Advancing antibody-drug conjugates in gynecological malignancies: myth or reality?

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Abstract

Antibody-drug conjugates (ADCs) represent a new class of therapeutic agents designed to target specific antigens on tumor cells, combining the specificity of monoclonal antibodies to the cytotoxicity of classic chemotherapy agents. These drugs have been extensively studied both in solid and hematologic malignancies, leading to substantial improvement in the therapeutic landscape for several tumors. Despite no ADC have been yet approved for the treatment of gynecological malignancies, some agents have shown promising results and might have the potential to become part of the standard of care. Among them, mirvetuximab soravtansine has shown activity in platinum-resistant ovarian cancer with high folate-α receptor expression, as a single agent and in combination. Tisotumab vedotin is active in patients with pre-treated cervical cancer, and further investigation is ongoing. The purpose of this review is to summarize the structural and functional characteristics of ADCs and analyze the most recent and promising data regarding the clinical development of ADCs in gynecological malignancies. The available data on the efficacy of the more studied ADCs in ovarian, endometrial, and cervical cancers will be discussed along with toxicities of special interest, the mechanisms of resistance, and future possible drugs combination.

Keywords

Antibody-drug conjugates, gynecological malignancies, ovarian cancer, endometrial cancer, cervical cancer

Introduction

Antibody-drug conjugates (ADCs) are a relatively recently developed class of drugs with a unique structure consisting of an antibody capable of recognizing a specific cellular antigen, a cytotoxic molecule bounded to this antibody, and a linker that holds the two parts together ensuring the stability of the molecule. These drugs were introduced with the aim of improving chemotherapy efficacy, while limiting systemic toxicity since the specific antigen-antibody interaction aims to directly deliver the cytotoxic agent into the tumor cells, sparing healthy tissue that does not express or only minimally express the targeted antigen [1]. This approach to selectively deliver a cytotoxic agent to the cancer cells (the ‘magic bullet’) was first developed by
Paul Ehrlich at the beginning of the twentieth century to overcome the limitation of the narrow therapeutic index of many potent chemotherapy agents [2]. Despite the possibility to directly drive the cytotoxic agent into the cancer cells, ADCs are commonly characterized by different adverse events (AEs). These are mainly due to the expression of the targeted antigen in non-cancer cells and the occurrence of off-target toxicities due to the release of the payload into the bloodstream, influencing the maximum tolerated dose (MTD) of these compounds [3].

The first ADC that has been used in clinical practice is gemtuzumab ozogamicin for acute myeloid leukemia, approved by the Food and Drug Administration (FDA) in 2001 [4], followed by brentuximab vedotin in Hodgkin lymphoma [5]. The first FDA-approved ADC in solid malignancies is trastuzumab emtansine (T-DM1) for the treatment of metastatic and early-stage breast cancer [6, 7]. Since then, this field has been rapidly evolving with currently > 100 different ADCs under investigation across solid and hematological malignancies. Four ADCs are available in clinical practice for the treatment of patients with solid tumors: T-DM1 and trastuzumab deruxtecan (T-DXd) for human epidermal growth factor 2 (HER2)-positive breast cancer [8], sacituzumab govitecan for triple-negative breast cancer [9], and enfortumab vedotin for metastatic urothelial carcinoma [10].

Different ADCs are under investigation for the treatment of gynecological malignancies and some with promising results. The aim of this review is to describe the state of the art of ADCs in gynecological malignancies at different stages of research and development.

**Structure and mechanism of action of ADCs**

**Key components of ADCs**

**Antibody/antigen:** The first step in the development of an ADC is the selection of the antibody, which must be specific to a defined antigen and have low immunogenicity [11]. Most of the antibodies from which the new generation ADCs are formed are fully humanized, typically immunoglobulin G (IgG). The introduction of fully humanized antibodies has been paramount to reduce the immunogenicity of the murine and the chimeric (mouse/human) first- and second-generation ADCs [12]. The antigen must be present on the cell surface and be expressed exclusively, or at least preferentially, in tumor cells as opposed to normal tissue, to limit the off-target systemic toxicities [1]. The antigen-antibody binding on the cancer cell surface is followed by internalization of the ADC with subsequent lysosomal degradation and intracellular release of the cytotoxic agents, a process that leads to cell death [13]. The amount of ADC that is internalized depends on the antigen density on the cell surface [14]. However, heterogeneous results are available on the correlation between the level of the antigen expression and the ADC’s efficacy [15, 16].

**Payloads:** Payloads are extremely small cytotoxic molecules, in the nanomolar or picomolar range, bounded to the antibody structure via a linker. Over the years, several classes of payloads have been developed, but the most employed are auristatins and maytansinoids [17]. Auristatins are synthetic analogs of dolostatin 10, which is a natural antimimotic that caused inhibition of tubulin assembly. Among auristatins, the most widely used is monomethyl auristatine E (MMAE, vedotin) [18]. The other group of commonly used payloads is the maytansinoids, synthetic analogs of maytansine that act similarly to the vinca alkaloids inhibiting microtubule assembly. Mertansine (DM1) maytansinoids include emtansine and mertansine; raktansine maytansinoids include soravtansine and raktansine (DM4) [19]. The most used payloads in ovarian cancer are MMAE (vedotin) and DM4, both potent microtubule inhibitors. In addition to the direct intracellular effect, MMAE is also able to permeate the cell membrane, ensuring that the cytotoxic molecule spreads from target cells to neighboring cells, exerting its cytotoxic effect even in those cells that do not express the cellular antigen on their surface: this is known as the “bystander effect” [20] (Figure 1).

Other payloads developed in clinical practice are calicheamicin, duocarmcins, and pyrrolobenzodiazepines, which are potent inhibitors of nucleic acid synthesis because of their ability to recognize and bind to specific sequences of the DNA minor groove. SN-38, the active metabolite of irinotecan that acts inhibiting the DNA topoisomerase-I, has also been used as a payload. Due to its potent activity and the consequent toxicity, SN-38 cannot be administered as a free drug. Therefore, ADCs containing SN-38 have been developed, such as
sacituzumab govitecan and T-DXd, both of which have already been approved by the FDA for the treatment of metastatic breast cancer [8, 9].

Each ADC is characterized by a specific drug-to-antibody ratio (DAR) [21]. A higher number of cytotoxic molecules (hence a higher DAR) confers greater cytotoxicity, as opposed to an antibody that can bind fewer payloads. However, a high number of payloads may alter the structure of the ADC, compromising its stability, reducing the antigen affinity, or affecting its distribution in the tumor microenvironment [22, 23].

Linker: The antibody portion of an ADC and the cytotoxic warheads are connected through a linker, which influences the stability of the ADC in the bloodstream. The characteristics of the linker impact also the ability to release the cytotoxic payload when the ADC is bounded to the antigen or internalized in the cancer cell, avoiding a premature release, which can lead to an increased incidence of off-target toxicities [24]. Linkers are divided into two main categories: cleavable and non-cleavable. Cleavable linkers can be degraded by protease, acid pH, endosome, or lysosome reactions, thus part of the cytotoxic payloads might be released into the tumor microenvironment, affecting both antigen-expressing targets cells but also non-antigen-expressing surrounding cells through the “bystander effect” [20]. Non-cleavable linkers need the lysosomal proteolytic activity of the antibody to release the payload. The product of this cleavage contains the payload still attached to the linker and this can affect its electrical charge, hydrophobicity, or hydrophilicity. Non-cleavable linkers impact the ability of the payload to cross the membrane and on the other hand, the presence of the linker portion can cause the linker-payload complex to be eliminated from the cell via efflux pumps compromising the intracellular concentration of the payload and leading to drug resistance [25].

Mechanism of action of ADCs
The main mechanism of action of ADCs relies on the internalization of the cytotoxic payload following the antibody binding on the cell surface target and the subsequent linker breakdown (Figure 1). However, the therapeutic effect of ADCs is exerted through different and complex processes [26]. After administration of an ADC, the conjugate antibody but also the naked antibody and the free payload, are found in the bloodstream and they might induce antitumor activity on their own. The monoclonal antibody part of an ADC, particularly the antigen-binding fragment (Fab) can induce antitumor activity after target engagement even before the cytotoxic payload is released into the cancer cell and this is of relevance for ADCs targeting oncogenic antigens as described for T-DM1 and T-DXd [27, 28]. Moreover, as well known for many monoclonal antibodies, the Fc component of an ADCs can recruit immune effector cells and elicit cancer
cells killings via antibody-dependent cell cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), or antibody-dependent cellular phagocytosis (ADCP), thus acting as a form of immunotherapy [27, 29].

Upon target recognition, the ADC-antigen complex is internalized into the cell via receptor-mediated endocytosis or antigen-independent pinocytosis. Therefore, the efficacy of the ADC might be influenced by the antigen-binding affinity and degree of target internalization [30]. Subsequently, the lysosomes and endosomes activity is necessary to release the free cytotoxic warhead into the cytoplasm, inducing apoptosis and cell death [31]. Ultimately, membrane-permeable payloads can result in cytotoxic activity in the neighboring cells regardless of the expression of the target antigen. This “bystander effect” has a crucial role in the efficacy of ADCs and depends also on linker properties as described above [32].

**ADCs in gynecological malignancies**

Despite the significant progress achieved in the treatment of different malignancies, few new therapeutic targets are available for women with gynecological cancer. This has unfortunately led to little improvement over the years in the survival rates of patients with ovarian, endometrial, or cervical cancer. Thus, there is still an unmet need to discover new treatment options to improve patients’ outcomes.

Currently, there are no ADCs approved for the treatment of gynecological malignancies, but several trials have shown promising results sustaining the ongoing clinical research to further develop these agents. The composition of the main ADCs under development in gynecological cancers is summarized in Figure 2.

**ADCs in ovarian cancer**

The standard of care for advanced ovarian cancer is optimal cytoreductive surgery combined with platinum-based chemotherapy. Maintenance treatment with the antiangiogenic agent bevacizumab and/or poly(ADP-ribose)polymerase (PARP) inhibitors have significantly improved patients’ outcomes and are now part of the standard treatment strategy in first-line setting [33–36]. Despite the initial high response rate, ~80% of patients will eventually experience disease recurrence and progressive development of chemoresistance. In a platinum-resistant setting, treatment options are limited and the prognosis is poor. Available standard treatments are associated with low response rates (15–20%) and limited progression-free survival (PFS; 3–4 months) and overall survival (OS; 12 months) [37, 38]. Furthermore, in the recurrent disease setting, therapeutic options are often limited by the cumulative residual toxicity from previous treatments. The introduction of ADCs might be a valuable opportunity to increase the chemotherapy efficacy, while at the same time minimizing systemic toxicities.
Different cellular surface antigens have been identified in ovarian cancer as possible targets for ADCs with the FRα and mesothelin representing the most investigated [39, 40].

The FRα is a transmembrane protein present on the cell surface that mediates the transport of folate into the cells. This protein is poorly expressed in normal tissue, while a high surface expression has been demonstrated in ovarian, endometrial, breast, and non-small cell lung cancer cells [41, 42]. The increased expression of FRα on tumor cells occurs as a response to an increased demand for folate to sustain tumoral cell growth and proliferation [43]. Notably, FRα expression is a prognostic biomarker in ovarian cancer and its expression correlates with poor response to chemotherapy and worse PFS and OS [44].

Mesothelin is a membrane glycoprotein characterized by minimal expression in normal tissues (limited to mesothelial cells of the pleura, pericardium, and peritoneum) and overexpression in mesotheliomas, ovarian, pancreatic, lung, gastric, and triple-negative breast cancers. Mesothelin promotes tumorigenesis through induction of interleukine-6 (IL-6) and induces resistance to tumor necrosis factor-alpha (TNF-α) induced apoptosis [45]. Notably, high mesothelin expression correlates with poor prognosis in ovarian cancer [46]. The main results from clinical trials investigating an ADC in ovarian cancer are summarized in Table 1. Ongoing clinical trials are reported in Table 2.

### Table 1. Main clinical trials of ADCs in ovarian cancer

| Target | ADC                  | Trial                          | Setting                      | Treatment                          | Primary endpoint | Results                      |
|--------|----------------------|-------------------------------|------------------------------|------------------------------------|-----------------|------------------------------|
| FRα    | Mirvetuximab soravtansine | FORWARD I [47] (NCT02631876) | III Platinum-resistant FRα positive | Mirvetuximab vs. chemotherapy of investigator’s choice | PFS | ORR: 24 vs. 10% (P = 0.014)  |
|        |                      | FORWARD II (NCT02606305)     | Platinum-sensitive FRα positive | Mirvetuximab soravtansine + carboplatin | Safety (phase I) | ORR: 71%                      |
|        |                      |                               | Platinum-resistant FRα positive | Mirvetuximab soravtansine + pembrozilumab | Safety (phase I) | PFS: 15 months                |
|        |                      |                               | Platinum-resistant FRα positive | Mirvetuximab soravtansine + bevacizumab | Safety (phase I) | PFS: 5.2 months               |
|        |                      |                               | Platinum-resistant and sensitive FRα positive | Mirvetuximab soravtansine + bevacizumab | Safety (phase I) | PFS: 6.9 months               |
|        | MORAb-202            | NCT03386942 [52]              | I Platinum-resistant FRα positive | Farletuzumab conjugated with eribuline | DLTs            | ORR: 37.5%                    |
| Mesothelin | Anetumab ravtansine          | NCT01439152 [53]               | I Platinum-resistant and partially platinum sensitive | Anetumab ravtansine | DLTs | ORR: 9%                       |
|        | DMOT4039A (RG7600)      | NCT01469793 [54]              | I Platinum-resistant | DMOT4039A | DLTs/RP2D | ORR: 30%                      |
|        | BMS-986148             | CA008-008 (NCT02341625)       | II/IIa Platinum unselected | BMS-986148 | Safety | ORR: 10%                      |
|        | Tisotumab vedotin       | InnovaTV 201 (NCT02001623)    | II Platinum unselected Advanced solid tumors including ovarian cancer platinum unselected | Tisotumab vedotin | Safety | ORR: 13.9%                    |
| MUC16  | DMUC4064A              | NCT02146313 [57]              | I Platinum-resistant | DMUC4064A | Safety | ORR: 25%                      |
| NaPi2B | Lifastuzumab vedotin    | NCT01363947 [58]              | I Platinum-resistant | Lifastuzumab vedotin | Safety | ORR: 36.7%                    |
|        | NCT019991210 [59]      | II Platinum-resistant Lifastuzumab vedotin vs. PLD | Safety | Lifastuzumab vedotin vs. PLD | PFS | ORR: 34 vs. 15% (PFS: 5.3 vs. 3.1 months (HR 0.78)) |

MUC16: mucine 16; PLD: pegylated liposomal doxorubicin; RP2D: recommended phase 2 dose; ORR: overall response rate; HR: hazard ratio; vs.: versus; DLTs: dose-limiting toxicities; TF: tissue factor
### Table 2. Main ongoing clinical trials of ADCs in ovarian cancer

| Target | ADC | Trial | Phase | Setting | Treatment | Primary endpoint |
|--------|-----|-------|-------|---------|-----------|------------------|
| FRα    | Mirvetuximab soravtansine | MIROVA (NCT0427442) | II     | Platinum-eligible | Mirvetuximab soravtansine + carboplatin vs. platinum-based chemotherapy | PFS |
|        |      | MIRASOL (NCT04209855) | III    | FRα positive | Mirvetuximab soravtansine vs. chemotherapy of investigator’s choice | PFS |
|        |      | SORAYA (NCT04296890) | III    | FRα positive high | Mirvetuximab soravtansine | ORR |
|        |      | NCT03552471 | I      | Platinum-resistant and BRCA mutated platinum-sensitive | Mirvetuximab soravtansine + rucaparib | RP2D |
|        |      | NCT02996825 | I      | FRα positive | Mirvetuximab soravtansine + gemcitabine | RP2D |
|        |      | NCT04606914 | II     | Neoadjuvant, newly diagnosed FRα positive high | Carboplatin + mirvetuximab soravtansine | PFS |
| Mesothelin | Anetumab ravtansine | NCT02751918 | Ib     | Platinum-resistant | Anetumab ravtansine + PLD | MTD |
|         |      | NCT03587311 | II     | Platinum-resistant | Bevacizumab + anetumab ravtansine or paclitaxel | PFS |
| TF     | Tisotumab vedotin | InnovaTV 208 (NCT03657043) | II     | Platinum-resistant | Tisotumab vedotin | ORR |

**BRCA**: breast cancer gene

### Anti-folate receptor α: mirvetuximab soravtansine

Mirvetuximab soravtansine is an anti-FRα ADC, formed by the humanized IgG1 antibody conjugated to a DM4 payload via a cleavable linker. Structurally, DM4 is conjugated to the antibody with a DAR of 3.5:1. The final payload metabolite inhibits tubulin and causes cell cycle arrest in the G2-M phase, ultimately causing cell death. DM4 is electrically neutral and lipophilic, thus capable of crossing cell membranes and causing the “bystander effect” [20]. Mirvetuximab soravtansine is one of the first ADC investigated in ovarian cancer, and it is the only one for which results from a phase III study are available to date. A phase I dose-escalation trial in solid tumors, including patients with pre-treated epithelial ovarian cancer (EOC), established the RP2D at 6 mg/kg every 3 weeks and preliminary signs of activity were observed [60]. The DLTs observed in this trial were grade (G) 3 hypophosphatemia and G3 punctate keratitis [60]. A subsequent study was then conducted in an expansion cohort of 46 patients with platinum-resistant EOC and FRα positivity assessed on immunohistochemistry (defined as ≥ 25% tumor cells with at least 2+ staining). The ORR in this study was 26%, including one complete response (CR) and 11 partial responses (PRs), with a median PFS (mPFS) of 4.8 months and a median duration of response (DoR) of 19.1 weeks [15]. A phase Ib study confirmed the correlation between the level of FRα expression and mirvetuximab soravtansine efficacy [61]. No objective response was observed in low expressors (25% to 49% of tumor cells with ≥ 2+ staining intensity), with a mPFS of 2.8 months, while in medium expressors (50% to 74% of tumor cells with ≥ 2+ staining intensity), ORR was 20% with a mPFS of 3.9 months. In high-expressors (≥ 75% tumor cells with ≥ 2+ staining intensity), ORR was 31% with a mPFS of 5.4 months [61]. Given the evidence of increased benefit in patients with medium or high FRα expression, a subsequent phase III study was designed incorporating the same immunohistochemical threshold.

FORWARD I is a phase III clinical trial that enrolled 366 women with platinum-resistant EOC with medium or high FRα expression and pre-treated with 1–3 lines of chemotherapy [47]. The FRα threshold for positivity by immunohistochemistry was defined as > 50% of tumor cells with any FRα membrane staining visible at 10 microscope objective with a value of 50–74% and ≥ 75% representing medium and high expression, respectively. Patients were randomized 2:1 to receive mirvetuximab soravtansine 6 mg/kg every 3 weeks versus investigator’s choice chemotherapy (weekly paclitaxel, PLD, or topotecan). A higher ORR was observed in patients treated with mirvetuximab soravtansine compared to chemotherapy (24% vs 10%, P = 0.014), with no significant improvement in PFS (4.1 months vs 4.4 months, HR = 0.98) and in OS (HR = 0.62) [47].
The most common all grades AEs reported in these trials included nausea (45.7% of patients), blurred vision (42%), keratopathy (32.5%) diarrhea (31.3%), fatigue (28.8%) and peripheral neuropathy (26.7%) [47]. An AE of special interest was the ocular toxicity, characterized by blurred vision, dry eyes, or corneal abnormalities, which could be managed with topical steroids and/or with dose reduction [47, 60, 62]. Pneumonitis is another AE of special interest and occurred in 2.9% of enrolled patients (G1–3) [47, 60].

To evaluate the potential efficacy of mirvetuximab soravtansine in a better-selected population, two subsequent studies in patients with platinum-resistant EOC and high FRα expression (defined as ≥ 75% of cells with at least a score 2 staining intensity) have been initiated. First, the single-arm SORAYA trial (NCT04296890; prior bevacizumab required), aimed at supporting accelerated approval, with ORR as the primary endpoint. Secondly, the randomized confirmatory phase III MIRASOL trial (NCT04209855) comparing mirvetuximab soravtansine monotherapy with investigator’s choice chemotherapy, is still ongoing and results are eagerly awaited.

Given the limited activity as a single agent, different combinations with chemotherapy, antiangiogenic agents, or immune checkpoint inhibitors have been explored. FORWARD II is a phase Ib/II trial evaluating the efficacy of mirvetuximab soravtansine in combination with bevacizumab, carboplatin, PLD, or pembrolizumab. In the cohort of platinum-sensitive EOC, FRα positive (≥ 25% tumor cells with at least 2+ staining) patients were treated with carboplatin (AUC5) and mirvetuximab soravtansine 6 mg/kg for six cycles followed by maintenance treatment with mirvetuximab soravtansine. In this study, the highest benefit was seen in patients with a medium to high FRα expression, with an ORR of 80% [48]. Preliminary data combining mirvetuximab soravtansine and pembrolizumab in patients with platinum-resistant EOC, showed an ORR of 43% with a mPFS of 5.2 months and a median DoR of 30.1 months, with higher PFS and DoR in medium-high FRα expressors [49]. In patients with the platinum-resistant disease, the combination of mirvetuximab soravtansine and bevacizumab achieved an ORR of 39% with a mPFS of 6.9 months and a median DoR of 8.6 months. In the bevacizumab-naive population the efficacy was higher (ORR 56%, PFS 9.9 months, and median DoR of 12 months). Overall, the combination regimen was well tolerated [50]. At the 2021 Annual Meeting of the American Society of Clinical Oncology (ASCO), new data on the combination of mirvetuximab and bevacizumab in a platinum agnostic population of patients with recurrent EOC were presented [51]. Patients with high FRα expression had significantly higher mPFS (10.6 months) compared to patients with medium FRα expression (5.4 months). Similarly, patients with platinum-sensitive ovarian cancer achieved a better ORR and mPFS compared to platinum-resistant ovarian cancer (PFS: 13.3 months versus 9.7 months). Notably, in patients with high FRα expression, ORR was 64% and median DOR 11.8 months, and these outcomes were achieved irrespective of platinum sensitivity [51].

Interestingly, an expansion cohort of the FORWARD II study is still ongoing to evaluate the triple combination of mirvetuximab soravtansine, carboplatin, and bevacizumab, in patients with platinum-sensitive recurrent EOC. Both mirvetuximab soravtansine and bevacizumab were continued as maintenance therapy after the six combination cycles. In this group of patients, the ORR was 80% and PFS data were still immature at the time of data presentation. G3 AEs included thrombocytopenia, neutropenia, hypertension, diarrhea, nausea, and fatigue [63].

Taken together, this data suggests that mirvetuximab soravtansine exhibits a higher activity in high FRα expressors and when is used in combination with other chemotherapy or targeted agents, including PARP inhibitors (NCT03552471). Nevertheless, many open questions still remain, particularly on the role of FRα expression when mirvetuximab soravtansine is used in combination with other agents and which predictive biomarkers of response might support a better patient selection.

Other anti-FRα ADCs are also under investigation in phase I trials, including STR0-002 [64] and MORAb-202 [52] which showed promising results in FRα-expressing solid tumors, including ovarian and endometrial neoplasms.

Anti-mesothelin: anetumab ravtansine

Anetumab ravtansine is an anti-mesothelin ADC composed of an IgG1 antibody conjugated to the DM4 payload. It has a DAR of 3.2 with a charged, cleavable linker capable of bystander effect also on adjacent
mesothelin-negative cells [65]. A phase I dose-escalation trial included 45 patients (4 with EOC) and defined the MTD at 6.5 mg/kg every 3 weeks, which was then used in the expansion cohort of the same trial that enrolled 21 patients with EOC. Among patients with ovarian cancer who received the MTD, 9% had a PR and 50% stable disease (SD) [53]. The treatment was well tolerated, with any grade fatigue (57.8% of all patients), nausea (50.5%), diarrhea (41.3%), anorexia (34%), vomiting (27.5%), peripheral sensory neuropathy (25.7%), asymptomatic aspartate aminotransferase (AST) increase (29.4%), blurred vision (22%) and keratitis (19%) being the main AEs, as also seen with other ADCs containing the ravidansine maytansinoid [53]. The reported DLTs were G3 AST increase, G3 hypertension, G3 hyponatremia, G3 peripheral neuropathy, G4 keratitis, and G4 amylase and lipase increase.

Anetumab ravidansine has also been evaluated in combination with other agents. A phase Ib study in patients with platinum-resistant EOC investigated the combination of anetumab ravidansine and PLD, showing a PR in 52% of patients (lasting > 250 days in 6) and SD in 33% [66]. A randomized phase II trial of anetumab ravidansine plus bevacizumab versus paclitaxel plus bevacizumab in patients with platinum-resistant or refractory EOC is ongoing (NCT03587311).

Other ADCs in ovarian cancer

Other ADCs have been developed and are under preclinical and clinical evaluation in ovarian cancer. These ADCs have been directed against specific antigens expressed in several solid tumors including ovarian cancer, among which the most investigated are cancer antigen 125 (CA125 or MUC16) [57, 67, 68], NaPi2b [58, 59, 69–71], Trop2 [72], TF [73–75], protein tyrosine kinase 7 (PTK7) [76], CD166 and Notch3 [77].

ADCs in endometrial cancer

Endometrial carcinoma is the most frequent gynecological neoplasm in western countries, and unlike ovarian and cervical cancer, its incidence is increasing [78]. The prognosis of this disease depends on the stage at diagnosis, histological subtype, grade, presence of lympho-vascular space invasion, and molecular characteristics [79]. Women diagnosed with early-stage well-differentiated endometrioid carcinoma have a 5-year survival rate of 90%. However, ~35% of endometrial cancer has more aggressive histology (poorly differentiated endometrioid, serous or clear cell carcinoma) which is more frequently present at stage III and IV and are poorly responsive to standard treatment [79]. Despite the recent advancement in the understanding of endometrial cancer biology and the introduction of novel treatment strategies, such as immunotherapy for microsatellite instable and a combination of immunotherapy and antiangiogenic agents for microsatellite stable tumors, the prognosis of patients with advanced or recurrent endometrial cancer remains poor [80–82]. Thus, the identification of new treatment options is paramount to improving patients’ outcomes.

In endometrial cancer, contrary to what is described in ovarian cancer, the field of ADCs is still in an early phase of development. However, therapeutic targets of potential interest have been identified and preliminary results are available (Table 3). Furthermore, different trials are ongoing to further explore the safety and efficacy of ADCs in this malignancy (Table 4).

Table 3. Main clinical trials of ADCs in endometrial and cervical cancer

| Target | ADC | Trial | Phase | Setting | Treatment | Primary endpoint | Results |
|--------|-----|-------|-------|---------|-----------|-----------------|--------|
| HER2   | T-DM1 | NCT02675829 [83] | II | HER2 pos tumors including endometrial cancer | T-DM1 | ORR | ORR: 22% |
|        |      | NCT02465060 [84] | II | HER2 pos including endometrial and ovarian cancer | T-DM1 | ORR | ORR: 9% |
| FRα    | Mirvetuximab soravtansine | NCT01609566 [60] | I | FRα pos tumors including metastatic endometrial cancer | Mirvetuximab soravtansine | MTD/RP2D | ORR: 0% |
| Trop2  | Sacituzumab govitcan (IMMU-132-01 (NCT01631552) [85] | I/II | Advanced epithelial cancer including endometrial, cervical and ovarian cancer | Sacituzumab govitcan | Safety (phase I) | ORR (phase II): 22.2% |
Table 3. Main clinical trials of ADCs in endometrial and cervical cancer (continued)

| Target | ADC | Trial | Phase | Setting | Treatment | Primary endpoint | Results |
|--------|-----|-------|-------|---------|-----------|-----------------|---------|
| TF     | Tisotumab vedotin | InnovaTV 204 (NCT03438986) | II | Previously treated recurrent or metastatic cervical cancer | Tisotumab vedotin | ORR | ORR: 24% |
|        |      | InnovaTV 205 (NCT03786081) | I/II | Recurrent or metastatic cervical cancer, first line | Tisotumab vedotin + carboplatin | DLT (phase I) | ORR (phase II) | ORR: 55% |
|        |      |                    |      | Recurrent or metastatic cervical cancer, second or third line | Tisotumab vedotin + pembrolizumab | DLT (phase I) | ORR (phase II) | ORR: 38% |

Table 4. Main ongoing clinical trials of ADCs in endometrial and cervical cancer

| Target | ADC | Trial | Phase | Setting | Treatment | Primary endpoint |
|--------|-----|-------|-------|---------|-----------|------------------|
| HER2   | Trastuzumab duocarmazine (SYD985) | NCT04205630 | II | HER2 pos metastatic endometrial cancer | Trastuzumab duocarmazine | ORR |
|        | T-DXd | NCT04482309 | II | HER2 pos tumors including ovarian, endometrial, and cervical cancer | T-DXd | ORR |
| FRα    | Mirvetuximab soravtansine | NCT03832361 | II | FRα pos persistent or recurrent endometrial cancer | Mirvetuximab soravtansine | ORR |
|        |      | NCT03835819 | II | FRα pos advanced or recurrent serous endometrial cancer | Mirvetuximab soravtansine + pembrolizumab | ORR/PFS |
| Trop2  | Sacituzumab govitecan | NCT04251416 | II | Trop2 pos persistent or recurrent endometrial cancer | Sacituzumab govitecan | ORR |
| TF     | Tisotumab vedotin | InnovaTV 301 (NCT04697628) | III | Previously treated recurrent or metastatic cervical cancer | Tisotumab vedotin vs. chemotherapy | OS |

Anti-epidermal growth factor receptor-2: T-DM1, trastuzumab duocarmazine, and T-DXd

HER2 is overexpressed in up to 35% of cases of endometrial cancer, particularly in the more aggressive histological subtypes, such as serous and carcinosarcoma [88]. This has supported the investigation of HER2 targeting agents in these aggressive gynecologic malignancies.

A phase II randomized study of trastuzumab in combination with platinum-based chemotherapy has been conducted in patients with HER2/neu overexpressing uterine serous carcinoma. The combination of trastuzumab with carboplatin-paclitaxel showed an improvement in PFS when used in first or subsequent lines of treatment (12.6 months versus 8 months, HR = 0.44 in the overall study population) [89].

Beyond trastuzumab, several preclinical studies evaluated the efficacy of the ADC T-DM1 in HER2-amplified ovarian and uterine carcinosarcomas, both on cell lines and xenografts, showing a greater antitumor efficacy compared to single-agent trastuzumab [90, 91] and to the combination of trastuzumab and pertuzumab [92].

Two small clinical trials have evaluated the efficacy of T-DM1 in patients with different types of HER2 amplified malignancies [83, 84]. A basket trial enrolled 58 patients with HER2 amplified advanced solid tumors (lung, endometrial, salivary gland, biliary tract, ovarian, bladder, colorectal, and other cancers) and were treated with T-DM1 3.6 mg/kg i.v. once every three weeks. The ORR was 26% (14/53), 22% (4/18), and 17% (1/6) in the overall population, endometrial and ovarian cancer, respectively [83]. Another study enrolled 38 patients with HER2 amplified tumors other than breast and gastric/gastroesophageal junction adenocarcinomas, to receive T-DM1. Fourteen patients were enrolled, including serous EOC, mixed serous and endometrioid endometrial adenocarcinoma, serous endometrial adenocarcinoma, carcinosarcoma, and mucinous adenocarcinoma of the cervix [84]. Eight out of ten patients with endometrial or ovarian cancer achieved an SD and in the overall study population, the median DoR was 4.6 months [84].
Another ADC targeting HER2, trastuzumab duocarmazine (SYD985), has been investigated in endometrial cancer [93]. Trastuzumab duocarmazine is an ADC composed of trastuzumab linked to the toxic payload duocarmycin via a cleavable linker. The linker cleavage by tumor proteases and the release of the membrane-permeable active toxin causes cell killing not only of the HER2 positive cells but also of the neighboring non-antigen-expressing tumor cells through the “bystander killing effect” [93]. This mechanism of action differs from T-DM1, in which the antibody-drug link is not cleavable and as a consequence, the “bystander killing effect” is less relevant. In vitro and in vivo studies demonstrated the higher antitumor potency of trastuzumab duocarmazine, both in carcinosarcoma and EOC cell lines and xenografts [94]. This compound is currently being evaluated as a single agent in phase II clinical trial in patients with HER2-positive endometrial cancer progressing after first-line platinum-based chemotherapy (NCT04205630).

T-DXd is another anti-HER2 ADC conjugated to a potent topoisomerase 1 inhibitor, that has shown significant and durable efficacy in patients with HER2 positive breast [8, 95] and gastric cancer [96] and has the potential to also improve the outcome of patients with other HER2 positive solid tumors. Different trials are ongoing to confirm its activity even in gynecological malignancies (NCT04482309).

**Anti-folate receptor α: mirvetuximab soravtansine**

The FRα has been identified as a potential therapeutic target also in endometrial cancer [97]. The overexpression of FRα has been associated with worse outcomes and co-occurs with other poor prognostic factors including advanced stage, non-endometrioid histology, and high grade.

A phase I dose-escalation study of mirvetuximab soravtansine in patients with solid tumors not selected for FRα expression, enrolled a total of 44 subjects including 11 with serous or endometrioid endometrial cancer [60]. The primary objectives of the study were to determine the MTD (not reached) and the RP2D, which was established at 6.0 mg/kg once every three weeks. Two patients with endometrial cancer achieved a clinical benefit: SD lasting more than 4 weeks in one patient and a CA125 response in the other [60]. These data encouraged the development of an ongoing phase II study evaluating the activity and safety profile of mirvetuximab soravtansine in patients with persistent or recurrent endometrial cancer overexpressing FRα (NCT03832361). Eligible tumor histology includes serous, G2–G3 endometroid endometrial carcinoma or carcinosarcoma with high grade serous or G2–G3 endometrioid components.

**Anti-human trophoblast cell-surface marker: sacituzumab govitecan**

Sacituzumab govitecan is a humanized anti-Trop2 antibody, conjugated to the active metabolite of irinotecan (SN-38) via a cleavable linker. Following the positive results achieved in breast and bladder [9, 98] cancers, this agent is now under investigation in other solid tumors, including serous and endometrioid endometrial cancer.

The cellular target of this drug is the Trop2, a transmembrane glycoprotein originally identified in human placental tissue and subsequently found to be highly expressed in various type of epithelial tumors. Preclinical studies have shown that Trop2 promotes cell proliferation, inhibits apoptosis, accelerates cell cycle progression and favors tissue invasion and metastasis [99]. Tissue overexpression of Trop2 is also an independent marker of poor prognosis in several neoplasms, including endometrial cancer [100, 101]. The low Trop2 expression in healthy tissues makes it a suitable target for the development of ADCs. SN-38 molecules are bound to the antibody by a cleavable linker with a high DAR (8:1) without a negative effect on pharmacokinetics [72]. The cleavable linker ensures that the cytotoxic molecule is also effective on the neighboring Trop2 negative cells through the “bystander effect”. This mechanism is of particular relevance in tumors with heterogeneous surface expression of Trop2, as it has been observed in endometrial cancer [102]. Preclinical studies demonstrated the in vitro and in vivo efficacy of sacituzumab govitecan in Trop2 positive endometrioid carcinoma cell lines and xenografts [100, 103].

In the phase I/II basket trial of single-agent sacituzumab govitecan in patients with epithelial cancer (NCT01631552), 18 women with advanced/recurrent endometrial carcinoma were included (histology unspecified) and determination of Trop2 expression was not required [85]. The most common treatment-related AEs were nausea (62.6%), diarrhea (56.2%), fatigue (48.3%), alopecia (40.4%), and
neutropenia (57.8%), consistently with the toxicity profile of the irinotecan-derived payload. Clinical activity was seen across tumors subtypes. In the endometrial cohort, the ORR was 22%, mPFS was 3.2 months [confidence interval (CI): 1.9–9.4], and median OS 11.9 months [85].

A phase II study of single-agent sacituzumab govitecan in patients with persistent or recurrent endometrial cancer, who have failed at least a prior platinum-based chemotherapy or refractory to platinum-based chemotherapy, is ongoing (NCT04251416). In this trial, elevated Trop2 expression (at least 2+) is required for patients’ selection.

**ADCs in cervical cancer**

Despite the ongoing progress made with the human papillomavirus (HPV) vaccination, cervical cancer remains the fourth most frequent and fatal cancer among women [104]. The current standard of care in relapsed or metastatic disease is the combination of paclitaxel, platinum, and bevacizumab, following the results of a clinical trial showing a survival benefit with the addition of bevacizumab to chemotherapy in this setting [105]. The therapeutic landscape for this disease is rapidly evolving with the incorporation of immune checkpoint inhibitors. The KEYNOTE-826 trial showed a PFS and OS benefit for patients treated in first line with the anti-programmed death 1 (PD-1) pembrolizumab in addition to platinum and paclitaxel +/- bevacizumab, regardless of programmed death-ligand 1 (PD-L1) expression [106]. When progressing after first-line, there is no effective standard of care treatment in cervical cancer and the available therapeutic options have shown little benefit with low survival rates and ORR (15% pemetrexed [107], 14% vinorelbine [108], 5% gemcitabine [109], 11% bevacizumab [110], 14% pembrolizumab [111]). A phase III trial investigating the anti-PD-1 agent cemiplimab versus single-agent chemotherapy of physician’s choice, resulted in an improvement in median OS (12 months versus 8.5 months, HR 0.69) and ORR (16.4 versus 6.3%) and similar mPFS (2.8 months versus 2.9 months) [112].

Thus, the use of drugs with alternative targets and different mechanisms of action is an important clinical need in patients with relapsed or metastatic cervical cancer after failure of first-line standard treatment.

Two main cellular antigens have been identified as possible targets for ADCs in cervical cancer.

The TF is a transmembrane protein involved in the extrinsic pathway of the coagulation cascade, but also in angiogenesis, cell adhesion, mobility, and cell survival [113]. It is highly prevalent in many solid tumors, including cervical and uterine cancer, and it is not expressed in endometrial or normal cervical tissue, representing an ideal therapeutic target.

Another promising therapeutic target, already described in endometrial cancer, is the Trop2, whose expression has been also evaluated in cervical neoplasms [114].

**Anti-tissue factor: tisotumab vedotin**

Tisotumab vedotin is an ADC consisting of a fully human monoclonal antibody conjugated to the microtubule inhibitor MMAE through a cleavable linker. Tisotumab vedotin releases MMAE into TF-expressing cells causing direct cytotoxicity and a “bystander killing effect” in neighboring cells that do not express TF or express it heterogeneously.

In the multicentre, single-arm, phase II innova204/GOG-3023/ENGOT-cx6 trial [86], 102 patients with squamous cell, adenocarcinoma, or adenosquamous cervical cancer previously treated with platinum-based chemotherapy and no more than two prior lines of therapy were enrolled. Patients received tisotumab vedotin at 2 mg/kg, up to a maximum of 200 mg, intravenously every 3 weeks until disease progression or unacceptable toxicity. The ORR was 24% (95% CI: 16–33), with 7 patients (7%) achieving a CR and 17 (17%) a PR. The median DoR, PFS, and OS were 8.3 (95% CI: 4.2–not reached), 4.2 (95% CI: 3.0–4.4), and 12.1 months (95% CI: 9.6–13.9), respectively [86]. Given the population of pre-treated patients for whom no standard of care is available, these results warrant further investigation. Main AEs were nausea (27%), conjunctivitis (26%), fatigue (26%), and dry eyes (23%). G3 toxicities were neutropenia (3%), fatigue (2%), ulcerative keratitis (2%), and peripheral neuropathy (2%). Interestingly, bleeding-related AEs occurred in 39% of patients, most of them G1 (34%) and the more frequent was epistaxis [86]. No significant changes in
prothrombin time, international normalized ratio, or activated partial thromboplastin time were observed. The occurrence of this AE is more likely due to the elevated TF expression in the nasal epithelium [115] and not to a treatment-induced coagulopathy. No association between TF membrane expression levels and efficacy was demonstrated. However, most of the analyzed archival tumor samples showed a TF membrane expression > 1% with variable levels [86]. Thus, TF expression may contribute to the drug response, although additional mechanisms of action such as the bystander killing effect and immunogenic effects are involved. A phase III trial of tisotumab vedotin is ongoing to confirm its activity as a single agent compared to physician's choice chemotherapy (NCT04697628).

The ENGOT-Cx8/GOG-3024/innovaTV 205 trials are investigating the efficacy of tisotumab vedotin in combination with carboplatin in first-line treatment of patients with recurrent/metastatic cervical cancer or in combination with pembrolizumab in the second or third line of treatment [87]. In the first-line setting, the combination of tisotumab vedotin and carboplatin resulted in an ORR of 55% and a mPFS of 9.5 months (4.0–not reached). In the second or third line, the combination of tisotumab vedotin and pembrolizumab showed an ORR of 38% and a mPFS of 5.6 months (2.7–13.7) [87]. These preliminary results support the continued investigation of tisotumab vedotin for the treatment of cervical cancer.

Anti-human trophoblast cell-surface marker: sacituzumab govitecan

Trop2 is highly expressed in cervical cancer tissue (88.7%), and its overexpression correlates with International Federation of Gynecology and Obstetrics (FIGO) stage, histological grade, lymphatic metastasis, depth of interstitial invasion, and high expression of Ki-67 [99]. As a consequence, patients with positive Trop2 expression had poorer OS and PFS [99].

In a preclinical study, the anti-Trop2 ADC sacituzumab govitecan was investigated on Trop2 positive cervical cancer cell lines and in xenograft models [116]. In this study, moderate to strong diffuse staining was seen in 95% of squamous cell carcinomas and in 81% of adenocarcinoma/adenosquamous subtypes. As previously described in endometrial cancers, Trop2 positive cell lines were highly sensitive to sacituzumab govitecan both in vitro and in vivo [116].

In the phase I/II basket trial of sacituzumab govitecan in patients with epithelial cancer only one patient with cervical cancer was included (efficacy data not shown) [72].

Main phase II and phase III studies of ADCs in relapsed or metastatic cervical cancer are summarized in (Tables 3 and 4).

**Mechanism of resistance to ADCs**

As already described for many anticancer agents, innate or acquired resistance remains a major obstacle for the successful implementation of a treatment. Since ADCs are structurally complex molecules and their mechanism of action consists of several sequential steps, drug resistance might occur at different levels, as summarized below [117]. It is important to recognize that the main knowledge on the resistance to ADCs is available from the experience with sacituzumab govitecan [118] and T-DM1 [118–120], given the longer clinical experience with these drugs in breast cancer.

- **Drug delivery:** A pharmacokinetic mechanism explaining possible resistance to ADCs is the premature release of the payload from the antibody before it reaches the target cell. This event not only decreases the antitumor efficacy but also increases off-target systemic toxicity [117].

- **Antibody-antigen binding:** ADCs are highly dependent on the presence of a cellular antigen to exert their target effect. A first obstacle to the efficacy of an ADC may be the downregulation of the expression of target antigen on the cell surface and this might occur after chronic exposure to the drug [119].

- **Drug catabolism:** At the intracellular level, reduced lysosomal proteolytic activity can decrease the payload cleavage from the linker leading to a reduced cytotoxic effect [120].

- **Mutation in the payload target:** At the cellular level, possible mutations in genes encoding tubulin composition may also represent another mechanism of resistance to ADCs whose payload targets the mitotic spindle [121].
- Increased cellular drug clearance: Many payloads are substrates of the cellular efflux pumps [multidrug resistance protein 1 (MDR1) and multidrug resistance related protein 1 (MRP1)]. An increased expression of these transporters could reduce the intracellular concentration of cytotoxic molecules to ineffective levels [122].

- Tumor cells heterogeneity: Neoplasms with heterogeneous surface antigen expression might be unresponsive to ADCs that lack a "bystander killing effect".

- Development of antidrug antibodies (ADA): ADA can develop against the different components of an ADCs (monoclonal antibody, cytotoxic payload, and linker). Their impact on ADCs safety and onset of resistance is under investigation [123, 124].

Different strategies are under investigation to overcome such mechanisms of resistance to improve ADCs efficacy [125]. A possible strategy to circumvent the drug clearance is to incorporate in the ADC a cytotoxic payload that is a poor efflux substrate. The payload of the ADC T-DXd, a topoisomerase I inhibitor deruxtecan (Dxd), is a poor substrate of the ATP-binding cassette (ABC) transporter that on contrary is involved in the resistance to T-DM1, due to the high affinity of DM1 to the efflux transporter. Thus, T-DXd has been shown to be active in overcoming the resistance to T-DM1 [126].

The heterogeneous expression of the surface antigen might limit the ADCs efficacy, particularly in the low antigen-expressing cells. To overcome this limitation, an increase in the bystander effect is foreseen and this might be obtained by incorporating cytotoxic payloads whose charge allows an easy cell membrane crossing to reach the neighboring cells [65].

Another possibility to avoid or to overcome ADC resistance is the use of combination therapies and trials are ongoing investigating ADCs in association with chemotherapy or targeted agents. Another interesting and promising approach is the combination of ADC with immunotherapy [127].

Conclusions

Despite the latest advancements and the introduction of targeted therapies, the prognosis of women with advanced/recurrent gynecological malignancies remains poor and new treatment options are urgently needed. Chemotherapy is usually effective in the first-line setting, but primary or acquired resistance inevitably occurs and subsequent treatment options are limited. The identification of novel agents with different mechanisms of action than standard cytotoxic chemotherapy is paramount to overcome drug resistance and to obtain disease control in subsequent lines of therapy. Furthermore, the use of chemotherapy is often limited by its toxicity profile, particularly hematological and neurological.

The development of ADCs offers the opportunity to selectively tackle the cancer cells expressing a particular target taking the advantage of the specificity of a monoclonal antibody to deliver potent cytotoxic agents. Despite the promise of reducing the toxicity through targeted delivery of the chemotherapy compound, different ADCs have shown significant off-target toxicities, due to the premature payload release into the circulation, the well-described 'bystander effect' and as a consequence of the expression of the target also in non-cancer cells. Since their first introduction, different generations of ADCs have been developed to improve their therapeutic index.

Different ADCs have been investigated for the treatment of women with gynecological malignancies and data from clinical trials, as presented in this review, are encouraging and support the continuous investigation of this innovative therapeutic strategy.

Among the drugs listed, mirvetuximab sorvatsine is the only one with available data from a phase III trial. In the FORWARD I study, the preliminary benefit observed in ORR, did not translate into a statistically significant prolongation of PFS [47]. Thus, it is necessary to wait for the results of other ongoing trials to define if this agent might represent a treatment opportunity particularly for patients with EOC and high FRα expression as a single agent or in combination.

The phase II, non-randomized study, innova204/GOG-3023/ENGOT-cx6 trial, showed both a PFS and OS benefit in patients with relapsed or metastatic cervical cancer treated with tisotumab vedotin [86]. Following
the results of this trial, the FDA recently granted accelerated approval of tisotumab vedotin, for adult patients with recurrent or metastatic cervical cancer with disease progression during or after chemotherapy. Moreover, patients with non-squamous histology (adenocarcinoma or adenosquamous carcinomas), usually characterized by poor prognosis, were also included in this trial and responses were similar to those observed in the whole study population [86]. Considering the limited efficacy of the available therapies in recurrent/metastatic disease and the poor prognosis of patients with cervical cancer progressing after first-line treatment, the approval of tisotumab vedotin could be practice-changing in the treatment landscape of this disease, regardless of TF expression, histology, or prior treatment. Results from the ongoing phase III trial (NCT04697628) comparing tisotumab vedotin versus physician choice chemotherapy are awaited to confirm this preliminary data.

Preliminary signs of activity of ADCs have been seen also in endometrial cancer, particularly in the more aggressive histological subtypes. Despite the available multimodal treatment strategy incorporating surgery, radiotherapy, and chemotherapy, OS for patients with serous endometrial cancer varies between 18–27% [88]. Thus, the preclinical activity of sacituzumab govitecan and T-DM1 in this tumor type represents an important step forward [85, 89].

Finally, an increasing number of studies assessing the combination of ADCs and chemotherapy or other targeted agents including immunotherapy are ongoing.

Although there is still a lack of high-level evidence, this class of drugs has expanded the therapeutic possibilities in gynecological oncology with the final aim of improving patients’ outcomes and quality of life. Further research is still needed to define the best treatment regimen, predictive biomarkers and to understand the mechanisms of resistance. Particularly, a better definition of biomarkers with a strong predictive value is paramount for the clinical development of ADCs and their incorporation as a selection criterion in clinical trials is necessary to correctly exploit their efficacy, as clearly observed with mirvetuximab soravtansine in ovarian cancer. Moreover, incorporation of translational research particularly in early phase clinical trials is warranted to understand the mechanisms of primary or acquired resistance and improve the subsequent development of these agents for the treatment of gynecological malignancies, taking also advantage of the knowledge already established in other tumor types.

**Abbreviations**

ADCs: antibody-drug conjugates  
AEs: adverse events  
CI: confidence interval  
DAR: drug-to-antibody ratio  
DM4: ravtansine  
DoR: duration of response  
EOC: epithelial ovarian cancer  
FDA: Food and Drug Administration  
FRα: folate receptor alfa  
G: grade  
HER2: human epidermal growth factor 2  
IgG: immunoglobulin G  
MMAE: monomethyl auristatine E  
mPFS: median progression-free survival  
MTD: maximum tolerated dose  
MUC16: mucine 16  
OS: overall survival
PFS: progression-free survival
PRs: partial responses
SD: stable disease
T-DM1: trastuzumab emtansine
T-DXd: trastuzumab deruxtecan
TF: tissue factor
Trop2: human trophoblast cell-surface marker 2

**Declarations**

**Author contributions**
MN and IC contributed to the conception and design of the manuscript. MN and IC wrote the first draft of the manuscript. MN, MDG, CS, and IC contributed to literature analysis. All authors contributed to manuscript revision, read and approved the submitted version.

**Conflicts of interest**
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**References**
1. Khongorzul P, Ling CJ, Khan FU, Ihsan AU, Zhang J. Antibody-drug conjugates: a comprehensive review. Mol Cancer Res. 2020;18:3–19.
2. Strebhardt K, Ullrich A. Paul Ehrlich’s magic bullet concept: 100 years of progress. Nat Rev Cancer. 2008;8:473–80.
3. Masters JC, Nickens DJ, Xuan D, Shazer RL, Amantea M. Clinical toxicity of antibody drug conjugates: a meta-analysis of payloads. Invest New Drugs. 2018;36:121–35.
4. Sievers EL, Larson RA, Stadtmauer EA, Estey E, Löwenberg B, Dombret H, et al.; Mylotarg Study Group. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. J Clin Oncol. 2001;19:3244–54.
5. Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010;363:1812–21.

6. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al.; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783–91.

7. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al.; KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380:617–28.

8. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al.; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382:610–21.

9. Bardia A, Mayer IA, Vahted LT, Tolane SM, Isakoff SJ, Diamond JR, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. N Engl J Med. 2019;380:741–51.

10. Powles T, Rosenberg JE, Sonpavde GP, Lorio Y, Durán I, Lee J, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med. 2021;384:1125–35.

11. Carter PJ, Lazar GA. Next generation antibody drugs: pursuit of the 'high-hanging fruit'. Nat Rev Drug Discov. 2018;17:197–223.

12. Vankemmelbeke M, Durrant L. Third-generation antibody drug conjugates for cancer therapy—a balancing act. Ther Deliv. 2016;7:141–4.

13. Ritchie M, Tchistiakova L, Scott N. Implications of receptor-mediated endocytosis and intracellular trafficking dynamics in the development of antibody drug conjugates. Mabs. 2013;5:13–21.

14. Krop IE, LoRusso P, Miller KD, Modi S, Yardley D, Rodriguez G, et al. A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. J Clin Oncol. 2012;30:3234–41.

15. Moore KN, Martin LP, O'Malley DM, Matulonis UA, Konner JA, Perez RP, et al. Safety and activity of mirvetuximab soravatansine (IMGN853), a folate receptor alpha-targeting antibody-drug conjugate, in platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a phase I expansion study. J Clin Oncol. 2017;35:1112–8.

16. Modi S, Park H, Murthy RK, Iwata H, Tamura K, Tsurutani J, et al. Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low-expressing advanced breast cancer: results from a phase Ib study. J Clin Oncol. 2020;38:1887–96.

17. Anderl J, Faulstich H, Hechler T, Kulke M. Antibody-drug conjugate payloads. Methods Mol Biol. 2013;1045:51–70.

18. Akaiwa M, Dugal-Tessier J, Mendelsohn BA. Antibody-drug conjugate payloads; study of auristatin derivatives. Chem Pharm Bull (Tokyo). 2020;68:201–11.

19. Remillard S, Rebhun LI, Howie GA, Kupchan SM. Antimitotic activity of the potent tumor inhibitor maytansine. Science. 1975;189:1002–5.

20. Burton JK, Bottino D, Secomb TW. A systems pharmacology model for drug delivery to solid tumors by antibody-drug conjugates: implications for bystander effects. AAPS J. 2019;22:12.

21. Hamblett KJ, Senter PD, Chace DF, Sun MMC, Lenox J, Cerveny CG, et al. Effects of drug loading on the antitumor activity of a monoclonal antibody drug conjugate. Clin Cancer Res. 2004;10:7063–70.

22. Sun X, Ponte JF, Yoder NC, Laleau R, Coccia J, Lanieri L, et al. Effects of drug-antibody ratio on pharmacokinetics, biodistribution, efficacy, and tolerability of antibody-maytansinoid conjugates. Bioconjug Chem. 2017;28:1371–81.

23. Lyon RP, Bovee TD, Doronina SO, Burke PJ, Hunter JH, Neff-LaFord HD, et al. Reducing hydrophobicity of homogeneous antibody-drug conjugates improves pharmacokinetics and therapeutic index. Nat Biotechnol. 2015;33:733–5.
24. Donaghy H. Effects of antibody, drug and linker on the preclinical and clinical toxicities of antibody-drug conjugates. MAbs. 2016;8:659–71.

25. Birrer MJ, Moore KN, Betella I, Bates RC. Antibody-drug conjugate-based therapeutics: state of the science. J Natl Cancer Inst. 2019;111:538–49.

26. Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody-drug conjugates for cancer therapy. Nat Rev Clin Oncol. 2021;18:327–44.

27. Junttila TT, Li G, Parsons K, Phillips GL, Sliwkowski MX. Trastuzumab-DX1 (T-DX1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer. Breast Cancer Res Treat. 2011;128:347–56.

28. Ogitani Y, Aida T, Hagihara K, Yamaguchi J, Ishii C, Harada N, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DX1. Clin Cancer Res. 2016;22:5097–108.

29. Ofllazoglu E, Stone JJ, Gordon KA, Grewal IS, van Rooijen N, Law CL, et al. Macrophages contribute to the antitumor activity of the anti-CD30 antibody SGN-30. Blood. 2007;110:4370–2.

30. Zuckier LS, Berkowitz EZ, Sattenberg RJ, Zhao QH, Deng HF, Scharff MD. Influence of affinity and antigen density on antibody localization in a modifiable tumor targeting model. Cancer Res. 2000;60:7008–13.

31. Peters C, Brown S. Antibody-drug conjugates as novel anti-cancer chemotherapeutics. Biosci Rep. 2015;35:e00225.

32. Li F, Emmerton KK, Jonas M, Zhang X, Miyamoto JB, Setter JR, et al. Intracellular released payload influences potency and bystander-killing effects of antibody-drug conjugates in preclinical models. Cancer Res. 2016;76:2710–9.

33. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al.; ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365:2484–96.

34. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al.; PAOLA-1 Investigators. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381:2416–28.

35. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379:2495–505.

36. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al.; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381:2391–402.

37. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol. 2014;32:1302–8.

38. Poveda AM, Selle F, Hilpert F, Reuss A, Savarese A, Vergote I, et al. Bevacizumab combined with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan in platinum-resistant recurrent ovarian cancer: analysis by chemotherapy cohort of the randomized phase III AURELIA trial. J Clin Oncol. 2015;33:3836–8.

39. Birrer MJ, Betella I, Martin LP, Moore KN. Is targeting the folate receptor in ovarian cancer coming of age? Oncologist. 2019;24:425–9.

40. Hilliard TS. The impact of mesothelin in the ovarian cancer tumor microenvironment. Cancers (Basel). 2018;10:2777.

41. Toffoli G, Cernigoi C, Russo A, Gallo A, Bagnoli M, Boiocchi M. Overexpression of folate binding protein in ovarian cancers. Int J Cancer. 1997;74:193–8.

42. Boogerd LSF, Hoogstins CES, Gaarenstroom KN, de Kroon CD, Beltman JJ, Bosse T, et al. Folate receptor-α targeted near-infrared fluorescence imaging in high-risk endometrial cancer patients: a tissue microarray and clinical feasibility study. Oncotarget. 2017;9:791–801.
43. Crider KS, Yang TP, Berry RJ, Bailey LB. Folate and DNA methylation: a review of molecular mechanisms and the evidence for folate's role. Adv Nutr. 2012;3:21–38.

44. Chen YL, Chang MC, Huang CY, Chiang YC, Lin HW, Chen CA, et al. Serous ovarian carcinoma patients with high alpha-folate receptor had reducing survival and cytotoxic chemo-response. Mol Oncol. 2012;6:360–9.

45. Hassan R, Ho M. Mesothelin targeted cancer immunotherapy. Eur J Cancer. 2008;44:46–53.

46. Hanaoka T, Hasegawa K, Kato T, Sato S, Kurosaki A, Miyara A, et al. Correlation between tumor mesothelin expression and serum mesothelin in patients with epithelial ovarian carcinoma: a potential noninvasive biomarker for mesothelin-targeted therapy. Mol Diagn Ther. 2017;21:187–98.

47. Moore KN, Oza AM, Colombo N, Oskin A, Scambia G, Lorusso D, 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;32:757–65.

48. Moore KN, O'Malley DM, Vergote I, Martin LP, Gonzalez-Martín A, Malek K, et al. Safety and activity findings from a phase 1b escalation study of mirvetuximab soravtansine, a folate receptor alpha (FRα)—targeting antibody-drug conjugate (ADC), in combination with carboplatin in patients with platinum-sensitive ovarian cancer. Gynecol Oncol. 2018;151:46–52.

49. O'Malley D, Richardson D, Vergote IB, Gilbert L, Martin LP, Mantia-Smaldone GM, et al. 1028P-Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with carboplatin and bevacizumab: initial results from a phase 1b study in patients (pts) with ovarian cancer. Ann Oncol. 2019;30:v419–20.

50. O'Malley DM, Matulonis UA, Birrer MJ, Castro CM, Gilbert L, Vergote I, et al. Phase Ib study 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. 2020;157:379–85.

51. O'Malley DM, Oza AM, Matulonis UA, Mantia-Smaldone G, Lim PC, Castro CM, et al. Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-agnostic ovarian cancer: final analysis. J Clin Oncol. 2021;39:5504.

52. Shimizu T, Fujiwara Y, Yonemori K, Koyama T, Sato J, Tamura K, et al. First-in-human phase 1 study of MORAb-202, an antibody-drug conjugate comprising farletuzumab linked to eribulin mesylate, in patients with folate receptor-α-positive advanced solid tumors. Clin Cancer Res. 2021;27:3905–15.

53. Hassan R, Blumenschein GR Jr, Moore KN, Santin AD, Kindler HL, Nemunaitis JJ, et al. First-in-human, multicenter, phase I dose-escalation and expansion study of anti-mesothelin antibody-drug conjugate anetumab ravtansine in advanced or metastatic solid tumors. J Clin Oncol. 2020;38:1824–35.

54. Weekes CD, Lamberts LE, Borad MJ, Voortman J, McWilliams RR, Diamond JR, et al. A phase I study of DMOT4039A, an antibody-drug conjugate targeting mesothelin (MSLN), in patients (pts) with unresectable pancreatic (PC) or platinum-resistant ovarian cancer (OC). J Clin Oncol. 2014;32:2529.

55. Rottey S, Clarke J, Aung K, Machiels JP, Markman B, Heinhuisk KM, et al. Phase I/IIa trial of BMS-986148, an anti-mesothelin antibody-drug conjugate, alone or in combination with nivolumab in patients with advanced solid tumors. Clin Cancer Res. 2022;28:95–105.

56. de Bono JS, Concinn N, Hong DS, Thistlethwaite FC, Machiels JP, Arkenau HT, et al. Tisotumab vedotin in patients with advanced or metastatic solid tumours (InnovaTV 201): a first-in-human, multicentre, phase 1–2 trial. Lancet Oncol. 2019;20:383–93.

57. Liu J, Burris H, Wang JS, Barroilhet L, Gutierrez M, Wang Y, et al. An open-label phase I dose-escalation study of the safety and pharmacokinetics of DMUC4064A in patients with platinum-resistant ovarian cancer. Gynecol Oncol. 2021;163:473–80.
58. Gerber DE, Infante JR, Gordon MS, Goldberg SB, Martin M, Felipe E, et al. Phase Ia study of anti-NaPi2b antibody-drug conjugate lifastuzumab vedotin DNIB0600A in patients with non-small cell lung cancer and platinum-resistant ovarian cancer. Clin Cancer Res. 2020;26:364–72.

59. Banerjee S, Oza AM, Birrer MJ, Hamilton EP, Hasan J, Leary A, et al. Anti-NaPi2b antibody-drug conjugate lifastuzumab vedotin (DNIB0600A) compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer in a randomized, open-label, phase II study. Ann Oncol. 2018;29:917–23.

60. Moore KN, Borghaei H, O’Malley DM, Jeong W, Seward SM, Bauer TM, et al. Phase 1 dose-escalation study of mirvetuximab soravtansine (IMGN853), a folate receptor α-targeting antibody-drug conjugate, in patients with solid tumors. Cancer. 2017;123:3080–7.

61. Martin LP, Konner JA, Moore KN, Seward SM, Matulonis UA, Perez RP, et al. Characterization of folate receptor alpha (FRα) expression in archival tumor and biopsy samples from relapsed epithelial ovarian cancer patients: a phase I expansion study of the FRα-targeting antibody-drug conjugate mirvetuximab soravtansine. Gynecol Oncol. 2017;147:402–7.

62. Eaton JS, Miller PE, Mannis MJ, Murphy CJ. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. J Ocul Pharmacol Ther. 2015;31:589–604.

63. O’Malley DM, Richardson DL, Vergote IB, Gilbert L, Castro C, Provencher D, et al. 833P-Mirvetuximab soravtansine (MIRV), a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with carboplatin (CARBO) and bevacizumab (BEV): final results from a study in patients (pts) with recurrent platinum sensitive ovarian cancer. Ann Oncol. 2020;31:S551–89.

64. Uyar D, Schilder RJ, Naumann RW, Braiteh FS, Hamilton E, Diab S, et al. Antitumor activity of STRO-002, a novel anti-folate receptor-α (FolRα) antibody drug conjugate (ADC), in patient-derived xenograft (PDX) models and preliminary phase I dose escalation safety outcomes in patients with ovarian carcinoma. Poster presented during the AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Conference; 2019 Oct 26–30; Hynes Convention Center Boston, MA.

65. Golfier S, Kopitz C, Kahnert A, Heisler I, Schatz CA, Stelte-Ludwig B, et al. Anetumab ravtansine: a novel mesothelin-targeting antibody-drug conjugate cures tumors with heterogeneous target expression favored by bystander effect. Mol Cancer Ther. 2014;13:1537–48.

66. Bulat I, Moore KN, Haceatreen A, Chung JW, Rajagopalan P, Xia C, et al. Phase Ib study of anti-mesothelin antibody drug conjugate anetumab ravtansine in combination with pegylated liposomal doxorubicin in platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. J Clin Oncol. 2018;36:5571.

67. Liu JF, Moore KN, Birrer MJ, Berlin S, Matulonis UA, Infante JR, et al. Phase I study of safety and pharmacokinetics of the anti-MUC16 antibody-drug conjugate DMUC5754A in patients with platinum-resistant ovarian cancer or unresectable pancreatic cancer. Ann Oncol. 2016;27:2124–30.

68. Moore K, Hamilton EP, Burris HA, Barroilhet LM, Gutierrez M, Wang JS, et al. Abstract CT036: targeting MUC16 with the THIOMAB™-drug conjugate DMUC4064A in patients with platinum-resistant ovarian cancer: a phase I expansion study. Cancer Res. 2018;78:CT036.

69. Burris HA, Gordon MS, Gerber DE, Spigel DR, Mendelson DS, Schiller JH, et al. A phase I study of DNIB0600A, an antibody-drug conjugate (ADC) targeting NaPi2b, in patients (pts) with non-small cell lung cancer (NSCLC) or platinum-resistant ovarian cancer (OC). J Clin Oncol. 2014;32:2504.

70. Moore KN, Birrer MJ, Marsters J, Wang Y, Choi Y, Royer-Joo S, et al. Phase 1b study of anti-NaPi2b antibody-drug conjugate lifastuzumab vedotin (DNIB0600A) in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2020;158:631–9.

71. Tolcher AW, Ulahannan SV, Papadopoulos KP, Edenfield WJ, Matulonis UA, Burns TF, et al. Phase 1 dose escalation study of XMT-1536, a novel NaPi2b-targeting antibody-drug conjugate (ADC), in patients (pts) with solid tumors likely to express NaPi2b. J Clin Oncol. 2019;37:3010.
72. Ocean AJ, Starodub AN, Bardia A, Vahdat LT, Isakov SJ, Guarino M, et al. Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: safety and pharmacokinetics. Cancer. 2017;123:3843–54.

73. Chenard-Poirier M, Hong DS, Coleman RL, de Bono J, Mau-Sorensen M, Collins D, et al. 1824-A phase I/II safety study of tisotumab vedotin (HuMax®-TF-ADC) in patients with solid tumors. Ann Oncol. 2017;28:v403–27.

74. Mahdi H, Schuster SR, O’Malley DM, McNamara DM, Rangwala RA, Liang SY, et al. Phase 2 trial of tisotumab vedotin in platinum-resistant ovarian cancer (innovaTV 208). J Clin Oncol. 2019;37:TPS5602.

75. Breij EC, de Goeij BE, Verploegen S, Schuurhuis DH, Amirkhosravi A, Francis J, et al. An antibody-drug conjugate that targets tissue factor exhibits potent therapeutic activity against a broad range of solid tumors. Cancer Res. 2014;74:1214–26.

76. Sachdev JC, Maitland M, Sharma M, Moreno V, Boni V, Kummar S, et al. A phase 1 study of PF-06647020, an antibody-drug conjugate (ADC) targeting protein tyrosine kinase 7 (PTK7), in patients with advanced solid tumors including platinum resistant ovarian cancer (OVCA). Ann Oncol. 2016;27:v1552–87.

77. Rosen LS, Wesolowski R, Baffa R, Liao KH, Hua SY, Gibson BL, et al. A phase I, dose-escalation study of PF-06650808, an anti-Notch3 antibody-drug conjugate, in patients with breast cancer and other advanced solid tumors. Invest New Drugs. 2020;38:120–30.

78. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.

79. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al.; ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27:16–41. Erratum in: Ann Oncol. 2017;28:iv167–8.

80. O’Malley DM, Bariani GM, Cassier PA, Marabelle A, Hansen AR, De Jesus Acosta A, et al. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. J Clin Oncol. 2022;40:752–61.

81. Oaknin A, Tinker AV, Gilbert L, Samouëlian V, Mathews C, Brown J, et al. Clinical activity and safety of the anti-programmed death 1 monovalent antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: a nonrandomized phase 1 clinical trial. JAMA Oncol. 2020;6:1766–72.

82. Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, et al.; Study 309–KEYNOTE-775 Investigators. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med. 2022;386:437–48.

83. Li BT, Makker V, Buonocore DJ, Offin MD, Olah ZT, Panora E, et al. A multi-histology basket trial of ado-trastuzumab emtansine in patients with HER2 amplified cancers. J Clin Oncol. 2018;36:2502.

84. Jhaveri KL, Wang XV, Makker V, Luoh SW, Mitchell EP, Zwiebel JA, et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. Ann Oncol. 2019;30:1821–30.

85. Bardia A, Messersmith WA, Kio EA, Berlin JD, Vahdat L, Masters GA, et al. Sacituzumab govetecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. Ann Oncol. 2021;32:746–56.

86. Coleman RL, Lorusso D, Gennigens C, González-Martín A, Randall L, Cibula D, et al.; innovaTV 204/GOG-3023/ENGOT-cx6 Collaborators. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2021;22:609–19.

87. Vergote IB, Monk BJ, O’Cearbhail RE, Westermann AM, Banerjee S, Collins DC, et al. 723MO-Tisotumab vedotin (TV) + carboplatin (Carbo) in first-line (1L) or + pembrolizumab (Pembro) in previously treated...
(2L/3L) recurrent or metastatic cervical cancer (r/mCC): interim results of ENGOT-Cx8/GOG-3024/innovaTV 205 study. Ann Oncol. 2021;32:S725–72.

88. Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006;94:642–6.

89. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/ neu. J Clin Oncol. 2018;36:2044–51.

90. English DP, Bellone S, Schwab CL, Bortolomi I, Bonazzoli E, Cocco E, et al. T-DM1, a novel antibody-drug conjugate, is highly effective against primary HER2 overexpressing uterine serous carcinoma in vitro and in vivo. Cancer Med. 2014;3:1256–65.

91. Nicoletti R, Lopez S, Bellone S, Cocco E, Schwab CL, Black JD, et al. T-DM1, a novel antibody-drug conjugate, is highly effective against uterine and ovarian carcinosarcomas overexpressing HER2. Clin Exp Metastasis. 2015;32:29–38.

92. Menderes G, Bonazzoli E, Bellone S, Black J, Altwerger G, Masserdotti A, et al. SYD985, a novel duocarmycin-based HER2-targeting antibody-drug conjugate, shows promising antitumor activity in epithelial ovarian carcinoma with HER2/Neu expression. Gynecol Oncol. 2017;146:179–86.

93. Black J, Menderes G, Bellone S, Schwab CL, Bonazzoli E, Ferrari F, et al. SYD985, a novel duocarmycin-based HER2-targeting antibody-drug conjugate, shows antitumor activity in uterine serous carcinoma with HER2/Neu expression. Mol Cancer Ther. 2016;15:1900–9.

94. Menderes G, Bonazzoli E, Bellone S, Black J, Predolini F, Pettinella F, et al. SYD985, a novel duocarmycin-based HER2-targeting antibody-drug conjugate, shows antitumor activity in uterine and ovarian carcinosarcoma with HER2/Neu expression. Clin Cancer Res. 2017;23:5836–45.

95. Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al. LBA1 trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (Pts) with HER2 metastatic breast cancer (mBC): results of the randomized phase III DESTINY-Breast03 study. Ann Oncol. 2021;32:S1287–8.

96. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al.; DESTINY-Gastric01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382:2419–30.

97. Brown Jones M, Neuper C, Clayton A, Mariani A, Konecny G, Thomas MB, et al. Rationale for folate receptor alpha targeted therapy in “high risk” endometrial carcinomas. Int J Cancer. 2008;123:1699–703.

98. Faltas B, Goldenberg DM, Ocean AJ, Govindan SV, Wilhelm F, Sharkey RM, et al. Sacituzumab govitecan, a novel antibody–drug conjugate, in patients with metastatic platinum-resistant urothelial carcinoma. Clin Genitourin Cancer. 2016;14:e75–9.

99. Liu T, Liu Y, Bao X, Tian J, Liu Y, Yang X. Overexpression of TROP2 predicts poor prognosis of patients with cervical cancer and promotes the proliferation and invasion of cervical cancer cells by regulating ERK signaling pathway. PLoS One. 2013;8:e75864.

100. Bignotti E, Zanotti L, Calza S, Falchetti M, Monardi S, Ravaggi A, et al. Trop-2 protein overexpression is an independent marker for predicting disease recurrence in endometrioid endometrial carcinoma. BMC Clin Pathol. 2012;12:22.

101. Trerotola M, Cantanelli P, Guerra E, Tripaldi R, Aloisi AL, Bonasera V, et al. Upregulation of Trop-2 quantitatively stimulates human cancer growth. Oncogene. 2013;32:222–33.

102. Perrone E, Manara P, Lopez S, Bellone S, Bonazzoli E, Manzano A, et al. Sacituzumab govitecan, an antibody-drug conjugate targeting trophoblast cell-surface antigen 2, shows cytotoxic activity against poorly differentiated endometrial adenocarcinomas in vitro and in vivo. Mol Oncol. 2020;14:645–56.
103. Han C, Perrone E, Zeybek B, Bellone S, Tymon-Rosario J, Altwerger G, et al. *In vitro* and *in vivo* activity of sacituzumab govitecan, an antibody-drug conjugate targeting trophoblast cell-surface antigen 2 (Trop-2) in uterine serous carcinoma. Gynecol Oncol. 2020;156:430–8.

104. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.

105. Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370:734–43. Erratum in: N Engl J Med. 2017;377:702.

106. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al; KEYNOTE-826 Investigators. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med. 2021;385:1856–67.

107. Miller DS, Blessing JA, Bodurka DC, Bonebrake AJ, Schorge JO; Gynecologic Oncology Group. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 2008;110:65–70.

108. Muggia FM, Blessing JA, Method M, Miller DS, Johnson GA, Lee RB, et al.; Gynecologic Oncology Group study. Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92:639–43.

109. Schilder RJ, Blessing J, Cohn DE. Evaluation of gemcitabine in previously treated patients with non-squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 2005;96:6–7.

110. Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE, Roman LD. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol. 2009;27:1069–74.

111. Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2019;37:1470–8.

112. Tewari KS, Monk BJ, Vergote I, Miller A, de Melo AC, Kim HS, et al.; Investigators for GOG Protocol 3016 and ENGOT Protocol En-Cx9. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med. 2022;386:544–55.

113. Hisada Y, Mackman N. Tissue factor and cancer: regulation, tumor growth, and metastasis. Semin Thromb Hemost. 2019;45:385–95.

114. Varughese J, Cocco E, Bellone S, Ratner E, Silasi DA, Azodi M, et al. Cervical carcinomas overexpress human trophoblast cell-surface marker (Trop-2) and are highly sensitive to immunotherapy with hRS7, a humanized monoclonal anti-Trop-2 antibody. Am J Obstet Gynecol. 2011;205:567.e1–7.

115. Shimizu S, Ogawa T, Takezawa K, Tojima I, Kouzaki H, Shimizu T. Tissue factor and tissue factor pathway inhibitor in nasal mucosa and nasal secretions of chronic rhinosinusitis with nasal polyp. Am J Rhinol Allergy. 2015;29:235–42.

116. Zeybek B, Manzano A, Bianchi A, Bonazzoli E, Bellone S, Buza N, et al. Cervical carcinomas that overexpress human trophoblast cell-surface marker (Trop-2) are highly sensitive to the antibody-drug conjugate sacituzumab govitecan. Sci Rep. 2020;10:973.

117. Loganzo F, Sung M, Gerber HP. Mechanisms of resistance to antibody-drug conjugates. Mol Cancer Ther. 2016;15:2825–34.

118. Coates JT, Sun S, Leshchiner I, Thimmiah N, Martin EE, McLoughlin D, et al. Parallel genomic alterations of antigen and payload targets mediate polyclonal acquired clinical resistance to sacituzumab govitecan in triple-negative breast cancer. Cancer Discov. 2021;11:2436–45.
119. Loganzo F, Tan X, Sung M, Jin G, Myers JS, Melamud E, et al. Tumor cells chronically treated with a trastuzumab-maytansinoid antibody-drug conjugate develop varied resistance mechanisms but respond to alternate treatments. Mol Cancer Ther. 2015;14:952–63.

120. Ríos-Luci C, García-Alonso S, Díaz-Rodríguez E, Nadal-Serrano M, Arribas J, Ocaña A, et al. Resistance to the antibody-drug conjugate T-DM1 is based in a reduction in lysosomal proteolytic activity. Cancer Res. 2017;77:4639–51.

121. Kavallaris M. Microtubules and resistance to tubulin-binding agents. Nat Rev Cancer. 2010;10:194–204.

122. Cianfriglia M. The biology of MDR1-P-glycoprotein (MDR1-Pgp) in designing functional antibody drug conjugates (ADCs): the experience of gemtuzumab ozogamicin. Ann Ist Super Sanita. 2013;49:150–68.

123. Carrasco-Triguero M, Dere RC, Milojic-Blair M, Saad OM, Nazzal D, Hong K, et al. Immunogenicity of antibody-drug conjugates: observations across 8 molecules in 11 clinical trials. Bioanalysis. 2019;11:1555–68.

124. Hock MB, Thudium KE, Carrasco-Triguero M, Schwabe NF. Immunogenicity of antibody drug conjugates: bioanalytical methods and monitoring strategy for a novel therapeutic modality. AAPSJ. 2015;17:35–43.

125. García-Alonso S, Ocaña A, Pandiella A. Resistance to antibody-drug conjugates. Cancer Res. 2018;78:2159–65.

126. Takegawa N, Nonagase Y, Yonesaka K, Sakai K, Maenishi O, Ogitani Y, et al. DS-8201a, a new HER2-targeting antibody-drug conjugate incorporating a novel DNA topoisomerase I inhibitor, overcomes HER2-positive gastric cancer T-DM1 resistance. Int J Cancer. 2017;141:1682–9.

127. Müller P, Kreuzaler M, Khan T, Thommen DS, Martin K, Glatz K, et al. Trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade. Sci Transl Med. 2015;7:315ra188.