Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer

In what state is this art?

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On behalf of the IASLC Pathology Committee

Abstract: Therapeutic antibodies to programmed death receptor 1 (PD-1) and its ligand PD-L1 show promising clinical results. Anti-PD-L1 immunohistochemistry (IHC) may be a biomarker to select patients more likely to respond to these treatments. However, the development of at least four different therapeutics, each with a different anti-PD-L1 IHC assay, has raised concerns among pathologists and oncologists alike. This article reviews existing data on the IHC biomarker aspects of studies using these drugs in non–small-cell lung cancer (NSCLC) and considers the challenges ahead, should these drug/IHC assay combinations reach routine practice. For each the known biomarker assays in development, there is a different monoclonal IHC antibody clone, produced by one of two diagnostics companies. Each test requires proprietary staining platforms and uses different definitions of a "positive" test for PD-L1 expression, on tumor cells and, in one test, also on tumor infiltrating immune cells. There are still considerable gaps in our knowledge of the technical aspects of these tests, and of the biological implications and associations of PD-L1 expression in NSCLC, considering heterogeneity of expression, dynamic changes in expression, and prognostic implications among other factors. The International Association for the Study of Lung Cancer Pathology Committee raises the prospect of trying not only to harmonize and standardize testing for PD-L1 by IHC, at least at a technical level, but also, ideally, as a predictive marker, to facilitate availability of this test and a promising treatment for patients with NSCLC.

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Disclosure: The authors declare no conflict of interest.

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DOI: 10.1097/JTO.0000000000000526

ISSN: 1556-0864/15/1007-0985

Key Words: Immune check-point inhibitors, PD-1, PD-L1, Immunohistochemistry, Biomarker assay.

(*J Thorac Oncol.* 2015;10: 985–989)

IMMUNE CHECKPOINT INHIBITION: A PROMISING THERAPEUTIC STRATEGY FOR LUNG CANCER

In the search for effective therapies in patients with lung cancer, immune checkpoint inhibitory approaches have shown considerable promise.[1–4] A number of ligand–receptor interactions, including PD-1/PD-L1 and B7/CTLA-4, seem to switch off the immune response in lung cancer, a tumor that in general has a high rate of somatic mutations, which may make such tumors more immunogenic.[5,6] Much of this therapeutic focus in lung cancer, particularly in non–small-cell lung cancer (NSCLC), has been on interrupting the interaction of programmed death receptor-1 (PD-1) and its ligand (PD-L1) between tumor cells and immune effectors cells, using monoclonal antibodies against PD-L1 or PD-1. In this era of personalized medicine using targeted biological agents, biomarkers predictive of response to therapy are central to treatment decision making.

AVAILABLE THERAPIES AND BIOMARKERS

There are a number of therapeutic anti-PD-L1 (e.g., MPDL3280A [Roche, Basel, Switzerland] and MEDI-4736 [Astra Zeneca, London, UK]) or anti-PD-1 (nivolumab [Bristol Myers Squibb, New York, NY]) and pembrolizumab [Merck, Kenilworth, NJ]) agents at various stages of development, and the favored biomarker seems to be the expression of PD-L1 assessed by immunohistochemistry (IHC; Fig. 1). There are limited data currently available, for these therapeutic agents, in lung cancer, in particular in patients with advanced NSCLC. Different approaches have been taken to PD-L1 IHC assessment, using different diagnostic antibodies to assess PD-L1 expression, different technical staining platforms, and different definitions of a "positive" predictive IHC stain. In some cases, expression of PD-L1 on immune effector cells as opposed to, or in combination with, expression in tumor cell, has been chosen as the biomarker.

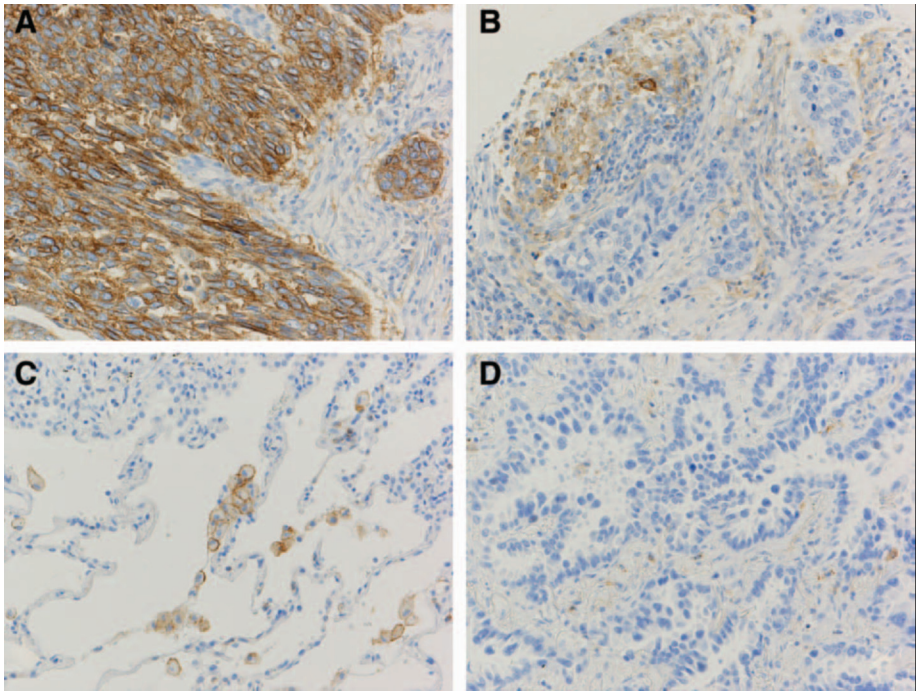

FIGURE 1. Programmed death receptor-1 with its ligand (PDL-1) immunostaining performed using the E1LN3N clone anti-PD-L1 from Cell Signaling Technology (Boston) with standard detection techniques. *A*, Squamous cell carcinoma showing a strong, uniform positive reaction in tumor cells. *B*, Despite being negative in tumor cells in the center of the image, there is a positive reaction in macrophages and other immune cells in the tumor stroma. *C*, Most alveolar macrophages are positive for PD-L1. *D*, This adenocarcinoma is negative for PD-L1. It should be noted that this immunohistochemistry clone was not used for PD-L1 detection in any of the trials discussed in this review.

PROBLEMATIC ISSUES WITH EXISTING DATA

Some of the essential findings so far reported are presented in Table 1.[7–20] Data are limited and most remain unpublished at the time of writing. Depending on definitions, positivity rates for PD-L1 range from 13% to 70%, and correlation between biomarker positivity and treatment response rates vary from 13% to 83% depending upon the biomarker-defined cohort and therapy used. Most studies also report significant response rates (3–20%) in PD-L1 IHC negative cases. Most of the studies assess PD-L1 expression in tumor cells and regard membrane staining as most significant. There is variable interpretation of the intensity and distribution of staining and variable definition of a positive PD-L1 stain ranging from staining of ≥1% to ≥50% of cells assessed. In some cases, the test requires at least 100 tumor cells to be assessed.

Biomarker Positivity and Response

The value of the chosen biomarker seems to vary in terms of predicting a response to therapy, and in some cases this also seems to depend on which line of therapy for which the immune checkpoint inhibitory agent is given (Table 1). The biomarker test may not represent the true PD-L1 status of the tumor, either because of heterogeneity of expression and sampling error, or because the test sample predates earlier lines of therapy (see below). In general, however, there is a higher response rate in the PD-L1 positive population compared with the PD-L1 negative group of patients, although in some studies this difference is not significant. The presence of patients who respond to therapy, in the PD-L1 negative cohort, calls into question the value of PD-L1 IHC as a predictive biomarker to select a patient subgroup for therapy.

Biomarker Thresholds

Determining the threshold that defines a positive, predictive test is a difficult issue. Thresholds may be predetermined, before outcome data are known, or as a more useful approach, the response data may be used to indicate the threshold that gives best discrimination between responders and nonresponders, or between patients who do or do not derive significant survival benefit from the therapy. It has, however, been noted that traditional response evaluation criteria in solid tumors for assessing tumor response may not be best suited to assessing clinically significant responses to immune checkpoint inhibitor therapy, at least in a small proportion of the cases. There is then a potential trade-off between improving upon the response rates seen in an unselected treated population, the acceptability of this response rate in an unselected population versus that seen with standard of care treatment, and any considerations to maximize the population eligible for treatment. In addition, to date, response (overall response rate) alone does not seem to be the best way to evaluate the benefit of immunotherapy; this is probably better captured by progression-free or overall survival data. Finally, if very low staining thresholds such as 1% or even 5% of cells are chosen, there is a greater risk that scoring will be inconsistent and is more likely to reflect inaccurately the patient's tumor burden overall, because of heterogeneity.

Heterogeneity and Prior Therapy

Limited data suggest that PD-L1 expression is heterogeneous, reflected in low thresholds being used to define positive staining. Little is understood regarding the relationship between PD-L1 expression in the primary tumor and any metastases. Earlier lines of chemotherapy or targeted therapy may well induce PD-L1 expression, consequently PD-L1 expression in the original "chemo-naive" diagnostic