

[CASE REPORT]

Successful Treatment with Crizotinib to Overcome Drug Resistance Possibly Due to *Mesenchymal-epithelial Transition* Amplification in a Lung Cancer Patient with the *Echinoderm Microtubule-associated Protein-like 4-anaplastic Lymphoma Kinase* Fusion Gene

Tomoko Shiraishi¹, Kei Yamasaki¹, Moe Kidogawa¹, Tatsuya Shingu¹, Fuki Ujimiya¹, Takanobu Jotatsu¹, Shingo Matsumoto², Hiroki Izumi², Chinatsu Nishida¹, Koichi Goto² and Kazuhiro Yatera¹

Abstract:

Amplification of the *mesenchymal-epithelial transition (MET)* gene plays an important role in anticancer drug resistance to anaplastic lymphoma kinase-tyrosine kinase inhibitors (ALK-TKIs) in *echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK)*-rearranged lung cancer cells. We encountered an *ALK*-rearranged lung cancer patient who developed *MET* amplification after alectinib treatment and showed an effective response to fifth-line crizotinib. First-line alectinib treatment was effective for 2.5 years; however, liver metastases exacerbated. Liver biopsy specimens revealed *MET* and human epidermal growth factor receptor 2 (*HER2*) amplifications. Switching to the *MET* inhibitor crizotinib improved liver metastases. Crizotinib may be effective in *ALK*-positive patients with *MET* amplification.

Key words: lung cancer, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*), mesenchymal-epithelial transition (*MET*) amplification, human epidermal growth factor receptor 2 (*HER2*), crizotinib, alectinib

(Intern Med 62: 3215-3221, 2023)

(DOI: 10.2169/internalmedicine.1164-22)

Introduction

The echinoderm microtubule associated protein like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*) fusion gene (*EML4-ALK*), identified in 2007, is known as a driver gene in patients with lung cancer and can be found in approximately 5% of non-small-cell lung cancer patients (1).

Drug resistance, including that to anticancer tyrosine kinase inhibitors (TKIs; such as *ALK* inhibitors), is a serious clinical problem in non-small-cell lung cancer treatment (2, 3). *Mesenchymal-epithelial transition (MET)* amplification is a main drug resistance mechanism after TKI

treatment. *MET* is a proto-oncogene that encodes c-MET, a receptor-type tyrosine kinase. c-MET binding to its ligand, hepatocyte growth factor (HGF), activates various intracellular signaling cascades that promote tumor cell proliferation, migration, invasion, and angiogenesis (4, 5). *MET* activation occurs upon *MET* gene amplification, *MET* protein overexpression, overstimulation by HGF, and *MET* exon 14 skipping mutations (6).

MET amplification is one of the main drug resistance mechanisms after alectinib treatment. In addition, *MET* amplification is also associated with resistance to other TKIs in non-small-cell lung cancer treatment, such as epidermal growth factor receptor (EGFR)-TKIs (7). Therefore, com-

¹Department of Respiratory Medicine, University of Occupational and Environmental Health, Japan and ²Department of Thoracic Oncology, National Cancer Center Hospital East, Japan

Received: October 20, 2022; Accepted: January 11, 2023; Advance Publication by J-STAGE: March 15, 2023

Correspondence to Dr. Kei Yamasaki, yamasaki@med.uoeh-u.ac.jp

bined EGFR-TKIs and MET inhibitors may help treat non-small-cell lung cancer patients with resistance to EGFR inhibitors promoted by *MET* amplification (8). *MET* amplification was detected in approximately 10% of tumor biopsies from patients that relapsed after TKI treatment (9). Several case reports (10-14) and one study (15) have suggested that *MET* amplification can mediate resistance to ALK-TKIs, and the reported rate of *MET* amplification is 15% among tumor biopsies from patients that relapse after treatment with selective ALK inhibitors (15). Overall, sequential therapy using MET inhibitors may also be effective in treating non-small-cell lung cancers, but proper screening of genetic mutations is essential for achieving effective treatment strategies in these patients.

Crizotinib was first approved in Japan for the treatment of *ALK* fusion gene-positive lung cancers. In addition to *ALK*, crizotinib is also a kinase inhibitor of *MET* and *c-ros* oncogene 1 (*ROS-1*). Alectinib was approved for the treatment of *ALK* fusion gene-positive lung cancer patients in Japan in 2014 (16) and is often administered as the first-line treatment, since it has a reduced rate of adverse effects and greater efficacy than other *ALK* inhibitors (17-21). Several reports have demonstrated the efficacy of crizotinib as a *MET* inhibitor (10-15).

We herein report a Japanese patient with *ALK*-positive lung cancer that recurred after transiently successful alectinib treatment, showing confirmation of *MET* amplification in metastatic liver lesions, that was successfully treated with crizotinib.

Case Report

A non-smoking Japanese woman in her 40s was diagnosed with lung adenocarcinoma (cT1cN3M1c, clinical stage IVB, 8th edition of the International Union against Cancer/American Joint Committee on Cancer TNM staging system) in August 20XX-3. Her initial general health condition was poor, with pericardial effusion, hoarseness associated with recurrent laryngeal nerve palsy, and multiple liver metastases. Biopsy specimens were taken from the mediastinal lymph nodes, and the diagnosis of *ALK*-positive lung adenocarcinoma was made based on immunohistochemical (IHC) analysis and break-apart fluorescence *in-situ* hybridization (FISH) results.

Alectinib (300 mg twice daily) was used as first-line therapy, and her general condition and radiological findings improved. One year after initiating alectinib treatment, a single brain metastasis was observed in the cerebellum, and brain radiotherapy was added to the treatment plan (36 Gy/3 fractions). Approximately 2.5 years after alectinib administration (January 20XX), the number of liver metastases rapidly increased, and alectinib was switched to lorlatinib as second-line treatment, resulting in no response and exacerbated liver metastases on computed tomography (CT) in March 20XX (Fig. 1).

Since the liver metastases increased rapidly, while the pri-

mary lesions did not, we considered the acquisition of a resistance mechanism to *ALK*-TKI in the liver metastases. In addition, there were mixed areas of both increasing and decreasing liver metastases in size, indicating tumor heterogeneity. A liver biopsy was performed to analyze gene alterations of the tumor (Fig. 2A, white arrowhead, Fig. 3A-ii) in March 20XX, but the sample volume was not sufficient to perform next-generation sequencing (NGS). Other organs did not exhibit signs of metastases, but the liver metastases were rapidly growing; palliative radiotherapy (30 Gy) was therefore performed in April 20XX.

Subsequent systemic chemotherapy with carboplatin (CBDCA) and nanoparticle albumin-bound paclitaxel (nab-PTX) were administered as third-line chemotherapy, and bevacizumab (BEV) was also initiated in June 20XX. However, these systemic chemotherapy and radiotherapy rounds were ineffective, and new liver metastases (Fig. 1, white arrowheads) and paratracheal lymph node enlargement were observed, on CT in August 20XX. At this time, a second liver biopsy of the new liver metastases was performed (Fig. 2B, white arrow, Fig. 3A-iii), and biopsied specimens were submitted to the Lung Cancer Genomic Screening Project for Individualized Medicine Molecular Testing for Resistant Tumors to Systemic Therapy (LC-SCRUM-TRY), a project for the genomic screening of cancers, for the analysis of chemotherapy resistance genes using NGS (22). The genetic analysis was conducted using the OncoPrint™ Precision Assay (Thermo Fisher Scientific, Waltham, USA). Before obtaining the results of the genetic analysis, a second round of palliative radiotherapy (30 Gy) and hyperthermia therapy were administered, and brigatinib was started as fourth-line treatment in September 20XX. Despite these treatments, the growth of liver metastases and peritoneal dissemination was observed. Opioid analgesics were started for abdominal pain due to the peritoneal metastasis dissemination.

A genetic analysis (conducted using the OncoPrint™ Precision Assay; Thermo Fisher Scientific) revealed amplification of the *MET* (9.91 gene copies) and human epidermal growth factor receptor type 2 (*HER2*) genes (4.26 gene copies), but no point mutations in *ALK* [*EML4-ALK* fusion (variant 2: E20; A20) was detected]. Furthermore, FISH images of biopsies showed a high copy number of *MET* (*MET/CEP7* ratio 5.6, Fig. 3B) (23).

Crizotinib (250 mg twice daily) was introduced in October 20XX to target *MET* amplification, and her abdominal pain gradually improved. Abdominal echography performed 11 days after crizotinib administration showed a decreased size of the liver metastases. Abdominal CT performed 30 days after the start of crizotinib showed shrinkage of liver metastases and para-aortic lymph nodes (Fig. 1, November 20XX). Grade 2 dysgeusia and appetite loss appeared as adverse effects of crizotinib, but these symptoms abated over time. Crizotinib was effective for four months until a re-increase in the liver metastases occurred.

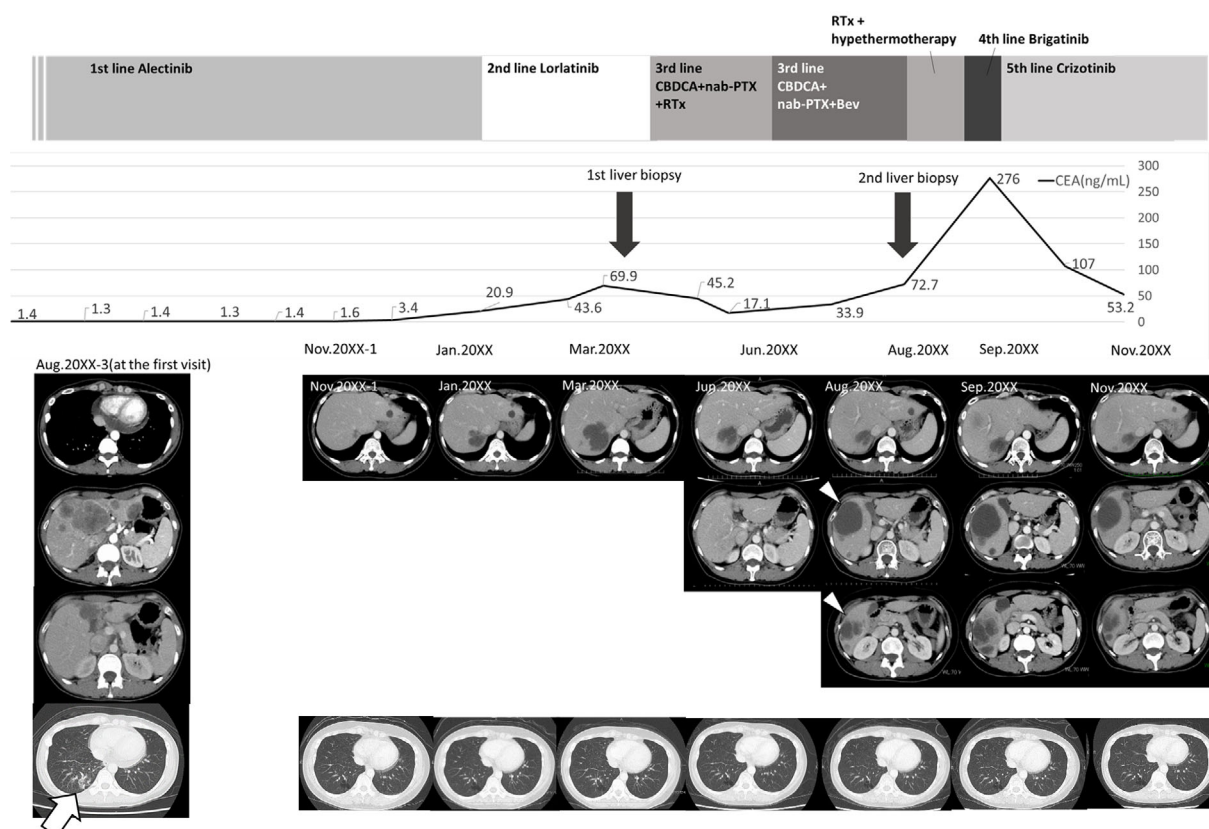


Figure 1. Clinical course of the patient. The patient was diagnosed with stage IVB ALK-positive lung adenocarcinoma in August 20XX-3 and given alectinib as first-line treatment. A positive treatment effect continued for about 2.5 years. However, in January 20XX, liver metastases rapidly developed, and the patient was switched to lorlatinib as second-line treatment. Nevertheless, the liver metastases increased further, and levels of tumor markers also tended to increase. A liver biopsy was performed to confirm the resistance mechanism, but an adequate specimen could not be obtained. The treatment regimen was changed to third-line CBDCA+nab-PTX in April 20XX, and BEV was started in June 20XX. However, computed tomography in August 20XX revealed new liver metastases (white arrowheads), and a second liver biopsy of these metastases was performed. The biopsied specimens were subjected to next-generation sequencing. In September 20XX, before obtaining the results of the analysis, palliative radiotherapy and hyperthermia therapy were administered, and brigatinib was started as fourth-line treatment. Despite these treatments, growth of the liver metastases and peritoneal dissemination were observed. After the second liver biopsy confirmed *MET* amplification, crizotinib was administered as fifth-line treatment, and all liver metastases were reduced in size. A marked reduction in the CEA level was also observed. During the entire treatment period, the primary lesion in the lower right lobe (white arrow) did not increase. ALK: anaplastic lymphoma kinase, BEV: bevacizumab, CBDCA: carboplatin, CEA: carcinoembryonic antigen, *MET*: mesenchymal-epithelial transition gene, nab-PTX: nanoparticle albumin-bound paclitaxel, RTx: radiation therapy

Discussion

Mechanisms of resistance to ALK inhibitors include secondary mutations in their receptors, such as L1196M, C1156Y, L1152R, and G1202R (3); activation of bypass pathways; overexpression of P-glycoproteins (2, 24, 25); and cancer cell transformations, such as conversion to small-cell carcinoma (26, 27). First- and second-generation ALK inhibitors (crizotinib, alectinib, ceritinib) exhibit different types of inhibitory activities to counter secondary muta-

tions (3). The activation of c-KIT, EGFR, and *MET* is known to activate the bypass pathways of tumor proliferation (3). Crizotinib, a multi-kinase inhibitor, including targeting *MET*, is suggested to be effective in downregulating *MET* activation, and *in vitro* studies have also demonstrated the therapeutic potential of crizotinib for inhibiting *MET* activation (28).

In the present patient, *MET* amplification was suggested to be the mechanism responsible for the development of alectinib resistance, as 1) the third-generation ALK-TKIs lorlatinib and brigatinib were ineffective in inhibiting the ef-

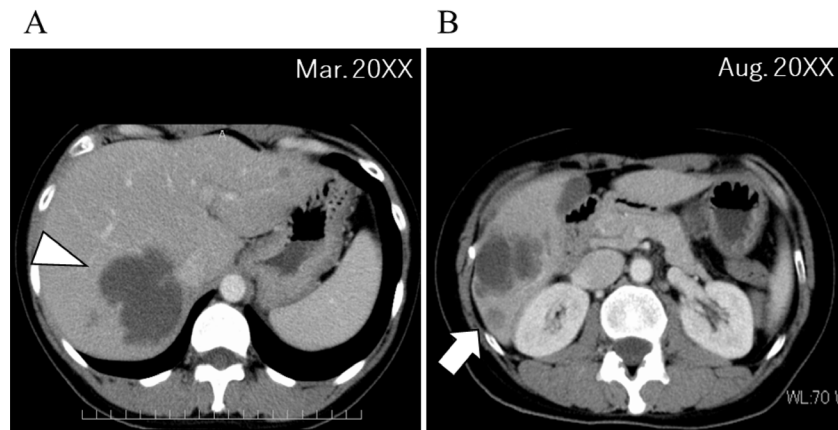


Figure 2. Location of the liver biopsy. (A) An initial liver biopsy was performed, but the specimen collected at the cystic metastatic site (white arrowhead) was in a liquid state, indicating necrosis, and adequate tissue sample could not be obtained. (B) For the second liver biopsy, a large area was selected within the vicinity of emerging liver metastases (white arrow) and evaluated by abdominal ultrasonography, resulting in sufficient tissue sampling.

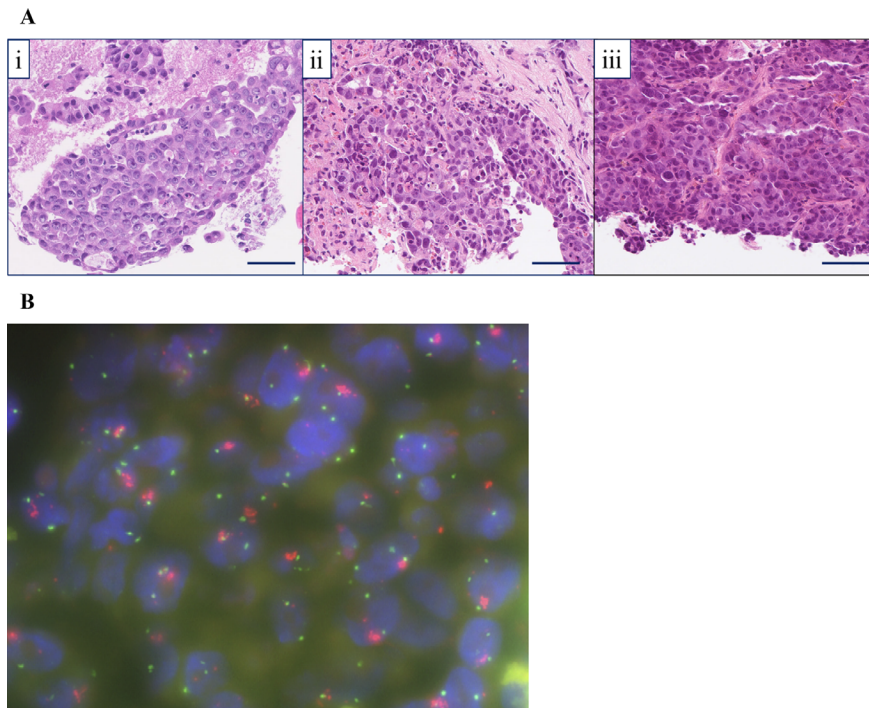


Figure 3. (A) Hematoxylin and Eosin (H&E) staining sample of the metastatic tumor. Each tissue sample had similar tumor cell characteristics. i) Lymph node metastasis of lung adenocarcinoma (EBUS-TBNA, H&E staining, $\times 200$): the specimen showed the proliferation of atypical epithelial cells arranged in a tubular or cribriform growth fashion. ii) Liver metastasis of lung adenocarcinoma (needle biopsy in March 20XX, H&E staining, $\times 200$): atypical epithelial cells arranged in a tubular or cribriform growth fashion were seen (immunohistochemically, the atypical cells were diffusely positive for TTF-1, Napsin A, and ALK and negative for synaptophysin and INSM-1). iii) Liver metastasis of lung adenocarcinoma (needle biopsy in Aug 20XX, H&E staining, $\times 200$): the specimen revealed a proliferation of atypical epithelial cells arranged in nests, sheets, or a trabecular growth fashion (immunohistochemically, the atypical cells were diffusely positive for TTF-1, Napsin A, and ALK and negative for synaptophysin and INSM-1). Scale bar=50 μm . (B) A *MET/CEP7* FISH assay (red signal: *MET* gene; green signal: CEP7). This representative case with *MET/CEP7* 5.6 (≥ 5) was classified as having high-level *MET* amplification. EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration, TTF-1: thyroid transcription factor-1, INSM-1: insulinoma-associated protein 1, *MET/CEP7*: ratio of *MET* to centromere chromosome 7 probe, CEP7: centromere of chromosome 7, FISH: fluorescence *in-situ* hybridization

Table. Case Reports of MET Gene Amplification in ALK-positive Lung Cancer.

Case	Age	Sex	Prior chemotherapy	Duration time between starting other prior ALK-TKI and receiving crizotinib	Recurrent sites and complications	Outcome		Reference
						Duration of administration	Response	
1	43	F	CDDP+PEM, DOC, CBDCA+GEM, alectinib	Alectinib (10.5 months)	Multiple liver metastases, DIC	ND	ND	10
2	44	F	Alectinib, lorlatinib	Alectinib (9 months), lorlatinib (4 weeks)	Pericardial effusion, pulmonary embolism	1 month	PR	11
3	40	F	Crizotinib, CBDCA+PEM, alectinib, DOC, lorlatinib	Lorlatinib (7 months)	Brain metastasis, right adrenal gland metastasis	14 months	PR	13
4	ND	ND	Alectinib, CBDCA+PEM	Alectinib (9 months)	Chest wall metastasis, liver metastasis, bone metastasis	10 weeks	PR	15
5	64	F	Alectinib, CBDCA+PTX	Alectinib (6 months)	Right adrenal gland metastasis, bone metastasis, abdominal and retroperitoneal lymph nodes metastasis	10 months	PR	14
Present case	42	F	Alectinib, CBDCA+nab-PTX+Bev, lorlatinib, brigatinib	Alectinib (2.5 years), lorlatinib (2 months), brigatinib (1 month)	Brain metastasis, liver metastasis, peritoneal dissemination	4 months	PR	-

CDDP: cisplatin, PEM: pemetrexed, DOC: docetaxel, CBDCA: carboplatin, GEM: gemcitabine, PTX: paclitaxel, nab-PTX: nanoparticle albumin-bound paclitaxel, Bev: bevacizumab, DIC: disseminated intravascular coagulation, PR: partial response, PD: progressive disease, ND: not described

fects of *ALK* mutations; 2) no secondary mutations in *ALK* were observed; 3) the coexistence of *ALK* and *MET* mutations is rarely observed prior to ALK-TKI administration, especially in high-level *MET* amplification cases (29-32); and 4) an improvement in the clinical condition of our patient was observed after crizotinib administration.

Lower levels of *MET* amplification were reported in ALK-positive lung cancer patients receiving crizotinib therapy than in those treated with other ALK-TKIs (15). This finding highlights the importance of *MET* amplification in the development of drug resistance to alectinib, which is being used increasingly frequently as the first-line treatment in ALK-positive lung cancer patients. Our patient developed resistance to alectinib after showing a favorable anticancer response for 2.5 years, with a rapid increase in the number of hepatic metastases and consequent carcinomatous peritonitis. In a previous report on *MET* amplification in a patient with ALK-positive lung cancer, disease aggravation was accompanied by an extremely progressive and deteriorating clinical condition, such as one characterized by pericardial effusion and disseminated intravascular coagulation (Table). In these severe disease cases, it may not be possible to confirm the resistance mechanism by a biopsy and rescue the patient with systemic anticancer therapy in time. Therefore, it is essential to confirm the type of drug resistance mechanism as soon as the symptoms of progressive disease (PD) appear for the proper selection of therapeutic modalities. In addition, the primary lung lesions were not consistently enlarged in this case, and only the liver metastases were noticeably enlarged. This suggests tumor heterogeneity, and it is important to search for resistance mechanisms targeting tumors that tend to increase in size.

The FISH method was used to evaluate the copy number of the *MET* gene in our patient. FISH evaluates the copy number by assessing the ratio of the total number of signals in the *MET* gene and the centromere region of chromosome 7 (*MET/CEP7* ratio). Unlike the polymerase chain reaction method, it can also distinguish between *MET* gene amplification and polysomy of chromosome 7. Although there is still no international consensus on the *MET* gene copy number and *MET/CEP7* ratio thresholds, we used a high amplification threshold of the *MET* gene when the *MET/CEP7* ratio was ≥ 5 , based on previous reports (23, 33, 34). In cases of *MET* amplification in the EGFR-TKI resistance mechanism, the higher the amplified copy number, the stronger the combination effect of EGFR-TKI and *MET* inhibitor (35). Therefore, determining the burden of severe *MET* amplification may help determine the drug resistance mechanism.

HER2 amplification was simultaneously detected with *MET* amplification in our patient. *HER2* amplification is observed in EGFR mutation-positive patients as a drug resistance mechanism (36), and reports suggest that *HER2* amplification can also contribute to ALK-TKI resistance (37). Thus, *HER2* amplification might also have been responsible for the anticancer drug resistance in our patient. Effective treatment strategies to suppress *HER2* amplification in EGFR- and ALK-positive cancers have not yet been established. Nevertheless, the administration of *HER2*-TKI to a patient with *HER2*-positive lung cancer (without respective driver mutation) was effective in alleviating symptoms (38). *HER2*-TKIs might therefore be an alternative effective strategy of treatment in cancer patients with drug resistance developed due to *HER2* amplification.

Conclusions

We encountered a patient with ALK-positive lung cancer who became refractory to ALK-TKI treatment, possibly due to *MET* amplification confirmed by re-biopsy specimens after 2.5 years of successful treatment, and in whom crizotinib was clinically effective. The present findings suggest the importance of the early detection of gene alterations responsible for drug resistance using re-biopsy specimens.

The authors state that they have no Conflict of Interest (COI).

References

- Soda M, Choi YL, Enomoto M, et al. Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer. *Nature* **448**: 561-566, 2007.
- Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. *Sci Transl Med* **4**: 120ra17, 2012.
- Gainor JF, Dardaei L, Yoda S, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov* **6**: 1118-1133, 2016.
- Bladt F, Riethmacher D, Isenmann S, Aguzzi A, Birchmeier C. Essential role for the *c-met* receptor in the migration of myogenic precursor cells into the limb bud. *Nature* **376**: e768-e771, 1995.
- Sattler M, Salgia R. c-Met and hepatocyte growth factor: potential as novel targets in cancer therapy. *Curr Oncol Rep* **9**: 102-108, 2007.
- Organ SL, Tsao MS. An overview of the c-MET signaling pathway. *Ther Adv Med Oncol* **3**: S7-S19, 2011.
- Engelman JA, Zejnullahu K, Mitsudomi T, et al. *MET* amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* **316**: 1039-1043, 2007.
- Scagliotti G, Moro-Sibilot D, Kollmeier J, et al. A randomized-controlled phase 2 study of the *MET* antibody emibetuzumab in combination with erlotinib as first-line treatment for *EGFR* mutation-positive NSCLC patients. *J Thorac Oncol* **15**: 80-90, 2020.
- Coleman N, Hong L, Zhang J, et al. Beyond epidermal growth factor receptor: *MET* amplification as a general resistance driver to targeted therapy in oncogene-driven non-small-cell lung cancer. *ESMO Open* **6**: 100319, 2021.
- Toyokawa G, Takenoyama M, Watanabe S, et al. Dramatic response to crizotinib in an ALK-positive adenocarcinoma patient with disseminated intravascular coagulation. *J Thorac Oncol* **8**: e96-e98, 2013.
- Mazzotta M, Filetti M, Rossi A, et al. Is there a place for crizotinib in *c-MET* alterations? A case of efficacy in ALK positive NSCLC patient with secondary *c-MET* amplification. *Ann Oncol* **31**: 440-441, 2020.
- Gouji T, Takashi S, Mitsuhiro T, Yukito I. Crizotinib can overcome acquired resistance to CH5424802: is amplification of the *MET* gene a key factor? *J Thorac Oncol* **9**: e27-e28, 2014.
- Sakakibara-Konishi J, Kitai H, Ikezawa Y, et al. Response to crizotinib re-administration after progression on lorlatinib in a patient with ALK-rearranged non-small-cell lung cancer. *Clin Lung Cancer* **20**: e555-e559, 2019.
- Ji J, Mitra A, Camidge DR, Riess JW. Early alectinib resistance from *MET* amplification in ALK-rearranged NSCLC: response to crizotinib with re-response to alectinib and crizotinib. *Clin Lung Cancer* **22**: e851-e855, 2021.
- Dagogo-Jack I, Yoda S, Lennerz JK, et al. *MET* alterations are a recurring and actionable resistance mechanism in ALK-positive lung cancer. *Clin Cancer Res* **26**: 2535-2545, 2020.
- Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. *Lancet Oncol* **14**: 590-598, 2013.
- Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* **390**: 29-39, 2017.
- Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* **377**: 829-838, 2017.
- Zhou C, Kim SW, Reungwetwattana T, et al. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. *Lancet Respir Med* **7**: 437-446, 2019.
- Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol* **31**: 1056-1064, 2020.
- Nakagawa K, Hida T, Nokihara H, et al. Final progression-free survival results from the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. *Lung Cancer* **139**: 195-199, 2020.
- Matsumoto S. Development of molecular-targeted therapy through large-scale genome screening for rare oncogene driver-positive lung cancer. *Jpn J Lung Cancer* **58**: 252-257, 2018 (in Japanese, Abstract in English).
- Tong JH, Yeung SF, Chan AW, et al. *MET* amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. *Clin Cancer Res* **22**: 3048-3056, 2016.
- Choi YL, Soda M, Yamashita Y, et al. *EML4-ALK* mutations in lung cancer that confer resistance to ALK inhibitors. *N Engl J Med* **363**: 1734-1739, 2010.
- Katayama R, Sakashita T, Yanagitani N, et al. P-glycoprotein mediates ceritinib resistance in anaplastic lymphoma kinase-rearranged non-small cell lung cancer. *EBioMedicine* **3**: 54-66, 2015.
- Cha YJ, Cho BC, Kim HR, Lee HJ, Shim HS. A case of ALK-rearranged adenocarcinoma with small cell carcinoma-like transformation and resistance to crizotinib. *J Thorac Oncol* **11**: e55-e58, 2016.
- Zhu YC, Liao XH, Wang WX, et al. Patients harboring ALK rearrangement adenocarcinoma after acquired resistance to crizotinib and transformation to small-cell lung cancer: a case report. *Oncotargets Ther* **10**: 3187-3192, 2017.
- Isozaki H, Ichihara E, Takigawa N, et al. Non-small cell lung cancer cells acquire resistance to the ALK inhibitor alectinib by activating alternative receptor tyrosine kinases. *Cancer Res* **76**: 1506-1516, 2016.
- Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov* **7**: 596-609, 2017.
- Tong JH, Yeung SF, Chan AWH, et al. *MET* amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. *Clin Cancer Res* **22**: 3048-3056, 2016.
- Le X. Heterogeneity in *MET*-aberrant NSCLC. *J Thorac Oncol* **16**: 504-506, 2021.
- Kron A, Scheffler M, Heydt C, et al. Genetic heterogeneity of *MET*-aberrant NSCLC and its impact on the outcome of immunotherapy. *J Thorac Oncol* **16**: 572-582, 2021.
- Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF 02341066), a dual mesenchymal-epithelial transition (*MET*) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell

- lung cancer patient with *de novo* *MET* amplification. J Thorac Oncol **6**: 942-946, 2011.
34. Cappuzzo F, Jänne PA, Skokan M, et al. *MET* increased gene copy number and primary resistance to gefitinib therapy in non-small-cell lung cancer patients. Ann Oncol **20**: 298-304, 2009.
35. Guo R, Luo J, Chang J, et al. *MET*-dependent solid tumors - molecular diagnosis and targeted therapy. Nat Rev Clin Oncol **17**: 569-587, 2020.
36. Westover D, Zugazagoitia J, Cho BC, Lovly CM, Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol **29**: i10-i19, 2018.
37. Minari R, Gnetti L, Lagrasta CA, et al. Emergence of a *HER2*-amplified clone during disease progression in an *ALK*-rearranged NSCLC patient treated with *ALK*-inhibitors: a case report. Transl Lung Cancer Res **9**: 787-792, 2020.
38. Li BT, Smit EF, Goto Y, et al. Trastuzumab deruxtecan in *HER2*-mutant non-small-cell lung cancer. N Engl J Med **386**: 241-251, 2022.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).