Response of a Novel KANK1::ALK Fusion to Alectinib in an Advanced Lung Adenocarcinoma: A Case Report

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ABSTRACT

More than 90 distinct fusion partners of ALK rearrangement have been identified. Different ALK fusions may exhibit different sensitivities to ALK tyrosine kinase inhibitors. The emergence of rare fusions poses significant challenges to targeted therapies. This study aimed to investigate the response of KANK1::ALK fusion to alectinib in an advanced lung adenocarcinoma. A novel KANK1::ALK fusion was identified by next-generation sequencing (NGS) and Ventana immunohistochemistry assessments. A 73-year-old woman who had never smoked was admitted with hemoptysis in May 2020. PET/CT revealed a nodule in the left upper lobe, with bilateral pulmonary and multiple lymph node metastases. The upper lobe nodule of the left lung was diagnosed as adenocarcinoma through bronchofiberscopy biopsy, resulting in a clinical diagnosis of stage IVA (cT1c,N3,M1a). Because the biopsy tissue was insufficient for NGS analysis, a blood-based genetic analysis was performed, revealing the presence of KRAS p.Q61R mutations. The patient received carboplatin and pemetrexed with pembrolizumab as first-line therapy, followed by maintenance therapy of pembrolizumab monotherapy. Although the tumor initially showed significant shrinkage, it unfortunately progressed further after 11 months. Subsequently, the patient was given carboplatin and pemetrexed with pembrolizumab again, but the tumor progression continued. An NGS using a rebiopsy of the left upper lobe tumor suggested a KANK1::ALK fusion. Alectinib was prescribed in January 2022, and a durable partial response was observed after 18 months. ALK rearrangements were observed in the broader spectrum of lung cancers. This study provided a potential treatment option for patients with KANK1::ALK fusions. Further studies are needed to understand the function of these fusions.

ALK gene rearrangement is found in approximately 4% of patients with lung cancer, with the most frequent ALK rearrangement being EML4::ALK. Patients with ALK-positive lung cancer can achieve remarkable effects from ALK tyrosine kinase inhibitors (TKIs), including crizotinib, alectinib, ceritinib, brigatinib, and lorlatinib. Alectinib is considered the first-line treatment for patients with metastatic ALK-positive non–small cell lung cancer (NSCLC). It is noteworthy that >90 ALK fusion partners have been reported, and different ALK fusions exhibit distinct responses to ALK TKIs. This study was novel in reporting the detection of KANK1::ALK fusion by next-generation sequencing (NGS) in a patient with lung adenocarcinoma.

The study was approved by the ethics committee of Tianjin Medical University General Hospital. Written informed consent was obtained from the patient to publish case details and images.

Case Presentation

In May 2020, a 73-year-old woman who had never smoked was admitted to Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital with hemoptysis. The treatment flowchart for this patient is depicted in Figure 1. Chest CT revealed a soft tissue density nodular shadow in the upper lobe of the left lung, multiple suspicious metastatic nodules in the middle lobe and the lower lobe of the right lung, and enlarged mediastinal lymph nodes. MRI of the head and abdominal CT revealed no abnormalities. PET/CT revealed a hypermetabolic nodule in the left upper lobe, as well as bilateral pulmonary and multiple lymph node metastases. The bronchoscopic biopsy confirmed adenocarcinoma in the upper lobe nodule of the left lung, leading to a clinical diagnosis of stage IVA disease (cT1c,N3,M1a). Immunohistochemical stains were positive for TTF-1, CK7, NapsinA, p63, and CK5/6, but negative for p40, CD56, CgA, and Syn. The Ki-67 index was approximately 30% (see Figure S1 in the supplemental materials, available online).

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with this article). The patient refused a rebiopsy of lung tumor, and the remaining biopsy tissue was insufficient for immunohistochemistry and NGS analysis. Therefore, a blood-based 420-gene NGS (depth 10,000; Illumina, YinFeng Gene Technology Co., Ltd.) was conducted, revealing the presence of a KRAS p.Q61R mutation (0.6%).

The patient was then treated with pemetrexed (500 mg/m² intravenously on day 1 every 3 weeks) and carboplatin (area under the plasma concentration-time curve, 5 mg/mL per min intravenously on day 1 every 3 weeks) in combination with pembrolizumab (200 mg/bodyweight intravenously on day 1 every 3 weeks). An almost complete response was achieved after 5 treatment cycles, followed by maintenance therapy of pembrolizumab monotherapy. However, the tumor relapsed after 11 months. The patient was subsequently treated with carboplatin and pemetrexed with pembrolizumab, but the tumor continued to progress further. A rebiopsy of the left upper lobe tumor was performed, revealing the presence of a KANK1::ALK fusion (12.58%) through NGS analysis (206-gene panel, depth 1,200; MGISEQ-2000, BGI Genomics) (Figure 2A), which was validated by Ventana immunohistochemical staining of ALK (see Supplementary Figure S2B). Alectinib was prescribed at 600 mg orally twice daily beginning January 2022, and a rapid clinical response was observed. As of the time of writing, a continuous partial response (PR) had been noted for >18 months.

Discussion
This study was novel in reporting the case of a patient with alectinib-responsive lung adenocarcinoma having a KANK1::ALK fusion. The ALEX study recommends alectinib as the first-line treatment in patients with NSCLC having advanced ALK positivity.9 However, patients with NSCLC having different ALK fusions respond to ALK TKIs differently.8,10 Our study detected the KANK1::ALK fusion, which represented a translocation between KANK1 exons 1–3 on chromosome 9 and ALK exons 20–29 on chromosome 2. It retained the N-terminal coiled-coil domains of KANK1 and the intracellular ALK region containing the tyrosine kinase domain (Figure 2B). Additionally, the Ventana ALK (D5F3) CDx IHC assay confirmed ALK protein expression. Previous reports11 have suggested that KANK1, a tumor suppressor gene, can mediate paclitaxel resistance in lung adenocarcinoma A549 cells. In addition, a previous study also reported a pancreatic neuroendocrine carcinoma patient with a KANK1::ALK fusion who exhibited a rapid and profound response to the ALK inhibitor lorlatinib.12 Like our case, the ALK protein tyrosine kinase domain located between exons 20 and 28 is expected to be retained in the fusion product. ALK fusion resulted in the production of oncogenic ALK tyrosine kinase, which activated several downstream signaling pathways.13 This led to tumorigenesis due to uncontrolled cell proliferation. The growth of cancer cells with ALK-positive signals was inhibited by ALK TKIs, which blocked the abnormal ALK

Figure 1. Clinical treatment history and imaging data of the patient. May 2020 is when the KRAS mutation was detected, and January 2022 is when the KANK1::ALK fusion was detected.

Abbreviations: NGS, next-generation sequencing; PD, progressive disease; PFS, progression-free survival; PR, partial response.
The patient experienced a significant PR after treatment with alectinib, and progression-free survival exceeded 18 months. Therefore, the novel KANK1::ALK fusion was sensitive to alectinib in lung adenocarcinoma. Due to the small amount of tumor tissue, it was impossible to perform a primary culture of the tumor cell or establish a PDX/CDX model; therefore, a lack of functional validation of the KANK1::ALK fusion is a limitation of our study.

Immunotherapy produces a poor response compared with targeted therapies for advanced NSCLC harboring driver mutations such as EGFR or ALK mutations. PD-1/PD-L1 inhibitors, however, are more effective in patients with KRAS mutations than in those with wild-type KRAS. The findings revealed that KRAS mutations led to a tumor microenvironment that was inflammatory and immunogenic, resulting in a superior response to PD-1 inhibitors in patients with KRAS mutations. However, not all patients with KRAS mutations benefit from anti–PD-1 immunotherapy. Previous articles have mentioned different immunotherapy benefits for different KRAS mutation

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**Figure 2.** NGS analysis of genomic DNA identified a fusion variant of KANK1 intron 3 with ALK intron 19. (A) Paired-end sequencing data from tumor tissue samples indicated somatic interchromosomal KANK1::ALK fusion as demonstrated by Integrative Genomics Viewer program (Broad Institute; https://igv.org/app). (B) Diagram depicting the KANK1::ALK fusion (K3::A20). Abbreviations: bp, base pairs; cc, coiled coil domain; Chr, chromosome; NGS, next-generation sequencing.
subtypes. For example, a recent study elucidated the molecular mechanisms by which \textit{KRAS} G12D mutations drive immunosuppression and enhanced resistance to immune checkpoint inhibitors in NSCLC. At the same time, the results also suggest that immune checkpoint inhibitors combined with chemotherapy may be more effective in patients with NSCLC with \textit{ALK} G12D mutation. However, how NSCLC with \textit{KRAS} p.Q61R mutation responded to immunochemistry was still not clear. \textit{ALK} p.Q61R mutations were detected in the patient. Because no positive driver gene mutations were detected by the blood-based NGS, we prescribed pemetrexed and carboplatin with pembrolizumab for the patient. Due to significant grade 3 leukopenia during maintenance therapy, the patient was treated with pembrolizumab monotherapy. The tumor exhibited a significant response after 5 cycles of chemoinmunotherapy but further relapsed after 11 months. An NGS using a rebiopsy of the left upper lobe tumor suggested a \textit{KANK1::ALK} fusion. Multiplex immunostaining (GeneCast Biotechnology) was performed using the tumor tissue of prior and post immunochemistry to explore the characterization of immunochemistry resistance. The staining data (see Supplementary Figure S2C, D) demonstrated that the proportion of M2 macrophages increased after the immunochemistry resistance. The number of CD4+ FOXP3+ cells increased, although without statistical significance. Therefore, these changes suggest that the tumor microenvironment (TME) turns into a more immunosuppressive state. The reason is probably due to the redistribution of immune and inflammatory cells and the \textit{ALK}-mutant tumor cell expansion after immunochemistry. The exact underlying mechanisms need to be further explored.

We retrospectively performed Ventana immunochemical staining of \textit{ALK} on the tumor tissue from a bronchoscopic biopsy, and it also showed positive \textit{ALK} expression (see Supplementary Figure S3). This patient may have \textit{KRAS} and \textit{ALK} co-mutations in the baseline stage, probably due to the tumor heterogeneity. We hypothesized that only \textit{KRAS} mutation was detected at the baseline due to the limited sequencing depth from the blood and less quantity of \textit{ALK}-mutated cells. Previous studies\textsuperscript{19} revealed primary resistance to \textit{ALK} inhibitors due to \textit{KRAS} mutation, and platinum-containing chemotherapy should be used as first-line therapy for \textit{ALK/KRAS} double-mutant NSCLC. Therefore, the use of chemoimmunotherapy for first-line treatment in this study is also reasonable. Moreover, \textit{KRAS} and \textit{ALK} mutations might occur exclusively in NSCLC.\textsuperscript{20} At first, the cell population with \textit{KRAS} mutation might occupy most of the tumor. However, \textit{KRAS}-mutated tumors were significantly killed after the immunochemistry. Also, the tumor cells with \textit{ALK} mutation eventually expanded faster and dominated, forming an immunosuppressive microenvironment. This was also consistent with findings from our previous study,\textsuperscript{21} suggesting that patients with \textit{ALK}-positive NSCLC are more likely to have an immunosuppressive TME than those with \textit{KRAS}-positive NSCLC.

**Conclusions**

This study was novel in reporting the case of a patient with lung adenocarcinoma harboring a \textit{KANK1::ALK} (K3::A20) fusion. Data analysis in this study confirmed that the ALK TKI alectinib was effective in this rare type of NSCLC with fusion. Moreover, the tumor immunologic microenvironment was also explored. \textit{ALK} arrangement types can be expanded and treatment regimens for lung adenocarcinomas can be explored based on the findings of this study.

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