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Insights from ICARUS-Lung01: Efficacy and Safety of Dato-DXd for NSCLC

Announcer:
You're listening to *On the Frontlines of Non-Small Cell Lung Cancer.* Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *On the Frontlines of Non-Small Cell Lung Cancer*on ReachMD. I'm your host, Dr. Charles Turck, and joining me to discuss the phase 2 study called ICARUS-Lung01, which focused on datopotamab deruxtecan, or Dato-DXd for short, in patients with previously treated advanced non-small cell lung cancer, is Dr. Joshua Reuss. He's an Assistant Professor in the Department of Medicine at Georgetown University Medical Center as well as a thoracic medical oncologist at MedStar Georgetown University Hospital. Dr. Reuss, it's great to have you with us today.

Dr. Reuss:
Happy to be here and thanks for the invitation to discuss this exciting research.

Dr. Turck:
So if we start with some background, Dr. Reuss, what did we previously learn about Dato-DXd from the phase 3 TROPION-Lung01 study?

Dr. Reuss:
Sure, so datopotamab deruxtecan, or Dato-DXd, is a TROP2-targeted antibody drug conjugate. So early data has suggested that in a heavily pretreated non-small cell lung cancer population, Dato-DXd showed very encouraging and promising efficacy. So the TROPION-Lung01 study was a large phase 3 randomized trial that pitted Dato-DXd against one of our current subsequent line standard-bearers, docetaxel. So the study enrolled patients with previously treated non-small cell lung cancer, both without and with actionable genomic driver alterations. Those without alterations had to have been treated with at least one to two lines of prior platinum doublet chemotherapy and immunotherapy. And those with driver alterations had to have been treated with one to two prior lines of targeted therapy and/or chemo or immunotherapy. So the study randomized patients 1:1 to Dato-DXd or docetaxel chemotherapy with dual primary endpoints of progression-free and overall survival.

And the first data that we saw from this was presented at the 2023 ESMO Annual Meeting, which showed that the trial met its primary PFS endpoint with a hazard ratio of 0.75, favoring Dato-DXd in the intent-to-treat population. Now I will say it was somewhat of a modest benefit with a median progression-free survival of 4.4 months for Dato-DXd compared to 3.7 months for docetaxel. So when you do the math there, it's maybe under a month in terms of median PFS benefit. But then you look a little further, response rates favor Dato-DXd at 26.4 percent versus roughly12.8 percent and median duration of response 7.1 months versus 5.6 months. And importantly, the benefit appeared to be primarily pronounced in those with non-squamous non-small cell lung cancer, where the PFS benefit was 0.63 with a median PFS of 5.6 versus 3.7 months compared to squamous, where there really was no benefit; in fact, maybe a signal of detriment. In adeno, there was a response; we have 31.2 percent with a median duration of response of 7.7 months compared to squamous, where the response rates were just under 10 percent with a median duration of response of just under 6 months.

Dr. Turck:
Well, with that in mind, let's zero in on the ICARUS-Lung01 study. Would you tell us about its design and methods?

Dr. Reuss:
Absolutely. And to take one step back, these antibody drug conjugates are a very exciting class of therapeutic. The current antibody

drug conjugates that are in development and approaching prime time, or perhaps in prime time, utilize an antibody conjugated to a highly potent chemotherapeutic warhead. So the idea is that you're really shepherding a very potent chemotherapeutic molecule to a specific target. Now there are other mechanisms to that potentially antibody-dependent cell cytotoxicity and other metrics, but really the key here is shepherding a highly potent chemotherapeutic. But what we don't quite know yet are key aspects to prognostic and predictive biomarkers of response. What are mechanisms of resistance? And the ICARUS-Lung01 study really sought to hone in on this. The study had a very novel design. It was a multicenter, single-arm, phase 2 trial of Dato-DXd given at 6 mg/kg every 3 weeks, which is the recommended phase 2 dose. It enrolled patients that were treated with one to three prior lines of therapy and had asymptomatic brain metastases, and in total, about 100 patients were enrolled. And then, really importantly, key correlative studies; so while the primary endpoint of this study was objective response rate, the real novelty here was in the correlates. And there were mandatory pretreatment tissue biopsies and blood collections as well as an on-treatment tissue biopsy and blood collection and an end-of-treatment biopsy and blood collection. So to really mandate this and make this a component of the study was critical to try to get to the underlying answers to some of these correlative analysis questions.

Dr. Turck:
And as a follow-up to that, what else do we need to know about the patients who participated in this study? Were there any other salient characteristics of the patients who were enrolled?

Dr. Reuss:
So I think one critical piece of information to know about this patient population is that it closely mirrored the study population in TROPION-Lung01. So patients enrolled had to have been treated with one to three prior lines of therapy, and it included both adenocarcinoma and squamous non-small cell lung cancer, though importantly, patients with asymptomatic brain metastases were allowed to enroll in this study. Other than that, I would say the population really did closely mirror the TROPION-Lung01 trial.

Dr. Turck:
For those just tuning in, you're listening to *On the Frontlines of Non-Small Cell Lung Cancer*on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Joshua Reuss about ICARUS-Lung01, which is a phase 2 study of datopotamab deruxtecan, or Dato-DXd, for short, in patients with previously treated advanced non-small cell lung cancer.

So if we turn our attention to the findings, Dr. Reuss, what were the efficacy results? And how did they compare to those from the TROPION-Lung01 study?

Dr. Reuss:
So as I mentioned, 100 patients were included in the ICARUS trial. And in terms of efficacy data, a response rate of 26 percent was seen for the entire population with a median duration of response of 7 months and median progression-free survival of 3.6 months.

And I think the important takeaway there is that it really closely mirrored what we saw in TROPION-Lung01. And to me, as a clinical investigator and clinician, it's important to see that consistency and to say that this signal is consistent; it reinforces what we're seeing with this compound. And that was true when you took a little bit of a deeper dive as well. So the non-squamous population enrolled to ICARUS was 82 patients compared to 18 with squamous. So with that kind of population difference aside, the response rate in non-squamous was 30.5 percent compared to 5.6 percent with squamous, with a median progression-free survival of 4.8 versus 2.9 months.

Now what was interesting is when you drilled a little deeper into some of the mutation subsets. Mutation subsets were not reported in TROPION-Lung01 exclusively. There was data that was presented with TROPION-Lung05 showing that those with driver mutations did perform consistently similar to those who were driver negative with lung adenocarcinoma. And what we saw from ICARUS was that those who had EGFR or BRAF alterations—there were 12 of those patients—the response rate was 50 percent compared to those where those mutations were absent—there was 73 of those patients—the response rate was 23.2 percent. Similarly with KRAS mutations, 11 patients had KRAS mutations, and the response rate of 63.6 percent. Those without KRAS mutations—73 patients—had a response rate of 23.2 percent.

Now I really highlighted the numbers there because when you talk about these small subsets, it's hard to make any large, dramatic conclusions. And the confidence of that response rate is probably quite wide, but I think it highlights that those with certain alterations definitely do perform no worse and perhaps are subsets that we need to explore further for possible enrichment of efficacy.

Dr. Turck:
And what can you tell us about the biomarkers that were associated with response and resistance?

Dr. Reuss:
So just as a background, at baseline, 78 patients were evaluable for TROP2 expression using IHC, with 71 patients having RNA

sequencing data and 71 patients having genomic alterations accessible for response and resistance. On treatment, that number dropped a little bit to 66 patients for RNA sequencing, and at progression, 5 patients were evaluated for resistance by whole exome sequencing. So kind of showing that there is some attrition with the ability to keep these important correlates going, which is completely natural with studies like this.

But then if we hone in on the data, what was looked at first was really TROP2 expression. And so earlier data that we've seen with datopotamab deruxtecan suggest that the expression levels perhaps don't particularly strongly correlate with efficacy. And what I mean by that is that the TROP2 levels in the cancer themselves—which again, datopotamab is targeting TROP2—did not appear to strongly correlate. Now what we saw in this study was when we divided by an H-score—basically an expression level to less than 100, 100 to 200, or greater than equal to 200; you could think of that as low, moderate, and high expressors—there was a range in median progression-free survival that we saw: 2 months for that lower cutoff, 6.1 for the middle, and 3.5 for the high. And what I interpreted is that perhaps there is a minimum level of expression where we would see benefit, but there does not appear to be a strong correlation that those with the highest level of TROP2 expression are the patients that definitely do the best.

Some other interesting aspects of the correlates: no baseline mutations that were identified in patients' cancers were found to be correlated with response or resistance. Though it was difficult to determine on-treatment evolution because there were, unfortunately, only five paired biopsies. And then when genome sequencing and gene set enrichment analyzes were performed, it did appear that DNA repair and suppression of immune-related pathways may be enriched in those that did not respond to Dato-DXd. So definitely some flares of some really interesting correlative science that hopefully will be fleshed out with further evaluations.

Dr. Turck:
And what can you tell us about the safety findings from ICARUS-Lung01?

Dr. Reuss:
Yeah. So Dato-DXd is a targeted compound, but it does carry a chemotherapeutic warhead, so we still do see many of the chemotherapeutic toxicities that we've come to expect with more traditional chemotherapies: nausea, vomiting, and diarrhea. Specifically with Dato-DXd, we also can see stomatitis. So these were noted that by and large, low-grade was probably in the range of 30 to 40 percent and high-grade was much lower at 3 to 5 percent; that was seen in TROPION-Lung01. And I would say that ICARUS closely mirrored this.

Now one important adverse event that we look out for with Dato-DXd is interstitial lung disease, or ILD. All-grade ILD was seen in 8 percent of patients in TROPION-Lung01, and grade 3 and higher was seen in 3 percent. Now in ICARUS, adjudicated ILD was only seen in 1 percent of patients. Now where does that true incidence lie? Perhaps somewhere in between, it's hard to say; real world is always difficult to compare to a regulated trial setting. But it is a very real toxicity that while not observed in high frequencies, is something very important for clinicians to be aware of.

Dr. Turck:
Thanks for breaking those results down for us, Dr. Reuss. And before we close, what might these results mean for the current and future management of advanced non-small cell lung cancer?

Dr. Reuss:
Yeah, so I think there's a couple takeaways here. So I think that antibody drug conjugates, in general, are a very exciting class of therapeutic. I think we're seeing multiple TROP2-targeted ADCs; there's HER2, which is approved in non-small cell lung cancer, that's trastuzumab deruxtecan that targets HER2. There's a HER3-targeted ADC that's very close to approval, and many other ADCs that we won't have time to talk about. So I think this is an exciting class of therapeutic.

But it's important that there's still a lot that we need to know about these therapies, so we know who is most likely to benefit from them. Who do we need to combine other therapeutics for to enhance efficacy? And for whom will these therapies be unlikely to work? And should we be looking at other therapeutics to really give patients the best shot to fight their cancer and extend their life and their quality of life? And I think that the ICARUS study is a really great example of how excellent translational research can be done. I think it's a model for this type of investigation that will hopefully get to the heart of some of these questions.

Dr. Turck:
Well, with those final thoughts in mind, I want to thank my guest, Dr. Joshua Reuss, for joining me to discuss the ICARUS-Lung01 study. Dr. Reuss, it was great having you on the program.

Dr. Reuss:
Thank you so much.

Announcer:
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