



Transcript Details

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Poster Pearl: Dato-DXd Demonstrates Intracranial Efficacy in NSCLC

Announcer:

You're listening to On the Frontlines of Non-Small Cell Lung Cancer. Here's your host, Dr. Jacob Sands.

Dr. Sands:

Welcome to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm your host, Dr. Jacob Sands. And joining me to discuss a post-hoc analysis of the TROPION-Lung05 data, which focused on the intracranial efficacy of datopotamab deruxtecan in patients with previously treated advanced metastatic non-small cell lung cancer, is lead investigator Dr. Aaron Lisberg. Dr. Lisberg is a thoracic medical oncologist at the University of California, Los Angeles. And this is a special one for me because I had the pleasure of working with Dr. Lisberg on this as well as other datopotamab deruxtecan studies. Dr. Lisberg, it is wonderful having you on the program today.

Dr. Lisberg:

Thank you, Jacob. Thank you for having me.

Dr. Sands:

So let's get started with some background. How common are brain metastases in advanced non-small cell lung cancer? And what are the challenges in treating them?

Dr. Lisberg:

As many of our viewers will know who treat lung cancer, unfortunately, brain metastases are a frequent complication of lung cancer. The reported rate is approximately 10 percent. And I think what can be interesting in this case is sometimes those brain metastases can be asymptomatic. So as many are probably aware, at the time of a metastatic disease diagnosis in non-small cell lung cancer, NCCN guidelines recommend a baseline brain MRI to look for brain metastases. Certainly, in the setting of brain metastases with the exception of some therapies that can be highly effective in the CNS space, we typically need to give definitive therapy, which is oftentimes in the form of radiation, to these brain metastases before starting systemic therapy. Thereafter, these patients are certainly on systemic therapies.

And the poster that I presented from the TL05 study of Dato-DXd in patients with actionable genomic alterations with advanced metastatic non-small cell lung cancer was specifically looking at these patients that had a history of brain metastases and whether Dato-DXd provided benefit throughout duration of the trial.

Dr. Sands:

Switching gears a little bit, just to speak about datopotamab deruxtecan and what we know from that drug, of course, you presented also the TROPION-Lung01, so maybe you can give us some information about Dato-DXd, TROPION-Lung01, TROPION-Lung05; what are we seeing as far as the efficacy of this drug?

Dr. Lisberg:

Sure. So Dato-DXd is a TROP2-targeted antibody drug conjugate. It's being evaluated in a number of solid tumors. And as you mentioned, you and I have been working on this drug for several years now, and there was some high-level phase 3 data presented at ESMO by myself as well as Dr. Bardia in breast cancer, which is really the highest-validated data for this drug so far. And so what we saw was Dato-DXd performed very well in a direct comparison on a randomized phase 3 trial called TROPION-Lung01 versus docetaxel. This trial was a randomized trial for patients with advanced metastatic non-small cell lung cancer. Patients could have both actionable genomic alterations or not have actionable genomic alterations. These patients were then randomized 1:1 to receive Dato-





DXd at a dose of 6 mg/kg every 3 weeks versus docetaxel. And the trial had two dual primary endpoints: progression-free survival and overall survival.

So what we saw at the analysis presented at ESMO 2023 was there was a statistically significant improvement in progression-free survival for Dato-DXd over docetaxel, with a hazard ratio of 0.75. But when we really looked at this data a little closer, we identified that there was a clear divergence in terms of this benefit by histology; in those patients with non-squamous histology, there was clearly a much greater benefit to Dato-DXd compared to docetaxel with a hazard ratio of 0.63, a median progression-free survival improvement of 1.9 months. And in the squamous cell patients, we really didn't see a benefit. Actually, docetaxel performed better.

When we looked at the forest plot and the data a little closer, it did appear that the actionable genomic alteration patients—the majority of which had non-squamous disease—performed the best with Dato-DXd. However, we did see that the PFS benefit in the non-squamous patients did exist for those patients without actionable genomic alterations as well. So the further development of this drug in non-small cell lung cancer in the advanced metastatic setting is really focused on the non-squamous population that's inclusive of the actionable genomic alteration population.

In terms of the poster today, that was from the TL05 study, and that was a single-arm study that only enrolled the actionable genomic alteration patient population, and it is the first non-small cell lung cancer-specific data to look at the intracranial efficacy of this drug.

Dr. Sands:

Now before we get into a bit of the more specific brain discussion, can you talk a bit about the population enrolled? So it was actionable genomic alterations, but there were a number of different ones. Who was accrued to this trial? And what did those tumors look like?

Dr. Lisberg

Yeah, of course. And I think that's very important as we talk about this poster specifically. So these are patients with advanced metastatic non-small cell lung cancer as we've discussed. They had to have an actionable genomic alteration, which was defined as the following: the most common was EGFR, but the others that were included were ALK, ROS1, NTRK, BRAF, MET exon 14 skipping mutation, and RET. So those were the patients that were enrolled. The patient's other kind of standard criteria, such as ECOG performance status 1 or less, they must have received at least one line of targeted therapy but essentially exhaust the targeted therapy options for their actionable genomic alterations, and they must have also received platinum-based chemotherapy.

Importantly, for the poster we're going to talk about, patients across this trial, the TL01 trial, and really a Dato-DXd development program in general were allowed to enroll if they had a history of brain metastases or if they had brain metastases that were considered inactive. So only patients with untreated symptomatic brain metastases were excluded, meaning that patients with untreated, asymptomatic brain metastases that the investigator on site felt like were appropriate for trial were allowed to enroll on trial. And so that's who was enrolled. Again, for the TL05 study, it was single-arm Dato-DXd 6 mg/kg given every 3 weeks. And the primary endpoint was objective response rate.

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. Aaron Lisberg about a post-hoc analysis of the TROPION-Lung05 trial, focusing on the use of datopotamab deruxtecan in patients with advanced metastatic non-small cell lung cancer.

Now, Dr. Lisberg, you've described the TROPION-Lung05 cohort as well as how common brain metastases are. Let's turn our attention now to the key findings from this post-hoc analysis. What did we learn about the intracranial efficacy of Dato-DXd in patients with previously treated non-small cell lung cancer?

Dr. Lisberg:

Yeah. So we learned a number of things, which were presented at ASCO 2024 and are on the poster. And so to kind of level this discussion, patients were essentially divided into two general categories: patients with baseline brain metastases, which made up 53 of the patients, and patients without baseline brain metastasis, which is 84 of the patients. The poster looks at these populations in a number of different ways. The first analysis was just looking at overall systemic efficacy. We do know that patients that have brain metastases typically have poorer outcomes with non-small cell lung cancer. It is interesting to see how these patients did on trial. So when we look at that that systemic efficacy, we can see the objective response rate was lower in the patients with baseline brain metastases, at 28 percent compared to 40 percent in the patients without baseline brain metastases.

But if we look at the outcome that really matters in terms of patients here in progression-free survival, specifically, we can see that the outcomes were very similar between the two groups, despite the lower objective response rate in the patients with baseline brain metastases, where the median PFS in patients with baseline brain mets was 5.4 months. And without the baseline brain mets, the





median PFS was 5.6 months. We showed progression-free survival in Kaplan-Meier curves. And you can see the curves are very similar here, suggesting that irrespective of whether a patient had a baseline brain metastases or not, they seemed to perform very similarly on trial, which I think is encouraging within the construct of us anticipating the patients with baseline brain metastases would perform poorer.

Additional information that was shown here was looking at systemic safety that appeared to be very similar, and then we turned our attention on the poster to the intracranial efficacy. So we do know that with other ADCs in the DXd portfolio, including trastuzumab deruxtecan in a HER2- mutant and overexpressed population as well as HER3-DXd in the EGFR-mutant population, there has been intracranial efficacy presented for these agents, which is very encouraging. We also see that with other TROP2 ADCs, such as sacituzumab govitecan in breast cancer, but this was the first time we looked at intracranial efficacy of Dato-DXd in non-small cell lung cancer.

And you know, Jacob, you and I have talked about this—I don't think that the data and the number is small here. So the intracranial efficacy was assessed in 18 patients with baseline brain metastases. But it's important to point out there were only 3 of these patients that were untreated at the time of evaluation. And so knowing at a high level of certainty exactly what the objective response rate intracranially for this drug is, it's beyond the balance of what we can really assess from this poster. But I think what we can identify is that there appears to be intracranial activity, which is consistent with what we've seen again across the DXd ADC portfolio and with other TROP2 ADCs.

So specifically, the intracranial objective response here in the 18 patients, again, 15 of who had had prior therapy, was 22 percent. It was broken down by patients with EGFR mutations, without, and patients with ALK alterations. And interestingly, in the 3 patients that had not had any local therapy, we did see a response in 1 of those patients.

Dr. Sands:

What about toxicity? What did the safety outcomes look like when you compare patients with and without baseline brain metastases?

Dr. Lisberg:

We see essentially equivalent safety between patients that had baseline brain mets and those that did not. If we look at this data a little closer, grade 3 or higher treatment-related AEs were actually higher in the patients without baseline brain metastases, at 32 percent compared to 23 percent. That's really meaningless. There's no reason to believe that that is of any consequence, but it does support the idea that the patients with baseline brain metastases are certainly not doing worse systemically from a safety perspective. And in terms of the intracranial safety outcomes, they appear to be very similar as well.

So I think that the systemic efficacy of Dato-DXd looks very similar in terms of PFS, irrespective of if a patient has a baseline brain metastases or not, and the safety summary seems very similar as well. These hints of intracranial activity are encouraging. And I think the global takeaway message here is that when we start patients on this drug—and this has been my experience, and I suspect yours as well, Jacob—we can have some level of confidence that the CNS will be protected throughout the duration of administration.

Dr. Sands:

Lastly, Dr. Lisberg, where do we go from here with these findings? You've described encouraging efficacy outcomes as well as sounds like manageable toxicity profile. There's more to that toxicity profile discussion, which, of course, you've addressed in many other settings as well. But any studies on the horizon? What's next for datopotamab deruxtecan? And in particular, are there studies around brain efficacy ongoing as well?

Dr. Lisberg:

Yeah, it's a great question. So as indicated on the poster, there's a couple of dedicated brain metastases studies that are ongoing. So the Dato-based study that's being done in breast cancer as well as the TUXEDO-2 study are specifically geared to answer this question more definitively. And some of these studies also enroll patients with leptomeningeal disease, which, as we both know, is a patient population that's very hard to treat and typically excluded from trials. So I think that the investigators leading these trials should be lauded for the enrollment of these patients to allow us to understand this. Because if someday Dato-DXd and these other DXd ADCs are being used in the clinic, we do have patients with leptomeningeal disease, so having some data to guide those treatment decisions can be very helpful.

I think it will also be interesting to see CNS activity in the non-AGA patient population, specifically CNS activity from the TL01 study. I anticipate data in that regard coming out in the coming months to years and continuing to build the story. I think this is a first step in the right direction. It's a very encouraging first step. But certainly, we need to increase the number of patients evaluated who we can truly assess intracranial activity—those that have untreated brain metastases—to help guide those clinical decisions moving forward.





Dr. Sands:

Well, I look forward to the maturing of those datasets and hearing more about those as well as the datopotamab story and ongoing studies within the first line. But for now, I want to thank my guest, Dr. Aaron Lisberg, for joining me to discuss the post-hoc analysis of the TROPION-Lung05 trial examining the intracranial efficacy of datopotamab deruxtecan in patients with previously treated advanced metastatic non-small cell lung cancer. Dr. Lisberg, it was wonderful having you on the program.

Dr. Lisberg:

Thanks, Jacob. And we look forward to talking with you again soon.

Announcer:

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