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Background

Cell proliferation is an important marker of survival in many tumors, and we hypothesized that this attribute could be related to response to immune checkpoint inhibitors (ICIs) in RCC. Previously we reported (PMID: 30709424) that moderately proliferative lung cancer have a much higher response rate to checkpoint inhibitors than either poorly or highly proliferative tumors.

Methods

64 FFPE tumor samples of RCC from patients previously treated with nivolumab were evaluated by PD-L1 IHC (22C3) and RNA-seq to measure transcript levels of 394 immune related genes. Cell proliferation was defined as the mean mRNA expression of 10 genes (*BUB1, CCNB2, CDK1, CDKN3, FOXM1, KIAA0101, MAD2L1, MELK, MKI67, TOP2A*) which was evaluated for association with ORR to ICIs by RECIST v1.1 criteria for both PD-L1 IHC positive and negative cases. Cell proliferation for each case was split into 3 tertiles of poorly (<33), moderately (33-66) and highly (>66) proliferative versus a reference population. Poorly and highly proliferative were grouped for comparison to moderately proliferative tumors. PD-L1 IHC was performed using DAKO 22C3 antibody and scored by FDA guidelines for both tumor proportion score (TPS) and combined positive score (CPS). Tumors were considered positive if TPS or CPS ≥1% and negative if <1%.

Immune Expression Signature in RCC

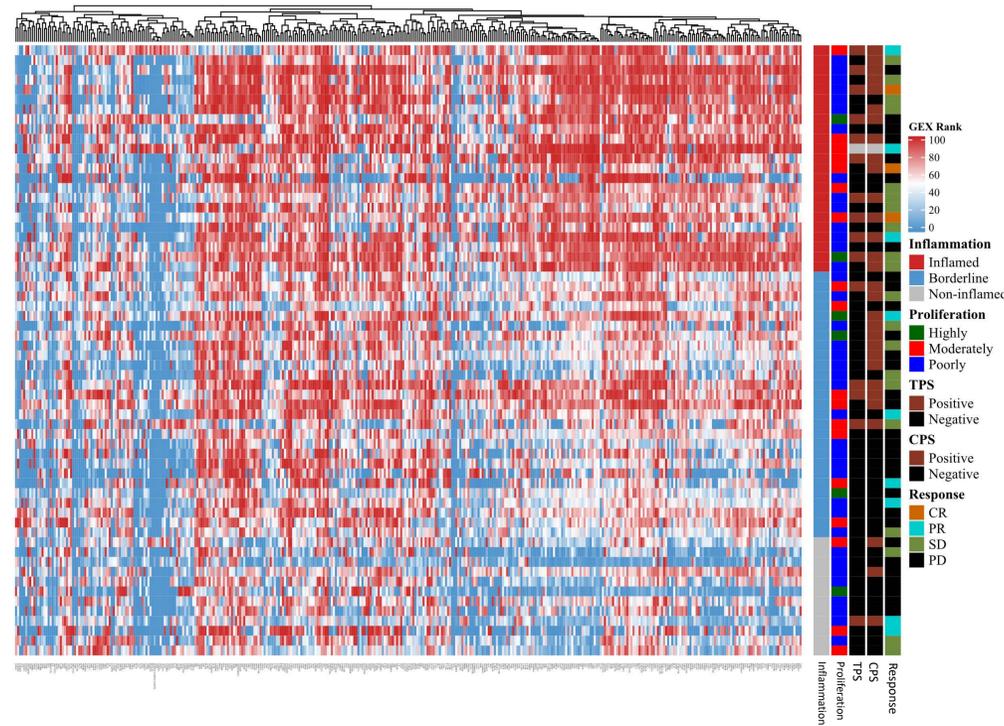


Figure 2: Unsupervised clustering of 395 immune gene expression signature sorted by inflammation status with PD-L1 IHC (TPS & CPS), cell proliferation as well clinical annotations of response to nivolumab.

Response to Nivolumab and Tumor Inflammation

Non-Inflamed Tumors Highly Inflamed Tumors

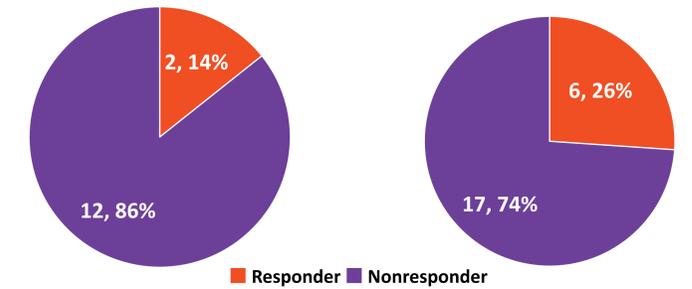


Figure 4: Response to nivolumab is not significantly different between highly and non-inflamed tumors. In inflamed tumors the ORR was 26% (6/23), compared to non-inflamed tumors of 14% (2/14) (Chi square test $p = 0.6643$).

Response to Nivolumab and Cell Proliferation

Moderately proliferative inflamed & non-inflamed tumors Highly and poorly proliferative inflamed & non-inflamed tumors

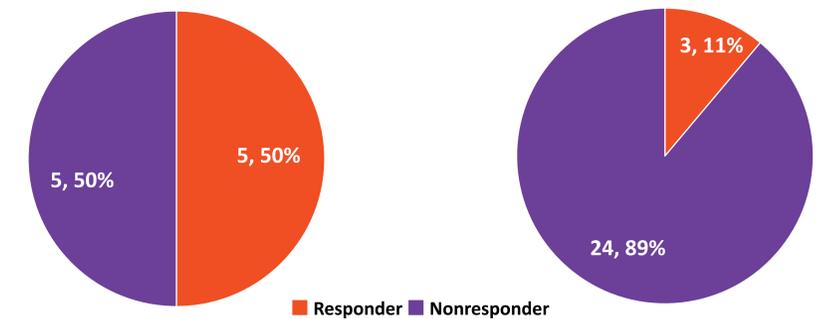


Figure 5: Response to nivolumab is significantly different between moderately proliferative at 50% (5/10), versus that of highly and poorly proliferative combined at 11% (3/27) (Chi square test $p = 0.03553$).

Cell Proliferation and Tumor Inflammation

Non-Inflamed Tumors Highly Inflamed Tumors

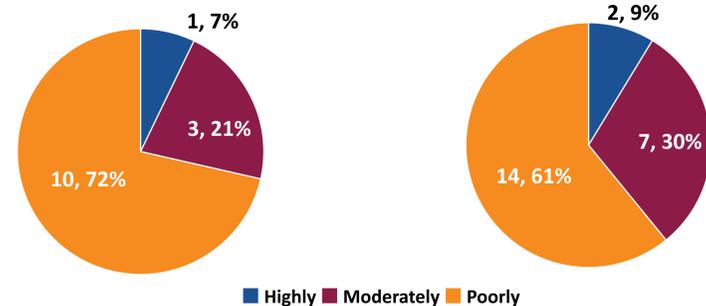


Figure 3: Proliferation is not significantly different between highly and non-inflamed tumors. For the 14 non-inflamed tumors the majority (10/14; 71.4%) were poorly proliferative, and with 3/14 (21.4%) moderately and 1/14 highly proliferative. For the 23 inflamed tumors the majority (14/23; 60.9%) were also poorly proliferative, and with 7/23 (30.4%) moderately and 2/23 highly proliferative.

Results and Conclusions

- A distinct inflammation signature highly correlated with CD8 gene expression signature is observed in 64 RCC cases.
- Proportions of cell proliferation categories were not significantly different between highly inflamed and non-inflamed RCC cases.
- Although inflammation status itself did not present with significantly different response to nivolumab, however, the cell proliferation for both inflammation types showed significant difference in response to nivolumab in RCC.

Figure 1: Study design