Case Report

# Primary resistance to ALK inhibitors in *KLC1/ALK*-rearranged pleural metastatic lung adenocarcinoma: a case report

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**Background:** Anaplastic lymphoma kinase (*ALK*) rearrangement confers sensitivity to second- and third-generation ALK inhibitors, which have become the standard of care for ALK-positive non-small cell lung carcinoma (NSCLC). However, primary resistance to these inhibitors remains a rare and poorly understood phenomenon, especially in cases involving kinesin light chain 1 (*KLC1*)/*ALK*-rearranged metastatic NSCLC.

**Case Description:** In this report, we present a unique and challenging case of primary resistance to second- and third-generation ALK tyrosine kinase inhibitors (TKIs) attributed to *KLC1/ALK* gene fusion partners in a patient with ALK-positive pleural metastatic NSCLC. The patient's disease progression was rapid and unresponsive to multiple lines of ALK-targeted therapies, including alectinib, brigatinib, and lorlatinib, underscoring the need for a deeper understanding of primary resistance mechanisms in such cases.

**Conclusions:** The occurrence of primary resistance to ALK inhibitors in metastatic NSCLC with *ALK* rearrangement is an infrequent occurrence, and its underlying mechanisms remain elusive. This case emphasizes the importance of further research to elucidate the specific mechanisms of primary resistance to ALK TKIs in non-canonical *ALK* fusion partners like *KLC1*. Developing targeted therapies for such rare cases is a clinical challenge that warrants continued investigation and innovation in the field of precision oncology.

**Keywords:** Kinesin light chain 1/anaplastic lymphoma kinase rearrangement (*KLC1/ALK* rearrangement); non-small-lung carcinoma; primary resistance; case report

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## Introduction

Anaplastic lymphoma kinase (*ALK*) translocations are found in 3% to 8% of non-small cell lung carcinomas (NSCLCs) (1,2). These oncogenic driver mutations are common in young and never smokers (3). As *ALK* rearrangement is targetable and confers sensitivity to tyrosine kinase inhibitors (TKIs), alectinib, brigatinib or lorlatinib, second- and third-generation ALK inhibitors have become the standard of care in metastatic *ALK*-rearranged NSCLC (4). Echinoderm microtubule-associated protein 4 (*EML4*) is the most common fusion partner of *ALK* (3). Several other fusion partners, such as kinesin light chain 1 (*KLC1*), *KIF5B*, *TFG*, *TPR*, *HIP1*, *STRN*, *DCTN1*, *SQSTM1*,

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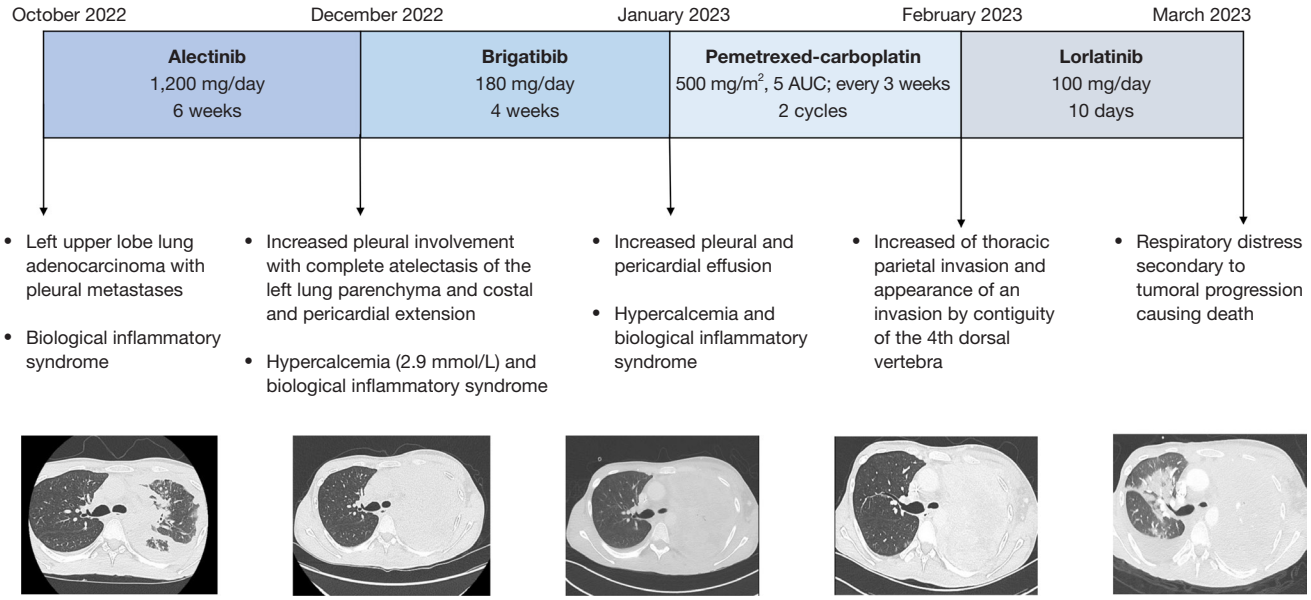


**Figure 1** Timeline of therapeutic management. AUC, area under the curve.

*NPM1*, *BCL11A*, and *BIRC6*, have been described (5,6). Sensitivity to ALK inhibitors remains unclear in these cases. Mechanisms of acquired resistance to ALK inhibitors have been identified, such as *ALK* mutations (L1196M, I1171T, D1203N, G1269A/F1174L, G1202R, W1295C, G1202R/L1196M, G1202R/G1269A) and bypass mutations in other genes, such as *NRAS* G12V, *EGFR* R108K, *PIK3CA* E545K, *EGFR* P753S, *BRAF* V600E, and *MET* D1246N (7-9).

This is a report of a rare case of primary resistance to second- and third-generation ALK inhibitors in *KLC1/ALK*-rearranged pleural metastatic lung adenocarcinoma. We present this article in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-482/rc).

### Highlight box

**Key findings**

- Kinesin light chain 1 (*KLC1*) is a fusion partner gene of anaplastic lymphoma kinase (*ALK*) which induces primary resistance to ALK tyrosine kinase inhibitors (TKIs).

**What is known and what is new?**

- Echinoderm microtubule-associated protein 4 (*EML4*) is the most common gene fusion partner in *ALK*-rearranged lung adenocarcinoma and confers sensitivity to ALK TKIs.
- The efficacy of ALK TKIs in non-*EML4/ALK*-rearranged lung adenocarcinoma is unclear.

**What is the implication, and what should change now?**

- Additional investigations of *ALK* fusion partners are needed to understand the mechanisms of primary resistance to treatments.
- Targeted therapy development for non-*EML4/ALK*-rearranged non-small cell lung cancer is required within clinical practice.

## Case presentation

In September 2022, a 34-year-old male never smoker with a medical history of acquired immunoglobulin deficiency was diagnosed with left pleural metastatic ALK-positive lung adenocarcinoma (*Figure 1*). Molecular analysis confirmed *ALK* rearrangement with *KLC1* gene fusion partner. The diagnosis was made on pulmonary biopsy and the fusion transcripts were identified by a technique of New Generation Sequencing using the panel FusionPlex Lung, #SK0133, ArcherDx. Alectenib, as a first-line treatment, was started in October 2022. Six weeks later, dyspnea worsened. A thoracic computed tomography (CT) scan confirmed left pulmonary progression with costal extension and increased pleural involvement. Paraneoplastic hypercalcemia (2.90 mmol/L) and biological inflammatory syndrome (C reactive protein at 135.3 mg/L) were also present. Liquid biopsy revealed 10,600 copies/mL of circulating plasmatic tumor cell DNA and concomitant *E285K* mutation in exon 8 of the *TP53* gene. Brigatinib, as a second-line treatment, was started in December 2022, without any clinical or

radiological efficacy after 5 weeks of treatment. His dyspnea and performance status worsened. A thoracic CT scan revealed left pleuropulmonary tumor progression and non-compressive pericardial effusion, which was confirmed by transthoracic echocardiography. Due to primary resistance against two ALK inhibitors, carboplatin plus pemetrexed was administered on 10 January. Bevacizumab was not administered due to hemoptysis. After two cycles of chemotherapy, a thoracic CT scan showed locoregional tumoral progression with contiguous invasion of the 4th dorsal vertebra. Liquid biopsy confirmed progression with >30,000 copies/mL circulating tumor cell DNA. Circulating plasmatic tumor cell DNA next-generation sequencing (Foundation oneCDx) identified the *KLC1/ALK* fusion associated with *MTAP* loss of exons 6–8, *CDKN2A* loss, *CDKN2B* loss, Q2274 *EP300* gene mutation, and E285K mutation in exon 8 of the *TP53* gene. There was no microsatellite instability, and the tumor mutational burden was low (2 Muts/Mb). Hypercalcemia and biological inflammatory syndrome persisted. Seven days after beginning lorlatinib as fourth-line treatment, the patient presented respiratory distress secondary to tumoral progression, leading to death at 7 months after diagnosis. A pulmonary biopsy was performed shortly before the patient's passing, confirming that there had been no transformation in a small cell lung cancer.

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 Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made. We made sure that this case report was sufficiently anonymized and patient identifiers were all removed.

## Discussion

Second-generation and recently third-generation ALK inhibitors are the standard of care for metastatic *ALK*-rearranged NSCLC, with a 24- and 34.8-month median progression free survival (PFS) with brigatinib and alectinib, respectively and a 12-month PFS rate of 78% with lorlatinib. After failure of ALK inhibitors, chemotherapy based on platinum, pemetrexed and bevacizumab has clinical efficacy, with a 4.3-month median PFS (4,10-12). Data about acquired resistance mechanisms of ALK inhibitors have been reported. On the one hand, ALK-dependent resistance leads to structural changes in the kinase domain that interfere with binding of the drug; on the other hand, ALK-independent resistance leads to activation of bypass signaling pathways (13). There are few data evaluating mechanisms of primary resistance to ALK inhibitors.

As *EML4* is the most common gene fusion partner in ALK-rearranged lung adenocarcinoma, some non-*EML4* genes have been identified, such as *KLC1* (5). Despite a lack of guidelines, second- and third-generation ALK inhibitors are recommended in non-*EMLA4*/ALK-rearranged lung adenocarcinoma. Some studies have evaluated ALK inhibitor sensitivity in these cases, with conflicting results (14,15). Due to the rarity of *KLC1* fusion, there is a lack of data evaluating ALK inhibitor outcomes in *KLC1/ALK*-rearranged NSCLC. One study including 31 patients with uncommon *ALK* fusion partners in which two cases of *KLC1/ALK*-rearranged NSCLC treated with crizotinib found a shorter median PFS than for those with canonical *ALK* fusion (8.4 in the non-*EMLA4* group versus 12.0 months in the *EMLA4* group, P=0.004) (16). A case report showed crizotinib efficacy in a patient with both hepatocyte growth factor receptor (*MET*) gene amplification and *KLC1/ALK* fusion (17). Crizotinib efficacy might be explained by concomitant *MET* amplification. In the present case, next generation sequencing (NGS) revealed *KLC1/ALK* fusion associated with *MTAP* loss of exons 6–8, *CDKN2A* loss, *CDKN2B* loss, Q2274 mutation of the *EP300* gene, and E285K mutation in exon 8 of the *TP53* gene. None of these genetic alterations are targetable. Those co-mutations are described in the literature as responsible of primary resistance to TKI and may explain the ALK inhibitor resistance observed in this case (18-20). Moreover, the presence of TP53 mutations in ALK-positive adenocarcinomas is associated with significantly shorter progression-free survival regardless of the treatment received, highlighting the potential role of TP53 as a predictive biomarker for TKI resistance (21). Repeat liquid biopsies might be helpful to detect resistance mechanisms throughout the patient follow-up (22).

This unique case report assessing the importance of investigating *ALK* fusion partners at diagnosis of ALK positive NSCLC to highlight potential primary resistance to ALK TKIs. Development of targeted therapies in non-*EML4/ALK*-rearranged *NSCLC* is needed to improve the prognosis of these patients.

## Conclusions

To our knowledge, this case reported at first time primary

resistance to second- and third-generation ALK inhibitors in an *ALK*-rearranged metastatic NSCLC with *KCL1* gene fusion partner.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-482/rc

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-482/coif). The authors have no conflicts of interest to declare.

*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 Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made. We made sure that this case report was sufficiently anonymized and patient identifiers were all removed.



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