SWISS ONCOLOGY & HEMATOLOGY CONGRESS

Methylthioadenosine Phosphorylase (MTAP)-loss and *KRAS* Mutations in patients with advanced non-small cell lung cancer (NSCLC)

Category: Clinical Solid Tumor Oncology

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Introduction

Homozygous MTAP loss, observed in 13–15% of NSCLC, is being investigated for its role in conferring sensitivity to PRMT5 inhibitors currently in early-phase trials, though it is linked to poorer outcomes. However, its prognostic relevance and associations with established biomarkers remain unclear. This exploratory study evaluates the prognostic role of MTAP loss and biomarker associations in advanced NSCLC.

Methods

We included all patients with advanced NSCLC treated at University Hospital Basel (2022–2025) from a prospective clinical registry. Endpoints included the association between MTAP expression status (measured by immunohistochemistry) and established relevant biomarkers (next-generation sequencing (NGS)-assessed: KRAS, BRAF, ERBB2, MET, EGFR; IHC-assessed PD-L1) and overall survival (OS) stratified by MTAP status (intact expression vs. loss of expression). The study was approved by the research ethics committee.

Survival analyses used the Kaplan-Meier method with log-rank tests; biomarker associations were analysed using Fisher's exact test with Benjamini-Hochberg correction. We did not apply imputation techniques for missing values.

Figure 1

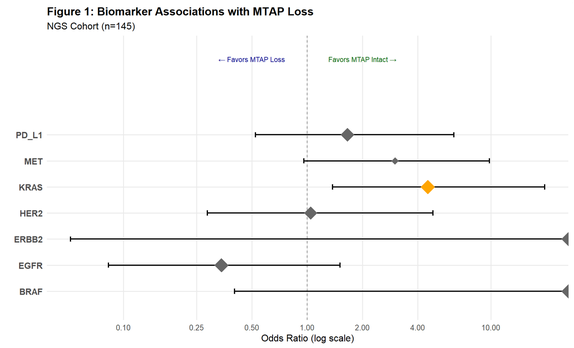

Figure 2

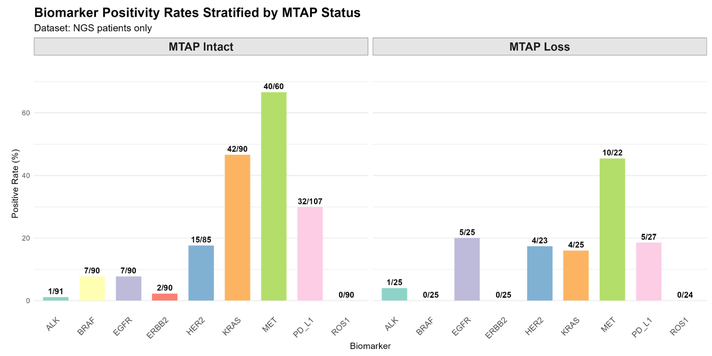

Figure 3

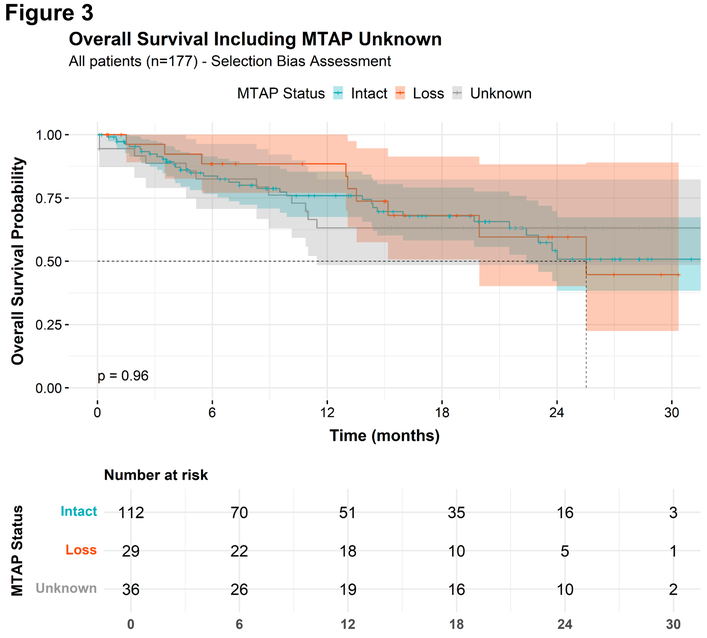

Figure 4

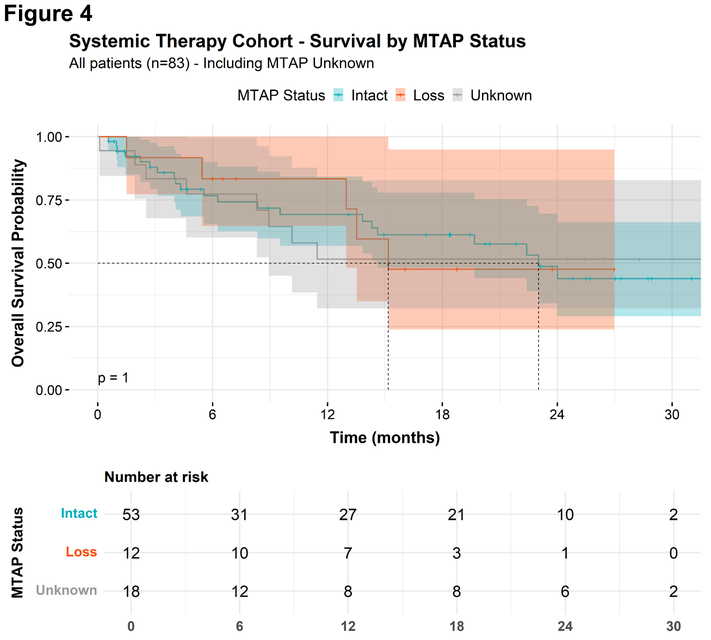

Table 1: Baseline Characteristics - All Patients

	Intact (N=112)	Loss (N=29)	Unclear (N=36)	Total (N=177)
Age – years				
– Median (Q1, Q3)	71 (61, 76)	66 (62, 73)	71 (64, 78)	70 (61, 77)
– Range	40 - 91	44 - 87	44 - 87	40 - 91
Sex – n (%)				
– Female	29 (25.9)	7 (24.1)	20 (55.6)	56 (31.6)
– Male	83 (74.1)	22 (75.9)	16 (44.4)	121 (68.4)
Histology – n (%)				
– Lung Adenocarcinoma	73 (65.2)	15 (51.7)	27 (75.0)	115 (65.0)
– Lung Squamous Cell Carcinoma	21 (18.8)	8 (27.6)	7 (19.4)	36 (20.3)
– Other*	18 (16.0)	6 (20.7)	2 (5.6)	26 (14.7)
ECOG Performance Status – n (%)				
– ECOG 0 - 1	79 (70.5)	25 (86.2)	23 (63.9)	127 (71.8)
– ECOG 2 - 3	28 (25.0)	3 (10.3)	11 (30.6)	42 (23.7)
– Unknown	5 (4.5)	1 (3.4)	2 (5.6)	8 (4.5)
Treatment setting – n (%)				
– Systemic therapy	53 (47.3)	12 (41.4)	18 (50.0)	83 (46.9)
– Chemoradiotherapy	17 (15.2)	7 (24.1)	5 (13.9)	29 (16.4)
– Perioperative treatment concepts	29 (25.9)	7 (24.1)	10 (27.8)	46 (26.0)
– Other	13 (11.6)	3 (10.3)	3 (8.3)	19 (10.7)

*Includes adenosquamous, poorly differentiated, and NOS NSCLC.

Results

Patient Cohorts and Biomarker Associations:

- 178 advanced NSCLC patients were included: 112 (63.3%) with intact MTAP, 29 (16.4%) with MTAP loss, and 36 (20.2%) with unknown MTAP status.
- NGS data were available for 145 patients, with MTAP status unknown in 30 (20.7%).
- **MTAP intact tumors showed significantly more KRAS mutations (adjusted $p = 0.04$**, OR = 4.54 [95% CI: 1.38–19.65]). Among 56 KRAS-mutant tumors, KRAS G12C was the predominant variant ($n = 20$).

Overall Survival (OS):

- No significant OS difference was observed in the overall cohort between patients with intact MTAP and MTAP loss ($n = 112$ vs $n = 29$, log-rank $p = 0.96$).
- Similarly, in the systemic therapy subgroup ($n = 53$ intact vs. $n = 12$ loss), OS did not differ (log-rank $p = 1$).
- The MTAP-unknown group showed no significant OS differences compared to intact or loss groups in both the overall and systemic therapy cohorts (pairwise log-rank $p = 0.98$).

Conclusion

- MTAP loss tumors had significantly less KRAS mutations compared to the MTAP intact ones, which indicates a potential biological link between the two biomarkers.
- MTAP status was not associated with worse OS prognosis. However, the power for the prognostic analyses was limited.
- Whether the link between MTAP loss and KRAS mutation has relevant meaning remains to be investigated in larger datasets.

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