#8579: Longitudinal Plasma Proteomic Analysis: A Monitoring Strategy for NSCLC Patients Treated with Immunotherapy

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Background

Real-time monitoring is critical for tailoring treatments to individual patient responses in clinical oncology. Plasma proteomics offers a comprehensive systemic view of disease progression [2], tumor activity, immune responses, and various biological processes [3,4]—while remaining rapid, scalable, and minimally invasive—positioning it as a powerful tool for clinical decision-making and addressing a critical unmet clinical need. This study explores the feasibility of three specific plasma proteomic signatures for longitudinal monitoring of treatment responses in patients with non-small cell lung cancer (NSCLC) undergoing therapy with immune checkpoint inhibitors (ICIs).

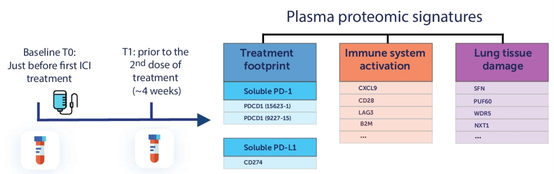
High-throughput plasma proteomics provides a real-time picture of drug dynamics, immune system activation and tissue damage.

Proteomic signature generation

1 Three proteomic signatures of biological mechanisms associated with ICI-based therapies were identified using plasma samples from patients with advanced NSCLC receiving PD-1/PD-L1 inhibitors [1]. Cohort-1 (n = 225) included samples collected pre-treatment (T0) and ~4 weeks post-treatment initiation (T1, prior to cycle 2). Proteins were quantified using SomaScan aptamer-based technology.

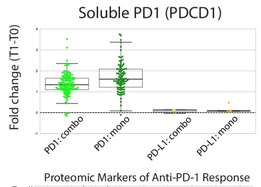
T0/T1 Cohort description (n=225)

Parameters		n(%)
n		225 (100)
Treatment	ICI +Chemo	125 (56)
	ICI	100 (44)
Sex	Male	141 (63)
	Female	84 (37)
ECOG	0 - 1	203 (90.2)
	≥2	21 (9.3)
	NA	1 (0.4)
Histology	Adenocarcinoma	156 (70)
	Squamous cell carcinoma	46 (20)
	Other	23 (10)



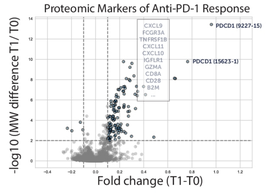
1. Anti-PD-(L)1 Treatment Footprint

Soluble PD-1 (sPD-1) was the most significantly upregulated protein following ICI therapy, particularly in patients receiving PD-1 inhibitors. Elevated sPD-1 fold-change at T1 was associated with longer overall survival (OS), suggesting its utility as a blood-based surrogate marker of therapeutic engagement and prognosis.



2. Immune System Activation

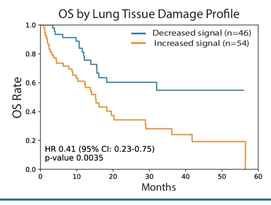
ICI monotherapy induced a robust T cell-related plasma proteomic signature, featuring elevated levels of proteins such as CD8A, IL2RA, LAG3, and B2M. This signature was detectable in both responders (R) and non-responders (NR), indicating systemic immune activation occurs regardless of clinical outcome.



3. Monitoring Patient Response and Lung Tissue Damage

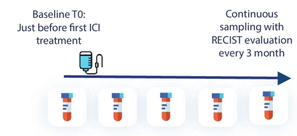
In patients treated with ICI monotherapy, responders showed a decrease in intracellular alveolar-origin proteins. This plasma profile may indicate reduced tumor burden and lung tissue damage, serving as a potential marker for favorable drug response. Thus, this plasma profile may serve as a monitoring tool for therapeutic efficacy.

Kaplan–Meier survival analysis of ICI monotherapy-treated NSCLC patients stratified by on-treatment change in lung tissue damage alveolar-associated plasma proteins.
A decrease in signal was significantly associated with prolonged overall survival (HR = 0.41, p = 0.0035).

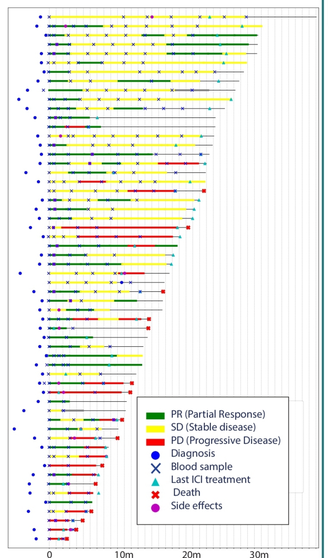


Longitudinal monitoring for ICI treated patients

2 We evaluated the three signatures in a separate, longitudinal cohort of NSCLC patients (n = 56) treated with anti–PD-(L)1 immunotherapy. Serial plasma samples were collected pre-treatment and every three months for up to 36 months, in parallel with imaging-based response assessments.



Parameters		n(%)
n		57 (100)
Treatment	ICI +Chemo	34 (60)
	ICI	22 (39)
	IPI Nivo	1 (2)
Sex	Male	34 (60)
	Female	23 (40)
ECOG	0-1	43 (75)
	≥2	6 (10)
	NA	8 (14)
Histology	Adenocarcinoma	40 (70)
	Squamous cell carcinoma	11 (19)
	Other	6 (11)



Conclusions

- Our study demonstrates the feasibility of using plasma proteomic signatures to monitor responses to ICIs in NSCLC.
- Signatures were developed and validated across independent patient cohorts, enabling a blinded validation that reinforces the robustness of our findings.
- Prospective validation is needed to confirm clinical utility, and correlation with ctDNA is in progress to enhance translational relevance.

References

1. Bar, J. et al. Biological insights from plasma proteomics of non-small cell lung cancer patients treated with immunotherapy. Front. Immunol. 15, 1364473 (2024).
2. Harel, M. et al. Plasma Proteomic Hallmarks of Resistance to Immune Checkpoint Inhibitors in Patients with Non-Small Cell Lung Cancer. Cancer Research (accepted 2025)
3. Oh, H.S. et al. Organ aging signatures in the plasma proteome track health and disease. Nature 624, 164–172 (2023).
4. Malmström, E. et al. Human proteome distribution atlas for tissue-specific plasma proteome dynamics. Cell 188, 2810–2822.e16 (2025).

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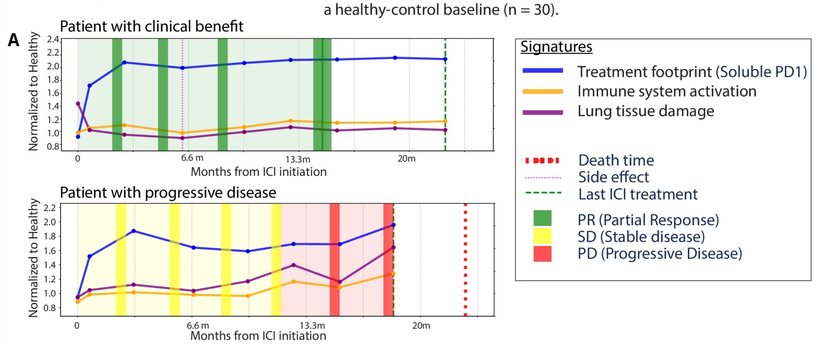
Representative NSCLC cases

Signature scores were calculated as the mean z-score of their constituent proteins and then normalized to a healthy-control baseline (n = 30).



Key observations

- Early rise in soluble PD-1 signature confirms drug presence in circulation.
- Immune activation signature emerges at treatment initiation.
- Lung tissue damage signature distinguishes response patterns:
  - Responder: sustained decline parallels tumour regression.
  - Non-responder: delayed increase (~10 months) anticipates RECIST-defined progression.

B

	Days	Month
average	200	6.5
stdev	128	4.30
CI (0.05)	77	2.60
upper	277	9.2
lower	123	4.1

In 13 patients, plasma proteomic changes enabled early detection of treatment response or progression—on average 200 days (~6.5 months) ahead of radiologic evaluation (range: 123–277 days).

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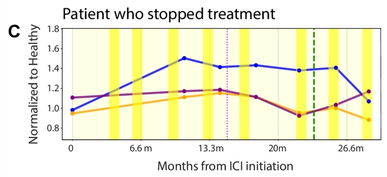
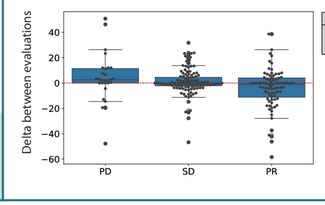


This case highlights a 59-year-old male with NSCLC treated with anti-PD-1 and chemotherapy, illustrating the consequences of halting ICI therapy. A sharp decline in soluble PD-1 levels was followed by reduced immune activation and a subsequent rise in lung tissue damage markers—potentially signaling early relapse. Continuous plasma monitoring could have supported a decision to maintain treatment.

4

Lung Damage Signature Shows Significant Agreement With RECIST Evaluation

Agreement between the proteomic response signature and RECIST imaging outcomes was evaluated with a Kruskal–Wallis rank-sum test, contrasting the observed change in the signature (Δsignature) with the direction of change expected from RECIST categories. A significant result (p-value = 0.009) confirms strong concordance between the coupled samples plasma-based signature and radiographic response to immunotherapy.



Tissue damage signature	all treatments	N	PR	SD	PD	KW P-Value
	#patient (n=55)	Mean[Q1,Q3]	-3.9[-11.1, 4]	0.9[-2.1, 4.5]	3.2[0, 11.4]	0.009