Co-mutational status and PD-L1 expression in *KRAS* mutant non-small cell lung cancer (NSCLC): Role in treatment selection and association with clinical outcomes.

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Background

- Mutations in *KRAS* gene are common oncogenic drivers in advanced non-small cell lung cancer. The different *KRAS* mutations define unique subgroups and certain co-mutations (co-mt) could have prognostic and therapeutic implications.
- It is unclear if PD-L1 expression and co-mt in *KRAS* mt NSCLC impact clinical outcomes. Retrospective studies associate poor prognosis with co-mts in *STK11* and *KEAP1* with *KRAS*.
- We aim to interrogate a large real-world genomic database to understand the co-mutational status and PD-L1 expression of *KRAS* mutant NSCLC and their association with clinical outcomes.
- A comprehensive analysis of the genomic landscape relative to each *KRAS* mt subset may help guide treatment selections.

Methods

- Molecular profiles of 27748 NSCLC tumors were tested with next-generation sequencing (Caris Life Sciences, Phoenix, AZ) and classified by *KRAS* mt.
- PD-L1 IHC (22C3) was reported as TPS.
- Co-occurring genomic alterations, tumor mutational burden (TMB) and PD-L1 IHC (22C3, TPS score) were analyzed by *KRAS* mt type.
- Real-world post-immunotherapy (IO) overall survival (OS) was obtained from insurance claims and calculated from start of an immune check-point inhibitor (with or without chemotherapy) to the last day of follow-up.
- Prognosis was evaluated by rwOS calculated from tissue collection to last contact
- Molecular groups including K-only, KP, KL, KK and KKL were defined based on distinct mutational status of four genes as described below.

	Gene mutations			
Molecular Groups	**KRAS**	**STK11**	**TP53**	**KEAP1**
K-only	MT	WT	WT	WT
KP	MT	WT	MT	WT
KL	MT	MT	WT	WT
KK	MT	WT	WT	MT
KKL	MT	MT	WT	MT

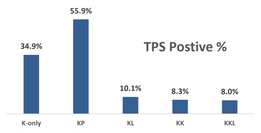
Table 1: Molecular sub-groups

Results

- Across 27734 NSCLC samples analyzed, 7634 (28%) samples harbored a *KRAS* mutation. The most common was G12C (11%), followed by G12V (5.3%), G12D (3.9%) and G13X (2.0%).
- The most frequent *KRAS* co-mutation was *KRAS-TP53* (KP) (34%), similar across all *KRAS* subtypes.
- *KRAS-STK11*(KL) was co-mutated in 7 % of overall *KRAS* cohort, enriched in G13X (33%) and lowest in the G12D (16%) cohort.
- *KRAS-KEAP1* (KK) was co-mutated in 2 % of all *KRAS* cases, highest in G13X (16%) and lowest in the G12D cohort (8%).
- *KRAS* only (K) comprised 27% of overall *KRAS* cohort, highest rates in G12D (36%) and lowest in G13X (16%).
- A small subgroup, 4.5 % was *KRAS-STK11-KEAP1* co-mt (KKL).
- The majority of pts in the KL, KK and KKL cohorts had TPS < 1%; as opposed to K and KP with higher proportion of TPS >1% tumors.

Molecular Groups	Total Patient N	Female	Female %	Male	Patient N treated with IO Therapy
K-only	2055	1234	60%	821	465
KP	2549	1491	58%	1058	622
KL	537	308	57%	229	105
KK	122	58	48%	64	23
KKL	345	182	53%	163	68

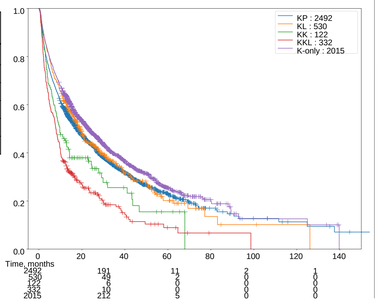
Molecular Groups	TPS=0 (N)	TPS=1-100 (N)
K-only	633	340
KP	424	538
KL	349	39
KK	66	6
KKL	229	20



Table/Fig. 2: Patient Characteristics and prevalence of PD-L1 expression in each *KRAS* Molecular groups

End point: Median rwOS (Tissue collection to Last Contact)		
	mrwOS (m)	95% CI
K-only	23.1	20.9-25.3
KP	17.7	16.2-19.35
KL	19.1	16.6-21.2
KK	9.7	7.4-14.2
KKL	8.0	6.6-9.0

Table/Fig. 3: Patient prognosis in *KRAS* subgroups.
KKL group showed the worst prognosis while K-only groups showed the best prognosis.

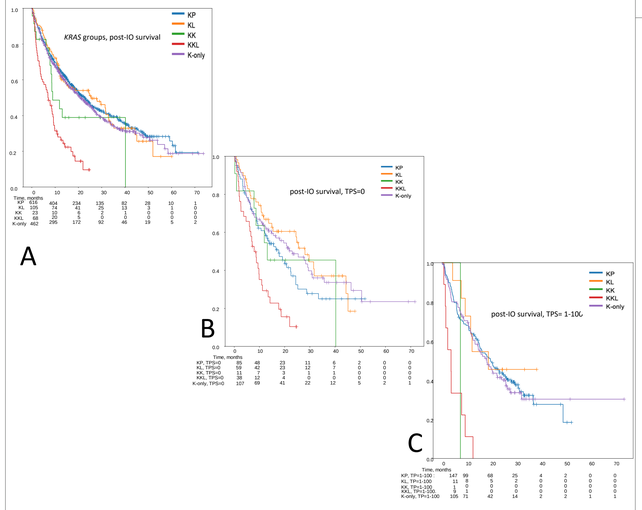


Results

Table/Fig. 4: Outcomes with Immune checkpoint inhibitors in *KRAS* molecular subgroups in all patients (A); PD-L1: TPS negative patients (B) and TPS positive patients (C)

End point: Median Post IO Survival (atezolizumab, pembrolizumab, nivolumab)		
	mOS (m)	95% Confidence Interval (m)
K-only	20.7	17.3-25.4
KP	22.5	19.6-25.4
KL	25.5	12.7-32.9
KK	8.98	7.4-40.2
KKL	6.9	3.9-9.3

End point: Median Post IO Survival (atezolizumab, pembrolizumab, nivolumab)					
	TPS=0			TPS 1-100	
	mTOT (m)	95% Confidence Interval (m)		mTOT (m)	95% Confidence Interval (m)
K-only	23	14.7-30.7	K-only	18.1	13.3-24.2
KP	17.6	10.6-22.5	KP	19.6	15.0-25.4
KL	28	14.9-44.3	KL	18.7	7.7-inf
KK	13.1	0.89-40.2	KK	7.4	7.4-7.4
KKL	7.9	4.7-10.9	KKL	3.6	0.7-9.3

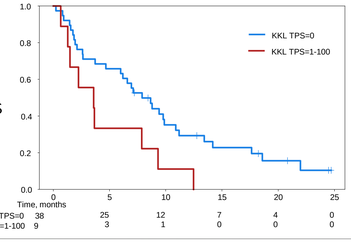


- In 17237 *KRAS* mt NSCLC pts treated with IO, post IO survival was similar in TPS positive vs. negative tumors (HR=1.096, p=0.286)
- KKL had significantly worse post-IO OS compared to K, KP and KL groups; regardless of PD-L1 TPS score (≥ 1% or <1%), KKL group had worse post-IO OS compared to K, Kl and KP groups.

Results

	TPS=0 vs. TPS 1-100		
	HR	HR 95% Confidence Interval	p
K-only	0.883	0.62-1.256	0.49
KP	1.159	0.821-1.634	0.402
KL	0.934	0.387-2.251	0.878
KK	0.201	0.018-2.219	0.146
KKL	**0.433**	**0.201-0.931**	**0.028**

Table/Fig. 5: Effects of TPS in *KRAS* molecular subgroups
Hazard ratios of TPS=0 vs. TPS 1-100 groups for each molecular group.
Kaplan- Meier curves with comparison between PDL1 groups in KKL group.



Conclusions

- We report a large real-world dataset evaluating outcomes with check-point inhibitors in NSCLCs with *KRAS* and specific co-mts. Across the subgroups, KKL (KRAS mt/STK-11 mt/KEAP-1 mt) demonstrated universally poor outcomes in all *KRAS* subtypes; irrespective of PD-L1 expression.
- Among all *KRAS* co-mutant groups, K-only NSCLC tumors showed the best prognosis, followed by KL and KP groups while KKL showed the worst outcome.
- In the PD-L1 <1% group, KP group showed worse outcome than K-only however comparable outcomes to K-only in PD-L1 positive (TPS ≥1%).
- Interestingly, positive TPS score was not associated with significantly improved outcome in the molecular groups investigated and was in fact, associated with worse outcome in KKL. Pts with KKL co-mts have adverse post-IO outcomes in TPS ≥1% but favorable in TPS <1%.
- These observations emphasize that co-mutation patterns have a clear association with clinical outcomes in *KRAS*-mt NSCLC and must be used in predictive models for individualized therapy while the role of PD-L1 score may be limited in *KRAS*-mt NSCLC.

References

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