Objectives

- Understand how TMB and PD-L1 differ between K-RAS/TP53 co-mutants compared to K-RAS/TP53 wt NSCLC.
- Assess differences in TMB and PD-L1 for various K-RAS exons and codons.
- Study metastatic site specific variations in TMB and PD-L1 for K-RAS/TP53 co-mutated metastatic NSCLC.
- Evaluate distribution of STK-11 and KEAP-1 mutations within the K-RAS/TP53 co-mutated subset.

Methods

- Caris life sciences NGS dataset consisting of 1317 mNSCLC tissue samples from 2016-18 was queried.
- PD-L1++ was defined as ≥ 1% staining using 22c3 Dako assay.
- TMB was measured by counting all somatic non-synonymous mutations using targeted NGS (592 genes).
- TMB-high (H) was defined as ≥ 10 mutations/Megabase (mut/Mb).
- P-values were calculated using Chi-square and Mann Whitney test.

Results

- Early data suggests that co-occurring genetic events define biological heterogeneity in K-RAS mutant NSCLC, with K-RAS/TP53 co-mutated (KP) subset having potential therapeutic vulnerabilities to anti-PD-1 therapy with (A) improved response rates and (B) durable clinical benefit.
- To explore the immunological basis for these findings, we evaluated the immune biomarker profile (TMB/PD-L1) in KP mutant in NSCLC using a large next-generation sequencing (NGS) dataset.

Difference in PD-L1 distribution for K-RAS/TP53 co-mutated subset vs K-RAS mut/TP53 wt

PD-L1 positivity

< 1% 1-4% ≥ 5%

TP53 Mutations were identified in 49.4% of K-RAS mutant NSCLC.

Missense mutations accounted for a majority (69.5%) of TP53 mutations.

TMB Distribution in PD-L1 negative subset:

- PD-L1 negative = 42.1% (153/378) K-RAS mut/TP53 wt; 67.3% (107/159) K-RAS/TP53 co-mutated.
- Median TMB for the two subgroups: 14.9 vs 29.8 Mbp; p < 0.001.
- TMB-H was 86.5% in K-RAS/TP53 co-mutated groups vs 43.3% in the K-RAS TP53 wt (p < 0.001).

Conclusions

- Largest dataset to date demonstrating that K-RAS/TP53 co-mutation displays a distinctly high TMB, especially in the PD-L1 negative subgroup.
- No significant differences in TMB were identified among the K-RAS alleles. G12D had the highest PD-L1% with 76.6%, having PD-L1>50%.
- K-RAS/TP53 co-mutated patients with brain involvement have higher TMB compared to skeletal involvement.
- K-RAS/TP53 co-mutated subset with STK-11 have low TMB and are present mostly in the skeletal compartment.
- Those findings could have therapeutic implications in guiding patient selection for ICB and merit prospective investigation.

Acknowledgement:

Caris Life Sciences for providing access to data to conduct the study.

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Brain was the most common metastatic site followed by bone.

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