119 SENSITIVE PREDICTION OF IMMUNOTHERAPY RESPONSE BY INTEGRATING IMMUNE INFILTRATION AND NEOANTIGEN PRESENTATION SCORE IN LATE-STAGE MELANOMA

[1]Bailiang Li*, [1]Charles Abbott, [1]Lee McDaniel, [1]Rachel Pyke, [1]Fabio Navarro, [1]Hima Anbunathan, [2]Michael Synder, [3]Sekwon Jang, [1]Sean Boyle, [1]Richard Chen. [1]Personalis, Inc, Menlo Park, CA, USA; [2]Standford University, Palo Alto, CA, USA; [3]Inova Schar Cancer Institute, Fairfax, VA, USA

Background Single-modality biomarkers such as tumor mutational burden (TMB) often fail to reliably predict response to immune checkpoint blockade (ICB), likely due to incomplete characterization of the complex tumor-immune interactions that influence treatment efficacy. We previously developed the composite biomarker, neoantigen presentation score (NEOPS[TM]), which integrates neoantigen processing and presentation potency and showed it outperformed TMB and other single-modality biomarkers in predicting ICB response in melanoma.[1,2] Here, we combined NEOPS with the assessment of tumor immune infiltration, and demonstrated more accurate patient stratification for ICB response.

Methods We assessed the interaction effect of 17 immune and stromal cell types on NEOPS, as measured with the ImmunoID NeXT Platform®, using logistic regression in a retrospective cohort of 45 stage III/IV melanoma patients who received anti-PD1 therapy. Next, we evaluated the impact of the resulting immune-selected phenotype on the accuracy of NEOPS, built integrated models, and validated them in a cohort of 109 anti-PD1 treated late-stage melanoma.

Results The predictive value of NEOPS was increased in patients with higher levels of naïve CD4/CD8 T cell, exhausted CD8 T cell, and CD8 T cell gene expression signatures. Correlated cell signatures were further engineered into features reflecting naïve T lymphocytes (naïve CD4/8 T) and total CD8 (exhausted and CD8 T) T cell infiltrations. Both features were shown to independently boost the accuracy of NEOPS in the validation cohort (naive: $p_{interaction} < 0.05$; CD8: $p_{interaction} = 0.11$). In immune-selected patients displaying both high naive and CD8 features, NEOPS achieved an improved accuracy of 77.2% (vs 69.7% baseline performance, p<0.05) and an AUC of 0.74 (vs 0.66, p<0.1) in the validation cohort (table 1). In anti-CTLA4 treatment naïve patients, NEOPS prediction in the immune-selected group was also enhanced with an accuracy of 81.8% (vs 70.6%, p<0.05) and an AUC of 0.89 (vs 0.68, p<0.01) in the validation cohort (table 1). Integrating NEOPS with naïve and CD8 features into a single composite biomarker results in an AUC of 0.82 (cross validation: 0.78 vs 0.71).

Conclusions Identifying immune-selected patients based on cellular composition of the tumor microenvironment significantly increased the accuracy of our neoantigen-based biomarker of ICB response, NEOPS. These data highlight the potential utility of integrating tumor microenvironment data with neoantigen information into an extended composite biomarker to provide more accurate prediction of immunotherapy response.

Abstract 119 Table 1 NEOPS performances in different immune groups

		Discovery		Validation	
		Full	Immune-selected	Full	Immune-selected
All	n	45	26	109	57
	Accuracy	76%	89%	70%	77%
	AUC	0.79	0.95	0.66	0.74
	C-index (PFS)	0.68	0.74	0.58	0.62
anti-CTLA4 naive	n	36	22	68	33
	Accuracy	78%	91%	71%	82%
	AUC	0.85	0.94	0.68	0.89
	C-index (PFS)	0.69	0.73	0.59	0.61

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0119

REFERENCES

1. Abbott CW, Boyle SM, Pyke RM, McDaniel LD, Levy E, Navarro FCP, *et al*. Prediction of immunotherapy response in melanoma through combined modeling of neoantigen burden and immune-related resistance mechanisms. Clinical Cancer Research. *American Association for Cancer Research Inc.*; 2021;**27**:4265–76.
2. Pyke RM, Mellacheruvu D, Dea S, Abbott CW, Zhang S v., Phillips NA, *et al*. Precision neoantigen discovery using large-scale immunopeptidomes and composite modeling of MHC peptide presentation. Molecular and Cellular Proteomics. *American Society for Biochemistry and Molecular Biology Inc.*; 2021;20.