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Treating Second-Line NSCLC: The Efficacy of ADCs Targeting Predictive Biomarkers

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

Dr. Turck:
This is *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Charles Turck, and today I'm joined by Dr. Laura Alder to discuss research presented at the 2024 World Conference on Lung Cancer that focused on antibody drug conjugates in second-line non-small cell lung cancer treatment. Dr. Alder is an Assistant Professor of Medicine at Duke University School of Medicine in Durham, North Carolina. Dr. Alder, welcome to the program.

Dr. Alder:
Thank you. It's great to be here. Thanks for having me today.

Dr. Turck:
Well, to start us off in our conversation in which we'll be talking about metastatic non-small cell lung cancer, Dr. Alder, would you tell us about the current second-line treatment options and their limitations?

Dr. Alder:
So right now, when we talk about second-line treatment for driver-negative non-small cell lung cancer, we really are limited. We know that we have docetaxel, which is a very standard second-line option after a patient has progressed on standard frontline treatment with platinum-based chemotherapy with immunotherapy or doublet immunotherapy. And there's been some recent advances. Docetaxel can be paired with ramucirumab; that was studied in the REVEL trial. Docetaxel, though, is a tricky drug. It's been approved at 75 mg/m^2. Usually, we don't use that dose just because it's so very toxic. So usually, we're dose-reducing to 60 every 3 weeks, or we're using it more frequently so the patient can better tolerate it.

Dr. Turck:
Now what can you tell us about how antibody drug conjugates might help address the unmet needs of patients who progressed on first-line therapy?

Dr. Alder:
Yeah, so there's a lot of excitement recently about antibody drug conjugates. And just to take a step back, what is an antibody drug conjugate? You have an antibody, a linker, and then you have that chemotherapy, cytotoxin. And so a lot of times, how I describe it to my patients is it's a type of targeted, smarter chemotherapy, if you will. How smart it actually is can vary quite a bit, and the antibody binds to an antigen that's expressed in the tumor cell surface. And in this way, it becomes more targeted and smarter. Of course, it's not perfect, and there is still a lot of toxicity, a lot of which is similar to the toxicities you see with standard chemotherapy, and then a few unique toxicities that have to be closely monitored, such as ILD, or interstitial lung disease.

Dr. Turck:
Now let's discuss some of the latest research on antibody drug conjugates. What was the objective of the research you'll be discussing with us, and what methods did the authors employ?

Dr. Alder:
Yeah, so this was a really nice analysis of the current trials going on in the antibody drug conjugate, or ADC, space. So this looked at

four phase 2 or 3 trials comparing the antibody drug conjugates to non-antibody drug conjugate treatments in second-line metastatic non-small cell lung cancer. The three drugs that were included were trastuzumab deruxtecan, otherwise known as T-DXd, the TROP2-targeted agent datopotamab deruxtecan, otherwise known as Dato-DXd, and the HER3-targeting agent patritumab deruxtecan, otherwise known as HER3-DXd. And so the authors of this study did a systematic review in LARVOL CLIN, which is an outcomes database of 100,000 trials, to identify trials comparing these treatments to standard of care. And then they also used a database called LARVOL VERI, which had predictive biomarkers of response and is a precision oncology database.

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. Laura Alder about research presented at the 2024 World Conference on Lung Cancer that focused on second-line treatment of non-small cell lung cancer with antibody drug conjugates.

So let's dive into the results. Dr. Alder, what were the key findings from this research comparing second-line treatments?

Dr. Alder:
Yeah, great question. So for a little bit of background on the three ADCs that were analyzed, T-DXd, the HER2-targeted agent, is the only one that's currently FDA approved and is the one that's utilized every day in clinical practice as standard of care. So HER2 mutations are seen in about 2 to 4 percent of patients with lung cancer, mostly in females and mostly without a smoking history. It does carry a worse prognosis and a higher incidence of brain mets. So this study focused on two of the trials that led to the FDA approval of T-DXd: DESTINY-Lung01 and DESTINY-Lung02. DESTINY-Lung01 used a higher dose at 6.4 mg/kg dosing and did show good clinical benefit. But what really honed in on the right dose was DESTINY-Lung02, which looked at the 5.4 mg/kg dose that we use every day in clinical practice. And they found much less toxicity, of note, much less interstitial lung disease, which is the side effect that we really worry about and look out for when patients are on this treatment. And they found the treatment efficacy was very similar.

And then another trial they looked at was the TROPION-Lung01; this was on that TROP2-targeted agent Dato-DXd. We know that TROP2 is overexpressed in up to about 64 percent of adenocarcinoma and about 75 percent of squamous cell lung cancer. And this highlights that in those previously treated non-small cell lung cancer patients, the endpoint of progression-free survival benefit versus docetaxel was met, and the group that drove that was the non-squamous lung cancer population.

And then finally, we have the HER3-targeted agent HER3-DXd, which was assessed in EGFR-mutated non-small cell lung cancer. So this looked at the HERTHENA-Lung01 trial, which was assessed in patients after progressing on a TKI-directed agent, such as osimertinib, as well as chemotherapy. And that showed significant benefit as well with durable responses in that patient population.

Dr. Turck:
Now you've talked a little bit about biomarkers. Are there any that may predict response to treatment with antibody drug conjugates?

Dr. Alder:
Yeah, so that's a great question, and one that we're still learning a lot more about in order to better predict and have better outcomes for the patients that we treat. And so currently, T-DXd is FDA approved only in HER2-mutated lung cancer. So this is different than the breast indication where a lot of times, we use IHC staining and FISH activity in breast cancer; this has been shown to be most effective in mutants but less effective in amplified as seen in DESTINY-Lung01 and 02. Similarly, HER3-DXd has shown good benefit in the EGFR-mutated lung cancer population, but the HER3 expression itself does not appear to affect the efficacy at all.

But interestingly, there was actually a Presidential Symposium at World Lung this past year, 2024, and a study was presented that discussed the normalized membrane ratio of TROP2 by quantitative continuous scoring as a predictive clinical outcome. And I do think this was a really interesting study. This was presented by Dr. Garassino at World Lung. And QCS is a deep learning trained algorithm to identify compartments of each individual tumor cell across the slide image. And so this model was used to measure TROP2 expression in the membrane relative to the cytoplasm of that tumor cell. And so they developed this ratio of normalized membrane ratio, and they showed in TROPION-Lung01 that Dato-DXd did have stronger efficacy in patients who had a higher expression of this score. This score was also elevated in non-squamous versus squamous. And we know from the results that I had just mentioned that that's where this drug really works the best.

And so this is very exploratory, but I think as a lot of us are wondering about the use of AI and more learning-based mechanisms, this is a really exciting tool that I'm eager to apply more here as well as to other platforms with the shared goal of better treatment selection for our patients.

Dr. Turck:
And finally, to close out our conversation, Dr. Alder, big picture, how might these findings inform patient selection and treatment

optimization in clinical practice?

Dr. Alder:
At World Lung 2024, there was lots of great data from that meeting. We know with Dato-DXd in the TROPION-Lung trial, it did not have significant overall survival benefit over docetaxel. So in some ways, we're still learning a lot about ADCs. We're still learning where they can be most effective. Because of that finding for Dato-DXd, it's actually being assessed in the EGFR-mutant population of non-small cell lung cancer as well based on TROPION-Lung05 that was presented at ESMO 2023. From this trial and updates at World Lung as well, I think we're all eagerly anticipating the approval of HER3-DXd post-osimertinib. I think overall, ADCs still offer a lot of promise. I think it's just a matter of learning more about which patient population and finding better predictive biomarkers so we could be sure that we're using them in the right settings for the right patients.

Dr. Turck:
Well, with those final thoughts in mind, I want to thank my guest, Dr. Laura Alder, for joining me to discuss antibody drug conjugates as second-line treatment options for non-small cell lung cancer. Dr. Alder, it was great having you on the program.

Dr. Alder:
Yeah, it was a pleasure. Thanks for having me today.

Announcer:
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