Case Report

Partial response to lorlatinib in thoracic inflammatory myofibroblastic tumor harboring complex and rare ALK fusions: a case report

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Background: Targeted therapy has dramatically altered the treatment paradigm for some patients with inflammatory myofibroblastic tumor (IMT) that possesses specific molecular aberrations. IMT is an exceedingly rare type of sarcoma, with about 50% of cases featuring anaplastic lymphoma kinase (*ALK*) gene rearrangements. The treatment of IMT with ALK fusions using ALK tyrosine kinase inhibitors (TKIs) has become increasingly common. However, until now, there is a lack of evidence supporting the efficacy of third-generation ALK-TKIs in this disease category.

Case Description: Here, we report the first case of a patient with advanced IMT harboring the EML4-ALK fusion gene along with two rare ALK fusion genes: PLB1-ALK, which has only been reported in two cases of lung adenocarcinoma and large cell neuroendocrine carcinoma, and unreported ALMS1-ALK. The patient achieved partial response (PR) following first-line treatment with lorlatinib and subsequently underwent successful surgical intervention.

Conclusions: This is the inaugural case of a third-generation ALK-TKI achieving therapeutic success in advanced IMT with complex ALK rearrangements, including rare and previously uncharacterized fusion subtypes. Although the biological functions of these two rare ALK fusions still need to be confirmed, this case underscores the dependency of ALK-rearranged IMT on ALK-mediated signaling, suggesting that third-generation ALK-TKIs may offer an optimal targeted therapeutic strategy for ALK-dependent mesenchymal tumor subtypes.

Keywords: Anaplastic lymphoma kinase (ALK); inflammatory myofibroblastic tumor (IMT); lorlatinib; case report

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Introduction

Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal tumor, with a global incidence rate ranging from 0.04% and 0.70% (1). This entity can manifest in any anatomical site but is more frequently encountered within the lungs or abdominal soft tissues of children and young adults. The histological spectrum of IMT is broad, encompassing spindle cell proliferation in a background of hyalinization and chronic inflammation, to highly cellular myofibroblastic proliferation, with a minority of cases exhibiting distinct atypical tumor components (2). Despite being categorized as a tumor with intermediate biological potential due to its relatively low risk of recurrence and metastasis, IMT is typically treated surgically because of its resistance to conventional chemotherapy and radiotherapy, suggesting that treatment options for advanced cases are quite limited (3,4).

The fusion of the anaplastic lymphoma kinase (*ALK*) gene is a hallmark molecular feature of IMTs, with over 50% of IMT cases featuring rearrangements at the *ALK* locus on chromosome 2p23 (5). *ALK* rearrangements are indeed associated with *ALK* expression. *ALK* fusion proteins activate downstream signaling pathways through ligand-independent autophosphorylation, leading to prolonged survival of tumor cells, increased proliferation, and enhanced cell migration capabilities (6). As a result,

ALK tyrosine kinase inhibitors (TKIs) represent a potential therapeutic strategy for IMTs.

Lorlatinib is a targeted small molecule TKI that inhibits both *ALK* and *ROS1* (ROS proto-oncogene 1, receptor tyrosine kinase). As the third generation of *ALK*-TKIs, it exhibits superior resistance to drug resistance, a more potent ability to penetrate the blood-brain barrier, and a broader range of binding site capabilities compared to its predecessors (7). It has shown increased clinical efficacy in non-small cell lung cancer (NSCLC) with *ALK* rearrangements and has been approved for the treatment of patients with advanced-stage NSCLC with *ALK* fusions (8,9).

With the advancement of related research, *ALK*-TKIs are gradually reshaping the current treatment landscape for *ALK*-positive IMTs. We present the first case globally of an IMT patient with an *EML4-ALK* fusion and two rare *ALK* rearrangements (*PLB1-ALK* and *ALMS1-ALK*) who achieved a partial response (PR) following treatment with lorlatinib. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-963/rc).

Case presentation

A 48-year-old female with a non-smoking history presented with a persistent dry cough, prompting a medical evaluation. Chest computed tomography (CT) disclosed an extensive mass within the right pleural cavity, interlobar regions, and mediastinum. Further characterization using positron emission tomography (PET)/CT delineated a 108 mm × 128 mm solid neoplasm adjacent to the diaphragmatic aspect of the right pleura, coincident with pronounced lymphadenopathy of stations 2R, 4R, 7, and 10R. Bilateral pulmonary fields exhibited multiple solid nodules and ground-glass opacities (GGOs), with heterogeneously elevated metabolic activity noted across these lesions. A transthoracic needle biopsy of the lung mass confirmed the histopathological diagnosis of an IMT (*Figure 1A-1C*), staged as T4N2bM1a, corresponding with stage 4A per the American Joint Committee on Cancer (AJCC) classification. Advanced molecular profiling via next-generation sequencing (NGS) used OncoScreenPlus™ [Burning Rock, Guangzhou, China; panel covering 520 human cancer-related genes; *ALK* gene sequencing in this panel covers all exon regions (exons 1–29), as well as introns 18–19 and 21] (table available at https://cdn.amegroups.cn/static/public/tlcr-24-963-1.xlsx) by tumor tissue uncovered the presence of three distinct *ALK* gene fusions: *EML4-ALK*, *PLB1-*


Highlight box

Key findings

• Anaplastic lymphoma kinase (ALK)-rearranged inflammatory myofibroblastic tumor (IMT) responded well to third-generation ALK-tyrosine kinase inhibitors (TKIs) and the initially reported ALMS1-ALK and PLB1-ALK may be sensitive to ALK-TKIs.

What is known and what is new?

• IMT is a rare mesenchymal tumor, with over 50% of cases featuring ALK rearrangements, and first- and second-generation ALK-TKIs have been proven effective for ALK-rearranged IMT.

• In this case report, we present the first-ever patient with advanced IMT harboring ALK rearrangements who was treated with the third-generation ALK-TKI (lorlatinib), resulting in partial response. Furthermore, we have also discovered two novel rare ALK rearrangements that may be sensitive to ALK-TKIs.

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

• Third-generation ALK-TKIs may represent an optimal precision treatment strategy for ALK-rearranged IMT.

• The widespread adoption of genetic testing, especially next-generation sequencing, in mesenchymal tumors is highly necessary.
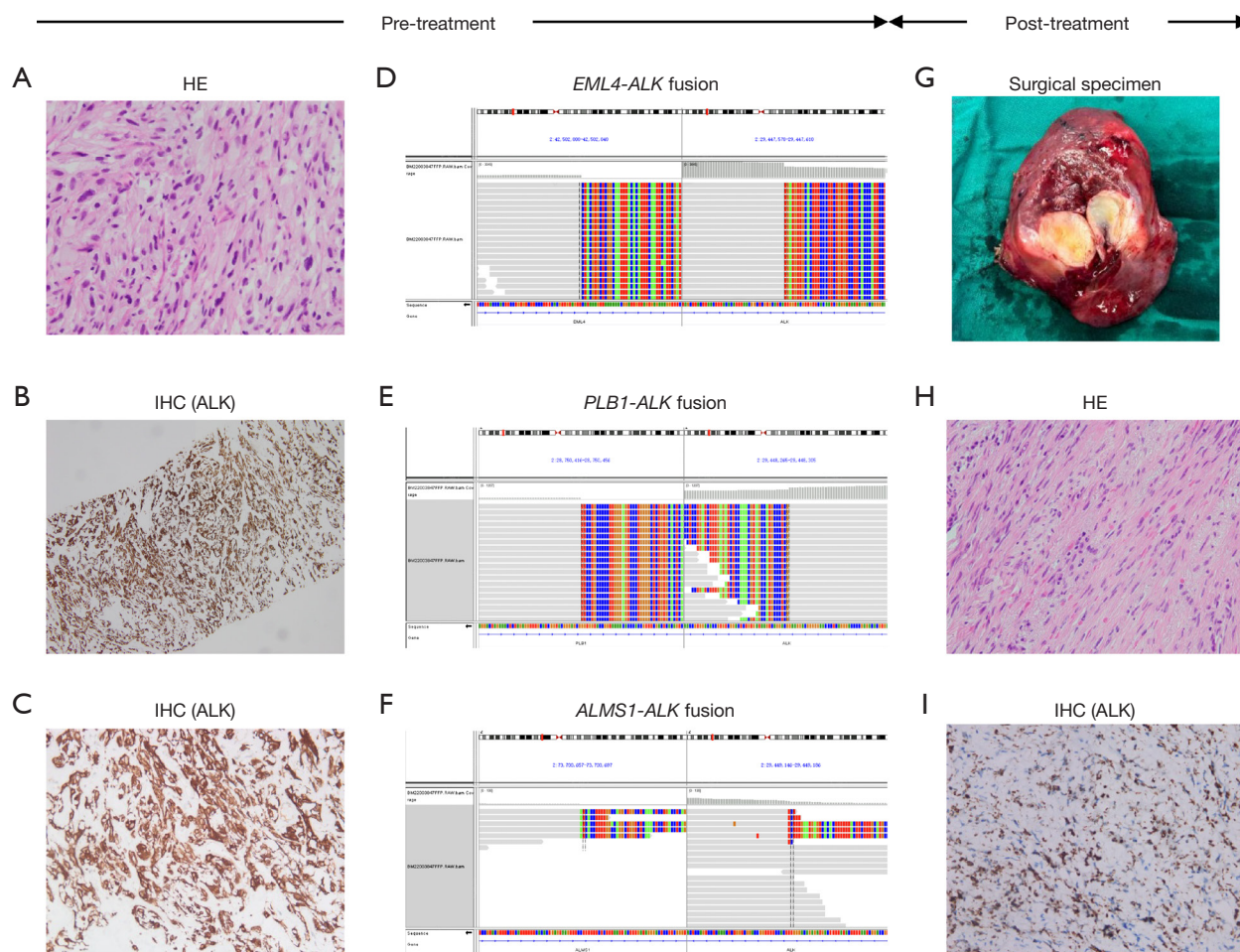
Figure 1 Comprehensive pathological and molecular profiling. (A) PTNB biopsy of the mass before lorlatinib treatment showed diffuse distribution of spindle cells or epithelioid cells with deeply stained large nuclei and notable cellular atypia (×40). (B,C) Immunohistochemistry staining confirmed the positivity of *ALK* (×10; ×40). (D-F) Next-generation sequencing results of baseline tumor tissue revealed *EML4-ALK* fusion, *PLB1-ALK* fusion, and *ALMS1-ALK* fusion. (G) Gross specimen of the resected pulmonary lobe. (H) Hematoxylin-eosin staining of the surgical specimen showed a large proliferation of collagen fibers with residual tumor cells. Tumor cells accounted for 15% of the tumor bed and the neoadjuvant therapy did not reach MPR or CPR (×40). (I) Immunohistochemistry staining confirmed the positivity of *ALK* after lorlatinib treatment (×40). HE, hematoxylin-eosin; *EML4*, echinoderm microtubule-associated protein-like 4; *ALK*, anaplastic lymphoma kinase; IHC, immunohistochemistry; *PLB1*, phospholipase B1; *ALMS1*, Alström syndrome protein 1; PTNB, percutaneous transthoracic needle biopsy; MPR, major pathological response; CPR, complete pathological response.

ALK, and *ALMS1-ALK* (*Figure 1D-1F*). Subsequently, the patient started lorlatinib (100 mg orally once a day) as primary systemic therapy. Three months post-initiation, an updated thoracic CT scan, revealed a marked reduction in the size of the primary thoracic tumor to 55 mm × 39 mm. Concurrently, there was a significant reduction in the size of the involved lymph nodes. Utilizing the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as the standard for assessment, the radiographic

changes were unequivocally classified as PR. The patient continued lorlatinib, and subsequent imaging surveillance at the third and sixth months suggested maintaining the PR status. By 15 months post-initiation, a PET/CT scan revealed a further diminution of the right pleural mass to 29 mm × 24 mm, with significant amelioration of the lymphadenopathy and pulmonary nodules, alongside a pronounced reduction in metabolic activity, reaffirming the PR designation (−75.6%). Given the profound clinical
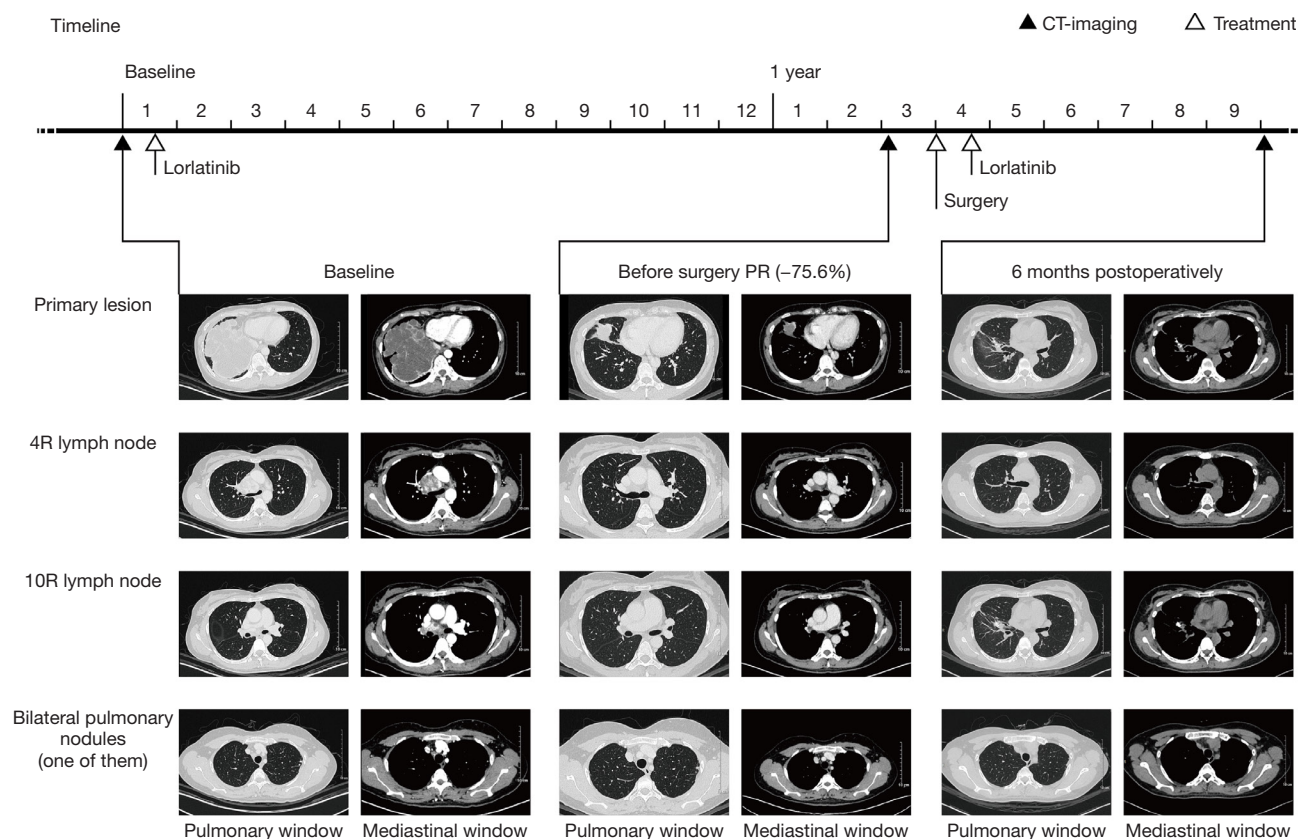
Figure 2 Treatment timeline and chest CT scan. CT, computed tomography; PR, partial response.

response to lorlatinib and the prospect of curative intent, a right middle lobectomy with systematic lymph node dissection was performed via video-assisted thoracoscopic surgery. The procedure encompassed an R0 resection of the primary pulmonary lesion, meticulous dissection of the 2R, 4R, 7, and 10R lymph nodes, and extirpation of suspect metastatic nodules within the pericardial mediastinum. Postoperative histopathological examination of the excised specimens was devoid of any residual neoplastic cells. However, subsequent immunohistochemical (IHC) analysis paradoxically disclosed a 15% residual tumor burden within the primary right lung lesion's resection bed (*Figure 1G-1I*). In light of the ambiguous nature of the pulmonary nodules' pathology and the postoperative evidence of residual disease, the patient was initiated on adjuvant therapy with lorlatinib (100 mg orally once a day) 2 weeks post-surgery. Subsequently, the patient underwent regular CT scans every 3 months, with the most recent postoperative imaging from 6 months after surgery, showing no change from prior and no evidence of progression. Until the submission of this manuscript, the patient continues to receive lorlatinib

(*Figure 2*). Notably, during the administration of lorlatinib, the patient experienced grade 3 liver function abnormalities and grade 3 hyperlipidemia, both preoperatively and during the adjuvant therapy phase. Symptomatically, the patient developed paresthesia in the extremities and weight gain. These are common side effects of lorlatinib. After treatment with hepatoprotective and lipid-lowering medications (e.g., evolocumab, rosuvastatin), these abnormal indicators were all controlled to Grade 1 (table available at https://cdn.amegroups.cn/static/public/tlcr-24-963-2.xlsx), and the symptoms were also alleviated. Additionally, due to the stable control of adverse events and the good clinical benefits, we did not adjust the dosage and administration of lorlatinib throughout the patient's treatment process.

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). The study was approved by the Ethics Review Committee of Guangdong Provincial People's Hospital (No. KY2024-071-01). Written informed consent was obtained from the patient for publication of

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this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

This case involves advanced pulmonary IMT with complex *ALK* fusions. Pulmonary IMT may be asymptomatic or present with symptoms such as cough, hemoptysis, dyspnea, and pleurisy pain. Some patients may also experience systemic symptoms like fever, weight loss, and fatigue (10). Radiographically, pulmonary IMT manifests as a solitary, lobulated lesion, predominantly occurring in the peripheral lung parenchyma and subpleural locations, with a predilection for the lower lobes. Pleural effusion may occasionally be present (11). In the case we are reporting, the patient presented with a chronic dry cough. Subsequent PET/CT revealed a large, lobulated mass in the right hemithorax, accompanied by ipsilateral pleural nodules and pleural effusion, with additional solitary nodules visible in both lungs. The clinical presentation is consistent with the known manifestations of IMTs.

Antonescu *et al.* (12) have identified significant molecular heterogeneity in *ALK* and a similar function of most ALK gene partners in providing strong promoters and oligomerization domains, which may drive the abnormal activation of the same kinase signals across different tumor types, leading to oncogenesis. In our case, NGS revealed the concurrent presence of *EML4-ALK* (E6:A20, mutation abundance: 43.89%), *PLB1-ALK* (P6:A20, mutation abundance: 36.71%), and *ALMS1-ALK* (A9:A19, mutation abundance: 30.78%) rearrangements. Upon querying the internal genetic databases of Gene Plus and Burning Rock Biotech, the incidence rate of *PLB1-ALK* ranged from 0.006–0.21%, and that of *ALMS1-ALK* was 0.002–0.05%. To our knowledge, this is the first report to reveal the existence of *ALMS1-ALK* fusion and also the first to identify *PLB1-ALK* fusion in IMT. It is also the first report of the simultaneous occurrence of three types of *ALK* fusions, two of which are rare. For *EML4-ALK*, extensive research has already demonstrated its association with the development of various tumors, including IMT. Simultaneously, IMT with *EML4-ALK* fusion have long been confirmed to be sensitive to *ALK*-TKIs (13). In contrast, *PLB1-ALK* has been less reported, initially identified by NGS in lung adenocarcinoma, and later confirmed in a case of large cell neuroendocrine carcinoma of the lung to have oncogenic driving force and sensitivity to crizotinib (14,15). Although

the current evidence is limited, we hyposize that it has an inseparable relationship with the oncogenesis of IMT, and IMT with this fusion may also be sensitive to *ALK*-TKIs. As for *ALMS1-ALK*, no related reports have been seen to date. Current knowledge of *ALMS1* mutations is limited to its basis in Alström syndrome (AS), a progressive disease characterized by neurosensory and metabolic defects, and its specific biological function remains unknown (16). Research on *ALMS1-ALK* is a blank slate, with no information available regarding its impact on tumorigenesis or its sensitivity to *ALK*-TKIs. It is noteworthy that NGS analysis in this case suggests that all three types of *ALK* fusions retain the kinase domain at the 3' end of *ALK*, which implies that they likely maintain robust biological functions and are functionally similar. This theory is consistent with existing clinical evidence for *EML4-ALK* and *PLB1-ALK*, and it also seems to suggest the possibility that ALMS1-ALK possesses biological functionality. Regrettably, based on the current evidence, we cannot affirm that *ALMS1-ALK* possesses biological functionality. Moreover, given its association with two types of *ALK* fusions that have been clearly linked to tumorigenesis and sensitivity to *ALK*-TKIs, the impact of *ALMS1-ALK* on the development of IMT and other tumors, as well as its sensitivity to *ALK*-TKIs, still warrants further exploration. Notably, we have given particular attention to the origin and destination of the three types of fusions. We observed that while their mutational abundances are strikingly similar, the sum of the mutational abundances of the three exceeds 100%. If the three types of fusions were to originate from different clones, it would imply an exceptionally high tumor purity in the patient, a scenario that is very rare. Therefore, this result strongly supports the notion that the three types of fusions originate from a monoclonal rather than a polyclonal source. However, the exact situation still awaits confirmation by methods such as single-cell sequencing. Additionally, the phenomenon of DNA fusion is quite complex; each gene's breakage and recombination could potentially occur again at unknown genomic locations. Taking the three types of fusions in this case as an example, PLB1-ALK (P6:A20) and ALMS1-ALK (A9:A19) might also accompany the main fusion EML4-ALK (E6:A20) during the process. Nevertheless, rearrangements seen through DNA-targeted sequencing often represent local regions and require additional RNA-level fusion detection to determine their transcript forms and further explore their impact on protein expression. Overall, the discovery of three types of ALK fusions, particularly the novel identification of

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PLB1-ALK and ALMS1-ALK in IMT, has broadened our understanding of the genetic landscape of IMT. The limited knowledge we have about them has, in turn, spurred the exploration and investigation of their roles in IMT.

Given the variable phenotypes and lack of distinctive IHC characteristics, the diagnosis of IMT has long been one of exclusion. Additionally, the clinical predisposition to mesenchymal tumors often leads to direct treatment without genetic testing. However, the increasing success of targeted therapies in IMTs underscores the importance of genetic testing for these tumors. It is noteworthy that NGS plays an essential role in identifying the driver gene spectrum of IMTs, particularly for *ALK*. In contrast to the earlier methods of fluorescence in situ hybridization (FISH), IHC, and quantitative reverse transcription polymerase chain reaction (qRT-PCR), NGS can more precisely distinguish between various subtypes of driver genes, making targeted therapy for different subtypes of driver genes a possibility. Therefore, we strongly advocate for the widespread adoption of NGS in the diagnosis of IMT. Furthermore, for other sarcomas with unclear diagnoses, we also support further research to explore the role of NGS in their characterization.

The utilization of *ALK*-TKIs to impede the *ALK*-associated signaling pathways indispensable for the sustained proliferation of IMT has markedly transformed the therapeutic landscape for this disease. In 2010, the first cases of patients treated with crizotinib (a first-generation *ALK*-TKI) were reported, indicating that IMTs with *ALK* fusions are responsive to this treatment (17). A subsequent phase II basket trial (EORTC 90101 CREATE) investigated the efficacy of crizotinib in IMTs with or without *ALK* fusions, with results showing a 50% objective response rate in patients with *ALK* fusions. Long-term survival outcomes reported a median progression-free survival (PFS) of 18.0 months [95% confidence interval (CI): 4.0–not estimable (NE)] for those with *ALK* fusions and 14.3 months (95% CI: 1.2–31.1) for those without, with 3-year overall survival rates of 83.3% (95% CI: 48.2–95.6%) and 34.3% (95% CI: 4.8–68.5%), respectively. This further supports the feasibility of crizotinib as a standard treatment for unresectable or metastatic IMTs with *ALK* fusions (18,19). Second- and third-generation *ALK*-TKIs, which exhibit higher selectivity for *ALK*, have demonstrated superior efficacy in advanced NSCLC with *ALK* fusions (8,20). An increasing number of case reports suggest therapeutic activity of second-generation TKIs in IMTs with *ALK* fusions. Interestingly, activity has also

been observed in crizotinib-resistant IMTs, suggesting the potential to manage IMTs like the management of *ALK* fusion-positive NSCLC (21,22). Concurrently, a clinical trial assessing brigatinib (a second-generation *ALK*-TKI) in pediatric IMT patients is underway (NCT04925609) (23). The initially reported *ALMS1-ALK* and *PLB1-ALK* may be sensitive to *ALK*-TKIs, but the presence of *EML4-ALK* in this case makes this possibility still to be explored.

Conclusions

We report the inaugural case of a third-generation *ALK*-TKI achieving therapeutic success in advanced IMT with complex *ALK* rearrangements, including rare and previously uncharacterized fusion subtypes. This case underscores the dependency of *ALK*-rearranged IMT on *ALK*-mediated signaling, suggesting that third-generation *ALK*-TKIs may offer an optimal targeted therapeutic strategy for *ALK*-dependent mesenchymal tumor subtypes. Furthermore, we encourage larger clinical trials to elucidate further the potential benefits of third-generation *ALK*-TKIs for *ALK*-rearranged IMT and more research into the synergistic mechanisms of *PLB1-ALK* and *ALMS1-ALK* fusions in TKI therapy.

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). The study was approved by the Ethics Review Committee of Guangdong Provincial People's Hospital (No. KY2024-071-01). 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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