Clinical, genomic, and tumor microenvironment characterization of *MTAP*-deletion in advanced/metastatic non-small cell lung cancer

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Introduction

- Homozygous deletion of methylthioadenosine phosphorylase (*MTAP*) is observed in approximately 10%-15% of cancers and has been associated with poorer clinical outcomes[1,2]
  - Tumors harboring *MTAP* deletion (*MTAP*-del) are associated with inferior prognosis compared with *MTAP*-wild-type (*MTAP*-WT) tumors, highlighting a substantial unmet clinical need[2]
  - Therapeutic approaches that exploit synthetic lethal vulnerabilities in *MTAP*-del cancers, including protein arginine methyltransferase 5 (PRMT5) inhibition, are currently under clinical investigation[3]
- Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases and remains a leading cause of cancer-related mortality worldwide[4]
  - Homozygous *MTAP*-del occurs in approximately 13% of NSCLC and frequently co-occurs with *CDKN2A*-del, due to its proximity to tumor suppressor gene *CDKN2A* on the 9p21 locus[5-7]
- Here, we evaluated *MTAP*-del prevalence in advanced NSCLC and its associations with genomic features, the tumor microenvironment (TME), and clinical outcomes across multiple real-world and clinical trial datasets

Methods

Study design and data sources

- This retrospective analysis extracted information from de-identified patient records from real-world databases (TEMPUS and Flatiron) and CheckMate trials evaluating immunotherapy-based regimens in advanced NSCLC, including CheckMate 227 (parts 1 and 2), 9LA, 568, 592, and 817 (cohorts A and A1)
  - Among 2223 treatment-naive patients in the CheckMate studies, 1004 were from CheckMate 227 part 1, 353 from 227 part 2, 455 from 9LA, 98 from 568, 100 from 592, and 213 from 817
- Patients were eligible if they:
  - Were aged ≥ 18 years
  - Had advanced NSCLC
    - TEMPUS and Flatiron databases included patients with stage III/IV disease; Flatiron also captured patients with earlier-stage NSCLC that later recurred or progressed
    - The CheckMate studies included patients with recurrent/metastatic disease; patients with *EGFR* mutations or known *ALK* translocations sensitive to targeted therapy were excluded
- Patients were stratified into treatment-naive and treatment-exposed groups
  - Treatment-naive patients had biopsy samples obtained before first-line (1L) therapy
  - Treatment-exposed patients had biopsy samples collected after 1L initiation with a 14-day buffer to ensure treatment exposure
  - The TEMPUS and Flatiron databases included treatment-naive and treatment-exposed patients, and the CheckMate studies included treatment-naive patients

Genomic and transcriptomic analyses

- Genomic profiling was performed using FoundationOne CDx for patients from the Flatiron database and CheckMate studies, and TEMPUS xT for patients from the TEMPUS database
- Tumor gene expression from patients in CheckMate 227 Part 1 was assessed by bulk RNA sequencing
- CD8 T-cell infiltration was assessed using CD8 immunohistochemistry for patients from the CheckMate 227 and 9LA studies

Outputs

- Prevalence of homozygous *MTAP*-del, demographics and baseline characteristics of patients by *MTAP* status, and association of *MTAP*-del with other genomic alterations
- Relationship between *MTAP*-del, clinicopathological factors, and other biomarkers
- Overall survival (OS) for patients in the TEMPUS treatment-naive group who received a regimen containing pembrolizumab (pembro) as 1L treatment (pembro monotherapy, pembro + chemotherapy [chemo], or pembro + nonchemo)
- OS for patients in the TEMPUS treatment-naive group who received pembro + chemo as 1L treatment by programmed death-ligand 1 (PD-L1) expression (< 1%, 1%-49%, ≥ 50%)
- TME features were compared by *MTAP* and *CDKN2A* status in CheckMate studies

Results

MTAP-del prevalence

- *MTAP*-del was observed in 13.5% of 1L treatment-naive and 17.1% of 1L treatment-exposed patients from TEMPUS, 12.6% of 1L treatment-naive and 14.8% of 1L treatment-exposed patients from Flatiron, and 10.8% of 1L treatment-naive patients from the CheckMate studies
- Demographics and baseline characteristics by *MTAP* status are presented in **Table 1**
  - In the CheckMate studies, the rate of *MTAP*-del by region was 10.4% in Europe, 12.4% in Asia, 12.9% in North America, and 9.0% in the rest of the world
  - All TEMPUS and Flatiron data were derived exclusively from US patients
- The prevalence of potentially actionable genomic alterations (AGAs; *EGFR*, *KRAS*, *MET*, and *BRAF*) was similar by *MTAP*-del status in the 1L treatment-naive TEMPUS cohort, although some subgroups were limited by small sample sizes (**Figure 1**)
  - In the 1L treatment-exposed TEMPUS cohort, *EGFR* mutations were numerically more frequent in *MTAP*-del than *MTAP*-WT tumors (26% vs 20%)
- In the treatment-naive TEMPUS cohort, the prevalence of additional relevant NSCLC genomic alterations (*STK11*, *KEAP1*, and *SMARCA4*) was numerically higher in *MTAP*-del than *MTAP*-WT tumors; the sample sizes in the 1L treatment-exposed group limit evaluation of the relationship between *MTAP* status and co-alterations (**Figure 2**)
  - Nearly all tumors with *MTAP*-del (97.8%) also had *CDKN2A*-del

OS

- In the treatment-naive TEMPUS cohort, patients who received 1L pembro-containing regimens and had *MTAP*-del tumors had numerically shorter OS than those with *MTAP*-WT tumors (median [95% CI], 11.2 months [8.0-14.8] vs 16.3 months [15.0-19.2]; HR, 1.22 [0.97-1.54]; **Figure 3**)
- Similar trends were observed across PD-L1 expression strata (< 1%, 1%-49%, and ≥ 50%) for patients who received 1L pembro + chemo (**Figure 4**)

TME features associated with *MTAP*-del

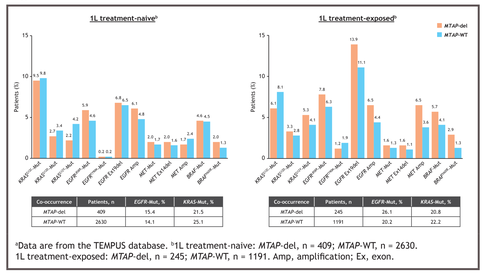
- In patients with NSCLC in CheckMate 227, *MTAP*-del was associated with a lower abundance of immune cell populations within the TME (**Figures 5** and **6**)
  - The immunologically cold TME appeared to be predominantly associated with *MTAP*-del, rather than *CDKN2A* deletion alone
- *MTAP*-del tumors exhibited reduced CD8 T-cell infiltration in the total tumor area and stromal and tumor epithelial compartments in CheckMate 227 and CheckMate 9LA (**Figure 7**)
  - The observed reduction in CD8 T cells was primarily attributable to *MTAP*-del, rather than *CDKN2A*-del in CheckMate 227 and CheckMate 9LA

Table 1. Demographics and baseline characteristics by *MTAP* status[a]

Baseline factors		Patients, n (%)									
		TEMPUS				Flatiron				Pooled CheckMate studies	
		1L treatment-naive (n = 3039)		1L treatment-exposed (n = 1436)		1L treatment-naive (n = 4228)		1L treatment-exposed (n = 716)		1L treatment-naive (n = 2223)	
		MTAP-del (n = 409)	*MTAP*-WT (n = 2630)	*MTAP*-del (n = 245)	*MTAP*-WT (n = 1191)	*MTAP*-del (n = 533)	*MTAP*-WT (n = 3695)	*MTAP*-del (n = 106)	*MTAP*-WT (n = 610)	*MTAP*-del (n = 239)	*MTAP*-WT (n = 1984)
PD-L1 TPS[b]	< 1%	121 (29.6)	729 (27.7)	56 (22.9)	275 (23.1)	118 (22.1)	731 (19.8)	22 (20.8)	98 (16.1)	86 (36.0)	722 (36.4)
	1%-49%	98 (24.0)	677 (25.7)	50 (20.4)	278 (23.3)	109 (20.5)	721 (19.5)	11 (10.4)	91 (14.9)	97 (40.6)	666 (33.6)
	≥ 50%	73 (17.8)	509 (19.4)	26 (10.6)	147 (12.3)	107 (20.1)	794 (21.5)	12 (11.3)	79 (13.0)	54 (22.6)	566 (28.5)
Histology[c]	SQ	123 (30.1)	745 (28.3)	57 (23.3)	298 (25.0)	147 (27.6)	961 (26.0)	31 (29.2)	154 (25.2)	84 (35.1)	592 (29.8)
	NSQ	280 (68.5)	1861 (70.8)	185 (75.5)	880 (73.9)	358 (67.2)	2579 (69.8)	69 (65.1)	430 (70.5)	155 (64.9)	1392 (70.2)
KRAS^{G12C}	Mut	39 (9.5)	258 (9.8)	15 (6.1)	96 (8.1)	75 (14.1)	459 (12.4)	8 (7.6)	74 (12.1)	24 (10.0)	219 (11.0)
	WT	370 (90.5)	2372 (90.2)	230 (93.9)	1095 (91.9)	458 (85.9)	3236 (87.6)	98 (92.5)	536 (87.9)	215 (90.0)	1765 (89.0)
Sex	Male	211 (51.6)	1436 (54.6)	128 (52.2)	557 (48.3)	289 (54.2)	1955 (52.9)	51 (48.1)	318 (52.1)	161 (67.4)	1332 (67.1)
	Female	198 (48.4)	1994 (45.4)	117 (47.8)	616 (51.7)	244 (45.8)	1740 (47.1)	55 (51.9)	292 (47.9)	78 (32.6)	652 (32.9)
ECOG PS[d]	0-1	164 (40.1)	1020 (38.8)	125 (51.0)	577 (48.4)	-	-	-	-	229 (95.8)	1921 (96.8)
	≥ 2	42 (10.3)	239 (9.1)	22 (9.0)	102 (8.6)	-	-	-	-	10 (4.2)	59 (3.0)

[a]Data are from the TEMPUS and Flatiron databases, and pooled CheckMate studies. [b]In TEMPUS, 117 (28.6%) 1L treatment-naive *MTAP*-del, 715 (27.2%) 1L treatment-naive *MTAP*-WT, 113 (46.1%) 1L treatment-exposed *MTAP*-del, and 491 (41.2%) 1L treatment-exposed *MTAP*-WT patients did not have approved PD-L1 22c3 testing documented. In Flatiron, 199 (37.3%) 1L treatment-naive *MTAP*-del, 1449 (39.2%) 1L treatment-naive *MTAP*-WT, 61 (57.5%) 1L treatment-exposed *MTAP*-del, and 342 (56.1%) 1L treatment-exposed *MTAP*-WT patients had PD-L1 testing with metrics other than TPS and were excluded. In the pooled CheckMate studies, 2 (0.8%) 1L treatment-naive *MTAP*-del and 30 (1.5%) 1L treatment-naive *MTAP*-WT patients could not be evaluated for PD-L1. [c]In TEMPUS, 6 (1.5%) 1L treatment-naive *MTAP*-del, 24 (0.9%) 1L treatment-naive *MTAP*-WT, 3 (1.2%) 1L treatment-exposed *MTAP*-del, and 13 (1.1%) 1L treatment-exposed *MTAP*-WT patients had adenosquamous NSCLC. In Flatiron, 28 (5.3%) 1L treatment-naive *MTAP*-del, 155 (4.2%) 1L treatment-naive *MTAP*-WT, 6 (5.7%) 1L treatment-exposed *MTAP*-del, and 26 (4.3%) 1L treatment-exposed *MTAP*-WT patients had histology not specified. [d]Patients with unknown ECOG PS: TEMPUS, 203 (49.6%) 1L treatment-naive *MTAP*-del, 1371 (52.1%) 1L treatment-naive *MTAP*-WT, 98 (40.0%) 1L treatment-exposed *MTAP*-del, and 512 (43.0%) 1L treatment-exposed *MTAP*-WT; pooled CheckMate studies, 4 (0.2%) 1L treatment-naive *MTAP*-WT. ECOG PS, Eastern Cooperative Oncology Group performance status; Mut, mutated; NSQ, non-squamous; SQ, squamous; TPS, tumor proportion score.

Figure 1. Co-occurrence of AGAs by *MTAP* status[a]

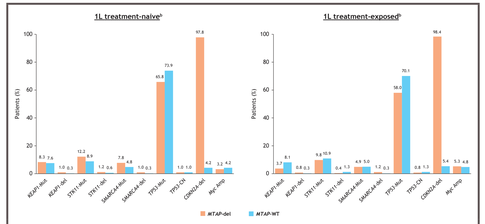


Co-occurrence	Patients, n	*EGFR*-Mut, %	*KRAS*-Mut, %
MTAP-del	409	15.4	21.5
MTAP-WT	2630	14.1	25.1

Co-occurrence	Patients, n	*EGFR*-Mut, %	*KRAS*-Mut, %
MTAP-del	245	26.1	20.8
MTAP-WT	1191	20.2	22.2

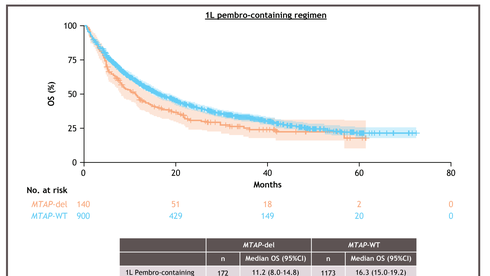
[a]Data are from the TEMPUS database. [b]1L treatment-naive: *MTAP*-del, n = 409; *MTAP*-WT, n = 2630. 1L treatment-exposed: *MTAP*-del, n = 245; *MTAP*-WT, n = 1191. Amp, amplification; Ex, exon.

Figure 2. Co-occurrence of relevant NSCLC genomic alterations by *MTAP* status[a]



[a]Data are from the TEMPUS database. [b]1L treatment-naive: *MTAP*-del, n = 409; *MTAP*-WT, n = 2630. 1L treatment-exposed: *MTAP*-del, n = 245; *MTAP*-WT, n = 1191.

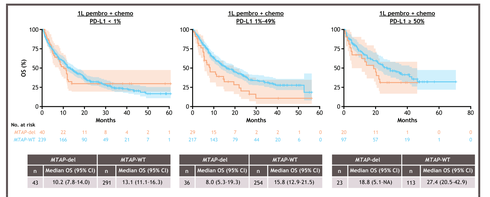
Figure 3. OS by *MTAP* status[a]



	MTAP-del		*MTAP*-WT	
	n	Median OS (95%CI)	n	Median OS (95%CI)
1L Pembro-containing	172	11.2 (8.0-14.8)	1173	16.3 (15.0-19.2)

[a]Data are from the TEMPUS database.

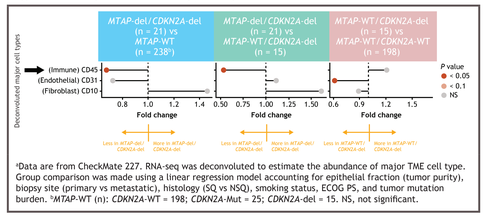
Figure 4. OS by *MTAP* status across PD-L1 strata[a]



	MTAP-del		*MTAP*-WT	
	n	Median OS (95% CI)	n	Median OS (95% CI)
1L pembro + chemo PD-L1 < 1%	43	10.2 (7.8-14.0)	291	13.1 (11.1-16.3)
1L pembro + chemo PD-L1 1%-49%	36	8.0 (5.3-19.3)	254	15.8 (12.9-21.5)
1L pembro + chemo PD-L1 ≥ 50%	23	18.8 (5.1-NA)	113	27.4 (20.5-42.9)

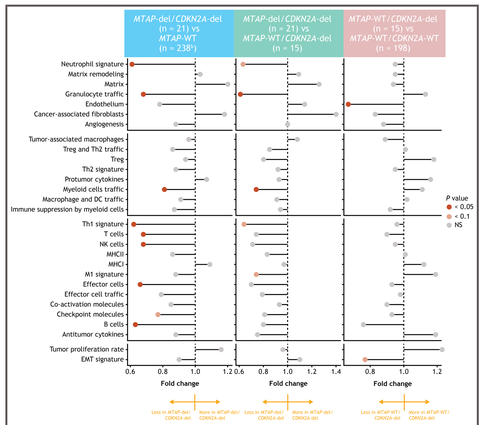
[a]Data are from the TEMPUS database. NA, not available.

Figure 5. Major TME cell types by *MTAP* and *CDKN2A* status[a]



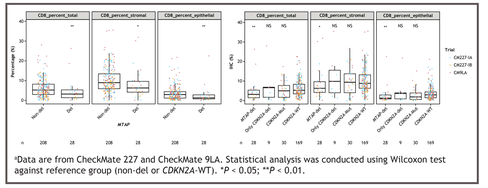
[a]Data are from CheckMate 227. RNA-seq was deconvoluted to estimate the abundance of major TME cell type. Group comparison was made using a linear regression model accounting for epithelial fraction (tumor purity), biopsy site (primary vs metastatic), histology (SQ vs NSQ), smoking status, ECOG PS, and tumor mutation burden. [a]*MTAP*-WT (n): *CDKN2A*-WT = 198; *CDKN2A*-Mut = 25; *CDKN2A*-del = 15. NS, not significant.

Figure 6. TME gene signatures by *MTAP* and *CDKN2A* status[a]



[a]Data are from CheckMate 227. Median z-scores of the gene signature were calculated using RNA-seq, followed by the group comparison method described in Figure 5. Gene signatures were defined in Bagaev A et al.[8] [a]*MTAP*-WT (n): *CDKN2A*-WT = 198; *CDKN2A*-Mut = 25; CDKN2A-del = 15. DC, dendritic cell; EMT, epithelial-mesenchymal transition; MHC, major histocompatibility complex; NK, natural killer; Th2, T helper type 2; Treg, regulatory T cell.

Figure 7. CD8 T-cell infiltration by *MTAP* and *CDKN2A* status[a]



[a]Data are from CheckMate 227 and CheckMate 9LA. Statistical analysis was conducted using Wilcoxon test against reference group (non-del or *CDKN2A*-WT). *P < 0.05; **P < 0.01.

Conclusions

- This retrospective analysis across real-world and clinical trial datasets highlighted *MTAP*-del as a commonly observed genomic alteration in advanced NSCLC
- *MTAP*-del was observed in tumors both with and without AGAs, indicating its presence across distinct molecular subgroups
- *MTAP*-del was associated with poor outcomes with 1L pembro-containing regimens
  - Numerically shorter OS was observed in patients receiving pembro + chemo regardless of PD-L1 expression level
- *MTAP*-del tumors demonstrated features of an immunologically cold TME, including reduced immune cell populations and CD8 T cell infiltration
  - The contribution of interferon cluster codeletion cannot be assessed as F1CDx does not cover these genes
- **These results highlight an unmet need for additional therapies for patients with *MTAP*-del NSCLC**
- **Navlimetostat (BMS-986504), an MTA-cooperative PRMT5 inhibitor, is currently being investigated in this patient population and in the MountainTAP-9 and MountainTAP-29 studies**

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Disclosures

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