Background

Immune checkpoint inhibitors (ICIs) have become standard of care in NSCLC. Programmed death ligand-1 (PD-L1) as measured by immunohistochemistry (IHC) is an accepted biomarker for predicting response but has many limitations. We previously described the 27-gene IO assay as a classifier of the tumor immune microenvironment (TIME) and its association with response to immune checkpoint inhibitor (ICI) therapy in multiple tumor types. We explore here the utility of CD274 expression as a biomarker and determine its contribution with the 27-gene IO assay in terms of their association with efficacy to ICI therapy in NSCLC.

Methods

Fifty-nine late-stage NSCLC FFPE specimens were obtained with one-year PFS and PD-L1 IHC tumor proportion score (TPS-22c3) status. The CLIA-validated 27-gene RT-qPCR IO assay was run to produce the IO score and CD274 mRNA expression was quantified by RT-qPCR. A generalized linear model was created using CD274 expression and PD-L1 IHC positivity (≥1%), then plotted to measure AUC. The optimal threshold for CD274 expression was determined by the Closest-topleft method. Cox proportional hazard ratios (HRs) were calculated for IO score, PD-L1 IHC, and binary CD274. A model combining IO score and CD274 at the 100% specificity threshold was also analyzed.

Results

The optimal CD274 threshold was found at 82% sensitivity by AUC. The IO score and the CD274, but not PD-L1 IHC, were significantly associated with 1-year PFS (IO score, HR=0.24; p=0.001, 32/59 positive; CD274, HR=0.33; p=0.009, 46/59 positive; PD-L1 IHC HR=0.76; p=0.6; 45/59 positive). Both CD274 and PD-L1 IHC were approximately 77% positive with 75% agreement between classifiers. In a bivariate analysis of IO score and CD274, only the IO score retained significance (HR=0.28, p=0.01; HR=0.48, p=0.12, respectively), demonstrating IO score independence from CD274 expression. Modeling of an algorithm combining IO score with the CD274 mRNA threshold set at 100% specificity was also analyzed.

Conclusions

Quantification of CD274 mRNA expression is correlated with PD-L1 IHC expression. Although the CD274 model outperformed PD-L1 IHC for one-year PFS, it failed to retain significance with IO score. Combining IO score with a more stringent CD274 threshold led to modest improvement in its association with one-year PFS. Together, these data demonstrate measuring CD274 mRNA may help to better inform clinical decision making and help contribute to a better understanding of the TIME.

REFERENCES


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