



Efficacy of MET-TKI in ALK-rearranged, MET-aberrant advanced NSCLC after resistance to ALK-TKI

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Introduction

Mesenchymal-epithelial transition (MET) aberrations occur in 10% – 22% of drug-resistant cases of anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC). However, the exploration of subsequent treatments remains limited in ALK-rearranged NSCLC patients with MET aberrations.

Methods

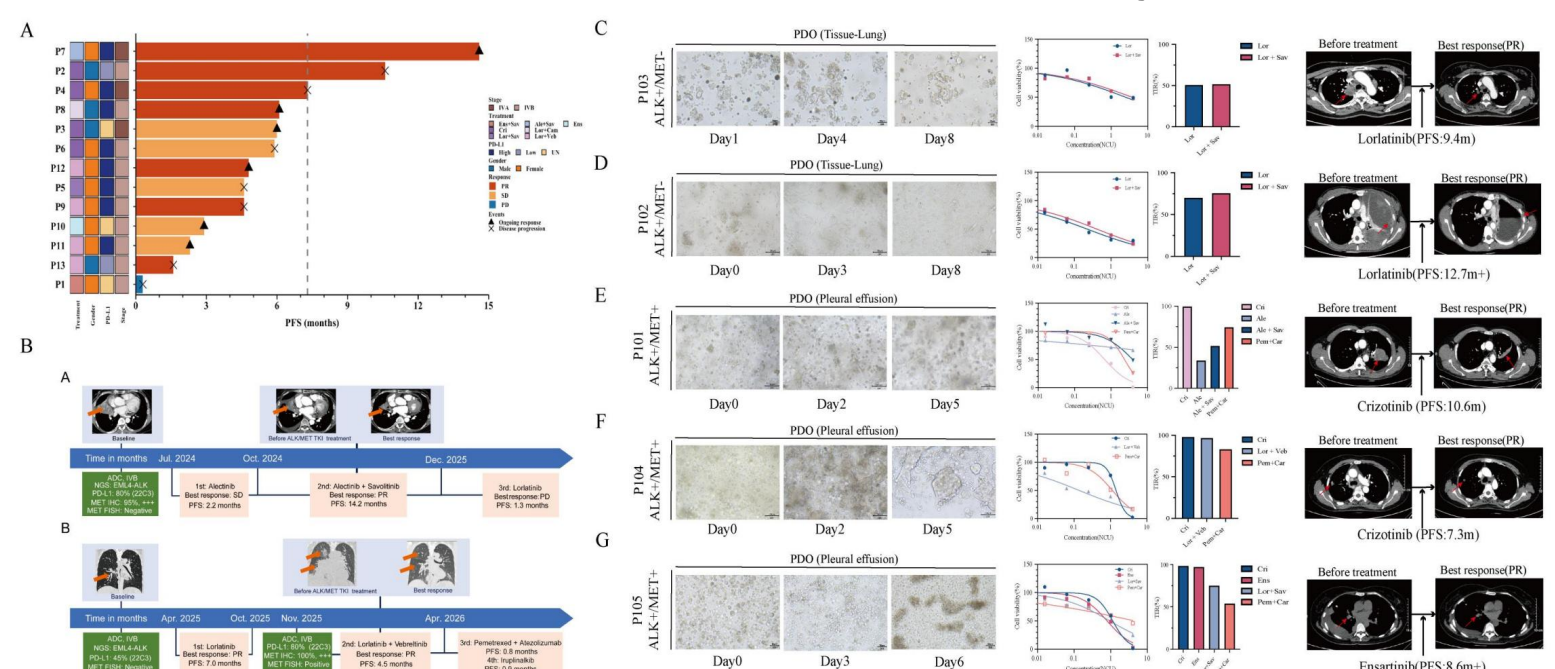
This study enrolled thirteen ALK-rearranged patients with MET overexpression or amplification after tyrosine kinase inhibitors (TKIs) resistance at the Guangdong Provincial People's Hospital from April 2022 to October 2025. The clinical efficacy and safety of subsequent treatment regimens were evaluated. Patient-derived organoid (PDO) models were established to conduct ex vivo drug sensitivity testing and assess its concordance with real-world clinical responses.

Conclusion

ALK TKI combined with MET TKI and multi-targeted TKI showed promising antitumor activity and manageable safety in ALK-rearranged NSCLC harboring MET aberrations. Lung cancer drug-sensitive organoids could offer personalized medication guidance. Further research is needed for further exploration in the future.

Results

Thirteen patients with MET aberrations after ALK TKIs resistance were enrolled in this study. Among them, 12 patients had fluorescence in situ hybridization-confirmed MET amplification, and 1 patient had MET overexpression detected by immunohistochemistry. Five patients received crizotinib or ensartinib, while 8 patients received alectinib/lorlatinib combined with savolitinib/vebreltinib/capmatinib. The overall response rate of these patients to treatment was 53.8%, with a median progression-free survival of 7.3 months. Treatment-related adverse events of grade 3 or higher occurred in 6 patients (46.2%). The concordance for overall consistency of drug sensitivity with the clinical response reached 100% (5/5). The results of PDO drug sensitivity assays showed that the drug sensitivity results of ALK TKI combined with MET TKI or multi-targeted inhibitors were antitumor activity to those of single-agent ALK TKI in ALK-rearranged NSCLC with concurrent MET aberrations, and were consistent with clinical efficacy.



Abbreviations: MET, Mesenchymal-Epithelial Transition; IHC, Immunohistochemistry; ALK, Anaplastic lymphoma kinase; ADE, Adenocarcinoma; EML4-ALK, Echinoderm Microtubule-Associated Protein-Like 4-Anaplastic Lymphoma Kinase; PR, partial response; SD, stable disease; UK, unknown; PD, progressive disease; PFS, progression-free survival; TIR, tumor inhibition rate; Cri, crizotinib; Lor, lorlatinib; Veb, vebreltinib; Ens, ensartinib; Sar, savolitinib; Car, capmatinib; PDO: patient-derived organoid.