

Identifying *HER2* Mutations for T-DXd Use in NSCLC

The Oncology Brothers, Rahul Gosain and Rohit Gosain, spoke with Benjamin P. Levy, MD, regarding treatment updates for patients with non-small cell lung cancer (NSCLC) with *HER2* expression. Additionally, they focused on biomarker testing and clinical trial updates.

Rahul Gosain, MD, is a hematology/oncology clinician from the University of Rochester Medicine; Rohit Gosain, MD, is the medical director and assistant professor of oncology at Roswell Park; and Levy is the clinical director of Medical Oncology at Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital.

Together, the experts discussed how to best implement these updates into their clinical practice. They also focused on outcomes they hope to see in the future.

***HER2* Alterations and Biomarker Testing**

Levy kicked off the conversation, noting that complexity is occurring around NSCLC, and it is translating to better patient outcomes. Specifically, when looking at *HER2* alterations, exon 20 occurs in 1% to 2% of all patients with advanced adenocarcinomas and *HER2* overexpression, which is still being studied as possibly relating to lung cancer. Additionally, there is *HER2* amplification, which can be identified with fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS).

He emphasized that there are different alterations and different ways to identify them. “I’ll just give you the spoiler alert here...in 2024 right now it’s *HER2* exon 20 mutations that are...the most important thing to test for.” These can be found through immunohistochemistry (IHC) testing.

Rohit asked Levy how he approaches testing in his clinic. Levy highlighted the consistent need for NGS to be completed on all patients. Currently, all of his patients receive NGS, and his

institution has integrated liquid biopsies into testing. From his experience, Levy believes conducting liquid and tissue biopsies in a method he calls “layering in the liquid” will help to identify more alteration, and currently there is not as much pushback from insurance companies.

Rahul has also begun to use the layer in the liquid method because the liquid biopsy turnaround time is quicker. He waits for the tissue results to return before making a treatment decision but notes that he may start chemotherapy on select patients before the results are in.

Treatment selections were questioned based on biomarker results. For example, if a patient has a *HER2* mutation and it is amplified or overexpressed, is trastuzumab deruxtecan (T-DXd; Enhertu) the best option?

Currently, T-DXd is approved for patients with unresectable or metastatic *HER2* NSCLC.¹ In April 2024, it also received approval for patients with unresectable or metastatic *HER2*-positive solid tumors for those who had received prior therapy, and there are no alternative treatments.²

Levy focused on the pan tumor indication, where the response rates in the phase 2 DESTINY-Lung01 (NCT03505710) trial were higher than 50%. The challenge was the lack of patients with lung cancer. More studies need to be conducted to determine if second-line treatment of T-DXd is feasible. This approval, however, has forced everyone to look at the prioritization of tissue biopsy.

For Levy, if a drug can create a response rate north of 50%, and it’s well tolerated, he considers that a win. He noted dosing



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does make a difference when looking at various studies with doses at either 5.4 mg/kg or 6.4 mg/kg and the rates of interstitial lung disease.

“Remember that [this indication is for the] second line. My guess is when this moves to the first line, for reasons that I could go on and on about, the responses are going to be higher. When you take an active drug and move it to the first line after witnessing activity in the second line, there’s less heterogeneity within the tumor. Maybe the cells are more clonal. We try to give it to all of our patients up front. Sometimes we’re successful. Sometimes insurance [gives us] pushback, but it’s a great drug, and this is just the beginning,” said Levy.

Sequencing Therapies

When all the pertinent information comes back from the NGS, liquid, and tissue biopsies, Rohit asked about the next steps of first-line treatment, and subsequent ones as well.

Levy cautioned that the field is ever-changing, and a response now vs 3 months from now may change how to approach it. He feels there is no need to wait for the tissue results to come back before planning on a treatment strategy. Typically, T-DXd is given as first-line treatment in the treatment-naïve setting.

Using your best drug first is where Levy believes all treatment plans should begin, even if T-DXd currently isn’t indicated in the first line. For a patient with a *HER2* mutation, T-DXd will be first line, and if it cannot be, chemotherapy will replace it.

“We just started doing *HER2* IHC at Hopkins.... We need to remember tissue is precious. We have to be very careful about how much we’re using now—an IHC is just 1 or 2 slides—but we have to be careful with this,” said Levy.

Levy also highlighted community oncologists who use commercially available platforms to request IHC.

Rahul, who is a community oncologist and treats a variety of cancers, will use T-DXd up front, too. He also exposes patients to immunotherapy, specifically in breast and gastric cancers, to help with the active agent. He also has to consider the adverse effect (AE) profile of these agents and determine how to best manage them.

The top AE that Levy sees is alopecia, which is uncommon with targeted therapies. He noted the need to be mindful when having this conversation with patients. Additionally, although complete hair loss may not occur, hair thinning could be observed as well.

Cytopenias are also a cause for concern. Clinicians should also be aware of the usual chemotherapy AEs such as nausea or interstitial lung disease (ILD).

ILD is often seen in treatments for lung care, and clinicians are familiar with it. However, there are no stopping metrics for T-DXd because antibody-drug conjugates are different than immunotherapy. If patients experience grade 2 ILD with immunotherapy, there is wiggle room to continue with treatment to see how it progresses. With T-DXd, the current recommendation is to stop.

Levy reminds his patients that he is not doing a service to them if their life span will be prolonged, but their quality of life suffers for it.

“[ILD] can’t be ignored as you stress the importance of it, especially when you’re used to the immunotherapy aspect of it, when you talk about grade 2, even for grade 1, these patients need to be monitored very closely,” Rohit said.

Rahul asked Levy how often scans are repeated for patients receiving T-DXd. At Johns Hopkins, they are completed every 12 weeks because of the tumors in the lungs. If patients do develop ILD, scans between treatments for the AE occur every 4 to 6 weeks, but it can be difficult to convince insurance companies of this need.

Closing Remarks

As the conversation concluded, Rahul asked Levy if there were any pearls for the community oncologist. Levy gave them kudos, knowing how they deal with multiple forms of cancer and have to learn and identify how to treat each one. ■

Take-home messages included the following:

- Learn to identify *HER2* mutations
- Closely read the NGS reports
- Know it is OK to phone a colleague and ask for help in parsing the results
- Establish what type of mutation the *HER2* is
- Keep an eye on tyrosine kinase inhibitor development

REFERENCES

1. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for *HER2*-mutant non-small cell lung cancer. News release. FDA. August 11, 2022. Accessed November 6, 2024. <https://shorturl.at/j3FWy>
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