

PRMT5 expression associates with increased DNA-damage repair signaling in non-small cell lung cancer (NSCLC)

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INTRODUCTION

- Protein arginine methyltransferase 5 (PRMT5) regulates tumor progression, immune evasion, and DNA damage response (DDR) pathways.

- While MTAP deletion (MTAPdel) partially inhibits PRMT5 through accumulation of methylthioadenosine, the relationship between PRMT5 expression, DDR signaling, and clinical outcomes in NSCLC remains incompletely defined.

- Here, we characterized the tumor-intrinsic and clinical implications of PRMT5 expression, focusing on DDR pathways and interactions with MTAP.

METHODS

- The Tempus Lens platform was utilized to identify patients with NSCLC who underwent DNA (Tempus xT) and RNA (Tempus xR) sequencing from samples obtained within 30 days of diagnosis and prior to first-line (1L) therapy (n=5,610).

- For patients with multiple samples, the sample closest to diagnosis was selected. *PRMT5* expression was quantified as log2(TPM+1) and dichotomized at the median into *PRMT5*-high and *PRMT5*-low groups.

- MTAP* status was defined by biallelic loss (*MTAPdel*) versus intact (*MTAPwt*). Enrichment in the hallmark pathways was estimated using gene set enrichment analysis (GSEA).

- Associations between categorical variables were assessed using Chi-squared or Fisher's exact tests, and continuous variables using Wilcoxon or Kruskal-Wallis tests, at q≤0.05.

- Real-world overall survival (rwOS) and progression-free survival (rwPFS) were calculated from initiation of 1L therapy to death/second line or loss to follow up.

- Multivariable Cox proportional hazards models adjusted for age, sex, histology, smoking status, and PD-L1 expression were used to estimate hazard ratios (HR) with 95% confidence intervals (CI). Analyses were restricted to prospective-like patients sequenced prior to treatment initiation.

SUMMARY

- PRMT5*-high expression is associated with upregulated DDR pathways and worse rwOS, especially to ICI.

- MTAP loss with elevated PRMT5 expression associates with worse overall survival in all treatment groups except chemotherapy and Osimertinib. However, in chemotherapy-treated patients with ICI, MTAP-deletion and high PRMT5 expression associate with worse PFS.

- These findings support further investigation of DDR-targeting strategies in *PRMT5*-high tumors and highlight the importance of integrating *PRMT5* and *MTAP* status in biomarker-driven trial design.

RESULTS

Table 1. Cohort Overview

Characteristic	Overall N = 5,610 ¹	MTAP-del + PRMT5high, N = 374 (6.7%) ¹	MTAP-del + PRMT5low, N = 310 (5.5%) ¹	MTAP-wt + PRMT5high, N = 2449 (44%) ¹	MTAP-wt + PRMT5low, N = 2477 (44%) ¹	p-value ²
Age at diagnosis						<0.001
Median (Q1, Q3)	67 (60, 73)	68 (60, 74)	67 (60, 74)	66 (60, 73)	67 (60, 74)	
Min, Max	20, 89	41, 88	30, 87	21, 88	20, 89	
Age at sample collection						<0.001
Median (Q1, Q3)	67 (61, 74)	68 (61, 75)	67 (61, 74)	67 (61, 73)	68 (61, 75)	
Min, Max	20, 89	41, 88	30, 88	21, 88	20, 89	
Unknown	1	0	0	1	0	
Sex						<0.001
Male	2,967 (53%)	200 (53%)	147 (47%)	1,369 (56%)	1,251 (51%)	
Female	2,643 (47%)	174 (47%)	163 (53%)	1,080 (44%)	1,226 (49%)	
Race						0.2
White	3,651 (78%)	246 (80%)	195 (76%)	1,637 (79%)	1,573 (77%)	
Black or African American	521 (11%)	32 (10%)	24 (9.4%)	232 (11%)	233 (11%)	
Other Race	284 (6.1%)	13 (4.2%)	18 (7.0%)	116 (5.6%)	137 (6.7%)	
Asian	218 (4.7%)	16 (5.2%)	19 (7.4%)	86 (4.2%)	97 (4.8%)	
Unknown	936	67	54	378	437	
Ethnicity						0.016
Not Hispanic or Latino	3,494 (94%)	228 (93%)	203 (95%)	1,561 (95%)	1,502 (93%)	
Hispanic or Latino	223 (6.0%)	17 (6.9%)	11 (5.1%)	77 (4.7%)	118 (7.3%)	
Unknown	1,893	129	96	811	857	
Smoking status						<0.001
Ex-smoker	2,998 (57%)	197 (56%)	168 (57%)	1,274 (55%)	1,359 (59%)	
Current smoker	1,460 (28%)	107 (30%)	67 (23%)	734 (32%)	552 (24%)	
Never smoker	822 (16%)	50 (14%)	58 (20%)	305 (13%)	409 (18%)	
Unknown	330	20	17	136	157	

PRMT5 expression associates with upregulation in DNA damage repair (DDR) genes and pathways, while MTAP deletion has a more modest association

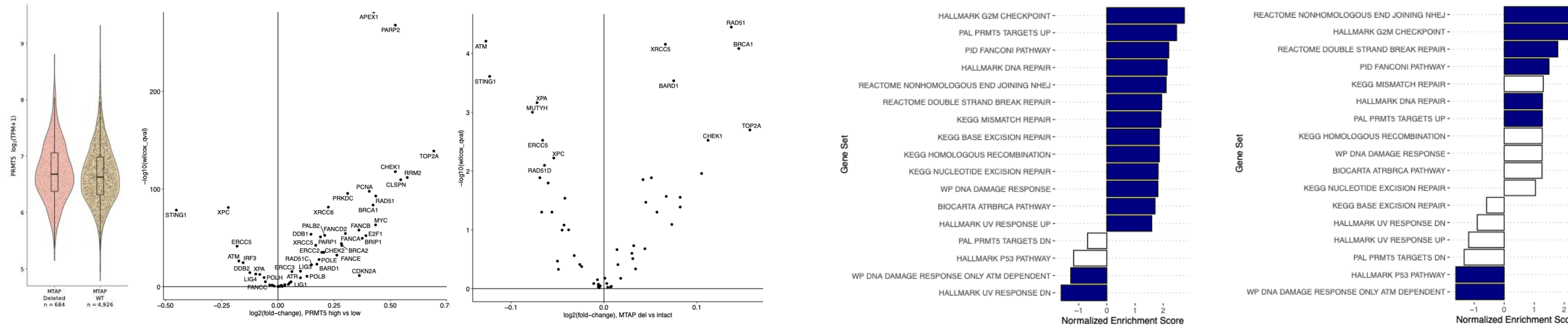


Figure 1. A) PRMT5 expression is not increased in MTAP-deleted vs wild-type samples (linear regression adjusted for tumor purity p=0.48). B) Differential expression of DDR genes in PRMT5 high vs low expressing samples. C) Differential expression of DDR genes in MTAP deleted vs wild-type samples.

High PRMT5 expression is a poor prognostic marker for rwOS

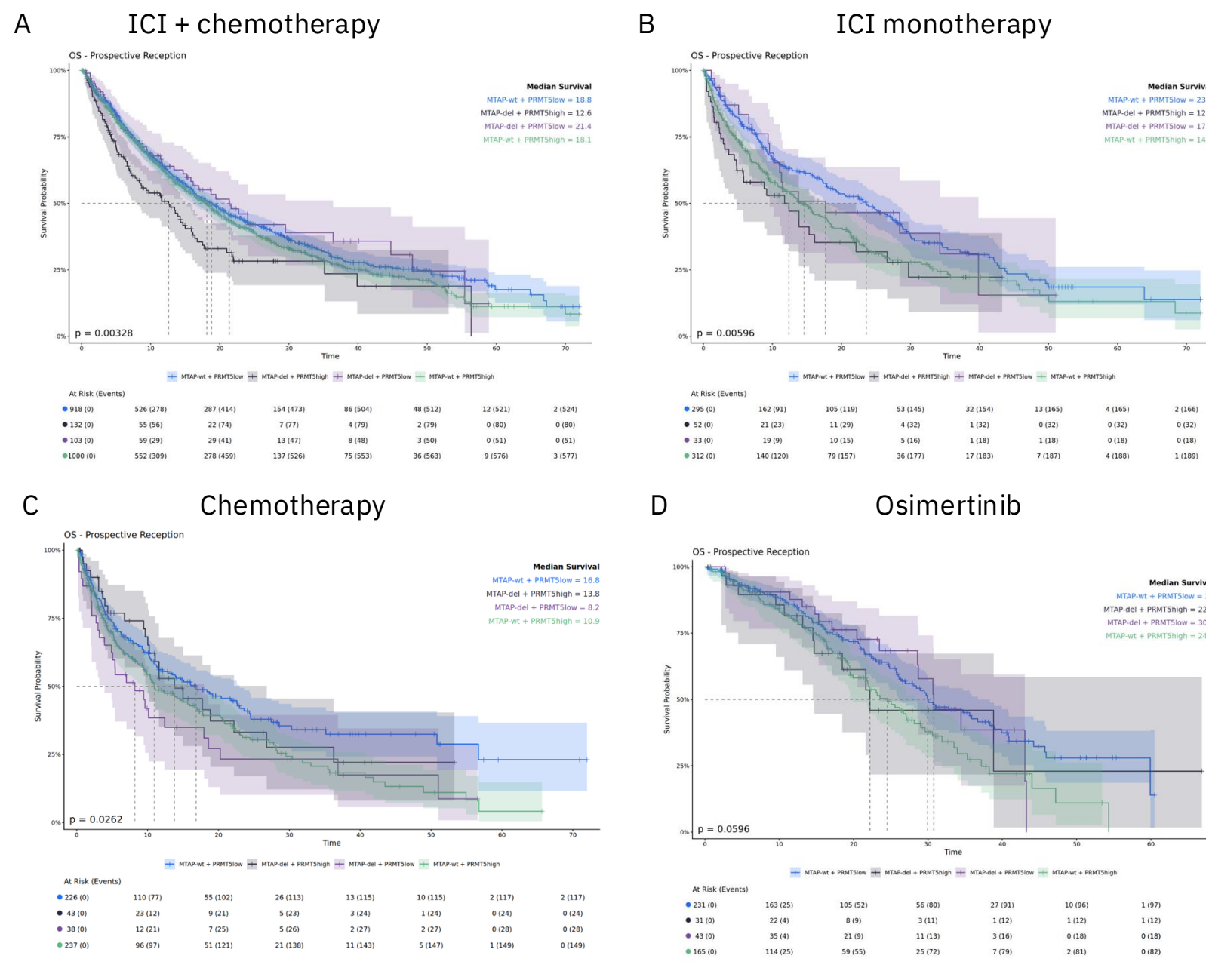


Figure 2. Gene set enrichment analysis using Hallmark DDR gene sets in PRMT5 high vs low samples (left) and MTAP deleted vs wild-type samples (right).

Real-world PFS multivariate analysis

E ICI + chemotherapy

Multivariate CoxPH	Characteristic	N	Event	HR	95% CI	p-value
groups						
	MTAP-wt + PRMT5low	715	426	—	—	
	MTAP-del + PRMT5high	106	72	1.45	1.12, 1.86	0.004
	MTAP-del + PRMT5low	74	42	1.12	0.82, 1.54	0.5
	MTAP-wt + PRMT5high	814	518	1.11	0.92, 1.26	0.12
Age at sample collection		1,709	1,058	1.00	1.00, 1.01	0.4
Sex						
	Female	701	427	—	—	
	Male	1,008	631	1.00	0.88, 1.13	>0.9
Histology Rollup						
	Adenocarcinoma	1,071	674	—	—	
	Other	127	77	0.99	0.76, 1.29	>0.9
	Squamous cell carcinoma	511	307	0.90	0.70, 1.04	0.15
pdL1_tps_bin						
	<1	687	454	—	—	
	1-49	709	421	0.84	0.74, 0.96	0.012
	>=50	313	183	0.76	0.64, 0.90	0.002

F ICI monotherapy

Multivariate CoxPH	Characteristic	N	Event	HR	95% CI	p-value
groups						
	MTAP-wt + PRMT5low	226	134	—	—	
	MTAP-del + PRMT5high	40	24	1.04	0.62, 1.61	0.9
	MTAP-del + PRMT5low	27	12	0.64	0.35, 1.16	0.14
	MTAP-wt + PRMT5high	247	151	1.16	0.92, 1.48	0.2
Age at sample collection		540	321	1.01	1.00, 1.02	0.2
Sex						
	Female	255	146	—	—	
	Male	285	175	1.15	0.92, 1.43	0.2
Histology Rollup						
	Adenocarcinoma	332	185	—	—	
	Other	50	34	1.30	0.90, 1.88	0.2
	Squamous cell carcinoma	158	102	1.19	0.92, 1.54	0.2
pdL1_tps_bin						
	<1	93	60	—	—	
	1-49	150	92	0.84	0.65, 1.17	0.3
	>=50	297	169	0.69	0.51, 0.94	0.017

G Chemotherapy

Multivariate CoxPH	Characteristic	N	Event	HR	95% CI	p-value
groups						
	MTAP-wt + PRMT5low	169	116	—	—	
	MTAP-del + PRMT5high	27	20	1.25	0.72, 2.04	0.4
	MTAP-del + PRMT5low	32	24	1.34	0.86, 2.09	0.2
	MTAP-wt + PRMT5high	168	121	1.28	0.98, 1.65	0.066
Age at sample collection		396	281	1.00	0.99, 1.02	0.7
Sex						
	Female	193	134	—	—	
	Male	203	147	1.24	0.97, 1.57	0.084
Histology Rollup						
	Adenocarcinoma	252	187	—	—	
	Other	25	20	1.08	0.68, 1.74	0.7
	Squamous cell carcinoma	119	74	0.68	0.52, 0.91	0.009
pdL1_tps_bin						
	<1	143	108	—	—	
	1-49	159	103	0.93	0.71, 1.22	0.6
	>=50	94	70	1.22	0.88, 1.67	0.2

H Osimertinib

Multivariate CoxPH	Characteristic	N	Event	HR	95% CI	p-value
groups						
	MTAP-wt + PRMT5low	171	85	—	—	
	MTAP-del + PRMT5high	22	12	1.30	0.70, 2.40	0.4
	MTAP-del + PRMT5low	31	21	1.65	1.01, 2.67	0.044
	MTAP-wt + PRMT5high	122	70	1.19	0.87, 1.64	0.3
Age at sample collection		346	188	1.00	0.99, 1.01	0.8
Sex						
	Female	251	136	—	—	
	Male	95	52	0.92	0.67, 1.28	0.6
Histology Rollup						
	Adenocarcinoma	335	181	—	—	
	Other	6	4	0.96	0.35, 2.61	>0.9
	Squamous cell carcinoma	5	3	1.32	0.41, 4.19	0.6
pdL1_tps_bin						
	<1	151	80	—	—	
	1-49	138	73	1.06	0.76, 1.46	0.7
	>=50	57	35	1.45	0.97, 2.19	0.072

Figure 3. Left panels: Kaplan-meier curves of real-world overall survival (OS), stratified by PRMT5 expression status and MTAP deletion status. Panels show patients treated with ICI + chemotherapy (A), ICI monotherapy (B), chemotherapy (C), or osimertinib (EGFR mutated patients only; D). Right panels: multivariate analysis of progression-free survival (PFS), for ICI + chemotherapy (E), ICI monotherapy (F), chemotherapy (G), or osimertinib (H).

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