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Antibody–Drug Conjugates for the Treatment of Gynecologic Cancer

A Review of the Current Evidence and Clinical Application

Mary Towner, MD[a,*], Jenna Marcus, MD[b]
[a]Department of Obstetrics and Gynecology, McGaw Medical Center of Northwestern University, Chicago, IL, USA; [b]Department of Obstetrics and Gynecology, Northwestern Feinberg School of Medicine, Chicago, IL, USA

KEYWORDS
• Antibody–drug conjugate • Ovarian cancer • Cervical cancer • Mirvetuximab soravtansine • Tisotumab vedotin

KEY POINTS
- Antibody–drug conjugates deliver cytotoxic drugs to cancer cells by binding to tumor-specific antigens.
- Two antibody–drug conjugates are currently approved by the Food and Drug Administration for use in gynecologic cancers: mirvetuximab soravtansine for platinum-resistant ovarian, fallopian tube, and primary peritoneal cancer and tisotumab vedotin for cervical cancer previously treated with chemotherapy.
- Objective response rates for mirvetuximab and tisotumab are 30% and 22%, respectively; median time to response is approximately 6 weeks for both.
- Antibody–drug conjugates are associated with many commonly encountered toxicities, such as fatigue, nausea, neutropenia, and neuropathy, as well as ocular toxicities; most can be mitigated by prophylactic measures and/or dose modifications.
- Many trials are actively investigating the use of antibody–drug conjugates in gynecologic cancers.

INTRODUCTION

It is estimated that in 2023, gynecologic cancers (composed of ovarian, uterine, cervical, vulvar, and vaginal cancers) will represent the fourth most common cancer type in women in the United States. Most of these cases arise from the ovary or uterus, diseases of which are estimated to be the fifth and sixth leading causes of cancer-related deaths in US females, respectively [1]. Despite advancements in cancer-directed therapy, survival from uterine cancers has not improved particularly in Black women [2].

Treatment of advanced and recurrent gynecologic cancers poses many challenges, including a high risk of progression and inherent or acquired chemotherapy resistance that result in poor response rates to systemic therapy. In the past 15 years, the need for effective treatment options for patients with gynecologic malignancies has inspired a frenzy of research and clinical development of novel therapeutic agents. One such class of drug is the antibody–drug conjugate (ADC). In this review, the authors discuss the current approved uses for ADCs in gynecologic cancer treatment and provide an overview of ongoing clinical trials likely to impact the gynecologic cancer treatment landscape in coming years.

Mechanism of Action

The mechanism of action of ADCs is unique among cancer therapies. Every ADC has three components: (1) a monoclonal antibody (mAb), (2) cytotoxic

*Corresponding author. 250 East Superior Street, Suite 05-2175, Chicago, IL 60611. *E-mail address:* mary.towner@nm.org

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payload, and (3) linker molecule. The mAb is specific to an antigen, which is ubiquitously expressed on the tumor cell surface and allows for specific targeting and delivery of drug to the cancer cell with a reduction in toxicity to nontarget tissues. The cytotoxic drug, called the payload, is a potent molecule which allows delivery of the cytotoxic agent to cancer cells directly; in doing so, drugs which are too potent for typical systemic use can be used [3]. Once active, the cytotoxic payload acts as either a tubulin inhibitor or a DNA-disrupting agent. The payload and mAb are joined by a linker molecule, which are either cleavable or non-cleavable. Although seemingly inert, the function of the linker molecule is critical to ensuring the cytotoxic drug is released within the tumor cell to deliver its intended effect. If the cytotoxic drug is released too early into the systemic circulation, toxicity may result, but if it cannot be released within the tumor cell, it will not be effective [4]. Should premature cleavage between the active drug and linker molecule occur, the cytotoxic payload can be delivered to nearby normal cells and/or antigen-negative tumor cells, a phenomenon known as the bystander effect [5].

History of Antibody–Drug Conjugates in Cancer

The first ADC was approved in 2000 for the treatment of acute myeloid leukemia. ADCs officially entered the armamentarium of gynecologic oncologists in September 2021, when the Food and Drug Administration (FDA) granted accelerated approval of tisotumab vedotin (TV) for the treatment of recurrent or metastatic cervical previously treated with platinum-based chemotherapy [3,6]. Since then, a second ADC, mirvetuximab soravtansine (MIRV), was similarly granted accelerated FDA approval in November 2022 for use in patients with folate receptor alpha (FRα)-positive, platinum-resistant epithelial ovarian, fallopian tube, and primary peritoneal cancers [7,8]. Many additional clinical trials are underway further evaluating the use of additional ADCs in the treatment of gynecologic malignancies.

ANTIBODY–DRUG CONJUGATES FOR THE TREATMENT OF EPITHELIAL OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCERS

High-grade epithelial ovarian, fallopian tube, and primary peritoneal cancers, with no current effective screening strategy and often nonspecific presenting symptoms, are typically diagnosed at an advanced stage, after disease has spread beyond the pelvis. Although 80% of such patients will respond to the initial standard combination of surgical resection and platinum-based chemotherapy, including approximately 50% of patients who will have a complete response, the vast majority of these patients will ultimately experience disease recurrence [9]. Although recurrent platinum-sensitive ovarian cancer may initially respond to rechallenge with a platinum-based chemotherapy regimen, platinum resistance eventually develops and renders the disease more challenging to treat [10]. Unfortunately, there is a dearth of effective and durable treatment options in this setting. Best response rates to chemotherapy in the platinum-resistant patient are approximately 30%, with subsequent lines achieving responses in only 10% to 15% of patients, highlighting the need for additional treatment options [10,11].

Clinical Application

MIRV is indicated for treatment of patients with platinum-resistant, epithelial ovarian, fallopian tube, and primary peritoneal cancers found to highly express FRα, as determined by folate receptor alpha protein (FOLR1) immunohistochemical staining. Patients must have received 1 to 3 prior lines of treatment [12]. Although the approval carries no limitations on histologic subtype, it should be noted that only patients with high-grade serous ovarian, fallopian tube, and primary peritoneal cancers were enrolled in the SORAYA trial that secured the drug's approval [13].

Mechanism of Action

FRα, the target of the mAb component of MIRV, is a cell surface protein that binds and internalizes folic acid. It is normally expressed by a select few normal tissue types, including thyroid and breast, but FRα is not expressed by normal ovarian tissue [14]. Some degree of FRα expression is seen in up to 90% of epithelial ovarian cancer cells, though this varies by histologic subtype, with high-grade serous the most likely to have FRα expression (76%) and low-grade serous (50%) and clear cell (32%) less likely [14,15]. The FOLR1 RxDx assay defines high FRα expression as 2+ staining in $\geq$75% of cells and is reported to occur in approximately 35% of ovarian cancer cases [16,17].

After binding to its FRα target, MIRV is internalized into the cell and catabolized, where the cleavable linker allows the mAb to separate from the payload. This results in release of the ADCs cytotoxic payload: the maytansinoid DM4, a potent inhibitor of microtubule assembly [18].

Efficacy

In an early phase I trial, MIRV demonstrated an objective response rate (ORR) of 39% (95% CI 19.7–61.5) among patients with 3 or fewer prior lines of treatment. These encouraging results inspired FORWARD I, the first phase III clinical trial comparing MIRV to investigator-choice chemotherapy in patients with platinum-resistant epithelial ovarian cancer [19,20]. FORWARD I failed to identify a significant difference in its primary endpoint, progression-free survival (PFS), between the treatment groups. However, many secondary endpoints, including ORR and an improved toxicity profile, favored MIRV compared with chemotherapy. In addition, a subset analysis identified a progression-free and overall survival (OS) advantage in patients with tumors who tested positive for high-FRα (HR for disease progression or death 0.7, 95% CI 0.48–1.00) [20].

The SORAYA trial was a phase II single-arm trial examining the efficacy and safety of MIRV in high-FRα, platinum-resistant ovarian cancer patients who had received no more than three prior lines of chemotherapy. All patients had previously received bevacizumab and 48% had previously received a PARP inhibitor. Patients were treated with MIRV at a dose of 6 mg/kg every 3 weeks intravenously until disease progression, unacceptable toxicity, or death. The primary endpoint, ORR was 32.4% (95% CI 23.6–42.2) with a median duration of response (DOR) of 6.9 months (95% CI 5.6–9.7) as assessed by the investigator. Although 86% of patients experienced a treatment-related adverse event (TRAE), serious grade $\geq$3 events were reported in 9% and no new safety signals were identified [13]. The MIRASOL trial, now closed to patient enrollment and awaiting data maturation, is a randomized phase III confirmatory trial comparing MIRV to investigator-choice chemotherapy in platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancers with high FRα expression (NCT04209855).

Treatment-Related Adverse Events

According to clinical trial data, most patients (86%) treated with MIRV experienced at least one TRAE and approximately 30% of patients reported at least one Grade 3 to 4 event. Many of the most common toxicities of MIRV are the same as those seen with other standard chemotherapy agents, such as fatigue, asthenia, gastrointestinal upset (either nausea or diarrhea), neutropenia, and peripheral neuropathy. In the SORAYA trial, these were generally mild, with between 0% and 2% being rated as Grade 3 to 4 in severity [13].

Unlike standard chemotherapy, MIRV has a unique off-target toxicity to the eyes. Ocular toxicity of MIRV manifests in a variety of ways, including blurred vision, dry eye, photophobia, and keratopathy, which might include corneal erosion or corneal cyst formation. Data from SORAYA show 17% of patients experienced Grade 3 to 4 ocular toxicity of some kind, though no ocular toxicity resulted in permanent sequelae and most resolved with supportive care and/or dose adjustments [13].

Preventing and Diagnosing Ocular Toxicities Associated with Mirvetuximab Soravtansine

As the incidence of any ocular toxicity is relatively high, FDA approval of MIRV included a boxed warning recommending several prophylactic measures. Before initiating treatment with MIRV, patients should undergo a comprehensive ophthalmologic examination; this examination should be repeated every other cycle for the first 8 cycles, and as clinically indicated by patient-reported symptoms. To reduce the risk of ocular toxicity, patients should be directed to use over-the-counter preservative-free lubricating eye drops daily and prescription corticosteroid eye drops, starting the day before treatment and continuing until day 8 of each cycle [21].

Managing Toxicities of Mirvetuximab Soravtansine

Most toxicities of MIRV can be managed by withholding and/or reducing drug doses. In the SORAYA trial, treatment was delayed in 33% of patients and dose reductions were necessary in 20%. Drug discontinuation due to toxicity was necessary in 9% of study participants [13]. General recommendations for toxicity-directed dose modifications of MIRV are shown in Table 1.

ONGOING TRIALS IN EPITHELIAL OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCERS

Given the positive results observed in the SORAYA trial, several ongoing trials are investigating the addition of MIRV to existing treatment regimens, in both the platinum-resistant and sensitive settings. Currently enrolling is IMGN853 to 0420 an open-label, phase 2 trial combining MIRV with carboplatin in the platinum-sensitive recurrent setting following treatment with one prior line of platinum-based chemotherapy (NCT05456685). The rationale for this combination was determined after the phase Ib escalation trial in patients with platinum-sensitive and minimum FRα

TABLE 1
General Guidance for Toxicity-Directed Dose Modifications of Mirvetuximab Soravtansine

Toxicity[a]	Dose Modification[b]
Peripheral neuropathy	Grade 2: withhold until Grade 1, then resume at lower dose Grade ≥3: permanently discontinue
Ocular (eg, uveitis, keratitis)	Grade 2: withhold until Grade 1, then resume at same or lower dose (prescriber discretion) Grade 3: withhold until Grade 1, then resume at lower dose Grade 4: permanently discontinue
Pneumonitis	Grade 2: withhold until Grade 1, then resume at same or lower dose (prescriber discretion) Grade ≥3: permanently discontinue
Other	Grade 3: withhold until Grade 1, then resume at lower dose Grade 4: permanently discontinue

[a] As defined by 2017 Common Terminology Criteria for Adverse Events, published by National Cancer Institute.
[b] For all Grade 1 toxicities, continued monitoring at current dose is appropriate.

positivity (≥25% of cells with ≥2+ staining intensity) reported an ORR of 71% (95% CI 44–90) and a median PFS of 15 months demonstrating activity in this population [22]. Additional platinum-sensitive trials will evaluate the combination of MIRV and bevacizumab. Promising phase I data in the platinum-resistant setting using the combination of MIRV and bevacizumab demonstrated an ORR of 39% including 5 complete responsess and 21 partial responses, which prompted the evaluation of this regimen in the platinum-sensitive setting. The GLORIOSA trial will compare bevacizumab alone versus bevacizumab with MIRV as maintenance for high-FRα, platinum-sensitive disease in patients who have not progressed after second-line platinum-based chemotherapy plus bevacizumab (NCT05445778) [23].

The FORWARD II investigated the combination of MIRV and carboplatin, bevacizumab ± carboplatin, pegylated doxorubicin, or pembrolizumab in both platinum-resistant and platinum-sensitive, FRα-positive disease. These data are largely not yet available (NCT02606305), though efficacy in the bevacizumab + MIRV platinum-resistant cohort was recently published and reported an ORR of 44%. Of note this cohort accepted patient with a lower FRα positivity (≥25% of cells staining 2+) [24]. Preliminary results from the pembrolizumab + MIRV cohort demonstrate an ORR of 43% [3]. Finally, the efficacy of single-agent MIRV in the recurrent platinum-sensitive, high-FRα setting will be reported by the PICCOLO trial (NCT05041257).

Additional trials evaluating other FRα-targeting agents in ovarian cancer are underway in early phase trials. The agent STRO-002 is a FRα mAB with a cleavable linker to a hemosiderin derivative payload. The early phase I dose-expansion study demonstrated a 37.5% ORR and median DOR of 5.5 months in patients with FRα greater than 25% regardless of staining intensity. They also observed a higher ORR of 43.8% in patients treated with the higher dose of 5.2 mg/kg. The efficacy of this drug will be studied in the phase II/III REFRaME-01 trial. Last, the ADC farletuzumab ecteribulin (MORAb-202) with a cleavable linker to the payload eribulin mesylate is being evaluated across multiple solid tumor types.

Another receptor being evaluated as a potential target in the ovarian cancer space is sodium-dependent phosphate transport protein 2B (NaPi2B). While not expressed in normal ovarian cells, NaPi2B is highly expressed by ovarian cancer cells rendering it a prime target for drug development. The ADC, upifitamab rilsodotin (UpRi), binds the NaPi2B receptor and releases the auristatin F-hydroxypropylamide (AF-HPA) payload using a cleavable ester linker [25]. Despite promising preliminary results from the expansion cohort demonstrating an ORR of 34% in the NaPi2B high subgroup, the pivotal cohort in UPLIFT failed to meet its primary endpoint with an ORR of 15.6% (95% CI 10–22.7). The UPLIFT trial evaluated UpRi monotherapy in a heavily pretreated population with platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. In the platinum-sensitive setting, UpRi is being evaluated as a maintenance therapy in the phase III trial UPNEXT in NaPi2B-high recurrent, high-grade serous ovarian cancers (NCT05329545). It is also being added in combination with carboplatin in the phase 1 UPGRADE (NCT04907968) in patients with recurrent, platinum-sensitive high-grade serous ovarian cancers.

ANTIBODY–DRUG CONJUGATES FOR THE TREATMENT OF CERVICAL CANCER

Cervical cancer, despite widespread availability of vaccinations against the causative human papillomavirus in industrialized nations, continues to contribute significantly to morbidity and mortality in women worldwide. Although the vast majority of cervical cancers in the United States are diagnosed at an early stage, age-adjusted incidence of distantly metastatic cervical

cancer increased 27% from 2001 to 2018 [26]. Survival depends on stage at diagnosis; 5-year survival for local disease is approximately 92%, whereas advanced-stage disease carries a 5-year survival rate of only 17% [27].

The current first-line standard of care for distantly metastatic cervical cancer is treatment with combination chemotherapy that includes a platinum-taxane and bevacizumab, along with pembrolizumab in patients with a programmed death ligand 1 (PD-L1) combined positive score of 1 or more [28,29]. In cases of disease progression during or following standard chemotherapy, there had been no widely accepted standard of care subsequent therapy and response rates were poor around 20% [30,31].

Clinical Application

TV was granted accelerated approval by the FDA in September 2021 for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy [7]. Unlike MIRV, no diagnostic tumor testing is necessary for the use of TV in cervical cancer.

Mechanism of Action

TV is composed of a mAB to tissue factor (TF), cleavable linker, and cytotoxic payload monomethyl auristatin E (MMAE). The mAb component of TV recognizes and binds to TF, a protein that is expressed by many organs and plays a major role in the coagulation cascade, as well as the production of proteins promoting cellular growth and angiogenesis. Under physiologic circumstances, TF remains intracellular until tissue damage occurs, making its activation necessary for repair. Many solid tumors express TF at high levels on the cell surface. In cervical cancer, TF is ubiquitous; 96% express TF, which enables the tumor to take advantage of the pro-growth and pro-angiogenic downstream effects of TF binding [6,32].

Binding to TF by TVs anti-TF mAB results in delivery of the cytotoxic payload, MMAE, into the cancer cell. MMAE ultimately causes cellular death as a potent tubulin disrupter [32]. Unlike MIRV, the binding of the antibody has its own direct effect in addition to the drug delivery: inactivation of the pathway results in production of factors promoting cellular division and angiogenesis [6].

Efficacy

In the open-label, dose-escalating, and dose-expansion phase I/II innovaTV201 trial, TV yielded an ORR of 24% (95% CI 16–33) in patients with cervical cancer. In the subsequent open-label, phase II, single-arm innovaTV 204/ENGOT-cx6/GOG-3023 trial, patients with recurrent, progressive cervical cancer during or after systemic treatment with a platinum-based doublet with or without bevacizumab were given TV at a dose of 2.0 mg/kg every 3 weeks. The primary endpoint was ORR. Confirming the results of the innovaTV201 trial, the ORR was also 24% (95% CI 15.9–33.3), including 7% who achieved a complete response and 17% a partial response. The median time to response was 1.4 months and median DOR was 8.3 months. A summary of the efficacy data from this trial is shown in Table 2.

TABLE 2
Efficacy of Antibody-Drug Conjugates Approved by Food and Drug Administration for Gynecologic Cancers

	Median OS, Months (95% CI)	Median PFS, Months (95% CI)	ORR % (95% CI)	Median Time to Response, Months (IQR)	Median Duration of Response, Months (95% CI)
Mirvetuximab soravtansine					
SORAYA	13.8 (12-NR)	4.3 (3.7–5.2)	30.2 (21.3–40.4)	1.5 (1–5.6)	6.9 (5.6–9.7)
Tisotumab vedotin					
InnovaTV204/ GOG-3023/ ENGOT-cx6	12.1 (9.6–13.9)	4.2 (3–4.4)	22 (16–33)	1.4 (1.3–1.5)	8.3 (4.2-NR)

Abbreviations: CI, confidence interval; IQR, interquartile range; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Treatment-Related Adverse Events

Overall, 92% of patients on trial experienced at least one TRAE and 12% discontinued treatment as a result. The rate of Grade 3 and 4 events was 25% and 2%, respectively. There was one report of Grade 5 septic shock. The TRAE reported in ≥20% of patients treated with TV included alopecia (38%), nausea (27%), fatigue/asthenia (36%), and myalgias/arthralgias (27%). Nearly all of these were assessed to be Grade 1 to 2. Some form of neuropathy was reported in 33% of patients, of which 7% was rated as Grade 3. Mucosal hemorrhages were seen in 39% of patients, with most cases being mile epistaxis or hematuria, but 2% presenting as a Grade 3 gastrointestinal or genitourinary bleed. Although exceptionally rare, there have been postmarketing reports of severe dermatologic reactions to TV, including Stevens–Johnson syndrome.

Much like MIRV, TV has a risk of off-target effect on the eyes; possible TRAE include conjunctivitis, dry eye, and keratitis (including ulcerative). Overall, 53% of patients in the innovaTV204 trial experienced an ocular adverse event; 96% of these were Grade 1 to 2. The median time for ocular TRAE to present was 1.4 months. On follow-up, 86% of ocular TRAE had resolved within 30 days of the last dose of TV.

Preventing and Diagnosing Ocular Toxicities Associated with Tisotumab Vedotin

As was the case with MIRV, the accelerated approval of TV by the FDA carried a boxed warning about the risk of ocular toxicity and recommendations for prevention. Patients should undergo a comprehensive ophthalmologic examination before initiating therapy and before each cycle of TV. In addition, any new ocular symptoms should prompt repeat evaluation by an ophthalmologist. During the 30-min infusion, cold packs should be placed on the eyes and rotated to keep the eyes cool for a duration of 60 minutes. In addition, patients should be instructed to use vasoconstrictor eye drops and corticosteroid eye drops before infusion; the corticosteroid eye drops are then continued for 72 hours thereafter [33]. Throughout treatment preservative-free lubricating eye drops should be used daily and for 30 days after completion of treatment. Importantly, patients should be instructed not to wear contact lenses while undergoing treatment with TV [34].

Managing Toxicities of Tisotumab Vedotin

Like many cytotoxic therapies, toxicities may resolve with dose reductions or drug discontinuation. In the innovaTV204 trial, TRAEs led to dose reduction(s) in 22% of patients and discontinuation of the drug in 12% [6]. General guidance for managing toxicities related to TV treatment is shown in Table 3. Of note, if a dermatologic reaction to TV is suspected, the drug should be held until diagnosis can be determined, and if confirmed, Grade 3 to 4 toxicity should prompt permanent discontinuation of the drug.

ONGOING TRIALS IN CERVICAL CANCER

TV is under investigation for the treatment of cervical cancer in additional trials. InnovaTV 205/ENGOT-cx8/GOG-3024 is a phase Ib/II dose escalation and expansion trial evaluating several combinations of TV, carboplatin, bevacizumab, and pembrolizumab in both chemotherapy naïve and recurrent patients. Preliminary data from this trial have been reported and demonstrated an ORR of 55% in frontline TV/carboplatin combination and an ORR of 41% in frontline TV/pembrolizumab combination. InnovaTV 301/ENGOT-cx12/GOG 3057 is the confirmatory phase III trial comparing TV monotherapy to investigator's choice chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, pemetrexed) for cervical cancer previously treated with no more than two chemotherapy regimens. In late 2023, an announcement was made declaring that the primary outcome of OS was met. Key secondary endpoints (PFS and ORR) also reached statistical significance without new safety signals. The results from this trial will now solidify TV as a viable treatment option in patients who seldom have robust, effective options available for this challenging disease.

ANTIBODY–DRUG CONJUGATES FOR THE TREATMENT OF ENDOMETRIAL CANCER

Although there are currently no ADCs FDA-approved for the treatment of endometrial cancer, there are several clinical trials investigating this critical area of unmet need, especially in prognostically poor biomarker subgroups. Thus far, drugs under investigation are those ADCs targeting FRα, human epidermal growth factor receptor 2 (HER2), and trophoblast cell surface antigen-2(Trop-2). Targeting FRα, IMGN853 is evaluating the combination of MIRV with pembrolizumab in FRα positive (≥50% of cells with ≥2+ IHC), microsatellite stable recurrent, or persistent endometrial cancer (NCT03835819). Patients eligible for this trial could have received one to three prior lines of therapy and were allowed prior treatment with an immune checkpoint inhibitor. Another FRα-targeting ADC, farletuzumab ecteribulin (MORAb-202), is being evaluated in

TABLE 3
General Guidance for Toxicity-Directed Dose Modifications of Tisotumab Vedotin

Toxicity[a]	Dose Modification
Conjunctival ulceration	Any grade First occurrence: withhold until completely healed, then resume at lower dose. Second occurrence: permanently discontinue.
Conjunctival scarring	Any grade: permanently discontinue
Keratitis	Superficial punctate: monitor Superficial confluent: withhold until improved, then resume at lower dose. If recurs, permanently discontinue. Ulcerative: Permanently discontinue
Conjunctivitis	Grade 1: monitor Grade 2 First occurrence: withhold until improved, then resume at same dose Second occurrence: withhold until improved, then resume at lower dose Third occurrence: permanently discontinue Grade ≥3: permanently discontinue
Peripheral neuropathy	Grade 2: withhold until improved, then resume at lower dose Grade ≥3: permanent discontinue
Hemorrhagic complication	Central nervous system (CNS) or pulmonary, any grade: permanently discontinue Grade 2: withhold until resolved, then resume at same dose Grade 3 First occurrence: withhold until resolved, then resume at same dose Second occurrence: permanently discontinue Grade 4: permanently discontinue
Pneumonitis	Grade 2: withhold until Grade 1, then resume at lower dose Grade ≥3: permanently discontinue

[a] As defined by 2017 Common Terminology Criteria for Adverse Events, published by National Cancer Institute.

the phase I/II trial in patients with platinum-resistant advanced, recurrent, or metastatic endometrial cancer (NCT04300556). Another potential target for ADC therapy is the HER2 receptor. HER2 is overexpressed in several solid tumors including endometrial cancer in greater than 60% of uterine serous carcinomas, making it an attractive therapeutic target. The drug trastuzumab deruxtecan (T-DXd) is composed of the anti-Her2 IgG1 mAb and a topoisomerase I inhibitor with a tetrapeptide-based cleavable linker. It exhibits a direct ADC effect as well as an indirect bystander antitumor effect. DESTINY-PanTumor02 evaluated T-DXd evaluated HER2-expressing solid tumors in a phase II, open-label study. Patients with HER2+ tumors (IHC 2+ or 3+) were included, prior HER2-targeted therapy was also allowed. The ORR was 57.5% in the overall endometrial cohort with an ORR of 84.6% in the IHC3+ group and 47.1% in the IHC2+ group. Of note, 7.5% of patients experienced interstitial lung disease (ILD)/pneumonitis (of any grade) with the majority as Grade 1 or 2. with a median DOR that has not been reached. Additional trials with T-DXd are underway evaluating its combination with olaparib in a phase I trial for patients with HER2-expressing, advanced cancers, or endometrial cancer (NCT04585958). Last, the anti-HER2 IgG1 mAb agent DB-1303, which was granted fast track designation by the FDA, demonstrated activity in HER2+ and HER2-low advanced/metastatic solid tumors with a DCR of 88.5%.

Finally, the ADC sacituzumab govitecan (IMMU-132) is composed of an anti-Trop-2 mAb conjugated with the active metabolite of irinotecan (SN-38). Trop-2 is highly expressed in high-grade endometrial cancers and demonstrated a favorable response in preliminary results of the early phase trial (NCT04251416). This agent demonstrated an ORR of 35% with an acceptable safety profile in patients with recurrent high-risk histologies.

SUMMARY

ADCs offer patients with certain gynecologic cancers, who have historically had very limited treatment options, the possibility of durable disease response. Their unique mechanism of action yields a higher efficacy than many traditional chemotherapeutic agents. While generally well tolerated, ADC carries the risk of toxicities not previously encountered by gynecologic oncologists. With the extensive number of ADC currently being investigated in the gynecologic oncology sphere, their use is likely to become more common. Oncologists must take care to counsel patients on the risks, use prophylactic measures, and monitor for early symptoms of adverse events.

CLINICS CARE POINTS

- Comprehensive ophthalmologic examinations are required before initiating treatment with either mirvetuximab soravtansine (MIRV) or tisotumab vedotin (TV).
- Routine ophthalmologic examination should be performed before every TV cycle and before every other MIRV cycle.
- Risk of ocular toxicities can be reduced by adherence to prophylactic eye drop administration guidelines.
- Most treatment-related adverse event associated with TV or MIRV is not permanent and can be managed with dose modifications.

DISCLOSURE

J. Marcus is on the speaker's bureau for Seagen and GSK.

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