



P1.245: TP53 Functional Domain-Specific Mutations Define Distinct Clinical Outcomes in Non-Small Cell Lung Cancer Treated With Immunotherapy

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BACKGROUND

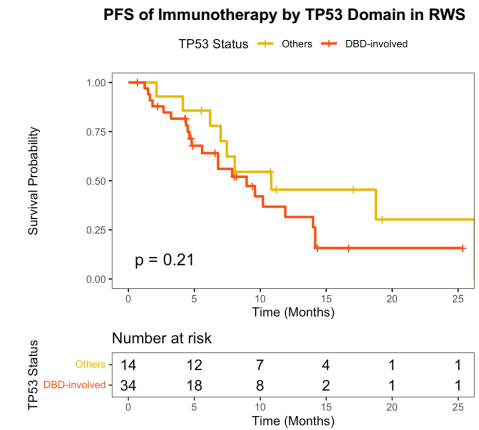
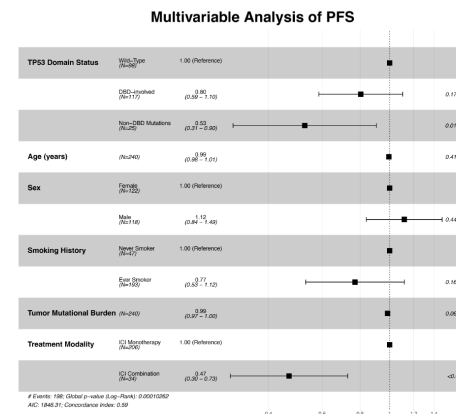
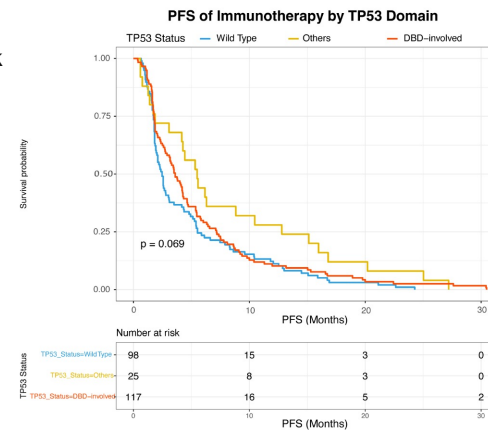
- TP53 is frequently altered in NSCLC, yet its prognostic value during immune checkpoint inhibitor (ICI) therapy remains inconsistent.
- Binary wild-type/mutant grouping may obscure functional heterogeneity across structurally distinct TP53 domains.
- We tested whether domain-specific TP53 classification identifies clinically distinct PFS outcomes across public and real-world ICI-treated cohorts.

METHODS

- Cohorts: public ICI-treated NSCLC discovery cohort and advanced NSCLC real-world validation cohort.
- TP53 groups: wild-type (WT), DNA-binding-domain (DBD)-involved, and non-DBD mutations.
- Endpoint: progression-free survival (PFS).
- Statistics: Kaplan–Meier/log-rank testing and multivariable Cox models accounting for treatment modality and baseline covariates.

RESULTS

- Discovery cohort: overall domain-group separation approached significance (log-rank $p=0.069$).
- Non-DBD vs WT: HR=0.47; $p=0.015$ — associated with longer PFS.
- DBD-involved vs WT: HR=0.97; $p=0.865$ — no detectable PFS difference.
- Real-world validation: unadjusted log-rank $p=0.210$.
- Adjusted non-DBD vs WT: HR=0.54; $p=0.047$.
- Clinical context: combination regimens showed a strong protective effect, potentially masking the genomic signal before adjustment.



CONCLUSIONS

- Structural resolution: domain-specific TP53 classification refines PFS stratification beyond a binary mutant/WT model.
- Consistent favorable signal: non-DBD mutations were associated with longer PFS in discovery and after multivariable validation adjustment.
- Clinical interpretation: genomic effects should be evaluated alongside treatment modality and other

REFERENCES & CONTACT

- [1]. Dong ZY, Zhong WZ, Zhang XC, et al. Potential Predictive Value of TP53 and KRAS Mutation Status for Response to PD-1 Blockade Immunotherapy in Lung Adenocarcinoma. Clin Cancer Res. 2017;23(12):3012–3024. [2]. Sun H, Liu SY, Zhou JY, et al. Specific TP53 Subtype as Biomarker for Immune Checkpoint Inhibitors in Lung Adenocarcinoma. EBioMedicine. 2020;60:102990.

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