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Review

China's Contribution to the Clinical Development of Antibody-Drug Conjugates in Gynecologic Cancers: A Review

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Abstract

Objective: This review summarizes global advances in antibody-drug conjugate (ADC) research for the treatment of gynecologic cancers and highlights China's rapidly evolving role in developing these agents, aiming to contextualize their growing impact on future therapeutic standards. **Mechanism**: ADCs represent a transformative class of targeted therapies, coupling monoclonal antibodies with potent cytotoxic payloads through linkers, thereby enabling selective drug delivery to tumor cells while minimizing systemic toxicity. **Findings in Brief**: Globally, ADCs such as mirvetuximab soravtansine and tisotumab vedotin have demonstrated significant clinical benefits in platinum-resistant ovarian and recurrent cervical cancers. Parallel progress in other ADCs has expanded therapeutic options across ovarian, endometrial, and cervical cancers. In China, ADC development is accelerating, with several domestically developed agents targeting folate receptor alpha, human epidermal growth factor receptor 2, trophoblast cell surface antigen 2, cadherin-6, nectin-4, B7 homolog 4, and epidermal growth factor receptor/human epidermal growth factor receptor 3 advancing into phase II and III trials. Early results show encouraging efficacy and safety, underscoring China's emergence as a key contributor to global anticancer innovation. Nevertheless, variability in biomarker assay, regulatory differences, and future challenges related to pricing and equitable access remain important considerations. **Conclusions**: ADCs are redefining the treatment landscape for gynecologic cancers. China's expanding pipeline, supported by domestic innovation and international collaboration, is poised to significantly influence future standards of care. Continued progress in clinical validation, regulatory alignment, and the development of diagnostic and reimbursement infrastructures will be essential to ensure that these novel therapies achieve meaningful and equitable global impact.

Keywords: antibody-drug conjugates; gynecologic cancers; ovarian cancer; cervical cancer; endometrial cancer; clinical trials; China

1. Introduction

An antibody-drug conjugate (ADC) is a targeted anticancer agent that comprises a monoclonal antibody linked via a specialized chemical linker to a potent cytotoxic payload, enabling selective delivery of the latter to tumor cells (Fig. 1) [1]. In gynecological oncology, ADCs have emerged as a promising strategy for improving objective response rates (ORRs), progression-free survival (PFS), and overall survival (OS) in patients with challenging cases (e.g., relapsed or metastatic cancers) whose tumors are resistant to conventional therapies such as platinum-based chemotherapy.

Globally, several ADCs have gained regulatory approval for treating gynecological malignancies. For example, mirvetuximab soravtansine (MIRV), a folate receptor alpha (FRα)-targeting ADC, has been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of platinum-resistant ovarian cancer (PROC) [2]. Similarly, tisotumab vedotin, an ADC that targets tissue factor, has received FDA approval for treating recurrent or metastatic cervical cancer that progresses after chemotherapy; phase III data from the InnovaTV 301 trial showed a 30% reduction in mortality risk compared with that of the investigators' choice chemotherapy [3]. Recently published reviews provide up-to-date guidance on the management of ovarian cancer and human epidermal growth factor receptor 2 (HER2)-positive endometrial cancer [4,5].

In contrast, China's regulatory landscape for ADC use in patients with gynecological malignancies remains nascent, with only MIRV approved by the National Medical Products Administration (NMPA) for PROC in November 2024. Despite this, China is swiftly positioning itself as a pivotal contributor to anticancer therapies through a rapid expansion in ADC development; this effort is being driven by substantial investments, abundant patient resources, expedited regulatory pathways (e.g., the NMPA's 30-day fast-track mechanism), and cost-effective clinical environments [6]. This surge has positioned China as a key player in global oncology research, with several domestically produced ADCs against novel targets like nectin-4 and epi-

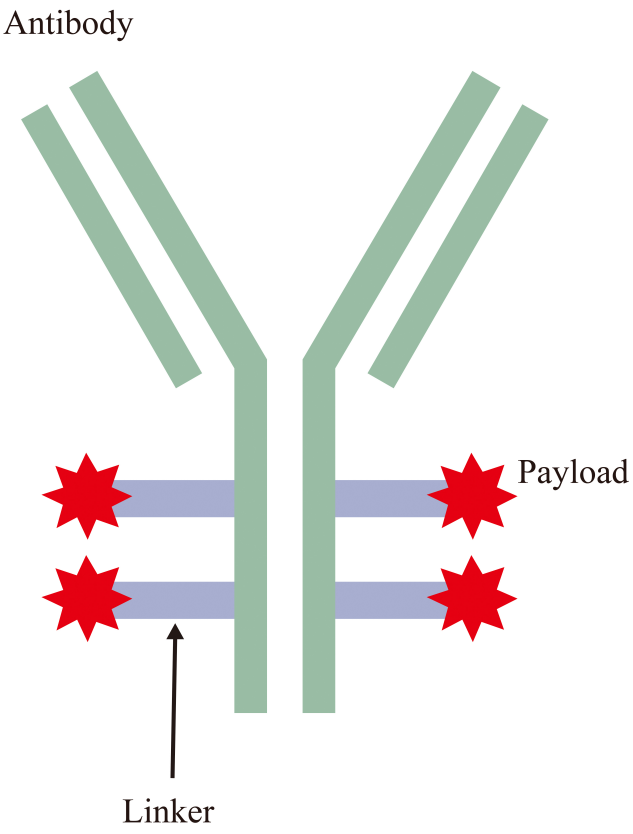

Fig. 1. Schematic illustration of the structural components of an antibody-drug conjugate.

dermal growth factor receptor (EGFR)/human epidermal growth factor receptor 3 (HER3) entering late-stage trials.

This comprehensive review describes China's contribution to the global progress in the research and development of ADCs that target gynecological tumors. Emphasis is placed on current phase III clinical trials for patients with ovarian, cervical, and endometrial cancers being conducted in China and on assessing the future accessibility of these novel therapies for women with gynecologic malignancies in the country.

2. Literature Review

Although a formal systematic review framework was not applied for this descriptive review, we adopted a structured approach to ensure transparency in literature identification and performed a targeted search of ClinicalTrials.gov and the Chinese Clinical Trial Registry (http://www.chinadrugtrials.org.cn) to identify phase III clinical trials conducted in China involving ADCs used to treat gynecologic malignancies. Disease-related search terms included "ovarian cancer", "cervical cancer", "endometrial cancer", "vulvar cancer", "vaginal cancer", and "gestational trophoblastic neoplasia". Trials were screened for relevance based on cancer type, phase, study design, and availability of ADC-related interventions.

For each ADC that had progressed to phase III trials in China, we conducted additional searches in PubMed and Embase to collect supporting evidence from earlier-phase (I/II) studies. Search terms included combinations of the ADC name, molecular target, and the gynecologic cancer terms listed above. Both peer-reviewed publications and major conference abstracts were considered if they reported efficacy, safety, or mechanistic data relevant to the ADCs being evaluated in China.

Literature and trial information published or updated as of August 31, 2025, were included. Reference lists of key articles were also reviewed to ensure completeness. As this is a narrative review, no Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram was generated; however, care was taken to avoid selective reporting by cross-checking trial identifiers and verifying that all ADCs entering phase III investigations in China were acquired.

3. ADCs for Gynecologic Cancer in China

Twenty-one phase III clinical trials of ADCs in patients with gynecological malignancies are currently underway in China, reflecting an unprecedented expansion in late-stage development. These studies span three major cancer types: endometrial cancer (six trials), cervical cancer (three trials), and ovarian cancer (12 trials). Moreover, the trials encompass eight distinct molecular targets, highlighting the diversity of China's ADC pipeline: HER2 (seven trials); trophoblast cell surface antigen 2 (TROP-2) (five trials); FRα (four trials); and cadherin-6 (CDH6), nectin-4, B7 homolog 4 (B7-H4), EGFR/HER3, and tissue factor (one trial each) (Fig. 2).

3.1 FRα-Targeting ADCs

FRα is commonly overexpressed in several types of solid tumors, particularly in ovarian cancers [7]. MIRV is an FRα-targeted ADC with a cleavable linker that attaches to maytansinoid DM4 (DM4), a potent tubulin-targeting maytansinoid. The FDA fully approved it for the treatment of adult patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who previously received 1–3 systemic treatment regimens. This approval was supported by prior data from the phase III MIRASOL trial that compared MIRV to the investigators' choice chemotherapy in patients with FRα-positive (defined as at least 75% of viable tumor cells scoring $\geq$2 in membrane staining intensity on immunohistochemistry [IHC] using the Ventana folate receptor 1 [FOLR1] assay), platinum-resistant, advanced high-grade epithelial ovarian cancer. MIRV treatment resulted in longer PFS (5.62 vs. 3.98 months, hazard ratio [HR]: 0.65, $p < 0.001$) and OS (16.46 vs. 12.75 months, HR: 0.67, $p = 0.005$) (Table 1) [2]. MIRV also exhibited a manageable safety profile, with lower rates of grade $\geq$3 adverse events (AEs) and serious AEs compared with those with the investigators' choice

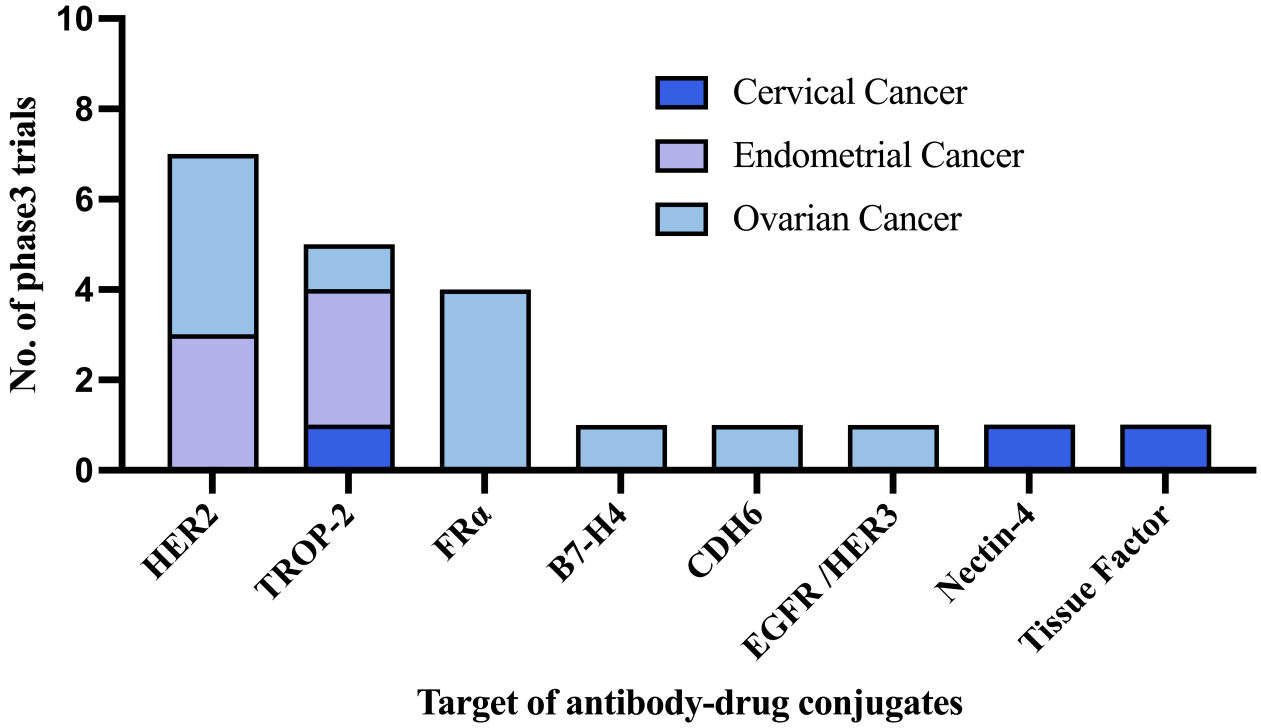

Fig. 2. Landscape of phase III antibody–drug conjugate trials in patients with gynecologic malignancies in China. HER2, human epidermal growth factor receptor 2; TROP-2, trophoblast cell surface antigen 2; FRα, folate receptor alpha; B7-H4, B7 homolog 4; CDH6, cadherin-6; EGFR/HER3, epidermal growth factor receptor/human epidermal growth factor receptor 3.

of chemotherapy. The most common treatment-related toxicities included blurred vision, keratopathy, abdominal pain, and fatigue, which were consistent with prior studies using MIRV. Ocular AEs occurred in 56.0% of patients and were primarily low-grade, including grade 3 blurred vision (7.8%), keratopathy (9.2%), and dry eye (3.2%); nearly all events resolved to grade 0–1 with supportive care. Data on safety and efficacy in Chinese patients with FRα-high PROC were consistent with those from the MIRASOL trial. The NMPA approved MIRV for PROC in November 2024. Additionally, several ongoing trials are investigating the use of MIRV and bevacizumab in ovarian cancer. The GLORIOSA phase III randomized trial (NCT 05445778) investigating maintenance MIRV with bevacizumab vs. bevacizumab alone in patients with FRα-high, platinum-sensitive ovarian cancer is recruiting participants in China and has an estimated primary completion date of March 2027 [8].

BAT8006, discovered by Bio-Thera Solutions, Ltd. in China, is an ADC consisting of a humanized anti-FRα monoclonal antibody linked to the topoisomerase I inhibitor exatecan. In the BAT-8006-001-CR trial, 131 patients with PROC received different doses of BAT8006; the ORR among 108 efficacy-evaluable patients was 32.4% (35/108). The median PFS was 6.9 months (95% confidence interval [CI]: 4.3–7.9), while the median OS was not reached (Table 1) [9]. The safety profile of BAT8006 was manageable; common treatment-emergent AEs (TEAEs) included anemia, leukopenia, neutropenia, and thrombocytopenia, while no cases of interstitial lung disease or ocular toxicities were reported. Two phase III trials evaluating the efficacy of BAT8006 monotherapy in patients with PROC (CTR20251345) and of BAT8006 with bevacizumab vs. bevacizumab alone in patients with FRα-high platinum-sensitive ovarian cancer (CTR20252907), respectively (Table 2), are ongoing.

3.2 Tissue Factor-Targeting ADC

Tissue factor is expressed on normal mesenchymal cell types such as endothelial cells; however, it is also expressed on the surfaces of tumor cells in up to 95% of patients with cervical cancers [10]. Tisotumab vedotin is an ADC that targets tissue factor using a cleavable linker attached to the microtubule-disrupting agent monomethyl auristatin E [11]. It was granted full FDA approval in April 2024 by Hong Kong's Department of Health in September 2024 for recurrent or metastatic cervical cancer progressing during or after chemotherapy after results from the InnovaTV-301 trial were published. The InnovaTV-301 phase III trial (NCT04697628) aimed to compare tisotumab vedotin to the investigator's choice chemotherapy and showed a significant improvement in PFS (4.2 vs. 2.9 months; HR: 0.67, 95% CI: 0.54–0.82; $p < 0.001$) and OS (11.5 vs. 9.5 months, HR: 0.70, 95% CI: 0.54–0.89, p =

0.004) as a second-line treatment for recurrent or metastatic cervical cancer (Table 1) [3]. Tisotumab vedotin demonstrated a manageable safety profile, with the most common AEs including nausea, conjunctivitis, and anemia. Ocular events occurred in 52.8% of patients, although grade ≥3 events were uncommon. Peripheral neuropathy and bleeding events were also observed, typically at low-to-moderate severity. Seventy-four of the 502 patients in this trial were Chinese; this subgroup also showed a significant improvement in OS (22.3 vs. 10.1 months, HR: 0.44, 95% CI: 0.23–0.87), PFS (4.4 vs. 2.8 months, HR: 0.52, 95% CI: 0.27–1.03), and ORR (14.3 [95% CI: 4.8–30.3] vs. 5.1 [95% CI: 0.6–17.3]) [12]. The safety profile was manageable, with no new safety parameters specific to the Chinese subgroup. The results from the Chinese subgroup were consistent with those from the global cohort, supporting tisotumab vedotin as an effective second-line treatment option for these patients. In mainland China, a Biologics License Application was submitted to the NMPA in March 2025 and is under review; if approved, it could become the first ADC indicated for recurrent or metastatic cervical cancer in China.

3.3 HER2-Targeting ADCs

HER2 expression data vary widely across studies; its overexpression has been observed in 12–31% of endometrial cancers, 20–38% in ovarian cancers, and 2–6% in cervical cancers [13]. Trastuzumab deruxtecan (T-DXd) is a HER2-directed ADC with a potent Top1 inhibitor payload; it has been approved by the FDA for HER2-positive (IHC 3+) solid tumors based on the DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 trials. The DESTINY-PanTumor02 trial included patients with cervical, endometrial and ovarian cancers with HER2 scores of 2+/3+ on IHC, with 40 patients in each cohort. The ORRs in patients with endometrial, cervical, and ovarian cancer with IHC scores of 2+/3+ were 57.5%, 50.0%, and 45.0%, respectively; those in the subset of patients with IHC scores of 3+ were 84.6%, 75.0%, and 63.6%, respectively (Table 1) [14]. The most common treatment-related AEs (TRAEs) owing to T-DXd were nausea, anemia, diarrhea, and vomiting, which were generally manageable. Interstitial lung disease (ILD)/pneumonitis occurred in 10.5% of patients, with most cases being low-grade (1 and 2).

The ongoing phase III DESTINY-Endometrial01 (NCT06989112/CTR20244095) trial is evaluating the efficacy of T-DXd in combination with rilvegostomig or pembrolizumab as a first-line therapy for patients with HER2-expressing (IHC 2+/3+), mismatch repair-proficient, primary advanced or recurrent endometrial cancer. The DESTINY-Endometrial02 study (NCT07022483/CTR20253443) will enroll post-surgical patients with HER2-expressing (IHC scores of 2+ or 3+) endometrial cancer who have not received prior systemic or neoadjuvant therapy and will assess the efficacy and safety of T-DXd compared with those of standard-of-care chemotherapy with or without radiotherapy as adjuvant treatment. Additionally, the DESTINY-Ovarian01 trial (CTR20251716/NCT06819007) is a phase III, multicenter, randomized study designed to evaluate the efficacy and safety of T-DXd in combination with bevacizumab vs. bevacizumab monotherapy as a first-line maintenance therapy in patients with HER2-expressing (IHC score of 1+, 2+, or 3+) high-grade epithelial ovarian cancer. All three trials are international, multicenter studies that include Chinese participants from mainland China (Table 2).

In addition to T-DXd, several HER2-targeted ADCs developed in China have demonstrated encouraging clinical activity, and phase III trials of these agents in patients with gynecologic malignancies are currently underway (Table 2). In a phase II study of SHR-A1811, a novel HER2-directed ADC conjugated to a Top1 inhibitor payload, the ORR was 66.7% among 30 patients with ovarian cancer, 43.5% among 23 patients with endometrial cancer, and 66.7% among 24 patients with cervical cancer exhibiting HER2 expression (IHC score 2+ or 3+) (Table 1) [15]. Grade ≥3 TRAEs occurred in 77.8% of patients (84 cases), with decreased neutrophil count being the most common (62.0%). A phase III clinical trial (NCT06990503/CTR20250550) evaluating the efficacy and safety of SHR-A1811 compared with those of the investigators' choice chemotherapy in patients with HER2-expressing (IHC score 1+, 2+, or 3+) PROC (Table 3) is ongoing.

JSKN003 is a biparatopic HER2-targeting ADC conjugated to a Top1 inhibitor payload. Results from two clinical studies conducted in Australia and China demonstrated its promising efficacy in patients with PROC. Among 46 patients who received JSKN003 every 3 weeks (Q3W) at varying doses, the ORR was 64.4% with a median PFS of 7.1 months among all patients. In a subset of patients with HER2-expressing tumors (IHC scores of 1+/2+/3+), the ORR reached 72.2% with a median PFS of 9.4 months (Table 1). JSKN003 showed good tolerability, with predominantly low-grade toxicities and nausea as the most common TRAEs. Low-grade ILD was observed in 8.7% of the patients, with no higher-grade cases identified [16]. A confirmatory phase III trial (NCT06751485) is ongoing in an all-comer population with any level of HER2 expression, evaluating the efficacy and safety of JSKN003 vs. the investigators' choice of chemotherapy (Table 3).

IBI354 is another HER2-targeted ADC bearing a Top1 inhibitor payload. In a phase I study of 40 patients with ovarian cancer treated with IBI354 (12 mg/kg Q3W), the ORR was 55.0%, and the median PFS was 7.1 months. Notably, the ORR remained 55.6% in patients with low HER2 expression (IHC 1+) (Table 1) [17]. IBI354 showed a manageable safety profile, with most TRAEs being hematologic with generally low-to-moderate severity. ILD/pneumonitis occurred in one patient (1.1%); this grade 2 event was deemed unrelated to treatment, supporting the overall tole-

Table 1. Summary of key clinical data from studies of antibody–drug conjugates in patients with gynecologic cancers.

Target	ADC	Payload	Linker	Study design and phase	Cancer type/sample size	Key outcomes
FRα	Mirvetuximab soravtansine (MIRV)	Tubulin inhibitor DM4	Cleavable disulfide-containing linker	Randomized controlled Phase III (MIRASOL)	PROC 453	PFS 5.6 mo; OS 16.5 mo
FRα	BAT8006	Top1 inhibitor Exatecan	Cleavable linker	Single-arm Phase II	PROC 108	ORR 32.4%; PFS 6.9 mo
Tissue factor	Tisotumab vedotin (TV)	Tubulin inhibitor MMAE	Valine–citrulline cleavable linker	Randomized controlled Phase III (InnovaTV-301)	Second-line CC 502	PFS 4.2 mo; OS 11.5 mo
HER2	Trastuzumab deruxtecan (T-DXd)	Top1 inhibitor deruxtecan	Cleavable GGFG tetrapeptide linker	Single-arm Phase II	OC 40; EC 40; CC 40	ORR EC 57.5%, CC 50.0%, OC 45.0%
HER2	SHR-A1811	Top1 inhibitor	Cleavable tetrapeptide linker	Single-arm Phase II	OC 30; EC 23; CC 24	ORR EC 43.5%, CC 66.7%, OC 66.7%
HER2	JSKN003	Top1 inhibitor	Cleavable tetrapeptide linker	Single-arm Phase II	OC 46	ORR 64.4%; PFS 7.1 mo
HER2	IBI354	Top1 inhibitor: amptothecin derivative	Cleavable linker	Single-arm Phase I	OC 40	ORR 55.0%; PFS 7.1 mo
HER2	BNT323/DB-1303	Top1 inhibitor P1003	Cleavable linker	Single-arm Phase I/II	EC 17	ORR 58.8%; DCR 94.1%
TROP-2	Sacituzumab tirumotecan (MK-2870)	Top1 inhibitor Belotecan derivative	Cleavable tetrapeptide linker	Single-arm Phase II	EC 44; OC 40	ORR EC 34.7%, OC 40%; PFS EC 5.7 mo; OC 6.0 mo
TROP-2	Sacituzumab govitecan (SG)	Top1 inhibitor SN-38	Hydrolysable linker	Single-arm Phase II	CC 40; EC 41	ORR CC 43–48%, EC 22%; PFS CC 7.4 mo; EC 4.8 mo
TROP-2	SHR-A1921	Top1 inhibitor	Cleavable tetrapeptide linker	Single-arm Phase I	OC 43	ORR 48.8%; DCR 97.7%; PFS 7.2 mo
CDH6	Raludotatug deruxtecan (R-DXd)	Top1 inhibitor DXd	Cleavable linker	Single-arm Phase I	OC ~40	ORR 38%
Nectin-4	9MW2821	Tubulin inhibitor MMAE	Valine–citrulline cleavable linker	Single-arm Phase I/II	CC 45	ORR 35.6%; DCR 75.6%
B7-H4	HS-20089	Top1 inhibitor	Cleavable tetrapeptide linker	Single-arm Phase I	OC 44	ORR 24.2%; DCR 63.6%

Abbreviations: mo, months; CC, cervical cancer; DCR, disease control rate; DXd, deruxtecan; DM4, maytansinoid DM4; EC, endometrial cancer; MMAE, monomethyl auristatin E; OC, ovarian cancer; ORR, objective response rate; PROC, platinum-resistant ovarian cancer; PFS, progression-free survival; Top1, topoisomerase I.

Table 2. Ongoing phase 3 clinical trials of globally developed antibody–drug conjugates for treating gynecologic cancer in China.

Target	ADC	Clinical trial identifier	Patients/estimated enrollment	Setting	Interventions	Primary outcome measures	Estimated study completion date
TROP-2	*Sacituzumab Tirumotecan/MK-2870	CTR20252559/NCT06952504	EC/1123	First-line Maintenance Treatment	MK-2870 + Pembrolizumab vs. Pembrolizumab	PFS and OS	May, 2032
TROP-2	Sacituzumab Tirumotecan/MK-2870	CTR20241248/NCT06132958	EC/710	Post Platinum and Immunotherapy	MK-2870 vs. Chemotherapy	PFS and OS	January, 2028
TROP-2	Sacituzumab Tirumotecan/MK-2870	CTR20243424/NCT06459180	CC/686	as second-line treatment	MK-2870 vs. Chemotherapy (PC)	OS	October, 2028
TROP-2	Sacituzumab Govitecan (SG)	CTR20244107/NCT06486441	EC/640	Post Platinum-based Chemotherapy and Immunotherapy	SG vs. Chemotherapy (PC)	PFS and OS	June, 2029
Tissue factor	Tisotumab Vedotin	CTR20223290/NCT04697628	CC/502	second-line recurrent or metastatic	Tisotumab Vedotin vs. Chemotherapy (PC)	OS	Completed
HER2	Trastuzumab Deruxtecan (T-DXd)	CTR20244095/NCT06989112	EC/600	First-Line Treatment	T-DXd Plus Rilvegostomig or Pembrolizumab vs. Chemotherapy Plus Pembrolizumab	PFS	January, 2029
HER2	Trastuzumab Deruxtecan (T-DXd)	CTR20251716/NCT06819007	OC/582	First-line Maintenance Therapy	T-DXd With Bevacizumab vs. Bevacizumab	PFS	November, 2028
HER2	Trastuzumab Deruxtecan (T-DXd)	CTR20253443/NCT07022483	EC/600	Post-surgery adjuvant therapy	T-DXd vs. SoC Chemotherapy	DFS	March, 2032
FRα	Mirvetuximab soravtansine (MIRV)	CTR20211628/NCT04209855	OC/453	Post Platinum-based Chemotherapy	MIRV vs. Chemotherapy (PC)	PFS	Completed
FRα	Mirvetuximab soravtansine (MIRV)	CTR20241552/NCT05445778	Platinum-sensitive OC/520	Maintenance after platinum-based Chemotherapy	MIRV + Bevacizumab vs. Bevacizumab	PFS	March, 2027
CDH6	Raludotatug Deruxtecan (R-DXd)	CTR20240778/NCT06161025	PROC/710	Post Platinum-based Chemotherapy	R-DXd vs. Chemotherapy (PC)	PFS	December, 2027

Abbreviations: DFS, disease-free survival; PC, physician's choice; SoC, standard of care.

*Sacituzumab tirumotecan was developed in China and licensed to Merck, Sharp & Dohme.

Table 3. Ongoing phase 3 clinical trials of domestically developed antibody–drug conjugates for treating gynecologic cancer in China.

Target	ADC	Clinical trial identifier	Patients/estimated enrollment	Setting	Interventions	Primary outcome measures	Estimated study completion date
TROP-2	SHR-A1921	CTR20241535/NCT06394492	PROC/440	Post Platinum-based Chemotherapy	SHR-A1921 vs. Chemotherapy (PC)	PFS	May, 2026
Nectin-4	9MW2821	CTR20243246/NCT06692166	CC/420	Post Platinum-based Chemotherapy	9MW2821 vs. Chemotherapy (PC)	OS	December, 2027
HER2	BNT323/DB-1303	CTR20252691/NCT06340568	EC/540	Post Platinum and Immunotherapy	BNT323/DB-1303 vs. Chemotherapy	PFS	October, 2027
HER2	SHR-A1811	CTR20250550/NCT06990503	PROC/300	Post Platinum-based Chemotherapy	SHR-A1811 vs. Chemotherapy (PC)	PFS	June, 2030
HER2	JSKN003	CTR20244822/NCT06751485	PROC/430	Post Platinum-based Chemotherapy	JSKN003 vs. Chemotherapy (PC)	PFS	December, 2026
HER2	IBI354	CTR20250364/NCT06834672	PROC/450	Post Platinum-based Chemotherapy	IBI354 vs. Chemotherapy (PC)	PFS and OS	December, 2027
FRα	BAT8006	CTR20251345	PROC/476	Post Platinum-based Chemotherapy	BAT8006 vs. Chemotherapy	PFS	NA
FRα	BAT8006	CTR20252907	Platinum-sensitive OC/100	Maintenance after platinum-based Chemotherapy	BAT8006 + Bevacizumab vs. Bevacizumab	PFS	NA
EGFR/HER3	BL-B01D1	CTR20251986/NCT06994195	PROC/84	Post Platinum-based Chemotherapy	BL-B01D1 vs. Chemotherapy (PC)	PFS and OS	June, 2027
B7-H4	HS-20089	CTR20250629/NCT06855069	PROC/468	Post Platinum-based Chemotherapy	HS-20089 vs. Chemotherapy (PC)	PFS	March, 2027

Abbreviations: DB-1303, BNT323/DB-1303; NA, not available.

rability of IBI354. A confirmatory phase III trial (CTR20250364/NCT06834672) is currently underway to compare IBI354 monotherapy with the investigators' choice of chemotherapy in patients with HER2-expressing PROC (Table 3).

BNT323/DB-1303, developed by DualityBio, is a HER2-directed ADC with a cleavable linker and a TOP1 inhibitor payload (P1003). It has been granted a 'Breakthrough Therapy' designation by the FDA for the treatment of advanced or metastatic HER2-expressing endometrial cancer that has progressed following immune checkpoint inhibitor therapy. This decision was supported by topline results from a phase I/II study (NCT05150691) in which BNT323/DB-1303 achieved an ORR of 58.8% and a disease control rate (DCR) of 94.1% among 17 evaluable patients treated at doses of 7.0 mg/kg or 8.0 mg/kg; the safety profile was manageable (Table 1) [18]. An ongoing global phase III trial (CTR20252691/NCT06340568) is evaluating BNT323/DB-1303 vs. the investigators' choice of chemotherapy in patients with HER2-expressing endometrial cancer previously treated with immune checkpoint inhibitors (Table 3).

3.4 TROP-2-Targeting ADCs

TROP-2 is a transmembrane glycoprotein that is widely expressed in different cancer types including endometrial, cervical, and ovarian tumors [19,20]. Sacituzumab tirumotecan (sac-TMT; also known as MK-2870/SKB264) is a TROP-2-targeted ADC developed with a hydrolytically cleavable linker conjugated with a Belotecan-derivative Top1 inhibitor; this agent was developed by China's Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. and licensed to Merck, Sharp & Dohme in May 2022. Sac-TMT has shown promising anti-tumor activity with a manageable safety profile in patients with pre-treated advanced endometrial, cervical, and ovarian cancers. The ORR among 44 patients with endometrial cancer treated with Sac-TMT was 34.1%, although it was higher (41.7%) among those with a TROP-2 IHC H-score $>$200. Among 40 patients with ovarian cancer, the ORR was 40.0% but was 61.5% among those with a TROP-2 IHC H-score $>$200 (Table 1) [21,22]. Sac-TMT monotherapy exhibited a manageable safety profile with the most common TRAEs being stomatitis and hematologic conditions such as decreased neutrophil and white blood cell counts as well as anemia. The TroFuse-033 trial (CTR20252559/NCT06952504) is a phase III randomized study evaluating sac-TMT plus pembrolizumab vs. pembrolizumab monotherapy as a maintenance therapy in patients with mismatch repair-proficient advanced or recurrent endometrial cancer. Furthermore, the TroFuse-005 trial (CTR20241248/NCT06132958) is assessing sac-TMT monotherapy compared with the physicians' choice of chemotherapy in patients who have experienced disease progression following platinum-based chemotherapy and immunotherapy. Additionally, the TroFuse-020 trial (CTR20243424/NCT06459180) is a phase III multicenter study comparing sac-TMT monotherapy with the physicians' choice chemotherapy as a second-line treatment for patients with recurrent or metastatic cervical cancer (Table 2).

Sacituzumab govitecan (SG) is another TROP-2-targeting ADC composed of an anti-TROP-2 monoclonal antibody conjugated to the cytotoxic payload SN-38, a Top1 inhibitor. In the China-based EVER-132-003 study, SG demonstrated encouraging antitumor activity in patients with recurrent or metastatic cervical cancer, achieving an ORR of 43–48%, along with a manageable safety profile consistent with that of prior studies [23]. In the endometrial cancer cohort of the TROPiCS-03 study, SG achieved an ORR of 22% and a median PFS of 4.8 months, with a safety profile also consistent with those previously observed (Table 1) [24]. SG demonstrated a manageable safety profile; the most common TEAEs were gastrointestinal and included diarrhea (56%), nausea (54%), and fatigue (51%). Grade $\geq$3 TEAEs primarily comprised hematologic toxicities and diarrhea (20%). The ongoing ASCENT-GYN-01 trial (CTR20244107/NCT06486441) is comparing SG to the physicians' choice of treatment in patients with recurrent or persistent endometrial cancer following platinum-based therapy (Table 2).

SHR-A1921 is a novel TROP-2-targeted ADC comprising a humanized anti-TROP-2 Immunoglobulin G1 (IgG1) antibody conjugated via a cleavable tetrapeptide linker to a DNA Top1 inhibitor payload. This ADC demonstrated promising efficacy in patients with PROC in a phase I study, achieving an ORR of 48.8% and a DCR of 97.7% (Table 1) [25]. Grade $\geq$3 TRAEs occurred in 50.0% of the patients, with stomatitis (28.3%), anemia (8.7%), and decreased neutrophil count (6.5%) being the most common; no ILD was reported. Given these encouraging preliminary data, an ongoing phase III trial (CTR20241535/NCT06394492) is evaluating the efficacy and safety of SHR-A1921 compared with those of the investigators' choice of chemotherapy in patients with PROC (Table 3).

3.5 CDH6-Targeting ADC

CDH6 is a single-pass transmembrane protein expressed in several malignancies, including renal cell carcinoma and ovarian cancer. Up to 85% of advanced ovarian tumors overexpress CDH6, and this has been associated with a poor prognosis [26]. Raludotatug deruxtecan (R-DXd; DS-6000) is a CDH6-targeted ADC that employs a DNA Top1 inhibitor payload (DXd). In a phase I study, R-DXd demonstrated encouraging antitumor activity and a manageable safety profile in patients with ovarian cancer who had previously undergone extensive therapies but were not preselected for CDH6 expression, achieving an ORR of 38%, a cancer antigen 125 (CA-125) level decrease

in 52%, and durable responses across multiple dose levels [27]. Grade ≥3 TEAEs were observed in 21 patients (50%); the most common all-grade TEAEs were nausea (55%), fatigue (40%), vomiting (38%), and diarrhea (33%). Based on these promising results, the REJOICE-Ovarian01 trial (CTR20240778/NCT06161025)—a global, multicenter, randomized phase II/III study—is currently evaluating R-DXd vs. the investigators' choice of chemotherapy in patients with PROC. Owing to its clinical potential, the U.S. FDA has granted 'Breakthrough Therapy' designation to R-DXd for the treatment of adult patients with CDH6-expressing PROC previously treated with bevacizumab (Table 2).

3.6 Nectin-4-Targeting ADC

Nectin-4 is a cell adhesion molecule that is highly expressed in various solid tumors, particularly in cervical and breast cancers [28]. A novel nectin-4-targeted ADC, 9MW2821, was developed by Mabwell Bioscience Co., Ltd. in Shanghai to selectively deliver the cytotoxic payload monomethyl auristatin E to tumor cells. In a phase I/IIa study, 9MW2821 demonstrated encouraging antitumor activity and a manageable safety profile in 45 patients with advanced cervical cancer, achieving an ORR of 35.6% and a DCR of 75.6% (Table 1) [29, 30]. The most common TRAEs were hematologic toxicities, elevations in liver transaminases, rash, and gastrointestinal symptoms such as decreased appetite and nausea. Based on these promising results, an open-label phase III trial (CTR20251843/NCT06946527) is currently evaluating 9MW2821 vs. the physicians' choice of chemotherapy in patients with recurrent or metastatic cervical cancer who previously received platinum-based therapy (Table 3).

3.7 B7-H4-Targeting ADCs

B7-H4 is a transmembrane immune checkpoint glycoprotein that is highly expressed in several solid tumors; its expression is limited in normal tissues [31–33]. B7-H4 is expressed in approximately 70–90% of ovarian cancers, 60–80% of endometrial cancers, and 50–70% of cervical cancers [34–36]. Currently emerging B7-H4-targeting ADCs include SGN-B7H4V, XMT-1660, and AZD8205 [37–39].

HS-20089 is a B7-H4-targeted ADC with a Top1 inhibitor payload developed by Hansoh Pharmaceutical. In a phase I study, 44 patients with advanced solid tumors (including two with ovarian cancer) achieved an ORR of 24.2% and a DCR of 63.6% following HS-20089 treatment, demonstrating encouraging efficacy in B7-H4-expressing tumors (Table 1) [40]. The most common TRAEs were hematologic toxicities, gastrointestinal symptoms (nausea and vomiting), fatigue, and elevations in liver transaminases. HS-20089 was granted a 'Breakthrough Therapy' designation by the NMPA of China for the treatment of PROC, based on results from the phase I and II HS-20089-201 trials. HS-20089 is also being evaluated internationally by GlaxoSmithKline under an exclusive licensing agreement. A phase III trial (NCT06855069) is ongoing in patients with PROC to evaluate the efficacy and safety of HS-20089 vs. the investigators' choice of chemotherapy.

3.8 EGFR/HER3-Targeting ADC

EGFR (also known as Erythroblastic Leukemia Viral Oncogene Homolog erb-b2 receptor tyrosine kinase 1 [ERBB1] or human epidermal growth factor receptor 1 [HER1]) and HER3 (also known as erb-b2 receptor tyrosine kinase 3 [ERBB3]) are receptor tyrosine kinases that belong to the ERBB family [41,42]. Both are highly expressed in multiple solid tumor types including lung and gynecologic malignancies [43,44]. Therefore, therapeutic strategies that simultaneously target EGFR and HER3 are sensible treatment approaches for patients with these cancers. BL-B01D1 is a first-in-class EGFR-HER3 bispecific ADC developed by Sichuan Baili Tianheng Pharmaceutical; it comprises a bispecific antibody, a tetrapeptide-based cleavable linker, and the toxin Ed-04 (a camptothecin derivative Top1 inhibitor) [45]. In a first-in-human phase I clinical trial (NCT05194982) involving 195 patients with heavily pretreated advanced solid tumors, BL-B01D1 treatment resulted in an ORR of 34%. It also had an acceptable safety profile, with 71% of 195 patients experiencing grade ≥3 TRAEs, most commonly neutropenia (47%), anemia (39%), leukopenia (39%), and thrombocytopenia (32%). Additionally, only a single case of ILD was reported.

Based on the results of the Phase Ib/II study of BL-B01D1 in patients with recurrent metastatic ovarian cancer, a phase III trial (CTR20251986/NCT06994195) is currently underway to compare BL-B01D1 with the investigators' choice of chemotherapy in patients with PROC (Table 3).

4. Discussion

4.1 Safety Profiles and Management

The safety profiles of ADCs are heavily influenced by the types of payloads and linkers used. Tubulin inhibitors (e.g., monomethyl auristatin E in tisotumab vedotin or DM4 in MIRV) are commonly associated with ocular toxicities (e.g., keratopathy and blurred vision), peripheral neuropathy, and gastrointestinal toxicities (nausea and diarrhea). Topoisomerase I (Top1) inhibitors (e.g., deruxtecan in T-DXd) cause hematologic and gastrointestinal toxicities, although ocular toxicities are less common. A major concern with these agents is ILD and pneumonitis, which require close monitoring.

Currently, most ADCs targeting gynecologic cancers use cleavable linkers, which are chemically or enzymatically labile, enabling payload release at the tumor site. Less-stable linkers (e.g., Gly-Gly-Phe-Gly in T-DXd) can cause earlier payload release into circulation, increasing the risk of chemotherapy-related toxicities such as cytopenia,

alopecia, and gastrointestinal issues owing to higher peak cytotoxin concentrations. In contrast, more-stable linkers (e.g., valine-citrulline in tisotumab vedotin) lead to longer circulation times for the intact ADC but release the payload more slowly; this can lead to ocular toxicities and other off-target effects owing to the drug being released in tissues other than the tumor [46].

Strategies for managing ADC-related adverse events include (i) dose modifications for ocular maladies (often combined with steroidal eye drops) and for hematologic toxicities (which may be combined with growth factor treatment), (ii) supportive care that includes symptom control for peripheral neuropathy and antiemetics for gastrointestinal issues, and (iii) frequent monitoring of ocular health, pulmonary function, and blood counts, which is essential for early detection.

4.2 Biomarkers and Efficacy

The expression levels of biomarkers such as FRα, HER2, and TROP-2 are critical for determining patient eligibility and determining efficacy. Data from the FORWARD I [47], SORAYA [48], and MIRASOL [2] trials highlight the importance of selecting FRα-high patients for MIRV treatment. While the FORWARD I trial did not meet its primary PFS endpoint in the overall population, promising antitumor activity was observed in FRα-high patients. This led to the design of the MIRASOL and SORAYA trials, which specifically focused on FRα-high patients with PROC as they were hypothesized to be more likely to benefit from MIRV. The SORAYA trial showed appreciable results with an ORR of 32.4% in such patients, while the MIRASOL trial confirmed that MIRV significantly improved PFS and ORR compared with those after chemotherapy in this biomarker-selected group. These findings emphasize the importance of FRα as a key eligibility criterion for MIRV therapy, with IHC testing for FRα becoming a crucial companion diagnostic and increasingly becoming a standard test for patients with PROC [4].

As for patients with 2+/3+ IHC expression scores for HER2, the DESTINY-PanTumor02 trial revealed ORRs of 57.5%, 50.0%, and 45.0% in patients with endometrial, cervical, and ovarian cancers, respectively; among those with HER2 IHC 3+ expression, the ORRs were higher at 84.6%, 75.0%, and 63.6%, respectively. These results demonstrate that HER2 IHC expression is linked to treatment efficacy [5]. However, there is currently no standardized companion diagnostic for HER2 IHC, nor are there established evaluation criteria for IHC testing in patients with gynecologic cancers, leading to differences in testing methods that can make it difficult to compare results across clinical trials. This underscores the need for standardized HER2 IHC assessment to optimize treatment and improve trial comparability.

4.3 Limitations and Future Perspectives

China's rapidly expanding ADC pipeline holds significant potential to reshape the treatment landscape for gynecologic cancers. However, its clinical impact remains constrained by heterogeneous biomarker testing, regional regulatory differences, high costs, and unequal access to diagnostics and therapies. Intense competition among developers of ADCs that target similar antigens, as well as the challenges of aligning with global trial designs, further delay progress.

Future efforts should prioritize standardizing key biomarker assays (e.g., FRα and HER2), advancing regulatory harmonization, developing sustainable reimbursement strategies, and strengthening diagnostic infrastructure. As domestically developed ADCs such as BL-B01D1, BAT8006, SHR-A1811, and SHR-A1921 enter pivotal trials, coordinated collaboration among regulators, clinicians, and the pharmaceutical industry will be essential to translate these innovations into accessible and globally impactful treatments for gynecologic malignancies.

5. Conclusions

ADCs have become a transformative class of therapeutics in gynecologic oncology that demonstrate high clinical efficacy across multiple settings including PROC and recurrent cervical cancer. The rapid advancement of China's ADC pipeline highlights its growing contribution to global anticancer treatment innovation. Continued clinical validation and multi-stakeholder collaboration will be critical for ensuring the effective and equitable integration of these promising therapies into routine care.

Availability of Data and Materials

All data and materials referenced in this review are derived from publicly available publications and clinical trial databases cited in the manuscript.

Author Contributions

PC and ZM conceived and designed the review. DT and YS were responsible for the literature search, data extraction, and analysis. XK made significant contributions to the conceptual design, literature interpretation, and critical revision of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Dongmei Tan and Zhaoqing Meng are employees of Hongjitang Pharmaceutical Group Co., Ltd. However, the company had no role in the handling or conduct of the study. The authors had full access to all data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used ChatGPT-5 to assist with spelling and grammar checking. After using this tool, the authors carefully reviewed and edited the content as necessary and take full responsibility for the final version of the manuscript.

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