Immune Deserts: Low CD8 Gene Expression Correlates with Non-response to Checkpoint Inhibition

The right drug or right trial…
For Every Patient

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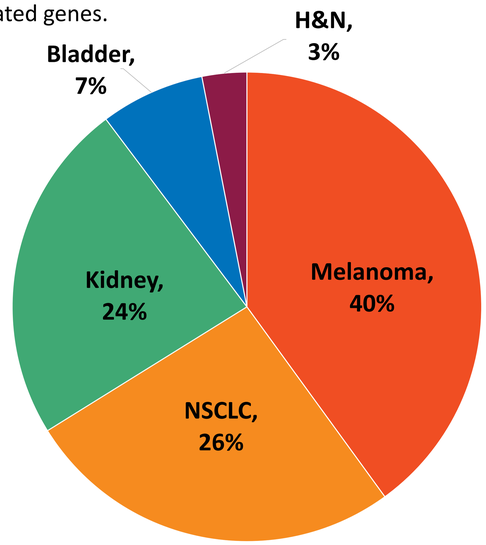
Introduction

Associations between presence and density of effector T-cells (CD8+) and response to checkpoint inhibitors (CPIs) has been established for protein biomarkers using immunohistochemistry but less work has been done to characterize this relationship through gene expression.

We hypothesized that patients with in the bottom quartile of CD8 expression, as measured by the rank of the sum of normalized CD8A and CD8B transcripts compared to a reference population, would be unlikely to respond to checkpoint therapy (immune deserts), and that "hot" tumor environments (TME) with the highest quartile of expression would be most likely to respond.

Methods

193 formalin-fixed, paraffin-embedded (FFPE) cancer samples of diverse histologies from patients treated with one or more FDA-approved checkpoint inhibitors were evaluated by the RNA-seq component of a comprehensive immune profiling panel to measure transcript levels of 394 immune related genes.

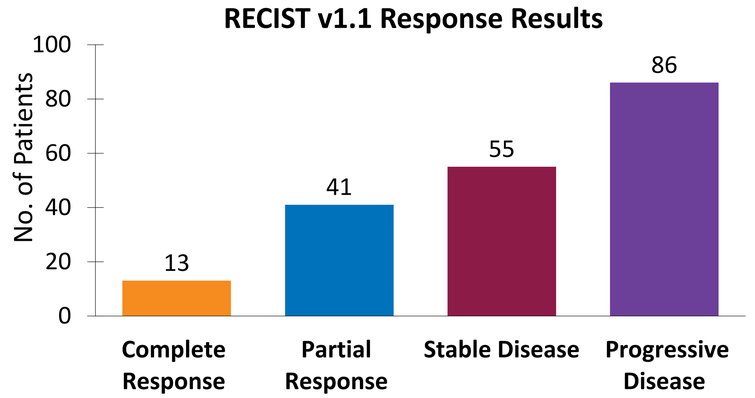


Resultant data was QC filtered, normalized and ranked based on an assorted reference population of various tumor types. Gene signatures were determined using these ranked expression values with a rank value > 85th percentile considered high. Tumors are also defined as inflamed, borderline, or non-inflamed 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).

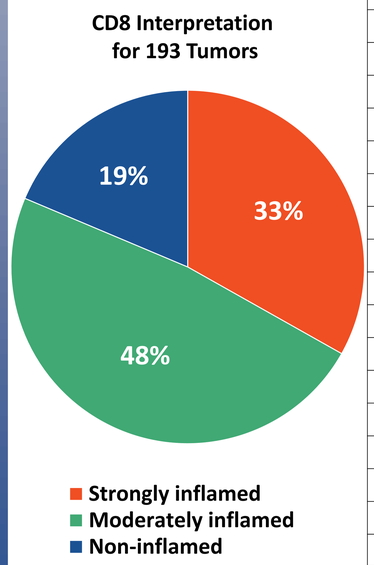
Response data (RECIST v1.1) was collected and patients with CR, PR or SD were considered as clinical benefit.

CPIs & Overall Response

FDA Approved Checkpoint Inhibitors Used in Study	
Checkpoint Inhibitor	**No. (%)**
Nivolumab	85 (44%)
Pembrolizumab	50 (26%)
Ipilimumab	35 (18%)
Ipilimumab + Nivolumab	21 (11%)
Atezolizumab	4 (2%)

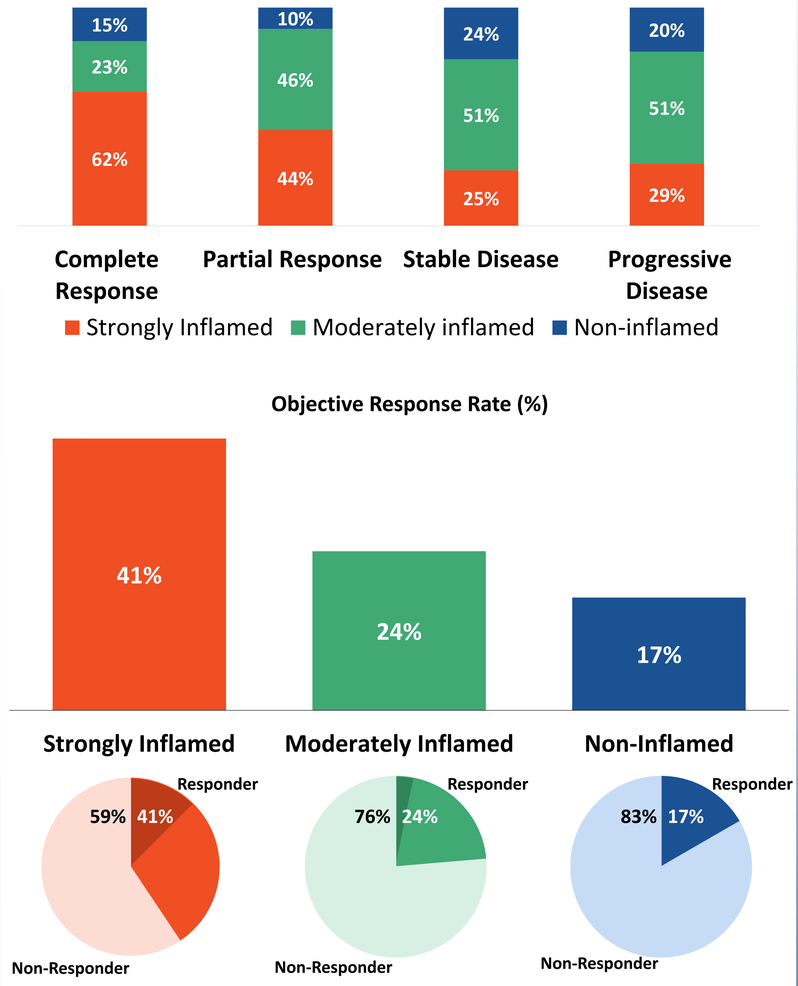


Stratification of CD8 Phenotypes



No. (%)	Tumor Type	CD8 Interpretation
3 (21%)	Bladder	Non-Inflamed
7 (50%)	Bladder	Moderately Inflamed
4 (29%)	Bladder	Strongly Inflamed
0 (0%)	H&N	Non-Inflamed
5 (100%)	H&N	Moderately Inflamed
0 (0%)	H&N	Strongly Inflamed
6 (13%)	Kidney	Non-Inflamed
23 (50%)	Kidney	Moderately Inflamed
17 (37%)	Kidney	Strongly Inflamed
19 (24%)	Melanoma	Non-Inflamed
30 (39%)	Melanoma	Moderately Inflamed
29 (37%)	Melanoma	Strongly Inflamed
8 (16%)	NSCLC	Non-Inflamed
28 (56%)	NSCLC	Moderately Inflamed
14 (28%)	NSCLC	Strongly Inflamed

CD8 & Response



Conclusions

- Immune deserts, or "cold" tumors, which represent slightly less than one-fourth of total cases among the most immunogenic tumor types, have a much lower response to CPIs than "hot" tumors.
- Strongly inflamed tumors represent an estimated one-third of tumors among the most immunogenic tumor types, with and objective response rate almost 3x that of "cold" tumors, which is very similar to the difference in PD-L1 positive and negative lung cancer.
- CD8 should be considered as a viable marker of response in checkpoint inhibition therapy.