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# CONTEMPORARY TREATMENT OF ALK POSITIVE NON SMALL CELL LUNG CANCER PATIENT WITH BRAIN METASTASES: OUR EXPERIENCE

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**Abstract**

Purpose: The aim of this study is to show alectinib efficacy and safety, with focus on alectinib intracranial efficacy.
Case presentation: We report on a 46-year-old woman diagnosed as non small cell lung cancer harboring echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase fusion gene. She has intracranial metastases and poor performance status of 3. We treated this patients with alectinib after whole brain irradiation and discontinuation of chemotherapy after two 2 cycles due to progressive brain and liver metastases. Good response was obtained with improving of her performance status without adverse events.
Conclusions: We recommend alectinib as a treatment approach for ALK+ NSCLC patients, especially those with CNS metastases at the time of the diagnosis and poor PS.
**Key words:** CNS metastasis, ALK+ NSCLC patients, alectinib

## Introduction

Lung cancer remains a worldwide epidemic. Approximately 1.2 million people die from lung cancer each year (1). NSCLC represents over 80% of all lung cancers and 60% to 70% of the patients with NSCLC suffer from stage III or IV disease. The molecular profile of the tumor currently determines the therapeutic strategy for advanced lung cancer. Distinctive chromosomal rearrangements in the ALK gene (ALK-positive) were first described in 2007 and occur in approximately 2%–5% of patients with nsclc (2,3). The most common ALK rearrangement is a fusion between the N-terminal half of eml4 and the intracellular kinase domain of alk (eml4–alk) (4,5), leading to an active oncogenic driver. Other variations of ALK rearrangements exist. Additional ALK-related oncogenic drivers include point mutations in the kinase domain and alk overexpression (6,7). Patients with ALK-positive nsclc are typically younger and tend to be light or never-smokers (8). Incidence of brain metastases (BMs) is higher in patients with ALK-positive NSCLC and among those patients up to 50-60% will develop BMs during the course of their disease (8). Alectinib is potent second-generation ALK inhibitor and was shown to be effective for a broad spectrum of ALK rearrangement and ALK mutations. The aim of this study is to show alectinib efficacy and safety with focus on alectinib intracranial efficacy.

## Case presentation

A 46-year-old woman with light smoking history (15 years 10 cigarettes per day) was admitted to our hospital because of cerebral simptomatology, dizziness and headache for at list 15 days. Patient has a poor performans status (PS) of 3. Chest X-ray and computed tomography (CT) scans showed a tumor lesion in the inferior left lung lobe. Bronchoscopy established a pathological diagnosis of adenocarcinoma with a component of signet ring cells. Along with CT scan of abdomen and brain magnetic resonance imaging (MRI) scan, reveled multiple liver and brain metastases. The patient was finally diagnosed as having stage IV lung adenocarcinoma cTNM=T3N2M1b (LIV, BRA). Patient was first treated with whole brain irradiation (WBI) to a 30 Gy with 300 cGy daily dose and two cycles of first-line chemotherapy with carboplatine/gemcitabine. Although chemotherapy yielded temporary tumor regression, progressive brain and liver metastases led to discontinuation of chemotherapy after the two courses. In turn alectinib 300 mg bid was administered, because of the positive results of EML-4-ALK fusion protein and gene from immunohistochemical analysis. Alectinib is covered by the national health insurance system in our country. She is currently responding to alectinib 600 mg daily. After 9 months, CT and MRI showed lung and brain disappearance and substantial tumor regression in liver (Fig.1, 2, 3) The patient continues to be treated with alectinib without critical adverse events. At the latest follow-up, 10 months after commencing alectinib treatment, there was no evidence of progression or any remarkable toxicity.

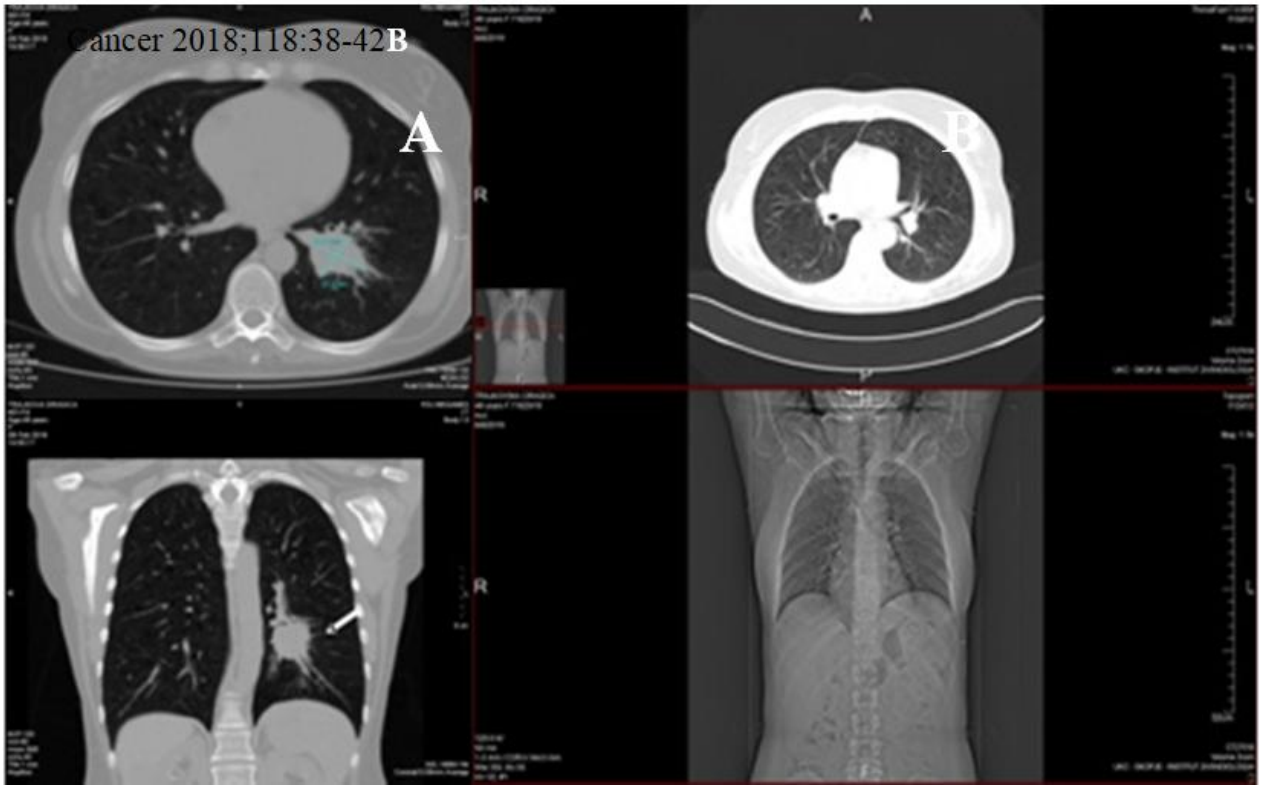


**Figure1:** Computed tomography scans depicting the tumor response at the inferior left lung lobe, 9 months after alectinib treatment (A pretreatment lung foci, B positive response to the alectinib after 9 months)

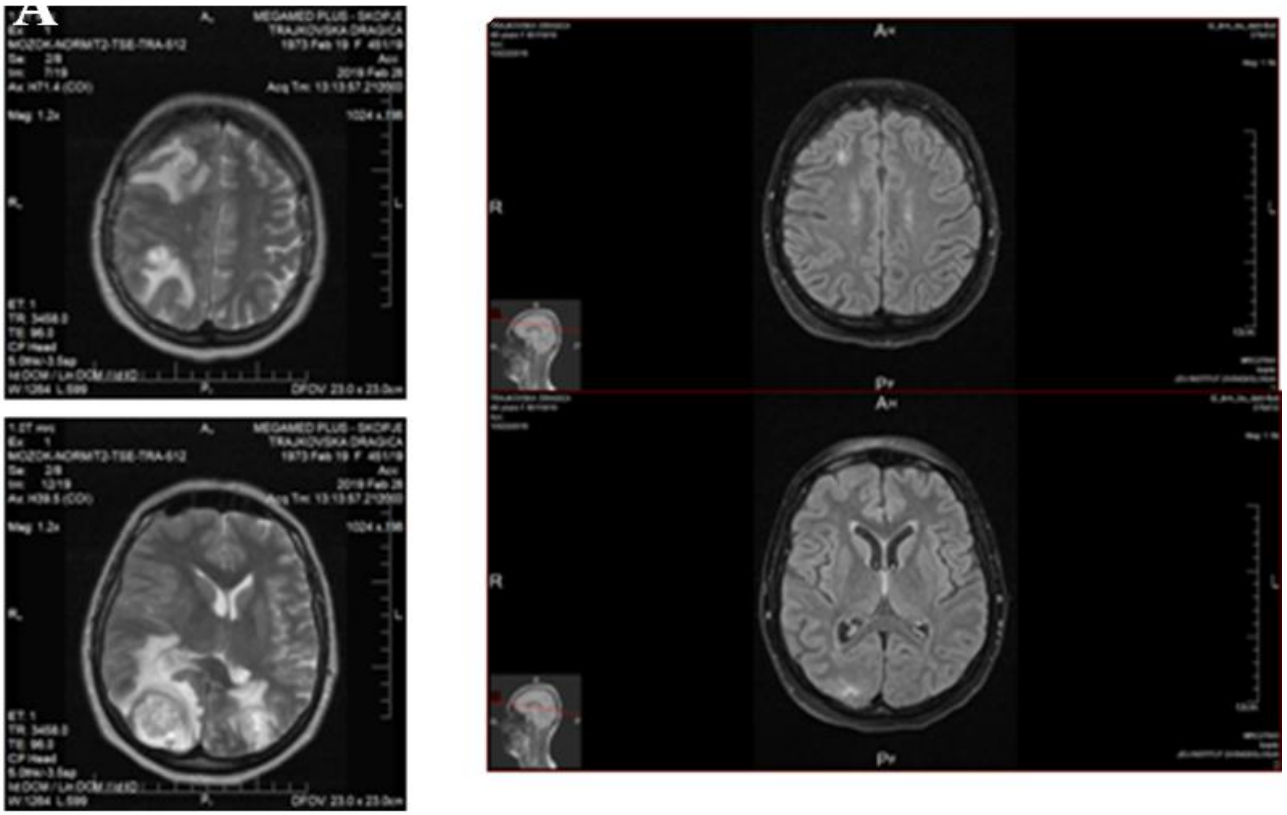

**Figure 2:** Magnetic resonance imaging scans depicting the response of intracranial metastases after alectinib treatment (A pretreatment metastatic foci, B positive response to the alecinib after 9 months)

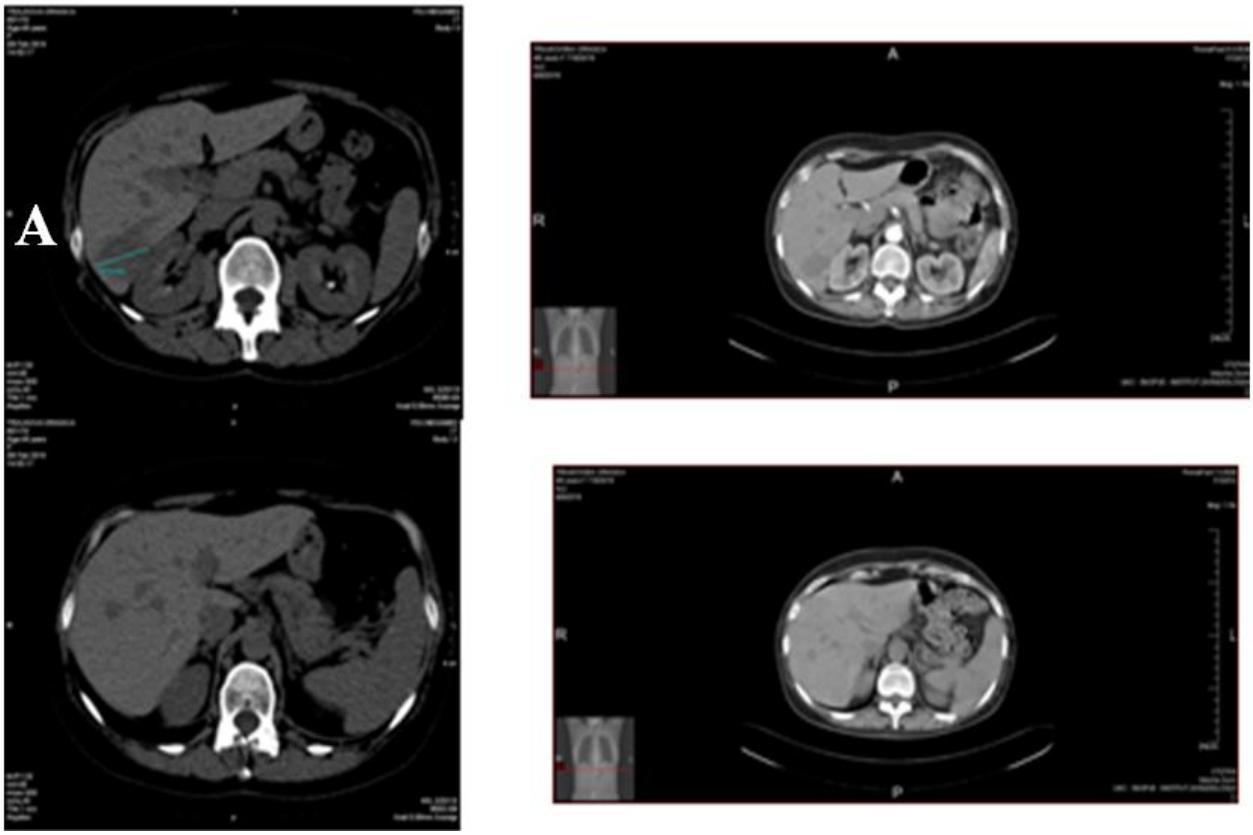


**Figure 3:** Computed tomography scans depicting the tumor response at the liver, 9 months after alectinib treatment (A pretreatment liver metastatic foci, B positive response to the alectinib after 9 months)

**Discussion**

Our study describe the case of an ALK-positive NSCLC patient with sever cerebral simptomatology and poor PS. There has been little clinical benefit of WBI and chemotherapy in NSCLC with poor PS and BMs with a median OS of about 3 months (9) The indication for molecular targeted therapy for NSCLC patients harboring corresponding target genes therefore needs to be determined separately from that for cytotoxic chemotherapy for non-selected population. In the context ALK inhibitor developed and has demonstrated a systemic efficacy and strongly improved out-comes in patients with ALK-positive advanced NSCLC in comparison with chemotherapy. First line median progression-free survival PFS was longer with crizotinib in comparison with chemotherapy (10.9 versus 7 months). However, the intracranial efficacy of crizotinib is poor, due to poor blood-brain barier (BBB) penetration (10,11). There was a need for development of other ALK inhibitors to improve intracranial disease control and enlarge the spectrum of ALK mutations targeted. For these reasons, the second generation ALK inhibitors ceritinib, alectinib and brigatinib and the third-generation ALk inhibitor loratinib were developed (12). More recently, Kodama and colleagues showed alectinib to have a higher antitumor activity than crizotinib in intracranial tumors in mouse model of EML4-ALK-positive NSCLC due a higher BBB penetration (13). Alectinib is not P-glycoprotein substrate and this may play a role in the higher BBB penetration. P-glycoprotein overexpression has indeed been showed to be a mechanism of resistance to ALK inhibitors, especially in the brain (14). Alectinib efficacy in patients with BMs was also assessed in phase III clinical trials. In the ALUR study (15), 24 patients in the alectinib arm and 16 patients in the chemotherapy arm had baseline measurable CNS metastases. The icORR was significantly higher with alectinib 54.2% versus chemotherapy 0% p<0.001. Several real-life retrospective case series confirmed the high efficacy of alectinib on BMs and leptomeningeal metastases LM (16,17). Moreover, Ou and colleagues reported the cases of the two patients with ALK-positive NSCLC with BMs who received stereotactic radiosurgery (SRS) to the brain prior to alectinib treatment. Both patients had radiation necrosis presenting as pseudo-progression confirmed by neurosurgery and pathologic examination (18). This specific brain evolution after SRS and alectinib has to be known to avoid incorrect classification into progressive disease and alectinib discontinuation. Therefore we chose alectinib for our patient. At present, crizotinib and alectinib are available as ALK inhibitors in our country. Results from approach in J-ALEX and ALEX trials provided further evidence of alecitinib's systemic and CNS efficacy, with complete CNS response rates of 38% in patients with measurable CNS lesions at baseline. In the ALEX ITT population, the cumulative incidence rate (CIR) of CNS progression,

considering the challenging risks of non-CNS progression and death, was 9.4% with alectinib versus 41.4% with crizotinib (19,20) Our patients with ALK-positive NSCLC who was previously treated with cytotoxic drugs and radiotherapy and still was without response with alectinib treatment demonstrated a good response regarding brain metastasis. At the latest follow-up, 10 months after commencing alectinib treatment, there was no evidence of progression or any remarkable toxicity.

**Conclusion**

Considering its efficacy and tolerability in this case, we recommend alectinib as a best treatment approach for ALK+ NSCLC patients, especially those with CNS metastasis at the time of the diagnosis and poor PS.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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