3017 NSCLC with high PD-L1 expression on tumor cells or tumor-infiltrating immune cells represents distinct cancer subtypes

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Background: Programmed death-ligand 1 (PD-L1) expression on tumor cells (TC) or tumor-infiltrating immune cells (IC) is associated with OS, PFS and ORR in pts with advanced NSCLC treated with atezolizumab (anti-PDL1, MPDL3280A; Spigel et al, Spira et al, ASCO 2015), indicating that PD-L1 expression on both TC and IC is important for anti-tumor immunity. However, these 2 distinct expression patterns suggest the existence of previously unidentified NSCLC subtypes with distinct immunologic profiles.

Material and Methods: Pre-treatment NSCLC specimens from atezolizumab trials (n = 498) and a non-trial cohort (n = 706) were evaluated for PD-L1 expression on TC and IC using the SP142 IHC assay. Specimens were scored as TC0–3 and IC0–3 based on increasing PD-L1 expression. A subset of samples was further characterized by histopathologic review, gene expression, mutational load and epigenetic analysis.

Results: TC3 or IC3 tumors, which have the highest PD-L1 expression, represented ~20% of NSCLC and were similarly distributed between squamous and non-squamous NSCLC. Strikingly, TC3 and IC3 tumors represented 2 distinct populations, with <1% overlap. IC3 tumors had a high frequency of immune infiltrates localized to the stroma, tumor and tumor/stroma interface. IC3 tumors exhibited higher expression of Teff signatures than TC3 tumors, suggesting that PD-L1 on IC reflects pre-existing active T-cell immunity. TC3 tumors, on the other hand, exhibited distinct histopathologic characteristics, including a dense desmoplastic and sclerotic tumor microenvironment. TC3 tumors had a lower frequency of immune infiltrates than IC3 tumors, which, when present, were primarily located in surrounding stroma. TC3 tumors were also characterized by increased expression of genes associated with epithelial-mesenchymal transition (eg, Snail1, ZEB1 and vimentin) and molecular markers of desmoplasia, including collagen VI. A clear inverse correlation was seen between methylation of 2 non-canonical CpG sites, near STAT3 consensus binding regions, within the PD-L1 promoter and PD-L1 expression in TC, suggesting that PD-L1 expression may be influenced by epigenetic regulation rather than by T-cell-derived cytokines. Despite their different immunologic profiles, however, both IC3 and TC3 subtypes were highly responsive to treatment with atezolizumab.

Conclusions: These data suggest that PD-L1 expression is regulated by different mechanisms in TC and IC. In addition, NSCLC can be classified into previously unidentified, distinct molecular and histopathologic subsets that define sensitivity to PD-L1-targeted therapy. Expression of PD-L1 on TC and/or IC confers sensitivity to atezolizumab, despite exhibiting distinct immunologic profiles. These results emphasize the non-redundant roles played by PD-L1 expression by IC and TC in regulating cancer immunity and response to therapy.