Editorial

Histology versus cytology: PD-L1 testing in non-small cell lung cancer

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Comment on: Torous VF, Rangachari D, Gallant BP, *et al.* PD-L1 testing using the clone 22C3 pharmDx kit for selection of patients with non-small cell lung cancer to receive immune checkpoint inhibitor therapy: are cytology cell blocks a viable option? J Am Soc Cytopathol 2018;7:133-41.

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Immune checkpoint inhibitors (ICIs) such as nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab have been developed to treat malignant tumors, including non-small cell lung cancer (NSCLC). ICIs inhibit programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) signaling between tumor cells expressing PD-L1 and cytotoxic T lymphocytes expressing PD-1. In the first-line treatment of advanced NSCLC, pembrolizumab monotherapy was more effective than standard chemotherapy in patients with high PD-L1 expression (≥50% tumor cells) (1). While pembrolizumab is approved for PD-L1-positive tumors (≥1%) (2), nivolumab and atezolizumab can be used regardless of PD-L1 expression in salvage treatment for NSCLC (3-5). In locally advanced NSCLC, the progression-free survival was significantly longer with durvalumab than with placebo after concurrent chemoradiation, irrespective of PD-L1 expression (6). Although avelumab as second-line treatment did not improve the overall survival in patients with PD-L1-positive (≥1%) NSCLC, the survival was significantly prolonged in those with high PD-L1 expression (≥50%) (7).

The PD-L1 expression has been evaluated using PD-L1 immunohistochemistry (IHC) assays (*Table 1*) (8). The blueprint (BP) 1 and BP2 studies compared four and five IHC assays, respectively, for companion or complementary diagnostics to select the patients for treatment. The BP1 study showed that 22C3, 28-8, and SP263 gave similar percentages of positive tumor cells, whereas fewer tumor cells stained using the SP-142 assay than with the other assays (9). The BP2 study also revealed that 22C3, 28-8, and SP263 had comparable staining characteristics and SP142 had less sensitivity. The 73-10 IHC assay showed greater sensitivity for detecting PD-L1 expression (10). Consequently, commercial PD-L1 IHC assays using histological samples were established by an international panel of pathologists (10).

Unfortunately, more than half of NSCLC patients in some countries possess only cytological samples available for diagnosis (11). Although cytology cell blocks can be used for PD-L1 evaluation, the PD-L1 IHC assays using them have not been recommended for clinical application (10). In a recent article, Torous *et al.* evaluated the 22C3 assay using

Table 1 Anti PD-1/PD-L1 antibodies and companion/complementary diagnostic PD-L1 IHC assays

Antibody	Pembrolizumab	Nivolumab	Atezolizumab	Durvalumab	Avelumab
Target	PD-1	PD-1	PD-L1	PD-L1	PD-L1
Clone used for assay	22C3	28-8	SP142	SP263	73-10
Company	Dako	Dako	Ventana	Ventana	Dako

PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

Table 2 Correlation of PD-L1 expression of tumor cells between paired cytological and histological specimens

N	Clone used for assay	Findings
86	28-8/22C3	Pearson's r^2 =0.87–0.89 (14)
56*	E1L3N	Spearman's r =0.69 (15)
4	22C3	100% concordance rate (16)
25	Not specified	88% concordance rate (17)

*, 56 matched cytology and surgical specimens from 47 patients. PD-L1, programmed cell death ligand 1.

either formalin-fixed, paraffin-embedded 94 cytology cell blocks or 138 surgical pathology samples (12). The clinical outcome of first-line pembrolizumab in patients with high tumor PD-L1 expression (≥50%) in cytology cell blocks versus surgical pathology samples was also mentioned. The diagnostic cytology samples included cell blocks from endobronchial ultrasound-guided transbronchial needle aspirates (57.4%), pleural or pericardial fluid (27.7%), fine-needle aspirates (12.8%), and bronchial lavage or bronchial brushing samples (2.1%). There was no significant difference in the proportions of PD-L1 expression (<1%, 1–49%, ≥50%) between cytology cell block samples and surgical pathology ones. Although the cytological and histological samples were not compared directly, they found similar clinical outcomes for pembrolizumab monotherapy in chemotherapy-naïve patients with high PD-L1 expression (≥50%) based on testing either cytology cell blocks or surgical pathology samples. The clinical outcome of patients who were judged to be eligible for pembrolizumab monotherapy using cytological samples has never been reported, to our knowledge.

While PD-L1 testing has not been validated for cytology specimens (13), PD-L1 expression between paired histology and cytology specimens was compared (*Table 2*). Skov *et al.* showed high agreement of PD-L1 expression between histological and cytological specimens (n=86, Pearson r^2 =0.87–0.89) for the 22C3 and 28-8 assays (14). There was a significant correlation for the E1L3N staining of tumor cells (Spearman's r =0.69), but not for tumor-infiltrating immune cells (Spearman's r =0.14) between 56 matched cytology and surgical specimens from 47 patients (15). There was concordance of the PD-L1 expression evaluated using the 22C3 assay among four cytological and histological samples (16). The concordance rate of positive staining with PD-L1 antibody in 25 cytology-histology NSCLC specimen pairs was 88% (22/25) (17). Because there is heterogeneous PD-L1 expression in surgical specimens, at least four biopsy specimens are necessary to minimize the risk of misclassification (18). Therefore, large numbers of tumor cells in cytology specimens seem to be required to validate heterogeneous PD-L1 expression.

The results of recent trials (ICI plus chemotherapy or ipilimumab) showed that PD-L1 tests are not always necessary to select patients for first-line treatment (19,20). The importance of PD-L1 testing for selecting advanced NSCLC patients may be attenuated in first-line combined treatment with ICI and in salvage ICI monotherapy, except for pembrolizumab. However, biomarkers should be established to maximize the effectiveness of ICI, including PD-L1 expression and the tumor mutation burden (19,20). It is necessary to validate the evaluation of PD-L1 expression using available cytology samples in the absence of histology ones. Comparison of the diagnostic values using large and small histology samples, and cytology ones from the same tumors are ongoing in BP2B study (10).

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Footnote

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