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Clinical Evidence Behind Emerging Targeted Therapy Strategies Across Gynecologic Malignances

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Colombo:
This is CME on ReachMD, and I'm Dr. Nicoletta Colombo. In this brief lecture, I will take you through some clinical data evaluating emerging targeted therapy strategies across gynecological malignancies.

Folate receptor alpha is a cell surface folate receptor, and its expression is limited on normal cells but is upregulated on cancers, particularly ovarian but also endometrium, non-small cell lung cancer, and triple-negative breast.

There are several ADC-targeted folate receptor alpha. Today, I will focus mainly on mirvetuximab soravtansine, which is the only approved drug in ovarian cancer.

The MIRASOL study was the registrational study and was an open-label, phase 3, randomized trial of mirvetuximab vs investigator choice chemotherapy in patients with folate receptor alpha-high, platinum-resistant ovarian cancer. So to be randomized, folate receptor alpha was detected through immunohistochemistry with the intensity of 2+ in more than 75% of tumor cells and up to 3 prior lines of chemotherapy were allowed. Patients receive either mirvetuximab or treatment of physician choice.

The trial met the primary endpoint and demonstrated a significant benefit not only in progression-free survival, which was the primary endpoint of the study, but also in overall survival. So the hazard ratio for PFS was 0.65 and the hazard ratio for overall survival was 0.67. Toxicity profile is different for this compound. There was some peripheral neuropathy and diarrhea and nausea. But particularly what is typical of this ADC is ocular toxicity in terms of blurred vision, keratopathy, and dry eye.

Moving to the second target I want to talk about today is the HER2. And HER2 alterations are observed in cervical cancer, endometrial cancer, and ovarian cancer. The drug is trastuzumab deruxtecan, which is an ADC composed of humanized monoclonal antibody, a topo-I inhibitor payload, and a cleavable linker. The DESTINY-PanTumor02 study treated, with trastuzumab deruxtecan, patients with solid tumors, including gynecological malignancies, endometrial, cervical, and ovarian cancer. These were heavily pretreated patients, and the HER2 expression was detected with immunohistochemistry and had to be 3+ or 2+. Response rate was very high in cervical cancer. Overall response rate was 50%, in endometrial cancer was 57%, and in ovarian cancer 45%. Of course, it was much higher response rate in the 3+ tumor with 75% for cervical cancer, 85% for endometrial cancer, and 64% for ovarian cancer. And the median PFS was 6.9 months and the median OS was 13.4 months.

You can see some hematological toxicity, nausea, fatigue, and diarrhea. But also I want to focus on ILD and pneumonitis. Most of them were grade 1 and 2, but there were also 3 patients with grade 5 ILD.

So to conclude, I think that mirvetuximab soravtansine is the first ADC approved for epithelial ovarian cancer and the first agent to

demonstrate a benefit in both progression-free survival and overall survival in a randomized phase 3 trial. Mitigation strategies and careful attention to ocular disorders allow patients to maintain dosing and benefit from mirvetuximab without permanent ocular impairment. Trastuzumab deruxtecan has shown unprecedented activity in heavily pretreated gynecological cancer patients in terms of response rate and duration of response. And on April 6, 2024, FDA granted accelerated approval to trastuzumab deruxtecan for unresectable or metastatic HER2-positive IHC 3+ solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. Both mirvetuximab and trastuzumab deruxtecan developments now move to earlier line of therapy.

Well, my time is up, and I hope I've given you something to think about. Thank you so much for listening.

Announcer:
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