BV should look at the complexity of tumoral angiogenesis at different levels and not only from the genetic perspective.

P – 0263 PROSPECTIVE STUDY OF EGFR INTRON 1 CA TANDEM REPEATS AS PREDICTIVE FACTOR OF BENEFIT FROM CETUXIMAB AND IRINOTECAN

Carlotta Antoniotti[1], Fotios Loupakis[2], Chiara Cremolini[3], Wu Zhang[4], Dongyun Yang[4], Takeru Wakatsuky[4], Marta Schirripa[3], Lisa Salvatore[3], Vincenzo Ricci[5], Francesco Graziano[6], Gianluca Masi[7], Melissa Janae Labonte[4], Yan Ning[4], Alfredo Falcone[1] and Heinz Joseph Lenz[4]

[1]Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [2]Azienda Ospedaliero-Universitaria Pisana and University of Southern California, Pisa, Italy, [3]Oncologia Medica 2, Azienda Ospedaliero Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [4]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, [5]Unità di Oncologia, Istituto Scientifico San Raffaele, Milano, Italy, [6]Department of Oncology, Azienda Ospedaliera "Ospedali Riuniti Marche Nord", Presidio San Salvatore, Pesaro, PU, [7]U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy

Introduction: Retrospective experiences have investigated the potential influence of *EGFR* intron 1 *CA* repeats on the efficacy of cetuximab-containing treatments. Different series, adopting different criteria to define short (S) and long (L) variants, have provided contrasting results.

Methods: We designed a prospective confirmatory study, to detect a HR for PFS of 1.75 for L- compared to SS genotypes in a population of *KRAS* and *BRAF* wild-type irinotecan-resistant mCRC pts treated with cetuximab and irinotecan. Estimating a prevalence of 60% of the SS variant and setting a two-sided alfa=0.05 with a power of 80%, 104 events were required. We defined S and L allelic variants those presenting<and ≥20 CA repeats, respectively. *EGFR* (*CA*)n repeat polymorphism was assessed following a 5'-end [γ-33P] ATP-labeled PCR protocol.

Results: One-hundred-fifteen pts were included. At a median follow up of 21.9 months, PFS and OS were 5.2 and 13.4 months, respectively. Thirty-three (29%) out of 114 evaluable pts achieved response. *EGFR* (*CA*)n repeat genotype was L- and SS in 45 (40%) and 68 (60%) out of 113 evaluable cases. No differences in PFS or OS were observed between L- and SS genotypes (median PFS: 4.4 vs 5.3 months, HR: 1.00 [95%CI: 0.67-1.51], p=0.991; median OS: 11.3 vs 14.2 months, HR: 1.30 [95% CI: 0.80-2.22], p=0.261). Ten (22%) out of 45 L- pts achieved response compared to 22 (33%) out of 67 SS pts (Fisher's Exact test: p=0.617). Other exploratory analyses adopting different cut-off values reported in literature led to similar results.

Conclusion: This prospective study, including a clinically homogenous and molecularly selected population, does not confirm any predictive or prognostic effect for *EGFR* (*CA*)n repeat allelic variants with respect to the efficacy of cetuximab and irinotecan in advanced lines of treatment. The present experience strengthens the need of prospectively challenging retrospective findings, as an essential step on biomarkers' way toward clinical practice.

P – 0264 CARBOXY-TERMINAL TELOPEPTIDE OF TYPE I COLLAGENE AND TARTRATE-RESISTANT ACID POSPHATASE MEASUREMENT IN PATIENTS WITH COLORECTAL CANCER AND BONE METASTASES

Franco Lumachi[1], Davide Santeufemia[2], Salvatore Tumolo[3], Paolo Doretto[4], Renato Tozzoli[5], Giordano Chiara[6] and Stefano Basso[6]

[1]Department of Surgical, Oncological & Gastroenterological Sciences, University of Padua, School of Medicine, Padova, PD, [2]Clinical Oncology, S. Maria degli Angeli Hospital, Pordenone, PN, [3]Clinical Oncology, S. Maria degli Angeli Hospital, Poedenone, PN, [4]Department of Clinical Pathology, S. Maria degli Angeli Hospital, Pordenone, PN, [5]Department of Clinical Pathology, S. Maria degli Angeli Hospital, Pordenone, PD, [6]Chirurgia 1, S. Maria degli Angeli Hospital, Pordenone, PN

Introduction: Despite significant advances in detection and treatment, colorectal cancer (CRC) still remains one of the most prevalent cancers, and one of the leading causes of mortality due to malignancy. In patients with stage I-II CRC surgical resection usually represents the sole treatment, while in those with metastasized tumor (stage IV) any therapy is rarely successful. Unfortunately, up to 60% of patients with CRC undergoing primary surgery with curative intention die from metastatic disease. Thus, occult tumor cells, not detected preoperatively, likely colonize and remain vital in different tissues of these patients, such as lymph nodes, blood, and bone marrow. Usually, CRC metastasizes to the liver and lungs more frequently than to bone. Isolated bone metastasis (BM) is considered truly rare, but it has been observed that the improved survival for patients with metastatic CRC following expanded treatment options is associate with an increased incidence of BMs. Because metastases in uncommon sites often indicates the terminal phase of CRC, clinicians should be more vigilant about possible BMs. For this purpose, several serum biomarkers have been tested for early detection of BMs, such as carboxy-terminal telopeptide of type I collagen (ICTP), a cross-link product of collagen I degradation, and tartrate-resistant acid phosphatase 5b (TRACP), specifically derived from osteoclasts. Recent studies showed that TRACP activity and ICTP were increased in up to 90% of patients with breast cancer and BM. The aim of this study was to evaluate the usefulness of TRACP, ICTP, and bone alkaline phosphatase (BAP) measurements in patients with CRC and BM.

Methods: Fourteen patients (9 men, 5 women, mean age 56.1±4.8, range 49-63 years) with CRC and confirmed BMs (cases), and a group of 15 age- and gender matched (10 men, 4 women, age 57.1±4.9 years, p=0.08) patients (controls) without BM (negative F-18 FDG PET/CT) underwent serum TRACP, ICTP, and BAP measurements. Written informed consent was obtained from all the participants. TRACP and BAP were measured by two-site enzyme-linked immunosorbent assay (ELISA), while ICTP was measured by commercially available radioimmunoassay. The sensitivity and specificity of serum TRACP, ICTP, and BAP as a marker for BM were estimated by receiver operator characteristic (ROC) curves.

Results: The mean levels of TRACP, ICTP, and BAP (cases vs. controls) were: 5.9 ±1.6 vs. 4.8±1.3 U/L (95% CI 0.11-2.11, p=0.08), 6.9±1.4 vs. 5.9±1.3 U/L (95% CI 0.94-3.04, p=0.0003), and 82.6±18.2 vs. 79.3±16.2 (95% CI 9.81-16.39, p=0.59). ROC analysis established a cutoff value for ICTP of 4.51 U/mL to identify patients with extensive BM with a specificity of 97% and a sensitivity of 92% (area under the curve=0.97; 95% CI=0.95-0.98). A strong relationship was found only between TRACP and ICTP (R=0.95, p<0.0001) serum levels among cases, while there was no correlation between age and biomarkers.

Conclusion: Serum ICTP is a useful diagnostic marker in the detection of BMs in patients with CRC, more accurate than TRACP and BAP.

P – 0265 MSI+ STAGE II/III COLON CANCER PATIENTS BENEFIT FROM CAPECITABINE ADJUVANT MONOTHERAPY

Aleksandar Dimovski[1], Nadica Matevska[1], Aleksandar Eftimov[1], Aleksandra Kapedanovska Nestorovska[1], Natalija Angelovska Petrusevska[2], Biljana Angelovska[2], Djingis Jashar[2], Nikola Mitrevski[2] and Toni Josifovski[3]

[1]Faculty of Pharmacy, Skopje, Republic of Macedonia, [2]Clinic for Radiotherapy and Oncology, Skopje, Republic of Macedonia, [3]Clinic for Abdominal surgery, Skopje, Republic of Macedonia

Introduction: There is a significant variation in survival among patients with colon cancer treated with 5-FU-based therapies. Microsatellite instability (MSI) and 18q loss of heterozygosity (18qLOH) are most frequently associated with lack of benefit from fluoropyrimidine based therapies but the clinical validity of the use of these markers in unselected patients is still controversial. The aim of this study was to evaluate the predictive and prognostic value of MSI, 18q LOH, and MTHFR C677T and TS promoter polymorphisms on efficacy (defined as relapse-free survival, RFS) and toxicity (adverse events and laboratory tests, graded according to the NCI-CTCAE v3.0) in colon cancer patients treated with capecitabine adjuvant monotherapy.

Methods: A total of 188 patients with resected colon cancer (122 in the treatment and 66 in the control group) were included in the analysis. Inclusion criteria for the treatment group were stage III (53 patients) or high-risk stage II (69 patients) colon cancer and capecitabine monotherapy in adjuvant setting (1250mg/m2 bid 12 hours apart for 14 days, repeated every 3 weeks for a total of 8 cycles). The control group consisted of 66 patients (40 stage II and 26 stage III) treated with surgery only. The follow-up data on relapse-free survival were available for a median of 44 months for both groups. Paired DNA samples from tumors and peripheral blood were genotyped for TS promoter and MTHFR C677T variants, mismatch repair and 18q LOH status of tumors using QF-PCR and/or PCR-RFLP.

Results: The treatment with capecitabine was generally well tolerated; 114 (93.4%) patients completed the treatment protocol. A 25% dose reduction was necessary in 30 (24.5%) patients mainly due to mild to moderate hand-foot syndrome, diarrhea and/or nausea. None of the evaluated markers was predictive for toxicity. Disease relapse was diagnosed in 38 patients (33.3%) in the treatment group and in 28 patients (42.4%) in the control group (HR 0.71, 95%CI 0.43 to 1.18, p=0.17). MSI+ genotype was a positive predictive factor for RFS compared to MSI- genotype in the treatment group (HR 0.27, 95%CI 0.11-0.64, p=0.05). A statistically significant difference was obtained in RFS between MSI+ patients treated with capecitabine and control MSI+ patients that did not receive any adjuvant treatment (HR 0.19, 95%CI 0.05-0.71, p=0.02) indicating that MSI+ colon cancer patients can benefit from capecitabine adjuvant monotherapy. Similar trend was observed for the presence of 18q LOH, but the data did not reach statistical significance (HR 0.54, 95%CI 0.20 – 1.46, p=0.17). MTHFR C677T and TS promoter variants, tumor stage or localization and age and gender of the patients were not predictive of RFS of the adjuvant treatment.

Conclusion: Microsatellite instability (MSI+) can be used as a predictive marker for relapse-free survival of colon cancer patients treated with capecitabine adjuvant monotherapy.