Cell proliferation as a biomarker for response to immune checkpoint inhibitors in PD-L1 negative renal cell carcinoma

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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%.

Results and Conclusions

For 64 RCC there were 28% moderately proliferative tumors (18/64), while the majority were poorly proliferative tumors (40/64; 62.5%) and with highly proliferative being uncommon (6/64; 9.4%). A. The rate of PD-L1 positive results in this study was very similar to prior clinical trials, with PD-L1 TPS status was positive in 25.4% (15/63), B. PD-L1 CPS was positive (CPS ≥1%) in 47.6% (30/63).

Figure 2: A. For 64 RCC there were 28% moderately proliferative tumors (18/64), while the majority were poorly proliferative tumors (40/64; 62.5%) and with highly proliferative being uncommon (6/64; 9.4%). B. The rate of PD-L1 positive results in this study was very similar to prior clinical trials, with PD-L1 TPS status was positive in 25.4% (15/63), C. PD-L1 CPS was positive (CPS ≥1%) in 47.6% (30/63).

Overlap of Cell Proliferation and PD-L1 IHC

Figure 3: A. Moderately proliferative tumors had a statistically higher number of PD-L1 positive results (41.2%, 7/17), as compared to poorly proliferative tumors (15%, 6/40) by TPS scoring (p = 0.03), B. but not by CPS scoring (p = 0.19).

Figure 4: A. Patients with PD-L1 positive tumors have 2x or higher objective response rate for either TPS (positive 33.3%, 5/15; negative 12.5%, 6/48) or B. CPS (positive 23.3%, 7/30; negative 12.1%, 4/33) method of scoring, but statistical significance was not reached with either (p = 0.06, 95% CI 0-46, p = 0.24, 95% CI 0-30, respectively). C. Objective response for moderately proliferative (6/18, 33.3%) tumors was higher than that of their poorly (5/40, 12.5%) proliferative counterparts, but not statistically significant (p = 0.06, 95% CI 0-46). D. Statistically significant results were achieved when cell proliferation and negative PD-L1 TPS were combined (p = 0.03, 95% CI 0-54), showing that patients with poorly proliferative and PD-L1 negative tumors have a very low response rate (2/34, 6%) as compared to their moderately proliferative counterparts (3/10, 30%).

Results and Conclusions

- Poorly proliferative RCC tumors with lack of expression of PD-L1 in neoplastic cells is associated with a very limited clinical response to nivolumab.
- Assessing the expression levels of ten proliferation-related genes by RNA-seq stands out as a promising strategy for improving clinical decision making for nivolumab versus combination therapies.