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Dato-DXd's Intracranial Efficacy in NSCLC: Insights from TROPION-Lung01

Announcer:
You're listening to *Project Oncology* on ReachMD. Here's your host, Dr. Jacob Sands.

Dr. Sands:
This is *Project Oncology* on ReachMD, and I'm Dr. Jacob Sands. Today, we'll be examining a post-hoc analysis of the TROPION-Lung01 trial that looked at the intracranial efficacy of datopotamab deruxtecan, or Dato-DXd for short, in patients with advanced metastatic non-small cell lung cancer and baseline brain metastases. This review was presented at the 2025 World Conference on Lung Cancer.

And joining me to discuss this data is Dr. Aaron Lisberg, a thoracic medical oncologist at the University of California, Los Angeles. Dr. Lisberg, welcome to the program.

Dr. Lisberg:
Thank you, Jacob. Thank you for inviting me to join you today.

Dr. Sands:
So I'd like to start by giving some background on TROPION-Lung01 and this post-hoc analysis. TROPION-Lung01 is a global phase 3 study comparing Dato-DXd to docetaxel in patients with advanced or metastatic non-small cell lung cancer. The post-hoc analysis focused specifically on patients with baseline brain metastases to evaluate central nervous system objective response rates, disease control rate, and progression-free survival.

With that context in mind, Dr. Lisberg, could you comment on the significance of TROPION-Lung01 and the importance of looking at these outcomes in this particular patient subgroup?

Dr. Lisberg:
Of course, yeah. So, Jacob, I know you and I have talked about this trial a lot and the development of Dato-DXd. It's very exciting that this drug is approved for our patients with advanced metastatic non-small cell lung cancer who have EGFR mutations.

And so the TROPION-Lung01 study, as you mentioned, are randomized patients with advanced metastatic non-small cell lung cancer eligible for Dato-DXd or docetaxel. And I think one of the real key important qualities that the sponsor should be lauded for was the ability for us to, as investigators, enroll patients in the trial that had brain metastases.

Certainly, those brain metastases needed to be inactive, which was defined as asymptomatic or having received previous treatment. But as long as those brain metastases were asymptomatic, patients were allowed to enroll. And I think that because of that, we were able to generate this exciting data that we'll be talking about today, really emphasizing that Dato-DXd appears to have CNS activity, which I think is meaningful for our patients with lung cancer who do have brain metastases.

Dr. Sands:
Absolutely. And related to that, I also want to highlight the very transparent outline of the brain mets that had prior radiation as compared to brain mets that were untreated or with clear progression after prior radiation—so, really highlighting the known active brain mets and what we see from that.

With that, let's talk about the review's methodology for a moment. So patients were randomized to Dato-DXd or docetaxel. Now, some of the patients included did have active and untreated brain mets or previously radiated brain mets. But these baseline brain metastases were identified by blinded independent central review per CNS RECIST. And then, after treatment, their response rate and disease

control rate and progression-free survival were analyzed.

Now, what I loved from the presentation was how it was particularly looking at the untreated active brain mets or brain mets that were clearly progressing after radiation and seeing the response rates. Now, we really saw response within the group that got Dato-DXd, but not docetaxel. We saw an improvement in the progression-free survival intracranially that fits somewhat with what we're seeing systemically. And I think the broad view we're getting is essentially intracranial efficacy that seems to be somewhere in the ballpark of systemic efficacy, which I found particularly encouraging.

Now, in the EGFR population—which now we're getting into sub-subgroups within that—we also saw an encouraging signal. It was in one of those patients with an EGFR-mutant lung cancer that we also saw the intracranial CR. So again, I find that quite encouraging.

But Dr. Lisberg, what were your thoughts on that and my overview? Is there anything you want to add to that?

Dr. Lisberg:
Yeah, I agree with you, Jacob. I think it's really important, as I mentioned earlier, that we do have these patients who are appropriately enrolled on trial, and now we have the ability to truly evaluate the intracranial efficacy of this drug. And I think that, as you identified, there's a really stark contrast between the patients that receive Dato-DXd and those receive docetaxel.

CNS PFS hazard ratio was in favor of Dato-DXd at 0.48. These numbers are small. The Dato-DXd group was 38 patients and docetaxel was 30 patients. But certainly, we can see those curves are separating activities occurring across subtypes. We are seeing a preferential benefit in the patients with non-squamous disease, which, as you mentioned earlier, is consistent with what we saw systemically. And most importantly, in the non-small cell lung cancer population, at least for now, where we're using this drug in the EGFR-immune population, we're seeing that those patients are benefiting.

I agree with you, the waterfall plot was really exciting. Again, limited numbers, but it was 16 patients with Dato-DXd compared to 11 with docetaxel. And we do see a number of PRs in that CR you identified.

And we're not seeing any other complications coming in the CNS. I think that the stark difference between Dato-DXd and docetaxel, at least from this subset analysis, is very clear. You mentioned the improved objective response rate with Dato-DXd. In those 16 patients, the confirmed CNS objective response rate was 38 percent with Dato-DXd, and it was 0 with docetaxel. And that, again, is consistent with our thought process. We do not see a lot of CNS activity, or any CNS activity with docetaxel. And I think this is another reason why Dato-DXd is appropriate therapy for our patients with EGFR disease.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Aaron Lisberg about the intracranial efficacy of datopotamab deruxtecan in patients with advanced metastatic non-small cell lung cancer.

So we've discussed the design and some of the data, but let's dive a little bit more into that. As you highlighted, CNS-confirmed response rate with Dato-DXd was 38 percent in patients with measurable disease. Now, measurable disease is at least a centimeter in size, so that is something when we're talking about intracranial, even if asymptomatic. In the docetaxel group, there were no responses, as you highlighted. In addition, 88 percent of all evaluable patients treated with Dato-DXd achieved CNS disease control.

With all that being said, you've highlighted the results overall, and let's dive a little bit more into that, because it was the non-squamous, non-small cell population where you first presented at ESMO that was the population we saw the systemic benefit from. It was actually in the non-squamous, non-small cell. I highlighted at the beginning, this trial enrolled all of non-small cell, including squamous, which is where we don't really see the benefit.

And so when we're talking about intracranial efficacy across the entire population, we really need to focus that then into where Dato-DXd matters most, in the non-squamous broadly, but more specifically eGFR.

So, what were your thoughts on the non-squamous population and the EGFR population? And then how does this fit into your management?

Dr. Lisberg:
Yeah. I agree with all of that. I mean, I think it is important to remember that this trial did enroll the squamous population, as you mentioned. And as we showed at ESMO, there clearly wasn't activity in the squamous population.

So when we look at this data, we see a forest plot, and we do see that CNS activity is enriched in the non-squamous population, as well as the EGFR-mutant patient population. So, again, I think that this further emphasizes this is the right population to be thinking about. And not only are there not CNS progression events, we know that EGFR-mutant, advanced metastatic non-small cell lung cancer

oftentimes has a disease in the CNS. These patients will be coming off TKI therapy and potentially additional chemotherapy in combination, or subsequently. And whether or not their brain mets are well controlled at time of trial enrollment, that disease control rate in the CNS that you highlighted of 88 percent, I think is really meaningful for this patient population.

Even if those patients have previously treated inactive brain metastases, we know that the disease has crossed the blood-brain barrier. And we know that in these patients, if we don't have a therapy that's active in the CNS, there is a possibility of new issues occurring. So, I think that not only seeing responses in a significant subset of that limited patient population with that objective response rate on the CNS of 38 percent, that's meaningful. But almost more meaningful in some ways, as you said, is those patients had to cross a certain threshold in terms of size of brain metastases. But having a CNS-confirmed disease control rate of approximately 90 percent, again, I think that should give clinicians, as well as patients, a high level of confidence that on Dato-DXd, their disease in the CNS will be well controlled.

Certainly, we still need to be vigilant in terms of monitoring and things like that. But I think that it's a real attribute to this therapy. And again, going back to trial design, there's a real tribute to the sponsor to allow these patients to be enrolled, which now allows us to generate this data and provide this data, which I think is very meaningful in a real-world environment.

Dr. Sands:
And now, you've highlighted really well the response rates. Let's dive a little bit more into the progression-free survival. The median in the Dato-DXd group was five months, and the median in the docetaxel was three months. In your experience, what does a median of two months look like as far as in clinical practice? Is that meaningful? How does that impact decision-making?

Now, that is along with the response rates you've already highlighted.

The one other part I would add to that is to make sure we don't get too focused on just median, because oftentimes when we do, we're kind of missing the bigger picture in that there were some with more durable responses as well, with more durable intracranial progression-free survival. And so just kind of add that into part of your answer.

Dr. Lisberg:
Yeah. No, no, and I agree. And again, we're dealing with very limited patient numbers. And I think as you've said multiple times, subsets of subsets. So when we look at those medians, the two-month delta is from three to five months, so it's almost doubling there, and the hazard ratio is 0.48.

As you said, there are some patients with durable benefit, and the curves clearly separate. So I think that all of these data points are lining up with the discussion that we're having today, which is that this drug has activity. I'd like to also mention the CNS presentation that I gave at ASCO 2024 that was specifically from the TL05 study.

So the TL05 study was single-arm, and it looked at patients with actionable genomic alterations who received Dato-DXd. The vast majority of them had EGFR. The data there was more limited in terms of these patients with untreated brain mets or progression after RT. As you know, Jacob, I think there were three patients in that group and a response in one of those patients.

But the data I'd like to highlight there I think speaks to what we were just talking about, which is the systemic overall benefit appeared to be very similar. So the median progression-free survival in patients with brain metastases was very similar to those patients without brain metastases, which again, I think is very meaningful.

We know that the patients that have brain metastases are a sicker patient population and are more likely to have bad outcomes, unfortunately. And the idea that this drug would have similar efficacy across patient populations both with and without brain metastases on that trial, I think, tells us a lot.

And so, as providers and patients are deciding upon a therapy, certainly, this is the decision with the current approval: do we give Dato-DXd or do we give docetaxel? There's certainly many other criteria that go into that decision, and I think that's beyond the discussion today. I would argue the data does support Dato-DXd, but if we're focused on specifically CNS efficacy, when it comes to the overall outcomes—stratifying patients by brain metastases or not—I think it's pretty unequivocal to say that the Dato-DXd-treated patients will do better. And I think that in patients that have brain metastases, it really should be the direction we're going for our patients.

Dr. Sands:
To add just a little bit more to this, the timing. So responses were observed early in the course of treatment. Of course, that's important: saying that, okay, someone has asymptomatic, untreated brain mets, now we start treatment. Generally, if we're seeing a response, those responses are happening quickly, which further adds to that intracranial efficacy. And there were many that were durable, as you highlighted as well, and there was a nice spider plot highlighting some of those patients with real durability.

Now, the other thing is that although patients may ultimately still need radiation to the brain, to be able to delay that further out, it really helps to improve quality of life as well.

So, that's the key data I'd like to summarize. But before we close, Dr. Lisberg, I'll turn it over to you. Any final insights you'd like to share with our audience?

Dr. Lisberg:
Yeah. I think that, Jacob, you and I have summarized the data well, both from World Lung as well as ASCO. And I think that, again, this data really supports the idea that in patients with brain metastases, certainly with EGFR disease, this is an appropriate therapy. We should have confidence that we're going to control that disease, there'll be a decreased number of progression events, but we need to remain vigilant. And certainly, this data does not support an approach that would forego definitive therapy.

So although we have protection, we still need to remain vigilant and treat those brain metastases that are causing symptoms. And as I think you very rightly pointed out, the ability to delay some of those definitive therapies with control on Dato-DXd, I think, is meaningful. Certainly, we've both seen radiation necrosis and things like that, even when brain metastases aren't progressing. So the complications from those definitive therapies and the complications and consequences of CNS progression or loss of CNS control are really devastating to our patients in isolation, and so having a new therapy for our patients that has that CNS control and has that CNS activity, I think is very exciting.

Dr. Sands:
I appreciate those comments. As we come to the end of our discussion, I want to thank my guest, Dr. Aaron Lisberg, for joining me to discuss the latest TROPION-Lung01 data on datopotamab deruxtecan's efficacy in advanced non-small cell lung cancer in patients with brain metastases.

Dr. Lisberg, always wonderful having you on the program.

Dr. Lisberg:
Thank you, Jacob.

Announcer:
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