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STK11/TP53 co-mutated non-small cell lung cancer (NSCLC) displays a unique tumor microenvironment (TME) and metabolic profile

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CARIS POA PRECISION ONCOLOGY ALLIANCE

Introduction

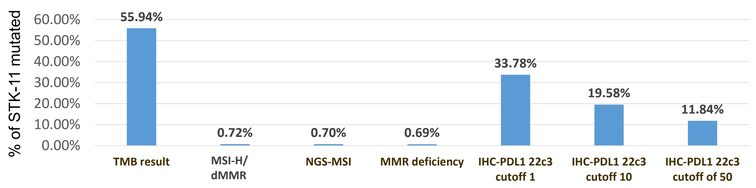
- Recent data indicate inferior responses to immune checkpoint inhibitors (ICIs) in *STK11*-mt NSCLC [1].
- *TP53* is a critical tumor suppressor gene regulating DNA repair by arresting cells in the G1 phase in response to critical double strand breaks [2].
- We hypothesized that accumulated DNA damage from mutations in the *TP53* gene might increase immunogenicity and potentially enhance benefit of ICIs in *STK11-mt* NSCLC.

Methods

- A total of 16,896 NSCLC tumor samples (FFPE) were submitted to Caris Life Sciences (Phoenix, AZ) for targeted NGS profiling (DNA-Seq, 592 genes).
- Using Illumina NovaSeq 6500, a subset (N=5034) also had gene expression profiling (RNA-Seq, whole transcriptome). Tumor immune cell content was obtained using Microenvironment Cell Population-counter (MCP). PD-L1 (TPS) was tested with 22c3 antibody.
- Neoantigen load for *STK11*-mt NSCLC was obtained for TCGA from published analysis (Thorsson et al.[3]). Tumor mutational burden (TMB) and neoantigen load were compared using non-parametric tests. WTS gene expression TPM values were log10 transformed, scaled, and compared.
- Hierarchical clustering (Ward D) was performed using expressions of STING genes (CCL5, CXCL10 and MB21D1) in STK11-mt NSCLC. Two main clusters were identified displaying high and low immune gene (Chen et al.[4]) signatures. Chi-squared test was performed on the numbers of cases with mutant and wild type in genes of interest.
- Publicly available data from the POPLAR/OAK trials of atezolizumab in advanced NSCLC were used to model PFS and OS for *STK11*-mt with *TP-53*-mt (n=14) and without *TP-53*-mt (n=20).

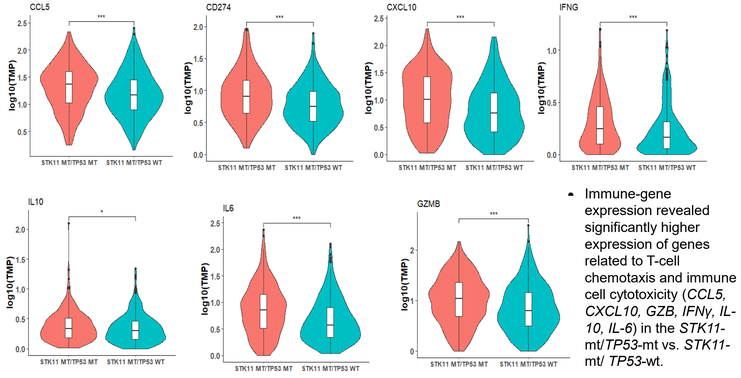
Results

Figure 1: Clinically relevant biomarkers of IO therapy in STK11-mt NSCLC



- Of 16,896 NSCLC tumors samples (Caris), 12.6% had an STK-11-mt with the proportions of TMB-high (≥10 Mut/Mb), PD-L1 ≥ 50% and MSI-high being 55.9%, 11.8%, and 0.72%, respectively.
- *STK11*-mt vs. *STK11*-wt NSCLC did not differ in median TMB (Caris:10 vs. 10 Mut/Mb;p>0.1) and neoantigen load (TCGA: 154.5 vs. 165; p>0.1).
- Median TMB (13 vs.9 Mut/Mb; p<0.001) and neoantigen load (263 vs. 134; p<0.001) were higher in *STK11*-mt/*TP53*-mt vs. *STK11*-mt/*TP53*- wt

Figure 2: Differential immune gene expression



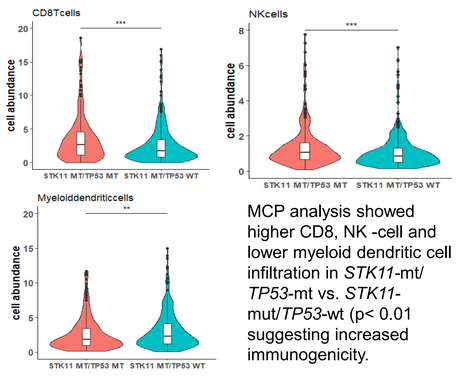
- Immune-gene expression revealed significantly higher expression of genes related to T-cell chemotaxis and immune cell cytotoxicity (*CCL5, CXCL10, GZB, IFNγ, IL-10, IL-6*) in the *STK11*-mt/*TP53*-mt vs. *STK11*-mt/ *TP53*-wt.

Figure 3: Differences in tumor metabolic profile

Glutamine/Glycolysis metabolism genes	STK11 MT/TP53 MT	STK11 MT/TP53 WT	p vlaue
N=	266	310	
MYC	12.6533	8.08786	p<0.001
HIF1A	180.5015	140.055	p<0.001
HK2	1.35231	0.9367945	0.0016
LDHA	392.6095	319.527	0.0014
GOT2	12.104	10.47565	0.0316
PPAT	8.177035	5.638235	p<0.001
PFAS	3.60584	3.014615	0.0132
GFPT1	92.0106	99.81585	0.307
CAD	18.0447	13.0064	p<0.001
GLS2	3.001285	2.78792	0.8428
ASNS	17.18835	12.70585	p<0.001
ODC1	74.87455	114.729	p<0.001
SRM	45.26595	33.5508	p<0.001
ALDOA	389.0505	358.5945	0.0242

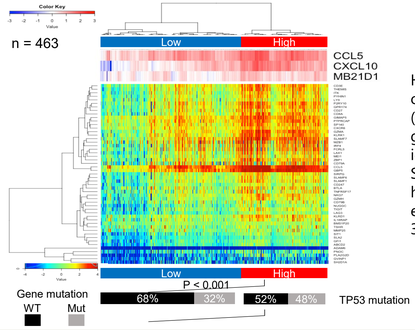
Expression of *MYC* and *HIF-α* were increased in the *STK11*-mt/*TP53*-mt vs. *STK11*-mt/*TP53*-wt (p <0.01) along with differentially higher expression (p<0.01) of genes associated with both glycolysis (*HK2, LDHA, ALDOA*) and glutamine metabolism (*GOT2, PPAT2*)

Figure 4: MCP displaying differences in immune cell infiltration



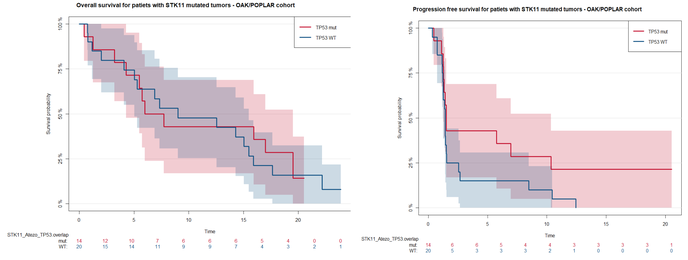
MCP analysis showed higher CD8, NK -cell and lower myeloid dendritic cell infiltration in *STK11*-mt/ *TP53*-mt vs. *STK11*-mut/*TP53*-wt (p< 0.01 suggesting increased immunogenicity.

Figure 5: Hierarchical clustering of STK11-mt adenocarcinoma



Hierarchical clustering of *STK11*-mt adenocarcinomas (n = 463) for STING pathway genes (CCL5, CXCL10, cGAS) identified a STING-high and a STING low cluster. The STING high cluster was significantly enriched in *TP53*-mt (48 vs. 32%; p < 0.01)

Figure 6: PFS/ OS projections of STK11-mt NSCLC using OAK/POPLAR data



- In the OAK/POPLAR cohort, median OS (HR is 1.14, 95% CI 0.53 - 2.48); p > 0.1) and PFS (HR 1.88, 95% CI 0.89-3.97, p = 0.098) were not statistically different between STK11-mt/TP53-mt vs. STK-mt/TP53-wt. However, the 15-months PFS was 21% in the STK11-mt/TP53-mt vs 0% in the STK11-mt/TP53-wt.

Conclusions

- *STK11*-mt NSCLC with *TP53*-mt are associated with an immunologically active TME with metabolic reprogramming compared to the TP53-wt counterpart.
- These intrinsic properties could be exploited to improve outcomes to ICIs in combination with metabolically directed agents.

References

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