Composite neoantigen score is more strongly associated with therapeutic response than tumor mutational burden in a cohort of late-stage anti-PD-1-treated melanoma patients

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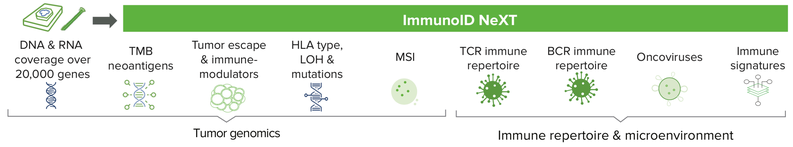
Background

Checkpoint inhibitor therapy has demonstrated meaningful, if varied, antitumor activity, with patient response influenced by a variety of biological factors, including complex interactions between the tumor and immune system. Thus, it is of increasing interest to identify composite biomarkers integrating multiple biological features to better predict immunotherapy response. In this study we use a comprehensive tumor immunogenomics profiling platform to examine the effectiveness of our composite neoantigen score for stratifying patient response to checkpoint blockade therapy compared to tumor mutational burden and other biomarkers.

Methods

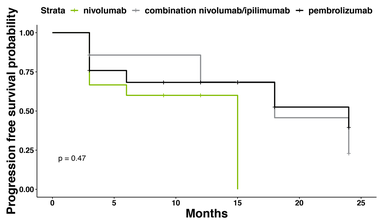
Pre-treatment tumor/normal samples from 55 unresectable, stage III/IV melanoma patients who underwent anti-PD-1 therapy were characterized to assess factors influencing response. RECIST criteria were used to evaluate tumor response to therapy, with a median follow-up of 18 months. For each patient, a single paired FFPE tumor and normal blood sample was collected and profiled using the Personalis® ImmunoID NeXT Platform®: an augmented exome/transcriptome platform and analysis pipeline, which produces comprehensive tumor mutation information, gene expression quantification, neoantigen characterization, HLA typing and allele-specific HLA loss of heterozygosity data (HLA LOH), TCR repertoire profiling and tumor microenvironment profiling. These data were then analyzed together with clinical outcome, and a composite neoantigen score computed for each patient along with other biomarkers such as tumor mutational burden (TMB).



Results

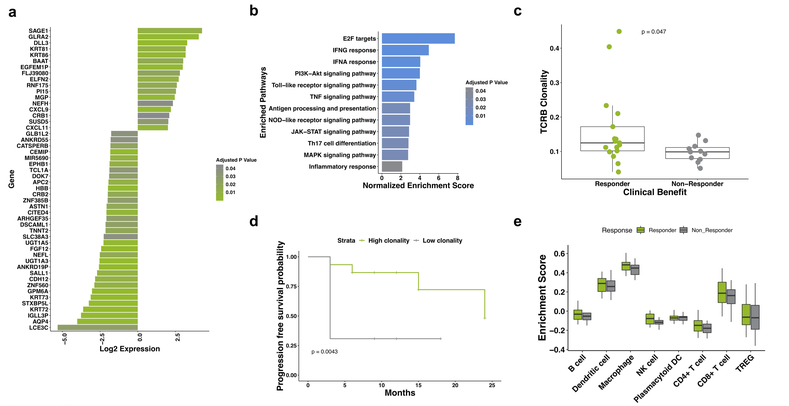
Patient demographics

n	Responder (33)	Non-responder (18)	P-value
Age at treatment	68(61-81)	66.5(56.5-76)	0.4536
Disease origin			0.9901
Acral	2(6.1%)	1(5.6%)	1
Extremity	8(24.2%)	5(27.8%)	1
Head neck	11(33.3%)	5(27.8%)	0.926
Mucosal	1(3%)	1(5.6%)	1
Trunk	1(3%)	0(0%)	1
PD1 therapy	10(30.3%)	6(33.3%)	1
Nivolumab			0.8976
Nivolumab (in combination with ipilimumab)	8(24.2%)	6(33.3%)	0.7137
Pembrolizumab	5(15.2%)	2(11.1%)	1
Sex	1(3%)	0(0%)	1
Female	19(57.6%)	10(55.6%)	1
Male			0.7513
Stage at treatment	9(27.3%)	6(33.3%)	0.8947
Unresectable III	24(72.7%)	12(66.7%)	0.8947
M1a			0.2068
M1b	1(3%)	1(5.6%)	1
M1c	5(15.2%)	0(0%)	0.2127



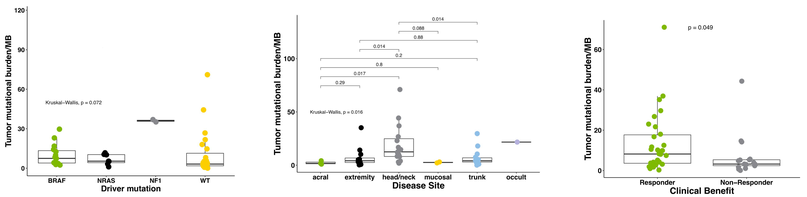
Complete demographics data were available for 51 of the 55 patients enrolled. Patient responses, as defined by standard RECIST criteria, were classified as either responder or non-responder. Few patients (n = 5) had a partial response to therapy. Analysis of progression free survival (PFS) revealed no significant variation between treatment groups.

Transcriptomic features associated with response



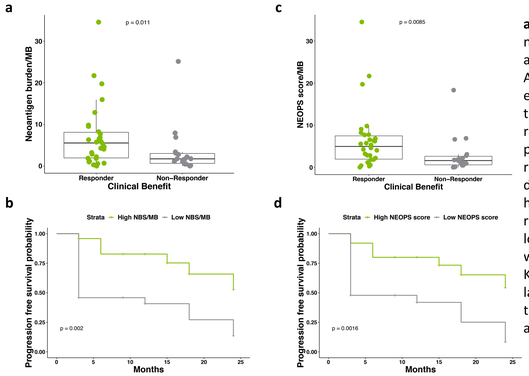
a, Genes differentially expressed in responding vs. non-responding patients. **b**, Using gene set enrichment analysis (GSEA) we identified significant enrichment of immune related pathways in responding patients, suggesting possible immune response in those individuals. **c**, Elevated TCR beta clonality is associated with therapeutic response (MWW; P=0.047). **d**, Significantly longer PFS was observed in patients with high pretreatment clonality when compared to those with low clonality (two-sided KM log-rank test; P=0.0043). High/low clonality was stratified independently for old and young populations (median cohort age used as cut point). **e**, Characterization of tumor infiltrating lymphocytes revealed no significant associations with therapy response. NK cell, natural killer cell; plasmacytoid DC, plasmacytoid dendritic cell; TREG, regulatory T cell.

Tumor mutational landscape varies with disease site and driver



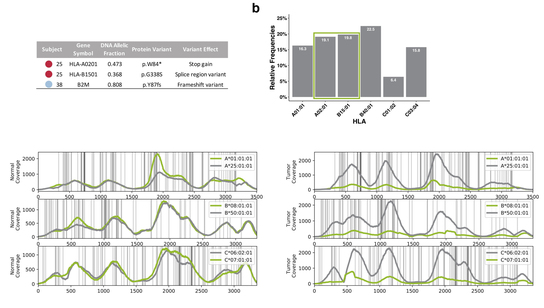
a, TMB did not vary significantly between tumors harboring different driver mutations (KW; P=0.072). **b**, TMB levels varied significantly between different melanoma subtypes and disease sites of origin (KW; P=0.016), with significant variation detected when compared with melanomas originating in the head and neck. **c**, TMB was significantly higher in responding vs nonresponding patients despite the observed sensitivity to site of disease origin (MMW; P=0.049)

Composite neoantigen presentation score demonstrates increased association with response compared to TMB or neoantigen burden alone



a, Refinement of tumor mutational information into neoantigen burden yielded a biomarker more strongly associated with response to therapy (MWW; P=0.011). Additionally, individuals with high neoantigen burden exhibit significantly longer PFS (**b**) when compared to those with low neoantigen burden (two-sided KM log-rank test; P=0.002). **c**, Composite neoantigen presentation score (NEOPS), which incorporates response and resistance mechanisms such as damaging APM mutations and HLA LOH, is significantly higher in responding patients compared to non-responding patients (MWW; P=0.0085). **d**, Significantly longer PFS was observed in patients with high NEOPS when compared to those with low NEOPS (two- sided KM log-rank test; P=0.0016). These results represent a large increase in the strength of association with therapeutic response over traditional biomarkers such as TMB.

Changes to antigen presenting machinery that may contribute to immune evasion



a, Somatic HLA mutations detected in patient 25 may lead to loss of surface expression of HLA-A02:01 and possible misfolding of HLA-B15:01. A damaging frameshift variant detected in beta-2-microglobulin (B2M) in patient 38, likely impairs all MHC class I presentation in that patient. **b**, The damaged HLA alleles identified in patient 25 are predicted to present 38.9% of their neoantigens. **c**, Allele specific HLA LOH likely results in reduced capacity for neoantigen presentation, facilitating immune escape. The left panel shows even allele specific coverage across HLAs A, B and C in normal tissue. In contrast, the right panel shows imbalanced allele specific coverage in the tumor, spanning large portions of each HLA, with reduced coverage in HLA-A01:01, HLA-B08:01 and HLA-C07:01, indicating HLA LOH in this patient.

Conclusion

In summary, our composite neoantigen score, which integrates multiple components of MHC class I presentation into a single score, is more significantly associated with response to therapy than individual biomarkers such as tumor mutational burden. These findings highlight the promise of composite biomarkers for the optimization of anti-PD-1 therapy patient selection.

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