Companion and Complementary Diagnostics for PD-L1 Expression Assessment in Non-Small Cell Lung Cancer

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ABSTRACT

Recently two different immunohistochemical (IHC) assays for the assessment of PD-L1 expression in Non-Small Cell Lung Cancers (NSCLC) have been approved in conjunction with two immune checkpoint inhibitor based therapies. One assay, using the rabbit anti-PD-L1 clone 22C3 on the Dako pharmDx™ platform, is a companion diagnostic for Pembrolizumab (KEYTRUDA®). The second assay, using the rabbit anti-PD-L1 clone 28-8 on the Dako pharmDx™ platform is a complementary diagnostic for Nivlolumab (OPDIVO®). A companion diagnostic is defined as a test that is necessary for the safe and efficacious use of a specific therapy. A complementary diagnostic has been defined as a test that may provide additional information about how a drug is used for patient management. Both assays were approved in conjunction with the specific therapy and were available through designated reference laboratories at the time of the therapy approvals in October of 2015. Because the assays rely on different assay procedures and have different intended uses, our laboratory network has provided both formats in order to assist clinicians in decisions regarding the two therapeutic approaches in NSCLC. In this report, we have evaluated the trends in utilization of the two assays, given their different uses, and the analytical performance features of the assays post-approval. In the first few months since testing has become available, we have observed approximately a 6 fold difference in clinician orders for the two assays. More tests have been ordered for the assay associated with the potential use of Pembrolizumab versus Nivolumab, which may at least in part be ascribed to the difference in labeling and intended use of the assays. Regarding the analytical performance of the assays, we have evaluated the two formats for the percentage of samples considered positive for PD-L1 staining, the spectrum of staining results (i.e. range of positivity) and percentage of samples that are not evaluable for PD-L1 expression (i.e., not adequate number of tumor cells). Results with the 22C3 antibody demonstrated staining (>1%) in 64.5% of the samples, with 28.9% of the samples showing high levels of PD-L1 expression (≥50% of the tumor staining positive). Approximately 14% of the samples were not evaluable, mainly because of insufficient tumor cells (<100). Staining results with the 28-8 antibody, demonstrated positive tumor cell staining (>1%) in 55.6% of the tested samples, and 16% of the samples submitted for testing could not be evaluated, mainly because of the lack of sufficient tumor cells. The results of this analysis show that both companion and complementary diagnostic assays are being used for patient management in non-small cell lung cancer. While the companion diagnostic assay in this initial assessment seems to have greater utilization among clinicians, both assays show expected analytical performance characteristics.

BACKGROUND

PD-L1 expression has been an important biomarker used in the evaluation of patient samples for the consideration of treatment with checkpoint inhibitors such as KEYTRUDA®, OPDIVO® and TEBCENTRIQ™ . While other biomarkers such as mutational burden, genetic alterations resulting in neo-antigens, genomic instability, and blood based markers of immune function have also been investigated, PD-L1 expression continues to be a primary means of assessing for the potential patient response to treatment (1). Recently several assays have been approved for use as companion or complementary diagnostics for the specific therapy considerations. A companion diagnostic assay is required for the utilization of a specific therapy, whereas a complementary diagnostic provides useful information regarding the therapy and potential response, but is not required.(2)

METHODS

Non-small cell lung cancer samples submitted between October 2015 and April 2016 for PD-L1 immunohistochemistry were included in this evaluation.

The PD-L1 immunohistochemistry (IHC) companion diagnostic for KEYTRUDA® involves the use of a Mouse Monoclonal antibody (clone 22C3), run on the Dako Link48 platform with standard HRP-DAB detection. For this assay the tissue sample must contain at least 100 cells for evaluation. Partial to complete membrane staining (≥1+ intensity) is considered positive for PD-L1 staining. A Tumor Proportion Staining (TPS) score of ≥50% is considered as a positive result.

The PD-L1 immunohistochemistry (IHC) complementary diagnostic for OPDIVO® involves the use of a Rabbit Monoclonal antibody (clone 28-8), run on the Dako Link48 platform with standard HRP-DAB detection. For this assay the tissue sample must contain at least 100 cells for evaluation. Partial to complete membrane staining (≥1+ intensity) is considered positive for PD-L1 staining. A sample is considered positive for PD-L1 staining if >1% of the tumor cells exhibit staining.

RESULTS

A comparison of the clinical use and analytical performance of two commercially available PD-L1 IHC assays is provided in the figures and tables below.

Figure 1 . Test volumes (a) by indication and average orders by clients for the 22C3 (b) and 28-8 (c) pharmDx assays

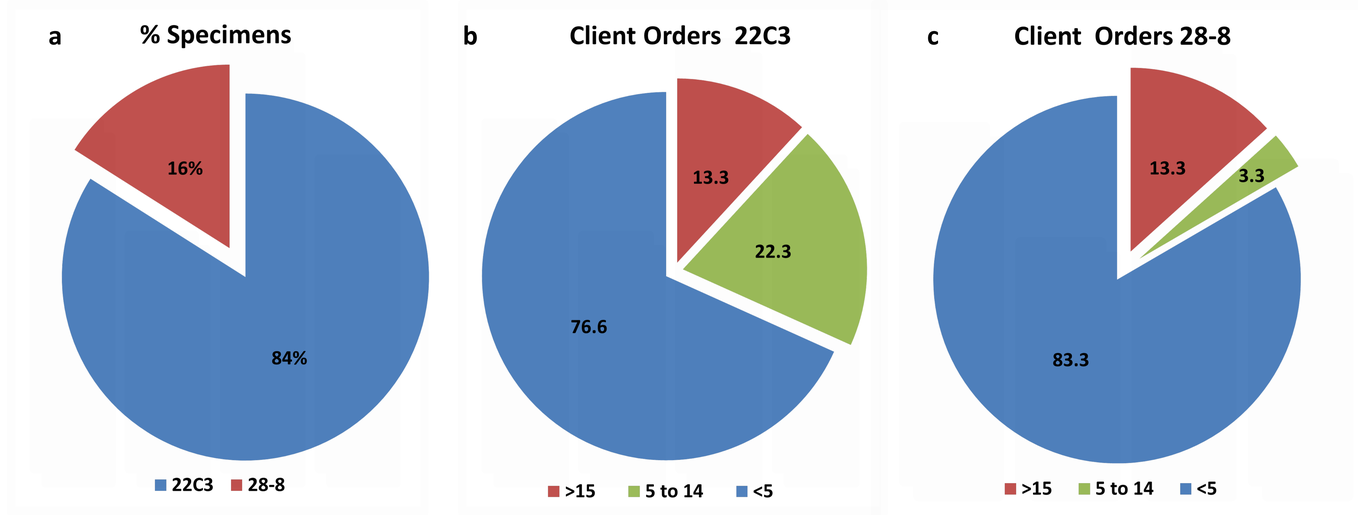

Table 1. Staining Results with the Two PD-L1 pharmDx Assays

	% Positive	% Negative
PD-L1 IHC 22C3 pharmDx	28.9	71.1
PD-L1 IHC 28-8 pharmDx	55.6	44.4

Table 2. Tumor Percentages Staining with the Two PD-L1 pharmDx Assays

	<1%	1-10%	11-25%	26-49%	50-75%	>76%
PD-L1 IHC 22C3 pharmDx	35.5	20.1	8.2	7.3	14.6	14.3
PD-L1 28-8 pharmDx	44.4	20.3	5.3	3.3	12.8	13.9

DISCUSSION

- Immunohistochemical (IHC) assays for PD-L1 expression are currently being implemented for routine clinical use
  - In our reference lab setting the IHC assay with the companion diagnostic designation is more frequently ordered by clinicians than that with the complementary diagnostic indication
- The two assays evaluated in this comparison show very similar analytical performance features
  - Differences in the frequency of samples indicated as positive for PD-L1 expression is more strongly associated with the different assay cutoffs rather than analytical performance differences of the two assays

REFERENCES

1. Hedge et al. (2016) CCR 22: 1865
2. Hanson et al. (2016) JAMA Oncology 2:15

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