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Targeting HER2-Mutant NSCLC with Trastuzumab Deruxtecan: Initial Study Findings

Announcer:
You're listening to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. And now, here's your host, Dr. Jacob Sands.

Dr. Sands:
This is *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Jacob Sands, and today I'm joined by my friend and colleague, Dr. Julia Rotow, to discuss part 1 of the DESTINY-Lung03 study, which examined trastuzumab deruxtecan as a therapeutic option for pretreated patients with HER2 overexpressing, non-squamous, non-small cell lung cancer. Dr. Rotow is a thoracic medical oncologist at Dana-Farber Cancer Institute and Assistant Professor of Medicine at Harvard Medical School. Dr. Rotow, welcome to the program.

Dr. Rotow:
Hi, Dr. Sands. Thanks for the invitation. It's a pleasure to be here today.

Dr. Sands:
So, let's start out with a discussion about trastuzumab deruxtecan. We've seen a lot of different data about this drug in lung cancer as well as other tumors, and we're going to focus on lung cancer specifically. How has trastuzumab deruxtecan shown promise as a potential treatment option in recent clinical trials for lung cancer?

Dr. Rotow:
HER2 has become an established therapeutic target broadly across solid tumor oncology. Now, there are some areas we've been using therapeutic agents targeting HER2 for the longest. I think about breast cancer, some of the GI cancers, like gastric cancer, and, of course, in lung cancer with agents like trastuzumab deruxtecan, the HER2 antibody-drug conjugate.

And here, for quite some time, we've been using this in the lung cancer space to target HER2-activating mutations. And this is a subset of oncogene-driven non-small cell lung cancer that we find on our genomic testing results, and in the second-line setting, or later. We've been using T-DXd trastuzumab deruxtecan as our go-to agent for this subset of disease.

This is very distinct from many other solid tumors, where we've always used HER2 overexpression or HER2 amplification as measured by FISH or IHC as our go-to biomarker to identify patients for therapy. Now, it's exciting for us in non-small cell lung cancer, as we'll discuss in the Lung03 study. We are now seeing data come out showing activity for HER2 overexpressing non-squamous, non-small cell lung cancer as well, which allows us to open up our biomarkers for how we're identifying patients for possible treatment.

Dr. Sands:
Can you give us a bit of background for what the space is like before we even get into this new therapy?

Dr. Rotow:
In non-squamous, non-small cell lung cancer, a small percent of patients will have activating HER2 mutations, and these are often young, non-smoking patient populations. We know also that depending on the series of why the variable percentage of patients will have high-level HER2 overexpression as measured by IHC.

This is likely a very distinct patient population, a little less associated with a young, non-smoking status, and perhaps a little more overlap with a lot of more traditional lung cancer patient demographics. Now, for HER2-mutant lung cancer and for HER2 overexpressing lung cancer, for that matter, our first-line standard of care remains traditional platinum histology-guided platinum-based

chemotherapy, typically with the addition of checkpoint inhibitor immunotherapy, or in select patients, immunotherapy alone. For example, those with HER2 overexpression might consider that if they're PDL-1 high.

Now, this is all in the front-line setting, and then here, when we think about HER2-directed therapies in lung cancer, we're really thinking about second-line treatment or a later-line treatment in the setting of overexpressing disease.

The standard of care in the second-line or later has been mostly docetaxel in patients most fit for a taxane-based therapy. And then we're moving on to other single-agent chemotherapies where their response rates are dropping really, quite a bit lower than we'd like for clinical practice. Or we're looking for a clinical trial, of course, in an academic setting, something we're always interested in trying to find patients who can access to potential novel therapeutics in a clinical trial setting.

Dr. Sands:
Now, we've previously seen trastuzumab deruxtecan approval for HER2 mutant non-small cell lung cancer. We're going to focus a little bit on overexpression, and specifically within the DESTINY-Lung03 trial. First of all, can you describe the study design for us?

Dr. Rotow:
So, DESTINY-Lung03 was, in some ways, a follow-on DESTINY-PanTumor02 and DESTINY-Lung01, which looked at trastuzumab deruxtecan for various other HER2-expressing cohorts, either in solid tumors more broadly, as in the case of PanTumor02, or in patients with a little more heavily-pretreated HER2 overexpressing non-small cell lung cancer, DESTINY-Lung01. Now, we're seeing data in Lung03, which is looking at a slightly earlier line of therapy across a few different cohorts.

So, which patients were enrolled in DESTINY-Lung03? These were patients with non-squamous advanced or metastatic non-small cell lung cancer who are HER2 overexpressing. And this was defined by HER2 IHC score of either 2+ or 3+. These patients had measurable disease, and they could have had one or two prior lines of therapy. So, these patients were not allowed to be very late-line, and if patients had an actionable oncogenic driver, at least one of those of lines of therapy had to be an appropriate targeted therapy for that driver.

This was actually a multi-arm study with multiple different cohorts, including a dose escalation phase looking at T-DXd with various chemoimmunotherapy combinations and some expansion arms ongoing looking at, again, checkpoint inhibitor chemotherapy T-DXd combinations. The data we saw at World Lung was really looking at the T-DXd monotherapy cohort with patients dosed at our standard monotherapy dosing of 5.4 mg/kg.

Dr. Sands:
Now, you mentioned testing for overexpression, and that, I believe, was IHC testing. But how exactly would that be ordered as part of a standard of care when we get there?

Dr. Rotow:
So the good news is that HER2 IHC has been a standard clinical assay for quite some time. If you treat patients outside of lung cancers, or breast cancer, or gastric cancer, for example, you're quite familiar with getting back clinical HER2 IHC testing. Now, there are a number of different scoring systems, and I believe most of the DESTINY-Lung studies utilize the gastric scoring system within IHC if you want it to be very precise. But the key thing is that this is a clinical assay, and it's not something that comes up on a standard NGS report if you're doing pure DNA-based NGS. This is not a genomic biomarker; it's not a HER2 amplification like you might find in genomics overexpression of the protein level of the IHC.

So this is available in most pathology labs because it's being sent so broadly in other solid tumors already for some time. And a number of the commercial testing platforms—we're including both NGS and IHC-based biomarkers—may include in HER2 score as well as part of their report. So, it's often there, but depending on what test you're sending, it may happen automatically as part of your testing request for biomarkers in lung cancer. Or it may require you to specifically order it in your lung cancer patients. The thing is, for a lung oncologist, that's a little bit of a challenge, and it's something different because we don't historically send a lot of IHC-based biomarkers for treatment in lung cancer, and really, our key one has been PDL-1 thus far, and I think this now joins our list of biomarkers that, ideally, we should be sending, I think, our diagnosed patients. Understand, this may be a future treatment option.

Now, there are still unanswered questions here. I think we're still trying to understand to what extent is HER2 expression dynamic over the course of time or for the course of lines of therapy. Is this something where patients should be retested if it's been a long time since their original testing? Is it okay to look back on the original archival sample versus getting a new biopsy to test more proximally to when you're considering initiating T-DXd therapy? I think that's still up for discussion and up for understanding as we use this more in a real-world setting.

In clinical practice, what I do is, in a newly diagnosed patient, I am now checking HER2 IHCs, so I know if this could be a future option. I

think it's convenient to do it as part of my initial biomarker testing. I consider it part of my comprehensive biomarker testing now. And for patients who have been on therapy already, often if I'm considering changing therapy, that's my trigger to get this sent, and whatever their most biopsy sample is. Sometimes that's the original diagnostic sample, sometimes that's more recent testing.

And, certainly, for patients with oncogene-driven lung cancer who are receiving targeted therapy, where I'm already interested in what's the new mutational profile acquired resistance—I'm probably already going to be resending NGS at acquired resistance—I'll use that acquired resistance biopsy as my sample to do HER2 ICH testing. So, a little variation depending on the exact practice setting.

Dr. Sands:
For those just tuning in, you're listening to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Julia Rotow about the newest findings from part 1 of the DESTINY-Lung03 study.

So, Dr. Rotow, if we zero in on the results now, what were the safety and efficacy findings for trastuzumab deruxtecan in patients with pretreated HER2 overexpressing, non-squamous, non-small lung cancer?

Dr. Rotow:
Yeah. So, at first, we'll say, "Who were the patients who actually enrolled on the study?" And these patients mimicked some of our lung cancer population. They did run, in this trial, a little bit towards female predominance in about 68 percent of patients, and they were about evenly balanced. I think a little under a half IHC 3+ HER2, a little over half HER2 IHC 2+, about a third had brain metastases at baseline. And again, this is a little less heavily pretreated population, so a little under a quarter percent of patients had prior immunotherapy, and a little over a third—38 percent—had prior platinum doublet-based chemotherapy. And then a few had other treatment modalities utilized. So, a little less heavily pretreated than the data we've seen before.

So overall, if we look at response rates here again, the T-DXd monotherapy across HER2 IHC 2+ and 3+, the confirmed response rate was 44.4 percent. So, clinically meaningful, and actually a little higher in the numbers we had seen reported for the DESTINY-Lung01 study, where response rates were ranging from the mid-20s to the mid-30 percents depending on the specific patient cohort. This may simply reflect that these patients are a little less heavily pretreated. PFS is very similar to what we've seen before with the median progression-free survival of 8.2 months for this patient population.

You may wonder, does it matter if you're higher level HER2 expressing or is moderate expression sufficient? The answer is that patients who are HER2 IHC 3+ did indeed have a higher response rate than those who were 2+ positive. So 56 percent response rate if you were HER2 3+ and only 35 percent response rate if you were HER2 2+, and, in fact, the current FDA approval for T-DXd for HER3 overexpressing solid tumors is really for that 3+ positive patient population, which goes along with this kind of data as well.

Dr. Sands:
So, if we digest all of those results then, within the background of what has been the standard of care, how do think this fits in? You mentioned the 3+ being the group you'd focus on more, I imagine. How do you feel like this fits in, and how does this impact your treatment of patients?

Dr. Rotow:
Yeah. I think for patients in general with non-small cell lung cancer, the NCCN guidelines currently include this as a later-line option that can be considered in patients who are HER2 overexpressing. And that's how I'm using it in my practice as well. I think for our patient who's newly diagnosed—without an oncogenic-driver mutation, just non-squamous, non-small cell lung cancer—they're going to have their platinum doublet-based chemotherapy, and they're going to have their immunotherapy either together or as two lines of treatment.

As I go past that when I'm considering, do I want to use docetaxel or something like an ADC in a patient whose 3+ expressing? I think that this is a space where I would certainly consider trastuzumab deruxtecan as a reasonable option for these patients. And, certainly, at that point, clinical trial involvement is also a very reasonable option if there's an appropriate study. So, that's where I think I see myself putting this into my treatment paradigm as I'm seeing patients. And, again, it means I have to actually have to be testing for HER2 IHC status now, so I that I know it for my patients.

For patients with actionable oncogene, certainly that becomes much more complex because there's such a richness of data for sequential therapy across other drivers. I think where that will fit in will be very, very, very driver oncogene specific. But, again, it speaks to the need for comprehensive biomarker testing so we know all treatment options for our patients.

Dr. Sands:
Well, this has been a very helpful overview, but as we approach the end of our program, Dr. Rotow, any final takeaways that you'd like to leave with our audience?

Dr. Rotow:

This is an antibody-drug conjugate, so we are watching for traditional cytotoxic-related toxicities—most classically, cytopenias or GI side effects like nausea, and that is certainly something that requires attention and management during the course of therapy. Now, for patients with lung cancer who are getting T-DXd, ILD has also been seen and reported in the clinical trial, so it's something that I make sure that I am aware but also that my patients and their families are aware of—what to watch for in terms of signs and symptoms so we can rapidly initiate appropriate you know evaluation and treatment if needed.

There's a little pitfall in that some of the original T-DX studies had dosing a little higher at 6.4 mg/kg, but more recent data suggests that 5.4 mg preserves efficacy but is safer with less ILD and less high-grade toxicities, and that is actually the approved dose. So, certainly that's something to be mindful of if you're going to start the drug.

We're seeing a lot of progress in non-small cell lung cancer with personalized selection of therapy. I think this continues that trend and it, again, speaks to the ever-increasing need to be sure that all of our patients are receiving comprehensive biomarker testing. That now includes both genomic testing, so ideally their NGS or their broad-based platforms, and it now includes also IHC biomarkers. We've been doing PD-L1, and I think HER2 IHC is now part of that comprehensive testing list as well.

Dr. Sands:
With those final thoughts in mind, I want to thank my guest, Dr. Julia Rotow, for joining me to discuss part 1 of the DESTINY-Lung03 study. Dr. Rotow, it was wonderful having you on the program.

Dr. Rotow:
Thanks. It was a pleasure to be here today.

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