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Dato-DxD for NSCLC: A Review of Final Overall Survival Data from TROPION-Lung01

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 am your host, Dr. Jacob Sands, and today I am joined by Dr. Aaron Lisberg to discuss the final overall survival data from the TROPION-Lung01 trial, which focused on datopotamab deruxtecan in patients with non-small cell lung cancer. 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 ESMO last year and at the World Conference on Lung Cancer this year. Dr. Lisberg, welcome to the program.

Dr. Lisberg:
Thank you, Jacob.

Dr. Sands:
So to start us off, could you give us a bit of background on the current second-line therapies for non-small cell lung cancer and their limitations? And I'm focusing on when second line has become so complicated—let's say, after chemotherapy and immunotherapy—for those without actionable genomic alterations, and you can explain what that means for those with actionable genomic alterations.

Dr. Lisberg:
Sure. Really, our standard of care here is docetaxel +/- ramucirumab. And although the addition of ramucirumab certainly can improve outcomes in these patients, I do think there is significant limitations of docetaxel-containing regimens, which are a number of things.

First of all, tolerability. There is a lot of toxicity associated with docetaxel, specifically bone marrow toxicity; febrile neutropenia is a frequent event, and it can, in some events, land patients in the hospital. So it can be life-threatening itself. And because of those cumulative toxicities, it's often difficult to continue to administer the therapy for extended periods of time for patients. Oftentimes, counts over time and bone marrow damage will cause problems there.

And so it's not a wonderful therapy. It's what we have, and certainly, I think that we could all agree in the field that we are looking to do better.

Dr. Sands:
So that's really helpful background, and now we're going to be discussing a trial that uses datopotamab deruxtecan, but before we get into that trial specifically, can you give us a little background on Dato-DXd, what an antibody-drug conjugate is, and the components of this one in particular?

Dr. Lisberg:
Yeah. Well, as the audience is probably fairly well aware, antibody-drug conjugates are a more targeted or directed chemotherapy approach. So the mechanism of action for these drugs is the chemotherapy payload acting on the tumor cell itself, but the mechanism by which that payload is delivered to the cell is a little different.

In the setting of Dato-DXd, the antibody is designed to target the TROP2 protein. We do have TROP2 ADCs approved in cancer, but none in lung cancer. So as the audience may be aware, sacituzumab govitecan is a TROP2-targeting ADC approved in both breast and bladder cancer. And the protein of interest on the tumor cells that's highly expressed in non-small cell lung cancer is TROP2. The

payload in the setting of Dato-DXd is a topoisomerase 1 payload called deruxtecan. It is an exatecan derivative and thereby acts in a DNA-damaging mechanism.

Dr. Sands:
So with all of that in mind, let's dive into the latest research we conducted on this subject. Can you describe the design of TROPION-Lung01?

Dr. Lisberg:
Sure. Yeah, so TROPION-Lung01 was a large global, randomized phase 3 study evaluating Dato-DXd randomized against docetaxel, so the two therapies we've been speaking about up until this point in the setting that we discussed. So this was for patients who were eligible for second-line chemotherapy with docetaxel, again, in the non-AGA patients—those were patients that had received both chemotherapy and immunotherapy either together or sequentially.

And the AGA patients must have received and exhausted all targeted therapies. They must have received platinum doublet chemotherapy, and they could have received up to one line of immunotherapy. Patients were then randomized received Dato-DXd or docetaxel; both agents were given intravenously every 3 weeks. And importantly, the trial had two dual primary endpoints: progression-free survival and overall survival.

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 newest findings from the TROPION-Lung01 trial.

Now before we get into the updated overall survival data, can you just give us a background on what you previously presented with the progression-free survival results, which is the first of the dual primary endpoints you just mentioned, as well as some of the other supporting data that you presented?

Dr. Lisberg:
Of course. So the initial presentation on this was at ESMO in 2023. As you mentioned, I presented that, and at that time, we showed progression-free survival data that showed a statistically significant improvement in favor of Dato-DXd over docetaxel. This has a hazard ratio of 0.75, the median improvement was 0.7 months, and in the intention-to-treat population, there was a more than doubling in the objective response rate, and there was a longer-duration response.

However, given the incremental benefit in terms of median improvement, which certainly isn't always the best way to assess these things, we did look further and we identified that there was a clear distinction in terms of the benefit based on histology where in patients with non-squamous histology, there was a more pronounced PFS benefit in favor of Dato-DXd over docetaxel with a hazard ratio of 0.63, a median improvement of 1.9 months—5.6 months in the Dato-DXd arm compared to 3.7 in docetaxel—and almost tripling in the objective response rate, 31 percent in Dato-DXd versus 12 percent in docetaxel. When we look at the PFS curves, they're clearly separating. The exact opposite was seen in the squamous population where there was clearly no benefit for Dato-DXd over docetaxel, suggesting that in an unselected matter, this was not an appropriate therapy for squamous disease.

Now another important point to pull out of it was that the patients with actionable genomic alterations, a population we've already been discussing at length today, appeared to have the greatest benefit with Dato-DXd over docetaxel with a hazard ratio for PFS of 0.38. And we also found that the PFS hazard ratio for non-squamous patients without actual genomic alterations also suggested an improvement in favor of the non-squamous patient without AGAs with a hazard ratio of 0.71.

In terms of additional data at the time, I showed an interim overall survival analysis—and you're going to be talking about the overall survival analysis shortly—but in the interim analysis, there was a trend in favor of Dato-DXd over docetaxel. It was more pronounced in non-squamous again, and we talked about the toxicity profile. I think that's probably beyond the discussion today, but it's important to know that there are some unique but manageable toxicities to this therapy: most importantly, stomatitis, and I would say, ILD.

Dr. Sands:
Yeah. And that's really helpful data that you just mentioned. So it was already positive by one of the dual primary endpoints. Now the overall survival data, although it had looked very encouraging at the time of your presentation in the non-squamous histology, we ultimately saw a hazard ratio of 0.84 with a confidence interval that did cross one. So we saw a trend of what looked like improvement in OS, and it was a median 14.6 months compared to 12.3 months in docetaxel—so fitting a timeframe that was also similar to what we saw from PFS but, again, did not meet statistical significance for the non-squamous non-small cell cohort.

In the squamous cohort, it looked similar as well to what we had seen from PFS, and the curves look more in favor of docetaxel. We also saw there was no real update to the toxicity profile. Ultimately, we saw dose reductions that were fewer in the Dato-DXd arm at 20

percent as compared to 30 percent from docetaxel. Also, fewer treatment discontinuation at 8 percent of Dato-DXd compared to 12 percent of docetaxel.

And so in the end, we did see a statistically significant improvement in median PFS, as you have described, and that's what you presented. We saw an improvement in the response rate, as you described. What looks favorable as far as treatment discontinuation and dose reductions from a toxicity standpoint in favor of Dato-DXd, and an overall survival that looks like it trends but did cross the confidence interval.

We also see numbers that separate out more amongst the non-squamous subset. In those who had tumors with actionable genomic alterations, we see a median overall survival of 15.6 months for Dato-DXd as compared to 9.8 months in docetaxel, with a hazard ratio of 0.65. But again, it is broad, so the confidence interval does cross one still. And in those without actionable genomic alterations, we see 13.6 months with Dato-DXd as compared to 12.3 months with docetaxel.

So with all of that together, how do you process all of this? And what do you now see as the treatment paradigm and any further possible path for the drug?

Dr. Lisberg:
Yeah. Thanks, Jacob, for all those updates. So for the EFGR-mutant patient population, I think that we have a lot of data to support that Dato-DXd is outperforming docetaxel, and we've talked about that. The PFS data is much stronger in those patients, and the OS data also looked very strong. So if we're really focused on identifying the patient population based on the data we have right now, the patient population that will have a PFS benefit and the patient population that we have the highest level of confidence that there is an OS benefit is a subset of the non-squamous patients and a subset of the AGA patients, certainly—so we're continuing to subset, which has always brought with it some risk—it would be these EGFR-mutant patients. That is, I think, a very strong path forward and clear path forward for that patient population. But outside of the AGA patient population, certainly outside EGFR specifically, I think there's still additional work potentially that needs to be done to identify those patients that are most likely to benefit.

Dr. Sands:
With those impacts in mind, I want to thank my guest, Dr. Aaron Lisberg, for joining me to discuss our research on datopotamab deruxtecan in patients with non-small cell lung cancer. Dr. Lisberg, it was wonderful having you on the program.

Dr. Lisberg:
Thank you, Jacob.

Announcer:
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