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MOA: CDH6-Targeted Antibody-Drug Conjugates

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Dr. Moore:
This is CE on ReachMD, and I'm Dr. Kathleen Moore. Today, I'll review the mechanism of action of CDH6, or cadherin-6, targeted antibody-drug conjugates in development for ovarian cancer.

So what I want to start with in this conversation is kind of why CDH6, or why cadherin-6, why is this of interest in ovarian cancer and probably will be of interest in other gynecologic cancers moving forward. CDH6 is a transmembrane protein that is embryonically involved in the development of central nervous system circuitry as well as proximal renal tubules. CDH6 is overexpressed in a lot of cancers but really overexpressed and at least ubiquitously expressed and then overexpressed in high-grade serous ovarian cancer.

The prognostic role of having CDH6 overexpression is not clear at this point. There are some small studies that suggest it may be related to poor outcomes, but those are premature and are still an area of clinical equipoise. But what we know to date is that amongst high-grade serous ovarian cancer, any expression of CDH6 is not quite 100%, it's about 80%, but high overexpression is very common, making this an ideal target for antibody-drug conjugates or other antibody-directed therapies.

And indeed, this has been of interest for quite a while. There was a CDH6 ADC that never got a name, but it was called HKT288. This was an antibody-drug conjugate that had a maytansine-based or microtubule inhibitor payload that went into clinical trials with a priority around ovarian cancer. We were very excited about it, but it was discontinued early in development really because of unexplained and quite significant neurologic events. And so enthusiasm around CDH6 decreased a little bit until the second CDH6 ADC in raludotatug deruxtecan, what we call R-DXd, entered clinical testing.

Now, this is an entirely different molecule even though it has the same target. It's a different antibody, it has different linkers, and it has a different payload, here, a deruxtecan or a topoisomerase-1 inhibitor payload. And we have seen early activity in platinum-resistant ovarian cancer, and actually even some early activity in platinum-sensitive ovarian cancer. But just speaking to the platinum-resistance space, the data presented to date has a confirmed overall response rate of just under 50%, it's 48.6%. And excitingly, the median duration of response was just under a year, and this was in a small number of patients, 45 patients, and I think we'll see some updated data later this year. But they were treated over the 3 active dose levels under development in R-DXd.

R-DXd has moved into a registration-enabling global phase 2/3 trial called REJOICE-01, as well as early kind of phase 2 studies in non-serous epithelial ovarian cancer, recurrent endometrial cancer, recurrent cervical cancer, and now in combination with other agents such

as bevacizumab. So the development continues with this agent.

There are 2 additional antibody-drug conjugates targeting cadherin-6. One is a little further along. We know a little bit more about the agent called CUSP06, which is another cadherin-6-directed antibody-drug conjugate. Not much is known about its structure yet in public domain. We do know that, as all of them do, a monoclonal antibody directed at CHD-6. It is conjugated with a different type of linker here, protease cleavable linker, to exatecan. R-DXd is deruxtecan; CUSP06 is exatecan. Both are topoisomerase-1 inhibitors, and whether or not there are differences in efficacy and safety profiles between deruxtecan and exatecan will require quite a bit more clinical trial data really before we can sort that out.

And so it is quite exciting that we have several of these agents now moving forward into clinical trials, and this leads to kind of the obvious question: What are the potential clinical implications for these, at least preliminarily, very active agents? Well, we're already seeing the efficacy in platinum-resistant ovarian cancer, which is an area of high unmet need. And so the ongoing registration trial in this space, we're kind of waiting for that efficacy data with some anticipation.

So in summary, cadherin-6, or CDH6, is a target of high interest, in particular in high-grade serous ovarian cancer, but that may expand. We have early data of efficacy with R-DXd and a nice safety profile. We're awaiting data on CUSP06 and some of the other molecules, and I think the next stage of development will really be around where in the treatment paradigm do these agents best serve our patients to help them live the longest and highest quality life.

Thank you.

Announcer:
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