The Inflamed Phenotype in PD-L1 Negative NSCLC and Response to Checkpoint Inhibitors

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Background

NSCLC with a PD-L1 tumor proportion score (TPS) by immunohistochemistry (IHC) of greater than 50 has a positive predictive value (PPV) of 42% for response to pembrolizumab. Across all tumor types and different checkpoint inhibitors (CPIs), the evidence supports that the inflamed phenotype is associated with response. Currently very little is known about predicting response to CPIs in PD-L1 negative NSCLC. Additionally, the association of the PD-L1 negative NSCLC with the inflamed phenotype has not been well described. In this study we evaluated the expression of PD-L1 in the context of CD8 expression using a DNA and RNA-seq panel of 400 genes applicable to next generation sequencing (NGS).

Methods

PD-L1 (22C3) IHC and a custom NGS cancer immune gene expression (GEX) assay were used to interrogate 50 NSCLC samples of which 21 were treated with one or more CPIs. RNA-seq analysis was previously validated such that high PD-L1 GEX coincided with a TPS >30% IHC. Overexpression of CD8 was considered positive for the inflamed phenotype. RECIST v1.1 was used to assess patient response.

Immune Response NGS Workflow

Traditional Biomarkers (50 samples)

Eleven (11) samples with high PD-L1 IHC for which 5 were inflamed and 6 non-inflamed. For the 39 samples without high PD-L1, 14 were inflamed and 25 non-inflamed.

Six (6) samples with a high MuB for which all were non-inflamed.

Additional Checkpoint Blockade Biomarkers

Five (5) samples with high PD-1 GEX for which 4 were inflamed and 1 non-inflamed. For the 45 samples without high PD-1, 15 were inflamed and 30 non-inflamed.

Six (6) samples with high TIM3 GEX for which 5 were inflamed and 1 non-inflamed. For the 44 samples without high TIM3, 14 were inflamed and 30 non-inflamed.

Four (4) samples with high BTLA GEX for which 3 were inflamed and 1 non-inflamed. For the 46 samples without high BTLA, 16 were inflamed and 30 non-inflamed.

Ten (10) samples with high VISTA GEX for which 4 were inflamed and 6 non-inflamed. For the 40 samples without high VISTA, 15 were inflamed and 25 non-inflamed.

One (1) sample with high LAG3 GEX which was inflamed. For the 49 samples without high LAG3, 18 were inflamed and 31 non-inflamed.

Response and Single Biomarkers (21 patients)

Response and Combined Biomarkers (21 patients)

Conclusions

- High PD-L1 does not define an inflamed phenotype.
- MuB was more common in a non-inflamed phenotype.
- High expression of other checkpoint blockade targets does not define an inflamed phenotype.
- MuB and single or combined markers of checkpoint blockade do not define response.
- Response to checkpoint inhibitors is more complex than analysis of single biomarkers such as PD-L1 expression or mutational burden.