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Looking Ahead: Integrating CDH6-Targeted Therapies Into Ovarian Cancer Treatment Paradigms

Announcer:
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Dr. Liu:
This is CE on ReachMD, and I'm Dr. Joyce Liu. Here with me today is Dr. Kathleen Moore. We're focusing on the potential role of CDH6-targeted therapies in the treatment paradigm for ovarian cancer.

Let's start with the rationale for investigating CDH6-targeted therapies in ovarian cancer. Dr. Moore, what can you tell us about this?

Dr. Moore:
As we know, kind of across oncology right now, antibody-drug conjugates are really, I think, what many of us are most excited about. Finally, the opportunity to really leverage tumor-associated antigens that are overexpressed or solely expressed on the surface of cancer cells and use them to deliver kind of highly potent, right now, molecules of chemotherapy, but in the future, probably immune conjugates, other targeted agents as well. I think we're on the cusp of this technology. But really to pretty extraordinary clinical outcomes for patients. So these are moving rapidly into phase 3.

Dr. Liu:
I think we're starting to see these really interesting agents emerge, as you were saying, these antibody-drug conjugates. There is raludotatug/deruxtecan and then there's also been, more recently, sort of reported the initial results from CUSP06, which is another CDH6-targeting ADC, both of these with topoisomerase-1 inhibitor payloads.

Dr. Moore:
We were very recently at the European Society of Medical Oncology in Berlin, in October of 2025, where we saw raludotatug deruxtecan. I'll just call it R-DXd for now. REJOICE 01 one is the clinical trial. It's designed as a seamless phase 2/3.

All patients participating were generous enough to allow for a pretreatment biopsy. So the understanding of whether or not cadherin-6 level is predictive of benefit from raludotatug could be assessed.

So we saw the efficacy data at ESMO and it was really quite compelling. Across the 3 dose levels, the efficacy was quite high. At the 4.8 mg/kg level it was 44% response rate, 5.6 it bumped up to 50%, and 6.4 it bumped up to 57%, with disease control rates for all 3 of those levels above 75%. So very profound clinical disease control really at all 3 dose levels.

We did see the spider plots, which give us a sense of duration of response, and all of these also looked quite promising across the board. And then the other thing we saw was the early evaluation of the change in imaging, change in the RECIST, correlating or not correlating with the baseline tumor cadherin-6 membrane positivity. And at this point, there really isn't a clear correlation telling us that the amount of cadherin-6 matters.

And so the go-forward dose into the phase 3 is that middle dose, that 5.6 mg/kg, based both on efficacy, pharmacokinetics, as well as safety, with a very low, thus far, reported rate of the kind of key adverse event of special interest is, of course, ILD, and this is in the 5% range. We'll still need to follow this for longer, but that does appear to be our effective, safe dose to move forward for patients with platinum-resistant ovarian cancer. So really exciting.

Hot on its heels, though, is a number of other agents, one of which we haven't heard data from yet, but one of which we had.

A little bit apples and oranges with this comparison because we have pretty mature randomized phase 2 data with R-DXd and we have dose escalation phase 1 data thus far with CUSP06, so take these estimates with that grain of salt and that it's a little unfair to compare them. But the efficacy for CUSP06 is looking quite strong to date in the phase 1, where we have a response rate of about 36%, and that's across multiple, even low-dose levels. So this has a quite strong response signal thus far. Different safety profile, not seeing ILD, but are seeing probably more hematologic toxicity, which again, isn't surprising given an exatecan payload, and also isn't surprising in a phase 1 dose escalation. So I think we have to give that drug a little more time to figure out its dose and maturity of data before we can start comparing. I think, at this point, I would say looks promising and we'll have to see which one looks most effective and most safe.

Dr. Liu:
I think one of the things that's really promising about the CDH6 as a target in these ADCs is, as you said, so far in the early data, it's not clear that CDH6 level of expression is going to correlate with activity. And CDH6 expression in high-grade serous ovarian cancer is very high, 90% plus, right? So it's really sort of could be a very promising thing in terms of thinking about an agent that could be given potentially broadly without biomarker testing. I think it may come down to that.

Dr. Moore:
Yeah, I think that's going to be one of the key, sort of, scientific queries, like we're going to be on a quest with all of these antibody-drug conjugates for a bit. Because it’s true; right now, it doesn't look like there's correlation between response rate and CDH6 level.

Even if a biomarker is not required for use, if it correlates or doesn't correlate with that duration of clinical control, I think that's going to be really critical for us to assess out for our patients moving forward so that we're making the best decisions for them—or trying to help make the best decisions with them, I should say.

Now we’ve got to figure out how to use them, and in whom, and when. And can we reuse them, and in what combinations? We have a lot of work to do.

Dr. Liu:
We have a lot of work to do.

Dr. Moore:
To optimize this, yeah.

Dr. Liu:
Dr. Moore, thank you so much for a great discussion. I love talking with you, as always. And we thank the audience for joining us today. See you next time.

Announcer:
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