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Analyzing Dato-DXd for Non-Squamous NSCLC with Brain Metastases

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:
Welcome to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Jacob Sands, and today I'm joined by Dr. Aaron Lisberg to discuss the results from the phase 3 TROPION-Lung01 trial focusing on datopotamab deruxtecan in patients with advanced non-squamous non-small cell lung cancer with brain metastases. Dr. Lisberg is a thoracic medical oncologist at the University of California Los Angeles, and I had the pleasure of working with him on this research, which was presented at the 2024 ESMO Congress. Dr. Lisberg, thanks for being here.

Dr. Lisberg:
Thanks, Jacob.

Dr. Sands:
Well, let's dive right in, Dr. Lisberg. Could you explain what we currently know about treating patients who have advanced non-squamous non-small cell lung cancer with brain metastases?

Dr. Lisberg:
Sure. Unfortunately, in non-small cell lung cancer, brain metastases are very common. And so in terms of definitive therapies, we're always thinking about radiotherapy or surgery in some cases. In the non-squamous population, it's also worth mentioning that in patients with actionable genomic alterations, such as EGFR, ALK, ROS1, for some of those patients—if they have limited brain metastases that are asymptomatic—we can forego a definitive therapy, use close monitoring of the CNS, start the targeted therapy, and have good CNS benefit and avoid those definitive therapies for patients. But in general, most of our patients do need to undergo definitive therapy, and so it is a difficult problem that we have. It's not unique to non-small cell lung cancer, but it's highly prevalent. And so I think that given those issues, it's important as we're developing new therapies in this space to be thinking about and evaluating the CNS activity.

Dr. Sands:
And before we dive specifically into the activity in the brain, give us a little background on TROPION-Lung01 trials and what we've seen as far as results thus far.

Dr. Lisberg:
Sure. The TROPION-Lung01 study was a large randomized, phase 3 study evaluating Dato-DXd, which is a TROP2-targeted antibody drug conjugate with the topo-I payload versus docetaxel in patients both with and without actionable genomic alterations. Patients must have received chemotherapy in the non-AGA group. They must have also received immunotherapy in the patients with actionable genomic alterations. They could have received immunotherapy, but they must have exhausted all target therapy approaches. The trial had two dual independent primary endpoints. PFS was positive as there was statistically significant improvement in PFS in favor of Dato-DXd over docetaxel. However, when we looked at that closer, we saw that the PFS benefit was entirely driven by the non-squamous patient population, and that within the non-squamous patient population, or in general, the actionable genomic alteration population appeared to derive the greatest benefit from a PFS with Dato-DXd over docetaxel.

In terms of overall survival, this did not meet statistical significance. There was a trend in favor of overall survival in favor of Dato-DXd

over docetaxel. Again, this appeared to be more pronounced in the non-squamous population, certainly not seen in the squamous population, and most pronounced in the actionable genomic alteration patient population.

Dr. Sands:
So now looking specifically more at that brain metastases component which is part of the methodology behind this study, brain metastases were allowed if treated and stable or untreated and stable; any other aspects of the cohort before we get into the results?

Dr. Lisberg:
So in terms of the breakdown, the patients with brain metastases were 84 patients; 43 were treated with Dato-DXd, 41 with docetaxel, and the remaining 384 patients did not have baseline brain metastases. When we look at demographics, I think that most of the characteristics are very similar, but I do think that the difference in patients with baseline brain metastases by actionable genomic alteration status is an important thing to note. So when we look at the patients with baseline brain metastases, 33 percent of patients treated with Dato-DXd who had baseline brain metastases had actionable genomic alterations. This is compared to only 18 percent of patients treated with Dato-DXd without baseline brain metastases. And the same thing was seen with the docetaxel as 39 percent of the patients with baseline brain metastases had actionable genomic adulterations that were treated with docetaxel, and of the patients without baseline brain metastases treated with docetaxel, only 18 percent had actionable genomic alterations.

I say this because this poster itself focuses on the systemic safety and efficacy. And in the context of understanding the systemic safety and efficacy, the fact that there is an imbalance in the baseline brain metastases group in favor of the actionable genomic alteration group—a group we already know does better with Dato-DXd for a number of reasons—could bias some of these results. And so I think that's an important thing to understand.

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 the results of the phase 3 TROPION-Lung01 trial on datopotamab deruxtecan, looking specifically at patients who have advanced non-squamous non-small cell lung cancer with brain metastases.

Now, Dr. Lisberg, let's talk results. What did we find in terms of efficacy and safety?

Dr. Lisberg:
In terms of the safety summary, nothing new to draw out here. Bottom line is it appears that the safety was similar with Dato-DXd, whether a patient had baseline brain mets or without baseline brain mets. If you do look at the data, it's actually somewhat surprising. You'll see that some of the markers suggest that patients with baseline brain metastases actually had better safety outcomes: 7 percent of patients with grade three or higher treatment-related adverse events with baseline brain mets were treated with Dato-DXd compared to 25 percent with grade 3 or higher treatment-related AEs treated with Dato-DXd without baseline brain mets.

When we get into the systemic efficacy, we see in the baseline brain metastases group that there is an improvement for patients with Dato-DXd over docetaxel: median PFS at 4.9 months compared to 3.6 months, a hazard ratio 0.59. And in the patients without baseline brain metastases, we see a median PFS of 5.7 with Dato-DXd to 3.7 with docetaxel with a hazard ratio of 0.64. When we turn to the overall survival data, we see something similar in the patients with baseline brain metastases. There is a trend in favor of Dato-DXd over docetaxel at 12.9 months compared to 8.9 months, a hazard ratio of 0.94. Without baseline brain metastases, those numbers are, in the Dato-DXd group, 14.8 months compared to 12.6 months, and a hazard ratio 0.82. Again, we're not going to take this data and start making overarching claims, but I think what we can say from this data, similar to what we saw in the TL05 data, is there appears to be some level of CNS penetration and CNS control here.

And that's further played out by another table that was presented on this poster, essentially looking at patterns of relapse by brain mets at baseline. So what we're seeing in the patients with baseline brain metastases, the site of progression in one patient—2 percent—was the brain. And similarly, in patients without baseline brain metastases, four patients—or 2 percent—had a progression in the brain. So only 2 percent of progression for patients, irrespective if they had baseline brain mets or not, was in the brain. And this is in contrast to the docetaxel arm. In the patients with baseline brain metastases who were treated with docetaxel therapy—who we know doesn't have a lot of great CNS activity—10 percent of the progression events were in the brain. And when we look at the docetaxel arm in patients without baseline brain metastases, 5 percent of the progression events were in the brain, suggesting that irrespective of baseline brain met status, we are seeing more progression in the brain in patients treated with docetaxel compared to Dato-DXd.

And finally, when we look at systemic efficacy broken down by baseline brain metastases status, we see a similar objective response rate for Dato-DXd-treated patients, whether they had baseline brain mets or not, at 30 percent for those patients with baseline brain mets and 31 percent without. We do see landmark improvement in terms of duration response in the patients without baseline brain mets; patients' duration response greater than 9 months who were treated with Dato-DXd without baseline brain mets is 27 percent

compared to only 8 percent in the docetaxel arm. And so maybe the longer duration does matter more. And without the baseline brain mets, maybe patients are going to have longer outcomes, which is what we would anticipate. But I think collectively, this data supports the idea that, from both the safety and efficacy perspective, Dato-DXd is providing benefit to patients, irrespective of whether they have baseline brain mets or not. The only caveat on this dataset is the AGA imbalance in favor of the baseline brain mets, which could skew that group to better outcomes simply based on the AGA status. And maybe that, in some ways, overcomes some of the detriment that could occur with the brain mets.

Dr. Sands:
Now with all of those results in mind, assuming this drug becomes widely available, how do those impact your treatment decisions? And what do you think are the implications on how we treat patients with brain metastases?

Dr. Lisberg:
I think that these two datasets are consistent with what we've seen with other ADCs, such as sacituzumab govitecan in breast cancer as well as trastuzumab deruxtecan and patritumab deruxtecan in lung cancer. Where we're seeing CNS activity of these ADCs, I think it's definitely not to the level of an osimertinib or something like that where we could forgo definitive therapy and simply treat with a systemic agent. I think in the setting of Dato-DXd, it's important to treat any problematic brain mets, certainly any symptomatic brain met. But I think that once we start patients on therapy, we can have a reasonable level of confidence that Dato-DXd is going to provide CNS protection, CNS benefit, and there will be CNS activity. And I think this is an important piece in the puzzle that continues to build on the story of Dato-DXd and how this therapy may be effective for our patients.

Dr. Sands:
With those key take-home points in mind, I want to thank my guest, Dr. Aaron Lisberg, for joining me to discuss our research on datopotamab deruxtecan in patients with advanced non-squamous non-small cell lung cancer with brain metastases. Dr. Lisberg, it was great having you on the program.

Dr. Lisberg:
Thank you, Jacob.

Announcer:
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