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Evaluating Dato-DXd for EGFR-Mutated Advanced NSCLC: Data from a Pooled Analysis

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, and I'm Dr. Jacob Sands. Here with me today are Dr. Elaine Shum and Dr. Estelamari Rodriguez, and together we'll be discussing a pooled analysis of the TROPION-Lung01 and TROPION-Lung05 studies, which focused on the efficacy and safety of datopotamab/deruxtecan, or Dato-DXd for short, in patients with previously treated, EGFR-mutated advanced non-small cell lung cancer.

Dr. Shum is an Assistant Professor in the Department of Medicine at NYU Grossman School of Medicine, and I had the pleasure of working with her on this research, which was presented at the 2024 ESMO Asia Congress. Dr. Shum, thanks for being here today.

Dr. Shum:
Hi Jacob. It's great to see you. Thanks for having me.

Dr. Sands:
And Dr. Rodriguez is an Associate Director of Community Outreach, Thoracic Oncology at Sylvester Comprehensive Cancer Center at the University of Miami Health System. Dr. Rodriguez, it's great to have you with us as well.

Dr. Rodriguez:
Great. Thank you for the invitation.

Dr. Sands:
To kick things off, Dr. Rodriguez, can you give us an overview of the TROPION-Lung01 and Lung05 studies and what led to this pooled analysis of Dato-DXd in patients with previously treated, EGFR-mutated, advanced non-small cell lung cancer?

Dr. Rodriguez:
So both of these trials are trying to answer an area of need, which is: what is the next line of therapy for patients? So the TROPION-Lung01 trial was a trial testing in the second-line space; it was a randomized, open label trial of Dato-DXd versus docetaxel. And in that large trial of about 299 patients, there was a group of patients that had EGFR mutations that were included in this pooled analysis.

But then, we had the TROPION-Lung05 after we saw a signal of activity in that trial, and that trial really concentrated on patients that had actionable mutations and not only included patients with EGFR, but also included patients with ALK, BRAF, and other mutations. And these are patients that were different. That was a Phase 2, global trial that was single-arm, so every patient got Dato-DXd, and these patients had been previously treated with either platinum-based chemotherapy or there was prior use of immunotherapy, and all those patients had prior targeted therapy for their specific mutation.

Dr. Sands:
And from a study design perspective, Dr. Shum, how was this pooled analysis conducted, and what were the primary endpoints?

Dr. Shum:
We actually looked specifically at the EGFR-mutated lung cancer patients. So in total for both of the studies, there were 117 patients that were found to have EGFR. The majority came from the TROPION-Lung05 study where there were 78 patients, and there were 39 patients in the TROPION-Lung01 study. For both of these studies, patients had to have received at least one or more EGFR-targeted

therapies, as well as platinum-based chemotherapy, and prior immunotherapy was also permitted.

In both of the studies, the patients received Dato-DXd at 6 milligrams per kilogram every 3 weeks. And so when we put the data together for all of these EGFR patients, this was retrospectively pooled, and we were focusing on these exploratory endpoints. These included overall response rate, which was by blind independent central review, or BICR, best overall response, median duration of response, disease control rate, median PFS, median OS, and also safety.

Dr. Sands:
Now, if we zero in on the patient population included in this pooled analysis, Dr. Shum, what do we know about their prior treatments and baseline characteristics?

Dr. Shum:
In this pooled population, the median age of the patients was about 63 years old. The majority were women at 62 percent, and about 69 percent were of Asian descent. There were about 31 percent of patients who could have clinically inactive or treated asymptomatic brain mets. And in terms of the EGFR mutations that they had, most commonly, they were having the common EGFR mutation, so EGFR exon 19 deletions and EGFR L858R. However, there were a few patients that also had atypical or uncommon EGFR mutations that were in this pooled analysis as well. In regard to the median number of prior treatments, this was 3. So this was a heavily pretreated cohort of patients. About 25 percent actually received four or more prior lines of treatment.

For all patients, except for one, everyone received platinum-based chemotherapy, and about 82 percent had previously received osimertinib, of which about 40 percent received osimertinib as first-line therapy.

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. Elaine Shum and Dr. Estelamari Rodriguez about a pooled analysis of the TROPION-Lung01 and TROPION-Lung05 studies, focusing on the use of datopotamab/deruxtecan in patients with EGFR-mutated, advanced non-small cell lung cancer.

Now, if we turn our attention to the results, Dr. Shum, what did the pooled data show in terms of efficacy outcomes, such as objective response rates and progression-free survival?

Dr. Shum:
So in this pooled analysis, the overall response rate was 43 percent. There were five patients who had a complete response, and about 45 patients who had partial responses. The median PFS was 5.8 months, and the median overall survival was 15.6 months. They did actually do an ad hoc analysis as well looking at patients who had previously received osimertinib, and they showed that they were actually similar outcomes to the overall pooled population as well.

Dr. Sands:
And how about the safety outcomes, Dr. Rodriguez? What adverse events were most commonly observed, and were there any notable safety signals that clinicians should be aware of?

Dr. Rodriguez:
So Dato-DXd is a different drug than what we have traditionally used, and it has very specific side effects that have already been described in prior trials. The main adverse event that was seen in this trial and others has been stomatitis. And in this particular trial, TROPION-Lung05, there was a lot of care for these patients with mouthwashes to decrease the stomatitis. But that was really the leading adverse event that was seen, and it was not surprising; it was expected. It's a class effect of this particular drug.

The other side effect of note is that there was a lot of attention on monitoring patients for interstitial lung disease and pneumonitis. And the importance of that is, especially in the TROPION-Lung05 trial, these patients were previously treated with targeted therapies, and we have seen in other trials that include immunotherapy that sometimes when you add the drug after patients have had immunotherapy, you might get more pneumonitis. So it was really important to understand if there was some signal of excess pneumonitis. And we actually found that no, there was no excess pneumonitis in this trial of patients that were previously treated with targeted therapies and then received Dato-DXd.

So besides the mucositis, stomatitis, and the interstitial lung disease, which is low—less than 10 percent—we also saw patients that had ocular surface events, which have been described as brightness in the eye and then keratitis. For some patients, they have blurry vision. So this is a new side effect that is not traditionally described in chemotherapy trials and for which there's also a lot of care that was placed in this trial. So patients could use preservative-free eye drops to improve these symptoms.

With all that being said, Dato-DXd has a payload, which is chemotherapy. And for that reason, patients did experience some amount of

cytopenias in this trial, but they were manageable. I will say that in general, the discontinuation rate was very low—less than 5 percent—and there were about 20 percent of patients that required some dose reduction and 20 percent of patients required some dose interruptions. So it was manageable in this group population. There was a lot of care, again, to manage the stomatitis and the ocular surface events. But besides that, the rest was really what we expected to see in a drug that has some kind of chemotherapy effect.

Dr. Sands:
Given those results, Dr. Rodriguez, and considering the new ORCHARD data presented at the 2025 European Lung Cancer Conference, which focused on combining osimertinib with Dato-DXd, how do you see this approach potentially fitting into future treatment strategies for this patient population?

Dr. Rodriguez:
That is a great question because we have seen over the last two years a big revolution in the management of EGFR-positive lung cancer where we're considering intensification of treatment for patients from the get-go. So now, we move some later therapies into earlier stages of disease so that since we're either adding the FLAURA2 protocol, which is chemotherapy and osimertinib, or the MARIPOSA protocol, which is amivantamab and lazertinib, our patients are seeing prior drugs. So what do we do for those patients when they progress? And that's why I think the ORCHARD data and the TROPION-Lung05 data is really key because we need next lines of therapy for these patients that are receiving intense treatments upfront with extra drugs.

So where I see this drug fitting in is that patients that had the FLAURA2 protocol—where they had chemotherapy upfront with osimertinib—when they progress, they need an active agent. And what was really great about this pooled analysis is that it shows that, specifically in the EGFR population, there is an activity of this drug that gets these patients to have responses of close to 40 percent. So we are seeing duration of responses that are close to 7 months and really significant reductions in tumor volume and activity in areas like the brain where it has been very difficult to manage when patients progress on osimertinib upfront.

So I do think that this has a role immediately after for patients that had an intense treatment upfront. It also has a role for patients that have gone through two lines of therapy, either if they had single-agent osimertinib and they went to chemotherapy or amivantamab; now, the third option might be this Dato-DXd as an antibody drug conjugate that has activity, CNS penetration, and a manageable toxicity profile.

Dr. Sands:
What a wonderful discussion about the potential for datopotamab/deruxtecan as a treatment for EGFR-mutated, advanced non-small cell lung cancer. With that, I'd like to thank my guests, Dr. Elaine Shum and Dr. Estelamari Rodriguez, for joining me to share the efficacy and safety findings from this pooled analysis. Dr. Shum, Dr. Rodriguez, it was wonderful having you both on the program.

Dr. Shum:
Thanks so much, it was great being here.

Dr. Rodriguez:
Thank you so much.

Announcer:
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