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Anti-tumour Treatment

The evolving landscape of antibody-drug conjugates in gynecologic cancers

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ABSTRACT

Despite significant advances in the treatment of cervical, ovarian, and uterine cancers with the approvals of checkpoint and PARP inhibitors into standard treatment, patients with recurrent metastatic gynecologic malignancies still experience poor outcomes, and most of these patients will experience disease relapse. Once standard preferred treatments are exhausted, options have historically been limited to treatments associated with poor outcomes and notable toxicities. Consequently, novel therapies that are effective and well-tolerated are needed for patients with recurrent and metastatic gynecologic malignancies. Antibody-drug conjugates (ADCs) are a class of targeted therapies that are well established in several cancers including hematologic malignancies and some solid tumors. Significant strides in ADC technology and design have led to improvements in efficacy and safety with newer-generation ADCs. Consequently, ADCs are gaining traction in gynecologic cancers with the recent US Food and Drug Administration approvals of tisotumab vedotin in cervical cancer and mirvetuximab soravtansine in ovarian cancer. Many additional ADCs against various targets are being explored in patients with metastatic or recurrent gynecologic malignancies.

The purpose of this review is to summarize the nuanced structural and functional properties of ADCs, while outlining opportunities for innovation. Further, we highlight the ADCs in clinical development for gynecologic malignancies, exploring how ADCs may be able to address the clinical care gap for patients with gynecologic cancers.

Introduction: Unmet needs in recurrent and metastatic gynecologic malignancies

Gynecologic malignancies, particularly ovarian, cervical, and uterine cancers, represent a substantial healthcare burden in women. In the United States alone, nearly 100,000 new cases of gynecologic malignancies and 30,000 related deaths have been estimated for 2022 [1–3]. Among all cases diagnosed between 2012 and 2018, the 5-year survival rate for patients with metastatic tumors was approximately 31% for ovarian cancer, 17% for cervical cancer, and 18% for uterine cancer [1–3].

Treatment of gynecologic malignancies is highly dependent on the stage and origin of disease, with curative surgery being the primary option when possible. For advanced or metastatic disease, platinum-based chemotherapy remains the primary backbone for systemic treatment. The identification and development of targeted therapies has been a significant focus across treatment of gynecologic malignancies, and several have altered the treatment landscapes of these cancers in recent years. The vascular epithelial growth factor (VEGF) inhibitor bevacizumab improved progression-free survival (PFS) in combination with platinum-based doublet chemotherapy in ovarian cancers in the frontline, frontline maintenance, and platinum-sensitive recurrent settings [4,5]. Bevacizumab also improved PFS in combination with platinum-based doublet therapy in advanced cervical cancer [6]. As the first biomarker-based treatment for a gynecologic malignancy, the PD-1 inhibitor pembrolizumab was approved in combination with platinum-based doublet chemotherapy with or without bevacizumab in patients with PD-L1-positive metastatic cervical cancer based on improved PFS, overall survival (OS), and overall response rate (ORR) [7]; likewise, pembrolizumab in combination with the VEGF inhibitor lenvatinib received approval for patients with recurrent endometrial cancer based on significantly improved OS and PFS [8]. In ovarian cancer, the recent addition of poly (ADP-ribose) polymerase (PARP) inhibitors as frontline maintenance options has significantly improved PFS [9–11]. VEGF inhibitors, immunotherapies, and PARP inhibitors have altered the treatment paradigm for each of these cancers over the past decade; however,

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these important advancements raise additional questions regarding how to treat patients who progress on these treatments.

Despite the recent improvements to care, advanced or metastatic gynecologic cancers remain incurable, and most patients eventually progress and exhaust these therapeutic options, leaving next line of therapy to be single-agent chemotherapy. Although outcomes vary with the specific type of cancer, patients treated with chemotherapy for recurrent disease experience response rates under 20%, median PFS less than 4 months, and median OS less than 12 months [12–16]. In platinum-resistant ovarian cancer, non-platinum chemotherapy has been associated with response durations of only 3–7 months [14,15,17]. Moreover, these chemotherapeutic agents are associated with toxicities, including neutropenia, anemia, thrombocytopenia, alopecia, renal toxicities, and neuropathy, which can impact patient quality of life and limit their therapeutic applicability [12,15,18–20]. Consequently, there is a great unmet need for effective and well tolerated novel therapies for patients with recurrent and metastatic gynecologic malignancies.

Antibody-drug conjugates (ADCs) represent one type of targeted therapeutic modality that offers opportunities to expand biomarker-based treatment options in patients with recurrent gynecologic malignances. The purpose of this review is to discuss recent advances in ADC technology, summarize currently approved ADCs, and introduce new ADCs under development in gynecologic malignancies.

ADCs as targeted therapeutic approaches in oncology

ADCs are a class of targeted therapies developed to provide more precise drug delivery by using antibody-antigen interactions to specifically release cytotoxic agents directly to tumor cells and/or the tumor microenvironment [21,22]. The fundamental role of ADCs is to control the biodistribution of the payload to provide more precise drug delivery to the target; thus, ADCs have the potential to improve clinical efficacy while minimizing toxicity. Conceptually, ADCs are designed to have an expanded therapeutic index, however, in practice, this idea has been challenged recently [23], as ADCs are associated with toxicities, leaving room for continued improvement [24–27]. In addition to inducing targeted cytotoxicity, some ADCs have the potential to induce immunogenic cell death through activation of the immune system [25,28,29]. However, despite these challenges, ADC technology has made important advancements in recent years.

ADC mechanism of action

The main components of ADCs are the antibody, the cytotoxic payload, and the linker technology that connects the antibody to the payload [25,27]. The canonical mechanism of action of ADCs involves a cascade of events (Fig. 1): (1) binding of the antibody to its tumor antigen on cancer cells; (2) internalization of the ADC-antigen complex through endocytosis; (3) trafficking through the endolysosomal compartment and degradation of the ADC; (4) release of the payload into the cytoplasm; and (5) payload action commonly on microtubules or DNA, resulting in cell death [21,25]. Although this mechanism of action may appear straightforward, each component of an ADC (the antibody, cytotoxic payload, and linker) must be optimized in combination with one another to maximize therapeutic efficacy and limit toxicities.

Antibody

The role of the antibody portion of the ADC is to provide targeted delivery to the tumor by binding to an antigen that is selectively expressed on tumor cells [25,30]. Several antibody properties should be considered when selecting the optimal component for an ADC. First, to ensure efficient uptake into target cells, the antibody must selectively bind to the target antigen with high affinity, and the antigen should be effectively internalized by receptor-mediated endocytosis [30–33]. The

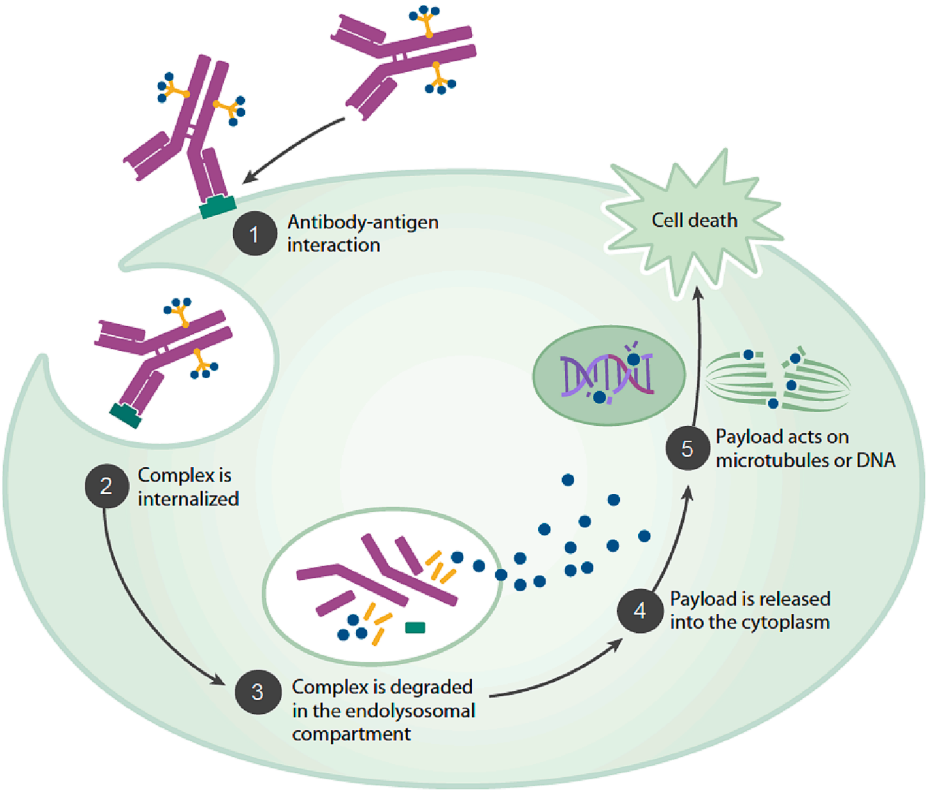

Fig. 1. Canonical mechanism of action of ADCs. (1) Antibody binds to the target antigen at the surface of the cancer cell. (2) ADC-antigen complex is internalized and trafficked through the endolysosomal compartment. (3) Payload is released in the endolysosomal compartment. (4) Drug payload enters the cytoplasm. (5) Drug payload acts on microtubules or DNA, resulting in cell death. Abbreviations: ADC, antibody-drug conjugate.

tumor targeting ability of the antibody is dictated by expression of the target antigen [21,34]. As such, the optimal target antigen should have high expression on the surface of the tumor cells and limited or no expression in healthy tissues [21,25,32]. A key consideration regarding the optimal function of the ADC-antigen complex derives from the fact that few antigens are truly tumor-specific with no expression in healthy tissue. Rather, most are regarded as tumor-enriched and have some expression in healthy tissue [27,34]. This antigen distribution may result in on-target toxicity occurring on non-tumor cells (on-target/off-tumor toxicity) [27,34].

Second, it is important to consider antibody immunogenicity, which can lead to immune reactions and premature elimination of the antibody from circulation [31]. First-generation ADCs used conventional chemotherapeutic agents coupled to mouse monoclonal antibodies that were highly immunogenic and susceptible to unwanted immune reactions and rapid clearance leading to low anti-tumor efficacy [32,35]. To overcome this limitation, second-generation ADCs utilized mouse/human chimeric monoclonal antibodies, which reduced immunogenicity and improved half-life [31,32]. Technology has since evolved to develop humanized monoclonal antibodies, as well as purify fully human monoclonal antibodies. The third generation of ADCs, which comprises many of those with current marketing approval in the United States, primarily utilizes human or humanized monoclonal antibodies [31]. Such antibodies have lower immunogenicity, allowing for significantly improved half-life [31,32,36]. The evolution of the antibody engineering field has also led to alterations in the Fc region to decrease Fc receptor (FcR) binding in the reticuloendothelial system, which can alter biodistribution away from the tumor [37,38]. Normal steric hinderance provided by fucosyl residues can be manipulated to reduce clearance by FcRγ.

Payload

In most current ADCs approved or under development the payload is a cytotoxic agent that ultimately induces cell death [25,32]. Because ADCs aim to deliver the cytotoxic drug to tumors in a precise manner, and because limited tumor penetration is anticipated to prevent a portion of ADC molecules from reaching tumor cells, most cytotoxic payloads used for ADCs are approximately 100–1000 × more potent than small molecule chemotherapeutic agents that are used on their own [31]. This potency of the payload relative to traditional chemotherapy can also enable activity with lower antigen expression on the target cancer cell or at lower drug-to-antibody ratios (DARs) [31]. The most common cytotoxic payloads are either microtubule inhibitors (eg, auristatins, eribulin, hemiasterlin, maytansinoids, and tubulysin) that cause cell cycle arrest and selectively target dividing cells, or DNA damaging agents, (eg, calicheamicin, duocarmycin, doxorubicin, pyrrolobenzodiazepine, and topoisomerase inhibitors) that prevent cell division and induce DNA damage that could target dividing or non-dividing cells [25,32,39]. Additionally, ADCs with novel mechanisms of action, such as small-molecule nicotinamide phosphoribosyltransferase (NAMPT) inhibitors and stimulator of interferon genes (STING) agonists, are under investigation [40].

Linker

The linker portion of the ADC joins the antibody to the cytotoxic payload. An ideal linker is highly stable in circulation, meaning it will not release the payload before delivery to the target, but will efficiently release it inside the tumor cell [25,41]. Linkers can be either cleavable (eg, by enzymes or low pH) or non-cleavable (eg, by catabolism of the ADC in the lysosome). Cleavable linkers may have increased efficiency of payload release within the tumor cells, but also have the potential for premature payload release, which can result in off-target toxicity [31,42]. The most common cleavable linkers include hydrazone or phosphoramidate-based linkers, which are sensitive to pH; disulfide linkers, which are sensitive to glutathione; and dipeptide linkers, which are sensitive to intracellular enzymes [31,42,43]. Dipeptide linkers are insensitive to pH and serum proteases, and thus may be more stable than hydrazone and disulfide linkers [31,41]. The most common non-cleavable linkers include maleimidocaproyl, which is often used in conjunction with the monomethyl auristatin F (MMAF) payload, and 4-maleimidomethyl cyclohexane-1-carboxylate [31].

Toxicities associated with ADCs

The clinical use of ADCs has been accompanied by a wide range and incidence of adverse events (AEs), with each ADC having a unique safety profile. Some toxicities are common among many ADCs. In a recent *meta*-analysis the most frequent grade ≥3 AEs associated with ADCs in clinical trials were lymphopenia, nausea, neutropenia, blurred vision/ocular toxicity, and peripheral neuropathy. Ocular toxicity is common among many ADCs, with 2 FDA approved ADCs (tisotumab vedotin, and mirvetuximab soravtansine), as well as recently withdrawn belantamab mafodotin, having black box warnings for ocular toxicity [44,45]. Pulmonary toxicity has also been associated with multiple ADCs, though the incidence and severity vary. Interstitial lung disease (ILD), pulmonary toxicity, and pneumonitis have been reported with several approved anti-human epidermal growth factor receptor 2 (HER2) ADCs, the tissue factor (TF)-targeting ADC tisotumab vedotin, approved and investigational FRα-targeting ADCs (mirvetuximab soravtansine and farletuzumab ecteribulin), and investigational NaPi2b-targeting ADCs (lifastuzumab vedotin and upifitamab rilsodotin [UpRi]) [25,46–52]. Dose optimization studies with investigational ADCs have revealed that ILD/pneumonitis decreases in frequency and severity with lower doses tested in some cases [47,53]. For example, ILD/pneumonitis with UpRi tended to be less common at lower doses investigated, suggesting a strategy for potentially mitigating the risk of pulmonary toxicity through dose optimization. In general, these complications require careful patient selection and monitoring.

Mechanistically, ADC-associated toxicities can arise from the target (on-target, off-tumor toxicity), or the payload (off-tumor, off-target toxicity). For example, ocular toxicity has been associated with ADCs carrying the MMAF, monomethyl auristatin E (MMAE), or maytansinoid ravtansine (DM4) payloads; myelosuppression (anemia, neutropenia, and thrombocytopenia) and peripheral neuropathy have been associated with MMAE; and cytopenias and hepatotoxicity have been observed with the maytansinoid DM1 [21,25,44,45,54,55]. In general, off-target/off-tumor toxicity is more commonly dose limiting than on-target toxicity [21,25]. Nevertheless, owing to the sophisticated structure and functional attributes of ADCs, the toxicity profile is challenging to accurately predict in clinical practice, underscoring the need for improved ADC design strategies as well as studies to unravel various mechanisms of AEs.

Innovations in ADC design

The clinical activity and therapeutic index of an ADC is influenced by the distinct features of each of its three components (antibody, payload, and linker). Several techniques are currently being explored to optimize the combinations of these components to further improve the therapeutic index of ADCs. These methods include enhancing internalization rates, controlling the bystander effect, and increasing DAR (defined as the average number of drug molecules bound to each antibody) while maintaining drug-like properties, and achieving homogeneity in ADC preparation [21,25–27,31,56].

The rate of internalization is an important consideration for ADC optimization. Because the delivery of the payload requires processing of the ADC via internalization and intracellular trafficking within the endolysosomal compartments, slow internalization rates can impact ADC potency. Thus, rapid internalization is generally desired to increase the antitumor activity and reduce the risk of off-target delivery [27,57].

Bispecific antibodies are being explored as a novel method of improving internalization and lysosomal trafficking to enhance ADC potency. These antibodies contain non-identical paratopes in their two F_{ab} regions, enabling binding to two different epitopes on either the same antigen or different antigens [27,57]. For example, zanidatamab is a humanized, bispecific, immunoglobulin G1 (IgG1)-like antibody that targets the juxtamembrane extracellular domain and the dimerization domain of HER2 that showed increased internalization and anti-tumor activity compared with trastuzumab [58]. Moreover, emerging preclinical data indicate that ADCs can target the tumor microenvironment using cleavable linkers that can release the payload extracellularly, which could eliminate the need for ADC internalization [25,33,39,59]. Examples of this technology include experimental ADCs targeting components of the stroma, including collagen 4, tenascin-C, and galectin-3-binding protein [60–62]. Consequently, eliminating the internalization step could serve to streamline the mechanism of action, potentially resulting in improved anti-tumor efficacy, particularly in tumors in which target expression is heterogeneous.

Payload properties impacting diffusion and cell permeability also represent an avenue for optimization. A bystander effect occurs when the payload diffuses to and can penetrate and kill nearby cancer cells in an antigen-independent manner. Bystander killing may be beneficial for tumors in which antigen expression is highly heterogenous [31,63]. For example, sacituzumab govitecan is designed with a hydrolysable linker and a membrane-permeable payload (SN-38) in order to deliver cytotoxic activity to both antigen-expressing target cells and nearby antigen-negative cells after ADC localization and extracellular release of free SN-38 in the tumor microenvironment [64]. Potential limitations to the bystander effect include the inefficient exit of payload from targeted tumor cells, and the diffusion of the payload into healthy cells, resulting in off-target toxicity [31,32]. Notably, linker stability is an important variable in ADC toxicity; linkers with low stability may be subject to non-specific cleavage and therefore could lead to systemic toxicities [65].

Optimization of linker/payload conjugation as well as linker attributes that increase DAR also have potential for improving ADC efficacy. In vitro studies have shown a direct correlation between DAR and potency, with low DAR associated with decreased ADC potency, presumably due to the reduced number of cytotoxic payload molecules entering the tumor [66]. In contrast, a high DAR results in increased ADC potency. However, hydrophobic linker and payload moieties can cause ADCs with higher DAR to aggregate, which can negatively impact pharmacokinetic properties and possibly result in faster plasma clearance and hepatic uptake. Consequently, most ADC platforms have been historically limited to a DAR of 2–4 to maintain suitable drug-like properties [21,25,31,33,39]. Several methods to increase DAR without negatively impacting pharmacokinetic properties have been explored, which primarily involve increasing hydrophilicity of the linker [31]. For example, introduction of a highly hydrophilic polyethylene glycol (PEG) group into the linker compensated for hydrophobicity of the SN-38 payload, allowing for a DAR $>$ 7 for sacituzumab govitecan, which translated into significant clinical activity in patients with breast tumors [64,67]. Another successful approach to generate ADCs with increased DAR is the use of a hydrophilic polymer scaffold linker technology, such as the biodegradable polyacetal polymer carrier poly-1-hydroxymethylethylene hydroxymethylformal, also known as fleximer. Using this scaffold, ADCs could be produced that have DARs of 10–15 that maintain suitable pharmacokinetic and physicochemical properties [68].

As each antibody can be conjugated to multiple linkers and cytotoxin moieties, achieving homogeneity in ADC preparation, defined as consistency in the number of linker-payload groups attached to an antibody, is important for consistent payload delivery to the tumor. Although the average DAR of a heterogenous preparation may be 2–4, the broad range of DARs across the ADC preparation could lead to premature payload release and/or altered biodistribution, and thus significantly impact anti-tumor efficacy as well as tumor penetration and clearance [27,66,69]. The method of bioconjugation is a determinant of ADC homogeneity, and conjugation can be either stochastic or site-specific. Stochastic conjugation involves conjugation to cysteine and lysine residues and affords less control over ADC preparation and therefore results in a heterogeneous mix of ADCs with variable DAR. In contrast, site-specific conjugation involves engineering reactive cysteine residues, glycan remodeling and glycoconjugation, disulfide rebridging, or introduction of unnatural amino acids in order to attach linker-payload moieties to precise residues on the antibody [63]. These efforts are intended to ensure more stable and homogenous ADCs with increased plasma exposure and improved therapeutic index [63].

Novel ADC platforms

The optimization strategies discussed above have been applied to several novel linker-payload platforms that are in various stages of development. The Dolaflexin platform consists of the fleximer hydrophilic polymer-scaffold, which can improve the solubility and pharmacokinetics of the ADC as well as reduce the immunogenicity, and an auristatin F-hydroxypropylamide (AF-HPA) payload conjugated via a cleavable linker [56]. The use of a polymer scaffold allows for a substantial increase in the DAR (to approximately 10), which can improve drug concentration at the tumor site and result in a lower dose or less frequent ADC administration, which could in turn minimize the risk of toxicity [34,56]. The AF-HPA payload also allows for a controlled bystander effect. Once released in the target cell, AF-HPA can diffuse across cell membranes and exert bystander effect. In parallel, AF-HPA is metabolized to auristatin F, which remains highly potent but loses the ability to cross the cell membrane and is not a P-glycoprotein efflux pump substrate, consequently trapping the drug inside tumor cells and limiting the impact on adjacent healthy cells [56,70]. Data from preclinical toxicology studies suggest that Dolaflexin ADCs result in minimal occurrence of neutropenia, which is associated with some auristatin ADC platforms [56]. The ADC UpRi, generated using the Dolaflexin platform, has a DAR of approximately 10 and suitable pharmacokinetic and drug-like properties. UpRi is under clinical investigation in several trials in patients with ovarian cancer [47,71].

Dolasynthen is another novel, fully synthetic platform based on the AF-HPA payload that generates homogeneous ADCs with site-specific antibody bioconjugation and a controlled bystander effect. The platform, together with site-specific bioconjugation techniques, allows for the precise modulation of DAR to maximize the therapeutic index [72]. XMT-1660 is a novel ADC targeting the tumor antigen B7-H4 that utilizes the Dolasynthen platform to achieve a site-specific DAR of 6. In preclinical studies, XMT-1660 was shown to have superior anti-tumor activity compared with a stochastically conjugated B7-H4-targeting ADC [72,73].

Several novel platforms are being explored to develop ADCs with topoisomerase I inhibitor payloads, which have recently gained interest as ADC payloads with the approval of 2 ADCs using this payload class, trastuzumab deruxtecan and sacituzumab govitecan. Topoisomerase I inhibitors tend to have reduced potency compared with anti-tubulin or DNA alkylating agents, which could theoretically improve the therapeutic index of resulting ADCs (reviewed in [74]). The PSARlink platform uses a hydrophilic polysarcosine drug-linker with an exatecan payload to reduce overall hydrophobicity of the conjugate with a resulting DAR of 8. An ADC generated with PSARlink and trastuzumab was associated with superior anti-tumor activity over trastuzumab deruxtecan [75]. Another new linker, CL2A, has a short, non-cleavable seven PEG segment that enables attachment of a large number of hydrophobic SN-38 molecules via reduced cysteines (DAR of 6.97). Attached to a trastuzumab antibody, CLA2-SN-38 resulted in improved toxicity over time compared with trastuzumab emtansine [76].

Additional promising technologies include site-specific conjugates (such as transglutaminase-mediated conjugation of amino-PEG6-C2-

monomethyl auristatin D [MMAD] that resulted in stable linkage; DAR of 6–8; and increased anti-tumor activity compared with similarly loaded conventional ADCs or site-specific conjugates with low loading) [69] and cysteine-mediated conjugation of dual auristatin (MMAE/MMAF) ADCs that enabled high levels of drug loading and activity on cells refractory to either of the payloads, potentially allowing for complementary or synergistic activity [77]. The Azymetric platform utilizes in silico modeling to insert cysteine residues into an antibody in order to precisely control conjugation [78]. Using this method, conjugation locations can be specifically chosen to mask hydrophobicity, thereby improving hydrophilicity and biophysical properties of the ADC. The platform can achieve a precisely controlled DAR of up to 6. The new ADC zanidatamab zovodotin (ZW49) developed using the Azymetric platform additionally utilizes the anti-HER2 biparatopic antibody zanidatamab to enhance internalization [58,79]. The payload of zanidatamab zovodotin is a proprietary auristatin derivative conjugated via cleavable linkers with an average DAR of 2. Preclinical data revealed that zanidatamab zovodotin exhibited similar pharmacokinetic properties as unconjugated zanidatamab antibody [79]. Recently reported dose-finding data for zanidatamab zovodotin in patients with HER2-positive cancers indicated an ORR of 28% and manageable safety profile, though all-grade treatment-related keratitis was observed in 42% of patients [80].

Overall, the current and emerging ADC technologies are focused on refining the antibody, linker, and payload together to generate fully optimized ADCs. These important developments have ushered in a new era of anti-tumor therapies.

ADCs in gynecologic oncology

Overview of ADCs in oncology

At the time of this publication, 11 ADC therapies are approved for oncology use in the United States, of which 9 are also approved in the European Union [31,34] (Table 1). In many indications, ADCs have become mainstream therapies, and findings from randomized clinical trials have shown considerably improved efficacy compared with standard of care. ADCs were first approved in hematologic cancers. Gemtuzumab ozogamicin, a CD33-targeting ADC, received accelerated approval from the FDA in 2000 for patients with acute myeloid leukemia. In the decade following its initial approval, post-marketing findings indicated an increased risk for veno-occlusive disease, and a confirmatory trial failed to support an increased benefit. Gemtuzumab ozogamicin was withdrawn from the market in 2010 but eventually gained reapproval in 2017 at a lower dose for patients with relapsed/refractory CD33-positive acute myeloid leukemia (reviewed in [81]). Despite its complicated history, gemtuzumab ozogamicin paved the way for future ADCs. In 2011, brentuximab vedotin (targeting CD30) was approved for patients with previously untreated stage III/IV Hodgkin lymphoma based on the ECHELON-1 trial. In this study, addition of brentuximab vedotin to chemotherapy significantly reduced the risk of progression or

Table 1
ADCs currently approved in oncology in the United States and the European Union.

ADC	Target Antigen	mAb	Linker	Payload	Indication	Approval
Tisotumab vedotin (Tivdak®)	Tissue factor	IgG1	Val-Cit	MMAE	Recurrent or metastatic cervical cancer	FDA: September 2021
Brentuximab vedotin (Adcetris®)	CD30	Chimeric IgG1	Val-Cit	MMAE	Relapsed/refractory and previously untreated stage III/IV Hodgkin lymphoma Relapsed/refractory and untreated systemic anaplastic large cell lymphoma	FDA: August 2011 EMA: October 2012
Trastuzumab emtansine (Kadcyla®)	HER2	IgG1k	MCC	DM1	Metastatic HER2-positive breast cancer	FDA: February 2013 EMA: November 2013
Inotuzumab ozogamicin (Besponsa®)	CD22	IgG4	Cleavable acid-labile acetyl butyrate	Calicheamicin	Relapsed/refractory B-cell acute lymphoblastic lymphoma	FDA: August 2017 EMA: June 2017
Gemtuzumab ozogamicin (Mylotarg®)	CD33	IgG4 k	Cleavable acid-labile acetyl butyrate	Calicheamicin	CD33-positive acute myeloid leukemia	FDA: September 2017 EMA: April 2018
Polatuzumab vedotin (Polivy®)	CD79b	IgG1	Val-Cit	MMAE	Diffuse large B-cell lymphoma	FDA: June 2019 EMA: January 2020
Enfortumab vedotin (Padcev®)	Nectin-4	IgG1 k	Val-Cit	MMAE	Locally advanced/metastatic urothelial cancer	FDA: December 2019 EMA: April 2022
Trastuzumab deruxtecan (Enhertu®)	HER2	IgG1	Maleimide–GGFG	DXd	Unresectable/metastatic HER2-positive and HER2-low breast cancer; unresectable/ metastatic non-small cell lung cancer	FDA: December 2019 EMA: January 2021
Sacituzumab govitecan (Trodelvy®)	Trop-2	IgG1 k	CL2A	SN-38	Unresectable/metastatic triple negative breast cancer	FDA: April 2020 EMA: November 2021
Belantamab mafodotin (Blenrep®)	BCMA	IgG1	MC	MMAF	Relapsed or refractory multiple myeloma	FDA: August 2020 then withdrawn[a] EMA: August 2020
Loncastuximab tesirine (Zynlonta®)	CD19	IgG1 k	Val-Ala	SG3199/PBD dimer	Relapsed/refractory large B-cell lymphoma, diffuse large B-cell lymphoma	FDA: April 2021
Mirvetuximab soravtansine (Elahere™)	FRα	IgG1	Sulfo-SPDB cleavable linker	DM4	FRα-positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	FDA: November 2022

[a] GlaxoSmithKline initiated the withdrawal of belantamab mafoditin US marketing authorization based on a request by the FDA. **Abbreviations:** ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CD, cluster of differentiation; DM4, ravtansine; DXd, deruxtecan; EMA, European Medicines Agency; FDA, US Food and Drug Administration; FR, folate receptor; HER2, human epidermal growth factor receptor 2; Ig, immunoglobulin; mAb, monoclonal antibody; MC, maleimidocaproyl; MCC, maleimidomethyl cyclohexane-1-carboxylate; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; PBD, pyrrolobenzodiazepine; Trop-2; trophoblast cell -urface antigen 2; US, United States; Val-Cit, valine-citrulline; Val-Ala, valine-alanine.

death by 23% ($P = 0.04$) and is now a standard-of-care therapy for newly diagnosed stage III/IV Hodgkin lymphoma [82].

Noteworthy improvements with ADCs over standard-of-care have also been observed in solid tumors. The first ADC to gain approval for treatment of a solid tumor was trastuzumab emtansine (targeting HER2) in 2013 for metastatic HER2-positive breast cancer. Its approval was based on the phase III EMILIA trial, which showed a significant improvement in both PFS (9.6 versus 6.4 months) and OS (30.9 versus 25.1 months) vs lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer [83]. Since then, ADCs have led to several important developments in the treatment of breast cancer. In the ASCENT trial of relapsed or refractory metastatic triple negative breast cancer, sacituzumab govitecan (targeting Trop-2, approved in 2020) significantly reduced the risk of disease progression or death by 59% and the risk of death by 52% ($P < 0.001$ for both) [64]. Recently, in patients with HER2-positive metastatic breast cancer who had previously received treatment with trastuzumab and a taxane, trastuzumab deruxtecan (targeting HER2, approved in 2019) reduced the risk of disease progression or death by 67% ($P < 0.0001$) compared with trastuzumab emtansine in the DESTINY-Breast03 trial [84]; in patients with HER2-low breast tumors who had received 1 or 2 prior lines of chemotherapy enrolled in DESTINY-Breast04, trastuzumab deruxtecan significantly reduced the risk of progression or death by 50% ($P < 0.001$) [51]. The results from the latter trial have shifted the treatment paradigm for nearly half of the patients diagnosed with metastatic breast cancer and continue to emphasize the importance of ADC development in solid tumors alongside proper selection of patients who are most likely to benefit from these therapies.

ADCs approved in gynecologic malignancies

There have been several important recent developments in gynecologic malignancies with 2 ADCs having received accelerated approval by the FDA in gynecologic oncology: tisotumab vedotin for adult patients with recurrent or metastatic cervical cancer who have had disease progression on or after chemotherapy, and mirvetuximab soravtansine for adult patients with FRα-positive, platinum-resistant epithelial ovarian cancer who have received 1–3 prior lines of therapy [48,49]. Tisotumab vedotin is a TF-directed ADC composed of a human anti-TF IgG1 antibody conjugated to MMAE via a protease-cleavable valine-citrulline linker [49]. Based on data from the phase II, single-arm innovaTV 204/GOG-3023/ENGOT-cx6 trial in patients with previously treated metastatic or recurrent cervical cancer, objective responses were achieved by 24% of patients, including 7 patients (7%) with a complete response and 17 patients (17%) with a partial response, with median duration of response of 8.3 months [85]. Overall, 53% of patients had treatment-related ocular AEs, predominately conjunctivitis; 2% of patients had grade 3 events (ulcerative keratitis). In patients with metastatic cervical cancer, the ORR with tisotumab vedotin represented a considerable improvement over chemotherapy agents, which have been shown to elicit responses in up to 15% of patients [85–89]. It is important to note that approval of tisotumab vedotin was accompanied by a black box warning for ocular toxicity [49], underscoring that eliminating these AEs is an area of improvement in ADC clinical research. Additional warnings are included for peripheral neuropathy, hemorrhage, pneumonitis, and embryo-fetal toxicity. The confirmatory trial, innovaTV 301/ENGOT cx12/GOG-3057 (NCT04697628) is currently ongoing.

Mirvetuximab soravtansine comprises an antibody against FRα, a cleavable disulfide-containing hydrophilic linker *N*-succinimidyl 4-(2-pyridyldithio)-2-sulfo-butanoate, and a maytansinoid DM4 tubulin-targeting agent, with a DAR of 3–4 [90–92]. In the phase III single arm SORAYA study, mirvetuximab soravtansine has shown clinical activity in 106 patients with FRα-positive (as assessed by immunohistochemistry proportion score 2+ ≥75) platinum-resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancers [92,93]. Overall, 32% of patients achieved objective responses, with 5 (5%) complete responses and 29 (28%) partial responses [92,93]. Median duration of response was 6.9 months and investigator-assessed median PFS was 4.3 months [92,93]. Ocular AEs were observed in 61% of patients, with 9% reporting grade ≥3 ocular toxicities including visual impairment, keratopathy/keratitis, dry eye, photophobia, and eye pain [48]. Based on results from SORAYA, in 2022, mirvetuximab soravtansine was granted accelerated approval by the United States FDA for patients with FRα-positive platinum-resistant ovarian cancer who have received 1–3 prior therapies [94]. The approval of mirvetuximab soravtansine was accompanied by a black-box warning for ocular toxicity, as well as further warnings for pneumonitis and peripheral neuropathy. At the time of this review, mirvetuximab soravtansine is still being investigated in several clinical trials (Table 2), including the phase II single-arm PICCOLO trial (mirvetuximab soravtansine monotherapy; NCT05041257) and the phase III randomized GLORIOSA trial (maintenance therapy with mirvetuximab soravtansine plus bevacizumab vs bevazicumab monotherapy; NCT05445778) in patients with FRα-positive platinum-sensitive high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancers, as well as the phase III randomized MIRASOL trial (mirvetuximab soravtansine vs chemotherapy) in patients with FRα-positive platinum-resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancers (NCT04209855) [95].

ADCs under investigation in gynecologic malignancies

A growing number of ADCs against various targets, including NaPi2b, HER2/3, FRα, trophoblast cell-surface antigen 2, and mesothelin, which are expressed in ovarian, cervical, or uterine tumors, are under investigation in additional ongoing trials in early phases of clinical development (Table 2; also reviewed in [96]). One ADC in late-stage development in gynecologic oncology is UpRi, a first-in-class NaPi2b-targeting ADC [97,98]. NaPi2b is a cell surface sodium-dependent phosphate transporter that is broadly expressed in solid tumors, particularly ovarian and endometrial cancer, with limited expression in healthy tissue [71,99–102]. As noted above, UpRi utilizes the novel Dolaflexin platform with a DAR of approximately 10 and an AF-HPA payload with a controlled bystander effect [56,71,98]. Data from a phase Ib study of 97 patients with high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancers and 1–3 prior lines of therapy in the platinum resistant setting and 4 prior lines regardless of platinum status showed promising clinical activity with UpRi administered at 36 mg/m^2 [47]. UpRi also had an encouraging safety profile, with AEs being mostly low-grade and the most common all-grade AEs including fatigue (79%), nausea (59%), transient aspartate aminotransferase increase (38%), decreased appetite (34%), pyrexia (34%), vomiting (31%), and transient thrombocytopenia (31%) at a dose of 36 mg/m^2; in the reported data, no patients experienced grade ≥3 neutropenia, peripheral neuropathy, or ocular toxicity, which are common toxicities associated with other ADCs [47,54]. At the 36 mg/mg^2 dose there were 2 cases of grade 1–2 pneumonitis, but no cases at grade ≥3; there were 4 cases of grade ≥3 pneumonitis at a higher dose of 43 mg/m^2. Among patients with measured NaPi2b expression in the phase Ib study, 50 (64%) had NaPi2b-positive (tumor proportion score ≥75) ovarian tumors and achieved ORR of 34% in evaluable patients, with 5% complete responses and 29% partial responses [47]. UpRi is being investigated in three clinical trials in ovarian cancer (Table 2), including the phase II registrational UPLIFT trial to assess UpRi monotherapy in patients with platinum-resistant, high-grade serous ovarian cancer who have received up to four prior lines of therapy (NCT03319628), the phase I UPGRADE-A trial to investigate UpRi in combination with carboplatin in patients with metastatic or recurrent platinum-sensitive high-grade serous ovarian cancer (NCT04907968), and the phase III randomized UP-NEXT trial to evaluate UpRi maintenance monotherapy vs placebo in patients with recurrent, platinum-sensitive high-grade serous NaPi2b-positive ovarian cancer (NCT05329545).

Table 2
Select ADCs under clinical investigation in gynecologic malignancies.

Target	ADC	Study	Patient Population	Estimated Primary Completion Date
B7-H4	XMT-1660	Phase I NCT05377996	Recurrent, advanced, or metastatic tumors, including ovarian, peritoneal, Fallopian tube, and endometrial cancer	January 2025
	AZD8205	Phase I/II NCT05123482	Advanced or metastatic solid malignancies, including serous ovarian cancer and endometrial cancer	May 2025
	SGN-B7H4V	Phase I NCT05194072	Unresectable, locally advanced or metastatic solid tumors, including ovarian, peritoneal, fallopian tube, and endometrial cancer	June 2025
FRα	STRO-002	Phase I NCT03748186	Relapsed and/or progressive high-grade serious epithelial ovarian, fallopian tube, or primary peritoneal cancer	August 2022
	STRO-002	Phase I NCT05200364	With bevacizumab in relapsed and/or progressive high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer	December 2023
	Mirvetuximab soravtansine (Mirv)	Phase II NCT03835819	With pembrolizumab in patients with FRα-positive microsatellite stable recurrent or persistent endometrial cancer	October 2023
		Phase II NCT04606914	With carboplatin in first-line treatment of patients receiving neoadjuvant chemotherapy with advanced-stage high-grade serious epithelial ovarian, fallopian tube, or primary peritoneal cancer who are FRα-positive	May 2023
		Phase II NCT05456685	With carboplatin in FRα-positive, recurrent platinum sensitive, high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer following 1 prior line of platinum-based chemotherapy	June 2024
		Phase II PICCOLO NCT05041257	FRα-positive, platinum-sensitive, high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancer	May 2023
		Phase III MIRASOL NCT04209855	Vs investigator's choice of chemotherapy in FRα-positive, platinum-resistant, high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancer	December 2022
		Phase III GLORIOSA NCT05445778	With bevacizumab vs bevacizumab alone as maintenance in FRα-positive, platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer	March 2027
	Farletuzumab ecteribulin (MORAb-202)	Phase I/II NCT04300556	Platinum-resistant advanced, recurrent or metastatic endometrial cancer Platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer	March 2025
HER2	Trastuzumab duoacarmazine (SYD985)	Phase II NCT04205630	HER2-expressing recurrent, advanced or metastatic endometrial carcinoma	December 2022
	Trastuzumab deruxtecan (T-DXd)	Phase I NCT04585958	With olaparib in HER2-expressing advanced cancers or endometrial cancer	January 2023
HER2 Trop-2	Trastuzumab deruxtecan (T-DXd) Datopotamab deruxtecan (Dato-DXd)	Phase I/II PETRA NCT04644068	With AZD5305 PARP inhibitor in ovarian, cervical, and endometrial cancers	July 2025
Mesothelin	Anetumab ravtansine	Phase II NCT03587311	With bevacizumab vs bevacizumab + paclitaxel in platinum-resistant or platinum refractory high-grade serous endometrioid, ovarian, fallopian tube, or primary peritoneal cancer	October 2023
NaPi2b	Upifitamab rilsodotin (UpRi)	Phase I UPGRADE NCT04907968	With carboplatin in platinum-sensitive recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer	November 2024
		Phase II UPLIFT NCT03319628	Platinum-resistant metastatic or recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer	April 2023
		Phase III UP-NEXT NCT05329545	In platinum-sensitive recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer expressing high levels of NaPi2b	September 2024
Trop-2	Sacituzumab govitecan (IMMU-132)	Phase II NCT04251416	Persistent or recurrent endometrial carcinoma that progressed after prior platinum-based chemotherapy or is platinum-refractory with elevated Trop-2 expression	February 2024
	SKB264	Phase I/II NCT04152499	Locally advanced unresectable/metastatic solid tumors including epithelial ovarian cancer refractory to available standard therapies	November 2024

Abbreviations: B7-H4, B7 family homolog 4; FR, folate receptor; HER2, human epidermal growth factor receptor 2; NaPi2b; sodium-dependent phosphate transport protein 2B; PARP, poly(ADP-ribose) polymerase; Trop-2, trophoblast cell surface antigen 2.

Two ADCs targeting FRα, luveltamab tazevibulin (STRO-002) and farletuzumab ecteribulin (MORAB-202), have published results from early studies in platinum-resistant ovarian cancer. Luveltamab tazevibulin utilizes a FRα-targeting human monoclonal antibody and proprietary drug-linker (SC239) with a 3-aminophenyl-hemiasterlin payload and has a DAR of 4 [103]. In a phase I dose escalation study, luveltamab tazevibulin was associated with an ORR of 32% [104]. The most common grade 3/4 treatment-related AEs included neutrophil count decreased (36%) and neutropenia (33%); 8% experienced grade 3 neuropathy and 13% had grade 3 arthralgia, but there were no reports of ocular toxicities. Interim results from a dose expansion study of luveltamab tazevibulin in patients with advanced ovarian cancer have been publicly shared [105], and formal presentation of these results are anticipated in the near future. Farletuzumab ecteribulin employs a humanized FRα monoclonal antibody with an eribulin payload and has a DAR of 4. Recently, a phase I dose expansion study reported an ORR of 25% at 0.9 mg/kg and 52% at 1.2 mg/kg farletuzumab ecteribulin. The most common AEs at 0.9 and 1.2 mg/kg, respectively, were ILD/pneumonitis (38% and 67%) and pyrexia (33% and 43%). Of note, ILD/pneumonitis was observed in 1 patient at grade $\geq$ 3 at the 1.2 mg/kg dose, but it led to discontinuation in 5 patients at this dose. Dose optimization studies for farletuzumab ecteribulin are ongoing [53].

Sacituzumab govitecan, which gained approval in 2020 for the treatment of metastatic breast cancer, is currently being evaluated in endometrial cancer. In a phase I basket study, sacituzumab govitecan was shown to have preliminary efficacy in patients with advanced relapsed endometrial cancer, with an ORR of 22% [106]. A phase II study (NCT04251416) is underway. Data are sparse for additional ADCs in early clinical development, but many trials are underway with expected readouts in the next 3 years (Table 2).

Future directions and conclusions

During the past decade, successful ADC trials have provided valuable lessons that can lead to improved designs for future compounds and clinical trials. Discovery and validation of appropriate target antigens are critical to successful ADC-based strategies. Because the down-regulation and/or mutation of the antigen can trigger therapeutic resistance to the ADC, it is important that surface expression of the antigen not be downregulated by the effects of repeated stimulation during treatment [30,107]. There are numerous potential mechanisms of resistance to ADCs, including increased expression of drug transporters and decreased antibody binding (Fig. 2); the modularity of ADCs allows for the replacement of specific components to overcome various resistance mechanisms [107–109].

The implications of ADC resistance regarding treatment sequencing with therapies acting on the same target or ADCs acting via the same payload remain unknown, but these questions are areas of active research. Through advanced research in protein engineering, innovative immunostimulatory ADC platforms that use stimulator of interferon gene agonists, toll-like receptor agonists and antibody-chemokine conjugates, may enable engagement of immune responses in addition to the expected cytotoxic activity of these compounds [25]. ADCs in clinical development also include novel constructs in which standard cytotoxic payloads were replaced with proapoptotic proteins, such as BCL-X_L [110]. Further, several trials in patients with gynecologic malignancies assess the benefits of combining ADCs with established therapies such as PARP inhibitors, bevacizumab, or chemotherapy (Table 2).

In conclusion, metastatic gynecologic malignancies are difficult to treat, and suitable therapies in this setting represent a significant care gap for patients. ADCs have emerged as an encouraging class of targeted therapies designed to deliver potent cytotoxic drugs directly to cancer cells while sparing healthy cells, thus limiting systemic toxicity. The evolving landscape of ADC therapies in gynecologic cancers has proven their potential for better outcomes in patients with metastatic disease, and current and future innovative research will provide opportunities for optimal design and improved clinical activity.

CRediT authorship contribution statement

Anthony Tolcher: Conceptualization, Writing – review & editing. **Erika Hamilton:** Conceptualization, Writing – review & editing. **Robert L. Coleman:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

A. Tolcher: President and Founder of Experimental Therapeutics, LLC d/b/a/ NEXT Oncology; Consulting/advisory role with: AbbVie, Aclaris Therapeutics, Agenus, Asana Biosciences, Ascentage, AxImmune, Bayer, BluPrint Oncology, Daiichi Sankyo, Gilde Healthcare Partners, HBM Partners, Idea Pharma, Immuneering, Immunomet Therapeutics, Impact Therapeutics, Karma Oncology, Kirilys Therapeutics, Lengo Therapeutics, Link Immunotherapeutics, Mekanistic Therapeutics, Menarini Ricerche, Mersana, Nanobiotix, Novo Nordisk, Nerviano Medical Sciences, Nurix Therapeutics, Ocellaris Pharma, Inc. & Eli Lilly, Partner Therapeutics, Pfizer, Qualigen Therapeutics, Pierre Fabre, Roche, Ryvu Therapeutics, Seagen, SK Life Science, Sotio Biotechnology, Spirea Limited Inc, Sunshine Guojian Pharmaceutical (Shanghai) Co., Ltd, Transcenta Therapeutics, Trillium Therapeutics, Verastem Oncology, Vrise Therapeutics, and Zentalis Pharmaceuticals; Advisory board for: Adagene, Aro Biotherapeutics, Bioinvent, Boeringer Ingelheim International, Bright Peak Therapeutics, Deka Biosciences, Eleven Bio, Elucida, EMD Serono/Merck, Hiber Cell, Ikena Oncology, Immunome, Janssen, NBE Therapeutics, Pelican, Jazz, Pieris Pharma, Pyxis Oncology, Senti Biosciences, Vincerx, Zielbio, Zymeworks Biopharmaceuticals, Mirati, and Roche. **E. Hamilton:** Research funding to institution from: AbbVie, Acerta Pharma, Accutar Biotechnology, ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, Compugen, Cullinan-Florentine, Curis, CytomX, Daiichi Sankyo, Dana Farber Cancer Inst, Dantari, Deciphera, Duality Biologics, eFFECTOR Therapeutics, Ellipses Pharma, Elucida Oncology, EMD Serono, FujiFilm, G1 Therapeutics, H3 Biomedicine, Harpoon, Hutchinson MediPharma, Immunogen, Immunomedics, Incyte, Infinity Pharmaceuticals, InventisBio, Jacobio, Karyopharm, K-Group Beta, Lilly, Loxo Oncology, Lycera, Mabspace Biosciences, Macrogenics, MedImmune, Mersana, Merus, Millennium, Molecular Templates, Novartis, Nucana, Olema, OncoMed, Onconova Therapeutics, Oncothyreon, ORIC Pharmaceuticals, Orinove, Pfizer, PharmaMar, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Plexxikon, Radius Health, Regeneron, Relay Therapeutics, Repertoire Immune Medicine, Rgenix, Roche/Genentech, SeaGen, Sermonix Pharmaceuticals, Shattuck Labs, StemCentRx, Sutro, Syndax, Syros, Taiho, TapImmune, Tesaro, Tolmar, Torque Therapeutics, Treadwell Therapeutics, Verastem, Vincerx Pharma, Zenith Epigenetics, and Zymeworks; Consulting/advisory role with: Arcus, AstraZeneca, Daiichi Sankyo, Deciphera Pharmaceuticals, Ellipses Pharma, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo,

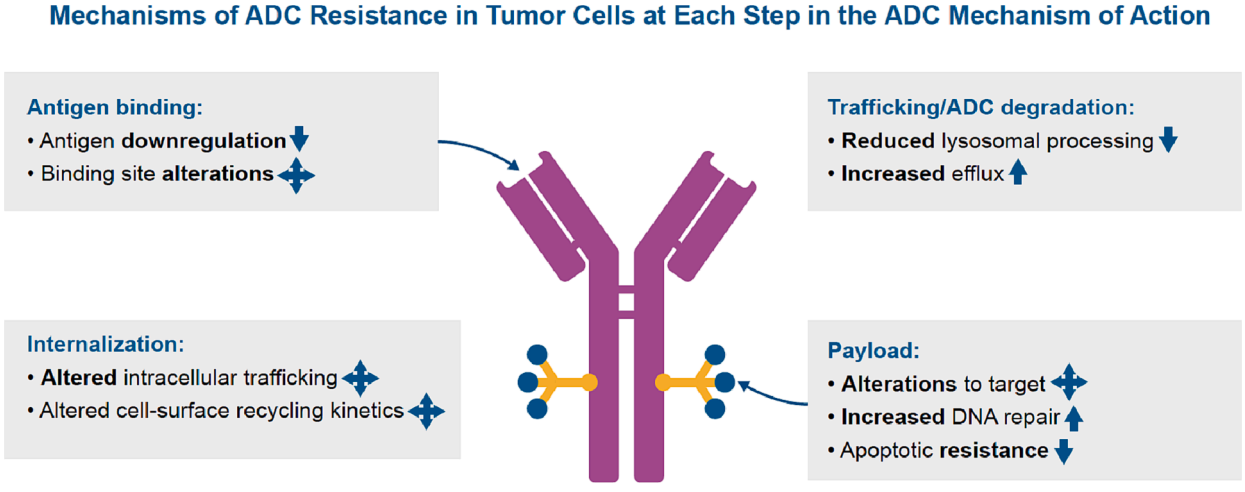

Fig. 2. Mechanisms of resistance to ADCs [107–109]. Resistance may occur at any stage in the ADC mechanism of action. Abbreviations: ADC, antibody-drug conjugate.

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References

[1] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Ovarian Cancer. <https://seer.cancer.gov/statfacts/html/ovary.html> [accessed July 20, 2022].
[2] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Uterine Cancer. <https://seer.cancer.gov/statfacts/html/corp.html> [accessed July 20, 2022].
[3] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Cervical Cancer. <https://seer.cancer.gov/statfacts/html/cervix.html> [accessed July 20, 2022].
[4] Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039–45.
[5] Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473–83.
[6] Tewari KS, Sill MW, Long 3rd HJ, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014;370:734–43.
[7] Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med 2021;385:1856–67.
[8] Makker V, Colombo N, Casado Herraez A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med 2022;386:437–48.
[9] Gonzalez-Martin A, Pothuri B, Vergote I, DePont CR, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391–402.
[10] Monk BJ, Parkinson C, Lim MC, O'Malley DM, Oaknin A, Wilson MK, et al. A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J Clin Oncol 2022;40:3952–64.
[11] 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.
[12] Creutzberg CL, Lu KH, Fleming GF. Uterine cancer: adjuvant therapy and management of metastatic disease. J Clin Oncol 2019;37:2490–500.
[13] Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N, et al. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv72 -iv83.
[14] Gaillard S, Oaknin A, Ray-Coquard I, Vergote I, Scambia G, Colombo N, et al. Lurbinectedin versus pegylated liposomal doxorubicin or topotecan in patients with platinum-resistant ovarian cancer: a multicenter, randomized, controlled, open-label phase 3 study (CORAIL). Gynecol Oncol 2021;163:237–45.
[15] Moore KN, Oza AM, Colombo N, Oaknin 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.
[16] Pujade-Lauraine E, Fujiwara K, Ledermann JA, Oza AM, Kristeleit R, Ray-Coquard IL, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. Lancet Oncol 2021;22:1034–46.
[17] Hamanishi J, Takeshima N, Katsumata N, Ushijima K, Kimura T, Takeuchi S, et al. Nivolumab versus gemcitabine or pegylated liposomal doxorubicin for patients with platinum-resistant ovarian cancer: open-label, randomized trial in Japan (NINJA). J Clin Oncol 2021;39:3671–81.
[18] Lundqvist EA, Fujiwara K, Seoud M. Principles of chemotherapy. Int J Gynaecol Obstet 2015;131(Suppl 2):S146–9.
[19] Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022.
[20] Pang SS, Murphy M, Markham MJ. Current management of locally advanced and metastatic cervical cancer in the United States. JCO Oncol Pract 2022;18:417–22.
[21] Calo CA, O'Malley DM. Antibody-drug conjugates for the treatment of ovarian cancer. Expert Opin Biol Ther 2021;21:875–87.
[22] Tarantino P, Carmagnani Pestana R, Corti C, Modi S, Bardia A, Tolaney SM, et al. Antibody-drug conjugates: smart chemotherapy delivery across tumor histologies. CA Cancer J Clin 2022;72:165–82.
[23] Colombo R, Rich JR. The therapeutic window of antibody drug conjugates: a dogma in need of revision. Cancer Cell 2022;40:1255–63.
[24] Coats S, Williams M, Kebble B, Dixit R, Tseng L, Yao NS, et al. Antibody-drug conjugates: future directions in clinical and translational strategies to improve the therapeutic index. Clin Cancer Res 2019;25:5441–8.
[25] Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody-drug conjugates for cancer therapy. Nat Rev Clin Oncol 2021;18:327–44.
[26] Tarcsa E, Guffroy MR, Falahatpisheh H, Phipps C, Kalvass JC. Antibody-drug conjugates as targeted therapies: are we there yet? A critical review of the current clinical landscape. Drug Discov Today Technol 2020;37:13–22.
[27] Tolcher AW. The evolution of antibody-drug conjugates: a positive inflexion point. Am Soc Clin Oncol Educ Book 2020;40:1–8.
[28] Cetinbas NM, Catcott KC, Monnell T, Soomer-James J, Bentley K, Clardy S, et al. Abstract 2114: Tumor cell-targeted STING-agonist antibody-drug conjugates achieve potent anti-tumor activity by delivering STING agonist specifically to tumor cells andFcγRI-expressing subset of myeloid cells. Cancer Res 2022;82:2114 -.
[29] Martin-Sabroso C, Lozza I, Torres-Suarez AI, Fraguas-Sanchez AI. Antibody-antineoplastic conjugates in gynecological malignancies: current status and future perspectives. Pharmaceutics 2021:13.
[30] Hoffmann RM, Coumbe BGT, Josephs DH, Mele S, Ilieva KM, Cheung A, et al. Antibody structure and engineering considerations for the design and function of Antibody Drug Conjugates (ADCs). Oncoimmunology 2018;7:e1395127.
[31] Baah S, Laws M, Rahman KM. Antibody-drug conjugates-a tutorial review. Molecules 2021;26.
[32] Khongorzul P, Ling CJ, Khan FU, Ihsan AU, Zhang J. Antibody-drug conjugates: a comprehensive review. Mol Cancer Res 2020;18:3–19.
[33] Tang H, Liu Y, Yu Z, Sun M, Lin L, Liu W, et al. The analysis of key factors related to ADCs structural design. Front Pharmacol 2019;10:373.
[34] Tong JTW, Harris PWR, Brimble MA, Kavianinia I. An insight into FDA approved antibody-drug conjugates for cancer therapy. Molecules 2021;26.
[35] Vankemmelbeke M, Durrant L. Third-generation antibody drug conjugates for cancer therapy–a balancing act. Ther Deliv 2016;7:141–4.
[36] 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.
[37] James BH, Papakyriacou P, Gardener MJ, Gliddon L, Weston CJ, Lalor PF. The contribution of liver sinusoidal endothelial cells to clearance of therapeutic antibody. Front Physiol 2021;12:753833.
[38] Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. Exp Mol Med 2019;51:1–9.
[39] Lee EK, Liu JF. Antibody-drug conjugates in gynecologic malignancies. Gynecol Oncol 2019;153:694–702.
[40] Bohnke N, Berger M, Griebenow N, Rottmann A, Erkelenz M, Hammer S, et al. A Novel NAMPT inhibitor-based antibody-drug conjugate payload class for cancer therapy. Bioconjug Chem 2022;33:1210–21.
[41] Lu J, Jiang F, Lu A, Zhang G. Linkers having a crucial role in antibody-drug conjugates. Int J Mol Sci 2016;17:561.
[42] Sheyi R, de la Torre BG, Albericio F. Linkers: an assurance for controlled delivery of antibody-drug conjugate. Pharmaceutics 2022;14.
[43] Choy CJ, Geruntho JJ, Davis AL, Berkman CE. Tunable pH-sensitive linker for controlled release. Bioconjug Chem 2016;27:824–30.
[44] 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.
[45] 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.
[46] 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.
[47] Richardson DL, Hamilton EP, Barve M, Anderson CK, Taylor SK, Lakhani N, et al. Updated results from the phase 1b expansion study of upifitamab rilsodotin (UpRi; MT-1536), a NaPi2b-directed dolaflexin antibody drug conjugate (ADC) in ovarian cancer. Society of Gynecologic Oncology (SGO) Annual Meeting on Women's. Cancer 2022.
[48] ELAHERE™ (mirvetuximab soravtansine-gynx) injection, for intravenous use. Prescribing Information. ImmunoGen, Inc. Waltham, MA, United States. 2022.
[49] TIVDAK® (tisotumab vedotin-tftv) for injection, for intravenous use. Prescribing information. Seagen Inc. Bothell, WA, United States; 2022.
[50] Hamilton EP, Bragaia VPH, Yeo W, Kim S-B, Bianchini G, Yamashita T, et al. Trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in patients (pts) with HER2-positive (HER2+) unresectable and/or metastatic breast cancer (mBC): Safety follow-up of the randomized, phase 3 study DESTINY-Breast03. J Clin Oncol 2022;40.
[51] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 2022;387:9–20.

[52] Heitz N, Greer SC, Halford Z. A review of tisotumab vedotin-tftv in recurrent or metastatic cervical cancer. Ann Pharmacother 2022.

[53] Nishio S, Yunokawa M, Matsumoto K, Takehara K, Hasegawa K, Hirashima Y, et al. Safety and efficacy of MORAb-202 in patients (pts) with platinum-resistant ovarian cancer (PROC): results from the expansion part of a phase 1 trial. J Clin Oncol 2022;40.

[54] Zhu Y, Liu K, Wang K, Zhu H. Treatment-related adverse events of antibody-drug conjugates in clinical trials: a systematic review and meta-analysis. Cancer 2023; 129:283–95.

[55] Kim SK, Ursell P, Coleman RL, Monk BJ, Vergote I. Mitigation and management strategies for ocular events associated with tisotumab vedotin. Gynecol Oncol 2022;165:385–92.

[56] Yurkovetskiy AV, Bodyak ND, Yin M, Thomas JD, Clardy SM, Conlon PR, et al. Dolaflexin: a novel antibody-drug conjugate platform featuring high drug loading and a controlled bystander effect. Mol Cancer Ther 2021;20:885–95.

[57] Nejadmoghaddam MR, Minai-Tehrani A, Ghahremanzadeh R, Mahmoudi M, Dinarvand R, Zarnani AH. Antibody-drug conjugates: possibilities and challenges. Avicenna J Med Biotechnol 2019;11:3–23.

[58] Weisser NE, Wickman G, Abraham L, O'Toole J, Harbourne B, Guedia J, et al. Abstract 1005: the bispecific antibody zanidatamab's (ZW25's) unique mechanisms of action and durable anti-tumor activity in HER2-expressing cancers. Cancer Res 2021;81.

[59] Staudacher AH, Brown MP. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? Br J Cancer 2017;117:1736–42.

[60] Gebleux R, Stringhini M, Casanova R, Soltermann A, Neri D. Non-internalizing antibody-drug conjugates display potent anti-cancer activity upon proteolytic release of monomethyl auristatin E in the subendothelial extracellular matrix. Int J Cancer 2017;140:1670–9.

[61] Giansanti F, Capone E, Ponziani S, Piccolo E, Gentile R, Lamolinara A, et al. Secreted Gal-3BP is a novel promising target for non-internalizing Antibody-Drug Conjugates. J Control Release 2019;294:176–84.

[62] Yasunaga M, Manabe S, Tarin D, Matsumura Y. Cancer-stroma targeting therapy by cytotoxic immunoconjugate bound to the collagen 4 network in the tumor tissue. Bioconjug Chem 2011;22:1776–83.

[63] Fu Z, Li S, Han S, Shi C, Zhang Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduct Target Ther 2022;7:93.

[64] Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med 2021;384:1529–41.

[65] Donaghy H. Effects of antibody, drug and linker on the preclinical and clinical toxicities of antibody-drug conjugates. MAbs 2016;8:659–71.

[66] Hamblett KJ, Senter PD, Chace DF, Sun MM, 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.

[67] Goldenberg DM, Cardillo TM, Govindan SV, Rossi EA, Sharkey RM. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). Oncotarget 2015;6:22496–512.

[68] Yurkovetskiy AV, Yin M, Bodyak N, Stevenson CA, Thomas JD, Hammond CE, et al. A polymer-based antibody-vinca drug conjugate platform: characterization and preclinical efficacy. Cancer Res 2015;75:3365–72.

[69] Strop P, Delaria K, Foletti D, Witt JM, Hasa-Moreno A, Poulsen K, et al. Site-specific conjugation improves therapeutic index of antibody drug conjugates with high drug loading. Nat Biotechnol 2015;33:694–6.

[70] Clardy SM, Yurkovetskiy A, Yin M, Gumerov D, Xu L, Ter-Ovanesyan E, et al. Abstract 754: Unique pharmacologic properties of Dolaflexin-based ADCs—a controlled bystander effect. Cancer Res 2018;78:754 -.

[71] Bodyak ND, Mosher R, Yurkovetskiy AV, Yin M, Bu C, Conlon PR, et al. The dolaflexin-based antibody-drug conjugate XMT-1536 targets the solid tumor lineage antigen SLC34A2/NaPi2b. Mol Cancer Ther 2021;20:896–905.

[72] Toader D, Damelin M, Dirksen A, Fesler SP, Collins SD, Nehilla BJ, et al. Abstract 2687: Dolasynthen–a novel, homogeneous Auristatin F hydroxypropyl amide antibody-drug conjugate platform. Cancer Res 2019;79:2687 -.

[73] Fessler SP, Wang J, Collins SD, Qin L, Avocetien K, Xu L, et al. Abstract 907: XMT-1660, a B7-H4-targeted Dolasynthen antibody-drug conjugate for the treatment of breast cancer. Cancer Res 2021;81:907 -.

[74] Conilh L, Sadilkova L, Viricel W, Dumontet C. Payload diversification: a key step in the development of antibody-drug conjugates. J Hematol Oncol 2023;16:3.

[75] Conilh L, Fournet G, Fourmaux E, Murcia A, Matera EL, Joseph B, et al. Exatecan antibody drug conjugates based on a hydrophilic polysarcosine drug-linker platform. Pharmaceuticals (Basel) 2021:14.

[76] Singh H, Leyton VJ. Abstract P062: The CL2A-SN38 linker-payload system conjugated to trastuzumab results in improved cellular cytotoxicity over time relative to T-DM1. Mol Cancer Ther 2021;20:P062 -P.

[77] Levengood MR, Zhang X, Hunter JH, Emmerton KK, Miyamoto JB, Lewis TS, et al. Orthogonal cysteine protection enables homogeneous multi-drug antibody-drug conjugates. Angew Chem Int Ed Engl 2017;56:733–7.

[78] Das S, Sanches M, Farber P, Wong J, Hernandez A, Ding T, et al. Novel IgG1 Cystein Insertion Sites Enable Site-Specific Conjugation and Precise Control of Drug to Antibody Ratio. Presented at: Antibody Engineering and Therapeutics; December 4–8, 2022; San Diego, CA. <https://www.zymeworks.com/wp-content/uploads/2023/01/Site-specific-Poster_AET_2022-final.pdf>.

[79] Hamblett K, Barnscher S, Davies R, Hammond P, Hernandez A, Wickman G, et al. Abstract P6-17-13: ZW49, a HER2 targeted biparatopic antibody drug conjugate for the treatment of HER2 expressing cancers. Cancer Res 2019;79:P6-17-3-P6–3.

[80] Jhaveri K, Han H, Dotan E, Oh D, Ferrario C, Tolcher AW, et al. Preliminary results from a phase I study using the bispecific, human epidermal growth factor 2 (HER2)-targeting antibody-drug conjugate (ADC) zanidatamab zovodotin (SW49) in solid cancers. Ann Oncol 2022;33(suppl_7):S197–224.

[81] Norsworthy KJ, Ko CW, Lee JE, Liu J, John CS, Przepiorka D, et al. FDA Approval Summary: Mylotarg for Treatment of Patients with Relapsed or Refractory CD33-Positive Acute Myeloid Leukemia. Oncologist 2018;23:1103–8.

[82] Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. N Engl J Med 2018;378:331–44.

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

[84] Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet 2022.

[85] Coleman RL, Lorusso D, Gennigens C, Gonzalez-Martin A, Randall L, Cibula D, et al. 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.

[86] 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.

[87] Garcia AA, Blessing JA, Vaccarello L, Roman LD, Gynecologic Oncology Group S. Phase II clinical trial of docetaxel in refractory squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Am J Clin Oncol 2007;30:428–31.

[88] Lorusso D, Ferrandina G, Pignata S, Ludovisi M, Vigano R, Scalone S, et al. Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. Ann Oncol 2010;21:61–6.

[89] Miller DS, Blessing JA, Bodurka DC, Bonebrake AJ, Schorge JO, Gynecologic OG. 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.

[90] Ab O, Whiteman KR, Bartle LM, Sun X, Singh R, Tavares D, et al. IMGN853, a Folate Receptor-alpha (FRalpha)-targeting antibody-drug conjugate, exhibits potent targeted antitumor activity against FRalpha-expressing tumors. Mol Cancer Ther 2015;14:1605–13.

[91] Manzano A, Ocana A. Antibody-Drug Conjugates: A Promising Novel Therapy for the Treatment of Ovarian Cancer. Cancers (Basel). 2020;12.

[92] Matulonis U, Lorusso D, Oaknin A, Pignata S, Denys H, Colombo N, et al. Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study. Presented at: Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer 2022; Phoenix, AZ.

[93] Matulonis UA, Oaknin A, Pignata S, denys H, Colombo N, Gorp TV,, et al. Mirvetuximab soravtansine (MIRV) in patients with platinum-resistant ovarian cancer with high folate receptor alpha (FRα) expression: Characterization of antitumor activity in the SORAYA study. J Clin Oncol 2022;40:5512-..

[94] ImmunoGen announces acceptance of biologics license application for mirvetuximab soravtansine in ovarian cancer by US food and drug administration with priority review. News release. ImmunoGen, Inc; May 23, 2022. <https://investor.immunogen.com/news-releases/news-release-details/immunogen-announces-acceptance-biologics-license-application> [accessed August 8, 2022].

[95] Moore KN, Konecny GE, Garcia Y, Martin L, Floquet A, O'Malley D, et al. MIRASOL: a randomized, open-label, phase 3 study of mirvetuximab soravtansine vs investigator's choice of chemotherapy in advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor alpha expression. Presented at: Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer 2022. Phoenix, AZ.

[96] Tymon-Rosario J, Gorman M, Richardson DL, Washington C, Santin AD. Advances in antibody-drug conjugates for gynecologic malignancies. Curr Opin Obstet Gynecol 2023;35:6–14.

[97] Hamilton EP, Barve MA, Tolcher AW, Buscema J, Papadopoulos KP, Zarwan C, et al. 836P Safety and efficacy of XMT-1536 in ovarian cancer: a subgroup analysis from the phase I expansion study of XMT-1536, a NaPi2b antibody-drug conjugate. Ann Oncol 2020;31:S627–8.

[98] 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.

[99] Banerjee S, Drapkin R, Richardson DL, Birrer M. Targeting NaPi2b in ovarian cancer. Cancer Treat Rev 2023;112:102489.

[100] Gryshkova V, Goncharuk I, Gurtovyy V, Khozhayenko Y, Nespryadko S, Vorobjova L, et al. The study of phosphate transporter NAPI2B expression in different histological types of epithelial ovarian cancer. Exp Oncol 2009;31: 37–42.

[101] Jarzab B, Wiench M, Fujarewicz K, Simek K, Jarzab M, Oczko-Wojciechowska M, et al. Gene expression profile of papillary thyroid cancer: sources of variability and diagnostic implications. Cancer Res 2005;65:1587–97.

[102] Lin K, Rubinfeld B, Zhang C, Firestein R, Harstad E, Roth L, et al. Preclinical development of an anti-NaPi2b (SLC34A2) antibody-drug conjugate as a therapeutic for non-small cell lung and ovarian cancers. Clin Cancer Res 2015;21: 5139–50.

[103] Li X, Abrahams C, Zhou S, Krimm S, Henningsen R, Stephenson H, et al. Abstract 1782: Discovery and activity of STRO-002, a novel ADC targeting folate receptor alpha for ovarian and endometrial cancer. Cancer Res 2018;78.
[104] Naumann RW, Braiteh FS, Martin LP, Hamilton EP, Diaz JP, Diab S, et al. Phase 1 dose-escalation study of STRO-002, an antifolate receptor alpha (FRα) antibody drug conjugate (ADC), in patients with advanced, progressive platinum-resistant/refractory epithelial ovarian cancer (EOC). J Clin Oncol 2021;39.
[105] Sutro Biopharma Announces Interim Data From Dose-Expansion Cohort of STRO-002 Phase 1 Study for Patients With Advanced Ovarian Cancer. News release. Sutro Biopharma, Inc; Jan 5, 2022. <https://www.sutrobio.com/sutro-biopharma-announces-interim-data-from-dose-expansion-cohort-of-stro-002-phase-1-study-for-patients-with-advanced-ovarian-cancer/> [accessed Dec 15, 2022].
[106] Bardia A, Messersmith WA, Kio EA, Berlin JD, Vahdat L, Masters GA, et al. Sacituzumab govitecan, 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.
[107] Collins DM, Bossenmaier B, Kollmorgen G, Niederfellner G. Acquired resistance to antibody-drug conjugates. Cancers (Basel) 2019;11.
[108] Loganzo F, Sung M, Gerber HP. Mechanisms of resistance to antibody-drug conjugates. Mol Cancer Ther 2016;15:2825–34.
[109] Diaz-Rodriguez E, Gandullo-Sanchez L, Ocana A, Pandiella A. Novel ADCs and strategies to overcome resistance to anti-HER2 ADCs. Cancers (Basel) 2021;14.
[110] Tolcher AW, Carneiro BA, Dowlati A, Razak ARA, Chae YK, Villella JA, et al. A first-in-human study of mirzotamab clezutoclax as monotherapy and in combination with taxane therapy in relapsed/refractory solid tumors: Dose escalation results. J Clin Oncol 2021;39.