Characterization of *TP53* Mutations in Actionable Driver-negative Non-Small Cell Lung Cancer (NSCLC)

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Abstract # 458534

BACKGROUND

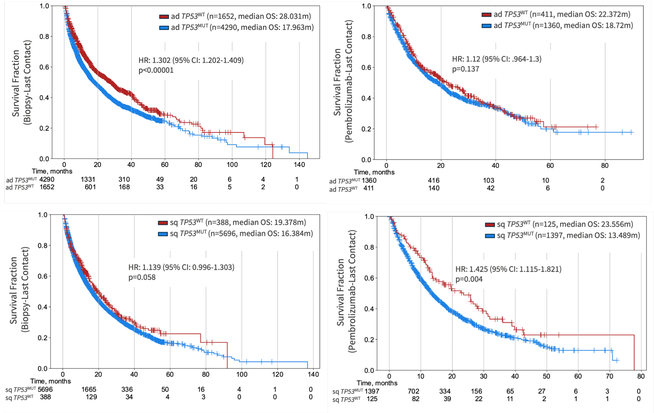
- Despite the increased prevalence in actionable driver-negative (DN) NSCLC, the role of TP53 mutations in this subtype is not fully explored.
- We characterize the association of TP53 mutations with the molecular and immune landscapes, as well as outcomes, in in the context of histologic subtypes.

METHODS

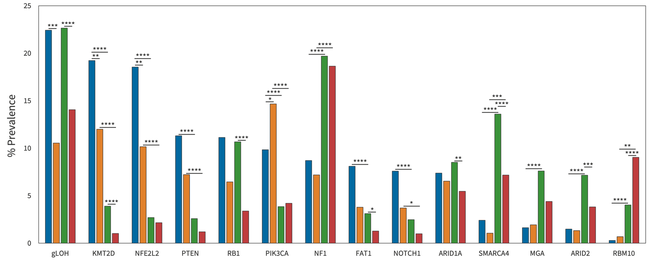
- 12,026 NSCLC specimens were analyzed using NGS DNA (DNA-592 panel) or RNA (whole transcriptome) at Caris Life Sciences (Phoenix , AZ).
- Tumors with *KRAS*, *EGFR*, *BRAF*, *MET*, *HER2*, *ALK*, *ROS1*, *NRG1*, and *NTRK* 1-3 alterations were excluded.
- Specimens were grouped as *TP53*^{WT} (wild type) or *TP53*^{MUT} (pathogenic/likely pathogenic mutations only).
- PD-L1 expression was analyzed by IHC (Dako 22c3; PD-L1 positive: TPS ≥1%).
- Overall survival was extracted from insurance claims data and calculated from the time of tissue collection (OS) or initiation of Pembrolizumab treatment (Pembro-OS) to the last contact. Hazard ratio (HR) was calculated using the Cox proportional hazards model, and P values were calculated using the log-rank test.
- Composition of the tumor microenvironment (TME) was estimated from bulk RNA sequencing using QuanTIseq method.
- Significance was determined using chi-square, Fisher's Exact, Mann Whitney U and logrank tests and corrected for multiple comparisons (q-value < 0.05).

RESULTS

Association of *TP53* Mutation Status with OS and Pembrolizumab-OS by histology

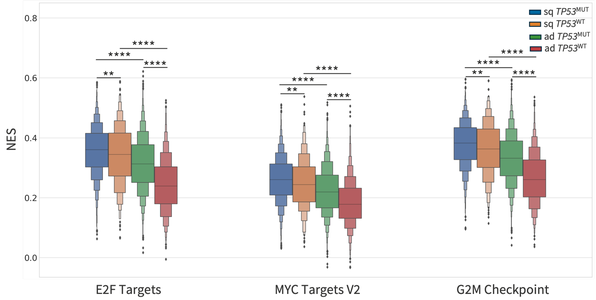


TP53^{MUT} was associated with poor OS in adenocarcinoma (AC) (HR: 1.3, p < 0.05), and shorter Pembro-OS in squamous cell carcinoma (SCC) (HR:1.425, q< 0.05).

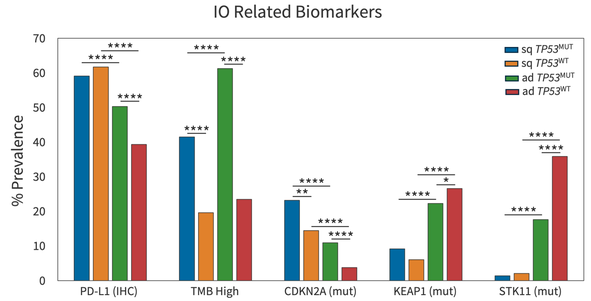


In AC, mutations in *FAT1*, *ARID1A*, *SMARCA4*, *ARID2* and *RBM10* were enriched, while in SCC, mutations in PIK3CA were less common with TP53MUT.

Significant Gene sets involved in cell cycle regulation associated with *TP53* Mutations

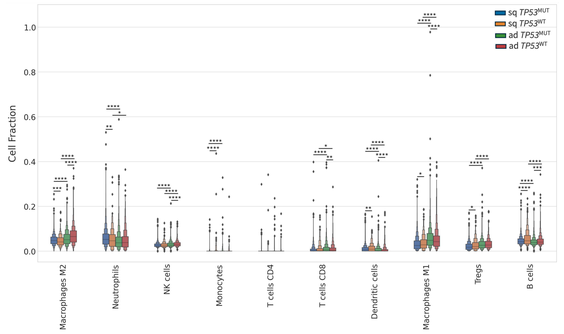


Gene sets involved in cell cycle regulation such as G2M, MYC, and E2F targets were enriched in *TP53*^{MUT} and to a greater extent in AC (1.22-1.29) vs SCC (1.06-1.08, both q<0.05).



Immunotherapy-related biomarkers, such as PD-L1+ and STK11/KEAP1 mutations, were reduced in *TP53*^{MUT} AC but not SCC.

Association of Tumor Microenvironment with *TP53* Mutations



M2 Macrophage (1.25-fold) and NK cell (1.3-fold) fractions were enriched, and B cell fractions (1.25-fold) were reduced in *TP53*^{MUT} SCC TMEs (all q<0.05).

CONCLUSION

- *TP53*^{MUT} were associated with poor OS and Pembro-OS exclusively in AC and SCC, respectively.
- The distinct molecular and immune landscapes associated with *TP53*^{MUT} in AC and SCC potentially explain the differences in outcomes mentioned above.
- Further research is needed to better understand therapeutic implications of *TP53*^{MUT} in DN-NSCLC.

CONTACT INFORMATION

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