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REVIEW

Antibody-Drug Conjugates in Ovarian Cancer: Promises and Challenges

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Ovarian cancer (OC) remains one of the most lethal gynecological malignancies globally, often detected at advanced stages which contribute to its high mortality rate. Recurrent and drug-resistant cases further complicate the therapeutic landscape, underscoring the urgent need for innovative treatment modalities. This review article addresses the transformative potential of antibody-drug conjugates (ADCs) as a novel therapeutic strategy for OC. ADCs, which combine the specificity of monoclonal antibodies with the potency of cytotoxic drugs, offer a targeted approach to cancer cell elimination with minimized damage to normal tissues. Among ADCs that demonstrated promising activity in OC are mirvetuximab soravtansine, luveltamab tazevibulin, upifitamab rilsodotin, trastuzumab deruxtecan, sacituzumab govitecan, datopotamab deruxtecan and tisotumab vedotin. Here, we provide an overview of the ADCs' mechanism of action, highlight the specific tumor cell antigens targeted and present a comprehensive evaluation of clinical trials that have assessed the efficacy and safety of various ADC candidates in patients with OC.

PEER REVIEWED ARTICLE

Introduction

Ovarian cancer (OC) ranks as the eighth most commonly occurring cancer in women and the leading cause of mortality among gynecological cancers, accounting for over 200,000 global deaths annually.[1] In Switzerland, an average age-adjusted OC incidence rate of 14.6 cases per 100,000 women per year was reported between 2004 and 2012.[2] The disease is often diagnosed at advanced stages that leads to poor prognosis, with survival rates of only 42% and 26% for stages III and IV, respectively.[3] The current standard first-line therapy for advanced OC includes surgery followed by platinum-

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based chemotherapy.[4] Despite favorable initial response rates, the majority of patients will experience a relapse within 3 years, with a high incidence of resistance to standard platinum-based therapy and unfavorable prognosis.[5] In recent years, targeted agents have transformed the treatment landscape and significantly improved the clinical outcomes of patients with OC. These include poly(ADP-ribose) polymerase inhibitors (PARPis) olaparib, niraparib and rucaparib, as well as anti-angiogenic agent bevacizumab, which may be incorporated into the treatment regimen depending on the patient's *BRCA* and homologous recombination deficiency (HRD) status.[5-7] However, with the transition of the targeted drugs to the first-line setting, patients with recurrent disease often face limited curative options due to the development of resistance and systemic toxicity,[8] that underscores the urgent need for alternative therapeutic strategies for OC.

Antibody-drug conjugates in cancer therapy

Antibody-drug conjugates (ADCs) represent a rapidly growing class of targeted cancer treatments that combines the specificity of therapeutic antibodies with the efficacy of potent chemotherapy agents.[9-11] ADC molecules are comprised of three main components: a monoclonal antibody (mAb) directed against a tumor-specific antigen, a cytotoxic agent and a chemical linker that conjugates both parts of the complex.[12] Once bound to tumor cells, the ADC is internalized through receptor-mediated endocytosis, leading to lysosomal degradation and subsequent release of the cytotoxic payload. Due to the precise delivery of the drug to tumor cells, ADC therapy allows to overcome the limitations of conventional chemotherapy by minimizing systemic toxicity and enhancing therapeutic efficacy.

The antibody part of most ADCs is based on humanized immunoglobulin G (IgG) mAbs, with IgG1 being the most common subtype. The cytotoxic "missile" compounds of currently used ADCs belong to the classes of microtubule inhibitors (including auristatin derivatives, such as auristatin E and F, and maytansinoid derivatives, such as DM1 and DM4) or DNA damaging agents that induce DNA double-stranded breaks, intercalation, alkylation and cross-linking (such as calicheamicins, topoisomerase inhibitors, duocarmycins and pyrrolobenzodiazepines).[12] The structure of a linker defines the pharmacokinetic properties of ADCs and must achieve a balance between ensuring drug stability in the circulation on the one hand, and efficient and timely release of the toxic payload inside tumor cells on the other hand.[13] The majority of currently approved ADCs utilize cleavable linkers that degrade after drug internalization by tumor cells. Depending on the linker class, cleavage may occur in response to a change in pH, protease activity or glutathione (GSH) concentrations in the intracellular environment. The main advantage of cleavable linkers is specific intracellular payload release, while disadvantages include potential premature non-specific cleavage in normal tissues leading to systemic toxicity. Non-cleavable linkers

rely on the complete lysosomal proteolytic degradation of ADC after internalization to release the payload. They are more stable in plasma than cleavable ones and may increase the therapeutic index of the drug, along with reducing off-target effects; however, they are more dependent on the biology of tumor cells which may limit their effectiveness.[13]

ADCs have demonstrated clinical activity in many types of malignancies, including those refractory to standard treatments. There are currently 13 ADCs approved by the US Food and Drug Administration (FDA) for various cancer types, among them CD30-targeting brentuximab vedotin for Hodgkin lymphoma and anaplastic large cell lymphoma, ado-trastuzumab emtansine and trastuzumab deruxtecan binding to HER2 receptor on breast cancer cells, MMAE-targeting enfortumab vedotin-ejfv for metastatic urothelial cancer and others.[14-16] Many more agents are in early- or late-phase trials and in development, with continuous efforts to overcome existing limitations of the approach, such as acquired resistance to therapy, off-target toxicity, as well as limited efficacy caused by low ADC binding affinity and internalization rates or low expression levels of the target antigen on the cell surface. Furthermore, ADCs are being increasingly used in combination with other therapeutic strategies, such as chemotherapy, immunotherapy and anti-angiogenic agents, to achieve synergistic clinical benefits in cancer patients.[17]

ADCs in ovarian cancer

This section focuses on clinical trials that assessed ADCs as therapeutic agents for OC. The drugs and trials are listed based on the specific protein targeted by these ADCs on tumor cells.

Folate receptor alpha

Folate receptor alpha (FRα) is a glycosylphosphatidylinositol (GPI)-anchored membrane protein that mediates folate transport into the cell via receptor-mediated endocytosis. While its expression in normal tissues is limited, FRα is overexpressed in many types of cancer tissues such as ovarian, breast and lung cancers.[18] High FRα expression is associated with a poorly differentiated aggressive tumor phenotype and resistance to chemotherapy,[19] as well as with more pronounced anti-tumor effects of FRα-targeted therapy.[20] Together, these findings make FRα a promising target for tumor-specific drug delivery.

Mirvetuximab soravtansine

The first ADC approved by the U.S. Food and Drug Administration (FDA) for OC was mirvetuximab soravtansine (MIRV).[21,22] MIRV is comprised of a humanized monoclonal antibody against FRα linked via a cleavable disulfide linkage to the cytotoxic anti-tubulin agent maytansinoid DM4.[21] The following studies evaluated MIRV in OC.

FORWARD I

The open-label, randomized, phase III FORWARD I trial compared MIRV with chemotherapy in patients with platinum-resistant OC.[23] Overall, 366 patients (age ≥18 years) with 1–3 prior lines of therapy and tumors positive for FRα were randomly assigned at a 2:1 ratio to receive MIRV (6 mg/kg) or investigator's choice chemotherapy (paclitaxel, pegylated liposomal doxorubicin or topotecan) and stratified according to number of prior therapies, FRα expression, and the chemotherapy regimen. This study implemented a simplified score to detect FRα (10x Score) positivity compared to previous studies (PS2+ score).[24] In FORWARD 1 trial, a tumor was considered positive if ≥50% of tumor cells with any FRα membrane staining were visible at ≤10X microscope objective magnification. Overall, 59.6% of patients constituted the prespecified FRα-high subgroup. The primary endpoint was progression-free survival (PFS) in the intention-to-treat (ITT) and the FRα-high populations. Secondary endpoints included objective response rate (ORR), overall survival (OS), a patient-reported outcome (PRO), PFS2 defined as the time from randomization to second disease progression or death, duration of response (DoR) and cancer antigen-125 (CA-125) response rate.

The study unexpectedly did not meet its primary endpoint. There was no significant difference in PFS between the MIRV and chemotherapy groups in the ITT population (HR: 0.98 [95% CI: 0.73–1.31]; p=0.897). In the prespecified FRα-high subgroup, the median PFS was longer with MIRV versus chemotherapy (4.8 months vs 3.3 months; HR: 0.69 [95% CI: 0.48–1.00]; p=0.049). However, these results did not reach statistical significance since the statistical analysis plan required p value of <0.025 in this population. For all secondary endpoints, MIRV showed superior outcomes over chemotherapy in the FRα-high population including ORR (24% vs 10%), PRO (27% vs 13%), median PFS2 (10.0 vs 8.4 months) and CA-125 responses (53% vs 25%).

With respect to safety, MIRV was well tolerated, with fewer ≥grade 3 treatment-related adverse events (TRAEs, 25.1% vs 44.0%), dose reductions (19.8% vs 30.3%) and treatment discontinuations (4.5% vs 8.3%) versus chemotherapy. The most common TRAEs included nausea (all grades: 45.7%; grade ≥3: 1%), diarrhea (all grades: 31.3%; grade ≥3: 2.1%) and fatigue (all grades: 28.8%; grade ≥3: 1.2%). The most frequent ocular disorders included blurred vision (all grades: 42.0%; grade ≥3: 2.5%) and keratopathy (all grades: 32.5%; grade ≥3: 1.2%).

A retrospective analysis demonstrated that the scoring system adopted in this study was not superimposable to the one assessing the percentage of FRα positive cells and the intensity of the expression (PS2+ score: ≥25% of tumor

cells with ≥2+ staining intensity (low= 25–50%, medium= 50–74%, high ≥75%). Thus, two subsequent studies (SORAYA and MIRASOL) have been conducted applying the original scoring system.

SORAYA

In a single-arm, multicenter phase II SORAYA study, MIRV demonstrated clinically meaningful efficacy and a favorable safety profile in patients with platinum-resistant epithelial OC harboring high FRα expression (≥75% of cells with PS2+ staining intensity).[25] The study enrolled 106 patients (age ≥18 years) with a confirmed diagnosis of high-grade serous OC and high FRα tumor expression who had received up to three prior therapies, including bevacizumab. Among them, 51% had three prior lines of therapy, 48% received a prior PARPi and all had received prior bevacizumab. Patients with primary platinum-refractory disease who did not respond to first-line platinum therapy or progressed within 3 months of the last dose of first-line platinum therapy were excluded from the cohort. The primary endpoint was ORR and the key secondary endpoint was DoR defined as the time from the initial complete (CR) or partial response (PR) until progressive disease, as well as safety, PFS and OS. The median follow-up was 13.4 months.

The study met its primary endpoint, with an ORR of 32.4% (95% CI: 23.6–42.2), including five CRs and 29 PRs.[25] In a subgroup analysis, ORR was 35.3%, 30.2%, 38.0% and 27.5% in patients with one to two prior lines of therapy, with three prior lines, those with a prior PARPi and those without it, respectively. The median DoR was 6.9 months. The median PFS per investigator was 4.3 months and the median OS was 13.8 months.

TRAEs occurred in 86% of patients, with 30% experiencing grade 3–4 events. The most common all grade and grade ≥3 TRAEs were blurred vision (41% and 6%), keratopathy (29% and 9%), and nausea (29% and 0%). The most common hematologic TRAEs included neutropenia (2% grade 3), thrombocytopenia (92% grade 3) and anemia (1% grade 3).

MIRASOL

MIRASOL is the first phase III study that unequivocally demonstrated the improvement in PFS and OS for MIRV compared with chemotherapy in patients with platinum-resistant OC and high FRα.[26] This open-label, randomized trial included 453 patients with platinum-resistant OC and high tumor expression of FRα (positive staining intensity ≥2 on ≥75% of viable tumor cells) after 1–3 prior lines of therapy. Patients were randomized 1:1 to receive either MIRV or the investigator's choice of chemotherapy and stratified according to the chemotherapy agent (paclitaxel, pegylated liposomal doxorubicin or topotecan) and the number of prior lines of therapy (1 vs 2 vs 3). The primary endpoint was PFS, and the secondary endpoints were ORR, OS, PRO, safety and tolerability.

At a median follow-up of 13.1 months, MIRV was associated with a 35% reduction in the risk of disease progression or death compared with chemotherapy (HR: 0.65 [95% CI: 0.52–0.81]; p<0.0001), with a median PFS of 5.62 months versus 3.98 months, respectively.[26] The data further showed a highly statistically significant benefit in ORR for MIRV versus chemotherapy (42% vs 16%; odds ratio: 3.81 [95% CI: 2.44–5.94]; p<0.0001), including CR rates of 5% and 0%, respectively. The maximum percentage change in target lesion size from baseline was 80% among patients receiving MIRV versus 55% among those receiving chemotherapy. The median OS in the MIRV arm was 16.46 months versus 12.75 months in the chemotherapy arm which corresponded to a 33% reduction in the risk of death (HR: 0.67 [95% CI: 0.50–0.89]; p=0.0046). Importantly, the exploratory analysis demonstrated consistent OS and PFS benefits with MIRV versus chemotherapy irrespective of the prior exposure of patients to bevacizumab.

The safety profile of MIRV was consistent with prior reports.[23,25] The MIRV regimen displayed lower rates of grade ≥3 TEAEs (42% vs 54% with chemotherapy), serious TEAEs (24% vs 33%) and TEAE-related discontinuations (9% vs 16%).[26] Patients in the MIRV arm experienced fewer hematologic TEAEs, neuropathy and alopecia compared with chemotherapy, while the frequency of gastrointestinal TEAEs was similar between the arms. The key safety signal for MIRV was low-grade ocular TEAEs, including blurred vision, keratopathy and dry eye that occurred in 41%, 32% and 28% of cases, respectively.

FORWARD II

Apart from the above-mentioned trials investigating the monotherapy regimen, MIRV is being evaluated in various combinations with chemotherapy and targeted drugs to explore the potential synergistic effects of the agents. The multi-arm, phase Ib/II FORWARD II trial aims to assess the safety and clinical activity of MIRV in doublet combinations with bevacizumab, carboplatin, pegylated liposomal doxorubicin or pembrolizumab, as well as a triplet regimen in combination with carboplatin and bevacizumab in patients with FRα-positive advanced epithelial OC.[27,28]

In the platinum-resistant setting, the combination of MIRV with bevacizumab was well tolerated and demonstrated a favorable efficacy compared with reported outcomes for bevacizumab plus standard chemotherapy. The eligibility criteria included recurrent platinum-resistant disease and FRα expression by immunohistochemistry (≥25% of cells with ≥2+ intensity). Prior treatments with bevacizumab and/or PARPi were permitted. The endpoints included safety, tumor response and PFS.

The primary analysis included 66 patients with a median of 3 prior lines of therapy who received the combination of MIRV and bevacizumab during the escalation and expansion stages of the study.[28] The regimen was associated mostly with mild-to-moderate treatment-related toxicity (≤grade 2), with diarrhea, blurred vision, nausea and fatigue being the most common TRAEs. Additionally, grade 1 or 2 pneumonitis was observed in 9% of cases. The median PFS was 6.9 months, and ORR was 39%, including 5 CRs and 21 PRs. The regimen achieved the best efficacy in less heavily pretreated (1-2 prior lines) bevacizumab-naïve patients with medium-to-high FRα tumor expression (ORR: 56%; median DoR: 2 months; PFS: 9.9 months).

The recently published final analysis of the cohort treated with MIRV plus bevacizumab included 94 patients; among them, 59% had been previously treated with bevacizumab and 27% with a PARPi.[27] The analysis confirmed the clinical activity of the combination, with ORR of 44% (including 5 CRs), a median DoR of 9.7 months and a median PFS of 8.2 months. The safety profile was consistent with previous reports and the individual profiles of each agent, with the most common TRAEs being blurred vision (57% and 1%), diarrhea (54% and 1%) and nausea (51% and 1%) for all-grade and grade 3 events, respectively. In summary, the combination of MIRV with bevacizumab was well tolerated and demonstrated encouraging efficacy in patients with platinum-resistant, recurrent OC.

Ongoing studies: PICCOLO and GLORIOSA

Several ongoing studies are investigating MIRV in different clinical settings and in combination with other agents. A global, single-arm, phase II study PICCOLO study aims to evaluate the efficacy of MIRV as monotherapy in 75 patients with recurrent platinum-sensitive epithelial OC and high FRα expression who cannot receive or tolerate platinum for their next line of therapy.[29] The primary endpoint is ORR and secondary endpoints include DoR, PFS, OS, CA-125 response, safety and tolerability.

GLORIOSA is a randomized, open-label, phase III trial designed to evaluate the efficacy of MIRV in combination with bevacizumab as maintenance treatment in FRα-positive platinum-sensitive recurrent setting.[30] The study will enroll 418 patients who will be randomized 1:1 to receive MIRV plus bevacizumab or bevacizumab alone. The primary efficacy endpoint is PFS, and secondary endpoints include ORR, quality of life (QoL), OS, safety and tolerability.

Luveltamab Tazevibulin (STRO-002)

STRO-002 is a novel homogeneous ADC with potent specific cytotoxicity toward FRα-expressing tumor cells, superior stability and favorable pharmacokinetic characteristics. Its molecule is comprised of a high affinity anti-FRα antibody, a tubulin-targeting 3-aminophenyl hemiasterlin cytotoxic

warhead and a novel cleavable linker.[31] STRO-002 was evaluated in a global, phase I study **STRO-002-GM1** in patients with recurrent epithelial OC who had progressive platinum-resistant disease after 1–3 prior lines or platinum-sensitive disease after 2–3 prior lines of platinum chemotherapy.[32] Patients were randomized 1:1 to receive luveltamab tazevibulin at a dosage of 4.3 mg/kg or 5.2 mg/kg. FRα expression was determined retrospectively in archival tissue, and the efficacy was analyzed in subjects with tumor proportion score (TPS) >25%. In the population available for analysis according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, ORR was 37.5% overall (n=32), 31.3% with the dose of 4.3 mg/kg (n=16) and 43.8% with the dose of 5.2 mg/kg (n=16). The median DoR was 5.5 months, 13 months and 5.4 months in all RECIST-available patients and in the groups treated with 4.3 mg/kg and 5.2 mg/kg, respectively. In the overall enrolled population (n=35), the median PFS was 6.1 months, among them 6.1 months in the 4.3 mg/kg group and 6.6 months in the 5.2 mg/kg group. In summary, the study confirmed the clinical activity of luveltamab tazevibulin. The registration-directed phase II/III trial **REFRaME** will further evaluate this agent in platinum-resistant OC.

Sodium phosphate transporter NaPi2B

NaPi2b belongs to the SLC34 family of type-2 sodium-dependent phosphate transporters that regulate phosphate homeostasis by transporting phosphate across the plasma membrane. NaPi2b is aberrantly expressed in many cancer types, including ovarian, breast, and lung tumors.[33] Its overexpression in malignancies, combined with its limited distribution in normal tissues, makes NaPi2b a potential target for targeted cancer therapies.

Upifitamab rilsodotin (UpRi) is a first-in-class ADC comprising a humanized antibody conjugated with 10-15 auristatin F-HPA payload molecules via the dolaflexin platform characterized by high drug-to-antibody ratio and a controlled bystander effect.[34] UpRi was evaluated in a **phase I expansion study** in 97 patients with high-grade serous OC.[35] Among them, 67% received 1-3 prior lines of therapies, 70% had been previously treated with bevacizumab and 59% with a PARP inhibitor. Three doses of UpRi were evaluated, and clinical activity was achieved starting from the lower dose of 36 mg/m^2. In 38 evaluable patients with high tumor NaPi2b expression, confirmed ORR was 34%, including two CRs, and the median DoR was five months. In the overall population the confirmed ORR and disease control rate (DCR) were 23% and 72%, respectively, regardless of NaPi2b expression. The most common grade ≥3 TRAEs were transient aspartate transaminase (AST) increase, fatigue, anemia and thrombocytopenia, with no grade ≥3 neutropenia, peripheral neuropathy or ocular toxicity reported. Dose reductions and discontinuations due to TRAEs occurred in 28% and 10% of patients, respectively.

Based on these results, UpRi was further evaluated as monotherapy in a single-arm registration-directed **UPLIFT** trial that included platinum-resistant, high-grade serous OC after ≤4 prior lines of therapy and the cutoff for high NaPi2b expression of TPS ≥75.[36] Notably, while pending formal presentation, the preliminary data indicate that the UPLIFT study failed to meet its primary endpoint of investigator-assessed ORR in the NaPi2b-positive population.[37] At the data cut-off of May 31, 2023, ORR was 15.6%, including CR rate of 1.4%, and the median DoR was 7.4 months. Current investigative efforts on UpRi encompass the phase III, randomized **UP-NEXT** study evaluating UpRi maintenance monotherapy compared to placebo in patients with recurrent, platinum-sensitive, high-grade, NaPi2b-positive OC after 2–4 prior lines of platinum therapy,[38] as well as **UPGRADE**, a phase I dose escalation and expansion umbrella study, that evaluates UpRi in combinations with carboplatin in recurrent OC.[39]

HER2

Human epidermal growth factor receptor 2 (HER2, ErbB-2) is a member of the epidermal growth factor receptor (ErbB) family of receptor tyrosine kinases that regulate cell proliferation, differentiation and survival and play a key role in the pathogenesis of several cancer types, including breast, gastric, colorectal and lung cancer.[40-42] *HER2* overexpression or amplification has been reported in OC; however, the efficacy of HER2-targeted therapies in patients with OC is limited and may depend on HER2 expression level, tumor heterogeneity and activation of other molecular pathways.[43]

Trastuzumab deruxtecan (T-DXd) is an ADC composed of a humanized anti-HER2 mAb trastuzumab, a tetrapeptide-based cleavage linker and a cytotoxic payload deruxtecan (DXd), a derivative of a topoisomerase I inhibitor DX-8951.[44] T-DXd has been approved by FDA as SoC for HER2-positive metastatic or unresectable breast cancer, HER2-positive locally advanced or metastatic gastric cancer and *HER2*-mutant metastatic or unresectable non–small cell lung cancer (NSCLC).[45-48] In the open-label, phase II **DESTINY-PanTumor** basket study, T-Dxd demonstrated activity and a manageable toxicity profile in several types of HER2-expressing solid tumors, with the best responses achieved in endometrial and cervical tumors, as well as in OC.[49] The study population included 267 patients, among them 40 with OC. At the median follow-up of 12.7 months, the interim results in the OC subpopulation treated with T-Dxd showed ORR of 45%, with CR and PR rates of 10% and 35%, respectively. DCR was 70% at 12 weeks, and the median DoR was 11.3 months. High ORR was achieved in OC patients with a HER2 immunohistochemistry (IHC) score of both 2+ or 3+ (63.6% and 36.8%, respectively). The trial data on PFS and OS are highly anticipated.

Trop-2

Trophoblast cell-surface antigen 2 (Trop-2) is a transmembrane calcium signal transducer that regulates cell proliferation, invasion, survival and self-renewal. It promotes tumor progression and is overexpressed in many solid tumors including breast, lung, urothelial, ovarian and gastrointestinal cancers, which prompted studies on its potential as a target for ADC development.[50]

Sacituzumab Govitecan

Sacituzumab govitecan (SG) is an ADC comprised of a humanized mAb coupled to the topoisomerase inhibitor SN-38 (the active metabolite of irinotecan) via a pH-sensitive cleavable linker.[51,52] SG is approved in several countries for pretreated patients with triple-negative and HR+/HER2- metastatic breast cancer. In the phase III ASCENT trial, SG improved PFS (HR: 0.41 [95% CI: 0.32–0.52]; p<0.001) and OS (HR: 0.48 [95% CI: 0.38–0.59]; p<0.001) over single-agent chemotherapy in patients with metastatic triple-negative breast cancer.[53] In preclinical studies SG demonstrated remarkable activity against aggressive and chemotherapy-resistant OC.[54] However, in the phase I/II **IMMU-132-01** basket trial that evaluated the safety and efficacy of SG across 17 types of epithelial tumors, an ORR of 0% was observed in a small (n=8) subgroup of patients with OC.[55] In the phase Ib **SEASTAR** study, the combination of SG with the PARPi rucaparib showed clinical activity in OC[56]; however, the study was terminated due to a change in development priorities. Two trials plan to further evaluate SG in platinum-resistant OC[57] and the platinum-sensitive setting in combination with cisplatin.[58]

Datopotamab Deruxtecan

SG is characterized by a short half-life in the organism,[52] leading to frequent dosing and related side effects. In order to increase the therapeutic window, a novel Trop-2-targeting ADC datopotamab deruxtecan (Dato-DXd) incorporating a topoisomerase I inhibitor DXd payload has been developed using the optimized DXd-ADC technology platform.[59] Dato-DXd has demonstrated the potential to be an effective therapy in breast and lung cancer and is currently being evaluated in the ongoing phase II TROPION-PanTumor03 study as monotherapy and in combination with other agents in patients with advanced/metastatic solid tumors including OC.[60]

Tissue factor

Tissue factor (TF) plays an essential role in hemostasis by activating blood coagulation. The complex of TF with factor VIIa (FVIIa) initiates the coagulation protease cascade leading to fibrin deposition and platelet activation, as well as induces angiogenesis via protease-activated receptor 2

(PAR2).[61] TF is aberrantly expressed in many solid tumors and contributes to tumor growth and metastasis, with its expression being associated with poor prognosis.[62]

Tisotumab vedotin (TV, HuMax-TF-ADC) is a first-in-class ADC comprised of an anti-TF-targeted humanized mAb conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker.[63,64] In a pivotal phase II innovaTV 204 trial, TV demonstrated clinical efficacy in cervical cancer.[65] The phase I/II **InnovaTV 201** trial investigated the efficacy and safety of TV in heavily pretreated patients with different types of advanced or metastatic solid tumors including OC.[66] In the OC subgroup (n=36), reported ORR was 13.9%. In both studies TV treatment was associated with notable TRAEs, with the most common grade ≥3 ones being fatigue, anemia, abdominal pain, hypokalemia, hyponatremia, ocular toxicity, hemorrhage, vomiting and peripheral neuropathy, inter alia.[65,66] Two cases of death, one due to pneumonia[66] and one to septic shock[65] were considered possibly related to treatment. A recently completed **innovaTV 208** trial aims to evaluate the efficacy of TV in platinum-resistant OC.[63]

Conclusion

ADCs represent a promising frontier in the evolving landscape of OC therapeutics. Their unique ability to harness the specificity of monoclonal antibodies and the potency of cytotoxic drugs offers an innovative and targeted approach to address the complexities of OC, including recurrent and drug-resistant disease. Many studies demonstrated high response rates and clinical benefits of ADCs, primarily due to their ability to selectively target tumor cell antigens while sparing healthy tissues. The remaining challenges include the need to further optimize the molecular design of ADCs to improve their efficacy and minimize side effects, evaluate candidate drugs in larger cohorts of OC patients as monotherapy and in combination with other treatment modalities to amplify therapeutic benefits, as well as broaden the range of existing agents by identifying novel specific targets on tumor cells. In summary, while ADCs usher in a new era of hope for OC patients, continuous research and multi-faceted clinical evaluations are crucial to realize their full potential.

Conflicts of Interest

Ilaria Colombo received travel grants from Tesaro, AstraZeneca, GSK, Johnson and Johnson; expert/advisory fees from AstraZeneca, GSK, Novartis and MSD; institutional grants for clinical trials (PI): MSD, Bayer, Oasmia and Incyte. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way. Other authors have

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