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Clinical Evidence: Insights From Early Trials of CDH6-Targeted Therapies

Announcer:
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Dr. Liu:
This is CE on ReachMD, and I'm Dr. Joyce Liu. Today, I'm reviewing the current clinical trial data from CDH6-directed therapies under investigation in platinum-resistant ovarian cancer.

The first CDH6-directed antibody-drug conjugate to report out clinical trial data was raludotatug-deruxtecan, or R-DXd. R-DXd is comprised of a humanized anti-CDH6 IgG1 monoclonal antibody attached to a topoisomerase 1 inhibitor payload via a cleavable linker and has a drug-antibody ratio of approximately 8. Initial results from the first-in-human phase 1 trial of R-DXd were presented at the 2022 ASCO meeting, where the investigators observed clinical activity of R-DXd, including radiographic and CA-125 responses, in a number of patients with recurrent ovarian cancer.

Subsequently, at the ESMO meeting in 2023, Dr. Kathleen Moore presented a subgroup analysis from 42 patients with recurrent ovarian cancer who had received R-DXd across 3 separate doses of the agent within the phase 1 study.

In this group of patients, the confirmed overall response rate in the 34 patients with measurable disease was 38%. Notably, 69% of these patients had received prior bevacizumab, and 62% had received a prior PARP inhibitor.

In updated data that Dr. Moore then presented at the SGO meeting in 2024, the confirmed objective response rate was 49%, with activity seen across all 3 dose levels being explored. The median duration of response was 11.2 months, and the median progression-free survival was 8.1 months.

A preliminary assessment of CDH6 expression demonstrated no clear correlation between CDH6 expression and clinical response. The side effect profile of R-DXd is similar to that of other DXD payload antibody-drug conjugates, with the most common adverse events being nausea, vomiting, and fatigue, and the most common grade 3 or higher adverse events being hematologic events such as anemia and neutropenia.

Based upon the findings from the phase 1 trial, a phase 2/3 study, REJOICE-Ovarian01, was developed. REJOICE-Ovarian01 is an international open-label phase 2/3 trial being conducted in patients with platinum-resistant ovarian cancer, with histologies limited to high-grade serous or endometrioid ovarian cancer. REJOICE-Ovarian01 is a 2-part study, with an initial phase 2 dose optimization portion, followed by a randomized phase 3 portion, where the activity of R-DXd at the determined optimal dose is compared against

physician's choice chemotherapy.

Results from the phase 2 dose optimization were presented at the 2025 annual ESMO meeting.

The overall confirmed response rate across these 3 dose levels was 50.5%, with observation of activity noted across all of the dose levels. Interestingly, as was seen in the original phase 1, clinically meaningful tumor responses were observed independent of the tumor's CDH6 expression levels. The safety profile was similar to what was previously reported, with drug discontinuation occurring in less than 10% of all of the patients in part 2. However, it was noted that while the safety profile of the 4.8 and 5.6 mg/kg cohorts were similar, the treatment-related adverse events appeared to occur with greater frequency in the 6.4 mg/kg cohort.

Thus, after evaluating the risk-to-benefit profile of R-DXd across the 3 different dose levels, R-DXd at a dose of 5.6 mg/kg is considered the optimized dose, and the REJOICE-Ovarian01 study is now recruiting to the randomized phase 3 portion of the study with this dosing level.

A second CDH6-targeting ADC, CUSP06, has also now reported out early clinical data. CUSP06 is comprised of a CDH6-directed IgG1 monoclonal antibody conjugated via a protease cleavable linker, the topoisomerase 1 payload inhibitor exatecan, also with a drug-antibody ratio of 8. The initial clinical data from the ongoing first-in-human phase 1 study of CUSP06 were presented at the 2025 ASCO meeting and reported that in 25 patients with high-grade serous ovarian cancer enrolled to the study across all dose levels, an unconfirmed response rate was observed of 36%. At the higher dose levels, considered to be the likely randomized phase 2 dosing, 4.0 mg/kg and 4.4 mg/kg, 4 out of 8 patients to date have experienced disease response to CUSP06.

The safety profile of CUSP06 is similar to those of other topoisomerase 1 inhibitor payload antibody-drug conjugates, with nausea, fatigue, and hematologic AEs being the most common events. Additionally, 3 cases of pneumonitis were reported. CUSP06 currently continues in development in its phase 1 trial.

Two additional CDH6-targeting antibody-drug conjugates, HS-20124 and SIM0505, both of which also utilize topoisomerase 1 inhibitor payloads, have been announced to be in phase 1 clinical development in China. Clinical results of these agents are not yet available.

Overall, the available experience from clinical trials to date suggests that CDH6 is a promising ADC target for ovarian cancer. Although as we see with some of the other ADCs, clinical activity of the CDH6 targeting ADC, R-DXd, appears to be present across the various CDH6 expression levels. The final results from REJOICE-Ovarian01 are highly anticipated to understand whether this is a therapy that might become a standard of care therapy option for recurrent platinum-resistant ovarian cancer and whether its activity is correlated with tumor CDH6 expression.

The side effect profile of these drugs will also be very important for us to understand. To date, a small number of pneumonitis cases have been reported on these agents, and of course this remains an important consideration for antibody-drug conjugates as a whole.

Thanks for listening! I hope this information will be useful in your clinical practice.

Announcer:
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