Editorial

Quantification of PD-L1 expression in non-small cell lung cancer

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Constituting a large proportion of patients with non-small cell lung cancer (NSCLC), disease that is recurrent and/or metastatic is a major oncologic concern. The poor prognosis of such cases has led to enormous recent efforts in developing targeted therapies that can provide better efficacy than standard chemotherapy, whose high specificity could also result in improved tolerance. One particular realm of targeted agents that has experienced rapid emergence is immunotherapy, whereby biologic molecules are administered in efforts to sensitize the immune system to a neoplasm. Immunologic tumoral destruction occurs in a much more specific and controlled manner than the nonspecific delivery of cytotoxic compounds, and could also interact with other local therapies to achieve additional oncological effects (1,2).

A major focus of several published and ongoing clinical trials is the onco-immunological interaction between tumor- or tumor-infiltrating immune cell-expressed programmed cell death ligand-1 (PD-L1), and its receptor PD-1, on cytotoxic T lymphocytes. This communication decreases T-cell signaling and activation of the antineoplastic immune response, which decreases the immune system's potentially large contribution to cancer therapy and allows tumor evasion of the immune system (3). As a result, antibodies disrupting the PD-L1 and PD-1 interaction have now come to the forefront of oncologic care of select NSCLC cases.

Owing to the positive results of multiple phase III trials, the National Comprehensive Cancer Network (NCCN) now recommends immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab, atezolizumab) as first-line treatment of appropriately-selected recurrent (after previous therapy) and/or metastatic NSCLC (4). One such selection criteria (especially for pembrolizumab consideration) is immunohistochemical detection of PD-L1 expression in tumor tissue, defined by the NCCN as ≥50% for metastatic cases and ≥1% in the recurrent setting, similar to inclusion criteria from randomized evidence (5).

Although this recommendation seems relatively straightforward in theory, ascertaining eligibility based on PD-L1 expression in clinical practice is more difficult. PD-L1 is a protein that displays variable and dynamic expression in response to factors at the immunological, oncologic cellular, and therapy levels (6,7). As such, though it has been posited that higher expression levels influence prognosis, biases in expression based on numerous uncontrollable factors can never be excluded (8). Moreover, as immunohistochemistry on a histopathological specimen is inherently dependent on tissue sampling from an intrinsically heterogenous, three-dimensional tumor, obtaining a truly accurate level of PD-L1 expression is difficult.

An often-overlooked element in detection of PD-L1 expression is the assay utilized for detection, which aside from approval by the Food and Drug Administration (FDA), is more ambiguously defined by national recommendations (4). To this extent, the recent investigation by Ratcliffe and colleagues (9) sought to address, using a large sample size, whether PD-L1 expression was similarly detectable and concordant between three commercially available, FDA-approved assays. In 493 patients nearly split between squamous and non-squamous histology, correlative agreements between the assays was over 0.9 (90%), which reassures clinical confidence in utilization of any of these three assays in clinical practice.

An interesting aspect of this study was the pursuance of independent pathological review in just under half of cases, wherein the authors varied the thresholds of PD-L1 expression (utilizing the clinically applicable values of 1%, 10%, 25%, and 50%) and evaluated agreement thereafter. Notably, the Ventana assay displayed the numerically highest rate of agreement at all thresholds except 1%. Moreover, there was a positive correlation between threshold value and agreement, as higher thresholds displayed higher agreement values (including over 95% for the NCCN-recommended cutoff of 50%).

These results have salient clinical ramifications, including changes in patient management. First, because the 1% and 50% thresholds can influence payment of pembrolizumab by insurance companies, it is unlikely that detection of PD-L1 expression below the cutoff in one assay would lead to its reporting as above the threshold with another assay. This is also relevant in part because performing further assays takes time, which risks further malignant progression during the diagnostic interval. Additionally, the finding of lower concordance with lower thresholds places extra emphasis on reducing inter-pathologist variability, and it is certainly possible that observer bias can lead to the non-approval of pembrolizumab in certain patients.

However, if a patient's sample does not meet the requirement for PD-L1 positivity at low thresholds, regardless of observer bias, it may lead to a shift towards the utilization of nivolumab, which notably does not require PD-L1 testing. This, in turn, could have major economic implications in the arena of biotechnological pharmaceuticals, as pembrolizumab and nivolumab are marketed by the competing companies Merck and Bristol Meyers Squibb, respectively. The utilization of pembrolizumab versus nivolumab, for which no phase III data currently exist, is extensively debated; often, the availability (and willingless) of PD-L1 expression testing influences whether a patient receives either compound. As such, illustrating that there is high concordance between three FDA-approved assays could spur greater dissemination of (any) assay (and thus, potentially greater utilization) to clinics worldwide. The results by Ratcliffe *et al.* are thus undoubtedly important to strategic plans by both Merck and Bristol Meyers Squibb, as well as for other immune checkpoint inhibitors currently being tested in the laboratory and in patients.

What these results also impart to the oncology community is the increasingly important notion of what the immunohistochemical cutoffs should ideally be in order to be under consideration for immune checkpoint inhibitors. As mentioned above, some thresholds currently exist owing to the association with inclusion criteria in seminal phase III studies. However, it is naturally logical to question whether, as referenced above, patients with low levels (e.g., 1–10%) of PD-L1 derive the same benefit to immune checkpoint inhibitors as those with higher expression levels. Clearly, no randomized evidence for this notion exists, but further refining cutoffs for drug administration is undoubtedly a major goal of the future. This is true not only for oncologic patient selection purposes, but also for economic purposes, as the current cost-effectiveness of such immune therapies is questionable, and refining patient selection for receipt of these expensive agents will likely result in an improved cost-effectiveness profile.

On the other hand, changing the currently recommended cutoffs is also difficult, not only for insurance/economic purposes, but also for ethical reasons (e.g., depriving a patient who is eligible for a drug, owing to detection threshold purposes). There are many well-known prognostic factors of recurrent and/or metastatic NSCLC, such that PD-L1 expression, regardless of threshold, may one day be part of the equation.

It is also imperative to evaluate the effect and/or interaction with PD-L1 expression levels and prognosis of oligometastatic disease, locally advanced and even early stage NSCLC. There is now randomized evidence that for well-selected oligometastatic NSCLC cases, local consolidative radiotherapy improves progression-free survival (10). However, the role of immune checkpoint inhibitors in this setting is unclear, as well as corresponding cutoff values for optimal benefit in progressive cases (as these were excluded from the trial). It is becoming increasingly possible that stimulating the immune system through immunotherapy could result in enhanced responses to radiotherapy at both the primary and distant sites of metastatic disease (11,12). For the same reason, combined immune therapy with radiotherapy including stereotactic ablative radiotherapy have being studied in early stage lung cancer and locally advanced lung cancer (1,2). As such, these emerging ideas may lend themselves favorably to highly conformal modalities of lung radiotherapy, such as proton beam therapy (13), which results in decreased lung volumes receiving low doses of radiation, which could better spare circulating immune cells and more completely establish an antineoplastic immune response.

Despite the multitude of questions in need of further evaluation, this study (9) takes a large step towards

standardizing and unifying logistical aspects of PD-L1 testing, which undoubtedly has direct implications on managing patients with immune checkpoint inhibitors. In this nascent but rapidly developing field of immunotherapy, it is often the technical facets of diagnosis that are the most important, yet most overlooked. Future work will build upon these data in order to further refine patient selection and continue testing of further immune checkpoint inhibitors.

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