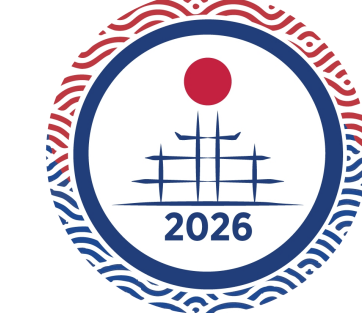




P3.215: Baseline Genomic and Immunological Divergence Shapes TKI Resistance Trajectories and Sequential Immunotherapy Efficacy in NSCLC



IASLC 2026 World
Conference on Lung Cancer

SEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

Ming-Yi Yang^{1,2}, Jia-Yi Deng², Xiao-Rong Yang², Hong-Hong Yan², Wei-Chi Luo², Zhi-Hong Chen², Yu-Deng², Chong-Rui Xu², Qing Zhou^{1,2}

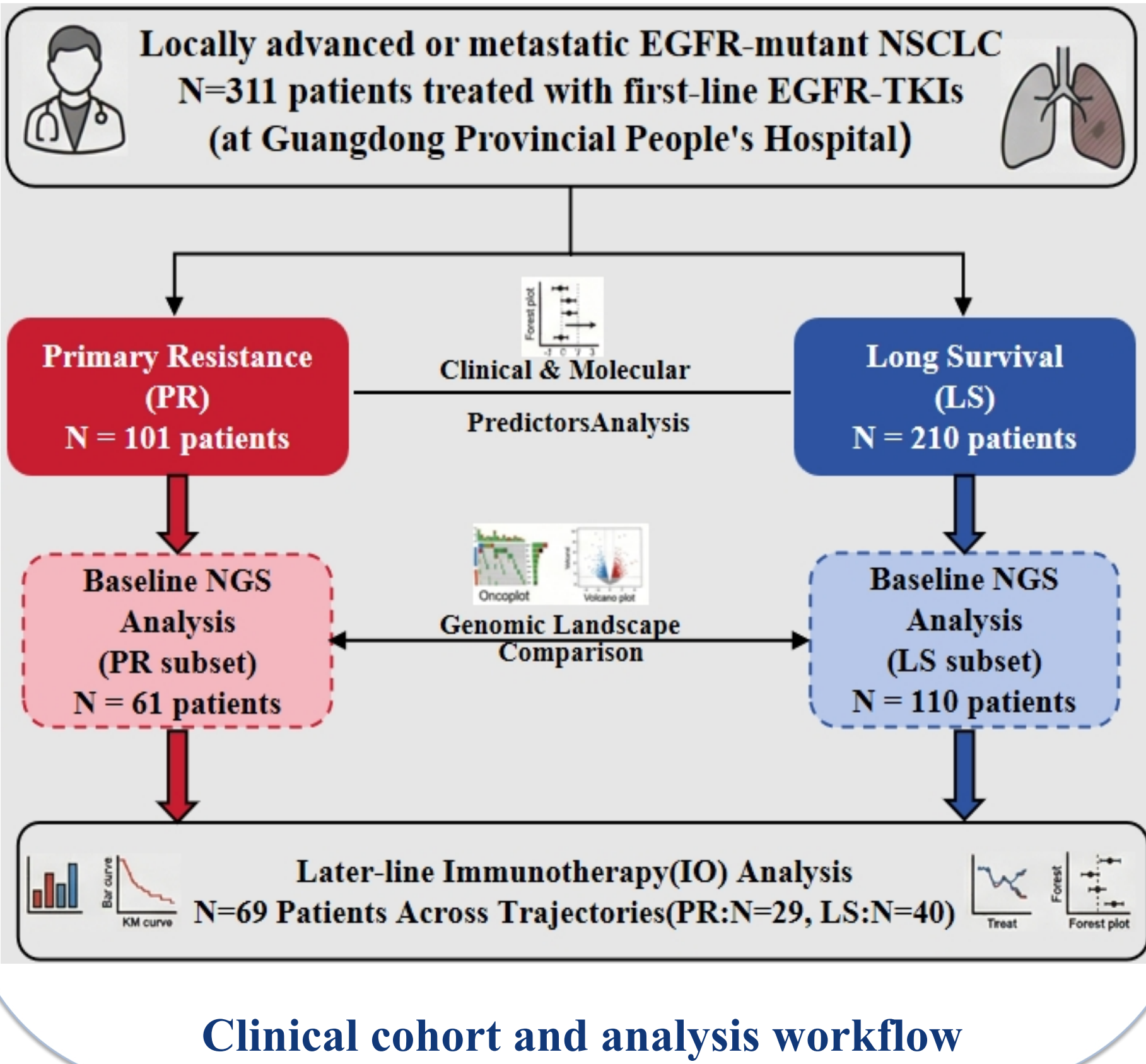
1.South China University of Technology, Guangzhou/CN , 2.Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou/CN

INTRODUCTION

- First-line EGFR-TKIs show heterogeneous benefit in advanced EGFR-mutant NSCLC.
- Baseline genomic and immune heterogeneity may define two distinct trajectories: primary resistance (PR) versus long survival (LS).
- These trajectories may also influence the efficacy of later-line immunotherapy (IO).
- Objective: integrate clinical and multi-omics analyses to define baseline divergence and its therapeutic implications.

METHODS

- Retrospective cohort: 311 patients with advanced EGFR-mutant NSCLC treated with first-line EGFR-TKIs.
- Baseline targeted NGS before TKI initiation evaluated in 171 patients using a harmonized core gene set across 8 NGS panels.
- NGS subset: PR n=61; LS n=110.
- Later-line immunotherapy cohort: n=69.
- Public mechanistic validation: TCGA-LUAD, KM-plotter, and scRNA-seq GSE148071.
- Statistical framework: multivariable analyses, genomic enrichment comparison, and immune microenvironment interrogation.



Internal validation

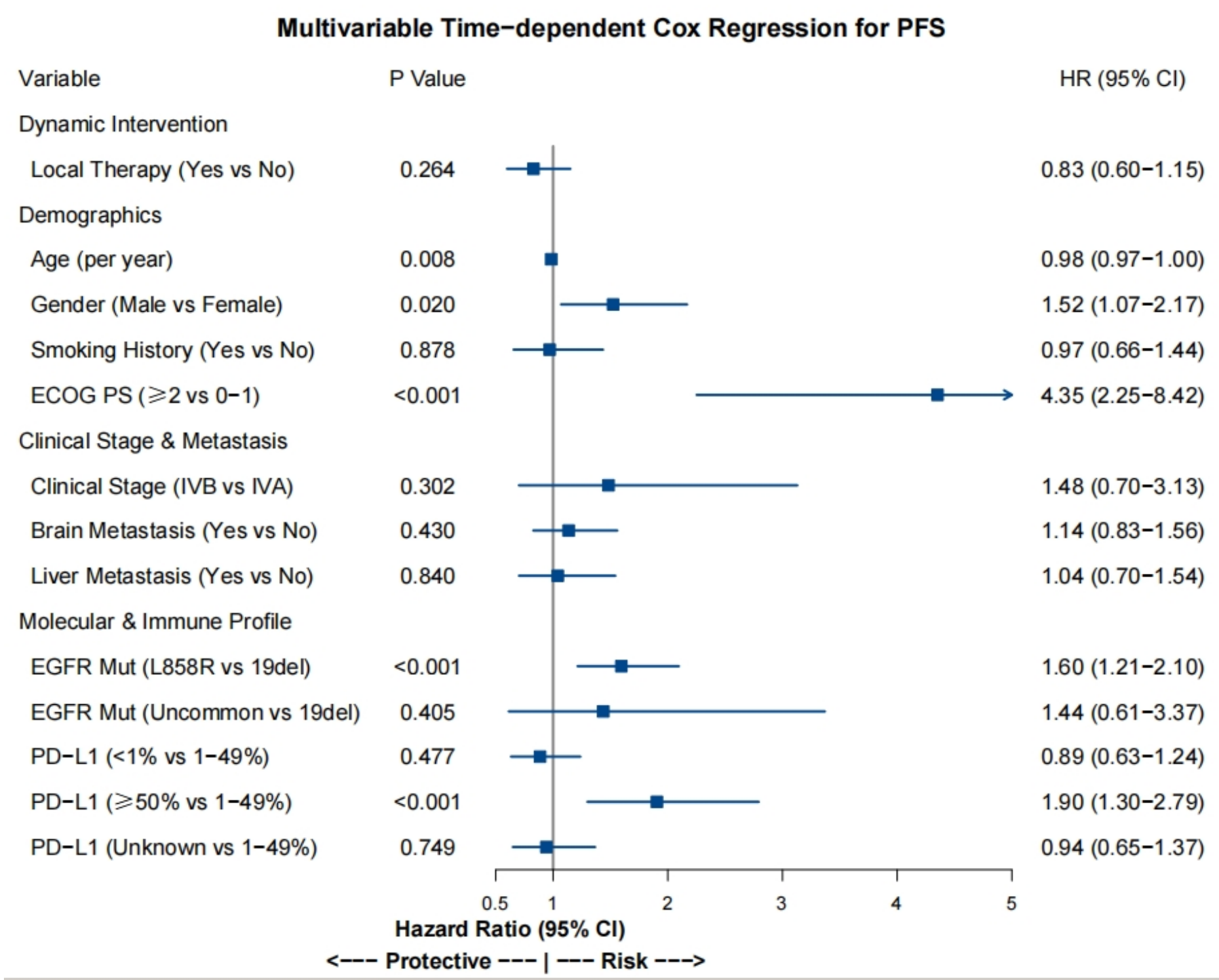
- Baseline predictors of PR
- Genomic divergence
- IO efficacy across trajectories

External validation

- TCGA-LUAD (bulk RNA-seq)
- KM-plotter (overall survival)
- scRNA-seq GSE148071

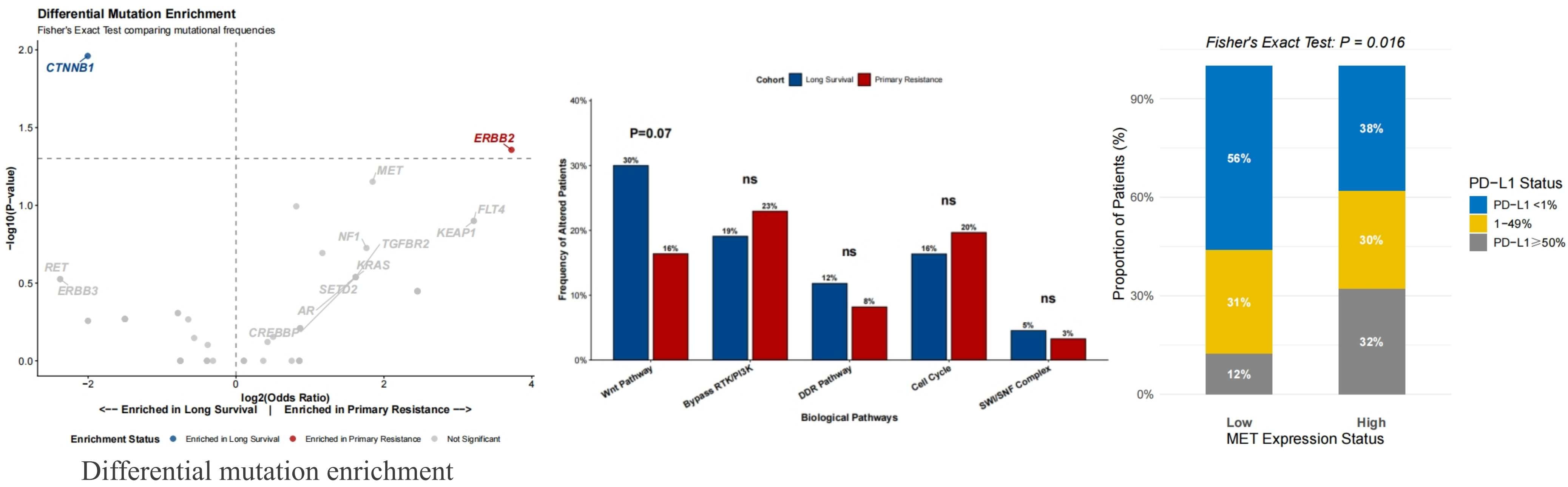
RESULTS

A. Baseline clinical and molecular predictors of primary resistance



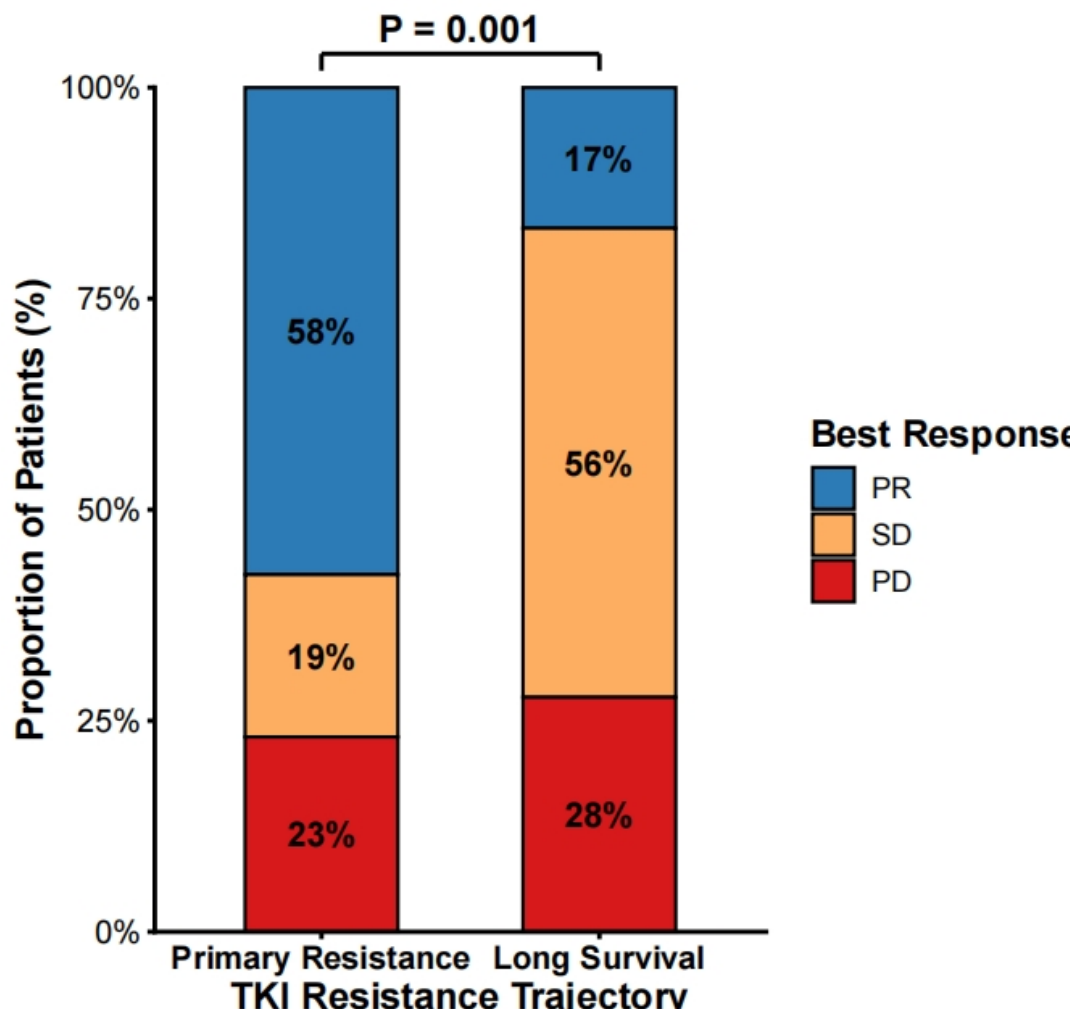
Multivariable analysis of the baseline cohort (N=311) identified ECOG PS ≥ 2 , brain metastasis, PD-L1 $\geq 50\%$, and EGFR L858R mutation as independent predictors of PR.

B. Distinct genomic divergence defines PR and LS trajectories



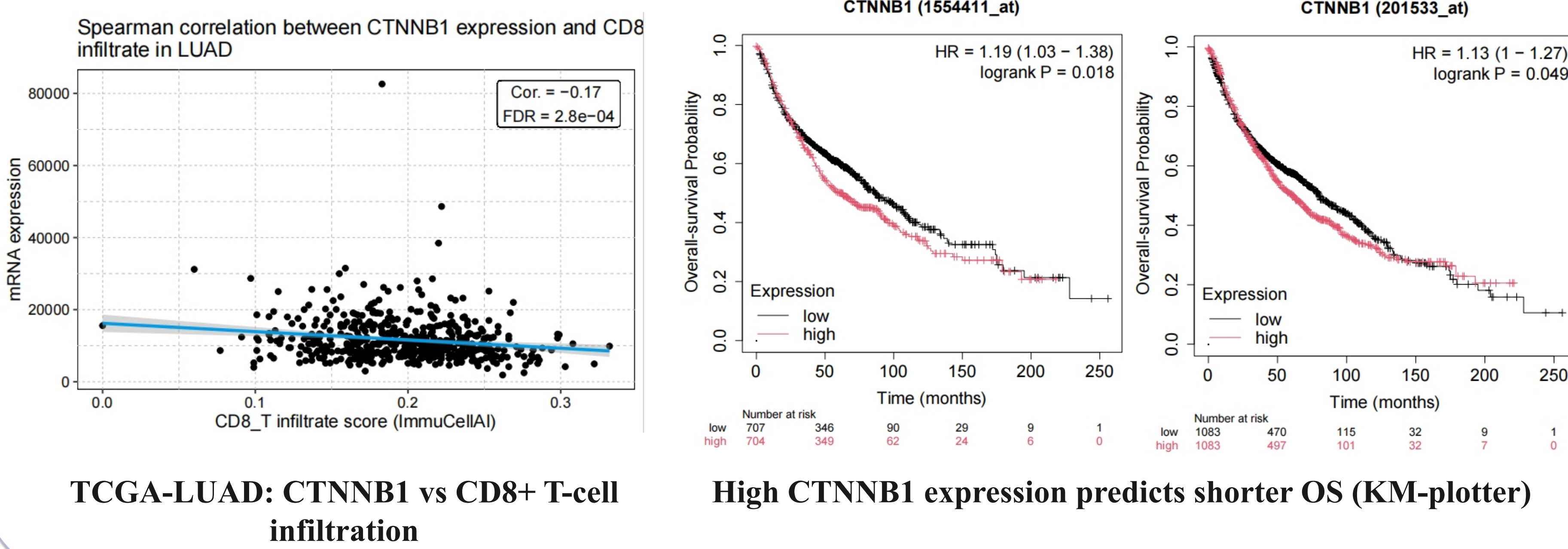
PR was enriched for bypass RTK activation (ERBB2/MET), whereas LS was enriched for Wnt pathway alterations, notably CTNNB1 mutations (19% vs 5%). MET-high tumors were more frequently PD-L1 $\geq 50\%$ (P=0.016).

C. Despite poor TKI benefit, PR demonstrates improved later-line IO sensitivity

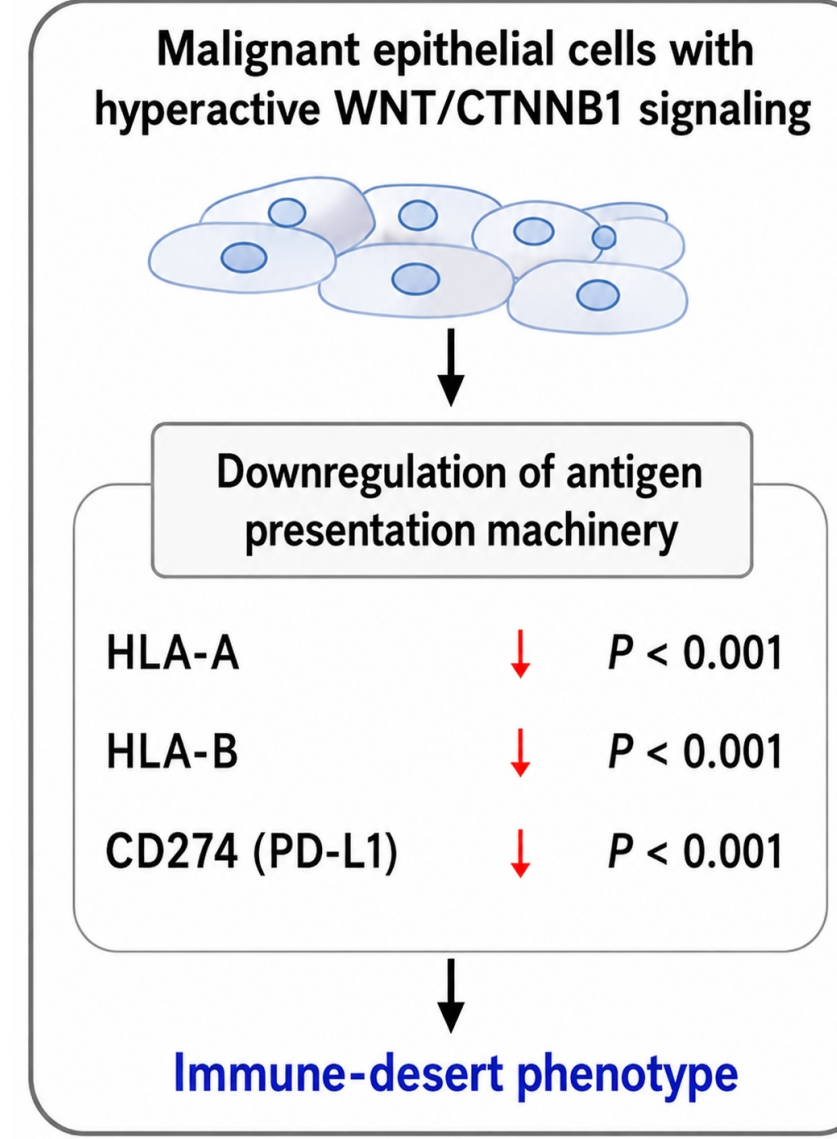


PR ORR 58% vs LS 17% (P=0.001).
LS trajectory independently predicted inferior IO-PFS: HR=2.31, P=0.030.

D. Hyperactive Wnt/CTNNB1 signaling promotes immune exclusion



scRNA-seq mechanistic validation (GSE148071)



DISCUSSION AND CONCLUSION

- Pre-existing genomic divergence shapes distinct tumor microenvironments and sequential therapeutic outcomes.
- Baseline bypass RTK activation defines a more inflamed, PD-L1-high, IO-sensitive phenotype despite primary resistance to TKIs.
- Intrinsic Wnt/CTNNB1 alterations are associated with immune exclusion, impaired antigen presentation, and poor IO benefit in TKI long survivors.
- These findings support a biologically informed framework for sequencing immunotherapy in EGFR-mutant NSCLC.

REFERENCES / ACKNOWLEDGEMENTS

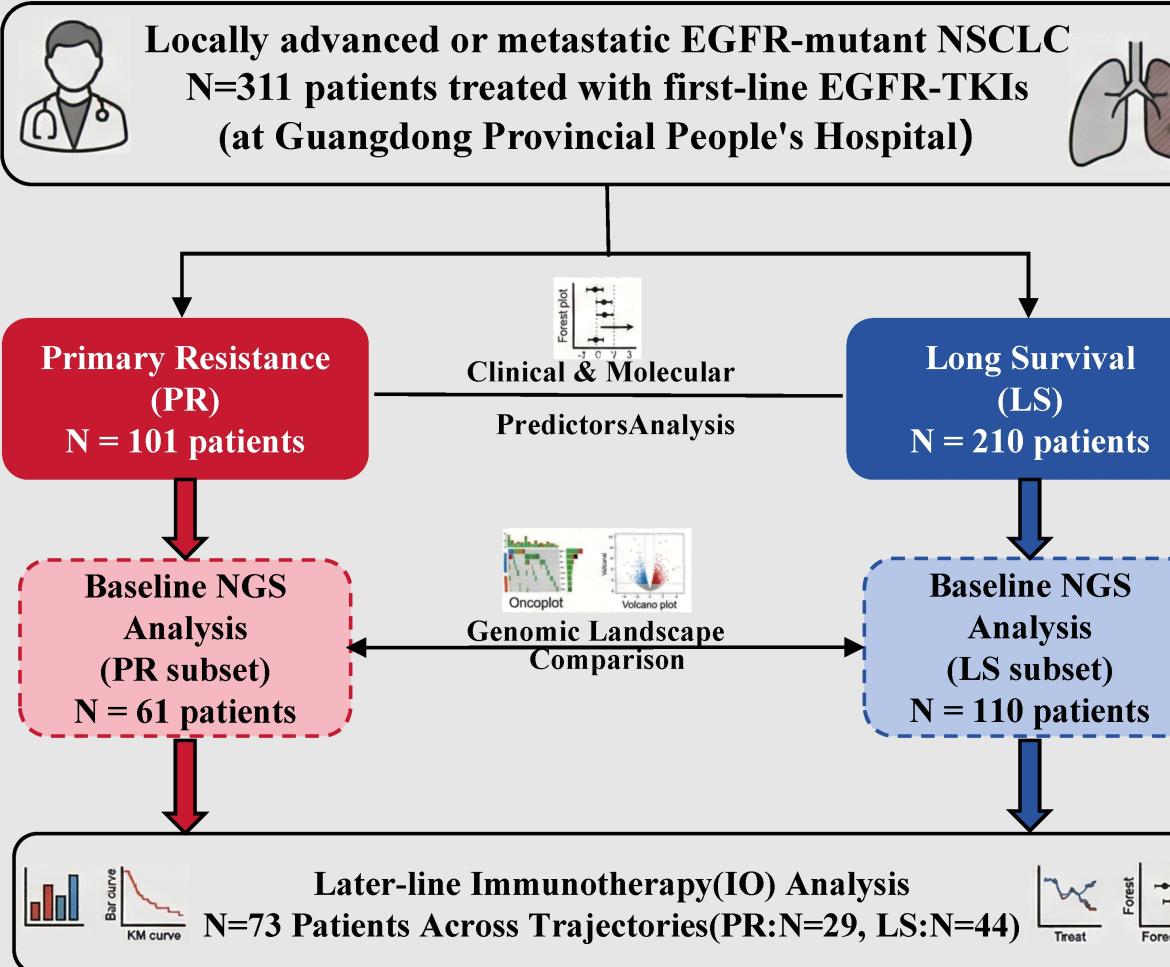
- TCGA-LUAD
- KM-plotter lung cancer cohorts
- GSE148071 scRNA-seq
- Guangdong Provincial People's Hospital clinical cohort

Acknowledgement: We thank the patients and investigators contributing to the clinical and public datasets.

KEY TAKEAWAY

Bypass RTK activation and Wnt/CTNNB1 alteration define two contrasting resistance ecosystems with opposite implications for later-line immunotherapy.

Internal Discovery & Real-World Validation



External Mechanistic Validation Cohort

