

P2.381

Whole Genomic Landscape of Advanced *EGFR*-mutant NSCLC Treated With First-Line Osimertinib



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Introduction

- First-line (1L) osimertinib ± chemotherapy is the standard of care for advanced *EGFR*-mutant NSCLC.
- However, the genomic landscape and prognostic determinants of these tumors remain poorly defined, as large-scale whole-genome sequencing (WGS) studies linked to clinical outcomes remain limited.
- Here, we characterized the whole-genome landscape of baseline tumors from the **WARRIOR** (**W**hole Genomic **L**andscape of *EGFR* Mutation-Positive Advanced NSCLC Treated with First-Line **O**simertinib) cohort (NCT03969823) and evaluated its association with clinical outcomes.

Methods

- Prospective cohort of treatment-naïve, advanced *EGFR*-mutant NSCLC (ex19del or L858R) initiating 1L osimertinib 80 mg daily (SNUH & branches, May 2019 – Dec 2020).
- WGS performed on baseline fresh tumor biopsies (median 66x, range 55-147x); 119 of 147 enrolled patients passed WGS QC and were used for downstream analyses. Paired post-progression WGS available in a subset of patients for longitudinal comparison.
- Mutational signatures assigned by SigProfilerAssignment (≥ 5% contribution threshold). APOBEC3-High was defined as SBS2/13 contribution ≥20%; APOBEC3A (A3A) vs APOBEC3B (A3B) bias evaluated from TCW-context enrichment.
- Survival analyzed by Kaplan-Meier and Cox proportional hazards models.

RESULTS

Cohort overview

Characteristics (WARRIOR WGS QC PASS)	
Median age (range) -yr	65 (30-86)
Sex – no. (%)	
Female	69 (58)
Male	50 (42)
Race/ethnic group – no. (%)	
Asian (South Korean)	119 (100)
EGFR mutation baseline – no. (%)	
Exon 19 deletion (ex19del)	67 (56)
L858R mutation	52 (44)
Smoking history – no. (%)	
Former Smoker	36 (30)
Current Smoker	6 (5)
Never Smoker	77 (65)
Best overall response – no. (%)	
PR	94 (79)
SD	18 (15)
PD	6 (5)
Not evaluable	1 (1)
Clinical outcomes – mo	
Median PFS	21.8
Median OS	35.0

Conclusion

- *EGFR* ex19del and L858R tumors exhibited distinct co-alteration patterns at baseline.
- Baseline APOBEC3-High status (≥20% SBS2/13) was an independent prognostic factor for worse OS (HR 2.55, p<0.001) and PFS (HR 1.77, p=0.015), and showed predominantly A3A-like context bias.
- Longer time on treatment showed a trend toward increases in APOBEC3 contribution, but baseline APOBEC3-High status was largely retained with infrequent Low → High transitions, supporting baseline assessment as a clinically informative timepoint.
- Ongoing whole-genome analyses of paired post-progression samples aim to comprehensively characterize acquired resistance mechanisms.

Acknowledgement & AI Use Disclosures

- This study is an investigator-initiated biomarker trial (PI: Tae Min Kim, MD, PhD) supported by AstraZeneca.
- AI use: Claude (Anthropic) and ChatGPT (OpenAI) were used to assist with code development. All analytical outputs and interpretations were reviewed and verified by the authors.

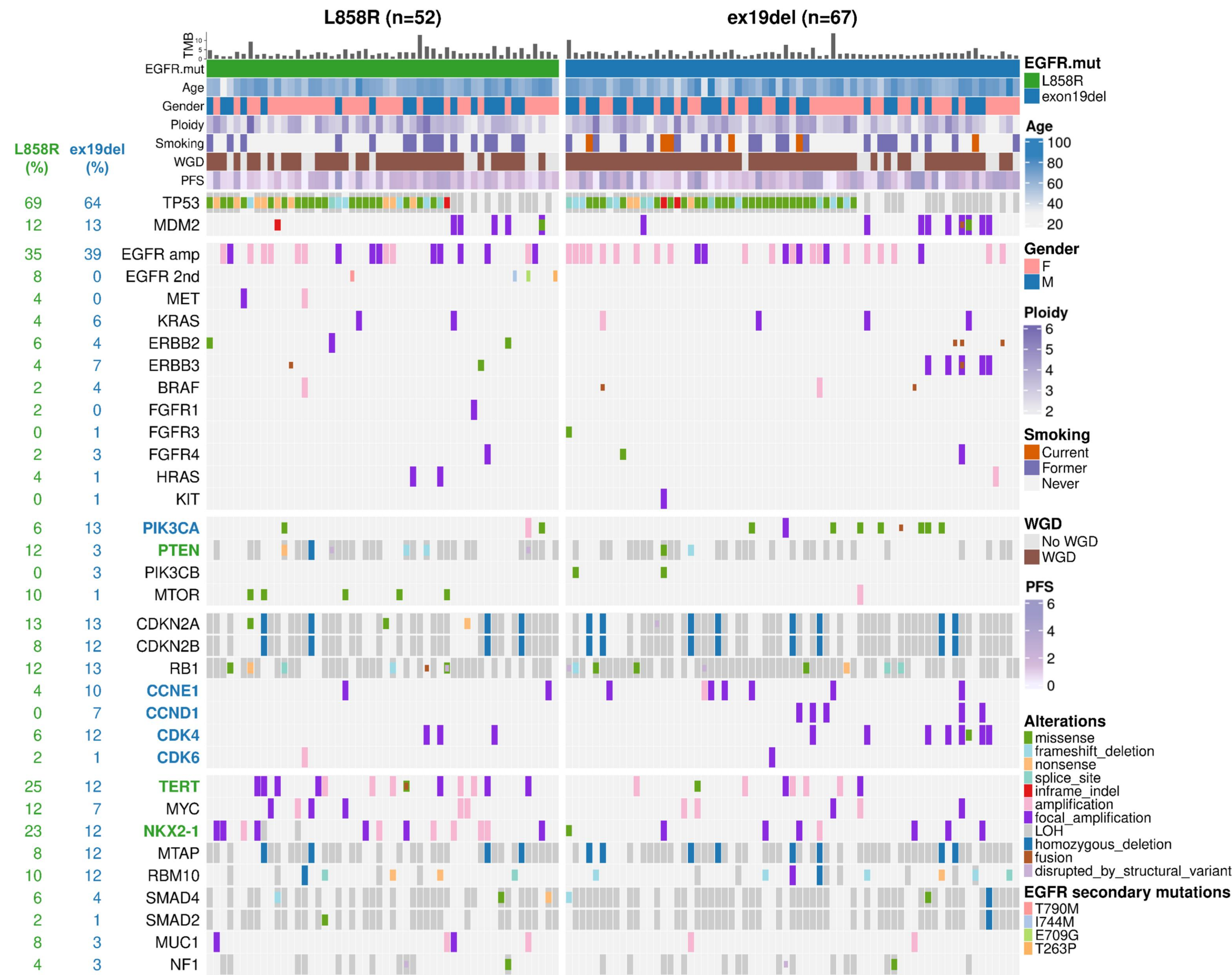
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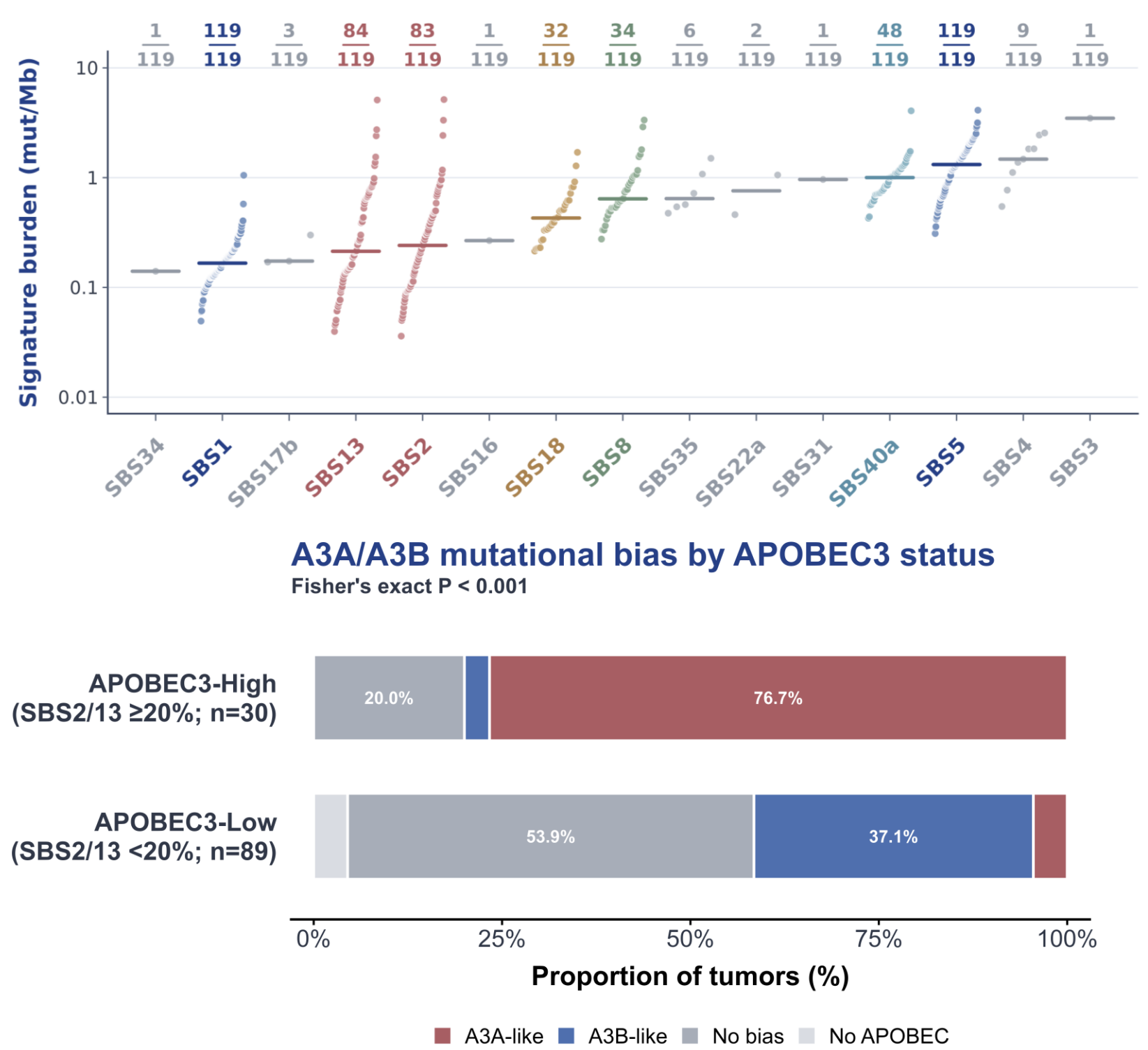
Poster PDF

Genomic landscape



L858R-enriched: PTEN loss, NKX2-1 and TERT amplifications
Ex19del-enriched: PIK3CA alterations, cell cycle amplification (CCND1/E1, CDK4/6)

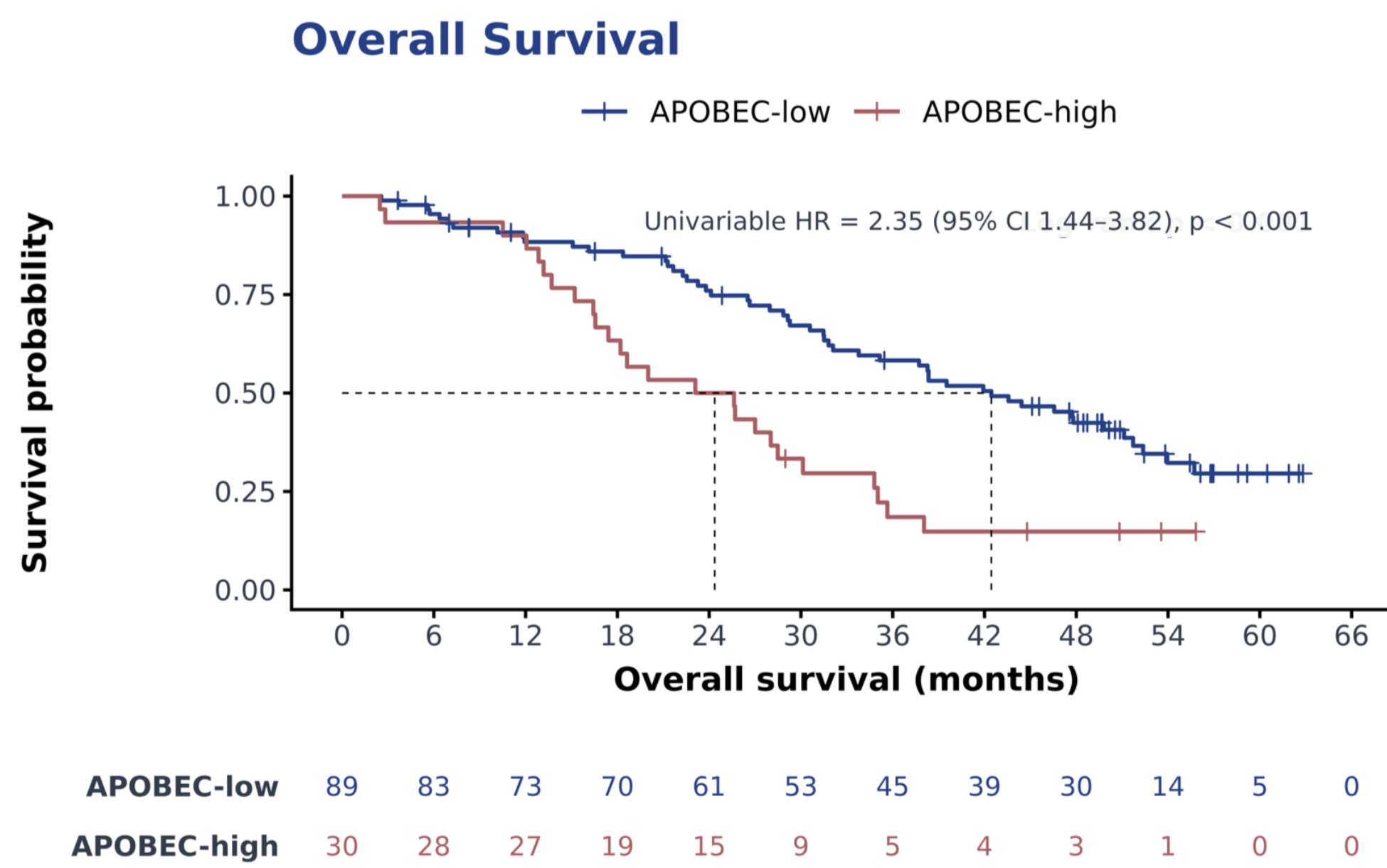
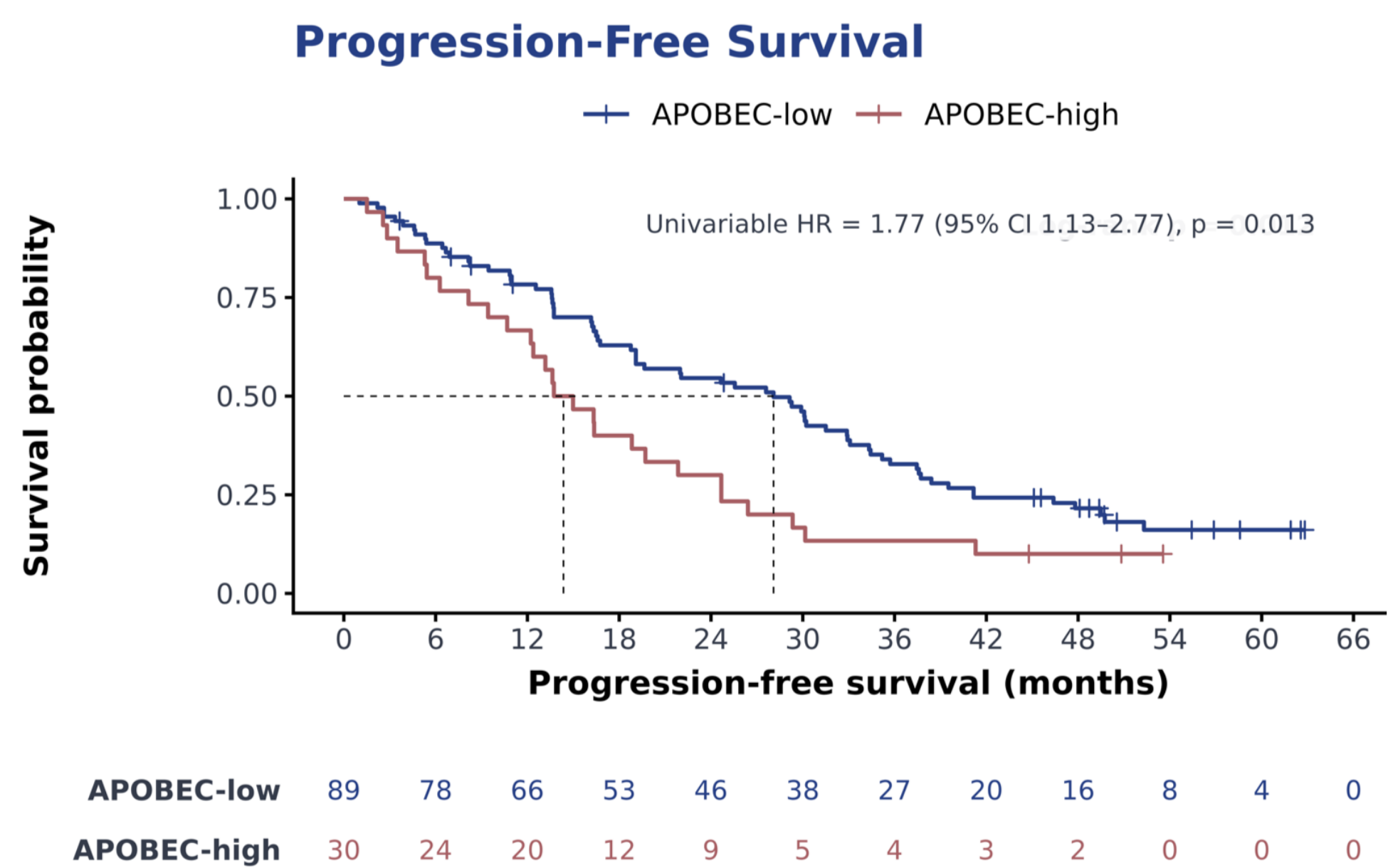
Mutational signature landscape and APOBEC3 bias



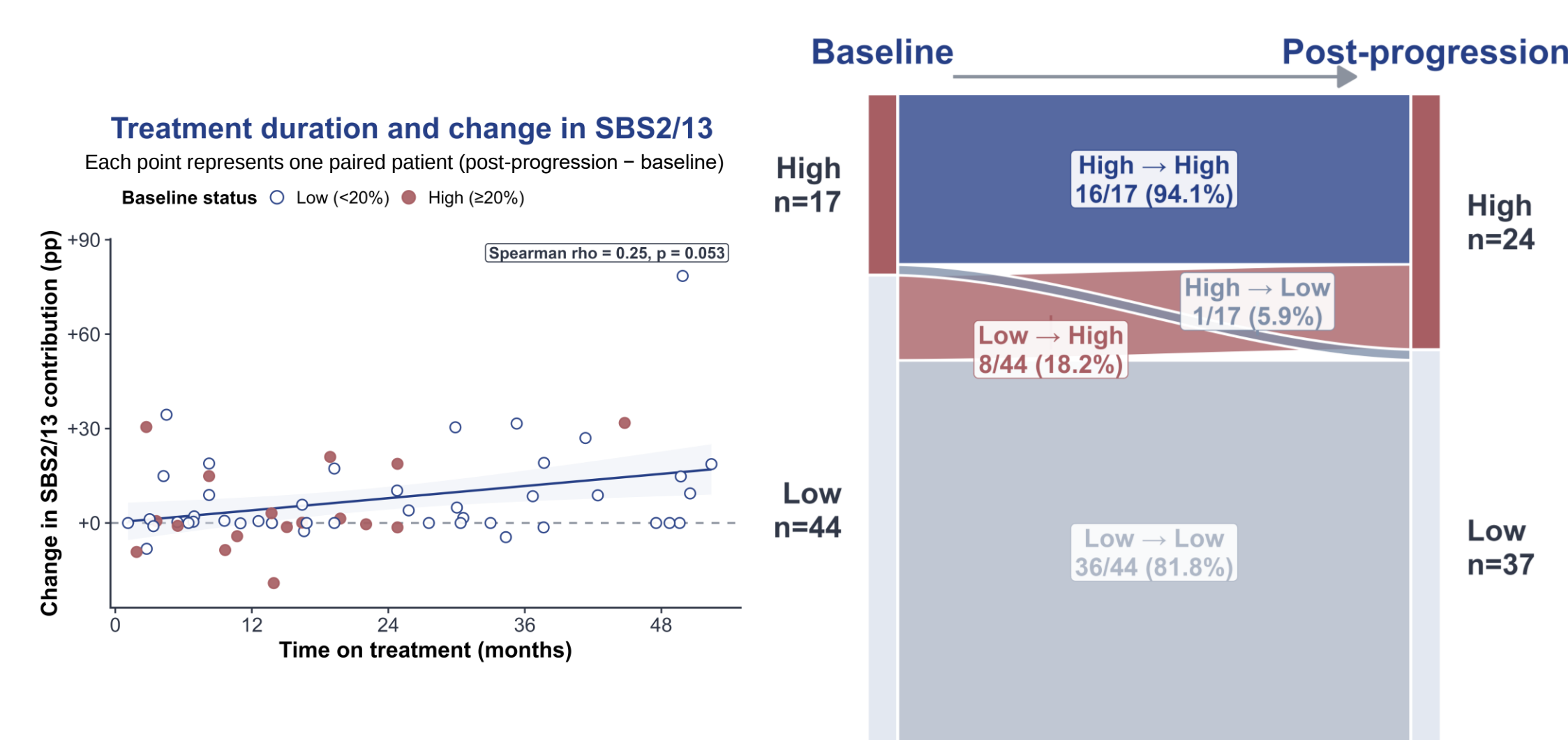
- APOBEC3-mediated mutagenesis (SBS2/13) was the second most prevalent mutational process, present in approximately 70% of tumors (84/119 for SBS13, 83/119 for SBS2).

- APOBEC3-High tumor s were predominantly A3A-like (23/30, 76.7%), while APOBEC3-Low tumors were predominantly A3B-like or showed no clear bias.

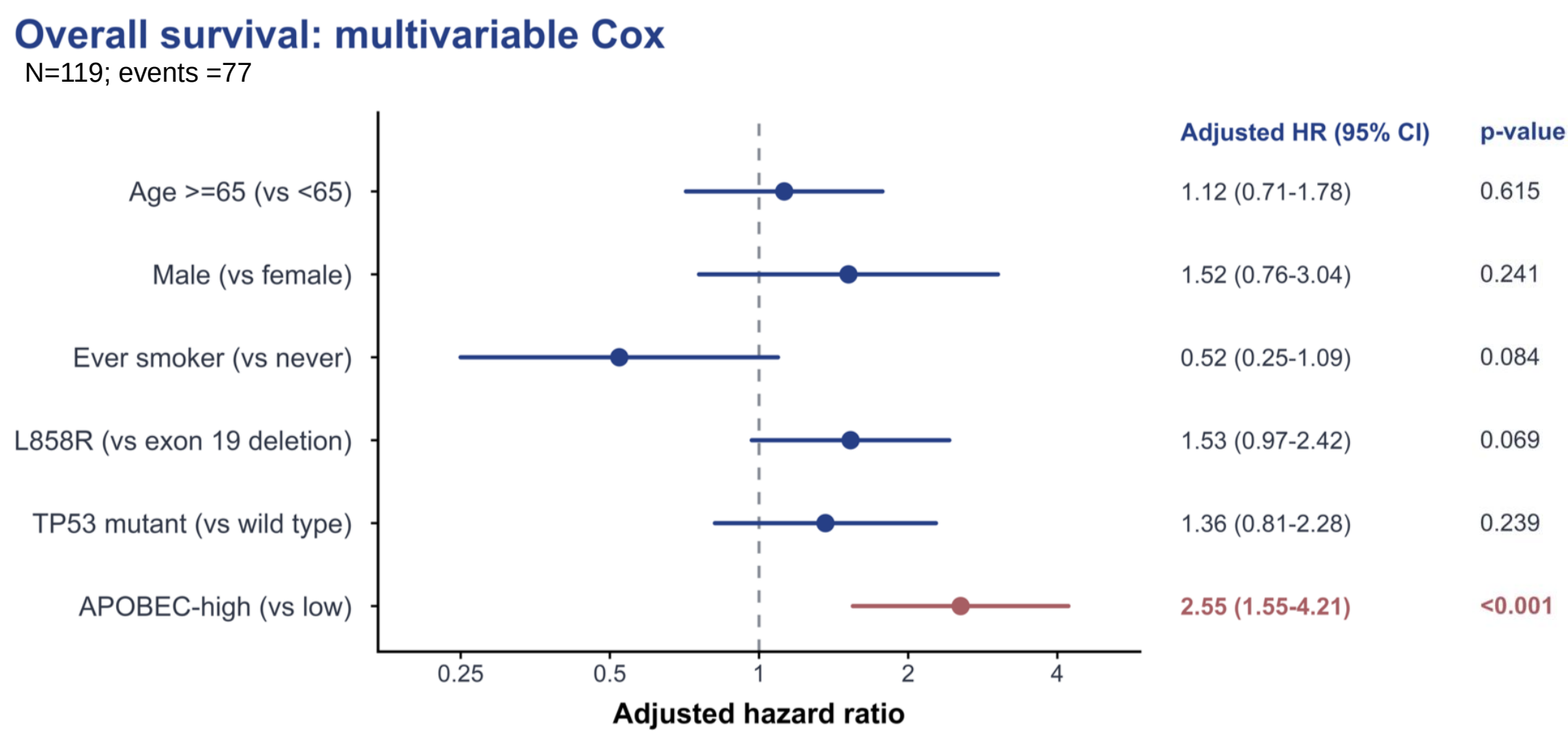
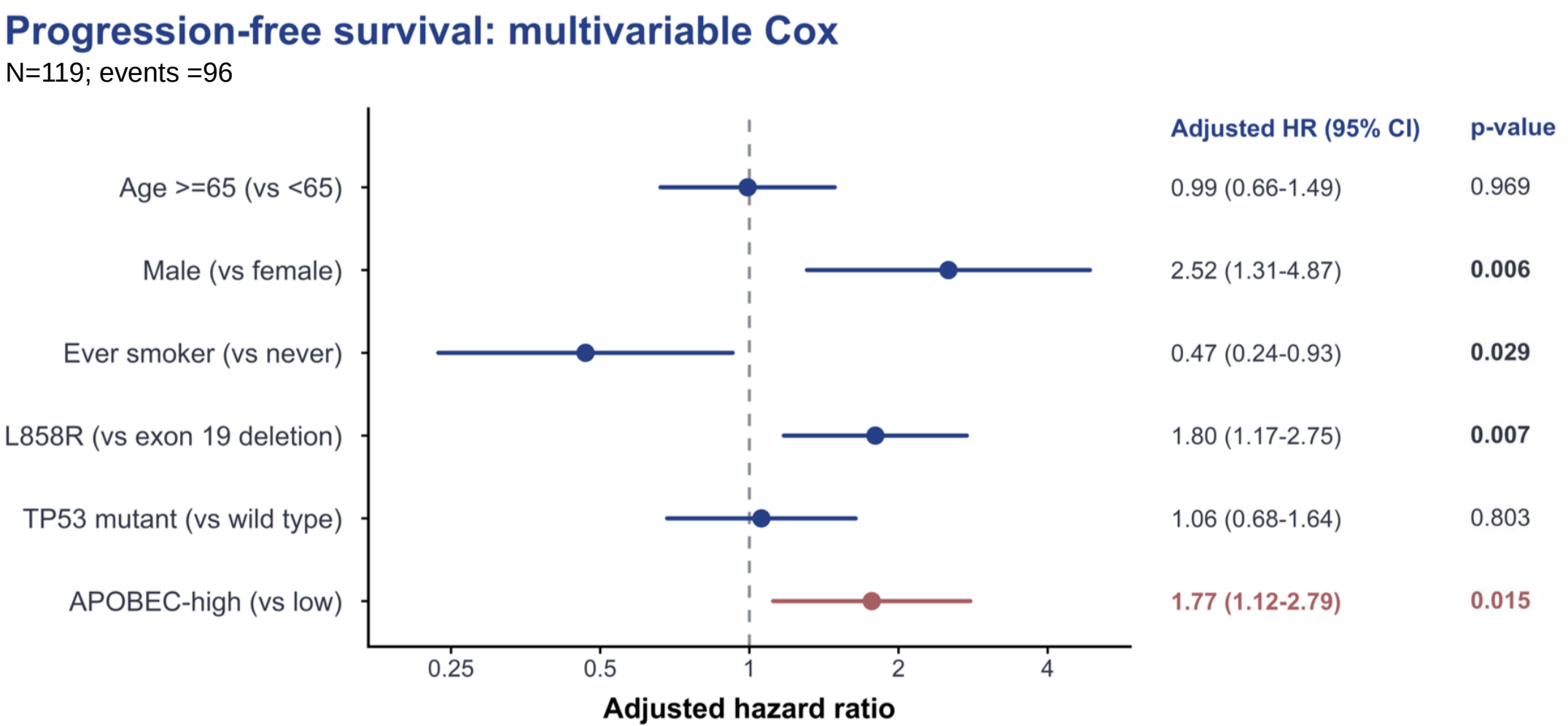
APOBEC3 prognostic association



Longitudinal APOBEC3 dynamics



- Baseline APOBEC3-High status was largely maintained at post-progression (16 of 17 High tumors remained High, 94.1%), while 8 of 44 Low tumors (18.2%) transitioned to High over time.



- Baseline APOBEC3-High status independently predicted worse OS (HR 2.55, p<0.001) and PFS (HR 1.77, p=0.015).

