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Triple inhibition of ALK, BRAF, and MEK for acquired BRAF V600E after lorlatinib resistance in ALK-rearranged lung adenocarcinoma: a case report

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Case Report

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Abstract

Background

Acquired resistance to *ALK* tyrosine kinase inhibitors (TKIs) is molecularly heterogeneous, and *BRAF* V600E as a bypass mechanism after *ALK*-TKI therapy has been rarely reported. The optimal treatment strategy after its detection remains undefined. **Case presentation**: A 42-year-old man with stage IVA lung adenocarcinoma (PD-L1 tumor proportion score, 60%) progressed after sintilimab and subsequent platinum-pemetrexed plus bevacizumab. Re-biopsy identified *EML4-ALK*, and lorlatinib was initiated as first *ALK*-targeted therapy, achieving durable disease control for over 36 months. In January 2026, thoracic progression prompted repeat next-generation sequencing, revealing persistent *ALK* rearrangement and newly acquired *BRAF* V600E. Lorlatinib was continued with dabrafenib and trametinib added. Computed tomography showed marked tumor shrinkage after 1 month, and subsequent follow-up demonstrated continued lesion shrinkage with ongoing disease control for more than 6 months.

Conclusion

Repeat molecular profiling at *ALK*-TKI progression is essential. Concurrent *ALK/BRAF/MEK* inhibition may be effective when post-progression profiling demonstrates persistent *ALK* rearrangement and acquired *BRAF* V600E.

Introduction

ALK rearrangements define a clinically important subset of advanced non-small cell lung cancer (NSCLC). The development of *ALK* tyrosine kinase inhibitors (TKIs) has substantially improved survival for patients with *ALK*-rearranged NSCLC. Among these agents, the third-generation *ALK*-TKI lorlatinib has demonstrated durable systemic and intracranial efficacy. In the phase III CROWN study, after 7 years of follow-up, median progression-free survival (PFS) remained unreached with lorlatinib (7-year PFS rate, 55% vs. 3% with crizotinib; hazard ratio [HR], 0.19), accompanied by a 94% reduction in the risk of intracranial progression (HR, 0.06)—representing the longest PFS reported with any single-agent targeted therapy in advanced NSCLC.[1,2] Moreover, no new intracranial progression events occurred after the first 30 months, with a 92% probability of remaining free of intracranial progression at 7 years. Real-world data from China have confirmed durable efficacy outside the trial setting, with a median PFS of 37.8 months in a multicenter cohort.[3] Resistance to *ALK* inhibition, however, remains inevitable and may involve secondary *ALK* alterations, bypass pathway activation, or phenotypic transformation. *BRAF* V600E is a rare reported bypass alteration after *ALK*-TKI exposure, and the optimal treatment after its detection is unclear.[4–6] We report a case of acquired *BRAF* V600E after prolonged lorlatinib benefit in which continued lorlatinib plus dabrafenib and trametinib produced a rapid radiographic response.

Case Presentation

A 40-year-old man presented in June 2020 with left pleural effusion. computed tomography (CT) showed a left upper lobe lesion with pleural disease, and pleural fluid cytology confirmed lung adenocarcinoma. He was diagnosed with stage IVA lung adenocarcinoma (cT3N2M1a) involving the left upper lung, mediastinal lymph nodes, and pleura. Brain magnetic resonance imaging was negative. PD-L1 tumor proportion score was 60%. Initial molecular testing of pleural effusion sediment cells did not identify any actionable alterations.

Sintilimab monotherapy was started on August 6, 2020. After four cycles, disease control was unsatisfactory. On October 21, 2020, the patient began pemetrexed, carboplatin, and bevacizumab for four cycles, followed by pemetrexed plus bevacizumab maintenance, achieving partial response. In December 2022, CT showed systemic progression, including intrathoracic lymph node enlargement, new liver lesions, abdominal and retroperitoneal lymphadenopathy, left adrenal thickening, and new bone lesions. Axillary lymph node biopsy confirmed metastatic lung adenocarcinoma. Targeted next-generation sequencing (NGS) of the formalin-fixed paraffin-embedded axillary lymph node sample identified *ALK* rearrangements, including *EML4-ALK* fusion (variant allele fraction, VAF, 1%) and *ZNF804A-ALK* (VAF, 16%). Lorlatinib 100 mg once daily was initiated on January 7, 2023, as first *ALK*-targeted therapy. Follow-up CT on February 3, 2023, showed shrinkage of mediastinal lymph nodes, liver lesions, and abdominal lymph nodes. The patient continued lorlatinib with durable disease control for more than 36 months.

In January 2026, CT showed thoracic progression, with enlargement of a left upper lung/mediastinal lesion compared with September 2025. Hybrid-capture targeted NGS using an Illumina MiSeqDx platform identified newly acquired *BRAF* p.V600E (VAF, 2.10%), while the previously detected *EML4-ALK* fusion (VAF, 1.43%) and *ZNF804A-ALK* fusion (VAF, 1.61%) remained detectable. Given persistent *ALK* rearrangement and newly detected *BRAF* V600E, lorlatinib was continued and dabrafenib 150 mg twice daily plus trametinib 2 mg once daily were added on February 3, 2026. CT on March 2, 2026, showed marked shrinkage of the dominant left upper lung/mediastinal lesion and a posterior left upper lobe nodule, suggestive of partial response. Serial follow-up CT scans thereafter showed further lesion shrinkage, and disease control was maintained for more than 6 months after initiation of triple targeted therapy. The combination was generally well tolerated, with grade 1 hyperlipidemia, anemia, and hyperbilirubinemia reported; no diarrhea, fever, or clinically significant hepatic toxicity occurred. The patient's treatment history, molecular findings, and serial imaging changes are summarized in Fig. 1.

Discussion

Acquired resistance to *ALK*-TKIs is molecularly diverse. Secondary *ALK* kinase-domain mutations, particularly compound mutations such as G1202R/L1196M, are common on-target mechanisms, whereas bypass activation—including *MET* amplification, MAPK pathway activation, and *EGFR* upregulation—represents an important off-target mechanism.[7,8] Recent integrated genomic and proteomic analyses have further confirmed that MAPK signaling activation contributes to acquired lorlatinib resistance, and preliminary preclinical data suggest that combining lorlatinib with the *MEK* inhibitor trametinib may overcome this resistance.[9] In the present case, after more than 36 months of disease control on lorlatinib

—a duration that compares favorably with the 7-year PFS rate of 55% reported in CROWN[1,2]—thoracic progression was accompanied by persistent *ALK* rearrangement and newly detected *BRAF* V600E, suggesting ongoing *ALK* dependence together with MAPK pathway bypass activation.

However, the optimal treatment strategy after detection of *BRAF* V600E in *ALK*-rearranged NSCLC remains uncertain. In *BRAF* V600E-mutant metastatic NSCLC without another dominant oncogenic driver, dabrafenib plus trametinib has established activity.[10] In the setting of acquired resistance to *ALK*-TKIs, however, the biology may be distinct: persistent *ALK* dependence may coexist with the newly acquired bypass driver, and simply switching *ALK*-TKIs or administering *BRAF/MEK* inhibition alone may be insufficient. Indeed, several reported patients had limited benefit from either switching *ALK*-TKI alone or administering *BRAF/MEK* inhibition without continued *ALK* suppression.[4–6] The preclinical study by Shi et al. provides a plausible explanation: when *ALK* rearrangement persists together with a *BRAF*-driven bypass pathway, the present case suggests that concurrent inhibition of both *ALK* and MAPK signaling may represent a rational therapeutic approach in selected patients.[8]

Previously reported cases are summarized in Table 1. The present case is clinically informative because continuing lorlatinib with the addition of dabrafenib and trametinib produced rapid radiographic tumor shrinkage after 1 month, followed by continued lesion shrinkage and disease control beyond 6 months. Together with the absence of grade 2 or higher adverse events, these findings suggest that triple targeted therapy achieved marked and durable antitumor activity with favorable tolerability in this patient. This observation is mechanistically consistent with recent preclinical evidence that lorlatinib combined with trametinib can overcome MAPK pathway-mediated resistance[9] and supports the concept that concurrent *ALK/BRAF/MEK* inhibition may be appropriate in selected patients when post-progression profiling demonstrates both persistent *ALK* rearrangement and acquired *BRAF* V600E.

Table 1
Published clinical reports of BRAF V600E detected after ALK-TKI resistance.

Study	Setting	Prior *ALK*-TKI	Resistance finding	Treatment after *BRAF* detection	Outcome/conclusion
Urbanska et al., 2020	Serial re-biopsies in *ALK*-rearranged metastatic NSCLC	Crizotinib, ceritinib, and alectinib sequentially	*BRAF* V600E emerged after ceritinib and persisted after later progression	Alectinib with mixed response; later pemetrexed, alectinib rechallenge, and lorlatinib	Supports *BRAF* V600E as a rare bypass resistance alteration; *BRAF*/*MEK* inhibitors were not used at that time; ultimately, lorlatinib was ineffective
Zhang et al., 2022	Advanced lung adenocarcinoma with *EML4-ALK* and high PD-L1	Alectinib	Liver biopsy showed *BRAF* V600E with persistent *EML4-ALK*	Ensartinib + dabrafenib, then lorlatinib + dabrafenib	Ensartinib + dabrafenib caused fever, chills, fatigue, and anorexia; PD after 1 month. Lorlatinib + dabrafenib: PD. OS: 10 months.
Ogimoto et al., 2024	Young adult with HIP1-*ALK*-rearranged lung adenocarcinoma	Alectinib, then lorlatinib	Pericardial effusion showed *BRAF* V600E with *ALK* V1180L	dabrafenib + trametinib; later chemotherapy and brigatinib	Dual *BRAF*/*MEK* inhibition: worsening pericardial effusion and lung mass after 1 month. Subsequent brigatinib improved abdominal distension and ascites.
Present case	*ALK*-rearranged lung adenocarcinoma after durable lorlatinib benefit	Lorlatinib for > 36 months	Lung biopsy showed ZNF804A-*ALK*, *EML4-ALK*, and *BRAF* V600E	Lorlatinib + dabrafenib + trametinib	Partial response at 1 month; longer follow-up pending

PD, progressive disease; OS, overall survival.

However, This report has several limitations. First, the observation is based on a single patient and therefore cannot establish causality. Second, although disease control has been maintained for more than 6 months after initiation of triple therapy, longer follow-up is needed to define the durability of response and safety. Third, no functional studies were performed to confirm *BRAF* V600E as the dominant resistance driver. Therefore, further clinical and translational studies are warranted.

Conclusion

Acquired *BRAF* V600E is a potential bypass resistance mechanism after prolonged *ALK*-TKI therapy in *ALK*-rearranged NSCLC. In this patient, who derived over 36 months of disease control from first-line lorlatinib, continued lorlatinib with dabrafenib and trametinib produced an early partial response with ongoing disease control for more than 6 months, supporting further investigation of repeat NGS-guided reassessment and combined *ALK*/MAPK pathway inhibition in carefully selected cases.

Declarations

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The Tenth Affiliated Hospital, Southern Medical University (Dongguan People's Hospital) (Approval No. LW2026-018) and was conducted according to the Declaration of Helsinki. Patient provided informed written consent.

Consent for publication

The patient provided written consent for the publication of the present case report.

Competing interests

The authors declare that they have no competing interests.

Clinical trial number

Not applicable.

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Author Contribution

JJ and ZGL designed the investigation and supervised the study. KJL, ZHL, QLZ performed the investigation, analyzed data and wrote the paper. All authors reviewed and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Solomon BJ, Bauer TM, Mok TSK, et al. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. Lancet Respir Med. 2023;11(4):354–66. 10.1016/S2213-2600(22)00437-4.
2. Shaw AT, Solomon BJ, Felip E et al. Lorlatinib versus crizotinib as first-line treatment for advanced ALK-positive non-small cell lung cancer: 7-year update from the phase 3 CROWN study. Ann Oncol. 2026:S0923-7534(26)00876-8. 10.1016/j.annonc.2026.05.692
3. Tian G, Nie J, Dai L, et al. Real-world analysis of the efficacy and safety of lorlatinib in ALK-positive non-small cell lung cancer patients in China. Front Oncol. 2025;15:1577607. 10.3389/fonc.2025.1577607.
4. Urbanska EM, Sorensen JB, Melchior LC, Costa JC, Santoni-Rugiu E. Changing ALK-TKI-resistance mechanisms in rebiopsies of ALK-rearranged NSCLC: ALK- and BRAF-mutations followed by epithelial-mesenchymal transition. Int J Mol Sci. 2020;21(8):2847. 10.3390/ijms21082847.
5. Sui A, Song H, Li Y, et al. BRAF V600E mutation as a novel mechanism of acquired resistance to ALK inhibition in ALK-rearranged lung adenocarcinoma: a case report. Med (Baltim). 2021;100(8):e24917. 10.1097/MD.0000000000024917.
6. Ogimoto A, Katsurada N, Yatani A, Mimura C, Yamamoto M, Tachihara M. HIP1-ALK-rearranged lung cancer in a young adult with BRAF V600E mutation detected after ALK tyrosine kinase inhibitor therapy: a case report. JTO Clin Res Rep. 2024;5(1):100612. 10.1016/j.jtocrr.2023.100612.
7. 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. 2016;6(10):1118–33. 10.1158/2159-8290.CD-16-0596.
8. Shi R, Filho SNM, Li M, et al. BRAF V600E mutation and MET amplification as resistance pathways of the second-generation anaplastic lymphoma kinase (ALK) inhibitor alectinib in lung cancer. Lung Cancer. 2020;146:78–85. 10.1016/j.lungcan.2020.05.018.
9. Wu D, Wei S. Evaluating activation of MAPK signaling as a potential mechanism of acquired resistance to lorlatinib in ALK-rearranged lung cancer. J Clin Oncol. 2025;43(16suppl):e20000. 10.1200/JCO.2025.43.16_suppl.e20000.
10. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF V600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017;18(10):1307–16. 10.1016/S1470-2045(17)30679-4.

Figures

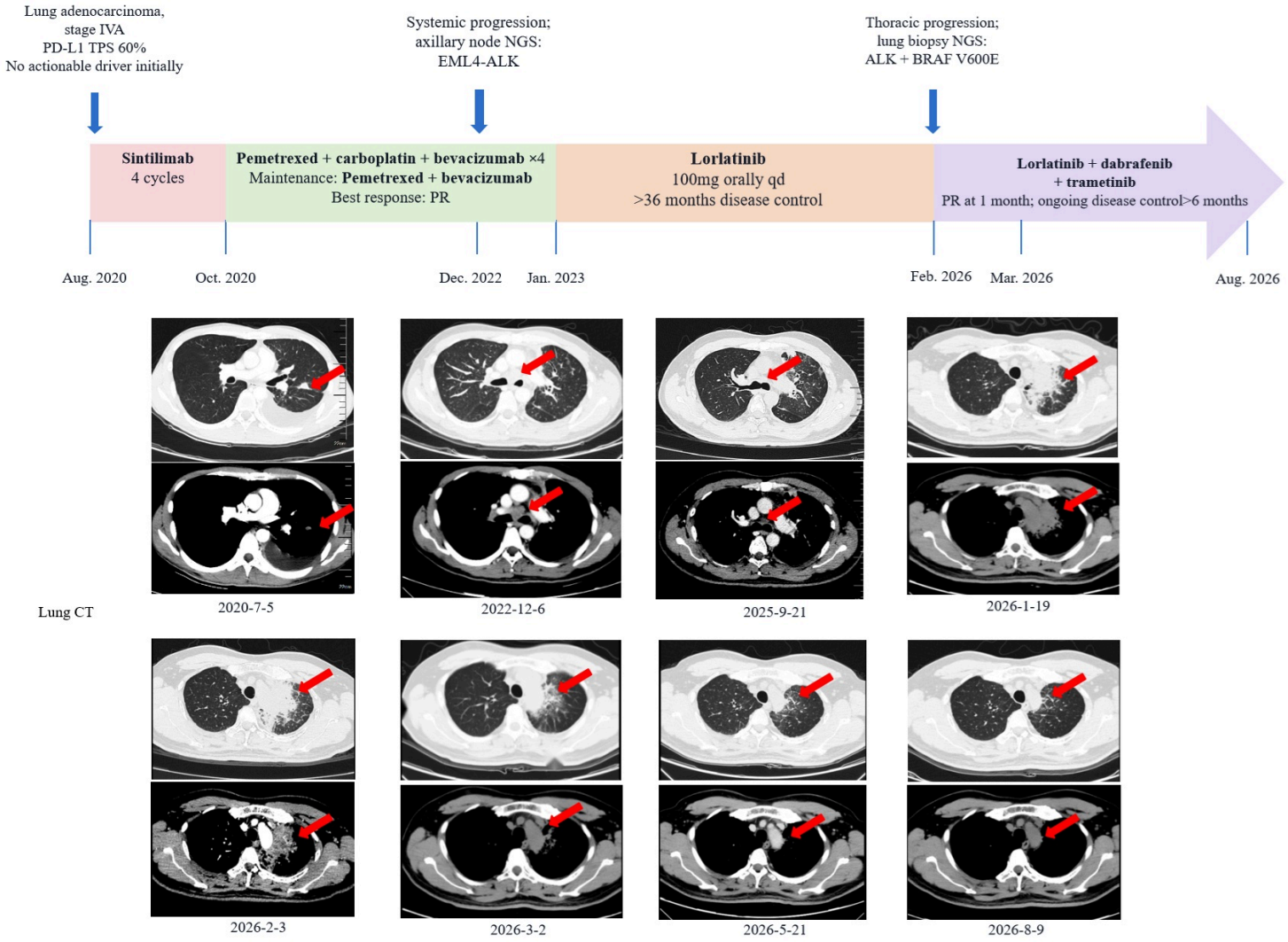


Figure 1

Timeline of treatment history, molecular findings, and serial imaging changes. Representative CT images show thoracic progression before triple therapy, marked tumor shrinkage after 1 month, and continued lesion shrinkage with ongoing disease control beyond 6 months.

Triple therapy: lorlatinib 100mg qd + dabrafenib 150mg bid + trametinib 2mg qd. Abbreviations: NGS, next-generation sequencing; PR, partial response; qd, once daily; bid, twice daily.

Supplementary Files

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- Table1.docx