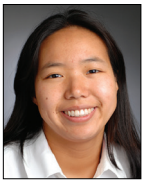
GYNECOLOGIC CANCER IN FOCUS

Current Developments in the Management of Gynecologic Cancer

Section Editor: Ursula A. Matulonis, MD

The Use of Antibody-Drug Conjugates in Gynecologic Cancers



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H&O What makes antibody-drug conjugates (ADCs) particularly promising for treating gynecologic cancers in comparison with traditional chemotherapy?

JL ADCs are a form of targeted chemotherapy. When antibodies are used to deliver chemotherapies to cancer cells in a targeted manner, they can open the therapeutic window and allow more potent chemotherapeutic agents to be delivered than is possible with traditional systemic chemotherapy. ADCs have been in development for many years across multiple types of cancer, but the newest-generation ADCs are now emerging in the solid tumor space. We are still learning a lot about the best ways to make ADCs more effective than systemic therapies and to reduce their side effect profiles, and we should expect to see continued advances among ADCs in the future.

H&O How significant is the recent full US Food and Drug Administration (FDA) approval of tisotumab vedotin for recurrent cervical cancer?

JL Tisotumab vedotin (Tivdak, Seagen) is a very important drug for us to have in our armamentarium for cervical cancer. In the innovaTV 301 trial, which led to the full approval of tisotumab vedotin, the objective response rate (ORR) was 17.8%. Although this rate may seem modest, the ORR with chemotherapy was 5.2%, emphasizing just how poorly traditional chemotherapy works in this setting and why tisotumab vedotin is such an improvement. The need for more effective therapies remains, however, and early-phase trials of other ADCs are showing some exciting preliminary results in cervical cancer.

H&O What are some of the ADCs that are being studied in these early-phase trials?

JL We have begun to see results from some of the approved ADC-targeting agents—namely, sacituzumab govitecan (Trodelvy, Gilead), which targets TROP2, and trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca), which targets human epidermal growth factor receptor 2 (HER2). Although these are single-arm studies, we are seeing more promising activity than what we have seen with traditional chemotherapy.

H&O Could you discuss the use of T-DXd in endometrial cancer?

JL Interim results from the phase 2 DESTINY-PanTumor02 study have shown good responses to T-DXd in patients with gynecologic cancers.[1] This trial enrolled 267 patients with a variety of solid tumors—specifically, urothelial bladder, biliary tract, cervical, endometrial, ovarian, and pancreatic cancers—plus rare tumors such as head and neck cancers and intestinal adenocarcinoma. Patients were required to have a HER2 immunohistochemistry (IHC) score of 2+ or 3+ to be eligible; they also had to have received at least one prior systemic therapy or have no other treatment options. The ORR with T-DXd was 37.1% overall among all enrolled patients, and it was higher among the 40 patients with endometrial cancer (57.5%), 40 patients with cervical cancer (50.0%), and 40 patients with ovarian

cancer (45.0%). The ORR was even higher, 84.6%, among the 13 patients who had confirmed IHC 3+ endometrial cancer. Progression-free survival (PFS) was 11.1 months in the overall cohort and was not reached among the patients who had HER2 IHC 3+ disease.

The phase 2 STATICE study, from Japan, evaluated the use of T-DXd in 32 patients with advanced or recurrent uterine carcinosarcoma who had a HER2 IHC score of 1 or higher and had previously been treated with chemotherapy. After a median follow-up of 13.5 months, the ORR was 54.5% among the 22 patients with HER2-high (IHC 2+ or 3+) disease and 70.0% among the 10 patients with HER2-low (IHC 1+) disease. These are very high response rates for uterine carcinosarcoma, which can be highly resistant to chemotherapy. The median PFS was 6.2 months in the HER2-high group and 6.7 months in the HER2-low group, results that are somewhat more modest than those in DESTINY-PanTumor02 but are still exciting signals of activity in endometrial cancer.

Additional studies that are just starting to examine the use of T-DXd in endometrial cancer are the phase 3 DESTINY-Endometrial01 and DESTINY-Endometrial02 trials. In DESTINY-Endometrial01, approximately 600 patients with HER2-positive (IHC 2+ or 3+), advanced or recurrent, mismatch repair–proficient endometrial cancer will be randomly assigned to first-line therapy with T-DXd plus the experimental bispecific antibody rilvegostomig, T-DXd plus the immune checkpoint inhibitor pembrolizumab (Keytruda, Merck), or chemotherapy plus pembrolizumab (NCT06989112). In DESTINY-Endometrial02, approximately 710 patients with HER2-positive (IHC 2+ or 3+) endometrial cancer will be randomly assigned to T-DXd or standard chemotherapy as adjuvant treatment (NCT07022483).

H&O Which biomarkers are most critical for selecting patients for ADC therapy in gynecologic oncology?

JL This is a space that we are still exploring. HER2 is clearly a very important biomarker, and of course T-DXd has FDA tumor-agnostic approval for the treatment of HER2-positive (IHC 3+) tumors in patients who have received prior systemic treatment and have no satisfactory alternative treatment options. A HER2 IHC level of 3+ is relatively uncommon in comparison with IHC 1+ or 2+ disease, so the prospect of expanding eligibility to those with 2+ and 1+ disease is very appealing. Recommendations from the National Comprehensive Cancer Network currently allow patients in the United States with HER2-positive (IHC 2+/3+) ovarian, endometrial, or cervical cancer to receive T-DXd.

The other important validated biomarker for ADC selection in gynecologic cancers is folate receptor alpha (FRα), used to select patients with ovarian cancer for treatment with mirvetuximab soravtansine (Elahere, AbbVie). Studies have shown that patients whose level of FRα expression is at least 75% are most likely to benefit from mirvetuximab soravtansine. Next-generation ADCs that target FRα are also being developed; it remains to be seen what the cutoff might be for these agents.

We have seen in other cancers that biomarker expression of the target sometimes is strongly linked to the activity of the agent and sometimes does not seem to be strongly linked. We will need to examine carefully the biomarkers for each ADC that we are developing in the gynecologic cancer space.

H&O What are the most concerning toxicities that clinicians should monitor when prescribing ADCs?

JL Because ADCs ultimately are still chemotherapy, they produce chemotherapy-like adverse events such as fatigue, nausea, neutropenia, and neutropenia-related infections. In addition, prescribers need to be on the alert for ADC-specific toxicities. For example, the risk of hematologic side effects is lower with mirvetuximab soravtansine than with standard cytotoxic chemotherapy, but both mirvetuximab soravtansine and tisotumab vedotin carry a Black Box Warning about ocular toxicities. As a result, patients receiving these agents require regular eye examinations. If ocular toxicities occur, they usually resolve after the drug is withheld; afterward, the agent can often be reintroduced at a lower dose.

Another toxicity that is important to be on the alert for is pneumonitis, which has been shown to occur across multiple ADCs. The management of pneumonitis depends on the ADC. For example, when grade 1 pneumonitis is observed with mirvetuximab soravtansine, we have the option of monitoring carefully and continuing to treat the patient with this agent. But if pneumonitis is observed with T-DXd, the agent must be paused even if the patient has asymptomatic, radiographic-only pneumonitis. Continuing treatment can lead to substantial worsening of the pneumonitis and even death. I recommend that oncologists who use T-DXd read an excellent practice management article on this agent by Dr Hope Rugo and colleagues.[2]

H&O How do you see ADCs fitting into the current sequencing of treatment for ovarian cancer?

JL Treatment sequencing is highly dependent on biomarkers and context. Right now, we know that mirvetuximab

soravtansine improved both PFS and overall survival in comparison with standard-of-care chemotherapy in FRα-high, platinum-resistant ovarian cancer. In my mind, this finding makes mirvetuximab soravtansine the preferred therapy in this setting, barring a contraindication or a specific concern. Between 65% and 70% of patients with platinum-resistant ovarian cancer do not have tumors that are FRα-high, however. We have some evidence that mirvetuximab soravtansine still has some activity in these patients, but we have not seen it be superior to chemotherapy here. However, as new FRα-targeting ADCs enter the space, we may have different thresholds. One of the ADCs that is in development is rinatabart sesutecan, which has a TOPO1-targeting payload. According to data from the phase 1/2 RAINFOL-01 trial, recently presented at the Society for Gynecologic Oncology Annual Meeting, the ORR with rinatabart sesutecan dosed at 120 mg/m^2 every 3 weeks in a small cohort of 20 patients with platinum-resistant ovarian cancer was 55.6%.[3] These encouraging results point to the potential for more widespread use of ADCs before traditional chemotherapy, even in earlier-line spaces.

Indeed, we have begun to see the earlier-line use of ADCs explored in clinical trials. For example, the phase 2, single-arm PICCOLO trial looked at the use of mirvetuximab soravtansine in 79 pretreated patients with recurrent FRα-positive, platinum-sensitive ovarian cancer. This trial showed some nice signals of activity with mirvetuximab soravtansine, with an ORR of 51.9%.[4] Similarly, the phase 3 GLORIOSA trial is examining whether the addition of mirvetuximab soravtansine to bevacizumab as maintenance therapy improves results in patients with platinum-sensitive ovarian cancer (NCT05445778). Additionally, a lot of interest is being shown in moving ADCs into the frontline space in the right context. For example, the phase 3 DESTINY-Ovarian01 trial is looking at first-line maintenance therapy with T-DXd plus bevacizumab in patients with HER2-expressing tumors for whom PARP inhibition is not appropriate as maintenance therapy (NCT06819007). Overall, more and more studies are being developed in these first-line and platinum-sensitive spaces.

H&O What is the potential for combining ADCs with immunotherapy in gynecologic cancers?

JL This is an area in which we do not have a lot of data, but it is an intriguing prospect. We know that combining tisotumab vedotin with pembrolizumab produces manageable side effects and has shown a signal of clinical activity in early-phase trials of cervical cancer, including the phase 1/2 innovaTV 205 trial.[5] Similarly, we have seen activity with the combination of sacituzumab tirumotecan and pembrolizumab in cervical cancer.[6]

H&O Which ADCs in development show the most promise for expanding treatment options in this space?

JL In addition to ADCs targeting folate receptor alpha, CDH6, and TROP2 that are now in phase 3 trials, agents are currently being developed to target Claudin-6 and 6 NaPi2B, among other exciting new targets. Also being developed are bispecific ADCs, which may be able to identify and bind 2 different targets, and dual-payload ADCs, which may be able to deliver 2 different payloads simultaneously. A tremendous amount of well-warranted excitement is being shown about the potential that ADCs offer our patients across gynecologic cancers. As new ADCs are developed, we need to be thoughtful about biomarker selection, as previously discussed, as well as about the sequencing of ADCs. Finally, we need to understand how ADC resistance develops and how to manage it to maximize the potential of these agents for our patients.

Disclosures

Dr Liu reports consulting/advisory board participation for AbbVie, AstraZeneca, Bristol Myers Squibb, Clovis Oncology, Daiichi Sankyo, Eisai, Genentech/Roche, Genmab, GlaxoSmithKline, Loxo/Lilly, SystImmune, Regeneron Therapeutics, Revolution Medicine, and Zentalis Pharmaceuticals.

References

1. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. *J Clin Oncol.* 2024;42(1):47-58.
2. Rugo HS, Crossno CL, Gesthalter YB, et al. Real-world perspectives and practices for pneumonitis/interstitial lung disease associated with trastuzumab deruxtecan use in human epidermal growth factor receptor 2-expressing metastatic breast cancer. *JCO Oncol Pract.* 2023;19(8):539-546.
3. Lee EK, Yeku O, Winer I, et al. Rinatabart sesutecan (Rina-S®) for patients with advanced ovarian cancer: results from dose expansion cohort B1 of a phase 1/2 study. Presented at the 2025 Society of Gynecologic Oncology Annual Meeting on Women's Cancer (SGO); March 14-17, 2025; Seattle, WA. Abstract 809034.
4. Alvarez Secord A, Lewin SN, Murphy CG, et al. The efficacy and safety of mirvetuximab soravtansine in FRα-positive, third-line and later, recurrent platinum-sensitive ovarian cancer: the single-arm phase II PICCOLO trial. *Ann Oncol.* 2025;36(3):321-330.
5. Vergote I, Van Nieuwenhuysen E, O'Cearbhaill RE, et al. Tisotumab vedotin in combination with carboplatin, pembrolizumab, or bevacizumab in recurrent or metastatic cervical cancer: results from the innovaTV 205/GOG-3024/ENGOT-cx8 Study. *J Clin Oncol.* 2023;41(36):5536-5549.
6. Wang J, An R, Huang Y, et al. Efficacy and safety of sacituzumab tirumotecan (sac-TMT) plus pembrolizumab in patients with recurrent or metastatic cervical cancer [ESMO abstract 716MO]. *Ann Oncol.* 2024;35(suppl 2).