Monotherapy and combination therapy using antibody-drug conjugates for platinum-resistant ovarian cancer

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Abstract. Platinum-resistant ovarian cancer (PROC) is a significant clinical challenge due to the limited number of treatment options and poor outcomes. Moreover, cytotoxic drugs have an unsatisfactory therapeutic efficacy, high toxicity and side effects. An antibody-drug conjugate (ADC) is a novel cancer therapeutic strategy that combines an antibody, a linker and a payload. ADCs precisely target the tumor cells by binding to the antigen on the surface of tumor cells, thus accurately delivering the cytotoxic drugs and minimizing systemic toxicity. The approval of mirvetuximab soravtansine by the US Food and Drug Administration for treating folate receptor alpha-positive, platinum-resistant epithelial ovarian cancer has promoted studies on the use of ADCs in ovarian cancer. A phase III clinical trial showed that mirvetuximab soravtansine achieved an objective remission rate of 42.3% in platinum-resistant, FRα-positive ovarian cancer, compared with 15.9% using chemotherapy, demonstrating its immense potential for ADC development. The present review summarizes the research progress on the use of ADCs in PROC as a monotherapy and combination therapy and considers the future development direction of ADCs in PROC.

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1. Introduction

Ovarian cancer is the second most lethal gynecologic malignancy, with an estimated 206,839 mortalities associated with the disease in 2022 according to the recent global cancer statistics (1). The data from the American Cancer Society in 2024 indicated that there has been no improvement in the mortality/incidence rate of 62% of ovarian cancers in the last 30 years (2). More than 80% of patients with ovarian cancer experience recurrence and eventually develop treatment resistance after surgery and platinum-based chemotherapy (3,4). The mainstay of treatment for platinum-resistant ovarian cancer (PROC), which progresses within 6 months of completing the platinum treatment, has been the sequential use of cytotoxic drugs, including pegylated liposomal doxorubicin (PLD), gemcitabine, paclitaxel and topotecan, in recent years (4). However, the effective proportion of these drugs is only 10-15%, and the expected survival time is ~12 months (5,6). The ongoing research on developing new drugs and identifying new therapeutic targets is constantly evolving.

ADCs selectively deliver cytotoxic payloads to tumor cells, representing a rapidly evolving cancer therapy (6-8). At present, 15 ADCs have been approved by the US Food and Drug Administration for tumor treatment, and the development of these drugs for PROC has gained interest. In November 2022, mirvetuximab soravtansine (MIRV; ELAHERE®) was approved by the US Food and Drug Administration (FDA) as the first ADC for ovarian cancer (9). MIRV targets folate receptor α (FRα) on the surface of tumor cells to induce tumor cell killing, thereby displaying promising clinical activity in patients with FRα-positive ovarian cancer (10). Other ADCs are still under active development in the treatment of PROC. In addition, studies on using ADCs in combination therapy

with various anticancer drugs are underway (NCT05887609, NCT06660511, NCT05941507) .

The present review aimed to describe the structure and mechanism of action of ADCs, present an overview of the progress in the effectiveness of various types of ADCs in treating PROC in preclinical studies and clinical trials, and to discuss the recent advances in combining ADCs with chemotherapeutic agents, targeted agents and immunotherapies for PROC treatment. The present study also analyzed the toxicity characteristics and management of ADCs and finally considered the future development of ADCs for ovarian cancer.

2. Literature search

A literature search was performed using the Web of Science (https://www.webofscience.com/wos/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/) databases. 'ADC', 'monotherapy', 'combination therapy', 'platinum-resistant ovarian cancer' and 'research progress' were used as the core search terms. Each core search term was searched separately, and then Boolean logical operators 'AND' and 'OR' were applied for combined searches, for example, '(ADC AND monotherapy AND platinum-resistant ovarian cancer) OR (ADC AND combination therapy AND platinum-resistant ovarian cancer)'. The search fields were limited to the title, abstract and keywords to pinpoint relevant literature. The inclusion criteria were as follows: i) Studies focused on ADC monotherapy or combination therapy for PROC; ii) clinical research, basic research or review articles; iii) language limited to English; and iv) published within the last 10 years (January 1, 2014 to December 1, 2024) to obtain the latest research developments. The literature needed for the writing process was also included where appropriate. The exclusion criteria were as follows: i) Duplicate publications or highly similar content; ii) non-research literature such as conference abstracts, reviews, letters, news reports and so forth; and iv) literature with weak relevance or missing key data.

The quality of clinical studies was assessed by evaluating randomization methods, implementation of blinding, and descriptions of loss of visits and withdrawals; the assessment for the quality of basic research covered dimensions such as rationality of experimental design, sample size and statistical methods of data; and that of review articles focused on the comprehensiveness of their literature coverage, depth of analysis and logic. Two professionals performed independent assessment, and a third expert was asked to adjudicate in case of disagreement.

3. Structure and mechanism of action of ADCs

Structure and mechanism of action. ADCs are complexes comprising an antibody, a cytotoxic payload and a connecting linker. They specifically recognize tumor cell surface antigens, induce endocytosis and release cytotoxic drugs into tumor cells, ultimately leading to the death of tumor cells (6,11). The connection of cytotoxic drugs with antibodies was first realized in the 1950s (12). Researchers conducted clinical trials on the mouse immunoglobulin G (IgG)-based ADCs in the 1980s (13). Following a long and slow development, the field has become active again in the last decade, with ADCs entering the global market at a much faster pace. Usually, ADCs are administered intravenously. Then, the antibodies of ADCs bind to the antigen on cancer cells, penetrate the cells via receptor-mediated endocytosis to form endosomes and fuse with lysosomes. The cytotoxic payload detaches from the antibody and diffuses into the cell in the presence of various lysosome enzymes, resulting in tumor cell death by disrupting DNA structures or inhibiting microtubule polymerization (8,14,15). In addition, the payload can penetrate the extracellular matrix and surrounding cells, resulting in a bystander effect (16). Fig. 1 shows a schematic representation of the structure and mechanism of action of conventional ADCs.

The most commonly used antibody backbone in ADCs is IgG. The antibody-binding antigen should be highly expressed on the surface of tumor cell membranes with minimal expression on normal tissues (17,18) to enhance the effectiveness of the drug by delivering it to specific targets, protect the non-target tissues from the damage caused by chemotherapy, and reduce the systemic toxicity. FRα, human epidermal growth factor receptor 2 (HER2), trophoblast cell surface antigen-2 (TROP2), mesothelin, sodium-dependent phosphate transporter 2b (NaPi2b) and CDH6 are usually overexpressed in epithelial ovarian cancer, making them the most commonly used conjugated antigens (19).

The covalent binding of antigen-targeting antibodies to cytotoxic payloads requires connecting linkers (20). Linkers have two main functions; the primary one is maintaining stability in the bloodstream, keeping the cytotoxic payload attached to the antibody when it moves through the plasma; the other aspect is to efficiently release the payload into the tumor (8). The linkers should keep this attachment stable and unchanged in the bloodstream, with the drug being released only after antigen-antibody binding (21). Linkers are cleavable or non-cleavable depending on their chemical characteristics. Cleavable linkers are chemically unstable structures that can deliver drugs extracellularly and induce the killing of nearby tumor cells (22,23). The non-cleavable linker releases the drug solely when the antibody undergoes internalization and degradation within the lysosomes of the target cells. However, the cytotoxic payloads are released after the apoptosis of tumor cells, which may also result in the non-specific killing of surrounding tumor cells (24).

The cytotoxic payloads in ADCs now encompass a range of DNA-targeting agents, microtubule-binding proteins and some topoisomerase 1 inhibitors. The agents targeting microtubules are the most frequently used payloads, targeting the medenosine and periwinkle alkaloid sites. They interfere with the kinetics of microtubule protein polymerization and maintain the cell cycle in the G_2/M phase, leading to cell death (25,26). Not all tumor types are sensitive to a given type of payload and, therefore, diversifying payloads is critical to expanding the indications of ADCs.

ADCs in tumor therapy. Alternative strategies based on the use of ADCs are highly effective in treating cancer. The use of ADCs in clinical oncology has increased with the advent of novel technologies and the discovery of new targets (9,27). To date, 15 ADCs have received marketing approval from the FDA, and hundreds more are undergoing preclinical and clinical evaluation (28). Besides hematological tumors, ADCs

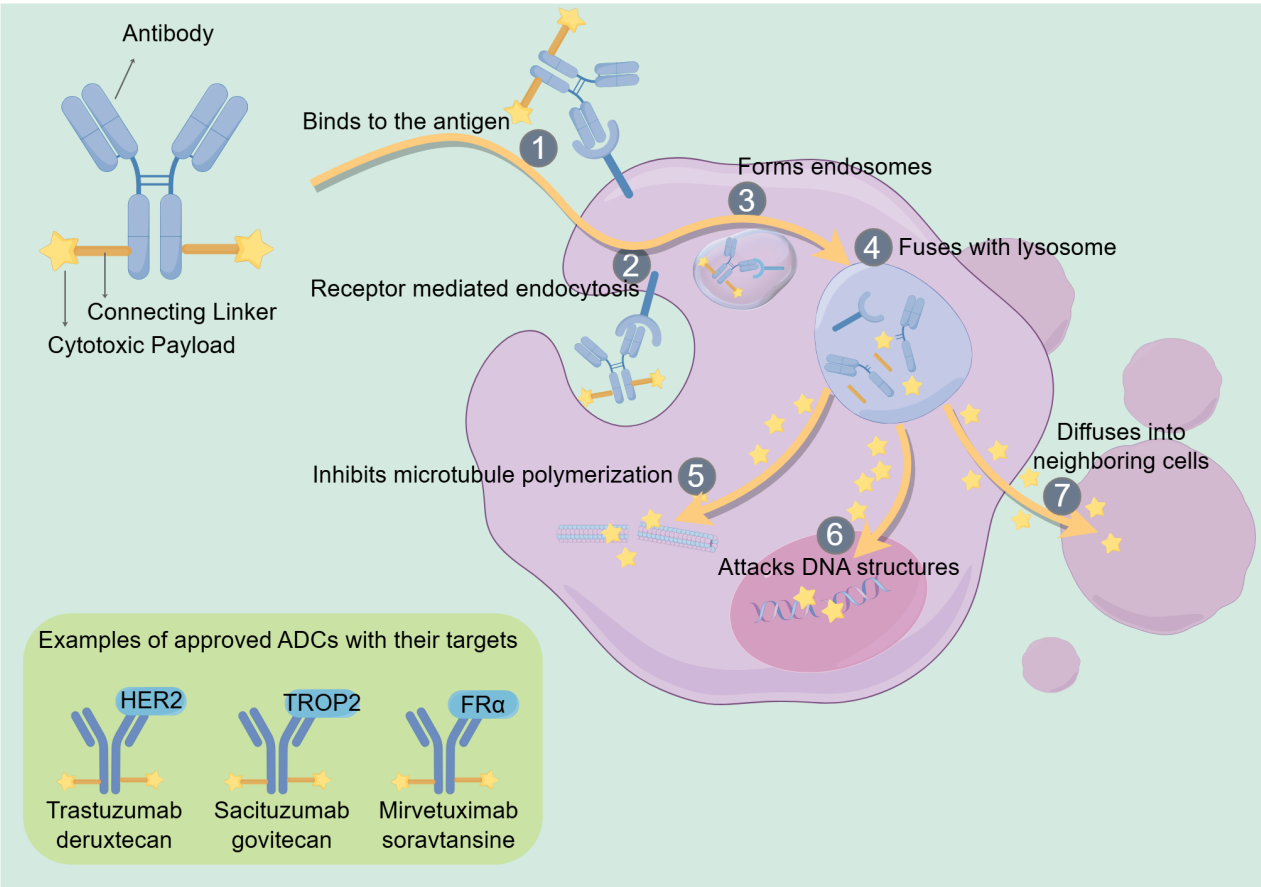

Figure 1. ADC consists of an antibody, a cytotoxic payload and a connecting linker. (1) The antibody portion of ADC binds to the target antigen on the cancer cells; (2) it enters the cell through receptor mediated endocytosis; (3) forms endosomes; (4) fuses with a lysosome; (5) inhibits microtubule polymerization; (6) attacks DNA structures; and (7) diffuses into neighboring cells and induces a bystander effect. Figure created using Figdraw (https://www.figdraw.com/static/index.html#/; ID: UWYPR914b8). ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; TROP2, trophoblast cell surface antigen-2; FRα, folate receptor α.

have been approved for use in breast, gastric, lung, uroepithelial, cervical, ovarian and head-and-neck squamous cell carcinomas. Several previous studies have described the ADC drugs approved for oncology treatment (29-31).

Solid tumors offer a broad opportunity for ADC development. The treatment choices for advanced or metastatic recurrent solid tumors are limited, and current immunotherapies rarely cure the disease (9). Therefore, ADCs have immense potential and unique advantages in a wide range of solid tumors.

4. Efficacy of ADC in PROC treatment

ADC monotherapy for PROC

Targeting FRα. FRα, one of the four members of the FR family, is a glycosylphosphatidylinositol-anchored membrane protein (32) that binds to folic acid and related compounds and transports them into the cell through receptor-mediated endocytosis (33,34). FRα is seldom expressed in normal tissues but is specifically expressed in epithelial tumors, including ovarian cancer, endometrial cancer, triple-negative breast cancer and non-small-cell lung cancer (35,36), making FRα a promising target for tumor therapy.

In November 2022, MIRV was approved by the FDA as the first ADC for ovarian cancer (37). Targeting FRα, MIRV comprises an antibody, a cleavable linker and a small-molecule microtubule inhibitor DM4 (a maytansine derivative) (38). MIRV is endocytosed by tumor cells and transferred to lysosomes, where it is degraded to release lysine-DM4. Lysine-DM4 produces metabolites that can inhibit tubulin polymerization and microtubule assembly, causing cell cycle arrest and leading to cell death (39). Further, the disintegration of tumor cells leads to the release of catabolic metabolites, which may induce bystander killing (40-42).

Several recent clinical studies have been conducted on the efficacy and safety of MIRV in ovarian cancer (43-45). A phase II trial (NCT04296890) including 106 patients with PROC showed a reduction in tumor size in 71.4% of patients, an objective response rate (ORR) of 32.4% and a median duration of remission (DOR) of 6.9 months (43). This result supports the clinically meaningful efficacy of MIRV in PROC expressing FRα, regardless of prior therapy or sequencing. Recently, a phase III trial (NCT04209855) compared MIRV with chemotherapeutic drugs (paclitaxel, PLD or topotecan) (45). The results showed a median progression-free survival (PFS) of 5.62 months in the MIRV group and 3.98 months in the chemotherapy group. The ORR of MIRV (42.3%) was significantly higher compared with that of chemotherapy (15.9%). The median overall survival of MIRV (16.46 months) was also significantly longer compared with that of chemotherapy

(12.75 months). Fewer adverse events also demonstrated the safety of MIRV over chemotherapy. These results support the use of MIRV for treating platinum-resistant epithelial ovarian cancer, providing a new alternative for treating PROC (46). Some ongoing clinical trials are assessing the efficacy and adverse effects of MIRV in PROC (NCT06365853, NCT06682988 and NCT05622890).

Besides MIRV, luveltamab tazevibulin (STRO-002) is the second ADC drug targeting FRα. STRO-002 acts as a tumor killer by releasing the tubulin-targeting cytotoxin 3-aminophenyl hemiasterlin (SC209) and reducing the potential for drug efflux (47). STRO-002 is still in phase I-III trials (NCT03748186, NCT05200364, NCT06238687 and NCT05870748), both as a monotherapy or in combination with bevacizumab in a variety of solid tumors, including PROC.

Farletuzumab ecteribulin (MORAb-202) is another ADC that targets FRα-expressing tumor cells. MORAb-202 initially inhibited tumor growth in a patient-derived xenograft (PDX) model of triple-negative breast cancer, demonstrating durable efficacy proportional to FRα expression (48). In clinical trials, MORAb-202 showed promising antitumor activity and good tolerability in a phase I study (NCT03386942) of FRα-positive solid tumors, including PROC (49). Also, two phase I/II trials of MORAb-202 for treating PROC (NCT05613088 and NCT04300556) are underway.

Targeting HER2. HER2 is another promising target that can enhance cell proliferation, differentiation and migration and inhibit apoptosis (50). HER2 is upregulated in a range of solid tumors, including breast, gastric and gynecological tumors (51). However, HER2-targeted therapies are not yet approved for use in diseases other than breast, lung, gastric and colorectal cancers (52). Trastuzumab deruxtecan (T-DXd) targets HER2 and contains a topoisomerase I inhibitor payload (53). T-DXd is approved for treating HER2-expressing breast and gastric cancers and HER2-mutated non-small-cell lung cancer (50). Preclinical studies demonstrated the antitumor activity of T-DXd against primary and metastatic ovarian tumors over-expressing HER2 (54). A global multicenter phase II study (NCT04482309) was conducted to evaluate the efficacy and safety of T-DXd in patients with HER2-expressing solid tumors across seven cohorts, including three major gynecological tumors. T-DXd treatment exhibited robust clinical efficacy, conferring sustained clinical benefits for patients with HER2-expressing solid tumors (55). Among all studied tumor types, the highest ORR was observed in the three major gynecological tumor cohorts, with an ORR of 57.5% for endometrial cancer, 50.0% for cervical cancer and 45.0% for ovarian cancer. Among the ovarian cancer cohort, 35.0% of the patients had previously received five or more lines of treatment and the median overall survival time was 13.2 months; by contrast, the median overall survival time for patients with high HER2 expression (IHC 3+) increased to 20.0 months (55). These findings indicate that T-DXd is a promising drug for HER2-expressing recurrent PROC (56).

Targeting TROP2. TROP2 is another tumor target highly expressed in ovarian cancer. This is a type I cell surface glycoprotein first discovered in human trophoblasts (57). It is upregulated in a variety of malignant tumors and plays an important role in tumor development, invasion and metastasis (58). Datopotamab deruxtecan (Dato-DXd; DS-1062a), an effective topoisomerase I inhibitor, is an ADC that targets TROP2. Dato-DXd specifically binds to TROP2, transports it intracellularly to lysosomes and releases DXd. In preclinical experiments, Dato-DXd induced DNA damage and apoptosis of tumor cells *in vitro* and displayed antitumor activity *in vivo* in xenograft tumors with high TROP2 expression (59). When mixed with TROP2 (IHC 3+) tumor cells, Dato-DXd showed a significant bystander-killing effect on tumor cells with low TROP2 expression, thus prolonging the survival time of epithelial ovarian cancer xenograft models and reducing toxicity (60). Most clinical trials are conducted on breast cancer. A phase II clinical trial (NCT05489211) is currently evaluating Dato-DXd for treating advanced/metastatic solid tumors, including ovarian cancer (61). The efficacy of Dato-DXd in ovarian cancer expressing TROP2 deserves continued attention.

Targeting mesothelin. Mesothelin represents a promising potential target for ovarian cancer. High expression of mesothelin is associated with chemotherapeutic resistance and poor prognosis in epithelial ovarian cancer (62). Anetumab ravtansine exhibits a high degree of affinity for mesothelin, using the microtubule inhibitor DM4 as a payload. It has displayed high antitumor activity and good tolerability as a monotherapy in the preclinical models of ovarian cancer (63). A phase I study (NCT02751918) determined the antitumor activity, safety and pharmacokinetics of anetumab ravtansine in PROC-expressing mesothelin. The result showed an ORR of 27.7%, DOR of 7.6 months and PFS of 5.0 months (64). This result suggests that targeting mesothelin is an effective and well-tolerated treatment option in patients with PROC. The development of other combination therapy regimens for anetumab ravtansine (65) and other ADCs targeting mesothelin (BMS-986148) (66) has also provided preliminary evidence of clinical activity and tolerable adverse reactions and toxicity in ovarian cancer.

Targeting NaPi2b. NaPi2b is another promising target for ADC, which is expressed in 95% of ovarian cancers (67). Lifastuzumab vedotin (LIFA) targeting NaPi2b displayed activity and acceptable safety in phase I studies (68,69). A phase II study compared the efficacy of LIFA and polyethylene glycol liposome doxorubicin in patients with PROC. The results showed that LIFA was well-tolerated, and ORR increased (34 vs. 15%; P=0.03) (70). Moreover, XMT-1536 and TUB-040 are other ADCs targeting NaPi2b. Currently, the safety and efficacy of these drugs in PROC are under evaluation in clinical trials (NCT06517485, NCT03319628, NCT06517433 and NCT06303505).

Other ADCs. New ADCs for ovarian cancer are constantly being developed. Raludotatug deruxtecan (R-DXd) targets cadherin 6 (CDH6) and was effective and safe in a preclinical study using PDX tumor models of serous ovarian cancer expressing CDH6 (71). B7-H4-directed ADC, using a pyrrolobenzodiazepine-dimer payload, displayed antitumor activity in a PARP inhibitor and platinum-resistant PDX model of high-grade serous ovarian cancer (72).

Table I. Ongoing clinical trials of ADCs monotherapy in ovarian cancer.

NCT identifier	ADC	Target	Ovarian cancer	Phase	Completion time
NCT06303505	TUB-040	NaPi2b	Platinum-resistant, high-grade ovarian cancer	I/II	2027-01
NCT06457997	PHN-010	-	Advanced/metastatic serous, endometroid, or clear-cell epithelial ovarian cancer	I	2027-07
NCT06390995	Mirvetuximab Soravtansine (TAK-853)	FRα	FRα-positive advanced ovarian cancer	I/II	2026-09-30
NCT04152499	SKB264	TROP2	Locally advanced unresectable/metastatic epithelial ovarian cancer	I/II	2026-07-16
NCT06234423	CUSP06	CDH6	Platinum-refractory/resistant ovarian cancer	I	2027-08-31
NCT06003231	Disitamab vedotin (DV)	HER2	Previously treated, locally-advanced, unresectable or metastatic ovarian neoplasms	II	2028-05-31
NCT06173037	RC88	Mesothelin	Platinum-resistant recurrent epithelial ovarian cancer	II	2026-12-31
NCT05103683	TORL-1-23	CLDN6	Advanced ovarian cancer	I	2025-11-15
NCT06523803	ZW171	Mesothelin	Mesothelin-expressing advanced or metastatic ovarian cancer	I	2027-12
NCT05527184	IMGN151	FRα	Recurrent, HGS epithelial ovarian cancer	I	2025-12-30
NCT06014190	HS-20089	B7-H4	Recurrent or metastatic ovarian cancer	II	2027-12-31
NCT05613088	Farletuzumab Ecteribulin (MORAb-202)	FRα	Platinum-resistant HGS ovarian cancer	II	2026-10-11
NCT06466187	SGN-MesoC2	-	Advanced ovarian neoplasms	I	2028-11-01
NCT04300556	MORAb-202	FRα	Platinum-resistant HGS epithelial ovarian cancer	I/II	2024-10-30
NCT06084481	ABBV-400	c-Met	Platinum resistant, high grade epithelial ovarian cancer	I	2026-07-01
NCT06238479	LY4101174	Nectin-4	Recurrent, advanced or metastatic ovarian cancer	I	2027-03-04
NCT06465069	LY4052031	Nectin 4	Advanced or metastatic ovarian cancer	I	2027-05
NCT06545617	BAT8006	FRα	Platinum-resistant epithelial ovarian cancer	I/II	2028-01-31

NaPi2b, Sodium-dependent phosphate transporter 2b; HGS, high-grade serous; ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; TROP2, trophoblast cell surface antigen-2; FRα, folate receptor α; CLDN6, Claudin 6.

The findings of several newly completed clinical trials examining the use of ADCs in ovarian cancer (NCT06517485 and NCT06517433) are yet to be published. Table I lists the clinical trials investigating ADC monotherapy for ovarian cancer that deserve continued attention in the future.

Combination therapy using ADCs and other agents

Combination therapy using chemotherapeutic agents. Chemotherapeutic agents such as platinum, which can damage DNA, target the S phase of the cell cycle and induce the G_2/M phase. Preclinical studies described below have shown that these chemotherapeutic agents can bind effectively to ADCs containing microtubule-disrupting payloads. MIRV has been demonstrated to arrest the cell cycle and enhance DNA damage. The combination of MIRV with carboplatin, Adriamycin or doxorubicin has been found to inhibit proliferation synergistically in ovarian cancer cell lines and PDX models (73). The combination therapy of carboplatin and STRO-002 further improved the efficacy of STRO-002 (47). The combination of anetumab ravtansine with carboplatin or PLD demonstrated enhanced efficacy *in vivo* and *in vitro* (in ovarian cancer cell line and PDX models) compared with monotherapy in ovarian cancer (74). MIRV combined with carboplatin in early clinical trials achieved an ORR of 71%, with only minor adverse events (75), making it a highly active therapy for ovarian cancer.

Combination therapy with the molecularly targeted drug bevacizumab. A prevalent issue in solid tumors is inadequate blood flow and hypoxia within the vasculature (76). Using drugs such as anti-vascular endothelial growth factor antibodies (e.g., bevacizumab) can modulate angiogenesis and vascular porosity, thereby altering the tumor vascular system. Bevacizumab, the first targeted drug indicated for ovarian cancer, has been approved for use in combination with chemotherapy (77). Administering bevacizumab in combination with platinum-based chemotherapy after disease progression still improved PFS (78). ADCs have also shown safety and

efficacy in combination with bevacizumab, particularly in PROC. Preclinical studies demonstrated that MIRV combined with bevacizumab resulted in rapid destruction of the tumor microvascular system and extensive areas of necrosis (73,74). Moreover, it was highly effective in a PDX model of PROC, causing significant regression and complete remission (73). Anetumab ravtansine combined with bevacizumab also demonstrated enhanced antitumor efficacy (74). These results emphasized the superior biological activity of the combination and further advanced the combination into clinical trials.

In clinical trials, the combination of MIRV and bevacizumab demonstrated efficacy and was well-tolerated in patients with PROC (79). In another cohort from the same study (NCT02606305), 94 patients with PROC treated with MIRV and bevacizumab had an ORR of 44%, an median duration of remission (mDOR) of 9.7 months, and an median progression-free survival (mPFS) of 8.2 months (80). Furthermore, incorporating MIRV into dual therapy with platinum and bevacizumab demonstrated enhanced efficacy and safety profiles in platinum-sensitive ovarian cancer (81). All these results point to the importance of ADCs combined with bevacizumab. Currently, a number of ongoing trials are investigating several additional combinations of different ADCs with bevacizumab (NCT05445778, NCT05200364 and NCT03587311).

Combination therapy with immunotherapy. Other than directly inducing cancer cell death using cytotoxic payloads, ADC also has antitumor immune activity (8,82,83). The related mechanisms, including Fc-mediated effector function, immune cell death, dendritic cell maturation, enhancement of T-cell infiltration and enhancement of immune memory, among others, have been the subject of discussion (84-87). ADCs have been shown to possess considerable immunomodulatory capacity in animal models (88). Combination of ADCs with immunotherapy in refractory tumors is a promising strategy for clinical treatment; its improved antitumor effects have been initially demonstrated in many preclinical studies and early clinical trials.

Immune checkpoint inhibitors (ICIs) combined with ADCs have synergistic effects in triple-negative breast cancer (89); the rationale behind this combination is that ADCs activate the immune system, whereas ICIs remove the brakes, allowing the immune system to regain its ability to recognize and kill tumor cells (90). Durvalumab combined with T-DXd (NCT03742102) exhibited an ORR of 100% and was found to be safe in a small group of patients with low expression of HER2. The interim results of T-DXd alone and combined with patulizumab (NCT04538742) showed ORRs of 77.3 and 82.0% and 12-month PFSs of 77.3 and 89.4%, respectively, demonstrating promising efficacy and controllable safety. The clinical benefits of ADCs combined with immunotherapy have been observed in clinical trials on both uroepithelial cancer (NCT03288545 and NCT04264936) and lung cancer (NCT02099058), besides breast cancer (91). MIRV combined with other agents, including pembrolizumab, was evaluated in FRα-positive PROC. Preliminary data showed good tolerability and therapeutic activity, with an ORR of 43%, mDOR of 6.9 months, and mPFS of 5.2 months for MIRV combined with pembrolizumab (NCT02606305). The synergistic effect of ADCs and immunotherapy can overcome treatment resistance, displaying encouraging efficacy and safety in tumor treatment. However, large, randomized phase III clinical trials are needed to test their efficacy against conventional therapy.

Table II lists the ongoing clinical trials on ADC combination therapy for ovarian cancer.

5. Toxicity characteristics and management of ADCs

Adverse reactions and toxicity. ADC has fewer side effects compared with conventional chemotherapy due to its ability to target tumor cells. The toxicity of ADCs arises primarily from the payload and secondarily from linker and bystander effects (92).

A common treatment-related adverse event (TRAE) associated with MIRV is ocular toxicity. A systematic review and meta-analysis showed that the most common TRAEs in patients treated with MIRV were blurred vision (all grades, 45%; grade III, 2%; no grade IV), nausea (all grades, 42%; grade III, 1%; no grade IV) and diarrhea (all grades, 42%; grade III, 2%; no grade IV) (93). In a previously mentioned phase II trial of MIRV (NCT04296890), the most common TRAEs were blurred vision (all grades, 41%; grade III, 6%; no grade IV), keratoconus (all grades, 29%; grade III, 8%; grade IV, 1%) and nausea (all grades, 29%; no grade III or grade IV) (43). Further, ocular events requiring dose reductions occurred in 12 patients (11%). One patient required discontinuation of therapy.

T-DXd is associated with interstitial lung disease (ILD)/pneumonia due to the expression of HER2 in lung epithelial cells (94). It is mainly localized to alveolar macrophages; the incidence and severity of ILD/pneumonia depend on the T-DXd dose and frequency of administration, suggesting that this ILD/pneumonia may be caused by cytotoxic lung injury (95). It is mild in most cases and can be effectively treated, but may be fatal in some cases (96). Respiratory disease (pneumonia) has been the most common cause of treatment-related mortalities in all types of ADC therapy (97). Other TRAEs include nausea and diarrhea, which are effectively controlled using antiemetic and antidiarrheal medications.

Management and prevention. Toxicity management includes implementing supportive measures, suspension of treatment, dosage adjustments, or permanent discontinuation of therapy. Most ocular adverse events are mild and reversible; they improve or subside upon discontinuation or therapy improvement (98). Scheduling regular eye examinations to monitor early signs and symptoms, detecting ocular adverse effects in an early stage and prompting pharmacological intervention, promoting the prophylactic use of corticosteroids and lubricating eye drops, adjusting ADC dosage when needed, and maintaining clear communication with the ophthalmologist can help relieve symptoms before the vision is affected, ultimately helping the patient to continue treatment (98,99).

New guidelines for T-DXd-associated ILD/pneumonia toxicity have been published. A multidisciplinary team and timely management with steroids are recommended (100). Careful monitoring by a multidisciplinary team facilitates early detection [e.g., grade I (100)] of ILD/pneumonia, leading to timely discontinuation of medication and initiation of steroids, which prevents the development of fatal ILD/pneumonia.

Table II. Ongoing clinical trials of ADCs combination therapy in ovarian cancer.

NCT Identifier	ADC combination therapy	Target	Ovarian cancer	Phase	Completion time
NCT05887609	MIRV in combination with Olaparib	FRα	Recurrent platinum-sensitive ovarian cancer	II	2027-12
NCT06660511	Disitamab vedotin in combination with anlotinib hydrochloride	HER2	HER-2-expressing recurrent platinum-resistant ovarian cancer	I	2025-10-15
NCT05941507	LCB84 single agent and in combination with an anti-PD-1 Ab	TROP2	Advanced ovarian cancer	I/II	2027-05
NCT04606914	MIRV in combination with carboplatin	FRα	FRα-positive advanced-stage ovarian cancer	II	2028-05-31
NCT05797168	Saruparib (AZD5305), bevacizumab, carboplatin	-	Advanced ovarian cancer	I/II	2028-01-06
NCT05293496	Vobramitamab duocarmazine (MGC018) in combination with lorigerlimab (MGD019)	B7-H3	Advanced epithelial ovarian cancer	I	2026-03
NCT05445778	MIRV in combination with bevacizumab	FRα	FRα-high recurrent platinum-sensitive epithelial ovarian cancer	III	2029-04
NCT05489211	Dato-DXd as monotherapy and in combination with anticancer agents	TROP2	Advanced/metastatic ovarian cancer	II	2026-08-19

MIRV, Mirvetuximab Soravtansine; ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; TROP2, trophoblast cell surface antigen-2; FRα, folate receptor α; PD-1, programmed cell death protein 1; Dato-DXd, Datopotamab Deruxtecan.

6. Challenges in ADC development

The development of ADCs has some challenges. The target expression is not uniform in tumors due to the heterogeneity of tumor cells, and ADCs have limited effects on tumor cells with low or no target expression. Normal tissues expressing the target are attacked by the drug, limiting the drug dose. When combining drugs, the optimal dose of each drug and the order of administration also need to be re-explored. Other challenges include tumor cells developing resistance to ADCs through multiple mechanisms, the need to identify potential biomarkers for patient selection and limitations in current clinical trial designs.

Mechanisms of ADC resistance. ADC resistance can be caused by various mechanisms, including change in antigen expression, failure of ADC transportation, failure of ADC internalization, change in tumor sensitivity, exocytosis of ADC payload and activation of signaling pathways (101-103). Some of these mechanisms are not fully understood.

First, alterations occur in target antigen expression, including target downregulation, loss or mutations in target genes. Some tumor cells may evade ADC recognition and binding by reducing or completely losing target expression. Mutations in the target gene may also alter the structure and function of the target, thus affecting the binding affinity of the ADC to the target (101,102).

Second, the abnormal expression or defective function of endocytosis-related proteins, such as cell surface grid proteins, in some tumor cells can lead to the inability of ADC to enter the cell effectively during the internalization and processing of ADC. ADCs that enter the cell are usually transported to the lysosome for degradation, releasing cytotoxic drugs to play a role. If tumor cells enhance the stability of lysosomes or change the microenvironment of lysosomes, ADCs cannot release drugs in lysosomes, resulting in drug resistance (103,104).

Furthermore, a resistance mechanism related to drug metabolism and clearance involves high expression of drug efflux pumps (e.g., drug transporter proteins such as multidrug resistance protein 1 and multidrug resistance-associated protein 1), which can pump ADCs or their released cytotoxic drugs out of the cell, decreasing the drug concentration in the cell, thus leading to drug resistance (104). In breast cancer, acquired resistance to ADC developed in two different cancer cells after months of drug treatment, primarily due to increased expression of the drug efflux protein ABCC1 or decreased expression of HER2 antigen (105).

Finally, the alterations in multiple signaling pathways in tumor cells are also closely related to ADC resistance. For example, the activation of the PI3K/Akt/mTOR signaling pathway can promote the proliferation, survival and metabolism of tumor cells, making them resistant to the cytotoxic effects of ADCs. The abnormal activation of the JAK/STAT signaling pathway may also lead to the development of ADC resistance in tumor cells (106). Alterations in some signaling pathways involved in regulating the cell cycle and apoptosis (such as aberrant activation of STAT3) can also lead to the development of ADC resistance (106).

Selection of potential biomarkers. The selection of potential biomarkers for ADC drug development is also challenging. Normal tissues and cells may also partially express ADC targets, and therefore ADC payloads may have serious side

effects on these normal cells (15). The biomarker should preferably be present only on tumor cells or tumor tissue and not expressed in normal cells and tissues. Uniform criteria to determine the expression level that accurately predicts ADC efficacy are lacking. For example, in the case of gosatuzumab, the TROP-2 ADC drug, although TROP-2 expression is associated with efficacy, the exact threshold of expression needs to be further defined with more sufficient evidence. In addition, the biomarker expression of different cells within the same tumor may vary or the biomarker expression levels of the same types of tumors originating from different patients may be different due to the existence of intra-tumor and inter-tumor heterogeneity. All of these increase the difficulty in finding universal biomarkers (107), making the selection of specific targets highly challenging. Moreover, the tumor cells lacking a specific target can proliferate rapidly in the presence of ADCs, leading to a new round of recurrence and drug resistance (108), again demonstrating the importance of finding tumor-specific targets.

Limitations of clinical trials. Current clinical trials are mostly limited to the efficacy of ADC monotherapy. The information on the safety and toxicity of monotherapy and the efficacy of combination therapy is still in the preliminary stages. First, like-for-like comparisons of newer ADC drugs with standard-of-care or other comparable ADC drugs in clinical trials are scarce, limiting their status and superiority in their class and creating difficulties in dosing choices for clinicians and patients. Second, the maximum tolerated dose is usually derived from safety data in phase I trials. However, the cumulative toxicity of a drug may not be apparent until after multiple courses of therapy, which needs further investigation. In addition, the complexity of the design of sequencing, dosage and duration of combination therapy, as well as the lack of established theoretical and practical guidance, makes the design and implementation of clinical trials more difficult.

Practical challenges in clinical practice. A number of other novel approaches to tumor treatment are currently available, which include tumor cell therapy, chimeric antigen receptor T-cell therapy (109), T-cell receptor engineered T-cell therapy (110), tumor-infiltrating lymphocyte therapy (111), ICI therapies, therapies using gene editing techniques such as CRISPR-Cas9 (112) and oncolytic virotherapy (113). ADCs have shown good efficacy in treating various hematological malignancies and solid tumors, with relatively good safety, controllable adverse effects and fewer serious adverse effects such as cytokine release syndrome (114). The precise delivery mechanism, excellent therapeutic effect and safety of ADC indicate its great developmental potential in the field of tumor therapy and wide recognition in the tumor therapy market.

However, the development of ADCs faces several practical challenges in clinical practice. First, comprehensive patient stratification from both clinical and molecular characteristics is needed for specific clinical applications. Besides determining the molecular typing of the patient's tumor cells to select sensitive ADC drugs, the patient's general conditions, such as age, physical status and comorbidities, and other tumor-related characteristics, such as tumor site, size, stage and metastasis, need to be comprehensively considered. For example, the tolerability of ADC therapy may need to be more carefully evaluated in patients with advanced stage and poor physical status. Further, patient tumor samples can be comprehensively analyzed using multi-omics technologies, such as genomics, transcriptomics, proteomics and metabolomics, to mine highly specific and sensitive biomarker combinations for individualized and precise treatment. Second, as ADCs are expensive, a study suggested a reduction in total drug acquisition costs by at least 50% to make it a cost-effective strategy (115). The present study recommends using advanced computer simulation and artificial intelligence techniques to improve drug design and screening efficiency, optimize research and development processes, and enhance production by increasing coupling efficiency and product purity, ultimately reducing research and development and manufacturing costs.

7. Future perspectives of ADC therapy

Treatment of PROC remains a major challenge. Despite the development of systemic therapies for ovarian cancer, bevacizumab, PARP inhibitors and ICIs still fail to meet the therapeutic needs of patients with PROC. ADC-specific delivery payload reduces side effects and has been shown to be superior to conventional monotherapy in PROC, resulting in patient benefits (116). ADCs combined with bevacizumab have displayed superior activity and tolerability in PROC. Therefore, ADCs may become the preferred combination with bevacizumab, providing a superior treatment option for patients with PROC. However, the results from applications in other cancers have shown that ADCs can eventually allow disease progression due to the emergence of drug resistance. These ADC-resistant cells remain sensitive to standard chemotherapeutic agents or other ADCs, which suggests that ADC resistance can be overcome by the appropriate use of other alternative drugs.

Several possible ways to overcome ADC resistance have been proposed, such as the use of cytotoxic agents with poor efflux potential and combinations with other drugs (117,118). With technological advancement, dual-targeting ADCs and dual-drug ADCs have been further developed. Dual-targeting ADCs can recognize and bind to two different targets at the same time and also bind to tumor cells more precisely and effectively, thus overcoming the therapeutic challenges posed by tumor heterogeneity. These strategies are expected to reduce the likelihood of tumor cells becoming resistant to treatment and extend the effective duration of drug therapy (119). Dual-drug ADCs, on the contrary, use two different cytotoxic drugs as payloads; more significant antitumor activity can be obtained, and the occurrence of drug resistance can be reduced by precisely controlling the ratio of the two drugs (120). Enhancing the bystander-killing effect by converting non-cleavable linkers into cleavable linkers is also a way to overcome drug resistance (105). Moreover, ADCs release tumor-associated antigens while killing tumor cells, thus activating the antitumor immune response, making ADCs synergistic with ICIs (121). The combination of the two can enhance the killing effect on tumor cells, thus overcoming the drug resistance of ADCs. For example, one study has shown that combining ADCs and ICIs can improve the ORR of patients, prolong PFS and also have certain therapeutic effects

on some patients resistant to ADC in triple-negative breast cancer (NCT03742102). These studies are expected to provide additional insights into the optimal use of these agents.

The optimization of the ADC drug structure and innovative developments are expected to further improve its therapeutic efficacy and safety. Consequent to the ongoing advancement of science and technology, the search for ADCs more precisely targeting tumor cells and more stable in the circulation may represent a prominent research focus in the future. The continuous discovery and validation of new drug targets can propel the advancement of ADCs, thereby broadening the range of ADC applications in clinical settings. This may have a significant and far-reaching impact on the landscape of cancer treatment. Combining ADCs with various antitumor agents is a promising strategy that needs further exploration and optimization to improve efficacy and mitigate adverse effects. The current ADCs in PROC are primarily directed toward high-grade plasmacytoid ovarian cancer. Further studies may include other histological subtypes.

The safety and resistance after long-term drug use needs to be further evaluated as research continues. At present, the research on the discovery, related mechanisms and solutions of drug resistance in ADC mainly focuses on breast cancer, lung cancer and gastric cancer. The corresponding data on ovarian cancer is still lacking. ADC resistance may be discovered in the future due to reduced FRα expression. Therefore, inspiration should be drawn from the studies on other cancers and actively address potential drug resistance by developing novel ADC designs or implementing appropriate alternative and combination therapies.

8. Conclusions

ADCs have demonstrated potent clinical activity in PROC by selectively delivering cytotoxic drugs to tumor cells, improving therapeutic efficacy and reducing toxicity. The approval of MIRV for treating FRα-positive PROC has led to the rapid evolution of ADC monotherapy and combination therapies, which offers hope for patients with PROC. The gradual use of more effective ADCs for treating PROC may be observed in the future.

The development of novel drugs that can more accurately target tumor cells and are more stable in the circulation will be the future pursuit of researchers. The possible emergence of ADC resistance and the mechanism behind it during clinical application should be considered, so as to more effectively use ADCs as a weapon to optimize the therapeutic regimens for patients.

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Authors' contributions

KS and SY were responsible for conceptualization, data curation and writing the original draft. NS and FT participated in the topic selection and were responsible for data collection and analysis. SR and HaW were responsible for software and validation, managing the literature and editing the table section of the manuscript. YZ and YW were responsible for creating the figure and participated in drafting the manuscript. HoW and HG were responsible for reviewing and editing the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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