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Safety and Tolerability of CDH6-Directed Antibody-Drug Conjugates

Announcer:
Welcome to CE on ReachMD. This activity is provided by Prova Education. This episode is part of our MinuteCE curriculum.

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Dr. Moore:
This is CE on ReachMD and I'm Dr. Kathleen Moore. My mini lecture today will focus on the safety profile of CDH6-targeted antibody-drug conjugates as observed thus far just in clinical trials.

When we look at our R-DXd thus far, there are some things that are quite reassuring. When we look just at the 3 dose levels that are active and were deemed safe for evaluation—4.8, 5.6, 6.4 mg/kg—when we look at just the kind of high-level look at safety, the majority of patients who discontinue from clinical trial did so for progression. Only about 11% or so did so because of toxicity, and that's a reassuring number. Patients weren't discontinuing because they felt so terrible or something bad happened that made them discontinue from the clinical trial.

We can also look at other signals of tolerance. Dose interruption, for example. That was in 30% of patients. So some patients needed a pause for an adverse event. But that didn't necessarily translate to dose reductions in every case. We only saw dose reductions in about 15%, 16% of patients who were participating on the clinical trial. And so that's reassuring, at least at a high level, that in a platinum-resistant patient population, this drug appears to be at least tolerated enough to continue.

Now, I will note that during the dose escalation component of R-DXd, not dissimilar to other deruxtecan payloads, one of the adverse events of special significance was pneumonitis, or ILD. And at higher dose levels than 6.4, we were seeing not only higher rates but more severe cases of ILD. And again, not dissimilar to the development of T-DXd and other deruxtecan payloads. So those dose levels were discontinued and we do still have to watch for ILD or pneumonitis, even at these lower-dose levels. But the rate is much, much lower and thus far has been all low grade. So this remains an adverse event of importance, but probably because of appropriate dose optimization and better familiarity by investigators, we're not seeing more than grade 1 or 2 at very low percentages.

We can go even a little bit more granular and just talk about the most common treatment-emergent adverse events with R-DXd. And these are really class effects of a deruxtecan payload. So we see high nausea. It's almost 60% of patients will report some nausea. The vast majority is grade 1 to 2. And I'll tell you, this is a phase 1, phase 2 trial where often in the first dose level, we're not using the pre-medications. And once you use that, you really can mitigate this much more successfully. Similarly, vomiting was common, 40%. The vast majority grade 1-2, and once we do appropriate pre-medications, is something that we can mitigate very effectively for patients.

And then, we do see some hematologic toxicities with these medications. Anemia is the most common at about 26%, 27%, and you can

see about 15% or more have grade 3 or higher anemia, so we do have to watch baseline iron levels, folate, make sure that we are correcting nutritional deficiencies before we start these types of medications. But we do see anemia. We do see neutrophil count decreases in about 24% of patients. 11% is grade 3 or higher.

We have a little less data, but we have some data in the public domain for CUSP06. In fairness, the data that I'm going to present for CUSP06 is just early phase 1 data, still in dose-finding. Treatment-emergent adverse events and dose discontinuation thus far on the phase 1 for toxicity was only 8%, dose delay 32%. That's very similar to R-DXd, and dose reductions were a little higher, 24%, but this is still dose-finding.

In over 15% of patients, anemia is quite common. Fatigue, quite common, over 50%, and vast majority grade 1 to 2. Thrombocytopenia is more common here. This is an exatecan payload, so maybe not surprising. 24-ish percent, grade 1-2, 27% grade 3 or higher. Neutropenia, we have about 35% of patients presenting with grade 3 or higher. There are some class effects, GI toxicities of camptothecin payloads. The hematologic toxicities may be different with an exatecan versus a deruxtecan payload, but way too early at this point to make comparisons and just something we'll have to keep an eye on as this medication moves forward and really identifies its recommended phase 2 dose and what's the toxicity around that or that range of doses.

We do see off-target, off-tumor toxicity. For example, mirvetuximab soravtansine, we see ocular toxicity even though there's not folate receptors in the eye, and that's because of off-tumor, off-target toxicity via macropinocytosis of the drug, for whatever reason, into the corneal epithelium. We don't see ocular toxicity with these medications, but we do see more hematologic toxicity.

So we're seeing a class effect with these camptothecins. Deruxtecans, we see some pneumonitis. Exatecans, thus far, less pneumonitis but perhaps more hematologic toxicity. All of these sorts of factors paired with efficacy will be central to our appropriate development of these medications in the right line of therapy and for the right patient.

We haven't even talked about biomarkers to optimize outcomes and quality of life. But I do think these initial safety signals are reassuring that these drugs can be used safely, and we just need to optimize through dose and regimen optimization kind of how we move them forward. But exciting times for our patients.

Thank you.

Announcer:
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