Immune Profiling and Targetable Biomarkers in NSCLC: Toward Rational Design of CKI-Based Combinations

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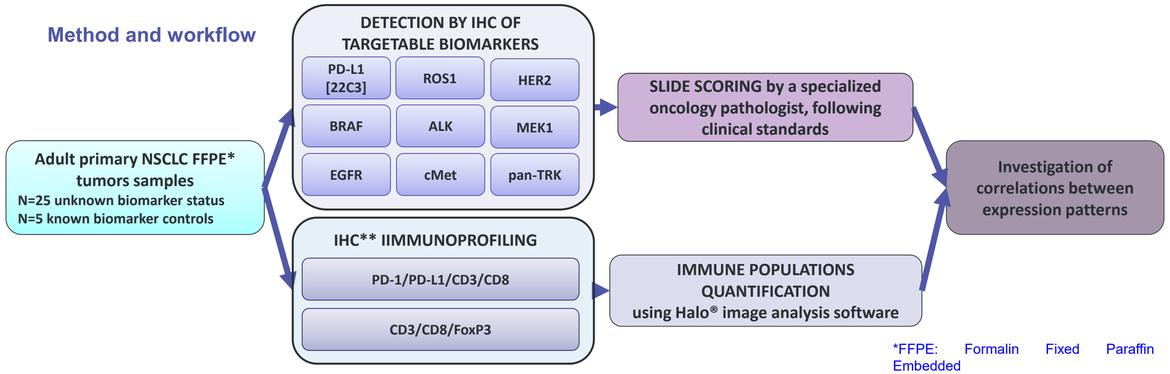
Background

Actionable mutations now guide first-line targeted therapies in non-small cell lung cancer (NSCLC), but resistance often reduces long-term effectiveness. Immune checkpoint inhibitors (ICIs) provide meaningful benefit for selected patients, and emerging evidence suggests potential synergy between targeted agents and immunotherapy—especially in tumors harboring rare biomarkers. This study investigates how actionable molecular alterations relate to the tumor immune contexture, with the goal of informing future combination treatment strategies.

Method and workflow



*FFPE: Formalin Fixed Paraffin Embedded
**IHC: Immunohistochemistry

Results: Staining of targetable biomarkers along with ICI and T-reg panels

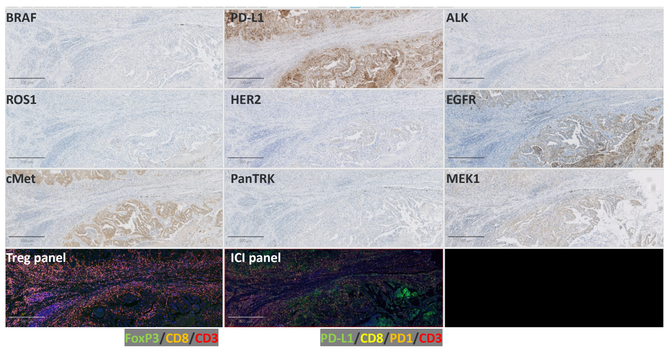


Fig 1. Example of IHC staining observed for one screened NSCLC sample of unknown target status

IHC screening of NSCLC samples provides immediate insight into potential targeted treatment options. When additional clarification is needed, reflex testing can further refine therapy selection. Integrating immune profiling through multiplex panels adds complementary information on the tumor immune contexture, helping to better predict patient response and guide more informed treatment decisions.

Table 1. Druggable and exploratory targets with pre-identified antibodies to be tested through simplex and/or multiplex IHC on NSCLC formalin-fixed paraffin-embedded (FFPE) tissue.
*Select treatments that target the specific biomarker; **ICI: immune checkpoint inhibition; ***Treg: regulatory T cells

Target		Select Rx*	Antibody Clone
PD-L1		Atezolizumab, Pembrolizumab, Cemiplimab	22C3
ICI**	CD3	/	2GV6
	CD8	/	4B11
	PD-1	Nivolumab, Pembrolizumab	EPR4877(2)
	PD-L1	Atezolizumab, Pembrolizumab, Cemiplimab	E1L3N
Treg***	CD3	/	2GV6
	CD8	/	AMC908
	FoxP3	/	236A/E7
ALK		Crizotinib, Ceritinib, Alectinib, Brigatinib, Lorlatinib	D5F3
ROS1 (+/- FISH)		Crizotinib, Lorlatinib, Entrectinib	SP364
HER2		Trastuzumab, Pertuzumab	DG44
EGFR		Erlotinib, Gefitinib, Dacomitinib, Osimertinib	3C6
Pan-TRK		Larotrectinib, Entrectinib	EPR17341
BRAF		Vemurafenib, Dabrafenib	VE1
cMET		Crizotinib, Tivantinib, Onartuzumab	SP44
MEK1		Trametinib, Binimetinib, Selumetinib	H-8

Results: Sample-specific biomarker signature

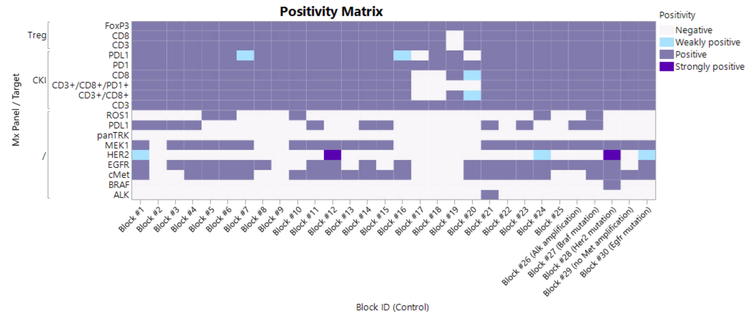


Fig 2. Positivity matrix showing biomarker positivity for each tested sample

In the 30 NSCLC samples from the Cerba Research biobank, IHC demonstrated heterogeneous biomarker expression across the cohort. Pan-TRK, BRAF, and ROS1 showed very low staining levels, preventing reliable interpretation. Although some cases displayed focal staining up to 50%, none met the criteria for true positivity, as no diffuse 2+/3+ ROS1-like patterns were observed by the reviewing international pathologist. The figure illustrates the distribution of detectable biomarkers, highlights the low prevalence of rare targets, and shows how IHC-based biomarker matrices can support more precise treatment assignment.

Results: Evaluating biomarker relationships

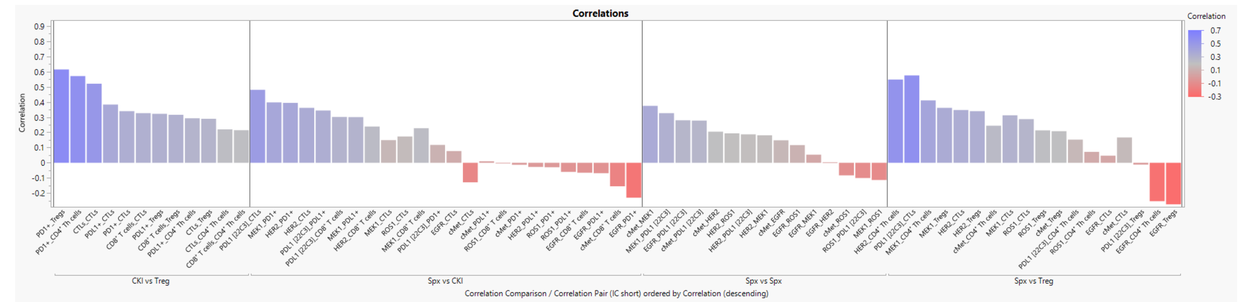


Fig 3. Correlation between the tested biomarkers per type of comparison

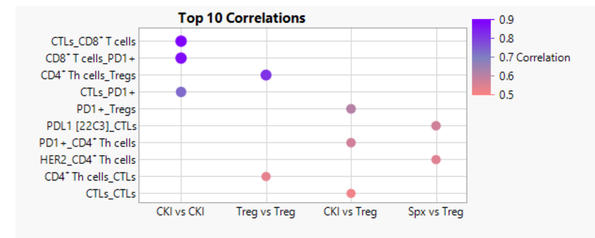


Fig 4. Top 10 correlations

A notable correlation was observed between expression MEK1 and cMet (43%), as well as between MEK1 and PD-L1 [22C3] (30%), indicating meaningful associations among phenotypes with overlapping signaling pathways. Strong relationships were also seen between PD-1$^+$ cells and both CD3$^+$/CD8$^-$/FoxP3$^+$ and CD3$^+$/CD8$^-$ T cells populations. In contrast, PD-1$^+$ cells showed weaker correlation with CD3$^+$/CD8$^+$ T cells in the Treg panel, while a clearer association emerged when analyzing the corresponding subsets within the ICI panel.

Conclusion

Targetable protein expression in the cohort largely matched published prevalence. PD-L1 showed positive associations with cMET, MEK1, and EGFR, but not with HER2. HER2 expression correlated with higher densities of helper and cytotoxic T cells, supporting reports of limited responsiveness to PD-1/PD-L1 blockade in HER2-positive NSCLC and pointing toward alternative immunomodulatory strategies. MEK1$^+$ tumor cells displayed strong correlations with infiltrating immune populations and PD-1 expression, reinforcing MEK1 inhibition as a potential approach to counter immune escape. No meaningful association was observed between PD-L1 and PD-1$^+$ cytotoxic T cells, underscoring the importance of assessing both markers independently when guiding ICI-based therapy. **IHC remains an essential, cost-effective first-line method for NSCLC biomarker screening, with reflex testing improving accuracy when needed. Adding multiplex immune profiling provides deeper insight into the tumor microenvironment, complementing actionable-target testing and helping guide more informed ICI-based combination strategies.**

References: NCCN 2025

Disclosures: M G-D, AJ, RB, JS & AF are Cerba Research employees or past employees. RG is a consultant. Study is sponsored by Cerba Research.