



Classical *ALK* G1202R resistance mutation was identified in a lung adenocarcinoma patient with rare *LOC388942-ALK* fusion after sequential treatment with *ALK*-TKIs and anlotinib: a case report

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Background: Anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) is a heterogeneous disease. To date, more than ninety *ALK* fusions in lung cancer have been found. Here, we report for the first time a rare *LOC388942-ALK* fusion in NSCLC was sensitive to crizotinib but resistant to the sequential ceritinib and alectinib and acquired classical *ALK* G1202R resistance mutation after long-term treatment with anlotinib. This case highlights dynamic monitoring of gene alteration using next-generation sequencing (NGS) is necessary during the anti-tumor process.

Case Description: A 55-year-old male, with no history of smoking history and no family history of cancer, was found malignant pleural effusion and multiple metastasis nodules in the left lung. He was histopathologically diagnosed with *ALK*-positive cT4N0M1a adenocarcinoma in June 2016. NGS of the tumor identified a rare *LOC388942-ALK* fusion (L intergenic: A 20, 1.41%). Then, the patient was treated with chemotherapy, crizotinib, ceritinib, alectinib, and anlotinib sequentially. The patient achieved partial response (PR) to chemotherapy and crizotinib. No evidence of a secondary resistant molecular event was found after resistance to crizotinib, ceritinib, or Alectinib. After 8 months of alectinib treatment, the tumor gradually enlarged again. Anlotinib was followed for 13 months. Thirteen months later, new lesions in the lower lobe of the right lung appeared and increased gradually, indicating definite progression of the tumor. Classical *ALK* G1202R resistance mutations was detected using cfDNA NGS. The patient refused to receive lorlatinib targeting G1202R resistance mutations and continued with anlotinib. He died in August 2022, achieving 5-year overall survival (OS).

Conclusions: Distinct *ALK* fusions in NSCLC have different cancer biology, leading to different response to *ALK* tyrosine kinase inhibitors (*ALK*-TKIs), even developed different resistance mechanism. Reporting the clinical details of rare *ALK* fusions in NSCLC is necessary to guide the treatment for clinicians and researchers.

Keywords: *LOC388942-ALK*; *ALK* G1202R mutation; resistance mechanism; lung cancer; case report

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Introduction

Anaplastic lymphoma kinase (*ALK*) gene rearrangements have been reported in approximately 5–7% of lung adenocarcinomas (LADCs) (1). *ALK*-positive LADC patients can significantly benefit from *ALK* tyrosine kinase inhibitors (*ALK*-TKIs). However, *ALK* fusion non-small cell lung cancer (NSCLC) is a heterogeneous disease. Distinct *ALK* fusions have different responses to various *ALK*-TKIs (first-generation: crizotinib; second-generation: alectinib, ceritinib, brigatinib, and ensartinib; third-generation: lorlatinib) (2–7). In addition, despite the impressive efficacy of *ALK*-TKIs in NSCLC patients, acquired resistance will inevitably develop (8,9). *ALK* inhibitors have two major resistance modes: *ALK*-dependent and non-*ALK*-dependent modes (10). The former mainly includes *ALK* kinase domain resistance mutations and increased copy numbers of *ALK* rearrangements. The latter includes bypass activation, such as emergence of *MET* and *KRAS* alterations, and histologic transformation, among others. It has been reported that different patterns of *ALK* fusion present with different stabilities of the resulting fusion proteins and different resistance mutation sites (11,12). Even among cancers harboring the same *ALK* fusion partner, such as *EML4*, unique fusion variants display a different biology—with clear differences in both duration of response and mechanism of resistance (13). Different *ALK*-TKI treatments also lead to different acquired resistance mutations due to their unique molecular structures and different binding patterns (14). For tumors that acquire an *ALK*-dependent resistance mechanism, treatment with another appropriate *ALK*-TKI that is tailored to that mutation may continue to provide antitumor therapeutic effects, while antitumor therapies other than *ALK*-TKIs would be preferred for tumors that acquire an *ALK*-independent resistance mechanism (15,16). Therefore, accurate molecular diagnosis of the *ALK* fusion pattern and dynamic monitoring of resistance mechanisms during treatment is key to achieving precision medicine and individualized treatment for optimal survival benefit to these patients. Here, we report that a lung cancer patient with a rare *LOC388942-ALK* fusion was sensitive to crizotinib but resistant to sequential ceritinib and alectinib and then developed a classical *ALK* G1202R resistance mutations after long-term anlotinib treatment, achieving 5-year overall survival (OS). This case highlights dynamic monitoring of gene alteration using next-generation sequencing (NGS) is necessary during the anti-tumor process. We present

the following case in accordance with the CARE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5194/rc>).

Case presentation

A 55-year-old Chinese male patient, with no history of smoking history and no family history of cancer, presented with left chest pain and dyspnea and was admitted to our hospital in August 2017. Physical examination showed his chest tender to palpation and decreased breath sounds in the left lung. Chest computed tomography (CT) found large pleural effusion and multiple round nodules in his left lung (Figure 1A). Pathological examination revealed the LADC staging as IVa (cT4N0M1a). Immunohistochemistry (IHC) showed *ALK*-V (+) (Ventana), which was also confirmed by fluorescence in situ hybridization (FISH). NGS results revealed a *LOC388942-ALK* fusion (L intergenic: A 20, 1.41%) (Figure 1B). He received first-line pemetrexed and cisplatin combined with antiangiogenic therapy for 6 cycles from August 2017 to April 2018, with a best response of partial response (PR). After the disease progressed, crizotinib was prescribed to the patient with a PR for 7 months from September 2018 to March 2019. When the primary lung lesion slowly progressed again, NGS was performed using blood samples that showed the same *ALK* fusion pattern as *LOC388942-ALK* fusion (L intergenic: A 20, 0.38%), without any other acquired molecular resistance events (Figure 1B). As the patient declined further chemotherapy and his renal function was inadequate for chemotherapy, ceritinib was administered from May 2019 to November 2019, during which the lesion still gradually enlarged. Meanwhile the renal function was deteriorated with high creatinine. Therefore, liquid biopsy performed again only revealed the same *LOC388942-ALK* fusion with a variant allele fraction of 1.11% and a *TP53* mutation (exon 10 nonsense mutation, 0.61%). The patient started alectinib combined with radiotherapy (IMRT with a total dose of 60 Gy in 30 fractions was delivered to the tumor lesion in left lower lobe) in January 2020. The tumor responded to radiotherapy for the first 2 months but gradually enlarged again over the following 6 months, with the best response being stable disease (SD). After 8 months of alectinib treatment, the patient was unsuitable for chemotherapy due to his poor condition as well as his abnormal renal function. Anlotinib was utilized as a fifth-line treatment due to disease progression with no new NGS findings in October 2020. The tumor was responsive to antiangiogenic therapy.

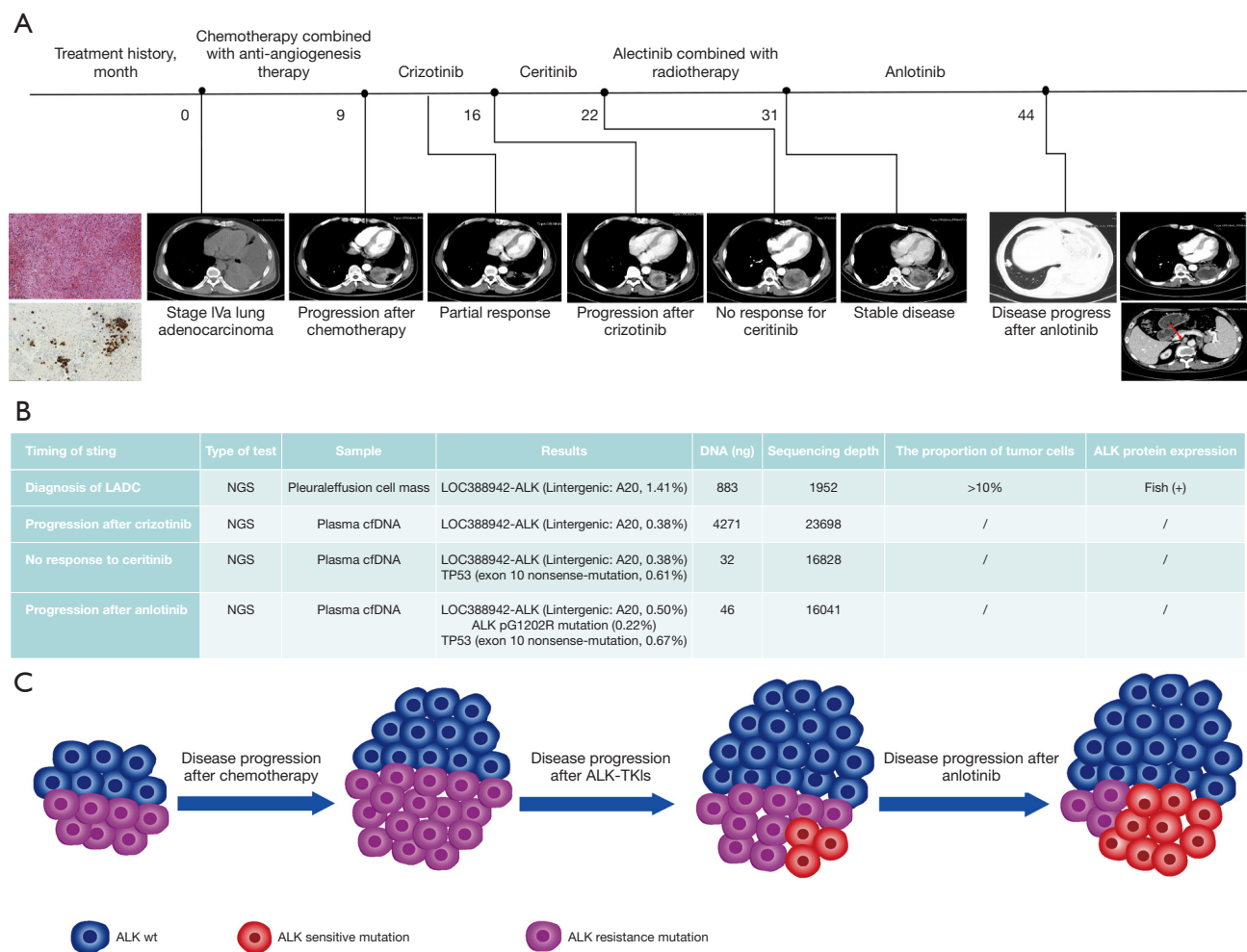


Figure 1 Histological findings and clinical characteristics of the patient. (A) The patient’s diagnosis and treatment history and the disease development. We use HE stain for pathological examination of pleural effusion sample at diagnosis, scale bar 100 μm. Meanwhile, IHC showed ALK-V (+) (Ventana) scale bar 100 μm. The red arrow indicates retroperitoneal lymph nodes. (B) The changes of tumor oncogenes in the process of antitumor therapy. (C) The clonal evolution of the tumor under different treatment pressures. Blue tumor cells represent wide-type clone, orange cells represent ALK-sensitive mutation clone, and purple tumor cells represent ALK-resistant mutation clone. ALK, anaplastic lymphoma kinase; wt, wide type; LADC, lung adenocarcinoma; NGS, next generation sequencing; FISH, fluorescence in situ hybridization; HE, hematoxylin-eosin; IHC, immunohistochemistry.

Thirteen months later, new lesions in the lower lobe of the right lung appeared and increased gradually. Meanwhile, retroperitoneal lymph nodes, including at hepatogastric ligament and para-aortic sites, were also enlarged, indicating definite progression of the tumor. Genetic testing by cfDNA NGS was performed again, which detected the *LOC388942-ALK* fusion (L intergenic: A 20, 0.50%) and the previously detected *TP53* mutation (exon 10 nonsense mutation, 0.67%), but the classical *ALK* G1202R resistance mutation was also detected (0.22%), providing rationale for

the patient to receive treatment with the third-generation ALK-TKI, namely, lorlatinib. However, the patient refused to receive lorlatinib targeting G1202R resistance mutations due to high fee and continued with anlotinib. He dead in August 2022, achieving 5-year OS. We summarized and described clonal evolution of the tumors during the whole clinical history (Figure 1C). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013).

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

LOC388942-ALK fusions are very rare, accounting for approximately 0.01% (1/9,889) of NSCLC cases (17,18). To our knowledge, this study is the first to report the details of the clinical response and resistance mechanism of *LOC388942-ALK* (L intergenic: A20) fusion in *ALK* + NSCLC patients. *LOC388942-ALK* (L intergenic: A20) fusion occurred upon *LOC388942* and *SLC8A1* intergenic region rearrangement to the *ALK* kinase domain (exons 20–29) (Figure 2). In addition, in clinical practice, we also found another *LOC388942-ALK* fusion subtype: dual *ALK* fusions *EML4-ALK* (E6:A20) and *LOC388942-ALK* (L1:A20). For dual *ALK* fusions, the 5' end of *EML4* fused to the entire *ALK* kinase domain (exon 20–29), while *LOC388942* (breakpoint in exon 1) rearranged to exons 1–19 of *ALK* (Figure S1). These two fusion mechanisms are different. As previous study has shown, two different breakpoint *ALK* variants may respond differently to *ALK* inhibitors, such as V1 and V3 of *EML4-ALK* (19). In this regard, the above two different *LOC388942-ALK* fusions may not have the same clinical response and resistance mechanisms. For the *LOC388942-ALK* (L intergenic: A20) fusion in our case, the patient achieved an optimal efficacy of PR with crizotinib as the second-line treatment after progression with first-line chemotherapy, demonstrating that this subtype of fusion site can be sensitive to crizotinib.

After the cancer developed crizotinib resistance, we performed continuous ctDNA monitoring during treatment, with no clear resistance mutation mechanism found over time. According to the literature, a direct switch to a second-generation *ALK*-TKI may be effective in a subset of patients after resistance to a first-generation *ALK*-TKI, even if no clear *ALK* secondary resistance site is found (15). Accordingly, we sequentially administered ceritinib and alectinib to the patient, while radiotherapy for the lung lesions was applied during treatment with alectinib. The pulmonary lesion enlarged slowly, suggesting that the tumor was at least to some extent insensitive to ceritinib and alectinib. After alectinib, as no specific resistance target emerged at that time, we chose anlotinib, a small-molecule multitarget TKI, to extend the patient's progression-free survival (PFS) by another 13 months until comprehensive

tumor progression occurred. Liquid biopsy was performed again, and this time, the classical resistance mutation *ALK* G1202R was identified, thus providing the patient with an opportunity to receive lorlatinib (20). However, the patient refused to receive lorlatinib targeting G1202R resistance mutations due to high fee and continued with anlotinib. He died in August 2022, achieving 5-year OS. To our knowledge, this is the first report to describe detailed clinical information of the rare fusion site *LOC388942-ALK*. Based on the treatment experience of this patient, If he continue to take lorlatinib, longer OS might be observed. Dynamic detection of genetic changes for oncogene-addictive NSCLC can help patients achieve better survival rates. Further, according to current consensus, different generations of *ALK*-TKIs are more likely to produce different types of secondary resistance mutations, while different *ALK* fusion patterns may also affect their resistance mutation sites, as the expression efficiency and signaling strength of *ALK* fusion proteins are influenced by the fused partner genes. For example, two mutation patterns of R1192P and T1151M, which arise in *NPM-ALK*, have never been reported in *ELM4-ALK* fusion genes (12).

Another special feature of this case is that the patient did not develop a known resistance mutation during the course of continuous *ALK*-TKI therapy until after a year of subsequent relatively broad-spectrum anlotinib treatment. This may be due to the sensitivity of liquid biopsy in relation to tumor burden. But this phenomenon also highlights the continuous evolution and clonal evolution of tumors. As Stanková *et al.* (21) suggested the *ALK* fusion-prominent tumor population is gradually reduced to non-dominant *ALK*-positive clones under the continuous therapeutic pressure of *ALK*-TKIs, which is reflected in the slow resistance to *ALK* inhibitors, while other non-dominant clones that are not inhibited by *ALK*-TKIs gradually grow into the main body. After relatively broad-spectrum anticancer treatment with anlotinib, all tumor clones, including non-*ALK*-dependent tumor clones, could have been balanced, at which time the *ALK* G1202R tumor strain, which was latent in the non-dominant clone population but with higher malignancy, was reassessed, evolved toward the dominant clone again, and was finally detected.

This case suggests that in the process of antitumor therapy, real-time dynamic monitoring of tumor dominant subclones by ctDNA and NGS technologies and selecting the most appropriate treatment regimen according to the clonal population of the tumor are important strategies for

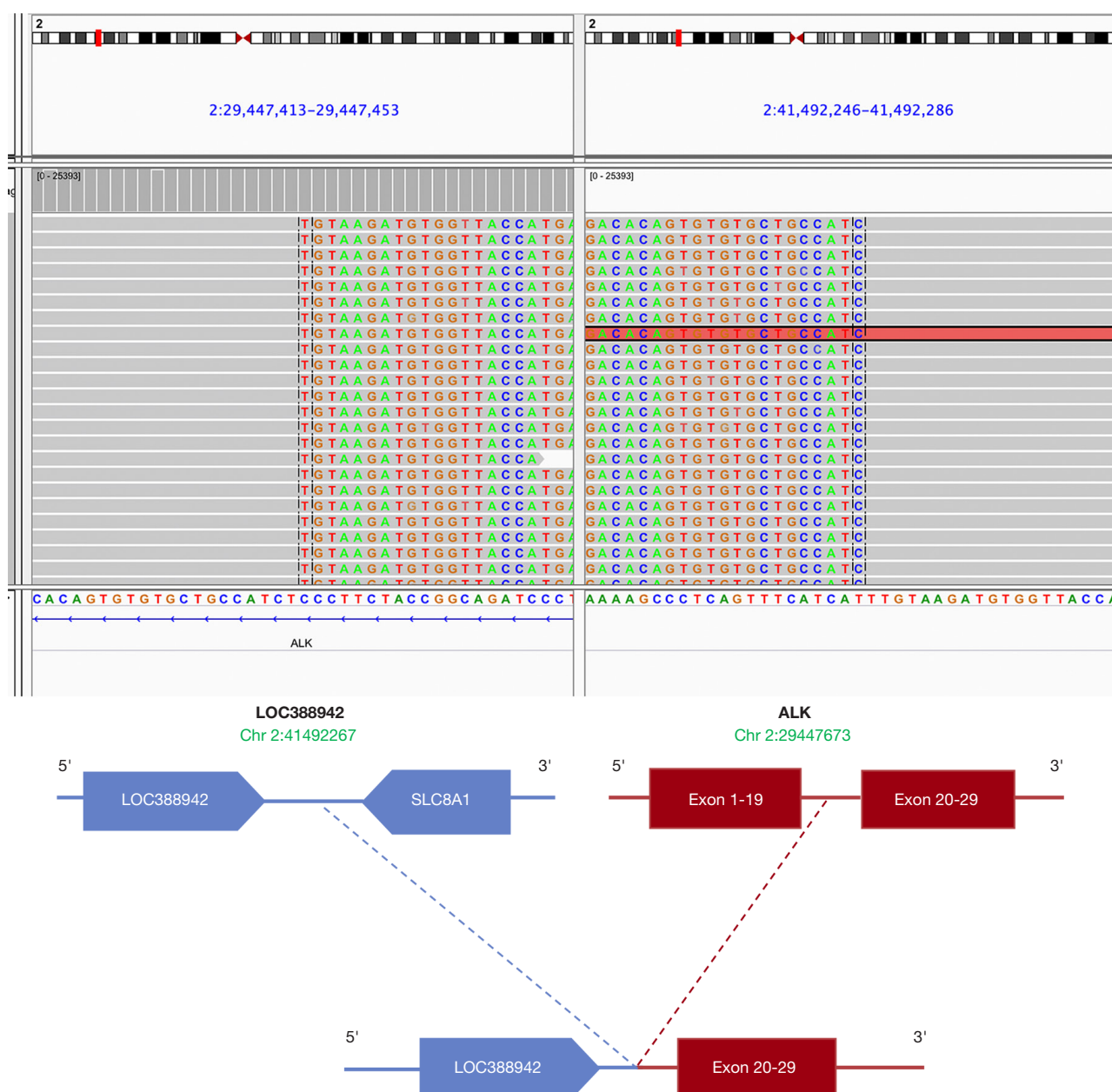


Figure 2 Next-generation sequencing findings of the patient presented by the IGV and diagram. The case harbored LOC388942-ALK (L intergenic: A20) rearrangement, which was the *LOC388942* gene and *SLC8A1* gene intergenic region rearranged to ALK kinase domain (exons 20–29). IGV, integrative genomics viewer; ALK, anaplastic lymphoma kinase.

the precise and individualized treatment of patients. In the era of precision targeted therapy, broad-spectrum antitumor treatment modalities, including chemotherapy and small-molecule multitarget drugs, still have value. How to combine the two therapies will naturally determine whether the longest survival and optimal treatment effect can be

achieved for patients.

Conclusions

In conclusion, here we report for the first time that a LADC patient with a rare *LOC388942*-*ALK* fusion was

sensitive to crizotinib but relatively resistant to ceritinib and alectinib. The patient acquired classical *ALK* G1202R resistance mutations after long-term anlotinib treatment. Distinct *ALK* fusions in NSCLC have different cancer biology, leading to different response to ALK-TKIs, even developed different resistance mechanism. Reporting the clinical details of rare *ALK* fusions in NSCLC is necessary to guide the treatment for clinicians and researchers.

Questions to be further discussed and considered

Question 1: *What might be the reason that NGS of plasma cfDNA did not detect ALK resistance mutation? And what might be the mechanism of no response after the use of crizotinib and ceritinib?*

Stephen V. Liu: This is speculative—could be due to limited sensitivity of the assay or a different mechanism of resistance.

Sang-Won Um: There is a possibility that the allele frequency of ALK resistance mutation might be below the detection limit of plasma NGS. In this case report, the patient was responsive to crizotinib and alectinib, but not ceritinib. Interestingly, Li *et al.* (22) also reported the benefit of sequential ALK-TKIs (alectinib and lorlatinib) for patients with two concurrent non-EML4-ALK rearrangements (LOC388942-ALK and LINC00211-ALK) (1). There was no information on the response of crizotinib and ceritinib for LOC388942-ALK rearrangement in the literature. The mechanism of no response after the use of ceritinib might be due to the intrinsic resistance of this rare non-EML4-ALK rearrangement (LOC388942-ALK) to ceritinib or the development non-ALK dependent bypass mechanisms.

Question 2: *What might be the other mechanism underlying why the patient did not develop a known resistance site during the course of continuous ALK-TKI therapy until after a year of subsequent relatively broad-spectrum anlotinib treatment?*

Stephen V. Liu: It's hard to know for sure. One would not necessarily expect an ALK G1202R mutation to give the lung cancer a competitive advantage in the face of anlotinib. Why would anlotinib apply selective pressure to allow that clone to thrive? Perhaps anlotinib targeted other resistance clones, as you suggest, and 1,202 emerged in the absence of

other, formerly robust clones, but hard to know.

Sang-Won Um: I think that the resistance mutation of ALK G1202R might not develop after anlotinib treatment. It might develop after the use of crizotinib or alectinib. There was no known literature about the development of ALK resistance mutation after anlotinib treatment in patients with ALK-rearranged NSCLC.

Question 3: *How should this patient be treated after disease progression after lorlatinib treatment?*

Stephen V. Liu: Docetaxel or a novel ALK TKI such as NVL-655 or TPX-0131.

Sang-Won Um: The patient already received pemetrexed and cisplatin combined with antiangiogenic therapy for 6 cycles as a first line treatment. One of possible treatment options after progression following lorlatinib treatment would be an IMpower 150 regimen (carboplatin/paclitaxel/bevacizumab/atezolizumab) which demonstrated an improvement in PFS in either EGFR mutant or ALK rearranged non-squamous NSCLC in post-hoc analysis (23). Since the main resistance mechanism of lorlatinib is the dual ALK mutations, double mutant active 4G ALK-TKIs (TPX-0131 or NVL-655) would be the future treatment options (24). They are now under phase 1/2 clinical trials (NCT04849273 and NCT05384626).

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5194/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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