# In NSCLC, biomarker testing rates fall short

## Charna Albert

June 2020—Testing rates for actionable biomarkers in metastatic non-small cell lung cancer patients are below where they should be, and the overlap of PD-L1 expression with genomic targets causes confusion for oncologists and patients, said Geoffrey R. Oxnard, MD, oncologist at Dana-Farber Cancer Institute and associate professor of medicine at Harvard Medical School, in a recent CAP TODAY webinar.

He and co-presenter Lauren Ritterhouse, MD, PhD, associate director of the Center for Integrated Diagnostics, assistant pathologist at Massachusetts General Hospital, and assistant professor at Harvard Medical School, addressed how to optimize molecular testing. The webinar was made possible by a promotional sponsorship from AstraZeneca and is at captodayonline.com.

The 2018 CAP/IASCLC/AMP guideline advises testing for *EGFR* mutations and *ALK* and *ROS1* rearrangements. The 2020 NCCN guidelines recommend, in addition, testing for *BRAF* mutations and PD-L1 expression. Both of these guidelines say broad sequencing panels are important in capturing a wider range of targetable variants, to include *MET, RET, ERBB2*, and *KRAS*, Dr. Oxnard said. Both also say plasma-based testing is an emerging alternative.

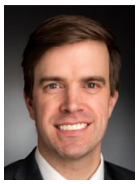
"For efficiency in time of testing and in use of tissue, in our practice we're now using tumor NGS with an in-house panel as our go-to approach" for results on the five key variants and the emerging variants.

Despite the guideline recommendations and the benefits of targeted therapy, Dr. Oxnard said, "current testing rates for actionable biomarkers are just inadequate."

He reported data presented last year (Gierman H, et al. ASCO annual meeting, 2019, Abs 1585) showing that patients with NSCLC continue to be undergenotyped for the NCCN-recommended genes. The percentage of NSCLC patients tested for *EGFR* was found to be 54 percent, *ALK* 51 percent, *ROS1* 43 percent, *BRAF* 29 percent, *RET* 17 percent, *MET* 15 percent, and *ERBB2* 11 percent. In the same study, the rate of testing for PD-L1 expression was 48 percent.

Twenty-two percent of patients were tested for all four genes with FDA-approved on-label drugs. Seven percent were tested for all seven genes with associated therapies included in NCCN guidelines.

Other studies have found that for genes with associated targeted therapies, the rate of testing for *EGFR* was the highest, at 72 percent, followed by the rates of testing for *ALK* (69 percent) and *ROS1* (38 percent) (Kim ES, et al. *J Thorac Oncol.* 2019;14[3]:338–342). But the rate of comprehensive testing for four major types of alterations—NCCN-recommended and emerging biomarkers at time of study—was eight percent.



Dr. Oxnard

"One of the things we're struggling with is how we can improve these testing rates," Dr. Oxnard said, to increase the likelihood that patients will be connected to the oral targeted therapies or, in the case of high PD-L1 expression, to immunotherapies.

But another problem: "These two paths straight overlap," confusing oncologists and patients, he said. Several studies have shown that up to 70 percent of patients who are *EGFR* mutation positive also express at least one

percent PD-L1. (For *ROS1*, it's 100 percent overlap, for *ERBB2* it's 53 percent, for *MET* and *RET* it's 75 percent. Mazieres J, et al. ASCO annual meeting, 2019, Abs 9010.) How to proceed? In the same ASCO presentation by Gierman H, et al., 37 percent of patients with known actionable biomarkers such as *EGFR* and *ALK* and no evidence of progression on targeted therapy (n = 84) were reported to have received immune checkpoint inhibitors. For 65 percent of the 37 percent, the test result was available prior to checkpoint inhibitor initiation.

Yet the molecularly targeted subsets of lung cancer do poorly with immunotherapy despite PD-L1 expression. So he sees the role of tumor genotyping as twofold: "It tells which patients to steer toward an oral targeted therapy, but it also tells us which patients are less likely to benefit from immunotherapies."

"PD-L1 expression can be seen in *EGFR*, *ALK*, and *RET*," he said, "and yet it's somewhat of a false-positive in those instances because it's not then associated with immunotherapy sensitivity." Eight of the nine most recognized first-line trials of immunotherapy excluded patients with treatment-naive metastatic *EGFR*-mutation-positive NSCLC, so all of the FDA-approved labels for first-line immunotherapy, as a single agent or in combination, exclude those patients. Thus, the recommended molecular testing is essential, he said, "to steer them toward an effective oral therapy and away from an ineffective immunotherapy that may add toxicity."

There may be a role for immunotherapy in genotype-defined molecular subtypes of lung cancer, but "it's not a first-line therapy," he said. "It's a later-line approach" when the treatment options are fewer. It's targeted therapy, he said, not immunotherapy, that improves overall survival rates for these patients, according to the evidence.

He presented a case seen commonly in the clinic. "I see a 48-year-old male who is a former light smoker and presents with lung adenocarcinoma, stage IV NSCLC metastatic to the lungs." The patient is eager to begin an effective therapy. "When I see him, his pathology is signed out, and testing for PD-L1 has already been completed" (greater than 90 percent positive). "What I struggle with is, do I dive in and treat this patient with immunotherapy, or do I hold off and wait for next-generation sequencing results, which can help clarify the role of PD-L1 in his care?"

When planning first-line therapy, Dr. Oxnard said he waits for the NGS results. For this patient, the results revealed an *ALK-EML4* fusion. He starts the patient on an ALK inhibitor, rather than initiate a first-line immunotherapy, "which would have been a mistake for this patient," because of the low likelihood of its having benefit.

The growing number of predictive emerging targets in lung cancer will put additional pressure on tissue, Dr. Ritterhouse said, naming a few: *MET* exon 14 skipping mutation or high-level *MET* amplification, *RET* rearrangements, *KRAS* G12C mutation, *EGFR* exon 20 insertion mutations (a subset of the *EGFR*-mutated lung cancers), and tumor mutational burden.

Of the patients who get a tissue biopsy, about three percent to 26 percent can't undergo molecular testing owing to insufficient tissue, she said, citing the literature, and up to 19 percent of samples don't contain tumor tissue. One strategy is to use cytology specimens as source material rather than tissue, if a laboratory has validated its test on such specimens. The CAP/IASLC/AMP guideline says that any cytology sample with adequate cellularity and preservation can be tested (this doesn't include PD-L1 testing). And the American Society of Cytopathology and Papanicolaou Society of Cytopathology say cytologic specimens are a useful source of cellular material for *EGFR/ALK/ROS1* analysis.

Dr. Ritterhouse

Another strategy is to use plasma-based testing, early in the diagnostic pathway, when tissue is insufficient or unavailable, Dr. Ritterhouse said. And if tissue is going to be insufficient, "communicate this information as soon as possible to the clinical team so that an alternative testing strategy"—rebiopsy or plasma testing—"can start to be pursued as soon as possible."

Dr. Oxnard shared a second case: A 60-year-old female former light smoker with stage IV lung cancer metastatic to the bone and brain presents with neurologic symptoms. The symptoms are mild, he said, "but I'm feeling an urgency to get her moving on treatment. I reach out to the outside institution where she had her biopsy, and I'm trying to figure out where the tissue testing stands. Someone says genotyping has been ordered, but I'm not sure where it is in the process." Knowing that time is of the essence and that he can't rely on the tumor results to pull through for her, Dr. Oxnard orders a liquid biopsy.

The in-house plasma test, performed at Brigham and Women's Hospital, uses Droplet Digital PCR, he said. "It's available just for a setting like this, as an alternative to a comprehensive test" when results are needed quickly. Within three days, he had a result revealing an *EGFR* exon 19 deletion, and the next day the patient is started on an EGFR TKI. "By the time she shows up the following week to meet her radiation oncologist, she's already feeling better."

With inadequacy of specimens for NGS "a real and recurring problem," Dr. Oxnard said, alternative strategies and flexibility are important. And a coordinated, multidisciplinary approach is needed to "maximize the chance of getting the yield you need from the specimen you have."

If he isn't confident that the specimen is adequate, he orders a liquid biopsy "as a backup plan."

"More and more our pathologists are commenting on the adequacy of the specimen in their review of it, so that I know whether to order genotyping on the tumor or a liquid biopsy," he said.

Dr. Oxnard sees liquid-based NGS as a "kind of democratized NGS offering that any patient can get ordered from anywhere in the U.S." If a couple of tests have been done and the results are negative, "this is a way of getting NGS for your patients. You just need to make sure you send it at a moment when a patient has disease progression and when disease is shed."

In *EGFR* mutation testing, there's a role for tissue-based testing and plasma-based testing in parallel, he said. "If either one is positive, you can have confidence that you can start *EGFR* targeted therapy." Specificity with plasma samples is greater than 98 percent, but sensitivity is about 70 to 80 percent, so a negative plasma result requires confirmation with tissue-based testing (Gray JE, et al. Presented at IASLC 18th World Conference on Lung Cancer, 2017, Yokohama, Japan. Abs OA 05.02; Leighl NB, et al. *Clin Cancer Res.* 2019;25[15]:4691–4700). "I don't think all patients need both," he said. But "these are two directions to get a patient to effective genotyping."

Integrating the two has been found to increase detection of therapeutically targetable mutations, he said. A prospective study of 323 patients with metastatic NSCLC performed at the University of Pennsylvania found that concurrent tissue- and plasma-based NGS testing identified actionable mutations is 35.8 percent of patients, compared with 28.8 percent of patients who opted for concurrent testing but had only plasma-based testing, 20.5 percent of patients who opted for both but had only tissue-based testing, and 33 percent of patients who had plasma-based testing only (Aggarwal C, et al. *JAMA Oncol.* 2019;5[2]:173–180).

"As oncologists, we are increasingly trying to figure out which of our patients do best with tumor," Dr. Oxnard said. "Those are patients with tissue available who have time to get the testing done or where tissue [testing] has started reflexively earlier on, so by the time they see you, they already have a result." Plasma-based testing may be more appropriate in patients whose tissue is of "a certain adequacy and when you have some urgency to get a result back in a week or two. And sometimes, if there's uncertainty, I'll send tissue and plasma at the same time in hopes of getting something that gets my patient toward an effective therapy."

Dr. Ritterhouse cited three approaches to facilitating the acquisition of adequate tissue samples, ensuring good

stewardship of tumor tissue, and optimizing biomarker testing.

- Rapid on-site evaluation, or ROSE, of cytology specimens. A randomized controlled trial that evaluated the role of ROSE in endobronchial ultrasound-guided transbronchial fine-needle aspiration identified a 10 percent increase in successful lung cancer genotyping when this procedure was used.
- Reflex cutting 15 to 20 unstained slides when processed initially, which may reduce sample loss. The downsides: labor time spent on sections that don't contain tumor tissue, storage space use, and "previously sectioned and stored paraffin slides that may have less stability over time depending on application and storage conditions," she said.
- Implementation of a reflex testing protocol, which has been shown to improve time to optimal systemic therapy and the quality of biomarker testing (Cheema PK, et al. *J Oncol Pract*. 2017;13:e130–e138).

*Charna Albert is CAP TODAY associate contributing editor.*