



Prognostic relevance of *MTAP* loss in advanced NSCLC treated with targeted therapies: a clinicogenomic analysis

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BACKGROUND

Background

- Methylthioadenosine phosphorylase (*MTAP*)** is a key enzyme in the methionine salvage pathway and is frequently lost across multiple solid tumors. In NSCLC, *MTAP* deletion often co-occurs with 9p21 deletions, particularly involving *CDKN2A/B*, and has gained attention because of its biological and therapeutic relevance.
- MTAP* loss has been associated with **tumor progression, altered cellular metabolism, and sensitivity to therapies targeting the PRMT5-MAT2A axis**. However, its independent prognostic significance remains **uncertain**.
- While *MTAP* has been studied in immunotherapy-treated NSCLC, its prognostic role in patients receiving molecularly targeted therapies remains poorly characterized. Clarifying its clinical relevance may improve biomarker development and patient stratification.

METHODS

Data Source

- Retrospective clinicogenomic cohort study using the publicly available AACR Project GENIE Biopharma Collaborative (BPC) NSCLC version 2.0 database.
- All data were de-identified and collected in accordance with institutional and consortium protocols.

Eligibility Criteria

- Stage IV NSCLC
- Treatment with at least one targeted therapy
- Available next-generation sequencing (NGS)
- Available *MTAP* copy-number status
- Clinical follow-up available for survival analyses

Genomic Variables

- MTAP* loss: homozygous deletion identified by NGS copy-number analysis.
- MTAP* intact: no *MTAP* deletion detected.
- Co-alteration: presence of additional oncogenic genomic alterations occurring within the same tumor sample.

Objectives

- Primary:** Evaluate the association between *MTAP* loss and **overall survival (OS)** and **progression-free survival (PFS)** in patients with advanced NSCLC treated with targeted therapies.
- Secondary (exploratory):** Characterize the genomic landscape of *MTAP*-deficient tumors; Describe patterns of co-occurring genomic alterations; Explore survival outcomes according to major genomic co-alterations.

Clinical Variables

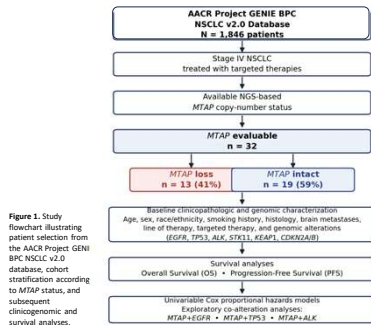
- Age; Sex; Race/ethnicity; Smoking history; Histology; Brain metastases; Line of therapy; Targeted therapy received; Genomic alterations involving *EGFR*, *TP53*, *ALK*, *STK11* and *KEAP1*

Primary endpoints

- Overall Survival (OS)
- Progression-Free Survival (PFS)

Statistical Analysis

- Baseline characteristics were summarized using medians (IQR) or proportions, as appropriate.
- Group comparisons were performed using Wilcoxon rank-sum tests, chi-square tests, or Fisher's exact tests.
- Associations between *MTAP* status and survival outcomes were evaluated using univariable Cox proportional hazards models.



RESULTS

Table 1. Baseline clinicopathologic and treatment characteristics of the study population stratified by *MTAP* status.

Characteristic	Overall N = 32 ¹	0 N = 19 ¹	1 N = 13 ¹	p-value ²
Age	60 (53.68)	57 (52.67)	61 (58.68)	0.5
Sex				0.7
Female	24 (75%)	15 (79%)	9 (69%)	
Male	8 (25%)	4 (21%)	4 (31%)	
Race				0.5
AAAP (Asian, Asian American, and Pacific Islander)	5 (16%)	4 (21%)	1 (7.7%)	
Non-Hispanic Black	1 (3.1%)	1 (5.3%)	0 (0%)	
Non-Hispanic White	26 (81%)	14 (74%)	12 (92%)	
Smoking history				0.3
Current/Former	16 (50%)	11 (58%)	5 (38%)	
Never	16 (50%)	8 (42%)	8 (62%)	
Regimen				>0.9
Bevacizumab, Carboplatin, Paclitaxel	1 (3.1%)	0 (0%)	1 (7.7%)	
Bevacizumab, Cisplatin, Pemetrexed	1 (3.1%)	1 (5.3%)	0 (0%)	
Brigatinib	2 (6.3%)	1 (5.3%)	1 (7.7%)	
Erlotinib	23 (72%)	14 (74%)	9 (69%)	
Gefitinib, Osimertinib	1 (3.1%)	1 (5.3%)	0 (0%)	
Osimertinib	4 (13%)	2 (11%)	2 (15%)	
Treatment lines				0.3
1	21 (66%)	14 (74%)	7 (54%)	
2	6 (19%)	2 (11%)	4 (31%)	
3+	5 (16%)	3 (16%)	2 (15%)	
Histology				0.5
Adenocarcinoma	24 (75%)	15 (79%)	9 (69%)	
Other	4 (13%)	3 (16%)	1 (7.7%)	
Squamous cell	2 (6.3%)	0 (0%)	2 (15%)	
Unknown	2 (6.3%)	1 (5.3%)	1 (7.7%)	
Brain metastasis	21 (66%)	14 (74%)	7 (54%)	0.3
Bone metastasis	26 (81%)	17 (89%)	9 (69%)	0.2
Liver metastasis	13 (41%)	8 (42%)	5 (38%)	0.8

¹Median (Q1,Q3); n (%)

²Wilcoxon rank-sum test; Fisher's exact test; Pearson's Chi-squared test

Table 3. Univariable Cox regression analysis for progression-free survival according to *MTAP* status and genomic co-alterations.

Characteristic	N	HR	95% CI	p-value
<i>MTAP</i> Deletion	32	0.71	0.30, 1.68	0.4
<i>MTAP</i> + <i>STK11</i>	32	0.27	0.03, 2.05	0.2
<i>MTAP</i> + <i>KEAP1</i>	32	0.26	0.03, 2.03	0.2
<i>MTAP</i> + <i>TP53</i>	32	0.64	0.25, 1.64	0.4
<i>MTAP</i> + <i>EGFR</i>	32	0.59	0.24, 1.44	0.2
<i>MTAP</i> + <i>ROS1</i>	32	0.47	0.11, 2.07	0.3
<i>MTAP</i> + <i>ALK</i>	32	1.72	0.22, 13.3	0.6
<i>MTAP</i> + <i>BRAF</i>	32			
<i>MTAP</i> + <i>MET</i>	32	0.00	0.00, Inf	>0.9
<i>MTAP</i> + <i>ERBB2</i>	32	1.95	0.25, 15.2	0.5

Table 2. Univariable Cox regression analysis for overall survival according to *MTAP* status and genomic co-alterations.

Characteristic	N	HR	95% CI	p-value
<i>MTAP</i> Deletion	32	1.57	0.69, 3.60	0.3
<i>MTAP</i> + <i>STK11</i>	32	0.51	0.07, 3.91	0.5
<i>MTAP</i> + <i>KEAP1</i>	32	0.37	0.08, 1.65	0.2
<i>MTAP</i> + <i>TP53</i>	32	1.17	0.50, 2.72	0.7
<i>MTAP</i> + <i>EGFR</i>	32	2.00	0.82, 4.84	0.13
<i>MTAP</i> + <i>ROS1</i>	32	0.78	0.25, 2.39	0.7
<i>MTAP</i> + <i>ALK</i>	32	1.55	0.20, 11.9	0.7
<i>MTAP</i> + <i>BRAF</i>	32			
<i>MTAP</i> + <i>MET</i>	32	0.32	0.04, 2.59	0.3
<i>MTAP</i> + <i>ERBB2</i>	32	4.20	0.51, 35.0	0.2

Table 4. Frequency of genomic alterations in the *MTAP*-loss subgroup (n = 13). *MTAP* loss universally co-occurred with *CDKN2A* and *CDKN2B* deletions, while *TP53* and *EGFR* represented the most frequent additional genomic alterations.

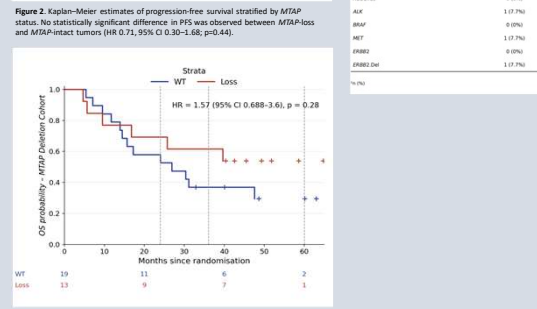
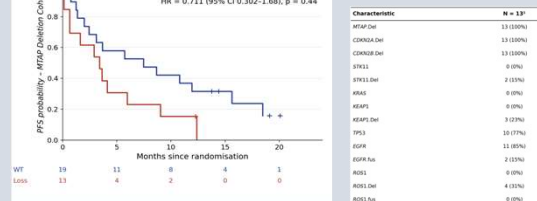
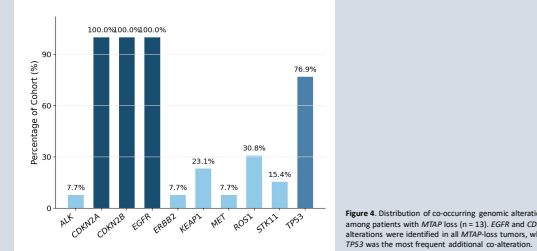


Figure 4. Distribution of co-occurring genomic alterations among patients with *MTAP* loss (n = 13). *EGFR* and *CDKN2A/B* alterations were identified in all *MTAP*-loss tumors, whereas *TP53* was the most frequent additional co-alteration.



Study Population (N = 32) and Baseline Characteristics

We screened 1,846 patients. Only 32 (1.7%) had evaluable *MTAP* copy-number data and were included in the final analysis. Median age was 60 years (IQR 53-68); 75% were female, and 81% were Non-Hispanic White. Adenocarcinoma histology was present in 75%, and brain metastases in 66%. First-line targeted therapy was used in 66% of patients, and erlotinib was the most frequently prescribed targeted therapy (72%). Baseline clinicopathologic characteristics were generally similar between *MTAP*-loss and *MTAP*-intact groups.

Genomic Landscape

Among evaluable patients:

- MTAP* loss: 41%
 - Universal co-deletion with *CDKN2A/B*
 - EGFR* alterations: 100%
 - TP53* co-alterations: 77%
 - ALK* alterations: uncommon
 - KEAP1* alterations: uncommon
 - STK11* alterations: uncommon
- These findings show that *MTAP* loss occurred predominantly in *EGFR*-driven tumors and rarely appeared alongside other major genomic drivers.

Overall Survival

No statistically significant association was observed between *MTAP* loss and OS.

Median OS

- MTAP* loss: 29.11 months
- MTAP* intact: 44.74 months

Hazard ratio:

- HR 1.57 (95% CI 0.69-3.60; p = 0.30)

PFS

No statistically significant association was observed between *MTAP* loss and PFS.

Median PFS

- MTAP* loss: 7.53 months
- MTAP* intact: 7.37 months

Hazard ratio:

- HR 0.71 (95% CI 0.30-1.68; p = 0.40)

CONCLUSION

Key Findings

- MTAP* loss was **not independently associated** with inferior overall survival.
- MTAP* loss was **not associated** with progression-free survival among patients treated with targeted therapies.
- MTAP* loss consistently co-occurred with *EGFR* alterations and *CDKN2A/B* deletion, suggesting that its biological relevance may largely reflect the broader genomic context rather than acting as an isolated prognostic biomarker.
- Exploratory analyses of major genomic co-alterations likewise failed to identify significant survival differences.

Limitations

- Retrospective observational design; Small number of *MTAP*-evaluable patients (n=32); Only 1.7% of the screened cohort had available *MTAP* copy-number information, introducing potential selection bias; Univariable survival analyses; Limited statistical power to detect modest survival differences; Predominance of *EGFR*-mutant tumors may limit generalizability to the broader NSCLC population.

Clinical Implications

- Current findings do not support using *MTAP* loss alone as an independent prognostic biomarker in advanced NSCLC treated with targeted therapies.
- Instead, interpret *MTAP* status within the broader genomic landscape, particularly given its close relationship with *EGFR*-driven disease and 9p21 genomic alterations.
- These results also reinforce the need to distinguish prognostic biomarkers from potentially targetable metabolic vulnerabilities, as *MTAP*-deficient tumors remain promising candidates for therapies directed against the PRMT5/MAT2A pathway.

Future Directions

- Validation in larger multicenter cohorts with broader *MTAP* testing.
- Multivariable analyses incorporating additional clinical covariates.
- Evaluation of *MTAP* within composite genomic biomarker models.
- Investigation of *MTAP* as a predictive biomarker for emerging PRMT5- and MAT2A-targeted therapies.
- Integration of genomic and metabolic biomarkers to improve personalized treatment strategies in oncogene-driven NSCLC.

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.