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NOVEL ANTIBODY-DRUG CONJUGATES: CURRENT AND FUTURE ROLES IN GYNECOLOGIC ONCOLOGY

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Abstract

Purpose of review—Antibody-drug conjugates (ADCs) represent a new class of drugs that combine a surface receptor-targeting antibody linked to a cytotoxic molecule. This review summarizes the current literature demonstrating their tremendous promise as therapeutic agents in the treatment of aggressive gynecologic malignancies.

Recent findings—Several antigens have proven to be differentially overexpressed in a variety of gynecologic tumors when compared to normal surrounding tissue and serve as novel targets for ADC therapy. In the last few years HER2/neu, folic acid-alpha (FRα) and Trop-2 overexpression have been exploited as excellent targets by novel ADCs such as Trastuzumab emtansine (T-DM1), SYD985, IMGN853 (Mirvetuximab soravtansine), and Sacituzumab govitecan (SG, IMMU-132) in multiple tumors including ovarian, endometrial and cervical cancers. While the selectivity of ADCs with non-cleavable linkers (i.e. T-DM1) has shown negligible effect on surrounding antigen negative cells, those ADCs with cleavable linkers (i.e. SYD985, IMGN853, and SG) may kill both antigen-positive target cells and surrounding antigen-negative cells via the bystander effect.

Summary—Preclinical data strongly supports these ADCs and ongoing clinical trials will shed further light into the potential of making these drugs part of current standard practice and providing our patients with a higher level of personalized cancer care.

Keywords

gynecologic malignancy; chemotherapy; antibody-drug conjugate

Introduction

This year in the United States alone, an estimated 113,520 women will be diagnosed with a gynecologic malignancy and an estimated 33,620 deaths will occur as a result of their cancer [1]. Chemotherapy is widely utilized in the treatment of gynecology malignancy, which includes the adjuvant setting after surgery, neoadjuvant therapy prior to surgery or as a sensitizer concomitantly with radiation treatment [2]. Since the advent of conventional

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chemotherapy in cancer treatment, the significant unwanted side effects and narrow therapeutic window has proven that there is a compelling need for newer biologic agents. Antibody-drug conjugates (ADCs) have recently strengthened the armamentarium in the era of molecularly targeted therapy. ADCs are sophisticated biological agents linking a surface receptor-targeting antibody to a cytotoxic molecule [3]. This permits the selective delivery and internalization of a toxic payload to tumor cells expressing the antigens targeted by the ADC, while decreasing the side effects to the healthy tissue that expresses low or no levels of the targeted antigen [4]. Additionally, the chemical structure of the linker (non-cleavable vs. cleavable) provides unique characteristics to the different ADCs [3,4]. ADC with non-cleavable thioether linkers need to be internalized and degraded by lysosomes to manifest their anti-tumor activity and show no bystander toxic effect on surrounding antigen negative cells [4]. Whereas, ADCs with cleavable linkers may release some of the toxic payload in the tumor microenvironment killing both antigen-positive target cells and surrounding antigen-negative cells via the bystander effect [4]. This review aims to describe the promising therapeutic benefits that ADCs have demonstrated in the treatment of gynecologic malignancy in both the preclinical and clinical setting.

Preclinical Data

HER2-targeted Therapies

The human epidermal growth factor type 2 receptor (HER2, erbB-2, or HER2/neu) gene encodes the HER2/neu tyrosine kinase receptor which plays an important role in the coordination of the complex erbB signaling network that is responsible for the regulation of cell growth, survival and proliferation [5]. C-erbB2 gene amplifications and mutations have been identified in a variety of cancers, and it is predictive of a higher mortality in early-stage disease, reduced time to relapse and a higher incidence of metastases [6,7]. Recent whole-exome sequencing (WES) and confirmatory immunohistochemistry (IHC) studies have reported HER2/neu amplification in up to 35% of uterine serous carcinoma (USC) patients [8,9]. Nonetheless, gynecologic carcinosarcomas (CSs) have been found to share similarities in their HER2 expression/amplification profiles to those found with USC [9]. Taken together, this supports HER2 as an attractive pathway for targeted therapies in such highly aggressive gynecologic malignancies.

Trastuzumab emtansine (T-DM1, Kadcyla, Genentech/Roche) is an ADC composed of trastuzumab covalently linked with a non-cleavable linker to the antimitotic agent emtansine (DM1). Once internalized into tumor cells, DM1 binds to tubulin and inhibits microtubule assembly resulting in apoptosis in dividing tumor cells [10–13]. Preclinical studies have demonstrated that T-DM1 was considerably more effective than trastuzumab (T), the unconjugated recombinant humanized monoclonal antibody targeting the HER2 receptor, which has recently shown to improve progression-free survival and overall survival for patients with both advanced and recurrent HER2/neu-positive USC [14,15]. In fact, T-DM1 was considerably more effective than T in inhibiting cell proliferation and in causing apoptosis ($p= 0.004$) of primary USC cell lines demonstrating HER2 overexpression. Importantly, T-DM1 was highly active at reducing tumor formation *in vivo* in USC xenografts overexpressing HER2 ($p= 0.04$) and mice treated with TDM-1 had significantly

longer survival when compared to T-treated mice and control mice ($p \leq 0.0001$) [16]. Similarly, T-DM1 demonstrated preclinical efficacy in uterine and ovarian CSs as it was dramatically more effective than T in inhibiting cell proliferation ($P < 0.0001$) and in inducing G2/M phase cell cycle arrest in the HER2 expressing cell lines ($p < 0.0001$). T-DM1 was also highly active at reducing tumor formation *in vivo* in CS xenografts overexpressing HER2 (P=0.0001 and P<0.0001 compared to T and vehicle respectively) with a significantly longer survival when compared to T and vehicle mice (p=0.008 and p=0.0001 respectively) [17]. Interestingly, despite observed rates of HER2/neu overexpression/amplification in epithelial ovarian cancer (EOC) showing considerable variation ranging from 8% to 66% with considerable intra-tumoral heterogeneity in receptor expression, T-DM1 induced significantly more apoptosis when compared with T + pertuzumab (P) (p<0.0001) [18,19]. T-DM1 was also significantly more effective in tumor growth inhibition *in vivo* in EOC xenografts overexpressing HER2/neu when compared to T alone, P alone and T+P (p=0.04) [19].

Another novel HER2/neu targeting ADC, SYD985 (Synthon Biopharmaceuticals BV), is composed of trastuzumab linked to the toxic payload valine-citrulline-seco Duocarmycin hydroxyl Benzamide Azaindole (vc-seco-DUBA), via a cleavable linker which allows significant bystander killing of surrounding tumor cells not expressing HER2/neu [20]. The toxic payload in SYD985 (i.e. DUBA), binds to the minor groove of DNA and subsequently causes irreversible DNA alkylation leading to DNA damage and ultimately cell death in both dividing as well as non-dividing cells [20]. SYD985 has demonstrated impressive preclinical antitumor activity in USC with a 10-to 70- fold increase in potency when compared to T-DM1 [20]. Interestingly, SYD985 not only demonstrated activity against USC with strong (3+) HER2 expression but it also demonstrated activity against USC with low to moderate (i.e. 1+/2+) HER2/neu expression both *in vitro* and *in vivo* [20]. Similarly, SYD985 was 7- to 54-fold more potent than T-DM1 when tested *in vitro* against CS cell lines. SYD985, unlike T-DM1, was also active against CS demonstrating low or heterogeneous HER2/neu expression [21]. *In vivo* studies also confirmed that SYD985 is more active than T-DM1 in CS and highly effective against HER2/neu expressing xenograft [21]. When SYD985 was tested against EOC cell lines it was found to be 3-to 42-fold more cytotoxic when compared to T-DM1 (p<0.0001) and SYD985 induced an efficient bystander killing of HER2/neu 0/1+ tumor cells when admixed with HER2/neu 3+ EOC cells [22]. The *in vivo* studies also confirmed that SYD985 is significantly more active than T-DM1 against HER2/neu 3+ EOC xenografts [22].

DHES0815A (Genentech/Roche) is an ADC that is comprised of an engineered humanized immunoglobulin G1 (IgG1) monoclonal antibody, which binds specifically to HER2, conjugated to a novel DNA mono-alkylating agent, pyrrolo[2,1-c][1,4]benzodiazepine monoamide (PBD-MA), via a stable disulfide-based linker. The released payload covalently binds to DNA, leading to DNA alkylation but not cross-linking. Interestingly, DHES0815A binds to domain I of the HER2 extracellular domain and recognizes a distinct epitope from that bound by trastuzumab, pertuzumab and T-DM1 [23]. Taken together DHES0815A will not compete with these previously studied HER2 targeted agents when binding to the HER2 receptor and as such it can potentially be used in combination treatments while providing a more favorable toxicity profile for the patient. Currently there is an ongoing phase I trial

(NCT03451162) of DHES0815A as a single agent in participants with advanced and/or metastatic HER2-positive breast cancer and the use of this ADC both as a single agent and in combination treatments for USC is currently being investigated in the preclinical setting.

Folic acid receptor alpha (FRα) targeted Therapies

Folate receptor alpha (FRα) is a cell-surface transmembrane glycoprotein that facilitates the unidirectional transport of folates into cells [24]. FRα shows restricted distribution pattern in normal tissues, with expression limited to a variety of polarized epithelia, such as those found in the choroid plexus, kidney, uterus, ovary, lung, and placenta [24, 25]. Aberrant FRα overexpression is characteristic of a number of epithelial tumors, including ovarian and endometrial cancers [26]. In EOC specifically, approximately 80% of tumors express FRα and elevated receptor expression may be a negative prognostic factor with respect to chemotherapeutic response [27,28]. Similarly, several studies have confirmed that overexpression of FRα in both USC and endometrioid carcinoma [29,30]. Therefore, FRα has emerged as an attractive contender for molecularly targeted therapeutic approaches.

IMGN853 (Mirvetuximab soravtansine, Immunogen) is composed of a humanized antibody (M9346A) with high affinity to folic acid receptor alpha (FRα) attached via a cleavable disulfide-containing hydrophilic linker (sulfo-SPDB), to the maytansinoid DM4, a potent microtubule toxin [31,32]. Once intracellular, IMGN853 is degraded by acidic lysosomes allowing DM4 to inhibit microtubules, resulting in cell-cycle arrest and apoptosis. IMGN853 can also induce bystander cytotoxic activity. This action is considered to be particularly important for the activity against tumors with heterogeneous expression of FRα [32]. In preclinical studies, IMGN853 has shown excellent antitumor activity in FRα-positive tumors, including in models of EOC [32]. More recently, IMGN853 has also shown impressive preclinical antitumor activity in primary endometrioid and USC cell lines as well as in their respective xenograft/patient-derived xenograft (PDX) models [30]. The most robust cytotoxic activity of IMGN853 was against uterine tumor cells overexpressing FRα; however, IMGN853 did demonstrate bystander killing of FRα negative tumor cells [30].

Trop-2 targeted Therapies

Human trophoblast cell-surface marker (Trop-2) is a surface glycoprotein originally identified in human placental tissue and subsequently found to be highly expressed by various types of human epithelial solid tumors where its overexpression is considered to be an independent marker for poor prognosis as it is associated with the promotion of increased proliferation, invasion and metastasis [33,34]. Low level expression in normal healthy tissue makes Trop-2 a promising target for cancer immunotherapy. Sacituzumab govitecan (SG, IMMU-132, Immunomedics) is an ADC that consists of a humanized Trop-2 antibody, conjugated with active metabolite of irinotecan (SN-38) through the cleavable CL2A linker that is subject to time dependent hydrolysis supporting the bystander effect in the tumor microenvironment [35].

Recently, SG has demonstrated remarkable preclinical activity against several gynecologic malignancies [36*–40*]. Specifically, in uterine and ovarian carcinosarcoma tumors strong/diffuse staining for Trop-2 was seen in approximately 30% [38*]. Trop-2 positive CS cell

lines showed higher sensitivity to SG *in vitro* when compared to Trop-2 low/negative CS cell lines. In CS xenograft models, SG demonstrated significant tumor growth inhibition (p=0.004) and improved overall survival at 90 days (p<0.0001) [38*]. In poorly differentiated endometrial adenocarcinomas (EC), moderate-to-strong staining for Trop-2 was detected in 84% of the tumors and EC cell lines overexpressing Trop-2 were significantly more sensitive to SG compared to control ADC (p=0.014 and p=0.005) [36*]. SG also induced significant bystander killing of Trop-2-negative EC tumors co-cultured with Trop-2-positive EC tumors [36*]. In the xenograft EC model, administration of SG was well tolerated and demonstrated impressive tumor growth inhibition against poorly differentiated, chemotherapy-resistant EC xenografts (p= 0.011) [36*]. Nonetheless, for USC Trop-2 expression by IHC was detected in 95.1% of USC samples and tumor cell-lines overexpressing Trop-2 were significantly more sensitive to SG when compared to control ADC (p <0.05). Here SG also induced significant bystander killing of Trop-2- tumors when admixed with Trop-2+ tumors and caused growth-inhibition and increased survival in SG treated mice harboring Trop-2+ xenografts when compared to controls (p <0.05) [40*]. In EOC, moderate-to-strong staining was seen in 47% of ovarian tumors by IHC [39*]. Again, in EOC, Trop-2+ cell lines were significantly more sensitive to SG compared to control ADC (p < 0.05) and *in vivo* experiments with SG treatment demonstrated impressive anti-tumor activity against chemotherapy-resistant EOC xenografts [39*]. Lastly, in cervical cancer moderate to strong diffuse staining was seen in 95% (108/113) of SCCs, and 81% (29/34) of adenocarcinoma/adenosquamous cancers on immunohistochemistry [37*]. Trop-2 positive cell lines were also highly sensitive to SG *in vitro* and in xenografts a significant tumor growth inhibition was detected (p < 0.0001) with a significantly improved overall survival at 90 days (p = 0.014) [37*].

Clinical Data

HER2-targeted Therapies

Clinical data regarding the use of a humanized monoclonal antibody targeting HER2/neu in gynecologic malignancies is mostly focused on uterine serous carcinoma (USC). Whole exome sequencing and immunohistochemistry (IHC) studies have shown that one-third of USC patients harbor c-erbB2 gene amplification and/or HER2/neu overexpression [8,18], thus making it an attractive target for this highly aggressive histologic type of endometrial cancer. However, there are caveats that need special attention while targeting HER2 in USC. In contrast to breast cancer, where HER2/neu is homogenously overexpressed on tumor cells in the striking majority of patients, more than 50% of USC cells that overexpress HER2/neu at 3+ levels demonstrate high heterogeneity in HER2/neu protein expression by IHC [18]. Data suggests that combining the monoclonal antibody that targets HER2/neu with chemotherapy would be more effective than using it as single agent. Santin et al. recently led a consortium of USA institutions to conduct a phase II trial that compared carboplatin-paclitaxel with and without trastuzumab in patients with advanced or recurrent uterine serous carcinoma who overexpress HER2/neu [15]. A total of 61 patients with stage III/IV or recurrent disease were randomly assigned to receive carboplatin-paclitaxel (control arm) for six cycles with or without intravenous trastuzumab (experimental arm) until progression or unacceptable toxicity. Among all patients, median progression-free survival (PFS) was

8.0 months in the control arm, whereas it was 12.6 months in the experimental arm (p= 0.005; hazard ratio [HR], 0.44; 90% CI, 0.26 to 0.76). When stage III/IV patients (n=41) were taken into consideration separately, median PFS were 9.3 and 17.9 months in the control and experimental arms, respectively (p = 0.013; HR, 0.40; 90% CI, 0.20 to 0.80). In terms of patients with recurrent disease (n=17), the difference in PFS was 3.2 months; 6.0 months in the control versus 9.2 months in the experimental group (p = 0.003; HR, 0.14; 90% CI, 0.04 to 0.53). Toxicity was not different between treatment arms. The results of this study led the National Comprehensive Cancer Network (NCCN) to update its guidelines emphasizing carboplatin/paclitaxel/trastuzumab combination as the preferred treatment for stage III/IV or recurrent HER2 positive USC (http://www.jnccn.org).

The clinical evidence for other HER2 targeting agents (e.g. ado-tratuzumab emtansine, SYD985) is scarce. In a multi-histology basket trial, 58 patients with HER2 amplified cancers (advanced lung, endometrial, salivary gland, biliary tract, ovarian, bladder, colorectal and other cancers) were treated with 3.6 mg/kg IV ado-trastuzumab emtansine once every three weeks [41]. The median lines of prior systemic therapy were 2 (range 1–7). ORR was 26% across all groups. With regards to gynecologic malignancies, ORR was 22% (4/18, 2 complete response) for endometrial cancer and 17% (1/6) for ovarian cancer. There was 1 (2%) grade 3 neutropenia. In this study HER2 amplification was identified via next generation sequencing (NGS) and interestingly the degree of HER2 amplification (NGS fold change 1.7 to 27.9) did not predict response, although amplification by NGS correlated well with HER2/CEP17≥2 by FISH (40/41 tested) or IHC3+ (31/40 tested).

In another multi-center study, 38 patients (36 included in the efficacy analysis) with HER2 amplified tumors other than breast and gastric/gastroesophageal junction adenocarcinomas were treated with ado-trastuzumab emtansine at 3.6 mg/kg I.V. every three weeks until toxicity or disease progression [42**]. Patient with HER2 amplification with a copy number (CN)>7 based on targeted NGS were included. Median prior therapies was 3 (range 0–9). Partial responses were observed in two patients (5.6%) with parotid gland cancer (one mucoepidermoid carcinoma, one squamous cell cancer). With regards to gynecologic cancers, 8/10 uterine and ovarian carcinomas had stable disease. Overall, median duration of response was 4.6 months.

The safety and efficacy of SYD985 is currently being evaluated in patients with HER2 expressing recurrent, advanced or metastatic endometrial carcinoma (NCT04205630). This is a single arm phase II trial, in which HER2-expression is defined as a 1+, 2+ or 3+ score on immunohistochemistry (IHC) or positive by in situ hybridization (ISH). Patients are eligible if they have progressed on or after first line platinum-based chemotherapy. Patients who have had two or more lines of chemotherapy for advanced/metastatic disease will be excluded.

Lastly, newer ADCs targeting HER2/neu might show better clinical efficacy due to their more potent payloads and higher antibody drug ratios. DS-8201a is an ADC that granted accelerated approval by FDA in December 2019 for HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 based regimens in the metastatic setting. The approval was based on a phase II clinical trial that included 184

patients with HER2 positive breast cancer, who had received previous treatment with trastuzumab emtansine [43**]. Overall response rate was 60.3% (95% confidence interval [CI] = 52.9–67.4), with a 4.3% complete response rate and a 56% partial response rate. Median response duration was 14.8 months (95% CI = 13.8–16.9). The most common adverse events of grade 3 or higher were a decreased neutrophil count (in 20.7% of the patients), anemia (in 8.7%), and nausea (in 7.6%). On independent adjudication, the trial drug was associated with interstitial lung disease in 13.6% of the patients (grade 1 or 2, 10.9%; grade 3 or 4, 0.5%; and grade 5, 2.2%). Studies that are assessing the efficacy of DS 8201a in gynecologic malignancies (especially USC) are needed.

Folic acid receptor alpha (FRα) targeted Therapies

Phase 1 dose escalation study of IMGN853 included 44 patients with solid tumors that included ovarian (n=23), endometrial (n=11), cervical (n=1), renal (n=5) and non-squamous cell lung cancers (n=4) [44*]. After evaluation of safety, activity and pharmacokinetics data, 6 mg/kg (adjusted ideal body weight) once every three weeks was established. The most common side effects were fatigue (43%), blurry vision and keratopathy (29%), the majority of which were grade 1 or 2. The dose-limiting toxicities observed were grade 3 hypophosphatemia (5.0 mg/kg) and grade 3 punctate keratitis (7.0 mg/kg).

After dose escalation and determination of the recommended phase II dose, an expansion cohort was opened that included 46 patients with platinum resistant ovarian cancer, who have met the minimum requirement of FRα positivity on archival tumor samples by IHC (≥25% of tumor staining at ≥2+ intensity) [45]. Patients were given IMGN853 intravenously once every 3 weeks at 6.0 mg/kg (adjusted ideal body weight) until intolerable toxicity or disease progression. There was one complete and 11 partial responses with an objective response rate (ORR) of 26% and median PFS of 4.8 months. The median duration of response was 19.1 weeks. In the subset of patients, who had received three or less prior lines of therapy (n = 23), the results were more promising; ORR was 39%, PFS was 6.7 months, and duration of response was 19.6 weeks. These data has led to a phase 3 clinical trial, FORWARD I, in which the safety and efficacy of IMGN853 were assessed and compared with investigator's choice of chemotherapy (pegylated liposomal doxorubicin, paclitaxel, topotecan) in women with FRα-positive, platinum resistant epithelial ovarian, primary peritoneal or fallopian tube carcinoma [46*]. The study completed enrollment in April 2018 and final results are eagerly awaited.

Incorporation of a second targeted agent in addition to FRα targeted therapy has been recently assessed in a phase Ib study that investigated safety and clinical activity of IMGN853 in combination with bevacizumab in 66 patients with FRα platinum resistant ovarian cancer [47**]. Median prior lines of therapy was 3, (range, 1–8). Adverse events were generally grade 2 or less, which included diarrhea, blurred vision, nausea, and fatigue. There were 5 complete and 21 partial responses that correspond to an ORR of 39% and median PFS was noted to be 6.9 months. The effect of combination was more robust in a subset of patients with 1–2 prior lines of therapy, who were bevacizumab naïve, and whose tumors exhibited medium/high FRα expression. In this cohort, ORR was 56% with PFS of 9.9 and median duration of response of 12 months. There are currently eight clinical trials

that are recruiting patients to investigate the effects of IMGN853 in a variety of gynecologic malignancies (Table).

Trop-2 targeted Therapies

Several promising preclinical data in various gynecologic malignancies [36*-40*] have led the initiation of the first trop-2 targeted therapy in uterine cancer (NCT04251416). In this non-randomized phase 2 study, patients with persistent or recurrent endometrial carcinoma of epithelial origin that is refractory to platinum or has progressed after prior platinum based chemotherapy and has at least 2+ staining for Trop-2, will be administered at 10 mg/kg weekly as an infusion for 2 consecutive weeks (D1,8) on a 21-day-cycle. Treatment will be continued without a rest period in the absence of progression of disease or unacceptable toxicity. Patients with measurable recurrent disease of any previous substage (I-IV) are eligible to enrollment and they may have received multiple prior lines of chemotherapies and/or immunotherapy. Patients who have previously received topoisomerase I inhibitors are not eligible. Primary outcome will be the ORR and secondary outcomes include OS, PFS, durable disease control rate (the percentage of patients who have achieved complete response, partial response, and stable disease) and assessment of the safety profile of sacituzumab govitecan in endometrial cancer patients.

Conclusion

Undoubtedly, there is an enormous unmet medical need for novel therapeutic agents that can be used to treat patients with aggressive gynecologic malignancies that portend a poor prognosis. Traditional chemotherapeutic drugs have a narrow therapeutic window and undesired toxic side effects for the patient. ADCs offer the opportunity to target specific antigens on tumor cells while sparing normal surrounding tissue, which dramatically improves the toxicity profile of the delivered toxic payload and ultimately provides an improvement in the patient's quality of life during treatment. This review highlights the recent preclinical and clinical studies that demonstrate that HER2/neu, FRα, and Trop-2 have proven to be excellent antigens that serve as targets for ADCs such as T-DM1, SYD985, IMGN853, and SG. The preclinical data for these ADCs shows much promise for their use in the clinical setting. Ongoing clinical trials will shed further light into the potential of making these drugs part of current standard practice and providing our patients with a higher level of personalized cancer care.

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Key points

- There is an enormous unmet medical need for novel therapeutic agents that can be used to treat patients with aggressive gynecologic malignancies that portend a poor prognosis.
- Traditional chemotherapeutic drugs have a narrow therapeutic window and undesired toxic side effects for the patient.
- ADCs offer the opportunity to target specific antigens on tumor cells while sparing normal surrounding tissue, which dramatically improves the toxicity profile of the delivered toxic payload.
- HER2/neu, FRα, and Trop-2 have proven to be excellent antigens that serve as targets for ADCs such as T-DM1, SYD985, IMGN853, and SG.
- The preclinical data for these ADCs shows much promise for their use in the clinical setting. Ongoing clinical trials will shed further light into the potential of making these drugs part of current standard practice and providing our patients with a higher level of personalized cancer care.

Clinical trials investigating the clinical effects of IMGN853 in several gynecologic malignancies

Clinical Trials Identifier	Objective	Study Type	Arms	Primary Outcome	Secondary Outcome
NCT04296890 (SORAYA)	To evaluate the efficacy and safety of IMGN853 in patients with platinum-resistant high-grade serous epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer, whose tumors express a high-level of FRα	Phase 3	- Single-arm - IMGN853 at 6 mg/kg AIBW administered on Day 1 of every 3-week cycle	ORR	- DOR - Adverse events - PFS - OS
NCT03832361	To evaluate the activity and safety profile of IMGN853 in patients with type II endometrial cancers that overexpress FRα	Phase 2	IMGN853 at 6 mg/kg AIBW administered on Day 1 of every 3-week cycle	ORR	- OS - PFS - DDCR - Safety profile
NCT03552471	To evaluate the side effects and best dose of mirvetuximab soravtansine and rucaparib camsylate in treating participants with endometrial, ovarian, fallopian tube or primary peritoneal cancer	Phase 1	- Single arm - Participants receive mirvetuximab soravtansine IV on day 1 and rucaparib PO BID on days 1 through 21. Courses repeat every 21 days in the absence of disease progression or unacceptable toxicity.	To determine the recommended phase 2 dose	- Safety and tolerability of the combination - Objective anti-tumor activity - PFS
NCT02631876 (FORWARD I)	To compare the safety and efficacy of IMGN853 to that of selected single-agent chemotherapy (Investigator's choice) in women with platinum-resistant FR-alpha positive advanced EOC, primary peritoneal cancer and/or fallopian tube cancer.	Phase 3 RCT	Arm1: IMGN853 administered at 6 mg/kg AIBW once every three weeks (Q3W) Arm2: Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan	PFS	-ORR - OS - Patient reported outcome using QLQ-OV28 - Quality of Life questionnaire.
NCT04274426	To evaluate Mirvetuximab Soravtansine (IMGN853), in FRα high recurrent platinum sensitve ovarian cancer	Phase 2 Two arm Open label	Arm A: Control arm with Platinum-based chemotherapy - Carboplatin (AUC 5, d1) as monotherapy q21d - Carboplatin (AUC5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m^2, d1) q28d - Carboplatin (AUC4, d1) combined with gemcitabine (1000 mg/m2, d1 & d8) q21d - Carboplatin (AUC5, d1) combined with paclitaxel (175 mg/m^2, d1) q21d Arm B: Carboplatin (AUC5, d1) + Mirvetuximab soravtansine (IMGN853) 6 mg/kg IV d1 × 6 cycles q21d, followed by subsequent monotherapy of Mirvetuximab soravtansine (IMGN853) 6 mg/kg IV q3w until disease progression.	PFS	- OS - ORR - Efficacy regarding PFS - Efficacy regarding OS - Efficacy regarding ORR - Serological progressive disease - Time to first subsequent treatment - Time to second subsequent treatment - Patient reported outcomes, Quality of life EORTC C-30 - Patient reported outcomes, Quality of life EORTC OV-28 - Safety and tolerability
NCT02996825	To evaluate the side effects and best dose of mirvetuximab soravtansine and gemcitabine hydrochloride in treating patients with folate receptor (FR) alpha-positive recurrent ovarian, primary peritoneal, fallopian tube,	Phase 1	Patients receive mirvetuximab soravtansine IV on day 1 and gemcitabine hydrochloride IV over 30 minutes on days 1 and 8. Cycles repeat every 3 weeks in the absence of disease progression or unexpected toxicity.	To determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of gemcitabine hydrochloride	- Adverse events - Response - PFS - Assessment of biological correlatives assessed by biopsy

Clinical Trials Identifier	Objective	Study Type	Arms	Primary Outcome	Secondary Outcome
	endometrial, or triple negative breast cancer			(gemcitabine) when given in combination with mirvetuximab soravtansine (IMGN853)	

FRα: Folate Receptor-Alpha

AIBW: Adjusted ideal body weight

ORR: Objective response rate

DOR: Duration of response

OS: Overall survival

PFS: Progression free survival

DDCR: Durable disease control rate

AUC: Area under the curve