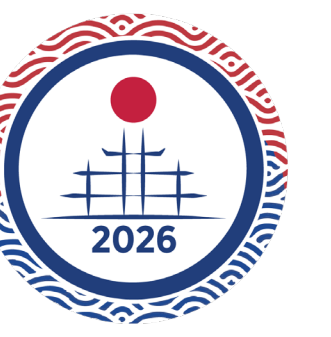




Genomic Biomarkers for Whole-Process Stratification in *KRAS*^{G12C}-Mutant NSCLC: A Phase 1/2a Trial Analysis of Glecirasib Plus Sitneprotafib

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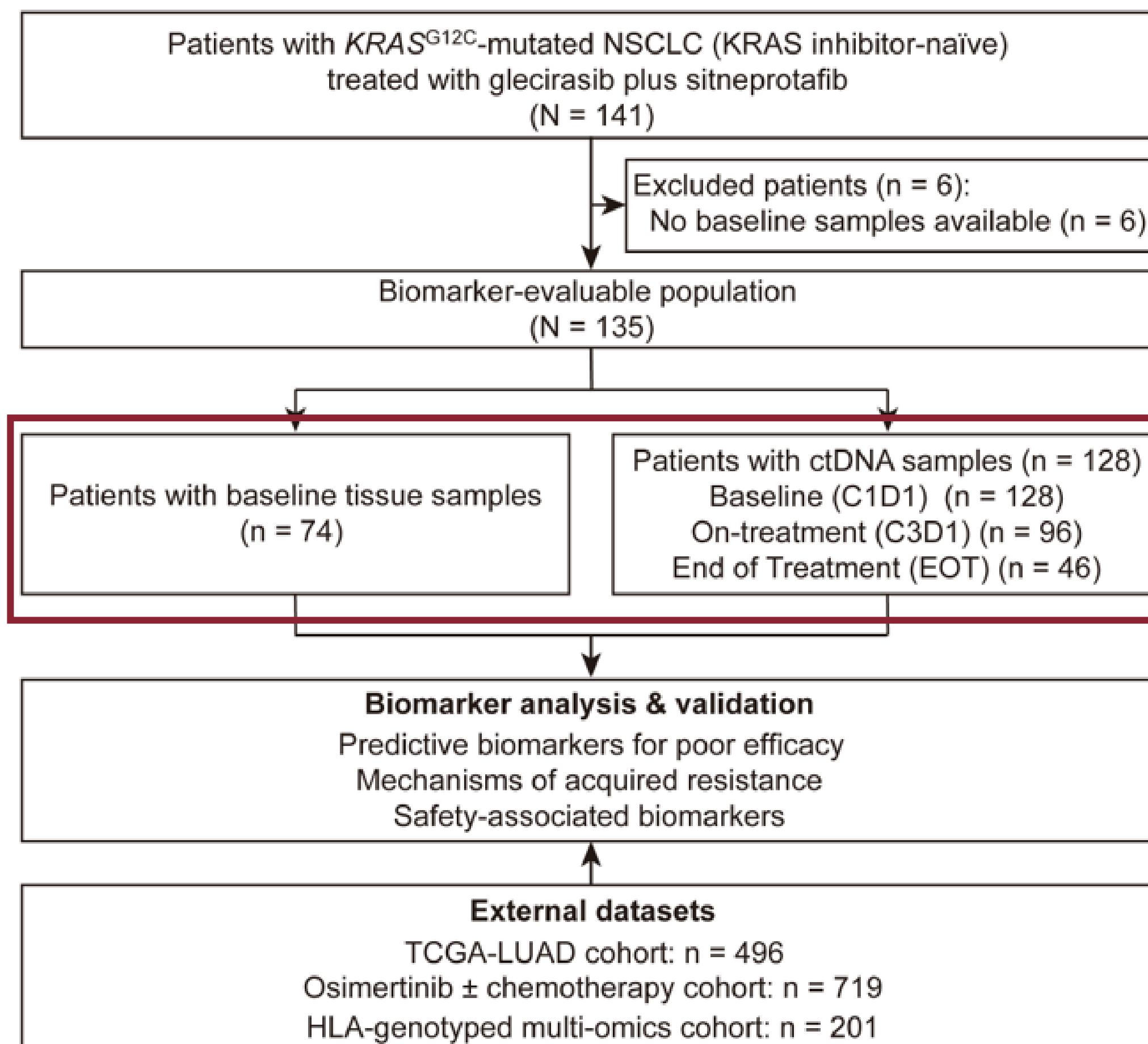
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INTRODUCTION

- *KRAS*^{G12C} inhibitors are effective in *KRAS*^{G12C}-mutant non-small-cell lung cancer (NSCLC), but their efficacy is often limited by primary or acquired resistance.
- Dual *KRAS*^{G12C} and SHP2 inhibition may suppress feedback reactivation and prolong disease control; however, clinical benefit remains heterogeneous.
- We report a post hoc analysis of biomarkers associated with response and resistance to glecirasib (a *KRAS*^{G12C} inhibitor) plus sitneprotafib (an SHP2 inhibitor) in advanced *KRAS*^{G12C}-mutant NSCLC

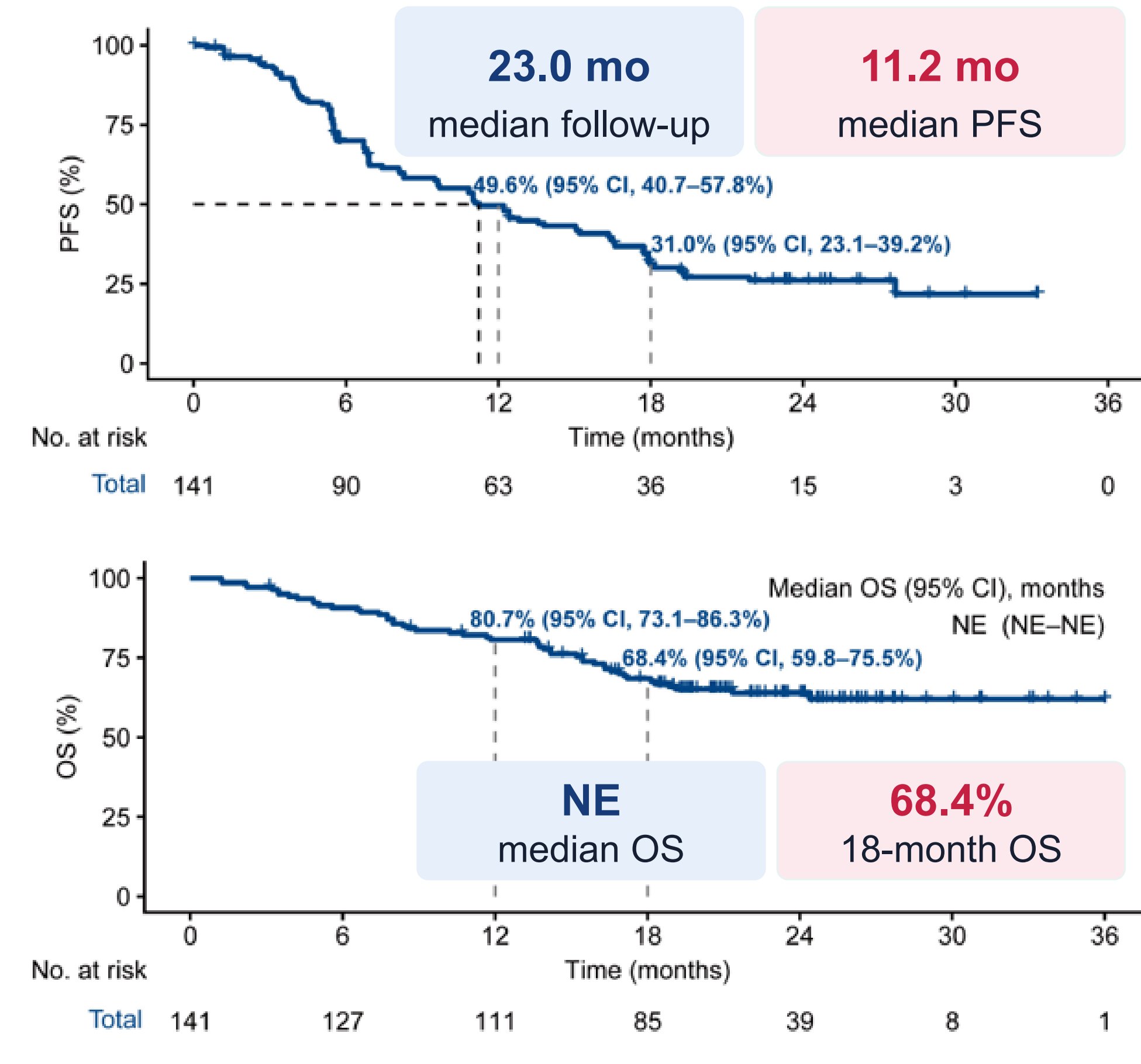
METHODS

- This study was a post hoc biomarker analysis of a multicenter, open-label phase 1/2a trial conducted across 26 hospitals in China (NCT05288205).
- The trial enrolled 141 patients with advanced *KRAS*^{G12C}-mutant NSCLC who had not previously received *KRAS* inhibitor, of whom 135 were included in the biomarker-evaluable population.
- Patients received glecirasib plus sitneprotafib. Radiographic tumor assessments were performed every 6 weeks according to RECIST v1.1.
- Baseline genomic features, longitudinal *KRAS*^{G12C} ctDNA dynamics, treatment-emergent resistance alterations, and associations of HLA genotype and hepatic treatment-related adverse events with clinical outcomes were evaluated.

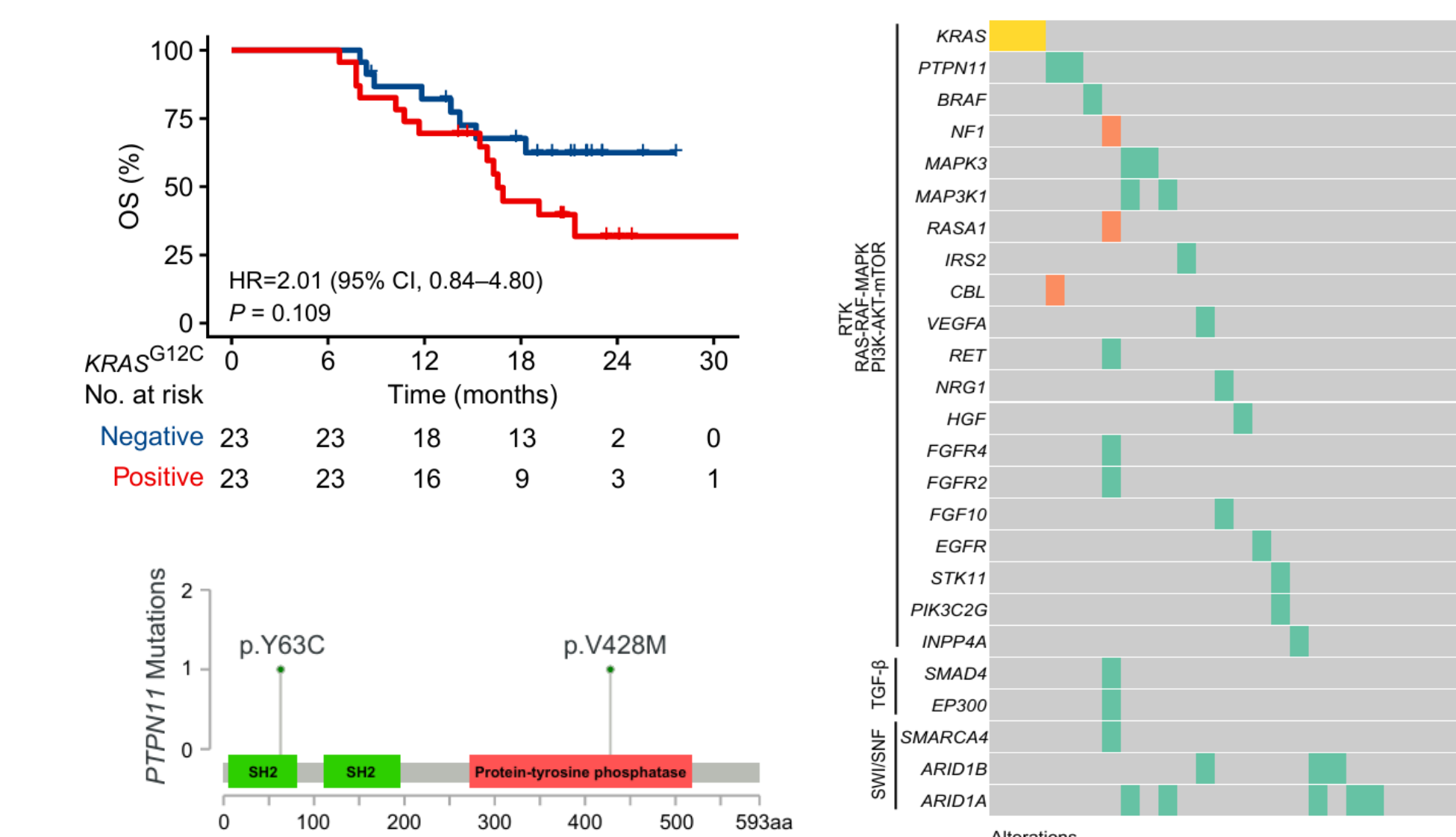


RESULTS

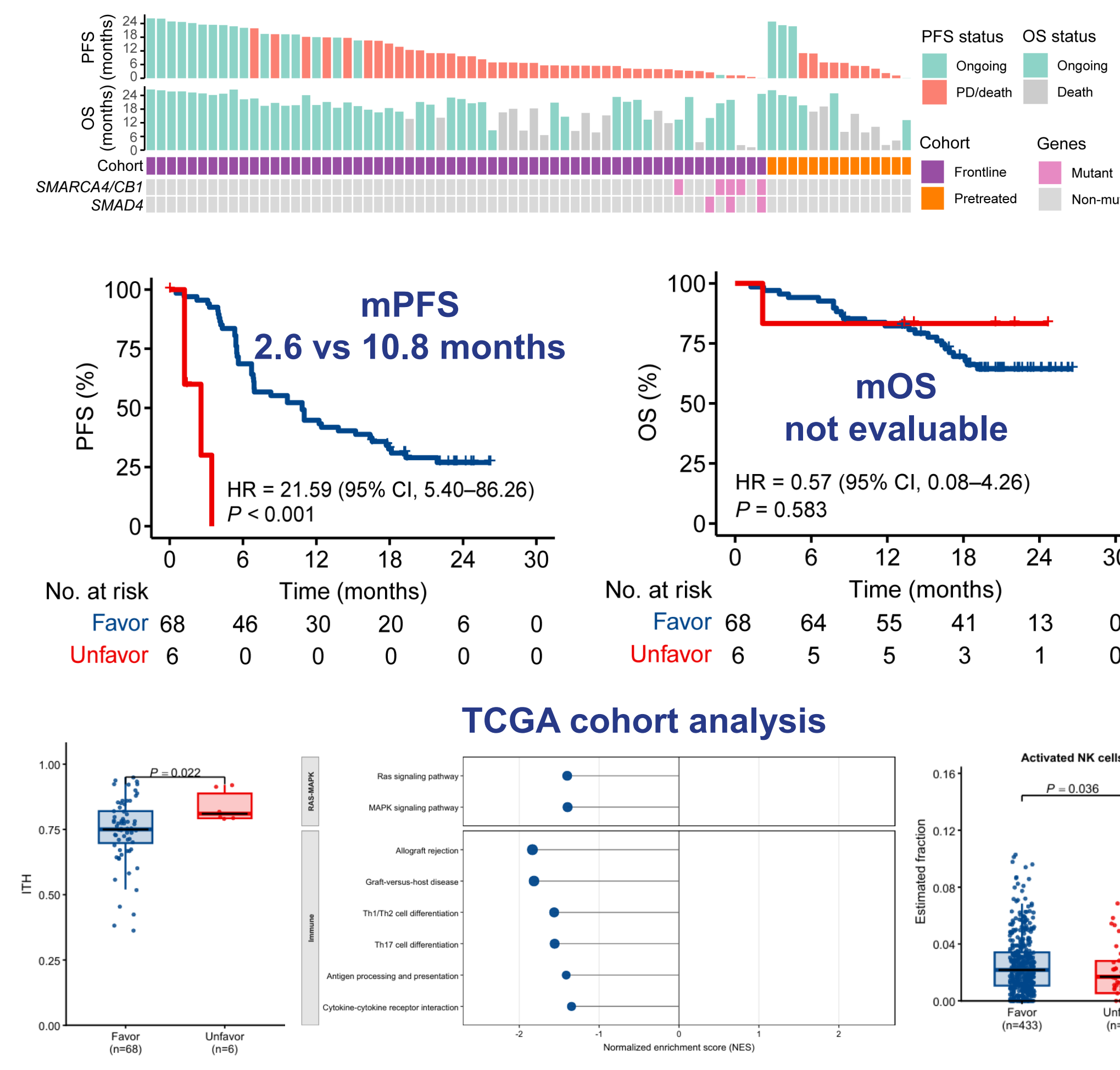
- 23.0-month follow-up shows durable disease control.



- Paired baseline and end-of-treatment genomic profiling revealed acquired resistance mechanisms unique to *KRAS*^{G12C} plus SHP2 inhibition, including *KRAS* amplification and *PTPN11* (SHP2) mutations (Y63C, V428M).

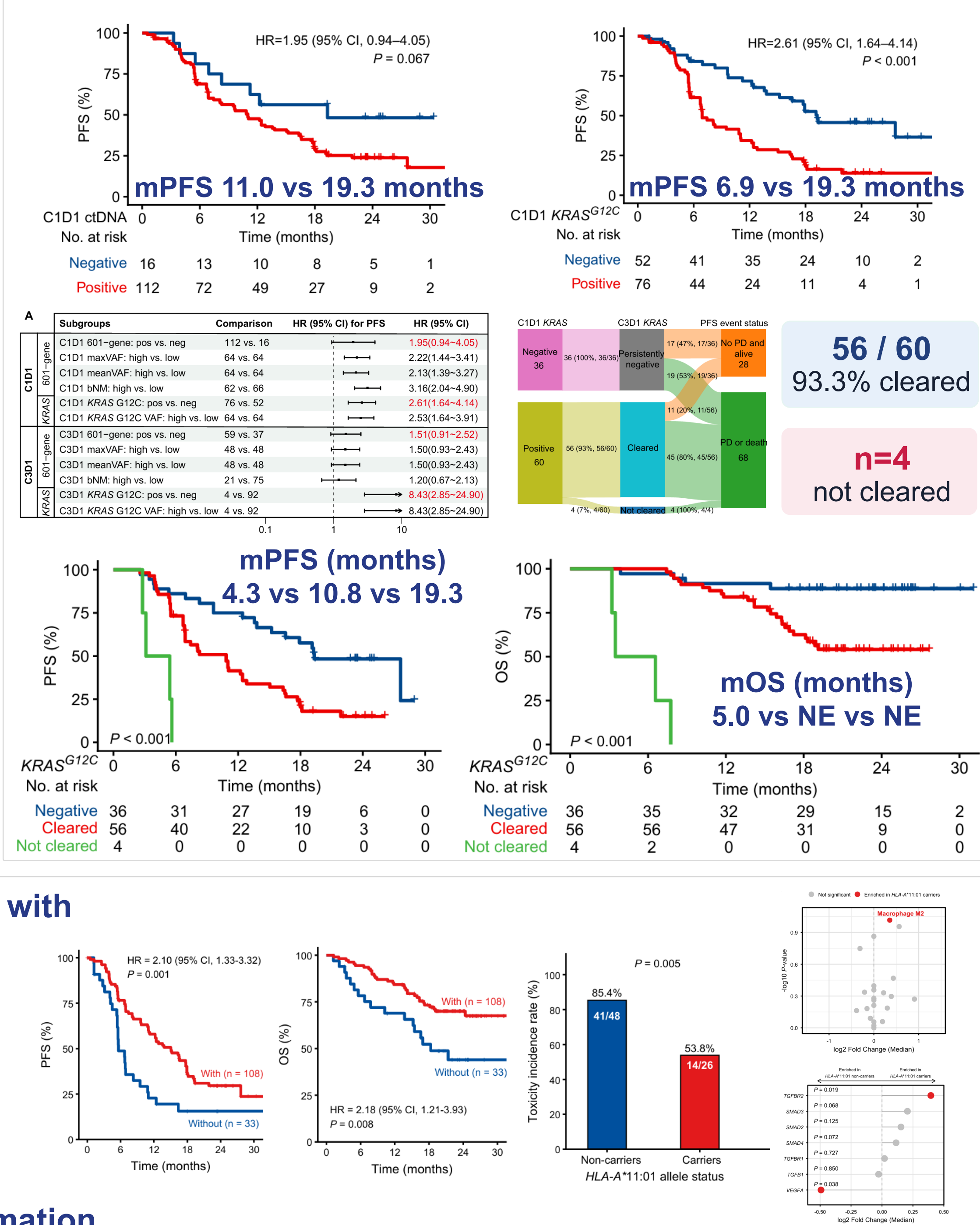


- The unfavorable signature was defined as any mutation in *SMARCA4*, *SMARCB1*, or *SMAD4*.
- All six patients harboring the unfavorable signature had PFS <3.5 months.
- A baseline tissue genomic signature is associated with primary resistance.
- Unfavorable tumors are less *KRAS*-dependent and immune-cold.



- Treatment-related hepatic adverse events were associated with improved survival.
- The *HLA-A*11:01* allele was associated with a lower risk of treatment-related hepatic adverse events.
- *HLA-A*11:01* was also associated with enhanced M2 macrophage polarization and increased TGFB1–TGFB2 pathway activity, suggesting attenuation of hepatic inflammation.

- Longitudinal monitoring of plasma *KRAS*^{G12C} circulating tumor DNA (ctDNA) variant allele frequency (VAF) outperformed multi-gene panel analysis in predicting therapeutic efficacy.
- Among patients with detectable *KRAS*^{G12C} ctDNA at baseline, 93.3% achieved molecular clearance by cycle 3 day 1 (C3D1) during combination therapy.
- Patients with persistent *KRAS*^{G12C} ctDNA at C3D1 had shorter median PFS (4.3 months) and OS (5.0 months).



CONCLUSIONS

- Our findings provide a molecular framework for the precision management of *KRAS*^{G12C}-mutant NSCLC treated with glecirasib plus sitneprotafib.
- Baseline *SMARCA4*, *SMARCB1*, or *SMAD4* mutations may identify patients at increased risk of poor clinical outcomes.
- Longitudinal *KRAS*^{G12C} ctDNA monitoring may facilitate early efficacy assessment, while emerging *KRAS* amplification and *PTPN11* mutations may indicate acquired resistance.
- Hepatic treatment-related adverse events were associated with longer PFS and may serve as an on-treatment indicator of clinical benefit.

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