

Associating Homozygous Losses with Outcomes for Patients with Advanced NSCLC in a Real-World Clinico-Genomic Database



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BACKGROUND

- Validated homozygous loss (homozygous deletion) detection is becoming increasingly important in clinical practice, with ongoing multi-tumor trials of PRMT5 and MAT2A inhibitors targeting *MTAP* loss.
- Homozygous losses are challenging to detect and require intentional NGS assay design and validations.
- Prevalence and prognostic impact of losses are poorly characterized.
- Using an algorithm that supports an FDA-approved test, we explored the most common clinically relevant homozygous losses in advanced non-small cell lung cancer (aNSCLC), their prognostic associations on standard of care therapies, and their prevalence before and after such treatments.

MATERIALS AND METHODS

- This study used the US-based deidentified Flatiron Health-Foundation Medicine NSCLC Clinico-Genomic Database (FH-FMI CGDB). Clinical data from the Flatiron Health Research Database[1] are linked to genomic data, derived from Foundation Medicine comprehensive genomic profiling (CGP) tests (FoundationOne®CDx), in the FH-FMI CGDB by deterministic matching, providing a deidentified dataset[2-4]. Patients with advanced NSCLC (aNSCLC) between 2011-2025 and who received tissue-based genomic testing were eligible for analysis.
- Biomarkers of interest were homozygous losses detected by CGP with a copy number of 0. Gene loss of function from other mechanisms was not in scope for this study.
- Actionable (first line) drivers were defined as: *EGFR* (L858R, S768I, L861Q, G719X, exon 19 deletion, exon 20 insertion), *ALK* rearrangement, *ROS1* rearrangement, *BRAF* V600E, *NTRK* rearrangement, *MET* exon 14 skipping, *RET* rearrangement.
- Treatment regimens classified into: chemotherapy only, immune checkpoint inhibitor (ICI) only, tyrosine kinase inhibitor (TKI) only, chemo-ICI, chemo-TKI, and other.
- Endpoints included real-world progression-free survival (rwPFS) and real-world overall survival (rwOS), indexed to start of first-line (1L) therapy.
- Differences between groups were assessed with chi-squared tests or multivariable models, with prognostic differences assessed with Cox proportional hazards models.
- Multivariable adjustment variables: presence of an actionable driver, age at line start, sex, ECOG performance status, genetic ancestry, areal socioeconomic status, histological subtype, opioid prescription pretherapy, smoking status, presence of bone metastases, presence of brain metastases. Analyses across therapy classes additionally included therapy class. Analyses on ICI-treated patients included TMB binarized at 10mut/Mb and PD-L1 Tumor Proportion Score binarized at 50%.

HOMOZYGOUS LOSS DETECTION

- There are 4 common types of genomic alterations that could lead to loss of function of a gene.

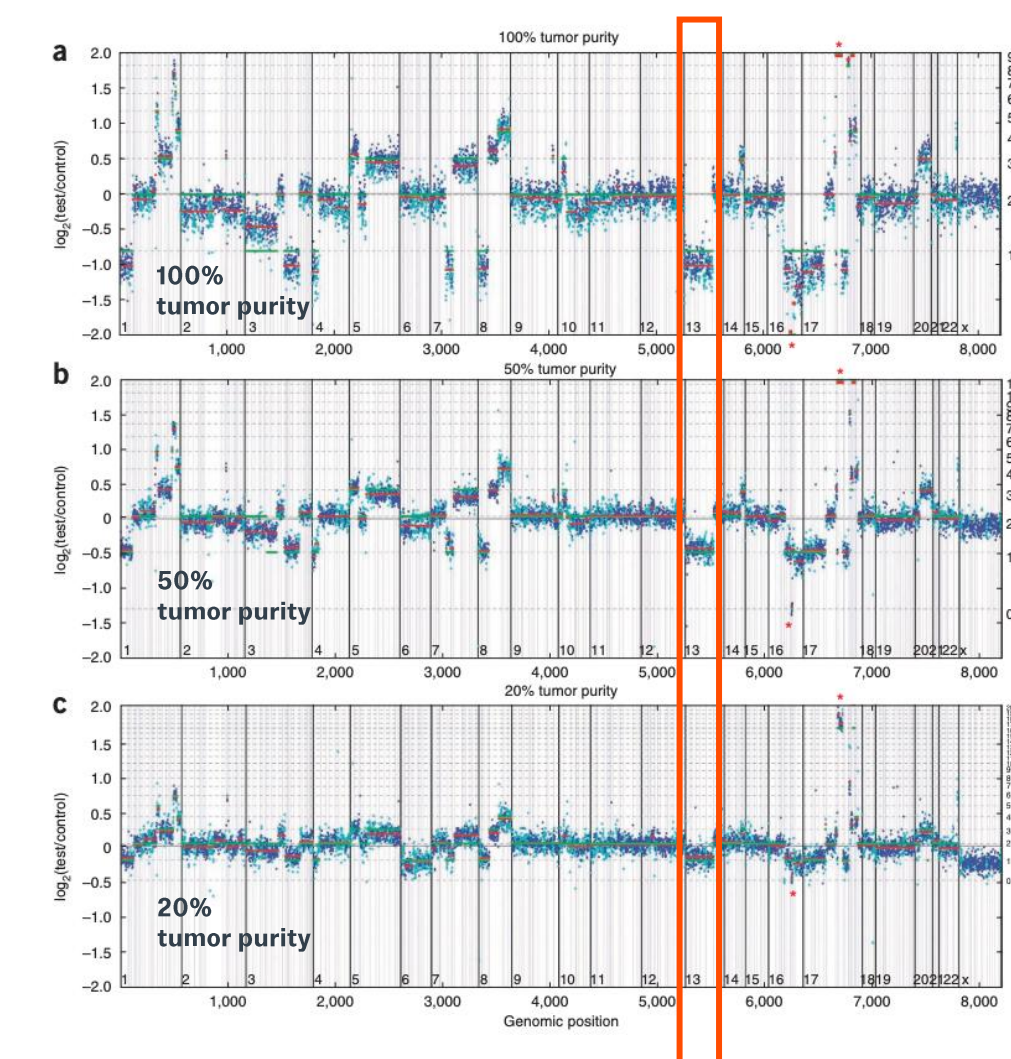
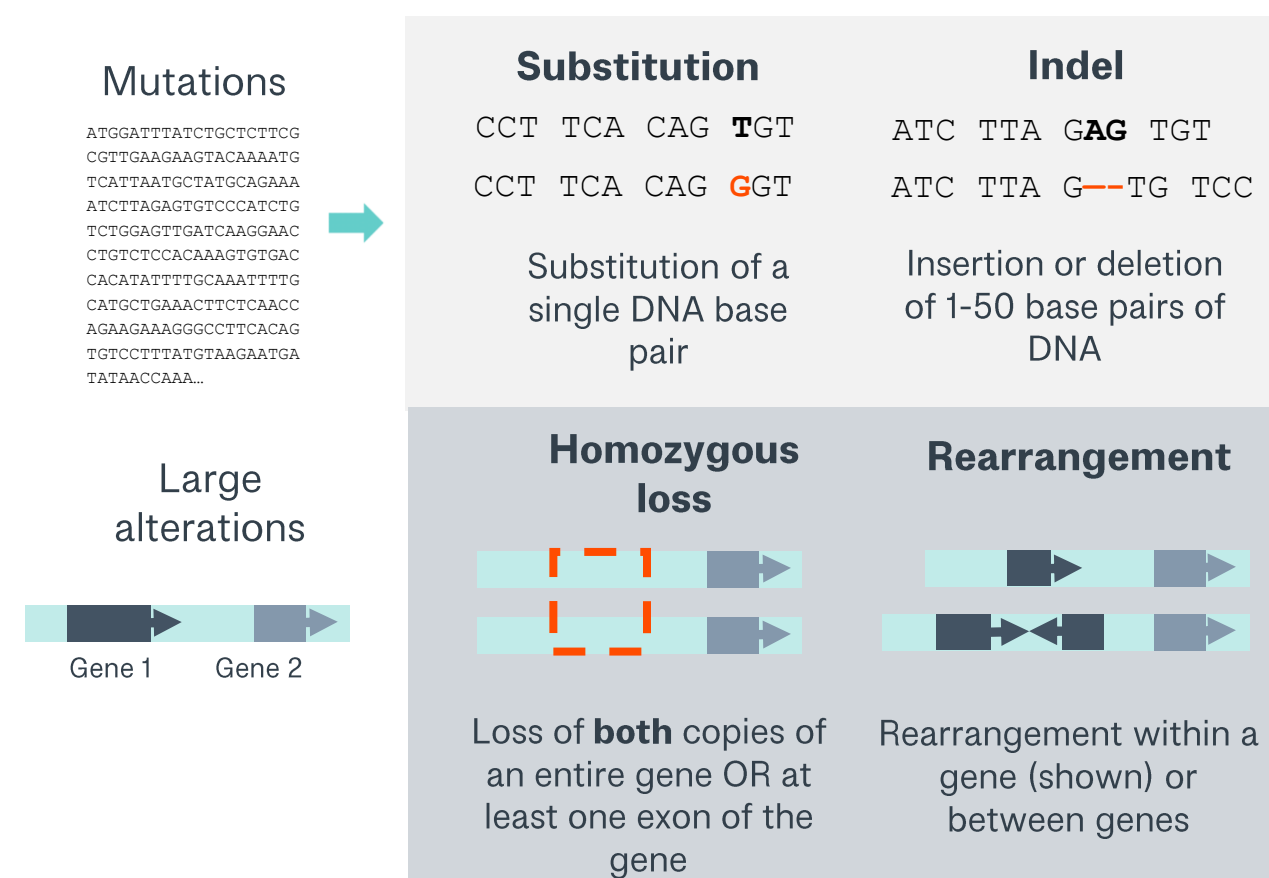
- Different genes have different alteration patterns.

- Homozygous losses can be detected by NGS using read frequency assessment.

- Copy number calling can have a low signal-to-noise ratio, making it harder to identify these alterations as confidently as for mutations.

- Some commercial NGS panels additionally bait SNPs at shallow depth across the genome to aid with ploidy assessments.

- Rigorous bioinformatic pathways and curation are critical to identify and report homozygous losses, especially at lower tumor purity.^{4,5}



One example of a homozygous loss is marked, showing how detectability varies with tumor purity.

RESULTS

Cohort Selection

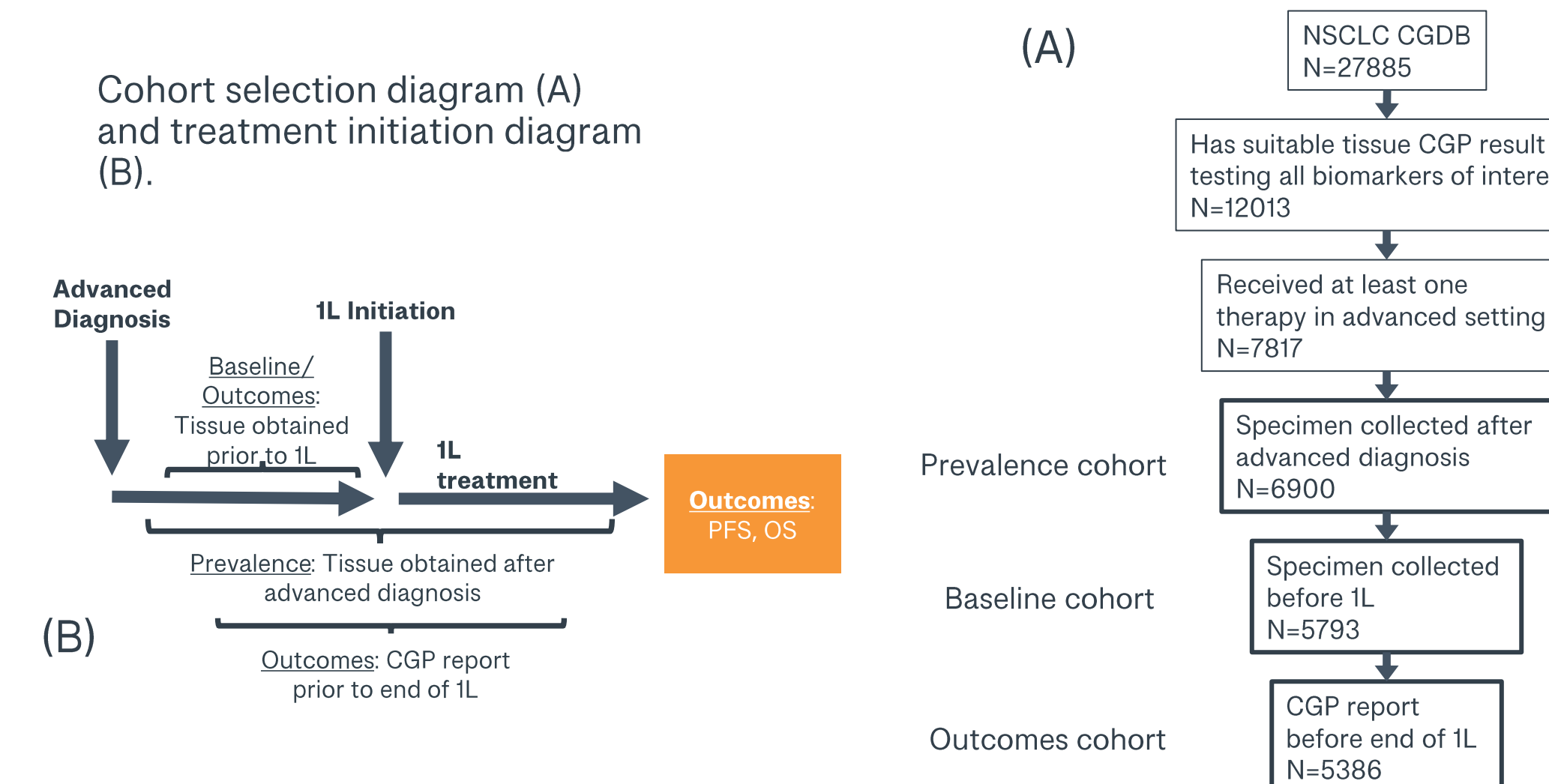
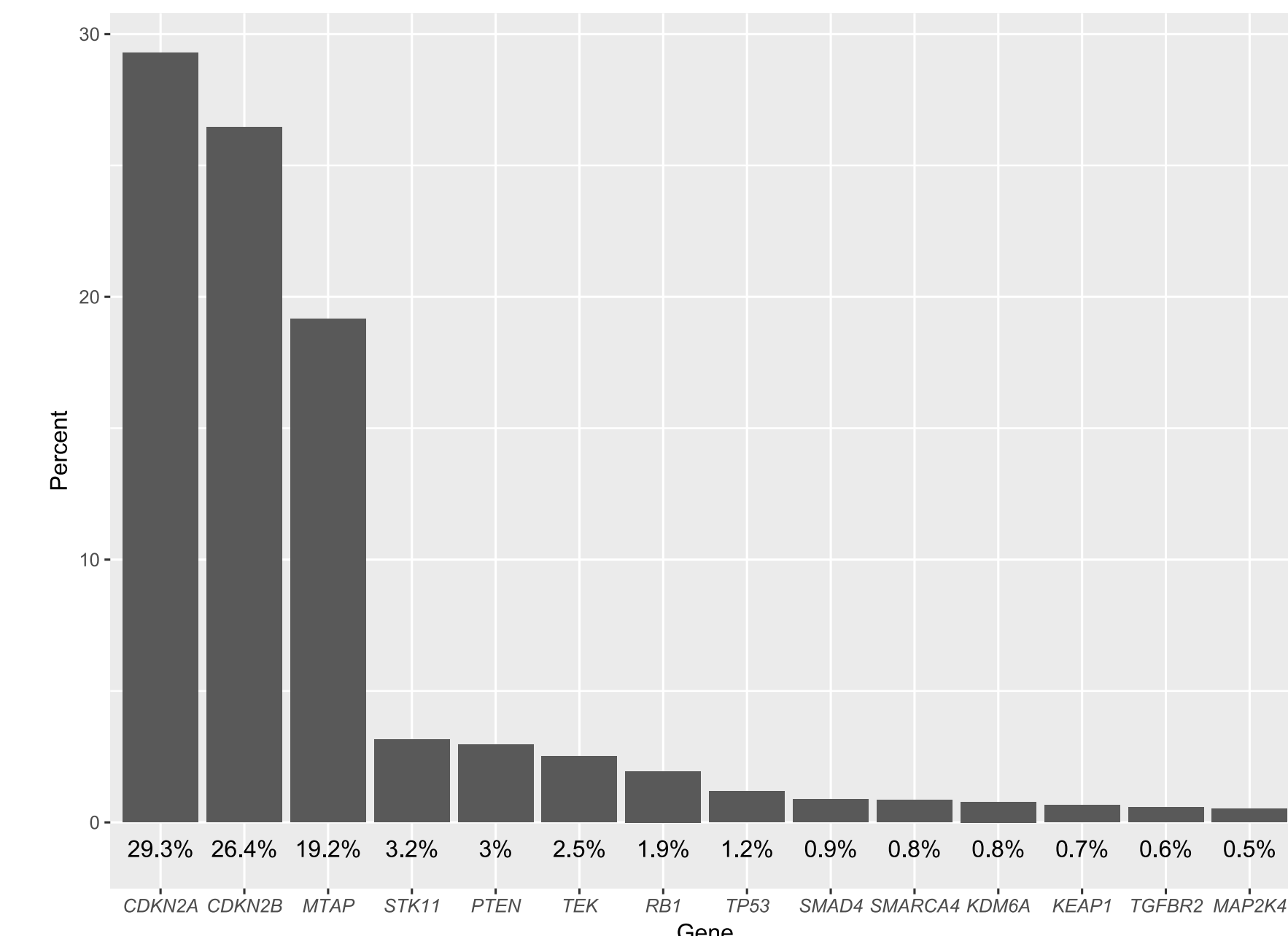
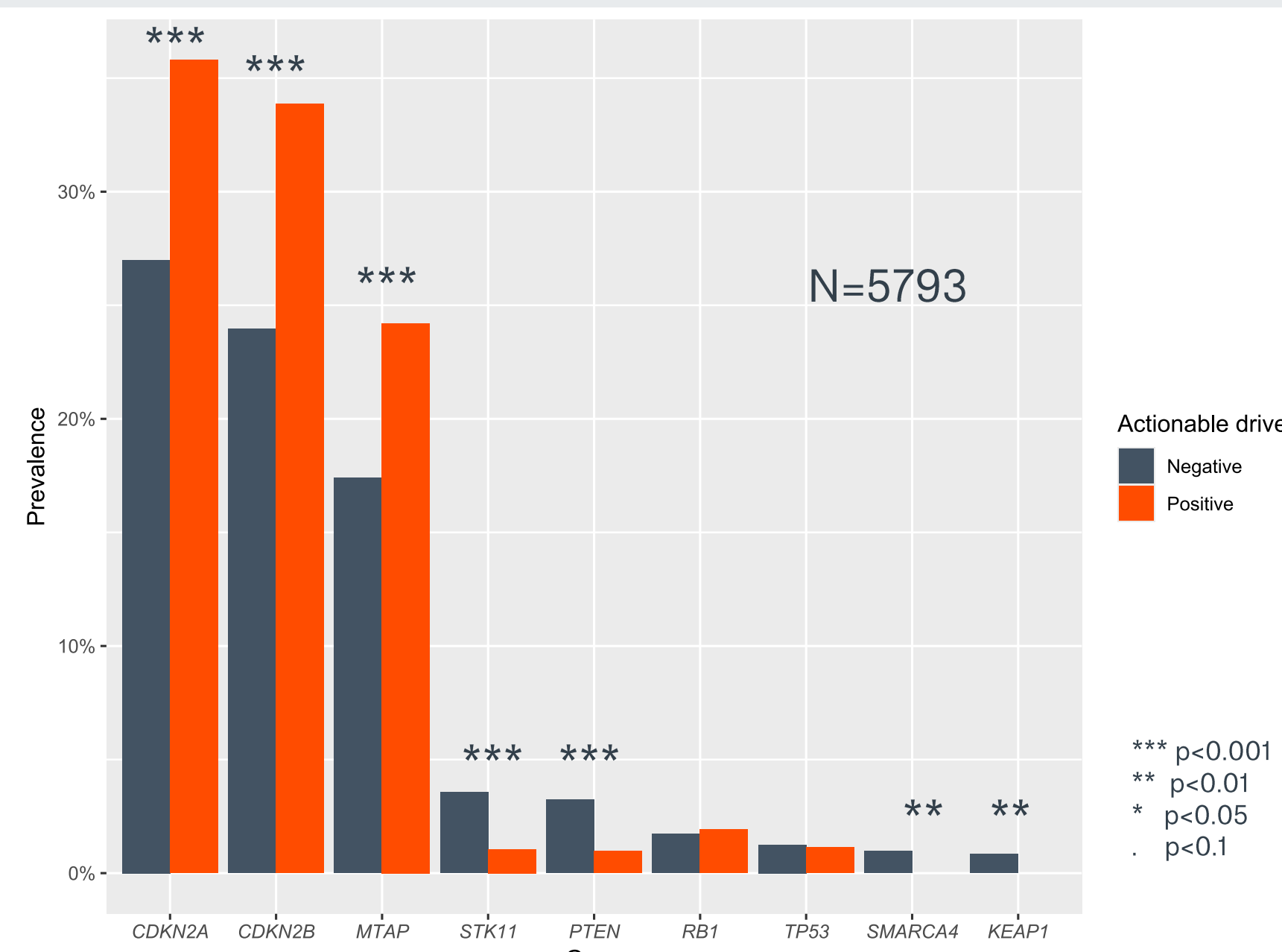


Figure 1: Prevalence of most common homozygous losses



Overall prevalence of copy number losses by gene in the Prevalence cohort (N=6900). For patients with multiple specimens, results are summarized as ever-positive per gene per patient (total 7074 specimens). The top 3 most commonly deleted genes are *CDKN2A*, *CDKN2B*, and *MTAP*.

Figure 2: Homozygous loss profiles are different between driver-positive and negative disease



Homozygous loss prevalence differed between patients with actionable drivers (alterations listed in the NCCN guidelines) and those without actionable drivers. This suggested distinct homozygous loss profiles between driver-positive and driver-negative disease.

Figure 3: *STK11* loss is associated with poor prognosis overall and worse outcomes on TKI

Kaplan-Meier analysis of rwPFS from start of 1L therapy, by *STK11* loss status. Adjusted HR based on multivariable Cox model. rwPFS is shown, but rwOS was also tested and showed similar results. (A) All therapy classes (multivariable adjustment additionally included therapy class). (B) Only patients who received TKI.

While *STK11* loss appears prognostic for worse outcomes across all therapy classes, this effect is magnified among patients receiving TKI. However, this observation is based on very few *STK11* loss cases (n=167), so further validation will be necessary to confirm this finding.

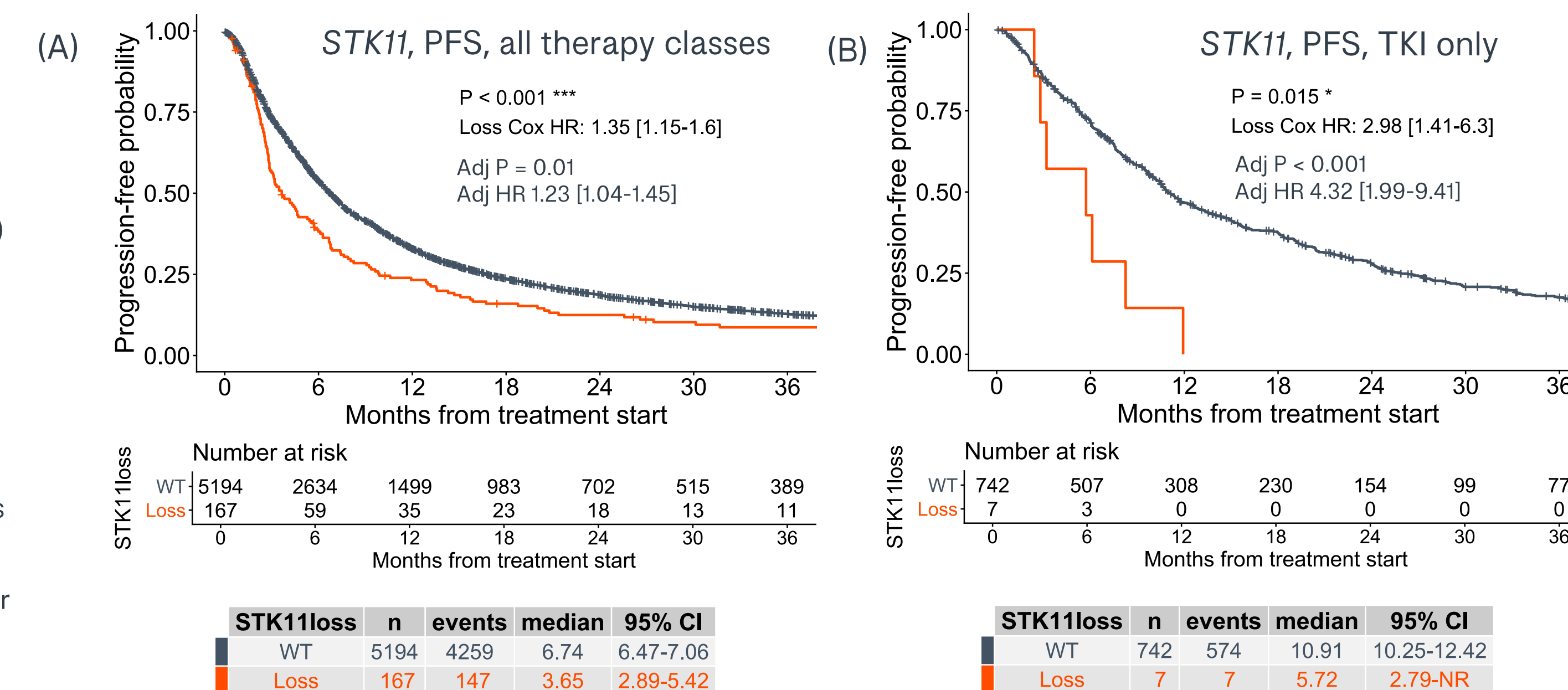
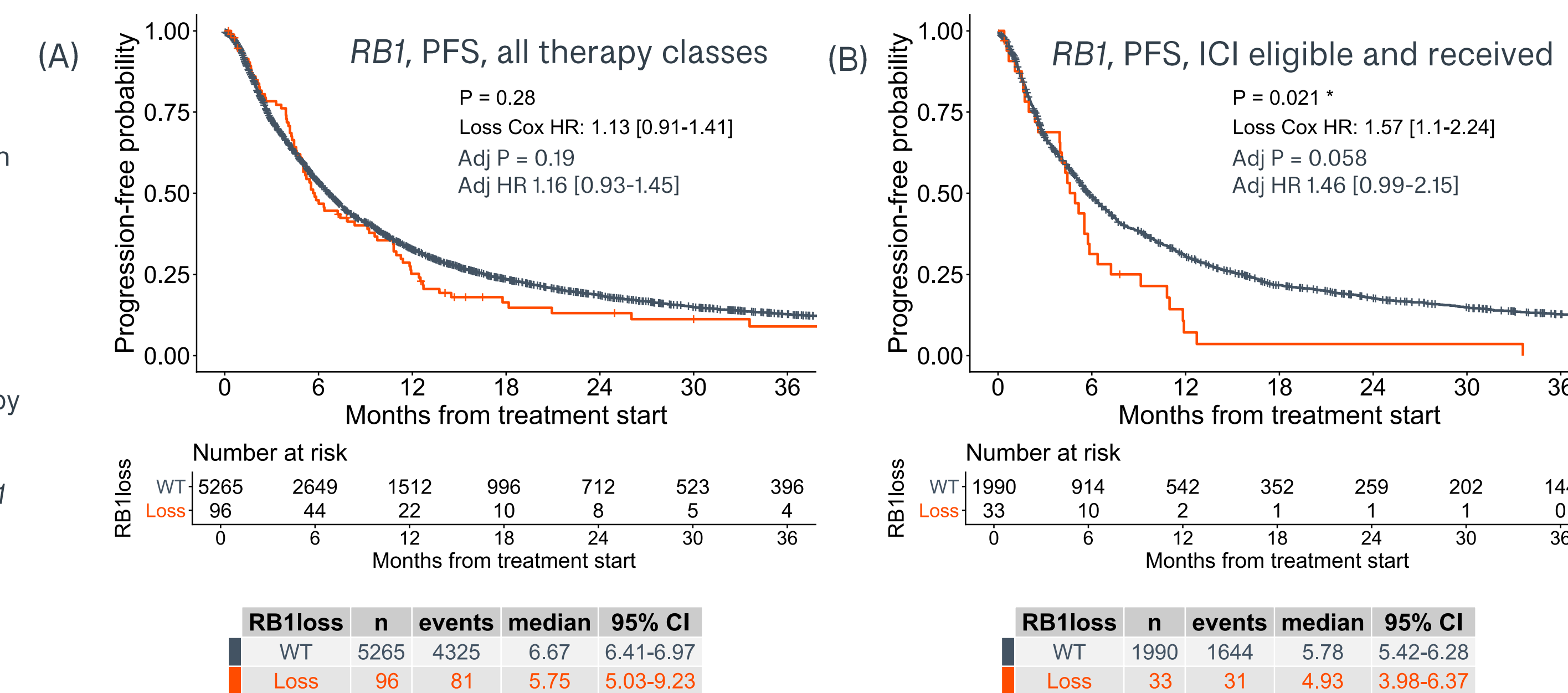


Figure 4: *RB1* loss associated with worse outcomes on ICI

Kaplan-Meier analysis of rwPFS from start of 1L therapy, by *RB1* loss status. Adjusted HR based on multivariable Cox model. rwPFS is shown, but rwOS was also tested and showed similar results. (A) All therapy classes. (B) Only patients who were eligible for and received ICI (PD-L1 TPS $\geq$ 1% or TMB $\geq$ 10mut/Mb and no actionable alterations for TKI; ICI monotherapy or combined with chemotherapy).

While patients with or without *RB1* loss have similar outcomes when aggregated across all therapy classes, in the ICI subcohort, *RB1* loss was associated with worse outcomes.



CONCLUSIONS

- Using an FDA-approved assay, homozygous losses in *CDKN2A*, *CDKN2B*, *MTAP*, *STK11*, and *PTEN* were frequently detected in NSCLC. However, the homozygous loss profile was different between driver-positive and negative disease.
- Among other findings, exploratory analyses suggest *STK11* loss may predict worse outcomes on TKI, while *RB1* loss may predict worse outcomes on ICI.
- Emerging copy number loss biomarkers may be the focus of future clinical trials, underscoring the importance of testing with a validated assay capable of robust homozygous loss reporting.

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