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Overexpression of Immunotherapeutic Targets in the Immune Desert Phenotype

The right drug or right trial…
For Every Patient

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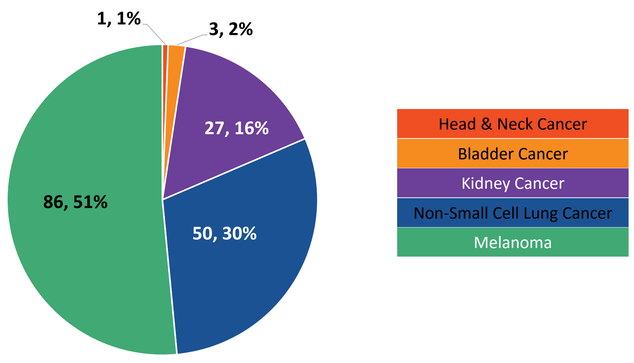
Introduction

Immunotherapy using checkpoint blockade with monoclonal antibodies has gained increasingly high importance in treatment for cancer patients. However, a large proportion of cancer patients do not highly express cancer immune response biomarkers such as PD-1/PD-L1, MSI, and mutational burden, which have been associated with response. Here we present immune-related expression signatures for patients that present with an immune desert phenotype, distinguished by lack of CD8 positive T-cells and characteristic T-cell receptor signaling expression levels. As part of our clinical immune cell analysis assay, Immune Report Card℠ (IRC), we identified immunotherapeutic targets that are singularly expressed in the otherwise non-inflamed tumor microenvironment, and are potential clinical immunotherapy targets.

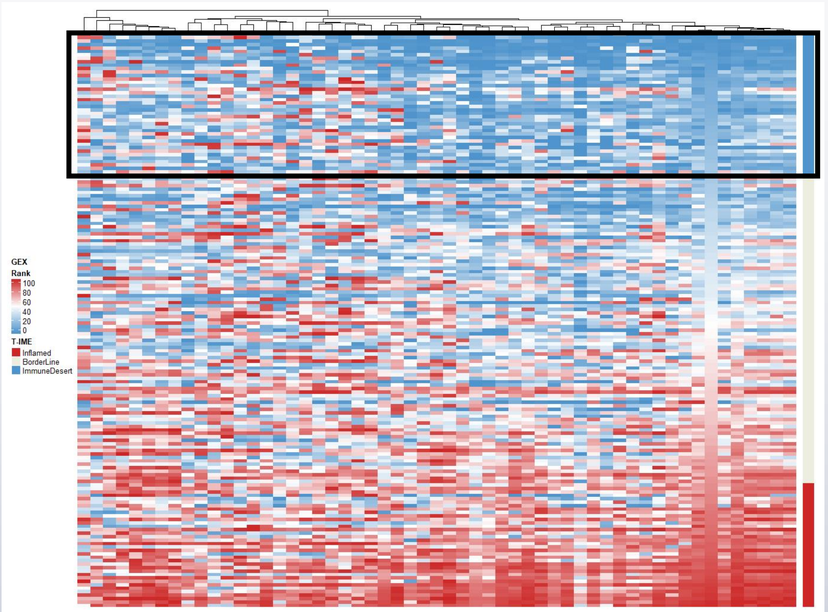
Methods

167 formalin-fixed, paraffin-embedded (FFPE) cancer samples of diverse histologies were evaluated by the RNA-seq component of IRC to measure transcript levels of genes related to T-cell receptor signaling and tumor infiltrating lymphocytes.



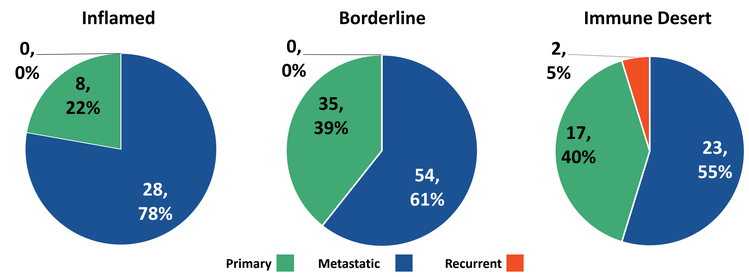
Resultant data was QC filtered, normalized and ranked based on an assorted reference population of various tumor types. Gene signatures were determined using these ranked expression values with a rank value > 85th percentile considered high. Tumors are also defined as inflamed, borderline, or non-inflamed based upon RNA-seq analysis of CD8, wherein, tumors ≥ 75th percentile of rank for CD8 are considered inflamed, while those ≤ 25th percentile are considered non-inflamed (>25th to <75th percentile are considered borderline).

Immune GEX Landscape

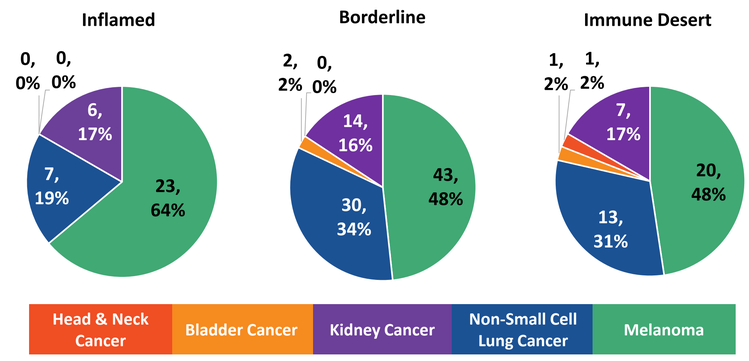


Supervised hierarchical clustering based on CD8 gene expression. Stratification of 167 samples (rows) across 395 genes (columns) measured as part of the RNA-seq component of IRC. Black box denotes the ≤ 25th percentile of tumors with low CD8+ expression representing the Immune Desert phenotype used to interrogate immunotherapeutic targets.

Stratification based on CD8 Phenotypes

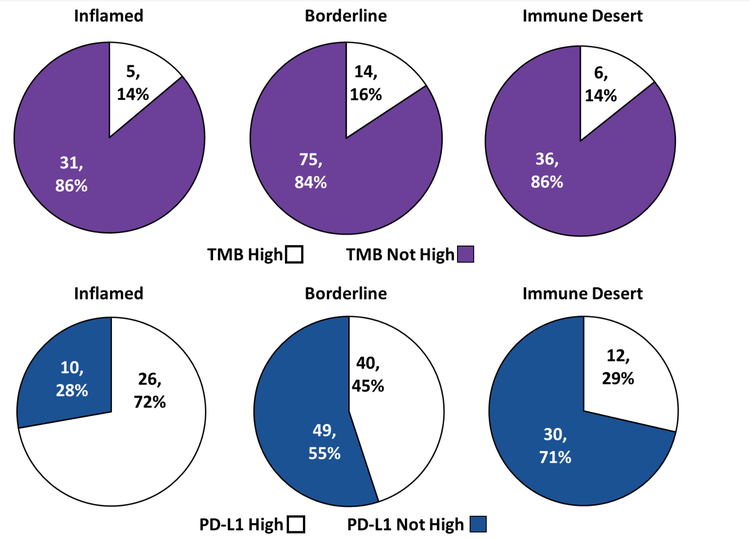


Stratification of PMR status across three distinct CD8 phenotypes with non-significant correlation to any given tumor phenotype and CD8 status.



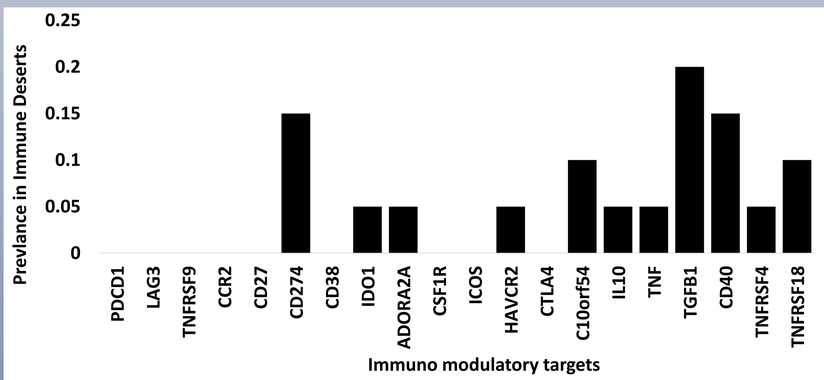
Tumor types present in each of the three CD8 phenotypes. Even distribution of Kidney, NSCLC, and Melanoma across CD8 categories with H&N and Bladder being under represented due to low number of these histologies.

Response Markers



Interrogation of response biomarkers (tumor mutational burden upper panel, PD-L1 IHC lower panel) versus CD8 gene expression status. TMB High as measured by DNA-seq did not correlate with any specific CD8 phenotype. PD-L1 status was highest (72% of samples) within the inflamed phenotype and lowest in Immune Desert (29% of samples).

Immunotherapeutic Targets



Identification of immunotherapeutic targets in the Immune Desert phenotype as defined by CD8 expression. These immune biomarkers are potential checkpoint inhibitor therapy targets.

Conclusions

Immune Report Card allows for the profiling of the tumor immune microenvironment to delineate underlying immune biology of solid tumor samples. With a significant number of non-inflamed tumors lacking high expression of any immune biomarker, IRC results suggests that an underlying biological immune ignorance state exists in the tumor microenvironment of many patients. However, IRC could identify so-called “oasis” targets that could be potentially targeted with mono or combination immune therapy in the immune desert phenotype. With the ever-increasing numbers of FDA-approved therapies and clinical trials, IRC offers a robust tool to identify patients that might benefit from these options.