Close-up on HER2 alterations in advanced NSCLC

Sherrie Rice

August 2022—*HER2* is a known oncogenic driver and emerging biomarker in non-small cell lung cancer, and while the therapeutic implication is not yet fully known in NSCLC, "we need to pay attention to it," said Fred R. Hirsch, MD, PhD, executive director of the Mount Sinai Center for Thoracic Oncology and associate director, Tisch Cancer Institute, in a CAP TODAY webinar sponsored by Daiichi-Sankyo and AstraZeneca.

The estimated prevalence of a *HER2* gene mutation in advanced NSCLC is two to four percent, he said. The prevalence of *HER2* gene amplification varies by test method: two to four percent by next-generation sequencing and 10 to 20 percent by FISH. And the prevalence of HER2 protein overexpression by immunohistochemistry varies by study and antibody, he said, and ranges from six percent to 35 percent. NSCLC patients with mutation, amplification, or overexpression are currently in clinical practice treated comparably to patients who have no molecular alteration.

Dr. Hirsch

Most of the mutations (about 50 percent) occur in exon 20, but the abnormalities also occur in exons 18, 19, and 21. "*HER2* mutations are not frequently seen alongside other actionable mutations in non-small cell lung cancer. In fact, they are mutually exclusive of other driver mutations," said Dr. Hirsch, citing a study of 1,007 patients in which 2.4 percent (24) had a *HER2* mutation and all but one was mutually exclusive of other driver mutations—*EGFR, KRAS, BRAF,* and *ALK*. They can co-occur, however, with several nonactionable mutations. Co-occurring *TP53* mutations have been reported at a rate of more than 50 percent, and co-occurring mutations in *RB1* have been reported in 8.9 percent.

"We don't know exactly what the therapeutic implication of that is or the prognostic implication," said Dr. Hirsch, who is also professor of medicine and pathology and the Joe Lowe and Louis Price professor of medicine at Icahn School of Medicine at Mount Sinai. Clinical trials are underway.

The data on immunotherapy in *HER2*-mutated NSCLC are derived from retrospective studies and "not very encouraging," he said. "In non-oncogenic driver populations, we would expect 30 to 40 percent response rates for immunotherapy," but the response rates in patients with tumors having a molecular driver in multiple studies with and without chemotherapy were found to be lower—from seven percent to 29 percent. "We also see lower progression-free survival and overall survival." Thus, immunotherapy "is not a good choice in the future for the oncogenic driver population," Dr. Hirsch said. Many possible approaches are being studied in patients with *HER2*-mutant metastatic NSCLC, including antibody-drug conjugates, immunotherapy combinations, and small-molecule inhibitors.

HER2 mutations are different from *HER2* amplification and HER2 overexpression, and each of the HER2 alterations is discovered using different testing methods. For *HER2* mutations, NGS is the preferred method. For *HER2* amplification, in situ hybridization and NGS are used, and immunohistochemistry is used for protein overexpression. In each of the three, the relevance in metastatic NSCLC is under investigation.

Broad molecular profiling, typically with NGS, is recommended in patients with metastatic non-squamous NSCLC and some squamous cell carcinoma NSCLC, "and we recommend that the profiling include the *HER2* mutation," Dr.

Hirsch said. Tissue is still for many the preferable source for NGS, he said. Specificity is 95 to 100 percent, and sensitivity is 90 percent or greater. Though the turnaround time today—from seven to 20 working days—is acceptable, he said he'd like to see it at seven to 10 working days.

"Liquid biopsy is coming quicker and quicker into the diagnostic scenario," he noted, adding that specificity is close to 100 percent. If the liquid biopsy is positive, "you can make a treatment decision based on it." With sensitivity at about 80 percent, he recommends trying to get a tissue biopsy when the blood-based result is negative. "The technology is getting better—more and more sensitive," he said, and among its benefits is its typically faster turnaround time and that it can capture tumor heterogeneity.

"So I'm a believer that we will see further advantages and use of NGS based on liquid biopsy."

The National Comprehensive Cancer Network and International Association for the Study of Lung Cancer have said there may be advantages to doing tissue and liquid characterization in parallel, he said. "But everything comes with a cost, and in our institution, tissue assay is still preferable, particularly in the initial diagnosis. But we are starting to do more and more liquid biopsies in parallel."

In disease monitoring, liquid has potential benefits, though more data are needed to show advantages over imaging and other modalities, he said. In therapy, too, "its clinical relevance is still to be demonstrated in clinical research."

The AMP/ASCO/CAP guideline for interpreting and reporting sequence variants says tier one (variants with strong clinical significance) and tier two (variants with potential clinical significance) biomarker status should be reported with an interpretive comment, and *HER2* mutations are currently a tier two biomarker in metastatic NSCLC, with level C evidence, defined as: "FDA-approved therapies for different tumor types or investigational therapies. Multiple small published studies with some consensus" (Li MM, et al. *J Mol Diagn.* 2017;19[1]:4–23).

Reporting of *HER2* mutation status should be uniform, contain consistent nomenclature, and include the key information needed to inform clinical decisions. "And, yes, reports should show *HER2* mutation status alongside driver mutations and actionable biomarkers," Dr. Hirsch said. NGS reports should be annotated properly in the electronic health record. And if reports are from an external laboratory, the *HER2* mutation status should be noted or highlighted in the list of other clinically relevant biomarkers for patients with metastatic NSCLC.

Dr. Hirsch said he found "shocking" the MYLUNG Consortium data, reported in 2021 at the virtual ASCO annual meeting and most recently in *Lung Cancer* (Robert NJ, et al. *Lung Cancer.* 2022;166:197–204), that only 46 percent of patients with metastatic NSCLC had five or more guideline-recommended biomarker results available before first-line treatment was selected. "For me personally," he said, "it was a shocking experience to learn that testing for five important predictive biomarkers when we have approved drugs occurs in less than 50 percent of patients with advanced NSCLC."

Within the US Oncology Network of more than 1,000 providers, 90 percent of patients were found to have had at least one test performed for *ALK, BRAF, EGFR, ROS1,* or *PD-L1,* according to the MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) Consortium data presented in 2021. But only 46 percent had testing for all five.

In a poster session at this year's ASCO annual meeting in June, further findings were reported (Robert NJ, et al. *J Clin Oncol.* 2022;40[suppl 16]:91300. doi:10.1200/JCO.2022.40.16_suppl.9130). In a retrospective observational chart review study of patients with metastatic NSCLC whose first-line treatment was initiated between April 1, 2018 and March 31, 2020, MYLUNG Consortium researchers examined patient factors associated with rates of biomarker testing. They concluded: "Black or African American race, smaller practice size, Southern practice, and squamous cell histology were significantly associated with lower comprehensive biomarker testing rates."

"We need to act on it, and we need to act very quickly," Dr. Hirsch said of the data reported in 2021. "There is a clear need for education, particularly in community practices," he said. "That is very clear. Most of our patients

today, if not all, should have molecular testing."

"So the bottom line: education, education, education. I cannot repeat it enough."

Sherrie Rice is editor of CAP TODAY. *The full webinar is at* captodayonline.com.