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# Comprehensive overview of antibody drug-related clinical studies in gynecology: insights from ClinicalTrials.gov

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Antibodies have been widely used globally over the past decade and play an increasingly important role in modern medicine. Notably, significant advancements have been achieved in the realm of gynecology, particularly in gynecological cancers. This study endeavors to present a thorough overview of antibody-related drug clinical studies in gynecology registered on ClinicalTrials.gov, focusing on the basic characteristics of trials, geographical distribution, administration routes, indications, and targets. The analysis indicates a rising prevalence of antibody–drug conjugates (ADCs), bispecific antibodies, and Fc-fusion proteins. This study will help develop new ideas for future research on antibodies in gynecology.

## KEYWORDS

Clinicaltrials.gov, antibodies, gynecology, antibody–drug conjugates, bispecific antibodies, Fc-fusion proteins, administration route

## 1 Introduction

Antibody therapeutics have emerged as one of the most prominent sectors in the biopharmaceutical industry. Since the approval of the first monoclonal antibody in 1986, the field has experienced rapid and substantial expansion (1). The development of antibodies has evolved from initial mouse-derived forms to chimeric, humanized, and fully human antibodies (2). They have already made a significant impact on the overall sales of biopharmaceutical products in recent years (3).

Antibody-related drugs exhibit high specificity for their target sites and demonstrate superior efficacy compared to conventional drugs, with fewer side effects (4). These agents have been widely applied in gynecology, especially for the treatment of gynecological cancers (5–7). For instance, bevacizumab combined with paclitaxel and carboplatin has been considered first-line therapy for patients with primary peritoneal cancer, fallopian tube cancer, or epithelial ovarian cancer at stage III or IV (8). Furthermore, the results of the KEYNOTE-826 study (9) reveal that pembrolizumab in conjunction with chemotherapy, with or without bevacizumab, is recommended as a category 1 therapy for patients with metastatic, recurrent, or persistent cervical cancer (10). Additionally, an increasing number of antibodies are currently under clinical

trial evaluation (11–13). Despite these advancements, there is a lack of research providing a comprehensive overview of clinical trials involving antibody-related drugs in gynecology. To address this gap, registered clinical trials from [ClinicalTrials.gov](https://clinicaltrials.gov) are reviewed in this study to provide new insights for future research into antibodies in gynecology.

## 2 Materials and methods

### 2.1 Data sources

The keywords “antibody” and “marketed antibody-related drugs in gynecology” were used to thoroughly search data on [ClinicalTrials.gov](https://clinicaltrials.gov). This was identified from the databases of the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). Subsequently, entries containing “antibody” and specific terms—“Denosumab,” “Bevacizumab,” “Pembrolizumab,” “Romosozumab,” “Dostarlimab,” “Tisotumab vedotin,” or “Mirvetuximab soravtansine”—were retrieved in the field of “other terms.” The search was restricted to studies in “Early Phase 1, Phase 1, Phase 2, Phase 3, and Phase 4” with a study initiation date before 27 May 2024. Following the identification of all the keywords, the data were consolidated and duplicate entries were removed.

The protocols established in previous investigations of [ClinicalTrials.gov](https://clinicaltrials.gov) were followed (14–16). A comprehensive manual review of all Medical Subject Headings (MeSH) and disease terms cataloged in the National Library of Medicine was conducted to identify those relevant to gynecology. Subsequently, the identified terms were used to extract potential gynecological clinical trials. The study conditions were manually reviewed by a team of trained researchers to select gynecology-related trials. The exclusion criteria were as follows: (1) studies in which antibodies were used as control drugs, and (2) clinical trials in which antibodies were utilized as adjunctive therapies, with a major focus on assessing other drugs rather than the antibodies themselves. Ultimately, a total of 589 clinical trials were included. The data retrieval process is illustrated in [Figure 1](#).

A variety of data were collected for analysis, including study title, condition, status, start date, trial phase, intervention, funder type, location, enrollment, administration route, and drug target. This study was not subjected to review by the institutional review board, since it used publicly available data without involving personal information.

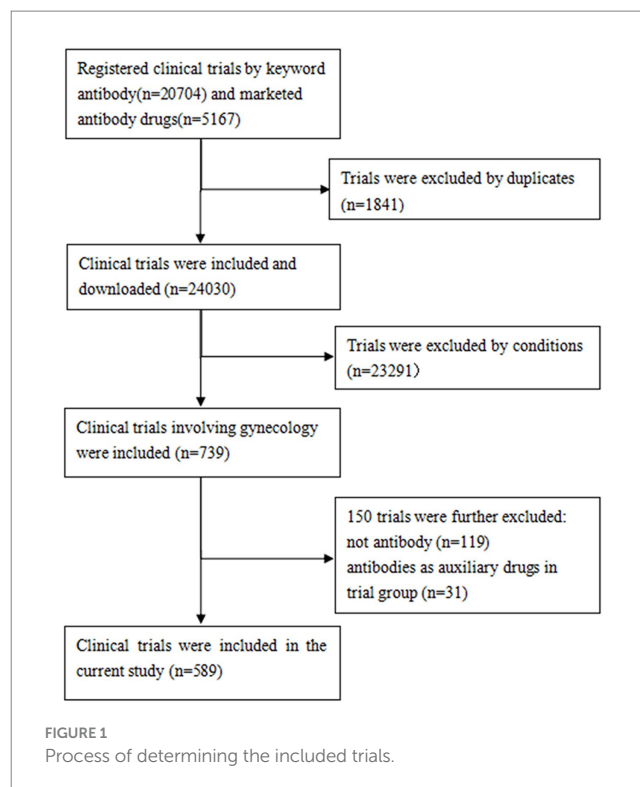
### 2.2 Statistical analysis

Descriptive analysis was conducted using numerical and percentage formats for categorical variables, while data processing and analysis were performed via Microsoft Excel. Furthermore, network analysis was performed using Gephi to determine the locations and partnerships of the principal research institutions involved in the trials.

## 3 Results

### 3.1 Basic characteristics

A total of 589 clinical trials involving antibody-related drugs in gynecology were analyzed, including 2 basket trials and 2 umbrella trials, which encompassed 646 antibody drugs. The fundamental characteristics



of these trials are presented in [Table 1](#). The antibody-related drugs investigated comprised 17 (2.69%) murine, 12 (1.90%) chimeric, 458 (72.35%) humanized, and 146 (23.06%) human antibodies. It is important to note that Fc-fusion proteins were not included. Approximately half of the studies (291, 49.41%) had planned or actual enrollment of 50 participants or fewer. The majority of antibody drug trials were funded by sources categorized as “other,” comprising 308 studies (52.29%). Meanwhile, 236 studies (40.07%) received funding from industry sources, and 45 studies (7.64%) were funded by the National Institutes of Health (NIH). Furthermore, all antibody-related drugs were classified into five categories: canonical antibody, ADCs, Fc-fusion protein, and bispecific and radiolabeled antibody. [Figure 2](#) depicts the annual distribution of these different antibody-related drug formats, while [Figure 3](#) gives an overview of antibody clinical research.

### 3.2 Geographical distribution

There were 566 trials conducted by 32 countries after the exclusion of trials lacking geographical information. In terms of regional distribution, North America enrolled the largest number of antibody trials (341, 57.89%), followed by East Asia (122, 20.71%) and Europe (80, 13.58%), while other regions had limited trials on this issue. As for countries, the United States possessed an obvious advantage in the development of antibody-related drugs, conducting 335 trials, which accounted for more than half of the world. China represented the most in Asia, with 104 trials. [Figure 4](#) shows the distribution of clinical trials.

In addition to the aforementioned leading countries, there were 124 trials conducted across multiple countries, which illustrated a network of international cooperation among trial sites. A total of 63 countries participated in these international multi-center trials, of which the United States served as the leading site in 97 instances and collaborated with up to 24 different countries. The primary collaborators with the

TABLE 1 Basic characteristics of trials.

| Characteristic         | No. (%)    |
|------------------------|------------|
| Types of antibodies    |            |
| Murine                 | 17(2.69)   |
| Chimeric               | 12(1.90)   |
| Humanized              | 458(72.35) |
| Human                  | 146(23.06) |
| No. of site            |            |
| 1                      | 239(40.58) |
| ≥2                     | 327(55.52) |
| Not reported           | 23(3.90)   |
| Enrollment of patients |            |
| ≤50                    | 291(49.41) |
| 51–100                 | 110(18.68) |
| 101–500                | 139(23.60) |
| 501–1,000              | 37(6.28)   |
| 1,001–10,000           | 12(2.04)   |
| Funding source         |            |
| NIH                    | 45(7.64)   |
| Industry               | 236(40.07) |
| Other                  | 308(52.29) |
| Recruitment status     |            |
| Completed              | 213(36.16) |
| Active, not recruiting | 87(14.77)  |
| Not yet recruiting     | 31(5.26)   |
| Recruiting             | 132(22.41) |
| Suspended              | 2(0.34)    |
| Terminated             | 50(8.49)   |
| Unknown status         | 55(9.34)   |
| Withdrawn              | 19(3.23)   |
| Phase                  |            |
| Early Phase 1          | 6(1.02)    |
| Phase 1                | 85(14.43)  |
| Phases 1–2             | 50(8.49)   |
| Phase 2                | 322(54.67) |
| Phases 2–3             | 9(1.53)    |
| Phase 3                | 103(17.49) |
| Phase 4                | 14(2.38)   |
| Interventional mode    |            |
| Parallel               | 243(41.26) |
| Single group           | 303(51.44) |
| Sequential             | 31(5.26)   |
| Crossover              | 1(0.17)    |
| Factorial              | 1(0.17)    |
| Not reported           | 10(1.70)   |

(Continued)

TABLE 1 (Continued)

| Characteristic | No. (%)    |
|----------------|------------|
| Allocation     |            |
| Randomized     | 230(39.05) |
| Non-randomized | 65(11.04)  |
| Not reported   | 294(49.92) |
| Masking        |            |
| Open           | 491(83.36) |
| Single         | 8(1.36)    |
| Double         | 32(5.43)   |
| Triple         | 17(2.89)   |
| Quadruple      | 37(6.28)   |
| Not reported   | 4(0.68)    |

Percentages may not sum to 100% due to rounding. Fc-fusion proteins are not included in different types of antibodies.

United States included Australia (17 trials), Canada (16 trials), and Belgium (15 trials). [Figure 5](#) illustrates the interconnection between the participating countries.

### 3.3 Administration routes

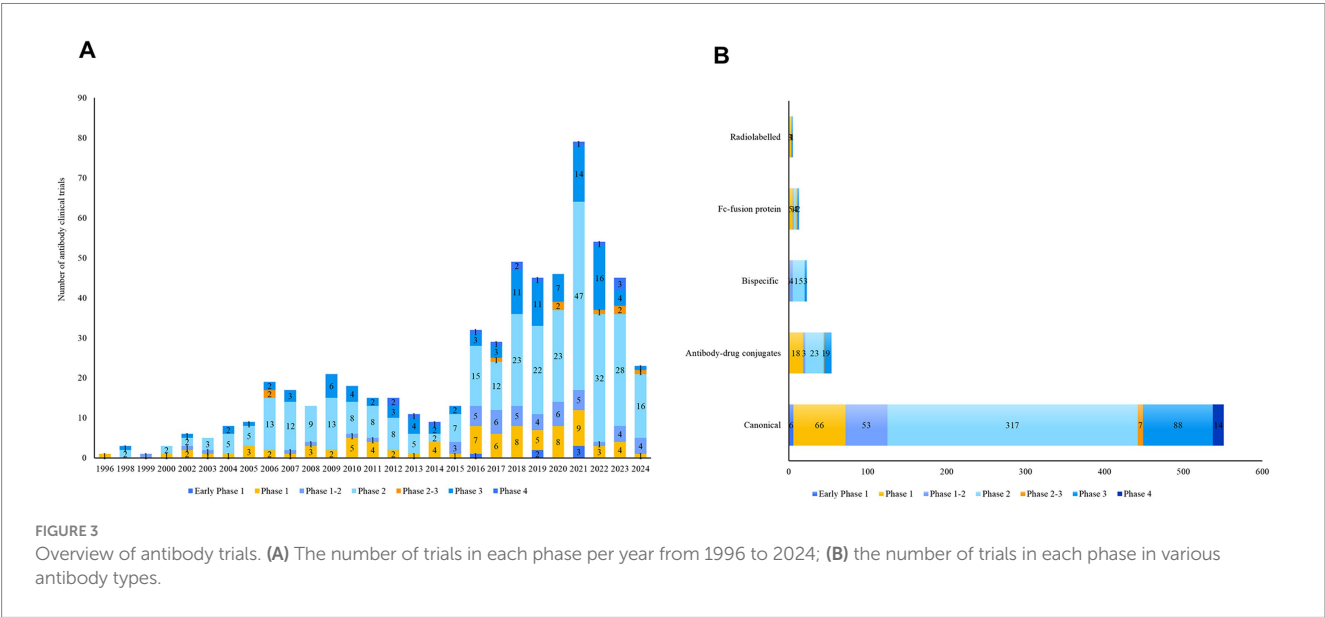
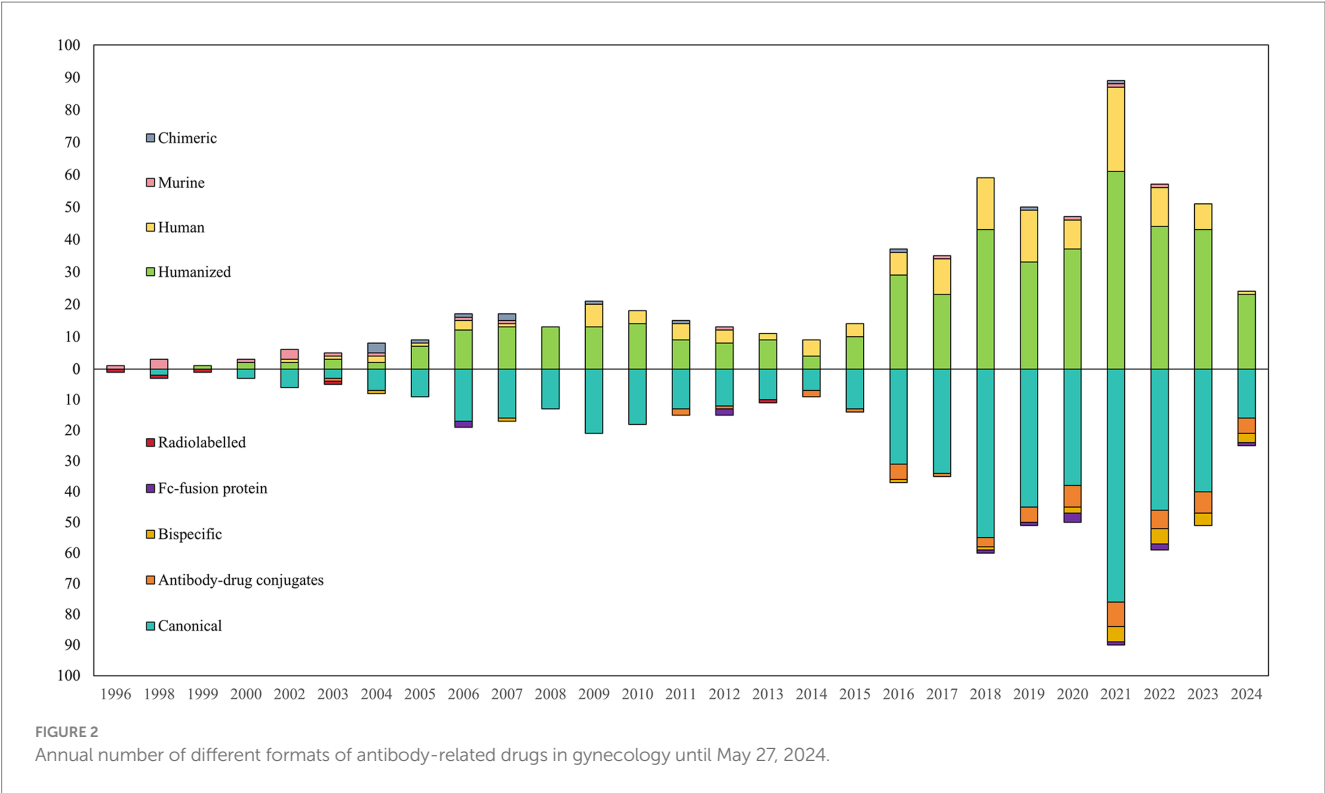
Intravenous (IV) injection constituted the predominant method of antibody-related drug administration, which represented 568 cases (87.93%). Additionally, Subcutaneous (SC) injection was utilized in 72 cases (11.15%), intraperitoneal injection in 3 cases (0.46%), and vaginal administration in 1 case (0.15%). It is worth noting that two clinical trials used dual administration routes: combined IV and SC administration, and combined IV and intraperitoneal administration. [Figure 6](#) illustrates the annual number of registered clinical trials categorized by drug administration.

### 3.4 Indications

Antibodies utilized for treating gynecological cancers were predominantly represented in clinical studies. These included ovarian cancer (158, 26.83%), cervical cancer (107, 18.17%), endometrial cancer (66, 11.21%), gestational trophoblastic neoplasm (7, 1.19%), uterine cancer (4, 0.68%), vulvar tumor (4, 0.68%), Paget’s disease of the vulva (1, 0.17%), and multiple cancers (173, 29.37%). Furthermore, antibodies were used in 63 studies (10.70%) that addressed osteoporosis in postmenopausal women. It is noteworthy that a relatively small number of registered clinical trials have explored antibodies for conditions such as endometriosis (3, 0.51%), genital herpes (1, 0.17%), ovarian insufficiency (1, 0.17%), and contraception (1, 0.17%). [Figure 7](#) illustrates the distribution of clinical trials according to indications.

### 3.5 Targets

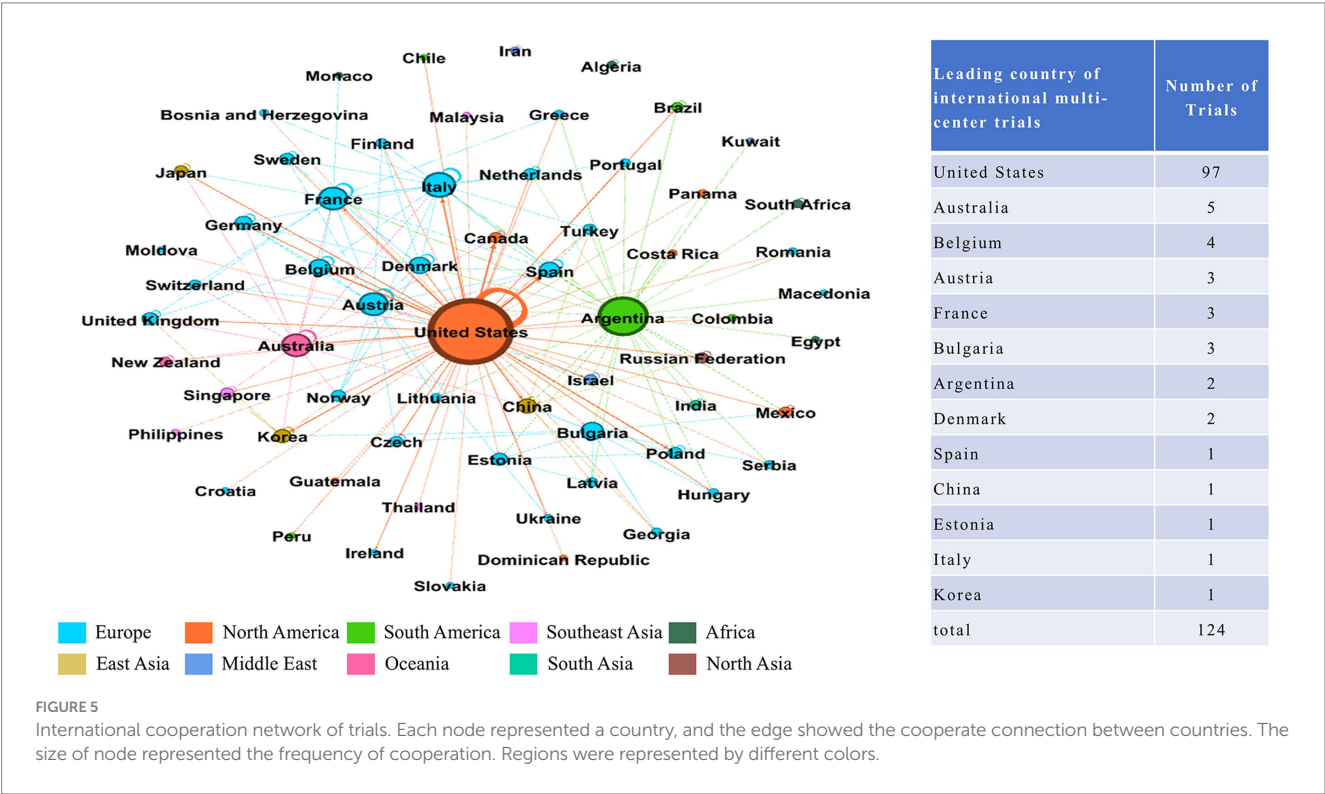
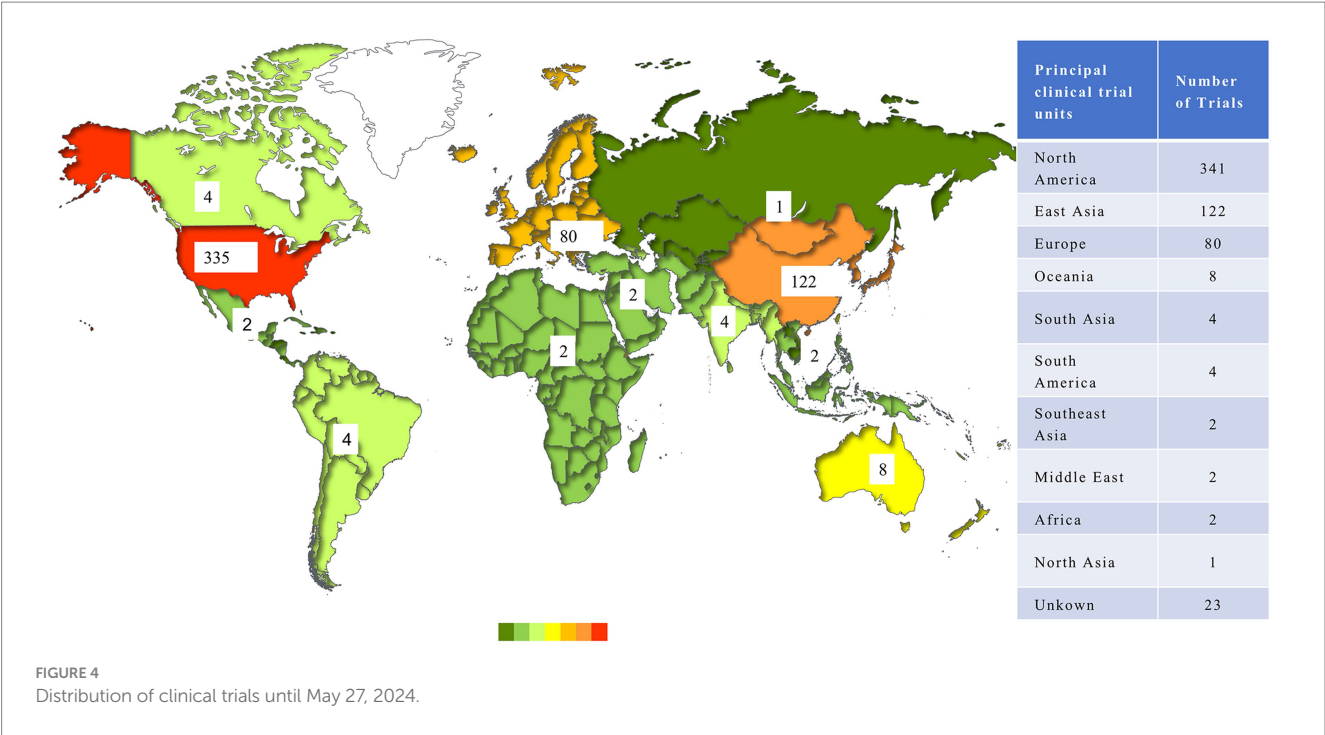
All the developing antibody-related drugs that are currently undergoing clinical trials in gynecology were cataloged



systematically. The developed antibody-related drugs in gynecological clinical trials are summarized in Table 2. Currently, there are 44 antibodies in gynecological clinical development, but approximately 34% act on just 5 validated and novel targets. Predominantly, mesothelin emerged as the most prevalent (4, 9.09%), followed by programmed cell death protein 1 (PD-1) (3, 6.82%), folate receptor  $\alpha$  (FR $\alpha$ ) (3, 6.82%), receptor tyrosine-protein kinase erbB-2 (HER2) (3, 6.82%), and T cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domain (TIGIT) (2, 4.55%).

## 4 Discussion

Since 1996, research into antibodies has significantly expanded in the field of gynecology. Innovative clinical trials, such as umbrella and basket trials, have been implemented to advance the development of antibody-related drugs in the field of gynecology. This study identified two basket trials (NCT04965519 and NCT03827837) and two umbrella trials (NCT03699449 and NCT03574779). Basket trials are characterized by the evaluation of targeted therapy for multiple diseases that share common molecular alterations. Umbrella trials



involve the assessment of multiple targeted therapies within a single disease and can be further classified into various subgroups (17). The advantage of basket trials lies in the ability to test smaller sample sizes for a given tumor type, which facilitates research in less common tumor types. By contrast, umbrella trials allow for a more comprehensive analysis of treatment for a specific tumor type (18). The application of these novel clinical trials in gynecology is

anticipated to accelerate the evaluation and approval of antibody-related drugs and promote molecular-based individualized treatment strategies (19, 20). In addition, innovative forms, such as ADCs, bispecific antibodies, and Fc-fusion proteins, have gained prominence and are the subjects of extensive investigation. In this review, studies were divided into four distinct groups according to the development of antibody-related drugs.



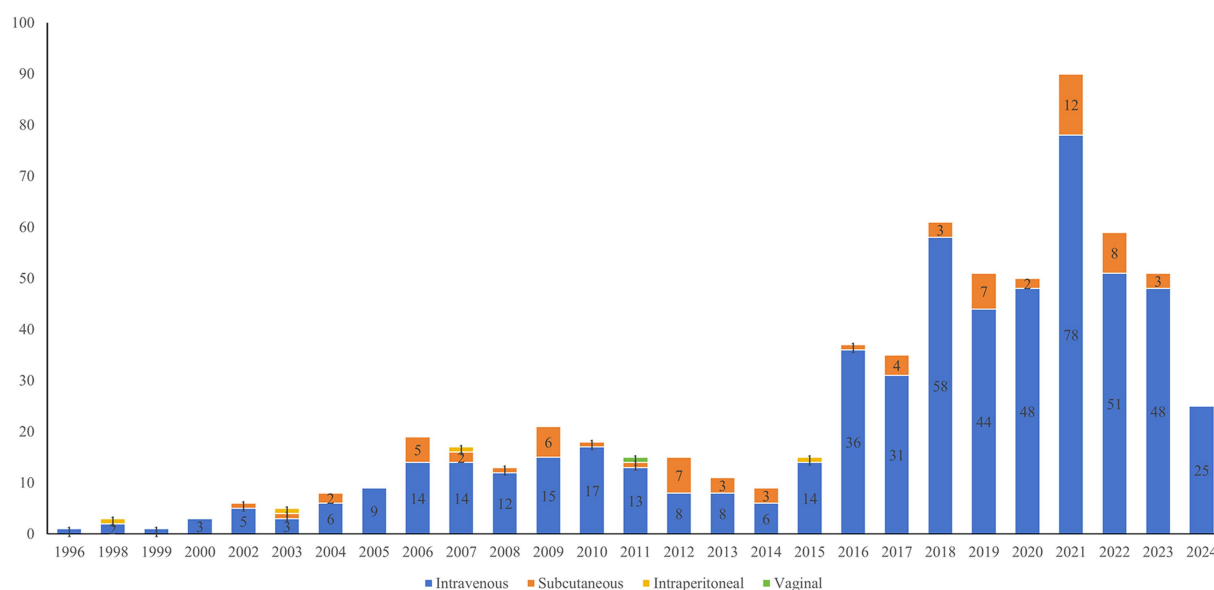


FIGURE 6  
Annual number of antibody drug clinical trials in gynecology by drug administration until May 27, 2024.

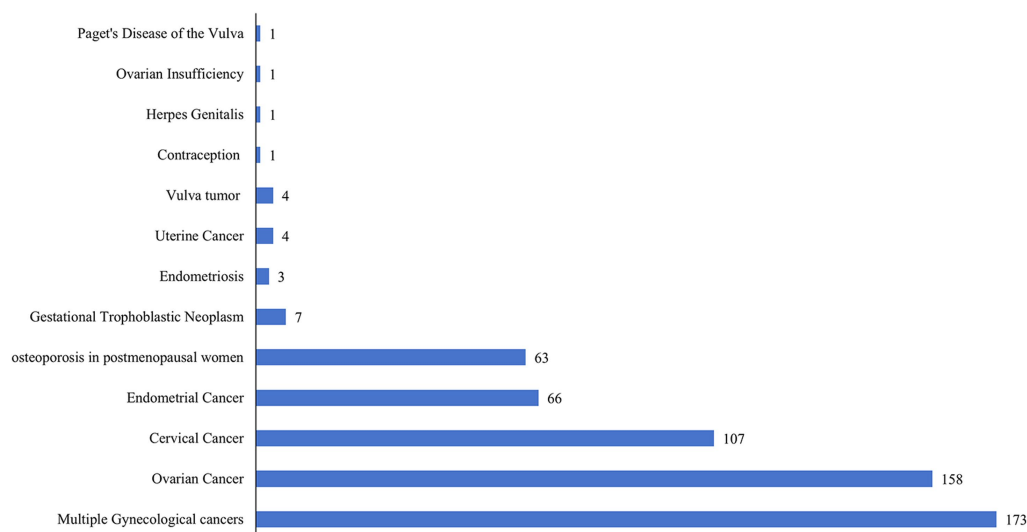


FIGURE 7  
Number of new antibody drug clinical trials in gynecology by indications until May 27, 2024.

## 4.1 Canonical antibodies

Canonical antibodies exhibit a complete antibody structure, which contains two light chains and two full-length heavy chains (21). According to research, these antibodies represent more than 80% of all clinical trials in the field of gynecology.

Since the approval of ipilimumab in 2011, immune checkpoint inhibitors have significantly advanced the treatment of gynecological malignancies (22). In this field, significant inhibitors encompass PD-L1, PD-1, CTLA-4, and LAG-3 (23), among which PD-1/PD-L1 is the most extensively studied (24). Pembrolizumab and dostarlimab have been approved by the FDA

to treat gynecological cancers (21). An increasing number of real-world studies contribute to the expanding body of evidence that supports the use of PD-1 inhibitors for recurrent or advanced gynecologic cancers. In a multi-center retrospective cohort study, Korean patients with recurrent endometrial cancer were administered pembrolizumab in combination with lenvatinib for a median duration of 4.5 cycles. During this period, the disease control rate was 76.2% (95% CI, 61.9–88.1), and the best objective response rate was 23.8% (95% CI, 11.9–38.1) (25). The most common treatment-related adverse events included fatigue, hypertension, and hypothyroidism. Additionally, another retrospective study suggested that a lower dosage of

TABLE 2 Target and indication of developing antibody-related drugs in gynecological clinical trials.

| Antibody type/<br>name | Target         | Phase        | Trial number | Study Status   | Indication                           |
|------------------------|----------------|--------------|--------------|----------------|--------------------------------------|
| <b>Canonical</b>       |                |              |              |                |                                      |
| Balstilimab            | PD-1           | Phases 1–2   | NCT03495882  | Completed      | Cervical cancer                      |
|                        |                | Phases 1–2   | NCT03104699  | Completed      | Cervical cancer                      |
|                        |                | Phase 2      | NCT03894215  | Not recruiting | Cervical cancer                      |
|                        |                | Phase 1      | NCT06095674  | Not recruiting | Cervical cancer                      |
| Oregovomab             | CA125          | Phase 3      | NCT04498117  | Not recruiting | Ovarian cancer                       |
|                        |                | Phases 1–2   | NCT04938583  | Recruiting     | Ovarian cancer                       |
|                        |                | Phase 2      | NCT01616303  | Completed      | Ovarian cancer                       |
|                        |                | Phase 2      | NCT05335993  | Not recruiting | Ovarian cancer                       |
| BAT1308                | PD-1           | Phases 2–3   | NCT06321068  | Recruiting     | Endometrial cancer                   |
|                        |                | Phases 2–3   | NCT06123884  | Not recruiting | Cervical cancer                      |
| ZB-06                  | CD52g          | early phase1 | NCT04731818  | Completed      | Contraception                        |
| Zalifrelimab           | CTLA4          | Phases 1–2   | NCT03495882  | Completed      | Cervical cancer                      |
| Utomilumab             | 4-1BB          | Phases 1–2   | NCT03318900  | Completed      | Ovarian cancer                       |
| Tiragolumab            | TIGIT          | Phase 2      | NCT04300647  | Not recruiting | Cervical Cancer                      |
| Sirexatamab            | DKK1           | Phase 2      | NCT03395080  | Completed      | Multiple gynecological cancers       |
| Setrusumab             | SOST           | Phase 2      | NCT01406548  | Completed      | Osteoporosis in postmenopausal women |
| Rulonilimab            | PD-1           | Phase 2      | NCT06226350  | Completed      | Cervical cancer                      |
| Ociperlimab            | TIGIT          | Phase 2      | NCT04693234  | Completed      | Cervical cancer                      |
| Murlentamab            | AMHRII         | Phase 1      | NCT02978755  | Completed      | Ovarian cancer                       |
| MK-4830                | ILT4           | Phase 2      | NCT05446870  | Not recruiting | Ovarian cancer                       |
| Matuzumab              | EGFR           | Phase 2      | NCT00073541  | Completed      | Ovarian cancer                       |
| Mapatumumab            | TRAIL-R1       | Phases 1–2   | NCT01088347  | Completed      | Cervical cancer                      |
| Magrolimab             | CD47           | Phase 1      | NCT03558139  | Completed      | Ovarian cancer                       |
| HMI-115                | PRLR           | Phase 2      | NCT05101317  | Recruiting     | Endometriosis                        |
| HDIT101                | Glycoprotein B | Phase 2      | NCT04165122  | Completed      | Herpes genitalis                     |
| Ganitumab              | IGF-1R         | Phase 2      | NCT00719212  | Completed      | Multiple gynecological cancers       |
| EMD 273066             | EPCAM          | Phase 1      | NCT00132522  | Completed      | Ovarian cancer                       |
| CDX-1140               | CD40           | Phase 2      | NCT05231122  | Recruiting     | Ovarian cancer                       |
| Carotuximab            | endoglin       | Phase 2      | NCT01381861  | Completed      | Multiple gynecological cancers       |
| Amatuximab             | Mesothelin     | Phase 1      | NCT00325494  | Completed      | Ovarian cancer                       |
| NP137                  | netrin-1       | Phases 1–2   | NCT04652076  | Not recruiting | Multiple gynecological cancers       |
| <b>ADCs</b>            |                |              |              |                |                                      |
| STRO-002               | FR $\alpha$    | Phase 1      | NCT03748186  | Recruiting     | Multiple gynecological cancers       |
|                        |                | Phases 2–3   | NCT05870748  | Recruiting     | Multiple gynecological cancers       |
|                        |                | Phase 1      | NCT05200364  | Recruiting     | Ovarian cancer                       |
| Anetumab Ravtansine    | Mesothelin     | Phase 2      | NCT03587311  | Not recruiting | Multiple gynecological cancers       |

(Continued)

TABLE 2 (Continued)

| Antibody type/<br>name   | Target              | Phase      | Trial number | Study Status   | Indication                     |
|--------------------------|---------------------|------------|--------------|----------------|--------------------------------|
|                          |                     | Phase 1    | NCT02751918  | Completed      | Ovarian cancer                 |
| HS-20089                 | B7-H4               | Phase 2    | NCT06014190  | Recruiting     | Multiple gynecological cancers |
| IMGN151                  | FR $\alpha$         | Phase 1    | NCT05527184  | Recruiting     | Multiple gynecological cancers |
| Trastuzumab duocarmazine | HER2                | Phase 2    | NCT04205630  | Completed      | Endometrial cancer             |
| DP303c                   | HER2                | Phase 2    | NCT04828616  | Not recruiting | Ovarian cancer                 |
| RC88                     | Mesothelin          | Phase 2    | NCT06173037  | Not recruiting | Multiple gynecological cancers |
| Farletuzumab ecteribulin | FR $\alpha$         | Phase 2    | NCT05613088  | Recruiting     | Multiple gynecological cancers |
| Raludotatug deruxtecan   | CDH6                | Phase 1    | NCT04707248  | Recruiting     | Ovarian cancer                 |
| DMOT4039A                | Mesothelin          | Phase 1    | NCT01469793  | Completed      | Ovarian cancer                 |
| DMUC4064A                | MUC16               | Phase 1    | NCT02146313  | Completed      | Ovarian cancer                 |
| BNT323/DB-1303           | HER2                | Phase 3    | NCT06340568  | Not recruiting | Endometrial cancer             |
| Fc-fusion protein        |                     |            |              |                |                                |
| Batiraxcept              | GAS6                | Phase 1    | NCT05826015  | Not recruiting | Endometrial cancer             |
|                          |                     | Phases 1–2 | NCT04019288  | Not recruiting | Multiple gynecological cancers |
|                          |                     | Phase 1    | NCT03639246  | Completed      | Ovarian cancer                 |
| SL-172154                | SIRP $\alpha$ /CD47 | Phase 1    | NCT05483933  | Not recruiting | Multiple gynecological cancers |
|                          |                     | Phase 1    | NCT04406623  | Completed      | Multiple gynecological cancers |
| SHR-1701                 | PD-L1/TGF- $\beta$  | Phase 3    | NCT05179239  | Recruiting     | Cervical cancer                |
| <b>Bispecific</b>        |                     |            |              |                |                                |
| Navicixizumab            | VEGF/DLL4           | Phase 3    | NCT05043402  | Not recruiting | Multiple gynecological cancers |
|                          |                     | Phase 1    | NCT03030287  | Completed      | Multiple gynecological cancers |
| ZG005                    | PD-1/TIGIT          | Phases 1–2 | NCT06241235  | Recruiting     | Cervical cancer                |
| Ubamatamab               | CD3/MUC16           | Phases 1–2 | NCT03564340  | Recruiting     | Multiple gynecological cancers |
| REGN5668                 | MUC16xCD28          | Phases 1–2 | NCT04590326  | Recruiting     | Multiple gynecological cancers |
| Vudalimab                | PD-1/CTLA-4         | Phase 2    | NCT05032040  | Recruiting     | Multiple gynecological cancers |
| <b>Canonical</b>         |                     |            |              |                |                                |
| Balstilimab              | PD-1                | Phases 1–2 | NCT03495882  | Completed      | Cervical cancer                |
|                          |                     | Phases 1–2 | NCT03104699  | Completed      | Cervical cancer                |
|                          |                     | Phase 2    | NCT03894215  | Not recruiting | Cervical cancer                |
|                          |                     | Phase 1    | NCT06095674  | Not recruiting | Cervical cancer                |
| Oregovomab               | CA125               | Phase 3    | NCT04498117  | Not recruiting | Ovarian cancer                 |
|                          |                     | Phases 1–2 | NCT04938583  | Recruiting     | Ovarian cancer                 |
|                          |                     | Phase 2    | NCT01616303  | Completed      | Ovarian cancer                 |

(Continued)



TABLE 2 (Continued)

| Antibody type/<br>name | Target | Phase        | Trial number | Study Status   | Indication         |
|------------------------|--------|--------------|--------------|----------------|--------------------|
|                        |        | Phase 2      | NCT05335993  | Not recruiting | Ovarian cancer     |
| BAT1308                | PD-1   | Phases 2–3   | NCT06321068  | Recruiting     | Endometrial cancer |
|                        |        | Phases 2–3   | NCT06123884  | Not recruiting | Cervical cancer    |
| ZB-06                  | CD52g  | early phase1 | NCT04731818  | Completed      | Contraception      |
| Zalifrelimab           | CTLA4  | Phases 1–2   | NCT03495882  | Completed      | Cervical cancer    |
| Utomilumab             | 4-1BB  | Phases 1–2   | NCT03318900  | Completed      | Ovarian cancer     |

pembrolizumab represents a cost-effective and efficacious treatment strategy for patients with refractory gynecologic cancer (26).

The vascular endothelial growth factor (VEGF) serves as a crucial mediator in the process of neovascularization, which is predominantly secreted by cancer cells (27). Bevacizumab is the first anti-angiogenic agent approved for oncological use. Numerous clinical trials have demonstrated the efficacy of bevacizumab in the treatment of gynecologic malignancies (28). There is an increasing body of evidence that supports its efficacy and safety in routine clinical practice. In a retrospective study, bevacizumab was found to be effective and well-tolerated in the real-world treatment of ovarian cancer (29). Furthermore, a multi-institutional retrospective cohort study indicated that bevacizumab maintenance therapy prolonged progression-free survival for metastatic, recurrent, or persistent cervical cancer (30).

In addition, canonical antibodies are also used in the treatment of postmenopausal osteoporosis (31). Notably, denosumab, a fully human antibody targeting RANK-L (32), and romosozumab, a humanized monoclonal antibody targeting sclerostin (SOST) (33), are utilized in this therapeutic context.

4.2 ADCs

ADCs have emerged as one of the most promising therapeutic modalities in oncology due to their ability to provide tumor cells with chemotherapy in a more targeted and safer manner (34, 35). ADCs comprise a highly selective antibody, a cytotoxic payload, and a linker connecting the two components (36). Currently, several ADCs have acquired FDA approval for the treatment of gynecologic cancers, including mirvetuximab soravtansine for ovarian cancer and tisotumab vedotin for cervical cancer (37). Although no ADCs have been approved for endometrial cancer, 8 clinical trials (NCT04205630, NCT06132958, NCT03836157, NCT04251416, NCT06340568, NCT03835819, NCT03832361, and NCT04585958) have been identified to address this unmet critical need. Notably, mirvetuximab soravtansine is currently being evaluated in two phase II clinical trials for endometrial cancer (NCT03835819 and NCT03832361).

Fam-trastuzumab deruxtecan-nxki (T-DXd) contains a topoisomerase I inhibitor payload, a cleavable tetrapeptide linker, and the anti-HER2 antibody trastuzumab (38). On 5 April 2024, the approval of T-DXd was accelerated by the FDA to treat adults with unresectable or metastatic HER2-positive (IHC3+) solid tumors. Previous clinical trials have suggested its potential efficacy in patients with endometrial cancer (39). In the STATICE trial, patients with

endometrial cancer expressing HER2 were categorized into HER2-low and HER2-high expression groups. The overall response rate was 70.0% (95% CI, 34.8–93.3) for the HER2-low group and 54.5% (95% CI, 32.2–75.6) for the HER2-high group. These results indicated that T-DXd is effective in patients with endometrial cancer, irrespective of the HER2 expression status (40). Furthermore, the combination of T-DXd and olaparib was assessed in HER2-expressing cancers, including an extension to patients with endometrial cancer (NCT04585958).

Sacituzumab govitecan, ADCs against trophoblast cell surface antigen-2 (Trop-2), has demonstrated its potential efficacy in the treatment of endometrial cancer (41). In a Phase I/II basket study, the objective response rate was 22.2% (95% CI, 6.4–47.6) in the endometrial cancer cohort (42). Currently, a Phase II study of sacituzumab govitecan in patients with persistent or recurrent endometrial carcinoma is ongoing (NCT04251416).

However, in this context, clinical data on other ADCs remain limited.

4.3 Bispecific antibodies

Bispecific antibodies are designed to simultaneously bind to separate antigenic epitopes or distinct antigens (43). Compared with traditional antibodies, bispecific antibodies exhibit greater specificity, which contributes to improved therapeutic efficacy and safety, while reducing the likelihood of adverse reactions (44). This characteristic makes bispecific antibodies a promising strategy in cancer therapy (45). An increasing number of bispecific antibodies with diverse mechanisms are currently under development for oncological applications, including checkpoint inhibitors (CPIs), T-cell engagers (TCEs), natural killer cell engagers (NKCEs), and immune cell engagers (ICEs) (46). In the realm of gynecological cancer, the majority of bispecific antibodies in registered clinical trials are concentrated on checkpoint inhibition. Notably, catumaxomab (NCT00189345, NCT00563836), navicixizumab (NCT05043402, NCT03030287), REGN5668 (NCT04590326), and ubamatamab (NCT03564340) are identified as agents targeting CD3xEpCAM, VEGFxDLL4, MUC16xCD28, and CD3xMUC16, respectively. A selection of representative findings is described in this subsection.

Cadonilimab is a bispecific antibody against PD-1 and CTLA4, which has completed two Phase II studies in patients with metastatic or recurrent cervical cancer (NCT04380805, NCT04868708). The findings of these studies indicated that cadonilimab may provide patients with substantial therapeutic benefits (47, 48). In China, cadonilimab was approved in June 2022 for the treatment of metastatic cervical cancer based on these promising outcomes (49). Furthermore,

several clinical studies involving cadonilimab are currently ongoing (NCT05687851, NCT05824494, NCT06066216, NCT04982237, NCT05227651, and NCT05932212).

Navicixizumab is a bispecific agent that targets both DLL4 and VEGF (50). A Phase 1a study of navicixizumab provided preliminary evidence of anti-tumor activity in ovarian cancer, with manageable toxicity (51). A subsequent Phase 1b study combining navicixizumab with paclitaxel (NCT03030287) demonstrated an ORR of 43.2% (95% CI, 28.3–59.0) in patients with platinum-resistant ovarian cancer. Furthermore, 90.9% of patients experienced treatment-related adverse events, including hypertension, fatigue, and headaches (52). A Phase III trial to assess the efficacy and safety of navicixizumab in the treatment of ovarian cancer is currently underway (NCT05043402).

## 4.4 Fc fusion proteins

Fc fusion proteins contain the Fc domain of an immunoglobulin (IgG) and a desired linked protein (53). Compared to traditional antibodies, Fc fusion proteins exhibit an extended half-life, multiple targeting capabilities, and superior specificity (54). Currently, there are 13 studies on Fc fusion proteins in the field of gynecology. This report highlights the bifunctional fusion proteins Bintrafusp alfa (NCT04246489, NCT04551950), SHR-1701 (NCT05179239), and SL-172154 (NCT05483933, NCT04406623).

Bintrafusp alfa is a bifunctional fusion protein that comprises an extracellular domain of TGF- $\beta$  receptor II fused to a human IgG1 monoclonal antibody against PD-L1 (55). This agent has completed both Phase 1 and Phase 2 clinical trials in patients with metastatic or recurrent cervical cancer (NCT04551950, NCT04246489). The findings of these studies have confirmed the safety profile and clinical efficacy of Bintrafusp alfa. Anemia is the most common treatment-related adverse event (56, 57).

SHR-1701 is a bifunctional fusion protein that comprises an extracellular domain of TGF- $\beta$  II and an antibody targeting PD-L1 (58). Recent data have indicated that SHR-1701 has an ORR of 15.6% in patients with metastatic or recurrent cervical cancer. Additionally, 11 patients (34.4%) experienced treatment-related adverse events of grade 3 or grade 4 severity. Consequently, SHR-1701 may be a potential therapeutic option for patients with cervical cancer (59). Currently, the safety and efficacy of SHR-1701 are being evaluated in a Phase 3 clinical trial (NCT05179239).

SL-172154 is a hexameric fusion protein that comprises SIRP $\alpha$  and CD40L domains connected by an inert Fc linker. This agent has completed a Phase 1 clinical trial in ovarian cancer patients (NCT04406623). Additionally, a subsequent Phase 1 trial is currently underway, which targets patients with platinum-resistant ovarian cancer (NCT05483933).

## 4.5 Challenges

### 4.5.1 Subcutaneous delivery of antibodies

Historically, antibody-related drugs are delivered by IV injection due to their inherent physicochemical and biological characteristics (60). However, this method has several disadvantages, including pain, low patient tolerance, and elevated costs. Consequently, there has been a progressive transition in the administration route of antibody-based

therapeutics from IV to SC injection. This shift is attributed not only to the reduced administration time but also to the feasibility of home-based administration (61). In recent years, approximately 30% of the approved antibody-related drugs have been administered through SC injection (62). Although several drugs have reached clinical trials, only denosumab and romosozumab have been approved by the EMA and FDA to treat postmenopausal osteoporosis (63).

There were no statistically significant differences in safety and immune response between intramuscular and SC administration routes, according to a Phase 1 clinical trial (NCT00058435) (64). Similarly, the findings of another Phase 1 clinical study (NCT00103545) were also promising (65). However, a subsequent Phase 3 trial (NCT00418574) indicated that patients with ovarian cancer in first remission received no therapeutic benefits from abagovomab (66).

Dalantercept, a recombinant fusion protein designed to target the activin receptor-like kinase 1 (ALK1) receptor, was evaluated in a Phase II clinical trial that comprised 28 patients with endometrial cancer. Patients were administered a dosage of 1.2 mg/kg subcutaneously every 3 weeks (NCT01642082). The majority of participants withdrew from the study primarily due to disease progression. It was concluded that dalantercept had inadequate efficacy as a single-agent treatment (67). Additionally, a separate Phase II trial that evaluated dalantercept in patients with ovarian and fallopian tube cancers failed to exhibit any objective response (68).

Hyaluronidase-zzxf/pertuzumab/trastuzumab is an SC injection that contains a fixed-dose combination of trastuzumab and pertuzumab, which has been approved for treating patients with HER2-positive breast cancer (69). Currently, a Phase 2/3 clinical trial is underway to assess the efficacy of hyaluronidase-zzxf/pertuzumab/trastuzumab in patients with HER2-positive endometrial serous carcinoma (NCT05256225).

Furthermore, a Phase 2 clinical trial is currently underway to assess the efficacy of HMI-115 in patients with endometriosis-related pain. Herein, HMI-115 is administered SC on a bi-weekly basis.

This study shows that the availability of antibody-related drugs for SC administration is limited in the field of gynecology. This is because this route of administration is hindered by challenges such as immunogenicity, high viscosity, and protein aggregation (70, 71). To enhance the SC delivery of antibodies, various strategies have been developed, including the combination of proprietary excipients and proteins to address the issues related to the ionic strength and hydrophobic regions of antibodies (60).

Overall, the demand for SC antibodies is high on the market. However, significant obstacles persist and the SC administration is making ongoing advancements.

### 4.5.2 Potential targets

According to the results, the hottest and most potential targets for developing antibody-related drugs in gynecology are mesothelin, PD-1, FR $\alpha$ , HER2, and TIGIT. Mesothelin is a membrane-bound surface glycoprotein that is highly expressed in ovarian cancer, pancreatic adenocarcinoma, mesothelioma, and several other malignancies. However, its expression is limited in normal tissues (72). Furthermore, mesothelin plays an important role in cell adhesion, drug resistance, and tumor metastasis, which makes it a potential therapeutic target for ovarian cancer (73). Examples are amatuximab (NCT00325494), anetumab ravtansine (NCT03587311, NCT02751918), and RC88 (NCT06173037).

PD-1 is a checkpoint protein that belongs to the CD28 family. It is predominantly expressed in activated CD4 + T cells, CD8 + T cells, and peripheral B cells (74). The PD-1 signaling pathway plays a significant role in the tumor microenvironment of various malignancies and contributes to T cell inactivation and depletion, which facilitates the evasion of antitumor immunity (75). Consequently, PD-1 is a promising target for therapeutic strategies. Examples are balstilimab (NCT03495882, NCT03104699, NCT03894215, NCT06095674), BAT1308 (NCT06321068, NCT06123884), and rilonilimab (NCT06226350).

FR $\alpha$  is a glycoprotein attached to the membrane and is encoded by the FOLR1 gene (76). It is critically involved in cell proliferation, DNA synthesis, and intracellular signaling, which are fundamental to tumorigenesis. The receptor is a promising target for the development of anticancer drugs due to its overexpression in various solid tumors, such as ovarian, lung, and breast cancers (77). Examples are STRO-002 (NCT03748186, NCT05870748, and NCT05200364), IMGN151 (NCT05527184), and farletuzumab ecteribulin (NCT05613088).

HER2 is a constituent of the EGFR family of receptor tyrosine kinases (78). Aberrations of the HER2 gene, including mutations, deletions, and amplifications, have been identified in ovarian, cervical, and endometrial cancers (79). Examples are trastuzumab duocarmazine (NCT04205630), DP303c (NCT04828616), and BNT323/DB-1303 (NCT06340568).

TIGIT is a newly recognized immune checkpoint. It is predominantly expressed in natural killer cells, regulatory T cells, CD4 + T cells, CD8 + T cells, and tumor-infiltrating lymphocytes (80). TIGIT is associated with the exhaustion of NK cells *in vivo* and is observed in individuals with various types of cancer (81). Examples are tiragolumab (NCT04300647) and ociperlimab (NCT04693234).

## 5 Conclusion

This study provides a thorough review of clinical trials involving antibody-related drugs in the field of gynecology. The analysis revealed a growing prevalence of ADCs, bispecific antibodies, and Fc-fusion proteins. It has been found that these therapeutic modalities play a crucial role in advancing gynecological oncology. Meanwhile, it also explores the challenges associated with SC administration. The findings of this review may provide valuable insights and new ideas for future research on antibodies in gynecology.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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XZ: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. LX: Conceptualization, Supervision, Writing – review & editing. FL: Data curation, Funding acquisition, Project administration, Supervision, Writing – review & editing. WC: Data curation, Methodology, Writing – review & editing. CZ: Supervision, Writing – review & editing. YD: Investigation, Supervision, Writing – review & editing. TW: Data curation, Writing – review & editing. SX: Supervision, Validation, Writing – review & editing. HD: Supervision, Validation, Writing – review & editing. MT: Supervision, Validation, Writing – review & editing. WG: Supervision, Validation, Writing – review & editing. EL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Validation, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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