Cell Proliferation Defines an Additional Mechanism of Immune Escape in Non-Small Cell Lung Cancer

Prior to this study, the most important mechanisms of immune escape in NSCLC include checkpoint blockade and low tumor mutational burden (TMB). Resistance to immune checkpoint inhibitors (ICIs) has been linked to local immunosuppression independent of major ICI targets (e.g., PD-1). Clinical experience with response prediction based on PD-L1 expression suggests that other factors influence sensitivity to ICIs in non-small cell lung cancer (NSCLC) patients. In this study, we have identified a third equally important mechanism of immune escape of cell proliferation in NSCLC.

A) Tumors were classified into poorly, moderately and highly based on the tumor cell density of this gene signature as compared to a separate reference population of 167 patients with multiple tumors. Based on this analysis, poorly proliferative tumors were the least frequent (21/167, 12.6%), followed by an equal distribution of highly (47/167, 27.9%) and moderately proliferative tumors (40/167, 23.8%). B) PD-L1 TPS, defined as the percentage of neoplastic cells displaying membranous positivity of any intensity staining with the DAKO 22C3 antibody, ranged from 0 to 120 and 32/167 (20.0%) of all cases were PD-L1 TPS ≥ 50, while 67/120 (55.8%) of all cases were PD-L1 TPS ≥ 1%.

A) The survival analysis for PD-L1 as a positive result for TPS ≥ 50% tumors showed very similar results to TPS ≥ 50% whereby moderately proliferative tumors with a median survival of 14.6 months was almost twice that of PD-L1 TPS ≥ 1% (p = 0.038). There was a slight difference with a greater differential for median survival in moderately proliferative PD-L1 TPS > 1% tumors at 12.6 months to that of high/poorly proliferative PD-L1 TPS ≥ 1% at 9.8 months (p = 0.086), but in both instances less than that of moderately proliferative PD-L1 TPS ≥ 50% tumors.

Conclusions

- A highly or poorly proliferative tumor microenvironment is associated with limited sensitivity to ICIs amongst NSCLC patients.
- Moderately proliferative tumors, both PD-L1 positive and negative, showed enhanced sensitivity to ICIs with greater effect seen with weakly PD-L1 positive and negative tumors.
- A combination of cell proliferation and PD-L1 IHC status may be an important predictor of overall survival in ICI treated patients.