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Evaluating Valemetostat and Dato-DXd for NSCLC: An Upcoming Trial

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'm Dr. Jacob Sands, and here with me today is Dr. Alex Spira, the Director of the Thoracic and Phase 1 Program at Virginia Cancer Specialists Research Institute and a Clinical Assistant Professor at Johns Hopkins. Together, we'll be discussing our study that was presented at the 2024 World Conference on Lung Cancer that evaluates the combination of valemetostat and datopotamab/deruxtecan in patients with previously treated advanced unresectable or metastatic non-squamous non-small cell lung cancer. Dr. Spira, welcome to the program.

Dr. Spira:
It's good to see you again, Jacob.

Dr. Sands:
Good to see you. So in this study that we're going to talk about, it incorporates a combination of an EZH2-1 inhibitor and a Trop2 antibody drug conjugate. Can you give us a little bit of background on those two classes of drugs and why we hypothesize synergy between the two drugs we're going to discuss?

Dr. Spira:
Sure. I'd be happy to. So let's start with datapotamab/deruxtecan, or Dato-DXd as we all call it. Dato-DXd is an antibody drug conjugate. To remind everybody, that's an antibody that binds to a cancer cell with a linker protein, and then the drug is the warhead that brings in small amounts of very potent cytotoxic chemotherapy. Trop2 is widely expressed; there have been approved drugs for this. Sacituzumab, as an example, has been approved for Trop2 in certain malignancies—breast cancer, for one, and it was approved in bladder. And obviously, the hope is to make new and better ones of that. There's a lot of data about datopotamab/deruxtecan. I think you and I participated on the Phase 1 study and then on the randomized study comparing it to docetaxel via TROPION-Lung studies. But some modest efficacy there and clearly proof of concept where this works by binding Trop2-positive cells.

Valemetostat is an EZH1 and 2 inhibitor. To remind everybody, there's also an approval here for this with tazemetosat. Tazemetostat is for rare diagnoses; I think it's approved for epithelioid sarcomas and follicular lymphomas, so relatively rare. But there's already proof of concept for this mechanism of action. But this is an EZH1/EZH2 inhibitor, which has multiple different ways of working. It affects gene expression, including those in DNA damage and DNA helicases, so a little bit in DNA damage and DNA strand breaks. So there's an idea that it would be synergistic with a drug like datopotamab to basically work in combination. That's why the initial plan for this is to work in second-line lung cancer where we know datopotamab has efficacy. Obviously, we want to do better because the efficacy is somewhat limited, so the hope is to combine it together to really improve the efficacy in this very hard-to-treat population.

Dr. Sands:
Can you give us a bit of an overview on that Dato-DXd and your impression of that in the non-small cell lung space?

Dr. Spira:
It's a potent drug. We've both given the drug. I remind everybody that these antibody drug conjugates are still not completely benign. They are very targeted chemotherapy, and where you run into issues is if there's expression of the target in normal cells or the linker, which needs to be a little unstable as the drug conjugate part is in the bloodstream. So there's clear evidence of efficacy with response

rates in the 20 percent range or so. So clearly, an active drug. The question is, which patient population? I think the first thing we looked at, and were a little surprised at, is that it did not work that well in the squamous population for reasons that I'm not altogether sure about because sacituzumab did show some activity there. Maybe it's patient selection; maybe they are different drugs. Although there's evidence of efficacy and it met progression-free survival, the overall survival confidence intervals crossed 1, and just recently, the licensing application was withdrawn before it went to FDA decision. And this is all a little surprising to us because we've both seen evidence of efficacy. It's a situation where docetaxel is the drug that keeps on giving—despite that it's always in these control arms, it always appears to do better.

Datopotamab is still not without toxicities, we've all seen that. It can cause some GI toxicity, and there's some ocular toxicity; mucositis, I think, is the biggest one, and that's why I point out that we have to remember that antibody drug conjugates still can be potent and have some chemotherapy-like side effects, and that's what we need to figure out.

I think the real question for datopotamab is will there be an effective biomarker? We were all hoping there was going to be a biomarker, i.e. higher Trop2 expression, correlated with responses, so you can pick those patients where it's more likely to work. Unfortunately, that did not pan out on the Phase 1. There may be some hints that there's a new biomarker being developed, but we're not there yet, and I think that's what the new studies will be looking at going forward.

So it's an active drug. Certainly, if combining with an EZH1 or 2 inhibitor, we hope that there's increased efficacy without a lot of increased toxicity that will make up for it and make for better-acting drugs. So that's what we hope to take this for right now.

Dr. Sands:
So now enter this combination: valemetostat, an EZH1 and 2 inhibitor, along with Dato-DXd, the Trop2 antibody drug conjugate. Hopefully, it has some synergy in the way that we've already described. But can you take us first through the study design of the trial?

Dr. Spira:
So it's a very straightforward Phase 1 study design. So you're starting with a fixed dose of Dato-DXd at 6 milligrams per kilogram and starting with a low dose of valemetostat, which is a perfect design, right? We know where we want to be with Dato-DXd. You can argue, 4 milligrams per kilogram versus 6 milligrams per kilogram. There's obviously been a lot of discussion about that. But starting valemetostat at 50 and escalating up to 200. Very straightforward Phase 1 study.

So the first thing is, of course, safety. Second thing is safety and tolerability to make sure that you have a tolerable combination, looking for adverse events. Then, of course, beginning to look at, as we get more into expansion, efficacy. What is that efficacy signal going to be? Progression-free survival, overall survival, PKs, and the typical things that we would see.

I think one of the important things to think about is you're not going to be able to have a true judge of efficacy. I don't think any of us, I think, are going to double or triple the response rates in this patient population. And if you did, the caveat of that is these are highly selected patients, right? These are patients that will be able to travel to get clinical trials or to a Phase 1 center, so they're likely to be healthier with maybe less burden of disease. So we hope to get a hint of efficacy, but the idea ultimately is to take this into a larger scenario because we've all seen over time early Phase 1 studies show much higher efficacy. And as you get into a real-world population, you have more real-world patients, of course.

Dr. Sands:
Now can you add for us the primary and secondary endpoints? You mentioned the safety and tolerability essentially being the focus. Are there any other endpoints that are part of the design at this point, or is that something that will come as the study gets further developed over the next trial to follow?

Dr. Spira:
Yeah. So I think we're obviously going to look at other endpoints, as well. But I think that the focus of this is going to be safety and tolerability. Progression-free survival, overall survival, response rates, and biomarkers are all going to be looked at, probably a little bit more closely later on. Again, small numbers, it's always going to be really hard to judge how these patients do.

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. Alex Spira about our study examining the efficacy and safety of valemetostat and datopotamab/deruxtecan in previously-treated advanced unresectable or metastatic non-squamous non-small cell lung cancer.

So now that we've gone through the trial design and some of the plan, as far as completing the dose escalation and expansion, where do we stand and what do you foresee as the course forward with this combination?

Dr. Spira:

A great question. I think we're going to have to decide as a group as things go on. I think one of the easiest things to look at would be in the true second-line situation—expanding, getting a good sense, and then getting a sense of what the response rates are really going to be. And are we doing better than we were before? So I think looking at a second-line population, and I believe there's a thought about even moving this maybe to the frontline population eventually as well. But I think what we have to figure out over the next 6 to 24 months is how efficacious is this going to be? Are we seeing a signal of what we hope is more efficacy? And that comes with more patience, obviously, as well.

Dr. Sands:
Now you have a lot of experience enrolling patients and treating them with datopotamab/deruxtecan. You spoke to some of the toxicity that patients already experience on Dato-DXd as a single agent. As far as the combination, what is your expectation on tolerability, and are these the same kinds of side effects that you're monitoring for? Any insights you can give us as to what you're specifically looking at?

Dr. Spira:
Yeah. So for me—and you might think differently—I'm a little bit concerned about cytopenias just because whenever you add drugs that might increase sensitivity to DNA damaging agents—we have this history of PARP inhibitors, again, all different classes, but we've seen it—and so making sure we're not increasing excess cytopenias. We do not see that with single-agent datopotamab, so we have some room to give, especially the doses that we go forward with, the recommended Phase 2 doses. So that's to me what we're going to watch.

I don't think we're going to see a lot more mucositis just because it's a completely different mechanism of action, as long as there's not a lot of pancytopenia from this. And I don't think we're going to see increased eye toxicity. For those of you who haven't given it—it's obviously not currently available—the big things that I saw in my clinic and reported were mucositis, ocular toxicity—dryness, there's irritation there—and very rarely, pulmonary toxicity. That was really at the higher doses, not really seen at the 4 and 6 milligram per kilogram doses.

Dr. Sands:
Yeah, just to add to those, I agree that the mucositis or stomatitis as a single-agent is really an area of a lot of discussion with Dato-DXd. For the eye surface toxicity, by and large lubricating eye drops are sufficient to control those symptoms. Although we don't entirely know the mechanism and involving ophthalmology when someone is having substantial symptoms, I'm not aware of any big events from the eye surface toxicity. And then, of course, interstitial lung disease, being aware of that. Usually, that's lower grade and far less in numbers.

Dr. Spira, before we close, can you tell us any other take-away messages that you'd like to leave with the audience today?

Dr. Spira:
Docetaxel has been around for 20-plus years as second-line. We're still not able to supplant it for non-driver mutation patients. We need to do a better job, and our patients ask that and deserve it, so find patients and refer them for clinical trials appropriately. For most patients in the United States, they can get reasonable access. Of course, not everybody can, but we have to be doing a better job.

But this is a great concept here, right? It's a very straightforward concept. And for patients, it's a drug we know that works, right? And I think my take-home message is datopotamab had it's BLA withdrawn only because it wasn't better than docetaxel, but it's at least as good, I think, in my eyes if you look at the curves. But if we can make it a little bit better, what a difference it will make for our patients with this combo or another.

Dr. Sands:
And with that thought in mind, I want to thank my guest, Dr. Alex Spira, for joining me to discuss our study on a potential new treatment for patients with previously treated advanced unresectable or metastatic non-squamous non-small cell lung cancer. Dr. Spira, it was great having you on the program.

Dr. Spira:
Thanks, Jacob. Good to see you.

Announcer:
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