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Authors

Campos, Maira P
Konecny, Gottfried E

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The target invites a foe: antibody–drug conjugates in gynecologic oncology

Maira P. Campos and Gottfried E. Konecny

Purpose of review

Antibody–drug conjugates (ADCs) represent a promising new class of cancer therapeutics. Currently more than 60 ADCs are in clinical development, however, only very few trials focus on gynecologic malignancies. In this review, we summarize the most recent advances in ADC drug development with an emphasis on how this progress relates to patients diagnosed with gynecologic malignancies and breast cancer.

Recent findings

The cytotoxic payloads of the majority of the ADCs that are currently in clinical trials for gynecologic malignancies or breast cancer are auristatins (MMAE, MMAF), maytansinoids (DM1, DM4), calicheamicin, pyrrolobenzodiazepines and SN-38. Both cleavable and noncleavable linkers are currently being investigated in clinical trials. A number of novel target antigens are currently being validated in ongoing clinical trials including folate receptor alpha, mesothelin, CA-125, NaPi2b, NOTCH3, protein tyrosine kinase-like 7, ephrin-A4, TROP2, CEACAM5, and LAMP1. For most ADCs currently in clinical development, dose-limiting toxicities appear to be unrelated to the targeted antigen but more tightly associated with the payload. Rational drug design involving optimization of the antibody, the linker and the conjugation chemistry is aimed at improving the therapeutic index of new ADCs.

Summary

Antibody–drug conjugates can increase the efficacy and decrease the toxicity of their payloads in comparison with traditional cytotoxic agents. A better and quicker translation of recent scientific advances in the field of ADCs into rational clinical trials for patients diagnosed with ovarian, endometrial or cervical cancer could create real improvements in tumor response, survival and quality of life for our patients.

Keywords

antibody–drug conjugates, breast cancer, gynecologic oncology, mirvetuximab soravtansine (IMGN853), sacituzumab govitecan (IMMU-132), anatumab ravtansine (BAY 94-9343)

INTRODUCTION

Despite significant progress in the treatment of certain forms of cancer, it must be emphasized that very little progress has been made in the identification of novel targeted therapies for women diagnosed with gynecologic malignancies. Consistent with this lack of progress survival rates for patients diagnosed with ovarian, endometrial, or cervical cancer have at large remained unchanged or have only minimally improved over the last 30 years [1,2]. Advances in the understanding of the molecular pathogenesis of ovarian, endometrial, and cervical cancer coupled with the development of novel, targeted therapies are needed to improve patient outcomes.

Antibody–drug conjugates (ADCs) represent a very promising new class of cancer therapeutics that are designed to harness the specificity of antibodies with the cytotoxicity of chemotherapeutic agents.

Emerging clinical data with ADCs suggest that these new drugs have great potential to become effective and well tolerated anticancer therapeutics. The recent approvals of brentuximab vedotin (Adcetris), directed at CD30, which is expressed in Hodgkin lymphoma and anaplastic large cell lymphoma and ado-trastuzumab emtansine (T-DM1, Kadcyla) directed at HER2 expressed in breast cancer, have

Division of Hematology/Oncology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

Correspondence to Gottfried E. Konecny, Division of Hematology-Oncology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, CA 90095, USA.

E-mail: gkonecny@mednet.ucla.edu

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KEY POINTS

- Antibody–drug conjugates can increase the efficacy and decrease the toxicity of their payloads in comparison with traditional cytotoxic agents.
- An optimal ADC requires the appropriate combination of three well defined components, the antibody, the linker, and the payload.
- Optimization of the antibody, the linker and the conjugation chemistry is aimed at improving the therapeutic index of new ADCs.
- A better translation of recent scientific advances in the field of ADCs into rational clinical trials for patients diagnosed with women's cancers will create real improvements in survival and quality of life.

prompted the clinical development of other novel ADCs [3,4]. Currently more than 60 ADCs are in clinical development [5,6[¶]]. However, only very few of these trials focus on gynecologic malignancies. Clearly, ADCs need to be explored more intensively in gynecologic oncology because there is little doubt that a better and quicker translation of recent scientific advances in the field of ADCs into rational clinical trials for patients diagnosed with ovarian, endometrial or cervical cancer could create real improvements in tumor response, survival and quality of life for our patients. In this review, we summarize the most recent advances in ADC drug development with an emphasis on how this progress relates to patients diagnosed with gynecologic malignancies and breast cancer. ADCs are composed of three well defined components, the antibody, the linker, and the payload. An optimal ADC that achieves maximum efficacy with minimal toxicity requires the appropriate combination of each of these components.

PAYLOADS

The majority of payloads utilized in ADCs are highly potent cytotoxic agents with an efficacy in the low nanomolar or picomolar range, which is required because only a very small amount (<1%) of the injected dose of an antibody localizes to the antigen-expressing tumor. The cytotoxic payloads of the majority of the ADCs that are currently in clinical trials are primarily based on two families of antimetabolic agents: auristatins and maytansinoids [6[¶]]. The auristatins and maytansinoids act by inhibiting tubulin assembly. The auristatins monomethyl auristatin E (MMAE, vendotin) and MMAF (mafodotin) are synthetic analogues of dolastatin 10, which is a natural antimetabolic drug that is extracted from the

sea hare *Dolabella auricularia* and is by itself too toxic to be used in an unconjugated form [7]. MMAE and MMAF have high potency, are water soluble, and are suitable for the attachment of stable linkers. Moreover, ADCs are now designed to not only kill antigen-positive cells but also other cells in the vicinity, irrespective of the expression of the target antigen on their surface; this is known as the 'bystander' effect. The charge of the drugs that are released from ADCs determines the 'bystander' potency. For ADCs that incorporate MMAE, such as brentuximab vedotin, cleavage of the ADC releases MMAE, which is neutral and able to cross biomembranes and kill neighboring epithelial cells. In contrast, for ADCs that incorporate MMAF, cleavage results in a metabolite with a charged residue, which does not cross membranes and is so less toxic to 'bystander' cells than MMAE. Another class of ADCs are those based on the maytansinoids (DM1 and DM4). DM1 (emtansine, mertansine) and DM4 (soravtansine, ravtansine) are derived from maytansine, which is a natural benzoansamacyclolide product isolated from the bark of the African shrub *Maytenus ovatus* [6[¶]]. Maytansine inhibits the assembly of microtubules by binding to tubulin similar to the vinca alkaloids, but is a far more potent cytotoxic agent. In fact, it failed as an anticancer agent in clinical trials because of its systemic toxicity whenever given as an unconjugated drug [8]. Other novel payloads that are in clinical development include calicheamicin, which is a highly potent antitumor antibiotic originally isolated from the actinomycete *Micromonospora echinospora*. It binds to the minor groove of DNA and cleaves double-stranded DNA in a site-specific manner [9]. Duocarmycins are DNA minor groove-alkylating agents and analogues that have been conjugated to trastuzumab, and the resultant ADCs are being investigated as 'biobetter' versions of trastuzumab emtansine [10], which have demonstrated antitumor activity in preclinical breast cancer models that have low expression levels of HER2 [11]. Further novel payloads that are in clinical development include pyrrolobenzodiazepines (PBDs), which are based on naturally occurring antitumor antibiotics that bind to the DNA minor groove in a sequence-specific manner [12]. A PBD-based ADC, SC-003, is currently being tested in a phase I trial in patients with recurrent ovarian cancer. SN-38, the active metabolite of the anticancer prodrug irinotecan, which acts via inhibition of DNA topoisomerase 1 is approximately 1000 times more potent than irinotecan but cannot be given directly to patients because of its toxicity and poor solubility. The antibody-SN-38 conjugate sacituzumab govitecan (IMMU-132) targets TROP2 [13^{¶¶}]. Sacituzumab govitecan has received the Food and Drug

Administration (FDA) breakthrough therapy designation for the treatment of patients with triple negative breast cancer (TNBC) who have failed at least two previous therapies for metastatic disease.

The expression of a target antigen on normal cells may result in specific toxicities whereas early cleavage of the linker, releasing free drug, may produce more systemic toxicities.

However, for most ADCs currently in clinical development, dose-limiting toxicities appear to be unrelated to the targeted antigen but more tightly associated with the payload. For example, reversible ocular toxicity specific to the cornea has been reported as the dose-limiting toxicity for DM4 conjugated antibodies targeting antigens as diverse as CD19, folate receptor alpha and mesothelin, none of which are thought to have significant expression in the eye [14]. MMAE may induce peripheral neuropathy and neutropenia; MMAF has been associated with thrombocytopenia and ocular toxicities. DM1 causes gastrointestinal effects as well as thrombocytopenia and neutropenia. Ocular toxicity is the most common adverse event with DM4 conjugated ADCs. Calicheamicin causes thrombocytopenia and hepatic dysfunction. Early studies with SN-38 conjugated drugs suggest neutropenia to be a frequent toxicity. A recent comprehensive review of the ocular toxicities reported for ADCs has highlighted the variety of ocular events that are associated with ADCs, with blurred vision, keratitis, dry eye and microcystic epithelial damage being the most commonly reported [15]. There is a clear payload association, with ocular toxicity typically induced by ADCs that include DM4 and MMAF. Conversely, ocular events are rarely described for ADCs utilizing MMAE [15].

LINKERS

The stability of the linker has great impact on the toxicities, which are then exerted by the payload. A more stable linker will release the payload in a target-specific manner, inducing more specific toxicities whereas a less stable linker is more likely to undergo nonspecific cleavage, resulting in broader systemic toxicity. Both cleavable and noncleavable linkers are currently being investigated in clinical trials [6]. Cleavable linkers include motifs that are either sensitive to lysosomal proteases (such as cathepsin B) or sensitive to an acidic pH, or they can contain disulfide bridges that can be reduced by glutathione. Conversely, noncleavable linkers (maleimidocaproyl and succinimidyl 4-*N*-maleimidocaproyl) require complete lysosomal proteolytic degradation of the antibody, in order to generate a toxic free payload. An example of noncleavable linkers includes the thioether linker succinimidyl

4-*N*-maleimidocaproyl, which is used in the ADC trastuzumab emtansine (T-DM1).

Cancer cells frequently become resistant to drugs by upregulating the expression of the multidrug resistance 1 (MDR1) drug efflux pump. MDR1 is known to transport water-soluble compounds less efficiently. As a consequence, charged or water-soluble linkers were developed and the resulting ADCs were shown to produce highly charged or polar metabolites, which led to improved potency against MDR1+ cells. *N*-Hydroxysuccinimidyl-4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB) is an example of such a polar linker. Mirvetuximab soravtansine (IMGN853), the lead ADC based on sulfo-SPDB, demonstrated notable single-agent activity in patients with folate receptor- α (FR α)-positive platinum-resistant ovarian cancer where MDR1 expression is believed to play a major role in drug resistance [16].

ANTIBODY TARGETS

Successful development of ADCs for gynecologic malignancies will in part also depend on the identification of satisfactory antibody targets. Several factors need to be considered in selecting the correct target. First, target antigens should ideally have high expression levels in tumors and little or no expression in normal tissues. Second, the target antigen should be present on the cell surface to be accessible to the circulating ADC. Third, it should be an internalizing antigen so that, after binding, the ADC is transported into the cell, where the cytotoxic agent can exert its effects. A number of novel target antigens have been identified and are currently being validated in ongoing clinical trials. Here we list those that are of greatest importance for gynecologic malignancies.

Folate receptor alpha

Folate receptor alpha (FR α) is a cell-surface transmembrane glycoprotein that facilitates the unidirectional transport of folates into cells. This receptor shows low expression in normal tissues, with expression limited to a variety of polarized epithelia, such as those found in the choroid plexus, kidney, uterus, ovary, lung, and placenta [17,18]. In contrast, aberrant FR α overexpression is characteristic of a number of epithelial tumors, including ovarian, endometrial, and non-small cell lung cancers [19]. In ovarian cancer specifically, approximately 80% of tumors constitutively express FR α [20]. The differential expression of FR α and its ability to internalize large molecules make this receptor well suited for ADC-based strategies. In this regard, mirvetuximab

soravtansine (IMGN853) is an ADC comprising a humanized FR α -binding monoclonal antibody conjugated to the cytotoxic maytansinoid DM4. Mirvetuximab soravtansine binds with high affinity and specificity to FR α on the surface of tumor cells, which, upon antigen binding, promotes ADC internalization and intracellular release of DM4 [21]. The safety and clinical activity of mirvetuximab soravtansine was recently evaluated in patients with FR α -positive and platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer [16²²]. Forty-six patients were enrolled. Adverse events were generally mild ($\leq$ grade 2), with diarrhea (44%), blurred vision (41%), nausea (37%), and fatigue (30%) being the most commonly observed treatment-related toxicities. Grade 3 fatigue and hypotension were reported in two patients each (4%). For all evaluable patients, the confirmed objective response rate was 26%, including 1 complete and 11 partial responses, and the median PFS was 4.8 months. The median duration of response was 19 weeks. Notably, in the subset of patients who had received three or fewer prior lines of therapy ($n = 23$), an objective response rate of 39%, PFS of 6.7 months, and duration of response of 20 weeks were observed [16²²]. Mirvetuximab soravtansine exhibited a manageable safety profile and was active in platinum-resistant ovarian cancer, with the strongest signals of efficacy observed in less heavily pretreated individuals. On the basis of these findings, the dose, schedule, and target population were identified for a phase III trial of IMGN853 monotherapy in patients with platinum-resistant disease in which mirvetuximab soravtansine is compared with the physician's choice of standard-of-care chemotherapy in platinum-resistant ovarian cancer.

Mesothelin

Mesothelin is a tumor differentiation antigen frequently overexpressed in tumors such as mesothelioma, ovarian, pancreatic, and lung cancer whereas showing limited expression in nonmalignant tissues. Anetumab ravtansine (BAY 94-9343) is a novel, selective and highly potent ADC consisting of a humanized antimesothelin antibody conjugated to the maytansinoid tubulin inhibitor DM4 via a cleavable disulfide-containing linker. *In vitro*, anetumab ravtansine has demonstrated potent and selective cytotoxicity of mesothelin-expressing cells with an IC₅₀ of 0.72 nmol/l, without affecting mesothelin-negative cells. *In vivo*, anetumab ravtansine localized specifically to mesothelin-positive tumors and inhibited tumor growth in both subcutaneous and orthotopic xenograft models. Furthermore, anetumab ravtansine was able to induce a 'bystander' effect

on neighboring mesothelin-negative tumor cells [22]. Anetumab ravtansine is currently being investigated in a variety of mesothelin-positive tumors, including patients with recurrent platinum-resistant ovarian cancer. Anetumab ravtansine was investigated in a randomized phase II study as second line treatment in patients with advanced or malignant pleural mesothelioma, whose disease had progressed after treatment with first-line platinum/pemetrexed-based chemotherapy. In this study, 248 patients were randomized in a 2:1 ratio to receive either anetumab ravtansine or weekly vinorelbine. However, the primary endpoint of progression-free survival improvement was not met based on a recent interim analysis (<https://adcreview.com/news/anetumab-ravtansine-not-meet-primary-endpoint-second-line-mesothelioma/>). Review of the published study results will be necessary to better understand potential reasons for the futility of this study.

CA-125

CA-125 (MUC16) is a membrane-associated mucin that possesses a single transmembrane domain. CA-125 is also the most frequently used serum biomarker for ovarian cancer. The ADC DMUC5754A contains a humanized anti-MUC16 monoclonal antibody conjugated to MMAE, linked through a protease-labile linker, maleimidocaproyl-valine-citrulline-*p*-amino-benzoyloxycarbonyl. DMUC5754A binds to the MUC16 extracellular domain with high affinity, and shows potent and selective antitumor activity in MUC16-expressing human ovarian cancer mouse xenograft models [23]. A phase I–Ib, multicenter, open-label, dose-escalation study was designed to evaluate the safety, tolerability of DMUC5754A. Following determination of the maximum tolerated dose, dose-expansion cohorts were enrolled to further characterize DMUC5754A [24]. The response rate was 17% (5/29) in patients who received the drug thrice weekly. All responders were assessed to have MUC16 IHC scores of 2+/3+, supporting the hypothesis that MUC16 target expression may be important for clinical benefit from DMUC5754A treatment. The most common treatment-related adverse events were fatigue (57% of patients), peripheral neuropathy (39%), nausea (37%), decreased appetite (30%), vomiting (28%) and diarrhea (24%) in patients treated thrice weekly. Grade 3/4 adverse events occurring in at least 5% patients included neutropenia (10%) and fatigue (10%) [24].

NaPi2b

NaPi2b is a transmembrane, sodium-dependent phosphate transporter expressed in ovarian cancer

and non-small cell lung cancer. DNIB0600A is an ADC consisting of a humanized IgG1 anti-NaPi2b monoclonal antibody and the antimetabolic agent MMAE. A phase I study enrolled 43 patients with non-small cell lung cancer and 30 patients with ovarian cancer [25]. The most common treatment-related adverse events regardless of grade were fatigue (43%), decreased appetite (37%), nausea (30%), constipation, dysgeusia, vomiting, and peripheral neuropathy (each 17%), and diarrhea (13%). Approximately 85% of ovarian cancers expressed high levels (IHC 2+/3+) of NaPi2b. Of the 60 patients treated at higher dose levels, 14 patients had a partial response. A randomized phase II study compared DNIB0600A with pegylated liposomal doxorubicin (PLD) in patients with platinum-resistant ovarian cancer, however, this study has been terminated because the primary objective of PFS improvement did not meet prespecified criteria (<https://clinicaltrials.gov/ct2/show/NCT01991210>).

NOTCH3

NOTCH3 signaling regulates a broad spectrum of cell fate decisions and differentiation. NOTCH3 pathway activation reprograms tumor cells to express embryonic stem cell markers and is associated with chemotherapy resistance in ovarian cancer [26]. Anti-NOTCH3 ADCs exhibited robust antitumor activity and induce prolonged tumor regressions in preclinical models of breast, lung, and ovarian cancer regardless of the antibodies' ability to block signaling [27]. PF-06650808 is an anti-NOTCH3 ADC that is composed of a humanized antibody targeting the NOTCH3 receptor linked to an auristatin-based cytotoxic agent. In a Phase 1 study, PF-06650808 showed an acceptable safety profile in patients with advanced malignancies, including triple negative breast cancer, ovarian cancer, and non-small cell lung cancer [28]. PF-06650808 also showed early indication of antitumor activity in an unselected patient population [28].

Protein tyrosine kinase-like 7

Protein tyrosine kinase-like 7 (PTK7) also known as colon carcinoma kinase 4 (CCK4) is a receptor tyrosine kinase that in humans is encoded by the *PTK7* gene. The protein encoded by this gene may function as a cell adhesion molecule and was initially found to be expressed in colon carcinomas but not in normal colon [29]. PF-06647020 is an anti-PTK7 ADC that is composed of a humanized monoclonal antibody directed against PTK7 linked to an auristatin microtubule inhibitor payload through a cleavable valine–citrulline linker. In a Phase 1 study,

PF-06647020 showed an acceptable safety profile in patients with advanced malignancies, including triple negative breast cancer, ovarian cancer, and non-small cell lung cancer [30]. In this study, 76 patients were treated with PF-06647020. Most commonly reported drug-related adverse events for all patients (mainly grades 1 and 2) were nausea (46%), alopecia (34%), headache (32%), fatigue (30%), neutropenia (26%), vomiting (22%), decreased appetite (17%), myalgia (15%), arthralgia (11%), and diarrhea (11%). Fourteen patients (18%) experienced grade ≥ 3 drug-related neutropenia. The response rate was 27% and 12 patients (55%) had stable disease, and 4 patients (18%) had progressive disease [30].

Ephrin-A4

Ephrin-A4 is overexpressed in a number of human tumors and is a member of the ephrin receptors that constitute the largest subfamily of receptor protein-tyrosine kinases, which have been implicated in mediating developmental events. PF-06647263 is an anti-Ephrin-A4 ADC that is composed of a humanized monoclonal antibody against Ephrin-A4 linked to the cytotoxic agent calicheamicin and has shown promising preclinical activity in breast cancer and ovarian cancer models [31]. In a Phase 1 study, PF-06647263 showed an acceptable safety and efficacy profile in patients with advanced malignancies, including triple negative breast cancer and ovarian cancer [32]. Of note, the Ephrin-A4 ADC may specifically target cancer stem cells that have been recognized in triple-negative breast cancer and ovarian cancer [32].

TROP2

TROP2 is a glycoprotein initially identified in a trophoblast cancer cell line and is overexpressed in many epithelial cancers [33]. It plays a multifunctional role, including the regulation of cytoplasmic Ca^{2+} [34]. The overexpression of TROP2 correlates with a poor prognosis in several cancers, including breast cancer [34,35]. Sacituzumab govitecan combines a TROP2 antibody with SN-38, which is a topoisomerase I-inhibiting drug that causes double-stranded DNA breaks. Irinotecan, the prodrug of SN-38, has activity in solid tumors, including metastatic breast cancer and ovarian cancer [36,37], but, SN-38 its metabolite has a 1000-fold higher potency than irinotecan such that it cannot be given as an unconjugated drug. In contrast, sacituzumab govitecan can deliver SN-38 to tumors with an improved therapeutic index [38]. In a recently completed clinical study on 69 patients with metastatic breast cancer who had received a

median of five prior therapies, the confirmed objective response rate was 30%, the median response duration was 9 months, and the clinical benefit rate was 46% [39]. Grade ≥ 3 adverse events included neutropenia (39%), leukopenia (16%), anemia (14%), and diarrhea (13%); the incidence of febrile neutropenia was 7%. The majority of archival tumor specimens (88%) were moderately to strongly positive for TROP2 by immunohistochemistry [13[■]].

Carcinoembryonic antigen-related cell adhesion molecule 5

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), also known as CEA, is a heavily glycosylated cell membrane protein that is involved in mediating cell adhesion as well as regulating differentiation, apoptosis, and cell polarity. CEACAM5 is used as a clinical biomarker for gastrointestinal cancers and its abnormal expression is associated with cancer progression, making it a good target for antibody-based immunotherapies. Labetuzumab is a humanized antibody, which targets CEACAM5 that has been conjugated with SN-38, the active metabolite of irinotecan. SAR408701 is an ADC, where similarly a humanized antibody that targets CEACAM5 has been linked to the maytansinoid DM4, which is in development for the treatment of solid tumors including ovarian cancers that express CEACAM5 [39].

Human tissue factor

Human tissue factor is a transmembrane protein involved in angiogenesis, cell adhesion, motility, and cell survival, and is aberrantly over-expressed across a broad range of solid tumors, including cervical cancer. Tisotumab vedotin is composed of a human monoclonal antibody that is specific for human tissue factor and is covalently coupled via a protease-cleavable peptide linker to monomethyl auristatin E (MMAE). Tisotumab vedotin was evaluated in the cervical cancer [40]. Thirty-four patients with relapsed, recurrent, and/or metastatic cervical cancer received tisotumab vedotin at 2.0 mg/kg administered intravenously every 3 weeks. Efficacy results after 12 weeks of treatment revealed 50% of patients showed clinical benefit. Eleven patients showed tumor reduction for an overall response rate of 32% including eight confirmed and three unconfirmed partial responses [40].

Lysosome-associated membrane protein 1

Lysosome-associated membrane protein 1 (LAMP1) is involved in the maintenance of lysosome membrane

integrity and phagolysosome formation. LAMP1 shows very limited expression at the cell surface in normal tissues whereas, a moderate-to-high expression was found at the cell surface in a number of solid tumors including ovarian cancer. SAR428926 is an ADC constituting an anti-LAMP1 humanized monoclonal antibody conjugated via a cleavable linker to the maytansinoid derivative DM4. In-vivo efficacy of SAR428926 was demonstrated in a panel of over 50 human patient-derived xenograft models [41]. Although the presence of the antigen is required for SAR428926 to have activity (there is no efficacy in LAMP1-negative PDX models), there appears to be no linear correlation between the level of antigen expression and the antitumor activity across the panel of PDX tested [41].

CONCLUSION

Taken together, the data summarized in this review support further clinical evaluation of mirvetuximab soravtansine (IMGN853), sacituzumab govitecan (IMMU-132), anetumab ravtansine (BAY 94-9343) and other ADCs in women's cancers. Antibody-drug conjugates can increase the efficacy and decrease the toxicity of their payloads in comparison with traditional cytotoxic agents. However, optimization of the antibodies, the linkers and the conjugation chemistry is now aimed at further improving the therapeutic index of new ADCs. Clearly, a better and quicker translation of recent scientific advances in the field of ADCs into rational clinical trials for patients diagnosed with ovarian, endometrial, and cervical or breast cancer will create real improvements in tumor response, survival and quality of life for our patients.

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Conflicts of interest

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