Sensitive prediction of immunotherapy response by integrating immune infiltration and neoantigen presentation score in late-stage melanoma

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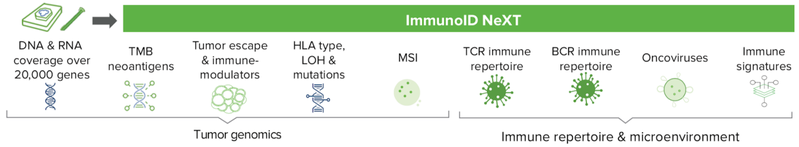
Background

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. NEOPS demonstrated increased performance over TMB and other single-modality biomarkers in predicting ICB response in melanoma [1,2]. Here, we combine NEOPS with the assessment of tumor immune infiltration and demonstrate more accurate patient stratification for ICB response.

Methods

We assessed the interaction effect of malignant cells and 16 immune and stromal cell types [3] on NEOPS, the latter as measured with the ImmunoID NeXT Platform®, using logistic regression with interaction terms 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 patients [4].



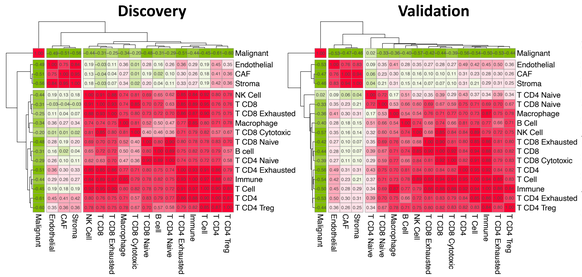
Results

Cohort demographics

A total of 45 patients with stage III to IV melanoma receiving either nivolumab, a combination of nivolumab and ipilimumab, or pembrolizumab were retrospectively collected and used as the discovery cohort. An independent cohort of 109 late-stage melanoma patients receiving anti-PD1 therapy was used as the validation cohort. The difference of key clinicopathological factors was compared. The significant differences observed in response rate may be the results of earlier disease stage, and higher immunogenicity in the discovery cohort.

	Discovery cohort (Inova)	Validation cohort	P value
Total # of patients	45	109	
# of Female (%)	13 (29)	44 (40)	0.25
Anti-PD1 therapy (%)			
Pembrolizumab	25 (56)	63 (58)	0.94
Nivolumab	20 (44)	46 (42)	
# of Responder (%)	29 (64)	41 (38)	<0.05
Stage (%)			
III	17 (40)	10 (9)	<0.01
IV	26 (60)	99 (91)	
Disease type (%)			
Skin	39 (87)	80 (73)	
Acral	3 (7)	6 (5.5)	0.12
Mucosal	2 (4)	6 (5.5)	
Occult	1 (2)	17 (16)	
NEOPS (SD)	11.42 (16.72)	4.43 (6.66)	<0.01

Cooccurrence of TME compositions

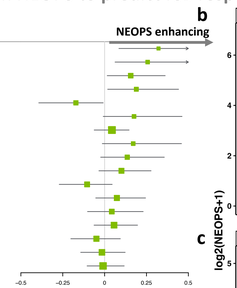


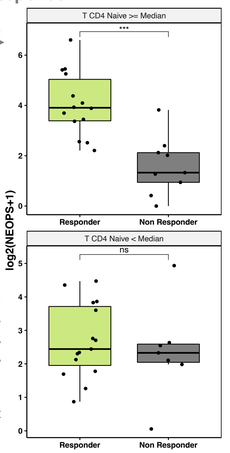
We assessed the pairwise correlations among 17 cell types in the TME. Malignant cells showed significant negative correlations with all other cell types in both cohorts. Stromal cells and immune cells exhibited consistent cooccurrence in both the discovery and validation cohorts.

The interaction effect of TME composition on NEOPS to predict ICB response

a

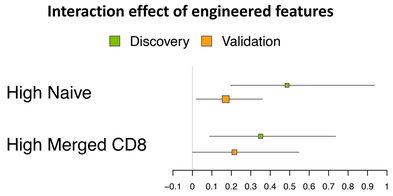
Cell Type	Interaction Coefficient (95% CI)	P
T CD4 Naive	0.32(0.09 – 0.71)	0.006
T CD8 Naive	0.26(0.06 – 0.55)	0.011
T CD8 Exhausted	0.16(0.02 – 0.36)	0.075
T CD8	0.19(0.02 – 0.44)	0.076
Stroma	−0.17(−0.39 – −0.01)	0.115
B cell	0.18(−0.01 – 0.46)	0.130
Malignant	0.04(−0.06 – 0.15)	0.198
T CD4 Exhausted	0.17(−0.01 – 0.46)	0.203
NK Cell	0.14(−0.02 – 0.36)	0.231
T Cell	0.1(−0.03 – 0.28)	0.363
CAF	−0.1(−0.27 – 0.05)	0.366
T CD8 Cytotoxic	0.07(−0.05 – 0.24)	0.380
T CD4	0.04(−0.1 – 0.23)	0.521
Immune	0.06(−0.06 – 0.2)	0.622
Endothelial	−0.05(−0.2 – 0.09)	0.733
T CD4 Treg	−0.02(−0.14 – 0.12)	0.749
Macrophage	−0.01(−0.1 – 0.12)	0.763





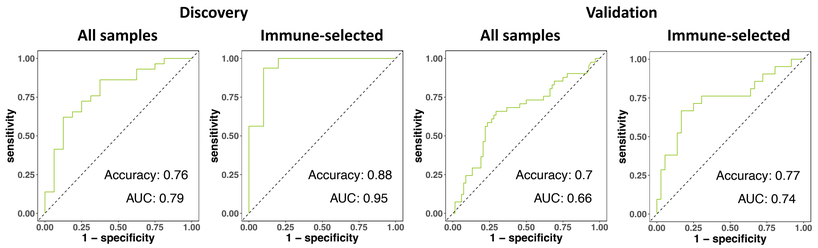
Using a logistic regression model, we assessed the interaction effect of each cell type, and how it modifies NEOPS's ability to predict ICB response in the discovery cohort (a). The likelihood ratio tests indicated the quantity of four immune cells, naïve CD4/CD8 T cells, CD8 exhausted and total CD8 T cells, can significantly improve the ability of NEOPS to predict ICB response. Panel b and c illustrate the interaction effect of naïve CD4 T cells. Interestingly, stromal components in the TME showed trends of adverse effect on the predictive strength of NEOPS, consistent with the observation that tumors with fibrotic or immune desert phenotypes benefit the least from IO therapy [5].

The interaction effect of identified features remained significant in the validation cohort

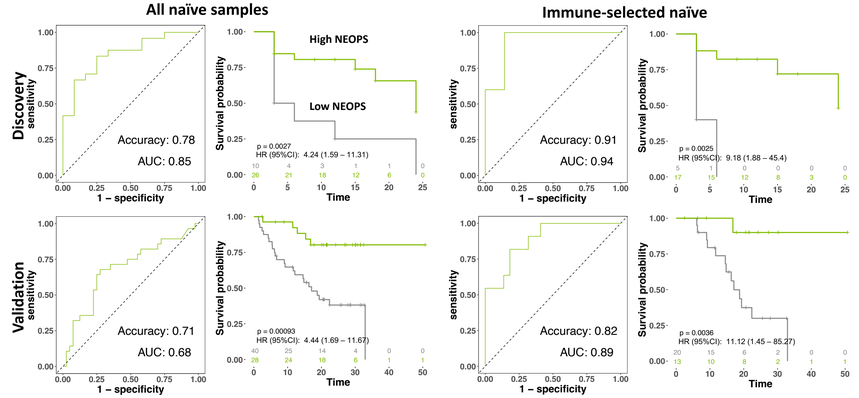


Gene signatures of naïve CD4/CD8 T cells, CD8 exhausted and total CD8 T cells were further engineered into features reflecting naïve T lymphocytes (naïve CD4/8 T) and total CD8 (exhausted and CD8 T) T cell infiltrations according to their pairwise correlations. We applied a grid search approach to identify the cutoff of each feature to stratify the patient population into 2 groups which minimize the interaction p value. The resulting features and cutoffs independently boost the accuracy of NEOPS in the validation cohort. Next, we defined the immune-selected subgroup as the patients with high levels of both features.

NEOPS achieves even better prediction of ICB response in immune-selected patients



NEOPS achieved the highest performance in the ICB treatment naïve patient subgroup



We assessed the ability of NEOPS to predict treatment response in patients without previous exposure to ICB in the discovery and validation cohorts. Accuracy of both the dichotomized NEOPS and the AUC of continuous NEOPS showed significant improvement in the immune-selected patient population. Additionally, we found that elevated NEOPS corresponded with further improved progression free survival rates and overall survival rates in both the discovery and validation cohorts.

Models integrating immune-selected phenotype and NEOPS lead to more robust and accurate prediction of ICB response

We trained a full logistic regression model which incorporates the main effects of high NEOPS and immune-selected phenotype, as well as their interaction term in the discovery cohort. Using 5-fold cross validation, we confirmed that the integrated model achieved superior predictive ability (mean AUC of 0.78) relative to the the baseline NEOPS model (mean AUC of 0.71).

Conclusion

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 which provides more accurate prediction of immunotherapy response.

Reference:

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