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Abstract 2626
Board #270

Tumor mutational burden (TMB) profile of K-RAS/TP-53 co-mutation in metastatic non-small cell lung cancer (m-NSCLC)

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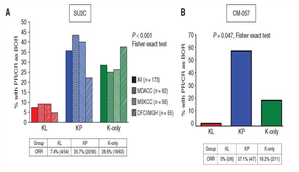
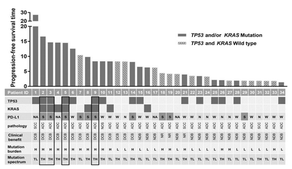
BACKGROUND



Skoulidis et al. Cancer Discov 2018



Dong et al. Clin Cancer Res 2017

- Early data suggests that co-occurring genetic events define biological heterogeneity in K-RAS mutant NSCLC, with *K-RAS/ TP-53* 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 m-NSCLC using a large next-generation sequencing (NGS) dataset

OBJECTIVES

- Understand how TMB and PD-L1 differ between K-RAS/TP-53 co-mutants compared to K-RAS mut/TP-53 wt.
- Assess differences in TMB and PD-L1 for various K-RAS exons and codons.
- Study metastatic site specific variations in TMB and PD-L1for K-RAS/TP-53 co-mutated metastatic NSCLC.
- Evaluate distribution of STK-11 and KEAP-1 mutations within the K-RAS/TP-53 co-mutated subset.

METHODS

- Caris life sciences NGS dataset consisting of 1317 m-NSCLC tissue samples from 2016-18 was queried.
- PD-L1^{pos} was defined as ≥ 1% staining using 22c3 Dako assay.
- TMB was measured by counting all somatic non-synonymous missense 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

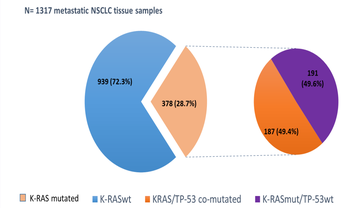
Next-Generation Sequencing
DNA
- Illumina NextSeq System -

- ✓ 592 full gene coverage
- ✓ 750x depth of coverage
- ✓ Includes point mutations, indels, and copy number alterations
- ✓ Includes all SNVs and indels on guidelines

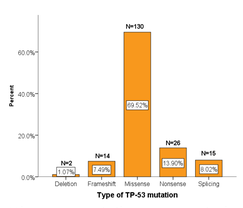
Genomic signatures also reported:
- Tumor Mutational Burden (TMB)
- Microsatellite Instability

RESULTS

TP-53 Distribution:



TP-53 Mutation was identified in 49.4% of K-RAS mutant NSCLC.



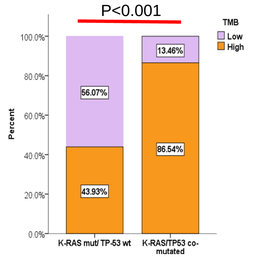
Missense mutations accounted for a majority (69.5%) of TP-53 mutations.

TMB Distribution in PD-L1 negative subset:

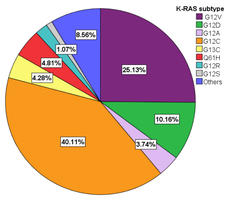
- PD-L1 negative = 42.1% (159/378)

  K-RAS mut/TP-53 wt= 67.3% (107/159)

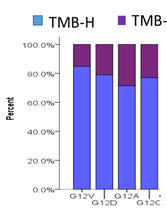
  K-RAS/ TP-53 co-mutated= 32.7 (52/159)
- Median TMB for the two sub groups: 14 vs 9 mut/Mb; p<0.001.
- TMB-H was 86.5% in K-RAS/TP-53 co-mutated groups vs 43.9 % in the K-RAS mut/ TP-53 wt (P <0.001)

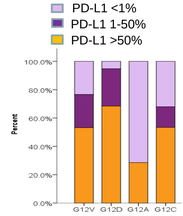


K-RAS subtypes and correlation with PD-L1 and TMB in K-RAS/TP-53 co-mutated subset:



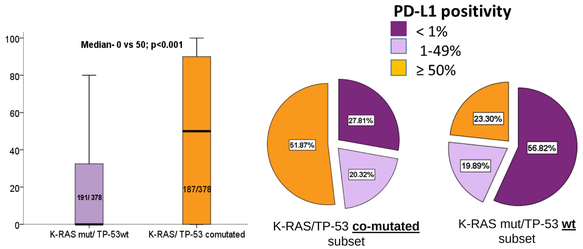
G12C was the most common allele enriched in the K-RAS/TP-53 co-mutated subset.





G12A had the lowest TMB-H% and PD-L1%. G12D had the highest PD-L1% with >60% having PD-L1 >50%.

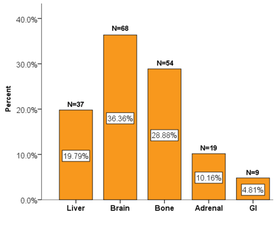
PD-L1 Distribution:



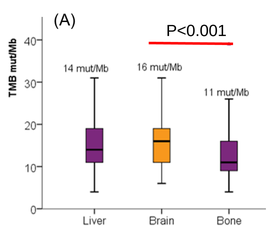
Difference in PD-L1 distribution for K-RAS/TP-53 co-mutated subset vs K-RAS mut /TP-53 wt

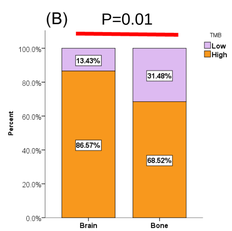
PD-L1 ≥ 50% = 51.8% in K-RAS/TP-53 co-mutated groups vs 23.3% in the K-RAS mut/ TP-53 wt p <0.001

Metastatic site specific distribution for TMB in K-RAS/TP-53 co-mutated subset:



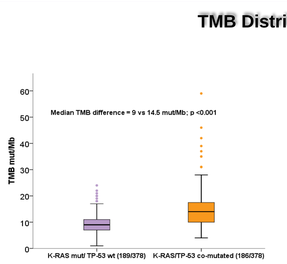
Brain was the most common metastatic site followed by bone.



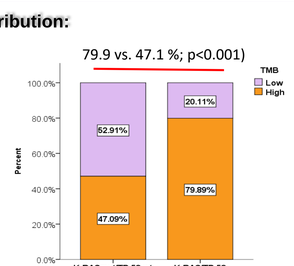


Brain tissue demonstrated (A) higher median TMB and (B) greater TMB-H compared to bone.

TMB Distribution:

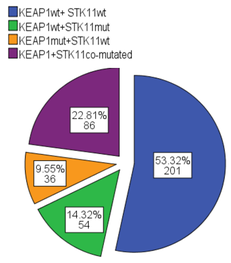


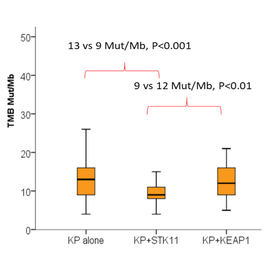
Median TMB was significantly higher for K-RAS/TP-53 co-mutated subset vs K-RAS mut /TP-53 wt



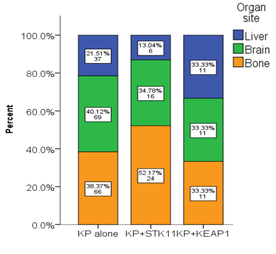
TMB-H was greater for K-RAS/TP-53 co-mutated subset vs K-RAS mut /TP-53 wt

STK-11 and KEAP-1 mutations in K-RAS/TP-53 co-mutated (KP) subset:





STK-11 mutations within the KP subset demonstrated the lowest median TMB.



STK-11 mutations within the KP subset were more prevalent in the skeletal compartment.

CONCLUSIONS

- Largest dataset to date demonstrating that K-RAS/TP-53 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 >60% having PD-L1 >50%.
- K-RAS/TP-53 co-mutated patients with brain involvement have higher TMB compared to skeletal involvement.
- K-RAS/TP-53 co-mutated subset with STK-11 have low TMB and are present mostly in the skeletal compartment
- These findings could have therapeutic implications in guiding patient selection for ICB and merit prospective investigation.

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