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Intercomparison of PD-L1 expression measured with direct mRNA counting and immunohistochemistry in advanced NSCLC

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Background

Programmed death-ligand 1 (PD-L1) protein expression tested with immunohistochemistry (IHC) is currently accepted to select advanced NSCLC patients who are candidates for immune check-point (PD-1/PD-L1) inhibitor therapy. However, the use of various antibodies and cut-offs as well as the certain degree of subjectivity in pathological evaluation has overshadowed the clear-cut predictive performance of PD-L1 expression. NanoString's nCounter multiplexed gene expression technology is an alternative method to measure *PD-L1* gene expression by digital counting proving a direct measurement of mRNA levels.

Objectives

We aimed to correlate PD-L1 protein expression evaluated by IHC with *PD-L1* mRNA expression measured with direct digital counting (nCounter) in an advanced cohort of NSCLC patients.

Methods

A 7-gene 'immune signature' comprising *CD4, CD8,* programmed cell death-1 *(PD-1),* programmed death-ligand 1 *(PD-L1)*, interferon gamma *(IFNG)*, granzyme M *(GZMM)* and forkhead box P3 (*FOXP3)* was included in a customized nCounter panel (NanoString Technologies), used in our institution on a routine basis to simultaneously screen for relevant oncogenic-drivers (*ALK*, *ROS1*, *RET*, *NTRK1* gene fusions and *MET*^{e14} mutations). Total RNA obtained from formalin-fixed paraffin embedded (FFPE) samples was used for *PD-L1* digital counting (NanoString's nCounter) and compared with PD-L1 protein IHC evaluation using whole tissue section with 22C3 monoclonal mouse anti–PD-L1 antibody measured on tumor cells (TPS).

Results

Since 2017, a total of 296 FFPE samples were analyzed with the nCounter panel. Among them, PD-L1 IHC staining was performed in 113 FFPE samples, as requested by the oncologist and used for final comparison. All samples were evaluable for nCounter and IHC (100%). By IHC, 48/113 samples (42.5%) were scored as negative for PD-L1 protein expression, whereas 65/113 (57.5%) were evaluated as positive. Among positive samples, 39 (34.5%) and 26 (23%) presented moderate ($\geq$ 1-49%) and high (≥50%) TPS, respectively. Using an appropriate cut-off value, PD-L1 mRNA expression levels determined by nCounter panel closely correlated the PD-L1 IHC evaluation, with a 78% of concordance and a 0.554 Cohen's kappa (confidence interval 95% 0.400- 0.709).

Conclusions

PD-L1 mRNA gene expression shows promising in predicting PD-L1 protein expression in NSCLC. Further clinical validation is ongoing to confirm if *PD-L1* gene expression by nCounter can be an alternative to IHC to select patients' candidates for immune check-point inhibitors.

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