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Impact of *KRAS* co-mutations and *MTAP* loss on outcomes in advanced NSCLC treated with immune checkpoint inhibitors

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IASLC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

BACKGROUND

Background

- STK11* and *KEAP1* co-mutations are established drivers of ICI resistance in *KRAS*-mutant NSCLC, yet their interaction with PD-L1 expression remains incompletely characterized in real-world settings.
- MTAP* loss (~10–21% of NSCLC) leads to MTA accumulation, a targetable vulnerability via PRMT5/*MTA2A* inhibition. Its role as a prognostic or predictive biomarker during ICI therapy is poorly defined.

METHODS

Data Source

- AACR Project GENIE Biopharma Collaborative NSCLC v2.0 – publicly available, de-identified, no IRB required.

Eligibility Criteria

- Stage IV NSCLC | ≥1 ICI-containing regimen (any line)
- NGS data available (tumor tissue, MSK-IMPACT, FoundationOne, or equivalent panel)
- Adequate clinical follow-up data in GENIE BPC v2.0

Genomic Definitions

- Mutation: SNV/indel detected by NGS (*KRAS*, *STK11*, *KEAP1*, *TP53*). Oncogenic *KRAS* variants (G12C/D/V/A/R/S) required.
- MTAP* loss: homozygous deletion of 9p21 locus on NGS panel (not IHC). Co-deletion with *CDKN2A/B* assessed separately.
- Co-mutation: presence of ≥2 predefined alterations in the same tumor sample.

Objectives

- Primary: assess *KRAS*+*STK11*, *KRAS*+*KEAP1*, *STK11*+*KEAP1*, *KRAS*+*STK11*+*KEAP1* co-mutations and association with OS and PFS in ICI-treated stage IV NSCLC.
- Secondary (exploratory): *MTAP* loss as prognostic biomarker; PD-L1 TPS ≥50% subgroup analysis.

Genomic Variables

- KRAS* (any oncogenic variant), *STK11*, *KEAP1*, *TP53* (any pathogenic variant)
- MTAP*: homozygous deletion of 9p21.3 by NGS copy-number analysis; evaluable in n=66
- CDKN2A/B* loss assessed for *MTAP* co-deletion analysis

Clinical Variables

- Age, sex, smoking (current/former vs. never), histology, metastatic sites (brain, bone, liver), PD-L1 TPS (0, 1–49%, ≥50%), ICI class (monotherapy/chemo-combo/dual ICI), line of therapy

Statistical Analysis

- Endpoints: OS and PFS from ICI initiation (KM method)
- Univariable Cox proportional hazards models with predefined co-mutation profiles
- Prespecified subgroups: 1st-line, ICI monotherapy, PD-L1 TPS ≥50%
- Multivariable Cox models adjusting for age, sex, smoking, histology, treatment class, line of therapy; PD-L1 missing treated as separate category
- Baseline comparisons: Wilcoxon rank-sum, chi-squared, or Fisher's exact tests
- Software: R v4.5.3 (survival, survminer packages)

Patient Selection Flowchart

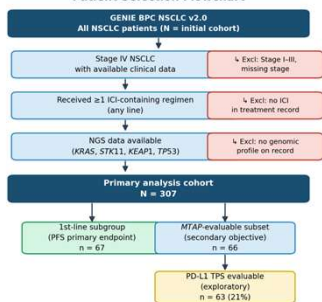


Figure 1. Patient selection flowchart. *MTAP*-evaluable subset n=66; PD-L1 evaluable subset n=63 (21%).

RESULTS

Study Population (N = 307)

The cohort comprised 307 patients with a median age of 63 years (IQR 55–70); 54% were female, and 80% were current/former smokers. Histology was predominantly adenocarcinoma (69%), followed by squamous cell (9%) and other/unknown (21%).

Most patients received ICI monotherapy (89%), followed by ICI + chemotherapy (6%) and dual ICI (3%). Treatment line distribution was 1st-line 22%, 2nd-line 44%, and 3rd-line+ 35%. PD-L1 TPS was evaluable in n=63 (21%), of whom 63% had TPS ≥50%; PD-L1 status was missing in 79% of the cohort. *MTAP* data were available for n=66 patients, among whom *MTAP* loss was observed in 35%. Metastatic sites included bone (69%), brain (53%), and liver (42%).

Co-mutation Frequencies

- KRAS* 36% | *STK11* 21% | *KEAP1* 21% | *TP53* 48% | *KRAS*+*STK11* 10% | *KRAS*+*KEAP1* 9%
- Smoking history was observed in 100% of *KRAS*+*STK11* and *KRAS*+*KEAP1* groups (vs. 77% WT; p<0.005).

Overall Survival (OS) – Key Findings

- KRAS*+*STK11*: HR 1.71 (95% CI 1.16–2.52), p=0.007 – adj HR 2.23 (95% CI 1.46–3.40)
- KRAS*+*KEAP1*: HR 1.72 (95% CI 1.15–2.57), p=0.008
- STK11*+*KEAP1*: HR 1.65 (95% CI 1.12–2.42), p=0.011 – adj HR 1.90 (95% CI 1.26–2.86)
- KRAS*+*STK11*+*KEAP1*: HR 1.73 (95% CI 1.10–2.71), p=0.017
- PD-L1 ≥50% + *KRAS*+*STK11*: HR 5.99 (95% CI 1.53–23.5), p=0.010 – adj HR 4.50 (95% CI 1.45–13.91)
- KRAS*+*TP53* (1st-line): HR 2.12 (95% CI 1.02–4.42), p=0.044

Progression-free survival (PFS) – Key Findings

- Overall cohort: no co-mutation profile significantly associated with PFS
- 1st-line: *STK11* HR 6.76 (95% CI 2.31–19.8), p<0.001; *KRAS*+*STK11* HR 4.58 (95% CI 1.86–11.3), p<0.001
- Effect confined to 1st-line setting; not replicated in later lines

MTAP Loss (n=66)

- Worse PFS overall: HR 2.24 (95% CI 1.29–3.89), p=0.004; adj HR 2.08 (95% CI 1.14–3.78)
- 1st-line: HR 2.80 (95% CI 1.10–7.11), p=0.031
- MTAP*+*CDKN2A/B* loss: HR 1.95 (95% CI 1.23–3.12), p=0.005 for PFS
- OS: no significant association (HR 1.17, p=0.6)
- KRAS*+*MTAP*: not associated with OS or PFS

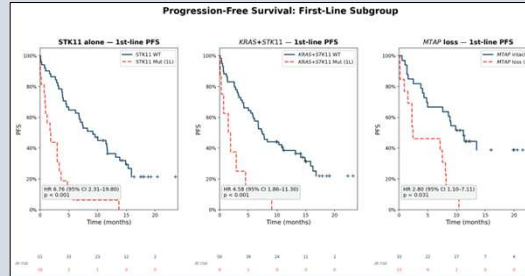


Figure 4. Kaplan-Meier curves for progression-free survival. First-line subgroup: *STK11* alone (HR 6.76), *KRAS*+*STK11* (HR 4.58), and *MTAP* loss (HR 2.08).

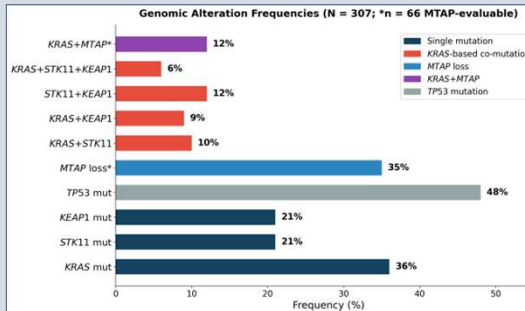


Figure 2. Genomic alteration frequencies (N=307; n=66 MTAP-evaluable). Co-mutation frequencies relative to total cohort.

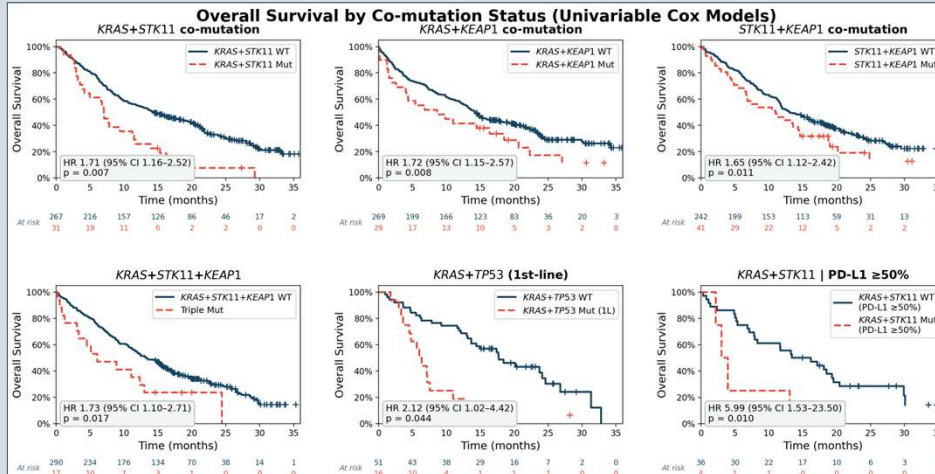


Figure 3. Kaplan-Meier curves for overall survival by co-mutation status. Representative simulated curves based on reported HRs and medians; censoring marks and numbers at risk are shown. WT = wild-type.

Table 1. Baseline characteristics by *KRAS*+*STK11* status. *Significant (p<0.05). †PD-L1 evaluable only (n=63).

Characteristic	Overall (n=307)	<i>KRAS</i> + <i>STK11</i> WT (n=217)	<i>KRAS</i> + <i>STK11</i> Mut (n=90)	p-value
Age, median (IQR)	63 (55–70)	62 (54–70)	67 (55–71)	0.2
Sex – Female	166 (54%)	143 (66%)	23 (26%)	0.6
Current/former smoker	245 (80%)	205 (94%)	40 (44%)	0.003*
Never smoker	62 (20%)	62 (28%)	0 (0%)	—
Adenocarcinoma	213 (69%)	181 (83%)	32 (36%)	0.4
Squamous cell	29 (9%)	28 (13%)	1 (1%)	—
ICI monotherapy	274 (89%)	238 (89%)	36 (40%)	0.8
ICI + chemotherapy	19 (6%)	18 (8%)	1 (1%)	—
Dual ICI	9 (3%)	8 (4%)	1 (1%)	—
1st-line therapy	67 (22%)	57 (26%)	10 (11%)	0.084
2nd-line therapy	134 (43%)	111 (51%)	23 (26%)	—
3rd-line	106 (35%)	99 (46%)	7 (8%)	—
Brain metastases	142 (46%)	140 (65%)	2 (2%)	0.6
Bone metastases	213 (69%)	182 (84%)	31 (34%)	0.5
Liver metastases	130 (42%)	113 (52%)	17 (19%)	0.8
PD-L1 ≥50%	40(63%)	32(50%)	8(9%)	0.4
PD-L1 <50%	22(63%)	13(55%)	9(10%)	—

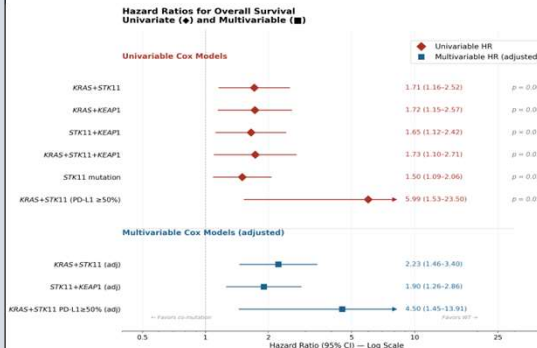


Figure 5. Forest plot: univariable (●) and multivariable (■) HRs for OS. Log scale. Adj = adjusted Cox model.

CONCLUSION

Key Findings

- STK11*- and *KEAP1*-containing *KRAS* co-mutations were independently associated with worse OS, which persisted after multivariable adjustment – confirming these co-mutations as clinically relevant markers of ICI resistance.
- Among PD-L1 ≥50% patients, *KRAS*+*STK11* co-mutation conferred markedly worse OS (HR 5.99), indicating that high PD-L1 expression does not overcome the adverse prognostic effect (exploratory; no formal interaction test performed; n=40).
- MTAP* loss was associated with worse PFS, particularly in 1st-line therapy, positioning it as a secondary prognostic biomarker warranting prospective validation.

Limitations

- Retrospective; univariate primary analyses; PD-L1 missing in 79%; no formal interaction testing; no PS or volume-of-disease data in GENIE BPC.

Clinical Implications

- Consider co-mutation profiling (*KRAS*+*STK11*+*KEAP1*) alongside PD-L1 TPS when selecting patients for ICI monotherapy in 1st-line advanced NSCLC.
- MTAP* status is a complementary genomic variable with the potential to stratify ICI outcomes – and a targetable vulnerability for novel PRMT5 inhibitors.

Future Directions

- Prospective validation with composite genomic biomarker panels
- Formal interaction testing (*KRAS* co-mutations × PD-L1 TPS) in adequately powered cohorts
- Integration of *MTAP* IHC as surrogate for NGS-based deletion in clinical practice

References & Acknowledgements

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Acknowledgements: The authors acknowledge the AACR and the GENIE BPC Consortium for data sharing. All interpretations are the responsibility of the study authors.