2)	1 (0.2)	-
• Others	68 (10.6)*	56 (8.7)	10 (1.6)

Keywords: chemo-immunotherapy, lung adenocarcinoma, real-world

EP08.01-008 Immune Checkpoint Inhibitors in Oncogenic Driven Non-small Cell Lung Cancer

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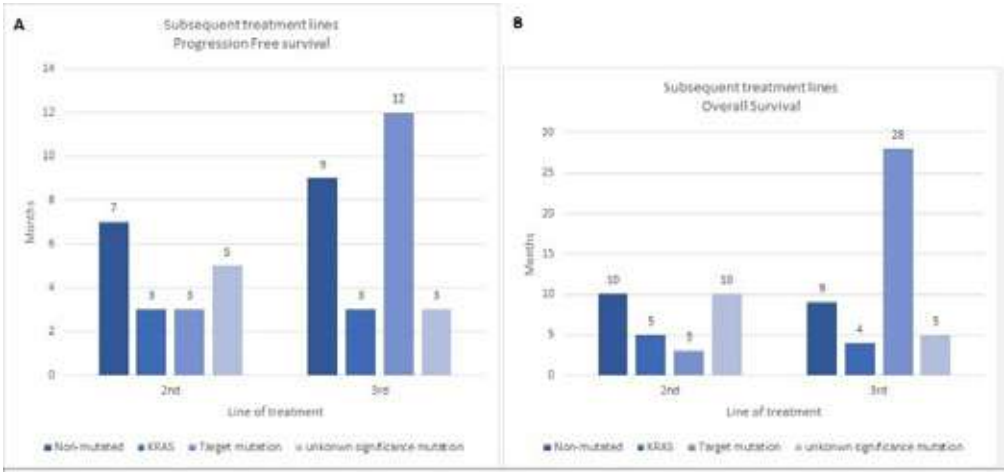
Introduction: Immune checkpoint inhibitors (ICIs) are a treatment option for advanced non-small cell lung cancer (NSCLC), but efficacy may differ in different immune and molecular tumor profiles. Particularly, the efficacy of ICIs in oncogenic driven NSCLC remains controversial. Several studies reported poor responses to ICIs in patients with targetable mutations as EGFR or ALK, but data regarding ICIs efficacy in other oncogenic driven NSCLC is still scarce.The aim was to analyze ICIs monotherapy outcomes in NSCLC patients according to their mutational profile.

Methods: Retrospective analysis of advanced NSCLC patients who received ICIs monotherapy, between January of 2016 and December of 2021. All patients performed the molecular study of tumor by next generation sequency method (NGS). Patients were divided into groups: non-mutated, KRAS mutation, targetable mutations and mutations of unknown significance. PFS and OS were analyzed.

Results: We included 131 patients. Most were male (78,8%), mean age was 64±11 years. Adenocarcinoma was the most frequent histology (86,4%), followed by poorly differentiated NSCLC (5,3%) and squamous cell carcinoma (5,3%). NGS identified 98 mutations, corresponding to 82 patients (62%). KRAS mutations were the most frequent (57,9%), followed by BRAF (9,6%) and MET (7,5%). Only 11 patients (8,4%) had mutations with approved targeted therapy. Analyzing PD-L1≥50%, 71% of mutated NSCLC and 85% non-mutated received ICIs as first-line treatment. In this setting, PFS and OS in non-mutated were respectively 8 and 15 months; in patients with mutations of unknown significance were 6 and 12 months; in KRAS group were 4 and 6 months and in targetable mutations (MET mutations) were 3 and 5 months. PFS and OS of ICIs in subsequent lines of treatment are illustrated on graph 1.

Conclusions: Most of patients receiving ICIs monotherapy had at least one mutation but a minority of patients with targetable mutations have received ICIs. As first-line treatment, PFS and OS of ICIs were superior in non-mutated group or in patients with mutations of unknown significance. In subsequent treatment setting, PFS and OS seems to be higher when it is used after more lines of chemotherapy/targeted therapy than when ICIs are chosen as a second line, mainly in patients with targetable mutations. These data should be confirmed by larger and more robust studies.



Graphic 1: A. Progression Free Survival (PFS) in subsequent treatment setting, according to mutational profile; **B.** Overall Survival (OS) in subsequent treatment setting, according to mutational profile.

Keywords: Immune checkpoint inhibitors, oncogenic driven, Non-small cell lung cancer

EP08.01-009 TRBV Haplotype Profile Was Related to Immune-Induced Adverse Events in Chinese Patients with Advanced NSCLC

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Introduction: Immune-related adverse events (irAE) are inevitable following immunotherapy, which significantly impact the quality of life and possibly cause therapy discontinuation or interruption in cancer patients. Previous studies reported that T-cell receptor beta variable (*TRBV*) gene was related to irAE in Caucasian patients with non-small cell lung cancer (NSCLC). However, the relationship between *TRBV* gene and irAE remains to be revealed in Chinese NSCLC patients.

Methods: In 143 Chinese advanced NSCLC patients who received first- or second-line immunotherapy from Feb 2016 to Apr 2020 with a median follow-up duration of 23.3 months, *TRBV* allele profile was analyzed through TCR sequencing by Oncomine TCR-LR (long-read) assay at RNA level for complete characterization of CDR1, CDR2, and CDR3. Among these patients, 15 patients received first-line anti-PD-(L)-1 monotherapy; 79 patients were treated by first-line combination of anti-PD-(L)-1 treatment and chemotherapy; and 49 patients received second-line anti-PD-(L)-1 monotherapy. Fisher's exact test was used to evaluate the effect of *TRBV* haplotype on irAE risk. In a subgroup of 47 patients, circulating tumor DNA (ctDNA) was collected at the beginning of treatment. The genomic profiling was assessed by targeted sequencing with 670 cancer-related genes in these patients.

Results: Six *TRBV* haplotype groups (N=26 in group 1, N=27 in group 2, N=29 in group 3, N= 29 in group 4, N=16 in group 5, N=14 in group 6) with characterized TCR V beta usage was identified according to the results of TCR sequencing. The proportion of irAE-high (grade≥II) in group 1 was significantly higher than that in other groups (46.4% vs. 22.6%, $p<0.05$). Interestingly, average number of *TRBV* genes (47.86±4.42) and uncommon V alleles (2.57±0.94) were higher in group 1 when compared to other groups ($p<0.05$, $p<0.05$, respectively). The mutation frequency of *Wnt* signaling pathway was significantly increased in patients from *TRBV* haplotype group 1 than those from other subgroups ($p<0.05$) in 47 patients performing ctDNA targeted sequencing including 8 patients from group 1 and 39 patients from the other groups.

Conclusions: The proportion of irAE-high (grade≥II) was positively related to number of *TRBV* genes and of uncommon V alleles in Chinese NSCLC patients, indicating that the profile of *TRBV* haplotype group 1 might predict higher risk to develop irAE-high during immunotherapy. These results could be helpful to stratify the subpopulation of Chinese NSCLC patients who have high risk to develop irAE. More robust studies with larger sample size will be needed to accumulate further supportive data.

Keywords: Non-small cell lung cancer (NSCLC), T-cell receptor beta variable (TRBV) haplotype, immune-related adverse event (irAE)

EP08.01-010 Troponin Elevation and the Risk of Myocarditis Among NSCLC Patients Treated with Immune Checkpoint Inhibitors

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Introduction: Immune checkpoint inhibitors among non-small cell lung cancer (NSCLC) have changed the landscape of cancer treatment demonstrating superior efficacies. Nevertheless, immune related toxicity carries clear potential for morbidity and mortality. Among other side effects are the cardiovascular toxicity including myocarditis as the most common cardiovascular side effect. The burden of cardiovascular side effects is relatively low, but its real prevalence is unproven. The clinical relevance of troponin elevation as an early sign of myocarditis is yet to be determined.

Methods: We evaluated NSCLC patients' records who received treatments with immune checkpoint inhibitors and had baseline troponin levels. We assessed demographic and clinical data regarding the oncological disease and the cardiological sequel of immunotherapy.

Results: Among 146 patients who received immunotherapy and had baseline troponin measurement, 65 (44.5%) were NSCLC patients. The median age was 73, 24 females (37%) and 45 patients received immunotherapy as a single agent. At baseline, 5 (7.7%) had a pathological troponin level (>50 nanogram\liter) and were treated accordingly. Among those who had normal baseline troponin level (60 patients, 92.3%), 8 (12%) had troponin elevation during the immunotherapy treatment in a median treatment number of cycle number four. Three patients (37.5%) had clinical myocarditis (based on echocardiogram) and one patient (12.5%) died as a result.

Conclusions: Myocarditis is a rare although serious side effect of immune checkpoint inhibitor treatment with fatal potential. The repetitive measurements of troponin level are essential for early diagnosis and treatment and may be considered as part of the guidelines for immunotherapy follow-up.

Keywords: Immunotherapy, NSCLC, Troponin

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-011 Diabetes Mellitus (DM) is Associated with Poor Outcome in Pembrolizumab-treated Non-Small Cell Lung Cancer (NSCLC) Patients

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Introduction: Pembrolizumab among other immune check-point inhibitors was established as the mainstay of treatment in ample malignancies, including NSCLC. Though DM causes an immune dysfunction, the influence of DM on the immunotherapy's efficacy has not been adequately addressed.

Methods: Medical records of consecutive NSCLC patients treated with first-line pembrolizumab as a single agent or combined with chemotherapy at Tel Aviv Medical Center from January 2017 to July 2021 were reviewed for demographical and clinical characteristics. Patients who received a single cycle were excluded.

Results: Among 234 reviewed patients' files, 203 were included in the analysis. Their median age was 69 years, 128 were men (63%), 152 had adenocarcinoma (75%), and 51 patients had DM (25%). Diabetic patients were older (73 vs. 67, p <0.001) and had a higher mean body mass index (27 vs. 24, P<0.001). Median progression free survival (PFS) and overall survival (OS) were significantly shorter in diabetic compared to non-diabetic patients (5.9 vs. 7.1 months, respectively, P=0.004, and OS 12 vs. 21 months, respectively, p=0.006). The difference in OS was more pronounced for patients receiving pembrolizumab alone (12 vs. 27 months, p=0.03), than for those receiving pembrolizumab together with chemotherapy (14.3 vs. 19.4 months, p=0.06). Multivariate analysis indicated DM as an independent risk factor for inferior PFS (HR 1.7, 95% CI 1.11-2.5, p=0.014) and OS (HR 1.7, 95% CI 1.09-2.76, p=0.02).

Conclusions: In this study we point at a potential deleterious effect of DM on the efficacy of pembrolizumab in metastatic NSCLC patients. While further validation is required, this result might indicate that administration of immune checkpoint inhibitors and specifically single agent pembrolizumab is not competent enough in DM patients. If further validated, the administration of single agent pembrolizumab in this setting should be reconsidered.

Keywords: Immunotherapy, NSCLC, Diabetes Mellitus

EP08.01-012 First-line Chemo-Immunotherapy in Advanced Non-Small Cell Lung Cancer with 0-49% PD-L1: A Real-world Experience

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Introduction: The combination of immune checkpoints inhibitors (ICIs) and chemotherapy is the standard of care in untreated advanced non-small cell lung cancer (aNSCLC) patients with PD-L1 < 50% and no targetable mutations. In this work, we provide data about toxicity profile and outcome in a multicenter real-word setting.

Methods: We retrospectively analysed clinical data concerning aNSCLC patients consecutively treated with first-line chemo-immunotherapy at Veneto Institute of Oncology (Padova, Italy), San Bortolo General Hospital (Vicenza, Italy) and Dell'Angelo Hospital (Mestre, Italy) from January 2020 to November 2021. We registered clinico-pathological data, treatment response and immune-related adverse events (irAEs). We estimated the association between irAEs and treatment response using logistic regression. Survival outcomes were obtained through the Kaplan-Meir estimator. The impact of variables on outcomes was assessed using Cox regression.

Results: 162 patients were included: most patients were males (n=105, 64.8%), former or current smokers (n=128, 79%), with Eastern Cooperative Oncology Group Performance Status (PS) of 1 (n=116, 71.6%). Median age at diagnosis was 66 years (IQR 59-72). The majority of patients had adenocarcinoma (n=131, 80.9%), PD-L1 ≥ 1% (n=81, 51.9%), presented with extra-thoracic disease (n=92, 56.8%) and achieved disease control as best response (n=123, 75.9%). At the time of analysis (February 2022), median follow up was 8.1 months (IQR 4.2-13.7). Sixty-eight patients experienced PD and median progression-free survival (mPFS) was 11.76 months (95% CI 8.16-20.04); 58 deaths were registered and median overall survival (mOS) was 15.05 months (95% CI 12.94-not reached). Forty-seven patients (29.4%) developed at least one any grade irAE: five (11%) required hospitalization and 33 (70.2%) temporarily interrupted therapy due to toxicity. The most common irAEs were diarrhea (n=19, 11.7% of all patients), followed by aminotransferase increased (n=8, 4.9%). Logistic regression analysis showed that the development of irAEs was associated with a lower risk of PD, after correcting for confounding by relevant prognostic factors (histology, presence of driver mutation, PD-L1 expression, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio at baseline) (OR=0.22, 95% CI 0.061-0.820, p=0.024). Longer PFS and OS were observed when an irAE occurred, with an ECOG PS of 0, in the absence of extra-thoracic disease, with 2 metastatic sites or less, and without liver metastases or bone metastases. Cox regression showed that development of irAEs, PS ECOG=0 and ≤ 2 metastatic sites were independently associated with OS (p=0.004, p=0.002 and p=0.032 respectively).

Conclusions: Combination of ICI and chemotherapy as front-line therapy in aNSCLC patients confirmed efficacy and safety in a real-life scenario. The development of irAEs is associated with lower risk of PD and is a favorable prognostic factor in terms of survival.

EP08.01-013 Ramucirumab plus Atezolizumab in Patients with Stage IV NSCLC Previously Treated with Immune Checkpoint Blockade

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Introduction: Angiogenesis is an important mechanism of immune evasion and there are emerging data suggesting a benefit from combining immune checkpoint inhibitors (ICIs) with anti-angiogenic therapies. We evaluated the combination of atezolizumab and ramucirumab in patients (pts) with previously treated non-small cell lung cancer (NSCLC).

Methods: In this single institution phase II study, pts with advanced stage NSCLC previously treated with at least one line including ICI were treated with ramucirumab 10 mg/kg and atezolizumab 1,200 mg intravenously every 21 days until tumor progression or intolerable toxicity. The primary endpoint was overall response rate (ORR).

Results: Twenty-one pts were enrolled between June 2019 and April 2021. The median age was 67 (range 42-82), 17 (81%) were female, and 14 (67%) had non-squamous histology. PD-L1 expression was unknown in three pts, <1% in 4, 1-49% in 8 and 50% or more in 6 pts. All pts had received at least 2 prior lines of therapy, with a median number of prior therapies in general and immunotherapies of 3.0 and 1.0, respectively. The most common adverse events included hypertension (86%), proteinuria (62%), and nausea (52%). The most common grade 3/4 event was hypertension (33%). The ORR was 4.8% with one pt achieving complete response and 16 pts (76.1%) stable disease. Tumor reduction was observed in 10 pts (47.6%) (Figure 1). The median progression-free survival (PFS) was 3.3 months. The median overall survival (OS) and 12-month OS were 12.2 months and 52.4%, respectively (Figure 2).

Conclusions: Although the primary endpoint of ORR was not met, our study showed that the combination of ramucirumab and atezolizumab is well-tolerated and associated with prolonged OS in a subset of heavily pretreated pts who progressed on ICI. Exploratory analyses are ongoing.

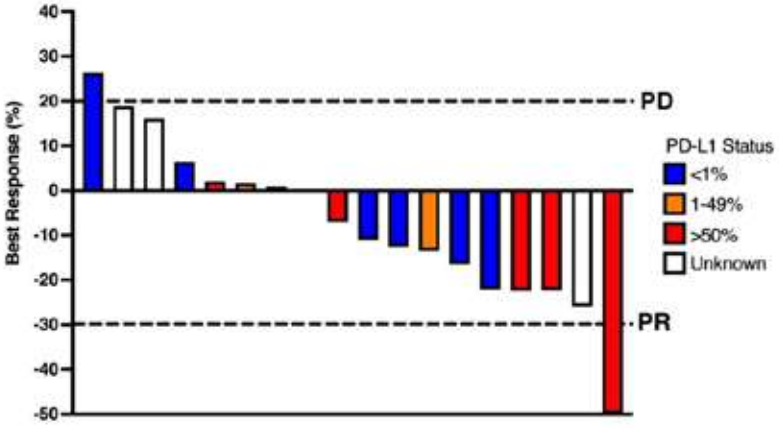

Figure 1. Best response for target lesions by patient based on maximal percentage of tumor reduction by RECIST.

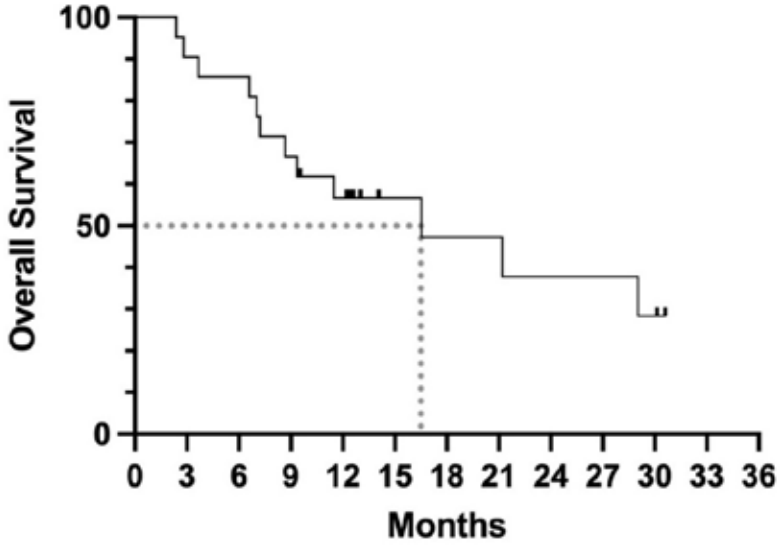

Figure 2. Kaplan-Meier plot of overall survival.

Keywords: Immunotherapy, Ramucirumab, Stage IV NSCLC

EP08.01-014 Tislelizumab versus Docetaxel in Previously Treated Advanced Non-Small Cell Lung Cancer: Final Analysis of RATIONALE-303

C. Zhou[1], D. Huang[2], Y. Fan[3], X. Yu[3], Y. Liu[4], Y. Shu[5], Z. Ma[6], Z. Wang[7], Y. Cheng[8], J. Wang[9], S. Hu[10], Z. Liu[11], E. Poddubskaya[12], U. Disel[13], A. Akopov[14], M. Dvorkin[15], Y. Wang[16], S. Li[17], C. Yu[16], G. Rivalland[18]

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Introduction: In RATIONALE-303 (NCT03358875) tislelizumab significantly improved OS vs docetaxel in the ITT population at the interim analysis (IA), based upon which, tislelizumab was approved in China for treatment of advanced NSCLC patients with progressive disease after chemotherapy. Here, we report outcomes of the final analysis (FA) and *post hoc* biomarker analysis.

Methods: Patients ≥18 years with histologically confirmed, locally advanced or metastatic squamous or non-squamous NSCLC were randomized (2:1) to IV tislelizumab 200 mg or IV docetaxel 75 mg/m^2 every 3 weeks. Co-primary endpoints were OS in the ITT and PD-L1 TC ≥25% populations. The study had one planned IA only in the ITT population. The FA was conducted in the PD-L1 TC ≥25% population with secondary endpoints (PFS_{INV}, ORR_{INV}, DoR_{INV}) tested sequentially once superiority of OS in PD-L1 TC ≥25% population was demonstrated in the FA. Exploratory biomarker analyses included PD-L1 expression, tumor mutation burden (TMB), and gene expression profile.

Results: Between November 30, 2017 and April 8, 2020, 805 patients were randomized to tislelizumab (N=535) or docetaxel (N=270). The co-primary endpoint of OS (ITT) was met at IA (data cut-off August 10, 2020). At data cut-off (July 15, 2021), FA was conducted in the PD-L1 TC ≥25% population. Median follow-up times (reverse Kaplan-Meier method) were 30.9 months for tislelizumab and 27.5 months for docetaxel. In ITT population, tislelizumab continued to improve OS vs docetaxel (median OS 16.9 months vs 11.9 months, respectively; HR=0.66). In PD-L1 TC ≥25% population, tislelizumab showed a statistically significant OS benefit vs docetaxel (median OS 19.3 months vs 11.5 months; HR=0.53; p<0.0001). A consistent OS benefit was observed for almost all pre-defined subgroups. The study also met secondary endpoints at this FA. In the *post hoc* biomarker analysis, the association of TMB and genetic alterations including single target gene mutation or pathway mutations with clinical outcomes was further explored. Compared with TMB which was correlated with PFS benefit for tislelizumab vs docetaxel but was not correlated to OS benefit, except at the highest cutoff (≥14 mut/Mb), *NOTCH1-4* mutations showed association with better tislelizumab efficacy, which was correlated with both PFS and OS benefit (**Table**). No new safety signals were identified.

Conclusions: Tislelizumab continued to improve OS versus docetaxel in pretreated advanced NSCLC regardless of PD-L1 expression at final analysis. Biomarker analysis implied the potential association of *NOTCH1-4* mutations with greater tislelizumab efficacy for both OS and PFS.

Table

	ITT population		PD-L1 TC ≥25% population		*NOTCH1-4* mut population		*NOTCH1-4* WT population	
	TIS (N=535)	**D (N=270)**	**TIS (N=227)**	**D (N=116)**	**TIS (N=26)**	**D (N=15)**	**TIS (N=218)**	**D (N=101)**
OS events, n (%) [IA]	365 (68.2) [275 (51.4)]	206 (76.3) [166 (61.5)]	141 (62.1)	87 (75.0)	13 (50.0)	13 (86.7)	152 (69.7)	79 (78.2)
Median OS (95% CI), mos [IA]	16.9 (15.2, 19.1) [17.2 (15.3, 20.0)]	11.9 (9.6, 13.5) [11.9 (10.2, 13.9)]	19.3 (16.5, 22.6)	11.5 (8.2, 13.5)	24.7 (14.2, NE)	7.7 (3.3, 14.3)	15.7 (13.9, 17.9)	12.9 (10.4, 14.9)
Stratified HR‡ (95% CI) [IA]	0.66 (0.56, 0.79) p<0.0001*† [0.64 (0.53, 0.78) p<0.0001*]		0.53 (0.40, 0.70) p<0.0001*		0.22 (0.10, 0.49) p=0.0002*†		0.75 (0.57, 0.99) p=0.0390*†	
PFSINV events, n (%)	451 (84.3)	208 (77.0)	177 (78.0)	94 (81.0)	14 (53.8)	14 (93.3)	187 (85.8)	83 (82.2)
Median PFSINV (95% CI), mos	4.2 (3.9, 5.5)	2.6 (2.2, 3.8)	6.5 (6.2, 8.3)	2.4 (2.1, 4.1)	14.1 (6.2, NE)	2.6 (2.0, 4.1)	4.1 (2.2, 6.2)	3.3 (2.1, 4.1)
Stratified HR‡ (95% CI)	0.63 (0.53, 0.75)		0.37 (0.28, 0.49)		0.17 (0.08, 0.37)		0.72 (0.55, 0.95)	
ORRINV, n (%)	121 (22.6)	19 (7.0)	85 (37.4)	8 (6.9)	-	-	-	-
Median DoRINV, (95% CI), mos	13.5 (8.5, 19.6)	6.0 (2.1, 7.2)	11.9 (8.3, 19.6)	4.2 (0.6, 6.1)	-	-	-	-

IA data cut-off: August 10, 2020
FA data cut-off: July 15, 2021
**1-sided stratified log-rank test*
†Descriptive p value
‡Stratified by histology (squamous vs non-squamous) and lines of therapy (second vs third)
Abbreviations: CI, confidence intervals; D, docetaxel; DoRINV, investigator-assessed duration of response; FA, final analysis; HR, hazard ratio; IA, interim analysis; ITT, intent-to-treat; IV, intravenous; mos, months; mut, mutation; NE, not estimable; NSCLC, non-small cell lung cancer; ORRINV, investigator-assessed objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFSINV, investigator-assessed progression-free survival; TC, tumor cell; TIS, tislelizumab; vs, versus; WT, wild type

Keywords: Non-small cell lung cancer, Tislelizumab, NOTCH

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-015 Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the Anti-oxMIF Antibody ON203 in Malignant Solid Tumors

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Introduction: Macrophage migration inhibitory factor (MIF) is often described as a pleiotropic cytokine whose overexpression is associated with tumor aggressiveness, metastases, and poor prognoses. Due to its ubiquitous nature, MIF is considered an unsuitable target for therapeutic intervention. However, presence of a disease-related isoform of MIF, oxidized MIF (oxMIF), has been specifically found in tumor tissue, including tissue from patients with non-small cell lung cancer (NSCLC). A first-generation anti-oxMIF monoclonal antibody (mAb) was able to demonstrate an acceptable safety profile and signs of efficacy in a Phase 1 clinical trial in patients with malignant solid tumors, seven of which were patients with NSCLC. After treatment, two patients showed signs of stable disease of greater than 4 months. Since then, a bioengineered second-generation anti-oxMIF mAb, ON203, with highly improved biophysiochemical and biological properties, was generated. ON203 was designed to have improved pharmacokinetics (PK), increased effector functions and *in vitro* and *in vivo* efficacy, while maintaining specificity and low nanomolar affinity to oxMIF. In the first-in-human, Phase 1, open-label, dose-escalation study we will assess the safety, tolerability, PK, and pharmacodynamics of the anti-oxMIF antibody ON203 in patients with malignant solid tumors including NSCLC.

Methods: A total of 3-6 participants will be enrolled in 5 dosing groups (0.3, 1.0, 3.0, 10.0, and 30.0 mg/kg) in a 3+3 study design. In the event that dose-limiting toxicity (DLT) is observed, 3 additional patients will enter the same dose level. Participants may escalate to next dose level if only 1 out of 6 participants per cohort experience a DLT; otherwise, the maximum tolerated dose (MTD) will be reached. Eligible participants must be age ≥18 years with a confirmed malignant tumor that is either refractory to, has failed, or refused standard treatments; have an Eastern Cooperative Oncology Group (ECOG) performance status of ≥1; and have an anticipated life expectancy of ≥4 months at the time of screening. Key exclusion criteria include patients with known brain tumors or central nervous system metastases; uncontrolled hypertension or clinically significant cardiovascular disease; and active or chronic infections requiring antibiotics. Primary outcome measures will be the number and severity of adverse events (AEs) and relation to ON203, if any, according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) toxicity grading. Secondary measures will explore PK parameters, tumor response, and time to progressive disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Exploratory measures will look at levels of total MIF, oxMIF, and cancer cell DNA in circulation, along with development of anti-drug antibodies, and examination of immune cell contexture before and during treatment in tumor biopsies, where applicable. Treatment will continue until progressive disease (as defined by the RECIST criteria), unacceptable toxicity, DLT, or withdrawal of patient's consent, with an estimated study duration of 10 months. A dose expansion phase will follow to further substantiate the safety profile, gain additional signals of efficacy, as well as to correlate outcomes with biomarkers.

Keywords: Oxidized Macrophage migration inhibitory factor, ON203, dose-escalation study

EP08.01-016 A Review of Real-World Treatment Outcomes of mNSCLC Patients Following Progression on or After Platinum-Based Chemotherapy

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Introduction: Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer cases. The objective of this study is to identify the current real-world effectiveness of treatments for patients with stage IV NSCLC progressing on or after platinum-based therapy.

Methods: A systematic literature review of English language studies examining the real world burden and outcomes of patients with stage IV NSCLC progressing on or after platinum-based therapy was conducted. PubMed and Embase were used to identify full-text and conference abstracts published between 9/28/2016 and 9/28/2021. Only studies reporting real-world treatment outcomes (response, overall survival, and/or progression-free survival) were included in this review. Non-real-world studies such as clinical trials were excluded. Data extracted from included studies were study characteristics (first author, year of the study, study type, setting, the data source(s), time period(s), and patient population) and the endpoints and results.

Results: We identified 8 studies with real-world treatment outcomes for patients with stage IV NSCLC that have progressed on or after platinum-based chemotherapy. Data sources, study types, settings, sample size, and timelines are described in Table 1. Interventions studied included nivolumab (n=4), apatinib (n=2), chemotherapy (n=3), pembrolizumab, irinotecan + bevacizumab, and ramucirumab (n=1). The overall response rate (ORR) ranged from 10% (apatinib) to 33.3% (docetaxel + apatinib) (Table 2). Complete and partial responses ranged from 0% (apatinib, and docetaxel + apatinib) to 9.09% (nivolumab) and 10% (apatinib) to 33.3% (docetaxel + apatinib), respectively. Median OS ranged from 101 days (nivolumab) to 18.0 months (irinotecan + bevacizumab) and PFS ranged from 2.8 months (apatinib) to 8 months (nivolumab) respectively.

Conclusions: Real-world treatment outcomes for patients with stage IV NSCLC that have progressed on or after platinum-based therapy are very poor. Effective therapies delaying progression and extending survival in this patient population are urgently needed.

Table 1. Description of Real-World Studies

Study	Study Type	Country	Data Source	Sample (n)	Time Period
Somani et al. 2019	Prospective	India	Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, India	29	Oct. 2016 - Jan. 2018
Li et al. 2020	Retrospective	China	Huanggang Central Hospital	20	Last Follow-Up Dec. 30, 2017
Moezi et al. 2017	Prospective	United States	Multicenter (Community Setting)	383	Cutoff May 16, 2017
Qin et al. 2017	Retrospective	United States	University of Michigan and the Ann Arbor VA	91	N/A
Wills et al. 2017	Prospective	Colombia	Single Institution in Bogota, Colombia	49	Mar. 2011 - Nov. 2014
Abbas et al. 2020	Retrospective	India	Max-Super Speciality Hospital	11	Apr. 2016 - Dec. 2018
Brueckl et al. 2020	Retrospective	Germany	9 German Thoracic Oncology Centers	67	Cutoff Aug. 1, 2019
Jiang et al. 2017	Prospective	China	Three teaching hospitals centers in the Sichuan	12	Cutoff Dec. 28, 2017

Table 2. Summary of Real-World Treatment Response, Overall Survival, and Progression-Free Survival

Study	Intervention	Response	Overall Survival	Progression-Free Survival
Somani et al. 2019	Nivolumab	CR: 3.4% PR: 17.2%	Median OS: 101 days 3-Month OS: 41.4% 6-Month OS: 58.6 % 12-Month OS: 62.1%	------
Li et al. 2020	Apatinib	ORR: 10% CR: 0% PR: 10%	Median OS: 6 months	Median PFS: 2.8 months
Moezi et al. 2017	Nivolumab	------	Median OS: 11.5 months	------
	Chemotherapy	------	Median OS: 8.3 months	------
Qin et al. 2017	Nivolumab or Pembrolizumab	------	------	Progression after 3.2 months: 61.5%
Wills et al. 2017	Irinotecan + Bevacizumab	ORR: 32%	Median OS: 18.0 months	Median PFS: 4.4 months
Abbas et al. 2020	Nivolumab	OR: 54.5% CR: 9.09% PR: 18.18%	Median OS: 15 months	Median PFS: 8 months
Brueckl et al. 2020	Ramucirumab + Docetaxel	ORR: 36%	Median OS: 11 months	Median PFS: 6.8 months
Jiang et al. 2018	Docetaxel + Apatinib	ORR: 33.33% CR: 0% PR: 33.33%	6-Month OS: 80%	Median PFS: 2.92 months

Abbreviations: CR, complete response; OR, objective response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response

Keywords: metastatic non-small cell lung cancer, real world outcomes, systematic literature review

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-017 Evaluation of Blood Tumor Mutation Burden for Efficacy of Second-Line Atezolizumab Treatment in Non-small Cell Lung Cancer

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Introduction: We aimed to investigate the feasibility of using blood tumor mutation burden (bTMB) as a biomarker of atezolizumab, anti-programmed death-ligand 1 (PD-L1) inhibitor, efficacy in previously treated patients with relapsed/advanced non-small cell lung cancer (NSCLC).

Methods: We prospectively recruited patients diagnosed with relapsed/advanced NSCLC who had received one or two previous platinum-based combination chemotherapy. Patients received atezolizumab 1200 mg every 3 weeks. Blood was collected to obtain plasma cell-free DNA (cfDNA) before the first cycle (C0) and at the fourth cycle (C4) or end-of-treatment (EOT) visit. The measurement of bTMB was performed in patients with cfDNA >10 ng amount using CT-ULTRA, a targeted NGS panel specifically designed for ctDNA analysis. The primary endpoint was to evaluate objective response rate (ORR) in bTMB-high (bTMBhi) and -low (bTMBlo) population.

Results: Between December 2019 and April 2021, 100 patients were enrolled. bTMB was measured in cfDNA of 89 samples at C0 and paired 64 samples at C4/EOT. ORR was 10% and there was no difference in ORR according to bTMB (cutoff: 7.7 muts/Mb) at C0 (bTMBhi 9.3% vs. bTMBlo 11.4%; p=0.734). At a median follow-up of 12.3 months, the median PFS was 2.1 months. Patients with high PD-L1 (≥50%), low cfDNA at C0 (cutoff: 8.6 ng/mL) or decreased bTMB from C0 to C4/EOT showed significant PFS benefit (p<0.05), and the median PFS was significantly different between patients with high PD-L1/bTMBhi and with low or negative PD-L1/bTMBlo (not reached vs. 2.0; hazard ratio [HR] 3.32, p=0.015). In multivariable analysis, EGFR mutation (HR 2.92, p=0.029) and increased bTMB from C0 to C4/EOT (HR 2.97, p=0.047) were the significant risk factors for PFS.

Conclusions: In previously treated NSCLC patients, improvement in treatment efficacy of atezolizumab was correlated with high PD-L1 expression and serial decrease in bTMB after treatment, suggesting that PD-L1 expression combined with bTMB could be predictive for atezolizumab benefit.

Keywords: cell-free DNA, blood tumor mutation burden, atezolizumab

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-018 Patterns of Failure in Metastatic NSCLC Treated with First Line Pembrolizumab and Impact of Local Therapy in Patients with Oligoprogression

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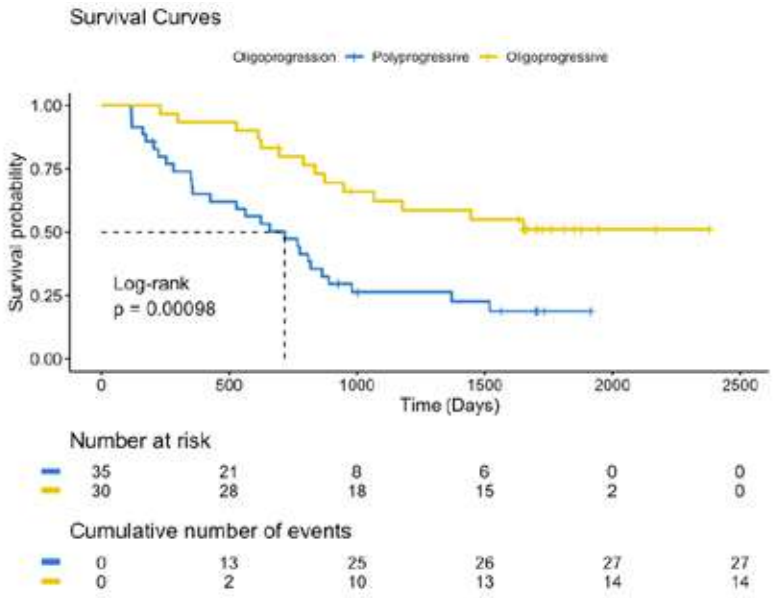
Introduction: The patterns of failure (POF) of metastatic non-small cell lung cancer (mNSCLC) treated with first line pembrolizumab are not well described. If oligoprogression (OPD) occurs in a limited number of anatomic sites, local ablative therapy may allow continuation of otherwise effective immunotherapy (CPIs). We sought to characterize POF and OPD in this population and estimate the potential benefits of local therapy.

Methods: Consecutive treatment-naïve patients with de-novo or recurrent mNSCLC receiving pembrolizumab +/- chemotherapy were retrospectively identified at a single institution between 2015 and 2018. Initial POFs while on immunotherapy were classified in two ways: 1) local, regional, distant, or any combination of these and 2) disease growth in existing lesions, new lesions, or combination. OPD was defined as < 3 anatomic sites of intracranial or extracranial disease growth. Overall survival (OS) and progression-free survival (PFS) were calculated using Kaplan Meier methodology and groups were compared using the log-rank test.

Results: A total of 91 patients were treated with first line pembrolizumab alone (n=50, 55%) or in combination with chemotherapy (n=41, 45%). After a median follow up of 28.8 months, 65 patients (71%) exhibited disease progression (PD) and 53 patients (58%) had died. For the entire cohort, median PFS and OS were 13.0 (95% CI 7.7 - 18.5) months and 31.6 (95% CI 25.9 - NR) months, respectively. POF (classification 1) included distant (n=28, 43%), followed by combination failure (n=27, 42%), local (n=7, 11%), and regional (n=3, 5%). POF (classification 2) included tumor growth in a combination of new/existing lesions (n=30, 46%), existing lesions (n=22, 34%), and new lesions (n=13, 20%). OPD occurred in 30 patients (46%): 70% at one site, 20% at two sites, 10% at three sites, most commonly in the lung parenchyma (39%). Patients with OPD had a significantly longer OS than patients with polyprogression (2-year OS 80% vs. 47%, p<0.001). Of patients with OPD, 16 (54%) were treated with local therapy (15 with radiation and 1 with surgery). Patients with OPD who received local therapy had an absolute numeric difference in OS (3-year OS 67% vs 57%, p=0.18) compared to those who switched to another systemic therapy.

Conclusions: Oligoprogression is common in mNSCLC treated with immunotherapy. In this small series, patients who exhibited OPD had better survival than those with polyprogression. Randomized prospective data may further elucidate the benefits of local therapy in this population while continuing CPIs.



Keywords: Pembrolizumab, oligoprogression, local therapy

EP08.01-019 Modifiable Biomarkers of Response to Immune Checkpoint Inhibitor Treatment in Non-small Cell Lung Cancer

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Introduction: Lung cancer is the leading cause of cancer-related deaths annually worldwide. Survival rates have improved with the use of immune checkpoint inhibitors (ICIs); however, the objective response rate in advanced non-small cell lung cancer remains low. The gut microbiome has been shown to predict response to ICIs and can be modified to reverse resistance to prior ICI treatment. The microbiome can be modified by lifestyle factors such as diet and physical activity. We therefore sought to understand how to use lifestyle factors to improve response to ICIs via their effects on the microbiome. Our studies involved (1) measuring gut microbiome and physical activity in lung cancer patients, and (2) measuring the causal effects of the microbiome on response to immunotherapy in preclinical models.

Methods: We conducted a prospective cohort study of adults ≥60 years with a new diagnosis of non-small cell lung cancer (NSCLC). Biospecimens (gut microbiome) and longitudinal geriatric assessments (Cancer and Aging Research Group cancer-specific geriatric assessment (CARG GA), short physical performance battery (SPPB), functional status) were collected longitudinally. Generalized linear regression was used to relate baseline microbiome composition to geriatric assessments. To assess the causal role of the gut microbiome in treatment response, we gavaged gut microbiome samples from participants with high and low SPPB scores into C57/B6 mice to create human microbiome avatar models. The mice were then injected with mc38 colon cancer cells subcutaneously and treated with anti-PD1 antibodies or isotype control.

Results: Most geriatric assessment scores were significantly associated with baseline microbe relative abundances including SPPB. Participants with higher (more impaired) SPPB scores showed increased relative abundance of the genus Blautia over time. Participants lower (less impaired) SPPB showed increased relative abundance of the species Faecalibacterium prausnitzii over time. In preliminary studies, mice that received stool from individuals with good functional status (SPPB >9) showed smaller tumors after ICI treatment than mice that received the gut microbiome of a patient with physical impairments (SPPB <9).

Conclusions: The gut microbiome is associated with longitudinal measures of functional status (SPPB). The microbiomes of these individuals is causally related to response to ICIs. These results suggest a mechanism by which the gut microbiome can be used to improve response to immunotherapy in older adults undergoing treatment for lung cancer.

Keywords: Microbiome, Immunotherapy, Functional status

EP08.01-020 Phase 2 Platform Trial of Anti-TIGIT GSK'859A/EOS-448 + Anti-PD-1 Dostarlimab in Non-small Cell Lung Cancer (NSCLC)

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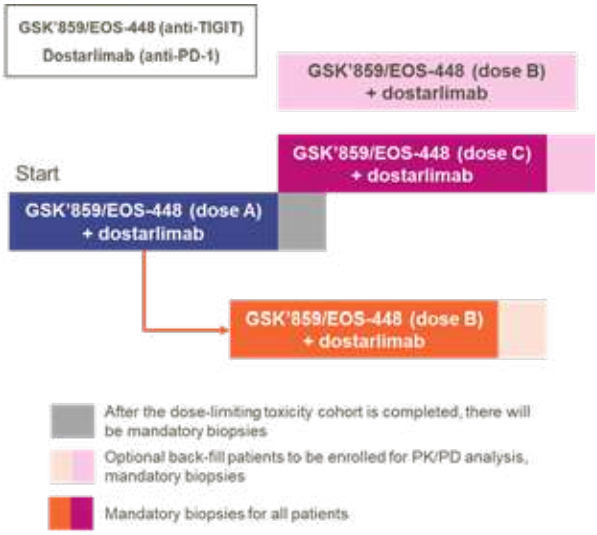
Introduction: Despite intrinsic resistance to immunotherapy, some NSCLC tumors are susceptible to T-cell-mediated antitumor effects. Targeting multiple cancer immunity processes may enhance response in relapsed or refractory NSCLC. The CD226 Axis includes the T- and NK-cell inhibitory receptors TIGIT, CD96, and PVRIG (CD112R); the T-/NK-cell activating receptor CD226 (DNAM-1); and cognate ligands CD155 (PVR) and CD112. These immune receptors play a critical role regulating antitumor responses. The immune checkpoints TIGIT, CD96, and PVRIG may prevent CD226's interactions with CD155 and CD112, directly impairing NK- and T-cell function; this impairment reduces antitumor response. The anti-TIGIT IgG1 monoclonal antibody (mAb) GSK4428859A (GSK'859A)/EOS-448 inhibits TIGIT's immunosuppressive activity via multiple mechanisms of action. GSK'859A/EOS-448 binds TIGIT with high affinity, blocking it from binding to its ligands, CD155 and CD112, preventing direct inhibitory signaling, and allowing the ligands to bind to the costimulatory receptor CD226. GSK'859A/EOS-448 engagement with FcγR on APCs, macrophages, and NK cells can drive proinflammatory signaling in the tumor microenvironment, activate antitumor immune cell responses, and induce antibody-dependent depletion of immunosuppressive Tregs and TIGIT+ (exhausted) CD8 T cells. Preliminary phase 1 data on GSK'859A/EOS-448 suggest early signs of clinical activity and an acceptable tolerability profile in patients with advanced cancer. Anti-TIGIT/anti-PD-(L)1 combination therapy exhibited improved clinical activity vs checkpoint blockade alone. Early data also showed modest antitumor activity in heavily treated solid tumors refractory to PD-(L)1 inhibition. Here, we describe the part 1 safety component of the GSK'859A/EOS-448 + dostarlimab (anti-PD-1 mAb) combination arm of ENTRÉE, a phase 2 NSCLC platform study (NCT03739710) exploring multiple checkpoint-inhibitor(s) as an approach to overcome immunotherapy resistance.

Methods: Adults (≥18 years old) with ECOG PS 0-1 are eligible if they have histologically or cytologically confirmed NSCLC (nonsquamous or squamous) that has progressed during or after ≤2 lines of systemic treatment for locally/regionally advanced stage IIIb/IIIc/IV or metastatic disease, including 1 line of PD-(L)1 mAb therapy and 1 line of platinum-containing chemotherapy in the same or separate lines of therapy. Patients who received prior docetaxel or have known molecular alterations with therapeutic options available (eg, EGFR, ALK, ROS1) are excluded. Patients will receive intravenous GSK'859A/EOS-448 (per-protocol dose escalation) and dostarlimab, both q3w for ≤35 cycles or 2 years or until intolerability, consent withdrawal, disease progression, or death. Part 1 primary endpoints are safety and tolerability, and secondary endpoints are efficacy and pharmacokinetics. Four patients have been treated at the starting dose (Figure) as of March 1, 2022.



Keywords: CD226 Axis, TIGIT, GSK4428859A (GSK'859A)/EOS-448

EP08.01-021 Phase 2 Study Evaluating Inupadenant in Combination with Chemotherapy in Adults with NSCLC who Progressed on Immunotherapy

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Introduction: In cancer, the accumulation of adenosine in the tumor microenvironment (TME) mediates immune suppression mainly via the high affinity A2A receptor (A2AR), causing dysregulation of innate and adaptative immune cell subsets and dampening the antitumor immune response. This results in increased tumor cell survival and immune escape (Blay 1997; Merighi 2003; Muller-Haegele 2014). Therefore, inhibiting A2AR could reverse immunosuppression and re-establish immune surveillance in the tumor microenvironment. Inupadenant is an antagonist of the A2AR with potent inhibition of A2AR even at the high concentrations of adenosine present in the tumor microenvironment. Ongoing clinical studies have established inupadenant as a molecule with a favorable safety profile with preliminary evidence of clinical activity in multiple tumor types, including durable PRs in patients who have exhausted standard treatment options (Buisseret 2021). The standard treatment for patients without a driving mutation who progress on first-line IO is a platinum-based doublet chemotherapy regimen. Carboplatin plus Pemetrexed (C+P) is the preferred chemotherapy in nonsquamous mNSCLC. Study A2A-005 will evaluate the efficacy of inupadenant in combination with C+P as a second-line therapy in adult patients with nonsquamous mNSCLC (post-IO). A successful outcome from study A2A-005 will help address a high unmet need for this patient population and could lead to new therapeutic options.

Methods: This is a 2-part study. The first part is an open label dose-finding part to determine the safety and recommended Phase 2 dose (RP2D) of inupadenant in combination with C+P (N=40). In Part 2, 150 patients will be randomized 1:1 to inupadenant or placebo, both in combination with C+P. Tumor response will be determined according to RECIST 1.1 criteria and safety findings will be reviewed by the Safety Review Committee (for Part 1) and the Data Monitoring Committee (for Part 2). Key eligibility criteria include 1) mNSCLC of nonsquamous pathology, 2) have received only 1 line of anti-PD-(L)1 therapy in the metastatic setting, without concomitant chemotherapy, and have progressed (IO/IO combination therapy is allowed), 3) have measurable disease as defined by RECIST v1.1 criteria and 4) Eastern Cooperative Oncology Group status ≤1. Primary endpoints are RP2D (for Part 1) and PFS (for Part 2). Secondary endpoints include change in tumor size, ORR, OS, and adverse events. Correlative aims include assessing blood and tissue biomarkers for association with clinical benefit. The study will be conducted in approximately 11 countries in North America and Europe.**Clinical trial information:** EudraCT 2021-005487-22

Keywords: NSCLC, immunotherapy, second line

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-022 Treatment Outcomes of Second-Line Immune Modulators in Steroid Refractory/Resistant Immune Related Adverse Events

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Introduction: Immune checkpoint inhibitors (ICI) have transformed the therapeutic paradigm of many malignancies but are associated with a variety of Immune-related adverse events (irAEs). The optimal treatment options for severe irAEs from ICI are limited and are still not well defined, especially in steroid-refractory/resistant irAEs.Consensus guidelines suggest alternative immunosuppressants, primarily on the basis of limited literature, expert opinion and experience extrapolated from other autoimmune diseases The objective of this study was to evaluate the use and outcomes of second-line immune modulators in lung cancers & malignant melanoma who experienced a steroid-refractory or resistant irAE.

Methods: Retrospective study of patients with advanced lung cancer and MM who started ICI at three tertiary cancer centres between June 2016-June 2021. The study population included all patients who experienced a steroid-refractory or resistant irAE before June 1, 2021, and followed up through December 31, 2021.The irAE grade was determined using the Common Terminology Criteria for Adverse Events version 5.0. Pharmacy records were queried to identify patients who received systemic steroids as well as second-line immune modulators. Electronic medical records were reviewed to collect Clinicopathologic characteristics, management, and outcomes data. Patient outcomes were summarized at 60 days after the start of the additional immune modulators.

Results: Among 654 patients with lung cancers and malignant melanoma treated with ICI, we identified 56 patients (8.6%) treated with both steroids and second-line immunosuppressant for a severe irAE. Thirty-nine patients (69.6 %) were NSCLC, 2 (3.5%) were SCLC and 15 (26.7%) were malignant melanoma. Additional immune modulation consisted of TNFα inhibitor (n=40 71.4%), mycophenolate mofetil (n=12 21.4%) and immunoglobulin (n=4 7.1%).Indications for an additional immune modulator were: *Initial non-response to steroids (steroid-refractory, 64.2%), later intolerance to/dependence on steroids (steroid-resistant, 28.5%), or upfront use (7.1%).* The most common events were *Colitis (n=29, 51.7%), Pneumonitis (n=11, 19.6%), Hepatitis (n=7, 12.5%), Neuromuscular (n=5, 9%) & Myocarditis n=2, 3.5%).* Improvement was more common in hepatitis (5/7) and colitis (19/29) but less common in neuromuscular (1/5) and pneumonitis (3/11).At 60 days after the start of the second-line immunosuppressant, 57% (23/56) were improved from their irAE, 18% (10/56) were unchanged, and 26% (14/56) were deceased. Improvement was more common in hepatitis (5/6) and colitis (18/27) but less common in neuromuscular (1/5) and pneumonitis (3/10). Of patients who died, 64.2% (8/14) were attributable directly to the irAE and 28.5%(4/14) related to toxicity from immunosuppression (3, infection-related deaths; 1, drug-induced liver injury leading to acute liver failure).

Conclusions: Steroid-refractory/resistant irAEs are a rare but growing challenge. Response to second-line immunosuppressants in steroid-refractory/resistant irAEs is heterogeneous. While these treatments help some patients, many remain refractory, can die and/or experience other unintended toxicities from immunosuppression Treatment options for irAEs are limited and still not well defined. Personalized immunomodulatory treatments to address specific irAEs is needed to guide biologically-informed treatments for severe irAEs.

EP08.01-023 Factors Associated with Survival and Refusal of Physician Recommended Immunotherapy in Metastatic Non Small Cell Lung Cancer

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Introduction: Much work has been done to explore how social determinants of health are associated with disparities in access to treatment for non-small cell lung cancer (NSCLC). We used a large national registry to investigate sociodemographic, and disease characteristics associated with refusal of physician-recommended immunotherapy and prognosis in patients with metastatic NSCLC.

Methods: We used the National Cancer Database to study factors associated with patient decision-making and survival in patients diagnosed with AJCC clinical stage IV NSCLC between 2004-2017. We identified patients recommended immunotherapy by their physicians but who declined treatment. Multivariable logistic regression and Cox Regression analysis were performed to explore these variables. Furthermore, Kaplan Meier analysis compared survival between patients who accepted or denied immunotherapy. P <0.05 was considered statistically significant.

Results: A total of n=11216 patients with stage IV NSCLC were included. Patients aged ≥70 (OR 2.950, 95% CI 2.251-3.866, p < 0.001) and with higher number of comorbidities (Charlson/Deyo score ≥3: OR 2.245, 95% CI 1.437 - 3.508, p<0.001) had higher chances of refusing recommended immunotherapy. In contrast, patients who were residing in areas with the lower education (OR 0.639, 95% CI 0.447 - 0.914, p=0.014), Medicare-insured (OR 0.511, 95% CI 0.273 - 0.956, p = 0.036), and privately insured (OR 0.289, 95% CI 0.151 - 0.555, p<0.001), receiving treatment at academic programs (OR 0.544, 95% CI 0.369 - 0.801, p = 0.002), adenocarcinoma on their histology (OR 0.385, 95% CI 0.294 - 0.505, p<0.001) were more likely to accept immunotherapy than others. In terms of survival characteristics, patients who aged ≥70 (HR 1.098, 95% CI 1.041 - 1.158, p < 0.001), with a higher number of comorbidities (Charlson/Deyo score ≥3: HR 1.574, 95% CI 1.373 - 1.804, p<0.001), and poorly differentiated tumors (HR 1.476, 95% CI 1.283 - 1.697, p < 0.001) were associated with poorer survival. Conversely, Asians (HR 0.656, 95% CI 0.569 - 0.757, p < 0.001), receiving treatment at academic centers (HR 0.844, 95% CI 0.780 - 0.914, p < 0.001) and adenocarcinoma histology (HR 0.804, 95% CI 0.743 - 0.870, p < 0.001) was associated with better prognosis. Refusal of recommended immunotherapy was associated with a significantly lower median survival than accepting treatment (HR 3.778, 95% CI 3.275 - 4.360, p < 0.001, 2.60 versus 12.35 months, p<0.001).

Conclusions: Our analysis highlights that patients who were older, Black, uninsured, with higher comorbidities, receiving treatment at Community Cancer Programs, and squamous tumors on histology were seen to have higher refusal than the rest. Furthermore, refusal of recommended immunotherapy was seen to substantially lower survival. Patients who were younger, Asians, with lower comorbidities, well-differentiated tumors, receiving treatment at academic cancer centers, and adenocarcinoma on histology were seen to have a significantly better prognosis. These findings highlight the importance of understanding the complexity of patient decision-making and physician-patient communication in establishing trust and adherence to recommended treatment.

Keywords: Metastatic Non-small cell lung cancer, Immunotherapy, Refusal of treatment

EP08.01-024 Multicenter Real Life Clinical Outcomes of PDL-1 Tested Patients with Non Small Cell Lung Cancer (NSCLC) in Turkey

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Introduction: The current study aimed to evaluate the real life clinical outcomes of PD-L1 tested NSCLC patients.

Methods: The PD-L1 tested NSCLC patients and clinical parameters were retrospectively evaluated.

Results: Total 338 patients (pts) were included in the study and 79.6% (269) of them were male. The mean age of pts was 63 (±11). Smoking status of pts were 39.3% (n=133) active smoker, 43.5% (n=147) ex smoker and 14.2% (n=48) non-smoker. Histopathology of pts were 65.7% (n=222) adenocarcinoma, 20.7% (n=70) squamous cell carcinoma, others. PDL was evaluated from primary tumor (67.2%), metastatic region (14.2%) and pleural effusion (3.6%). The median PFS of pts was 7 (95% CI 5.9 - 8) months and OS was 13 (95% CI 11 - 14.9) months. The regions of metastasis were 30.8% brain, 15.7% liver, 24.6% adrenal gland, 39.9% contrary lung, 32% distant lymph node, 33% pleural metastasis. Detected driver mutations were 9.8% EGFR, 3% ALK fusion, 0.6% ROS-1 fusion, 0.6% BRAF. PDL-1 ≥1% was in 49.4% of patients (n=167), 86 pts (25.4%) have PDL-1 ≥50%, 46 pts (13.6%) have PDL-1 ≥80%. In PDL positive and negative group PFS was similar [7 months (95CI 5.7 -8.2) vs 8 months (95% CI 6.1- 9.8), p=0.11] and also PFS was similar in pts with PDL1 ≥ 50% compared with <50%. OS was not statistically significant in PDL positive and negative groups [17 months (95% CI 11.5- 22.4) vs 12 months (95% CI 10.5- 13.4), respectively (p=0.24)]. In PD-L1 ≥ 50% and <50% OS was 17 months (95% CI 7.7- 26.2) vs 13 months (95% CI 11.4- 14.5), respectively (p=0.11). First line treatments were platin combination chemotherapy 63.6% (n=215), single agent chemotherapy 3.9% (n=13), tyrosine kinase inhibitors 8.9% (n=30), chemotherapy-immunotherapy combination 3.6% (n=12), immunotherapy 7.7% (n=26) and others. As a second line therapy most of the patients received chemotherapy 25.7%, TKI 5.6%, immunotherapy 6.5%. 12.month OS rates of pts who did not receive immunotherapy, receive immunotherapy as 1. and 2. line of treatment were, 56% vs 51% vs 66%, respectively and difference was not significant. The median OS in pts who received immunotherapy as 1. or 2.line therapy was 17 months compared with non-immunotherapy group 13 months 95% CI (11.2 - 14.7), p=0.13.

Conclusions: The real life median OS in pts who received immunotherapy was 17 months. Immunotherapy should be undeniable and accessible part of treatments against NSCLC in underdeveloped and developing countries.

Keywords: lung cancer, immunotheraphy, prognosis

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-025 PD-L1 Tumor Tissue Expression and Its Relation with Clinico-pathological Profile in Advanced NSCLC

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Introduction: Targeted therapies against Programmed Death Ligand 1 (PD-L1) in advanced NSCLC has revolutionized the management in recent years. As there is limited data on the significance of PD-L1 expression in NSCLC from India, we aimed to study the prevalence of PD-L1 expression and its relation with different clinic-pathological parameters in patients of stage IV NSCLC from a tertiary care centre in Eastern India

Methods: All consecutive patients with stage 4 NSCLC diagnosed during January 2020 to December 2021 were prospectively evaluated for PD-L1 expression in formalin fixed-paraffin embedded tumor tissue specimens using clones SP-263 and 22-C3 pharmDX. A PD-L1 expression of <1%, 1-49%, ≥50% were considered negative, low and high expression respectively and correlation with various parameters was performed.

Results: Out of 104 patients who were diagnosed with stage 4 NSCLC during the study period, 10 patients were excluded (due to nonviable tumor tissue for PD-L1 testing). A total of 94 patients (mean age 60.3±12.7years, 63.8% males) were finally analyzed. 61.7% (58) had stage IVa disease while, 38.3% (36) had stage IVb disease. PD-L1 positivity was seen in a total of 42 (44.7%) patients (1-49%:29, >50%:13). 50% of males and 35.3% of females showed PD-L1 positivity. Similarly, 37% of those aged <60 years and 49% of those aged >60 years showed PD-L1 positivity. There were no statistically significant differences in PD-L1 positivity with respect to gender, age group and smoking habits (table 1). Epidermal Growth Factor Receptor (EGFR) mutations were seen in 28 (29.8%) patients and 4.2% (4) were ALK positive. 46.4% of EGFR positive and 44% EGFR negative patients showed PD-L1 positivity (p=0.8). Compared to PD-L1 negative group, patients with PD-L1 positivity had significantly increased rates of advanced tumor stage (p=0.03) and higher nodal stage (p=0.02). Median overall survival in the cohort was 6.5 months (range 1-24 months) and it was not significantly different between the PD-L1 positive and negative groups (p=0.6).

Conclusions: 45% of stage IV NSCLC cancer patients in our cohort showed PD-L1 positivity. There was no association of PD-L1 positivity with patient demographics, however it was associated with more aggressive tumor characteristics

Table 1

Characteristics	PD-L1 negative (n=52)	PD-L1 positive (n=42)	p value
Age>60 years	50.8% (30)	49.2% (29)	0.25
Males	50% (30)	50% (30)	0.16
Smokers	40% (12)	60% (18)	0.04
T stage T1+T2	23 (44.2%)	2 (4.7%)	<0.001
N stage N0+N1	17 (32.7%)	1 (2.4%)	<0.001
EGFR mutatnt	15 (53.6%)	13 (46.4%)	0.82
Metastasis sites>2	14 (53.6%)	13 (46.4%)	0.82

Keywords: PD-L1, NSCLC, EGFR

EP08.01-026 Influence of Brain Metastases on Survival of KRASG12C Mutated Stage IV Immune Checkpoint Inhibitor Treated Non-Small Cell Lung Cancer Patients

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Introduction: Recently, targeted therapy has become available as second-line treatment and beyond for KRASG12C mutated (KRAS G12C+) advanced non-small cell lung cancer (NSCLC). First-line standard of care, however, is immune checkpoint inhibitor (ICI) +/- chemotherapy ((chemo)-ICI). Although ICI efficacy has been shown in NSCLC patients with brain metastases (BM+), data regarding KRAS G12C+ is lacking**.** We describe incidence and outcome (overall survival [OS] and progression free survival [PFS]) on first-line (chemo)-ICI in advanced KRAS G12C+ NSCLC with or without BM (BM+ vs. BM-, respectively).

Methods: Data on baseline- and treatment characteristics of first-line (chemo)-ICI treated stage IV KRAS G12C+ NSCLC patients diagnosed between January 1 2019 and June 30 2019 were retrospectively collected from the population-based Netherlands Cancer Registry. Follow-up ended February 2021. OS and PFS were estimated from start of first-line systemic treatment using Kaplan-Meier curves and BM+ and BM- groups were compared using log-rank tests.

Results: 641 out of a total of 1851 patients with stage IV NSCLC received first-line (chemo)-ICI. 49% (312/641) were KRAS+, of which 49% (153/312) were KRAS G12C+. Of the KRAS G12C+ patients, 35% (53/153) underwent brain imaging, of which 85% (45/53) MRI and 55% (29/53) had BM. Generally, compared to BM-, BM+ patients were younger and had more organs affected with metastasis. Around one third of BM+ patients had ≥ 5 brain metastases at diagnosis. 38% of BM+ and 50% of BM- patients had PD-1L expression ≥50%. Regardless of BM, the majority of patients received (chemo)-ICI. BM+ patients received slightly more often (chemo)-ICI than BM- patients (66% vs. 57%). 76% of BM+ patients received cranial radiotherapy prior to start of (chemo)-ICI (31% whole brain radiotherapy [WBRT], 41% stereotactic radiotherapy [SRT], and 4% no specification of RT). 66% of patients had symptomatic BM at start of (chemo)-ICI. In our cohort 28% of BM+ had BM progression within one year of starting systemic treatment. 88% of them received cranial radiotherapy (13% WBRT, 62% SRT, and 13% no specification of RT). 5% of BM- developed BM within one year of starting systemic treatment. However, cerebral imaging is not routinely used during follow-up. Median OS was 15.4 (95% confidence interval [CI]: 6.1-not estimated [NE]) and 17.6 (95% CI: 12.9-NE) months for BM+ and BM- (p=0.59), respectively. Median PFS was 7.0 (95% CI: 2.6-15.9) and 8.2 (95% CI 5.8-9.6) months for BM+ and BM- (p=0.98), respectively.

Conclusions: Baseline BM are frequent in patients with KRASG12C+ NSCLC treated with (chemo)-ICI. During systemic treatment, intracranial progression was more frequent in BM+ patients, advocating for regular imaging during follow-up. Our data suggests that presence of BM at baseline did not influence survival for (pretreated) KRAS G12C mutated stage IV NSCLC patients treated with first-line (chemo)-ICI.

Keywords: KRASG12C, Brain metastases, Immune Checkpoint Inhibitor

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-027 Durvalumab (D) ± Tremelimumab (T) + Chemotherapy (CT) in 1L Metastatic NSCLC: Outcomes by Tumour PD-L1 Expression in POSEIDON

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Introduction: In the Phase 3 POSEIDON study (NCT03164616), first-line T+D+CT demonstrated statistically significant improvements in both progression-free survival (PFS) (HR, 0.72; 95% CI, 0.60-0.86; p=0.0003) and overall survival (OS) (HR, 0.77; 95% CI, 0.65-0.92; p=0.0030) versus CT in patients with *EGFR/ALK* wild-type metastatic NSCLC (mNSCLC). CT supports initial tumour control, and can prime an anti-tumour immune response, while PD-(L)1 inhibition prevents local immune evasion to enhance tumour killing by activated T cells, and CTLA-4 inhibition has been shown to promote T-cell expansion, diversification and activation, potentially generating new anti-tumour T-cell responses. The latter is thought to be particularly important for PD-L1-negative (tumour cell [TC] expression <1%) NSCLC, which is more likely to lack existing activated anti-tumour T cells. Here we report outcomes in POSEIDON patient subgroups based on a PD-L1 expression cutoff of TC 1%.

Methods: Patients were randomised 1:1:1 to first-line T+D+CT (platinum-based), D+CT, or CT, with stratification by PD-L1 expression (TC ≥50% versus <50%), disease stage (IVA versus IVB), and histology (squamous versus non-squamous). PD-L1 TC expression was evaluated using the VENTANA PD-L1 (SP263) assay. OS, PFS, objective response rate, duration of response, and safety were assessed in patient subgroups with PD-L1 TC ≥1% versus <1% and further subdivisions based on histology.

Results: 1012/1013 randomised patients had known PD-L1 status. Baseline characteristics were generally balanced across the treatment arms and between PD-L1 TC ≥1% and <1% subgroups. OS benefit for T+D+CT versus CT appeared consistent with the intention-to-treat (ITT) population in both TC ≥1% and TC <1% subgroups; median OS was longer with T+D+CT versus CT, with 24-month OS rates indicating sustained benefit (Table). In contrast, for D+CT versus CT, OS benefit was clearest in the TC ≥1% subgroup. PFS and objective response followed similar trends (data will be presented). The OS benefit for T+D+CT versus CT in patients with TC <1% was observed regardless of histology (Table). The safety profile in the TC ≥1% and TC <1% subgroups was generally consistent with the ITT population.

Conclusions: In POSEIDON, the addition of T to D+CT extended clinical benefit to patients with PD-L1 TC <1% across both histologies, consistent with the role of CTLA-4 and PD-(L)1 checkpoints in the immune response. This has particular relevance for a subgroup with hard-to-treat disease and outcomes that can be suboptimal in clinical practice with currently available treatment options.

	T+D+CT	D+CT	CT
PD-L1 TC ≥1%, n	213	224	207
Median OS (95% CI), months	15.6 (11.6–18.1)	14.4 (11.8–17.5)	12.5 (10.4–15.2)
OS HR vs CT (95% CI)	0.76 (0.61–0.95)	0.79 (0.64–0.98	–
24-month OS rate (95% CI), %	38.1 (31.6–44.7)	35.5 (29.3–41.8)	24.8 (19.1–30.9)
PD-L1 TC <1%, n	125	113	130
Median OS (95% CI), months	12.7 (9.9–15.5)	10.9 (8.1–13.5)	11.0 (8.7–12.7)
OS HR vs CT (95% CI)	0.77 (0.58–1.00)	0.99 (0.76–1.30)	–
24-month OS rate (95% CI), %	23.9 (16.8–31.7)	17.6 (11.1–25.3)	17.8 (11.7–25.0)
Non-squamous histology*			
PD-L1 TC ≥1%, n	133	129	132
Median OS (95% CI), months	22.1 (15.9–27.8)	17.1 (13.3–23.9)	13.5 (10.6–18.8)
OS HR vs CT (95% CI)	0.67 (0.50–0.90)	0.77 (0.58–1.03)	–
24-month OS rate (95% CI), %	48.9 (40.1–57.1)	41.1 (32.6–49.4)	29.9 (22.2–38.0)
PD-L1 TC <1%, n	81	79	82
Median OS (95% CI), months	13.4 (9.8–18.7)	11.7 (7.5–17.0)	12.3 (9.3–14.1)
OS HR vs CT (95% CI)	0.75 (0.53–1.06)	0.94 (0.67–1.32)	–
24-month OS rate (95% CI), %	29.2 (19.7–39.3)	25.7 (16.4–35.9)	22.1 (13.6–31.8)
Squamous histology*			
PD-L1 TC ≥1%, n	80	94	74
Median OS (95% CI), months	9.8 (7.6–12.5)	12.3 (9.5–15.7)	10.6 (9.0–15.2)
OS HR vs CT (95% CI)	0.95 (0.68–1.34)	0.78 (0.56–1.08)	–
24-month OS rate (95% CI), %	20.3 (12.3–29.7)	28.1 (19.4–37.5)	16.2 (8.9–25.4)
PD-L1 TC <1%, n	44	34	48
Median OS (95% CI), months	12.7 (7.7–14.1)	9.8 (7.4–13.5)	8.8 (4.8–11.8)
OS HR vs CT (95% CI)	0.79 (0.51–1.22)	1.28 (0.80–2.03)	–
24-month OS rate (95% CI), %	14.0 (5.7–26.0)	0.0 (0.0–0.0)	10.6 (3.9–21.3)

Data cutoff: 12 March 2021. HRs calculated by unstratified analysis. *One patient each in the D+CT and CT arms had 'other' or 'missing' histology.

Keywords: Durvalumab, Tremelimumab, POSEIDON

EP08.01-028 Overestimation with Cox HR - Cox-TEL-Adjusted Associations of PD-L1 Expression with Immune Checkpoint Inhibitor Survival Benefit in Lung Cancer

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Introduction: Survival benefit of immune checkpoint inhibitor (ICI) therapy in lung cancer is not fully understood.

Methods: PubMed-catalogued publications through February 14, 2022, were queried for randomized controlled trials of ICI in lung cancer, and identified publications were reviewed for inclusion. Reported Cox hazard ratios (HR) for overall survival were transformed to Cox-TEL HR (ST-HR, for ICI short-term responders) and differences in proportion (LT-DP, for patients with long-term survival). Meta-analyses were performed using a frequentist random-effect model. Outcomes of interest were pooled overall survival Cox HR, ST-HR, and LT-DP in non-small cell lung cancer stratified by PD-L1 level (primary) and ICI treatment line (secondary).

Results: A total of 430 publications was identified, and 32 publications, representing 16 clinical trials comparing ICI or ICI plus chemotherapy versus chemotherapy, were qualified for final review. Nine publications remained eligible for final inclusion per piecewise regression criteria. These nine papers represented eight reported clinical trials in non-small cell lung cancer: CheckMate 017/057, OAK, KEYNOTE 010, and KEYNOTE 024 which compared second-line ICI versus chemotherapy; KEYNOTE 042, IMpower 110, and CheckMate 227 which compared first-line ICI versus chemotherapy; and Impower 132 which compared first-line ICI plus chemotherapy versus chemotherapy. In the primary analyses, the PD-L1 >1% subpopulation had a long-term survival probability increment of 9%, while the PD-L1 >50% subpopulation had a long-term survival probability increment of 11%. For the PD-L1< 1% subpopulation, both pooled LT-DP and ST-HR were not statistically significant. In the secondary analysis, the trend of pooled LT-DP coincided with that of PD-L1 expression in both ICI treatment lines; and pooled ST-HR was greater (implicating a smaller percent reduction of risk with ICI) in the ICI first-line setting than in the ICI second-line setting (Table 1).

Conclusions: This study showed a ~10% long-term survival probability increment in ICI long-term responders across PD-L1 positively-expressed subpopulations in both ICI treatment lines. Meanwhile, ST-HR was consistently inferior to unadjusted (biased) Cox HR. For patients with PD-L1 <1%, neither LT-DP nor ST-HR achieved statistical significance. These suggest the overall overestimation of ICI survival benefit in published trials.

Table 1. Associations of PD-L1 expression and ICI survival benefit

	Pooled Cox HR	Pooled ST-HR	Pooled LT-DP
Primary analysis			
PD-L1 <1%	0.71 (95% CI, 0.62-0.82)	0.91 (95% CI, 0.79-1.05)	0.10 (95% CI, 0.00-0.20)
PD-L1 ≥1%	0.74 (95% CI, 0.68-0.82)	0.88 (95% CI, 0.82-0.94)	0.09 (95% CI, 0.06, 0.12)
PD-L1 ≥50%	0.62 (95% CI, 0.54-0.70)	0.70 (95% CI, 0.60-0.83)	0.11 (95% CI, 0.05-0.17)
Secondary analysis			
ICI first-line setting			
ITT population	0.82 (95% CI, 0.75-0.89)	0.91 (95% CI, 0.83-0.99)	0.07 (95% CI, 0.02-0.12)
PD-L1 ≥1%	0.81 (95% CI, 0.74-0.89)	0.93 (95% CI, 0.84-1.02)	0.08 (95% CI, 0.03-0.13)
PD-L1 ≥50%	0.71 (95% CI, 0.59-0.85)	0.84 (95% CI, 0.70-1.00)	0.11 (95% CI, 0.02-0.21)
ICI second-line setting			
ITT population	0.72 (95% CI, 0.66-0.78)	0.84 (95% CI, 0.78-0.91)	0.08 (95% CI, 0.05-0.11)
PD-L1 ≥1%	0.67 (95% CI, 0.60-0.75)	0.81 (95% CI, 0.73-0.90)	0.10 (95% CI, 0.06-0.14)
PD-L1 ≥50%	0.56 (95% CI, 0.48-0.65)	0.62 (95% CI, 0.53-0.72)	0.11 (95% CI, 0.03-0.18)

Keywords: Immune Checkpoint Inhibitor, Survival Benefit, Cox Hazard Ratio and Cox-TEL Adjustment

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-029 NIVIPI-BRAIN, A Phase II Study of Nivolumab plus Ipilimumab Combined with Chemotherapy for Patients with NSCLC and Synchronous Brain Metastases

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Introduction: Brain metastases (BM) are a common complication in cancer patients and have major impact on quality of life and prognosis. Chemotherapy plus immunotherapy has significant efficacy in patients with advanced non-small cell lung cancer (NSCLC) who have untreated brain metastases. In the CheckMate-9LA, nivolumab (NIVO) was combined with ipilimumab (IPI) and 2 cycles of chemotherapy and achieved high intracranial efficacy in patients with advanced NSCLC with previously treated BM. This combination was not previously assessed in patients with NSCLC and untreated BM.

Methods: This is an ongoing multicenter, open-label, phase 2 study (EUDRACT: 2021-000425-27) to evaluate the efficacy and safety of two cycles of platinum-based chemotherapy (according to the histological type) combined with NIVO 360mg every 3 weeks plus IPI 1 mg/kg every 6 weeks. Double immune checkpoint inhibition will be maintained until tumor progression, unacceptable toxicity, or a maximum of two years. Patients with multiple, untreated and measurable BM, adequate performance status and organ function, without EGFR, ALK or ROS1 genomic alterations, treatment naïve and without contraindication to receive immunotherapy were assigned to two cohorts: (A) Asymptomatic BM not requiring systemic corticosteroids (n=44); (B) BM causing neurologic signs and symptoms controlled with doses of corticosteroids equivalent to ≤ 4mg/d of dexamethasone with good performance status (n=27). Exclusion criteria consist of dexamethasone dose ≥4 mg QD, presence of leptomeningeal carcinomatosis, spinal or hemorrhagic metastases in the central nervous system. Primary endpoint: to determine the rate of intracranial clinical benefit, defined as the percentage of patients who had lack of radiological or clinical progression for at least 6 months based on RANO-BM criteria. Secondary endpoints: to assess systemic and intracranial overall response rate and progression-free survival measured by RECIST v1.1 and RANO-BM respectively, duration of response, overall survival, safety based on CTCAE v5.0. Exploratory endpoints: to assess neurocognitive function and quality of life; to determine time to neurological deterioration and time to need of salvage brain radiotherapy; to explore the efficacy according to the PD-L1 expression, cytokine levels in blood and radiomic signatures. Enrollment started on 19/11/2021 and currently 10 patients have been included in the study.

Results: Clinical trial in progress

Conclusions: Clinical trial in progress

Keywords: NSCLC, Synchronous brain metastases, Chemotherapy plus immunotherapy

EP08.01-030 Nivolumab+Ipilimumab Vs Platinum-Based CT+Nivolumab In Advanced Lung Squamous-Cell Carcinoma: The Randomized SQUINT Trial

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Introduction: Single-agent immunotherapy or the combination of chemotherapy and immunotherapy are the standard of care for metastatic non-small-cell lung cancer (NSCLC), regardless of histology. The combination of the anti PD-1 nivolumab and the anti CTLA-4 ipilimumab (NI) activates anti-tumor T-cell response through distinct but complementary mechanisms. This combination showed efficacy in NSCLC, including lung squamous cell carcinoma (LSCC). Nevertheless, no trial has specifically investigated the efficacy of NI or chemotherapy + nivolumab (CT-Nivo) in LSCC.

Methods: The SQUINT trial was a randomized, phase II trial which assesses the efficacy of two different immunotherapy strategies in patients with advanced/metastatic LSCC. All eligible patients were randomly assigned to either NI or to investigator-choice platinum-based CT and nivolumab. Nivolumab was administered at the standard dose of 360 mg every 3 weeks, while ipilimumab was administered at the dose of 1 mg/kg every 6 weeks. In both arms, immunotherapy was continued up to disease progression, toxicity, or patient refusal, for a maximum of 24 months. Platinum-based CT was given up to 6 cycles. The primary endpoint was overall survival (OS) at 12 months.

Results: From September 2017 to February 2022, a total of 91 patients were included in the study; 45 were assigned to NI and 46 to CT-Nivo. In both arms,the majority of patients were males (84.4% and 73.9%, respectively), with a performance status 0-1 (97.8% and 100%), current or former smokers (95.6% and 95.7%). Bone, liver or brain metastases were present in 26.7%, 13.3% and 6.7% of patients in the NI arm and in 26.1%, 10.9% and 6.5% of patients on CT-Nivo, respectively. Carboplatin or cisplatin in combination with gemcitabine was the most common CT regimen used in patients assigned to CT-Nivo (98%, 28% CDDP, 70% Carbo). At the time of the present analysis, with a median follow-up of 11 months, 62 patients are evaluable for response. At 1 year, OS rate was 59.1% with NI and 62.4% with CT-Nivo. Median progression-free survival was 3.8 months in the NI arm and 6.1 months in the CT-Nivo arm. Response rate was 22.2% and 30.4%, respectively. Grade 3-4 treatment-related adverse events were more frequently reported with CT-Nivo (34.8%) than with NI (15.5%), and mainly consisted in hematological toxicity.

Conclusions: The preliminary results of the SQUINT trial suggest that NI or CT-Nivo have similar activity in advanced LSCC. Additional analyses are ongoing and will be presented at the meeting.

Keywords: Immunotherapy, Nivolumab, Squamous cell carcinoma

EP08.01-031 Blood Gene Expression Changes in Metastatic Lung Cancer under second-line Immunotherapy according to Clinical Response

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Introduction: PD-(L)1 monotherapy can be used as a second-line treatment for metastatic non-small-cell lung cancer (NSCLC) with PD-L1 expression. However, many patients do not respond, and reliable biomarkers are lacking.

Methods: Blood samples of 25 patients with metastatic NSCLC were analyzed at baseline (BL) and after four cycles of PD-(L)1 monotherapy (FU) (Pembrolizumab n=11, Nivolumab n=14). All patients had received first-line platinum-based chemotherapy. The expression of 12 genes involved in tumor-specific immune responses (*FAS, RORgt, FOXP3, IFN*γ, *FASLv1, PRF1, GATA3, PD1, CD247, GZMB, MKI67, TBX21*) in whole blood RNA was quantified by RT-PCR in absolute terms using plasmids as standards. 33 newly diagnosed patients were used as controls.

Results: Expression of most genes was higher in second-line patients at baseline, compared to the newly diagnosed control group (*FAS, RORgt, IFN*γ, *FASLv1, PRF1, PD1, CD247, GZMB, TBX21*; Fold changes [FC] 2,35 - 4,52, p<0,001 and *GATA3* FC 1,49, p=0,018). After immunotherapy, expression of *MKI67* increased (FC 1,38, p=0,021) while expression of *RORgt* decreased (FC -1,37, p=0,003). Blood neutrophil, total leukocyte and lymphocyte counts did not change (ANC BL: 5,80/nl vs. FU: 6,74/nl p=0,130; Leu BL: 7,80/nl vs. FU: 8,82/nl, p=0,122; ALC BL: 1,11/nl vs. FU:1,16/nl, p=0,363). Changes in the expression of *MKI67* and *RORgt* remained significant (FC 1,38 and -1,29; p=0,035 and 0,009) even after correction for the blood lymphocyte/leukocyte ratio (Ly/Lc BL: 0,149 vs. FU: 0,159; p=0,504).

Patients with long-term response (LTR, i.e. lasting > 12 months, n=13) had significantly lower ANC (RP:+2,19/nl vs. LTR:-0,21/nl, p=0,043) and leucocytes (RP:+2,32/nl vs. LTR:-0,18/nl, p=0,046), than patients with rapid disease progression (within 9 months, RP, n=12) while ALC did not change (RP:-0,06/nl vs. LTR:+0,15/nl, p=0,068). After Ly/Lc correction (RP:-0,03 vs. LTR:+0,05, p=0,003), expression of *MKI67* showed a significant decrease in LTR, whereas in RP expression increased (FC 6,75, p<0,001). Similar, but less pronounced changes were noted for other genes (*FAS, RORgt, FOXP3, IFN*γ, *FASLv1, GATA3* and *GZMB*; FC 1,72-15,8, p<0,032).

Conclusions: Patients starting second-line PD-(L)1 monotherapy of metastatic NSCLC show increased expression of various immunologically relevant genes as evidence of systemic immune activation, compared to newly diagnosed controls. Second-line treatment causes significant changes in the blood expression of *MKI67* and *RORgt*, which correlate with long-lasting responses better than changes in blood cell counts.

These results are currently being validated in a larger prospective study.

Keywords: Immunotherapy, Non-Small Cell Lung Cancer, Gene expression changes

EP08.01-032 Sintilimab in Combination with Anlotinib in NSCLC Patients with Uncommon EGFR Mutations: A Phase II, Single-arm, Prospective Study

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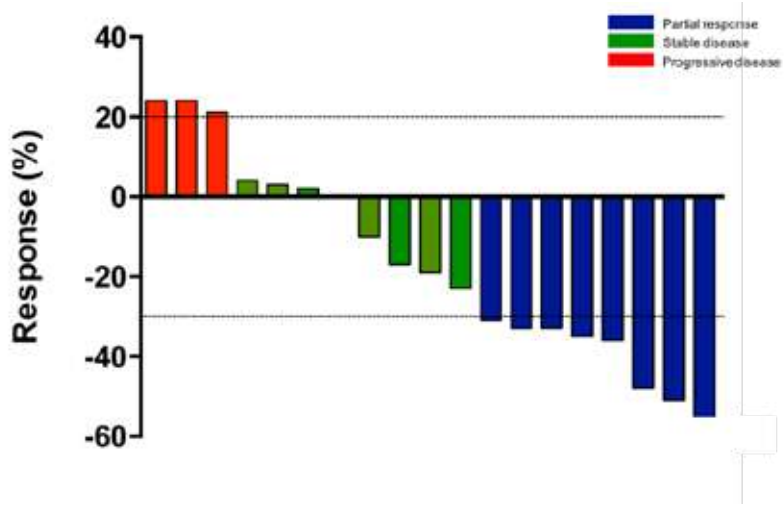
Introduction: Compared with classic epidermal growth factor receptor (*EGFR*) mutations, uncommon *EGFR* alterations showed poorer outcomes in non-small-cell lung cancer (NSCLC) patients. This study aimed to investigate the efficacy and safety of PD-1/PD-L1 blockade and anti-angiogenesis treatments in NSCLC patients with uncommon *EGFR* mutations.

Methods: Twenty-one patients of NSCLC harboring rare *EGFR* mutations after previous treatments, including a platinum-based regimen and a targeted treatment (regardless of *EGFR* Ex20ins), were enrolled. Patients received sintilimab (anti-PD-1) combined with anlotinib (multi-target anti-angiogenesis). The primary endpoint was the objective response rate (ORR).



Results: At the data cut-off time (February 20, 2022), the median follow-up was 10.0 months. Twelve cases had EGFR Ex20ins and remaining nine cases had EGFR other mutations such as L861Q, G719A, and G709T. In nineteen efficacy-evaluable patients, the ORR was 36.8% (7/19), and the disease control rates (DCR) was 84.2% (16/19). Patients harboring uncommon EGFR mutations exhibited a median progression-free survival of 6.7 months (95% CI, 2.4, 11.0), a median overall survival of 20.0 months (95% CI, 3.6, 36.4). Moreover, patients carrying EGFR Ex20ins showed similar ORR/DCR and PFS with other mutation patterns (ORR: 36.4% [4/11] vs. 37.5% [3/8], p=1.00; DCR: 90.9% [10/11] vs. 75.0% [6/8], p=0.348, PFS: 4.3 vs. 7.1 months, p=0.327). The most commonly observed grade 3 or greater treatment-related adverse events were hypertension (5.3%,1/21), immune-related pneumonitis (5.3%,1/21), fatigue (5.3%,1/21), cerebral infraction (5.3%,1/21) and hand-foot syndrome (10.5%,2/21). Therefore, the use of sintilimab and anlotinib did not result in increased safety concerns.

Conclusions: Combination of sintilimab and anlotinib demonstrated durable efficacy and good tolerability in NSCLC patients with uncommon *EGFR* mutations. And further investigate is warranted to confirm this new chemo-free strategy.

Keywords: NSCLC patients, immunotherapy, uncommon EGFR mutation

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-033 ML40471: Preliminary Analysis of Atezolizumab in Previously Treated Patients with Locally Advanced or Metastatic NSCLC

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Introduction: Atezolizumab (atezo) has been approved globally for patients (pts) with advanced non-small cell lung cancer (NSCLC), but data for Chinese pts who received 1-2 prior lines of therapy are lacking. In this study, we examined the outcomes and genetic profiles of clinically diverse Chinese pts treated with atezo, who had previously treated advanced NSCLC, including pts often excluded from pivotal trials.

Methods: ML40471 was an open label, single arm, multicenter, phase III study. This study enrolled pts with stage IIIb or IV NSCLC that progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy or after anti-PD-1 as monotherapy). Pts with asymptomatic CNS metastases were eligible. EGFR- or ALK-positive pts were excluded. All pts received atezo 1200 mg IV q3w until the loss of clinical benefit, unacceptable toxicity, withdrawal of informed consent, or death. Efficacy was evaluated by investigators per RECIST 1.1. Primary tumor biopsies and blood samples were obtained at the screening stage for biomarker studies.

Results: In total, 101 pts were enrolled from June 2019 to August 2020 and received atezo as 2L+ treatment (male, 69.3%; ECOG PS 0-1, 98%; active chronic HBV infection, 7.9%; resolved HBV infection, 45.5%; prior anti-PD-1 therapy, 7.9%). The median patient age was 62.0 years. At the cutoff date of August 5, 2021, the median follow-up time was 16.2 months (95% confidence interval [CI] = 15.2-20.3). Median progression-free survival (PFS) was 2.9 months (95% CI = 2.7-4.2). Median overall survival was 15.3 months (95% CI = 11.2-21.0). The best overall response rate was 15.5% in the evaluable population (n = 97). Exome sequencing data were available for the 31 pts with tumor biopsies. The most commonly altered genes were TP53 (74%), TTN (65%), MUC19 (42%), MUC16 (39%), and PTGER4 (39%). Both PRRC2C (odds ratio [OR] = 12.780, p = 0.014) and ZMYND8 (OR = 19.963, p = 0.016) gene mutations were significantly enriched in atezo responders versus non-responders. The odds of CD8+TILs>10% in responders was different from that in non-responders (OR = 0.043, p= 0.006). Pts with CD8+ TILs > 10% had better PFS versus CD8+ TILs ≤10% (p = 0.024). Univariate Cox regression analysis suggested that ATXN7, KCNB1, STK11, and XAB2 mutations were significantly associated with worse PFS. PD-L1 IHC, TMB, Teff ([CXCL9, IFN, PD-L1], blood samples) had no significant correlation with survival.

Conclusions: Our study identified clinically meaningful benefits of atezo, consistent with previous data. Gene landscape analysis identified multiple genes associated with survival and atezo responses. A CD8+ TILs cutoff of 10% appeared to be associated with PFS. These results may guide future therapeutic strategies.

EP08.01-034 Association of Sarcopenia with Survival in Advanced NSCLC Patients Receiving Concurrent Immunotherapy and Chemotherapy

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Introduction: Frailty, sarcopenia and malnutrition have been shown to be powerful predictors of clinical outcomes. However, these factors are not routinely measured in patients with advanced non-small cell lung cancer (NSCLC) prior to treatment initiation. The primary aim of this study was to determine if the psoas muscle index (PMI) is associated with overall survival (OS) in patients with advanced NSCLC receiving concurrent immune checkpoint inhibitor (ICI) and chemotherapy (CTX).

Methods: We retrospectively reviewed data from a cohort of patients with locally advanced or metastatic NSCLC who were treated between 2015 and 2021 at the University of Virginia Medical Center. The cross-sectional area of the psoas muscle and the intramuscular adipose tissue content (IMAC) were assessed at the inferior aspect of the third lumbar vertebra on CT or PET/CT imaging obtained prior to treatment initiation. The PMI was calculated as cross-sectional area of both psoas muscles (cm) / height^2 (m^2). The prognostic nutritional index was calculated as 10 x serum albumin (g/dl) + 0.005 x peripheral lymphocyte count/mm^3. OS was analyzed using the Kaplan-Meier method, and differences between groups were compared with the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression models.

Results: A total of 92 patients (median age: 64 years, range 36-89 years), 48 (52.2%) men and 44 (47.8%) women, were included in the study. All patients had locally advanced (n = 9, 9.8%) or metastatic (n = 83, 90.2%) NSCLC. The median follow-up was 29.6 months. The median OS was 17.8 months. Sarcopenia, defined by a PMI below the 25th percentile (6.04 cm^2/m^2 for men and 5.11 cm^2/m^2 for women), was associated with significantly lower OS (9.1 months in sarcopenic patients vs. 22.3 months in non-sarcopenic patients, P = 0.002). This was dependent on the PMI and not related to IMAC. Additionally, there was a linear association between increasing PMI and body mass index (Spearman r = 0.40, P < 0.0001). Finally, multivariate analysis revealed that sarcopenia (HR 2.12, P = 0.0209), ECOG >= 2 (HR 2.88, P = 0.0027), prognostic nutritional index (HR 3.02, P = 0.0034) and the absence of immune related adverse events (HR 2.04, P = 0.0185) were independently associated with inferior OS.

Conclusions: Sarcopenia is independently associated with poor survival in patients with advanced NSCLC undergoing concurrent ICI and CTX. The assessment of muscle mass fundamental to the diagnosis of sarcopenia should be routinely included in NSCLC trials as a predictor of OS. Additional studies are needed to explore strategies to improve muscle mass and function in patients with advanced NSCLC.

Keywords: Non-small cell lung cancer, Immunotherapy, Sarcopenia

EP08.01-035 Personalized ctDNA Detection to Monitor Outcome and Predict Immunotherapy Benefit in Locally Advanced and Metastatic NSCLC

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Introduction: Immune checkpoint inhibitors (ICIs) of programmed death-1 or its ligand provide clinical benefits to a minority of cancer patients. Increasing studies have shown that circulating tumor DNA (ctDNA) assay has emerged as a novel sensitive method for prognostication and response monitoring in patients with various malignant tumors. Especially, considering tumor heterogeneity, personalized ctDNA detection presents an apparent advantage in the aspect of specificity and convenience.

Methods: We conducted a retrospective study to assess a tumor-informed assay OriMIRACLE STM (stably detecting mutations with VAF≥0.02%) for monitoring therapeutic efficacy in 16 locally advanced and metastatic non-small-cell lung cancer (NSCLC) who were treated by first-line ICIs combined with chemotherapy. For all patients, samples of tumor tissues and matched peripheral blood were collected before treatment and whole exome sequencing (WES) was performed. Serial plasma samples were collected at baseline and beginning of cycle 2/3. Plasma samples from 3 out of 16 patients were additionally sequenced with a tumor-agnostic assay. The ctDNA burden was calculated as mean mutant tumor molecules per mL of plasma based on mean VAF and cfDNA yield.

Results: Tumor-informed assays were successfully designed for all patients and demonstrated sensitive ctDNA detection in 93.75% (N=15/16) of patients. Among 3 patients underwent both tumor-informed and agnostic assays, the ctDNA was positively detected in only 1 patient by tumor-agnostic assay with mean variant allele fraction (VAF) of 8.83%, while failed in the other 2 patients who positively detected by tumor-informed assay with mean VAF of 0.176% and 0.154%. The trend of ctDNA level from baseline to first assessment timepoint was consistent with macroscopic neoplastic change and disease progression. In patients with partial response (PR, N=10/16), the mean ctDNA burden was decreased to 17.9% of baseline level. In patients with stable disease/progressive disease (SD/PD, N=3/16), the mean ctDNA burden was decreased to 88.3% of baseline level. Furthermore, the probability of PFS in patients with ≥0.5-fold ctDNA drop from baseline was significantly longer than those without ≥0.5-fold ctDNA drop from baseline (HR=4.49e-10, p=0.01), even in 11 TMB low (TMB<10) patients (HR=5.41e-10, p= 0.02).

Conclusions: The tumor-informed assay as personalized ctDNA detection turned to be a better option than tumor-agnostic assay. Our preliminary data and findings suggested that the variation tendency of ctDNA before and after treatment of ICIs combined with chemotherapy could be a valuable biomarker for outcome prediction in NSCLC patients.

Keywords: Immune checkpoint inhibitors, circulating tumor DNA, Response monitoring

EP08.01-036 Low-dose EGFR-TKIs Directly Induce Maturation and Functional Activity of Human Dendritic Cells in an EGFR-independent manner

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Introduction: Recently, several epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have been administered concurrently with the anti-PD-1 antibody pembrolizumab in patients with EGFR mutated non-small cell lung cancer (NSCLC) in clinical trials. EGFR-TKIs with immune checkpoint inhibitors (ICIs) does have preclinical rationale in tumor-bearing syngeneic mouse models. However, the direct effect of EGFR-TKIs on APC (antigen presenting cells) such as DCs (dendritic cells) remains elusive.

Methods: Immature human monocyte-derived DCs (moDCs) were generated *in vitro* from peripheral blood CD14+ monocytes by the addition of GM-CSF and IL-4 to the cell culture. We evaluated the effects of EGFR-TKIs including afatinib and osimertib on human moDCs by investigating phenotypic analyses of maturation-associated markers and functional analyses for immune-stimulatory capacities to antigen-uptake and allogeneic T cells simulation.

Results: Exposure of immature human moDCs to low-dose afatinib (10 nM) and osimertinib (10 nM) substantially increased their surface expression levels of maturation-associated markers, although they did not express surface EGFR. Interestingly, human moDCs treated with high-dose EGFR-TKIs (100 nM) mitigated the DCs aggregate formation with lower expression levels of CD11c compared with immature human moDCs, suggesting their negative effects on DCs biology might be a consequence of unknown off-target effects in human moDCs. These activated moDCs treated with low-dose EGFR-TKIs produced greater levels of pro-inflammatory cytokines and chemokines in the supernatants than those from immature human moDCs. Furthermore, functional assays demonstrated that moDCs treated with low-dose EGFR-TKIs showed decreased capacity of antigen (dextran) uptake and increased proliferation activity of CFSE-labelled T-cells evident in allogeneic mixed lymphocyte reaction.

Conclusions: In current study, we showed that low-dose EGFR-TKIs directly induced maturation and functional activity of human moDCs in an EGFR-independent manner. Our results indicated that low-dose EGFR-TKIs may have immunostimulatory potentials to augment or restore antitumor immune responses for NSCLC by targeting both DCs and cancer cells and provide a rationale for combined use of EGFR-TKIs and ICIs-based immunotherapy for NSCLC inherent or acquired resistance to ICIs.

Keywords: Dendritic cells, EGFR-TKIs, NSCLC

EP08.01-037 Association of Baseline NLR and BMI with Clinical Outcomes in NSCLC Patients Treated with Immunotherapy Alone Versus Chemo-Immunotherapy

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Introduction: Immunotherapy (IO) as monotherapy and combinations with chemotherapy (IO/CT) have been associated with greater survival than chemotherapy alone. However, there is some evidence of higher rates early progression and deaths in subsets of stage IV non-small cell lung cancer (NSCLC) patients receiving IO versus IO/CT. Several underlying mechanisms including high tumor burden and poor performance status may be associated with early progression on IO alone. There is need for accessible clinical markers that can identify non-responders before IO monotherapy initiation. The objective of this retrospective, non-randomized study is to evaluate interactions of high pre-treatment neutrophil-lymphocyte ratio (NLR) and low body mass index (BMI), at baseline, with survival outcomes in stage IV NSCLC patients who were treated with frontline IO alone versus IO/CT as frontline therapy.

Methods: 88 patients with stage IV NSCLC were included, of which 47% received IO only and 53% received IO/CT combination as frontline therapy. 44% were female, 69% white, 93% current or former smokers and 81% had adenocarcinoma. OS and PFS, including early PFS at 3 and 6 months were estimated using Kaplan-Meier method. Associations of outcomes with baseline BMI (<20 vs. 20-30 and >30) and baseline NLR (gated at 5; >5 vs. <5) were assessed using log-rank test and Cox proportional hazards regression.

Results: Median PFS (95% CI) was better in the group treated with IO/CT vs. IO monotherapy, 8.94 months (5.52-14.24) and 3.78 months (2.5-7.96), p= 0.024, respectively; Early PFS was also better in the IO/CT group at 3 months (p=0.003) and 6 months (p=0.026). There was no significant difference in OS (p=0.233). Baseline NLR and BMI characteristics were comparable with no significant difference between the two therapy groups. Patients from the IO only group with baseline NLR >5 had significantly worse OS (HR: 3.048, p=0.002), PFS (HR: 2.816, p=0.004) and early PFS at 3 months (HR: 3.057, p=0.018) than patients with ≤5 baseline NLR. However, no significant differences in survival outcomes were observed between the two NLR categories in patients treated with IO/CT. A statistical interaction analysis including all 88 patients, associated differentially poorer outcomes with baseline NLR >5 in patients receiving IO only (compared to IO/CT): OS (interaction HR: 3.73, p=0.01), PFS (interaction HR: 3.04, p=0.02) and early PFS at 3 months (interaction HR: 7.58, p=0.03).Similarly, baseline BMI of <20 was differentially associated with worse prognosis in the IO only group- OS (interaction HR: 6.86, p=0.02) and PFS (interaction HR: 6.61, p=0.03) - compared to the IO/CT group. Tumor PD-L1 expression data was only obtained for 78% of the cohort, hence excluded from the analysis.

Conclusions: The benefit of combination IO/CT is in line with previous studies and may provide improved survival benefit for patients with a baseline NLR value of >5 or low BMI. Though institutional practice typically limits IO monotherapy to those with high PDL1 expression, additional evaluation of NLR as biomarker in treated patients with known levels of tumor PD-L1 expression is warranted.

Keywords: Neutrophil Lymphocyte Ratio, Frontline Immunotherapy, Clinical Markers

EP08.01-038 Clinical Predictors of Treatment Efficacy in Patients with Lung Adenocarcinoma Receiving Immune Checkpoint Inhibitors

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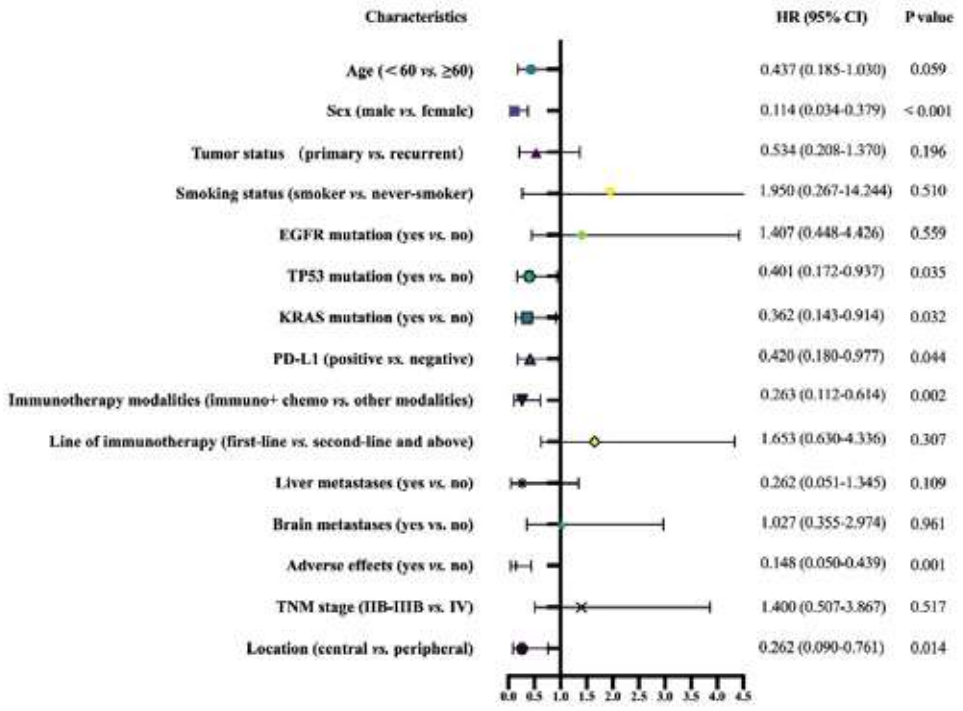
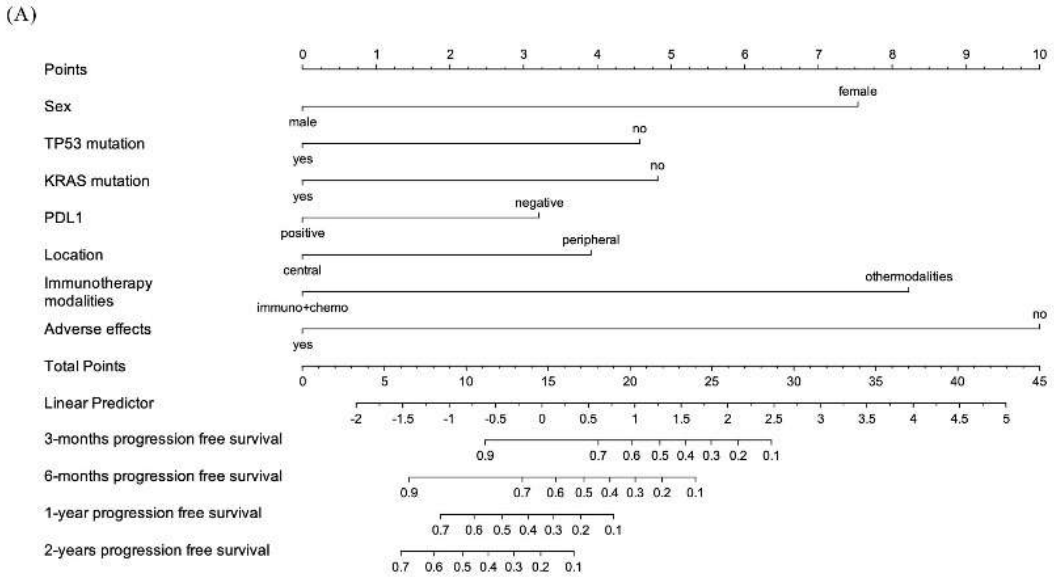
Introduction: In patients with lung adenocarcinoma, how to effectively predict the population benefiting from immune checkpoint inhibitors (ICIs) therapy remains a clinical problem that needs to be addressed. This study aims to investigate the relationship between clinical characteristics factors and immunotherapy efficacy in lung adenocarcinoma patients and to develop a predictive model for immunotherapy efficacy.

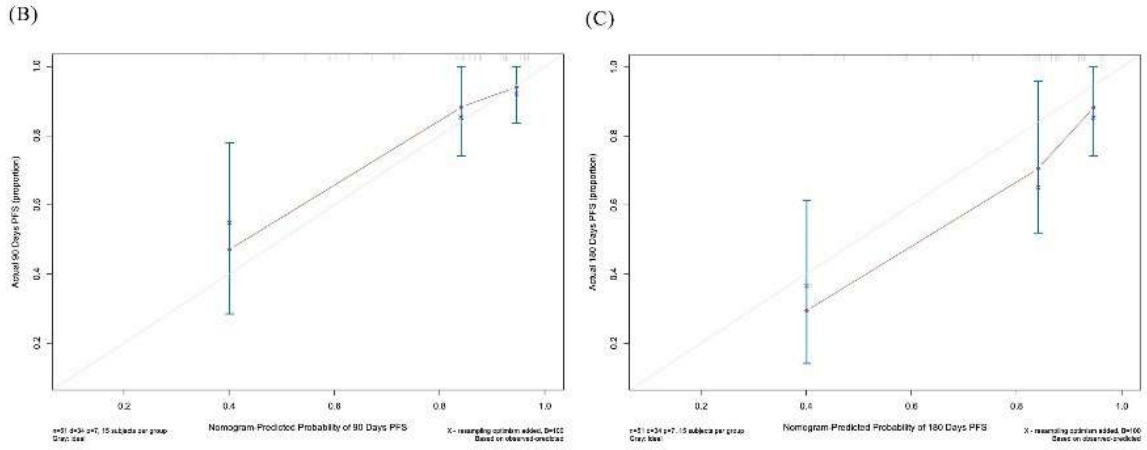
Methods: We collected and retrospectively analyzed the relationship between immunotherapy efficacy and clinicopathologic features in lung adenocarcinoma patients treated with immune checkpoint inhibitors. Progression-free survival (PFS) and overall survival (OS) were analyzed. In addition, a clinical prediction model was established to predict PFS in patients with lung adenocarcinoma after ICIs treatment.

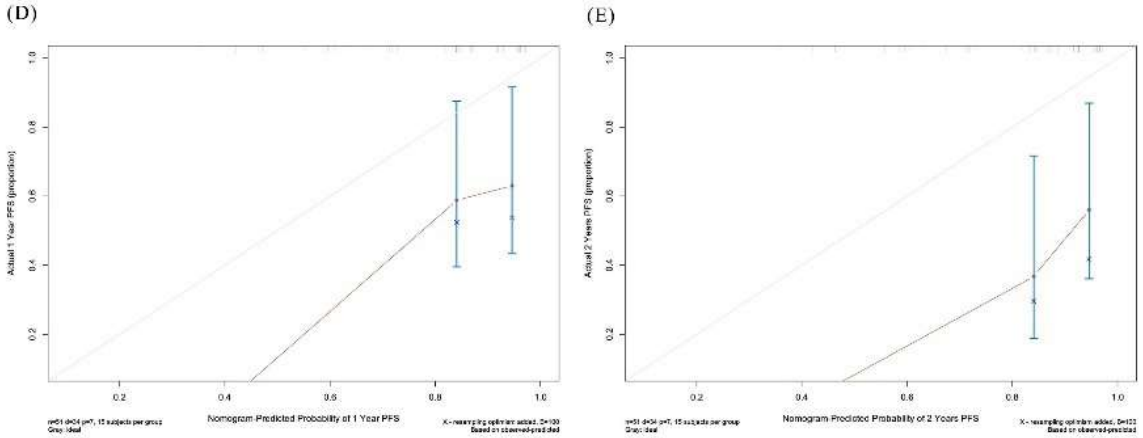
Results: A total of 201 lung adenocarcinoma patients treated with ICIs were studied assessed, including 101 patients received ICIs as first-line treatment and 100 patients received ICIs as second-line and above treatment. Univariate analysis showed that male, smoking, EGFR wild type, KRAS mutation, positive programmed death ligand 1 (PD-L1) expression, early TNM stage, no liver metastasis, ICIs combined with chemotherapy and having immune-related adverse effects were significantly associated with better PFS in patients with lung adenocarcinoma receiving immunotherapy. Multivariate analysis showed that sex, TP53 mutation, KRAS mutation, PD-L1 expression, immunotherapy modalities, immune-related adverse effects and tumor location were independent prognostic factors affecting PFS in lung adenocarcinoma patients receiving immunotherapy. A clinical prediction model was established to predict the PFS of lung adenocarcinoma patients treated with ICIs. The model showed good predictive ability through the validation of calibration curves.

Conclusions: Lung adenocarcinoma patients who were male, had TP53 mutations, KRAS mutations, positive PD-L1 expression, immune combination chemotherapy, had immune-related adverse reactions and central tumor location were more likely to have a survival benefit after ICIs treatment. The clinical prediction model developed in this study can effectively predict PFS after immunotherapy in lung adenocarcinoma patients.









Keywords: real-world study, immune checkpoint inhibitors, clinical prediction model

EP08.01-039 Impact of Pulmonary Function Indexes on Immunotherapy Efficacy in Lung Adenocarcinoma Patients and the Potential Prognostic Factors

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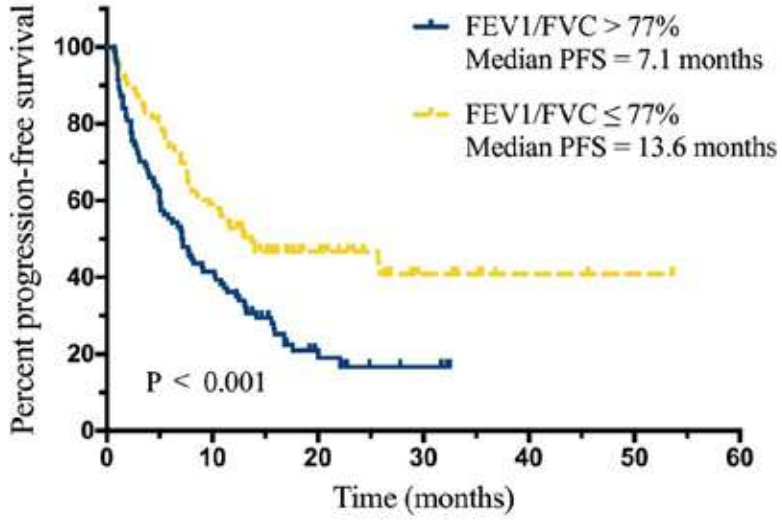
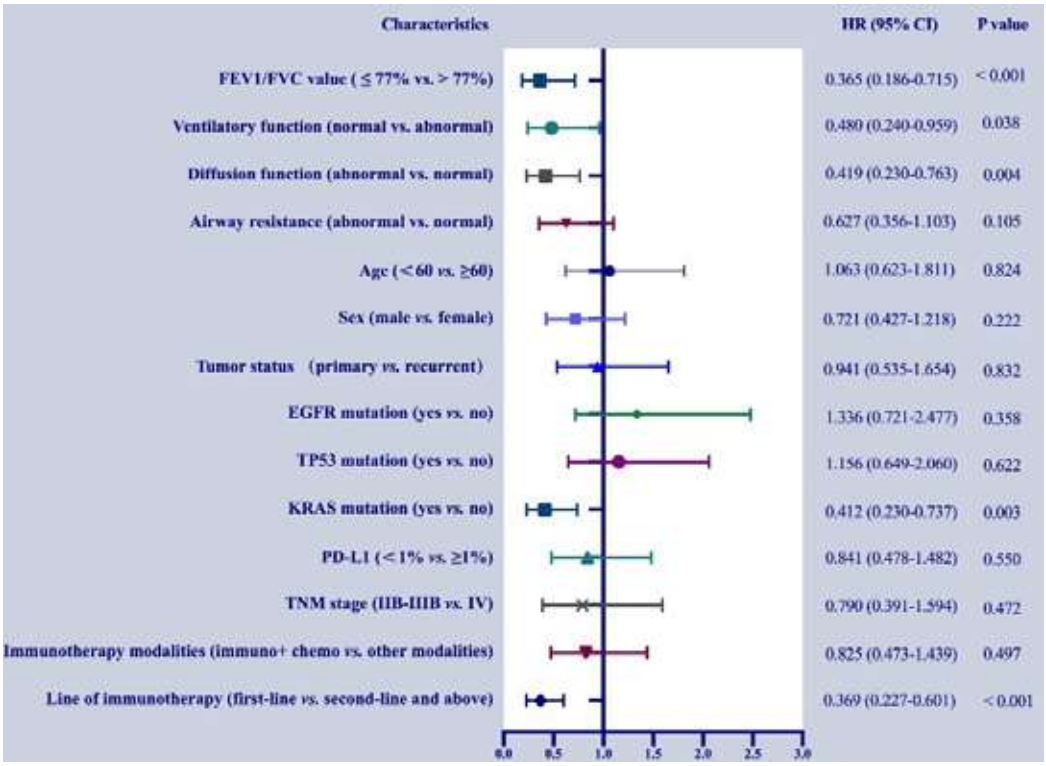
Introduction: There is currently a lack of good predictors for immunotherapy efficacy in patients with lung adenocarcinoma. The purpose of this study was to explore the relationship between pulmonary function indexes and the efficacy of immunotherapy in patients with lung adenocarcinoma.

Methods: We conducted a retrospective study to evaluate the predictive role of lung function indicators in patients with lung adenocarcinoma receiving immunotherapy. The patients were divided into two groups according to the median value of FEV1/FVC index, including 94 patients with lung adenocarcinoma with FEV1/FVC>77% and 94 patients with lung adenocarcinoma with FEV1/FVC≤77%. The primary endpoint was progression-free survival (PFS); the secondary endpoints was overall survival (OS).

Results: A total of 188 lung adenocarcinoma patients treated with immunotherapy were assessed. Median PFS was significantly longer in the FEV1/FVC≤77% group (13.6 months; 95% confidence interval [CI], 1.019-26.181) than in the FEV1/FVC>77% group (7.1 months; 95% CI, 5.010-9.190; hazard ratio=0.523, 95% CI, 0.365-0.749, P<0.001). The median OS in the FEV1/FVC≤77% group was not reached versus 25.4 months (95% CI, 18.768, 32.032) in the FEV1/FVC>77% group (hazard ratio =0.771; 95% CI, 0.487-1.220; P=0.265). Multivariate analysis showed that FEV1/FVC value, KRAS mutation status, line of immunotherapy, ventilatory function and diffusion function were independent prognostic factors of PFS in immunotherapy of lung adenocarcinoma.

Conclusions: Pulmonary function indexes were associated with survival in lung adenocarcinoma patients treated with immunotherapy. FEV1/FVC value were potential prognostic factors for clinical outcome.





Keywords: immunotherapy, pulmonary function indexes, Real-world study

EP08.01-040 Peripheral Blood Cells as Predictors for Efficacy of Immunotherapy in Patients with Advanced Non-small Cell Lung Cancer

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Introduction: In lung cancer immunotherapy, biomarkers to guide clinical decisions are limited to PD-L1. We explore whether one or several peripheral blood mononuclear cells (PBMC) subpopulations from treatment-naïve patients with advanced non-small-cell lung cancer are associated with the efficacy of anti-PD-1 immunotherapy.

Methods: We determined 107 PBMCs subpopulations in a prospective cohort of NSCLC patients before starting single-agent immunotherapy with nivolumab or pembrolizumab (study group). As a control group, we studied patients with advanced malignancies before initiating non-immunotherapy treatment. A customized immunophenotype panel was designed that included subsets of T and B-lymphocytes, NK and myeloid cells, analyzed by flow cytometry. The frequency of immune subpopulations was correlated with treatment outcome in terms of overal survival (OS) as primary objective. Univariate and multivariate survival analyses were performed.

Results: The study group included 39 patients and the control group 40. Patients were categorized in either high- or low-expression for each biomarker, defined as those above the 55th or below the 45th percentile of the overall marker expression within the cohort. In the study group, three subpopulations were associated with significant differences in outcome: high pretreatment levels of circulating CD4+CCR9+, CD4+CCR10+ or CD8+CXCR4+ T cells correlated with poorer OS (15.7 vs 35.9 months, HR 0.16, p = 0.003; 22.0 vs NR months, HR 0.10, p=0.003, and 22.0 vs NR months, HR 0.29, p = 0.02). These differences were specific to immunotherapy-treated patients and were not observed in the control cohort.

Conclusions: High baseline levels of circulating T cell subpopulations related to tissue lymphocyte recruitment are associated with poorer outcomes of immunotherapy-treated advanced lung cancer patients.

Keywords: non small cell lung cancer, immunotherapy, peripheral blood mononuclear cells

EP08.01-041 Impact of Gender on Response to Immune Checkpoint Inhibitors in Patients with Non-small Cell Lung Cancer

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Introduction: Several previous clinical trials have reported that male patients with non-small cell lung cancer (NSCLC) respond better to immunotherapy than females. However, the impact of gender on prognosis remains uncertain because no real-world study considering various factors that affect patients' response to immunotherapy with gender exists. Therefore, we evaluated the effect of gender on immunotherapy response adjusted by multiple factors in actual clinical practice.

Methods: This study was a single-center real-world retrospective cohort study, comprising 387 patients with NSCLC who received pembrolizumab, nivolumab, or atezolizumab alone as second- or later-line treatments. Subsequently, we compared their progression free survival (PFS) and overall survival (OS) scores based on gender, then analyzed prognostic factors accounting for immunotherapy response.

Results: The mean age of the understudied patients was 64.0 years old, comprising 65.3% males, with non-squamous cell carcinoma accounting for 70.3% of these patients. Male patients also showed higher smoking habits, programmed death-ligand 1 (PD-L1) expression, and expression of wild type epidermal growth factor receptor (EGFR), known as favorable prognostic factors. However, no difference in PFS and OS according to gender was observed (PFS 2.2 [male] *vs.* 2.1 [female] months, $p = 0.144$; OS 7.6 [male] *vs.* 8.8 [female] months, $p = 0.383$). Furthermore, an Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, high expression of PD-L1, and EGFR mutations were proposed as prognostic factors in multivariate analysis for PFS. Besides, ECOG performance status ≥ 2 and squamous cell carcinoma were poor prognostic factors accounting for OS. Yet, gender was not an independent prognostic factor in PFS and OS.

Conclusions: Gender was not an independent prognostic factor for immunotherapy in real-world data although various factors affected immunotherapy response, such as wild type EGFR and high expression of PD-L1, which frequently occur in males.

Keywords: immunotherapy, gender, lung cancer

EP08.01-042 NEPTUNE China Cohort: First-Line Durvalumab + Tremelimumab versus Chemotherapy in Chinese Patients with Metastatic NSCLC

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Introduction: The open-label, international, Phase 3 NEPTUNE study (NCT02542293) evaluated durvalumab + tremelimumab versus chemotherapy as first-line treatment for metastatic NSCLC. We present results from a prespecified exploratory analysis to assess efficacy and safety in an extended cohort of patients enrolled in China.

Methods: Patients with *EGFR/ALK* wild-type metastatic NSCLC were randomised (1:1) to first-line durvalumab (20 mg/kg q4w until progression) + tremelimumab (1 mg/kg q4w for up to 4 doses) or chemotherapy (q3w for up to 6 cycles [maintenance pemetrexed permitted]). Randomisation was stratified by PD-L1 expression on tumour cells (TC; ≥25% versus <25%), histology, and smoking history. In contrast to the NEPTUNE global cohort analysis, which had a primary endpoint of OS in patients with blood tumour mutational burden (bTMB) ≥20 mut/Mb, patients from China did not undergo bTMB testing. The primary endpoint for the China cohort was overall survival (OS) in patients with PD-L1 TC <1%. Secondary endpoints included OS and progression-free survival (PFS) (RECIST v1.1) in the intention-to-treat (ITT) population and PD-L1 TC ≥25% and ≥50% subsets, PFS in the PD-L1 TC <1% subset, and safety. No alpha was allocated to analyses in the China cohort.

Results: 160 patients were randomised in China (ITT population), of whom 55 (34%) had PD-L1 TC <1%. Baseline characteristics were generally balanced between arms. As of 21 September 2020, median follow up for OS in censored patients was 32.3 months in the ITT population and 30.2 months in patients with PD-L1 TC <1%. OS favoured durvalumab + tremelimumab versus chemotherapy in the ITT population and in patients with PD-L1 <1%, ≥25%, and ≥50% (Table). Although PFS was not improved with durvalumab + tremelimumab versus chemotherapy in the ITT population or in patients with PD-L1 <1%, 12-month PFS rates favoured durvalumab + tremelimumab. In the overall safety population, the incidence of Grade 3/4 treatment-related adverse events (TRAEs) was 31.2% with durvalumab + tremelimumab and 52.6% with chemotherapy, and 3.9% versus 10.3% of patients discontinued treatment due to TRAEs.

Conclusions: In this exploratory analysis, first-line durvalumab + tremelimumab showed a trend towards improved OS versus chemotherapy in Chinese patients with metastatic NSCLC, both in the PD-L1 TC <1% subset and in the ITT population. Both 24-month OS rates and 12-month PFS rates favoured durvalumab + tremelimumab, indicating benefit in the tails of the survival curves with this regimen. Durvalumab + tremelimumab was well tolerated in Chinese patients, with no new safety signals.

	Durvalumab + tremelimumab	Chemotherapy
PD-L1 TC <1%, n	26	29
Median OS (95% CI), months	15.0 (10.5–27.4)	11.7 (8.6–20.5)
OS HR (95% CI)	0.60 (0.32–1.11)	–
24-month OS rate (95% CI), %	36.0 (18.2–54.2)	17.9 (6.5–33.7)
Median PFS (95% CI), months	5.1 (2.8–7.2)	6.0 (4.0–7.5)
PFS HR (95% CI)	1.13 (0.59–2.14)	–
12-month PFS rate (95% CI), %	15.6 (4.0–34.4)	11.3 (2.3–28.5)
ITT, n	78	82
Median OS (95% CI), months	20.0 (15.0–28.7)	14.1 (9.5–19.4)
OS HR (95% CI)	0.70 (0.48–1.02)	–
24-month OS rate (95% CI), %	44.2 (32.9–54.8)	30.4 (20.7–40.6)
Median PFS (95% CI), months	4.2 (2.8–7.2)	6.0 (5.5–7.5)
PFS HR (95% CI)	0.95 (0.66–1.36)	–
12-month PFS rate (95% CI), %	23.9 (14.8–34.2)	16.6 (8.5–27.0)
PD-L1 TC ≥25%, n	31	32
Median OS (95% CI), months	36.6 (15.5–NE)	15.8 (9.0–26.9)
OS HR (95% CI)	0.56 (0.29–1.07)	–
Median PFS (95% CI), months	6.8 (4.1–8.4)	5.7 (4.2–8.5)
PFS HR (95% CI)	0.72 (0.39–1.32)	–
PD-L1 TC ≥50%, n	25	28
Median OS (95% CI), months	36.6 (16.9–NE)	15.8 (9.0–26.9)
OS HR (95% CI)	0.47 (0.22–0.96)	–
Median PFS (95% CI), months	6.8 (4.2–20.2)	5.7 (4.2–8.5)
PFS HR (95% CI)	0.65 (0.34–1.25)	–
NE, not estimable		

Keywords: Durvalumab, Tremelimumab, NEPTUNE

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-043 Clinicopathologic and Genomic Factors Impacting Efficacy of First-Line Chemoimmunotherapy in Advanced Non-small Cell Lung Cancer (NSCLC)

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Introduction: While recent studies have examined the impact of clinicopathologic features on clinical outcomes to PD-(L)1 monotherapy in NSCLC, factors that influence chemoimmunotherapy efficacy are in need of further investigation.

Methods: In this multicenter retrospective analysis, clinicopathologic and genomic data were collected from patients with metastatic NSCLCs lacking genomic alterations in *EGFR* and *ALK* who received first-line pembrolizumab in combination with platinum-doublet chemotherapy. Clinical outcomes were compared in patients based on their ECOG performance status (PS), age, smoking status, histology, PD-L1 tumor proportion score (TPS), baseline derived neutrophil-to-lymphocyte ratio (dNLR), and genotype.

Results: A total of 1200 patients treated with first-line pembrolizumab in combination with platinum-doublet chemotherapy were identified. There was no difference in clinical outcomes to chemoimmunotherapy according to age (<65y vs ≥65y) or smoking status (never vs current/former). A worsening ECOG PS from 0 (N=374) to 1 (N=633) to ≥2 (N=161) was associated, respectively, with a progressively lower objective response rate (ORR) (44.9% vs 40.4% vs 24.1%, P<0.001), shorter median progression-free survival (mPFS 7.5 vs 6.0 vs 3.2 months, P<0.001), and shorter median overall survival (mOS 20.0 vs 13.7 vs 6.7 months, P<0.001). Although there was a higher ORR in squamous (N=143) versus nonsquamous (N=1053) NSCLCs (48.5% vs 37.9%, P=0.02), this did not translate to a significant difference in PFS or OS. With increasing PD-L1 TPS levels from <1%, to 1-49%, to 50-89%, to ≥90% there was, respectively, a progressive improvement in ORR (33.6% vs 38.8% vs 50.6% vs 60.3%, P<0.001), mPFS (5.2 vs 6.1 vs 6.9 vs 13.0 months, P<0.001), and mOS (13.1 vs 14.6 vs 34.7 vs 23.1 months, P=0.01). Clinical outcomes improved with decreasing dNLR values when dNLR was divided into tertiles; moving from upper, to middle, to lower tertile, respectively, we observed improvements in ORR (28.9% vs 39.4% vs 50.8%, P<0.001), mPFS (3.4 vs 6.5 vs 8.5 months, P<0.001), and mOS (7.8 vs 15.0 vs 23.9 months, P<0.001). Of 682 nonsquamous NSCLCs with comprehensive genomic data, *KRAS* mutations were detected in 271 cases, and deleterious *STK11* and *KEAP1* mutations were found in 182 and 184 cases, respectively. There was no difference in ORR, mPFS, or mOS in *KRAS* mutant vs *KRAS* wild-type (wt). *STK11* and *KEAP1* mutations were associated with significantly worse mPFS (*STK11* HR:1.93, P<0.001; *KEAP1* HR:1.79, P<0.001) and mOS (*STK11* HR:1.72, P<0.001; *KEAP1* HR:1.75, P<0.001) to chemoimmunotherapy among *KRAS* mutant cases. Among KRAS wt tumors, *KEAP1* mutations were associated with shorter mPFS (HR: 1.37, P=0.01) and mOS (HR: 1.61, P<0.001) to chemoimmunotherapy, but *SKT11* mutations showed no significant impact on mPFS (HR: 1.17, P=0.23) or mOS (HR: 1.16, P=0.32). *KEAP1* mutation held a significant association with shorter mPFS (HR: 1.70, P<0.001) and mOS (HR: 2.04, P<0.001) among *KRAS* wt cases in multivariable model.

Conclusions: Patients with better performance status, a low dNLR level, and increasing levels of PD-L1 expression are more likely to benefit from first-line chemoimmunotherapy. Although deleterious *STK11* and *KEAP1* mutations impact chemoimmunotherapy efficacy similarly among *KRAS* mutant NSCLCs, only *KEAP1* mutations are associated with impaired outcomes among *KRAS* wt.

Keywords: chemoimmunotherapy, first-line, efficacy

EP08.01-044 A Phase 2 Multi-Cohort Study of Tiragolumab, Atezolizumab and Bevacizumab in Advanced Non-Squamous Non-Small Cell Lung Cancer

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Introduction: Checkpoint inhibitor immunotherapy (CPI) offers durable, immune-mediated, anti-tumor responses for a subset of patients (pts) with advanced non-small cell lung cancer (NSCLC), but not all derive meaningful benefit. Two clinical unmet needs where CPI has fallen short include *EGFR*-mutated NSCLC, where CPI is minimally effective, and NSCLC with primary or acquired resistance to currently available CPI. Novel combination strategies have shown promise. Two agents that have demonstrated synergy with the anti-PD-L1 CPI atezolizumab in NSCLC are bevacizumab, a vascular endothelial growth factor (VEGF)-blocking antibody, and tiragolumab, a T-cell immunoglobulin and ITIM domain (TIGIT) immune checkpoint-blocking antibody. This multi-cohort single-arm phase II trial seeks to evaluate the efficacy of tiragolumab with atezolizumab plus bevacizumab in two CPI-resistant cohorts: (1) *EGFR*-wild type, CPI-refractory, PD-L1+ NSCLC and (2) *EGFR*-mutated, targeted-therapy refractory, CPI-naïve NSCLC. Critically, the study incorporates novel genomic and immunologic analyses of pre- and on-treatment tumor/blood specimens to deliver mechanistic insight into the biology of CPI-resistance in NSCLC.

Methods: This open-label, phase II study has two cohorts. Cohort A includes pts with advanced PD-L1+ (TPS ≥ 1%), *EGFR/ALK/ROS1* wild-type NSCLC with progression on prior anti-PD(L)1-based CPI therapy. Cohort B includes pts with targeted therapy-refractory, *EGFR*-mutated NSCLC who are CPI-naïve. Pts must have measurable disease and those with symptomatic and/or untreated brain metastases are excluded. Pts in both arms receive tiragolumab 600mg IV with atezolizumab 1200mg IV and bevacizumab 15mg/kg IV every 3 weeks until progressive disease or unacceptable toxicity. The primary efficacy endpoint will be assessed separately in each cohort by investigator-assessed objective response rate (ORR) according to RECIST v1.1. Both cohorts utilize a Simon 2-stage design in which a null ORR of 4% is tested against a one-sided alternative of 20%. A sample size of 21 pts/cohort provides 80% power with a one-sided type 1 error rate of 5% to determine a true ORR of 20%. Secondary efficacy endpoints include: duration of response, progression-free survival (PFS), 6-month PFS, overall survival. Blood and tumor specimens will be acquired pre- and on-treatment. Correlative analyses to illuminate the biology of CPI resistance will include multiplex imaging mass cytometry of tumor tissue and whole blood cytometry by time-of-flight (CyTOF). In addition, whole exome sequencing, T-cell receptor sequencing, and MANAFEST neoantigen prediction will be used to identify neoantigen-specific T-cells and track these temporally (during/post treatment) and spatially (across biologic compartments). Both cohorts are accruing simultaneously with enrollment ongoing. The study is active, with 2 patients enrolled at the time of submission. Clinical trial information: NCT04958811.

Keywords: advanced NSCLC, immunotherapy, clinical trial

EP08.01-045 The Impact of Current Smoking Status at Initiation of Immune Checkpoint Inhibitor Therapy on Tumor Mutation Burden and Survival

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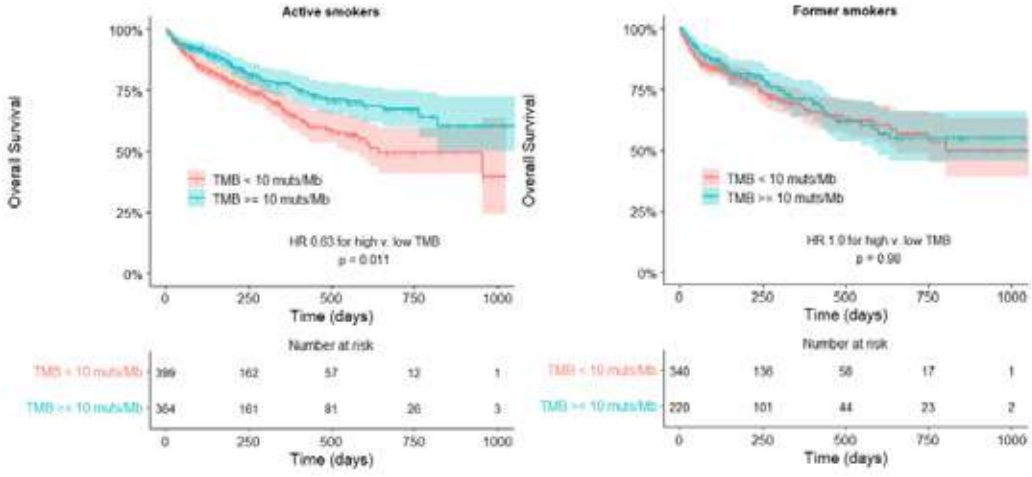
Introduction: Smoking associates with better immune checkpoint inhibitor (ICI) therapy response in patients with advanced non-small cell lung cancer (NSCLC). This may be because smoking correlates with increased tumor mutation burden (TMB), a known ICI response predictor. However, it is unknown whether benefits from smoking are static (i.e., ICI response benefit continues after smoking cessation) or ongoing (i.e., smoking cessation mitigates ICI response benefit). We assess the relationship between TMB and smoking status at initiation of ICI therapy and evaluate how treatment response may vary by TMB and ongoing smoking versus cessation.

Methods: We used retrospective, multi-center cohort data from the Veterans Affairs (VA) Precision Oncology database, a nationwide next-generation sequencing resource, and the VA Corporate Data Warehouse. Patients with advanced NSCLC who initiated first-line ICI at the VA between January 1, 2019 and December 30, 2021 were followed until study end on March 2, 2022. Patients were required to have TMB measured within +/- 3 months of ICI initiation and be an active or former smoker at ICI initiation. Association between smoking status and TMB was assessed with odds ratios (OR) using logistic regression adjusted for age, race/ethnicity, and histology. Overall survival after ICI initiation was estimated using Kaplan-Meier method. The associations between overall survival, smoking status, and TMB were estimated with hazard ratios (HR) using Cox regression adjusting for PD-L1, histology, performance status, and use of concurrent platinum chemotherapy.

Results: Active smokers (n=763, 58% of overall cohort) were likelier to have high TMB (>=10 muts/Mb) than former smokers (n=560, 42%) (OR 1.35, 95%CI 1.07-1.70, p=0.012). Over median follow-up of 9.2 months (range:0-36 months), there was no significant difference in survival on ICI therapy between active and former smokers (1-year survival: 69% vs. 72%, respectively, HR 0.91, 95%CI 0.72-1.20, p=0.46). As expected, high TMB trended with improved survival (1-year survival: 75% v. 67% for high vs. low TMB, HR 0.79, 95%CI 0.62-1.0, p=0.063). While high TMB significantly predicted survival among active smokers, (HR 0.63, 95%CI 0.45-0.90, p=0.011), there was no association among former smokers (HR 1.0, 95%CI 0.70-1.40, p=0.98) (Figure). Survival was highest among active smokers with high TMB (1-year survival 78%).

Conclusions: Our study of a large VA dataset suggests that the predictive impact of TMB on ICI response may vary by the smoking status at ICI initiation, with the association between high TMB and better survival after ICI more pronounced in active smokers compared to former smokers.



Keywords: Immunotherapy, Real-world data, Smoking

EP08.01-046 Examination of Long-Term Administration of Pembrolizumab in Patients with Non-small Cell Lung Cancer at Our Institution

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Introduction: There are many reports suggesting the effectiveness of combination therapy of cytotoxic agents and immune checkpoint inhibitors in patients with non-small cell lung cancer. There have been some cases of long-term administration of pembrolizumab because good disease control of the patient can be maintained. We assessed the prognosis of patients who continued to be administer pembrolizumab at our institution for more than one year.

Methods: From December 2015 to December 2021, we retrospectively reviewed the records of non-small cell lung cancer patients in which a pembrolizumab-based regimen was continuously administered for one year or more at our institution.

Results: Regimen including pembrolizumab were used in 33 cases during this period. Of these, long-term administration of one year or longer was observed in nine cases. There were eight males and one female. All men had a history of smoking. The median age at the start of treatment is 68 years (range 62-79 years). Histological diagnoses were four Squamous cell carcinoma, four adenocarcinoma and one non-small cell lung cancer. Two patients had stage IIIA, one patient had stage IIIB, one patient had stage IIIC and five patients had stage IVB. Four patients had Tumor proportion score (TPS) ≧ 50%, four patients had TPS 1% to 49% and one patient had TPS <1%. EGFR mutation and ALK/ROS1 fusion gene mutation were negative in all cases. Seven patients received platinum plus pemetrexed or paclitaxel plus pembrolizumab and two patients received pembrolizumab. Four of nine patients had surgery and two of them had salvage surgery. The median administration period was 17 months (range 12-49 months). Immune- related adverse events (irAE) was observed in two patients (hypothyroidism in two cases, adrenocortical insufficiency in one case). Three patients have already died and six patients are still on survival. The 5-year overall survival rate was higher in patients with long term administration (57.1%) than in patients with less than 1 year (14.6%) (p=0.003).

Conclusions: We examined the results of long-term administration including pembrolizumab at our institution. One patient of irAE was able to continue administration even now, and other side effects of grade 3 or higher were observed in only two patients, which seemed to be well tolerated. Good disease control with a regimen including immune checkpoint inhibitors may allow complete resection of cases that were not previously targeted for surgery.

Keywords: pembrolizumab, non-small cell lung cancer, salvage surgery

EP08.01-047 Chemo-immunotherapy is Associated with Better Survival Than Chemotherapy Alone In Stage IV Non-small Cell Lung Cancer

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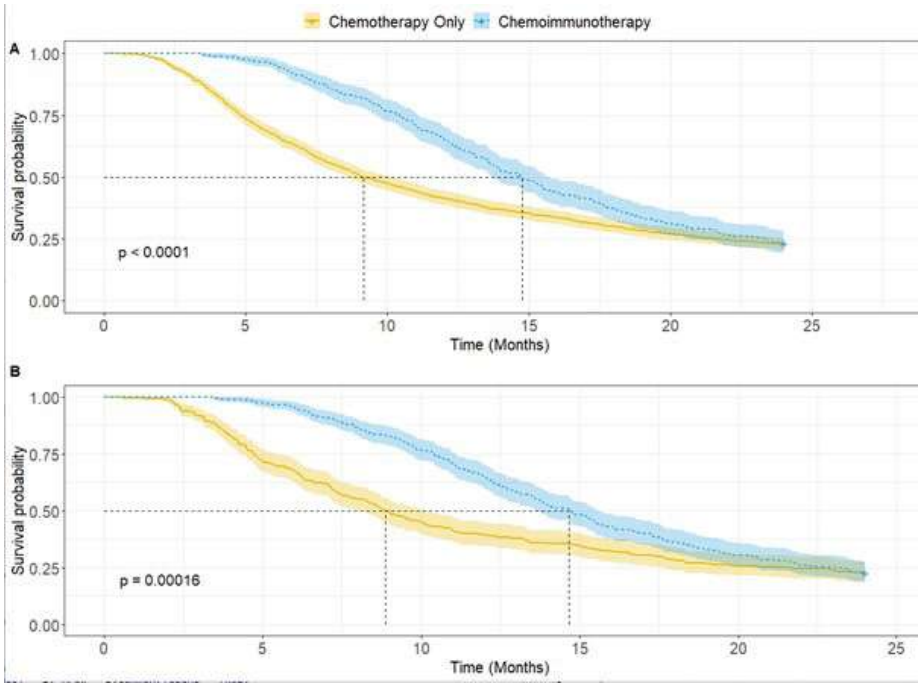
Introduction: Response rates to immunotherapy in metastatic non-small cell lung cancer (NSCLC) are low and survival varies significantly. It has been suggested that factors like age, sex, race, and histology may modulate immunotherapy response. Existing analyses are limited to clinical trials, with limited generalizability, and meta-analyses where data cannot be adjusted for potential confounders. Here, we present a patient-level analysis to explore how personal and clinical characteristics moderate the effectiveness of chemo-immunotherapy in metastatic NSCLC.

Methods: Stage IV NSCLC patients diagnosed in 2015 were drawn from Surveillance Epidemiology, and End Results (SEER)-Medicare linked data. Overall survival was studied in those treated with chemo-immunotherapy vs. chemotherapy alone. Multivariable Cox-proportional hazards regression models and propensity-score matching were performed to evaluate the effectiveness of chemo-immunotherapy versus chemotherapy.

Results: 349 patients were treated with chemo-immunotherapy and 1122 (76%) received chemotherapy alone. Survival was significantly better among those treated with chemo-immunotherapy compared to those who received chemotherapy alone (HR_{adj}: 0.72, 95% CI: 0.63-0.83), after adjustment for age, sex, race, marital status, Charlson comorbidity status, and histology. Males treated with chemo-immunotherapy reported significantly better OS than those treated with chemotherapy alone (HR_{adj}: 0.62, 95% CI: 0.51-0.75), but females did not (HR_{adj}: 0.81, 95% CI: 0.65-1.01) (p[interaction] = 0.0557). After propensity-score matching, the effect of chemo-immunotherapy was statistically significantly different by sex (p[interaction]=0.0414), but not by age or histology (Figure 1).

Figure 1: Overall survival according to treatment in the (a) overall cohort (n=1471); (b) the propensity matched cohort (n=662)



Conclusions: Chemo-immunotherapy is associated with better overall survival compared to chemotherapy alone. Male patients may benefit more from chemo-immunotherapy, but there is limited evidence suggesting age, histology, race, and comorbidities contribute to differences in immunotherapy effectiveness.

Keywords: Immunotherapy, Non-small cell lung cancer, Survival disparities

EP08.01-048 Spanish Immunotherapy Registry of Cardiovascular Toxicity (SIR-CVT): Preliminary Analysis of the Lung Cancer Cohort

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Introduction: Immunotherapy has transformed the landscape of lung cancer treatment. Owing to the growing use of ICIs in the treatment of lung cancer, we will increasingly be confronted with common but also rare immune- related adverse events (irAEs). Acute cardiovascular irAEs occur in less than 5% of patients treated with ICIs; however they involve a potentially fulminant toxicity. On the other hand, ICIs also have a potential role in the development and exacerbation of long-term cardiovascular complications. In addition, the diagnosis and treatment of cardiovascular irAEs may be delayed due to poor specificity of symptoms and the absence of monitoring protocols.

Methods: We present the Spanish Immunotherapy Registry of Cardiovascular Toxicity (SIR-CVT). The aim of this registry is to identify cardiovascular toxicity events in the short and medium term in patients with solid tumors, including lung cancer, who will be treated with immunotherapy for the first time, conducting a systematic baseline study based on blood test including cardiac biomarkers, electrocardiograms, advanced imaging test such as echocardiogram and cardiac magnetic resonance (CMR) and joint clinical follow-up. Other objectives are to validate the usefulness of a new biomarker of myocarditis, the micro RNA721, which could help in the early diagnosis of patients who develop myocarditis; and to define the inflammation profile of these patients. This registry includes the participation of 19 Spanish centers and is already recruiting patients in some of them. It is expected to include 500 patients. At present, 29 patients with lung cancer have been included in the registry from July 2021 to February 2022.

Results: The majority (n=25, 86.2%) are males with a median age of 65 years old. 23 patients (79.3%) have smoking history. Regarding cardiovascular risk factors, 11 patients (37.9%) have hypertension, 8 patients (27.6%) have diabetes mellitus and 13 patients (44.8%) have dyslipidemia. Concerning previous cardiovascular disease, 7 patients (24.1%) have previous myocardial infarction, 3 patients (10.3%) have previous heart failure and 2 patients (6.9%) have previous non-ischemic cardiomyopathy. The median left ventricular ejection fraction by echocardiogram and CMR at baseline visit was 57.2% and 55.7%, respectively; and the median left ventricular global longitudinal strain was -17.3%. The median cardiac troponin was 10.5ng/L and the median NT-pro-BNP was 1039.5pg/ml. Regarding the type of cancer, 19 patients (65.5%) have lung adenocarcinoma and 10 patients (34.5%) have lung squamous cell carcinoma. Most patients (n=22, 75.9%) have stage IV, 5 patients (17.2%) stage III and 2 patient (6.9%) stage II. Two third of the patients (n=21, 72.4%) receive pembrolizumab, 4 patients (13.8%) durvalumab, 3 patients (10.3%) atezolizumab and 1 patient (3.5%) nivolumab.

Conclusions: The results of this real-world registry will allow us to know the incidence, symptoms and improve the management of cardiovascular irAEs. All of that will lead to the development of monitoring protocols, the discovery of specific biomarkers in this high cardiovascular risk population and the prevention of potentially fulminant adverse events. It would be advisable to perform a baseline cardiovascular study prior to starting immunotherapy to find out if patients have any unknown cardiovascular disease.

Keywords: Lung cancer, Immunotherapy, Immune- related adverse events

EP08.01-049 Unscheduled Hospitalizations in Patients with Thoracic Tumors in the Era of Immunotherapy

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Introduction: Patients with advanced lung cancer and other thoracic tumors (TT) generally have higher hospitalization rates than other tumors due to their high mortality and associated comorbidity. Immune checkpoint inhibitors have changed the treatment paradigm of these tumors and are generally well tolerated but they can be associated with rare and life-threatening immune related adverse events (irAEs). The aim of this study was to assess the characteristics of patients that require hospital admission over a period of 6 months, focusing on patients with TT.

Methods: We retrospectively reviewed the 454 unscheduled hospitalizations that occurred between June 2021 to November 2021 in the Medical Oncology Service of La Paz University Hospital, Madrid (Spain). In this study we specifically analyzed the cohort of patients with TT. The patients were followed up until February 2022.

Results: 348 patients were admitted. Most patients (n = 90, 26%) had TT. In the TT cohort, the majority were males (n=54, 60%) with a median age of 66 years old (range 27-89). The most frequent histology was non-small-cell lung cancer (n=69, 77%), composed of adenocarcinoma (n=43, 48%), squamous cell (n=18, 20%), undifferentiated (n=7, 8%) and giant-cell (n=1, 1%), followed by small-cell lung cancer (n=17, 19%) and other less common TT such as carcinoid (n=1, 1%), salivary gland (n=1, 1%), mesothelioma (n=1, 1%) and thymoma (n=1, 1%). Only a few patients (n=7, 8%) underwent previous surgery. The majority (n=78, 87%) had stage IV disease. Regarding the last treatment received prior to admission, most patients (n=82, 91%) were receiving systemic treatment, of whom 54 patients (60%) were receiving immunotherapy.

The main cause of admission recorded was tumor-related (n=44, 49%), followed by infection (n=24, 27%), irAEs (n=9, 10%), venous thromboembolic disease (n=6, 7%), non-infectious chemotherapy-related toxicity (n=5, 6%) and heart failure (n=2, 2%). 50 patients (56%) died during admission or during the follow-up. The median overall survival since diagnosis was 25.2 months (95%CI: 15.5 - 35.0) and since admission 3.7 months (95%CI: 0.7 - 6.8).

IrAEs were observed in 20 of the 54 patients (37%) treated with immunotherapy. The most frequent irAE was pneumonitis (n=10), followed by cutaneous irAEs (n=3), hepatitis (n=3), thyroid irAEs (n=2), musculoskeletal irAEs (n=3), colitis (n=2), myocarditis (n=1), myasthenia gravis (n=1), nephritis (n=1) and hypophysitis (n=1). More than one irAE occurred in seven patients. The average number of cycles until the onset of irAE was 7 (range 1-53). Discontinuation of immunotherapy was required in 10 patients (19%). Of the 9 patients who required hospitalization due to irAEs, 4 patients died during hospitalization (3 patients due to pneumonitis and 1 patient due to myocarditis), and 1 patient died during follow-up due to other causes.

Conclusions: TT (especially non-small-cell lung cancer) were the most frequent malignancies among patients admitted in our department. Within this subgroup, the main cause of admission was tumor-related. IrAEs were the third cause of admission. However, they had a high rate of mortality. Therefore, we must keep in mind that irAEs that require hospitalization can be a life-threatening medical condition.

Keywords: Thoracic tumor, Immunotherapy, Hospitalization

EP08.01-050 Survival Outcome of Metastatic Pulmonary Sarcomatoid Carcinoma Treated with Immunotherapy: An Analysis of National Cancer Database (NCDB)

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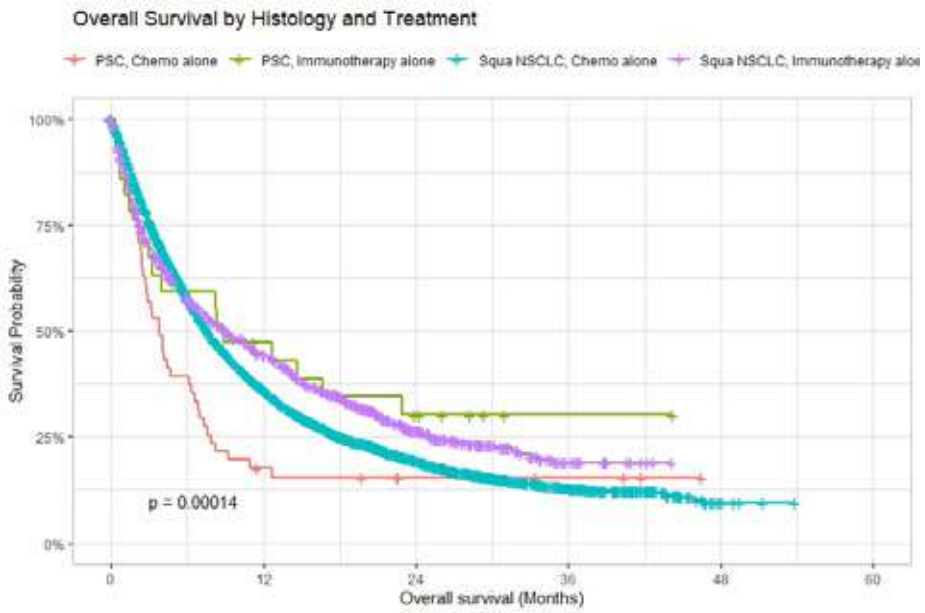
Introduction: Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of non-small cell lung cancer (NSCLC), associated with aggressive disease course, refractoriness to chemotherapy, and poor survival. Excellent response of PSC to immune checkpoint inhibitors were reported in small case reports/series, but it remains unclear whether PSC is still associated with poor prognosis compared to other NSCLC when treated with immunotherapy.

Methods: NCDB, a US national database capturing more than 70% of newly diagnosed lung cancer was queried for stage IV PSC diagnosed from 2016 to 2017, as pembrolizumab was approved in the US for NSCLC in 2016. Patients who were treated with chemotherapy doublets only or immunotherapy only in the first course of treatment are included. Because bevacizumab is part of first line treatment for nonsquamous NSCLC in the US and bevacizumab is recorded as immunotherapy in NCDB, only squamous NSCLC diagnosed during the same period is used as comparison. Log-rank was used for survival analysis and adjusted by cox regression for age, gender, race, academic center, insurance, and comorbidity.

Results: A total of 80 PSC patients were identified, of whom 59% were male. The median age was 67 years old. 29 patients (36%) received immunotherapy alone, while 51 (64%) received chemotherapy alone. Receipt of immunotherapy alone was associated with numerically longer survival than chemotherapy alone (median overall survival: 8.9 vs. 3.8 months, log-rank p = 0.054). After adjustment by multivariate analysis, this association became significant (HR 0.44, 95% CI 0.24-0.83). When comparing PSC to squamous cell NSCLC, there is significant interaction between histology and immunotherapy treatment for survival (p = 0.049). Among patients who have received immunotherapy, PSC was not associated with worse survival compared to 964 squamous NSCLC (median survival: PSC 8.9 vs. Squamous 9.1 months, log-rank p =0.68; Cox HR 0.92, 95% CI 0.58 - 1.48). In the subgroup of chemotherapy only, PSC remains associated with poorer prognosis compared to 4617 squamous NSCLC patients (median survival: PSC 3.8 vs. 7.6 months, log-rank p = 0.012; Cox HR 1.60, 95% CI 1.18 - 2.17).

Conclusions: When treated with modern immunotherapy, PSC is not associated with worse survival compared to squamous NSCLC like in the era of chemotherapy. Further studies on the role of PD-L1 expression is needed, as it is not collected in NCDB.



Keywords: Pulmonary Sarcomatoid Carcinoma, Immunotherapy, Chemotherapy

EP08.01-051 Clinical Characterization and Outcomes of Non Small Cell Lung Cancer with HER2 Alterations in the Era of Immunotherapy

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Introduction: HER2-altered Non Small Cell Lung Cancer (NSCLC) is a rare subgroup (2-4%) of NSCLC. Previous studies, using small cohorts, report poor outcomes and shorter survival in HER2-altered NSCLC compared to the other subtypes of NSCLC. However, most studies were done before immunotherapy is used as the first-line therapy in stage IV NSCLC. The detailed outcomes of those patients treated under the most recent guidelines are largely unknown.

Methods: We identified a total of 50 NSCLC patients harboring HER2 alterations at Mayo Clinic Florida. We conducted a retrospective study and investigated the tumor molecular alteration via next-generation sequencing (NGS), the treatment modalities, progression-free survival (PFS), overall survival (OS), and compared those outcomes to the general patient population with NSCLC using historical data from previous large clinical trials.

Results: In our study, the most common histology is adenocarcinoma (n=37, 74%), followed by squamous cell carcinoma (n=8, 16%). Staging of cancer at time of diagnosis was divided as following: Stage I (n=9, 18%), stage II (n=2, 4%), stage III (n=9, 18%), and stage IV (n=30, 60%). The most common site of metastases is brain (38.5%), followed by bone (33.3%) and liver (30.8%). Among stage IV patients, eight of them received chemotherapy as the first line. The median PFS is 3.9 months, and the median OS is 13.0 months. Eighteen of them received immunotherapy (alone or combined with chemotherapy) as the first line. The median PFS is 12.5 months, and the OS is 19.3 months. Six of them received immunotherapy as the second line. The median PFS is 3.4 months, and the OS is 9.3 months. The median OS of all stage IV patients is 14.6 months. The HER2 alterations include mutation (n=36, 72%), amplification (n=13, 26%), and protein overexpression (n=1, 2%). The median PFS of patients with HER2 alterations and treated with immunotherapy does not differ significantly between HER2 mutation and HER2 amplification (8.6 vs. 7.7 months, P = 0.65). The most common co-mutation is TP53 (72%), followed by KRAS (32%) and EGFR (26%). Patients with TP53 co-mutation tend to have longer PFS (12.5 vs. 4.0 months, P = 0.06) and OS (17.0 vs. 9.9 months, P = 0.35). Patients with KRAS co-mutation tend to have shorter PFS (4.2 vs. 11.0 months, P = 0.13) and OS (12.3 vs. 16.2 months, P = 0.62). Seven patients had actionable EGFR mutations and received EGFR inhibitors. The median PFS is 32.0 months, and the median OS is 39.6 months.

Conclusions: In our cohort of HER2-altered NSCLC patients, we observed similar efficacy of immunotherapy and clinical outcomes in HER2-altered NSCLC compared to the general patient population with NSCLC. Patients with either HER2 mutation or amplification responded similarly to immunotherapy. Patients with concurrent TP53 mutation tend to have a prolonged PFS and patients with KRAS co-mutation tend to have a shorter PFS compared to other HER2-altered NSCLC patients. Patients with concurrent actionable EGFR mutations responded well to EGFR inhibitors. Further studies using a larger dataset with more HER2-altered NSCLC patients to validate these findings are warranted.

Keywords: HER2, immunotherapy, EGFR

EP08.01-052 Toripalimab in Combination with CIK Cells in Patients with Advanced NSCLC: An Exploratory Study

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Introduction: Immune checkpoint inhibitors (ICIs) act as a crucial treatment of advanced NSCLC (non-small cell lung cancer). In order to optimize patients' prognosis, combination therapies based on ICIs are being constantly explored. CIK (cytokine induced killer) therapy is one of the adoptive immune cell therapies, which has shown certain effects in previous clinical trials. The combination of ICIs and CIK therapy is theoretically synergistic, as PD-1 monoclonal antibody can restore the activity of T cells, and CIK cells are a subgroup of T cells. Previous studies on PD-1 monoclonal antibody combined with CIK cells in the treatment of metastatic renal cell carcinoma achieved better clinical effects, consistent to the hypothesis. Whether this combination can improve survival in advanced NSCLC remains unknown, calling for further research. This trial is a single-center, exploratory study, aiming to explore the safety and efficacy of toripalimab (240mg Q3W) in combination with CIK cells (Q6W) in NSCLC.

Methods: We recruited newly-diagnosed advanced NSCLC patients with positive PD-L1 expression (PD-L1>1%). Eligible patients are assigned to groups A, B and C: toripalimab + CIK (group A, n=20), toripalimab + CIK + chemotherapy (group B, n=20) and CIK+chemotherapy group (group C, n=20). The total number of CIK cells reinfused in each patient needs to be more than 10^{10}. The primary endpoint is safety and progression free survival (PFS). The secondary endpoints include overall response rate (ORR), disease control rate (DCR), and overall survival (OS). We will also conduct evaluation of biomarkers and characterize the role of PD-L1 and TMB in this combination therapy. Enrollment for this trial began in July, 2021 and will last 18 months in all.

Results: Until now, 25 patients have been enrolled. 9 (60%) of the 15 patients in group A achieved a partial response (PR), 4 (26.67%) had stable disease (SD). 3 (33.33%) of the 9 patients in group B achieved a partial response (PR), 5 (55.56%) had stable disease (SD). As the control group, group C has so far enrolled 1 patient.

Conclusions: Not applicable.

Keywords: advanced NSCLC, CIK, toripalimab

EP08.01-053 PD-1 Inhibitors Plus Chemotherapy in Patients with Brain Metastasis and EGFR/ALK-positive Non-small Cell Lung Cancer after EGFR/ALK-TKIs

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Introduction: Resistance in epidermal growth factor receptor (EGFR) / anaplastic lymphoma kinase (ALK) rearrangements-tyrosine kinase inhibitors (EGFR/ALK-TKIs) have become an enormous challenge for non-small cell lung cancer (NSCLC) treatment. Immune checkpoint inhibitors (ICIs) have exhibited an encouraging clinical activity in heavily pretreated patients with EGFR+ NSCLC. However, previous studies of ICIs plus chemotherapy excluded those with EGFR-mutation, ALK-rearrangement. Thus, it is unknown that the effectiveness of ICIs plus chemotherapy for them, specially those with baseline brain metastasis (BM).

Methods: We collected data for previous treated NSCLC patients with EGFR-mutated or ALK-rearranged BM receiving ICI combined with chemotherapy ± bevacizumab therapy after EGFR/ALK-TKIs resistance between April 2019 to August 2021 at Cancer Hospital of the Chinese Academy of Medical Sciences (CAMS), and retrospectively analyzed the efficacy, toxicity and progression site after ICIs treatment.

Results: A total of 19 patients were included in the study. Sixteen (84.4%) patients were EGFR mutations, 2 (10.5%) with ALK translocation and 1 (5.3%) with RET rearrangement. All of them had received TKIs therapy and underwent disease progression before ICIs. The overall response rate (ORR), disease control rate (DCR) were 15.8% and 57.9%, respectively. The median progression free survival (PFS) and overall survival (OS)were 4.7 (95% CI=0.43-8.96) and 19.2 (95% CI=15.08-23.29) months, respectively. We found BMs have a similar benefit from ICIs combined with chemotherapy as extracranial disease. The intracranial ORR and extracranial ORR were 10.5% and 15.8%. The intracranial DCR and extracranial DCR were 68.4% and 63.2%. The common progression site was extracranial failure, and represented primary extracranial lesions enlargement, rather than new site metastases. The common grade 3-4 adverse events (AEs) successively were leukopenia (31.6%), neutropenia (26.3%), thrombocytopenia (10.5%) and rash (5.3%). No grade 5 AE and discontinuing ICIs therapy for severe AEs were observed.

Conclusions: The combination of ICIs and chemotherapy might have activity and safety in BM similar with its systemic activity and can result in prolonged survival in EGFR/ALK+ NSCLC patients with BM and disease progression after target therapies. But it would develop rapid progression in patients with multi-site metastases and extracranial progression before ICIs treatment.

Keywords: immune checkpoint inhibitors (ICIs), EGFR-mutated or ALK-rearranged, brain metastasis

EP08.01-054 ICIs combined with Single-agent Chemotherapy in Two or More Lines Treatment for Advanced Non-Small Cell Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) monotherapy has been recommended currently by the guidelines in the second-line treatment for advanced non-small cell lung cancer (NSCLC). However, the efficacy and safety of ICIs combined with chemotherapy in second-line treatment for advanced NSCLC remain unclear.This study observed and analyzed the efficacy and safety of ICIs combined with single-agent chemotherapy in two or more lines treatment for advanced NSCLC, and explored EVs markers as medication guidance and as markers for monitoring therapeutic efficacy.

Methods: Clinical data of patients diagnosed with advanced NSCLC who received ICIs combined with single-agent chemotherapy as two or more lines treatment were retrospectively collected from March 2019 to January 2022. A total of 30 patients met the inclusion criteria, and all patients were pathologically confirmed as NSCLC. Short-term efficacy, progression-free survival (PFS), EVs markers and adverse events were observed.

Results: The efficacy of the 30 patients included in the study was evaluated, including 0 patients with complete response (CR), 5 patients with partial response (PR), 18 patients with stable disease (SD) and 7 patients with disease progression (PD) after treatment. Objective response rate (ORR) was 16.7%, disease control rate (DCR) was 76.7%, and median PFS was 3.2 months (95%CI:2.684-3.716). Univariate analysis and multivariate analysis showed that there was no significant difference in PFS among patients with different gender, age, smoking status, number of treatment lines, whether they had used ICIs before or not, and whether they had used antivascular drugs before (P>0.05). EVs membrane proteins C-Met, EGFR and VEGFR2 were negatively correlated with the efficacy of ICIs. According to ROC curve and KM curve analysis, C-MET, EGFR and VEGFR2 can be used as diagnostic markers and drug guidance for lung cancer patients with disease progression after the ICIs combined with chemotherapy. During treatment, the expression level of VEGFR2 increased in beneficial patients and decreased in non-beneficial patients, which can be used as a marker for monitoring therapeutic efficacy. In terms of safety, the most common grade 2 or above adverse events were neutropenia, gastrointestinal reactions and thyroid dysfunction, and the overall adverse events were tolerable.

Conclusions: The combination of ICIs combined with single-agent chemotherapy shows safety, efficacy, and tolerable adverse events in two or more lines treatment for advanced non-small cell lung cancer. EVs markers can be used as medication guidance and as markers for monitoring therapeutic efficacy.

Keywords: Non-small cell lung cancer, Immune checkpoint inhibitor, Chemotherapy

EP08.01-055 Utilization of Tumor Mutational Profiling to Identify the Immunotherapy Response in Non-small Cell Lung Cancer

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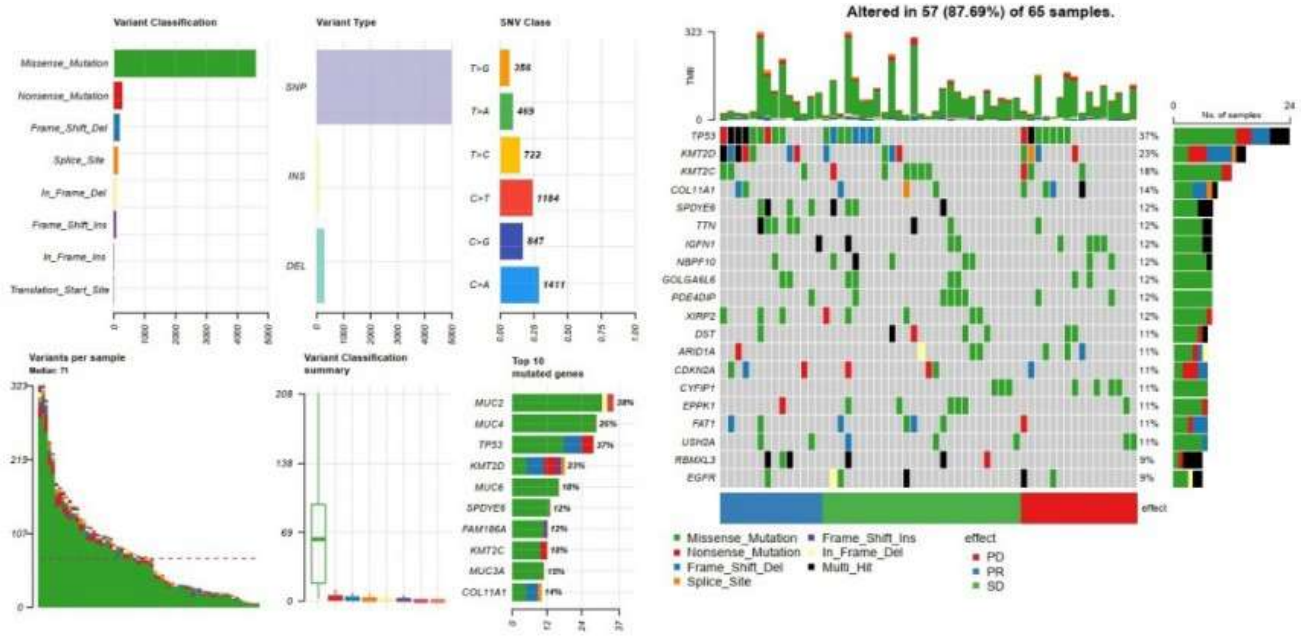
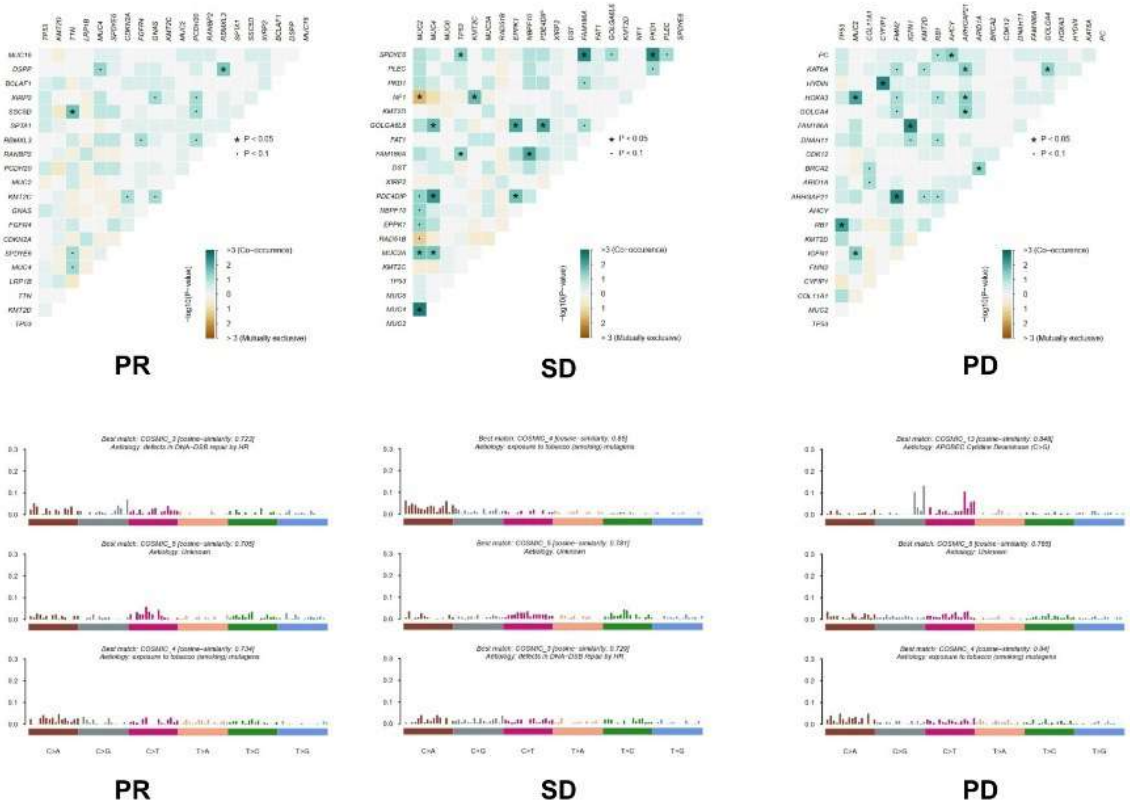
Introduction: Immune checkpoint inhibitors targeted programmed cell death 1 (PD-1) and its ligand (PD-L1) elicit durable clinical benefit and shift the paradigm in non-small cell lung cancer (NSCLC). The identification of biomarkers that can predict the immunotherapy response is still an unmet need in clinical practice. We explore the genomic profiling of NSCLC with immunotherapy.

Methods: 65 histologically confirmed NSCLC patients received immunotherapy were included and basline tumor specimens were collected from the Cancer Institute and Hospital, Chinese Academy of Medical Sciences. Tumor specimens including 15 partial response (PR), 30 stable disease (SD) and the other 20 progressive disease (PD) were assessed on the basis of the RECIST V1.1. Whole-exome sequencing and targeted sequencing were applied to 43 and 22 tumor tissues respectively.

Results: The dominant bases substitution was C>A transversions associated with smoking. TP53, KMT2D, and KMT2C were the frequently mutated genes which detected in more than 20% cases. The co-occurrence mutation of SSC5D and TTN, DSPP and RBMXL3 occurred in PR group; co-mutation of SPDYE6 and TP53/ FAM186A/ PKD1,NF1 and KMT2C, GOLGA6L6 and EPPK1/ PDE4DIP, FAM186A and TP53/ NBPF10, PDE4DIP and EPPK1 were shown in patients with SD; TP53 and RB1, CYFIP1 and HYDIN, ARHGAP21 and FMN2, FAM186A and IGFN1, AHCY and PC, ARHGAP21 and KAT6A/ HOXA3/ GOLGA4, ARID1A and BRCA2, GOLGA4 and KAT6A co-mutation were mainly detected in PD patients. The most relevant mutational signature in PR and SD group was signature 4 associated with direct exposure to tobacco mutagens, and in PD group was APOBEC Cytidine Deaminase (C>G).

Conclusions: The mutational features in tumor DNA of NSCLC patients with response (PR+SD) to immunotherapy were different from that without response (PD). The co-mutation of SSC5D and TTN, DSPP and RBMXL3 may be helpful in identifying the response to immunotherapy and making the personal treatment in NSCLC.





Keywords: non-small cell lung cancer, immunotherapy, tumor mutational profiling

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-056 Pemetrexed-Based Chemotherapy Plus ICIs or Bevacizumab as First-Line Strategy for Patients with Lung Adenocarcinoma in Real-World Setting

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Introduction: Immune checkpoint inhibitors (ICIs) have hugely altered the first-line treatment strategies of advanced lung adenocarcinoma patients (aLUAD), especially when in combination with standard chemotherapy (Chemo). However, few registered clinical trials directly compared the efficacy of ICIs + Chemo versus bevacizumab (Bev) plus Chemo in aLUAD, while the latter has been solidly proven to enhance patients' progression-free survival (PFS) when compared to Chemo alone in advanced non-small-cell lung cancer patients. Hence, we conducted this retrospective analysis to assess the efficacy of ICIs + Chemo vs. Bev + Chemo in Chinese patients with aLUAD in the real-world setting.

Methods: Patients pathologically confirmed with aLUAD (stage IIIb - IV) with negative detection of EGFR sensitive mutations / ALK fusion / ROS1 fusion and treated with standard pemetrexed-platinum doublet chemotherapy with bevacizumab or PD1/PD-L1 ICIs at Hangzhou Cancer Hospital were retrospectively selected. Clinicopathological information, such as age, gender, smoking history, pathology, and stage were collected and survival outcomes were assessed according to records in the electronic health system and telephone follow-up.

Results: A total of 49 patients who met with the inclusion criteria were finally enrolled, in which 32 patients were administrated with Bev + Chemo while the rest 17 patients received ICIs + Chemo as the first-line treatment until progression. The median age at diagnosis was 62 and 66 years old in the Bev + Chemo and ICIs + Chemo group, respectively; 81.3% (26/32) of the Bev + Chemo group and 82.4% (14/17) of the ICIs + Chemo group were male. 13 patients achieved partial response (PR) and the rest 4 patients had stable disease (SD), while 18 patients achieved PR and 14 patients remained SD (ORR 76.5% versus 56.3%, $p = 0.16$). Median PFS was 17.3 months in the ICI + Chemo group versus 7.3 months in the Bev + Chemo group (Log-rank test, HR [95%CI] = 0.39 [0.20-0.74], $p = 0.012$). For the overall survival (OS), ICI + Chemo treatment also showed a superior trend when compared to Bev + Chemo group, with the median OS of 27.9 months and 17.8 months, respectively (Log-rank test, HR [95%CI] = 0.48 [0.22-1.07], $p = 0.116$). Leucopenia, as the most common ≥ 3 grade adverse event (AEs), occurred similarly in both groups, at an incidence rate of 25.0% (8/32) for Bev + Chemo and 23.5% (4/17) for ICI + Chemo. ICI + Chemo caused an elevated frequency of≥ 3 grade thrombocytopenia (3/17, 17.6% vs 2/32, 6.2%, $p = 0.210$) and anemia (4/17, 23.5%; 1/32, 3.1%, $p = 0.025$), however, no ≥ 4 grade AEs were observed.

Conclusions: For the treatment of first-diagnosed aLUAD patients without EGFR/ALK/ROS1 driver gene alterations in the real-world setting, pemetrexed-platinum doublet chemotherapy combined with PD1/PD-L1 based ICIs showed surpassing efficacy and controllable toxicity when compared to Bevacizumab combination.

Keywords: Immune checkpoint inhibitors, Bevacizumab, Lung Adenocarcinoma

EP08.01-057 Pembrolizumab Maintenance in Patients with Metastatic Squamous Non-Small Cell Lung Cancer (sNSCLC) - AIO-TRK-0115/PRIMUS

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Introduction: Platinum-containing chemotherapy represents one treatment opportunity for patients with advanced squamous NSCLC. With respect to comorbidities and decreased performance status, frequently seen in patients with sNSCLC novel effective and well tolerable treatment opportunities are required to enhance efficacy of systemic treatment. The PRIMUS trial was conducted to explore the potential of pembrolizumab maintenance treatment after induction treatment with platinum-based chemotherapy.

Methods: In this phase II multi-center, double-blind trial, patients with stage IV squamous NSCLC and at least stable disease after at least 2 cycles of first-line chemotherapy with cisplatin or carboplatin were randomized 1:1 between Q3W maintenance treatment with pembrolizumab 200 mg and placebo, respectively. Patients were included irrespective of tumor PD-L1 expression. Maximum treatment duration was 2 years. The primary endpoint was progression-free survival (PFS) measured from randomization, secondary endpoints included objective response rate (ORR), overall survival (OS) measured from randomization, PD-L1 expression in tumor samples, safety and tolerability, and quality of life by FACT-L and LCSS questionnaires.

Results: Planned patient enrollment of 65 per arm was not met due to changes of clinical treatment standards for first-line treatment. Pembrolizumab (P) maintenance was administered to 16 patients, while 18 patients received placebo (Pla). Survival results favor P maintenance over placebo: Median PFS with P was 9.5 mo [95% CI 1.5-23.5] versus 4.8 mo [95% CI 1.8-10.5] with Pla. PFS rate at 6, 12 and 18 months was 50.3% [95% CI 23.1-72.4%], 35.9% [95% CI 13.1-59.6%] and 35.9% [95% CI 13.1-59.6%] with P and 36.1% [95% CI 15.0-57.9%], 18.1% [95% CI 4.5-39.0%] and 9.0% [95% CI 0.7-30.9%] with Pla. Median OS was 24.0 mo [95% CI 9.5-30.9] with P and 10.9 mo [95% CI 4.8-39.2] with Pla. OS rates at 6 and 12 months were 86.7% [95% CI 56.4-96.5%] and 79.4% [95% CI 48.8-92.9%] with P versus 69.3% [95% CI 41.1- 85.9] and 44.1% [95% CI 20.0-65.9%] with Pla. Response and SD from start of maintenance: 11.1% vs 14.4% and 42.3% vs 23.1% (P vs Pla). AEs ≥ grade 3 potentially related to P according to investigator assessment occurred in 4 patients: grade 3 hyperthyreosis, myocarditis, nephritis and acute renal failure, and grade 4 bronchopulmonary hemorrhage.

Conclusions: Our results indicate a notable benefit of the pembrolizumab maintenance strategy compared to placebo maintenance treatment, both in terms of PFS and OS. This is a remarkable finding given that the number of treated patients was considerably lower than planned. Further exploration is warranted.

Keywords: Immunotherapy, Maintenance, Squamous Cell NSCLC

EP08.01-058 Access to Immunotherapy in Control Arms of Pivotal First Line Immunotherapy Trials in Metastatic Non-Small Cell Lung Cancer

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Introduction: Immunotherapy has significantly improved outcomes for patients with non-small cell lung cancer (NSCLC). Pembrolizumab and nivolumab received FDA approval in 2015 for patients with previously treated NSCLC. Since then, several pivotal first-line clinical trials have shown improved outcomes compared to control arms of chemotherapy. It is unknown how access to later line immunotherapy in control arms varies between these trials.

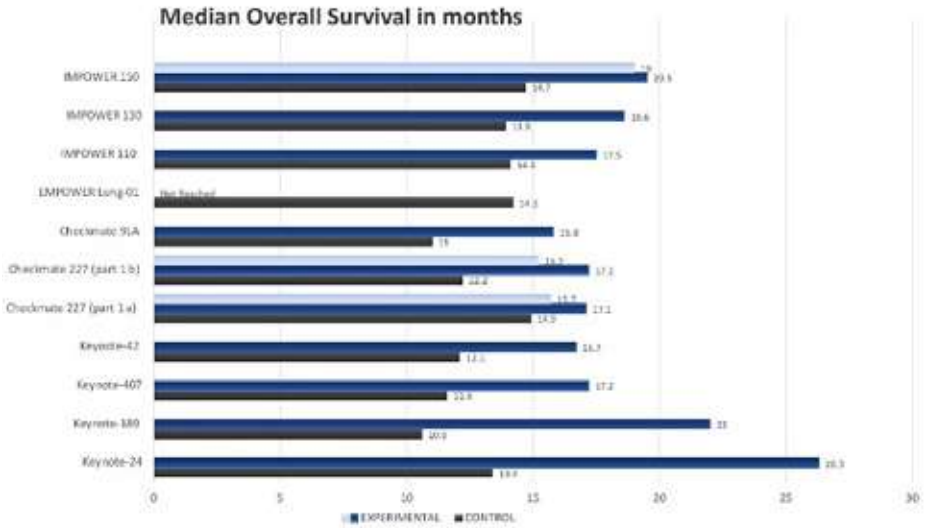
Methods: We reviewed first-line immunotherapy trials in NSCLC that have led to regulatory approval in the US. We analyzed publications, trial protocols, and supplementary indices to determine the percentage of patients on control arms who received any subsequent therapy, including immunotherapy.

Results: A total of 3339 patients received chemotherapy in the control arms of these eight trials. About 2079 (62.3%) of these patients on control arms received subsequent therapy. 1361 patients (40.8%) received subsequent immunotherapy. Of patients who received subsequent treatment, about 65.5% of them received immunotherapy. Immunotherapy access in control arms varied between trials.

Conclusions: Access to later line immunotherapy varied between control arms of these trials. Trials with higher rates of subsequent immunotherapy in control arms are more likely to represent clinical practice in the US, providing a higher level of evidence for first-line immunotherapy in NSCLC.

	Trial	Population included	NSCLC Subtype	Experimental Arm	Control Arm	No. of Patients in Control arm	Cross Over Allowed (Y/N)	Received Subsequent Therapy No. (%)	Received Subsequent Immunotherapy No. (%)	Immunotherapy/subsequent therapy (%)
1	Keynote-24	PDL>50%	Sq and NSq	Pembrolizumab	Chemotherapy	151	Y	103 (68.2)	99 (65.6)	96.1
2	Keynote-189	All PDL1 levels	NSq	Pembrolizumab + Chemotherapy	Chemotherapy	206	Y	122 (59.2)	111 (53.9)	91
3	Keynote-407	All PDL levels	Sq and NSq	Pembrolizumab + Chemotherapy	Chemotherapy	281	Y	167 (59.4)	138 (49.1)	82.6
4	Keynote-42	PDL1>1%	Sq and NSq	Pembrolizumab	Chemotherapy	637	N	448 (70.3)	126 (19.8)	28.1
5	Checkmate 227 (part 1a)			Nivolumab + Ipilimumab						
		PDL1>1%	Sq and NSq	Nivolumab	Chemotherapy	397	N	248 (62.5)	171 (43.1)	69
	Checkmate 227 (part 1b)			Nivolumab + Ipilimumab						
		PDL1<1%	Sq and NSq	Nivolumab + Chemotherapy	Chemotherapy	186	N	106 (57)	67 (36)	63.2
6	Checkmate 9LA	All PDL1 levels	Sq and NSq	Nivolumab + Ipilimumab + Chemotherapy	Chemotherapy	358	N	181 (50.6)	127 (35.5)	70.2
7	EMPOWER Lung-01	PDL1>50%*	Sq and NSq	Cemipilimab	Chemotherapy	280	Y	203 (72.5)	150 (53.6)	73.9
8	IMPOWER 110	PDL1>1% TC or IC	Sq and NSq	Atezolizumab	Chemotherapy	277*	N	137 (49.5)	80 (28.9)	58.4
9	IMPOWER 130	All PDL1 levels	NSq	Atezolizumab + Chemotherapy	Chemotherapy	228*	Y#	151 (66.2)	135 (59.2)	89.4
10	IMPOWER 150			Atezolizumab + bevacizumab + chemo (ABCP)						
		ALL PDL 1 levels	NSq	Atezolizumab + Chemo (ACP)	Chemotherapy + bevacizumab (BCP)	338*	N	213 (63)	157 (46.4)	73.7
Total						3,339		2,079 (62.3)	1,361 (40.8)	65.5

Summary of pivotal first line immunotherapy trials in non-small cell lung cancer and rates of subsequent immunotherapy in control arms.
*excluding EGFR and ALK mutation, #cross over not allowed for patients enrolled after 6/2016.



Keywords: NSCLC, Immunotherapy

EP08.01-059 Safety, Tolerability and Clinical Activity of Selinexor in Combination with Pembrolizumab in Metastatic Non-small Cell Lung Cancer

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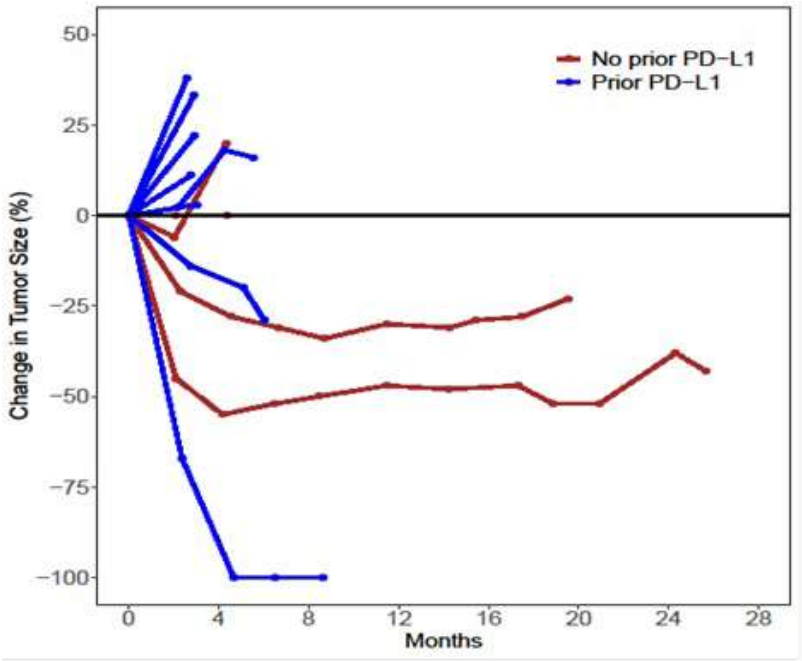
Introduction: Immune checkpoint therapies have revolutionized the therapy of metastatic Non-Small Cell Lung Cancer (mNSCLC), leading to durable therapeutic responses not typically seen with traditional cytotoxic anti-cancer agents. However, primary and acquired resistance to anti-PD-(L)1 therapy impacts the majority of the patients, and new strategies are investigated to prevent or reverse resistance to therapy. Here we present clinical safety and early efficacy data of the combination of Pembrolizumab with a first in class, oral selective inhibitor of nuclear export, Selinexor in mNSCLC.

Methods: The primary objectives of this investigator-initiated study (NCT 02419495) were to determine the safety and tolerability of Selinexor in combination with Pembrolizumab in mNSCLC. Secondary objectives included objective tumor response rate (complete or partial response), disease control rate (CR + PR + stable disease ≥ six months) and progression-free survival (PFS) assessed according to RECIST v1.1. The Kaplan-Meier method was used to estimate OS and PFS. NCI CTCAE 4.03 was used to grade adverse events.

Results: A total of 17 patients were included in the final analysis. The median age was 67.5 (38.5-80.7). 14 (82%) had adenocarcinoma, 2 with squamous cell, and one patient with sarcomatoid NSCLC. 15/17 (88%) received more than two lines of prior systemic therapy, and 10/17 (59%) had prior exposure to anti-PD-(L)1 therapy. Grade ≥3 treatment-related adverse events (TRAEs) reported in 10 (58%) patients. Non-hematologic TRAEs were reported in 7 patients. These TRAEs include dehydration, hyponatremia, vomiting, hyperglycemia, confusion, and febrile neutropenia. The median (95% CI) OS and PFS for all patients was 11.4 (3.4, 19.8) months and 3.0 (1.7, 5.7) months, respectively. PR was observed in 3 (18%), SD ≥6 months was observed in 5 (29%) patients and DCR was 47%. Responses were observed in both previously anti-PD-(L)1 treated and untreated patients (figure 1 summary of the change in tumor size over time by tumor PD-L1 IHC).

Conclusions: Selinexor in combination with Pembrolizumab showed promising antitumor activity. in patients with mNSCLC, including patients who had previously received anti-PD-(L)1. Therapy-related toxicities were consistent with prior safety data for both drugs and no overlapping toxicities were observed. The final presentation will include results of detailed safety and clinical data.



Keywords: primary and acquired resistance to anti-PD-(L)1, Non Small Cell Lung Cancer, Selinexor

EP08.01-060 Long term Survival Outcomes in NSCLC Patients with Targeted Therapy and Immunotherapy: An IASLC Analysis of ASCO CancerLinQ Discovery Data

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Introduction: Both immunotherapy and targeted therapies have become part of routine lung cancer therapy; we analyzed the ASCO CancerLinQ database to study long-term outcomes for patients treated with targeted therapy and immunotherapy for advanced NSCLC.

Methods: The ASCO CancerLinQ Discovery dataset was queried to identify patients diagnosed with lung cancer between the years 2010-2018. Data on demographics, tumor stage, histology and treatments were extracted. Stage IV patients that had been treated with targeted therapy (TT), immunotherapy alone (ICI) or both in sequence (TIC) were included in this analysis. Univariate association (UVA) of each clinicopathological variable with treatment group was performed using Chi-square tests for categorical variables and ANOVA test for numerical variables. 5 year overall survival (OS) was investigated as the primary outcome. OS was calculated as the time from first diagnosis to the date of death or date of last available follow-up, and was estimated using the Kaplan-Meier method. The treatment groups of interest were compared using log-rank tests, and pair-wise comparisons were reported, where applicable. Other clinicopathological variables were similarly compared. 5-year overall survival rates were reported. All analyses were conducted using SAS 9.4.

Results: A total of 3,911 NSCLC patients with stage IV disease were included in this analysis. Patient characteristics: median age 65 years, 52% male, 73% White and 2.5% Hispanic. Approximately 77% were treated with ICI, 21% with TT and 3% received TT followed by ICI (TIC). On the UVA, 55% of patients treated with ICI comprised of males compared to 43% in TT and 31% in TIC groups (p<0.001). On KM analysis, the 5-year survival rates were 19% in ICI, 15% in TT, and 21% in TIC subgroups. The median survival was 1.9y vs 1.6y vs 3.2y in ICI, TT and TIC subgroups respectively. Females had significantly higher 5-year survival rate compared to males (17% vs. 12%; log-rank p=0.004) in the TT subgroup but were comparable with males in the other two subgroups [18.2% vs. 19.5% in ICI and 21.6% vs.20.3% in TIC]. Black patients had significantly higher 5-year survival rates compared to White [27.5% (CI 21.3%-34.1%) vs.16.5% (CI 14.2%-18.9%); log-rank p=0.0001) in the ICI subgroup but no significant differences in survival were seen in patients in the other two treatment subgroups based on race.

Conclusions: The 5-year survival rates with immunotherapy and targeted therapy were greater than 15% for advanced NSCLC; Black patients had a significantly better 5-year survival with immunotherapy.

Keywords: Immunotherapy, Targeted therapy, Treatment sequence

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-061 A Pilot Study of Avelumab and SABR in Non-Responding and Progressing NSCLC Patients Previously Treated with a Checkpoint Inhibitor

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Introduction: Significant preclinical and early clinical data suggest radiotherapy may augment the effects of immune checkpoint inhibitors (ICI). Limited successful treatment options are available following progression on ICI. We hypothesized that fractionated, stereotactic ablative radiotherapy (SABR) would induce a response in combination with the PD-1 inhibitor avelumab in patients with non-small cell lung cancer (NSCLC) who previously progressed on ICI, either as monotherapy or combination therapy.

Methods: We activated a prospective, pilot clinical trial that enrolled NSCLC patients who either did not respond to ICI (non-responders) or responded initially with either sustained disease stability, partial response (PR) or complete response (CR), but subsequently progressed on ICI (progressors). Enrolled patients were required have at least one site of disease amenable to 5-fraction SABR and at least one additional site of disease for response assessment. Enrolled patients underwent SABR (35-50 Gy in 5 fractions on non-consecutive days) to one lung, liver, or soft tissue site of disease starting day 1 cycle 1 of avelumab. Avelumab was given at 10 mg/kg IV every 14 days until progression or unacceptable toxicity. Our primary objective was to estimate the overall response rate (ORR) by RECIST 1.1 criteria in each cohort with this approach. Secondary endpoints included safety, toxicity, and progression-free survival (PFS). We planned to enroll 13 patients in each of the non-responder and progressor cohorts. With 13 patients per cohort, we would have a power of 80% to detect a response rate of 30% or better.

Results: We enrolled a total of 8 patients between Sept 2017—Jan 2020, including 6 in the progressor cohort and 2 in the non-responder cohort, with 4 men and 4 women enrolled. The trial was closed in July 2020 due to slow accrual and changes in the NSCLC treatment landscape. We observed one confirmed partial response to treatment in a patient in the progressor cohort, which was durable at 7 months when he elected to come off study. Confirmed stable disease was seen in 2 patients, both on the progressor cohort. Duration of disease stability prior to progression was 5.8 months and 3.9 months, respectively. The ORR for the entire cohort (CR+PR) was 12.5%. Median PFS in the entire cohort was 2.75 months (CI 1.6-5.8 months). Treatment was well-tolerated, with no-grade 3 or higher treatment related toxicity observed. One patient was taken off avelumab after developing grade 2 pneumonitis.

Conclusions: The combination of avelumab and SABR had a manageable safety profile in patients previously non-responding or progressing on ICI. The response rate of 12.5% was disappointing, although the enrolled population of 8 patients is too small to draw firm conclusions. Future studies should focus on identifying the subset of patients, such as the one responder in our cohort, who may benefit from similar approaches.

Keywords: non small cell lung cancer, Stereotactic radiation, Avelumab

EP08.01-062 Body Mass Index, Immune Related Adverse Events, and Survival in Patients with Metastatic Non-small Cell Lung Cancer Treated with Immunotherapy

M. Li, S. Zhao, J. Guo, T. Gauntner, J. Schafer, K. Chakravarthy, G. Lopez, A. Secor, P. Das, N. Surya, M. Husain, S. Patel, M. Grogan, D. Spakowicz, A. Miah, L. Wei, K. He, E. Bertino, A. Alahmadi, R. Memmott, J. Kaufman, C. Presley, P. Shields, D. Carbone, G. Otterson, D. Owen

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Introduction: Obesity is a major risk factor for cancer but has unclear impact on immunotherapy outcomes. While obesity alters the pharmacokinetics and pharmacodynamics of many drugs, its interplay with immune function may alter immunotherapy via more complex mechanisms. Recent studies have linked androgen signaling to T-cell exhaustion and given that adipose tissue is a key site of androgen metabolism, we hypothesized that obesity is closely linked with immunotherapy response. We studied the association between obesity, immune related adverse events (irAE), and overall survival (OS) in patients with metastatic non-small cell lung cancer (NSCLC) who were treated with checkpoint inhibitor-based regimen.

Methods: We retrospectively studied 459 patients with stage IV NSCLC who were treated with immune checkpoint inhibitor between 2011 and 2020 with known baseline weight and height. Baseline patient characteristics were obtained via electronic chart review. Body mass index (BMI) was calculated from weight and height obtained prior to first cycle of treatment. There were 2 patients in our cohort with unknown irAE status. Cox proportional hazard model used to assess the hazard ratios in univariate analysis. Statistical analysis was performed in SAS 9.4

Results: In our study, 211 (46.0%) of patients were females. 296 (64.5%) had adenocarcinoma, 107 (23.3%) had squamous cell carcinoma, and 56(12.2%) had others. 273 (59.5%) received first line therapy, 132(28.8%) received second line, and 52 (11.3%) received third or beyond, and 2 (0.4%) patients with unknown line of therapy. The mean BMI were 26.6 with standard deviation (SD) 5.99, and median was 25.8 with interquartile range 22.3-30.2. In our study, for one unit increase in BMI, the hazard of death decreased by 2.5% (HR=0.975 with 95% CI 0.957-0.994 and p=0.008). More specifically, 15 (3.3%) patients with BMI ≥40 had lower HR at 0.459 (95% CI 0.225-0.937) when compared to 185 (40.3%) patients with normal BMI between 18.5 and 25, p=0.032. 182 (39.7%) patients developed at least one episode of any grade irAE. Developing any grade irAE was associated improved OS with HR=0.40 (95% CI 0.32-0.51) and P<0.001. BMI was not associated with the risk of developing irAE with HR=0.987 (95% CI 0.963-1.010) and p=0.269.

Conclusions: In our study, greater BMI was associated with better OS for patients with metastatic NSCLC who received immune checkpoint inhibitor-based regimen. Developing any grade irAE was associated with improved survival. However, no significant association between BMI and developing irAE was seen. Future studies with larger cohorts are needed to validate these findings and elucidate the underlying mechanisms.

Keywords: Immunotherapy, Immune Related Adverse Events, Body Mass Index

EP08.01-063 Chemoimmunotherapy versus Immunotherapy for First Line Treatment of Advanced Non-small Cell Lung Cancer with a PD-L1 Score of 50-100%

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Introduction: Anti-PD-(L)1 immunotherapy with or without chemotherapy has shown superior overall survival as first-line treatment for patients with advanced non-small-cell lung cancer (aNSCLC) and high tumor expression of PD-(L)1 (PD-L1 score ≥50%) compared to chemotherapy alone. However, evidence on the cross-comparative effectiveness of chemoimmunotherapy versus immunotherapy alone in patients with PD-L1 ≥50% and in those with PD-L1 ≥90% is limited due to lack of head-to-head efficacy trials making it difficult to decide who can be spared the additional side effects associated with combination therapy. We sought to compare survival in aNSCLC patients with PD-L1 score ≥50% receiving first-line pembrolizumab with or without chemotherapy.

Methods: Cohort study of aNSCLC patients with PD-L1 score ≥50% who initiated first-line treatment with pembrolizumab monotherapy or in combination with carboplatin-based chemotherapy between Oct 24th, 2016, and Oct 29th, 2021, using the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. Kaplan-Meier curves and Cox regression were used to estimate 6- and 12-month overall survival and hazard ratios, respectively, for all patients with PD-L1 ≥50% and in the subgroup of patients with PD-L1 ≥90%. Multiple imputation was used to impute missing covariates. Propensity score-based inverse probability of treatment weighting (IPTW) was used to address confounding by age, race, sex, smoking history, PD-L1 score ≥90%, tumor histology, presence of KRAS/BRAF mutation, practice type, and ECOG performance status. Because of non-proportionality of hazards, we estimated separate hazard ratios for the first 6 months and after 6 months.

Results: The cohort included 3086 aNSCLC patients. 52% of whom were male, median age at therapy initiation was 71 years, 27% had a KRAS mutation and 93% had a history of smoking. Sixty-eight percent received pembrolizumab as monotherapy. PD-L1 score ≥90% was split evenly between the treatment groups (n=946 (45%) in immunotherapy alone group vs n=426 (43%) in the chemoimmunotherapy group). IPTW adjusted survival was higher for chemoimmunotherapy compared to immunotherapy alone at 6 months (74% vs 68%) and at 12 months (57% vs 55%). Similarly, chemoimmunotherapy was associated with lower mortality compared to immunotherapy alone in the first 6 months after therapy initiation [**IPTW-adjusted Hazard Ratio (aHR) 0.74, 95% CI 0.61-0.90**] and higher mortality in patients who survived beyond 6 months [**aHR 1.24, 95% CI 1.04-1.48**]. In patients with PD-L1 score ≥90%, point estimates were similar but no statistically significant survival benefit was detected among chemoimmunotherapy recipients relative to immunotherapy, [6-month survival 77% vs 70%, ≤6-month **aHR 0.77, 95% CI 0.56-1.05**:12-month survival 62% vs 57%, >6-month **aHR 1.25, 95% CI 0.94-1.65**].

Conclusions: In a propensity score-weighted analysis of aNSCLC patients with PD-L1 score ≥50%, chemoimmunotherapy was associated with improved survival in the first six months, but worse survival after 6 months when compared to immunotherapy alone. In the PD-L1 ≥90 subgroup there was no significant difference in survival between chemoimmunotherapy and immunotherapy alone. Point estimates were similar although confidence intervals were broad due to the smaller sample size. Prospective randomized data or a larger observational dataset should confirm the utility of chemoimmunotherapy over immunotherapy alone in this subgroup.

Keywords: CHEMOIMMUNOTHERAPY, IMMUNOTHERAPY, Non-small cell lung cancer

EP08.01-064 Serum NY-ESO-1 and XAGE1 Antibodies Predict and Monitor Clinical Responses to Immune Checkpoint Therapy for NSCLC

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Introduction: Immune checkpoint (IC) therapy is the mainstay in the treatment of non-small-cell lung cancer (NSCLC). IC therapy prolonged overall survival (OS) as compared with conventional chemotherapy; however, long-term survival benefits from IC therapy were moderate and limited. IC chemo-combinations highly cost and have high discontinuation rates due to adverse events. A long-term OS of IC monotherapy is very similar to those of IC chemo-combinations. Presently, tumor PD-L1 expression levels/tumor proportion score (TPS) are used as predictive biomarkers of response to IC monotherapy, though the clinical validation and performance are modest. Therefore, precision IC therapy is urgently needed, and biomarkers monitoring response during IC therapy have been never found. We previously reported that serum antibodies (Ab) against NY-ESO-1 and XAGE1 of cancer-testis antigens (CTA) were potentially predictive biomarkers of clinical benefits from IC monotherapy and that the CTA Ab levels were positively correlated with tumor reduction rates in IC monotherapy. Thereafter, we newly developed an automated immunoassay system of HSCL in the measurement of serum CTA Ab, which were easily and rapidly measured by using 10 micro-litter of serum/plasma (Sakai Y, Clin Chim Acta 2021). The HISCL is a highly reproducible and reliable diagnostic system to specifically detect serum CTA Ab. Here, we retrospectively analyzed the relationships between CTA Ab and clinical benefits from IC monotherapy and monitored response during IC monotherapy by using HISCL.

Methods: Sera from 263 patients with advanced NSCLC were obtained before IC therapy, and the serum CTA Ab values in the patients and 175 controls were measured by HISCL. The CTA Ab in some of the patients were serially measured after IC therapy. Among them, 188 NSCLC patients received IC monotherapy (nivolumab, pembrolizumab, or atezolizumab) in first- and second-line or latter setting. Objective response was evaluable in 174 out of 188 patients, and TPS using 22C3 and 28-8 assay being in 148.

Results: Serum CTA Ab values were significantly higher in NSCLC (n=263; range 0-37,085 SU/mL) than those in non-malignant diseases and healthy controls (n=175; range 0-6.1 SU/mL). Five patients had both NY-ESO-1 and XAGE1 Ab. Overall positive rate of CTA Ab was 26% (68/263) as a cutoff value of 10 SU/mL, because NSCLC patients with ≥ 10 SU/mL had the longest OS with IC monotherapy among those at cutoff of 15 and 20 SU/mL. ORR was 36%, 50%, and 30% in overall, and CTA Ab-positive and -negative patients, respectively. During IC monotherapy, CTA Ab values correlated well with tumor burden/response. Particularly, OS with ≥ 10 SU/mL was the longest in second-line or later setting. In combinatory prediction with CTA Ab and TPS, NSCLC with CTA Ab ≥ 10 SU/mL and/or TPS ≥ 50% survived significantly longer than those with CTA Ab <10 SU/mL and/or TPS < 50% (p=0.012).

Conclusions: Our study suggests that CTA Ab in NSCLC is one of predictive biomarkers in response to IC monotherapy but also a novel monitoring marker of response. HSCL assay is a non-invasive and rapid diagnostic test in response prediction and monitoring of IC therapy.

Keywords: Immune checkpoint inhibitors, Biomarkers, Prediction

EP08.01-065 Prevalence of Non-driver Mutations and Characterization of Patients with Advanced or Metastatic Non-small Cell Lung Cancer

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Introduction: Non-driver mutations have been shown to impact survival outcomes in patients with advanced or metastatic non-small cell lung cancer (aNSCLC). However, real-world evidence describing this population is limited. We performed a descriptive analysis on the prevalence of non-driver mutations and the baseline characteristics of an aNSCLC cohort.

Methods: This retrospective cohort study analysed the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine aNSCLC clinico-genomic database (FH-FMI CGDB). The de-identified data originated from approximately 280 US cancer clinics (~800 sites of care). We selected aNSCLC patients who had initiated first-line (1L) treatment under routine care. A descriptive analysis of the sociodemographic and clinical characteristics of this population was performed. Prevalence of tumour non-driver mutations was estimated for the overall population and by diagnosis type.

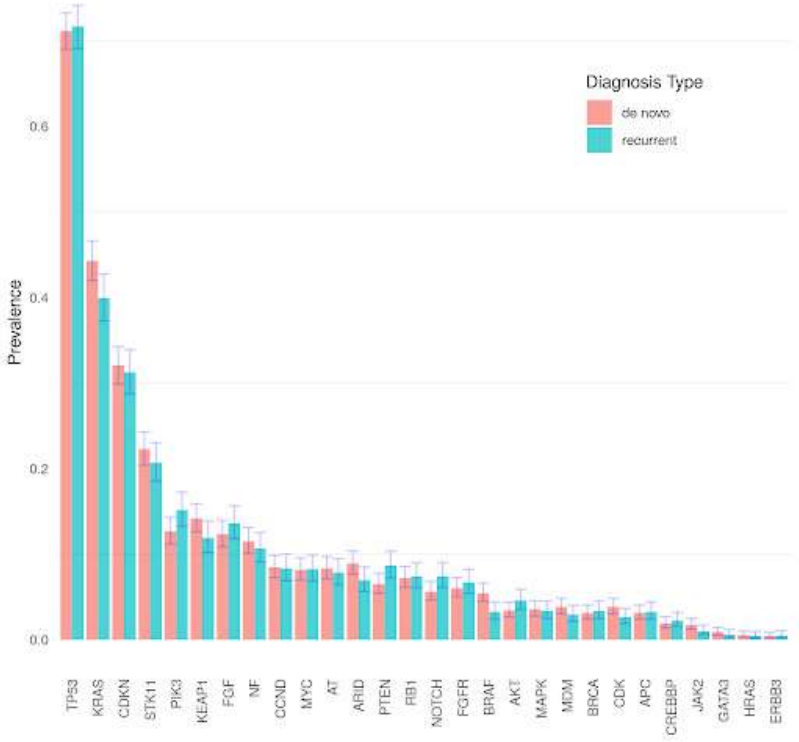
Results: In total, 10,795 patients were selected and 2,999 met inclusion criteria. Mean age was 67.9 years and 53% were men. Non-squamous was the most frequent histology (68%) (Table 1). More than 58% of patients had *de novo* diagnosis and 26.2% were PD-L1 negative. 22.9% of patients showed ECOG PS 0 and 95.1% a previous history of smoking. Overall, 185 mutations were detected in this population. Variants of the same mutation were grouped into 58 clusters. Of these, the most prevalent mutations were *TP53* (70%), *KRAS* (42%), *CDKN2A/B* (31%) and *STK11* (21%). When stratifying prevalence by status at diagnosis, no statistically significant differences between *de novo* and recurrent patients were observed (Figure 1).

Conclusions: To our knowledge, this is the largest real-world study describing the non-driver mutational profile of 1L aNSCLC patients. The mutation pattern of this cohort was overall in line with that reported in previous studies, except for a higher prevalence of *TP53* mutation which is commonly associated with squamous histology.

Table 1. Baseline characteristics of the population.

Variable	Category	Patients (n=2999)
Age at advanced diagnosis, n (%)	<65 years	1058 (35.3)
	≥65 years	1941 (64.7)
Histology, n (%)	Non-squamous CC	2029 (67.7)
	NSCLC - NOS	128 (4.3)
	Squamous CC	842 (28.1)
Smoking status, n (%)	History of smoking	2851 (95.1)
	No or unknown	148 (4.9)
Advanced diagnosis, n (%)	De novo	1752 (58.4)
	Recurrent	1247 (41.6)
ECOG PS, n (%)	0	687 (22.9)
	1	1150 (38.3)
	2	437 (14.6)
	≥3	117 (3.9)
	Unknown	608 (20.3)
PD-L1 status, n (%)	High (>50%)	817 (27.2)
	Low (1%-49%)	758 (25.3)
	Negative (0%)	786 (26.2)
	Unknown	111 (3.7)

Figure 1. Prevalence in selected mutations by diagnosis type.



Keywords: Advanced non-small cell lung cancer, non-driver mutations, prevalence

EP08.01-066 Assessing Immunotherapy in Real Life: Have We Transferred the Increase in Overall Survival in Stage IV NSCLC from Trials to Clinical Practice?

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Introduction: In recent years, immunotherapy (IO) clinical trials have improved overall survival (OS) for stage IV non-small cell lung cancer (NSCLC) without a driver mutation. However, it is necessary to check whether the results observed in the field of research are reproduced in real life.

Methods: We conducted a retrospective study selecting all patients with stage IV NSCLC without driver mutation treated at the Medical Oncology Department of Puerta de Hierro University Hospital (PDUH) between 2016 and 2020. Data cutoff: June 30, 2021. Our objective was to evaluate treatments for NSCLC as IO reaches clinical practice, with OS as the main outcome.

Results: 380 patients stage IV NSCLC at diagnosis were evaluated in PHUH, 319 without driver mutation. 234 received systemic treatment. IO was used in the 59% of patients (43% in 2016 and 70% in 2020). Median follow-up: 37.1 months.The median OS for patients treated with IO (any line) was 24 months (95% CI: 18 - 29.1), greater than the median OS observed in patients treated without IO, 5.7 months (95% CI: 4.4-7).These differences are probably due in part to the baseline characteristics of the groups described. However, in our study we observed that patients treated with IO in clinical practice obtained results similar to those described in clinical trials, with survival rates of 50.6% and 34.4% at 24 and 36 months, respectively.Despite possible selection bias, multivariate analysis adjusted for histology, stage, sex, age, ECOG, and Charlson comorbidity index shows a decreased risk of death with IO versus without, HR 0.30 (95% CI: 0.21 - 0.43). ;p<0.001). Stage IVB increases the risk of death, HR 2.08 (95% CI: 1.44 - 2.99; p<0.001) compared to stage IVA, since ECOG 2: HR 3.90 (95% CI : 2.15 - 7.08) and ECOG 3: HR 18.28 (95% CI: 8.24 - 40.57), each comparing with ECOG 0. Sex, age, histology or comorbidity were not associated with the risk of death.

Conclusions: Our study shows that IO reduced risk of death: HR 0.30 (95%CI: 0.21 - 0.43) in stage IV NSCLC, observing a median OS of 24 months (95%CI: 18 - 29,1) and a 36-month survival rate of 34.4%, suggesting that the use of IO has transferred the benefit observed in clinical trials to the general population. Real-world data studies are not designed for comparison of treatments, although our study assesses access to new treatments and the reproducibility of the efficacy of clinical trials.

Baseline characteristics and Overall Survival data				
	Immunotherapy	**No Immunotherapy**	**Total treated stage IV NSCLC**	**p**
Patients: n (%)	138 (59%)	96 (41%)	234	
Sex (%): male / female	63.7% / 36.2%	80.2% / 19.8%	70.5% / 29.5%	**0.007**
Age >=75 years	13.8%	14.6%	14.1%	0.860
ECOG 0-1	79.7%	46.9%	66.2%	**<0.001**
Stage IVA / IVB	39.9% / 60.1%	31.3% / 68.8%	36.3% / 63.7%	0.178
Deaths: n (%)	85 (61,6%)	86 (89,6%)	171 (73,1%)	**<0.001**
Overall Survival: Median (95%CI)	24 (18 – 29,1)	5,7 (4,4 - 7)	12,5 (9,9 – 16,8)	Log rank **<0.001**
Survival rate at:				
6 months	89.1%	47.1%	72.1%	
12 months	70.7%	20.9%	50.7%	
18 months	59.8%	12.6%	40.8%	
24 months	50.6%	7.2%	33.2%	
36 months	34.4%	7.2%	23.7%	

Keywords: Immunotherapy, Advanced disease, Real World Data

EP08.01-067 Rechallenging with PD-1 Inhibitors: Incidence and Management of Immune-Related Adverse Events in Metastatic NSCLC

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Introduction: PD-1 inhibitors are an integral part of treatment in metastatic (m)NSCLC. Immune-related adverse events (irAE) are reported to occur in approximately 30% of patients. However, rates of irAEs in real-world populations are incompletely characterized. Furthermore, there is a paucity of data on PD-1 inhibitor rechallenge and long-term survival benefit specific to NSCLC patients.

Methods: We conducted a single institution review of all mNSCLC patients who received at least one dose of PD-1 inhibitors between 2013-2021. Combination treatment with CTLA-4 inhibitors was excluded. All occurrences of irAEs were reviewed for grade (CTCAE v5) and management.

Results: 442 mNSCLC patients received at least one dose of PD-1 inhibitor: median age 66.2 years, 53% male and mean Charlson comorbidity index of 6.8 (SD 1.2). Median lines of treatment were 2 (1-11) and median duration of anti-PD-1 treatment was 3.3 months. The overall irAE incidence was 38%. Median time to development of first irAE from the start of immunotherapy was 2.7 months. The most common irAEs of any grade were dermatitis (10%), thyroiditis (9.7%), pneumonitis (8.6%) and arthritis (3.4%). 48 patients experienced ≥ 2 irAEs (11%). There were 13% of patients with grade ≥3 irAEs, with the most common being pneumonitis (3.4%), colitis (1.4%), cytopenias (1.4%) and dermatitis (1.4%). Among patients who developed irAEs (n=166), 37% required high dose steroids and 5% patients required additional immunomodulatory agents. Hospitalization for irAE management was necessary in 22%, and 80 patients (48%) had permanent discontinuation of therapy due to irAE. 86 patients (52%) had their PD-1 inhibitor continued, or were rechallenged, 11 of whom (13%) had grade ≥3 irAEs. Rechallenge was successful in 46% of patients but led to a recurrence of the same irAE (53%) or occurrence of a different irAE (1%). There were no treatment-related deaths associated with rechallenge. The overall median PFS from the time of first irAE is 6.0 months (95%CI 4.8-9.6) and by subgroups, 4.8 months if PD-1 inhibitor was continued, 6.0 months if rechallenged, or 8.4 months if permanently discontinued; p = 0.83. The median OS from the time of first irAE is 21.6 months (95%CI 15.6-34.8) and was similar if PD-1 inhibitor was continued (24.0 months), rechallenged (34.8 months) or permanently discontinued (14.4 months); p = 0.18.

Conclusions: This large population-based cohort demonstrated the incidence of irAE in 442 mNSCLC patients who received at least one dose of PD-1 inhibitor to be 38%, with 13% grade 3 and above. Rechallenging with PD-1 inhibitors is a controversial practice. We did not identify significant differences in clinical outcomes amongst patients who were rechallenged with PD-1 inhibitors after an irAE compared to those who discontinued therapy. Subset analyses of specific irAEs might provide further information on the benefits of PD-1 inhibitor rechallenge.

Keywords: immunotoxicity, NSCLC, PD-1 inhibitor

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-068 Going for the Ligand After a Stint with the Receptor: Can Switching Target From PD-1 to PD-L1 (Or Vice-Versa) Be Beneficial?

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Introduction: Immune checkpoint inhibitors (ICI) have transformed the standard of care of non-small cell lung cancer (NSCLC) without actionable mutations and can induce a sustained response in a cohort of patients. For those who progress on ICIs, treatment with cytotoxic chemotherapy or enrollment in clinical trials are ideal options. Frequently, patients are not candidates for either of these options due to performance status, comorbidities, or personal preference. Switching the checkpoint target from the receptor to ligand (or vice-versa) after progression or intolerance has theoretical advantage but has not been explored in clinical trials. We evaluated the efficacy of receiving a 2nd agent targeting the PD-1/PD-L1 axis (referred to as ICI in this abstract) with/without chemotherapy in NSCLC patients after progression or intolerance to the 1st ICI.

Methods: This is a single-center, IRB-approved retrospective analysis of NSCLC patients treated sequentially with PD-1 and PD-L1 inhibitors (or vice-versa) after progression or intolerance to the other from March 2015 to December 2021. Progression free survival (PFS) of 1st ICI (PFS1) was calculated from the start of immunotherapy to documented progression of disease (POD). PFS for 2nd ICI (PFS2) was calculated from the start of 2nd ICI to POD or death. Patients who were alive without POD or experienced an adverse event (AE) prior to POD were censored at last follow-up or time of AE, respectively. Median PFS2 was compared between groups stratified by a cutoff PFS1 of 4 months (m), smoking status, comorbid conditions, gender, and history of receiving chemotherapy as part of their NSCLC treatment at some point.

Results: 43 patients (51% female and 49% male) were included in the final analysis. 37/43 (86%) received 2nd ICI after progression on the 1st and 6/43 (13.9%) received 2nd ICI after experiencing an AE on the 1st. 2nd ICI was discontinued in 6/43 (13.9%) patients due to an AE and in 32/43 (74%) patients due to POD or death. Median PFS2 was 4.7m for the entire population (95% CI:2.3-9.1). Median overall survival was 23.5m (95% CI:16.1-38.9). Median PFS2 was similar for patients who had PFS1 of ≤4m or >4m (p=0.794). In addition, smoking status (p=0.741), pre-existing COPD (p=0.979), gender (p=0.213), and history of chemotherapy as part of the 1st ICI regimen (p=0.786) did not have a statistically significant influence on PFS2. For patients who continued the 2nd ICI past the first 3m without POD (n=22), median PFS2 was 13.9m (95% CI:6.8-36.2). For those patients who had an AE with the 1st ICI (n=6), PFS2 was 6.8m (95% CI:1.5-45.0).

Conclusions: Treatment with a 2nd ICI after failure on the 1st may provide benefit in NSCLC, with median PFS comparing favorably to single agent chemotherapy. Duration of PFS1, smoking status, sex, and comorbid conditions did not show significant correlation to PFS2. Patients who were alive without POD at 3m on 2nd ICI and those who had an AE with 1st ICI did particularly well with impressive PFS. Using a 2nd ICI should be considered for advanced NSCLC patients with limited treatment options.

Keywords: NSCLC, Immune checkpoint inhibitor, PD-1 and PD-L1

EP08.01-069 A Retrospective Study of Immune Checkpoints Rechallenge/ Retreatment in Metastatic NSCLC Progressing after Previous ICIs

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Introduction: Immune checkpoints (ICIs) targeting PD-1 or PD-L1 and CTLA-4 axis have demonstrated unprecedented clinical activity in thoracic tumours, becoming a crucial component of its therapeutic arsenal. ICIs in monotherapy or associated with chemotherapy (CHT) or the combination of anti-CTLA-4 and anti-PD-1 agents are approved as first line in NSCLC patients (pts) without an actionable oncogenic driver. The role of ICIs in second or later lines for metastatic NSCLC pts progressing after previous ICIs is yet to be determined. Data from ICIs rechallenge/retreatment are scarce, in the context of heterogeneous series, and often report on metastatic NSCLC pts having discontinued ICIs for toxicity or based on clinical decision, and not for progression disease. A long period of withdrawal of all oncological treatment following the discontinuation of ICI might also represent a distinct subgroup of patients for a challenge assessment. Here, we describe a study that will retroactively assess data from metastatic NSCLC pts having previously progressed on ICIs that underwent rechallenge/retreatment with ICIs.

Methods: This retrospective cohort study will include all pts with advanced/metastatic NSCLC treated at the Lausanne University Hospital with ICIs as monotherapy or in combination with CHT or dual ICIs having been rechallenged/retreated with ICIs after progression. They will be compared to patients treated according to ESMO/NCCN guidelines after progression on ICIs, between January 2016 and March 2022. Patients with central nervous system metastasis will be included. Rechallenge/retreatment with experimental ICIs will be excluded, as well as, neuro-endocrine carcinomas and previous discontinuation for toxicity or clinical decision. Clinical data from medical records will be entered into an electronic case report form (eCRF). Source data verification will be performed by medical oncologist for all clinical data. Clinical, laboratory, pathologic and radiologic data will be extracted directly from the hospital electronic health records. The primary objective of the study is to evaluate overall survival (OS) in these pts. The secondary objectives include evaluation of progression-free-survival (PFS) and 2nd PFS, response rates, duration of response, time to progression and toxicity. The study will assess the correlation between outcome and clinical variables such as sex, age, smoking history, genetic and immune parameters. Descriptive statistics will be computed in R using built-in functions and Kaplan-Meier time-to-event analysis for the OS and PFS will be performed with the survival package. With median follow-up time of 6 years, this study will allow for a long-haul appraisal of retreatment/rechallenge with ICIs in patients with metastatic NSCLC having previously progressed on ICIs.

Keywords: Rechallenge, Immune checkpoints, NSCLC progressing on ICI

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-070 Safety and Efficacy of Sitravatinib + Tislelizumab in Patients with PD-L1+, Locally Advanced/Metastatic, Squamous NSCLC

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Introduction: Patients with programmed death-ligand 1 positive (PD-L1+), locally advanced or metastatic, squamous non-small cell lung cancer (NSCLC) have a poor prognosis and more effective treatments with better tolerability profiles are needed. Sitravatinib, a selective tyrosine kinase inhibitor, reduces the number of myeloid-derived suppressor cells and regulatory T cells, which promotes expansion and migration of antitumor cytotoxic T cells, and increases the ratio of M1/M2-polarized macrophages. Tislelizumab, an anti-programmed cell death protein 1 (PD-1) antibody engineered to minimize binding to FcγR on macrophages, has shown clinical activity in patients with advanced solid tumors, including NSCLC. This Phase 1b study assessed safety, tolerability, and antitumor activity of sitravatinib and tislelizumab in advanced solid tumors (NCT03666143). We present results from patients with PD-L1+, squamous NSCLC.

Methods: This was an open-label, non-randomized study. Eligible patients had PD-L1+, locally advanced or metastatic, squamous NSCLC without prior systemic treatment in the metastatic setting and without prior exposure to immunotherapy, including anti-PD-1/PD-L1, anti-CTLA-4, anti-OX40 and anti-CD137. Patients with a documented *EGFR* mutation, *ALK/ROS1* rearrangement, or *BRAF* mutation were not eligible. Patients received sitravatinib 120 mg orally once daily plus tislelizumab 200 mg intravenously every three weeks until unacceptable toxicity, withdrawal, or death. The primary endpoint was safety/tolerability. Secondary and exploratory endpoints included investigator-assessed objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and PD-L1 expression and the association with clinical benefit. Tumor response was assessed using RECIST v1.1. PD-L1+ was defined as PD-L1 staining on ≥ 1% of tumor cells (VENTANA SP263 immunohistochemistry assay).

Results: Between May 12, 2020 and February 10, 2021, 24 patients were enrolled. All patients were included in the safety analysis set, and 23 patients in the efficacy evaluable analysis set. The median age was 65.0 years (range: 56-71), and 91.7% of patients were male. Median study follow-up was 9.5 months (range: 0.4-16.2). At the data cut-off (November 8, 2021) treatment-emergent adverse events (TEAEs) of any Grade/≥ Grade 3 were reported in 95.8%/66.7% of patients. Serious TEAEs were observed in 50.0%, and the most common ≥ Grade 3 TEAE was hypertension (16.7%). A total of two TEAEs led to death, death and pneumonia and were not considered to be treatment related. In total, 70.8%/41.7% patients required dose modification of sitravatinib/tislelizumab due to TEAEs, respectively. Treatment-related AEs (TRAEs) of any Grade/≥ Grade 3, were observed in 91.7%/62.5% of patients. Serious TRAEs were reported in 37.5% of patients, and the most common ≥ Grade 3 TRAE was hypertension (16.7%). Confirmed ORR was 30.4% (95% confidence interval [CI]: 13.2, 52.9), with all seven patients achieving partial response. DCR was 78.3% (95% CI: 56.3, 92.5), median PFS was 5.4 months (95% CI: 2.8, 8.6), and median OS was not reached (95% CI: 6.7, not estimable).

Conclusions: Sitravatinib plus tislelizumab demonstrated a manageable safety and tolerability profile as well as antitumor activity in patients with PD-L1+, locally advanced or metastatic squamous NSCLC who had not received prior systemic treatment in the metastatic setting.

Keywords: sitravatinib, tislelizumab, NSCLC

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-071 Safety and Efficacy of Sitravatinib + Tislelizumab in Patients with PD-L1+, Locally Advanced/Metastatic, Non-Squamous NSCLC

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Introduction: Patients with programmed death-ligand 1 positive (PD-L1+), locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) have a poor prognosis and treatment options are limited. Sitravatinib, a selective tyrosine kinase inhibitor, reduces the number of myeloid-derived suppressor cells and regulatory T cells, promotes the expansion and migration of antitumor cytotoxic T cells, and increases the ratio of M1/M2-polarized macrophages. Tislelizumab, an anti-programmed cell death protein 1 (PD-1) antibody engineered to minimize binding to FcγR on macrophages, has shown clinical activity in patients with advanced solid tumors, including NSCLC. This Phase 1b study assessed safety, tolerability, and antitumor activity of sitravatinib and tislelizumab in advanced solid tumors (NCT03666143). We report results from patients with PD-L1+, non-squamous NSCLC.

Methods: This was an open-label, non-randomized study. Eligible patients had PD-L1+, locally advanced or metastatic, non-squamous NSCLC without prior systemic treatment in the metastatic setting and without prior exposure to immunotherapy (anti-PD-1/PD-L1, anti-CTLA-4, anti-OX40 and anti-CD137). Patients were required to have a documented wild-type *EGFR* status; patients with *ALK/ROS1* rearrangements or *BRAF* mutations were ineligible. Patients received sitravatinib 120 mg orally once daily and tislelizumab 200 mg intravenously every three weeks until unacceptable toxicity, withdrawal, or death. The primary endpoint was safety/tolerability. Secondary and exploratory endpoints included investigator-assessed objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and PD-L1 expression and the association with clinical benefit. Tumor response was assessed using RECIST v1.1. PD-L1+ was defined as PD-L1 staining on ≥ 1% of tumor cells (VENTANA SP263 immunohistochemistry assay).

Results: Between November 7, 2019 and December 23, 2020, 22 patients were enrolled. All patients were included in the safety analysis set, and 21 patients in the efficacy evaluable analysis set. The median age was 60.5 years (range: 41-78), and 68.2% of patients were male. Median study follow-up was 11.8 months (range: 0.9-17.9). At the data cut-off (November 8, 2021) treatment-emergent adverse events (TEAEs) of any Grade/≥ Grade 3 were reported in 100.0%/59.1% of patients. Serious TEAEs were observed in 45.5%, and the most common ≥ Grade 3 TEAE was hypokalemia (18.2%). A total of two TEAEs, death (death unexplained) and multiple organ dysfunction syndrome, led to death and were considered treatment related. In total, 72.7%/59.1% patients required dose modification of sitravatinib/tislelizumab due to TEAEs, respectively. Treatment-related AEs (TRAEs) of any Grade/≥ Grade 3, were observed in 95.5%/50.0% of patients. Serious TRAEs were reported in 36.4% of patients, and the most common ≥ Grade 3 TRAE was hypertension (13.6%). Confirmed ORR was 57.1% (95% confidence interval [CI]: 34.0, 78.2) with all 12 patients achieving partial response. DCR was 85.7% (95% CI: 63.7, 97.0), median PFS was 11.1 months (95% CI: 5.5, not estimable [NE]), and median OS was 17.4 months (95% CI: 11.8, NE).

Conclusions: Sitravatinib plus tislelizumab showed a manageable safety and tolerability profile and demonstrated antitumor activity in patients with PD-L1+, locally advanced or metastatic non-squamous NSCLC who had not received prior systemic treatment in the metastatic setting.

Keywords: sitravatinib, tislelizumab, NSCLC

EP08.01-072 Clinical Value of Patras Immunotherapy Score (PIOS) Formula in Patients with Advanced NSCLC Treated with Immunotherapy/Chemotherapy

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Introduction: Clinical course of patients with advanced non-small cell lung cancer (aNSCLC) has tremendously changed the last decade due to immune checkpoint inhibitors (ICIs). However, clinical useful biomarkers remain an unmet need. Recently, our group has proposed a new score, Patras Immunotherapy Score (PIOS), based on the results of aNSCLC patients treated with ICIs monotherapy. The objective of the current study was to assess the clinical significance of PIOS formula in aNSCLC patients treated with combination of immunotherapy with chemotherapy.

Methods: PIOS formula is derived by combining the following non-interventional clinical parameters, Performance Status (PS), Body Mass Index (BMI), age and Line Of Treatment (LOT) and it is calculated as PIOS = (PS×BMI)/(LOT×AGE). In the current study, 159 aNSCLC patients, treated with combination of immunotherapy with chemotherapy, were retrospectively selected, blindly to the clinical outcome, and enrolled. In addition, a second group with 444 aNSCLC patients, treated with chemotherapy alone, were also retrospectively enrolled. The primary endpoint of this study was to evaluate the prognostic value of PIOS in terms of progression free survival (PFS) and overall survival (OS).

Results: Higher PIOS score was associated with longer PFS compared to patients with lower PIOS score (HR 0.575, 95% CI 0.364-0.908, p=0.016), while this association persisted upon multivariate analysis for PFS, adjusted for PD-L1 (HR 0.561, 95% CI 0.352-0.893, p=0.015). In addition, PIOS score was also related to prognosis (p=0.003). The median OS for the favorable group was 1067 days compared to 528 days for the unfavorable group with low PIOS score (HR 0.487, 95% CI 0.302-0.787, p<0.001) at univariate analysis. This association remained statistically significant (HR 0.468, 95% CI 0.286-0.764, p=0.002) after adjusting for PD-L1 expression. Specificity of PIOS score was also confirmed in the group of patients (n=444) with metastatic disease who had been treated with chemotherapy alone, since in no prognostic significance for PIOS was observed.

Conclusions: This study confirmed the prognostic value as well as the specificity of PIOS model in aNSCLC patients treated with immunotherapy/chemotherapy combination.

Keywords: PIOS, NSCLC, IMMUNOTHERAPY

EP08.01-073 AdvanTIG-105: Phase 1b Dose-Expansion Study of Ociperlimab plus Tislelizumab in Patients with Metastatic NSCLC

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Introduction: T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) inhibitor plus an anti-programmed cell death protein 1 (PD-1) antibody is a promising combination and shows potent efficacy in non-small cell lung cancer (NSCLC). Ociperlimab is a humanized IgG1 monoclonal antibody (mAb) designed to bind to Fc-intact TIGIT with high affinity and specificity. Tislelizumab is an anti-PD-1 mAb approved for the treatment of NSCLC in China. AdvanTIG-105 is a Phase 1/1b open-label study designed to assess the safety and preliminary antitumor activity of ociperlimab plus tislelizumab in patients with advanced, metastatic unresectable solid tumors (NCT04047862). In the dose-escalation part, ociperlimab plus tislelizumab was well tolerated, preliminary efficacy was observed, and the recommended Phase 2 dose of ociperlimab 900 mg intravenously (IV) every three weeks (Q3W) plus tislelizumab 200 mg IV Q3W was established. Here we report results from the dose-expansion part (Cohort 3) of the AdvanTIG-105 study.

Methods: Treatment-naïve adult patients with histologically or cytologically confirmed metastatic squamous or non-squamous NSCLC with programmed death-ligand 1 (PD-L1) positive (tumor cell [TC] ≥ 1% by VENTANA PD-L1 [SP263] Assay) and non-squamous patients with *EGFR/ALK/ROS-1* wild-type tumors were enrolled. Patients received ociperlimab 900 mg IV plus tislelizumab 200 mg IV Q3W until disease progression, intolerable toxicity, or withdrawal of consent. The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included investigator-assessed duration of response (DoR), disease control rate (DCR) per RECIST v1.1, and safety. The association between PD-L1 expression and efficacy was also analyzed.

Results: As of December 27, 2021, 36 patients, with a median age of 65.0 years (range 46-81), were enrolled. The median study follow-up time was 15.9 weeks (range 6.1-47.6). All 36 patients were efficacy evaluable; the confirmed ORR was 22.2% (95% confidence interval [CI]: 10.1, 39.2) and the unconfirmed ORR was 44.4% (95% CI: 27.9, 61.9). The DCR was 88.9% (95% CI: 73.9, 96.9). The confirmed ORR in PD-L1 TC ≥ 50% (n=13) was 23.1%, while the confirmed ORR in PD-L1 TC 1-49% (n=23) was 21.7%. The unconfirmed ORR in PD-L1 TC ≥ 50% was 53.8%, while the unconfirmed ORR in PD-L1 TC 1-49% was 39.1%. In total, 33 patients (91.7%) experienced ≥ 1 treatment-emergent adverse event (TEAE), and 10 patients (27.8%) had ≥ Grade 3 TEAEs. Serious TEAEs occurred in eight patients (22.2%). The most common TEAEs were pyrexia (30.6%), pruritus (22.2%), and nausea (19.4%). TEAEs leading to treatment discontinuation occurred in two patients (5.6%). TEAEs leading to death occurred in one patient (2.8%), but the event (cerebral infarction) was not related to the study drugs.

Conclusions: The treatment combination of ociperlimab 900 mg plus tislelizumab 200 mg IV Q3W was well tolerated and showed antitumor activity in patients with treatment-naïve metastatic squamous or non-squamous NSCLC with PD-L1 positive tumors (TC ≥ 1%).

Keywords: TIGIT antibody, PD-1 inhibitor, metastatic NSCLC

EP08.01-074 'Long Responders' Compared to 'Non-Responders' to a First Line Immune Checkpoint Inhibitor in Incurable Non-Small Cell Lung Cancer

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Introduction: KEYNOTE-024 compared single agent pembrolizumab to platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC) with PDL1 >50%, illustrating improved progression free survival (PFS) and overall survival (OS) for pembrolizumab. The objective of this study is to identify the proportion of real-world NSCLC patients who have a long-term benefit with first line pembrolizumab and examine their characteristics compared to patients who show limited benefit to the drug.

Methods: A retrospective study of stage IV NSCLC patients referred to BC Cancer between 2018-2021 with PDL1 >50% who received first line pembrolizumab was undertaken. "Long responders" were defined as patients who received at least 35 cycles of pembrolizumab or >2 years of treatment. "Non-responders" were defined as those having at least 2 cycles of pembrolizumab but less than 3 months of treatment. Patient demographics, Eastern Cooperative Oncology Group(ECOG) performance status (PS), staging, treatment, and survival data were collected retrospectively. NGS assay included multiple oncogenes and tumor suppressor genes for solid tumors. Baseline characteristics were compared using descriptive statistics including the Chi squared and Mann-Whitney U test. Kaplan-Meier curves were used to calculate OS.

Results: A total of 718 patients received first line pembrolizumab. Median number of cycles received was 4 within the full population. Long responder status was seen in 49 (7%) of patients and non-responder in 204 (28%), baseline characteristics are found in Table 1. Long versus non responders were more likely to be female (65% versus 48%, p=0.025) and non-squamous histology (90% versus 78%, p=0.049). Mutations were found in 40% of long responders, most common *KRAS* mutation G12C (n=8) and G12A (n=4), compared to 36% of non-responders, G12C (n=26) and G12V (n=10). Mean OS was 52.9 months in long responders compared to 16.7 months in non-responders. At time of data analysis, 48 patients remained on pembrolizumab.

Conclusions: In our real-world NSCLC population, only 7% of NSCLC patients with PDL1 >50% received 35 cycles or 2 years of pembrolizumab while 28% of the population received less than 3 months of treatment suggesting limited benefit. Long responders were more likely to be female and have non-squamous histology compared to non-responders. Improved understanding of patient characteristics who might receive long term benefit from first line immune checkpoint inhibitors will allow us to better select treatment.

Table 1: Baseline characteristics of patients with incurable NSCLC with PDL1 ≥50% classified as "non-responders" or "long responders" to pembrolizumab.

	Non-Responders (Minimum 2 cycles and less than 3 months of treatment) (n=204)	Long Responders (Minimum 35 cycles or greater than 2 years of treatment) (n=49)	p-value
Age (mean), years	69.4	69.2	0.852
Sex			
Male	105 (52%)	17 (35%)	
Female	99 (48%)	32 (65%)	**0.025**
Histology			
Non-Squamous	160 (78%)	44 (90%)	
Squamous	44 (22%)	5 (10%)	**0.049**
Smoking Status			
Never	19 (9%)	2 (4%)	
Former	144 (71%)	33 (69%)	
Active	36 (18%)	12 (25%)	
Unknown	5 (3%)	1 (2%)	0.498
Smoking years (median)	35	46	0.076
ECOG PS			
0-1	102 (50%)	29 (60%)	
≥2	99 (49%)	18 (38%)	
Unknown	3 (1%)	1 (2%)	0.383
CNS Metastases	20 (10%)	4 (8%)	0.486
Mutation			0.409
KRAS	50 (29%)	16 (33%)	
BRAF	11 (6%)	0	
KRAS and BRAF	2 (1%)	2 (5%)	
Other	0	1 (2%)	

Keywords: immune checkpoint inhibitor, treatment duration, non-small cell lung cancer

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-075 Combination of Baseline Disease and Smoking Pack-Years Can Guide The 1st-line Treatment Decision in Advanced NSCLC with High PD-L1 Expression

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Introduction: KN024 showed pembrolizumab improved survival compared to platinum doublet chemotherapy (PDC) in 1st-line setting for advanced NSCLC with PDL1≥50%. KN189/KN407 demonstrated pembrolizumab/PDC in advanced NSCLC achieved superior 12-month survival compared with PDC. In patients with PDL1≥50% cross 3 trials, objective response rate with pembrolizumab in KN024 was 45% compared to 60% with pembrolizumab/PDP in KN189/407. The clinical question is: can we distinguish this 45% of patients who are best treated with pembrolizumab alone, and who need additional PDC? Currently, there are no biomarkers or clinicopathological features to distinguish this population.

The objective of this study is to identify baseline clinical factors that predict response to pembrolizumab in advanced NSCLC with PDL1≥50%, hence can serve as a decision-making tool in choosing the first-line treatment for this cohort.

Methods: We retrospectively identified 138 NSCLC patients with stage III/IV, PDL1≥50%, no EGFR/ALK aberration, and received 1st-line pembrolizumab. All had CT at baseline and 1st follow-up, 9~12 weeks after commencing pembrolizumab. Response was assessed using RECIST 1.1 standard definitions ("disease control" vs. "progression"). Baseline disease burden was quantified as the number of organs with metastases on baseline CT. Multivariate logistic regression was used to identify predictive baseline variables and categorize patients into "disease control" or "progression" based on predicted probabilities, and Time-to-Progression was compared by Kaplan-Meier plot.

Results: Ninety-two versus 46 patients were in "Disease Control" versus "Progression" group. Patients with >35 pack-years smoking and low baseline disease burden were more likely to achieve disease control with 1st-line pembrolizumab.

Conclusions: Our data suggest that advanced NSCLC patients with high PD-L1 expression can be effectively treated with single-agent pembrolizumab if they have low disease burden at baseline and a heavy smoking history of > 35 pack years. Otherwise, patients may need additional PDC. This may become an important decision-making tool to guide therapy.

Table 1. Bivariate Descriptive of Baseline Factors for "Disease Control" and "Disease Progression" groups; and Multivariate Logistical Regression to Identify the Predictive Factors

Baseline patient's clinical and CT data		Bivariate Descriptive		Multivariate logistic regression model
		Disease Control	Disease Progression	Adjusted Odds Ratio for "Disease Control" (95%CI)
Gender [n (row %)]	Female	52 (71)	21 (29)	[ref] 1.00
	Male	40(62)	25 (38)	0.52 (0.22, 1.23)
Age, median (Q1, Q3)		73 (69, 78)	72 (65, 77)	1.79 (0.93, 3.59)[1]
smoking status & packyears[2] [n (row %)]	CS/EX & >35	46 (81)	11 (19) **	[ref] 1.00
	CS/EX & ≤35	39 (60)	26 (40) **	0.35 (0.14, 0.87) *
	Never smoker	2 (7)	5 (63) **	0.04 (0.004, 0.30) **
ECOG[3] [n (row %)]	0-1	61 (75)	20 (25) *	[ref] 1.00
	≥ 2	29 (55)	24 (45) *	0.49 (0.20, 1.16)
Tumor histology [n (row %)]	Non-squamous	80 (69)	36 (31)	na
	squamous	10 (53)	9 (47)	
	NOS	3 (67)	1 (33)	
Baseline CT data, median (Q1, Q3)	Lung tumor (D_{max}, mm)	35 (24, 47)	38 (24.5, 51.5)	na
	Disease Burden: No. of organs with metastasis	3 (2, 3.25)	3 (2.25, 4.75) **	0.65 (0.47, 0.86) **

[1]. The Adjusted Odds ratio is for per 10-year increment in age.
[2]. Nine individuals with unknown smoking status & packyears are not shown in the table.
[3]. Four individuals with unknown status in ECOG are not shown in the table.
Significance levels: * 0.01<p<0.05; ** p<0.01

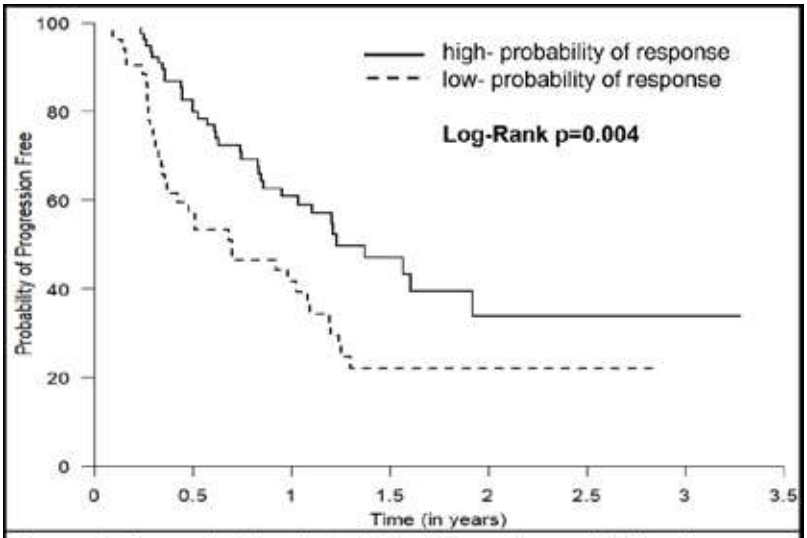

Figure 1. Progression-Free-Survival for high- vs. low-probability of response. Multivariate logistic model (using: age, gender, smoking status & packyear, ECOG, and No. of organs with metastasis) was used to categorize patients into two groups based on the predicted probability of response (i.e., disease control) (high: ≥0.67 vs low: <0.67). The time-to-progress is significantly different between the two groups.

Keywords: Immunotherapy, prediction, radiology

EP08.01-076 KEYNOTE B36: A Pilot Study of First-line Tumor Treating Fields (150 kHz) Plus Pembrolizumab for Advanced or Metastatic Non-small Cell Lung Cancer

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Introduction: Tumor Treating Fields (TTFields) are a locoregional, anti-mitotic treatment modality approved for glioblastoma and unresectable malignant pleural mesothelioma. Phase 1/2 data of TTFields (150 kHz) plus chemotherapy in recurrent non-small cell lung cancer (NSCLC) were promising and provided rationale for further investigation. The LUNAR (NCT02973789) phase 3 study, comparing TTFields plus docetaxel or immune checkpoint inhibitors (ICI) vs docetaxel or ICI alone in patients with stage IV NSCLC following platinum failure is ongoing. Preclinical data have shown that TTFields induce immunogenic cell death and enhance the efficacy of PD-1 inhibitors, providing rationale for investigation of this combination in a clinical setting.

Methods: KEYNOTE B36 (NCT04892472) is a multicenter, single arm, phase 2 open-label study designed to evaluate the safety and efficacy of TTFields (150 kHz) plus pembrolizumab for first-line treatment of advanced NSCLC. Patients (≥ 22 years of age) with an Eastern Cooperative Oncology Group performance status of 0-1 and treatment-naïve advanced or metastatic intrathoracic, PD-L1 positive (tumor proportion score [TPS] ≥ 1%) NSCLC are eligible. Patients with epidermal growth factor receptor-sensitizing mutations or anaplastic lymphoma kinase translocation-positive NSCLC are ineligible. Patients will be stratified by PD-L1 expression (TPS ≥ 50% vs TPS 1-49%) to receive TTFields (150 kHz) ≥ 18 h/day, using the NovoTTF-200T System with pembrolizumab 200 mg intravenously every 3 weeks, until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Follow-up visits and computerized tomography (CT) scans of the chest, abdomen and pelvis will be carried out every 3 weeks and 9 weeks, respectively. Post-disease progression follow-up visits will be conducted every month until death. The primary endpoint is objective response rate (ORR; per RECIST v1.1). Secondary endpoints include overall survival (OS), progression-free survival (PFS), PFS at 6 months, 1-year survival rate, duration of response, disease control rate, and safety (per Common Terminology Criteria for Adverse Events v5.0). ORR, OS and PFS will also be assessed in patients with TPS ≥ 1-49% and ≥ 50% as secondary endpoints. A sample size of N = 66 will be required to achieve a power of 80% to detect an ORR of 40% at a 1-sided alpha level of 0.1, using 1 sample exact test for proportion, and considering a loss to follow-up of < 10%. Recruitment is ongoing, and a planned interim analysis will take place after 15 patients with ≥ 1 follow-up CT scan have been enrolled.

Keywords: NSCLC, TTFields, Pembrolizumab

EP08.01-077 Predicting Response to Checkpoint Inhibitors Using Complex Molecular Characteristics and Immunoprofiling in Patients with NSCLC

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Introduction: Despite the wide use of immunotherapy in the treatment of solid tumours, it is effective only in 20 - 40 % of patients according to histopathological type. The aim of our project is to predict response to immunotherapy based on a comprehensive analysis of the tumour, its microenvironment, and the host. To date, we have prospectively enrolled 70 patients with advanced or metastatic solid tumours who were treated with anti-PD-1 / anti-PDL-1 antibodies. Here we present preliminary results from a subanalysis of 23 patients with NSCLC.

Methods: We performed complex molecular characterization of the tumour and immunoprofiling of the patient's peripheral blood. Tumour tissue is assessed by IHC staining for different subpopulations of immune cells (CD3 +, CD8 +, CD20 +, CD68 +, FoxP3 +) and markers (PD-L1, PD1, IDO1, LAG3, TGFbeta, MMR proteins). TMB is evaluated by whole-exome sequencing. Furthermore, complex genomic sequencing is performed. We study descriptive immunoprofiling of baseline immune regulators and effectors within peripheral blood cells and their dynamics during immunotherapy.

Results: Of 23 included patients with NSCLC, 16 and 7 patients were diagnosed with adenocarcinoma squamous cell carcinoma, respectively. The median age in this group was 67 years, and 19 patients were men. The median progression-free survival was 8,0 months (95% CI 5,1 to 13,7), and the median overall survival was 11,5 months (95% CI 9,3 to 15,2). According to our preliminary results from IHC staining of tumour tissue in patients with lung cancer TGFbeta immune cell (IC) negativity (HR 0.23, P = 0.048), FOXP3 nuclear negativity (HR 0.26, P = 0.038), CD 8+ stromal negativity (HR 0.19, P = 0.23), CD3 intraepithelial negativity (HR 0.12, P = 0,011) were associated with prolonged survival.

Conclusions: IHC staining could be used as a biomarker to predict response to immunotherapy. However, our results suggest that biomarkers appear to be specific for different tumour types, as these results were specific for NSCLC.

Keywords: Immunotherapy, Predictors, Metastatic NSCLC

EP08.01-078 Clinical Outcomes in Metastatic Non-small Cell Lung Cancer Harboring BRAF Mutations Treated with Immune Checkpoint Inhibitors

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Introduction: Non-small cell lung cancer (NSCLC) with actionable alterations treated with immune checkpoint inhibitors (ICI) have usually poor clinical outcomes. BRAF mutation have been identified in about 4% of NSCLC and targeted therapy combinations have shown little efficacy in this population. IMMUNOTARGET registry aimed to address the efficacy of ICI in oncogenic addicted NSCLC, but characterization of BRAF tumors treated with ICI are still scarce.

Methods: Thirty-three patients (pts) with BRAF-mutated NSCLC were retrospectively reviewed between 2015 and 2021 at our institution. Clinical outcomes were analyzed using RECIST 1.1 and medical charts. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints were objective response rate (ORR) and subgroup analysis according to BRAF type of mutation (V600E vs. other pathogenic mutation), programmed cell-ligand 1 (PD-L1) status (<1% vs. >1%) and line of ICI therapy (first, second, third or beyond). Statistical analysis was obtained using R 1.1.

Results: Median OS of the whole cohort was 13.2 months (95% CI 7.9-31.6). Those pts harboring BRAF V600E mutation (n=10) presented a median OS of 6.6 months (95% CI 1.8-13.0) compared to those with a non-BRAF V600E mutation (n=22) (29.9 months, [95%CI 12.1-42.6]). Among pts who received ICI (N=16 [48.5%]) median age was 68 years (range 51-83), all had adenocarcinoma and were current/former smokers, two pts had V600E BRAF mutation and six (37.5%) were programmed death-ligand 1 (PD-L1) positive. ICI therapy was administered as first line in five pts, six in second line and five in third or beyond. One patient received targeted therapy (vemurafenib) against V600E mutation in a subsequent line after ICI. Median PFS for ICI treated pts was 11.6 months (95%CI 3.8-63.2), median OS was (95%CI 29.3-76.6). ORR was 25% (4 partial responses and any complete response). Five pts (31.6%) achieved disease stabilization for six months of more. Median PFS in V600E pts were 10.9 months (95%CI 10.9-24.8) vs. 14.0 (95%CI 3.6-63.2) in non-V600E pts, meanwhile median OS was13.0 (95%CI 13.0-32) and 40.3 (95%CI 29.3-76.6), respectively. In PD-L1 negative pts, median PFS was 10.9 months (95%CI 3.6-13) compared to 14 months (95%CI 3.6-63.2) in PD-L1 expressors pts, meanwhile median OS was 29.8 months (95%CI 13.0-93.9) and 40.3 (95%CI 12.6-132.4), respectively (p=0.3). Median PFS among pts who received ICI in firs line was 24.8 months (95%CI 9.7-NA) vs. 14 months (95%CI 3.6-NA) in second line and 5.4 months (95%CI 3.6-63.2) in third line or beyond.

Conclusions: ICI may have efficacy for BRAF addicted NSCLC. In our cohort, the sample of BRAF V600E mutated pts was too little to make a conclusion about this subgroup. PFS and OS were both longer in PD-L1 positive pts. Earlier ICI therapy was associated with better PFS. However, the lack of a BRAF wild type as a control group is possibly a limitation.

Keywords: BRAF mutation, Immunotherapy, NSCLC

EP08.01-079 Long Term Use of Immune Checkpoint Inhibitors in Patients with Non-Small Cell Lung Cancer (NSCLC) and Abnormal Marrow Pathology: A Case Series

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Introduction: Immune Checkpoint Inhibitors (ICIs) are part of standard NSCLC therapy for adjuvant, locally advanced and metastatic patients. ICI's are generally safe but can be associated with immune-related adverse events (irAEs). While most toxicities tend to be acute, data show that long term use of ICIs can cause toxicity as well.[1]Additionally, ICI's can be associated with hematologic toxicity, although rare.[2] One study of nearly 1000 patients showed a 0.5% incidence of hematologic irAE in the setting of PD-1/PD-L1 inhibitor use.[3] Here we report a series of three patients with NSCLC who were on ICI's for more than one year and subsequently developed peripheral blood cytopenia with evidence of bone marrow effect.

Methods: We performed a retrospective chart review of three patients with a diagnosis of metastatic NSCLC who received immunotherapy and were found to have subsequent bone marrow dysfunction. We analyzed total duration of immunotherapy, hematologic immune-related adverse events, bone marrow biopsy results, and treatments received.

Results: Patient 1 is a 62-year-old Asian female with stage IIIb PDL-negative NSCLC (adenocarcinoma). She received Pembrolizumab/Bevacizumab for five months. Due to progression, she was switched to Nivolumab on which she remained for 23 months. She developed thrombocytopenia two months after the last dose of Nivolumab. The platelet count nadir was 10. Bone marrow biopsy showed a hypocellular marrow without infiltrative process. Patient 2 is a 70-year-old white female with Stage IV PDL+ NSCLC (squamous cell). She received Durvalumab for 13 months. Due to progression, she was switched to Carboplatin/Paclitaxel/Pembrolizumab for two months, followed by Pembrolizumab maintenance for 25 months. 22 months into maintenance therapy, she developed neutropenia with absolute neutrophil count 800, hemoglobin 10, platelet count 131. Bone marrow biopsy showed myelodysplastic syndrome and excessive blasts, for which she was started on Azacitidine. Patient 3 is a 69-year-old white male with Stage III PDL+ NSCLC (squamous cell). He received Durvalumab for 12 months with clinical response. 12 months into treatment, he developed bi-cytopenia with white blood cell count of 2.5, hemoglobin 12.5, and treatment was stopped. Two months after last dose, he had pancytopenia with nadir white blood cell count 1.4, hemoglobin 9, and platelet count 98. Bone marrow biopsy nine months after last dose of immunotherapy showed 4% monoclonal plasma cell population and decreased granulocytosis. He was treated with six doses of Pegfilgrastim.

Conclusions: This series demonstrated an association between long-term immunotherapy and bone marrow dysfunction. Further retrospective and prospective analysis is required to determine a causative relationship between immunotherapy and hematologic adverse events.

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Keywords: Immunotherapy, Bone Marrow Toxicity, NSCLC

EP08.01-080 Tislelizumab Plus Chemotherapy as First-Line Treatment for Advanced NSCLC in Patients Aged ≥ 70

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Introduction: Although ICIs combined with platinum-based chemotherapy have become the standard first-line treatment for advanced NSCLC, elderly pts especially aged ≥ 75 years were generally excluded of clinical trials, leading to a lack of safety data in these pts. Optimization of chemotherapy regimens is also important given the specificity of elderly pts (such as organ function, immune function, comorbidities, etc.). We aim to prospectively evaluate the efficacy and safety of tislelizumab (TIS) plus albumin-bound paclitaxel with or without platinum as first-line treatment for advanced NSCLC pts aged ≥70 (ChiCTR2000032509).

Methods: This is an ongoing single-institution trail which aims to enroll 36 pts. Eligible pts enrolled received albumin-bound paclitaxel (130mg/m^2, d1,8) plus TIS (200mg, d1) with or without platinum (carboplatin or nedaplatin, whereby choice of investigator's discretion) every 3 weeks for up to 4 cycles. Once combination therapy completed, patients with objective response or stable disease would receive TIS maintenance until confirmed disease progression, death, or unacceptable toxicity. Primary endpoints were objective response rate (ORR) and safety. Secondary endpoints were progression free survival rate (PFS), and disease control rate (DCR).

Results: 33 pts were enrolled form from June 2020 to February 2022. Median age was 74 years (range 70-83), 26 (66.7%) male, 15 (45.5%) current or former smokers, 12 (36.4%) with squamous cell carcinoma, 12 (36.4%) PD-L1 expression positive. Of the 20 evaluable pts with a median follow-up of 9.2 months, 12 pts achieved PR, 7 pts achieved SD, 1 pts PD; ORR was 60.0%, DCR was 95.0%, median PFS 15.3 months, 1-year PFS rate was 73.3%. In safety analysis set, grade ≥ 3 treatment related adverse events (TRAEs) occurred in 7 (21.2%) pts. The most common reported 1-2 grade TRAEs were anemia (36.3%), anorexia (18.2%), alanine aminotransferase increased (15.2%), aspartate aminotransferase increased (15.2%) and alkaline phosphatase increased (12.1%). The most common irAE was mild hypothyroidism (12.1%).

Conclusions: Tislelizumab plus albumin-bound paclitaxel with or without platinum might be an optional choice as first-line treatment for advanced NSCLC in patients aged ≥ 70, with a good tumor response rate and safety profile.

Keywords: NSCLC, Tislelizumab

EP08.01-081 A Phase I Dose-Escalation Study of HBM4003, an anti-CTLA-4 Heavy Chain Only Monoclonal Antibody, in Combination with Pembrolizumab

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Introduction: Combination therapy with ipilimumab plus PD-1 inhibitors has shown promising efficacy in various tumor types, demonstrating higher rates of response than either agent alone. HBM4003 is a fully human heavy chain only monoclonal antibody targeting CTLA-4, which has been engineered to deplete Treg cells and enhanced antibody-dependent cellular cytotoxicity. HBM4003 has shown preliminary clinical activity in phase (Ph) I trial in patients (pts) with advanced solid tumors. Pembrolizumab is a humanized immunoglobulin G4 monoclonal antibody against PD-1 and has been approved by FDA in various indications.

Methods: This is a Ph I study to evaluate the safety, anti-tumor activity, PK/PD and recommended phase II dose (RP2D) of HBM4003 in combination with PD-1 inhibitors. In part 1 (presented here), 12 pts were enrolled to receive HBM4003 at 3 dose levels (DLs) combined with pembrolizumab 200 mg: 0.1 mg/kg Q3W, 0.3 mg/kg Q3W, and 0.45 mg/kg Q3W. Part 2 is a dose-expansion phase. ClinicalTrials.gov number: NCT04866485.

Results: The study is ongoing. As of 20 Dec 2021, a total of 12 pts have been treated at 2 sites in China, including 8 pts with NSCLC and 4 pts with other tumor types. 10 pts received ≥ 2 lines of previous systemic therapies and 6 received previous anti-PD-1/PD-L1 treatment. The most common treatment-related adverse event (TRAE) (≥10%) of all grades was rash (5 [41.7%] pts). Grade (Gr) 3 TRAE anemia occurred in 1 pt (8.3%). All other TRAEs were Gr 1 or 2. Three serious adverse events related to HBM4003 occurred in 2 pts (0.3 mg/kg Q3W): 1 pt with Gr 2 interstitial lung disease, and 1 pt with Gr 2 tympanic membrane perforation and Gr 2 arthralgia The Gr 2 interstitial lung disease (0.3mg/kg Q3W DL) was a DLT and led to discontinuation of HBM4003 and pembrolizumab. No DLT was observed in other two DLs.Tumor assessments (RECIST v1.1.): 10 pts evaluable for efficacy: 3 pts had SD as best response. 1 pt (0.3 mg/kg Q3W) with SD discontinued from study treatment due to Gr 2 interstitial lung disease and was provided with tislelizumab 200 mg Q3W based on the investigator's decision. The pt had partial response (PR) at cycle 3 of tislelizumab treatment. 1 pt (0.3 mg/kg Q3W) had 55.9% maximum tumor shrinkage of target lesions. However, new lesions developed, and non-target lesions were assessed as PD.

Data indicated no interaction between HBM4003 and pembrolizumab.

In peripheral blood, the temporal depletion of Treg cells, sustaining increase of CD4+Ki67+ T cells together with CD8+Ki67+ T cells were observed at 0.3 and 0.45 mg/kg.

Conclusions: HBM4003 0.3 mg/kg Q3W+ pembrolizumab showed preliminary antitumor activity and a tolerable safety profile in advanced NSCLC.

Keywords: CTLA-4, Heavy Chain Only Monoclonal Antibody, HBM4003

EP08.01-082 Therapeutic Resistance and Clonal Evolution Assessed with Liquid Biopsy in ICIs Treated NSCLC Patients: A Prospective Study

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Introduction: Treatment of non-small cell lung cancer (NSCLC) with immune checkpoint inhibitors (ICIs) can produce remarkably durable responses in a subset of patients but not in others. A retrospective study showed that integrated ctDNA and circulating immune cell profiling can provide accurate, noninvasive, and early forecasting of ultimate outcomes for NSCLC patients receiving ICIs. This prospective clinical trial was designed to establish and validate such a model and to explore the underlying resistance mechanism of ICIs treatments (NCT04566432).

Methods: *EGFR*, *ALK* negative advanced NSCLC patients treated with first line ICIs were recruited. Pre-treatment circulating tumor DNA (ctDNA), peripheral blood mononuclear cell (PBMC) and early on-treatment ctDNA were collected and analyzed with NGS based panel sequencing (1021 genes) or RNA sequencing (Geneplus, Beijing, China). Pre-treatment ctDNA and peripheral immune features, together with early on-treatment ctDNA dynamics were integrated with a multiparameter Bayesian Frameworks.

Results: To date, 58 NSCLC patients were recruited and 22.4% of the patients were treated with ICI monotherapy while 77.6% were treated with combined ICI and chemotherapy. With a median follow-up of 7 months (range, 2-11.2 months), 11 patients experienced disease progression in less than 6 months (non-durable benefit, NDB) and 15 patients had an PFS longer than 6 months (durable clinical benefit, DCB). Though adjusted bTMB, ctDNA dynamic or peripheral immune features alone could not distinguish NDB patients from DCB patients, combined modeling of these 3 parameters could predict the clinical outcome (accuracy = 85%, AUC = 0.89). Briefly, 8 of the 9 patients predicted to be NDB had progression in less than 6 months, and 14 of 17 patients predicted to be DCB had PFS longer than 6 months, with 2 of them had PFS of 5.1 months and 5.9 months respectively. Mutation and clonal analysis were still ongoing.

Conclusions: The preliminary data of this prospective trial showed the high accuracy of the integrated model. With more patients and more data included in the trial, we could optimize this prediction model of ICIs and analyze the potential mechanism of early resistance of ICIs in advanced NSCLC patients.

Keywords: immunotherapy, predictive model, liquid biopsy

EP08.01-083 Real-World PD-(L)1 Inhibitor Treatment Pattern and Outcomes in Advanced Non-Small Cell Lung Cancer in Sweden

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Introduction: Since the introduction of immune-oncology therapies (IO) as treatment for advanced non-small cell lung cancer (aNSCLC), the treatment landscape for patients with aNSCLC has evolved significantly. This study aims to describe the PD-L1 testing rates, treatment patterns and associated real-world outcomes in the Swedish setting.

Methods: Data were extracted from the Swedish National Lung Cancer Registry for patients with locally advanced or metastatic NSCLC with ECOG 0-2 who initiated first line systemic treatment from 1-Apr-2017 to 30-Jun-2020, with data cutoff 30-June-2021. Data on PD-L1 testing and results were available in the registry from 1-Jan-2018. In patients with ECOG 0-1, Kaplan-Meier was used to determine overall survival (OS) by histology and commonly used treatment classes.

Results: Of 2,204 eligible patients, 1,568 (71.1%) had a PD-L1 testing status record, of which 1,346 (85.8%) were tested for PD-L1 expression. Among those tested, PD-L1 expression was ≥50%, 1-49%, <1% and unknown for 492 (36.6%), 416 (30.9%), 371 (27.6%) and 67 (5.0%) patients, respectively. Among patients with ECOG 0-1 receiving first-line treatment, 308 (27.6%), 102 (9.1%), 605 (54.3%) and 100 (9.0%) with non-squamous NSCLC and 85 (30.1%), 17 (6.0%), 161 (57.1%) and 19 (6.7%) with squamous NSCLC initiated a PD-(L)1 monotherapy, PD-(L)1 combination therapy, platinum-based chemotherapy and other therapy, respectively. Majority of patients receiving first-line PD-(L)1 monotherapy had PD-L1 expression ≥50% (84.9% and 74.2% in patients with non-squamous and squamous histology, respectively, among those with known PD-L1 expression). For patients with non-squamous histology treated with first-line PD-(L)1 combination therapy, more patients had PD-L1 expression <50% (23.2%, 48.9% and 27.9% had PD-L1 expression ≥50%, 1-49% and <1%, respectively, among those with known PD-L1 expression). Only 17 patients with squamous histology initiated a PD-(L)1 combination therapy during this study's identification period. OS estimates by commonly used treatment class and by histology are summarized in Table 1.

Conclusions: Since 2018, the majority of patients diagnosed with aNSCLC were tested for PD-L1 expression. Real-world OS estimates observed in Swedish patients with aNSCLC receiving a PD-(L)1 inhibitor-based regimen in frontline were generally similar to findings reported in pivotal PD-(L)1 inhibitor clinical trials.

Table 1. Overall survival (OS) by commonly used treatment class and by histology among patients with ECOG 0-1 treated with 1L systemic therapy

	PD-(L)1 inhibitor monotherapy	PD-(L)1 inhibitor combination	Platinum-based chemotherapy combination
NON-SQUAMOUS			
Number of patients	308	102	605
Events	183	48	497
Median, months (95% CI)	18.6 (14.8 - 23.4)	24.0 (14.3 - NE)	9.5 (8.5 - 10.5)
OS rates			
12 months	59.7 (54.4 - 65.4)	62.7 (53.9 - 72.8)	40.8 (37.1 - 44.9)
24 months	43.2 (37.7 - 49.6)	48.8 (38.1 - 62.4)	22.7 (19.5 - 26.4)
SQUAMOUS			
Number of patients	85	17	161
Events	61	4	135
Median, months (95% CI)	13.3 (10.5 - 17.7)	NE	11.7 (10 - 13.9)
OS rates			
12 months	54.1 (44.5 - 65.8)	NE	49.7 (42.5 - 58)
24 months	29.2 (20.5 - 41.7)	NE	26.6 (20.4 - 34.7)

Abbreviations: CI=confidence interval; NE=not estimable

Keywords: PD-L1 testing rates, Treatment patterns, Real-world outcomes

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-084 Non-Invasive Detection of Predictive Biomarkers for PD-1 Inhibitor Treated Non-Small Cell Lung Cancer Patients

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Introduction: Immunotherapy has altered the therapeutic landscape for advanced non-small cell lung cancer (NSCLC) patients. The immune checkpoint inhibitor pembrolizumab targets the PD-1 signaling axis and has produced durable clinical response. Despite PD-L1 expression being used as a biomarker for treatment eligibility, its predictive value remains ambiguous. Using blood samples from pembrolizumab-treated NSCLC patients, we aimed to identify biomarkers with predictive value for therapeutic response.

Methods: We analyzed the expression of 92 plasma proteins using the Olink proximity extension assay and used targeted Next-Generation Sequencing to detect circulating tumor DNA (ctDNA) with a panel of 197 genes.

Results: Patients with above median PFS (median=220 days) had significantly higher expression of Fas Ligand (FASLG) and Inducible T Cell Costimulator Ligand (ICOSLG) at baseline (p=0.0021 and p=0.0230) than patients with PFS below median. We identified a subgroup of patients with high expression of FASLG and/or ICOSLG who cleared their ctDNA 3-6 weeks after treatment initiation. This subgroup showed longer PFS and OS (p=0.0154 and p=0.0990) compared to patients with high expression of FASLG and/or ICOSLG plus detectable ctDNA.

Conclusions: These findings suggest that the expression of FASLG and ICOSLG at baseline and the dynamics of ctDNA in the early part of treatment may predict response to pembrolizumab

Keywords: Immunotherapy, Biomarker, Circulating tumor DNA

EP08.01-085 Sintilimab versus Pembrolizumab as Monotherapy or in Combination with Chemotherapy for Treatment Naïve Metastatic Non-small Cell Lung Cancer

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Introduction: Immunotherapy has become standard therapy for advanced non-small-cell lung cancer (NSCLC). However, no direct comparison between different PD-1 inhibitors were reported.

Methods: This is an open label, randomized, phase II clinical trial to compare sintilimab versus pembrolizumab as monotherapy or in combination with chemotherapy for treatment naïve local advanced or metastatic NSCLC. Eligible patients were *EGFR* or *ALK* negative. Patients with asymptomatic brain metastasis were allowed. PD-L1 tumor proportion score (TPS) ≥50% patients were randomly assigned to sintilimab (A) or pembrolizumab (B) monotherapy arms. TPS<50% patients were randomly assigned to sintilimab (C) or pembrolizumab (D) with platin-based chemotherapy arms. The primary endpoint was objective response rate (ORR). Sample size were determined per Optimal Two-Stage Design, 1st stage would recruit 20 patients. Recruitment of the 2nd stage would start if ≥4 patients achieve partial response (PR) in sintilimab arms, and sample size would be determined based on the ORR of the 1st.

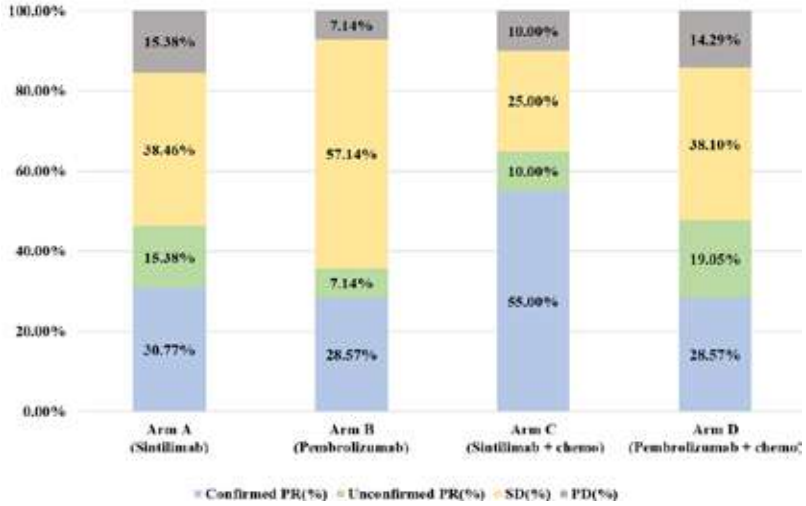
Results: The ORR of the 1st stage was 57.1% in sintilimab and 33.3% in pembrolizumab arms, thus the study successfully entered into the 2nd stage. From Mar. 2020 to Jan. 2022, a total of 68 patients were enrolled. Histologic subtypes and brain metastasis were well balanced between arms. Until Dec. 31st 2021, the median follow-up was 5.6 months. ORR was 57.6% in sintilimab arms vs. 42.9% in pembrolizumab arms, and the confirmed ORR was 45.5% (15/33) vs. 28.6% (10/35), separately. (Figure 1). The disease control rate was 87.9% vs. 91.4% in sintilimab and pembrolizumab arms, respectively. The primary endpoint was reached, with 15 confirmed PRs achieved in sintilimab arms. Survival data was still immature. Treatment-related adverse events were comparable between sintilimab and pembrolizumab arms (Table 1).

Conclusions: This head-to-head study of PD-1 inhibitors suggested comparable tumor response and similar safety profile between sintilimab and pembrolizumab.

Table 1: Baseline and safety summary in sintilimab and pembrolizumab arms.

	Arm A(Sintilimab)	Arm B(Pembrolizumab)	Arm C(Sintilimab + chemo)	Arm D(Pembrolizumab + chemo)
Histology (SQ/NSQ)	3/10	3/11	5/15	2/19
Brain metastasis (Y/N)	3/10	5/9	1/19	3/18
Any Grade TRAEs	100% (13/13)	100% (14/14)	100% (20/20)	100% (21/21)
3-4 Grade TRAEs	46% (6/13)	36% (5/14)	79% (15/50)	75% (15/21)

Figure 1: Tumor response in sintilimab and pembrolizumab arms.



Keywords: non-small cell lung cancer, PD-1 inhibitor, immunotherapy

EP08.01-086 Pooled Mutant KRAS-Targeted Peptide Vaccine with Nivolumab and Ipilimumab in Advanced KRAS Mutated Non-Small Cell Lung Cancer

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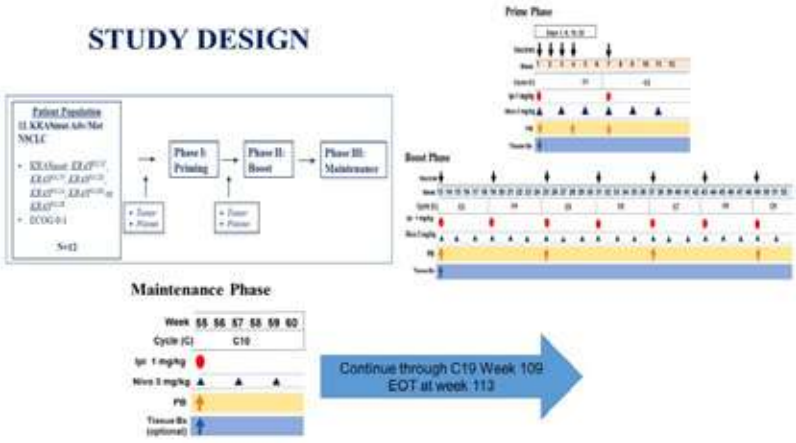
Introduction: Treatment for advanced non-small cell lung cancer (NSCLC) has been revolutionized by the development of both immunotherapeutic and genomic based therapies. There is increasing appreciation for the interplay between genomic alterations and response to immune checkpoint blockade (ICB), as exhibited by alterations in driver mutations (e.g. EGFR/ALK) and non-driver co-mutations (e.g. STK11/KEAP1). Special attention has been paid to the most common oncogenic driver, KRAS, which is mutated in approximately 30% of NSCLC. Historically a poor therapeutic target, there have been recent advances in the treatment of KRASG12c mutated cancers through small molecule inhibitors. While a significant first step, the relatively short duration of disease control and lack of activity across codon mutations, means further development of KRAS-targeted therapy is needed. Given KRAS is an oncogenic driver, and less likely to be immunologically edited, it is an attractive vaccine target. Through preclinical and early (ongoing) clinical trial data, our institution has shown the benefits of combining targeted synthetic long peptide vaccines with ICB and adjuvant stimulants in treatment of solid malignancies.

Methods: This is a single institution, phase I study for patients with Stage III/IV unresectable KRAS-mutated NSCLC to evaluate safety of the pooled mutant-KRAS peptide vaccine with poly-ICLC adjuvant in combination with nivolumab and ipilimumab in the first line treatment setting. Patients will have untreated advanced NSCLC harboring selected KRAS mutations (*KrasG12C, KrasG12V, KrasG12D, KrasG12A, KrasG13D or KrasG12R*). Treatment is divided into 3 phases: (a) prime phase, (b) boost phase and (c) maintenance phase (Figure 1). The primary objectives of this study are to determine the safety and feasibility of administering the KRAS peptide vaccine with poly-ICLC adjuvant in combination with nivolumab and ipilimumab. The study will enroll up to 12 patients to evaluate the co-primary endpoints of safety and feasibility. The secondary objectives are to assess the impact of therapy on mutant-KRAS specific T cell responses in the peripheral blood and estimate the progression free survival (PFS) for patients treated with this combination. Correlative studies will assess the impact of predicted KRAS mutations on mutant-KRAS specific T cell responses in the peripheral blood, as well as evaluate dynamic genomic alterations of response and resistance through ctDNA analysis.



Keywords: KRAS, Vaccine, Immunotherapy

EP08.01-087 First-Line Pembrolizumab-Combination Therapy for Advanced Squamous NSCLC: Real-World Outcomes at US Oncology Practices

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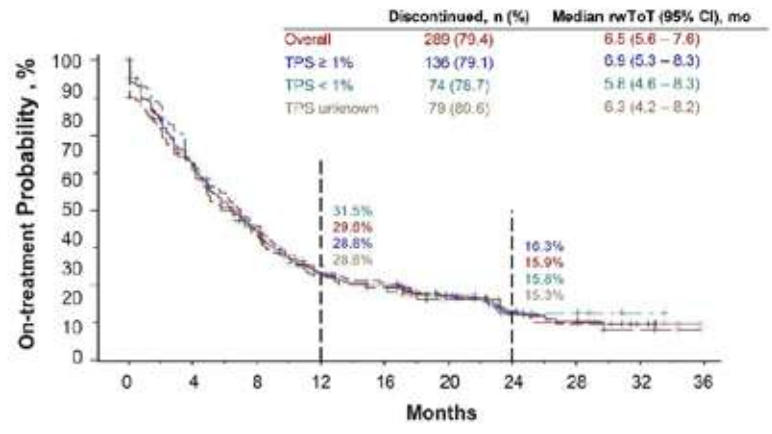
Introduction: In KEYNOTE-407, median overall survival (OS) was 17.1 months (95% CI, 14.4-19.9); 12- and 24-month OS rates were 64.7% and 37.5%, respectively; and median duration of exposure was 7.1 months (range, 0.03-26.3) for patients with metastatic squamous NSCLC treated with first-line pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel (pembrolizumab-chemotherapy). This study aimed to examine real-world time on treatment (rwToT) and OS among patients with advanced squamous NSCLC treated with first-line pembrolizumab-chemotherapy at US oncology practices.

Methods: Using the nationwide, electronic health record-derived, deidentified Flatiron Health database, we selected adult patients with stage IIIB/IIIC/IV (newly diagnosed and/or recurrent disease) squamous NSCLC, good performance status (ECOG 0-1), who initiated first-line pembrolizumab-chemotherapy from 1-Nov-2018 to 31-May-2020, with data cutoff 31-Oct-2021. Median follow-up from pembrolizumab-chemotherapy initiation was 26.2 months (range,17.1-36.0) to data cutoff and 17.1 months (range, <0.01-35.8) to patient death/data cutoff. Kaplan-Meier was used to determine rwToT and OS overall, stratified by programmed death-ligand 1 (PD-L1) tumor proportion score (TPS).

Results: Of 364 eligible patients, 243 (67%) were men; median age was 70 (range, 43-84); 245 patients (67%) had stage IV at initial NSCLC diagnosis. PD-L1 TPS was ≥1, <1%, and unknown for 172 (47%), 94 (26%), and 98 (27%) patients, respectively. Overall, median pembrolizumab rwToT was 6.5 months (95% CI, 5.6-7.6) and increased with PD-L1 TPS (Figure 1). Median OS was 15.3 months (95% CI, 11.7-18.6), with 12- and 24-month OS rates of 54.9% and 37.3%, respectively, among all patients. Survival did not differ with PD-L1 TPS: 16.2 months (95% CI, 10.3-20.6) for TPS ≥1% and 17.2 months (95%CI, 10.8-20.6) for TPS <1% (Figure 2).

Conclusions: Approximately one in six patients (16%) remained on pembrolizumab at 2 years. Patients with advanced squamous NSCLC treated in real-world settings with first-line pembrolizumab-chemotherapy experienced rwToT and OS similar to treatment duration and OS reported in KEYNOTE-407.

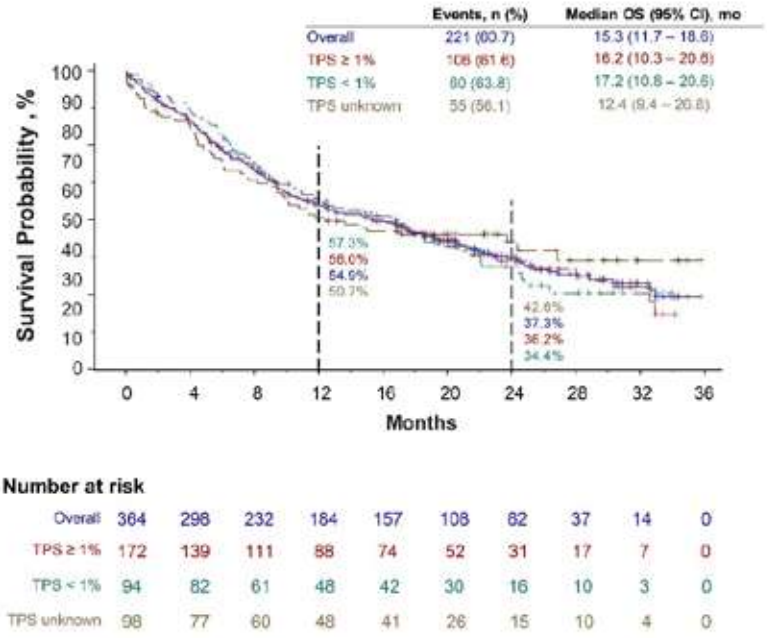
Figure 1. Pembrolizumab real-world time on treatment (rwToT) by PD-L1 expression



Number at risk

Overall	364	232	149	97	80	49	25	17	7	0
TPS ≥ 1%	172	110	73	45	39	26	13	8	3	0
TPS < 1%	94	62	36	26	19	13	6	4	1	0
TPS unknown	98	60	40	26	22	10	6	5	3	0

Figure 2. Overall survival (OS) by PD-L1 expression



Number at risk

Overall	364	298	232	184	157	108	62	37	14	0
TPS ≥ 1%	172	139	111	88	74	52	31	17	7	0
TPS < 1%	94	82	61	48	42	30	16	10	3	0
TPS unknown	98	77	60	48	41	26	15	10	4	0

Keywords: advanced squamous NSCLC, first-line pembrolizumab-chemotherapy, real-world settings

EP08.01-088 Direct Acting Antivirals (DAA) and Immune Checkpoint Inhibitors (ICIs) Therapy in Patients with Lung Cancer and Hepatitis C

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Introduction: Patients with cancer and viral hepatitis have usually been excluded from many clinical trials with ICIs. Therefore, the clinical impact of hepatitis C virus (HCV) infection in these patients has been poorly explored. DAA agents lead to a viral clearance of HCV in more than 90% of cases, and preclinical data correlated the decline of HCV-RNA at 14 days from the start of DAA therapy with the virological outcome (i.e. the sustained virological response [SVR], defined as undetectable HCV-RNA at 12 [SVR12] or 24 [SVR24] weeks from the end of the DAA therapy).

Methods: After a baseline assessment including serum virological and biochemical profile, HCV genotype, viral load, Metavir score and Child-Pugh, patients with advanced non-small cell lung cancer (NSCLC) and HCV infection, candidates to single-agent anti-PD-(L)1, started a DAA therapy (time 0). HCV-RNA level and hepatic function lab tests were monitored at 14, 30, 60 and 90 days (the latter only for DAA therapy lasting three months). ICIs treatment was started before achieving the SVR, and at least 14 days from the beginning of DAA, if a deep decay in the viral load was observed. Patients were monitored for response to ICIs and occurrence of adverse events (AEs) according to clinical practice.

Results: Five patients with advanced NSCLC (four adenocarcinoma, one squamous-cell lung cancer) were treated with the sequential approach. The median age was 57 years (IQR 53-77), four patients had an ECOG performance status 0 or 1, and two patients had liver metastases. One patient had a concomitant HBV chronic infection. All subjects had a Child-Pugh A score, none presented overt cirrhosis >F3 at the baseline evaluation. Treatment's characteristics are displayed in the table. All patients exhibited negative HCV-RNA at day 30 and at the end of DAA treatment, and all achieved the SVR12. No flare of viral hepatitis during the combined DAA-ICIs treatment and during ICIs only therapy was observed. One patient had a temporary grade 2 AST elevation. No grade >3 AEs were observed. One patient had a partial response per RECIST 1.1 as best response, while the disease control rate was 80% (three stable disease). Patient 1 is alive and maintains a disease response at 53 months from ICI start.

Conclusions: We tested a potential way to combine DAA agents and ICIs, avoiding the delay of immunotherapy initiation in patients with active HCV infection. This sequential treatment approach appeared to be feasible and safe.

DAA and ICIs Treatment Detail

Patient	HCV genotype	Metavir score	Baseline HCV-RNA (UI/ml)	DAA type	ICIs type	ICIs line of treatment
1	4	F0-F1	2,7x10^6	Sofosbuvir/Velpatasvir	Nivolumab	5
2	1B	F2	3,7X10^5	Glecaprevir/Pibrentasvir	Nivolumab	2
3	1A	F1	1,7x10^5	Sofosbuvir/Velpatasvir	Pembrolizumab	1
4	1B	F3	5,6X10^5	Elbasvir/Grazoprevir	Pembrolizumab	1
5	1A	F0	2,0X10^6	Sofosbuvir/Velpatasvir	Atezolizumab	2

Keywords: Lung Cancer, Immunotherapy, Viral Hepatitis

EP08.01-089 Efficacy and Safety of Immune Checkpoint Inhibitors in Treating Brain Metastases in Patients with Non-small Cell Lung Cancer

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Introduction: This study aimed to investigate the efficacy and safety of immune checkpoint inhibitors (ICIs) in the treatment of brain metastases (BM) in patients with non-small cell lung cancer (NSCLC).

Methods: The clinical data of 16 patients with BM of NSCLC who were treated with immune checkpoint inhibitors from April 2019 to April 2021 were retrieved. The inclusion criterion was patients with BM of NSCLC confirmed by magnetic resonance imaging (MRI) scan with pathological diagnosis and treated with immune checkpoint inhibitors. The exclusion criteria were patients with small cell lung cancer and patients with epilepsy, cerebral infarction, cerebral hemorrhage, and other brain diseases. All patients received at least two cycles of immune checkpoint inhibitor (ICI) therapy, with an MRI enhancement scan performed before and after each treatment cycle for two weeks. Evaluation of the treatment efficacy was performed according to resist1.1 standard.

Results: The median progression-free survival (mPFS) was 24.17 months, while the median overall survival (mOS) was not achieved. Nine patients were evaluated for efficacy, among which three patients had a partial response (33.3%), one patient had advanced progressive disease (6.25%), and five patients had stable disease (31.25%). Five patients underwent brain radiotherapy, three of whom were pretreated with ICIs. Only one patient stopped the ICI treatment during radiotherapy and no radiation encephalitis or immune-associated hypophysitis occurred in all patients undergoing brain radiotherapy.

Conclusions: ICIs have a high intracranial control rate in patients with BM of NSCLC and prolong mPFS in these patients. No adverse immune reactions were observed in patients with concurrent brain radiotherapy.

Keywords: Non-small cell lung cancer, Brain metastases, Immune checkpoint inhibitors

EP08.01-090 Association of Gender and Outcomes in Patients with Advanced NSCLC Treated with Immunotherapy Alone or in Combination with Chemotherapy Upfront

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Introduction: In advanced non-small cell lung cancer (aNSCLC), several clinical factors have been associated with prognosis in the context of the immunotherapy. Among them, female gender was proposed as negative factor for immuno-checkpoint inhibitors (ICI); however its independent impact of other prognostic factors (i.e., PS, smoking or biological parameters, etc) remains unclear. We assessed whether the female gender correlates with ICI-outcomes in patients with aNSCLC treated upfront with ICI-alone or combined to chemotherapy (CT).

Methods: Multicenter retrospective study of patients with aNSCLC treated upfront with ICI-alone or combined with platinum-based-CT between Aug/11 and Sep/21. Clinical/biological data was collected from medical reports. dNLR =neutrophils/[leucocytes/neutrophils] and dNLR score were calculated as previously reported. Primary endpoint was overall survival (OS).

Results: A total of 285 patients were included; 30% were female. Overall, median age was 65 (38-89), 76% were smokers, 87% with PS 0-1; 80% had non-squamous histology; PD-L1 was ≥50% in 51% (96% in ICI-cohort, 15% in ICI+CT cohort) In the overall population, similar baseline characteristics were observed in female-male population except for age (median 63 vs. 66 in male, p=0.025), smoking status (80% vs. 97% male, p=0.001) and non-squamous histology (87 % vs. 75 % in male, p=0.025). In the ICI-cohort (N=116), 26% were females. Smoking status was the only baseline characteristic with significant differences according to gender, less frequent in female population (87% vs 98 % in male, p=0.038). In the ICI+CT-cohort (N=169), 33% were females. Smoking status distribution was also different according to gender, less frequent in females (80% vs. 91 % in male, p=0.01), and histology, with more cases of non-squamous histology in females (91% vs. 79% in male, p=0.046). No correlation was observed between gender and outcomes, neither on OS and PFS in the overall population, in the ICI-cohort and in the ICI+CT-cohort. The multivariate analysis for OS in both cohorts is summarized in Table 1. No negative prognostic impact was observed in females.

Table 1. Multivariate analysis for overall survival (OS) in the ICI-cohort and in the ICI-CT- cohort.

Conclusions: In our study, female gender is not a negative prognostic factor in patients treated with ICI alone or combined to CT in aNSCLC upfront. Additional studies should be performed to prospectively explore the impact of gender on ICI-outcomes.

	Immunotherapy			Chemo-immunotherapy		
	HR	**95 % CI**	**p value**	**HR**	**95 % CI**	**HR**
Age			0.641			0.86
<65 years	1			1		
>65 years	1.19	0.56-2.49		1.09	0.47-2.46	
Gender			0.46			0.42
Female	1			1		
Male	0.75	0.35-1.60		1.08	0.47-2.46	
Smoking			1			1
Non-smoker	1			1		
Smoker	0.41	0.11-1.64		1.758	0.81-3.82	
PS			0.07			<0.001*
0-1	1			1		
≥2	2.36	0.91-6.12		5.28	2.17-12.80	
Histology			0.82			0.155
Non-squamous	1			1		
Squamous	0.91	0.42-1.97		1.75	0.81-3.82	
dNLR			0.005*			0.002*
Good-Intermediate	1			1		
Poor	3.93	1.71-9.03		7.19	2.08-24.85	

Keywords: Gender, Immunotherapy alone, Immunotherapy combination with chemotherapy

EP08.01-091 Association of dNLR Score with Outcomes in Patients with Advanced NSCLC Under Immunotherapy Alone +/- Chemotherapy Upfront

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Introduction: Derived neutrophils/[leucocytes-neutrophils] (dNLR) and dNLR-score based on dNLR at baseline (B), and at cycle 2 (C2) correlate with immune-checkpoint inhibitors (ICI) outcomes in pretreated patients with advanced non-small cell lung cancer (aNSCLC). However, its dynamic impact upfront and combined with chemotherapy (CT) remains unknown. We assessed the impact of dNLR score on outcomes in patients with aNSCLC treated in first line with ICI alone or combined to CT.

Methods: Multicenter retrospective study of patients with aNSCLC treated with ICI alone or combined with platinum-based-CT in first line between Aug/11 and Sep/21. Clinical and biological data was collected from medical reports. dNLR was determined at B and C2 [dNLR>3=high]. B+C2 were combined in one dNLR-score: good= persistently-low (B+C2), poor= persistently-high (B+C2), intermediate=other situations, as previously reported. The primary endpoint was overall survival (OS).

Results: To date, 285 patients were included (N=116 in ICI-cohort, N=169 in ICI+CT-cohort); overall, median age was 65, 70% were male, 93% smokers, 87% PS0-1; 79% had non-squamous histology. Similar characteristics were observed in both cohorts, except for high-PD-L1 (96% in ICI-cohort vs. 15% in ICI+CT cohort) and PS >2 (9% in ICI cohort vs. 20% ICI+CT cohort).In ICI-cohort, dNLR was high in 35% at B and 31% at C2, both significantly associated with poor outcomes (logrank test, p<0.05/0.001). dNLR-score classified them in 3 groups: good 56%, intermediate 25%, poor 19%.In ICI+CT-cohort, dNLR was high in 30% at baseline and 17% at C2, both also associated with poor outcomes (logrank test, p<0.0001/0.02). By dNLR-score: 65% were good, 28% intermediate and 7% poor groups.In both cohorts, dNLR-score was significantly associated with PFS/OS (table 1).In the multivariate analysis (with age, smoking, gender, histology, PS), the dNLR-score was an independent prognostic factor for OS both in ICI-cohort (poor group= HR 3.9, 95% CI 1.7-9) and ICI+CT-cohort (poor group= HR 7.1, 95% CI 2.1-24.8). Under ICI+CT, the % high-dNLR at C2 (17% vs. 31% under ICI-alone; p=0.03) and the % persistently-high dNLR [=poor group] (7% vs. 19% under ICI-alone, p=0.02) were significantly lower compared to under ICI alone.

Conclusions: The dNLR-score, based on dNLR B+C2, associates with outcomes under ICI alone or combined to CT upfront in aNSCLC. Persistently high-dNLR is independently associated with the poorest OS. dNLR-dynamics under treatment seems to be different under ICI+CT vs. ICI alone; more detailed data will be presented in the meeting.

Distribution of dNLR-score groups and OS and PFS according to treatment

	N=222	OS (months, 95%CI)	P-value	PFS (months, 95%CI)	P-value
Immunotherapy					
dNLR score					
Good	49 (56%)	NR (30.5-NR)	0.002	NR (7.7-NR)	0.002
Intermediate	22 (25%)	12.5 (9.8-NR)		4.6 (2.1-NR)	
Poor	17 (19%)	11.1 (5-NR)		3.1 (2.3-25.1)	
Immunotherapy plus Platinum based Chemotherapy					
dNLR score					
Good	87 (65%)	25.5 (24.7-NR)	<0.0001	13 (10.9-15.5)	0.02
Intermediate	38 (28%)	16.9 (7.6-NR)		5.5 (4.5-10.9)	
Poor	9 (7%)	9.9 (6.2-NR)		6.9 (6.2-NR)	

Legend: OS= overall survival; PFS= progression free survival; NR= not reached

Keywords: dNLR-score, Immunotherapy, Prognostic Factor

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-093 ICI in Combination with Chemotherapy or Anti-angiogenic Agents as Second-Line Orbeyondtreatment for Advanced Non-small Cell Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs), which are currently used in the standard second-line treatment for non-small cell lung cancer (NSCLC), have largely improved the prognosis of advanced NSCLC. However, patients treated with ICI monotherapy have low response rates; hence, there is an urgent need to expand the population responding to immunotherapy treatment. This study aimed to explore the efficacy and safety of the combination of ICI with chemotherapy or anti-angiogenic therapy compared to ICI monotherapy in patients previously treated for advanced NSCLC.

Methods: Data was collected from previously treated patients with NSCLC who further received ICI monotherapy or combination therapy. The distribution of clinical variables was assessed using the chi-square test or Fisher's exact test. The relationship between descriptive variables and survival was described using Kaplan-Meier curves and compared by log-rank test. Cox proportional-hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) to confirm survival differences.

Results: A total of 145 patients were included in this study, of which 63 were in the ICI monotherapy group, 57 were in the ICI with chemotherapy group, and 25 were in the ICI with anti-angiogenic therapy group. Compared with the ICI monotherapy group, the ICI with chemotherapy group had significantly higher ORR (31.6% vs. 11.1%, *P=0*.006), DCR (84.2% vs. 61.9%, *P*=0.006), PFS (mPFS: 6.37 vs. 3.47 months, *P*<0.0001; HR=0.42, 95% CI: 0.29-0.63, *P*<0.0001), and OS (mOS: 18.60 vs. 8.47 months, *P*<0.0001; HR=0.40, 95% CI: 0.25-0.64, *P*=0.0001). In addition, the ICI with anti-angiogenic therapy group also had significantly elevated DCR (88% vs. 61.9%, *P*=0.02), PFS (mPFS: 8.17 vs. 3.47 months, *P*<0.0001; HR=0.30, 95% CI: 0.17-0.53, *P*<0.0001), and OS (mOS: 19.20 vs. 8.47 months, *P*=0.006; HR=0.44, 95% CI: 0.24-0.80, *P*=0.007) compared with the ICI monotherapy group. There was no significant difference between the ICI with chemotherapy group and the ICI with anti-angiogenic therapy group. Meanwhile, the addition of chemotherapy or anti-angiogenics did not increase immune-related adverse events and had a good safety profile.

Conclusions: For previously treated patients with advanced NSCLC, treatment with ICI in combination with chemotherapy led to enhanced ORR, DCR, PFS, and OS compared to treatment with ICI monotherapy. Moreover, treatment with ICI combined with anti-angiogenic therapy led to enhanced DCR, PFS, and OS compared to treatment with ICI monotherapy. The combination of immunotherapies is a promising second-line treatment option for some of the patients in this study, and the findings of this study necessitate the need for further exploration.

Keywords: Immune checkpoint inhibitors, chemotherapy, anti-angiogenic agents

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-094 A Phase II Study of Camrelizumab combined with Apatinib and Albumin Paclitaxel in Advanced Non-squamous NSCLC (CAPAP-lung)

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Introduction: Cytotoxic chemotherapy and anti-angiogenic therapy may enhance the therapeutic efficacy of immune checkpoint inhibitors (ICIs). Platinum-containing dual-agent chemotherapy combined with ICIs is the standard first-line treatment for non-small cell lung cancer (NSCLC), however, the optimal combination regimen remains unclear. The adverse effects of platinum-based chemotherapy are relatively serious, whether platinum chemotherapy can be eliminated in the first-line treatment of non-small cell lung cancer is a hotspot and difficulty in current research. Based on these results, we initiated CAPAP-lung study, which is a single-arm, multicenter Phase II trial to evaluate the efficacy and safety of Camrelizumab in combination with apatinib and albumin paclitaxel without platinum as the first-line therapy for non-squamous non-small cell lung cancer.

Methods: Patients diagnosed with IIIB-IV non-squamous NSCLC without EGFR and ALK sensitive mutations received Camrelizumab (200mg/3w) in combination with Albumin Paclitacxel (135mg/m^2, d1, d8/3w, 4-6 cycles) and Apatinib (250mg Qd po for 5 days, resting for 2 days every week). From August 2020 to February 2022, 54 of the planned 63 patients have been enrolled. The primary endpoint is progression-free survival (PFS), and secondary endpoints were overall survival (OS), duration of Response (DOR), objective response rate (ORR), and disease control rate (DCR) assessed by RECIST v1.1. This study is registered with ClinicalTrials.gov, NCT04459078 (follow-up is ongoing).

Results: The data for a total of 38 patients out of 54 enrolled patients were evaluable. Median PFS was 10.97 mo (95%CI 7.1-NR). The objective response rate (ORR) and disease control rate (DCR) were 71.1% (27/38, 95%CI 53.9-84.0) and 97.4% (37/38, 95%CI 84.6-99.9), respectively. The incidence of grade 3 and worse treatment-related adverse events was acceptable, with grade 3 events in 25(46.3%) patients and grade 4 events in 3(5.6%) patients. The most common grade 3 treatment-related adverse events were decreased neutrophil count (8 [14.8%]), liver function damage (9 [16.7%]), rash (3 [5.6%]), and decreased white blood cell count (3 [5.6%]).

Conclusions: Camrelizumab combined with albumin paclitaxel and apatinib showed encouraging antitumor activity with an acceptable safety profile for the first-line treatment of advanced lung adenocarcinoma.

Keywords: immunotherapy, advanced non-squamous NSCLC

EP08.01-095 Efficacy and Safety of Combining Endostar with Camrelizumab plus Chemotherapy in Advanced NSCLC Patients: A Multi-Center Retrospective Study

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Introduction: Recombinant human endostatin (Endostar) and Camrelizumab have been approved for NSCLC treatment combining with chemotherapy in China. This study aimed to investigate the efficacy and safety of combining Endostar with Camrelizumab plus chemotherapy in patients with advanced NSCLC.

Methods: Patients (pts) with advanced stage (IIIB and IV) NSCLC were enrolled in this retrospective study. Eligible pts received Camrelizumab (200 mg) every 3 weeks and continuous intravenous infusion of Endostar (210 mg) by infusion pump from day 1 to 3 every 3 weeks. RECIST 1.1 was used to evaluate tumor response, and NCI-CTC AE 4.0 for Adverse events (AEs) classification. The primary endpoint was progress-free survival (PFS). The secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety.

Results: As of Sep. 2021, 27 pts were enrolled, of which 23 had at least one efficacy evaluation. The median age of pts was 56.5 years and 74% was male. Pts diagnosed at stage IV was 93%. 74% was adenocarcinoma and 19% was squamous cell carcinoma. 52% received endostar combined with Camrelizumab and chemotherapy as first-line. The ORR was 48% and DCR was 85%, with one CR patient. The median PFS (mPFS) was 8.9 months, median OS (mOS) was not reached. In subgroup analyses, pts were grouped according to treatment cycles (≥4 cycles and < 4 cycles). The ORR was 68.75% and 18.18% in subgroup (those pts receiving ≥4 cycles) and (those pts receiving < 4 cycles), respectively. The DCR was 100% in pts with ≥4 cycles of treatment, higher than 63.64% in pts with <4 cycles. The mPFS and mOS showed a similar trend. The mPFS of pts with ≥4 cycles and <4 cycles of treatment was 12.4m and 2.9m (p=0.003), respectively. The mOS of pts with ≥4 cycles was not reached, significantly longer than 14.9m in pts with <4 cycles (p=0.008). In the safety-evaluable population, the most common AEs were anemia (67%, ≥3 grade 11%) and nausea/vomiting (41%, ≥3 grade 4%). One pt was considered as immune-related hepatitis. Reactive cutaneous capillary endothelial proliferation (RCCEP) related with camrelizumab was 41%, and all were grade I/II.

Conclusions: This retrospective study showed that Endostar combined with Camrelizumab plus chemotherapy has promising efficacy and good tolerability in pts with advanced NSCLC. Pts with ≥4 cycles of treatment achieved greater clinical benefit. This combination regimen may become a new choice and a prospective study in furture was expected.

Keywords: Endostar, Chemotherapy, Advanced NSCLC

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-096 Lung Immune Prognostic Index is Prognostic in Patients Treated with PD-1 Inhibitor Combined with Chemotherapy for Non-small Cell Lung Cancer

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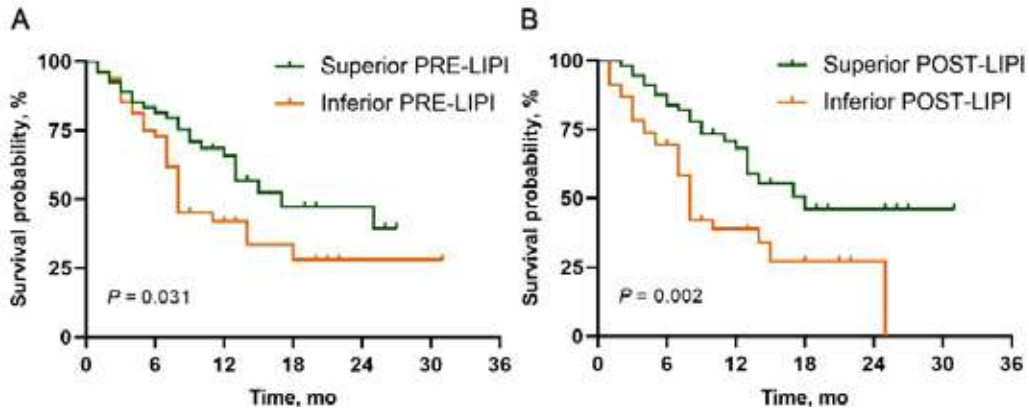
Introduction: The prognostic value of lung immune prognostic index (LIPI) has been reported in non-small cell lung cancer (NSCLC) patients received immunotherapy. However, it is still controversial whether it is a prognostic biomarker in patients treated with immune checkpoint inhibitors (ICIs) plus chemotherapy. Therefore, we conducted this study to investigate the relationship between LIPI and treatment outcomes in this population.

Methods: We collected and analyzed the data of 102 stage III to IV or recurrent NSCLC patients received programmed cell death ligand 1 (PD-1) inhibitor-based combination therapy in this retrospective study. The LIPI scores were calculated at baseline (PRE-LIPI) and after two cycles of the combination administration (POST-LIPI). The association of clinical outcomes with LIPI was assessed using the Kaplan-Meier method, Cox proportional hazards regression analysis and logistic regression analysis.

Results: There were 48 (47.1%) patients and 46 (45.1%) patients in the inferior PRE-LIPI group and the inferior POST-LIPI group, respectively. A lower ORR was observed in the inferior POST-LIPI group compared with the superior POST-LIPI group (30.4% vs 66.1%) in the multivariate logistic analysis (adjusted HR, 0.20; 95% CI, 0.08-0.52; *P* = 0.001). Patients with an inferior PRE-LIPI score had a worse progression-free survival (PFS), though the difference was not significant (median, 8.0 months vs 17.0 months; adjusted HR, 1.76; 95% CI, 0.95-3.26; *P* =0.071) (**Figure 1A**). An inferior POST-LIPI was also significantly associated with a shorter PFS (median, 8.0 months vs NR; adjusted HR, 2.36; 95% CI, 1.25-4.47; *P* =0.008) (**Figure 1B**).

Conclusions: In conclusion, an inferior LIPI score was associated with a lower ORR in NSCLC patients received first-line PD-1 inhibitor-based combination therapy. Moreover, patients with an inferior LIPI had a shorter PFS in the population.



Keywords: Inflammation Index, Immune-checkpoint Inhibitors, Combination Chemothe, Non-small Cell Lung Cancer

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-097 Landscape and Dynamic Changes of Peripheral Immune Cells in Non-small Cell Lung Cancer Patients with First-line Immunotherapy

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Introduction: Early identification of patients who would benefit most from immune checkpoint inhibitors (ICIs) and dynamic monitoring of disease can help to reduce unnecessarily long-term therapy and optimize patient management. Peripheral blood-based biomarker exploration is attractive as the ease of noninvasive resource collection and the ability of dynamic assessment. Here, we aimed to describe landscape and dynamic changes of circulating immune cells and to identify potential biomarkers that reflect response to ICIs-based treatment.

Methods: Peripheral blood mononuclear cells (PBMCs) were analyzed by full spectrum flow cytometry, including CD4+ T cells, CD8+ T cells, regulatory T (Treg), T helper (Th), B cells, dendritic cells (DC), natural killer (NK), monocytes and myeloid-derived suppressor cells. PBMCs were collected at baseline and after 2 cycles of immunotherapy.

Results: A total of 33 non-small cell lung cancer (NSCLC) patients who received first-line immunochemotherapy combination regimens were included, in which 14 patients achieved at least nine-months progression-free survival (PFS) (DCBc group), the other 19 patients experienced less than nine-months PFS (NDBc group). Over the course of treatment, a significant reduction in frequency of CD4+ effector memory T cells (T_{EM}) was observed in NDBc group (P = 0.025), while decreased frequency of CD8+ T_{EM} was associated with DCBc (P = 0.026). Reduction in frequency of PD-1+memory T cells tended to be a high likelihood of DCBc, especially PD-1+ CD4+ T_{EM} and PD-1+ CD8+ central memory T cells (T_{CM}). Besides, a significant increase in proportion of myeloid DC (mDC) in patients with NDBc (P = 0.004), but not observed in DCBc group.

Conclusions: Collectively, dynamic changes of memory T cells and mDC can provide information regarding clinical efficacy to immunochemotherapy and potentially facilitate treatment stratification.

Keywords: immunotherapy, non-small cell lung cancer, peripheral blood mononuclear cells

EP08.01-098 Evaluating Risk Factors for Pneumonitis in Stage III NSCLC Patients Receiving Durvalumab after Definitive Chemoradiation

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Introduction: Both radiation pneumonitis (RP) and immune checkpoint inhibitor pneumonitis (ICI-p) are toxicities that can occur in stage III NSCLC patients undergoing concurrent chemoradiation (CCRT) followed by durvalumab consolidation. We set out to evaluate potential risk factors for the development of symptomatic pneumonitis in a cohort receiving varied doses of combined CCRT and durvalumab.

Methods: We conducted a retrospective study of pts with stage III NSCLC treated with CCRT followed by durvalumab from 2018-21. Median follow up time was 18.8 mo from the last day of RT to last contact. Treatment related toxicities were extracted from electronic medical records and a prospectively collected database. RT dose parameters were extracted from each treatment plan. Normal lung volume (NLV) was defined as total lung volume minus clinical target volume (Lung -CTV). Percentage of NLV receiving more than 5, 10, or 20 Gy (V5, V10, V20), and mean lung dose (MLD) were calculated. The primary endpoint was development of symptomatic pneumonitis (≥gr 2), assessed via clinical presentation and available imaging. The association between the % NLV of radiation and the probability of developing pneumonitis was analyzed using logistic regression, and odds ratios (OR) were estimated.

Results: Of the 80-pts included in this study, 31 (38.8%) developed any IRAE, and 21 (26.3%) developed symptomatic pneumonitis following durvalumab initiation. 69 (86.3%) received carboplatin-paclitaxel and 11 (13.8%) received cisplatin-etoposide chemotherapy. 73 (91.2%) had received standard RT dose of 60 Gy, while 7 (8.8%) received an additional 12-16 Gy SBRT boost to the primary tumor on a clinical trial. On average, pts received 12.6 doses of Durva at 10 mg/kg/dose. 59 pts (74.0%) had dosing interruptions; of these, 25 (25.3%) was due to IRAE. We found no significant association between incidence of pneumonitis and demographic characteristics, history of DM, CAD, COPD, smoking, ECOG, PDL1 expression, chemotherapy regimen, or RT total dose, MLD, or V20 of lung (all p >0.05). Other IRAE included 4 (5%) colitis, 4 (5%) Myalgia/arthralgia, 1 (1.3%) dermatitis, and 1 (1.3%) thyroid abnormality.

Conclusions: About 26.3% pts developed symptomatic pneumonitis similar to prior studies. The treatment is overall well tolerated. Other than pneumonitis, incidence of all other IRAE are low.

Keywords: pneumonitis, Chemoradiation, Durvalumab

EP08.01-099 Activity of aPD1-MSLN-CART Cells against Metastatic Lung Cancer in a Phase 1 Trial

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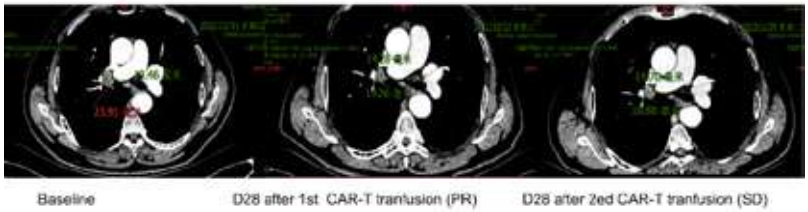
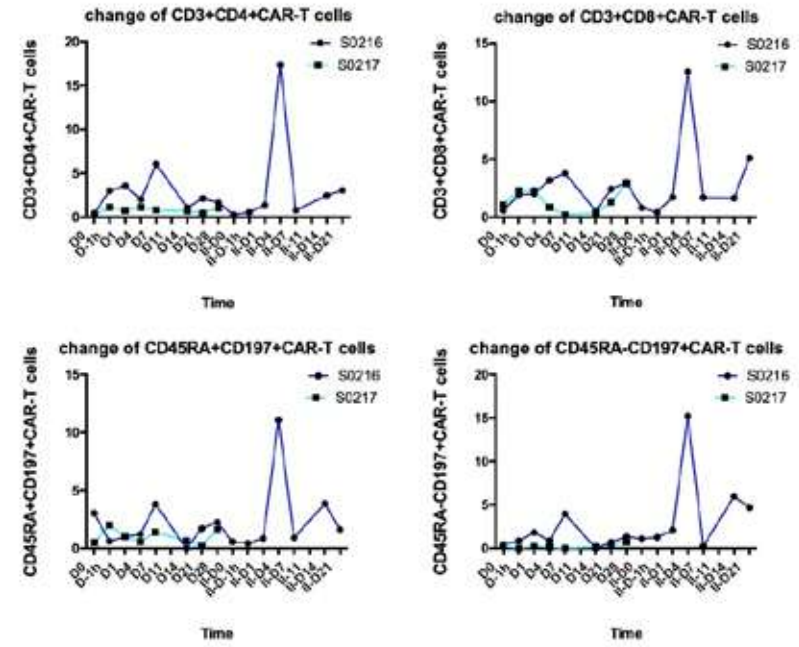
Introduction: Mesothelin (MSLN) has been found to be highly expressive in multiple solid tumors including lung cancer. We engineered autocrine PD-1 nano antibodies MSLN CAR-T cells (aPD1-MSLN-CART), targeting MSLN positive tumor cells by chimeric antigen receptor-modified T (CAR-T) cells as well as secretion of PD1 antibodies, playing dual antitumor immune mechanism.

Methods: We performed a phase 1 study to evaluate the safety and efficacy of adoptive cell therapy with aPD1-MSLN-CART in 5 patients with chemotherapy-refractory metastatic lung cancer. Patients were given intravenous aPD1-MSLN-CART cells at most two cycles.

Results: A total of 40 patients have been screened, 5 cases have been successfully enrolled in the group, 2 cases have completed 1 cycle transfusion and 2 cases completed 2 cycles, 1 case withdraw before transfusion. None of the patients developed cytokine release syndrome or neurologic symptoms and there were no dose limiting toxicities. Partial response in 1 patient, disease stable in 2 and with 1 progression disease. Transient CAR expression was detected in patients' blood after infusion and led to change of CD3+CD4+CAR-T and CD3+CD8+CAR-T cells as well as cytokines IL-6, IL-10, INF-γ and TNF-α.

Conclusions: Our results provide evidence for the potential anti-tumor activity of aPD1-MSLN-CART cells in chemotherapy-refractory metastatic lung cancer.





Keywords: CAR-T, mesothelin, lung cancer

EP08.01-100 Unlocking Primary Resistance to Checkpoint Inhibitors in Non-small Cell Lung Cancer by Metagenomic and Metabolomic

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Introduction: Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis generate sustained therapeutic responses in a sizable minority of advanced non-small-cell lung cancer (NSCLC) patients. Several studies have shown that abnormal gut microbiome composition which may influence antitumor immune responses via metabolome led to primary resistance to ICIs, and therapeutic responses can be improved via its modulation. But functions of antitumor gut microbiome strains and metabolomic characteristics for advanced NSCLC have not been fully elucidated.

Methods: To better recognize the function of the gut microbiome in response to ICIs, we prospectively collected fecal and blood samples from 44 participants with advanced NSCLC starting treatment with PD-1-based immunotherapy. We investigated the molecular mechanisms underlying the impacts of specific strains through metagenomic sequencing and metabolomic analyses using participant samples.

Results: Significant differences were identified in the diversity and composition of the participant gut microbiome of responders (R) versus non-responders (NR) to immunotherapy in the baseline period. In metagenomic studies of fecal samples from participants with NSCLC (n=44, 22R, 22NR), *Actinobacteria* including *Bifidobacterium bifidum* was abundant in responding participants (P=0.047). By the Kyoto Encyclopedia of Genes and Genomes (KEGG) Orthology Database, metabolomic analyses of participant blood samples revealed functional differences in gut microbiome in R including enrichment of alpha-galactosidase (P=0.008), as well as in the pathway of galactose metabolism (P=0.042).

Conclusions: *Bifidobacterium bifidum* modulates alpha-galactosidase, which influences the efficacy of PD-1-based immunotherapy against advanced NSCLC, via the pathway of galactose metabolism. Together, these data have useful implications for the primary resistance of advanced NSCLC patients with ICIs.

Keywords: Immune checkpoint inhibitors, Metagenomic, Metabolomic

EP08.01-101 Factors Predictive of Primary Resistance to Immune Checkpoint Inhibitors in Asian Patients with Advanced NSCLC

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Introduction: Immune checkpoint inhibitors (ICI) have transformed the therapeutic landscape of advanced non-small cell lung cancer (NSCLC). Despite this, primary resistance to ICI occurs. Primary resistance, according to the Society for Immunotherapy of Cancer (SITC), is defined as progression within 6 months of ICI treatment. Patients must receive at least 6 weeks of ICI monotherapy with best response of progressive disease (PD) or stable disease (SD). Using this definition, we aim to determine factors predictive of primary resistance to ICI in Asian patients with advanced NSCLC.

Methods: Between June 2014 to Oct 2021, we retrospectively analyzed records of advanced NSCLC who had received ICI monotherapy at the National University Cancer Institute Singapore. Patients on dual ICI-combination and ICI-chemotherapy combination were excluded. Patients who discontinued treatment early due to adverse events were also excluded from analysis. Logistic regression model was used to determine the risk factors predictive of primary resistance to ICI.

Results: Ninety-one patients were evaluable. Amongst them, n=57 (62.6%) had primary resistance to ICI. Median age was 63.7. Majority were male (71.4%), Chinese (76.9%), smokers (64%), of ECOG PS 0-1 (72%) and of adenocarcinoma histology (73.6%). The majority received pembrolizumab (n=61, 67%), followed by nivolumab (n=15, 16.5%) and atezolizumab (n=10, 11%), respectively.

Forty-one percent received ICI in the 1st line setting, 31% in 2nd line, and 28.6% in 3rd line and beyond setting, respectively. PD-L1 TPS was ≥50% in 42% of patients. Median duration of ICI therapy was 81 days. Median duration of follow-up was 295 days.

On univariate logistic regression, baseline Neutrophil-Lymphocyte Ratio (NLR) ≥3, 6th week NLR ≥3, females, non-smokers were predictive of increased odds of developing primary resistance to ICIs (odds ratio (OR) 2.84 (95% CI 1.08-7.66), p=0.035; OR 7.35 (95% CI 2.59-22.77), p<0.001; OR 3.38 (95% CI 1.2-11.1), p=0.029; OR 3.31 (95% CI 1.27-9.43), p=0.018).

Multivariate logistic regression demonstrated that 6th week NLR ≥3 and female gender remained as predictors for primary resistance to ICIs (OR 7.14 (95% CI 1.81-34.76), p=0.008; OR 5.32 (95% CI 1.36-27.03), p=0.026).

Conclusions: Elevated NLR (≥3) at 6th week and female gender are predictive factors for developing primary resistance to ICI monotherapy in Asian patients with advanced NSCLC. Future larger studies are required to validate the above findings.

Keywords: primary resistance, Asian patients, immune checkpoint inhibitors

EP08.01-102 Anlotinib Combined with PD-1 Inhibitors May Benefit Advanced Non-small Cell Lung Cancer Patients After Failure of EGFR-TKI Therapy

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Introduction: Approximately 50% of patients with lung adenocarcinoma (LUAD) in Asian populations harbor epidermal growth factor receptor (EGFR) mutations. Although the current front-line third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) targeted therapy can benefit these EGFR mutation-positive patients, treatments for non-small cell lung cancer (NSCLC) patients with EGFR-TKI resistance are limited. The study aimed to explore the application of both angiogenic and PD-1 blockade in NSCLC patients who had failed EGFR-TKIs.

Methods: This study reviewed the medical history of 6020 lung cancer patients who underwent PD-1/PD-L1 inhibitors and 1563 who received anlotinib at Shanghai Chest Hospital from 2018 to 2021. A total of 38 LUAD patients with EGFR-TKI resistance who had received anlotinib and PD-1 inhibitors combination therapy were enrolled in final analysis. Re-biopsy was performed in all the 38 patients.

Results: The median progression-free survival (mPFS) was 4.33 months [95% confidence interval (CI): 2.62-6.04]. The median overall survival (mOS) was 11.83 months (95% CI: 7.37-16.3). Most of patients (73.7%) received combination therapy in the fourth- and later-lines, with a mPFS of 4.03 months (95% CI: 2.41-5.66) and a mOS of 11.83 months (95% CI: 7.95-15.72). The disease control rate (DCR) was 92.1%. There were three patients who discontinued the combination therapy due to adverse events, but the other adverse reactions such as asthenia, poor appetite, oral ulcers, etc. were manageable and reversible.

Conclusions: The combination of anlotinib and PD-1 inhibitors is a promising regimen for the late-line treatment of LUAD patients with EGFR-TKI resistance, which warrants further validation in prospective trials.

Keywords: non-small cell lung cancer, EGFR, antiangiogenics

EP08.01-103 Combination of Anlotinib and PD-1/PD-L1 Inhibitors as Second-line and Subsequent Therapy in Advanced Small-cell Lung Cancer

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Introduction: Treatment options in late-line advanced small-cell lung cancer (SCLC) were unmet. This study evaluated the efficacy and safety of anlotinib combined with programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitors as second-line and beyond therapy for advanced SCLC.

Methods: We retrospectively analyzed SCLC patients who received anlotinib plus PD-1/PD-L1 inhibitors at Shanghai Chest Hospital from November 2016 to November 2020.

Results: A total of 40 patients were enrolled in the final analysis. Best objective responses (BORs) to anlotinib plus PD-1/PD-L1 inhibitors included progressive disease (20.0%), stable disease (65.0%), partial response (15.0%) and complete response (0%). Disease control rate (DCR) was 80.0%. Median progression-free survival (PFS) was 3.40 months, while median overall survival (OS) was 8.20 months. Fatigue and decreased appetite were the most pronounced adverse events (AEs). 2 patients discontinued the combined therapy due to intolerable AEs. However, the rest of the patients, who presented with tolerable AEs, completed the therapy or were still in the combination therapy.

Conclusions: The combination of anlotinib and PD-1/PD-L1 blockade has promising efficacy and safety as second-line and subsequent therapy for SCLC.

Keywords: small-cell lung cancer, anlotinib, PD-1/PD-L1

EP08.01-104 Baseline Tumor Size and Survival Outcomes among Patients with Advanced NSCLC treated with First-Line Immunotherapy

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Introduction: The baseline tumor size (BTS) is known as a prognostic of overall survival (OS) in patients with non-small cell lung cancer (NSCLC) who received immune checkpoint inhibitor monotherapy (ICI-mono). However, prognostic impact of BTS among patients treated with ICI in combination with chemotherapy (ICI-chemo) has not been well investigated.

Methods: 159 patients with advanced NSCLC who received first-line ICI-mono or ICI-chemo from January 2016 to April 2021 in our institution were retrospectively analyzed. BTS was measured both as the max BTS (maximum target lesions' longest diameter) and total BTS (sum of target lesions' longest diameters) in accordance with RECIST ver 1.1. Using Cox proportional hazards regression model, we explored the association between baseline BTS values and survival outcomes.

Results: In patients who received ICI-mono, the median PFS was 16.7 months (95% CI [confidence interval], 10.7- not available [NA]) in the small max BTS group and 3.3 months (95% CI, 1.4-9.9) in the large max BTS group, with the former having a significantly better PFS (HR [hazard ratio], 0.39; 95% CI, 0.22-0.70; P=0.0012). However, in patients with who received ICI-chemo, the median PFS was 7.8 months (95% CI, 6.4-14.3) in the small max BTS group and 15.6 months (95% CI, 6.3-NA) in the large max BTS group, and there was no significant difference in PFS between the small max BTS and large max BTS groups (P=0.21). In multivariable analysis, the small max BTS group was significantly associated with longer progression-free survival (PFS) in patients treated with ICI-mono (HR, 0.43; 95% CI, 0.23-0.81; P=0.009); however, it was not associated with longer PFS in patients treated with ICI-chemo (HR, 0.58; 95% CI, 0.29-1.18; P=0.132). The group treated with ICI-chemo achieved a statistically significant improvement in PFS compared to the group treated with ICI-mono in patients with max BTS ≥ 50 mm (HR, 0.26; 95% CI, 0.11-0.64; P=0.004), and the group treated with ICI-chemo was not associated with longer PFS compared to the group treated with ICI-mono in patients with max BTS < 50 mm (HR, 0.56; 95% CI, 0.28-1.13; P=0.107).

Conclusions: While a small max BTS was associated with better outcomes in patients treated with ICI-mono, it was not associated with them in patients treated with ICI-chemo. The max BTS could be a potential marker for predicting whether patients with NSCLC will respond to ICI-mono or ICI-chemo.

Keywords: Predictive, Immune checkpoint inhibitor (ICI), Baseline tumor burden

EP08.01-105 Efficacy of First-Line Immune Checkpoint Inhibitors in Patients with Advanced NSCLC harboring KRAS, MET, FGFR, RET, BRAF, and HER2 Alterations

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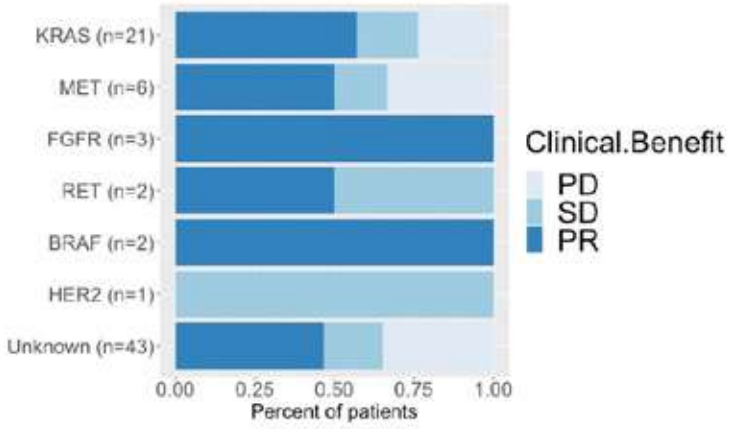
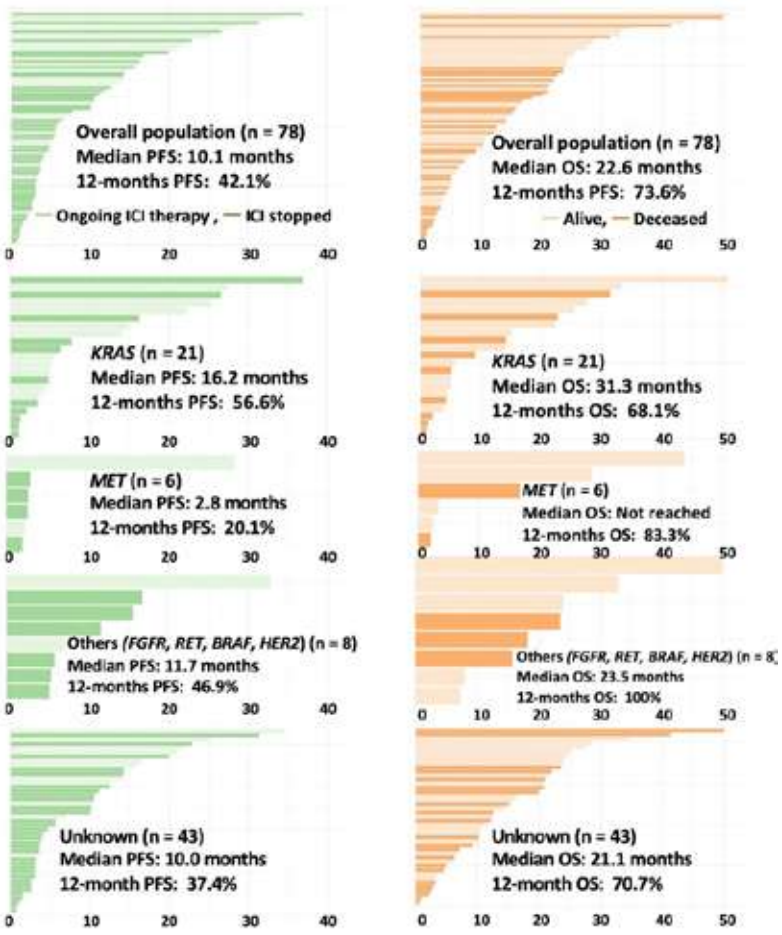
Introduction: In patients with NSCLC harboring molecular alterations, the efficacy of immune checkpoint inhibitors (ICI) remains unknown. The aim of our study was to examine the efficacy of first-line ICI among patients having NSCLC with *KRAS*, *MET*, *FGFR*, *RET*, *BRAF*, and *HER2* alterations, compared to those with driver-unknown.

Methods: A single-center, retrospective cohort study (n =160) was conducted. Patients diagnosed with advanced NSCLC harboring *KRAS*, *MET*, *FGFR*, *RET*, *BRAF*, and *HER2* alterations or driver-unknown and who received the first-line ICI therapy were analyzed. Progression-free survival (PFS), overall survival (OS), and objective response were evaluated.

Results: There were 78 patients with NSCLC (median age, 72 years): 67% were men, 15% were never-smokers, and 83% had adenocarcinoma. Among them, 21 had *KRAS* alteration, six had *MET* alteration, three had *FGFR* alteration, two had *RET* alteration, two had *BRAF* alteration, one had *HER2* alteration, 43 had driver-unknown. Median PFS (in months) was 16.2 (95% confidence interval [CI]: 6.3- not reached [NR]) for *KRAS*, 2.8 (95% CI: 2.7-NR) for *MET*, 11.7 (95% CI: 5.9-NR) for other alterations (*FGFR*, *RET*, *BRAF*, and *HER2*), and 10.0 (95% CI: 3.7-14.3) for driver-unknown, respectively. Median OS (in months) was 31.3 (95% CI: 9.0-NR) for *KRAS*, not reached for *MET*, 23.5 (95% CI: 18.3-NR) for others alterations (*FGFR*, *RET*, *BRAF*, and *HER2*), and 21.1 (95% CI: 15.2-NR) for driver-unknown, respectively. One patient with *MET* alterations presented with pneumonitis as immune-related adverse events, preventing the use of the following MET inhibitors.

Conclusions: The clinical benefit of the first-line ICI was similar in advanced NSCLC regardless of the driver alterations (*KRAS*, *FGFR*, *RET*, *BRAF*, and *HER2*). However, the outcome for patients with *MET* alterations was inferior, and the first-line ICI could be considered after targeted therapies, given their adverse events.




Overall population (n = 78)
Median PFS: 10.1 months
12-months PFS: 42.1%
Ongoing ICI therapy , ICI stopped
Overall population (n = 78)
Median OS: 22.6 months
12-months PFS: 73.6%
Alive, Deceased
KRAS (n = 21)
Median PFS: 16.2 months
12-months PFS: 56.6%
KRAS (n = 21)
Median OS: 31.3 months
12-months OS: 68.1%
MET (n = 6)
Median PFS: 2.8 months
12-months PFS: 20.1%
MET (n = 6)
Median OS: Not reached
12-months OS: 83.3%
Others (FGFR, RET, BRAF, HER2) (n = 8)
Median PFS: 11.7 months
12-months PFS: 46.9%
Others (FGFR, RET, BRAF, HER2) (n = 8)
Median OS: 23.5 months
12-months OS: 100%
Unknown (n = 43)
Median PFS: 10.0 months
12-month PFS: 37.4%
Unknown (n = 43)
Median OS: 21.1 months
12-month OS: 70.7%
0 10 20 30 40
0 10 20 30 40 50

EP08.01-106 PD-1/PD-L1 Inhibitors Increase Myocardial Infarction in Osimertinib-Treated Patients with Non-Small Cell Lung Cancer

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Introduction: Osimertinib is now a standard of care for patients harboring T790M mutation or first-line EGFR-sensitive mutations. And it is emerging as the optimal choice for completely resected IB-IIIA non-small cell lung cancer (NSCLC) harboring EGFR mutation. While most of patients will inevitably develop resistance to osimertinib. PD-1/PD-L1 inhibitors have changed the paradigm of NSCLC therapy. Many attempts have also made with PD-1/PD-L1 inhibitors in tyrosine kinase inhibitor (TKI) resistance patients. Both BGB-A317-2001-IIT and ORIENT-31 study showed the benefit of PD-1/PD-L1 inhibitors in TKI resistance patients. Cardiac disorders are one of most important adverse effects of Osimertinib. Whether PD-1/PD-L1 inhibitors combination with osimertinib would increase the incidence of cardiac disorders is unknown. This study aims to determine whether PD-1/PD-L1 inhibitors increase osimertinib-associated cardiac disorders.

Methods: A database study of 11993 participants with NSCLC in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, performed between April 2014 and December 2021. We compared the incidence of osimertinib-associated cardiac disorders in patients receiving and not receiving PD-1/PD-L1 inhibitors treatment.

Results: The mean age of patients treated with osimertinib, with and without PD-1/PD-L1 inhibitors, was 63.6±12.9 and 68.7±12.1 years, respectively. The proportion of male patients with and without PD-1/PD-L1 inhibitors was 42.0% and 29.9%. Of the 11993 patients treating with osimertinib, 714 cases (6%) developed cardiac disorders. Of 11893 patients treated without PD-1/PD-L1 inhibitors, 707 developed cardiac disorders (5.9%). Of 100 patients treated with both EGFR-TKI and PD-1/PD-L1 inhibitors, 7 developed cardiac disorders (7%). The odds ratio of EGFR-TKI-associated cardiac disorders in cases with and without PD-1/PD-L1 inhibitors treatment was 1.191 (95%CI, 0.550-2.577). We further analyzed the impact of PD-1/PD-L1 inhibitors on myocardial infarction. Of 11893 patients treated without PD-1/PD-L1 inhibitors, 62 developed myocardial infarction (0.5%). Of 100 patients treated with both EGFR-TKI and PD-1/PD-L1 inhibitors, 2 developed myocardial infarction (2%). The odds ratio of EGFR-TKI-associated myocardial infarction in cases with and without PD-1/PD-L1 inhibitors treatment was 3.894 (95%CI, 0.939-16.144; P=0.043).

Conclusions: We found that PD-1/PD-L1 inhibitors did not increase osimertinib-associated cardiac disorders but increase osimertinib-associated myocardial infarction in NSCLC. Owing to small number size of myocardial infarction of this study, the results need further confirmation. However, careful consideration should be given to the possibility of an increased risk of myocardial infarction when PD-1/PD-L1 inhibitors are administered in patients with osimertinib history or current using osimertinib.

Keywords: osimertinib, immunotherapy, cardiac disorder

EP08.01-107 The Increase of Blood Intratumor Heterogeneity Is Associated with Unfavorable Outcomes of ICIs Plus Chemotherapy in NSCLC

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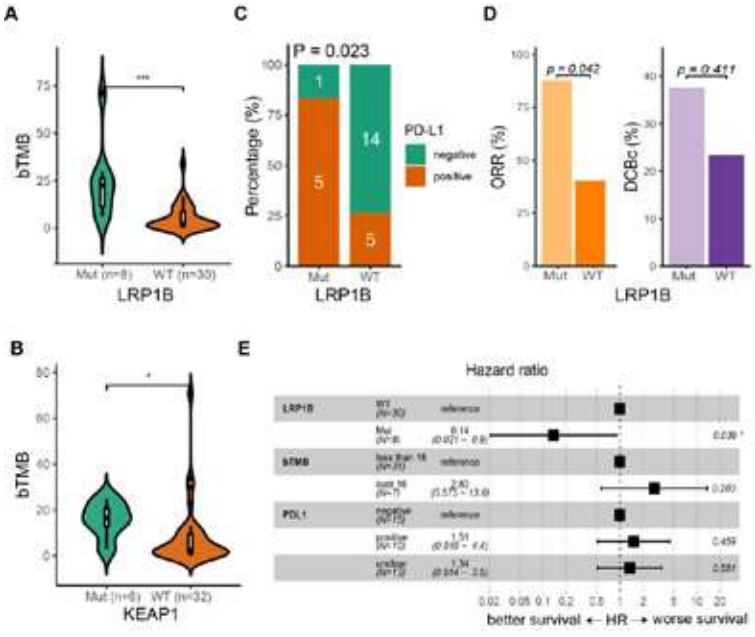
Introduction: The combination of immune checkpoint inhibitors (ICIs) and chemotherapy has been the standard first-line treatment for advanced non-small cell lung cancer (NSCLC) patients with driver-gene negative. However, efficacy biomarker for ICIs-based combination therapy is lacked. We aimed to identify potential factors associated with outcomes of ICIs plus chemotherapy at baseline and dynamic changes in peripheral blood.

Methods: We collected plasma samples of 51 advanced NSCLC patients without EGFR/ALK/ROS1 alteration at baseline and/or after two treatment cycles of ICI plus chemotherapy. NGS targeted sequencing was then performed using a 520-gene panel (OncoScreen PlusTM) in Burning Rock Biotech, a commercial clinical laboratory which has demonstrated impressive performance SEQC2 liquid biopsy program (Nat Biotechnol, 2021). We utilized a weighted Shannon diversity index (SDI) suitable for blood to evaluate intratumor heterogeneity (ITH), which we called blood-based ITH (bITH). bITH up was defined as a ≥ 10% increase in bITH score from baseline, with a second confirmatory measurement after treatment.

Results: At baseline, neither bITH, nor other common biomarkers, including ctDNA level, blood-based tumor mutational burden (bTMB) and PD-L1 expression, was associated with progression-free survival (PFS) of ICIs plus chemotherapy. LRP1B mutation at baseline was significantly associated with favorable outcomes to ICIs plus chemotherapy. There were 37 patients who had paired samples at baseline and after two cycles treatment, with the median interval of 53 days. However, in this study, no significant difference was found in PFS between patients with and without ctDNA clearance, or between patients with and without MSAF drop. Intriguingly, patients with bITH up had significant shorter PFS (HR, 4.92; 95% CI, 1.72-14.07; P = 0.001), and lower durable clinical benefit (DCB) rate (0 vs 41.38%, P = 0.036) than those with bITH stable or down. Moreover, we found that all seven patients with progressive disease (PD) after two cycles treatment have increased bITH score and seven of eleven (63.6%) of patients with increased bITH were confirmed to have PD to treatment. Cases studies showed that MSAF was decreased but bITH was increase in two patients with PD and bITH-up was detected before radiography in one patient, which indicated that bITH was a promising biomarker to predict disease progression.

Conclusions: The present study is the first to report that the increase of bITH is associated with unfavorable outcomes of ICIs plus chemotherapy in advanced NSCLC patients.



Keywords: non-small cell lung cancer, immune checkpoint inhibitors, blood-based intratumor heterogeneity

EP08.01-108 Real-Life Costs and Benefit of First-Line Pembrolizumab for Advanced NSCLC - A Propensity-Score Matched Case-Control Study

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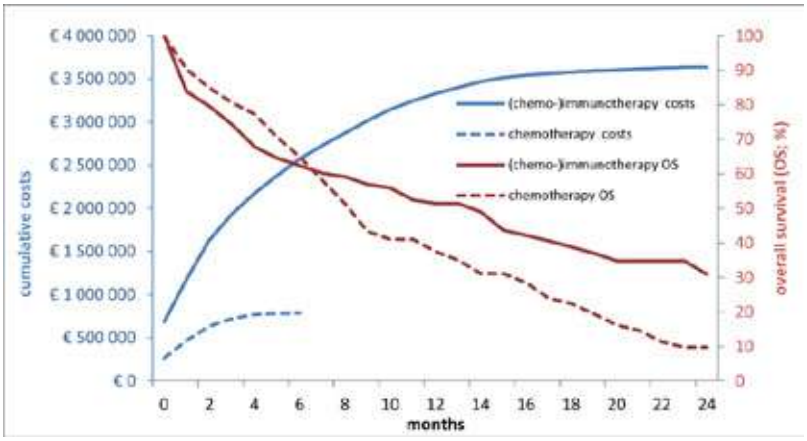
Introduction: Pembrolizumab is approved as first-line monotherapy for advanced NSCLC with a programmed death-ligand 1 (PD-L1) expression of ≥50% or as chemotherapy-combination in patients with any level of PD-L1 expression. We aimed to investigate the real-life benefit and costs of first line immune checkpoint inhibitor (ICI) therapy by comparing a pembrolizumab-treated cohort with a matched historical chemotherapy (CHT) cohort.

Methods: Ninety-three subsequent patients having received first line pembrolizumab as monotherapy (n=17) or as combination therapy together with platinum-based doublet CHT (n=76) between 2017 and 2019 were retrospectively identified. Using propensity-score matching for age, sex, Eastern Co-operative of Oncology Group (ECOG) performance status and histological subtype, the ICI-treated cohort was compared to a historical cohort of patients having received first-line platinum-based doublet CHT between 2011 and 2016, whereas patients who had received ICI in later therapy lines were excluded. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method; the log-rank test was used for statistical comparison between the cohorts. Therapy costs were calculated based on the respective average drug prizes between 2017 and 2019 for both treatment groups.

Results: Both cohorts did not significantly differ in terms of matching criteria. Among the patients treated with first line pembrolizumab, median PFS was 6 months (M) (95% confidence interval [CI] 4,9) and significantly longer (p<0.001) than in the historical CHT cohort (4M; 95% CI 3, 5). Median OS was significantly longer in the ICI group (14M [95% CI 8, 19] vs. 8M [95% CI 7, 10]; p=0.01). Total therapy costs were €3,635,572 and €867,000 in the ICI and the CHT cohort respectively, average costs per patient were €39,092 and €8,179. Therapy costs for one additional month of PFS and OS on ICI therapy as compared to CHT amounted to €6,332 and €5,152, respectively.

Conclusions: Patients with advanced NSCLC treated with first line pembrolizumab have significantly longer PFS and OS as compared to historical fist-line CHT patients. This benefit however goes along with considerably higher treatment costs.



Keywords: pembrolizumab, real-life, costs

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-109 TACTI-002: A Phase II Study of Eftilagimod Alpha (Soluble LAG-3) & Pembrolizumab in 2nd line PD-1/PD-L1 Refractory Metastatic NSCLC

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Introduction: Eftilagimod alpha (efti) is a soluble LAG-3 protein binding to a subset of MHC class II molecules to mediate antigen presenting cell (APC) and CD8 T-cell activation. Stimulating APCs and subsequent T cell recruitment with efti may revert PD-1 resistance. We hereby report updated results from part B of the TACTI-002 trial: 2nd line PD-1/PD-L1 refractory non-small cell lung carcinoma (NSCLC) pts treated with efti plus pembrolizumab.

Methods: Patients (pts) with previously treated metastatic NSCLC, refractory to PD-1/PD-L1 and unselected for PD-L1 expression were enrolled. A Simon's 2-stage design was used, with objective response rate (ORR) by iRECIST as the primary endpoint (EP). Secondary EPs include tolerability, disease control rate (DCR), progression free survival, overall survival and other efficacy parameter. Pts received 30 mg efti (SC) q2w for 8 cycles (1 cycle= 3 wks) and then q3w (up to 1 yr) together with pembrolizumab (200 mg IV q3w for up to 2 yrs). Imaging was performed every 9 weeks and evaluated locally. PD-L1 TPS scoring was performed centrally.

Results: 36 pts were enrolled. Data cut-off was 21 Jan 2022 with a minimum follow-up of 5 months (m). Median age was 67 years (46-84) and 61 % were male. The ECOG PS was 0 and 1 in 33 % and 67 % of pts, respectively. Pts had squamous (19 %) and non-squamous (78 %) histology. Pts were pretreated with a PD-1/ PD-L1 antagonist alone (28 %) or in combination with platinum-based chemo (72 %). All PD-L1 subgroups were included with 36% being PD-L1 negative and 69% having a TPS <50 %. Pts received a median of 5 (range 2-31) pembrolizumab and 7 (range 2-22) efti administrations. The most common (>15 %) adverse events were decreased appetite (33 %), dyspnea (31 %), cough (25 %), asthenia (22 %), fatigue (17 %) and weight decreased (17 %). All (N=36) pts were evaluated for response. ORR (iRECIST) and DCR was 6 % (2/36) and 36 % (13/36), respectively. Both PRs were reported in pts pre-treated with chemo + IO and are on study for 9+ and 23+ m, respectively. Progression free survival rate at 6 m was 26 % and 73 % were alive at 6 m. Analysis of tumor growth kinetics showed a deceleration of tumor growth or shrinkage of target lesions in 74 % of evaluable pts.

Conclusions: Efti in combination with pembrolizumab is safe and shows encouraging signs of antitumor activity in truly PD-1/PD-L1 refractory 2nd line NSCLC pts.

Keywords: LAG-3, NSCLC, PD-1/PD-L1 refractory

EP08.01 METASTATIC NON-SMALL CELL LUNG CANCER - IMMUNOTHERAPY

EP08.01-110 Trial in Progress: A Phase 2 Multicenter Study (IOV-LUN-202) of Autologous Tumor-infiltrating Lymphocyte (TIL) Cell Therapy (LN-145) in mNSCLC

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Introduction: Patients with mNSCLC without actionable driver mutations have limited treatment options after progression on concurrent or sequential front-line immune checkpoint inhibitors (ICI) and platinum-based chemotherapy ± bevacizumab. LN-145, an autologous TIL cell therapy, has demonstrated feasibility, safety, and an early signal of efficacy with a 21.4% objective response rate (ORR) in heavily pretreated patients with mNSCLC, including responders with PD-L1-negative tumors (Schoenfeld AJ, SITC 2021 [abs 458]). Herein, we describe the amended, ongoing, IOV-LUN-202 study, which evaluates LN-145 in patients with stage IV mNSCLC after confirmed disease progression on front-line standard-of-care treatment (including concurrent or sequential ICI + chemotherapy ± bevacizumab).

Methods: IOV-LUN-202 (NCT04614103), an open-label, nonrandomized, phase 2 study, is actively enrolling patients into cohorts 1 (tumor proportion score [TPS] <1% prior to ICI use or with no available historical TPS) and 2 (TPS ≥1% prior to ICI use) to receive LN-145 manufactured using a 22-day Gen 2 process. In Cohort 3 (any TPS), tumor tissue is procured using core biopsies in patients unable to undergo surgical resection, and LN-145 is manufactured using a 16-day Gen 3 process. A retreatment cohort (n not prespecified) will enroll patients from cohorts 1-3 who had initially responded to LN-145 and progressed or did not respond and had unconfirmed progressive disease (PD). A total of approximately 95 patients is planned for cohorts 1-3. Key eligibility criteria include diagnosis of stage IV mNSCLC, which has progressed after 1 prior line of therapy (if concurrent ICI + chemotherapy or 2 prior lines if sequential). An additional line of appropriate targeted therapy is allowed in those with actionable mutations other than EGFR, ALK, or ROS1 genomic alterations (e.g., MET, HER2, RET, BRAF, KRAS). Patients must have at least 1.5-cm lesion(s) for TIL generation, at least 1 RECIST-measurable lesion(s) remaining after tumor harvest, and ECOG PS of 0 or 1. Pre-progression tumor harvest and TIL manufacturing are allowed prior to documented PD with the intent to have TIL available at the time of progression. LN-145 is generated at centralized GMP facilities, and the final infusion product is cryopreserved and shipped to the sites. Upon disease progression, patients receive nonmyeloablative lymphodepletion with cyclophosphamide (2 doses at 60 mg/kg) and fludarabine (5 doses at 25 mg/m^2), followed by LN-145 infusion (1-150 × 10^9 cells) and up to 6 doses of IL-2 (600,000 IU/kg). The primary endpoint is ORR assessed by IRC per RECIST v1.1; secondary endpoints include complete response rate, duration of response, disease control rate, progression-free survival, overall survival, and safety (incidence of Grade ≥3 treatment-emergent adverse events [AEs] and serious AEs).

Keywords: Tumor-infiltrating lymphocytes, Adoptive cell therapy, mNSCLC

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-001 Concurrent Aumolertinib and Cerebral Radiotherapy as First-Line Treatment for EGFR Mutated Non-small Cell Lung Cancer with Brain Metastases

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Introduction: Patients with non-small cell lung cancer (NSCLC) are accompanied by 25%-40% brain metastases, who have a dismal prognosis and quality of life. The current therapeutic regimens for the treatment of brain metastases are poor efficacy. Currently, brain metastasis of epidermal growth factor receptor (EGFR) sensitive mutations is a hot and difficult point in targeted era of NSCLC treatment, meanwhile it is also the central issue of controversy in the field of lung cancer treatment. EGFR-TKIs is recently shown to be a potential treatment option for brain metastases of NSCLC patients. However, whether the combination of EGFR-TKIs and cerebral radiotherapy is better than EGFR-TKIs alone remains unclear. Among which, aumolertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), efficiently penetrates the blood brain barrier. This study was intended to conduct a study on the safety and efficacy of early craniocerebral radiotherapy combined with aumolertinib as first-line treatment for EGFR positive non-small cell lung cancer patients with brain metastasis.

Methods: The study is a single-arm study. NSCLC patients with EGFR mutations who have brain metastases are eligible for this study. This trial planned to enroll approximately 50 patients. Drug: aumolertinib 110mg p.o qd. Cerebral radiation combined with continuously aumolertinib orally until progression or unacceptable toxicity.Radiation: Stereotactic Radiotherapy(SRT) or Stereotactic Radiosurgery(SRS) or Whole-Brain Radiotherapy(WBRT). Image guided, 15-24 Gy*1F was recommended if use SRS. 9-12 Gy*3F/1W or 6Gy×5F/1W was recommended if use SRT. 30Gy/10F/2W for WBRT, large residual lesions will be treated with a local dose (≤DT 45Gy/15F).The primary endpoint is intracranial progress free survival (iPFS) by the investigator using RECIST 1.1 criteria. Secondary endpoints are adverse events of grade 3-4 or higher, rate of long term adverse events, rate of change in tumor microenvironment, changes in EGFR mutations, overall survival. As of November 2021, 6% of the planned 50 subjects have been enrolled. ClinicalTrials.gov Identifier: NCT04905550.

Keywords: brain metastases, Aumolertinib, radiotherapy

EP08.02-002 Aumolertinib in the Treatment of Activated EGFR Mutation Advanced NSCLC Patients with Interstitial Pneumonia

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Introduction: Interstitial pneumonia is a rare and serious adverse reaction during treatment with EGFR-TKIs and has a high mortality rate when it occurs. After the occurrence of interstitial pneumonia, treatment with osimertinib should be stopped immediately and glucocorticoids, anti-infection and respiratory support should be given. After the interstitial inflammation subsides, there is still no clear basis for whether EGFR-TKIs can be reintroduced and in what manner. The third-generation EGFR-TKI, aumolertinib, has demonstrated significant efficacy and a good safety profile in patients with NSCLC with EGFR-sensitive mutations, especially with a low incidence of interstitial lung disease. The incidence of interstitial lung disease was 0 (0/244) in the phase II APOLLO study with aumolertinib and 0.9% (2/214) in the phaseIII AENEAS study, but the mechanism needs to be further explored with aumolertinib.

Methods: An 81-year-old male patient with NSCLC was considered to have a tumor diagnosis of stage IB adenocarcinoma (pT2aN0M0) in 2013. Three years after surgical treatment, PET-CT imaging revealed multiple enlarged lymph nodes in the neck and genetic testing of the nodes suggested EGFR exon 19 deletion.This patient has undergone chemotherapy, 1st generation EGFR-TKI treatment, 3rd generation EGFR-TKI treatment, and a new 3rd generation EGFR-TKI aumolertinib re-challenge.

Results: Chemotherapy was treated with standard dose pemetrexed combined with cisplatin for 1 course, then changed to gefitinib 250 mg/day for 1 month due to poor efficacy, with partial remission, then changed to icotinib due to recurrent drug-related liver injury, with first generation EGFR-TKIs for 38 months in remission, with T790M mutation after disease progression. He was switched to 80 mg/day osimertinib, which was in partial remission, but developed interstitial pneumonia after 4 months of treatment, which was remitted after discontinuation, but recurred after re-dosing, so he was switched to 110 mg/day aumolertinib targeted therapy with stable efficacy and no recurrence of interstitial pneumonia.

Conclusions: Discontinuation of osimertinib may affect the patient's prognosis and replacement of chemotherapy may affect the patient's quality of life, so the third-generation EGFR-TKI aumolertinib was chosen for follow-up treatment, which resulted in a survival benefit and did not cause interstitial pneumonia. This provides a new option for patients who develop interstitial lung disease after treatment with EGFR-TKIs.

Keywords: EGFR-TKI, Interstitial pneumonia, re-challenge

EP08.02-003 Aumolertinib Plus Chemotherapy as 1st Line Treatment in Advanced Lung Cancer EGFR Mutation andctDNA Cleared Analysis

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Introduction: Aumolertinib is a novel third-generation epidermal growth factor receptor (EGFR)-targeted oral tyrosine kinase inhibitor (TKIs). The positive phase III trial (AENEAS) reported objective response rate (ORR) was 73.8% and medium progression-free survival (mPFS) was 19.3 months which aumolertinib as 1st line treatment of patients with EGFR mutation Non-Small Cell Lung Cancer (NSCLC). An improved efficacy of the combination of first-generation EGFR-TKI and carboplatin plus pemetrexed was confirmed in NEJ009 study. This study was designed to evaluate if aumolertinib adding pemetrexed and carboplatin chemotherapy could further improve outcomes as the 1st line treatment in NSCLC patients with EGFR mutation. Circulating tumor DNA (ctDNA) has emerged as an effective non-invasive tool to detect minimal/molecular residual disease (MRD) and potentially guide systemic therapies to improve outcomes. We hereby monitored ctDNA EGFR clearance in this trial to further assess this therapeutic strategy.

Methods: We are conducting a phase II trial in untreated patients with advanced NSCLC EGFR-sensitizing mutation and performance status of 0 to 2. Approximately 42 patients will be recruited. Patients are treated with aumolertinib 110mg orally perday plus pemetrexed 500mg/m2 and carboplatin area undercurve 5 intravenously every 3weeks for four cycles, followed by maintenance pemetrexed. The primary endpoint is mPFS, secondary endpoints include objective response rate (ORR), disease control rate(DCR), overall survival(OS) and toxicity. Circulating tumor DNA (ctDNA) EGFR clearance is also investigated.

Results: Form 7 November 2020 to 7 November 2021, 34 patients were enrolled and evaluated (Table 1). Preliminary overall ORR was 88.2% (30/34) and mPFS was not reached so far. The most common adverse events (AE, all grades) were neutropenia, fatigue, anorexia. 2 patients were intolerant to chemotherapy and had been receiving aumolertinib monotherapy since then. In this study, 28 patients received ctDNA EGFR testing during treatment and 22 of them (78.6%) had at least one ctDNA EGFR clearance after 2 or 4 cycles. The ORRs of patients with ctDNA EGFR cleared and the ones with no clearance were 91% and 33% respectively.

Conclusions: This is the first report that the combination of aumolertinib and chemotherapy provided a promising therapeutic strategy for advanced EGFR mutation NSCLC patients, even with CNS metastasis. And preliminary data from this trial suggests patients harboring EGFR exon19 deletion mutation and TP53 mutation would benefit more from this combination strategy (Table 1). Besides, we found that after 2-4 cycles of aumolertinib treatment, ctDNA clearance could be expected, which would indicate a remarkable better curative effect for patients.

ORR by Subgroups

		n	ORR
All patients		34	88.2%
Gender	Male	14	92.8%
	Female	20	85.0%
CNS metastases	Yes	19	89.4%
	No	15	86.6%
EGFR mutation	19del	19	94.7%
	21L858R	15	80.0%
TP53 mutation	Yes	13	92.3%
	No	21	85.7%
At least one ctDNA EGFR cleared at 2 or 4 cycles	Yes	22	90.9%
	No	6	33.3%

Keywords: NSCLC, Aumolertinib, ctDNA

EP08.02-004 Aumolertinib in Treatment-Naïve EGFR-mutant NSCLC Patients with Brain Metastases: Primary Efficacy and Safety Data from the ARTISTRY

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Introduction: ARTISTRY (NCT04778800) is an ongoing dose-escalation study evaluating third-generation EGFR-TKI aumolertinib (formerly almonertinib; HS-10296) in three cohorts of EGFR-mutant NSCLC patients with brain/leptomeningeal metastases. The study design was previously presented at ESMO 2021. Here we report primary efficacy and safety data of the brain parenchyma metastases cohort from the ARTISTRY.

Methods: Treatment-naïve EGFR-mutant NSCLC patients with brain parenchyma metastases received aumolertinib 110mg orally once daily. The dose was then escalated to 165mg in case of only intracranial progression. Assessments were performed every 4 weeks and then every 8 weeks after 2 consecutive disease control until extracranial progression as per RECIST v1.1. Endpoints included intracranial ORR (iORR), intracranial DCR (iDCR), and safety.

Results: At data cut-off (March 1, 2022), a total of 14 patients were enrolled and the median follow-up time was 7.8 months (range, 2.4-15.1), of which 12 patients with ≥1 measurable and/or non-measurable CNS lesion at baseline were included in the CNS full analysis set (cFAS) and 10 patients with ≥1 measurable CNS lesion at baseline were included in the CNS evaluable for response set (cEFR). The iORR was 66.7% (8/12; 95% CI: 34.9-90.1) in the cFAS and 80.0% (8/10; 95% CI:44.4-97.5) in the cEFR. The iDCR was 100% in both cFAS and cEFR. In the 165mg group, the iORR and iDCR were 0 (0/3) and 100% (3/3), respectively. The most common grade 1-2 adverse events (AEs) in all patients were anemia (3/14; 21.4%), alanine aminotransferase increased (3/14; 21.4%), fatigue (2/14; 14.3%), and edema limbs (2/14; 14.3%). No grade ≥3 AEs were observed.

Conclusions: Aumolertinib showed preliminary antitumor activity with a manageable safety profile as first-line therapy in EGFR-mutant NSCLC patients with brain metastases. Enrollment for this trial will continue, and further analyses are warranted to determine longer-term outcomes.

Table. Summary of CNS Efficacy

	110mg	165mg
cFAS, n	12	3
CNS objective response, n		
CR	2	0
PR	6	0
SD	4	3
PD	0	0
iORR, % (95% CI)	66.7 (34.9-90.1)	0 (NA)
iDCR, % (95% CI)	100 (NA)	100 (NA)
cEFR, n	10	3
CNS objective response, n		
CR	2	0
PR	6	0
SD	2	3
PD	0	0
iORR, % (95% CI)	80.0 (44.4-97.5)	0 (NA)
iDCR, % (95% CI)	100 (NA)	100 (NA)

cFAS: CNS full analysis set; cEFR: CNS evaluable for response set; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; iORR: intracranial overall response rate; iDCR: intracranial disease control rate.

Keywords: aumolertinib, EGFR-TKI, brain metastases

EP08.02-005 A Prospective Non-randomized Observational Study on Efficacy and Its Relative Factors of Pemetrexed Combined with EGFR-TKIs in NSCLC

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Introduction: This study aims to analyze the efficacy and its relative factors of pemetrexed combined with EGFR-TKIs in first-line treatment of advanced NSCLC patients.

Methods: Data were collected from August 2014 to December 2021 and analyzed in our institute. The median progression-free survival (mPFS) time was the primary endpoint, and median objective response rate (mORR), disease control rate (DCR) and median overall survival (mOS) time were secondary endpoints.

Results: A total of 242 patients diagnosed with EGFR mutated advanced NSCLC were screened and finally met the eligibility criteria for the study, most of them (215/242) had accepted pemetrexed-platinum chemotherapy combined with EGFR-TKIs, and were enrolled in platinum-based group, while the other 27pts had accepted mono chemotherapy of pemetrexed combined with EGFR-TKIs and were enrolled in the mono chemotherapy group. Among the platinum-based group, 169 pts had finished more than or equal to 4 cycles of pemetrexed-platinum induction chemotherapy, and they were divided into ≤2 cycles (n=93) group, and >2 cycles (n=76) group, accroding to the median cycles of the maintenance treatment with pemetrexed combined with EGFR-TKIs. The mPFS of the platinum-based group had significantly longer than the mono chemotherapy group (15.23 vs 9.90 months, P=0.029). As was expected, the mPFS and mOS of those who had been administered maintenance treatment >2 cycles had been remarkably prolonged when compared with those who had been administered ≤2 cycles(20.73m vs 12.77 m, P<0.0001 and 54.03m vs 40.20 m, P=0.012, respectively). The Multivariate Cox regression analysis revealed that brain metastasis (HR=2.22, P<0.0001) was a significant predictive factor for shorter mPFS, but >2 cycle (HR=0.464, P<0.0001) was a significant predictive factor for longer mPFS in patients treated with standardized induction therapy group.

Conclusions: Our study showed platinum-based chemotherapy was an indispensable factor in the first line treatment of advance NSCLC with pemetrexed and combined with EGFR-TKIs, and maintenance therapy of >2 cycles after four cycles of induction chemotherapy might be warranted to significantly improve survival.

Figure 1 Median progression-free survival of patients with or without platinum-based chemotherapy

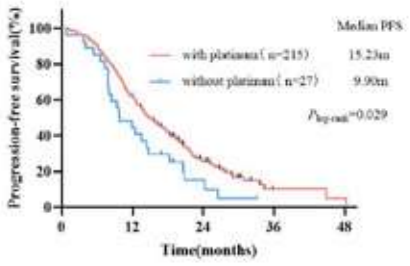
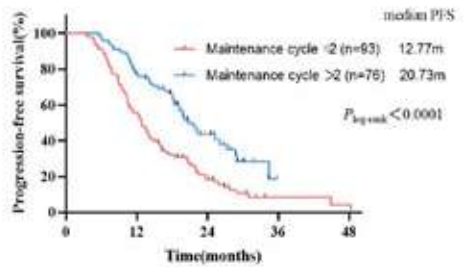


Figure 2A Median progression-free survival of patients ≤2 cycles (n = 93) group and > 2 cycles (n = 76) group



Keywords: Non-small-cell lung cancer, EGFR-TKI, chemotherapy

EP08.02-006 Data from Real World to Evaluate the Efficacy of Almonertinib in EGFR-mutant NSCLC Patients

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Introduction: As a new third-generation EGFR-TKI, almonertinib has already been approved for the treatment of EGFR-mutant advanced non-small cell lung cancer(ANSCLC) in China. The purpose of this study is to further evaluate the efficacy and safety of almonertinib during the real world.

Methods: 100 patients' medical records were reviewed for EGFR mutated ANSCLC treated with almonertinib, Data from 2020/4/1 to 2021/3/1 in Henan Cancer Hospital were also collected and retrospectively analyzed. We observed the progression-free survival (PFS), objective response rate(ORR), disease control rate (DCR) and overall survival (OS), the prognostic factors and safety were also studied.

Results: Among the 100 patients, 71% (71/100) were female, 54% (54/100) were less than 60 years old, 19% (19/100) had a history of smoking, and 71% (71/100) had a PS score less than 2. Patients with brain or meningeal metastasis prior to treatment accounted for 70% (70/100). 55% had EGFR 19Del mutation, and 41% had EGFR 21 L858R mutation. Up to the study cut off date, 2021/12/1, the median follow-up time was 12.9 months. The ORR of the patients who received almonertinib as first-line treatment (n=45) was 71%, mPFS was 16.7 months, and mOS was still not reached. Among patients (n=55) who received almonertinib after progression on prior EGFR-TKI therapy. The ORR of T790M(+) patients' (n=12) was 50.0%, mPFS was 11.9 months, and mOS was still not reached. While, the ORR of T790M (-) patients's(n=43) was 25.6%, mPFS was 12.1 months, and mOS was not reached, either. There was no significant difference of the efficacy between T790M(+) and T790M(-) groups(X2=2.620, PORR=0.106, PPFS=0.589, POS=0.924). Whatever the patients received almonertinib as first-line or later-line treatment, their Kaplan-Meier survival analysis both showed that the efficacy was no statistically significant difference between the patients with or brain metastases and those without (16.7m VS N/A, P=0.521; 12.1m VS 11.9m, P=0.601). A multivariate Cox regression analysis revealed that elevated creatine kinase (HR=0.176, P=0.001) was a significant predictive factor for longer mPFS.

Conclusions: Almonertinib has been shown good efficacy and safety in EGFR-mutant ANSCLC. Whatever patients diagnosed with brain metastases or not, they both benefit from almonertinib. Patients without T790M mutation after prior EGFR-TKI progression can also be a target population for almonertinib. Elevated creatine kinase is an important predictor of longer mPFS.

Fig 1. Kaplan-Meier analysis of progression-free survival (A) and overall survival (B) in patients treated with almonertinib after EGFR-TKI progressed.

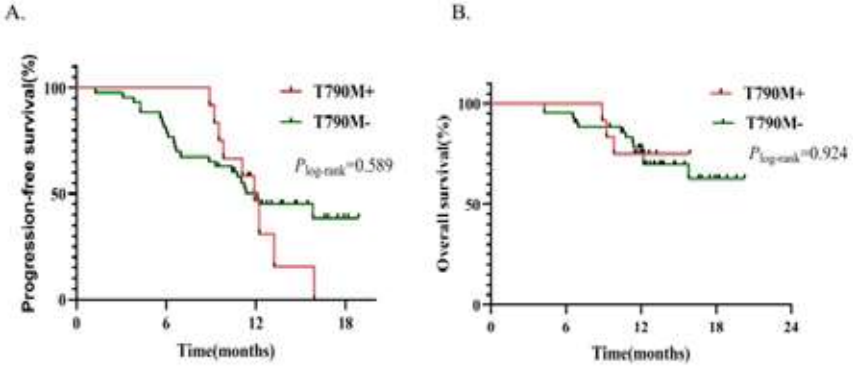
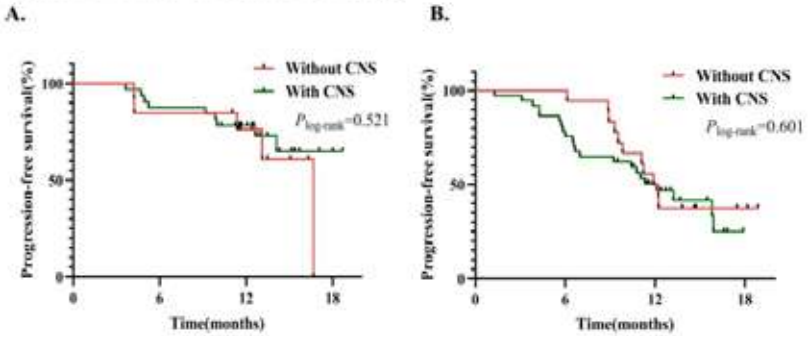


Fig 2. Kaplan-Meier analysis of mPFS between patients with brain metastases and without brain metastases . A.The patients receined almonertinib as first line therapy. B.The patients receined almonertinib as later line therapy.



Keywords: Non-small-cell lung cancer, EGFR-mutant, almonertinib

EP08.02-007 Disease Burden and Clinical Outcomes of Advanced ROS1 Positive NSCLC with Different Fusion Partners

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Introduction: There has been limited data about disease burden and clinical outcomes of advanced ROS1+ NSCLC with different fusion partners.

Methods: Data for patients with advanced ROS1+ NSCLC were retrospectively collected in our center. Metastases in contralateral lung, pleural or pericardial effusion, metastases in non-regional draining lymph nodes and lesions in extrathoracic organs were deemed as distant metastases. Metastases in symmetrical organs like adrenal glands or in osseous tissues were counted as one organ involved.

Results: 35 patients were included in our study. CD74-ROS1+ NSCLC seemed to be more inclined to develop metastases in distant organs especially in osseous tissues(47.1% vs 11.1%, p=0.027) than non-CD74-ROS1+ NSCLC. For patients who received crizotinib as initial ROS1-TKI(n=31), CD74-ROS1+ NSCLC demonstrated similar PFS compared with their counterparts(17.7m vs 18.4m, HR=0.74,p=0.54). 18 patients experienced disease progression following the treatment of crizotinib, the tendency to develop CNS progression in CD74 and non-CD74-ROS1+ NSCLC was closed(62.5% (5/8)vs 50%(5/10)). CD74-ROS1+ NSCLC seemed to be more prone to develop secondary mutation in ROS1 kinase domain after the treatment of ROS1-TKI although the difference was not statistically significant(83.3%(5/6) vs 33.3%(1/3), p=0.226).

Conclusions: Patients with CD74-ROS1+ NSCLC seemed to be more prone to develop distant metastases especially in osseous tissues and ROS1 secondary mutation. However, crizotinib demonstrated similar efficacy and tendency to develop CNS progression between CD74 and non-CD74-ROS1+ NSCLC.

	CD74-ROS1	Non-CD74-ROS1	P value
Distant metastases	88.2%	72.2%	0.402
Extrathoracic metastases	70.6%	38.9%	0.092
CNS metastases	17.6%	11.1%	0.658
Liver metastases	17.6%	0	0.104
Bone metastases	47.1%	11.1%	0.027
≥3 distant organs involved	41.2%	11.1%	0.06

Keywords: ROS1+NSCLC, Crizotinib

EP08.02-008 Tumor Invasiveness and Clinical Outcomes between Metastatic ROS-1 and ALK Positive NSCLC

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Introduction: ROS-1 protein bears highly structural similarity with ALK protein. However, there has been limited data about tumor invasiveness and clinical outcomes between metastatic ROS-1 and ALK+ NSCLC.

Methods: Data for patients diagnosed of ROS-1 or ALK positive NSCLC with distant metastases were retrospectively collected in our center. Metastases in symmetrical organs like adrenal glands or in osseous tissues were counted as one organ involved. Patients with >3 intracranial lesions were deemed as having multiple CNS metastases. CNS time to progression (CNS-TTP) for patients with baseline intracranial metastases was defined as the period from the start of crizotinib until CNS progression while CNS-TTP for those without was calculated from the start of crizotinib to the date of CNS lesions first being identified.

Results: 85 patients in total(ROS-1:n=40, ALK:n=45) were included in our study. There was no significant difference in baseline disease burden between metastatic ROS-1 and ALK+ NSCLC. For patients who received crizotinib as initial ROS-1 or ALK inhibitors(ROS-1:n=36, ALK:n=36), ROS-1+ NSCLC demonstrated more favorable PFS compared with their counterparts(16.5m vs 10.5m, p<0.001,HR=0.39, 95%CI: 0.23 to 0.67); CNS-TTP was also found to be significantly longer in ROS-1+ NSCLC(for patients with baseline CNS lesions: 18.4m vs 6.8m, p=0.035, HR=0.30, 95%CI: 0.10 to 0.9; for patients without baseline intracranial metastases: NE vs 13.2m, p=0.023, HR=0.39, 95%CI: 0.18 to 0.89). As for patients who underwent rebiopsy following the progression of ROS1 or ALK inhibitors, the incidence of secondary mutation in kinase domain(ROS-1:58.3%(7/12) vs ALK: 61.5%(8/13), p=1) or solvent front mutation(G2032R or G1202R) was similar(ROS-1:50% (6/12) vs ALK: 38.5%(5/13), p=0.695).

Conclusions: Patients with ALK+ NSCLC experienced more unfavorable prognosis and were more prone to develop CNS progression compared with those with ROS-1+ NSCLC following the treatment of crizotinib.

	ROS-1	ALK	P value
Extrathoracic metastases	62.5%(25/40)	77.8%(35/45)	0.155
CNS metastases	20%(8/40)	26.7%(12/45)	0.61
Multiple CNS metastases	62.5%(5/8)	50%(6/12)	0.67
Measurable CNS lesions	37.5%(3/8)	50%(6/12)	0.67
Liver metastases	7.5%(3/40)	17.8%(8/45)	0.204
Bone metastases	27.5%(11/40)	42.2%(19/45)	0.117
≥3 distant organs involved	25%(10/40)	31.1%(14/45)	0.632

Keywords: ROS-1+NSCLC, ALK+ NSCLC, Crizotinib

EP08.02-009 Progression Pattern, Resistance Mechanism and Subsequent Therapy for ALK Positive NSCLC in the Era of Second—Generation ALK—TKIs

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Introduction: In real-world setting, there has been limited data about progression pattern, resistance mechanism and subsequent therapy for ALK positive NSCLC in the era of second-generation ALK-TKIs.

Methods: Patients who showed treatment failure to second-generation ALK-TKIs were retrospectively collected in our center. Patients who underwent progression following the treatment of first-line alectinib was included in Cohort 1(n=20) while patients who experienced progression after the sequential therapy of crizotinib followed by second-generation ALK-TKIs were enrolled in Cohort 2(n=52). Oligo-progression was defined as disease progression in ≤3 lesions, local ablative therapy(LAT) was deemed inaccessible for pulmonary lymphangitis, pleural/serous effusion, and meningitis.

Results: The proportion of CNS progression(15% vs 57.7%, p=0.001) and symptomatic CNS progression (5% vs 32.7%, p=0.016) was much lower in Cohort 1 than patients treated with first-line crizotinib. Resistance mutation in ALK kinase domain(24/43, 55.8%) especially G1202R(15/43, 34.9%)was dominant resistance mechanism for second-generation ALK-TKIs. MET amplification(n=1), BRAF fusion(n=1), BRAFV600E mutation(n=1), KRAS amplification(n=2), KRAS mutation(n=1) and squamous carcinoma transformation(n=2) could possibly be other resistance mechanisms. Subsequent ALK-TKIs demonstrated more favorable efficacy in patients with ALK secondary mutation(patients with ALK compound mutation were excluded) than those without(242d vs 75d p=0.05, HR=0.46, 95%CI: 0.18-1.2). ALK compound mutation which appeared following the treatment of multiple ALK-TKIs(F1194L+G1202R*2, L1196M+G1202R*1) conferred primary resistance to lorlatinib. Some patients who didn't underwent rebiopsy after initial ALK-TKI presented dismal response to subsequent ALK-TKIs, results of rebiopy after multiple lines of treatments indicated that resistance mechanism might have already existed during the progression of initial ALK-TKI. LAT was applied to 52.5%(21/40) of oligo-progression. For overall population and patients deceased, 57.2%(30/52) and 51.8%(14/27) of them received at least one line of chemotherapy which showed better PFS compared with ALK-TKIs for patients without ALK resistance mutation(168d vs 75d, p=0.035, HR=0.47, 95%CI:0.19-1.2).

Conclusions: Patients who received first-line alectinib experienced less chance of CNS progression and symptomatic CNS progression compared with those treated with first-line crizotinib. In the era of second-generation ALK-TKIs, rebiopsy which could be beneficial to establish clinical regimens and estimate the effectiveness of subsequent treatments should be highly paid attention to. Patients should not lose the chance of chemotherapy which is still an important strategy especially for patients insensitive to targeted therapy.

Keywords: ALK+ NSCLC, second-generation ALK-TKI, crizotinib

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-010 Low-Dose Dacomitinib as First-Line Therapy for Driver-Positive Advanced Non-small Cell Lung Cancer: A Multicenter Real-World Study in China

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Introduction: In the ARCHER 1050 study, dacomitinib was shown to be more effective than gefitinib in patients with EGFR-mutant NSCLC, especially in patients with the EGFR exon 21L858R mutation. However, adverse events (AEs) were common with the 45 mg initial dose. Currently, real evidence of low-dose dacomitinib activity against the EGFR exon 21 L858R mutation is lacking.

Methods: This is a multi-center retrospective study of advanced non-small cell patients with EGFR mutations who received dacomitinib treatment from January 2019 to 2021.All patients received a 30 mg oral dose of dacomitinib. Collect patients' clinicopathological types, objective response rate (ORR), disease control rate (DCR), and adverse reactions (AE).

Results: Among the 30 patients, 3 had EGFR 19del mutation, 26 had EGFR 21L858R mutation, and 1 had EGFR rare mutation. The median follow-up time was 8.5 months, 19 had PR, and 11 had SD. The objective response rate (ORR) was 63.3%. The control rate (DCR) was 100%, and PFS and OS were not reached in 30 patients. Diarrhea, rash, stomatitis, paronychia and dry skin occurred in all 30 patients. The incidence of adverse reactions was 100%, of which the incidence of grade 1-2 adverse reactions was 93.33%, and the incidence of adverse reactions of grade 3 and above was 6.67%.

Conclusions: As a first-line treatment, 30 mg dacomitinib has a good curative effect on patients with classic EGFR mutations and has fewer adverse reactions of grade 3 or higher. It may be a more suitable EGFR-TKI for Chinese patients, especially for patients with 21 L858R mutations.

EP08.02-011 Design of a Phase I Trial (TOTEM) to Test Repotrectinib in Combination with Osimertinib in Advanced, Metastatic EGFR-Mutant NSCLC

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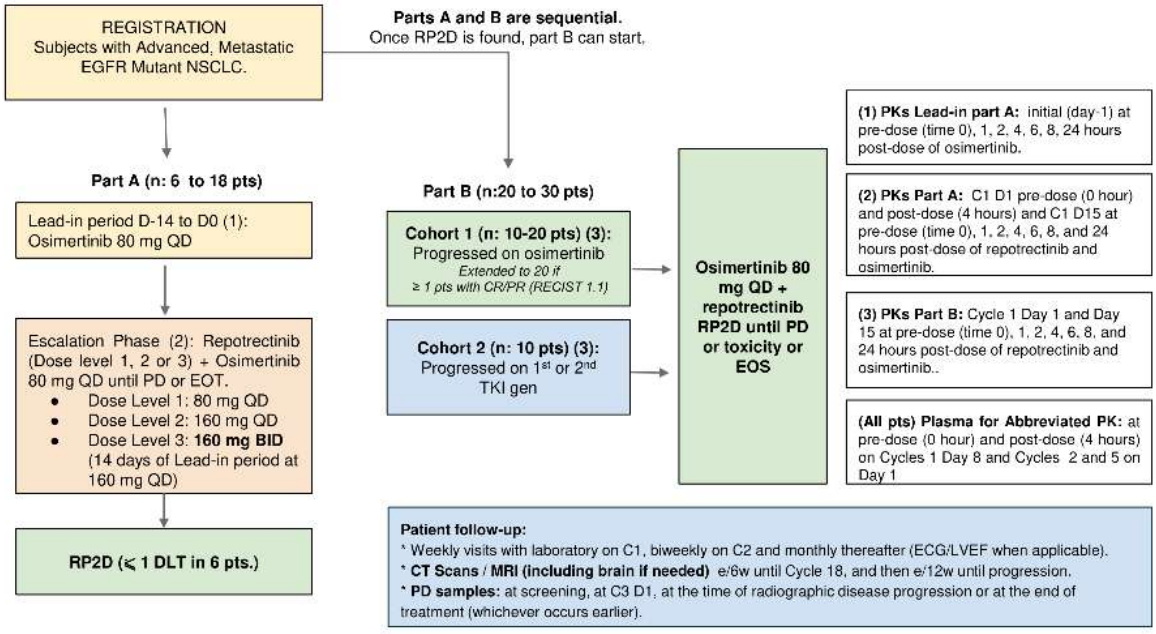
Introduction: Osimertinib has robust efficacy and is the standard first-line treatment for advanced EGFR-mutant non-small cell lung cancer (NSCLC). The combination of osimertinib with reprotrectinib inhibited Src/FAC/Janus kinase 2 (JAK2) in EGFR-mutant cell lines and abrogated STAT3 and YAP1 signaling with tumor growth inhibition in vitro and in vivo. There was no substantial toxicity in nude mice models. Based on this evidence and repotrectinib's unique inhibition affinity for Src, FAC and JAK2, we designed the current trial. The TOTEM trial will evaluate the tolerability / safety of repotrectinib in combination with osimertinib, the preliminary efficacy of the combination, the pharmacokinetic (PK) profile for both TKIs, and the pharmacodynamic (PD) changes that could lead to treatment resistance in EGFR-mutant NSCLC.

Methods: Eligible patients are ≥ 18 years, diagnosed with locally advanced, unresectable or metastatic NSCLC with local/central determination of EGFR exon 18, exon 19, exon 21, or T790M mutation. Patients with asymptomatic brain metastasis are eligible. Patients must have an ECOG 0-1, and a creatinine clearance >50 mL/min. Treatment with previous chemotherapy, immunotherapy, and TKIs, including osimertinib, is allowed.The study includes two parts: Part A consists of a dose escalation phase following a 3+3 design (6-18 patients) to determine the recommended phase 2 dose (RP2D). Patients in Part A will receive osimertinib monotherapy for 14 days at 80 mg per day (QD), followed by osimertinib in combination with repotrectinib at the assigned dose level (80 mg QD, 160 QD, or 160 mg twice a day); Part B is an expansion phase enrolling 20-30 patients that have progressed to osimertinib or first /second-generation TKIs. Patients in Part B will receive the combination at the RP2D. Treatment will continue until confirmed radiographic disease progression according to RECIST 1.1 criteria, confirmed by blinded independent central review, or unacceptable toxicity. Tolerability is evaluated by the incidence of dose-limiting toxicities (DLTs), and the determination of RP2D, defined as the dose level with less than 33% of patients experiencing a DLT. Safety is assessed by frequency and severity of adverse events throughout the study. Secondary endpoints include objective response rate (ORR), intracranial ORR (for patients with brain metastases), progression free survival (PFS), and overall survival (OS). Tumor and blood samples are collected at several time points during the study for PKs and NGS/Nanostring translational study (See figure for schedule of assessments).The study is currently open to recruitment, with results expected in 2026.



Keywords: Repotrectinib and Osimertinib, EGFR-mutant NSCLC, Phase I dose escalation trial

EP08.02-012 Real-world Analysis of the Efficacy and Safety of lorlatinib in Patients with ALK-Positive Non-small Cell Lung Cancer in Korea

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Introduction: Anaplastic lymphoma kinase (ALK) translocation is a targetable driver mutation in non-small cell lung cancer (NSCLC). Lorlatinib, a next-generation central nervous system-penetrant ALK tyrosine kinase inhibitor (TKI), is approved to treat TKI-refractory ALK-positive NSCLC based on results from previous studies. This study was aimed to report on the efficacy and safety of lorlatinib in real-world practice of Korea.

Methods: A real-world analysis was performed on ALK-positive NSCLC patients enrolled in lorlatinib early or expanded access programs form National cancer center and Yonsei cancer center Korea during,11 April 2018 to 11 Janary 2022. We retrospectively evaluated patients regarding its lorlatinib efficacy, the impact of prior ALK inhibitor treatments and the adverse events.

Results: A total of 90 ALK-positive patients were analyzed. The median age was 53 years and 58.4% of patients were female. Majority of the patients were adenocarcinoma histology (98.9%) and never smoker (66.7%). All patients had received at least one second-generation ALK inhibitor(s), while 48 patients also had a history of crizotinib treatment. For lorlatinib, the objective response rate was 36.7%, and disease control rate was 83.0%. Their median progression-free survival (PFS) and overall survival (OS) were 7.5 months and 87.9 months respectively. With prior therapies, patients receiving one or two ALK inhibitor(s) treatment showed PFS longer than those with three or more ALK inhibitors with no significant difference (9.5 vs. 6.3 months, p=0.085). Fifty-seven patients had brain metastasis at the start of the lorlatinib. The intracranial ORRs were 60% (95% CI: 35-93) for the patients with measurable brain metastasis. Regarding adverse events, 62.2% of patients had dyslipidemia and 17.8% were in grade 3 or 4. Psychosis were found in 7.8% of the patient and five of them were in grade 3 or 4 who needed dose reduction. No acute complication or discontinuation related to lorlatinib occurred.

Conclusions: The real-world efficacy of lorlatinib were consistent with those reported in pivotal trials. Interestingly, the history and responses of prior ALK inhibitor treatments may influence the efficacy of subsequent lorlatinib treatment. Also, safety signals regarding psychosis were observed which needs precaution to use lorlatinib.

Keywords: Non-small cell lung cancer, anaplastic lymphoma kinase, lorlatinib

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-013 Prognostic Utility of the ALI (Advanced Lung Index) in Crizotinib-Treated ALK and ROS1Fusion-Positive NSCLC

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Introduction: The tumour microenvironment, impacted by chronic systemic inflammation, is recognized as playing a significant role in cancer development, progression, and outcome. Blood component-based prognostic indices have shown association with outcome in NSCLC, but evaluation of these indices in relation to targeted systemic therapy remains largely underexplored, with performance status relied upon to help determine treatment suitability. This study sought to evaluate the potential of the Advanced Lung Index (ALI) as a prognostic marker in ALK and ROS1 fusion-positive NSCLC treated with crizotinib.

Methods: All Alberta NSCLC patients with ALK or ROS1-fusions treated with crizotinib between 2014 and 2020 were identified. Demographic, clinical, treatment and outcome details were extracted from the Glans-Look Lung Cancer Research Database. ALI was calculated using pre-crizotinib initiation (<30 days) body-mass index multiplied by serum albumin, divided by neutrophil:lymphocyte ratio; patients were stratified by this factor using previously established cut-off values: high and low levels systemic inflammation are expressed by low (ALI<18) and high (ALI≥18) ALI scores, respectively. Univariate and multivariate analysis were used to compare ALI groups and potential impact on outcome and response.

Results: ALI scores were available for 59 patients; 83% ALK-rearranged, 61% female, 56% never-smokers, median 59 years at diagnosis, 20% with brain metastases. 57% possessed low ALI scores, and high and low ALI groups showed no statistically significant differences in terms of demographic or clinical characteristics, save for as a higher likelihood of those with brain metastases to have low-ALI scores (92% vs. 49%, p=0.004) ALI was significantly associated with treatment response and outcome: Compared to high ALI scores, low ALI scores demonstrated lower rates of clinical response to crizotinib (real-world ORR: 29% vs. 60%, p=0.018; real-world DCR: 61% vs 96%, p=0.001) and a higher rate of non-response to crizotinib, due to rapid progressive disease or death (35% vs. 4%, p=0.002); these findings were replicated in subgroup analysis for patients without brain metastases. Low ALI scores showed significantly decreased overall survival (27 months vs. not reached, log-rank p=0.04) both overall and among those without brain metastases, but PFS was not significantly different between ALI groups, although low ALI scores had numerically reduced time to progression (11 vs. 20 months, log-rank p=0.29). Trends observed among ALI groups were replicated when stratifying by ECOG (<2 vs. ≥2); however, ALI and ECOG did not show significant association and ALI appeared to be more sensitive at predicting non-response to crizotinib. Among non-responders, 92% had low ALI scores but only 31% were identified as having poor ECOG; binomial regression, controlling for known confounders confirms both poor ECOG and low ALI scores as significant predictors for non-response to crizotinib.

Conclusions: This study demonstrates that ALI may be a useful tool given that low ALI scores are predictive of lower rates of clinical response to crizotinib and poorer patient prognosis. ALI scores are an inexpensive and accessible tool complementing more subjective assessments of patient performance status and may have particular value in identifying patients at risk of poor clinical response to crizotinib, particularly among those without brain metastases.

Keywords: ALK/ROS fusion, crizotinib, prognostic index

EP08.02-014 Impact of East Asian Ancestry on Response to First-Line Osimertinib: A Real-World Canadian Cohort

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Introduction: The phase-III FLAURA clinical trial demonstrated benefit and effectiveness of osimertinib as a first-line treatment for EGFR-mutant NSCLC patients; however, subgroup analysis suggests the magnitude of benefit may differ between Asian and non-Asian patients. Prior real-world data from our institution also suggests EGFR-mutant NSCLC patients of Asian racial ancestry are the most likely to derive benefit from earlier generation EGFR-inhibitors. This study examined real-world clinical population of EGFR-mutant patients treated with first-line osimertinib to compare and contrast the characteristics and response to osimertinib among Asian and non-Asian patients.

Methods: Alberta patients with a diagnosis of advanced/metastatic NSCLC receiving first-line osimertinib between 2018 and 2021 were identified. Demographic, clinical, treatment and outcome details were extracted from the Glans-Look Lung Cancer Research Database. Patients were stratified according to presence/absence of Asian racial ancestry. Univariate and multivariate methods were used to compare groups and identify factors predictive of time to progression (PFS) on osimertinib.

Results: 77 patients were identified. Clinical characteristics did not differ significantly (Table 1); however, progression-free survival was reduced among Asian vs. non-Asian patients (PFS: 9.8 months vs. not reached, log-rank p=0.03). Although ECOG did not impact PFS in the population overall, among poor performance status patients (ECOG≥2), PFS was significantly reduced in Asian (compared to non-Asian) patients (7.5 months vs. not reached, log-rank p=0.04). Paradoxically, these findings arise in the context of better osimertinib-mediated disease control among Asian (compared to non-Asian) patients (DCR: 96% vs. 73%, p=0.008) and a higher rate of non-evaluable disease due to early osimertinib termination (primarily due to adverse events) among non-Asian patients (21% vs. 4%, p=0.03).In a multivariate model, controlling for known confounders of outcome (age, sex, EGFR mutation type, ECOG) Asian racial ancestry was independently prognostic of reduced PFS and (HR: 2.1 [95%CI:1.1-4.3], p=0.03. Survival following osimertinib initiation is not yet mature, but data to date suggests no significant differences between Asian and non-Asian patients (not reached; p=0.94).

Conclusions: This racially heterogenous real-world confirms that the majority of patients achieve disease stability (or better) with first-line osimertinib and an overall median PFS comparable to that from the FLAURA clinical trial (15.0 vs. 14.4 months). However, this study identified that despite achieving a period of osimertinib-mediated disease control, Asian patients experienced reduced PFS. Further investigation into understanding a possible differential response to osimertinib by racial ancestry is warranted.

Characteristic	Entire Cohort n = 77 n (%)	Asian Cohort n = 25 n (%)	Non-Asian Cohort n = 52 n (%)	Statistical Test p-value
Age at Diagnosis (years)				
Median (IQR)	68 (61-78)	70 (59-85)	67 (61-75.5)	$X^2(1)$,
< 65	32 (42)	11 (44)	21 (40)	p=0.76
≥ 65	45 (58)	14 (56)	31 (60)	
Sex				
Male	31 (40)	12 (48)	33 (63)	$X^2(1)$,
Female	46 (60)	13 (52)	19 (37)	p=0.3
Smoking History				
Ever Smoker	36 (47)	9 (36)	27 (52)	$X^2(1)$,
Never Smoker	39 (51)	15 (60)	24 (46)	p=0.2
Unknown	2 (2)	1 (4)	1 (2)	
ECOG at Osimertinib Initiation				
Good (< 2)	51 (66)	15 (60)	36 (69)	$X^2(1)$,
Poor (≥ 2)	25 (44)	10 (40)	16 (31)	p=0.4
EGFR Mutation				
Common (Exon19del; L858R)	72 (94)	24 (96)	47 (90)	$X^2(2)$,
Uncommon	1 (1)	0 (0)	1 (2)	p=0.5
Complex (duel common and uncommon mutation)	4 (5)	1 (4)	4 (8)	
M-stage at Osimertinib Initiation				
M0 (advanced)	9 (11)	2 (8)	7 (13)	
M1a	19 (25)	9 (36)	10 (20)	$X^2(3)$,
M1b	17 (22)	6 (24)	11 (21)	p=0.4
M1c	32 (42)	8 (32)	24 (46)	
Brain Metastases at Osimertinib Initiation				
Yes	15 (19)	3 (12)	12 (23)	$X^2(1)$,
No	62 (81)	22 (88)	40 (77)	p=0.3
Metastatic Disease Onset				
After relapse	14 (18)	5 (20)	9 (17)	$X^2(1)$,
At diagnosis	66 (82)	20 (80)	43 (83)	p=0.8
Meets FLAURA Inclusion Criteria (based on ECOG and type of EGFR mutation)				
Yes	50 (65)	15 (60)	35 (67)	$X^2(1)$,
No	27 (35)	10 (40)	17 (33)	p=0.5
Disease Control Rate (real-world DCR)				
DCR criteria met	62 (81)	24 (96)	38 (73)	$X^2(1)$,
DCR criteria not met	15 (19)	1 (4)	14 (27)	p=0.008*
Objective Response Rate (real-world ORR)				
ORR criteria met	34 (44)	14 (56)	20 (38)	$X^2(1)$,
ORR criteria not met	43 (56)	11 (44)	32 (62)	p=0.1
Non-Evaluable Disease Response				
Yes	12 (16)	1 (4)	11 (21)	$X^2(1)$,
No	65 (84)	24 (96)	41 (79)	p=0.03*
Treatment Post Osimertinib				
Yes	22 (29)	4 (16)	18 (23)	$X^2(1)$,
No	55 (71)	21 (84)	34 (67)	p=0.08

IQR: inter-quartile range; NR: not reached; * denotes significance, determined *a priori* at p<0.05

Keywords: osimertinib, asian, real-world

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-015 The Utility of Liquid Biopsies for Management of Stage IV Non-small Cell Lung Cancer (NSCLC) in an Academic Community Medical Center

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Introduction: The management of stage 4 non-squamous non-small cell lung cancer (NSCLC) requires tumor genotyping to identify driver mutations that indicate the use of small molecules as first line therapy. Such mutations have traditionally been characterized by genetic study of biopsied tumor tissues. Recently, the “liquid biopsy”, a non-invasive genomic analysis of circulating tumor DNA, has been deemed a suitable complementary method to identify actionable mutations in NSCLC patients. At our community-based academic medical system in suburban Philadelphia, we performed a retrospective chart review study to assess the impact of adding liquid biopsies to tissue molecular testing as part of the initial genetic characterization of stage IV non-squamous NSCLC. Our primary quality metrics were (1) the rate of detection of mutations that determine eligibility for first line small molecule treatments and (2) the time required to obtain a molecular diagnosis.

Methods: This retrospective cohort study used a bank of Main Line Health patients diagnosed with Stage 4 non-squamous NSCLC from 2018-2021. Chart review was used to extract variables from these patients regarding dates of tissue biopsies and treatments, information on liquid biopsies, and demographic information. We compared liquid biopsy + tissue biopsy vs. tissue biopsy only cohorts for detection of actionable mutations and KRAS mutations and measured the time interval (days) between the first tissue biopsy indicating NSCLC and a definitive molecular diagnosis. Overall survival was computed from the time of the first biopsy to death or censoring.

Results: 120 patients were identified with stage IV non-squamous NSCLC and underwent molecular tissue testing. 42 of these also underwent Guardant liquid biopsy testing as part of their initial evaluation. Of these 42, 57% (24) had actionable mutations detected and 21% (n=9) had KRAS mutations. In comparison, of the 78 patients who had only tissue biopsy, only 29% (n=21) had an actionable mutation detected, while 35% (n=25) had KRAS mutations. Overall, the tissue-only group identified mutations in 59% (n=46) whereas the combined strategy identified mutations in 79% (n=33). The time to identification of either an actionable or KRAS mutation occurred sooner for the group undergoing liquid biopsies, an average of 20.5 days (median 17.0 days, range 4-50) compared to 33.5 days (median 30.5 days, range 10-1134), p<.001 by two-tailed T-test.

Conclusions: In our community academic medical center, patients with stage IV non-squamous, NSCLC who underwent a liquid biopsy as part of their initial diagnostic workup had a higher rate of detection of actionable mutations and more rapid determination of their molecular status than patients who received only tissue-based molecular diagnostic testing. This data supports the feasibility and utility of performing liquid biopsies as part of the initial evaluation of stage IV non-squamous NSCLC.

Keywords: liquid biopsy, actionable mutation, community medical center

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-016 Frontline and Post-Osimertinib Therapy for EGFR-mutant Advanced NSCLC: Treatment Patterns, Outcomes, Healthcare Use and Costs

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Introduction: For patients with *EGFR*-mutant advanced non-small cell lung cancer (NSCLC), osimertinib is recommended frontline therapy. However, real-world treatment patterns, clinical outcomes, healthcare-resource utilization (HRU), and costs in frontline and post-osimertinib settings are unclear.

Methods: This retrospective, observational analysis used the US Optum Clinformatics Data Mart database. Included patients were insured adults (≥18 years) with an advanced lung cancer diagnosis, evidence of EGFR testing, and ≥12 months continuous insurance enrollment before NSCLC diagnosis, who received an EGFR TKI and ≥1 treatment line between 01Jan2008 and 31Mar2021. Treatment patterns, clinical outcomes (time to treatment discontinuation [TTD], time to next treatment [TTNT], overall survival [OS]), HRU, and costs were analyzed in three cohorts in the advanced disease setting: Cohort 1 were patients starting frontline therapy (2016 and later); Cohort 2 were patients with ≥1 line of therapy post-osimertinib; and Cohort 3 were patients with ≥1 line of therapy post-osimertinib and post-platinum chemotherapy in any sequence.

Results: Mean (median) follow-up duration from index date to end of continuous follow-up (earliest of end of continuous enrollment, death, or data cut) were 15.3 (12) months in Cohort 1 (n=920), 8.0 (6) months in Cohort 2 (n=163), and 6.8 (5) months in Cohort 3 (n=71). Treatment received in each cohort is shown in the **Table**. In Cohort 1, 45% received osimertinib monotherapy and 3% received osimertinib combination therapy; in Cohort 2, 8% received osimertinib retreatment monotherapy and 22% received osimertinib retreatment combination therapy; and in Cohort 3, 6% received osimertinib retreatment monotherapy and 23% received osimertinib retreatment combination therapy. Median TTD for Cohorts 2 and 3 were 4.4 and 4.1 months, respectively, while median TTD for Cohort 1 was 5.8 months (longer for patients on osimertinib versus non-osimertinib frontline regimens). For both Cohorts 2 and 3, median TTNT was <6 months, and median OS was <10 months; for Cohort 1, median TTNT was 10.4 months and median OS was 21.1 months. Cohorts 2 and 3 both had total healthcare costs ~25,000 USD per person per month (PPPM); cohort 1 had total healthcare costs ~18,500 USD; similar trends were observed for HRU **(Table)**.

Conclusions: While no formal comparative analysis was performed, *EGFR*-mutant NSCLC patients who progressed on osimertinib demonstrated numerically shorter median TTNT and median OS and higher healthcare costs compared with those on frontline therapy, suggesting a high unmet need among these patient groups. Therapeutic advances are needed to further improve patient outcomes.

Table

	Cohort 1: Frontline (n=920)	Cohort 2: Post-osimertinib (n=163)	Cohort 3: Post-osimertinib + platinum chemotherapy (n=71)
Index date	Start of first line of therapy for advanced disease	Start of subsequent line of therapy after first osimertinib treatment for advanced disease	Start of subsequent line of therapy after osimertinib and platinum chemotherapy (any order) for advanced disease
Therapy at cohort index, %			
Osimertinib monotherapy	44.6	8.0	5.6
Other TKI monotherapy	30.5	11.0	5.6
Osimertinib combinations	2.8	22.1	22.5
Platinum-based regimens	15.5	41.1	22.5
Non-platinum chemotherapy	1.7	6.1	22.5
Median time to event (95% CI), months			
Time to next treatment or death	10.4 (9.2, 11.4)	5.9 (4.8, 6.7)	5.2 (3.9, 8.1)
Overall survival	21.1 (19.5, 23.4)	9.2 (6.8, 13.2)	7.8 (5.0, 12.6)
Healthcare resource utilization			
Outpatient visits			
Mean outpatient visits PPPM[a]	3.7	4.5	4.5
Hospital stays			
Patients with ≥1 hospital stay, n (%)	480 (52.2)	84 (51.5)	35 (49.3)
Mean hospital stays PPPM	0.1	0.2	0.1
Mean hospital stays PPPM among patients with ≥1 hospital stay	0.2	0.3	0.3
Emergency room (ER) visits			
Patients with ≥1 ER visit, n (%)	605 (65.8)	98 (60.1)	40 (56.3)
Mean ER visits PPPM	0.1	0.2	0.2
Mean ER visits PPPM among patients with ≥1 ER visit	0.2	0.4	0.4
Total healthcare costs PPPM,[b] US dollars	$18,576	$26,384	$23,604
Pharmacy	$11,293	$14,508	$12,189
Total medical	$6,636	$10,242	$9,877

[a]PPPM was estimated from the cohort's corresponding index date to the end of follow-up (earliest of end of continuous enrollment, death, or data cut).
[b]Total healthcare costs include pharmacy costs, total medical costs, laboratory costs, and supportive care costs.
CI, confidence interval; ER, emergency room; PPPM, per person per month; TKI, tyrosine kinase inhibitor

Keywords: Real-world evidence, EGFR-mutant

EP08.02-017 Time on Treatment for Patients Treated with Anti-EGFR Tyrosine Kinase Therapy for Metastatic NSCLC: Real-World Experience Data

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Introduction: Clinical trials have established the role of tyrosine kinase inhibitor (TKI) targeted therapy for metastatic non-small cell lung cancer (mNSCLC) patients with driver mutation, but real-world data are limited. We describe time on treatment (rwTOT) for first-line (1L) mNSCLC patients with EGFR mutation in a 2.5-million-member state-mandated health provider in Israel.

Methods: Newly diagnosed stage IV NSCLC patients with EGFR mutation, who initiated 1L TKIs between Jan 2017-Dec 2020 were identified from the national cancer registry and icd-9 diagnosis codes. RwTOT was defined as the length of time between first and last administration date of TKI therapy. Patients were considered discontinued if they had a record of next line of therapy, death, or whose last activity date was ≥120 days from the last purchase date. The Kaplan-Meier median was estimated. All outcomes were assessed at minimum 6 months follow-up (cutoff: 30th Jun 2021).

Results: A total of 165 patients with an EGFR mutation initiated 1L TKI therapy. This cohort comprised of 59% females, median age=68 years, 42% ever smokers, 95% adenocarcinomas, 33% brain metastases, and 62%/15%/23% with 0-1/2-4/unknown Eastern Cooperative Oncology Group (ECOG) Performance Status (PS). The median rwToT was 12.5 months (95% CI: 10.6-17.2 months); with a significant difference between those that received osimertinib (19.2 [13.74, NA]) and those that received older generation TKI (9.4 [7.17, 12.1], P<0.001). Median follow up for this cohort was 28.04 months (23.7-32.4).

Conclusions: The results of this unselected real-world cohort of mNSCLC patients treated with TKI therapy, show that rwTOT rates for patients that received osimertinib as compared to other TKI drugs, compare favorably with published data from clinical trials which included similar patients. Our cohort also included patients with 2-4 PS who would not necessarily be included in clinical trials, allowing analysis of a real-world population.

Keywords: metastatic non-small cell lung cancer, Real-world experience data, anti-EGFR tyrosine kinase therapy

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-018 Phase 1/2 Study of BLU-451, a Small Molecule Inhibitor of EGFR, in EGFR Exon 20 Insertion-Mutant Incurable Advanced Cancers

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Introduction: Oncogenic *EGFR* exon 20 insertion (ex20ins) mutations, found in ~2% of non-small cell lung cancers (NSCLC) and a small percentage of other cancers, are generally not responsive to EGFR-targeted agents that have been approved for treatment of NSCLC with a common *EGFR* mutation, including L858R and exon 19 deletion. Similar to these more common types of *EGFR*-mutated NSCLC, central nervous system (CNS) metastases are a challenge with *EGFR* ex20ins mutant NSCLC and are associated with poor outcomes. While two EGFR ex20ins-targeting drugs were recently approved by the US Food and Drug Administration (amivantamab and mobocertinib), neither have established CNS activity. BLU-451 is a CNS penetrant, wild type-sparing, covalent small molecule investigational inhibitor of EGFR ex20ins as well as atypical (G719C, G719S, L861Q) and common EGFR mutants. Preclinical data have shown BLU-451 to have potent antitumor activity, including in an intracranial xenograft model, which has led to its clinical development in *EGFR*-mutant NSCLC. An abstract describing this study was previously submitted to the American Society of Clinical Oncology 2022 Annual Meeting.

Methods: BLU-451-1101 (NCT05241873) is a phase 1/2, global, open-label study designed to evaluate single-agent BLU-451 in patients with NSCLC harboring *EGFR* ex20ins mutations that have progressed following prior treatment for incurable recurrent or metastatic disease. Patients with Eastern Cooperative Oncology Group performance status 0-1 and *EGFR* ex20ins, exon 18 G719X or exon 21 L861Q mutant NSCLC (phases 1 and 2) or other cancers except primary CNS tumors (phase 1 only) are eligible. Patients with known *ROS*, *RAF*, *ALK*, or *EGFR* C797S mutations will be excluded. Stable, asymptomatic brain metastases are permitted, and active asymptomatic brain metastases are permitted in specific cohorts. Primary endpoints are determination of maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), safety and tolerability (phase 1), in addition to evaluation of antitumor activity at the RP2D by RECIST v1.1 (phase 2). Secondary endpoints are evaluation of pharmacokinetics (PK) and antitumor activity by RECIST v1.1. (phase 1), and PK, safety, tolerability, and CNS antitumor activity (phase 2). Dose escalation will utilize a 3+3 design with up to 6 patients per cohort in phase 1 dose escalation and up to 12 per cohort in phase 1 dose expansion. Phase 2 will enroll patients in 3 cohorts (n=18 each): patients treated with prior platinum-based chemotherapy and an EGFR ex20ins-targeted agent; patients treated with prior platinum but no EGFR ex20ins-targeted agent; and patients with active asymptomatic brain metastases treated with prior platinum with or without an EGFR ex20ins-targeted agent. The study is planned to enroll at approximately 40 centers in North America, the Asia-Pacific region, and/or Europe.

Keywords: EGFR TKI, EGFR ex20ins, Clinical trial

EP08.02-019 Phase 1/2 Study of BLU-701, a Highly Selective EGFR Inhibitor, in Patients with EGFR-Mutant Non-Small Cell Lung Cancer

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Introduction: Third-generation tyrosine kinase inhibitors (TKIs), such as osimertinib, are highly effective in front-line metastatic *EGFR*-mutated (*EGFR*m) non-small cell lung cancer (NSCLC), but treatment resistance can ultimately occur, including the emergence of the on-target C797X mutation for which there are no approved TKIs. BLU-701 is an investigational, reversible, central nervous system (CNS)-penetrant, wildtype-sparing oral TKI with nanomolar potency on common activating (exon 19 deletion and L858R) and C797X resistance mutations. BLU-701 has shown promising preclinical data, including antitumor CNS activity that may improve patient outcomes. Additionally, combining BLU-701 with standard of care therapies may provide enhanced disease control across multiple lines of treatment, including against heterogenous tumors, in patients with *EGFR*m NSCLC. An abstract describing this study was previously submitted to the American Society of Clinical Oncology 2022 Annual Meeting.

Methods: HARMONY (NCT05153408) is an ongoing, global phase 1/2, open-label, first-in-human study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of BLU-701 as a monotherapy or in combination with osimertinib or platinum-based chemotherapy in patients with *EGFRm* NSCLC. Key inclusion criteria include patients ≥18 years of age with metastatic *EGFRm* NSCLC; Eastern Cooperative Oncology Group performance status 0-1; and previous treatment with ≥1 EGFR-targeted TKI. Patients in the phase 2 monotherapy part must harbor an *EGFR* C797X resistance mutation (locally assessed). Key exclusion criteria are tumors harboring *EGFR* T790M mutations, *EGFR* exon 20 insertions, or other known driver alterations, including *KRAS*, *BRAF* V600E, *NTRK1/2/3*, *HER2*, *ALK*, *ROS1*, *MET*, or *RET*. Phase 1 primary endpoints are maximum tolerated dose, recommended phase 2 dose (RP2D), and safety. The phase 2 primary endpoint is overall response rate (ORR) by RECIST v1.1. Secondary endpoints include ORR (phase 1), duration of response, and PK/PD (phase 1 and phase 2); disease control rate, progression-free survival, overall survival, antitumor CNS activity, and safety (phase 2). The phase 1 dose escalation will adopt a Bayesian optimal interval design. Patients will be enrolled into 3 treatment cohorts: part 1A (n≈40-80; BLU-701), part 1B (n≈35; BLU-701 + osimertinib), and part 1C (n≈18; BLU-701 + carboplatin and pemetrexed). Patients in the phase 2 dose expansion (n≈24) will be treated at the RP2D of BLU-701 as monotherapy. Patients may receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met. Enrollment has started, and sites will be open across North America, Europe, and Asia.

Keywords: EGFR TKI, EGFR C797S, Clinical trial

EP08.02-020 Preclinical Activity of NVL-655 in a Patient-Derived NSCLC Model with Lorlatinib-Resistant ALK G1202R/T1151M Mutation

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Introduction: *ALK* rearrangements are detected in about 5% of advanced non-small cell lung cancer (NSCLC). Crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib are approved tyrosine kinase inhibitors (TKIs) for ALK-positive NSCLC, but durability of response is partly limited by ALK resistance mutations. The G1202R solvent-front mutation is commonly observed at progression following treatment with crizotinib, ceritinib, alectinib, or brigatinib. Patients with G1202R tumors often respond to lorlatinib but may relapse by acquiring compound mutations such as G1202R/L1196M and G1202R/G1269A. Our group previously reported the discovery of a novel compound mutation G1202R/T1151M in circulating tumor cells of a lorlatinib-relapsed NSCLC patient. Here, we identified another lorlatinib-relapsed NSCLC patient with G1202R/T1151M. The repeat observations suggest that G1202R/T1151M may be a recurrent lorlatinib-resistant mutation of significance. We generated a patient-derived cell line (PDC), a PDC-derived xenograft, and an engineered Ba/F3 model bearing EML4-ALK v3 G1202R/T1151M. Using these and other models, we characterized NVL-655 as a novel ALK inhibitor with potent preclinical activity against diverse ALK resistance mutations, including the lorlatinib-resistant G1202R/T1151M compound mutation.

Methods: MR448re cell line was established from ascites (effusion in the peritoneal cavity) of a NSCLC patient progressing on lorlatinib. Ascites mononuclear cells were isolated by Ficoll centrifugation and cultured in media (DMEM F12 Glutamax, 10% antibiotics/antimycotics, 10% FBS, hydrocortisone, adenine, RockInhibitor, and 1/10 cholera toxin). After stable cancer cells were obtained, the presence of EML4-ALK fusion and G1202R/T1151M compound mutation was confirmed by PCR and sequencing. Five million cells were injected into Swiss nude mice to derive a xenograft model. Ba/F3 cells were engineered to express EML4-ALK v3 with wild-type kinase domain or with G1202R, T1151M, or G1202R/T1151M mutations. ALK inhibitors were evaluated in cell viability assays, signaling pathway assays, and in vivo studies.

Results: In cell viability assays, NVL-655 showed highly potent activity (IC_{50} < 10 nM) against the MR448re PDC and Ba/F3 cells expressing EML4-ALK v3 G1202R/T1151M. By comparison, all approved ALK inhibitors, including lorlatinib, exerted only weak activity (IC_{50} > 100 nM), consistent with the resistance observed clinically. Western blot analysis confirmed that NVL-655 showed complete suppression of ALK phosphorylation in MR448re at 10 nM, comparable to lorlatinib at 1000 nM. Finally, the xenograft model generated from the MR448re PDC displayed fast growth kinetics and resistance to lorlatinib treatment, supporting its utility for investigating the ALK G1202R/T1151M compound mutation in vivo.

Conclusions: NVL-655 has demonstrated activity in many preclinical models bearing ALK compound mutations, including the MR448re (EML4-ALK v3 G1202R/T1151M) model. The potent preclinical activity of NVL-655 suggests potential clinical utility for ALK-positive patients, including those with resistant compound mutations. The MR448re PDC and xenograft are valuable additions to the ALK therapeutic research landscape where there is limited availability of patient-derived models with lorlatinib-resistant ALK compound mutations.

Keywords: ALK, resistance, PDX

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-021 A Phase II Trial of Upfront Aumolertinib (HS-10296) plus Radiotherapy for EGFR Mutated Non-small-cell Lung Cancer Patients with Brain Metastases

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Introduction: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) remains a standard treatment option for advanced non-small-cell lung cancer (NSCLC) patients harboring EGFR mutation. Aumolertinib, a third-generation EGFR-TKI, has shown to be highly effective and well-tolerated in first-line treatment for EGFR mutated advanced NSCLC patients with a median progression-free survival(PFS) reaching 19.3 months compared with 9.3 months for gefitinib. Radiotherapy, especially stereotactic radiosurgery(SRS) is proved to be a critical method for limited number of brain metastases. However, the optimal pattern of EGFR-TKI in combination with radiotherapy is still unknown. This study intends to explore the safety and efficacy of concurrent amolertinib, with radiotherapy in EGFR-mutated NSCLC patients presenting brain metastases.

Methods: In total this phase II trial aims to enroll 37 patients. EGFR-mutated (exon19del, L858R mutation or together with other EGFR mutation) advanced NSCLC patients with measurable central nervous system (CNS) lesions (according to RANO-BM standard) will be included in this trial. Firstly, patients orally take amolertinib 110mg daily for 3 consecutive months. After induction therapy, patients with brain metastases must meet the following criteria on a diagnostic MRI to start following radiotherapy: ≤10 brain metastatic lesions (each between 5 to 30mm), metastases >5mm from the optic nerve or chiasm. The SRS treatment will be conducted with total dose of 30 Gy in 5 fractions (day1, 3, 5) calibrated by cone-beam CT before each treatment, together with amolertinib. For patients who are assessed as oligometastasis after SRS, stereotactic body radiotherapy (SBRT) is recommended for oligometastatic lesions (The number of lesions received SBRT and radiation dose are not standardized). Aumolertinib is used until disease progression or intolerable toxicity. The primary endpoint is the central nerve system duration of response assessed by RANO-BM criteria. And the secondary endpoints are intracranial PFS, intracranial response rate(RR), extracranial RR, overall survival(OS), neurocognitive function and quality of life(QoL). The first patient had been enrolled in November 2020. Patients' enrollment will last 2 years. This trial protocol has been approved by the ethics committee of Hangzhou cancer hospital. The ethics number is HZCH-2020-029. This trial has been registered on clinicaltrials.gov(NCT04643847).

Keywords: Aumolertinib, Radiotherapy, Brain Metastases

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-022 Investigating Partners in Crime: Osimertinib Resistance Mechanisms in Non-small Cell Lung Cancer Using Focused CRISPR Screen

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Introduction: Non-small cell lung cancer (NSCLC) is the most prevalent and detrimental cancer type, accounting for 85% of all lung cancer cases. EGFR mutations, which can be targeted by tyrosine kinase inhibitors (TKIs), have been addressed as one of the cancer driving mechanisms in NSCLC adenocarcinomas. Osimertinib, a third generation EGFR-TKI, has been recently approved for clinical use in the first-line treatment of advanced NSCLC. Unfortunately, the long-standing obstacle in EGFR-TKI treatments, including Osimertinib, is the inevitable resistance. In this study, we aimed to delineate potentially druggable synthetic lethal interactions of non-genetic regulators with the EGFR pathway, mainly by focusing on transcriptional and epigenetic mechanisms driving acquired resistance.

Methods: We have developed Osimertinib resistant HCC827 subline (HCC827-OsiR) displaying 1000-fold greater IC50 value, with the dose escalation methodology. To elucidate the non-genetic regulators of the resistance phenotype, we developed a gRNA library enriched for epigenetic and transcriptional factors. Moreover, we utilized high-throughput methodologies such as RNA-seq to study transcriptome and focused CRISPR/Cas9 screen to unravel resistance related genes.

Results: As expected, HCC827-OsiR cells were resistant to other EGFR-TKIs (Erlotinib and Dacomitinib). When compared to parental cells, HCC827-OsiR cells displayed reduced phosphorylation of the EGFR, despite AKT, ERK and STAT3 signaling was augmented. We then performed the screen experiments in the presence and absence of Osimertinib in Cas9 expressing HCC827-OsiR cells. Parental cell line was used as a control. Currently, we are analyzing candidate genes driving the resistance. Besides, we compared the transcriptomes of parental HCC827 and HCC827-OsiR cells. In summary, OsiR cells were enriched with EMT gene signatures right along with an upregulation of FGFR pathway components, showing consistency with the literature. RNA-seq data also revealed differential expression of several key epigenetic and transcriptional factors further implying their potential role in the resistance.

Conclusions: Future studies and the potential candidate genes will help better understand and unveil non-genetic mechanisms of Osimertinib resistance with potential therapeutic implications.

Keywords: NSCLC, synthetic lethality, Osimertinib resistance

EP08.02-023 Differentiation Syndrome in a Patient with Non-Small-Cell Lung Cancer Harboring IDH2 Mutation Treated with Enasidenib

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Introduction: Mutation of IDH1/2 results in a gain-of-function causing production of an oncometabolite 2-hydroxyglutarate implicated in DNA and histone hypermethylation and ultimately interferes with cellular differentiation. Enasidenib, an IDH2 inhibitor, was approved in 2017 for refractory AML. Several recent clinical trials have evaluated the potential anti-tumor activity of IDH2 inhibitors in the treatment of solid tumors including non-small cell lung cancer (NSCLC). Differentiation syndrome (DS) is a life-threatening condition associated with acute promyelocytic and acute myeloid leukemias (AML) treated with all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO). Although the use of enasidenib for AML has been supported with improved survival and good tolerance, it has also been associated with delayed occurrence of DS compared to previous therapies.

Methods: A 54 year-old female presented with shortness of breath, fatigue and weight loss and was diagnosed with PDL-1 negative NSCLC. Blood based circulating tumor DNA (ctDNA) assay revealed EML4-ALK fusion and IDH2 mutation. Treatment with ALK-inhibitor alectinib demonstrated good initial response followed by stable disease. Six months later, disease progression was noted on imaging. Repeat ctDNA assay showed an increase in IDH2 allele frequency while other mutations became undetectable. Patient was switched to lorlatinib with clinical improvement. However, progression of disease was noted on follow-up imaging while IDH2 mutant allele frequency remained high. Enasidenib was added as an experimental targeted treatment for IDH2 mutation.

Results: Seven weeks after introduction of enasidenib, our patient had recurrence of bilateral lower extremity edema and new-onset shortness of breath. Chest CT showed large pericardial effusion and bilateral ground glass opacities favoring pneumonitis and inflammation; the primary target lesions remained stable per RECIST 1.1 criteria without new distant metastasis, and some areas of opacities were improved. These findings were more suggestive of pneumonitis/pericarditis versus metastatic disease progression. Enasidenib was discontinued immediately. Patient was treated with high doses of IV dexamethasone followed by a slow taper for high suspicion of differentiation syndrome. After recovery, the patient was switched to standard chemotherapy regimen with carboplatin, pemetrexed, nivolumab and ipilimumab.

Conclusions: Although uncommon in NSCLC at a prevalence of 0.4%-1.1%, IDH2 gain-of-function mutations and overexpression are correlated with poor disease outcomes due to prolonged tumor survival. IDH2 mutations are also found in subclonal populations with concurrent driver mutations such as KRAS and EGFR. Several studies in progress have suggested the potential anti-tumor activity of IDH2 inhibitors in the treatment of solid tumors. This is the first case of differentiation syndrome in a NSCLC patient treated with enasidenib for targeting IDH2 mutation. Considering the use of enasidenib in AML, clinical benefit is seen with a reduced rate of differentiation syndrome of 10% compared to 25% in patients treated with ATRA/ATO. Furthermore, a delayed-onset of differentiation syndrome is seen with enasidenib with a mean duration of occurrence of 48 days, compared to 11 days with ATRA/ATO and other therapies. Hence, differentiation syndrome should be considered as a differential diagnosis, and caution for early identification and management is necessary in patients with solid tumors undergoing targeted therapy with IDH2 inhibitors.

Keywords: Enasidenib, IDH2 inhibitor, Differentiation syndrome

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-024 Research Efforts in Systemic Therapy of Lung Cancer with Brain Metastasis From 2015-21: A clinicaltrial.gov Registry Analysis

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Introduction: Oncogene directed therapy and immune checkpoint inhibitor therapies (ICI) resulted in a paradigm shift in non-small cell lung carcinoma (NSCLC) management. With improved survival and extra cranial control, increased likelihood of brain metastasis (BM) is reported. Several clinical trials are evaluating targeted therapy or immunotherapy in BM in lung cancer.

Methods: ClinicalTrials.gov database was screened for trials containing the keyword “brain metastasis” between 1 January 2015 to 23 December 2021. Interventional trials with recruitment status - not yet recruiting, recruiting, enrolling by invitation, active not recruiting, completed, terminated and suspended were included. No filters were applied with regards to eligibility criteria, study results, type of funding and study documents. Trial sponsorship was broadly grouped to industry and others which included universities, individuals and community-based organizations. The interventions included were targeted agents like epidermal growth factor receptor (EGFR) directed and anaplastic lymphoma kinase (ALK) directed tyrosine kinase inhibitors (TKI), immune checkpoint inhibitors (ICI) with or without chemotherapy (CT).

Results: Our extensive search revealed 172 trials in the study period and 58 were eligible for assessment. Application of selection criteria excluded 114 trials, out of which 61 trials were non-lung primaries and 53 trials involved interventions that met our exclusion criteria. Of the 58, majority 48 (83%) involved brain metastasis with lung primary and 10 (17%) involved mixed primary of which lung cancer was an essential part. Majority of the trials were phase 2 [n = 45 (77.6%)], followed by phase 3 [n = 6 (10.3%)], phase 1&2 combined [n=6 (10.3%)], phase 2&3 combined [n=1 (1.7%)] in design. Thirty-one (53.4%) trials are still recruiting, 10 (17.2%) of them are not yet recruiting, 8 (13.8%) of them active but not yet recruiting, 5 (8.6%) are terminated, 3 (5.1%) are completed and 1 (1.7%) is enrolling by invitation at the time of analysis. This included 43 (74.1%) non-randomized trials and 15 (25.9%) randomized trials. Of the 15, 13 studies were open label and remaining 2 were quadruple masked. Most of the trials were initiated in Asia [n=27 (46.6%)], followed by the North Americas [n=17 (29.3%)], Europe [n=4 (6.9%)], inter-continent [n=3 (5.1%)], Australia [n=1 (1.7%)] and location not provided [n=6 (10.3%)]. There were 21(36.2%) trials enrolling <50 patients, 23(39.7%) trials with 50-100 patients and 14(24.1%) trials >100 patients. Nine trials (15.5%) were industry sponsored, 15 (25.9%) by both industry and others, 32(55.1%) by others. Out of the 58 trials investigating newer systemic therapies, the most common agents were EGFR or ALK directed TKIs [n=29 (50%)], ICI or TKI with CT [n=11 (19)], ICI alone [n=9 (15.5%)], Vascular endothelial growth factor inhibitor (VEGFI) with or without CT [n=4 (6.9%)], VEGFI with ICI [n=3 (5.1%)], cyclin dependent kinase inhibitor [n=2 (3.4%)].

Conclusions: Currently, significant research efforts are ongoing to evaluate the role of targeted therapy or ICI in BM. Majority of these trials are phase II, involving TKIs and initiated in Asia. Findings of these trials will help to improve current understanding and could be pivotal in establishing a role in lung cancer patients with BM.

Keywords: brain metastasis, lung cancer, systemic therapy

EP08.02-025 Lazertinib as a Frontline Treatment in Patients with EGFR Mutant Advanced Non-Small Cell Lung Cancer: Results from the Phase I/II Trial

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Introduction: Lazertinib is an oral, potent, highly mutant-selective, and brain-penetrant third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) targeting both EGFR activating mutations and EGFR T790M while sparing wild-type EGFR. We report the efficacy and safety of lazertinib 240 mg as a frontline treatment in EGFR mutated, advanced or metastatic non-small cell lung cancer (NSCLC) in Part C frontline cohort of a single-arm phase I/II study (ClinicalTrials.gov identifier: NCT03046992).

Methods: Patients with EGFR mutation-positive (Exon19Del (n=24), L858R (n=18), or G719X (n=1)), locally advanced or metastatic NSCLC who had not previously been treated EGFR-TKI therapy received once-daily lazertinib 240 mg. EGFR mutation status was confirmed by local or central testing using tissue or cytological sample. The study treatment continues until objective disease progression according to RECIST, version 1.1, development of unacceptable toxicities, or withdrawal of consent. Endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and safety evaluation.

Results: As of 8 Jan 2021 (data cut-off), a total of 43 patients (median age 61.0 years, female 53.5%), received at least one dose of lazertinib 240 mg. The median duration of follow-up was 28.8 months, and 17 patients were ongoing at data cut-off. The confirmed ORR as per independent central review (ICR) was 69.8% (95% CI, 56.0 to 83.5), of which 6 patients had complete response (CR) and 24 patients had partial response (PR). The DCR by ICR was 86.0% (95% CI, 75.7 to 96.4). The median duration of response (DoR) and PFS by ICR were 23.5 months (95% CI, 12.5 to not reached [NR]) and 24.6 months (95% CI, 12.2 to 30.2) respectively. In 35 patients out of 43, common EGFR mutation of either Exon19Del (n=23) or L858R (n=12) was centrally confirmed. In this group, the confirmed ORR as per ICR was 77.1% (95% CI, 63.2 to 91.1), of which 6 patients (17.1%) had CR and 21 patients (60.0%) had PR. The DCR by ICR was 94.3% (95% CI, 86.6 to 100.0). The median DoR and PFS by ICR were 23.5 months (95% CI, 11.0 to NR) and 24.9 months (95% CI, 13.6 to NR) respectively. The most common treatment-emergent adverse events (TEAEs) regardless of causality were rash (53.5%), diarrhoea (46.5%, grade ≥3; 7%), and pruritus (46.5%). There were no grade ≥3 rash or pruritus. Diarrhoea (7.0%) was the most common grade ≥3 treatment-related AE (TRAE) reported, followed by ALT increase (4.7%). TRAEs leading to discontinuation occurred in 4.7% (paresthesia and rash erythematous). No clinically relevant cardiac events, including significant QTc prolongation or LVEF decrease, was reported.

Conclusions: Lazertinib 240 mg demonstrated a median progression-free survival exceeding 2 years, promising and durable anti-tumor activity, including complete responses, and a favorable safety profile in this frontline cohort. A multinational, randomized, phase III trial evaluating lazertinib in frontline setting therapy is ongoing (LASER 301, ClinicalTrials.gov identifier: NCT04248829).

Keywords: Lazertinib, NSCLC, EGFR-TKI

EP08.02-026 Real-world Efficacy of EGFR-TKI in Advanced NSCLC and Clinical Predictors of Outcome in Maharaj Nakorn Chiangmai Hospital in Thailand

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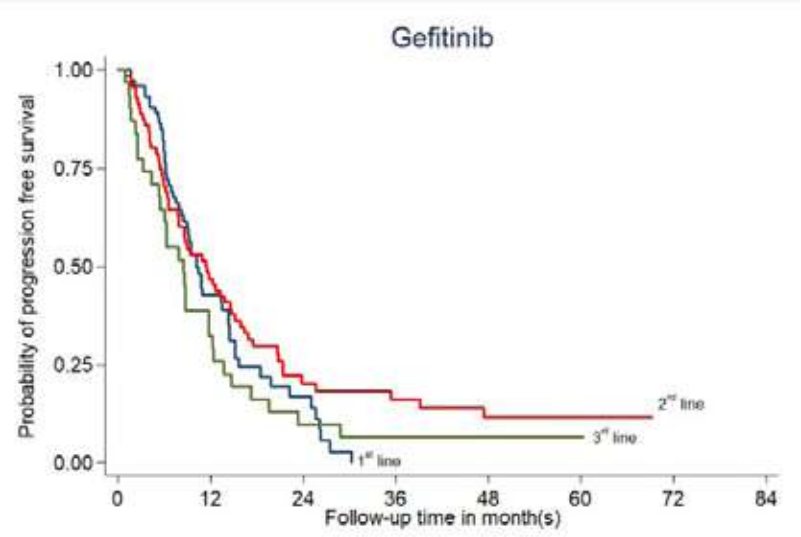
Introduction: Before January 2021, only15% of patients with advanced NSCLC could access the treatment with EGFR-TKI. We evaluated treatment outcomes of the EGFR-TKIs and the clinical predictors of outcome in patients with advanced NSCLC who received treatment under government regulation.

Methods: From November 2013 to August 2019, patients with advanced NSCLC who received gefitinib (G), erlotinib (E), afatinib (A), and osimertinib (O) under the Thai government reimbursement scheme were analyzed. We retrospectively reviewed medical records to obtain clinicopathologic characteristics, *EGFR* mutation status, and follow-up data. The primary endpoint was progression-free survival (PFS).

Results: There were 205 evaluable patients with median age of 64 years (24-87), 61%/39% female/male, non-smoker/smoker 70%/30%, ECOG PS 0-1 88% and adenocarcinoma in 93.7%. 167 (81%) patients had *EGFR* mutation (del19 58%, L858R 33%, 9% others), 10 (5%) patients with wild-type disease and 28 (14%) patients with unknown *EGFR* mutation status. Physicians had to apply for the pre-authorization approvals of the use of EGFR-TKIs and re-apply to continue treatment with results of imaging every 3 months. Majority 180 (87%) patients received G while only 13 (6.3%) with E, and 12 (5.8%) with A. Treatment was given in 1st-, 2nd-, 3rd-line in 90 (44%), 77 (37%) and 38 (19%) of patients respectively. The ORR from G / E / A was 49%, 69%, 42%. The median PFS and OS from G / E / A was 10.22 / 12.7/ 13.3 M (P0.55) and 17.4 / 26.8/ 20.9 M (P0.009), respectively. There was no difference of outcome with these 3 agents when given in 1st- v 2nd- v 3rd-line therapy, or in various *EGFR* mutation statuses. Osimertinib was allowed to use only in patients with acquired EGFR T790 mutation from other EGFR-TKIs in 30 patients which were used in 2nd- and 3rd-line therapy in 43% and 53%. Treatment with O achieved an ORR of 53% while the median PFS, OS was 8.2 M and 10.7 M, respectively. Adverse reactions were mostly mild including rash, mucositis, and diarrhea. The presence of adverse reactions did not associate with the treatment outcome. Only baseline *EGFR* mutation with exon 19 deletion was associated with increased OS. (P 0.022)

Conclusions: EGFR TKIs were highly effective and well-tolerated up to 3rd-line therapy in patients with advanced *EGFR*-mutant NSCLC in the resources-constrained setting. Our data support EGFR TKIs as the preferred treatment of choice whenever possible in advanced *EGFR*-mutant NSCLC.



Keywords: EGFR mutation, EGFR TKI, advanced lung cancer

EP08.02-027 T790M Detection Rate After First-Line Treatment with Bevacizumab Plus 1st or 2nd Generation EGFR-TKI in Advanced NSCLC

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Introduction: In this retrospective study, we proposed to demonstrate T790M mutation rate after 1st or 2nd generation EGFR-TKI plus bevacizumab in real world setting

Methods: This study collected 107 subjects' data from 11 study sites in Taiwan. Patients who completed the first-line NSCLC treatment and had re-biopsy data were enrolled. All the data were collected retrospectively for analysis

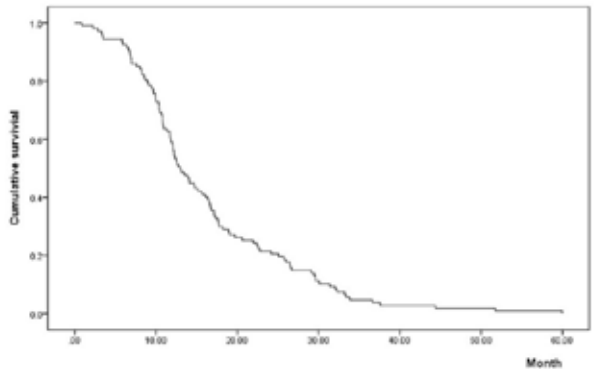
Results: After 1st or 2nd generation EGFR-TKI plus bevacizumab as first-line NSCLC treatment, the T790M alteration rate was 55.1% and was comparable to previous study. From different biopsy source, 52.8% T790M mutation was detected using blood specimen and 56.3% using tissue specimen. There are no significant differences mutation status between different specimen type.

Conclusions: This is the first study to demonstrate the T790M alteration rate after first-line treatment with 1st- or 2nd EFGR-TKI plus bevacizumab. It indicates that around half of patients occurred second mutation at T790M after first-line treatment and it coexisted with exon 19 del more than L858R in NSCLC patients

Table2 T790M Mutation Status and Subgroup Analysis

Parameter	Value n(%)
Re-biopsy specimen information	
Blood Sample	36(33.6)
Tissue Sample	71(66.3)
T790M Status after the last cycle	
Negative	48(44.9)
Positive	59(55.1)
Subgroup analysis for T790M (+)	
Re-biopsy specimen	
Blood Sample (n=36)	19(52.8)
Tissue Sample (n=71)	40(56.3)
First-line TKI	
Afatinib (n=30)	17(56.7)
Gefitinib (n=15)	8(53.3)
Erlotinib (n=62)	34(54.8)
EGFR Mutation Type	
L858R (n=44)	20(45.5)
19del (n=63)	39(61.9)

Figure 1. Progression Free Survival of All Enrolled Subjects



Keywords: NSCLC, T790M, EGFR-TKI

EP08.02-028 Germline HRR Mutations in Metastatic NSCLC and Impact on Progression-Free Survival: A Single-Center Retrospective Study

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Introduction: Germline mutations in genes involved in homologous recombination repair (HRR) represent a new target for various cancers. PARP (Poly-ADP-Ribose-Phosphate) inhibitors have been approved in prostate, pancreatic, breast, and ovarian cancers for patients with such mutations. These mutations are present in 5 to 10% of patients with lung cancer but have not been shown to be causal in the development of NSCLC and are not currently targetable as in other cancer types. At our hospital, we have noted that patients with stage IV oncogene-driven NSCLC and incidentally found germline HRR mutations appear to progress through first-line therapy more quickly compared with patients with oncogene-driven NSCLC without germline HRR mutations. The purpose of this study was to identify the number of advanced NSCLC patients with germline HRR mutations at our hospital, capture the frequency of concomitant driver mutations in this set of patients, and identify progression-free survival (PFS) on first-line therapy for all patients with such mutations.

Methods: We reviewed charts of patients with advanced NSCLC for whom Guardant360 testing had been done and in whom an incidental germline HRR mutation was identified; HRR mutations were reviewed in BRCAExchange or NIH ClinVar to confirm pathogenicity. Patients included were those with a confirmed pathogenic HRR germline mutation and known dates of systemic therapy.

Results: 11 patients were initially reviewed; 9 met inclusion criteria. Median age was 72 years; 4/9 were female. Stage at diagnosis - 5 stage IV, 4 stage III. 7/9 patients were never-smokers. Pathologic germline mutations were seen in BRCA1 (n=4), BRCA2 (n=3), ATM (n=1), FANCA (n=1), and PALB2 (n=1); 1 patient had mutations in both BRCA1 and ATM. Germline mutation was also noted on tissue biopsy in 6/9 patients. 7 of 9 (78%) patients had oncogene-driven NSCLC - 4 EGFR (all exon 19 deletions), 2 BRAF V600E, and 1 MET exon 14 skipping mutation. 4 patients had de novo stage IV NSCLC and 3 (2 EGFR, 1 MET) had initial earlier-stage disease with subsequent recurrence. All 7 patients received targeted therapy at time of metastatic diagnosis. Median PFS on targeted therapies was 11.4 months. mPFS was 9.2 months for those with de novo stage IV disease (n=4), and 44.2 months for those with early-stage disease that progressed (n=3) ($p = 0.22$). For the 4 patients with EGFR mutated disease, median PFS was 27.4 months - 9.3 months for those with de novo stage IV disease (n=2), and 49.8 months for those with early-stage disease that progressed (n=2) ($p = 0.09$).

Conclusions: The majority of our patients with incidentally found germline HRR mutations also had concurrent driver mutations and appeared to have a shorter PFS on targeted therapy compared to those seen in the landmark clinical trials validating such therapies, particularly patients with de novo stage IV disease. Our work highlights the need for testing for HRR genes in lung cancer patients and a larger cohort of patients for study.

Keywords: BRCA, Homologous recombination repair, Targeted therapy

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-029 Sunvozertinib in NSCLC Patients with EGFR Exon20 Insertion Mutations: Effect of Prior Treatment

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Introduction: While platinum-based chemotherapy is the standard of care for the 1st line treatment of NSCLC with EGFR Exon20 insertion (Exon20ins) mutations, there is no consensus for further treatment once disease progresses. EGFR TKIs, anti-PD(L)1, anti-angiogenesis, among others, are frequently used. Sunvozertinib is a rationally designed EGFR Exon20ins inhibitor with wildtype selectivity. Results from the ongoing phase 1/2 studies showed sunvozertinib's strong anti-tumor activity and benign safety profile. Based on these data, sunvozertinib was granted the Breakthrough Therapy Designation by both US FDA and China NMPA. Here we present the effect of prior therapies on sunvozertinib's safety and efficacy.

Methods: Data from the ongoing WK-KONG1 (NCT03974022) and WU-KONG2 (CTR20192097) studies were pooled together for the analysis. Patients were categorized based their prior treatment history. The relationship between prior treatment and sunvozertinib's safety and efficacy was analyzed.

Results: As of July 30, 2021, a total of 56 locally advanced or metastatic NSCLC patients with EGFR Exon20ins mutations were enrolled into WU-KONG1 and WU-KONG2 studies and included in the efficacy analysis set. Subjects received 1 to10 lines of prior treatment. including platinum-based chemotherapy (52, 92.9%), EGFR TKIs (25, 44.6%), PD(L)-1 (17, 30.4%), and others. Anti-tumor activity was observed in patients with different categories of prior treatment. Prior platinum-based chemotherapy, EGFR TKIs or PD(L)-1 treatment did not impact the safety profiles of sunvozertinib.

Conclusions: The data suggest sunvozertinib is active in NSCLC patients with EGFR Exon20ins, irrespective of categories of prior treatment. The updated data will be presented at the meeting. Sunvozertinib is currently in phase 2 pivotal clinical development (NCT03974022 and China CTR20211009).

Keywords: sunvozertinib, EGFR, Exon 20

EP08.02-030 Tusamitamab Ravtansine in Patients with NSQ NSCLC and Negative or Moderate CEACAM5 Expression Tumors and High Circulating CEA

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Introduction: Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), one member of the carcinoembryonic antigen (CEA) family, is a cell-surface glycoprotein that is highly expressed on epithelial tumor cells. Circulating CEA is the shed form of membranous CEA family proteins. Tusamitamab ravtansine (SAR408701) is an anti-CEACAM5 antibody conjugated to the cytotoxic maytansinoid agent DM4. Tusamitamab ravtansine 100 mg/m^2 every other week (Q2W) showed encouraging antitumor activity in the first-in-human study (NCT02187848) in a cohort of 64 heavily pretreated patients with nonsquamous non-small cell lung cancer (NSQ NSCLC) and high CEACAM5 expression (defined as ≥ 2+ intensity in ≥ 50% of the tumor cells) as determined by immunohistochemistry (IHC) methods, but fewer responses in a cohort of patients (n = 28) with moderate CEACAM5 expression (defined as ≥ 2+ intensity in ≥ 1% to < 50% of the tumor cells) (Gazzah A et al. *J Clin Oncol.* 2020;38[15 suppl]:9505). A Phase 3 study (NCT04154956) is currently ongoing in previously treated patients with NSQ NSCLC and high CEACAM5 expression comparing tusamitamab ravtansine to docetaxel. CARMEN-LC06 (NCT05245071) aims to evaluate whether patients with a high circulating CEA level at baseline benefit from tusamitamab ravtansine treatment despite negative or moderate CEACAM5 expression in archival biopsy sample.

Methods: CARMEN-LC06 is a single-arm, open-label, multicenter, Phase 2 study to evaluate tusamitamab ravtansine Q2W monotherapy in patients with negative or moderate CEACAM5-expressing NSQ NSCLC tumors and high circulating CEA levels. The primary objective is to assess the antitumor activity (objective response rate) of tusamitamab ravtansine. Secondary objectives are to assess the safety and tolerability, other efficacy parameters (progression-free survival, disease control rate, and duration of response) and immunogenicity of tusamitamab ravtansine. Inclusion criteria include: age ≥ 18 years; proven metastatic NSQ NSCLC with CEACAM5 expression that is negative (defined as intensity 1+ whatever the percentage of stained tumor cells or < 1% of tumor cells) or moderate (defined as intensity ≥ 2+ in ≥ 1% and < 50% of tumor cells) as assessed by a central IHC assay in an archival tumor sample; circulating CEA levels ≥ 100 ng/mL at screening; documented disease progression after prior platinum-based chemotherapy lines and an immune checkpoint inhibitor; at least one measurable lesion by RECIST v1.1, and Eastern Cooperative Oncology Group performance status 0 or 1. Key exclusion criteria are history of or unresolved corneal disorder; untreated brain metastases or history of leptomeningeal disease; life expectancy < 3 months; concurrent anticancer therapy; or prior CEACAM5 or maytansinoid therapy. Planned enrollment is approximately 38 treated patients. The study is designed to determine whether a broader patient population can benefit from treatment with tusamitamab ravtansine, compared with the patient population in the ongoing phase 3 study. Clinical Trials.gov identifier: NCT05245071.

Keywords: Tusamitamab ravtansine, CEACAM5, non-small cell lung cancer

EP08.02-031 NRF2 Pathway Signature Predicts KEAP1/NFE2L2 Mutations and Reveals Alternative Pathway-Activating Mutations in NSCLC

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Introduction: *KEAP1/NFE2L2* or *NRF2* (K1N2)-pathway activation leads to an aggressive phenotype in ~15% of non-small cell lung cancer (NSCLC) which is resistant to radio/chemotherapy as well as immune-checkpoint blockade (ICB) and is associated with unfavorable prognosis. Since specific therapy for these difficult-to-treat tumors is needed, we developed a transcriptomic signature for the identification of these patients irrespective of their underlying *KEAP1/NFE2L2*-pathway genetic or epigenetic alteration.

Methods: We explored a series of 108 antioxidant genes known to be induced by *NRF2* expression. This gene signature showed good performance for predicting *KEAP1/NFE2L2* alterations across various tumor types including NSCLC in The Cancer Genome Atlas (TCGA). To optimize and validate the antioxidant gene signature, RNA and whole exome sequencing data of 971 TCGA NSCLC samples was used to train a regularized (elastic net) logistic regression model predicting *KEAP1/NFE2L2* mutations by a transcriptomic NRF2 pathway signature. To validate the model, 348 in-house NSCLC tissue samples from Cologne including 147 *KEAP1*- and 49 *NFE2L2*-mutated samples were analyzed with a custom Nanostring gene expression panel. We used 240 Cologne cases for cutoff calibration prior to prediction on an independent validation dataset of 108 Cologne tumors. The mutational landscape of false-positive (signature score positives, K1N2-mutation negative) in NSCLC TCGA cases was explored through enrichment testing.

Results: The optimized anti-oxidant gene signature consisted of 46 genes and was used for score calculation. The K1N2 transcriptomic score predicted *KEAP1/NFE2L2* mutations at high area under the curve (AUC) in our independent Cologne NSCLC validation set irrespective of histology and gene mutated (AUC: 89.5, range: 87.2-95.2). At a sensitivity of 90.2% (range: 88.9-93.8), the score suggested that ~ 90% of *KEAP1/NFE2L2*-mutations result in pathway activation. Given that changed redox homeostasis (e.g. in context of tumor hypoxia) is a known characteristic of K1N2 activated and glutamine-addicted carcinomas, the K1N2 score outperformed *KEAP1/NFE2L2* mutational status in predicting tumor hypoxia. Importantly, lung adenocarcinomas (LUAD) with positive K1N2 transcriptomic scores but without mutations in *KEAP1* or *NFE2L2* ("false positives") were significantly enriched for mutations in *SMARCA4/BRG1*, with 36% *SMARCA4*mut cases classified as pathway-activated. Further, false positive lung squamous cell carcinoma (LUSC) were significantly enriched for *CUL3* mutations with 65% *CUL3*mut tumors classified as pathway-activated. TCGA whole-transcriptome data showed that 18% and 48% of differentially upregulated genes of *SMARCA4*mut LUAD and *CUL3*mut LUSC, respectively, were shared with upregulated genes in *KEAP1/NFE2L2*mut tumors. The overlapping upregulated genes of *KEAP1/NFE2L2*mut/*SMARCA4*mut/*CUL3*mut tumors were enriched for gene ontology terms involved in metabolic reprogramming representing a hallmark of the *KEAP1/NFE2L2*mut phenotype.

Conclusions: The newly developed and optimized K1N2-pathway signature robustly and precisely predicts functional mutations in *KEAP1* and *NFE2L2* and demonstrates that 90% of *KEAP1* mutations are linked to transcriptional activation of the anti-oxidant pathway. This signature also identified *SMARCA4/BRG1* and *CUL3* mutations as mimicries of *KEAP1/NFE2L2* mutations. The K1N2 score is thus a potential means to identify patients in clinical trials targeting specific NSCLC tumors driven by the anti-oxidant and glutamine-addicted K1N2- pathway. Patients with K1N2-pathway activation might be treated with antagonists of glutamine metabolism such as Sirpiglenastat.

Keywords: Biomarkers, Translational Research

EP08.02-032 High Efficiency Multiplex Detection of Molecular Alterations in Supernatants of Pleural Effusion and Cerebrospinal Fluid

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Introduction: A significant percentage of advanced lung cancer (LC) patients show central nervous system (CNS) metastasis or pleural involvement at diagnosis and/or after progression to therapies. In these cases, tumor cells can be often found in cerebrospinal fluid (CSF) or malignant pleural effusion (MPE). Although the detection of tumor derived mutations and gene fusions in the supernatant of MPE or CSF has been documented, the implementation in the routine practice of this type of biological material as a source of circulating free DNA (cfDNA) or RNA (cfRNA) is not standardized.

Methods: Thirty fluids from lung cancer patients (p) were prospectively collected, 14 baseline and 16 after progression to systemic therapies. Of them, 25 were MPE and 5 CSF. All samples were analyzed independently of the presence of tumor cells Between 1-500 mL were centrifuged, cfDNA and cfRNA automatically extracted from supernatants (QIAsymphony, Qiagen) and the concentration was measured using the Qubit® Fluorometer. Samples were genotyped using custom NGS 30-genes (GeneReader, Qiagen) and nCounter® (NanoString®) panels for mutations/copy number variants and fusions/splicing variants, respectively.

Results: Median nucleic acid concentration in extracted cfDNA and cfRNA was 13.5 ng/µL for MPE and 1.23 ng/µL for CSF. Evaluable results were obtained in 27 of the 30 MPE and CSF samples included in the study. Of the three non-evaluable samples, two were CSFs with limited volume (1 mL) and one was a MPE with low input of cfDNA. Clinically relevant alterations were detected in 24/27 (89 %) fluids. *KRAS* (n=5) and EGFR (n=5) mutations were the most prevalent, followed by *ALK-EML4* fusions (n=4). Other driver alterations detected were *BRAF* mutation, *ROS1* fusion, *MET14* splicing variant, *FGFR1*, *MYC* and *MET* amplification (n=1 in all cases). *TP53* mutations were found in 10 samples, co-occurring with other mutations in 5 of them. In 19/27 samples (70.3%) a paired cell pellet or FFPE biopsy were available. Genetic testing revealed a 94.7% concordance with fluids; the discordant sample was a baseline MPE where we failed to detect a *KRAS* mutation present in the FFPE biopsy. In the 8/27 patients not having additional samples, results from MPE and CSF were used for treatment decision.

Conclusions: MPE and CSF are a good source of tumor-derived cfDNA and cfRNA for genetic testing in LC patients with CNS and pleural involvement.

Keywords: next generation sequencing, pleural effusion, cerebrospinal fluid

EP08.02-033 Anlotinib in Elderly Patients with Advanced Non-squamous NSCLC Who Had Not Received Systemic Chemotherapy: A Single-Arm, Phase II Study

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Introduction: Elderly pts have limited therapy strategies compared to the younger pts. Anlotinib is a novel multi Tyrosine Kinase Inhibitor targeting the VEGFR, FGFR, PDGFR and c-Kit. In elderly pts subgroup of ALTER0303 trial (NCT02388919), significant advances in OS and PFS were found in anlotinib treated group with tolerable AE. In this trial, we assessed the efficacy and safety of anlotinib in elderly patients with advanced non-squamous NSCLC who had not received systemic chemotherapy.

Methods: In the phase II trial, Pts with non-squamous non-small cell lung cancer (NSCLC) aged 70 years or older who had not received systemic chemotherapy were included. Pts harboring EGFR or ALK mutations were enrolled after the failure of TKIs therapy. All included patients received anlotinib (12mg, QD, day 1 to 14 of a 21-day cycle) till progression or intolerable toxicity. The primary endpoints was PFS. ORR, DCR, OS and safety were secondary endpoints.

Results: At data cut-off (Feb 21, 2022), we recruited 49 patients in this trial, of which 34 patients were evaluable. The median age of patients was 75 years and 52.9% were female. The median PFS was 4.8 months (95% CI: 2.6-8.4) and the median OS was not reached, The ORR was 6% (2/34), and the DCR was 85% (29/34). The most common grade 1-2 adverse events (AEs) were hypertension (9/34, 26.5%). 26.5% of patients had treatment-related grade ≥3 AEs; foot skin reaction (3/34, 8.8%) and hypertension (2/34, 5.9%) were most frequent.

Conclusions: Anlotinib appears to be feasible and safe in patients over 70 years of age, with advanced non-squamous NSCLC who had not received systemic chemotherapy.

Keywords: Anlotinib, Elderly Patients, Non-squamous NSCLC

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-034 OCELOT - Osimertinib then Chemotherapy in EGFR+ Lung Cancer with Osi Third-line Rechallenge and Osimertinib for Uncommon EGFRm in 1L

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Introduction: The FLAURA study established osimertinib as a preferred first-line standard of care for patients with the two 'common' types of epidermal growth factor receptor mutation-positive (EGFR+) advanced non-small-cell lung cancer (aNSCLC). Second-line (2L) treatment is typically platinum pemetrexed chemotherapy and the standard third-line (3L) treatment is docetaxel, which has a modest response rate of 7 - 15%. Previously, when first generation (1G) EGFR tyrosine kinase inhibitors (TKIs) were standard of care in the first-line setting, a number of prospective and retrospective studies examined 3L rechallenge with the same 1G EGFR TKI following 2L chemotherapy, with varying levels of success. Osimertinib is a well-tolerated EGFR TKI which is active against the T790M resistance mutation, which would have limited the efficacy of rechallenge with 1G EGFR TKIs. Uncommon EGFR mutations (non-exon 19 del and L858R) occur in up to 20% of patients, however, the efficacy of osimertinib in this population is not well understood. To date small prospective studies, retrospective case series, and case reports have signaled that osimertinib has a role in the treatment of patients with uncommon EGFR mutations, but further study is needed.

Methods: This is a multicentered international phase II investigator-initiated study of osimertinib in the 3L rechallenge of patients with EGFR+ aNSCLC, following 1L treatment with osimertinib and 2L therapy with platinum pemetrexed chemotherapy. A maximum of 200 patients will be enrolled. Patients with 'common' EGFR exon 19 deletions or L858R mutations will enroll at the start of 2L chemotherapy or 3L osimertinib rechallenge. Thirty patients with uncommon EGFR mutations will be permitted to enroll at 1L osimertinib and then proceed to 2L platinum pemetrexed chemotherapy and 3L osimertinib rechallenge. The primary objective is 3L objective response rate (ORR) in the first 100 evaluable patients with common EGFR mutations, according to RECIST 1.1. Secondary objectives include disease control rate (DCR), progression free survival (PFS), time to treatment failure, overall survival and toxicity - all for 3L osimertinib rechallenge, and 1L ORR, DCR and PFS in patients with uncommon EGFR mutations. Exploratory objectives include assessment of osimertinib resistance based on serial ctDNA samples collected from all participants. The OCELOT study, NCT04335292, is actively enrolling participants.

Keywords: EGFR, TKI Rechallenge, osimertinib

EP08.02-035 Clinical Utility of Liquid Biopsy After Progression to First and Second-Generation TKIs in Advanced EGFR Mutant NSCLC Patients

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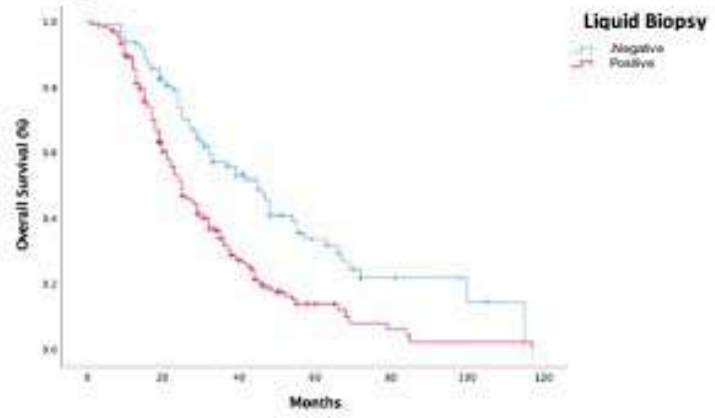
Introduction: Liquid biopsy (LB) has increased its usefulness in selecting precise therapy during different treatment phases in advanced EGFR-mutant (EGFRm) non-small cell lung cancer (NSCLC). In addition, it has played a prognostic and predictive role in EGFRm patients. Detection of main oncogenic driver alteration on LB has been associated with worse oncological outcomes and increased disease burden. This study aims to assess survival and clinical characteristics associated with LB findings at first EGFR-TKI progression.

Methods: We prospectively analyzed 295 patients with advanced EGFRm (PCR analysis) NSCLC diagnosis from January 2016 to December 2021. All patients received as upfront treatment a first or second-generation EGFR-TKI until progression. Liquid biopsies (LB) in plasma were collected in every patient at the time of TKI progression. Overall survival (OS) was associated according to LB result (EGFRm positive or negative), type of EGFRm (exon 19del and L858R vs. T790M), and the number of involved metastatic sites.

Results: Of 295 LB, 122 (41.4%) had a positive T790M mutation as a secondary resistance mechanism; 24 (19.6%) associated with T790M alone, 69 (56.5%) in combination with exon19del, 27 (22.1%) with L858R, and 2 (1.6%) with exon19del+L858R. Twenty-four patients underwent subsequent LBs due to an initial negative result; 23 patients a second LB, and one patient a third LB. In nine additional patients (3.1%), a positive T790M mutation was detected in subsequent LBs. Thirty-seven patients (28.2%) harboring a T790M mutation received osimertinib, 24 (64.9%) in a second-line setting, and 13 (35.1) patients in the third or further lines of therapy. The median OS was 45 months [95% CI (37.03-52.96)] vs. 25 months [95% CI (21.06-28.93); p<0.001] in patients with a negative and positive LB, respectively (Figure 1). Those patients with EGFR sensitive mutations vs. resistant mutations on LB did not show differences in OS. Regardless of the line of therapy (second-line or subsequent), the median OS was 44 months [95% CI (33.05-54.99)] in patients who received osimertinib vs. 21 months [95% CI (18.27-25.72); p<0.001] in those who did not. Clinical characteristics associated with a positive LB at progression were extrathoracic involvement, >3 metastatic sites, and presence of bone metastases.

Conclusions: Liquid biopsy confirmed its prognostic and predictive value in a real-world context. A positive liquid biopsy at progression was associated with worse survival and increased disease burden. Based on T790M detection on liquid biopsy, osimertinib improves overall survival in advanced EGFRm NSCLC after previous EGFR-TKI.

Figure 1.



Keywords: Liquid Biopsy, EGFRm, ctDNA

EP08.02-036 Selpercatinib Striking Response in a Case of Cerebral and Auditory Canal Metastasis of RET Fusion-Positive Non-Small-Cell Lung Cancer

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Introduction: RET gene fusions are oncogenic drivers known to occur in 1-2% of non-squamous non-small cell lung cancer (NSCLC) patients. Selpercatinib is a selective inhibitor approved by European Medicines Agency as a subsequent treatment for advanced NSCLC RET gene fusion-positive after first-line treatment with immunotherapy and/or platinum-based chemotherapy. Phase 1-2 (1) clinical trial with selpercatinib, showed a 91% response rate on patients with central nervous system (CNS) evolvement.

Methods: This case report presents a clinical case of a patient with advanced lung adenocarcinoma. The patient medical record between 03/June/2016 and 23/February/2022 was accessed and reviewed.

Results: A 72-year-old woman, never smoker, was diagnosed in 2016 with lung adenocarcinoma with acinary and micropapillary pattern with cT4N2M1a stage at diagnosis (heterogeneous nodule of 45 millimetres, single pre-carinal adenopathy of 11 millimetres, ipsilateral pulmonary effusion and metastasis). The initial molecular study was EGFR, ALK and ROS1 negative. The patient was started on first-line induction treatment with pemetrexed and carboplatin, completing 6 cycles with a good tumoral response, followed by manutention treatment with pemetrexed, completing a total of 71 cycles with stability. In November 2020, after local progression (a 21% increase in the sum of the longest diameter of target lesions), re-biopsy showed PDL1 expression of 5% and RET gene fusion-positivity, and off-label therapy with carbozantinib was started. This targeted therapy was poorly tolerated with severe asthenia and nausea, and neutropenia and thrombocytopenia and was switch to pembrolizumab. In May/2021, the patient presented with symptoms of hypoacusia, headache and dizziness, and magnetic resonance revealed metastatic progression with cerebral and auditory canal metastasis. Assuming tumour progression, 4th line treatment with selpercatinib was started on December/2021. After only one week of treatment with selpercatinib 160 mg two times daily, a significant improvement of symptoms was observed, with total hearing recovery and substantial dizziness and headache improvement. Blood test analysis revealed a 5.1 times elevation upper the normal limit of aspartate aminotransferase level, without other adverse effects, requiring dose adjustment. Radiological review is programmed at 3 months of treatment.

Conclusions: We present the case of a patient with NSCLC with RET fusion mutation on re-biopsy and a rare presentation with auditory canal metastasis, after platinum-based chemotherapy and immunotherapy failure. Selpercatinib 4th line of therapy, achieved immediate CNS related symptomatic response, corroborating the previously RCT results (1), and emphasizing the efficacy of this selective RET kinase inhibitor on this specific subgroup of NSCLC patients. **References:** 1) Drilon A, Oxnard GR, Tan DSW, Loong HHF, et al. Efficacy of Selpercatinib in *RET* Fusion-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Aug 27;383(9):813-824. doi: 10.1056/NEJMoa2005653. PMID: 32846060; PMCID: PMC7506467.

Keywords: Selpercatinib, RET gene fusions, Auditory canal metastasis

EP08.02-037 Small Cell Transformation in a Patient with RET Fusion Positive Lung Adenocarcinoma on Pralsetinib

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Introduction: Approximately 1-2% of non-small cell lung cancers harbor activating fusions between the 3' end of *RET* and the 5' end of various partner genes. Tumors with *RET* fusions respond to RET tyrosine kinase inhibitors, however secondary resistance to RET inhibitors invariably ensues.

Methods: We present the case of a patient with lung adenocarcinoma containing a *KIF5B::RET* fusion who developed resistance to pralsetinib with histologic transformation to small cell lung cancer and comprehensive pathology and molecular profiling at baseline and progression with the Mayo Clinic Solid Tumor Panel (MCSTP) and the Idylla GeneFusion assays. MCSTP is a 515 gene assay that assesses for single nucleotide variants, indels, tumor mutational burden, microsatellite instability, gene fusions in 55 genes, copy number alterations in 59 genes and three RNA splice variants (*MET*, *AR*, *EGFR*).

Results: A 72-year-old never smoker male patient was diagnosed with lung adenocarcinoma forming several lung nodules throughout the right lung as well as right hilar and mediastinal lymphadenopathy. Diagnosis was established with sampling of mediastinal lymph nodes and the tumor cells were positive for TTF-1 and Napsin A, final stage T4N2M0, IIIB. Molecular workup (MCSTP) identified a *KIF5B::RET* fusion along with a loss-of-function mutation in TP53 (H193R) and *MYC* amplification. Given the multifocality of disease in the right lung and bulky mediastinal lymphadenopathy, upfront surgery or chest radiation were not offered. Instead, front-line treatment with pralsetinib was initiated. After 3 months of treatment, the patient presented with hemoptysis. Imaging showed a mixed response with improving right lung nodules but worsening subcarinal lymph node, now invading and obstructing the adjacent right mainstem bronchus. The patient underwent bronchoscopy guided debulking with stent placement. Subsequently, concurrent chemotherapy and radiation to the progressing mediastinal lymph nodes were administered with response. Pralsetinib was resumed following completion of radiation therapy, however further progression was detected 2 months later in the chest, abdomen and brain with fistula formation between the right mainstem bronchus and the subcarinal lymph node block. Biopsy from a progressing site identified small cell carcinoma histology, positive for CD56, INSM1, ASCL1 and RB1 (retained) and negative for TTF-1 and Napsin A, distinct from the immunoprofile of the initial adenocarcinoma. Molecular analysis of tissue biopsy of the small cell carcinoma (MCSTP, Idylla GeneFusion) as well as a liquid biopsy identified retention of *KIF5B::RET*, *MYC* amplification and the same TP53 (H193R) mutation. In the presence of a bronchial fistula and high infection risk, the patient enrolled in hospice care and died 8 months following diagnosis.

Conclusions: Secondary resistance is nearly universal among NSCLC patients who receive TKIs for actionable mutations. Solvent front secondary mutations in RET (G810X) as well as activation of KRAS or MET molecular pathways have been reported to confer resistance to RET inhibitors. To our knowledge, this is the first case of a *RET* fusion lung cancer with resistance to a RET inhibitor mediated by transformation to small cell carcinoma. The *TP53* mutation detected at diagnosis may have pre-disposed the transformation to small cell carcinoma although no concurrent *RB1* mutation was detected.

Keywords: RET, small cell transformation, pralsetinib

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-038 Study of First-Line Aumolertinib Plus Bevacizumab and Pemetrexed Treated NSCLC with EGFR Mutation and Brain Metastasis

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Introduction: Brain metastases (BMs) are common among patients with lung cancer and have been associated with treatment failure and limited survival. Approximately 25% of NSCLC patients present with BMs at first diagnosis. Patients treated with 3rd generation EGFR-tyrosine kinase inhibitors (TKIs), including aumolertinib and osimertinib, showed a lower risk of progression and better responses with EGFRm NSCLC and BMs. Studies suggested EGFR-TKI plus bevacizumab had PFS benefits for patients with CNS metastases, and combination strategies of chemotherapeutic agents and TKI also demonstrated the potential to improve survival. According to the current remission rate, regression depth, and PFS data, the main benefit of combining anti-angiogenesis or chemotherapy is to reduce the tumor load and heterogeneou`s reserve to extend the remission time and delay the occurrence of drug resistance to extend the PFS. Guidelines recommend that platinum-based chemotherapy combined with 3rd generation cytotoxic drugs might bring survival benefits to patients with NSCLC BMs. While a study showed the immunomodulatory effects of pemetrexed or pacelitaxel appeared to be reduced when combined with platinum. Therefore, we proposed the concept of "chemo-weaken" strategy: the single-drug chemotherapy, platinum-free, combined with EGFR-TKI plus bevacizumab. Based on our real-world clinical practice experience and other ongoing trails, "chemo-weaken" strategy exhibited a promising efficacy and satisfied safety profile. Furthermore, for patients with EGFRm NSCLC and BMs in first-line combination therapy, brain radiotherapy might be postponed which could potentially reduce long-term adverse effects including neuro cognitive dysfunction. We hereby conducted a study to explore the efficacy and safety of aumolertinib plus bevacizumab and pemetrexed in first-line treatment of patients with EGFRm NSCLC and BMs, here is initial results of this multi-center study in China (Springlung150B)

Methods: NSCLC patients with EGFRm and BMs are recruited into this multicenter, prospective clinical trial. Patients received oral aumolertinib (110 mg QD) plus intravenous bevacizumab (7.5 mg/kg) and pemetrexed (500mg/m2) for 4 cycles in first-line treatment, then their maintenance treatment were adjusted for one of three modes: aumolertinib, aumolertinib + bevacizumab, or aumolertinib + pemetrexed. The primary endpoints are progression-free survival (PFS) and intracranial PFS, and secondary endpoints include objective response rate(ORR), intracranial ORR(iORR), and safety. The data cutoff date was Nov 30, 2021.

Results: Form Feb 2020 to Nov 2021, 10 patients were recruited. The primary endpoint was not reached, and the secondary endpoints were analyzed for the 4 cycles first-line treatment. Confirmed partial response (PR) were achieved in 8 patients and stable disease (SD) in 2 patients, the ORR was 80% and disease control rate (DCR) was 100%. 9 patients (90%) had intracranial response, of which 2 had complete response, 7 had PR and 1 had SD, the iORR was 90% and iDCR was 100%. The most common adverse event was rash (40%), and no grade 3-4 serious events occurred.

Conclusions: This is the first report that chemo-weaken therapy, aumolertinib plus bevacizumab and pemetrexed, exhibited superior activity and manageable toxicities for NSCLC patients with EGFRm and BMs. Though this trail is still ongoing, the initial results are encouraging and provide a promising therapy strategy.

Keywords: EGFR mutant NSCLC, Brain Metastasis, Aumolertinib combination therapy

EP08.02-039 An Effective Treatment for EGFR-mutated Lung Adenocarcinoma with Symptomatic Leptomeningeal Metastases Using Aumolertinib

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Introduction: Active epidermal growth factor receptor *(EGFR)* mutations predict sensitivity to EGFR tyrosine kinase inhibitors (TKIs). Central nervous system (CNS) metastases are a frequent and severe complication associated with *EGFR*-mutated non-small cell lung cancer (NSCLC). The novel third-generation EGFR-TKI aumolertinib has shown good CNS penetration and acceptable safety profile according to clinical trials.

Methods: We report a clinical case about a female lung cancer patient with CNS metastases and poor performance status.

Results: A 53 year-old Chinese women with no smoking history presented with severe headache and projectile vomiting in August 2020. Lumbar puncture pressure ranged from 190 to 320mmH2O at that time. She was diagnosed as stage IV (cT1N2M1) lung adenocarcinoma with leptomeningeal, mediastinal lymph node, liver, multiple bone metastases. The ECOG PS was 4 before she underwent anti-tumor therapies. Biopsy sample of peripheral blood and cerebrospinal fluid (CSF) cell-free DNA (cfDNA) was subjected to fluorescence PCR. The results showed *EGFR* 19-del mutation. Since enhanced mannitol treatment was ineffective, an exploratory strategy was used for this patient. She received aumolertinib 220mg per day on September 15,2020, as soon as the *EGFR* mutation status was confirmed. Three days later, as her symptoms of intracranial hypertension were relieved and her consciousness recovered, the dose of aumolertinib was adjusted to 110mg orally per day. A repeat lumbar puncture pressure went down to 120mmH2O 12 days after she started to receive aumolertinib. On September 28, it began to perform combination strategy with bevacizumab 400mg every three weeks. The ECOG PS was 1 after initial anti-tumor treatment. The best effect of lung and intracranial lesions both have reached PR. The disease was under control until December 15, 2021, as clinical and imaging progression in right pulmonary lymph-vessel and bone metastases occurred. PFS was 15 months. This patient continued to take chemotherapy and antiangiogenic therapy as subsequent treatment. No adverse events were observed during treatment.

Conclusions: This case demonstrated the safety and ability of the novel EGFR-TKI aumolertinib to treat CNS metastases in NSCLC patients and provided a practicable strategy of rescuing targeted therapy for patients with catastrophic symptoms of leptomeningeal metastases and poor performance status. What's more, fluid biopsy has already realized applications in molecular diagnosis and guiding the use of agents as alternatives or complements.

Keywords: EGFR-mutated NSCLC, leptomeningeal metastases, high-dose aumolertinib

EP08.02-040 Dacomitinib Induced Febrile Neutropenia: a Rare Serious Adverse Event

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Introduction: Dacomitinib, a second-generation oral irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has improved overall survival in metastatic non-small lung cancer patients harbouring EGFR mutations. The common adverse reactions associated with dacomitinib are diarrhoea and dermatological toxicities while severe febrile neutropenia has not been reported in literature.

Methods: We present the case of a gentleman with EGFR mutated metastatic NSCLC treated with dacomitinib at our institution, who developed febrile neutropenia.

Results: A 68-year-old male with EGFR mutated (deletion 19) stage IVB adenocarcinoma of lung which had spread to the bones and liver, presented to the emergency room (ER) with high-grade fever and chills, on day 33 of starting dacomitinib. He had a temperature of 102F, his vitals were otherwise stable, and there was no clinically obvious focus of infection. His bone marrow and organ functions were within normal limits and there was no bone marrow involvement on PET-CT prior to starting dacomitinib. His blood investigations showed leukopenia with grade 4 neutropenia (total leucocyte count [TLC] 200/µL, absolute neutrophil count [ANC] 100/µL) while other counts, indices, and serum biochemistry were within normal limits. Dacomitinib was stopped on in-patient admission, and he received intravenous piperacillin-tazobactam for febrile neutropenia as per institutional protocol. Procalcitonin was 0.4 ng/mL while his blood culture and comprehensive infectious diseases profile was negative. Fever subsided after 3 days of antibiotics and counts were recovered on the 10th day following stopping dacomitinib, with granulocyte colony-stimulating factor support [Figure 1]. Dacomitinib was resumed at a reduced dose of 15 mg once daily and subsequently escalated to 30 mg. He experienced no further neutropenia or any other severe adverse events and after 6 months of treatment he had a complete response. There was no other etiology that explained the febrile neutropenia which resolved on drug discontinuation and did not recur after resuming at a lower dose.

Conclusions: This is the first report of dacomitinib-induced febrile neutropenia in a patient with metastatic NSCLC. Clinicians should be aware of this adverse event and consider dose interruption followed by dose reduction in cases of severe neutropenia.

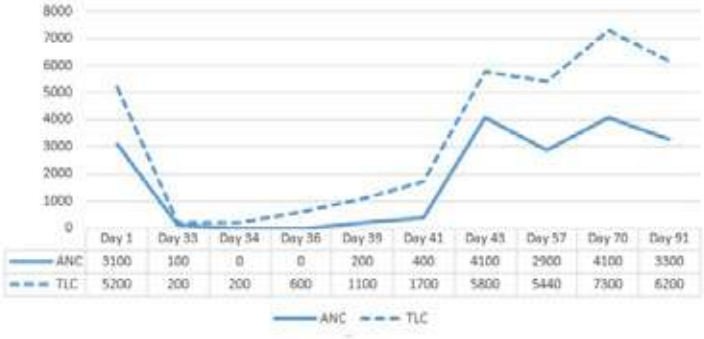

Figure 1 Time courses of absolute neutrophil and total leukocyte counts. Solid lines represent neutrophil counts (per microlitre) and broken lines represent leukocyte counts (per microlitre).

Keywords: EGFR mutated NSCLC, Dacomitinib, Febrile Neutropenia

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-041 NVL-520, a Highly Selective ROS1 Inhibitor, in Patients with Advanced ROS1-Positive Solid Tumors: The Phase 1/2 ARROS-1 Study

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Introduction: Oncogenic ROS1 gene fusions are implicated in the pathogenesis of various adult and pediatric cancers, including up to 3% of non-small cell lung cancers (NSCLC), where up to 40% of patients present with central nervous system (CNS) metastases. Tyrosine kinase inhibitors (TKIs) approved by the FDA and EMA for ROS1-positive NSCLC (crizotinib and entrectinib) are limited by acquired resistance, frequently mediated by secondary ROS1 kinase domain mutations. In addition, dual TRK/ROS1 kinase inhibitors such as entrectinib are associated with neurologic adverse events. NVL-520 is a novel, brain-penetrant ROS1-selective kinase inhibitor that exhibits preclinical activity against a diverse array of ROS1 fusions and ROS1 mutations including G2032R, while sparing inhibition of TRK. The ARROS-1 study evaluates the safety and activity of NVL-520 in patients with solid tumors harboring ROS1 fusions, including those with ROS1 resistance mutations and CNS metastases.

Methods: ARROS-1 (NCT05118789) consists of a phase 1 dose escalation, followed by phase 2 expansion in cohorts defined by tumor type and prior therapies that are designed to support potential registration. Phase 1 includes adult patients with any solid tumor type harboring a ROS1 gene fusion (by local testing), with evaluable disease, who have received ≥ 1 prior ROS1 TKI. Prior platinum-based chemotherapies and/or immunotherapies, as well as stable CNS disease, are allowed. Patients will receive NVL-520 by daily oral administration. Primary phase 1 objectives are to determine the NVL-520 recommended phase 2 dose, and, if applicable, maximum tolerated dose. Additional objectives include evaluation of safety/tolerability, preliminary activity, and characterization of the pharmacokinetic and pharmacodynamic profiles of NVL-520. Longitudinal analysis of circulating tumor DNA will be performed, including ROS1 mutation profiling and other relevant biomarkers. The phase 1 portion of the study is ongoing.

Keywords: NVL-520, ROS1, NSCLC

EP08.02-042 EGFR-TKI +/- Antiangiogenics for EGFR-mutated Advanced NSCLC

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Introduction: The development of genomic-driven strategies to tackle Non-Small Cell Lung Cancer (NSCLC) such as EGFR-TKIs improved Progression-Free Survival (PFS) but has failed to improve Overall Survival (OS) until the development of third-generation EGFR-TKI. More recently, a combination of EGFR-TKI plus antiangiogenic agents has emerged as another option for EGFR-mutated advanced NSCLC, although it remains unclear if this combination improves OS. Moreover, there is a paucity of data comparing third-generation EGFR-TKI with EGFR-TKI plus antiangiogenic combination.

Methods: This study is a network meta-analysis with a bayesian approach and a random effectsmodel. The authors used multivariate normal distribution and random effects models to account for between-arm correlation in multi-arm trials inside the frequentist network. We expressed OS and PFS outcomes as hazard ratios (HR) with the respective 95% credibility interval (95% CrI) and AEs as odds ratios (OR) with the respective 95% CrI. The authors indirectly compared erlotinib, erlotinib plus bevacizumab, erlotinib plus ramucirumab, osimertinib, and osimertinib plus bevacizumab. The study assessed the risk of bias according to the Cochrane Collaboration's tool (version 2.0).

Results: This study included a total of 8 clinical trials. EGFR-TKI plus antiangiogenic agents and osimertinib improved PFS compared to erlotinib alone. Furthermore, there was a trend towards superiority of osimertinib compared to erlotinib plus bevacizumab (HR 0.76, 95%CrI 0.50-1.20) and erlotinib plus ramucirumab (HR 0.77, 95% CrI 0.44-1.36). In this meta-analysis, EGFR-TKI plus antiangiogenic agents failed to show a statistically significant improvement in the OS compared to erlotinib alone. The table below summarizes OS indirect comparisons (the reference is the column). The combination of EGFR-TKI plus antiangiogenic agents increased the risk of grades 3-4 toxicities as well as proteinuria and hypertension. The risk of bias was low except for performance bias due to the high proportion of trials with an open label fashion (50%).

Conclusions: The combination of EGFR-TKI plus antiangiogenic agents improved PFS, but not OS. Osimertinib showed statistically significant improvement on PFS when compared to erlotinib alone as well as erlotinib plus antiangiogenic agents. In terms of safety, the combination of EGFR-TKI plus antiangiogenic agents also increased the risk of toxicities, especially proteinuria and hypertension.

erlotinib alone	0.904 (0.716, 1.152)	0.829 (0.477, 1.451)	0.800 (0.526, 1.215)	0.774 (0.338, 1.782)
	erlotinib+bevacizumab	0.915 (0.501, 1.689)	0.885 (0.546, 1.415)	0.856 (0.362, 2.034)
		erlotinib+ramucirumab	0.966 (0.480, 1.919)	0.934 (0.343, 2.533)
			osimertinib alone	0.967 (0.469, 2.016)
				osimertinib+bevacizumab

EP08.02-043 The Current State of Biomarker Testing in Lung Cancer as Seen by Health Care Providers

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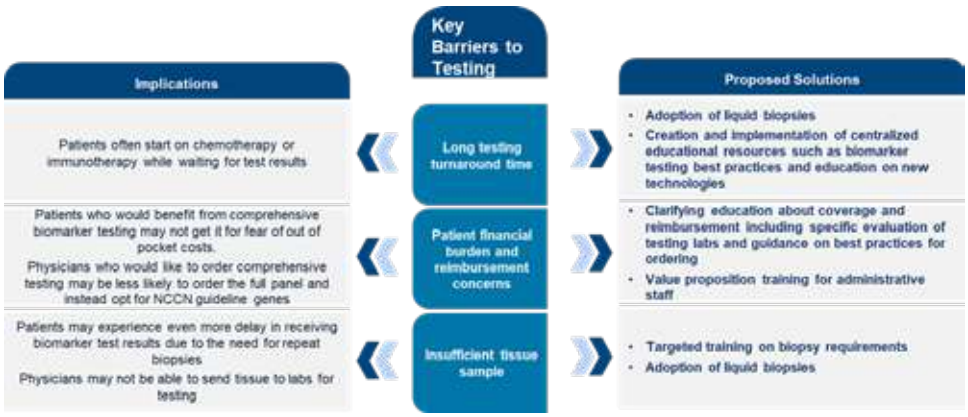
Introduction: Comprehensive biomarker testing, defined as a biomarker test that looks at the entire genome, or set of genes, and/or proteins in a person's tumor to determine if there are changes that could be related to the person's cancer and inform treatment for people diagnosed with metastatic non-small cell lung cancer (mNSCLC) with adenocarcinoma histology. Despite recent advancements and better implementation of testing and precision medicine, it has been documented for years that in community-based practices, people diagnosed with lung cancer are less likely to receive comprehensive biomarker testing and instead favor testing for one or two genes (Gutierrez et al, 2017). The lack of widespread comprehensive biomarker testing can also be seen in European countries such as Spain (Salas et al, 2022) where even PD-L1 was not tested in many people diagnosed with mNSCLC. In an effort to increase the quality of care for people diagnosed with mNSCLC, GO2 Foundation investigated clinician-identified barriers to biomarker.

Methods: Four health care providers (HCP) within GO2 Foundation's Centers of Excellence (COE) network were interviewed and asked to identify which testing barriers they experienced with their patients. Clinicians were asked to share their real-world experience about the implications of each barrier on their patient population and what if anything could be done to address the barriers. Clinicians were asked the same questions regardless of existing testing processes and types of patients served.

Results: Interview respondents shared three main barriers to comprehensive biomarker testing in their practice (see image): long testing turnaround times, defined as fourteen days or more from time of ordering, patient financial burden and reimbursement concerns, and insufficient tissue samples. Implications for these barriers ranged from suboptimal treatment choices for patients to an inability for physicians to order comprehensive biomarker testing in situations where they may want or intend to. Interestingly, HCP proposed solutions had overlap between the different barriers suggesting the potential for tackling multiple problems with singular actions.

Conclusions: Barriers to comprehensive biomarker testing are consistent among community-based cancer centers regardless of patient demographics suggesting that many patients seen at community-based cancer centers are vulnerable to similar negative implications on their treatment from not receiving testing. As part of the interview process, multiple solutions were identified that the entire lung cancer community should come together to address in an effort for higher rates of biomarker testing and better care for patients.



Keywords: Biomarker Testing Barriers

EP08.02-044 Adding Alectinib Rescues Progression on Osimertinib Due to Acquired ALK p.R1275Q Variant in EGFR p.L858R-mutated NSCLC

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Introduction: New resistance mechanisms and subsequent treatment options in NSCLC progressing on Osimertinib are being revealed in the real-world setting.

ALK-mutations represent an extremely rare, acquired resistance mechanism in EGFR-mutated NSCLC patients treated with Osimertinib. We present a case of an elderly patient having advanced NSCLC with concomitant EGFR p.L858R and TP53 p.C277F mutations, who progressed on Osimertinib treatment acquiring a pathogenic ALK variant. The case also underlines that although geriatric patients in reduced performance status (PS) may be unsuitable for tissue rebiopsy, longitudinal plasma cell-free (cfDNA) taken under the treatment course, may reveal further realistic treatment options.

Methods: Genomic DNA from the diagnostic tumour-biopsy at baseline was examined by targeted next-generation sequencing (NGS) for SNVs, indels and CNVs across 161 cancer-associated genes using the Oncomine™ Comprehensive Assay v.3 (ThermoFisher Scientific). For possible gene-fusions' detection, total RNA from the biopsy was analysed by Archer FusionPlex® Lung kit (ArcherDX, Inc). Plasma cfDNA was analysed for relevant mutations by Oncomine Lung cfDNA NGS-assay (ThermoFisher Scientific).

Results: An 80-year-old woman, smoker, with COPD and reduced lung capacity, in PS 2, was diagnosed with T3bN1M0 NSCLC harboring EGFR p.L858R and TP53 p.C277F co-mutations. The patient already progressed after 2 months on first line Osimertinib. Since tissue rebiopsy was unfeasible, plasma cfDNA was analysed revealing KRAS p.G12R mutation. The patient was unfit for platin-based doublet chemotherapy but was offered Pemetrexed, continuing Osimertinib in standard doses. Tumour regression was observed after three cycles. Corresponding cfDNA did not reveal any mutations. However, the treatment was temporarily paused because of increasing toxicity. Under treatment break cfDNA showed reappearance of the original EGFR p.L858R together with KRAS p.G12R and TP53 p.C277F mutations. The patient was re-challenged with Osimertinib and Pemetrexed in reduced doses. Unfortunately, radiographic progression was observed 3 months later. Despite no EGFR/KRAS/TP53 mutations, new cfDNA analysis showed acquired activating ALK p.R1275Q mutation in the ALK-TK-domain. This variant is characteristic for neuroblastomas and known to be Crizotinib-resistant. We assumed that it may also cause Osimertinib-resistance and be sensitive to second generation ALK-TKIs. Thus, Alectinib in reduced dose was initiated while continuing Osimertinib in reduced dose, due to the patient's fragile status. The treatment was well tolerated with no adverse events and improved quality of life. Three subsequent CT-scans of chest/abdomen showed stable disease, while no pathogenic variants were detected in plasma cfDNA.

Conclusions: Liquid biopsy-guided approach at progression in elderly patients with reduced PS may offer a feasible and effective therapy, as in this case by combining ALK- and EGFR-TKI. The treatment is ongoing and current progression-free survival is now 8 months, which is the longest under the whole treatment course. Effective combination of Osimertinib and Alectinib has been reported in single cases of disseminated EGFR-mutant NSCLC becoming resistant to Osimertinib through acquired ALK-fusions. However, to our knowledge, this case is the first to show durable response to combined Osimertinib-Alectinib treatment when the progression is associated with acquired ALK-mutation, indicating that the ALK p.R1275Q variant may represent a mechanism of Osimertinib-resistance that can be effectively counteracted by Alectinib.

Keywords: ALK R1275Q, EGFR L858R, Osimertinib resistance

EP08.02-045 Phase 1/2 Study of BLU-945 in Patients with Common Activating EGFR-Mutant Non-Small Cell Lung Cancer

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Introduction: EGFR-targeted therapies have improved outcomes in patients with non-small cell lung cancer (NSCLC) harboring *EGFR* mutations, such as *EGFR* ex19del and L858R; however, resistance to these drugs is inevitable. BLU-945 is an investigational next-generation EGFR tyrosine kinase inhibitor (TKI) designed to suppress common activating and on-target resistance EGFR mutations, such as C797S and T790M. Preclinically it has shown activity as monotherapy in osimertinib-resistant patient-derived xenograft (PDX) models. In addition, BLU-945 has >450-fold selectivity for C797S and T790M mutants over wildtype, which is advantageous for combinations with complementary EGFR-targeting agents, such as osimertinib. These combinations have shown enhanced activity in PDX models. An abstract describing this study was previously submitted to the American Society of Clinical Oncology 2022 Annual Meeting.

Methods: SYMPHONY (NCT04862780) is an international, open-label, first-in-human, phase 1/2 study designed to evaluate safety, tolerability, and antitumor activity of BLU-945 as monotherapy and in combination with osimertinib in patients with *EGFRm* NSCLC. Key eligibility criteria include adults with pathologically confirmed metastatic NSCLC with an activating *EGFR* mutation, Eastern Cooperative Oncology Group performance status 0-1, and previous treatment with ≥1 EGFR-targeted TKI. Patients with asymptomatic brain metastases who are on stable doses of corticosteroids are eligible. Tumors with additional known driver alterations, including *EGFR* exon 20 insertions and other kinase drivers, are excluded. Primary endpoints are maximum tolerated dose, recommended phase 2 dose (RP2D) and safety (all phase 1); as well as overall response rate (ORR) by RECIST v1.1 (phase 2). Key secondary endpoints include ORR, duration of response (DOR), pharmacokinetics (PK), and pharmacodynamics (PD; all phase 1); and DOR, progression-free survival, overall survival, CNS efficacy, PK, and safety (all phase 2). Phase 1 dose escalation will be done using Bayesian optimal interval design; ≈85 patients will receive BLU-945 monotherapy and ≈18 will receive combination BLU-945 and osimertinib. In the phase 2 dose expansion, patients will receive BLU-945 at the RP2D of the monotherapy in 3 groups based on *EGFR* mutational profile: T790M and C797S (n≈37), T790M, without C797S (n≈12), and C797S, without T790M (n≈12). In a combination group, BLU-945 plus osimertinib will be administered at RP2D of the combination to n≈24 patients, ≥12 with both T790M and C797S mutations. Patients may receive treatment until disease progression or unacceptable toxicity. Recruitment is ongoing and approximately 30 sites will be open for enrollment across North America, Europe, and Asia.

Keywords: EGFR TKI, EGFR resistance mutations, Clinical trial

EP08.02-046 Activity of OsimeRTInib in NSCLC with Uncommon EGFR Mutations: Retrospective Observational Multicenter Study (ARTICUNO)

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Introduction: Osimertinib is a third generation TKI representing the standard of care for treatment of metastatic NSCLC harboring classical *EGFR* mutations (exon 19 deletion and L858R). In 10-20% of patients with *EGFR* alterations, an assorted group of other uncommon mutations can also be detected. These mutations confer variable sensitivity to first- and second-generation TKIs, with overall lower therapeutic activity. Data of Osimertinib in this heterogenous group of mutations are limited and strongly warranted.

Methods: This is a retrospective multicenter study of patients with advanced NSCLC with any uncommon alteration of *EGFR* and treated with Osimertinib since August 2017. Investigators collected response in terms of overall response rate (ORR) and disease control rate (DCR) by RECIST 1.1 criteria. Progression free survival (PFS), duration of response (DOR) and overall survival (OS) were estimated by Kaplan-Meier method.

Results: As of February 2022, 50 patients with NSCLC with uncommon *EGFR* mutations were identified in 13 institutions in Italy. Patients' characteristics: 64% female, median age 64 (32-87) years, 86% ECOG PS 0-1, 66% smoking history, 90% Caucasian, 94% adenocarcinoma. Most frequent sites of metastasis were lung (60%), bone (44%), and brain (30%). The most frequent mutations were compound mutations (30%, N=15), L861Q (20%, N=10), and G719X (14%, N=7) (**Table 1**). In 84% (n=42) Osimertinib was used in TKI-naïve setting and in 78% as first treatment. Median time of follow up was 11.5 months. ORR and DCR were 49% (CI 95%, 34-64%) and 85% (CI 95%, 72-94%) in the overall evaluable population (N=47), and 53% (CI 95%, 35-70%) and 84% (CI 95%, 67-94%) in TKI-naïve (excluded ins20) cohort, respectively. Highest responses were observed in cases with L861X, followed by G719X and compound mutations. Median PFS and DOR in TKI-naïve were 11 months (CI 95%, 6.3-15.7) and 14 months (CI 95%, 5-14), respectively. Notably, one patient with EGFR-KDD and one with D770_N771insSVD (ins20) achieved long-term responses.

Conclusions: In this first analysis of 50 patients, the most frequent uncommon *EGFR* mutations were G719X, followed by L861X and S768I, largely occurring as compound, consistently with previously reported frequencies. Osimertinib showed activity with response in about half of patients, overall. Data from this first real-life Italian study appear comparable with those described in a prospective Korean phase 2 trial with Osimertinib and with those reported with Afatinib. ARTICUNO study is still ongoing and more updated data will be presented.

Table 1: Distribution of uncommon *EGFR* mutations in the study population and outcome with Osimertinib. Patients with at least one major uncommon mutations (G719X, L861X or S768I) are regrouped.
(aq=acquired, dn=*de novo*).

Major uncommon mutation +/- other mut.	N (%)	ORR% (95%CI), DCR% (95%CI), mPFS (months, 95%CI)
G719X	**16 (32)**	
G719A	3 (6)	53 [27-78], 93 [68-100], 9 [6.6-11.4]
G719A+aqT790M	1 (2)	
G719X	3 (6)	
G719X+I706T+aqT790M	1 (2)	
G719S+dnT790M	2 (4)	
G719X+S768I	1 (2)	
G719A+S768I	1 (2)	
G719S+S768I	2 (4)	
G719A+L861Q	2 (4)	
L861X	**12 (24)**	
L861Q	8 (16)	55 [23-83], 91 [59-100], 11 [5.8-16.2]
L861Q+aqT790M	2 (4)	
L861Q+G719A	2 (4)	
S768I	**9 (18)**	
S768I	1 (2)	56 [21-86], 100 [66-100], 17 [4.3-29.7]
S768I+aqT790M	1 (2)	
S768I+L858R	3 (6)	
S768I+G719X	1 (2)	
S768I+G719A	1 (2)	
S768I+G719S	2 (4)	

Mutations	N (%)	BOR
OTHERS	**13 (26%)**	
V738_A743del	1 (2)	SD
L858R+dnT790M	1 (2)	CR
L833V+L858R	1 (2)	CR
Del19+A750P	1 (2)	SD
Del19+L747Q	1 (2)	PR
Del19+S751V	1 (2)	SD
Del19+P753S+aqT790M	1 (2)	SD
Y801C	1 (2)	PD
EGFR-KDD	1 (2)	PR
R831C	1 (2)	PD
A702S	1 (2)	PD
I740_K745dup	1 (2)	PR
V765M	1 (2)	PD
Ins 20	**6 (12%)**	
V769_D770insASV	2 (4)	SD; NE
D770_N771insSVD	2 (4)	PR; PD
A767_V769dup	2 (4)	PD; SD

Keywords: Uncommon EGFR, NSCLC, Osimertinib

EP08.02-047 The Impact of CGP on the Decision-making Process in ALK+ aNSCLC After Failure of 2nd/3rd-Generation ALK TKIs

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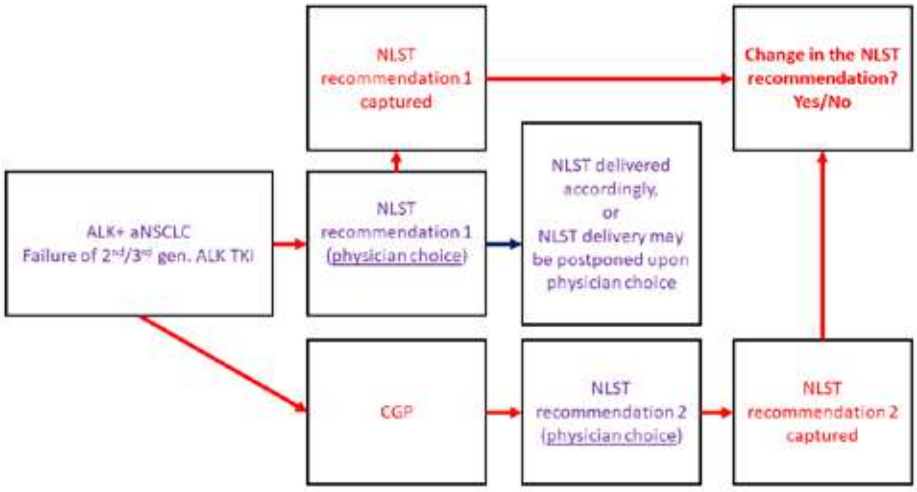
Introduction: The use of comprehensive genomic profiling (CGP) in guiding treatment decisions in advanced non-small cell lung cancer (aNSCLC) with acquired resistance to ALK tyrosine kinase inhibitors (TKIs) is questionable.

Methods: We prospectively assessed the impact of CGP on the decision-making process in ALK-rearranged aNSCLC patients following progression on 2nd/3rd-generation ALK TKIs. Physician's choice of the most recommended next-line systemic treatment (NLST) was captured before and after receival of CGP results; the percentage of cases in which the NLST recommendation has changed was assessed along with the CGP turnaround time (TAT) (Figure 1). Patients were divided into groups: patients in whom the NLST was initiated after (group 1) and before (group 2) receival of the CGP results. Time-to-treatment discontinuation (TTD) and overall survival (OS) with NLST were compared between the groups.

Results: In 20 eligible patients (median [m]age 63 years [range, 40-89], females 75%, adenocarcinoma 100%, failure of alectinib 90%, FoundationOne Liquid CDx 80%), CGP has altered NLST recommendation in 30% of cases (Figure 2). CGP findings were as follows: ALK mutations 30% (I1171X 10%, G1202R, L1196M, G1269A, G1202R+I1171N+E1210K 5% each), CDKN2A/B mutation/loss 10%, c-met amplification 5%. CGP mTAT was 2.9 weeks [IQR, 2.4-4.4]. mTTD was 11.3 months (95% CI, 2.1-not reached [NR]) and 5.4 months (95% CI, 2.0-NR) in groups 1 and 2, respectively (p-0.34). mOS was 13.2 months (95% CI, 2.9-NR) and 13.0 months (95% CI, 6.0-NR) in groups 1 and 2, respectively (p-0.86).

Conclusions: CGP has a significant impact on the decision-making process in ALK-rearranged aNSCLC following progression on 2nd/3rd-generation ALK TKIs.

Figure 1. Study design.



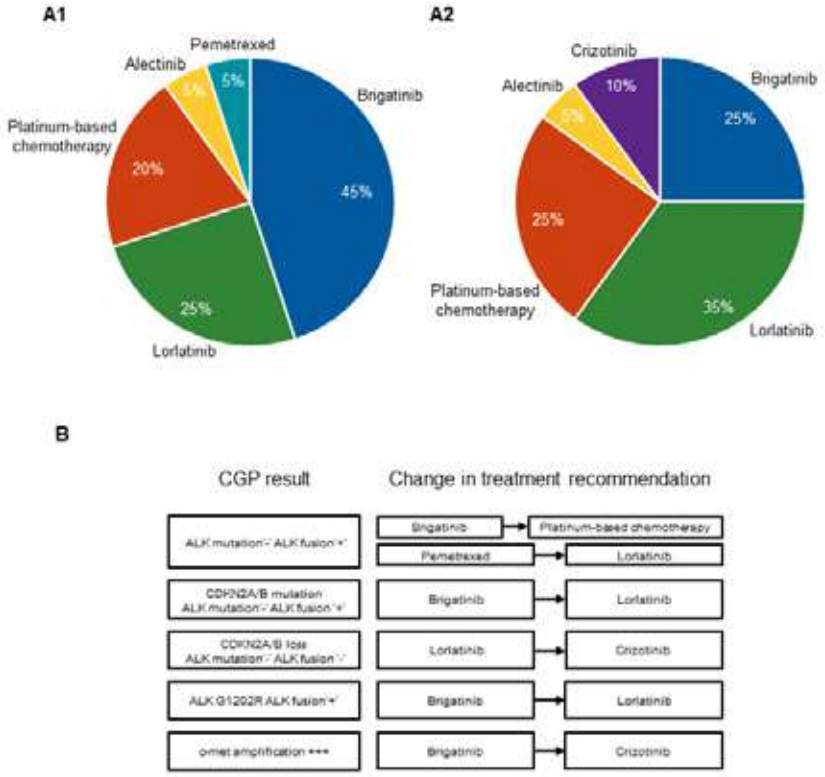


Figure 2. Physician's choice of the most recommended NLST captured before (A1) and after (A2) the receival of CGP results. Change in treatment recommendation upon the receival of CGP results (B).

Keywords: aNSCLC failure of ALK TKI, comprehensive genomic profiling, impact on the decision-making process

EP08.02-048 Crizotinib in ROS1+NSCLC: Long-term OS Analysis in Patients with Brain Metastases Included in the Phase II METROS Trial

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Introduction: Crizotinib has a well-established role in *ROS1+* non-small cell lung cancer (NSCLC). Few data exist on the activity of the drug in controlling brain disease in *ROS1+* patients. The METROS trial was a multicentric phase II trial aiming at investigating the efficacy of crizotinib in pretreated patients with NSCLC and *MET* deregulation (amplification or exon 14 mutations) or *ROS1* rearrangements. The study confirmed the efficacy of the drug in *ROS1+*, with modest activity in the *MET*-deregulated cohort (Landi L et al., Clin Cancer Res 2019). This analysis investigates long-term survival outcomes of *ROS1+* patients, according to presence of brain metastases (BM).

Methods: A total of 64 *ROS1+* patients included in the METROS trial (26 in the study cohort and 38 in the expansion cohort) were analyzed. All patients received crizotinib 250 mg BID orally until disease progression, unacceptable toxicity, withdrawal of consent, or death. Progression-free survival (PFS) and overall survival (OS) were analyzed in the whole population and according to presence of BM at baseline.

Results: In total, 17 patients had BM at baseline. Characteristics of patients with or without BM were similar in terms of median age (50 and 58 years) gender (male/female: 12/5 and 30/17) PS (0/1: 9/8 and 28/19), previous therapies (1/≥2 13/4 and 33/14). At data cut-off (February 2022), with a median follow-up of 54.4 months, in the whole population median PFS and OS were 13.8 months (95% CI: 7.4-20.2) and 40.5 months (95% CI: 27.9-53.1), respectively. Among patients with BM, the brain was among the sites of progression in all patients. Among patients without BM, progression in the brain was reported in 16 individuals (34.0%). Median PFS was 6.8 months (95% CI: 0.1-13.5) in patients with BM versus 17.4 months in those without BM [95% CI: 7.9-26.9, HR: 1.94 (95% CI: 0.99-3.40)]. Median OS was 16.4 months (95% CI: 15.5-17.3) in patients with BM versus 42.8 months (95% CI: 28.6-57.0) in patients without BM [HR: 1.63 (95% CI: 0.81-3.30)].

Conclusions: At a median follow-up >4 years, crizotinib confirmed its marked activity in *ROS1+* NSCLC. Risk of disease progression and death was higher in patients with BM, highlighting the need for brain-penetrant drugs in the management of *ROS1+*NSCLC.

Keywords: ROS1, Brain metastases, crizotinib

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-049 A Phase I Trial of the HER2 Exon 20 Inhibitor, BI 1810631, In Patients with Advanced Solid Tumors with HER2 Aberrations

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Introduction: HER2 mutations are present in 2-4% of NSCLC tumors; of these ~50% are exon 20 insertion (ex20ins) mutations. There is an unmet need for effective targeted therapy against HER2 mutations in solid tumors, particularly in NSCLC. Historically, ex20ins mutations have responded poorly to TKIs. Moreover, TKIs that inhibit both mutant EGFR and HER2 are typically limited by toxicities associated with inhibition of wild-type EGFR. Despite the promise of trastuzumab deruxtecan and other agents in this setting, the development of orally available selective TKIs is important given the heterogeneity of HER2 aberrations, potential for combination regimens, and the risk of interstitial lung disease with ADCs. BI 1810631 is a HER2 selective TKI that covalently binds to both wild-type and mutated HER2 receptors, including ex20ins, whilst sparing EGFR signaling; preclinical data suggest good tolerability and efficacy. This Phase Ia/Ib, open-label, non-randomized study aims to determine the safety, maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of BI 1810631 in patients with HER2 aberration-positive solid tumors (NCT04886804).

Methods: ~96 patients from 5-7 sites in the US, Netherlands, Japan, and China will be recruited. Phase Ia: consecutive cohorts of patients will receive BI 1810631 BID (~36 patients) or QD (~30 patients) at escalating doses. Starting dose level: 15 mg BID; QD schedule will begin after one dose level above estimated therapeutic dose of BI 1810631 is determined safe by the Dose Escalation Committee (expected starting dose: 60 mg). BI 1810631 dose escalation will continue until MTD/RP2D for each schedule is determined, as well as a preferred Phase Ib schedule. Phase Ib: an initial 30 patients with HER2 ex20ins mutation-positive, pre-treated NSCLC will be enrolled, with possible inclusion of additional cohorts in the future. Overall patient inclusion criteria (Phase Ia): ≥18 years of age; histologically/cytologically confirmed HER2 aberration-positive (defined as overexpression, gene amplification, non-synonymous somatic mutation, or gene rearrangement involving HER2 or NRG1) advanced/unresectable/metastatic solid tumor refractory/not suitable for standard therapy; exhausted treatment options; measurable/evaluable lesions (per RECIST v1.1); ECOG PS ≤1. Phase Ib criteria: HER2 ex20ins mutation-positive NSCLC; received ≥1 line of platinum-based combination chemotherapy in the advanced/metastatic setting. Primary endpoints: MTD based on number of dose-limiting toxicities (DLTs)/number of patients with DLTs (Phase Ia); objective response (Phase Ib). Secondary endpoints: number of patients with DLTs throughout entire treatment period and PK parameters (Phase Ia/Ib); duration of response, disease control, duration of disease control, and progression-free survival (Phase Ib). The trial is actively recruiting with 6 patients treated to date. Two dose levels have been completed to date with no DLTs. Recruitment to Phase Ia will continue until the MTD/RP2D is determined.

Keywords: HER2, BI 1810631, exon 20 insertion

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-050 A Retrospective Study of Aumolertinib in Combination with Bevacizumab for EGFR-mutated NSCLC with the Presence of Leptomeningeal Metastasis

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Introduction: Patients with non-small cell lung cancer (NSCLC) who develop leptomeningeal metastasis (LM) have a poor prognosis. There is no standard treatment for LM with EGFRm NSCLC. Recently, EGFR tyrosine kinase inhibitors (TKIs) has been shown to be a potential therapeutic option for patients with EGFRm NSCLC and LM. Preclinical evidence shows that third-generation EGFR-TKIs, being investigated as a therapy for LM, have greater penetration of the blood-brain barrier compared with first- and second-generation treatment. At the 2021 ASCO annual meeting, the preliminary results of phase III AENEAS study demonstrated that aumolertinib, a novel third-generation EGFR-TKI, significantly improved PFS compared with gefitinib in the first-line treatment of patients with EGFRm advanced NSCLC(19.3 vs 9.9months, hazard ratios: 0.46). Subgroup analysis showed that patients with brain metastases tended to profit more from aumolertinib treatment (hazard ratios =0.38). Herein, we presented 5 cases to further evaluate the effectiveness and tolerability of aumolertinib combined with bevacizumab for LM with EGFRm NSCLC. Several clinical trials have also confirmed that EGFR-TKIs combined with bevacizumab could significantly improve progression free survival (PFS) than EGFR-TKIs monotherapy for patients with EGFR-mutated NSCLC, especially in those with central nervous system metastasis. Herein, we retrospectively analyzed the results of aumolertinib combined with bevacizumab treatment in five patients with EGFRm NSCLC and LM.

Methods: We included 5 patients with EGFRm NSCLC and LM at Nanjing Chest Hospital, whose median age was 54 years, predominantly female (80%). EGFR mutations included exon 21 L858R mutation, T790M mutation, exon 19 deletion combined with TP53 mutation, and c-MET amplification. Prior to combination therapy, the mean number of lines of therapy was 1.2. The median length of therapy for Aumolertinib in combination with bevacizumab was 11 months, and the median PS score was 4 before treatment and 1 after combination therapy. To assess the clinical efficacy of a regimen of the third-generation TKI Aumolertinib (110 mg/day) in combination with bevacizumab (7.5 mg/kg, 21-day cycle) in patients with epidermal growth factor receptor (EGFR)-mutated NSCLC and LM.

Results: 2 patients (40%) had complete remission (CR) of LM lesions, 3 patients (60%) had partial remission (PR), and the intracranial objective remission rate (iORR) was 100%. 1 patient had stable disease (SD) in the whole lesion, 4 patients achieved PR, an overall ORR of 80%, and a disease control rate (DCR) of 100%. After 2 months of combination therapy, magnetic resonance imaging (MRI) of the brain was performed in all 5 patients and showed significant reduction of LM, with continued remission of LM as treatment continued, and no progression of systemic or LM lesions in any of the 5 patients, with a good safety profile and still under close follow-up.

Conclusions: Aumolertinib in combination with bevacizumab has shown significant efficacy in patients with LM NSCLC with exon 19 deletion and exon 21 L858R mutations, even in combination with non-sensitive mutations and poor physical status. This combination regimen is characterized by a rapid onset of action, sustained remission of meningeal lesions, and a long duration of remission.

Keywords: Aumolertinib, NSCLC, leptomeningeal metastasis

EP08.02-051 High-dose Aumolertinib as First-line Treatment in Patients with Brain Metastases Associated with EGFR Mutated NSCLC

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Introduction: Brain metastases are associated with significant morbidity and poor survival outcomes. They are found in 10-20% of patients with non-small cell lung cancer (NSCLC) at presentation, and in up to 50% of patients during the course of their illness. Brain metastases occur most frequently in patients with adenocarcinoma and tumor harbouring epidermal growth factor receptor (EGFR) mutations or ALK rearrangements, especially after treating with 1st or 2nd generation EGFR TKI. Aumolertinib, the third generation irreversible EGFR TKI, has been developed to target T790M mutation. Unlike other EGFR TKIs, aumolertinib is evenly distributed to the brain, suggesting high penetration of the blood-brain barrier. In addition, in the real world, high-does (165-220mg) of aumolertinib get meaningful clinical efficacy and safety in brain metastases NSCLC.

Methods: This study is a single-arm, multicenter study to evaluate the clinical efficacy of 165mg aumolertinib in patients with brain metastases in EGFR mutated, either exon 19 deletion or L858R, NSCLC. A total of 60 patients, will be recruited and treated with 165mg of aumolertinib until disease progression or intolerable adverse event. All patients will be required to have at least one site of brain metastases as identified by the radiologists from the central site that can be assessed by MRI which is suitable for repeat assessment. The performance status (Eastern Cooperative Oncology Group) is 0 or 1. The primary endpoint is progression free survival assessed by investigators using Response Evaluation Criteria in Solid Tumors 1.1. Secondary endpoints are disease control rate, duration of response, overall survival, and safety. Adverse effects were graded per CTCAE v.4.03. This trial is registered as NCT04808752. The first patient received treatment in May. 2021, and the expected timeline for the final analyses is Q4, 2022.

Keywords: NSCLC, EGFR TKI, Brain Metastases

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-052 Safety and Efficacy of Dabrafenib Plus Trametinib in Chinese Patients with BRAF V600E- Mutation Positive Metastatic NSCLC

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Introduction: The prevalence of *BRAF* V600 mutation in Chinese patients with non-small cell lung cancer (NSCLC) is 1.7%-1.8%; however, no BRAF targeted therapy is currently approved in China. The combination of dabrafenib plus trametinib is approved in the United States, the European Union, Japan and other countries for the treatment of *BRAF*- mutated NSCLC. The study evaluated the efficacy and safety of dabrafenib plus trametinib in Chinese patients with *BRAF* V600E- mutated metastatic NSCLC.

Methods: This single-arm, open-label, multicentre, phase II study (NCT04452877) enrolled Chinese patients with *BRAF* V600E-mutation positive, stage IV NSCLC (American Joint Committee on Cancer Staging Manual 8th edition) to receive dabrafenib 150 mg twice daily plus trametinib 2 mg once daily. The primary endpoint was overall response rate (ORR) by central independent review per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria. Secondary endpoints included ORR by investigator assessment, progression-free survival (PFS), duration of response (DOR), overall survival (OS), safety and tolerability.

Results: As of data cut-off date of 11 March 2021, 18 of the 20 enrolled patients were receiving treatment. Median age of the patients was 64 years; majority were female (55%), had never smoked (55%) and had ≥3 metastatic sites (70%). Nine patients had received prior anticancer therapy in therapeutic or metastatic setting. Median duration of follow-up was 5 months. The ORR was 75% (95% confidence interval: 50.9-91.3) by both, central as well as investigator assessment. Median DOR, PFS and OS were not reached due to a shorter follow-up period. Median duration of exposure was 4.11 months for trametinib and 4.39 months for dabrafenib. The most frequent adverse events (AEs) were pyrexia (45%), anaemia (40%), increased aspartate aminotransferase (35%) and hypoalbuminaemia (35%). Grade ≥3 AEs were reported in 11 patients (55%), with no grade 5 AEs.

Conclusions: Preliminary data suggest that the combination of dabrafenib plus trametinib was safe and effective in Chinese patients with *BRAF* V600E- mutated NSCLC. Efficacy and safety were consistent with that reported previously for the global phase II study.

Keywords: dabrafenib trametinib, BRAF V600E mutation, NSCLC

EP08.02-053 Non-small Cell Lung Cancer withMETExon14 Skipping Mutation: Literature Review of Real-World Evidence Data

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Introduction: *MET* exon 14 skipping mutations (*MET*ex14) occur in 3-4% of all non-small cell lung cancer (NSCLC) patients. Recent trials showed promising efficacy of selective *MET* inhibitors but the effect of currently used treatments in this sub-group of patients is not characterized. This review was conducted to identify real-world evidence (RWE) associated with advanced/metastatic *MET*ex14 NSCLC. The objective was to synthesize currently available information on epidemiology, effectiveness, safety/tolerability, healthcare resource utilization, economic burden, and patient reported outcomes (PROs).

Methods: This literature review was conducted via a search of EMBASE, MEDLINE and Cochrane from 2016-2021. It included observational studies assessing patients ≥18 years with advanced or metastatic *MET*ex14 NSCLC. Studies reporting data irrespective of line of therapy i.e., first-line, pre-treated, or mixed line were included. This review did not exclude studies if patients had co-mutations. Systematic review and data analysis on this topic are ongoing and will be presented at the conference.

Results: A total of 15 studies assessing *MET*ex14 NSCLC patients that met the inclusion criteria were included. The median age of the patients ranged from 63 to 77 years and percentage of female patients ranged from 37% to 66%. The current and former smoker ranged from 53% to 76%. Regarding clinical characteristics, most patients had a non-squamous carcinoma ranging from 69% to 94% with PD-L1 ≥50% expression ranging from 37% to 69%. Brain metastases were reported in 5% to 41% of patients. Most RWE studies reported mixed line of data for ORR, PFS or OS and not segregated by type of therapy. Of the 15 included studies, ORR and PFS were reported in 8 studies each, while 11 studies reported OS. Studies reported outcomes for different class of drugs i.e., Immune checkpoint inhibitors (ICI), *MET* inhibitors (METi), Chemotherapy (CT) and other systemic treatments. Studies with METi had mainly patients treated with crizotinib. Data regarding safety were scarce and no data were found regarding healthcare resource utilization, economic burden and PROs specific to *MET*ex14 NSCLC patients. Additional results will be presented at the conference.

Conclusions: *MET*ex14 is a rare mutation in advanced NSCLC. The review therefore found scarce information on efficacy and safety and no information on healthcare resource utilization. There was heterogeneity across the studies with respect to sample size, limited efficacy data reported segregation by line of therapy and data regarding METi was mostly driven by crizotinib. Further primary research is warranted to better understand the relevant characteristics of this population.

Keywords: NSCLC, METex14, RWE

EP08.02-054 Efficacy and Safety of TKI Dose Reduction - Can Less Mean More?

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Introduction: Several genomic variants that influence the treatment selection of patients with non-small cell lung cancer (NSCLC) has been identified. This has led to the development of agents that target specific molecular pathways (i.e. Tyrosine kinase inhibitors - TKIs), allowing an individualized therapy with fewer side effects thanchemotherapy. Nonetheless, these drugs can cause adverse effects and a dose reduction might be beneficial.

Methods: This was a retrospective study of patients under oral TKI for lung cancer between 2018 and 2021. Patients whowere prescribed TKIs but never started the treatment were excluded from this study.We divided the sample in 2 groups, considering treatment dose (I: reduced dose; II: full dose).The primary endpoint was to determine if the use of reduced doses of TKIs would provide the sametherapeutic outcomes as the standard dose.

Results: We obtained a sample of 45 patients (88,9% were adenocarcinoma; 66,7% EGFR-positive). The mean age was 71,2 ± 11,3 years.

Group I included 26 patients (50% males; 50% females). The mean Charlson score was 8,12 ± 1,9. Adverse reactions were seen in 57,7% (n=15), the most frequent being renal and hematological. At the time of this study, 46,2% (n=12) had died.

Group II included 19 patients, 5 (26.3%) males and 14 (73.7%) females. The mean Charlson score was 8,37 ±1,0. Adverse reactions were seen in 36,8% (n=7), the most frequent being dermatological. At the time of this study, 47,4% (n=9) had died.

The overall survival was around 30 months for group I and 19 months for group II, without a statistically significant difference (p=0.947).The progression free survival based on the recist 1.1. criteria was around 24 months for group I and 22 months for group II, without a statistically significant difference (p=0.800).

Conclusions: There was no statistically significant difference neither in the overall survival nor in the progression free survival between patients treated with full dose and those treated with a reduced dose.Although these results may not be enough to predict on which patients we could use reduced doses to have the same outcomes, they raise the question of whether reduced doses of TKIs could still be effective with the advantage of being better tolerated.Future studies are needed to further evaluate this topic.

Keywords: NSCLC, targeted therapy, dose reduction

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-055 Targeting Lung Adenocarcinoma Cells with a Novel Disulfide Reductase Inhibitor

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Introduction: High-throughput phenotypic screening of large libraries of novel compounds without known targets can identify small molecules that elicit a desired cellular effect, but additional strategies are required to identify and characterize their targets and mechanisms of action. Here we characterize the novel small molecule LCS3, identified in a phenotypic screen of ~190,000 compounds for its ability to selectively impair the proliferation of human lung adenocarcinoma (LUAD) cell lines, and investigate its mechanism of action.

Methods: We performed gene expression profiling to elucidate the cellular response to LCS3. To identify the molecular targets of LCS3, we applied thermal proteome profiling (TPP) and validated these hits with enzymatic assays using purified protein. We performed a genome-wide CRISPR-Cas9 knockout screen to understand the genetic factors that contribute to LCS3 resistance and sensitization.

Results: Transcriptome and proteome expression profiling by microarray and SILAC (stable isotope labeling of amino acids in cell culture)-based mass spectrometry, respectively, suggest that LCS3 is a strong inducer of oxidative stress in LUAD cells. The top four predicted upstream transcriptional regulators of LCS3-induced RNA expression changes all have key functions in the response to oxidative stress. We confirmed LCS3 induces NRF2 activation through western blot and flow cytometry analyses using a stably expressed antioxidant response element GFP reporter. In addition, flow cytometry detected reactive oxygen species (ROS) induction by LCS3 in sensitive but not resistant cell lines. Antioxidants including N-acetylcysteine partially rescued LCS3-induced cytotoxicity, which further implicates oxidative stress in the mechanism of LCS3-induced cell death. To identify the targets of LCS3 that mediate these effects, we used TPP and identified the disulfide reductases GSR and TXNRD1 as protein targets of LCS3. Through enzymatic assays, we confirmed that LCS3 inhibits disulfide reductase activity at a low micromolar IC50 through a reversible and uncompetitive mechanism. We also found that LCS3 inhibits the downstream molecular products of GSR and TXNRD1 in vitro. We demonstrate that LCS3-sensitive LUAD cells are correspondingly sensitive to the synergistic inhibition of glutathione and thioredoxin pathways. Further, we found that tert-butyl hydroperoxide, a direct-acting exogenous source of ROS, sensitizes non-responsive cells to LCS3, thus implicating oxidative stress as a requirement for LCS3-mediated toxicity. We performed a genome-wide CRISPR-Cas9 knockout screen and identified NQO1 loss as a mechanism of LCS3 resistance.

Conclusions: This work demonstrates the power of TPP to identify protein targets of compounds identified by phenotype-based screens and suggests that disulfide reductase inhibition can potentially be a therapeutic strategy for patients with LUAD. We are currently investigating why non-responsive cells are less dependent on the glutathione and thioredoxin pathways and how oncogenic transformation, and the inherent oxidative stress that coincides, confer sensitization to dual disulfide reductase pathway inhibition. Through this investigation, we aim to use LCS3 as a tool compound to characterize a cancer dependency that can be exploited for the benefit of lung cancer patients with advanced tumors, for whom treatment is urgently needed.

Keywords: target discovery, disulfide reductase inhibition, thermal proteome profiling

EP08.02-056 Coexisting MET Exon 14 Skipping Mutation and MET Amplification in a Patient with Complete Response to MET Inhibitors

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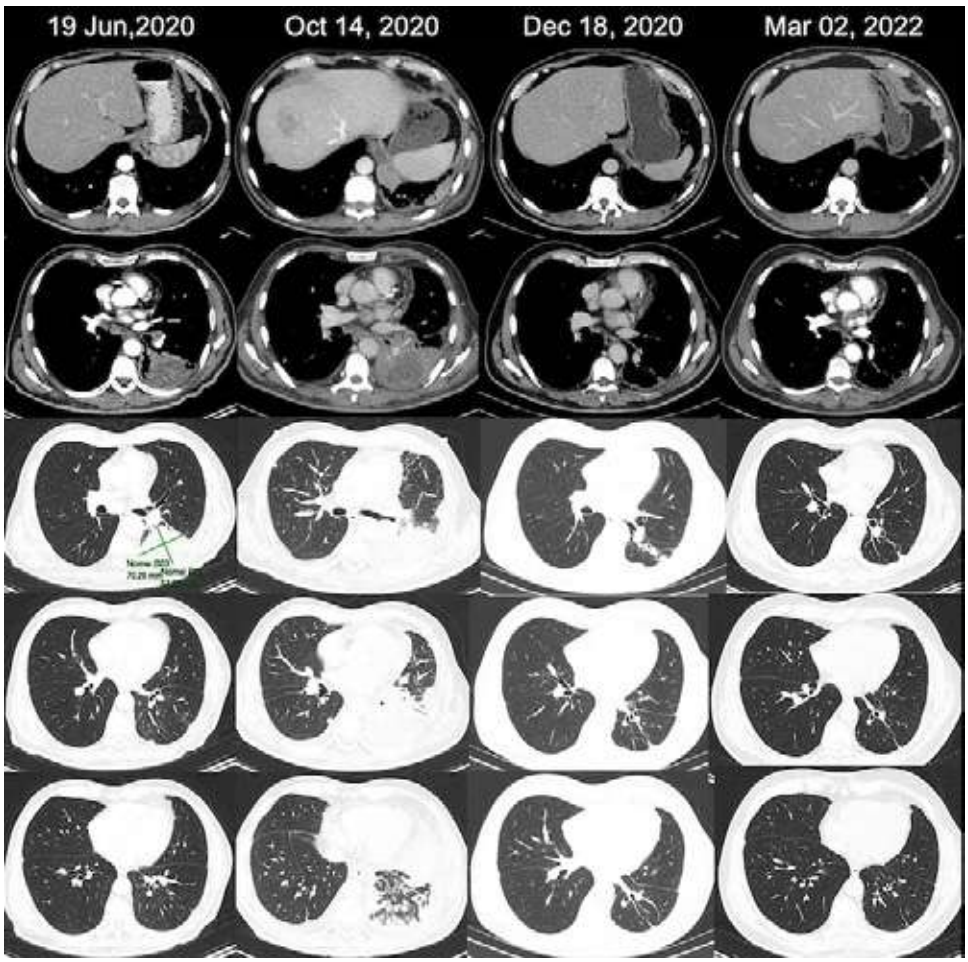
Introduction: Precision medicine has a prominent role in the improvement of the outcome of patients with non-small cell lung cancer (NSCLC). In this scenario, highly selective MET inhibitors such as tepotinib and capmatinib have a promising role in up to 4% of lung malignancies with MET exon 14 skipping mutations or high copy number gains in MET. However, complete responses with these agents are scarce. Herein, we report a case of outlier response with rapid, complete, and durable control of the disease with tepotinib in a patient harboring both the MET exon 14 mutation and the gene amplification.

Methods: This is a case report of a patient under treatment in a Brazilian private oncology center. Data were extracted retrospectively from the medical chart and written informed consent was obtained from the patient.

Results: This 64-year-old male patient, former smoker, had a 3-months onset of weight loss and back pain. Propaedeutics showed left inferior lobe mass, enlarged mediastinal lymph nodes, bone and liver involvement. In June 2020, he underwent a lung biopsy, whose path report showed lung adenocarcinoma. FoundationOne CDx panel demonstrated MET exon 14 skipping mutation (3038+3A>G, allelic fraction > 80%) plus MET amplification (12 copy numbers). PD-L1 expression (22C3) was 90%. Since there was no MET inhibitor approved in Brazil at that time point, the patient started on pembrolizumab, carboplatin, and pemetrexed regimen as the first line. After two cycles, his symptoms got worse, with dyspnea and grade 3 anemia. New images evidenced bulky disease progression. Crizotinib, an off-label drug for this indication, was started as second-line therapy in October 2020. In few weeks, the patient had major clinical improvement, a partial tumor regression was demonstrated on imaging. The patient had persistent grade 3 neutropenia that required dose reduction and eventually crizotinib discontinuation. Meanwhile, in February 2021, tepotinib compassion use program was initiated. Two months after tepotinib was started, complete radiologic response was achieved, and patient continues on treatment without evidence of disease after 1 year.

Conclusions: Our report highlights the potential mechanism for complete and durable response to MET inhibitor: coexisting MET amplification and gene mutation. The high allele fraction of MET exon 14 skipping indicates that both genomic events occurred in cis (in the same allele) and are a clonal event in all cancer cells. These data reinforce the value of comprehensive molecular characterization of outliers responders to novel kinase inhibitors in patients with lung adenocarcinomas.



Keywords: MET exon 14 skipping mutation, MET amplification, Complete response

EP08.02-057 Mechanism of Resistance to Second-Line Aumolertinib and Therapeutic Regime after Resistance

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Introduction: Aumolertinib is a novel, irreversible, 3rd generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) with structure-predicted pharmacologic properties that selectively inhibit both EGFR sensitizing and resistance mutations. In phase II single-arm APOLLO study (NCT02981108), the most common mechanisms of resistance to Aumolertinib were acquired EGFR C797S mutation (26%) and aberration in PIK3CA bypass track(21%), which were different from AURA3(NCT02151981), where most common mechanisms of resistance to Osimertinib were MET amplification (19%) and acquired EGFR C797S mutation (15%). These two pivotal studies showed that a diverse mixture of resistance mechanisms were detected between Aumolertinib and Osimertinib, performed by a panel consisting of 99 genes and 73 gene panel respectively. With the increasingly widespread use of high-throughput sequencing technology (NGS), the drug resistance maps of 3rd generation EGFR-TKIs have been extensively studied. Treatment approaches for patients progressing from third generation EGFR TKIs still have not been clearly established, real-world data is limited. We hereby conducted this real-world study, to analyze the resistance mechanisms acquired after treatment with Aumolertinib and related biomarkers with 539 large panel test, and to further explore the feasibility of Aumolertinib resistance related therapeutic regime.

Methods: Approximately 50 Chinese NSCLC patients will be enrolled in this open, single-arm study. Patients encountered resistance to first- and second-generation *EGFR* TKIs with T790M mutation will be screened out by multigene lung 9/69/539 panel test. They will then receive Aumolertinib as second-line treatment and been evaluated the efficacy and progression-free survival (PFS) by investigator assessment as per RECIST v1.1. After resistance to Aumolertinib, all patients will take the 539 panel genetic test again to analyze possible resistance mechanism. With regard to subsequent therapy after progression in future, NGS will be an important basis. Several therapeutic combinations between Aumolertinib and antiangiogenics would be applied to overcome EGFR-dependent resistance mechanisms. Combination of Aumolertinib and relevant inhibitors would help overcome resistance mediated through alternative kinase activation, such as PIK3CA, MET, MEK, and BRAF. For most other patients, platinum-based doublet chemotherapy and immune checkpoint inhibitors(ICIs) in combination with chemotherapy or bevacizumab maybe the available options. The evaluation and benefit for all patients will be recorded according to the tolerance, efficacy and PFS of relevant treatment. The primary endpoint is to determine the mechanism of resistance to second-line Aumolertinib. Secondary endpoint is to explore the feasibility of combination treatments associated with Aumolertinib resistance. Recruitment of this study is ongoing, and the first patient had been enrolled in January 2022.

Keywords: resistance mechanisms, Aumolertinib, real-world study

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-058 A Case Series of Patients with Kras KRAS G12C Mutation Treated with Sotorasib - Croatian Experience

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Introduction: Recent improvements in therapies for advanced non-small-cell lung cancer (NSCLC) have substantially increased patients' quality of life and reduced mortality. Checkpoint inhibitors for patients without and new targeted therapies for patients with oncogenic driver mutations showed great clinical benefit. Treatment need for KRAS mutation has been unmet until sotorasib availability.

Methods: Patients with metastatic non-small-cell lung cancer were diagnosed with KRAS positive G12C mutation and treated with sotorasib, administered orally, with a dose of 960 mg once daily. The patients were enrolled in an early access program from May 2021 until December 2021 and were monitored for disease progression and side-effects until February 28th, 2022.

Results: We treated 4 patients with sotorasib since May 2021 until December 2021. KRAS G12C mutations were verified using next generation sequencing (FMI Roche). Two female and two male patients were involved, with a median age of 61 years (47-74). All of them were ex-somkers, with a median pack/year 20 (10-40). Three of them received sotorasib as a third line and one as fourth line therapy. All were previously treated with immune checkpoint inhibitors and platinum-based chemotherapy. Two patients had a partial response (PR) and two were verified with stable disease as a best therapy response. Only one of the patients progressed at the data cut-off date, with a total duration of response of 5 months. One patient did not experience any side-effects and remains on standard, 960 mg once daily dose ongoing for 6 months. The same patient had a partial response to therapy after 2 months. Three of our patients experienced hepatic side effects, alanine aminotransferase and aspartate aminotransferase elevation, CTCAE grade 2-3. The onset of side effects was 4, 8 and 12 weeks after the start of sotorasib, respectively. The treatment was stopped for a median of 14 days and resumed with a decreased dose of 480mg once daily. In two of the patients no further liver toxicities were observed. One patient experienced again both alanine and aspartate aminotransferase elevation, now CTCAE grade 3, which required another sotorasib treatment pause for 14 days, until recovery to grade 1. Sotorasib was again continued with a further dose reduction to 240 mg, for 8 weeks, when it was permanently discontinued due to disease progression.

Conclusions: Sotorasib showed deffinitve clinical efficacy in NSCLC patients with KRAS G12C mutation. Liver enzyme elevation, as the most common side effect, seems to be menageable with drug dose reductions, while preserving its efficacy. Further data from larger patient cohorts as well as longer follow-up are needed to confirm these findings.

Keywords: KRAS G12C, Sotorasib, NSCLC

EP08.02-059 EGFR Tyrosine Kinase Inhibitors and Combination Strategies in First-line Treatment of Advanced NSCLC: A Network Meta-analysis

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Introduction: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the standard first-line treatment for advanced EGFR-mutated non-small cell lung cancer (NSCLC). Many different combinations with EGFR-TKIs were tested with improved results; however, comparison data between these strategies are lacking.

Methods: We performed a systematic review: eligible phase IIB/III randomized controlled trials (RCTs) were searched using PubMed, EMBASE, Cochrane Library databases, and meeting abstracts between 2009-2020. Then, we conducted a random-effects frequentist network meta-analysis (NMA) to synthesize hazard ratios (HRs) to compare overall survival (OS), progression-free survival (PFS), and overall response rate (ORR). First-generation (FG) TKIs were used as the reference comparator.

Results: We included 17 RCTs enrolling 5,176 patients comparing 7 treatment strategies. Third-generation (TG) TKI and FG TKI plus chemotherapy (CT) showed potentially superior efficacy compared to second-generation (SG) TKIs (PFS: HR 0.59 [95% CI 0.26-1.34] and HR 0.64 [95% CI 0.33-1.23], respectively; OS: HR 0.95 [95% CI 0.73-1.24] and HR 0.73 [95% CI 0.56-0.94]), to FG TKI plus ramucirumab (RAM) (PFS: HR 0.78 [95% CI 0.28-2.18] and HR 0.85 [95% CI 0.34-2.08], respectively; OS: HR 0.96 [95% CI 0.58-1.59] and HR 0.73 [95% CI 0.45-1.21]) and to FG TKI plus bevacizumab (BVZ) (PFS: HR 0.77 [95% CI 0.26-2.23] and HR 0.83 [95% CI 0.33-2.13], respectively; OS: HR 0.80 [95% CI 0.51-1.25] and HR 0.61 [95% CI 0.39-0.95]). For ORR, FG TKI plus CT achieved the best response rates (see table).

Conclusions: TG TKI and FG TKI plus CT appear to be associated with more favorable outcomes and might be the preferred first-line treatment options in advanced EGFR-mutated NSCLC. Nevertheless, factors related to study patient selection, post-progression therapies, NMA inclusion criteria, and the degree of treatment lumping could explain the discrepancies in these treatments' results.

Table. Pooled hazard ratios (95% confidence intervals) for PFS and OS and pooled odds ratios (95% confidence intervals) for ORR.

PFS, HR and 95% CIs *						
FG EGFR TKI	1.28 (0.86,1.90)	2.17 (1.05,4.48)	1.67 (0.76,3.65)	2.00 (1.19,3.36)	1.69 (0.81,3.53)	0.43 (0.33,0.56)
0.78 (0.53,1.16)	**SG EGFR TKI**	1.70 (0.75,3.87)	1.30 (0.54,3.13)	1.56 (0.82,2.99)	1.32 (0.58,3.04)	0.34 (0.23,0.50)
0.46 (0.22,0.95)	0.59 (0.26,1.34)	**TG EGFR TKI**	0.77 (0.26,2.23)	0.92 (0.38,2.24)	0.78 (0.28,2.18)	0.20 (0.09,0.43)
0.60 (0.27,1.31)	0.77 (0.32,1.84)	1.30 (0.45,3.79)	**FG EGFR TKI + BVZ**	1.20 (0.47,3.07)	1.02 (0.35,2.97)	0.26 (0.11,0.59)
0.50 (0.30,0.84)	0.64 (0.33,1.23)	1.09 (0.45,2.64)	0.83 (0.33,2.13)	**FG EGFR TKI + CT**	0.85 (0.34,2.08)	0.22 (0.12,0.38)
0.59 (0.28,1.23)	0.76 (0.33,1.74)	1.28 (0.46,3.59)	0.98 (0.34,2.88)	1.18 (0.48,2.90)	**FG EGFR TKI + RAM**	0.25 (0.12,0.55)
2.32 (1.79,3.01)	2.98 (2.00,4.42)	5.05 (2.34,10.89)	3.87 (1.70,8.84)	4.65 (2.60,8.30)	3.94 (1.81,8.58)	**CT**
OS, HR and 95% CIs *						
FG EGFR TKI	1.19 (1.04,1.37)	1.25 (1.00,1.56)	1.00 (0.68,1.48)	1.64 (1.32,2.04)	1.20 (0.77,1.89)	1.01 (0.91,1.13)
0.84 (0.73,0.97)	**SG EGFR TKI**	1.05 (0.81,1.37)	0.84 (0.56,1.27)	1.38 (1.06,1.79)	1.01 (0.63,1.62)	0.85 (0.74,0.98)
0.80 (0.64,0.99)	0.95 (0.73,1.24)	**TG EGFR TKI**	0.80 (0.51,1.25)	1.31 (0.96,1.79)	0.96 (0.58,1.59)	0.81 (0.63,1.04)
1.00 (0.68,1.48)	1.19 (0.79,1.80)	1.25 (0.80,1.96)	**FG EGFR TKI + BVZ**	1.64 (1.05,2.56)	1.20 (0.67,2.18)	1.01 (0.67,1.51)
0.61 (0.49,0.76)	0.73 (0.56,0.94)	0.76 (0.56,1.04)	0.61 (0.39,0.95)	**FG EGFR TKI + CT**	0.73 (0.45,1.21)	0.62 (0.48,0.79)
0.83 (0.53,1.30)	0.99 (0.62,1.58)	1.04 (0.63,1.71)	0.83 (0.46,1.50)	1.36 (0.83,2.24)	**FG EGFR TKI + RAM**	0.84 (0.53,1.33)
0.99 (0.89,1.10)	1.18 (1.02,1.36)	1.24 (0.96,1.59)	0.99 (0.66,1.48)	1.62 (1.27,2.07)	1.19 (0.75,1.89)	**CT**
ORR, OR and 95% CIs †						
FG EGFR TKI	0.71 (0.47,1.07)	0.79 (0.38,1.64)	0.75 (0.32,1.73)	0.47 (0.27,0.82)	0.91 (0.43,1.94)	4.03 (2.97,5.47)
1.41 (0.93,2.14)	**SG EGFR TKI**	1.11 (0.48,2.59)	1.05 (0.41,2.68)	0.66 (0.33,1.32)	1.29 (0.55,3.04)	5.69 (3.74,8.65)
1.27 (0.61,2.65)	0.90 (0.39,2.09)	**TG EGFR TKI**	0.95 (0.31,2.89)	0.60 (0.24,1.50)	1.16 (0.41,3.32)	5.12 (2.31,11.35)
1.34 (0.58,3.11)	0.95 (0.37,2.42)	1.06 (0.35,3.23)	**FG EGFR TKI + BVZ**	0.63 (0.23,1.72)	1.23 (0.40,3.78)	5.40 (2.21,13.20)
2.13 (1.22,3.72)	1.51 (0.76,3.02)	1.68 (0.67,4.22)	1.59 (0.58,4.35)	**FG EGFR TKI + CT**	1.95 (0.77,4.97)	8.59 (4.55,16.22)
1.09 (0.52,2.32)	0.78 (0.33,1.83)	0.86 (0.30,2.47)	0.82 (0.26,2.52)	0.51 (0.20,1.31)	**FG EGFR TKI + RAM**	4.41 (1.96,9.93)
0.25 (0.18,0.34)	0.18 (0.12,0.27)	0.20 (0.09,0.43)	0.19 (0.08,0.45)	0.12 (0.06,0.22)	0.23 (0.10,0.51)	**CT**

* HR < 1 favors bottom right treatment; HR > 1 favors column treatment.
† OR < 1 favors column treatment; OR > 1 favors bottom right treatment.

Abbreviations: BVZ, bevacizumab; CIs, confidence intervals; CT, chemotherapy; FG, first generation; HR, hazard ratio; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RAM, ramucirumab; SG, second generation; TG, third generation; TKI, tyrosine kinase inhibitor

Keywords: EGFR TKIs, network meta-analysis, non-small-cell lung cancer

EP08.02-060 How Do Oncologists Treat Patients with EGFR Exon-20 Mutant NSCLC Outside of Clinical Trials? Updated Analysis From the European EXOTIC Registry

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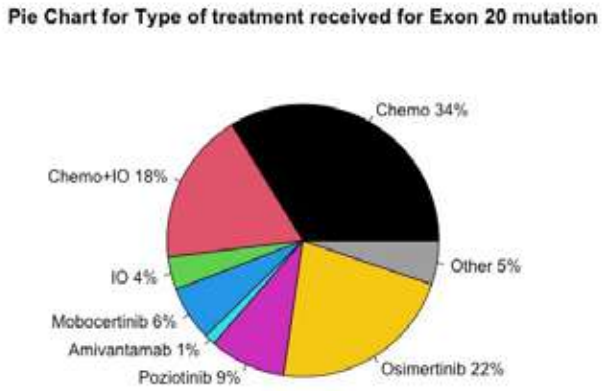
Introduction: We have previously reported molecular epidemiology and real-world management patterns of patients with epidermal growth factor receptor (EGFR) exon-20 mutated, advanced non-small-cell lung cancer (NSCLC) within the European EXOTIC registry (ELCC 2022). We now report updated results from final analysis.

Methods: We created a European registry for patients with advanced EGFR exon 20-mutant NSCLC diagnosed from January 2019 to December 2021. Patients enrolled in clinical trials were excluded. Clinicopathological and molecular epidemiology data were collected and treatment patterns were recorded. Clinical endpoints according to treatment assignment were assessed using Kaplan-Meier curves and Cox-regression models.

Results: Data on 175 patients from 33 centers across 9 European countries were included in final analysis. Median age was 64.0 years (range: 29.7-87.8); Main features included female sex (56.3%), never or past smokers (76.0%), adenocarcinoma histology (95.4%) and tropism for bone (47.4%) and brain (32.0%) metastases. Mean PD-L1 TPS score was 15.8% (range 0-95%) and mean TMB was 7.06 mut/MB (range 0-18.8). Exon 20 was detected in tissue (90.7%), in plasma (8.7%) or both (0.6%), using mostly targeted NGS (64.0%) or PCR (26.0%). Mutations were mainly insertions (59.3%) followed by duplications (28.1%), deletions-insertions (7.7%) and the T790M point mutation (4.5%). Insertions and duplications were located mainly in the near-loop (codons 767-771, 83.1%) and the far-loop (codons 771-775, 13%) and only in 3.9% of cases within the C-helix (codons 761-766). Main co-alterations included mutations in TP53 (61.8%) and MET amplifications (9.4%). First-line treatment included chemotherapy (33.8%), chemo-Immunotherapy (18.2%), osimertinib (22.1%), poziotinib (9.1%), mobocertinib (6.5%), mono-immunotherapy (3.9%) and amivantamab (1.3%), (Figure 1). Mode of drug acquisition was through regular approval in 77%, early access/compassionate use program in 10% and off-label use in 7% of cases. Disease control rates were 66.2% with chemo-Immunotherapy 55.8% with osimertinib, 64.8% with poziotinib and 76.9% with mobocertinib. Corresponding median survival (OS) was 19.7, 15.9, 9.2 and 22.4 months respectively. In multivariate analysis, type of treatment (new targeted agents vs Chemo+/-IO) affected PFS (p=0.051) and OS (p=0.03).

Conclusions: EXOTIC represents the largest academic, real-world dataset on EGFR exon 20 mutant advanced NSCLC in Europe. Indirectly compared, treatment with new exon 20-targeting agents (TKIs and bi-specific antibodies) seem to confer survival benefit over chemotherapy +/- immunotherapy. Updated data will be presented in the congress.



Keywords: Epidermal Growth Factor Receptor, Exon 20, poziotinib, mobocertinib, amivantamab

EP08.02-061 Treatment Sequences in ALK-rearranged Non-small Cell Lung Cancer; What Happens in the Real World?

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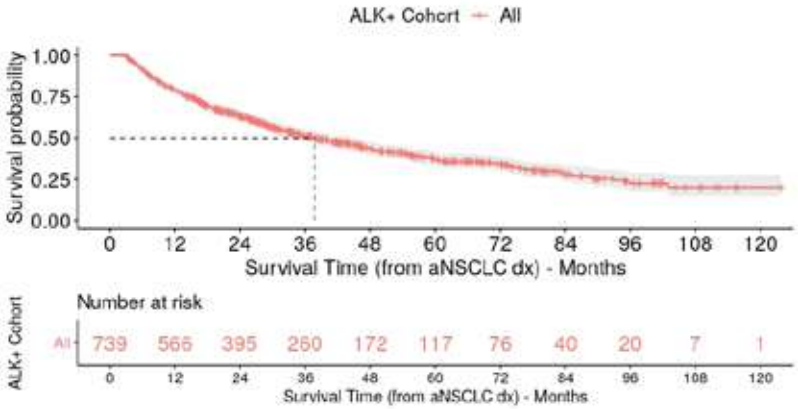
Introduction: In the era of targeted therapy and a multitude of agents to manage *anaplastic lymphoma kinase (ALK)*-rearranged advanced non-small cell lung cancer (aNSCLC), optimal treatment sequencing to achieve the best patient outcomes is yet to be elucidated. Relevant contemporary randomised trials compare single lines of treatment head-to-head but are not designed to investigate this important question.

Methods: This study used the nationwide (US-based) Flatiron Health electronic health record (EHR)-derived de-identified database. Eligible patients were diagnosed with ALK+ aNSCLC between 2011-2020. Systemic cancer treatments were categorised as ALK-inhibitor (1st/2nd/3rd generation) and chemotherapy +/- immunotherapy. Descriptive statistics were used to summarise cohort characteristics and treatment utilisation (lines and sequences of therapy), with Sankey and Sunburst plots to visualise sequences. Kaplan Meier and Cox proportional hazards model were used to determine survival outcomes. Exploratory analyses investigating survival outcomes according to treatment sequence are ongoing.

Results: Of 63 667 patients with aNSCLC in the real-world database, 739 ALK+ patients were eligible for this analysis. Median age was 63 years, male/female was 46%/54% and 52% were never-smokers. Patients received up to 11 lines of treatment: 68% had at least 2 lines, 38% had at least 3 lines; over 200 treatment patterns were observed. Almost 89% received an ALK-inhibitor and 45% received platinum-based chemotherapy at some point in their treatment. The most common treatment sequences (to third line) were A. 1st generation ALK-inhibitor, 2nd generation ALK-inhibitor, no subsequent treatment (10.8%), B. platinum-based chemotherapy, 1st generation ALK-inhibitor, 2nd generation ALK-inhibitor (4.6%) and C. 1st generation ALK-inhibitor, 2nd generation ALK-inhibitor, re-challenge with same or different 2nd generation ALK-inhibitor (4.3%). The cohort median overall survival (OS) was 38 months (95%CI 33-45 months), Figure 1. There was no OS difference between males/females (p=0.18), although there was the suggestion of more female long-term survivors. Longer OS was observed in patients diagnosed in recent compared to earlier years (p=0.025), with median OS of 28 and 38 months in 2013/2014 and 2017/2018, respectively.

Conclusions: Patients with ALK+ aNSCLC receive an array of treatment sequences without strong evidence to guide practice. Whilst survival time and opportunity for subsequent lines of therapy has increased over recent years, the impact of treatment sequence remains unclear. Forthcoming analyses in this cohort will attempt to address this question to aid patients and clinicians in decision making with regards to how to obtain the most benefit out of the multitude of available agents for ALK+ aNSCLC.



Keywords: ALK+ non-small cell lung cancer, treatment sequence, real-world

EP08.02-062 Evaluation of In Silico Tools to Determine Potential Actionability of Missense Variants with Experimental Therapies for NSCLC

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Introduction: Recent advances in next-generation sequencing (NGS) technology have led to the discovery of a large number of variants of unknown significance (VUS), for which there is no clear classification of their significance to cancer risk. Various *in silico* mutation prediction tools have been developed to categorize such variants by pathogenicity and shed insight into their clinical actionability. Given differences in their algorithms, however, many of these *in silico* tools fail to generate the same predictions for pathogenicity. This study aimed to evaluate the performance of six widely used *in silico* tools in predicting the pathogenicity of potentially actionable missense variants of non-small cell lung cancer (NSCLC).

Methods: We identified a group of 15 genes (PIK3CA, MTOR, FGFR2, IDH1, PTEN, MAP2K1, MAPK1, BRCA1/2, KEAP1, STK11, ERBB2, AKT1/2/3) based on their 'potential actionability,' defined as having preclinical/clinical evidence for actionability but without FDA-approved targeted therapy options, for NSCLC. For each gene, we gathered data for a select sample of 10 or fewer of the most frequently occurring missense variants, yielding a total sample of 101 variants. The pathogenicity of each variant was defined through the cBioPortal database, which combined assertions from OncoKB, CiVIC, MyCancerGenome, and Cancer Hotspots. Variants with two or more concordant classifications of pathogenicity were prioritized, and others with only one classification were included as necessary. We assessed the performance of six widely used *in silico* tools (Polyphen-2, Align-GVGD, MutationTaster2021, CADD, CONDEL, REVEL) in classifying the same group of variants by calculating and comparing overall accuracy, sensitivity, specificity, Matthews correlation coefficient (MCC), and likelihood ratio (LR+, LR-). However, REVEL was excluded because it yielded a specificity of 0.

Results: All five *in silico* tools demonstrated high sensitivity (0.76-0.99) and low specificity (0-0.6). The overall accuracy of the tools ranged from moderate to high (0.73-0.94). The MCCs of the tools were low, some even below 0 (-0.02-0.42). LR+ values ranged from 0.95 to 2.36, indicating minimal increase in likelihood of disease for positive test results. LR- values ranged from 0.09 to 1.2 (excluding CADD, which had a specificity of 0 and thus an incalculable LR- score), with lower scores indicating larger decrease in likelihood of disease for negative test results. MutationTaster2021 showed the highest level of performance, yielding the highest specificity (0.6), highest MCC (0.42), highest LR+ (2.36), lowest LR- (0.09), and generally high sensitivity (0.94) and accuracy (0.93). Conversely, CONDEL showed the lowest level of performance, yielding the lowest accuracy (0.73), lowest sensitivity (0.76), lowest LR+ (0.95), highest LR- (1.2), and generally low specificity (0.2) and MCC (-0.02).

Conclusions: Each *in silico* tool displays different performance and is limited in various scopes. Tools with high sensitivity (CADD: 0.99, MutationTaster2021: 0.94, Polyphen-2: 0.90) can be useful in ruling out pathogenic variants, but none of the tools have high-enough specificity to effectively rule in pathogenic variants. MutationTaster2021 seems to be the most reliable of the tools. However, clinicians should remain cautious about solely using these tools to determine actionability.

Keywords: biomarkers, variant classification, in silico

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-063 SANOVO: A Phase 3 Study of Savolitinib or Placebo in Combination with Osimertinib in Patients with EGFR-mutant and MET Overexpressed NSCLC

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Introduction: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have improved clinical outcomes for patients with EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC); however, patients will inevitably progress often due to acquired resistance mutations. Coexisting MET overexpression is known to be associated with resistance to EGFR TKIs. Savolitinib is a potent and highly selective oral MET TKI that has shown encouraging antitumor activity and a favorable safety profile in patients with pulmonary sarcomatoid carcinoma and other NSCLC with MET exon 14 skipping alterations in a phase 2 study (NCT02897479). Osimertinib is an oral, third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI-sensitive and EGFR T790M resistance mutations. Combination of savolitinib and osimertinib may potentially delay resistance of osimertinib caused by MET overexpression.

Methods: SANOVO is an ongoing randomized, double blind, multicenter phase 3 study of savolitinib or placebo in combination with osimertinib in patients with both de novo EGFRm and MET overexpression NSCLC (NCT05009836). 320 patients from about 80 sites are planned to be enrolled. Patients with previously untreated, EGFRm-positive (exon 19 deletion or L858R) and MET overexpression (IHC2+ or 3+) advanced NSCLC are randomized in a 1:1 ratio to receive either savolitinib or placebo (400 mg, < 50 kg or 600 mg, ≥ 50 kg once daily) combined with osimertinib (80 mg once daily). Stratified factors include EGFR exon 19 deletion or L858R, MET IHC2+ or 3+, with or without brain metastases. The primary endpoint is progression-free survival (PFS) by investigator assessment in accordance with the response evaluation criteria in solid tumors (RECIST) 1.1. The primary endpoint will be analyzed in the c-MET overexpression (IHC 3+) set and in the intent-to-treat (ITT) set. Key secondary endpoints include PFS assessed by independent review committee (IRC), objective response rate, duration of response, overall survival and safety. Tumor response will be assessed every 6 weeks by the investigator and IRC using RECIST, v1.1. Safety assessments will include monitoring AEs, clinical laboratory tests, ophthalmologic examination, ECG, and ECHO. An independent data monitoring committee (IDMC) is established for regular monitoring of safety and review of the results of an interim analysis.

Keywords: savolitinib, EGFRm, NSCLC

EP08.02-064 ASTRIS China: A Real-world Study of Osimertinib in Patients with EGFR T790M Positive Non-small-cell Lung Cancer (NSCLC)

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Introduction: ASTRIS is the largest global wide study of osimertinib in a real-world setting in patients with EGFR T790M mutation-positive advanced NSCLC. Here we present the final analysis of Chinese subset of the ASTRIS study.

Methods: Eligible patients (≥18 years) had advanced, metastasis NSCLC, WHO performance status (PS) 0-2 and received prior EGFR-TKI treatment with EGFR T790M mutation. Patients with asymptomatic, stable CNS metastases were allowed. EGFR T790M mutation-positive confirmed by local validated molecular test. All patients received osimertinib 80 mg, orally once daily. The primary endpoint was overall survival, secondary endpoints were progression-free survival (PFS), response rate (RR), time to treatment discontinuation (TTD) and safety profile. Data cutoff (DCO) was December 11, 2020.

Results: 1350 patients were enrolled from September 27, 2016 to September 22, 2017. At DCO, 1001 (74.1%) patients discontinued study treatment. 349 (25.9%) patients still continued study treatment and transitioned to commercial supply per ASTRIS protocol. Until January 5, 2022, 80 (6%) patients still benefit from the supply and have duration of treatment more than 4 years from last patient enrolled. At DCO, median TTD was 13.9 months (95%CI 13.1-15.2). Disease progression or death was reported in 1059 (78.4%) patients, with mPFS of 11.7 months (95%CI 11.1-12.5). The mPFS in T790M-positive patients confirmed by tissue (n=783) and plasma (n=567) was 13.1 months (95%CI 12.5-13.8) and 10.0 months (95%CI 9.5-11.0), respectively. Among 341 (25.3%) patients with CNS metastases at baseline, the mPFS was 11.0 months (95% CI 9.7-12.4). Overall, 389 patients (28.8%) had at least one protocol-defined AE. 3 (0.2%) patients had ILD. SAEs were reported in 297 (22%) patients, including 52 (3.9%) patients were treatment related. No new safety signals were observed.

Conclusions: Our analysis of a subset of Chinese patients in ASTRIS study are consistent with Asians reported in AURA studies. These data support osimertinib as a standard second-line treatment in patients with EGFR T790M-positive NSCLC after first-line EGFR-TKI therapy in real world. **Funding:** This study was funded by AstraZeneca.

Keywords: Non-small-cell lung cancer, Osimertinib, EGFR T790M-positive

EP08.02-065 Response to Systemic Anti-Cancer Therapy in Uncommon EGFR Mutations

H.M. O'Sullivan[1], S. MacMahon[1], N. Cunningham[1], S. Farag[1], P.D. d'Arienzo[1], C. Milner-Watts[1], N. Tokaca[1], M. Davidson[1], A. Minchom[1], J. Bhosle[1], N. Yousaf[1], W. Cui[1,2], M. O'Brien[1,3], S. Popat[1,3,4]

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Introduction: Exon 19 deletions, exon 21 L858R and exon 20 insertions represent the most frequent alterations in *EGFR* mutated non-small cell lung cancer (NSCLC). These alterations now all have approved targeted therapies. In contrast, there is limited data assessing activity of *EGFR*-directed therapy for uncommon *EGFR* alterations. We sought to describe clinical outcomes of patients with rare *EGFR* mutations that received systemic anticancer therapy (SACT) at our institution.

Methods: The database of the clinical genomic lab at the Royal Marsden Hospital was retrospectively analysed to identify NSCLC samples with *EGFR* mutations in exons 18-21. Exon 19 deletions, L858R, T790M and exon 20 insertions were excluded. Patient records were reviewed for baseline demographics, SACT, and efficacy.

Results: Between January 2017-September 2021, 23 patients with uncommon *EGFR* mutations received SACT. Median age at diagnosis was 65 years, 60% were female and 39% were never-smokers. Brain metastases were present at diagnosis in 30%. Compound *EGFR* mutations were present in 6 (26%) cases. The most frequent single mutations were G719X and L861Q, accounting for 6 (26%) and 5 (22%) cases, respectively (table 1). *EGFR* kinase inhibitors (TKIs) were prescribed as first-line in 18 (78%) cases, with an overall response rate (ORR) of 50% (9/18), 80% (4/5) in patients with compound alterations and 38% (5/13) in patients with single alterations. Median time to first line TKI discontinuation for compound and single alterations was 6 (range 1-32) and 4 months (range 1-40), respectively (table 2). The most frequently prescribed first-line TKIs were afatinib (7/18) and osimertinib (6/18). Median time to first-line TKI discontinuation for afatinib was 6 months (range 1-36), 3 months (range 1-12) with osimertinib, and 4 months (range 1-40) overall.

Conclusions: *EGFR* TKIs have heterogeneous efficacy in uncommon single and compound *EGFR* mutations.

Table 1: Patient Clinical Characteristics

Baseline Characteristic	N=23 (%)
Age (years), median (range)	65 (36-89)
Gender	
Male	9 (40%)
Female	14 (60%)
Smoking Status	
Never Smoker	9 (39%)
Ex-smoker	14 (61%)
Histology	
Adenocarcinoma	21 (92%)
Squamous Cell	1 (4%)
Other	1 (4%)
Stage at diagnosis	
IIIA	3 (13%)
IIIB	1 (4%)
IVA	9 (39%)
IVB	10 (43%)
Brain metastases at diagnosis	7 (30%)
Uncommon Mutation Subtype	
Exon 18 G719X	6 (26%)
Exon 20 S768I	3 (13%)
Exon 21 L861Q	5 (22%)
Exon 18 deletion	1 (4%)
Exon 19 L747P	1 (4%)
Exon 20 G779F	1 (4%)
Compound EGFR Mutations	
Exon 18 G719C, Exon 20 S768I	3 (13%)
Exon 18 G719X, Exon 21 L861Q	2 (7%)
Exon 18 G719A, Exon 18 G709A	1 (4%)
Lines of SACT	Median 2 (range 1-5)
First Line SACT	
TKI	18 (78%)
Chemo	4 (17%)
Chemo-IO	1 (4%)
ORR to First Line SACT	
TKI	50%
Chemo	67%
Chemo-IO	0%

Chemo; Chemotherapy; IO: Immunotherapy; ORR: Overall Response Rate; SACT: Systemic anti-cancer therapy.

Table 2: Individual Patient Mutations and Treatment Outcomes

EGFR Mutation	Case	First Line Treatment	Best response	TTD (mo)	Second Line Treatment	Best Response	TTD (mo)	OS
Exon 18 G719X	1	Osimertinib	PR	12	Chemo	SD	4	33
	2	Osimertinib	SD	4	Nil			5
	3	Osimertinib	PD	2	Nil			2
	4	Gefitinib	SD	17	Nil			18
	5	Gefitinib	PR	40	Osimertinib	SD	14	NA
	6	Afatinib	CR	27	Osimertinib	PD	2	48
Exon 20 S768I	7	Afatinib	PD	4	IO	PD	3	12
	8	Chemo-IO	SD	6	Afatinib	SD	5	NA
	9	Chemo	PR	4	Afatinib	PD	3	14
Exon 21 L861Q	10	Afatinib	PR	36	Chemo	SD	5	NA
	11	Afatinib	PD	3	Chemo	PR	5	21
	12	Erlotinib	PD	3	Nil			3
	13	Gefitinib	NA	1	Chemo	PR	4	36
	14	Osimertinib	PD	1	Nil			3
Exon 18 deletion	15	Afatinib	PD	1	Nil			2
Exon 19 L747P	16	Osimertinib	PR	1	Nil			5
Exon 20 G779F	17	Chemo	PD	3	Chemo-IO	PR	6	NA
Compound Mutations								
Exon 18 G719C, Exon 20 S768I	18	Gefitinib	PD	3	Nil			4
	19	Chemo	PR	4	Erlotinib	PR	12	82
	20	Osimertinib	PR	*	NA			NA
Exon 18 G719X, Exon 21 L861Q	21	Erlotinib	PR	12	Osimertinib	PR	17	40
	22	Afatinib	PR	32	Chemo	SD	*	NA
Exon 18 G719A, Exon 18 G709A	23	Afatinib	PR	6	Erlotinib	PD	4	25

TTD: Time to treatment discontinuation; mo: months; OS: Overall survival; Chemo; Chemotherapy; PD: Disease progression; SD: Stable disease; PR: Partial response; IO: Immunotherapy; *:treatment ongoing; NA: not applicable.

Keywords: Uncommon EGFR Mutations, EGFR TKI

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-066 Real-World Data on the Side Effects of Alectinib, Brigatinib and Lorlatinib

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Introduction: Established in 2018, ALK Positive UK is a registered charity with the fundamental aim of providing support, empowerment, and advocacy for patients of ALK positive lung cancer. The charity regularly carries out surveys of its members to collect data concerning all aspects of their diagnosis and treatment. The information gathered informs the charity as to the direction of its campaigns to ensure that all patients throughout the UK receive a high level of care.

Methods: This November 2021 survey was distributed online to all members of ALK Positive UK's support group community, and 93 participated.

Results: Respondents reported 24 individual side effects* to taking Alectinib, of which the top three were: sun sensitive (82%), fatigue (75%), and constipation (71%). Other common side effects included muscle aches / weakness, weight gain, and swelling / bloating.

Respondents reported 24 individual side effects* to taking Brigatinib, of which the top three were: diarrhoea (43%), nausea (36%), and high blood pressure (36%). Other common side effects included muscle aches, fatigue and neuropathy.

Respondents reported 14 individual side effects* to taking Lorlatinib, of which the top four were: neuropathy (62%), increased appetite (54%), weight gain (46%), and mood swings (46%). Other common side effects included bloating / swelling, visual disturbances and hot / cold sweats.

In terms of side effect* frequency - fatigue, muscle ache, sun sensitivity and constipation all occurred at a higher frequency for those receiving Alectinib. For hallucinations, cognitive difficulties, mood swings and visual disturbances, all occurred at a higher frequency for those receiving Lorlatinib. **reported by at least 20% of the respondents*

Considering only the side effects, 63% of respondents reported that Lorlatinib was the preferable drug.

Conclusions: There is a huge range of side effects which are common with the taking of all three drugs aforementioned. Their frequency is substantial. It is important that patients are well-informed of possible side effects in order to contribute to the management of ALK Positive lung cancer. This should be a key part of post-diagnosis discussions.

Keywords: Side effects, Treatment, ALK Positive

EP08.02-067 Concurrent Aumolertinib Plus Icotinib for First-Line Treatment of EGFR Mutated Non-small Cell Lung Cancer with Brain Metastases

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Introduction: Brain metastases are associated with significant morbidity and are found in up to 50% of patients with advanced non-small cell lung cancer (NSCLC), and seriously affect the prognosis of lung cancer patients. Currently, brain metastasis of epidermal growth factor receptor (EGFR) sensitive mutations is a hot and difficult point in targeted era of NSCLC treatment, meanwhile it is also the central issue of controversy in the field of lung cancer treatment. Additionally, EGFR tyrosine kinase inhibitors (EGFR-TKIs) have been recommended as standard therapy for asymptomatic NSCLC patients with EGFR mutations with brain metastases. However, how to optimize the use of existing targeted drugs is an important way to address the clinical needs of the central nervous system in the individualized treatment of NSCLC. Some researches showed that response rates of brain metastases to EGFR-TKIs treatment in patients with NSCLC harboring EGFR mutations reach 60-80%, with a complete response rate as high as 40%. Aumolertinib and icotinib are respectively the third-generation EGFR-TKI and first generation EGFR-TKI which proved efficiency and safety for EGFR mutated NSCLC with brain metastases. This study aims to investigate the efficacy and safety of aumolertinib + icotinib as a first-line therapy for EGFR mutated NSCLC with brain metastases.

Methods: This ongoing phase I/II study enrolled patients with stage IV EGFR-mutated (L858R or del19) NSCLC with brain metastases. Treatment in dose escalation (n = 6): concurrent aumolertinib 55 mg or 110 mg (once a day) + gefitinib 125 mg (3 times a day). In dose expansion (n = 40): aumolertinib + icotinib at the maximum tolerated dose (MTD). Prior to protocol amendment 6 patients received alternating monthly cycles of TKI monotherapy and were excluded from this analysis. The primary endpoints in the dose escalation and expansion phases were, respectively, identification of the MTD and feasibility, defined as receipt of combination therapy for ≥ 6 four-week cycles. Secondary endpoints included objective response rate (ORR), disease control rate(DCR), progression free survival(PFS), duration of response(DoR), overall survival(OS). The primary efficacy analysis was done by intention to treat in patients who had at least one post-baseline tumor assessment. The safety analysis was done in all patients who received at least one dose of study treatment.

Results: From June 2021 to March 2022, 12 patients were enrolled and evaluable for the primary endpoints. The MTD was aumolertinib 110 mg plus icotinib 375 mg orally daily. The ORR of 6 patients in phase I was 100%. And no grade 4 or 5 AEs were observed. At 9 months median follow up the median progression free survival was not yet reached in phase I.

Conclusions: This is the first study to demonstrate that aumolertinib plus icotinib have preliminary efficacy and a tolerable safety profile in EGFR-mutated NSCLC patients with brain metastases. This study is still in progress and further analyses are undergoing to determine longer-term outcomes. Clinical trial information: ChiCTR2100044216.

Keywords: aumolertinib, icotinib, brain metastases

EP08.02-068 ALK-Dependent Resistance Mechanism to Ensartinib Differs Between the ALK Fusion Subtypes Variant 1 (V1) and Variant 3 (V3)

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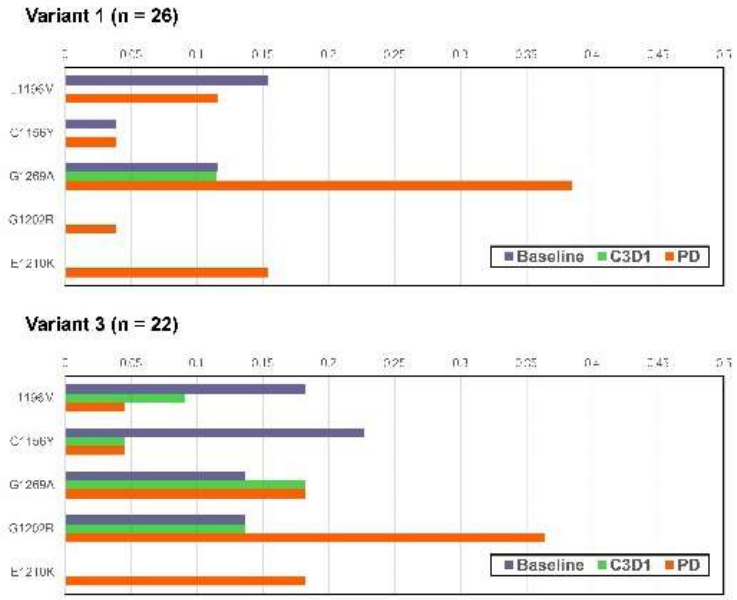
Introduction: Ensartinib is a next-generation (NG) ALK TKI that showed comparable efficacy to other NG ALK TKIs in the first-line and post-crizotinib settings. We have reported that ensartinib has similar efficacy between ALK fusion subtypes V1 and V3, and their median PFS were 5.5 (4.2, 7.7) and 6.6 (4.1, 9.8) months, respectively. Here, we further explored the ALK-dependent resistance mechanisms of these two subtypes.

Methods: In the phase II clinical trial (NCT03215693), plasma samples from progressive disease non-small cell lung cancer patients after crizotinib treatment were prospectively collected for ctDNA analysis at baseline, cycle 3 day 1 (C3D1), and the end of treatment (EOT). Plasma DNA was analyzed using a 212-gene next-generation sequencing panel.

Results: Based on baseline ctDNA, we identified 36 patients with the V1 subtype and 28 patients with the V3 subtype. Twenty-six and Twenty-two EOT plasma samples were collected in V1 and V3 groups, respectively, and these 48 patients were included in the analysis. At baseline and C3D1, V3 subtype tended to harbor more ALK mutations, although the difference was not statistically significant (baseline: 38.5% vs 59.1%, p = 0.154; C3D1: 11.5% vs 36.4%, p = 0.082). After resistance, the frequency of ALK mutations was similar between the two groups (47.2% vs 59.1%, P = 0.371). For the V1 subtype, the most common mutation at baseline was L1196M (15.4%, 4/26). Unlike the V1 subtype, the V3 subtype had high frequencies of both L1196M (18.2%, 4/22) and C1156Y (22.7%, 5/22) at baseline. After resistance, the V1 subtype mainly developed G1269A mutation (V1, 38.4%, 10/26 versus V3, 18.2%, 4/22, p = 0.124), while the V3 subtype mainly developed G1202R mutation (V1, 3.8%, 1/26 versus V3, 36.4%, 8/22, p = 0.004). The frequencies of E1210K mutation were similar in both groups (V1, 15.4%, 4/26 versus V3, 18.2%, 4/22, p = 0.796).

Conclusions: This study found that the incidence of the ensartinib-associated ALK resistance mutation is different in V1 and V3 subtypes. Under ensartinib pressure, the V1 subtype was more prone to the G1269A mutation, while the V3 subtype was more prone to the G1202R mutation, although there was no significant difference in survival between the two groups. This difference may allow for a more precise selection of later-line therapy.



Keywords: ALK-positive NSCLC, ALK variant, Resistance mechanism

EP08.02-069 A Retrospective Study of Aumolertinib Monotherapy or Combination Therapy Treated EGFR-mutated NSCLC Patients with Leptomeningeal Metastases

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Introduction: The incidence of leptomeningeal metastases (LM) is approximately 9% in epidermal growth factor receptor-mutated (EGFRm) NSCLC with extremely poor prognosis. Aumolertinib (formerly almonertinib; HS-10296) is a novel 3rd generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI). The preclinical evidence in nonhuman primates shows that aumolertinib has high penetration of the blood-brain barrier and brain exposure compared with other EGFR-TKI. In this study, we researched the efficacy of aumolertinib monotherapy or combination therapy with EGFR-mutated NSCLC leptomeningeal metastases.

Methods: Retrospective analysis of 11 EGFR-mutated NSCLC patients with LMs from April 2020 to December 2021 in the first Affiliated Hospital of Zhengzhou university. Patients were administrated almonertinib monotherapy (110mg QD) or combined with chemotherapy (chemotherapy or bevacizumab) until progression or intolerance. The primary endpoint was progression free survival (PFS).

Results: The study retrospectively analyzed 11 patients with advanced EGFR-mutated positive NSCLC confirmed LM by cerebrospinal fluid(CFS). The median age was 60.5 years (range, 49-76years), 45% were female, and 72.7% were never-smokers, 36% were 19del. The median follow-up were 8.5 months, all the patients had progressed. The confirmed partial response (PR) were 6 (54.5%) patients and stable disease (SD) were 3 (27.3%) patients, the ORR was 54.5% (6/11) and the DCR was 81.8 % (9/11). The median PFS for all patients was 8.1 months. In subgroup analysis, the median PFS of 19del or L858R patients were 12 or 8 respectively, and median PFS of EGFR positive mutation combined with TP53 were 8 months and without TP53 were 13 months.

Conclusions: Aumolertinib monotherapy or combination therapy demonstrated superior activity for LMs of advanced EGFR-mutated NSCLC and larger sample size or further prospective studies are warranted to investigate the role of Aumolertinib in LM patients.

Keywords: Aumolertinib, Leptomeningeal Metastases, EGFR-TKI

EP08.02-070 High Incidence of Peridiagnosis Thromboembolic Events In Patients with BRAF Mutant Lung Cancer

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Introduction: A higher risk of thromboembolic events (TEE) has been recently reported in patients (pts) with non-small-cell lung cancer (NSCLC) harboring ALK or ROS1 gene rearrangements (incidence rate 20-30%). BRAF mutations have been described in 4% of NSCLC. Whether pts with BRAF mutant NSCLC show higher risk of TEE is unknown. We aimed to describe the incidence, characteristics and time of onset of TEE in pts with advanced BRAF mutant NSCLC.

Methods: A total of 182 pts with BRAF mutant NSCLC (70 pts BRAF V600E [38.5%]/ 112 pts BRAF non-V600E [61.5%]), were retrospectively identified from 18 participant centers in Spain between 2008 and 2021. BRAF mutational status was determined by NGS in 82% of pts. Clinicopathologic, therapeutic and molecular data were extracted from electronic medical records. Venous TEE [deep venous thrombosis (DVT), superficial venous thrombosis (SVT), visceral venous thrombosis (VVT), thrombosis associated with CVC (CVCT) or pulmonary embolism (PE)] and arterial TEE [myocardial infarction (MI), cerebrovascular accident (CVA), peripheral arterial disease (PAD) or mesenteric ischemia (MIS)], number of events, dates, treatments received and survival were assessed.

Results: The incidence rate of TEE was 26.4% (n=48). A total of 72 TEE were documented among 48 pts, as 18 pts (37.5%) developed more than one event. The median time to TEE onset was 1.5 months, representing the form of disease presentation in 42.5% cases (n=17). Venous TEE included 59 cases (81.7%): 33 PE, 16 DTV, 2 VVT, 2 CVCT, 1 SVT, 4 in other vessels and 1 not specified; whereas 13 cases corresponded to arterial TEE (18.3%): 8 CVA, 1 PAD, 1 MIS, and 3 in other vessels. Personal history of thrombosis, ECOG PS, type of BRAF mutation (V600E/non-V600), Khorana score, or type of oncological treatment (targeted therapy n=40; immunotherapy n=69; chemotherapy n=102; immunotherapy + chemotherapy n=37) were not related to TEE occurrence. Median overall survival was numerically shorter in stage IV patients with TEE vs. without-TEE: 10.5 months (m) vs 19.36 m (p=0.4) but significantly shorter in arterial TEE vs venous TEE in all patients (9.8 m vs 41 m; p=0.001).

Conclusions: BRAF mutant NSCLC could be associated with a higher risk of TEE, both arterial and venous, and negatively impact on pts survival. If these results were confirmed in larger cohorts, prophylactic anticoagulation may be recommended in these patients.

Keywords: BRAF Mutant Lung Cancer, Thrombosis, Targeted Therapy

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-071 Brain Metastases in EGFR-mutant NSCLC: Outcome of Osimertinib +/- Radiation Therapy in a Real-World Canadian Cohort

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Introduction: Intracranial metastasis is a significant complication in patients with EGFR-mutant non-small cell lung cancer (NSCLC). Osimertinib is an oral tyrosine kinase inhibitor which has central nervous system (CNS) activity. However, many patients with intracranial metastases are treated with cranial radiation therapy (RT), which can have considerable toxicities. The optimal treatment for this patient population has not been elucidated. The purpose of this study was to assess CNS outcomes of real-world patients treated with Osimertinib +/- RT.

Methods: EGFR-mutant NSCLC patients with brain metastases in Alberta, Canada treated with Osimertinib from the dates of July 2018 to January 2021 were identified. Demographic, clinical, treatment and outcome details were extracted from the Glans-Look Lung Cancer Research Database. Osimertinib-treated patients were grouped according to presence/absence of concurrent cranial RT. Univariate and multivariate analysis were used to compare groups and potential impact on outcome and response.

Results: 36 patients were identified: 15 (42%) received Osimertinib alone (Osi) and 21 (58%) received both Osimertinib plus RT (OsiRT). Of those receiving RT, 7 (33%) received stereotactic radiosurgery (SRS) and 12 (57%) received whole brain radiation therapy (WBRT). Osi and OsiRT groups did not differ significantly in terms of demographic or clinical characteristics, including CNS-specific clinical characteristics like number of brain metastases, and presence of cerebral edema or leptomeningeal metastases. mTTF and mOS were 16.8 and 19.2 months respectively and did not differ significantly between the Osi and OsiRT groups. CNS-specific objective response rate (ORR) in the Osi group was 85% vs. 50% in the OsiRT group, p=0.04. The disease control rate (DCR) was 92% in the Osi group vs 60% in the OsiRT group, p=0.03. A multivariate model accounting for sex, age, and Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and RT to the brain showed ECOG ≥ 2 to be an independent factor for poor survival (HR: 33.8, p=0.002).

Conclusions: There were no significant differences in mOS and mTTF between the Osimertinib patients treated with or without RT in our sample. Notably, the CNS-specific ORR was high in the Osi group, and 19% of patients treated with Osimertinib alone were observed to have a complete response to their brain metastases. These findings suggesting that in a subset of patients, Osimertinib alone has good real-world effectiveness in providing CNS control. Notably, brain metastases may be handled through systemic therapy alone for a significant duration of time, sparing potential RT-associated toxicities for patients who are achieving both intra and extracranial disease control on Osimertinib.

Keywords: Non-small cell lung cancer, Targeted Therapies, Brain Metastases

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-072 The Predictive Value of Longitudinal Monitoring of Mutated EGFR in Plasma of Advanced NSCLC Patients on First-Line EGFR-TKIs

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Introduction: The analysis of cell-free DNA in plasma, so called liquid biopsy, significantly improved the detectability of activating and resistance *EGFR* mutations in advanced non-small cell lung cancer (NSCLC) patients prior EGFR-TKI therapy and upon clinical progression, in particular when sufficient tumor tissue material is not available. Since the acquired resistance to EGFR-TKIs develops gradually under the inhibitor-specific selective pressure, the longitudinal analysis of mutated *EGFR* in both qualitative and quantitative manner may be more beneficial in term of the real-time treatment monitoring and early detection of resistance mutations. The aim of the study was to assess the predictive value of longitudinal quantitative monitoring of mutated *EGFR* in plasma of NSCLC patients during first-line EGFR-TKI treatment.

Methods: The *EGFR* mutation status and level were evaluated using diagnostic allele-specific qPCR platform (Cobas EGFR Mutation Test v2, Roche, Germany) in plasma samples collected prospectively from 51 advanced NSCLC patients (with *EGFR*-mutation-positive tumor) at the time of diagnosis (baseline) and then every month during the first-line EGFR-TKI treatment (erlotinib, gefitinib, afatinib) until clinical progression. The qPCR results for *EGFR* exon 19 deletions were verified using droplet-digital PCR (ddPCR) assay (Bio-Rad, USA).

Results: The median (min-max) PFS was 10.3 (1.8-35.6) months. In the Kaplan-Meier analysis, significant differences in PFS were found between patients who demonstrated complete clearance of baseline *EGFR* mutation level in plasma within 1-2 months of treatment and patients whose mutated *EGFR* levels were similar or higher than baseline [12 (4.5-35.6) vs. 8.35 (1.8-17.5) months, p=0.0099], and patients with undetectable *EGFR* mutation in plasma at diagnosis and during treatment [9.8 (1.8-30) months, p=0.04620]. *EGFR* p.T790M mutation was detected in plasma of 13/51 (25.5%) NSCLC patients upon clinical progression using qPCR. The dynamics of plasma *EGFR* mutation levels correlated well with the changes in the sum of the longest diameters of target lesions by RECIST1.1. The Cobas test demonstrated high overall concordance with ddPCR in quantification of mutated *EGFR* in 135 plasma samples collected during the whole EGFR-TKI treatment period (Spearman's rank correlation coefficient, R=0.76, p<0.0001). The highest concordance between Cobas and ddPCR values was observed in plasma samples collected before EGFR-TKI treatment (R=0.87, p<0.0001) whereas the correlation was slightly lower in samples collected upon clinical progression (R=0.58, P<0.049). In our study 25% patients did not present detectable mutated EGFR allele at baseline and during the whole treatment period.

Conclusions: We demonstrated that the allele-specific qPCR assay, namely Cobas EGFR mutation test V2, provides reliable qualitative and quantitative results on the *EGFR* mutation status and level in plasma of advanced NSCLC patients at diagnosis and during the EGFR-TKI treatment. The longitudinal monitoring of mutated EGFR in plasma shows predictive value for the treatment outcome in advanced NSCLC patients on first-line EGFR-TKIs. The complete clearance of mutated *EGFR* levels in plasma within the first months from the drug administration may predict the long duration of the first-line EGFR-TKIs. The dynamics of plasma mutated *EGFR* (exon 19 deletion) levels measured by Cobas test followed very well the values presented by ddPCR during the EGFR-TKI treatment.

Keywords: non-small cell lung cancer, EGFR mutations, liquid biopsy

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-073 Clinical and Genomic Analysis of Primary and Secondary MET Fusions with Intact Kinase Domain in Lung Cancer

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Introduction: Several kinase gene fusions, including *MET*, have been uncovered as oncogenic alterations in lung cancer beyond the well-studied *ALK*, *RET*, and *ROS1* fusions. As amplification and exon 14 skipping were the two most frequent *MET* alterations, *MET* fusions are rarely reported and less investigated. Though the potential role of *MET* fusions as a resistance mechanism to tyrosine kinase inhibitors (TKIs) has been proposed in a series of case reports, comprehensive studies remain to be performed in large cohorts.

Methods: A total of 44 patients harboring *MET* fusions with intact kinase domain (KD) were identified from a large cohort of lung cancer patients who underwent targeted next-generation sequencing (NGS). The clinical and molecular profiles including concurrent alterations, tumor mutational burden (TMB), chromosome instability syndromes (CIS), mutational signatures of baseline and progressed samples were retrospectively reviewed.

Results: A total of 46 KD-intact *MET* fusions were detected in the 44 patients and the breakpoints of fusion partners were located in intergenic regions (IGRs) in 45.7% (21/46) of *MET* fusions. Other recurrent fusion partner genes included *HLA-DRB1/5* (N = 5), *ST7* (N = 4), *CAPZA2* (N = 3), and *CD47* (N = 2). A subgroup of patients (N = 19) had multiple types of baseline samples, including tissue, plasma, and other liquid biopsies, and the detection concordance rate of *MET* fusions among different samples was 47.4% (9/19). Baseline samples were available in a total of 34 patients and 29 of them harbored primary *MET* fusions, a small proportion of which were accompanied by *MET* amplification (17.2%, 5/29) and *MET* exon 14 skipping (6.9%, 2/29). The allele frequencies (AFs) of eleven primary *MET* fusions were the highest among all alterations detected in the baseline samples, suggesting a potential oncogenic role of *MET* fusions in these patients. Nearly a half (14/29) of primary *MET* fusions contained IGR breakpoints, which were associated with higher frequencies of *TP53* (85.7% vs. 42.9%, $p = 0.046$) and *EGFR* (42.9% vs. 0%, $p = 0.016$) mutations than non-IGR *MET* fusions. The overall median TMB of patients with primary *MET* fusions was 4.6 mutants/Mb and the TMB level in patients with concurrent oncogenes, including *EGFR*, *ALK*, *KRAS*, *RET*, *HER2*, *BRAF*, *NTRK1/2/3*, and *ROS1*, was significantly higher than that without these oncogenes (5.7 vs. 3.2, $p = 0.044$). The most dominant mutational signature was dMMR (deficient DNA mismatch repair) in all *MET*-fusion baseline samples and age-related mutational signature was more frequently observed in patients with IGR-*MET* fusions (median: 0.080 vs. 0.00, $p = 0.021$). Five patients acquired secondary *MET* fusions upon disease progression and three of them were exposed to *EGFR* TKIs, suggesting the potential resistance mechanism.

Conclusions: To our knowledge, we comprehensively investigated the clinical and molecular characteristics of *MET* fusions in the largest lung cancer cohort so far. Both primary and secondary *MET* fusions existed, which might serve the role of oncogene and resistance mechanism to TKIs, respectively. In addition, NGS with multiple sample types could promote personalized treatment by providing comprehensive molecular portraits.

Keywords: MET fusions, NSCLC, resistance mechanisms to EGFR TKIs

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-074 Impact of Germline BRCA1/2 Alterations on EGFR Mutant Advanced Non-small Cell Lung Cancer Outcomes

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Introduction: Incidental pathogenic germline variants (iPGV) in BRCA1/2 may be identified in patients with advanced non-small cell lung cancer (aNSCLC) by somatic genotyping via tissue or plasma-based assays. However, impact of iPGVs on patient outcomes is not well understood. Because of the sensitivity of BRCA-deficient cancers to various therapies, it is of interest to understand the impact of these iPGVs on molecularly homogenous lung cancer population. Using real-world evidence (RWE), we aimed to explore the impact of iPGV findings in BRCA1/2 (gBRCA), identified by a well-validated liquid biopsy assay, on outcomes in patients with aNSCLC who received EGFR targeted therapy.

Methods: RWE was sourced from the GuardantINFORM (Guardant Health) database, which comprises aggregated commercial payer health claims and de-identified records from over 190,000 patients with Guardant360 results. After identifying patients who had iPGVs in BRCA1/2 on Guardant360 from October 2018 - September 2021, we selected only alterations classified as pathogenic/likely pathogenic in the OncoKB database to form a gBRCA+ cohort. A retrospective matched cohort analysis was conducted among gBRCA+ patients and matched controls that did not have iPGVs in BRCA1/2 (gBRCA-) based on age (+/- 5 years), gender, year of Guardant360 test, line and type of EGFR TT (monotherapy only). Real-world time to treatment discontinuation (rwTTD) and real-world time to next treatment (rwTTNT) were assessed as proxies for progression free survival. Wilcoxon's ranked tests were used to compare outcomes across gBRCA+/gBRCA- groups.

Results: 450 patients with aNSCLC were included in the gBRCA+ cohort of whom 48% (216) had at least 1 therapy record; 33 (15%) had EGFR TT at any line. The matched cohort for outcomes analysis included 32 gBRCA+ and 160 gBRCA- patients; 66% of each group were female, the mean age was 59 years, 81% had EGFR TT in the first line, 62% had Guardant360 testing in 2020 and 2021. Patients who had EGFR TT and gBRCA+ had shorter rwTTD and rwTTNT compared to control gBRCA- patients, though this was not significant [median rwTTD = 8.6 months (95% CI 5.2-11) vs. 11 months (95% CI 8.6-13.5) p=0.43; median rwTTNT = 19.9 months (95% CI 11-not reached) vs. 25.5 months (95% CI 17.8-35.9 p=0.78]. Overall survival (OS) data was immature, with OS not reached for the gBRCA+ group; the gBRCA- group had median OS of 80.6 months (95% CI 59.5-not reached).

Conclusions: In this small dataset, a non-significant trend emerged that suggests gBRCA+, ERGR mutant aNSCLC patients treated with EGFR monotherapy may have subpar outcomes relative to gBRCA- matched controls. Additional studies may help elucidate significance for aNSCLC patients with and without gBRCA findings. While patients who are both EGFR mutant and gBRCA+ may benefit from combination therapy (e.g., PARP inhibition) in clinical trials, studies should also assess how gBRCA impact patient outcomes even if not directly driving tumorigenesis.

Keywords: BRCA, EGFR, NSCLC

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-075 Maintained Complete Response for 8+ Years with Erlotinib Alone in Advanced Lung Adenocarcinoma Harboring EGFR Exon 19 Deletion

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Introduction: The prognosis for patients with advanced epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) has significantly improved with the use of EGFR-tyrosine kinase inhibitors (EGFR-TKIs), such as the widely used first-generation EGFR-TKI, Erlotinib. The association between EGFR exon 19 deletions (ex19del) and prolonged survival in EGFR-TKI-treated patients has previously been widely reported, with median overall survival (OS) of approximately 31 months. Molecular factors indicating prolonged survival are not defined. Metastatic NSCLC patients with ultra-long survival remain rare, especially those with unchanged treatment since diagnosis, and one such cases is presented.

Methods: Diagnostic tumor cytological material at baseline was initially examined for 42 known mutations in EGFR exon 18-21 using Cobas 4800 EGFR v.2 (Roche). Genomic DNA was subsequently examined by targeted next-generation sequencing (NGS) for driver mutations across 147 cancer-associated genes using the Oncomine™ Comprehensive Assay v.3 (ThermoFisher Scientific).

Results: A 59-year old female, former smoker, was examined by PET/CT in February 2014 due to cough and dyspnea, revealing a 3.4 cm tumor in right upper lobe, pericardial effusion, supraclavicular lymph nodes and mediastinal stations 2R, 2L, 4R, 4L, 7, 8, and 11R, accordingly stage T2N3M1a. Cytologic material obtained by EBUS-FNA of stations 4R, 4L, and 11R, revealed metastatic pulmonary adenocarcinoma. The above-described Cobas EGFR-mutation assay on material from station 4R in March 2014 identified an ex19del. Immunohistochemistry for ALK protein was negative. NGS performed on genomic DNA from the remaining diagnostic EBUS-FNA-material of station 4R using Oncomine™ Comprehensive Assay v.3 in February 2022 revealed the following mutations: EGFR p.L747_A750delinsP (i.e., the known ex19del, now more specified), ATM p.S1455fs*36, most likely a loss-of-function mutation, and the rare pathogenic MYC variant c.184G>A, p.E62K.

The patient initiated Erlotinib 150 mg daily in March 2014, obtained a partial response by June 2014, and gradually reached complete remission (CR) in May 2015. The CR has persisted ever since (latest CT scan in February 2022). Since May 2015, Erlotinib dose has been reduced to 100 mg daily due to transitory exanthema, and paronychia, without any other side effect, so that since 2015 the patient has been in performance status 0.

Conclusions: Five-year survival rate for patients with EGFR-mutant metastatic lung adenocarcinoma treated with Erlotinib or Gefitinib have been reported to be up to 15%, and ex19dels, non-smoking habit, and absence of extrathoracic or brain metastases have previously been associated with prolonged survival. The current case fits well into that in general. However, most such patients need several lines of medical antineoplastic therapy, radiotherapy or have had previous surgery, neither of which has been the case for our patient. It cannot be ruled out that the subtype of ex19del with additional pathogenic MYC variant may play a role, and this topic could be explored among patients having such ultra-long survival on the same single treatment. This issue may be further elucidated to better define the optimal therapeutic possibilities in EGFR-mutations.

Keywords: EGFR mutation, Exon 19 deletion, Erlotinib

EP08.02-076 Efficacy and Safety Evaluations of Anlotinib in Patients with Advanced Non-small Cell Lung Cancer Treated with Bevacizumab

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Introduction: Both bevacizumab and anlotinib have the anti-angiogenic ability, the purpose of this study was to evaluate the efficacy and safety of anlotinib in patients with advanced NSCLC who failed from the prior bevacizumab treatment.

Methods: In this open-label, phase 2 study, NSCLC patients with previously treated with at least one time of systemic therapy and failed of prior bevacizumab, received anlotinib (10 mg QD from day 1 to 14 of a 21-day cycle) until disease progression or treatment intolerance. The primary end point was overall survival (OS),and secondary end points were progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and safety.

Results: A total of 30 patients were enrolled in this study. One patient withdraw the consent, and 29 patients were included in the evaluation of the treatment.The median follow-up period was 12.1 months (range, 3.6-25.0 months). Among the 29 patients, no CR cases occurred, 3 patients (10.2%) showed PR, 21(72.4%) had SD, and 5 (17.2%) had PD. The ORR was 10.2%, and the DCR was 82.7%. The median PFS was 5.6 months (95% CI, 5.0 to 6.1 months). The median OS was 10.6 months (95% CI, 9.4 to 11.8 months). The overall tolerance of the anlotinib treatment was very well among the enrolled patients. No treatment-related grade four or five toxicities were observed. One patient's anlotinib administration was reduced to 8mg/day due to hypertension and headache. Most adverse events (AEs) were grade one or two, and the most common AEs were fatigue (51.7%), hypertension (41.3%), hand-foot syndrome (38.0%), anorexia(34.5%), and hypertriglyceridemia(34.5%).

Conclusions: Anlotinib demonstrated favorable activity and manageable toxicity in NSCLC with patients treated with bevacizumab previously.

Keywords: Anlotinib, Non-small cell lung cancer (NSCLC), Bevacizumab

EP08.02-077 Two Phase III Trials of Aumolertinib Plus Chemotherapy for NSCLC with EGFR and Concomitant non-EGFR Driver Genes /Tumor Suppressor Genes

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Introduction: EGFR tyrosine-kinase inhibitors (EGFR-TKIs) are the standard treatment for advanced non-small cell lung cancer (NSCLC) patients with EGFR mutation. However, this therapy ignored poorer efficacy of patients with EGFR concomitant mutations. In the BENEFIT study, median progression-free survival (mPFS) of NSCLC patients was 13.2/9.3/ 4.7 months for three groups (only EGFR-sensitizing mutations/EGFR-sensitizing mutations and concomitant tumor suppressor gene/multiple driver genes), respectively. EGFR-TKI combined with chemotherapy demonstrated a better efficacy than EGFR-TKI alone. aumolertinib (HS-10296) is a novel, third-generation EGFR-TKI approved in China to treat EGFR mutation positive NSCLC. This study aims to compare the efficacy and safety of aumolertinib alone versus aumolertinib plus chemotherapy as first-line treatment in patients with advanced/metastatic NSCLC with EGFR and concomitant mutations.

Methods: There are two multicenter, open-label, randomized, controlled phase III studies. Adult patients with histologically confirmed stage IIIB/IV NSCLC harboring sensitive EGFR mutations with concomitant non-EGFR active gene (ACROSS 1, NCT04500704) or tumor suppressor gene (ACROSS 2, NCT04500717) mutation without prior EGFR-TKI treatment is eligible for this study. The performance status (Eastern Cooperative Oncology Group) is 0 or 1. The planned sample size of ACROSS 1 is 166, ACROSS 2 is 460. Patients will be randomized (1:1) to receive aumolertinib once daily 110 mg plus carboplatin (AUC=5) and pemetrexed 500 mg/m2 Q3W or aumolertinib once daily 110 mg until disease progression. Stratified by EGFR mutation (Ex19del/ L858R) and CNS metastases (yes/no). The primary endpoint is PFS (RECIST v.1.1) assessed by an independent review committee, Secondary endpoints are objective response rate (ORR), disease control rate (DCR), disease control rate (DoR), overall survival (OS) and safety. Adverse effects were graded per CTCAE v.4.03.

Results: Trials in progress.

Conclusions: Trials in progress.

Keywords: NSCLC, concomitant mutations, EGFR-TKI

EP08.02-078 Myeloprotection with Trilaciclib in Chinese Patients with Extensive-Stage Small Cell Lung Cancer Receiving Standard Chemotherapy (TRACES)

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Introduction: Chemotherapy-induced myelosuppression (CIM) is a common toxicity, resulting in dose modifications and serious complications. Trilaciclib is a transient cyclin-dependent kinase 4/6(CDK4/6) inhibitor approved by US FDA for decreasing the incidence of CIM in adult patients with extensive-stage small cell lung cancer (ES-SCLC) who receive a platinum/etoposide-containing regimen or topotecan-containing regimen based on data from three randomized studies conducted in western countries with the dose of 240 mg/m^2. TRACES is a phase III study designed to assess the safety, efficacy and pharmacokinetics (PK) of trilaciclib in combination with standard chemotherapies in Chinese patients with ES-SCLC.

Methods: This phase III study includes an open-label safety run-in part (Part 1) and a double-blind, placebo-controlled part with patients randomized 1:1 to receive trilaciclib or placebo prior to standard-of-care chemotherapy (Part 2). Patients with treatment-naïve or previously treated ES-SCLC were to receive intravenous trilaciclib (240mg/m^2) or placebo before etoposide/cisplatin (E/P, 100 mg/m^2, AUC=5) on days 1-3 of each 21-day cycle for a maximum 6 cycles or before topotecan (TPT, 1.25 mg/m^2) on days 1-5 of each 21-day cycle till disease progression. The primary endpoints were PK, safety and the duration of severe neutropenia (DSN) in cycle 1 for Part 1 and DSN in cycle 1 for Part 2.

Results: From May 2021 to December 2021, a total of 95 Chinese patients were enrolled into the study**.** 12 patients were enrolled in Part 1, 6 patients receiving trilaciclib in combination with E/P and 6 patients receiving trilaciclib in combination with TPT. The PK, safety and myelopreservation in these Chinese patients were comparable with the historic data from patients in western countries, supporting the use of trilaciclib 240 mg/m^2 in Part 2. 83 patients were enrolled in Part 2, 41 patients receiving trilaciclib (23 with E/P and 18 with TPT), and 42 patients receiving placebo (23 with E/P and 19 with TPT). Compared with placebo, trilaciclib treatment prior to chemotherapy resulted in clinically meaningful and statistically significant decreases in DSN in cycle 1 (mean [standard deviation] 0 [1.7] versus 2 [3.0] days; P =0.0003) with 0(0.8) versus 2(2.8) days (trilaciclib+E/P versus placebo+E/P, P=0.0021) and 1(2.4) versus 2(3.3) days (trilaciclib+TPT versus placebo+TPT, P=0.0418) in treatment-naïve and previously treated respectively. Trilaciclib was well tolerated in Chinese patients, with fewer ≥ grade 3 adverse events reported in the trilaciclib group comparing with placebo group. No treatment emergent adverse event leading to death were reported related to trilaciclib.

Conclusions: Trilaciclib 240 mg/m^2 is well tolerated in Chinese patients. The PK profile is comparable with those from patients in western countries. The result from Chinese patients further confirmed that administration of trilaciclib prior to chemotherapy for the treatment of patients with ES-SCLC improves the patient tolerability of chemotherapy, as demonstrated by a reduction in DSN and improved overall safety profile.

Keywords: Trilaciclib, SCLC, Myelopreservation

EP08.02-079 The Use of Lung Adenocarcinoma Patient-Derived Xenografts and Organoids to Study GDP-KRAS G12C Inhibitor Resistance

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Introduction: *KRAS*-mutations are present in 25-30% of the most common form of lung cancer, lung adenocarcinoma (LUAD), and *KRAS*G[12]C mutations account for 40% of *KRAS*-mutations in LUAD. Recent development of covalent GDP-KRASG[12]C inhibitors (G12Ci) have reignited efforts to target the once "undruggable" protein. Preclinical studies have identified mechanisms of adaptive resistance in cell lines. However, patient-derived xenografts (PDX) and xenograft-derived organoids (XDO) have not yet been extensively used to study mechanisms of primary and acquired resistance. Here, we leveraged our *KRASG*[12]C LUAD PDX and XDO model development program to study resistance to these novel targeted agents.

Methods: We developed 12 *KRASG*[12]C PDX models that recapitulate patient response and disease on multi-omic levels. We have also generated 5 long-term (passage >10 or 100 days in culture) XDO from these 12 PDX. PDX models were treated with a covalent G12Ci for four weeks and tumors were harvested for downstream analyses.

Results: A PDX G12Ci drug screen generated responses reminiscent of patients in G12Ci clinical trials, where we observed sensitivity and tumor regression in 4 of 12 models. Tumor necrosis was identified in sensitive tumors, while resistant models remained healthy and proliferative. One model (PHLC194) exhibited adaptive resistance whereby tumor regression occurred for 20-25 days but subsequently grew despite treatment. Continuous G12Ci treatment of PHLC194 for five months led to slow, incremental growth of tumors. These resistant tumors were re-implanted into additional mice and exhibited continued growth and G12Ci resistance. Brief-re-sensitization was noted following drug holiday with subsequent rapid resistance/growth suggesting an initial dependence on *KRASG*[12]C that quickly deteriorated. Continuous treatment with a G12Ci resulted in slower growth than models subjected to drug holiday (Figure 1).

XDO models recapitulate their parent PDX when characterized by flow cytometry, histology, DNA sequencing, and G12Ci response.

Conclusions: *KRASG*[12]C NSCLC PDX models exhibit treatment resistance at similar rates observed in clinical trials. Adaptive resistance in PHLC194 after G12Ci drug holiday and re-initiation suggests that resistance in this model may be driven by G12Ci-resistant subclones. We are presently characterizing mechanism(s) of resistance in G12Ci-resistant PHLC194 using scRNA-/ATAC-seq and these data will be forthcoming. Proteomic analyses of acute and chronically dosed sensitive and resistant tumors are ongoing and will inform of adaptive molecular changes leading to G12Ci resistance. Thus, PDX and XDO are extremely promising models to study resistance to this novel class of inhibitor.

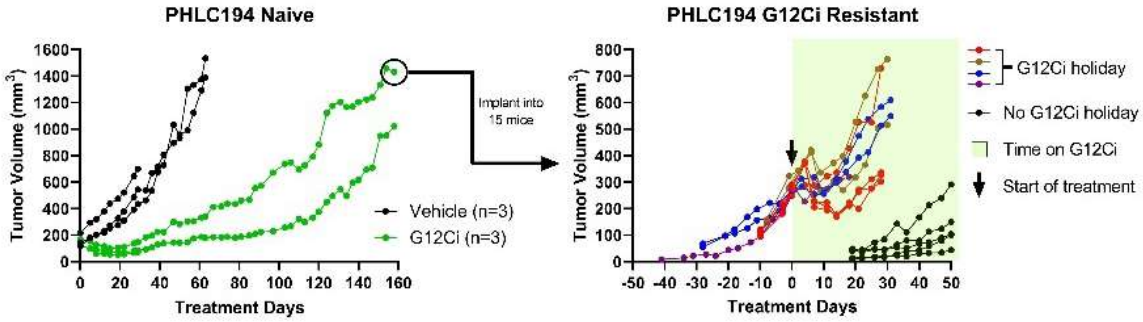

Figure 1. PHLC194 growth curves. Treatments began at day 0 for both plots.

Keywords: KRASG12C inhibitor resistance, Lung adenocarcinoma, patient-derived modeling

EP08.02-080 EGFR Testing Practices, Treatment Choice and Clinical Outcomes in Advanced NSCLC in a Real-World Setting

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Introduction: For patients with advanced NSCLC, clinical guidelines recommend routine testing for EGFR mutations prior to treatment and initiation of an EGFR-TKI at first-line (1L) in patients with EGFR mutation-positive (EGFRm) NSCLC. Real-world implementation of testing and biomarker-informed treatment remains unclear. This retrospective, real-world, US, electronic health records database study describes EGFR testing practices, treatment choice and clinical outcomes in patients with advanced NSCLC.

Methods: Adults with an index diagnosis of stage IIIB-IV NSCLC between 01 January 2015 and 31 January 2020, who received 1L treatment from the Flatiron Health network (>245 US cancer clinics) were included. Demographics/clinical characteristics, EGFR status, turnaround time (TAT; time from advanced diagnosis to EGFR test result), 1L treatment, and time from treatment initiation to discontinuation/death (TTD) or next treatment/death (TTNTD) were extracted from the database. Cox proportional hazards model was used to analyse the association between 1L treatment and TTD/TTNTD, adjusted for EGFR status and other baseline characteristics.

Results: 16,309 patients were eligible: median age was 68 years (range 21, 83); 7581 (46%) were female; 13,507 (83%) had metastatic disease at diagnosis; 12,577 (77%) had ≥1 EGFR test. 1914/12,577 (15%) patients were EGFRm, of whom 1778/1914 (93%) had their result before initiating 1L treatment. Of patients with an EGFRm result before initiating 1L treatment (n=1778), 75% received EGFR-TKIs, 11% chemotherapy, 9% immunotherapy and 4% other treatment, vs 13%, 50%, 19% and 18%, respectively, for patients who received an EGFRm result after initiating 1L treatment (n=136). Median (interquartile range) TAT for test results in patients with EGFRm NSCLC (n=1914) was 18 (12.0, 28.5) days in patients who received 1L EGFR-TKIs vs 31 (19.5, 67.5), 30 (19.8, 49.2) and 32.5 (20.0, 66.2) days for 1L chemotherapy, immunotherapy and other treatment, respectively. Of patients with EGFRm NSCLC who did not receive 1L EGFR-TKIs (n=563), 311 (55%) received an EGFR-TKI at 2L and beyond. Patients with EGFRm NSCLC who received 1L chemotherapy, immunotherapy or other treatment had shorter TTD and TTNTD vs those who received 1L EGFR-TKIs (Table).

Conclusions: This preliminary real-world analysis shows that not all patients received an EGFR test, and a quarter of those with an EGFRm result before initiating 1L treatment did not receive an EGFR-TKI. Clinical outcomes (TTD/TTND) were better in patients receiving 1L EGFR-TKIs vs other treatments. These data reinforce the need to improve testing implementation and reduce TAT to ensure patients receive optimal 1L therapy.

Table. TTD and TTNTD by 1L treatment type*

	EGFR-TKI (n=1426)	Chemotherapy (n=4912)	Immunotherapy (n=4245)	Other (n=1994)
Median TTD, months (95% CL)	11.3 (10.5, 12.1)	3.2 (3.2, 3.3)	3.0 (3.0, 3.1)	4.2 (4.1, 4.2)
Event rate, %	76.3	93.5	87.7	91.9
HR (multivariable) from the CPhM for TTD, adjusted for EGFRm status and BL characteristics (95% CI; p-value)	Reference	3.06 (2.72, 3.44; p<0.001)	2.70 (2.40, 3.03; p<0.001)	2.56 (2.26, 2.88; p<0.001)
Median TTNTD, months (95% CL)	13.4 (12.6, 14.1)	6.2 (6.1, 6.4)	8.4 (8.1, 8.8)	7.7 (7.3, 8.0)
Event rate, %	76.3	89.6	77.8	90.6
HR (multivariable) from the CPhM for TTNTD, adjusted for EGFRm status and BL characteristics (95% CI; p-value)	Reference	2.81 (2.50, 3.15; p<0.001)	1.63 (1.45, 1.83; p<0.001)	2.07 (1.84, 2.34; p<0.001)

*Of the cohort of patients with evidence of ≥1 EGFR test, irrespective of EGFR mutation status (N=12,577)
1L, first-line; BL, baseline; CI, confidence interval; CL, lower and upper bounds of confidence limit; CPhM, Cox proportional hazards model; EGFRm, epidermal growth factor receptor mutation-positive; HR, hazard ratio; IQR, interquartile range; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation/death; TTNTD, time to next treatment/death.

EP08.02-081 Cabozantinib Plus Atezolizumab in First or Second-Line Advanced NSCLC and Previously-Treated EGFR Mutant Advanced NSCLC

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Introduction: Cabozantinib, a multitargeted receptor tyrosine kinase inhibitor (TKI), promotes an immune-permissive environment that may enhance immune checkpoint inhibitor (ICI) activity. COSMIC-021 (NCT03170960) is a multicenter phase 1b study evaluating cabozantinib plus atezolizumab in advanced solid tumors. In COSMIC-021, cabozantinib plus atezolizumab demonstrated encouraging clinical activity in a cohort of patients with advanced NSCLC (aNSCLC) previously treated with ICIs (Neal. ASCO 2020. Abstr 9610). Outcomes of cabozantinib plus atezolizumab in first or second-line aNSCLC (cohort 8 [C8]) and previously-treated EGFR mutant aNSCLC (cohort 9 [C9]) are presented.

Methods: Patients with stage IV nonsquamous aNSCLC were eligible for C8 and C9. Patients with PD-L1 positive aNSCLC (≥1% in tumor tissue) and ≤1 prior lines of systemic anticancer therapy, no prior ICI, and without EGFR, ALK, ROS1, or BRAF V600E mutations were eligible for C8. C9 enrolled EGFR mutant aNSCLC previously treated with ≥1 EGFR-TKI with no limit on the number of prior therapies. Patients received cabozantinib 40 mg PO QD plus atezolizumab 1200 mg IV Q3W. Primary endpoint was ORR per RECIST 1.1 by investigator. Other endpoints included safety, duration of response (DOR), PFS, and OS. CT/MRI scans were performed Q6W for the first year and Q12W thereafter.

Results: Twenty-nine and 30 patients received cabozantinib plus atezolizumab in C8 and C9, respectively; baseline characteristics were as follows: median age, 65 y, 62 y; male, 55%, 40%; ECOG PS 1, 76%, 87%; liver metastasis, 21%, 17%; 0,1, ≥2 lines of therapy, 79%, 21%, 0 and 33%, 23%, 43%. As of Nov 30, 2021, median follow-up (range) was 19.9 months (6.1, 37.8) and 26.2 months (18.9, 32.3) for C8 and C9, respectively, with 9 (31%) and 1 (3%) on study treatment. Preliminary clinical activity was observed in both cohorts and in C8 irrespective of PD-L1 expression levels (Table). Most common treatment-related adverse events (TRAEs) of any grade for C8 and C9 respectively, included diarrhea (38%, 20%), aspartate aminotransferase increased (31%, 17%), nausea (21%, 20%), decreased appetite (17%, 20%), palmar-plantar erythrodysesthesia (17%, 17%), and fatigue (17%, 17%); grade 3/4 TRAEs occurred in 41% and 27%, and one grade 5 TRAE occurred in C8 (drug hypersensitivity).

Conclusions: Cabozantinib plus atezolizumab demonstrated clinical activity in first or second-line PD-L1- positive aNSCLC and more modest activity in previously-treated EGFR mutant aNSCLC; toxicities were manageable in both cohorts.

	First or second-line PD-L1 positive aNSCLC (C8)‡			EGFR mutant aNSCLC, previously treated (C9) (N=30)
	All patients (N=29)	PD-L1 1%-49% (n=17)	PD-L1 ≥ 50% (n=11)	
ORR, % (95% CI)	28 (13, 47)	24 (7, 50)	36 (11, 69)	7 (1, 22)
Best overall response, n (%)				
- Complete response (CR)	1 (3)	0	1 (9)	0
- Partial response (PR)	7 (24)	4 (24)	3 (27)	2 (7)
- Stable disease (SD)	15 (52)	10 (59)	4 (36)	17 (57)
- Progressive disease	2 (7)	1 (6)	1 (9)	7 (23)
Disease control rate, % (95% CI)*	79 (60, 92)	82 (57, 96)	73 (39, 94)	63 (44, 80)
Median DOR, mo (95% CI)	NE (2.8, NE)	7.4 (2.8, NE)	NE (NE, NE)	15.2 (NE, NE)
Median PFS, mo (95% CI)	4.7 (2.8, 8.4)	4.7 (2.8, 8.4)	7.5 (1.5, NE)	2.7 (1.5, 3.5)

Median OS, mo (95% CI)	14.7 (5.1, 20.5)	12.0 (3.3, 20.5)	15.7 (1.6, NE)	6.1 (3.9, 11.8)

*CR + PR + SD.

‡PD-L1 level was unknown in one patient.

Keywords: non-small cell lung cancer, cabozantinib, atezolizumab

EP08.02-082 Treatment Patterns and Outcomes of First-line Osimertinib-treated Advanced EGFR Mutated NSCLC Patients: A Real-world Study

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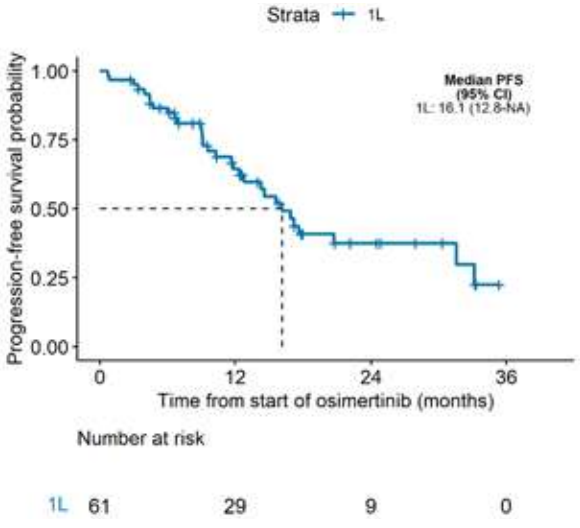
Introduction: Based on the survival benefit seen in the FLAURA trial, first-line osimertinib has become the standard-of-care for patients with EGFR mutation in advanced non-small cell lung cancer (NSCLC). However, treatment options are limited after progression on osimertinib. We explored survival outcomes, subsequent treatment lines, and metastatic sites post-osimertinib in patients with EGFR-mutated NSCLC treated with first-line osimertinib in a real-world setting.

Methods: All patients with stage IV EGFR-mutated NSCLC treated with first-line osimertinib at Princess Margaret Cancer Centre (Toronto, Canada) were included. Clinico-demographic data were retrospectively collected from electronic records. Progression free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method.

Results: Between January 2019 and September 2021, 61 patients with EGFR-mutated NSCLC treated with first-line osimertinib were identified. Median age was 66.5 years (IQR, 59.0-74.0), 32.8% were male, 73.9% were Asian. Median PFS was 16.1 (95% CI 12.8-NR) months, and median OS was not reached (95% CI 24.7-NR). The median follow-up time for PFS and OS were 12.6 (range, 2.7-35.3) and 16.3 (2.7-37.6) months, respectively. Twenty-seven (44.3%) patients discontinued osimertinib permanently due to disease progression or death (66.7% of n=27), toxicity (22.2%) or complications from comorbidities (11.1%). Subsequent lines of treatment after stopping first-line osimertinib were pemetrexed platinum chemotherapy (52.2% of all who discontinued), osimertinib + trial agent (13.0%), or afatinib (4.3%); 30.4% of patients received no further treatment due to frailty (57.1%) or death shortly after stopping osimertinib (42.9%). Thirty (49.2%) patients progressed on osimertinib. Bone (n=12), brain (n=4), locoregional lymph node (n=11), distant lymph node (n=3), adrenal (n=3), liver (n=3), lung (n=14), pleura (n=6) and pancreas (n=1) were the sites of metastatic progression on osimertinib.

Conclusions: In a real-world setting, patients with EGFR-mutated NSCLC treated with first-line osimertinib demonstrated comparable median PFS to the FLAURA trial. Disease progression constituted the main reason for osimertinib permanent discontinuation; under 10% of patients discontinued osimertinib due to toxicity. Chemotherapy was the most common subsequent treatment after disease progression, though one-third did not go onto a second-line therapy. Osimertinib in the Canadian real-world setting has similar outcomes as FLAURA trial with low discontinuation rates due to toxicity, and a subset having treatment beyond progression. Eventual failure of osimertinib from progressive disease continues to be a major obstacle to long term EGFR-mutated NSCLC control, especially when one-third of patients who progressed on osimertinib does not go onto other systemic therapy.



Keywords: osimertinib, EGFR, NSCLC

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-083 Real World Treatment and Outcomes in EGFR-mutated Advanced Non-small Cell Lung Cancer Patients: A Nationwide Cohort for 1,932 Thai Patients

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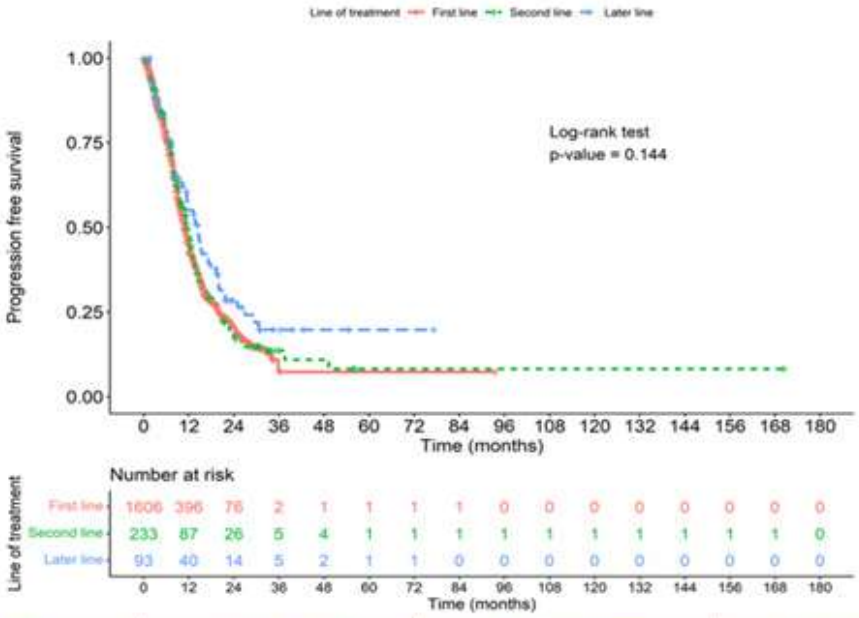
Introduction: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) are a standard of care for patients with advanced *EGFR* mutated non-small cell lung cancer (NSCLC). In Thailand, gefitinib has been approved for reimbursement under the Civil Servant Medical Benefit Scheme (CSMBS) for the treatment in these patients. Therefore, this retrospective cohort study examined the patient characteristics and clinical outcomes of Thai patients with *EGFR*-mutated NSCLC in a real-world setting.

Methods: Data were extracted from the Oncology Prior Authorization program (OCPA) database under the Comptroller General's Department of Thailand. All advanced *EGFR*-mutated NSCLC patients who had received gefitinib between January 2018 and December 2020 were included. Patient demographic, treatment data, and outcome data were collected and analyzed.

Results: Among the total of 1,932 advanced *EGFR*-mutated NSCLC patients were identified, the number of patients who received gefitinib as first-line, second-line, and later-line treatment were 1,606 (83.2%), 233 (12%), and 93 (4.8%), respectively. Median age was 66 years (range, 18-96 years) and the majority were female (62%), Eastern Cooperative Oncology Group performance status of 0 to 1 (79.9%), and adenocarcinoma histology (92.8%). The most common *EGFR* mutation was Exon 19 deletion (53.9%), followed by L858R mutation (38.8%), uncommon mutations (3.4%), and complex mutations (1.9%). Majority of patients (73.1%) had metastasis site ≤ 2 and brain metastasis was present at baseline in 13.4% of patients. The median progression free survival (PFS) in first-, second-, and later-line treatment were 11.2 months (95% CI, 10.6-11.5), 11.6 months (95% CI, 10.1-12.9), and 14.5 months (95% CI, 11.5-19.3), respectively. The overall response rate (ORR) was not different across treatment lines. The ORR and disease control rate in all patients were 48.5% and 72.8%, respectively. On multivariate analysis, the significant worse prognostic factors for PFS were age<70 years, poor performance status, the number of metastases > 2 sites, liver metastasis, bone metastasis, non-adenocarcinoma histology, and L858R *EGFR* mutations ($P < 0.05$).

Conclusions: Our data from a nationwide real-world cohort showed the characteristics and outcomes of *EGFR*-mutated advanced NSCLC in Thai patients, including *EGFR* mutation pattern and PFS, were generally consistent with randomized phase III trials. EGFR TKI has exhibited efficacy for *EGFR*-mutated NSCLC patients in all lines of treatment. Further real-world studies are needed to characterize patient outcomes for emerging therapies or a rare subgroup of NSCLC patient, outside of a clinical trial setting.

Figure 1 Kaplan-Meier curves of progression-free survival stratified by the line treatment groups



PFS	First-line (N=1,606)	Second-line (N=233)	Later line (N=93)
Median PFS, months (95%CI)	**10.9** (10.3-11.5)	**11.6** (10.1-12.9) **HR 0.97** (0.82-1.15), P=0.718	**14.5** (11.5-19.3) **HR 0.77** (0.59-1), P=0.051
1 Year PFS, % (95%CI)	**43.5** (40.7-46.6)	**47.9** (41.4-55.3)	**55.0** (45.1-67.1)
2 Year PFS, % (95%CI)	**20.6** (17.8-23.9)	**17.8**(12.8-24.6)	**28.4** (19.6-41.1)

Keywords: EGFR mutation, gefitinib, NSCLC

EP08.02-084 Evaluation of Tumor Heterogeneity (TH) as a Prognostic Biomarker in Osimertinib treated Non-Small Cell Lung Cancer Patients

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Introduction: Precision oncology has largely focused on the development of predictive biomarkers for targeted and immunotherapies, however little is understood about prognostic genomic biomarkers associated with duration of response. Predicting the duration of therapeutic benefit at baseline could have significant clinical implications for combinatorial treatment strategies, next-line therapy decisions and tailoring novel monitoring capabilities based on likelihood of relapse. Measuring the genomic heterogeneity of tumors based on a single, pre-treatment tissue biopsy may give insight into the duration of therapeutic response based on Darwinian evolution principles of tumors under a given selection pressure. Tumors with little genomic diversity and from an evolutionary standpoint have less overall fitness, may require more time to accumulate the necessary mutations required to achieve resistance. In contrast, tumors with higher genomic diversity may require less time to accumulate and select for a resistance mutation and therefore associate with shorter response durations. In this way, measuring the baseline tumor's genomic heterogeneity may serve to predict the duration of response to a particular therapy.

Methods: This retrospective study evaluated 135 *EGFR* driver alteration positive pre-treatment tissue tumor specimens, sequenced from non-small cell lung cancer patients treated with 1L osimertinib, from a real-world (rw) de-identified Flatiron Health-Foundation Medicine clinico-genomic (CGDB) database. Cancer cell fraction (CCF), defined as the fraction of tumor cells from the sequenced specimen carrying a given short variant, was estimated for every somatic short variant detected per specimen. A novel TH score defined as the ratio of the median to the quartile co-efficient of dispersion (QCD) of the CCF of all short variants, was calculated per patient. A binary TH score threshold of >=1 (median greater than or equal to the QCD) was used to identify a TH high group.

Results: Amongst the 135 patients, median age was 69.0 years, 65.9% were female, 85% had stage IV disease and 54.1% had an ECOG (Eastern Cooperative Oncology Group) status under 2. *EGFR* L858R and exon 19 deletion constituted 45.9% and 54.1% of the cohort, respectively. The rw median progression free survival from start of 1L osimertinib (rwPFS), was 12.7 [10.5-16.0] months for the cohort. TH low group (n=49) had a significantly higher rwPFS when compared to the TH high group (n=86; 16.0 vs 10.8 months, hazard ratio=0.55, p=0.02). Further subgroup analysis to identify oncogene addicted tumors based upon high *EGFR* CCF (>= 0.5) and low TH (n=39) compared to low *EGFR* CCF (< 0.5) and high TH (n=12) yielded a rwPFS of 16.0 months vs. 6.5 months (p=0.05), respectively.

Conclusions: These findings suggest that a TH metric from a single baseline pre-treatment tissue biopsy can potentially predict the durability of response to osimertinib in *EGFR* driver alteration positive NSCLC cases. These results require further validation in external clinical cohorts; however, our preliminary analysis suggests that this method can effectively stratify responses to targeted therapy in a 1L setting.

Keywords: Tumor heterogeneity, Non-small cell lung cancer, EGFR targeted therapy

EP08.02-085 In vitro Activity and Potential Resistance Mutations Against BI-4020, a 4th-generation EGFR-TKI

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Introduction: First-, second-, and third-generation (G) epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are now available in clinical practice. Since acquisition of T790M and C797S mutations confer resistance to 1G/2G and 3G EGFR-TKIs, respectively, several 4G EGFR-TKIs that can inhibit triple mutations of activating mutation/T790M/C797S are now being developed. In this study, we evaluated an *in vitro* activity and potential resistance mutations to one of the 4G EGFR-TKIs, BI-4020, using Ba/F3 models.

Methods: Ba/F3 cells driven by *EGFR* mutation(s) were used in this study. Ba/F3 cells with wild-type *EGFR* (+ 10ng/ml EGF supplemented) were also used to evaluate wild-type EGFR sparing ability of the TKIs. *In vitro* growth inhibitory assay was performed using Cell Counting Kit-8 after 72 h of TKI exposure. ENU (N-ethyl-N-nitrosourea) mutagenesis technique was applied to obtain acquired resistant cells against BI-4020.

Results: We observed that BI-4020 was active against Ba/F3 cells with *EGFR* exon 19 deletion (Del19) or L858R mutation irrespective of the presence of T790M and/or C797S mutations (Table 1). Although BI-4020 was wild-type EGFR sparing, BI-4020 was less active against *EGFR* exon 20 insertion mutations including A763insFQEA that is sensitive to the 1G-3G EGFR-TKIs. Several secondary mutations involving codons E709, L718, K754, and T854 were detected in the ENU mutagenesis as a potential mechanism of resistance. Among them, however, only E709G and L718Q conferred high-level resistance to BI-4020 when L858R was present as a sensitizing mutation. None of these secondary mutations conferred high-level resistance to BI-4020 when Del19 was a sensitizing mutation.

Table 1. Summary of IC50 values

Mutation type	Elrotinib (1G)	Afatinib (2G)	Dacomitinib (2G)	Osimertinib (3G)	BI-4020 (4G)
Parental Ba/F3 + IL3 (5ng/ml)	10000>	3298	2601	2842	2034
Wild-type EGFR + EGF (10ng/ml)	52	17	34	221	158
Del19	2.3	0.2	0.2	1.2	0.7
Del19+T790M	2036	34	225	1.7	0.4
Del19+C797S	2.0	2.2	2.3	869	0.4
Del19+T790M+C797S	3643	1300	1244	1134	0.4
L858R	7.6	0.3	0.4	2.6	6.3
L858R+T790M	10000>	105	329	6.0	1.3
L858R+C797S	15	20	27	2799	4.4
L858R+T790M+C797S	10000>	2987	1295	2685	1.1
A763insFQEA	NE	NE	NE	17	125
V769insASV	NE	NE	NE	220	809
D770insSVD	NE	NE	NE	140	596
H773insNPH	NE	NE	NE	114	290
H773insH	NE	NE	NE	156	366

Conclusions: BI-4020, a 4G EGFR-TKI, will be able to overcome both of T790M/C797S exon 20 mutations. However, acquisition of exon 18 mutations (E709G and L718Q) may cause resistance to BI-4020 when L858R is a sensitizing mutation.

Keywords: acquired resistance, EGFR tyrosine kinase inhibitors, EGFR mutation

EP08.02-086 Randomized Double-blind Placebo-controlled trial of Nicotinamide and EGFR-TKIs for EGFR-mutated Lung Adenocarcinoma

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Introduction: Runt-related gene 3 (RUNX3) inactivation by promoter hypermethylation correlates with poor clinical outcome and occurs in 70% of lung adenocarcinomas. Nicotinamide, a well-known sirtuin inhibitor, re-activates the epigenetically silenced tumor suppressor RUNX3 in cancer cells. We examined whether the addition of nicotinamide to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) increases the survival of stage IV lung cancer patients with EGFR mutations (exon 19 or 21 mutation).

Methods: From 2015 to 2018, a total of 110 consecutive patients were randomized into nicotinamide (1g/day, n=55) or placebo (n=55) groups, stratified by EGFR mutation status, ECOG performance status, and type of TKIs. Nicotinamide or placebo was administered upto 2 years.

Results: The mean age was 68.5 years, and 63.6% were female and 76.4% were never-smokers. Gefitinib was used in 59.1% of patients and erlotinib in the remaining 40.9%, resulting in an objective response of 56.0%. The number of adverse events, such as skin rash, mucositis, and diarrhea, was not different between the two groups. After a median follow up duration of 54.3 months, the median PFS of the nicotinamide group was 12.7 months (95% confidence interval: 10.4~18.3) whereas that of the placebo group was 10.9 months (9.0~13.2) (Log-rank p=0.2, Fig 1A). After a median follow up duration of 58.4 months, the median OS of the nicotinamide group was 31.0 months (25.2~45.2) whereas that of the placebo group was 29.4 months (20.3~35.6) (p=0.2, Fig 1B). After progression, the EGFR T790M mutation was found in 44 (40.0%) of patients using re-biopsy or plasma DNA samples, and third generation EGFR TKIs were used in 42 (38.2%) subjects, without a significant difference between the two groups.

Conclusions: PFS and OS were numerically longer when EGFR TKIs were used in combination with nicotinamide than when patients were treated with EGFR TKIs alone. (ClinicalTrials.gov Identifier: NCT02416739)

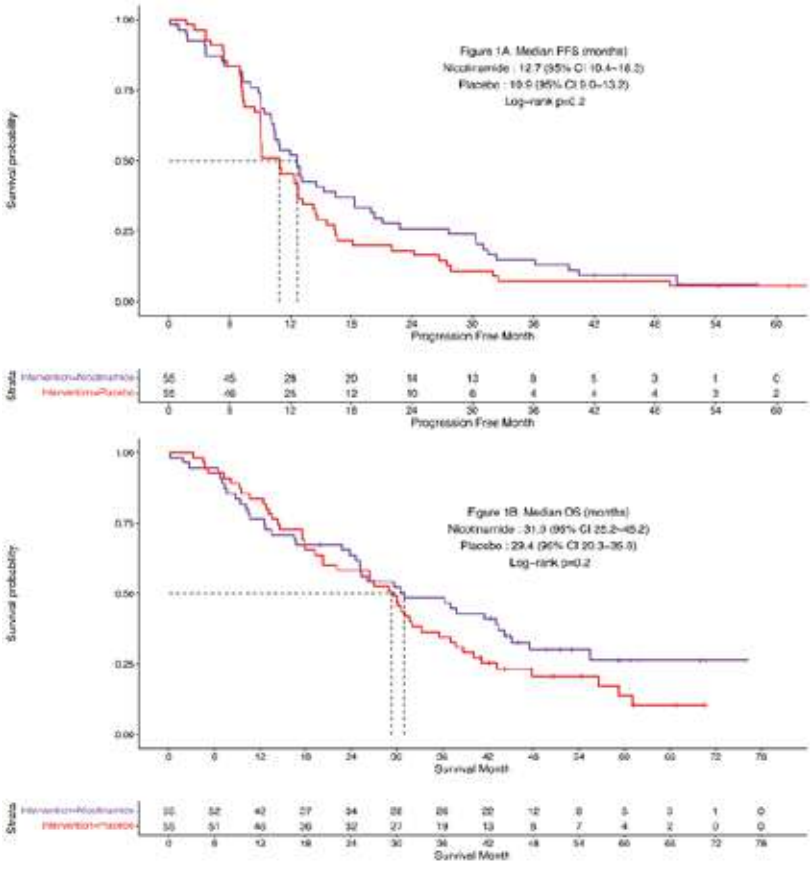

Table 1. Characteristics of patients in the Nicotinamide and Placebo groups.				
(%)	**Total (n=110)**	**Nicotinamide (n=55)**	**Placebo (n=55)**	**P value**
Age (years ± SD)	68.5 ± 10.4	67.7 ± 10.0	69.2 ± 10.9	0.450
Sex Female	7063.6)	34(61.8)	36(65.5)	0.843
Weight (Kg ± SD)	60.0 ± 10.0	61.2 ± 10.1	58.7 ± 9.8	0.190
Smoking (Never, Current, Ex-smoker)	84(76.4), 11(10.0), 15(13.6)	39(70.9), 8(14.5), 8(14.5)	45(81.8), 3(5.5), 7(12.7)	0.251
ECOG PS score (0, 1, 2)	13(11.8), 76(69.1), 21(19.1)	5(9.1), 40(72.7), 10(18.2)	8(14.5), 36(65. 5),11(20.0)	0.622
EGFR mutation (Ex 19 del, Ex 21 point mutations)	66(60.0), 44(40.0)	33(60.0), 22(40.0)	33(60.0), 22(40.0)	0.489
Erlotinib, Gefitinib	45(40.9), 65(59.1)	23(41.8), 32(58.2)	22(40.0), 33(60.0)	1.000
Response (CR or PR, SD, PD, NE)	61(56.0), 43(39.4), 2(1.8), 3(2.8)	31(56.4), 20(36.4), 2(3.6), 2(3.6)	30(55.6), 23(42.6), 0(0.0), 1(1.9)	0.098
PD state (Progressed, Not progressed, Lost)	102(92.7), 7(6.4), 1(0.9)	50(90.9), 5(9.1), 0(0)	52(94.6), 2(3.6), 1(1.8)	0.280
Survival state (Live, Dead, Lost)	22(20.0), 84(76.4), 4(3.6)	15(27.3), 38(69.1), 2(3.6)	7(12.7), 46(83.6), 2(3.6)	0.160
T790M (Negative, Positive, Not Done)	34(30.9), 44(40.0), 32(29.1)	19(34.5), 20(36.4), 16(29.1)	15(27.3), 24(43.6), 16(29.1)	0.659
3rd generation TKI (Yes, No)	42(38.2), 68(61.8)	20(36.4), 35(63.6)	22(40.0), 33(60.0)	0.292

Keywords: RUNX3, Nicotinamide, EGFR

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-087 A 28-Years Old Pregnant Woman Diagnosed as ALK-Rearrangement Lung Adenocarcinoma with Multiple Brain Metastasis - Case Report

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Introduction: Lung adenocarcinoma is the most common lung cancer type representing about 40% of all cases. ALK gene rearrangement is present in 3-5% of lung adenocarcinoma patients, typically in younger women and non-smoker subgroup. The incidence of malignant tumors during pregnancy is low (0.1%), the most common types are breast, uterine, cervical, and ovarian cancer. The incidence of lung cancer among pregnant women has risen slightly in the past two decades due to a higher incidence of smoking in young women and a higher age at the time of first pregnancy. However, it is still a rare diagnosis.

Methods: Case presentation.

Results: A 28-year-old woman, a non-smoker at 37 weeks of gestation, was acutely referred to the gynecology and obstetrics department for sudden confusion, nausea, and memory impairment with suspected eclampsia. On December 8, 2020, an urgent C-section was performed. Postpartum the patient had recurrent seizures, which progressed to *status epilepticus*. The condition required continuous analgesic-sedative and anticonvulsant treatment at ICU. According to serious neurological symptoms, the patient underwent a CT scan of the brain, which showed multiple expansive metastatic lesions of the brain. CT staging described a primary tumor in the left lung upper lobe with metastasis in the left lung lower lobe and suspect liver metastatic lesion. CT-guided core-needle biopsy of the primary lung tumor confirmed the adenocarcinoma. MRI confirmed multiple supra- and infratentorial brain metastatic lesions. Due to the number, size, location of metastases, and persistent neurological symptoms, the patient underwent whole-brain radiotherapy. Further genetic examination of the bioptic sample confirmed ALK rearrangement. Due to the need for high intracranial efficacy, the first-line treatment with second-generation ALK-tyrosine kinase inhibitor (alectinib) was started immediately. Brain MRI scan after 4 weeks of treatment (22.01.2021) showed 70-90% size regression of brain metastases, as well as partial remission of the primary tumor in the control chest x-ray. After 11 months of alectinib treatment, the patient's clinical condition and performance were excellent, except for the newly presented pain located in the left pelvic area. MRI documented persisting almost complete remission of intracranial metastases. However, a control chest CT scan verified a 20% progression of the size of the primary tumor. PET-CT scan showed systemic disease progression, in addition to the progression of the primary tumor, a new skeletal metastasis in the left ilium was found. After 11 months of alectinib patient´s treatment was changed to the third generation ALK-TKI lorlatinib. During the lorlatinib treatment, the patient developed severe hyperlipidemia due to which treatment had to be discontinued repeatedly.

Conclusions: It is a big challenge for clinicians to manage malignant intracranial lesions in pregnant patients, deciding on the optimal strategy to minimize the risk to the mother and fetus. In this case report, we present significant intracranial and systemic effects of second and third-generation ALK-TKI in advanced lung adenocarcinoma. We also aim to the importance of molecular-genetic testing in young non-smokers, with lung adenocarcinoma. Malignancy during pregnancy is a scarce condition, however, it is important to keep this option in mind.

Keywords: ALK-TKI, advanced lung adenocarcinoma, pregnancy

EP08.02-088 Mutational Status of KRAS, STK11 and CDKN2A Genes as Predictors of Response to Antiangiogenic Agents in Non-small Cell Lung Cancer Patients

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Introduction: Lung cancer is the leading cause of cancer deaths worldwide. Antiangiogenic agents have been established as one of the various treatment options for this type of tumor. However, it has not been possible to establish a biomarker that allows the selection of patients who will most benefit from this treatment. Recent publications suggest that the response to antiangiogenic agents is influenced by the presence of *KRAS*, *TP53* or *STK11/LKB1* gene mutations. The aim of this study was to establish the relationship between the presence of tumor mutations and the response to antiangiogenic agents.

Methods: We conducted a retrospective study, which included patients diagnosed with non-small cell lung cancer in our hospital from 2014 to 2020 and treated with antiangiogenic agents. An inclusion criterion was that all patients had a next generation sequencing (NGS) performed on tumor tissue or blood (FoundationOne or Guardant360). Data regarding baseline and molecular characteristics, treatment response and survival were collected. A descriptive analysis was carried out, followed by a survival analysis using the Kaplan-Meier estimator.

Results: We enrolled 18 patients throughout this period. The male-female ratio was 3-1, with an average age of 53 years old. All patients received antiangiogenic agents at some point during their disease: bevacizumab and nintedanib were the most frequent drugs (44,4% each) followed by cabozantinib and ramucirumab. Regarding the molecular profiling, the most frequently found mutations were: *TP53* (50%), *STK11* (38,9%), *KRAS* (33,3%), *APC* (22,2%), *CDKN2A* (22,2%) and *MTOR* (22,2%). Progression-free survival (PFS) during antiangiogenic therapy was evaluated according to the most frequent mutations found. The median PFS in patients with *KRAS* mutations was shorter (10 months [95% confidence interval (CI): not reached]) than patients with *KRAS* wild-type (31 months [95%CI: 0 - 20]), without statistically significant differences. The median PFS among patients with *STK11* mutations was longer (30 months [95%CI: 19.7 - 40.3]) than patients with *STK11* wild-type (20 months [95%CI: 4.5 - 35.5]), without statistically significant differences. The median PFS in patients with *CDKN2A* mutations was shorter (10 months [95%CI: 0 - 21.8]) than patients with *CDKN2A* wild-type (30 months [95%CI: 21.8 - 38.2]) without statistically significant differences.

Conclusions: Our study is framed in the context of translational oncology and showed that patients treated with antiangiogenic agents with mutations in *CDKN2A* and *STK11* and *KRAS* wild type had longer PFS without reaching statistical significance, possibly due to the small sample size of our study. Therefore, the presence of these mutations could predict the response to antiangiogenic agents. However, it is recommended that future studies be conducted with a larger sample to confirm these findings.

Keywords: Lung cancer, Antiangiogenic agents, Mutational status

EP08.02-089 Toxicity of Sequential Tyrosine Kinase Inhibitors After Immune Checkpoint Inhibitors in Advanced Non-small Cell Lung Cancer

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Introduction: Concerning safety signals have been noted with immune checkpoint inhibitors (ICI) in patients concurrently or sequentially treated with tyrosine kinase inhibitors (TKIs) with increased rates of pneumonitis and hepatotoxicity. The objective of this study is to characterize and evaluate the toxicity of real-world non-small cell lung cancer (NSCLC) patients who receive sequential ICI then targeted therapy.

Methods: A retrospective study of stage IV NSCLC patients referred to BC Cancer between 2017-2021 treated with ICI followed by TKI was conducted. Patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status (PS), staging, mutation status, treatment, toxicity, and survival data were collected retrospectively. Toxicity resulting in treatment break/discontinuation or initiation of oral steroids was recorded. The next generation sequencing panel included oncogenes and tumor suppressor genes for solid tumors. Descriptive statistics were produced.

Results: Between 2017-2021, 1643 Stage IV NSCLC patients received ICI with 30 patients receiving sequential ICI prior to TKIs. Baseline characteristics of the 30 patients: median age 67.5 years, male 37%, never/former/current smoker 40/33/27%, median 40 pack-year smoking history, ECOG 0-1/≥2 87/13%, Asian/non-Asian race 55/45%. Tumor characteristics: non-squamous histology 80%, PDL1 <1/1-49/≥50%/unknown 20/20/33/27%. NGS assay found mutations in 2 MET exon 14 skip, 2 HER2 exon 20, 2 EGFR exon 20, 3 activating EGFR mutation and 21 had no identified mutations. Treatment details: first/second line IO 9/21; pembrolizumab/nivolumab 8/22, crizotinib/poziotinib/afatinib/gefitinib/erlotinib 1/1/3/3/22. Immune related adverse events were seen in 5 patients while on ICI requiring treatment break/discontinuation and/or steroids included pneumonitis, autoimmune hemolytic anemia, adrenal insufficiency, colitis and stomatitis. Median onset to ICI toxicity was 4.1 months. Patient characteristics included: PDL1 <1/1-49/≥50%/unknown 1/2/0/2, 1 mutation: EGFR exon 20. One patient who received sequential IO and TKI required treatment break/discontinuation on TKI (afatinib) due to pneumonitis. This patient had a PDL1 >50% with an EGFR exon 19 deletion.

Conclusions: Less than 1% of our targeted mutation positive population received ICI upfront, demonstrating appropriate initiation of treatment after the availability of the NGS assay results. In our stage IV NSCLC population, there was no significant safety signal with sequential treatment of ICI followed by TKI; only one patient required treatment break/discontinuation due to pneumonitis. This differs from existing literature possibly because the majority of our population did not harbour a driver mutation and there were limited patients treated with crizotinib, ceritinib and osimertinib, other agents that have been associated with this safety signal. Further studies should be conducted to understand the frequency and treatment implications of sequential ICI and targeted therapy.

EP08.02-090 Sotorasib Drug-Drug Interactions: Essential Guidance Requested by Physicians Worldwide

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Introduction: The life expectancy of advanced stage non-small cell lung cancer patients has increased significantly over the last years due to the introduction of immunotherapy and multiple targeted therapies. One of the most recent important developments is the registration of the KRAS p.G12C targeting agent sotorasib (LUMAKRAS/LUMYKRAS®). The KRAS p.G12C driver mutation is one the most prevalent driver mutations in NSCLC, occurring in 13% of lung adenocarcinomas. Sotorasib causes relevant drug-drug interactions (DDIs), both as a perpetrator (P-gp inhibitor, CYP3A4 inducer) and as a victim (CYP3A4 and P-gp substrate) which may lead to (cancer) treatment inefficacy or serious side effects. As polypharmacy occurs in more than half of all patients with lung cancer, DDIs with sotorasib challenge optimal drug treatment. The aim of this research was to investigate the need for physician guidance on DDIs to support safe and effective treatment with sotorasib in routine clinical practice worldwide.

Methods: To identify the most relevant DDIs with sotorasib in the real-world setting, the most requested drug combinations from the Cancer Interaction Checker developed by RadboudUMC and University of Liverpool (www.cancer-druginteractions.org) were determined. Next, their DDI potency was mapped by determining the DDI grading using an established grading system with a 'traffic light' classification.

Results: Potential DDIs between sotorasib and 409 comedications have been classified. Of all sotorasib-comedication combinations requested, 48% of them are categorised red or amber and thus, require intervention by the treating physician (figure 1). The most frequently requested sotorasib-comedication combinations include direct oral anticoagulants (DOACs, 16% of all requests) and acid-reducing drugs (H2-antagonists, proton-pump inhibitors and antacids, 12% of all requests).

Conclusions: Clearly a clinical need exists for guidance on combining sotorasib with other medication. Questions about real-life drug combinations applied to relevant DDI in approximately half of all cases. Guidance is often requested for DOACs and acid-reducing drugs and often requires intervention when coadministered with sotorasib. Our results underline the need for practical guidance for handling relevant DDIs with the novel drug sotorasib in daily practice. Furthermore, there is clear need for DDI studies of sotorasib with DOACs, to enable safe treatment in daily practice.

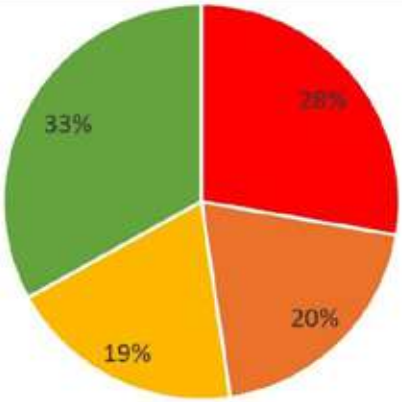

Figure 1. Sotorasib-comedication combinations requests: frequencies and categorisation. Green: no DDI / irrelevant DDI; yellow: DDI of weak intensity, no action required; amber: DDI of potent intensity, requires strict monitoring and/or dose adjustment(s); red: DDI of potent intensity, combination is contra-indicated.

Keywords: sotorasib, drug-drug interactions

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-091 Disease Monitoring of EGFR-mutated NSCLC Patients Treated with TKIs via EGFR Status in Circulating ctDNA

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Introduction: Circulating tumor DNA (ctDNA) monitoring proves to be a promising approach to assess response and predict survival in epidermal growth factor receptor (*EGFR*)-mutated non-small-cell lung cancer (NSCLC) patients treated with tyrosine kinase inhibitors (TKIs). However, whether the dynamic changes in ctDNA *EGFR* mutation status have the same predictive value as ctDNA remains unknown. This study aims to explore the predictive value of dynamic changes in both ctDNA and ctDNA *EGFR* status.

Methods: A retrospective analysis was performed using 91 ctDNA samples from a cohort of 28 patients who were diagnosed with *EGFR*-mutated NSCLC and treated with *EGFR*-TKIs, including 14 patients treated with first-/second-generation TKIs, and 14 treated with Osimertinib. Blood samples at baseline (BL), within 4 weeks after TKI initiation (Week4), within 12 weeks before progression (pre-PD), and at progression were collected. The relationship alternatives in ctDNA status, ctDNA *EGFR* status and response to *EGFR*-TKIs as well as progression-free survival (PFS) were analyzed.

Results: We categorized 20 BL-ctDNA positive patients with available Week4-ctDNA into two groups: ctDNA-clearance (N=7, 35%), and ctDNA-non-clearance (N=13, 65%). ctDNA-clearance group had better PFS than ctDNA-non-clearance group (ctDNA-clearance vs ctDNA-non-clearance, p=0.091, HR=0.42, 95%CI=0.15-1.19). According to Week4-*EGFR* status, we observed that PFS was significant longer in *EGFR*-clearance patients than *EGFR*-non-clearance groups, (p=0.011, HR=0.23, 95%CI=0.08-0.72). We then categorized patients into three subgroups according to Week4-ctDNA and Week4-*EGFR* status: non-clearance group (N=9), only-*EGFR*-clearance (concomitant alterations non-clearance) group (N=4), and all-clearance group (N=7). Non-clearance group had a significant worse PFS than all-clearance group (median PFS=5.07 vs 11.40 months, p=0.029, HR=3.45, 95%CI=1.05-11.49). Only-*EGFR*-clearance group had a similar PFS with all-clearance group (p=0.607), which was longer than non-clearance group (median PFS=9.20 vs 5.07 months, p=0.060, HR=0.25, 95CI=0.05-1.18). We found that all-clearance group had a similar objective response rate (ORR) with only-*EGFR*-clearance group (p=1.000) and a higher ORR than non-clearance group (p=0.012).

Conclusions: Monitoring of *EGFR* clearance in ctDNA is promising and cost-effective in assessing response and predicting survival in *EGFR*-mutated NSCLC patients treated with *EGFR*-TKIs, with similar predictive value as ctDNA surveillance.

Keywords: EGFR-mutated NSCLC, ctDNA monitoring, EGFR clearance

EP08.02-092 Coexistence of a Novel NBAS-ALK, EML4-ALK Double-Fusion in a Lung Adenocarcinoma Patient with LM and Response to Ensartinib

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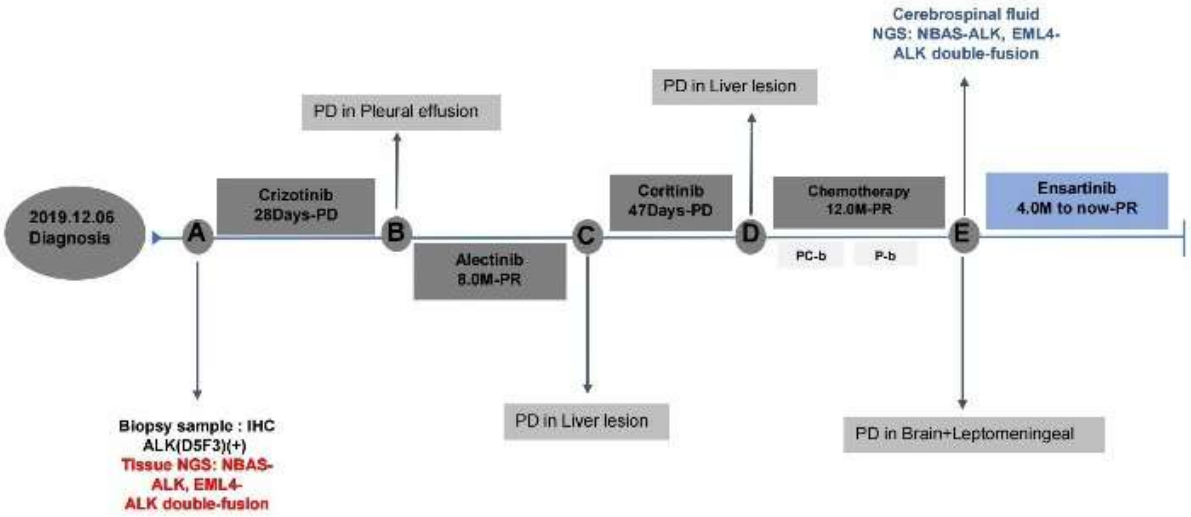
Introduction: ALK gene rearrangement accounts for approximately 5%-7% in non-small cell lung cancer (NSCLC), and usually demonstrate a response to ALK tyrosine kinase inhibitors (TKIs). However, a recent study showed that the presence of nonreciprocal/reciprocal ALK translocation was predictive for shorter PFS and greater risk of brain metastases (BM) in patients with ALK-rearranged NSCLC. Herein, we report that, for the first time, one NSCLC patient with the coexistence of a novel NBAS-ALK, EML4-ALK double-fusion responds to ensartinib after disease progression on sequential crizotinib, alectinib, ceritinib, and then chemotherapy.

Methods: Hematoxylin-eosin staining was adopted on the biopsy sample and next-generation sequencing (NGS) was performed on the cerebrospinal fluid (CSF) sample. The duration of the PFS was calculated from the first claim for ALK-TKIs therapy to the date of disease progression or the last follow-up visit.

Results: In the first setting, crizotinib was demonstrated useless after only 28 days. Immediately afterward, after 8 months of treatment of alectinib, the patient presented with the progression of bone and liver metastases. After 47 days administration of ceritinib, the patient experienced disease progression on liver metastases. Platinum-based chemotherapy was adopted as a forth-line treatment but finally appeared as brain and leptomeningeal metastases. The treatment was then switched to ensartinib. The patient responded to ensartinib as a fifth-line therapeutic regimen and has manifested disease control for more than 4 months, with the significant relief of leptomeningeal metastases symptoms and shrink of brain lesion. Hitherto, the survival benefit from the administration of ensartinib was sustainably presented in the patient, and follow-up is still ongoing. Moreover, the NGS also validated better clinical benefits compared to HE detection.

Conclusions: Double-ALK fusion mutations may confer resistance to common ALK-TKIs. We firstly report that one patient with CNS metastases and a novel NBAS-ALK, EML4-ALK double-ALK fusion is sensitive to ensartinib. NSCLC patients with double-ALK fusion may benefit from ensartinib and the NGS could help predict the sensitivity and efficacy of ALK-TKIs.



Keywords: ALK, non-small cell lung cancer (NSCLC), leptomeningeal metastases (LM)

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-093 Loss of Tumor Endothelial QKI Expression Results in Pronounced Reductions in Metastasis and Remodeling of the Tumor Microenvironment

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Introduction: The TME encompasses cross talk between different cells and stromal elements within the tumor. While the interplay between the tumor microenvironment (TME) and metastasis is well established, only a few TME targets have resulted in approved therapeutic agents against highly metastatic lung cancers. Quaking (QKI) is a highly conserved RNA-binding protein that plays critical roles in vascular development during embryogenesis. Previous work in our lab revealed that the miR-200 family regulates tumor angiogenesis by targeting QKI, and loss of QKI resulted in inhibition of sprouting angiogenesis and endothelial proliferation. The objective of our study is to elucidate the role QKI expression in the tumor endothelial cells (TECs) have on the TME during metastatic progression of lung cancer.

Methods: We developed a conditionally deleted QKI knock-out model by crossing QKIflox/flox mice with a tamoxifen-inducible VE-Cadherin-Cre mouse on a C57BL/6 background. In addition, crossing with Lox-STOP-Lox-ZsGreen reporter resulted in a QKIiECKO/ZsG (QKIKO) model. Tamoxifen was given to adult mice one week prior to cell injection to induce a conditional QKI-/- and activation of ZsG. LLC (lung adenocarcinoma), or a novel metastatic cell line of lung squamous carcinoma (JH18-LN2A) was injected either subcutaneously or orthotopically. Survival differences and tumor progression were evaluated in each model, and the effects on vascular indices were extensively characterized. To study the effect of QKI loss on EC function, QKI was silenced in HUVECs using sgRNAs and were grown in a novel microfluidic device and microvascular networks were systematically evaluated for various vascular indices.

Results: The QKIKO group showed a 35% increase in survival for LLC (Log-rank p=0.009) and a 62% increase in survival for LN2A (p=0.0003) when compared to the respective WT control groups. In both models we observed that the QKIKO groups demonstrated 45-60% less tumor burden compared to the WT control groups ($p \leq 0.05$). Loss of QKI in TECs resulted in significantly reduced metastasis and prolonged survival in both NSCLC models. Both models also demonstrated that the microvessel density and vascular branching were markedly reduced by 50% in QKIKO group when compared to WT ($p \leq 0.0001$). Perfusion studies showed that loss of QKI in TECs resulted in 46% reduction of functional tumor vasculature ($p \leq 0.0001$). EC functional studies in the microfluidic devices showed that, compared with controls, QKIKO resulted in a 40% decrease in area and number of vessels ($p \leq 0.001$), a 52% decrease in number of junctions ($p \leq 0.001$) and a 26% ($p \leq 0.001$) increase in lacunarity. These findings in our microfluidic platform corroborated our tumor vascular results and suggests QKI has critical roles on EC biology

Conclusions: Our results show that loss of QKI in TECs has a significant role on tumor angiogenesis and metastasis development in lung cancer. These findings suggest that targeting tumor endothelial QKI could be novel therapeutic strategy for controlling tumor angiogenesis and metastasis in lung cancer. Ongoing studies are focused on the mechanistic relationship of TEC QKI and the crosstalk within the TME.

Keywords: Tumor microenvironment, QKI, metastasis

EP08.02-094 Aumolertinib as First-line Treatment in EGFR-Mutant Pulmonary Adenosquamous Carcinoma (ARISE): A Multicenter, Open-Label, Single-Arm Trial

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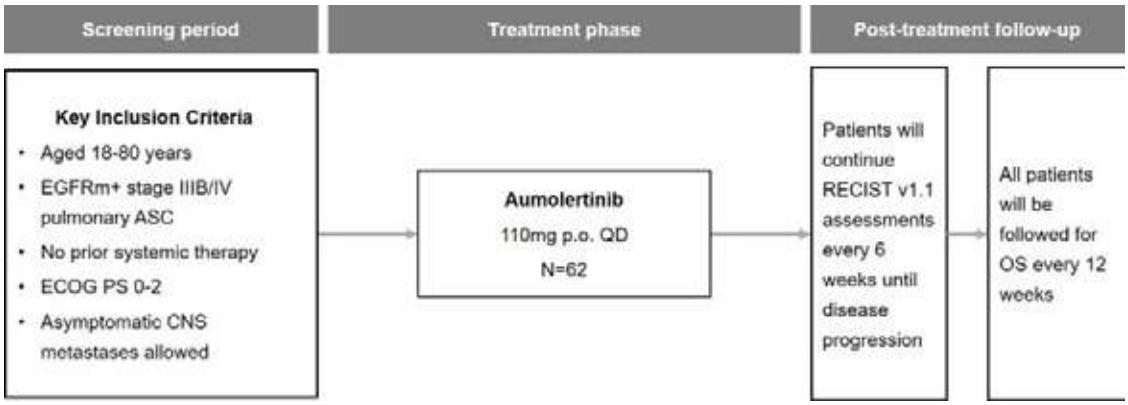
Introduction: Our prior study suggests that Asian pulmonary adenosquamous carcinoma (ASC) may represent a subtype of adenocarcinoma with EGFR mutations being the most common oncogenic driver (51.8%, 268/517) and sharing similar efficacy to EGFR-TKIs (Lin G et al. Ann Oncol. 2020). However, whether a third-generation EGFR-TKI could improve outcomes in this patient population remains inconclusive. Since there are no prospective data of targeted therapies in ASC, we conduct this study to prospectively evaluate the efficacy and safety of third-generation EGFR-TKI aumolertinib (formerly almonertinib; HS-10296) as first-line treatment in patients with EGFR-mutant ASC for the first time.

Methods: This multicenter, open-label, single-arm trial (NCT04354961) aims to enroll approximately 62 treatment-naïve patients with histologically confirmed stage IIIB/IV pulmonary ASC harboring sensitive EGFR mutations, aged 18-80 years, ECOG performance status 0-2, and had at least one measurable lesion per RECIST v1.1. Eligible patients receive aumolertinib 110 mg orally once daily, continuously in 21-day cycles until disease progression or other discontinuation criteria are met. The primary endpoint is progression free survival (PFS). Secondary endpoints include objective response rate (ORR), disease control rate (DCR), overall survival (OS), intracranial ORR (iORR), intracranial DCR (iDCR), intracranial PFS (iPFS), quality of life, and safety. Adverse effects are graded using CTCAE v4.03. The first patient in (FPI) was in March 2021, and the estimated study completion date is Q1 2025.



Results: To be drafted when primary data are available.

Conclusions: To be drafted when primary data are available.

Keywords: aumolertinib, EGFR-TKI, adenosquamous carcinoma

EP08.02-095 Successful Treatment of EGFR Exon 19 Deletion with TP53 and ERBB2 20ins Mutation in Stage IVB NSCLC Patient with Aumolertinib

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Introduction: Based on BENEFIT study, EGFR sensitive mutation NSCLC patients could benefit from first-line EGFR-TKI treatment regardless of combination with tumor suppressor or driver gene mutation. However, for patients combined with both tumor suppressor and driver gene mutations, it is still an unresolved challenge for clinical practice. Herein, we reported a case happened to be this intractable situation.

Methods: Mutation and copy number variation analysis were performed on lung tumor tissues by high-throughput sequencing combined with DNA hybridization capture. Radiographic follow-up was performed with computed tomography (CT) of the chest, followed by CT of the neck as the disease progressed,and then every two months after that. The response was measured using the Response Criteria in Solid Tumors (RECIST)1.1 Criteria.

Results: A 53-year-old female patient presented on September 26, 2019 with an intermittent cough for 5 months and a mass in the left lung for 3-month. CT showed a soft tissue mass in upper lobe of her left lung, and pathology revealed poorly differentiated adenocarcinoma of left lung. The patient was diagnosed with left upper lobe adenocarcinoma stage IVB (cT2aN3M1c), accompanied by bilateral hilar, mediastinal lymph nodes, both lungs, and multiple bone metastases. Lung tumor biopsy was performed for genetic testing and an EGFR exon 19 deletion and mutations of TP53 were observed. In the first line treatment, the patient received gefitinib and attained a PR. However, 9 months later, she developed multiple new metastatic lesions in both lungs. Genetic testing analysis showed an EGFR exon 19 deletion and mutations of TP53 and ERBB2 20ins.Due to the lack of effective treatment method, aumolertinib, a novel third-generation EGFR-TKI approved in China 2020, was given 110 mg per day orally. After 3-month treatment, both the primary tumor and the lung metastases shrank, and the patient obtained PR. Unfortunately, another 4 months later, chest CT revealed the primary lesion increased, and multiple lymph node metastases appeared in her neck and clavicle area. Subsequently, a new combination strategy was adopted: aumolertinib combined with Pemetrexed plus bevacizumab. One month later, the patient's lymph nodes in the neck and clavicle area shrank, and her primary lesions and recurrent tumors shrank as well. Then she received this treatment plan for 7 months, and her response evaluation indicated stable disease. After that, she continued to take a combination treatment of aumolertinib and bevacizumab.Up to now, this patient has achieved a PFS of more than 29 months and she is still under a close follow-up. Of note, there were only milder drug-related adverse events during treatment, mostly grade 1, including dysgeusia and hepatotoxicity, as well as epistaxis and hypertension associated with bevacizumab.

Conclusions: In this case, we reported a NSCLC patient with EGFR-sensitive combining TP53 and ERBB2 20ins mutations, who obtained a remarkable curative effect after a series of therapies based on aumolertinib. This was the first report applied aumolertinib to a complex mutation patient, which provided promising treatment regimen to prolong the survival of EGFR sensitive patients with complicated mutation background.

Keywords: NSCLC, EGFR TKI, complicated mutation

EP08.02-096 Different Epidermal Growth Factor Receptor Inhibitor Generations Plus Antiangiogenic for EGFR-Mutated NSCLC: A Meta-Analysis

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Introduction: Three generations of epidermal growth factor receptor - tyrosine kinase inhibitors (EGFR-TKIs) have been developed to treat advanced non-small cell lung cancer (NSCLC) patients harboring EGFR-activating mutations. Although initially effective, multiple resistance mechanisms developed. Therefore, the combination with other therapeutic agents has emerged as a promising strategy to overcome resistance. However, no meta-analysis compared the efficacy and safety of different EGFR-TKI generations in combination with antiangiogenic, thus results remain elusive.

Methods: Up to March 2022, we systematically searched PubMed, Cochrane Library, Scopus, and conference proceedings of ASCO, ESMO, and IASLC for randomized controlled trials investigating EGFR-TKIs administered with or without antiangiogenic agents for advanced EGFR-mutated NSCLC. The endpoints included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and grade 3 or higher adverse events (AEs). Hazard ratios (HR) and Risk ratios (RR) were calculated using the fixed-effects model.

Results: We included 16 reports on 13 trials with a total of 1775 patients. Regimens were first-generation EGFR-TKIs (erlotinib or gefitinib) in ten trials and third-generation EGFR-TKIs (osimertinib) in 3 trials combined with bevacizumab in most studies (n=9) compared to erlotinib, gefitinib, or osimertinib monotherapy for the control group. The combination group showed remarkably longer PFS over monotherapy [HR: 0.71, 95% CI: 0.66 - 0.77]. The combination of antiangiogenic agents with first-generation but not third-generation EGFR-TKIs was significantly better than monotherapy in terms of PFS [HR: 0.70, 95% CI: 0.64 - 0.76, HR; 0.83, 95% CI: 0.67 - 1.04]. However, OS, ORR, and DCR showed no difference between the two groups in both generations. The overall grade 3 or higher AEs increased in the combination group compared to the control group across the two generations [RR: 1.60, 95% CI: 1.43 - 1.79; RR: 1.61, 95% CI: 1.26 - 2.07], especially the incidence of hypertension and proteinuria [RR: 5.56, 95% CI: 3.84 - 8. 06, RR: 8.35, 95% CI: 2.85 - 24.47]. The combination as a first-line treatment is of a higher benefit than other lines [HR:0.76, 95% CI: 0.69 - 0.84, HR: 0.61, 95% CI: 0.53 - 0.70, respectively]. The experimental group had better PFS outcomes than monotherapy among smokers [HR: 0.80, 95% CI: 0.69 - 0.92], but not in non-smokers population [HR: 0.82, 95% CI: 0.67 - 1.01]. Additionally, subgroup analysis revealed better PFS benefits among non-Asian patients [HR:0.76, 95% CI: 0.69 - 0.84].

Conclusions: First-generation EGFR-TKIs plus antiangiogenic agents significantly improve PFS but with no OS benefit. Thus, constituting a good treatment option for patients with advanced EGFR-mutated NSCLC, particularly those who are smokers, non-Asians or treatment naïve. Third-generation EGFR-TKIs were associated with increased AEs without increased efficacy over single-agent EGFR-TKI.

Keywords: NSCLC, EGFR-TKIs, Antiangiogenic

EP08.02-097 Prevalence, Clinical Characteristics and Survival of Patients with Brain Metastases and KRAS Mutation Lung Cancer in Argentina

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Introduction: Between 20-35% of lung adenocarcinomas harbor KRAS gene mutations (KRASm). With the development of KRAS G12C covalent inhibitors as novel targeted therapies in this population, there is renewed interest in understanding the clinical features and outcomes of patients with KRAS mutant non-small cell lung cancer (NSCLC) worldwide.

Methods: A multicenter study of patients with KRASm lung cancer was conducted in 5 academic centers in Argentina, clinical and pathologic data were collected. Molecular profiling of tumor samples was done in a cohort of 369 patients using targeted next generation sequencing and/or RT PCR. We estimated the prevalence and type of KRAS mutations using both testing methods. We estimated the overall survival (OS) of patients from the date of metastatic disease diagnosis using Kaplan-Meier. We focus on OS of patients with brain metastasis.

Results: KRASm was detected in 87 patients of the cohort, the prevalence was 24%, KRAS G12C was 53% of KRASm, followed by G12A 16% G12V 15%, Q16H 3%. The median age was 66 years (IQR57-72), there was a higher proportion of female patients (65%) and smoking history in 94% of the patients, the most common histology was adenocarcinoma in 97%. First line treatment included immunotherapy in 61% of patients, alone or in combination with chemotherapy. 78% were tested for PD-L1, with a median of 20% (IQR 0-68). The ORR with immunotherapy treatments was 51%, and DCR was 77%.With a median follow up of 35 months, the median overall survival was 26 months (IC95 14,5-not riched). The factors associated with a worse prognosis were the presence and number of brain metastases, and a negative level of PD-L1.Median survival in patients with central nervous system involvement was 11 months, significantly lower than the general population (Hazard Ratio 1,58 IC95 1,28-3,44).The prevalence of brain metastases at diagnosis was 25%, among patients without brain metastases at diagnosis, 22% had central nervous system (CNS) progression, with a median time to brain progression of 10,5 months (IQR 5-12) from diagnosis, therefore 40% developed CNS involvement during the course of the disease. The median number of brain metastases was 3, the most frequent site corresponding to cerebellar involvement in 33%, with an incidence of meningeal involvement of 10%.38% of the brain metastases were treated with surgery and 27% with radiosurgery and 16% whole-brain radiotherapy.

Conclusions: In this real-life experience, we observed in our country a prevalence of KRASm similar to previously reported, with high response rates with immunotherapy alone or in combination with chemotherapy, in our research the prevalence of brain metastases is elevated, being one of the main factors of an unfavorable evolution. At the moment there is limited data about the intracranial efficacy of TKI in advanced NSCLC with KRASm and previously untreated brain metastases. Results from real life experience are awaited for this population with worse prognosis and the development of new drugs for non-G12C KRASm also.

Keywords: KRAS, lung cancer, brain metastasis

EP08.02-098 Phase 2 EVOKE-02 Study of Sacituzumab Govitecan and Pembrolizumab±Platinum in First-Line Metastatic NSCLC

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Introduction: Most patients with advanced NSCLC do not harbor genomic alterations associated with approved first-line targeted therapies. The standard of care for these patients is a programmed death (ligand)-1 (PD-[L]1) inhibitor alone, if the tumor highly expresses PD-L1, or in combination with platinum doublet chemotherapy, independent of PD-L1 expression. However, most patients do not respond to these therapies or achieve only a transient response, highlighting an unmet need. Sacituzumab govitecan (SG) is an antibodydrug conjugate composed of an anti-Trop2 antibody coupled to the cytotoxic SN38 payload via a proprietary, hydrolyzable linker. In the phase 1/2 IMMU-132-01 basket study (NCT01631552), SG demonstrated an objective response rate (ORR) of 17% and median overall survival (OS) of 9.5 months, with a manageable safety profile in 54 patients with metastatic NSCLC after multiple prior therapies (Heist RS, et al. *J Clin Oncol. 2017*). We hypothesize that combining SG with pembrolizumab or with pembrolizumab + platinum chemotherapy will improve outcomes for patients with advanced NSCLC.

Methods: EVOKE-02 (NCT05186974) is an open-label, multicenter, multicohort, global phase 2 study evaluating SG plus pembrolizumab with or without carboplatin (carbo) or cisplatin (cis) in advanced NSCLC. Key eligibility criteria include age ≥18 years, stage IV NSCLC at enrollment, measurable disease by RECIST v1.1, ECOG performance status of 0 or 1, and adequate organ function. Patients must not have actionable genomic alterations and must not have received prior systemic therapy for metastatic NSCLC. Up to 164 patients will be enrolled. SG plus pembrolizumab will be assessed in squamous/nonsquamous NSCLC with Tumor Proportion Score (TPS) ≥50% (cohort A, ~30 patients) and TPS <50% (cohort B, ~30 patients) and SG plus pembrolizumab with carbo/cis in nonsquamous (cohort C, ~40 patients) and squamous (cohort D, ~40 patients) NSCLC regardless of PD-L1 expression. Patients are randomly assigned if cohorts enrolling concurrently have overlapping eligibility. SG will be administered intravenously (IV) at 10 mg/kg on day 1 and 8 until disease progression or unacceptable toxicity, pembrolizumab 200 mg IV on day 1 for up to 35 cycles, carbo AUC 5 or cis 75 mg/m^2 on day 1 for up to 4 cycles in 21-d cycles. A safety run-in will be conducted for cohorts C and D (up to 24 patients each) to determine the optimal SG dose by dose de-escalation. Choice of platinum will be based on preliminary efficacy in safety run-in. The primary endpoints are ORR assessed by independent review per RECIST v1.1 and the incidence of dose-limiting toxicities per dose for the first 21 days of the safety run-in to determine the recommended phase 2 dose of SG in combination with pembrolizumab and a platinum. Key secondary endpoints include progression-free survival by independent review, OS, duration of response, disease control rate, and safety. This study is open for recruitment and is enrolling globally.

Keywords: antibody-drug conjugate, immune checkpoint inhibitors, phase II clinical trial

EP08.02-099 Liquid Biopsies as a Tool for Monitoring Patients with Metastatic ALK-positive NSCLC

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Introduction: Lung cancer is the leading cause of cancer-related death worldwide. Therefore, improving the lung cancer treatment trajectory is crucial. In metastatic non-small cell lung cancer (NSCLC) the development of oncogene directed therapy has improved survival significantly. In approximately 5% of all NSCLCs the ALK translocation is detected. The standard treatment for metastatic ALK-positive (ALK+) NSCLC is ALK-inhibitors. This treatment is effective, well-tolerated, and several ALK-directed drugs are available for clinical use. However, treatment resistance is inevitable, and little is known about the underlying molecular resistance mechanisms. This is important as knowledge of the oncogene composition of the cancer is needed for guiding the sequential medical treatment of these patients.

Methods: We aim to investigate if circulating tumour DNA (ctDNA) from blood samples (liquid biopsies) can be used for monitoring the treatment in patients with metastatic ALK+ NSCLC. This study is a Danish national multi-center study. Inclusion criteria are patients aged >18 years with histologically or cytologically confirmed metastatic ALK+ NSCLC who are naïve to ALK-directed therapy. Exclusion criteria are pregnancy/breast-feeding or patients who do not wish to participate. We aim to include up to 60 patients during the period June 2019 - June 2022. All patients receive standard 1st line treatment with Alectinib (Alecensa®) according to Danish lung cancer treatment guidelines. Blood samples are collected prospectively during every routine outpatient visit. 4mL of plasma are extracted from the blood sample. ctDNA is extracted from the plasma and analysed by next generation sequencing (NGS) analysis. We use a targeted NGS analysis with a lung gene panel specifically designed to detect gene mutations associated with lung cancer. The NGS analyses is performed retrospectively on blood samples taken at 3 time points: before treatment start, at 14 days after treatment start and at clinical progression or when last blood sample before death was taken. In this way the ctDNA dynamics during treatment course is captured and we will be able to determine if liquid biopsies can be helpful in managing the targeted therapy of these patients.

Keywords: ALK, NSCLC, liquid biopsies

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-100 Combination of Bevacizumab and Continuation of EGFR-TKIs in NSCLC Patients beyond Gradual Progression

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Introduction: Continuation of epidermal growth factor receptor (*EGFR*)-tyrosine kinase inhibitors (TKIs) has shown potential in prolonging survival of non-small cell lung cancer (NSCLC) harboring *EGFR* mutaion who had gradual progression at initial targeting therapy. However, it remains unknown whether the combination of bevacizumab and *EGFR*-TKIs would benefit the sub-popularity. This study retrospectively explored the effect of combining bevacizumab and *EGFR*-TKIs in NSCLC patients beyond gradual progression in the real-world setting.

Methods: The records of 48 patients were reviewed who received bevacizumab and continuation of *EGFR*-TKI beyond gradual progression at initial targeting therapy. The response to the treatment and post progression survival (PPS) was reviewed and analyzed.

Results: The median PPS was 11.4 months (95% CI 7.368-15.492) for all patients included at the median follow-up time of 17.3 months. The objective response rate (ORR) was 8.3% and the disease control rate (DCR) was 86.1% (with 3 partial response and 28 stable disease) in 36 patients who were evaluable for response with at least one measurable lesion. Univariate Cox analysis showed that age<60, male, and *EGFR* exon19 deletion mutation were associated with longer PPS (P<0.05). Patients harboring *EGFR* exon19 deletion mutation had significantly longer PPS than those with *EGFR* exon21 L858R mutation, with an mPPS of 15.5 months and 5.7 months, respectively (HR=0.251, 95%CI 0.112-0.561, P=0.019). Multivariate Cox analysis indicated that age<60 and *EGFR* exon19 deletion mutation were associated with longer PPS (P<0.05).

Conclusions: Continuation of *EGFR*-TKI with the combination of bevacizumab is a reasonable strategy in NSCLC patients beyond gradual progression in previous *EGFR*-TKI treatment. Younger patients with *EGFR* exon19 deletion mutation may benefit more from the combination therapy.

Keywords: EGFR-TKI, bevacizumab, gradual progression

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-101 Real-world Data from KRAS-mutant Advanced NSCLC: the ATLAS Multicenter Cohort Study

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Introduction: Kirsten rat sarcoma (KRAS) mutations are the most common oncogenic driver in non-squamous Non-Small Cell Lung Cancer (NSCLC), occurring in approximately 25-30% of cases. Despite recent advent of novel selective KRAS inhibitors, the majority of KRAS-mutant patients still receive either immunotherapy alone or in combination with chemotherapy as upfront treatment in the routine practice. This study investigated real-world clinical features and survival outcomes of patients with advanced NSCLC harboring KRAS mutation who received standard first-line therapies in Italy.

Methods: Data were retrospectively collected from ATLAS, an Italian web-based platform created to share clinical, pathological and molecular variables about oncogene-addicted NSCLC among Italian institutions. Patients with a newly diagnosed, KRAS-mutated NSCLC, between January 2019 and December 2020, across five different Italian institutions were analyzed.

Results: A total number of 123 patients with stage IV disease treated with first-line therapy were identified. Median age at diagnosis was 67 years, males were 64.2%, current/former smokers were 94.3%. ECOG Performance Status at diagnosis was 0 or 1 in 85.4% of patients, while 20% reported brain involvement. The most frequent histology was adenocarcinoma (92.7%). Distribution of KRAS mutations was as follow: p.G12C (37.4%), p.G12A (15.4%), p.G12D (13%), p.G12V (13.8%), others (20.4%). PD-L1 expression levels were: ≥50%, 1-49%, <1% and unknown/not tested in 34.1%, 30.1%, 32.5%, and 3.3% of cases, respectively. First-line systemic treatment was chemo-immunotherapy (35.8%), anti-PD1/PD-L1 single agent therapy (24.4%), platinum-based chemotherapy (22.8%), single agent chemotherapy (9.7%). Nine patients (7.3%) were enrolled in clinical trials. Thirty-two patients (26%) experienced grade ≥ 3 toxicity, in particular hematological (14.6%) and gastrointestinal toxicity (10.6%). Only 11 patients (8.9%) discontinued treatment due to toxicity. Forty-eight patients (39%) received a second-line therapy, 6 of whom in clinical trials (3 with sotorasib). Eighteen patients received a third-line therapy. At median follow-up of 25.1 (95% CI 19.8-31.3) months, the median overall survival (mOS) of the entire series was 12.9 months (95% CI 8.77-19.5). mOS in patients with p.G12C, p.G12A, p.G12D, p.G12V mutations was 12.94 (95% CI 8.28-28.6), 14.98 (95% CI 5.06-NA), 7.13 (95% CI 5.49-19.9), and 11.4 months (95% CI 6.67-NA), respectively. No significant mOS differences have been reported among the different KRAS mutation subtypes (p=0.23).

Conclusions: The prevalence of KRAS mutations subtypes as well as the survival outcomes of our cohort of KRAS-mutant advanced NSCLC patients were consistent with those reported in the literature. Such data confirmed once again the high heterogeneity of KRAS-mutant NSCLC population and highlight the urgent need of novel personalized treatment strategies.

Keywords: Real-world data, NSCLC, KRAS

EP08.02-102 Feasibility and Clinical Utility of ctDNA for Detection of Sensitizing and Resistance EGFR Mutations in Patients with Non-small Cell Lung Cancer

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Introduction: *EGFR* mutations (*EGFR*m) represent ≈10% of advanced non-small cell lung cancer (aNSCLC) in European patients (pts). Tissue molecular profiling is the gold-standard, but liquid biopsy (ctDNA) offers a non-invasive alternative for molecular profiling. Crystal Digital PCR™ (cdPCR) is a highly-sensitive technique to detect specific molecular alterations. Here, we aimed to illustrate cdPCR clinical utility for *EGFR*m detection in aNSCLC.

Methods: Prospective blood samples were collected in pts with aNSCLC harboring any *EGFR*m either at diagnosis or at progression (PD), between Jul/20 and May/21 at Hospital Clinic Barcelona (Spain). ctDNA was analyzed by cdPCR (6-color Crystal-Digital PCR™; Stilla) including sensitizing (ex19 delections, ex21 [L858R]); uncommon ex18/ex20 insertions and *T790M/C797S/other* resistance *EGFR*m. We also analyzed *EGFR*m clearance under treatment (early timepoint; 1 month since tyrosine-kinase inhibitor (TKI) beginning). Tissue molecular analysis was performed with NGS.

Results: In 24 pts, 56 samples were collected: 7 at diagnosis, 41 under response and 7 at PD. The median allelic frequency (AF) for driver *EGFRm* was 4.5 [0.5-7.1] and for resistance *EGFRm* was 1.2 [0.1-3.2]. The frequency of occurrence of the different *EGFRm* was: 52% (n=13) ex19del, 24% (n=6) ex21 (L858R), 16% (n=4) ex18 and 8% ex20 ins (n=2).

At baseline, *EGFR*m were detected in all patients (N=7/7); 5 ex19del, 1 ex21 (*L858R*) and in 1 patient, the *novo T790M* was detected together with ex21 [L858R]. For 2 pts with insufficient tissue (25%), cdPCR detected *EGFRm* in ctDNA, 2 ex19del. Both pts received osimertinib, with ongoing response (7 and 16m of duration to date, respectively). All pts with positive cdPCR at baseline received TKI (n=7) with objective response (6 partial; 1 complete), and a 6-month-progression free survival rate (6m-PFSr) of 75% (95% CI 60%-100%). At early timepoint, 83% (5/7) presented complete *EGFR*m clearance and 6m-PFSr of 83% vs. 50% in those with incomplete clearance (*P*=0.03). cdPCR was significantly associated with the radiological response; under response only 19% of samples (8/41) were positive, compared to 57% (4/7) of positive samples at progresion.

At PD any resistance mutation was detected in 1/7 pts (1 C797S). The 2 pts with negative cdPCR at PD had isolated brain and pericardial involvement (1 ex20, 1 ex21). In 3 pts with tissue available at PD (75%), the tissue/blood *EGFR*m concordance was 100%.

Conclusions: cdPCR is feasible and clinically useful for detection and monitoring of sensitizing, uncommon, and resistance *EGFR*m in patients with NSCLC. Crystal Digital PCR is a straightforward and easy-to-use technique yielding fast and reliable results that can guide treatment strategy upfront and at TKI failure.

Keywords: Liquid biopsy, EGFRm lung cancer, ctDNA

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-103 Lorlatinib for ALK+ NSCLC Patients Pretreated with Second-Generation ALK Inhibitors: Canadian Real-World Experience

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Introduction: Lorlatinib, a third-generation anaplastic lymphoma kinase inhibitor (ALKi), demonstrated clinically meaningful outcomes in the post second-generation ALKi settings in a Phase II study. In Canada, lorlatinib is approved as monotherapy in adult patients with ALK-positive (ALK+) metastatic non-small cell lung cancer (NSCLC) who have progressed on crizotinib and at least one other ALKi, or have progressed on ceritinib or alectinib. To date, no Canadian real-world evidence on lorlatinib has been published. The objective of this project is to understand the real-world utilization and effectiveness of lorlatinib, including its persistence, and changes in patient Quality of Life (QoL) in the latter settings.

Methods: Sixty-nine ALK+ NSCLC patients pretreated with second-generation ALKi were enrolled into the manufacturer-sponsored lorlatinib patient access program (PAP) between August 2020 and May 2021. Of these, 59 patients (85.5%) consented to study participation, agreed to follow-up contact, and initiated lorlatinib treatment (i.e., lorlatinib PAP cohort). All PAP services were available to enrolled patients, regardless of study participation. Demographics, clinical characteristics and treatment history were collected at baseline (i.e., lorlatinib initiation). The time on lorlatinib therapy (i.e., lorlatinib initiation to discontinuation) was used to estimate lorlatinib persistence using Kaplan-Meier methodology. Patient QoL was captured over telephone using the EQ-5D-5L questionnaire. Patient QoL at baseline was compared to 3, 6 and 12 months post-lorlatinib initiation. The health utility score (HUS) was calculated using the EQ-5D-5L responses and the Canadian tariff.

Results: At baseline, the average age of the cohort was 61.9 years and consisted of 47.5% females. Central nervous system metastases were present in 32.2% of patients. Approximately half (50.9%) of patients received two or more ALKi's prior to lorlatinib. Alectinib was the most common prior ALKi (72.9%) before lorlatinib initiation, including 44.1% of patients who received alectinib only (i.e., no other ALKi) before lorlatinib. To date, median patient follow-up is 7.3 months, and 61% (n=36) patients remain on lorlatinib treatment. Lorlatinib persistence was 83.1% (95% confidence interval (CI): 70.8-90.5%) at 3 months, 77.9% (95% CI: 65.0-86.5%) at 6 months, and 55.3% (95% CI: 39.8-68.3%) at 12 months. The average baseline HUS (n=59) was 0.744 (SD=0.200). Among patients who received lorlatinib therapy at 3, 6, and 12 months, the QoL questionnaire completion rate was 91.8% (45/49), 77.3% (34/44) and 68.8% (11/16), respectively. At 3 months, patients had a statistically significant increase in HUS of 0.064 (95% CI, 0.015-0.113) from baseline. At 6 months, patient HUS had a non-significant decrease of -0.006 (95% CI, -0.065-0.053) from baseline. Lastly, at 12 months, there was a non-significant increase in HUS of 0.036 (95% CI, -0.070-0.142) from baseline.

Conclusions: The data from this cohort of Canadian patients treated in the real-world setting corroborate the clinically meaningful lorlatinib outcomes in the post second-generation ALKi setting shown in clinical trials. With median follow-up of 7.3 months, lorlatinib median time-to-discontinuation has not been reached. The interim findings indicate QoL was maintained among patients receiving lorlatinib. Future analyses are planned, and results will be updated with additional follow-up.

Keywords: ALK+ NSCLC, Lorlatinib, Real-world study

EP08.02-104 Osimertinib in Untreated EGFR-Mutant Non-small Cell Lung Cancers: Overall Survival and Budget Impact Analysis in Real-World

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Introduction: The observational prospective multicenter FLOWER study (NCT04965701) confirmed effectiveness and safety of osimertinib in the real-world (RW) management of untreated *EGFR*-mutant advanced non-small cell lung cancer (aNSCLC) patients (Lorenzi M. et al., The Oncologist, 2021, DOI:https://doi.org/10.1002/onco.13951). Herein, we report updated effectiveness data, post-progression diagnostic-therapeutic pathway and the budget impact (BI) of osimertinib on the national health system (NHS).

Methods: Median time to treatment discontinuation (mTTD) and overall survival (mOS) were reported with an updated follow-up. The monthly BI of osimertinib was calculated by multiplying the 28-days cost/patient by mTTD. Incremental cost-effectiveness ratio (ICER) was calculated as the ratio between difference in costs and effectiveness, taking as comparison RW data achieved by an overlapping population receiving gefitinib or erlotinib before osimertinib approval. Finally, the difference (BI-gap) between real-BI calculated on the mTTD in the present study and theoretical-BI calculated on median progression-free survival (mPFS) and mTTD from the FLAURA study, was investigated.

Results: At data cut-off (February 2022), data from 91 patients (out of the overall population of 126) referred to six Italian centres were included. Patients features, safety and effectiveness data were previously presented (Lorenzi M et al. 149P, ELCC 2021,DOI:https://doi.org/10.1016/S1556-0864(21)01991-2). After a median follow-up of 21.1 months, 47(51.6%) patients discontinued osimertinib. Updated mTTD was 23.2 (95%CI, 17.4-29.0) and mOS 30.2 months (95%CI, -inf,+inf). At progression, tissue rebiopsy was performed in 14(43.8%), liquid in 13(40.6%) and both in 5(15.6%) patients. One (3%) histological transformation was detected (large cell neuroendocrine cancer). Next generation sequencing was performed in 10(21.2%) cases. *MET* amplification was found in 9(28.0%), *EGFR plus MET* amplification in 1(3.1%), *HER2* amplification in 1(3.1%) and other complex mutation patterns in 5(15.6%) cases. Twenty-two (24.2%) patients were treated with second-line therapy: 7(31.8%) received EGFR and MET-TKIs in combination, 12(54.5%) chemotherapy alone, 2(9.1%) in combination with atezolizumab and 1(4.5%) with EGFR-TKI. Overall response rate (ORR) to second-line therapy was 50%, mPFS 7.3 months (95%CI, 5.2-9.4), without any difference in mPFS or mOS between patients receiving TKIs compared with chemotherapy (p=0.598 and p=0.324, respectively). Eight (8.8%) patients received third-line therapy; ORR was 25%, mPFS 1.9 months (95% CI,1.7-2.2). The BI analysis showed a monthly expense estimation per patient of 3.921€, 1.864€ and 2.190€ for osimertinib, erlotinib and gefitinib, respectively. The ICER in terms of cost per life-year-gained was not available due to the short follow-up and lacking events for survival analysis (40.6% maturity). Considering TTD as a surrogate of survival, the ICER for osimertinib was 7.173€ and 6.898€ compared to erlotinib and gefitinib, respectively. We observed a BI-gap of 17.725,5€ and 10.165,0€ considering mPFS and mTTD from FLAURA trial, respectively.

Conclusions: This updated analysis confirms the effectiveness of osimertinib as first-line treatment in *EGFR*-mutant aNSCLC patients although mOS has just been reached. BI of osimertinib seems in line with previous data and the ICER calculated on TTD is lower than the Italian willingness-to-pay threshold. The BI-gap suggests mTTD as a more reliable measure for BI estimation compared with mPFS. Updated OS and final BI analysis will be presented at the conference.

Keywords: EGFR, osimertinib, cost-effectiveness

EP08.02-105 KRAS p.G12 Mutated Advanced Non-Small Cell Lung Cancer. Characteristics and Outcomes from a Danish Nationwide Observational Study

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Introduction: Treatment targeting the KRAS p.G12C (G12C) mutation was approved by both the U.S. Food and Drug Administration and the European Medicines Agency in the past year as second line of treatment (LOT2) for advanced non-small-cell lung cancer (aNSCLC). However, the treatment-eligible G12C mutant NSCLC population has not been well characterized, nor has its outcomes with current treatment approaches. The aim of this study was to characterize a nationwide real-world G12C mutant NSCLC population and to estimate its overall survival (OS) in Denmark.

Methods: Adult aNSCLC patients diagnosed between January 1st, 2018 and October 31st, 2020 were identified in the Danish Lung Cancer Register. The register has captured data on all Danish lung cancer patients since 2003. Additional information was gathered from the following registers: the Danish National Patient Register, the Danish Pathology Register, the Danish Civil Registration System, the Danish National Prescription Register, the Danish Education Register, and the Income Statistics Register. Patient and tumor characteristics, molecular profiles, treatment patterns, time-to-next-treatment (TTNT) and OS from diagnosis, first line of treatment (LOT1), and LOT2 were analyzed.

Results: We identified 6,058 patients with aNSCLC. A total of 36.5% (n=2,214) were tested with next-generation sequencing (NGS) or polymerase chain reaction (PCR) tests for a KRAS mutation prior to LOT1. Among those tested, 40.5% (n=896) were KRAS mutated, 9.3% (n=206) were G12C mutated, and 39.0% (n=864) were KRAS/EGFR/ALK wild-type (Triple WT). Co-mutation with EGFR was present in 11% of G12C-mutated patients. Key characteristics and outcomes are presented in Table 1. TTNT was similar among G12C-mutated patients and Triple WT patients for LOT1. Among patients who received any systemic treatment, OS from LOT1 and LOT2 was longer for KRAS G12C compared to Triple WT. Specifically, KRAS G12C mutant patients with a PD-L1 expression of ≥50% had a longer OS of 28.1 months (95% CI 14-NE) compared to KRAS G12C patients with a PD-L1 expression of PD-L1 <1% and 1%-49% where OS was 9.9 months (95% CI 6.9-NE) and 18 months (95% CI 6.4-NE), respectively.

Conclusions: This Danish real-world study evaluating aNSCLC patients after the implementation of targeted therapy and immunotherapy showed that patients with a KRAS G12C mutation had a longer OS from LOT1 and LOT2 compared with Triple WT patients. The longer OS observed in patients with KRAS G12C mutant aNSCLC may be driven by higher PD-L1 expression and consequently more frequent use of immunotherapy.

Table 1. Key characteristics and outcomes of KRAS G12C and Triple WT aNSCLC patients		
Table 1. Key characteristics and outcomes of KRAS G12C and Triple WT aNSCLC patients	**G12C n=206**	**Triple WT n=864**
Age, mean (SD)	69 (9)	70 (9)
Sex, n (%)		
Male	62 (30%)	459 (53%)
Smoking history, n (%)		
Yes	179 (87%)	700 (81%)
Missing	22 (11%)	112 (13%)
PD-L1 expression, n (%)		
<1%	44 (21%)	330 (38%)
1%-49%	47 (23%)	198 (23%)
≥50%	99 (48%)	305 (35%)
Missing	16 (8%)	31 (4%)
OS from diagnosis, median KM-estimate (95% CI)	7.2 (6.1-10.1)	7.6 (CI 6.8-8.8)
Any systemic treatment, n (%)	126 (61.2%)	542 (62.7%)
Platinum without anti-PD-1/L1	10 (8%)	60 (10%)
Platinum with anti-PD-1/L1	60 (46%)	170 (32%)
Anti-PD-1/L1 mono	55 (42%)	300 (54%)
LOT1, n (%)	126 (61.2%)	542 (62.7%)
OS from start of LOT1, median KM-estimate (95% CI)	16.9 (9.5-NE)	11.7 (10.2-13.9)
TTNT or death, median KM-estimate (95% CI)	6.8 (5.1-9.5)	5.9 (5.2-6.4)
LOT2, n (%)	45 (21.8%)	213 (24.7%)
OS from start of LOT2, median KM-estimate (95% CI)	16.2 (6.6-NE)	9.7 (7.8-12.5)
TTNT or death, median KM-estimate (95% CI)	4.7 (3.6-12.7)	5.3 (4.9-6.0)
Abbreviations: KM: Kaplan-Meier, LOT1: first line of treatment, LOT2: second line of treatment, OS: overall survival, SD: standard deviation, TTNT: time-to-next-treatment.		

Keywords: KRAS p.G12C, Non-Small-Cell Lung Cancer, Real World Evidence

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-106 KEAP1/NFE2L2 Transcriptomic Signature Predicts Survival in Advanced Stage NSCLC Patients Without Actionable Driver Mutations

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Introduction: We developed a *KEAP1/NFE2L2* pathway signature that robustly predicts functional mutations of *KEAP1*- and *NFE2L2*-mutated NSCLC. To determine the prognostic value of this signature, we identified a cohort with *KEAP1/NFE2L2* mutations and compared it with a control cohort lacking established targetable driver mutations.

Methods: We followed up the clinical course of NSCLC patients identified between 2015 and 2018 with *KEAP1* or *NFE2L2*mutations and formalin-fixed tumor tissue available in the local pathology archives. All biopsies underwent next-generation sequencing (NGS). For the control cohort, we identified patients using the same NGS panel in the same timeframe and excluded the following genotypes: *EGFR* exon 18-21 mutations; rearrangements of *ROS1*, *ALK*, *RET*, and *NTRK*; *BRAF* class I and II mutations; *MET* exon 14 skipping mutations; and *KEAP1/NFE2L2* mutations. Our analysis focused on overall survival (OS) assessed by Kaplan Meier (KM) statistics. Follow-up (FU) was estimated by "reverse" KM method. Survival was compared using log-rank test.

Results: We identified 125 stage IV patients with *KEAP1* (n=106) or *NFE2L2* (n=19) mutations, and 93 patients in the control cohort. After a median FU of 5.9 years (95% CI, 2.7-9.1 years), median OS (mOS) was 5.7 months (95% CI, 4.8-6.5 months). When focusing on the patients with OS ≤ one year (73% of patients), both mutational status (4.4 vs 4.1 months, p=0.027) and signature prediction (5.1 vs 4.1 months, p=0.005) could distinguish the patients prognostically. When analyzing the whole cohort considering the exceptionally long FU, only the signature prediction (7.2 vs 5.0 months, p=0.047) but not the mutational status (7.2 vs 5.4 months, p=0.316) could significantly identify patients with worse prognosis. Neither *TP53* mutational status (p=0.826), *KRAS* mutations (p=0.567), nor PD-L1 expression (≥50% vs below, p=0.105) had a significant impact on survival.

Conclusions: The KEAP1/NFE2L2 transcriptomic signature outperforms mutational status in identifying patients with a bad prognosis. Our analysis confirms the poor prognosis of this NSCLC-subgroup in the real-world setting, even when favorable subgroups are excluded for comparison.

Keywords: KEAP1, signature, mutation

EP08.02-107 Molecular Biomarker Testing and Initiation of Targeted Therapy in Minority Patients with Stage IV Non-small Cell Lung Cancer

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Introduction: Molecular biomarker testing is the standard of care for identifying potentially effective targeted therapies for patients with stage IV non-small cell lung cancer (NSCLC). Minority patients are less likely to undergo next-generation sequencing (NGS) and be enrolled in clinical trials compared to Non-Hispanic Whites (NHW). As such, frequencies of tumor biomarkers in minority populations in the United States are not well-defined and survival data for minority patients receiving targeted therapy is lacking. This study aimed to determine the extent of tumor gene expression profile (GEP) diversity in minority patients and NHW.

Methods: This retrospective study included patients with stage IV NSCLC that had a baseline NGS of tumor tissue or blood performed from 2015-2021 at an academic cancer center in South Florida. Minority populations included Hispanic, Black, and Asian patients. Comparisons of actionable epidermal growth factor receptor (EGFR) mutation frequency between NHW and minority patients were done using Chi-squared and Fisher's exact tests. Kaplan Meier analysis was used to compare overall survival (OS) and progression-free survival (PFS) between NHW and minority patients receiving EGFR-targeted therapy.

Results: Of the 250 patients evaluated, 47.6% were male, 68.4% former smokers, 53% NHW, 33.6% Hispanic, 8.8% Black, and 4% Asian. The median age at diagnosis was 65 ± 12 years. Actionable mutations (EGFR, KRAS, BRAFv600, ROS-1, ALK, MET, NTRK 1-3) were found in 44.4% of patients. The frequency of actionable EGFR mutations was higher in minority patients compared to NHW (32.7% vs 18%; p<0.01). The frequency of actionable EGFR mutations was similar between NHW and Hispanic patients (18% vs 22.6%; p=0.41); however, differences were observed comparing NHW to African American (18% vs 45.5%; p=0.01) and Asian (18% vs 90%; p<0.01) patients, respectively. Among patients receiving EGFR-targeted therapy, median PFS was 13.8 months for NHW and 18.1 months for minorities (HR 0.65; 95% CI 0.31 to 1.37). Median OS was 66.1 months for NHW and 34.7 months for minorities (HR 0.99; 95% CI 0.40 to 2.5).

Table 1. Actionable Mutations by Race and Ethnicity

Actionable Mutation	NHW (n=133)	Hispanics (n=84)	Blacks (n=22)	Asians (n=10)
EGFR, n (%)	24 (18)	19 (22.6)	10 (45.5)	9 (90)
KRAS, n (%)	12 (9)	7 (8.3)	1 (4.5)	0 (0)
BRAFv600, n (%)	4 (3)	2 (2.4)	0 (0)	0 (0)
ROS-1, n (%)	3 (2.3)	2 (2.4)	0 (0)	0 (0)
ALK, n (%)	1 (0.8)	4 (4.8)	0 (0)	0 (0)
MET, n (%)	5 (3.8)	3 (3.6)	0 (0)	0 (0)
NTRK1-3, n (%)	3 (2.3)	1 (1.2)	0 (0)	0 (0)
Total	52 (39.2)	38 (45.2)	11 (50)	9 (90)

Conclusions: GEP of minority patients with stage IV NSCLC varied from that of NHW, highlighting the need for increasing molecular biomarker testing in minority patients. Additionally, despite having a higher frequency of actionable mutations, there was a trend towards inferior OS among minority patients. A larger sample size could determine if this trend is statistically significant and if social determinants of health contribute to poorer outcomes in minority patients.

Keywords: Molecular biomarkers, Targeted therapy, Health disparities

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-108 Osimertinib Long-Term Tolerability in Patients with EGFRm NSCLC Enrolled in the AURA Program or FLAURA Study

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Introduction: Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits EGFR TKI-sensitizing (EGFRm) and EGFR T790M resistance mutations, including CNS metastases. Osimertinib is the preferred first-line treatment in metastatic EGFRm NSCLC, approved as ≥second-line treatment in EGFRm NSCLC with T790M mutations, and approved as adjuvant treatment in resectable EGFRm NSCLC. This post-hoc analysis of AURA program and FLAURA trials reports for the first time, long-term safety data in EGFRm metastatic NSCLC treated with osimertinib 80 mg once-daily (QD) for ≥36 months.

Methods: Safety and best-response data were analysed in patients in the AURA program (AURA, NCT01802632; AURA2, NCT02094261; AURA3, NCT02151981) who received ≥36 months treatment with ≥second-line osimertinib, and in patients in FLAURA (NCT02296125) who received ≥36 months (safety) and ≥54 months (response) first-line osimertinib. All patients received 80 mg QD, with dose reductions/interruptions due to AEs allowed. The post-study global safety database was used to capture serious adverse events (SAEs) in patients who continued osimertinib beyond the final data cut-off of the respective trials. Data in this database were reported voluntarily by treating physicians; therefore, all SAEs that may have occurred may not have been reported. Best-response data (per RECIST v1.1) were collected during trial conduct.

Results: Patient demographics and baseline disease characteristics were generally consistent with those in the respective overall trial populations. Across AURA trials, 124/799 (16%) patients received osimertinib for ≥36 months (AURA, n=43/344 [13%]; AURA2, n=35/210 [17%]; AURA3, n=46/245 [19%]); median duration of exposure (range) was 44.7 (36.0-81.2) months. In FLAURA, 76/267 (28%) and 36/267 (13%) patients received osimertinib for ≥36 and ≥54 months, respectively; median duration of exposure (range) in ≥36- and ≥54-month subgroups was 52.5 (37.4-70.2) and 64.5 (54.5-70.2) months, respectively. Following final data cut-offs in the AURA program and FLAURA trial, 26/124 and 8/76 patients reported SAEs, respectively, none treatment-related (**Table**). In patients who received ≥36 months osimertinib treatment across the AURA program (n=124), complete response (CR), partial response (PR) and stable disease (SD) occurred in 4 (3%), 95 (77%) and 19 (15%) patients, respectively. In patients in FLAURA who received ≥54 months osimertinib treatment (n=36), CR, PR and SD occurred in 1 (3%), 31 (86%), and 4 (11%) patients, respectively.

Conclusions: Patients receiving long-term osimertinib for 3 years or more demonstrate a positive tolerability profile. Available data are limited and should be interpreted with caution due to the constraints of post-study data collection.

Summary of adverse events in patients who received osimertinib 80 mg QD treatment for ≥36 months	**AURA program (N=124)**	**FLAURA (N=76)**
Clinical data collected during trial conduct, n* (%)		
Any AE	123 (99)	73 (96)
Any treatment-related† AE	113 (91)	68 (89)
Any AE ≥Grade 3	48 (39)	27 (36)
Any treatment-related† AE ≥Grade 3	16 (13)	8 (11)
Any AE resulting in death (including treatment-related† AEs)	1 (1)	0
Any SAE‡	44 (35)	13 (17)
Any treatment-related† SAE‡	6 (5)	2 (3)
Any SAE leading to interruption of treatment	19 (15)	8 (11)
Any SAE leading to discontinuation of treatment	2 (2)	0
Post-study data (SAEs only reported)§		
Any SAEs‡	26 (21)	8 (11)
Any treatment-related† SAEs‡	0	0
Any SAEs leading to interruption of treatment††	6 (5)‖	3 (4)¶
Any SAEs leading to discontinuation of treatment††	3 (2)**	0

*Multiple SAEs may be reported in a single patient
†As assessed by the investigator
‡Including those with an outcome of death
§Data on SAEs were provided voluntarily by physicians in the post-study global safety database; therefore, all SAEs that occurred may not have been reported in the post-study period
‖Pancreatitis acute/pancreatitis (n=1), impaired healing (n=1), pneumonia (n=2), arrhythmia (n=1), lower respiratory tract infection (n=1), gastroenteritis (n=1)
¶Abdominal pain (n=1), sepsis (n=1) and intestinal obstruction (n=1)
**Chronic myelomonocytic leukaemia (n=1), cardiac arrest (n=2)
††Dose interruptions and discontinuations were likely performed to allow recovery of the patient, as no reported SAEs were considered related to osimertinib by investigator
Abbreviations: AE, adverse event; QD, once daily; SAE, serious adverse event

Keywords: Osimertinib, EGFRm NSCLC, long-term tolerability

EP08.02-109 A Drug-Drug Interaction Study of Mobocertinib and Midazolam in Patients with Advanced Non-Small Cell Lung Cancer

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Introduction: Mobocertinib is an oral tyrosine kinase inhibitor designed to selectively target epidermal growth factor receptor (*EGFR)* exon 20 insertion (*EGFR* ex20ins) mutations in non-small cell lung cancer (NSCLC). In vitro studies indicated the potential for time-dependent inhibition and/or induction of cytochrome P450 (CYP) 3A after mobocertinib administration. Thus, a phase 1 drug-drug interaction study (NCT04051827) was conducted to assess the effect of repeat-dose administration of mobocertinib on the pharmacokinetics (PK) of midazolam, a sensitive CYP3A substrate.

Methods: In Cycle 1, patients with locally advanced or metastatic NSCLC refractory to standard therapies received a single 3-mg oral dose of midazolam on Days 1 and 24, and a single 1-mg intravenous dose on Days 2 and 25; mobocertinib 160 mg was administered QD on Days 3-30. After Cycle 1, patients could continue receiving mobocertinib in 28-day cycles until Cycle 24, progressive disease, or intolerable toxicity (**Figure**). The primary objective was to evaluate midazolam PK with and without mobocertinib; the secondary objective was to assess safety and tolerability of mobocertinib.

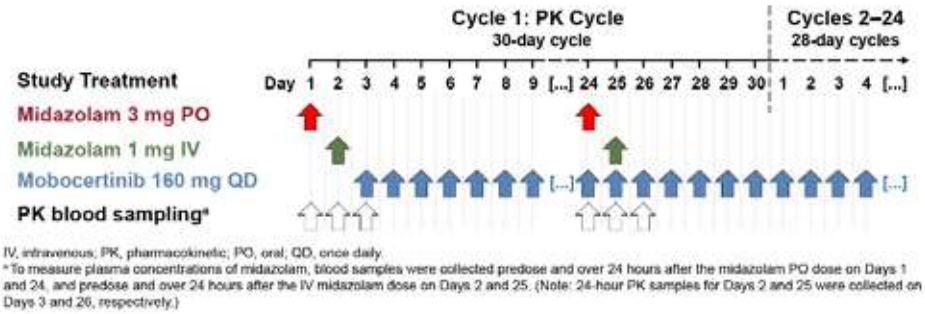
Results: Twenty-six patients were enrolled and included in the safety analysis population (median age, 65.5 years; female, 53.8%; 61.5% had baseline *EGFR* ex20ins mutations); 13 patients were evaluable for PK assessments. Coadministration of mobocertinib with oral or intravenous midazolam decreased the area under the plasma concentration-time curve (AUC_{∞}) for midazolam by 32% and 16%, respectively (**Table**). The most common treatment-related adverse events (TRAEs) with mobocertinib were diarrhea (96%), nausea (58%), decreased appetite (50%), fatigue (46%), and vomiting (35%). The only Grade ≥3 TRAE observed in ≥2 patients was diarrhea (42%).

Conclusions: Coadministration of mobocertinib reduced systemic exposures of midazolam, consistent with mobocertinib being a weak inducer of CYP3A. AEs were consistent with the known safety profile of mobocertinib.

Table. Geometric Mean (Geometric % Coefficient of Variation) Pharmacokinetic Parameters of Midazolam

	Midazolam Alone	Midazolam + Mobocertinib	Geometric LS Mean Ratio (90% CI)
Oral midazolam (3 mg)	**Day 1**	**Day 24**	
N	13	13	
$C_{max,}$ ng/mL	17.0 (60)	17.5 (61)	1.03 (0.74-1.42)
$AUC_{last,}$ ng·h/mL	53.5 (61)	39.6 (66)	0.74 (0.58-0.94)
$AUC_{\infty,}$ ng·h/mL	58.3 (61)	39.0 (61)[a]	0.68 (0.53-0.86)
IV midazolam (1 mg)	Day 2	Day 25	
N	13	13	
C_{max}, ng/mL	70.8 (151)	92.2 (132)	1.30 (0.89-1.92)
AUC_{last}, ng·h/mL	85.3 (116)	79.0 (123)	0.93 (0.72-1.19)
AUC_{∞}, ng·h/mL	90.4 (113)	71.6 (96)[a]	0.84 (0.67-1.04)

AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}, area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; IV, intravenous; LS, least squares; PK, pharmacokinetic; QD, once daily. [a] N=12.



IV, intravenous; PK, pharmacokinetic; PO, oral; QD, once daily.
[a] To measure plasma concentrations of midazolam, blood samples were collected predose and over 24 hours after the midazolam PO dose on Days 1 and 24, and predose and over 24 hours after the IV midazolam dose on Days 2 and 25. (Note: 24-hour PK samples for Days 2 and 25 were collected on Days 3 and 26, respectively.)

Keywords: mobocertinib, drug-drug interaction, midazolam

EP08.02-110 Plasma-based Molecular Profiling to Guide Treatment Decisions in Patients with Advanced NSCLC and Limited Tissue Biopsy

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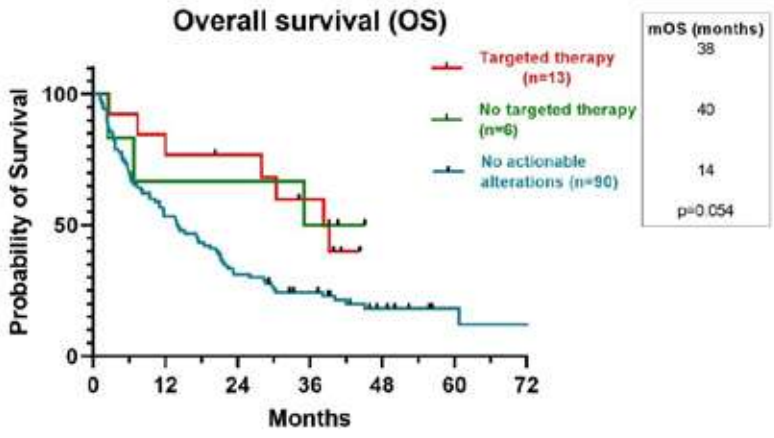
Introduction: Molecular profiling of tumor tissue is the gold standard for treatment decision making in advanced non-small cell lung cancer (NSCLC). However, tumor genotyping may be unavailable due to insufficient tissue samples. Plasma-based next-generation sequencing (NGS) is emerging as either complementary or alternative to standard tissue genotyping in advanced NSCLC. We present our experience using plasma-based NGS in advanced NSCLC.

Methods: We conducted a retrospective analysis of advanced NSCLC patients who underwent plasma-based NGS in our institution in Madrid (Spain) between August 2017 and March 2019. Patients underwent either Foundation One Liquid® or Guardant 360® as part of molecular prescreening for clinical trials (NCT03178552 and NCT02864992, respectively). Standard tissue genotyping, when feasible, was performed using PCR for *EGFR*, and immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) for *ALK* and *ROS1.* We analyzed the frequency of oncogenic drivers detected, the proportion of patients treated with genotype-directed therapy, and survival.

Results: 109 patients (pts) with advanced NSCLC were included for analysis. Median age was 63 years (range 37-83), 50% were women, 15% never smokers, 80% had adenocarcinoma histology. One third of the pts did not have enough tissue for conventional testing (*EGFR*, *ALK* and *ROS1*). Actionable alterations were identified in 19 pts (17%): 6 pts *EGFR* exon 19/21, 4 pts *MET* exon 14 skipping mutation, 3 pts ALK fusion, 2 pts *RET* fusion, 2 pts *BRAF V600E*, 1 pt EGFR exon 20 insertion and 1 pt *ERBB2* exon 20 insertion mutation. 70% of patients with actionable alterations were matched to targeted therapies: 100% of patients with an *EGFR exon 19/21* mutation (Erlotinib or Gefitinib), *ALK* fusion (Crizotinib or Alectinib) or *ERBB2* exon 20 insertion mutation (Poziotinib, clinical trial); 50% of patients *RET* fusion (Alectinib, clinical trial), 50% of patients with *MET* exon 14 skipping mutation (Tepotinib or Capmatinib, clinical trial) and 0% of patients with *BRAF V600E* mutation or *EGFR* exon 20 insertion mutation. Median OS was 14 months for patients without oncogenic driver mutations detected, 40 months for patients with actionable alterations and no targeted therapy, and 38 months for patients matched with targeted therapy (p= 0.054).

Conclusions: With the increasing number of targeted therapies developed for molecularly-driven NSCLC, genomic profiling of all patients with advanced adenocarcinoma is crucial. When there is not enough tissue for molecular testing, plasma-based NGS can guide first-line treatment decisions in metastatic NSCLC and increase access to targeted therapy, which may lead to prolonged survival.



Keywords: Liquid biopsy, molecular profiling, targeted therapy

EP08.02-111 RMC-4630, a SHP2 Inhibitor, in Combination with Sotorasib for Advanced KRASG12C NSCLC After Failure of Prior Standard Therapies: A Phase 2 Trial

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Introduction: RMC-4630 is a potent, selective, orally bioavailable allosteric inhibitor of SHP2, a protein tyrosine phosphatase functioning downstream of multiple RTKs as a convergent node in RAS signaling. In a Phase 1b monotherapy study, RMC-4630 demonstrated acceptable safety and tolerability with a novel intermittent dosing schedule (Day 1 and Day 2 of each week) and single agent activity in *KRAS^{G12C}* NSCLC tumors. Tumor and blood-based immune-oncology biomarkers demonstrated preliminary evidence of anti-tumor immune activation, supporting an immune-mediated mechanism of action for SHP2 in addition to modulation of RTK signal transduction. Combination treatment with RMC-4630 and a *KRAS^{G12C}* inhibitors significantly enhanced antitumor activity in preclinical models due to the fact that SHP2 inhibition can abrogate residual or bypass upstream RTK activity that occurs in response to *KRAS* inhibition. The combination of RMC-4630 and sotorasib is also being tested in advanced *KRAS^{G12C}* mutant solid tumors, including NSCLC in an ongoing Phase 1b study sponsored by Amgen (CodebreaK 101 Subprotocol C) within the US.

Methods: This Phase 2 multicenter, global, open-label study (RMC-4630-03; NCT05054725) sponsored by Revolution Medicines will characterize the efficacy, safety, tolerability, and PK of the RMC-4630 and sotorasib combination in previously treated subjects with *KRAS^{G12C}* NSCLC. Adult subjects (n=46) with locally advanced or metastatic *KRAS^{G12C}* NSCLC who have progressed on no more than 3 prior standard therapies are eligible. Patients with actionable mutations must have received standard-of-care anticancer treatments for oncogenic drivers in their tumor type and be naïve to prior G12C inhibitor treatment. Emerging clinical data from sotorasib and adagrasib monotherapy studies in *KRAS^{G12C}* NSCLC has revealed heterogeneity in the response of subpopulations defined by co-mutations in associated targets such as KEAP1 and STK11. The present study is designed to evaluate the antitumor effects of RMC-4630 and sotorasib in *KRAS^{G12C}* NSCLC subjects with and without co-existing genetic aberrations (including STK11, KEAP1, and PIK3CA). The primary endpoint is ORR per RECIST v1.1 as assessed by the investigator. Secondary endpoints include DOR, DCR, PFS, OS, safety/tolerability, and PK of RMC-4630 in combination with sotorasib. Initially, up to 6 subjects will be enrolled during the safety run-in portion of the study, in which RMC-4630 will be administered at the starting dose twice weekly (BIW) on D1D2 of each week for a treatment cycle of 21 days (3 weeks) in combination with 960 mg PO QD of sotorasib. The decision to increase the RMC-4630 dose will be guided by an mTPI-2 algorithm. The ultimate dose or doses of RMC-4630 for expansion will be determined by the sponsor after taking into consideration the totality of available data. This trial is currently enrolling in the United States and additional sites will also be open in Europe, UK, Australia, and Asia in 2022. The first patient was enrolled at the end of 2021 and enrollment is ongoing.

Keywords: SHP2, RAS, NSCLC

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-112 Precision Treatment of Non-small Cell Lung Cancer Has a Profound Impact on Outcomes in a Canadian Province

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Introduction: Identifying actionable driver mutations in NSCLC has enabled the broad adoption of precision oncology approaches into routine clinical practice. Improvements in testing infrastructure and tissue acquisition processes have made biomarker analysis increasingly available to patients diagnosed with NSCLC. While the benefit of these new systemic anti-cancer therapy (SACT) regimes was initially demonstrated in clinical trials, real world data are necessary to evaluate their societal contribution and confirm value to the health care system. Our objectives are to assess overall survival (OS) in de novo metastatic patients treated with TKI and compare these outcomes to those experienced by patients who received either cytotoxic chemotherapy (CTX), or those who were not treated with SACT.

Methods: The institutional Glans-Look Lung Cancer Research program database (GLR) is a resource that provides patient-level demographic, diagnostic, treatment, and outcome data on all patients with lung cancer diagnoses in Alberta. The GLR was used to identify four de novo metastatic NSCLC groups: 71 patients treated with TKI against confirmed anaplastic lymphoma kinase (ALK) rearrangement between 2014 and 2020 provincially, 416 patients treated with TKI against confirmed epithelial growth factor receptor (EGFR) mutation between 2010 and 2020 provincially, 250 patients who received first-line cytotoxic chemotherapy (CTX) as standard of care between 2010-2014 in Calgary, and 1,031 who were not treated with SACT (noSACT) between 2010-2014 in Calgary. Both CTX and noSACT groups represent patients in which biomarkers were not investigated.

Results: Univariate survival analysis shows that patients treated with TKI received the greatest benefit. The ALK group experienced the highest OS (50 months), followed by the EGFR group at 21.8 months. CTX patients experienced an OS of 11.6 months, while the no SACT group experienced the lowest OS (2.57 months). Overall, TKI-treated patients experienced a significantly longer survival time than those treated with CTX (23.1 vs. 11.6 months, log-rank p<0.001). A multivariate model controlling for known confounders of outcome (age, sex, histological subtype) demonstrates that the use of TKI in patients with detected driver mutation reduced the risk of death by 48% compared to CTX (HR: 0.52 [95%CI:0.44-0.62] p<0.001).

Conclusions: The successful execution of precision oncology in Alberta by combining tissue testing capabilities with the appropriate treatment yields profound improvements in OS for biomarker positive NSCLC patients. These findings highlight the importance of access to biomarker testing and associated TKI and demonstrate that Alberta is exhibiting OS trends consistent with globally published clinical real-world data. The unique capabilities of the GLR database allow researchers to differentiate these outcomes in diverse Albertan populations.

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-113 Clinico-genomic Characteristics of Patients with Non-small Cell Lung Cancer Harboring EGFR Exon 20 Insertion Mutations

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Introduction: *EGFR* in-frame insertions in exon 20 (Ex20ins) occur in 2-5% of non-small cell lung cancer (NSCLC). Several drugs for *EGFR* Ex20ins have recently been developed. However, due to the low frequency of *EGFR* Ex20ins in NSCLC, there was no large-scale cohort study investigating the clinico-genomic characteristics of NSCLC patients with *EGFR* Ex20ins.

Methods: A large-scale, prospective, multi-institutional lung cancer genomic screening project, LC-SCRUM-Asia, was initiated in February 2013, to identify lung cancer patients with targetable gene alterations and establish lung cancer precision medicine. A targeted next generation sequencing (NGS) has been performed for identifying cancer-related genes since March 2015. The patient characteristics and clinical outcomes of NSCLC patients with *EGFR* Exon20ins were compared with NSCLC patient with *EGFR* common mutations (exon19 deletions and L858R mutation) using a large-scale clinic-genomic database in LC-SCRUM-Asia. The treatment outcomes in NSCLC patients with *EGFR* Ex20ins were also investigated.

Results: A total of 8322 NSCLC patients were enrolled in LC-SCRUM-Asia between March 2015 and September 2020. Of the 8322 NSCLC patients, tumor specimens from 7717 patients (93%) were successfully analyzed by a targeted NGS, and 1491 NSCLC patients with EGFR mutations (19%) were screened. *EGFR* Ex20ins and common mutations were detected in 148 patients (1.9%) and 1122 patients (15%), respectively. Among the 148 NSCLC patients with *EGFR* Ex20ins, the most common subtype of *EGFR* Ex20ins was A767_V769dupASV (28%) and the second was S768_D770dupSVD (14%). Of the NSCLC patients with *EGFR* Ex20ins, the median age was 63 years old (range, 34-90), 66 patients (45%) were male, 76 patients (51%) were never smokers and the histology of 143 patients (97%) was adenocarcinoma. The NSCLC patients with *EGFR* Exon20ins was younger than the NSCLC patients with *EGFR* common mutations (67 years old [range, 26-97], $P < 0.01$). Among patients diagnosed with advanced or recurrence NSCLC and received systemic anti-cancer therapy, the patients with *EGFR* Ex20ins had a shorter overall survival (median: 26.2 vs 39.2 months, HR [95%CI]: 1.84 [1.4-2.3], $P < 0.01$) and a shorter progression-free survival (PFS) of TKIs compared to the patients with common mutations (median: 3.0 vs 13.9 months, HR [95%CI]: 5.2 [3.7-7.3], $P < 0.01$). In the NSCLC patients with *EGFR* Ex20ins, the objective response rate (ORR) and the median PFS of 1st line platinum-containing chemotherapies were 22% and 7.5 months (95%CI, 6.1-10.2), respectively. The ORR and median PFS of 2nd-4th line docetaxel with or without ramcirumab/bevacizumab were 29% and 6.1 months (95%CI, 5.1-8.5), respectively. The ORR of 2nd-4th line PD-1/PD-L1 monotherapy and TKIs were 4% and 12%, respectively. The median PFS of 2nd-4th line PD-1/PD-L1 monotherapy and TKIs were 2.9 months (95%CI, 1.8-3.4) and 2.6 months (95%CI, 1.7-3.6), respectively.

Conclusions: The NSCLC patients with *EGFR* Ex20ins responded poorly to TKIs and had a worse prognosis compared to the NSCLC patients with *EGFR* common mutations. Development of a novel treatment strategy for *EGFR* Ex20ins is needed. The NSCLC patients with *EGFR* Ex20ins showed poor responses to PD-1/PD-L1 monotherapy and TKIs. Cytotoxic agent chemotherapies are still standard therapies for NSCLC patients with *EGFR* Ex20ins.

Keywords: EGFR exon 20 insertion mutations, non-small cell lung cancer, next generation sequencing (NGS)

EP08.02-114 Comprehensive Analysis of ROS1 Aberrations without Rearrangements in Non-small cell Lung Cancer Patients

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Introduction: Fusions in the *ROS1* proto-oncogene are among the best treatable genetic aberrations in Non-small cell lung cancer (NSCLC). Besides the occurrence of solvent-front mutations (SFM) in acquired resistance to targeted therapy, little is known about small-scale *ROS1* aberrations. We comprehensively analyzed clinical and molecular characteristics of *ROS1* mutations in NSCLC patients without activating *ROS1* fusions or SFMs.

Methods: Next-generation sequencing (NGS) was performed on tissue samples from NSCLC patients within the National Network Genomic Medicine (nNGM). Patients with activating *ROS1* fusions detected by fluorescence in-situ hybridization (FISH) were excluded. We analyzed the molecular and clinical characteristics such as histology, smoking history, co-occurring mutations, stage and metastatic patterns. PD-L1 expression was quantified using immune-histochemistry (IHC).

Results: Of 8072 patients analyzed by NGS between 2018 and 2021, 118 (1.5%) patients harbored *ROS1* mutations. Most patients were male (76.3%) and had adenocarcinoma histology (57.6%). The median age at diagnosis was 68 years (range: 43-90 years). Nearly all of the patients (96.5%) had a smoking history, amassing 40 pack-years on average. At diagnosis, most patients presented with Eastern Cooperative Oncology Group's (ECOG) performance state 1 (31.4%) followed by state 2 (15.3%). Only a minority had state 0 (11%).

The majority (59.3%) of patients had UICC stage IV whereby 27.2% of patients featured Stage III; about 7% fall upon stage I and II. The metastatic pattern of all stage IV patients shows that 22.9% of metastasis is allotted to cerebral, 12.5% to lung, 16.7% to subdiaphragmatic, 14.9% to bone and 6.3% to skin metastasis. The patients' subgroup with mutually exclusive *ROS1* mutations resembles this trend: about a half of these patients had UICC stage IV, and the metastasis distribution featured similar characteristics.

Most *ROS1* mutations were transversions (53.6%), without defining a genomic hotspot region. Besides, *TP53* mutations (61.0%), *KRAS* (25.4%), *EGFR* (7.6%), *PIK3CA* and *FGFR1-4* mutations (5.9% each) co-occurred most frequently. In 12 (10.2%) patients, *ROS1* mutation was the only detected aberration. Most (52%) tumors expressed 1-49% of PD-L1, whereas 36.3% of tumors expressed no PD-L1.

Conclusions: The cohort contrasts the clinical characteristics of patients with *ROS1* fusion regarding sex, age, smoking history and histology. This evidence implies a basic clinical impact exerted by this molecular subtype. We warrant further research on the detected mutations to characterize the biological impact and the potential to act as a drug target.

Keywords: NSCLC, ROS1, targeted therapy

EP08.02-115 A Retrospective, Multicenter, Observational Study to Evaluate Outcomes with Lorlatinib After Alectinib in ALK+ NSCLC in Japan

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Introduction: Three years have passed since lorlatinib was approved in Japan in September 2018 for the treatment of *ALK*+ NSCLC. As not much is known about lorlatinib efficacy when given after first-line (1L) alectinib, we have conducted a real-world observational study. Here, we present the characteristics of patients treated with lorlatinib and determine its clinical efficacy in patients with *ALK*+ NSCLC.

Methods: This was a multicenter, retrospective, observational study (NCT04979988) conducted at 16 sites in Japan that included patients who had been treated with lorlatinib in any line after 1L alectinib treatment as a systemic therapy. Patients in this study started treatment with lorlatinib between May 1, 2019, and December 31, 2020, in clinical practice. The primary endpoints were to (1) characterize patient demographics at baseline and summarize them using descriptive analyses and (2) estimate time to treatment failure (TTF) by the Kaplan-Meier method in patients treated with lorlatinib as second-line (2L) or third-line or later (≥3L) treatment. Secondary endpoints included objective response rate (ORR) with lorlatinib beyond the 2L or ≥3L. Adverse event data were not collected except for reasons for discontinuation.

Results: Of 51 patients, 29 (56.9%) and 22 (43.1%) received lorlatinib in the 2L and ≥3L, respectively, after 1L alectinib treatment. In patients treated with 2L and ≥3L lorlatinib, the median age (range) was 57 years (36-76 years) and 63 years (33-79 years), respectively; 20 (68.9%) and 7 (31.8%) patients were male. In patients receiving 2L lorlatinib treatment, 65.5% had Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, 13.7% had ECOG PS 2 and beyond, and 20.7% had unknown ECOG PS. In patients receiving ≥3L lorlatinib treatment, 59.1% had ECOG PS 0 or 1, 18.2% had ECOG PS 2 and beyond, and 22.7% had unknown ECOG PS. At the start of lorlatinib treatment, 13 (44.8%) and 12 (54.5%) patients receiving 2L and ≥3L lorlatinib had brain metastases, respectively. The TTF was 10.8 months (95% CI, 3.9-13.8 months) with 2L lorlatinib and 11.5 months (95% CI, 2.9 months-not evaluable [NE]) with ≥3L lorlatinib after 1L alectinib. The median TTF was 11.5 months (95% CI, 3.9-NE months) in patients with brain metastases and 9.9 months (95% CI, 4.3-13.8 months) in patients without brain metastases. The ORR was 44.0% (95% CI, 24.4%-65.1%) with 2L lorlatinib and 23.5% (95% CI, 6.8%-49.9%) with ≥3L lorlatinib after 1L alectinib.

Conclusions: In patients without information of genetic resistant mechanism, TTF exceeded 10 months when lorlatinib was given after alectinib. The results of this study were consistent with the efficacy of lorlatinib observed in a clinical phase 2 study (NCT01970865).

Keywords: non-small cell lung cancer, lorlatinib, observational study

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-116 Design of a Phase 1 Study of AMG 193, an MTA-Cooperative PRMT5 Inhibitor, in Patients with Advanced MTAP-Null Solid Tumors

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Introduction: Protein arginine methyltransferase 5 (PRMT5) is an emerging target for cancer treatment. MTAP homozygous deletion occurs in 15% of cancers and often coincides with deletion of the tumor suppressor gene CDKN2A, leading to buildup of its substrate MTA. MTA shares close structural similarity to S-adenosyl methionine (SAM), the substrate methyl donor for PRMT5. By competing with SAM, MTA partially inhibits PRMT5. Thus, MTAP-null cancers are susceptible to further PRMT5 inhibition (Kryukov *Science* 2016). Current direct/indirect PRMT5 inhibitors (PRMT5i) showed preliminary anticancer activity, albeit with considerable toxicities due to their indiscriminate activities. AMG 193 is an MTA-cooperative PRMT5i that preferentially targets the MTA-bound state of PRMT5 that is enriched in MTAP-null tumors and represents a novel strategy to increase the therapeutic margin of this class of inhibitors. AMG 193 potently inhibits MTAP-null cancer cell lines and patient-derived xenografts.

Methods: NCT05094336 is a first-in-human (FIH), multicenter, open-label, phase 1/1b/2 trial evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of AMG 193 in patients with advanced MTAP-null solid tumors. Eligible patients (≥ 18 years) with histologically confirmed locally advanced/metastatic solid tumors not amenable to curative treatment with surgery and/or radiation, homozygous MTAP and/or CDKN2A deletion (by local next generation sequencing), or MTAP protein loss in tumors (by central immunohistochemistry), measurable disease, ECOG PS 0-1, adequate hematopoietic, renal, liver, pulmonary, cardiac, coagulation function and glucose control will be included. The study will be conducted in 3 parts, each with subparts. Here, we describe Part 1a/b (dose exploration). Five dose levels are planned. Treatment continues until progression or withdrawal. The primary objectives are to evaluate the safety and tolerability of AMG 193 monotherapy; endpoints include dose-limiting toxicities, treatment-emergent adverse events, serious adverse events, electrocardiograms, laboratory abnormalities, and vital signs. Secondary objectives include the characterization of the PK parameters of AMG 193 including C_{max}, T_{max}, and AUC after single or multiple doses. This study is expected to enroll approximately 30 patients in Part 1a/b. This is the first FIH trial open for enrollment for this new class of PRMT5i and enrollment is ongoing.

Keywords: PRMT5 inhibitor, MTAP-null, MTA-cooperative

EP08.02-117 Online CME Improves Clinicians' Ability to Identify and Manage Patients with NSCLC and EGFR Exon 20 Insertion Mutations

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Introduction: *EGFR* exon 20 insertion mutations occur infrequently and represent a small proportion of all *EGFR* mutations seen in NSCLC. These mutations are associated with de novo resistance to clinically available inhibitors that target *EGFR* with "classic" mutations like exon 19 deletions and exon 21 L858R. Recent scientific advancements have led to FDA approvals of targeted therapies that are selective for *EGFR* exon 20 insertion mutations and help fill an unmet need for these patients. However, due to the rarity of these mutations and the complexity of molecularly altered NSCLC overall, members of the multidisciplinary care team, including oncologists, pathologists, and pulmonologists, may be unfamiliar with optimal strategies to both identify and manage affected patients. The objective of this study was to assess the educational impact of a series of continuing medical education (CME) activities, developed through collaborations with Medscape Oncology, the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP), on the knowledge, competence, and confidence of oncologists, pathologists, and pulmonologists with respect to the identification and management of patients with NSCLC and *EGFR* exon 20 insertion mutations.

Methods: The educational series consisted of 3 online, CME-certified activities. Educational impact was assessed with repeated pre-/post-education including multiple choice knowledge/competence questions and 5-point Likert scale confidence questions. Data from all oncologists, pathologists, and pulmonologists who completed pre- and/or post-education assessments were aggregated across activities and stratified by learning theme. Relative changes in percentage of correct responses and clinicians who were confident (value of 4 or 5) were used to measure improvement in knowledge, competence, and confidence. A McNemar's test assessed significant levels of changes reported with P values <.05 considered statistically significant. The first activity launched July 2021 and the last launched January 2022; data were collected until February 2022.

Results: The educational series resulted in improvements in oncologists', pathologists', and pulmonologists' knowledge, competence, and confidence after education (N=52 to 277). Moreover, 92% of oncologist, 86% pathologist, and 88% pulmonologist learners experienced improvement in or reinforcement of knowledge/competence from the CME, which translated to measurable improvements in confidence after education.

Learning Theme	Oncologist (% Relative Change; *P* Value)	Pathologist (% Relative Change; *P* Value)	Pulmonologist (% Relative Change; *P* Value)
Knowledge of clinical trials evaluating therapies for NSCLC and *EGFR* exon 20 insertion mutations	60%; <.001	39%; <.05	79%; <.001
Knowledge of testing methodologies used to identify *EGFR* exon 20 insertion mutation s	4%; NS	12%; NS	50%; <.05
Competence diagnosing NSCLC with *EGFR* exon 20 insertion mutations	25%; <.001	20%; <.05	18%; NS
Confidence recognizing the role of *EGFR* exon 20 insertion mutations in NSCLC	89%; <.001	111%; <.01	100%; NS

Conclusions: This analysis demonstrates that oncologists', pathologists', and pulmonologists' knowledge, competence, and confidence regarding the identification and management of patients with NSCLC and *EGFR* exon 20 insertion mutations improved after education. Despite these improvements, additional educational activities are needed to address residual gaps and further increase clinicians' ability in this clinical setting.

Keywords: Continuing Education, EGFR Exon 20, NSCLC

EP08.02-118 TRUST-II: A Global Phase II Study for Taletrectinib inROS1fusion Positive Lung Cancer and Other Solid Tumors

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Introduction: Taletrectinib (AB-106/DS-6051b) is a next-generation, brain-penetrant, ROS1/ NTRK tyrosine kinase inhibitor (TKI) and has shown clinically meaningful effect and safety profile in ROS1+ Non-Small Cell Lung Cancer (NSCLC) patients in phase 1 studies (Fujiwara et al, Oncotarget 2018; 9(34): 23729-23737; Ou et al, JTO Clin Res Rep. 2020 Oct 21;2(1):100108). Taletrectinib has also demonstrated activity against ROS1 G2032R resistance mutation and CNS metastases in the ongoing phase 2 TRUST study (NCT04395677) in China. Also, taletrectinib has shown preliminary efficacy against NTRK positive solid tumors in an ongoing phase 2 study (NCT04617054)

Methods: TRUST-II study (NCT04919811) is a phase 2, global, multicenter, open-label, single-arm multi-cohort study evaluating the efficacy and safety of taletrectinib for *ROS1* fusion-positive advanced metastatic NSCLC and other solid tumors. Taletrectinib will be given at 600 mg once daily in 21-day cycle. The patients with ROS1 fusions detected by local tests are eligible to enroll with retrospective confirmation by a central laboratory. The study consists of four cohorts: cohort 1: systemic chemotherapy naïve or ≤ one prior line and ROS1 TKI naïve NSCLC (N=53); cohort 2: previously treated with one ROS1 TKI (crizotinib or entrectinib) and with progression who are either chemotherapy naïve or ≤ one line of platinum and/or pemetrexed based therapy for NSCLC (N=46); cohort 3: ≤ 2 prior ROS1 TKIs and with progression who are either chemotherapy naïve or ≤ 2 lines of platinum and/or pemetrexed based therapy for NSCLC (N=10); and cohort 4: systemic chemotherapy naïve or ≤ 2 prior lines of chemotherapy, but ROS1-TKI naïve ROS1 positive solid tumor other than NSCLC (N=10). The primary endpoint is objective response rate (ORR) (RECIST v1.1) by independent review committee (IRC) assessment for cohorts 1 and 2. Key secondary endpoints include IRC-assessed duration of response, IRC-assessed intra-cranial ORR, progression free survival (PFS), overall survival (OS), and safety. This study is currently recruiting in Japan, Republic of Korea, and USA. Additional accrual is planned in Canada, China, and European Union.

Keywords: Taletrectinib, ROS1 fusion, NSCLC

EP08.02-119 RNA Sequencing to Characterize Pathways in EGFR-mutated Non-Small Cell Lung Cancer

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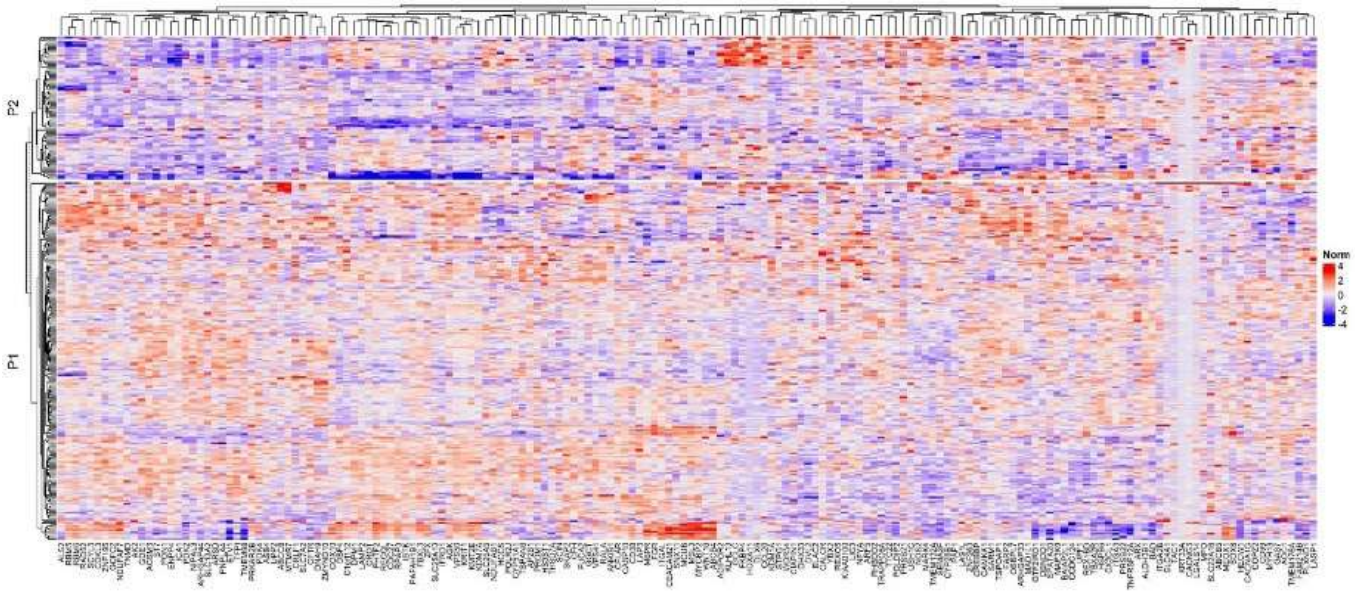
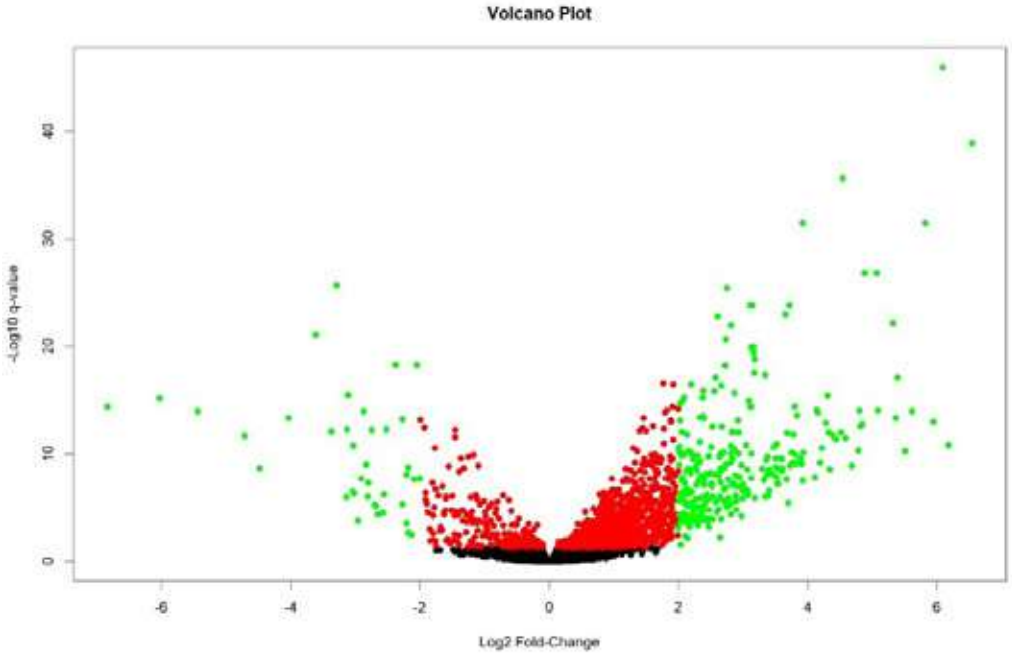
Introduction: The purpose of our study is to identify potential subgroups of patients with *EGFR*-mutated non-small cell lung cancer (NSCLC) based on phenotypic (gene expression) features and to compare patient characteristics with gene expression.

Methods: 287 patients with *EGFR*-mutated lung cancer were identified using the Tempus Lens database. Unsupervised clustering was performed using partitioning of data into 'k' number of clusters around medoids. Sequences were filtered for the top 1% of genes. RNA sequencing expression analysis was performed using age at the time of cancer diagnosis (< 70 years old vs. ≥ 70 years old) as one study parameter of interest. Volcano plots were generated within the edgeR package in the R programming language.

Results: The top 1% of genes (172 genes) were represented in clusters (Figure 1). 2-cluster analysis contained the most uniformly divided number of patients in each subgroup (205 in cluster P1 vs. 82 in cluster P2. In comparing patients < 70 years old to patients ≥ 70 years old, there were differences in gene expression between the two groups, depicted on volcano plot (Figure 2). All the genes were labeled 'black.' Those passing the significance threshold of qvalue < 0.05 were labeled 'red'. Genes with absolute log2 fold change > 2 were labeled 'orange'. Genes that passed both qvalue significance threshold of < 0.05 and log2 fold-change > 2 were labeled 'green'

Conclusions: Two distinct subgroups of patients with *EGFR*-mutated lung cancer were identified from unsupervised gene cluster analysis. Significant differences in gene expression were observed when stratifying patients by age using cutoff of 70. RNA sequencing is a promising tool to identify differentially upregulated gene expression pathways in patients with *EGFR*-mutated lung cancer. Future directions also include examining early (stage I-II) vs. late (stage III-IV) presentations and patients who progress early on tyrosine kinase inhibitors.





Keywords: RNA Sequencing, Non-small cell lung cancer, EGFR-mutation

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-120 MET Alterations at Presentation in NSCLC Patients Harboring EGFR Mutations and ALK, RET and ROS1 Fusions

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Introduction: Although *EGFR*-mut and *ALK*, *RET* and *ROS1* fusion-positive NSCLC patients are treated first-line with tyrosine kinase inhibitors (TKIs), some present intrinsic resistance and could benefit from combined treatments.To determine the frequency of *MET* gene amplification, *MET* mutations and *MET* mRNA high expression baseline in a large cohort of *EGFR*-mut and *ALK*, *ROS1* and *RET* fusion-positive NSCLC patients; (ii) To analyze paired biopsies of *EGFR* and fusion positive patients showing *MET* amplification at progression to targeted therapies.

Methods: Stage IIIB-IV NSCLC biopsies of patients arrived to our institutions were submitted to Next Generation Sequencing (NGS) for mutations and copy number variations and nCounter for mRNA analysis. Immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) were used for confirmatory purposes.

Results: Baseline biopsies from 72 *EGFR*-mut advanced NSCLC patients were submitted to NGS. Of them, 3/72 (4%) harbored *MET* amplifications, the three cases were confirmed by FISH. No mutations in the MET kinase domain were observed. Among the 72 cases, 26 had mRNA available for nCounter. Very high expression of *MET* was observed in 2/26 patients (8%) and was confirmed by IHC. In addition, 53 fusion-positive patients were included in the study, harboring ALK (n=36), ROS1 (n=10) and RET (n=7) translocations. *MET* amplification was observed in 1/53 (2%) case and 2/53 (4%) patients showed very high levels of *MET* mRNA. Finally, paired biopsies at presentation were available from 3 patients showing *MET* amplification at progression to osimertinib (n=2) and lorlatinib (n=1). The baseline biopsy from one of the patients treated with osimertinib was positive by IHC (50%, 3+) but negative by FISH, the other two pretreatment biopsies were negative by both techniques

Conclusions: A significant number of NSCLC patients with targetable alterations present with *MET* amplification or very high expression. Clinical trials should determine if first line combination treatment could be beneficial in this setting

Keywords: MET, Combined theraphy, Pretreatment

EP08.02-121 The Landscape of Anti-neoplastic Drugs for Malignant Pleural Effusion in Non-small Cell Lung Cancer: A Systematic Review of Clinical Trials

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Introduction: Malignant pleural effusion (MPE) occurs in 7-25% of patients with advanced non-small cell lung cancer (NSCLC). Anti-neoplastic agents are emerging as a treatment for MPE, but many usage details need to be determined, especially for the effective regimens. Thus, we conducted this systematic review to determine the optimum anti-neoplastic agent in managing MPE in NSCLC patients.

Methods: We systematically searched PubMed, Scopus, CENTRAL, ASCO, ESMO, and IASLC meeting libraries to identify relevant studies. All clinical trials in which patients were treated for MPE with anti-neoplastic agents such as chemotherapy and/or targeted therapy were included without any dose limitation. Patients treated with radiotherapy were excluded. Efficacy was evaluated according to either the Response Evaluation Criteria In Solid Tumors (RECIST) or World Health Organization Standards (WHO) criteria. Data extracted from each study included number of patients, sex, histology, type of treatments, Route of Administration (ROA), type of response criteria, and outcomes. We pooled objective response rate (ORR) in studies that used WHO criteria and median overall survival (mOS). Furthermore, we calculated the odds ratio (OR) of ORR according to ROA.

Results: We screened 2639 article abstracts and 75 full-text articles to include 17 relevant articles with a total of 1278 patients. There were eight randomized clinical trials, 8 phase II trials, and one phase I trial with 25 relevant treatment arms. Four arms used platinum-based monotherapy (PBM), 2 arms for paclitaxel monotherapy (PM), two arms for bevacizumab (BEV) monotherapy, 8 combination chemotherapy (CC), 7 BEV combination therapy and 2 arms for gefitinib. The reported median age was 68 (range 35-87 years). 62.8% of the patients were males and adenocarcinoma was the most common type (85.9%). In fourteen arms, drugs were administered by intrapleural infusion (IP), while nine arms were by intravenous infusion (IV), and two arms orally. The outcomes were evaluated using RECIST in 5 trials and 12 were evaluated using the WHO criteria. As for efficacy, pooled ORR from 12 studies was 59%. The use of IP ROA had higher odds of better ORR for BEV-based treatment (OR=4.90; 95%CI: 2.11-11.3) and CC (OR= 1.59; 95%CI: 1.04-2.41). The pooled mOS was reported in 11 studies with a range of 7-27 months. Regarding adverse events (AEs), 15 trials reported grade 3/4 AEs with a total occurrence rate of 14.1%. Nausea and vomiting were higher in CC than PBM (10.9% vs 9.6%). Chest pain was only seen in CC with a rate of 1.4%, leukopenia was higher in BEV regimens than PBM (14.7% vs 9.1%), and neutropenia was more common in BEV than both PBM and CC (14.7%, 9.1%, and 2.1, respectively).

Conclusions: Our study demonstrated the feasibility of different modalities in managing MPE. IP was superior to IV in the case of BEV-based and CC regimens. The studies were heterogeneous which might be explained by the use of different modalities, sample size and inconstancies reporting. Also, there were different reporting methods in the included studies, thus we recommend using both criteria for assessing MPE and NSCLC response in further trials.

Keywords: malignant pleural effusion, non-small cell lung cancer, route of administration

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-122 Real-world Experience with Capmatinib in MET Exon 14-mutated Non-small Cell Lung Cancer (RECAP)

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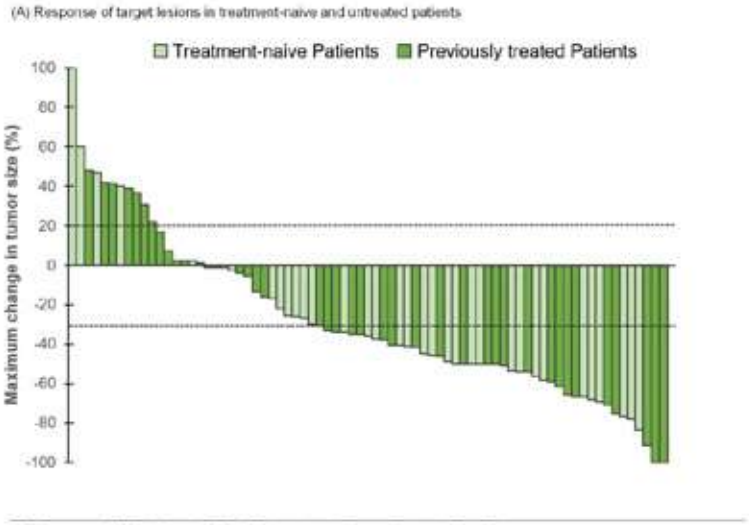
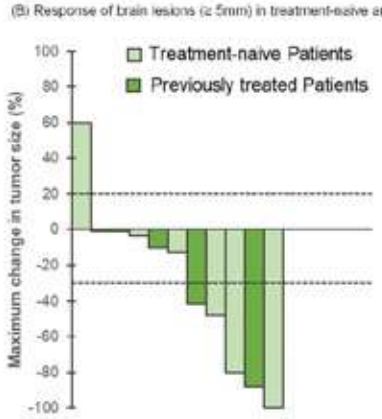
Introduction: Patients with non-small-cell lung cancer (NSCLC) presenting with *MET* exon 14 skipping mutation have an unfavorable prognosis with standard treatments. Capmatinib is a selective MET-inhibitor, which showed promising efficacy in this patient population in early trials.

Methods: We performed a retrospective efficacy and safety analysis in patients with NSCLC treated with capmatinib in an early access program.

Results: Data from 81 patients with advanced *MET* exon 14 mutated NSCLC treated with capmatinib in first- or later-line therapy were analyzed. Median age was 77 years (range, 48-91), 56% were women, 86% had stage IV disease, and 27% had brain metastases. For all patients the objective response rate (ORR) to capmatinib was 58% (95% CI, 47-69), while it was 68% (95% CI, 50-82) in treatment-naïve and 50% (95% CI, 35-65) in pretreated patients. The median progression-free survival (PFS) was 9.5 months (95% CI, 4.7-14.3), while it was 10.6 months (95% CI, 5.5-15.7) in first-line and 9.1 months (95% CI, 3.1-15.1) in pretreated patients. After a median follow-up of 11.0 months, the median overall survival (OS) was 18.2 months (95% CI, 13.2-23.1). In patients with measurable brain metastases (n=11) the intracranial ORR was 46% (95% CI, 17-77). Capmatinib showed a manageable safety profile. Grade ≥ 3 treatment-related adverse events included peripheral edema (13%), elevated creatinine (4%) and liver enzymes (3%).

Conclusions: In patients with *MET* exon 14 skipping mutation, capmatinib shows durable systemic and intracranial efficacy and a manageable safety profile. This analysis confirms previously reported phase II data in a real-world setting.





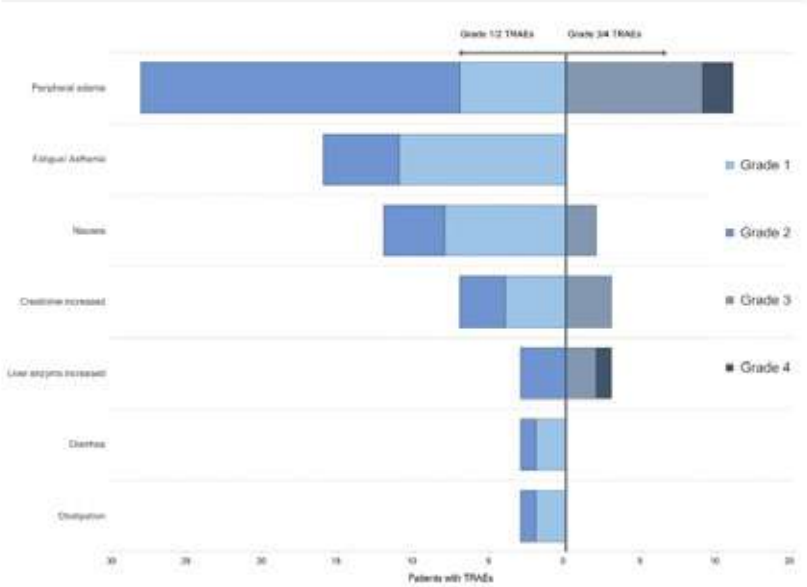


Figure 2. Treatment-related adverse events (TRAEs): Data cut-off date: November 8, 2021; treatment-related adverse events (TRAEs) that occurred at any grade in at least 2% of treated patients. The analysis included all patients who received at least one dose of capmatinib. Relatedness of any adverse event to the treatment was assessed by the treating physician. TRAEs were graded as per Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) as determined by the treating physician. Liver enzymes were including aspartate aminotransferase

Keywords: targeted therapy, MET exon 14 skipping mutation, capmatinib

EP08.02-123 First Line Osimertinib in Lung Cancer Patients with Postoperative Recurrence

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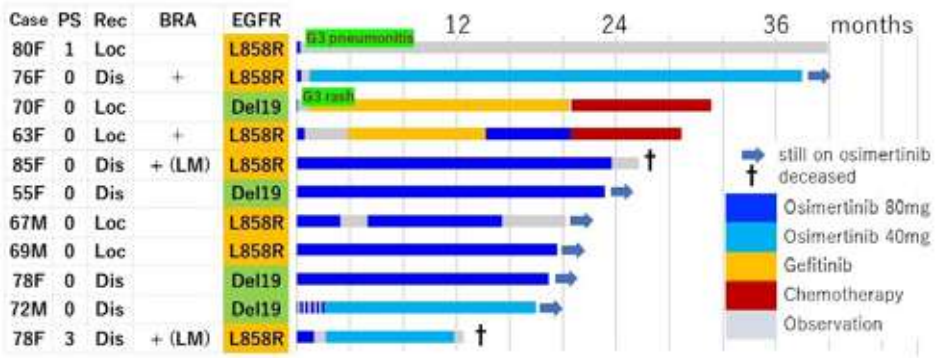
Introduction: Although osimertinib was recently approved by the FDA as adjuvant therapy for non-small cell lung cancer (NSCLC) patients with EGFR exon 19 deletion or exon 21 L858R mutation based on positive PFS results from the ADAURA trial (Osimertinib versus placebo in patients with stage IB-IIIA NSCLC, following complete tumor resection with or without adjuvant chemotherapy, NCT02511106), it remains controversial whether all eligible patients should receive osimertinib as adjuvant therapy following tumor resection.

Methods: Patients who received osimertinib as first line treatment for postoperative recurrence between September 2018 and November 2020 were included. Patients who received other EGFR-TKI(s) prior to osimertinib treatment were excluded. Duration of treatment, adverse events, and survival data were collected and analyzed.

Results: Eleven patients received osimertinib, three of whom were male, ranging in age from 55 to 85 years (median 72); EGFR mutation type was L858R in seven patients and exon 19 deletion in four patients; Performance Status (PS) was 0 or 1 in all but one patient, who had LM (leptomeningeal metastasis) and was therefore PS 3. The first site of postoperative recurrence was locoregional in five patients and distant metastases in seven patients, including four patients with CNS metastasis. As of March 2022, six patients were still on osimertinib, including one with CNS metastasis, and the median duration of treatment was 18 months (Figure). Two patients whose first site of recurrence was LM initially responded to osimertinib, but both died of disease progression after 23.7 and 11.8 months of treatment, respectively. Two patients were unable to continue osimertinib due to serious adverse effects (pneumonitis, drug eruption).

Conclusions: Osimertinib, a third-generation EGFR-TKI, is known to penetrate the blood-brain barrier and improve disease control even in patients with CNS metastases. This explains why the ADAURA trial showed a lower hazard ratio than the CTONG1104 trial, which showed superiority of erlotinib given daily for 2 years over adjuvant platinum doublet in patients with completely resected, EGFR positive, stage II-IIIA NSCLC patients. Our data showed a favorable overall response to osimertinib in patients with postoperative recurrence, but two patients with LM as the site of first recurrence had a poor prognosis due to low or worsening PS. Because CNS metastases, especially LM, may have a poor prognosis even with osimertinib treatment, the use of osimertinib as adjuvant therapy is recommended unless contraindicated.

Figure



Keywords: EGFR, recurrence, leptomeningeal metastasis

EP08.02-124 Lorlatinib Treatment Related Adverse Events: Single Centre Real-World Experience in ALK and ROS1-driven NSCLC

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Introduction: Lorlatinib is an ALK and ROS1 targeted next-generation tyrosine kinase inhibitor (TKI). Real-world treatment related adverse event (TRAE) data are limited. We reviewed TRAEs and therapeutic efficacy for advanced non-small-cell lung cancer (NSCLC) patients receiving lorlatinib at our centre.

Methods: Patients were identified through pharmacy lists. Demographics, TRAEs and efficacy metrics were retrospectively collated from medical records. Treatments and imaging frequency were per routine clinical care. The primary outcome was safety and tolerability; the secondary outcome was response rate (ORR).

Results: Thirty-three patients commenced lorlatinib between 2016 and 2021 (demographics: table 1). Lorlatinib TRAEs are summarised in Table 2; 93% were grade (G) 1-2, nine (5%) were G3. Three (9%) patients experienced G4 TRAEs: two had G4 depression and thoughts of self-harm; one experienced G4 psychosis requiring hospitalisation and later G3 psychotic depression after lorlatinib dose re-escalation. One patient died due to disease progression (PD), the death was considered unrelated to lorlatinib. Fifteen patients (45%) required treatment interruption, commonly for oedema (5/15) and mood disturbance (4/15). Twelve (36%) required dose-reduction (DR): again, most commonly for mood disturbance (5/12) and oedema (5/12). Other reasons included neuro-cognitive abnormalities, dizziness and QTc prolongation. Twenty-two patients discontinued lorlatinib, 19/22 (86%) due to disease progression, and one due to pneumonitis. Overall, the ORR was 53.8% and 71.4% for ALK- and ROS1-positive NSCLC, respectively. Of 20 patients with evaluable intracranial disease, 7 (35%) achieved intracranial complete response, 7 (35%) partial response, and 5 (25%) stable disease. The median time to extracranial and intracranial progression were 242 days (range 50-1084) and 350 days (range 55-785), respectively.

Conclusions: Lorlatinib is an effective treatment for ALK- and ROS1-driven NSCLC. TRAE, particularly mood, neurocognitive disturbance and oedema are challenging in clinical practice. First-line lorlatinib will require optimal AE management.

Demographics	All patients N = 33 N (%)	ALK N = 24 N (%)	ROS1 N = 9 N (%)
Molecular subtype			
ALK	24 (73%)		
ROS1	9 (27%)		
Age (years) Median (range)	51 (28-75)	54 (30-73)	48 (28-75)
Gender			
Male	14 (42%)	11 (46%)	3 (33%)
Female	19 (58%)	13 (54%)	6 (67%)
Smoking history			
Never	23 (70%)	17 (71%)	6 (67%)
Ex-smoker	10 (30%)	7 (29%)	3 (33%)
Current	0 (0%)	0 (0%)	0 (0%)
NSCLC subtype			
Adenocarcinoma	32 (97%)	23 (96%)	9 (100%)
SqCC	0 (0%)	0 (0%)	0 (0%)
Adenosquamous	1 (3%)	1 (4%)	0 (0%)
Prior lines of treatment			
1	10 (30%)	6 (25%)	4 (44%)
2	7 (21%)	5 (21%)	2 (22%)
3	10 (30%)	7 (29%)	3 (33%)
4-5	6 (18%)	6 (25%)	0 (0%)
Prior treatments			
Chemotherapy			
Platinum-pemetrexed	15 (45%)	12 (50%)	3 (33%)
Platinum-vinorelbine			
Tyrosine kinase inhibitors	1 (3%)	0 (0%)	1 (11%)
Alectinib			
Brigatinib	12 (36%)	12 (50%)	0 (0%)
Crizotinib	8 (24%)	8 (33%)	0 (0%)
	23 (70%)	15 (62%)	8 (89%)

Table 1. Patient demographics

	All patients (N=33)						
Adverse event	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (%)
Hypercholesterolaemia	30	14	14	2	0	0	91
Hypertriglyceridemia	24	15	7	2	0	0	73
Oedema	17	10	7	0	0	0	52
Mood	13	9	1	1	2	0	39
Peripheral neuropathy	11	9	1	1	0	0	33
CPK rise	11	7	3	1	0	0	33
Neurological	10	8	2	0	0	0	30
Arthralgia	7	6	1	0	0	0	21
Raised amylase	6	6	0	0	0	0	18
Cognitive	6	5	1	0	0	0	18
Cardiac conduction abnormality	3	3	0	0	0	0	9
Fatigue	2	2	0	0	0	0	6
Weight gain	2	2	0	0	0	0	6
Diarrhoea	1	1	0	0	0	0	3
Pneumonitis/ILD	1	1	0	0	0	0	3
Rash	1	1	0	0	0	0	3
Psychosis	1	0	0	0	1	0	3
Other	26	19	5	2	0	0	79

Table 2. Frequency and grade of treatment related adverse events for patients treated with lorlatinib. Grade as per CTCAE v5.0. * Other AEs include (n): myalgia (4), alanine transferase rise (2), alopecia (2) anaemia (2), dizziness (2), dyspnoea (2), GGT rise (2), alkaline phosphatase rise (1), hyperkalaemia (1), hypertension (1), hyperglycaemia (1), hypocalcaemia (1), low libido (1), mouth ulcers (1), myocarditis (1), nausea (1), skin infection (1).

Keywords: Lorlatinib, Non-small cell lung cancer

EP08.02-125 Tumor Suppressor Gene Alterations Identified at Disease Progression Impact Outcomes in Patients with EGFR-mutant Lung Cancer

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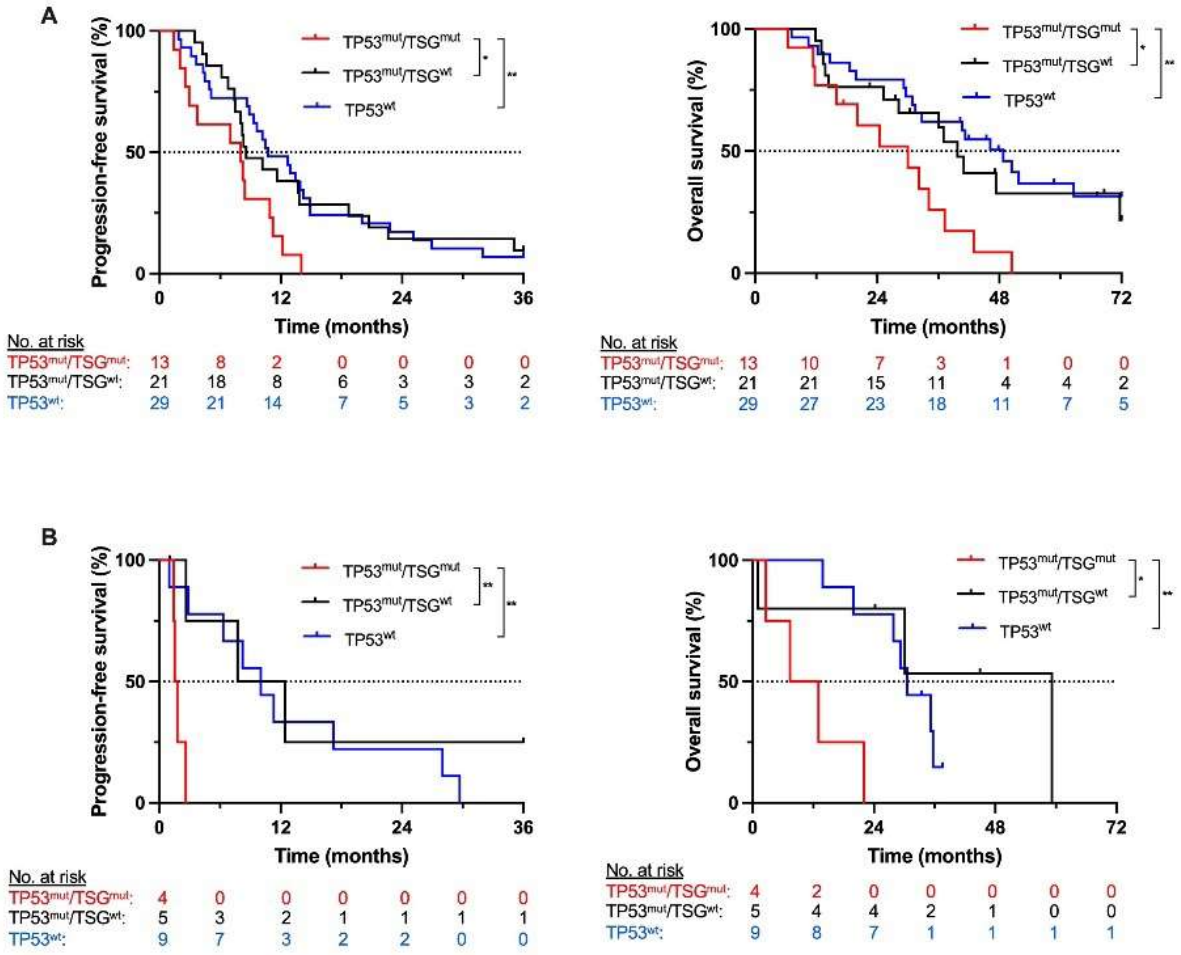
Introduction: Despite improvements in outcomes for patients with *EGFR*-mutant NSCLC, tumors inevitably relapse during tyrosine kinase inhibitor (TKI) treatment. Alterations in tumor suppressor genes (TSGs) have been described as determinants of molecular and clinical heterogeneity in *EGFR*-mutant NSCLC, however, detailed outcome analyses based on specific TSGs are limited.

Methods: Patients with *EGFR*-mutant NSCLC with targeted next-generation sequencing on blood or tumor tissue at disease progression on EGFR-TKI were included. Clinicopathological characteristics and outcomes including progression-free survival (PFS) and overall survival (OS) were assessed in the following subsets: presence of a *TP53* mutation plus a mutation in ≥1 of the four most frequently altered additional TSGs surveyed (*TP53*^{mut}/TSGmut), *TP53* mutation without another TSG mutation (*TP53*^{mut}/TSGwt), and *TP53* wild-type (*TP53*^{wt}). Using the AACR Project GENIE database, analyses were also performed on a separate cohort of patients who progressed on EGFR-TKI.

Results: Sixty-three patients at the Yale Cancer Center were retrospectively included. *TP53* mutations were identified in 34 (54%) cases, 13 (38%) of which also harbored mutations in ≥1 additional TSG including *NF1* (n=6), *RB1* (n=4), *BRCA1* (n=4) and *PTEN* (n=3). *TP53* mutations were more common in tumors with *EGFR* exon 19 deletion mutations versus L858R or compound mutations (68.6% vs 50% vs 11.1%, p=0.007). Strikingly, patients with *TP53*^{mut}/TSGmut tumors had worse outcome on first-line TKI than *TP53*^{mut}/TSGwt (median PFS 8.0 vs 8.6 months, p=0.03; median OS 30.0 vs 39.9 months, p=0.03) and *TP53*^{wt} cases (median PFS 8.0 vs 10.7 months, p=0.005; median OS 30.0 vs 48.8 months, p=0.002, figure 1A). Similarly, outcomes for second-line osimertinib were worse in the *TP53*^{mut}/TSGmut subgroup compared to *TP53*^{mut}/TSGwt (median PFS 1.6 vs 10.1 months, p=0.007; median OS 10.2 vs 59.2 months, p=0.048) and *TP53*^{wt} cases (median PFS 1.6 vs 10.0 months, p=0.003; median OS 10.2 vs 30.6 months, p=0.002, figure 1B). In multivariate Cox regression analysis, *TP53*^{mut}/TSGmut status independently associated with PFS (HR 2.6, p=0.008) and OS (HR 3.1, p=0.004) after controlling for major clinical characteristics. These findings were confirmed in the AACR GENIE database, with a shorter PFS and OS among patients with *EGFR*-mutant NSCLC with *TP53*^{mut}/TSGmut tumors versus *TP53*^{mut}/TSGwt and *TP53*^{wt} cases.

Conclusions: Although *TP53* mutations in *EGFR*-mutant NSCLC are known to predict for worse outcomes on EGFR-TKIs, we demonstrate that additional TSG alterations detected at disease progression on EGFR-TKI are common and associated with outcomes more than *TP53* mutation status itself. Accordingly, identifying TSG alterations may contribute significantly to risk-stratification in *EGFR*-mutant NSCLC.

FIGURE 1.



Keywords: EGFR-mutant NSCLC, Resistance, Tumor suppressor genes

EP08.02-126 The MOMENT Disease Registry of Patients with Advanced Non-Small Cell Lung Cancer Harboring MET Exon 14 Skipping

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Introduction: *MET* exon 14 (*MET*ex14) skipping activates oncogenic MET signaling in 3-4% of patients with non-small cell lung cancer (NSCLC). The low frequency of this alteration has influenced the investigation of MET inhibitors, often leading to an open-label, single-arm trial design, in order to maximize the number of patients receiving these compounds. One example is the global Phase II VISION single-arm study of the oral, highly selective MET inhibitor tepotinib in patients with *MET*ex14 skipping NSCLC, in which tepotinib demonstrated robust and durable activity with an objective response rate of 49.1% (data cut off: Feb 1, 2021). Availability of historical real-world data from patients with *MET*ex14 skipping NSCLC under conventional therapies is limited because broad MET biomarker testing was only recently introduced in most countries. Given the rarity of this patient population and to address the limitations of existing real-world data sources, the MOMENT registry aims to collect data prospectively and enable analyses of uniform, comprehensive, and high-quality data on the baseline characteristics, treatment patterns, and clinical outcomes of patients with advanced NSCLC harboring *MET*ex14 skipping in routine clinical practice.

Methods: MOMENT is a multinational, non-interventional disease registry collecting data on patients with advanced NSCLC harboring *MET*ex14 skipping receiving any systemic treatment. Both newly diagnosed patients and those already receiving therapy are eligible. Patients with previous participation in any clinical trial can be included, provided they receive at least one subsequent therapy line in a routine clinical setting. Eligible systemic treatments include all available anticancer therapies, including those approved, conditionally approved, or available through Early Access Programs; for example, immune checkpoint inhibitors, chemotherapy, and MET inhibitors. Data collection will include biomarker testing results (e.g. *MET*ex14 skipping confirmation, PD-L1 status, and co-mutational profile), patient demographics, baseline clinical characteristics, treatment details for each therapy line, efficacy parameters (e.g. longitudinal radiologic tumor assessment, including physician reports and primary imaging data), as well as safety information (standardized using NCI-CTCAE and MedDRA terminologies). Prior to the initiation of a site, the local *MET*ex14 skipping detection methods will be assessed and, if required, central confirmation of *MET*ex14 skipping using available biopsy samples will be arranged. Data collection will begin in 2022 and continue for five years. The registry is planned to operate at >30 sites across Europe and North America and is expected to enroll approximately 700 patients.

Results: None

Conclusions: The MOMENT registry will collect comprehensive, high-quality real-world clinical data from patients with advanced NSCLC harboring *MET*ex14 skipping undergoing systemic treatment in a routine clinical setting to facilitate future studies in this rare patient population and thus inform on the optimal treatment for these patients.

Keywords: NSCLC, METex14 skipping, disease registry

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-127 Resistance Mechanisms to Osimertinib in Advanced EGFR-mutated NSCLC: A Single Institution Prospective Cohort Study

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Introduction: Osimertinib is a recommended first-line treatment for advanced *EGFR*-mutated (deletion in exon 19 and exon 21 L858R) and EGFR-TKI pretreated T790M-positive non-small cell lung cancer. Resistance to osimertinib inevitably developed after a period of treatment and this study aims to evaluate the mechanisms of resistance.

Methods: We prospectively collected tissue samples from patients having advanced *EGFR*-mutated NSCLC previously treated with osimertinib as first-line or later line treatment who developed resistance to osimertinib. Tissue sample was analyzed utilizing the FoundationOne platform.

Results: Among 39 eligible patients, 4 received osimertinib as first-line therapy and 35 patients received osimertinib as a later line treatment. The median time from commencement of osimertinib to tumor rebiopsy was 12.2 months. The original activating mutations were detected in 94.9% and T790M was detected in 15.4% of the patients (including 2 patients with de novo T790M). Alterations in TP53 (69.2%), Rb1, PIK3CA, CDKN2A (17.9%) and MTAP (15.4%) were detected. Amplification of MET (23.1%), NKX2-1 (20.5%), NFKBIA (17.9%), EGFR (15.4%), CCNE1 and MYC (12.8%) were detected. Five patients developed acquired *EGFR* C797S (n = 3) and L718V/Q (n = 2) mutations. Five patient developed histological transformation of squamous cell (n = 2), small cell (n = 1), sarcomatoid (n = 1) and pleomorphic (n = 1) carcinoma. The time from commencement of osimertinib therapy to tumor biopsy was significantly longer in those who developed potentially druggable *MET* amplification and acquired *EGFR* mutation (median 20.5 vs. 10.4 months, p = 0.03).

Conclusions: In patients with *EGFR*-mutated advanced NSCLC who received osimertinib therapy, Potentially druggable *MET* amplification and acquired *EGFR* mutation took a longer time to develop as compared to other resistance mechanisms.

Keywords: EGFR mutations, osimertinib resistance, next-generation sequencing

EP08.02-128 Long Term Efficacy of SNK01 Plus Pembrolizumab for NSCLC: Expanded Observation from a Phase I/II A Randomized Controlled Trial

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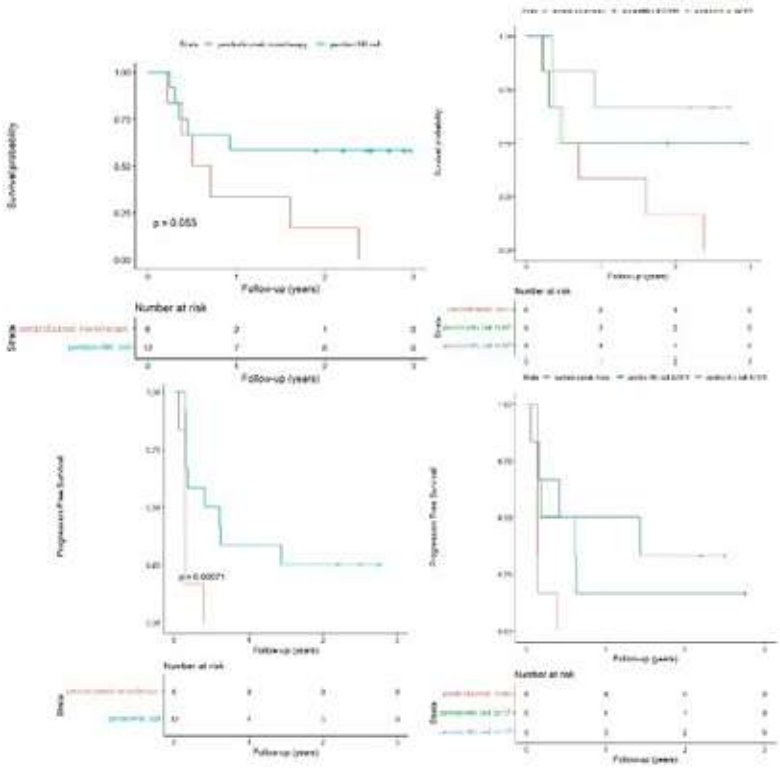
Introduction: Previous NK cell role with pembrolizumab for advanced NSCLC showed better efficacy than pembrolizumab alone. However, the prolonged effect of NK cells with pembrolizumab was not evaluated yet. This study evaluates the role of NK cells with pembrolizumab for more than 2 years from a previous randomized controlled trial.

Methods: This trial recruited 20 patients with advanced NSCLC with a PD-L1 tumor proportion score of 1% or greater who failed prior frontline platinum-based therapy were randomized to receive pembrolizumab with SNK01 (N=14) or pembrolizumab monotherapy(n=6). Among the group treated with Pembrolizumab plus NK cell, two different doses were administered with 2 x 10^9 cells/dose (N = 7) and 4 x 10^9 cells/dose (N = 7). Patients who showed more than grade 3 adverse event were excluded in the analysis. The primary study endpoint was overall survival (OS), the secondary endpoint was progression-free survival. Kaplan-Meier curve was used to compare the treatment and the p-value was calculated by log-rank test.

Results: Among the 20 patients, 2 patients were excluded for serious adverse event (N=1, arthralgia might related to pembrolizumab, N=1; pneumonia not related to NK cell). 11 patients have died and 5 patients from the pembrolizumab + NK cell group (41.6%, n=5/12), and 6 patients from pembrolizumab monotherapy (100%, n=6/6). The estimated two-year survival rate was 58.3% vs 16.7% (Pembrolizumab + NK cell vs Pembrolizumab monotherapy). The hazard ratio (HR) of survival was 0.32 [95% CI: 0.1, 1.08, p-value: 0.066]. The Survival rate did not statistically differ between the two NK cell dose groups. The median PFS was 6.2 vs 1.7 months (Pembrolizumab + NK cells vs Pembrolizumab monotherapy), with significantly higher PFS by log-rank test [HR 0.15 95% CI: 0.05-0.53, p-value: 0.003]. The PFS did not statistically differ between the two NK cell dose groups.

Conclusions: Although the number of participants was small, this study shows that NK cells with pembrolizumab could be better than pembrolizumab alone for NSCLC. Moreover, prolonged PFS of more than 2 years of NK cells with pembrolizumab might represent the prolonged effect of pembrolizumab and NK cells.



Keywords: Natural Killer cell, NSCLC, pembrolizumab

EP08.02-129 Closing the Gaps with Blood-Based Next Generation Sequencing

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Introduction: Next generation sequencing (NGS) of tumor has become an integral part of cancer diagnostics and therapeutics today. While tissue-based (TB) NGS is still considered gold-standard, cell-free DNA NGS obtained from peripheral blood (blood-based or BB) offers many advantages because of its quicker turnaround time, minimally-invasive nature, ability to address tumor heterogeneity, and track development of resistance mutations over time. Integration of BB and TB NGS can both optimize turnaround time and increase detection of targetable mutations.

Methods: We conducted a single institution, IRB approved, retrospective study evaluating NGS testing patterns in patients with advanced NSCLC treated at our institution between 1/1/16 and 3/31/20. Our primary endpoint was to evaluate the number of patients who had BB NGS performed at any point during their clinical course in addition to TB NGS testing. Our secondary endpoint was to evaluate the number of patients for who BB NGS led to change in treatment plan by evaluating if BB NGS led to earlier initiation of treatment and if there were patients that were initiated on treatment exclusively based on liquid NGS including patients who had quantity not sufficient (QNS) on tissue or had no mutations detected on tissue biopsy.

Results: There was a total of 437 eligible advanced NSCLC patients who were treated at our institution between January 2016 and March 2020. Out of these, 104 (23.8%) had BB NGS performed at some point in their disease course. The median number of BB NGS testing done for these patients was 2 and ranged from 1 to 4. 32/104 (30.8%) of patients had change in management because of BB NGS results. 13/104 patients (12.5%) were initiated on treatment regimens based initially on BB NGS either due to faster turnaround time, QNS on tissue, or no mutations detected on tissue. The median lead time to initiation of treatment from initial BB NGS draw for these 12 patients was 14.25 days. TB and BB NGS were performed within one month of each other in 52 patients. 11 of these (21.2%) had detection of identical actionable mutations (AM) on both BB and TB NGS. 5 of the patients (9.6%) had AM detected on TB NGS alone and 6 of the patients (11.5%) had AM detected on BB NGS alone. 30/52 patients (57.7%) had no AM identified on both BB and TB NGS.

Conclusions: BB NGS has added tremendous value to diagnosis and treatment of NSCLC. It is increasingly used in practice, with nearly a fourth of our patients having BB NGS performed at some point in their clinical course. Nearly 20% of simultaneously performed BB and TB NGS were discordant with an AM identified in only one of the biopsies. In patients with QNS on TB or no AM present, BB NGS at times was able to pick up AM and initiate treatment in about two weeks allowing for quick and prompt treatment decisions. Although further research is needed, our study supports simultaneous BB and TB testing at diagnosis and progression thereby maximizing therapeutic potential.

Keywords: Blood Based NGS, NSCLC, Liquid Biopsy

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-130 Tegavivint Exhibits Antitumor Activity and Modulates Macrophage Phenotype in the Non-small Cell Lung Cancer Tumor Microenvironment

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Introduction: While immunotherapy with checkpoint blockade for advanced non-small cell lung cancer (NSCLC) has become first-line in select patients, durable responses are only seen in 15-20% of cases. As such, there is an urgent need to identify new therapeutic targets to overcome immunosuppression in the tumor microenvironment (TME). Activation of the Wnt/ß-Catenin pathway in non-small cell lung cancer (NSCLC) is associated with tumor growth, metastasis, and polarization of tumor-associated macrophages to an immunosuppressive M2-like phenotype. Tegavivint (Iterion Therapeutics) suppresses nuclear translocation of ß-Catenin through inhibition of TBL1. This small molecule inhibitor is in early-phase clinical trials for advanced cancers (NCT04851119) but has not yet been studied in preclinical models or clinical trials in NSCLC. We aimed to investigate the preclinical efficacy of Tegavivint on tumor cell growth and its effects on macrophage phenotype in a novel co-culture model of the NSCLC TME.

Methods: Our prior work investigating a co-culture model using a large panel (~70) of molecularly and clinically-annotated patient-derived NSCLC cell lines (70% of the cells) mixed with cancer-associated fibroblasts (CAFs) (25%) and mouse bone marrow-derived macrophages (BMDMs) (5%) demonstrated that most NSCLC lines induced an immunosuppressive *Arginase-1*-positive macrophage phenotype. MTS cell viability assays were conducted on high-*Arginase-1* inducing NSCLC lines, H1666 and H2009. Protein expression of total, cytoplasmic, and nuclear levels of ß-catenin in Tegavivint-treated cells was studied through Western blotting and downstream gene expression was assayed through qRT-PCR. Co-cultures systems of NSCLC cells, CAFs, and macrophages were treated with Tegavivint (at concentrations achievable in patients) for 72 hours. qRT-PCR assays for mouse macrophage-specific genes were performed to investigate expression of either an immunosuppressive M2-like (*Arginase-1*) or an inflammatory, immunostimulatory M1-like phenotype (*iNos*). Positive controls consisted of stimulation of macrophages with IL-4 and LPS (known to generate M2-like and M1-like phenotypes, respectively).

Results: Tegavivint was potently cytotoxic to NSCLC cells *in vitro* with mean IC50 values of 100 nM (H1666) and 38 nM (H2009). Tegavivint treatment (IC50) suppressed total and nuclear ß-catenin protein expression at 24 hours. Downstream *cMYC* gene expression was significantly reduced in treated cells after 24 hours (H1666: 51% relative fold change reduction vs. control, p=0.0004; H2009: 47% reduction, p=0.0029). Bulk RNAseq analysis demonstrated that enrichment of *MYC* target genes was suppressed in treated cells compared to controls for both cell lines. Treatment of macrophages in co-culture with H2009 and H1666 cells with Tegavivint (10 nM) significantly suppressed *Arginase-1* gene expression at 72 hours (H1666: 43% relative fold change reduction, p=0.011; H2009: 52% reduction, p<0.0001). *In vivo*, Tegavivint therapy markedly reduced tumor volume and weight in H1666 and H2009-derived murine xenografts.

Conclusions: Tegavivint exhibits potent cytotoxic activity against NSCLC cells *in vitro* and *in vivo* with evidence of on-target suppression of ß-catenin protein expression and downstream activity. Furthermore, at pharmacologically achievable doses, Tegavivint significantly reduces immunosuppressive *Arginase-1* expression in co-cultured macrophages. Our preclinical studies suggest that Tegavivint may be a promising targeted therapy with antineoplastic and immunomodulatory potential.

Keywords: ß-Catenin, Tegavivint, Macrophage

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-131 Alectinib after Crizotinib Failure in Patients with Advanced ALKPositive NSCLC: Results from the Spanish Early Access Program

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Introduction: Survival of patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (ALK+ NSCLC) has significantly improved in the last 5 years, following the incorporation of new generation ALK-tyrosine kinase inhibitors into the therapeutic armamentarium. However, there is still scarce information on the effect of patient clinical features, real-world treatment patterns and management of central nervous system (CNS) metastases on survival rates**.** We performed this real-world study to describe our experience with the use of alectinib in heavily pre-treated patients.

Methods: This multicentre retrospective study was conducted to analyse the clinical characteristics, treatment approaches, associated toxicities and efficacy outcomes of alectinib in 120 patients with advanced ALK+ NSCLC who had previously received crizotinib and were included in a local expanded access program in Spain. All available data from case report forms were collected between November 2019 and November 2020 from 38 Spanish hospitals. The primary objective of this observational study was the demographic and clinical characterization of this patient population. Secondary objectives were assessment of the efficacy and safety of alectinib after crizotinib failure, and to characterize the most common therapeutic strategies used to manage brain metastases.

Results: Records from a total of 120 selected patients were carefully examined. Median age was 58.7 years (range: 25-86), and 50% were female. ECOG performance status (ECOG PS) 0 or 1 was determined in 64.1% of patients. At the time of inclusion in the study, 85% of patients had stage IV disease, 95% had adenocarcinoma histology and 20.8% presented brain metastases. Most patients were non-smokers (45.8%), while 29.2% were former smokers and 25%, current smokers. One or two treatment lines had been administered prior to alectinib in 46.7% and 38.6% of patients, respectively. After a median duration of alectinib treatment of 9.6 months, the objective response rate (ORR) was 54.5%, disease control rate (DCR) was 80%, median progression-free survival (PFS) was 9.4 months and median overall survival (OS) was 24.1 months. Almost 40% of patients received some treatment after alectinib, most often lorlatinib (65.2%) and brigatinib (32.6%). Adverse events were reported by 35.8% of patients during alectinib treatment, of which only 14.2% were grade ≥3. Brain metastases were confirmed in a high number of patients, irrespective of the time at which they were analysed (45.2% of patients prior to alectinib and 38.7% during alectinib treatment). Whole-brain radiotherapy (50%) or radiosurgery (50%) were the most common local approaches for management of CNS metastases at diagnosis, and whole-brain radiotherapy was the preferred option during alectinib and subsequent lines of therapy (83.3% and 100%, respectively). The intracranial DCR was 71.4% in patients with brain metastases treated with alectinib.

Conclusions: These findings from real-world clinical practice confirm that the prolonged PFS and OS achieved with alectinib in clinical trials can also be observed in unselected advanced ALK+ NSCLC patients with ECOG PS 2 and brain metastases, and reinforce the tolerability of alectinib in heavily pre-treated patients. Additionally, this study provides details on real-world treatment patterns following the incorporation of new ALK inhibitors into the therapeutic repertoire.

Keywords: ALK-NSCLC, Crizotinib, Alectinib

EP08.02-132 Fatal Interstitial Lung Disease Induced by Osimertinib: A Case Report

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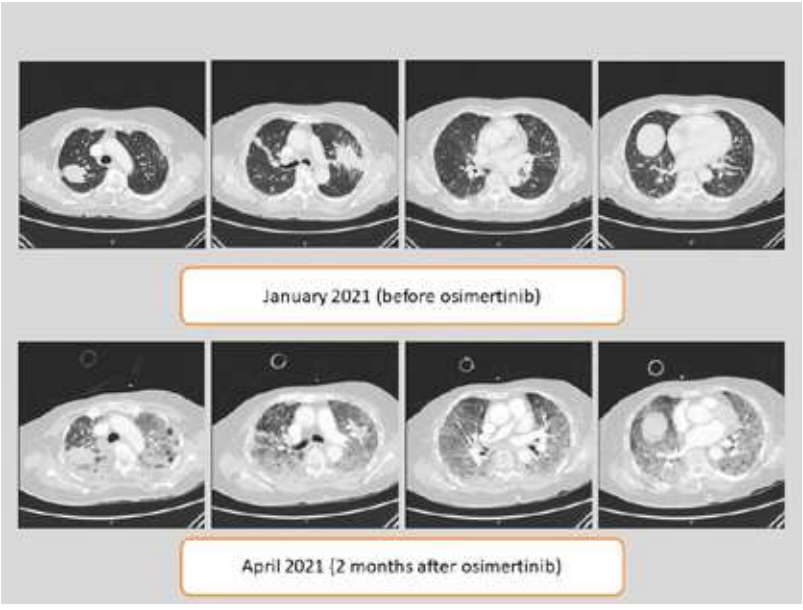
Introduction: Osimertinib is a selective third-generation EGFR-TKI inhibitor with an inhibitory effect on the T790M mutation. Interstitial lung disease (ILD) occurred in 3.9% of the Osimertinib-treated patients (with 0.4% fatal cases).

Methods: Case report of fatal ILD induced by Osimertinib in a patient with metastatic lung adenocarcinoma.

Results: We present the case of an 81-year-old female patient diagnosed with stage IVB lung adenocarcinoma (May 2020) with pulmonary, adrenal, and brain metastasis. Genetic sequencing showed an exon 19 deletion. She started erlotinib until documentation of disease progression in January 2021. In this context, she performed a liquid biopsy with the detection of a T790M resistance mutation. She started Osimertinib in February 2021. Her past medical history showed diabetes and dyslipidemia. Two months after starting Osimertinib, she went to the emergency department (ER) with a one-week evolution with progressive dyspnea, cough, and fever. Upon admission to the ER, she was conscious and cooperative, with respiratory distress signs, normal blood pressure, and hypoxemia. She had decreased breath sounds, and coarse crackles were audible bilaterally. In the blood sampling, Haemoglobin was 7.7 mmol/L, creatinine 0.08 mmol/L, platelets 257000x10^9/L, C-reactive protein 28.6 nmol/L, and NT-proBNP 98 pmol/L. Rt-PCR for sars-CoV-2 detection was negative. X-ray showed bilateral diffuse infiltrates. She started oxygen therapy via nasal cannula at 3l/min and IV antibiotics. ABG values were pH 7.44, pCO2 37 mmHg, pO2 69 mmHg, HCO3 26 mEq/L, sO2 94%. On reassessment after 3 hours, she presented worsening dyspnea and dizziness, with higher oxygen needs (venturi mask, 60%). Chest CT angiography showed extensive bilateral diffuse ground-glass densification with crazy-paving areas. It also showed no signs of pulmonary embolism. We admitted her to a level 2 ICU unit for surveillance. Due to suspected drug toxicity, she started Methylprednisolone pulses (1000mg/3days). Six hours after admission, due to hypoxemia worsening, non-invasive ventilation was started with the need to escalate oxygen therapy to 100% FiO2. At 24h, she showed clinical and blood analysis improvement. Nonetheless, she still needed 100% fiO2 to maintain >92% oxygen saturation. On the 4th day of hospitalization, she was hypotensive, prostrated, and with little reaction to painful stimulation. She started palliative treatment and died on the same day.

Conclusions: ILD is a rare adverse effect of the treatment with Osimertinib, and fatal ILD is even rarer. The time from starting Osimertinib to this side effect is variable between patients. Awareness is necessary for a rapid diagnosis and early treatment.



Keywords: Osimertinib, Intersticial Lung Disease, Adverse effect

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-133 Sequential Afatinib to Osimertinib in EGFR-mutant NSCLC: A Prospective Observational Study, Gio-Tag Japan Interim Report

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Introduction: The global observational study (Gio-Tag) demonstrated prolonged time on treatment (ToT) with sequential afatinib followed by osimertinib post detection of T790M in EGFR-mutant NSCLC. However, real world data (RWD) has not been fully evaluated in Japan.

Methods: This study is a prospective, multicentre observational study. We evaluated the medical records of patients who received afatinib as first-line treatment. Primary endpoint was ToT of sequential afatinib and osimertinib. This interim report presents starting dose, overall response rate (ORR), and progression-free survival (PFS) of afatinib. This clinical trial was registered in the University Hospital Medical Information Network (UMIN: 000018248) and approved by the institutional review boards.

Results: From September 2019 to July 2020, 121 patients were enrolled from 64 participating institutions in Japan. Total 119 cases were evaluated, except two ineligible cases. Median age was 72 (range, 38-94), including 45 males and 74 females. All patients were ECOG PS 0-1. One hundred and eight patients (91%) had adenocarcinoma, with 85 stage IV and 34 stage III/ recurrence diseases. Del-19 mutations were identified in 52 patients and L858R in 67. The starting dose of afatinib was as follows: 20mg/30mg/40mg in 14 (12%)/ 42 (35%)/ 63 (53%), respectively. Main reasons for dose adjustment were elderly age (55%) and toxicity concern (35%). The ORR in all patients was 67% (95%CI: 57-75%), and disease control rate (DCR) 96% (95%CI: 90-99%). The median PFS (mPFS) was 18.4 (95% CI, 13.2-23.7) months (58 censored cases). ORR/mPFS were 67%/18.4 months in Del-19, and 61%/15.8 months in L858R. ORR/mPFS were 50%/not reached in patients who received 20mg, 62%/21.5 months in 30mg, and 68%/15.4 months in 40mg, respectively.

Conclusions: Japanese RWD of afatinib demonstrated comparable ORR and DCR, plus a possibly more favorable PFS compared with those shown in previous trials. The clinical starting dose was reduced in approximately half of the patients, mainly because of elderly age and toxicity concern.

Keywords: afatinib, sequential osimertinib, EGFR-TKI

EP08.02-134 Real-world Efficacy of Dacomitinib in Patients with Previously EGFR-TKI Treated Non-small Cell Lung Cancer

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Introduction: Multiple studies have reported that retreatment with erlotinib is an alternative option for patients with *epidermal growth factor receptor* (*EGFR*)-mutant non-small cell lung cancer (NSCLC) who had benefited from previous EGFR-tyrosine kinase inhibitor (TKI) therapy and progressed after chemotherapy. Dacomitinib is a second-generation EGFR-TKI for the first-line treatment of *EGFR*-mutant advanced NSCLC. The efficacy of dacomitinib in previously EGFR-TKI treated NSCLC remains unclear in real-world practice.

Methods: In this retrospective study, 21 enrolled patients who had progressed on previous EGFR-TKI and chemotherapy were treated with dacomitinib 45 mg or 30 mg orally daily until disease progression or intolerability. The progression free survival (PFS), time to treatment failure (TTF), and overall survival (OS) from dacomitinib initiation were analyzed.

Results: Among 21 enrolled patients with advanced pulmonary adenocarcinoma, there were 9 patients with exon 19 deletion, 11 patients with L858R mutation, and 1 patient with exon 18 G719X mutation. 10 patients received dacomitinib 45 mg initially, among whom one patient's dacomitinib was reduced to 30 mg due to adverse events. The other 11 patients received dacomitinib 30 mg without dose reduction. Four partial responses were documented (19% objective response rate; 95% confidence interval [CI], 5.4 to 41.9). The duration of response was 4.6 months (95% CI, 0 to 9.9). Three patients with an original sensitizing EGFR L858R mutation and one patient with exon 19 deletion had partial responses, whereas 0 of the 7 patients with acquired EGFR resistance mutations (T790M) met the response criteria. The median PFS, TTF, and OS were 1.6 months (95% CI, 1.4 to 1.86), 1.87 months (95% CI, 0.9 to 2.8), and 10.2 months (95% CI, 7.7 to 12.7), respectively. One partial intracranial response (7.1% response rate; 95% CI, 0.2 to 33.9) was recorded among 14 patients with brain metastases. Median PFS, TTF, and OS in patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 compared to those with ECOG PS of 1 were 0.3 vs. 1.87 months (HR=5.3, P=0.008), 0.3 vs. 2.5 months (HR=8.5, P=0.002) and 0.3 vs. 12.2 months (HR=38.9, P=0.001), respectively.

Conclusions: This study demonstrated that dacomitinib in previously EGFR-TKI treated NSCLC has limited benefit in real-world practice. Higher risks of disease progression, treatment failure, and death for dacomitinib were found in patients with worse performance status.

Keywords: Dacomitinib, Non-small cell lung cancer

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-135 Anti-EGF Antibodies Significantly Improve the Activity of MET and KRAS Inhibitors in Preclinical Models of Non-small Cell Lung Cancer (NSCLC)

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Introduction: The EGF/EGFR pathway is involved in the emergence of resistance to MET and KRAS inhibitors. Vaccination represents an alternative to the administration of anti-EGFR monoclonal antibodies such as cetuximab or panitumumab, and we have shown that antibodies against EGF (anti-EGF VacAbs) potentiate the effects of tyrosine kinase inhibitors *in vitro* (TKIs). Also, a progression-free survival of 18 months was obtained in a recent Phase Ib clinical trial combining afatinib with anti-EGF VacAbs. In this study, we tested if anti-EGF VacAbs could improve the antitumor activity of capmatinib, tepotinib and sotorasib in *MET* amplified, *MET Δ14* and *KRAS* mutant non-small cell lung cancer (NSCLC) cell lines.

Methods: Cell lines with *MET* amplification (EBC1), *MET Δ14* (Hs746T) and *KRAS* G12C mutations (H2122 and H23) were used. Anti-EGF VacAbs were obtained by immunizing rabbits with the IN01 fusion protein. Cell lines were treated with capmatinib, tepotinib or sotorasib in combination with anti-EGF VacAbs; in *KRAS* mutant cell lines, the antitumor effects were compared to the combination sotorasib/panitumumab. Cell viability was determined by MTT, changes of total and phosphorylated proteins by Western blotting and emergence of resistance by direct microscopic examination in low density cultures.

Results: Anti-EGF VacAbs suppressed the EGF-induced proliferation and blocked the EGFR signaling pathway in all cell lines tested. In combination, anti-EGF VacAbs significantly enhanced the antitumor activity of capmatinib and tepotinib in EBC1 (*MET*-amplified) and Hs746T (*METΔ14*), potentiating the blockade of EGFR, Akt and Erk 1/2 phosphorylation. The same effects were observed when combining anti-EGF VacAbs with sotorasib in H2122 and H23 (G12C) cells. The antiproliferative effects of anti-EGF VacAbs in combination were comparable to those of panitumumab in *KRAS* mutant cells. Finally, the addition of anti-EGF VacAbs to the culture medium significantly delayed the emergence of resistant clones to capmatinib in EBC1 and in Hs746T.

Conclusions: Anti-EGF VacAbs potentiate the antitumor effects of capmatinib, tepotinib and sotorasib in cancer cell lines. Our data provide a rationale for clinical trials testing the combination of anti-EGF VacAbs with targeted inhibitors in *MET* amplified, *MET Δ14* and *KRAS* G12C mutant NSCLC patients.

Keywords: anti-EGF vaccine antibodies, Targeted therapy, Colorectal cancer and NSCLC

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-136 Final Analysis of a Phase II Study: Anlotinib Plus Docetaxel in Patients with Previously Treated Metastatic Non-small Cell Lung Cancer

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Introduction: Advanced non-small cell lung cancer (NSCLC) patients with treatment failure of platinum-based doublet chemotherapy are still facing unmet needs. Anlotinib, as a multi-target anti-angiogenic agent, has shown potential chemo-sensitization in our pre-clinical research. Thereafter, we conducted this study to assess the efficacy and safety of anlotinib plus docetaxel in these patients who failed with previous chemotherapy. The interim analysis was formerly reported at the ESMO 2020 annual meeting, and currently we present the final efficacy and safety results.

Methods: This is a single-arm phase II trial, in which advanced NSCLC patients with treatment failure of platinum-based doublet chemotherapy were enrolled and administrated with anlotinib (12 mg per day, orally taken) on Day 1-14 of each 21-day cycle and docetaxel (60 mg/m^2, intravenously) on Day 1 of initial 4 cycles. Efficacy and safety analysis are reported in intention-to-treat (ITT) population, which include the patients having received at least one cycle of combined treatment. This study was registered with chictr.org.cn (ChiCTR1800020011).

Results: Between December 2018 and June 2021, 48 patients were enrolled and 3 of them were excluded. Among these patients (n=45), median age at diagnosis was 61 years old (range 37-74), and 77.8% (35) were male; 66.7% (30) had adenocarcinoma, and 26.7% (12) had squamous cell carcinoma. Besides, mutations in EGFR were detected in 20.0% (9) patients and fusion in ALK in 6.7% (3) patients. A total of 14 participants had been previously treated with anti-VEGF monoclonal antibody therapy. As of February 10, 2022, no patient had a complete response and 16 patients had a partial response (ORR 35.6%, 95% CI: 23.2-50.2), while 22 patients had a stable disease (DCR 84.4%, 95% CI: 71.2-92.3). Median PFS was 5.3 months (95% CI: 4.2-7.4) and median OS was 13.8 months (95% CI: 10.8-18.4). The median DoR in 16 responders was 5.7 months (95% CI: 3.1-8.3). Notably, at the cut-off time, one patient with PR was still free of tumor progression after 33.0 months of treatment. All grades of treatment-emergent adverse events with an incidence of over 20% were hand-foot skin reaction (HFSR) (13, 28.9%), hypertension (12, 26.7%), hemorrhage (9, 20.0%), and stomatitis (9, 20.0%), however, no ≥ 4 grade AEs were observed. Subgroup analysis revealed longer OS in patients occurring HFSR (not reached vs. 10.8 months, p=0.012), although the benefit of PFS was not significant (7 vs. 4.6 months, p=0.155). Besides, no significant difference in OS (p=0.421) and PFS (p=0.651) were demonstrated in patients with prior anti-VEGF antibody treatments.

Conclusions: For advanced NSCLC patients failed with platinum-based chemotherapy, anlotinib in combination with docetaxel demonstrated a surpassing ORR and improved PFS and OS with tolerable AE when compared with historical results of docetaxel alone. Besides, patients with HFSR caused by anlotinib were shown to achieve longer survival.

Keywords: Non-small cell lung cancer, Anlotinib, docetaxel

EP08.02-137 Prospective Study of Aumolertinib in NSCLC Patients with EGFR Sensitive Mutations Who Are Intolerant to Osimertinib Treatment

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Introduction: Data from phase II and phase III clinical studies of the third-generation EGFR-TKI Aumolertinib showed significant treatment efficacy and a favorable safety profile for patients with EGFR-sensitive mutations (EGFRm+) in advanced non-small cell lung cancer (NSCLC). There is a difference in the incidence of AEs caused by osimertinib with the same 3rd generation EGFR-TKI, especially the low incidence of AEs caused by Aumolertinib in interstitial lung disease, cardiotoxicity, and hematotoxicity. The aim of this study was to evaluate the safety and efficacy of Aumolertinib in EGFRm+ advanced NSCLC patients with safety intolerance after treatment with oxitinib. For the first time, this study used the success rate of drug switching due to poor safety as the primary endpoint.

Methods: This study is a prospective, multicenter, single-arm clinical trial that is expected to enroll 40 patients with EGFRm+ advanced non-small cell lung cancer (NSCLC) who developed ≥ grade 2 hematologic toxicity or ≥ grade 3 other adverse events after treatment with osimertinib. Subjects received 110 mg/day of Aumolertinib until disease progression (PD) after toxicities had resolved to ≤ grade 1, or developed ≥ grade 2 hematologic toxicity or ≥ grade 3 other adverse events. All AEs were graded by CTCAE according to the grading criteria in the Common Terminology Criteria for the Evaluation of Adverse Events (CTCAE), 4th edition. The primary endpoint was the 3-month conversion success rate, defined as the proportion of subjects who did not experience grade ≥2 hematologic toxicity, or grade ≥3 other adverse events within 3 months of switching to Aumolertinib treatment. Secondary endpoints were progression-free survival (PFS), objective remission rate (ORR), overall survival (OS), duration of remission (DoR), disease control rate (DCR), and depth of tumor remission (DepOR) for Aumolertinib treatment.

Results: The study is ongoing and the Clinical trial website registration number is NCT04882345.

Conclusions: The study is ongoing and the Clinical trial website registration number is NCT04882345.

Keywords: Osimertinib, Intolerant, Aumolertinib

EP08.02-138 SAFFRON: Ph3 Savolitinib + Osimertinib vs Chemotherapy in EGFRm NSCLC with MET Overexpression/Amplification Post-Osimertinib

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Introduction: Osimertinib is a potent, third-generation, irreversible, oral EGFR-TKI which has demonstrated efficacy in NSCLC and related central nervous system metastases. Osimertinib is the preferred first-line treatment in advanced EGFRm NSCLC; however, patients may develop resistance to osimertinib. MET overexpression and/or amplification is the most common acquired resistance mechanism to osimertinib. However, there is no approved targeted therapy for these patients; platinum-based chemotherapy remains the standard of care but has limited efficacy. Savolitinib is an oral, potent, and highly selective MET-TKI. Combination of osimertinib and savolitinib showed acceptable tolerability and preliminary evidence of clinical activity in patients with *MET*-overexpressed/amplified, EGFRm NSCLC following progression on an EGFR-TKI in the Phase 1B TATTON study (NCT02143466). This led to the combination being investigated in the Phase 2 SAVANNAH study (NCT03778229) in patients with EGFRm, MET- overexpressed and/or amplified, locally advanced or metastatic NSCLC, who experienced disease progression on prior osimertinib. SAFFRON (NCT05261399) is designed to assess the efficacy and safety of savolitinib in combination with osimertinib versus platinum-based chemotherapy in patients with EGFRm, MET-overexpressed and/or amplified, locally advanced or metastatic NSCLC, who had disease progression on osimertinib.

Methods: This global, open-label Phase 3 study will randomize approximately 324 patients from 225 sites in 27 countries: adults ≥18 years (≥20 years in Japan) who have locally advanced or metastatic NSCLC with documented EGFRm (Ex19del/L858R) and/or T790M, and with MET overexpression and/or amplification determined prospectively by central laboratory using IHC (≥90% of tumor cells staining at 3+ intensity) or FISH (≥10 copies of *MET* gene in tumor cells). Patients must have had disease progression on first- or second-line treatment with osimertinib as the most recent anti-cancer therapy (no prior chemotherapy in the metastatic setting allowed) and have Eastern Cooperative Oncology Group performance status 0-1. Patients will be randomized 1:1 to receive oral savolitinib 300 mg twice-daily plus osimertinib 80 mg once-daily, or intravenous pemetrexed 500 mg/m^2 plus carboplatin area under the plasma drug concentration-time curve of 5 mg/mL/min or cisplatin 75 mg/m^2 on Day 1 of 21-day cycles for four cycles, followed by maintenance pemetrexed 500 mg/m^2 every three weeks. Treatment will continue until disease progression by investigator assessed RECIST 1.1, unacceptable toxicity, or patient withdrawal; cross-over from chemotherapy to the combination treatment within the study is not permitted. Patients may continue to receive savolitinib plus osimertinib or osimertinib monotherapy beyond progression if they are deriving clinical benefit, as judged by the investigator. Randomization will be stratified by line of therapy (second-/third-line), baseline brain metastases (yes/no) and race (Asian/non-Asian). The primary endpoint is PFS by RECIST 1.1, assessed by blinded independent central review. Key secondary endpoints include OS (overall population and in patients with MET overexpression), PFS in patients with MET overexpression, ORR, DoR, and pharmacokinetics. Safety and tolerability will be evaluated by Common Terminology Criteria for Adverse Events v5.0. Patient samples will be used in an exploratory analysis to understand mechanisms of treatment response and resistance. SAFFRON's primary analysis is anticipated in June 2025.

Keywords: Locally advanced/metastatic NSCLC, osimertinib, savolitinib

EP08.02-139 A Phase 2 Study of Befotertinib in Patients with EGFR T790M Mutated NSCLC after Prior EGFR TKIs

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Introduction: Befotertinib (D-0316) is a novel, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). This study aimed to evaluate the efficacy and safety of befotertinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that had EGFR T790M mutation after prior first- or second-generation EGFR TKIs.

Methods: This study was a single-arm, open-label, phase 2 study at 49 centers in China. Pts with locally advanced or metastatic NSCLC harboring EGFR T790M mutations with disease progression after prior first- or second-generation EGFR TKIs received oral befotertinib of 50 mg (cohort A) or 75-100 mg (cohort B) once daily. The primary endpoint was overall response rate (ORR) assessed by independent review committee (IRC).

Results: A total of 176 and 290 pts were included in cohorts A (50 mg) and B (75-100 mg), respectively. At data-cutoff (August 15, 2021), IRC-assessed ORR was 67.6% (95% confidence interval [CI]: 61.9%-72.9%) in cohort B. The investigator-assessed ORR was 54.0% (95% CI: 46.3%-61.5%) in cohort A and 65.9% (95% CI: 60.1%-71.3%) in cohort B. The investigator-assessed DCR was 93.2% (95% CI: 88.4%-96.4%) and 94.8% (95% CI: 91.6%-97.1%) in two cohorts. The median DOR assessed by investigator was 12.5 (95% CI: 11.1-15.2) months and 12.4 (95% CI: 11.0-14.6) months in cohorts A and B, respectively. Investigator-assessed intracranial ORR was 26.7% (95% CI: 7.8%-55.1%) and 57.1% (95% CI: 34.0%-78.2%) in cohort A and B. The median investigator-assessed PFS was 11.0 (95% CI: 9.6-12.5) months in cohort A and 12.5 (95% CI: 11.1-13.8) months in cohort B. The median intracranial PFS (assessed by investigator) was 16.5 (95% CI: 8.6-NE) months in cohort A and NE (95% CI: 13.8-NE) in cohort B. The overall survival was immature. Grade 3 or higher treatment-related adverse events (TRAEs) and treatment-related serious adverse events occurred in 20.5% and 11.4% of patients in cohort A, respectively, and in 29.3% and 10.0% of patients in cohort B.

Conclusions: Befotertinib has shown favorable efficacy and manageable safety in pts with locally advanced or metastatic NSCLC harboring T790M mutation as a second-line option in the Chinese population.

Keywords: third-generation EGFR-TKI, befotertinib, T790M

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-140 MET Biomarker-based Preliminary Efficacy Analysis in SAVANNAH: savolitinib+osimertinib in EGFRm NSCLC Post-Osimertinib

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Introduction: Osimertinib, a 3rd-generation, irreversible, oral EGFR-TKI, is standard of care for patients with EGFRm NSCLC. Early data suggest that savolitinib, an oral, potent, and highly selective MET-TKI, in combination with osimertinib may overcome common acquired MET-based molecular resistance mechanisms following osimertinib monotherapy. The SAVANNAH (NCT03778229) study is investigating the efficacy and safety of targeted combination therapy with savolitinib+osimertinib, and exploring optimum MET detection methods and thresholds to identify patients most likely to respond.

Methods: SAVANNAH is a single-arm, PhII study in which patients with EGFRm NSCLC who have MET overexpression and/or amplification upon disease progression post-osimertinib received oral savolitinib 300/600mg once-daily (QD) or 300mg twice-daily, in combination with oral osimertinib 80mg QD. Central MET testing was performed on tumor tissue collected after disease progression on osimertinib to determine eligibility. MET overexpression was detected by IHC (3+ in ≥50% of tumor cells [IHC50+]) and MET amplification by FISH (MET copy number ≥5 and/or MET:CEP7 signal ratio ≥2 [FISH5+]). The ORR, DoR, and PFS were assessed in subgroups identified by each assay, including efficacy in patients identified by exploratory, higher cut-off levels: 3+ staining ≥90% tumor cells (IHC90+) and MET copy number ≥10 (FISH10+). All efficacy endpoints were assessed by investigator in accordance with RECIST 1.1. Safety was also assessed by CTCAE v5.

Results: This analysis was based on patients who received savolitinib 300mg QD plus osimertinib. At data cut-off (August 27, 2021) from the ongoing study, 193 patients with IHC50+ and/or FISH5+ status had been dosed and had ≥2 post-baseline RECIST scans; of these, 108 (56%) had IHC90+ and/or FISH10+ status. Efficacy in the IHC90+ and/or FISH10+ subgroup (ORR 49%, median DoR 9.3 months, median PFS 7.1 months) was improved compared to the overall population; particularly versus the subgroup without IHC90+ and/or FISH10+ status (ORR 9%, median DoR 6.9 months, median PFS 2.8 months) (Table). Safety outcomes were in-line with the known profile of each drug. Estimated prevalence of MET overexpression and/or amplification in patients centrally tested for enrolment was 62% for IHC50+ and/or FISH5+ status, and 34% for IHC90+ and/or FISH10+ status.

Conclusions: Encouraging outcomes were observed in patients with EGFRm NSCLC with MET IHC90+ and/or FISH10+ status following disease progression on osimertinib, confirming the necessity for appropriate MET biomarker-based patient selection in this population. Future data from SAVANNAH is expected to enable additional insights into the efficacy of savolitinib+osimertinib; the combination will be further assessed in SAFFRON (NCT05261399).

Table

	All patients; IHC50+ and/or FISH5+ status (N=193; evaluable for efficacy set)*		Patients with IHC90+ and/or FISH10+ status (n=108)		Patients without IHC90+ and/or FISH10+ status (n=77)	
Endpoint	**Total (N=193)**	**2nd/≥3rd-line no prior chemotherapy (n=157)**	**Total (n=108)**	**2nd/≥3rd-line no prior chemotherapy (n=87)**	**Total (n=77)**	**2nd/≥3rd-line no prior chemotherapy (n=63)**
ORR, % (95% CI)	32 (26, 39)	33 (26, 41)	49 (39, 59)	52 (41, 63)	9 (4, 18)	10 (4, 20)
Median DoR, months (95% CI)	8.3 (6.9, 9.7)	9.6 (7.6, 15.3)	9.3 (7.6, 10.6)	9.6 (7.6, 14.9)	6.9 (4.1, 16.9)	7.3 (4.1, NC)
PFS events (%)	153 (79)	120 (76)	80 (74)	61 (70)	68 (88)	55 (87)
Median PFS, months (95% CI)	5.3 (4.2, 5.8)	4.5 (4.0, 5.8)	7.1 (5.3, 8.0)	7.2 (4.7, 9.2)	2.8 (2.8, 4.3)	2.8 (1.8, 4.2)

*Includes eight patients who were excluded from the 'with IHC90+and/or FISH10+ status' and 'without IHC90+and/or FISH10+ status' subgroups due to invalid or missing test results

CI, confidence interval; DoR, duration of response; FISH, fluorescence in situ hybridization; FISH5+, FISH (MET copy number ≥5 and/or MET:CEP7 signal ratio ≥2); FISH10+, FISH (MET copy number ≥10); IHC, immunohistochemistry; IHC50+, 3+ IHC overexpression in ≥50% of tumor cells; IHC90+, 3+ IHC overexpression in ≥90% of tumor cells; NC, not calculable; ORR, objective response rate; PFS, progression free survival

Keywords: EGFRm, NSCLC, MET

EP08.02-141 'Our' EGFR Population - Experience in a Secondary Center

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Introduction: Epidermal growth factor receptor (EGFR) mutations are the most common among non-small cell lung cancer (NSCLC), with available target treatment with tyrosine-kinase inhibitor (TKI) as first-line on advanced disease. The aim of this study was to evaluate the demographic characteristics of patients with advanced NSCLC EGFR mutated, treatments performed and outcomes.

Methods: Retrospective data analysis of patients with EGFR metastatic NSCLC who attended Pneumology/Oncology clinic in a secondary hospital between 2014 and 2021. Molecular study was made in all adenocarcinomas and squamous carcinoma in non-smokers or light smokers. From 2014 to 2016, EGFR mutations were performed by real-time polymerase chain reaction. Since 2016, molecular test was performed by next-generation sequencing, targeting EGFR and several other mutations and rearrangements. The demographic and clinical variables analyzed were age at diagnosis, sex, smoking history, family history of cancer, metastasis in central nervous system (CNS), histology and EGFR mutation, antineoplastic treatments, progression-free survival (PFS) and overall survival (OS). Data was analyzed using SPSS® version 26.0 (IBM Statistics®).

Results: From June 2014 until December 2021, 832 patients were diagnosed with thoracic tumors in our center. We identified 51 patients with metastatic NSCLC with EGFR mutations. 9.8% had exon 18 mutation, 58.8% exon 19 deletions, 3.9% exon 20 mutations, 23.5% exon 21 mutations and 3.9% had mutations in more than one exon, including exon 20. 68.6% were female and ages ranged from 46 to 89, with median of 69 years-old (P25: 58; P75: 74). 70.6% were non-smokers. 29.4% had CNS metastasis at diagnosis and 9.8% developed later. 17.6% of patients had stage II or III disease at diagnosis, received definitive treatment and experienced progression or recurrence, with metastatic disease. These patients were treated with first-line therapy for advanced disease. 15.7% of the patients died before starting systemic treatment. 5.9% started chemotherapy while waiting for TKI availability. 62.7% received first-generation TKI as first-line treatment of metastatic NSCLC. Median PFS was 11.5 months and median OS 23.5 months. 5.88% received second-generation TKI and PFS was 13.4 months and median OS 26.3 months. 7.84% received front-line third-generation TKI and median PFS was 3.8 months and median OS 7.4 months. Between those who received first or second-generation TKI, 13.7% experienced progressive disease with T790M resistance mutation and were treated with osimertinib. This group had 4.6 months of median PFS and OS 39.12 months. 23.53% received at least one TKI and platino-based chemotherapy, with half of them receiving several chemotherapy ± immunotherapy regiments; OS was 30.99 months.

Conclusions: In our study, patients who received subsequent TKI therapies, with or with chemotherapy and others systemic regiments, were the ones with better outcomes. Unlike other studies, patients received osimertinib as first-line had less PFS and OS. In authors' opinion this may be due to four factors: lack of target therapy after osimertinib, unidentified mechanisms of resistance, high performance status of patients not allowing other systemic therapies and specific patients' characteristics with worst prognosis. Authors would like to enlighten the need for more clinical trials recruiting patients who progress after osimertinib and chemotherapy.

Keywords: EGFR, tyrosine-kinase inhibitor, advanced disease

EP08.02-142 Effects of Afatinib on the Treatment and Prognosis of Brain Metastasis in Advanced EGFR Mutation (+) NSCLC

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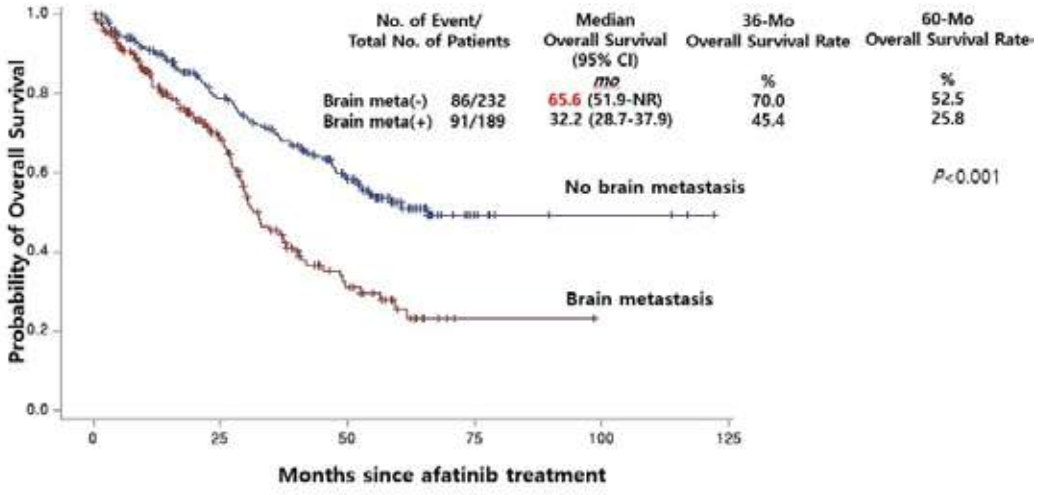
Introduction: Afatinib has shown encouraging results in EGFR mutation (+) patients. According to LUX-Lung trials, afatinib is known to be effective in delaying the occurrence of brain metastases, and it is also known to be effective in treating patients with brain metastases by penetrating the blood-brain barrier. We conducted a study on the effect on brain metastasis in EGFR M(+) patients who received afatinib as the 1st line from the KATRD EGFR cohort data.

Methods: We retrospectively reviewed data from 422 patients who started afatinib therapy among patients enrolled in the KATRD EGFR cohort between April 2007 and August 2021. A total of 15 sites participated in patient registration.

Results: The mean age was 64 (SD, 10.9). The progression free survival and overall survival (OS) of the KATRD afatinib cohort were 20.2 and 48.6 months, respectively. Compared to those with brain metastases, afatinib significantly prolonged overall survival in patients without brain metastases (65.6 vs. 32.2 months, P < 0.001). The best overall responses for all patients and those with brain metastasis were 65.3% and 64%, respectively. At the time of diagnosis of lung cancer, 34% (145/422) of patients had brain metastasis, of which 14% (60/422) were treated only with afatinib, and the remaining patients were treated with surgery, gamma knife, CyberKnife, whole brain radiation therapy or stereotactic radiosurgery. Especially, there was no difference in survival between the two groups in patients treated with afatinib alone compared with those who received radiotherapy or surgery (32.7 vs. 30.3 months, P=0.77).

Conclusions: The OS of the cohort was promising, especially in patients without brain metastasis. Further studies are needed to determine whether afatinib monotherapy or afatinib treatment after surgery or radiotherapy is more appropriate in patients with brain metastases when diagnosed with lung cancer.



Keywords: EGFR Mutation, Afatinib, Brain metastasis

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-143 Shortening of the Turn Around Time (TAT) in the Examination of Rapid On-Site Cytologic Evaluation (ROSE) at Transbronchial Biopsy

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Introduction: ROSE has been shown to reduce bronchoscopy time in patients with lung cancer. However, next-generation sequencing (NGS) test is now required in cases of lung cancer, it is unclear whether ROSE can contribute to the implementation of NGS testing. In this study, we examined the diagnostic rate of ROSE cases, the success rate of driver genetic testing, and the success rate of NGS testing.

Methods: We divide into two group, ROSE group and non-ROSE group. From April 2020 to June 2021, we performed a total of 485 bronchoscopy, and evaluated 88 patients with lung cancer who underwent transbronchial biopsy for diagnostic purposes.

Results: 88 patients were identified. Median patient age was 71 years, 63 males and 25 females. 64 patients in the ROSE group and 24 patients in the non-ROSE group. The number of patients diagnosed by bronchoscopy was 55/64 (85.9 %) in the ROSE group and 16/24 (66.7 %) in the non-ROSE group. Bronchoscopy using Endobronchial Ultrasonography(EBUS) was 43/64 (67.2 %) in the ROSE group and 15/24 (62.5%) in the non-ROSE group. The number of patients requiring additional biopsy to search for driver oncogenes was 3/64 (4.7 %) in the ROSE group and 4/24 (16.7 %) in the non-ROSE group. Among the 47 patients who analyzed by genetic testing to find cancer driver gene, the ROSE group (34 cases) needed 14 days for analysis, and the non-ROSE group (13 cases) needed 17 days to analysis, because of biopsy rechallenge. Among the 24 patients who underwent NGS, the success rate of NGS was 10/14 (71.4 %) in the ROSE group and 6/10 (60 %) in the non-ROSE group. The ROSE group (14 cases) needed 21 days (median), and the non-ROSE group (10 cases) needed 29 days (median) before NGS results were obtained.

Conclusions: The diagnosis rate was higher than the non-ROSE group, and the proportion of patients who required additional tests was small number. The success rate of NGS testing tended to be higher in the ROSE group. In addition, the number of days required for driver gene search tended to be short. The limitations of this study are considered to be the small number of cases, and the tendency for cases with peripheral lesions which are difficult to diagnose by bronchoscopy to be included in the ROSE group. But in this study, it was suggested that ROSE may increase the success rate of transbronchial lung biopsy, and start treatment may be rapidly.

Keywords: Rapid On-Site cytologic Evaluation (ROSE), Transbronchial biopsy, next-generation sequencing (NGS)

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-144 The Impact of CNS Recurrence on Post-recurrence Survival in Patients with EGFR-mutation-positive Non-small-cell Lung Cancer

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Introduction: Adjuvant therapy with osimertinib has been demonstrated to prolong disease-free survival (DFS) after surgery in patients with EGFR-mutation-positive lung cancer; however, it is still unclear whether treatment prolongs overall survival. The trial data suggested that osimertinib could reduce the risk of central nervous system (CNS) recurrence. We assessed the prognostic impact of CNS recurrence using a cohort from a prospective observational study (Kyushu University Lung Surgery Group Study 2: KLSS-2), that investigated the treatment and prognosis of patients with postoperative recurrence between 2010 and 2015.

Methods: Based on the data of 340 patients in whom EGFR mutations were assessed among 498 total patients in the KLSS-2 cohort, factors related to CNS recurrence and the prognosis after postoperative recurrence were statistically analyzed. Data on the first-line treatment after recurrence were also assessed in patients with EGFR mutation.

Results: Among the overall population in the cohort, we noted no marked difference in the presence of EGFR mutations (p=0.14) or post-recurrence survival between patients with CNS recurrence (CNS group) and those without CNS recurrence (no-CNS group). Among the patients with stage IV recurrence in whom the EGFR mutation status was tested (n=219), the survival analysis of patients without EGFR mutation revealed that the prognosis of the CNS and no-CNS groups was not significantly different (median survival time [MST]: 25.5 vs. 18.8 months, p=0.33). Conversely, the survival analysis of patients with EGFR mutations showed that the CNS group had significantly poorer post-recurrence survival in comparison to the no-CNS group (MST: 43.9 vs. 61.5 months, p=0.038). Among EGFR mutation-positive patients with stage IV recurrence, 72% of patients received 1st generation EGFR-TKIs as first-line treatment, while 3% received 2nd generation EGFR-TKIs. In the multivariate survival analysis of EGFR-mutation-positive cases with stage IV recurrence, recurrence in multiple organs and recurrence of brain metastases were independently associated with a poor prognosis (hazard ratio: 2.2, p=0.029; hazard ratio: 3.2, p=0.0006, respectively). Among the EGFR-mutation-positive cases with stage IV recurrence, there were no differences in the first-line post-recurrence treatment or in the number of treatment lines delivered between the CNS and non-CNS groups. Sixty-five percent of the EGFR mutation-positive patients in the CNS group received any type of radiotherapy to treat CNS metastasis; this rate was not significantly different from that in the EGFR mutation-negative patients in the CNS group.

Conclusions: Postoperative CNS recurrence in patients with EGFR mutation-positive lung cancer was associated with a poor prognosis in the period when 3rd generation EGFR-TKIs were not available. In EGFR-mutation positive lung cancer, the prevention of CNS recurrence after surgery may improve the post-recurrence prognosis.

Keywords: post-operative recurrence, EGFR mutation, central nervous system metastasis

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-145 An Efficacy Analysis of Advanced Non Small Cell Lung Cancer with MET Exon 14 Skipping in the Real World

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Introduction: Lung cancers harboring mesenchymal-to-epithelial transition factor (MET) genetic alterations, such as exon 14 skipping mutations or high-level gene amplification, respond well to METselective tyrosine kinase inhibitors (TKI). Crizotinib is approved for use in patients with non-small cell lung cancer with MET14 mutations. However, there is a lack of real-world data to support the efficacy of crizotinib.

Methods: From November 1, 2013, to August 1, 2020, a total of 21 patients were enrolled in this study. Crizotinib was orally administered once every day at a dose of 250 mg, regardless of food intake, and must be taken at the same time every day at approximately 24-hour intervals. Subsequent evaluations were conducted bimonthly to evaluate the efficacy of crizotinib.

Results: 21 patients included in this study. The median progression-free survival were 7.87 months (range: 5.8-10.4months), respectively. The median overall survival were 41 months (range: 10.38-71.62months). A total of 20 patients were subjected to response analysis. Of the 20 patients, 7(35%) had a partial response, 12(60%) had stable disease, and 1(5%) had progressive disease. The overall response rate was 35%. All patients were evaluated for the toxic effects of the drugs.

Conclusions: Treatment with crizotinib is associated with improvement in survival of patients with MET exon 14 mutation.

Keywords: non-small-cell lung cancer, Crizotinib, MET exon 14 mutation

EP08.02-146 Proposal of Foretinib as Second-Line TKI after Capmatinib/ Tepotinib Treatment Failure in NSCLC with MET Exon 14 Mutation

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Introduction: Two type Ib MET-TKIs, capmatinib and tepotinib are approved for non-small-cell lung cancer (NSCLC) patients carrying *MET* exon 14 skipping mutations (*METex14*) in USA and in Japan. In vitro and clinical reports suggested that mutations at MET D1228 and Y1230 residues would be frequent among secondary resistant mutations against these type Ib TKIs. To propose an ideal sequential treatment after capmatinib/tepotinib treatment failure in NSCLC patients with *METex14*, we aimed to explore agents that will be active against both *MET* D1228X and Y1230X.

Methods: Initial screening (300 drugs, including 33 MET-TKIs) was performed using Ba/F3 cells carrying *METex14* plus *MET* D1228A/Y because anecdotal case reports suggested that D1228X mutations were more refractory to second-line MET-TKIs than Y1230X mutations.This screening found four candidate type II MET-TKIs (altiratinib, CEP-40783, foretinib and sitravatinib). We then performed further growth inhibitory assays using these four candidates plus other four MET-TKIs (type Ib; capmatinib and tepotinib, type II; cabozantinib and merestinib) in Ba/F3 cells carrying *METex14* plus one of *MET* D1228A/E/G/H/N/V/Y or Y1230C/D/H/N/S secondary mutations. We also performed analyses using Hs746t cell models carrying *METex14* with/without D1228X or Y1230X in vitro and in vivo to confirm the findings in Ba/F3 models. Furthermore, we compared the differences in binding between type II MET-TKIs through molecular dynamics (MD) simulations.

Results: Two type Ib MET-TKIs, capmatinib and tepotinib were inactive against all D1228X and Y1230X. All 6 type II MET-TKIs were active against Y1230X secondary mutations. However, among these 6 agents, only foretinib showed potent activity against D1228X secondary mutations in Ba/F3 models (table) and Hs746t in vitro and in vivo models. MD analysis suggested that the long tail of foretinib plays an important role in binding D1228X MET through interaction with a residue at the solvent front (G1163). Tertiary G1163X mutations occurred as acquired resistance mechanisms to the second-line treatment foretinib in Ba/F3 cell models.

Conclusions: The type II MET-TKI foretinib may be an appropriate second-line MET-TKI for NSCLCs carrying *METex14* after campatinib/tepotinib treatment failure by secondary mutations at D1228 or Y1230 residues.

Summary of IC50s of MET-TKIs for each MET mutation

IC_{50} (nM) capmatinib		Type I		Type II					
		tepotinib	altiratinib	CEP-40783	foretinib	sitravatinib	cabozantinib	merestinib	
MET WT + IL3		>1000	>1000	>1000	>1000	906	>1000	>1000	452
Exon 14 skip		0.4	3.5	3.6	1.1	3.2	3.6	11.4	3.7
D1228	A	>1000	>1000	92	32	11	98	295	99
	E	50	>1000	10	10	1.4	14	37	14
	G	348	>1000	32	31	10	49	90	34
	H	>1000	>1000	11	11	10	35	103	33
	N	>1000	>1000	12	12	11	37	37	34
	V	>1000	>1000	18	3.6	1.5	19	110	39
	Y	402	>1000	37	11	12	98	451	119
Y1230	C	>1000	>1000	1.3	4.1	0.4	10	18	10
	D	>1000	>1000	3.7	10	0.4	10	31	4.3
	H	470	>1000	4.6	12	3.6	32	18	11
	N	>1000	>1000	11	35	3.6	33	36	4.1
	S	>1000	>1000	0.2	4	0.1	0.8	32	12

Keywords: MET exon 14 skipping mutation, Resistance mechanism, Sequential treatment

EP08.02-147 Clinical Outcomes in Patients with or without Cell Cycle Gene Alterations in EGFR mutated Non-Small Cell Lung Cancer

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Introduction: Epidermal Growth Factor Receptor (*EGFR*) exon 19 deletions and L858R mutations are oncogenic drivers in a subset of non-small cell lung cancers (NSCLC). While tyrosine kinase inhibitor (TKI) therapies against mutant EGFR have significantly improved response rates and progression free survival (PFS) compared to cytotoxic chemotherapy for patients with metastatic EGFR-mutated NSCLC, responses to therapy are incomplete and resistance to EGFR-targeted therapies is inevitable. Somatic and copy-number alterations in cell cycle genes concurrent with EGFR mutations have been suggested to play a role in EGFR-TKI resistance, however this has not been completely characterized.

Methods: We conducted a retrospective review of patients with metastatic NSCLC with EGFR exon 19 deletions, L8585R, or T790M mutations who received targeted EGFR-TKI therapy between 2010-2021 at a single tertiary medical center. We analyzed tumor genomics using the UCSF 500 Cancer Gene test, which uses next generation sequencing to detect somatic alterations in 529 cancer genes. Positive cell cycle gene alteration status was defined as having any of the following: CDKN1A/B deletion, CDKN2A/B/C deletion, CCND1/2/3 amplification, CCNE1 amplification, CDK4/6 amplification, RB1 mutation/truncation/deletion, E2F3 amplification. We compared clinical outcomes in patients whose tumors harbored pre-TKI treatment cell cycle gene alterations (CC+) with those whose tumors did not harbor cell cycle gene alterations (CC-). We evaluated PFS with Kaplan Meier analyses and compared groups using the log-rank test. We analyzed depth of response (DR), Objective Response Rate (ORR) and Disease Control Rate (DCR) by measuring radiographic changes in tumor size using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Results: A total of 62 patients (50 CC- vs. 12 CC+) who received an EGFR-TKI (53 Osimertinib, 7 Erlotinib, 2 Gefitinib) were included in the analysis. Median PFS to EGFR TKI treatment was longer in the CC- cohort compared to the CC+ cohort. (21.5 months vs. 13.8 months; Hazard Ratio (HR): 0.35; 95% Confidence Interval [CI] 0.13 to 0.92; p = 0.03). Fifty-three patients (42 CC- vs 11 CC+) had data available to determine ORR, DCR, and DR. There was no significant difference in median DR to EGFR-TKI treatment between CC- and CC+ cohorts (-38% change in tumor size, p = 0.22). ORR to EGFR-TKI treatment was 61.9% (95% CI 46.8% to 75%) in the CC- cohort as compared to 54.6% (95% CI 28% to 78.7%) in the CC+ cohort (p = 0.7). DCR was 100% (95% CI 91.6% to 100%) in the CC- cohort as compared to 81.8% (95% CI 52.3% to 94.9%) in the CC+ cohort (p = 0.04).

Conclusions: In patients with metastatic EGFR-mutated NSCLC receiving EGFR-TKI therapy, PFS was significantly shorter in patients whose tumors harbored co-occurring cell cycle gene alterations as compared to those without. In addition, CC+ patients exhibited decreased DCR compared to CC- patients. These data suggest that co-occurring cell cycle gene alterations may enable EGFR-mutated tumor cells to more readily develop resistance to EGFR TKI therapy and that combination therapies targeting both EGFR and cell cycle alterations may lead to improved clinical outcomes in this patient population.

Keywords: EGFR mutations, Cell Cycle Gene Alterations, TKI Resistance

EP08.02-148 Extended Follow-up of Efficacy and Safety of Larotrectinib in Patients with TRK Fusion Lung Cancer

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Introduction: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a variety of tumour types, including lung cancer. Larotrectinib is a highly selective, central nervous system (CNS)-active tropomyosin receptor kinase (TRK) inhibitor that demonstrated an objective response rate (ORR) of 87% across 15 independent review committee (IRC)-evaluable patients with TRK fusion lung cancer as of July 2020 (Drilon et al, JCO Precis Oncol 2021). We report data on these patients with longer follow-up and on an expanded dataset of patients with TRK fusion lung cancer treated with larotrectinib.

Methods: Patients with TRK fusion lung cancer enrolled in two larotrectinib clinical trials (NCT02576431, NCT02122913) were included for this analysis. Larotrectinib was administered at 100 mg twice daily. Response was assessed by IRC (RECIST v1.1).

Results: As of July 2021, 20 patients from the 2020 data-cut (median age 48.5 years [range 25.0-76.0]) had an additional year of follow-up. Patients received a median of 3 prior lines of systemic therapies with 13 (65%) receiving ≥2. ORR for the 15 IRC-evaluable patients remained the same (87%). Median duration of response (DoR) was not reached; median follow-up was 24.0 months. Median progression-free survival (PFS) was 33.0 months at a median follow-up of 35.8 months. The 24-month rates for DoR and PFS were 64% and 62%, respectively. Median overall survival (OS) was 40.7 months at a median follow-up of 35.8 months.

As of July 2021, there were an additional six patients (26 total) with TRK fusion lung cancer included in the expanded dataset (overall median age 51.5 years [range 25.0-76.0]). The gene fusions involved *NTRK1* (n=21; 81%) or *NTRK3* (n=5; 19%). Patients received a median of 2 prior lines of systemic therapies. ORR for the 23 patients evaluable per IRC was 83% (95% confidence interval [CI] 61-95): two complete response, 17 partial response (PR) and four stable disease (SD). Duration of treatment ranged from 2.1 to 52.7+ months. The median DoR and PFS were not reached; median follow-ups were 12.9 and 14.6 months, respectively. The 24-month rates for DoR and PFS were 72% and 67%, respectively. Median OS was 40.7 months; median follow-up was 12.9 months. There were 10 patients with baseline CNS metastases evaluable per IRC; ORR for these patients was 80% (95% CI 44-97): eight PR and two SD. The median DoR, PFS and OS were 9.5 (95% CI 3.6-not estimable [NE]), 9.9 (95% CI 5.3-NE) and 19.4 (95% CI 7.6-NE) months, respectively, with median follow-ups of 9.3, 11.0 and 12.0 months. Treatment-related adverse events (TRAEs) were predominantly Grade 1-2. Grade 3-4 TRAEs were reported in five patients (increased alanine aminotransferase, increased aspartate aminotransferase, hypersensitivity, myalgia and increased weight). There were no treatment discontinuations due to TRAEs.

Conclusions: Larotrectinib demonstrated rapid and durable responses, extended survival and a favourable long-term safety profile in patients with advanced lung cancer harbouring *NTRK* gene fusions, including in patients with CNS metastases. These results support testing for *NTRK* gene fusions in patients with lung cancer.

Keywords: TRK fusion, NTRK gene fusion, larotrectinib

EP08.02-149 Spanish Multicenter Retrospective Study of Real-Life Experience of Advanced NSCLC with EGFR Exon 20 Insertions Treated with Amivantamab

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Introduction: Amivantamab is a novel anti-EGFR/c-MET bispecific antibody with clinical activity in EGFR mutated(m) advanced non-small cell lung cancer (aNSCLC) harboring exon20 insertions (ex20ins), recently approved by FDA; the activity/safety in real-world data (RWD) is very limited. We aimed to assess the activity/safety of amivantamab in a RWD-cohort of patients with Ex20ins aNSCLC from an Expanded Access Program (EAP).

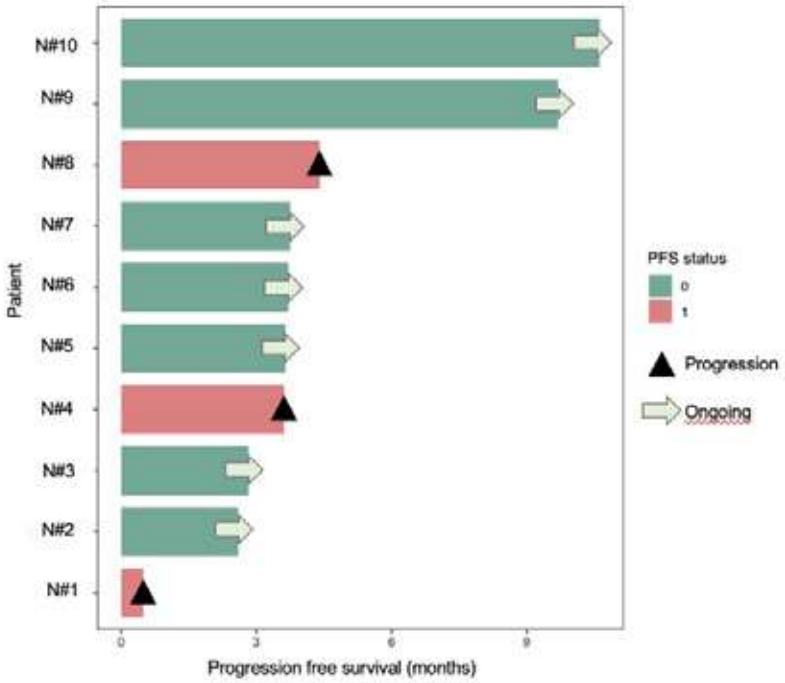
Methods: Retrospective multicenter study of patients with ex20ins *EGFR*m aNSCLC treated with amivantamab after progression to standard therapy from 15 centers participating in the EAP in Spain between May/2021-Feb/2022. Clinical/molecular data was collected from medical records. We assessed overall response rate (ORR), disease control rate (DCR) evaluated by investigator criteria, adverse events (AE), progression-free survival (PFS) and overall survival (OS).

Results: Out of 15 patients included, 12 received amivantamab (3 screening failures: n=1 clinical deterioration, 2 included in clinical trials). In the first 10 patients, median age was 69; 60% were female, 60% non-smokers, all with adenocarcinoma histology. PD-L1 was positive in 60%; 70% had ≥2 metastatic sites, most commonly lung (90%); 20% had intracranial involvement. *EGFR*m ex20ins was diagnosed by NGS in 70%; co-alterations were detected in 30% (1 *EGFR* amplification; 1 *MET*m and 1 *TP53*m). Median number of previous lines was 1 (1-3). One patient received sequential therapy with amivantamab after mobocertinib. ORR was 30% (all partial responses) and DCR was 70%; 1 patient had progressive disease (PD) as best response. In 2 patients with intracranial disease, DCR was 50% with no ORR observed. 70% of patients had any grade of infusional reaction at C1D1 (20% grade (G) ≥3), and only 1 had a second-infusional reaction after resuming infusion. No reactions were observed beyond C1D1. Most common AE were rash (90%); hypoalbuminemia (40%); fatigue (20%), elevated-AST/ALT (20%). AE leading to dose reduction were G3 fatigue (n=2) and G3 elevated-AST/ALT (n=1). One patient discontinued treatment due to G3 fatigue.

Survival outcomes were immature, with a median follow-up of 3,7 months; median PFS and OS were both not reached (NR-NR). Treatment duration is summarized in **Figure 1**.

Conclusions: Our preliminary RWD-data shows clinical activity consistent with previously reported in EGFR ex20ins, including some durable responses. Spectrum of AE and infusional reactions were similar to previous data, although with higher rates of dose reductions/treatment discontinuation compared to clinical trials. This preliminary data will be updated in the meeting.

Figure 1: Swimming plot of patients treated with amivantamab from the Spanish EAP cohort.



Keywords: Amivantamab, EGFR mutated NSCLC, Exon 20 insertion

EP08.02-150 Molecular Heterogeneity of Compound Epidermal Growth Factor Receptor (EGFR) Mutations in Lung Adenocarcinoma (LAC)

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Introduction: EGFR exon 19 deletions and exon 21 L858R point mutation represent nearly 90% of all EGFR gene mutations. Compound mutations are defined as the presence of more than one EGFR mutation in the same tumour. The incidence of LAC with compound EGFR mutations is reported to be around 5% in the Caucasian population[1]. We report our experience with LAC with compound EGFR mutations from a regional cancer centre in United Kingdom.

Methods: The electronic health records of 17 patients (pts) diagnosed between 2014 and 2021 with LAC with compound EGFR mutations were reviewed. Demographics, clinical, tumour and molecular characteristics and treatment outcomes were analysed. EGFR mutations identified using Ion Ampliseq™ Cancer Hotspot Panel v2 primers sequenced using Ion PGM System and analysed for mutation status using Torrent Suite Software and Ion Reporter Software (Thermo Fisher Scientific Inc).

Results: N=17. Males=4, Females=13. Median age 65 years (range 42-82). 6 pts had brain metastases at presentation. 11 pts had been treated with EGFR tyrosine kinase inhibitors (TKIs) (1st line TKIs n=10 and 3rd line TKIs n=1. 5 pts were treated with afatinib, 3 pts with osimertinib, 4 pts with gefitinib and 1 pt with erlotinib). Some pts had more than one TKI. Median overall survival for patients in the TKI treated cohort is 8 months (0.25 - 41). Table 1 demonstrates the distribution of the EGFR mutations. 5/17 tumours had common mutations (1 pt with exon 19 deletion and 4 pts with exon 21 L858R point mutation). 12 had uncommon + uncommon compound mutations. 1 had an additional exon 20 T790M mutation on subsequent biopsy. There were additional mutations in TP53 (4), PTEN (2), SMAD4 (1) and CTNNB (1). 8/17 tumours had extra copies of ALK gene but no translocation**.**

Conclusions: EGFR LAC with compound mutations is a heterogeneous group. The incidence of common mutations was lower than expected. The most frequent uncommon mutations involved EGFR exons 20 and 21. We have not observed any common + common compound mutations. Overall survival in this cohort treated with TKIs is much shorter than expected overall survival in LAC patients with single mutation.

Evans, M et al. Large-Scale EGFR Mutation Testing in Clinical Practice: Analysis of a Series of 18,920 Non-Small Cell Lung Cancer Cases. Pathol. Oncol. Res. 2019: 25, 1401-1409.

Table 1 : Distribution of Compound EGFR Mutations

EGFR mutation 1 (n)	EGFR mutation 2 (n)
Exon 18 (4) • c.2156 G>C p.(Gly719Ala) • c.2156 G>C p.(Gly719Ala) • c.2153 T>A p.(Leu718Gln) • c.2156 G>C p.(Gly719Ala)	Exon 20 (2) • c.2303 G>T p.(Ser768Ile) • c.2303 G>T p.(Ser768Ile) Exon 21 (2) • c.2582 T>G p.(Leu861Arg) • c.2582 T>A p.(Leu861Gln)
Exon 19 (4) • c.2240 T>C p.(Leu747Ser) • c.2239 T>G p.(Leu747Val) • c.2235_2249del p. (Glu746_Ala750del) • c.2281 G>T p.(Asp761Tyr)	Exon 18 (2) • c.2156 G>C p.(Gly719Ala) • c.2156 G>C p.(Gly719Ala) Exon 20 (1) • c.2305 G>A p.(Val769Met) Exon 21 (1) • c.2573 T>G p.(Leu858Arg)
Exon 20 (1) • c.2303 G>T p.(Ser768Ile)	Exon 18 (1) • c.2155 G>T p.(Gly719Cys)
Exon 21 (8) • c.2582 T>A p. (Leu861Gln) • c.2573 T>G p.(Leu858Arg) • c.2573 T>G p.(Leu858Arg) • c.2573 T>G p.(Leu858Arg) • c.2582 T>A p.(Leu861Gln) • c.2582 T>G p. (Leu861Gln) • c.2582 T>G p. (Leu861Gln) • c.2582 T>G p.(Leu861Gln)	Exon 18 (1) • c.2156 G>C p.(Gly719Ala) Exon 20 (7) • c.2326 C>T p.(Arg776Cys) • c.2327 G>A p.(Arg776His) • c.2327 G>A p.(Arg776His) • c.2320 G>A p.(Val774Met) • c.2327 G>A p.(Arg776His) • c.2326 C>T p.(Arg776Cys) • c.2326 C>T p.(Arg776Cys)

Keywords: Lung Adenocarcinoma, EGFR, Compound mutations

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-151 A Real World Evidence of Lorlatinib for Taiwanese with advanced ALK Positive Non-Small Cell Lung Cancer

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Introduction: Anaplastic lymphoma kinase (ALK) rearrangement is a rare driver mutation in non-small cell lung cancer and lorlatinib is the 3rd generation ALK tyrosine kinase inhibitor (TKI) approved for treating such patients. We aimed to report result of lorlatinib in real-world practice.

Methods: This is a multi-center, retrospective study. Treatment pattern, efficacy and adverse event of lorlatinib were captured and reviewed from medical record.

Results: A total 52 ALK -positive patients were enrolled. Ten patients had lorlatinib as 2nd ALK TKI, while 25 patients as 3rd and 17 as 4th or later respectively. The objective response rate was 22% and disease control rate was 88%. Median progression-free survival for lorlatinib as 2nd, 3rd or later TKI was immature, 14 months and 6.4 months respectively. Hyperlipidemia (34/52, 65.4 %), body weight gain (7/52, 13.5 %) and edema (4/52, 7.7%) were the most common three adverse events reported.

Conclusions: This real-world efficacy and adverse event on lorlatinib for Taiwanese ALK-rearranged NSCLC are compatible to those reported in global clinical trial.

Keywords: real world, lorlatinib, lung cancer

EP08.02-152 Long-Term Survival with Anlotinib in a Patient with Advanced Undifferentiated Large-Cell Lung Cancer and Rare Tonsillar Metastasis

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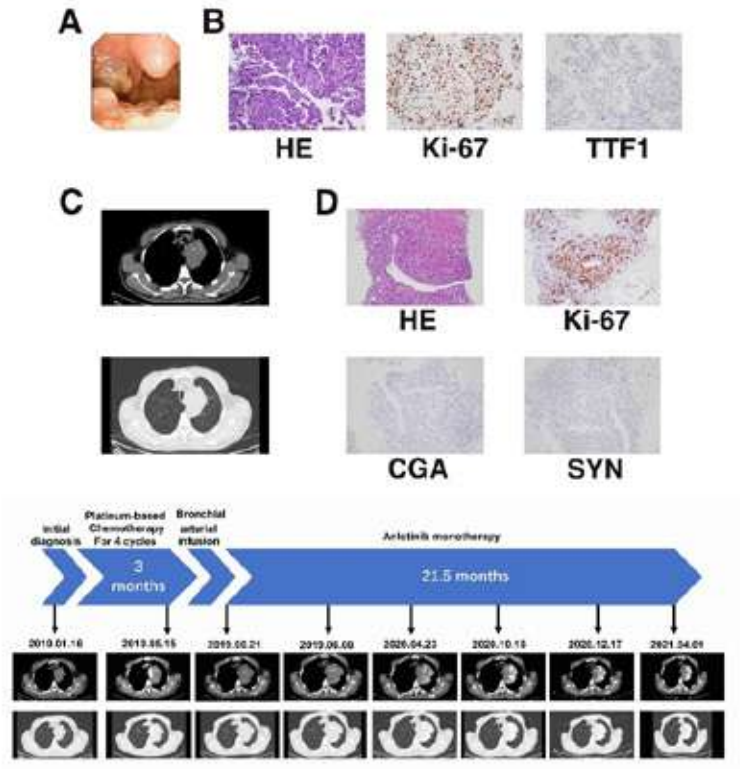
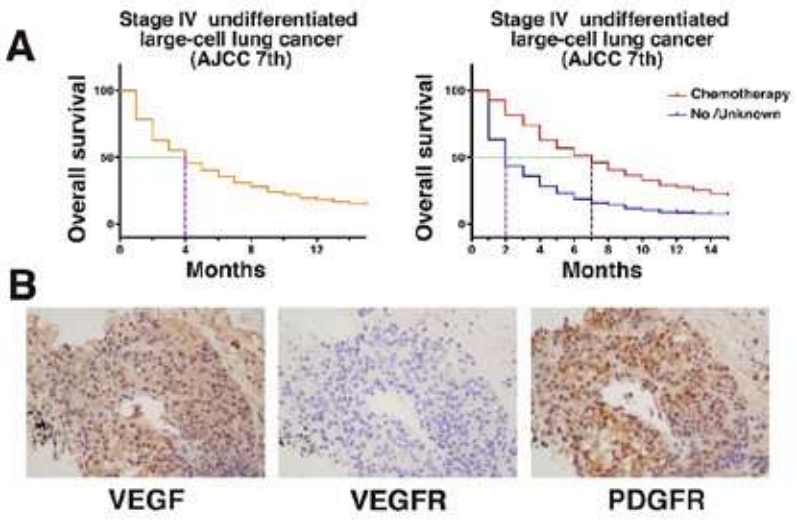
Introduction: Undifferentiated large-cell lung cancer is a rare type of non-small cell lung cancer (NSCLC) with a poor prognosis. It is insensitive to chemotherapy and easily develops drug resistance. We present the first case of a patient with undifferentiated large-cell lung cancer with rare tonsillar metastases who achieved a long survival time with anlotinib treatment after chemotherapy failure.

Methods: We retrospectively collected the data of NGS, imaging, Laryngoscopy and survival of the patients.Data from the Surveillance, Epidemiology, and End Results (SEER) database were analyzed to confirmed the survival of undifferentiated large-cell lung cancer. Immunohistochemical analysis was used to explore the potential targets for therapy.

Results: Analysis of SEER database showed that patients with stage IV undifferentiated large-cell lung cancer had a median overall survival (OS) of only 4 months and that those who received chemotherapy had a median OS of only 5 months longer than those who did not. For the first time, we report a case of advanced large-cell undifferentiated lung cancer with rare tonsil metastasis. The patient developed resistance after 3 months of platinum-based systemic chemotherapy and local treatment. Anlotinib, an orally delivered small-molecule antiangiogenic tyrosine kinase inhibitor (TKI), was administered to this patient after chemotherapy resistance occurred, and the outcome was assessed as continued stable disease (SD). As of the last follow-up evaluation, the progression-free survival (PFS) of the patient was 21.5 months, and the OS was 27.5 months. Retrospective immunohistochemical analysis showed that the patient was positive for one of the targets of anlotinib (PDGFR).

Conclusions: In general, the findings in this case suggest that anlotinib may be an option with good efficacy for patients with large-cell undifferentiated lung cancer after chemotherapy resistance that may have good efficacy and also suggest that PDGFR may be the target underlying this effect.





Keywords: Undifferentiated large-cell lung cancer, Antiangiogenic therapy, Tonsillar metastasis

EP08.02-153 The Efficacy and Safety of EGFR-TKIs plus Anlotinib in Maintenance Therapy for Oligoprogressive Advanced or Metastatic EGFR Mutant NSCLC

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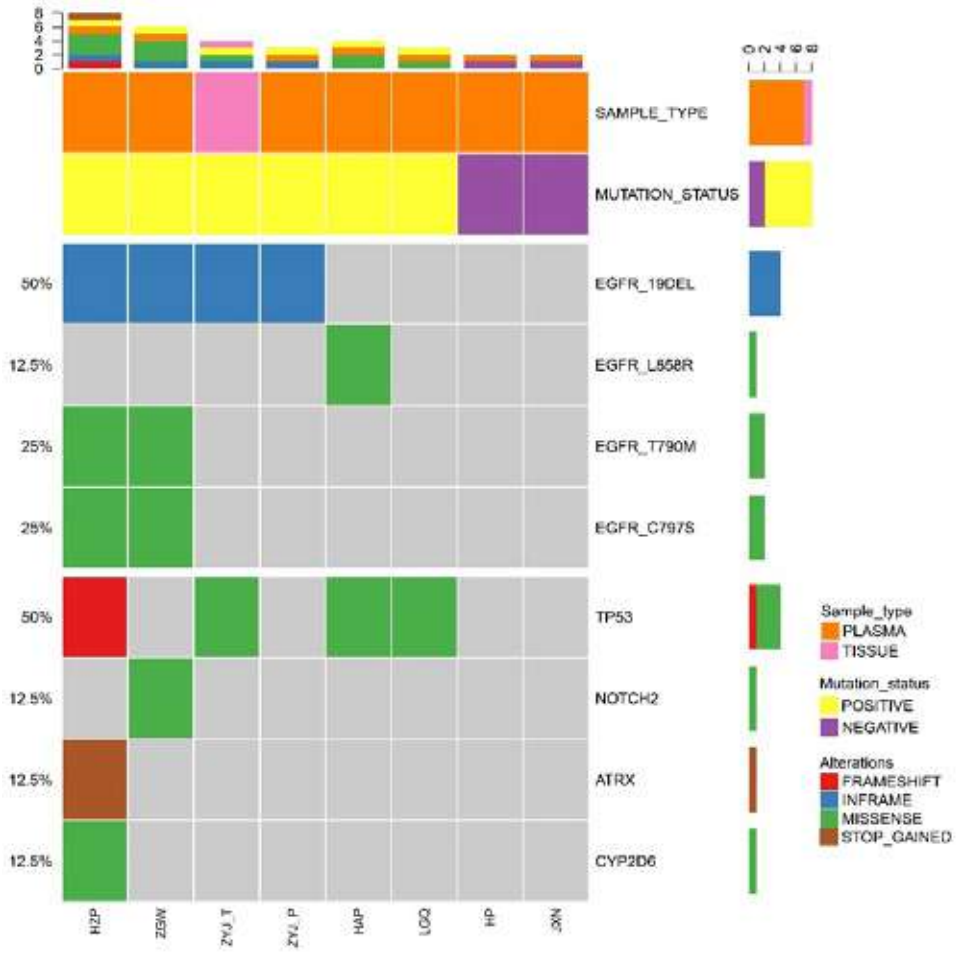
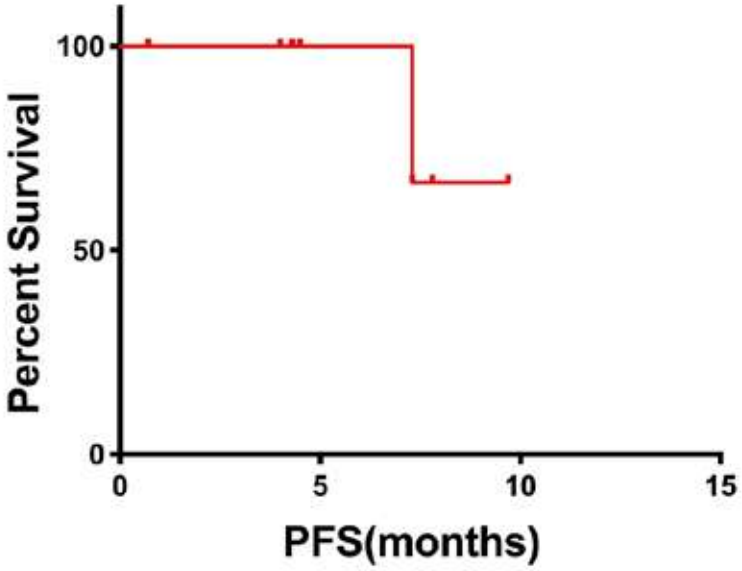
Introduction: In recent years, Tyrosine kinase inhibitors (TKIs) targeting Epidermal growth factor receptor (EGFR) have been successfully developed and marketed globally. EGFR-TKIs is recommended for first-line treatment of EGFR-mutant NSCLC because of its advantages of convenience, better efficacy and higher quality of life compared with traditional inpatient chemotherapy. Unfortunately, resistance to EGFR-TKIs will inevitably occur eventually. Currently, there are few options for further targeted therapy after drug resistance. ASPIRATION studies indicate that continuing original EGFR-TKIS maintenance therapy after oligoprogressive still benefits, but only extends progression-free survival (PFS) by ~ 3.1 months. Anti-angiogenesis therapy is another treatment options for lung cancer. Clinical trials such as NEJ026 shows that bevacizumab in combination with erlotinib for treatment can significantly improve curative effect. Anlotinib is an oral small molecule antiangiogenic agent that has been shown to be effective in NSCLC by ALTER0303. Compared with bevacizumab, it has the advantages of convenient administration, high quality of life and good compliance. This study is a prospective, single-arm clinical study designed to evaluate the efficacy and safety of anlotinib combined with EGFR-TKIs as maintenance therapy for oligoprogressive advanced or metastatic EGFR mutant NSCLC after EGFR-TKIS therapy.

Methods: Oligoprogressive advanced or metastatic EGFR mutant NSCLC after EGFR-TKIS therapy were selected to enter the study and receive anlotinib combined with EGFR-TKIs. The primary endpoint was progression-free Survival (PFS), the secondary endpoint was Overall Survival (OS) and safety (CTCAE 5.0), and the exploratory endpoint was the screening of various potential molecular markers. We plan to enroll 18 patients in this clinical trial. Patients who are clearly T790M mutation and have not been treated with third-generation EGFR-TKIs should be excluded. We expected this regimen to extend patients' PFS by 7 months.





Results: As of February 28, 2022, we have successfully enrolled 7 patients (Table1). NGS test was performed on accessible peripheral blood or tumor tissue of enrolled patients before the use of anlotinib (Figure 1). At present, the study has not reached the end point (Figure 2). The most common adverse reactions were skin rash and peeling, which resolved spontaneously after two cycles of treatment or reduced dose. So far, no adverse events above grade 3 have been observed (CTCAE 5.0).

Conclusions: In this study, no obvious adverse events were observed in the enrolled patients, indicating the safety of this experimental protocol. Patient enrollment and follow-up in this clinical trial are ongoing.

Table 1. Patient Clinical Characteristics Data Sheet

No.	Age	Gender	The pathologic types	EGFR mutation after oligoprogressive	EGFR-TKIs
Patient 1	60	Male	LAD	EGFR 19del	Icotinib
				EGFR 19del	
Patient 2	65	Female	LAD	EGFR T790M	Osimertinib
				EGFR C797S	
				EGFR 19del	
Patient 3	55	Male	LAD	EGFR T790M	Osimertinib
				EGFR C797S	
Patient 4	45	Female	LAD	ND	Osimertinib
Patient 5	66	Female	LAD	ND	Iressa
Patient 6	71	Female	LAD	ND	Iressa
Patient 7	64	Female	LAD	EGFR L858R	Almonertinib

Keywords: EGFR-TKIs, Anlotinib, oligoprogressive advanced or metastatic EGFR mutan

EP08.02-154 Aumolertinib Plus Anlotinib as 1st-Line Treatment for EGFR Mutant Non-Small Cell Lung Cancer: A Phase II Trial

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Introduction: The third-generation EGFR targeted oral tyrosine kinase inhibitors (TKIs) are recommended as first-line options for EGFR mutant NSCLC. However, how to further prolong the median progression-free survival (PFS) of first-line treatment with EGFR-TKIs still be a concern in the field of lung cancer targeted therapy. First-generation EGFR-TKIs combined with anti-angiogenic drugs has obtained promising results in clinical studies. The BOOSTER study showed that the combination of osimertinib and bevacizumab was not superior to monotherapy. Anlotinib is a small molecule anti-angiogenic targeted drug proven to be safe and effective in advanced lung cancer. Although bevacizumab and anlotinib are both anti-angiogenic drugs, anlotinib is a multi-target tyrosine kinase inhibitor, and it is convenient to take orally. Aumolertinib (HS-10296) is a novel, third-generation EGFR-TKI with a different structure from osimertinib approved in China to treat Mutated EGFR NSCLC. The combination of aumolertinib and anlotinib may have broad clinical application prospects. There is no clinical study reported on the combination of the third-generation EGFR-TKIs aumolertinib and the oral anti-angiogenic drug anlotinib in the treatment of EGFR-mutant advanced NSCLC. This study aims to exploring a new mode of treatment with third-generation EGFR-TKI combined with oral anti-angiogenic drugs, and to provide new ideas for further prolonging the progression-free survival time of first-line treatment of advanced NSCLC patients with EGFR mutations.

Methods: This study is a single-arm, single-center, phase II clinical study. Untreated patients with advanced EGFR-mutant NSCLC receive aumolertinib 110mg orally QD plus anlotinib 12mg orally QD. Anlotinib is continuously used for 2 weeks and then stopped for 1 week, that is, a 3-week (21-day) cycle program. The primary endpoint was PFS, secondary endpoints included objective response rate (ORR), disease controlRate (DCR), overall survival (OS), duration of response (DoR) and safety.

Results: From Jan, 2020 to Feb, 2021, 11 patients were recruited. The median age was 67 years, 8 (72.7%) were male, and 10 (90.0%) were multiple metastases which include 7 (63.6%) brain metastases. Of 11 response-evaluable subjects, all patients achieved partial response (PR) as their best response, so overall ORR was 100% (11/11). 7 patients with brain metastases were evaluated for intracranial target lesions, with 5 achieving PR and 2 SD as their best response. iORR was 71.4% (5/7) and iDCR was 100% (7/7). No patients discontinued the drug due to adverse reactions. This study is currently ongoing and the primary endpoint has not been reached so far.

Conclusions: This is the first study to demonstrate that combination therapy with aumolertinib and anlotinib have preliminary efficacy and a tolerable safety profile in EGFR-mutated NSCLC patients. The observed ORR is better than any EGFR-TKI reported first-line response rates for EGFR-mutated NSCLC. In addition, this combination also showed preliminary efficacy in patients with brain metastases. The study is currently ongoing and will further observe long-term outcomes.

Keywords: Aumolertinib, Anlotinib, NSCLC

EP08.02-155 The Difference in Clinical Outcomes Between Osimertinib and EGFR-TKI plus Anti-angiogenic Agent in EGFR-mutant NSCLC Patients

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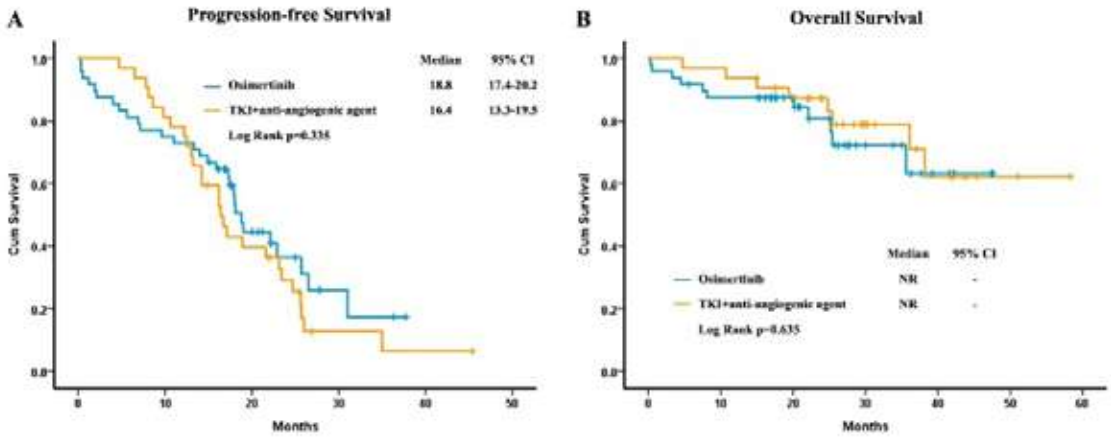
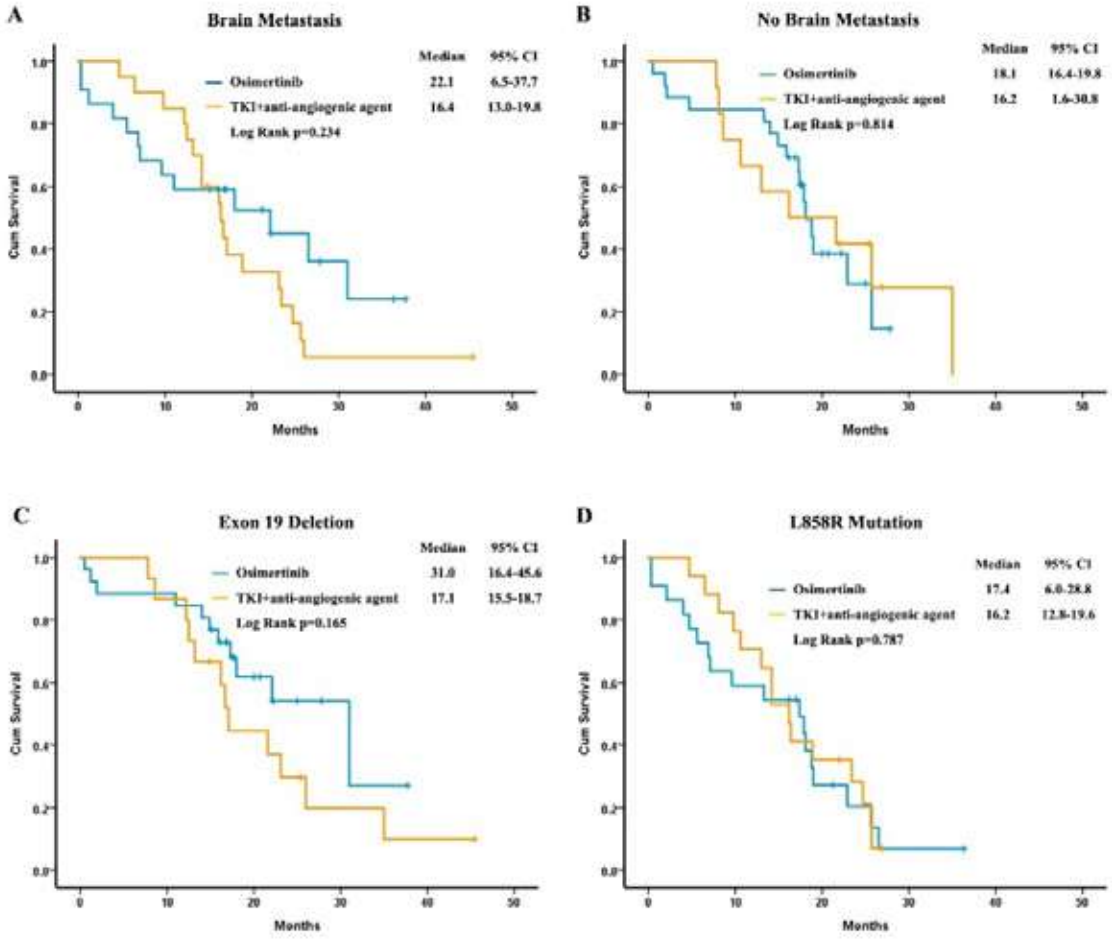
Introduction: The aim of this study was to investigate the difference of the efficacy between osimertinib and Epidermal Growth Factor Receptor (EGFR)-Tyrosine Kinase Inhibitor (TKI)s combined anti-angiogenic agents as first line treatment in advanced and recurrence *EGFR*-mutant Non-small Cell Lung Cancer (NSCLC) patients.

Methods: From January 2017 to December 2020, we enrolled advanced and recurrence NSCLC patients who harbored exon 19 deletion or L858R mutation with osimertinib and first- or second-generation EGFR-TKIs plus anti-angiogenic agents as first-line treatment to analyze the clinical outcomes including Progression-Free Survival (PFS) and Overall Survival (OS).

Results: A total of 80 patients were enrolled for final analysis. Forty-eight patients received osimertinib (group O), 32 patients received gefitinib, erlotinib and afatinib plus anti-angiogenic agent (group A) as first-line treatment. The median PFS was 18.8 months in group O, and the median PFS was 16.4 months in group A (Figure 1A). The median OS was not reached in both groups (Figure 1B). There was no statistically significant difference between group O and group A in PFS and OS. Among patients with brain metastasis, the median PFS was 22.1 months in group O, and the median PFS was 16.4 months in group A (p=0.234) (Figure 2A). In patients without brain metastasis, the median PFS was 18.1 and 16.2 months in group O and group A, respectively (p=0.814) (Figure 2B). Regarding the subtypes of *EGFR* mutation, the clinical efficacies in group O were equal to group A among patients harboring exon 19 deletion and L858R mutation (Figure 2C and 2D).

Conclusions: Our research demonstrated that both osimertinib and first- or second-generation EGFR-TKIs plus anti-angiogenic agents as first line treatment provided good clinical outcomes in advanced and recurrence *EGFR*-mutant NSCLC patients.





Keywords: NSCLC, EGFR-TKI, Anti-angiogenic agent

EP08.02-156 Real-World Treatment Patterns and Impact of Comorbidity Burden on Treatment Duration for Patients with ALK+ NSCLC in the US

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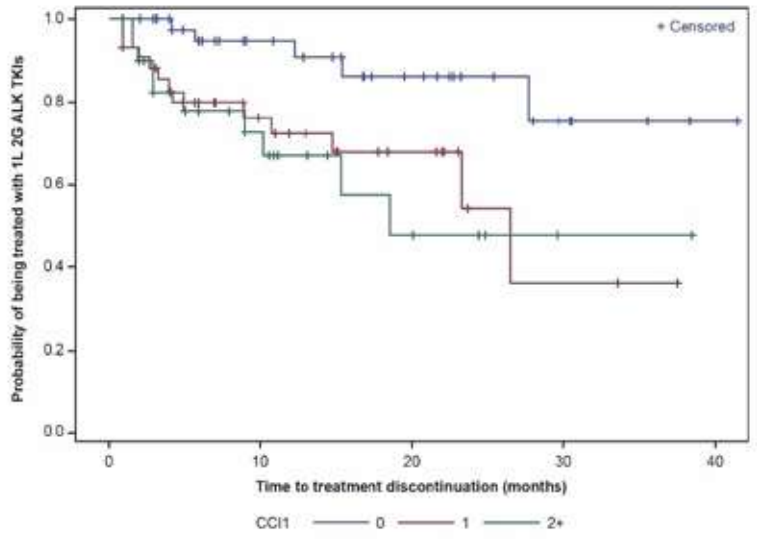
Introduction: This study aims to describe treatment patterns of patients with advanced *ALK*+ NSCLC and to evaluate the impact of comorbidity burden on duration of first-line (1L) treatment with next-generation ALK TKIs.

Methods: This is a retrospective study using a large US Commercial and Medicare Supplemental database. Adult patients diagnosed with advanced lung cancer (i.e., index date) who have had continuous enrollment of ≥ 6 months before and ≥1 month after index date were identified. Patients must have been treated with at least one ALK TKI and initiated 1L treatment from Jan 1, 2018 to Feb 28, 2021. Comorbidity burden is defined using Charlson Comorbidity Index (CCI). The outcome measurement is time to treatment discontinuation (TTD) from 1L initiation.

Results: A total of 219 advanced *ALK*+ NSCLC patients received 1L treatments. The median age was 56 years (range 25 - 97) and 54% were female. The median follow up was 12.1 months (range 0.4 - 39.0). Most patients received next generation ALK TKIs as 1L treatment at the time of data cut - including 116 (53%) patients treated with alectinib, 2 (1%) with brigatinib and 2 (1%) with ceritinib. A total of 43 (20%) patients received 1L crizotinib and 20 (9%) patients received 1L chemotherapy. Approximately 35% of these 219 patients received second-line (2L) treatments. Majority of the 2L treatments were next generation ALK TKIs (57%), including alectinib, brigatinib and lorlatinib. The most common comorbidities were COPD (26.9%), mild liver disease (16.9%) and uncomplicated diabetes mellitus (16.4%). Among the patients treated with 1L next generation ALK TKIs (N=120), the overall median TTD was not reached. The median TTD for CCI=0 (N=48), CCI=1 (N=43) and CCI≥2 (N=29) groups were not reached, 26.5 months (95% CI: 14.8-NA) and 18.5 months (95% CI: 10.2-NA), respectively (Figure). After adjusting for age, gender, baseline brain metastasis and smoking status, patients with CCI≥2 (HR=4.1, 95% CI: 1.4-11.6, P=0.009) and CCI=1 (HR=5.4, 95% CI: 1.7-16.9, P=0.004) had increased risk of discontinuing 1L treatment compared to patients with CCI=0.

Conclusions: The most common 1L treatments were next-generation ALK TKIs among patients with advanced *ALK*+ NSCLC. Comorbidity is associated with increased risk of treatment discontinuation among patients receiving current first-line next generation ALK TKIs (majority alectinib). The effectiveness of additional novel therapies for 1L treatment will be evaluated in future studies.

Figure. Kaplan-Meier curve of time to treatment discontinuation stratified by CCI group (0, 1, ≥2)



Keywords: ALK+ NSCLC, ALK tyrosine kinase inhibitor, Comorbidity burden

EP08.02-157 Acquired EGFR Exon 19 Deletion Is a Resistance Mechanism to BRAF/MRK Inhibition in BRAF V600Emutant NSCLC

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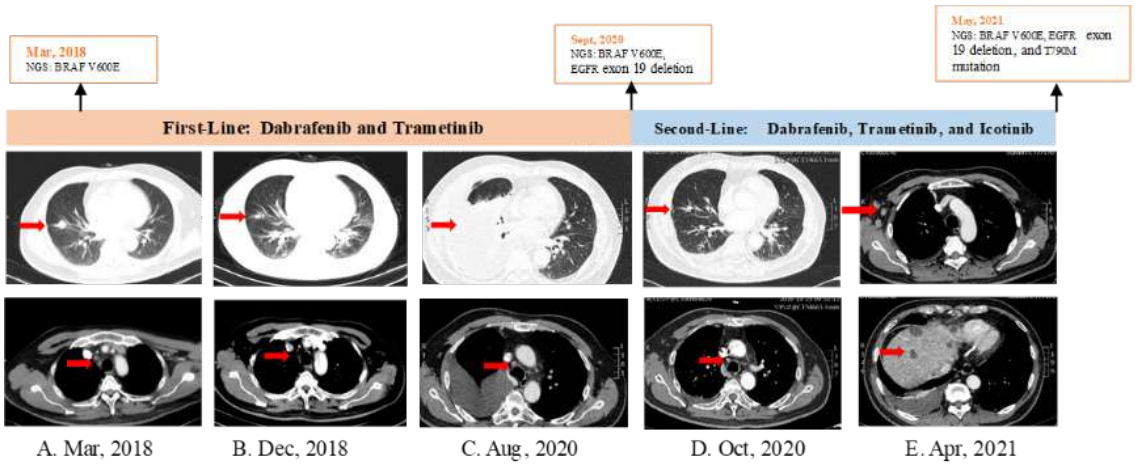
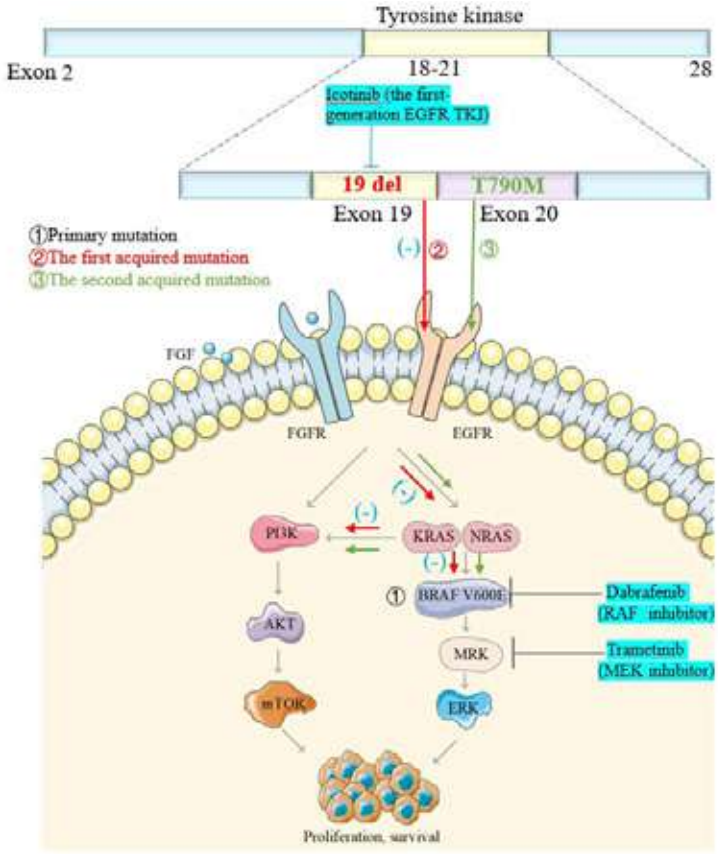
Introduction: BRAF mutation, commonly BRAFV^{600}E, occurs in approximately 2% of non-small cell lung cancer (NSCLC) patients. FDA has approved dabrafenib plus trametinib as the standard therapy for BRAFV^{600}E-mutant NSCLC. The objective response rate is 64% with a median progression-free survival of about 10 months. Despite great anti-tumor activities of BRAF/MRK inhibitors, the resistance mechanism is not fully understood. Here, we reported a NSCLC patient whose acquired resistance to BRAF/MRK inhibition was caused by EGFR exon 19 deletion.

Methods: We followed up a 57 year old smoking male who was diagnosed as lung adenocarcinoma with metastases to mediastinal and supraclavicular lymph nodes in March 2018 (cT1bN3M0, stage IIIB).

Results: Next-generation sequencing (NGS) (Nanjing Geneseeq Technology Inc, Jiangsu, China) revealed an EGFR exon 19 deletion and BRAFV600E mutation in plasma at first. Finally, the patient died of diffuse intravascular coagulation (DIC). Acquired EGFR T790M mutation was also detected in plasma by NGS. In addition, the EGFR exon 19 deletion and the BRAFV600E mutation could still be observed.

Conclusions: we reported for the first time EGFR exon 19 deletion as an acquired resistance mechanism to BRAF/MRK inhibition in NSCLC. Our case showed triple BRAF/MRK/EGFR inhibition is an efficacious therapeutic strategy for patients with acquired EGFR exon 19 deletion after progression on BRAF/MRK inhibition. In addition, ambulatory monitoring of gene mutation status during treatment could more effectively explore the mechanism of resistance and provide more targeted therapy opportunities for patients that develop drug resistance. For patients with advanced lung cancer, especially those who can not do tissue biopsy due to poor physical condition, liquid biopsy plays an important role in diagnosis.





Keywords: BRAF mutation, EGFR exon 19, acquired resistance

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-158 Final Analyses of ALTER-L018: A Randomized Phase II Trial of Anlotinib Plus Docetaxel vs Docetaxel as 2nd-line Therapy for EGFR-negative NSCLC

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Introduction: Docetaxel is one of the standard 2nd-line treatments for advanced non-small cell lung cancer (NSCLC), but the effect is limited. The combination of docetaxel and ramucirumab/nintedanib has demonstrated antitumor activity as 2nd-line therapy in advanced NSCLC. Anlotinib, an oral multi-target angiogenesis, can prolong both PFS and OS of refractory advanced NSCLC patients in phase III trial (ALTER0303). We conducted ALTER-L018 to evaluate improvement of the efficacy and safety of anlotinib plus docetaxel in EGFR-negative advanced NSCLC.

Methods: In this multi-center, randomized, controlled comparative, phase II trial, patients from 10 sites in China, with EGFR wild-type NSCLC progressing after 1st-line platinum-based therapy (combined with or without Immune checkpoint inhibitors), were randomly allocated (1:1) to receive anlotinib (12mg QD from day 1 to 14 of a 21-day cycle) plus docetaxel (75mg/m^2 Q3W) (group A+D) or docetaxel (75mg/m^2 Q3W) only (group D). Primary end point was PFS, and secondary end points included OS, ORR, DCR and safety. [Clinical Trials Registration: NCT03624309].

Results: Between Jan 14, 2019, and Jun 18, 2021, 96 patients (pts) were enrolled and 13 pts were excluded due to inclusion violations. At data cutoff (Feb 24, 2022), 83 pts. (demographics are shown in Table 1) were available for efficacy and safety analysis. The median PFS in group A+D was significantly improved compared with group D [4.36m (95%CI: 2.78-5.94) vs 1.64m (95%CI: 1.48-1.80); HR 0.38 (95%CI: 0.22-0.65), p<0.001)]. The median OS was 11.97m (95%CI: 3.08-20.86) in group A+D and 10.85m (95%CI: 5.44-16.26) in group D [HR 0.82 (95%CI: 0.45-1.47), p=0.501)]. For tumor response, ORR were 35.14% vs 9.52% (p=0.007) and DCR were 83.78% vs 54.76% (p=0.006) in group A+D and group D, respectively. We noted treatment-related adverse events (TRAEs) of grade 3 or above occurred in in 12 (30.0%) of 40 pts in group A+D safety population and 8 (18.6%) of 43 pts in group D safety population. The most common grade 3 or worse TRAEs were Leucopenia (15.0% vs 7.0%), Neutropenia (10.0% vs 4.7%) in group A+D and group D, respectively. The toxicities in both groups were manageable with appropriate dose reductions and supportive care.

Conclusions: The combination of anlotinib plus docetaxel improves survival as second-line treatment of EGFR wild-type NSCLC patients in terms of PFS, ORR, DCR, and has a manageable safety profile. It has been proved to be an effective regimen for EGFR wild-type NSCLC patients progressing after first-line platinum-based chemotherapy combined with Immune checkpoint inhibitors.

Table 1 Demographics

	Group A+D (anlotinib + docetaxel) (n=40)	Group D (docetaxel) (n=43)
Median age, years	54 (40-71)	58 (39-74)
Age group, years, n (%)		
< 60	27 (67.50)	26 (60.47)
≥ 60	13 (32.50)	17 (39.53)
Sex, n (%)		
Men	33 (82.50)	35 (81.40)
Women	7 (17.50)	8 (18.60)
Disease stage, n (%)		
III	9 (22.50)	4 (9.30)
IV	31 (77.50)	39 (90.70)
ECOG PS, n (%)		
0	13 (32.50)	9 (20.93)
1	27 (67.50)	34 (79.07)
Histologic subtype, n (%)		
ADC	26 (65.00)	26 (60.47)
Non-ADC	14 (35.00)	17 (39.53)
Smoking history, n (%)		
Never smoker	10 (25.00)	12 (27.91)
Former smoker	24 (60.00)	23 (53.49)
Current smoker	6 (15.00)	8 (18.60)
History of prior therapy, n (%)		
platinum-based chemotherapy with ICIs	15 (37.50)	17 (39.53)
platinum-based chemotherapy	25 (62.50)	26 (60.47)
Brain metastasis, n (%)		
Yes	5 (12.50)	5 (11.63)
No	35 (87.50)	38 (88.37)

* Data Cut-off: Feb 24, 2022

Keywords: anlotinib, EGFR-negative NSCLC, second-line treatment

EP08.02-159 Post Hoc Analyses of Dacomitinib-Associated Skin Disorders and Efficacy in the ARCHER 1050 Study

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Introduction: In the phase 3 ARCHER 1050 study, patients treated with dacomitinib experienced skin disorders. A subsequent post hoc analysis of the dacomitinib arm showed that patients who had dose reductions due to adverse events had numerically longer survival than in the overall population. We investigated whether dacomitinib-associated skin disorders might associate with the efficacy of dacomitinib and prognosis in patients with *EGFR*-mutant non-small cell lung cancer (NSCLC).

Methods: In these post hoc analyses, progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) were assessed in subgroups of patients with/without any grade ≥2 skin disorders in the dacomitinib arm during the study. To evaluate the influence of grade ≥2 skin disorders on efficacy outcomes, landmark analyses with landmarks at 3 and 6 months were conducted.

Results: Improvements in PFS, OS, and ORR were observed in subgroup of patients with vs without grade ≥2 skin disorders (**Table 1; Figure 1**). Landmark analyses showed improvement in OS in patients with vs without grade ≥2 skin disorders (**Figure 2**).

Conclusions: Grade ≥2 dacomitinib-associated skin disorders may associate with a clinically valuable biomarker for the prediction of efficacy in patients with advanced NSCLC treated with dacomitinib. Further large-scale validation studies are warranted.

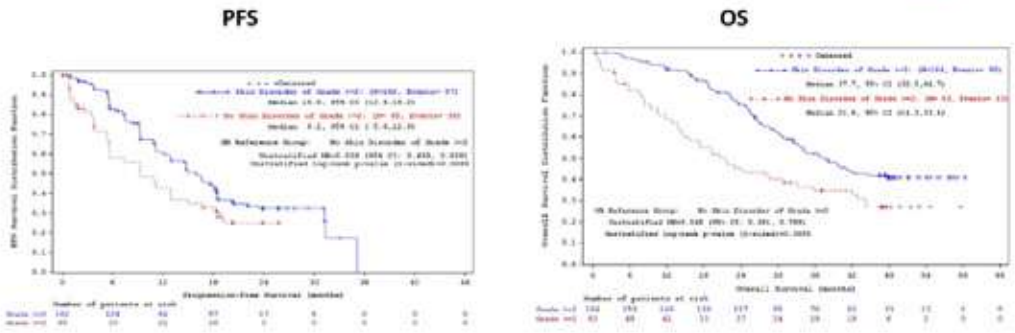
Table 1

Best overall response and objective response rate by independent review in subgroup of patients with/without grade ≥2 skin disorders in the safety population in the dacomitinib arm[a]

	Any grade ≥2 skin disorders (n=162)	No grade ≥2 skin disorders (n=65)
Best overall response, n (%)		
Complete response	11 (6.8)	1 (1.5)
Partial response	119 (73.5)	39 (60.0)
Stable disease/no response	21 (13.0)	9 (13.8)
Stable disease/no response and TTF ≥168 days	11 (6.8)	1 (1.5)
Stable disease/no response and TTF <168 days	10 (6.2)	8 (12.3)
Progressive disease	5 (3.1)	7 (10.8)
Indeterminate	6 (3.7)	9 (13.8)
Objective response rate (95% CI),[b] %	80.2 (73.3-86.1)	61.5 (48.6-73.3)

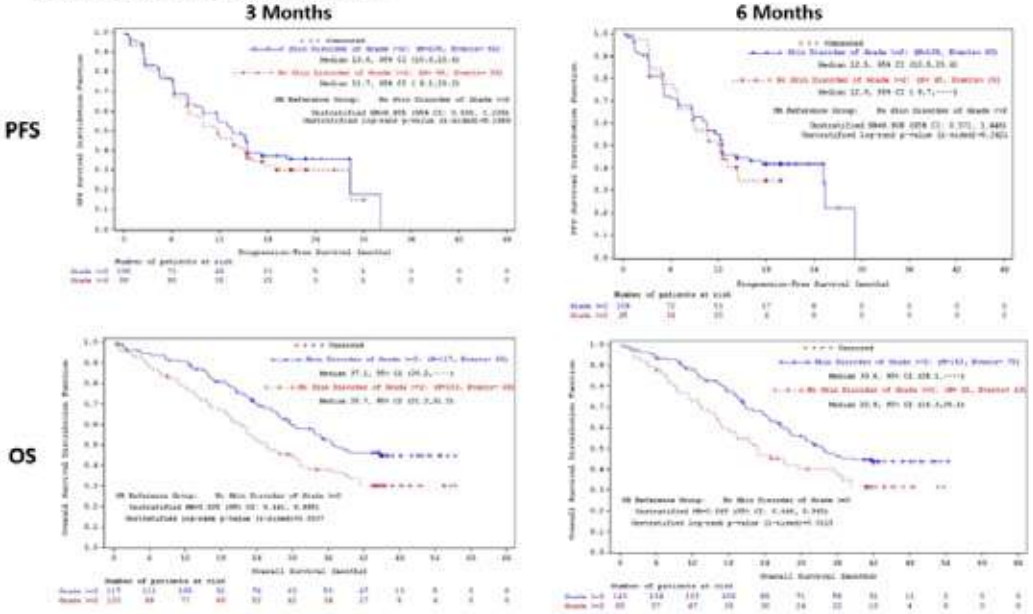
TTF, time to treatment failure. [a] Data cutoff was July 29, 2016 for response. [b] Using exact method based on binomial distribution.

Figure 1. PFS and OS in subgroup of patients with/without grade ≥2 skin disorders in the dacomitinib arm[a]



[a] Data cutoff was February 17, 2017 for OS and July 29, 2016 for PFS.

Figure 2. PFS and OS landmark analysis[a] for patients experiencing grade ≥2 skin disorders versus without grade ≥2 skin disorders in the dacomitinib arm[b]



[a] Landmark set at 3 and 6 months respectively. Patients with a PFS or OS time ≤ landmarks were excluded from the corresponding analysis. [b] Data cutoff was February 17, 2017 for OS and July 29, 2016 for PFS.

Keywords: non-small cell lung cancer, dacomitinib, skin disorders

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-160 A Pooled Efficacy and Safety Analysis of Anlotinib Plus Docetaxel in Advanced NSCLC Previously Treated with Immunotherapy

L. Wu[1], Y. Fang[2]

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Introduction: Immune checkpoint inhibitors (ICIs) are widely used in 1st -line or 2nd -line treatment of advanced NSCLC, but effective treatment after resistance to ICIs is still controversial. We previously reported that anlotinib plus docetaxel as 2nd-line treatment in advanced NSCLC showed better clinical efficacy than docetaxel alone in two phase II trials (ALTER-L016, ALTER-L018). Therefore, to further assess the efficacy and safety of anlotinib plus docetaxel in advanced NSCLC patients (pts) who had been pre-treated with ICIs by pooling raw data from the two phase II trials.

Methods: Efficacy and safety data from 2 multi-institutional, randomized, controlled comparative, phase II trials of 73 advanced NSCLC pts who had progressed after 1st-line platinum-based chemotherapy were pooled for this analysis. The studies shared similar dosing intervals and doses, pts were randomly allocated to receive anlotinib (10/12 mg QD from day 1 to 14 of a 21-day cycle) plus docetaxel (60/75 mg/m^2 Q3W) (group A+D) or docetaxel (60/75 mg/m^2 Q3W) only (group D). Safety assessments included adverse events (AEs), physical examination and clinical laboratory tests. [Clinical Trials Registration. NCT03726736 and NCT03624309.].

Results: At data cut-off (Mar 1, 2022), 73 pts. were available for efficacy and safety analysis (demographics are shown in Table 1). The median PFS was 7.60 months (95%CI: 4.44-10.76) vs 2.50 months (95%CI: 1.34-3.66) in group A+D and group D, respectively (HR: 0.28; 95%CI: 0.15-0.53, p<0.0001). The median OS has not been reached. For tumor response, the ORR was 34.88% vs 12.50% (p=0.048) and the DCR was 93.02% vs 62.50% (p=0.002) in group A+D and group D, respectively. The adverse events that possibly or definitely related to therapy occurred in 38 (88%) of pts. experienced total of 43 grade 1-2 adverse events in group A+D, and in 21 (70%) of pts. experienced total of 30 grade 1-2 adverse events in group D. The most common grade ≥3 TRAEs were neutropenia (5, 12%), leukopenia (2, 7%), and oral mucositis (1, 2%) in group A+D, and leukopenia (1, 3%), pneumonia (1, 3%) in group D.

Conclusions: Anlotinib plus docetaxel exhibited clinically meaningful efficacy and a manageable safety profile in advanced NSCLC pts who had been pre-treated with ICIs, which might be an especially effective option in this setting.

Table 1 Demographics

	Group A+D (anlotinib + docetaxel) (n=43)	Group D (docetaxel) (n=30)
Median age, years	62 (31-74)	60 (41-73)
Age group, years, n (%)		
< 60	18 (41.86)	14 (46.67)
≥ 60	25 (58.14)	16 (53.33)
Sex, n (%)		
Men	40 (93.02)	24 (80.00)
Women	3 (6.98)	6 (20.00)
Disease stage, n (%)		
III	5 (11.63)	2 (6.67)
IV	38 (88.37)	28 (93.33)
ECOG PS, n (%)		
0	13 (30.23)	9 (30.00)
1	30 (69.77)	21 (70.00)
Histologic subtype, n (%)		
ADC	20 (46.51)	13 (43.33)
Non-ADC	23 (53.49)	17 (56.67)
Smoking history, n (%)		
Never smoker	9 (20.93)	10 (33.33)
Current/ Former smoker	34 (79.07)	20 (66.67)
Brain metastasis, n (%)		
Yes	6 (13.95)	4 (13.33)
No	37 (86.05)	26 (86.67)

* Data Cut-off: Mar 1, 2022

Keywords: anlotinib, NSCLC, pre-treated with immunotherapy

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-161 An Exploratory Study on Biomarkers Related to Primary Resistance of EGFR-TKIs Therapy in Lung Cancer

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Introduction: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have significantly improved the prognosis of non-small cell lung cancer patients with EGFR mutation. However, 20-30% of patients show a poor response, suggesting a risk for primary or intrinsic resistance. Identifying these patients is an urgent need in clinical diagnosis and treatment.

Methods: Next generation sequencing of 825 genes and programmed cell death ligand 1 (PD-L1) expression test were performed in tumor tissues and peripheral blood samples of the enrolled patients. To explore the biomarkers of primary resistance to EGFR-TKIs, in this study, we compared the gene mutation spectrum in primary resistance group and sensitive group, combined with the difference analysis of signal pathway, PD-L1 expression, tumor mutation burden and other biomarkers.

Results: The median progression free survival (PFS) and overall survival (OS) of the primary resistance group were significantly shorter than those of the sensitive group. The biomarkers of primary resistance which has been reported previously included: primary T790M mutation, PIK3CA mutation, KRAS mutation, CDK6 mutation, PTEN deletion and MET amplification, other novel mutations potentially related to primary resistance were also found. The unique signal pathways only enriched in primary resistance group were PIK3CA/Akt/mTOR signal pathway, VEGF pathway, Apelin signaling pathway, AMPK signaling pathway and Wnt signaling pathway. The positive expression of PD-L1 in primary resistance group was higher than that in sensitive group, higher expression of PD-L1 was significantly associated with shorter OS and PFS.

Conclusions: 1. Some mutations affecting the function of tumor cells and the activation of special signaling pathways may be related to the primary resistance of EGFR-TKIs. 2. Expression of PD-L1 may be related to the primary resistance of EGFR-TKIs.

Keywords: Next generation sequencing, Epidermal growth factor receptor tyrosine kinase i, Primary resistance

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-162 Tepotinib with an EGFR-Tyrosine Kinase Inhibitor (TKI) in Patients with EGFR-mutant MET-amplified NSCLC: A Case Series

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Introduction: *MET* amplification (*MET*amp) is a mechanism of acquired resistance to EGFR-TKIs. In INSIGHT (NCT01982955; data cut-off: September 3, 2021), the combination of tepotinib (a potent, highly selective MET-TKI) and the EGFR-TKI gefitinib (n=12) improved outcomes compared with chemotherapy (n=7) in patients with *EGFR*-mutant *MET*amp NSCLC and EGFR-TKI resistance (progression-free survival hazard ratio [HR]=0.13, 90% confidence interval [CI]: 0.04, 0.43; overall survival HR=0.10, 90% CI: 0.02, 0.36). Tepotinib combined with an EGFR-TKI may therefore overcome MET-related EGFR-TKI resistance. Outside of clinical trials, patients have received this combination treatment through compassionate use requests; a series of these cases are presented here.

Methods: Early access to tepotinib has been provided through compassionate use. Cases include patients with NSCLC and acquired resistance to EGFR-TKIs due to *MET*amp who received tepotinib outside of a clinical trial (500 mg [450 mg active moiety] once daily; first dose before October 2021) plus an EGFR-TKI.

Results: Twelve cases of patients with *EGFR*-mutant *MET*amp NSCLC, who received tepotinib plus an EGFR-TKI, are presented (four patients received treatment in second-line, three in third-line, and five in fourth-or-later line; **Table**). Patients were aged 47-86 years, nine were female, two had smoking history, and all had adenocarcinoma histology. *MET*amp was detected by tissue biopsy in nine patients and by liquid biopsy in three patients. Of six patients with *MET*amp detected by FISH, *MET* gene copy number ranged from 5.5-33.4, and *MET:CEP7* ratio from 1.8-15.1. Ten patients received tepotinib plus osimertinib, one patient received tepotinib plus gefitinib (who also received this combination in the INSIGHT study), and one patient received both combinations sequentially. At the time of data collection, treatment was ongoing in seven patients. Eleven patients had clinical benefit per the treating physician's assessment, of whom eight were considered to have a partial response. Of 11 patients with adverse events considered related to tepotinib, six had edema. Two patients had Grade 3 adverse events; one patient had Grade 3 peripheral edema and dermatitis, and one patient had Grade 3 pneumonia and pneumonitis.

Table

Patient case	Sex	Age[a], yrs	Smoking history	Prior treatment(s)	EGFR TKI received w/ tepotinib	Time on treatment (tepotinib + EGFR-TKI), months	Treatment ongoing (tepotinib + EGFR-TKI)
1	Female	76	No	Osimertinib, Pemetrexed/carboplatin	Osimertinib	14	Yes
2	Female	62	No	Pemetrexed/carboplatin, Afatinib, Osimertinib, T-cell therapy	Osimertinib	13	No
3	Male	86	Yes	Gefitinib, Osimertinib	Osimertinib	9	Yes
4	Female	55	No	Erlotinib, Osimertinib, Carboplatin/paclitaxel/ atezolizumab/bevacizumab	Osimertinib	9	No
5	Female	69	No	Gefitinib, Carboplatin/pemetrexed, Docetaxel	Osimertinib	8	Yes
6	Female	47	No	Afatinib	Gefitinib	8[b]	Yes
7	Female	82	No	Afatinib, Osimertinib	Osimertinib	7	Yes
8	Female	76	No	Osimertinib	Osimertinib	6	Yes
9	Male	70	Yes	Gefitinib, Carboplatin/pemetrexed, Docetaxel, Osimertinib	Gefitinib, osimertinib (sequentially)	6[c]	No
10	Female	63	No	Osimertinib	Osimertinib	6	Yes
11	Female	50	No	Osimertinib	Osimertinib	2	No
12	Male	77	No	Pemetrexed/carboplatin (adjuvant), Erlotinib, Carboplatin/pemetrexed, Paclitaxel/carboplatin/ bevacizumab/atezolizumab	Osimertinib	1	No

[a]Age at the start of combination therapy (tepotinib plus EGFR-TKI) through compassionate use request; [b]Patient received tepotinib plus gefitinib in the INSIGHT study (NCT01982955) for a total of 56.5 months until study completion, and continued to receive tepotinib for an additional 8 months (ongoing) via compassionate use request following study completion; [c]Patient received tepotinib plus gefitinib for 5 months followed by tepotinib plus osimertinib for 1 month.

Conclusions: In this case series, the combination of tepotinib plus EGFR-TKIs showed promising clinical activity for patients with *MET*amp NSCLC who have progressed on previous EGFR-TKIs, including those with several lines of prior treatment. Tepotinib plus osimertinib is being investigated in INSIGHT 2 (NCT03940703) in patients with *MET*amp *EGFR*-mutant NSCLC with acquired resistance to first-line osimertinib.

Keywords: Tepotinib, EGFR, MET

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-163 Real-World Case Series on Efficacy and Safety of Amivantamab for EGFR-mutant Non-small Cell Lung Cancer

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Introduction: Amivantamab-vmjw is a newly approved bispecific EGFR/MET antibody for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR Exon 20 insertion mutations, after platinum-based chemotherapy. However, the benefit of Amivantamab for other EGFR-mutant NSCLC, as well as the safety of radiation therapy (RT) concurrent with Amivantamab, were less known.

Methods: We queried the MD Anderson Lung Cancer GEMINI Database for patients with EGFR-mutant NSCLC treated with Amivantamab from May 2021 to January 2022. The data analyzed included initial response, duration on treatment, and concurrent radiotherapy safety.

Results: Sixteen patients received Amivantamab (median age 62), 11 (69%) were women and 12 (75%) were never smokers. Six patients had EGFR Exon 20 insertion without T790M; 10 patients had other types of EGFR mutations, including classical mutations with and without T790M, atypical mutations, and amplification. In the Exon 20 group, 4 patients received poziotinib prior to starting Amivantamab, while 2 were tyrosine kinase inhibitor (TKI) naïve. In the other EGFR group, 9 received prior osimertinib and 1 poziotinib.

In the EGFR Exon 20 group, 3 patients (50%) showed clinical response (PR) and stable disease (SD), 3 had progression. In the other EGFR group (**Table 1**), 7 (70%) had clinical PR and SD, while 3 progressed. In total, 10 of 16 patients (62.5%) demonstrated an initial benefit clinically and in their imaging studies. One patient with osimertinib-resistant Ex19Del+T790M achieved a near complete response with Amivantamab+osimertinib and has been on treatment for over 200 days. At the time of cut off, 4 patients (all from the EGFR other group) are still on treatment.

Eight of 16 patients also received radiation therapy (RT) within 3 months before or after Amivantamab initiated. Of the 8, 5 patients had clinical benefit to Amivantamab (62.5%). Three patients received whole brain radiation therapy (WBRT), of which 2 patients received WBRT immediately prior to starting Amivantamab and 1 patient received WBRT concurrently while starting Amivantamab. One patient received RT to the lung immediately after stopping Amivantamab. No additional safety concerns were reported for these 8 cases.

Conclusions: Our data demonstrate that Amivantamab is a potentially effective treatment option for patients with other EGFR mutations outside of Exon 20 insertion mutations. Radiation therapy also seems to be safe immediately adjacent to Amivantamab.

Table 1: Other EGFR mutation NSCLC response to Amivantamab

Sex	Age (years)	EGFR mutations at Amivantamab starting	Last line of treatment	TKI received with Amivantamab	Time on treatment (days)	Clinical benefit
F	58	Exon 19 Deletion (L747_ P753delinsS); Exon 20 T790M	Gemictabine (Last TKI: Osimertinib)	Osimertinib	204	PR on-going
M	31	Exon 19 Complex (L747_ A755delinsSRD)	Osimertinib	Osimertinib	57	PD
F	78	Exon 21 L858R	Docetaxel (Last TKI: Osimertinib/ Capmatinib)	Osimertinib	56	SD
F	53	Exon 20 duplication (V769_ D770insE); Exon 20 T790M	Osimertinib	N/A	138	PD
M	70	Exon 19 deletion (E746_ A750del); Exon 20 T790M	Osimertinib	Osimertinib	142	PR
M	69	EGFR amplification; Exon 19 duplication (I740_ K745dupIPVAIK)	Carboplatin/Paclitaxel/ Atezolizumab/Bevacizumab (maintenance Atezo/Bev) (Last TKI: Poziotinib)	N/A	129	PR on-going
F	65	EGFR amplification; Exon 18 G724S; Exon 19 deletion (L747_ S752del)	Carboplatin/Pemetrexed/ Osimertinib	Osimertinib	71	PD
F	69	Exon 21 L858R	Osimertinib	Osimertinib	122	PR on-going
F	52	Exon 18 G719S; Exon 20 R776H	Osimertinib	Osimertinib	99	PR on-going
F	40	Exon 19 deletion (E746_ A750del); Exon 20 C797S	Osimertinib/Selpercatinib	Osimertinib	66	SD

Keywords: EGFR, Amivantamab

EP08.02-164 The Effect of Metformin on Survival Outcomes of Advanced EGFR-mutant NSCLC Patients Treated with EGFR TKIs in Thailand

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Introduction: EGFR tyrosine kinase inhibitor (TKI) is mainstay treatment of advanced mutant NSCLC. Mechanism of action of EGFR TKI is inhibitory effects on cell proliferation via through down regulation of AKT and MAPK signaling pathways. Metformin may have direct effect on cancer cells by the similar pathway. The synergistic effect of metformin and EGFR TKI on survival outcomes has been explored. This is the first study in Thailand aim to evaluate the progression free survival (PFS) and overall survival (OS) in advanced EGFR-mutant non-small cell lung cancer (NSCLC) patients with or without type 2 diabetes (T2DM) who were treated with EGFR TKI and metformin/ or other oral hypoglycemic agent, and EKFR TKI alone, respectively.

Methods: This study was retrospective, 177 advanced EGFR-mutant NSCLC patients with or without type 2 diabetes (T2DM) at Phramongkutklao hospital between January 2012 and December 2021 were reviewed. Kaplan-Meier methods were used to analyze the survival outcomes. Adverse events were analyzed by Chi-square test.

Results: All patients were classified into 3 groups. One hundred thirty-eight of 177 patients without T2DM were treated with EGFR TKI alone (group A), 34 of 177 patients with T2DM were treated with EGFR TKI and metformin (group B), and 5 of 177 patients with T2DM were treated with EGFR TKI and other oral hypoglycemic agents (group C). The mean PFS among group A, B and C were 11.48, 17.75 and 5.51 months, respectively, *p-value*=0.003 and mean OS in group A, B, and C were 17.75, 23.07 and 11.12 months, respectively, *p-value*=0.069. The 1-year PFS rate among group A, B and C were 35.51%, 52.94% and 0%, respectively, *p-value*=0.007 and the 1-year OS rate among group A, B and C were 60.07% 70.15% and 20%, respectively, *p-value*=0.053. The adverse events (AEs) were not statistically significant difference among 3 groups. However, one patient in group A developed drug reaction with eosinophilia and systemic symptoms (DRESS), and another one patient in group C had EGFR-TKI induced pneumonitis.

Conclusions: This study demonstrated that concomitant use of EGFR TKI and metformin was associated with increased OS, and PFS in patients with advanced EGFR-mutant NSCLC and T2DM. There were no additional concomitant medications-related adverse events. Further large-scale of clinical study should be investigated.

Keywords: advanced NSCLC, Metformin, EGFR TKIs

EP08.02-165 Small Cell Transformation After Lorlatinib ALK Resistance - A Case Report with Clonal Evolution

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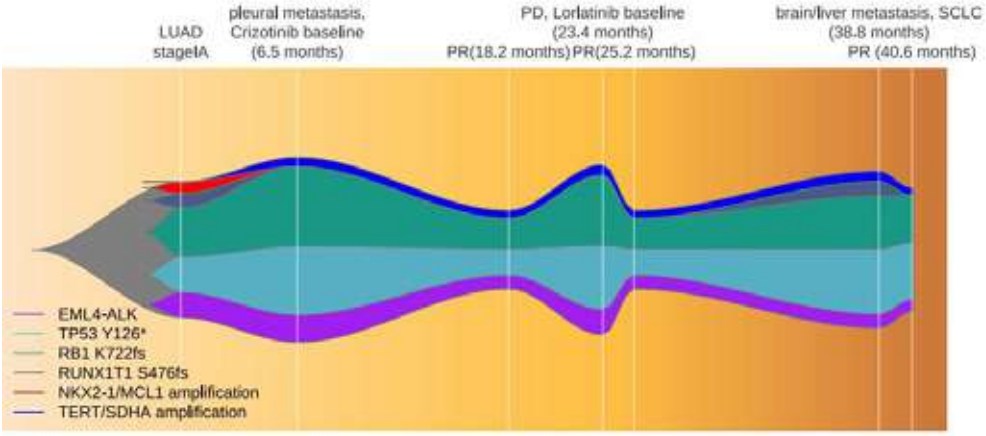
Introduction: Multiple different molecular mechanisms can cause resistance to third-generation ALK inhibitor lorlatinib, such as ALK point or compound mutations, ALK copy-number gains, the activation of bypass signaling through the activation of other oncogenes. Small Cell Transformation is reported as resistance mechanism for EGFR or ALK inhibitors. However, it has not been reported in patients who are resistant to loratinib.

Methods: The patient provided written informed consent to participate in the clinical trial. All biopsies and molecular testing were performed in accordance with protocols approved by the Ethics Committee at Zhejiang Cancer Hospital. ALK rearrangement was detected by VETENA immunohistochemistry. ALK resistance mutations were identified with the use of a targeted next-generation sequencing (NGS) assay.

Results: A 46-year-old non-smoker female receive radical resection of right lung cancer diagnosis as adenocarcinoma stage pT1N0M0 IA in 2017. In January 2018, multiple metastases to the right pleura were found due to the continuous and significant increase in CEA. Immunohistochemistry suggested ALK(D5F3)(+). Crizotinib was started in April 2018. Due to the progress of brain metastases, oral lorlatinib was enrolled in a clinical trial in September 2019. Progression-free survival was 13 months. In October 2020, liver metastasis was found by CT examination. Liver biopsy showed that small cell carcinoma was considered. Immunohistochemistry results: NapsinA(-), TTF-1(+), P40(-), P63(-), CK7 (focal +), Sy(+), CD56(+), CgA (focal weak +), Ki-67 (+, 90%). EC regimen (etoposide + carboplatin) was taken for chemotherapy. Subsequent treatment continued on the small cell regimen until death in October 2021.The best curative effect was partical response. Subsequent treatment continued according to small cell lung cancer until death in October 2021. NGS showed that the patient's lesions always had TP53 and RB gene abnormalities.

Conclusions: For the first time, we reported a patient who had metastatic anaplastic lymphoma kinase (ALK)-rearranged lung cancer, resistance to lorlatinib developed to small cell lung cancer. Patients with TP53 and RB1 gene abnormalities should be alert for the possibility of small cell transformation.



Keywords: Small Cell Transformation, Lorlatinib, ALK inhibitors

EP08.02-166 Brain Metastases in Patients with ALKrearranged or ROS1-fusion Non-small-Cell Lung Cancers in China

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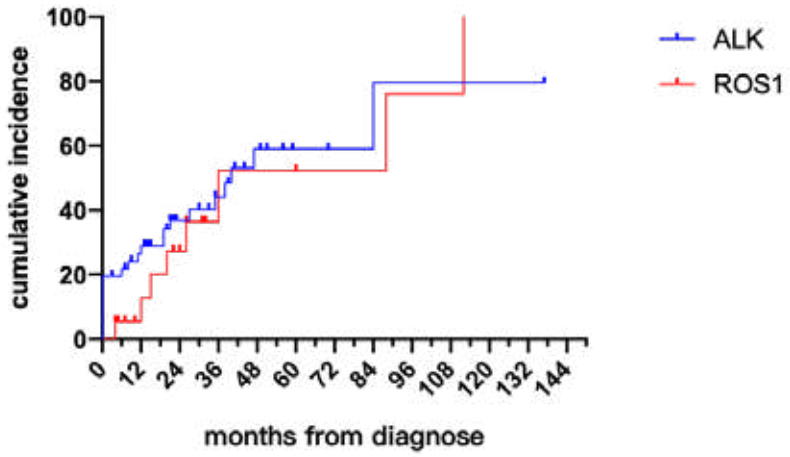
Introduction: Brain metastases (BM) are common in ALK rearranged or ROS1-fusion non-small-cell lung cancer (NSCLC) and are usually associated with a poor outcome, but the baseline incidence and evolution of BM over time in those NSCLCs are seldom reported. In this study, we evaluated the frequency of BM in patients with anaplastic lymphoma kinase (*ALK*)-rearranged or c-ros oncogene 1(*ROS1*)-fusion NSCLC.

Methods: The presence of BM, clinicopathologic data, and tumor genotype were retrospectively compiled and analyzed from a cohort of 64 patients.

Results: We identified 46 *ALK*-rearranged (89.1% with metastatic disease at first diagnosed; 100% received at least one ALK inhibitor) and 18 *ROS1*-fusion(88.9% with metastatic disease at first diagnosed; 100% received at least ALK inhibitor) NSCLCs. BM were present in 19.6% of *ALK*-rearranged and 11.1% of *ROS1*-fusion NSCLCs at the time of diagnosis of advanced disease. This study did not demonstrate a difference in the cumulative incidence of BM over time between the two cohorts (ALK/ROS1 cohort [95% CI 0.42-1.74], p=0.64). In still living patients with advanced *ALK*-rearranged NSCLC, 12.8% had BM at 1 year, 27.4% at 2 years, 44.2% at 3 years, and 59.0% at 5 years. In still living patients with advanced *ROS1*-fusion NSCLC, 13.8% had BM at 1 year, 27.4% at 2 years, and 52.3% at 3 years.

Conclusions: BM are frequent in advanced *ALK*-rearranged or *ROS1*-fusion NSCLCs, with an estimated about 50% of patients with CNS involvement by three years of survival with the use of targeted therapies.



Keywords: NSCLC, brain metastases, Alk

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-167 Diverse Effects of Radiotherapy for Osimertinib Acquired Resistance Non-small Cell Lung Cancer: Gene Matters

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Introduction: The role of osimertinib in the first-line treatment for metastatic non-small cell lung cancer (NSCLC) has been established by FLAURA study. Acquired resistance would inevitably occur even with initially well response. Most acquired resistance were limited progression or oligo progression. Radiotherapy played important role in the era of first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) (gefitinib, erlotinib), while the role of radiotherapy in the era of third-generation EGFR TKIs was unknown. In this study, we hypothesized different osimertinib acquired resistance subclone had different radiosensitivity. We established osimertinib acquired resistance cell lines and aimed to explore the value of radiotherapy in these subclones.

Methods: Osimertinib-resistance NSCLC cells (H1975 and PC-9) were established by stepwise exposure to increasing concentrations of osimertinib (termed as H1975-OR and PC-9-OR). Sub-clones were established from osimertinib-resistance NSCLC cells. Whole-exome sequencing were performed with osimertinib-resistance NSCLC cells with or without radiotherapy.

Results: The IC50 for osimertinib were 2.45 μM and 0.06 μM in H1975-OR and H1975 cells. It was 2.65 μM and 0.06 μM in PC-9-OR and PC-9 cells. There were 403 and 945 SNPs changes in PC-9-OR and H1975-OR cells after radiotherapy. There were 8321 and 8444 INDEL changes in PC-9-OR and H1975-OR cells after radiotherapy. When we cross-checked the SNPs between PC-9-OR and H1975-OR cells, a total of 25 SNPs were both changed in two cells. Colony-formation assay identified six subclones. The SER for PC-9-OR cell, the most radioresistant subclone (subclone I), the most radiosensitive subclone (subclone M) were 0.69, 0.26 and 1.43, respectively.

Conclusions: Osimertinib resistance has complex mechanism. Different osimertinib resistance mechanism had different radiosensitivity. This study showed SER of the most radiosensitive subclone and radioresistant varied from 0.69 to 1.43.

Keywords: osimertinib, radiosensitivity, acquired resistance

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-168 Efficacy, Safety and Treatment Courses for Patients with ALK Oncogene Positive NSCLC; Retrospective Data in Single Institute

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Introduction: Anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK-TKI) are recognized as the standard of care for advanced or recurrent patients with ALK fusion oncogene positive non-small cell lung cancer (NSCLC). Several world-wide clinical trials demonstrated that ALK-TKIs provide preferable outcome over cytotoxic chemotherapy. Recently, safety and efficacy of ALK-TKIs for patients with brain metastasis have proved. We intended to show real-world data of treatment courses about patients with ALK-positive NSCLC.

Methods: We retrospectively analyzed the treatment processes of advanced or recurrent 26 patients with ALK-positive NSCLC who started first-line treatment after January 2012 at our institute. All of them have been treated by at least one regimen of ALK-TKI.Among 26 patients, 13 of them were female. Twenty-five had adenocarcinoma, and one had large cell carcinoma histology. Median age at first-line treatment was 53 years old (range, 34 - 85). Three patients had stage III, 14 had stage IV, and 5 were post-operation recurrence. As for first-line treatment, 5 patients received systemic chemotherapy, 2 patients with stage 3 were treated by chemo-radiotherapy, and 19 received AKI-TKI. Most of them (85%) had ECOG performance status of 0 or 1.

Results: At March 1, 2022, 22 patients are alive and 4 died of disease progression. Median period of observation was 1215 days, and median overall survival days was not reached (range, 1868 - not assessed). Nineteen patients started ALK-TKI for first-line treatment (crizotinib for one patient, and alectinib for 18), and 10 of them have been taking alectinib at the time of abstract submission. Response rate for first-line treatment by ALK-TKI was 100%, and median time to treatment failure was 1174 days (709 - not assessed). Cumulative number of ALK-TKI treatments was 53. Severe adverse events of grade 3 or 4 hyperlipidemia were observed in 2 patients who received lorlatinib. However, toxicity was managed by reducing the dose of lorlatinib intake and then continued treatment. Ten patients had brain metastasis at initial diagnosis, and four and one patient developed brain metastasis and meningeal carcinomatosis respectively later during their treatment courses. In most cases with brain metastasis, brain metastasis lesions were controlled by ALK-TKIs (The cumulative response rate of brain metastasis was 73%).In first-line treatment with ALK-TKI, there was no difference in time to treatment failure between patients with initial brain metastasis and those without it (1476 days [95% CI 1014 - NA] vs 1040 days [460 - NA], respectively; p=0.397). In patients who were treated with ALK-TKI for 1st-line, initial existence of brain metastasis did not affect median overall survival, neither (NA [1472 - NA] vs NA [1868 - NA], respectively; p=0.947).

Conclusions: Brain metastasis at diagnosis is usually associated with poor prognosis among patients with NSCLC. Patients with brain metastasis are likely to take the treatment measure of ALK-TKIs sequence. ALK-TKIs provide promising treatment outcome for patients with brain metastasis.

Keywords: ALK-TKI, brain metastasis, real-world data

EP08.02-169 Research of Aumolertinib Combined with Bevacizumab for Advanced NSCLC Lung Cancer with EGFR Sensitive Mutation

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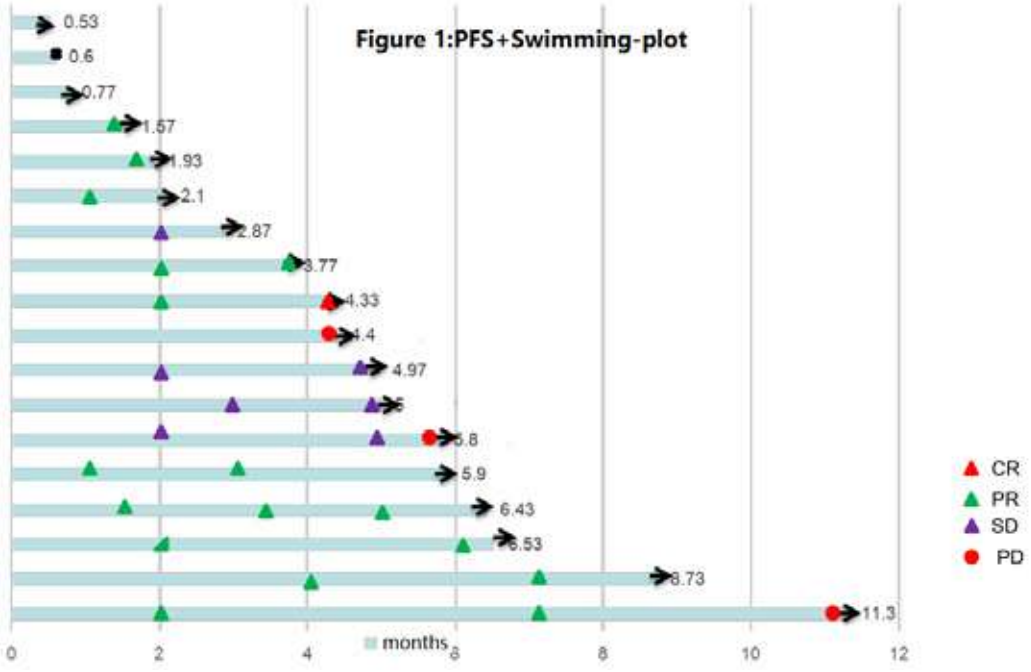
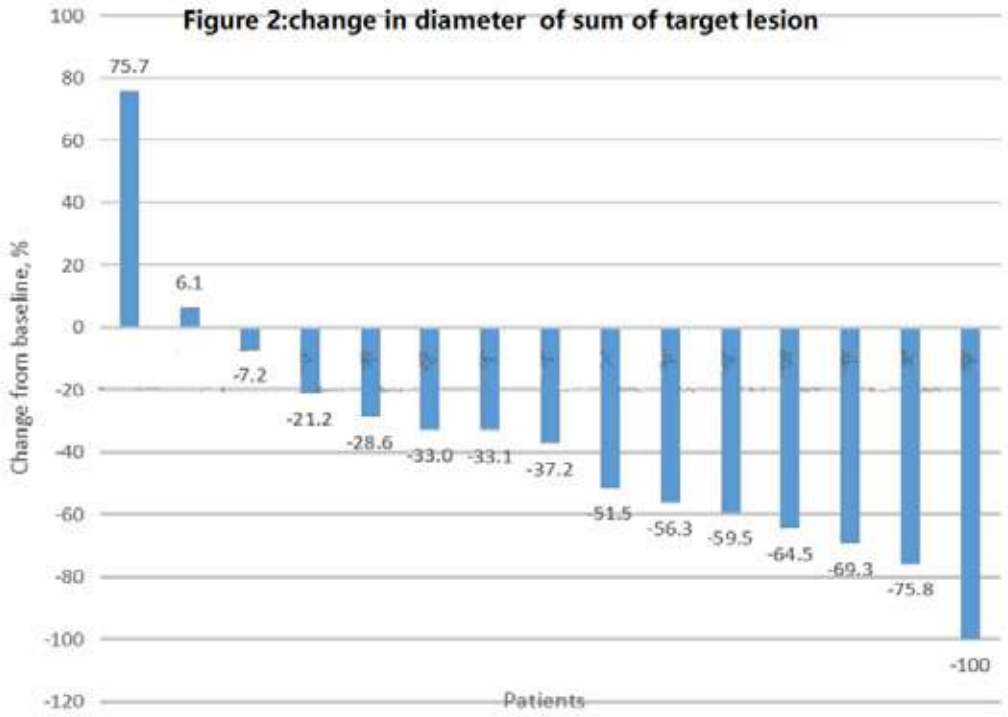
Introduction: Aumolertinib (formerly almonertinib; HS-10296) is a novel third-generation EGFR-TKI with proved efficiency and safety for untreated NSCLC patients with EGFR sensitizing mutations in China. The efficacy of the combination of first-generation EGFR-TKI and bevacizumab was confirmed by NEJ026, JO25567 ARTEMIS studies, but the effect of 3rd generation TKI plus bevacizumab is still under debate. This study was conducted to evaluate aumolertinib plus bevacizumab for untreated NS-NSCLC patients with EGFR sensitizing mutations.

Methods: The study was expected to enroll 36 eligible patients who would receive oral aumolertinib (110 mg QD) plus intravenous bevacizumab (15 mg/kg Q3W) in first-line treatment and been stratified according to sex, smoking history, stage, EGFR mutation status and brain metastasis (BMs). The primary endpoint was PFS% at 12 months. the secondary endpoints were objective response rate (ORR), overall survival (OS) and progress free survival (PFS).

Results: Form Sep 16, 2020 to Sep 16, 2021, 19 patients were enrolled, and at a median follow-up 9.3 months (0.5m-11.3m) (Figure 1), 15 patients were evaluated. Their ORR was 66.7% (10/15), with an average reduction of the target lesions of 37.0%(Figure 2). CNS metastases ORR was 80.0% (8/10), and for those with measureable intracranial lesions, intracranial ORR was 87.5% (7/8), the average reduction of the intracranial target lesions was 48.8%. the most common AEs were creatine phosphokinase increased(27.8%), proteinuria(22.2%), AST/ALT increased(22.2%) and weak(16.7%). 3 patients had grade 3 AEs and one patient stopped bevacizumab due to chest pain(5.6%).





Conclusions: Aumolertinib plus bevacizumab exhibited superior activity for advanced EGFR-mutated NS-NSCLC, especially for patients with BMs. This trial is currently ongoing and may provide a new and effective therapy strategy.

Keywords: NSCLC, Aumolertinib, Bevacizumab

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-171 PRO-CTCAE Analysis of Mobocertinib in EGFR Exon 20 Insertion-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Mobocertinib is an oral tyrosine kinase inhibitor selectively targeting epidermal growth factor receptor gene (*EGFR)* exon 20 insertion-positive *(*ex20ins+) NSCLC. In the EXCLAIM extension of a Phase 1/2 study in patients with *EGFR* ex20ins+ metastatic NSCLC, mobocertinib demonstrated a favorable objective response rate with manageable toxicity; diarrhea was the most common adverse event (AE). We present patient-reported symptomatic AE data from EXCLAIM.

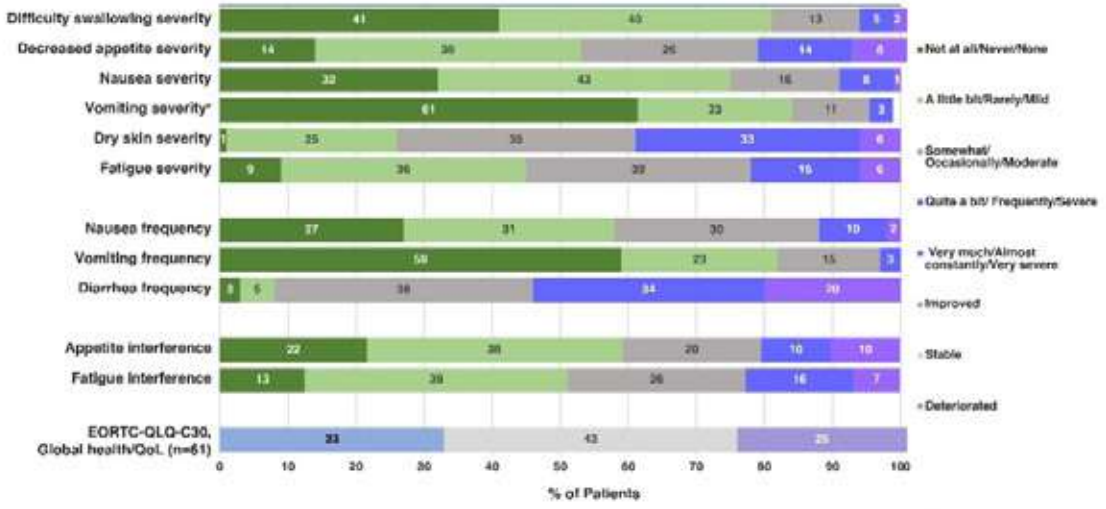
Methods: EXCLAIM (NCT02716116) evaluated mobocertinib 160 mg once daily in previously treated patients with *EGFR* ex20ins+ metastatic NSCLC. Symptomatic AEs from Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) were assessed by frequency, severity, and/or interference with daily activities. Evaluated symptomatic AEs included decreased appetite, difficulty swallowing, nausea, vomiting, diarrhea, fatigue, and dry skin. PRO-CTCAE and additional PRO instruments including EORTC-QLQ-C30 were administered at baseline, each 28-day cycle, and 30 days after last dose.

Results: Ninety of the 96 patients enrolled in EXCLAIM met PRO analysis criteria (baseline and ≥1 post-baseline measurement with compliance rate >90%). Median time on study was 12.5 months. Through Cycle 6, most patients reported none or mild as their worst category for the symptomatic AEs evaluated except diarrhea, dry skin, and fatigue (**Figure**). Severity and/or interference improved or remained stable compared with baseline for most patients at Cycles 2 and 6 for all items evaluated except diarrhea and dry skin (76% and 80% worsening at Cycle 2, respectively; 82% and 72% at Cycle 6). Severity categories for diarrhea, fatigue, vomiting, and dry skin (baseline and Cycles 2 and 6) are summarized (**Table**). EORTC-QLQ-C30 global health scores were maintained or improved in >75% of patients through Cycle 6.

Conclusions: Most patients receiving mobocertinib reported stable or improved symptomatic AEs compared with baseline, except for diarrhea and dry skin. Health-related quality of life was maintained or improved in most patients during treatment.

Table. Severity of Selected Patient-Reported Symptomatic AEs at Baseline, Cycle 2, and Cycle 6				
	% of Patients			
AE Severity	**Baseline**	**Cycle 2**	**Baseline**	**Cycle 6**
Diarrhea	n=76	n=76	n=54	n=54
None	75	16	72	11
Mild	18	18	20	30
Moderate	5	39	4	37
Severe	1	22	2	22
Very Severe	0	4	2	0
Fatigue	n=75	n=76	n=53	n=53
None	25	16	28	24
Mild	43	54	43	52
Moderate	19	18	15	19
Severe	12	8	13	6
Very Severe	1	4	0	0
Vomiting	n=71	n=72	n=52	n=53
None	85	75	87	85
Mild	10	19	8	13
Moderate	1	3	4	2
Severe	3	3	2	0
Very Severe	1	0	0	0
Dry Skin	n=75	n=76	n=53	n=54
None	68	8	70	20
Mild	24	45	26	39
Moderate	5	32	2	30
Severe	3	14	2	11
Very Severe	0	1	0	0
Note: Data are presented as a percentage of patients. Patients who have data at both baseline and respective cycles are listed.				
AE, adverse event.				

Figure. Frequency of Worst Reported Symptomatic AEs Through Cycle 6 (n=88 unless otherwise noted)



AE, adverse event; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life questionnaire; QoL, quality of life.
*One patient did not answer.

Keywords: non-small cell lung cancer, exon20 insertion, patient-reported outcomes

EP08.02-172 Effect of EGFR Inhibition on Bone Health in NSCLC Patients without Skeletal Metastasis

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Introduction: The Epidermal Growth Factor Receptor (EGFR) signaling has known effects in bone homeostasis by modulating proliferation and differentiation of osteoblasts, osteoclasts and bone marrow osteoprogenitor cells. Studies in EGFR-deficient mice or in mice treated with EGFR-inhibitors, showed impaired bone formation. Patients affected by metastatic non-small cell lung cancer (NSCLC) with sensitizing mutations of the EGFR gene (mEGFR) are treated with EGFR-specific tyrosine kinase inhibitors (EGFR-TKIs), obtaining long-term disease control and improvement of quality of life (QOL). However, to which extent long term-inhibition of EGFR signaling can ultimately alter bone health is unknown. A survey from our group has shown a 28% frequency of skeletal-related events (SREs) in NSCLC patients with bone metastases treated with EGFR-TKIs. The aim of this study was to investigate the prevalence of morphometric vertebral fractures in advanced NSCLC patients treated with EGFR-TKIs.

Methods: This was a retrospective study conducted at two oncological institutions (Spedali Civili, Brescia and S. Gerardo Hospital, Monza) in Italy. Patients with metastatic mEGFR NSCLC treated with first, second or third generation EGFR-TKIs were eligible for the study. We excluded patients with bone metastases, severe osteoporosis or in treatment with anti-resorptive bone medications. Vertebral fractures assessment was performed by the Genant's semi-quantitative morphometric analysis of vertebral bodies (T4-L4). Height reduction of vertebral bodies was evaluated by CT scans and graded as follows: mild (0-25% height reduction and 10-20% area reduction), moderate (25-40% and 20-40% reduction, respectively) or severe (40% or more reduction in both height and area).

Results: From January 2010 to June 2020, 82 patients were enrolled. Median age was 70 years and 57% of patients were female. After a median follow-up of 38 months, median survival was 25 months (range 6-145) with a median duration of treatment of 15 months (range 1-95). Overall, 11 (13.4%) patients experienced vertebral fractures (Table 1). Most (11%) of vertebral fractures were mild, two (2.4%) were moderate and none were of severe degree. We observed a positive correlation between morphometric fractures and corticosteroid therapy (p 0.03). Morphometric fractures had not significant impact on overall survival (p=0.267).

Conclusions: This real-world study of bone health in advanced mEGFR NSCLC shows that:

• patients treated with EGFR-TKIs have a low incidence of SREs;

• lower rates of fractures were observed in NSCLC patient compared with healthy caucasian individuals;

• different generation EGFR-TKIs were equally safe in terms of SREs.

Vertebral fractures				
Grade	**N (%)**	**corticosteroids**	**TKIs**	**OS**
mild	9 (13.4%)	p=0.03	p=0.692	p=0.267
moderate	2 (2.4%)			
severe	0 (0%)			

Keywords: vertebral fractures, EGFR-tyrosine kinase inhibitors, metastatic NSCLC

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-173 Treatment Patterns and Outcomes Among Patients with EGFR-mutant Advanced NSCLC in the Frontline and Post-Osimertinib Settings

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Introduction: Osimertinib is recommended frontline therapy for patients with EGFR-positive advanced non-small cell lung cancer (NSCLC). This study characterizes real-world treatment patterns and outcomes in frontline and post-osimertinib settings.

Methods: Data from the ConcertAI Patient360 NSCLC database (electronic medical records from >100 US oncology practices) were curated by nurse practitioners to determine date of metastatic diagnosis, tumor progression, treatment patterns, survival outcomes, etc. Included patients (≥18 y) had confirmed diagnosis of advanced/metastatic NSCLC ≤30 days after frontline therapy initiation and genetic testing confirming common *EGFR* mutation (exon 19 deletions, L858R); patients on osimertinib began treatment 8/2015-7/2020. Treatment patterns and outcomes in the advanced/metastatic disease setting were assessed in three cohorts: 1) patients receiving any frontline therapy regardless of osimertinib use (assessed from start of frontline therapy for advanced disease); 2) patients whose disease progressed on osimertinib monotherapy and who started a subsequent line of therapy (LOT) (assessed from start of LOT following osimertinib); and 3) patients whose disease progressed after osimertinib, progressed after platinum chemotherapy, and who started a subsequent LOT (assessed from start of LOT following the platinum-containing therapy that immediately followed osimertinib).

Results: In cohort 1, frontline therapy (n=979) comprised osimertinib alone or in combination in 40% of patients and other tyrosine kinase inhibitor (TKI) regimens in 52%. In cohort 2 (n=167), 44% received platinum-chemotherapy and 20% osimertinib retreatment as combination therapy. In cohort 3 (n=38), 47% went on to receive non-platinum-based chemotherapy or immuno-oncology monotherapy, and 32% were re-exposed to osimertinib, either as monotherapy (5%) or in combination therapy (26%). Outcomes are shown in the **Table**. Patients in cohort 2 were further examined by LOT in which osimertinib was used. For those who progressed on frontline osimertinib (n=53), median progression free survival (mPFS) and overall survival (mOS) were 4.3 and 10.4 months from the start of post-osimertinib LOT; 55% received a platinum-based combination in the LOT following osimertinib progression. For cohort 2 patients who progressed on 2nd- or later-line osimertinib (n=114), mPFS and mOS were 3.2 and 10.1 months from the start of post-osimertinib LOT; 28% of patients received TKI combination therapy and 39% received a platinum-based combination in the LOT following osimertinib progression.

Conclusions: A variety of treatments are used after osimertinib including osimertinib retreatment; outcomes demonstrate reduced duration of treatment and survival after each additional LOT, correlated with disease progression. There is an urgent need for newer, more effective therapeutics after osimertinib treatment.

Table

Median outcome, months	Cohort 1: All frontline (n=979)	Cohort 1: 1st/2nd generation TKI monotherapy (n=407)	Cohort 1: Osimertinib monotherapy (n=256)	Cohort 1: Other (n=316)	Cohort 2: Post-osimertinib (n=167)	Cohort 3: Post-osimertinib then platinum (n=38)	Endpoint definition
Progression-free survival	11.2	9.3	15.9	13.0	3.4	1.8	Time from cohort index date until progression event or death due to any cause
Overall survival	35.2	37.5	26.6	37.0	10.1	7.4	Time from cohort index date until date of death due to any cause
Time to treatment discontinuation	12.3	12.5	11.5	12.0	3.2	2.3	Time from cohort index date until end date of that LOT or death, whichever comes first
Time to next treatment	16.8	14.9	21.7	17.9	5.0	3.7	Time from cohort index date until start of subsequent LOT or death, whichever comes first

Keywords: Real-world evidence, EGFR-mutant

EP08.02 METASTATIC NON-SMALL CELL LUNG CANCER - MOLECULAR TARGETED TREATMENTS

EP08.02-174 RET Fusions as Primary Oncogenic Drivers and Secondary Acquired Resistance to EGFR TKI in a Large Cohort of Non-Small-Cell Lung Cancers

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Introduction: *RET* fusions occur in 1-2% of non-small-cell lung cancers (NSCLCs), which are associated with unique clinical features and poor prognosis and may contribute to resistance to EGFR-TKIs. Despite the development of highly potent RET inhibitors, the genetic architecture of primary and secondary *RET* fusions in NSCLCs remains to be systematically elucidated.

Methods: Mutational profiles of a total of 456 *RET* fusion-positive NSCLC patients, whose tissue specimen and/or circulating cell-free DNA (cfDNA) samples were subjected to targeted next-generation sequencing between June 2015 and June 2020, were retrospectively reviewed. Clinical characteristics and treatment history were extracted from medical records.

Results: The study cohort included 381 EGFR TKI-naïve cases (primary *RET* fusions; median age 56 years, 55.4% females) and 75 cases at resistance to EGFR TKIs (secondary *RET* fusions; median age 56 years, 64.0% females). The most common fusion partners were *KIF5B* (58.6%) and *CCDC6* (19.1%) in primary *RET* fusions. By contrast, secondary *RET* fusions were characterized by an enrichment of *CCDC6-RET* (49.3%) and *NCOA4-RET* (16.0%) and a decrease in the proportion of *KIF5B-RET* fusions (8.0%). Structural variant of unknown significance (SVUS), which included those with novel fusions partners, such as *FXYD4*, *VSTM4*, *RABEP1* and *RIC1*, as well as partners mapped to intergenic regions, accounted for 7.3% (28/381) and 14.7% (11/75) of primary and secondary *RET* fusions, respectively. In primary *RET* fusion cohort, top frequently altered genes included *TP53*, *MDM2*, *ATM*, *RB1*, and *CDKN2A/B*. Interestingly, *SMAD4* (5.3% vs. 0.0%, P=0.044*)* mutations and *MYC* (6.9% vs.0.0%, P=0.009) amplification were more frequently found in patients with *KIF5B-RET* fusions compared with those harboring *CCDC6-RET* fusions, whereas *CDKN2A* mutations were associated with *CCDC6-RET* fusions (2.4% vs. 11.3%, P=0.003). In addition, concomitant oncogenic *EGFR* alterations were identified in 2.8% (11/381) of primary *RET* fusion cohort, including 19del (45.4%, 5/11), L858R (18.2%, 2/11) and other rare mutations (36.4%, 4/11). On the other hand, in patients with secondary *RET* fusions, *EGFR* mutations were mainly 19del (66.7%, 50/75), followed by L858R (30.7%, 23/75) and rare mutations (2.6%, 2/75). Acquisition of *RET* fusions were detected in 13 cases treated with first- and second-generation TKIs and 8 cases with third-generation TKIs in the first-line setting. Fifty-one *RET* fusions were identified as resistance mechanisms to third-generation EGFR TKIs as second-line therapy and dynamic monitoring in a subset of cases further suggested that acquisition of *RET* fusions was more likely to occur at resistance to third-generation, rather than first-/second-generation EGFR TKIs. Finally, while no significant difference was observed in the second-line PFS of osimertinib among different fusion partners (*CCDC6* mPFS=8.3m; *KIF5B* mPFS=13.8m; *NCOA4* mPFS=7.3m, P=0.770), differences in their genetic background might result in variable response to RET TKIs.

Conclusions: Our study systematically evaluated the genetic landscape underlying *RET* fusions as a rare driver gene and provide important insights into secondary resistance to EGFR TKIs in Chinese NSCLCs, which will be important considerations in improving the efficacy and clinical outcome of existing RET inhibitors and facilitating the development of new therapeutics.

Keywords: RET fusions, NSCLC, resistance mechanisms to EGFR TKIs

EP08.03 METASTATIC NON-SMALL CELL LUNG CANCER - OLIGOMETASTATIC DISEASE

EP08.03-001 A Clinical Study on the Safety and Efficacy of Aumolertinib Combined with SBRT in the EGFR-mutant NSCLC with Brain Parenchymal Oligometastases

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Introduction: Oligometastases have changed our understanding of stage IV NSCLC and created conditions for local treatments such as surgery and stereotactic radiotherapy. The study showed that local therapy combined with EGFR-TKIs had good PFS in patients with EGFR-mutated advanced non-small cell lung cancer with CNS progression or isolated progression outside the CNS. Aumolertinib (formerly almonertinib; HS-10296) is a novel 3rd generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI). The preclinical evidence in nonhuman primates shows that aumolertinib has high penetration of the blood-brain barrier and brain exposure compared with other EGFR-TKI and radiation therapy can increase blood brain barrier permeability. Aumolertinib combined with SBRT may show a better clinical benefit and less cerebral injury.

Methods: This study is a prospective, monocentric, single-arm clinical trial that is expected to recruit 50 patients with EGFRm+ advanced non-small cell lung cancer (NSCLC) who have parenchymal brain metastasis (less 5). The patients treat with aumolertinib (110mg po. qd.) and brain oligometastasis treat with SBRT. The lesions are evaluated by CT or MR after radiotherapy 3 months according to RECIST criteria. The primary endpoint is objective response rate, the second endpoint is progression-free survival and overall survival.

Results: The study is ongoing and the Clinical trial website registration number is ChiCTR2100043666.

Conclusions: The study is ongoing and the Clinical trial website registration number is ChiCTR2100043666.

Keywords: Aumolertinib, SBRT, oligometastases

EP08.03 METASTATIC NON-SMALL CELL LUNG CANCER - OLIGOMETASTATIC DISEASE

EP08.03-002 Local Ablative Therapy in Oligoprogressive NSCLC - Results from a Tertiary Cancer Center of India

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Introduction: Approximately half of the NSCLC patients on targeted therapy or after curative treatment of localized disease experience oligoprogression (OP). Local ablative therapy (LAT) of OP sites can eradicate the resistant clones at and restore the overall sensitivity of systemic therapy. LAT can either delay the initiation of systemic therapy or allow to continue usage of same systemic therapy especially tyrosine kinase inhibitors (TKI) and immunotherapy. In this retrospective study, we evaluated the outcomes of LAT for NSCLC patients with OP disease.

Methods: Consecutive 68 NSCLC patients with 84 OP lesions treated at our institute from 2018 - 2020 were identified. OP was defined as radiological progression in ≤ 3 intracranial or extracranial lesions. Patients with leptomeningeal disease, new-onset pleural effusion, or undergoing reirradiation to OP sites were excluded. Continuing or changing systemic therapy was decided by the treating medical oncologists. Local control of OP sites was defined as absence of radiological progression. The progression-free survival-1 (PFS-1) was calculated from the initial treatment to the date of progression and PFS-2 from the date of OP to any subsequent progression or death whichever is earlier. Overall survival (OS) was calculated from diagnosis date to death date and OS-LAT was calculated from OP date to death date. The Kaplan-Meier method was used to calculate the survival outcomes.

Results: The median age was 52 years and majority had adenocarcinoma (n=60). 14 had oligometastatic disease at presentation. The initial treatment was curative in 25 and palliative in 43 patients. Driver mutation was detected in 46 patients (EGFR-32 and ALK-14). 57 patients had 1 site of OP, 6 had two, and 5 had three sites of OP. The 3 most common sites of OP were brain (44%), lung (25%) and bone (11%). The median PFS-1 was 13.4 months (range:1-104.3). Ten patients (16 sites) did not receive any LAT (No-LAT cohort) whereas 58 patients (68 sites) received LAT (LAT cohort) with stereotactic radiotherapy (RT) (n=35) or hypofractionated RT(n=33). Systemic therapy was not changed in 42 patients (LAT-38, No LAT-4). 2nd progression was experienced by 31/68 (46%) patients where 10/68 (15%) had progression at OP sites (7-LAT, 3-No LAT). After a median follow up of 13.8 months (95% CI, 5.0 - 22.6) since the development of OP, the local control of treated OP sites was 88%. The estimated median PFS-2 in LAT and No-LAT cohort were 18.9 months (95% CI, 9.4 - 28.3) and 8.7 months (95% CI, 1.1-16.4), respectively (p=0.2). The median total OS in the LAT and No-LAT cohort was 50.6 months (95% CI, 9.4-28.3) and 36.5 months (95% CI, 16.3-56.6), respectively (p=0.02) and OS after OP was 22.1 months (95% CI, 9.4-28.3) and & 12.3 months (95% CI, 3.7-20.9), respectively (p=0.03).

Conclusions: LAT after oligoprogression provides excellent local control and durable progression-free survival in NSCLC. LAT can allow continuing the ongoing effective systemic therapy in carefully selected patients. Our ongoing prospective study (OligoChrome) will help to validate these findings and better selection of patients who can derive maximum benefit from LAT.

Keywords: Oligoprogression, Local Ablative therapy, Stereotactic radiotherapy

EP08.03 METASTATIC NON-SMALL CELL LUNG CANCER - OLIGOMETASTATIC DISEASE

EP08.03-003 Surgery for Primary Tumor is Associated with Prolonged Overall Survival in Patients with Oligometastatic NSCLC

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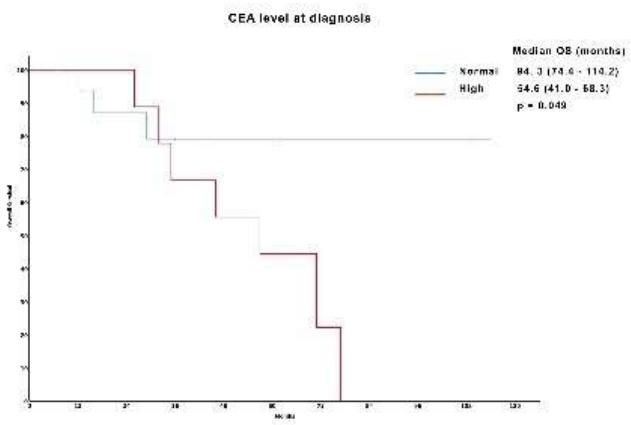
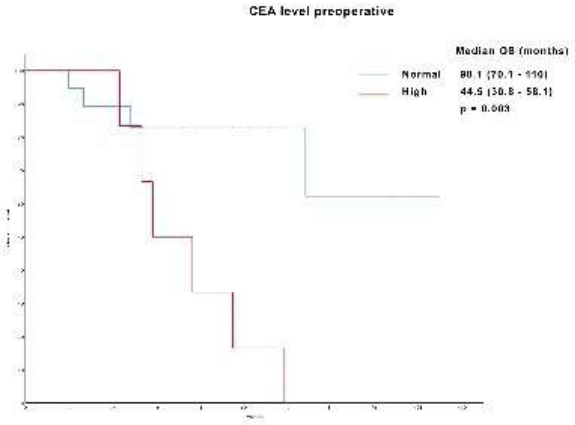
Introduction: Multidisciplinary treatment of oligometastatic NSCLC, including local consolidative therapies (LCT), has been associated with improved survival. We analyze the role and outcomes of pulmonary resection in this scenario as well as the possible role of CEA level as a predictive factor of survival.

Methods: Observational, single institution cohort of patients with synchronous oligometastatic NSCLC (up to five metastatic lesions) who received multi-modal treatment including surgery for primary lung tumor between January 2010 to December 2020. Primary endpoint was overall survival (OS) analyzed by Kaplan-Meier method. Secondary endpoints were morbidity and mortality of pulmonary resection.

Results: We identified 27 patients. There were 17 female (63.0%). Mean age 54.96 years. Most frequent histology was adenocarcinoma in 23 (85.2%). At diagnosis carcinoembryonic antigen (CEA) was elevated in 10 (37.0%). Mutation driver was present in 12 (44.4%). All patients received up-front systemic therapy. Most common site of metastases were central nervous system (CNS) in 9 (33.3%), contralateral lung nodules in 7 (25.9%) and pleura in 4 (14.8%). Most common local consolidative therapy (LCT) for metastases was radiotherapy in 14 (51.9%). For pulmonary resection 23 patients underwent thoracotomy (85.2%) and 4 (14.8%) VATS. Lobectomy was performed in 21 (77.8%), pneumonectomy in 4 (14.8%) and sub-lobar resection in 2 (7.4%). Morbidity was 33.3% and mortality 3.7%. A complete resection was achieved in 23 (85.2%). CT-PET was considered negative after LCT in 14 (51.9%) and CEA levels persisted elevated in only 3 (11.1%). Median follow-up was 47.1 months (1-113). Median overall survival was 77.0 months (53.2-100.7). On univariate analysis, factors associated with a better survival were normal CEA at diagnosis (94.3 vs 54.6 months, p = 0.049) and preoperative normal CEA (90.1 vs 44.5 months, p = 0.003).

Conclusions: Surgery for primary NSCLC remains a key component on multi-modal treatment for oligometastatic disease. In our cohort, this approach is associated with an encouraging prolonged survival and low morbidity and mortality. CEA level could be considered as an important predictive factor for overall survival and patient selection that requires further research.





Keywords: oligometastatic, pulmonary resection, metastasectomy

EP08.03-004 Outcomes of Oligometastatic Non-Small Cell Lung Cancer Patients Undergoing Surgical Resection: A Single Center Experience

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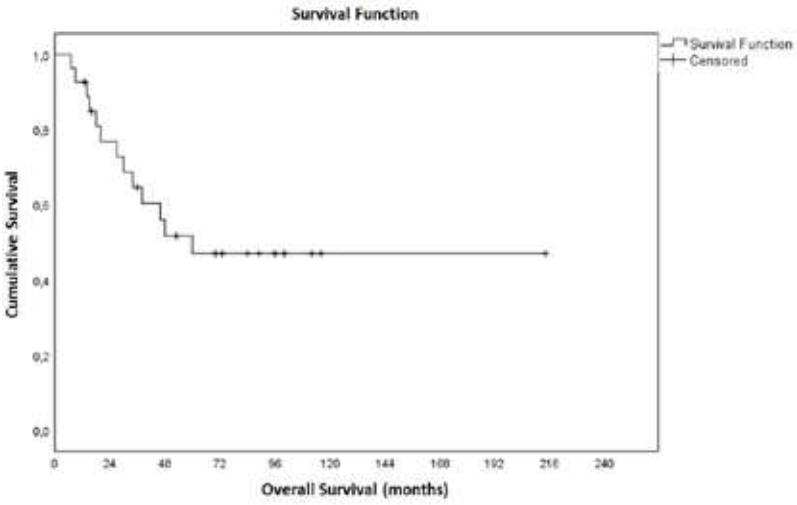
Ankara University Faculty of Medicine, Ankara/TR

Introduction: Although the survival rate is low in metastatic lung cancer, better survival is achieved with local ablative treatment of the primary tumor and its metastasis in selected oligometastatic patients. The aim of this study is to present the results of the cases that underwent surgical treatment for oligometastatic stage IVA non-small cell lung cancer (NSCLC) in our center.

Methods: 27 patients with stage IVA NSCLC with cranial or adrenal metastases were radically treated with consequent complete pulmonary resection and metastasis surgery at our center between 2010 and 2020, were included and their survival outcomes were investigated. All patients were evaluated preoperatively with thorax computed tomography, cranial magnetic resonance imaging and positron emission tomography. Invasive mediastinal staging methods were performed for all patients. For statistical analysis, SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used. The Kaplan-Meier method was used for calculating survival. Statistical significance was considered with a p-value <0.05 within the 95% confidence interval.

Results: All patients had a single metastasis in a single organ with 17 cranial and 10 adrenal metastases. Craniotomy or adrenalectomy was performed on all metastases. Postoperative 30 or 90-day-mortality was not observed. Demographic, pathological, survival and treatment data of the patients are shown in Table 1. Survival analysis is shown in Table 2. Overall survival at 2 and 5 years were 76% and 47%, respectively. Recurrence within 24 months postoperatively in 8 patients (29%) [locoregional; lung and mediastinal lymph node (n=5), local metastasis recurrence (n=3)] were observed.

Conclusions: The overall survival results are satisfactory with radical local treatment applications for cranial or adrenal metastases in young patients without mediastinal lymph node metastases, who can undergo complete surgery for the primary lung tumor. Although prospective randomized studies are needed, surgery should have a place in the multimodal treatment of oligometastatic lung cancer.



PATIENT CHARACTERISTICS		n	%	MEDIAN	RANGE
Age (year)				56	(35-74)
Gender	Male	24	88		
	Female	3	12		
Distant metastasis status	Brain	17	62		
	Adrenal gland	10	38		
Type of resection	Sublobar	3	12		
	Lobectomy	19	70		
	Pneumonectomy	5	18		
Histopathology	Adenocarcinoma	18	66		
	Squamous cell carcinoma	6	22		
	Large cell neuroendocrine carcinoma	3	12		
pT status	T1	8	30		
	T2	11	40		
	T3	6	22		
	T4	2	8		
pN status	N0	20	74		
	N1	4	14		
	N2	3	12		
Neoadjuvant treatment	Present	4	16		
	Absent	23	84		
Adjuvant treatment	Present	20	74		
	Absent	7	26		
Survival status	Alive	14	51		
	Dead	13	49		

Keywords: Oligometastatic disease, Lung cancer

EP08.03 METASTATIC NON-SMALL CELL LUNG CANCER - OLIGOMETASTATIC DISEASE

EP08.03-005 HALT - Targeted Therapy with or without Dose-Intensified Radiotherapy in Oligo-Progressive Disease in Oncogene Addicted Lung Tumours

F. McDonald[1], M. Guckenberger[2], S. Popat[1], C. Faivre-Finn[3], N. Andratschke[2], A. Riddell[1], G.G. Hanna[4], C. Hiley[5], V. Prakash[6], A. Nair[5], P. Diez[7], P. Patel[1], L. Kilburn[8], A. Emmerson[8], C. Toms[8], J. Bliss[8]

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Introduction: Following initial response to TKI, advanced NSCLC patients with actionable mutations ultimately develop treatment resistance. In a proportion of patients (15-40%), initial, limited progression (≤5 lesions) is observed, termed oligoprogressive disease (OPD). SBRT offers hypofractionated, targeted radiotherapy treatment hypothesised to prolong clinical benefit from TKI prior to widespread disease development. With limited evidence to date, and poor clinical/biological selection criteria, the potential benefit offered by SBRT to ablate OPD sites prior to change in systemic therapy is an important question to address.

Methods: HALT is a randomised, multi-centre, phase II/III international trial with seamless transition to phase III incorporated. Eligible patients (stage IV NSCLC, actionable mutation, TKI response prior to OPD) are randomised 2:1 to SBRT/continued TKI or continued TKI alone. Eligibility is confirmed by a virtual MDT (vMDT) comprising trial clinicians and radiologists (confirmation of OPD, SBRT suitability). Follow-up assessments are aligned with routine care at 3-monthly intervals until change in systemic therapy is clinically indicated, with imaging and toxicity assessment at each visit.

Results: Recruitment commenced November 2017 with 25 centres (17 UK; 8 non-UK) open to date. Following the COVID-19 pandemic, recruitment is recovering with 129 registered and 74 randomised patients. Over the last 4 years, little evidence has emerged to confirm any potential benefit of SBRT in this patient group and the impact on patient toxicity remains unknown. Therefore, with persisting questions around clinical equipoise, HALT remains highly relevant. With an 18-month extension and a recent amendment to the HALT inclusion criteria (≤5 OPD lesions, ≤7cm and OPD assessments by PET-avidity), the target of 110 randomised patients remains achievable.

Conclusions: As the first randomised trial assessing SBRT benefit in this mutation-positive NSCLC patient population, HALT will provide valuable treatment efficacy and safety information, informing subsequent trial design and contribute to the development of international guidelines for the identification and clinical management of oligoprogression in mutation positive lung cancer.

Keywords: Stereotactic body radiotherapy, NSCLC, Phase II

EP08.03 METASTATIC NON-SMALL CELL LUNG CANCER - OLIGOMETASTATIC DISEASE

EP08.03-006 Survival After Radical Treatment of Oligometastatic Non-small Cell Lung Cancer: A Multicenter Analysis

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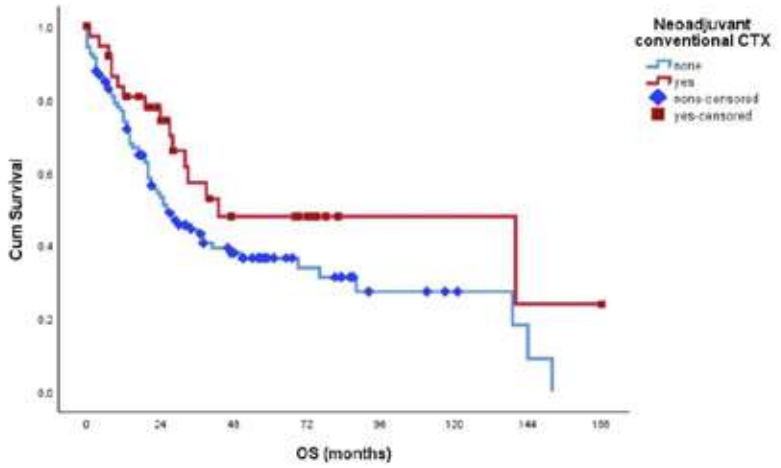
Introduction: Approximately 57% of all non-small cell lung cancer (NSCLC) diagnoses are made in an advanced stage of the disease. Despite recent advancements in personalized cancer treatment, survival in stage IV NSCLC remains poor with 5-year survival rates between 0% and 10%.[1] However, patients with low systemic tumor burden and few distant metastases may benefit from a local ablative treatment (LAT) including resection of the primary tumor and radical treatment of metastatic sites. Our aim was to assess the outcomes of LAT including surgery of the primary tumor in a multicenter analysis of patients with oligometastatic NSCLC.

Methods: Clinical data of patients with oligometastatic NSCLC who underwent surgery of the primary tumor and radical treatment of distant metastases were retrospectively reviewed. Lung resections were performed at 2 high-volume centers in Europe and Asia. Data were analyzed using descriptive statistics and overall survival (OS) was assessed using Kaplan-Meier curves.

Results: Between 2001 and 2021, 144 patients with oligometastatic NSCLC were treated. 50.7% of all patients were male and mean age was 61.8 ± 10.2 (IQR: 55.2-68.7)) years. The cohort included 111 adenocarcinoma cases (77.1%), 23 squamous-cell carcinoma cases (16%), 6 large-cell carcinoma cases (4.2%) and 1 adenosquamous carcinoma case (0.7%). Most common metastatic site was brain (n=46), followed by bone (n=27) and adrenals (n=21). 45.8% of all patients had no nodal metastases (cN0). 30- and 90-day mortality rates were 4.9% (7/144) and 7.6% (11/144), respectively. Surgical resection was performed by lobectomy in 106 (73.6%) cases, by bilobectomy in 2 (1.4) cases, by pneumonectomy in 25 (17.4%) cases, by non-anatomical (wedge resection) in 10 cases (6.9%) and segementectomy in 1 case. R0 resection was achieved in 98.6% (142/144). Median overall survival (OS) after surgery was 33 months [95%CI: 22.939; 43.061]. 1-, 2-, and 5-year OS was 76%, 59% and 40%, respectively. Neoadjuvant systemic treatment had a trend to significantly influence median OS (43 months [95%CI: -; 105.769] vs. 26 months [95%CI: 15.096; 36.904], p=0.05.

Conclusions: In patients with oligometastatic NSCLC and limited systemic tumor burden, LAT with surgical resection of the primary tumor can be safely performed. In this selected subgroup of patients, 5-year OS exceeds substantially the reported survival rates of stage IV NSCLC.



Keywords: Oligometastatic lung cancer, local ablative therapy, lung cancer surgery

EP08.03-007 Spontaneous Regression in Metastatic Non-small Cell Lung Cancer: A Case Report

M. La Mantia[1], L. De Monte[2], G. Tancredi[2], D. Giunta[2], P. Ferrigno[2], V. Gristina[1], A. Galvano[1], N. Barraco[1], S. Rizzo[3], T.D. Bazan Russo[1], D. Salemi[4], A. Santoro[4], R. Liotta[5], A. Bertani[2], A. Russo[1], V. Bazan[1]

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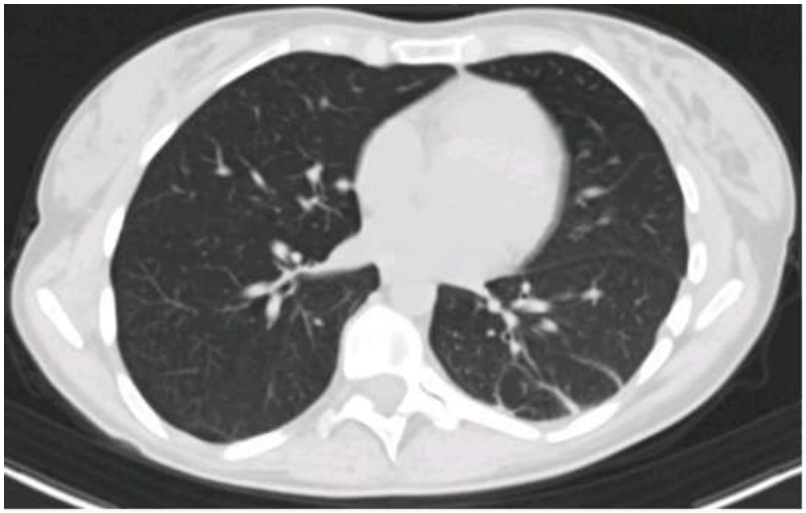
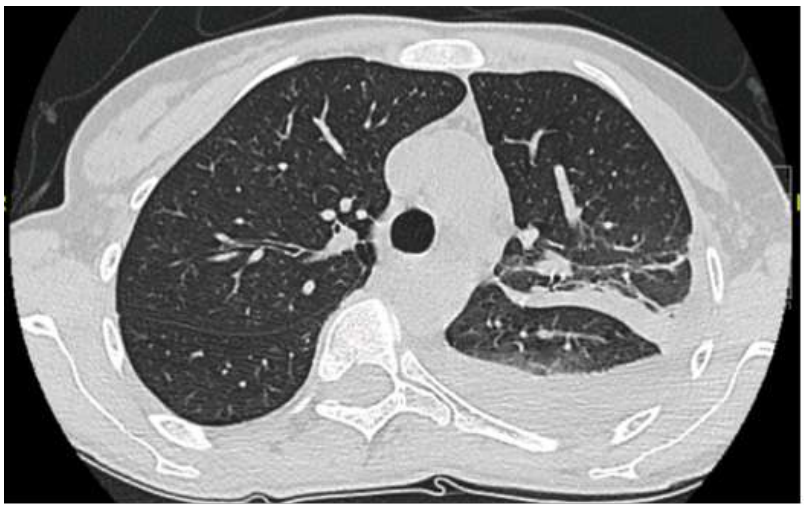
Introduction: Spontaneous regression is defined as temporary or permanent disappearance of a tumor without anticancer treatment, which develops after surgery or biopsy for primary and metastatic tumors. We report the case of a 40-year-old woman with a spontaneous regression of metastatic Non-Small Cell Lung Cancer who was admitted to our hospital on December 2021.

Methods: In November 2021, the patient underwent a CT scan due to dyspnoea. CT findings revealed bilateral pleural effusion, linear atelectasis, and a centimeter left lower lobe (LLL) nodule (Figure 1). FDG-PET scan showed increased tracer uptake of the left nodule (SUV) 1.8), and in the left hilar region (SUV 1.2). Endobronchial ultrasound bronchoscopy evidenced no lesions. The patient underwent diagnostic pleural drainage, and the cytological examination was suggestive for lung adenocarcinoma cT1bN0M1a, stage IV, according to the TNM classification of the Union for International Cancer Control 8th edition. Genomic analysis identified the epidermal growth factor receptor gene del19ex. Immunohistochemical analysis detected a programmed death-ligand 1 tumor proportion score of 50%.

Results: In December 2021, the patient was referred to our hospital. Interestingly, the whole-body CT scan revealed the complete disappearance of the disease (Figure 2). We discussed available options with the patient who agreed to thoracoscopy. On January 2021, the patient underwent thoracoscopy with pleural biopsies. The pathological report was suggestive for tissue repair. A second opinion on the previous pathological report was made. The report suggested uncertain findings TTF1+ BAP1+ with a potential differential diagnosis between adenocarcinoma versus pneumocytoma versus Atypical Pneumocyte Hyperplasia.

Conclusions: The case was presented at the Multidisciplinary Tumor Board, and the treatment strategy consisted in a three-month follow-up CT scan.In conclusion, spontaneous regression is a sporadic event in lung cancer, and knowledge of the mechanisms involved in such cases is still unknown.





Keywords: Non-Small-Cell Lung Cancer, EGFR, Spontaneous regression

EP08.03 METASTATIC NON-SMALL CELL LUNG CANCER - OLIGOMETASTATIC DISEASE

EP08.03-008 Whether Immunotherapy Should Be Maintained or Not After Acquired Resistance in Advanced Nsclc

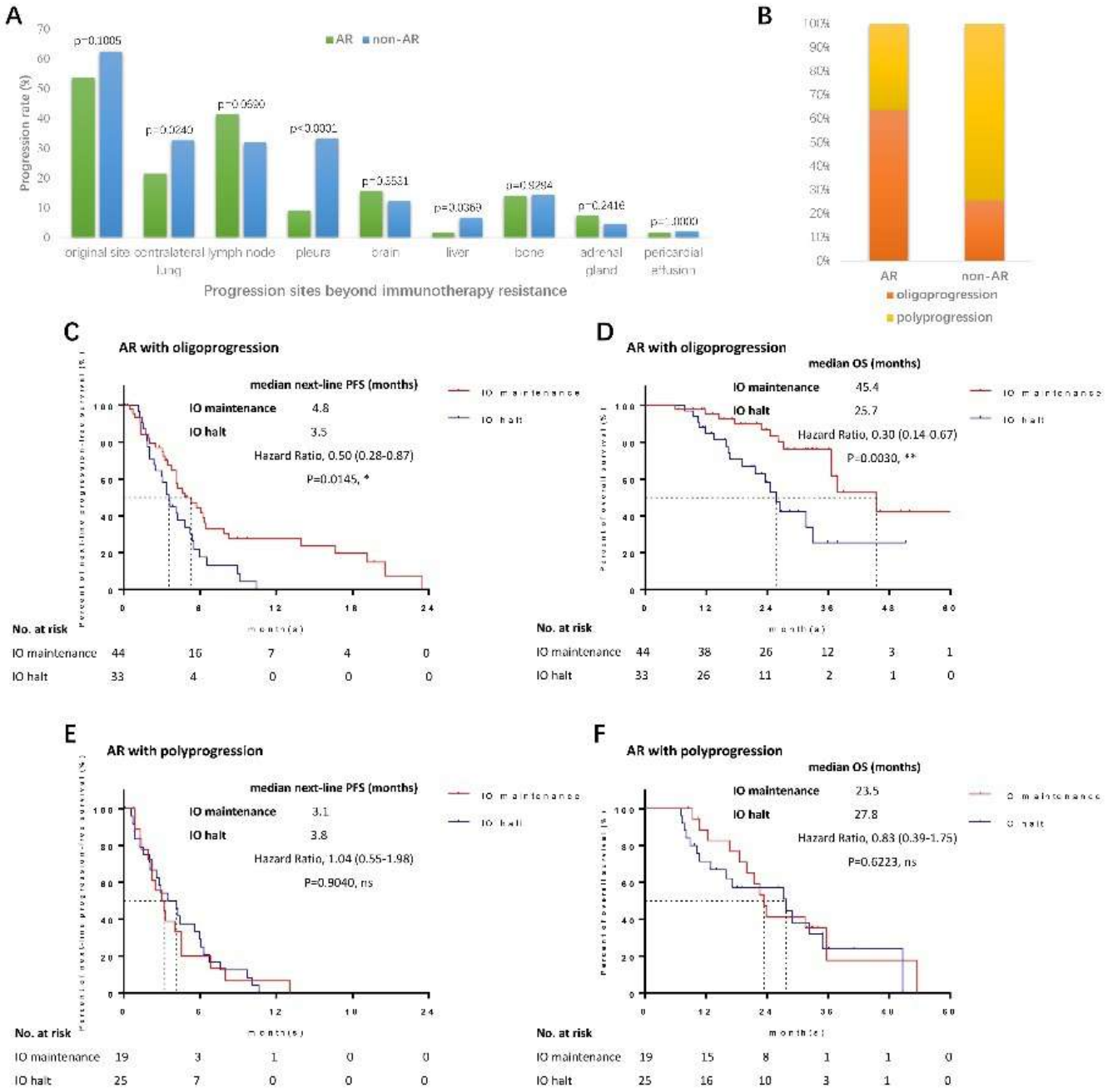
H. Huang, Z. Xu, Y. Yu, S. Lu
Shanghai Chest Hospital, Shanghai/CN

Introduction: In non-small cell lung cancer (NSCLC), acquired resistance to immunotherapy (IO) remains common and poorly understood, and the optimal treatments are unknown.

Methods: We retrospectively analyzed advanced NSCLC patients who received immunotherapy at Shanghai Chest Hospital between Jan 2016 and Jul 2021. The last follow-up date was Jan 1, 2022. The median follow-up duration was 29.4 months (range, 5.2-66.3 months). According to the ESMO consensus, acquired resistance (AR) was defined as objective response to PD-(L)1 blockade and had progressive disease occurring within 6 months of last anti-PD-(L)1 antibody treatment. Among those AR patients, oligoprogression was defined as ≤5 progressive lesions in ≤3 organs, and polyprogression was defined as >5 progressive lesions or >3 organs. Survival curves were plotted using the Kaplan-Meier method and differences in variables were calculated using the log-rank test. Differences in the categorical variables were evaluated using Chi-square test or Fisher exact test, as appropriate.

Results: A total of 516 driver mutation negative NSCLC patients were included in this study. Before the last follow-up date, 406 patients developed disease progression after immunotherapy, in which 29.8% (n=121) of patients developed AR. Compared with non-AR patients, contralateral lung (p=0.0240), pleural (p<0.0001), and liver (p=0.0369) progression were less frequently detected in AR patients. The proportion of oligoprogression was higher in AR group versus non-AR group (63.6% vs 25.6%; p<0.0001). After developed AR to immunotherapy, patients with oligoprogression (n=77) showed substantial survival advantages from IO maintenance, and the median next-line progression-free survival (nPFS) and overall survival (OS) were significantly prolonged compared with IO halt group (nPFS, 4.8 vs 3.5 months; p=0.0145; OS, 45.4 vs 25.7 months; p=0.0030). However, patients with polyprogression (n=44) in AR group could not benefit from IO maintenance by compared with IO halt (nPFS, 3.1 vs 3.8 months; p=0.9040; OS, 23.5 vs 27.8 months; p=0.6223).

Conclusions: For the patients who experienced objective response from PD-(L)1 blockade and developed acquired resistance, only those with oligoprogression could benefit from immunotherapy maintenance.



Keywords: immunotherapy, acquired resistance, oligoprogression

EP08.04 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE CHEMOTHERAPY

EP08.04-001 Weekly versus 3-Weekly Regimens of Carboplatin and Paclitaxel in Metastatic NSCLC: A Real-World Data

B. Waissengrin[1,2], T. Stern[1], S. Shamai[1,2], O. Merimsky[1,2]

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Introduction: The current non-small cell lung cancer (NSCLC) treatment algorithm is based on personalized medicine, nevertheless platinum based chemotherapy is still a major component of patients' treatment plan. The carboplatin and paclitaxel 3-weekly protocol (D1,Q21) is the conventional treatment that might presents potentially serious toxicity. In this study, we retrospectively evaluated the weekly protocol of carboplatin and paclitaxel (d1,8,15,Q28) attempting for assessment its efficacy and toxicity.

Methods: Medical records of consecutive patients treated between 2015 to 2020 were reviewed and 100 patients were analyzed for demographic and clinical characteristics, efficacy, and toxicity.

Results: The 3-weekly protocol was administered to 63 patients (63%, median age, 64 years) and weekly protocol to 37 patients (37%, median age, 67.5 years). Except for age (p 0.008) there was no statistical difference between the groups' demographic characteristics. Median PFS was 3.2 months in the weekly regimen compared to 1.86 months in the 3-weekly regimen (P=.078) and median OS was 26.3 months compared to 21.5 months (P=.443). The toxicity profile was similar between the two groups.

Conclusions: This retrospective study, real world data, addressed the two-scheduling regimen of carboplatin and paclitaxel. We found similar results among the two approaches in terms of efficacy and toxicity profile. This trial highlights the carboplatin-paclitaxel weekly protocol as a valid treatment option, especially among elderly patients and those with significant comorbidities.

Keywords: Chemotherapy, NSCLC, Toxicity

EP08.04 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE CHEMOTHERAPY

EP08.04-002 Australian Vinorelbine Use in Advanced Lung Cancer (The AVAL Study)

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Introduction: Immunotherapy has become a standard early line therapy for advanced non-small cell lung cancer (NSCLC). Post-progression sequencing and utilization of subsequent active therapies is of increasing importance and currently lacks expert consensus. Vinorelbine, a member of the vinca alkaloid family, is an active anti-cancer chemotherapy agent in NSCLC that may offer patients clinical benefit in this setting.

Methods: Advanced NSCLC patients who received treatment with vinorelbine in the post immunotherapy setting were identified from pharmacy records at four health services across three Australian states. Patient records were accessed for demographic, lung cancer diagnosis, staging and treatment information and the data was captured in the secure online platform REDCap.

Results: 25 patients were identified, with 13 (52%) male and median age of 63 years at lung cancer diagnosis (range 45 -75). 21 (84%) were metastatic at diagnosis, 17 (68%) had adenocarcinoma, 3 had activating EGFR mutations. Patients commonly received three (6) or four (6) lines of systemic treatment (range 2-7). Platinum doublet chemotherapy was the most common initial therapy (16, 64%) with immunotherapy the most common second line therapy (13, 50%). Vinorelbine was frequently given in the third (6), fourth (7) or fifth (7) line of treatment. It was given as monotherapy in 24 (96%) patients or in combination with carboplatin in 1 (4%) patient. In 10 (40%) patients vinorelbine was sequenced immediately following immunotherapy. Vinorelbine was given intravenously (IV) in 21 (84%) with the median dose 30mg/m2 (range 21-30mg/m2). The median time on vinorelbine was 10.0 weeks (range 0-102 weeks). 8 patients required dose reduction, predominantly for neutropaenia (5/8, 63%). 14 (56%) patients achieved clinical benefit with vinorelbine; with partial response (1) or stable disease (13). Patients with clinical benefit remained on vinorelbine for a median of 22.1 weeks. 2 patients who received oral vinorelbine remained on therapy for 53 and 45 weeks, respectively. Vinorelbine was predominantly ceased for disease progression (21, 84%).

Conclusions: Vinorelbine was well tolerated in this population of heavily pre-treated NSCLC patients all of whom had previously received immunotherapy. There was evidence of clinical benefit that was durable in some cases. The treatment sequencing reflects the rapidly changing lung cancer therapy paradigm, which now favours immunotherapy first line. The result from this study suggests that vinorelbine remains a valid anti-cancer treatment option in the post immunotherapy setting.

Keywords: Vinorelbine, Post-immunotherapy

EP08.04-003 A Simple Clinical Prediction Score to Determine Response to First Line Chemotherapy Treatment in Advanced Non-Small Cell Lung Cancer Patients

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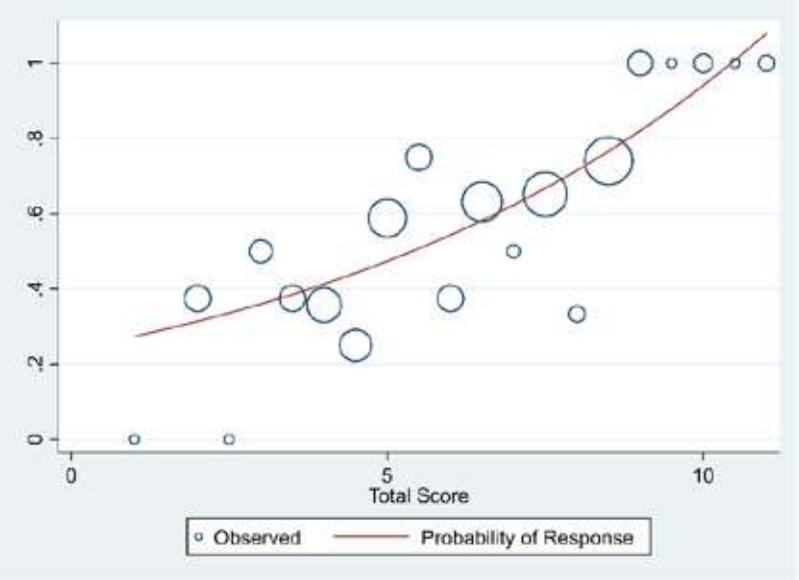
Introduction: The outcomes of advanced non-small cell lung cancer (NSCLC) patients have been significantly improved with novel therapies such as tyrosine kinase inhibitors and immune checkpoint inhibitors. However, in many limited-resource countries, platinum-doublets chemotherapy is mainly used as the first line regimen. We investigate several clinical parameters to predict the response after chemotherapy which may be useful for physician in patient selection.

Methods: Clinical prediction score (CPS) was developed, based on clinical data from a retrospective cohort study of NSCLC patients with unresectable stage IIIB or IV according to TNM 7th edition who received platinum doublets chemotherapy as the first line treatment at least two cycles and evaluated response by RECIST 1.1 at Surin Hospital Cancer Center between July 2014 to December 2018. Clinical parameters included in the prediction model were derived by using risk regression analysis.

Results: In this study, 207 patients with unresectable stage IIIB or IV NSCLC were included. There were 117 responders (partial or complete response) and 90 non-responders (stable or progressive disease). The clinical prediction score was defined by six clinical parameters including gender, age, smoking status, ECOG score, pre-treatment albumin, and histologic subtype. The AuROC of the model was 0.71 (95%CI 0.63 - 0.78). The internal validation was done by bootstrap technique, which showed a consistent AuROC 0.66 (95%CI 0.59 - 0.72). The prediction score ranged from 0-13, with score 0-8 yielded a low probability for chemotherapy response (PPV = 50%) and score 8.5-13 gave a high probability for chemotherapy response (PPV = 83.7%).

Conclusions: Our study indicated that advanced NSCLC patients who received first line platinum-doublets chemotherapy only with high CPS of 8.5-13 had a high probability to respond to treatment. This CPS may be a useful tool for communication and decision-making discussion with patients and family regarding risk-benefit of using cytotoxic agents.

Distribution of Risk of Responders, PPV, LR+ and 95% CI of LR+						
Risk Level	**Responders, n (%)**	**Non-responders, n (%)**	**PPV (%)**	**LR+**	**95% CI of LR+**	***p*-value**
Low (0-8)	65 (50.0)	65 (50.0)	50.0	0.34	0.18-0.66	<0.001
High (8.5-13)	36 (83.7)	7 (16.3)	83.7	3.67	1.73-7.77	<0.001



Keywords: NSCLC, Palliative Chemotherapy, Clinical Decision Rules

EP08.04 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE CHEMOTHERAPY

EP08.04-004 Impact of Comorbidity Scores on Overall Survival in Advanced Non-Small Cell Lung Cancer Patients -A Real-World Experience from Eastern India

S.G. Mamidi, P.R. Mohapatra, S. Bhuniya, S.K.D. Majumdar, P. Mishra, M.K. Panigrahi, S.K. Bal, A. Datta, P. Venkatachalam, D. Chatterjee, S. Sarkar, R.B. Shirgaonkar, A. Girija, S. Ghosh, M.S. Padmaja, V.R.M. Acharyulu, G. Durgeshwar

All India Institute of Medical Sciences, Bhubaneswar/IN

Introduction: Lung cancer is the most common cancer, and it is the leading cause of cancer-related death. Smoking is the commonest risk factor for the development of lung cancer. There is a lack of data on comorbidities and outcomes of advanced Non-Small Cell Lung Cancer (NSCLC) from the eastern part of India. This prospective study evaluated the impact of comorbidity scores on overall survival (OS) in these patients.

Methods: This prospective cohort study was conducted in newly diagnosed advanced NSCLC patients between June 2020 and April 2021. These patients were given platinum-based doublet chemotherapy guided by histology and targeted therapy based on molecular studies. Palliative radiotherapy was given wherever indicated. Comorbidities were assessed using Charlson Comorbidity Index (CCI), Simplified Comorbidity Score (SCS) and Adult Comorbidity Evaluation-27(ACE-27). Comorbidity scores were grouped into 2-3 groups. The Outcome assessed was OS. Overall survival was calculated in days from the date of start of anticancer therapy to the date of last follow up or date of death. All enrolled patients were followed at regular intervals whenever they visited the hospital and also telephonically till February 2022. The patients were censored who are alive on 28 February 2022. The survival probability and median OS overall survival were calculated by Kaplan-Meier analysis, and group differences of comorbidity scores were analyzed with the log-rank test.

Results: A total of 114 patients were enrolled in the study period, and the mean age of patients was 56.54 ±11.03 years. The majority of the patients were males (68.4%), and 52.6 % were smokers. Adenocarcinoma was the most common histology (73.6%), followed by squamous cell carcinoma (25.4%). Median OS was 127 days (95% CI, 61-192 days). 38 (33.3%) patients had a CCI score of 0, a CCI score of 1 was seen in 57% of patients, and ≥ 2 scores in 9.6% of patients. SCS score ≤ 9 and >9 was seen in 92.1% and 7.9% of patients, respectively. ACE-27 score was none in 47 subjects, mild in 59, moderate in 12, and 3 NSCLC subjects had severe ACE-27 score. Median OS for patients with CCI score 0 was 275 days (95% CI, 7-543 days), 114 days (95% CI, 85-142 days) for subjects with CCI score 1 and 402 days (95% CI, 0-874 days) for patients with CCI score ≥2 (log-rank p =0.215). Individuals with SCS score ≤ 9 had a median OS of 175 days (95% CI, 93-256 days), and median OS was 92 days (95% CI, 80-103 days) for patients with SCS score<9 (log-rank p = 0.292). Median OS of the patients with ACE-27 score 0,1,2,3 were 297 days (95% CI, 76-517 days), 117days (95% CI, 81-152 days), 87 days (95% CI, 49-124 days) and 66 days respectively (log-rank p=0.393). There was no statistically significant difference between comorbidity scores and OS.

Conclusions: In our study, the advanced NSCLC patients who were given chemotherapy or oral tyrosine kinase inhibitors showed no significant influence of comorbidities on overall survival.

Keywords: comorbidities, NSCLC, Overall survival

EP08.04 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE CHEMOTHERAPY

EP08.04-005 Phase II Study of Ramucirumab and Docetaxel for NSCLC Patients with Malignant Pleural Effusion

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Introduction: The prognosis of non-small cell lung cancer (NSCLC) patients with malignant pleural effusion (MPE) due to pleural carcinomatosis is said to be poor. Several reports discussed that the anti-VEGF antibody had the effect of decreasing vascular permeability and reducing pleural effusion. Ramucirumab (RAM), a VEGFR-2 antibody that inhibits tumor angiogenesis, is widely used with docetaxel (DTX) after failure of platinum doublet chemotherapy. Presently, there is no data concerning the tolerable safety profile and efficacy of administering RAM+DTX to patients with NSCLC with MPE.

Methods: NSCLC patients with MPE, PS 0-1, normal organ function and progression on platinum therapy were enrolled. The patient requiring treatments for pleural effusion such as urgent and continuous drainage of pleural effusion for displacement of the mediastinum due to accumulation of pleural effusion was excluded. RAM 10 mg/kg + DTX 60 mg/m2 every 3 weeks until the patient meets the discontinuation criteria. The primary objective of this study is to evaluate the pleural effusion control rate at 8 weeks after the start of treatment of RAM+DTX. The definition of the pleural effusion control was “not requiring drainage within 8 weeks”. The secondary objectives of the study are to evaluate efficacy and toxicity of RAM in combination with DTX in terms of: objective response rate (ORR), progression-free survival (PFS), overall survival (OS), adverse events (AEs) and tolerable safety profile. The definition of tolerable safety profile was percentage of patients that required treatments like continuous pleural effusion drainage by Day 21 after the start of treatment.

Results: From September 2019 to February 2022, 14 patients were enrolled and 13 were evaluated. Median age was 70 y.o, 2 female, ECOG PS (0/1): 3/10, histology (adeno/squamous/pleomorphic): 11/1/1, prior ICI (no/yes): 8/5, prior bevacizumab (no/yes): 11/2, smoking history (no/yes): 4/9, prior MPE management (none/ Thoracentesis/ Chest tube drainage): 6/5/2. There were no patients that required treatments like thoracentesis or continuous pleural effusion drainage by Day 21 after the start of treatment. The pleural effusion control rate at 8 weeks was 100 % (13 out of 13 cases, 95%CI: 75.3-100). 35.8% (95%CI: 13.9-68.4) of patients had decreased pleural effusion determined by Chest X-ray or CT. ORR was 7.2% (0.2-36.0). Median PFS was 5.1 months (10 events occurred) and median OS was 6.5 months (6 events occurred). Severe AEs; Grade 3 febrile neutropenia (n=2, 15.3%), pneumonitis (n=1, 7.6%), edema limbs (n=1, 7.6%) and Grade 4 neutropenia (n=2, 15.3%) were occurred. No treatment-related deaths were observed.

Conclusions: RAM+DTX seemed to be a safe and promising for NSCLC patients with MPE. This study is ongoing until the target number of cases is 15.

Keywords: Non-small cell lung cancer, malignant pleural effusion, ramucirumab

EP08.04-006 Risk Factors of Chemotherapy-Induced Severe Neutropenia in Elderly Lung Cancer: Data From a Regional Hospital in Thailand

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Introduction: Advance stage Non-Small Cell Lung Cancer (NSCLC) is a leading cause of cancer death in the elderly. Chemotherapy is a backbone treatment in non-targetable advance stage NSCLC, especially in limited-resource countries. Chemotherapy—although an effective treatment for NSCLC—has multiple side effects including severe neutropenia. It requires dose reduction, delay in treatment, or discontinuation and induces neutropenic complications resulting in poor oncologic outcomes and increased healthcare costs. Therefore, it is important to recognize the risk factors for chemotherapy-induced severe neutropenia and outcome in elderly advanced-stage NSCLC.

Methods: From July 2014-June 2019, elderly (age≥ 65-year-old) advanced-stage NSCLC who received chemotherapy were retrospectively analyzed. Demographic and risk factors data were collected from the electronic medical record system. This study defines severe neutropenia as grade 3-4 neutropenia according to the Common Toxicity Criteria of Adverse Events (CTCAE) version 4.0. Univariate and multivariate logistic regression analyses were performed to identify risk factors for severe neutropenia. Survival curves were estimated using the Kaplan-Meier method

Results: Among 134 patients, 20 (14.92%) developed severe neutropenia and 2 (1.5%) occurred febrile neutropenia. Infection rate was not difference between among groups (5% vs 8.8%; P=0.571 in severe and non-severe neutropenia respectively). 128 (95.5%) received palliative chemotherapy and 132 (98.5%) treatment with platinum-based chemotherapy. In univariate analysis, ECOG 2-3 (OR 8.418; 95%CI 1.084-65.38; P=0.017), restriction protein diet (OR 6.22; 95%CI 0.824-47.00; P=0.046), renal disease (OR 2.677; 95%CI 0.016-7.054; P=0.041), GFR <60 ml/mim/1.73m^2 (OR 3.250; 95%CI 1.00-8.641; P=0.014), ≥ 2 organs metastasis (OR 2.955; 95%CI 1.097-7.07; P=0.025), and combination platinum-based chemotherapy (OR 7.09 95%CI 0.911-55.27; P= 0.032) were associate chemotherapy induced severe neutropenia. In multivariate analysis, restriction of protein diet (OR 14.05; 95%CI 1.31-150.77; p= 0.029) and ≥2 organs metastasis (4.012; 95%CI 1.24-12.97; P=0.020) were significant predictors of severe neutropenia. No difference in Progression Free Survival (PFS) and Overall Survival (OS); median PFS; 7.81 vs 7.03 months; P=0.399, median OS 8.04 vs 9.28 months; P=0.654 in severe and non-severe neutropenia respectively.

Conclusions: The present study indicates that restriction of protein diet and ≥2 organs metastasis were predictive factors of chemotherapy-induced severe neutropenia in elderly advance stage NSCLC. Therefore, patients with these risk factors should be monitored more carefully during chemotherapy treatment. However, there is no difference in infection rate, progression-free survival, and overall survival.

Table 1 Univariate and Multivariate analysis for severe neutropenia

Factors	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
ECOG 2-3 vs 0-1	8.418(1.084-65.38)	0.017	0.193 (0.021-1.779)	0.147
Restriction protein diet	6.22(0.824-47.00)	0.046	14.05(1.31-150.77)	0.029
Renal disease	2.677(0.016-7.054)	0.041	1.936(0.275-13.617)	0.507
Metastasis ≥2 vs 2 organs	2.955(1.097-7.07)	0.025	4.012(1.24-12.97)	0.020
GFR <60 vs ≥ 60	3.250(1.00-8.641)	0.014	0.182(0.26-1.28)	0.087
Combination platinum vs Single platinum	7.09(0.911-55.27)	0.032	0.164(0.19-1.425)	0.164
Age > 75 vs ≤ 75	0.415(0.114-1.510)	0.171	1.311(0.264-6.5174)	0.740
Weight loss	1.05(0.385-2.67)	0.975		
Histology adenocarcinoma vs SCCA	1.439(0.458-4.528)	0.532		
Cycle > 4 vs ≤ 4	1.209(0.404-3.150)	0.697		
WBC < 5000 vs ≥ 5000	1.183(1.009-1.274)	0.340		
ANC < 3000 vs ≥ 3000	1.434 (0.10-12.132)	0.740		
Hb <10 vs ≥ 10	0.793 (0.206-3.058)	0.736		
Platelet < 150000 vs ≥ 150000	0.691(0.0473-6.521)	0.747		

Keywords: Chemotherapy induced severe neutropenia, Non-Small Cell Lung Cancer, Risk factors

EP08.05 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE RADIOTHERAPY

EP08.05-001 Evaluation of Pneumonitis in EGFR-Mutated Non-Small Cell Lung Cancer Patients Receiving Osimertinib and Thoracic Radiation

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Introduction: Osimertinib and thoracic radiotherapy (TRT) are established therapies for epidermal growth factor receptor mutated (EGFR+) metastatic non-small cell lung cancer (mNSCLC). However, pneumonitis is a known side effect independently associated with both treatment modalities. The objective of this study was to examine the impact of concurrent Osimertinib and TRT on the incidence of pneumonitis, and to observe patterns of practice regarding the cessation of Osimertinib during TRT.

Methods: This single institution retrospective cohort study included patients with EGFR+ mNSCLC who received both Osimertinib and TRT between 2016 and 2020. TRT was defined as any course of radiation that deposited dose within the lung parenchyma, regardless of the location of the targeted lesion. The primary endpoint was the incidence of symptomatic (CTCAE grade ≥ 2) pneumonitis. Comparisons were made with multivariable Cox proportional hazards regression for both grade ≥ 2 and any grade pneumonitis.

Results: During the study period, 151 patients received Osimertinib, of which 41 received 147 courses of radiation either during or within 6 months of Osimertinib initiation. A total of 68 (46.3%) lesions were treated with TRT. Five patients developed RT-related symptomatic pneumonitis (12.2%), of which 1 was grade 4 and another grade 5. Mean (±SD) age at TRT was 65.5 (±12.0) years. Most patients had de novo metastatic disease (n=31; 75.6%), adenocarcinoma histology (n=38; 92.7%), and 16 (39%) were on Osimertinib as first line systemic therapy. The mean (±SD) number of cycles of Osimertinib was 9.6 (±4.3). Median total dose and fractionations were 20 Gy (interquartile range [IQR]: 20-30 Gy) and 5 (IQR: 1-5), respectively. During TRT, Osimertinib was knowingly held in 12 patients (29.3%), most commonly for 1-2 days (n=7; 17.1%) before and after radiation, while it was knowingly continued during TRT for 5 patients (12.2%). Multivariable analysis identified that each additional cycle of Osimertinib was associated with an increased incidence of grade ≥ 2 pneumonitis (hazard ratio [HR]: 1.54, 95% confidence interval [CI]: 1.15-2.07, p=0.004). Total radiation dose was also associated with increased incidence of any grade of pneumonitis (HR per 5 Gy: 1.38, 95% CI: 1.03-1.86, p=0.031). There was no association with incidence of pneumonitis (any grade) if Osimertinib was continued during TRT (HR: 3.36, 95% CI: 0.13-86.56, p=0.47) or if TRT was given within 6 months of Osimertinib initiation (HR: 0.20, 95% CI: 0.02-2.21, p=0.19).

Conclusions: In patients with EGFR+ mNSCLC treated with Osimertinib and TRT, the risk of symptomatic pneumonitis was moderate, but serious in 2 instances (including 1 death). Symptomatic pneumonitis with TRT was associated with prolonged Osimertinib use. Practice patterns on whether to hold Osimertinib during TRT (and for how long) were variable, although concurrent treatment did not appear to influence the incidence of pneumonitis. Further research is required to clarify the safety of concurrent radiotherapy and targeted systemic agents.

Keywords: Pneumonitis, Osimertinib, Thoracic Radiotherapy

EP08.05-002 Sequencing of T cell Receptor Revealed Radiotherapeutic Efficacy and Prognosis in Non-small Cell Lung Cancer Patients with Brain Metastasis

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Introduction: Liquid biopsy has played a unique role in long-term surveillance of brain metastasis in non-small cell lung cancer (NSCLC), due to the inaccessibility of solid metastatic biopsies. T cell-mediated immunity is critical in the oncogenesis and metastasis of NSCLC, and sequencing in T cell receptor (TCR) provides a robust method to quantify T cell diversity. Therefore, we aimed to explore the alteration of TCR through liquid biopsy before and after radiotherapy of NSCLC brain metastases.

Methods: Thirty NSCLC patients with brain metastases receiving brain radiotherapy were enrolled in this study. Cerebrospinal fluid (CSF) and peripheral blood were collected at baseline, 24 hours (T0) and 28 days (T28) after treatment. TCR sequences were identified by high-throughput sequencing in both compartments.

Results: At baseline, dimension reduction analysis identified distinct signatures of V and J gene recombination in blood and CSF TCR sequences. Throughout treatment, both compartments experienced a TCR diversity decrease, however, the degradation of low-abundance clones and the expansion of emerging clones might be two separate processes underwent in blood and CSF, respectively. Diversity changes in blood were possibly related to pulmonary responses, while the increase of maximal clone abundance in CSF might indicate a favorable intracranial response. Superior blood TCR diversity at T28 against baseline was associated with longer OS (HR = 5.700, p = 0.039). Patients with increase of maximal clone abundance ≥ 50 in CSF also had a better intracranial PFS (HR = 8.320, p = 0.011). The predictive effects of these markers were independent of other clinical factors in multivariate Cox analysis

Conclusions: CSF and peripheral blood were independent compartments showing disparate TCR signatures. Longitudinal surveillance of both compartments could be a promising method to predict clinical outcomes for NSCLC patients with brain metastases.

Keywords: T cell receptor, non-small cell lung cancer, brain metastasis

EP08.05 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE RADIOTHERAPY

EP08.05-003 Evaluation of Dose Changes in Different Periods after 125I Seed Implantation in Lung Cancer

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Introduction: ^{125}I seed brachytherapy has the characteristics of sustainable, low dose rate and low damage to peripheral organs in the treatment of non-small cell lung cancer, and it is a better choice for local treatment of lung cancer patients. According to the location and size of the target volume, the preoperative plan simulates the seed implantation situation that achieves the optimal dose, and the postoperative verification plan evaluates the quality of the seed implantation. The number of seeds, the angle of needle insertion and the distribution of seeds in the monolayer implant surface are all determinants of dose. Since the seeds are permanently implanted, as the implantation time increases, in addition to the decay of the seed's activity, the target volume also changes. After the first verification plan, the doses formed by the seeds and the target volume are both In the event of a change, will the changed dose still be within the effective therapeutic dose range? There are relatively few studies on later dose assessment, we evaluated the dose parameters in different periods within six months after implantation, and explored the trend of changes and the key factors causing the changes of dose parameters, so as to provide a reference for preoperative planning for more accurate implantation of seeds in spatial distribution and number.

Methods: With the brachytherapy treatment planning system, a treatment plan or verification plan was made for each patient at the time points of pre-implantation, the day after implantation, and the first month, third month, sixth month. The target volume size (V), dose parameters D_{90}, D_{100}, V_{90}, V_{100}, V_{150}, etc. in each patient's plan in different periods were counted. The average value of each dose parameter in each period under all samples was taken, and the changes of dose parameters at different time nodes were counted.

Results: With the increase of the implantation time, the target volume of tumor showed a decreasing state (k=-4.1±0.6, k is the slope value of the fitted line), and the volume shrinkage in 1~3 months (k=-6.8±0.7) was significantly higher than that in the later 3~6 months (k=-3.5±0.3) (P=0.007). Besides, the deviation of the dose parameters value from the standard dose value of the preoperative plan was lower in the first 3 months (D_{90}:14.1±2.3%; D_{100}:45.2±12.7%; V_{90}:17.6±4.1%; V_{100}:18.1±3.3%; V_{150}:20.4±5.2%), but there was a significant dose drop in the next three months (D_{90}:66.3±17.7%; D_{100}:80.5±11.3%; V_{90}:62.3±9.1%; V_{100}:66.4±23.3%; V_{150}:90.4±5.7%).

Conclusions: In the first three months, increase in dose parameter value due to decrease in seed spacing as target volume decreases was slightly smaller than the decrease caused by the attenuation of the seed dose rate, and the overall downward trend of the dose parameter was low, the radiation dose can still be maintained within the effective therapeutic dose range. In addition, the third month can be used as a time node to evaluate the quality of 125I seed implantation surgery.

Keywords: 125I seed, brachytherapy, dose

EP08.05 METASTATIC NON-SMALL CELL LUNG CANCER - PALLIATIVE RADIOTHERAPY

EP08.05-004 The Optimal Intervention Timing of Hypofractionated Stereotactic Radiotherapy for EGFR Mutated NSCLC Patients with Limited Brain Metastases

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Introduction: Tyrosine kinase inhibitors (TKIs) plus stereotatic radiosurgery/hypofractionated stereotactic radiotherapy (SRS/HSRT) are a common treatment strategy for epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer (NSCLC) patients with limited brain metastases (BMs). However, for patients who eventually receive both TKIs and brain radiotherapy, the optimal intervention timing of radiotherapy is not clear. We performed this retrospective analysis aimed to partly solve this problem.

Methods: Totally 84 EGFR-mutated NSCLC patients with limited BMs received both TKIs and HSRT, whether at the time of initial diagnosis of brain metastases (upfront HSRT), intracranial lesion volume had no further decrease during two contiguous MRI detections (consolidative HSRT), or intracranial disease progression (salvage HSRT), were enrolled. The clinical efficacy and toxicities were evaluated.

Results: The median intracranial and overall progression-free survival 1 (iPFS1 and PFS1, starting from the initiation of radiotherapy) of all patients was 17.5 and 13.1 months, respectively. The median iPFS2 and PFS2 (starting from the initiation of TKI treatment) of all patients were 24.1 and 18.4 months, respectively. Upfront HSRT improved iPFS1 (not reached vs. 17.5 months vs. 11.0 months, p<0.001) and PFS1 (18.4 months vs. 9.1 months vs. 7.9 months, p<0.001) compared to consolidative and salvage HSRT and reduced the initial intracranial failure rate (12.5% vs. 48.1% vs. 56%, p<0.001). However, for iPFS2 and PFS2, there were no significant differences between the three groups. The cerebral radiation necrosis (CRN) rate of all patients was 14.3%. The CRN incidence rate was lowest in the consolidative HRST group (3.6%), followed by the savage HRST group (16%) and was highest in the upfront HRST group (21.9%), although there was no statistical significance among the groups (p=.124). Hepatic metastases and Ds-GPA at 2-3 were poor prognostic factors for survivals.

Conclusions: Upfront HSRT improved the intracranial response duration starting from the initiation of radiotherapy and reduced the initial intracranial failure rate. However, for patients who received both TKIs and HSRT, the intervention timing of HSRT did not seem to influence the eventual therapeutic effect. Further validation in prospective clinical studies is needed.

Keywords: Brain radiotherapy, Oligometastases, Non-small-cell lung cancer

EP09.01 NURSING AND ALLIED HEALTH PROFESSIONALS

EP09.01-001 International Collaboration for Thoracic Oncology Education

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Introduction: The International Thoracic Oncology Nursing Forum (ITONF) is an international lung cancer nursing organization with a mission to educate nurses around the world about caring for patients with thoracic cancers. The mission of ITONF is accomplished through educational workshops, online educational modules and networking opportunities.

Methods: During 2020-2021 ITONF had been collaborating with the Mersal Cancer Center in Egypt to provide an educational program to educate Egyptian oncology nurses on the latest treatments in thoracic cancers as well as nursing management strategies. This was based on a regional need's assessment. Due to the COVID pandemic, as well as practical needs, a hybrid delivery was required. ITONF developed 5 learning modules to meet identified needs. Educational modules with detailed slides were pre-recorded and presented to the Egyptian nurses during an educational conference.

Results: A total of 18 Egyptian nurses and social workers attended the conference. Participants viewed the 5 educational modules, each covering a different topic about lung cancer. On the final day of the conference, 3 ITONF presenters joined the conference via Zoom for a live question and answer session. One Egyptian nurse was present to translate questions and facilitate an interactive discussion. During the question and answer session, expert international thoracic oncology nurses from the United States and Australia were able to provide valuable nursing education and answer questions. The Egyptian nurses submitted feedback after the completion of the conference with positive results and constructive feedback. Also, several nurses joined the ITONF organization and have since attended ITONF virtual webinars.

Conclusions: ITONF serves as a unified source of international thoracic oncology nurses eager to provide education to any country or organization using a robust educational program. The collaboration with the Mersal Cancer Center in Egypt was the first customized educational program to fit the needs of the Egyptian nurses. During the pandemic, when in person educational opportunities were limited, ITONF collaborated internationally to meet the needs of thoracic oncology nurses. Based on the positive feedback, ITONF feels that this effort can be replicated for other countries and cancer centers. A hybrid educational model of live meetings, recordings, and live-streaming education is a practical model for international oncology nursing education.

Keywords: ITONF, Mersal Cancer Center, Collaboration

EP09.01 NURSING AND ALLIED HEALTH PROFESSIONALS

EP09.01-002 Patient with Immune-associated Dermatomyositis Caused byAdvanced NSCLC Treated with ICIs

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Introduction: In recent years, immune checkpoint inhibitor (ICI) has made breakthrough progress in the treatment of NSCLC, and the immune-related adverse events (irAE) mediated by it have attracted the attention of researchers. There are few case reports related to treatment and nursing in the world, and clinical experience is limited.

Methods: Anti-PD-1 antibody 200 mg intravenously, along with oral anrotinib 12 mg/d for 14 days, 24 days for 1 cycle and then readmitted to the hospital, day 2 laboratory blood biochemistry results showed: ALT 83.90 U/L, AST 483.50 U/L day 6 of admission, the patient's liver function continued to be poor, follow-up cardiac enzymes showed. Creatine kinase 7678.40 U/L, creatine kinase isoenzyme 132.70 U/L, myoglobin >1200.0 ng/mL, and the patient had muscle weakness and pain in the extremities and generalized skin flushing, consistent with the characteristics of irAEs, and was considered IMDM with grade IV and potentially life-threatening at any time after an in-hospital multidisciplinary consultation. High-dose methylprednisolone sodium succinate (methylprednisolone) shock therapy was immediately administered for 6 days. The results of liver function and cardiac enzyme-related indexes were repeated, suggesting significant improvement compared with before, so methylprednisolone was gradually reduced, and the grade was changed to persistent grade IV IMDM, which was considered to be definitely related to anti-PD-1 antibodies and possibly related to Anrotinib hydrochloride, so the anti-PD-1 antibodies and Anrotinib hydrochloride capsules were permanently discontinued. On the 15th day of admission, the patient developed oral and pharyngeal pain, viscous sputum with white film formation, and sputum culture showed white Pseudomonas aeruginosa, which disappeared after 6 days of aggressive antifungal treatment. The investigator and team proposed a clear care plan after discussion, and after targeted care, the patient was discharged on day 22 of admission with improvement in all symptoms, signs and laboratory tests.

Results: While doing basic care, strengthen early identification, early reporting, early treatment and continuous monitoring, skin care, medication care for complications, psychological care, rehabilitation guidance and discharge health guidance, and timely diagnose and treat diseases and prevent related complications for doctors provide evidences and help to improve the treatment rate of NSCLC patients.

Conclusions: The onset of irAEs is insidious, lacks specificity, and has a wide spectrum of toxicity, which requires effective management by medical staff to effectively control the patient's condition, which can provide a certain reference for clinical care of irAEs.

Keywords: NSCLC, Immune checkpoint inhibitors, Care

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-001 Hypofractionated Stereotactic Radiotherapy for Brain Metastases in Lung Cancer: Dose-Response Effect and Toxicity

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Introduction: Lung cancer is the main cause of brain metastases. For patients with limited brain metastases, hypofractionated stereotactic radiotherapy (HSRT) has been proven feasible. However, the optimal dose schedule of HSRT remains inconclusive. Our research aims to investigate the dose response and toxicity in patients treated with HSRT.

Methods: A retrospective analysis was performed of patients treated with HSRT for 1-10 brain metastases at Hangzhou cancer hospital from January 1, 2019 to January 1, 2021. All patients were simulated with thin-cut (1-1.5 mm) CT of the brain fused with gadolinium-contrast-enhanced axial 3-dimensional T1-weighted MRI. Gross tumor volume (GTV) included all contrast-enhancing brain metastases. The planning target volume (PTV) was created by adding a 3 mm margin to the GTV. All patients were followed with MRI every 3 months after HSRT. 1-year local failure (LF) rate and intracranial progression-free survival (iPFS) were estimated using Kaplan-Meier method. The adverse radiation effect (ARE) was evaluated according to the criteria of the CTCAE 5.0.

Results: 48 lung cancer patients with 77 brain metastases were reviewed, including 33 adenocarcinoma, 7 squamous cell carcinoma, 6 small cell carcinoma, 2 other histologic types. Among them, 16 received chemotherapy, 23 received targeted therapy, 9 received Immunotherapy concurrently with HSRT. The median BED_{10} (biological effective dose with an alpha/beta of 10Gy) was 48 (range,37.5-72) Gy. Median follow up was 10 months. The median maximum diameter and volume of brain metastases were 1.3 (range,0.6-4.0) cm and 2.4 (range,0.2-16.7) cm^3. The median iPFS was 7.5 (range, 2-16) months. The 1-year LF rate of all lesions was 15.6%, with 20.5% for patients with BED_{10}≤48Gy vs. 10.5% for patients with BED_{10}>48Gy. LF rate was higher in patients with a BED_{10} of≤48Gy (*P*=0.168, Fig1). Neither the histologic tumor type nor systemic therapy had a significant effect on the local control rate. The rate of all grade ARE was 27%. Among 13 patients of ARE, 69.2% were occurred within 6 months after HSRT (median 5.8 months). The most common ARE was headache (53.8%), others include localized edema (15.4%), nausea (15.4%), hearing loss (7.7%), ataxia (7.7%), memory impairment (7.7%). All AREs were grade 1-2 except for 2 patients with a BED_{10} of 72Gy who experienced grade 3 headache.

Conclusions: Increasing the total dose of HSRT for brain metastases is expected to improve the local control, but at the same time, the occurrence of side effects should also be careful.

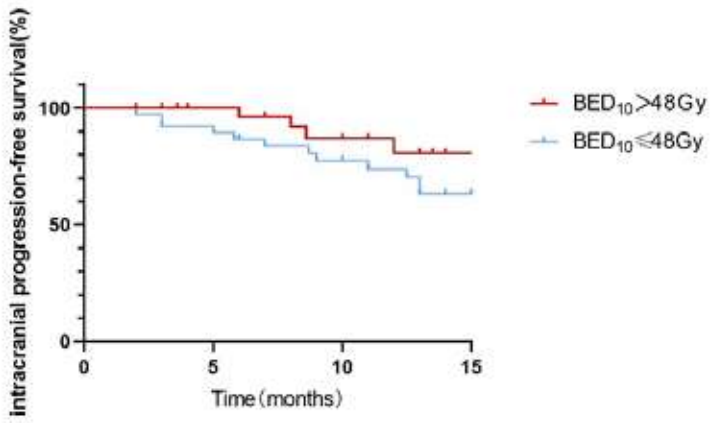

Figure 1 Kaplan-Meier methods were used to estimate local control probability.

Keywords: hypofractionated stereotactic radiotherapy, brain metastases, lung cancer

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-002 The Effect of Group Rehabilitation Training in the Ward on the Psychological Status and Quality of Life of Lung Cancer Patients

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Introduction: The progression of lung cancer disease causes patients to suffer from frequent and severe coughing, fatigue and poor sleep quality. Patients are often worried about the recurrence of the disease and are unable to take care of family responsibilities, resulting in a very high rate of anxiety and depression among lung cancer patients, which in turn severely affects their quality of life and reduces their survival rate.

Methods: Seventy-eight lung cancer patients admitted from January 1 to October 31, 2021 were randomly divided into a control group and an observation group, 39 patients each. The control group was given conventional nursing interventions and the observation group was given ward group rehabilitation training according to conventional nursing interventions; patients in the observation group signed an informed consent form and underwent ward group rehabilitation training from Monday to Friday, the rehabilitation training video was displayed on the screen in the comprehensive lobby and the group rehabilitation training was conducted under the guidance of three specialist nurses.

Results: After 2 weeks of group rehabilitation, the scores of somatization, obsessive-compulsive disorder, interpersonal relationship, depression, anxiety, hostility, fear, paranoia and psychosis were lower in the test group than in the pre-intervention group and the control group ($p<0.05$)

Conclusions: Through group rehabilitation training, the communication between patients is strengthened, which helps to break the barriers within the patients to a certain extent, promotes the communication between patients and the outside world, improves the psychological state of patients, increases the level of hope for recovery and psychological resilience of patients in the face of the disease to improve their quality of life.

Time	Content	Place	Object
08：10-08：13	The breathing exercise, lasting 3 minutes.	First Floor Lobby	Enhances the patient's lung function and reduces symptoms of respiratory distress.
08：13-08：17	Rehabilitation exercises for the arms, lasting 4 minutes.	First Floor Lobby	It is used to prevent thrombosis caused by PICC catheterization and increase the flexibility of fingers, wrists, elbows, and shoulder joints.
08：17-08：21	Aerobic training: gymnastics	First Floor Lobby	Carry out whole-body training to enhance the body's endurance and coordination ability, and require patients to exercise according to their own conditions.
15：00-15：15	Complete about 1180 steps of training around the *15-minute fitness	Streets outside the tumor center	Enhance patient endurance.

Keywords: rehabilitation training, psychological, quality of life

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-003 Non-Small Cell Lung Cancer Treatment Preferences Among EGFR Mutation Patients and Physicians in Japan

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Introduction: Novel EGFR inhibitors are under development and would provide more options for *EGFR* exon 20 insertion mutant non-small cell lung cancer (NSCLC) patients, whose treatment options have been limited due to low treatment response of EGFR TKIs such as erlotinib, gefitinib, afatinib, and osimertinib. The candidate inhibitors vary across several attributes including method and frequency of administration, efficacy, side effects, mutation test requirements, and out of pocket cost. There is limited evidence available on Japanese patient and physician preferences that consider the attribute profiles of exon 20 insertion mutation treatments that are currently under development. The key purpose of this study was to quantitatively examine treatment preferences for NSCLC treatments among an *EGFR* positive mutation cohort using a choice-based elicited preference survey. The features and levels included in the survey were reflective of the range of treatment profiles for NSCLC *EGFR* therapies, incorporating attributes of novel NSCLC *EGFR* exon 20 insertion mutation therapies. Incorporating patient and physician preferences into health care decision making is becoming increasingly important throughout frameworks for optimising cancer care and this study will provide insight on preferences which will benefit for patient-centered treatment choice.

Methods: This study consisted of two phases. In phase one, 60-minute phone interviews were conducted with three patients with NSCLC who are *EGFR* positive and three physicians who treat NSCLC patients. All physicians had experience with exon 20 insertion treatment. In phase two, a 20-25-minute online quantitative survey including a choice-based experiment known as a Discrete Choice Experiment (DCE) was conducted with a target of 60 patient and 60 physician participants. The attributes derived from the first phase and investigated in the choice experiment included; mode and frequency of administration, chance of response, progression-free survival, chance of experiencing mild-moderate gastrointestinal side effects, chance of experiencing mild-moderate skin-related side effects, chance of experiencing any severe side effects and yearly out of pocket cost. All participants were over the age of 18 and fluent in Japanese. This study was approved by Non-Profit Organization MINS Institutional Review Board (JS2021-29266).

Results: Based on preliminary findings, the results indicated that attributes of value among patients and physicians include progression-free survival, likelihood of treatment response, and chance of experiencing severe side effects (in order of importance). Other attributes also significantly impacted choice, but with less importance. Compared to the strong preference for a more efficacious drug, the preference of oral vs. IV was slight.

Conclusions: Results from this study demonstrates what Japanese physicians and patients prefer in treatment options for *EGFR* mutation NSCLC in Japan. Understanding how different stakeholder groups value treatment attributes, and where they are aligned or differ, facilitates a prioritisation of intervention strategies to align with the goals and preferences of those making treatment decisions. In addition, this evidence can potentially be used by healthcare decision makers in health technology assessment to incorporate the patient perspective into the decision context.

Keywords: NSCLC EGFR mutation, Exon 20 insertion, Preference

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-004 Perspectives of Patients with Metastatic Lung Cancer on Symptom Screening and Patient-Reported Symptom Trajectory Data

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Introduction: Symptom screening and collection of patient-reported outcome (PRO) data are increasingly prevalent in the care of patients with metastatic non-small cell lung cancer (mNSCLC). We explored the perspectives of patients with mNSCLC on symptom screening and utilization of symptom trajectory PRO data for patient education.

Methods: Ten patients with mNSCLC were selected by convenience sampling at a Canadian tertiary cancer centre to participate in a qualitative study. Baseline participant and treatment characteristics were obtained via chart review. Semi-structured interview guides were designed by a multidisciplinary team of lung cancer and PRO investigators. One-on-one interviews were conducted with each participant by two investigators. Interviews were audio-recorded and transcribed verbatim. Anonymized transcripts underwent inductive coding by two investigators and thematic content analysis was performed.

Results: Participants were 50% female and had a median age of 68 years (56-77). Sixty percent of participants had smoking histories. Median time since diagnosis was 28.5 months (6-72). The most common treatments were palliative radiotherapy (80%) and EGFR inhibitors (60%). Participants identified a knowledge gap regarding expected symptom trajectory through treatment and recovery. Participants sought symptom trajectory information from a variety of sources, including informational websites and informational documents from pharmaceutical companies as the most common sources. Seven themes were identified in total. Three themes were identified regarding symptom screening: 1) symptom screening is useful for symptom self-monitoring and disclosure to the healthcare team, 2) symptom screening tools are variably utilized by participants and their healthcare providers, and 3) screening of additional quality-of-life domains (smoking-related stigma, sexual dysfunction, and financial toxicity) is commonly desired. Four themes were identified regarding symptom trajectory PRO data for patient education: 1) symptom trajectory data provide reassurance and motivation to improve symptoms, 2) symptom trajectory data should be disclosed after an oncologic treatment plan is developed, 3) symptom trajectory data should be communicated via in-person discussion with accompanying patient-education resources, and 4) communication of symptom trajectory data should include reassurance about symptom stabilization, acknowledgement of the variability in patient experience, and strategies to improve symptoms.

Conclusions: Symptom screening tools require more standardized utilization and should include common quality-of-life concerns of patients with mNSCLC. Symptom trajectory PRO data derived from routine screening should inform novel knowledge translation tools to satisfy an unmet need for patient education.

Keywords: Patient Reported Outcomes Measures, Qualitative Research, Patient Education as Topic

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-005 Australian Lung Cancer Survivors Experiences of Novel Treatments, Healthcare, and Ongoing Physical and Psychological Needs

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Introduction: People living with lung cancer remain underrepresented in survivorship research largely because of poorer survival rates and a focus on acute illness. However, earlier detection and improved treatments, such as immunotherapy (IO) and targeted therapy (TT), have led to higher numbers of individuals living longer. Given the profound impact lung cancer and treatments can have on physical and psychological wellbeing, understanding post-treatment experiences of survivors is crucial. In 2019, our group published a meta-review of the qualitative cancer survivorship literature and found a paucity of evidence about *lung cancer* survivor's experiences. This study aimed to understand lung cancer survivors' ongoing physical/psychological challenges, healthcare experiences (including IO/TT), and coping/adjustment strategies.

Methods: Adults treated for lung cancer were recruited 3-24 months post-initial active treatment completion through their ongoing participation in an Australian lung cancer clinical cohort study (Embedding Research (and Evidence) in Cancer Healthcare - EnRICH Program). Participant demographic, clinical, quality of life (EORTC-QLQ-C30) and distress (NCCN-Distress-Thermometer) data were obtained through the EnRICH database. Participants completed qualitative telephone interviews, analysed using Framework methods.

Results: Twenty interviews were conducted, with 10 male/10 female survivors. Participants were an average of 69 years (30-84 years). Stage of disease at diagnosis was: Stage I=2, Stage II=4, Stage III=8, and Stage IV=6. Of those diagnosed with Stage I/II, two reported subsequent disease progression. Histological type was 18 NSCLC and 2 SCLC. The majority had received a novel therapy such as IO (n=10) or TT (n=4). Most survivors were living with 2≥ other chronic health conditions (n=14). Qualitative analysis revealed three themes. *Theme 1: Living with Symptoms and Side Effects:* Most participants reported functioning well despite ongoing physical effects. Those treated with newer therapies (IO/TT) reported common (e.g. rash, fatigue, pain), serious (e.g. endocrine dysfunction) or unexpected side effects. For many, these were considered tolerable given perceived treatment success. Given the novelty of IO/TT, there was uncertainty about the trajectory/treatment of side effects. *Theme 2: Hope and Struggle:* Most survivors expressed hope for the future whilst simultaneously preparing for disease progression. For some, fear of progression and lost physical abilities caused sadness and anxiety. Uncertainty was compounded for survivors receiving IO/TT, given limited long-term survival information. Participants described adjustment and coping strategies, such as remaining present-focused, deriving meaning/distraction from hobbies, and spirituality. *Theme 3: Interacting with the health system:* Participants valued coordinated care from their cancer team, particularly the specialist nurse coordinator. The role of their general practitioner (GP) into survivorship was unclear, with many reporting not having a GP knowledgeable about their cancer. Participants with multimorbidity described the overwhelming nature of juggling lung cancer with other conditions- some of which were caused or worsened by lung cancer treatments.

Conclusions: Results suggest many people with lung cancer cope relatively well in survivorship. Survivors expressed hope about novel treatments, despite the complexity/uncertainty surrounding side effects and effectiveness. Findings may help guide development of supportive care resources/interventions, particularly around areas of need for survivors including uncertainty, fear of progression, IO/TT side effects, survivorship care, and multimorbidity.

Keywords: survivorship, immunotherapy, psycho-oncology

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-006 Differences In Toxicity Among Platinum-Based Combinations As Reported By Non-Small Cell Lung Cancer (NSCLC) Patients

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Introduction: Platinum-based combinations constitute the backbone of chemotherapy in NSCLC. Furthermore, the regimens resulting from the addition of immunotherapy are considered the state of the art in treating advanced disease. Different platinum analogues are considered to exhibit similar activity; however, toxicity may differ. In an effort to identify these differences, we collected NSCLC patients' reported data on side-effects.

Methods: Lung cancer patients using the CareAcross personalised and multilingual online support platforms from 8 countries (in the Americas, Europe and Asia) report their diagnoses, biomarkers, treatments, comorbidities, side-effects, among other data, through structured questionnaires. Treatments and side-effect data get reported by selecting among specific options.

As of March 2022, a total of 845 patients had reported treatment regimens, and responded to the side-effects questionnaire at least once. The analysis focused on treatment combinations with options considered at clinicians' discretion.

Results: Most of the treatment combinations analysed exhibited similar safety profiles. Patterns of differences were identified between combinations that included cisplatin vs carboplatin, across the 9 most common side-effects.

Pembrolizumab combinations included cisplatin vs carboplatin in 31 vs 37 patients, respectively. Among these, patients receiving cisplatin generally reported the least side-effects. Specifically, the frequency of toxicity reported for pembrolizumab-cisplatin based combinations was lower for the following side-effects: fatigue, breathlessness, sleeping problems, rash & dry skin, dry mouth, constipation, food taste issues and appetite loss. The only exception was cough.

Pemetrexed combinations included cisplatin vs carboplatin in 56 vs 49 patients, respectively. In general, the least side-effects were reported by patients on cisplatin- compared to carboplatin-based treatment: fatigue, breathlessness, sleeping problems, dry mouth, constipation, food taste issues and appetite loss. However, cisplatin reportedly led to marginally more cough, and rash & dry skin.

(Please refer to the below Table for reported incidence rates.)

Incidence rate of side-effects per treatment combination										
Pembrolizumab + platinum	**N**	**Fatigue**	**Cough**	**Breathlessness**	**Sleeping problems**	**Rash & dry skin**	**Dry mouth**	**Constipation**	**Food taste issues**	**Appetite loss**
Pembrolizumab + Cisplatin	31	77%	58%	39%	36%	36%	32%	23%	19%	16%
Pembrolizumab + Carboplatin	37	92%	51%	57%	41%	38%	38%	46%	41%	32%
Pemetrexed+platinum	**N**	**Fatigue**	**Cough**	**Breathlessness**	**Sleeping problems**	**Rash & dry skin**	**Dry mouth**	**Constipation**	**Food taste issues**	**Appetite loss**
Pemetrexed + Cisplatin	56	71%	48%	32%	30%	36%	30%	25%	20%	23%
Pemetrexed + Carboplatin	49	86%	47%	47%	41%	33%	39%	41%	35%	29%

Conclusions: Real world data from patient-reported outcomes of toxicity indicate that cisplatin-based combinations are better tolerated than carboplatin-based ones. These findings may guide more personalised treatment decisions, incorporating patient status, preferences, comorbidities and other factors. Prospective randomised clinical studies with larger patient populations can lead to more substantial evidence bases.

Keywords: immunotherapy, platinum, toxicity

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-007 Real World Data Comparing Lung Cancer Side-Effects Between Past/Current Smokers And Never Smokers

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Introduction: Although the relationship between smoking and lung cancer has been documented, lung cancer side-effects reported by patients have not been adequately correlated with their history of smoking. This analysis aimed to compare lung cancer patients' quality of life between those who smoked before their diagnosis and those who did not.

Methods: Lung cancer patients who use the CareAcross online platform have the opportunity to provide information about their daily habits and quality of life, and receive personalised support. In March 2022, data from patients from 8 countries, who had entered information on their smoking history and responded to side-effect questionnaires, was deidentified, extracted and analysed to identify correlations.

Results: 664 patients reported having been smokers before their lung cancer diagnosis (past or current smokers). Of the 649 who reported their smoking habits after diagnosis, 542 (84%) quit smoking (past smokers).

471 of the 664 past or current smokers, and 359 never smokers, also reported side-effects.

The side-effect incidence rates of past or current smokers ranged from 4% to 74%, and those of never smokers from 3% to 67%.

Past or current smokers reported higher incidence than never smokers for almost every side-effect. The difference was calculated to be statistically significant ($p<0.05$) for fatigue (74% vs 67%), breathlessness (49% vs 38%) and appetite loss (30% vs 23%). Differences between sleeping problems (39% vs 33%) and pain (35% vs 29%) were calculated as only marginally significant.

Other frequent side-effects with the same pattern included cough, dry mouth and constipation.
The only common side-effect (>=20%) with the inverse correlation was rash/dry skin.

(Please refer to the Table for details on the most common side-effects.)

Incidence of side-effect per smoking status before diagnosis			
Side-effects	**Among smokers before diagnosis (N=471)**	**Among non-smokers before diagnosis (N=359)**	**p value**
Fatigue	74%	67%	0.03
Breathlessness	49%	38%	0.002
Cough	48%	44%	0.22
Sleeping problems	39%	33%	0.06
Pain	35%	29%	0.05
Dry mouth	34%	32%	0.53
Constipation	34%	31%	0.49
Appetite loss	30%	23%	0.04
Rash / dry skin	28%	31%	0.25
Feeling full quickly	26%	24%	0.52
Nausea	26%	21%	0.09
Food taste issues	25%	23%	0.37
Diarrhea	22%	20%	0.48

Conclusions: Smoking cessation after a lung cancer diagnosis is broadly acknowledged as beneficial for patients' outcomes. Although patient-reported cessation efforts approach satisfactory levels, even better results are feasible.

Past or current smokers with lung cancer report consistently higher incidence of side-effects compared to never smokers. This is particularly evident in many of the most common ones such as fatigue, breathlessness and others, reaching statistical significance in some.

Personalised support activities based on smoking history and habits (with due consideration to relevant stigma concerns) may help improve patients' quality of life.

Keywords: smoking, side-effects, quality of life

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-008 Examining Social Determinants of Health Among Newly Diagnosed Lung Cancer Patients Contacted for Early Specialist Palliative Care Consultation

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Introduction: Timely palliative care interventions can help to alleviate the distress people experience after diagnosis of an incurable, life-threatening cancer. However, referrals to palliative care are often late and inequities have been described across sociodemographic groups. The Palliative Care Early and Systematic (PaCES)-Automatic study was co-designed with patients and providers. It provides an automatic early palliative care intervention triggered by pre-determined clinical criteria, without the need for formal clinician referral, for automatically offering an early supportive and palliative care (SPC) consultation to all patients newly diagnosed with stage IV non-small cell lung cancer (NSCLC). We sought to describe and compare the demographic characteristics of patients/caregivers who accepted or declined the offer of consultation.

Methods: This is a descriptive analysis of data evaluating a patient-provider co-designed, automatic palliative care referral pathway in a tertiary cancer centre. Two SPC nurses screened out-patient clinic lists at a tertiary cancer center weekly and called all eligible patients to offer an in-home consultation. Eligibility: >18 years, newly diagnosed/suspected Stage IV NSCLC and had first medical/radiation oncologist visit. Patients/caregivers were surveyed about the acceptability (5-point Likert scale) of the automatic phone call offering a palliative care consultation and their demographics. Bivariate analysis of demographic factors with rates of acceptance was conducted.

Results: Of 81 patients/caregivers who were contacted by the SPC specialist nurses and offered the consultation, 72% accepted. 70 patients/caregivers agreed to be contacted for a follow-up survey about the acceptability of receiving a call offering a consult. Of these, 4 did not recall the call offering SPC, 3 declined participating in the survey, and 15 could not be reached. In the end, demographics were collected for 35 patients/caregivers that completed the full survey. 80% of these patients/caregivers accepted the consult. Demographic comparisons amongst those who accepted the consult (compared to those who declined) revealed: 67.9% female (vs. 42.9% female amongst those who declined), 53.6% ≤65 years (vs. 71.4% declined), 32.1% ≤ high school education (vs. 14.3% declined), 61.9% <$60,000 household income (vs. 33.3% declined), 82.1% spoke only English/French (vs. 71.4% declined), and 71.4% Caucasian (vs. 71.4% declined). In this small sample, no statistical differences were seen between those who accepted or declined the palliative care consultation.

Conclusions: In this study offering SPC consultation routinely to all patients, there was no statistical differences in demographic factors in those who accepted compared to those who declined the consultation offer. It is important to identify and address inequities in cancer and palliative care service utilization. Routine calls offering SPC consultation are one way to ensure all patients are offered access to supportive and palliative services. The next steps in this study are to compare demographic characteristics through chart review of the larger cohort of patients originally identified by the SPC specialist nurses of those who accepted or declined the consultation.

Keywords: early palliative care, supportive care, equity in care

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-009 The Impact of the COVID-19 Pandemic on Palliative Care for Cancer: A Preliminary Cross-Country Survey of Clinical Oncologists

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Introduction: Palliative care is a crucial intervention to improve the quality of life for patients with cancer, although the impacts of the COVID-19 pandemic on palliative care remain unclear. This preliminary survey across China aims to investigate the influence of COVID-19 on palliative care, from the perspective of oncologists.

Methods: Electronic questionnaire surveys were distributed to clinicians in China. Participants working in cancer-related departments are eligible. Data was collected including demographic characteristics, subjective perception, and personal suggestions.

Results: A total of 37 oncologists participated in the survey, 78% of whom were male. The median age was 40 (22-56). A large proportion of them have doctor degrees (68%) currently working in urban areas (81%). One-third participants are from the department of radiation oncology (33%) and 24% from medical oncology. They usually practice palliative care in professional medical centres or hospitals (70%), yet 57% had only non-accredited training experience. Most agree that COVID-19 has a significant negative impact on their clinical work (76%) and palliative care practice (65%). 73% of them believe the current palliative care system is underdeveloped in China, and 78% think other factors besides COVID-19 relate to this inadequacy. Participants further tabled suggestions (**Figure 1**), such as more online guidance on palliative care for patients (35%), strengthening remote multidisciplinary cooperation (29%), promoting home-based palliative care (18%), and involving more information on COVID-19 in palliative care guidelines (6%).

Conclusions: The COVID-19 pandemic has a significant negative impact on palliative care for cancer, whereas other factors cannot be overlooked. The corresponding measures should be taken to improve clinical practice of palliative care during COVID-19.

Figure 1. Suggestions from oncologists on how to encourage palliative care during the COVID-19 pandemic

Keywords: Palliative care, COVID-19, Cancer

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-010 Real-world Study of the Incidence and Risk Factors of Venous Thromboembolism in Chinese Lung Cancer (RIVAL)

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Introduction: Patients with lung cancer have high incidence of venous thromboembolism (VTE), which might aggravate the overall survival. This prospective real-world study aims to investigate the incidence of VTE and determine the VTE-high-risk population of lung cancer.

Methods: Patients clinically diagnosed with lung cancer providing written informed consent was enrolled. Clinicopathological characters, complete blood count, comprehensive metabolic panel and liver function at baseline and following anti-cancer treatments were recorded. Peripheral blood was drawn for detection of reportedly VTE risk related SNPs including ABO_EX7, MTHFR_R677, ABO_IN1, FGG_3UT, ABO_IN2. All patients were followed up until occurrence of VTE or termination of trial.

Results: From 2018-7-19 through 2020-03-31, there were 1051 patients under screening and totally 985 eligible patients were enrolled onto analysis by excluding 41 benign disease and 25 non-lung cancer malignant disease, with median age 63y (18 - 94y), male 649 (65.9%), stage I-III 218 (22.1%) and stage IV 767 (77.9%). Pathology included 670 (68.0%) adenocarcinoma, 126 (12.8%) squamous cell carcinoma, 105 (10.7%) small cell lung cancer and 84 (8.5%) others, which contained 19 lymphoepithelioma-like carcinoma, 9 adenosquamous cell carcinoma, 9 large cell carcinoma, 9 sarcomatoid carcinoma, 3 sarcoma, 3 endocrine carcinoma, 3 spindle cell carcinoma, 1 mucoepidermoid carcinoma, 8 non-small cell lung cancer not otherwise specified (NOS), 6 lung cancer NOS, and 14 cases diagnosed with lung cancer by symptoms and radiology. Multivariate analysis by logistic regression included possible VTE risk factors found by univariate analysis, which were age (>=75y *vs* <75y), overweight (body mass index ≥25 *vs* <25), ABO blood type (A *vs* B *vs* AB *vs* O), SNPs mentioned above (mutation *vs* wild type), bone metastasis (*vs* not), Serous effusion (*vs* not), anti-angiogenic therapy (*vs* not), pathology (adenocarcinoma *vs* squamous cell carcinoma vs small cell lung cancer *vs* others), driving mutation (mutant *vs* wild type), PS (0-1 *vs* >=2), elevated white blood cells (WBC) (*vs* normal), hypoalbuminemia (*vs* normal), and clinical stage (1-3 *vs* 4). It was revealed that VTE risk factors were overweight (OR, 2.326; 95%CI, 1.175 - 4.604; *P*=0.015), AB blood type (3.308; 1.290 - 8.487; 0.013), bone metastasis (1.953; 1.041-3.667; 0.037), anti-angiogenic therapy (2.727; 1.447 - 5.138; 0.002) and elevated WBC (2.180; 1.089 - 4.366; 0.028).

Conclusions: In lung cancer patients VTE risk factors include overweight, AB blood type, bone metastasis, receiving anti-angiogenic therapy, and elevated WBC.

Keywords: lung cancer, venous thromboembolism, risk factor

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-011 Prognostic Impact of Body Composition Phenotypes in Non-small Cell Lung Cancer Patients Receiving First-Line Pembrolizumab

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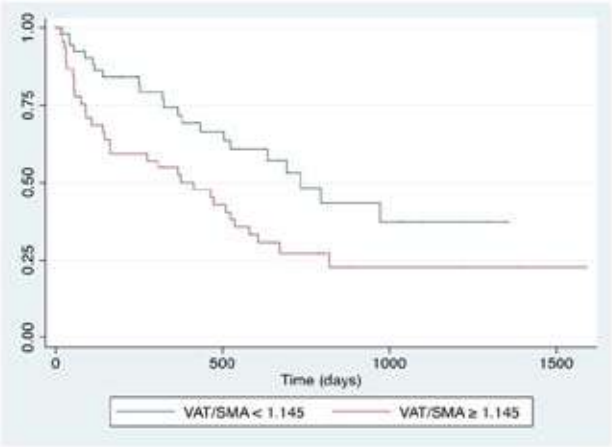
Introduction: The recent successes of immunotherapy have shifted the paradigm in lung cancer treatment. Only a percentage of patients are responsive to immunotherapy, thus, it is imperative to identify factors impacting outcome. Body composition phenotypes may reflect aspects of patients' immunology and thereby their ability to respond to immunotherapies. Therefore, our study aimed to describe the pre-treatment body composition profile of patients and explore the possible associations between these parameters and clinical outcomes in non-small-cell lung cancer (NSCLC) patients receiving first-line Pembrolizumab monotherapy.

Methods: A retrospective review of consecutive advanced NSCLC patients treated with Pembrolizumab as first-line therapy at two academic medical institutions from August 2017 to October 2021 was performed. The estimation of skeletal muscle and adipose tissue were performed using pre-treatment computed tomography scans at the level of the third lumbar vertebra, obtaining Skeletal Muscle Area (SMA), Intermuscular Adipose Tissue (IMAT, Subcutaneous Adipose Tissue (SAT), and Visceral Adipose Tissue (VAT). Data were correlated to progression-free/overall survival (PFS/OS) using a Cox and logistic regression model. Log-Rank analysis was used for Kaplan-Meier curves comparison.

Results: Data from 102 patients (median age: 68 years [range 36-85]; median follow-up: 12 months [range 1-131]) were collected. More than a quarter of the patients were overweight or obese. Overall, 52% and 58.8% of patients met established radiographic criteria for evidence of sarcopenia and myosteatosis, respectively, which occur across the BMI spectrum. Sarcopenia and myosteatosis were at significantly higher frequencies in patients with poor performance status (80% vs 48.2%, *p = 0.01* and 81% vs 61.5%, *p = 0.041,* respectively*)*. Median OS was 17.2 months; higher SAT (HR 1.01, 95% CI 1.00-1.02; p=0.017) and higher VAT/SMA ratio (HR 1.48, 95% CI 1.07-2.05; p=0.016) were significantly associated to OS. A ROC curve was constructed to obtain a VAT/SMA ratio cut-off for OS (Figure).

Conclusions: These findings showed that pre-treatment skeletal muscle wasting was frequently present in NSCLC patients receiving pembrolizumab, in all BMI categories. Moreover, our preliminary results support the hypothesis that BC may impact on survival of these patients, suggesting a potential interaction between the immune system and BC. Further analyses are ongoing in this patients' cohort, to expand knowledge in this field combining clinical and biological factors with preclinical and analytic studies.



Keywords: immune-checkpoint inhibitor, non-small-cell lung cancer, body composition

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-012 Geriatric Assessment in Patients Undergoing Lung Cancer Surgery and Their Family Caregivers

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Introduction: Informal family caregivers (FCGs) play a vital role in supporting lung cancer patients. The majority of lung cancer patients are older adults and may face caregiving issues related to aging. Likewise, FCGs themselves are often older and may experience significant physical and psychological distress while caregiving. Multiple studies have demonstrated that geriatric assessments (GAs) help predict treatment complications and outcomes in cancer patients. However, there is limited data regarding GA for FCGs.

Methods: We are currently conducting a randomized controlled trial of a multi-media self-management intervention for patients undergoing lung cancer surgery and their FCGs. As part of the study, we perform baseline GAs of patients and FCGs before surgery. This is an interim analysis of the baseline GA measures. The validated GA includes the following self-reported measures: Instrumental Activities of Daily Living (IADL), Medical Outcomes Study (MOS) Physical Health Scale, MOS Social Activity Limitations Measure, MOS Social Support Survey, Karnofsky Performance Rating (KPS), Number of Falls in Last 6 Months, Older American Resources and Services Questionnaire Physical Health Section (OARS), and Percent Unintentional Weight Loss. The GA also includes the Blessed Orientation-Memory-Concentration Test (BOMC), which screens for cognitive impairment and Timed Up and Go (TUG), which measures functional mobility.

Results: A total of 122 patient and caregiver dyads have been enrolled. FCGs tended to be younger than patients (median age 64 vs 68, $p < 0.001$), but the majority of both groups (52% of FCGs and 61% of patients) were ≥ 65 years old. Even before surgery, patients had worse baseline scores than FCGs with lower KPS, worse physical functioning (MOS physical health scale), more comorbidities (OARS), and less social support (Table 1). FCGs also reported significant deficits in multiple measures, particularly social activity limitations and social support.

Baseline Geriatric Assessment of Lung Cancer Surgery Patients and Their Family Caregivers

Geriatric Measure	Patients (n=122)	FCGs (n=122)	P-value
Median age (years)	68	64	<0.001
% Female	51	58	0.37
IADL (± SD)	13.28 (1.59)	13.07 (1.07)	0.06
MOS Physical Health Scale (± SD)	76.7 (21.5)	87.1 (18.7)	<0.001
Social Activity Limitations (± SD)	31.9 (19.6)	59.1 (16.5)	<0.001
Social Support Survey (± SD)	59.6 (18.1)	77.3 (21.2)	<0.001
KPS (± SD)	94.3 (6.2)	97.4 (4.9)	0.005
TUG (seconds ± SD)	9.2 (4.2)	8.1 (2.7)	0.14
Number of Falls (± SD)	0.17 (0.69)	0.19 (0.48)	0.86
OARS (± SD)	2.2 (1.8)	1.27 (1.50)	<0.001
BOMC (± SD)	3.2 (3.8)	1.9 (2.8)	0.04
Percent Weight Loss (± SD)	5.5 (17.4)	1.16 (2.81)	0.13

SD = standard deviation. IADL is scored 0-14. MOS surveys and KPS are scored 0-100. For IADL, MOS physical health scale, social activity limitations, social support survey, and KPS, higher scores indicate better function. For TUG, OARS, and BOMC, higher scores are worse.

Conclusions: Lung cancer patients as well as their FCGs tend to be older and GA deficits are common. GAs for lung cancer FCGs may identify unique needs and concerns related to their caregiving role. Our ongoing study will correlate GA with FCG quality of life outcomes.

Keywords: Geriatric, Caregiver, Quality of Life

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-013 Erector Spinae Plane Block for Post-thoracotomy Analgesia; Comparison with Intercostal Block; Preliminary Results

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Introduction: Post-thoracotomy analgesia is an important issue, not only for maintaining analgesia but also for recovering respiratory mechanics. Many analgesic methods have been tried for this kind of surgery. Erector spinae plane block is relatively new method and new studies are coming up. This study is designed to compare the analgesic effects of analgesia provided by intercostal block to erector spinae plane block after thoracotomy.

Methods: Patients undergoing thoracotomy, ASAI-II, 18-75 aged were divided into two groups by sequential randomization. After the patients intubated with double lumen tube, anesthetic maintenance provided with desflurane %5-6, O2/air %50-50 and fentanyl 1mcg/kg every hour. For erector spinae plane block group (group I); after surgery an anesthesiologist placed the catheter to the erector spinae plane space after making erector spinae plane block. For intercostal catheter group (group II), the surgeon put the intercostal catheter to the intercostal place after performing the block. As the patient extubated, analgesic infusion started for both groups. The dose of analgesic is setted as total 400 mg/day for both groups. As a rescue analgesic, both groups had iv fentanyl pca. A blind anesthesiologist recorded the data for different times and activities. Both groups' catheters removed as the chest tube removed.The data is evaluated with one sample and independent sample t-test and chi-square if show normal distribution with Kolmogorov-Smirnov test.

Results: Both group showed similiar values for demographics. VAS values for Group II was lower compared to Group I but only at 48 and 72 hours aftersurgery showed significantly difference. Analgesic requirements were statistically lower in Group II when compared to Group I (p>0,005).

Conclusions: Post-thoracotomy pain is one of the most challenging problem for thoracic anaesthesiologists. Thoracic epidural analgesia is known as the best method for now but epidural analgesia may have systemic effetcs. Intercostal catheter may provide advantages about systemic effects besides analgesia. Erector spinae plane block is also an easy method and a promising way for analgesia. By catheter analgesia may be continued. When comparing these two methods ; where both are easy to apply and both don't have systemic effects But when compared according to these preliminary results; erector spinae plane block does not seem to improve analgesia. Still more studies needed to decide most effective way for post-thoracotomy analgesia.

Keywords: post-thoracotomy analgesia, erector spinae plane block, intercostal block

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-014 A Multidisciplinary Team to Manage Patients with Lung Cancer and Opioid Use Disorder

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Introduction: Many patients with cancer may have concomitant opioid use disorder (OUD) or non-medical opioid use (NMOU). Though the prevalence is not well characterized, patients with lung cancer may have higher prevalence of OUD related to known relationships with other substance use disorders including alcohol and tobacco. However, little is known about optimal ways to manage pain and reduce the risk of harm for these patients. Single center studies suggest multidisciplinary management may improve care though the optimal implementation and feasibility of this management is unknown.

Methods: We began one-hour weekly meetings with representatives from oncology, addiction medicine, palliative care, cancer survivorship, social workers, and pharmacists. Patients with current or prior cancer and any clinician concern for OUD or NMOU were referred to this team to develop interdisciplinary plans for comprehensive management. Team members then met individually or jointly with patients in clinical encounters to discuss and enact the plans with patient support. Patient demographics, OUD, and encounter information were abstracted from the medical record and evaluated using descriptive statistics.

Results: From September 2019 to Jan 2022, 88 patients were referred for interdisciplinary management. Of these, 29 (33%) had lung cancer and this was the most prevalent cancer type referred. Among patients with lung cancer and OUD or NMOU, the mean age was 60 (SD 13), 18 patients (62%) were female, and 25 patients (93%) were Black. 20 patients (69%) had stage IV disease, 6 patients (21%) had stage III disease, and 3 patients (10%) had stage I disease. 17 patients with lung cancer (59%) were referred for a diagnosis of OUD and the remainder referred for NMOU concern. Less than half of patients with lung cancer and OUD were taking medications for OUD at the time of referral, with 7 enrolled in a methadone clinic and 1 prescribed suboxone by a primary care physician.

Conclusions: The plurality of patients referred to a multi-disciplinary team for management of cancer, OUD, and NMOU had a diagnosis of lung cancer. Fewer than half of these patients were receiving treatment for OUD and opportunities exist to engage patients with lung cancer in OUD treatment and harm reduction across the disease spectrum.

Keywords: opioid use disorder, pain, supportive care

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-015 The Role of CT-Scan as a Body Composition Tool in Oncogene-Addicted Advanced Non-Small Cell Lung Cancer (aNSCLC) Patients

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Introduction: Sarcopenia causes shorter survival and severe treatment-induced toxicities in aNSCLC pts, including oncogene -addicted ones treated with tyrosine kinase inhibitors (TKIs). The CT-scan, routinely used in follow-up, may also be an additional tool for assessing body composition. The aim of the present study was to define an algorithm, combining radiological data with clinical parameters, in order to achieve early identification of malnourished patients with oncogene-addicted aNSCLC.

Methods: In oncogene-addicted aNSCLC pts (EGFR mutated or OTHER, including ALK, ROS1, BRAF addiction), a nutritional screening was performed at the beginning of TKIs therapy (T0). Handgrip score (Kg), 3-months weight loss (%), hemoglobin (gr/dl) were collected. With CT-scan, total adipose tissue (TFAT, cm^2), sum of subcutaneous adipose tissue (SFAT, cm^2), visceral adipose tissue (VFAT, cm^2), and muscle adipose tissue (MFAT, cm^2) were calculated. Lean compartment, defined as Muscle Area (MA, cm^2) at L3 level, was also detected. Correlations between the nutritional parameters and the radiological data were analysed using Mann-Whitney U and Spearman tests.

Results: 49 pts were enrolled; their characteristics were as follows: median age (range) 67 (35-84); male/female 12/37; mutations in EGFR/ALK/ROS1/BRAF 32/8/6/3; BMI ≤18.5/18.5-24.9/>25 3/32/14; median MA (range) 100.71 (75.35- 153.89) cm^2, median TFAT 252.97 (60.91- 711.67) cm^2. Grouping pts according BMI, low/normal BMI (≤18.5 and 18.5-24; G1) vs those with high BMI (>25, G2), median TFAT was 212.75 cm^2 in G1 vs 480.28 cm^2 in G2 ($p<0.001$); median MA was 98.66 cm^2 vs 271 cm^2 ($p<0.03$). Focusing on tumor mutation (EGFR vs other), median TFAT was 222.56 cm^2 vs 381.33 cm^2 ($p<0.06$); median MA was 98.66 cm^2 vs 102.80 cm^2 ($p<0.2$). Regardless BMI and type of oncogene addiction, MA was strongly associated to BMI (R+0.58) while TFAT was negatively related to 3-months weight loss (%) (R-0.32). Additionally, handgrip test was directly influenced by baseline weight (R+0.34), MA (R+0.32) and hemoglobin (R+0.33).

Conclusions: According to our results, a relationship between clinical and radiological parameters is disclosed. Beside BMI, handgrip, and hemoglobin levels, CT-scan emerges as a promising tool to optimize the oncogene addicted aNSCLC nutritional pathway. Finally, our preliminary data suggest a difference in nutritional features according with the type of mutation worthy of validation on a larger scale in future trials.

Keywords: Nutrition, Radiology, Oncogene addiction

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-016 Cachexia's Impact on Immunotherapy Dose Reduction, Treatment Discontinuation, and Survival: a Systematic Review

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Introduction: A large proportion people with advanced cancer experience cachexia, a metabolic state which includes involuntary weight loss, sarcopenia, and loss of appetite. This syndrome can have a negative impact on different areas of oncologic disease management, such as surgical, radiation, and chemotherapy outcomes, but its impact on immunotherapy outcomes requires further investigation. This qualitative systematic literature review aimed at assessing the impact of cachexia on immunotherapy dose reduction, treatment discontinuation, and survival.

Methods: On November 26th, 2021, a systematic search was performed on Embase and PubMed including, but not restricted to, the following search terms: "cancer", "cachexia", "sarcopenia", "muscle loss", "body weight loss", "immunotherapy", "survival", "treatment interruption", "treatment withdrawal", and "drug dose reduction". The search identified 123 single entries published between 2018 and 2021 which were then screened for eligibility, restricting the list to original research articles published in peer-reviewed journals. The analysis included studies on immunotherapy agents alone or in combination with chemotherapy or radiotherapy; studies reporting on cachexia, body weight, or body composition changes; and studies reporting data on survival, immunotherapy dose reduction or discontinuation, or occurrence of toxicities which may lead thereto. An additional 68 studies had been identified in a parallel systematic literature review on the impact of cachexia on chemotherapy outcomes, but then excluded from that analysis because such studies were focused on immunotherapy. These 68 studies were added to this systematic literature review and were re-analyzed with the same criteria, as described above.

Results: Twenty-five studies, comprising 3,202 patients, were included in this review. Twenty-four studies (96%) were retrospective assessments of patient records, and one was a prospective observational study (4%). Every patient in these studies received immunotherapy, and all studies showed reduced survival in patients with cachexia related characteristics (such as weight loss, low body mass index, or sarcopenia) versus no cachexia. Two of the studies (8%) also reported increased treatment discontinuation, with one of these two studies additionally reporting dose reductions and increased toxicity (4%). Non-small cell lung cancer (8 studies [32%]) and melanoma (3 studies [12%]) were the most frequent types of cancer. Additionally, the most reported immunotherapy agents were immune checkpoint inhibitors (21 studies [84%]).

Conclusions: In patients receiving immunotherapy, cancer cachexia-related parameters were associated with increased treatment discontinuation (8% of studies), reduced dosing and increased toxicity (4% of studies), and worse survival (100% of studies). These observations suggest that it may be important to detect and treat cachexia in patients with advanced cancer when immunotherapy is initiated. Disclosure: This study was funded by Helsinn Healthcare SA.

Keywords: Cachexia, Immunotherapy, Systematic literature review

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-017 Use of Lalaby in Lung Cancer Patients to Trace Performance from Phone Sensors and Reported Outcomes Involving Quality of Life

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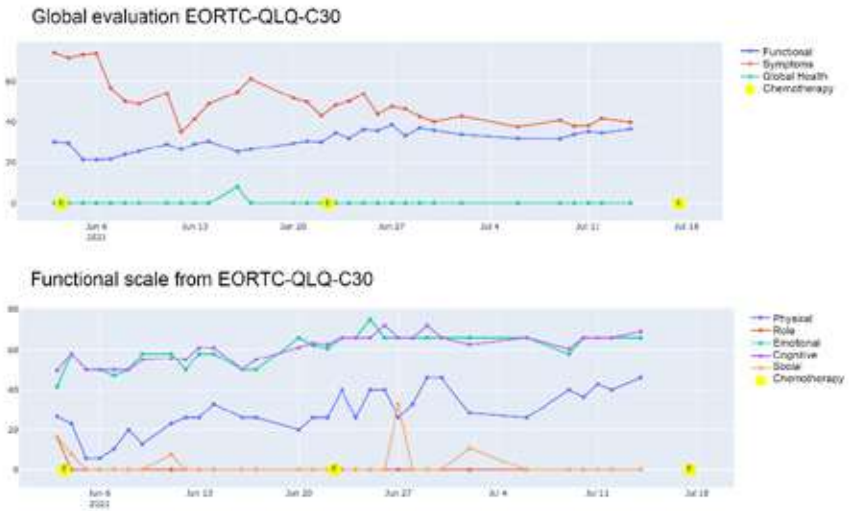
Introduction: Non-small cell lung cancer (NSCLC) constitutes a healthcare problem because of its incidence, mortality, and the burden of symptoms that it produces. Therefore, treatment goals include symptom control and maintenance of quality of life (QoL). However, QoL is not fully evaluated in clinical practice. The higher acceptance of wearables technology enables to automatically monitor health parameters. Sensors from smartphones allow continuous quantification of parameters regarding QoL along with patient reported outcomes measures (PROMs) using a single app. Our objective is to assess the feasibility of using smartphone sensors and self-registering PROMs through the app Lalaby® in outpatients with NSCLC receiving systemic treatment.

Methods: A pre-pilot prospective study of the feasibility of 6-week use of the app Lalaby® including two patients with advanced NSCLC was conducted in Hospital Universitario Doctor Peset (Valencia, Spain). Lalaby® offers two functionalities: automatic collection of the number of calls and face-to-face conversations, data usage, amount of movement, and distance traveled from smartphone sensors; and digital registry of patients' activities, symptoms, and response to EORTC QLQ-C30, ECOG, and UEQ-S questionnaires. Patients were also asked about usability problems (according to the user-based development).

Results: Both patients were male (58 and 74 years). Lalaby® was installed on the patients' smartphones (AdroidOS). Automatic data from sensors were adequately gathered. Sensors showed that distance traveled of patient-1 decreased after each treatment cycle but recovered rapidly and improved overall. PROMs indicated a decrease in the burden of symptoms, and specifically, pain and constipation improved; fatigue was stable. Agreeing to these facts, reported functionality ameliorated, and disease partial response (PR) was observed. However, perceived global health was deficient during the follow-up, parallel to the loss of life-role (Figure 1). Patient-2 presented with diarrhea after every cycle but did not report it in medical visits; furthermore, sensors did not capture changes in functionality; globally, the burden of symptoms improved. We concluded diarrhea did not interfere with his perceived and quantified QoL; PR was also achieved. Interestingly, ECOG scale reported by patients was significantly higher than the assessment by oncologists. Finally, both patients valued Lalaby® positively.

Conclusions: In our pre-pilot, the use of the app Lalaby® was feasible in patients with NSCLC receiving systemic treatment. The data acquired by Lalaby® showed patients' daily activity and reported status, allowing oncologists to understand the continuous impact of the disease, treatment, and symptoms in patients' functionality and QoL. Currently, we are conducting a larger prospective study with Lalaby®.



Keywords: phone sensors, patient-reported outcomes measures (PROMs), quality of life (QoL)

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-018 Thromboprophylaxis for Lung Cancer Patients: Results From ACT4CAT Trial

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On behalf of The Hellenic Society of Medical Oncology (HeSMO, http://www.hesmo.gr/en), Athens/GR

Introduction: Malignancies can exaggerate thrombosis risk up to 20%. For Lung Cancer (LC) up to 14% [Lung Cancer Associated Thrombosis-LCAT). Moreover, thrombosis amplifies the LC progression, i.e. thrombosis-associated lung cancer (TALC). LCAT & TALC have multifactorial pathophysiology, depending on LC characteristics, specific anti-cancer management, patient characteristics, and biomarkers such as tissue factor, neutrophil extracellular traps, cancer procoagulant, and cytokines.

Methods: ACT4CAT is a prospective observational phase IV study conducted by HeSMO (Hellenic Society for Medical Oncology), recording the clinical practice of prophylaxis against venus thromboembolism (VTE) in active cancer patients. Ambulatory patients receiving thromboprophylaxis enrolled after signing informed consent. The study was approved by the bioethics committee and conducted according to Helsinki declaration.

Results: Results reported for 177 patients with LC administered thromboprophylaxis from 17 oncology departments, 78% were males. Age ≥65 was in 57.6% and BMI≥30 in 19.2%. High-Risk for Thrombosis Agents (HRTAs) received 89.3%, specifically: platinum agents (72.9%), immunotherapy (37.3%) and antimetabolites (28.3%). Therapeutic lines were: 1st line 71.8%, 2nd line 17.5%, 3rd line or higher: 2.8%, adjuvant 3.4% and neoadjuvant 0.5%. High Burden for Thrombosis (HTB) factors presented in table. Average thromboprophylaxis duration was 5.2±3.5 months. Main antithrombotic agents were: tinzaparin 88.6%, fondaparinux 8.5%, bemiparin 2.8% and enoxaparin 1.1%. Notably, 58.2% of the anticancer agents reported had a potential drug-drug interaction with DOACs. Intermediate thromboprophylaxis dose was administered in 68.9% of patients. No special relation of the intermediate or prophylactic doses with metastatic status or chemotherapy line or other patient characteristics was identified. Three thrombotic events reported (efficacy: 98.3%, 95%CI: 95.1-99.4%), two deep vein thrombosis and one pulmonary embolism, all occurred in patients treated with prophylactic doses. In terms of safety, three grade1 bleeding events reported (1.7%, 95%CI: 0.6-4.9%), two with prophylactic doses and one with intermediate dose.

Conclusions: Thromboprophylaxis with Low Molecular Weight Heparins (LMWHs) using intermediate doses in high thrombotic burden patients with active lung cancer was both effective and safe. LMWHs administration does not increase bleeding risk and there is no reported interference with the anticancer treatment. Further clinical research is needed.

Table: Patients with active lung cancer and High thrombotic burden factors related to disease, treatment, biomarker and patient.

Cancer	%	Treatment	%	Biomarkers	%	Patient	%
Lung	100	Platinum based chemotherapy	73	PLT>350 K	32	Age >65 years	58
Metastatic	89%	Anti-metabolites	28	Hg<10	15	BMI≥35	5
		Immunotherapy	37	WBC>11000	34	Reduced mobility history	4
		Transfusion or Erythropoietin	18			Thrombosis history	4
		Radiotherapy	27			Surgery history	29
						Khorana score ≥2	60

Keywords: Thromboprophylaxis, Lung Cancer, Low Molecular Weight Heparins (LMWHs)

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-019 Rowing Against Cancer: From a Support Project to a Research Program. Perspectives and Challenges of Rowing in Metastatic Lung Cancer Patients

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Introduction: Lung cancer symptoms and secondary effects of cancer treatments impact quality of life and induce patients to excessive rest and lack of physical activity resulting in severe deconditioning. Exercise has been shown to increase performance status, strength, endurance and reduce emotional issues in lung cancer patients. Despite these benefit this approach is a poorly utilized strategy and several barriers must be overcome due to limited data, lack of awareness of the benefits of exercise, and limited patient motivation. Several programs of adapted physical activity are developing to support lung cancer patients during oncological treatments, adopting a personalized approaches.

Rowing programs have been reported in cancer survivors to reduce risk factors and the impact of treatments complications, particularly lymphedema in breast cancer survivors. A pioneering program of adapted physical activity was developed by a multidisciplinary team in collaboration with an association for the support of cancer patients (Sicilian Association for Oncological Support), using rowing in patients with active metastatic cancer, to evaluate feasibility, response of patients, and to increase awareness of the benefits of physical activity in the fight against lung cancer.

Methods: The program was launched in December 2019 from the idea of a young world rowing champion, but the advent of the COVID-19 pandemic led to the postponement of this project, which was subsequently developed from March 2021 to July 2021. The team was composed by oncologists, sports medicine specialists, two coaches specialised in adapted physical activity programs and a cardiologist. The voluntary logistic assistance was warranted by the rowing society “Canottieri Peloro”, which effectively allowed the project to be carried out, providing patients with equipment, a specialised team doctor and a well-equipped gym. In this preliminary experience we managed to include a small number of patients to assess the feasibility/validity of this approach and improve patients’ needs and satisfaction.

Results: Four patients affected by metastatic lung adenocarcinoma with EGFR mutations joined the project (1 M/3 F; median age was 59.5, range 47-68; ECOG PS: 1). All patients presented well-controlled and mild symptoms related to the disease (cough, dyspnea, bone or chest pain) and were receiving active oncological treatments (first line EGFR-TKI: 2 patients; second line EGFR-TKI and maintenance chemotherapy). After a baseline clinical, oncological and cardiological evaluation personalized training program was developed. Briefly, indoor training and individual rowing sessions have been administered to patients. All patients reported full adherence to the training, developing a growing motivation and interest in improving physical performance. We did not recorded any worsening of symptoms or problems related to cancer treatments. The full contact with water and nature and the peculiar backwards motion of rowing had a positive impact on patients, that enjoyed the experience, reducing their anxiety for the future.

Conclusions: This preliminary experience, previous developed as a support activity for lung cancer patients, might pave the way for further exploration of the role of rowing in this setting and promote a pivotal project to better define specific programs for metastatic cancer patients to improve compliance and response to cancer treatments.

Keywords: Lung cancer, Adapted physical activity, Rowing

EP10.01 PALLIATIVE AND SUPPORTIVE CARE

EP10.01-020 Nutritionassessment for with Common Cancer Patients in a Cancer Hospital of China

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Introduction: To investigate the nutritional status of hospitalized patients with common malignant tumor in a cancer hospital of Southwest China.

Methods: From April 2017 to May 2021, we enrolled 891 patients with cancer hospitalized for treatment in Chongqing university Cancer Hospital. These patients were diagnosed with one of the following 16 different types of malignant tumors: lung cancer, gastric cancer, liver cancer, colorectal cancer, breast cancer, esophageal cancer, cervical cancer, endometrial cancer, nasopharyngeal carcinoma, malignant lymphoma, leukemia, pancreatic cancer, ovarian cancer, prostate cancer, bladder cancer and brain tumor. Patient-generated subjective global assessment (PG-SGA), anthropometric measurements, and laboratory examination were used to evaluate the nutritional risk or nutritional status.Cancer pain status were assessed with the Numerical Rating Scale (NRS). We also investigated the nutritional therapy of these cancer patients

Results: According to the PG-SGA score, 48.7% (434/891) of the cancer patients were severe malnutrition (PG-SGA≥9), 31.2% (312/891) were moderate malnutrition (8≥PG-SGA≥4), 14.7% (131/891) were mild malnutrition (PG-SGA 2~3), and only 5.4% (48/891) patients were no malnutrition (PG-SGA 0~1). The rate of malnutrition for gastrointestinal cancer patients is higher than Nongastrointestinal cancer patients (67.3% vs. 44.6%, x2=31.48, P <0.001). Multiple linear regression analysis, PG-SGA scores and body mass index (P<0.001), serum total protein(P<0.001), hemoglobin serum(P<0.001), albumin (P<0.001), prealbumin (P<0.001), calf circumference (left side, P=0.001) were correlated. Age(≥65 years), albumin(<40g/L), prealbumin (<150mg/L) and cancer pain (NRS≥4) are the risk factors of severe malnutrition. However, only 26.8% (200/746) of all the moderately and severely malnourished patients received nutritional therapy.

Conclusions: 94.6% of the common malignant tumor patients enrolled in the present study were malnutrition. PG-SGA is an effective tool to assess malnutrition in cancer patients, it is recommended to conduct routine assessment of cancer patients at the beginning of admission. Nutritional therapy of malignant tumor patients with malnutrition is very low. Suggestions for patients with malignant tumor after admission nutritional risk screening, and comprehensive nutritional evaluation, including PG-SGA score, and to give the right nutritional therapy.

Keywords: Cancer, Nutritional assessment, PG-SGA

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-001 Training Increases Concordance in Classifying Pulmonary Adenocarcinomas According to the Novel IASLC Grading System

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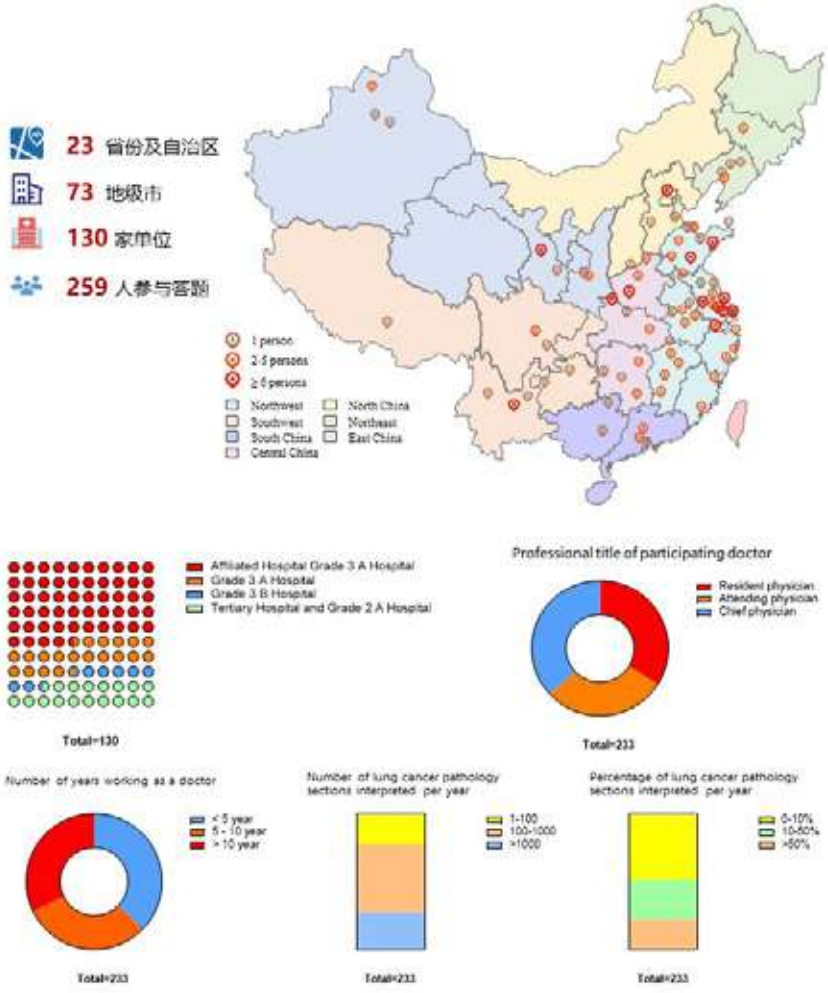
Introduction: The International Association for the Study of Lung Cancer (IASLC) has proposed a new grading system that could stratify the prognosis for patients with lung adenocarcinoma (LUAD) based on the growth pattern percentage. The grading system has been shown to have prognostic and maybe even predictive impact. However, until now, the reproducibility of this grading has not been sufficiently demonstrated.

Methods: Digital images of 50 selected LUAD cases were shown twice to the Pulmonary Pathology Working Group of Intraoperative Frozen Section members. Each time online answers on the LUAD cases were performed.

Results: The accuracy of the predominate patterns were ranged between (lepidic 82.7%; acinar 73.1 %; papillary 92.7 %; solid 94.4%; micropapillary 97.4 %; complex glandular 88.9%), and the accuracy of the new grading system were ranged between (Grade1 83.3%; Grade2 70.9 %; Grade3 79.9 %), respectively. The extent of diagnosing errors decreased after the training session. However, this decrease was heterogeneous for the different patterns, with acinar being the pattern with the greatest improvement.

Conclusions: The IASLC new grading system of LUAD can be applied with reasonable consensus even for difficult cases in a nationwide context. The reproducibility improves following educational sessions, even among experienced lung pathologists.



Keywords: Frozen section, IASLC grading system, lung adenocarcinoma

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-002 Malignant Pleural Effusion Cell Blocks Are Reliable Resources for PD-L1 Analysis in Advanced Lung Adenocarcinomas

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Introduction: In lung cancer patients presenting with malignant pleural effusion (MPE), cytology may represent the only source of tumor tissue for diagnosis and predictive biomarker testing. Programmed death ligand-1 (PD-L1) expression in tumor cells is a predictive biomarker for immunotherapy in non-small cell lung carcinomas and is tested by immunohistochemistry. However, there is limited knowledge on the validity of PD-L1 testing on MPE samples. The aim of the study was to evaluate the feasibility of immunocytochemistry (ICC) for PD-L1 in MPE cell blocks (CB) and assess concordance in expression with patient-matched histology samples.

Methods: ICC for PD-L1 was performed on formalin-fixed paraffin-embedded (FFPE) CBs of MPEs and patient matched histology samples, wherever available, using the automated Ventana PD-L1 SP263 assay. In CBs with any degree of PD-L1 expression, ICC for CD163 highlighting macrophages was done to exclude non-specific PDL1 expression in macrophages. For each case, the hematoxylin and eosin (H&E), TTF-1 (only when positive), PD-L1 and CD163 stained slides were digitized using a digital slide scanner and analyzed on Slide Viewer. At x20 magnification, the section was virtually divided into four quadrants. Tumor cells were manually tagged in each quadrant by analyzing H&E and PD-L1 scanned slides together with TTF-1 in cases where the latter was positive. PD-L1 protein expression was determined on tumor cells in each quadrant as a tumor proportion score (TPS) i.e., percentage of tumor cells showing partial or complete membranous staining of any intensity relative to all tumor cells. Non-specific PD-L1 expression in macrophages was excluded by comparing with corresponding area on CD163 stained scanned slide, which highlighted macrophages but not tumor cells. Average of all the four sections was taken as final TPS. Based on TPS, PD-L1 was clustered into three groups: (a) tumors with less than 1% PD-L1-positive cells (negative), (b) those with 1% to 49% PD-L1-positive cells (low score), and (c) those with at least or more than 50% PD-L1-positive cells (high score). CB PDL1-TPS were compared with those obtained on patient-matched histology samples.

Results: Our study included 43 patients of lung adenocarcinoma having MPE available as CB. One case did not have adequate number of tumor cells for interpretation on the PD-L1 stained sections and was excluded. Among the remaining 42 cases, twenty-five showed cytoplasmic and membranous PD-L1 positivity in ≥1% tumor cells (59%), of which thirteen cases (30.9%) showed 1% to 49% expression (low expression), and twelve (28.5%) demonstrated more than 50% expression (high expression). Paired histology sample was available in 11 patients. At a cut off >1% TPS, 7/11 (63%) pleural effusions and 6/11 (54%) patient matched biopsies were positive for PDL1. The categories of PDL1 expression were concordant in 10/11 cases (91%).

Conclusions: PD-L1 expression in MPE CBs showed good concordance with expression levels in histology samples and is feasible as a source for PDL1 testing. Concurrent use of CD163 immunostains aided in manual assessment of PDL1 TPS.

Keywords: PDL1, cell block, effusion

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-003 Advanced Non Small Cell Lung Cancer with EGFR Exon 20 Insertion Gene Mutation

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Introduction: The EGFR Exon 20 Inserton mutation is belongs to the group of rare EGFR mutations and that is resistant to TKIs generation I-II-III. We conduct research with the following objectives: a. Survey on the rate of EGFR Exon 20 Insertion mutations in patients with advanced NSCLC. b. Survey of subtypes of EGFR mutations Exon 20 Insertion offers applications in clinical practice.

Methods: A research with retrospective, cross-sectional descriptive statistics. Analysis with SPSS 20.0 software, two-sided analysis with T-Test, test value with P < 0.05.

Results: 1.General data: *Total number of research: 497 cases of advanced NSCLC in 2020. All cases were diagnosed at hospital admission without specific treatment (chemotherapy, targeted therapy, immunotherapy ect.). Number of cases diagnosed with NGS: Genetic variation detected: 378 cases (76.06%). No genetic variation detected: 119 cases (23.94%).***2.Distribution of types of EGFR mutations**: *203 cases of EGFR (+) # 40.85%: Exon 18 G719X: 5 cases. Exon 19 Deletion: 107 cases. Exon 20 T790M: 6 cases. Exon 20 Insertion: 21 cases. Exon 20 S768I: 3 cases. Exon 21 L858R: 45 cases. Exon 21 L861Q: 4 cases. Combined mutations: 12 cases.***3.Distribution of combined EGFR mutations**: *Exon 18 G719X + Exon 20 T790M: 1 case. Exon 19 Deletion + Exon 20 T790M: 2 cases. Exon 21 L858R + Exon 20 T790M: 1 case. Exon 18 G719X + Exon 20 Insertion: 1 case. Exon 19 Deletion + Exon 20 Insertion: 3 case. Exon 21 L858R + Exon 20 Insertion: 1 case. Exon 21 L861Q + Exon 20 Insertion: 1 case. Exon 20 T790M + Exon 20 S768I: 1 case. Exon 19 Deletion + Exon 20 T790M + Exon 18 G719X: 1 case.***4.Distribution of EGFR mutation subtypes Exon 20 Insertion:**- *C-helix loop: 761D (D761-E762 InsX): 2 cases. 762E: 3 cases. 763A (A763-Y764 InsX): 1 case. 764Y (Y764-V765 InsX): 4 cases. 765V (V765-M766 InsX): 2 cases. 766M: 1 case.- The following segment of the C-helix loop: 767A (A767-S768 InsX): 3 cases. 786S (S768-V769 InsX): 1 case. 769V (V769-D770 InsX): 3 case. 770D (D770-N771 InsX): 1 case. 771N (N771-P772 InsX): 1 case. 772P (P772-H773 InsX): 2 cases. 773H (H773-V774 InsX): 1 case. 774V (V774-C775 InsX): 1 case. 775C: 1 case.***5.Comments**:- *Number of cases with individual EGFR Ex20 Insertion mutations: 21 cases/203 cases (10.34%)- Number of cases with combined EGFR Ex20 Insertion mutation: 6 cases/203 cases (2.96%)- Total number of cases with EGFR Ex20 Insertion mutation: 28 cases/203 cases (13.79%)- Number of cases of EGFR Ex20 Insertion with C-helix loop subtype: 13 cases/28 cases (46.43%) and sensitive to TKIs group I-II-III - Number of cases of EGFR Ex20 Insertion with subtypes in following C-helix loop: 15 cases/28 cases (53.57%) and sensitive to new generation TKIs (Amivantamab, Mobocertinib).*

Conclusions: EGFR mutations Exon 20 Insertion account for about 10% of the subtypes of EGFR mutations in advanced NSCLC. There are many smaller subtypes of the EGFR Exon 20 Insertion mutation. Therefore, it is necessary to use NGS to identify these subgroups. Currently, there are medecines to target all subtypes of EGFR mutation Ex20 Insertion.

Keywords: EGFR gene mutations, EGFR Exon 20 Insertion Mutation, Next Generation Sequencing

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-004 An Effective Two-step Reflex Test for 10 Biomarkers Analysis in Non-small Cell Lung Cancer

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Introduction: The treatment of non-small cell lung cancer (NSCLC) has become increasingly biomarker-driven over the last decade, with a growing number of targeted therapies available for patients with specific genomic alterations. A fast-track screening of multiple molecular biomarkers is therefore required for first-line treatment selection in NSCLC, although challenging considering both turnaround time and sample quality. In an effort to improve the molecular diagnostic workup at our institution, we implemented a two-step reflex test (RT) at the time of pathological diagnosis of non-squamous NSCLC for EGFR, KRAS, BRAF, ERBB2, ALK, ROS1, PDL-1, RET, MET, and NTRK testing. The aim of this study was to evaluate the clinical utility of reflex-ordered molecular testing in NSCLC.

Methods: We retrospectively analyzed all consecutive cases of NSCLC evaluated for molecular RT from November 2020 to January 2022. A DNA-based multitargeted panel by MassARRAY was used for EGFR, KRAS, BRAF, and ERBB2 testing; ALK and PDL-1 expression was analyzed by immunohistochemistry and ROS1 rearrangements were investigated by FISH. All DNA-ALK-ROS1 negative cases were reflexed to a second level RNA RT for testing MET exon 14 skipping mutations, RET, and NTRK fusions by RT-PCR. Time from diagnosis to RT is defined as the number of consecutive days from the release of the pathology report to the release of the final molecular report.

Results: A total of 251 patients with newly diagnosed NSCLC of any pathologic stage were included in our retrospective analysis. Genetic alterations detected thought first- and second-level RT, failure rates, and time from diagnosis to RT are reported in table 1.

Conclusions: Our study shows that a two-step reflex testing approach is effective in NSCLC, with low failure rates and short turnaround times. Also, the prevalence ad type of pathogenetic variants identified were consistent with literature data, although the limited sample size. Our findings show that a standardized comprehensive strategy for molecular testing increases timely opportunities for personalized therapy in NSCLC patients and is feasible to implement, including RT strategies.

Biomarker Tested	Total n. (%)
EGFR	33 (13,1%)
KRAS G12C	43 (17,1%)
KRAS total	97 (38,6%)
BRAF V600E	8 (3,1%)
ERBB2	3 (1,2%)
ALK	10 (3,9%)
ROS1	1 (0,4%)
MET	9 (3,6%)
RET	2 (0,8%)
NTRK	0 (0%)
All WT after first-level RT	94 (37,4%)
All WT after second-level RT	85/251 (33,9%)
Patients who required a re-biopsy for biomarkers	15/251 (5,9 %)
Samples non adequate for first-level RT	3/251 (1,2 %)
Samples non adequate for PDL-1 testing	18/251 (7,2 %)
Samples non adequate for second-level RT	8/96 (8,3 %)
Time from diagnosis to first-level RT including PDL-1 days, median (25-75P)	8 (7-11)
Time from diagnosis to second-level RT days, median (25-75P)	16,5 (13-22)

Keywords: NSCLC, Precision oncology, Reflex biomarker testing

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-005 Ultra-Fast Gene Fusion Assessment as a Reflex Testing in Daily Clinical Practice for Advanced Non-small Cell Lung Cancer Patients

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Introduction: There is an urgent need to improve the broad molecular profiling of advanced non-squamous non-small cell lung carcinoma (NS-NSCLC) patients, notably for a rapid assessment of multiple genomic alterations.

Methods: 250 NS-NSCLC patients (68 *ALK*, 26 *ROS1*, 15 *RET*, 6 *NTRK,* 11 *MET* positive and 125 wild type patients) from 8 centers were included. 83% of patients were stage IIIB-IV. We compared two ultra-fast gene fusion assessment assays, using a next generation sequencing (Genexus, Oncomine™ Precision Assay, Thermo-Fisher) or an RT-PCR (Idylla™, GeneFusion Assay, Biocartis) approaches, set up as a reflex testing at diagnosis.

Results: The sensitivity (98%) and specificity (99%) of the two approaches were analogous, when compared to gold standard methods, accredited according to the ISO15189 norm in the Laboratory of Clinical and Experimental Pathology (Nice, France).

Conclusions: Ultra-fast gene fusion evaluation using NGS or RT-PCR approaches should be developed as a reflex testing for NS-NSCLC at diagnosis in order to treat these patients according to the international recommendations and guidelines.

Keywords: gene fusion, NSCLC, next-generation sequencing

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-006 Setting Up an Ultra-Fast Next-Generation Sequencing Approach as a Reflex Testing at Diagnosis in Non-squamous Non-small Cell Lung Cancer

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Introduction: The number of targetable genomic alterations in non-squamous non-small cell lung cancer (NS-NSCLC) patients increased these last few years, while the tissue material reduced in size. Therefore, molecular pathologists are facing challenges to maintain a strategy allowing a rapid diagnosis.

Methods: We report here our experience (LPCE, Nice, France) between September 20, 2021 and December 31, 2021 for the development of an optimal workflow for genomic alteration assessment as a reflex testing in routine clinical practice at diagnosis in patients with NS-NSCLC using an ultra-fast next generation sequencing approach (Genexus OPA DNA RNA panel, Thermo-Fisher).

Results: 325 patients were included in the study. 74% of patients had stage IIIB-IV NS-NSCLC, and 26% were stage I-IIIA. Ultra-fast NGS was performed in 182 bronchial biopsies, in 68 transthoracic biopsies, in 50 surgical specimens and in 25 cellblocks from 16 pleural effusion and 9 EBUS with a short mean turnaround time of 72h. Mean tumor cell was 40% (ranging from 5% to 95%). The analytical validation of the Genexus OPA workflow, performed on 30 NS-NSCLC cases, demonstrated 100% concordance with the gold standard methods.

Conclusions: We demonstrate that molecular targets accessible to personalized medicine in NS-NSCL were identified using the Genexus system in a rapid turnaround time. Ultra-fast NGS integration as a reflex testing can be an optimal option for genomic alteration assessment at diagnosis for all stage NS-NSLC. This approach enables for a sensitive and a specific identification of mutations, CNVs, and fusion variants types across 50 key genes, on tumor material with a low amount of nucleic acids.

Keywords: ultra-fast, next-generation sequencing, NSCLC

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-007 Tracking ROS1 Fusions in NSCLC - Mirage or Truth When Screening the Desert

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Introduction: Patients with a ROS1-rearrangement are sensitive to targeted treatment with ROS1-inhibitors. However, only 0.5-2% of NSCLC-patients harbor this activating fusion. In order to detect these cases, immunohistochemical (IHC) screening for ROS1-protein expression has been suggested. However, there is a debate about the reliability of such an assay and the comparability of available antibody clones. The aim of this study was to determine the presence of ROS1 fusions in two large NSCLC-cohorts and to evaluate the diagnostic performance of current detection strategies.

Methods: Two large Swedish cohorts of operated NSCLC patients (n=682) were analyzed. Representative patient tissues were compiled in tissue microarrays (TMAs) and subjected for ROS1 IHC-staining using three different antibody clones (D4D6, Cell Signaling; SP384, Ventana; EPMGHR2, Zytomed). Staining intensity and quantity of stained tumor cells was multiplied to obtain an overall IHC score. Fluorescence *in situ* hybridization (FISH) was performed on the same TMAs using a break-apart probe (ZytoVision) and fusion-positivity was defined when ≥15% of at least 50 tumor cells showed split or single green signals. Gene expression microarray data (Affymetrix) was available for 187 patients and RNA-sequencing data was available for 182 other patients, respectively. NanoString fusion-analyses was executed for patients with clear or equivocal FISH results, elevated protein expression, or elevated RNA-expression (n=20).

Results: Using FISH, 2/630 (0.3%) cases were positive for ROS1 fusion. Additionally, eight cases demonstrated an uncertain FISH result. The immunohistochemical staining ranged from weak staining in 1-10% of the tumor cells to strong staining in 90-100% of the tumor cells. Moderate to strong immunohistochemical ROS1-expression (moderate in >60% of tumor cells or strong in >50% of tumor cells) was detected in 24/665 (3.6%) for clone D4D6, in 18/639 (2.8%) for clone SP384, and in 1/592 (0.2%) for clone EPMGHR2. Elevated RNA-levels were seen in 19/369 (5.1%) of the cases (Affymetrix and RNA-sequencing combined). The overlap of positivity between the different assays was poor. However, one FISH-positive case revealed consistent positive ROS1-staining using all antibody clones as well as high RNA-levels. The second FISH-positive case demonstrated no relevant IHC-staining with any of the clones and also low RNA-levels. The Nanostring fusion-assay confirmed that only the consistent FISH and IHC positive case was truly rearranged. Other cases with high protein or RNA- expression or equivocal FISH results did not show any indication of gene fusion in the Nanostring assay. Consequently, the sensitivity of the IHC assays was high when only the Nanostring-positive case was regarded as real fusion, although, depending on choice of cut-off, the number of false positive cases was generally high.

Conclusions: Our data indicate that the occurrence of ROS1 fusions is exceedingly low in resected NSCLC. IHC assays are able to detect this fusion, however, the accuracy is variable depending on the used clone. The false positive FISH and several uncertain FISH results neither support the use of FISH as a screening nor as a reference method to detect ROS1-rearrangement in NSCLC. Thus, when immunohistochemical protocols are used for screening, transcript-based assays are preferable for validation in clinical diagnostics.

Keywords: ROS1, NSCLC, screening

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-008 Discrepancy in MET Exon 14 Skipping Mutation Measurement Between ArcherMET and Oncomine Dx Target Test System

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Introduction: Hepatocyte growth factor receptor gene (*MET*) is one of the important therapeutic target genes in non-small cell lung cancer (NSCLC). Above all *MET* exon 14 skipping mutation (METex14skipping), which is caused by whole exon 14 deletion, base substitutions, insertions/deletions at the splice donor and acceptor sites, and Y1003 mutation, it is important in determining the decision for administration of selective MET inhibitor. One of the selective oral MET inhibitors, tepotinib, is only used in Japan when METex14skipping is detected by ArcherMET, a next generation sequencer. This indicates that tepotinib administration must be stopped even though METex14skipping is detected by Oncomine Dx Target Test System (ODxTT). Discrepancies in the results are confusing since several cases show positive results on testing with the ODxTT but negative on testing with ArcherMET. A patient displayed a better partial response following administration of tepotinib; however, METex14skipping was detected by ODxTT, not by ArcherMET. We suspected the possibility that ODxTT had a higher chance of detecting METex14skipping than ArcherMET. METex14skipping may be undetectable if the quantity or quality of the specimen is insufficient; however, there are still discrepancies even when specimens are adequate. This study aimed to explore the factors that may cause such discrepancies.

Methods: From August 2019 to December 2021, genetic mutations were detected by ODxTT in patients diagnosed with NSCLC at the Department of Thoracic Oncology, Kanagawa Cancer Center. When METex14skipping was detected on ODxTT, the same tissue sample was tested using ArcherMET. Treatment course, history, and pathology data were retrospectively analyzed for these patients. Whole exome sequencing (WES) was performed on one discordant case. Amplicon sequencing was performed to determine the entire sequence from the 3' side of intron 12 to the 5' side of exon 15.

Results: METex14skipping was identified using ODxTT in 20 patients with NSCLC, of whom nine were male, with a median age of 73 years (46-84 years). Ten had a history of smoking. Histologic types included 11 adenocarcinomas, four pleomorphic carcinomas, three NSCLC not otherwise specified, and two squamous cell carcinomas. As reported, the clinical characteristics of NSCLC with METex14skipping were less related to sex, smoking history, and histologic type, with adenocarcinoma being the most common. METex14skipping was detected in 13 patients, whereas seven tested negative. Allele frequencies were low (<1%) in all cases of discrepancy. WES suggested that the mutations with low allele frequencies may be in the intronic regions involved in splicing. Amplicon sequencing was performed to analyze more detail.

Conclusions: The discrepancies observed between these systems may be owing to low allele frequencies. More analysis for these are warranted.

Keywords: MET exon 14 skipping, Oncomine, ArcherMET

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-009 Amplicon-Based Next-Generation Sequencing Rescues "Quantity Not Sufficient" NSCLC Samples and Provides Clinical Information

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Introduction: Amplicon or PCR-based Next-Generation Sequencing (NGS) can efficiently detect genomic alterations in tumor biopsies from patients with advanced solid tumors, however, obtaining sufficient tissue for molecular profiling is a common problem. When tumor biopsies with limited surface area or tumor content do not contain enough DNA or RNA for analysis, they are referred to as "quantity not sufficient" (QNS) samples. Here, we tested whether amplicon-based NGS has significant value for the "rescue" of non-small cell lung cancer (NSCLC) samples that had been previously reported as QNS.

Methods: Twenty-one formalin-fixed, paraffin-embedded (FFPE) NSCLC samples that had been previously submitted from RUSH University to a commercial laboratory for hybrid-capture based somatic NGS were re-tested using Thermo Fisher's Oncomine Precision Assay (OPA)-Genexus system in a CAP-accredited, CLIA-approved laboratory. The 50-gene OPA panel detects DNA and RNA alterations including SNVs, indels, CNVs and fusions with results available in as little as 24 hours. Remnant FFPE samples were from the same biopsy procedure as previously tested. An average of 2.6 x 5µm slides per sample was used for OPA-Genexus with a range of 1-8 slides.

Results: Of the 21 samples, 5 had successful commercial NGS results for DNA and RNA, 9 for DNA only (RNA failure), and 7 that failed both DNA and RNA. OPA-Genexus produced successful DNA and RNA runs for 20 samples, 1 of the 7 DNA/RNA failures was reported as QNS. Clinically actionable oncogenic mutations were seen in 5 of the 16 commercial failures including ALK (from RNA failure), PIK3CA, EGFR, KRAS, and ERBB2 (from DNA/RNA failures).

Conclusions: Our results show that amplicon-based NGS on the OPA-Genexus system can rescue QNS samples using minimal tissue input and provide treatment options for NSCLC patients that may not otherwise have been eligible for targeted therapy.

Keywords: NGS, Next generation sequencing, molecular profiling

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-010 A Prospective Validation Study of Lung Cancer Gene Panel Testing Using Cytological Specimens

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EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-011 Clinical Application of Liquid Biopsy for Assessing Early EGFR Mutation Detection in Non-Small Cell Lung Carcinoma

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Introduction: Liquid biopsy has already entered clinical practice in non-small cell lung carcinoma (NSCLC) patient care by means of analysing cell-free DNA (cfDNA) for detection of *EGFR* resistance mutations due to low success rate of repeat biopsy in NSCLC patients. However, being minimally invasive the use of liquid biopsy for early detection of *EGFR* mutation in treatment naïve patients is less explored.

Methods: Peripheral blood samples were collected from 100 lung cancer patients of which 45 patients were ineligible for further analysis as described in *Figure 1.* Out of eligible 55 patients, their blood samples were collected at the time of registration into lung cancer clinic before acquisition of tissue biopsy and their matched plasma cfDNA were tested for *EGFR* mutation detection at the time of diagnosis (T_0).

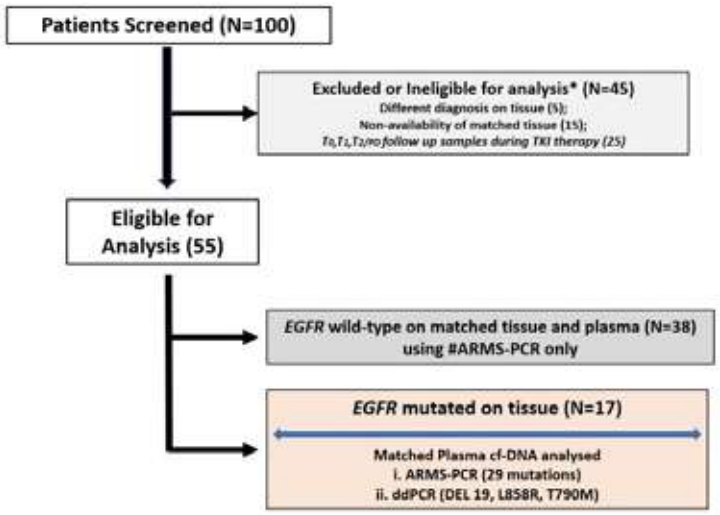

Figure 1: Lung Cancer patients screened, followed by exclusion of 45 patients as depicted and ultimately leaving 55 eligible for analysis; (T_0= time of diagnosis before treatment, T_1= 3 months post TKI therapy, $T_{2/PD}$= 6-8 months post TKI therapy or Disease Progression)

Results: Fifty-five patients enrolled in study were analysed as shown in *Figure 2*. For 17 *EGFR*-tissue mutated patients, their matched plasma cfDNA was primarily tested at T_0 using ARMS-PCR which gives sensitivity of 70.59% later subsequently improved to 88.24% when tested by ddPCR. One case was detected only on liquid biopsy where tissue was scant and could not be processed further. All patients those underwent plasma followed by tissue EGFR genotyping, median turnaround time (TAT) for revelation of *EGFR* mutation status to the clinician by cfDNA was shorter (5 days, range 1-18 days) when compared to tissue (13 days, range 3 days up to 2 months); (TAT of Tissue biopsy vs. Liquid biopsy; p-value <<0.05).

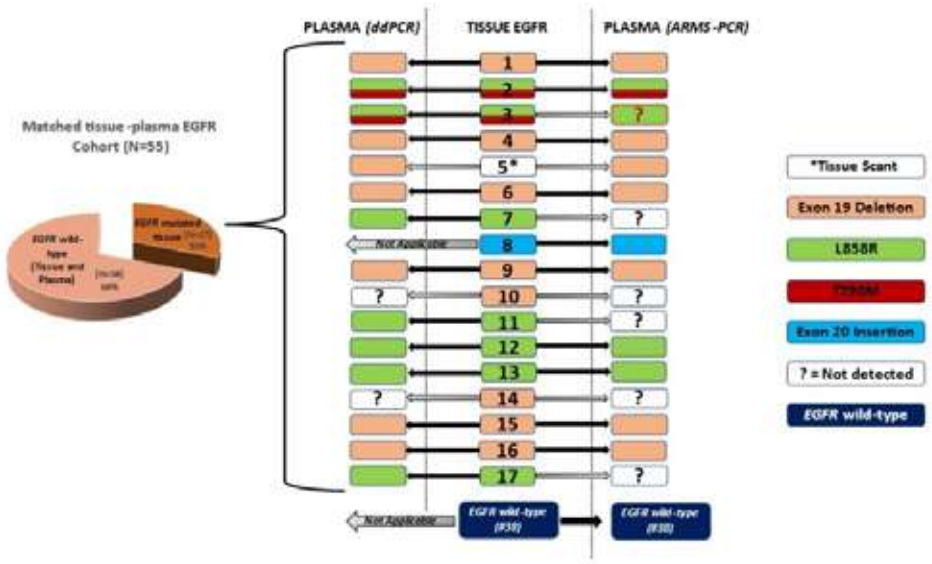

Figure 2: Matched plasma cfDNA of eligible thirty-eight *EGFR*-wild type on both tissue and liquid biopsy using #ARMS-PCR only while matched cfDNA of seventeen *EGFR*-mutated on tissue (*exception of one being scant) were analysed by ARMS-PCR followed by ddPCR

Conclusions: Liquid biopsy for *EGFR* mutation detection at the baseline in treatment naïve patients demonstrates a shorter TAT as compared to standard tissue biopsy thereby, reducing potential delays of patients eligible for EGFR TKI therapy and also particularly effective in revolutionizing care of NSCLC patients with unfeasible or inadequate tissue biopsy at the time of diagnosis.

Keywords: Non-Small Cell Lung Carcinoma (NSCLC), EGFR, Liquid Biopsy

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-012 Genomic Landscape of Liquid Biopsy in Advanced Lung Cancer Patients, an Indian Experience

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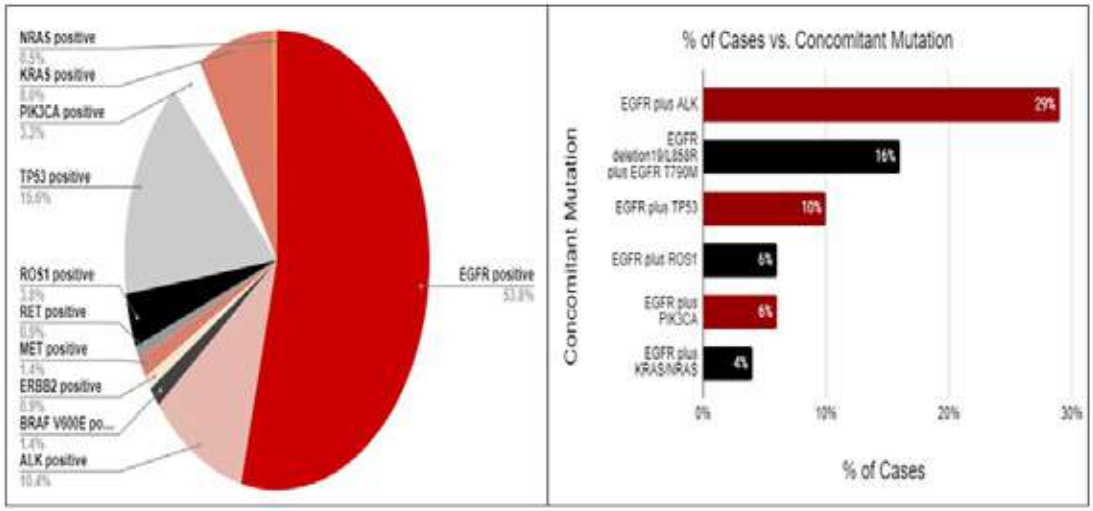
Introduction: Liquid biopsy is a promising non interventional diagnostic approach in advanced lung cancer patients, especially during disease progression. Cell free DNA (cfDNA) and circulating tumor cells are valuable in detection of molecular signatures during screening or first time diagnosis, therapy monitoring, and resistance mechanisms that cause disease progression in non-small cell lung carcinoma (NSCLC). Herein we present the genomic landscape of 246 NSCLC patients who underwent next generation sequencing (NGS) on blood samples.

Methods: The samples were run on an AmpliSeq based Oncomine Lung Cell-free total nucleic acid (cfTNA) assay, that targets *ALK, BRAF, EGFR, ERBB2, KRAS, MAP2K1, MET, NRAS, PIK3CA, RET, ROS1,* and *TP53* genes. The assay was based on the proven ION AmpliSeq technology and has been validated on clinical research samples and allows the detection of somatic variants as low as 0.1% frequencies in cfDNA from the plasma. The assay enabled analyses of all types of key mutations, including SNV, indels, CNVs, and fusions.

Results: A total of 246 patients underwent NGS on blood samples, of which 63% (n=156) had a detectable mutation. 114 patients were positive for *EGFR*, which was the most common mutation (46%) seen. *EGFR* deletion 19 was seen in 29% of the total population, followed by *L858R* (13%), *T790M* (11%), and exon 20 mutations (9%). *TP53* (13%) was the second most common mutation, followed by *ALK* rearrangement (9%), *KRAS* (n=17), *ROS1* (n=8), *PIK3CA* (n=7), *BRAF V600E* (n=3), *MET* exon 14 skipping (n=3), *RET* (n=2), *ERBB2* (n=2), and *NRAS* (n=1) mutations. Additionally, *EGFR* mutation is seen more commonly with *ALK* rearrangements (29%) patients, followed by additional *EGFR T790M* mutation (16%), *TP53* mutation (10%), *ROS1* rearrangements (6%), *PIK3CA* mutation (6%), *KRAS/NRAS* mutations (4)% and *BRAF V600E* point mutation (2%).

Conclusions: A high positivity rate of detection of actionable and prognostic genomic alterations in the liquid biopsy has established the importance of blood as an important resource of detecting mutations in advanced NSCLC which directly impacts the clinical outcome in these patients. Furthermore, presence of co-positivity of mutations highlights the biologic mechanisms responsible for drug resistance in NSCLC patients.



Keywords: NGS, EGFR, NSCLC

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-013 Genomic Landscape of Pulmonary Sarcomatoid Carcinoma

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Introduction: Pulmonary sarcomatoid carcinoma (PSC), a rare subtype of non-small cell lung cancer (NSCLC), is well known for its clinical aggressiveness and limited therapeutic strategies. Here we tried to find insight into the genomic features relevant to morphologic heterogeneity and progression of PSC.

Methods: Thirty-one patients diagnosed with PSC by surgical resection at Seoul National University Bundang Hospital were retrospectively reviewed. The carcinomatous and sarcomatous components of the primary tumors were microdissected in selected cases and were analyzed respectively. Eleven cases had available metastatic tumor tissue of lymph nodes or bone which were also included in the study. Whole exome sequencing, digital droplet polymerase chain reaction (ddPCR), and PD-L1 immunohistochemistry using the Ventana SP263 assay were performed.

Results: The most frequently altered gene was *TP53* in primary (74%) and metastatic (73%) samples. Known NSCLC driver mutations including *EGFR* (29%), *KRAS* (6%), *MET* (19%) and *KEAP1* (19%) were found. *MET* mutations, validated by ddPCR, showed mutual exclusivity with *TP53* mutations and frequently co-occurred with *MDM2* amplifications. Most of the cases with available metastatic tissue samples had a long common trunk in phylogenic analysis, and higher similarity in genetic alterations was found between primary carcinomatous and sarcomatous components than metastatic tumors. The APOBEC mutational signature was characteristically absent in metastatic samples. Metastatic tumors showed more genomic alterations in cancer-related, differentiation-related pathways than primary tumor components. PSC harbored higher *MET* and *KEAP1* mutations than pulmonary adenocarcinoma or pulmonary squamous cell carcinoma. Stonger PD-L1 protein expression was observed in PSC (more than 50% expression in 61.3%) than in other NSCLC.

Conclusions: Clinical aggressiveness and therapeutic difficulties of PSC may come from the profound intratumoral and intertumoral genetic diversity. More frequent *MET* and *KEAP1* mutations and stronger PD-L1 expression distinguishes PSC from other NSCLC. Next generation sequencing may be important in PSC for deciding the right treatment strategy.

Keywords: Pulmonary sarcomatoid carcinoma, whole exome sequencing

EP11.01 PATHOLOGY - GENOMICS & ANALYTICS

EP11.01-014 Optimizing Targetable Gene Screening by Sequential Multi-platform Detection Applied to Driver-negative mNSCLC Patients Detected by DNA-NGS

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Introduction: Screening for targetable gene alteration is critical for patients with metastatic non-small cell lung cancer (mNSCLC) and is now mainly detected by next-generation sequencing (NGS) of DNA. For the patients without driver alteration, we estimated the value of additional sequential multi-traditional platform in the identification of targetable gene alteration in mNSCLC with limited tissue biopsy sample.

Methods: A total of 1926 patients with mNSCLC with limited tissue biopsy sample who had undergone DNA-NGS in our laboratory were retrospectively collected. The types of biopsy samples included core biopsy, bronchoscopic biopsy and pleural effusion. 415 of 494 driver-negative cases with available tissue were further checked by ARMS-PCR for EGFR mutation, IHC for ALK expression and FISH for ROS1fusion and MET amplification respectively. Besieds, 81 cases were also tested by 11 mutant gene of lung cancer detection kit. For patients who were identified to have actionable gene alteration in the following check after NGS, clinical responses were assessed on the basis of radiographic imaging.

Results: Among all the patients, 1654 (85.9%) patients were TKI-naïve and 1174 of them (71.0%) were detected positive for oncogenic drivers and the gene alterations amenable to clinical targeted therapy included EGFR (43.4%), KRAS (9.4%), ALK (5.3%), HER2 (2.8%), MET (2.7%), PIK3CA (2.2%), BRAF (1.8%), RET (1.6%), ROS1 (1.3%), NRAS (0.4%) and FGFR2 (0.1%). 494 of 1926 cases were negative for a driver gene alteration in DNA-NGS test. In the sequential multi-traditional platform detection, 15 of 415 driver-negative cases were identified to have targetable gene alteration, including 8 cases of EGFR mutation, 4 cases of ALK fusion, 1 case of ROS1 fusion and 2 cases of MET amplification. Of these 15 cases, 11 patients received targeted therapy, 6 of whom achieved partial response, and the remaining patients were with stable status. Meanwhile, in 11 mutant gene of lung cancer detection results, there was 1 positive case each of EGFR, ALK, MET, RET and ROS1 alteration.

Conclusions: Optimizing targetable gene mutation and fusion detection in mNSCLC is of great significance, for target therapy could obviously provide improvements in the survival and quality of life. The sequential multi-traditional platform detection applied to driver-negative cases screened by DNA-NGS could definitely improve the detection accuracy and benefit more patients.

Keywords: metastatic non-small cell lung cancer, targetable gene alteration, multi-platform

EP11.02 PATHOLOGY - NEW TECHNOLOGY

EP11.02-001 Natural Language Processing to Abstract Preneoplastic and Incidental Pulmonary Lesions from Pathology Reports

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Introduction: With a paucity of pre-neoplastic lung models, identifying incidental pulmonary pre-neoplasia could provide tissue for molecular profiling and experiments to better understand carcinogenesis pathways. Ideally, these findings should be identifiable through manual or automated review of the pathology report texts. Natural language processing (NLP) is a digital method for analyzing and structuring free text, capable of parsing thousands of medical reports at once. Thus, we aim to utilize NLP to identify and extract preneoplastic pathological features from an initial pilot consisting of resected non-small cell lung cancer (NSCLC) patients, using unstructured pathology reports. If successful, our pipeline will minimize the amount of manual abstraction, and facilitate the use of pathological data and archival tissue samples for critical research.

Methods: We evaluated the pathology report text from a cohort of early-stage lung cancer patients surgically resected at Princess Margaret Cancer Centre-University Health Network (Toronto, Canada) from 2014-2019. A comprehensive list of precancerous lung lesion terms, along with their variations, was approved by thoracic pathologists: carcinoma in situ (CIS), adenocarcinoma in situ, squamous dysplasia, atypical adenomatous hyperplasia, and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). In addition, we also included two additional terms to determine generalizability of this method: squamous metaplasia and idiopathic pulmonary fibrosis (IPF). Pathology report text, stored as a single text-file in JavaScript Object Notations (JSON) format, was parsed by a rule-based NLP algorithm that matched text to the list of terms. For each mention of a term, a text excerpt including 100 characters before and 200 characters after, was extracted. If another key term was identified in this window, the excerpt would extend 100 characters in that direction. These excerpts, organized by patient and source pathology report, were manually reviewed by clinical experts, and labeled as lesion present, absent or uncertain.

Results: Of the 942 patients with resected lung lesions, 259 (27%) had at least one term extracted through our NLP pipeline (in total, 645 excerpts from 279 unique pathology reports); 206 (22%) patients had at least one term identified. Of the 942 patients, 134 (14%) had a positive mention of one of the precancerous lesion terms, 18 (1.9%) for squamous metaplasia and 74 (7.8%) for IPF. Positivity was evaluated for each term separately: for individual key terms, more than 90% of terms captured by NLP had a lesion present. There were two exceptions: CIS and DIPNECH had 59% and 41% positivity, respectively, accounting for 92% of all identified terms that turned out not to have a lesion.

Conclusions: We have demonstrated the ability to rapidly extract and evaluate lung pathology terms from the unstructured text of pathology reports using NLP, reducing the need for time-consuming manual abstraction. Our next steps are to improve the performance by integrating machine learning methodologies and expanding our cohort to include all patients with resected lung tissue. When accurate, this semi-automated identification of all incidentally-discovered pre-neoplastic lesions of the lung could greatly improve the feasibility of molecular precancer research.

Keywords: Preneoplasia, non-small cell lung cancer (NSCLC), Natural Language Processing (NLP)

EP11.02 PATHOLOGY - NEW TECHNOLOGY

EP11.02-002 A Comparative Study of PD-L1 Scoring: Humans versus AI

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Introduction: Immunotherapy with PD-1/PD-L1 inhibitors has revolutionized the treatment of non-small cell lung cancer (NSCLC). In clinical practice, PD-L1 expression by immunohistochemistry has been implemented as a companion or complementary diagnostic for anti-PD-1/PD-L1 agents. A widely adopted measure of PD-L1 expression in NSCLC is the tumor proportion score (TPS), defined as the ratio of positive membranous stained tumor cells and the total number of viable tumor cells. Several automatic image analysis algorithms for determining the TPS on the whole slide images (WSI) of NSCLC have been developed recently. In our study, two PD-L1 analysis algorithms were compared to the manual PD-L1 scoring by pathologists.

Methods: Six pulmonary pathologists from different institutions independently scored 51 SP263 stained NSCLC cases under the microscope. In addition, two different commercially available PD-L1 algorithms for automatic PD-L1 TPS analysis on the same set of WSIs were applied. Algorithm 1 was CE IVD certified for usage with the SP263 assay, algorithm 2 was for research use only, without any assay specifications. The results were compared at the therapeutically relevant TPS cutoffs of 1% and 50%. Kappa statistics (weighted kappa and Fleiss' kappa) were calculated to evaluate intra- and inter-observer agreement among the pathologists and between the mean manual scores by the pathologists and the algorithm scores.

Results: Comparing the TPS results between the pathologists, we found lower bounds of the 95% confidence interval of Fleiss' kappa being 0.488 for TPS<1%, 0.503 for TPS 1% to <50%, and 0.803 for TPS≥50%. We compared the results of automatic image analysis algorithms with the median result of the six participating pathologists at the TPS 50% cutoff because algorithm 1 is CE IVD certified for this cutoff. The results of this comparison and the inter-observer comparison of the six pathologists at the TPS 50% cutoff are shown in Table 1.

Conclusions: Our comparative study found almost perfect inter-observer agreement between study pathologists. The algorithms showed lower agreement with the median manual reading by the pathologists. A detailed analysis of discordances between manual and computed analysis is needed in order to improve algorithm performance.

Table 1: Comparing Algorithms' Results with Median Result of 6 Pathologists at TPS 50% Cutoff

	Fleiss' Kappa	95% confidence interval lower bound	95% confidence interval upper bound
Pathologists (inter-observer agreement at TPS 50% cutoff)	0.873	0.803	0.944
Algorithm 1	0.354	0.068	0.64
Algorithm 2	0.652	0.423	0.882
Fleiss' Kappa interpretation: 021-0.40 fair agreement; 0.41-0.60 moderate; 0.61-0.80 substantial and 0.81-1.00 almost perfect			

Keywords: PD-L1, lung, scoring

EP11.03 PATHOLOGY - TUMOUR BIOLOGY

EP11.03-001 Loss of SUSD2 Expression in Lung Adenocarcinoma Correlates with Solid Pattern, Higher Histological Grading and Higher Ki-67 Cycling Index

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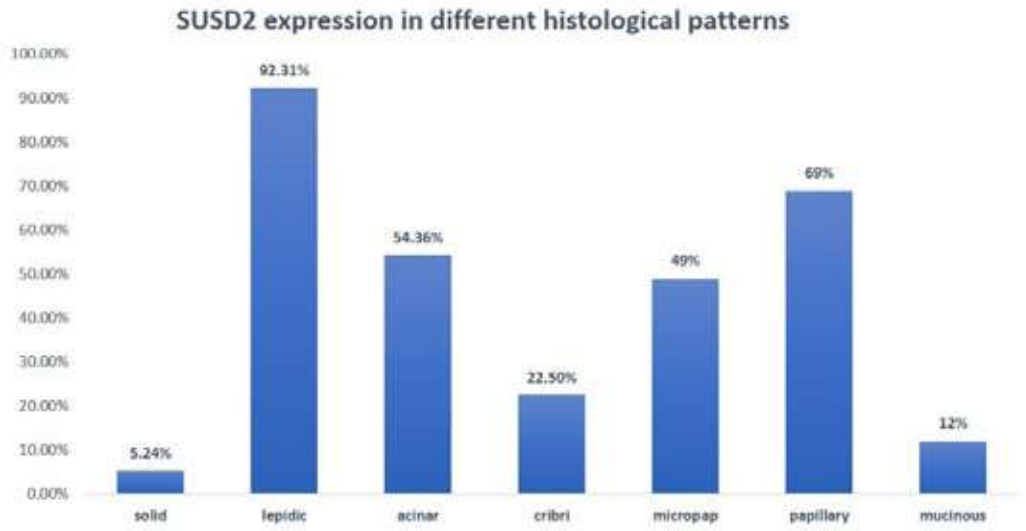
Introduction: SUSD2 is a type I membrane protein that plays a crucial role in cell-cell and cell-matrix adhesion. It has been reported to have a role in the lung adenocarcinoma (LA) microenvironment as surface proteins on the mast cells. To further understand the putative role of SUSD2 protein expression in LA progression and its association with tumor histophenotype, we performed a retrospective cross-sectional analysis looking at SUSD2 immunohistochemical (IHC) staining.

Methods: Tissue microarrays (TMAs) from 80 surgically resected LA specimens were constructed. Histological patterns on TMAs were classified based on the 2015 WHO classification. Histological grading was evaluated on the whole tumors using the 2021 IASLC proposed grading system. IHCs for SUSD2, Ki-67, PD-L1 and CD8 were performed. The first three were scored as a percentage of positive tumor cells. Correlation between SUSD2 and other parameters was analyzed together with survival analysis for PFS as the main clinical endpoint.

Results: Loss of SUSD2 expression was significantly associated with low PFS. SUSD2 protein expression was significantly decreased in solid histological pattern ($P<0.05$), in higher grade ($p<0.05$) and correlated with higher Ki-67 index. On the contrary, high SUSD2 expression was preferentially observed in the LA with the lepidic pattern ($p<0.05$). SUSD2 immunostain also negatively correlated with CD8 tumor-infiltrating lymphocytes and high PD-L1 TPS (Tumor Proportion Score).

Conclusions: Loss of SUSD2 expression in lung adenocarcinoma correlates with solid pattern, higher histological grading, and shorter PFS**.** Overall, these data point out an important role of SUSD2 in the LA immune infiltrate through a multimodal mechanism and an association of SUSD2 loss in more aggressive tumors.



Keywords: SUSD2, Lung adenocarcinoma, histological pattern

EP11.03 PATHOLOGY - TUMOUR BIOLOGY

EP11.03-002 Prognostic Significance of YAP1 and Its Association with Neuroendocrine Markers in Pulmonary Large Cell Neuroendocrine Carcinoma (LCNEC)

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Introduction: YAP1 (yes-associated protein 1), an important effector in the Hippo pathway, acts as oncogene and is overexpressed in various malignant tumors. However, the function and expression pattern of YAP1 in pulmonary large cell neuroendocrine (LCNEC) has not been systematically established. This study aims to explore the relationship between YAP1 expression and neuroendocrine differentiation markers and its prognostic significance in LCNEC.

Methods: YAP1 protein and neuroendocrine markers (INSM1, NeuroD1 and DLL3 protein) expression was examined by immunohistochemical (IHC) staining in 80 resected pulmonary LCNEC patients. The possible association between these markers were evaluated and survival analyses were also performed.

Results: YAP1 is low expressed in LCNECs (60/80, 75%),especially in a relatively early T stage (p=0.015). YAP1 expression was negatively correlated with INSM1 (x^2=11.53,p=0.001) and DLL3(x^2=8.55,p=0.004), but not significantly correlated with NeuroD1(p=0.482). For survival analyses, YAP1 expression was associated with worse disease-free survival (DFS) and overall survival (OS) (DFS: 13 months vs. not reached (NR), P=0.01; OS: not reached, NR vs. NR, P=0.038), and was an independent poor prognostic factor for DFS (P=0.003, HR:2.907; 95%CI: 1.427-5.920) in pulmonary LCNEC. However, there were no significant independent prognostic factors for OS.

Conclusions: YAP1 was found to be low expressed in LCNEC patients and is a prognostic factor for worse survival, which may be related to the dedifferentiation of neuroendocrine characteristic of tumors. To be further investigated.

Keywords: pulmonary LCNEC, YAP1, NE-related markers

EP11.03 PATHOLOGY - TUMOUR BIOLOGY

EP11.03-003 Adenocarcinoma Grade Correlates with PD-L1 and TP53, but not EGFR/KRAS Status and Diagnostic Yield: Analysis of 346 Cases

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Introduction: We aim to investigate association between IASLC three-tier adenocarcinoma grading system and common genomic alterations as well as PD-L1 status and molecular diagnostic yield, in surgically resected lung adenocarcinoma.

Methods: This is a prospective study including 346 consecutive cases with reflex biomarker testing including targeted DNA/RNA next generation sequencing and PD-L1 IHC, and 150 biopsies across the same period as control. Grading was performed according to predominant and minor growth patterns. Additional clinicopathological data were extracted from an institutional lung cancer database. Diagnostic yield was calculated in relation to (1) mean number of actionable target/case, (2) percentage of cases with ≥1 target, and (3) their respective number-needed-to-treat (NNT).

Results: Resected adenocarcinoma, compared with biopsies, were associated with higher frequency of *KRAS* mutations (*P*=0.004) but no significant difference was observed for *EGFR* mutations (*P*=0.126). *KRAS* mutations were more prevalent in invasive mucinous adenocarcinoma than other subtypes (*P*=0.006). Elevated PD-L1 expression (TPS ≥50%) and *TP53* mutations were more frequently detected in non-mucinous adenocarcinoma (*P*<0.001), and among which, grade 3 tumours (*TP53*: 62.6% vs 29.8% in grade 2 vs 9.1% in grade 1). Similarly for *EGFR/TP53*, *KRAS/TP53* and PD-L1 TPS ≥50%/*TP53* co-mutations. In non-mucinous adenocarcinoma, no significant difference was observed for *EGFR/KRAS* mutational frequencies, as well as molecular diagnostic yield. Presence of minor high grade pattern did not predict *TP53* mutation in grade 2 tumours (*P*=0.565). Lower grade tumours were associated with early stage, female sex (*P*=0.014) but not age.

Conclusions: Adenocarcinoma grade was independent of *EGFR/KRAS* status. Our data support priority rather than grade-restricted testing strategy, given the likelihood requiring adjuvant treatment and frequency of *TP53* co-mutations in grade 3 tumours. Furthermore the data suggested a potential genetic basis for subclassifying grade 2 tumours by *TP53* status. These findings may have implications in developing future risk-based diagnostic and management strategies.

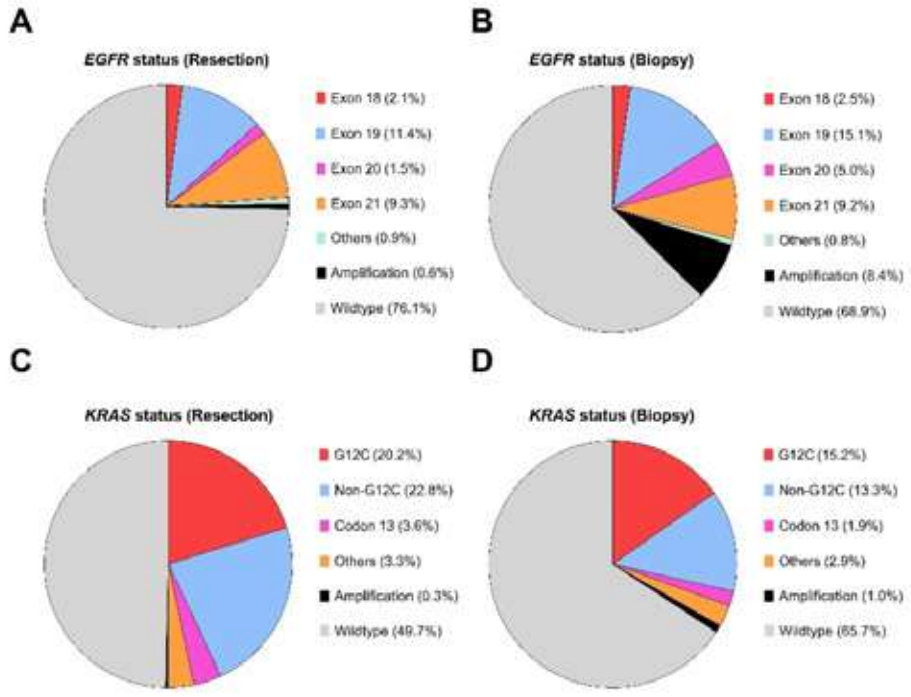

Figure 2 Pathological and Key Mutational Profiles

Variable	AIS/MIA (*n*=24)	IMA (*n*=26)	MMA (*n*=29)	G1 NMA (*n*=16)	G2 NMA (*n*=99)	G3 NMA (*n*=152)	*P*†
Stage							
0	6 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
I	18 (75.0%)	13 (50.0%)	23 (79.3%)	16 (100%)	90 (90.9%)	94 (61.8%)	
II	0 (0.0%)	5 (19.2%)	3 (10.3%)	0 (0.0%)	6 (6.1%)	18 (11.8%)	7.4×10^{-5}
III	0 (0.0%)	8 (30.8%)	3 (10.3%)	0 (0.0%)	2 (2.0%)	37 (24.3%)	
IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	3 (2.0%)	
IB (high risk) – IV*	0 (0.0%)	15 (57.7%)	12 (41.4%)	0 (0.0%)	22 (22.2%)	86 (56.6%)	5.1×10^{-11}
***EGFR* status**							
Wildtype	17 (73.9%)	23 (92.0%)	25 (89.2%)	7 (50.0%)	68 (71.6%)	114 (77.0%)	
Mutant (all)	6 (26.1%)	2 (8.0%)	4 (13.8%)	7 (50.0%)	27 (28.4%)	34 (23.0%)	0.078
Mutant (actionable)	4 (17.4%)	2 (8.0%)	4 (13.8%)	7 (50.0%)	23 (24.2%)	29 (19.6%)	**0.033**
NNT (actionable)	5.7	12.5	7.3	2.0	4.1	5.1	
EGFR/TP53 co-mutation	0 (0.0%)	2 (100%)	1 (25.0%)	0 (0.0%)	8 (29.6%)	19 (55.9%)	**0.017**
***KRAS* status**							
Wildtype	11 (52.4%)	4 (16.0%)	13 (50.0%)	6 (72.7%)	39 (45.9%)	75 (58.0%)	
Mutant (all)	10 (47.6%)	21 (84.0%)	13 (50.0%)	3 (27.3%)	46 (54.1%)	59 (44.0%)	0.141
Mutant (actionable)	4 (19.0%)	6 (24.0%)	4 (15.4%)	1 (9.1%)	24 (28.2%)	22 (16.4%)	0.068
NNT (actionable)	5.3	4.2	6.5	11.0	3.5	6.1	
KRAS/TP53 co-mutation	0 (0.0%)	1 (4.8%)	3 (23.1%)	0 (0.0%)	10 (21.7%)	28 (47.5%)	**0.012**
PD-L1 status							
TPS <1%	7 (41.2%)	18 (69.2%)	15 (51.7%)	11 (100%)	35 (38.8%)	35 (23.6%)	
TPS 1-49%	9 (52.9%)	7 (26.9%)	8 (27.6%)	0 (0.0%)	43 (45.3%)	56 (37.8%)	2.3×10^{-10}
TPS ≥50%	1 (5.9%)	1 (3.8%)	6 (20.7%)	0 (0.0%)	17 (17.9%)	57 (38.5%)	
NNT (TPS ≥50%)	17.0	26.0	4.8	n/a	5.8	2.6	
TPS ≥50%+*TP53* mutation	0 (0.0%)	0 (0.0%)	2 (33.3%)	n/a	8 (35.3%)	36 (63.2%)	**0.022**
***TP53* status**							
Wildtype	21 (100%)	23 (88.5%)	20 (74.1%)	10 (90.9%)	59 (70.2%)	52 (37.4%)	
Mutant (all)	0 (0.0%)	3 (11.5%)	7 (25.9%)	1 (9.1%)	25 (29.8%)	87 (62.6%)	3.6×10^{-7}
Yield (all stages)							
Actionable target/case	0.8 (9/24)	0.4 (10/26)	0.5 (15/29)	0.6 (10/16)	0.7 (70/99)	0.8 (123/152)	0.636
Case with ≥1 target, n (%)	8 (33.3%)	9 (34.6%)	15 (51.7%)	10 (62.5%)	60 (60.6%)	101 (66.4%)	0.257
NNT per target	1.3	2.5	1.9	1.6	1.4	1.2	
NNT/case with ≥1 target	3.0	2.9	1.9	1.6	1.7	1.5	
Yield (IB (high risk)–IV*							
Actionable target/case	0 (0/24)	0.4 (6/15)	0.4 (5/12)	0 (0/0)	0.8 (18/22)	0.8 (73/86)	0.528
Case with >1 target	0 (0.0%)	6 (40.0%)	5 (40.0%)	0 (0.0%)	16 (72.7%)	56 (65.1%)	0.016
NNT per target	n/a	2.5	2.4	n/a	1.2	1.2	
NNT/case with ≥1 target	n/a	2.5	2.4	n/a	1.4	1.5	

AIS, adenocarcinoma in situ; G, grade; IMA, invasive mucinous adenocarcinoma; MMA, mixed mucinous adenocarcinoma, NMA, non-mucinous adenocarcinoma; NNT, number needed to treat; TPS, tumour proportion score.

† For non-mucinous adenocarcinoma only.
* High risk stage IB defined as either of (1) histological subtype of mixed mucinous adenocarcinoma or grade 3 non-mucinous adenocarcinoma, (2) pleural invasion or uncertain pleural status, or (3) positive resection margin.

Keywords: Adenocarcinoma, Grade, TP53

EP11.03 PATHOLOGY - TUMOUR BIOLOGY

EP11.03-004 Identification of Filigree Pattern Increases Diagnostic Accuracy of Micropapillary Pattern on Frozen Section for Lung Adenocarcinoma

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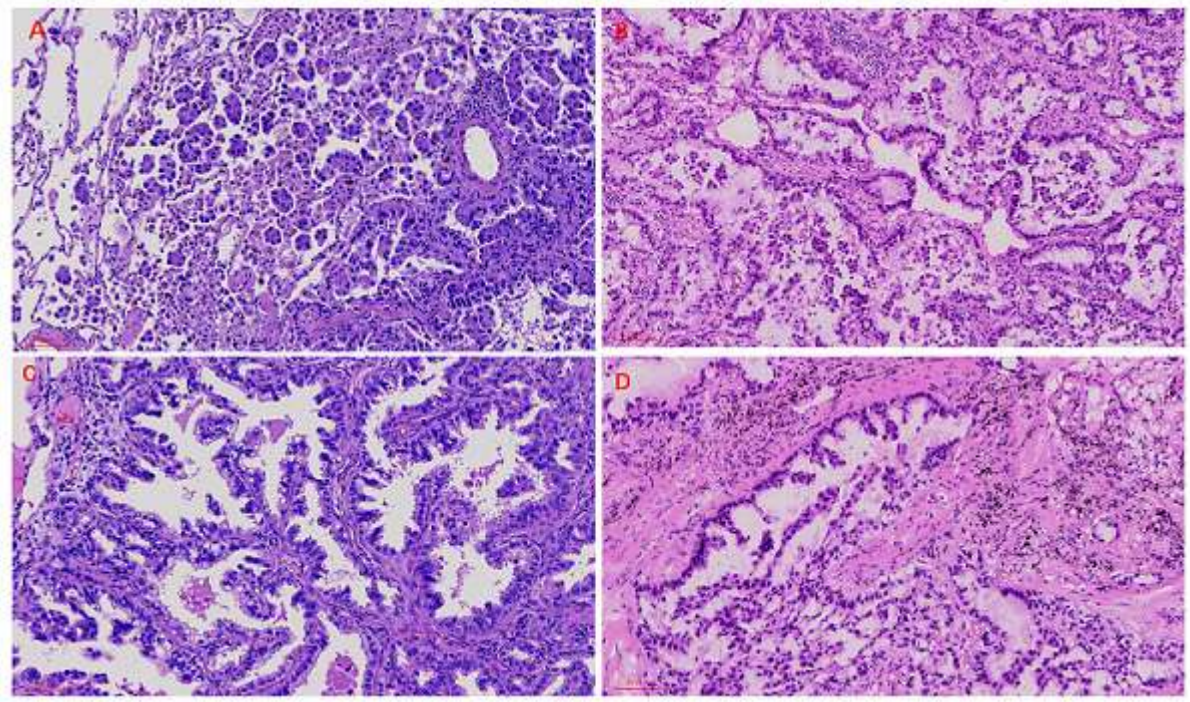
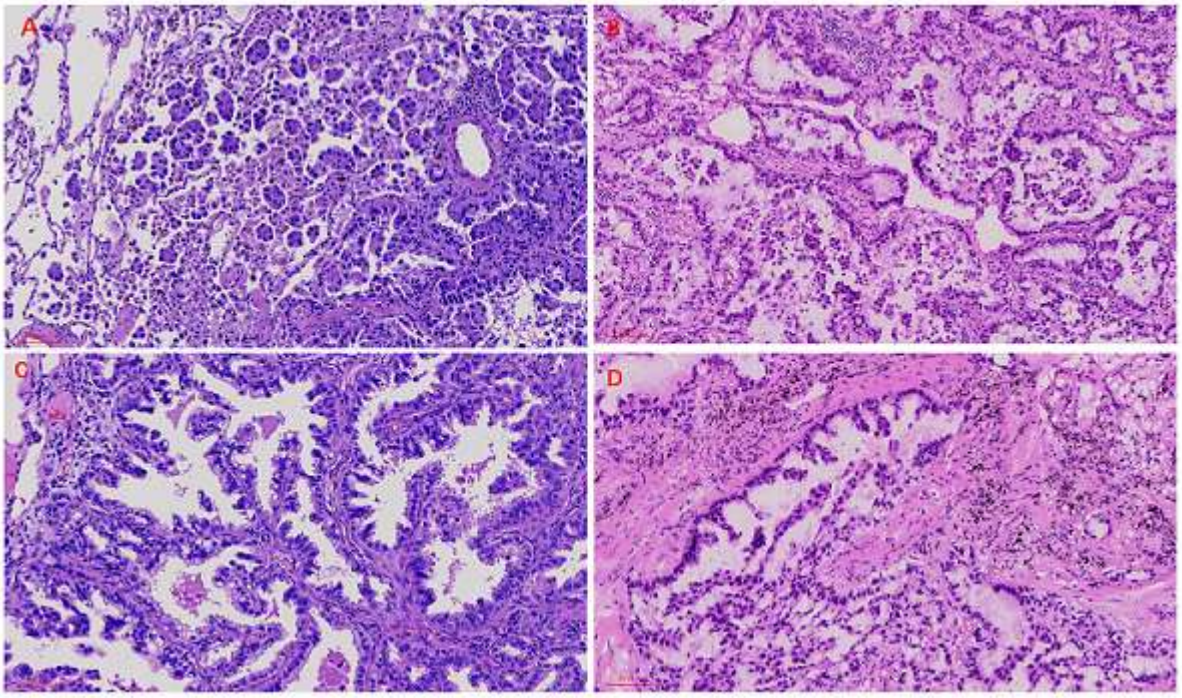
Introduction: The presence of micropapillary (MIP) in early-stage lung adenocarcinoma was associated with a poorer prognosis, especially in patients undergoing sublobectomy. However, data on the sensitivity of frozen section (FS) evaluation of MIP was still limited. We included the concept of filigree pattern on FS to assess its effect on the diagnostic sensitivity and specificity of MIP and verify its prognostic value in stage T1 lung adenocarcinoma.

Methods: A panel of five pathologists evaluated 125 patients with T1 lung adenocarcinoma as a study cohort from January to February 2014, and 151 patients as a validation cohort from January to February 2020. The diagnostic accuracy of filigree and classical micropapillary (cMIP) pattern on FS was investigated.

Results: Diagnostic sensitivity of MIP pattern on FS increased from 43.2% to 65.3% and 56.8% to 81.1% with good specificity in the study cohort and validation cohort. Filigree increased the sensitivity identification MIP without cMIP increased the sensitivity when the amount of cMIP is low. The almost perfect agreement was reached on cMIP pattern and substantial agreement on the filigree pattern in the two cohorts. Moreover, the cMIP and filigree pattern were correlated with poorer recurrence-free survival (p_{cMIP} = 0.003; $p_{filigree}$ = 0.032) and overall survival (p_{cMIP} = 0.004; $p_{filigree}$ = 0.005).

Conclusions: Identification of filigree help to improve the diagnostic sensitivity of MIP pattern on FS. FS was feasible for the detection of filigree and cMIP patterns in stage T1 lung adenocarcinomas.





Keywords: Frozen Section, Micropapillary, Filigree

EP11.04 PATHOLOGY - TUMOUR DIAGNOSTICS

EP11.04-001 Cytokeratin 5-Positive Pulmonary Adenocarcinoma: A Study with Resected Specimens

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Introduction: Cytokeratin 5 (CK5) is a marker for squamous cell carcinoma; however, it expresses in pulmonary adenocarcinoma. This study aimed to explore the clinicopathological characteristics of CK5-positive pulmonary adenocarcinoma (CK5-positive PADC) using resected specimens.

Methods: Immunohistochemical CK5 analysis was performed with 220 resected PDACs. CK5-positive PADC was defined as a tumor with 10% or over of CK5-positive tumor cells.

Results: We found that CK5-positive PADCs were 29 (13.2%). CK5-positive PADCs were associated with a higher stage ($p<0.001$), larger size ($p<0.001$), lymph node metastasis ($p=0.019$), pleural invasion ($p<0.001$), vascular invasion ($p<0.001$), lymphatic invasion ($p<0.001$), mucinous differentiation ($p<0.001$), and STAS ($p<0.001$). In addition, CK5-positive PADCs were associated with TTF-1 negative expression ($p<0.001$), wild-type *EGFR* mutations ($p<0.001$), and *ROS1* rearrangement ($p=0.024$). In terms of histological details, over half of CK5-positive PADCs contained mucinous cells (19 cases, 65.5%), whereas all non-mucinous CK5-positive PADC cases harbored high-grade components, such as solid and discohesive patterns.

Conclusions: CK5-positive PADCs showed aggressive clinical behavior, with high-grade morphology and mucinous differentiation.

Keywords: pulmonary adenocarcinoma, cytokeratin 5, mucinous differentiation

EP11.04 PATHOLOGY - TUMOUR DIAGNOSTICS

EP11.04-002 The Histopathological Reasons for Better Survival of Patients with Lepidic Pattern Dominant Adenocarcinoma

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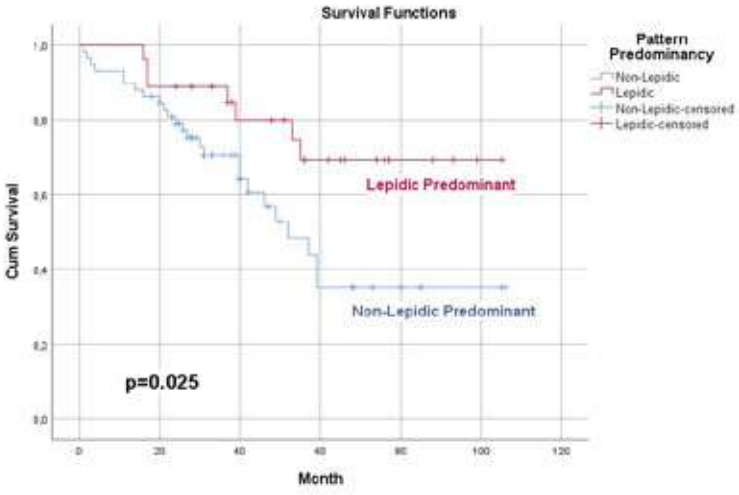
Introduction: Survival in patients with lung cancer may vary depending on TNM, histopathological types, patient-related factors and tumor biology. Lepidic adenocarcinoma is characterized by non-invasive tumor growth within the alveolar wall. Lepidic pattern (LPA) predominance shows survival advantage compared to acinar, papillary and solid predominant adenocarcinomas. In this study, we aimed to investigate the reasons behind LPA being associated with better survival.

Methods: We retrospectively reviewed the records of 105 patients with adenocarcinomas operated for non-small cell lung cancer in our department between 2011 and 2018. Patients with small cell components, insufficient data were excluded. Eighty-six patients were age, gender, histopathology, TNM stages, perineural or lymphovascular invasions of the patients were recorded. Patients with adenocarcinoma were analyzed under two groups as lepidic dominant (Group 1) and non-lepidic predominant (Group 2). The patients were followed up for an average of 64 months. Univariate (log-rank) and multivariate analyses (Cox) were performed.

Results: There were 28 patients in Group 1 and 58 patients in Group 2. There was a survival advantage in patients with LPA. The overall survival was 84 months (95% Confidence Interval: 70-97 months) in Group 1 and 60 months in Group 2 (95% Confidence Interval: 48-72 months)(p=0,025). Univariate analysis showed LPA, N0 stage, negative LVI and PNI is associated with better survival while STAS and gender were not significant. Multivariate analysis revealed that there were no independent factor among those and that they were all related.

Conclusions: Lepidic cell type is a subgroup of adenocarcinomas that is considered minimal to non-invasive. We found that LPA is related with better survival but wasn't independent. It was found to be related with N stage and LVI and PNI status. Better survival of LPA can be attributed to these less invasive features of tumors. Multicenter, larger databases should be studied to support this conclusion.



Univariate and Multivariate analysis for the prognostic factors						
	Univariate			**Multivariate**		
	Hazard Ratio	**95% Confidence Interval**	**p Value**	**Hazard Ratio**	**95% Confidence Interval**	**p Value**
Predominant pattern						
Non-Lepidic / Lepidic	2.549	1.092-5.949	0.031	2.05	0.861 - 4.88	0.105
Gender						
Female / Male	0.455	0.175 - 1.184	0.107	-	-	-
N stage						
N0 / N1-2	0.399	0.197 - 0.807	0.011	0.591	0.284 - 1.226	0.158
STAS						
Negative / Positive	0.851	0.382 - 1.896	0.693	-	-	-
LVI						
Negative / Positive	0.192	0.046 - 0.805	0.024	0.306	0.069 - 1.360	0.12
PNI						
Negative / Positive	0.429	0.211 - 0.874	0.02	0.62	0.297 - 1.296	0.204

Keywords: lung cancer, lepidic patern, adenocarcinoma

EP12.01 PATIENT ADVOCACY

EP12.01-001 What Do Patients Want - a European Study Into ALK-Positive Patients Perspectives

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Introduction:

In order for patient advocacy organisations to represent and advocate for their members appropriately, it is critical to understand the patient perspective. In this study, we polled European ALK-positive patients and analysed their responses.

Methods: We presented patients with a 10 question survey, designed to extract their views on treatment and care availability, where organisations should spend their fundraising money and direct their advocacy efforts. We elected to restrict respondents to Europe as healthcare systems are similar, allowing for stronger conclusions to be drawn.

Results: 135 responses were received, 3 of which were discarded as they were patients outside Europe and therefore invalid. Over one third of responses were from the UK, Germany and France were the second and third most represented countries. In total, 14 different countries participated. When asked to prioritise research, patient support or public awareness, 91% selected research as their highest priority initiative. Over 80% of respondents answered that they would be willing to try a treatment or combination of treatments, without enough evidence to prove its efficacy over standard of care. Higher still, the number of patients who want more open access to treatments based on next generation sequencing, rather than treatments being allowed only in specific orders. Over two thirds of patients (69.5%) would consider joining a clinical trial, even if they still had treatment options available. Over two thirds (72.5%), would consider local consolidative therapy proactively (without disease progression), if given the option. 35% of patients were not offered mental health counselling at diagnosis, slightly less than those who were offered but chose not to use the services(40%). The remaining respondents used the service and found it useful (22%) or not useful (3%). When diagnosed, 39% of respondents received results of biomarker testing within 2 weeks, but 24% waited more than one month. When asked where they wanted relevant research projects to take place, 61% selected the location with the best infrastructure, and 31% wanted research in their country.

Conclusions: By exploring the data received in the survey, it is overwhelmingly evident that patients value research extremely highly, and most want it to happen where the best infrastructure and researchers are. Patients are also in favour of clinical trials, and changes to the way treatments are approved by regulators. Using this information, patient advocacy organisations such as ours know what the people we are representing want, and this is of utmost importance.

Keywords: patient, advocacy, perspectives

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-001 The Burden of Incidental Extra-thoracic Positron Emission Tomography-CT (PET-CT) Findings in Thoracic Malignancies

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Introduction: NICE recommends PET-CT scans to improve diagnostic and stage accuracy in the assessment of patients with suspected/confirmed lung cancer. PET-CT scans, however, identify incidental findings, of 9.2% of patients in one study, which often warrant further investigations.

Methods: We performed a retrospective analysis of the incidence and significance of incidental extra-thoracic findings, suspicious for cancer, on PET-CT scans performed to investigate patients with possible lung cancer in Glenfield Hospital between February 2019 and October 2021.

Results: A total of 4229 patients were referred to our local Lung MDT with 851 patients (20%) undergoing PET-CT scans as part of their assessment. 241 incidental extra-thoracic findings were found in 202 patients (23.7%). Of whom 25 patients had two and seven patients had three additional findings. The most common extra-thoracic sites were bowel (n=67, 27.8%), head and neck including thyroid (n=61, 25.3%) and prostate (n=21, 8.7%).Of the 239 incidental findings, there was incomplete data for 11 findings. Of 228 findings, 158 underwent further investigation of which 49 (31%) were malignant (including histological and radiological diagnosis), 99 (62.7%) were benign and 10 were indeterminate. 67 (28%) incidental findings were not referred for further investigations, including patients not suitable for investigation.

Conclusions: In our study, PET-CT identified suspicious extra-thoracic findings in almost one-fifth of patients. On further assessment, 21% were identified to be primary malignancies. This highlights the importance of further investigations. Furthermore, kidneys, upper-gastrointestinal sites and bones had the highest proportions of malignancy while peritoneum, non-renal urological sites and breast had the highest proportion of benign causes.

Site	Gender		Mean Age	Benign (% of investigated findings)	Indeterminate (% of investigated findings)	Malignant (% of investigated findings)	No further investigations
	Male	Female					
Adrenal	3	6	80	4 (67%)	1	1 (16%)	3
Bone	11	6	67	7 (44%)	0	9 (56%)	1
Breast	0	7	77	5 (71%)	0	2 (29%)	0
Colon	38	29	73	22 (69%)	0	10 (31%)	35
Gynaecological	0	9	72	3 (43%)	0	4 (57%)	2
Head & Neck	23	18	72	16 (76%)	3	2 (9%)	20
HPB	11	6	72	9 (56%)	1	6 (36%)	1
Kidney	2	1	71	0	0	2 (100%)	1
Lymph nodes	14	5	60	8 (50%)	3	5(31%)	3
Peritoneum	1	0	55	1 (100%)	0	0	0
Prostate	21	0	76	11 (73%)	0	4 (27%)	6
Thyroid	4	15	76	8 (73%)	2	1 (9%)	8
Upper Gastrointestinal	3	2	85	2 (40%)	0	3 (60%)	0
Urology (non-renal)	3	1	63	3 (75%)	0	1 (25%)	0

Keywords: PET-CT, extrathoracic, malignancy

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-002 Radiomic Signature on CT Images: A Noninvasive Biomarker for Pretreatment Discrimination of EGFR Mutations in NSCLC Patients

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Introduction: Identification of the molecular pathways that drive malignancy led to the development of targeted therapy in cancer. Epidermal Growth Factor Receptor (EGFR), the leading one of these molecular targets, plays a key role in cell proliferation, angiogenesis, metastasis. This study aimed to assess the performance of pretreatment computed tomography (CT) radiomics features for predicting EGFR mutation status for predicting EGFR mutation status in patients with non-small cell lung cancer (NSCLC).

Methods: Between 2012 and 2020, there were 1243 patients with histologically proven NSCLC and were tested for EGFR mutation. 430 of these patients who underwent CT examination in our institution whose lesion was suitable for segmentation were included. Two groups were defined; EGFR Wild Type (n=372) and EGFR Mutant (n=58). The patients were randomly divided into a validation set (50 patients) and a training set (380 patients) according to a balanced distribution of clinical and radiological features. A total of 1409 quantitative imaging features were extracted from CT images with the Radcloud platform. The Lasso algorithm was used for feature selection, machine learning methods were used to construct radiomics models. Receiver operating characteristic (ROC) curve analysis was applied to evaluate the performance of the radiomic signature between different data and methods.

Results: We selected 89 features (Figure 1), finally we selected 3 optimal features with Lasso algorithm. The AUC of XGBoost machine learning methods was the highest for training data (AUC 1 %95 CI 0.91-0.98) and test data (AUC 0.658, %95 CI 0.61 to 0.70), respectively. For differentiation of groups XGBoost classifier was the best method. In these ML classifiers; The range for EGFR- group in training set was; Precision (1), Recall (1), F1-score (1), and Support (116) while the range for EGFR+ group was; Precision (0.9), Recall (1), F1-score (0.96), and Support (15). The range for EGFR- group in the test set was; Precision (0.88), Recall (1), F1-score (0.94), and Support (30) while the range for EGFR+ group was; Precision (0.17), Recall 0.50), F1-score (0.25), and Support (4). The highest scores were achieved with XGBoost machine learning methods**.**

Conclusions: Radiomics modeling can predict tumor's EGFR mutation status. This valuable analysis shows that radiomics can be an option for patients in whom biopsy is technically not feasible or not adequate to detect EGFR mutations. In the future, radiomics may be the essential tool in determining the molecular subgroups of NSCLC. More studies are needed in this field.

	All cases % (n)	EGFR Wild Type % (n)	EGFR Mutant % (n)	P Value
Patient number	430	(n=372)	(n=58)	
Age (mean) ± SD	62.15±10	62.06±9.8	62.7±11.3	NS
Gender (n, %)				
Female	26.7 (n=115)	21 (n=78)	63.8 (n=37)	0.00
Male	73.3 (n=315)	79 (n=294)	36.2 (n=21)	
Smoking (n=274)				0.00
Yes	76.6 (n=210)	82.6 (n=195)	39.5 (n=15)	
No	23.4 (n=64)	17.4 (n=41)	60.5 (n=23)	
Histopathological type				
Adenocarcinoma	66.7 (n=287)	64.8 (n=241)	79.3(n=46)	0.035
Others	33.3 (n=143)	35.2 (n=131)	20.7 (n=12)	

Keywords: Machine Learning, EGFR, Lung cancer

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-003 Diagnostic Yield of Radial Probe Endobronchial Ultrasonography without Fluoroscopic guidance in Peripheral Pulmonary Lesions

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Introduction: Although the radial probe endobronchial ultrasound (R-EBUS) has been used for the investigation of peripheral pulmonary lesions (PPLs), it's diagnostic performance has remained unclear. The aim of the present study was to evaluate the diagnostic yield of R-EBUS guided TBB (transbronchial biopsy) without fluoroscopy to diagnose PPLs through systematic review and meta-analysis.

Methods: A systematic literature search was performed using the Pubmed, Embase, and the Cochrane Central Register. A proportional meta-analysis was performed to calculate the pooled diagnostic yield of R-EBUS guided TBB without fluoroscopy. Diagnostic yield was calculated as dividing the number of successful diagnoses through the index tool by the total number of PPLs. We included not only trials comparing R-EBUS with other tools but also studies from only the R-EBUS arms. In cases of substantial heterogeneity, the subgroup and meta-regression analysis were explored to identify potential sources of bias.

Results: We identified 31 studies with a total of 6,491 patients. The pooled overall diagnostic yield of R-EBUS guided TBB without fluoroscopy was 0.70 (95% CI, 0.67-0.74). There was the presence of significant heterogeneity across studies (I^2 = 89.45%, P <0.001). Because substantial between-study heterogeneity was present for diagnostic yield among studies of index test, subgroup analysis and meta-regression was carried out. The lesions with air bronchus sign on PPLs in chest CT had a significantly higher diagnostic yield than those without air bronchus sign (0.81, 95% CI 0.75-0.86 vs. 0.46, 95% CI 0.32-0.61; P < 0.001). For the location, the diagnostic yield from upper lobe was statistically lower than that from middle and lower lobes (0.71, 95% CI 0.68-0.74 vs. 0.76, 95% CI 0.71-0.81; P = 0.046). And a larger size PPLs were associated with a significantly high diagnostic yield (0.81, 95% CI 0.77-0.86 vs. 0.62, 95% CI 0.56-0.67; P < 0.001 for cutoff 3 cm, and 0.75, 95% CI 0.71-0.80 vs. 0.53, 95% CI 0.45-0.61; P < 0.001 for cutoff 2 cm, respectively). Finally, subjects in which the probe was located within the lesions had a statistically high diagnostic yield (0.81, 95% CI 0.77-0.85). If the probe could be put adjacent to the lesions rather than in the lesions, the diagnostic yield of TBB decreased largely (0.47, 95% CI 0.39-0.55; P < 0.001). Among the included studies, the percentage of the incidence of pneumothorax and significant bleeding ranged from 0.60 to 5.12 and 0 to 8.12, respectively.

Conclusions: R-EBUS guided TBB without fluoroscopy seems to be relatively useful tool in the diagnosis of PPLs. Factors mentioned above seemed to have a statistically significant impact on the diagnostic yield of R-EBUS without fluoroscopy guidance. Because of substantial between-study heterogeneity, our results should be interpreted with caution.

Keywords: Radial probe endobronchial ultrasound, Fluoroscopy, Peripheral pulmonary lesions

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-004 Accuracy of Clinical Stage in Resectable Non-small Cell Lung Cancer (NSCLC)

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Introduction: Accuracy of clinical staging is important in non-small cell lung cancer (NSCLC), because unnecessary morbidity and mortality of treatment can be minimized with correct clinical stage. Although each diagnostic modalities have high sensitivity and specificity, the accuracy is generally low; about 50-60%. Therefore, we evaluated clinical stage accuracy between 2019 and 2020. Moreover, we evaluated factors affecting the clinical staging accuracy of NSCLC.

Methods: A total of 811 patients, those who had undergone curative lung resection surgery with primary NSCLC in Severance hospital from January 2019 to December 2020, were retrospectively reviewed. The 8th AJCC TNM staging system for NSCLC was used in this study.

Results: TNM, T, N staging accuracy were 68.7% (557/811), 77.7% (630/811), 85.7% (695/811), respectively. Clinical staging accuracy is lower in male sex (OR 0.59; 95% CI 0.44-0.80, P=0.001), heavy smokers (OR for smoker 0.57; 95% CI 0.42-0.77, P<0.001; OR for pack-years 0.99; 95% CI 0.98-1.00, P<0.001), presence of diabetes mellitus (OR 0.70; 95% CI 0.50-0.99, P=0.040), higher clinical TNM stage (P<0.001), clinical N1 stage (OR 0.32; 95% CI 0.16-0.64, P<0.001, compared to N0), performing EBUS (OR 0.68; 95% CI 0.50-0.93, P=0.016), presence of PET (positron emission tomography) uptake (OR for metastasis 0.27; 95% CI 0.17-0.43, P<0.001) in univariable logistic regression analysis. In multivariable analysis, current smokers (OR 0.49; 95% CI 0.31-0.77, P=0.002), performing EBUS (OR 0.14; 95% CI 0.06-0.30, P<0.001), higher clinical stage (P<0.001), larger node size (OR 0.11; 95% CI 0.06-0.21, P<0.001) showed lower accuracy in clinical staging. And patients who diagnosed in 2020 compared to 2019 (OR 1.49; 95% CI 1.05-2.10, P=0.025) showed higher accuracy in clinical staging.

Conclusions: The agreement between the clinical stage and the pathologic stage is improved. The concordance is much higher in male, never-smoker, and early stage NSCLC.

	Clinical stages							
Pathologic stages	cIA	cIB	cIIA	cIIB	cIIIA	cIIIB	Total	% of total
pIA	**423**	39	4	3	0	1	470	58.0
pIB	54	**65**	7	5	0	0	131	16.2
pIIA	0	4	**18**	2	0	0	24	3.0
pIIB	28	22	13	**29**	6	0	98	12.1
pIIIA	19	16	2	19	**22**	0	78	9.6
pIIIB	1	1	1	3	3	**0**	9	1.1
pIV	1	0	0	0	0	0	1	0.1
Total	526	147	45	61	31	1	811	
% of total	64.9	18.1	5.5	7.5	3.8	0.1	100	
Underestimation (%)	19.6	29.3	35.6	36.1	9.7	–	23.1	
Overestimation (%)	–	26.5	24.4	16.4	19.4	100	8.3	
cTNM=pTNM (%)	80.4	44.2	40.0	47.5	71.0	73.5	**68.7 (557/811)**	

	cT1	cT2a	cT2b	cT3	cT4	Total	% of total
pT1	**458**	46	5	3	0	512	63.1
pT2a	74	**102**	9	4	0	189	23.3
pT2b	0	6	**29**	4	0	39	4.8
pT3	10	9	3	**27**	2	51	6.3
pT4	0	1	0	5	**14**	20	2.5
Total	542	164	46	43	16	811	
% of total	66.8	20.2	5.7	5.3	2.0	100	
Underestimation (%)	15.5	9.8	6.5	11.6	–	13.4	
Overestimation (%)	–	28	30.4	25.6	12.5	9	
cT=pT (%)	84.5	62.2	63.0	62.8	87.5	**77.7 (630/811)**	

	cN0	cN1	cN2	cN3	Total	% of total
pN0	**671**	4	1	1	677	83.5
pN1	57	**17**	0	0	74	9.1
pN2	39	14	**7**	0	60	7.4
pN3	0	0	0	**0**	0	0
Total	767	35	8	1	811	
% of total	94.6	4.3	1.0	0.1	100	
Underestimation, (%)	12.5	40.0	–	–	13.6	
Overestimation, (%)	–	11.4	12.5	100	0.7	
cN=pN (%)	87.5	48.6	87.5	0.0		**85.7 (695/811)**

Keywords: NSCLC, clinical stage, staging accuracy

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-005 Role of Artificial Intelligence on Chest Radiographs for Detecting Resectable Early Lung Cancer

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Introduction: Despite the importance of early screening of lung cancer, detecting early lung cancer with chest radiographs remains challenging. The aim of this study was to investigate whether artificial intelligence (AI) can detect resectable early lung cancer on chest radiographs.

Methods: This study was conducted on patients who underwent lung cancer surgery at 3 referral hospital from March 2020 to February 2021. We conducted a retrospective evaluation of AI-based lesion detection software that analyzes lung nodule on chest radiographs. Medical records of patient's demographic characteristics, pathologic and radiologic results were retrospectively reviewed.

Results: Among the 827 patients with resectable lung cancer, median age was 66 years and 51.3% were male. In pathologic diagnosis, adenocarcinoma was 82.7% and Squamous cell ca was 12.6%. Of all patients, 75.4% of patients had stage I (stage IA: 60%, stage IB: 15.4%) lung cancer, and stage II and III were 15% and 9.4%, respectively. 55.9% of patients were detected by Lung cancer through AI lung nodule software (AI nodule detection cutoff: 15%), and the average nodule abnormality score was 40.4. The mean size of resected lung cancers was 2.3 cm (IQR : 1.4 - 3.0 cm) and tumor size and nodule detection abnormality showed a statistically significant correlation (r: 0.348, $p<0.001$)

Conclusions: Our results showed that significant number of resectable early lung cancers were detected by AI lung nodule software. Further large-scale, well-designed study on the role of AI chest radiographs in early lung cancer detection is needed in the future.

Keywords: Lung cancer, artificial intelligence, chest radiographs

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-006 Safety of Image Guided Research Biopsies in Patients with Thoracic Malignancies

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Introduction: Remarkable progress has been made in treatments for advanced thoracic malignancies based on comprehensive biomarker testing at diagnosis and at tumor progression. Investigation of treatment resistance requires examination of both the tumor and its microenvironment. A common opportunity to collect research samples is during image guided percutaneous core needle biopsies (CNBs) performed as clinically indicated and for assessing eligibility for a clinical trial. The relative safety of extra CNBs collected for research is thus far undefined.

Methods: This retrospective cohort study included patients who underwent CNB for research purposes only [RO], as clinically indicated [CI] or as part of a clinical trial [CT]. Immediate and 30-day post procedure adverse events (AEs) were reviewed. Poisson regression with robust standard errors was used to compare the relative risk of AEs between cohorts. Outcomes were the AE rate between RO and CI+CT CNBs and the association between number of samples and AEs. Outcomes were compared to the 2020 SIR QI guidelines.

Results: 217 patients with thoracic cancers (89% NSCLC, 2% SCLC, 3% mesothelioma, 2% thymus cancers and 4% suspected thoracic cancer) had 246 CNBs (62 RO and 184 CI+CT) between 1/1/2019 and 6/30/2021. Median age was 66 (range: 23-90), 57% were women. The most common targets were lung 34%, liver 25%, and lymph nodes 7%. AEs occurred in 15% in the RB group and 10% in the CI+CT group. Compared to the CI+CT group, the RO group did not have a significantly higher pneumothorax incidence (19% [5/27] with one chest tube placement vs 10% [9/88] with one chest tube placement, p=0.31, Fisher's exact test). Both groups were well below the QI threshold of 45% and 20% for pneumothorax and chest tube placements, respectively. There was no significant difference in risk between the RO vs CI+CT CNB groups (relative risk (RR)=1.48, 95% CI 0.70, 3.13; p=0.30). Interestingly, there was a negative association between number of cores obtained and risk of AE (AE vs no AE mean cores = 3.8 vs 4.9). After adjusting for the number of cores, RO vs CI+CT lung biopsies had a higher risk of AEs (RR=3.52, 1.49-8.30; p=0.004 vs non-lung RR=1.63, 0.29-9.25; p=0.58).

Conclusions: Overall CNBs performed for research purposes do not have a significant increased risk of AEs when compared to those performed for clinical trial and/or when clinically indicated. However, AEs were more frequent in lung biopsies when compared to other sites. When performing a biopsy for research purposes, a target other than lung may be preferred.

Keywords: research biopsy, interventional radiology, correlative research

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-007 Differentiation Between Heterogeneous GGNs and Part Solid Nodules Using Histogram on Thin-section CT

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Introduction: To evaluate the patients with surgically resected lung adenocarcinoma (Ad) with heterogenous ground-glass nodules (GGNs) and part-solid nodules, and to clarify the difference between these lesions using grayscale histogram on thin-section CT.

Methods: Between 2006 and 2015, 320 patients with proven lung Ad in stage IA were retrospectively reviewed. Preoperative lung Ad lesions were investigated visually, and were classified into solid nodule, part-solid nodule, heterogeneous GGN, and pure GGN group on thin-section CT. In this study histogram features on thin-section CT between heterogeneous GGNs and solid nodules were compared. Pathological diagnoses based on IASLC/ATS/ERS new classification of lung Ad advocated in 2011 have been obtained in 133 patients. 31 heterogeneous GGNs were classified into 9 invasive adenocarcinomas (IVAs) (29.0%), 14 minimally invasive adenocarcinomas (MIAs) (45.2%), and 8 adenocarcinomas in situ (AIS) (25.8%), and 102 part-solid nodules were classified into 72 invasive adenocarcinomas (70.6%), 25 MIAs (24.5%), and 5 AIS (4.9%).

Results: The numbers of the types including solid nodule, part-solid nodule, heterogeneous GGN and pure GGN in stage IA were 70, 181, 60 and 9, respectively. We found significant differences in average CT value (-571 ± 120 vs -364 ± 139; $P < 0.0001$), Max CT value (60 ± 112 vs 209 ± 76; P < 0.0001), standard deviation (206 ± 38 vs 286 ± 38; $P < 0.0001$), area (165 ± 86 vs 234 ± 167; $P < 0.0001$), percentage of solid part (15.2 ± 13.6 vs 44.8 ± 18.6; $P < 0.0001$), skewness (0.53 ± 0.65 vs -0.14 ± 0.64; $P < 0.0001$), kurtosis (3.53 ± 1.49 vs 2.44 ± 0.74; $P < 0.0001$), and entropy (7.95 ± 0.57 vs 8.39 ± 0.52; $P < 0.0001$) between the heterogeneous GGN and part-solid nodule group, respectively. On the other hand, we found no significant differences in Minimum CT value (-1008 ± 136 vs -1039 ± 102; $P = 0.0586$). Pathologically in heterogeneous GGN group, we found significant differences in average CT value (-496 ± 151 vs -617 ± 112; $P = 0.0247$), Max CT value (128 ± 66 vs 25 ± 110; P = 0.0165), standard deviation (227 ± 27 vs 188 ± 38; $P = 0.0099$), and skewness (0.20 ± 0.90 vs 0.80 ± 0.59; $P = 0.0404$)) between the IVAs and MIAs+AIS group, respectively. In part-solid nodule group, we found significant differences in average CT value (-352 ± 143 vs -430 ± 130; $P = 0.0114$) and skewness (-0.24 ± 0.69 vs 0.19 ± 0.57; $P = 0.0042$)) between the IVAs and MIAs+AIS group, respectively.

Conclusions: Quantitative evaluation by using grayscale histogram can clearly distinguish heterogeneous GGNs and part-solid nodules and may be useful in estimating pathology.

Keywords: Computed tomography, Heterogeneous ground glass nodule, Grayscale histogram

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-008 Needle Aspiration versus Forceps Biopsy Using Electromagnetic Navigation Bronchoscopy: CONFIDENT-ENB Trial Design

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Introduction: Electromagnetic navigation bronchoscopy (ENB) is an emerging advanced imaging-guided bronchoscopy technique for diagnosing pulmonary lesions. However, the selection strategy for the optimal biopsy device and whether adopting a multi-tool strategy increases the diagnostic yield remains undetermined. The CONFIDENT-ENB trial (NCT05110131) is a prospective randomized crossover study on ENB performed in a least-invasive setting with two primary aims: 1) compare the diagnostic value of needle aspiration and forceps biopsy in diagnosing lung lesions suspected of malignancy; and 2) evaluate whether a combination of the two devices improves the diagnostic performance.

Methods: The trial will recruit 140 participants with lung lesions suspected of malignancy who are eligible for an elective ENB procedure under moderate sedation. Participants will undergo ENB-guided needle aspiration and forceps biopsy in a randomized order without the use of any complementary techniques. All participants will be followed up subsequently for 12 months to conclude the final diagnosis of the biopsied lesions. Primary outcomes include the diagnostic yield and sensitivity of each biopsy modality and the diagnostic yield of the combined modalities.

Table. Definitions and overview of study endpoints.

Primary endpoint: diagnostic values
- Primary endpoints will be calculated separately for needle aspiration and forceps biopsy. The final diagnosis will be confirmed based on the 12 months of clinical follow-up.
- Diagnostic yield:
Proportion of subjects in whom the ENB-guided biopsy yielded a definite diagnosis
= (malignant and benign diagnosis by modality)/(biopsied lung lesions)
- Sensitivity:
= (Malignancy confirmed by modality)/(Number of malignancies confirmed at 12-month follow-up)
- Specificity:
= (Benign confirmed by modality)/(Number of benign lesions confirmed at 12-month follow-up)
- Positive predictive value:
= (True malignant lesions)/(Number of malignant lesions by modality)
- Negative predictive value:
= (True benign lesions)/(Number of benign lesions by modality)
Secondary endpoints
- Secondary outcomes will be calculated separately for needle aspiration and forceps biopsy.
- Navigation success:
Target lesion successfully reached with the biopsy tool, identified by the dedicated navigation software.
- Procedure time:
Duration between the initial introduction of the tool and final removal of the biopsy tool
- Time per biopsy attempt:
Procedure time divided by the number of biopsy attempts
- Successful acquisition of core tissue:
Acquisition of a fresh tissue available for histologic examination
Procedure-related adverse events
-Pneumothorax
-Bronchopulmonary hemorrhage
-Respiratory failure

ENB-guided biopsy: Electromagnetic navigation bronchoscopy-guided biopsy

Results: No results yet to submit

Conclusions: The CONFIDENT-ENB trial will prospectively evaluate the comparative accuracy and synergistic effectiveness of ENB-guided needle aspiration and forceps biopsy in a least-invasive setting. The results are expected to improve our understanding of the optimal tool-selection strategy for ENB.

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-009 A Modified T Categorization for Pathological Stage I Lung Adenocarcinoma with Lepidic Component in Chinese Population

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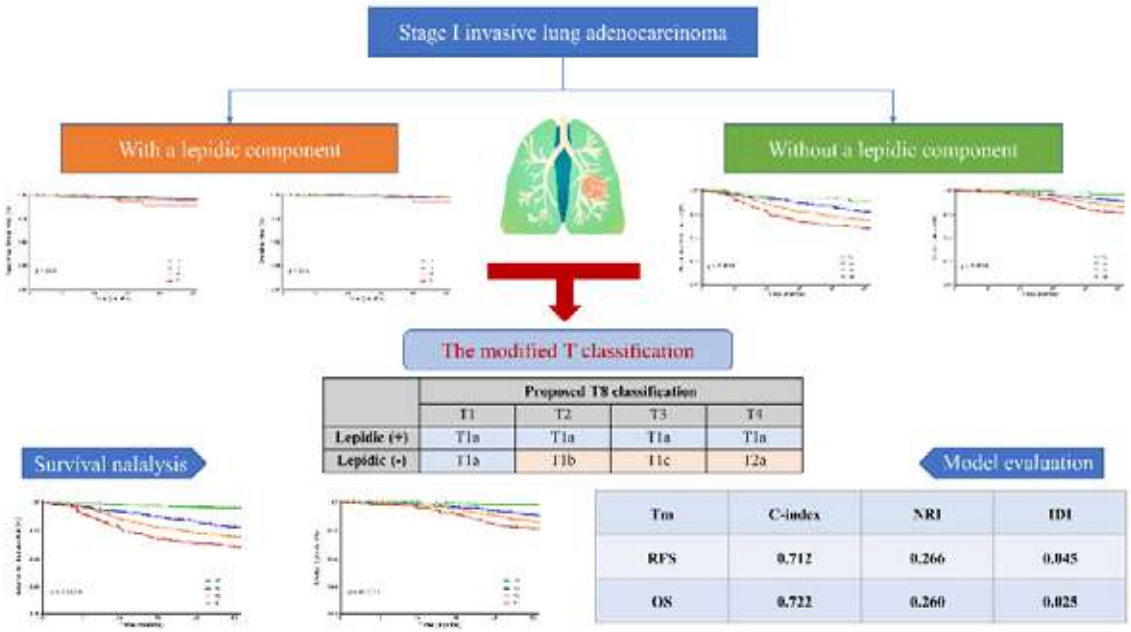
Introduction: We evaluated the prognostic impact of lepidic component and compared a modified T categorization (Tm) with the current 8th classification (T8) for survival prediction in Chinese patients with pathological stage I lung adenocarcinoma (LAD).

Methods: A total of 1871 stage I invasive LAD were retrospectively analyzed to evaluate the T8 and Tm classifications. The recurrence-free survival (RFS) and overall survival (OS) were analyzed by Kaplan-Meier method and Cox proportional hazard model. The concordance index (C- index), reclassification improvement (NRI), integrated discrimination improvement (IDI), and decision curve analysis (DCA) were performed to estimate reclassification net benefits of Tm for survival prediction.

Results: The current T8 classification was associated with survival in LAD without a lepidic components but not in those with a lepidic component. RFS and OS were significantly better for patients with a lepidic component in each corresponding T stage. The C-index was significantly improved from 0.651 to 0.712 for RFS (p<0.001) and 0.662 to 0.722 for OS (p<0.001) after reclassifying by Tm categorization. The DCA, NRI (RFS: 0.266, OS: 0.260), and IDI (RFS: 0.045, OS: 0.025) demonstrated that the Tm classification provided more net benefit in the survival prediction compared with the current T8 classification.

Conclusions: The current T8 classification may not be appropriate for LAD with a lepidic component, which is associated with excellent prognosis despite pathological T stage. The Tm classification for LAD showed an improvement in survival prediction.



	Proposed T8 classification			
	T1	T2	T3	T4
Lepidic (+)	T1a	T1a	T1a	T1a
Lepidic (-)	T1a	T1b	T1c	T2a

Tm	C-index	NRI	IDI
RFS	0.712	0.266	0.045
OS	0.722	0.260	0.025

Keywords: lung adenocarcinoma, T classification, lepidic component

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-010 Effect of Perioperative Respiratory Muscle Training with Gamification for Lung Cancer

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Introduction: It has already been reported that pre- and postoperative respiratory muscle trainings are effective in preventing perioperative respiratory complications and improving postoperative respiratory function in patients undergoing lobectomy. However, since it is a simple repetitive task, it is extremely difficult to have it continued for a long time. In this study, we developed a new respiratory training application using a tablet game and verified to what extent it is possible to continue respiratory training by applying gamification techniques.

Methods: Patients who underwent lobectomy for lung cancer or metastatic lung cancer at our hospital between April 2020 and March 2021 and who agreed to participate in this study were enrolled and played the tablet game. In the game, the width of the rail changes to an arbitrary size, and the size of the ball changes in proportion to the loudness of the user's voice through the microphone of the tablet, so that the ball rolls on the rail and reaches the goal by preventing the ball from falling through the gap between the rails. By playing the game, the patients can naturally perform the actions of speaking and breathing. We investigated how much the breathing training continues with the addition of this game element.

Results: Five patients who met the criteria during the period participated in this study. Forty-two patients who underwent lobectomy at the same hospital during same period were used as a control group. None of the five patients had perioperative complications, and although the time to improve inspiratory volume with Portex Coach-2 incentive spirometer to 70% of preoperative levels was somewhat shorter compared to control group. There was no significant difference between them and the control group in respiratory function tests at 3 months postoperatively.

Conclusions: Respiratory muscle training with gamification was used for lung cancer patients and no perioperative complications were observed. Gamification-based respiratory training has been suggested to improve respiratory function in the early postoperative period and may reduce perioperative complications.

Keywords: respiratory muscle training, gamification, lung cancer

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-011 Combining Automated Malignancy Risk Estimation with Lung Nodule Detection May Reduce Physician Effort and Increase Diagnostic Accuracy

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Introduction: Automated detection of lung nodules is gaining traction to reduce false-negative CT scans, and to accelerate this routine analysis for radiologists. While these tools detect nodules, radiologists still have to assess the associated risk. In this study we assess whether automated malignancy risk assessment may assist in review of nodules and analyze the impact on patient follow-up.

Methods: A balanced random sample of CT scans from the U.S. NLST study were selected for analysis (15 patients with benign nodules and 17 that included a malignant nodule). These scans were first analyzed using the nodule detection functionality of *contextflow SEARCH Lung CT* that produced image coordinates of nodules that are ≥ 3mm (includes calcified nodules). These coordinates and the CT series were then used as input to *RevealAI-Lung* to assess malignancy risk (the mSI score). A < 1% risk threshold was used as a cutoff to filter likely benign nodules. For each patient, an index nodule identified within NLST was confirmed and assigned a LungRADS score. Diagnostic performance and comparisons to Lung-RADS are reported. Values are reported as mean (median).

Results: Using a sensitivity threshold of 94%, contextflow's analysis found 12.25 (8) nodules per patient. Of the manually selected index nodules, 30/32 (94%) were detected by contextflow's analysis. Using a malignancy risk threshold of under 1%, mSI labeled 59% of the detected benign nodules as low-risk (reduction $p < 0.001$). Of the confirmed malignant nodules, one 6.5mm nodule would be included in this low-risk group. While a small sample size, if mSI were used in conjunction with LungRADS, four of the 17 patients with malignant nodules could be shifted to earlier diagnosis, and three of 15 patients with benign nodules could be shifted to lower-risk compared to Lung-RADS.

Conclusions: If adopted into clinical practice, combining automated detection with accelerated review of low-risk nodules could save a significant amount of physician time. Furthermore, the increased diagnostic accuracy from use of CADx may lead to early diagnosis for cancer patients and reduced follow-up procedures for benign nodules.

Keywords: pulmonary nodule, radiology, artificial intelligence

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-012 Exploring Factors Affecting Variability in Lung Cancer Outcomes Across Southeastern Ontario, Canada

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Introduction: Lung cancer (LC) is the leading cause of cancer-related mortality. The five-year relative LC survival varies across Ontario, ranging from 22-32% (2014-2018), with the lowest survival in Southeastern (SE) Ontario. Lung Diagnostic Assessment Program (LDAP) is a rapid assessment clinic that provides specialist care for patients undergoing evaluation for suspected LC. We sought to characterize patient, disease, and system factors, including the influence of LDAP care on survival outcomes, that may contribute to regional differences in LC outcomes.

Methods: A population-based retrospective cohort study was conducted using data obtained from the LDAP database from January 2017 to December 2019. We identified patients with newly diagnosed LC through Ontario Cancer Registry. We then linked this data to the LDAP database to identify patients that received LDAP management. Descriptive data were collected, including patient and disease characteristics. Using a cox-model approach, we compared 2-year survival (adjusted for patient and disease characteristics) for patients receiving care through LDAP versus non-LDAP pathways.

Results: A total of 1741 patients with LC were identified. The median age at diagnosis was 71 and 52.8% were female. Adenocarcinoma was the most common LC subtype (38.8%) and the most common LC stage at diagnosis was stage IV (38.4%). Of LC cases, 818 (47.0%) were managed through LDAP while 923 (53%) were in the non-LDAP cohort. In the unadjusted analysis, factors associated with a lower probability of dying at 2 years included younger age, female sex, residing closer to SE cancer center, and earlier stage. Factors associated with a higher probability of dying were lower income quintile, non-adenocarcinoma subtype, and non-LDAP management. Data shown in Table1.

In the adjusted analysis, all variables remained significant. LDAP management remained significant in the adjusted model for 2-year survival (HR 1.18 for non-LDAP vs. LDAP, p= 0.0162), suggesting that patient and disease characteristics alone did not account for all observed variability in outcomes.

Patient and disease factors associated with LDAP assessment included ages 61-70 (HR 1.36 vs. ages 71-80, p=0.012), income quintile (HR 1.52 for middle quintile vs. reference lowest quintile, p=0.023), and earlier stage (HR >2.20 for Stages I-III vs. IV, p<.0001). Increasing distance from SE cancer center lowered the probability of LDAP assessment (HR 0.76 for every 20km increase, p<.0001).

Conclusions: While several patient and disease factors influence LC survival in SE Ontario, LDAP management is an independent factor influencing survival, suggesting that system characteristics play a contributing role in survival.

Table 1 Factors affecting 2-year Overall Survival in LC		
Factor	**unadjusted HR (95% CI)**	**unadjusted p-value**
Age		
18 - 60	0.71 (0.57, 0.87)	0.0015
61 - 70	0.79 (0.66, 0.94)	
71 - 80	0.88 (0.74, 1.04)	
> 80	referent	
Sex		
female	0.68 (0.61, 0.77)	<.0001
male	referent	
Distance from SE Cancer center (kms)		
< 50	0.82 (0.72, 0.93)	0.0027
50 - 100	referent	
> 100	1.05 (0.86, 1.27)	
Income Quintile		
1 (lowest)	2.27 (1.53, 3.36)	0.0003
2	1.79 (1.21, 2.63)	
3	1.89 (1.28, 2.77)	
4	1.81 (1.22, 2.70)	
5 (highest)	referent	
Histology Type		
Adenocarcinoma	referent	<.0001
Squamous cell carcinoma	1.44 (1.21, 1.73)	
Poorly differentiated carcinoma	2.55 (2.20, 2.95)	
Small cell	2.65 (2.18, 3.23)	
Other	1.27 (0.93, 1.73)	
Stage		
I	0.16 (0.13, 0.20)	<.0001
II	0.24 (0.17, 0.32)	
III	0.50 (0.42, 0.59)	
IV	referent	
unknown	0.71 (0.61, 0.83)	
LDAP		
No	1.64 (1.45, 1.85)	<.0001
Yes	referent	

Keywords: Lung Cancer Diagnosis, Lung Cancer Outcomes, Health Quality

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-013 Determination of the Timing of Bevacizumab Administration in Osimertinib and Bevacizumab Combination Therapy

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Introduction: Preclinical and clinical evidence suggests that EGFR-TKIs may work synergistically with vascular endothelial growth factor inhibitors. In osimertinib and bevacizumab combinatorial treatment, the timing for the addition of bevacizumab is yet to be clearly defined.

Methods: From April 1, 2018, to January 1, 2021, a total of 31 patients with metastatic EGFR-mutant lung cancers were enrolled in this study. Osimertinib was orally administered daily (once) at a dose of 80 mg, regardless of food intake. The administration was done at the same time each day at approximately 24-hour intervals. A complete cycle of the administration consists of 21 days. Bevacizumab (7.5 mg/kg) was administered by drip infusion on the first day of each cycle.

Results: 31 patients included in this study. The median progression-free survival were 13.47 months (range: 7.72-19.21 months), respectively. A total of 26 patients were subjected to response analysis. Of the 26 patients, 6 (23.08%) had a partial response, 20 (72.92%) had stable disease, and none had progressive disease. The overall response rate was 23.07%. Sixteen patients had central nervous system (CNS) disease. The CNS response rate in patients with measurable and non-measurable diseases was 71%. All patients were evaluated for the toxic effects of the drugs. The average use of bevacizumab was 9.13 months (range: 3.5-13.03 months). The treatment modality of “T to A+T” was found to yield better benefits to the patients than the treatment modality of “A+T” (HR=0.165, 95% CI: 0.029-0.928, P=0.041). EGFR21 had a significantly higher risk of progression than EGFR19 (HR=6.998, 95% CI: 2.101-23.311, P=0.002).

Conclusions: The treatment modality of “T to A+T” was found to be better than that of “A+T” and can prolong the time of drug resistance. Patients with EGFR19 had a better prognosis than those with EGFR21, regardless of the treatment modality.

Keywords: osimertinib, bevacizumab, non-small-cell lung cancer

EP13.01-014 Evaluation of Malignancy and Survival in Patients Operated with a Preliminary Diagnosis of Interstitial Lung Disease

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Introduction: Interstitial Lung Diseases (ILD) are a group of diseases that diffusely affect the lung, causing varying degrees of inflammation, fibrosis and structural degeneration. Especially in patients with idiopathic pulmonary fibrosis, lung cancer development is among the most important comorbidities. In our study, it was aimed to evaluate the pathological diagnosis, presence of malignancy and survival status of interstitial lung patients who were operated for diagnostic purposes in our clinic.

Methods: A retrospectivel analysis was performed in cases with a diagnosis of interstitial lung disease (ILD) with or without nodules who were operated for diagnostic purposes in our clinic. Pathologically detected ILD type, presence of malignancy, and survival of the cases were evaluated.

Results: 122 cases (79 males, 43 females) operated between January 2010 and December 2021 were included in the study. Parenchyma sampling was performed with videothoracoscopic wedge resection in all cases with a median age of 64 years (24-81), and any accompanying nodules were removed. 66 (54.1%) patients were diagnosed with usual interstitial pneumonia (UIP), and 56 (45.9%) were diagnosed as other or unsubtyped ILD (non-UIP). Mean survival was 97.8±6.7 and 99.4±7.4 months in the UIP and non-UIP group, respectively. There was no significant difference in survival between the two groups (p=0.941). Survival was statistically significantly lower in patients whose age at diagnosis was over 65 (p=0.005). When patients with malignancy were excluded in this patient group, survival was again statistically significant (p=0.029). In addition, when patients with malignancy were excluded, survival was statistically significantly shorter in patients with FVC below %60 (p=0.031). Histopathologically, lung malignancy was detected in 20 (16.4%) patients. While lung malignancy was observed in 13 non-UIP patients and 7 patients in the UIP group, the difference was not statistically significant (p=0.061). The most common pathological malignancy type in patients with UIP was adenocarcinoma (4 cases), and squamous cell carcinoma (6 cases) in non-UIP patients. All patients who developed malignancy were male. The development of malignancy was statistically significantly higher in patients with a smoking history of more than 40 pack-years compared to non-smoker patients (p=0.044). In patients who developed malignancy, statistically significantly shorter survival was observed (p=0.002). It was detected that 18 (90%) of the patients with malignancy had peripheral localized nodules and 2 (10%) had central localized nodules. While 34 patients (51.5%) diagnosed with UIP were using antifibrotic drugs (pirfenidone: 20 patients, nintedanib: 14 patients), 10 (20.2%) non-UIP patients were using antifibrotic drugs (pirfenidone: 8, nintedanib: 2 patients). There was no significant difference in survival between patients using and not using antifibrotic drugs (p=0.704). No statistically significant difference was found between the use of antifibrotic drugs and survival when malignancy was excluded. There was no statistically significant difference in terms of malignancy development between patients using and not using antifibrotic drugs (p=0.537).

Conclusions: Patients with interstitial lung disease should be followed closely for the development of lung cancer. The development of malignancy worsens the prognosis of interstitial lung disease. The long-term effects of antifibrotic drugs used still arouse curiosity.

Keywords: Interstitial Lung Disease, Lung Malignancy, Antifibrotic Drugs

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-015 Correlation Between CT Signs and Ki67 Expression in Non-small Cell Lung Cancer

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Introduction: The incidence of lung cancer is increasing year by year, and Ki67 is closely related to the pathological characteristics of NSCLC proliferation, infiltration, metastasis and prognosis. However, it can only be detected by immunohistochemistry and cannot be evaluated by noninvasive methods. CT has the advantages of being simple, rapid and noninvasive, and is the main imaging tool for diagnosis, treatment and detection of lung cancer in clinical practice. The aim of this study was to investigate the correlation between CT signs and Ki67 expression in non-small cell lung cancer and to evaluate the value of CT in diagnosing Ki67 expression.

Methods: Cox-regression analysis was performed in 265 cases of non-small cell lung cancer with Ki67 immunohistochemical results diagnosed by chest CT scan and confirmed by surgery and pathology. According to the percentage of Ki67 expression, they were divided into two groups, 63 cases in high expression group (Ki67>20%) and 202 cases in low expression group (Ki67≤20%). The multivariate logistic regression model was used to screen out the predictors and predicted probability values, and the ROC curve was used to compare the diagnostic efficacy of the multi-parameter model and each single-factor parameter for Ki67 expression.

Results: The univariate results revealed statistically significant differences (P < 0. 05) between the two groups for border, density bronchial inflation sign, nodular/mass type, obstructive emphysema, pleural effusion, enlarged lymph nodes, multiple enlarged lymph nodes, CT_{mean}, CT_{min}, SD, and long and short diameters. Logistic regression results showed that border, density, bronchial inflation sign, obstructive emphysema, multiple enlarged lymph nodes, CT_{min}, SD, and short diameters were statistically significant. The ROC curve results showed that the area under the curve of the multiparameter model was 0. 909, the sensitivity was 88. 3%, and the specificity was 83. 1%, which were all better than the single-factor parameters.

Conclusions: CT-related parameters can be used to identify Ki67 expression levels in NSCLC, of which reliable predictors are border, density, bronchial inflation sign, obstructive emphysema, multiple enlarged lymph nodes, and CT_{min}, SD and short diameter. These CT signs may provide a reference for assessing the proliferative capacity of NSCLC.

Keywords: NSCLC, Ki67 expression, computed tomography

EP13.01-016 Are Follow-up Tests Useful in NSCLC? Experience of a Tertiary Hospital

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Introduction: A significant portion of patients operated of non-small cell lung cancer (NSCLC) will relapse eventually. Strategies to identify these relapses are necessary, in order to propose an earlier oncological treatment. There is currently no consensus regarding the best program for postoperative follow-up and surveillance after a curative resection for non-small-cell lung cancer (NSCLC) patients. The objective of this study is to analyse the diagnostic capability of the diagnostic tests performed in our centre during the follow-up of patients with non-small cell lung cancer after surgical resection.

Methods: This was a retrospective review of 392 patients with surgically resected stage I-IIIA NSCLC. Data were collected for all patients treated between January 1, 2010 and December 31, 2020. We analysed demographic data and clinical data, and recollected clinical, laboratory and radiological exams during their follow-up, identifying those that were relevant in the diagnosis of tumour relapses.

Results: Demographic and clinical data are shown in Table-1. The data related to the follow-up tests performed and their diagnostic capability are shown in Table-2.

	N = 392
Sex	Male: 263 (67.1) Female: 129 (32.9)
Age (median, range)	66.0 (25.0-86.0)
Stage at diagnosis	IA: 114 (29.1) IB: 79 (20.2) IIA: 43 (11.0) IIB: 44 (11.2) IIIA: 112 (28.6)
Histology	Adenocarcinoma: 237 (60.5) Squamous cell carcinoma: 111 (28.3) Large cell carcinoma: 19 (4.8) Large cell neuroendocrine carcinoma: 12 (3.1) Adenosquamous carcinoma: 4 (1.0) Sarcomatoid carcinoma: 1 (0.3) NOS/undifferentiated: 1 (0.3) Carcinoid tumor: 1 (0.3) Other: 6 (1.5)
Median follow up (months)	48.5
PFS (median, CI 95%)	55.0 (39.7-70.3)
OS (median, CI 95%)	90.0 (76.3-103.7)

	Routine	**Non routine**							
Total	**Mean**	**Diagnostic of relapse**	**%**	**Total**	**Mean**	**Diagnostic of relapse**	**%**		
Stage I	Clinical revision	1029	5.33	2	0.19	15	0.08	15	100
Body CT	966	5.01	48	4.96	10	0.05	7	70	
Stage II	Clinical revision	473	5.44	3	0.63	7	0.08	7	100
Body CT	457	5.25	32	7	3	0.03	2	66.6	
Stage IIIA	Clinical revision	502	4.48	7	1.39	23	0.21	23	100
Body CT	482	4.30	48	9.96	13	0.05	9	69.2	

Conclusions: The vast majority of routine follow-up evaluations performed were not relevant in the management of the patient and only the body TC exceeded the threshold of 5% profitability, but without reaching 10% even in the highest stage. The profitability of the tests increased when they were carried out in an Non-routine follow-up evaluations. New follow-up strategies based on scientific evidence must be defined to improve the profitability of the tests performed.

Keywords: NSCLC, Follow-up, Surgery

EP13.01 PULMONOLOGY, RADIOLOGY, AND STAGING

EP13.01-017 Assessing Variance Between Radiology versus Multidisciplinary Clinic Recommendations in the Pulmonary Nodule and Lung Screening Clinic

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Introduction: A multidisciplinary approach presents many benefits to treating patients. When providers from an array of expertise come together, health outcomes of patients can be enhanced. The Pulmonary Nodule and Lung Screening Clinic is a multidisciplinary clinic that consists of a collaboration between the Cancer Center, Thoracic Imaging, Pulmonary Medicine, Radiation Oncology and Thoracic Surgery. Providers of each department assess the best treatment for patients attending the PNLSC. We analyzed if there are significant benefits of having multiple providers assess each patient by comparing the recommendation from the PNLSC in comparison to the recommendation from the Radiology Department.

Methods: Patients recommended to the PNLSC are evaluated in a group setting by the following types of providers: Medical Oncologist, Radiologist, Surgeon, Radiation Oncologist, Pulmonologist, Nurse Practitioner. Patients are referred to the PNLSC after pulmonary nodules are incidentally found on CT scans or through low-dose computed tomography (LDCT) screening. The providers assess the imaging scans of each patient as well as past medical history to recommend the best plan of action. Routine radiology recommendations include: follow-up CT Scan interval, biopsy, intervention, PET Scan, other, or no specific recommendation. Recommendations by the multidisciplinary clinic include: Follow-up Scan (LDCT, CT, MRI, PET/PET CT), Biopsy, Surgery, Radiation, Other, or a combination. Data was analyzed between the radiology recommendation and multidisciplinary clinic recommendation and placed into the following categories: discordant-less aggressive vs. discordant-more aggressive vs. concordant-equal.

Results: Data was collected using Research Electronic Database Capture (REDCap). Forty-four dates (between February 12, 2021 through February 4, 2022) of PNCSL were analyzed which included a total of 742 patients. Completed assessments indicate that 50% of clinic recommendations are concordant to that of the radiology recommendations, 33% of clinic recommendations are discordant-more aggressive than the radiology recommendations and 17% of clinic recommendations are discordant-less aggressive than the radiology recommendations.

Conclusions: Preliminary data shows that half of clinic recommendations are concordant and equally aggressive than that of radiology recommendations. However, a significant percentage of the data shows that clinic recommendations are discordant with more aggressive recommendations than that of the original radiology recommendations. Therefore, this may indicate that the use of a multidisciplinary clinic, with intra-specialty discussion is beneficial to the treatment of patient's pulmonary nodules as compared to a single radiology provider determining the correct follow-up. Research is needed to determine if these results remain consistent dependent on the patient's smoking status and number of visits to the PNLSC.

Clinic Recommendation vs. Radiology Recommendation Aggression:	
Aggression	**Number of patients**
Discordant - Less Aggressive	127
Discordant - More Aggressive	246
Concordant	369

Keywords: Pulmonary, multidisciplinary, radiology

EP14.01-001 SCLC Transformation from ALK-rearranged Lung Adenocarcinoma after Alectinib Resistance and Response to Atezolizumab: Case Report

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Introduction: The genotypic and histological evolution of non-small cell lung cancer (NSCLC) to small cell lung cancer (SCLC) has been described as a mechanism of acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy. However, it is extremely rare in ALK-rearranged adenocarcinomas, and the follow-up care and outcomes of patients in this rare condition are unclear. We describe a unique case in which a patient with ALK-rearranged adenocarcinoma underwent small-cell transformation at a metastatic site with retained ALK rearrangement after alectinib treatment.

Methods: Next-generation sequencing (NGS) on the tissue biopsy was performed.

Results: A 77-year-old man came to our hospital in August 2020 due to left submandibular and cervical lymphadenopathy. In July 2019, he went to a local hospital for gastrocnemius spasm in his left lower extremity and was diagnosed with *ALK*-positive stage IVB NSCLC (cT4N3M1c) with lymph node metastasis and multiple brain metastases. He received alectinib (600 mg, BID) and his best response was partial response. After 11 months of alectinib treatment, brain magnetic resonance imaging revealed progression of brain metastases. Whole brain radiotherapy was subsequently given, and secondary epilepsy and metastatic progression occurred one month later. Radiotherapy was stopped and oral alectinib was continued. Chest computed tomography (CT) in our hospital shows left submandibular mass with multiple lymph node metastasis, left lower lung mass, and right pleura thickening. Left submandibular biopsy revealed SCLC, with immunoreactivity to CD56, Synaptophysin, CgA and Ki-67 (about 80% positive), and negative for CK7 and p40 on. In addition, laboratory examinations revealed elevations in the levels of neuron specific enolase (NSE; 106 ng/mL), carbohydrate antigen 19-9 (CA19-9; 49.4U/mL) and carcinoembryonic antigen (CEA; 4.18ng/mL). The biopsy was subjected to NGS analysis, and *EML4-ALK* was identified. Based on these findings, the patient was administered with atezolizumab (1200mg d1) in combination with etoposide (0.13g d1-d3) and carboplatin (350mg d1). After treatment, CT scan showed the left neck mass was significantly reduced with a partial response until in December, 2020. The patient eventually died in April 2021 due to refusal to continue treatment.

Conclusions: The cases highlighted the importance of re-biopsy that identified pathologically SCLC transformation after ALK-TKI resistance, and suggested the treatment of atezolizumab plus carboplatin, and etoposide, which could provide a reference for such phenotype.

Keywords: small cell lung cancer, lung squamous cell carcinoma, ALK-TKI resistance

EP14.01 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - INFORMING ES-SCLC

EP14.01-002 Efficacy and Safety of Tiselizumab Combined with Anlotinib and 2-cycle Irinotecan as Second-line Treatment of Small Cell Lung Cancer

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Introduction: Second-line therapy for small cell cancer is mainly chemotherapy, but the outcome is poor especially for patients with relapse within six months. In addition to the known antiangiogenic, the inhibition of VEGF has immunomodulatory effects. The efficacy of PD-1 inhibitor may be enhanced through the addition of anti-VEGF to reverse VEGF-mediated immunosuppression. Based on this, the second-line treatment exploration for SCLC of the PASSION Study had showed anti-angiogenic combined with PD-1 inhibitors could improve anti-tumor activity and safety. However overall survival benefit is limited and further improvement in treatment strategies are needed.Checkmate9LA Study indicated that immune checkpoint inhibitor in combination with 2-cycle chemotherapy could improve the short-term efficacy in NSCLC, revealed less cycles chemotherapy could trigger exposure of antigens while killing immunosuppressive cells synergistic antitumor effect.We hypothesis that Tislelizumab combined with Anlotinib and 2-cycle Irinotecan can improve effectiveness and safety better in second-line treatment of SCLC. Tislelizumab demonstrated promising antitumor activity with good tolerability in ES-SCLC based on the RATIONALE 206 Study. Anlotinib is widely used anti-angiogenic treatment in SCLC patients based on the ALTER1202 Study.

Methods: This trial (NCT05027100) is an open-label, single-center, single-arm, Phase II study. Eligible patients are with histological confirmed Small-Cell Lung Cancer, relapsed after Platinum-doublets chemotherapy and the interval time ≤6months from the last systemic treatment, and Eastern Cooperative Oncology Group score ≤1. Patients who had previously used antiangiogenic drugs, Tislelizumab injection or other checkpoint inhibitors and had received two or more lines of platinum-based chemotherapy are excluded. All patients will receive Anlotinib (10mg, QD, for 2W, Q3W) in combination with Tislelizumab(200mg, IV,Q3W)and 2-cycle Irinotecan(100mg/m2, D1, D8,Q3W),patients assessed with no progression will receive continued treatment of Anlotinib and Tislelizumab until disease progression, unacceptable toxicity, or patient withdrawal of consent. Primary endpoint is objective response rate (ORR), and key secondary objectives are progress-free survival (PFS), overall survival (OS), duration of response (DOR), and safety. It is assumed the primary endpoint ORR is 35%, the ORR of the chemotherapy group in CheckMate 331 is used as historical control (ORR=16.5%), α=0.05, β=0.2, the sample size was calculated by binomial distribution accurate test method, a total of 33 patients are estimated to be enrolled.

Keywords: Small Cell Lung Cancer, Immune checkpoint inhibitors, Efficacy and Safety

EP14.01-003 Parotid Metastases from Primary Lung Cancer: Case Series and Systematic Review on the Clinical Features

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Introduction: Most parotid metastases have been reported to come from head and neck; however, cases metastasized from lung are extremely rare. Missed diagnose and misdiagnose occurred quite a few. Thus, accurately identify the clinical features of parotid metastasis of lung cancer do matters. However, current studies about this issue are mostly case reports, little is known about the detailed and systematic aspects.

Methods: We reported three cases of parotid metastases from lung cancer and then systematically searched case reports aimed at lung cancer parotid metastases through Pub-med and Web of Science with no restrictions on publication years. The latest search date was December 5, 2021. Studies did not fit the topic, or were duplicated, or not full text, or had incomplete clinical information were excluded. Since all the articles involved were case reports, the risk bias assessment tool was not used in this study. The following data was extracted from the included studies for analysis: gender, age, initial symptoms, smoking history, pathological type, tumor positions, treatment methods, and survival time.

Results: Twenty patients were included for study. Eighty-five percent of which were males, and 17 patients were over 50 years old. In all cases where the smoking history were mentioned, 91% were smokers. The predominant pathological type was SCLC (13 patients, 65%). The majority had parotid metastases on the ipsilateral side of the primary site. Fifteen combined with other site metastasis, while more than half of which were brain metastases. The survival time ranged from 3months-17years, and as for SCLCs, it was only 3months-40months.

Conclusions: Risk factors, such as sex, age, smoking history, clinical features, such as the relative position, pathological types, metastasis patterns, could provide valuable evidence for diagnosis. For cases presented as SCLC, more aggressive strategies such as chemotherapy with immunotherapy and maintenance therapy may be more suitable. Due to the greater tendency of brain metastasis in such disease, WBRT, SRS or PCI should be applied to the corresponding patients in time.

Summary of the characteristics of lung cancer parotid metastases

total	sex	age(years old)	smoking	pathological type	parotid metastasis relative position	combined with other site metastasis	survival
20	M:17 F:3	rang:40-72 average:57.6 median: 59 ≥50: 17	yes:10	SCLC:13	ipsilateral :11	total: 15 brain metastasis: 8	3months-17years (SCLC:3months-40months)
			no:1	AC:5	opposite:6		
			NM: 9	SCC:2	bilateral :2		
					NM:1		

M= male; F= female; SCLC= small cell lung cancer; SCC= squamous cell carcinoma; AC= adenocarcinoma; NM= not mentioned.

Keywords: Lung cancer, Parotid Metastasis, Clinical feature

EP14.01-005 Weekly Sequential ACOCEV Chemotherapy (ADR, CTX, CBDCA, VP16, VCR) for Elderly - Poor PS SCLC Patients: An Observational Study

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Introduction: SCLC is characterized by rapid kinetics, early metastatic involvement and frequent development of drug resistance. A dose-intense (i.e. weekly) sequential use of active drugs with non-overlapping toxicities, may play a role for a better disease control owing to a non-cross resistant mechanism of action in elderly or poor PS pts. Aim of this study is to determine the toxicity profile and the response rate of this treatment.

Methods: Sequential ACOCEV (Doxorubicin 30 mg/m2, Cyclophosphamide 400 mg/m2 on day 1 of every first week, Vincristin 1,4 mg/m2 on day 1 of every second and fourth week, Carboplatin AUC 4 and VP16 60 mg/m2 on day 1 of every third week, every 28 days for 3 to 4 cycles) was administered to 59 patients from July 2015 to March 2022. These patients were enrolled from two different departments: Thoracic Oncology / Lung Unit - Pederzoli Hospital (Peschiera D.G., VR, Italy) and Department of Medical Oncology of University of Verona (Verona, Italy). Median age was 71 years (range 51-85); 21 patients were >75 years old (35,59%); 38 patients were men (64.41%) and 21 women (35.59%). In order to determine the response rate and the toxicity of the treatment we evaluated patients who had completed almost 2 cycles of chemotherapy (47 pts). Among patients evaluable, 11 (23,40%) had PS 3 (ECOG), 19 (40.42%) had PS 2, 14 (29,79%) had PS 1, and only 3 (6,38%) had PS 0. Regarding stage at diagnosis, 41 patients (87.23%) had Extensive Disease (ED), and 14 (29.78%) were previously treated.

Results: The overall disease control rate was 70.21% (partial response PR and stable disease SD). 29 patients (61.70%) achieved a PR, 4 (8.51%) had a SD and 14 (29.79%) had a progression disease (PD). Median time to progression (TTP) was 5 months, median overall survival (OS) was 9.25 months. ACOCEV provided a high response rate and good tolerability. G3-4 hematological toxicities, including febrile neutropenia and thrombocytopenia, occurred respectively in 4 patients (8.51%) and 1 patient (2.13%). Moreover, we observed G2 neurotoxicities (paresthesia) in 4 pts (8.51%); constipation in 2 pts (4.26%) and alopecia in 3 pts (6.38%).

Conclusions: ACOCEV has a comparable efficacy to conventional chemotherapy schedules, showing a more favourable toxicity profile and significant clinical benefit; as a result it is feasible also in patients with a poor PS or elderly. Further prospective studies are needed to confirm these data.

Keywords: sclc, chemotherapy, elderly / poor ps

EP14.01-006 CeLEBrATE: Phase II trial of CarbopLatin, Etoposide, Bevacizumab and Atezolizumab in Patients with exTEnsive-Stage SCLC-GOIRC-01-2019

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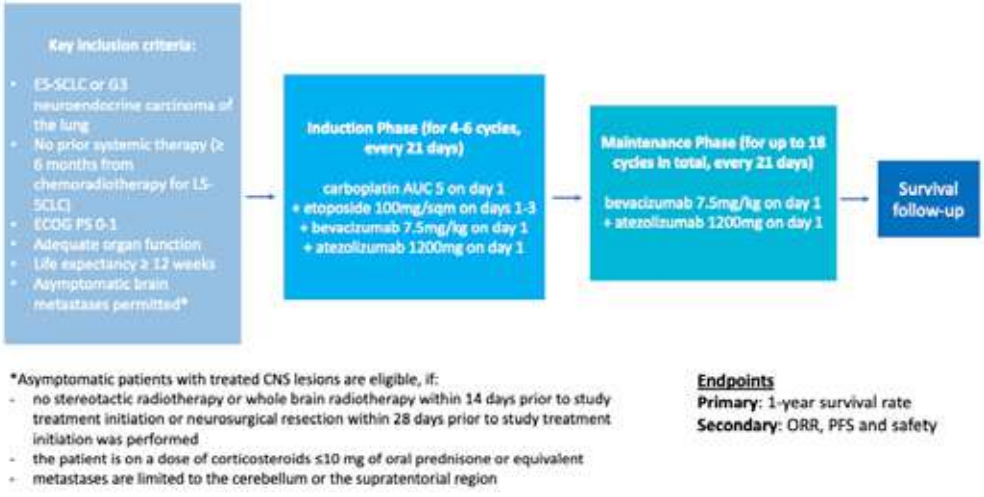
Introduction: The addition of programmed-death ligand 1 (PD-L1) inhibition with atezolizumab or durvalumab to platinum-doublet chemotherapy is the new standard treatment for extensive-stage small-cell lung cancer (ES-SCLC) as it improved survival in phase III trials, raising overall survival rate at 1 year (1-year OS) from 35% to about 50%. The vascular endothelial growth factor (VEGF) sustains angiogenesis and has immunosuppressive effects. The phase II SALUTE and the phase III FARM6PMFJM trial, the latter lead by our GOIRC group, have shown safety and provided signals of activity of bevacizumab, an anti-angiogenic agent, added to platinum doublet chemotherapy in patients with ES-SCLC. Moreover, a preclinical SCLC model shown synergistic antitumor effect of the combination of PD-L1 and VEGF inhibition. We hypothesized that adding bevacizumab to atezolizumab, carboplatin and etoposide would improve survival in pts with ES-SCLC.

Methods: An investigator-initiated multicenter phase II single arm trial sponsored by GOIRC designed to assess efficacy and safety of the combination of bevacizumab plus atezolizumab, carboplatin and etoposide in treatment-naïve pts with ES-SCLC. Patients will receive carboplatin (AUC 5 on day 1), etoposide (100 mg/sqm on days 1-3), bevacizumab (7.5 mg/kg on day 1) and atezolizumab (1200 mg on day 1) every 3 weeks for 4-6 courses (induction phase), followed by bevacizumab and atezolizumab every 3 weeks (maintenance phase) for up to 18 total cycles. Patients with asymptomatic brain metastases are eligible if certain criteria are met. Treatment beyond radiological progression for atezolizumab is allowed if clinical benefit is ongoing. The primary endpoint is 1-year OS. The null hypothesis that true 1-year OS is <50% will be tested against a one-sided alternative of 1-year OS >70% (power= 90%; 2-sided α= 5%). The overall complexity and costs of the trial justify such ambitious endpoint. Positive results are considered achievable also based on the strict selection of pts. Accrual is ongoing and 48 out of 52 pts across 15 Italian centers have been enrolled. Results are awaited in the second half of 2023.



Keywords: ES-SCLC, Bevacizumab, Immunotherapy combinations

EP14.01-007 Next-Generation Sequencing to Dynamically Detect Mechanisms of Resistance to ALK Inhibitors in ALK-positive SCLC Patient: A Case Report

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Introduction: Tyrosine kinase inhibitors (TKIs) of the anaplastic lymphoma kinase gene (*ALK*) significantly improve quality of life and survival in non-small cell lung cancer (NSCLC) with *ALK* fusion. However, *ALK* fusion is extremely rare in small-cell lung cancer (SCLC), and there is no standard treatment at present, and the mechanism of resistance of ALK-TKIs in SCLC is unknown.

Methods: Tumor markers were detected.

Results: We present the case of a 26-year-old man who was diagnosed with *ALK*-positive extensive-stage SCLC and treated with 2 cycles of first-line chemotherapy, but the disease progression rapidly and subsequently underwent Alectinib. After 2 cycles of Alectinib, the CT scan showed a partial response. However, after 9 cycles of treatment, a metastatic lesion enlarged, and a new brain lesion appeared. The disease continued to progress after radiotherapy to the brain lesions. NGS analysis of a series of liquid biopsies revealed a new mutation, *ALK p.G1202R*, which resulted in resistance to Alectinib during disease progression. Meanwhile, the mutant allele frequency (MAF) of original *RB1* and *TP53* mutations increased. Ensartinib was subsequently given as the third-line treatment, but the primary lung lesion was enlarged. The MAF of *RB1*, *TP53* and *ALK p.G1202R* increased, while the concentrations of NSE, CA19-9 and CEA increased. The patient is currently receiving Anlotinib in combination with CPT-11 and is stable with an OS of more than 18 months.

Conclusions: Plasma levels of *ALK* resistance mutations correlated well with tumor response assessed by CT scanning, suggesting that non-invasive tumor molecular profiling by NGS would provide effective dynamic monitoring in patients with *ALK*-positive SCLC. However, the treatment of ALK-TKIs resistance remains to be discussed.

Keywords: SCLC, ALK, resistance

EP14.01-008 Checkpoint Inhibitors Prevent New Onset of Brain Metastases in Relapsed Extensive Disease Small-Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) tends to disseminate earlier in the course of its natural history. Approximately 10% of patients present with brain metastases at the time of initial diagnosis, and an additional 40% to 50% will develop brain metastases during the course of their disease. Few studies suggest that checkpoint inhibitors (CPI) have activity against brain metastases from melanoma and non-small cell lung cancer, however, data in SCLC are lacking.

Methods: We conducted a retrospective multicenter cohort study to analyze SCLC patients receiving second or further-line CPI or chemotherapy between 2010 and 2020. In primary analysis, we calculated the hazard ratio for 1-year mortality using a multivariable-adjusted Cox regression model. Secondary outcomes included intracranial time to progression in a subgroup where brain imaging was available. To further address potential unbalanced confounding factors, we used propensity score analyses (inverse probability weighting, 1:1 matching).

Results: Among 306 patients included, 115 (37%) received CPI treatment and 198 (63%) patients were treated with chemotherapy only. Brain metastases were present in 143 (46%) patients, of whom 125 had already received whole brain irradiation.

CPI was associated with a lower risk of 1-year mortality (Hazard Ratio [HR] 0.64, 95% confidence interval [CI] 0.44 to 0.92, p=0.017). Inverse probability weighting and propensity score matching for mortality showed robust results (adjusted risk difference -27.5%, 95% CI -41% to -14%, p<0.001). There was no difference in 1-year PFS (HR 0.95, 95% CI 0.70 to 1.29, p=0.74).

Brain imaging (+/- 6 weeks of treatment initiation) was available in 63% of all patients, brain metastases were present in 38% and 39% in the respective treatment groups (p=0.5). In the subgroup of patients with brain metastases that have been previously irradiated, intracranial time to disease progression (iTTP) did not differ between patients who had received CPI versus CTX (median, 56 days vs. 36 days; HR 0.77, 95% CI 0.47-1.2; p=0.23). In the subgroup of patients without brain metastases that have been previously irradiated, iTTP in patients treated with CPI was significantly prolonged versus patients treated with CTX (median not reached vs. 296 days; HR, 0.15 95% CI, 0.07-0.34; p<0.001). In an exploratory interaction analysis to test for effect modification by brain metastases and CPI, improvement in 1 year survival in patients treated with CPI was driven by patients without brain metastases.

Conclusions: In a propensity score match analysis, CPI were associated with improved survival in patients with R/R SCLC compared to treatment with chemotherapy only, In particular in those subgroups without (irradiated) brain metastases. In addition, we provide first evidence, that CPI prolong intracranial occurrence and time to progression of metachronic brain metastases compared to conventional chemotherapy.

Keywords: small cell lung cancer, checkpointinhibitors, brain metastases

EP14.01-009 A Comparative Study of Histological Predictors of Outcome in Patients with Lung Typical and Atypical Carcinoids

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Introduction: Lung carcinoids fall in the most indolent extreme of the spectrum of lung neuroendocrine tumors, being considered malignancies with a favorable prognosis. They can be subdivided histologically in typical and atypical carcinoids and this classification difference reflects on the rates of recurrence and metastasis, with atypical carcinoids being slightly more aggressive that typical ones.The main goal of this study is to assess the differences in prognosis between typical and atypical carcinoids and potential criteria that should raise our awareness and prolong the follow-up time of our patients.

Methods: We have therefore conduced a retrospective study including all patients with an histological diagnosis of lung carcinoid on definitive surgical specimen analysis, operated at our center between January 2014 and December 2020. Data on patients' characteristics, surgical procedures and post-operative outcomes were collected from patients' medical records. Patients were divided into two groups: those with diagnosis of either typical or carcinoids. Both groups were independently characterized and subsequently compared regarding rates of local or distant recurrence, morbidity and mortality. Histological details regarding Ki67 expression, and vascular or pleural invasion were also registered to evaluate their impact on prognosis. Follow-up times were recorded, as well as time until recurrence. Statistical analysis was performed using SPSS statistics.

Results: A total of 100 patients were included in our study. There was a remarkably higher incidence of lung typical carcinoids (85 patients) than atypical carcinoids (15 patients) in our population. Distribution according to gender was similar (1:1) and there was no difference in mean age across groups (μ=58 years). Recurrence rate was higher within the atypical carcinoid group (28.6% vs. 3.2 %), although only a total of only seven patients showed recurrence within the 36,25 months mean follow-up time. Mean time until recurrence was not statistically different (atypical: μ=31 months; typical: 25.3 months), recurrence being independent from staging in our study sample. Eleven patients died during follow-up, but only one death was disease related. Surgical morbidity was not significantly different. There was a statistically significant difference between Ki67 expression in patient with typical (μ=2.59%) and atypical carcinoids (μ=11.11%). Higher Ki67 expression was also related with higher risk of recurrence (μ expression in patients with recurrence = 7%).

Conclusions: Histological characteristics may be more relevant than staging when predicting disease recurrence in lung carcinoid patients. Typical carcinoids can be precociously discharged while atypical carcinoids should be kept in surveillance for at least three to five years, as is currently recommended.

Keywords: carcinoid, Ki-67, surgery

EP14.01 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - INFORMING ES-SCLC

EP14.01-010 CAN: A Phase II Trial of Combination of Niraparib and Anlotinib in Patients with Recurrent Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) accounts for 14% of all lung cancers. Despite immunotherapy approved, SCLC is still associated with a poor prognosis and many patients relapse and develop drug resistance. Subsequent therapies are limited and the overall survival for recurrent SCLC is around 26 weeks. Anlotinib is a multi-target receptor tyrosine kinase inhibitor that can significantly inhibit angiogenesis. The ALTER 1202 trial showed anlotinib monotherapy has a longer median PFS compared with placebo (4.1 vs. 0.7 months) in patients (pts) with SCLC who had received ≥ 2 prior lines of chemotherapy. National Medical Products Administration (NMPA) has approved anlotinib in the third- or further-line treatment for SCLC. Niraparib is a highly selective PARP1 and PARP2 inhibitor approved in advanced ovarian cancer. ZL-2306-005 trial is a phase 3 study evaluating the efficacy and safety of niraparib as first-line maintenance therapy in Chinese pts with platinum-responsive extensive stage-SCLC (ES-SCLC). Although the study did not reach primary end points, niraparib showed a modest effect in prolonging the PFS of platinum-responsive pts with ES-SCLC.

Methods: CAN study is a prospective, open-label, single-arm phase II trial aims to investigate the efficacy and safety of niraparib in combination with anlotinib in recurrent SCLC pts. Eligible pts with aged 18-75 years and ECOG performance status 0-2 must have histologically confirmed recurrent SCLC who had received ≥1 platinumbased chemotherapy. Each patient has evaluable target lesion according to RESCIST v1.1. Prior anti-PD-L1 treatment is allowed. Pts will receive niraparib (300 mg or 200 mg QD) and anlotinib (12 mg QD, Day1-14), 21 days for a cycle. Treatment will continue until disease progression, unacceptable toxicity, death, or withdrawal of informed consent. The primary endpoint is ORR; secondary endpoints include PFS, OS, DCR, DOR and safety. Exploratory analyses are planned. The study will enroll up to 62 pts with a Simon's two-stage design. In the first stage, 19 pts will be enrolled. If there are ≤3 responses in these 19 pts, study will be stopped. Otherwise, 43 additional pts will be enrolled for a total of 62.Registration number : ChiCTR2100046269.

Keywords: SCLC, Niraparib, Anlotinib

EP14.01 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - INFORMING ES-SCLC

EP14.01-011 Carcinoid Tumor of the Lung with Osteomimicry. Case Report

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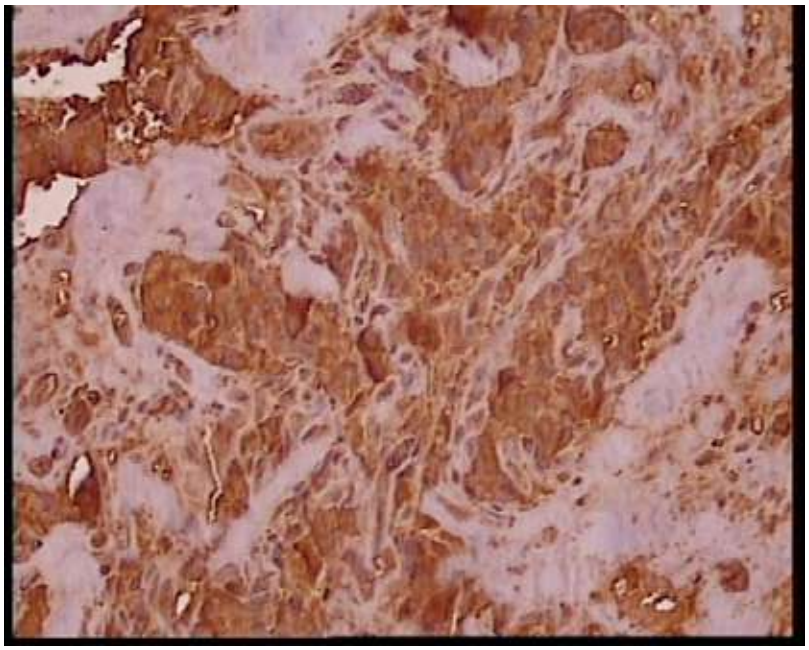
Introduction: Carcinoids are recognised entities of lung neuroendocrine neoplasms, also in 5th WHO classification. Carcinoid tumors may have foci of calcification in up to 30%, but ossification is rare.

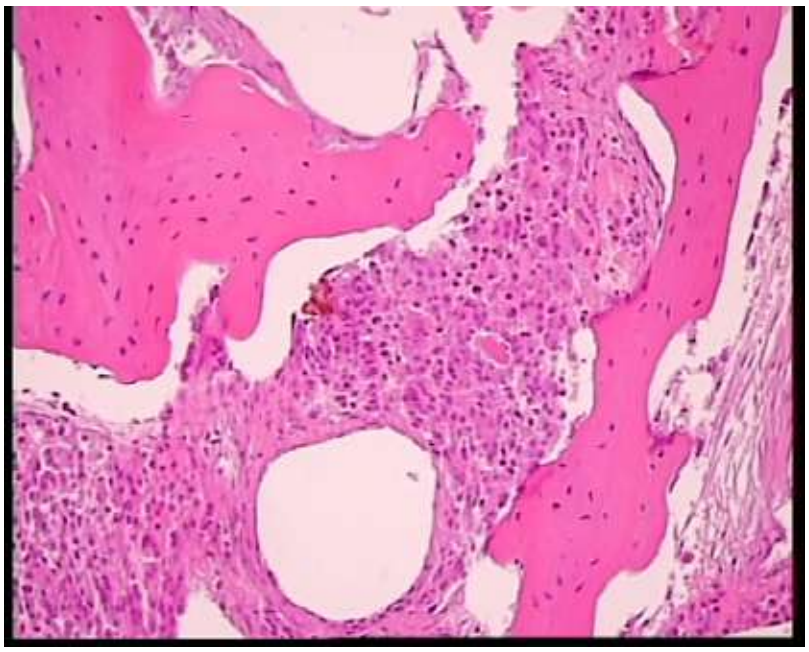
Methods: A 58 year old male, former smoker, with medical history of tuberculosis (diagnosed and treated 35 years ago) and with clear cell renal adenocancer (diagnosed in 2018.), was asymptomatic. An abnormal chest's X-ray was detected during regular oncological monitoring in 2019.

A biopsy was performed and related patohistological diagnosis was a carcinoid. Based on the radiological, bronchoscopic finding and patohistological diagnosis middle lobectomy and hilar and mediastinal lymphectomie were done. The patient had an uneventful postoperative course. Macroscopically, tumor was centrally located, well-circumscribed and encapsulated, measuring 2.6 cm in diametar. Histologically the tumor showed solid and trabecular pattern, tumor cells were uniformly, polygonal, with a wide cytoplasm and round nuclei. In between the tumor were numerous mature bone's trabeculae (Figure 2.). No necrosis was identified. The mitotic count was <1/2mm^2. The Ki67 indeks was <5%. Imunohistochemically, the tumor cells were diffuse positive for CD 56, chromogranin (Figure 1.) and synaptofizin. All nineteen lymph nodes were reactive changed, without tumor infiltration.

Results: Final diagnosis was; typical carcinoid of the lung with prominente ossification. A patient did not receive any adjuvant therapy. 36 months after surgery he is without relapse of diagnosed tumor.

Conclusions: Ossification has been described in about 10% of the lung carcinoides, and prominente ossification is much more rare. It's result of the interaction between osteogenic factors produce by the tumor cells and surrounding stroma.We do not have enough data on the biological behavior of this carcinoid subtype. According to some authors intratumoral ossification may reflect the aggressiveness of the tumor, so patients shoud be follow more carefully versus patient with more usual forms.





Keywords: lung neuroendocrine tumor, carcinoid, ossification

EP14.01-012 A Case Report of Lung Large Cell Neuroendocrine Carcinoma with Carcinoid Morphology

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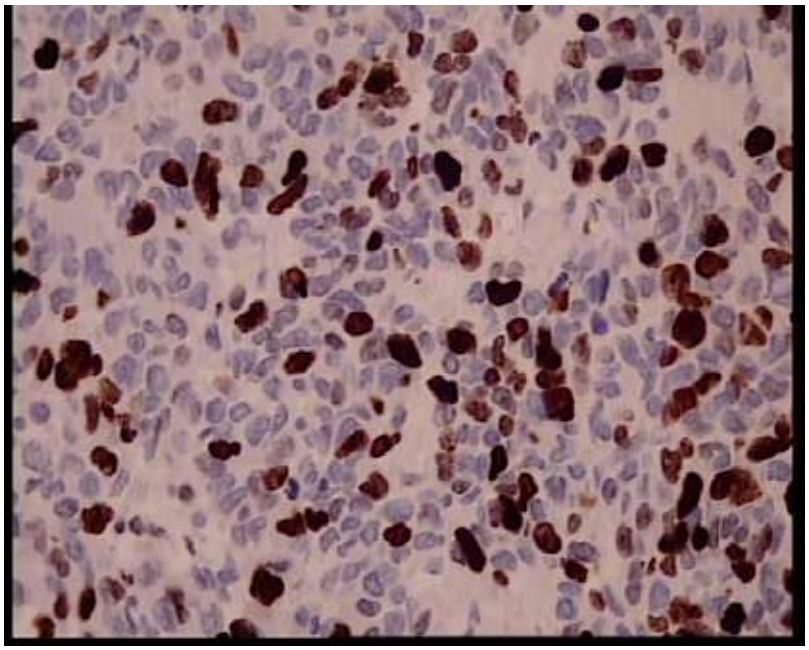
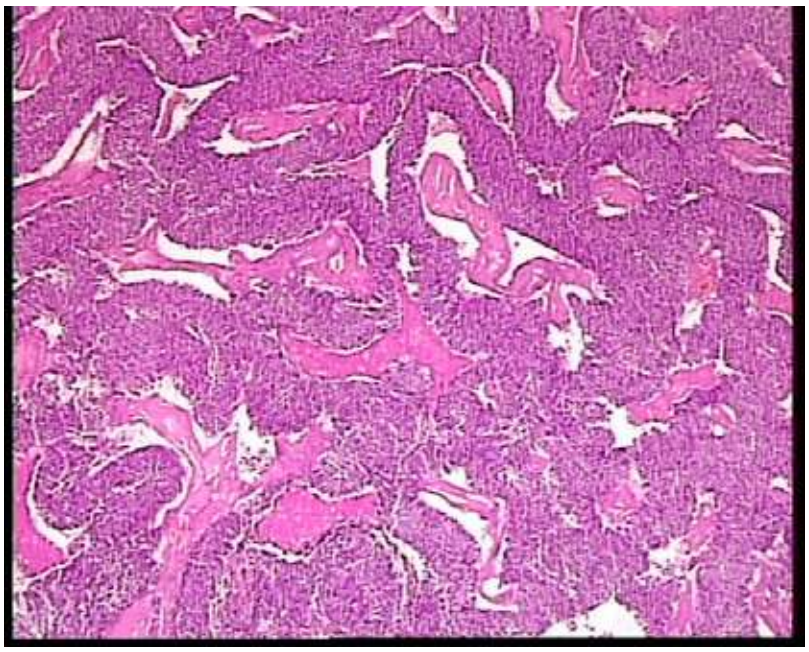
Introduction: This entity was recognised in the 2017 World Health Organisation classification of neuroendocrine neoplasms of the pancreas, and it is new entity in 2021 WHO classification of the neuroendocrine neoplasms of the lung.

Methods: 69 years old male, smoker, with pronounced cough, his past medical history included hypertension. Chest CT imaging showed central tumour mass of the left lower lobe. Left lobectomy and mediastinal lymphectomie were done. The patient had an uneventful postoperative course. Macroscopically, the tumor was a well-circumscribed, measuring 2.6cm in diameter. Histologically tumor showed solid pattern (Figure 1.), tumor cells were round-to ovoid with scant cytoplasm, immunohistochemically CD 56, chromogranin, synaptophysin and TTF-1 positive. Multiple, small foci of necrosis were present. Lymphovascular and pleural invasion weren't identified. The mitotic count was 11/2mm^2 (according to the actual recommendation for mitotic index evaluation) and Ki 67 indeks was 40% in hot spots (Figure 2.). All lymph nodes were reactive changed, without tumor infiltration.

Results: According to the current WHO classification we diagnosed this tumor as large cell neuroendocrine lung cancer with carcinoid morphology stage of IA(pT1c pN0). A patient did not receive any adjuvant therapy. 25 months after surgery he is without relapse of lung cancer.

Conclusions: Lung large cell neuroendocrine carcinoma with features of carcinoid tumor are rare, and we still don't have insufficient clinical and pathological and also genetic data and defined approach to these patients.





Keywords: lung, large cell neuroendocrine carcinoma, carcinoid morphology

EP14.01-013 First-Line Chemotherapy vs Chemoimmunotherapy in Stage IV Large Cell Neuroendocrine Carcinoma of the Lung, a Retrospective Study

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Introduction: Large cell neuroendocrine cancer of lung (LCNEC) is a rare type of lung cancer and data regarding the effect of immune checkpoint inhibitors (ICI) on LCNEC is limited. This retrospective study aims to investigate the efficacy of adding ICI to standard chemotherapy (CT) in the treatment of patients with stage IV LCNEC.

Methods: We included all patients diagnosed with stage IV LCNEC from the Moffitt Cancer Center database that received systemic therapy between June 2016 and June 2021. Group A included patients who received first line CT and ICI (anti-PD-1 or anti-PD-L1 therapy for ICI, n= 11) and group B received CT only (n= 13). We collected data on overall survival (OS), progression free survival (PFS), objective response rate (ORR) and toxicities since treatment initiation. Survival analysis was performed using Kaplan-Meier curves and Log-rank tests. Cox proportional hazard model was used for univariate analysis.

Results: Twenty-four subjects met the inclusion criteria and were included for all evaluations. Kaplan-Meier survival analysis revealed median OS was 13.1 months (95% CI 5.2 to 20.9) and 6.5 months (95% CI 3.8 to 9.3) in groups A and B, respectively. Log-rank test showed the difference was significant (p= 0.029). Median PFS was 7.5 months (95% CI 3.4 to 11.5) in group A and 4.7 months (95% CI 3.2 to 6.1) in groups B, but the difference is not significant (p= 0.136, log-rank). Univariate Cox proportional hazards regression analysis confirmed that the addition of ICI to CT significantly improved overall survival in stage IV LCNEC patients (hazard ratio = 0.350, 95% confidence interval = 0.129- 0.949, p = 0.039). The ORR tended to be higher in group A than in group B but the difference was not significant (58.3% vs 41.7, p= 0.474). Toxicity profile was as expected for these agents.

Conclusions: In this retrospective study, the addition of ICI to standard CT demonstrated a positive effect on OS, and a trend in PFS and ORR, with known toxicity profile in stage IV LCNEC. Limitations to this study include the retrospective nature and small sample size, but the inclusion of all consecutive patients limited selection bias. Larger and prospective studies are warranted.

Keywords: large cell neuroendocrine carcinoma of the lung, immune checkpoint inhibitors, chemoimmunotherapy

EP14.01 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - INFORMING ES-SCLC

EP14.01-014 Risk Factors for Brain Metastasis in Patients with Small Cell Lung Cancer: A Systematic Review and Meta-analysis

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Introduction: The use of prophylactic cranial irradiation (PCI) for small cell lung cancer (SCLC) is controversial. Risk factors for brain metastasis (BM) are largely unknown, hampering personalized treatment strategies. This study aimed to identify possible risk factors for BM in SCLC.

Methods: We systematically searched the Pubmed database (01-01-1995 ~ 18-01-2021) according to the PRISMA guideline. Studies were eligible if they reported detailed BM data with adequate sample size (randomized clinical trials [RCTs]: N≥50; non-RCTs: N≥100) in patients with SCLC. The Revised Cochrane risk-of-bias tool for randomized trials (RoB2) was used to assess risk of bias for RCTs. We summarized the reported risk factors and performed meta-analyses to estimate the pooled hazard ratios (HR) if enough qualified data (i.e. two or more studies; the same study type; the same analysis method; HRs retrievable) were available. The impact on overall survival (OS) was also analyzed if available.

Results: Out of 536 identified records, 61 met the inclusion criteria (22 records for 18 RCTs comprising 5060 patients, and 39 non-RCTs totaling 8128 patients). Baseline brain imaging or data regarding asymptomatic BM development was lacking in the majority of the trials. All RCTs except for two were at high risk of bias. In total, 57 factors were reported, including 8 baseline characteristics, 27 tumor-related factors, and 22 treatment-related factors. Only 10 factors had qualified BM data from 21 studies and four factors had qualified OS data for meta-analysis. Limited stage disease (LD) patients had significant less BM (HR=0.34, 95%CI: 0.17-0.67; P=0.002) and a better OS (HR=0.60, 95%CI: 0.37-0.98; P=0.04) than extensive disease (ED); A higher T stage (≥3) (HR=1.72, 95%CI: 1.16 -2.56; P=0.007) was a significant risk factor for BM. Age (≥65) (HR=0.70, 95%CI: 0.54-0.92; P=0.01) was associated with less BM. Male sex (HR=1.24, 95%CI: 0.99-1.54; P=0.06) tended to be a risk factor for BM and better PS(0-1) (HR=0.66, 95%CI: 0.42-1.02; P=0.06) was associated with a lower risk for BM. PCI significantly decreased BM in both LD-SCLC (P<0.00001) and ED-SCLC (P=0.0007), but did not significantly improve OS in ED-SCLC (HR=0.93, 95%CI: 0.50-1.71; P=0.81). A higher PCI dose did not improve OS (HR=1.14, 95%CI: 0.97-1.34; P=0.11). Competing risk regression data showed that higher PCI dose (>25Gy) prevented BM more effectively (HR=0.74, 95%CI: 0.55-0.99; P=0.04). Compared to M0-M1a, M1b was a risk factor for OS (HR=1.46, 95%CI: 1.10-1.95; P=0.01) in ED-SCLC, but not for BM (HR=1.26, 95%CI: 0.89-1.77; P=0.19); Smoking and thoracic radiotherapy dose (<45Gy vs ≥45Gy) were not significant risk factors for BM (P>0.05). Other factors such as N-stage and blood biomarkers had no qualified data to perform meta-analysis.

Conclusions: Current available data indicate that younger age, higher T stage, and ED were significant risk factors for BM, males tended to be at higher risk for BM, suggesting that PCI should be especially discussed in such cases; A higher PCI dose is not necessary. As high-quality data was lacking, individual patient data (IPD) meta-analysis and well-designed RCTs are needed to better identify BM risk factors and further confirm our findings.

Keywords: small cell lung cancer, brain metastasis, risk factors

EP14.01-015 IMforte: A Phase III Study of Lurbinectedin and Atezolizumab Versus Atezolizumab as Maintenance Therapy in ES-SCLC

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Introduction: Despite the effectiveness of PD-L1 inhibitors in combination with platinum-based chemotherapy as first-line treatment for extensive-stage small-cell lung cancer (ES-SCLC), most patients still have disease progression and prognosis remains poor. In the IMpower133 study, the addition of atezolizumab (monoclonal anti-PD-L1 antibody) to chemotherapy improved median overall survival (mOS) to 12.3 months compared with 10.3 months in the chemotherapy plus placebo arm (HR 0.70; 95% CI: 0.54, 0.91; *P*=0.007; Horn et al, 2018). Single-agent lurbinectedin, a selective inhibitor of oncogenic transcription, has shown promising activity in many tumor types, including as second-line (2L) treatment for SCLC (objective response rate [ORR] by investigator assessment, 35%; Trigo et al, 2020), which led to its approval in the US for patients with metastatic SCLC who have previously received platinum-based chemotherapy. In the Phase I part of the 2SMALL study, the combination of lurbinectedin and atezolizumab showed promising preliminary anti-tumor activity (ORR, 57.7%) as a 2L treatment for ES-SCLC (Ponce Aix et al, SITC 2021). The current study assesses lurbinectedin in combination with atezolizumab as a maintenance treatment for ES-SCLC in patients who have received atezolizumab plus carboplatin and etoposide as first-line induction therapy without experiencing disease progression.

Methods: IMforte (NCT05091567; GO43104) is a Phase III, randomized, open-label, multicenter study of atezolizumab plus lurbinectedin compared with atezolizumab alone. The study consists of an induction phase and a randomized maintenance phase. Patients eligible for the induction phase will be ≥ 18 years old and have an ECOG performance status of 0 or 1 and measurable disease per the Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 criteria. Patients with central nervous system metastases, autoimmune disease or prior anti-cancer therapy for ES-SCLC will be excluded. During the induction phase, patients will receive four 21-day cycles of atezolizumab (1200 mg intravenously [IV]) plus carboplatin and etoposide. Patients must have an ongoing response or stable disease per RECIST 1.1 after the completion of 4 cycles of induction treatment to be randomized into the maintenance phase of the study. In the maintenance phase, patients will be randomized 1:1 to receive either atezolizumab (1200 mg IV) plus lurbinectedin (3.2 mg/m^2 IV) or atezolizumab (1200 mg IV) every 3 weeks until disease progression. Independent review facility-assessed progression-free survival (PFS) per RECIST 1.1 and OS are the co-primary endpoints. Secondary endpoints include investigator-assessed PFS, ORR, duration of response, quality of life and safety/tolerability.

Keywords: Atezolizumab, Lurbinectedin, Small-cell lung cancer

EP14.01-016 Anlotinib Plus Toripalimab as Maintenance Treatment in Extensive-Stage Small Cell Lung Cancer: a Single-Arm Phase II Study

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Introduction: Most patients (pts) with ES-SCLC would experience disease recurrence and drug resistance within six months after first-line treatment, although there was a higher objective response rate (ORR). Immunotherapy maintenance in ES-SCLC pts who had completed first-line chemotherapy only did not improved survival outcomes. Anlotinib, an oral multitarget tyrosine kinase inhibitor, could effectively inhibit angiogenesis and improve tumor immune microenvironment. Here, we presented the efficacy and safety of anlotinib plus toripalimab, a novel PD-1 inhibitor, as maintenance treatment in ES-SCLC pts after first-line platinum-based chemotherapy, hoping to delay disease recurrence.

Methods: Eligible pts with cytologically or histologically confirmed ES-SCLC, evaluated as complete response (CR), partial response (PR) or stable disease (SD) after 4 to 6 cycles of first-line platinum-based chemotherapy and it was up to the investigators to determine whether radiotherapy was needed, received anlotinib (12mg, QD, from day 1 to 14 of a 21-day cycle) plus toripalimab (240mg, iv, q3w) until disease progression or unacceptable toxicity. The primary endpoints were PFS (defined as the time from the diagnosis of ES-SCLC to disease progression or death from any cause) and OS (defined as the time from the diagnosis of ES-SCLC to death from any cause). Secondary endpoints were ORR, disease control rate (DCR), time to response (TTR) and safety.

Results: As of Feb 10, 2022, 15 pts (13 PR, 2 SD) were enrolled. The median age was 65.7 years (range 53-78), 14 (93.3%) were males, 9 (60%) were ECOG PS 1 and 4 (26.7%) were liver metastasis. The median PFS was 12.5 months (95%CI: 11.2-13.8). Of 15 evaluable pts, 1 reached PR and 11 had SD. The ORR was 6.7% and the DCR was 80.0%. Most common grade 1-2 treatment-related adverse events (TRAEs) were rash (40.0%),weakness (26.7%), leukopenia (20.0%), hypothyroidism (20.0%), hoarse voice (20.0%), mouth pain (20.0%) and headache(20.0%). Grade 3 TRAEs included hypothyroidism (13.3%), rash (6.7%), myalgia (6.7%) and radiation pneumonia (6.7%).

Conclusions: Anlotinib plus toripalimab showed significant efficacy and manageable toxicities as maintenance treatment in ES-SCLC pts after first-line platinum-based chemotherapy, which provided a new treatment strategy to delay drug recurrence and prolong the survival times.

Keywords: Extensive-Stage Small Cell Lung Cancer, Maintenance Treatment, Anlotinib

EP14.01-018 Small Cell Lung Carcinoma in Morocco

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Introduction: Small Cell Lung Carcinoma (SCLC) constitutes approximately 13-15% of all lung cancers. It is aggressive neuroendocrine neoplasia, characterized by a high proliferative index and poor overall survival. Several studies report distinct clinical and pathological features of SCLC from non-small cell lung carcinoma (NSCLC). This study aims to describe the characteristics of patients with SCLC and identify differences between SCLC and NSCLC in Morocco.

Methods: A retrospective study of patients diagnosed with primary lung cancer, between 1 January 2014 and 31 December 2017, was conducted at Ibn Sina Hospital Center in Morocco. All patients with available data were included in this study. Patients' and disease characteristics were collected and compared, between SCLC and NSCLC, using the chi-square test and student test. Statistical tests were conducted using Jamovi version 2.0.0. P values<0.05 were considered statistically significant.

Results: During the study period, 606 patients with lung cancer were included. Among these, 45 patients had SCLC, which accounted for 7.41% of all lung cancer cases. Studying the number of new cases each year, the proportion of SCLC increased from 6.62% in 2014 to 8.55% in 2017. The male-to-female ratio was 21.5. The average age at diagnosis was 58.58 years (29-85 years). Based on the age group distribution, the highest proportion of SCLC was in patients aged between 54-64 (35.55%), followed by the age group 45-54 (31.11%). The smallest proportion was observed in patients younger than 45 years (44%). Regarding smoking habits, 80% of patients were smokers. Almost all cases (90.91%) were diagnosed at an advanced stage. Results of immunohistochemistry showed positivity for Synaptophysin, Chromogranin, and CD56. Compared with NSCLC, SCLC was highly metastatic (p=0.007) and more diagnosed at stage IV of the disease (p<0.001). However, no significant differences were noted according to sex, age at diagnosis, or smoking status between the two histological types.

Conclusions: Our findings showed a significant increase in SCLC in Morocco. This pathology appears with high metastatic potential and advanced stages of the disease. Further studies on metastatic mechanisms are warranted to control the spread of SCLC metastases and develop novel therapeutic biomarkers.

Keywords: Small Cell Lung Carcinoma, Epidemiology, Morocco

EP14.01 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - INFORMING ES-SCLC

EP14.01-019 Identifying Circulating DNA Methylation Patterns in Small Cell Lung Cancer Patients

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Introduction: Small cell lung cancer (SCLC) is a deadly disease and patients often suffer from recurrent disease. Biologic mechanisms of recurrence are unclear. Epigenetic mechanisms, like DNA methylation, may be operant. SCLC is rarely resected; therefore, the SCLC methylome is understudied due to scarce tumour tissue.

Methods: In this study, we examined the pre-treatment methylome of 72 SCLC patients at our institution through cell-free methylated DNA immunoprecipitation sequencing (cfMeDIP-seq) on plasma cell-free DNA (cfDNA) and on sheared genomic DNA from paired peripheral blood leukocytes (PBLs) (n = 72) to improve tumour signal specificity. Also, cfMeDIP-seq was performed on an independent cohort of healthy non-cancer controls (n = 20). For all bioinformatic analyses, chromosomes 1-22 were binned into 300-bp windows (n = 9.6e6 genome-wide windows); reads from cfMeDIP-seq were tallied per bin. The R package DESeq2 and annotatr was used for differential methylation analysis and annotation of features of interest. Windows with a log2-foldchange of >2 or <-2 with a p-adjusted value < 0.05 were called as significant. Kaplan-Meier survival analysis log-rank test and cox proportional hazards model was fitted. Lastly, we applied a series of filters to enrich for tumour-derived signal: ENCODE-blacklist and PBL-associated regions were removed, and CpG-rich (>5 CpGs per window) regions were retained. Subsequent cfDNA analyses were performed using the remaining 190,769 windows.

Results: Of the 72 patients, 31 (43%) and 41 (57%) had limited-stage (LS) and extensive-stage (ES) SCLC, respectively. Median follow up duration was 13 months (IQR: 7-23 months). Most were current or former smokers (65/72, 90%). Our novel SCLC **P**e**RI**pheral blood leukocytes **ME**thylation (PRIME) filter has enabled us to identify SCLC-specific windows in cfDNA. Using PRIME windows (n = 190,769), methylated cfDNA from SCLC were distinguished from healthy controls: SCLC cfDNA was enriched for hypermethylated CpG islands and shore regions, whereas controls had more methylated open-sea regions. SCLC cohort by consensus clustering of the top 5000 most variant windows revealed two distinct cfDNA methylation patterns: a Lower-risk cluster (median OS = 21 months, one-year OS = 72%) and a Higher-risk cluster (median OS = 11 months, one-year OS = 48%) (HR 2.3, p=0.004). After adjusting for stage, the association between the Higher-risk cluster and worse survival maintained a weak trend (HR: 1.5, p = 0.2). There was no significant difference in sex (p = 0.81) or plasma DNA content (p = 0.33). Several regulatory and noncoding features including CCCTC-binding factor (CTCF) sites, long non-coding RNA (lncRNA), long terminal repeats (LTRs), short interspersed nuclear elements (SINEs), and long interspersed nuclear elements (LINEs) were found to be differentially hypermethylated in Higher-risk vs Lower-risk clusters.

Conclusions: We identified methylation patterns in the plasma of SCLC patients using the cfMeDIP-seq assay and identified two distinct clusters with stage and prognostic associations. These clusters are differential methylated at regulatory and non-coding features suggesting biologic mechanisms of SCLC disease progression. Lastly, we developed an SCLC-specific cfDNA filter, PRIME, that will help inform future liquid biopsy analyses.

Keywords: small cell lung cancer, liquid biopsy, DNA methylation

EP14.01 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - INFORMING ES-SCLC

EP14.01-020 Trial in Progress: [177Lu]Lu-DOTA-TATE Combination Therapy in Treatment-Naïve Extensive Stage Small Cell Lung Cancer

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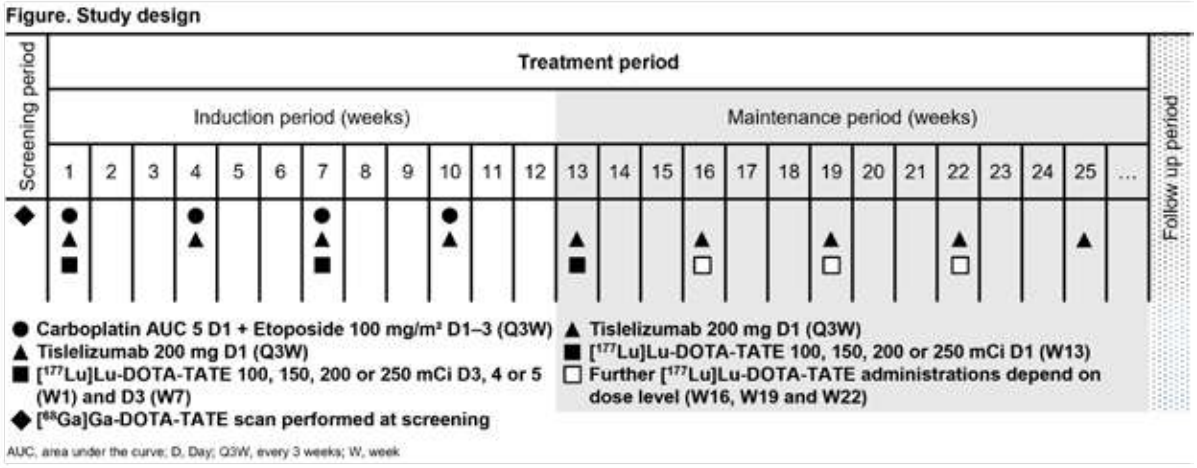
Introduction: New therapeutic agents are desperately needed for small cell lung cancer (SCLC), a high-grade, poorly differentiated neuroendocrine carcinoma of the lung, that often presents at an extensive stage (ES), and has high mortality rates. Response to current standard of care (SOC) is generally short-lived with most patients experiencing disease progression and a poor prognosis. Up to half of SCLC tumors express somatostatin receptors (SSTR). [^{177}Lu]Lu-DOTA-TATE, a radioligand therapy, selectively targets SSTRs and has demonstrated a significant improvement in progression-free survival (PFS) and prolongation of overall survival (OS) in patients with SSTR-positive midgut neuroendocrine tumors. In SCLC, patients with SSTR-positive ES-SCLC, who have progressed following chemotherapy, have benefited from [^{177}Lu]Lu-DOTA-TATE treatment. We are conducting the first clinical trial of [^{177}Lu]Lu-DOTA-TATE combination therapy for first-line treatment in SSTR-positive ES-SCLC. This phase Ib study aims to establish the recommended dose and provide a preliminary assessment of efficacy of [^{177}Lu]Lu-DOTA-TATE in combination with carboplatin, etoposide and the programmed death-ligand 1 inhibitor, tislelizumab.

Methods: This multi-center, open-label study (NCT05142696) will enrol approximately 39 adult patients with newly diagnosed SSTR-positive (by [^{68}Ga]Ga-DOTA-TATE positron emission tomography imaging) ES-SCLC. Prior systemic treatment for ES-SCLC is not permitted. The treatment period is split into induction and maintenance periods (Figure). Eligible participants will be enrolled in cohorts of 3 to 6 participants to receive 4 cycles of carboplatin area under the curve 5 on Day 1 and etoposide 100 mg/m^2 on Days 1-3, every 3 weeks with tislelizumab 200 mg on Day 1 every 3 weeks in induction and maintenance period and 2 administrations of [^{177}Lu]Lu-DOTA-TATE on Day 3 during the induction period at Weeks 1 and 7 followed by 1-4 administrations (depending on dose) on Day 1 during the maintenance period (Weeks 13, 16, 19 and 22). Up to 6 different dose level combinations of [^{177}Lu]Lu-DOTA-TATE (100-250 mCi) will be assessed guided by dose limiting toxicity (DLT) rate and the Bayesian Optimal Interval design. The primary endpoint is frequency of DLTs within the first 6 weeks of treatment. Secondary endpoints include safety, objective response rate (RECIST 1.1), duration of response, PFS and OS. Pharmacokinetics and dosimetry of [^{177}Lu]Lu-DOTA-TATE will be assessed.

Figure. Study design



Keywords: [177Lu]Lu-DOTA-TATE, Trial in progress, Small Cell Lung Cancer

EP14.01-021 Anlotinib Plus Irinotecan or Docetaxel in Small-Cell Lung Cancer (SCLC) Relapsed within Six Months: a Single-Arm Phase II Study

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Introduction: There is still no unsatisfactory treatment strategy for patients (pts) with advanced SCLC relapsed within six months after first-line treatment, although chemotherapy alone is the standard treatment. Anlotinib, an oral multitarget tyrosine kinase inhibitor, effectively inhibits angiogenesis and enhances tumor cell response to chemotherapy. In the ALTER 1202 trial, anlotinib had significantly improved progression-free survival (PFS) and overall survival (OS) of advanced SCLC pts who received at least two lines chemotherapy. Therefore, we presented the updated efficacy and safety of anlotinib plus irinotecan or docetaxel in SCLC relapsed within six months after first-line treatment.

Methods: Eligible pts with advanced SCLC who have relapsed within six months after first-line platinum-based treatment received anlotinib (12mg, QD from day 1 to 14 of a 21-day cycle, the dose could be adjusted to 10mg or 8mg according to the patient's tolerance) and irinotecan (65mg/m2, day1,8, q3w, up to 4 cycles) or docetaxel (60mg/m2, q3w, up to 4 cycles) until progression or intolerable toxicity. The primary endpoint was the objective response rate (ORR). Secondary endpoints included PFS, the disease control rate (DCR), OS and safety.

Results: As of March 12, 2022, we recruited 34 pts, among which 32 pts (median age: 62.7 years, male: 84.4%, ECOG PS 1: 81.3%, brain metastasis: 46.9%, liver metastasis: 34.4%) were eligible for efficacy analysis. Median follow-up time was 13.3 months (95% CI, 6.18 -20.42). Median PFS was 4.5 months (95%CI: 3.48- 5.53). The median OS was 7.2 months (95%CI: 4.67-9.73). Of 32 evaluable pts, 1 pts had complete response (CR), 19 pts reached partial response (PR) and 10 pts had stable disease(SD). The ORR was 62.5% (20/32) and the DCR was 93.8% (30/32), respectively. Most common grade 1-2 treatment-related adverse events (TRAEs) included weakness (50.0 %), anorexia (37.5 %), anemia (31.3%), leucopenia (18.8%) and hypertension (15.6%). 3 pts (9.4%) suffered from grade 3 AEs, which were leukopenia, thrombocytopenia, and anemia.

Conclusions: Anlotinib plus irinotecan or docetaxel continued to show promising efficacy and manageable toxicities in SCLC relapsed within six months after first-line treatment. It may become a novel therapeutic strategy for the population.

Keywords: Small-Cell Lung Cancer, Anlotinib

EP14.01 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - INFORMING ES-SCLC

EP14.01-022 Immune Thrombocytopenia in a Patient with Large Cell Neuroendocrine Carcinoma Under Dual Immune Checkpoint Inhibition

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Introduction: Immune checkpoint inhibitors (ICIs) are associated with a wide range of immune-related adverse events (irAEs). Among them, immune thrombocytopenia is very rare and potentially life-threatening. Published reports of patients with immune thrombocytopenia are scarce.

Methods: Detailed description of symptoms, signs, diagnosis, treatment, and follow-up of an individual patient.

Results: A 68-year old male patient was diagnosed with large cell neuroendocrine carcinoma stage III (T4N2M0) in June 2021. According to the Multidisciplinary Tumor Board of our Hospital the tumor was inoperable, but the patient was eligible for a clinical trial. He enrolled in the trial and was randomized to receive concurrent chemoradiation (cisplatin-etoposide and radiation 60 Gray in 30 fractions) and immunotherapy with nivolumab (360mg q21). The restaging demonstrated a partial response, and therefore, the patient continued with maintenance therapy with nivolumab (360mg q21) and ipilimumab (1mg/kg q42) per study protocol. After Cycle 1, the patient presented hypothyroidism grade I, which did not require replacement treatment. On Cycle 3-Day 1, the patient presented with thrombocytopenia grade IV (PLT=4000). He did not report any symptomatology and the physical examination revealed only a few petechiae in the face and chest. The patient was hospitalized and further investigation included: (1) a detailed history with particular attention to recent changes in medication, personal or family history of autoimmunity, history of viral illnesses (2) a peripheral blood smear which confirmed thrombocytopenia and also revealed leukocytosis with left shift, (3) HbsAg (-), anti-HBV (-), anti-HCV (-), anti-HIV (-), EBV IgG (+) and IgM (-), anti-CMV IgG (+) and IgM (+) but PCR for CMV from peripheral blood was negative (4) thyroid function tests which demonstrated the already-known hypothyroidism. After the consultation of the hematologist and due to lack of alternative diagnosis, the case was considered immune thrombocytopenia related to immunotherapy. The patient was treated with corticosteroids (methylprednisolone 1.5mg/kg), but due to lack of improvement after five days, the dose was escalated to 2mg/kg, and a one-time dose of intravenous immune globulin was given (1g/kg). The patient improved after ten days from the admission; the platelet count retained >25000 for three consecutive days and the patient was discharged from the hospital. It was decided to discontinue immunotherapy permanently. The patient is on follow-up, with tapering of corticosteroids, the platelet count is within the normal range, and the last restaging demonstrated partial response.

Conclusions: Immune thrombocytopenia is a rare adverse event related to ICIs. In this specific case, it should be noted that the patient (1) had already received CCRT, (2) was under dual treatment with anti-PD-1/anti-CTLA-4 (3) had already presented another irAE (hypothyroidism). Specialist consultation is of utmost importance in managing irAEs. Investigation of irAEs may shed light on the pathogenic mechanisms of autoimmunity.

Keywords: Thrombocytopenia, Immune Checkpoint Inhibitors, LCNEC

EP14.01-023 A Randomized Phase II Study of Irinotecan Plus Cisplatin With or Without Simvastatin in Ever-Smoking Small Cell Lung Cancer

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Introduction: Smoking pack-years are associated with a sharper increase in the risk of small cell lung cancer (SCLC). Statins are recognized as powerful anti-inflammatory agents, which reduce the risk of lung cancer in chronic obstructive pulmonary disease. Previously, we found a potential survival benefit of irinotecan and cisplatin (IP) in combination with simvastatin in heavy-smoking extensive disease (ED)-SCLC patients. This study evaluated whether a combination of simvastatin with IP improve clinical outcomes of ever-smoker ED-SCLC patients.

Methods: This is an open-label and randomized phase II study which was conducted in the National Cancer Center (Goyang, Korea). Key eligibility criteria included age ≥ 18 years old, confirmed ED-SCLC, chemotherapy-naive, smoking history (≥100 cigarettes lifetime), a measurable lesion, and ECOG performance status (PS) of ≤ 2. Patients were randomized to receive IP alone (irinotecan 65 mg/m^2 and cisplatin 30 mg/m^2 intravenously on days 1 and 8 every 3 weeks) or with simvastatin (40mg daily per oral). Primary endpoint was progression-free survival (PFS). Secondary endpoints were response rate (RR), overall survival (OS), and toxicity. Exploratory study with serum lipid profile was performed.

Results: Between Sep 16, 2011, and Sep 9, 2021, a total of 125 patients was randomly assigned to simvastatin (n=62) or control (n=63) arms. Median follow-up duration was 75.0 months. Median age was 64 years old and the ECOG PS of 2 was 41 (32.8%). Male was predominant (n= 116, 92.8%) and median smoking pack-year was 40 years. Clinical characteristics were well balanced between the two arms. The simvastatin arm did not significantly prolong the PFS compared to the control arm (median PFS, 6.3 months vs 6.1 months; hazard ratio [HR] = 1.01 [95% confidence interval (CI), 0.70-1.47], *P*= 0.250). The RR was similar between two arms (54/61 [88.5%] vs. 50/59 [84.7%]; *P*= 0.599). The simvastatin arm did not improve the OS compared to the control arm (median OS, 14.4 months vs 15.4 months; HR = 1.18 [95% CI, 0.81-1.71], *P*= 0.388). The subgroup analysis was done according to smoking pack-year, body mass index, baseline serum levels of LDH, triglycerides, low-density cholesterol (LDL), and high-density cholesterol. No subgroups showed the survival benefit from the simvastatin treatment. The serum LDL level was significantly reduced after treatment in the simvastatin arm than in the control arm (-30.3% vs. 0.0%, *P* < 0.001). However, the survival improvement was not observed in patients with high baseline LDL level or patients whose LDL level was significantly decreased after treatment. Incidence rate of grade 3-4 treatment-related adverse events were 62.9% in simvastatin arm and 61.9 % in control arm.

Conclusions: Addition of simvastatin to IP chemotherapy provided no survival benefit in ever-smokers with ED-SCLC patients. Clinical trial information: NCT01441349.

Keywords: small cell lung cancer, simvastatin, smoking

EP14.01 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - INFORMING ES-SCLC

EP14.01-024 Transformation of SCLC to Lung Squamous Cell Carcinoma after First-Line Chemotherapy and Response to Sintilimab: A Case Report

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Introduction: Histological transformation of NSCLC to SCLC is a mechanism of resistance in EGFR-mutated tumors. However, histological transformation of SCLC to lung squamous cell carcinoma (LUSC) has never been reported.

Methods: Next-generation sequencing (NGS) on the biopsy was performed.

Results: The present case concerns a case of a 68-year-old man presenting with epigastric distension discomfort. A CT-guided tumor biopsy was then performed, and the tumor was pathologically diagnosed as stage IV SCLC of the right lung. Cisplatin combined with etoposide was subsequently given. After 4 cycles of treatment, the patient showed a progressive disease with skull metastases and radiotherapy was given. Regular review during the period, the disease is stable. Three years later, she felt unwell again, and a new lesion was found in his left lung. The repeat biopsy identified LUSC. The patient was initiated with sindilizumab based on higher tumor mutation burden and no standard treatment regimen. During the immunotherapy, the tumor lesion in the right lung decreased significantly and left lung remained stable and PFS was nearly 8 months.

Conclusions: As far as we know, this is the first report of SCLC transform to LUSC. And our case emphasizes both the profile of transformation from SCLC to LUSC and the importance of repeat biopsy dealing with disease progression.

Keywords: small cell lung cancer, lung squamous cell carcinoma, immunotherapy

EP14.01 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - INFORMING ES-SCLC,
SUNDAY, AUGUST 7, 2022 - 9:45 - 18:00

EP14.01-025 Anlotinib Plus Standard Chemotherapy as First-line Treatment in Extensive-Stage Small Cell Lung Cancer Patients

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Introduction: Extensive-stage small cell lung cancer was characterized by poor prognosis. Recently, anlotinib has demonstrated clinical activity as third- or further-line treatment. The aim of the study was to evaluate the efficacy and safety of adding anlotinib to first-line treatment with platinum and etoposide in patients with ES-SCLC.

Methods: This is a multicenter, single arm, retrospective study (NCT04684017), conducting in 3 Chinese sites. Eligible patients were aged from 18 to 75 years; cytologically or histologically confirmed untreated ES-SCLC with performance-status of 0 or 1. Patients with asymptomatic central nervous system metastases were allowed. Patients were treated with up to six cycles chemotherapy consisted of etoposide 80-100 mg/m^2 (administered on days 1-3 of each 21-day cycle), with either carboplatin (area under the curve 5-6 mg/mL per min) or cisplatin (75-80 mg/m^2) on day 1 of each cycle. Anlotinib (8mg, 10mg and 12mg at the treating physicians' discretion) was orally taken once daily on day 1 to 14 per cycle (2 weeks on and 1 weeks off). Treatment was continued until disease progression, intolerable side effect or withdraw of consent. The primary end points of the study were safety and investigator assessed objective response rate (ORR).

Results: Between August 2018 and September 2021, 101 patients were screened, and 86 patients were included into formal analysis. Most patients were male (91.9%) and smoker (75.6%). At the date of cut off, the ORR was 83.7% with 2 CRs and 70 PRs. Median time to response was 1.6 months and response depth was 55%. Meanwhile, the response was durable, with median DOR 7.2 months (95%CI: 5.3-9.2). DCR was 96.5% with 12 SDs. In the subgroup of patients with brain metastasis, the ORR was 92.9% with 13 PRs and the DCR was 100%. At the cut-off date, 78 patients experienced PFS events. The median PFS of 78 evaluable patients and patients with brain metastasis were 9.0 months (95%CI: 7.5-10.5) and 6.0 months (95%CI: 5.0-7.0), respectively. 79 (91.9%) patients experienced adverse events. Grade 3 or higher adverse events occurred in 50 (58.1%) patients. 38 (44.2%) and 24 (27.9%) patients experienced treatment-related adverse event (TRAE) of any grade and Grade 3 or higher, respectively. The most common TRAEs were leukopenia (13 cases, 15.1%), granulocytopenia (13 cases, 15.1%), oral mucositis (11 cases, 12.8%) and fatigue (7 cases, 8.1%).

Conclusions: In view of the encouraging efficacy, safety profile and durability, anlotinib combined with chemotherapy may provide a potential and novel treatment option for ES-SCLC patients. The study results need further validated in a randomized trial.

Keywords: SCLC, Anlotinib, Chemotherapy

EP14.02 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - PRECLINICAL/TRANSLATIONAL

EP14.02-001 Could the Oxidative Stress Be Used as a Marker for Neuroendocrine Lung Tumors?

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Introduction: In many neuroendocrine tumors, the vascular density (neuroendocrine main feature) is higher in the low-grade tumors than high-grade ones. This observation, so-called "neuroendocrine paradox", gives to the angiogenesis a role as differentiation marker instead of prognostic marker. But the neoplastic angiogenesis is associated also with the oxidative stress. Thus, our goal is to verify if the oxidative stress could have a preeminent role in the lung NET compared with other neoplasms. Furthermore, we try to identify specific markers of oxidative stress in these tumors.

Methods: From April 2010 to October 2021 84 patients were operated for typical (TC), atypical carcinoid (AC) and large cell neuroendocrine carcinoma (LCNEC). We analyzed angiogenesis by serum and tissue level of VEGFA and somatostatin type-2 receptor (SSTR2). Furthermore, we compared serum oxidative-stress parameters such as soluble Nox2-derived peptide (sNOX2-dp) release, hydrogen-peroxide (H2O2) production, H2O2 break-down activity (HBA) and endothelial-dysfunction (NO). For the study, we considered 20 patients operated for NET, 20 patients operated for NSCLC and 20 healthy non-operated patients (control group).

Results: The serum-VEGFA (pg/ml) was different between the groups ($p<0.001$). The NET group demonstrated a higher value (median 904.3, IQR 708.5; 1093.5) compared to NSCLC (median 699.6, IQR 634.5; 807.5) and controls (median 335.7, IQR 241.1; 384.1). This difference reflects that recorded also at the tissue level ($p<0.05$) where the VEGFA (pg/ml) in the NET (median 809.7, IQR 730.7; 906) was higher than NSCLC (median 567.2, IQR 476.5; 717.4). There is no linear relationship between the serum and tissue VEGFA ($r = 0.060$, 95% CI, -0.392: 0.492). The serum-SSTR2 (ng/mL) was different between groups ($p <0.001$). The SSTR2 was higher in the NET (median 17.5, IQR 15.4; 25.6) than NSCLC (median 10, IQR 6.8; 13.7) and the controls (median 3.1, IQR 1.5; 5.4). The difference was confirmed for the tissue-SSTR2 ($p <0.005$). In the NET the SSTR2 (ng/ml) was higher (median 17.5, IQR 14.9; 20.9) than NSCLC (median 9.5, IQR 7.2; 11.4). The oxidative stress was also different ($p<0.001$). The median sNOX2-dp (pg/ml) in the NET (45, IQR 35.8;47.8) was higher compared with NSCLC (31.2, IQR 26.9;38) and controls (31.2, IQR 24.6;42.2) respectively. The same can be said for H2O2 (μM, $p< 0.001$) where in the NET the median was higher (41.0, IQR 33.4;44.8) compared with NSCLC (27.3, IQR 22.7;36.0) and controls (10.3, IQR 9.1;12.7). There is a moderate linear relationship between the serum sNox2-dp and H2O2 ($r = 0.54$, 95% CI: 0.334; 0.699). The HBA inhibition-activity (%) is different ($p< 0.001$) but the NET showed a lower activity (32%, IQR 26;41) compared with NSCLC (41%, IQR 34;53) and controls (54%, IQR 47;62). There was a negative linear correlation between HBA and H2O2 ($r= -0.60$). Endothelial-dysfunction (NO, μM) confirmed the difference ($p< 0.001$) between groups. The median in the NET was lower (9.9, IQR 9.5;11.6) compared with NSCLC (13.5, IQR 10.8;19.5) and controls (25.9, IQR 20.2;29.1).

Conclusions: If further studies confirmed the role of the oxidative-stress in the lung NET as shown, they would give new perspectives especially in new drug treatments.

Keywords: Lung neuroendocrine tumors, Oxidative stress, Angiogenesis

EP14.02 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - PRECLINICAL/TRANSLATIONAL

EP14.02-002 Cisplatin in Combination with Entinostat exerts Synergistic Antineoplastic Activity in Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer cases and is associated with a poor survival rate. SCLC is a tremendously lethal disease characterized by rapid growth and a high propensity to metastasize. Hitherto, platinum-based chemotherapy is one of the key components of the standard first-line therapeutic regimen of SCLC. Despite the known initial chemosensitivity of SCLC, the prospect of therapeutic success is limited by early relapse and acquired resistance in almost all patients. In recent years, only little progress has been made in the management of the disease although considering the addition of immunotherapy to the therapeutic armamentarium. Entinostat, a class I histone deacetylase inhibitor (HDACi), has been reported to exhibit anti-cancer effects in various human cancers. Entinostat has been demonstrated to synergize with cisplatin and moreover reverses cisplatin resistance. In this study, we investigated the combined effect of cisplatin and entinostat in SCLC with the aim to determine the mechanisms behind differential responses to the combination treatment using proteomic data.

Methods: The synergistic potential of entinostat and cisplatin was determined by MTT-based cell viability assays and effects of drug interaction were calculated using the combenefit software. To address the underlying mechanism and the increased cytotoxic effect of cisplatin in the presence of entinostat, SCLC cell lines were treated with cisplatin alone or in combination with entinostat and intracellular platinum levels were determined by ICP-MS. Proteomic analysis was performed in order to decipher the principal regulator of such synergism. Further analysis included 1D annotation enrichment and KEGG pathway analysis.

Results: In this study, we demonstrate that human SCLC cell lines with neuroendocrine (NE) background display favorable responses to entinostat monotreatment compared to non-neuroendocrine (NNE) cell lines. Cisplatin displayed increased therapeutic efficacy in a subset of SCLC cell lines when combined with entinostat. Intriguingly, some cell lines which are resistant to both agents alone respond to combination treatment. Results from ICP-MS analysis revealed augmented intracellular platinum content when both agents were administered. Proteomic comparison between groups showing synergistic features or no improved response to the combination treatment revealed significantly altered proteins and pathways, associated with DNA damage repair, cell cycle and mitochondrial processes.

Conclusions: Our results demonstrate strong synergy between cisplatin and entinostat in a subset of human SCLC cell lines. Of note, combination treatment resulted in cell death of double resistant SCLC cell lines, implicating a way of overcoming therapy resistance. Addressing the underlying mechanism behind such synergism may constitute an even better benefit for patients. Especially in SCLC, efficient therapeutic options in relapsed patients are missing and deciphering the molecular basis of synergism between cisplatin and entinostat might lead to a more effective therapeutic option.

Keywords: Small Cell Lung Cancer, Cisplatin, Entinostat

EP14.02-003 Clinical Significance of MYC Family Members in Surgically Resected Limited-Stage Small Cell Lung Cancer: A Multicenter Study

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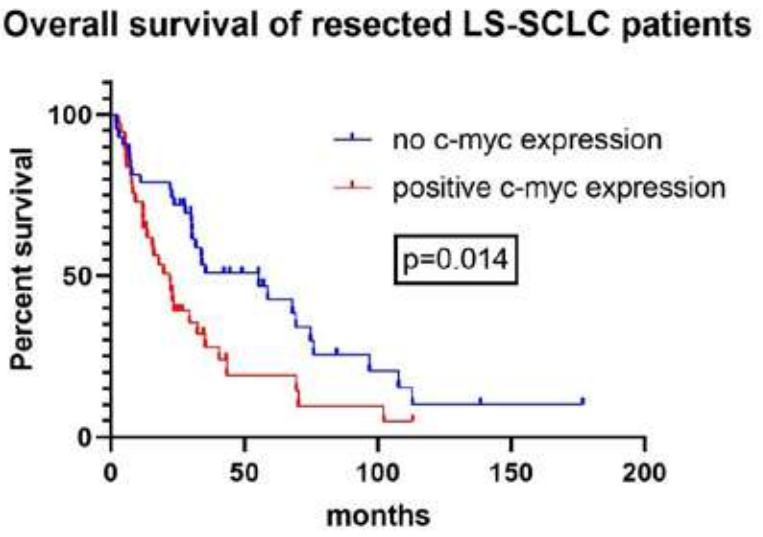
Introduction: Various preclinical studies have stated that members of the MYC transcription factor family (C-myc, L-myc and N-myc) are involved in disease progression and may represent promising therapeutic targets in small cell lung cancer (SCLC). However, there is limited knowledge on the clinical significance of MYC family members in surgically resected SCLC specimens. Our aim was to evaluate the expression and prognostic value of MYC family members in an international cohort of surgically resected SCLC patients.

Methods: Formalin fixed, paraffin-embedded primary tumor specimens of limited stage (stage I-III) SCLC (LS-SCLC) patients undergoing surgery at three participating European departments were collected for this study. Immunohistochemistry was performed for C-myc (Abcam, ab32072), L-Myc (ThermoFisher Scientific, PA5-41114) and N-myc (Cell Signaling Technology, D42BY). Expression levels were independently evaluated by two board-certified pulmonary pathologists. Clinical data of the patients was retrospectively collected. Kaplan-Meier method and log-rank test were applied for estimation and comparison of differences in overall survival (OS).

Results: In total, 85 LS-SCLC patients were evaluated. All patients underwent surgery between January 2000 and December 2019 in one of the participating centers. Median age was 64 (41-83) years, 45 (52.9%) patients were male and 75 (88.2%) received anatomic lung resection (segmentectomy, lobectomy or pneumonectomy). L-myc, C-myc and N-myc expressions were detectable in 61.9%, 44.7% and 7.1% of the specimens, respectively. Neither L-myc nor N-myc expression was associated with OS. In contrast, patients with positive C-myc expression had significantly impaired OS (vs. those with C-myc negative tumors; the median OSs were 22 vs. 55 months, respectively, p=0.014).

Conclusions: Our findings complement previous reports on the clinical presence of MYC family members in SCLC. Notably, expression of C-myc was associated with worse survival in patients undergoing surgical resection for LS-SCLC. Additional studies are warranted to further evaluate the role of MYC family members in SCLC.



Keywords: Small cell lung cancer, MYC paralogs, Clinical biomarkers

EP14.02-004 Barasertib Inhibits the Growth of SCLC Cell Lines and Transformed SCLC Patient Derived Model In Vitro and In Viv

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Introduction: Approximately 5% to 10% of EGFR (epidermal growth factor receptor) -mutant non-small cell lung cancers (NSCLCs) develops an acquired resistance to EGFR tyrosine kinase inhibitors with transformation into small-cell lung cancer (SCLC). After the transformation, clinical behavior mimics classic SCLC on many aspects, with frequent but transient responses to platinum-etoposide (EP) or taxanes, modest progression free survival and rare response to immune checkpoint inhibitors. Recently, four SCLC subtypes, defined largely by differential expression of transcription factors ASCL1, NEUROD1, and POU2F3 or low expression of all three transcription factor signatures, were suggested (Gay CM et al, Cancer Cell 2021) (SCLC-A, N, P and I, respectively). We used these subtypes to identify new therapeutic approach to tSCLC.

Methods: We have patient-derived tumor xenograft (PDX) and cell line (PDC) from a patient with EGFR mutant adenocarcinoma, who developed tSCLC after 1st line afatinib treatment. After the transformation, the patient showed no response to EP and irinotecan chemotherapies. The following SCLC cells were also evaluated: NCI-H69, H128, H146, H187, H417 and H526. We assessed cytotoxic response of these SCLC cells to barasertib by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) assay and anchorage independent growth in soft agar. Western blots were performed to assess the cellular activity of barasertib. Xenograft studies were performed to evaluate in vivo therapeutic efficacy of barasertib on PDX.

Results: Based on the suggested subgroups, H69, H146, and H187 were SCLC-A, H128 and H417 were SCLC-N, H526 and the PDC were SCLC-P. Barasertib showed anti-proliferative activity against POU2F3 positive SCLC cell lines as well as the PDC in dose-dependent manner. In order to demonstrate the specificity of inhibition of SCLC cells with barasertib, cell lysates were probed for reduction in phosphorylation of Histone H3 Serine 10 (pH3Ser10), a specific substrate for Aurora B. The all of the cells showed strong inhibition of pH3Ser10. In addition, barasertib exhibited profound anti-tumor efficacy in the PDX model with no significant toxicity.

Conclusions: Collectively, these data support that targeting aurora kinase with barasertib efficiently suppresses the growth of SCLC-P subtype cells and the PDC. Further studies are warranted to test this concept in clinical setting.

Keywords: transformed SCLC, Aurora Kinase Inhibitor, Patient derived model

EP14.02-005 Therapeutic targeting Mevalonate-Geranylgeranyl Diphosphate Pathway with Statins Overcomes Chemotherapy-resistance in SCLC

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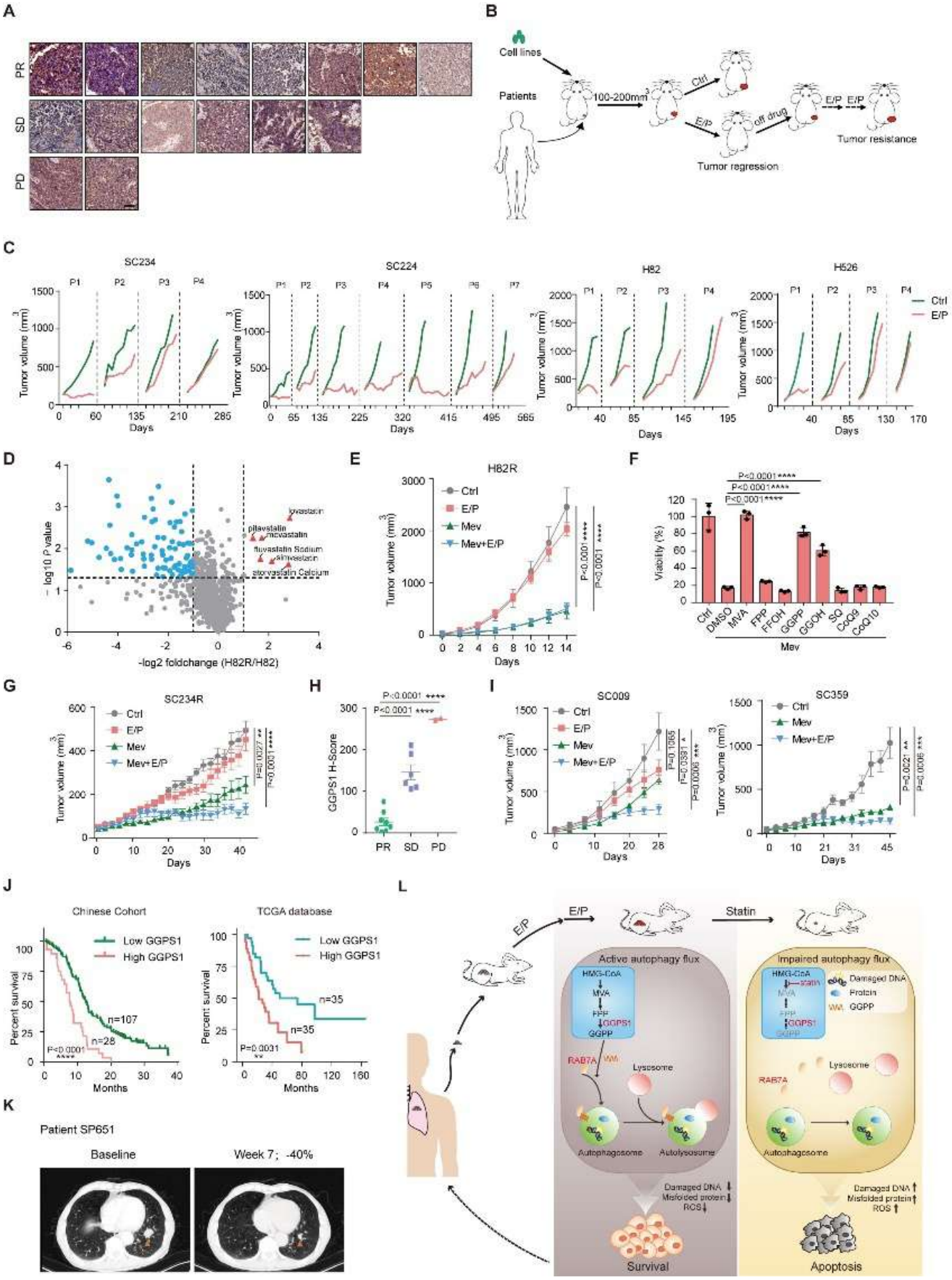
Introduction: Chemotherapy-resistance is the central problem in SCLC clinical management and the effective therapeutic strategy to improve the prognosis of SCLC patients relapsed from chemotherapy is urgently needed. Up to now, little is known about the metabolic alterations during SCLC chemotherapy-resistance acquisition. Moreover, whether chemotherapy-resistant SCLC is addicted to metabolic rewiring that can be exploited therapeutically remains to be clarified.

Methods: Acquisition of SCLC chemotherapy-resistance ex vivo in xenograft mouse models using 16 transbronchoscopic lung biopsy specimens as well as 6 human SCLC cell lines, through intermittent cycles of chemotherapy mimicking clinical strategy for as long as 600 days' treatments. 1971 FDA-approved drugs screening in our system. Statin treatment in PDX models. Observe a significant correlation of GGPS1 level with poor prognosis in 135 Chinese SCLC patients as well as TCGA dataset. Evaluate efficiency of staitn plus chemotherapy in three chemo-relapsed SCLC patients.

Results: Here we established human SCLC PDX models (8PR,6SD,2PD) and multiple SCLC chemoresistant xenograft models through long-term intermittent chemotherapy (A-C). Through different FDA-approved drug library screenings and comprehensive mechanistic studies, we discovered that chemoresistant SCLC tumors have undergone metabolic reprogramming towards the MVA-GGPP pathway, which can be targeted using clinically approved statins (D-F). Statins treatment overcomes both intrinsic and acquired SCLC chemoresistance in vivo across different SCLC PDX models bearing high GGPS1 levels (G-I). Moreover, we show that GGPS1 expression is negatively associated with survival in 135 Chinese SCLC patients as well as TCGA dataset (J). Finally, we demonstrate that combined statins and chemotherapy treatment results in durable responses in three patients with SCLC who relapsed from first-line chemotherapy (K). Mechanistically, statins induce oxidative stress accumulation and apoptosis through the GGPS1-RAB7A-autophagy axis (L).

Conclusions: Our study uncover the MVA-GGPP pathway as a metabolic vulnerability in SCLC and identify statins as a potentially effective treatment to overcome chemoresistance and provides a novel and practical strategy for treatment of chemotherapy-resistant SCLC with high GGPS1 expression in clinic. We also have now launched two phase II clinical trials (NCT04698941 and NCT04985201) to evaluate the efficacy of statin adjuvant therapy in SCLC patients who relapsed from first-line treatment. Data from this trial will provide further clinical evidence for statins in overcoming chemoresistance and explore the potential of GGPS1 as a biomarker in SCLC.



Keywords: SCLC chemoresistance, Mevalonate-Geranylgeranyl metabolism, Statin therapy

EP14.02 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - PRECLINICAL/TRANSLATIONAL

EP14.02-006 Subtype-specific Hypersensitivity to Oxidative Phosphorylation Inhibition in Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) is a very aggressive type of lung cancer with a poor prognosis due to a high proliferation rate and early metastasis. The current standard-of-care therapeutic treatment, a combination of a platinum-based chemotherapy and etoposide, does not take the four molecular subtypes (SCLC-A, -N, -P and -Y) into account. Oxidative phosphorylation (OXPHOS) is an integral part of cellular metabolism and is frequently altered in cancer. However, not much is known about the role of OXPHOS in SCLC. Therefore, the aim of the study was to investigate whether differences in OXPHOS among SCLC molecular subtypes could offer new treatment strategies.

Methods: Proteomic analysis following 1D annotation enrichment and KEGG pathway analysis on human SCLC cell lines was performed to decipher differences between the four molecular subtypes. Perhexiline was used to evaluate metabolic activity. Abundance of mitochondria was assessed by flow cytometry and confocal microscopy using Mitotracker Red CMXROS. Differential responses to inhibitors of complex 1 of the electron transport chain (metformin and IACS-010759) were tested with MTT-based cell viability assays. Clonogenic assays were performed to determine longterm effects of the above-mentioned drugs.

Results: Proteomic analysis revealed three significantly upregulated proteins (NDUFA5, COX4I1 and COX5B) of the electron transport chain (ETC) in the SCLC-A subtype compared to the other subtypes. Additionally, among others, KEGG pathway analysis identified several ETC-related pathways such as oxidative phosphorylation (OXPHOS), thermogenesis and metabolic pathways. Treatment with perhexiline, an inhibitor of carnitine palmitoyltransferase 1 (CPT1) that transfers long-chain fatty acids from the cytoplasm to mitochondria, confirmed increased OXPHOS activity solely in the SCLC-A subtype. In accordance with this, we found higher mitochondrial content in SCLC-A cells. Suggesting a differential sensitivity to OXPHOS inhibitors, SCLC cell lines with high and low oxidative activity were treated with metformin and IACS-010759. The response to treatment correlated positively with OXPHOS activity.

Conclusions: In this study, we demonstrate significant overactivation of OXPHOS in the SCLC-A subtype. Furthermore, our data show hypersensitivity of SCLC-A cells to specific inhibitors, suggesting targeting of upregulated oxidative phosphorylation as a potential new therapeutic approach in SCLC.

Keywords: Small Cell Lung Cancer, Oxidative Phosphorylation, Cell Metabolism

EP14.02-007 Hes1 Protein Expression and Its Significance in Resected Small Cell Lung Cancers

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Introduction: Small cell lung cancer (SCLC) is a highly aggressive malignancy prone to early recurrence and metastasis. Preclinical studies have found that Hes1, as a transcription repressor of the basic helix-loop-helix (BHLH) family, can not only prevent the proliferation and migration of SCLC tumor cells, but also inhibit the neuroendocrine transcription factor ASCL1. However, the prognostic implication of Hes1 protein on surgically resected SCLCs remains unclear. The current study aims to analyze the expression pattern and prognostic value of Hes1 protein in SCLC.

Methods: Two hundred and forty seven surgically resected pure SCLC specimens were reviewed and included in this study by using tissue microarrays (TMA) for immunohistochemistry(IHC)analysis of Hes1 protein on a fully automatic Roche immunohistochemical instruments. And the corresponding clinicopathological features such as age, lymph node metastasis, major cell shape and tumor infiltrating lymphocytes (TILs), etc were reviewed and collected. Correlation analysis of Hes1 protein with clinic pathological features and survival analysis was performed using SPSS 25.0 and Graphpad Prism 5.0 software.

Results: Among the 247 surgically resected pure SCLC patients, 175 (71%) were male and 202 (82%) were less than 65 years. According to the AJCC Cancer Staging Manual (seventh edition), 78 (31.6%) were stage I, 68 (27.5%) were stage II, and 101 (40.9%) were stage III. Hes1 expression was localized in the nucleus of SCLC tumor cells. A total of 129 of the 247 enrolled SCLC patients showed high expression of Hes1 with a positive rate of 52.2% (129/247), and was found positively correlated with a lower age(≤65 yrs., p=0.014), no lymph node metastasis(P=0.003), main cell morphology of round cells(p=0.002), and TILs≤30% (p=0.010). Univariate survival analysis revealed a favorable survival in high expression group for a significant disease free survival (DFS, HR=1.477,95%CI 1.025-2.129, P=0.036) and a positive trend of overall survival (OS, HR=1.181,95%CI 0.778-1.792, P=0.435).

Conclusions: In limited stage pure small cell lung cancer, high expression of Hes1 protein is related to age, lymph node metastasis, main cell morphology and TILs, which contributes as a potential biomarker for the prognosis of SCLC patients.

Keywords: Hes1 protein, small cell lung cancer, survival analysis

EP14.03-001 DARES: A Phase II Trial of Durvalumab and Ablative Radiation in Extensive Stage Small Cell Lung Cancer

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Introduction: Most patients diagnosed with small cell lung cancer have extensive stage disease (ES-SCLC), portending a poor prognosis with median survival rate of 9 - 11 months and a 2-year overall survival (OS) of less than 5%. Checkpoint inhibitors have recently transformed the landscape for first-line treatment for ES-SCLC patients with the CASPIAN and IMpower133 trials demonstrating an OS benefit with the addition of Durvalumab and Atezolizumab to chemotherapy, respectively. Hypofractionated ablative radiation therapy (RT) provides effective local metastasis control. Evidence suggests that apart from its direct effects, ablative RT can trigger the innate and adaptive immune system. Beyond synergistic mechanisms of modulating the immune response, direct tumor debulking by radiation may also be particularly well suited as an adjunct to immunotherapy. Such upfront cytoreduction can relieve tumor-related immunosuppression and prevent early failure at sites of initial involvement. Prior studies have demonstrated OS and PFS benefits to the addition of local therapy in metastatic NSCLC. Multi-site ablative RT has also been shown to be safe in the setting of immunotherapy in multiple published prospective trials. We hypothesize that the addition of ablative RT to upfront chemotherapy and Durvalumab will improve PFS.

Methods: 49 patients will be enrolled across four institutions. Treatment naive ES-SCLC patients with at least one RECIST measurable lesion meeting criteria for ablative radiation will be eligible. Patients with symptomatic brain metastasis will undergo cranial RT prior to enrollment. Patients will be treated with four cycles of platinum/etoposide and Durvalumab. During cycle 2, patients will undergo ablative RT to 1 - 4 sites of extracranial disease. Radiation dose and organ at risk (OAR) constraints are consistent with NRG BR001. OAR constraints will be prioritized over tumor coverage. Following four cycles of chemotherapy and Durvalumab, patients will continue with maintenance Durvalumab 1500 mg q28 days until progression, toxicity, or study withdrawal. The primary endpoint is PFS. Using a historic control of 5 month median PFS with chemo/immunotherapy from CASPIAN and IMpower133, we hypothesized that the addition of ablative RT would improve the PFS from 5 months to 8 months. Sample size of 49 patients was calculated for 80% power with alpha of 0.1. Secondary endpoints include OS, time to second line therapy, and rate of grade 3+ adverse events. Peripheral blood, stool, nasal, and buccal samples will be obtained at baseline, after RT, and at the time of progression and/or immune-related toxicity and will be used for exploratory analysis.

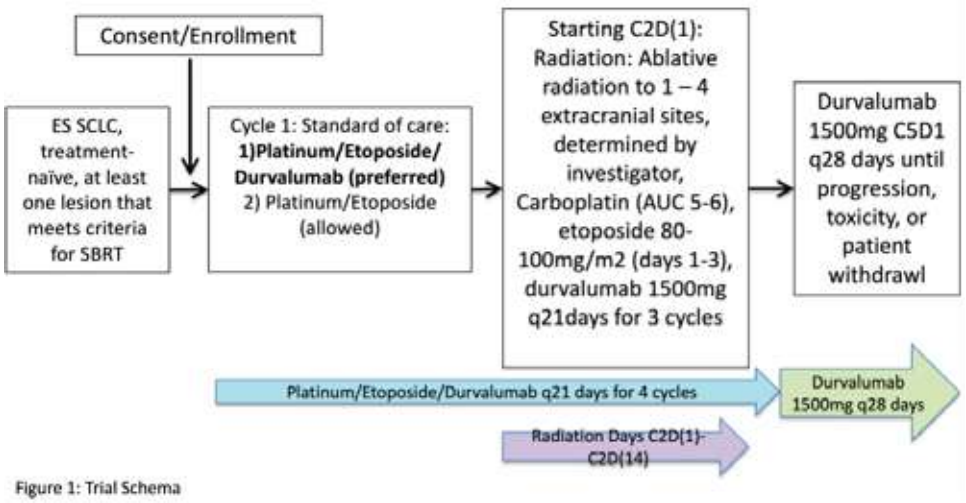

Figure 1: Trial Schema

EP14.03-002 Low-Dose Radiotherapy Plus Sugemalimab in Second-Line Treatment for Advanced-Stage Small-Cell Lung Cancer: Initial Results of a Phase I Study

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Introduction: Second line treatment for relapsed or progressed small-cell lung cancer (SCLC) remains challenging. Although mono-immunotherapy demonstrated certain effects, none of immune-checkpoint inhibitors (ICIs) had been proved in this setting. Theoretically and clinically, low-dose radiotherapy might enhance the anti-tumor ability of ICIs. Here, we report the initial results in a phase I study evaluating the safety of combined strategy among such patients.

Methods: In phase I study (NCT04421352), patients with relapsed or progressed SCLC were enrolled in the traditional-designed (3+3) cohort with 3 dose levels (3Gy/1 fraction, 9Gy/3 fractions and 15Gy/5 fractions respectively) and the radiation targets included the suitable primary or metastatic lesions. Standard dose of Sugemalimab (1200mg) began on the last day of the radiotherapy and could continue every 3 weeks up to 12 months. The primary objective of present study is to preliminarily evaluate the safety (treatment-related adverse events, TRAEs) and anti-tumor efficacy of Sugemalimab combined with low-dose radiotherapy in second-line treatment for SCLC.

Results: From February 2021 to January 2022, 11 patients (7 males and 4 females) were enrolled in this cohort: one in 3Gy/1F, seven in 9Gy/3F and three in 15Gy/5F respectively. Considering the 3Gy/1F radiotherapy plus Sugemalimab was well tolerated in the first patient, the safety monitoring conference agreed that the study was continued by the next irradiation dose (9Gy/3F group). Five (45.5%) patients had at least one TRAE, and 2 (18.2%) had at least one grade 3 or higher TRAEs (one had platelet count decreased; one had Immune-mediated myocarditis and Blood creatine phosphokinase MB increased). None of pneumonitis was observed, including radiation-induced or ICI-induced. As of this data cut-off (Feb 09th, 2022), 9 patients have completed at least one tumor assessment with a minimum follow-up time of 1.8 months and hence were included in the efficacy evaluation (2 of them were excluded for not reaching scheduled tumor assessment date). Among them, 2 patients (1 in 3Gy/1F and 1 in 9Gy/3F group) achieved partial response (ORR 18.2%) and both were subsequently confirmed, and the disease control rate (DCR) was 45.5% (5/11 patients).

Conclusions: Combinations of low-dose radiotherapy and Sugemalimab showed clinical tolerability and safety. Further prospective phase II study was under contemplation.

Keywords: low-dose radiotherapy, immune-checkpoint inhibitors, relapsed small-cell lung cancer

EP14.03 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RT

EP14.03-003 Phase I Study of Palliative Radiotherapy with Lurbinectedin in Patients with Extensive Stage Small Cell Lung Cancer

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Introduction: Outcomes for patients with relapsed extensive-stage small cell lung cancer (ES-SCLC) remain poor with few therapeutic options after progression on first-line chemoimmunotherapy. Recently, lurbinectedin, a novel transcription inhibitor and alkylating agent, demonstrated a favorable response rate, duration of response, and toxicity profile, leading to its accelerated FDA approval of its use in this population. ES-SCLC is distinguished by a propensity for rapid progression, such that palliative radiotherapy (RT) is often delivered with the intent of alleviating symptoms while minimizing interruptions of systemic therapy. Both lurbinectedin and RT ultimately induce lethal DNA damage, suggesting that the two may be at least therapeutically additive if not synergistic. However, it remains unclear whether RT can be delivered safely with concurrent, uninterrupted lurbinectedin.

Methods: This is a single-institution, open-label, non-randomized phase I study (NCT05244239) evaluating the safety and feasibility of delivering lurbinectedin and RT concurrently in patients with ES-SCLC. Eligible patients must have adequate organ function, disease amenable to RT, no active, untreated brain metastases, and be either currently receiving or be planned to initiate lurbinectedin. A maximum of five isocenters encompassing either bone (cohort 1) or lung/visceral metastases (cohort 2) will be treated to either 20 Gy in 5 fractions or 30 Gy in 10 fractions with concurrent lurbinectedin (3.2 mg/m^2 IV every 3 weeks). The composite primary safety endpoint is defined as grade 4/5 adverse events (CTCAE 5.0) occurring within 30 days of RT or adverse event leading to prolonged delay (two consecutive cycles) or permanent discontinuation of lurbinectedin. Patients will be followed regularly for 12 months after RT to report any adverse events, response rate, disease outcomes, and patient-reported outcomes (brief pain inventory, PRO-CTCAE). Exploratory endpoints include bone marrow dose-volume relationships with grade ≥3 hematologic toxicity following RT. This study was activated in March 2022 with an accrual goal of 11 patients each to cohort 1 and cohort 2 (n=22 total). This study is funded by Jazz Pharmaceuticals.

Keywords: Small cell lung cancer, radiation, lurbinectedin

EP14.03 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RT

EP14.03-004 Neuro-cognitive Effect of HS-PCI in LS-SCLC

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Introduction: Small-cell lung cancer (SCLC) is an aggressive type of cancer associated with poor prognosis due to rapid growth and early distant metastasis, especially brain metastasis. Patients with limited stage (LS) achieve a median survival of 18 months and a 5-year survival rate of 15%. Several studies have shown prophylactic cranial irradiation (PCI) to be an independent prognostic factor. Hippocampal sparing (HS) PCI 25 Gy/10 fractions has minimum impact on neuro-cognitive function.

Methods: 10 patients of LS-SCLC were administered HS-PCI with IMRT during 2020. All patients received 25 Gy/10 fractions. Baseline neuro-cognitive function was measured before administering HS-PCI and final neuro-cognitive function was measured after median follow up of 14 months. Neuro-cognitive function was assessed by Montreal Cognitive Assessment (MoCA).

Results: All patients are alive without any appreciable deterioration of neuro-cognitive function/score compared to baseline measurement. Mean pre-treatment MoCA score was 27/30 and mean post-treatment MoCA score was 26/30. None of the patients developed any brain metastasis at last follow up.

Conclusions: HS-PCI is effective in reducing symptomatic brain metastasis in LS-SCLC without affecting neuro-cognitive function in short term. Longer follow up is needed to know the impact in long term.

Keywords: HS-PCI, LS-SCLC, brain metastasis

EP14.03-005 Role of Radiotherapy Fraction in Limited-Stage SCLC: A Meta-Analysis of 8585 Reconstructed Individual Patient Data

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Introduction: The optimal thoracic radiotherapy (TRT) dose and fractionation for LS-SCLC remains unclear in clinical practice. We conducted a meta-analysis to assess the efficacy and safety difference between definitive hyperfractionated TRT (HyperTRT) (1.1Gy-1.6Gy, twice daily, with a minimum of 4-6h between fractions), hypofractionated TRT (HypoTRT) (2.5-4.0Gy/fraction, once-daily) or conventional TRT (ConvTRT) (1.8-2.2Gy/fraction, once-daily).

Methods: Following PRISMA guideline, eligible RCTs and real-world cohorts published between Jan 1, 1990 and July 31, 2021 were identified in PubMed, EMBASE and Web of Science. Considering that ConvTRT was widely adopted in routine practice, retrospective data for Group ConvTRT was assembled only when it served as a control arm to HypoTRT or HyperTRT arm in same literature. IPD was reconstructed for analysis using plot digitizer software and statistical algorithms. One-stage random-effect meta-analysis based on IPD was performed to evaluate the association between altered fractionations and overall survival (OS), expressed as pooled Hazard Ratios (HRs) and 95% Confidence Interval (95% CIs) after accounting for heterogeneity in patients and fractionations across studies. The incidences of radiation-related adverse events between TRT fraction modalities were compared using meta-regression analysis using random effects model.

Results: Overall, 62 of 3037 publications met inclusion criteria, and a total of 8585 IPD was reconstructed. Of these studies, a total of 3395 patients from 33 studies treated with HyperTRT, 1915 patients from 16 studies treated with HypoTRT, and 3275 patients from 31 studies treated with ConvTRT, respectively. Comparing OS rates, HypoTRT was similar to HyperTRT (HR=0.98, 95%CI 0.85-1.12, p=0.76), while ConvTRT was inferior to HyperTRT (HR=1.11, 95% CI 1.01-1.23, p=0.03). After adjusting for biologically effective dose (BED), concurrent chemoradiotherapy (CCRT), and whether TRT started within 2 cycles of induction chemotherapy, the findings remain similar, e.g., HypoTRT was similar to HyperTRT (HR=0.92, 95% CI 0.80-1.05, p=0.22), and ConvTRT was inferior to HyperTRT numerically (HR=1.08, 95% CI 0.99-1.18, p=0.07). Pooled estimates of grade 3-5 radiation esophagitis (RE) and radiation pneumonitis (RP) incidence were 15% and 4% for HyperTRT, 9% and 3% for HypoTRT, and 11% and 4% for ConvTRT, and not statistically different across fractionation groups. In subgroup of patients received 3D conformal or intensitymodulated radiotherapy in modern era, survival outcomes were comparable among altered faction schedule after adjusting aforementioned treatment characteristics (HypoTRT *vs* HyperTRT, HR=0.87, 95% CI 0.70-1.09, p=0.23; ConvTRT *vs* HyperTRT, HR=1.14, 95% CI 0.96-1.34, p=0.14). There was no statistically significant difference in either severe RE (HypoTRT *vs* HyperTRT, 13% *vs* 13%, p=0.97; ConvTRT *vs* HyperTRT, 12% *vs* 13%, p=0.85) or RP (HypoTRT *vs* HyperTRT, 4% *vs* 3%, p=0.54; ConvTRT *vs* HyperTRT, 5% *vs* 3%, p=0.26).

Conclusions: In modern era, HyperTRT, ConvTRT and HypoTRT obtained comparable survival outcomes and experienced similar toxicity effects for LS-SCLC patients treated with definitive chemoradiotherapy. Prospective randomized phase III trials are warranted.

Keywords: small cell lung cancer, limited stege, radiation dose fractionation

EP14.04 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW

EP14.04-001 Treatment and Outcomes of Patients with Limited-Stage Small-cell Lung Cancer in the Canadian SCLC Database (CASCADE)

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Introduction: Small cell lung cancer (SCLC) is an aggressive malignancy representing 15% of diagnosed lung cancers. Approximately 1/3 of patients are diagnosed with limited stage (LS) disease, which is potentially curable with concurrent chemoradiation therapy followed by prophylactic cranial irradiation (PCI). Despite curative intent treatment, relapses are common and median overall survival (OS) is poor. Although there is good prospective evidence available to guide upfront therapy, there is limited prospective evidence available to guide treatment after relapse. We have initiated a collaborative Canadian SCLC database (CASCADE) and used this to evaluate treatment patterns and outcomes for patients with LS-SCLC.

Methods: CASCADE is a multi-institutional real-world evidence (RWE) database of patients with SCLC including 8 academic institutions across Canada. Preliminary data is available from 3 sites: BC Cancer, Princess Margaret Cancer Centre (PMCC), and the Ottawa Hospital Cancer Centre (TOHCC). Baseline demographics, diagnostic details, and treatment information were obtained from CASCADE for patients with LS-SCLC. The primary outcome was overall survival (OS) from the date of diagnosis. Secondary outcomes included OS stratified based on treatments received (systemic therapy, thoracic radiotherapy, and PCI).

Results: A total of 1925 patients were included across 3 sites (1048 BC Cancer, 671 TOHCC, 206 PMCC). Of these, 698 (36%) had limited stage disease. Baseline characteristics of the LS-SCLC population: median age at diagnosis 68; 84 (12%) year of diagnosis 2010 or earlier / 368 (53%) 2011-2015 / 246 (35%) 2016-2020; 53% female; 54% current / 43% former smoking history; 66% ECOG performance status 0-1/ 34%% ECOG >=2. TNM staging included 103 (15%) stage I / 80 (12%) II / 509 (74%) III. For those with data available, staging investigations included a PET scan for 231/363 (64%), and brain imaging in 343/363 (234 [65%] MRI, 109 [30%] CT). With respect to treatment, 588 (84%) received thoracic radiotherapy (490 curative, 97 palliative), 280 (41%) PCI, and 625 (90%) systemic therapy. Data on surgical resections is pending harmonization. With median follow-up of 34.5 months (m), median OS was 19.8m (95% confidence interval [CI] 18.0-22.0m). Survival at 1 year was 68% (95% CI 65-72%), 2 years was 42% (95% CI 38-46%), and 5 years was 22% (95% CI 19-26%). Where data is available, of 325 patients who completed curative intent therapy, documented relapse occurred in 160 (49%) Median OS was longer in patients receiving curative intent radiotherapy (median OS 24.0m) compared to those receiving no radiotherapy (median OS 8.0m) or palliative radiotherapy (median OS 12.0m). Survival was also longer among patients receiving systemic therapy vs none (median OS 20.7m vs 8.0m) and PCI vs no PCI (median OS 30.6m vs 14.0m).

Conclusions: LS-SCLC is a potentially curable disease; however this RWE dataset identifies a significant minority are unable to receive curative intent therapy, and uptake of PCI in the real-world is low. We will continue to validate these results in CASCADE as patient information from 5 additional sites becomes available.

Keywords: small cell lung cancer, real-world evidence, radiotherapy

EP14.04 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW

EP14.04-002 The Impact of Response on Survival in Extensive-Stage Small-Cell Lung Cancer in the CASPIAN Study

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Introduction: Gains in overall and progression-free survival (OS, PFS) and a higher objective response rate were observed in the CASPIAN trial of patients with extensive-stage small-cell lung cancer who received durvalumab in combination with etoposide and platinum-based chemotherapy (D+EP) compared with EP alone. However, the extent to which response predicts long-term survival is unknown. We defined response/non-response at different landmark times and derived OS and PFS during follow-up after each landmark among D+EP and EP patients.

Methods: Analysis was conducted on the January 2020 data cut of CASPIAN (median follow-up for overall survival in censored patients of 25.1 months). Response (complete and partial) vs non-response was based on investigator RECIST 1.1-based assessments. Responder/non-responder OS and PFS differences were assessed using Kaplan-Meier methods at 6, 12, and 20-week landmark timepoints. Multivariate Cox models were estimated at each landmark timepoint and included treatment, response, a treatment/response interaction term, and covariates derived from clinical input.

Results: The 12-week landmark timepoint represented the completion of induction chemotherapy in CASPIAN and showed good predictive quality based on the C-index for OS and PFS. A higher proportion of patients were in response at the 12-week timepoint for D+EP than EP (48.1% vs. 44.5%). In the multivariate models, response at 12 weeks (p-value <0.001 for OS and PFS) and the interaction term of treatment and response at 12 weeks (which measures the extent that the effect of response on survival differs between D+EP and EP; p-values of 0.023 for OS and 0.004 for PFS), were significantly associated with longer OS and PFS. D+EP responders at 12 weeks were less likely to have an OS or PFS event during follow-up than EP responders (HR=0.56 [0.41, 0.77] for OS and 0.59 [0.44, 0.79] for PFS). Results were similar for the 6 and 20-week landmarks.

Conclusions: Response at a landmark time (6, 12 and 20 weeks) may be a good indicator of long-term survival for ES-SCLC patients since it was positively associated with significantly longer OS and PFS across both treatment arms. Moreover, longer OS and PFS was observed among responders treated with D+EP than responders treated with EP.

Keywords: Durvalumab, SCLC, Response

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-001 Chemoimmunotherapy as First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer and ECOG Performance Status of 2 or 3

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Introduction: Studies demonstrated that the addition of immunotherapy to chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer (ES-SCLC) prolongs progression-free survival (PFS) and overall survival (OS) in patients with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1. As such, chemoimmunotherapy is now the first-line treatment for these patients. However, patients with an ECOG-PS of 2 or 3 were excluded from prior studies, and so the benefit of chemoimmunotherapy in these patients is unclear. This study aims to evaluate the benefits of chemoimmunotherapy compared to chemotherapy in the first-line treatment of patients with newly diagnosed ES-SCLC with ECOG-PS of 2 or 3.

Methods: This retrospective study analyzed patients seen at Mayo Clinic Health System from 2017 to 2020. Eligible patients were adults with ES-SCLC and an ECOG-PS of 2 or 3 at the time of diagnosis who had not previously received any systemic treatment for SCLC in the past five years. Patients in the chemotherapy group received platinum-etoposide, and patients in the chemoimmunotherapy group received platinum-etoposide and atezolizumab. The primary endpoint was OS, and the secondary endpoint was PFS.

Results: A total of 46 patients met the inclusion criteria for the study. Twenty-six patients were in the chemoimmunotherapy group, and 20 patients were in the chemotherapy group. All patients in the chemoimmunotherapy group received atezolizumab as immunotherapy. Forty-four patients (96%) in the study received carboplatin and etoposide therapy. One patient in the chemoimmunotherapy group, and one patient in the chemotherapy group received cisplatin and etoposide therapy. A total of 18 patients (69%) in the chemoimmunotherapy group, and 20 patients (100%) in the chemotherapy group died. The chemoimmunotherapy group showed clinically meaningful improved OS compared to the chemotherapy group (9.3 months [95% confidence interval: 4.9-12.8] vs 7.6 [0.6-11.9], respectively; p = 0.21), though not statistically significant. PFS was longer in the chemoimmunotherapy group compared to the chemotherapy group (4.1 months [3.8-6.9] vs 3.2 [0.6-4.8], respectively; p = 0.0491).

Conclusions: The addition of immunotherapy to chemotherapy in the first-line treatment of newly diagnosed ES-SCLC prolongs PFS in patients with an ECOG-PS of 2 or 3. While chemoimmunotherapy did not show a definitive improvement in OS compared to chemotherapy, this may be due to the small size and thus lack of power of the study. Further research with a larger study size is needed to evaluate the potential benefit of chemoimmunotherapy compared with chemotherapy in the OS of patients with an ECOG-PS 2 or 3.

Keywords: chemoimmunotherapy, Eastern Cooperative Oncology Group, performance status

EP14.05-002 Impact of Body Mass Index on Survival in Patients with Small Cell Lung Cancer

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Introduction: Small-cell lung cancer (SCLC), accounts for approximately 13% of lung cancers. Despite recent advances in first line treatment, SCLC still represents a disease with a dismal prognosis. Previous studies in patients with non-SCLC (NSCLC) treated with immunotherapy, identified baseline Body Mass Index (BMI) as a surrogate marker of treatment benefit. We sought to determine whether baseline BMI had in impact in overall survival (OS) in patients with limited and extensive stage SCLC.

Methods: Retrospective data was collected from patients with SCLC in our institution from the year 2000 through 2021. Parameters evaluated included stage, gender, age at diagnosis, smoking history, baseline ECOG Performance Status, whether the patient received systemic treatment and baseline BMI, which was categorized as follows: <18.5 kg/m^2: underweight, 18.5-24.9 kg/m^2: normal weight, 25-29.9 kg/m^2: overweight, and >30 kg/m^2: obese. Kaplan Meier plots were performed to evaluate the association between BMI and OS.

Results: This study included a total of 264 patients, 169 patients were diagnosed at stage IV, and 95 patients were diagnosed at stages I-III. Median age at diagnosis was 67 years for patients in both groups. In stage IV 76% of patients were male, and in stages I-III 72%. Baseline ECOG PS 0-1 was 73% in patients with stage IV, and 77% in patients with stages I-III. 93% of the patients with stage IV, and 94% of patients with stages I-III received a chemotherapy-based treatment. BMI distribution in patients with stage IV was the following: underweight: 4%, normal weight: 48%, overweight:31%, and obese 17%. For patients with stage I-III the distribution was: underweight: 6%, normal weight: 30%, overweight: 44%, and obese: 19%. Median OS (mOS) according to BMI for stage IV patients were as follows: underweight 7.21m, normal-weight 6.16m, overweight 8.79m, and obese 7.39m (p= 0.13). A trend to different mOS for patients with stages I-III was observed based on BMI: underweight 14.62m, normal-weight 27.9m, overweight 22.52m, and obese 32.66m (p= 0.053) with a decreased in mOS in underweight patients, as well as an increase in obese patients.

Conclusions: BMI may be a prognostic marker in patients with stage I-III SCLC. Further studies on nutritional status and BMI impact on outcome in the era of chemo-immunotherapy in SCLC are warranted.

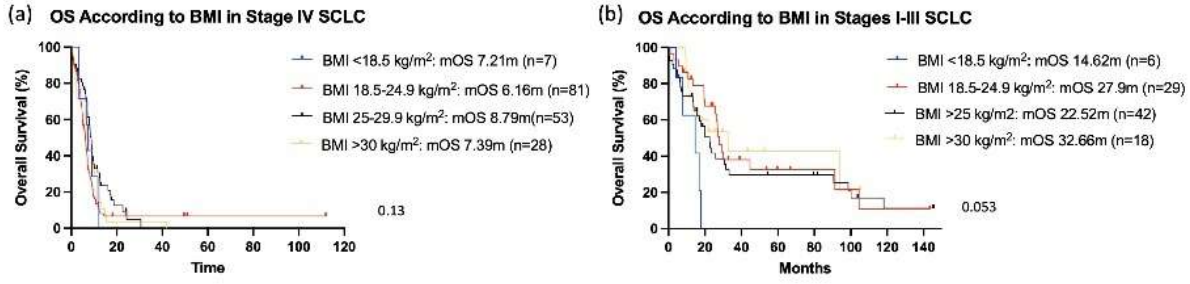

Figure 1. Overall Survival according to BMI in SCLC (a) Stage IV, and (b) Stages I-III

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-003 Recent Stage Shifts and Changes in the Treatment of Stage I Small Cell Lung Cancer in the United States

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Introduction: Small-cell lung cancer (SCLC) is historically associated with late-stage diagnoses, limited treatment options, and poor prognoses. However, over the last decade, improvements in diagnostic imaging, the advent of lung cancer screening in the U.S., and the increasing use of surgery for stage-I SCLC may have led to a shift towards earlier stages of disease identified together with corresponding increases in the number of SCLC operations performed. The objective of this study was to examine recent trends in the stage of SCLC diagnoses and the percentage and number of operations performed for SCLC in the U.S.

Methods: Patients diagnosed with SCLC from 2010-2017 in the National Cancer Database (NCDB) were identified for analysis. Changes in the percentage of SCLC cases diagnosed at stage-I and the percentage of patients diagnosed with stage-I SCLC who underwent surgery were evaluated, and national estimates were obtained using the indirect-multiplier method. Multivariable-ordinal logistic regression was used to examine whether there was a shift towards earlier stages of SCLC identified from 2010-2017. Multivariable-logistic regression was used to assess year-to-year changes in the odds of undergoing surgery for stage-I SCLC.

Results: The percentage of individuals diagnosed with stage-I SCLC increased from 4.34% in 2010 to 5.17% in 2017. In multivariable-adjusted analysis, from 2010-2017, there was a significant shift towards earlier stages of disease identified (adjusted odds ratio [aOR] for year-to-year changes in the odds of being diagnosed with one lung cancer stage lower: 1.04; 95% CI: 1.01-1.06, p=0.01). From 2010-2017, the percentage of patients diagnosed with stage-I SCLC who underwent surgery increased from 37.8% to 46.4% (aOR: 1.09; 95% CI: 1.05 to 1.12, p<0.001) (Figure 1A). The estimated number of stage-I SCLC diagnoses increased by 21% during the study period, from 1100 in 2010 to 1328 in 2017. The number of operations performed for stage-I SCLC in the U.S. increased by 47%, from 422 in 2010 to 620 in 2017 (Figure 1B).

Conclusions: From 2010-2017, in the U.S., there has been a significant increase in: 1) the percentage and number of patients diagnosed with stage-I SCLC and, 2) the percentage and number of patients undergoing surgery for stage-I SCLC. In the setting of recently expanded eligibility criteria for lung cancer screening under the newest United States Preventative Services Task Force guidelines, there may be an even more accelerated increase in the number of patients diagnosed annually with stage-I SCLC who undergo surgical resection in the next decade.

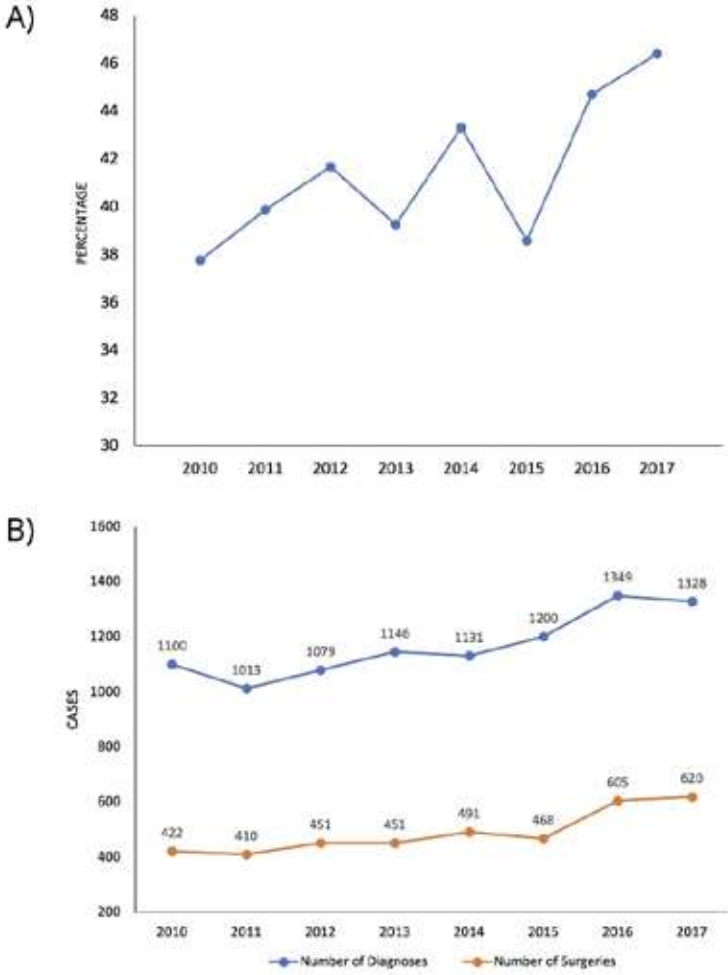

Figure 1A: Trends in the percentage of patients diagnosed with stage I SCLC who underwent surgery from 2010-2017, and 1B: Estimates of number of stage I SCLC diagnoses and operations performed for Stage I SCLC from 2010-2017

EP14.05-004 Temozolomide and Atezolizumab as Second Line Treatment for Extensive Stage Small Cell Lung Cancer: A Randomized, Multi-Cohort Phase 2 Trial

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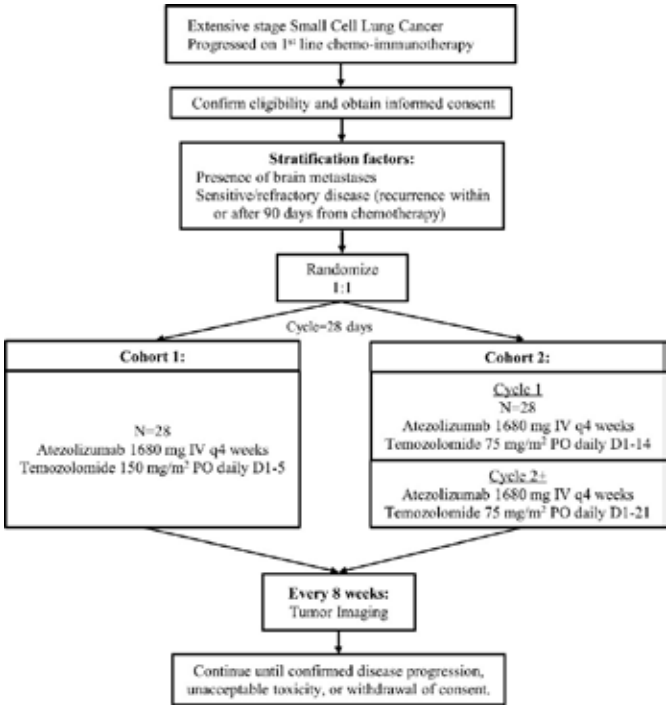
Introduction: Treatment options are limited for patients with extensive stage small cell lung cancer (ES-SCLC) after progression on first line chemo-immunotherapy (CIT). Temozolomide (TEM) is active in ES-SCLC and has been shown to have an immunomodulatory effect for patients with advanced cancers. Immune checkpoint inhibitor (ICI) therapy combined with TEM has demonstrated promising activity among patients in 2nd and 3rd line after CIT (NCT03728361, reported at this meeting). Two different dosing regimens of TEM monotherapy have been explored in ES-SCLC but the objective response rate among patients treated after first line CIT remains unknown.

Methods: NCT04919382 is a randomized, two-cohort, multiple-institution, open-label phase 2 trial of atezolizumab combined with TEM for patients with ES-SCLC. Patients who experienced disease progression after treatment with first-line CIT are eligible. Study treatment consists of atezolizumab 1680 mg IV and two dosing regimens of TEM based on prior phase 2 trials: TEM 150 mg/m2 for days 1-5 (cohort 1) and TEM 75 mg/m2 days 1-21 (cohort 2) out of 28 day cycles. Patients (N=28 in each cohort) will be randomized to each TEM dosing cohort and stratified by presence of brain metastases and platinum sensitive/resistant disease. The primary endpoint is disease response rate by RECIST v1.1. Progression free survival (PFS) and overall survival (OS) will be assessed using the method of Kaplan-Meier, and adverse events will be graded using CTCAE v5. Exploratory analyses include an evaluation of changes in myeloid derived suppressor cells (MDSC) and other immune subsets in peripheral blood induced by the different dosing of TEM, and differences in pre-treatment gut microbiomes between responders and non-responders. A response rate of 15% or less is the null hypothesis and an overall response rate of 35% or more would be considered promising. Based on these assumptions, this phase 2 design will require 28 evaluable patients in each cohort using a one-stage design with 80% power and one-sided significance level of 0.05. Conclusion: This randomized phase 2 trial will study the efficacy of atezolizumab and two different dosing regimens of temozolomide in patients with refractory/recurrent ES-SCLC as second line therapy including in patients with brain metastases. NCT04919382 is currently enrolling at Ohio State University and will soon be opening at additional sites in the Big 10 Cancer Research Consortium.



EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-005 Survival of Small Cell Lung Cancer in Relation to Chemotherapy Dose Intensity

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Introduction: Small cell lung cancer (SCLC) is a very aggressive disease with a poor prognosis. It usually affects patients with comorbidities and deterioration of the general condition. For this reason, the dose intensity (DI) of standard platinum and etoposide (PE) chemotherapy is not always received. We analyzed the impact on overall survival (OS) of patients in relation to the DI of chemotherapy and other relevant factors.

Methods: In this retrospective observational study, we analyzed the clinical data of 74 patients with SCLC who received treatment with PE between January 1, 2018 and January 31, 2022 at the Virgen de Valme University Hospital in Seville, with the last follow-up date of February 9, 2022. The data collected refers to the baseline characteristics of the patients at the start of treatment (age, comorbidities, tobacco use and functional status); stage at diagnosis of the disease and the treatments received in first, second and third line. The response variables analyzed were OS in relation to DI received in extensive disease (ED) (defined as mg/m2/week and stratified in ranges for analysis), functional status (ECOG: Eastern Cooperative Oncology Group) and whether or not they had received consolidation thoracic radiotherapy. We compared OS based on these variables using Kaplan-Meier survival analysis. The toxicity derived from the treatment has also been collected. The data has been processed with IBM ®-SPSS® Statistics v. 25. The information has been collected from Diraya Estación Clínica® v 4.0.80 and Farmis-Oncofarm®.

Results: In February 2022, data had been collected from 74 patients (60 men and 14 women) with SCLC, with a median age of 68 years (49-87 years). All patients had been smokers, 73% had a good functional status (ECOG 0-1) and 85% had comorbidities. At diagnosis, 62 patients had ED and 12 limited disease (LD). After performing an analysis of the collected data, the median OS was 7 months (95% CI=5.08-8.92). In relation to the DI received in patients with ED, we established percentage ranges: 0-49 (13 patients); 50-74 (17 patients); 75-100 (35 patients); being the median of the administered DI of 80 and the median of OS of 0 months, 6 months (CI95%=5.26-6.74) and 11 months (CI95%=8.27-13.73), respectively, with a Log Rank 0.00), ECOG (ECOG < 2 and ≥ 2, with median OS of 9 months (95% CI=7.3-10.7) and 6 months (95% CI=5.2-6.8), respectively, with a Log Rank of 0.001) and chest consolidation radiotherapy (administration vs no administration), with a median OS of 15 months (95% CI=4.26-25.73) vs 6 months (95% CI=5, 05-6.95), respectively, with a Log Rank of 0.011).

Conclusions: Patients with SCLC ED who receive a DI of less than 75% have a statistically significantly worse OS. Presenting an ECOG <2 and receiving thoracic consolidation radiotherapy are favorable factors for OS. Optimizing support treatment to maintain DI would be recommended. A more exhaustive analysis will be detailed in the face-to-face exhibition of the work.

Keywords: Small Cell Lung Cancer, Chemotherapy Dose Intensity, Survival

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-006 The Impact of Adjuvant Chemotherapy on Survival of Stage I Lung Large Cell Neuroendocrine Carcinoma: A Meta-Analysis of Comparative Studies

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Introduction: Large Cell Neuroendocrine Carcinoma (LCNE) of the lung is a less common and aggressive cancer. The standard treatment of early stages is surgical resection. However, recurrences remain common with increased mortality. The role of adjuvant chemotherapy has been controversial in stage I, and the optimal adjuvant strategies remain undefined. One meta-analysis was conducted, revealing no benefit to chemotherapy in stage I. However, it was flawed using several studies analyzing the same NCDB data and one study that combined LCNE and small cell lung cancer. This meta-analysis aims to evaluate the impact of adjuvant chemotherapy on overall survival in patients with completely resected stage I LCNE, incorporating more recent studies.

Methods: A review of the medical literature was conducted using online databases. Inclusion criteria consisted of English language, lung LCNE carcinoma diagnosis, comparative studies of adjuvant chemotherapy versus none in completely resected stage I, and studies that reported survival rates. Studies that combined stage I with other stages and those that combined LCNE with other pathologies were excluded. A meta-analysis using the Mantel-Haenszel method for calculating the weighted pooled relative risk (RR) under the fixed effects model was conducted. The heterogeneity statistic was subsequently incorporated to calculate the summary RR under the random-effects model.

Results: Seven retrospective comparative studies with 2,159 patients were included and analyzed. While all seven studies reported survival data for adjuvant chemotherapy in stage I, only two studies reported survival data for adjuvant chemotherapy in stages IA and IB separately. LCNE Adjuvant chemotherapy was significantly associated with lower RR of death in patients with stage I lung LCNE (RR=0.74, 95%CI 0.56-0.98, I^2=51%). There was also a significantly lower RR of death in patients with stage IA (RR=0.78, 95%CI 0.66-0.93, I^2=0%) and IB (RR=0.61, 95%CI 0.41-0.92, I^2=54%).

Conclusions: This is the first meta-analysis showing that adjuvant chemotherapy is associated with a lower relative risk of death in stage I lung LCNE carcinoma. In the absence of randomized clinical trials, this meta-analysis represents the most compelling data supporting the use of adjuvant chemotherapy in this patient population.

Keywords: Large Cell Neuroendocrine Carcinoma, Adjuvant Chemotherapy, Lung cancer

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-007 A Study of the Best Reduction in Target Lesion Size and Treatment Duration in the Durvalumab plus Platinum-Etoposide Regimen for ES-SCLC

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Introduction: Biomarker for the combination of chemotherapy and immune checkpoint inhibitor in extensive-stage small-cell lung cancer have not been identified at this time, and neither TC expression, IC expression, nor tTMB expression have been significant biomarkers in exploratory PD-L1 analysis of the CASPIAN study. Early identification of factors that would allow for long-term treatment duration of the durvalumab plus platinum-etoposide regimen is very important, and we focused on the best reduction from baseline in target lesion size.

Methods: We performed a retrospective analysis of patients with extensive-stage small-cell lung cancer treated with the durvalumab plus platinum-etoposide regimen from September 2020 to November 2021 in our institution.

Results: Twenty-six patients were included, median age was 67 years (range 48-82), 22 patients were male and 4 patients were female, ECOG-PS was 0 or 1 in 18 patients, 2 or 3 in 8 patients, 25 patients had a smoking history, all patients were Stage IV, and the regimens were durvalumab plus cisplatin-etoposide in 12 patients and durvalumab plus carboplatin-etoposide in 14 patients. The overall response rate was 69.2%, the median best reduction from baseline in target lesion size was -53.4% (range -92%-+26%), the median number of durvalumab doses was 5 (range: 1-17), median PFS was 5.9 months (95% CI: 4.5-8.3). The correlation coefficient between the best reduction from baseline in target lesion size and duration of treatment was 0.63. This value is high compared to the results of previous clinical trials in extensive-stage small-cell lung cancer without using immune checkpoint inhibitor. Nine patients had the best reduction from baseline in target lesion size of -60.4% (the median best reduction from baseline in target lesion size in the durvalumab plus platinum-etoposide group in CASPIAN study) or greater, and 13 patients had the best reduction from baseline in target lesion size of less than -60.4%. The median number of durvalumab doses in the former 9 patients was 10 (range 5-17), and 6 patients were still receiving durvalumab. In contrast, the median number of durvalumab doses in the latter 13 patients was 4 (range 1-11) and only 4 patients were still receiving durvalumab.

Conclusions: In the durvalumab plus platinum-etoposide regimen for extensive-stage small-cell lung cancer, a high rate of the best reduction from baseline in target lesion size may allow for long-term treatment duration.

Keywords: ES-SCLC, Durvalumab plus Platinum–Etoposide, treatment duration

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-008 Development of a Prognostic Model for High-Grade Neuroendocrine Carcinoma of the Lung Using Next-Generation Sequencing

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Introduction: The high-grade neuroendocrine carcinoma (HGNEC) of the lung, small cell lung cancer (SCLC), and large cell neuroendocrine carcinoma (LCNEC), remain fatal due to lack of new therapeutic options and prognostic milestone to guide efficient treatment. We aim to explore the prognostic value of genetic aberration and PARP expression of HGNEC and to establish a novel prognostic model.

Methods: Between March 2001 and February 2014, 191 formalin-fixed, paraffin-embedded (FFPE) samples from patients with HGNEC of the lung at National Cancer Center were analyzed with genomic analysis and immunohistochemistry. Targeted next-generation sequencing was performed in the case of available FFPE samples. Data consisting of clinical variables and genetic information were used to develop the integrated Cox-hazard model. Immunohistochemical PARP1 expression was assessed with both intensity (0, 1, 2, 3) and proportion (0~100), which yielded H-score from 0 to 300.

Results: A total of 43 LCNEC and 64 SCLC were sequenced using 409-gene Comprehensive Cancer Panel (the Ion Proton). Various mutations were found in both LCNEC and SCLC with different frequency. Among 191 FFPE, most HGNEC specimens showed strong PARP1 expression on immunohistochemistry. Mean PARP1 expression H-score was higher in patients who showed stable or progressive disease after platinum doublet treatments than in patients who showed complete or partial response after platinum doublet treatments in extensive-stage SCLC (276.3 vs 254.7, p=.02). The baseline Cox-hazard model identified prognostic effects with clinical variables including histology, stage, age, and PARP1 expression H-score. Integrated Cox-hazard model that combined mutation profiles from targeted sequencing to baseline model outperformed baseline model (maximum time-dependent AUC 0.85 vs. 0.78). The integrated model stratified patients into high-risk and low-risk groups with significantly different progression-free survival and overall survival (integrative model: hazard ratio 4.61: 95% CI 2.73-7.81, p<0.01; baseline model: 3.95: 2.46-6·32, p<0.01).

Conclusions: Integrated Cox-hazard model based on clinical variables and genetic aberration was established to predict survival for HGNEC. PARP1 expression may have prognostic implication in HGNEC patients, and high PARP1 expression in platinum resistant SCLC needs further study for therapeutic implications.

Keywords: Small cell lung cancer, Large cell neuroendocrine carcinoma, PARP1

EP14.05-009 LUMINANCE: A Phase IIIb Study of Durvalumab + Platinum-Etoposide for First-Line Treatment of Extensive-Stage SCLC (ES-SCLC)

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Introduction: Immune checkpoint inhibitors combined with chemotherapy have become standard-of-care first-line treatment for ES-SCLC in recent years. In the phase III CASPIAN study, the PD-L1 inhibitor durvalumab, in combination with platinum-etoposide (EP), demonstrated a statistically significant improvement in overall survival (OS) vs EP alone in first-line treatment of ES-SCLC (HR 0.73 [95% CI 0.59-0.91; p=0.0047]); OS benefit was sustained after >3 years median follow-up (HR 0.71 [95% CI 0.60-0.86; nominal p=0.0003]). In real-world practice, many patients with ES-SCLC have World Health Organization performance status (WHO PS) ≥2 at diagnosis but, in common with most registrational phase III studies, recruitment in CASPIAN was limited to patients with WHO PS 0 or 1. Although 4 cycles of EP are standard for ES-SCLC, in practice an additional 2 cycles are often given; in CASPIAN up to 6 cycles were allowed in the EP arm only. The role of prophylactic cranial irradiation (PCI) remains controversial in ES-SCLC and, while sometimes used in the real-world, PCI was permitted only in the EP arm of CASPIAN. Thus, data on the use of durvalumab in combination with up to 6 cycles of EP and/or in conjunction with PCI, as well as in unselected patients including those with WHO PS 2, would help to inform real-world clinical practice.

Methods: LUMINANCE (NCT04774380) is a phase IIIb, open-label, single-arm, multicentre, international study enrolling patients aged ≥18 years with previously untreated, histologically/cytologically documented ES-SCLC, WHO PS 0-2, and no prior exposure to immune-mediated therapy. Patients will receive durvalumab (1500 mg IV) + EP every 3 weeks for 4-6 cycles (investigator's choice), followed by durvalumab every 4 weeks until disease progression. PCI can be given at the investigator's discretion. The primary endpoint is safety and tolerability, defined by the incidence of grade ≥3 adverse events (AEs) and immune-mediated AEs. Secondary efficacy endpoints are progression-free survival (PFS; investigator-assessed per RECIST v1.1), OS, objective response rate, duration of response, 12-month PFS and OS, and percentage of patients remaining in response at 12 months. LUMINANCE will enrol approximately 150 patients in North America and Europe; the first patient was enrolled in November 2021.

Keywords: Extensive-stage SCLC, Durvalumab, LUMINANCE

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-010 Real-World Eligibility for Clinical Trials in Extensive Stage Small Cell Lung Cancer Patients

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Introduction: The IMpower 133 and CASPIAN trials showed a statistically significant survival benefit in extensive-stage small cell lung cancer (ES-SCLC) patients. However, clinical trials often have strict inclusion and exclusion criteria, which limits the generalizability of findings and can impact trial accrual in clinical practice. The current study evaluates the proportion of real-world patients who would have met eligibility for the IMpower 133 and CASPIAN trials and characterizes factors that would have impacted eligibility for these trials in the real-world setting.

Methods: A research ethics board-approved retrospective analysis was conducted on all stage IV SCLC patients diagnosed and included in the registry between 2016 and 2020 at the Cancer Centre of Southeastern Ontario (Kingston, Canada). Patient demographics, pathologic, treatment, and outcome data were collected. Patients were categorized as eligible, or ineligible based on the eligibility criteria used in the IMpower 133 and CASPIAN trials. Clinical characteristics and trial eligibility were summarized using descriptive statistics. Overall survival (OS) was assessed using the Kaplan-Meier method.

Results: A total of 91 patients were included in the analysis. The mean age at diagnosis was 70 years, and 29.7% of patients were ECOG 0-1 at diagnosis, while 28.6% were ECOG 2, and 41.8% were ECOG 3/4. Over one-third of patients (38.5%) presented with brain metastases. Only 11% of patients met the overall eligibility criteria for the IMpower 133 trial, and 14.3% for the CASPIAN trial. The most common reasons for ineligibility included: ECOG 2 or greater (70.4%), inadequate hematologic or end-organ function (38.5%), and presence of symptomatic or untreated brain metastases at diagnosis (33%). 41.8% had two or more major ineligibility reasons, and 9.9% had 3 or more. If trial eligibility was expanded to include ECOG 2 patients, an additional 12.1% would have met eligibility. In the current patient population, the median time from diagnosis to medical oncology consult was 7 days, and the median time from consult to treatment was 5 days. Sixty-two patients (68.1%) received chemotherapy, with 67.8% of those patients completing 4-6 cycles. Eleven patients (12.1%) received radiation alone, while 19.8% had the best supportive care with no cancer treatment. Prophylactic cranial irradiation was given to 9.9% of patients, while 17.6% received consolidation radiotherapy to the chest. The median OS (mOS) for all comers was 5.4 months. There was no significant difference in survival between trial eligible versus ineligible patients treated with chemotherapy (mOS 8.9 vs 7.0 months, p=0.24).

Conclusions: Only a small minority of real-world ES-SCLC patients would have met eligibility for the IMpower 133 and CASPIAN trials. Expanding the eligibility criteria to include ECOG 2 patients would modestly increase eligibility to approximately 25%. In addition, the time between consultation and treatment in real-world practice is short, highlighting a need for trials to require minimal delays/additional trial-related testing. Future clinical trials should evaluate the trial design and eligibility criteria to optimize the inclusion of ES-SCLC patients in order to generate results more applicable to real-world patient populations.

Keywords: small cell lung cancer eligibility, clinical trial, IMpower 133, CASPIAN

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-011 Real-World Impact of Platinum Sensitivity and Disease Stage on Survival Among Medicare Patients with Small Cell Lung Cancer

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Introduction: There is no real-world research evaluating the impact of platinum sensitivity and disease stage on survival among patients with small cell lung cancer (SCLC).

Methods: We identified patients with SCLC in 2017 using ICD-10 diagnosis (Dx) and drug codes in the 2016-20 Medicare Parts A/B/D 100% Research Identifiable Files. Patients had 1+ lung cancer Dx and continuous enrollment in Parts A/B/D from the month prior to first Dx in 2017 (index) through 2020 or death. Patients with end-stage renal disease, prior lung or any metastatic cancer within 12 months of index, lung resection/lobectomy, or use of drugs indicated only for non-SCLC or low-grade lung neuroendocrine cancer were excluded. Patients included in our study were treated with first-line platinum-based regimens. We defined cohorts of patients according to disease stage (limited vs. extensive) and platinum sensitivity (sensitive vs. refractory); patients initially treated with carboplatin/intravenous (IV) etoposide/atezolizumab, carboplatin/IV etoposide/durvalumab, carboplatin/irinotecan, cisplatin/IV etoposide/durvalumab, or cisplatin/irinotecan regimens were flagged with extensive stage (ES) disease. Patients not receiving these regimens were classified as having limited stage (LS) disease if they had 15+ days of radiation therapy. All other patients were labeled with ES disease. Patients were deemed platinum sensitive (PS) if we did not observe a second-line regimen, hospice, or death during or within 6 months of completing their first-line regimen. All other patients were deemed platinum refractory (PR). We compared survival 90-, 180-, and 360-days post-index for all cohorts.

Results: We identified 3,699 patients with SCLC. Overall, 91% survived ≥90 days, 82% ≥180 days, and 74% ≥360 days post-index. Platinum sensitivity was the best indicator of survival over all time periods; 99% of patients with PS SCLC survived at least one year compared with 53% of patients with PR disease. Patients with ES disease demonstrated poorer survival than patients with LS disease. Patients with PR ES stage disease experienced the worst outcomes.

Conclusions: Patients with platinum refractory small cell lung cancer are 46% less likely to survive at least one year post-diagnosis than platinum sensitive patients, regardless of disease stage (relative risk = 0.54). Patients with platinum refractory extensive stage small cell lung cancer have the poorest survivorship. One-fifth of these patients do not survive longer than 90 days post-diagnosis, and fewer than 50% survive longer than one year.

Survivorship over Time by Stage and Platinum Sensitivity		Patients	Post-Index Survival		
			90 days	180 days	360 days
Platinum Sensitive	Limited	1,051	100%	100%	99%
	Extensive	614	100%	100%	99%
	Total	1,665	100%	100%	99%
Platinum Refractory	Limited	518	95%	79%	63%
	Extensive	1,516	80%	64%	49%
	Total	2,034	84%	68%	53%
Total	Limited	1,569	98%	93%	87%
	Extensive	2,130	86%	74%	63%
	Total	3,699	91%	82%	74%

Keywords: survival, platinum refractory, extensive stage small cell lung cancer

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-012 Comparing Costs for Medicare FFS Patients Treated with Etoposide or Irinotecan for Extensive Stage Small Cell Lung Cancer

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Introduction: There is a major gap in research describing real-world costs and resource utilization among patients with extensive stage small cell lung cancer (SCLC).

Methods: We identified patients with SCLC in 2017 using ICD-10 diagnosis (Dx) and drug codes in the 2016-20 Medicare Parts A/B/D 100% Research Identifiable Files. Patients had 1+ lung cancer Dx and continuous enrollment in Parts A/B/D from the month prior to first Dx in 2017 (index) through 2020 or death. Patients with end-stage renal disease, prior lung or any metastatic cancer within 12 months of index, lung resection/lobectomy, or use of drugs indicated only for non-SCLC or low-grade lung neuroendocrine cancer were excluded. Use of systemic therapies cisplatin (CI), carboplatin (CA), intravenous etoposide (ET), atezolizumab (AT), durvalumab (DU) and irinotecan (IR) was observed. Patients included in our study were treated with first-line platinum regimens: CA/ET, CA/ET/AT, CA/ET/DU, CA/IR, CI/ET, CI/ET/DU, or CI/IR. First line of therapy (LoT1) was defined as a regimen administered from 14 days pre- to 90 days post-index. The end of LoT1 was defined as the earliest of death, 32 days after the last administration, or the start of a second line of therapy (LoT2). Patients with 15+ days of radiation therapy not receiving CA/ET/AT, CA/ET/DU, CA/IR, CI/ET/DU, or CI/IR were flagged as having limited stage disease and excluded from the study. We segmented the extensive stage population into two cohorts based on use of either etoposide- or irinotecan-based regimens during LoT1. We measured Medicare paid amounts and resource utilization by major service category per patient per month (PPPM).

Results: We identified 2,165 patients with extensive stage SCLC. 98% (2,120) initiated a first-line etoposide-based regimen, while 2% (45) received irinotecan-based regimens. Although this sample size did not allow for meaningful statistical testing, patients receiving irinotecan-based regimens demonstrated lower costs during LoT1 (IR $7,994 | ET $8,758). Differences were driven primarily by lower costs for outpatient (IR $1,107 | ET $1,937) and Part B professional services (IR $1,103 | ET $1,935), although patients receiving irinotecan-based regimens had higher radiation therapy costs (IR $1,112 | ET $264) and utilization (IR 4.5 claims | ET 0.9 claims). Inpatient utilization and costs were comparable between cohorts (IR $2,237; 0.2 admissions | ET $2,103; 0.2 admissions). Carboplatin was utilized more often in LoT1 than cisplatin for both groups (86% of ET-cohort vs. 76% of IR-cohort).

Conclusions: Only 2% of Medicare FFS patients with extensive stage small cell lung cancer receive first-line irinotecan-based regimens. However, patients who receive first-line treatment with irinotecan-based regimens demonstrate almost 10% lower mean per patient per month costs compared with patients receiving first-line etoposide-based regimens. These lower costs appear to be driven by differences in the intensity of services provided in the outpatient and professional settings.

Keywords: extensive stage small cell lung cancer, irinotecan, Medicare costs

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-013 Real-World Resource Use and Costs by Stage and Platinum Sensitivity among Medicare Patients with Small Cell Lung Cancer

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Introduction: There is no information available about the relationship between platinum sensitivity and real-world cost and utilization patterns among patients with small cell lung cancer (SCLC) in the United States.

Methods: We identified patients with SCLC in 2017 using ICD-10 diagnosis (Dx) and drug codes in the 2016-20 Medicare Parts A/B/D 100% Research Identifiable Files. Patients had 1+ lung cancer Dx and continuous enrollment in Parts A/B/D from the month prior to first Dx in 2017 (index) through 2020 or death. Patients with end-stage renal disease, prior lung or any metastatic cancer Dx within 12 months of index, lung resection/lobectomy, or use of drugs indicated only for non-SCLC or low-grade lung neuroendocrine cancer were excluded. Patients included in our study were treated with first-line platinum-based regimens. Patients were grouped into cohorts according to disease stage (limited vs. extensive) and platinum sensitivity (sensitive vs. refractory). Patients treated with first-line carboplatin/intravenous etoposide/atezolizumab, carboplatin/intravenous etoposide/durvalumab, carboplatin/irinotecan, cisplatin/intravenous etoposide/durvalumab, or cisplatin/irinotecan regimens were flagged with extensive stage (ES) disease. Patients were classified with limited stage disease (LS) if they did not receive those regimens and had 15+ days of radiation therapy. Patients were deemed platinum sensitive (PS) if we did not observe a second-line regimen, hospice, or death during or within 6 months of completing their first-line regimen. All other patients were deemed platinum refractory (PR). We measured resource utilization and Medicare paid amounts by major service category per patient per month (PPPM).

Results: We observed 3,699 patients with SCLC receiving first-line platinum-based regimens; 1,607 had LS disease, while 2,165 had ES disease. On average, Medicare costs were $7,776 PPPM across all patients in our study. Spending was higher for patients with LS disease ($8,024) compared with ES disease ($7,574). This difference was driven primarily by higher Part B radiation utilization among patients with LS disease (LS - 12.0 claims PPPM | ES - 1.0 claims PPPM). Among patients with ES disease, Part B chemotherapy ($1,771), inpatient ($1,527), and other Part B ($1,154) services were leading cost drivers; Part B and D drug costs contributed 38.5% of average total monthly expenditures. Costs were greater for patients with PR SCLC, regardless of stage (PR $8,133 | PS $7,395). This is explained by their higher average inpatient (PR $1,568 | PS $1,174) and Part B chemotherapy costs (PR $2,024 | PS $1,467). Among those with ES disease, patients with PR disease had greater PPPM costs than patients with PS disease (PR $8,023 | PS $6,682). Costs for patients with PR disease were higher across all service categories except Part B radiation therapy (PR $261 | PS $387), despite shorter durations of treatment across all lines of therapy.

Conclusions: Although patients with LS disease incur more costs than ES patients overall due to greater radiation therapy utilization, patients with PR ES SCLC experience the highest costs across nearly all service categories. Among patients with ES SCLC, those with PR disease sustain higher costs than those with PS disease due to greater inpatient and Part B chemotherapy spending.

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-014 Trends in Population Survival Among Adults Diagnosed with Small Cell Lung Cancer in the U.S. from 2013-2021

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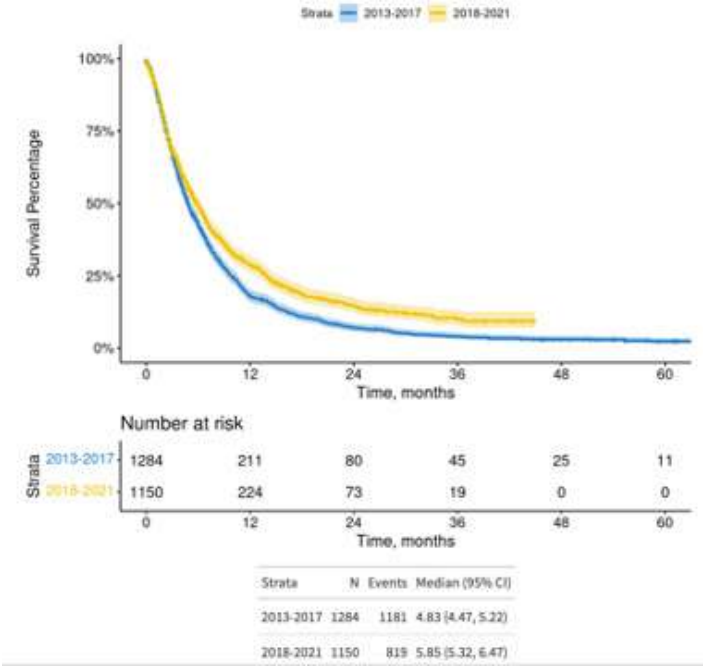
Introduction: Platinum-based chemotherapy plus irinotecan/etoposide was the standard of care for first line (1L) treatment of small cell lung cancer (SCLC) prior to 2018. Four checkpoint inhibitors (CPIs) have recently been approved for SCLC: nivolumab (2018), atezolizumab (2019), pembrolizumab (2019), and durvalumab (2020). SCLC was subsequently removed from the nivolumab and pembrolizumab labels in 2020 in 2021, respectively. Atezolizumab and durvalumab are approved for 1L. In this study we examined trends in overall survival (OS) for adults diagnosed with SCLC in the United States from 2013-2021 using data from electronic health records (EHR).

Methods: A retrospective analysis was conducted using EHR data from Flatiron Health's SCLC Enhanced Data Mart. Patients with a diagnosis of SCLC and initiation of 1L treatment in the database from 1/1/2013-7/31/2021 were included. Patients were required to have evidence of activity in the Flatiron network within 90 days of SCLC diagnosis. Patient characteristics and OS were stratified by time period of SCLC diagnosis (2013-2017 and 2018-2021).

Results: 7,528 patients met the study criteria. 85% (N=6,435) of patients initiated 1L treatment and among those treated 52% were female, mean age was 67 years, 74% were white, and 98% had a history of tobacco use. More than half (62%) were diagnosed with extensive stage disease. Only 38% (N=2,434) were observed initiating second line (2L) treatment. Median OS from start of 1L for those initiating 1L in 2013-2017 was 10.1 months (95% CI: 9.8-10.4 months) and median OS from start of 1L in 2018-2021 was 9.8 months (9.3-10.3 months). While 12-month survival was similar for both time periods (42% for both), 18-month OS from 1L increased from 27% (26%-29%) in 2013-2017 to 31% (29%-33%) in 2018-2021 and 24-month survival increased from 21% (19%-22%) in 2013-2017 to 24% (22%-26%) in 2018-2021. Median OS from start of 2L in 2013-2017 was 4.8 months (4.5-5.2 months) and median OS from start of 2L in 2018-2021 was 5.9 months (5.3-6.5 months). 12-, 18- and 24-month OS from 2L was higher for patients initiating 2L in 2018-2021 than for patients initiating 2L in 2013-2021 (Figure 1).

Conclusions: Patients diagnosed with SCLC in 2018-2021 receiving 2L treatment had significantly longer survival than SCLC patients diagnosed prior to the introduction of CPIs, however median OS from initiation of 1L remains below 12 months and below 6 months from initiation of 2L treatment, underscoring the ongoing need for effective therapies for SCLC.



Keywords: small cell lung cancer, real-world overall survival

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-015 Quantifying Recent Trends in Real-World Treatment Patterns Among Adults Diagnosed with Small Cell Lung Cancer in the U.S. from 2013-2021

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Introduction: Characterizing changes in the small cell lung cancer (SCLC) patient population and SCLC treatment landscape is essential for understanding drivers of outcomes among those patients. Four checkpoint inhibitors (CPIs) were approved for SCLC in 2018 (nivolumab), 2019 (atezolizumab and pembrolizumab), and 2020 (durvalumab), but SCLC was subsequently removed from the nivolumab and pembrolizumab labels in 2020 in 2021, respectively. Durvalumab and atezolizumab are approved for use in the first line (1L) SCLC setting. In this study, we examined trends in patient characteristics and treatment patterns for adults diagnosed with SCLC in the United States from 2013-2021 using data from electronic health records (EHR).

Methods: An observational study was conducted using EHR data from Flatiron Health's SCLC Enhanced Data Mart. Patients were included if they had a record with a diagnosis of SCLC in the database from 1/1/2013-7/31/2021. Patients were also required to have evidence of activity in the Flatiron network within 90 days of SCLC diagnosis. Characteristics and treatment patterns were stratified by time period of SCLC diagnosis (2013-2017 and 2018-2021).

Results: 7,528 patients met the study criteria. Overall, 52% were female, mean age was 67 years, 74% were white, and 98% had a history of tobacco use. The majority (62%) were diagnosed with extensive-stage (ES) disease. Only 38% (N=2,434) of those initiating 1L (N=6,435) were observed initiating second line (2L). There were no significant shifts in the demographic characteristics of patients diagnosed with SCLC over the study period. Between 2013 and 2021 the share of SCLC patients initiating 1L treatment increased 12% from 77% to 87%. Platinum-based chemotherapy (carboplatin or cisplatin + etoposide) was by far the most common 1L regimen (80%). Topotecan monotherapy was the most common (22%) 2L regimen and carboplatin + etoposide and nivolumab were each used for approximately 9% of 2L patients. While platinum-based chemotherapy was used in 1L by the vast majority (95%) of patients diagnosed in 2013-2017, only 59% of patients diagnosed in 2018-2021 received platinum-based chemotherapy in 1L. Among patients diagnosed in 2018 or later, 38% received check point inhibitors in combination with chemotherapies or as monotherapy. Topotecan monotherapy was the most common regimen received (27%) by those diagnosed in 2013-2017 receiving 2L treatment, but among patients diagnosed from 2018-2021 receiving 2L, 50% received check point inhibitors in combination with chemotherapies or as monotherapy.

Conclusions: The most recent trends suggest an increasing proportion of patients with SCLC are pursuing treatment, and the introduction of CPIs has significantly shifted treatment patterns for patients diagnosed with SCLC.

Keywords: small cell lung cancer, real-world treatment patterns

EP14.05-016 Patterns of Care for Small Cell Lung Cancer in Victoria Australia. A Prospective Population-Based Observational Study

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Introduction: Small cell lung cancer (SCLC) is an aggressive cancer, often metastatic at presentation and with a poor prognosis. Study of patterns of care enables the evaluation of the dissemination of state-of-the-art cancer therapy and diagnostics into community oncology practice to identify patient-, provider-, and system-level factors that are associated with receipt and utilization of cancer care and survival outcomes. The patterns of care for SCLC remain incompletely defined in the Australian population.

Methods: We aimed to analyse and report on the patterns of care for people diagnosed with SCLC in Victoria and to identify clinical quality indicators that can be used for benchmarking quality of cancer care.All patients diagnosed with SCLC between April 2011 and 18th December 2019 with data prospectively registered in the Victorian Lung Cancer Registry (VLCR) were included. Data collected included patient characteristics, treatments, and overall survival. We assessed survival using Kaplan Meier estimates and explored impacts of patient, disease, management related impacts on survival using cox proportional hazards regression analysis.

Results: Over the study period, 1006 people (43% female) were included with a median age of 69 years. Performance status was documented for 66% of cases with 74% ECOG 0-1 at diagnosis. Staging using limited or extensive (VA) or TNM was documented in 89% cases with 70% stage extensive (ES)/stage IV and 30% limited (LS)/stage I-III. Documentation of supportive care screening was evident for 37.4%, MDM discussion for 55% cases and palliative care referral 39%. Active treatment with systemic anti-cancer treatment (SACT), radiotherapy or surgery or a combination was delivered to 89% overall with chemotherapy 84% (carboplatin-etoposide doublet 83%), radiotherapy 46%, combined chemo-radiotherapy 42% and 2% surgery. Median overall survival for all cases was 8.9 months, 16 months for LS and 7 months for ES and 8 months for un-staged Figure 1. Survival was adversely affected in multivariate analysis by increasing age OR 1.03 (1.02-1.03, 0.000), ECOG 3-4 2.33 (1.64-3.33, 0.000) and improved by MDM presentation OR 0.66 (0.58-0.77, 0.000) and multimodality treatment OR 0.42 (0.36-0.49, 0.000) or no treatment 3.0 (2.44-3.67, 0.000).

Conclusions: Active treatment for SCLC and use of chemotherapy is high in Victoria with survival outcomes comparable to international series. Successful and meaningful future reporting of patterns of care in lung cancer will be dependent on the availability of a dataset fit for purpose. Improving documentation and establishing clinical quality indicators for SCLC could be beneficial for improving patient care.

Figure 1a.

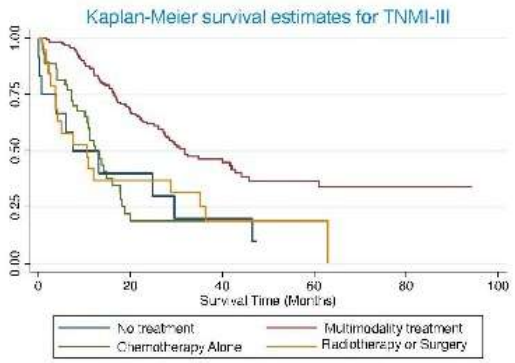
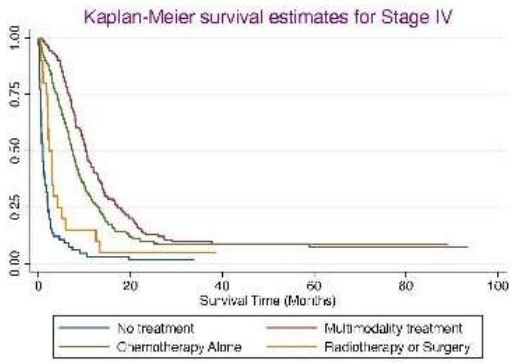


Figure 1b.



Keywords: Small Cell Lung Cancer, Survival, Patterns of care study

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-017 Real World Eligibility of Immune Checkpoint Inhibitors with Platinum-Doublet in Extensive Stage Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) is a rapidly progressing aggressive malignancy for which two-thirds of patients are diagnosed with incurable, extensive stage (ES) disease. Recent drug approvals in SCLC have added first line immune checkpoint inhibitors (ICI) to platinum-based chemotherapy for ES disease. Durvalumab in CASPIAN and atezolizumab in IMPower 133 were both found to improve overall survival (OS) by 2-3 months. Here we evaluate the proportion of real-world ES SCLC patients who may be eligible for first line ICI with platinum-doublet.

Methods: A retrospective cohort analysis was conducted of referred ES SCLC between 2015-2017 in British Columbia, Canada. Patient demographics, staging, treatment, and survival data were collected through the Cancer Registry. Retrospective chart review was completed to extract past medical history and missing variables. In CASPIAN/IMPower 133 excluded patients with autoimmune diseases, active infection, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2.

Results: Between 2015-2017, 350 patients were diagnosed with ES SCLC. Baseline characteristics: median age 62 years, male 49%, never/former/current smoker 2/35/62%, median pack years 50, ECOG 0-1/2/≥3 33/26/40%. Treatment details: 27% received best supportive care, 54% received 1 line of therapy, 15% received 2 lines and 4% received ≥3 lines. First line treatment was: 90% platinum doublet, 9% single agent etoposide and 1% cyclophosphamide, doxorubicin, and vincristine. Of the ES patients who received first line platinum doublet, 34% received cisplatin, 55% carboplatin and 11% switched between cisplatin and carboplatin. Medical contraindication to ICI were found in 20 patients. These included: inflammatory bowel disease (n=4), rheumatoid arthritis (n=4), idiopathic pulmonary fibrosis (n=3), psoriasis requiring disease-modifying drugs (DMARDs) (n=2), lupus (n=1), Sjogren's (n=1), Takayasu arteritis (n=1), hyperthyroidism (n=2) and active tuberculosis (n=1). Another 222 (63%) patients would be excluded for PS ≥2 or 135 (39%) for PS ≥3.

Conclusions: In our real-world SCLC population, 31% of all ES SCLC patients were eligible for CASPIAN/IMPower 133 ICI with platinum doublet therapy. Poor performance status was the primary reason for ineligibility. If eligibility was extended to include ECOG PS 2, 55% could receive combination therapy. Treatment strategies that include first cycle chemotherapy alone to control disease and improve PS may also expand the treatment eligible population.

Keywords: small cell lung cancer, Immune Checkpoint Inhibitors, Eligibility

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-018 Major Lung Resection for Carcinoid Tumor; Does It Affect Quality of Life?

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Introduction: Pulmonary carcinoids account for 1% of all lung cancers. Surgery remains the gold standard treatment which may include radical lung resection as well as minimally invasive procedures and parenchymal sparing bronchial resection. However, resection may impact patients' daily activities due to decreased lung reserve and postoperative pain. Our study aims to compare the impact of different types of surgical resection on the post-operative quality of life. To the best of our knowledge this is the first study that measures the change in lung function and quality of life following surgical resection of carcinoid tumors.

Methods: Data collected retrospectively for all patients underwent surgery for bronchopulmonary carcinoid tumors in King Hussein Cancer center (August 2017- March 2020) including Age, Gender, comorbidities, perioperative outcomes, pathological result. For the qualitative and quantitative assessment of pain we utilized the Arabic version of Short-form McGill Pain Questionnaire (SF-MPQ) (Cronbach's α = 0.85) To quantify the influence of lung resection on quality of life we used a translated Activity of Daily Living (ADL) instrument (Cronbach's α = 0.90 and 0.65). patients underwent pre and post-operative pulmonary function tests through values of Forced Expiratory Volume (FEV1) and diffusion capacity of the lungs for carbon monoxide (DLCO). Statistical analysis conducted on SPSS version 24.

Results: sixteen patients underwent different types of resection; 10 males(62.5%), mean age 43.5(19-81), 12 patients stage I(75%). 4 stage II(25%), typical carcinoid in 11 patient(68.8%), 5 atypical carcinoid(31.2%), one patient received adjuvant chemotherapy. one patient underwent endobronchial resection and 15 underwent surgical resection; parenchymal preserving (n=2), wedge resection (n=2), lobectomy (n=4) (two were sleeve lobectomies), bilobectomy (n=6) and pneumonectomy (n=1). complete microscopic resection R0 achieved in 100%.VATS was utilized in 8 patients(50%). Two patients found to have positive LNs, each one of them has only one hilar LN involved. no major post-operative morbidity or mortality were observed. all patients are alive with no local or distant tumor recurrence.The mean preoperative DLCO was 105.07 dropped to 95.92 postoperatively (p=0.437). The mean preoperative FEV1 value was 88.00 ±20.785 dropped to 75.75±19.82 postoperatively (p=0.133) ; changes in FEV1 and DLCO were statistically insignificant. Using the ADL tool we found that 15 out of 16 patients were totally independent (93.8%) and only one patient who had undergone endobronchial debulking due to his multiple comorbidities was partially dependent (6.3%). As described by SF-MPQ, mild intermittent pain was found in 7 patients scored an average intensity of 1.625 out of 10. The mean sensory pain was 0.085 out of 3 and affective pain was 0.078.

Conclusions: Excellent long-term outcomes can be achieved following surgical resection of pulmonary carcinoid tumors. Although aggressive surgical resection is presumed to affect patients' quality of life we found in our study that complete surgical resection did not significantly affect lung function nor their quality of life in regards to performance status and post-operative pain. Despite being limited by our sample size which we justify by the rarity of this entity, we believe our study validates the use of aggressive surgical resection.

Keywords: carcinoid, quality of life, surgical resection

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-019 Contemporary Real-World Adverse Events Associated with Small Cell Lung Cancer Diagnosed in a U.S. Population from 2013-2021

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Introduction: Platinum-based chemotherapy plus irinotecan or etoposide was the standard of care for first line (1L) treatment of small cell lung cancer (SCLC) prior to 2018. Since then, four checkpoint inhibitors (CPIs) have been approved for SCLC: nivolumab (2018), atezolizumab (2019), pembrolizumab (2019), and durvalumab (2020), although SCLC was subsequently removed from the nivolumab and pembrolizumab labels in 2020 in 2021, respectively. Atezolizumab and durvalumab are approved for use in the 1L setting. In this study we described adverse events (AE) experienced by adults diagnosed with and receiving > 1 line of treatment for SCLC in the United States from 2013-2021 using data from electronic health records (EHR).

Methods: A observational study was conducted using EHR data from Flatiron Health's SCLC Enhanced Data Mart. Patients were included if they had a record with a diagnosis of SCLC and initiation of 1L treatment in the database from 1/1/2013 - 7/31/2021. Patients were also required to have evidence of activity in the Flatiron network within 90 days of SCLC diagnosis. Patient characteristics and AEs were described.

Results: Of the 6,435 patients meeting the study criteria, 52% were female, mean age was 67 years, 74% were white, and 98% had a history of tobacco use. More than half (62%) were diagnosed with extensive-stage (ES) disease. 38% (N=2,434) were observed initiating second line (2L) treatment. The vast majority (91%) of patients experienced anemia. 55% of patients experienced neutropenia and two thirds (67%) experienced thrombocytopenia. Approximately one in five (22%) patients experienced grade 4 neutropenia (neutrophil count <0.5 x109 /L) and 14% experienced grade 4 thrombocytopenia (platelet count <25.0 x109/L). Elevated liver biochemistry was also common, with 38% of patients experiencing elevated alanine aminotransferase (ALT), 54% experiencing elevated alkaline phosphatase (ALP), and 43% experiencing some elevation of aspartate aminotransferase (AST), however grade 4 elevation (> 20xULN) of liver biochemistries was very rare (<1%). Nausea (18%), fatigue (6%), diarrhea (2%), and neuropathy (1%) were relatively less common than hematologic AEs and elevated liver biochemistries.

Conclusions: Gastrointestinal symptoms (i.e., nausea and diarrhea) were experienced by less than 20% of patients, whereas hematologic AEs and elevated liver biochemistries were common among patients undergoing systemic treatment for SCLC. These data aid in the understanding of real-world safety among SCLC therapies and help inform the development of patient supportive care plans by population-based health care decision makers.

Keywords: small cell lung cancer, adverse events

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-020 Population-based Outcomes for Patients with Extensive-Stage Small-cell Lung Cancer from the Canadian SCLC Database (CASCADE)

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Introduction: Small cell lung cancer (SCLC) is an aggressive malignancy representing 15% of lung cancers. Approximately 2/3 of patients are diagnosed with extensive stage (ES) disease. Initial treatment involves platinum-based chemotherapy, with recent evidence supporting the addition of immunotherapy, followed in some cases by thoracic radiotherapy and/or prophylactic cranial irradiation (PCI). Despite high response rates to initial therapy, relapses are common and overall survival is poor. There is limited prospective evidence to guide 2nd line systemic therapy and beyond. We have initiated a collaborative Canadian SCLC database (CASCADE), and used this to evaluate treatment patterns and outcomes for patients with ES-SCLC.

Methods: CASCADE is a multi-institutional real-world evidence (RWE) database of patients with SCLC from 8 academic institutions across Canada. Preliminary data is available from 3 sites: BC Cancer, Princess Margaret Cancer Centre (PMCC), and the Ottawa Hospital Cancer Centre (TOHCC). Baseline demographics, diagnostic details, and treatment information were obtained from CASCADE for patients with ES-SCLC. The primary outcome was overall survival (OS) from the date of diagnosis.

Results: A total of 1925 patients were included across 3 sites (1048 BC Cancer, 671 TOHCC, 206 PMCC). Of these, 1225 (64%) had extensive stage disease at diagnosis. Baseline characteristics of the ES-SCLC population: median age at diagnosis 68 years; 762 (62%) year of diagnosis 2011-2015 / 463 (38%) 2016-2020; 52% female; 62% current / 38% former smoking history; 36% ECOG performance status 0-1/ 64% ECOG >=2. For 511 patients with sites of metastatic disease available, 252 (49%) had baseline liver metastases; 208 (41%) bone; 134 (26%) brain; 101 (20%) adrenal; 91 (18%) pleura; 62 (12%) contralateral lung. With respect to treatment, 507 (42%) received thoracic radiotherapy (41 concurrent, 187 consolidative, 273 palliative), 120 (10%) PCI, and 940 (77%) systemic therapy (669 1 line, 196 2 lines, 70 >=3 lines). After median follow-up of 7.0 months (m), median OS was 6.5m (95% confidence interval [CI] 6.0-7.0m). Survival at 1 year was 24% (95% CI 21-26%), and 2 years was 7% (95% CI 6-9%). Patients who did not receive systemic therapy had very limited survival, median OS 1.0m (95% CI 1.0-1.1) compared to 8.5m (95% CI 8.0-9.0m) for those treated with systemic therapy. Survival was longer in patients treated with concurrent (median OS 19.0m) or consolidative radiotherapy (median OS 12.0m) compared to those receiving palliative (median OS 8.0m) or no radiotherapy (median OS 3.7m). Of 352 patients without confirmed baseline brain metastases, 83 received PCI with a median OS 14.2m compared to 269 patients with no PCI and median OS 5.4m.

Conclusions: Population-based survival of ES-SCLC is poor. Despite recognized high response rates to first-line systemic therapy, a significant proportion of patients do not receive any systemic therapy and have extremely poor survival. Although relapses are nearly inevitable, only a minority of patients are treated with 2nd line systemic therapy. The uptake of consolidative radiotherapy and PCI was low in this real-world population. We will continue to report on this population as data from 5 additional CASCADE sites becomes available.

Keywords: small cell lung cancer, real-world evidence, systemic therapy

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-021 Promising Long-Term Survival after Surgical Resection of Early Stage Small Cell Lung Cancer in a Modern Single-Center Cohort

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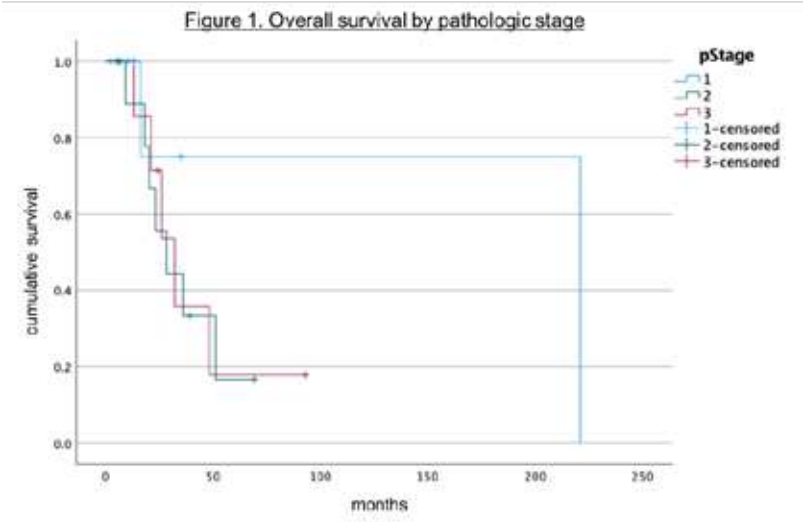
Introduction: Although some studies have demonstrated survival benefit from resection in limited-stage small cell lung cancer (SCLC), debate continues about the value and practical application of surgery in these patients.

Methods: We retrospectively reviewed resected SCLC cases identified from our institution's pathology database for patient, staging, operative, and adjuvant data as well as oncologic outcomes such as recurrence, disease-free survival (DFS), and overall survival (OS). Statistical comparisons were performed with t-test for univariate outcomes and Kaplan-Meier curves for survival outcomes.

Results: 27 patients underwent pulmonary resection of SCLC from 2000-2021. The majority of patients (n=20, 74%) underwent lobectomy. A minority (41%) of patients had preoperative diagnoses of SCLC (either NSCLC generally, or specific other non-small cell subtypes). The number of surgically resected SCLC cases was increased in recent years, with over one-third occurring within the last 3 years (2019-2021 n=11). Pathologic stage was significantly lower among recent patients (p=0.02), with only 1 stage III and 0 stage IV cases, compared to 6 stage III and 1 stage IV pre-2019 (2000-2018 n=16). SCLC was identified by screening more frequently in these 2019-2021 cases, 45.5% compared to 13.3% pre-2019. Similar proportions of unexpected SCLC postoperative diagnoses were seen in both periods as in the overall cohort.

Complete follow-up (either clinical data within 3mo preceding chart review or death) was available for 100% of patients. Overall 5-year OS for all patients was 25.3% and median OS was 32mo. Among pathologic stage I patients, 5-year OS was excellent (7/9, 78%) and median survival could not be calculated because this group did not reach 50% mortality within the available follow-up (Figure 1, log-rank p=0.43). Overall median DFS was 29mo, and again was much higher (95mo) among pathologic stage I patients (log-rank p=0.23). These differences were not statistically significant within this small sample size.



Conclusions: In this single-institution study, we observed DFS and OS in resected SCLC patients that exceeds those historically reported from national databases, with particularly promising survival among pathologic stage I patients. Despite that the landmark lung cancer screening trials identified a low proportion of SCLC, the increase in screen-identified earlier-stage SCLC within our patient population in recent years suggests the potential for a clinically significant impact of screening on SCLC diagnosis and outcomes. Longer follow-up and further accrual for this more recent patient group will determine if these early findings translate into a significant and durable survival improvement in this cohort.

Keywords: small cell lung cancer, long-term survival, surgical resection

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-022 The Drug Induced Interstitial Lung Disease in Chemoimmunotherapy for Extensive-Stage Small Cell Lung Cancer

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Introduction: Interstitial lung abnormalities (ILA) is defined as the changes affecting more than 5% of any lung zone, which included ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis. ILA has been reported to be a risk factor for the development of drug-induced interstitial lung disease (D-ILD) by immune checkpoint inhibitors (ICI) monotherapy in non-small cell lung cancer. Combination of chemotherapy and immunotherapy (Chemo-ICI) has become the new standard of treatment for extensive-stage small cell lung cancer (ES-SCLC). However, the data of incidence of D-ILD and the association of development of D-ILD and ILA in the baseline CT are limited in ES-SCLC.

Methods: We conducted a multicenter retrospective study to investigate the incidence of D-ILD and the risk factors of developing D-ILD in ES-SCLC patients who received Chemo-ICI from August 2019 to November 2021. The presence of ILA and emphysema was evaluated in CT before Chemo-ICI administration. The CT images were independently evaluated by two respiratory physicians.

Results: Seventy patients (median age 71 years, 58 men) were included from 9 institutions in Japan. Sixty-two (89%) received carboplatin+etoposide+atezolizumab, eight received carboplatin/cisplatin+etoposide+durvalumab. Twenty-nine (41.4%) had ILA in base-line CT. The median observation period was 332 days (23-804 days). Eleven patients (15.7%) developed D-ILD (Grade1/2/3; 3/3/5). The median time from the first dose of Chemo-ICI to the onset of D-ILD was 113 days (21-176 days). The number of patients with ILA was significantly higher in patients developed D-ILD than those who didn't (9/11 (81.8%) vs 20/59 (33.9%), P=0.0057). In addition, the ground-glass and reticular abnormalities were more frequently in patient who developed D-ILD. There was no difference in the age, sex, ECOG PS, smoking history, the history of chest radiation, and presence of emphysema (Table1). There was no significant difference in progression free survival and overall survival between patients who developed D-ILD and those who didn't (median PFS; 245 (95% CI, 167-288) vs 153 (95% CI, 137-171) days, P=0.11 and median OS; NR (95% CI, 264-NR) vs 555 (95% CI, 402-NR) days, P=0.20).

Conclusions: In the clinical trials, the incidence of D-ILD was reported to be 2.6% to 4.0%, but it was as high as 15.7% in this study which is conducted in a clinical setting. Pre-existing ILA may be a risk factor for D-ILD in ES-SCLC, and developing D-ILD was not associated with poor prognosis in our study.

	With D-ILD n=11	Without D-ILD n=59	p-value
Age, years: Median (range)	72 (69-81)	71 (42-84)	0.332
Sex: Male (%)	9 (81.8)	49 (83.1)	1.000
ECOG PS: 0/1/2/3 (%)	4 (36.4)/5 (45.5)/2 (18.2)/0	19 (32.2)/32 (54.2)/6 (10.2)/2 (3.4)	0.749
Smoking history: Current,ex (%)	11 (100.0)	53 (89.8)	0.580
Prior thoracic radiation (%)	1 (9.1)	3 (5.1)	0.504
CBDCA+etoposide+Atezolizumab/ CDDP/CBDCA+etoposide+Durvalumab (%)	10 (90.9)/ 1 (9.1)	52 (88.1)/7 (11.9)	1.000
Interstitial lung abnormalities (ILA) (%)	9 (81.8)	20 (33.9)	0.006*
Type of ILA			
Ground glass attenuation (%)	8 (72.7)	19 (32.2)	0.017*
Reticular shadow (%)	9 (81.8)	25 (42.4)	0.022*
Diffuse centrilobular nodularity (%)	1 (9.1)	0	0.157
Nonemphysematous cysts (%)	1 (9.1)	9 (15.3)	1
Emphysema (%)	11 (100.0)	43 (72.9)	0.058

(* P <0.05)

Keywords: extensive-stage small cell lung cancer, immunochemotherapy, interstitial lung disease

EP14.05 SMALL CELL LUNG CANCER AND NEURO-ENDOCRINE TUMORS - RW/SOC

EP14.05-023 Characterization of Real-World Use of Lurbinectedin in Adult Small Cell Lung Cancer Patients in the United States

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Introduction: Lurbinectedin received accelerated FDA approval in June 2020 for treatment of adult patients with metastatic small-cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy. Approval was based on a single-arm, phase 2 trial, which demonstrated an overall response rate of 35.2%, a duration of response of 5.3 months, and a manageable safety profile. This study explored patient characteristics and treatment patterns of patients treated with lurbinectedin during the 16 months after approval in the United States (US).

Methods: Adult SCLC patients (age ≥ 18 years) treated with lurbinectedin within 16 months following its US approval were included in this study from the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. Patients were excluded if they participated in a clinical trial or did not have any records in their EHRs within 90 days after the initial diagnosis. Clinical characteristics and demographics were assessed in the period between SCLC diagnosis and lurbinectedin treatment initiation. Treatment profile of patients with at least 3 months of available follow-up after lurbinectedin initiation was also assessed.

Results: Of 221 SCLC patients treated with lurbinectedin between June 15, 2020 and October 31, 2021 who met the eligibility criteria, 75% of patients had extensive stage disease at diagnosis, 17% of patients had a chemotherapy-free interval (CTFI) of less than 30 days, 24% had CTFI of 30-89 days, 37% had CTFI of 90-179 days, and 21% had CTFI ≥180 days. An ECOG score of ≤ 2 was seen in 95% of the 182 patients with an ECOG score recorded within 30 days prior to lurbinectedin initiation. Overall, lurbinectedin was received in 48% of patients as second-line therapy (2LT), and 29% and 23% as third-line and fourth-line+ therapy, respectively. Among patients with CTFI ≥180 days, 28% received lurbinectedin as 2LT. Among patients who received lurbinectedin in 2LT or later, 44% received platinum etoposide and immunotherapy in the immediate prior line of treatment. Among the 184 patients with at least 3 months of available follow-up, patients received a median of 3 cycles and 39% of patients also received concomitant growth factor medications. Subsequent treatment after lurbinectedin was seen in 42% of patients.

Conclusions: Lurbinectedin use to date reflects per-label treatment in metastatic SCLC patients who previously received platinum-based chemotherapy. Lurbinectedin approval represents a new therapy in the treatment landscape for 2LT+ SCLC patients.

	Patients who received lurbinectedin (n=221)
Age (years)	
Median [IQR]	65.0 [59.0, 72.0]
Sex, n (%)	
Female	99 (44.8%)
Male	122 (55.2%)
Race, n (%)	
White	165 (74.7%)
Black or African American	13 (5.9%)
Other Race	22 (9.9%)
Missing	21 (9.5%)
Stage at initial diagnosis of SCLC, n (%)	
Limited	55 (24.9%)
Extensive	166 (75.1%)
ECOG score (most recent value within 30 days of lurbinectedin initiation), n (%) (N = 182)‡	
0	46 (25.3%)
1	90 (49.4%)
2	36 (19.8%)
3	10 (5.5%)
Time from diagnosis to lurbinectedin treatment (months)	
Median [IQR]	9.2 [6.9, 16.4]
CTFI, n (%) *†	
Less than or equal to 29 days	38 (17.4%)
30 to 89 days	53 (24.2%)
90 to 179 days	82 (37.4%)
180 days or more	46 (21.0%)
Treatment regimen within immediate prior line, n (%)*	
Platinum Etoposide + Immunotherapy	97 (43.9%)
Platinum Etoposide	42 (19.0%)
Immunotherapy	36 (16.3%)
Topotecan	14 (6.3%)
Other	30 (13.6%)
Lurbinectedin line of therapy, n (%)††	
2nd Line	105 (47.5%)
3rd Line	64 (29.0%)
4th Line +	50 (22.6%)
	Patients who started lurbinectedin at least 3 months prior to data cutoff (October 31, 2021) (N=184)
Number of lurbinectedin cycles	
Median [IQR]	3.0 [1.2, 5.0]
Patients with subsequent therapy, n (%)	78 (42.4%)
Patients with growth factor use during lurbinectedin treatment, n (%)	72 (39.1%)

CTFI = Chemotherapy Free Interval, ECOG= Eastern Cooperative Oncology Group, IQR= Interquartile Range, SCLC= Small cell lung cancer.
* 2 patients with no prior treatment not counted; pool of patients includes those receiving lurbinectedin from second line to fourth line and beyond.
† CTFI calculated as the time from last administration of chemotherapy in first line to progression or start of subsequent line.
‡ECOG categories (0-3) reported among 182 patients with an ECOG score recorded in the 30 days prior to initiating lurbinectedin. Out of the 221 patients, ECOG was missing in the 30 days prior to initiating lurbinectedin in 39 (17.6%) patients.
†† 2 patients (0.9%) received lurbinectedin as first-line therapy.

Keywords: Lurbinectedin, Real-world Evidence, Small Cell Lung Cancer

EP15.01 TOBACCO CONTROL AND RISK REDUCTION

EP15.01-001 Ask, Advise, Help (AAH) Smoking Cessation Brief Advice Delivery in Patients with Diagnosed Lung Cancer: A Retrospective Audit

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Introduction: Smoking cessation has important benefits in people diagnosed with lung cancer, regardless of TNM stage. However, the majority of patients diagnosed with cancer continue to smoke following diagnosis. A systematic model of care, as per 2020 Clinical Oncology Society of Australia guidelines, could enhance smoking cessation rates and improve patient outcomes. Our lung cancer multidisciplinary team treats ~300 new patients per annum, but does not offer a systematic smoking cessation model of care. To benchmark current practice and consider areas for improvement, we undertook an audit of smoking prevalence and smoking cessation brief intervention (Ask, Advise, Help (AAH) smoking cessation brief advice model), among patients with newly diagnosed lung cancer. Interim results are presented.

Methods: Data abstraction of digital medical records of all patients presented at our lung cancer MDT with a focus on interventions provided in the out-patient setting following diagnosis.

Results: Medical records of current smokers at time of diagnosis were reviewed. Following lung cancer diagnosis patients attended 913 outpatient encounters (mean 5.8 per patient). 34.7% of encounters were in respiratory medicine, 36.2% medical oncology, 15.1% radiation oncology and 5.5% thoracic surgery. Of all outpatient encounters, 38.7% documented smoking status (“Ask”), 6.5% documented the best way to quit and why this is important (“Advise”), and 1.8% documented an offer of referral to behavioural intervention such as Quitline and/or smoking cessation pharmacotherapy (“Help”). 3.5% documented an offer of pharmacotherapy for smoking cessation.

Conclusions: Patients with lung cancer are followed up by a variety of clinicians. Documented provision of smoking cessation advice and assistance appears low in this cohort, suggesting the need for service-level improvements.

Keywords: Smoking, Intervention, cancer

EP15.01 TOBACCO CONTROL AND RISK REDUCTION

EP15.01-002 Lowering Rates of Smoking after Cancer Diagnosis: Use Social Networks

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Introduction: Continued smoking after a cancer diagnosis leads to worse morbidity and mortality. Unfortunately, smoking prevalence remains high amongst cancer patients and survivors. Few studies have been conducted to evaluate and target patients' social networks that may contribute to a patient continuing to smoke. We developed a questionnaire intended to assess patients' smoking status, motivation to quit, patient/family dynamics, and interest in enrolling in a smoking cessation program that includes the patient and the person closest to them in their social network that may be contributing to their continued smoking.

Methods: We designed a three-page questionnaire to gain more information about a patient's past and current smoking history, level of nicotine dependence, assessment of their motivation to quit smoking, their social network and family/friends who may be smoking, and willingness of the patient and close family to quit. Inclusion criteria included patients who have been diagnosed with any solid tumor malignancy and had a history of smoking or recently quit. Non-smokers were excluded. IRB approval was obtained and questionnaires were distributed to patients when checking in at the front desk of the Monter Cancer Center. 32 questionnaires were collected from July 2021 - January 2022.

Results: Of the questionnaires completed, 56% quit smoking after their cancer diagnosis, 39% tried and were unable, and 5% did not try or declined to answer. Of the 56% who quit, 65% were married, compared to 33% of the 43% who tried and were unable to quit. The odds of quitting among people who were married was 3.75 (95% CI 1.0 - 13.8; p-value 0.047) times the odds of quitting among people who were not married. In the quit group, 50% lived with a smoker at some point compared with 65% of those in the quit but unable to group. The odds of quitting among people who lived with a smoker was 0.55 (95% CI 0.15 - 2.0; p-value 0.36) times the odds of quitting among people who did not live with a smoker. Eight social network members quit after their relatives' cancer diagnosis No patients were currently enrolled in a tobacco cessation program. Three people answered they would be interested in being enrolled in a tobacco cessation program with a close family member that also smokes.

Conclusions: Our study highlights the high rates of continued smoking amongst cancer patients. Being diagnosed with cancer can serve as a teachable moment and motivate patients to quit smoking. Social network plays an important role in tobacco cessation. Our study showed that the odds of quitting was lower in patients who lived with smokers than those who did not, though not statistically significant likely due to small sample size. None of the active smokers were enrolled in a smoking cessation program highlighting the imminent need for innovative smoking cessation platforms that are engaging and effective in improving quit rates amongst cancer patients.

Keywords: smoking cessation after cancer diagnosis, social networks smoking cessation cancer diagnosis, relationships smoking cessation cancer diagnosis

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-001 Transforming Growth Factor-ßinhibitsInterferon- γmediated Immune Resistance in Lung Cancer

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Introduction: Immune checkpoint blockers (ICBs) have revolutionized the treatment of lung cancer. Immunosuppressive entities in the tumor microenvironment remain an impediment to ICBs. Substantial evidence has shown that transforming growth factor-beta (TGF-ß) plays a crucial role underlying the limited sensitivity of some tumors to ICBs. M7824, a fusion protein designed to block PD-L1 and sequester TGF-ß in the tumor microenvironment, aims to increase the T-cell-mediated immune response against cancer cells. Although preclinical studies and several clinical trials have shown a promising antitumor effect of M7824, the efficacy of M7824 in the treatment of advanced non-small-cell lung cancer remains unclear. The complex role of TGF-b in the context of immunotherapy may not be well recognized. For example, IFN-g, the most significant effector cytokine in immunotherapy, plays a crucial role in antitumor responses. However, it also promotes tumor immune escape mechanisms, such as upregulation of PD-L1. The role of TGF-ß in regulating IFN-γ-mediated immune escape remains unclear.

Methods: The expression of PD-L1 and IDO1 was assessed by quantitative real-time polymerase chain reaction and western blot analyses in both lung adenocarcinoma cell lines and fresh tumor tissues from patients with non-small-cell lung cancer. Western blot analyses and immunofluorescence methods were used to examine the IFN-γ mediated activation of JAK1, JAK2, and STAT1 in tumor cells. Silencing RNA was used to knock down Smad2, Smad3, Smad4, and SHP-1. The PI3K-AKT inhibitors LY294002 and GDC-0941 were also used.

Results: We showed that TGF-ß significantly inhibited IFN-γ-induced PD-L1 and IDO expression at the mRNA and protein levels in lung cancer cells. The results were verified in human lung cancer explants. PD-L1 and IDO1 play immunosuppressive roles in the tumor microenvironment. Our data indicate that TGF-ß may attenuate IFN-γ-mediated immune escape. Mechanistic analysis showed that knockdown of Smad3 but not Smad2 or Smad4 reversed the inhibitory effect of TGF-ß on IFN-γ-mediated upregulation of PD-L1 and IDO1. TGF-ß also activated the PI3K-AKT pathway in lung cancer cells. Interestingly, inhibition of the PI3K-AKT pathway using LY294002 resulted in a significant downregulation of Smad3 expression and reversed the effect of TGF-ß on IFN-γ-mediated upregulation of PD-L1 and IDO1. Our data suggest that canonical and noncanonical TGF-ß pathways are involved in regulating IFN-γ-mediated signaling. Furthermore, we found that TGF-ß inhibits the phosphorylation of JAK1, JAK2, and STAT1 at tyrosine sites but does not affect the phosphorylation of STAT1 at serine 727. Finally, knockdown of SHP-1 reversed the inhibitory effect of TGF-ß1 on IFN-γ-induced phosphorylation of STAT1 at tyrosine 701, suggesting that TGF-ß-mediated SHP-1 activity is involved in regulating IFN-γ signaling. The precise signaling cascade downstream of TGF-ß, including the interactions among PI3K-AKT, SHP-1, and Smad3, regulating the IFN-γ pathway requires further investigation.

Conclusions: TGF-ß1 inhibits IFN-γ-induced PD-L1 and IDO expression by reducing the phosphorylation of JAK1, JAK2, and STAT1 at tyrosine sites. Our data indicate that TGF-ß signaling may counteract IFN-γ-mediated adaptive immune resistance, thereby improving rather than compromising the efficacy of ICBs. Our study provides novel insight into the complex role of TGF-ß in immunotherapy.

Keywords: IFN-γ, transforming growth factor-ß, tumor immunotherapy

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-002 T Cell Receptor Diversity among Non-Small Cell Lung Cancer Patients Treated with Pembrolizumab Alone or in Combination with Chemotherapy

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Introduction: T cell receptors (TCR) repertoire plays a key role on the orchestration of the immune response. Here we aim to explore the correlation between pre-treatment circulating TCR profile and clinical outcome including clinical benefit rate (CBR), progression free survival (PFS) and overall survival (OS) among non- small cell lung cancer (NSCLC) patients treated with pembrolizumab alone or in combination with chemotherapy.

Methods: We prospectively collected baseline blood from 103 NSCLC patients treated with first line pembrolizumab monotherapy (n=50) or in combination with chemotherapy (n=53). High quality DNA was extracted from blood and TCR sequencing was performed. TCR number of unique clones, evenness, Shannon diversity and clonality were calculated and correlated with CBR using Fisher Exact test, with PFS and OS using Log rank test.

Results: Our data matured for 97 patients with a follow-up of at least 6 months. We observed a correlation between reduced number of clones and improved CBR among patients treated with pembrolizumab monotherapy **(RR=2.96, 95%CI 1.08-9.04, P=0.032)**. No statistically significant results were found to correlate between any of the TCR variables and CBR among those treated with pembrolizumab in combination with chemotherapy. Although, the trend suggests improved progression free survival (PFS) is associated with reduced pre-treatment TCR clones, Shannon Diversity or clonality as well as increased evenness among NSCLC patients treated with single-agent pembrolizumab, the opposite was found among patients treated with combination therapy. Improved PFS among the latter group was associated with increased pre-treatment TCR clones **(HR=0.43 (95%CI 0.2-0.92), P=0.025)**, Shannon Diversity **(HR=0.44 (95%CI 0.2-0.97), P=0.036)** or clonality **(HR=0.49 (95%CI 0.24-0.98), P= 0.041)** as well as reduced evenness **(HR= 2.05 (95%CI 1.02-4.13), P=0.041)**. None of these parameters were statically significant in relation to OS.

Conclusions: Pre-treatment TCR repertoire might serve as a predictive biomarker for clinical outcome among patients treated with pembrolizumab alone or in combination with chemotherapy. Further investigations with large prospective cohorts will demonstrate whether the circulating pre-treatment TCR repertoire is a prognostic factor for immune checkpoint inhibition.

Variables 1M downsampling	Clinical outcome	Pembro	PembroChemo
Clones (Low vs High)	ORR (RR, 95%CI, P)	**2.96 (1.08-9.04) P= 0.032** ↓ Clones...> Improved	0.5, P=0.125 ↑
	PFS (HR, 95%CI, P)	1.54 (0.71-3.36), P= 0.27 ↓	**0.43 (0.2-0.92), P=0.025** ↑
	OS (HR, 95%CI, P)	0.72 (0.31-1.65), P=0.346 ↓	**0.32 (0.11-0.91), P=0.024** ↑
Evenness (Low vs High)	ORR (RR, 95%CI, P)	0.74 (0.31-1.76) P=0.361 ↑	1.5, P= 0.125 ↓
	PFS (HR, 95%CI, P)	0.7 (0.33-1.5), P=0.36 ↑	**2.05 (1.02-4.13), P=0.041** ↓
	OS (HR, 95%CI, P)	0.48 (0.21-1.09), P= 0.074 ↑	2.19 (0.79-6.05), P= 0.12 ↓
Shannon Diversity (Low vs High)	ORR (RR, 95%CI, P)	1.01 (0.60-1.76) P=0.601 ↓	0.67, P= 0.382 ↑
	PFS (HR, 95%CI, P)	0.63 (0.3-1.3), P=0.21 ↑	**0.44 (0.2-0.97), P=0.036** ↑
	OS (HR, 95%CI, P)	1.94 (0.87-4.34), P= 0.107 ↓	2.58 (0.7-9.45), P= 0.335 ↓
Clonality (low vs High)	ORR (RR, 95%CI, P)	1.14 (0.78-1.78), P=0.361 ↓	0.5, P=0.125 ↑
	PFS (HR, 95%CI, P)	1.42 (0.67-3.03), P=0.36 ↓	**0.49 (0.24-0.98), P= 0.041** ↑
	OS (HR, 95%CI, P)	2.08 (0.92-4.71), P= 0.074 ↓	0.46 (0.17-1.25), P= 0.12 ↑

Keywords: T-Cell Receptor, Non-Small Cell Lung Cancer, Pembrolizumab

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-003 The Dynamic Immune Signature of Patients with Advanced Non-small Cell Lung Cancer in Prediction of Infection After Receiving Immunotherapy

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Introduction: Pulmonary infection has been an important concern in patients with non-small cell lung cancer. It is well-known that chemotherapy may increase the infection rate by suppressing the immune system. Whether the clinical outcome of pulmonary infection is association with immunotherapy is still unclear. Mass cytometry is a next-generation flow cytometry platform with multiparametric analyses. Previous studies of mass cytometry showed that exhausted T cell were implicated in disease progression and response to immunotherapy. By evaluating the immune signature, we hope to find the predictive model for infection post immunotherapy.

Methods: We prospectively collected peripheral blood specimens before and after chemotherapy and/or immunotherapy in patients with NSCLC. The clinical data were collected by medical records. By using mass cytometry and ELISA, we analyzed the immune profile (CD45, CD3, CD16, PD-1, TIM-3 and LAG-3; IL-2, IL-6, IL-10, TNF-α, and IFN-γ), and the relationship between infection and treatment outcomes. We also compared the dynamic change of immune signature and different impact of chemotherapy and immunotherapy.

Results: Patients were divided into three groups: chemotherapy alone (CT alone), immunotherapy alone (IO alone) and chemotherapy plus immunotherapy (CT+IO). Our data indicates that circulating immune cells were lower in CT alone. The expression of PD-1 and TIM-3 in the IO alone group and LAG-3 in the CT+IO group showed decreased after treatment. Higher expression of NK cells after treatment was found in the IO alone and CT+IO group (IO alone, $p<0.0001$; CT+IO, $p<0.001$) but not in the CT alone group. Patients with high expression of NK cells ($p<0.01$) in the IO group had better OS compared to those with low expression before treatment. Immunotherapy leaded to increased TNF-α ($p<0.01$) after treatment, while the addition of chemotherapy to immunotherapy attenuated the elevation of TNF-α. In the IO alone group, the tendency of decreased expression of LAG-3+ T cells after treatment was demonstrated in patients without pneumonia. The real-world evidence also indicated the significantly different incidence of infection between immunotherapy and chemotherapy ($p=0.008$). There was lower proportion of pneumonia in the group of immunotherapy compared to that of chemotherapy.

Conclusions: Elevated TNF-α by immunotherapy may possess a potential role in preventing pulmonary infection after treatment. Immunotherapy may decrease the incidence of pulmonary infection through the mechanism of increasing the level of NK cells and TNF-α. Further study is mandatory to elucidate the association between the wide spectrum of circulating lymphocyte subpopulations and occurrence of pulmonary infection.

Keywords: Non-small cell lung cancer, Immunotherapy, Immune signature

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-004 Pleural Mesotheliomas Related with Geographical Asbestos Exposure Show Higher PD-L1 Expression

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Introduction: The major risk factor in diffuse pleural mesothelioma (PM) is occupational and/or geographical asbestos exposure. Surgery is a treatment option in only a limited number of cases. Prognosis is very poor with current therapies and new treatment options are needed. Immune checkpoint inhibitors (ICIs) may be a treatment option in PM, as in other malignant tumors. However, it is necessary to use predictive biomarkers to determine which patients will benefit from treatment. PD-L1 immunohistochemistry is widely used to predict therapy response to ICIs in many tumors. According to the NCCN guideline, PD-L1 IHC is not required for prescribing anti- PD-L1 drugs in PM. However, expression patterns, the underlying genetic mechanism of PD-L1 expression, and prognostic significance are still controversial in PM. There is no data on PD-L1 expression and its relationship with clinicopathological parameters in cases with geographic asbestos exposure. In this study, it was aimed to compare PD-L1 expression and clinicopathological parameters in patients from two different ethnic origins with occupational or geographic asbestos exposure.

Methods: Formalin-fixed paraffin-embedded (FFPE) tumor samples of histologically confirmed and therapy-naive PMs from Turkish (n:56) and Japanese (n:37) patients, with at least 12 months follow-up were collected. Clinical data (age, gender, asbestos exposure, smoking status) were collected from medical records retrospectively. One representative whole section from all cases was stained immunohistochemically for PD-L1 (clone SP263). Histologic subtype (epitheloid, sarcomatoid, biphasic), grade, PD-L1 expression in tumor cells (TCs) were evaluated on HE stained slides, using a digital scanner (Panoramic 250 Flash III, 3DHISTECH Ltd., Hungary).

Results: Mean age, gender, smoking history, vital status, asbestos exposure (presence vs. absence and occupational vs. geographical), and PD-L1 expression in TCs were statistically different, between Turkish and Japanese PMs (see Table 1: Clinicopathological features of Turkish and Japanese PMs).

Conclusions: PMs related to geographic asbestos exposure have different clinical features and they show higher PD-L1 expression. Hypothetically, these tumors can show better immunotherapy responses than those, that are related to occupational exposure.

	All cases	Turkish cases	Japanese cases	p value
Patient number	93	56	37	
Age (mean)	59	54	69	0.000
Gender (n, %)				0.000
Female	30 (26.8%)	24 (43.6%)	2 (5.4%)	
Male	82 (73.2%)	32 (56.4%)	35 (94.6%)	
Smoking* (n,%)				0.000
Never	32 (34.8%)	27 (49.1%)	5 (13.5%)	
Current or former smoker	60 (65.2%)	28 (50.9%)	32 (86.5%)	
Vital status in last follow-up *(n,%)				0.035
Alive	30 (39.5%)	24 (48%)	6 (23.1%)	
Deceased	46 (60.5%)	26 (52%)	20 (76.9%)	
Asbestos exposure*				
Absent	8 (9.5%)	8 (14.5%)	0	0.046
Present	76 (90.5%)	47 (85.5%)	29 (%100)	
Asbestos exposure type*				
Geographical	40 (58%)	100 (100%)	0	0.000
Occupational	29 (42%)	0	100 (100%)	
Mesothelioma type *(n, %)				0.127
Epitheloid	51 (54.8%)	28 (50%)	23 (62.2%)	
-Low grade	36 (87.8%)	24 (85.7%)	12 (92.3%)	1.000
-High grade	5 (12.2%)	4 (14.3%)	1 (7.7%)	
Sarcomatoid	11 (11.8%)	5 (8.9%)	6 (16.2%)	
Biphasic	31 (33.3%)	23 (41.1%)	8 (21.6%)	
PD-L1 expression in tumor cells				
Mean	23.7%	34.3%	6%	0.000
≥ 1% (n,%)	63 (70%)	50 (89.3%)	13 (38.3%)	0.000
≥ 10% (n,%)	51 (56.7%)	44 (78.6%)	7 (20.6%)	0.000
≥ 50% (n,%)	24 (26.7%)	22 (39.3%)	2 (5.9%)	0.001

Keywords: Pleural mesothelioma, PDL1 expression, Immunotherapy

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-005 Cilia-related mRNA Profile Predicts Clinical Response to PD-1 Blockade in Lung Adenocarcinoma

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Introduction: Immune checkpoint blockades (ICBs) results improved clinical outcome and life quality in various types of malignancies. While immunotherapy does not fit for all patients. Developing appropriate biomarkers to maximize the clinical efficacy of ICBs is unmet clinical need.

Methods: FFPE tissue specimens of 45 patients with lung adenocarcinoma (LUAD) were collected before immunotherapy administration in Shanghai Pulmonary Hospital from April 2016 to November 2019. All samples were performed RNA-sequencing by Amoy Dx Co.,Ltd. Samples were divided into discovery (n=24) and validation cohort (n=21). Expression profile was compared in discovery cohort between patients with durable clinical benefit (DCB) and non-durable benefit (NDB). Differentially expressed genes were subjected to Gene Ontology (GO)/Kyoto Encyclopedia of Genes and Genomes (KEGG) to reveal pathways associated with anti-PD-1 response. The Least Absolute Shrinkage and Selection Operator (LASSO)-Cox regression was applied to select essential genes for constructing model predicting therapeutic efficacy. ROC-AUC was used to evaluate performance of constructed model for predicting response to immunotherapy in validation cohort (n=21). Association with reported tumor microenvironment gene sets and IFN-γ signature were analyzed and validated in TCGA LUAD cohort.

Results: Cilia-related pathways were significantly enriched in NDB LUAD patients. The ROC-AUC of constructed Cilia risk model was up to 0.958 in discovery cohort and 0.75 in validation cohort. Kaplan-Meier survival curve showed patients with lower scores in both discovery and training cohort could have long-term clinical benefit (discovery cohort, $p<0.001$; validation cohort, $p=0.045$). Further, Cilia risk model displayed higher performance than previously reported GEPs, such as IFN-γ, effector T cell signatures, in predicting the efficacy of immunotherapy in LUAD patients. IFN-γ signature as well as anti-tumoral immunity were significantly activated in LUAD with lower cilia score, which was further validated in TCGA LUAD cohort.

Conclusions: A Cilia risk model was constructed for the first time to predict the clinical efficacy of immunotherapy in patients with lung adenocarcinoma. In addition, this study also indicated the putative involvement of cilia phenotype in tumor microenvironment regulating tumor-immunity crosstalk, which may shed light for future onco-immunology investigations. Further validation of cilia model in perspective cohorts of larger population size is warranted.

Keywords: LUAD, Immunotherapy, RNA Sequencing

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-006 CD47 Inhibition Impairs the Growth of Orthotopic, Immune Competent Lung Tumour Models

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Introduction: The success of PD-1 and PD-L1-targeted immunotherapies in lung cancer patients demonstrates the power or harnessing the immune system to fight cancer. Thus, the next generation of immunotherapies holds great promise to achieve similar improvements in patient outcomes. CD47 is an immunosuppressive, cell surface protein that is overexpressed and associated with poor prognosis in lung and other cancers. Since tumours exploit CD47 to escape destruction by the immune system, therapeutic antibodies targeting CD47 are being evaluated as a new type of immunotherapy in ongoing clinical trials. Given its prognostic significance in lung cancer, we aimed to evaluate the consequence of CD47 inhibition on lung tumour growth in syngeneic models.

Methods: CRISPR/Cas9 technology was used to genetically inactivate CD47 using two different single guide RNAs in two murine, syngeneic lung tumour models (LLC and CMT167). Disruption of the CD47 gene and loss of cell surface expression were verified by sequencing and flow cytometry, respectively. The effect of CD47 loss-of-function (LOF) on tumour growth was assessed using two strategies. First, mCherry-tagged CD47 wild-type (WT) and GFP-tagged CD47 LOF cells were mixed 1:1 and implanted orthotopically into immune competent mice to conduct *in vivo* competition assays. After 10-12 days, tumours were resected, dissociated, and analyzed by flow cytometry to determine the relative abundance of mCherry+ WT and GFP+ CD47 LOF cells. Second, WT or CD47-inactivated tumour cells were orthotopically injected into syngeneic mice and survival studies were conducted.

Results: CD47 inactivation did not affect the growth of LLC or CMT167 cells *in vitro*. In contrast, *in vivo* competition assays revealed that cells with CD47 LOF were significantly underrepresented relative to WT cells in LLC and CMT167 tumours at endpoint. Consistent with these results, mice bearing CMT167 tumours with CD47 knockout (KO) survived significantly longer than their WT counterparts (median survival times: WT tumours = 13.5 days, sgCd47#1 KO tumours = 19 days, and sgCd47#2 KO tumours = 28 days). Despite this growth disadvantage *in vivo*, cells with CD47 LOF were not eradicated from tumours. Specifically, cells with CD47-inactivation were detected in tumours harvested at the endpoint of *in vivo* competition assays, and CD47 KO cells formed tumours that warranted euthanasia in immune competent hosts.

Conclusions: Genetic inhibition of CD47 significantly impaired the growth of two syngeneic lung tumour models. This suggests that CD47 blockade could be an effective immunotherapeutic strategy if delivery of therapeutic antibodies to lung tumours can be achieved. The persistence of lung tumour cells with CD47 inactivation implies that they may develop resistance to CD47 inhibition, and that combinations with other treatments may be needed to maximize the efficacy of CD47-targeted immunotherapy in the clinic.

Keywords: Cd47, immunotherapy

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-007 Molecular Characterization by Next-Generation Sequencing (NGS) of Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Immunotherapy

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Introduction: Immunotherapy has transformed the treatment of non-small cell lung cancer (NSCLC). On the other hand, the incorporation of Next-Generation Sequencing (NGS) techniques can provide great information at the molecular level. The aim of our study is to integrate the clinical and molecular information of a cohort of patients treated with immunotherapy to define molecular subtypes.

Methods: We conducted a retrospective study, which included patients diagnosed with NSCLC in our hospital from Jul-15 to Jan-21 and treated with immunotherapy in any therapeutic line. Inclusion criteria included a NGS performed on tumor tissue or blood (FoundationOne or Guardant360, respectively). Clinical and molecular characteristics were collected. A subgroup analysis was performed according to the site of metastasis in order to obtain a molecular characterization. A descriptive analysis was carried out, followed by a survival analysis using the Kaplan-Meier test.

Results: We enrolled 42 patients throughout this period. The male-female ratio was 3:1, with an average age of 63 years (range 44-86). The most frequent histology was adenocarcinoma (57.1%) followed by squamous cell carcinoma (35.7%). All the patients had received immunotherapy during their disease (69% as second line or more, and 30.9% as first line). The most frequent metastasis site was brain metastasis (31.2%), followed by adrenal or bone metastasis (23.8% each of one). Muscular, peritoneal, or hepatic metastatic sites were reported in fewer patients (11.9%, 9.5%, 7%, respectively). Regarding molecular study, the most frequently mutations were: *TP53* (50%), *KRAS* (26.2%), *MLL2* (19.0%), *ATM* (16.7%), BRCA*2* (16.7%) and *PIK3CA* (16.7%). In the analysis by subgroups according to metastatic involvement, relevant differences were found but they did not reach statistical significance, possibly due to low sample size, as detailed below. The subgroup of patients with brain metastases, was characterized by the absence of mutations in 4 genes (*EPHA3*, *FLT1*, *KLHL6*, and *NF1*), which appeared mutated in the subgroup of patients without brain metastasis. In the subgroup of patients with adrenal metastasis, *BRCA1* mutations were identified in more than 50% of the patients and no alterations were detected in other 4 genes (*EGFR, FLT1, KLK6, SOX2*), which were mutated with relative frequency in patients with no adrenal metastasis (27% each one). In the subgroup of bone metastasis, a very similar distribution was found between both groups, only highlighting that the most frequently mutated genes were *APC* (66.7%) and *ATM* (57.4%). Progression-free survival (PFS) to immunotherapy was evaluated according to the most frequent mutations found, without finding statistically significant differences. Note that in the group of MLL2 mutated, PFS was 8.6 months (CI: 1.5-15.8) vs 13.3 months in the *MLL2* wild-type group (CI, not reached). This data could indicate a better response to immunotherapy in this subgroup. PDL1 ≥50% was the best factor that had an impact on survival, PFS was 22.4 months (CI: 0-45.8) *versus* 8 months (CI: 3-11.7), respectively (p=0.059).

Conclusions: Preliminary data seem to support the idea of the existence of different profiles depending on the metastatic site. However, the small sample size means that further studies are required to validate these data.

Keywords: Non-small cell lung cancer, Next-Generation Sequencing (NGS), Immunotherapy

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-008 The Effect of Cytochrome P450 Family 4 Subfamily B Member 1 (CYP4B1) on Lung Adenocarcinoma (LUAD) Immune Microenvironment

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Introduction: Lung adenocarcinoma (LUAD) is a leading cause of cancer-related death worldwide. Nowadays, there is growing worldwide enthusiasm for cancer immunotherapy as an effective treatment option. Recently, extensive efforts are made to search for new and effective biomarkers to screen for candidates and predict the prognosis. Cytochrome P450 Family 4 Subfamily B Member 1 (CYP4B1), a member of the CYP450s superfamily, is predominantly expressed in the lungs. Herein, we analyzed the association of CYP4B1 with immune inhibitory components to understand its immune landscape properly.

Methods: Gene expression profiles were retrieved from The Cancer Genomic Atlas lung adenocarcinoma cohort (TCGA - LAUD) (n = 567). We used the TIMER 2.0 for immune inhibitory cell infiltrates analysis. Tumor mutational burden (TMB) and microsatellite instability (MSI) scores were measured using the cBioPortal tool. Subsequently, the enrichment analysis of function and signaling pathways of DEGs in LUAD were performed by gene ontology (GO) and The Kyoto Encyclopedia of Genes and Genomics (KEGG) analysis using Enrichr.

Results: CYP4B1 was found to be differentially expressed in LUAD tissues compared to normal liver tissues ($P < 0.000$). High CYP4B1 expression had favorable overall survival prognostic value in LUAD patients (HR: 0.64, 95% CI: 0.48 - 0.84, $P = 0.001$). CYP4B1 expression was negatively correlated with the infiltration of myeloid-derived suppressor cells (MDSC) (spearman's $\rho = -0.578$, $P < 0.001$), but positively with macrophage M2 cells ($\rho = 0.211$, $P < 0.001$). Moreover, survival analysis based on CYP4B1 expression and MDSC levels revealed a worse OS group identified by low CYP4B1 expression and high MDSC levels after adjustment for age, tumor purity, and stage. In terms of immune checkpoint genes expression, CYP4B1 expression was directly correlated with PD-1, PD-L1, VSIR, and LAG-3 ($\rho > 0.2$, Q value < 0.05). TMB count was inversely associated with CYP4B1 expression ($\rho = -0.23$, $P < 0.001$), as for the MSI MANTIS score, CYP4B1 had inverse association (CC = -0.05, P-value = 0.27). GO analysis showed that genes positively co-expressed with CYP4B1 were mainly located in the anchored and intrinsic component of the external side of the plasma membrane, and mainly participated in biological processes of cellular response to testosterone stimuli and actin filament reorganization by molecular function such as carbonate dehydratase and hydro-lyase activity. The top enriched KEGG pathways positively linked with CYP4B1 expression were nitrogen metabolism, proximal tubule bicarbonate reclamation, and GnRH secretion.

Conclusions: We found that CYPB41 expression is a useful marker of immunosuppression in LUAD patients and can predict the response to immunotherapy. Our results suggested that CYPB41 is a favorable prognostic marker and this can be explained by low MDSC levels. Further studies are needed for a better understanding of the CYP4B1 value in LAUD.

Keywords: Lung adenocarcinoma, CYP4B1, Immune microenvironment

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-010 A Machine-Learning Based Survival Prediction for Lung Adenocarcinma by Analyzing Infiltrated Lymphocytes Profiles with CIBERSORT

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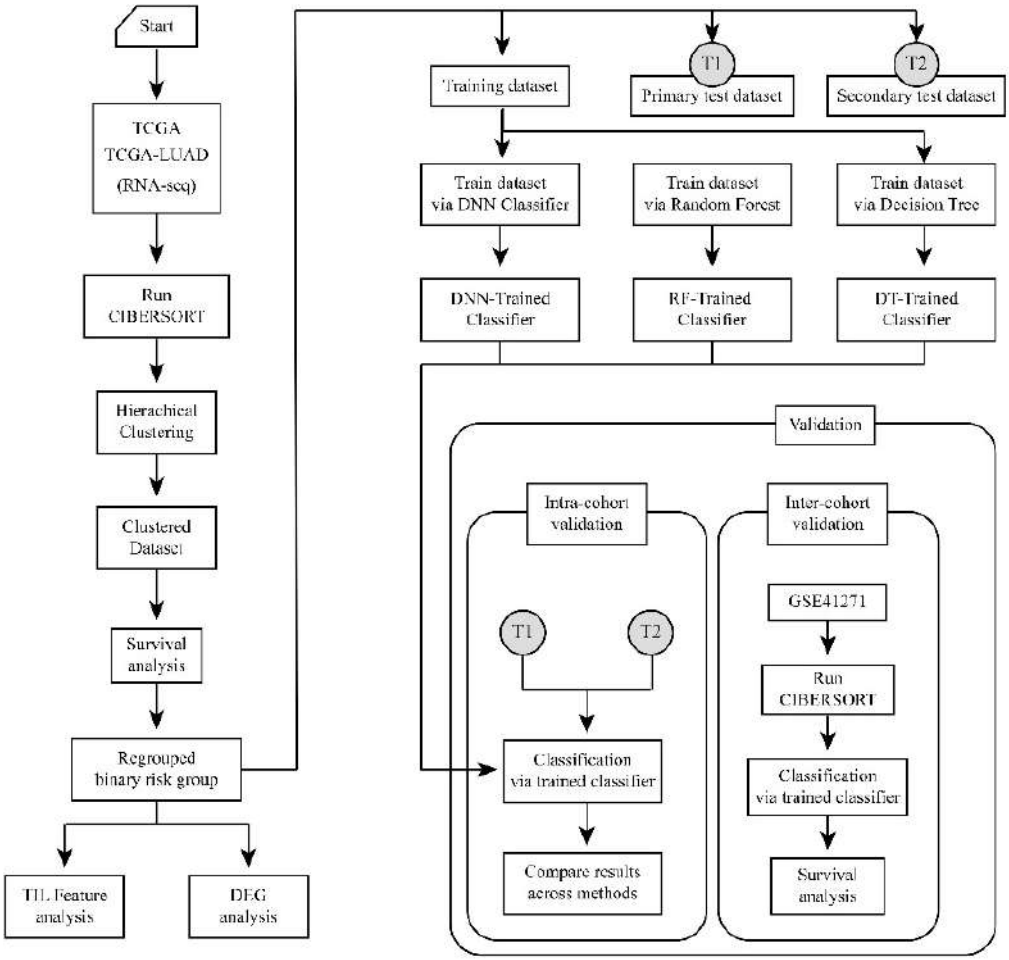
Introduction: Tumor-infiltrating lymphocytes (TILs) greatly influence lung adenocarcicoma (LUAD) tumor mircroenvironment (TME).

Methods: We used CIBERSORT profiles of LUAD data that were filtered from publicly accessible data of patients with LUAD in The Cancer Genome Atlas (TCGA) for hierarchical clustering. On the basis of clustering-measuring scores and survival patterns within individual groups, patients were categorized into binary risk groups.

Results: Clinically reasonable differences were found in 15 of the 22 TIL fractions between the two groups based on this analysis. Based on the TIL fraction patterns, a deep neural network classifier was trained. Using this classifier, we accurately predicted patient survival patterns from another individual LUAD dataset from the GSE41271. A total of seven genes with differential expression between the two risk groups were identified.

Conclusions: It is noteworthy that this new approach confirms the importance of TILs in the TME and further demonstrates the potential of a deep-learning approach for LUAD prognosis.



Keywords: Lung adenocarcinoma, Maching-learning, CIBERSORT

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-011 PD-L1 Expression on Cytological Imprints and Circulating Tumor Cells versus Standardized Immunohistochemistry in NSCLC

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Introduction: While samples of solid tumor tissue needed for morphological diagnosis and molecular testing might be lacking in a significant proportion of NSCLC patients, the reliability of tumoral PD-L1 expression on cytological imprints and liquid biopsies remains still undetermined. In this study, we aimed to compare tumoral PD-L1 expression on cytological imprints and circulating tumor cells (CTCs) with standardized PD-L1 expression testing defined by the tumor proportion score (TPS) from immunohistochemistry staining of solid tumor tissue.

Methods: In this prospective single-center study, we obtained liquid biopsies and cytological imprints of endoscopic and intraoperative samples from patients with suspected lung cancer. We evaluated PD-L1 expression using a PD-L1 antibody 28-8 in representative cytological imprints, i.e. in those with at least 100 intact tumor cells, and comparative histological samples from the same tumor lesion. CTCs were enriched using a size-based microfluidic approach and a rabbit anti-human PD-L1 clone HL1041 was used to assess PD-L1 expression on the cells. PD-L1 status was expressed as a percentage of PD-L1 positive tumor cells. We performed a ROC analysis to evaluate PDL-1 expression in cytology imprints as predictor for PDL-1 positivity (TPS ≥ 1%) and high PDL-1 expression (TPS ≥ 50%) from standardized immunohistochemistry. We used Cohen's kappa to assess the inter-rater reliability.

Results: In eighty-four patients with NSCLC (mean age 65.4 ± 9, 67% males, 61% non-squamous, 27% primary respectable tumor), the predictive capacity of PDL-1 positivity in cytology imprints indicated a PPV of 90%, NPV of 40%, AUC= 80% [95% CI: 68-91%]. Considering high PDL-1 expression, cytology imprints had a PPV of 78% and a NPV of 71%, AUC= 77% [95% CI: 66-89%]. The inter-rater reliability test showed slight concordance between histology and cytology specimens for PD-L1 positivity *(κ= 0.29)*, and a fair concordance for high PDL-1 expression *(κ= 0.47)*. The subgroup analysis did not demonstrate a greater reliability of cytology imprints that were obtained intraoperatively (PD-L1 positivity, κ= ≤ *0*), (high PDL-1 expression, κ= *0.37*), than those obtained via endoscopy (PD-L1 positivity, κ= *0.36*), (high PDL-1 expression, κ= *0.51*). CTCs were detectable in 37% of the patients. The presence of CTCs was comparable in patients with: non-respectable *vs* respectable (OR 1.80 [95% CI 0.57- 5.7]), non-squamous *vs* squamous (OR 0.64 [95% CI 0.23 - 1.98]), non-high *vs* high PDL-1 expression tumors (OR 0.98 [95% CI 0.32 - 2.87]). PD-L1 expression on CTCs was found in 82% of the patients and showed a poor concordance with histological PD-L1 positivity (κ= 0.18) and high PDL-1 expression (κ= 0.16).

Conclusions: Assessment of PD-L1 expression in cytological imprints and liquid biopsies has revealed a relatively low concordance rate with standardized immunohistochemistry. The variability of PD-L1 expression between cytology and histology was greater than the previously described intra-test variability between multiple histological tests, which might be attributable to intratumoral heterogeneity.

Keywords: NSCLC, PDL1, CTCs

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-012 Immunophenotyping of Lung Adenocarcinoma in situ Based on CD8-positive T Cell Infiltration

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Introduction: Lung adenocarcinoma in situ (AIS) has been reclassified as a glandular precursor lesion according to the latest fifth edition of the lung adenocarcinoma (LUAD) classification. This study was designed to investigate the immunophenotyping of AIS based on CD8-positive T cell infiltration and its changes in the progression progress to minimally invasive adenocarcinoma (MIA), then to invasive adenocarcinoma (IAC).

Methods: A total of 14 AIS patients with cancer tissue and matched paracancerous tissue samples for CD8 immunohistochemical staining, and 17 patients with MIA and 40 patients with IAC were also assessed for CD8 T cell infiltration. Positive CD8 T cell infiltration was defined as the proportion of CD8-positive lymphocytes in the entire tissue with a proportion of all nucleated stromal cells greater than 5%. Immunophenotyping of LUAD is divided into three subtypes: inflamed, immune excluded and immune desert.

Results: In AIS, the proportion of CD8-positive T cells infiltrated was 42.9% (6/14), which was significantly lower than that of MIA (64.7%) and IAC (80.%), P=0.033. In our study, we performed immunophenotyping according to CD8 T cells, and it is worth noting that we did not observe the existence of the immune excluded type, regardless of which type of LUAD. Next, we analyzed the association between histologic subtype of LUAD and immune subgroups, in AIS of this study, 57.1% of them were classified as immune desert, while in MIA, 64.7% were classified as inflamed, and when the tumor progressed to IAC, 70.0% of them were inflamed, although there was no statistical difference (P=0.220).

Conclusions: The increased infiltration of CD8-positive T cells is involved in the progression of LUAD from AIS to IAC. The immunophenotype of AIS is mainly immune desert type, while MIA and IAC mainly in the inflamed type.

Keywords: CD8T cell, adenocarcinoma in situ, immunophenotype

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-013 The Diagnostic Accuracy of Tumor Mutational Burden in Advanced NSCLC: An Individual Patient Data Meta-Analysis

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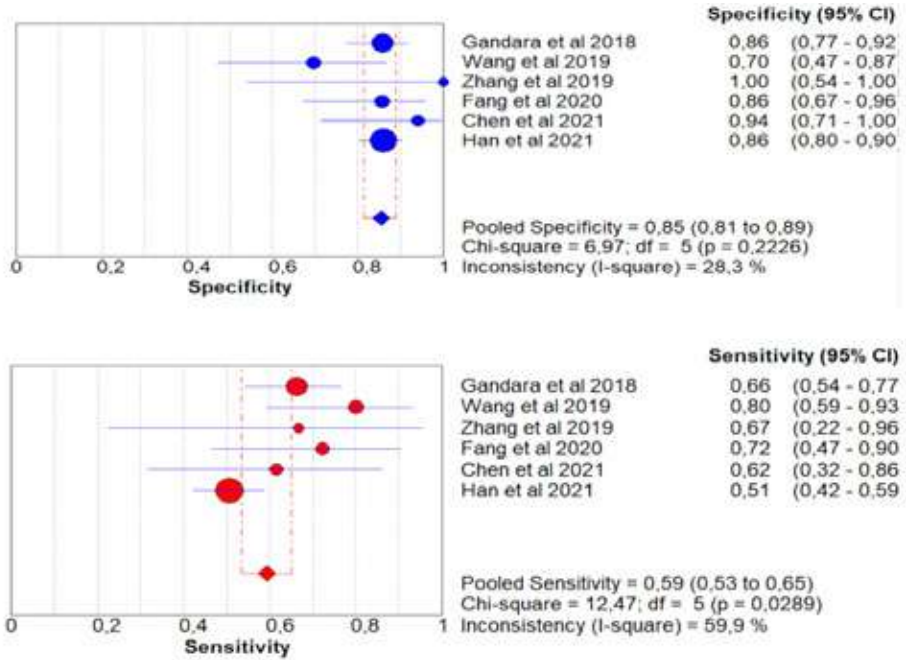
Introduction: Non-small cell lung cancer (NSCLC) accounts approximately for 85% of all lung cancer cases and still represents the leading cause of cancer-related death worldwide. The vast majority of NSCLC patients present with advanced disease, with their clinical course being dramatically influenced by cancer-specific features at the molecular level. Although immune checkpoint inhibitors (ICIs) and targeted therapies have revolutionized the therapeutic approach in this setting, a valid universal biomarker is still missing. A potential predictive biomarker of ICI efficacy that has been suggested is a high tumor mutational burden (TMB), the quantity of acquired mutations in a tumour's genome, but evidence in this regard is controversial and not mature enough to drive decisions in NSCLC. TMB might be evaluated from tissue (tTMB) and from plasma (bTMB) yet, generally they are not concordant. Our aim was to provide a comparative analysis between plasma and tissue TMB in patients with advanced NSCLC treated with ICIs.

Methods: Two reviewers selected studies published until April, 2021 from Medline (PubMed), EMBASE-databases, and Cochrane-Library using the following terms: 'non-small-cell lung cancer', 'NSCLC', 'tumor mutational burden', 'TMB', 'correlation', 'concordance', 'comparison', 'accuracy', 'matched', 'plasma', 'tissue', 'liquid biopsy', 'ctDNA'. Advanced NSCLC patients with matched tumor tissue and plasma ctDNA and under ICIs treatment were considered.Metaregression and subgroup analyses were performed to explore sources of heterogeneity concerning tumor burden, diagnostic technique, sample size, and biological subtype. Pooled sensitivity, specificity, PLR, NLR, DOR, and the related AUC were elaborated for the overall population and each subgroup.

Results: The pooled analysis was carried out on a total of 751 patients, enrolled in the six clinical trials included in the meta-analysis. The overall ctDNA sensitivity and specificity were 0.59 (95% CI: 0.53-0.65) e 0.85 (95% CI: 0.81-0.89) (Figure 1). The AUC was 0.83. Pooled PLR, NLR, and DOR of 3.86 (95% CI: 2.97-5.01), and 0.43 (95% CI: 0.33-0.56). Spearman's rank correlation coefficient resulted to be 0.81 (p-value = 0.50), thus not significantly associated with bias.

Conclusions: These findings seemed to reliably estimate the bTMB accuracy for the detection of TMB in the management of metastatic NSCLC, validating the role of liquid biopsy in this emerging context.



EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-014 Characterisation of Circulating Immune Cells in a Cohort of Non-small Cell Lung Cancer Patients Treated with Immunotherapy

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Introduction: Immunotherapy in lung cancer has been one of the most relevant therapeutic advances in recent years. Although many studies demonstrate its antitumor activity, there is still a great lack of knowledge about which may be the best prognostic biomarkers. In recent years, several studies suggest that different immune cell populations might be useful biomarkers to predict immunotherapy efficacy. Among them are specific T cell subsets, natural killer (NK) cells or the ratio between cytotoxic CD8+ T and regulatory CD4+ T (Treg) lymphocytes. In this sense, the objective of our study is to provide a detailed analysis of different circulating immune cell subsets within T and NK cell populations in a cohort of patients with non-small cell lung cancer (NSCLC) treated with immune-checkpoint inhibitors (ICI) and analyze their prognostic value.

Methods: Observational, prospective and analytical study of a cohort of 55 patients diagnosed with NSCLC (unresectable stage III and IV) receiving ICI. Demographic, clinical and tumor variables are collected, as well as a peripheral blood sample. A total of 43 cell subpopulations of CD4+ and CD8+ T and NK cells, including the main exhaustion, differentiation, memory, activation and inhibition markers are analyzed in peripheral blood, correlated with treatment response and survival.

Results: 55 patients were included (70.9% men) with a median age of 65 years. Regarding histology, there were 40% squamous cell carcinomas and 60% adenocarcinomas, 70.9% being stage IV. After minimum of one year of follow-up, 56.4% of patients had progressed with a median overall survival of 19 months (CI: 11.13-26.87). Regarding the descriptive data of the analyzed cell populations, the regulatory Granzyme B+ CD4+ T lymphocytes stand out with a median of 17.4% (SD 24.4%) and memory CD4+ and CD8+ T lymphocytes with a median of 4.9% (SD 8.9%) and 3.5% (SD 9.5%) respectively. Regarding the CD8+ T /CD4+ Treg ratio, it presents a median of 1 (SD 2.3). In addition, within the NK populations analyzed, most of the patients present activated cytotoxic NK cells (CD56+ CD3- CD16+ Granzyme B+; median 94.8% - SD 18.6%-) and around half of them present highly differentiated adaptive-like NK cells (CD56+ CD3- CD16+ CD57+; mean 59.8% -SD 17.9%-). Notably, in comparison with activated NK cells with cytotoxic potential that were presented in most patients, around one third of the patients included in the study did not express the activating receptors NKp46 or NKG2D, suggesting the emergence of dysfunctional NK cell subsets.

Conclusions: Circulating immune cell subpopulations are among the most promising prognostic biomarkers for ICI. Here we provide a detailed descriptive analysis of the main circulating T and NK cell subsets involved in cancer immunity in a cohort of NSCLC patients. Some of the results suggest dysfunctional T and NK cell responses that might be related with ICI efficacy, which relevance to predict survival and treatment outcome will be shortly available.

Keywords: inmune cells, inmune chekpoint inhibitors, biomarker

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-015 Introducing "BiomeOne" a Microbiome-based bBiomarker to Predict Immune Checkpoint Inhibitor Response in NSCLC 1patients

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Introduction: Immune checkpoint inhibitor (ICI) therapies have emerged as a potent option for the treatment of non-small cell lung cancer (NSCLC). ICI therapies fight the tumour through an up-regulation of the immune system and achieve a higher efficacy compared to traditional platinum-based chemotherapies. Major downsides of ICI-treatments are the varying response rates and sometimes even severe immune related adverse events (irAE).

To address these challenges one highly promising approach is to establish a prognostic biomarker - based on the intestinal microbiome. The complex ecosystem of the intestinal microbiome is strongly interconnected with the body's own immune system and hence has been a scientific focus for years as a potential biomarker to predict ICI therapy response as well as irAEs.

Methods: Over the last few years, the scientific team of Biome Diagnostics has worked on establishing a specific biomarker that utilises the genomic data from the human intestinal microbiome as a response predictor for ICI therapy. For the very first time we are going to present the data of a clinical study with nearly 100 NSCLC patients as well as a meta-analysis of additional 500 already published datapoints.

The datasets were analyzed using identical bioinformatic processes and evaluated with a compositional data analysis (CoDA) approach. All presented research uses methods such as the LEfSe (Kruskall-Wallis alpha < 0.05) differential abundance analysis, ANOVA-Like Differential Gene Expression Analysis (ALDEx), and further aspects. Overall, the selected features are analysed using diverse machine learning techniques and validated with different cross validation methods.

Results: The presented results represent the first microbiome-based biomarker to reliably identify responders and non-responders to ICI treatment with specificities above 87% and sensitivities above 82%!

Additionally, the results of the presented LEfSe and ALDEx analysis will highlight specific genera which are enriched in patients responding to ICI therapy whereas others are more abundant in non-responders. In particular, multiple genera of the order clostridia have been found to be differentially abundant in patients depending on their response to ICI therapy. Preliminary analyses have shown for these biomarkers to be cancer agnostic making them a valuable contribution to a lot of cancer therapy settings.

Conclusions: The presented research will give oncologists a clinical support tool to aid in therapy decision making. With this biomarker ICI therapies will be applied in a more targeted manner, improving patient well-being and recovery.

Additionally, presented research will show that the large number of included datasets lead to a robust biomarker taking into account multiple confounding factors such as sample preparation and analysis methods.

Keywords: microbiome, biomarker, ICI-response prediction

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-016 Tumor Treating Fields (TTFields) Application Promotes a Pro-inflammatory Phenotype in Macrophages

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Novocure Ltd, Haifa/IL

Introduction: Tumor Treating Fields (TTFields) are electric fields that disrupt cancer cell division via anti-mitotic effects. Recently, cancer cell death following delivery of TTFields has been shown to stimulate anti-tumor immunity and promotes maturation of dendritic cells. In the current research, effects of TTFields on phenotypic regulation of M1 and M2 macrophages was investigated.

Methods: Bone marrow-derived macrophages (BMDMs) were generated from the femurs and tibias of 5-8-week-old Balb\C mice. TTFields (150 kHz, 24 h) were applied to BMDMs stimulated with LPS+IFN-γ (M1 polarization) or IL-4 (M2 polarization). Flow cytometry was used to examine these cells for surface expression of the macrophage biomarker F4/80 and the activation markers CD80, major histocompatibility complex class II (MHC II), inducible nitric oxide synthase (iNOS), CD206, and ARG-1. Heterogeneity of the stimulated macrophages was further examined by multiplexed secretion assays, measuring levels of CXCL1 (KC), IL-18, IL-23, IL-12p70, IL6, TNF-α, IL-12p40, TGF-β1, CCL22 (MDC), IL-10, IL-6, G-CSF, CCL17 (TARC), and IL-1ß.

Results: The percentage of cells expressing the pro-inflammatory M1 markers CD80+ and MHC IIhigh was significantly increased, whereas expression of the M2 markers CD206 and ARG-1 was significantly decreased following TTFields application to BMDMs. Supernatants from TTFields-treated M1 and M2 BMDMs showed a pro-inflammatory secretion pattern, with increased levels of CXCL1, IL-18, IL-23, IL-12p70, TNF-α, IL-12p40, CCL22, G-CSF, CCL17 and IL-1ß. Taken together, TTFields induced phenotype skewing of M2 polarized BMDMs to the M1 phenotype.

Conclusions: This research uncovers a novel immunoregulatory role for TTFields, promoting a pro-inflammatory phenotype in macrophages. Future investigations will focus on defining the underlying mechanism of this phenotypic skewing.

Keywords: TTFields, Immunomodulation,, Macrophages

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-017 T-cell Repertoire Heterogeneity and Homogeneity in Synonymous Multiple Primary Lung Cancers

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Introduction: With the widespread application of computed tomography and lung cancer screening, multiple primary lung cancers (MPLCs) are increasing in our daily practice. However, MPLC is characterized with highly heterogeneous immune profile, hindering the application of immune checkpoint inhibitors (ICIs). A better understanding of the immune profiling of MPLCs is urgently needed.

Methods: We presented a detailed genomic and immune analysis on a collection of clinical specimens, consisting of 69 tumors from 27 patients with synonymous MPLCs and 132 tumors from patients with a single pulmonary nodule (SN), by performing 1021-gene next generation sequencing, immunohistochemistry staining of PD-L1 and T cell receptor (TCR) sequencing on these specimens. Two groups of TCR repertoire parameters were focused on: TCR diversity, indicated by clonotype, Shannon index and inverse Simpson index, and TCR expansion, indicated by clonality, evenness and the frequency of top 100 clonotypes.

Results: All these tumors are characterized with early stages, with a considerable proportion of precancerous lesions, especially in synchronous MPLCs, which included 13.1% (9/69) atypical adenomatoid hyperplasia subtype, 31.9% (22/69) adenocarcinoma *in situ*, 24.6% (17/69) minimally invasive adenocarcinoma, and 30.4% (21/69) invasive adenocarcinoma (IAC). The most common mutation in MPLC cohort was *EGFR* (46.4%), followed by *BRAF* (17.4%), *TP53* (14.5%), *KRAS* (13.0%), *ERBB2* (10.1%), *MAP2K1* (8.7%) and *MTOR* (8.7%), implying genetic aberrations of MPLCs involving in *EGFR* family of receptor tyrosine kinases and MAPK signaling pathway. Compared with SN cohort, MPLC cohort harbored significantly lower prevalence of *EGFR* mutation, but higher prevalence of *BRAF*, *MAP2K1* and *MTOR* mutations. No differences were found in PD-L1 expression and tumor mutation burden levels between MPLC and SN lesions, while IAC lesions of MPLCs exhibited higher TCR diversity and comparable TCR expansion than those in IAC lesions of SNs. Furthermore, the TCR repertoire of MPLC lesions correlate with their clinical and molecular features, that is, lesions with IAC subtype or *EGFR* mutations had significantly higher TCR diversity but lower TCR expansion than their counterparts. However, no associations between clinical or molecular features and TCR repertoire were found in SN lesions. Additionally, intrapatient analysis demonstrated that the vast majority of TCRs were restricted to individual lesions, with as little as 0.07% and at most 46.8% of T-cell clones found in different lesions of a same MPLC, suggesting the substantial intrapatient heterogeneity of TCR repertoire in MPLCs. Notably, only 100% shared TCR expand predominantly among same-patient lesions, which is supported by the proportion of the reads of 100% shared clones among same-patient lesions to all clone reads counted in an individual lesion is always higher than the proportion of the numbers of 100% shared clones to all clone numbers in an individual lesion.

Conclusions: Collectively, our work shows divergent T-cell response between SN and MPLC tumors, likely driven by distinct tissue microenvironment. Of note, the importance of constrained tumorigenic pathway in MPLC tumors in mediating immune response in the form of the predominant activity of shared T-cell clones among same-patient tumors, which might aid rational biomarker exploration of ICIs for MPLCs.

Keywords: Synonymous multiple primary lung cancers, T cell receptor sequencing

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-018 SAKK 16/14 -Peripheral Immune Cell Populations Inresponse to Neoadjuvant Durvalumab in Patients with Stage IIIA(N2) NSCLC

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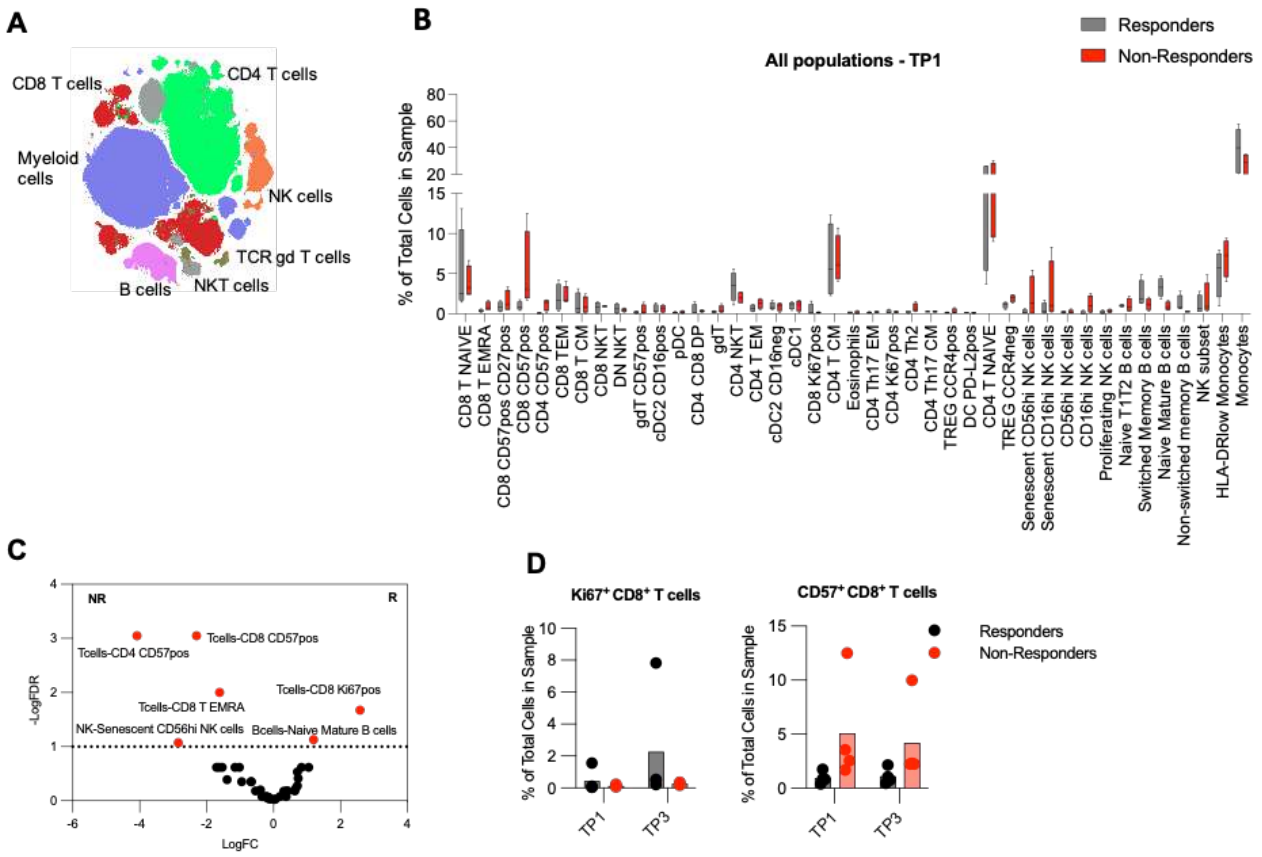
Introduction: Various peripheral immune cell populations have previously been implicated as potential biomarkers for response to immune checkpoint inhibition, although with inconsistent results between studies. The single-arm phase II trial SAKK 16/14 confirmed the efficacy of perioperative treatment with the andi-PD-L1 antibody durvalumab in patients with stage IIIA(N2) non-small cell lung cancer (NSCLC) with a clinically meaningful benefit compared to neoadjuvant chemotherapy alone. To evaluate the impact of treatment on the immune system, we comprehensively profiled immune cell populations derived from SAKK16/14 patients' peripheral blood mononuclear cells (PBMCs) by mass cytometry.

Methods: PBMCs were obtained from five responder and five non-responder patients. Responder patients showed complete pathological response (pCR) and nodal clearance at resection and remained event-free for at least 12 months. For each patient, we analyzed PBMCs obtained before neoadjuvant treatment (TP1) and after sequential neoadjuvant chemotherapy and durvalumab (TP3). PBMCs were stained with a custom antibody panel designed to assess the expression of 35 protein markers and analyzed with cytometry by time of flight (CyTOF).

Results: Four responder and four non-responder patients had sufficient cell events at both time points for analysis. Cells were displayed in two-dimensional space with optSNE and clustered using the FlowSOM algorithm (Fig. 1A) to identify major immune cell populations. Differential enrichment between responders and non-responders was assessed with edgeR. No significant differences in frequencies of major immune populations (including monocytes, dendritic cell subsets, B cells, natural killer cells, cytotoxic and helper T cells and others) were detected between the patients displaying different clinical outcomes (Fig. 1B). Senescent, CD57+ T cells were enriched in non-responder patients whereas Ki67+ proliferating CD8 T cells were enriched in responders (Fig. 1C). However, these differences were mainly driven by individual patients (Fig. 1D). There was also no on-treatment identified changes in peripheral immune cell populations in responding and non responding patients (TP1 vs TP3, Fig. 1D).

Conclusions: Although statistically significant enrichments of some immune populations were detected, the low number of samples prevented us to conclusively rule out changes in other peripheral immune populations. To increase confidence in the results, the analysis should be conducted in a larger patient cohort. Results obtained here will be put into context with other ongoing analyses of the trial SAKK 16/14, including T cell receptor sequencing as well as transcriptomic and pathological analysis of the tumor microenvironment.



Keywords: neoadjuvant immunotherapy, Peripheral immune cell populations, CYTOF

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-019 The Role of the Pregnancy Associated Protein Glycodelin and Its Influence on the Immune System in Non-small-Cell Lung Cancer

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Introduction: Lung cancer is the leading cause of cancer related death worldwide and the challenge of developing effective therapies especially for advanced stages remains. Novel approaches in immuno-oncology showed a favorable response in lung cancer patients, making this an interesting and promising field for future research. Glycodelin is an immunomodulatory lipocalin in reproduction and pregnancy maintenance. Interestingly, high expression levels were also observed in different cancer types, e.g. in non-small-cell lung cancer.

Methods: To investigate whether glycodelin has similar immunomodulatory characteristics in NSCLC, a lectin panel was used to compare the glycosylation pattern of glycodelin secreted by NSCLC tumor cells to immunosuppressive glycodelin A isolated from amniotic fluid. Furthermore, immune cell lines were treated with supernatant of glycodelin secreting tumor-derived cell line. Binding assays were performed and possible effects of the treatment have been evaluated using microarray gene expression analyses. Moreover, glycodelin and leucocyte markers were co-stained in formalin-fixed paraffin-embedded (FFPE) NSCLC tissue. To evaluate its predictive influence on the efficiency of immunotherapy, glycodelin was measured in the serum of inoperable immunotherapy-treated NSCLC patients (n = 139) prior to immunotherapy and progression-free survival was analyzed.

Results: We were able to analyze high similarities in the glycosylation pattern of glycodelin A and NSCLC-derived glycodelin. Both proteins were highly sialylated which is known to be the main driver of immune regulation. In addition, we could validate that glycodelin binds to immune cells *in vitro* and *in vivo*. The microarray gene expression analysis revealed a significant upregulation of genes involved in tumor microenvironment and immune response pathways. In patients, high serum concentrations of glycodelin were associated with a decreased progression-free survival ($p < 0.001$) of female patients receiving an anti-PD-1 / PD-L1 therapy.

Conclusions: In conclusion, we demonstrate that glycodelin is a protein with a high potential of being a novel target in immuno-oncology especially for NSCLC patients.

Keywords: NSCLC, Immuno-oncology, Immunomodulator

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-020 Predictive Effect of Spatial Protein Signature in Advanced NSCLC Receiving Immunotherapy with a Bispecific Antibody

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Introduction: Immunotherapy, targeting programmed death ligand-1 (PD-L1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), have shown promising antitumor effects and safety in patients with advanced non-small cell lung cancer (NSCLC), while predictive biomarkers remain largely unknown. Here, we investigated the predictive effect of spatial protein expression signature for KN046, a bispecific antibody (bsAb), as second or above line treatment in advanced NSCLC.

Methods: Digital spatial profiling (DSP) was used to evaluate the protein expression in both tumor and stroma areas of formalin fixation and paraffin embedding (FFPE) sections at baseline. Regions of interest (ROIs) were recorded after tricolor fluorescence labeling. Compartment-specific areas of interest (AOIs) were assigned from sequential mask assignment of the stroma (pan CK-) and tumor (pan CK+) compartments. The geometric means of differential protein expression in different spatial areas were combined to construct the tumor+stroma signature, the tumor signature, and the stroma signature. The accuracy of the signature score was evaluated by receiver operating characteristic (ROC) curve and the area under the curve (AUC).

Results: A total of 17 patients were enrolled, including 8 patients from partial response (PR) group and 9 from progressive disease (PD) group. Among 133 ROIs,14 proteins (B7-H3, CD45RO, Bcl-2, PD-L1, CD14, GITR, PTEN, progesterone receptor, FAP-alpha, CD11c, CD45, CD34, OX40L, STING) expressed differently between PR and PD groups (both $P<0.05$). Among 89 ROIs of tumor areas, OX40L, B7-H3, Bcl-2 and CD45RO were highly expressed in PR group, while STING was highly expressed in PD group (both $P<0.05$). Among 44 ROIs of stroma, patients from PR group had higher expression of Tim-3, PD-L1, CD11c and B2M (both $p<0.05$). Among three signatures, the stroma signature with Tim-3/PD-L1/CD11c/B2M showed the best predictive performance (AUC=0.840, $p<0.05$), followed by the tumor+stroma signature (AUC=0.732, $p<0.05$) and the tumor signature (AUC=0.670, $p<0.05$). The predictive effect of the stroma signature was much better than PD-L1 and tumor mutation burden (TMB).

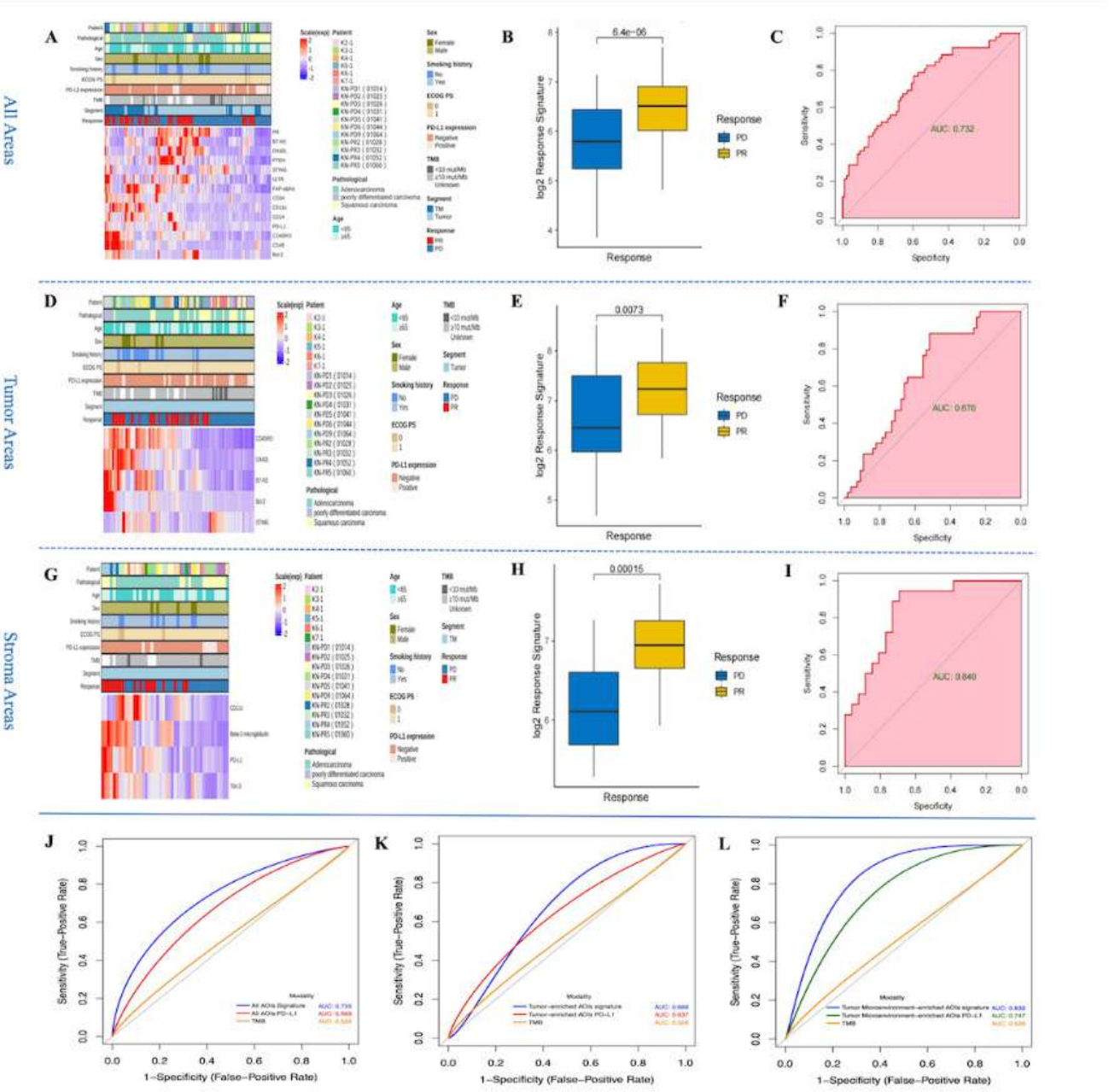

Figure: Predictive effect of signatures from different areas and compared with traditional makers.
(A) Heat map of differential proteins in signature from all AOIs (including tumor areas and stroma areas). (B) All AOIs' boxplot of response signature. (C) All AOIs' ROC curve of response signature. (D) Heat map of differential proteins in signature from tumor areas. (E) Tumor areas AOIs' boxplot of response signature. (F) Tumor areas AOIs' ROC curve of response signature. (G) Heat map of differential proteins in signature from stroma areas. (H) Stroma areas AOIs' boxplot of response signature. (I) Stroma areas AOIs' ROC curve of response signature. (J) The meta-graph of the ROC-AUC values in all AOIs. (K) The meta-graph of the ROC-AUC values in tumor areas. (L) The meta-graph of the ROC-AUC values in stroma areas.

Conclusions: In NSCLC, the PR and PD groups demonstrated differently spatial characteristics. We sucessfully developed a stroma signature with Tim-3/PD-L1/CD11c/B2M which could better predict the response of KN046. This signature might potentially complement the limitations of previous PD-L1 and TMB, and guide clinical treatment decisions for anti-PD-L1/CTLA-4 immunotherapy. Further validation was needed in the future.

Keywords: Immunotherapy, Digital spatial profiling, Predictive signature

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-021 Less Immune Cell Infiltration and Worse Prognosis for NSCLC Patients with XPO1 Copy Number Alterations

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Introduction: The nuclear export protein XPO1 (exportin 1) regulates the export of a range of cargoes from the nucleus to the cytoplasm and plays an important role in the maintenance of cellular homeostasis. XPO1 overexpression has been reported in multiple cancer types and can be associated with shorter progression free survival or overall survival (OS). However, the association and underlying mechanism for the relationship between XPO1 alterations and survival of non-small-cell lung cancer (NSCLC) patients remains unclear.

Methods: Using cBioPortal database, we collected the records of NSCLC patients from 20 studies. A total of 5792 samples and 5644 patients with both mutation and copy number alteration (CNA) data were included in this study. The prevalence of XPO1 mutations and CAN, as well as the relationship between clinical characteristics (gender and age) and XPO1 status were investigated in NSCLC patients. Kaplan-Meier analysis and log-rank test were used to compare the survival curves. Finally, we evaluated the tumor infiltration immune cells in patients with lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) harboring XPO1 CNA by TIMER database. The infiltration level for each CNA category was compared with the normal using a two-sided Wilcoxon rank-sum test.

Results: The total incidence of XPO1 alterations was 2.8 % (158/5644) in the entire NSCLC cohort, including 95 XPO1 CNA cases, 63 XPO1 mutation cases and one case coharboring XPO1 mutation and amplification. The prevalence of XPO1 mutations was similar in LUAD (1.1 %) and LUSC (1.1 %) samples. In contrast, the prevalence of XPO1 CNA was relatively higher in LUSC (6.2 %) compared to LUAD (0.3 %). There was no significant gender prevalence between different XPO1 mutation status ($p = 0.22$). However, our results suggested that XPO1 CNA were more common in male NSCLC patients ($p < 0.001$). There was no significant difference for the age between NSCLC patients with XPO1 mutations/CNA and their WT counterparts ($p = 0.569$ and $p = 0.588$). A total of 3517 NSCLC patients had available survival data in our entire cohort. Importantly, XPO1 mutations were not associated with OS ($p = 0.412$), and there was a significant negative association between XPO1 CNA and their WT counterparts ($p < 0.001$). In LUAD, arm-level deletion/gain and high amplification of XPO1 were significantly associated with less infiltration levels of B cell, CD4+ T cell and dendritic cell, respectively (all $p < 0.05$). And arm-level deletion of XPO1 was correlated with less CD8+ T cell infiltration ($p = 0.006$). In LUSC, arm-level gain of XPO1 was related with both B cell, CD8+ T cell, CD4+ T cell and dendritic cell ($p < 0.001$; $p = 0.056$; $p < 0.001$ and $p < 0.001$, respectively). In addition, arm-level deletion of XPO1 was associated with CD8+ T cell ($p = 0.037$).

Conclusions: XPO1 CNA was correlated with several immune cell infiltration and significant poor clinical outcomes of NSCLC patients.

Keywords: NSCLC, XPO1, Prognosis

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-022 A Signature of B Cells-Related Gene Pairs Predicts Oncologic Outcomes and Response to Immunotherapy in NSCLC Patients

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Introduction: Tumor-infiltrating B cells accompanying several widely used B cell-related biomarkers, such as CD19 and CD20, have inconsistent clinical prognostic values in non-small-cell lung cancer (NSCLC) patients. Considering only one B cell-related biomarker could not distinguish the anti-tumor and pro-tumor B cell subsets in tumor, we aimed to construct a more accurate B-cells related gene pairs (BRGPs) prognostic model and evaluate its potential predictive ability to immunotherapy in NSCLC patients.

Methods: Using public single-cell RNA sequencing data, the B cells-related genes (BRGs) in NSCLC samples were identified. The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) datasets were utilized to construct the BRGPs model which was not affected by the technical bias of different platforms. With no dependence upon specific gene expression levels, a novel signature based on BRGPs was established in this study. In addition, the prognostic value and immunotherapeutic response for this signature with regard to the TME components and potential molecular mechanism were explored.

Results: Based on the TCGA database, we built a novel prognostic signature of 23 BRGPs comprising 28 unique BRGs. This risk model showed significant power in distinguishing good or poor prognosis and could serve as an independent prognostic factor for NSCLC patients in the TCGA cohort. The prognostic accuracy of the model was further verified in the GSE31210 dataset from the GEO database. Likewise, the prognostic value of the risk score for the BRGPs model was demonstrated in the GEO cohorts by the univariate and multivariate cox regression analysis. In addition, the risk model was significantly associated with sex, TNM stage, immune score, tumor purity and various tumor-infiltrating immune cells. GSEA analysis indicated that low-risk group enriched with several immune-related pathways, such as activation of immune response, antigen receptor mediated signaling pathway, B cell activation and B cell mediated immunity, whereas several proliferation-related pathways, such as nuclear chromosome segregation, sister chromatid segregation and mitotic sister chromatid segregation were most enriched in high-risk group. Besides, the tumor mutational burden (TMB) score rather than CD274(PD-L1 mRNA) expression was positively correlated with the risk score ($P<0.001$; $P = 0.94$, respectively). NSCLC patients with high-risk exhibited significantly higher TMB score compared with low-risk patients ($P < 0.001$). Correspondingly, we demonstrated that immune checkpoint blockade therapy may be more efficacious in high-risk group NSCLC patients according to TIDE method ($P<0.01$).

Conclusions: This novel BRGPs model can assess the prognosis of patients with NSCLC, and may be helpful to guide immune checkpoint inhibitors treatment in our clinical practice.

Keywords: NSCLC, B cells, Signature

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-023 Comprehensive Analysis of a Dendritic Cell Marker Genes Signature to Predict Prognosis and Immunotherapy Response in Lung Adenocarcinoma

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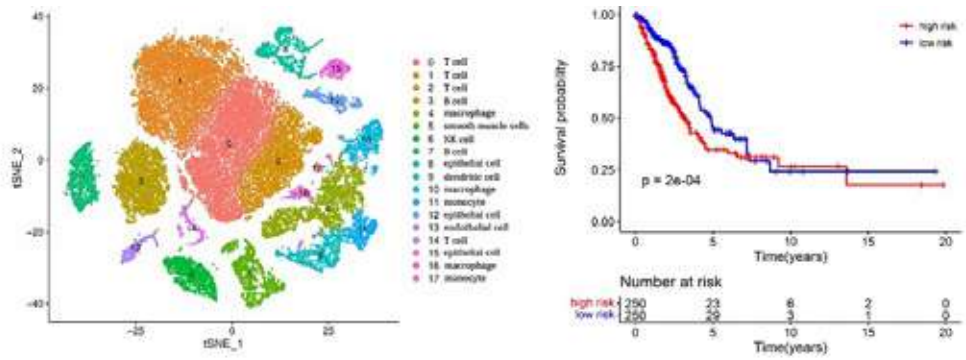
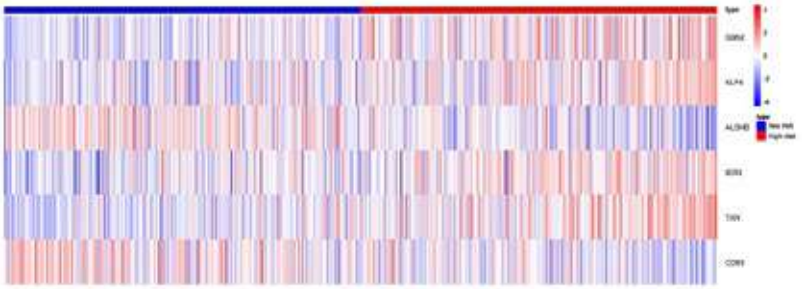
Introduction: With the development of immunotherapy, the treatment of lung adenocarcinoma (LUAD) has gradually stepped into a new stage. Dendritic cells (DCs), a central role in initiating, regulating and maintaining the immune response, exert complicated and important functions in antitumor immunity. This study aims to construct a novel prognostic dendritic cell marker genes signature (DCMGS) for LUAD.

Methods: DC marker genes in LUAD was identified by analysis of single cell RNA sequence data from 11 LUAD samples. DCMGS was constructed on a training cohort from TCGA LUAD dataset. Another six independent cohorts from GEO database were used to validate the predictive ability.

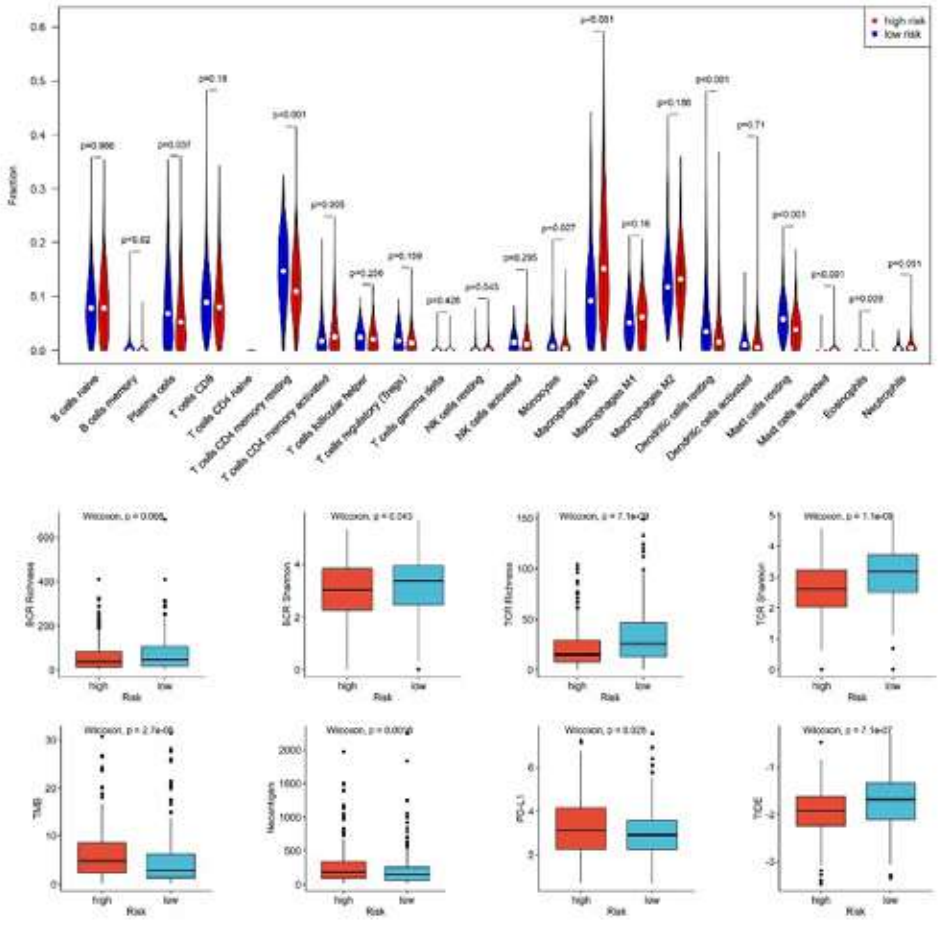
Results: 121 DC marker genes were identified from scRNA-seq data of 11 LUAD samples. Based on these genes, six genes (*G0S2, KLF4, ALDH2, IER3, TXN, CD69*) were screened as the most prognosis-related genes for constructing DCMGS through Cox proportional hazards regression analysis and LASSO analysis. Patients were divided into high- and low-risk groups by DCMGS risk score based on overall survival time. The strong predictive ability of this model for LUAD was validated on another six cohorts. DCMGS was verified to be an independent prognostic factor. Furthermore, we performed pathway enrichment and biological process analysis to explore possible biological mechanism of the powerful predictive ability of DCMGS, and immune cell infiltration landscape and inflammatory activities were exhibited to reflect the immune profile of LUAD with different risk scores. Notably, we linked DCMGS to biomarkers that have been shown to predict immunotherapeutic response, such as TMB, neoantigen load, PD-L1 and TIDE score.

Conclusions: DCMGS was suggested to be a promising prognostic indicator for LUAD and a desirable predictor for immunotherapeutic response, which can serve as an important complement to immunotherapy to further optimize individualized tumor therapy for LUAD patients.





Groups	Hazard Ratio (95% CI)	P value
GSE11969	2.225(1.084-4.566)	0.0250
GSE30219	1.900(1.042-3.463)	0.0320
GSE31210	2.630(1.231-5.617)	0.0094
GSE37745	2.280(1.136-4.575)	0.0170
GSE41271	2.573(1.448-4.570)	0.0008
GSE50081	2.541(1.323-4.882)	0.0038
Overall	2.332(1.783-3.021)	<0.0001



Keywords: Lung adenocarcinoma, Dendritic cell mark genes, Prognostic signature

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-024 Differential Efficacy of Combined GITR Co-stimulation with PD-1 Blockade in Preclinical Non-small Cell Lung Cancer Models

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Introduction: Lung cancer remains as the most lethal cancer disease in Hong Kong. Although blockade of inhibitory immune checkpoints achieved remarkable clinical outcomes, continuous efforts are being made to explore novel therapeutic strategies. We have previously found that anti-programmed cell death protein 1 (anti-PD-1) induced systemic and intra-tumoral upregulation of an immunoregulatory molecule, glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR) in a subcutaneous murine lung cancer model. The anti-cancer effect of combined PD-1 blockade and agonistic anti-GITR warrants further investigation.

Methods: Lewis lung carcinoma cells were inoculated subcutaneously on the flank or orthotopically on the left lung of C57BL/6J mice. Anti-PD-1 or anti-GITR alone, or in combination were administered at day 7 post-inoculation for two weeks. Tumor growth was measured by digital caliper or microCT in the subcutaneous and orthotopic model respectively. Mice under all treatments were sacrificed when the control group reached humane endpoint. Tumor and spleen tissues were harvested and expression of regulatory markers among immune cells were analyzed by flow cytometry.

Results: In the subcutaneous model, anti-cancer effect was evident in anti-GITR and anti-PD-1 combination therapy. Synergistic effect was mostly derived from increased tumor-infiltrating T lymphocytes and systemically rescued T cell population in tumor-bearing mice. Combination therapy also reduced frequencies of CD25+GITRhi T cells in the tumor microenvironment. Interestingly, induction of PD-1 by the single arm anti-GITR was abolished in the combination-treated mice. However, in the orthotopic model, no obvious tumor suppression was observed by the time of sacrifice. Increased frequencies of cytotoxic T lymphocytes were only observed in the non-tumor-bearing right lung and the periphery. Mixed responses of PD-L1 and GITR induction to either anti-GITR or anti-PD-1 lead to an overall non-significant difference in the combination arm.

Conclusions: The differential results obtained from the subcutaneous and orthotopic preclinical models mirror the moderate efficacy of anti-GITR combined with anti-PD-1 in human phase I clinical trials albeit the impressive results reported in other preclinical studies. Our data provides insights for future research directions on combined immunotherapy in NSCLC, emphasizing the potential interactions between T lymphocytes and the tumor microenvironment in the pulmonary niche.

Keywords: Immunotherapy, Preclinical models

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-025 Immune Evolution of Metastases & Underlying Molecular Mechanisms in Non-small Cell Lung Cancer

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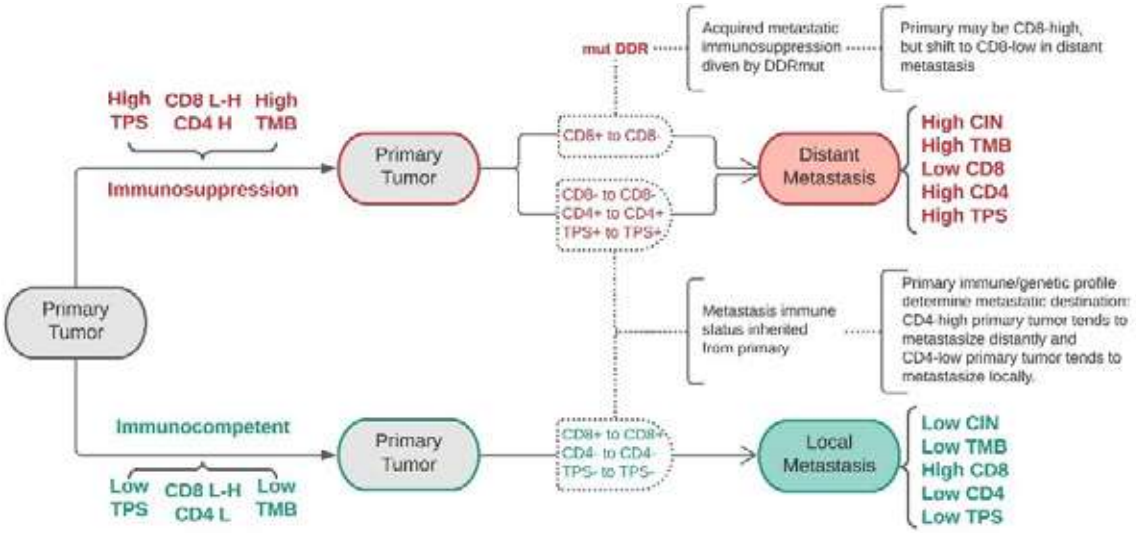
Introduction: Immune profile is a key player for cancer development and metastasis. However, the understanding of the evolution of immune profile from primary non-small cell lung cancers (NSCLC) to metastases and the underlying molecular mechanisms, as well as the difference of immune evolution in local metastasis and distant metastasis is limited so far.

Methods: We performed whole-exome sequencing and immunohistochemistry of CD8, CD4 and PD-L1 for 73 samples including 29 primary, 9 lymph nodes, 9 local (pleural) and 26 distant (brain, bone and adrenal gland) metastases from 41 NSCLC patients. The change of immune profile from primary tumors to metastases and associated genetic factors were analyzed by mutation and copy number alteration analysis, clonal evolution, mutation signature and adaptive selection analysis. The association of genetic and immune background of primary tumors and metastatic destinations were investigated.

Results: DNA damage repair (DDR) deficiency drives distant metastasis rather than local metastasis of NSCLC. Mutations in the DDR pathway underwent positive selection in the metastases. Distant metastases had significantly decreased CD8+ T cell level along with increased chromosomal instability compared with primary tumors which was partially ascribed to the DDR deficiency acquired during metastasis. Local metastases and distant metastases had different immune profiles. Distant metastases were characterized by immunosuppression (low CD8+ T cell level) and immune evasion (high PD-L1 level) whereas local metastases (pleura) were immune-competent with high CD8+ T cell, low CD4+ T cell and low PD-L1 level. The genetic and immune background of primary tumors including tumor mutation burden (TMB), CD4+ T cell level and PD-L1 level was associated with metastatic destinations. Primary tumors with high TMB, high CD4+ T cell and high PD-L1 were associated with distant metastases rather than local metastases. Furthermore, primary tumors with positive CD8 and negative CD4 were associated with a better progression-free survival (PFS). However, patients undergoing CD8 positive-to-negative (primary-to-metastatic tumor) conversion had a worse PFS. A model was put forward to explain the evolution of immune profile from primary to metastasis and the difference between local and distant metastases.

Conclusions: Acquired DDR deficiency is responsible for increased chromosomal instability in distant metastases of NSCLC. CD8 level is negatively correlated with chromosomal instability and decreased in distant metastases. Distant metastases and local metastases had different immune profiles. Immune and genetic background of primary tumors may affect metastatic destinations.



Keywords: metastasis, cancer evolution, tumor immune microenvironment

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-027 MIF ImprovesImmune Microenvironmentof Lewis Lung Cancer Brain Metastases after Radiotherapy ViaReducing M2 Macrophages

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Introduction: Our previous studies showed that inhibition of MIF/CD74 signaling pathway can promote the transformation of intracranial macrophages from M2 to M1 type after radiotherapy activation, and play the role of radiosensitization in brain metastases(BMs). It is reported that M2 macrophages are the main components of tumor immunosuppression microenvironment, and the surface marker, ARG-1, can decompose the Arginine which is essential in the growth and development of T cells. Therefore, this paper will focus on the mechanism of MIF regulating tumor infiltrating lymphocytes (TILs) by inducing macrophage phenotype transformation.

Methods: MIF-Knockdown in Lewis cells were constructed by lentiviral shRNA interference technique. The secretion of MIF in Lewis cell supernatant was detected by ELISA kit. The expression levels of MIF in Lewis and iNOS (M1 type marker), Arg-1 (M2 type marker) in BV2 cells were detected by Western Blotting(WB). The RNA expression levels of M1 and M2 tags were detected by qPCR. The expression of iNOS, Arg-1 and Iba-1 in lung cancer BMs model mice was detected by immunofluorescence staining(IF). The content of arginine in tumor tissue was detected by Arginine kit. The proportion of TILs *in vivo* was measured by flow cytometry. BMs tumor growth in mice was observed by Small Animals Imaging Technology.

Results: In animal experiments, WB, PCR and IF results showed that MIF knockdown (sh-MIF) combined with whole brain irradiation(IR) can raise the expression of iNOS, while the Arg-1 lessend, suggesting that downregulation of MIF can promote M1 phenotype and reduce M2 phenotype. Flow cytometry results showed that sh-MIF combined with IR increased the proportion of CD8+T/CD4+T and CD8+IFN-γ+T/CD4+Foxp3+T cells. Small Animals Imaging results showed that inhibition of MIF enhanced the shrinkage of tumor induced by whole brain irradiation. After clearance of macrophage, Flow cytometry showed no difference between the sh-MIF group and the control group (NC). Small Animals Imaging results also showed that the inhibition of tumor growth by sh-MIF was less significant than macrophages presence. It is indicated that down-regulation of MIF expression combined with irradiation promote T cell infiltration and inhibit tumor may be mediated by macrophages. Arginine kit results showed that the content of arginine increased after IR or sh-MIF, while it increased overall after macrophage clearance, but the difference between each groups was not significant, suggesting that IR or sh-MIF could increase the content of arginine by reducing M2-type macrophages. Flow cytometry and animals imaging results showed that the CD8+/CD4+TILs ratio was increased and tumor growth was inhibited after the addition of exogenous arginine. In conclusion, inhibition of MIF can reduce M2-type macrophages, then increase the content of arginine to improve the proportion of TILs and enhance the killing effect of IR on BMs.

Conclusions: Inhibitory MIF expression can reduce the expression of Arg-1 from M2 type macrophages in BMs, thus raise the content of arginine, promote the infiltration of lymphocytes, improve the immune microenvironment, achieve radiotherapy sensitization finally.

Keywords: Brain metastasis in non-small cell lung cancer, Tumor associated macrophages, MIF/CD74 signal axis

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-028 Immunomodulatory Effects of Cryoablation Combined with Immune Checkpoint Inhibitors in a Murine Lung Cancer Model

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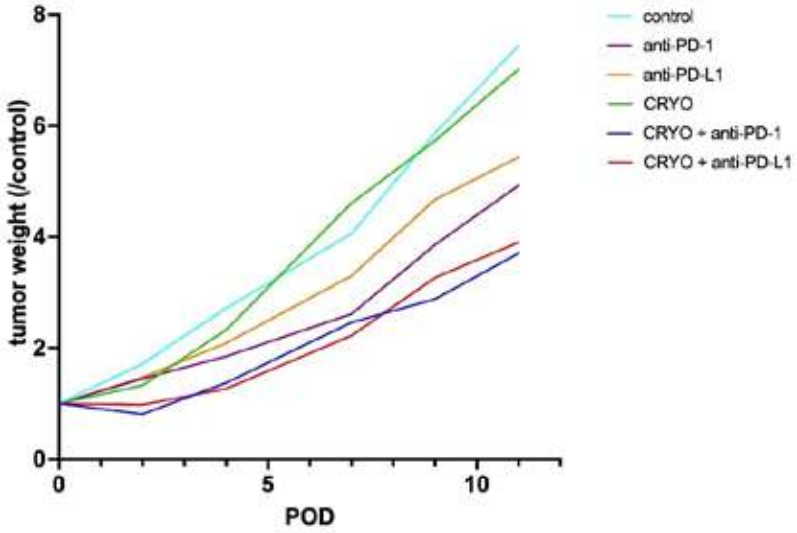
Introduction: As part of our research on cryoablation, a combination with immune checkpoint inhibitors (ICIs), such as inhibitors of the programmed cell death 1 (PD-1) receptor and its ligand, programmed cell death 1-ligand 1 (PD-L1), to disrupt the immunosuppressive tumor microenvironment has proven a beneficial effect on enhancing immune response. We specifically addressed myeloid-derived suppressor cells (MDSCs) and T-cell immunity, which are thought to play an important role in the formation of the tumor microenvironment. We investigated their role in tumor immunomodulation both in the tumor itself and in the tumor surrounding environment when combined with cryoablation and ICIs.

Methods: Wild-type C57BL/6J black mice were used. Subcutaneous tumors were created by injecting CMT167 murine lung cancer cells. When the tumor diameter reached 5 mm, 24 mice were equally divided into the following 6 groups: a) control group, b) PD-1 antibody (anti-PD-1) group, c) PD-L1 antibody (anti-PD-L1) group, d) Cryoablation group, e) Cryoablation+anti-PD-1 group, f) Cryoablation+anti-PD-L1 group. Cryoablation was performed only on the first day of the experiment, and the antibodies were administered intraperitoneally every two days. Body weight and tumor diameters were monitored continuously, and the animals were sacrificed on Day 11. Estimated tumor weight was calculated by tumor diameters. MDSCs and T cells were identified from samples obtained at the time of sacrifice death using flow cytometry to measure cell distribution and PD-L1 expression frequency.

Results: In all groups, the mice survived for 14 days and showed no weight loss. As shown in Figure, no significant difference of tumor growth was shown between Cryoablation group and control. ICI groups showed a suppression of tumor growth, but no significant difference was shown against the control. On the other hand, Cryoablation+ICI groups showed further suppression of tumor growth. Especially, both Cryoablation+anti-PD-1 group and Cryoablation+anti-PD-L1 group showed further suppression of tumor growth, with a significant difference against Cryoablation group on Day 11 ($p=0.047$ and $p=0.049$, respectively). Polymorphonuclear-MDSCs in bone marrow were significantly decreased in the Cryoablation+anti-PD-1 group and Cryoablation+anti-PD-L1 group, compared to Cryoablation group ($p=0.014$ and $p=0.031$, respectively). CD8-positive effector memory T cells in the tumor were increased in Cryoablation+anti-PD-1 and Cryoablation+anti-PD-L1 groups compared to Cryoablation group ($p=0.087$ and $p=0.002$, respectively).

Conclusions: Our findings suggest that the combination of cryoablation and ICI might have synergetic anti-tumor effects, which could be evaluated by monitoring of MDSCs and T-cell immunity.



Keywords: Cryoablation, immune checkpoint inhibitor, MDSC

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-029 Inter-tumor Heterogeneity of PD-L1 Expression in Non-small Cell Lung Cancer

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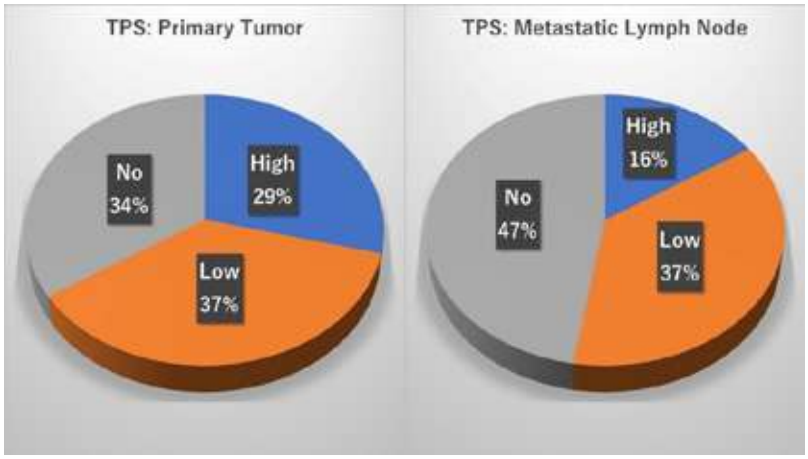
[1]Teikyo University School of Medicine, Tokyo/JP, [2]Saitama Cardiovascular and Respiratory Center, Saitama/JP

Introduction: The Dako PD-L1 immunohistochemistry (IHC) 22C3 pharmDx was approved by the US Food and Drug Administration, as a companion diagnostic test for pembrolizumab (Keytruda, Merk, Kenilworth, NJ, USA) in non-small cell lung cancer (NSCLC). Although increased PD-L1 expression levels can be associated with greater therapeutic efficacy of pembrolizumab, little is known about which tissue (primary or metastatic lesion) should be stained by 22C3 antibody. In this study, we investigated the concordant rate of PD-L1 expression between primary and metastatic lymph node.

Methods: This was a prospective cohort study in single institute. Among surgical cases, patients with pathological nodal positive NSCLC were enrolled into this study. PD-L1 expression was evaluated in tumor tissues from primary tumors and paired metastatic lymph nodes using the 22C3 IHC assays. All samples were surgically resected, formalin-fixed, and paraffin-embedded NSCLC tissues. Tumor cells which membrane exhibited complete or partial staining, were considered as PD-L1 positive. According to tumor proportion score (TPS), all samples were classified as no expression (TPS: <1%), low expression (TPS: 1-49%), or high expression (TPS: ≥50%).

Results: Primary tumors and paired metastatic lymph nodes were resected from 76 patients between August 2016 and April 2021 at Saitama Cardiovascular and Respiratory Center. Average age was 67.2 years old, and there were 49 males (64.5%). The number of patients with lobectomy, wedge resection, and pneumonectomy were 71 (93.4%), 3 (3.9%), and 2 (2.6%), respectively. Lymph node dissection was performed in all cases, and all pathological diagnosis was NSCLC. In histology, adenocarcinoma, squamous cell carcinoma, large cell carcinoma, adenosquamous cell carcinoma, and other histologic types indicated 55 (72.4%), 12 (N=15.8%), 3 (n=3.9%), 2 (n=2.6%), and 4 (n=5.3%), respectively. TPS of primary tumors showed 22 (n=28.9%) in high expression, 28 (n=36.8%) in low expression, and 26 (n=34.2%) in no expression, respectively. On the other hand, TPS of metastatic lymph nodes demonstrated 12 (n=15.8%) in high expression, 28 (n=36.8%) in low expression, and 36 (n=47.4%) in no expression, respectively. The concordance rate was 43.4% between primary tumors and metastatic lymph nodes, including 7 in high, 10 in low, and 16 in no expression.

Conclusions: The inter-tumor heterogeneity of PD-L1 expression in this study suggested that TPS must be an immature biomarker of pembrolizumab for patients with advanced NSCLC. It is an important issue for physicians which tissue should be taken for treatment option, and further study is strongly expected to investigate it.



Keywords: lung cancer, immunotherapy, programmed death-ligand 1

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-030 Peripheral T-Cell Receptor Repertoire Profiling in Non-small Cell Lung Cancer Using an Amplicon-Based Sequencing Assay

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Introduction: Diversity of the T-cell receptor (TCR) repertoire plays essential roles in the adaptive immune response, including against tumor-derived antigens. Within the tumor microenvironment, high TCR clonality is correlated with response to neoadjuvant chemoimmunotherapy in locally advanced non-small cell lung cancer (NSCLC), and an increase in CD8+ T cells recruitment and expansion results via the restoration of MHC I expression, in EGFR tyrosine kinase inhibitor (TKI) treated tumors. Whether peripheral TCR repertoire diversity indexes are similarly correlated with molecular subtypes of cancer and treatment responses has not yet been examined. Here we report the development and utility of a novel amplicon-based TCR sequencing assay to characterize the circulating peripheral TCR repertoire of NSCLC patients.

Methods: A multiplexed molecular-barcoded primer panel targeting the TCR-beta V- and J-genes was designed for nucleic acid-based detection of TCR-beta CDR3 rearrangement of T-cell populations. An in-house analysis pipeline was developed employing error correction to accurately identify the V-gene and J-gene usage and somatic hypermutations in TCR-beta CDR3 sequences. Peripheral TCR repertoire was determined for 92 metastatic NSCLC patients (79 treatment-naïve and 13 treated with first-line TKI) using genomic DNA extracted from peripheral blood (buffy coat). In the matched plasma samples, somatic mutations were characterized in cell-free DNA (cfDNA) using the LiquidHALLMARK assay. The TCR-beta repertoire was analyzed in terms of unique diversity, productive TCR d50 (percentage of unique CDR3 sequences that account for 50% of the total number of sequences observed) and clonality.

Results: The average peripheral TCR repertoire diversity in this dataset was 3997 (+/- 2572) unique clonotypes from 300 ng of buffy coat genomic DNA. Average productive TCR clonality was 0.123 (+/- 0.07) and productive TCR d50 index was 0.162 (+/- 0.08). Among treatment-naive samples, those that were positive for *TP53* mutation in cfDNA (n = 28) had a lower productive d50 index compared to those that were negative (n = 51) (0.143 vs 0.183, $p = 0.06$), in agreement with previous research findings. However, the diversity statistics were not significantly different between patients with (n = 42) and without (n = 37) *EGFR* mutation detected in cfDNA at baseline. Samples from patients treated with first-line TKI compared to treatment-naïve samples, had higher productive TCR clonality (0.155 vs 0.118, $p = 0.07$) and lower productive TCR d50 index (0.882 vs 0.831, $p = 0.02$), suggesting clonal expansion following treatment with TKI. Among EGFR-positive patients treated with first-line TKI, higher productive clonality was found in non-responsive patients (n = 6), compared to responsive patients (n = 7) but this was not statistically significant ($p = 0.28$), indicative of a lack of increase in diversity being associated with reduced response to treatment.

Conclusions: Our preliminary data demonstrates the differences in peripheral TCR repertoires by molecular subtypes of NSCLC, and treatment status. Compared to tumor infiltrating TCR repertoires, the determination of peripheral TCR repertoires can be done non-invasively and serially. The TCR sequencing method can complement plasma-based cfDNA sequencing through serial testing which provides insights into clonal diversity evolution and patient's immunological status.

Keywords: Immune repertoire, TCR-sequencing, clonality

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-031 Association Between Programmed Death Ligand-1 (PD-L1) Expression and Clinicopathological Features in Non-small Cell Lung Cancer (NSCLC)

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Introduction: Determinantion of PD-L1 has an important role in the management of NSCLC. However, data on incidence and prognostic role of PD-L1 expression in NSCLC tumor cells and its correlation with clinicopathological characteristics such as stage, histology, gender or smoking status are conflicting.

Methods: An observational, retrospective and single-center study was carried out in 274 patients diagnosed with localized disease (LD: stage I-III) or advanced disease (AD: IV) NSCLC between 2014 and 2020. The main objective was to analyze the expression of PD-L1 depending on the gender, smoking status, histology or stage disease. The secondary objective was to analyze the prognostic role of PD-L1 in terms of Disease-Free Survival (DFS), Progression Free Survival (PFS) and Overall Survival (OS).

Results: Statistically significant relationships between positive determination of PD-L1 and males, and negative determination of PD-L1 and females were found (p 0.03). There were not statistically significant relationships between PD-L1 and the smoking status, with a tendency to be negative in never-smokers, and positive in ever-smokers (p 0.086). No statistically significant relationship were found between PD-L1 expression and NSCLC histology (p 0.992) or stage disease (p 0.631). In LD, patients with PD-L1 expression had a median DFS of 17.3 months (95% CI 6.9-60.2) vs 23.3 months (95% CI 17.5-29.2) in those without PD-L1 expression (p 0.181) and an OS of 40.6 months (95% CI 21.1-60.3) vs 57.8 months (95% CI 45.7-69.9) respectively (p 0.243). In AD, patients with PD-L1 expression had a median PFS of 10.1 months (CI 95% 4.8-9.2) vs 10.2 months (95% CI 5.9-8.1) in those without PD-L1 expression (p 0.704) and an OS of 12.7 (95% CI 8.6-16.7) vs 11.3 (95% CI 5.9-16.6) months respectively (p 0.821).

Conclusions: In this retrospective analysis no differences in PD-L1 expression by stage disease and histology were observed. Nevertheless, a statistically significant relationship between PD-L1 expression and males as well as a trend with smokers status were observed. Patients with LD and expression of PD-L1 had a tendency to lower survival, suggesting a potential role of adjuvant anti PD-1/PD-L1.

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-032 Guiding Monotherapy with Docetaxel or Atezolizumab via the Tumour Mutation Index in Non-small Cell Lung Cancer Patients

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Introduction: Circulating tumour DNA (ctDNA)-based sequencing might provide a simple test for the genomic profile of non-small cell lung cancer (NSCLC) without the necessity of tissue biopsy. We aimed to assess the ctDNA sequencing-based tumour mutation index (TMI) model for screening responders (from non-responders) who received monotherapy with docetaxel or atezolizumab.

Methods: We performed a retrospective analysis of the POPLAR (NCT01903993) and OAK (NCT02008227) trials. ctDNA sequencing was performed on the blood samples at baseline from all enrolled NSCLC patients (n = 1137), including those from the OAK and POPLAR trials. For patients who passed quality control (QC), we identified three biomarkers, blood tumour mutation burden (bTMB), sensitive blood tumour mutation burden (sbTMB) and unfavourable mutation score (UMS), of the ctDNA profiles. After integrating the advantages and disadvantages of the three independent biomarkers, we developed the TMI model and identified NSCLC patients who may benefit from monotherapy with docetaxel or atezolizumab in terms of overall survival (OS).

Results: The TMI model as a stratified biomarker for docetaxel responders provided a median OS duration of 5.55 months longer than non-responders in the OAK cohort (median OS: 11.86 months vs 6.31 months, P < 0.0001), with a significantly decreased hazard ratio (HR= 0.51, 95% CI 0.39-0.66). Moreover, atezolizumab responders had a 10.21-month OS advantage over atezolizumab non-responders in the OAK cohort via TMI stratification (median OS: 18.10 months vs 7.89 months, P < 0.0001), and the HR was also decreased significantly (HR= 0.49, 95% CI 0.37-0.64). The TMI demonstrated effectiveness for stratifying responders in the POPLAR cohort (docetaxel: median OS: 11.89 months vs 6.70 months, P = 0.0009, HR= 0.47, 95% CI 0.30-0.73; atezolizumab: median OS: 15.77 months vs 7.38 months, P = 0.0024, HR= 0.46, 95% CI 0.27-0.76). Importantly, we found that the TMI model could screen additional responders upon combining the cohorts from the POPLAR and OAK trials after adjustment (docetaxel: median OS: 12.48 months vs 5.98 months, P < 0.0001, HR= 0.41, 95% CI 0.32-0.51; atezolizumab: median OS: 18.56 months vs 7.10 months, P < 0.0001, HR= 0.39, 95% CI 0.30-0.49).

Conclusions: Blood-based ctDNA sequencing offers simple, rapid tumour genomic profiling that provides screening for mutation-related therapeutic regimens for patients with NSCLC, with sufficient validity for clinical practice. Our study provides a novel TMI model for screening responders (from non-responders) among NSCLC patients who received the 2nd-line monotherapy with docetaxel or atezolizumab, and we believe that the biomarker TMI could be effective for the clinical treatment of NSCLC in the future.

Keywords: Precision therapy, Circulating tumour DNA, Tumour mutation index

EP16.01 TUMOR BIOLOGY AND BIOMARKERS - IMMUNE BIOLOGY & IMMUNOTHERAPY

EP16.01-033 Characterisation of T Cell Receptor Repertoire in Non-small Cell Lung Cancer Patients Treated with Immunotherapy

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Introduction: Non-small cell lung cancer (NSCLC) therapy has experienced important changes in survival benefit and durable anti-tumor responses due to immune checkpoint blockers (ICBs). However, ICBs show some major limitations including low response rate and drug resistance in unselected patients. Despite the development of new predictive biomarkers, such as PD-L1 expression, microsatellite instability (MSI), or tumor mutation burden (TMB), there is an urgent need for biomarkers that identify which patients will benefit more from ICBs and define the reasons for failure of the treatment. Analysis of peripheral blood T cell receptor beta chain (TCR-ß) repertoire and other serum biomarkers may provide information about the immune response in ICBs treated NSCLC patients.

Methods: Between April 2019 and October 2020 and with a minimum of one-year follow-up, a total of 55 unresectable locally advanced and advanced NSCLC patients treated with ICBs were enrolled. For all patients, demographic, clinicopathological characteristics and variables related to immune-mediated toxicity were collected. Written informed consents were provided. TCR-ß analysis was carried out in 44 peripheral blood samples pretreatment and complementarity determining region (CDR3) sequencing was performed using Ion Torrent Oncomine assay (Thermo Fisher Scientific). 11 samples could not be used for TCR-ß analysis due to insufficient sample or lack of RNA integrity.

Results: 55 patients were included. The majority were males (70.9%) and smokers (96.4%), ECOG 0 (65.5%) with a median age of 65 years. The most frequent histology was adenocarcinoma (60%), being stage IV 70.9% of all lung cancer included and the main indication for treatment with ICBs was palliative in pretreated patients. PD-L1 was >=50% in 34% of patients. The ORR was 63.6% (35/55), with a mean time from the start of ICBs to the response of 2.74 months (SD 2.59) and 16 patients presented durable clinical benefit. 45.5% patients presented immune-mediated toxicity. The median duration of follow-up was one year and 41.8% (23/55) were alive at the time of data cut-off with a median overall survival of 19 months (CI: 11.13-26.87). Regarding descriptive data of the TCR-ß features, the mean of shanon diversity pretreatment was 10.7 (SD 2.56), TCR-ß evenness 0´77 (SD 0´14) and the mean of TCR-ß convergence was 0´01 (SD 0´01) in the 44 peripheral blood samples analyzed.

Conclusions: TCR-ß repertoire has emerged as a novel prognostic and predictive biomarker of response to ICB therapy. This study provides a detailed descriptive analysis of pretreatment peripheral blood TCR-ß features and cytokines involved in the immune response. Nevertheless, a combination of biomarkers may be the optimal tool to predict ICBs efficacy in lung cancer patients.

Keywords: LUNG CANCER, BIOMARKER, T-CELL RECEPTOR

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-001 Integration of Primer Exchange Reaction and DNAzyme for Electrochemical Detection of PD-L1-Expressing Exosomes in Lung Cancer

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Introduction: Lung cancer is the most common malignant diseases and the leading cause of cancer-related deaths worldwide. To date, PD-L1-expressing exosomes, containing abundant tumor-related biological substances, have attracted great interest as a kind of tumor-specific biomarkers in liquid biopsy of lung cancer. Also,exosome PD-L1 has been reported to contribute to tumour immune evasion, and the potential role of its level in predicting immunotherapeutic efficacy has raised concerns but remains unclear.

Methods: In this work, we propose an electrochemical method integrating primer exchange reaction (PER) with RNA-cleaving DNAzyme, which shows high sensitivity and specificity for analyzing PD-L1-expressing exosomes in lung cancer. Specifically, target exosome is first captured by PD-L1 antibody-functionalized magnetic beads, and then recruits cholesterol-modified hairpin template via hydrophobic interaction. After magnetic separation, the hairpin template participates in the PER as a catalytic hairpin, triggering the synthesis of single-stranded DNA in a programmable manner. The synthesized DNA can act as a RNA-cleaving DNAzyme, and thus is able to turn on the cleavage of methylene blue-labeled signal strands. As a result, a large amount of methylene blue-labeled short fragments are produced, which finally arouse a significantly amplified electrochemical signal for the analysis of PD-L1-expressing exosome.

Results: The method allows sensitive detection of target exosomes in a wide linear range from 10^3 particles/mL to 10^8 particles/mL with a detection limit of 672 particles/mL.The electrochemical method is also used to determine the personalization level of PD-L1-expressing exosome in clinical samples from patients with non-small cell lung cancer. The same low peak currents as the background are observed in serum samples from healthy donors, while enhanced peak currents are observed in samples from patients. In addition, the enhancement of peak current is positively correlated with lung cancer progression and poor prognosis.

Conclusions: Through the application in the clinical samples, the method is proved to distinguish lung cancer patients from healthy people, but also realize the tumor staging regarding the disease progression. Therefore, our method may have a potential use in screening of lung cancer patients and monitoring of the progression of the disease.

Keywords: PD-L1-expressing exosome, lung cancer, electrochemical method

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-002 Circulating Tumor DNA (ctDNA) Changes in Patients with Lung Cancer from a Real-World Prospective Clinico-Genomic (PCG) Study

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Introduction: The impact of different treatments on ctDNA changes are poorly understood. The real-world PCG study provides an opportunity to study ctDNA in patients with lung cancer receiving treatment. We report preliminary results on associations between ctDNA and real-world response (rwR) by treatment, providing insights on the impact of therapies on ctDNA changes and its usage for response assessment.

Methods: As of 9/30/2021, 944 patients were enrolled. Patients with metastatic NSCLC or extensive-stage SCLC who initiated 1L or 2L systemic antineoplastic treatment in the Flatiron Health Research Network were investigated. Following consent, data were collected from electronic health records, including clinician assessment of disease burden change (real-world response [rwR]; cutoff 12/1/2021). ctDNA was analyzed using FoundationOne®Liquid at enrollment, and ≥1 of either on-treatment (±14 days of first tumor assessment) or end of therapy. ctDNA levels were estimated using tumor fraction (TF), an aneuploidy- and variant allele fraction-based method. Patients had ≥1 rwR assessments which were used to categorize patients as rw-responders (ever rw-partial or -complete response) or rw-non-responders (only rw-stable or -progressive disease). Therapies were chemotherapy, cancer immunotherapy (CIT), CIT+chemotherapy or other therapies (not including tyrosine kinase inhibitors alone). Progression hazard ratio was estimated using Cox proportional hazards regression.

Results: Median baseline TF was 2.2% (IQR 0.6%-9.5%) among 385 patients with NSCLC and 42.8% (19.5%-65.4%) among 90 patients with SCLC. Baseline TF was similar across treatments in NSCLC (P=0.8) and SCLC (P=0.9) (data not shown). More NSCLC rw-responders had a decrease of ≥50% in TF from baseline than rw-non-responders (P=0.002; Table). For patients with NSCLC receiving chemotherapy, a greater proportion had a TF decline of >50% and a lower proportion had a TF increase than patients receiving CIT (alone or combination). We observed a significant difference in TF change by rwR among patients with NSCLC receiving CIT alone (P=0.018), but not for chemotherapy or CIT combination (P=0.62, P=0.073 respectively). Compared with patients with NSCLC whose TF was undetectable at both time points, declined, or was stable, patients whose TF increased had nominally higher risk of disease progression (HR=1.54, 1.70, 1.92 across treatments).

Conclusions: Rw-responder patients with NSCLC had greater decreases in TF versus rw-non-responders. ctDNA increase was associated with higher risk for progression. We also observed different associations between ctDNA changes and rwR by treatments in patients with NSCLC. Our results indicated that ctDNA response may complement rwR in assessing patients' outcomes, however treatment may affect interpretation of ctDNA response.

Table. Change in TF from baseline to treatment

	NSCLC				SCLC			
Group	**Overall**	**rwR No**	**rwR Yes**	***P*-value***	**Overall**	**rwR No**	**rwR Yes**	***P*-value***
N	284	108	176		67	11	56	
TF change, N (%)				<0.001				0.06
TF undetectable at both	88 (31.0%)	30 (27.8%)	58 (33.0%)	0.36	3 (4.5%)	1 (9.1%)	2 (3.6%)	0.42
TF declined by >50%	101 (35.6%)	26 (24.1%)	75 (42.6%)	0.002	52 (77.6%)	6 (54.5%)	46 (82.1%)	0.11
TF declined by 0-50%	29 (10.2%)	13 (12.0%)	16 (9.1%)	0.43	7 (10.4%)	3 (27.3%)	4 (7.1%)	0.08
TF increased	66 (23.2%)	39 (36.1%)	27 (15.3%)	<0.001	5 (7.5%)	1 (9.1%)	4 (7.1%)	1.0
Chemotherapy	**Overall**	**rwR No**	**rwR Yes**	***P*-value†**				
N	**143**	**45**	**98**					
TF change, N (%)				0.62				
TF undetectable at both	50 (35.0%)	16 (35.6%)	34 (34.7%)	0.92				
TF declined by >50%	59 (41.3%)	16 (35.6%)	43 (43.9%)	0.35				
TF declined by 0-50%	7 (4.9%)	2 (4.4%)	5 (5.1%)	1.0				
TF increased	27 (18.9%)	11 (24.4%)	16 (16.3%)	0.25				
HR for progression comparing TF increased to TF undetectable at both, declined, or stable (95%CI)	1.54 (0.94, 2.51)	-	-	-				
CIT alone	**Overall**	**rwR No**	**rwR Yes**	***P*-value†**				
N	**59**	**25**	**34**					
TF change, N (%)				0.018				
TF undetectable at both	15 (25.4%)	7 (28.0%)	8 (23.5%)	0.70				
TF declined by >50%	15 (25.4%)	2 (8.0%)	13 (38.2%)	0.008				
TF declined by 0-50%	11 (18.6%)	4 (16.0%)	7 (20.6%)	0.75				
TF increased	18 (30.5%)	12 (48.0%)	6 (17.6%)	0.012				
HR for progression comparing TF increased to TF undetectable at both, declined, or stable (95%CI)	1.74 (0.88, 3.44)	-	-	-				
CIT combination	**Overall**	**rwR No**	**rwR Yes**	***P*-value†**				
N	**62**	**32**	**30**					
TF change, N (%)				0.073				
TF undetectable at both	16 (25.8%)	5 (15.6%)	11 (36.7%)	0.06				
TF declined by >50%	19 (30.6%)	8 (25.0%)	11 (36.7%)	0.32				
TF declined by 0-50%	10 (16.1%)	7 (21.9%)	3 (10.0%)	0.30				
TF increased	17 (27.4%)	12 (37.5%)	5 (16.7%)	0.07				
HR for progression comparing TF increased to TF undetectable at both, declined, or stable (95%CI)	1.92 (1.04, 3.55)	-	-	-				

*P-values were calculated using Pearson's Chi-square tests for NSCLC and Fisher's exact test for SCLC. Undetectable was defined as TF <1%. †Welch two sample t-test.

Keywords: ctDNA, NSCLC, response

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-003 Real World Experience and Feasibility of Tissue Informed CGP and ctDNA Testing in a Cohort of NSCLC Patients

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Introduction: Circulating tumor DNA (ctDNA) analysis is a promising approach for treatment response monitoring in patients with NSCLC. Additionally, comprehensive genomic profiling (CGP) is playing an integral role in the optimal management of this disease across stages. In this study, we analyzed patients with stage I-IV NSCLC who underwent serial monitoring with a personalized, tumor-informed ctDNA assay with or without concomitant CGP, with a focus on real-world feasibility and clinical utility.

Methods: A total of 267 plasma samples from 33 patients with stage I-IV NSCLC were processed for ctDNA detection as part of commercial testing using a personalized, tumor-informed ctDNA assay (Signatera™, bespoke mPCR-NGS). A subset of these patients also underwent CGP testing (Altera™) with complete exome and RNA transcriptome coverage, as well as tumor mutational burden (TMB) and microsatellite (MSI) analysis. The same tissue sample was used for the design of both assays in applicable patients. Analysis utilizing ctDNA results were compared to treatment modality dates, and clinical outcomes were assessed.

Results: ctDNA assay was successfully designed for all patients (n=33) either using resected tissue, core needle biopsies (CNB), EBUS-FNA specimens or resected/biopsied metastatic foci. Concomitant CGP, RNA transcriptome analysis, TMB, and MSI status evaluation were carried out in 18 patients. All 18 patients showed mutations that were candidates for potential clinical trial enrollment, 4 had targetable mutations and 3 had intermediate-high TMB status. Of the 33 patients, 8 patients had a pre-treatment time point available, of which 6 (75%) were ctDNA-positive. Twenty-one patients had a post-treatment time point collected while clinically no evidence of disease (NED). Of the 21, only 1 (5%) patient was found to be ctDNA-positive. This patient failed to clear ctDNA on adjuvant therapy and recurred 145 days following the initial positive test. No recurrences were observed in ctDNA-negative (n=20) patients (median follow-up 16.2 months, range 4.3 to 52.1 months). In patients (n=12) who began ctDNA testing in the presence of active disease, 83% (10/12) of patients had an initial positive ctDNA test result. Longitudinal ctDNA dynamics in this group were reflective of clinical response to treatment and offered a lead time advantage over imaging alone.

Conclusions: Our study shows the feasibility of performing CGP and ctDNA testing using a single source of tissue in patients with NSCLC. CGP allowed for the identification of patients who may derive benefit from targeted therapies and ICIs, while also informing appropriate clinical trials. ctDNA analysis was congruent with clinical findings, and ctDNA dynamics were indicative of response to therapy. Further studies evaluating a single source dual CGP and ctDNA approach for adjuvant decision making, surveillance monitoring, and personalization of systemic regimens in NSCLC are warranted.

Keywords: Circulating tumor DNA (ctDNA), comprehensive genomic profiling (CGP), NSCLC

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-004 Clinical Significance and Genomic Characteristics of CD56+ Circulating Tumor Cells in Small Cell Lung Carcinoma

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Introduction: Circulating Tumor Cells (CTC) have been studied in various solid tumors. However, clinical utility of CTC in Small Cell Lung Cancer (SCLC) remains poorly understood. Most published studies are based on Cellsearch® isolation methods that did not capture CTC undergoing epithelial-mesenchymal transition. The aim of the CTC-CPC study was to develop an EpCAM-independent CTC isolation method allowing isolation of living CTC from SCLC and decipher their genomic characteristics.

Methods: We conducted a monocentric prospective non-interventional study (CTC-CPC) from April 2016 to April 2021, including newly diagnosed treatment-naïve SCLC. CD56+CTC were isolated from whole blood samples using an immunofluorescence-based method, at diagnosis and relapse after first-line treatment. Whole-exome-sequencing (WES) was performed on isolated CTC, matched PBMC and tumor biopsies for genomic characterization. In addition, CTC Derived Xenografts (CDXs) were generated and submitted to RNA-sequencing for sub-type classification (ASCL1, POU2F3, YAP1, NEUROD1).

Results: On the 46 patients eligible for the study, numeration of CD56+CTC was performed for 33 patients at diagnosis. Phenotypic study confirms tumor lineage and tumorigenic properties of isolated cells for the 4 patients analyzed with WES. Notably, CDX model derived from CD56+CTC was successfully classified with an ASCL1 transcriptomic profile. WES of CD56+CTC and matched tumor biopsy reveal common genomic alteration and biological pathway frequently impaired in SCLC. Moreover, CD56+CTC are characterized by a high mutation load and a unique mutational signature. High numeration of CD56+CTC (>7/mL) at diagnosis was associated with ES-SCLC but not with clinical outcomes after first-line treatment. Finally, comparing genomic features of diagnosis and relapse CD56+CTC, we identify commonly altered oncogenic pathways (e.g. DLL3 or MAPK pathway) that are currently investigated in targeted therapy trials.

Conclusions: We report a versatile and easy-to-use method of CD56+CTC detection for newly diagnosed SCLC. Isolated CD56+CTC conserve tumorigenic properties and can be used for further biological application. Numeration of CD56+CTC at diagnosis is correlated with disease extension but not prognosis. Finally, genomic analysis suggests that studying CD56+CTC at relapse might help to identify oncologic pathways that seeds tumor resistance to first-line treatment.

Keywords: circulating tumor cell, small cell lung cancer, CD56

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-005 Liquid Biopsy Detects Genomic Drivers in Non-small Cell Lung Cancer without EGFR Mutations by Single-plex Testing: WJOG13620L

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Introduction: Nearly 70% of all patients with advanced nonsquamous non-small cell lung cancer (NSCLC) in Japan have actionable genomic alterations, with the vast majority being epidermal growth factor receptor (*EGFR*) mutations. Standard testing typically relies on rapid *EGFR* evaluation in tumor tissues using single-plex testing, which is often combined with *ALK* and *ROS1* fusion analysis. When employing this approach, a driver alteration can be missed due to improper sample quality or quantity or the presence of rare alterations that are not usually analyzed. In cases where single-plex tissue testing fails to detect a driver mutation, a comprehensive liquid biopsy may be used to identify actionable alterations prior to initiating first-line treatment. We conducted a prospective observational study (WJOG13620L) to determine whether a plasma-based next-generation sequencing assay (Guardant360) can detect clinically relevant alterations in circulating tumor DNA from patients with advanced nonsquamous NSCLC who had been tested for at least *EGFR* alterations by single-plex gene analysis and were negative for any driver mutations.

Methods: Patients from 24 Japanese institutions were eligible for this study if they had histologically confirmed stage IIIB-IV or relapsed, untreated nonsquamous NSCLC. Tumor tissues were tested for at least *EGFR* mutations using single-plex gene analysis and found to be negative for any driver mutations. Patients whose samples had undergone comprehensive genomic profiling were excluded. Whole blood was analyzed by Guardant360 (Guardant Health, Redwood City, CA). The primary outcome was the percentage of samples with a pathogenic alteration in at least one of the following genes: *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET*, *ERBB2*, *KRAS*, or *NTRK1*. The clinical data were collected for 6 months after study enrollment. A sample size of 72 was calculated using a binomial test ($\alpha = 0.05$, $\beta = 0.20$, H0 = 0.10, and H1= 0.25), with a case missing rate of 10%.

Results: Between November 2020 and May 2021, 72 patients were enrolled in this study. *ALK* and *ROS1* fusions were tested in 86.1% and 66.7% of patients, respectively, while other mutations were infrequently tested. Comprehensive genomic alterations were detected in 21 patients (29.2%; 95% confidence interval: 19.0-41.1, $p < 0.001$), including 11 *KRAS* mutations (2 G12C), 5 *EGFR* mutations, 3 *ERBB2* mutations, 1 *BRAF* V600E mutation, and 1 *RET* fusion. The median time interval between sample submission and getting results was 8 days (range: 5-17). Re-analysis of tumor tissues from two patients with Guardant360-detected mutations (*EGFR* L858R and *BRAF* V600E) validated the liquid biopsy findings. Two patients received targeted therapy based on their Guardant360 results.

Conclusions: After negative single-plex *EGFR* testing results, Guardant360 follow-up testing detected previously unknown driver alterations in 29.2% of patients with untreated advanced nonsquamous NSCLC. The results were accessible within a reasonable timeframe. Thus, follow-up testing with Guardant360 might be an option prior to initiating first-line treatment for advanced nonsquamous NSCLC in settings where no tissue is available or no mutations are detected after single-plex tissue testing.

Keywords: non-small cell lung cancer, genomic alterations, plasma-based next-generation sequencing assay

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-006 Evaluation of Carcinoembryonic Antigen (CEA) as Predictive Marker in Patients with Metastatic Non-small Cell Lung Cancer

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Introduction: Serum carcinoembryonic antigen (CEA) has been evaluated in several studies as a prognostic marker in patients with non-small cell lung cancer (NSCLC). Studies evaluating its predictive role in terms of response to systemic therapy in advanced NSCLC particularly in the Indian population are scarce.

Methods: In this prospective single center study 122 patients with metastatic NSCLC (Stage IVA and IVB) with an elevated serum CEA level (>10 ng/mL) at baseline, starting treatment between January 1 and December 31, 2020 were included. CEA levels were repeated after treatment with 4 cycles of platinum-based chemotherapy (69.7%) or 3 months of targeted therapy (30.3%) with EGFR (22.9%) or ALK (7.4%) tyrosine kinase inhibitors. The association of change in serum CEA levels with radiologic response (measured by RECIST 1.1) and survival were assessed.

Results: The patients who achieved an objective response (OR, 64%) had a median reduction of CEA levels by 68.4% (95% confidence interval [CI] 53.1-67.4) compared to pre-treatment levels. The area under the ROC curve (AURC) for OR was 0.872 (95% CI 0.79-0.95), with a sensitivity and specificity of 81.4% and 80%, respectively, for a CEA decline of ≥20%. Patients who had a CEA decline of ≥20% achieved an OR (1.6% complete response and 87.5% partial response [PR]) in 89%, stable disease (SD) in 9.3%, and progressive disease (PD) in 1.6% of cases, while patients with a CEA decline <20% had an OR in 35.1%, SD in 13.5% and PD in 51.4% ($p < 0.001$) of cases. Patients with PD (21.6%) had a median increase of CEA levels by 37.1% (95% CI 20.5-66.1) relative to baseline. The AURC for progressive disease was 0.944 (95% CI 0.89-0.99), with sensitivity and specificity of 75% and 96.3%, respectively, for a CEA increase of ≥10%. Progression-free survival (PFS) was longer in the patients with a ≥20% decline in CEA (16.8 vs. 5.1 months, hazard ratio [HR] 0.33 [95% CI 0.19-0.56]; $p < 0.001$). CEA decline ≥20% was associated with better overall survival (OS) (HR 0.34 [95% CI 0.12-0.91], $p = 0.32$).

Conclusions: Change in serum CEA level is a sensitive and specific marker of response as well as progression on systemic therapy in patients with metastatic NSCLC who had an elevated CEA at baseline. A decline in CEA levels by 20% or more is associated with a longer PFS and OS.

Keywords: CEA, Predictive Marker, Advanced NSCLC

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-007 Detection of Clinically Relevant Fusions and Exon Skipping Alterations in Non Small Cell Lung Cancer Patients Liquid Biopsies

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Introduction: The availability of tumor tissue is compromised in a significant number of NSCLC patients due to surgical complications or difficult access to the cancer lesion. Gene fusions and exon skipping testing using liquid biopsies, although challenging, can facilitate the detection of NSCLC patients harboring these aberrations. nCounter and Digital PCR (dPCR) have been adapted to detect fusions and skipping variants in FFPE tumor biopsies. In this study, we aim to validate these techniques for circulating cell free RNA (cfRNA) and RNA contained in extracellular vesicles (EV-RNA) isolated from plasma and other body fluids.

Methods: 15 plasma, 2 cerebrospinal fluid and 3 pleural fluid samples from fusion/exon skipping-positive NSCLC patients in FFPE biopsies have been analyzed. cfRNA was isolated from 17 patients using Qiasymphony automatic extraction method. In the remaining three cases, EV-RNA was isolated from plasma by sequential centrifugation followed by exoRNeasy® Serum/Plasma Maxi Kit. The 20 RNA samples were quantified using Qubit and subsequently analyzed by nCounter (NanoString Technologies), using a customized panel for *ALK, RET* and *ROS1* fusion transcripts and *MET* exon 14 skipping, and dPCR, with the QuantStudio® 3D Digital PCR System and specific TaqMan® assays for *ALK*, *RET, ROS1* and *MET*.

Results: 19 RNA samples yielded valid results by the nCounter (95%). Regarding dPCR, the genomic rearrangement or exon skipping was confirmed in 13 of the 20 liquid biopsy samples positive (65%). Considering the nCounter as the non-reference standard, the positive percentage agreement (PPA) for dPCR was 68.42%. Remarkably, the type of fusion detected in tumor samples (N=18) was always coincident with the fusion detected in the liquid biopsy sample. Discordant cases positive by nCounter but negative by dPCR correspond to patients that harbor *KIF5B*(17)-*ALK*(20) (N = 1), *EML4*(13)-*ALK*(20) (N=2), and *CD74*(6)-*ROS1*(32) (N = 3) fusions.

Conclusions: Our results demonstrate the feasibility of fusion and exon skipping analysis in cfRNA and EV-RNA from body fluids of advanced cancer patients using nCounter and Digital PCR.

GENOMIC ALTERATION	nCounter	dPCR
EML4(13)-ALK(20) (N = 4)	4	2
EML4(20)-ALK(20) (N = 1)	1	1
EML4(6a/b)-ALK(20) (N = 2)	1	1
EML4(18)-ALK(20) (N = 1)	1	1
KIF5B(17)-ALK(20) (N = 1)	1	0
KIF5B(15)-RET(12) (N = 3)	3	3
CCDC6(1)-RET(12) (N = 2)	2	2
CD74(6)-ROS1(32) (N = 3)	3	0
SCL34A2(4)-ROS1(32) (N = 1)	1	1
MET 14 exon skipping (N = 2)	2	2
TOTAL (N = 20)	19 (95%)	13 (65%)

Keywords: Liquid Biopsy, NSCLC, Gene fusions

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-008 Cerebrospinal Fluid as a Liquid Biopsy for Molecular Characterization of Brain Metastases in Patients with Non-small Cell Lung Cancer

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Introduction: Non-small cell lung cancer (NSCLC) with brain metastases (BM) is a challenging clinical issue with poor prognosis. Studies conducted with paired molecular analyses of BM and primary tumors have revealed clonal evolution and substantial differences in gene expression. No data exist regarding extensive molecular analysis of cerebrospinal fluid (CSF) and its correlation to different compartments.

Methods: We designed a novel study consisting of 5 NSCLC patients with available tumor material from 4 compartments; primary tumor, BM, plasma and CSF. An enrichment-based targeted next-generation sequencing panel (consisting of 153 genes) combining analysis of both ctDNA and exosomal RNA in CSF was performed and compared with the other 3 compartments.

Results: An average of 105 million reads per sample was generated with fractions of mapped reads exceeding 99% in all samples. All samples displayed a mean coverage of at least 10,000x with individual samples exceeding 50,000x. The vast majority of all reads were on target. The detection of variants with low mutant allele frequency (MAF) down to 1% was feasible. A high degree of overlap in variants between the primary lung tumor and the brain metastasis was observed, whereas biofluid comparison of plasma versus CSF revealed poor variant overlap. Variants specific for the BM/CSF compartment included in frame deletions in *AR*, *FGF10* and *TSC1* as well as missense mutations in *HNF1a*, *CD79B*, *BCL2*, *MYC, TSC2*, *TET2, NRG1, MSH3, NOTCH3, VHL and EGFR.* BM specific variants were commonly represented by phosphorylation-site mutations (*MYC, HNF1a, TSC1, VHL*).

Conclusions: Our novel approach of combining ctDNA and exosomal RNA analyses in the CSF seems to be a sufficient surrogate for BM biopsy. The specific mutations that were only observed in the CNS compartments could serve as potential targets for individually tailored therapies in NSCLC patients with BM and poor response to existing treatments.

Keywords: cerebrospinal fluid, brain metastases;, exosome analysis

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-009 Psychobiological Stress Responses to a Lung Cancer Diagnosis

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Introduction: A diagnostic work-up leading to a cancer diagnosis is a severely stressful experience as illustrated in the dramatic rise in distress, suicide, and cardiovascular deaths after diagnosis. Data are scarce on the underlying interaction between the psychological and biological components of stress during this critical time window. The aim of this study was to assess pre- to post diagnosis change in symptoms of psychological distress and urinary excretion of catecholamines in this population.

Methods: The LUCASS study (Lung CAncer, Stress and Survival study) is a prospective cohort study targeting all individuals referred to a diagnostic work-up for suspected lung cancer at Landspitali National University Hospital (n=166), Iceland and Uppsala University hospital (n=120), Sweden. The study population consisted of 172 patients who completed questionnaires on perceived distress (Hospital Anxiety and Depression Scale, HADS) before/during and after clinical evaluation for lung cancer *(study group I)* and a subpopulation of 89 patients who completed the HADS questionnaires on perceived distress AND collected overnight-urine for catecholamine analysis at both assessments. The median post-assessment timepoint was 28 days later but before any treatment *(study group II).*

Results: A lung cancer diagnosis was confirmed in 128 of patients (74.4%). Mean age was 69.3 years (+ 9.3), women representing 48.3%. In those diagnosed with lung cancer, there was a significant post-diagnosis increase in HADS-total scores (10.1 to 11.5, p=0.008) compared to before clinical evaluation. In contrast, those with other causes of lung pathology, showed a reduction in HADS-total score post-diagnosis (9.02 to 7.43, p=0.068). Both urinary-adrenaline (p=0.001) and noradrenaline (p=0.045) excretion was already higher before diagnosis among those individuals eventually diagnosed with lung cancer compared to those with other causes of lung pathology and there was no significant pre- to post diagnosis change in the lung cancer group. Moreover, we observed no association between mental distress and levels of urinary catecholamines.

Conclusions: Receiving a lung diagnosis is associated with an increase in self-reported psychological distress and there is a sign of increased biologic stress measured with urinary catecholamines already before diagnosis.

Keywords: Lung Cancer Diagnosis, Psychobiological Stress, Prospective Cohort Study

EP16.02-010 Predictive Value of Serum Reactive Oxygen Species Modulator 1 for Surgically Resected Lung Adenocarcinoma

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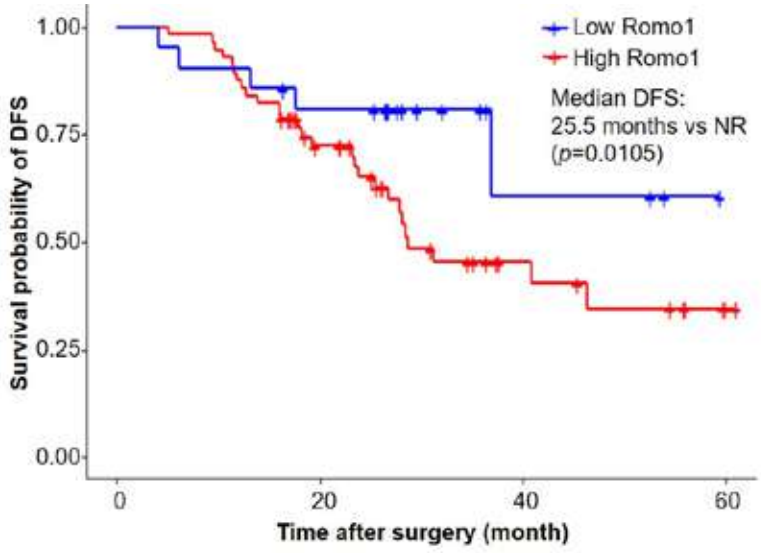
Introduction: Reactive oxygen species modulator 1 (Romo1), a novel mitochondrial membrane protein, is a key regulator of intracellular reactive oxygen species production. Previous studies have shown that Romo1 is abundant in various types of human cancer cells and the overexpression in tumor tissue is associated with poor clinical outcomes in several clinical settings of lung cancer treatment. However, the potential clinical utility of serum Romo1 in human malignancies had been scarcely investigated.

Methods: We collected data of patients with lung adenocarcinoma who underwent curative surgical resection between May 2016 and November 2018. Baseline serum Romo1 and carcinoembryonic antigen (CEA) levels were measured via enzyme-linked immunosorbent assay and electrochemiluminescence immunoassay, respectively. The cut-off for discriminating between low and high serum Romo1 and CEA levels was defined as the point with the lowest p value for disease-free survival (DFS) by the log-rank test for all possible levels for each biomarker. Univariate and multivariate analyses were performed to evaluate the association between serum Romo1 and DFS.

Results: A total of 88 samples were analyzed. Using the cut-off value of 872 pg/mL, the population was classified into low (n=50, 56.8%) and high (n=38, 43.2%) Romo1 groups. High Romo1 was significantly associated with advanced stage (p=0.0113) and poorly differentiated cancer (p=0.0369). The median DFS of the high Romo1 group was significantly shorter than that of the low Romo1 group (25.5 months *vs.* not reached [NR], p=0.0105). In addition, the median DFS of patients in the high CEA (>2.9 ng/mL) group was significantly shorter than those in the low CEA group (26.8 months *vs.* NR, p=0.0292). Multivariate analyses showed that both high Romo1 and CEA levels were independently associated with poor DFS (hazard ratio [HR]= 2.11; 95% confidence interval [CI]: 1.30-7.15, and HR=2.34; 95% CI: 1.35-8.46, respectively). Moreover, combination of these two biomarkers resulted in higher HR of 4.20 (95% CI, 1.55-12.38) for DFS than those of Romo1 and CEA.

Conclusions: High serum Romo1 level was significantly associated with early recurrence in patients with lung adenocarcinoma treated with surgical resection. Although further large-scaled studies are required, serum Romo1 could be a promising predictive biomarker for this patient group.



Keywords: reactive oxygen species modulator 1, biomarker, surgery

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-011 Liquid Biopsies in the Setting of Early-Stage Lung Cancer for the Detection of Actionable Mutations

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Introduction: Lung cancer (LC) is the deadliest tumour worldwide. The best subgroup of patients with a chance of surgery with curative intent are those at an early stage corresponding to approximately 16%. Liquid biopsies are a useful strategy to screen for actionable mutations that are routinely used in advanced lung cancer both at the diagnostic and post-progression stages. However, its usefulness in surgically resectable lung cancer has not been addressed. Our aim is to evaluate whether liquid biopsies collected at different timepoints in early-stage lung cancer would be suitable for the detection of actionable mutations.

Methods: A cohort of 40 patients sequentially recruited. Only 34 patients with early-stage lung cancer were included. All patients had a tissue specimen and five blood samples at preoperative stage, from the pulmonary vein, at surgical discharge, at first follow-up and at last follow-up. All blood samples were evaluated for cfDNA expression. Assess the importance of genotyping tumour and blood samples for actionable mutations.

Results: We found that there is an evolution on the average yield of cfDNA obtained in five timepoints. We found that on average the maximum yield of cfDNA is obtained in liquid biopsies at surgical discharge of the patients. However, liquid biopsies at surgical discharge have proved unsuitable for the detection of actionable mutations, as it was not possible to detect the somatic mutations identified in the respective tissue biopsies. Therefore, although the amount of cfDNA is maximized at surgical discharge timepoint, its most likely origin is not tumoral, but instead the traumatic and inflammatory events associated with the surgical procedure. We NGS sequenced all available liquid biopsies in the cases with actionable mutations in EGFR and BRAF (6 patients) identified in tissue biopsies. We found the expected mutation in 5 out of 6 patients the pre-operatory timepoint. However, the mutation allele fraction detected was always very low in the range 0.1-0.2%.

Conclusions: The pre-operatory timepoint is the one offering the highest sensitivity for the detection of actionable mutations in early-stage lung cancer.

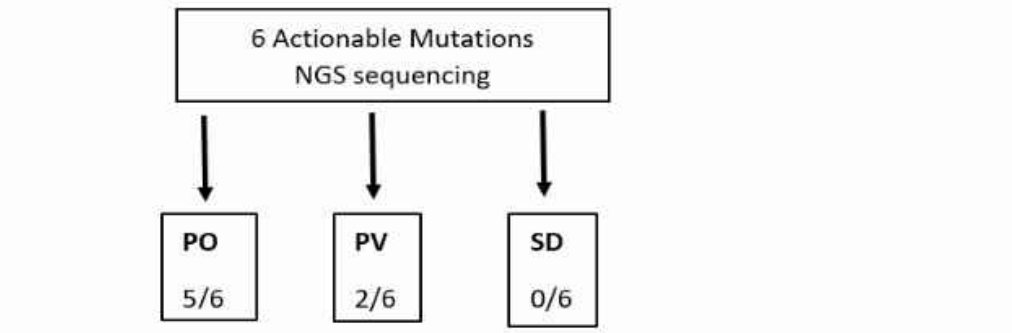

Figure1: Detection of actionable mutations through NGD in early-stage lung cancer.

Legend: PO: pre-operative; PV: pulmonary vein; SD: surgical discharge; NGS: next generation sequencing

Keywords: Early-stage lung cancer, Next Generation sequencing, Genotyping

EP16.02-012 cfDNA Analysis Implementation in Early Stage Lung Cancer

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Introduction: Liquid biopsies based on plasma cell-free tumour deoxyribonucleic acid (cfDNA) has shown to be promising in monitoring lung cancer evolution. The expression of cfDNA across time, its relationship with clinicopathological parameters, allows us to weigh how useful cfDNA could be in monitoring surgically resectable lung cancer. Our aim was to address the impact of cfDNA analysis implementation in early-stage lung cancer.

Methods: A cohort of 40 patients sequentially recruited. Only 34 patients with early-stage lung cancer were included. All patients had a tissue specimen and five blood samples at the preoperative stage, from the pulmonary vein, at surgical discharge, at first follow-up, and at last follow-up. All blood samples were evaluated for cfDNA expression. Assess the importance of genotyping tumor and blood samples for actionable mutations.

Results: We found that there is an evolution in the average yield of cfDNA obtained in the five-time points (figure 1). On average the maximum yield of cfDNA is obtained in liquid biopsies at the surgical discharge of the patients (figure 2). However, liquid biopsies at surgical discharge have proved unsuitable for the detection of actionable mutations, as it was not possible to detect the somatic mutations identified in the respective tissue biopsies. Therefore, although the amount of cfDNA is maximized at surgical discharge timepoint, its most likely origin is not tumoral, but instead the traumatic and inflammatory events associated with the surgical procedure.

Conclusions: Our results suggest that the pre-operatory timepoint is the one offering the highest sensitivity in liquid biopsies.

Figure 1. Study design

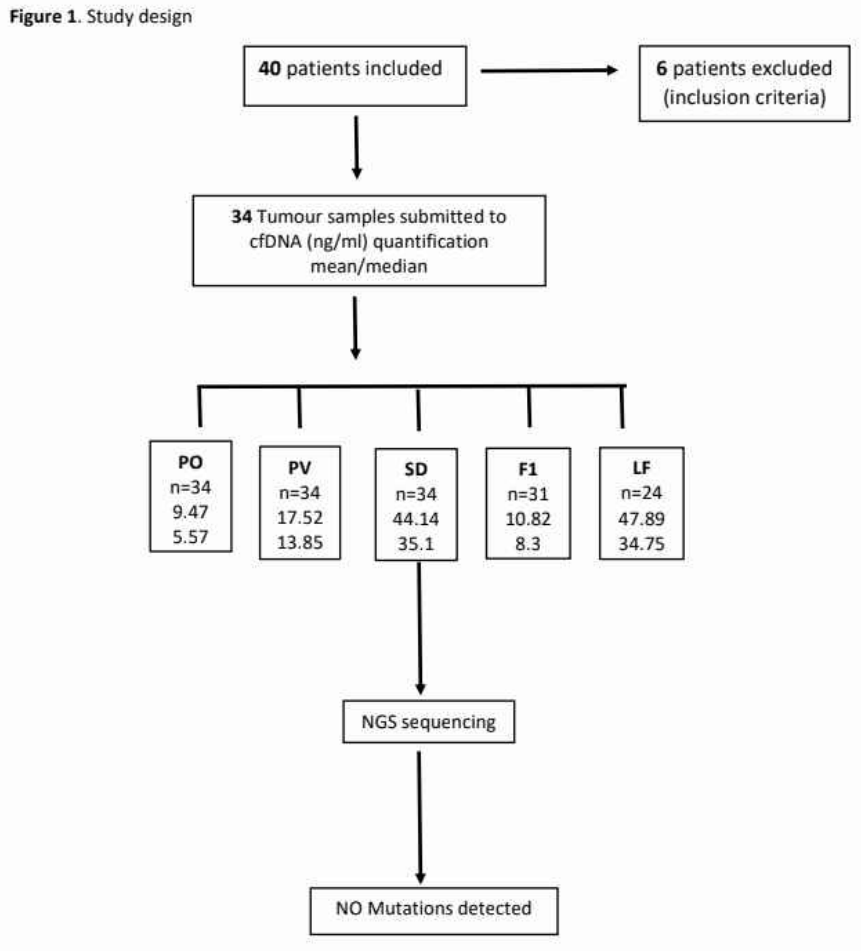
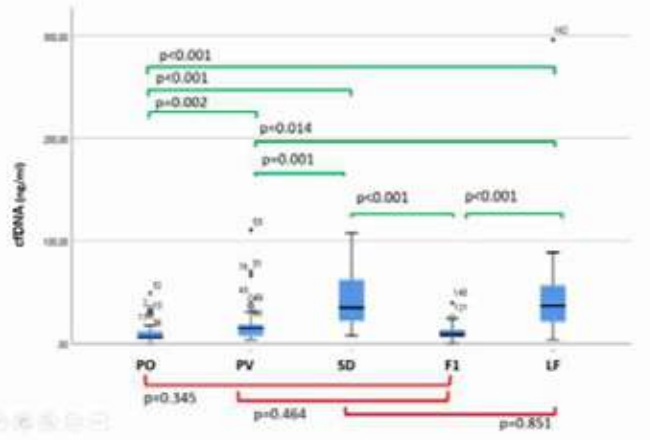


Figure 2. cfDNA concentration at five time points. Pairwise method analysis according to cfDNA concentration and the five time points. Significance values were adjusted using the Bonferroni correction for several tests.



Legend:
PO: Pre-Operative; **PV**: Pulmonary Vein; **SD**: Surgical Discharge; **F1**: First Follow-up; **LF**: Last Follow-up
Green Lines: Statistical significance.
Red Lines: Not statistically significant.

Keywords: Early-stage lung cancer, Next Generation sequencing, Genotyping

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-013 Retrospective Analysis of BRCA1/2 Alterations in Advanced NSCLC Using An Amplicon-based NGS Liquid Biopsy Assay

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Introduction: Homologous recombination deficiency (HRD), characterized by tumor genomic instability, frequently occurs due to alterations in *BRCA1/2*. HRD has been described in non-small cell lung cancer (NSCLC), but its biological and clinical relevance in NSCLC remains unclear. Recent evidence suggests genomic instability due to HRD may alter tumor immunogenicity and predict response to immune checkpoint inhibitors (ICI), highlighting the utility of screening pathogenic *BRCA1/2* alterations in NSCLC. Here, we examine the use of an ultrasensitive next-generation sequencing (NGS) liquid biopsy assay in the molecular analysis of pathogenic *BRCA1/2* alterations in metastatic lung adenocarcinomas.

Methods: Plasma cell-free DNA (cfDNA) samples from 320 consecutive lung adenocarcinoma patients underwent real-world NGS testing in a CAP-accredited and CLIA-certified laboratory from Jan 2020 to Aug 2021. Of these, 89.1% (285/320) were from metastatic tumors. Genomic alterations, including *BRCA1/2* mutations and deletions, were analyzed via an amplicon-based NGS liquid biopsy assay (LiquidHALLMARK) with previously validated single nucleotide variant (SNV)/indel and copy number alteration detection limits of 0.1% variant allele frequency (VAF) and 1.5X fold change respectively. Only pathogenic *BRCA1/2* SNV/indels and deletions were included in the analysis.

Results: Circulating tumor DNA (ctDNA) was successfully detected in 84.9% of metastatic lung adenocarcinoma samples (242/285). Fifteen patients (5.3%) harbored a somatic *BRCA1/2* mutation (11 *BRCA2*, 3 *BRCA1*, and 1 *BRCA1/2* co-mutant), three patients (1.1%) exhibited a *BRCA2* deletion in ctDNA, and one patient (0.4%) harbored a likely germline *BRCA1* mutation. Of the 18 somatic *BRCA*-mutant lung adenocarcinomas, seven (38.9%) were baseline cases and ten were treated (55.6%), including one patient treated with first-line ICI combination therapy. The prevalence of *BRCA1/2* alterations was non-significantly higher in males than females (11/110, 10.0% vs 8/175, 4.6%, $p = 0.09$). Between cases with or without NSCLC driver mutations co-detected (including *EGFR*, *KRAS*, *MET*, *ERBB2*, *BRAF*, *ALK*, *RET*, and *ROS1*), no difference in the prevalence of *BRCA1/2* alterations was observed (6.5% vs 7.0%, $p > 0.99$). The median cfDNA/mL plasma was higher in *BRCA1/2* mutants compared to ctDNA-positive *BRCA1/2* wild-type (WT) cases (27.0 ng/mL vs 16.6 ng/mL, $p = 0.03$). The median number of somatic variants was higher in *BRCA1/2* mutants compared to ctDNA-positive *BRCA1/2* WT cases (5 vs 3, $p < 0.0001$). Compared to driver mutations, which were all observed at clonal VAFs, somatic *BRCA1/2* SNV/indels were often observed at sub-clonal VAFs, both among driver-positive and driver-negative cases.

Conclusions: Ultrasensitive liquid biopsy enables detection of pathogenic *BRCA1/2* alterations in plasma cfDNA of lung adenocarcinomas, despite low VAFs. Retrospective analysis suggests a difference in cfDNA mutational profiles in *BRCA1/2* mutants, warranting further investigation on the role of *BRCA1/2*, HRD, and correlation with ICI treatment response in lung adenocarcinoma.

Keywords: liquid biopsy, next generation sequencing, non-small cell lung cancer

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-014 A Comparative Analysis of Gene Alteration Detected with NGS in Tumor Tissue and Peripheral Blood in Lung Cancer

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Introduction: In the last years the advances in NGS technology have improved the knowledge of the tumor molecular profile in different neoplasias. The detection of biomarkers as predictors of treatment response or identification of targeted therapies allow individualize treatments. Indeed, identifying patients with specific genomic alteration has relevant clinical implications. A problem to solve is the low availability of tumor sample in patients with lung cancer. Therefore, the possibility to analyse the circulating tumor DNA (ctDNA) in blood sample as a complementary diagnosis method is really important to consider in the near future. The aim of this study was to evaluate the concordance grade of gene alteration detected with NGS in samples from different tissue, tumor and peripheral blood, in patients diagnosed with lung cancer.

Methods: NGS testing from patients with newly diagnosed or recurrent lung cancer at La Paz University Hospital, Madrid (Spain) were retrospective reviewed. The analyzed patients had a NGS performed in two different biopsies, tumor tissue and peripheral blood. All tumor tissue samples were analysed with Foundation Medicine® assay (324 gene panel) and peripheral blood sample with Guardant360®, FoundationOne Liquid® or FoundationOne Liquid® CDX CTA assays (73, 70 and 324 gene panel respectively). Gene alterations consider to compare samples was those presents in all panel assays.

Results: A total of 27 patients were included. There were not NGS data results for two different samples (tumor and peripheral blood) in 14 patients (51.9%), due to insufficient amount of DNA available or no alterations detected. Therefore, this review is focused on the 13 patients (46.4%) with paired tumor and ctDNA successfully sequenced. Regarding the time period in which the NGS was performed, 7 patients (53.8%) underwent the NGS at diagnoses of the disease, 5 patients (38.5%) at disease progression and 1 patient during second line treatment. The majority were female (n=7, 53.8 %) and the most frequent histological subtype was adenocarcinoma (n=8, 61.5%). All of them were treated with platinum-based chemotherapy and 9 patients (53.8%) also received immunotherapy. The mutations most commonly found were TP53 (84.6% in tumor tissue and 61.5% in ctDNA), MTOR (23.1% / 30.8%), KRAS (23.1% / 23.1%), EGFR (15.4% / 19.2%) and ROS1 (7.7% / 23.1%). Moreover, 77% of the patients showed concordance in one or more gene alteration detected in both samples, tumor and ctDNA. On the other hand, there was an impact of NGS results in one patient treatment due to the detection of KRAS G12C alteration and the possibility to Sotorasib administration, mutation detected in tumor and peripheral blood.

Conclusions: The application of NGS assays in the clinical practice will allow in the near future to create a molecular profile of the different neoplasms to understand the clinical evolution of the patient. Liquid biopsy may be an alternative when tumor tissue is not available for molecular analysis. In our study, a high concordance was observed between NGS performed on peripheral blood and tumor tissue. Further studies with a larger population are needed to identify the sensibility of this technique.

Keywords: NGS, liquid biopsy, biomarkers

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-015 Phenotyping Malignant Pleural Effusions with Mass Cytometry: Evidence of EMT and MET States in Late-Stage NSCLC

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Introduction: Malignant pleural effusions (MPEs) signify late-stage disease and are associated with poor prognosis in non-small cell lung cancer (NSCLC). Cytopathology is the standard approach for diagnosing MPEs, however detection of malignant cells remains limited due to scarcity and difficulty in distinguishing them from other cell types. Despite these limitations and because MPEs are often drained from patients as palliative care, studies have proposed utilizing MPEs as a method of liquid biopsy for phenotyping malignant cells and for precision immunotherapy; yet MPEs and their cellular components are inadequately studied at the single-cell level. In this study we leverage mass cytometry to delineate epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET)- related changes in malignant cells and interrogate immune profiles in MPEs for assessing disease status and response to therapy.

Methods: We utilized mass cytometry to phenotypically distinguish and interrogate epithelial and immune cell types in pleural effusions (PEs) from 8 late-stage NSCLC patients. We developed a ~30 marker mass cytometry antibody panel with the intent to identify cytokeratin positive (CK+) epithelial cells along a spectrum of EMT-MET phenotypic states and five main immune populations: CD4+ T cells, CD8+ T cells, CD33+ Myeloid cells, CD56+ NK cells and CD20+ B cells. Markers such as E-Cadherin, Vimentin, CD44, CD24 and MUC1 were included to delineate EMT and MET status. Dimensionality reduction analysis (UMAP) was used to visualize the immune landscape of each clinical specimen. EMT states in CK+ cells were assessed by leveraging PHENOSTAMP (PHENOtypic STAte MaP), a 2D-mapping function previously developed by our group, through which EMT status of NSCLC clinical specimens can be evaluated at the single-cell proteomic level.

Results: Our analysis agreed with the cytological reports in six out of eight patient specimens: we detected CK+ cells in four out of six patients reported to be positive for malignant cells (MPEs) and did not detect CK+ cells in two PE specimens which were reported negative for malignant cells. We found that the presence of CD33+ myeloid cells co-occurred with CK+ cells (correlation=0.96). By projecting CK+ cells on PHENOSTAMP, we observed a variety of EMT states, and report for the first time detection of CK+ cells in an MET state. Importantly, we did not observe MET cells in the sole patient with no metastatic disease at the time of sample collection. Finally, longitudinal analysis of MPEs drawn 2 months apart from a patient undergoing targeted therapy, revealed that CK+ cells acquired heterogeneous EMT features (partial EMT, epithelial and stem-like) during treatment.

Conclusions: We present a translational, proof-of-concept approach, whereby through single-cell analysis, we study the cellular profile of MPEs from NSCLC patients with a specific focus on characterizing EMT-MET phenotypes in CK+ cells. With PHENOSTAMP, researchers can study EMT-MET profiles in MPEs with promise of evaluating treatment-driven phenotypic changes at a personalized level. This approach may serve as a future platform to better assess disease progression and response to treatment in late-stage NSCLC patients.

Keywords: NSCLC, Pleural Effusions, EMT, MET, Mass Cytometry, Single-cell Phenotypic Analysis

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-016 Exploration of Factors Affecting the Performance of MRD Tumor-Informed Assay in Chinese Lung Cancer Patients

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Introduction: Circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) is predictive for post-operative recurrence in lung cancer. However, the suitable approach for sensible MRD monitoring remains controversial. Currently, whole-exome sequencing (WES) is widely used to design the customized monitoring panels of tumor-informed assay for MRD monitoring. We investigated the potential factors which may affect the performance of whole-exome sequencing (WES) for monitoring panels' design.

Methods: The WES data obtained from 163 Chinese lung cancer patients were reviewed. The clonal and driver mutations (SNV only) were screened using the in-house algorithm based on cancer cell fraction and cellular prevalence. The number of variants and genes for each patient were accessed. Their correlations with clinic-pathophysiological significance were analyzed. For the factors which may influence the detection performance of WES, we subsequently compared the variant allelic frequency (VAF) for each SNV selected.

Results: A total of 3343 genes and 4549 variants (clonal or driver mutations) were detected in 163 patients. Among 3343 genes, 81.5% was present in only one patient. Actionable genes according to OncoKB were identified in only 57.7% of patients. Interestingly, 94.1% of 4549 variants detected by WES was classified as variants with unknown clinical significance, implying that tumor-agnostic assay might not be a suitable method for MRD detection in lung cancer patients due to the higher risk of false-negative when compared to tumor-informed assay. Significantly lower number of variants was found by WES in patients with age <60 vs. ≥60 years (n=97 vs. 66, average 23.5 vs. 34.3, p<0.01), female vs. male gender (n=83 vs. 80, average 25.5 vs. 30.4, p=0.04), clinical stage 0-I vs. II-IV (n=90 vs. 50, average 25.5 vs. 35.5, p<0.01), tumor cell content <20% vs. ≥20% (n=9 vs. 150, average 16.0 vs. 28.6, p=0.02), and no smoking history vs. smoking history (n=68 vs. 28, average 25.1 vs. 34.3, p=0.02), whereas tumor sample storage method (fresh [n=49] vs FFPE [n=111]: average 29.0 vs. 27.1, p=0.48) and tumor histological subtype (adenocarcinoma [n=141] vs. squamous cell carcinoma [n=9]: average 27.6 vs. 31.4, p=0.48) had no significant impact. In addition, significantly less VAF was observed in patients with age <60 years (average 13.1% vs. 20.3%, p<0.01), female gender (average 13.1% vs. 19.0%, p<0.01), clinical stage 0-I (average 12.5% vs. 22.8%, p<0.01), and no smoking history (average 12.4% vs. 21.7%, p<0.01). For samples with different tumor cell content, the average VAF was comparable (<20% vs. ≥20%: average 12.0% vs 16.1%, p=0.31).

Conclusions: In conclusion, most of variants detected by WES for MRD monitoring panels were classified as variants with unknown clinical significance, indicating that tumor-informed assay may be a more optimal method for MRD monitoring in lung cancer patients when compared to tumor-agnostic assay. Age, gender, clinical stage, smoking history and tumor cell content, but not tumor sample storage method and tumor histological subtype had significant impact on the number of detected variants and/or VAF, suggesting the algorithm for monitoring panels' design may be further adjusted and improved in consideration of these factors.

Keywords: minimal residual disease, whole-exome sequencing, lung cancer

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-017 Predictive Value of Peripheral Blood Immune Cell Profiling in EGFR-T790M Mutant Lung Adenocarcinoma

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Introduction: Peripheral immune cell profiles have been shown to correlate with clinical outcomes in cancer patients. Exploring the peripheral blood immune cell profile of lung adenocarcinoma (LUAD) patients will likely be a biomarker for predicting the efficacy of osimertinib.

Methods: Differences in B cells, NK cells, NKT cells, T cell subsets and 11 immune checkpoint molecules in peripheral blood samples from 27 plasma T790M-positive and 42 plasma T790M-negative LUAD patients were studied using flow cytometry. Peripheral immune cell profiles before treatment were compared between the patients with good and poor osimertinib efficacy.

Results: T790M-positive had higher levels of NK cells and lower T cells compared to T790M-negative, and CD244 expression was lower in CD8+T cells and NK cells. The level of CD272+NK cell, CD160+NK cell and CD95+B cell was significantly and positively correlated with plasma T790M mutation frequency. Osimertinib efficacy was significantly higher in B cells ($P<0.01$), effector CD4+T cells and CD4+/CD8+ values ($P<0.05$) in peripheral blood before treatment in patients with good efficacy compared to those with poor efficacy.

Conclusions: This study revealed the peripheral blood immune cell profile characteristics of T790M-positive patients. The peripheral immune cell profile may be a potential biomarker to predict the efficacy of osimertinib.

Keywords: T790M mutation, Lung adenocarcinoma, Peripheral immune cell profiles

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-018 Liquid Biopsies First to Make Treatment Decisions in Patients with Metastatic Non-small Cell Lung Cancer (NSCLC)

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Introduction: It is well established that liquid biopsies (LB) are non-inferior to tissue biopsies (TB) to identify actionable genetic alterations (AGA) in patients with metastatic non-small cell lung cancer (mNSCLC). Importantly, LB are able to report next generation sequencing (NGS) results significantly faster than TB NGS and overcome the logistical barriers of finding and shipping tissue samples for sequencing. This study aimed to illustrate that LB can be used first in treatment decision making for mNSCLC patients.

Methods: This is a retrospective review of 170 patients diagnosed with mNSCLC and treated at Memorial Cancer Institute from July 2015 to July 2020. NGS was conducted via TB (physician's choice) and LB (Guardant360®). These analyses were conducted on the 146 patients who had LB and TB results reported within 30 days of one another. Data collected from the electronic medical record included: demographics, sequencing turnaround times (TAT), test used to make treatment decision (i.e. LB vs. TB), date of disease progression and death, and identified AGA. Outcomes statistics were calculated using a log-rank Mantel-Cox test.

Results: In this analysis, the majority of the 146 patients had adenocarcinoma (93.2%) and were treated in the first line setting (74.7%). Amongst all therapy lines, the majority of treatment decisions were based on LB results (74.0%) vs. TB (24.7%). Two treatment decisions were based on both tests. The mean TAT for LB was 17.5 days shorter than TB (9.6d vs. 27.1d). The majority of patients were treated with a non-targeted therapy (64.4%), followed by targeted therapy (34.2%). Patient outcomes were analyzed from 92 patients with follow up data for PFS and OS. There were no statistical differences in outcomes for patients treated based on genotyping results-LB vs. TB (PFS p=0.6868, OS p=0.6553). Forty-five patients received a targeted therapy and had AGA data available for analysis. The driver mutations included *EGFR* (80.0%), *BRAF* (8.9%), *MET* (4.4%), *ALK* (2.2%), *NTRK* (2.2%), and *ROS1* (2.2%). Average concordance in AGA between LB and TB for these 6 genes was 98.9% with a range between 95.3-100%. Testing modalities were compared between LB first followed by reflex testing to TB and vice versa. LB first identified AGA in 80.0% of patients with reflex to TB identifying the other 20.0%. In contrast, TB first identified 51.1%, with reflex to LB identifying the other 48.9%.

Conclusions: In this study, treating oncologists based their treatment decisions on LB results three times more often than TB. NGS performed by LB is not only a good complement to TB to identify AGA in newly diagnosed patients with mNSCLC, but also, LB could be incorporated as standard of care to guide first-line therapy decisions in most patients with mNSCLC due to its accuracy and shorter TAT.

Keywords: Liquid biopsies, NSCLC, NGS

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-019 Metabolic Changes in Sputum and Exhaled Breath Condensate of Non-small Cell Lung Cancer Patients after Surgical Resection

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Introduction: Low-dose CT screening of the chest in the high-risk population is the current standard of care for early detection of lung cancer. CT screening is invasive due to radiation exposure and carries the risk of unnecessary biopsies of benign tumors. Here, we demonstrate metabolic changes in sputum and exhaled breath condensate (EBC) obtained from the *same* early-stage non-small cell lung cancer (NSCLC) patients pre-and post-surgical resection (SR), proposing the individual metabolic signature as a noninvasive diagnostic tool.

Methods: The median number of days for EBC (n=35) and cytologically confirmed sputum (n=15) pre-and post-SR was 7 and 42 and 7 and 36, respectively. Nuclear magnetic resonance (NMR) and liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) were performed to evaluate the metabolic profile of the samples. Mass Profiler Professional, 12.6) was used to calculate the fold change, ($p < 0.05$; ≥2-FC). Benjamini-Hochberg multiple correction was applied to identify statistically significant changes in metabolite levels. Mann-Whitney paired, and Bonferroni tests were used to remove the unidentified entities.

Results: All patients (n=35) had confirmed diagnosis of NSCLC. Eighty-eight % of the patients had node-negative cancers. The mean tumor size was 2.7 cm, mean SUV _PET was 8.2. Hierarchical heatmap of the significant metabolites is presented below. Metabolites (n=26) showed significant changes post-SR; 14 were lipids, and 12 belonged to 9 different chemical metabolite classes. Eighteen metabolites were significantly upregulated, and eight were downregulated. A respective 10 and 8 median fold change (MFC) was observed for all up-and downregulated metabolites (LC-QTOF-MS). MFC in the concentration of the up-and downregulated metabolites (NMR) amounted to 0.04 and 0.27, respectively. The pattern of dysregulation in sputum was predictable and consistent after SR compared to pre-surgery. Sputum levels of glucose (MFC 0.01, p=0.037), adenosine monophosphate (13 log fold, p=0.0037) and N1, N12-diacetylspermine (8 log fold, p=0.011) were significantly elevated post-SR.

Conclusions: Metabolic profile in sputum was more robust than EBC and of potential clinical significance. There was no specific trend of dysregulation (up/down) of metabolites post-SR. Metabolic alterations were most pronounced with regards to lipid metabolism compared to other classes of metabolites. The absence/decreased levels of glucose in sputum before surgery, and its subsequent rise post-SR, the identification of dysregulation in adenosine monophosphate and N1, N12-diacetylspermine levels post-SR was the most significant observation. These molecules may be indices of a pre-or an early malignant process and could serve as a promising noninvasive tool for early diagnosis of NSCLC.

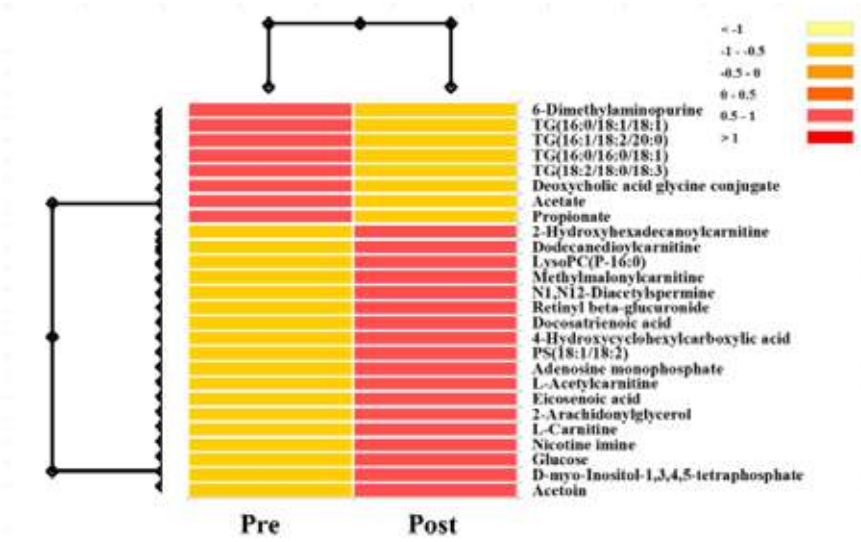

Figure. Hierarchical heatmap summarizing the 26 metabolites that showed significant changes (paired T-Test; P<0.05) between pre- and post-SR in sputum and EBC, as determined using LC-MS-QTOF and NMR methods. Concentration of the individual metabolites range between (log 2) < 1 to > 1.

Keywords: metabolites, lung, cancer

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-020 Lung Cancer Cell Dynamics Significantly Depended on Blood Cell Circuit, Biochemical Factors, Hemostasis System, Cancer Characteristics

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Introduction: We examined factors significantly affecting lung cancer (LC) cell dynamics.

Methods: We analyzed data of 768 consecutive non-small cell LC patients (LCP) (age=57.6±8.3 years; tumor size=4.1±2.4 cm) radically operated and monitored in 1985-2022(m=660, f=108; upper lobectomies=277, lower lobectomies=177, middle lobectomies=18, bilobectomies=42, pneumonectomies=254, mediastinal lymph node dissection=768; combined procedures with resection of trachea, carina, atrium, aorta, VCS, vena azygos, pericardium, liver, diaphragm, ribs, esophagus=193; only surgery-S=618, adjuvant chemoimmunoradiotherapy-AT=150: CAV/gemzar + cisplatin + thymalin/taktivin + radiotherapy 45-50Gy; T1=320, T2=255, T3=133, T4=60; N0=516, N1=131, N2=121, M0=768; G1=194, G2=243, G3=331; squamous=417, adenocarcinoma=301, large cell=50; early LC=214, invasive LC=554; right LC=412, left LC=356; central=290; peripheral=478. Variables selected for study were input levels of 45 blood parameters, sex, age, TNMG, cell type, tumor size. Regression modeling, clustering, SEPATH, Monte Carlo, bootstrap and neural networks computing were used to determine significant dependence.

Results: Overall life span (LS) was 2244.9±1750.3 days and cumulative 5-year survival (5YS) reached 72.9%, 10 years - 64.3%, 20 years - 43.1%. 502 LCP lived more than 5 years (LS=3128.7±1536.8 days), 145 LCP - more than 10 years (LS=5068.5±1513.2 days).199 LCP died because of LC (LS=562.7±374.5 days). Regression modeling displayed LC cell dynamics significantly depended on: phase transition (PT) early-invasive LC in terms of synergetics, PT N0—N12, histology, T, G, LC growth, cell ratio factors (ratio between cancer cells- CC and blood cells subpopulations), ESS, glucose, bilirubin (P=0.000-0.033). Neural networks simulation revealed relationships between LC cell dynamics and segmented neutrophils (rank=1), lymphocytes (2), PT N0—N12 (3), PT early-invasive LC (4), leucocytes (5), stick neutrophils (6), eosinophils (7), erythrocytes (8), monocytes (9), thrombocytes (10), Hb (11), ESS (12). Prediction was 92-95% by neural networks computing.

Conclusions: Lung cancer cell dynamics significantly depended on blood cell circuit, biochemical factors, hemostasis system, cancer characteristics, anthropometric data.

Keywords: lung cancer, cell dynamics, blood cell circuit

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-021 The Expression of CEACAMs and Serum CEA Levels as Biomarkers of Postoperative Cancer Recurrence in Non-small Cell Lung Cancer

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Introduction: The serum carcinoembryonic antigen (CEA) levels have been used as biomarkers and as a diagnostic tool for non-small cell lung cancer (NSCLC). However, no study has been conducted to compare the gene expression of CEA-related cell adhesion molecules (CEACAMs) in surgically resected cancer specimens matching CEA levels.

Methods: We identified 157 patients who underwent surgery for NSCLC and had access to cancer specimens for whole transcriptome sequencing (WTS) and CEA levels. CEA levels were determined preoperatively (pre-CEA) and at the time of recurrence (post-CEA). The most recent postoperative CEA levels were used as the post-CEA in those who did not experience recurrence. For 79 patients, normal lung tissue WTS data were also available.

Results: Elevated pre- or post-CEA levels (10ng/ml) were associated with recurrence (p=0.035, HR=7.341 pre-CEA; p=0.064, HR=6.265 post-CEA) Even if the pre-CEA level was low, the recurrence occurred frequently when the post-CEA level increased (Figure 1A). CEACAMs were frequently overexpressed in the majority of cases (79.7% CEACAM5, 53.2% CEACAM6). The levels of CEACAM5 and CEACAM6 expression were significantly correlated (R^2=0.62, p<0.001). The majority of patients with elevated CEA levels expressed high levels of CEACAM5 and CEACAM6, implying that the elevated serum CEA level was caused by CEA leaking from cancer tissue into the bloodstream (Figure 1B). Interestingly, many patients with elevated CEACAM expression showed low post-CEA levels at the time of recurrence, implying the existence of a novel molecular mechanism regulating the cancer cell's protein entry into the bloodstream.

Conclusions: Our data established that pre- or post-CEA levels greater than 10 ng/ml were a significant predictor of recurrence, particularly in patients with high CEACAMs expression in their cancer tissue. However, the presence of patients with recurrence who had low post-CEA levels despite elevated CEACAMs levels suggested that CEACAMs may not be a prognostic indicator for NSCLC.

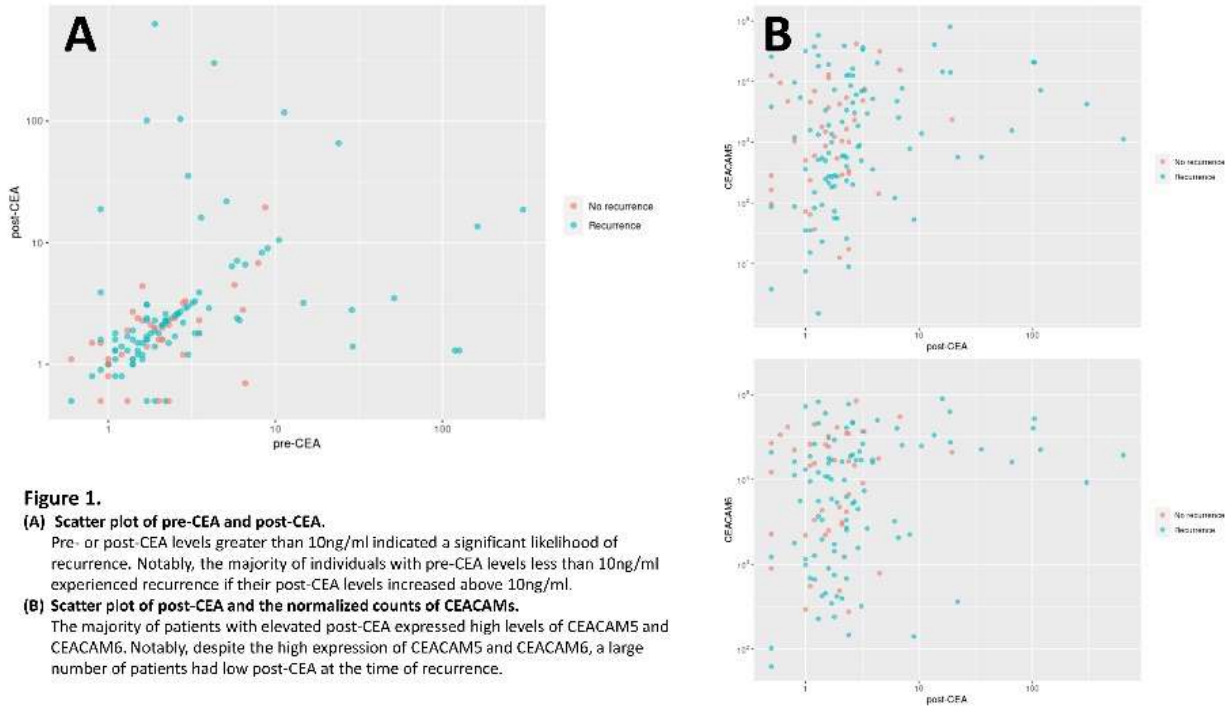

Figure 1.
(A) Scatter plot of pre-CEA and post-CEA.
Pre- or post-CEA levels greater than 10ng/ml indicated a significant likelihood of recurrence. Notably, the majority of individuals with pre-CEA levels less than 10ng/ml experienced recurrence if their post-CEA levels increased above 10ng/ml.
(B) Scatter plot of post-CEA and the normalized counts of CEACAMs.
The majority of patients with elevated post-CEA expressed high levels of CEACAM5 and CEACAM6. Notably, despite the high expression of CEACAM5 and CEACAM6, a large number of patients had low post-CEA at the time of recurrence.

Keywords: Carcinoembryonic antigen, Recurrence, Non-small cell lung cancer

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-022 Circulating Tumor DNA Minimal Residual Disease Assay Predicts Outcome in Lung Cancer Patients Who Had Curative Treatments

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Introduction: Circulating tumor DNA (ctDNA) minimal residual disease (MRD) assay is used to detect and monitor disease progression or relapse after curative treatment. This study aims to investigate the role of such assay in lung cancer.

Methods: This is a retrospective study of twenty-nine consecutive patients treated with curative intent (concurrent chemoradiation(CCRT), surgery ± chemotherapy) for stages I-IV lung cancer. The patients underwent mPCR-NGS assay for detection of ctDNA in plasma, as mean tumor molecules (MTM) per mL of plasma, based on 16 individual-specific passenger mutations identified by whole exome sequencing from tissues, to identify progression or relapse in disease.

Results: The patient group (n=27) had a mean age of 67.6 years-old and was 66% male. They were distributed across various cancer stages and histology, smoking status, treatment modalities, PD-L1 and EGFR status (Figure 1A). Patients underwent MRD assay testing at a median of 44 days post-treatment. Among 27 patients, five had pre-treatment MTM values measured, but only two were positive. Post-treatment, twenty-one patients showed negative MTM, while six had positive values ranging from 0.9 to 2227.8. The patient with the highest positive MTM had small cell lung cancer, but experienced a drastic conversion to negative four months post-CCRT. Three patients, with positive MTM post-surgery, encountered negative conversion in MTM post-adjuvant chemotherapy. However, the other three patients had persistent increases in MTM after surgery and adjuvant chemotherapy, resulting in progressive diseases, including one death. Two patients with CNS progression exhibited persistently negative MTM values. Post-treatment MTM positivity is associated with progression of disease ($p<0.01$), but not with PD-L1, EGFR mutation, stage, and smoking history. Compared to the group with negative MRD post-treatment, those with a positive value demonstrated worse progression-free-survival in extracranial disease ($p=0.05$). However, positive MTM post-treatment was not associated with cranial disease progression and overall survival (Figure 1B-D). In groups with persistently positive MTM, overall survival was found to be associated with inferior overall survival ($p<0.01$) but not with PFS (Figure 1E-F).

Conclusions: Patients who initially showed positive MTM that converted to negative after curative treatment sustained a stable disease course, while those whose MTM were persistently positive exhibited a progression of disease. Despite a relatively short-term follow-up period, the longitudinal ctDNA MRD assay demonstrated potential for predicting disease progression or death in lung cancer patients who underwent curative treatments.

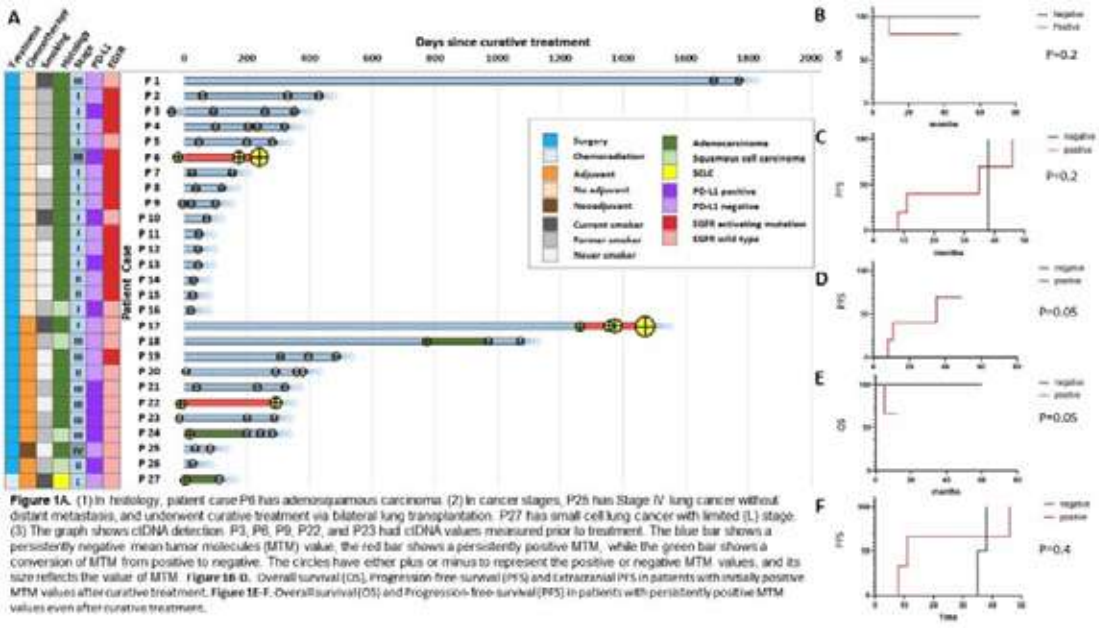

Figure 1A. (1) In histology, patient case P6 has adenosquamous carcinoma. (2) In cancer stages, P25 has Stage IV lung cancer without distant metastasis, and underwent curative treatment via bilateral lung transplantation. P27 has small cell lung cancer with limited (L) stage. (3) The graph shows ctDNA detection. P3, P8, P9, P22, and P23 had ctDNA values measured prior to treatment. The blue bar shows a persistently negative mean tumor molecules (MTM) value, the red bar shows a persistently positive MTM, while the green bar shows a conversion of MTM from positive to negative. The circles have either plus or minus to represent the positive or negative MTM values, and its size reflects the value of MTM. **Figure 1B-D.** Overall survival (OS), progression free survival (PFS) and extracranial PFS in patients with initially positive MTM values after curative treatment. **Figure 1E-F.** Overall survival (OS) and Progression-free survival (PFS) in patients with persistently positive MTM values even after curative treatment.

Keywords: Circulating tumor DNA, Minimal residual disease, lung cancer

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-023 Extracellular Vesicles Long RNA Sequencing as Diagnostic Biomarkers for Lung Adenocarcinoma Patients with Tumor Size Smaller than 2cm

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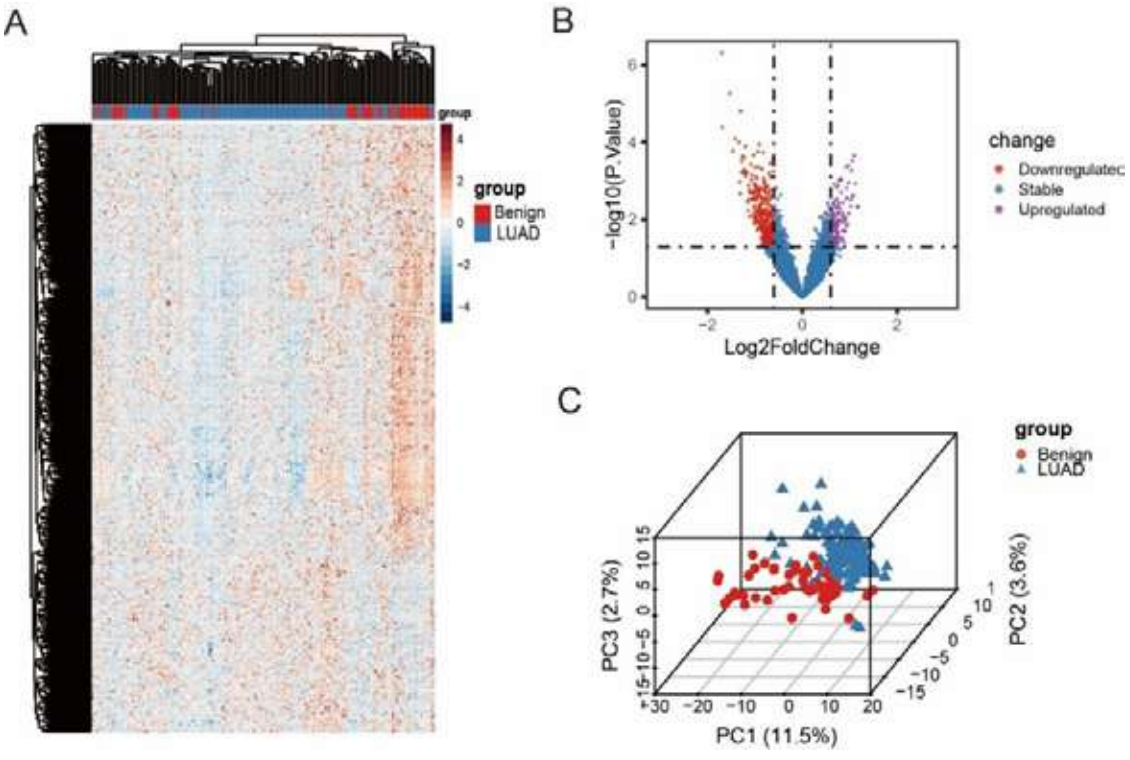
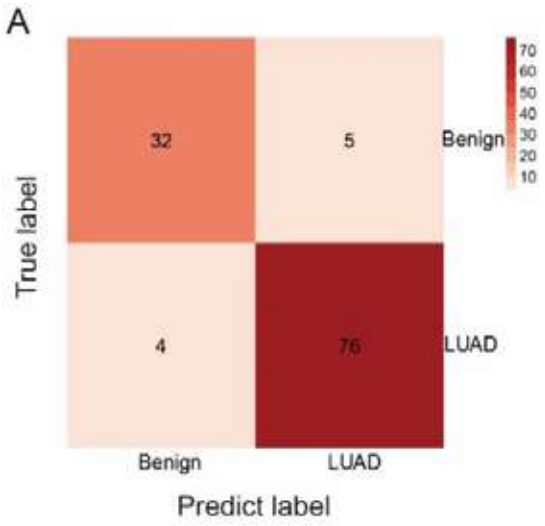
Introduction: Both NLST and NELSON have reported the ability of lung cancer screening with LDCT to detect lung cancer at an early stage and significantly reduce lung cancer mortality in high-risk groups. However, false-positive results cause the biggest controversy for conducting the LDCT screening studies. In the current study, we aimed to evaluate the efficacy of extracellular vesicles long RNA sequencing in diagnosing lung adenocarcinoma with tumor size ≤2cm.

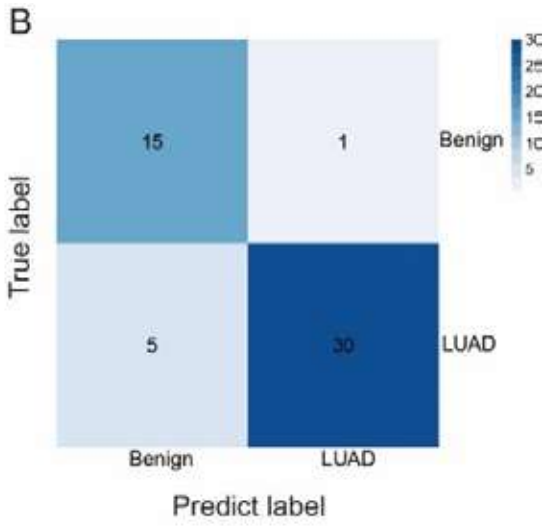
Methods: One hundred and fifteen lung adenocarcinoma cases (tumor size ≤2cm), and fifty-three controls were enrolled into the present study. EV-RNA from lung adenocarcinoma cases and controls was profiled by RNA-Seq. Classification of LUAD samples and noncancer samples was carried out with SVM using R package e1071.

Results: To explore the differently expressed genes from Benign individuals to LUAD patients, a total of 145 genes up regulated and 363 genes down regulated. The PCA analysis showed that the differentially expressed genes could distinguish the two groups. In the training set, the model built with the 23-gene signature distinguished EV samples from patients diagnosed with LUAD from Benign individuals with a sensitivity of 86.49%, a specificity of 95.00% and an accuracy of 92.31%. When applied to the validation set, LUAD was detected with a sensitivity of 93.75%, a specificity of 85.71% and an accuracy of 88.24%. The classifier could effectively distinguish patients with LUAD patients from benign controls both in the training (AUC 0.985) and validation (AUC 0.918) data sets.

Conclusions: Our findings demonstrated that the exosomal 23 genes RNA-seq panel has great diagnostic performance with high sensitivity and specificity in lung adenocarcinoma patients with tumor size ≤2cm, which may serve as an adjunct to lung cancer screening







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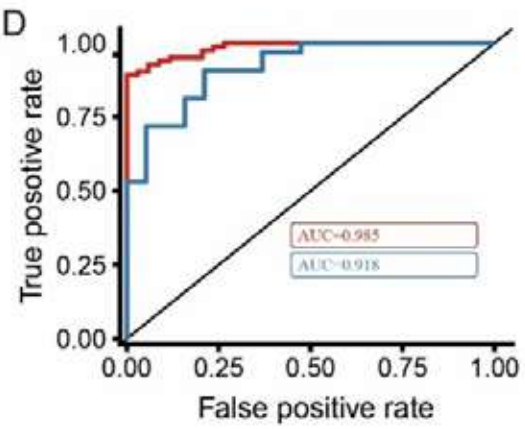
	Training set	Validation set
Sensitivity	86.49%	93.75%
Specificity	95.00%	85.71%
Accuracy	92.31%	88.24%



Keywords: Lung Adenocarcinoma, EV RNA, Diagnostic Biomarkers

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-024 Plasma ctDNA Organ-Specific Genomic Patterns and Origination Analysis in Advanced Non-Small Cell Lung Cancer

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Introduction: The utility of circulating tumor DNA (ctDNA) has been proven in guiding targeted therapies, predicting treatment responses, and monitoring disease recurrence. In advanced cancer, understanding the tissue origins, primary or metastatic lesions, of ctDNA may help more clearly interpret its clinical significance. However, the patterns of ctDNA mutations and their origins remained not fully investigated.

Methods: Our study enrolled 23 patients with advanced non-small cell lung cancer. We collected a baseline treatment-naïve plasma sample from each patient and a total of 93 tissue samples, including 40 regions from 23 primary tumors (one each patient) and 53 regions from 36 metastases at lymph nodes, pleura, bone, brain, and adrenal gland. Tissue samples underwent whole-exome sequencing with an average coverage of 136X. Plasma samples underwent targeted sequencing of 8051X average depth using a panel that covered 425 cancer-associated genes. Mutation calling of plasma samples was tumor-informed, involving only mutations detected in paired primary or metastatic tumor samples, and filtered with a background polishing method that controlled false positive rates.

Results: A total of 40873 mutations were detected in tissue samples. For each patient, mutations were classified into three types: primary tumor-private (PT-private), metastasis-private (MT-private), and shared by primaries and metastases (shared) based on their presence in tissue samples. In tissue samples, there were 6167(15.1%) mutations were PT-private, 32259 (78.9%) were MT-private, and the rest 2447 (6.0%) were shared. Eighteen plasma samples had a total of 113 mutations detected, among which 18 (15.9%) were PT-private, 62 (54.9%) were MT-private, and 33 (29.2%) were shared. In 6 patients with distant metastases to the adrenal gland or brain, a higher proportion (14/32, 43.8%) of PT-private mutations were detected in plasma than MT-private (8/32, 25.0%) and shared (10/32, 31.2%) ones. On the contrary, 11 patients with locoregional metastases to the pleura or lymph nodes showed a preference for MT-private mutations (50/74, 67.6%) in plasma. *EGFR* mutations were the most prevalent clonal mutations detected in tissues (15/23, 65.2%), almost half of which were also detected in plasma (7/15, 46.7%). In patients with pleura and lymph node metastases, (2/4, 50.0%) of *EGFR* mutations were detected in plasma. The ratio was 4/10 (40.0%) for patients with pleura metastases and further dropped to 1/3 (33.3%) in patients with bone metastases. *NOTCH2* was detected in plasma in 15.4%(2/13) patients with pleura metastases, and detection of that was significantly associated with poor prognosis (p=0.05).

Conclusions: Patients with locoregional metastases had more MT-private mutations detected in plasma, whereas those with distant metastases showed more PT-private mutations in plasma.

Keywords: ctDNA, Metastasis, Organ Origination

EP16.02-025 SerumTumor Markers as a Surrogate forRadiographicAssessment of Non-Small Cell Lung Cancer

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Introduction: In lung cancer, previous studies have explored the utility of conventional tumor biomarkers as surrogates for radiographic staging to improve diagnosis, prognosis, and augment treatment decisions. However, to date most have been performed in the context of a particular therapeutic regimen or prognostic variable. As such, the purpose of this study was to assess whether or not three commonly available, low-cost serum biomarkers (CEA, CA19-9, and CA-125) associated with radiographic disease response/progression during or after the treatment of non-small cell lung cancer (NSCLC).

Methods: This retrospective single-center review examined NSCLC patients treated between January 1, 2016 and August 1, 2020 who had radiographic imaging and tumor markers completed at baseline and at least one follow-up time-point. Disease response was assessed radiographically using RECIST 1.1 criteria. Statistical analyses were completed using paired nonparametric tests (Wilcoxon signed rank test).

Results: A total of 93 patients were identified as eligible and included in the analysis. The majority of patients had stage IV disease (59.8%). Treatment modalities included regimens containing chemotherapy (65.2%), immunotherapy (46.7%) and targeted therapy (15.2%). Female sex (53.3%) was slightly more common than male sex, and 81.6% of patients had non-squamous histology. At baseline imaging, an elevated CEA was seen in 54.3% of patients, elevated CA19-9 in 46.7% of patients, and elevated CA-125 in 22.8% of patients. The median (IQR) fold-change in tumor markers from nadir to their level at progression were 2.13 (IQR 1.24 - 3.02; p <0.001) for CEA (n=47), 1.46 (IQR 1.13 - 2.18; p <0.001) for CA19-9 (n=46), and 1.53 (IQR 0.96 - 2.12; p<0.001) for CA-125 (n=47). The median (IQR) fold-change in tumor markers from baseline to their level at radiographic response were 0.50 (IQR 0.27, 0.95; p<0.001) for CEA (n=39), 1.08 (IQR 0.74, 1.61; p=0.99) for CA19-9 (n=35), and 0.47 (IQR 0.18, 1.26; p=0.008) for CA-125 (n=35).

Conclusions: This retrospective analysis of 93 patients found that CEA, CA19-9, and CA-125 all demonstrated statistically significant associations with NSCLC disease progression in a population of patients with disease spanning a variety of stages, histologies, and types of systemic therapy. Additionally, CEA and CA-125 both showed statistically significant associations with treatment response. Testing CEA, CA-125 and CA19-9 can provide insight into disease response or progression, and results are often returned within hours and they are available for a small fraction of the cost of ctDNA testing. Validation within a prospective clinical trial should be considered.

Keywords: Biomarker

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-026 Dynamic Change of Indoleamine 2,3-dioxygenase Activity Predicts Survival in Radiotherapy- Received Unresectable Stage III NSCLC

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Introduction: High activity of Indoleamine 2,3-dioxygenase (IDO) in lung cancer patients converts tryptophan(Try), which is the essential amino acid for T cell metabolism, to kynurenine(Kyn) and consequently suppresses anti-tumor immune responses. We aimed to track the dynamic change of IDO activity in stage III non-small cell lung cancer (NSCLC) patients who received first-line radiotherapy and explore its association with survival outcomes.

Methods: Systemic IDO activity was calculated by Kyn:Try ratio. Serum levels of Kyn and Trp in 119 thoracic radiotherapy-received NSCLC patients, 115 of which was stage III, were measured by high-performance liquid chromatography before the initiation of radiotherapy. Dynamic change of IDO activity was followed in 24 patients by measuring K:T ratio before, during and after radiotherapy administration.

Results: There was no significant change of serum IDO activity at the three time points(Friedman test, p=0.13). The changing pattern of K:T ratio was divided into four groups: decreased constantly during radiotherapy, first increased then decreased, increased constantly, first decreased then increased. Patients whose K:T ratio kept decreasing or first increased then decreased were defined as good-change group. Multivariate analysis showed that good-change group is the only independent protective factor for overall survival(OS) and progression free survival(PFS)(p=0.04;p=0.01). Besides, patients with good change showed significantly superior local control than bad-change group(p=0.01, HR=0.22). In 113 stage III NSCLC patients, a trend that high pre-radiation K:T ratio was associated with short OS was observed(p=0.079). In subgroup analysis of 59 patients who received induction chemotherapy, multivariate analysis showed that pre-radiation K:T ratio lower than 0.07 was significantly associated with OS(p=0.04).

Conclusions: Favorable change of IDO activity during radiotherapy was associated with superior OS, PFS and local control. IDO activity also predicted the prognosis of patients who underwent induction chemotherapy before radiotherapy. IDO activity is a promising biomarker for prognosis in stage III NSCLC patients.

Keywords: Indoleamine 2,3-dioxygenase, non-small cell lung cancer, radiotherapy

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-027 Targeted Methylation Analysis of Circulating Cell-Free DNA to Predict Outcomes in Clinical Stage I NSCLC Patients

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Introduction: A cell-free DNA (cfDNA) targeted methylation assay developed at GRAIL for multi-cancer early detection (MCED) and to predict cancer signal origin (CSO) has demonstrated prognostic potential in a pan-cancer analysis. In this MCED, plasma cfDNA undergoes bisulfite sequencing targeting a panel of >100,000 methylation regions to detect the presence of circulating tumor DNA (ctDNA) and assess CSO.

Methods: We tested pre-operative plasma samples from clinically diagnosed stage I lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) patients using the MCED assay to evaluate prognostic utility in early-stage lung cancer. This retrospective cohort consisted of 260 patients with LUAD and 80 with LUSC. Patients were selected in a 2:1 ratio within each histology based on relapse (high-risk group) or non-relapse (low-risk group) within 5 years of tumor resection. Outcomes of interest were ctDNA detection, CSO, relapse after surgery, and clinical to pathological upstaging.

Results: Utilizing the classifier employed for MCED, ctDNA was detected in 86 of 260 (33%) patients with a detection rate of 63 of 174 (36%) in the high-risk group and 23 of 86 (27%) in the low-risk group (**Table 1**). Detection rate was lower in LUAD (40 of 180, 22%) than LUSC (46 of 80, [58%], **Table 1**). Top CSO prediction was accurate in 83% of ctDNA positive patients (71 of 86). The association between ctDNA detection and relapse within 5 years did not reach statistical significance (**Table 2**). ctDNA detection associated with clinical to pathological upstaging, particularly in LUSC (**Table 2**).

Conclusions: Pre-operative ctDNA detection using MCED did not significantly associate with recurrence within 5 years of surgery in clinical stage I LUAD and LUSC, however it did predict clinical to pathological upstaging. Customization of MCED algorithms may be required to improve prognostic utility in stage I NSCLC.

Table 1. Sensitivity of the methylation platform to detect stage I NSCLC by histology and risk group

	Test results (n)			
Subgroup	**Positive**	**Negative**	**Total**	**Sensitivity (95% CI)**
All	86	174	260	0.33 (0.27, 0.39)
Adenocarcinoma	40	140	180	0.22 (0.16, 0.29)
Squamous cell carcinoma	46	34	80	0.57 (0.46, 0.68)
High-risk group	63	111	174	0.36 (0.29, 0.44)
Low-risk group	23	63	86	0.27 (0.18, 0.37)

Table 2. Association of cancer detection with relapse and clinical to pathological upstaging

		Outcome				
Subgroup	**Test result**	**True**	**False**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Odds ratio (p value)**
Predict relapse within 5 years						
All	+	63	23	0.36 (0.29, 0.44)	0.73 (0.63, 0.82)	1.55 (0.13)
	-	111	63			
Adenocarcinoma	+	30	10	0.25 (0.18, 0.34)	0.83 (0.71, 0.92)	1.67 (0.21)
	-	90	50			
Squamous cell carcinoma	+	33	13	0.61 (0.47, 0.74)	0.50 (0.30, 0.70)	1.57 (0.35)
	-	21	13			
Identify patients that will be up-staged by pathology						
All	+	40	42	0.49 (0.38, 0.60)	0.76 (0.69, 0.82)	2.99 (0.0001)
	-	42	132			
Adenocarcinoma	+	16	23	0.29 (0.18, 0.43)	0.81 (0.73, 0.88)	1.8 (0.12)
	-	39	101			
Squamous cell carcinoma	+	24	19	0.89 (0.71, 0.98)	0.62 (0.47, 0.75)	13.05 (0.0002)
	-	3	31			

Keywords: cfDNA, relapse, staging

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-028 Schwann Cell Exosomes Promote Lung Cancer Progression via miRNA-21-5P Cargo

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Introduction: It is a new field that peripheral nerves participate in the construction of tumor microenvironment and the regulation of malignant biological behavior of lung cancer. We have previously reported that Schwann cells (SC) can promote lung cancer progression through secretory cytokines. In this study, we report the role of exosomal miRNAs in SC-mediated lung cancer progression.

Methods: Primary Schwann cells were obtained from the mouse sciatic nerve and cultured as previously reported. Exosomes were obtained by ultra-high speed centrifugation and observed by electron microscopy. Cell scratch assay, migration assay, CCK8 assay, Luciferase Reporter analysis and Fish assay were used to investigate tumor function and molecular mechanism.

Results: SC supernatant, SC exosomes, and the exosomal cargo exosomal miRNA-21 increased the proliferative, invasive, and migratory abilities of lung cancer cells *in vitro*. In addition, integrated bioinformatics analyses showed that hsa-miRNA-21-5P was associated with poor prognosis of NSCLC and particularly lung adenocarcinoma patients, while immunofluorescence analyses of human lung cancer tissues revealed co-expression of the SC marker S100B and hsa-miRNA-21-5P. Furthermore, SC exosomes and hsa-miRNA-21-5P enhanced H1299 lung cancer cell xenograft tumor growth *in vivo* in a mouse model. Dual-luciferase reporter gene assays showed that hsa-miRNA-21-5p binds to RECK, PAN3, and GID4 UTRs in 293T cells.

Conclusions: Taken together, SC secreted exosomal miRNA-21 plays an oncogenic role in lung cancer progression.

Keywords: Lung Cancer, Schwann Cells, microRNA

EP16.02 TUMOR BIOLOGY AND BIOMARKERS - MINIMALLY INVASIVE BIOMARKERS

EP16.02-029 Plasma-Based Next Generation Sequencing for Molecular Characterization of Lung Adenocarcinoma: A Multicentric Cohort From Argentina

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Introduction: Next-generation sequencing (NGS) has transformed molecular characterization of lung adenocarcinoma. Although tumor tissue has been considered the gold standard for molecular testing, it has several limitations. Liquid biopsy represents a non-invasive, feasible and reproducible alternative to tissue biopsy for the genotyping of non-small cell lung cancer (NSCLC).

Methods: We conducted a retrospective analysis of a multicenter cohort of patients (pts) with advanced non-squamous NSCLC who underwent liquid biopsy (FoundationoneLiquid) between Jun and Dec 2020 at diagnosis or disease progression to TKI treatment in *EGFR/ALK+* tumors. We describe the molecular alterations identified and characterized oncogenicity and actionability of the different genomic variants according to OncoKB. Samples collected at diagnosis were divided into two cohorts based on the presence or absence of oncogenic variants in potentially actionable genes. We categorized the most prevalent alterations found in non-actionable gene cohort and compared it frequency between both cohorts. Correlations were assessed using Fisher's exact tests.

Results: A total of 52 pts were included, median age was 71 years [41-92], 32 pts (60%) female, 35 pts (67%) current or former smokers. Liquid samples from 43 pts were collected at diagnosis and 9 at progression to treatment with TKI (*EGFR* n = 8, *ALK* n = 1). The median tumor mutational burden (TMB) value was 3 mut / mb [0-172] in 39 evaluable samples; microsatellite instability (MSI-H) was found in 1 of 3 evaluable samples. A total of 254 molecular alterations were identified in 80 genes (n = 50): *TP53* (57.7%), *DNMT3A* (38.5%), *STK11 / LKB1* (17.3%), *ATM* (15.4%), *KRAS* [15.4%, *G12V* (n = 4), *G12C* (n = 2), *Q61H* (n = 1)], *ASXL1* (13.5%), *TET2* (13.5%), *NF1* (9, 6%), *APC* (9.6%), *BRCA2* (9.6%), *BRCA1* (7.7%), *EGFR* (7.7%) and *ALK* (3.8%). Alterations in potentially actionable genes at diagnosis were identified in 49% of the patients (21/43) as follow: *KRAS* 18.6% (8/43), *NF1* 11.6% (5/43), *EGFR* 9.3% (4/43), *ALK* 4.6% (2/43), *MET* 4.6% (2/43), *BRAF* 4.6% (2/43), *PTEN* 4.6% (2/43), *CDKN2A* 4.6% (2/43), *ERBB2* 4.6% (2/43), *CDK12* 2.3% (1/43), *FGFR* 2.3% (1/43), *ROS1* 2.3% (1/43) and *MTOR* 2.3% (1/43). No actionable genomic alterations were identified in 51% of the pts (22/43), whereas most frequent alterations were: *TP53* 50% (11/22), *STK11* 23% (5/22), *ASXL1* 18% (4/22), *TET2* 18% (4/22), *CHEK2* 9% (2/22); *TP53* mutation was more frequently identified in the actionable-gene cohort (p=0.05). Potential germline pathogenic alterations with VAF > 40% were identified in 11% of the pts (6/52), including *ATM*, *BRCA1, BRCA2, TP53, CSF3R* and *CHEK2*. Loss of *T790M* and *C797S* mutation were identified at progression in the *EGFR+* cohort.

Conclusions: This analysis provides the first description of NGS genotyping on liquid biopsy of a cohort of patients with advanced NSCLC in Argentina.

Keywords: NSCLC, NGS, Liquid biopsy

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-001 High Frequency of KRAS Mutation, Uncommon EGFR Mutation and TMB-H in Xuanwei Female Patients with Lung Adenocarcinoma

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Introduction: In female patients from Xuanwei county of China, the incidence and mortality of lung adenocarcinoma (LUAC) are extremely high, mainly due to abnormal exposure to carcinogenic polycyclic aromatic hydrocarbons produced during indoor combustion of bituminous coal. Thorough understanding of molecular features of Xuanwei female LUAC patients, when compared to reference Chinese female LUAC patients, could be beneficial to improve the management strategy for precision treatment in this high-risk population.

Methods: Formalin-fixed paraffin-embedded tissue of LUAC was collected from 64 Xuanwei female patients (the Xuanwei female cohort) and 792 female patients from other regions in China (the reference Chinese female cohort). Targeted sequencing with 450 cancer-related genes was performed in a College of American Pathologists-accredited and Clinical Laboratory Improvement Amendments-certified laboratory. Genomic alterations and tumor mutational burden (TMB) were assessed.

Results: Diagnosis age of Xuanwei LUAC female patients was younger than that of reference Chinese female patients (54 years [36:78] vs. 59 years [27:91], $p < 0.01$). Family history of LUAC was found in 48.4% of Xuanwei female cohort and 27.4% ($p < 0.001$) of reference Chinese female cohort. Top 5 mutated genes were *EGFR* (60.9%), *TP53* (32.8%), *KRAS* (23.4%), *MED12* (21.9%) and *LRP1B* (17.2%) in Xuanwei female with LUAC, in contrast to *EGFR* (70.3%), *TP53* (42.9%), *TERT* (13.0%), *RBM10* (11.9%), *CDKN2A* (9.5%) in reference Chinese female with LUAC. In Xuanwei LUAC female, the mutation frequency of *KRAS* G12C (14.1% vs. 1.3%, $p < 0.001$) and G12V (9.4% vs. 0.8%, $p < 0.001$) was significantly elevated than that of reference Chinese female cohort. When compared to reference Chinese female cohort, Xuanwei female LUAC cohort had significant increase in *EGFR* G719X (28.1% vs. 2.9%, $p < 0.001$), *EGFR* L861Q (4.7% vs. 0.6%, $p < 0.05$), *EGFR* S768I (14.1% vs. 0.9%, $p < 0.001$), defined as uncommon *EGFR*-sensitive mutations; and a significant decrease in *EGFR* L858R (15.6% vs. 32.7%, $p < 0.01$) and *EGFR* exon 19del (3.1% vs. 18.4%, $p < 0.001$), defined as classical *EGFR*-sensitive mutations. Eighteen Xuanwei female patients with LUAC had at least two *EGFR*-related mutations; among them, 9 cases were *EGFR* G719X and S768I co-mutations. Furthermore, TMB-H (≥10 Muts/Mb) was detected in 37.5% of Xuanwei female cohort versus in 8.5% of reference Chinese female cohort. Mutations in the homologous recombination repair (HRR) signaling pathways occurred more frequently in LUAC patients from Xuanwei in comparison with corresponding reference Chinese cohort (12.5% vs. 4.7%, respectively, $p < 0.05$).

Conclusions: In conclusion, the present study evidenced that Xuanwei female patients with LUAC had specific genetic profile when compared to reference Chinese female patients, indicating this high-risk female population could possibly benefit from therapy targeting *KRAS* mutation, uncommon *EGFR* mutations and HRR pathway deficiency, as well as immunotherapy.

Keywords: lung adenocarcinoma, Xuanwei female patients, uncommon EGFR mutation

EP16.03-002 Mechanisms of Resistance to First-line Osimertinib in Hispanic Patients with EGFR mutant Non-Small Cell Lung Cancer (FRESTON-CLICaPʃ)

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Introduction: Osimertinib is a third-generation EGFR-TKI approved for advanced NSCLC treatment, initially in the relapse scenario with T790M mutation but currently in the first-line setting. Effectiveness and safety have been studied in multiple clinical trials and observational studies; however, data regarding the Hispanic population and post-progression after Osimertinib treatment is scarce. In this study, we present the most significant real-world analysis of Osimertinib in the first line setting for NSCLC among Hispanic patients, with an in-depth analysis of post-progression results.

Methods: A multicenter, multinational retrospective cohort study of Hispanic patients treated with Osimertinib as first-line therapy for EGFR mutated NSCLC. Subjects were adult patients with a confirmed diagnosis of metastatic NSCLC and evidence of an EGFR sensitizing mutation. All patients received Osimertinib at 80 mg/day until evidence of disease progression or intolerable adverse effects. NGS was performed in tumor samples or liquid biopsies in patients who progressed. The primary outcome was progression-free survival and the secondary outcome was survival post-progression.

Results: 94 patients from Mexico, Argentina, Costa Rica, Colombia, Panama, Chile, and the USA were included. The median age was 59 years. Median progression-free survival was 14.4 months (95%CI 12.4-18.2 months). Survival post-progression (SPP) under Osimertinib treatment was 7.73 months (95%CI 4.07 months-NA). Factors affecting progression-free survival included presence of liver metastases at diagnosis and a tumor mutation burden higher than 5 mut/Mb.

Conclusions: Osimertinib is effective and safe in treating Hispanic patients with mNSCLC as first-line therapy. Despite effectiveness, mechanisms of resistance, such as other actionable targets, were found. Liver metastases and a high tumor mutation burden were related to lower progression-free survival.

Figure 1. Progression free survival under Osimertinib treatment.

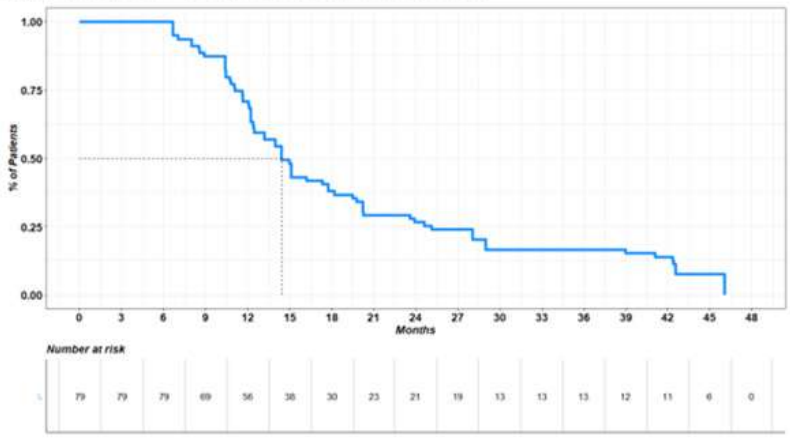
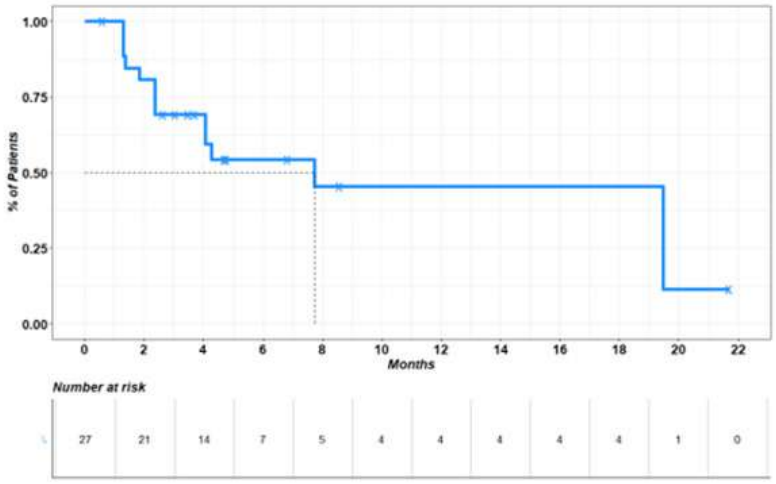


Figure 2. Survival post Osimertinib progression.



Keywords: Non-Small-Cell Lung cancer, Osimertinib, EGFR mutations

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-003 Systematic Population-based Identification of NTRK Fusion Genes Among Hispanic Patients with Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Neurotrophic tropomyosin-related kinases (NTRKs) A, B, and C constitute a receptor tyrosine kinase family involved in neuronal development. They are encoded by *NTRK1-3* genes, respectively. NTRK fusions create chimeric genes in which the 3' region of the *NTRK* gene is joined with a 5› sequence of a fusion partner gene. As a result of the fusion, a chimeric oncoprotein originates a ligand-independent constitutive activation of the kinase activity. This chimeric kinase varies among tumor histology and population, being 0.3-3% in non-squamous NSCLC; however, little is known about these mutations among the Hispanic population. We develop a systematic population-based identification of NTRK fusion genes in a large population of NSCLC Hispanic patients.

Methods: Patients were identified in the FICMAC's biobank database (N= 812). EGFR, ALK, and ROS-negative tumors were 'screened' for NTRK expression using the pan-TRK (EPR17341) Assay. Samples with positive results were analyzed for NTRK fusions by Next Generation Sequencing (NGS) using Oncomine Focus Comprehensive Assay (OFA). Confirmation was performed on each positive sample using RNA integrity assay and RNA-seq Nanostring-based screening.

Results: 812 cases of NSCLC were retrospectively obtained, and 26 were excluded due to insufficient tumoral representation. Of the 264 cases evaluated completely, 6 (2,27%) were positive for NTRK by IHC. In all cases positive by IHC, NTRK fusions were determined by NGS using Oncomine Focus Assay® (OFA). None of the samples processed by OFA were positive, so an RNA integrity assay was done, reporting highly degraded samples. Then, on two samples unequivocally positive by IHC, RNA-seq resulted positive for a *TP53-NTRK1* fusion. The global frequency of NTRK fusions among Hispanic patients with NSCLC detected in this study was 0,67%.

Conclusions: The frequency of NTRK fusions among Hispanic patients with NSCLC is similar to that previously reported worldwide. Negative results on NGS may be related to pre-analytical factors such as DNA quality. To the best of our knowledge, this is the first study using a systematic population-based identification of NTRK fusion genes in Latin America. This approach can be considered a validation of ESMO recommendations to detect NTRK.

Figure 1. Diagram of selection and processing of tumor RNA samples isolated from paraffin-embedded tissue. The software and methods for obtaining genotyping data from the samples recruited for the study are also shown.

Keywords: NTRK Fusions, Non-Small Cell Lung Cancer, Hispanic pupulation

EP16.03-004 Targeting SHP2 Reverts Oncogenic Mediated Resistance to KRAS-G12C Inhibition

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Introduction: Constitutively active mutant RAS GTPases are key oncogenic drivers in many cancers. Targeting mutant KRAS has gained momentum as the first KRAS-G12C mutant specific inhibitor, sotorasib, has been approved for the treatment of NSCLC. Activity of sotorasib was demonstrated in patients with advanced lung cancers harboring KRAS-G12C mutations, however, resistance development via on-target and off-target mechanisms has been monitored. Mechanistic data and strategies to overcome resistance to targeted KRAS-G12C inhibitors are largely lacking.

Methods: Biopsies were obtained from progressing lung cancer (NSCLC stage IV B, KRAS-G12C) at initial diagnosis and from relapse after treatment with the KRAS-G12C inhibitor sotorasib. To identify the underlying resistance mechanism, molecular analyses of both biopsies were performed. In addition, strategies to overcome KRAS-G12C inhibitor resistance were evaluated *in vitro* and *in vivo*.

Results: Molecular profiling of the post-progression biopsy revealed *de novo* acquisition of ERBB2/HER2 gene copy number gain and retention of the KRAS-G12C mutation. We generated KRAS-G12C lung cancer models overexpressing HER2 to investigate HER2 gain as the relevant resistance mechanism. Overexpression of HER2 significantly reduced sensitivity to sotorasib in KRAS-G12C models but not in KRAS-G12S mutant A549 cells. In resistant cells, MAPK signaling remained active despite sotorasib treatment. Combining a SHP2 inhibitor (TNO155) and sotorasib synergistically overcame HER2-mediated resistance *in vitro* and *in vivo*.

Conclusions: Our findings introduce HER2 gain as a clinically relevant off-target resistance mechanism to KRAS-G12C inhibition that can be rescued by co-targeting SHP2. This finding adds a rationale for combined targeting of KRAS-G12C and SHP2 in clinical settings.

Keywords: KRAS-G12C inhibition, Acquired resistance, SHP2 inhibition

EP16.03-005 Australian Non-Small Cell Lung Cancer (NSCLC) Biomarker Testing Practices - A Survey of Medical Oncologists and Pathologists

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Introduction: NSCLC is associated with an increasing number of molecularly defined subsets, several of which now have approved targeted therapies. Variation in how different biomarker assays are utilised is likely. We sought to determine the current biomarker testing practices from the perspective of medical oncologists (MO) and pathologists (P) at Australian sites to understand variations in practice and potential influencing factors.

Methods: An online survey was sent to MO and P with expertise in NSCLC to assess biomarker testing patterns. The unit of the study was the institution, such that only one response for each Australian cancer centre and laboratory was accepted. Survey candidates were identified through cooperative group databases, clinical networks and online searches. This study was supported by an unrestricted educational grant from Amgen, who had no input into the survey conduct.

Results: 64 responses were received, representing 42 Australian cancer centres and 22 laboratories. Site variables are summarised in Table 1. 86% of sites were using multigene panels for biomarker testing, the majority of which were next generation sequencing (NGS) assays. The median number of genes assessed was 7 (range 5-50) for the cancer centres and 15 (range 5-50) for laboratories. Reflex biomarker testing was initiated at diagnosis in 38% of cancer centres. MO reported numerically higher testing rates compared to P for almost all individual biomarkers (PDL1 100% vs 91%, ALK 100% vs 91%, EGFR 98% vs82%, ROS1 95% vs91%, KRAS 83% vs 64%, BRAF 74% vs68%, HER2 45% vs 45%). Turnaround times (TAT) for biomarker test were reported as more than 14 days in 43% by MO and 14% by P. Both groups considered inadequate funding to be the major barrier to broad implementation of NGS panel testing (64% each).

Table 1. Data comparing cancer centres (MO) and laboratories (P)

Variables	Cancer Centres (MO) N=42	Laboratories (P) N=22
Institution type		
Public, n (%)	29 (69%)	17 (77%)
- Metropolitan : Regional	- 20 : 9	- 15 : 2
Private, n (%)	13 (31%)	5 (23%)
- Metropolitan : Regional	- 10 : 3	
Tests utilised		
Multigene assay, n (%)	36 (86%)	19 (86%)
- NGS assay	- 28 (79%)	- 15 (78%)
Single gene, n (%)	6 (14%)	3 (14%)
Barriers to implementation of NGS		
- Inadequate funding	27 (64%)	14 (64%)
- Long turn around time	26 (62%)	7 (32%)
- Cost to patient	17 (41%)	7 (32%)
- Lack of infrastructure	15 (36%)	12 (55%)
- Lack of access to panel testing	12 (29%)	3 (14%)
- Lack of expertise to perform and interpret the test	8 (19%)	6 (27%)

Conclusions: The majority of surveyed sites have moved to multigene panel testing (most often NGS), but reflex testing is yet to be widely adopted. Discordant responses between MO and P in testing rates could be driven by more than one laboratory performing biomarker testing for some cancer centres, or by P seeing more early stage cancers where testing is not always routine. Longer perceived TAT by MO could reflect the additional time required for samples to reach the laboratory. Biomarker testing was greatest for targets for which there are approved therapies in Australia (currently PDL1, EGFR, ALK, ROS1).

Keywords: Biomarkers, NSCLC, Survey

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-006 Genetic Characteristics of EGFR Concurrent Variants with RB1 and TP53 in NCSLC Patients

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Introduction: EGFR-TKIs (tyrosine kinase inhibitor) can effectively improve the survival rate of NSCLC patients with *EGFR* sensitive mutations. However, concomitant alterations along with *EGFR* mutations often affect the effect of EGFR-TKIs. The genome characteristic of *EGFR* co-mutation is of great significance for guiding clinical treatment. In this study, we first reported the genetic characteristics of *EGFR/RB1/TP53* co-variation in the Chinese non-small cell lung cancer (NSCLC) cohort.

Methods: Retrospective cohort was collected and somatic variants including short variants, copy number variations and gene rearrangements were analyzed following CAP/CLIA-certificated workflows. Chi-Square Test was applied to significance statistics.

Results: 10,182 NSCLC patients were investigated and 48.9% (4978/10182) harbored *EGFR*-sensitive alterations. The patients with *EGFR*-sensitive alterations includes 3,135 (63.0%) female and 1,843 (37.0%) male. Among them, 2,209 (44.4%) were diagnosed as advanced stage (stage ≥ III). And, the median age was 60 years old (range, 20-92 years old) and median TMB (Tumor Mutation Burden) was 3.7 muts/Mb (range, 0-138.7 muts/Mb). Further, these patients were performed IHC with PD-L1 antibody and 593 (11.9%) showed positive (TPS>1%) and 2,579 (51.8%) showed negative. Among the *EGFR*-sensitive altered cases, the most frequent alterations were detected in *TP53* (48.5%), *RBM10* (9.7%), *CDKN2A* (9.3%), *TERT* (8.5%) and *PIK3CA* (7.3%). *RB1* variants showed in 342 cases with a percentage of 6.9%, including 90.0% short variants, 8.7% copy number change and 2.0% gene rearrangements; *TP53* showed in 2,415 cases with a percentage of 48.5%, including 99.6% short variants, 0.23% copy number change and 0.3% gene rearrangements. Next Generation Sequencing (NGS) showed obvious advantage in the detection of copy number change and gene rearrangements, which couldn't be detected by the traditional experiment method. *EGFR/TP53/RB1* triple-altered account for 85.3% in *EGFR/RB1*-altered cases and 5.9% in *EGFR*-altered cases (comparable to Offin et.al 2019). We followed up a patient with *EGFR/TP53/RB1* triple mutation and found that TKI required resistance appeared rapidly after only 5 months of SD.

Conclusions: In NSCLC, 3.4% and 23.7% of patients with *EGFR* sensitive mutations were accompanied by *RB1* and *TP53* alterations, respectively, and nearly 2.9% of patients showed triple changes. *EGFR* sensitive mutations with alterations in *RB1* and *TP53* may affect the effect of EGFR-TKIs. NGS plays an important role in the precise treatment of NSCLC patients with *EGFR* sensitive mutation.

Keywords: EGFR-TKIs, NCSLC, EGFR/RB1/TP53

EP16.03-007 Comprehensive Analysis of m6A-Related Gene Mutation Characteristics and Prognosis in Lung Adenocarcinoma

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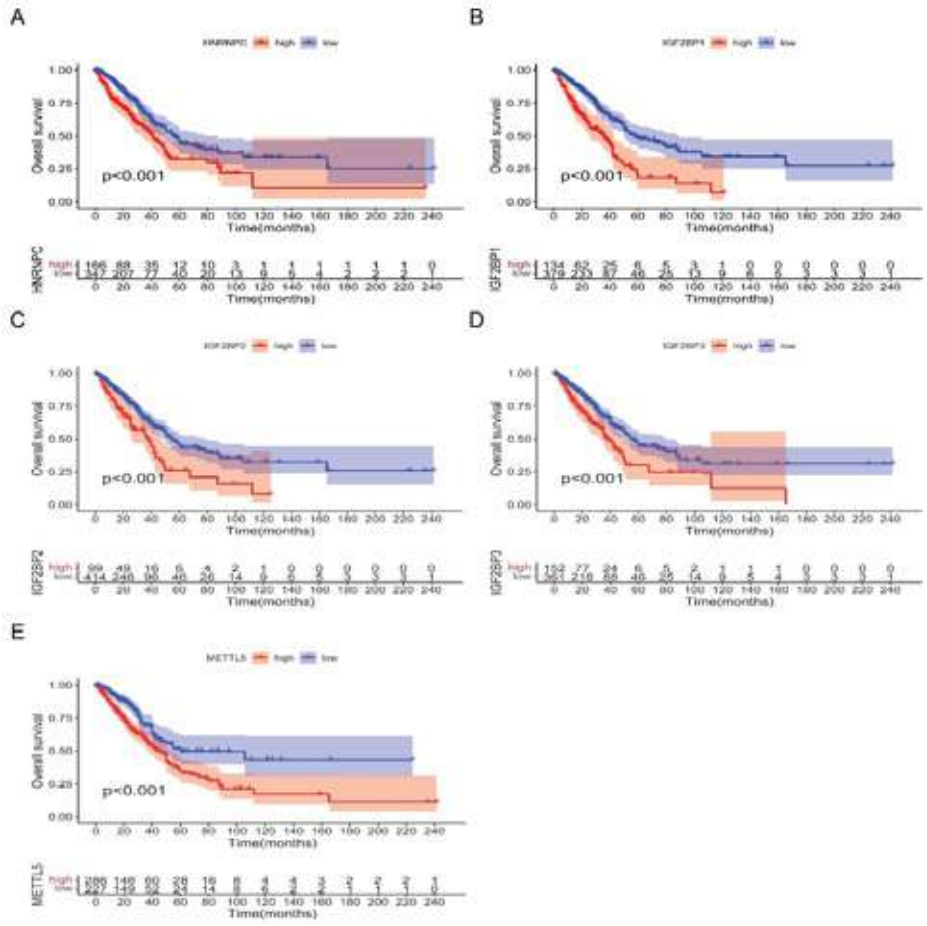
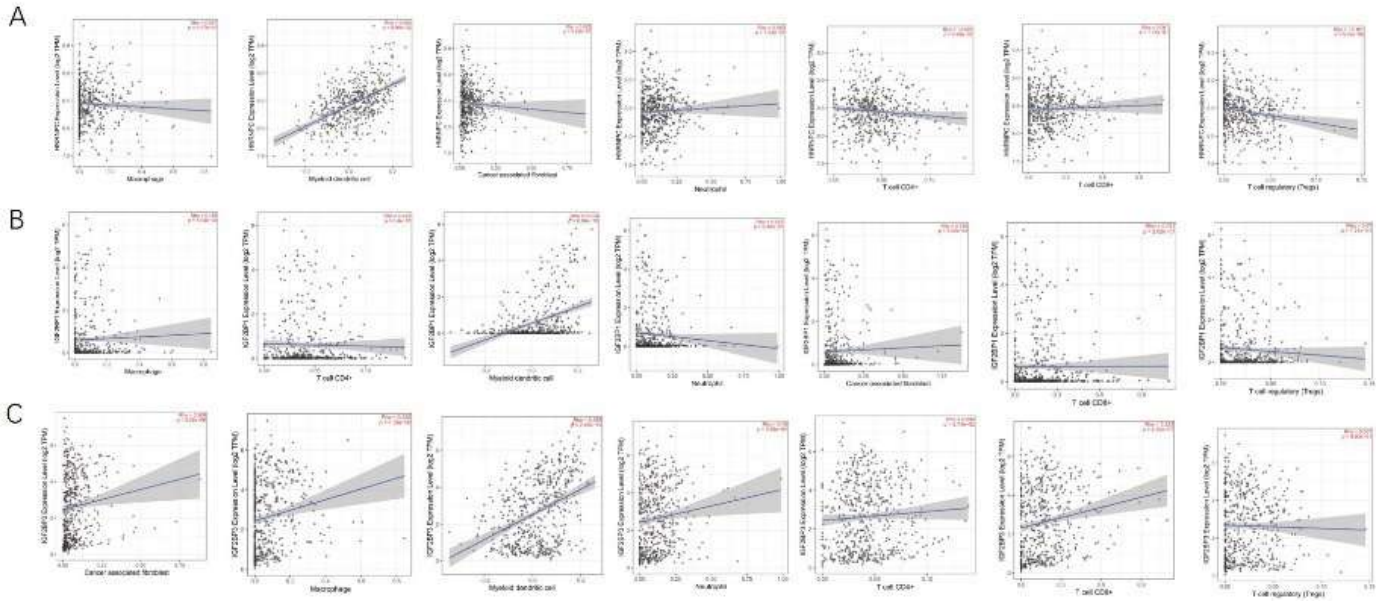
Introduction: Lung adenocarcinoma is an invasive disease. Studies have shown that m6A RNA methylation abnormalities play an important role in the pathogenesis of lung cancer. However, the specific molecular mechanism remains unclear. This study was designed to characterize the mutation of m6A related genes and explore their prognostic role in lung adenocarcinoma.

Methods: RNA-seq data and somatic mutation data of TCGA-LUAD were downloaded from UCSC XENA. M6A related genes were selected from previous literatures. Univariate Cox regression analysis and Kaplan-Meier were used to explore the correlation between m6a-related genes and LUAD prognosis. The correlation between m6a-related genes and clinical parameters and immune-related indicators was explored by Spearman correlation analysis.

Results: In LUAD, m6a-related genes have a high mutation frequency. C>A and C>T are the two main mutation types. Patients with high expressions of HNRNPC, IGF2BP1, IGF2BP2, IGF2BP3, METTL5 have poor prognosis in LUAD (**Figure 1A-E**). HNRNPC, IGF2BP1 and IGF2BP3 were correlated with clinical correlation analysis and immune cells (**Figure 2A-C**). Then, we enriched the co expressed genes of the three m6A genes. It is found that HNRNPC is mainly enriched in ribonucleoprotein complex biogenesis. IGF2BP1 was mostly related to mitotic cell cycle checkpoint. IGF2BP3 was related to nuclear division pathway.

Conclusions: Our study identified novel immune-related prognostic markers and investigated the potential mechanisms of prognostic markers in regulating the etiology of LUAD. These findings enrich our understanding of the relationships between m6A-related genes and LUAD, and may provide new ideas in the treatment of LUAD patients.





Keywords: LUAD, m6A-related genes, prognostic markers

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-008 The Landscape of NFE2L2 Alteration in Chinese Lung Cancer Patients

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Introduction: *NFE2L2* encodes a transcription factor which is a member of a small family of basic leucine zipper (bZIP) proteins. *NFE2L2* variations were detected in many tumors, such as lung cancer, esophageal cancer, renal cell carcinoma and other cancer types. The landscape of *NFE2L2* gene in lung cancer of Chinese population has not been descripted.

Methods: 1103 normal-paired samples from patients with lung cancer were analyzed using hybridization capture-based next generation sequencing, and alterations including single base substitution, short and long insertion/deletions, copy number variations, gene fusions and rearrangements.

Results: *NFE2L2* gene was altered in 3.0% (33 of 1103) of all lung cancer samples. A total of 34 variations of *NFE2L2* were found, including in exon 2 (27/34), exon 5 (4/34), exon 3 (2/34) and exon 4 (1/34), no variation in exon 1. In exon 2, *NFE2L2* D21H, V36_E45del, F37_E45del, R42P, E67Q and L76_E78delinsQ have not been reported before. In addition, we identified copy number amplifications of *NFE2L2* in three lung squamous cell carcinomas patients. Furthermore, in our cohort, *NFE2L2* mutation carriers also owned other actionable or driver mutation, the most frequent one was *TP53* (84.8%), followed by *CDKN2A* (33.3%), *LRP1B* (33.3%), *PIK3CA* (27.3%), and *MLL2* (27.3%). Analysis of co-mutation correlation of *NFE2L2* showed that *NFE2L2* variation was correlated with *IRF2*, *TERC*, *ATR*, *ZMAT3* and *SOX2* ($p<0.001$). *TERC*, *ZMAT3* and *SOX2* located at chromosome 3q36, which has a higher frequency of amplification in squamous cell carcinoma. In TCGA cohort (Pulmonary Squamous Carcinoma project), the patients with *NFE2L2* variations and 3q36 amplification had a longer median survival than those group without 3q36 amplification (63.59 *vs* 32.04 months, $p = 0.0459$).

Conclusions: *NFE2L2* deleterious mutations are highly diverse and present at low to moderate frequencies in lung cancer. Meanwhile, our study showed the genomic characterization and prognostic analysis among *NFE2L2* population with lung cancer should be considered in further study.

Keywords: NFE2L2, Lung cancer, 3q36 amplification

EP16.03-009 Patterns of KEAP1 Genomic Co-alterations in Advanced Non-small Cell Lung Cancer Identified by Plasma-Based Genyotyping

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Introduction: Pathogenic genomic alterations (GA) in KEAP1 may result in oncogenesis and/or drug resistance and have been shown to be prevalent across solid tumors. Patients (pts) with advanced non-small cell lung cancer (aNSCLC) and KEAP1 and/or STK11 alterations have been shown to have poorer response to immune checkpoint inhibitors (ICI) which appears to be modulated by KRAS mutational status in aNSCLC, however broader understanding of KEAP1 itself is limited including in the setting of oncogenic mutations with targeted therapy options. We aimed to describe KEAP1 GAs as identified by a well-validated liquid biopsy (Guardant360).

Methods: Genomic results from patients (pts) with aNSCLC who had Guardant360 testing as part of routine clinical care were queried from 10/1/2020-12/31/2021. Analysis was limited to the first Guardant360 test in pts who had more than one test. Clinical features were extracted form test requisition forms. Pts were considered to be KEAP1mut if they had nonsynonymous, characterized GAs in KEAP1. GAs in genes listed as recommended or emerging in NCCN guidelines for aNSCLC were assessed for co-mutation status.

Results: 542 (3.7%) pts were KEAP1mut in the study period; 7 pts had multiple KEAP1mut GAs. Most pts were newly diagnosed (430/542, 79%) at the time of testing; median age was 68 years (range:34-91), 310 (57%) were male. 407 (75%) had adenocarcinoma, 72 (13%) had squamous cell carcinoma, all others had aNSCLC NOS. 189 (35%) KEAP1mut pts also had STK11 GAs. 268 (50%) KEAP1mut pts had >1 co-occurring GAs in guideline-recommended/emerging biomarkers for aNSCLC (table 1); there were no significant differences based on STK11 status. Of pts who had at least 1 KRAS GA (n=228), 45 had multiple RAS findings while 14 had RAS alongside another biomarker including EGFR, MET, and BRAF. RET and ERBB2 did not co-occur with other GAs; ALK and NTRK fusions co-occurred only with MET amplifications. 479 (88%) KEAP1mut pts had TMB evaluable, of which the median TMB was 18.78 mut/Mb (range: 2.78-106.8). 259 (54%) KEAP1mut patients had TMB >16 mut/Mb (>20 mut/Mb - 225, 47%).

Conclusions: KEAP1mut are identified in aNSCLC pts by plasma-based testing which may help expedite identification of KEAP1 alterations and identify patients for clinical trials. KEAP1mut pts had did not have different rates of guideline-based biomarkers based on STK11 status, suggesting KEAP1 impact on outcomes may be investigated independent of STK11 status. The clinical relevance of KEAP1 GAs in oncogenic driver mutation aNSCLC warrants investigation.

Table 1. Co-occurring GAs in pts with KEAP1 mutations stratified by STK11 mutation status

	STK11 status	
Guideline-recommended or emerging biomarker	*STK11 wildtype*	*STK11 mutation*
KRAS G12C	66 (12%)	70 (13%)
KRAS non-G12C	70 (13%)	56 (10%)
EGFR	12 (2%)	4 (<1%)
ALK fusion	1 (<1%)	0
ROS1 fusion	0	0
RET fusion	2 (<1%)	0
NTRK fusion	1 (<1%)	0
BRAF V600E	2 (<1%)	0
MET exon 14 skipping	1 (<1%)	1 (<1%)
MET amplification	9 (2%)	1 (<1%)
ERBB2 mutation	6 (1%)	3 (<1%)

Keywords: non-small cell lung cancer, NSCLC, KEAP1, STK11

EP16.03-010 Molecular and Clinical Characterization of Lung Adenocarcinoma with Respect to Patient Age at Diagnosis

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Introduction: Lung cancer is primarily a disease of the elderly, with <10% of patients being under 55 years (US, www.seer.cancer.gov) and a median age at diagnosis of approximately 71 years. Based on registry studies, lung cancer survival has been found to be better in younger patients, although the latter could be influenced by co-morbidities. Interestingly, there has been little in-depth analysis of whether genome-wide molecular alterations like copy number alterations, transcriptional, epigenetic and mutational patterns differ with respect to age at diagnosis both in lung cancer in general and in AC specifically. Moreover, of the few reported to date, differences exist in how patients were stratified, and whether histology was accounted for. In this study we sought to address the question of whether and how clinical characteristics, molecular alterations, and molecular phenotypes differ between patient populations with early-stage lung adenocarcinoma with respect to age at diagnosis.

Methods: We used compiled datasets from public repositories with available age at diagnosis and other clinicopathological data. Patients were stratified into age at diagnosis 10-year bins corresponding to < 50, 50-60, 60-70, 70-80, and > 80 years. Available molecular data included copy number profiles, gene expression profiles, methylation profiles and mutational data; these were used to investigate focal and genome-wide DNA alterations, epigenetic alterations, immune composition, and transcriptional patterns in relation to age at diagnosis.In parallel, to assess clinicopathological variables on a population-based level, we accessed data from over 2000 lung cancer patients with AC from the national quality registry for lung cancer in Sweden (NLCR, www.cancercentrum.se) diagnosed between 2002-2020.

Results: Previously reported associations of younger patient age with the likelihood of harboring certain driver mutations (ex EGFR and ALK) were confirmed. We also found an association between age at diagnosis and certain mutational signatures. Signature 4, the smoking related signature, decreased over age and signature 7, UV light exposure and nucleotide excision repair related signature, increased over age. Signatures 1 (age related) and 3 (BRCA-ness) showed, though not statistically significant, a tendency to increase over age. However, larger patient groups would be needed to confirm whether these trends hold true or not. Overall tumor mutational burden decreased over age in the investigated cohort. However, age could not strongly capture transcriptional variation across the cohorts investigated; and overall gene expression, immune cell marker gene expression, gene expression-based signatures representative of different biological processes, amount of copy number alterations, and neoantigen burden did not appear distinct across the age groups.

Conclusions: Based on our findings, age at diagnosis alone does not appear to provide an additional layer of biological complexity above that of proposed genetic and transcriptional phenotypes of lung cancer. Consequently, an individual patient's response to treatment is probably less influenced by age and more driven by tumor biology.

Keywords: Lung adenocarcinoma, age at diagnosis, molecular characterisation

EP16.03-011 The European Program for ROutine Testing of Patients with Advanced Lung Cancer (EPROPA) 1 Year Activity

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Introduction: To fill the gap affecting the relevant heterogeneity of molecular testing and cancer care across Europe, the Women Against Lung Cancer Europe (WALCE) Association promoted the European Program for Routine testing of Patients with Advanced lung cancer (EPROPA) and provides a molecular screening platform for NSCLC samples characterization with the aim of increasing the detection of targetable drivers and optimizing patients' access to clinical trials.

Methods: From January 2021 to February 2022, 24 centers sited at 6 different European countries (Greece, Slovenia, Romania, Slovakia, Italy, Portugal) joined EPROPA with overall 205 advanced NSCLC patients registered to the program. Anonymized patients' clinical pathological data were shared through EPROPA platform and formalin fixed paraffin embedded (FFPE) tissue samples were shipped to the molecular pathology unit of the Reference Center (University of Turin) for molecular analysis. A targeted next generation sequencing (NGS) approach, using the Ion Torrent platform (ThermoFisher Scientific) with Oncomine™ Comprehensive Assay v3 (OCAv3) has been performed, allowing to cover 161 cancer associated genes in hot spot region and full length, including CNV analysis and fusion detection. Molecular reports have been discussed within molecular tumour board (MTB) to assess patients' eligibility for targeted therapies available either in clinical trials or in real world practice. For those patients included in clinical trials, WALCE provides logistic and financial support during the treatment journey.

Results: Among 205 NSCLC patients registered to EPROPA, 121 (59%) were over 65 years/old, 72 (35%) aged between 50-65 years/old and 12 (6%) <50 years/old. About half of patients (99/48%) were females, and 158 (77%) were never/former smokers. The majority of analyzed samples were adenocarcinoma (169/82%), 19 (9%) squamous cell carcinoma and 18 (9%) other histological subtypes. 85 (41%) patients received molecular profiling by EPROPA for a newly diagnosed metastatic disease since NGS was not available at their center, while 121 (59%) had previously received non-NGS molecular profiling and were on anticancer treatment. A median turnaround time of 10 (8-12) days was reported for providing the NGS molecular report. A targetable oncogenic alteration was identified in 117 out of 205 (56%) analyzed samples, including: KRASp.G12C (18), KRAS p.G12V (3), other KRAS mutations (25), EGFR activating mutations (25), EGFRex20ins (6), ERBB2 mutations (7), ALK (7), ROS1 (4), RET (5), and NRG1 (1) rearrangements, METex14skipping (6), MET amplification (1), FGFR mutations (2) and amplification (1) and molecular alterations within the homologous recombination repair genes (6). A total of 82/117 (70%) patients harboring driver alterations received a targeted therapy either in clinical practice or in clinical trials. A clinical trial was proposed by the MTB to 64/117 (55%) of patients, but only six of them were enrolled since worsening of clinical status and/or their medical oncologist's decision.

Conclusions: These preliminary results confirm the feasibility of the program in the real world practice scenario, supporting the implementation of NGS based molecular characterization of advanced NSCLC samples in highly specialized centers with the availability of MTB in order to reduce the unequal access to tests, drugs and clinical trials in Europe.

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-012 Novel Human-derived EML4-ALK Fusion Cell Lines Identify Ribonucleotide Reductase RRM2 as a Target of Activated ALK in NSCLC

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Introduction: Echinoderm microtubule-associated protein-like 4 (EML4)-Anaplastic Lymphoma Kinase (ALK) rearrangements occur in 7% to 10% of lung adenocarcinomas and are targets for treatment with tyrosine kinase inhibitors. Here we have developed three novel EML4-ALK-positive patient-derived Non-Small-Cell-Lung-Cancer (NSCLC) cancer cell lines, CUTO8 (variant 1), 9 (variant 1), and 29 (variant 3), and included a fourth ALK-positive cell line YU1077 (EML4-ALK variant 3) to study ALK-positive signaling and responses. Variants 1 and 3 are the most common EML4-ALK variants expressed in ALK-positive NSCLC, and currently, cell lines representing these EML4-ALK variants are limited.

Methods: Resazurin assay was performed to evaluate cell viability. Protein levels were determined using western blotting. RNA sequencing was performed in all four cell lines to identify differentially expressed genes. Whole-genome sequencing was performed to determine the presence of EML4-ALK fusion and ALK tyrosine kinase inhibitor resistance mutations.

Results: In this study, we have confirmed the expression of the corresponding ALK fusion protein and assessed their sensitivity to a range of ALK tyrosine kinase inhibitors (TKIs). These patient-derived cell lines exhibit differential sensitivity to ALK TKIs, such as lorlatinib, brigatinib and alectinib, with EML4-ALK variant 3 containing cell lines exhibiting an increased sensitivity to lorlatinib and brigatinib as compared to alectinib. These cell lines were further characterized by RNA-seq analysis, identifying the ribonucleotide reductase regulatory subunit 2 (RRM2) as a putative co-driver [RP1] and therapeutic target in ALK-positive NSCLC. Interrogation of publically available data revealed that high RRM2 expression is associated with poor prognosis in the ALK-positive NSCLC patient subgroup. The importance of RRM2 activity in our ALK-driven NSLCL cell lines was validated by *in vitro* knockdown and pharmacological inhibition. Further, combinatorial inhibition of RRM2 and ALK showed mild synergy and increased apoptosis.

Conclusions: In conclusion, we have identified and characterized three novel EML4-ALK-positive NSCLC cell lines and identified RRM2 as a novel dependency gene that is a promising target for synergistic drug combinations with ALK TKIs in ALK-positive NSCLC.

Keywords: RRM2, ALK, NSCLC

EP16.03-013 Psychological Distress and Beta-2 Adrenergic Receptor Expression in Non-small Cell Lung Cancer Cells

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Introduction: Beta-2 Adrenergic Receptor (ß2-AR) expression in cancer cells has been associated with tumour cell proliferation, both in animal models and clinical studies suggesting a role for ß2-AR signalling in lung cancer progression. The association of patients' psychological distress and ß2-AR expression on lung cancer cells is unknown. The aim of the study is to explore the association of patient´s psychological distress to ß2-ARs expression in patients operated for newly diagnosed non-small cell lung cancer (NSCLC).

Methods: The LUCASS (Lung CAncer, Stress and Survival) study is a prospective cohort study targeting all individuals referred to a diagnostic work-up at Landspitali National University Hospital (n=166), Iceland and Uppsala University hospital (n=120), Sweden, due to suspicion of lung cancer. This study population consisted of 54 patients of the Icelandic arm of the study completing questionnaires on perceived distress (Hospital Anxiety and Depression Scale, HADS) before/during clinical evaluation for lung cancer and that underwent therapeutic thoracic surgery for NSCLC at a median 32 days after diagnosis. The HADS questionnaire was used to measure pre-diagnostic distress and the total score, HADS-T, > 13 indicating mental distress of potential clinical significance. ß2-AR expression was evaluated with specified immunohistochemical staining in a blinded fashion by two pathologists. The ß2-AR expression scores were assessed based on the extent of the membranous staining as follows: 1, ≤10% of the tumour area stained or negative; 2, 11%-25% of the tumour area stained; 3, 26%-50% of the tumour area stained; and 4, ≥51% of the tumour area stained. Intensity of the staining was rated from weak (+) to strong (+++). Tumours in which the stained tumour cells were scored as ≥ 3 were defined as showing positive expression.

Results: Mean age was 69.4 years (+ 8.1), women representing 50.0%. The pathology was in 34 (63%) adenocarcinoma and 20 (37%) non-adenocarcinomas. Psychological distress of potential clinical significance (HADS-T > 13) was detected in 10 participants (18.5%). ß2-AR expression was positive in 12% of adenocarcinoma and 36% in non-adenocarcinoma (p=0.048). Age- and sex-adjusted regression model indicated a significant association between psychological distress and ß2-AR expression (OR 9.0, 95% CI 2.11-56.5, p=0.007).

Table 1. Age and sex adjusted percentage and association[1] of ß2-AR expression in lung cancer cells to distress and lung cancer pathology.

	% with positive ß2-AR expression[2]	OR[1]	p-value[3]	95%CI[4]
HADS-T[5] score				
<13	10.4	ref		
≥13	59.3	9.0	0.007	2.11-56.5
Lung Cancer Pathology				
Adenocarcinoma	11.6	ref		
Non-Adenocarcinoma	35.8	4.3	0.049	1.05-19.9

Conclusions: Preliminary results indicate an association of patients´ distress and beta-2 adrenergic receptor expression in the cancer cells of newly diagnosed lung cancer patients.

Keywords: Lung Cancer Diagnosis, Psychological Distress, Beta-2 Adrenergic Receptor

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-014 Simultaneous Detection of FGFR Gene Aberrations in Squamous Non-small Cell Lung Cancer Using Targeted DNA- and RNA-based NGS

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Introduction: The reliability of the fibroblast tyrosine kinase receptor 1 (FGFR1) amplification as a biomarker for FGFR inhibitors in the squamous non-small cell lung cancer (Sq-NSCLC) is not satisfactory. There is an urgent need to comprehensively characterize genetic aberrations of the FGFRs and other oncogenesis-related genes in hope to improve predictive assessment for FGFR inhibitors and treatment outcomes. Simultaneous RNA- and DNA-based detection of gene fusions, single-nucleotide variants and deletion/insertion seems the most comprehensive and informative approach to characterize genes critically involved in Sq-NSCLC tumorigenesis and progression.

Methods: DNA and RNA isolated from 15 primary NSCLC (squamous (n=14) and adenosquamous (n=1) histotype, stage IA3-IIIA) fresh-frozen tumor samples and corresponding adjacent tissue (n=10) with previously known FGFR1-3 gene expression status (Real-time PCR) was sequenced with the use of targeted next-generation sequencing (NGS: DNA-TST15 (Illumina) and/or RNA-FusionPlex Lung panel (Archer)). The TST15 panel identifies hotspot mutations in *KRAS, EGFR, TP53, PIK3CA, BRAF, ERBB2, FOXL2, GNA11, GNAQ, KIT, NRAS, PDGFRA, RET, AKT1* and *MET* while the Archer FusionPlex lung panel detects gene fusions, variants and expression in 14 gene of interest (*ALK, BRAF, EGFR, FGFR1-3, KRAS, MET, NRG1, NTRK1-3, RET* and *ROS1*). Additionally, the FGFR1-3 protein expression and FGFR1 amplification were simultaneously determined by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH), respectively.

Results: Moderate (n=3) and high (n=4) FGFR1 amplification was found in 46% of tumors. Among highly amplified tumors two had simultaneously enhanced *FGFR1* m-RNA and protein expression. Tumors with enhanced protein expression (FGFR1 n=3; FGFR2 n=1; FGFR3 n=1) accounted 33%. 14 of 15 (93%) tumors carried deleterious variants of *TP53*: 12 (85%) were reported as pathogenic or likely pathogenic, while 3 had unrecognized clinical significance (Clin Var data base). Five tumors with co-occurrence of additional pathogenic, probably damaging or uncertain significance variants in *TP53* (n=1), *GNAQ* (n=1), *AKT1* (n=1), *FGFR2* (n=2) and *FGFR3* (n=1) were FGFR1-amplified. Analysis of 10 corresponding adjacent tissue samples confirmed somatic origin of variants. One tumor, negative for *TP53* mutation, carried pathogenic variant of *FGFR1* c.893T>C (p.(Ile298Thr)) and had moderate FGFR1 amplification, while was negative for gene fusions and enhanced *FGFR1* mRNA and protein expression. Additionally, we found new somatic LOC101929418:ALK gene fusion (n=2) and low confidence fusions MEGF6:ROS1 (n=1), without corresponding gene-expression imbalance and with FGFR1 amplification.

Conclusions: Our data provide insight into the presence of various molecular aberrations simultaneously on DNA and RNA level alongside with the FGFR1 amplification and protein expression. *TP53* mutations approved to be most common in analysed Sq-NSCLC tumors, while the *FGFR* fusions and pathogenic variants were rare. Our results highlight the necessity of detailed and extended molecular analysis (i.e. RNA-Seq, WES) especially of tumors negative for FGFR1 amplification and FGFR protein expression.

Keywords: FGFR aberrations, lung cancer, biomarkers

EP16.03-015 Centrosome Amplification Is a Prognostic Indicator and Potential Therapeutic Vulnerability in Non-small Cell Lung Cancer

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Introduction: Centrosomes are organelles that facilitate chromosome segregation. The number of centrosomes in a cell is tightly regulated to ensure the genome is divided equally during cell division. In normal cells, two centrosomes form a bipolar mitotic spindle for faithful chromosome segregation. Cancers often exhibit centrosome amplification (CA), an increase in centrosome number that can be caused by cellular insults such as cell cycle defects and carcinogen exposure. Cells with CA are prone to forming abnormal, multi-polar mitotic spindles which can induce aneuploidies that promote tumour progression. While CA has been reported in non-small cell lung cancer (NSCLC), its prevalence and association with clinical and demographic factors have not been thoroughly explored. Thus, we sought to characterize CA in NSCLC to define its clinical significance.

Methods: CA was inferred using an established gene expression signature comprised of 20 genes whose deregulation promotes CA (CA20). CA20 scores derived from RNA-sequencing data were obtained for lung adenocarcinomas (LUAD, N=515) and squamous cell carcinomas (LUSC, N=501) from The Cancer Genome Atlas (TCGA), as well as non-malignant samples from LUAD (N=59) and LUSC (N=51) patients (*deAlmeida et al, 2019*). CA20 scores were also calculated from microarray expression data for independent cohorts from the British Columbia Cancer Agency (BCCA; N = 83 LUAD) and the University Health Network (UHN; N = 106 NSCLC). CA was also assessed by immunohistochemistry (IHC) for the centrosomal protein, pericentrin, in the UHN cohort. Mitotic cells with more than 2 centrosomes were classified as having CA. Correlations between CA20 scores, KIFC1 expression, and clinical factors were assessed using Mann-Whitney U, Anova, and Pearson's correlation tests. Survival associations were evaluated using a Mantel-Cox log-rank test.

Results: Consistent with previous findings, CA20 scores were elevated in LUAD and LUSC relative to non-malignant tissues in all cohorts evaluated. CA20 was positively correlated with the fraction of genome altered, a measure of genomic instability, in the TCGA LUAD and LUSC cohorts. CA20 scores were higher in current and former smokers compared to never smokers, and CA20 increased with increasing tumour stage in the TCGA LUAD. Furthermore, CA20 was significantly lower in *EGFR* and *KRAS* mutant compared to *EGFR* and *KRAS* wildtype LUAD, and high CA20 scores were associated with worse survival than low CA20 in TCGA LUAD patients. Although not significant in the smaller BCCA and UHN cohorts, similar trends between CA20 and stage, smoking status, mutation status, and survival were observed. Preliminary IHC experiments in NSCLC tissues detected CA in 20-70% of mitotic cells in 10 of 10 tumours.

Conclusions: Genomic and IHC strategies confirmed that CA is a frequent phenomenon in NSCLC and revealed its association with several clinical features including smoking history, disease stage, and prognosis. Ongoing IHC studies in large NSCLC cohorts will confirm these observations. Despite the potentially lethal consequences of CA-induced mitotic errors, its prevalence and association with genomic instability in NSCLC could suggest that CA promotes lung cancer biology. Thus, CA may represent a targetable vulnerability and studies to assess its therapeutic potential are warranted.

Keywords: centrosome amplification, NSCLC

EP16.03-016 Targetable Alterations in Non-Small Cell Lung Cancer According to Age and Sex

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Introduction: Lung cancer is the second most common malignancy and the leading cause of cancer-related death worldwide. It is critical to understand lung cancer tumor biology to better predict cancer behavior across various populations. This study aimed to evaluate differences in genomic alterations in patients with advanced non-small cell lung cancer (NSCLC) and is an update to a prior abstract.

Methods: We conducted a retrospective review using the Guardant Health database and included NSCLC patient profiles from March 2018 through October 2020. We assessed for genomic alterations in up to 83 genes using circulating-tumor DNA (ctDNA) from the first serial sample of these patients. Synonymous mutations, variants of undetermined significance, and subclonal mutations were excluded. We assessed for differences in the frequency of alterations in genes with prognostic and therapeutic implications. The frequencies of *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK*, *ERBB2*, *RET*, *MET*, *PIK3CA*, *STK11,* and *TP53* alterations were analyzed according to sex and age (<70 and ≥70) using Fisher's exact test. We also assessed whether these alterations co-occurred using the publicly available cBioPortal.

Results: Of the 34,278 evaluable patients, 90% (n=30,791) had a genomic alteration detected by the ctDNA assay, Guardant360. 65% (n=19,924) of those patients had an alteration in one of our genes of interest (Figure 1). The median age was 68, 54% (n=10,671) were female, and the majority had adenocarcinoma histology (>93%). Females had significantly higher number of alterations in *EGFR*, *KRAS G12C*, *and ERBB2*. Males were significantly more likely to have *MET amplifications* and alterations in *STK11* and *TP53.* There were no significant differences between males and females in the frequency of *KRAS G12D/V, ALK, ROS1, BRAF, NTRK1*, *RET*, *MET exon 14 skipping,* or *PIK3CA* alterations. Patients <70 years of age were more likely to have alterations in *EGFR exon 19 del/exon 20 ins/T790M*, *KRAS G12C/D, ALK*, *ROS1*, *BRAF, ERBB2*, *MET amplifications, STK11,* and *TP53*. Patients ≥70 were more likely to have *EGFR L861Q*, *MET exon 14 skipping,* and *PIK3CA* alterations. There were no differences in the distribution of *EGFR G719X/L858R/S768I*, *KRAS G12V*, *NTRK1*, or *RET* by age. Alterations in *KRAS* often co-existed with alterations in *STK11* (*p*=<0.001) within this cohort (n=19,924).

Conclusions: Our study demonstrated differences in the distribution of targetable genomic alterations according to age and sex. While these alterations tend to occur in isolation, some co-exist. These findings will likely help individualize treatment and improve outcomes in patients with NSCLC.

Figure 1. Prevalence of genomic alterations of interest in NSCLC patients with positive ctDNA profile

Gene	Alteration	Female	Male	p-value	<70	≥70	p-value
EGFR	Ex 19 del	9.55%	5.86%	<0.0001	10.14%	5.59%	<0.0001
	Ex 20 ins	1.25%	0.95%	0.0139	1.47%	0.75%	<0.0001
	G719X	0.96%	0.59%	0.0003	0.82%	0.77%	0.6528
	L858R	6.81%	3.96%	<0.0001	5.71%	5.33%	0.1475
	T790M	1.08%	0.57%	<0.0001	1.04%	0.66%	0.0003
	S768I	0.47%	0.25%	0.0013	0.39%	0.35%	0.6405
	L861Q	0.58%	0.34%	0.002	0.32%	0.63%	<0.0001
KRAS	G12C	7.10%	6.41%	0.0169	7.58%	6.01%	<0.0001
	G12D	2.46%	2.54%	0.6604	2.72%	2.29%	0.0176
	G12V	3.10%	2.81%	0.1383	3.16%	2.80%	0.0649
ALK	Fusion	1.38%	1.23%	0.269	2.11%	0.51%	<0.0001
ROS1	Fusion	0.15%	0.21%	0.274	0.26%	0.09%	0.0005
BRAF	V600E	0.94%	1.02%	0.4848	1.09%	0.86%	0.0422
NTRK	NTRK 1 Fusion	0.01%	0.00%	>0.9999	0.01%	0.00%	>0.9999
ERBB2	Ex20 insertions	1.40%	1.00%	0.0012	1.48%	0.95%	<0.0001
RET	Fusion	0.08%	0.04%	0.2554	0.07%	0.05%	0.6477
MET	Ex14 skipping	1.12%	1.09%	0.827	0.52%	1.71%	<0.0001
	Amp medium	0.78%	1.12%	0.0024	1.08%	0.79%	0.0108
	Amp high	0.60%	1.09%	<0.0001	1.10%	0.54%	<0.0001
PIK3CA	Mutant	1.32%	1.26%	0.649	1.12%	1.48%	0.0065
STK11	Mutant	5.10%	7.61%	<0.0001	7.39%	5.11%	<0.0001
TP53	Mutant	38.02%	46.36%	<0.0001	44.62%	39.13%	<0.0001

Keywords: Non-small cell lung cancer, Mutations, Genomics

EP16.03-017 Spatial Heterogeneity of Tumor Microenvironment of Lung Adenocarcinoma Associated with Genomic Alterations

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Introduction: Inter-patient and intra-tumoral heterogeneous tumor microenvironment (TME) is one of the major challenges in cancer treatment. Here, we first constructed and investigated high-resolution spatial transcriptomics of advanced lung adenocarcinoma.

Methods: We constructed spatial transcriptomics of 6 samples from two patients: two samples from patient 1, and four samples from patient 2. We performed transcriptomic analysis of 14798 spots and extracted distinct characteristic of different clusters. As each spot of spatial transcriptomic data consisted of a few cells, the cell types were inferred by CellDART, a domain adaptation-based method to estimating immune/stromal cells defined by single cell RNA-seq data. We additionally performed network analysis between clusters to investigate spatial relationship between clusters. To capture the genetic heterogeneity, we performed laser capture dissection from six regions within one slide of patient 2 and analyzed whole genome sequencing with average 30X coverage per region.

Results: Transcriptomic analysis showed 13 distinct clusters and the composition of clusters were widely varied across the samples. We could identify tumoral heterogeneity in the same patient by clustering analysis. Even in the same tumor, cell type distributions showed spatially mixed patterns in a small region of the tumor while another region showed a spatial zonation with distinct immune cell infiltration. In addition, spatial topological patterns of clusters revealed that common and distinctive relationships between clusters across samples. In genomic analysis, no significant difference of copy number alteration was found among all regions in spite of different clusters in spatial transcriptomics. Furthermore, all regions originated from MRCA carrying EGFR 18bp out-of-frame deletion mutation, and no branched evolution happened.

Conclusions: Our study reveals the spatial transcriptomic-genomic alterations in multiple regions in lung adenocarcinoma, and the complex network between immune-stromal cells within TME.

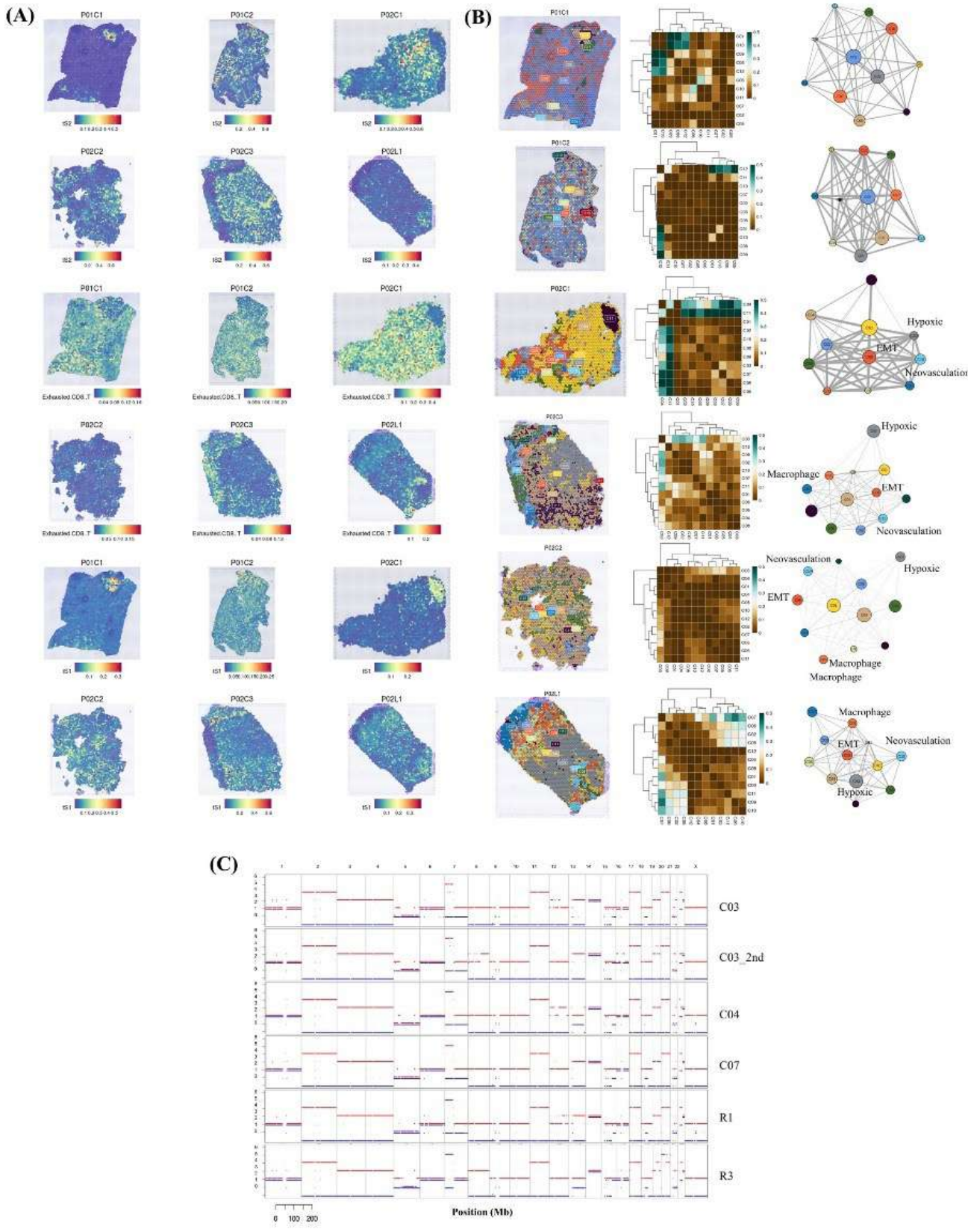

Figure 2. (A) Few examples of CellDART analysis to characterize the immune/stromal cell distribution of each sample. (B) Topological analysis between clusters in each sample. (C) Copy number variation of six regions that have distinct transcriptomic features in sample 3 of patient 2.

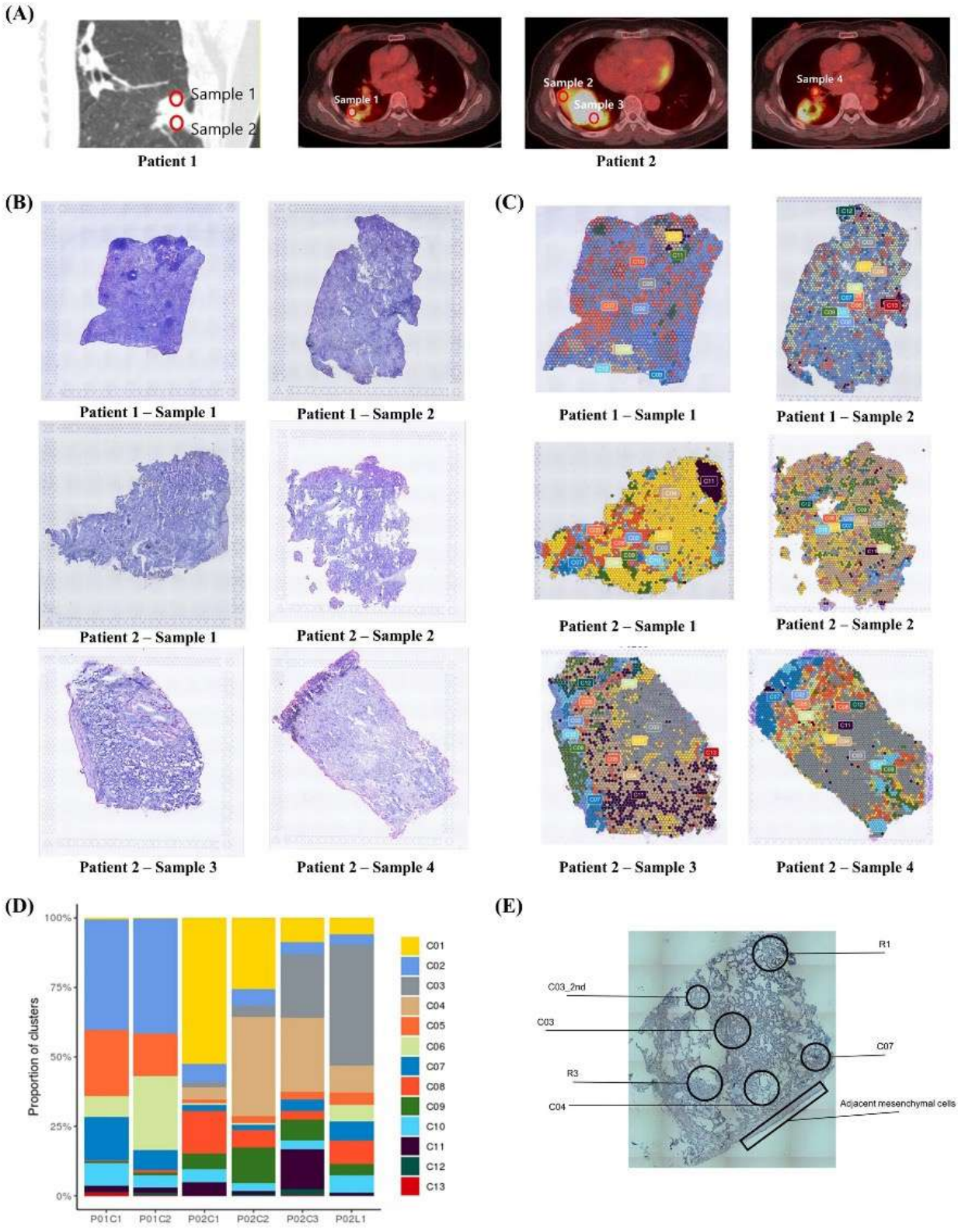

Figure 1. (A) Radiologic characteristics and location of samples from each patient. (B) H&E-stained image of six spatial transcriptome data. (C) Unsupervised clustering analysis of spatial transcriptome data. (D) The proportion of clusters in each sample. (E) Six regions for laser capture microdissection in sample 3 of patient 2.

Keywords: Spatial transcriptomics, lung cancer, heterogeneity

EP16.03-018 Molecular Features of Subtypes Classified Based on Predominance and Components in Chinese Patients with Lung Adenocarcinoma

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Introduction: Certain driver mutations have been proven to associate with different lung adenocarcinoma (ADC) subtypes. However, there is a lack of comprehensive mutational profiling for each subtype, especially for non-predominant components. Thorough understanding of the molecular features of ADC subtypes classified based on predominance and components could be beneficial to improve the management strategy for precision treatment in these patients.

Methods: To explore the correlation between mutations and ADC subtypes, targeted sequencing data of 331 pathologically diagnosed ADC patients were retrieved. Subtypes were defined according to the International Association for the Study of Lung Cancer classification based on predominance and components of ADC. Targeted sequencing using panels covering at least 47 cancer-related genes and immunohistochemistry for PD-L1 were performed in surgically-resected primary tumor tissue specimens by OrigiMed. Patients with non-invasive ADCs, mixed histological subtypes or unclear predominant subtype were excluded. P <0.05 was considered statistically significant.

Results: Our cohort consisted of 331 ADC patients: 62 lepidic-, 200 acinar-, 31 papillary-, 5 micropapillary-, 30 solid-, and 3 mucinous-predominant subtypes. As expected, a significantly higher proportion of lepidic-predominant patients was at stage I (p<0.01) with well-differentiated profile (p<0.001). More current smokers were found in solid-predominant patients (p<0.01). *BRCA1*, *FGFR3* and *KIT* mutations were more frequently occurred in solid-predominant patients, while *CCND1* were preferentially mutated in micropapillary-dominant patients. PD-L1 expression was present more frequently in micropapillary- and solid-predominant patients (p<0.001) and tumor mutation burden (TMB) was significantly higher in solid-predominant patients (p<0.001), indicating that these patients may benefit from immune-checkpoint inhibitors (ICIs). Regardless of predominance, the presence of lepidic, acinar, papillary, micropapillary, solid, and mucinous components were observed in 134, 278, 74, 62, 65, and 4 patients, respectively. For patients with lepidic components, *EGFR* mutations (75% vs. 62%) were more commonly observed, but the proportions of *CDKN2B* mutations (0% vs. 4%), *TP53* mutations (26% vs. 42%), and PD-L1 positive (14% vs. 40%) cases were significantly lower. For patients with acinar components, *EGFR* mutations (71% vs. 51%) occurred more frequently while *CCND1* mutations (1% vs. 8%) less frequently. For patients with micropapillary components, more *CDKN2B* mutations (6% vs. 1%), *MAP2K1* mutations (8% vs. 2%), and PD-L1 positive (44% vs. 26%) cases were observed. For patients with solid components, more *BRCA1* mutations (6% vs. 1%), *NF1* mutations (8% vs. 2%), *NTRK1* mutations (8% vs. 2%), *PDGFRA* mutations (6% vs. 0%), and PD-L1 positive (64% vs. 19%) cases were observed. TMB value was significantly higher in patients with the presence of micropapillary (median 3.9 vs. 2.7 muts/Mb) and solid (median 4.2 vs. 2.7 muts/Mb) components, and lower in patients with the presence of lepidic (median 2.5 vs. 3.0 muts/Mb) components. No preferentially mutated genes or immune-related biomarkers were observed in patients with papillary and mucinous components.

Conclusions: In consideration of both predominant subtyping and presence of components, different ADC subtypes possess unique mutational profiles. ADC patients with lepidic and acinar components might be favorable to receive the treatment with EGFR-TKIs, whereas ADC patients with micropapillary and solid components might be beneficial from ICIs therapy.

Keywords: precision medicine, biomarker, lung adenocarcinoma

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-019 Landscape of EGFR Extracellular Domain Mutations in Advanced Non Small Cell Lung Carcinoma

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Introduction: Plasma next generation sequencing (NGS) is a non-invasive method for tumor genomic profiling that offers personalized treatment options via cell free DNA analysis for patients with advanced cancers. Targeted therapies direct activity toward specific functional protein domain(s) to inhibit tumor cell survival. The EGFR protein is comprised of an extracellular domain (ECD) that spans amino acids 1-620 and an intracellular tyrosine kinase domain (TKD) that can be targeted in multiple cancer types. In advanced non-small cell carcinoma (NSCLC), EGFR directed-therapies mainly focus on mutations within the TKD. Limited data exists for EGFR ECD mutations in NSCLC. EGFR ECD mutations in other cancers, including colorectal cancer have been well described as these alterations confer sensitivity or resistance to various monoclonal antibody therapeutics. The aim of this study is to describe the spectrum of EGFR ECD mutations identified in advanced NSCLC via liquid biopsy.

Methods: Somatic alterations detected using clinical-grade NGS of plasma circulating tumor (ctDNA) (Guardant360® and Guardant360CDx®) from patients with documented stage IIIB or IV lung cancer tested from 2018 to 2021 were retrospectively evaluated. The assays detect single nucleotide variants, copy number variants, select fusions, and indels in up to 83 genes. If serial testing was performed for a patient, the analysis was limited to the initial sample result. EGFR ECD alterations were defined as any reportable non-synonymous result from amino acids 1-620 of the EGFR protein.

Results: 2,065 patient samples harbored EGFR ECD alterations. Of this, (51%) were male with a median age of 72 (range: 32-98) years. The most frequently identified EGFR ECD alterations classified as mutations were A289V (3.0%), L62R (2.9%), E114K (2.5%), R108K (2.4%), R229C (2.6%), and A289T (1.3%). EGFR ECD alterations and other NSCLC oncogenic driver mutations, as denoted by NCCN guidelines, were detected concurrently in 1,033 samples. Of samples with concurrent EGFR ECD mutations and non-EGFR driver mutations, KRAS was the most altered gene (43.9%), of which the majority mutated at sites G12X, G13X or Q61H. Concurrent EGFR ECD mutations were also detected with ERBB2 mutations (13.0%), MET exon 14 skipping mutations (3.6%), BRAF V600E (2.7%), ALK fusions (1%), RET fusions (0.5%), and ROS1 fusions (0.4%). Concomitant EGFR alterations were most frequently observed within the TKD domain (34.9%).

Conclusions: This analysis describes the largest EGFR ECD mutational landscape of advanced NSCLC patients detected via ctDNA. EGFR ECD mutations in NSCLC do not appear to be mutually exclusive with other oncogenic driver mutations, and further evaluation of biological and clinical relevance is warranted.

Keywords: Circulating tumor DNA, biomarkers, EGFR

EP16.03-020 High Tumor Mutational Burden by Whole-Genome Sequencing in Resected NSCLC in Never Smokers is Associated with Worse Prognosis

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Introduction: Tumor mutational burden (TMB) is a measure of the number of somatic mutations in a tumor. For all comers with non-small-cell lung cancer (NSCLC), high TMB defined as ≥ 10 mutations/megabase (mut/Mb) has been associated with positive and durable response to immunotherapy (IO). For never smokers with NSCLC, TMB is typically lower, but the clinical application of this biomarker remains to be established. In this study, using gold-standard whole-genome sequencing (WGS), we aimed to 1) test whether TMB is a prognostic biomarker of survival after surgery in never smokers with NSCLC, 2) define a prognostic TMB cutoff, and 3) compare TMB derived from WGS with exome sequencing (WES) and commercial NGS gene panels.

Methods: TMB was assessed by WGS in 93 paired tumor-normal snap-frozen samples from never smokers who underwent lung cancer resection with curative intent. Kaplan-Meier and multivariate Cox proportional hazards regression analyses were performed to test for association with survival after surgery and to identify the optimal prognostic TMB cutoff. TMB derived from WGS was compared to *in silico*-reduced sequencing size of WES and targeted NGS panels.

Results: Histological types included adenocarcinoma (n=83; 89%), sarcomatoid carcinoma (n=6; 7%), squamous cell carcinoma (n=2; 2%) and adenosquamous carcinoma (n=2; 2%). By incorporating coding and non-coding variants, the median TMB was 1.10 mut/Mb with a range of 0.01-14.71. A TMB cutoff based on Youden index of 1.40 ± 0.15 mut/Mb was associated with a 5-year overall survival (OS) of 54% in the high-TMB compared to 82% in low-TMB patients (log-rank p = 0.0017, **Figure 1**). WGS number of mutations was on average 140-fold higher than with WES, but both correlated significantly (Pearson r = 0.98, p < 2.2e-^{16}; Spearman ρ = 0.91, p < 2.2e-^{16}). No such correlation was found with commercial NGS gene panels TMB, either with WGS or WES.

Conclusions: As expected, tumors of never smokers with NSCLC had low TMB scores. High TMB based on a cutoff of >1.40 mut/Mb was observed in 31% of cases and was associated with worse prognosis. WES is an accurate approach to capture the genuine TMB. In contrast, targeted NGS panels seem to lack the depth and resolution to estimate TMB in this setting of low mutation burden. Further studies are needed to evaluate TMB as a predictive biomarker for IO in never smokers.

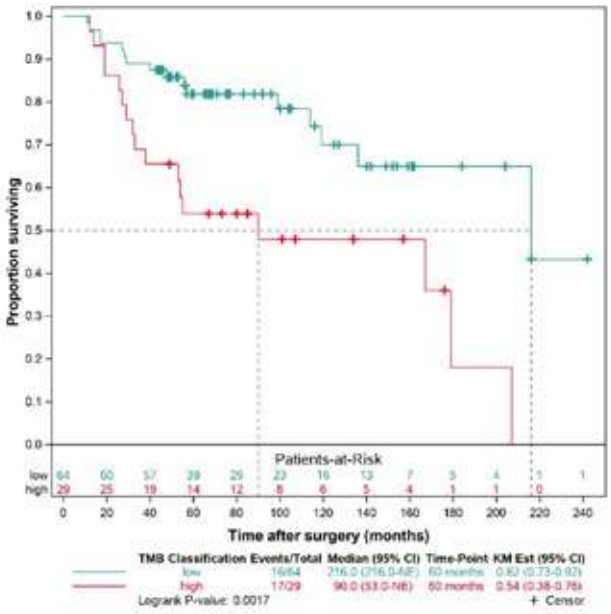

Figure 1. Kaplan-Meier plot of OS for tumors with high versus low TMB defined as above or below 1.40 mut/Mb.

Keywords: Tumor mutational burden, People who never smoke / Never smokers, Whole-genome sequencing

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-021 Developing of EGFR resistant mutations to Tyrosine Kinase Inhibitors (TKI) in Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Tyrosine kinase inhibitors (TKIs) are effective in EGFR mutant non-small cell lung cancer (NSCLC), but acquired resistance is virtually inevitable. Known resistance mechanisms include acquired EGFR mutations (e.g, 718V, c797x, 724s, 721s or T790M); copy number amplifications in MET, ERBB2, and PIK3CA; gene fusion events; and histological transformation. We herein present the prevalence of resistance mutations in the largest reported cohort of EGFR mutant NSCLC.

Methods: NSCLC tumor samples were submitted to Caris Life Sciences (Phoenix, AZ) for NextGen Sequencing (NextSeq, 592 Genes) and whole exome sequencing (NovaSeq, WES). PD-L1 expression was tested by IHC using 22C3 (Dako) and TPS scores were reported (cutoff >1). TMB was measured by totaling somatic mutations (TMB-high cut-off >10 mutations per MB); genomic loss of heterozygosity (gLOH) was determined by WES. Patient treatment information was obtained from insurance claims data.

Results: A total of 27,848 NSCLC tumors were evaluated and 3,223 (12%) had an EGFR sensitizing mutation. We found 60 tumors with common missense resistance mutations: 790M (n=30, 0.9%), 797S (n=38, 1.2 %), L718V (n=11, 0.3%), G724S (n=7, 0.2%) and G721S (n=4, 0.1). Table 1 describes the frequencies, PD-L1 expression and the most common co-mutations. TMB-H (>=10) was found in 12.5% of the tumors and dMMR/MSI-H in 1.8%. The most prevalent co-alterations were TP53 54%), gLOH (28%), CTNNB1 (19%), NFKB1A (13%), APC (10%), PIK3CA (11%), SMAD4 (9%). Fifteen additional co-mutations were observed in less than 7% of pts. Of the 30 with T790M mutations, in addition to TP53 mutations, other prevalent co-mutations included: PIK3CA (14%) and CTNNB1 (17%). In those with T797 mutations, the most prevalent co-mutations were T790M (68%) TP53 (53%), CTNNB1 (22%), APC (16%) and PIK3CA (11%). L718V mutations co-occurred with either L858R (6/11), exon 19 (3/11) or T790M mutations (3/11); 5/11 patients were treated with osimertinib before developing L718V. G724s mutations were found in 7 patients (0.02%) and G721s mutations in 4 patients (0.01%).

EGFR MT	N	%	T790M co-mt	PD-L1	TP53	LOH
797X	38	1.2	26/38 (68%)	11/36 (30%)	20/38 (53%)	4/14 (28%)
L718V	11	0.3	3/11 (27%)	4/9 (44%)	7/10 (70%)	0/1 (0%)
724S	7	0.2	1/7 (14%)	5/7 (71%)	3/7 (43%)	0/1 (0%)
721S	4	0.1	0/4 (0%)	3/4 (75%)	2/4 (50%)	1/2 (50%)
Total	**60**			**23/56 (41%)**	**32/59 (54%)**	**5/18 (28%)**

Conclusions: Acquired resistance in EGFR mutant NSCLC remains very heterogeneous; the frequency of individual mutations is low, one of the reasons might be lack of testing at resistance. While T790M and C797S mutations are well described, this report also documents a significant number of L718V mutations, primarily in osimertinib-treated pts with an original L858R. These data support the need to increase NGS evaluation of patients with EGFR mutant lung cancers who have developed clinical resistance.

Keywords: EGFR, Next Generation Sequencing, NSCLC

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-022 Endobronchial Ultrasound Guided Transbronchial Needle Aspiration Sampling Is Sufficient for Lung Cancer Molecular Profiling

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Introduction: Molecular testing of non-small cell lung cancer (NSCLC) specimens for somatic gene alterations is important for identification of potentially efficacious targeted therapies, as well as avoidance of therapies that are unlikely to provide clinical benefit. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technique that is effective for diagnosis and staging NSCLC. Although several studies have shown two to six needle passes are sufficient for adequate molecular profiling, concern remains that EBUS-TBNA samples do not provide enough material. This study aims to review our experience to determine if Next Generation Sequencing (NGS) was able to identify actionable genetic aberrations (AGA) in our EBUS-TBNA samples.

Methods: This is a retrospective review of adult patients within the Memorial Cancer Institute who were diagnosed with stage III or IV NSCLC and who had NGS done on EBUS-TBNA samples between 1/1/2015 and 6/30/2021. The EBUS-TBNA tissue sample is formed from multiple aspirates pooled into Roswell Park Memorial Institute (RPMI) cell culture solution to create a cell block that is then sent for NGS. Patients were excluded if they were diagnosed with stage I or II NSCLC. Data collection included: patient demographics, smoking history, clinical stage, histology, detection of genomic biomarkers, occurrence of insufficient tissue samples, biopsy turnaround time, biopsy type used to make the final treatment decision (tissue versus liquid), treatment regimen initiated, and response to therapy. Descriptive statistics were calculated for all patients.

Results: Of the 44 evaluated patients, 19 (43%) were male, the median age at diagnosis was 66 years (range 43-83 years), and 33 (75%) were smokers. Patient race and ethnicity were as follows: White/Caucasian (35, 79.5%), Black/African American (3, 6.8%), Asian (4, 9.1%), Unknown (2, 4.5%); Hispanic (16, 36.4%), Non-Hispanic (26, 59.1%), Unknown (2, 4.5%). EBUS-TBNA samples were sufficient for NGS for 42 (95.5%) patients. In the remaining two patients an EGFR mutation was detected by liquid biopsy (LB). The median turnaround time (TAT) for tissue NGS was 38.5 days compared with 8 days for LB NGS. Most of the delays with obtaining NGS results were due to insurance authorization. Thirty (71%) patients had an AGA. Among patients with an AGA, the following were identified by NGS from EBUS-TBNA samples: BRAF (1, 3%), EGFR (9, 30%), KRAS (9, 30%), MET (5, 16%), NTRK1 (1, 3%), PD-L1 (24, 80%). For patients with a sufficient EBUS-TBNA sample for NGS, all AGA identified by LB were also found by EBUS-TBNA.

Conclusions: EBUS-TBNA is a successful, minimally invasive method to obtain sufficient material for identification of AGA in patients with advanced NSCLC that may be equivalent to traditional core tissue biopsies. Specimens should be collected in cell block form and not for cytology. Based on the results of our study, EBUS-TBNA might be incorporated as standard of care to guide first line therapy decisions. A prospective study with a larger sample size and attention to sample collection methods is warranted to validate these results**.**

Keywords: Next Generation Sequencing, NSCLC, EGFR

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-023 KRAS Alterations, Clinicopathological Features and Co-occurring Drivers Associated with Prognosis in Advanced NSCLC Patients

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Introduction: Genetic profiling has proven essential and changed the landmark in non-small cell lung cancer (NSCLC). Next-generation sequencing (NGS) has increased the identification of patients with different genomic alterations, which are novel targets for personalized therapies. Among them, KRAS is the isoform most commonly mutated in NSCLC, with a prevalence that is higher in Western populations compared to Asian (26 vs 11%). However, the information about the frequency, clinical characteristics and prognostic significance of KRAS in patients with NSCLC from Mexico has been limited

Methods: NGS was performed in patients with advanced NSCLC. Clinical and demographic information was collected retrospectively from electronic medical records. Patients were categorized into two groups based on KRAS mutation: KRAS-mutant or wildtype (KRAS-mut or KRAS-wt) and if mutated they were also stratified into two groups according to KRAS subtype: G12C and non-G12C

Results: A total of 313 patients were included. Median age was 61 years. The majority of patients were female (66.8%), non-smokers (63.3%) and had no previous wood-smoke exposure (70%). The most common sites of metastasis were bone (33.4%), lung (29.6%), pleural (23.8%), lymph node (23.2%) and central nervous system (CNS, 20.6%). Nearly 46% of the patients had a high histological grade tumor, 51.8% had a carcinoembryonic antigen above 10ng-mL and 62.8% had a PDL1 positive. The frequency of KRAS mutation was 15.4% (48 patients). The most frequent mutations occur in codon 12, with the most common subtypes including G12C (32.7%), G12D (28.6%) and G12V (16.3%). 3 patients had a KRAS amplification and 1 patient had a mutation in codon 66 (A66A). The G12C subgroup had more CNS metastasis and had a history of smoking than the non-G12C subgroup (p=0.021 and p=0.049 respectively). No other significant associations were found between KRAS status and clinicopathologic characteristics. KRAS co-occurrence partners most frequently were TP53 (47.1%), CDKN2A (11.5%), PIK3CA (7.6%), GNAS (5.1%) and STK11 (4.8%). PDL1 expression was similar between KRAS-mut and KRAS-wt (p=0.797) but was higher in patients with KRAS G12C vs non-G12C (p=0.026). Patients with KRAS-mut had a higher frequency of STK11 (p<0.001) and GNAS (p=0.001) vs KRAS wt. Among patients with KRAS G12C, CDKN2A was significantly higher (p=0.047) vs non-G12C. The median overall survival for the total population was 12.6 months. There was a trend in OS in favor of KRASG12C when compared to nonG12C (median OS 24 vs 9.79 months, p=0.379), as well as, patients with KRAS-TP53 positive tend to have a longer OS vs KRAS-TP53 negative (median OS 24 [KRAS-TP53 +] vs 9.16 months [KRAS-TP53 -], p=0.247). No statistically significant difference in OS were found between KRAS-mut vs KRAS-wt (median OS 25 vs 12.6 months, p=0.143) and KRAS G12C vs KRAS-wt (median OS 24.01 [G12C] vs 22.8 months [KRAS-wt], p=0.939)

Conclusions: Our study found that 15.4% of NSCLC patients harbor a KRAS mutation, less than the reported in the literature. Interestingly, CDKN2A was significantly higher among G12C patients, could be a worse prognosis feature. There are still unmet therapeutic needs for these patients

Keywords: KRAS, NGS, TP53

EP16.03-024 Cellworks Singula™ Therapy Response Index (TRI) Identifies Superior OS Outcomes for NSCLC Patients: myCare-203A

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Introduction: The Cellworks Singula™ TRI was developed to assist clinicians with therapeutic decisions. Cellworks utilizes each patient's tumor NGS results and Computational Omics Biology Model to biosimulate molecular pathway aberrations and the impact of therapies on restoring normal signaling in patient-specific *in-silico* diseased cells. For each patient and therapy, Cellworks integrates this multi-omics information into a continuous TRI Score, scaled from 0 to 100 (predicting low to high therapeutic benefit).

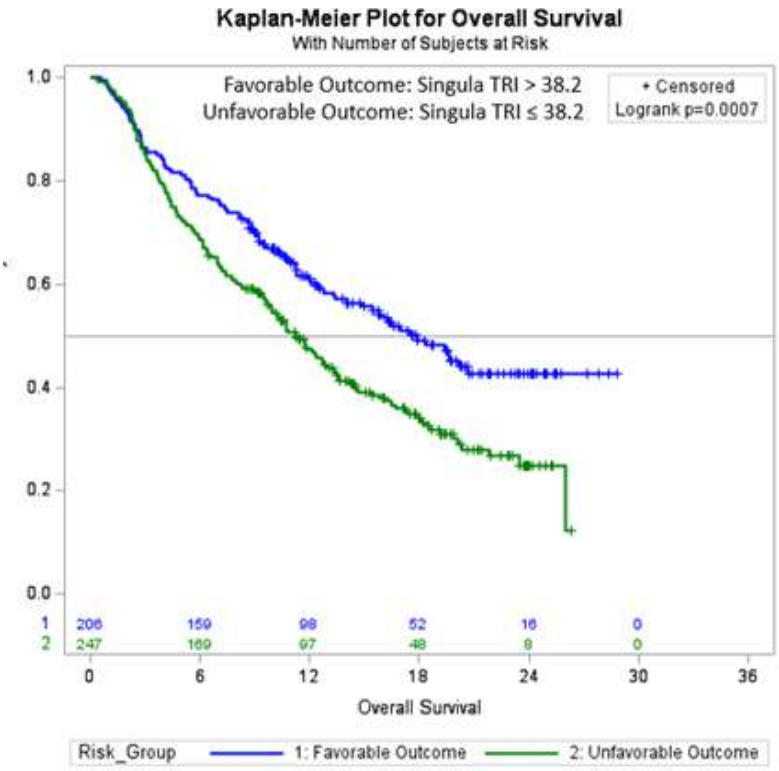
Methods: The pre-defined Singula TRI algorithm was prospectively validated in a retrospective cohort of 453 NSCLC patients ages 39-87 (22 female, 431 male) from Veterans Affairs facilities treated with physician-prescribed therapy (PPT). TRI scores were generated for 109 alternate therapies for each patient enabling selection of optimal therapies with estimates of improvements in median OS compared to standard care. The hypothesis that Singula TRI provides predictive value of OS above and beyond PPT, NCCN-guideline genomic biomarkers, patient age and patient sex was tested using multivariate Cox Proportional Hazards regression. A p-value < 0.05 for the corresponding likelihood ratio (LR) was considered significant.

Results: Multivariate analyses demonstrate that Singula TRI is a significant predictor of OS (LR x2= 11.52, p-value = 0.0007, HR per 25 units = 0.635) and provides predictive value above and beyond PPT. Patients with favorable (TRI > 38.2) and unfavorable (TRI ≤ 38.2) outcomes had median survival times of 17.9 months and 11.3 months respectively. Table 1 identifies that Singula TRI provides predictive value of OS above and beyond PPT, standard clinical factors and NCCN-guideline genomic factors.

Conclusions: The Singula TRI Score provides a continuous measure for alternative NSCLC therapeutic options with an estimator of clinical benefit that may help guide therapeutic decisions for patients with NSCLC. In this retrospective cohort, Singula™ was strongly predictive of OS and provided predictive value beyond the aforementioned covariates.

Table 1. Likelihood Ratio Analysis for TRI; OS multi-variate analysis

Effect	df	χ^2	Probability > χ^2
Patient Age [≤70 years old vs > 70 years old]	1	0.3738	0.5409
Patient Sex [male vs. female]	1	0.0230	0.8793
Drug Class [Radiation vs Chemo vs IO vs Targeted]	3	3.4665	0.3251
Physician Prescribed Treatment	10	13.4833	0.1979
EGFR	1	0.8952	0.3441
KRAS+G12C	1	0.0083	0.9273
ALK	1	0.4218	0.5160
ROS1	1	4.3834	0.5160
BRAF V600E	1	2.0576	0.1514
MET EXON 14	1	2.7385	0.0980
PDL1	1	2.2911	0.1301
Singula TRI	1	11.5215	0.0007



Keywords: Personalized Oncology, Personalized Therapy Biosimulation, Multi-omics Computational Biology Model

EP16.03-025 Immunogenomics of Clinical Resistance to KRAS G12C Inhibition

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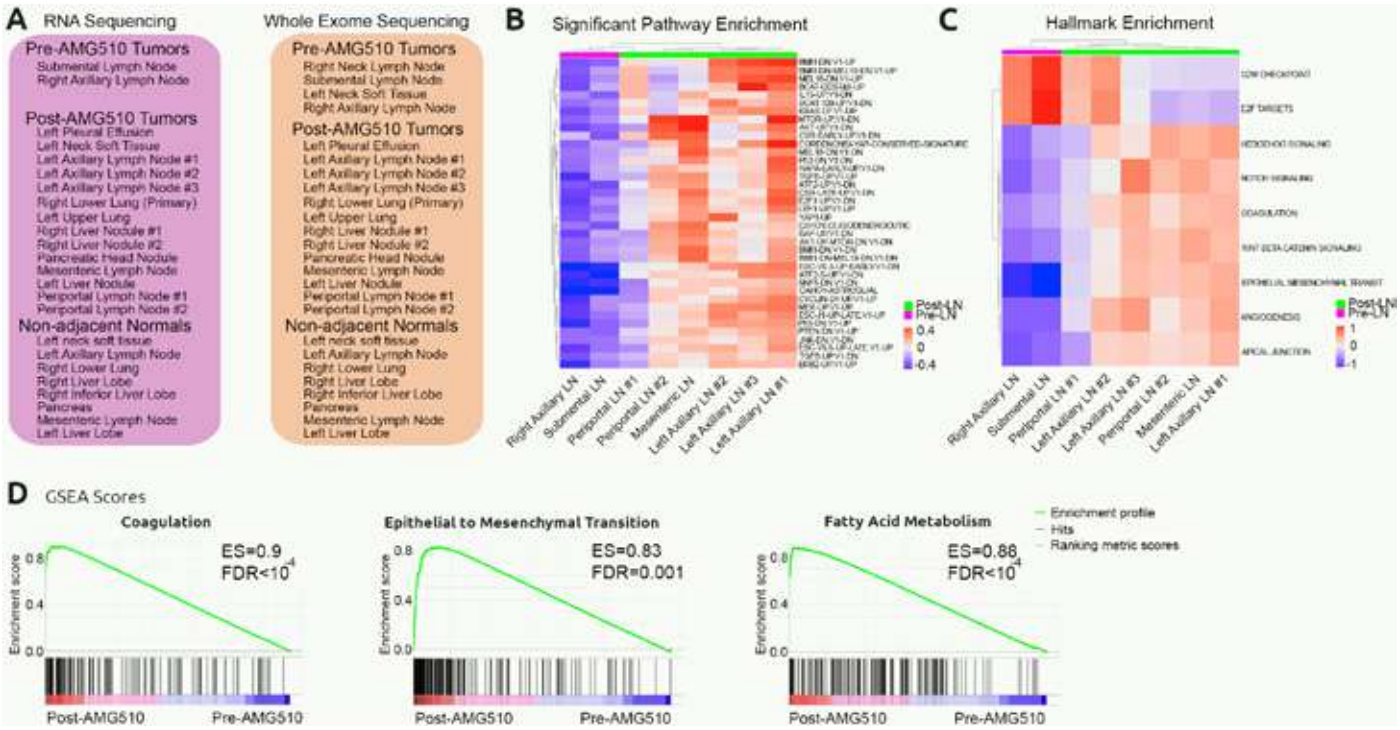
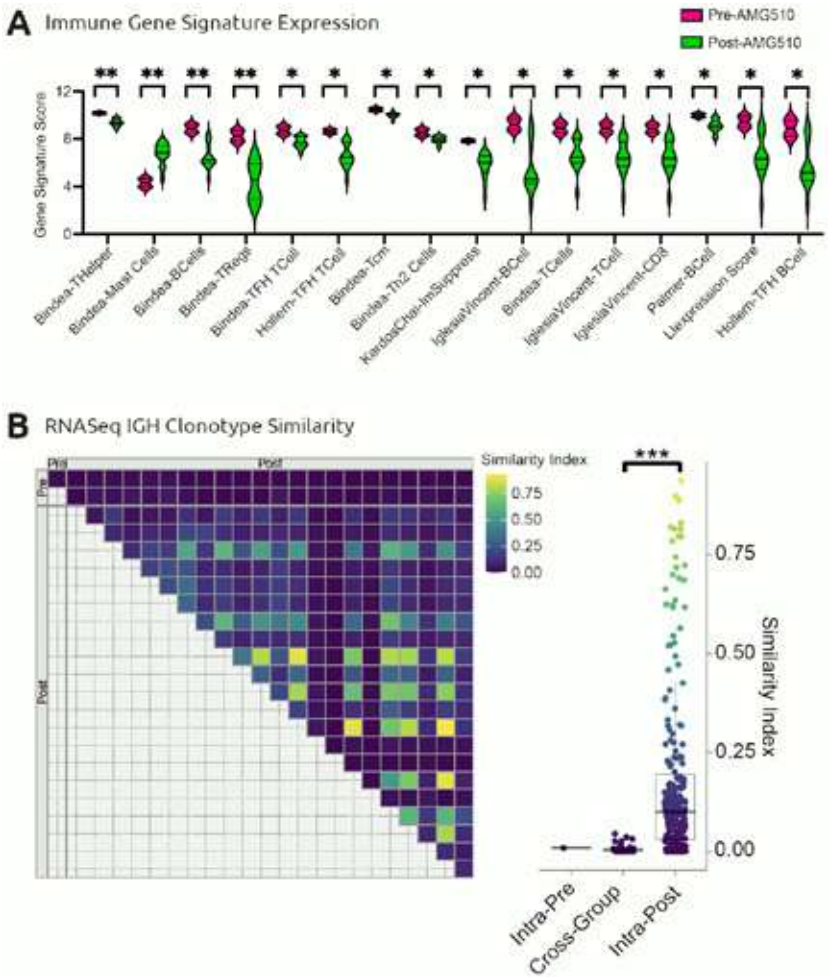
Introduction: Activating mutations in KRAS are a frequent source of oncogenesis but have lacked clinical targeted therapies despite being first identified four decades ago. Selective drugs for the G12C KRAS mutation have recently been approved for use in the United States, and have been granted conditional marketing authorization in the EU. Pre-clinical data indicate that tumors harboring KRAS mutations can rapidly develop resistance to targeted inhibition, and non-durable responses have been observed in clinical use. Understanding mechanisms of resistance to G12C inhibition is essential to maximize the clinical benefit of these agents and guide future therapeutic developments.

Methods: A patient with KRAS G12C mutant lung adenocarcinoma was treated with a G12C inhibitor resulting in initial therapy response followed by rapid multi-site progression, death, and submission of their body to a rapid autopsy exam. Pre and post-treatment tumors with matched normal tissues were examined with RNA and whole exome sequencing (Fig. 1A) to examine potential genomic and immunologic mechanisms of therapy resistance.

Results: Post-treatment tumors exhibited broadly decreased KRAS G12C mutant allele frequency - without new mutations in KRAS or its downstream effectors - and persistent activation of the MAPK and AKT/mTOR pathways (Fig. 1B). Consistent with prior studies of acquired resistance in KRAS-dependent tumors we observed post-treatment upregulation of YAP1 and EMT transcriptional programs, as well as pathways related to coagulation, complement activation, and angiogenesis (Fig. 1C,D). Immunogenomic analyses demonstrated reduced adaptive immune cell activity in post-treatment tumors, an increase in mast cell activity, and remodeling and restriction of the intra-tumoral lymphocyte repertoires (Fig. 2A,B).





Conclusions: Multiple mechanisms drive tumor development following resistance to KRAS G12C inhibition, including reactivation downstream signaling independent of KRAS, and remodeling of the tumor transcriptomic and immune environments.

Keywords: KRAS, sotorasib

EP16.03-026 Metastasis Sites and Genomic Alterations in Advanced Non Small Cell Lung Cancer: A Retrospective Study

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Introduction: Non-small cell lung cancer (NSCLC) is one of leading causes of cancer incidence and death. Metastatic disease is the main clinical presentation, and the behavior of NSCLC is one of the hot topics in oncology research. Relationship between genomic alterations and metastatic patterns have not been yet clarified. Objective: to describe prevalence of genomic alterations according to metastatic sites in advanced NSCLC patients.

Methods: A single-center retrospective analysis was conducted including patients with stage IV at diagnostic, or recurrent NSCLC who had a next-generations sequencing test between January 2021 and February 2022 in the oncology department from a referral university hospital in Northeast Mexico. We used descriptive statistics to summarize clinical features, metastasis sites and genomic alterations. Chi-squared and Fisher's exact test were used to compare the proportion of mutations according to metastasis sites.

Results: We included 33 patients with stage IV or recurrent NSCLC, who had a next-generation sequencing analysis, either in solid biopsy or liquid. Mean age was 64 years (SD 10), 52% were males. Adenocarcinoma and squamous cell histology were most prevalent (91% and 9% respectively). Regional lymph node metastasis was present in 20 (63%) patients, of whom EGFR alterations occurred in 25%, ALK and KRAS in 15%, TP53 in 55%, CDKN2A/B in 25%, and MTAP in 15%. Pleural metastases were in 13 (41%) patients and alterations found were EGFR in 54% (vs 46% not present, P=0.07), ALK rearrangement and KRAS alteration were in 15%, TP53 in 46%, CDKN2A/B in 23%, MTAP in 15%. Bone metastasis was found in 13 (41%) patients and the alterations were EGFR in 46%, KRAS in 15%, TP53 in 62%, CDKN2A/B 15%. Metastasis in distal lymph nodes were in 12 (38%) patients whom 33% had EGFR alteration, TP53 in 58% and CDKN2A/B and SMAD4 in 17%. Contralateral lung Metastasis was present in 8 (25%) patients, and alterations found were EGFR in 38%, KRAS in 13%, TP53 in 50%, CDKN2A/B in 13%, and MTAP in 13%. Brain metastasis was detected in 6 (19%) of patients, of whom EGFR was present in 55% (vs 45% not present, P=0.001), KRAS in 17%, RAD21 in 33% (vs 67% not present, P=0.03), CDKN2A/B and TP53 alterations in 33%, MTAP in 33%, and SMAD4 and PTEN in 17%. Liver metastasis was present in 4 (13%) patients, with ROS1 in all patients, EGFR and KRAS alterations in 25%, TP53 in 50% and 25% had CDKN2A/B alterations. Pericardial metastasis was present in 3 (9%) patients, and the genomic alterations present were ALK with 67% (vs 33% not present, P=0.01), and CDKN2A/B and TP53 with 33%. Three patients had adrenal metastasis and TP53 was found in 66%.

Conclusions: We can identify a trend between metastatic sites and genomic alterations, mainly in brain metastasis with EGFR mutations, and pericardial metastasis with ALK rearrangements. Obtaining a comprehensive analysis with a larger sample will allow a correct understanding of biological behavior of NSCLC. Reaching a better knowledge of NSCLC will lead us to support approaches that improve the prognosis in this disease.

Keywords: Non-Small Cell Lung Cancer, Next-Generation Sequencing, Genomic Alterations

EP16.03-027 Routine Molecular Testing Using the TSO500+ NGS Panel in a Cohort of Patients with NSCLC

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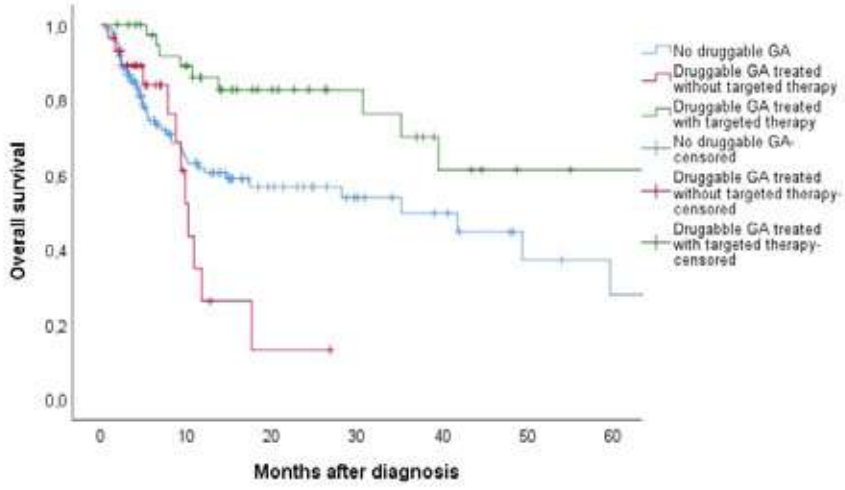
Introduction: Molecular testing of patients with advanced non-small cell lung carcinoma (NSCLC) for actionable genomic alterations (GA) is recommended. We aimed to assess the characteristics, molecular profile and clinical outcomes of patients with NSCLC assessed by next-generation sequencing (NGS) within routine clinical practice at our center.

Methods: This study included patients with NSCLC who were screened for actionable GA using the TruSight-Oncology-500 (TSO500+) NGS panel between July 2020 and February 2022 at a single center. This DNA and RNA assay covers full coding regions of 523 genes for small variants, 59 genes for copy number alterations and 55 genes for fusions and splice variants. We determine the frequency of actionable GA involving *EGFR/BRAF/KRAS/ERBB2* activating mutations (m), *MET* amplifications and exon 14 skipping mutations, *ERBB2* amplifications, and *ALK/ROS1/RET/NTRK* rearrangements (r). Overall survival (OS) was estimated according to the presence/absence of druggable GA and whether patients received targeted therapy.

Results: Out of 207 patients included 65.7% were males, median age was 63 (35-88), with 83.2% PS≤1. Most patients were smokers (84%) and were diagnosed with stage IV (66.2%). The most common histology was lung adenocarcinoma (82.6%), followed by squamous cell carcinoma (5.8%). NGS was performed to screen for a druggable GA (91.8%) or to search a resistance mechanism to previous targeted therapy (8.2%). DNA and RNA libraries failed in 1.4% and 5.8% of cases, respectively. Median tumor mutational burden was 9.5 mutations/megabase (0-119.7). A druggable GA was found in 31.1%. Frequency of actionable GA: *EGFRm*, 4.2%; *KRAS-G12Cm*, 10.0%; *BRAF-V600Em*, 2.6%; *ALKr*, 1.6%; *ROS1r*, 0.5%; *RETr*, 2.6%; *MET* alteration 3.2% (1.1% amplification, 0.5% rearrangement, and 1.6% exon 14 skipping mutation); *ERBB2m*, 4.2%; *ERBB2* amplification, 1.1%; *NTRKr*, 0.5%; *FGFR1r* or m; 1%. Among patients with a druggable GA, 53.2% received at least one targeted therapy. Median OS was 39.5 months (95% CI, 25.6-53.9) for the whole cohort. OS was significantly longer in patients harboring a druggable GA treated with targeted therapies (median not reached) compared with patients without druggable GA (35 months, 95% CI 8.5-61.9) and patients with a druggable GA treated without targeted therapies (10.2 months, 95% CI, 8.9-11.5; p-value=0.002).

Conclusions: The TSO500+ NGS panel is an efficient diagnostic tool to screen for actionable GA in patients with NSCLC. Patients with druggable GA receiving matched targeted therapy achieved longer survival. Access to NGS and targeted therapy are crucial for patients with NSCLC.



Keywords: NSCLC, targeted therapy, NGS

EP16.03-028 Cancer Cells May be Re-sensitized to Tumor Treating Fields (TTFields) Through Inhibition of the PI3K/AKT/mTOR Pathway

A. Klein-Goldberg, T. Voloshin, E. Zemer-Tov, R. Paz, L. Koren, K. Wainer-Katsir, A. Volodin, B. Koltun, B. Brant, Y. Barsheshet, T. Kan, A. Haber, M. Giladi, U. Weinberg, Y. Palti

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Introduction: Tumor Treating Fields (TTFields) are alternating electric fields with anti-mitotic effects on cancer cells. TTFields therapy is approved for treatment of patients with newly diagnosed glioblastoma (GBM), recurrent GBM, or unresectable malignant pleural mesothelioma. The potential of TTFields for treating other solid tumors, such as ovarian cancer, non-small cell lung carcinoma (NSCLC), and hepatocellular carcinoma (HCC), is under investigation. The current research aimed to identify potential escape mechanisms and explore the possibility of re-sensitizing cancer cells to TTFields through targeted inhibition of these pathways.

Methods: GBM U-87 MG, ovarian A2780, and NSCLC H1299 cells were treated with continuous long-term application of TTFields (1.7 V/cm RMS, 200 or 150 kHz, 7 or 13 days, specific conditions depending on the cell line). Changes in signaling pathways in these cells were examined by Luminex multiplex assay, and specific pathway markers were validated by Western blot. These markers were further examined in tumor sections from sham or TTFields-treated rats bearing N1S1 HCC tumors by immunohistochemistry. Next, TTFields were co-applied with inhibitors of the identified pathway, followed by cell count measurements and western blot examinations. Finally, the concomitant application of TTFields with a selected relevant inhibitor was evaluated in mice orthotopically inoculated with MOSE-L firefly luciferase (FFL) ovarian cancer cells. Tumor volume was measured at study end by luciferin signal detection using the *In Vivo* Imaging System (IVIS).

Results: Long-term application of TTFields decreased the sensitivity of cancer cells to TTFields. The signaling pathway activated in these cells was the PI3K/AKT/mTOR pathway, with significant increases in phosphorylation levels of AKT and RPS6. This elevation was also observed in tumor sections from rats treated with TTFields. PI3K inhibitors re-sensitized the cells to the cytotoxic effect of TTFields and down regulated AKT phosphorylation. *In vivo*, application of TTFields concomitant with the PI3K inhibitor alpelisib resulted in enhanced efficacy.

Conclusions: This research demonstrated the involvement of the PI3K/AKT/mTOR signaling pathway in reduced cancer cell sensitivity to long-term application of TTFields. As inhibition of this pathway could re-sensitize the cells to TTFields, TTFields concomitant with PI3K inhibitors warrants further examination.

Keywords: TTFields, Resistance, PI3K

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-029 SLIT2 Expression in NSCLC with Long-Term Response to Pemetrexed

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Introduction: The chemotherapy including the multitargeted antifolate (pemetrexed disodium; Alimta) is indicated for the 1st line treatment of patients with advanced non-small cell lung cancer (NSCLC). It is constructed by induction and maintenance chemotherapy, and some patients have the response over 12 months. We evaluated SLIT2 expression of immunohistochemistry (IHC) in NSCLC with long-term response to pemetrexed.

Methods: Six different NSCLC cell lines were used for microarray analysis, which were one squamous cell carcinoma (H157) and 5 adenocarcinomas (H1648, A549, H1975, H2122 and H358). These cells were growth at 37°C in humid atmosphere containing 5% CO_2 in RPMI-1640 medium supplemented with 10% fetal bovine serum. All cell counts were made with a hematocytometer using trypan blue exclusion to distinguish between live and dead cells. NSCLC cells were seeded at 1-2*10^4 /ml in 96-well plates (100µl/well) were added at the incubated concentration, and proliferation was assessed for all cell lines over a 6-day time course. MTT 50µl was added to each well, and plates were incubated at 37°C for 4 hours. A reading of each well was done using the MAXline Microplate Readers to evaluate pemetrexed IC50 value. Microarray analysis was performed with Affymetrix U-133 A&B and plus2 chips to detect putative biomarker genes which predict pemetrexed sensitivity. Data analysis with obtained chip data was made with GeneSpring software. The biomarker was evaluated with IHC in the surgical samples of NSCLC with long-term response to pemetrexed.

Results: Three NSCLC cell lines (H157, A549 and H1648) had over 100 nM/L IC50 value (high IC50), and remainder NSCLC cell lines (H2122, H1975 and H358) had under 20 nM/L (low IC50). In GeneSpring analysis, 12 genes which were 5 fold higher in sensitive cell lines than in resistant cell lines were chosen. Among them, tumor-related genes were SLIT2 and synovial sarcoma X (SSX) 3. SLIT2 is one of tumor suppression genes, which was expressed with IHC in 3 NSCLCs with the response to pemetrexed over 12 months.

Conclusions: It was suggested that SLIT2 would predict the long-term response to pemetrexed.

Keywords: pemetrexed, non-small cell lung cancer, SLIT2

EP16.03-030 AKT Inhibition as a Therapeutic Strategy to Constrain Histological Transdifferentiation in EGFR-mutant Lung Adenocarcinoma

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Introduction: In lung adenocarcinomas (LUADs), lineage plasticity drives neuroendocrine (NE) and squamous cell (LUSC) transdifferentiation in the context of acquired resistance to targeted inhibition of driver mutations, with up to 14% and 9% incidences in *EGFR*-mutant tumors relapsed on EGFR inhibitors, respectively. Notably, survival of patients with NE- or LUSC-transdifferentiated tumors is remarkably lower than those of LUAD or *de novo* LUSC patients. The paucity of transforming clinical specimens amenable for molecular analyses has hindered the identification of histological transformation drivers, and to date no specific therapies aimed to prevent or delay transdifferentiation-led therapy relapse are available for patients at high risk of transformation.

Methods: We performed multi-omic profiling of LUAD-to-LUSC and LUAD-to-NE transdifferentiating clinical samples, including comprehensive and integrative genomic (whole exome sequencing), epigenomic (bisulfite sequencing), transcriptomic (RNAseq) and protein (antibody arrays) characterization. Clinical findings were validated in preclinical models including cell lines as well as LUSC- and NE-transdifferentiation patient-derived xenograft models.

Results: Our data supports that histological transdifferentiation from LUAD to LUSC or NE tumors is driven by epigenetic remodeling rather than by mutational events, and indicate that transdifferentiated tumors retain epigenomic features of their previous LUAD state. Integrative epigenomic, transcriptomic and protein analysis revealed divergent biological pathways dysregulated for each histological outcome, such as downregulation of RTK signaling and Notch-related genes in NE-transformed tumors, and upregulation of genes involved in Hedgehog and Notch signaling and MYC targets in LUSC-transdifferentiated tumors. Most interestingly, these analyses identified commonly dysregulated pathways in both NE- and LUSC-transdifferentiating tumors, including remarkable downregulation of a variety of immune-related pathways and upregulation of genes involved in AKT signaling and in the PRC2 epigenetic remodeling complex. Concurrent activation of AKT and MYC overexpression induced a squamous phenotype in *EGFR*-mutant LUAD preclinical models, further accentuated by EGFR inhibition. Pharmacological targeting of AKT in combination with osimertinib delayed both squamous and NE transformation in different *EGFR*-mutant patient-derived xenograft transdifferentiation models.

Conclusions: These results identify common and divergent dysregulated pathways in NE and LUSC transdifferentiation, and nominate AKT as a therapeutic target to prevent the acquisition of resistance to EGFR-targeted therapies through histological transdifferentiation.

Keywords: Lineage plasticity, Transdifferentiation, Transformation

EP16.03-031 Transcriptomic Heterogeneity in Non-Small Cell Lung Cancer Harboring Different EGFR Exon 19 Del/Delins Variants

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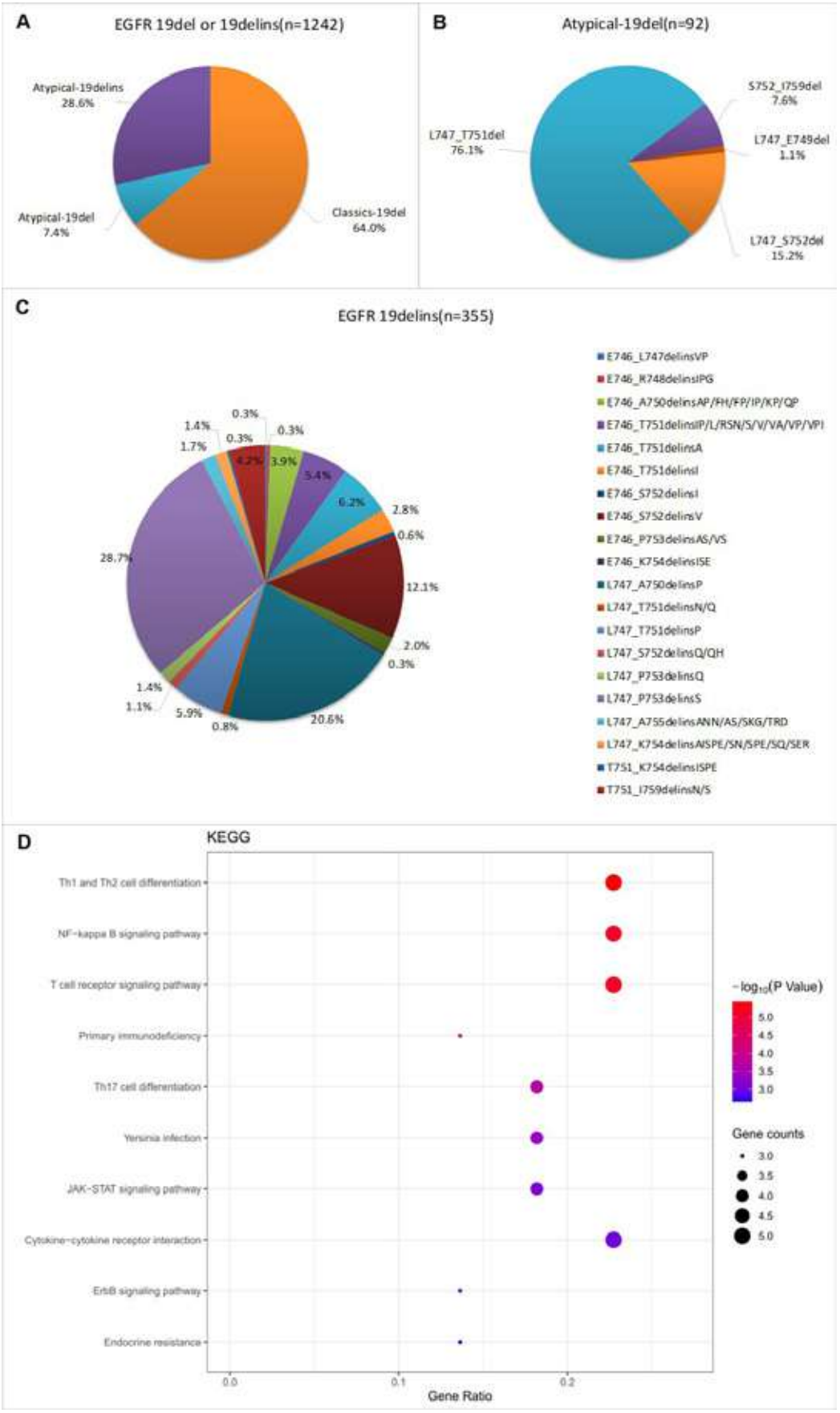
Introduction: Exon 19 deletion (19Del) and deletion-insertion (19Delins) of epidermal growth factor receptor (*EGFR*) gene were common drivers in non-small cell lung cancer (NSCLC). However, it was reported that response to EGFR-TKIs displayed a variant type-dependent manner for NSCLC with *EGFR* 19Del/Delins. It is of great importance to deepen the understanding of biological heterogeneity of NSCLC harboring different types of *EGFR* Exon 19Del/Delins.

Methods: NGS data of 1242 patients diagnosed as advanced NSCLC with *EGFR* 19Del/19Delins variant were retrospectively reviewed. 81 patients with 1813-gene expression data were further analyzed to compare biological difference. Gene-set enrichment analysis was conducted using the Cluster Profiler package in R 4.0.5.

Results: Total of 48 different *EGFR* 19Del/Delins variants were identified. Total 1242 patients were divided into classic 19Del subtype group (p.E746_A750Del, n=759, 64.0%) and atypical mutations group (36%) including 19Del group (n=92, 7.4%) and 19Delins group (n=355, 28.6%). The atypical classical 19Del group contains p.L747_T751Del (76.1%), L747_S752Del (15.2%), S752_I759Del (7.6%) and L747_E749Del (1.1%) variants. And the atypical 19Delins group, L747_P753DelinsS (28.7%), p.L747_A750DelinsP (20.6%), p.E746_S752DelinsV (12.1%) were the most frequent variants. Transcriptomic heterogeneity was firstly observed in 19Del group. 19Dels starting from E746 displayed activation of FGFR1/2 cascades through phospholipase C, SHC and PI3K. For variants starting from L747, these tumors showed upregulation of cell cycle related pathways like E2F targets, Meiotic recombination, and cell cycle checkpoints. While tumor with uncommon 19Delins displayed significant enrichment of immune-related pathways in REACTOME, including MHC II antigen presentation, PD-1 signaling. In parallel, Th1 and Th2 cell differentiation, T cell receptor signaling pathway, and NF-kappa B signaling pathway in KEGG were significantly enriched in EGFR 19Delins which were respond to EGFR-TKIs remain controversy, including p.E746_T752delinsV, p.L747_T750delinsP and p.T751_I759delinsS.

Conclusions: NSCLC with *EGFR* 19Del/Delins should not be considered as a homogenous disease. NSCLC with uncommon *EGFR* 19Del/Delins displayed a more active adaptive immunity in tumor microenvironment, which indicated the potential vulnerability of immunotherapy.



Keywords: Heterogeneity, EGFR Exon 19 Del/Delins, RNA Sequencing

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-032 Structure-Based Classification of Chinese Patients with Non-Canonical EGFR-Mutant Non-Small Cell Lung Cancer

L. Gu[1], Y. Yu[1], L. Shen[1], F. Yao[2], C. Zhu[2], J. Wang[2], S. Lu[1]

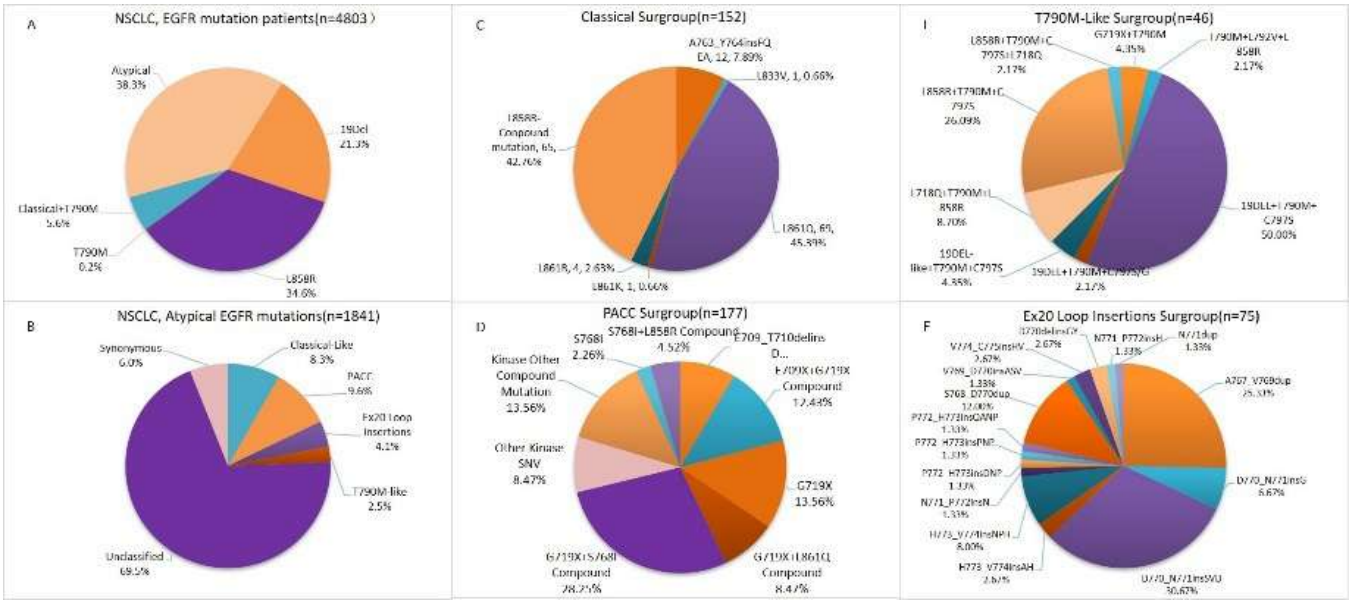
[1]Shanghai Chest Hospital, Shanghai/CN, [2]Amoy Diagnostics Co., Ltd., Xiamen/CN

Introduction: Non-canonical *EGFR* mutations in non-small cell lung cancer (NSCLC) could be re-classified into four subtypes (Classical-like, P-loop and αC-helical compressing (PACC), T790M-like, and exon 20 loop insertions) based on unique structures as well as response to various types of tyrosine kinase inhibitors (TKIs). Since *EGFR* most frequently mutated in East-Asian population, it is clinically crucial to investigate the distribution of structure-based *EGFR* classification in Chinses NSCLC patients.

Methods: 4692 *EGFR* mutant NSCLC patients with available next-generation sequencing result were collected (cohort 1). Another cohort (cohort 2) of 266 NSCLC patients with accessible *EGFR* testing results and time to treatment failure (TTF) for EGFR-TKI was retrospectively recruited from Department of Oncology, Shanghai Chest Hospital.

Results: For cohort 1, distribution of four subtypes were as follows, 60.5% of patients were Classical (like), PACC (3.77%), T790M-like (6.86%), Ex20ins (1.60%), and Unclassified (27.28%). In unclassified group, most of *EGFR* variants belong to non-classical *EGFR* 19Del. Dominant *EGFR* mutation subtypes in the four subgroups were as follows: L861Q (45.39%) and L858R compound mutation (42.76%) in Classical (like) subgroup, G719X+S768I compound mutation (28.25%) and E709X+G719X compound mutation (12.43%) in PACC subgroup, 19del+T790M+C797S compound mutation (50%) and L858R+T790M+C797S (26.09%) in T790M-like subgroup, and D770_N771insSVD (30.67%) and A767_V769dup (25.33%) in Ex20ins subgroup. In cohort 2, 60.78% categorized to classical (like) group, 22.55% of patients were T790M-like group, 10.78% belong to PACC, and Ex20-ins group in 4.9% of patients. Patients with Classical and T790M-like subgroup displayed longer TTF than PACC and Ex20ins subgroups. Especially, Ex20ins subgroup showed the shortest TTF. Further, 2nd generation TKI, afatinib significantly improved the TTF compared with 1st generation TKI.

Conclusions: In this study, for the first time, we applied the structure-based classification approach to characterize the mutational landscape of *EGFR*-mutant patients in Chinese patients with NSCLC. Adopting this structure-function-based *EGFR* classification into clinical practice may improve the precision medicine for *EGFR* mutant NSCLC patients as well as benefit future drug development and clinical trial design.



Keywords: Comprehensive profiling, EGFR, Structure Subtyping

EP16.03-033 Transcriptomic Heterogeneity in Non-Small Cell Lung Cancer with Four Structure-Based EGFR-Mutation Subgroups

L. Gu[1], Y. Yu[1], L. Shen[1], F. Yao[2], C. Zhu[2], J. Wang[2], S. Lu[1]

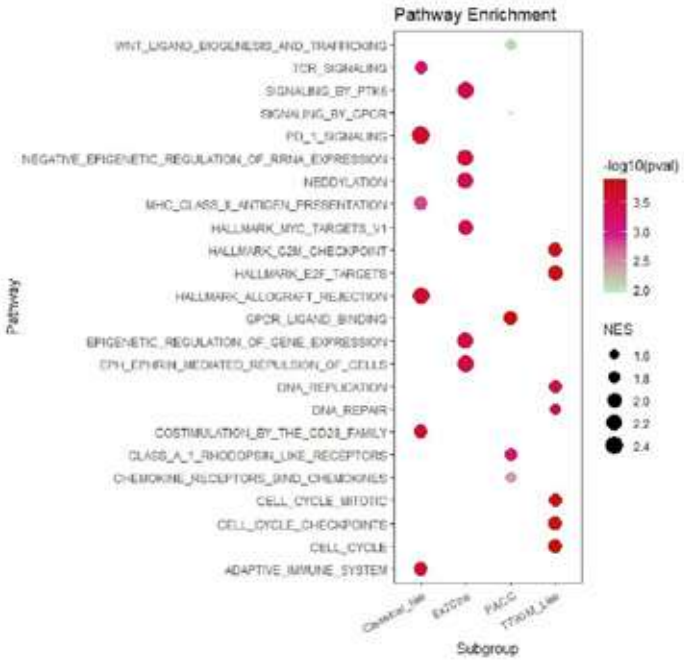
[1]Shanghai Chest Hospital, Shanghai/CN, [2]Amoy Diagnostics Co. Ltd., Xiamen/CN

Introduction: *EGFR* mutations were classified into four subtypes (Classical-like, P-loop and αC-helical compressing (PACC), T790M-like, and exon 20 loop insertions) based on unique structures as Jacqulyne previously reported (Nature, 2021).Thus, *EGFR* mutant non-small cell lung cancer (NSCLC) should be considered as a heterogeneous disease. And there is clearly an unmet need understanding the biology trait of NSCLC with distinct *EGFR* mutation subtypes.

Methods: Total 2731 *EGFR* mutant NSCLC patients with available next-generation sequencing results were retrospectively reviewed. 119 patients with 1813-gene expression data were further analyzed to compare biological difference. Gene-set enrichment analysis was conducted using the Cluster Profiler package in R 4.0.5.

Results: Total 2731 patients were divided into classic Classical-like group (n=2242, 82.09%), PACC (n=140, 5.13%), T790M-like (n=292, 10.69%), Ex20ins (n=57, 2.08%). 544 patients were included for co-occurrence of genomic alterations analyzing, TP53 was the most common co-occurring mutation in the four distinct subgroups, especially in 60% of T790M-like subgroups. However, APC mutations were mutually exclusive in Ex20ins group. Moreover, transcriptomic heterogeneity was first of time observed in the four subgroups. Classical-like group displayed enrichment of immune-related pathways in REACTOME, including PD1 signaling, CD28 family, and TCR signaling. PACC subgroup, these tumors displayed activation and triggering the G-protein-coupled receptors (GPCRs) signaling cascade towards a cellular event. For the T790M-like group, cell cycle related pathways like E2F targets, and cell cycle checkpoints (G2M) were significant upregulation. Ex20ins subgroup was characterized as enrichment of oncogenic process including PTK6, MYC activation, epigenetic regulation of gene expression as well as NEDDylation. Subsequently, the immune characteristics of tumors with different subtypes were investigated. Along with pathway analysis, classical subgroups displayed highest T cell infiltration. And PACC group showed highest level of protumor cytokine. Among Classical-like group, significant enrichment of MHCI/II signatures was observed in L858R group. In addition, Th2 signature was significantly enriched in L858R-compound subgroup.

Conclusions: This study, of first time, demonstrated the heterogenous biology of NSCLC driven by distinct *EGFR* mutations with distinct structures at transcriptional and functional level.



Keywords: EGFR, Heterogeneity, Transcriptome

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-034 Differential Prognostic Effect of EGFR Mutation According to Smoking Status and Pathologic Stage in Non-mucinous Lung Adenocarcinoma

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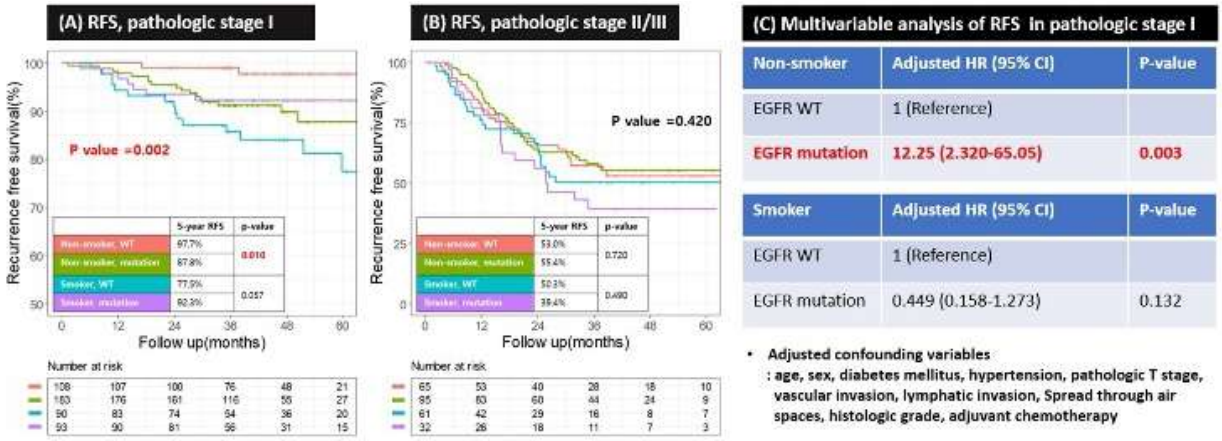
Introduction: We evaluate the prognostic effect of EGFR mutation in lung adenocarcinoma (LUAD) according to smoking status and pathologic stage.

Methods: We investigated the EGFR and KRAS mutation simultaneously in 773 patients who underwent lobectomy for pStage I-III non-mucinous LUAD in Seoul National University Bundang Hospital from 2011 to 2018. Due to the mutual exclusiveness of EGFR and KRAS mutation, 46 cases of KRAS mutation were excluded. Consequently, 727 patients were reviewed and categorized by smoking status and EGFR mutation, and subgroup analysis was performed according to pathologic stage (pStage). The primary outcomes was recurrence free survival (RFS), and secondary outcomes included overall survival (OS) and post-recurrence free survival (PRS). The multivariable Cox regression analysis was conducted to determine whether EGFR mutation itself could affect the survival outcomes.

Results: EGFR mutation was found in 55.4 % of patients, and was associated with female, non-smoker (p<0.001, respectively). In pStage I, RFS was the best in the non-smoker with WT and the worst in smoker with WT (p=0.002). In multivariable analysis, EGFR mutation was associated with increased risk of recurrence in non-smoker (HR 12.25, 95% CI 2.320-65.05, p=0.003). In pStage II/III, RFS was not different in each groups (p=0.420), whereas OS was the worst in smoker with WT (p<0.001). The multivariable analysis showed that EGFR mutation was associated with reduced risk of death in smoker (HR 0.059, 95% CI 0.013-0.276, p<0.001). PRS was better in patients with EGFR mutation, especially in smoker (p=0.005), which demonstrated similar outcomes in multivariable analysis (HR 0.246, 95% CI 0.079-0.768, p=0.016).

Conclusions: EGFR mutation had differential prognostic impact on recurrence in stratified analysis according to smoking status and pStage in non-mucinous lung LUAD. Moreover, patients with EGFR mutation showed reduced risk of post-recurrence death, especially in smoker, which might lead to better OS in pStage II/III.



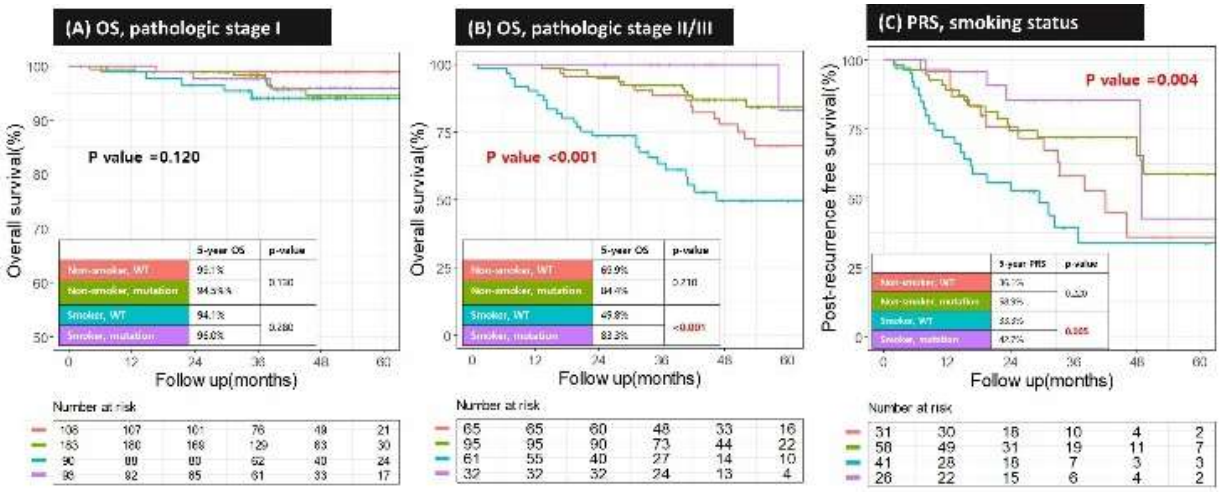
(C) Multivariable analysis of RFS in pathologic stage I

Non-smoker	Adjusted HR (95% CI)	P-value
EGFR WT	1 (Reference)	
EGFR mutation	12.25 (2.320-65.05)	0.003

Smoker	Adjusted HR (95% CI)	P-value
EGFR WT	1 (Reference)	
EGFR mutation	0.449 (0.158-1.273)	0.132

- Adjusted confounding variables
  : age, sex, diabetes mellitus, hypertension, pathologic T stage, vascular invasion, lymphatic invasion, Spread through air spaces, histologic grade, adjuvant chemotherapy

Primary survival outcomes of patients who underwent curative resection for non-mucinous lung adenocarcinoma. Patients were categorized according to smoking status and EGFR mutation [Non-smoker, wild-type (WT); Non-smoker, mutation; Smoker, WT; Smoker, mutation]. (A) Recurrence free survival (RFS) curves in pathologic stage I, (B) RFS curves in pathologic stage II/III, and (C) Multivariable Cox-regression analysis of RFS in pathologic stage I



Explorative survival outcomes of patients who underwent curative resection for non-mucinous lung adenocarcinoma. Patients were categorized according to smoking status and EGFR mutation [Non-smoker, wild-type(WT); Non-smoker, mutation; Smoker, WT; Smoker, mutation). (A) Overall survival (OS) curves in pathologic stage I, (B) OS curves in pathologic stage II/II, and (C) Post-recurrence free survival (PRS).

Keywords: EGFR mutation, adenocarcinoma, smoking status

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-035 Driver Mutations on Metastatic NSCLC - Experience in a Secondary Center

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Hospital Beatriz Angelo, Loures/PT

Introduction: Primary lung cancer is one of the most common cancers and non-small cell lung cancer (NSCLC) accounts for 80-90% of lung cancers. About 40% are diagnosed with metastatic disease. More than histology, the therapeutic strategy is increasingly defined by molecular drivers and biomarkers. The aim of this study was to evaluate the presence of driver mutations on patients with metastatic NSCLC, demographic characteristics and outcomes.

Methods: We performed a retrospective data analysis of patients with metastatic NSCLC on a secondary hospital between 2014 and 2021. Molecular study was made in all adenocarcinomas and squamous carcinoma in non-smokers or light smokers. From 2014 to 2016, only EGFR mutations and ALK and ROS1 rearrangements were performed. EGFR mutations were performed by RT-PCR, ALK and ROS1 rearrangements by FISH. Since 2016, the molecular tests were performed by next-generation sequencing (NGS), targeting mutations on EGFR, KRAS, NRAS, BRAF, MET, HER2, ALK and ALK, ROS1, RET and NTRK1 rearrangements. The demographic and clinical variables analyzed included age at diagnosis, sex, smoking history, family history of cancer, metastasis in central nervous system (CNS) at time of diagnosis or after, molecular characteristics, systemic treatments and overall survival (OS). Data was analyzed using SPSS®, version 26.0 (IBM Statistics®).

Results: Between June 2014 and December 2021, a total of 832 patients were diagnosed with lung cancer. Non-metastatic, small-cell lung cancer, neuroendocrine and other thoracic tumors were excluded. We identified 126 patients with driver mutations with metastatic NSCLC. 45.2% were female and ages ranged from 40 to 89, with mean 66.62 ± 11,40 years-old. 45.2% were non-smokers.The most common mutation was EGFR, in 40.5%. 68.6% were female and 29.4% had smoking history. Median OS was 16.7 months. K-RAS mutations were found in 27.8% (15.9% non-G12C and 11.9% G12C), 82.9% were male and 91.4% smokers; median OS was 7.8 months. In this group we identify a higher percentage of poorly differentiated tumors.ALK rearrangements were present in 11.1%, mostly men and 42.9% were smokers. OS was 8.3 months.ROS1 rearrangements were present in 2.4%, non-smokers and mostly in women. OS was 5.3 months.The most common histological pattern was adenocarcinoma, but in patients with MET exon 14 skipping mutation (METΔex14) squamous cell carcinoma was found in 75%. METΔex14 was found in 3%, 50% were smokers and patients had the shorter OS 4.5 meses.In all groups of patients, CNS metastasis were found in >30%, except for RET rearrangements and BRAF and MET mutations. Other mutations found were HER2 in 4.8%, BRAF 3.9%, ROS1 rearrangement 2.4% and RET fusion 1.6%, with OS 8.7, 6.6, 5.3 and 29.8 months, respectively.

Conclusions: In our study, the most common driver mutation found were EGFR, K-RAS and ALK rearrangements. EGFR were found more often than K-RAS, which may be explained by the fact that before 2016 K-RAS mutation wasn't performed in our center. In our analysis, some demographic and clinical characteristics were different from what was reported before, namely ALK rearrangements were more frequent in men and CNS metastasis weren't more prevalent, as well in ROS1 rearrangements patients.

Keywords: driver mutations, non-small cell lung cancer, advanced

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-036 Clinical and Genomic Features of HER2 exon 20 Insertion Mutations in East Asian NSCLC

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Introduction: *HER2*-mutated (*HER2*-M+) non-small cell lung cancer (NSCLC) represents a distinct molecular subtype with expanding therapeutic options including HER2 antibody-based therapies and tyrosine kinase inhibitors. We describe the molecular epidemiology and genomic features of *HER2*-M+ NSCLC in the setting of an Asian tertiary cancer centre.

Methods: We identified *HER2*-M+ NSCLC in our institutional database, collating clinicopathological features and treatment history. Whole exome sequencing (WES) data was available for 5 patients and were combined with 2 publicly available datasets to evaluate the genomic landscape of *HER2*-M+ NSCLC.

Results: Among 1252 consecutive lung adenocarcinoma patients undergoing routine next generation sequencing covering *HER2* hotspot mutations in exons 19 - 21 (June 2019-June 2021), the prevalence of *HER2*-M+ was 3.1%(n=39) - exon 20 insertion mutations (*HER2ex20)* comprised 2.7%(n=34). Excluding patients with *EGFR* mutations, the prevalence of *HER2*-M+ was 6.6%(39/593). We next examined the clinicopathologic features in an extended cohort of 39 *HER2*-M+ NSCLC patients comprising 26 *HER2ex20* and 13 non-exon 20 insertion mutations (*HER2other*). Both cohorts had similar median age at diagnosis, gender distribution and predominantly Chinese ethnicity although *HER2ex20* had a higher proportion of never-smokers (Table). Concurrent *EGFR* mutations were observed in 3.8%(1/26) of *HER2ex20* and 30.8%(4/13) of *HER2other*, while co-mutations in *TP53* were identified in 23.1%(6/26) and 7.7%(1/13) respectively. The most common *HER2ex20* was *HER2*Y^{772}_A^{775}dup in 38.5%(10/26), followed by *HER2*A^{775}_G^{776}insYVMA in 30.8%(8/26). A diverse range of *HER2other* were observed, of which *HER2*L^{755}Pwas most common in 23.1%(3/13). In 7 patients who received HER2-directed therapies, limited responses to afatinib (n=5), trastuzumab emtansine (n=3) and tucatinib (n=1) were observed and no responses were seen with immunotherapy monotherapy (n=2). We next compared the genomic features of *HER2ex20* (n=5) and *HER2other* (n=6) in the WES dataset. *HER2ex20* tumours demonstrated low tumour mutational burden (TMB), low incidence of cancer driver co-mutations, and a predominance of ageing mutational signature, similar to *EGFR*-mutated tumours. In contrast, *HER2other* tumours resembled *EGFR*-wildtype tumours in terms of higher TMB, higher frequency of cancer driver mutations and greater presence of smoking and APOBEC mutational signature.

Conclusions: The incidence of *HER2*-M+ is 3.1% in East Asian non-squamous NSCLC, with only 1/26 *HER2ex20* overlapping with activating *EGFR* mutations. The clinical phenotype and genomic features of *HER2ex20* tumours appear distinct from *HER2other*, the latter demonstrating higher TMB, co-occurring drivers and predominant non-ageing signature. The therapeutic implications of the genomic and clinical features of *HER2*-M+ warrant further investigation.

Patient characteristics comparing HER2ex20 and HER2other		
	***HER2ex20* (n=26)**	***HER2other* (n=13)**
Median age (range)	65 (43 - 78)	64 (48 - 73)
Female	14 (54%)	7 (54%)
Never-smokers	21 (81%)	7 (54%)
Chinese ethnicity	24 (92%)	12 (92%)
Stage at diagnosis		
I	9 (35%)	6 (46%)
II	1 (4%)	1 (8%)
III	3 (12%)	1 (8%)
IV	13 (50%)	5 (38%)
Brain metastases at diagnosis	4/13 (31%)	1/5 (20%)

Keywords: HER2, NSCLC

EP16.03-037 Poor Prognosis of Patients with EGFR Mutations Left behind by Selective Detection in NSCLC

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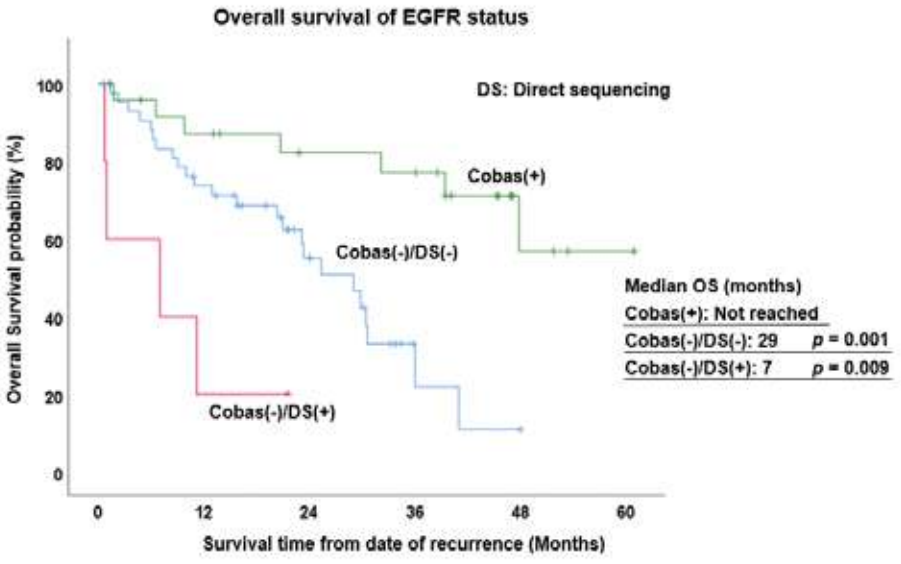
Introduction: Epidermal growth factor receptor (EGFR) mutations are the most significant driver genes in non-small cell lung cancer (NSCLC). The presence of the mutations indicates EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy. The clinical examinations selectively detect the majority of mutations among a lot of types. We demonstrated the prognosis of patients with EGFR mutations, which were clinically identified as wild type by selective detection.

Methods: A series of 254 NSCLC patients had cobas followed by direct sequencing to detect EGFR mutations from 2015 to 2017 after they had undergone surgery. Cobas is the widely used PCR method, which is beneficial for clinical use due to the short detection time and cost-effectiveness. EGFR mutations were detected in 109 patients. In the remaining 145 patients identified as wild type by cobas, direct sequencing was performed using a primer set flanking exons 18 to 21 with the surgical samples. Among total 254 patients, 74 patients had recurrent cancer, including 59 adenocarcinomas, 3 squamous cell carcinomas, 4 adenosquamous carcinomas, one large cell carcinoma, 6 pleomorphic carcinomas and one atypical carcinoid tumor. The prognosis as overall survival (OS) was analyzed with survival curves plotted using the Kaplan-Meier method and a log-rank test after the recurrence.

Results: Among 145 patients identified as wild type by cobas, there were one exon 18 deletion, 4 exon 20 insertions and 3 exon 21 point mutations. In total 254 patients, EGFR mutations were 46% (117/254), and undetected mutations were 6.9% (8/117). In 74 recurrent patients, there were 25 patients with EGFR mutations detected by cobas (median OS: not reached). Five patients had EGFR mutations detected by direct sequencing (median OS: 7 months), which were clinically identified as wild type at that time. There were 44 patients with wild type by both methods (median OS: 29 months). The mutations by direct sequencing had significant worse prognosis than those by cobas ($p < 0.001$) and wild type ($p = 0.009$) (Figure).

Conclusions: Before the era of molecular targeted therapy, the abnormality of EGFR correlated with poor prognosis. EGFR-TKI therapy significantly improves the prognosis of patients with EGFR mutations. The minority of the mutations are low frequency, in which it is difficult to evaluate the response to EGFR-TKI. The present study suggests that any EGFR mutations have poor prognosis without EGFR-TKI. It is expected that a screening test to be compatible with diverse mutations and wide-ranging EGFR-TKI.



Keywords: NSCLC, EGFR mutation, PCR method

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-038 Single-cell Analyses Reveal Tumor Microenvironment Differences between EGFR 19del and L858R mutations in Lung Adenocarcinoma

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Introduction: Lung cancer is the leading cause of cancer-related mortality among malignant tumors worldwide. Lung adenocarcinoma (LUAD) accounts for 40% of all cases and is the most common histological subtype of non-small cell lung cancer (NSCLC). Activating somatic mutations, mostly identified as 19del and L858R in EGFR tyrosine kinase domain, may predict response to EGFR tyrosine kinase inhibitors (TKIs) in NSCLC patients. Although EGFR 19del and L858R patients are sensitive to TKIs, they showed different clinical benefits such as prolonged PFS in 19del patients. Thus, to investigate the underlying mechanisms and decipher tumor microenvironment (TME) differences between the two mutation subtypes, therefore better understanding precision treatment of EGFR mutation patients, is interesting and necessary.

Methods: In this study, we adopted single-cell RNA sequencing(scRNA-seq) technology to study the differences between EGFR 19del and L858R mutant patients in lung adenocarcinoma (LUAD). We obtained scRNA-seq data from Gene Expression Omnibus (*GSE171145*) and this dataset includes two 19del patients, two L858R patients and two wild-type patients. We performed dimension reduction and unsupervised clustering of single cell expression data using standard workflow in *Seurat*. Each cell cluster was annotated according to the canonical cell markers, then R Package *CellChat* was conducted to infer and visualize the intercellular interaction networks based on a comprehensive signaling molecule interaction database.

Results: In total we obtained 31,484 cells, including 19del LUAD (10,688 cells), L858R LUAD (10,286 cells), and EGFR-wild type LUAD (10,510 cells), respectively. We identified 18 clusters that belonged to different cell types including Endothelial, Epithelial, Fibroblast, B/Plasma cells, Myeloid cells, T cells, and NK cells. Although most cell types have similar cell proportions between 19del and L858R patients, we found L858R patients had a lower proportion of Myeloid cells, nearly half compared with 19del patients. On the contrary, L858R patients had twice times of fibroblast cells than 19del patients. Furthermore, Cell Communication Analysis identified 54 signaling pathways in both EGFR mutation subtypes, including *CXCL, CCL, EGF, VEGF, IL2,* and so on. While *Nerve Growth Factor (NGF) Signaling Pathway* was only detected in L858R patients, *Tumor Necrosis Factor (TNF), Semaphorin 3A (Sema3A), and FAS-Ligand (FASLG) Signaling Pathways* were only detected in 19del patient. When further exploring the EGF pathway, four enriched ligand-receptor (LR) pairs(EREG_EGFR, EREG_EGFR/ERBB2, EREG_ERBB4, EREG_ERBB2/ERBB4)were only discovered in 19del patients. Interestingly, those uniquely identified pathways are all associated with cancer microenvironment. *NGF* Signaling Pathway can promote the formation of new blood vessels. By contrast, *TNF, FASLG, Sema3A* Signaling Pathways are associated with anti-cancer, tumor necrosis, and the inhibitor of angiogenesis, respectively. And Low EREG gene expression levels are associated with resistance to anti-EGFR therapy.

Conclusions: *In this study, we found NGF Signaling Pathway,* which was exclusively detected in Patients with L858R mutation. By contrast, *TNF, FASLG, Sema3A Signaling Pathways,* which were only detected in EGFR-19del patients. The uniquely identified pathways in 19del patients are associated with anti-cancer, tumor necrosis, and the inhibitor of angiogenesis, respectively. Such tumor microenvironment differences provide preliminary clues to further understand why 19del patients have better clinical outcomes after EGFR TKI treatment.

Keywords: lung cancer, tumor microenvironment, single-cell RNA sequencing

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-039 Characterizing SHPRH as a Novel Tumor Suppressor Gene in Lung Adenocarcinoma

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Introduction: The majority of lung cancers (LC) are diagnosed at an advanced stage, contributing to a poor five-year survival rate of 18% or less. Identifying factors that increase one's susceptibility to LC is therefore imperative for the development of early screening and treatment strategies. While smoking is the major aetiology of LC, genetic factors also play a critical role in enhancing LC risk. However, the specific genes responsible for increasing this risk are still poorly understood. In an effort to identify new genetic drivers of LC, our group used whole exome sequencing to profile a panel of never-smoker patients with lung adenocarcinoma (LUAD). Among the most significantly mutated genes was *SNF2 Histone Linker PHD RING Helicase* (*SHPRH*), which encodes for an E3 ubiquitin ligase that functions in DNA repair. Due to it's frequency of double allelic disruptions and chromosomal location within a major lung cancer susceptibility locus, we predicted that *SHPRH* may function as a tumor suppressor gene in LUAD. While the alteration of SHPRH has been observed in various other cancers, the functional characterization of SHPRH as a tumor suppressor and its role in LUAD has yet to be determined. Here we evaluate the effect of altered SHPRH expression on the development and progression of LUAD.

Methods: To evaluate the clinical relevance of SHPRH, we analyzed publicly available LUAD datasets for *SHPRH* copy number and expression level status, and assessed for their association to survival outcomes. To functionally characterize the role of SHPRH in LUAD tumorigenesis, we used a doxycycline-inducible lentiviral vector system to express wildtype SHPRH in LUAD cell lines with varying SHPRH expression statuses. Upon expression of SHPRH, we performed *in vitro* and *in vivo* assays to assess for alterations tumorigenic potential.

Results: Analysis of the TCGA LUAD dataset (n=230) reveals that *SHPRH* is mutated or homozygously deleted in 7% of tumors and 52.2% of LUADs demonstrate a single copy loss of *SHPRH*, which coincides with having significantly less SHPRH expression. Furthermore, ever- and never-smoker LUAD patients with reduced SHPRH expression have significantly worse overall and progression-free survival outcomes. Assessment of colony growth *in vitro* suggests that re-expression of SHRPH in cell lines with inactivating alterations of SHPRH reduces their anchorage-dependent and -independent growth in a tumor suppressive manner. In concordance with this observation, implantation of these cells into the flanks of mice kept on a doxycycline diet shows that SHPRH re-expression significantly reduces tumor burden compared to the control conditions.

Conclusions: This data suggests that the expression of SHPRH may positively be associated with enhanced patient outcomes and may function to reduce the tumorigenic potential of LUAD. However, investigations are ongoing to determine the biological relevance of SHPRH in LUAD pathogenesis. Because of its function in DNA repair and its chromosomal location in a LC susceptibility region, understanding the role of SHPRH may lead to it becoming an important clinical biomarker for identifying individuals with an increased risk of developing LUAD and to help improve disease outcomes.

Keywords: Tumor Suppressor, SHPRH, NSCLC

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-040 Biomarkersatlas.com: the Italian NSCLC Precision Medicine Knowledge Data Base

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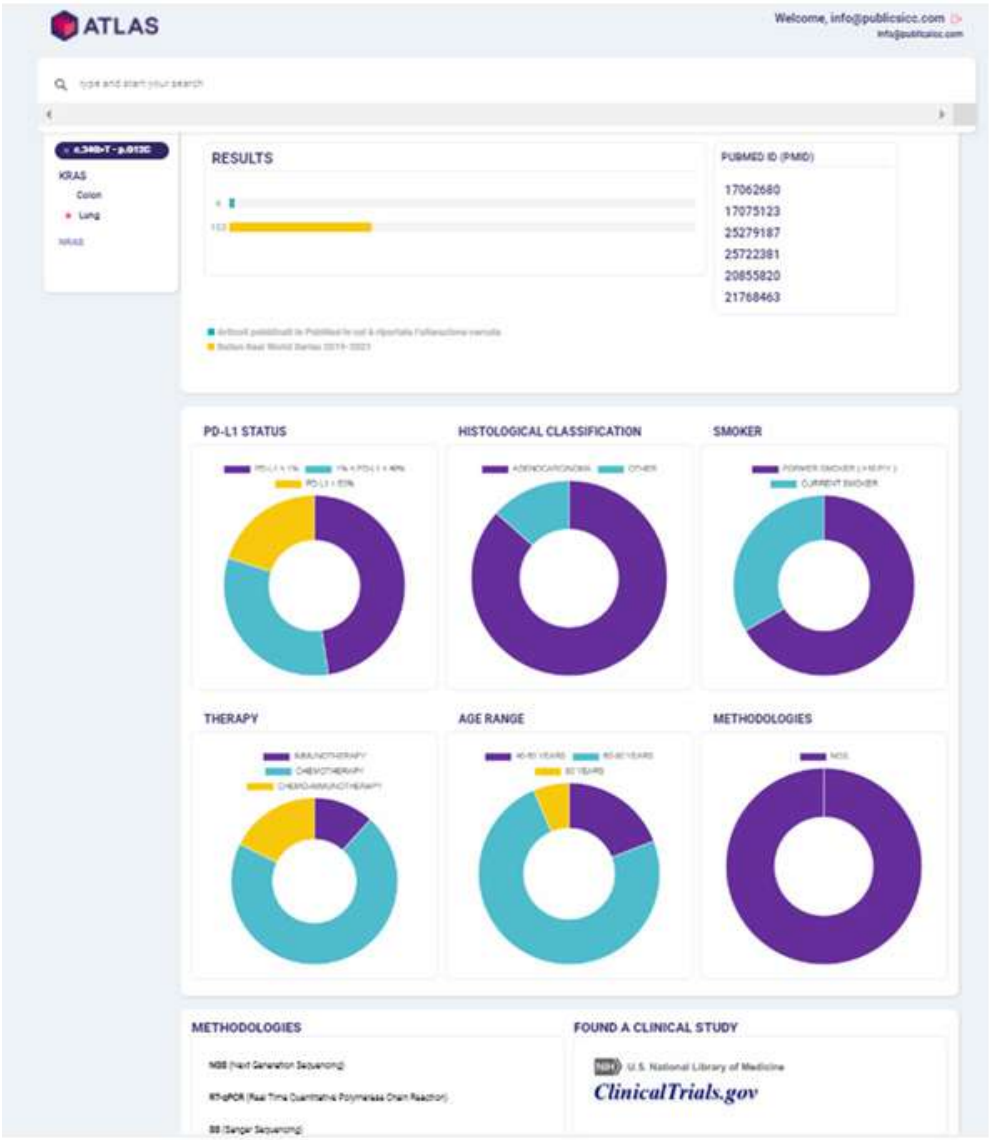
Introduction: Precision medicine has revolutioned the clinical management of advanced non-small cell lung cancer (NSCLC) patients. The number of biomarkers to be tested for the administration of targeted therapies is rapidly increasing and the paradigm shift from “one gene - one biomarker to one mutation - one biomarker”. The introduction of effective mutation specific drugs with the parallel widespread of Next Generation Sequencing (NGS), requires an adequate identification of each actionable molecular alteration in order to support the healthcare personnel in the real-word management of NSCLC patients in the landscape of precision oncology. To shed light in this complex scenario, the development of a knowledge-based system may be helpful for both molecular pathologists and thoracic oncologists to avoid leaving any patient behind.

Methods: We developed a real-world mutation knowledge-based system (https://biomarkersatlas.com/) to support the healthcare personnel in the clinical management of oncogene-addicted NSCLC patients. We carried out an overview of the mutation subtypes and testing practice across ten Italian institutions in order to cover all clinically relevant genomic alterations within the actionable biomarkers in the setting of advanced NSCLC. In addition, five different categories (sex, age, smoking status, tumor histotype, and Programmed death ligand 1 expression) were also collected from included patients with metastatic NSCLC and matched with their molecular background.

Results: The knowledge-based system currently includes (last access 03/05/2022) a total of n=62 unique genomic alterations across four different genes (n= 35 *EGFR,* n=20 *KRAS,* n=5 *NRAS* and n=2 *BRAF*) derived from n=608 advanced NSCLC patients. Overall, clinical data were available in n=269 cases. Briefly, n= 120 (44.7%) male and n= 149 (55.3%) female; n=4 (1.5%) <40 years, n=49 (19.0%) 40-60 years, n=181(70.1%) 60-80 years, n=24 (9.4%) >80 years; n=184 (88.9%) adenocarcinoma; n=5 (2.4%) squamous cell carcinoma, n=5 (2.4%) not other specified subtype and n=13 (6.3%) other histological subtypes; n=55 (32.0%) never smoker, n=32 (18.6%) current smoker, n=17 (9.9%) former (<10 p/y) and n=68 (39.5%) former (>10 p/y) smokers; n=91 (63.6%) of patients received target therapy, n=32 (22,3%) chemotherapy, n=8 (5,6%) immunotherapy and n=12 (8,5%) chemo-immunotherapy, respectively. Moreover, each mutation reported in the biomarkers ATLAS was connected to pubmed indexed references and clinicaltrials.gov. (Figure 1)

Conclusions: These data support the reliability of the italian NSCLC Precision Medicine Knowledge Data Base, supporting its implementation in the real word practice scenario. The program is expanding to include a total of 23 Italian institutions during the course of 2022.



Keywords: NSCLC, Variants Database, Web

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-041 Single Cell RNA Sequencing Reveals Phenotypic Predispositions to Developing Lung Cancer in Never-Smokers

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Introduction: There is a paucity of research into why never-smoking patients develop lung cancer. Preliminary results suggest there may be deficiencies in the genes which deal with cellular repair of DNA damage and response to chronic inflammation. These deficiencies may arise from small differences in the genetic variation of these genes. The relationship between genetic variation and gene expression can be studied through an expression QuantiTative Loci (eQTL) analysis, and our lab has developed methods to perform this at a cellular level. This method will be applied to pivotal genes in DNA damage repair and chronic inflammatory response to identify genetic variants that are associated with disease.

Methods: Peripheral circulating immune cells (PBMC) from never-smoking patients with lung cancer were collected from a state-based prospective study (EnRICH cohort). 17 patient samples were processed for single cell sequencing using the 10X genomics platform. Each patient had ~4500 cells sequenced individually, giving ~80,000 cells for study. Cellular analysis was performed to look for variation in expression of genes for DNA repair proteins and proteins involved in the inflammatory response using eQTLs. Reference PBMCs from our cohort of age-matched, healthy, never- smoking controls (n=265) was used for baseline comparison.

Results: A total of 17 patients with lung cancer who had never smoked were studied, median age 65, 62% female. An aged-matched control group was selected from our reference cohort, median age 64.2, 63% female. Standardised cell sub-typing using Azimuth revealed 27 distinct immune cell subtypes. Curated gene lists for DNA repair and inflammatory response are being used for eQTL analysis.

Conclusions: Using a large reference cohort, eQTL analysis in PBMCs is feasible to look for changes in DNA repair and inflammation response in patients with lung cancer who have never smoked. Inherited pre-dispositions to cancer development may aid in family counselling and risk reduction.

Keywords: never smoker, DNA damage repair, single cell sequencing

EP16.03-042 BET Inhibitors Stimulate NK Cytotoxic Activity in NSCLC through Attenuation of YAP/TAZ and SMAD3 Transcriptional Programs

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Introduction: Over the past years, the introduction of immune therapy in the treatment of lung cancer represented one of the most groundbreaking advances obtained in the cure of such deadly disease. In the field of immune-mediated therapies, Natural Killer (NK) cells represent an innovative cellular anti-tumor therapy and therapeutic target. Their cytotoxic activity is relevant to maintain immune surveillance in NSCLC patients, where the overall survival is positively related to NK cell infiltration. NK cytotoxicity is regulated through a wide range of receptors that allow them to rapidly respond to the absence of self molecules on target cells. The relative balance between inhibitory and activating receptors regulates the effectiveness of NK cytotoxic response against tumors. Inhibitors of Bromodomain and Extraterminal domain proteins (BETi) exerts anti-cancer activity through multiple mechanisms, including epigenetic reprogramming of both cancer cells and immune microenvironment. These drugs have shown a synergic effect with immunotherapy in NSCLC models, by increasing T-cell cytotoxic response and reducing T-reg infiltration.

Methods: We investigated NK cells cytotoxic activity through co-cultures with NSCLC cell lines and ex-vivo analysis of co-cultures with autologous patient-derived spheroids. NK activation and cytotoxicity were characterized by real-time imaging and flow cytometry analysis of INFg and CD107a markers. Characterization of BETi-induced transcriptional programs was performed by RNA-sequencing, master regulators role was investigated by siRNA approaches and Chromatin Immunoprecipitation analysis.

Results: We demonstrated for the first time that BETi increase the immune response mediated by NK cells toward NSCLC. BETi induce patient-derived primary NK cells and NK92 cell line activation both after PMA/ionomycin stimulation and co-culture with NSCLC cells. Importantly, BETi enhance the overall NK cell ability to kill tumor cells in co-cultures experiments with both NSCLC cell lines and autologous primary spheroids. We showed that BETi reprogram both tumor cells and NK cells, by downregulating a large set of immune checkpoint ligands and receptors, respectively. We identified the YAP and TAZ transcription factors as master regulators of BETi-dependent downregulation of immune checkpoint ligands in tumor cells. Moreover, we demonstrated that BETi-dependent downregulation of these factors is responsible for increased recognition of tumor cells by NK cells. We also characterized the transcriptional reprogramming induced by BETi in NK cells, by RNA-sequencing analysis. Through this approach, we identified and characterized the SMAD3 transcription factor as a key node for the BETi-dependent downregulation of immune checkpoint receptors in NK cells.

Conclusions: Overall, we demonstrated that BETi induce a transcriptional reprogramming in both NSCLC tumor cells and tumor-infiltrating NK cells, increasing NK cells recognition and killing of tumor cells. These data are relevant for possible use of BETi to empower current immunotherapy treatments or future NK-based cell therapy protocols.

Keywords: NSCLC, NK cells, BET inhibitors

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-043 Comprehensive Genomic Profiling of Tumor Mutational Burden-high in Chinese Lung Cancer Patients

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Introduction: Tumor mutational burden-high (TMB-H) is the indication biomarker for pan-cancer immunotherapy approved by FDA. However, the understanding of the molecular and clinical characteristics of TMB-H lung cancer still limited, especially in Chinese patients.

Methods: The next-generation sequencing and clinicopathological data of 566 Chinese lung cancer tissue sample were analyzed retrospectively between 2019 to 2021, including 453 cases of lung adenocarcinoma, 57 cases of lung squamous cell carcinoma, 6 cases of small cell lung cancer and 20 cases of other pathological lung cancer. Tumor mutational burden was defined as the number of somatic non-synonymous mutations per megabase of the panel region. TMB analysis interrogated single nucleotide variants, small insertion and deletion, with VAF 3%. TMB-H patients were identified with 9 mut/MB (upper quartile of data from Yinfeng).

Results: TMB-H was identified in 117 patients (20.7%), including 69 cases of lung adenocarcinoma, 36 cases of lung squamous cell carcinoma, 3 cases of small cell lung cancer and 9 cases of lung cancer with other pathological results. The median age of diagnosis was 63 (range: 38-91), and male patients accounted for 90.6%. In these patients, the driver alterations included *EGFR L858* or *19del* (5 cases) and *HER2* amplification (4 cases),but the *ALK* fusion, *ROS1* fusion, *BRAF V600* and *RET* fusion were not detected. The most recurrent mutant genes were *TP53* (79.5%), *LRP1B* (53.0%), *CDNK2A* (30.8%), *MLL2* (30.8%), *PIK3CA* (24.8%), *PTPRD* (23.9%), *SOX2* (23.9%), *MYC* (22.2%), *KRAS* (20.5%), *MLL3* (20.5%), *EGFR* (19.7%) and *RB1* (19.7%). Meanwhile, *POLE1* alterations were observed in 7% TMB-H patients. All patients were further divided into MMR group(18, 3.2%) and non-MMR group(548, 96.8%) according to somatic mismatch repair (MMR) genes mutated or not. 18 patients were included in MMR group, with *MLH1* (10, 55.6%), *MSH6* (4, 22.2%), *MSH2* (3, 16.7%) and *PMS2* (2, 11.1%) loss-of-function mutations, respectively. We also found that one TMB-H lung squamous cell carcinoma patient has a *MSH2-EIF2C2* fusion. The prevalence of high TMB in MMR group was significantly higher than that in non-MMR group (61.1% vs 19.3%).

Conclusions: TMB-H is relatively higher in Chinese lung cancer male patients, and it can be seen in various pathological subtypes. TMB-H may coexist with both gene mutations positively associated with immunotherapy and driver alterations negatively associated with immunotherapy. Our results revealed the potential immunotherapy strategies among TMB-H population with lung cancer should be considered in further study.

Keywords: TMB-H, MMR, Lung cancer

EP16.03 TUMOR BIOLOGY AND BIOMARKERS - MOLECULAR PROFILING AND TARGETED THERAPEUTICS

EP16.03-044 Genomic Evidence Depicting Clonal Evolution of Lung Adenosquamous Carcinoma

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Introduction: Adenosquamous carcinoma (ASC) is a rare subtype of non-small-cell lung cancer containing both adenocarcinoma (AC) and squamous cell carcinoma (SCC) components. However, the genomic background, tumor origins, and mechanisms of ASC are not fully understood.

Methods: Total 33 micro-dissected surgical ASC and seven primary *EGFR*-positive lung squamous cell carcinoma samples were taken for whole-exome sequencing. The genomic profiles, mutational signatures, evolutionary origins were analyzed to depict clonal relationships. Asian lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) cases were obtained from The Cancer Genome Atlas for comparison. A xenograft model was further established to show the histologic transformation. A separate cohort of *EGFR*-positive LUAD, ASC, and LUSC patients was evaluated for their response to tyrosine kinase inhibitors.

Results: *EGFR* (33%) and *MET* exon 14 skipping (15%) mutations were the two main driver genes in ASCs, followed by *KRAS* (9%) and *ERBB2* exon 20 insertion (3%). Other frequently detected cancer-related genes included mutations in *FAT3* (24%), *LPP1B* (24%), *PKHD1* (24%), *RELN* (24%), *FAT2* (21%), *NF1* (18%), *CDKN2A* (12%), and *RB1* (12%), and gain of *TERT* (64%), *RICTOR* (42%), *EGFR* (33%), and *MDM2* (33%). In all patients, micro-dissected AC and SCC components demonstrated shared mutations at various proportions (0.7% to 78.9%) and the overall mutational profiles were similar between AC and SCC. Comparison of arm-level copy number variations revealed that amplification of 16q was more enriched in AC, while deletions of 4p and 11q were primarily identified in SCC. Among different pathological subtypes, smoking-associated mutational signature was dominated in *EGFR*-wildtype LUSC, while *EGFR*-positive LUADs, ASCs, and LUSCs shared similar signature profiles. To illustrate clonal evolution, we reconstructed tumor phylogenies of *EGFR*-positive ASCs using micro-dissected primary and lymph node samples. *EGFR* mutations were always identified as trunk clonal events and two ASC components were more closely related on the evolutionary tree than other lesions. In the mouse model, we observed a *MET* exon14 skipping ASC-derived xenograft underwent a gradual histologic transformation into pure squamous cell phenotype without drug treatment. Finally, in the efficacy cohort, TKI treatment exerted median progression-free survival of 11.5, 15.3, and 11.7 months in *EGFR*-positive LUAD, ASC, and LUSC, respectively.

Conclusions: We confirmed that AC and SCC components of ASC were monoclonally originated through genomic and phylogenetic analyses. *EGFR*-positive NSCLC subtypes share similar mutation profiles and might undergo phenotypic transitions. First-line TKI should be considered for *EGFR*-positive ASC and LUSC patients to obtain optimal clinical benefit.

Keywords: lung adenosquamous carcinoma, clonal evolution, xenograft model

EP16.03-045 The Effect of Vascular Endothelial Growth Factor Gene Polymorphisms in the Clinical Outcome of Patients with Lung Cancer

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Introduction: Lung cancer is the most common cancer in terms of incidence and mortality, worldwide. Indeed, multiple genetic and epigenetic alterations contribute to carcinogenesis and disease progression. Thus, understanding the molecular bases of carcinogenesis has contributed not only to the development of personalized therapy but also to angiogenesis inhibitors targeting vascular endothelium growth factor *(VEGF)*, a key mediator of tumor angiogenesis. It has been proven that different polymorphisms in the *VEGF* gene result in a different expression of the VEGF protein in cancer cells, thus affecting the disease prognosis. Within this context, we conducted this prospective study to detect SNPs in the *VEGF* gene and then correlate the identified genotypes with different clinico-pathological parameters (histological type and grade).

Methods: The present study involved 50 fresh tissue from patients with lung cancer and who underwent surgery in the Thoracic Surgery Department at Ibn Rochd University Hospital, Casablanca. The two polymorphisms: -2578 C/A and -460 T/C in the *VEGF* gene were identified by PCR and Sanger sequencing.

Results: Our results showed a variety of genotypes: for SNP -2578 C/A, 23.7% had the wild-type genotype (AA), 50% had the heterozygous genotype (AC) while the mutated homozygous genotype (CC) was detected in 26.7% of the patients. For SNP -460 T/C, heterozygous genotype (TC) was predominant; 60%, while wild-type homozygous (CC) and mutated (TT) genotypes accounted for 30% and 10%, respectively. On the other hand, there was no correlation with these genotypes and clinico-pathological parameters (p-value greater than 0.05).

Conclusions: Although this preliminary study revealed two polymorphisms in the *VEGF* gene with different genotypes, it is difficult at this stage to speculate on the contribution of these functional polymorphisms in the diagnosis and/or prognosis of lung cancer in the Moroccan population. The work will be continued on a large panel for the screening of genotypes and/or haplotypes that can be used as biomarkers of occurrence, histological classification and grade, prognosis and development of targeted therapies for this cancer.

Keywords: Lung Cancer, VEGF, SNP

EP16.03-046 Tumor Grade Associated Genomic Mutations in Chinese Patients with Lung Cancer

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Introduction: Lung cancer is the most prevalent cancer worldwide. It also causes about 24% of cancer-related death in China every year. Of them, high-grade lung cancer is especially dangerous. Understanding the mechanism of high-grade lung cancer could help to develop a novel treatment for these patients.

Methods: Chinese patients with lung cancer were enrolled. The tumor samples were collected by surgery or puncture and applied for next-generation sequencing. A panel of pan-cancer genes was targeted. To improve the sensitivity of detecting mutations, the sequencing depth is over 1000. Gene mutations including short-length mutations (substitution, insertion, and deletion), copy number variation, gene fusion were called. Gene mutations within low-grade, middle-grade, and high-grade tumors were compared with Fisher's exact test. The enriched pathways in each grade of tumors were also inferred.

Results: A total of 173 Chinese patients with lung cancer, 98 (56.6%) patients were female and 75 (43.4%) were male. The mean age of these patients was 56.8 years. All the patients were at the status of microsatellite stability. Most of them (66.4%) were at the early stage (Stage 0, I, and II) and had tumor mutation burden around 2.5 (confidence interval = [0, 48.3]). When compared to low-grade tumors, high-grade tumor had an elevated percentage of mutations in TP53 (75.9% vs 34.4%, p = 1.86e-3) and PIK3CA (24.1% vs. 0%, p = 3.58e-3). Pathway analysis found that high-grade tumors were enriched with mutations in bacterial invasion of epithelial cells (31% vs. 0%, p = 5.8e-4), Epstein-Barr virus infection (79.3% vs. 37.5%, p = 1.72e-3), and Wnt signaling pathway (75.9% vs. 34.4%, p = 1.91e-3).

Conclusions: High-grade tumors from lung cancer patients could be more affected by bacteria such as Epstein-Barr virus than low-grade tumors. Tumors from these patients specially mutated in TP53 and PIK3CA, which could be good biomarkers for these patients. These findings underlined the importance of developing dedicated treatment in patients with these mutations.

Keywords: Lung cancer, Genomic mutations, Tumor grade

EP16.03-047 Genomic Landscape of Squamous Cell Carcinoma Lung in an Indian Cohort

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Introduction: Squamous cell carcinoma of lung accounts for nearly 30% cases of NSCLC in the Indian population. Understanding of mutational landscape of this entity is limited to short series and small studies of 9 and 20 patients respectively. Analogous to adenocarcinoma, where distinct ethnic differences have been reported in the genomic landscape, whether the same exists for SQCC still remains to be elucidated.

Methods: We performed Clinical Exome Sequenicng in 72 cases of SQCC at diagnosis. The SureSelect Clinical Exome panel was employed and sequenced on Illumina NextSeq platform. The basic demographic data, clinical features and outcomes were collated and recorded from the medical record archives

Results: We identified 20 significantly mutated genes among a total of 9126 alterations detected. The top 10 among them were TP53 (62%), CDKN2A (20.7%), NFE2L2 (17.5%), FGFR1 (15.6%), NAV3(13.2%), PTEN (11.7%), PIK3CA(11.2%), CDH10(10.3%), FAT4(9.6%) and KRAS (3%). With respect to actionable molecular targets, EGFR activating mutations were detected in 3.2% cases with del19 in 0.8% and L858R in 2.4%. Other targetable alterations detected included BRAF V600E in 1 case, ALK rearrangement in 8 cases, and KRAS G12C in 2 cases. The false discovery rate (FDR) Q value for these were less than 1, except for CDH10 which had a Q value of >20. Identifying frequently mutated pathways through KEGG analysis revealed that the cell-cell adhesion/Wnt/Hippo in 68.7%, oxidative stress response in 32.2% and phosphatidylinositol-3-OH kinase in 22.9% of the tested tumors. Mutually exclusive genetic alterations included NFE2L2 and KEAP1 ($p<0.03$), NFE2L2 and CRB1 ($p<0.02$) and CDH10 and CTNNA2 ($p<0.05$). With respect to clinical correlation, it was observed that mutations in PTEN gene were associated with early TNM stages ($p=0.06$). A distinct smoking signature was detected with NLRP3, NFE2L2 and FAM5C being the most frequently mutated genes among the smokers. The median number of mutations detected were 13.2 mutations/Mb in each case, and presence of any alteration in a tumor suppressor gene was significantly associated with smoking status and presence of extrathoracic metastases. ($p<0.05$; $p=0.06$).

Conclusions: This is by far the largest reported cohort unraveling the genomic landscape of Indian SQCC patients, with distinct differences in prevalence of EGFR, and KRAS alterations. Frequently mutated genes detected in Caucasian, Korean population like MLL2, CDH7 were not reported at significantly mutated gene frequencies. This study illustrates that once thought to be undruggable, almost 24% cases may be potentially druggable in future. Future studies and insights into tumorigenesis of this entity are warranted.

Keywords: Squamous cell carcinoma, Exome, genomics

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-001 The Role of Stromal PDGFRß-activation in NSCLC

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Introduction: An increased expression of stromal platelet-derived growth factor receptor beta (PDGFRß) has been associated with a poor prognosis in several solid tumor types. However, the prognostic relevance of PDGFRß in NSCLC remains unclear. Since general PDGFRß expression patterns do not reflect active PDGFRß-signaling, it is likely that the activation status of the receptor would represent a more robust biomarker. The aim of this study is therefore to develop an *in situ* assay to detect activated PDGFRß and to investigate its clinical relevance and prognostic potential for NSCLC patients.

Methods: The unfold proximity ligation assay (PLA) was performed to target tyrosine phosphorylation of PDGFRß, as a marker for active PDGFRß signaling. We adapted the signal detection for use with the tyramide signal amplification method, which allows to perform an additional pan-cytokeratin staining on the same tissue section in order to differentiate between stromal- and tumor areas. A CellProfiler pipeline was developed to analyze the frequency of PLA signals in the stroma. As positive controls for our PLA assay, we prepared FFPE blocks from human foreskin fibroblasts with or without PDGF-BB stimulation. Additionally, we included tissue sections from a subcutaneous xenograft model treated with or without the small molecule inhibitor CP-673,451 to block PDGFRß signaling.Finally, two NSCLC cohorts in form of tissue microarrays with a total of 708 patients were analyzed. The PLA data was associated to clinical parameters and the survival status of the patients using Kaplan Meier and cox regression analysis. The results were further related to analyses for general stromal PDGFRß protein expression as assessed by immunohistochemistry (IHC).

Results: The analysis of our control samples demonstrated an increased number of PLA signals per cell, and thus increased PDGFRß-activation, within sections from PDGF-BB treated fibroblasts as compared to the control fibroblasts. In sections from the xenograft tumor model, we noted a reduction in stromal PDGFRß-activation in those cases treated with PDGFRß-inhibitor. In the tissue sections from NSCLC patients, a weak association between general PDGFRß protein level in the tumor stroma and corresponding PDGFRß activation status was detected. Adenocarcinomas showed overall higher PDGFRß activation levels in the stroma than squamous cell carcinomas. While PDGFRß protein expression as investigated by IHC was not prognostic in our NSCLC cohorts, we found a trend for worse overall survival for patients with increased stromal PDGFRß-activation, both in the adenocarcinoma as well as squamous cell carcinoma patient groups.

Conclusions: Our PLA-based assay allows a sensitive and robust detection of PDGFRß-activation in diagnostic FFPE tissue samples. Stromal PDGFRß activation is generally higher in adenocarcinomas and was associated with worse overall survival. Our data suggests that PDGFRß-activation is a more sensitive prognostic marker for NSCLC than general PDGFRß protein expression. Furthermore, our finding might suggest therapeutical relevance of activated PDGFRß signaling in NSCLC, which should be experientially investigated in follow-up studies.

Keywords: PDGFRß, tumor-microenvironment, biomarker

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-002 Combining Patient-Derived Xenografts and Barcoding Technology to Evaluate Response to Targeted Therapies in ALK+NSCLC

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Introduction: About 5% of all non-small cell lung cancer (NSCLC) patients harbor the EML4ALK rearrangements. While ALK-targeted therapy is now clinical practice in these patients, the vast majority develops treatment resistance, frequently due to secondary mutations in the kinase domain of the ALK gene. In clinical settings, resistance can be determined only at endpoints, hampering the analysis of dynamic adaptation, selection, and tumor evolution under therapy. Previously, we generated patient-derived xenografts from malignant pleural effusions of ALK+ tumors. Here, we describe the use of single-cell barcoding for individual labeling of cells obtained from ALK+ lung cancers. Single-cell barcoding enables the unraveling of inherent or acquired unique vulnerabilities that can be used to devise novel therapeutic strategies. This model allows for tracing tumor evolution *in vivo* in response to various therapies and tracking cells that initiate and maintain the outgrowth of resistant subclones.

Methods: Patient-derived ALK+ lung cancer cells were cultivated *in vitro* and subsequently equipped with a unique label using a 9N-Barcode retroviral vector system. Barcoded cells were selected, expanded *in vitro* and used to generate a patient-derived xenograft (PdX). Established tumors were treated with different ALK inhibitors and subsequent analyses of barcode representation were performed.

Results: We established stable cell lines and PdX models derived from different tumor models of ALK+ lung cancer. The sensitivity and resistance of patient-derived ALK+ lung cancer models to ALK-directed therapies were validated *in vitro*. Furthermore, genomic differences between tumors at diagnosis and cells obtained from PdX tumors were determined by bulk sequencing. Labeling cells derived from ALK+ lung cancer with a GFP-9N-Barcode plasmid allowed tracking of selection processes upon treatment with ALK-targeting therapies *in vivo*.

Conclusions: Comprehensive analyses of molecular differences between primary tumors responding or resistant to ALK-directed therapy *in vivo* is feasible. Barcoding technology allows identifying selection processes and the emergence of resistant subclones. It remains to be determined if these models are suitable to predict resistance and sensitivity to ALK-directed therapies in co-clinical trials.

Keywords: ALK, Barcoding

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-003 High Dimensional Spatial Profiling of the NSCLC Tumour Microenvironment

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Introduction: Developing predictive biomarkers of response to immune checkpoint blockade are a current unmet clinical need for non-small cell lung cancer (NSCLC). The immune contexture of the tumour microenvironment (TME) is an important factor in dictating how well a tumour may response to immune checkpoint blockade therapy.

Methods: Here, we have used high-dimensional and high-fidelity spatial biomarker detection strategies to comprehensively characterise the tumour microenvironment of patients receiving Nivolumab or platinum based chemotherapy. This was performed using whole slide multiplex immunohistochemistry (mIHC) of multiple T-cell profiles, activation status, immune exhaustion, and immuno-modulatory markers across a minimum of 46 biomarkers with single cell resolution.

Results: Our study revealed deep tissue based insights of the tumour and stromal compartments, providing high-plex spatial profiles that dissected the immunotherapy response groups using discriminant analysis. The neighbourhood analysis identified unique cellular subtypes and localisations. Moreover, our study demonstrated the utility of high-plex profiling from single tissue sections, without the need to build multiple panels and process serial sections to obtain higher orders of plex.

Conclusions: There is growing consensus for the development of additional and more predictive biomarkers of response to ICI therapy. Spatial phenotyping of the immune landscape will reveal cell types and spatial signatures associated with outcomes to immunotherapy.

Keywords: spatial, tumour microenvironment, high plex

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-004 Impact of Gender on Cellular Response to Cigarette Smoke Extract

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Introduction: Females with both a smoking and non-smoking history are more at risk of developing lung cancer compared to their male counterparts. To date, the exact mechanisms accounting for these differences are unclear, however sex hormones and differential molecular pathways are plausible factors. Gender may impact cigarette-smoke induced inflammatory responses in the airways, as well as levels of tobacco carcinogen-driven DNA lesions, thus increasing susceptibility to the disease. There is an urgent need to utilize gender specific models to better understand sex as a risk factor for this disease.

Methods: Cigarette smoke extract (CSE) was generated using standard laboratory protocols to create CSE conditioned media. The effect of this conditioned media was analyzed using three normal human bronchial epithelial cell lines (n=2 female, n=1 male). Proliferative capacity was examined using a BrdU based ELISA. To determine differentially expressed genes between male and female cell lines, RNA was isolated post CSE exposure. cDNA was generated and gene expression changes were determined using QuantiNova LNA PCR Focus Panels, each containing 84 genes ('Inflammatory Cytokines and Receptors' and 'DNA Damage Signaling Pathway').

Results: A significant reduction in cellular proliferation was evident at 6 hr with 2.5% CSE, with approximately only 30% of cells remaining at 10% CSE. This trend continued in the female cell lines up until 48 hr post exposure, where less than half of the cells were viable at 2.5% CSE. The male cell line was less susceptible to CSE exposure at all concentrations and time points examined, for example only a 30% reduction in proliferation was observed at 10% CSE post 48 hr exposure. The analysis of targeted gene panels is currently ongoing.

Conclusions: Improving our understanding of gender responses to CSE in terms of pro-oncogenic inflammatory and DNA damage pathway related genes, may provide a better understanding of sex differences in lung cancer. Thus, aiding in lung cancer detection, diagnosis, and treatment for people at risk of this disease.

Keywords: Gender, Cigarette smoke extract, DNA damage

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-005 Investigating the Side Effects of Docetaxel on Rat Lung and Heart

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Introduction: Docetaxel (DTX) is widely used againstmany kinds of solid tumors such as breast, ovarian, prostate and lung. Inhibitionof microtubular depolymerization and attenuation of the effects of bcl-2 andbcl-xL gene expression are the main mechanisms of its antineoplastic effect.Additionally, taxanes are known to cause proliferation of cytotoxic T-cells,leading to a hypersensitivity type of lung damage, or might cause directpulmonary damage through reactive oxygen metabolites.This study has been investigated theside effects of two different doses of DTX on the lung and heart tissue of rats.

Methods: DTX (10-30 mg/kg/ weekly/ three times) has been administered to the 6-8months old Wistar rats; all experiments were performed according to theprinciples and guidelines of Animal Ethical Committee's approval (HADYEK64583101/2020/075). Animals of low dose of DTX treatment group were sacrificedat the day of 22nd; but high dose of treatment group were sacrificedat the day of 10th due to animal lose. The lung and heart tissue samples were takenout immediately in 10% formalin solution under the anesthesia of Ketamine andXylasine (50 mg/kg and 5 mg/kg, respectively).

Results: In the pathological examination of the heart tissue, necrosis andregeneration were observed in 2 of the 7 samples examined, while inflammatorycell infiltration was observed in 5 cases. These findings were observed morefrequently in the group of high-dose DTX treatment ($p<0.05$). Eighteen of lung samples were examined and enlargement ofthe interstitium was observed in 4 of them, interstitial pneumonia-like appearancewas observed in 7 cases, and focal foci of inflammation, hyperemia, andhemorrhage were observed in 7 cases. Fibrosis was detected in 10 of lung tissue.Pulmonary fibrosis was more common in the group of high DTX treatment group. Dueto the fact that our study was a preliminary study and the number of cases wassmall, detailed statistical analysis could not be performed.

Conclusions: We have demonstrated that DTX had many different kinds of toxic effecton both lung and cardiac tissues at low and high doses. Considering of thewidely use of DTX in clinics, specialists of chest disease and oncologist shouldbe aware of early signs of adverse effects on lung for the quality of life ofcancer patients.

Keywords: lung cancer, docetaksel, toxicity

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-006 A Novel Orthotopic Xenograft Mouse Model to Study Lung Cancer-Associated Fibroblasts and Lymphangiogenesis

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Introduction: Cancer-associated fibroblasts (CAFs) constitute a significant component of the tumour microenvironment, with a disputable role in cancer progression and metastasis. Nonetheless, the biological role of CAFs in relation to tumour lymphangiogenesis and regional lymph node metastasis in lung cancer is still poorly understood, which was elucidated in this study using an orthotopic xenograft model.

Methods: Lung CAFs were established by direct co-culture of non-small cell lung cancer (NSCLC) cell lines (H358 and HCC827) with a normal human fibroblast cell line (MRC-5). Activated fibroblasts (α-smooth muscle actin (SMA)+) were identified by immunofluorescence (IF), flow cytometry and Western blot. α-SMA+ fibroblasts activated by co-culturing with H358 and HCC827 cells (H358-CAFs and HCC827-CAFs) were isolated for subsequent experiments. NSCLC cells with or without lung CAFs were inoculated into the left lung of nude mice to establish orthotopic xenograft models for detecting tumour lymphangiogenesis and mediastinal lymph node metastasis by semi-quantitated immunohistochemistry (IHC)/IF. Tumour formation and size were detected by micro-computed tomography (CT). Inhibitor of CAFs (ABT-199) was administered by oral gavage for comparison with control.

Results: Inoculation of H358/H358-CAFs or HCC827/HCC827-CAFs had successfully developed desmoplastic and lymphangiogenic lung tumours in the left lung of nude mice. Comparing with NSCLC cells alone, lung tumours derived from H358/H358-CAFs or HCC827/HCC827-CAFs were associated with more developed intratumoral lymphangiogenesis [Lyve-1 fluorescence intensity area index: H358-CAFs (mean ± SD 1.084±0.281%) vs H358 (mean ± SD 0.245±0.026%), p=0.0002; HCC827-CAFs (mean ± SD 2.486±1.276%) vs HCC827 (mean ± SD 0.347±0.239%), p=0.0024] and increased mediastinal lymph node metastasis [Number of mediastinal lymph node metastasis: H358-CAFs (mean ± SD 4.0±1.2) vs H358 (mean ± SD 1.6±0.5), p=0.0039; HCC827-CAFs (mean ± SD 5.7±0.8) vs HCC827 (mean ± SD 1.8±0.8), p<0.0001]. Treatment with ABT-199 significantly reduced CAFs (p=0.0371) and tumour-associated lymphangiogenesis (p=0.0022) in H358/H358-CAFs orthotopic xenograft model.

Conclusions: Lung CAFs activated by H358 and HCC827 NSCLC cells could enhance tumour lymphangiogenesis and regional lymph node metastasis. Our orthotopic xenograft mouse model would provide the necessary tumour microenvironment for studying the biological function of CAFs and related therapeutic interventions.

Keywords: Cancer-Associated Fibroblasts, Lymphangiogenesis, Animal model

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-007 ALDH2 Downregulation, Aberrant DNA Methylation, and Loss of Stemness Pathways as an Enhanced Biomarker in Lung Adenocarcinoma

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Introduction: Lung adenocarcinoma (LUAD) is the most common type of lung cancer and is one of the major causes of growing mortality. Previous studies showed an association between LUAD and Aldehyde Dehydrogenase 2 (ALDH2), an essential enzyme involved in the detoxification of acetaldehyde. We aimed at discovering more informative prognosis signatures for early LUAD detection and targets for LUAD treatment by investigating the expression level, epigenetic mechanism, and signaling activities of ALDH2 in LUAD patients.

Methods: We conducted a meta-analysis of ALDH2 gene expression among different types of cancer and examined the differences among genomics and cellular alterations across distinctive cancer types by analyzing the multi-omics data from The Cancer Genome Atlas (TCGA) and The National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC) portal. Additionally, ALDH2 protein expression in LUAD sample tissues was also investigated by using UALCAN (Protein Exp-CPTAC) and Human Protein Atlas. The correlation between ALDH2 gene expression and the overall survival of LUAD patients was studied via Kaplan-Meier Plotter and UALCAN-Survival. Moreover, DNA methylation level of ALDH2 and its relation with the overall survival rate of LUAD patients was examined. We also investigated the immune-related interaction and signaling pathways of ALDH2 using TIMER and GeneMANIA.

Results: Gene expression analysis showed that ALDH2 was substantially downregulated in LUAD. Also, the protein expression level of ALDH2 in LUAD tissues was considerably decreased compared to matching non-tumor tissues. In addition, reduced expression of ALDH2 was strongly related to a poorer overall survival (OS) in first stage LUAD patients and different stages of LUAD by The American Joint Committee on Cancer (AJCC), including T2, N0, and M0. Considerably, the DNA methylation level of ALDH2 differed significantly between LUAD cancer and normal tissues; especially, the cg05054438 probe methylation level was strongly linked with the survival time of LUAD patients. Moreover, downregulated ALDH2 was observed in the proteomic expression profile in several cell biology signaling pathways, including the stemness WNT and p53/Rb-related pathways, which play a central role in modulating the delicate balance between stemness and differentiation in several adult stem cell niches. Additionally, ALDH2 significantly correlates to the activities of immunological B cells and CD4+ T cells.

Conclusions: The downregulation of ALDH2, aberrant DNA methylation, and the subsequent deficiency of stemness signaling pathways represent potential prognosis factors and therapeutic values in LUAD.

Keywords: ALDH2, Lung Adenocarcinoma, DNA methylation

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-008 Cytotoxic Effects of Carnosic Acid Are Mediated by Induction of Autophagy and Activation of Sestrin-2/LKB1/AMPK Signalling in H1299 NSCLC Cells

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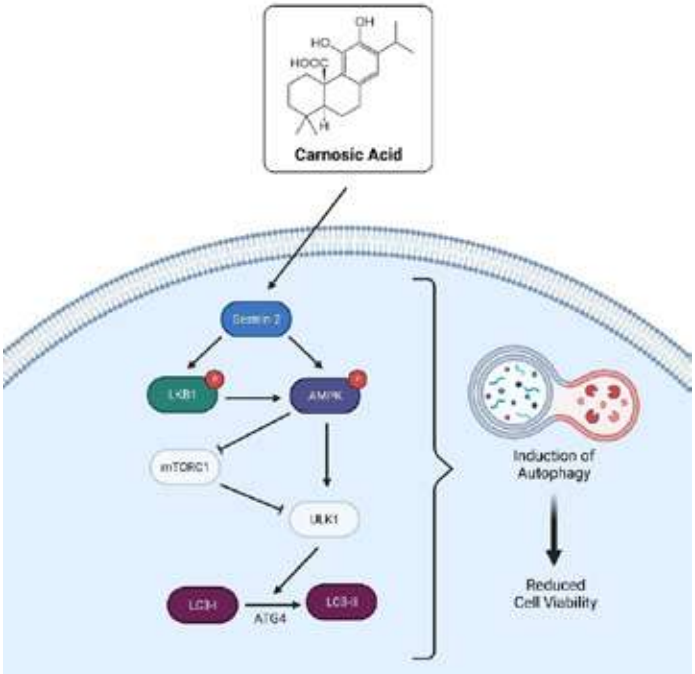
Introduction: Non-small cell lung cancer (NSCLC) represents around 80% of all lung cancer cases and is characterized by low survival rates, due to chemotherapy and radiation resistance. Novel treatment strategies for NSCLC are urgently needed. Liver kinase B1 (LKB1), a tumor suppressor commonly mutated in non-small cell lung cancer (NSCLC), activates AMP-activated protein kinase (AMPK) which in turn inhibits mammalian target of rapamycin complex 1 (mTORC1) and activates unc-51 like autophagy activating kinase 1 (ULK1) to promote autophagy. Sestrin-2 is a stress-induced protein that enhances LKB1-dependent activation of AMPK and it has been identified as a potential tumour suppressor in NSCLC. In previous studies, rosemary (*Rosmarinus officinalis*) extract (RE) inhibited proliferation, survival and migration, and induced apoptosis of NSCLC cells which coincided with increased activation of the AMPK pathway and inhibition of mTORC1. In the present study we focused on carnosic acid (CA), a major component of (RE), to investigate its potential anticancer properties and its effects on signalling molecules up and downstream of AMPK.

Methods: H1299 NSCLC cells were treated with increasing concentrations of CA for 48 h and cell viability was evaluated by MTT assay. Immunoblotting was used to assess AMPK, sestrin-2, LKB1, and autophagy marker light chain 3 (LC3) levels.

Results: CA caused concentration-dependent inhibition of H1299 cell viability with significant inhibition observed with concentrations greater than 25 μM. Treatment with CA time-dependently increased the levels of LC3, an established marker of autophagy. In addition, treatment with CA increased the levels of sestrin-2, and the phosphorylation/activation of LKB1 and AMPK.

Conclusions: Overall, these data indicate that CA is able to inhibit NSCLC cell viability and that the underlying mechanism of action of CA may involve induction of autophagy through a Sestrin-2/LKB1/AMPK signalling cascade. Future experiments will use siRNA and small molecule inhibitors to better elucidate the role of these signalling molecules in the mechanism of action of CA as well as tumor xenograft models to assess the anticancer properties of CA in vivo.



Keywords: Polyphenols, NSCLC, Autophagy

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-009 The Proliferative Effect of 27-Hydroxycholesterol as a Selective Estrogen Receptor Modulator on Pathology of NSCLC

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Introduction: An oxysterol 27-hydroxycholesterol (27HC) that is a cholesterol metabolite has been reported to aggravate pathological condition through promotion of cell proliferation in breast cancer via action of selective estrogen receptor modulator (SERM). Since 27HC is produced most in alveolar macrophages among the whole body by metabolizing from cholesterol through cytochrome P450 27A1 (CYP27A1), it has suggested that 27HC also aggravates the condition of lung cancer as SERM. So, we hypothesized that 27HC content and estrogen receptor (ER) expression might be increased in the lung cancer cells compared to those in non-cancer cells, and these factors might be related to the pathological condition of lung cancer patients. This study compared the 27HC content and the gene expressions of 27HC-metabolic enzymes, ERs, and cancer-relative factors between the tumor and nontumor regions collected from non-small cell lung cancer (NSCLC) patients, and evaluated the relationship of 27HC content on the pathological condition in lung cancer, as well as the effect of 27HC on the proliferation of cultured lung cancer cell line (H23) expressing ERß.

Methods: The tumor and nontumor regions of lung tissue were collected from 25 NSCLC patients who underwent lung cancer surgery. In both regions, 27HC content was quantified using HPLC-MS/MS system, and the mRNA expressions were measured by RT-PCR. The expression of CYP27A1 protein in the lung tissue was also evaluated by immunohistological (IHC) stain. In the H23 cell culture, the number of cells per well was compared before and after the treatments of 1nM-1μM of 27HC or 10 nM of estradiol (E2) with and without 1 μM of selective ERß antagonist PHTPP for 48h.

Results: 27HC content was significantly higher in tumor areas than in non-tumor regions in proportion of the differentiation degree in stages I-III and was associated with disease progression. The mRNA expressions of ERß, its possible target gene c-Myc, and 27HC-catabilize enzyme CYP8B1 as well as cancer proliferation factors (VEGF and HIF1) were significantly increased in the tumor region compared to those in the nontumor region. ERα mRNA was not expressed in both regions. Although there was no difference of CYP27A1 mRNA expression between both regions, the accumulation of CYP27A1-positive macrophages around the tumor region was observed by IHC stain. The proliferation of H23 cell was significantly increased by the treatments of 27HC (0.1 and 1 μM) and E2, and the effects were cancelled by the PHTPP treatment.

Conclusions: Present results support idea that, similar to the SERM action in breast cancer, 27HC is a factor that promotes the proliferation of lung cancer cells and aggravates the pathological conditions. Therefore, 27HC should be an important target to being lowered in production in the alveolar macrophages and being interfered to activate ER in lung cancer cells for cancer therapy in NSCLC.

Keywords: 27-hydroxycholesterol, selective estrogen receptor modulator, non-small cell lung cancer

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-010 Histological and Genetic Parental Tumor Characteristics are Conserved in Patient-derived Non-small Cell Lung Cancer Organoids

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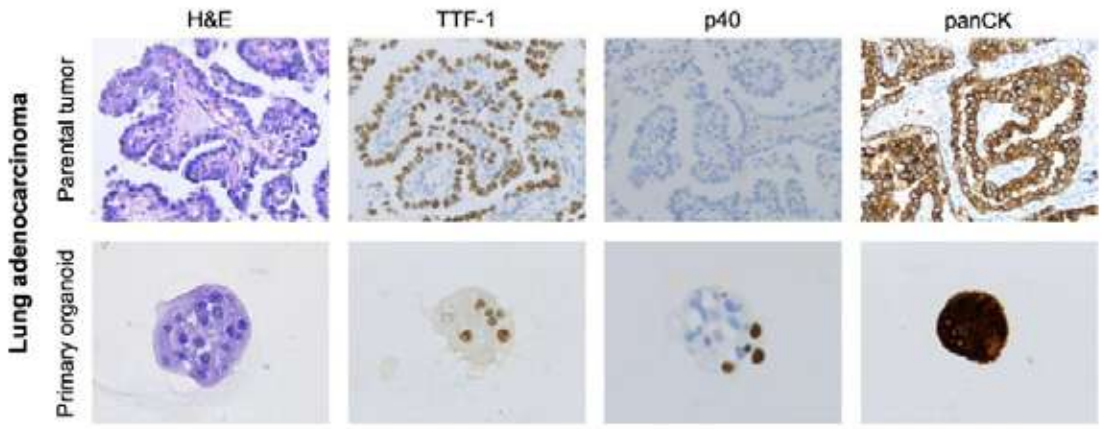
Introduction: Recent innovations in the treatment of non-small cell lung cancer (NSCLC) require a personalized approach and representative in-vitro model systems that reflect the primary tumor both morphologically and genetically. Clonally expanded cell lines are fundamentally limited in representing the complexity of NSCLC as they do not generally maintain intratumoral heterogeneity and the three-dimensional structure. For clinical applications such as an ex-vivo evaluation of personalized cancer treatments, patient-derived organoids have been suggested as promising models. We therefore aim to establish representative NSCLC organoids that offer a reliable platform for further investigations.

Methods: Since May 2020 we routinely collect and mechanically and enzymatically process surgically resected NSCLC tissue specimens. For organoid culture, cell suspensions are mixed with a gelatinous extracellular matrix and submersed in advanced DMEM/F12-based growth medium with defined growth factors and supplements. Organoids are cultured at 37°C and expanded over up to 3 months. Histomorphological validation is performed by histology and immunohistochemistry (Thyroid Transcription Factor-1, p40 and Pan-Cytokeratin). For genetic validation, DNA and RNA were extracted from tissue and organoid specimens and targeted next generation sequencing was performed using the Oncomine Focus Assay (ThermoFisher Scientific). Furthermore, to assess which growth factors are beneficial for the establishment and expansion of primary NSCLC organoids, 5 different medium compositions were compared and evaluated.

Results: From 50 resected NSCLC samples, 17 primary organoid cultures were successfully established and expanded during early passages. Upon histological and immunohistochemical validation, organoids showed similar characteristics when compared to the resected parental tumor, including adenocarcinoma, squamous-cell carcinoma, mucoepidermoid carcinoma and lung carcinoid morphology. Traceable genetic alterations were detected among 5 parental tumors. 2 corresponding organoids lines retained this mutational profile including a KRAS p.Gly12Val mutation and a RET-fusion. Preliminary cell proliferation data comparing the 5 different medium conditions suggest that a standard medium supplemented with both A83-01 and Noggin leads to highest establishment and growth rates for organoids from both adenocarcinoma and squamous cell carcinoma tissues. Immunohistochemical evaluation and confirmation of these preliminary data growth data on a morphological and pathological level is currently underway.

Conclusions: Primary patient-derived NSCLC organoids can be established from surgically resected tissue. In order to identify representative NSCLC organoids that maintain the morphological characteristics and genetic alterations of the parental tumor, the combination of histological, immunohistochemical and genetic validation is essential. While low establishment rates remain a challenge for broad clinical applications, the use of a well-defined medium composition may increase organoid growth.



Keywords: Primary organoid, ex vivo model, non-small cell lung cancer

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-011 Sex Hormone Signalling in Lung Adenocarcinoma Limits Tumour Virulence

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Introduction: Inhibition of steroid sex hormone receptors (SHR) is the mainstay of medical therapy for several common tumour types. We aimed to assess the extent of SHR expression in a large cohort of primary resected lung adenocarcinomas, and to investigate possible links with outcome and other measures of tumour

Methods: We examined a continuous cohort of 620 resected non-mucinous primary lung adenocarcinomas. Protein expression of Androgen Receptor (AR), Progesterone Receptor (PR), Estrogen Receptor (ER) and Forkhead box A1 (FOXA1) genes were assessed by automated quantification of multiplex chromogenic immunohistochemistry applied to tissue microarrays (TMAs). Statistical relationships between SHR/FOXA1 expression and patient outcome and key tumour hallmarks were examined.

Results: Overall 47.8% of lung adenocarcinomas express at least one sex hormone receptor. Striking sex-specific relationships between HR expression and cancer-specific survival (CSS) were seen: in men, AR+ HR=0.594 P=0.020 (CI 0.383-0.921), and in women ER/PR+ HR=0.616 P=0.019 (CI 0.410-0.925). Furthermore, these relationships were dependent upon the co-expression of the master steroid receptor transcription factor FOXA1. In addition, sex- and SHR/FOXA1-specific relationships with several features of tumour virulence were identified: growth pattern, size, pleural invasion, vascular invasion, pleural invasion, necrosis and PD-L1 expression.

Conclusions: The observation that expression of SHR acquires clinical significance only when co-occurring with appropriate hormonal environment (i.e., patient sex) and co-expression of FOXA1 strongly suggests that the anti-oncogenic effects of SHR expression are due to functional engagement of the hormone receptor. This raises the possibility of therapeutic targeting of SHRs in adenocarcinoma.

Keywords: Pulmonary adenocarcinoma, Steroid hormone, Sex hormone

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-012 Retrospective Analysis of Non-Small Cell Lung Cancer with Mucinous Histology Subtype

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Introduction: Adenocarcinoma (ADC), is the most common histologic type of non-small cell lung cancer. Mucinous adenocarcinoma (MC), an uncommon histologic subtype, accounts for a small subset of all lung ADCs. Previous studies have suggested MC confers a poorer prognosis when compared to its non-mucinous counterpart, however given the scarcity of these patients much about their real-world clinical outcomes is still unknown. In this study, we aim to compare outcomes and clinical features of patients with MC to those with non-MC ADC at our institution.

Methods: We performed a retrospective analysis of patients with NSCLC treated at our institution from Oct 2019 - March 2021. Baseline characteristics were compared between groups using the Wilcoxon rank-sum, Chi-square or Fisher's Exact tests as appropriate. The primary endpoints time to disease progression and time to all-cause mortality were compared using the Kaplan-Meier method, and the log-rank test was used to compare the survival curves between the groups. Cox proportional hazard model was used for multivariable analyses.

Results: Of the 428 patients evaluated, 61 (14.3%) displayed mucinous histology while 367 (85.7%) exhibited typical ADC histology. There was no difference amongst demographic data with the exception of slightly more stage 3 patients in the MC group which was statistically significant. In the total population, MCs demonstrated a statistically significant shorter time to disease progression vs. non-MCs (unadjusted Hazard Ratio (95% CI)= 1.51(1.02-2.24), p=0.039). This difference was not upheld when separated into early stage (1/2) HR (95% CI) = 1.90 (0.84-4.31) and late stage (3/4) HR (95% CI) = 1.12 (0.71-1.77). No significant difference was noted in the 5-year overall survival (OS) between groups (p =0.802). Amongst patients with available data, there was no difference in PDL-1 expression between groups (p=0.248). For patients with next generation data, KRAS mutation was more common in MC (33/46) 71.7% vs. (78/219) 35.6% (p<0.001). EGFR mutation was more common in non-MC ADC (58/222) 26.1% vs. (5/46) 10.9% (p=0.027). Univariate analysis showed KRAS and EGFR were positively and negatively associated with time to disease progression (HR=1.85, p<0.001, HR=0.56, p=0.005 respectively), and overall survival (HR=1.76, p=0.016 and HR=0.46, p=0.016 respectively).

Conclusions: We demonstrated a shorter time to progression for the MC group compared to the non-MC ADC group for the entire cohort, however, this result was not sustained when separated by stage. In addition, there was no significant difference in overall survival between the two groups. Our data suggests that patients with mucinous histology may not necessarily have significantly worse survival outcomes than those with non-mucinous adenocarcinomas. Consistent with current literature, KRAS mutation was found more commonly in patients with MC. Furthermore, our study identified KRAS mutation as a predictor of shorter time to progression, as well as worse overall survival. This suggests that any potential differences in survival outcomes may be primarily driven by the presence of KRAS mutations. Novel approaches targeting KRAS mutations may further diminish these differences historically observed.

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-013 Spatial Multi-Omics Landscape of Radiologically Preinvasive/ Invasive Lesion in Part-Solid Lung Adenocarcinoma

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Introduction: Spatial characterization of the tumor microenvironment (TME) is a key to understand cancer evolution and progression. Here, we constructed and examined high-resolution spatial transcriptomics of early-stage lung adenocarcinoma presented as part-solid nodules.

Methods: Eight samples from four lung cancer patients with part-solid nodules were used to create spatial transcriptomics. For each patient, one sample was taken from the radiologically solid region, while the second sample was taken from the ground-glass appearance area. As each spot of spatial transcriptomic data consisted of a few cells, the cell types were inferred by CellDART combining previously reported single cell RNA-seq of lung adenocarcinoma. To capture the genetic heterogeneity of radiologically pre-invasive/invasive lesion, we performed laser capture dissection from four regions within one patient (two from invasive, other two from pre-invasive lesion) and analyzed whole genome sequencing with average 30X coverage per region. The trajectory analysis using Monocle 3 was performed across spots to investigate molecular landscape associated with spatial evolution of early lung adenocarcinoma

Results: There was no discernible variation in spatial transcriptomic characteristic between solid and ground-glass lesions, according to unsupervised clustering analysis. Malignancy-specific epithelium was common across all samples, while normal-like epithelium was more numerous in pre-invasive lesions. CD8 T cells generally co-locates with malignancy-specific epithelium, whereas CD4 T-helper cells predominantly dispersed in places without normal-like epithelium. In genomic analysis, many somatic mutations, including an EGFR L858R mutation, are shared by all tumor regions. However, DNA copy numbers of chromosomes 8q, 9, 11, and 19 seem to be different among the invasive and pre-invasive regions. Two invasive regions share the copy number changes. Our data directly suggest a branched trajectory in the clonal evolution of the tumor. The clonal divergence of major clones in the invasive and pre-invasive regions occurred after acquiring the EGFR activating mutation, and the copy number alterations were acquired in clonal lineages of the invasive regions. The trajectory constructed across spots of central and peripheral portion of lung adenocarcinoma samples revealed molecular markers related to the central area that showed a solid portion on the gross tumor.

Conclusions: Our research uncovers the spatial transcriptomic-genomic alterations in pre-invasive and invasive regions of lung adenocarcinoma. The spatial genomic and transcriptomic change and alterations of immune cell compositions shed light to researchers to understand cancer evolution with TME change of lung adenocarcinoma.

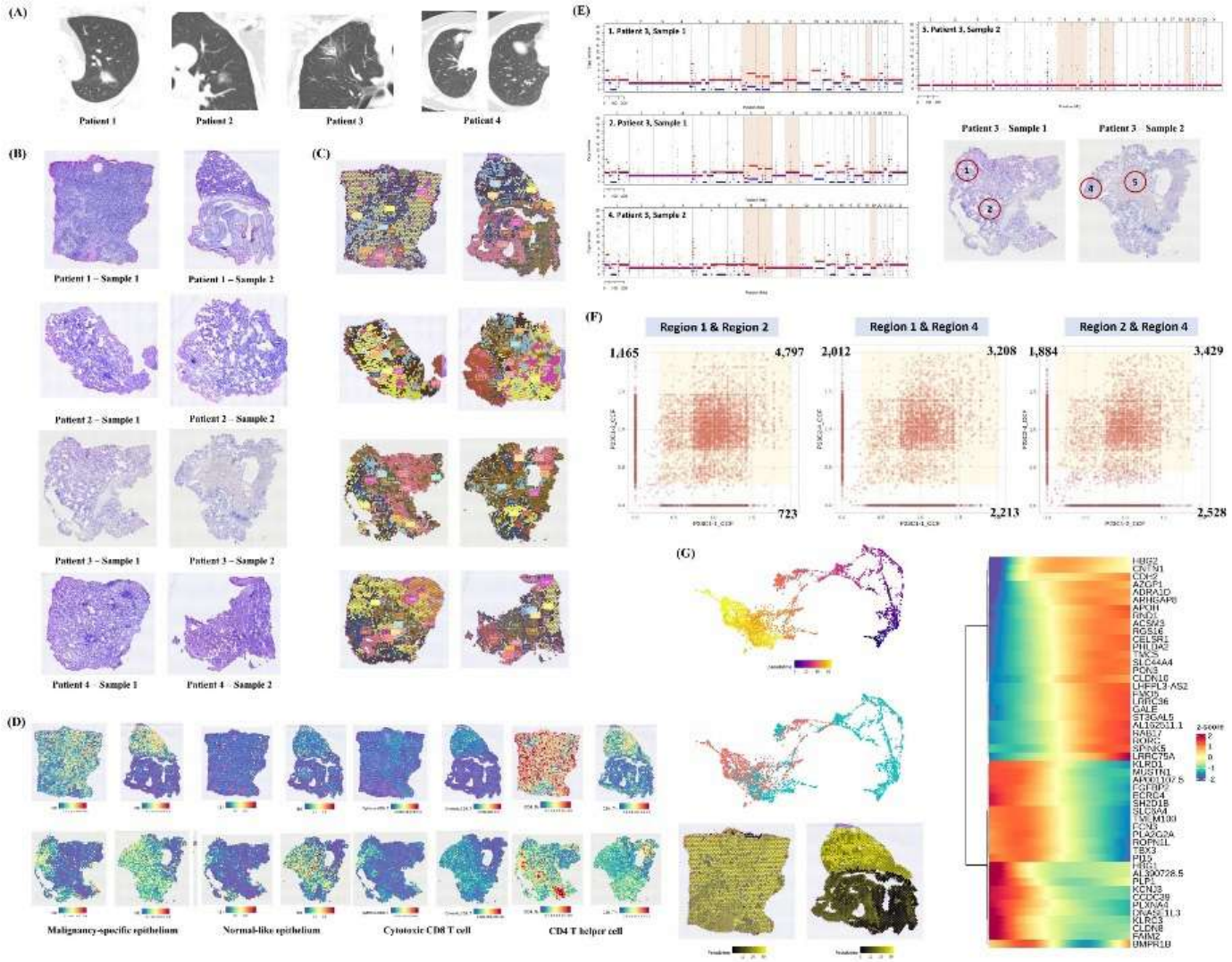

Figure. (A) Radiologic characteristics and location of samples from each patient. (B) H&E-stained image of six spatial transcriptome data. (C) Unsupervised clustering analysis of spatial transcriptome data. (D) CellDART results showing the spatial distribution of cancer and immune cell in single cell level. (E) Whole genome sequencing from four regions dissected by laser capture microdissection from invasive/pre-invasive lesion. (F) Cancer cell fraction plot between four regions. (G) Trajectory analysis across spots to investigate spatial evolution of part solid nodule.

Keywords: early stage lung cancer, spatial transcriptomics, part solid nodule

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-014 NTRK in Lung Cancer Patients with History of Hodgkin's Lymphoma

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Introduction: Hodgkin's lymphoma (HL) patients are usually long survivors, except for a small group who are at increased risk of relapse. The leading causes of death in this population are treatment-related toxicities, cardiovascular (CV) comorbidities and second malignancies (SM). Regarding SM, some meta-analysis have deepen into this topic, being lung cancer (LC) one of the most frequent second tumor observed in patients with history of HL. Previous treatments received seem to play a key role in the pathogenesis of secondary LC, mainly thoracic radiotherapy (RT), as well as individual risk factors, such as the smoking habit and age. Although scarce information regarding molecular factors is available, a few studies have described the presence of NTRK mutations in this scenario. The aim of the study was to assess whether there are common specific molecular alterations in LC patients with history of HL, specifically NTRK mutations.

Methods: We conducted a single-institution retrospective study that included patients diagnosed with HL and who subsequently developed LC. We analyzed their epidemiological, clinical and tumor characteristics, including molecular factors. Next-generation sequencing (NGS) was performed in tumor biopsies in order to detect NTRK mutations.

Results: A total of 403 patients diagnosed with HL were analyzed, of which, 12 developed a subsequent LC. Demographic and clinical characteristics are shown in table 1. Most of the patients with HL presented in localized stages (83.3%) and received treatments based on chemotherapy and RT. Likewise, when LC was diagnosed, the majority of patients (66.7%) presented in localized or locally advanced stages, probably due to their close follow-up. There was no predominance of a specific metastatic site in advanced diseases. Regarding molecular alterations, no NTRK mutations were detected by NGS in LC tumor samples. In addition, EGFR, ALK and ROS1 were also routinely tested, but only one patient had an ALK translocation. A total of 7 patients (58.3%) died, 5 of them due to LC progression and the other 2 due to CV comorbidities.

Conclusions: In our study, no molecular alterations were detected in LC patients with history of HL. While individual risk factors and previous thoracic RT seem to be relevant in the pathogenesis of secondary LC, further research is needed in order to establish whether other molecular alterations may be involved in this scenario. Our aim is to carry out a complete sequencing panel to detect possible molecular alterations in this subset of patients, as this has been little researched.

Table 1. Demographic, clinical and tumor characteristics

	Total (n=12)
Sex	Male: 9 (75%) Female: 3 (25%)
Median age (years)	HL: 42 LC: 59
Smoking habit	Never smoker: 1 (8.3%) Current smoker: 5 (41.7%) Former smoker: 6 (50%)
Previous tumours	2 (16.7%)
Cancer family history	3 (25%)
Histologic HL subtype	Classical HL: Nodular sclerosis: 5 (41.7%) Mixed cellularity: 3 (25%) Lymphocyte depletion: 0 Lymphocyte rich: 0 Not specified: 3 (25%) Nodular lymphocyte predominant HL: 1 (8.3%)
HL stage	I: 4 (33.3%) II: 6 (50%) III: 2 (16.7%) IV : 0
HL treatment	Chemotherapy: 3 (25%) RT: 7 (58.3%) Chemo + RT: 2 (16.7%) Stem cell transplantation: 0 Other treatment: 0
Median time between the 2 neoplasms	16 years
Histologic LC subtype	Adenocarcinoma: 10 (83.3%) Squamous cell carcinoma: 2 (16.7%) Large cell carcinoma: 0 Small cell lung cancer: 0 Other: 0
LC stage	I: 4 (33.3%) II: 3 (25%) III: 1 (8.3%) IV: 4 (33.3%)
LC treatment	Surgery: 6 (50%) Surgery + adjuvant chemotherapy: 2 (16.7%) Chemotherapy: 3 (25%) RT: 0 Chemo + RT: 0 Immunotherapy: 0 Palliative care: 1 (8.3%)

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EP16.04-015 Chemotherapy Upregulates Programmed Cell Death Ligand 1 Expression in Non-Small Cell Lung Cancer Cell Lines and Patient-Derived Organoid Models

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Introduction: Expression of Programmed Cell Death Ligand 1 (PD-L1) on tumour cells allows it to evade T-cell mediated killing, and therefore plays an important role in cancer progression. In non-small cell lung cancer (NSCLC) patients, the clinical efficacy of PD-1/PD-L1 inhibitor therapy is greatest in tumours with high PD-L1 expression. Additionally, atezolizumab (anti-PD-L1; Impower130 Trial) and pembrolizumab (anti-PD-1; Keynote-189) combined with cytotoxic chemotherapy has also demonstrated greater clinical efficacy than chemotherapy alone, even in patients with low-PD-L1 expressing tumours. The underlying mechanism mediating the enhancement of anti-PD-1/PD-L1 response by chemotherapy is unknown. Here we show that chemotherapeutic agents can induce PD-L1 expression in NSCLC models. We hypothesize that chemotherapy induced upregulation of PD-L1 can be exploited with combination treatment with anti-PD-1/PD-L1 to achieve better response especially in non-immunogenic tumours.

Methods: This study involves a use of panel of NSCLC cell lines that include MGH7, A549, HCC4006, and PDX-derived organoids PDXO274 and PDXO377. Standard of care chemotherapeutic agents were used to evaluate effects on PD-L1 mRNA and protein expression at varying doses and time points. Cell protein and mRNA extracts were analysed by Western blot, flow cytometry, and RT-qPCR.

Results: PD-L1 protein expression was significantly upregulated with cisplatin treatment after 72 hrs in A549, HCC4006, and MGH7 cell lines. At 48 hours of cisplatin treatment, PD-L1 mRNA significantly increased 9-fold and 4-fold in PDXO377 and PDXO274, respectively. PD-L1 protein expression was also induced in these organoid models after treatment. A549 and MGH7 cells lines were treated with gemcitabine, docetaxel, and pemetrexed. After 72 hrs of treatment, PD-L1 expression was upregulated with gemcitabine and pemetrexed in A549 and docetaxel and pemetrexed in MGH7 cell lines. Additionally, after treatment with cisplatin for 72 hrs, MGH7 and HCC4006 cells were taken off drug for another 72 hrs. PD-L1 protein upregulation was sustained in both cell lines after a 72 hr drug holiday indicating a stabilized increased expression of PD-L1. We also found that cisplatin treated MGH7 and HCC4006 cell lines showed an activation of cGAS-STING pathway. The protein expression of cGAS, STING, TBK1, and p-TBK1 (a kinase activated downstream of STING signalling) was upregulated in HCC4006, and MGH7 at 48 and 72 hrs after cisplatin treatment. cGAS-STING pathway activation is associated with increased tumour immunogenicity.

Conclusions: Cytotoxic chemotherapies used to treat NSCLC patients may induce PD-L1 expression and also activate the cGAS-STING pathway in NSCLC models. The underlying mechanism involved in PD-L1 upregulation after chemotherapy warrants further investigation to improve therapy outcomes for patients.

Keywords: NSCLC, Chemotherapy, Immune Checkpoints

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-016 Overexpression of CEACAM6 Activates Src-FAK Signaling and Inhibits Anoikis, through Homophilic Interactions in Lung Adenocarcinomas

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Introduction: Among carcinoembryonic antigen-related cell adhesion molecule (CEACAM) family proteins, CEACAM6, which consists of one variable-like N domain and two constant type 2-like immunoglobulin domains, is known to inhibit anoikis, but its presence and role in lung cancer are largely unknown.

Methods: Interactions between lung cancer cells were estimated using CellphoneDB. CEACAM6 expression was evaluated by tissue microarray from 311 lung adenocarcinomas. Intracellular location and effects on anoikis and the related signaling pathways were investigated using immunocytochemistry, anoikis assay, and immunoblotting.

Results: The application of CellphoneDB of the single cell RNA sequencing dataset showed that the homophilic interactions among CEACAM6 molecules, which are overexpressed in lung cancer cells were highly significant. CEACAM6 was overexpressed in 80.1% of lung adenocarcinomas and its overexpression had a significant relationship with non-smoking history and activating epidermal growth factor receptor mutations. The effect of CEACAM6 overexpression on patient prognosis was evaluated using the Cancer Genome Atlas Lung Adenocarcinoma dataset; the CEACAM6 overexpression group showed a shorter overall survival than that of the control group when matched for stage, age, sex, and pack-years. Immunoblotting of cell culture soup and enzyme-linked immunosorbent assay of human derived material suggested that the majority of CEACAM6 was present on the cancer cell surface and interacted with other cancer cells in the crowded tumor microenvironment. Treatment with CEACAM6 showed CEACAM6 homophilic interactions in the cell membrane and anoikis inhibition through the activation of the steroid receptor coactivator-focal adhesion kinase pathway.

Conclusions: Inhibition of CEACAM6 or its homophilic interactions in the cancer cell membrane may provide another therapeutic strategy for lung cancer.

Keywords: CEACAM6, anoikis, Src-FAK pathway

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-017 Lineage Switching and Tumor Microenvironment Roles of Tumor Suppressors in Autochthonous Lung Cancer Models

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Introduction: Non-small cell lung cancer (NSCLC) largely consists of lung squamous (LUSC) and lung adenocarcinoma (LUAD). While driver mutations are common in LUAD, LUSC has few if any actionable targetable drivers. Despite these unique differences, alterations in the p53 and PTEN tumor suppressors are common in both subtypes. This study seeks to determine the roles that p53 and PTEN have on lung cancer differentiation, metastasis, and their effects on tumor microenvironment (TME) composition.

Methods: We used tracheal instillation of lentivirus expressing Cas9, Cre, and an sgRNA targeting a safe harbor locus (SH), *Trp53,* or *Pten* to induce lung carcinomas in C57BL/6-*Sox2*^{High} *Nkx2-1*$^{-/-}$ *Lkb-1-/-* mice. After tracheal instillation of 5x10^5 transduction units of lentivirus, mice were followed by monthly CT scans for progression of disease. Separately, the JH18-16 (Sox2high, p53 KO, p16 KO, Pten KO) LUSC cell line was orthotopically passaged several times in B6 mice until a highly metastatic subclone (LN2A) was derived. All mice were sacrificed when the mice either became ill (LN2A transplant model), or CT imaging (autochthonous models) revealed tumors >5mm in diameter. Tumors were harvested for histological analyses and single cell RNA sequencing (scRNA-seq).

Results: The control SH Group had a median survival of 13 months, whereas *Trp53* and *Pten* KO groups both had a median survival of only 9 months (*Trp53*: Log-rank p=0.035, *Pten*: p=0.015). The p53 and Pten KO groups both had about a four-fold increase in tumor burden compared to the SH group (*Trp53*: p=0.0016, *Pten*: p=0.0022). The LN2A orthotopic transplant model had the worst survival out of all the groups (about 2 weeks) and the highest tumor burden. The SH tumors demonstrated mixed histopathologies with both LUSC and LUAD differentiation, while the *Trp53* KO and *Pten* KO groups showed LUAD features. The LN2A had only LUSC histologic and immunohistochemistry features (CK5 and p63 positivity). Tumor cell clusters from the scRNA-seq data expressed LUSC or LUAD signatures that were highly concordant with our histopathologic findings. scRNA-seq also revealed large variations in the TME composition between the four groups. For example, the LN2A model had the highest abundance of myeloid cells and expressed genes for cholesterol synthesis pathways, while *Trp53* KO tumors had high levels of neutrophils and T cells. Notably, the LN2A tumor cells had pathways related to atherosclerosis signaling upregulated while tumor cells from both the *Trp53* KO and *Pten* KO groups had increased natural killer cell signaling. The *Trp53* KO tumor cells also showed increases in genes related to neuroinflammation signaling.

Conclusions: The roles that common tumor suppressors have on NSCLC differentiation, disease progression and the TME are poorly understood. Using CRISPR-mediated *in vivo* model systems, we found p53 and Pten have important roles on cancer cell differentiation, metastases and remodeling the TME. Further studies are ongoing to further expand on the biology of candidate pathways identified in our scRNA-seq analyses of genetically defined transgenic NSCLC models.

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-018 DNA Mismach Repair in Lung Adenocarcinoma in Morocco

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Introduction: Microsatellite Instability (MSI) refers to the hypermutable state of cells as a consequence of DNA mismatch repair (MMR) deficiency. Identification of hypermutable tumors is clinically valuable for selecting patients suitable for immunotherapy treatment. These alterations in microsatellite sequences characterize hereditary nonpolyposis colorectal cancer, but they have been reported in other cancers. This study aims to evaluate the status of primary lung adenocarcinoma in Morocco.

Methods: Samples of primary lung adenocarcinoma were obtained from paraffin-embedded tissue derived from lung biopsy cases. Microsatellite analysis was performed on all tumors using immunohistochemistry to detect the presence or absence of four proteins that are carried out at the anatomy-pathology department of Ibn Sina University Hospital Center in Morocco.

Results: Twenty-eight samples of primary lung adenocarcinoma were analyzed by immunohistochemical technique. More than two-thirds of cases were men, giving a male-female ratio of 3.5. The average age at diagnosis was 59.1 years, and 75% of patients were smokers. In most cases (82.14%), patients were diagnosed at a locally advanced or metastatic stage. All adenocarcinoma were positive for both cytokeratin 7 (CK7) and thyroid transcription factor-1 (TTF-1), and negative for p40, p63, CK5/6, and CK20. Regarding microsatellite analysis, one of 28 lung adenocarcinoma was MSI-H.

Conclusions: MSI-H status is very rare in lung carcinomas. More studies on larger series are needed to confirm our findings. Increasing understanding of microsatellite instability may open new therapeutic avenues and merit further investigation.

Keywords: Microsatellite Instability, Lung adenocarcinoma, Immunohistochemistry

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-019 Impact of Chemotherapy on Tridimensional Multicellular Non-small Cell Lung Cancer Spheroids with Microenvironment Cells

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Introduction: Platinum-based chemotherapy in combination with immunotherapy is a standard of care in advanced non-small cell lung cancer (NSCLC) patients. However, some of them will not benefit from this combination. A better understanding of cancer mechanisms and drug resistance is highly needed, and 3D culture models might help to understand cell-cell and tumor cell-microenvironment interactions. Our study aimed to develop a model of tridimensional multicellular tumor spheroids (MCTS) including non-squamous NSCLC cells with various baseline PD-L1 expression with or without tumor microenvironment, to analyze the impact of chemotherapy.

Methods: In this study, we used three NSCLC cell lines derived from patients' samples: ADCA117 (PD-L1 negative), H1437 (PD-L1 low) and H1975 (PD-L1 high). Two types of MCTS were conceived : simple MCTS included tumor cells and complex MCTS included both tumor cells and microenvironment with 15% of fibroblasts (Human Foreskin Fibroblasts-2 (HFF-2)) and 15% of monocytes/macrophages from healthy donors. MCTS were treated with repeated chemotherapy drug combinations (carboplatin (50µM)-paclitaxel (150nM)(CaPa) or carboplatin (50µM)-gemcitabine (100nM)(CaGe)), similar to the clinical practice schedules. The impact of chemotherapy was evaluated using viability assays and confocal microscopy. 3' RNA-sequencing was used to study transcriptomic modifications induced by chemotherapy on MCTS containing ADCA117. Results validation was performed through flow cytometry and immunohistochemistry on simple and complex MCTS. RT-PCR was used on MCTS composed of H1437 and H1975 cells to validate results obtained on ADCA117 cells.

Results: Chemotherapy decreased ADCA117 MCTS size and cell viability. Fibroblasts were resistant to chemotherapy, whereas macrophages were strongly affected. A 3'RNA-Seq analysis showed modifications in numerous gene expression after treatment (138 up-regulated and 136 down-regulated for CaPa, 87 up-regulated and 79 down-regulated for CaGe, padj<0.001). Chemotherapy affected several pathways in tumor cells including P53 signaling, focal adhesion, PI3K-Akt signaling and cell senescence pathways. Regarding genes involved in immune response, we observed a significant increase of *CD274* (PD-L1) and *CD273* (PD-L2) gene expression coding for PD-1 ligands. PD-L1 up-regulation was confirmed using immunohistochemistry and flow cytometry on simple and complex MCTS. Induction of *CD274* and *CD273* gene expression was validated using RT-PCR on H1437 MCTS. However, *CD274* induction was observed only with the combination CaGe. In H1975 MCTS, treatments showed no change in basal high *CD274* gene expression.

Conclusions: Platinum-based chemotherapy up-regulated PD-L1 expression in several models of simple and complex MCTS, depending on baseline PD-L1 expression. This effect was concordant with previous observations shown in patients. Importantly, our results underlined that MCTS appeared as interesting tools to better understand the impact of chemotherapy on tumor cells and tumor microenvironment cells. MCTS should be used as relevant non-invasive methods for drug screening.

Keywords: immunotherapy, tumor microenvironment, tridimensionnel model

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-020 Dysregulation of 14-3-3 Signaling Adapters in Lung Adenocarcinoma, New Insights Into the Impact on Cancer Cell Biology

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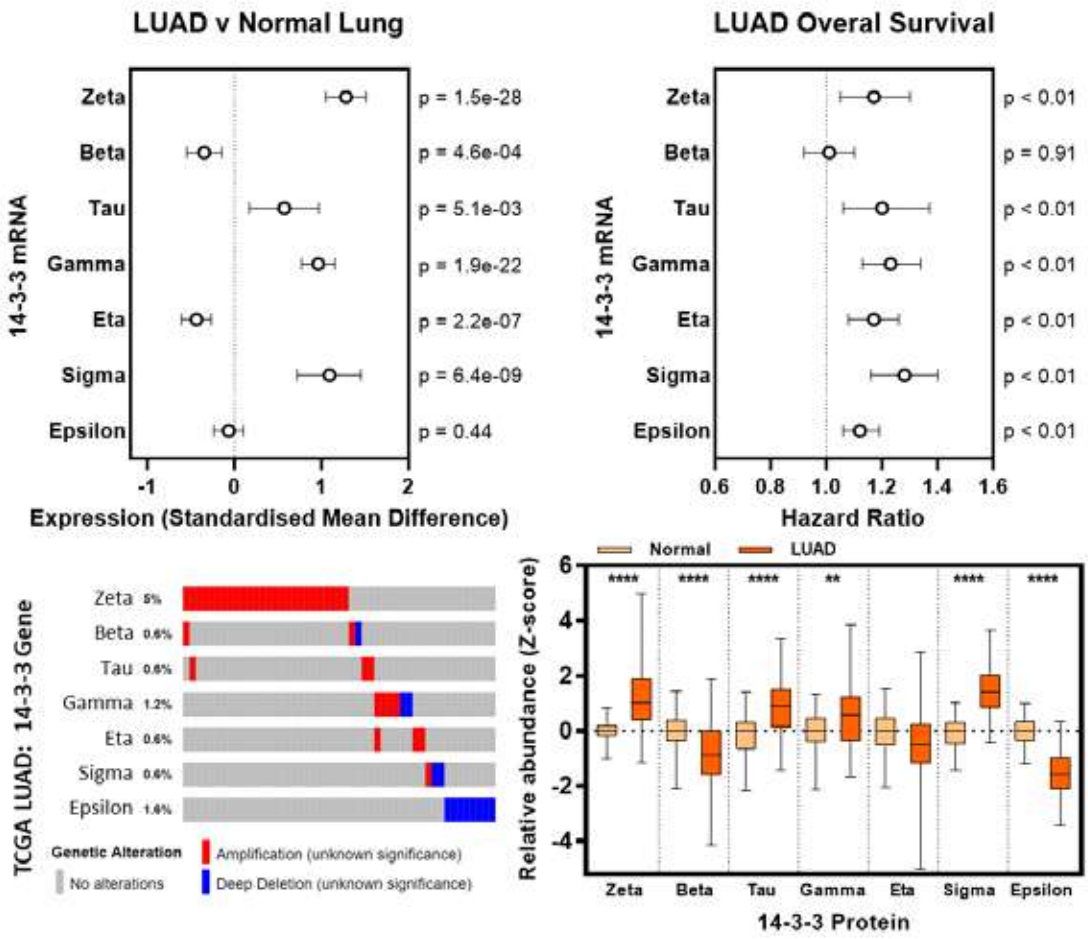
Introduction: Molecularly targeted drug therapies hold promise for many lung cancer patients, although acquired resistance to targeted therapies means identification of alternative targets is vital. 14-3-3 proteins are a highly conserved family of adapters, expressed from seven distinct genes that function as dimers to bind dual-phosphorylated client proteins and facilitate growth, survival and migration signalling in cancer. Importantly, the levels of some 14-3-3 isoforms are reportedly elevated in lung adenocarcinoma although the implications are unknown. The aim of this study was to understand how altered expression of different 14-3-3 isoforms influence cellular signalling in lung adenocarcinoma (LUAD).

Methods: An integrated analysis of publicly available genomic (TCGA via cBioPortal [cbioportal.org]), transcriptomic (Lung Cancer Explorer [lce.biohpc.swmed.edu]), and proteomic data (Clinical Proteomic Tumor Analysis Consortium data via UALCAN [ualcan.path.uab.edu]) of LUAD patients was applied to investigate the impact of dysregulation of 14-3-3 isoform expression on lung cancer traits and clinical outcomes. Using engineered lentiviral approaches, the LUAD cell line A549 was genetically altered to (i) achieve knockdown of individual 14-3-3 isoforms using short-hairpin RNA, (ii) generate 14-3-3 knockout using CRISPR-Cas9, or (iii) achieve constitutive 14-3-3 over-expression, in line with 14-3-3 dysregulation in the clinical data analysis. To identify the signaling pathways associated with dysregulation of 14-3-3 isoform expression, RNA-seq and gene set enrichment analysis (GSEA) was performed on the engineered cells and compared with publicly available datasets from LUAD samples.

Results: Meta-analysis of 14-3-3 mRNA expression across 7 studies (amassing 827 LUAD and 246 control lung samples) determined that 14-3-3 isoforms Zeta, Tau, Gamma and Sigma were significantly over-expressed, isoforms Beta and Eta were significantly under-expressed, and Epsilon remained unchanged in LUAD. Meta-analysis across 21 studies of 2968 patients also revealed that higher expression of most 14-3-3 isoforms resulted in poorer patient outcome. Genomic analysis of 14-3-3 genes in LUAD highlighted copy number variation as the dominant means of alteration with most isoforms chromosomally amplified whereas 14-3-3Epsilon was deleted. Protein abundance analysis from 110 LUAD and normal matched tissues identified higher abundance of 14-3-3 isoforms Tau, Sigma and Zeta, whereas isoforms Beta and Epsilon were less abundant. Analysis of A549 samples with higher 14-3-3Zeta or lower 14-3-3Epsilon expression had positive enrichment of gene sets related to LUAD including cytoskeleton remodelling and focal adhesion.

Conclusions: Our analysis in LUAD samples indicates that dysregulated expression of predominant 14-3-3 isoforms Zeta and Epsilon may change the dynamics of the dimer pool towards a more aggressive phenotype.



Keywords: 14-3-3, Lung adenocarcinoma, Cell Signaling

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-021 Chromatin Remodeling Drives Lung Pre-malignancy and is a Target for Prevention

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Introduction: Smoking cessation reduces lung cancer (LC) mortality; however, 50% of LC cases are diagnosed in former smokers, necessitating the need for effective preventive agents. Developing LC preventive drugs has been challenging because of the heterogeneity of this disease with respect to genetic and epigenetic alterations and the need for drugs to be non-genotoxic. Epigenetic deregulation involving methylation of cytosine to form 5-methylcytosine in conjunction with histone modifications in gene promoters to silence transcription is a key step in initiation and pre-malignancy affecting hundreds of genes involved in all aspects of cell regulation. Trimethylation of lysine 27 (H3K27me3) and dimethylation of lysine 9 (H3K9me2) of histone-H3 catalyzed by histone methyltransferases (HMTs) EZH2 and G9a impede gene transcription. Our human bronchial epithelial (HBEC) pre-malignancy model was used to study the role of histone modifications in transformation and the effect of targeting EZH2 and G9a on LC progression using the NNK A/J mouse model.

Methods: Four HBEC lines transformed by tobacco carcinogens were studied. Illumina expression arrays and HM450K BeadChip was used to characterize global expression and methylation changes in transformed lines. ChIP-on-chip evaluated global changes in H3K27me3 and H3K9me2. The effect of EPZ6438 and UNC0642, small molecule inhibitors of EZH2 and G9a and DZNep, an inhibitor of S-adenosylhomocysteine hydrolase that leads to depletion of EZH2 on transformation and transcriptional reprogramming was studied. A/J mice were treated with NNK for one wk, held for 20 wk, and then treated for 20 wk to evaluate effects of these agents on progression of hyperplasia to adenoma and gene expression by RNA-seq.

Results: Methylation of 12-96 genes was observed in the four HBEC transformed (T) lines that was perpetuated in tumors from The Cancer Genome Atlas. In contrast, hundreds of genes showed altered expression in HBECTs, many of which became methylated in tumors. ChIP-on-chip for HBEC2T identified 327 genes enriched for H3K27me3. Treatment of HBEC2T and HBEC13T with DZNep depleted EZH2, reversed transformation by 70-80%, and induced transcriptional reprogramming. Small molecule inhibitors to EZH2 and G9a were mostly ineffective. DZNep treatment prevented progression of hyperplasia to adenomas by 55% through reducing EZH2 to affect its chromatin mark H3K27me3 and modulate expression of 50 genes regulated by this HMT whose known functions impact tumor development.

Conclusions: The translational impact of these findings has provided a new avenue for chemoprevention targeting EZH2 that is strongly supported by the ability of DZNep, through reducing levels of this HMT, to potently reverse HBEC transformation, prevent progression of pre-malignancy in the NNK A/J lung tumor model, and induce reprogramming of the transcriptome. (Support-CA183296).

Keywords: EZH2, DZNep, Pre-malignant lung cancer

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-022 Prognosis of Epithelial-Mesenchymal Transition-Related lncRNA Profile in LUSC Patients

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Introduction: Epithelial-mesenchymal transition (EMT) process may affect tumor invasion, metastasis and proliferation in lung squamous cell carcinoma (LUSC). Due to this important biological role, EMT related genes and pathways are thought to be associated with clinical outcomes of LUSC patients. Currently, the expression profile of EMT-related lncRNA, the pathological features of LUSC and their prognostic values in LUSC have not been well understood.

Methods: The RNA-Seq data and clinical information of LUSC patients were obtained from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO), respectively. In total, 476 patients from TCGA and 61 patients from the GEO database were included in this study. To identify the EMT-related lncRNA, spearman correlations were firstly calculated between all the lncRNA expression data and EMT-related gene expression data. Then EMT-related lncRNA was identified using the computed correlation coefficients and statistical p-values. Univariate Cox regression analysis was performed to examine the independently correlated factors for overall survival(OS) among lncRNA signature and patient clinical information. To explore informative minimal molecular subtype, non-negative matrix factorization (NMF) was applied to cluster the LUSC samples. CIBERSORT algorithm was used to determine the infiltration levels of the two extracted subtypes for 22 common immune cell types (Neutrophils, T cells CD4 memory resting, etc). The immune and stromal scores were calculated using R-package “estimate”. The therapeutic responses were predicted based on the Genomics of Drug Sensitivity in Cancer (GDSC) database

Results: Using the above-mentioned strategy, a total of 322 EMT-related lncRNAs were identified with the Spearman coefficient > 0.3 and P-value ≤ 0.05 as previously reported. Univariate Cox regression analysis was performed both for TCGA and GEO datasets to identify highly OS-correlated ($p \leq 0.2$) lncRNA set, and found 11 intersected lncRNAs. Patients from the TCGA cohort were stratified into C1 subtype(n=138) and C2 subtype(n=338), and those two subtypes showed significant OS difference ($p < 0.01$), implied that the C1 subtype of the 11 lncRNAs was potentially associated with the prognosis of LUSC patients. Principal component analysis (PCA) results indicated that there was a significant expression difference between C1 and C2 subtypes additionally. Among the identified 11 lncRNAs, MBNL1-AS1, ROR1-AS1, WFDC21P have been reported to be associated with the development and progression of lung cancer. Based on the immune infiltration analysis, we found that Neutrophils and T cells CD4 memory resting of patients were significantly enriched in the C1 subtype. Patients’ immune and stromal scores were also higher in subtype C1 for both datasets. Using the GDSC database, we found subtype C2 was more sensitive to Erlotinib and Sorafenib compared with the C1 subtype, which is consistent with the longer OS exhibited in the C2 subtype.

Conclusions: We identified EMT-related 11 lncRNAs and found two subtypes in LUSC patients. C1 subtype is associated with a worse prognosis and demonstrated higher immune infiltration, high immune and stromal scores. The identified 11 lncRNAs and the two subtypes expanded our knowledge of the molecular signatures of LUSC prognosis.

Keywords: epithelial-mesenchymal transition, lncRNA, lung squamous cell carcinoma

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-023 Development and Validation of a Necroptosis-related Prognostic Model for Lung Adenocarcinoma

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Introduction: Necroptosis is a regulated caspases-independent cell death involved in the development and therapeutic response of lung cancer. In this study, we established a necroptosis-related signature to stratify the lung adenocarcinoma (LUAD) patients regarding the clinical prognosis and immune landscape profiles.

Methods: A total of 454 lung adenocarcinoma patients without receiving definite adjuvant treatment (59 normal and 476 tumor samples) from The Cancer Genome Atlas (TCGA-LUAD) were enrolled in this study. They were randomly grouped as training set and validation set (3:1 ratio). Differential gene expression analysis, univariate Cox regression, LASSO algorithm and stepwise multivariate Cox regression were performed to construct the prognostic risk score model based on 67 necroptosis-related genes previously reported. The overall survival (OS) difference between the high- and low-risk groups stratified by the median risk score was compared using Kaplan-Meier statistics. Furthermore, the immune-related phenotypes between the identified risk groups were evaluated, including tumor micro-environment scores calculated by ESTIMATE, abundance of immunocytes estimated by CIBERSORT, chemotherapeutics sensitivity predicted by pRRophetic and immune checkpoint expression. The identified signature was also validated with two independent GEO datasets, including GSE37745 (n = 181) and GSE30219 (n = 293).

Results: Among 28 genes differentially expressed between the normal and tumor samples (criterion using |log2-FC| > 0.5 and FDR < 0.05), three genes (PLK1, TERT, FADD) were identified to construct the prognostic model. The established model was found to significantly correlate with worse prognosis in TCGA cohort (Train set: HR = 1.69, 95%CI = 1.14-2.51, P = 0.008; Validation set: HR = 2.12, 95%CI = 1.11-4.02, P = 0.019; Whole set: HR = 1.78, 95%CI = 1.27-2.48, P < 0.001), and was found to be independent to clinicopathological parameters. In addition, the model was also validated in two independent GEO datasets and robustly predicted clinical outcomes of overall survival (GSE30219: n = 293, HR = 1.86, 95%CI = 1.40-2.47, P <0.001; GSE37745: n = 181, HR = 1.45, 95%CI = 1.03-2.05, P = 0.031) and disease-free survival (DFS) (GSE30219: n = 278, HR = 2.47, 95%CI = 1.68-3.63, P <0.001; GSE37745: n = 81, HR = 2.65, 95%CI = 1.36-5.18, P = 0.003). Immune-related evaluation revealed that the lower infiltration of non-tumor cells mostly presented in high-risk group, and the infiltrating cells including CD8/CD4 T cells, NK cells, M0/M1 macrophages, Mast cells, monocytes and resting dendritic cells were all significantly different between the two risk groups. Most immune checkpoint expression was relatively higher in the low-risk group, and only a small number of molecules were substantially increased in high-risk group (TNFRSF18/25, TNFSF4, PDCD1, CD276, LAG3), suggesting the different immune-environment in the two risk groups. Further analysis identified 29 lung cancer related drugs, which targeted pathways such as apoptosis regulation, cell cycle, mitosis, EGFR/IGF1R signaling, etc., exhibited significantly different responses in the two risk groups.

Conclusions: The established signature based on three necroptosis-related genes is a potentially interesting biomarker for predicting the prognosis and immune-related response in LUAD patients with further experimental and clinical validation.

Keywords: Lung adenocarcinoma, Necroptosis, Prognosis

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-024 HMGB1-mediated Autophagy Promotes Gefitinib Resistance in Human Non-small Cell Lung Cancer

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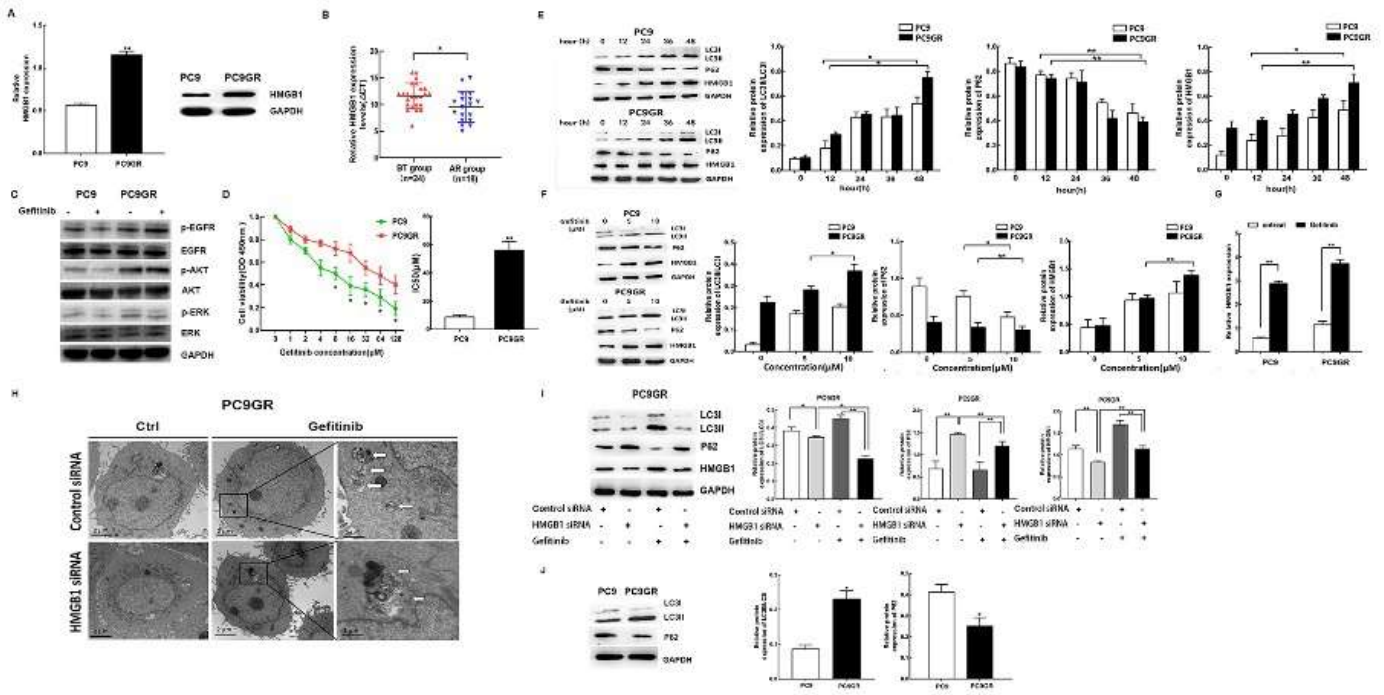
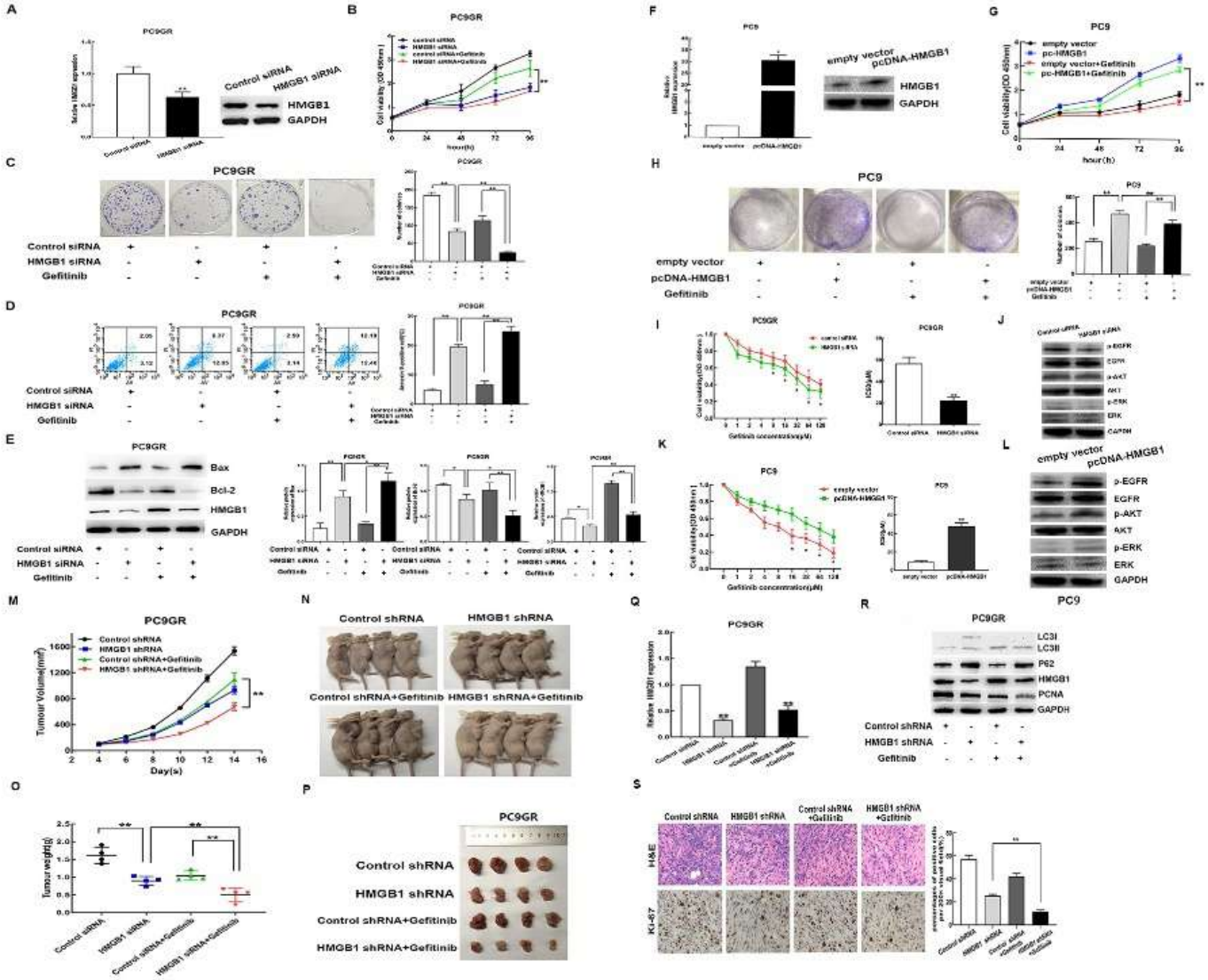
Introduction: The incidence of lung cancer in China ranks first among malignant tumors, and the incidence is increasing every year. More than 60% of patients are in advanced stage with poor prognosis. The epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), represented by gefitinib, is effective in treating patients with EGFR-sensitive mutations. However, most patients will have different degrees of resistance after treatment, which greatly affects the clinical treatment effect. High mobility group protein 1 (HMGB1) is a highly conserved nuclear protein that bends DNA and facilitates the assembly of transcribed proteins on specific DNA targets. Many studies have confirmed that HMGB1 overexpression is related to the proliferation and metastasis of many tumor types, including breast cancer, gastric cancer and colorectal cancer. However, the mechanism of its action in tumor resistance is unclear.

Methods: QRT-PCR,western blot,CCK8,cell transfection,colony formation assay,apoptosis assay,animal experiments and transmission electron microscopy were used in this study.

Results: In this study, we found that overexpression of HMGB1 is correlated with acquired resistance to gefitinib and gefitinib induces high expression of HMGB1 and activates autophagy in sensitive and resistant NSCLC cells. Knockdown of HMGB1 inhibited the proliferation and increased the apoptosis of PC9GR cells and upregulation of HMGB1 facilitates the gefitinib resistance of PC9 cells in vitro.HMGB1 knockdown enhances the sensitivity of PC9GR cells to gefitinib in vivo. Further exploration found that gefitinib-induced upregulation of HMGB1 expression induces autophagy.

Conclusions: This study suggests that HMGB1-mediated autophagy promotes gefitinib resistance in human non-small cell lung cancer.





Keywords: HMGB1, Autophagy, Gefitinib

EP16.04-025 Statins Suppress SOAT1 Expression & Reduce Cholesterol Esterification in Statin-sensitive Lung Cancer Cells

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Introduction: Statins, cholesterol-lowering drugs, act by inhibiting the rate-limiting enzyme, hydroxymethylglutaryl-CoA reductase, in the mevalonate pathway. Statins can delay metastasis *in vivo* and attenuate the growth of tumor cells *in vitro*. The latter effect is stronger in tumor cells with a mesenchymal-like phenotype than in those with an epithelial-like phenotype. However, the mechanisms by which they do so remain unclear. Here, we aimed to analyze the effects of statin treatment on cholesterol synthesis-related factors in statin-sensitive HOP-92 cells and statin-resistant NCI-H322M cells using comprehensive transcriptome analyses.

Methods: We performed comprehensive gene expression analyses and evaluated the differences in cell characteristics between a statin-sensitive lung cancer-derived cell line, HOP-92 (mesenchymal-like phenotype), and statin-resistant NCI-H322M (epithelial-like phenotype). First, the cells were seeded in 6-well plates at a density of 1×10^5 cells/mL and incubated overnight prior to treatment with 0.1-10 μM atorvastatin for 24 h. Cells treated with 0.1% DMSO were used as vehicle controls. After RNA extraction, transcriptome profiling was performed using RNA sequencing. Quantitative reverse transcription PCR (RT-qPCR) and western blot analyses were conducted to identify certain factors. The cellular contents of coenzyme (CoA), hydroxymethylglutaryl-CoA (HMG-CoA), and cholesterol were also measured.

Results: The basal gene expression levels related to cholesterol biosynthesis were lower in statin-sensitive cells than in statin-resistant cancer cells. In the Gene Ontology (GO) category "coenzyme A metabolic process," pantothenate kinase 2 (*PANK2*), and acetyl-CoA acetyltransferase 1 (*ACAT1*) genes showed remarkably reduced expression in response to statin treatment in statin-sensitive cancer cells. Furthermore, the amount of intracellular cholesterol ester in these cells was reduced after statin treatment, which also correlated with decreased sterol O-acyltransferase 1 (*SOAT1*) gene expression. In contrast, the levels of intracellular cholesterol esters and *SOAT1* were unaffected by statin treatment in statin-resistant cancer cells.

Conclusions: In addition to the vulnerability of the mevalonate pathway flux based on the lower basal gene expression levels related to cholesterol biosynthesis, the susceptibility of *PANK2* and *ACAT1* to the effect of statins and the reduction in intracellular cholesterol storage through the downregulation of *SOAT1* have the potential to strengthen the anticancer effect of statins in statin-sensitive cancer cells.

Keywords: Statin, Transcriptome, Mevalonate pathway

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-026 Effectiveness of Atorvastatin and SR-12813 Combination in Statin-resistant and Statin-sensitive Lung Cancer Cell Lines

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Introduction: Statins are therapeutic agents for dyslipidemia that lower blood cholesterol levels. However, they are expected to be applied as therapeutic agents for cancer in the coming years. Statins specifically inhibit hydroxymethylglutaryl (HMG)-CoA reductase (HMGCR) which reduces HMG-CoA to mevalonic acid. Statin-treated cells inhibit the ubiquitination of HMGCR, which prevents its degradation by the proteasome system. The resulting intracellular accumulation of HMGCR is considered to be one of the factors that weaken the anticancer effect of statins. Recently, it has been reported that HMGCR inhibition via combining both statins and the HMGCR degradation may be more effective than statins alone in treating cardiovascular diseases. In this study, we investigated whether the induction of HMGCR degradation by SR-12813, which is one of the HMGCR inhibitors that degrade HMGCR protein, enhances the anticancer effect of statins.

Methods: SR-12813 (0-20 μM) was used to treat two types of lung cancer cell lines with different statin susceptibilities (statin-resistant NCI-H322M and statin-sensitive HOP-92), and its effect on cell proliferation was examined. We first determined the concentration of SR-12813 alone that did not affect cell proliferation so as to combine this concentration with statins. Next, 5 μM SR-12813 was administered simultaneously with 0-30 μM atorvastatin, and the effect on cancer cells was investigated. Cell viability was evaluated using the cell counting kit-8.

Results: After 72 h of treatment with SR-12813 alone, cell proliferation was suppressed at concentrations of 10 and 20 μM in both cancer cell lines. Therefore, 5 μM SR-12813, which did not affect cell proliferation, was determined as the effective concentration to combine with atorvastatin. We analyzed the effect of the combined use of SR-12813 with each investigated concentration of atorvastatin on cell proliferation after 72 h. Our results demonstrated that, in NCI-H322M cells, SR-12813 reduced the effective concentration of atorvastatin that could inhibit cell proliferation by one-tenth the concentration required for treatment with atorvastatin alone (from 30 to 3 μM). In HOP-92 cells, cell viability was significantly reduced to approximately 70% with 0.3 μM statin treatment alone; however, in combination with SR-12813, the viability was reduced to approximately 10%.

Conclusions: Collectively, SR-12813 inhibits cancer cell proliferation by degrading HMGCR, suggesting that the combination of SR-12813 and atorvastatin is more effective in inhibiting cancer cell proliferation than atorvastatin alone.

Keywords: Statin, SR-12813, Hydroxymethylglutaryl-CoA reductase

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-027 Identification of Optimal Internal Reference Gene to Analyze the Anticancer Effects of Statins in Lung Cancer Cells

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Introduction: Statins are mainly used for the treatment of dyslipidemia. They exert their effects by specifically inhibiting hydroxymethylglutaryl (HMG)-CoA reductase (HMGCR), a rate-limiting factor in the mevalonate pathway. Statins have recently been reported to have anticancer effects and could be used in cancer treatment through drug repositioning. The mevalonate pathway synthesizes cholesterol as well as produces molecules involved in lipid modification of small G-proteins and molecules involved in the electron transfer system etc. Therefore, statins are considered to have a wide range of effects on cells. In reverse transcription (RT)-qPCR, the internal standard gene is generally used to normalize the expression level of the target gene. Therefore, the internal reference gene itself must not be affected under any experimental conditions. Since statins affect various signaling pathways, including the inhibition of the mevalonate pathway, there is a high possibility that these drugs might change the expression of internal reference genes, thereby misleading the obtained gene expression data. To avoid this, the study aimed to evaluate the expression stability of various internal reference genes and establish the foundation for gene expression analysis in in vitro experiments with statins.

Methods: Statin-sensitive HOP-92 cells and statin-resistant NCI-H322M cells, derived from the NCI-60 cancer cell line panel (lung cancer cells), were used for the analysis. Atorvastatin was administered for 24 h at seven different concentrations (0, 0.1, 0.3, 1, 3, 10, and 30 μM). RT-qPCR was performed for the 15 internal reference genes reported thus far (*ATP5F1*, *TFRC*, *YWHAZ*, *RPLP0*, *RPLP1*, *ACTB*, *RPLP2*, *HPRT1*, *B2M*, *RPS18*, *TBP*, *PGK1*, *PPIA*, *GAPDH*, and *GUSB*). The geNorm, BestKeeper, NormFinder, and RefFinder algorithms were used to evaluate suitable internal reference genes. The comparative ΔCt method (Silver *et al*., 2006) was also used to evaluate the expression stability of the internal reference genes.

Results: Both statin-sensitive and -resistant cancer cells showed that atorvastatin affected some internal reference genes in a dose-dependent manner. In statin-sensitive HOP-92 cells, the number of internal reference genes whose expression was altered by atorvastatin was higher than that of statin-resistant NCI-H322M cells. These results suggest that the internal reference genes in statin-sensitive cancer cells are more sensitive to statins than those in statin-resistant cancer cells.

Conclusions: The geometric mean of the rankings for each algorithm revealed that *RPLP2* was the most stable internal reference gene. In contrast, *ACTB* (ß-actin), which is commonly used as an internal standard, was less stable, indicating that it is not suitable for gene expression analysis in in vitro experiments with statins.

Keywords: Statin, internal reference genes, RT-qPCR

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-028 PHLPP2 Regulates Ferroptosis Through Nrf2 Pathway to Affected Cell Cycle and Apoptosisin Lung Squamous Cell Carcinoma

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Introduction: Lung cancer has the highest mortality rate of all cancers worldwide. Lung squamous cell carcinoma (LSCC) comprises a large fraction of non-small cell lung cancer (NSCLC), and annually accounts for 50,000 deaths in the US. Unlike lung adenocarcinoma, there is currently no first-line targeted therapy for LSCC. The PH domain and leucine-rich repeat protein phosphatase 2 (PHLPP2) has been reported to be a potent tumor suppressor in many human cancers. However, the underlying mechanisms by which PHLPP2 exerts tumor suppressive effects have not been fully investigated.

Methods: Data from 48 pairs of lung cancer patient tissues were analyzed in the Gene Expression Omnibus (GEO) database to determine the expression of PHLPP2 and Nrf2. The relationship between PHLPP2 and Nrf2 in lung squamous cell carcinoma was analyzed in The Cancer Genome Atlas (TCGA) database. Then, we verified in SK-MES-1 cell experiments. We used shRNA knockdown as well as overexpression of PHLPP2 in SK-MES-1 cells and examined the expression of Nrf2, HO-1. Western blotting was detected the expression of iron metabolism-related protein PTGS2. Flow cytometry was employed to analyze apoptosis and cell cycle progression.

Results: The GEO database results showed that compared with normal tissues, the expression of PHLPP2 was relatively low in tumors, while the expression of Nrf2 was relatively high. TCGA library data showed that the expressions of PHLPP2 and Nrf2 were negatively correlated in lung squamous cell carcinoma. Moreover, western blotting results showed that knocking down the expression of PHLPP2 increased the expression of Nrf2 and HO-1, whereas PTGS2 decreased; on the contrary, the expression of Nrf2 and HO-1 decreased after overexpression of PHLPP2, whereas PTGS2 decreased. Furthermore, the results of flow cytometry showed that after inhibiting the expression of PHLPP2, the ratio of G1/S decreased and apoptotic cells decreased, and the results in the overexpression group of PHLPP2 were the opposite.

Conclusions: The present study suggests that PHLPP2 regulates ferroptosis and affects cell cycle and apoptosis though Nrf2 pathway in lung squamous cell carcinoma.

Keywords: PHLPP2, ferroptosis, Nrf2 pathway

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-029 Downregulation of PHLPP2 Induced by Radiation Promotes GPX4-mediated Ferroptosis Defense and Radioresistance in Lung Cancer

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Introduction: Radiotherapy (RT) is one of the most widely used treatment strategies in cancer treatment in non-small cell lung cancer (NSCLC), but radioresistance remains a major clinical challenge. Ferroptosis is a recently identified form of non-apoptosis regulated cell death (RCD) driven by iron-dependent iron-dependent lipid peroxidation, and recent studies showed ferroptosis plays an important role in RT-induced cell death. However, the dysregulation of ferroptosis in radioresistance is poorly understood. Here we investigated the functional interaction between the ferroptosis induced by RT and PHLPP2 expression in NSCLC.

Methods: Clonogenic survival assay was used to assess radiosensitization in NSCLC cell line. Cell viability, protein alterations and the expression of indicated mRNA were measured by MTT assay, Western blotting and quantitative real-time polymerase chain reaction (qRT-PCR) respectively. Lipid peroxidation assessment by flow cytometry using the fluorescent probes C11-BODIPY staining. The lentivirus-mediated delivery of shRNA was used to generated stable knockdown of PHLPP2 expression, and retrovirus-mediated delivery was used to generated stable overexpression of PHLPP2 in NSCLC cells.

Results: We found RT treatment induced significant downregulation of PHLPP2 expression in NSCLC cell lines with a concomitant increased GPX4 expression. Knockdown of PHLPP2 in NSCLC cell lines significantly increased clonogenic cell survival, proliferation, and decreased radiotherapy-induced lipid ROS production and PTGS2 mRNA expression. Conversely, overexpression of PHLPP2 promoted GPX4 inhibitors/ radiotherapy-induced cell death in NSCLC cell lines and increased radiotherapy-induced lipid ROS production and PTGS2 mRNA expression. Mechanically, we show PHLPP2 promotes RT-induced cell death through repressing GPX4 expression.

Conclusions: Our study nominates PHLPP2 as a critical regulator of ferroptotic cancer cell death implied that pharmacological targeting of PHLPP2 synergizes with GPX4 inhibition to trigger ferroptosis induced by radiotherapy.

Keywords: PHLPP2, ferroptosis, radioresistance

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-030 Cancer-Associated Fibroblasts Attenuate DNA Damage Repair by Promoting Glycolysis in Non-small Cell Lung Cancer

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Introduction: Radiotherapy plays a curative or palliative role in the treatment of non-small cell lung cancer (NSCLC) patients. Cancer-associated fibroblasts (CAFs) are one of the most abundant components of tumor microenvironment (TME). Our study aimed to investigate whether CAFs were involved in DNA damage response of NSCLC cells and clarify the involved mechanisms.

Methods: By primary culture, two pairs of CAFs and their matched NFs (normal fibroblasts) had been successfully established from tumor tissues and normal lung tissues of primary NSCLC patients. The effect of CAFs on the radioresponse of NSCLC cells was explored in vitro. By establishment of xenograft tumors in BALB/c nude mice, CAFs-regulated tumor radioresponse was studied in vivo. The glycolysis of NSCLC cells was analyzed by detection of related genes expressions and glucose uptake and lactate secretion.

Results: CAFs attenuated irradiation-induced DNA damage while enhanced the expressions of DNA damage repair-associated proteins in A549 and PC-9 cells. Furthermore, CAFs induced cell cycle arrest of NSCLC cells in the radioresistant S phase. When co-cultured with CAFs, both A549 and PC-9 cells showed an increase in glycolysis with accelerated glucose uptake and lactate secretion. CAFs up-regulated and stabilized c-myc, which initiated the transcription of HK2 kinase, a critical rate-limiting enzyme of glycolysis through activation of Wnt/ß-catenin pathway. Inhibition of glycolysis significantly attenuated DNA damage response of NSCLC cells regulated by CAFs. By high throughput screening, we found CAFs-secreted midkine was responsible for the promotion of glycolysis by activation of Wnt/ß-catenin pathway. In vivo, CAFs also induced the radioresistant phenotype of NSCLC cells by regulating DNA damage response and inhibition of glycolysis significantly improved the radiosensitivity.

Conclusions: Together, our study highlighted the involvement of CAFs in DNA damage response of NSCLC cells by promoting glycolysis. These findings may provide novel insights into overcoming the radioresistance of NSCLC cells.

Figure 2

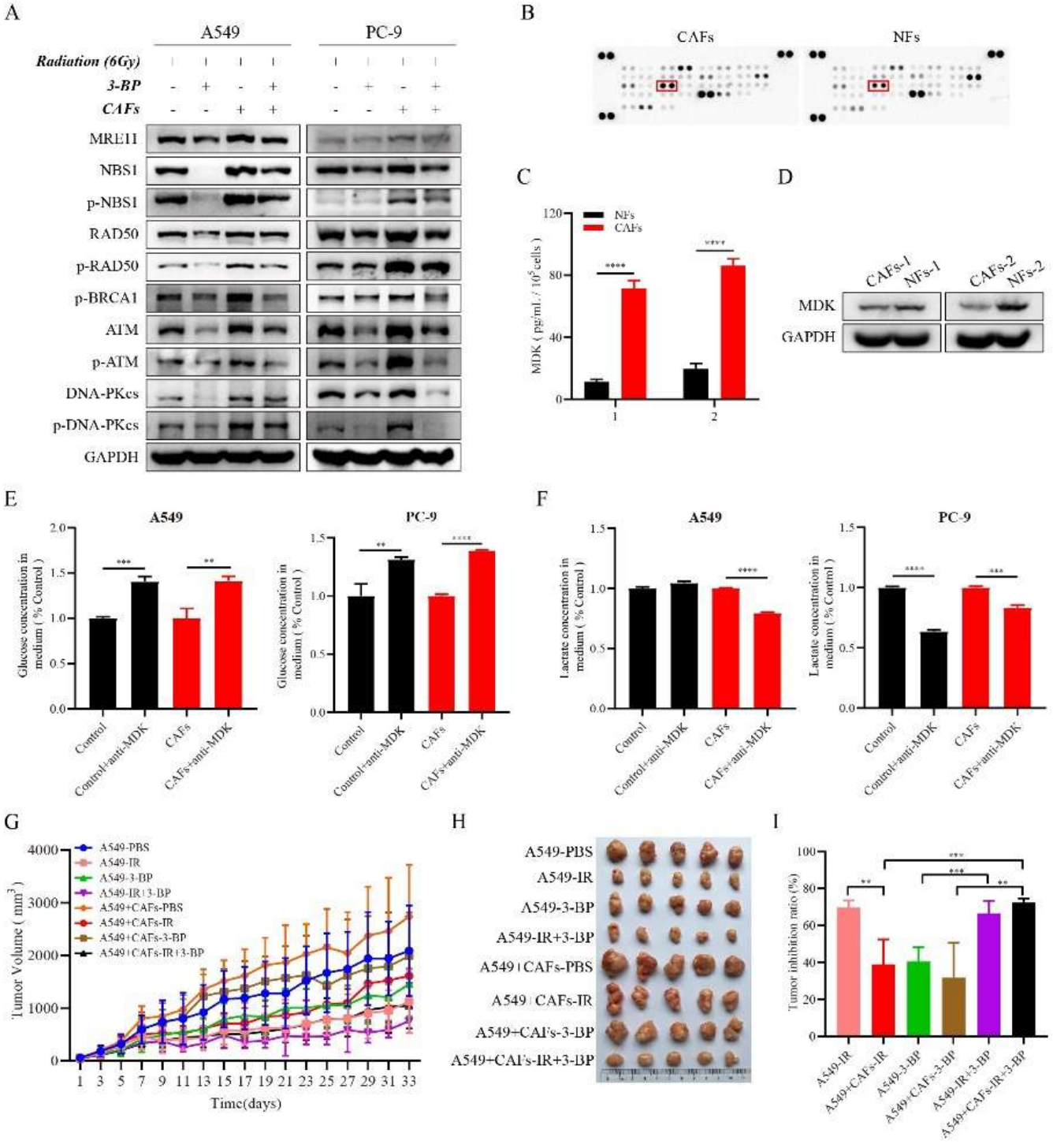
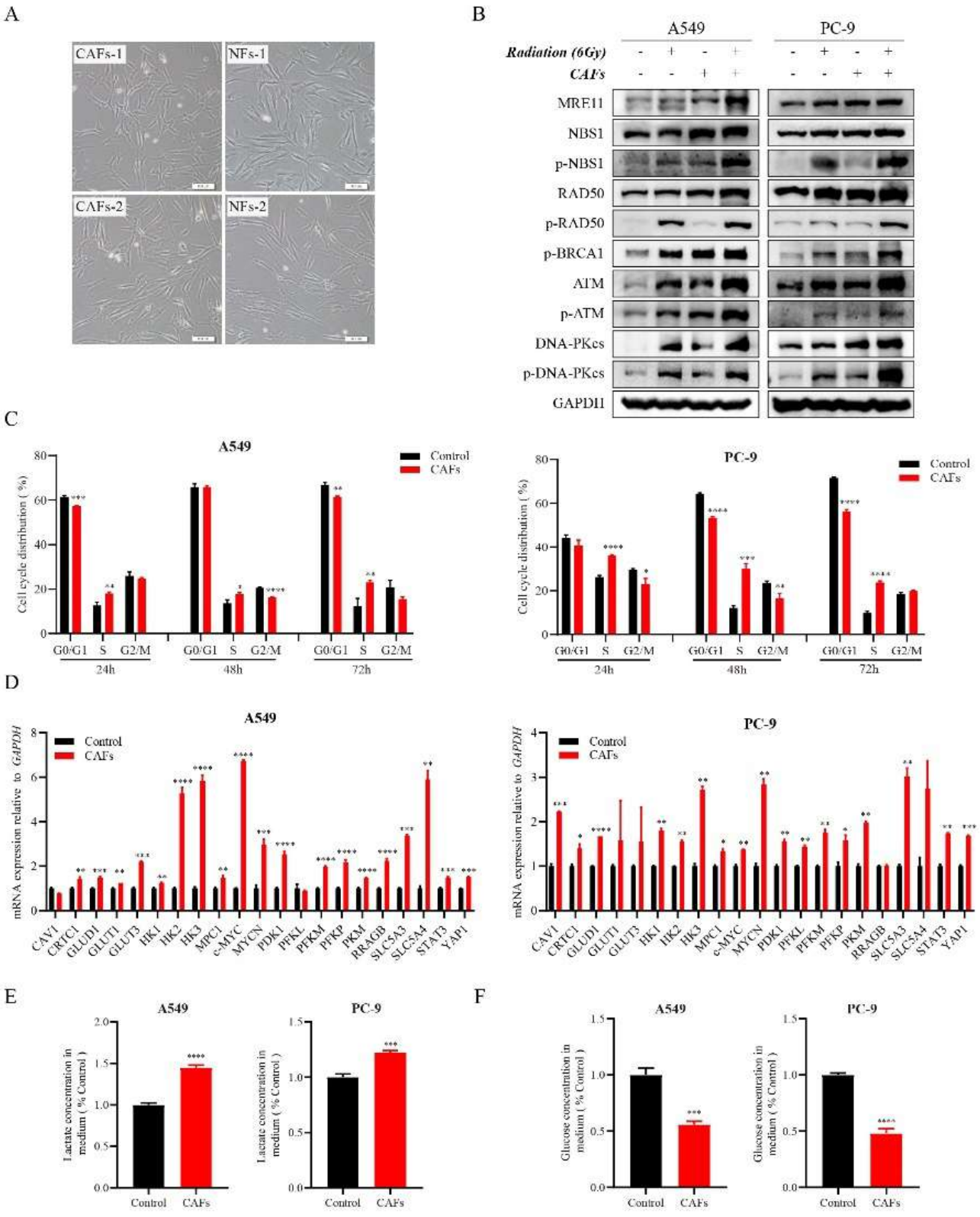

A
A549
PC-9
Radiation (6Gy)
3-BP
CAFs
MRE11
NBS1
p-NBS1
RAD50
p-RAD50
p-BRCA1
ATM
p-ATM
DNA-PKcs
p-DNA-PKcs
GAPDH
B
CAFs
NFs
C
NFs
CAFs
MDK (pg/mL / 10^5 cells)
D
CAFs-1
NFs-1
CAFs-2
NFs-2
MDK
GAPDH
E
A549
PC-9
Glucose concentration in medium (% Control)
Control
Control+anti-MDK
CAFs
CAFs+anti-MDK
F
A549
PC-9
Lactate concentration in medium (% Control)
G
A549-PBS
A549-IR
A549-3-BP
A549-IR+3-BP
A549+CAFs-PBS
A549+CAFs-IR
A549+CAFs-3-BP
A549+CAFs-IR+3-BP
Tumor Volume (mm^3)
Time(days)
H
A549-PBS
A549-IR
A549-3-BP
A549-IR+3-BP
A549+CAFs-PBS
A549+CAFs-IR
A549+CAFs-3-BP
A549+CAFs-IR+3-BP
I
Tumor inhibition ratio (%)
A549-IR
A549+CAFs-IR
A549-3-BP
A549+CAFs-3-BP
A549-IR+3-BP
A549+CAFs-IR+3-BP

Figure 1



Keywords: cancer-associated fibroblasts, DNA damage response, glycolysis

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-031 Connexin 43 Overexpression Induces Angiogenesis in Vitro Following Phosphorylation at Ser279 in its C Terminus

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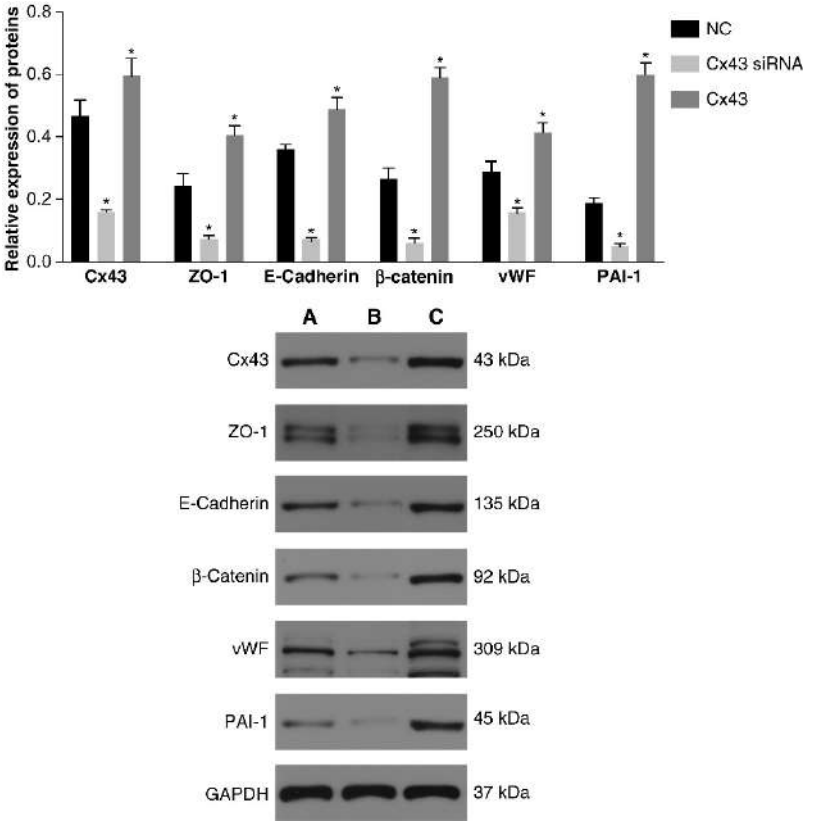
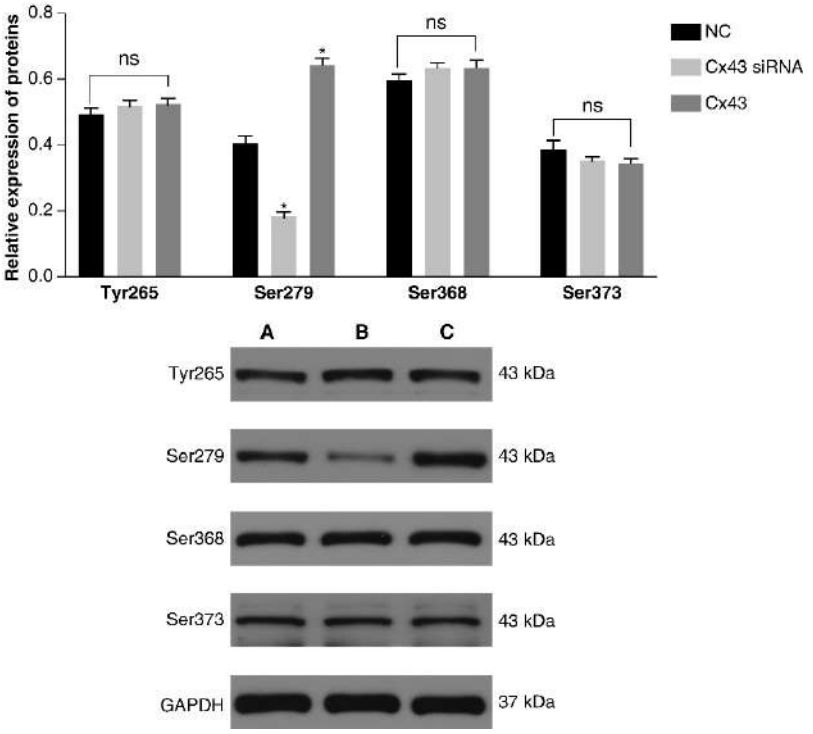
Introduction: Blocking angiogenesis can inhibit tumor growth and metastasis. However, the mechanism underlying regulation of lung cancer angiogenesis remains unclear. The gap junction protein connexin 43 (Cx43) is implicated in angiogenesis. We aimed to determine the role of Cx43 in angiogenesis in vitro and its signal pathways.

Methods: Human pulmonary microvascular endothelial cells were transfected with Cx43-targeting siRNA or Cx43-overexpressing recombinant plasmid vector. qRT-PCR and western blotting were performed to determine Cx43, ZO-1, E-cadherin, ß-catenin, vWF, and PAI-1 mRNA and protein expression, respectively. Tyr265, Ser279, Ser368, and Ser373 phosphorylation levels in the C terminus of Cx43 and intracellular and membranal Cx43 contents were determined using western blotting. Additionally, immunofluorescence, tube formation, CCK-8, and Transwell migration assays were performed.

Results: Compared with that in the control samples, Cx43, ZO-1, E-cadherin, ß-catenin, vWF, and PAI-1 mRNA and protein expression was significantly increased in the Cx43 overexpression group and significantly decreased in the Cx43 knockdown group. Moreover, Ser279 phosphorylation level as well as cell proliferation and migration rates were markedly increased in the Cx43 overexpression group, and tube formation showed that the angiogenesis potential was also increased. Conversely, in the Cx43 knockdown group, Ser279 phosphorylation level and cell proliferation and migration rates were reduced, and the angiogenesis potential was impaired greatly. Under Cx43 overexpression, membranal Cx43 content was significantly increased, whereas under Cx43 knockdown, it was significantly reduced.

Conclusions: The activation of the phosphorylation site Ser279 at C terminal of Cx43 is an important pathway for Cx43 to regulate angiogenesis in vitro. It promotes angiogenesis by stimulating cell proliferation, migration, and distribution of Cx43 to the cell membrane, possibly via the activation of the downstream ZO-1, E-cadherin, ß-catenin, vWF, and PAI-1 signaling proteins. The results indicate that Cx43 and its intracellular signaling site Ser279 on the C terminal are potentially new target for tumors.





Keywords: Cx43, Ser279, angiogenesis

EP16.04 TUMOR BIOLOGY AND BIOMARKERS - TUMOUR BIOLOGY & PRECLINICAL STUDIES

EP16.04-032 Indoleamine 2,3-dioxygenase 1 (IDO1) Blood Metabolites May Improve Predictive Accuracy for Radiation Pneumonitis

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Introduction: Symptomatic radiation pneumonitis (RP) is a critical dose-limiting factor for patients with lung cancer who received definitive radiotherapy. The individual sensitivity of the RP has been observed from numerous studies, which is often associated with baseline lung tissue condition. However, the identified biomarkers were various among different investigations. Indoleamine 2,3-dioxygenase 1 (IDO1) plays a pivotal role in immunosuppression and has been proved to suppress inflammation in infectious and autoimmune pneumonia. This study aimed to study whether combining IDO1 biomarker with computed tomography (CT) radiomics features can improve predictive accuracy for radiation pneumonitis.

Methods: Patients with lung cancer treated with thoracic radiotherapy were eligible from March 2018 to November 2021. The study included two centers: Taizhou hospital of Zhejiang Province (TZ) and the University of Hong Kong-Shenzhen Hospital (HK). Other eligibility included pathological confirmation of lung cancer, received radiotherapy with a prescribed dose larger than 50 Gy, baseline serum IDO1 data available, follow-up time of at least three months. The radiation pneumonitis was defined and graded according to CTCAE 5.0. The status of IDO1 was tested by measuring serum tryptophan and kynurenine using high-performance liquid chromatography. Radiomics features were extracted lung volume minus GTV in planning CT scans. The combining model was developed by XGBoost using a training dataset from TZ and an independent validation dataset from HK.

Results: This study included a training dataset of 95 eligible patients from TZ and an external validation set of 43 patients from HK. Eighteen out of 95 patients (18.9%) were identified with grade 2 or higher RP in TZ, and seven out of 43 (16.3%) in HK. 109 radiomics features were extracted from each planning CT. The combining model of IDO1 and radiomics has an AUC value of 0.80 [95% CI 0.59-1] in the training dataset, which is numerically higher than the AUC of 0.76 [95% CI 0.68-0.87] from radiomics features alone. However, we did not find an improved prediction performance of the combined model (AUC of 0.63 [95% CI 0.46-1]) compared with radiomics alone (0.66 [95% CI 0.50 - 0.80]) in the validation dataset.

Conclusions: This study explored a combined model of lung radiomics with baseline inflammatory biomarker IDO to predict the risk of RP. Even the combined model showed a higher prediction accuracy in the training set, we could not demonstrate this improvement using external validation data. Further model refinement with dynamic IDO changes and deep machine learning in a larger number of patients are needed.

Keywords: Radiation Pneumonitis, Indoleamine 2,3-dioxygenase 1, Radiomics

Workshops

WS07 LATAM WORKSHOP,
SATURDAY, AUGUST 6, 2022 - 15:00–16:30

WS07.03 Effect of Mirtazapine on Energy Intake in Patients with Anorexia Associated with NSCLC

O. Arrieta, D. Cardenas-Fernández, O. Rodriguez-Mayoral, L. Zatarain-Barrón, S. Gutierrez-Torres, D. Castañares, E. Reyes, D. López, P. Barragan, D. Heredia, L. Lara-Mejía, A.F. Cardona, D. Flores-Estrada, J.G. Turcott

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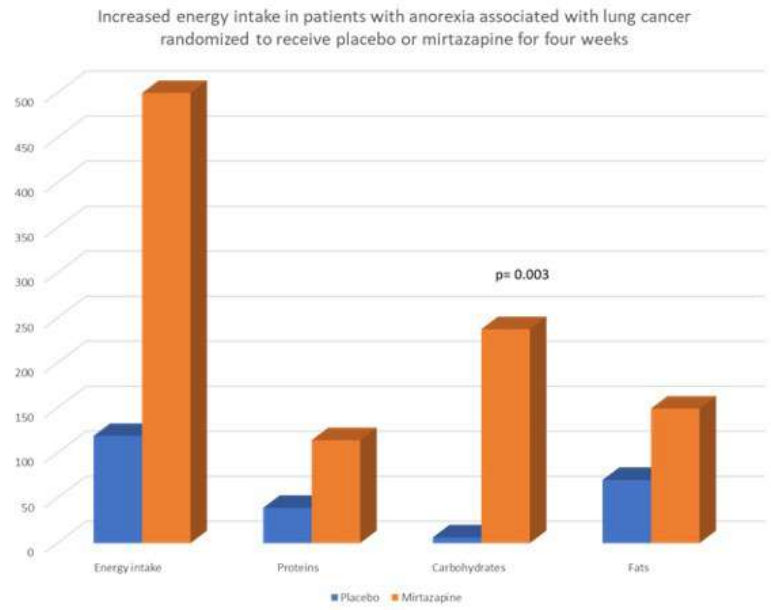
Introduction: Anorexia (lack of appetite), is a phenomenon which promotes malnutrition from insufficient food consumption; anorexia represents a widespread issue in patients with lung cancer, driving negative outcomes and hampering survival. Currently there is no standard therapy to improve cancer-related anorexia. This study sought to evaluate the effect of mirtazapine *vs.* placebo on nutritional parameters in patients with NSCLC diagnosed with anorexia.

Methods: Randomized, placebo-controlled clinical trial to evaluate the effect of supplementation with mirtazapine *vs.* placebo in terms of energy intake thorough 4 and 8 weeks in NSCLC patients diagnosed with anorexia using the validated Spanish version of the Anorexia Cachexia Scale (ACS). Patients were randomized 1:1 to receive 15 mg of mirtazapine or placebo for 2 weeks followed by a dose escalation to 30 mg until week 8. Dietary parameters were evaluated at baseline, 4 weeks and 8 weeks with a 24 hour dietary recall, and energy quantification based on the Mexican system of nutritional equivalents.

Results: A total of 65 patients met the inclusion criteria and were randomized to placebo group (n=32) or the mirtazapine group (n=33). The mean age was 63.5 ± 11.1, 37 (56.9%) were female and 28 (43.1%) were male. Baseline characteristics including sex, age, performance status, weight, body composition and ACS score were similar between study groups. Appetite was significantly increased in both study groups at 4 weeks post-intervention, no significant differences were identified at this study point (p=0.824). The percentage of energy requirement was significantly improved in the mirtazapine group compared with those who received placebo (34.9% vs. 8.8% p= 0.001). Energy consumption increase was greater in patients receiving mirtazapine as well (500 kcal *vs.* 119 kcal; p=0.001). This increase was reflected in protein (28.6gr *vs.* 9.8gr, p=0.011) and carbohydrate (59.4gr *vs.* 1.6gr, p= 0.003) intake. For the 8-week evaluation, patients in the mirtazapine showed a significant improvement in energy intake, percentage of requirement, proteins and fat from their baseline evaluation. Fats were also significantly improved among patients receiving mirtazapine *vs.* placebo (17.9 gr *vs.* 0.4 gr; p=0.009).

Conclusions: Patients with cancer-related anorexia can improve nutritional intake with the addition of mirtazapine, which promotes energy consumption reflected in diverse macronutrients.



Keywords: Anorexia, Mirtazapine, Malnutrition

WS07 LATAM WORKSHOP,
SATURDAY, AUGUST 6, 2022 - 15:00–16:30

WS07.04 KRAS Alterations, Clinicopathological Features and Co-occurring Drivers Associated with Prognosis in Advanced NSCLC Patients

M. Ramos-Ramirez[1], N. Hernandez-Pedro[1], P.D. Soberanis-Piña[1], L.A. Cabrera[1], E. Conde-Flores[2], D. Heredia[1], M. Morales-Garcia[2], D. Diaz-Garcia[1], A. Valencia-Velarde[1], L. Lara-Mejia[1], G. Cruz-Rico[1], O. Arrieta[1]

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Introduction: Genetic profiling has proven essential and changed the landmark in non-small cell lung cancer (NSCLC). Next-generation sequencing (NGS) has increased the identification of patients with different genomic alterations, which are novel targets for personalized therapies. Among them, KRAS is the isoform most commonly mutated in NSCLC, with a prevalence that is higher in Western populations compared to Asian (26 vs 11%). However, the information about the frequency, clinical characteristics and prognostic significance of KRAS in patients with NSCLC from Mexico has been limited

Methods: NGS was performed in patients with advanced NSCLC. Clinical and demographic information was collected retrospectively from electronic medical records. Patients were categorized into two groups based on KRAS mutation: KRAS-mutant or wildtype (KRAS-mut or KRAS-wt) and if mutated they were also stratified into two groups according to KRAS subtype: G12C and non-G12C

Results: A total of 313 patients were included. Median age was 61 years. The majority of patients were female (66.8%), non-smokers (63.3%) and had no previous wood-smoke exposure (70%). The most common sites of metastasis were bone (33.4%), lung (29.6%), pleural (23.8%), lymph node (23.2%) and central nervous system (CNS, 20.6%). Nearly 46% of the patients had a high histological grade tumor, 51.8% had a carcinoembryonic antigen above 10ng-mL and 62.8% had a PDL1 positive. The frequency of KRAS mutation was 15.4% (48 patients). The most frequent mutations occur in codon 12, with the most common subtypes including G12C (32.7%), G12D (28.6%) and G12V (16.3%). 3 patients had a KRAS amplification and 1 patient had a mutation in codon 66 (A66A). The G12C subgroup had more CNS metastasis and had a history of smoking than the non-G12C subgroup (p=0.021 and p=0.049 respectively). No other significant associations were found between KRAS status and clinicopathologic characteristics. KRAS co-occurrence partners most frequently were TP53 (47.1%), CDKN2A (11.5%), PIK3CA (7.6%), GNAS (5.1%) and STK11 (4.8%). PDL1 expression was similar between KRAS-mut and KRAS-wt (p=0.797) but was higher in patients with KRAS G12C vs non-G12C (p=0.026). Patients with KRAS-mut had a higher frequency of STK11 (p<0.001) and GNAS (p=0.001) vs KRAS wt. Among patients with KRAS G12C, CDKN2A was significantly higher (p=0.047) vs non-G12C. The median overall survival for the total population was 12.6 months. There was a trend in OS in favor of KRASG12C when compared to nonG12C (median OS 24 vs 9.79 months, p=0.379), as well as, patients with KRAS-TP53 positive tend to have a longer OS vs KRAS-TP53 negative (median OS 24 [KRAS-TP53 +] vs 9.16 months [KRAS-TP53 -], p=0.247). No statistically significant difference in OS were found between KRAS-mut vs KRAS-wt (median OS 25 vs 12.6 months, p=0.143) and KRAS G12C vs KRAS-wt (median OS 24.01 [G12C] vs 22.8 months [KRAS-wt], p=0.939)

Conclusions: Our study found that 15.4% of NSCLC patients harbor a KRAS mutation, less than the reported in the literature. Interestingly, CDKN2A was significantly higher among G12C patients, could be a worse prognosis feature. There are still unmet therapeutic needs for these patients

Keywords: KRAS, NGS, TP53

WS07 LATAM WORKSHOP,
SATURDAY, AUGUST 6, 2022 - 15:00–16:30

WS07.05 Artificial Intelligence in Lung Cancer Screening: Accuracy and Predictive Value

R.S.d. Santos[1,2], G.B.d.S. Teles[2], R.C. Chate[2], G. Szarf[2], J.P. Franceschini[3], C.A. de Araújo Neto[4,5], M. Ghefter[2], I. Drokin[6], M. Guimaraes[7], B. Hochhegger[8]

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Introduction: To investigate the performance of an Artificial Intelligence (AI) powered radiology platform in detecting solid pulmonary nodules on Low Dose Computed Tomography (LDCT) chest scans when compared against expert radiologists and to assess LungRADSTM categories agreement between software and radiologists.

Methods: Consecutive cohort with real-life data, which evaluated 790 LDCT of patients participating in a lung cancer screening program. All LDCT were reviewed by an experienced team of thoracic radiology. An AI algorithm was used, independently and anonymously, blind to CT results, to analyze the same set of LDCT. The LungRADSTM classification system was used for both groups and reported findings were compared, considering the expert analysis as the gold standard.

Results: AI group software showed high sensitivity and negative predictive value (97.8%), but low specificity and positive predictive value (56.1%), with an overall accuracy of 81.1%. A significant number of subsolid nodules were missed by the AI group; however, none of them were greater than 8 mm (LungRADSTM 4).

Conclusions: The AI software demonstrated high negative predictive value and relatively low positive predictive value. The device seems to be an important adjunct through the navigation team can prioritize exams with clinically significant nodules.

Diagnostic performance and agreement (negative vs positive CT)

	Botkin AI											
	Negative (LungRADS 1 and 2)		Positive (LungRADS 3 and 4)		Total		Kappa	Sensitivity	Specificity	AUC ROC	PPV	NPV
Radiogist	N	%	N	%	N	%	(IC 95%)	(IC 95%)	(IC 95%)	(IC 95%)	(IC 95%)	(IC 95%)
Negative (LungRADS 1 and 2)	496	63,7	136	17,5	632	81,1	0,535	92,5	78,5	0,855	50	97,8
Positive (LungRADS 3 and 4)	11	1,4	136	17,5	147	18,9	(0,474; 0,596)	(87; 96,2)	(75,1; 81,6)	(0,828; 0,882)	(43,9; 56,1)	(96,2; 98,9)
Total	507	65,1	272	34,9	779	100						

Lung-RADSTM categories in diagnosed lung cancer cases

Patient	LungRADS™ Radiologist	LungRADS™ Botkin	Diagnosis	Staging
1	4A	4B	Invasive squamous cell carcinoma	pT1a pN0
2	4B	4B	Adenocarcinoma of the lung	pT1a pN0
3	4B	4A	Adenocarcinoma of the lung	pT1a pN0
4	4B	4B	Adenocarcinoma of the lung	pT1a pN0
5	4A	4A	Squamous cell carcinoma	pT1a pN0
6	4X	4B	Non-small cell lung cancer	ypT1a ypN0
7	4B	4B	Invasive adenocarcinoma of the lung	pT2a pN0
8	4A	4A	Adenocarcinoma of the lung	pT1a pN0
9	3	3	Carcinoid tumor	

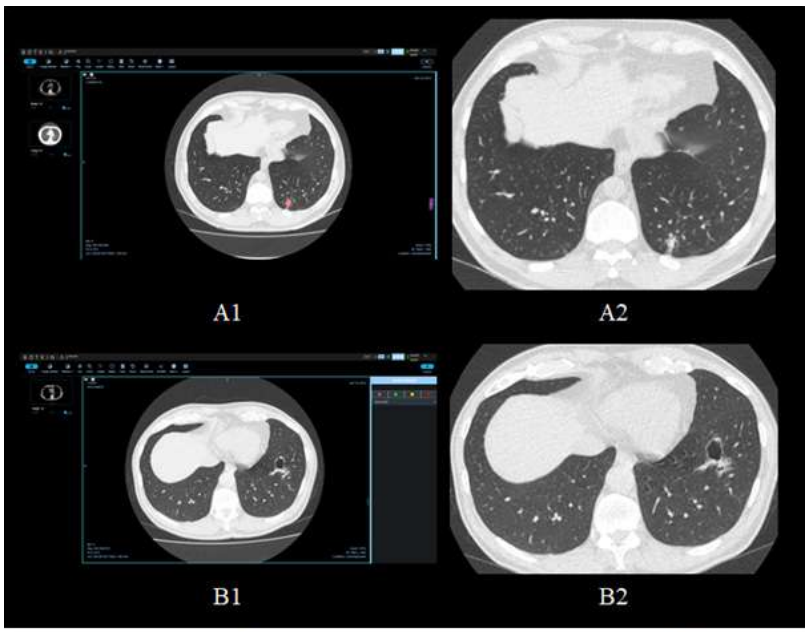

Figure 1. A1 Image from the AI software, pulmonary nodule classified as LungRADS 4A. A2. Radiologist analysis of the same pulmonary nodule, classified as LungRADS 4A. B1. Image from the AI software, pulmonary nodule classified as LungRADS 1. B2. Radiologist analysis of the same pulmonary nodule, classified as LungRADS 4A.

Keywords: lung cancer, screening, artificial intelligence

WS07 LATAM WORKSHOP,
SATURDAY, AUGUST 6, 2022 - 15:00–16:30

WS07.06 Real-world Evidence of Durvalumab for Stage III NSCLC: Survival Outcomes and Patterns of Care Post-progression

P. Aguiar Jr, P. Martins de Marchi, T. Caldas Montella, I. Favato Barcelos, G. Monte Tenório Taveira, R. Duarte Paes, R. Dienstmann, C.G. Moreira Ferreira

Grupo Oncoclínicas, Rio de Janeiro/BR

Introduction: Lung cancer is the leading cause of cancer-related death worldwide. In locally advanced NSCLC, there were few therapeutic options other than concomitant chemoradiation until immunotherapy consolidation with durvalumab has shown improved overall survival (OS) and became a standard of care. There is paucity of real-world evidence (RWE) on effectiveness of durvalumab, especially in Brazil, and limited studies have assessed treatment patterns after completion/discontinuation of durvalumab.

Methods: Retrospective observational study with de-identified data from patients diagnosed with stage III NSCLC who had received durvalumab until February 2022 in the largest private community oncology practice in Brazil. Patient-level information was extracted from an integrated multicenter database that combines structured longitudinal data from electronic health records (EHRs) with elements from unstructured sources using technology-based abstraction techniques by trained curators. Primary endpoint was median OS, and secondary endpoints were time to treatment discontinuation (TTD) and post-progression exposure.

Results: This study included 158 patients with median follow-up was 13 months. Median OS was 32 months with 12- and 24-month OS rates of 85% and 69%, respectively. Only 20 patients (13%) completed 1 year of durvalumab while 112 (71%) discontinued planned treatment after a median TTD of 7 months. Overall, 36 patients (23%) received post-progression therapy, most frequently chemotherapy (45%, exclusively in patients that discontinued durvalumab prematurely), followed by immunotherapy +/- chemotherapy combination (33%, mostly in patients that completed durvalumab) and tyrosine kinase inhibitors (22%). Median TTD of the treatment offered post-durvalumab was 4 months.

Conclusions: Our RWE on consolidation treatment with durvalumab for stage III NSCLC has shown survival outcomes comparable with randomized clinical trial data, despite the shorter median follow-up. Post durvalumab patterns of care differ according to whether patients have completed or not consolidation regimen, with limited effectiveness of existing rescue treatments.

Keywords: Durvalumab, Real World Evidence, Non-Small Cell Lung Cancer

WS07 LATAM WORKSHOP,
SATURDAY, AUGUST 6, 2022 - 15:00–16:30

WS07.10 Lung Cancer Disparities in Molecular Testing and Therapy Outcome in Hispanics in LATAM

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FL/USA

Introduction: We will have 130,000 deaths in the US in 2022, and more than 60,000 deaths per year in Latin America (LATAM). Hispanics are the largest minority group in the US (18% of the population), and there are more than 20 countries with Hispanic populations in LATAM. Disparities in the diagnosis and clinical outcomes of Hispanic patients with lung cancer compared with NonHispanic White (NHW) patients are welldocumented. Hispanics have disadvantages in social determinants of health: access to care, health insurance, cultural differences, and immigration status.There are also genetic and other biological differences (like EGFR frequency), Hispanics in LATAM have some extra hardships; most of them live in countries classified as low- and middle-income countries. Although Hispanics in the US have an overall lower incidence for all cancers, they generally experience greater health disparities because of structural, sociodemographic, psychosocial factors; however they have a better overall survival (OS) than other minorities: the so-called Hispanic Health Paradox (HHP).

Methods: We review here several recent publications in cancer disparities in Hispanics.

Results: Molecular Profile: We have shown that Hispanics living in the US have a higher rate of EGFR mutations (25%) than NHW patient's historic rates (15%) while the frequencies of other genetic aberrations (ALK, ROS-1, and KRAS) were similar. Also, EGFR mutation frequencies have varying rates among Hispanics from LATAM countries (15% in Argentina, 20% in Brazil, 25% in Mexico, and 55% in Peru). This genomic disparity favors Hispanics who have a better chance of survival than NHW patients.Biomarker access: Hispanics in LATAM mainly have access to testing EGFR or ALK genes and not broad access to NGS. Lack to adequate testing might be an impact in OS. Lenz evaluated 1,735 Hispanics with EGFR(+) NSCLC in Brazil. He estimated that, if treated with chemotherapy, only 71 patients would be free of progression after 24 months. In contrast, if all of the patients were treated with TKIs, the expectation was that 24-month PFS would be achieved in 312 patients.Immunotherapy: Most of the IO registration trials were done in the US/Europe, and they did not include anybody or enrolled a minimal number of Hispanics. We reported data from 256 Hispanics with NSCLC treated with IO as 2nd line in LATAM and US compared with 180 NHW controls, finding no difference in PFS and OS. Cardona included 296 Hispanic patients from the US and LATAM with NSCLC treated IO in 1st, 2nd or 3rd line; median OS was 19.9 months, compared with historical data from NHW patients; IO proved to be superior in terms of OS but not PFS. Despite the fact that biological speaking, the outcomes of Hispanics seem to be better or similar to NHW patients; other factors, mainly in Hispanics in LATAM, do not allow them to have these benefits because of lack of access, creating substantial disparities in outcomes.

Conclusions: Significant disparities in Hispanics with lung cancer care exist in the US and LATAM. Hispanics might have some biological advantages not well understood yet that created the Hispanic paradox and they tend to smoke less. However lack of biomarker access and targeted therapy due to the social determinants of health and other factors eliminate this potential biological benefits.More data are needed regarding molecular testing in Hispanics, access to target therapy, and immunotherapy in the US and abroad. This situation will not improve unless more Hispanics get enrolled in clinical trials and these are performed in areas where Hispanics live.

WS08 JOINT IASLC-CSCO-CAALC SESSION: LIQUID BIOPSY IN ONCOGENE DRIVEN NSCLC (ON-DEMAND),
SATURDAY, AUGUST 6, 2022 - 21:00–23:59

WS08.09 Sintilimab versus Pembrolizumab as Monotherapy or in Combination with Chemotherapy for Treatment Naïve Metastatic Non-small Cell Lung Cancer

S-Y. Liu[1], Q. Zhou[2], H-H. Yan[2], B. Gan[2], M-Y. Yang[2], J-Y. Deng[2], H-Y. Tu[2], X-C. Zhang[2], J. Su[2], J-J. Yang[2], Y-L. Wu[2]

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Introduction: Immunotherapy has become standard therapy for advanced non-small-cell lung cancer (NSCLC). However, no direct comparison between different PD-1 inhibitors were reported.

Methods: This is an open label, randomized, phase II clinical trial to compare sintilimab versus pembrolizumab as monotherapy or in combination with chemotherapy for treatment naïve local advanced or metastatic NSCLC. Eligible patients were *EGFR* or *ALK* negative. Patients with asymptomatic brain metastasis were allowed. PD-L1 tumor proportion score (TPS) ≥50% patients were randomly assigned to sintilimab (A) or pembrolizumab (B) monotherapy arms. TPS<50% patients were randomly assigned to sintilimab (C) or pembrolizumab (D) with platin-based chemotherapy arms. The primary endpoint was objective response rate (ORR). Sample size were determined per Optimal Two-Stage Design, 1st stage would recruit 20 patients. Recruitment of the 2nd stage would start if ≥4 patients achieve partial response (PR) in sintilimab arms, and sample size would be determined based on the ORR of the 1st.

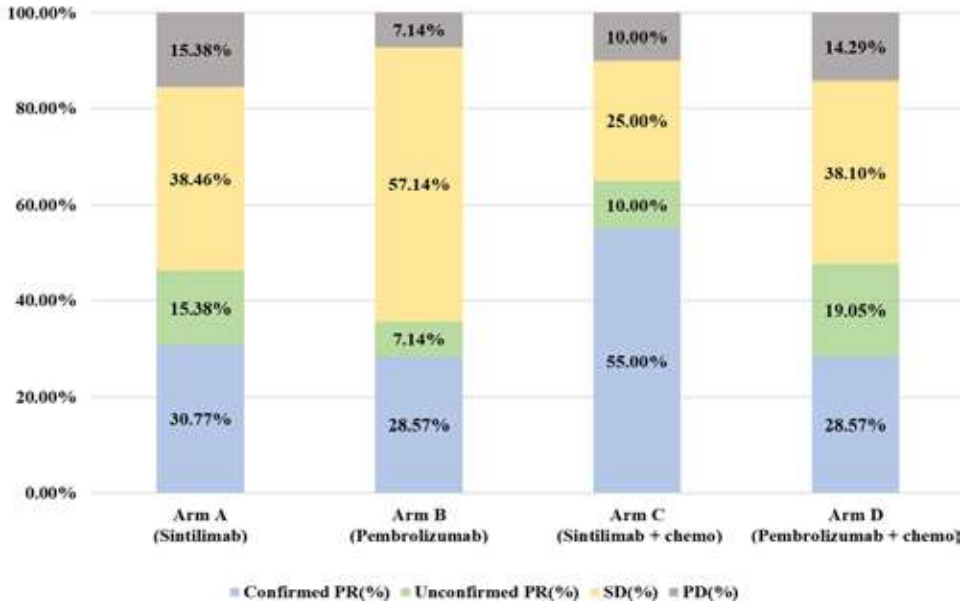
Results: The ORR of the 1st stage was 57.1% in sintilimab and 33.3% in pembrolizumab arms, thus the study successfully entered into the 2nd stage. From Mar. 2020 to Jan. 2022, a total of 68 patients were enrolled. Histologic subtypes and brain metastasis were well balanced between arms. Until Dec. 31st 2021, the median follow-up was 5.6 months. ORR was 57.6% in sintilimab arms vs. 42.9% in pembrolizumab arms, and the confirmed ORR was 45.5% (15/33) vs. 28.6% (10/35), separately. (Figure 1). The disease control rate was 87.9% vs. 91.4% in sintilimab and pembrolizumab arms, respectively. The primary endpoint was reached, with 15 confirmed PRs achieved in sintilimab arms. Survival data was still immature. Treatment-related adverse events were comparable between sintilimab and pembrolizumab arms (Table 1).

Conclusions: This head-to-head study of PD-1 inhibitors suggested comparable tumor response and similar safety profile between sintilimab and pembrolizumab.

Table 1: Baseline and safety summary in sintilimab and pembrolizumab arms.

	Arm A(Sintilimab)	Arm B(Pembrolizumab)	Arm C(Sintilimab + chemo)	Arm D(Pembrolizumab + chemo)
Histology (SQ/NSQ)	3/10	3/11	5/15	2/19
Brain metastasis (Y/N)	3/10	5/9	1/19	3/18
Any Grade TRAEs	100% (13/13)	100% (14/14)	100% (20/20)	100% (21/21)
3-4 Grade TRAEs	46% (6/13)	36% (5/14)	79% (15/50)	75% (15/21)

Figure 1: Tumor response in sintilimab and pembrolizumab arms.



Keywords: non-small cell lung cancer, PD-1 inhibitor, immunotherapy

WS08 JOINT IASLC-CSCO-CAALC SESSION: LIQUID BIOPSY IN ONCOGENE DRIVEN NSCLC (ON-DEMAND),
SATURDAY, AUGUST 6, 2022 - 21:00–23:59

WS08.10 Toripalimab in Combination with CIK Cells in Patients with Advanced NSCLC: An Exploratory Study

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Introduction: Immune checkpoint inhibitors (ICIs) act as a crucial treatment of advanced NSCLC (non-small cell lung cancer). In order to optimize patients' prognosis, combination therapies based on ICIs are being constantly explored. CIK (cytokine induced killer) therapy is one of the adoptive immune cell therapies, which has shown certain effects in previous clinical trials. The combination of ICIs and CIK therapy is theoretically synergistic, as PD-1 monoclonal antibody can restore the activity of T cells, and CIK cells are a subgroup of T cells. Previous studies on PD-1 monoclonal antibody combined with CIK cells in the treatment of metastatic renal cell carcinoma achieved better clinical effects, consistent to the hypothesis. Whether this combination can improve survival in advanced NSCLC remains unknown, calling for further research. This trial is a single-center, exploratory study, aiming to explore the safety and efficacy of toripalimab (240mg Q3W) in combination with CIK cells (Q6W) in NSCLC.

Methods: We recruited newly-diagnosed advanced NSCLC patients with positive PD-L1 expression (PD-L1>1%). Eligible patients are assigned to groups A, B and C: toripalimab + CIK (group A, n=20), toripalimab + CIK + chemotherapy (group B, n=20) and CIK+chemotherapy group (group C, n=20). The total number of CIK cells reinfused in each patient needs to be more than 10^{10}. The primary endpoint is safety and progression free survival (PFS). The secondary endpoints include overall response rate (ORR), disease control rate (DCR), and overall survival (OS). We will also conduct evaluation of biomarkers and characterize the role of PD-L1 and TMB in this combination therapy. Enrollment for this trial began in July, 2021 and will last 18 months in all.

Results: Until now, 25 patients have been enrolled. 9 (60%) of the 15 patients in group A achieved a partial response (PR), 4 (26.67%) had stable disease (SD). 3 (33.33%) of the 9 patients in group B achieved a partial response (PR), 5 (55.56%) had stable disease (SD). As the control group, group C has so far enrolled 1 patient.

Conclusions: Not applicable.

Keywords: advanced NSCLC, CIK, toripalimab

WS08 JOINT IASLC-CSCO-CAALC SESSION: LIQUID BIOPSY IN ONCOGENE DRIVEN NSCLC (ON-DEMAND),
SATURDAY, AUGUST 6, 2022 - 21:00–23:59

WS08.11 Entrectinib in Patients with ROS1 Fusion-Positive (ROS1-fp) NSCLC: Updated Efficacy and Safety Analysis

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Introduction: *ROS1* gene rearrangements can lead to constitutively active fusion proteins that are targetable oncogenic drivers in NSCLC. Entrectinib, a potent *ROS1* tyrosine kinase inhibitor (TKI), has demonstrated efficacy and CNS activity in patients with *ROS1*-fp NSCLC from the integrated analysis of the phase I/II studies STARTRK-1 (NCT02097810), STARTRK2 (NCT02568267) and ALKA-372-001 (EudraCT 2012-000148-8): objective response rate (ORR) was 67% (n=108/161; data cutoff: May 1, 2019; median duration of survival follow-up: 15.8 months). We present updated data from this ongoing analysis.

Methods: Adults with locally advanced/metastatic *ROS1*-fp NSCLC who received ≥1 dose of entrectinib and had ≥12 months of follow-up from first post-treatment initiation tumor assessment, were included in the efficacy analysis. The safety-evaluable population comprised all patients who received ≥1 dose of entrectinib. Tumor assessments (by blinded independent central review [BICR] per RECIST v1.1) were performed at the end of cycle 1 (Week 4) and then every 8 weeks. Primary endpoints: ORR and duration of response (DoR). Secondary endpoints included progressionfree survival (PFS), overall survival (OS), intracranial (IC)ORR, ICDoR, IC-PFS and safety. Efficacy endpoints were assessed by BICR. Enrolment cutoff: July 2, 2020; data cutoff: August 2, 2021.

Results: The efficacy-evaluable population comprised 172 patients with *ROS1*-fp NSCLC who were ROS1 TKI-naïve; median duration of survival follow-up: 37.8 months. Median age was 54.5 years (range 20-86); 61 patients (35%) were current/former smokers; 40 patients (23%) had received ≥2 prior lines of therapy; 60 patients (35%) had investigator-assessed baseline CNS metastases. Entrectinib demonstrated efficacy in patients with *ROS1*-fp NSCLC with and without investigator-assessed baseline CNS metastases (**Table**). In patients with BICR-assessed baseline CNS metastases (n=51), median IC-ORR was 49% (25/51; 95% CI 34.8-63.4); median IC-DoR was 12.9 months (95% CI 7.6-22.5); median IC-PFS was 12.0 months (95% CI 6.7-15.6). In patients who received entrectinib as first-line treatment (n=67; exploratory analyses; **Table**), ORR was 69% (95% CI 56.2-79.4), median DoR was 35.6 months (95% CI 13.9-38.8); median PFS was 17.7 months (95% CI 11.8-39.4). In the safety-evaluable population (N=247), most treatment-related adverse events (TRAEs) were Grade 1/2 (54%); 1 patient (<1%) died due to a TRAE. TRAEs leading to dose interruption, reduction and discontinuation occurred in 36%, 35% and 7% of patients, respectively.

Conclusions: In this updated analysis with longer follow-up and a larger patient population, entrectinib continues to demonstrate overall and intracranial efficacy, and a manageable safety profile in patients with *ROS1*-fp NSCLC.

ROS1 fusion-positive NSCLC				
	Overall efficacy-evaluable population (N=172)	**Baseline CNS metastases* (n=60)**	**No baseline CNS metastases* (n=112)**	**First-line cohort (n=67)**
ORR, n (%) [95% CI]	116 (67.4) [59.9-74.4]	38 (63.3) [49.9-75.4]	78 (69.6) [60.2-78.0]	46 (68.7) [56.2-79.4]
Best overall response, n (%)				
CR	23 (13.4)	4 (6.7)	19 (17.0)	10 (14.9)
PR	93 (54.1)	34 (56.7)	59 (52.7)	36 (53.7)
SD	16 (9.3)	6 (10.0)	10 (8.9)	7 (10.4)
PD	16 (9.3)	8 (13.3)	8 (7.1)	5 (7.5)
Non CR/PD	10 (5.8)	2 (3.3)	8 (7.1)	6 (9.0)
Missing/unevaluable	14 (8.1)	6 (10.0)	8 (7.1)	3 (4.5)
Median time-to-event, months (95% CI)				
DoR	20.4 (14.8-34.8)	14.6 (11.0-20.4)	28.6 (14.9-38.6)	35.6 (13.9-38.8)
PFS	16.8 (12.2-22.4)	11.8 (7.2-15.7)	25.2 (15.7-36.6)	17.7 (11.8-39.4)
OS	44.1 (40.1-NE)	28.3 (17.0-44.6)	NE (41.8-NE)	NA

*Investigator-assessed CNS metastases; CI, confidence interval; CR, complete response; NA, not available; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease

Keywords: ROS1 fusions, NSCLC, Entrectinib

WS08 JOINT IASLC-CSCO-CAALC SESSION: LIQUID BIOPSY IN ONCOGENE DRIVEN NSCLC (ON-DEMAND),
SATURDAY, AUGUST 6, 2022 - 21:00–23:59

WS08.13 Activity of aPD1-MSLN-CART Cells Against Metastatic Lung Cancer in a Phase 1 Trial

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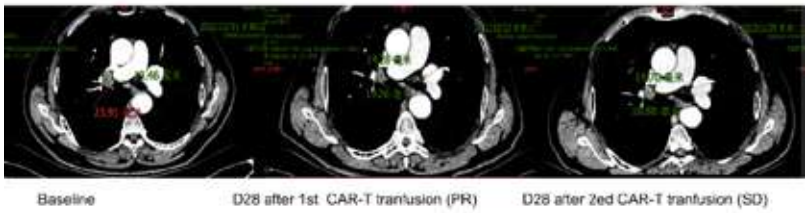
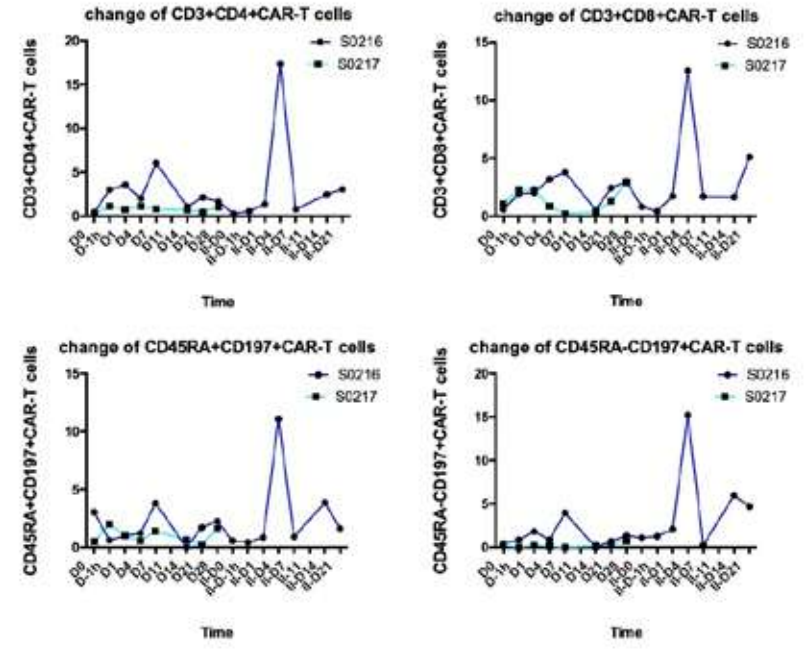
Introduction: Mesothelin (MSLN) has been found to be highly expressive in multiple solid tumors including lung cancer. We engineered autocrine PD-1 nano antibodies MSLN CAR-T cells (aPD1-MSLN-CART), targeting MSLN positive tumor cells by chimeric antigen receptor-modified T (CAR-T) cells as well as secretion of PD1 antibodies, playing dual antitumor immune mechanism.

Methods: We performed a phase 1 study to evaluate the safety and efficacy of adoptive cell therapy with aPD1-MSLN-CART in 5 patients with chemotherapy-refractory metastatic lung cancer. Patients were given intravenous aPD1-MSLN-CART cells at most two cycles.

Results: A total of 40 patients have been screened, 5 cases have been successfully enrolled in the group, 2 cases have completed 1 cycle transfusion and 2 cases completed 2 cycles, 1 case withdraw before transfusion. None of the patients developed cytokine release syndrome or neurologic symptoms and there were no dose limiting toxicities. Partial response in 1 patient, disease stable in 2 and with 1 progression disease. Transient CAR expression was detected in patients' blood after infusion and led to change of CD3+CD4+CAR-T and CD3+CD8+CAR-T cells as well as cytokines IL-6, IL-10, INF-γ and TNF-α.

Conclusions: Our results provide evidence for the potential anti-tumor activity of aPD1-MSLN-CART cells in chemotherapy-refractory metastatic lung cancer.





Keywords: CAR-T, mesothelin, lung cancer

WS08 JOINT IASLC-CSCO-CAALC SESSION: LIQUID BIOPSY IN ONCOGENE DRIVEN NSCLC (ON-DEMAND),
SATURDAY, AUGUST 6, 2022 - 21:00–23:59

WS08.14 Final Analyses of ALTER-L018: A Randomized Phase II Trial of Anlotinib Plus Docetaxel vs Docetaxel as 2nd-line Therapy for EGFR-Negative NSCLC

L. Wu[1], Z. Wu[2], Z. Xiao[2], Z. Ma[3], J. Weng[4], Y. Chen[5], Y. Cao[6], P. Cao[7], M. Xiao[8], H. Zhang[9], H. Duan[10], Q. Wang[1], J. Li[1], Y. Xu[1], X. Pu[1], K. Li[1]

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Introduction: Docetaxel is one of the standard 2nd-line treatments for advanced non-small cell lung cancer (NSCLC), but the effect is limited. The combination of docetaxel and ramucirumab/nintedanib has demonstrated antitumor activity as 2nd-line therapy in advanced NSCLC. Anlotinib, an oral multi-target angiogenesis, can prolong both PFS and OS of refractory advanced NSCLC patients in phase III trial (ALTER0303). We conducted ALTER-L018 to evaluate improvement of the efficacy and safety of anlotinib plus docetaxel in EGFR-negative advanced NSCLC.

Methods: In this multi-center, randomized, controlled comparative, phase II trial, patients from 10 sites in China, with EGFR wild-type NSCLC progressing after 1st-line platinum-based therapy (combined with or without Immune checkpoint inhibitors), were randomly allocated (1:1) to receive anlotinib (12mg QD from day 1 to 14 of a 21-day cycle) plus docetaxel (75mg/m^2 Q3W) (group A+D) or docetaxel (75mg/m^2 Q3W) only (group D). Primary end point was PFS, and secondary end points included OS, ORR, DCR and safety. [Clinical Trials Registration: NCT03624309].

Results: Between Jan 14, 2019, and Jun 18, 2021, 96 patients (pts) were enrolled and 13 pts were excluded due to inclusion violations. At data cutoff (Feb 24, 2022), 83 pts. (demographics are shown in Table 1) were available for efficacy and safety analysis. The median PFS in group A+D was significantly improved compared with group D [4.36m (95%CI: 2.78-5.94) vs 1.64m (95%CI: 1.48-1.80); HR 0.38 (95%CI: 0.22-0.65), p<0.001)]. The median OS was 11.97m (95%CI: 3.08-20.86) in group A+D and 10.85m (95%CI: 5.44-16.26) in group D [HR 0.82 (95%CI: 0.45-1.47), p=0.501)]. For tumor response, ORR were 35.14% vs 9.52% (p=0.007) and DCR were 83.78% vs 54.76% (p=0.006) in group A+D and group D, respectively. We noted treatment-related adverse events (TRAEs) of grade 3 or above occurred in in 12 (30.0%) of 40 pts in group A+D safety population and 8 (18.6%) of 43 pts in group D safety population. The most common grade 3 or worse TRAEs were Leucopenia (15.0% vs 7.0%), Neutropenia (10.0% vs 4.7%) in group A+D and group D, respectively. The toxicities in both groups were manageable with appropriate dose reductions and supportive care.

Conclusions: The combination of anlotinib plus docetaxel improves survival as second-line treatment of EGFR wild-type NSCLC patients in terms of PFS, ORR, DCR, and has a manageable safety profile. It has been proved to be an effective regimen for EGFR wild-type NSCLC patients progressing after first-line platinum-based chemotherapy combined with Immune checkpoint inhibitors.

Table 1 Demographics

	Group A+D (anlotinib + docetaxel) (n=40)	Group D (docetaxel) (n=43)
Median age, years	54 (40-71)	58 (39-74)
Age group, years, n (%)		
< 60	27 (67.50)	26 (60.47)
≥ 60	13 (32.50)	17 (39.53)
Sex, n (%)		
Men	33 (82.50)	35 (81.40)
Women	7 (17.50)	8 (18.60)
Disease stage, n (%)		
III	9 (22.50)	4 (9.30)
IV	31 (77.50)	39 (90.70)
ECOG PS, n (%)		
0	13 (32.50)	9 (20.93)
1	27 (67.50)	34 (79.07)
Histologic subtype, n (%)		
ADC	26 (65.00)	26 (60.47)
Non-ADC	14 (35.00)	17 (39.53)
Smoking history, n (%)		
Never smoker	10 (25.00)	12 (27.91)
Former smoker	24 (60.00)	23 (53.49)
Current smoker	6 (15.00)	8 (18.60)
History of prior therapy, n (%)		
platinum-based chemotherapy with ICIs	15 (37.50)	17 (39.53)
platinum-based chemotherapy	25 (62.50)	26 (60.47)
Brain metastasis, n (%)		
Yes	5 (12.50)	5 (11.63)
No	35 (87.50)	38 (88.37)

* Data Cut-off: Feb 24, 2022

Keywords: anlotinib, EGFR-negative NSCLC, second-line treatment

WS08 JOINT IASLC-CSCO-CAALC SESSION: LIQUID BIOPSY IN ONCOGENE DRIVEN NSCLC (ON-DEMAND),
SATURDAY, AUGUST 6, 2022 - 21:00–23:59

WS08.15 Safety and Efficacy of Sitravatinib + Tislelizumab in Patients with PD-L1+, Locally Advanced/Metastatic, Squamous NSCLC

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Introduction: Patients with programmed death-ligand 1 positive (PD-L1+), locally advanced or metastatic, squamous non-small cell lung cancer (NSCLC) have a poor prognosis and more effective treatments with better tolerability profiles are needed. Sitravatinib, a selective tyrosine kinase inhibitor, reduces the number of myeloid-derived suppressor cells and regulatory T cells, which promotes expansion and migration of antitumor cytotoxic T cells, and increases the ratio of M1/M2-polarized macrophages. Tislelizumab, an anti-programmed cell death protein 1 (PD-1) antibody engineered to minimize binding to FcγR on macrophages, has shown clinical activity in patients with advanced solid tumors, including NSCLC. This Phase 1b study assessed safety, tolerability, and antitumor activity of sitravatinib and tislelizumab in advanced solid tumors (NCT03666143). We present results from patients with PD-L1+, squamous NSCLC.

Methods: This was an open-label, non-randomized study. Eligible patients had PD-L1+, locally advanced or metastatic, squamous NSCLC without prior systemic treatment in the metastatic setting and without prior exposure to immunotherapy, including anti-PD-1/PD-L1, anti-CTLA-4, anti-OX40 and anti-CD137. Patients with a documented *EGFR* mutation, *ALK/ROS1* rearrangement, or *BRAF* mutation were not eligible. Patients received sitravatinib 120 mg orally once daily plus tislelizumab 200 mg intravenously every three weeks until unacceptable toxicity, withdrawal, or death. The primary endpoint was safety/tolerability. Secondary and exploratory endpoints included investigator-assessed objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and PD-L1 expression and the association with clinical benefit. Tumor response was assessed using RECIST v1.1. PD-L1+ was defined as PD-L1 staining on ≥ 1% of tumor cells (VENTANA SP263 immunohistochemistry assay).

Results: Between May 12, 2020 and February 10, 2021, 24 patients were enrolled. All patients were included in the safety analysis set, and 23 patients in the efficacy evaluable analysis set. The median age was 65.0 years (range: 56-71), and 91.7% of patients were male. Median study follow-up was 9.5 months (range: 0.4-16.2). At the data cut-off (November 8, 2021) treatment-emergent adverse events (TEAEs) of any Grade/≥ Grade 3 were reported in 95.8%/66.7% of patients. Serious TEAEs were observed in 50.0%, and the most common ≥ Grade 3 TEAE was hypertension (16.7%). A total of two TEAEs led to death, death and pneumonia and were not considered to be treatment related. In total, 70.8%/41.7% patients required dose modification of sitravatinib/tislelizumab due to TEAEs, respectively. Treatment-related AEs (TRAEs) of any Grade/≥ Grade 3, were observed in 91.7%/62.5% of patients. Serious TRAEs were reported in 37.5% of patients, and the most common ≥ Grade 3 TRAE was hypertension (16.7%). Confirmed ORR was 30.4% (95% confidence interval [CI]: 13.2, 52.9), with all seven patients achieving partial response. DCR was 78.3% (95% CI: 56.3, 92.5), median PFS was 5.4 months (95% CI: 2.8, 8.6), and median OS was not reached (95% CI: 6.7, not estimable).

Conclusions: Sitravatinib plus tislelizumab demonstrated a manageable safety and tolerability profile as well as antitumor activity in patients with PD-L1+, locally advanced or metastatic squamous NSCLC who had not received prior systemic treatment in the metastatic setting.

Keywords: sitravatinib, tislelizumab, NSCLC

WS08 JOINT IASLC-CSCO-CAALC SESSION: LIQUID BIOPSY IN ONCOGENE DRIVEN NSCLC (ON-DEMAND),
SATURDAY, AUGUST 6, 2022 - 21:00–23:59

WS08.16 The Increase of Blood Intratumor Heterogeneity is Associated with Unfavorable Outcomes of ICIs Plus Chemotherapy in NSCLC

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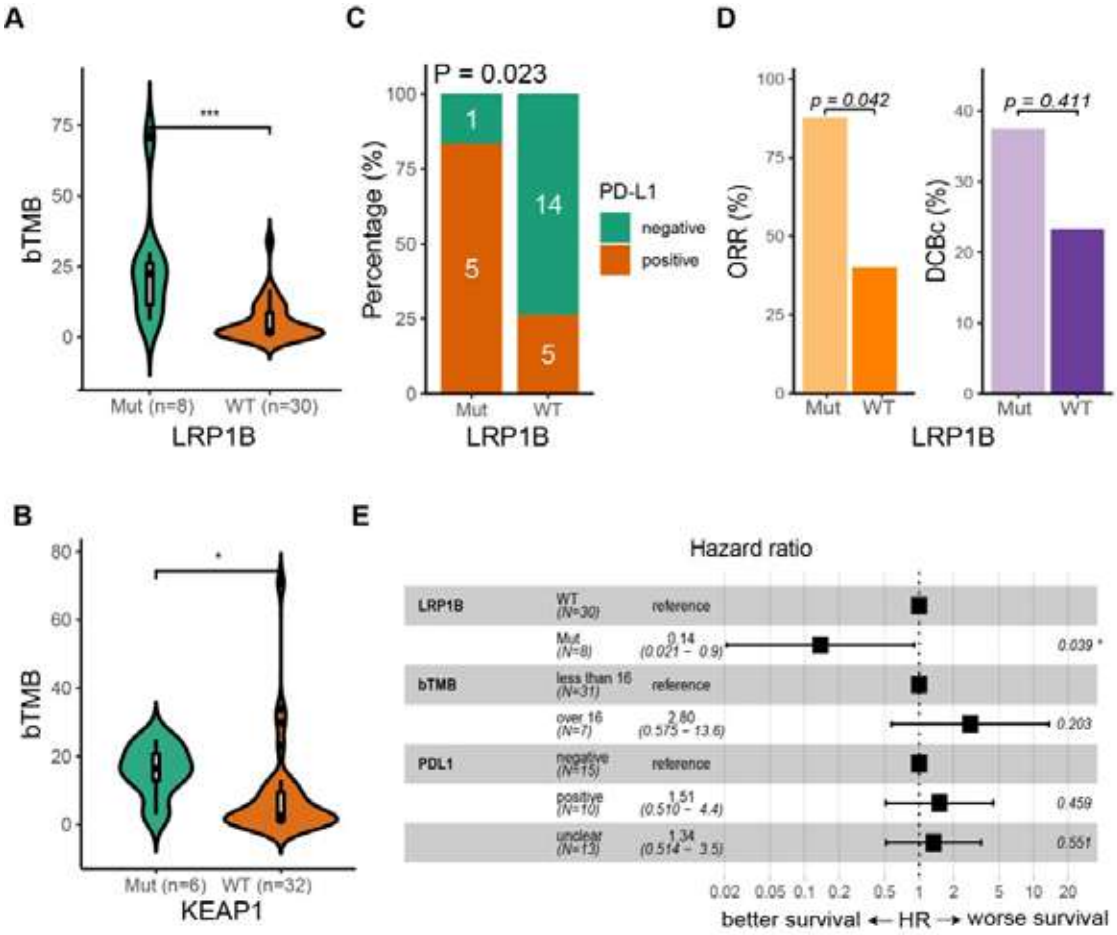
Introduction: The combination of immune checkpoint inhibitors (ICIs) and chemotherapy has been the standard first-line treatment for advanced non-small cell lung cancer (NSCLC) patients with driver-gene negative. However, efficacy biomarker for ICIs-based combination therapy is lacked. We aimed to identify potential factors associated with outcomes of ICIs plus chemotherapy at baseline and dynamic changes in peripheral blood.

Methods: We collected plasma samples of 51 advanced NSCLC patients without EGFR/ALK/ROS1 alteration at baseline and/or after two treatment cycles of ICI plus chemotherapy. NGS targeted sequencing was then performed using a 520-gene panel (OncoScreen PlusTM) in Burning Rock Biotech, a commercial clinical laboratory which has demonstrated impressive performance SEQC2 liquid biopsy program (Nat Biotechnol, 2021). We utilized a weighted Shannon diversity index (SDI) suitable for blood to evaluate intratumor heterogeneity (ITH), which we called blood-based ITH (bITH). bITH up was defined as a ≥ 10% increase in bITH score from baseline, with a second confirmatory measurement after treatment.

Results: At baseline, neither bITH, nor other common biomarkers, including ctDNA level, blood-based tumor mutational burden (bTMB) and PD-L1 expression, was associated with progression-free survival (PFS) of ICIs plus chemotherapy. LRP1B mutation at baseline was significantly associated with favorable outcomes to ICIs plus chemotherapy. There were 37 patients who had paired samples at baseline and after two cycles treatment, with the median interval of 53 days. However, in this study, no significant difference was found in PFS between patients with and without ctDNA clearance, or between patients with and without MSAF drop. Intriguingly, patients with bITH up had significant shorter PFS (HR, 4.92; 95% CI, 1.72-14.07; P = 0.001), and lower durable clinical benefit (DCB) rate (0 vs 41.38%, P = 0.036) than those with bITH stable or down. Moreover, we found that all seven patients with progressive disease (PD) after two cycles treatment have increased bITH score and seven of eleven (63.6%) of patients with increased bITH were confirmed to have PD to treatment. Cases studies showed that MSAF was decreased but bITH was increase in two patients with PD and bITH-up was detected before radiography in one patient, which indicated that bITH was a promising biomarker to predict disease progression.

Conclusions: The present study is the first to report that the increase of bITH is associated with unfavorable outcomes of ICIs plus chemotherapy in advanced NSCLC patients.



Keywords: non-small cell lung cancer, immune checkpoint inhibitors, blood-based intratumor heterogeneity

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WS08.17 Utilization of Tumor Mutational Profiling to Identify the Immunotherapy Response in Non-small Cell Lung Cancer

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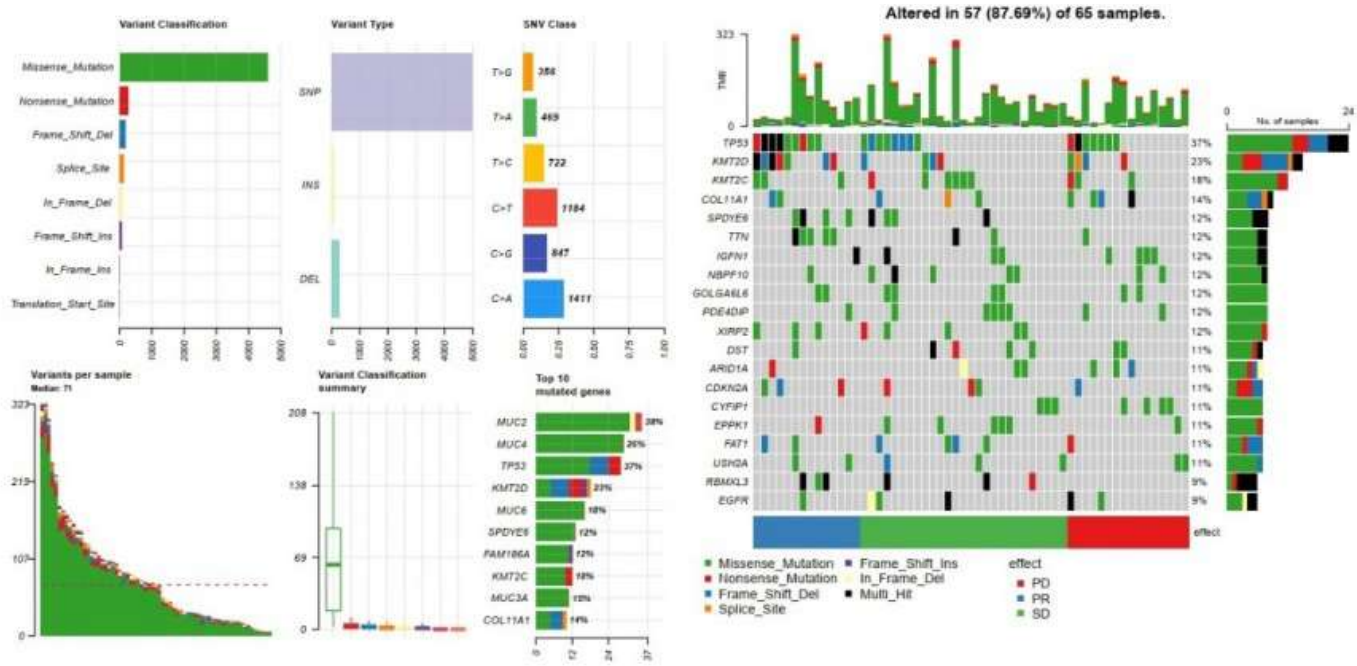
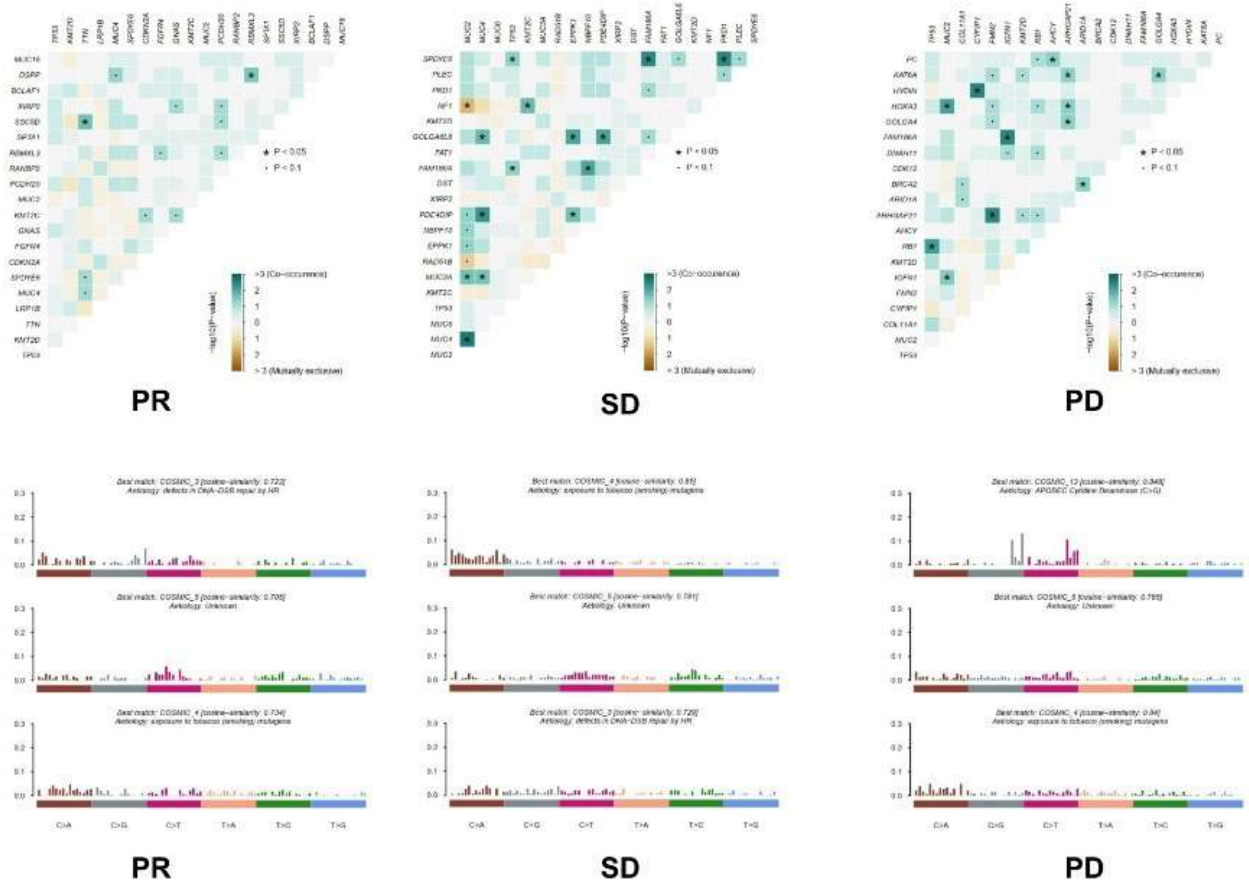
Introduction: Immune checkpoint inhibitors targeted programmed cell death 1 (PD-1) and its ligand (PD-L1) elicit durable clinical benefit and shift the paradigm in non-small cell lung cancer (NSCLC). The identification of biomarkers that can predict the immunotherapy response is still an unmet need in clinical practice. We explore the genomic profiling of NSCLC with immunotherapy.

Methods: 65 histologically confirmed NSCLC patients received immunotherapy were included and basline tumor specimens were collected from the Cancer Institute and Hospital, Chinese Academy of Medical Sciences. Tumor specimens including 15 partial response (PR), 30 stable disease (SD) and the other 20 progressive disease (PD) were assessed on the basis of the RECIST V1.1. Whole-exome sequencing and targeted sequencing were applied to 43 and 22 tumor tissues respectively.

Results: The dominant bases substitution was C>A transversions associated with smoking. TP53, KMT2D, and KMT2C were the frequently mutated genes which detected in more than 20% cases. The co-occurrence mutation of SSC5D and TTN, DSPP and RBMXL3 occurred in PR group; co-mutation of SPDYE6 and TP53/ FAM186A/ PKD1,NF1 and KMT2C, GOLGA6L6 and EPPK1/ PDE4DIP, FAM186A and TP53/ NBPF10, PDE4DIP and EPPK1 were shown in patients with SD; TP53 and RB1, CYFIP1 and HYDIN, ARHGAP21 and FMN2, FAM186A and IGFN1, AHCY and PC, ARHGAP21 and KAT6A/ HOXA3/ GOLGA4, ARID1A and BRCA2, GOLGA4 and KAT6A co-mutation were mainly detected in PD patients. The most relevant mutational signature in PR and SD group was signature 4 associated with direct exposure to tobacco mutagens, and in PD group was APOBEC Cytidine Deaminase (C>G).

Conclusions: The mutational features in tumor DNA of NSCLC patients with response (PR+SD) to immunotherapy were different from that without response (PD). The co-mutation of SSC5D and TTN, DSPP and RBMXL3 may be helpful in identifying the response to immunotherapy and making the personal treatment in NSCLC.





Keywords: non-small cell lung cancer, immunotherapy, tumor mutational profiling

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WS08.19 Phase II Trial of Neoadjuvant Tislelizumab with Chemotherapy for Resectable Stage IIB-III Non-small Cell Lung Cancer

Y-B. Lin[1], H. Long[1], Y-H. Chen[2], W-Y. Zhai[1], Y-Z. Wang[1], B-Y. Rao[1]

[1]Sun Yat-Sen University Cancer Center, Guangzhou/CN, [2]Sun Yat-sen University, Guangzhou/CN

Introduction: Preoperative immunotherapy has been shown to be promising in treating resectable NSCLC. The current study aimed to investigate the activity and safety of neoadjuvant chemoimmunotherapy with PD-1 inhibitor, tislelizumab, for resectable stage IIB-III NSCLC in Asian population.

Methods: This was an open-label, multicenter, single-arm phase 2 trial done at 3 hospitals in China. Eligible patients recruited were aged 18 years or older with histologically confirmed AJCC-defined stage IIB-III NSCLC deemed surgically resectable. Patients received 3~4 cycles of neoadjuvant treatment with intravenous tislelizumab (200mg), carboplatin (area under curve 5), and pemetrexed (500 mg/m^2 for adenocarcinoma) or nab-paclitaxel (260mg/m^2 for others) on day 1 of each 21-day cycle. Surgical resection was performed 4-6 weeks afterward. The primary end point was the incidence of treatment-related adverse events (TRAEs; within 90 d after first dose of tislelizumab plus chemotherapy or 30 d after operation). The major pathological response (MPR), defined as less than 10% residual tumor remaining at the time of surgery, and disease-free survival were also assessed in modified intention-to-treat population. Molecular markers, including PD-L1 expression, TMB, etc. on efficacy and adverse reactions of such chemoimmunotherapy were explored in tissue, blood and stool samples. This study is registered with ClinicalTrials.gov, NCT05244837.

Results: Between December 2020 and December 2021, 37 patients (median age:63, IQR:45-77; female:6 16.2%) were enrolled, of whom 33 (89.2%) had stage III disease, and received neoadjuvant treatment. Twenty-nine (78.4%) patients had squamous cell lung cancer. During neoadjuvant treatment period, a total of 34 patients (91.9%) experienced neoadjuvant TRAEs. The most common TRAEs were alopecia (n=23;62.2%), anemia (n=16;43.2%), rash (n =18; 48.6%) and increased ALT/AST (n =10; 27.0%). Most of the TRAEs were grade 1or 2. One patient (2.7%) experienced severe TRAE of grade 3 increased ALT/AST and decreased white blood cell count. No grade 4 or 5 TRAEs was observed. Among 37 enrolled patients, 27 (73.0%) patients had received surgical resection, of whom 26 (96.0%) achieved R0 resection. Twenty-two of those 27 patients (81.5%) had an MPR, including 13 (13/27, 48.1%) with a pathological complete response (pCR).

Conclusions: Tislelizumab plus platinum-based doublet chemotherapy yields a high MPR rate, manageable treatment-related toxicity, and feasible surgical resection in stage IIB-III NSCLC. Ongoing analysis of predictive biomarker on efficacy and adverse reactions will be available at the meeting.

Keywords: Neoadjuvant treatment, Chemoimmunotherapy, Tislelizumab

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WS08.20 Comprehensive Analysis of a Dendritic Cell Marker Genes Signature to Predict Prognosis and Immunotherapy Response in Lung Adenocarcinoma

Y. Li, P. Song, F. Bie, M. Zhang, S. Gao, J. He

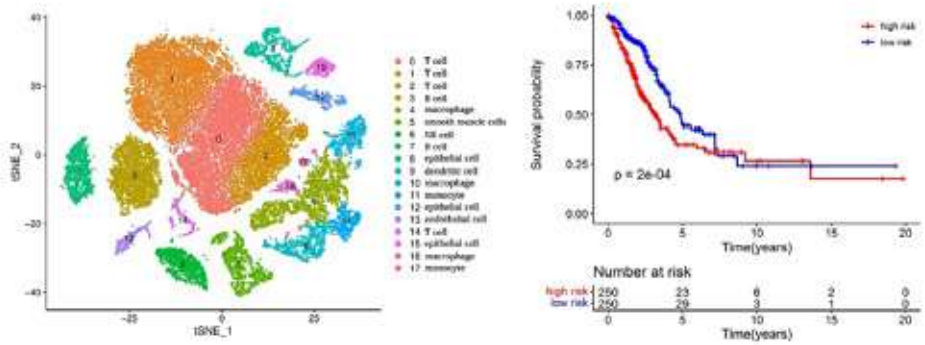
National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing/CN

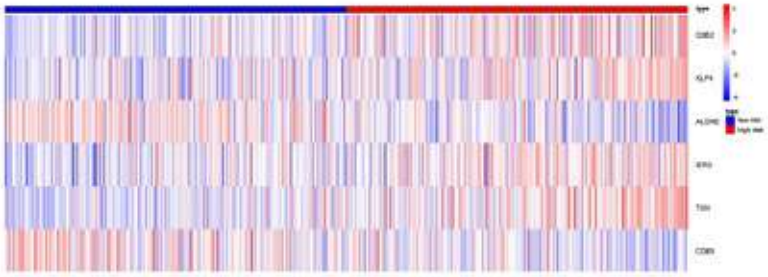
Introduction: With the development of immunotherapy, the treatment of lung adenocarcinoma (LUAD) has gradually stepped into a new stage. Dendritic cells (DCs), a central role in initiating, regulating and maintaining the immune response, exert complicated and important functions in antitumor immunity. This study aims to construct a novel prognostic dendritic cell marker genes signature (DCMGS) for LUAD.

Methods: DC marker genes in LUAD was identified by analysis of single cell RNA sequence data from 11 LUAD samples. DCMGS was constructed on a training cohort from TCGA LUAD dataset. Another six independent cohorts from GEO database were used to validate the predictive ability.

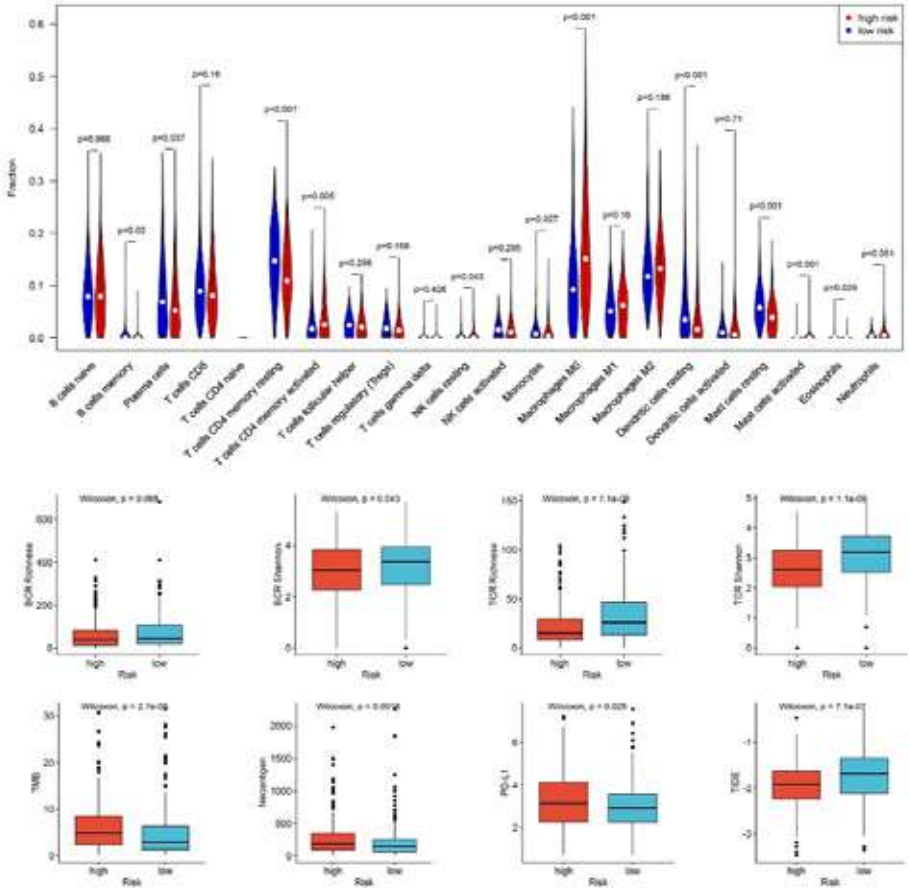
Results: 121 DC marker genes were identified from scRNA-seq data of 11 LUAD samples. Based on these genes, six genes (*G0S2, KLF4, ALDH2, IER3, TXN, CD69*) were screened as the most prognosis-related genes for constructing DCMGS through Cox proportional hazards regression analysis and LASSO analysis. Patients were divided into high- and low-risk groups by DCMGS risk score based on overall survival time. The strong predictive ability of this model for LUAD was validated on another six cohorts. DCMGS was verified to be an independent prognostic factor. Furthermore, we performed pathway enrichment and biological process analysis to explore possible biological mechanism of the powerful predictive ability of DCMGS, and immune cell infiltration landscape and inflammatory activities were exhibited to reflect the immune profile of LUAD with different risk scores. Notably, we linked DCMGS to biomarkers that have been shown to predict immunotherapeutic response, such as TMB, neoantigen load, PD-L1 and TIDE score.

Conclusions: DCMGS was suggested to be a promising prognostic indicator for LUAD and a desirable predictor for immunotherapeutic response, which can serve as an important complement to immunotherapy to further optimize individualized tumor therapy for LUAD patients.





Groups	Hazard Ratio (95% CI)	P value
GSE11969	2.225(1.084-4.566)	0.0250
GSE30219	1.900(1.042-3.463)	0.0320
GSE31210	2.630(1.231-5.617)	0.0094
GSE37745	2.280(1.136-4.575)	0.0170
GSE41271	2.573(1.448-4.570)	0.0008
GSE50081	2.541(1.323-4.882)	0.0038
Overall	2.332(1.783-3.021)	<0.0001



Keywords: Lung adenocarcinoma, Dendritic cell mark genes, Prognostic signature

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WS08.21 Immune Evolution of Metastases & Underlying Molecular Mechanisms in Non-small Cell Lung Cancer

W-F. Tang[1], R. Fu[2], X-J. Fan[3], H. Bao[3], M. Wu[3], X. Wu[3], Y. Shao[3], Z-B. Qiu[2], J. Su[2], Y-L. Wu[2], Y. Liang[1], W-Z. Zhong[2]

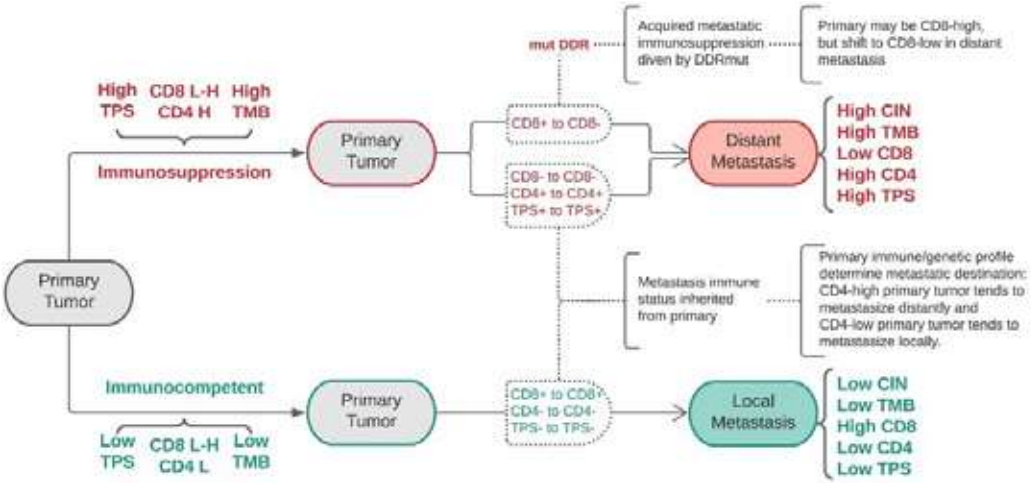
[1]Department of Cardiothoracic Surgery, Zhongshan City People's Hospital, Zhongshan/CN, [2]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou/CN, [3]Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing/CN

Introduction: Immune profile is a key player for cancer development and metastasis. However, the understanding of the evolution of immune profile from primary non-small cell lung cancers (NSCLC) to metastases and the underlying molecular mechanisms, as well as the difference of immune evolution in local metastasis and distant metastasis is limited so far.

Methods: We performed whole-exome sequencing and immunohistochemistry of CD8, CD4 and PD-L1 for 73 samples including 29 primary, 9 lymph nodes, 9 local (pleural) and 26 distant (brain, bone and adrenal gland) metastases from 41 NSCLC patients. The change of immune profile from primary tumors to metastases and associated genetic factors were analyzed by mutation and copy number alteration analysis, clonal evolution, mutation signature and adaptive selection analysis. The association of genetic and immune background of primary tumors and metastatic destinations were investigated.

Results: DNA damage repair (DDR) deficiency drives distant metastasis rather than local metastasis of NSCLC. Mutations in the DDR pathway underwent positive selection in the metastases. Distant metastases had significantly decreased CD8+ T cell level along with increased chromosomal instability compared with primary tumors which was partially ascribed to the DDR deficiency acquired during metastasis. Local metastases and distant metastases had different immune profiles. Distant metastases were characterized by immunosuppression (low CD8+ T cell level) and immune evasion (high PD-L1 level) whereas local metastases (pleura) were immune-competent with high CD8+ T cell, low CD4+ T cell and low PD-L1 level. The genetic and immune background of primary tumors including tumor mutation burden (TMB), CD4+ T cell level and PD-L1 level was associated with metastatic destinations. Primary tumors with high TMB, high CD4+ T cell and high PD-L1 were associated with distant metastases rather than local metastases. Furthermore, primary tumors with positive CD8 and negative CD4 were associated with a better progression-free survival (PFS). However, patients undergoing CD8 positive-to-negative (primary-to-metastatic tumor) conversion had a worse PFS. A model was put forward to explain the evolution of immune profile from primary to metastasis and the difference between local and distant metastases.

Conclusions: Acquired DDR deficiency is responsible for increased chromosomal instability in distant metastases of NSCLC. CD8 level is negatively correlated with chromosomal instability and decreased in distant metastases. Distant metastases and local metastases had different immune profiles. Immune and genetic background of primary tumors may affect metastatic destinations.



Keywords: metastasis, cancer evolution, tumor immune microenvironment

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WS08.22 Neoadjuvant Toripalimab Combination in Patients with Stage IIB-IIIB NSCLC: A Single-arm, Phase 2 Trial (Renaissance Study)

S. Yan, J. Chen, J. Wang, C. Lv, J. Bi, X. Yang, S. Li, Y. Wang, X. Li, Y. Yang, N. Wu
Peking University Cancer Hospital & Institute, Beijing/CN

Introduction: PD-1 inhibitors have displayed potential anti-tumor activities in non-small cell lung cancer (NSCLC). Here we conducted a single center, prospective study to investigate the efficacy and safety of neoadjuvant toripalimab (the first PD-1 inhibitor from china) plus double platinum-based chemotherapy for stage IIB-IIIB NSCLC.

Methods: Study eligibility involved stage IIB-IIIB, wildtype EGFR/ALK NSCLC pts with ECOG PS 0-1 status. Pts received 2-4 cycles of toripalimab (240mg, q3w) plus cisplatin-based chemotherapy. All pts were assessed by imaging/surgical indication after the second cycle of treatment. Pts who cannot undergo surgery will be reassessed after another 1-2 cycles of neoadjuvant therapy. Primary endpoints were major pathological response (MPR), complete pathological response (pCR). Secondary endpoints were objective response rate (ORR), R0 resection rate and safety. Clinical trial information: NCT04606303.

Results: A total of 53 eligible pts (median age: 62, IQR: 45-76; female: 5, 9.4%; squamous cell carcinoma: 42, 79.2%) were enrolled and received 2-4 cycles neoadjuvant treatment since Mar 2021. Disease distribution in stage IIB, IIIA and IIIB consisted of 15, 30 and 8 pts, respectively. 15 pts were in the preoperative stage or unsuitable for surgery. 39 pts underwent resection (median interval between neoadjuvant treatment and surgery: 67 days, IQR: 39-113). 25 pts (25/39, 64.1%) achieved MPR, including 20 pts (20/39, 51.3%) with pCR. R0 resection was achieved in all 39 pts (100%). 29 pts underwent surgery with cN2/N1 at baseline (29/31, 93.5%) achieved nodal downstaging. 49 pts finished the treatment schedule and radiological reassessment, ORR was 85.7% (42/49). Grade 1-2 TRAEs were reported in 46 pts (46/49, 93.9%). Grade 3-4 TRAEs were reported in 15 pts (15/49, 30.6%). Of the pts who underwent surgery, 3 pts (3/39, 7.7%) experienced grade 2-3 irAE (enteritis or rash) and received glucocorticoid therapy. Interestingly, all these 3 pts achieved pCR, and the median interval between neoadjuvant treatment and surgery was 56 days (IQR: 56-70). Compared with all pts underwent surgery, there were no treatment-related surgical delay and additional surgery difficulty for these 3 pts. It may suggest that pts who experienced grade 2-3 irAEs have a better pCR rate (100% vs 47.2%). Of the pts who were preparing or unsuitable for surgery, 2 pts experienced grade 2-3 irAE (enteritis or pneumonia) and received glucocorticoid therapy, 1 had partial response (PR) after neoadjuvant treatment and maintained stable disease (SD) after 10 months of observation, another had clinical complete response (cCR) after neoadjuvant treatment. Of all 5 pts who experienced irAEs and received glucocorticoid therapy, the median onset time of irAE was 12 days (IQR: 7-54), the median duration time of glucocorticoid therapy was 12 days (IQR: 7-79).

Conclusions: Neoadjuvant toripalimab plus platinum-based doublet is a promising, tolerable and effective treatment for pts with stage IIB-IIIB NSCLC. Interestingly, a potential correlation between grade 2-3 irAE and the efficacy of neoadjuvant toripalimab combination was observed. And we are looking forward to a more complete and solid correlation.

Keywords: Neoadjuvant, PD-1 inhibitor, NSCLC

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WS08.23 Transcriptomic Heterogeneity in Non-Small Cell Lung Cancer with Four Structure-Based EGFR-Mutation Subgroups

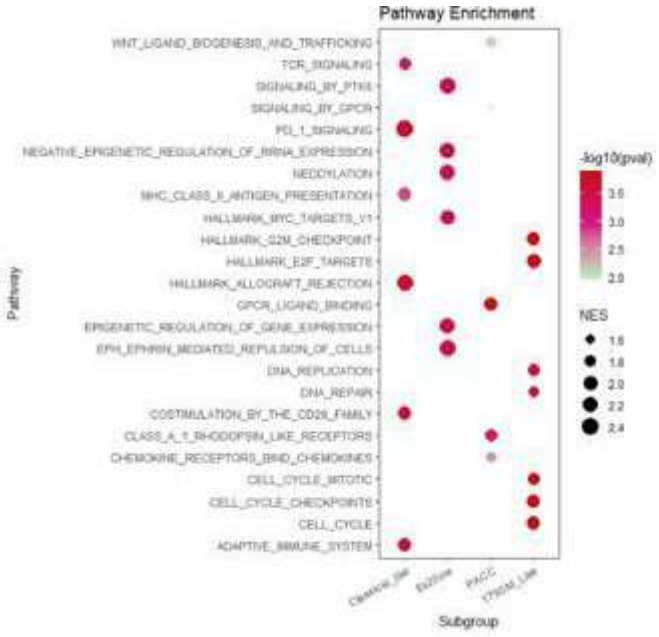
L. Gu, Y. Yu, L. Shen, F. Yao, C. Zhu, J. Wang, S. Lu
Shanghai Chest Hospital, Shanghai/CN

Introduction: EGFR mutations were classified into four subtypes (Classical-like, P-loop and αC-helical compressing (PACC), T790M-like, and exon 20 loop insertions) based on unique structures as Jacqulyne previously reported (Nature, 2021).Thus, EGFR mutant non-small cell lung cancer (NSCLC) should be considered as a heterogeneous disease. And there is clearly an unmet need understanding the biology trait of NSCLC with distinct EGFR mutation subtypes.

Methods: Total 2731EGFR mutant NSCLC patients with available next-generation sequencing results were retrospectively reviewed. 119 patients with 1813-gene expression data were further analyzed to compare biological difference. Gene-set enrichment analysis was conducted using the Cluster Profiler package in R 4.0.5.

Results: Total 2731 patients were divided into classic Classical-like group (n=2242, 82.09%), PACC (n=140, 5.13%), T790M-like (n=292, 10.69%), Ex20ins (n=57, 2.08%). 544 patients were included for co-occurrence of genomic alterations analyzing, TP53 was the most common co-occurring mutation in the four distinct subgroups, especially in 60% of T790M-like subgroups. However, APC mutations were mutually exclusive in Ex20ins group. Moreover, transcriptomic heterogeneity was first of time observed in the four subgroups. Classical-like group displayed enrichment of immune-related pathways in REACTOME, including PD1 signaling, CD28 family, and TCR signaling. PACC subgroup, these tumors displayed activation and triggering the G-protein-coupled receptors (GPCRs) signaling cascade towards a cellular event. For the T790M-like group, cell cycle related pathways like E2F targets, and cell cycle checkpoints (G2M) were significant upregulation. Ex20ins subgroup was characterized as enrichment of oncogenic process including PTK6, MYC activation, epigenetic regulation of gene expression as well as NEDDylation. Subsequently, the immune characteristics of tumors with different subtypes were investigated. Along with pathway analysis, classical subgroups displayed highest T cell infiltration. And PACC group showed highest level of protumor cytokine. Among Classical-like group, significant enrichment of MHCI/II signatures was observed in L858R group. In addition, Th2 signature was significantly enriched in L858R-compound subgroup.

Conclusions: This study, of first time, demonstrated the heterogenous biology of NSCLC driven by distinct EGFR mutations with distinct structures at transcriptional and functional level.



Keywords: EGFR, Heterogeneity, Transcriptome

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