

## INTRODUCTION

While second-generation anaplastic lymphoma kinase (ALK)-tyrosine kinase inhibitors (TKIs) have shown improved activity against central nervous system metastases, real-world evidence regarding their effectiveness, progression patterns, and rapid progression characteristics in non-small cell lung cancer (NSCLC) patients with baseline brain metastases (BM) remains limited.

## METHODS

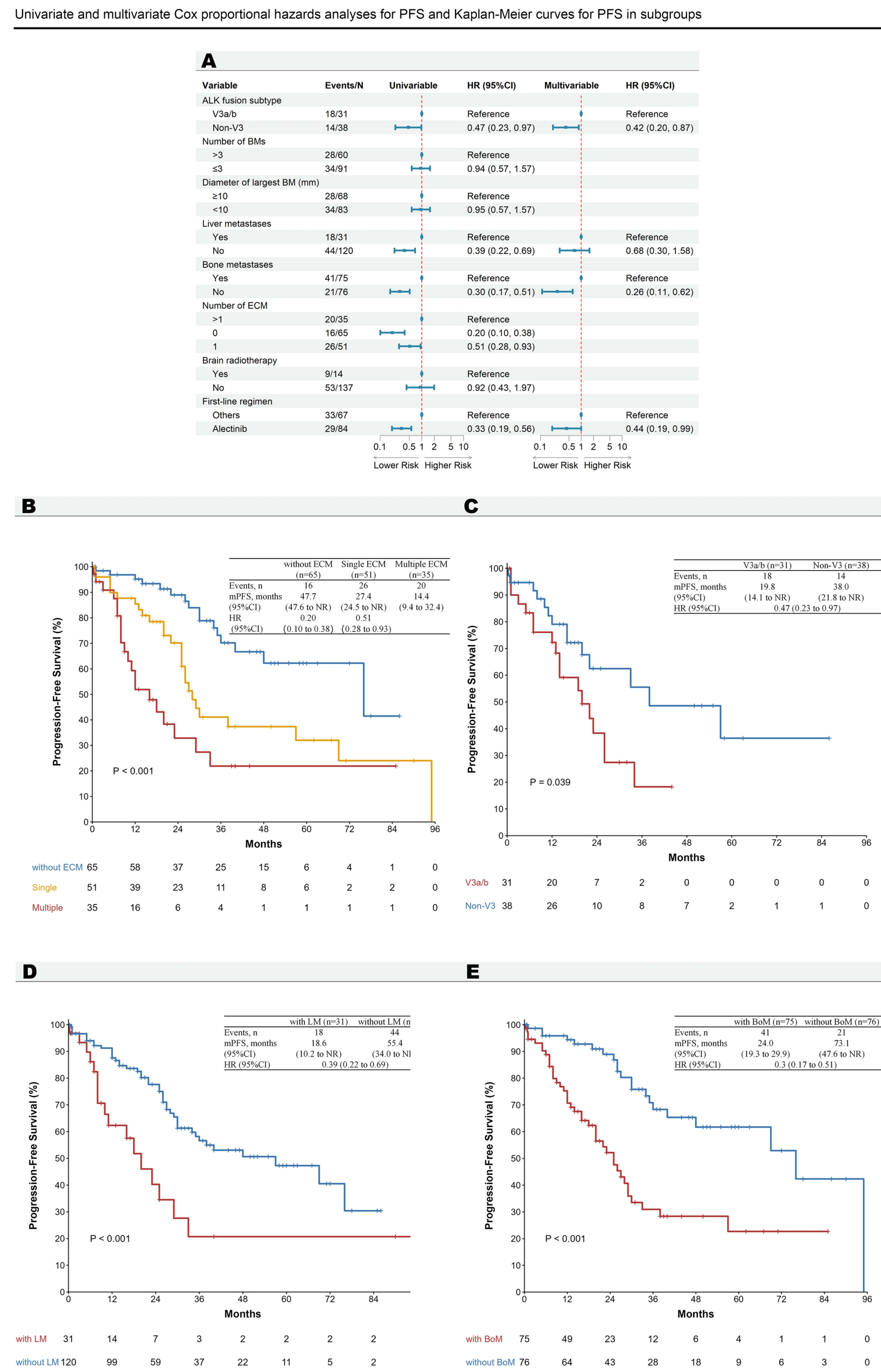
This retrospective study included 151 treatment-naïve ALK-positive NSCLC patients with BM treated across four Chinese hospitals between 2015 and 2024. All received first-line second-generation ALK TKIs. Tumor and intracranial responses were assessed using RECIST v1.1 and modified RECIST v1.1, respectively. Survival outcomes were calculated, and clinical and molecular characteristics of patients with rapid progression (within 12 months) were examined.

## RESULTS

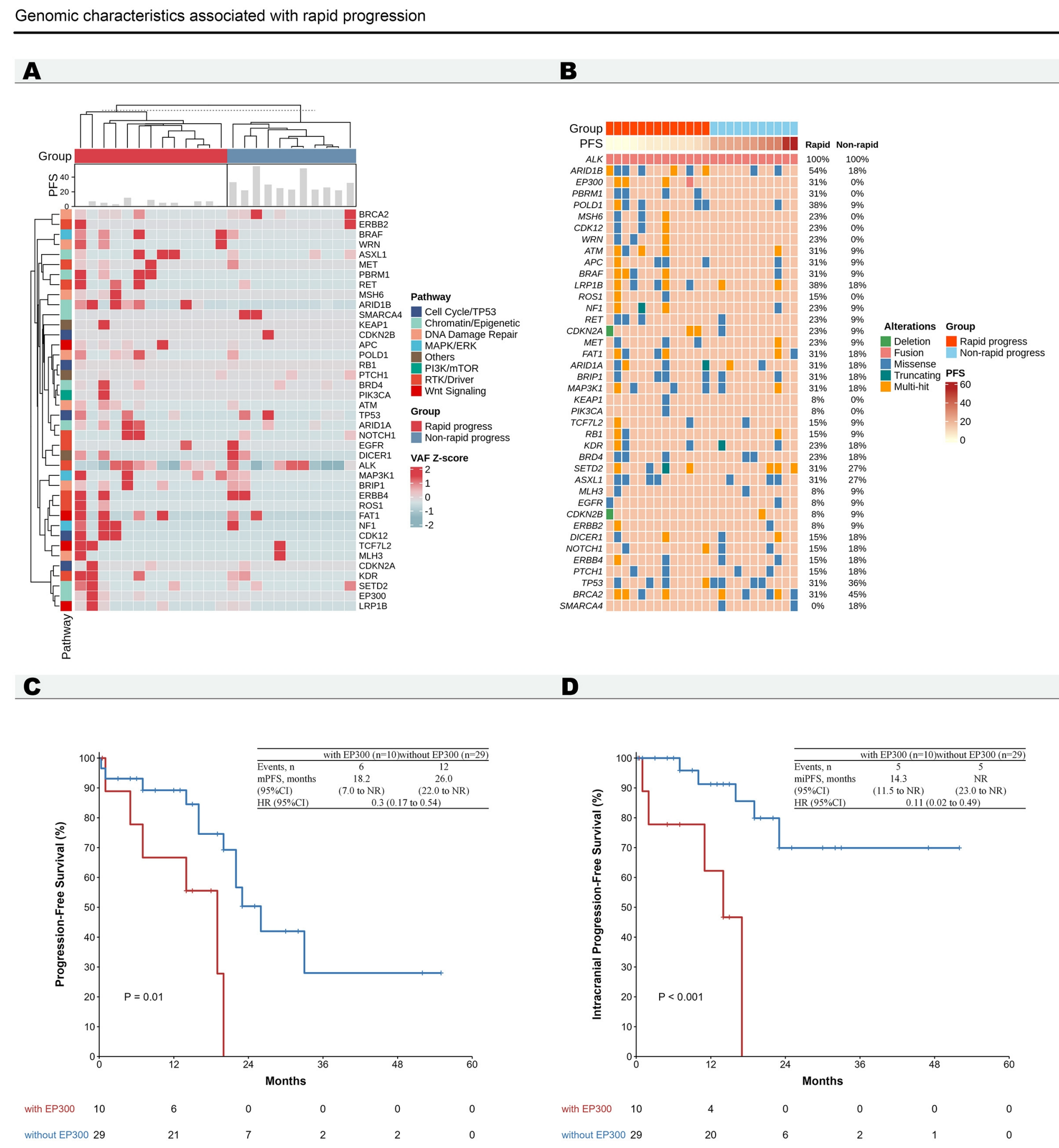
- During follow-up, the overall response rate (ORR) and intracranial response rate (iORR) were 70.9% and 78.1%, respectively. Median PFS was 37.0 months, median iPFS was 68.4 months, and median OS was not reached, with a 5-year OS rate of 80.3%.
- Subgroup analyses identified multiple extracranial metastases (versus none or single), ALK V3a/b subtype (versus non-V3), and liver or bone metastases as factors independently associated with shorter PFS.
- After propensity score matching, alectinib achieved a higher iORR than other second-generation ALK TKIs (91.7% vs. 68.8%) and was associated with significantly longer PFS (HR 0.42, 95% CI 0.23–0.75,  $P=0.003$ ) and iPFS (HR 0.22, 95% CI 0.10–0.51,  $P<0.001$ ).
- Rapid progression was linked to greater extracranial disease burden, V3a/b subtype, and EP300 mutation, all of which predicted shorter PFS and iPFS; treatment was well tolerated, with only 4.6% of patients discontinuing due to adverse events.

## DISCUSSION AND CONCLUSION

In treatment-naïve ALK-positive NSCLC patients with baseline BMs, first-line second-generation ALK TKIs yielded high response rates and durable disease control. Multiple ECMs, liver/bone metastases, and V3 subtype predicted poor prognosis, while alectinib demonstrated superior efficacy. Integrating clinical and molecular features may enhance risk stratification and guide management in high-risk patients.



**Figure 1. Univariate and multivariate Cox proportional hazards analyses for PFS and Kaplan-Meier curves for PFS in subgroups**  
A Univariate and multivariate Cox proportional hazards analyses for PFS; B PFS in patients with single, multiple or without ECMs (multiple ECMs as reference); C patients with V3a/b or Non-V3 ALK fusion subtype; D patients with or without liver metastases; E patients with or without bone metastases.



**Figure 2. Genomic characteristics associated with rapid progression**  
A The heatmap of mutational gene in patients with rapid progression and non-rapid progression; B The waterfall plots of mutation frequency differences greater than 20% in genes; C The Kaplan-Meier curve of PFS for EP300-the molecular biomarker of rapid progression; D The Kaplan-Meier curve of iPFS for EP300-the molecular biomarker of rapid progression.

## REFERENCES & ACKNOWLEDGEMENTS

- Key References**
- Gadgeel, S. et al. Alectinib versus crizotinib in treatment-naïve anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann. Oncol.* 29, 2214-2222 (2018).
  - Peters, S. et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N. Engl. J. Med.* 377, 829-838 (2017).
- Acknowledgments**
- This study is supported by the Natural Science Foundation of Guangdong Province (grant 2025A151012799). The funder had no role in the study design, data collection, data analysis, data interpretation, manuscript preparation, or decision to submit the article for publication.
- Artificial Intelligence (AI) Use Disclaimer**
- AI was not used to generate scientific data, analyses, or conclusions. All AI-assisted content was reviewed and verified by the authors, who take full responsibility for the accuracy and integrity of the final material.