OXFORD

Precision Clinical Medicine, 2023, **6**: pbad011

DOI: 10.1093/pcmedi/pbad011

Correspondence

Partial treatment response to alectinib in metastatic non-small cell lung cancer with KIDINS220-ALK fusion

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Dear Editor,

Anaplastic lymphoma kinase (ALK) rearrangement is a key driver gene in non-small cell lung cancer (NSCLC), and the effectiveness of targeted therapies directed at ALK fusion has been confirmed.[1] However, the activity of ALK-tyrosine kinase inhibitors (ALK-TKIs) against rare ALK rearrangements is variable, with limited clinical evidence. Here, we reported the case of a novel kinase D interacting substrate 220 (KIDINS220)-ALK fusion that showed favorable response to alectinib. Additionally, we examined the treatment option of 36 advanced lung adenocarcinoma cases with unusual ALK fusion types from PubMed in the past 3 years, which may provide valuable information for future treatment.

A 57-year-old Chinese woman without a smoking history initially presented with repeated cough in October 2020. Computed tomography (CT) revealed a soft tissue mass in the posterior segment of the left lower lobe (2.2 cm × 1.8 cm) with enlarged hilar and mediastinal lymph nodes (Fig. 1A). A left lower lobectomy with systematic mediastinal lymph node dissection was performed for definitive diagnosis and treatment in November 2020. Unfortunately, left axillary lymph node (LN) metastasis was confirmed through aspiration needle cytology after surgery. Finally, the patient was diagnosed with stage IV lung adenocarcinoma (pT2aN2M1b) with no targetable genomic alterations found by next-generation sequencing (NGS) (56 gene panel). Subsequently, she was treated with the programmed death 1 (PD-1) antibody camrelizumab plus chemotherapy containing carboplatin and pemetrexed for four cycles followed by maintenance pemetrexed and camrelizumab for ∼1 year until June 2022. During treatment, regular image review of chest CT suggested sustained status of stable disease. However, the carcinoembryonic antigen (CEA) level was slowly elevated during this period (Fig. 1B). 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET/CT) showed multiple abnormally high uptake on the bilateral lung, left pleura, axillary LN and multiple bone lesions in August 2022. Paclitaxel plus carboplatin and bevacizumab were adopted as second-line treatments, which showed poor efficacy, and the CEA level remained elevated. A repeat biopsy of the left axillary lymph node was performed in October 2022, and a wide panel genomic sequencing (pan-cancer 1021-gene panel) detected the KIDINS220-ALK fusion with an allele frequency of 14.9%, which was never previously reported. Immunohistochemical (IHC) staining also confirmed ALK expression (supplementary Fig. 1, see online supplementary material). Then, the patient was initiated on alectinib treatment in October 2022. One month later, the CT showed that the tumor lesions had shrunk, and the efficacy was judged as partial response. Moreover, the CEA level of the patient also decreased significantly (Fig. 1B). After 4 months, this patient still benefited and the lesions had shrunk further on CT. The patient's follow-up and treatment continued.

Targeted therapies stratified by oncogenic drivers have substantially improved outcomes in patients with NSCLC. For patients with driver-negative metastatic NSCLC, immune checkpoint inhibitors are the cornerstone of first-line therapy.[2] However, current approaches do not bring significant clinical benefit to most NSCLC patients due to intrinsic or acquired resistance to continuous treatment. Identifying mechanisms of resistance by studying biopsies taken from sites of secondary progression is important.

Secondary ALK mutations are one of many ways in which tumor cells have adapted to survive and resist therapy. With the rapid development and wide application of NGS technologies, various intergenic region ALK fusions have been reported. DNA-based NGS, fluorescence *in situ* hybridization, RNA and IHC assays may be significant in detecting the ALK rearrangements. When a rare or novel ALK fusion variant is found using DNA-NGS, subsequent RNA assay or IHC could confirm the presence of an active gene fusion that is transcribed and translated to form an oncogenic protein.

Echinoderm microtubule-associated protein-like 4 (EML4)-ALK is the most common and canonical ALK fusion reported in NSCLC. However, heterogeneity of treatment responses exists among different variants of EML4-ALK fusions. Moreover, a small number of patients carry double or triple ALK fusion variants simultaneously. Kang *et al.* showed that such patients potentially have better treatment outcomes with ALK-TKIs therapy.[3] For non-canonical ALK fusions, data on the efficacy of ALK-TKIs are limited and need

Received: March 22, 2023. **Accepted:** May 18, 2023. **Published:** 23 May 2023

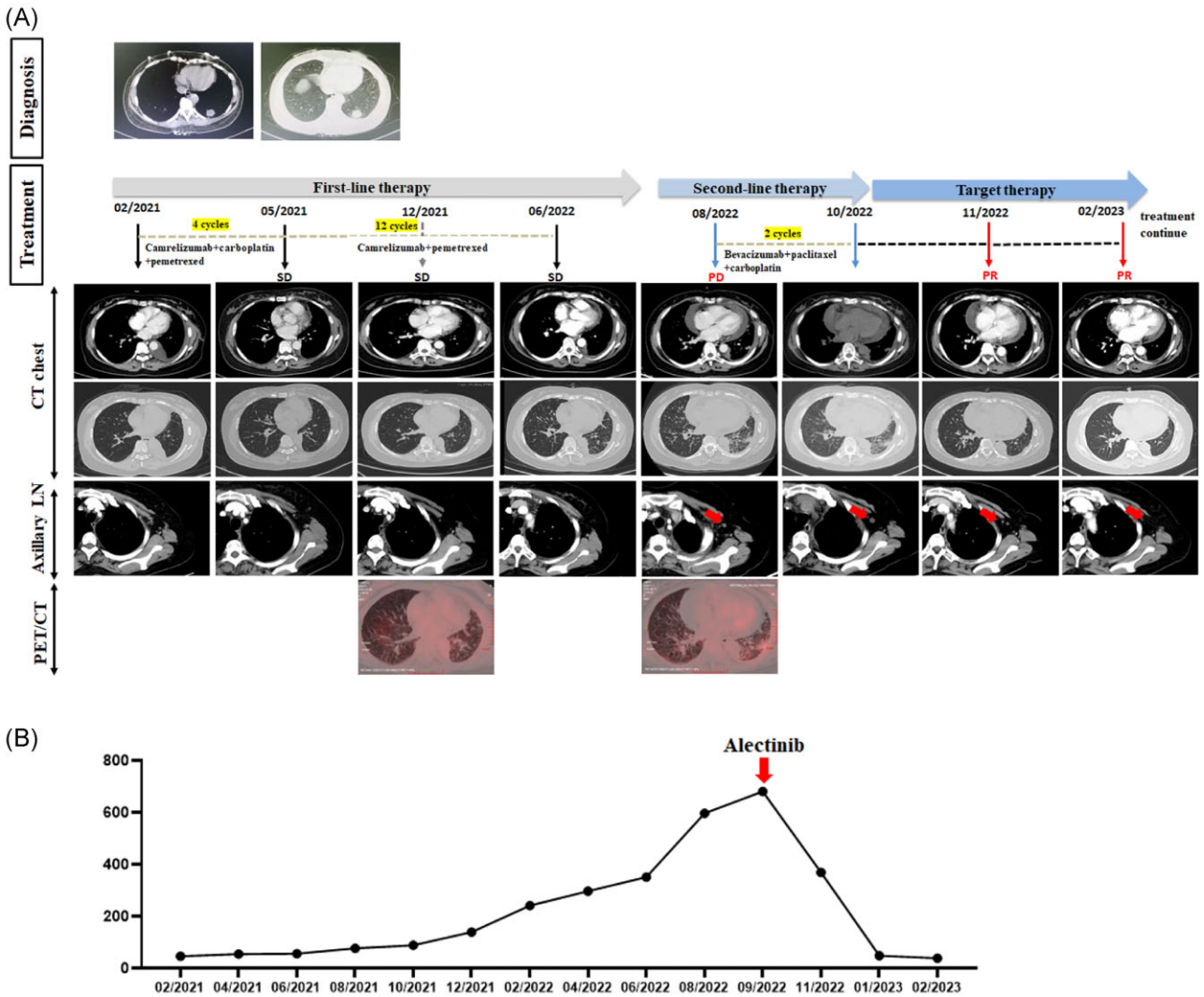

Figure 1. Treatment details, imaging radiographic findings and CEA level of the case. (**A**) Images of chest CT, PET/CT and the left axillary lymph node at different time points. (**B**) Changes in the concentrations of CEA in peripheral blood during treatment.

to be evaluated in the future. Recent studies suggested that the fusion partner may confer differential response to ALK-targeted therapy. ALK must dimerize to automatically activate, which is induced by the ALK partner protein, not the ALK ligand.[4] The fusion partners could determine the spatial and temporal expression patterns of the different ALK fusion proteins. In addition, different ALK fusion proteins exhibit variations in signaling, as well as in their capacity for transformation and tumorigenesis.[4] Another possible explanation for the heterogeneity of responses is the genetic alterations that accompany ALK rearrangements. Thus, it is significant to clarify the comprehensive molecular profile in patients with rare ALK. The NGS assays not only distinguish the subtypes of ALK fusion but also contribute to precise treatment, which goes beyond traditional examinations such as IHC.

To better understand the treatment options and efficacy of ALK-TKIs in patients with uncommon ALK fusions, we reviewed 36 cases reported in PubMed in the last 3 years. First-generation crizotinib or second-generation alectinib is the first treatment choice for these patients. A total of 15 patients (41.6%) received crizotinib and 13 patients (36.1%) received alectinib (supplementary Fig. 2, see online supplementary material). The remaining 8 patients chose other ALK-TKIs, such as ceritinib (8.3%), ensartinib (5.6%), and third-generation lorlatinib (2.7%). The reported mean progression-free survival (PFS) in cases with crizotinib was 10.53 months and with alectinib was 13.08 months. Nine patients experienced treatment failure, but they still benefited from another ALK-TKI drug. The brain and lung are the main metastatic sites. Further large clinical trials are still needed to prove our results. The PFS data in our study were obtained from relevant case reports. At the time of publication, most of those patients do not experience disease progression.

In addition, decisions on optimal treatment should also take into account the toxicity profile. Although generally well tolerated, careful management of adverse effects is still required. The adverse events (AEs) varied among different ALK-TKIs. Fatigue, rash, and edema were common systemic adverse effects of ALK-TKIs. Furthermore, gastrointestinal AEs and anemia were frequently observed in patients treated with ALK-TKIs.[5] Gastrointestinal toxicity is commonly reported with both crizotinib and ceritinib but is more severe with ceritinib.[6] Another characteristic AE of ceritinib is hepatic disorders. For crizotinib, the characteristic AEs are visual disturbances.[7] The most prevalent grade $\geq$ 3 AEs with

alectinib were anemia, increased aspartate transaminase (AST) and increased alanine aminotransferase (ALT).[8] The most common AEs of brigatinib were gastrointestinal AEs, elevated blood creatine kinase levels, and increased ALT levels.[9] Brigatinib also has a greater incidence of interstitial lung disease or pneumonitis than crizotinib. Lorlatinib has a relatively broad toxicity profile, hypercholesterolemia, hypertriglyceridemia, and edema are common AEs.[10] Additionally, lorlatinib is associated with increased central nervous system toxicity.

In conclusion, we first described a novel KIDINS220-ALK fusion in lung cancer that enriches the knowledge of ALK fusion types. And our patient rapidly responded to alectinib with remarkable therapeutic effect. Additionally, we reviewed the treatment options for rare ALK fusions, which may provide a reference for clinicians to make treatment decisions in the clinic.

Supplementary data

Supplementary data is available at *PCMEDI* online.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grants No. 81872489 and 82073369) and the Natural and Science Foundation of Sichuan Province (Grant No. 2022NSFSC1412). We thank the patient for providing informed consent for publication of this work.

Conflict of interest

All authors declare no conflicts of interest in relation to this work.

Author contributions

Y.W.: conceptualization. Y.L. and S.Z.: original draft preparation. All authors: supervision and editing of the original paper.

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Received: March 22, 2023. **Accepted:** May 18, 2023. **Published:** 23 May 2023