

# LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

Section Editor: Mark A. Socinski, MD

## Programmed Death Ligand 1 Testing: Is There One Best Test?



Fred R. Hirsch, MD, PhD  
Professor  
Division of Medical Oncology  
University of Colorado Denver School of Medicine  
Denver, Colorado

**H&O** Is programmed death ligand 1 (PD-L1) testing always done before prescribing a programmed death 1 (PD-1)/PD-L1 inhibitor in patients with non–small cell lung cancer (NSCLC)?

**FH** Yes, this became the standard of care with the US Food and Drug Administration (FDA) approval of pembrolizumab (Keytruda, Merck) as first-line therapy with the companion PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay from Dako. This assay is used routinely in all patients with NSCLC unless they have a mutation in epithelial growth factor receptor (*EGFR*), *ALK*, or *ROS1*.

**H&O** Which other PD-L1 diagnostic assays are used?

**FH** The Dako 22C3 assay is the only test used for first-line therapy in NSCLC. For second-line or later treatment, physicians have a choice among the Dako 22C3 assay for pembrolizumab, the 28-8 assay from Dako for nivolumab (Opdivo, Bristol-Myers Squibb), and the Ventana SP142 assay from Roche for atezolizumab (Tecentriq, Genentech). Assays for second-line or later treatment with nivolumab or atezolizumab are recommended but not required, whereas Dako 22C3 is a required diagnostic for pembrolizumab.

**H&O** What cut-off values are used to determine eligibility for a checkpoint inhibitor?

**FH** The cut-off value for the 22C3 assay is at least

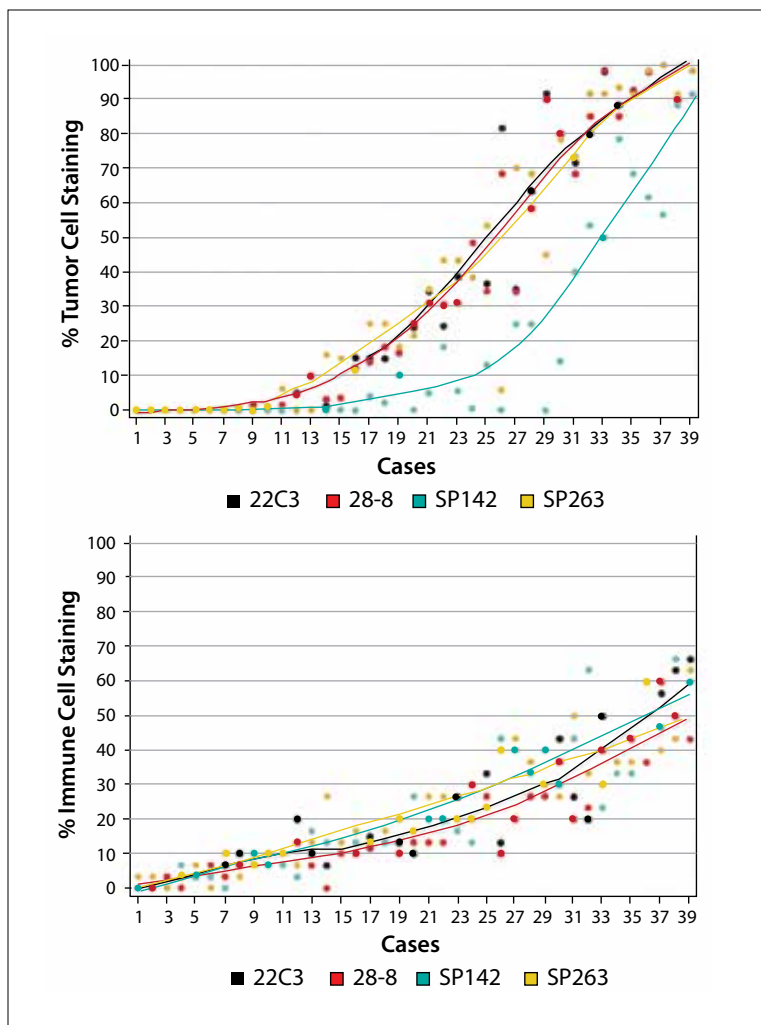
50% in first-line treatment and at least 1% in second-line treatment. The cut-off for the 28-8 assay is at least 1%, and the SP142 assay has one cut-off for tumor cell expression (at least 50%) and another cut-off for immune cell expression (at least 10%).

**H&O** Do physicians always need to use the companion assay for the specific agent they wish to prescribe?

**FH** The assays currently are linked to their specific agent, and we do not have any scientific data to establish interchangeability. Some data suggest that the 3 assays

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are similar in analytical performance, meaning PD-L1 expression on tumor cells, but they have not been compared in terms of clinical outcome. For example, we have no data relating the use of the 28-8 assay to pembrolizumab or the 22C3 assay to nivolumab.



**Figure.** Analytical comparison of the percentage of tumor cell staining and immune cell staining, by case, for each assay. Data points represent the mean score from 3 pathologists for each assay on each case. Superimposed points indicate identical values. No clinical diagnostic cut-off was required. “Best fit” colored curves allow for comparison of the score range among the 4 assays.

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### H&O Could you describe the study that you recently published in the *Journal of Thoracic Oncology*?

**FH** The Blueprint PD-L1 IHC Assay Comparison Project is a comparison of 4 assays that was undertaken by several academic medical centers and the International Association for the Study of Lung Cancer. It is a remarkable study because all the relevant pharmaceutical and diagnostic companies agreed to the comparison. The companies are, of course, competitors in a market valued at more than \$1 billion, so the fact that they agreed to the comparison was a diplomatic victory unto itself.

In phase 1 of the Blueprint study, which is what we just published, we stained 39 NSCLC tumors using the 4 PD-L1 IHC assays that have been used in clinical trials. We used a single cut-off for each assay.

After experts interpreted the results, we found that the percentage of PD-L1–stained tumor cells was comparable when the 22C3, 28-8, and SP263 assays were

used, although there were cases in which patients would be misclassified by switching assays. The percentage of tumor cells was significantly lower with the SP142 assay than with the other 3 assays (Figure). The assays had much greater variance related to immune cell expression, which is more difficult to interpret than tumor cell expression.

### H&O What would you say are the implications of the Blueprint study?

**FH** This was a feasibility study with a relatively limited number of cases, so we are validating our work in a phase 2 study called Blueprint 2. We are including a fifth assay (Dako 73-10) in Blueprint 2 that is associated with avelumab (Bavencio, EMD Serono/Pfizer). This study will include specimens from at least 80 tumors and we will examine 5 specimens from each tumor, so there will be approximately 400 specimens. We also are comparing larger tumor specimens with smaller specimens and with cytology.

**H&O** What is the status of Blueprint 2?

**FH** We hope to finish it in time to present our results at the World Conference on Lung Cancer in Yokohama, Japan, in October.

**H&O** Could you describe the study that you recently published in *JAMA Oncology*?

**FH** In this study, we examined the 22C3, 28-8, and SP142 assays along with the E1L3N assay from Cell Signaling, which is a laboratory developed test—it is not used in clinical trials. This study showed that the SP142 had a different analytical performance than the 3 other assays, which is consistent with the results of the Blueprint study.

**H&O** What course of action do you recommend that physicians take based on the status of these assays?

**FH** My current recommendation is to stick with the assay associated with the relevant drug, but that could change easily in response to more data. We may learn that 28-8, 22C3, and SP263 are interchangeable in practice, but at this point we do not have the scientific data to justify using them this way.

**H&O** How should future studies address these similarities and differences among the assays?

**FH** We first need to finish up the Blueprint 2 study,

which will give us a much better understanding. We also need to look at the specific staining equipment that is used for each of the assays because right now the Dako assays are linked to the Dako instruments and the Ventana assay is linked to the Ventana instrument. What would happen if we applied the Ventana instrument to the Dako assay? We need a cross-platform comparison to better understand the differences among the assays and their ability to be used interchangeably.

**Disclosures**

*Dr Hirsch has participated in advisory boards for Genentech/Roche, Pfizer, Bristol-Myers Squibb, Lilly, Merck, AstraZeneca, Boehringer-Ingelheim, and Ventana/Roche, and has received institutional research funding from Genentech/Roche, Bristol-Myers Squibb, Lilly, Bayer, Amgen, and Ventana/Roche.*

**Suggested Readings**

Gandini S, Massi D, Mandala M. PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2016;100:88-98.

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Rimm DL, Han G, Taube JM, et al. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in non-small cell lung cancer [published online March 9, 2017]. *JAMA Oncol*. doi:10.1001/jamaoncol.2017.0013.