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Dato-DXd in Non-Small Cell Lung Cancer: Implications of TROPION-Lung01 Data

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

Dr. Sands:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and today, we'll be discussing the clinical implications of TROPION-Lung01's post-hoc analysis, which was presented at the 2025 World Conference on Lung Cancer. The analysis 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.

Joining me to share their insights on this data's role in clinical practice, are Dr. Julia Rotow and Dr. Xiuning Le. Dr. Rotow is the Clinical Director of the Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute, as well as an Assistant Professor of Medicine at Harvard Medical School in Boston.

Dr. Rotow, thanks for being here.

Dr. Rotow:
Dr. Sands, it's great to be here for this conversation.

Dr. Sands:
And Dr. Xiuning Le is an Associate Professor in the Department of Thoracic Head and Neck Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston. Dr. Le, it's great to have you with us today.

Dr. Le:
Yeah, great to be here, too.

Dr. Sands:
To begin, Dr. Rotow, let's take a closer look at TROPION-Lung01 and this post-hoc analysis. For some background, TROPION-Lung01 is a global phase 3 study comparing Dato-DXd to docetaxel in patients with advanced metastatic non-small cell lung cancer. And this review focused specifically on patients with baseline brain metastases. It evaluated central nervous system objective response rates, or CNS-ORR, as well as disease control rate and progression-free survival.

So, given that we're starting to see trials examine CNS outcomes, Dr. Rotow, how do you think our priorities are evolving in lung cancer treatment?

Dr. Rotow:
Yeah. So, in non-small cell lung cancer, we know that CNS metastases are a significant clinical challenge, and they're really quite common in lung cancer compared to many other solid tumors. And therefore, the ability to offer systemic control of CNS disease is a critical feature of many of the therapies that we offer.

We do have other alternative options, like local therapies, radiation, etcetera. We can quickly exhaust those options, or those options can come with long-term toxicities related to the treatment itself, like radiation, nephrosis, and other complications. And therefore, having agents with systemic activity is really critical for offering our patients more long-term durable disease control.

The field has continued to increasingly recognize this. Historically, clinical trials would have often excluded patients with CNS involvement, and as we've moved forward, I think, with subsequent generations of therapies, you've seen agents with better preclinical

data and now clinical data offering CNS activity. And that's allowed us to have patients in clinical trials who have, for example, active untreated CNS disease to give us a better understanding of how these agents are really working for patients who need this form of disease control.

And that slides to, I think, hopefully, helping us to close the gap in data we often have where we're often lacking that CNS data. So here, we're going to talk about the post-doc analysis for CNS disease in the Lung01 trial. But this is really critical information that we need to know when making decisions for our patients.

Dr. Sands:
Yeah, very important consideration. And I also would just highlight as well that whenever we're seeing this data, we need to understand who has had prior radiation and who has not. And so I did like that the data also was transparent about that.

Turning to you now, Dr. Le, I'd like to zero in on some of the results. The analysis showed that CNS-confirmed response rate was achieved in 38 percent of cases with measurable disease in the Dato-DXd group, and all evaluable patients experienced CNS disease control. In the docetaxel group, however, no CNS responses were seen. With that in mind, how could these numbers influence the way you approach treatment planning when brain metastases are a part of the picture?

Dr. Le:
Yeah. This data is very encouraging. Jacob, like you pointed out, all the patients who had evaluable disease in the brain metastasis had complete disease control. And then 38 percent had tumor reduction, and then achieved the partial response in the CNS. This is very encouraging data. And then it translates into clinical use, probably two-fold. One is that we feel more comfortable offering this treatment to patients who have brain metastasis, and then we can move from line to line quickly. The other is we might be able to defer radiation therapy, because traditionally, before we had drugs that were very active in the brain, we kind of had to leverage radiation to control the same as brain metastasis. In this scenario, we might be comfortable deferring radiation, basically sparing patients from additional toxicity from radiation, and also save the time, so we can move from the one systemic therapy to the next line of treatment.

Dr. Sands:
Now, in terms of progression-free survival, the median in the datopotamab deruxtecan group was about five months. Median in the docetaxel group was about three months. Now, if we look at response rates, there's also a substantial difference, a substantial improvement in the response rate in the Dato-DXd group.

Now, that was particularly in the non-squamous, non-small cell lung cancer group, but the data looks even better when we focus on the EGFR subgroup from TROPION-Lung01—and then, of course, within TROPION-Lung05. And this is what then led to the FDA approval within the EGFR space.

Now, from my vantage point—just to add in about the progression-free survival—to see that improvement in progression-free survival and to see that carry forward and also play out in overall survival, at least within that same kind of scale, I think is quite meaningful. There's a lot of nuance to this because in TROPION-Lung01—that was the randomized trial—in all of non-small cell lung cancer, a meaningful and statistically significant improvement in progression-free survival. But when we get to the non-squamous, non-small cell lung cancer subgroup, overall survival medians fit what we're seeing from progression-free survival with the confidence interval crossing one.

When we get to the EGFR-specific subgroup, actually, that difference in overall survival looks even more meaningful, even larger, but it's a smaller population and therefore, a wider confidence interval in that setting as well.

When we add in TROPION-Lung05 to flush out more of that EGFR population, of course, that's the data that then led to the FDA approval.

Any comments from either of you on that kind of overview?

Dr. Rotow:
No. But I think the comment that was made earlier about nature of different CNS endpoints really matters. Because here, with the gold standard for us in clinical practice, we don't know outcomes in patients with untreated—so no local prior therapy—CNS lesions. And looking at their actual intracranial response rate in measurable lesions, then looking at durability of that response is really the gold standard for us to understand what's the true CNS activity of an agent. So, I appreciated that this post-hoc analysis provided that.

Certainly, there are other metrics. It's always hard sometimes to generate enough data in measurable CNS disease. So we do look at things more broadly, like CNS progression-free survival. And if you can demonstrate a difference there, it's still clinically meaningful. That's, in some ways, the endpoint our patients are interested in, right? We want to know how much the disease shrinks first, but we also want to know, how long does it remain under control before maybe the need for either changing the systemic therapy seeking CNS

control, or a local ablative therapy of the CNS disease?

So I do think both endpoints give us different information and both are quite valuable and useful when thinking about applying these agents in clinical practice.

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. Julia Rotow and Dr. Xiuning Le about how data from a post-hoc analysis of the TROPION-Lung01 study may inform clinical decision-making.

So, Dr. Rotow, having looked at the CNS response rates, disease control, and progression-free survival findings, let's talk more about what these data might mean in practice. When you look at the CNS activity we're seeing with Dato-DXd, are there certain types of patients, based on symptoms, prior treatment, or disease pattern, who seem to be the best candidates?

Dr. Rotow:
Yeah. And I think for our patients here, I'll speak mostly about patients with EGFR-mutated lung cancer because that's where we have the FDA approval and that's where we're getting clinical use right now. There's often this choice to be made between relying upon systemic therapy for control of the CNS disease or adding in some radiation. And the stakes for adding radiation, I think, are relatively high, because our patients with EGFR lung cancer are living longer and longer as therapies improve. And if you look at longer-term or durable survival, we're also looking at trying to avoid late toxicity of therapy, because we want disease control but also quality of life throughout the disease course. And that puts pressure on, if we can, putting off radiation in the CNS, if possible. At least, in my opinion.

Now, for the response rates we're seeing with Dato-DXd, here in these untreated lesions, the response rate is 38 percent. It's good, but it's not a 90 percent response rate in the CNS. So usually, my take on this is if it's for smaller lesions not causing symptoms, where I feel like even if I treat and there's a little progression where we're likely to still be okay, I would consider relying upon a systemic agent. And conversely, a patient with a lot of multifocal tiny lesions, where we're looking at whole brain, not stereotactic radiation therapy, I'm also much quicker to say, let's try for at least stable or decreased disease using a systemic agent like Dato-DXd with a very short interval follow-up to reassess if there's any evidence of progression or concern. So again, trying to put off that whole brain radiation intervention, which carries more toxicity than on average than the SRS.

Now, on the other hand, if I had a patient with more limited focal CNS lesions that were very large, had a lot of edema, they were causing symptoms, or in very sensitive areas like the brain stem or other areas where I expect symptoms soon, then I'm much faster to say, maybe ablate that one area with SRS and then start systemic therapy here trying to prevent new lesions or new microscopic lesions from developing.

And along the way, I'm very quick to connect patients with a neuro-radiation oncologist, if possible, so that we're ready to go depending on how those next scans look, so we can intervene quickly if we're not getting a response.

Dr. Sands:
And now, I'd like to talk about the logistics of implementing Dato-DXd in the real-world treatment pathways. Now, the EGFR space, which is where Dato-DXd is currently approved, has become really complex in all of the different studies, and so what you're using in the second line is really impacted by what you get in the first line.

Now, when we're talking about someone who has had targeted therapy as well as chemotherapy, I know there's an array of different practices depending upon what those specific regimens are. Now, I'd say in the setting where we're talking about a patient being considered for docetaxel, in my mind, that equation is a bit more clear, where docetaxel always feels so disappointing now to utilize.

I remember many years ago being like, okay, docetaxel is our second-line standard of care. This is back before the immunotherapies were approved and before many of the different targeted therapies. And so when we're going to docetaxel, which now has a toxicity profile that feels more harsh than back before we had all of these other different regimens, that's always really somewhat disappointing.

So the equation to me is very clear in that setting, particularly in somebody with active brain mets where they're asymptomatic and small enough that I can monitor them closely. I feel like Dato-DXd is then a very good option in that setting.

Now, that being said, there are multiple clinical trials still underway, and certainly in our centers, I know that we're all enrolling to clinical trials options, and I think that continues to be an important consideration for patients.

So those are my thoughts. But as we come to the end of the program, I'd like to come back to you, Dr. Le, and look ahead for a moment. Now that we have data like this coming out of TROPION-Lung01, do you think CNS outcomes will start becoming a standard part of lung cancer trials? And beyond that, what else needs to happen in research or in practice to improve care for patients with brain metastases?

Dr. Le:
Well, this is the beginning of our recognition of lung cancer brain metastasis to be a critical unmet need. We are recognizing the need, that's step one, and we are starting to have TROPION-Lung01 post-hoc analysis and those clinical trials start to integrate CNS subgroup analyses as a key secondary endpoints. So that part will happen probably more broadly in all the lung cancer trial investigations, either small molecule or large molecule.

While that's happening, I think there are a few areas that we probably need to align and standardize. For example, the regular RECIST might not be ideal for evaluating CNS brain metastasis and the CNS lesions. So renal BM, specific for brain metastasis, and the renal LMD, specific for leptomeningeal disease, should be implemented in the trial in a prospective manner. That will require multidisciplinary care. That will require that we, as medical oncologists, work very close with neuro-oncologists, the radiation team, and sometimes neurosurgery, and go forward together as a big team trying to close the gap and trying to meet unmet needs of CNS metastasis. That will, overall, benefit patients' quality of life and duration of life. I think that's our job to do next.

Dr. Sands:
With those forward-looking thoughts in mind, I want to thank my guests, Dr. Julia Rotow and Dr. Xiuning Le, for joining me to discuss the potential impact of recent data on datopotamab deruxtecan's efficacy in treating patients with advanced non-small cell lung cancer with brain metastases.

Dr. Rotow, Dr. Le, it was great having you both on the program.

Dr. Le:
Thank you.

Dr. Rotow:
Thanks for having us here today.

Announcer:
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