PD-L1 guideline panels hustle to keep pace with drug advances

Anne Paxton

October 2017—The expert and advisory panels for the CAP/IASLC/AMP guideline on molecular testing for lung cancer biomarkers started updating the guideline in 2014, and an important but fairly routine revision process may have seemed to lie ahead. Something like sedately stepping onto a moving sidewalk. The key question at that point was quotidian: Have new data emerged to warrant changing the original recommendations?

But the breakthrough therapies and fast-tracked FDA reviews of the past few years have made catching up with the sheer number of FDA drug and diagnostic approvals more like grabbing on to a speeding train. And with the agency's May 23 approval of pembrolizumab (Keytruda) for any solid tumor type with mismatch repair deficiency or high microsatellite instability—the first pure biomarker-driven approval of any drug ever, says expert panel member Lynette M. Sholl, MD—that train has taken to veering in unexpected directions.

"When we set out to write the guideline, the immunotherapy story was really in evolution," says Dr. Sholl, associate pathologist and associate director of the Center for Advanced Molecular Diagnostics at Brigham and Women's Hospital and assistant professor at Harvard Medical School. "In such a rapidly evolving area, there was an assumption from the beginning that updates would be necessary, but all the approvals in lung cancer hadn't taken hold when we started our systematic review." Given the panel's original focus on gene- or transcript-level alterations, "we weren't really looking at what is largely at this point an IHC biomarker-driven scenario."

Now that the revision process has wrapped up, the guideline is under review for publication. A separate guideline focused on PD-L1 expression testing in lung cancer is being driven now by the fact that there are a number of companion and complementary diagnostics, Dr. Sholl says. "But there's really only one that's required for initiating therapy for lung cancer, and that's the FDA-approved PD-L1 IHC 22C3 PharmDx companion diagnostic. And all the pathologists and clinicians involved in this are somewhat concerned about the proliferation of disparate assays that are used for testing for this indication."

Dr. Sholl

Clinical trials have tended to recommend one mandatory biomarker and that the comparability of other assays be determined, she points out. "As the field moves forward, we're seeing a lot more papers demonstrating the comparability of a lot of the antibodies and assay platforms, and that's somewhat outside the scope of the biomarker guidelines we wrote earlier this year."

Many laboratories are considering whether they need multiple platforms to stain for different antibodies, with different staining conditions for all the different drugs, Dr. Sholl says. But the clinical trials have been focused on lung cancer. "I think the jury is still out about how these biomarkers will be used for other indications."

Early phase one trial data on mesothelioma, for example, suggest there may be a need for a biomarker for that disease, and possibly a particular cutoff for that tumor type. "But we're talking about a single phase one trial that showed some promise with patients with PD-L1 expression, and whether that will pan out in phase two or three is

still to be determined."

In lung cancer, there's only one drug approval that mandates a diagnostic, Dr. Sholl says. "So that makes everybody's life a little easier. It's pretty hard for a lab to rationalize bringing on a whole bunch of platforms when three out of four are essentially optional."

A more likely question labs may ask is whether to bring on a laboratory-developed test (LDT) that is comparable to PharmDx C23. Dr. Sholl cites a new National Comprehensive Cancer Network study led by David L. Rimm, MD, PhD, of the Yale University Department of Pathology, which concluded that three of the four assays registered with the FDA to detect PD-L1 are concordant and reproducible as read by pathologists for tumor assessment of PD-L1 (*JAMA Oncol.* 2017;3[8]:1051–1058). (The exception, the SP142 antibody assay on the Ventana Benchmark, detected significantly less PD-L1 expression in tumor cells and immune cells; that finding has been replicated in multiple other studies, Dr. Sholl says.)

"That data would support that if you have a well-validated LDT—in this particular study, they used E1L3N antibody on the Leica Bond platform—you'll have essentially the same level of assay performance and inter-pathologist agreement as with the other companion and complementary diagnostics." Along with the E1L3N antibody, Dr. Rimm's study also found that the 22C3 antibody and the 28-8 antibody, both on the Dako Link 48 platform, are concordant and reproducible for tumor cell assessment of PD-L1.

"Then the question is how do you go about validating them," Dr. Sholl says. "It may be a matter of a cross-comparison, in a lab that's performing routine 22C3 PharmDx testing, of a batch of cases." One of the needs the national organizations could fill is development of a set of validation cases that labs can use as gold standards to validate an LDT, she adds. "There's probably still something of a bias against going the LDT route, but the data are evolving in this area, and we'll probably start to see more equivalency demonstrated between these LDTs and the companion diagnostics."

The subjectivity of pathologists' scoring can be a concern. "Do we need a quantitative assay that says, 'Yes, this is most definitely a 50 percent positive tumor and therefore the patient should go on therapy'? We're sort of accepting that a pathologist's experience scoring that PharmDx assay is the gold standard, but I think there's room for debate," Dr. Sholl says, noting that a recent *Clinical Cancer Research* study found interobserver variability around the 50 percent cutoff.

Additional bias can creep in because of the way a clinician frames a test order. "For instance, if a clinician calls and says a patient is not a great chemotherapy candidate—'Can you give me some information on PD-L1 as quickly as you can? This patient can't get chemo'—you can imagine the kind of bias that introduces, when I know, in reviewing the specimen, that if I just make it 50 percent he will get treated." Dr. Sholl doesn't believe immunofluorescence or chromogenic quantitative approaches are perfect, but she emphasizes the central question: "What's the best way to arrive at a very consistent read for a positive? And of course, is this IHC assay really the best way to select patients? Because we know there are still patients who are negative who respond and who are positive and don't respond."

Another running theme in the guideline discussion is how much responsibility falls to the pathologist versus the clinician in interpreting results. "The interpreter is really the pathologist; then the clinician's role is to integrate that into the broader picture for the patient. For instance, say you have a patient who progresses on first-line platinum therapy, and you are thinking maybe you want to give nivolumab [Opdivo] in second line, and you get a dead negative IHC result. Then you may choose to seek other options, but not necessarily. You could still choose to continue the nivolumab in that setting."

Some labs, in fact, refuse to comment on whether a result is positive or negative because the goalposts are always moving, Dr. Sholl says. "They may just give a number and leave it up to the clinician to say, 'Well, this is the drug I'm thinking of, let's look at the number and cross-compare,' and to put it into the context of what therapy the patient has received and what they would tolerate moving forward."

Another variable is that patients are aware of immunotherapy and that there are patients out there who have had remarkable responses. “This is a function of the heavy commercial marketing of these drugs. A patient may walk in the door and insist they have to try this type of therapy even if their type of tumor is unlikely to respond, or despite contraindications, like baseline autoimmune disease. But for most patients it’s often worth a try. Because you never know—some patients will respond quite robustly to the drug irrespective of biomarker status.” Has the commercial marketing gotten ahead of the ability of pathology and oncology to set sound guidelines? “It’s a bit of a confounder,” Dr. Sholl says.

The jury is still out on the question of whether IHC really is the best approach. The guidelines should address alternative emerging approaches to identifying patients and particularly what the role of understanding the tumor mutational burden is, she believes. “Should there maybe be a tripartite evaluation, including genomics, IHC, and immune profiling? At a minimum you need to understand the genomics of patients, since we know, for example, that *EGFR* and *ALK* rearrangements portend a poor response to immunotherapy, and that’s already written into the FDA label for pembrolizumab.”

The updated CAP/IASLC/AMP guideline on molecular testing is undergoing editorial review simultaneously at the *Archives of Pathology & Laboratory Medicine, Journal of Thoracic Oncology*, and *Journal of Molecular Diagnostics*. The PD-L1-focused guideline will follow.

Another guideline on the drawing board is related to PD-L1—but only indirectly. The goal for this new guideline, says panelist Russell Broaddus, MD, PhD, will be to respond to the FDA’s approval of pembrolizumab for the treatment of any microsatellite instability-high or mismatch repair-deficient cancer. Once the panel is able to meet, he hopes provisional guidance can be completed quickly. (The CAP plans to collaborate with targeted stakeholders such as ASCO.)
“Initially, when these checkpoint inhibitor drugs came out for treating cancers, it was thought that the patients’ tumors most likely to respond would be the tumors that expressed PD-L1 by immunochemistry, so a lot of tumors have been profiled with PD-L1,” says Dr. Broaddus, a professor of pathology at the University of Texas MD Anderson Cancer Center.

In lung cancer and melanoma, the expression of PD-L1 is more closely related to treatment outcomes with the drug. Not many other cancer types have good expression of PD-L1, he notes. “But what was noticed is that no matter what patients’ PD-L1 expression was, if their cancers had high levels of microsatellite instability or defective DNA mismatch repair, they were also responding to the pembrolizumab drug.”

That discovery is what spurred the FDA to announce approval of pembrolizumab as the first tissue-site-agnostic drug for the treatment of any MSI-high or MMR-deficient cancer. “This was the first time the FDA had ever issued an announcement across all cancer types for a drug. And they don’t mention PD-L1 at all in their announcement,” Dr. Broaddus says.

What motivated this FDA move was that the drug had such a good effect in the MSI-high or MMR-deficient patients in not only one trial but five different multicohort, multicenter trials. “This wasn’t something weird going on in one patient population. It was across a number of different trials,” he points out. “You hate to say this was picked up by accident, but I’m not sure they were specifically looking for this connection. They just happened to notice it when they were assessing patient response.”

So far, so good. But the tricky part of the approval is the diagnostic. “The drug is in place, and now it’s approved for any cancer type showing these characteristics. But what the FDA is very vague about is they don’t give any recommendations at all on how to test these patients. And I think this is putting pathology in a bind.” It opens up a huge can of worms, Dr. Broaddus says, because MSI and MMR are tested by two completely different assays, and some evidence suggests that one approach may be okay for certain cancer types but not for others.

“Sometimes they overlap with their results but sometimes they don’t, which is what makes this tough.” In addition, labs have to adjust to a new use for a familiar diagnostic. “Labs across the country have been using these assays,

but usually for colon and endometrial cancer patients to look for Lynch syndrome. It's in the treatment guidelines for colon and endometrial cancer to do that screening." Laboratories—at smaller community hospitals as well as at academic centers—are not used to testing all these other types of cancers, he adds.

He is working to form the workgroup to issue a recommendation regarding MMR and MSI testing for patients being considered for pembrolizumab therapy. A provisional clinical opinion might be a quicker measure to address the situation than a full guideline, Dr. Broaddus believes. He hopes the literature on PCR-based MSI testing and IHC-based MMR testing will suggest directions. "Do both tests have to be run for each cancer? Is one enough? Does it depend on the cancer type? These are the types of things we'd like to look at."

A second issue will also need to be explored for a provisional clinical opinion. "The FDA didn't touch on this, but there are a number of papers recently out there about measuring tumor mutation burden, and how high tumor mutation burden correlates to treatment response with this drug too," Dr. Broaddus says. Confusion can arise because many people equate high tumor mutation burden with high MSI, but often that is not the case. "So I think we need to have clarification on that issue too."

The FDA may not have brought up tumor mutation burden due to a lack of data for a sufficiently large number of patients analyzed with a multiple-gene assay, he suggests. Tumor mutation burden can't be picked up in the smaller next-generation sequencing assays, he points out. "We have a 50-gene assay and that's not enough. Even the larger NGS panels now testing for 130 to 150 genes aren't big enough."

The FDA approval in May of pembrolizumab for MSI-H or dMMR tumors marks a sea change in cancer treatment, Dr. Broaddus says. "Traditionally it's been one drug, one cancer type. That's the way oncology has worked. And this is the first time ever that the FDA has said a drug can be used for any cancer type that displays these molecular abnormalities. So it really does flip things on their ear a bit for pathologists and oncologists."

Pathologists are used to testing for MSI or defective DNA mismatch repair in colon and endometrial cancers, Dr. Broaddus adds. But now, oncologists can be well justified, if they've run out of the usual chemotherapy or radiotherapy treatment options for an advanced head and neck cancer, in saying they'd like to try a new inhibitor and requesting microsatellite instability testing.

He doesn't predict an explosion in the use of the drug, however. Realistically, only about 15 percent of colon and endometrial cancers have high MSI or a mismatch repair deficiency, and he believes the incidence will be even lower than 15 percent for other cancer types such as head and neck cancer. Much research on other cancer types remains to be done. "I think oncologists have seen enough patients like former president Jimmy Carter—who presented with a melanoma brain metastasis and had an incredible response to Keytruda—that they know there's some promise to the drug."

But finding the right assays to identify the patients who will respond well is critical. "One, the drug is expensive. Two, patients presenting with advanced cancers have a very finite lifespan. You don't want to waste time treating them with a drug with no chance of having any benefit."

Developing a guideline to meet this need is not that different from setting guidelines for HER2/neu testing in breast cancer, Dr. Broaddus says, except this guideline will have to span so many different cancer types. The solution may not be elegant. "What we may have to do is take information from the cancer types with a lot of literature and experience with this and project it onto these other types of cancer with less literature and less experience. And I know from painful experience that when we do that, we're more often wrong than right."

Dr. Broaddus

One common pitfall, for example: “There’s a prevalent opinion out there that if two tests overlap, if they’re essentially synonymous, you only have to do one. That’s not really the case. There’s some very good published evidence in peer-reviewed literature that says testing isn’t always concordant and the discordances can be very, very important. It’s not common, but a tumor may have high levels of MSI by a PCR test but have intact expression of MMR protein by IHC. So the other challenge is going to be: If we’re going to recommend just one test, what test will it be? Will it be immunochemistry? Will it be the PCR-based assay?”

Pathology will need to rethink traditions to adjust to the new scope of pembrolizumab, and that will take time, he thinks. “The pathology world is very familiar with these assays to screen for hereditary cancer syndrome, but they’re not used to thinking of them as a way to screen for a drug. The GI pathologists will have tons of experience with this, but other pathologists will have little to no experience. Now, all types of pathologists will need to gain experience in how to interpret a PCR-based slide test and IHC assays for mismatched repair proteins.” Many pathology residents, even after four or five years of training, have also never seen these assays before, he adds. “So that’s a key gap we need to address in the discipline of pathology—to get our residents in training more exposure to this type of diagnostic testing—because it’s not going to decrease anytime soon.”

“We see in pathology a lot of different treatment approaches that create excitement for six months and then kind of go away. This is something that keeps building and new advances keep coming, so I think this is a treatment approach that will keep its steam up for at least the next few years,” Dr. Broaddus says.

Dr. Sholl agrees. “There has definitely been a change of tone in the FDA’s way of looking at these drugs. That, in and of itself, is quite a tide change.” But caution will be needed because the full story isn’t known yet, she says. “Ultimately we need to be examining these cohorts of patients very carefully. The FDA’s approval of pembrolizumab for DNA mismatch repair deficiency across all tumor types is based on, outside of colon and endometrial cancers, a very low number of tumors. So the data is really still accumulating. And we’ll just need to keep studying it.”
[hr]

Anne Paxton is a writer and attorney in Seattle.