167P KRAS G12C lung adenocarcinoma represents a distinct group of patients with different response to immunotherapy

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Background: KRAS G12C mutation has recently become a targetable alteration for patients with lung adenocarcinoma (LUADs). However, it is still unknown if targeted treatment might be preferable to immunotherapy in these tumors. OBJECTIVE: We aimed to assess clinical, pathological characteristics, and outcomes on immunotherapy for tumors harboring KRAS G12C mutation compared to other KRAS mutations, other targetable genomic alterations, and tumors with no targetable alterations.

Methods: Patients with LUADs treated with immunotherapy were prospectively included between January 2017 and July 2020. Clinicopathological and molecular data were collected and interrogated to evaluate associations between patients' characteristics, treatment response and survival outcomes.

Results:

Table: 167P

Characteristics (n=89)	n (%)
Age median (range)	64 (range 40-78)
Sex	
Male	70 (78.6)
Female	19 (21.3)
Tobacco	
Never smoker	6 (6.7)
Former smoker	34 (38.2)
Current smoker	49 (55)
Tumor stage (8th Edition)	
I	2 (2.2)
II	7 (7.9)
III	13 (14.6)
IV	67 (75.2)
Molecular Alterations	
No targetable alterations	53 (59.5)
KRAS mutations	24 (26.9)
EGFR mutations	1 (1.1)
MET (amplification or exon skipping))	5 (5.6)
BRAF (Thr599dup, V600E and G469A)	3 (3.3)
RET rearrangement	1 (1.1)
NTRK rearrangement	1 (1.1)
HER2 mutation	1 (1.1)
Tumor PD-L1 %	
<1%	31 (34.8)
1-49%	18 (20.2)
≥50%	31 (34.8)
NA	9 (10.1)

KRAS mutations were detected in 24 patients, with KRAS G12C representing 58.3% of all KRAS mutations, followed by KRAS G12A, G12V, G12F and G13C (16.6%, 16.6%, 4.2% and 4.2% respectively). LUADs harboring KRAS G12C mutations displayed higher frequency of tumors with PD-L1≥50% (n=7, 50%) and less PD-L1 negative tumors (n=1, 16.25%) compared with patients with KRAS non-G12C mutations (n=2, 18.18% and n=6, 54.54% respectively, p=0.036). Overall response rate to immunotherapy was 31.25% for KRAS G12C mutated patients, compared with 18.2% (p=0.65) in other KRAS mutations. The median follow-up of this population was 16.6 months. Survival analysis showed a trend towards a better OS in KRAS G12C tumors compared with tumors harboring KRAS non-G12C mutations (16.32 vs 9.7months, respectively, p=0.34).

Conclusions: LUADs harboring KRAS G12C mutations displayed higher PD-L1 expression compared to other KRAS mutations and seem to benefit more from immunotherapy. Additional biomarkers might be helpful in selecting the best therapy for patients harboring KRAS G12C mutations.

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168P Characterization of the lung tumor microenvironment upon anti-PD-L1 therapy reveals an ambiguous role for TNF-α

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Background: Immune checkpoint blockade (ICB) of the PD-1 pathway revolutionized the survival forecast for advanced non-small cell lung cancer (NSCLC). Yet, the majority of PD-L1$^+$ NSCLC patients are refractory to anti-PD-L1 therapy. Recent observations indicate a pivotal role for PD-L1$^+$ tumor-infiltrating myeloid cells in therapy failure.

Methods: We evaluated the abundance, phenotype and function of 11 different myeloid subsets within an orthotopic squamous Lewis lung carcinoma (LLC) model over the course of anti-PD-L1 monoclonal antibody (mAb) treatment.

Results: We confirm that LLC represents an anti-PD-L1 therapy refractory model, despite increased levels of PD-1$^+$ lymphocytes and PD-L1$^+$ monocytes, macrophages, and type 2 dendritic cells. Furthermore, we show that anti-PD-L1 therapy significantly increased serological level of TNF-α, while it reduced the fraction of tumor-infiltrating MHC-II^{low} macrophages and monocytes. Notably, the latter were transcriptionally characterized by an increased responsiveness to TNF-α, suggesting a direct link between anti-PD-L1 therapy and TNF-α. However, co-blockade of PD-L1 and TNF-α did not reduce LLC tumor growth as quantified by 3D whole-lung imaging. Mechanistically, we show that the net impact of TNF-α on anti-PD-L1 therapy is immune cell specific: while TNF-α increases IFN-γ secretion by lymphocytes, their killing capacity is significantly reduced when co-cultured with TNF-α-treated monocytes. In line, we were able to show that TNF-α alone or combined with anti-PD-L1 mAb, resulted in elevated expression of the following alternative immune checkpoints: LAG-3 or VISTA, TIM-3 and SIRPα respectively. Currently we are deciphering if combined targeting of one or more of the latter checkpoints can revert the immunosuppressive impact of monocytes on tumor-specific T cells under anti-PD-L1 treatment.

Conclusions: To conclude, this study shows that anti-PD-L1 treatment of lung-tumor bearing mice results in a TNF-α-related increment of immunosuppressive monocytes. While this study further argues against TNF-α and PD-L1 co-blockade to improve therapy effectiveness, it warrants more research into strategies that block monocyte-mediated resistance to anti-PD-L1 therapy.

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