OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

Section Editor: Robert L. Coleman, MD

The Emerging Use of Antibody-Drug Conjugates in Ovarian Cancer

Debra L. Richardson, MD
Associate Professor, University of Oklahoma College of Medicine
Chief, Section of Gynecologic Oncology, Stephenson Cancer Center
Oklahoma City, Oklahoma

H&O Which patients with ovarian cancer are eligible for treatment with an antibody-drug conjugate (ADC)?

DR The only ADC that has received US Food and Drug Administration (FDA) approval for use in ovarian cancer is mirvetuximab soravtansine (Elahere, ImmunoGen), which is indicated for patients with platinum-resistant ovarian cancer that expresses folate receptor alpha (FRα).

H&O Which ADCs are being developed for use in ovarian cancer?

DR Multiple ADCs are being developed for use in ovarian cancer. These include STRO-002, also known as luveltamab tazevibulin, and MORAb-202, also known as farletuzumab ecteribulin; both these agents target FRα. Additional agents include upifitamab rilsodotin, which targets the sodium-dependent phosphate transport protein NaPi2b, and DS-6000a, which targets the adhesion molecule cadherin 6 (CDH6). The ADC tisotumab vedotin (Tivdak, Seagen), which has received FDA approval for use in recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, is also being investigated for ovarian cancer. This agent targets tissue factor. Another example is XMT-1660, which targets the T-cell checkpoint ligand B7-H4, but this is certainly not a complete list. ADCs are a very active area of research in gynecologic cancer, especially in ovarian cancer.

H&O What are the most important studies to look at the use of mirvetuximab in ovarian cancer?

DR There have been several trials, so I will concentrate on the more recent ones. FORWARD 1 was a phase 3 randomized, controlled trial of patients with platinum-resistant ovarian cancer who had received 1 to 3 prior lines of therapy and whose tumors expressed FRα. Patients were randomly assigned in a 2:1 ratio to receive either mirvetuximab or physician's choice of chemotherapy, which consisted of paclitaxel, pegylated liposomal doxorubicin, or topotecan. Although the trial failed to meet its primary endpoint of progression-free survival in both the overall and the FRα-high populations, the absence of an effect on progression-free survival in the latter population may have resulted from using an assay that was less accurate than the one used in earlier trials. Patients in the FRα-high population did better with mirvetuximab than chemotherapy on all secondary endpoints, including objective response rate, cancer antigen 125 (CA-125) responses, and patient-reported outcomes.

These results led to the phase 3 SORAYA study, which enrolled patients with FRα-positive, platinum-resistant ovarian cancer who had received 1 to 3 prior lines of therapy. SORAYA was a single-arm trial in which all 106 patients received mirvetuximab. In results that recently appeared online in the *Journal of Clinical Oncology* by Matulonis and colleagues, the overall response rate

to mirvetuximab was 32.4% and included 5 complete responses. The median duration of response was 6.9 months. Based on these results, the FDA granted accelerated approval to mirvetuximab in this patient population, with FRα positivity based on an FDA-approved companion test.

A confirmatory phase 3 trial called MIRASOL is currently assessing the use of mirvetuximab vs investigator's choice of chemotherapy in 453 patients to confirm the findings of SORAYA (NCT04209855). Although the study has closed enrollment, the data have not quite matured. We expect to see mature data sometime this year, and hope that these data continue to support the use of mirvetuximab in ovarian cancer and lead to FDA approval. The design of MIRASOL is similar to that of FORWARD 1, but it relies on the approved FRα assay.

Additional studies have looked at mirvetuximab in combination with other agents, such as bevacizumab.

I would not hesitate to use a combination of mirvetuximab and bevacizumab in patients without contraindications.

H&O What studies have looked at the use of upifitamab in ovarian cancer?

DR The first trial of upifitamab since the phase 1b expansion study is called UPLIFT (NCT03319628). UPLIFT is a phase 2, single-arm, international trial that was designed as a registration trial of upifitamab in recurrent ovarian cancer. This trial is now closed to enrollment, having enrolled approximately 180 patients with platinum-resistant ovarian cancer who have received 1 to 4 prior lines of therapy. Patients receive upifitamab at 36 mg/m^2 every 4 weeks. The primary outcome is objective response rate in the NaPi2b-high population. Results are expected later this year.

In the ongoing phase 3 UP-NEXT trial, patients with platinum-sensitive recurrent ovarian cancer who have received at least 4 cycles of platinum therapy, are NaPi2b-high, and are not receiving bevacizumab are randomly assigned in a 2:1 ratio to upifitamab at 30 mg/m^2 or placebo as maintenance therapy (NCT05329545). Patients can have a history of receiving bevacizumab, but not with the most recent platinum-based therapy. UP-NEXT is expected to enroll approximately 350 patients.

Finally, UPGRADE is a phase 1 trial that is looking at a combination of carboplatin and upifitamab in approximately 48 participants with high-grade serous ovarian cancer (NCT04907968). The trial is designed to determine the recommended dose of upifitamab in combination with carboplatin. The ultimate goal is to determine whether upifitamab can replace a chemotherapy agent such as paclitaxel. Upifitamab does not cause alopecia, which is a side effect of paclitaxel.

H&O What additional trials are looking at the use of ADCs in ovarian cancer?

DR A phase 1 trial is investigating the use of luveltamab in advanced ovarian cancer (NCT03748186). The trial, which recently closed enrollment, is studying the use of mirvetuximab in approximately 75 participants with FRα-high, platinum-sensitive ovarian cancer (NCT05041257). The phase 3 GLORIOSA trial is a maintenance trial, like UP-NEXT, that is randomly assigning 418 patients with FRα-positive, platinum-sensitive ovarian cancer to mirvetuximab plus bevacizumab or bevacizumab alone (NCT05445778).

H&O How should these agents be dosed?

DR The dosing depends on the ADC. Mirvetuximab was approved for use at a dose of 6 mg/kg, based on adjusted ideal body weight, given intravenously every 3 weeks. Upifitamab was studied at a dose of 36 mg/m^2 in the platinum-resistant setting, with a maximum dose of 80 mg, and at a dose of 30 mg/m^2 in the maintenance setting, capped at a maximum body surface area of 2.2/m^2. Upifitamab is given intravenously every 4 weeks.

H&O What are some of the adverse events associated with ADCs in ovarian cancer?

DR That depends on the specific ADC. Adverse events can be related to the target or the payload. There is a black box warning for mirvetuximab regarding ocular toxicity. Mirvetuximab is known to cause blurred vision, typically in the middle of cycle 2 at around day 15. The important thing to know is that this blurred vision is reversible and not permanent. We also have multiple mitigation strategies to reduce ocular toxicity. For example, patients should use lubricating eye drops and corticosteroid eye drops. Patients need to see an eye care provider prior to starting mirvetuximab, and then prior to every other cycle. If the patient does not experience any ocular toxicity in the first 8 cycles, close monitoring is no longer required.

Many of the adverse events we see with ADCs are grade 1 or 2 and are relatively manageable with supportive care and mitigation strategies. Mirvetuximab often causes gastrointestinal side effects, such as nausea, abdominal pain, diarrhea, and constipation. It can also cause pneumonitis, which seems to be a class effect with ADCs. Most of the pneumonitis associated with mirvetuximab is grade 1, so it is picked up on imaging, but the patient is asymptomatic.

Upifitamab is known to cause nausea, vomiting, fatigue, and fever. We also see pneumonitis, but less often and lower grade since we lowered the dose from 43 to 36 mg/m^2 based on dose optimization data. We do see some elevated aspartate aminotransferase levels; this is typically transient and reverses prior to the next dose. Thrombocytopenia can occur, which typically resolves by the next dose. Tisotumab, which I mentioned earlier, also requires eye toxicity mitigation.

We are not aware of any ocular toxicity with upifitamab. There is no neuropathy or severe neutropenia with upifitamab, whereas there is some neuropathy with mirvetuximab.

H&O How common is resistance to ADCs?

DR Recurrent ovarian cancer always becomes resistant over time to therapy, including ADCs. We are still working to understand the various resistance mechanisms, but we believe that resistance can probably develop to any part of the ADC, including the antibody, the linker, and the payload. The tumor may react to ADC therapy by downregulating or altering the expression of the cell-surface antigen that is being targeted, for example. Drug efflux can be increased, changes in the lysosome and degradation of the ADC can occur, and apoptosis resistance can develop. As a result, resistance to one ADC may lead to resistance to other ADCs or it may not—we are not yet sophisticated enough to be able to pinpoint the mechanism of resistance in a particular patient. This is an area of ongoing research.

H&O What strategies are used to try to overcome this resistance?

DR That is where we get into combinations of drugs. As we learn more about resistance, we should be able to determine which agents might be most effective when used in combination with ADCs. Many ADCs are being investigated in combination with other agents. Ideally, the side effects profiles would not overlap. We have data regarding the combination of mirvetuximab and bevacizumab in ovarian cancer. This combination is not FDA approved, but phase 1b/2 data showed an overall response rate of 44% in 126 patients with recurrent FRα-positive ovarian cancer. These data were presented by Dr David O'Malley at the 2022 annual meeting of the International Gynecologic Cancer Society and were published earlier this year in the *International Journal of Gynecological Cancer*. Based on these data, I would not hesitate to use a combination of mirvetuximab and bevacizumab in patients without contraindications.

H&O What do you see as the future of treatment with ADCs in ovarian cancer?

DR I anticipate being able to use ADCs earlier in treatment. It will be hard to improve upon the success of our current standard of care, carboplatin plus paclitaxel, but we know that this combination has limitations. It does not cure most patients with advanced ovarian cancer, and paclitaxel leads to alopecia and often peripheral neuropathy. It would be great to reduce toxicity and achieve efficacy that is at least as good or better with carboplatin plus an ADC, ideally as first-line therapy, but at least in platinum-sensitive patients experiencing a recurrence.

Disclosures

Dr Richardson has done consulting for Mersana, ImmunoGen, AstraZeneca, and GSK; and has received institutional research support from Mersana, ImmunoGen, AstraZeneca, GSK, Shattuck Labs, Lilly, Imunon, Hookipa, and Syros.

Suggested Readings

Collins DM, Bossenmaier B, Kollmorgen G, Niederfellner G. Acquired resistance to antibody-drug conjugates. *Cancers (Basel)*. 2019;11(3):394.

Gilbert L, Oaknin A, Matulonis UA, Mantia-Smaldone GM, Lim PC, Castro CM, Provencher D, Memarzadeh S, Method M, Wang J, Moore KN, O'Malley DM. Safety and efficacy of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. *Gynecol Oncol*. 2023;170:241-247.

Matulonis UA, Lorusso D, Oaknin A, et al. Efficacy and safety of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer with high folate receptor alpha expression: results from the SORAYA Study [published online January 30, 2023]. *J Clin Oncol*. doi:10.1200/JCO.22.01900.

Moore KN, Oza AM, Colombo N, et al. Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I. *Ann Oncol*. 2021;32(6):757-765.

O'Malley D, Oaknin A, Matulonis U, et al. Mirvetuximab soravtansine and bevacizumab in folate receptor alpha-positive ovarian cancer: efficacy in patients with and without prior bevacizumab [IGCS abstract O011/#496]. *Int J Gynecol Cancer*. 2022;32:A7-A8.

Richardson DL, Hamilton EP, Barve M, et al. Updated results from the phase 1 expansion study of upifitamab rilsodotin (UpRi; XMT-1536), a NaPi2b-directed dolaflexin antibody drug conjugate (ADC) in ovarian cancer [SGO abstract 076]. *Gynecol Oncol*. 2022;166(1)(suppl).

Richardson DL, Harter P, O'Malley DM, et al. UP-NEXT (GOG-3049/ENGOT-OV71-NSGO-CTU): a study of upifitamab rilsodotin (UPRI), a NAPI2B-directed antibody drug conjugate (ADC) in platinum-sensitive recurrent ovarian cancer [IGCS abstract 453]. *Int J Gynecol Cancer*. 2022;32(suppl 3).