Stratification Based on *PRAME* Gene Expression Shows Inverse Survival Associations Among Histology Subtypes in a First-Line Non-Small Cell Lung Cancer Real-World Cohort

Roosheel S. Patel[1], Sebastià Franch-Expósito[1], Sumaiya Islam[1], Paul A. Fields[1], and Catherine Igartua[1]
[1] Tempus AI, Inc., Chicago, IL

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INTRODUCTION

- *PRAME* (Preferentially Expressed Antigen in Melanoma) is an intracellular cancer-testis antigen over-expressed across solid tumor types.
- Elevated *PRAME* expression is associated with poor prognosis in lung cancer.
- *PRAME's* selective expression in tumor cells and ability to induce robust T-cell-mediated immune responses make it a promising target for cancer immunotherapy.
- This study investigates the influence of histological subtypes on *PRAME* expression and its impact on outcomes to immunotherapy in first-line (1L) Non-Small Cell Lung Cancer (NSCLC) patients.

METHODS

- Analyzed **4,519 non-small cell lung cancer** patients from the Tempus de-identified, multimodal real-world database.
- *PRAME* expression levels were classified into high and low based on median expression in the whole NSCLC cohort.
- Included pre-treatment biopsy samples from patients who received immunotherapy (IO) or chemotherapy (chemo), as individual monotherapies or in combination in the 1L setting.
- Compared real-world overall survival for high versus low expressers in each histological subtype (lung squamous cell carcinoma [LUSC] and lung adenocarcinoma [LUAD]) and treatment setting.

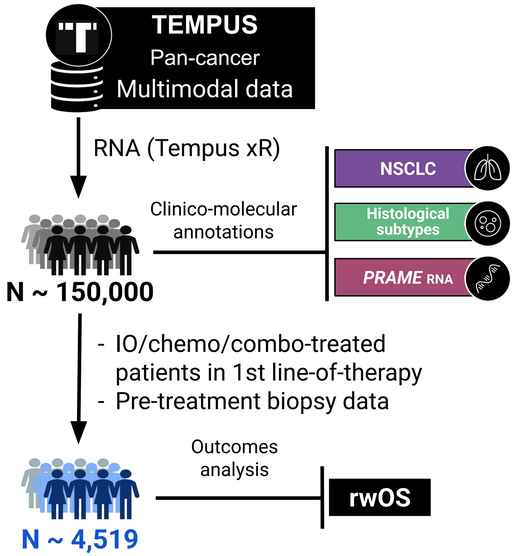

Figure 1. Pan-cancer Tempus multi-modal data model of clinico-molecular information to interrogate *PRAME* expression across NSCLC histological subtypes.

SUMMARY

- Our findings identify *PRAME* expression as a predictive therapeutic biomarker in NSCLC, with distinct implications based on histological context.
- High *PRAME* expressors may benefit from PRAME-targeted therapies combined with IO and chemo, highlighting the potential for personalized treatment strategies.

RESULTS

Table 1. Clinco-molecular NSCLC patient features

	Overall N = 4,519[†]	LUAD N = 3,213[†]	LUSC N = 1,306[†]	p-value[2]
PRAME GROUP				<0.001
High_PRAME	2,261 (50%)	1,288 (40%)	973 (75%)	
Low_PRAME	2,258 (50%)	1,925 (60%)	333 (25%)	
THERAPY SETTING				>0.9
IO + Chemo	2,692 (60%)	1,909 (59%)	783 (60%)	
IO Mono	957 (21%)	682 (21%)	275 (21%)	
Chemo	870 (19%)	622 (19%)	248 (19%)	
TUMOR PURITY	50 (30, 60)	50 (30, 60)	50 (40, 70)	<0.001
Unknown	68	50	18	
SAMPLE METASTATIC STATUS				<0.001
Metastatic	3,415 (79%)	2,564 (83%)	851 (69%)	
Pre-Metastatic	915 (21%)	531 (17%)	384 (31%)	
Unknown	189	118	71	
STAGE AT BIOPSY				<0.001
Stage 4	3,410 (79%)	2,559 (83%)	851 (69%)	
Stage 3	630 (15%)	331 (11%)	299 (24%)	
Stage 1	133 (3.1%)	101 (3.3%)	32 (2.6%)	
Stage 2	120 (2.8%)	77 (2.5%)	43 (3.5%)	
Unknown	226	145	81	
BIOPSY SITE				<0.001
Bronchus And Lungs	2,321 (51%)	1,472 (46%)	849 (65%)	
Lymphatics And Adrenal Gland	787 (17%)	610 (19%)	177 (14%)	
Pelvic And Upper Body Soft Tissue	505 (11%)	440 (14%)	65 (5.0%)	
Brain And Nervous System	262 (5.8%)	220 (6.8%)	42 (3.2%)	
Liver	214 (4.7%)	148 (4.6%)	66 (5.1%)	
Other Site	430 (9.5%)	323 (10%)	107 (8.2%)	
SEX				<0.001
Male	2,481 (55%)	1,645 (51%)	836 (64%)	
Female	2,038 (45%)	1,568 (49%)	470 (36%)	
SELF-REPORTED RACE				0.3
White	2,922 (65%)	2,068 (64%)	854 (65%)	
Black Or African American	429 (9.5%)	302 (9.4%)	127 (9.7%)	
Other Race	336 (7.4%)	230 (7.2%)	106 (8.1%)	
Asian	85 (1.9%)	65 (2.0%)	20 (1.5%)	
Unknown	747 (17%)	548 (17%)	199 (15%)	
AGE_AT_DIAGNOSIS	68 (61, 74)	67 (61, 74)	69 (62, 75)	<0.001
Unknown	87	65	22	
RESPONSE OUTCOME				0.027
Progressive Disease	1,592 (53%)	1,128 (52%)	464 (54%)	
Partial Response	794 (26%)	557 (26%)	237 (28%)	
Stable Disease	473 (16%)	365 (17%)	108 (13%)	
Complete Response	169 (5.6%)	126 (5.8%)	43 (5.0%)	
Unknown	1,491	1,037	454	

All samples have been profiled with the Tempus xT or xE assay and have RNA data
Indications stratified by the Tempus Medical Ontology (TMO) standard
[†] n (%); Median (Q1, Q3)
[2] Pearson's Chi-squared test; Wilcoxon rank sum test

High *PRAME* expression is enriched in LUSC in NSCLC

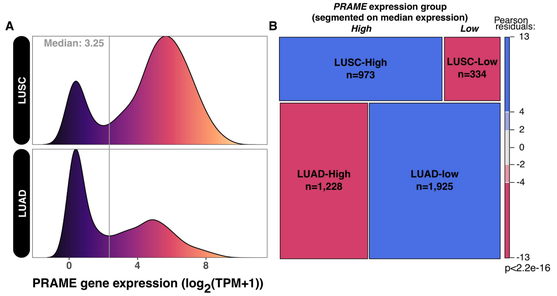

Figure 2. (A) Density plots of PRAME gene expression by histological subtypes (top: LUSC, bottom: LUAD) in the NSCLC cohort. The gray line represents the median expression threshold (defined across the whole NSCLC cohort) selected to define *PRAME*-high and *PRAME*-low expressors. **(B)** Mosaic plot illustrating the enrichment of PRAME high expressors in LUSC. A X^2 test of independence was performed, with the Pearson residuals quantifying each cell's deviation from its expected frequency.

Histology-specific *PRAME* expression is a predictive biomarker for IO and Chemo response in 1L-NSCLC

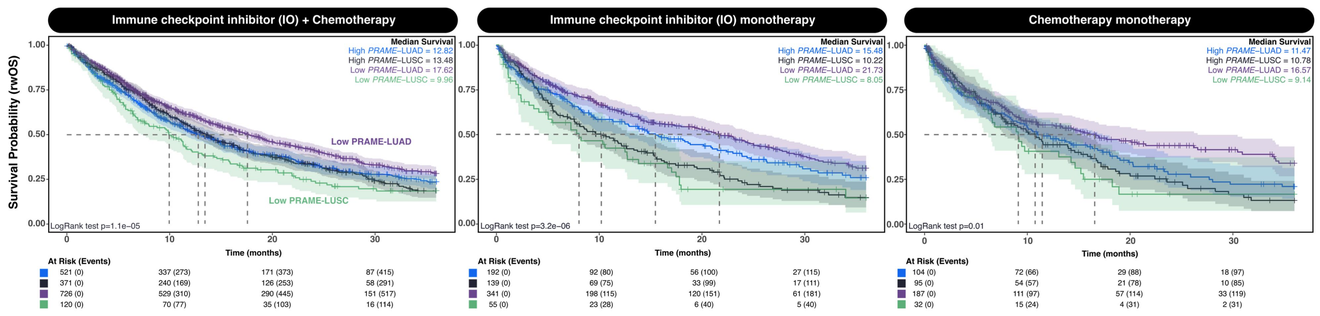

Figure 3: Kaplan-Meier curves for real-world overall survival (rwOS) in NSCLC patients treated with immunotherapy (IO) and chemotherapy (Chemo) in combination or as monotherapies in the first-line (1L) setting, stratified by *PRAME* expression levels (high vs. low) and histology type. Statistical testing to detect survival differences between groups was evaluated using the log-rank test and its p-value is reported on the bottom left of each facet.

High *PRAME*-LUSC expressors exhibit better survival after IO+Chemo in a 1L setting

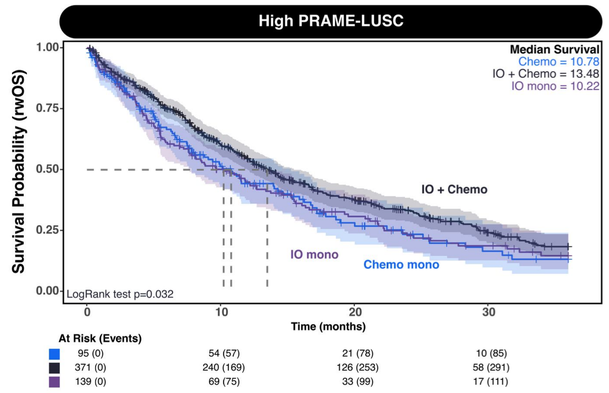

Figure 4: Kaplan-Meier curves for real-world overall survival (rwOS) in NSCLC patients treated with immunotherapy (IO) and chemotherapy (Chemo) in combination or as monotherapies in the first-line (1L) setting in high PRAME-LUSC expressors (no trend). Survival differences between treatment groups were evaluated using the log-rank test (p=0.032).

***PRAME* expression predicts differential rwOS in 1L-NSCLC based on histological subtype**

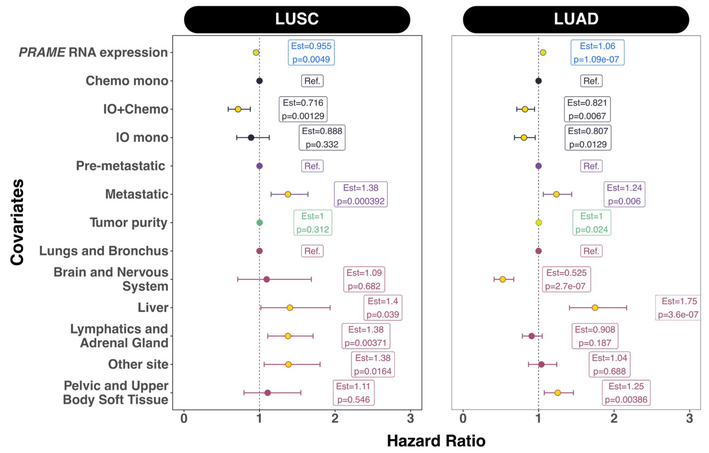

Figure 5: Multivariate CoxPH forest plots illustrate effects of PRAME expression and treatment effects on rwOS in LUSC (left) and LUAD (right) patients, accounting for clinical and molecular confounders (metastatic status, tumor purity, biopsy site). Forest plots depict hazard ratios (HR) with 95% CIs indicate risk of death. Yellow-colored dots identify significant results ($p < 0.05$).

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Correspondence: roosheel.patel@tempus.com