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Keeping Pace in Lung Cancer
HER2: Unveiling New Horizons in NSCLC Treatment

Announcer:
Welcome to CME on ReachMD. This activity, titled "**Keeping Pace in Lung Cancer - HER2: Unveiling New Horizons in NSCLC Treatment**" is provided by **Prova Education**.

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Dr. Aggarwal:
Hello and welcome to this Keeping Pace in Lung Cancer education series. HER2 mutations in non-small cell lung cancer, or NSCLC, represent approximately 3% of all patients with non-squamous non-small cell lung cancer, and are more common in patients without a history of smoking. Trastuzumab deruxtecan is now FDA approved to treat these patients. Today, we are going to discuss relevant clinical data, including dosing and management of adverse events. This is CME on ReachMD, and I am Dr. Charu Aggarwal.

Dr. Sands:
And I'm Dr. Jacob Sands.

Dr. Aggarwal:
Great to have you. Dr. Sands, can you start us off with a brief overview of HER2 alterations in non-small cell lung cancer, including appropriate testing?

Dr. Sands:
Well, this is another step forward in the now little more than a decade of genomic alterations that we've identified and ways that we can now target them. So, this started off with mutations, and of course, we now have fusions as well, and I specify that as part of the discussion of where HER2 fits into that. I guess I should also mention that in that we have amplification, and so this adds to some of the complexity of the understanding. Now, in the case of HER2, we are looking at mutations, and so that is a bit different than the way HER2 has been known now for a long time within breast cancer, where it was really looking at HER2 expression. In the setting of lung cancer, we're looking at mutations, so this is, looking at the DNA of the cancer cells themselves. That can be done by next generation sequencing, which is increasingly done as a way of really looking at a lot of different mutations, and fusions, throughout the spectrum. Given the increasing number of genomic alterations that we need to identify, because we have actually effective targeted therapy, this has really further led to the increasing use of next generation sequencing as a way of testing. Of course, there are other ways of looking at fusions, and expression, but that's not relevant so much to looking at HER2. I'll just point out that, you know, HER2 is really coming on

the tail of prior multiple genomic alterations that were known and able to be targeted.

And that's important to recognize, because there are patients where they had their genomic testing prior to initially starting treatment, and in notes people say there's no actionable alteration, which was true at the time of that testing being done, but now, particularly if it's been a while that the patient was on first-line treatment, it really makes it important to go back and look at if HER2 was looked at as part of that, to make sure that HER2 testing was done, really looking for mutation, specifically.

Dr. Aggarwal:
Absolutely, and I cannot recommend testing for this agent, or mutation, enough because even though it may not have an implication for first-line testing yet, it's completely clinically actionable in the second-line setting. And in fact, clinical trials are actually ongoing to test drugs in the first-line space.

Dr. Sands:
So, as a follow-up to that, Dr. Aggarwal, can you take us through the clinical data on trastuzumab deruxtecan in non-small cell lung cancer?

Dr. Aggarwal:
Absolutely. So we've seen a lot of data come through with this drug in the past few years in non-small cell lung cancer. The first was a phase 2 study in which this agent, trastuzumab deruxtecan, was studied at a dose of 6.4 mg/kg in patients with metastatic HER2-mutant non-small cell lung cancer, refractory to other standard treatments. This was the DESTINY-Lung01 study. A total of 91 patients were enrolled, with a median duration of follow-up of 13.1 months. For this pretreated population, we saw an objective response rate of about 55%, that was centrally confirmed. Median duration of response was quite long, at 9.3 months, with a median progression-free survival of 8.2, and a median overall survival for this group of patients at 17.8 months. Most recently at the World Congress in Lung Cancer meeting in 2023, we heard and we saw data from DESTINY-Lung02. This was also a phase 2 trial. It was blinded, noncomparative, again with similar patients with pretreated, HER2 mutant non-small cell lung cancer, but these patients were randomly assigned 2:1 to 2 doses of trastuzumab deruxtecan, to either 5.4 mg/kg or 6.4 mg/kg, respectively. And we found from these results that both of these doses continued to demonstrate strong and durable responses. For example, we saw a disease control rate of about 93.1%, with 5.4 mg/k, and 92% with 6.4mg/kg, and overall response rate about 49-56%, depending on which dose we used. Again, the 5.4 mg/kg dose was associated with a more favorable safety profile, and a reduced incidence of ILD [interstitial lung disease]/pneumonitis versus the slightly higher dose, and this was demonstrated in this DESTINY-Lung01 study, where we saw lower incidence of, adverse events, and this is actually the recommended dose now. This is the dose that I use in clinic. This is the dose that has been included in several of our guidelines, and I think it's just important to stress the importance of not just this as a target, and not just this as a drug, but the fact that there could be a more efficacious – or maybe similar efficacy but perhaps a better dose with safety data.

Dr. Aggarwal:
For those just tuning in, you are listening to CME on ReachMD. I'm Dr. Charu Aggarwal, and here with me today is Dr. Jacob Sands. We are discussing advancements in HER2 mutant, non-small cell lung cancer and emerging and current treatment options.

Dr. Sands, could you talk to us about early identification and monitoring strategies for adverse events, especially such as interstitial lung disease?

Dr. Sands:
Yeah, and this new drug now has a toxicity profile that's a little bit different, and so we'll dive into that, and just to stress, the dosing is so important, and I think complicated, because the initial dosing for breast cancer was a bit different. So, it does take, really for people to maybe go back and listen to what you said again, just to make sure they have it right. As far as the toxicity profile, first as you highlighted, interstitial lung disease is one of really, monitoring and reporting. And so within this trial, there were 26% of patients that were seen to have some grade 1 or higher toxicities. Now, in many of these cases, the drug is potentially held, or delayed in dosing, and monitored, but what it highlights is the importance of being aware about the possibility of interstitial lung disease, to make sure that clinicians are really monitoring and catching that earlier. But also, I'd highlight, you know, there are a lot of scans, or a lot of scenarios

where we see patients that have inflammatory markings on their skin, and of course, our lung cancer patients' waxing and waning respiratory symptoms. So I'd really highlight that I think it's important that people not just jump to a conclusion that something is ILD, because it's really hard to actually clinically pin that down. And recognize that, there's a possibility of other things, and really doing a workup. At the time where patients have symptoms that get too severe, it can be really hard to do workup. At the same time, really early on, of course, you don't want to be putting everybody through a bronch. So, I think, for each patient it's important to, 1, recognize and consider the possibility of ILD, but also recognizing the possibility of other things, and making sure you're not missing an opportunity to work up other potential diagnoses. Now, we did also see some GI toxicities. I think broadly, this was pretty well tolerated, but just to recognize that there are some toxicities that do overlap with some of our classic chemo toxicities. And also, there are some patients that experience alopecia. I know that's often really a question that patients have, and so it's not one necessarily to stress, but it is one to recognize and acknowledge.

Dr. Aggarwal:
Absolutely. I think early recognition and ensuring that we are not continuing to dose during these events can definitely help us in reducing the grade of these toxicities. But I'll circle back and highlight some data from DESTINY-Lung02, where, you know, drug-related ILD was actually adjudicated, and we saw that ILD, adjudicated related to drug was about 13% in the 5.4 mg/kg arm, but was as high as 28% in the higher dose. So, I think dosing can make a difference, and we should definitely think about that, as we start to manage more and more of these patients in the second-line setting.

So Dr. Sands, you've shared a lot of good information about ILD, early recognition, management, and I think we are going to start to see more and more of this drug be used in our, clinical setting, not just in second-line, but potentially in first-line, as clinical trial data emerge. Can you give us some take-home points that our audience can, you know, keep as pearls for management of these patients?

Dr. Sands:
Well, like any new drug, really just getting some experience. I think as people utilize the drug, you know, they get more comfortable with that. We've highlighted some of the things to look out for. I think if there's one thing that I'd really want to underline, it's to make sure that you really have checked for HER2 mutations. In these patients that have previously been treated, especially with initial limited PCR panels, you know, they may not have had HER2 testing. And we know from the data nationally, that despite long-term recommendations for EGFR, ALC, RAAS-1 – these have been around a long time – that there are a number of patients that aren't even getting that tested. And of course, there are going to be more that haven't gotten HER2 testing, just based on the way that the lung testing panels have been. So, first and foremost, make sure you know if there's a HER2 mutation, because that's the first step to even being able to consider whether this drug is right for that patient.

Dr. Aggarwal:
Absolutely. I think such important points, and that's all the time we have today, so I want to thank our audience for listening in, and thank you, Dr. Sands, for joining me. It was great speaking with you today. And be sure to tune in to our other episodes in the Keeping Pace series, for additional discussions on NSCLC.

Dr. Sands:
This was fun. Thank you so much.

Announcer:
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