INTRODUCTION

Gynecological malignancies, mainly including ovarian, cervical, and endometrial cancer, seriously affect the health of women worldwide, contributing considerably to the global cancer burden. Epithelial ovarian cancer (OC) comprises ~90% of the malignant ovarian neoplasms, which is one of the leading causes of death in women. The 5-year overall survival (OS) rate of OC is ~47% for all stages, and ~70% of patients are diagnosed at the advanced stage with an even lower 5-year OS rate. Although the response rate of first-line treatments for OC are debulking surgery and perioperative platinum-based chemotherapy. Although the response rate of the first-line treatment is high, most of the patients will eventually experience relapses within the subsequent 3 years. At first relapse, ~20–25% of patients have platinum-resistant (disease recurs ≥6 months from the last platinum-based chemotherapy) or platinum-refractory (disease progress during or within 4 weeks of platinum-based chemotherapy) disease, with poor prognosis. In the platinum-resistant disease, single non-platinum agent is used, such as paclitaxel, docetaxel, pegylated liposomal doxorubicin (PLD), gemcitabine and topotecan. However, the response rates and outcomes are disappointing. Cervical cancer (CC), as the fourth most common female cancer globally, is also a major health problem especially for women in developing countries. High-risk human papilloma virus (HPV) infection is considered to be responsible for more than 90% of CC development. HPV overexpresses E6 and E7 oncoproteins which inhibit TP53 and RB1 proteins from altering cell cycle, apoptosis, and DNA repair. Thus, HPV testing is an important part of CC screening, and immunization against HPV (e.g., vaccines) has been designed to prevent CC. With early screening and effective treatments such as radical surgery or concurrent chemoradiation (a combination of radiation and chemotherapy), the cure rate of CC can reach 80% in the early-stage disease (FIGO stage I-II). The 5-year OS rate for all stages is ~66%. However, treatment options are limited and the survival rate is low for patients who present with distant metastatic disease, as well as those with unresectable recurrent disease and those who recur at distant. Endometrial cancer (EC), also known as uterine cancer, is the sixth most common female cancer. Elevated estrogen levels and increasing age are well-known risk factors of EC. Thus, the incidence of EC is increasing due to the increased life expectancy and obesity (causing elevated estrogen level). The standard treatment consists of surgery with or without adjuvant radiotherapy and/or chemotherapy, which is based on the risk of disease recurrence. Traditionally, EC has been classified in two types mainly according to histology and estrogen dependence. Furthermore, the Cancer Genome Atlas (TCGA) identified EC into four molecular subgroups: polymerase epsilon (POLE) ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high, each with a distinct prognosis. Most low-risk patients with early-stage disease can be cured by surgery and have good prognoses. However, the prognosis for advanced EC is poor with 5-year OS rate of 40–65% in stage III and 15–17% in stage IV disease, respectively. All those malignancies, when progressed to the advanced stage, have very poor prognoses under conventional treatment. Due to the lack of effective treatment for advanced-stage, refractory, recurrent, and drug-resistance disease, we are facing very tough challenges. However, based on the improved understanding of the mechanisms on cancer progression, targeted therapies are emerging as groundbreaking and promising treatment strategies.

In targeted therapies, individual patients are treated by agents targeting the changes in tumor cells that help them grow, divide, and spread. Currently in gynecological malignancies, potential therapeutic targets include tumor-intrinsic signaling pathways, angiogenesis, homologous-recombination deficiency (HDR),...
Table 1. FDA-approved targeted drugs for gynecological cancers

| Target | Drug                  | Approval year | Indication                                    | Administration                      |
|--------|-----------------------|---------------|-----------------------------------------------|-------------------------------------|
| VEGF   | Bevacizumab (Avastin, Genentech) | 2014          | CC Persistent, recurrent, or metastatic disease | 15 mg/kg IV every 3 weeks with chemotherapy |
|        |                       | 2014          | OC Platinum-resistant recurrent, and received no more than 2 prior chemotherapy regimens | 10 mg/kg IV every 2 weeks with chemotherapy |
|        |                       | 2016          | Platinum-sensitive recurrent                   | 15 mg/kg IV every 3 weeks with chemotherapy |
|        |                       | 2018          | Advanced (FIGO stage III-IV)                   | 300 mg orally twice daily, until disease progression or unacceptable toxicity |
| PARPi  | Olaparib (Lynparza, AstraZeneca) | 2014          | OC Advanced, with BRCAm, and have received three or more prior lines of chemotherapy | 600 mg orally twice daily, until disease progression or unacceptable toxicity |
|        |                       | 2017          | Recurrent, and in complete or partial response to platinum-based chemotherapy | 300 mg orally once daily, until disease progression or unacceptable toxicity |
|        |                       | 2018          | Advanced, with BRCAm, and in complete or partial response to platinum-based chemotherapy |                                    |
|        | Rucaparib (Rubraca, Clovis) | 2016          | OC Recurrent, with BRCAm, and have received two or more chemotherapies |                                    |
|        |                       | 2018          | Recurrent and in a complete or partial response to platinum-based chemotherapy |                                    |
|        | Niraparib (Zejula, Tesaro) | 2017          | OC Recurrent and in a complete or partial response to platinum-based chemotherapy |                                    |
| Anti-  | Pembrolizumab (Keytruda, Merck) | 2017          | EC Unresectable or metastatic, with a biomarker as MSI-H or dMMR | 200 mg IV over 30 min every 3 weeks |
| PD-1   |                       | 2018          | CC Recurrent or metastatic, with disease progression on or after chemotherapy, and expressing PD-L1 |                                    |
| Anti-  | Pembrolizumab (Keytruda, Merck) + + PARP inhibitor | 2019*         | EC Advanced disease without MSI-H/dMMR who have disease progression following prior systemic therapy, but are not candidates for surgery or radiation | Lenvatinib 20 mg orally once daily with pembrolizumab 200 mg IV over 30 min every 3 weeks |

**Notes:**
- CC: cervical cancer
- OC: epithelial ovarian, fallopian tube, or primary peritoneal cancer
- EC: endometrial cancer
- VEGF: vascular endothelial growth factor
- PARPi: PARP inhibitor
- IV: intravenous infusion
- BRCAm: deleterious or suspected deleterious BRCA mutation
- MSI-H: microsatellite instability high
- dMMR: mismatch repair-deficient
- *Accelerated approval

### Hormone Receptors and Immunologic Factors

The corresponding targeted agents include signaling pathway inhibitors, antiangiogenic agents, poly (ADP-ribose) polymerase (PARP) inhibitors, selective estrogen receptor downregulators, and immune checkpoint inhibitors. For gynecological cancers, bevacizumab, olaparib, rucaparib, niraparib, and pembrolizumab have been approved by the US Food and Drug Administration (FDA) for selected patients with recurrent, metastatic, or high-risk diseases (Table 1). The clinical uses of these and other targeted agents are being actively and extensively investigated.

In this paper, we review the clinical efficacy and safety of the targeted therapies in gynecological cancers, by summarizing the results of previous clinical trials. We further describe the ongoing phase II/III clinical trials and expound future directions.

### METHODS

A comprehensive literature review was performed on PubMed, including systematic reviews, review articles, clinical trials, and observation studies published in English. ClinicalTrials.gov was queried to collect the data of completed and ongoing clinical trials. For each approved targeted drug, the FDA website was searched for indication, usage and references as the basis for approval. Search terms included “gynecological cancers”, “ovarian cancer”, “cervical cancer”, “endometrial cancer”, “targeted therapy”, “angiogenic agents”, “PARP inhibitor”, “signaling pathway inhibitors”, “immune checkpoint inhibitors”, and each name of the targeted agent (e.g., “bevacizumab”, “olaparib”). We also used the ESMO and ASCO websites for preliminary results reported from ongoing trials.

### Antiangiogenic Agents

Neovascularization is considered as a crucial process for tumor growth and progression. In decades, efforts have been made to develop vascular-targeted therapies for cancer treatment. Depending on the distinctly different mechanisms, vascular-targeted therapies include antiangiogenic agents and vascular-disrupting agents. Here, we focus on the action of antiangiogenic agents in this review.

Angiogenesis is a complex process regulated by various proangiogenic and antiangiogenic factors. Vascular endothelial growth factor (VEGF), a major driver of angiogenesis in solid tumors, binds to the VEGF receptors (VEGFR, including VEGFR-1/2/3) on target cells and initiates the signaling pathway through intracellular tyrosine kinases. It can initiate several endothelial cell signaling pathways and promote endothelial cell precursors from bone marrow. The VEGF pathway also interacts with the PI3K/AKT/mTOR pathway. Moreover, the process of angiogenesis is further modulated by the platelet-derived growth factor (PDGF) pathway, the fibroblast growth factor (FGF) pathway, the epidermal growth factor (EGF) pathway, and the angiopoietin family and their receptor tyrosine kinase (Tie2) pathways. There are complicated interplays of these pro-angiogenic pathways (Fig. 1). In addition, the VEGF expression can be induced by hypoxia-associated transcription factors, such as hypoxia inducible factors (HIF1A and HIF2A). It is also associated with other genetic alterations such as TP53, RAS, and EGFR.

In tumor cells, the expression levels of the pro-angiogenic factors, especially VEGF, are upregulated to develop tumor’s own endogenous blood vessels, which is associated with the poor prognosis. Therefore, antiangiogenic therapies are developed...
by inhibiting target signaling pathways at different points. The main classes of antiangiogenic agents are anti-VEGF monoclonal antibodies (e.g., bevacizumab), soluble VEGFRs (e.g., aflibercept), inhibitors of angiopoietin-Tie2 receptor (e.g., trebananib), and tyrosine kinase inhibitors (e.g., cediranib). Tyrosine kinases are enzymes that catalyze the transfer of phosphate from adenosine triphosphate (ATP) onto target proteins to elicit a response. Tyrosine kinase inhibitors (TKIs) are small molecules which can block intracellular tyrosine kinases in multiple signaling pathways (e.g., VEGF, EGF).

A number of antiangiogenic agents, such as bevacizumab, pazopanib, sunitinib, sorafenib, vandetanib, aflibercept, axitinib, regorafenib, ramucirumab, and lenvatinib are FDA-approved for cancer treatment (e.g., colorectal cancer, lung cancer, renal cell carcinoma, and thyroid cancer). For gynecological cancers, bevacizumab was the first and only FDA-approved anti-VEGF drug. As of January 2020, there are a dozen of completed phase III trials assessing the efficacy and safety of antiangiogenic agents for gynecological cancers, especially in OC. The main data from completed Phase II/III clinical trials are summarized in Tables 2 and 3.

Bevacizumab
Bevacizumab is a humanized anti-VEGF monoclonal antibody, which is the best-known antiangiogenic agent. In gynecological cancers, bevacizumab is currently approved by FDA as combination treatment and/or maintenance treatment for selected patients with: (1) persistent, recurrent, or metastatic CC; (2) advanced or recurrent OC (including stage III/IV epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer) (Table 1). The decisions of these indications are mainly grounded on findings from the following six Phase III clinical trials (five for OC and one for CC) (Table 2).

GOG-0218 trial (NCT00262847) evaluated the efficacy of bevacizumab (15 mg/kg intravenously every 3 weeks) in combination with chemotherapy plus/without bevacizumab maintenance for patients with newly diagnosed advanced OC following initial surgery. The median progression-free survival (PFS) was increased in the bevacizumab-concurrent plus maintenance arm when compared with control (chemotherapy alone) arm (3.8 months longer, \( P < 0.001 \)). PFS was not significantly increased in the bevacizumab-concurrent arm (without bevacizumab maintenance). However, final results of this trial were updated in July, 2019. When compared with the control arm, there is no significant increase in the median OS either in the bevacizumab-concurrent plus maintenance arm or in the bevacizumab-concurrent arm. In a subset analysis stratified by stage, for patients with stage IV disease, the control and bevacizumab-concurrent arms were associated with a median OS of 32.6 and 34.5 months, respectively. The median OS was increased in patients with stage IV disease who received bevacizumab-concurrent plus maintenance (42.8 months, HR, 0.75; 95% CI, 0.59–0.95). Another phase III trial, ICON7 (NCT00483782) found a modest increase in the median PFS (2.4 months longer, \( P = 0.25 \)) with no OS benefit in chemotherapy plus bevacizumab (both concurrence and maintenance) arm in the updated analyses. However, in a subset analysis of patients at high risk of progression, a significant difference in the median OS was noted between patients in chemotherapy plus bevacizumab arm and those in chemotherapy alone arm (39.3 vs. 34.5 months, \( P = 0.03 \)). Data from these two trials did not show a statistically different quality of life (QOL) in the whole study population. Owing to the above trials, the FDA approved bevacizumab in combination with chemotherapy and followed as maintenance therapy for newly diagnosed advanced OC patients after initial surgical resection.

For patients with platinum-sensitive recurrent OC, OCEANS trial (NCT00434642) showed that the median PFS was significantly increased (4 months longer, \( P < 0.0001 \)) in chemotherapy plus bevacizumab arm compared with chemotherapy alone. However, no significant difference in OS was observed at the final analysis. On the other hand, another phase III trial GOG-0213 (NCT00565851) showed that the addition of bevacizumab to chemotherapy led to a significant difference in both median PFS.
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(3.4 months longer, \(P < 0.0001\)) and OS (4.9 months longer, adjusted \(P = 0.0447\)) in patients with platinum-sensitive recurrent OC.\(^{41}\) The FDA approved bevacizumab in combination with first-line chemotherapy and followed as maintenance therapy for platinum-sensitive recurrent OC patients in 2016.

For patients with platinum-resistant recurrent OC, an open-label phase III trial, AURELIA (NCT00976911), found that the addition of bevacizumab to chemotherapy improved the median PFS (3.3 months longer, \(P < 0.001\)), with no benefit in OS at the final analysis.\(^{42,43}\) Based on this trial, the FDA approved bevacizumab in combination with chemotherapy for platinum-resistant recurrent OC patients who received no more than two prior chemotherapy regimens.

Another phase III trial (NCT01081262), studying different chemotherapy regimens with or without bevacizumab as the first-line therapy in treating patients with mucinous epithelial OC, was closed early due to slow accrual.\(^{44}\) An ongoing phase III trial (NCT03635489) is evaluating the efficacy and safety of bevacizumab plus chemotherapy in Chinese participants with newly diagnosed advanced OC.

For CC, phase II trials (e.g., NCT00548418) demonstrated that the combination of chemotherapy and bevacizumab in patients with recurrent or persistent CC had an objective response rate (ORR) of 59–88%.\(^{45–47}\) Furthermore, a phase III trial, GOG-0240 (NCT00803062), revealed an improvement in the median PFS (2.2 months longer, \(P = 0.0002\)) and OS (3.5 months longer, \(P = 0.07\)) among patients receiving chemotherapy plus bevacizumab compared with those receiving chemotherapy alone.\(^{48}\) Based on this trial, the FDA approved bevacizumab in combination with standard chemotherapy for metastatic, persistent, or recurrent CC. For locally advanced CC, a phase II trial (NCT00369122) showed concurrent cisplatin-based chemoradiotherapy and bevacizumab had an ORR of 68.7%.\(^{49}\) Another phase II/III trial (JCOG1311) has been initiated to compare different chemotherapy regimens with or without bevacizumab in stage IVb, recurrent or persistent CC.\(^{50}\)

Currently, there are limited results of phase III studies assessing the efficacy of bevacizumab for patients with EC. In a phase II trial (NCT00301964) for persistent or recurrent EC, the single-agent bevacizumab therapy was shown to have an ORR of 13.5%, with the median PFS and OS being 4.2 and 10.5 months, respectively.\(^{51}\) Another phase II trial (NCT00879359) for advanced or recurrent EC

### Table 2. Completed phase III trials of antiangiogenic agents in gynecological cancers

| ID          | Cancer/condition               | No. | Intervention                                                                 | mPFS (mon.) | mOS (mon.) | SAEs (%) | Refs |
|-------------|--------------------------------|-----|-------------------------------------------------------------------------------|-------------|------------|----------|------|
| NCT00483782 ICON7 | OC/high-risk stage I-IIa, IIb-IV | 1528 | (1) PC                                                                        | 17.5        | 58.6       | –        | 37   |
|             |                                |     | (2) PC + bevacizumab                                                         | 19.9, \(P = 0.25\) | 58.0, \(P = 0.85\) | –        |      |
| NCT00976911 AURELIA | OC/platinum-resistant recurrent | 361  | (1) Single-agent chemotherapy                                                | 3.4         | 13.3       | 27.1     | 42   |
|             |                                |     | (2) Chemotherapy + bevacizumab                                               | 6.7, \(P < 0.001\) | 16.6, \(P = 0.174\) | 31.28    |      |
| NCT00434642 OCEANS | OC/platinum-sensitive recurrent | 484  | (1) GC + placebo                                                             | 8.4         | 32.9       | 25.32    | 40   |
|             |                                |     | (2) GC + bevacizumab                                                         | 12.4, \(P < 0.0001\) | 33.6, \(P = 0.65\) | 36.44    |      |
| NCT00262847 GOG-0218 | OC/stage III-IV              | 1873 | (1) PC + placebo                                                             | 10.3        | 41.1       | 38.49    | 35   |
|             |                                |     | (2) PC + bevacizumab throughout                                              | 14.1, \(P < 0.001\) | 40.8, \(P = 0.34\) | 41.19    |      |
|             |                                |     | (3) PC + bevacizumab combination only                                         | 11.2, \(P = 0.16\) | 43.4, \(P = 0.53\) | 46.37    |      |
| NCT00565851 GOG-0213 | OC/platinum-sensitive recurrent | 674  | (1) PC                                                                        | 10.4        | 37.3       | 86       | 41   |
|             |                                |     | (2) PC + bevacizumab                                                         | 13.8, \(P < 0.0001\) | 42.2, \(P = 0.045\) | 96       |      |
| NCT00803062 GOG-0240 | CC/metastatic, persistent, or recurrent | 452  | (1) PC                                                                        | 6           | 13.3       | 37.5     | 42,43|
|             |                                |     | (2) PT                                                                 | –           | 34.58      | –        |      |
|             |                                |     | (3) PC + bevacizumab                                                         | 8.2, \(P = 0.002\) | 16.8, \(P = 0.007\) | 55.96    |      |
| NCT00532194 ICON6 | OC/platinum-sensitive recurrent | 486  | (1) Chemotherapy + placebo                                                    | 8.7         | –          | –        | 73   |
|             |                                |     | (2) Chemotherapy + cediranib throughout                                       | 9.9         | –          | –        |      |
|             |                                |     | (3) Chemotherapy + cediranib combination only                                 | 11, \(P < 0.0001\) | –          | –        |      |
| NCT01015118 AGO-OVAR12 | OC/stage IIb-IV            | 1503 | (1) PC + placebo                                                             | 16.6        | 62.8       | 34.89    | 67   |
|             |                                |     | (2) PC + nintedanib                                                          | 17.2, \(P = 0.24\) | 62, \(P = 0.087\) | 42.02    |      |
| NCT00866697 AGO-OVR16 | OC/stage II-IV, after first-line chemotherapy | 940  | (1) Placebo                                                                  | 12.3        | 64.0       | 11.06    | 63   |
|             |                                |     | (2) Pazopanib                                                                | 17.9, \(P = 0.0021\) | 59.1, \(P = 0.64\) | 25.37    |      |
| NCT01204749 TRINOVA-1 | OC/recurrent               | 919  | (1) Paclitaxel + placebo                                                     | 5.4         | 17.3       | 52       | 78   |
|             |                                |     | (2) Paclitaxel + trebananib                                                  | 7.2, \(P < 0.0001\) | 19.0, \(P = 0.19\) | 53       |      |
| NCT01281254 TRINOVA-2 | OC/recurrent               | 223  | (1) PLD + placebo                                                           | 7.2         | 17.0       | 72       | 81   |
|             |                                |     | (2) PLD + trebananib                                                         | 7.6, \(P = 0.57\) | 19.4, \(P = 0.76\) | 73       |      |
| NCT01493505 TRINOVA-3 | OC/stage III-IV            | 1164 | (1) PC + placebo                                                            | 15.0        | –          | 66       | 80   |
|             |                                |     | (2) PC + trebananib                                                          | 15.9, \(P = 0.36\) | –          | 73       |      |

ID: identifier, No: enrollment number, mPFS: median progression-free survival, mOS: median overall survival, Mon: months, SAEs: serious adverse events, Refs: references, Stage FIGO stage, PC: paclitaxel + carboplatin, GC: gemcitabine + carboplatin, PT: topotecan + paclitaxel, PLD: pegylated liposomal doxorubicin.
Table 3. Completed phase II trials of antiangiogenic agents in gynecological cancers

| ID          | Cancer/condition       | No. | Intervention                                           | ORR (%) | mPFS (mon.) | mOS (mon.) | SAEs (%) | Refs |
|-------------|------------------------|-----|-------------------------------------------------------|---------|-------------|------------|----------|------|
| NCT00025233 | CC/persistent or recurrent | 46  | Bevacizumab                                          | 10.9    | 3.4         | 7.29       | 58.7     | 45   |
| NCT00548418 | CC/persistent or recurrent | 27  | Bevacizumab + topotecan + cisplatin                  | 59      | 7.1         | 13.2       | 44.44    | 46   |
| NCT00369122 | CC/stage Ib–llb         | 60  | Bevacizumab + cisplatin + radiotherapy               | 68.7    | –           | –          | 22.03    | 49   |
| NCT00937560 | CC/advanced or recurrent | 34  | Bevacizumab + PC                                     | 88      | 9           | 26         | –        | 47   |
| NCT01010126 | EC/stage III–IV         | 26  | Bevacizumab + temsirolimus                            | 52.5    | 5.0         | 11.5       | 61.5     | 60,339|
| NCT01305213 | OC/recurrent            | 107 | Bevacizumab                                          | 28.2    | 4.8         | –          | 16.98    | 397  |
| NCT00966670 | OC/resistant            | 39  | Bevacizumab + erlotinib                               | 23.1    | 4           | –          | –        | 398  |
| NCT00945139 | OC/platinum-resistant recurrent | 46  | Bevacizumab + PLD                                     | 30.2    | 6.6         | 33.2       | 6.52     | 399  |
| NCT01091259 | OC/recurrent            | 29  | Bevacizumab + irinotecan                              | 27.6    | 6.8         | 15.4       | 31       | 400  |
| NCT00886691 | GOG-0186G              | 150 | (1) Bevacizumab                                       | 12.1    | 4.5         | 17.3       | 32       | 401  |
| NCT00105329 | OC/platinum-resistant recurrent | 48  | Bevacizumab + abraxane                               | 50      | 8.08        | 17.15      | 29.7     | 402  |
| NCT00967696 | OSU-05070              | 45  | Bevacizumab + GC                                     | 69      | 13.3        | 36.1       | 8.9      | 403  |
| NCT01770171 | EC/advanced or recurrent | 108 | (1) PC                                                | 53.1    | 10.5        | 29.7       | –        | 54   |
| NCT00276445 | EC/advanced or recurrent | 15  | Bevacizumab + PC                                     | 73      | 18          | 58         | 73.3     | 52   |
| NCT00977574 | GOG-0086P              | 339 | (1) Bevacizum + PC                                   | 60      | –           | 34         | 42.9     | 404  |
| NCT01770171 | EC/high risk            | 34  | Bevacizumab + cisplatin + radiotherapy               | 55      | 25          | 50.4       | –        | 53   |
| NCT00879359 | EC/persistent or recurrent | 56  | Bevacizumab                                          | 13.5    | 4.2         | 10.5       | 34.6     | 51   |
| NCT01468909 | OC/recurrent            | 106 | (1) Paclitaxel                                        | 31.8    | 7.5         | 23.3       | 30.00    | 407  |
| NCT00430781 | OC/stage Ic–IV          | 74  | (2) Pazopanib + paclitaxel                            | 22.7    | 6.2         | 20.7       | 42.31    | 408  |
| NCT02055690 | OC/recurrent            | 21  | (1) Pazopanib                                        | 9       | 4.22        | –          | 37.84    | 257  |
| NCT01669798 | OC/recurrent, bevacizumab-resistant | 27  | Nintedanib                                          | 7.4     | 1.8         | 16         | 22.2     | 68   |
| NCT00276445 | EC/recurrent            | 37  | Nintedanib                                          | 9.4     | 3.3         | 10.1       | 43.8     | 69   |
| NCT01210222 | EC/recurrent            | 35  | Trebananib                                          | 3.1     | 1.7         | 6.6        | 43       | 82   |
| NCT01253681 | OC/recurrent            | 61  | (1) Placebo                                          | 27      | 4.6         | –          | 64       | 409  |
| NCT01111461 | EC/recurrent            | 133 | Lenvatinib                                          | 14.3    | 5.4         | 10.6       | 46.62    | 410  |
| NCT00276445 | OC/recurrent            | 74  | Cediranib                                          | 26      | 4.9         | 18.9       | 6.8      | 72   |
| NCT01132820 | GOG-0229J               | 48  | Cediranib                                          | 12.5    | 3.65        | 12.5       | 41.7     | 74   |
showed that bevacizumab in combination with chemotherapy had an ORR of 73%, presenting a median PFS of 18 months and a median OS of 58 months.\textsuperscript{52} For patients with high-risk EC, postoperative bevacizumab added to chemotherapy and pelvic radiotherapy resulted in a high OS rate (at 2 years) of 96.7% and a disease-free survival rate of 79.1%, which was reported in a phase II trial (NCT01005329).\textsuperscript{53} However, bevacizumab plus chemotherapy failed to demonstrate a significant increase in PFS of patients with advanced or recurrent EC, reported by the MITO END-2 trial (NCT01770171) in 2019.\textsuperscript{54}

Grade 3 or worse adverse events (AEs) occurring at a higher incidence (incidence ≥ 2%) in patients receiving chemotherapy plus bevacizumab compared with chemotherapy alone (from data of those phase III trials) included fatigue, hypertension, neutropenia, thrombocytopenia, proteinuria, nausea, headache, dyspnea, epistaxis, abdominal pain, hyponatremia, pain in extremity, and palmar-plantar erythrodysesthesia syndrome.\textsuperscript{55}

### Pazopanib

Pazopanib is an oral TKI of VEGFR-1/-2/-3, PDGFR-α/-β, and c-Kit.\textsuperscript{56–58} Pazopanib showed promising activity in phase I/II trials for patients with platinum-sensitive recurrent OC with increased ORR and PFS.\textsuperscript{59–61} A phase III trial, AGO-OVAR16 (NCT00866697), investigated the efficacy and safety of pazopanib (800 mg daily) as maintenance therapy after first-line chemotherapy in patients with newly diagnosed stage II–IV OC. The study showed that the pazopanib maintenance significantly improved the median PFS (5.6 months longer, \(P = 0.0021\)).\textsuperscript{62} In subgroup analyses, the PFS benefit with maintenance pazopanib was observed in most subgroups except East Asian patients. To gain further insight, a concurrent study (NCT01227928) similar in design to AGO-OVAR16 was undertaken in the East Asian population, showing that pazopanib maintenance therapy was not associated with a benefit in PFS or OS. There was no satisfactory explanation for this result yet. However, the final analysis of the OVAR16 study was reported in 2019. No difference was observed in the median OS between pazopanib arm and placebo arm.\textsuperscript{63} Grade 3 or worse AEs occurring at a higher incidence in the combined treatment arm compared with placebo included hypertension, neutropenia, diarrhea, thrombocytopenia, increased alanine aminotransferase, and palmar-plantar erythrodysesthesia. A phase I/II trial (NCT02055690) recently reported that combination of pazopanib and fosbretabulin (a produg with vascular-disrupting activity) might potentially improve survival outcomes compared with pazopanib alone.\textsuperscript{64} However, this trial was prematurely stopped due to serious cardiac toxicity.

Currently, there are limited data of clinical trials investigating pazopanib for patients with CC or EC. A phase II trial evaluated pazopanib in the treatment of recurrent or persistent carcinosarcoma of the uterus with a result of no response.\textsuperscript{65}

### Nintedanib

Nintedanib is another oral TKI of VEGFR-1/-2/-3, FGF receptor (FGFR)-1/-2/–3, and PDGFR-α/β. A phase II trial in platinum-sensitive recurrent OC patients showed an improvement in PFS rate in nintedanib maintenance arm than placebo arm (16.3% vs. 5.0%, \(P = 0.06\)).\textsuperscript{66} Subsequently, a phase III trial, AGO-OVAR12 (NCT01015118), investigated the combination of nintedanib (200 mg daily) with first-line chemotherapy in patients with newly diagnosed stage IIb–IV OC. The median PFS was 0.6 month longer in the nintedanib arm than that in the placebo arm (\(P = 0.024\)).\textsuperscript{67} Increased incidences of AEs, including hypertension, gastrointestinal perforation, and bleeding, were reported in the nintedanib arm. The final result of OS is pending. However, for bevacizumab-resistant OC population, single-agent nintedanib was shown to have minimal activity with an ORR of 7.4% in a phase II trial (NCT01669978).\textsuperscript{68}

We found limited clinical data of phase II/III trials investigating the activity of nintedanib in EC and CC. One phase II trial, GOG-0229K (NCT01225887), evaluated nintedanib in the treatment of advanced, recurrent, or metastatic EC. It showed modest activity with an ORR of 9.4%.\textsuperscript{69}

### Cediranib

Cediranib is a TKI of VEGFR-1/–2/–3 and c-Kit.\textsuperscript{70,71} Given the activity of cediranib in OC showed by early-phase trials,\textsuperscript{72} a phase III trial, ICON6 (NCT00532194), investigated the combination of cediranib (20 mg orally daily) with chemotherapy and as maintenance treatment in patients with platinum-sensitive recurrent OC. The median PFS was 2.3 months longer in the cediranib maintenance arm than that in the placebo arm (\(P < 0.0001\)).\textsuperscript{73} The data of OS have not been updated. Currently, there are no differences in immature results of median OS across the arms. Increased incidences of diarrhea, neutropenia, hypertension, and voice changes were noted in arms with cediranib.

A phase II study, GOG 229J (NCT01132820), showed cediranib as a monotherapy treatment for recurrent or persistent EC was well-tolerated, with a median PFS of 3.65 months and a median OS of

### Table 3. continued

| ID              | Cancer/condition | No. | Intervention                  | ORR (%) | mPFS (mon.) | mOS (mon.) | SAEs (%) | Refs |
|-----------------|------------------|-----|-------------------------------|---------|-------------|------------|----------|------|
| NCT00888173     | GOG-0229I        | 43  | Sunitinib                     | 7       | 3.3         | 10.7       | 41.8     | 95   |
| NCT01267253     | GOG-0227G        | 28  | Brivanib                      | 8       | 3.2         | 7.9        | 50       | 94   |
| NCT02867956     | OC/platinum-refractory | 35 | Apatinib + etoposide         | 54      | –           | –          | 5.7      | 87   |
| NCT02867956     | OC/recurrent     | 29  | Apatinib                      | 41.4    | 5.1         | 14.5       | 31       | 86   |
| NCT00979992     | GOG-0254         | 30  | Sunitinib                     | 6.7     | 2.7         | 12.8       | –        | 91   |
| NCT00388037     | OC/recurrent     | 30  | Sunitinib                     | 3.3     | 4.1         | –          | 50.00    | 90   |
| NCT00543049     | AGO 2.11         | OC/platinum-resistant recurring | 76 | Sunitinib (noncontinuous/continuous) | 16.7/5.4 | 4.8/4.9 | 13.6/13.7 | –     | 89   |
| NCT00768144     | OC/recurrent, platinum-refractory | 35 | Sunitinib                     | 8.3     | 9.9         | –          | 19.4     | 88   |
| NCT00478426     | EC/metastatic or recurrent | 33 | Sunitinib                     | 18.1    | 3           | 19.4       | 52       | 92   |
| NCT00389974     | CC/advance or metastatic | 19 | Sunitinib                     | 0       | 3.5         | –          | 73.68    | 93   |

**ORR** objective response rate
12.5 months. Cediranib showed sufficient activity to warrant further investigation for recurrent EC. However, we found limited clinical data for patients with CC.

Trebananib
Trebananib is a peptide-Fc fusion protein that binds angiopoietin-1/-2, preventing the interaction of angiopoietin with the Tie2 receptor. Trebananib has shown single-agent activity and prolonged PFS in recurrent OC in early-phase trials. There are three completed phase III trials assessing trebananib in recurrent or newly diagnosed advanced OC. TRINOVA-1 trial (NCT01204749) investigated the addition of trebananib (15 mg/kg intravenously weekly) to single-agent weekly paclitaxel in patients with recurrent OC with platinum-free interval ≤12 months. As a result, the median PFS was 1.8 months longer in the trebananib arm than that in the placebo arm (P < 0.0001). Subsequently, TRINOVA-2 (NCT0128125) evaluated the addition of trebananib to PLD in patients with recurrent OC, and it showed that trebananib did not significantly prolong PFS. However, the addition of trebananib to PLD improved ORR compared with placebo arm (46% vs. 21%, P < 0.001). TRINOVA-3 trial (NCT01493505) showed that the addition of trebananib to first-line chemotherapy did not improve PFS or produce new safety signals for patients with newly diagnosed advanced OC. The result of OS was not mature. The major toxic effect associated with trebananib treatment was edema.

For recurrent or persistent EC, a phase II trial (NCT01210222) showed an ORR of 3.1%, with insufficient single-agent activity to warrant further investigation of trebananib.

Other antiangiogenic agents
Apatinib is a small-molecule TKI by binding to the VEGFR-2 ATP-binding site, which is taken orally. Given the promising results of a phase III study in Chinese gastric cancer patients, apatinib had been actively investigated as a salvage treatment for other advanced solid tumor, including OC. A phase II study of apatinib in patients with recurrent OC indicated that apatinib (500 mg daily) was a feasible treatment with an ORR of 41.4%. Grade 3 AEs were hand-foot syndrome, hypertension, and neutropenia. Another phase II trial (NCT02867956) demonstrated that apatinib plus etoposide showed promising efficacy and manageable toxicities in patients with platinum-resistant or -refractory OC with an ORR of 54%. An ongoing phase III trial in China (NCT04000295) is further evaluating the efficacy and safety of apatinib in patients with platinum-resistant recurrent OC compared with chemotherapy.

Sunitinib and brivanib are oral TKIs of VEGFR and PDGFR. Sunitinib was an FDA-approved drug for renal cell cancer and gastrointestinal stromal tumors. The safety and efficacy of sunitinib in OC were evaluated in several phase II trials with reported ORR ranging from 3.3% to 16.7%. In metastatic or recurrent EC, sunitinib showed promising activity in a phase II trial (NCT00478426) with an ORR of 18.1%. However, sunitinib had insufficient activity as a single agent in advanced or metastatic CC to warrant further investigation. Two phase II trials demonstrated that brivanib was well-tolerated and worthy of further investigation in persistent or recurrent EC/CC with an ORR of 7% and 8%, respectively.

For the development of antiangiogenic agents and other targeted therapies, the addition of bevacizumab to conventional chemotherapy in OC is a very important step. However, most of the analysis reported so far showed that antiangiogenic agents led to no significant improvement in OS for patients with gynecological cancers. Thus, identification of predictive biomarkers for antiangiogenic agents and development of other targeted drugs are anticipated.

Poly (ADP-ribose) polymerase (PARP) inhibitors
PARP is a sort of nuclear enzyme with 17 identified members. PARP-1 and 2 are involved in DNA repair. PARP-1, with a central automodification domain and the C-terminal catalytic domain, was originally found involved in the base-excision repair (BER) pathway, which is important in the repair of single-stranded DNA breaks (SSBs). Therefore, inhibition of PARP-1 leads to the accumulation of DNA SSBs and ultimately results in DNA double-strand breaks (DSBs) during DNA replication. The preferred pathway is HRR, since it is more accurate. Thus, in cells with functional HRR, PARP inhibition will not result in cell death since DSBs will be precisely and effectively repaired. However, in cells with homologous-recombination deficiency (HRD), as such as those with BRCA1/2 mutations, DSBs are left unrepaired or repaired by the error-prone NHEJ pathway, which result in genomic instability and ultimately cell death.

In gynecological cancers, germline and somatic BRCA1/2 mutations (gBRCAm and sBRCAm) occur in ~10–15% of OC.

**Fig. 2** Base-excision repair/single-strand break pathway and the mechanism of synthetic lethal interactions. Inhibition of PARP-1 causes the accumulation of DNA SSBs and ultimately results in DSBs during DNA replication. In cells with HRD, DSBs are left unrepaired or repaired by the error-prone NHEJ pathway, which result in genomic instability and ultimately cell death.
patients, and even more frequently in patients with high-grade serous OC (HGSOC), which is the most common type of OC. In addition, genomic alterations in other homologous-recombination (HR) genes including ATM, BRIPI, PALB2, and RAD51C are being studied. The comprehensive genomic analysis has identified that ~50% of high-grade serous tumors (including OC and EC) exhibit HRD. Moreover, the presence of HRD predicts a favorable response to platinum therapies and to PARP inhibitors. PARP inhibitors are also known to sensitize DNA-damaging agents, including carboplatin.

Based on the above facts, PARP inhibitors are supposed to be groundbreaking therapeutic strategies for patients with gynecological cancers, especially for OC.

Several PARP inhibitors, including olaparib, rucaparib, niraparib, veliparib, and talazoparib are actively investigated in clinical trials. The development of PARP inhibitors is productive. Olaparib is the first PARP inhibitor applied in clinic and approved by FDA for cancer treatment, followed by rucaparib and niraparib. The results from phase II/III clinical trials, assessing PARP inhibitors in gynecological cancers, are summarized in Tables 4 and 5. The ongoing clinical trials without results are listed in Table 6.

Olaparib

Olaparib is the best studied PARP inhibitor and approved by FDA for the maintenance treatment of selected advanced or recurrent OC patients. Early-phase clinical trials of olaparib demonstrated activity signals in patients with OC, with favorable tolerance and response rates. Following these promising results, a notable randomized placebo-controlled phase II trial, Study 19 (NCT00753545), evaluated olaparib as maintenance monotherapy for patients with platinum-sensitive recurrent OC. The median PFS was significantly longer in the olaparib arm compared with placebo (3.6 months longer, \( P < 0.001 \)). A retrospective pre-planned analysis suggested that patients with BRCAm gained the greatest PFS benefits from olaparib treatment (6.9 months longer, \( P < 0.0001 \)). An exploratory post hoc analysis of Study 19 also suggested a numerical improvement in the OS. Although the PFS benefit was less in patients without BRCAm (1.9 months longer, \( P = 0.0075 \)), this significant benefit suggested that a proportion of patients without BRCAm might also benefit from olaparib treatment.

Another single-arm phase II trial, Study 42 (NCT01078662), evaluated olaparib as treatment for cancer patients with gBRCAm, including ovarian, breast, prostate, and pancreatic cancer. The ORR was 31.1% in platinum-resistant recurrent OC cohort. Stable disease (SD) was seen in 40% of patients, confirming significant activity. Based on these findings, the FDA approved single-agent olaparib as recurrence therapy for patients with advanced OC with gBRCAm who have received three or more lines of chemotherapy in 2014.

Several large randomized phase III trials of olaparib in gynecological cancers (mainly in OC) are currently in progress. The following three of the phase III trials reported promising results in OC. SOLO-2 trial (NCT01874353) evaluated the efficacy of olaparib as maintenance therapy in platinum-sensitive recurrent OC patients with BRCAm who had received at least two lines of previous chemotherapy. The results demonstrated a statistically significant improvement in investigator-assessed median PFS in the olaparib arm compared with placebo (13.6 months longer, \( P < 0.0001 \)). At the time of the analysis of PFS, OS data were not mature with 24% of events. Based on this trial, the FDA approved olaparib as maintenance therapy for women with recurrent OC who are in complete or partial response to platinum-based chemotherapy in 2017.

Another phase III trial, SOLO-1 (NCT01844986), evaluated the efficacy of olaparib as maintenance therapy in newly diagnosed advanced OC patients with BRCAm in 2018. At the ESMO Congress 2019, new findings of a phase III trial, PAOLA-1/ENGOT-ov25 (NCT02477644), were presented. This is the first phase III trial to evaluate efficacy and safety of a PARP inhibitor plus bevacizumab as first-line maintenance therapy in advanced OC not restricted by surgical outcome or

Table 4. Phase III trials (with results) of PARP inhibitors in gynecological cancers

| ID           | Cancer/condition   | No. | Intervention                        | mPFS (Mos.) | SAEs (%) | Refs |
|--------------|--------------------|-----|------------------------------------|-------------|----------|------|
| NCT01844986  | SOLO-1             | 319 | (1) Placebo                         | 13.8        | 12.3     | 121  |
|              |                    |     | (2) Olaparib                        | Not reached | 20.8     |      |
|              |                    |     |                                    |             |          |      |
| NCT01874353  | SOLO-2             | 295 | (1) Placebo                         | 5.5         | 8.08     | 120  |
|              |                    |     | (2) Olaparib                        | 19.1, \( P < 0.0001 \) | 17.95    |      |
| NCT02477644  | PAOLA-1            | 806 | (1) Bevacizumab + placebo           | 16.6        | 31       | 122  |
|              |                    |     | (2) Bevacizumab + olaparib          | 22.1, \( P < 0.0001 \) | 31       |      |
| NCT01847274  | NOVA               | 553 | (1) Placebo                         | HRD: 10.4, All: 8.2 | 15.08    | 138  |
|              |                    |     | (2) Niraparib                       | HRD: 21.9, All: 13.8, \( *P < 0.0001 \) | 29.97    |      |
| NCT02665016  | PRIMA              | 733 | (1) Placebo                         | HRD: 8.2    | 18.9     | 140  |
|              |                    |     |                                    |             |          |      |
| NCT01968213  | ARIEL3             | 564 | (1) Placebo                         | BRCAm: 5.4, HRD: 5.4 | 10.58    | 136  |
|              |                    |     | (2) Rucaparib                       | BRCAm: 16.6, HRD: 13.6, \( **P < 0.0001 \) | 21       |      |
| NCT02470585  | GOG-3005           | 1140| (1) Placebo                         | BRCAm: 22.0, HRD: 20.5 | 32       | 150  |
|              |                    |     | (2) Veliparib combination only       |             | 27       |      |
|              |                    |     | (3) Veliparib throughout             | BRCAm: 34.7, HRD: 31.9, \( ***P < 0.0001 \) | 45       |      |

HRD homologous-recombination deficiency, HGSOC high-grade serous ovarian cancer. \( *P \)-value of both BRCAm and all population are <0.0001. \( ** \) and \( *** \) \( P \)-value of both BRCAm and HRD cohorts are <0.0001.
BRCA status. According to the results, patients with newly diagnosed OC had significantly improved the median PFS with addition of olaparib to bevacizumab maintenance treatment, as compared to placebo plus bevacizumab following first-line chemotherapy (5.5 months longer, \(P < 0.0001\)).\(^{122}\) Moreover, the PFS benefit in subgroups of patients with BRCAm and patients with other HRD was even more obvious (19.5 months longer and 11.5 months longer, respectively). In PAOLA-1 trial, the rate of AEs leading to treatment discontinuation is the highest figure reported across PARP inhibitor trials. However, there was no impact in QOL.

The FDA-recommended olaparib dose is 300 mg (two 150 mg tablets) taken orally twice daily. The most common serious AEs reported in SOLO-1 and SOLO-2 were anemia and neutropenia. There are other three ongoing phase III trials of olaparib (as monotherapy) registered in the ClinicalTrials.gov database without available results, including SOLO-3 (NCT02282020), OPINION (NCT03402841), and L-MOCA (NCT03534453) (Table 6).

A phase ii trial (NCT01116648) evaluated the efficacy and toxicity of the combination of cediranib and olaparib compared to olaparib alone in platinum-sensitive recurrent OC, based on the data from early clinical trial.\(^{123,126}\) This novel combination of angiogenesis inhibitor and PARP inhibitor improved the median PFS by 8.3 months compared with PARP inhibitor alone(\(P = 0.007\)).\(^{124,127}\) In the updated analysis in 2019, subset analyses within stratum defined by BRCA status demonstrated that this combination therapy significantly improved both median PFS (23.7 vs. 5.7 months, \(P = 0.002\)) and median OS (37.8 vs. 23.0 months, \(P = 0.047\)) in gBRCAwt/unknown patients.\(^{128}\) It encouraged the novel combination therapy of different targeted agents explored as a potential treatment strategy. Currently, we found only clinical case reports about efficacy of olaparib in other gynecological cancers (e.g., EC).\(^{129}\)

| ID            | Cancer/condition       | No. | Intervention                  | ORR (%) | mPFS (mon.) | mOS (mon.) | SAEs (%) | Refs |
|--------------|------------------------|-----|--------------------------------|---------|-------------|------------|----------|------|
| NCT0494442   | OC/advanced, BRCAm     | 58  | Olaparib                      | 33.3    | –           | –          | 36.4     | 411  |
| NCT00753545  | OC/serous, recurrent   | 265 | (1) Placebo: BRCAm/BRCAwt     | 4.2     | 4.3/5.5, \(P < 0.0001\) | 34.9/30.2, \(P = 0.025\) | 8.6 | 115,112 |
|              |                        |     | (2) Olaparib: BRCAm/BRCAwt    | 12.3    | 11.2/7.4, \(P = 0.0075\) | 26.6/24.5, \(P = 0.37\) | 22.8 |
| NCT00679783  | OC/recurrent, HGSOC    | 91  | Olaparib: BRCAm/BRCAwt        | 41/24   | 7.4/6.4     | –          | 16       | 111  |
| NCT00628251  | OC/advanced, BRCAm     | 98  | (1) Olaparib (200 mg twice daily) | 25      | 5           | 9          | 15.6     | 413  |
|              |                        |     | (2) Olaparib (400 mg twice daily) | 31.3    | 5           | 11         | 18.8     |      |
| NCT01078662  | OC/BRCAm               | 193 | Olaparib                      | 31.1    | 7.03        | 16.62      | 30.2     | 118  |
| NCT01081951  | OC/advanced or         | 173 | (1) PC                        | –       | 9.6         | –          | 20.99    | 414  |
|              | platinum-sensitive     |     | (2) Olaparib + PC             | 12.2, \(P = 0.0012\) | –          |           | 25.33    |      |
| NCT01116648  | OC/platinum-sensitive  | 90  | Olaparib                      | 48.7    | 8.2         | 33.3       | –        | 124,128 |
|              | recurrent              |     | (2) Cediranib + olaparib      | 79.6    | 16.5, \(P = 0.007\) | 44.2, \(P = 0.11\) | 70       |
| NCT02354586  | OC/HGSOC, recurrent    | 47  | Niraparib                     | 28      | 5.5         | 19         | 56       | 141  |
| QUADRA       | HRD                    |     | (1) Niraparib + PC            | –       | 12.2, \(P = 0.0012\) | –          | 25.33    |      |
| NCT02657889  | OC/platinum-resistant  | 62  | Niraparib                     | 18      | 3.4         | Not mature | –        | 143  |
| KEYNOTE-162  | recurrent, HRD         |     | (2) Niraparib + bevacizumab  | –       | 11.9, \(P < 0.0001\) | –         | 65       |
| NCT02354131  | OC/platinum-sensitive  | 97  | Niraparib                     | 30      | 5.5         | –          | –        | 142  |
| ENGOT-ov24   | recurrent              |     | (2) Niraparib + bevacizumab  | 62      | 11.9, \(P < 0.0001\) | –         | 65       |
| NCT01891344  | OC/platinum-sensitive  | 204 | Rucaparib: BRCAm/BRCAwt       | 80      | 12.8        | –          | 24.5     | 133  |
| ARIEL2       | recurrent, HRD         |     | BRCAwt, LOH-high              | 29.3    | 5.7         | –          | –        |      |
|              |                        |     | BRCAwt, LOH-low               | 10      | 5.2         | –          | –        |      |
| NCT01482715  | OC/BRCAm               | 42  | Rucaparib                     | 59.5    | 19.4        | 3          | 0       | *    |
| STUDY10      |                        |     | (2) Cyclophosphamide +       | 11.8    | 3, \(P = 0.68\) | –          | 8.11     |
|              |                        |     | veliparib                     | –       | –           | –          | –        |      |
| NCT01306032  | OC/HGSOC, BRCAm        | 75  | (1) Cyclophosphamide         | 19.4    | 3           | –          | 0*       |      |
|              |                        |     | (2) Cyclophosphamide+         | 11.8    | 3, \(P = 0.68\) | –          | 8.11     |
|              |                        |     | veliparib                     | –       | –           | –          | –        |      |
| NCT01540565  | OC/BRCAm               | 52  | Veliparib                     | 26      | 8.18        | –          | 20       | 146  |
| NCT01266447  | CC/persistent or       | 27  | Veliparib + topotecan +       | 7       | 2           | 8          | 59.3     | 151  |
|              | recurrent              |     | filgrastim                    | –       | –           | –          | –        |      |

| BRCAwt BRCA wild-type. LOH genomic loss of heterozygosity. *Unpolished data found in ClinicalTrials.gov |
| ID           | Cancer/condition                      | Setting     | No.  | Start date | Intervention                                      | Phase/assignment                  | Status                        |
|--------------|---------------------------------------|-------------|------|------------|---------------------------------------------------|-----------------------------------|-------------------------------|
| NCT02282020  | SOLO-3 OC/platinum-sensitive recurrent, BRCAm | Maintenance | 266  | 2015.2     | Olaparib vs. single-agent chemotherapy             | II/randomized, parallel            | Active, not recruiting        |
| NCT03402841  | OPINION OC/platinum-sensitive recurrent, without BRCAm | Maintenance | 279  | 2018.1     | Olaparib                                          | II/single group                   | Active, not recruiting        |
| NCT03534453  | L-MOCA OC/platinum-sensitive recurrent | Maintenance | 300  | 2018.5     | Olaparib                                          | II/single group                   | Active, not recruiting        |
| NCT02855944  | ARIEL4 OC/recurrent                    | Monotherapy | 345  | 2016.9     | Rucaparib vs. chemotherapy                        | II/randomized, crossover          | Recruiting                    |
| NCT04227522  | MAMOC OC/advanced                      | Maintenance | 190  | 2020.1     | Rucaparib vs. placebo                            | III/randomized, parallel          | Not yet recruiting            |
| NCT03519230  | OC/platinum-sensitive recurrent        | Maintenance | 216  | 2018.5     | Pamiparib vs. placebo                            | III/randomized, parallel          | Recruiting                    |
| NCT03709316  | OC/advanced                            | Maintenance | 381  | 2018.6     | Niraparib vs. placebo                            | III/randomized, parallel          | Recruiting                    |
| NCT03863860  | OC/platinum-sensitive recurrent        | Maintenance | 216  | 2019.1     | Fluzoparib vs. placebo                           | III/randomized, parallel          | Not yet recruiting            |
| NCT04169997  | OC/advanced                            | Maintenance | 393  | 2020.2     | IMP4297 vs. placebo                              | III/randomized, parallel          | Recruiting                    |
| NCT02489006  | OC/recurrent                           | Neoadjuvant | 24   | 2016.7     | Olaparib vs. platinum-based chemotherapy          | II/randomized, parallel           | Recruiting                    |
| NCT03470805  | OC/recurrent, after PLD                | Maintenance | 9    | 2018.6     | Olaparib                                          | II/single group                   | Active, not recruiting        |
| NCT04377087  | OC/recurrent                           | Delayed maintenance | 75  | 2020.5     | Olaparib                                          | II/single group                   | Not recruiting                |
| NCT03016338  | EC/recurrent                           | –           | 44   | 2017.11    | Niraparib                                        | II/single group                   | Recruiting                    |
| NCT03644342  | CC/metastatic invasive                 | Concurrently | 20   | 2019.7     | Niraparib + radiotherapy                          | II/single group                   | Recruiting                    |
| NCT03891576  | OC/platinum-sensitive recurrent        | Maintenance | 105  | 2019.10    | Niraparib                                        | II/single group                   | Not yet recruiting            |
| NCT04217798  | OC/platinum-resistant or -refractory   | Maintenance | 32   | 2020.1     | Niraparib + etoposide                            | II/single group                   | Not yet recruiting            |
| NCT03617679  | EC/metastatic and recurrent            | Maintenance | 138  | 2019.3     | Rucaparib vs. placebo                            | II/randomized, parallel           | Recruiting                    |
| NCT03795272  | CC/locally advanced                    | Maintenance | 162  | 2019.11    | Rucaparib vs. placebo                            | II/randomized, parallel           | Withdrawn                     |
| NCT04171700  | LODSTAR Solid tumor/HRD               | –           | 220  | 2019.11    | Rucaparib                                        | II/single group                   | Recruiting                    |
| NCT03509636  | OC/recurrent, BRCAm                    | –           | 113  | 2018.4     | Fluzoparib                                       | II/single group                   | Active, not recruiting        |
therapy for patients with platinum-sensitive OC. The median PFS was 7.6 months longer in the BRCAm subgroup (P < 0.0001).

In a phase III trial, ARIEL3 (NCT01968213), assessed the efficacy and safety of rucaparib as maintenance therapy in patients with platinum-sensitive recurrent OC. The median PFS in patients with BRCAm was 11.2 months longer in the rucaparib arm than that in the placebo arm (P < 0.0001). In patients with HRD, it was 8.2 months longer (P < 0.0001). In the intention-to-treat (ITT) population, the median PFS was 5.4 months longer in patients in the rucaparib arm than that in the placebo arm (P < 0.0001).

Based on this study, the FDA approved rucaparib for the maintenance treatment of recurrent OC patients who are in a complete or partial response to platinum-based chemotherapy. The ongoing ARIEL4 trial (NCT02855944) is another phase III study of rucaparib compared with chemotherapy in recurrent OC patients with BRCAm after two or more prior lines of therapy. The combination of rucaparib with other novel therapies (e.g., immune checkpoint inhibitor) is investigated for OC and EC in Phase I/II trials (NCT03101280, NCT03572478). A new phase III trial, MAMOC (NCT04227522), is going to investigate rucaparib maintenance therapy after bevacizumab maintenance following first-line chemotherapy in advanced OC.

The FDA-recommended rucaparib dose is 600 mg (two 300 mg tablets) taken orally twice daily. The most common serious AEs reported in ARIEL3 were anemia, pyrexia, vomiting, and small intestinal obstruction.

Niraparib

Niraparib is another FDA-approved PARP inhibitor.137 A phase III trial, ENGOT-OV16/NOVA (NCT01847274), evaluated the efficacy of niraparib as maintenance treatment for patients with platinum-sensitive recurrent OC. The results showed that niraparib increased PFS regardless of BRCA status when compared with placebo. Patients in the niraparib arm had significantly longer median PFS than those in the placebo arm, including 21.0 vs. 5.5 months in the gBRCAm cohort, 12.9 months vs. 3.8 months in the non-gBRCAm cohort for patients who had tumors with HRD, and 9.3 months vs. 3.9 months in the overall non-gBRCAm cohort (P < 0.001 for all three comparisons).138 Based on this study, niraparib was approved by FDA in 2017 as maintenance therapy for adult patients with recurrent OC who are in complete or partial response to platinum-based chemotherapy.139,140 Furthermore, a retrospective subanalysis demonstrated the safety and efficacy of niraparib in the subgroup of patients aged ≥70 years in this trial, suggesting that the use of niraparib should be considered in this population.139 Findings from another phase III trial, PRIMA (NCT02655016), were presented at the ESMO Congress 2019, and recently reported. This study evaluated the efficacy of niraparib following first-line chemotherapy in patients with newly diagnosed advanced OC and had similar findings with NOVA trial. Patients in the niraparib arm had substantial improvement in the median PFS compared to those in placebo arm (5.6 months longer, P < 0.0001). In the HRD cohort, the improvement of the median PFS was even greater in treatment group (21.9 vs. 10.4 months, P < 0.001). Another phase III trial (NCT03709316) of niraparib in advanced OC is under way (Table 6). Several other Phase II trials are studying the potential role of niraparib in different clinical settings. QUADRA trial (NCT02354586) assessed the activity of single-agent niraparib as the fourth or later line treatment for patients with platinum-sensitive recurrent HGSOC.141 This study met the primary endpoint, with an ORR of 28% in HRD-positive population. The median PFS in this population was 5.5 months. The median OS was 26 months in the BRCAm population, 19.0 months in the HRD-positive population, and 15.5 months in the HRD-negative population. NSGO-AVANOVA2/ENGOT-OV24 trial (NCT02354131) showed that niraparib (300 mg orally daily) plus bevacizumab (15 mg/kg intravenously every 3 weeks) significantly improved the median PFS compared with niraparib alone in patients with platinum-sensitive recurrent OC (5.4 months longer, P < 0.0001).142 TOPACIO/KEYNOTE-162 trial (NCT02657889) evaluated niraparib (200 mg orally daily) combined with pembrolizumab (an immune checkpoint inhibitor, 200mg intravenously on day 1 of each 21-day cycle) in patients with recurrent OC. The ORR was 18%, with a disease control rate of 65%. This novel combination therapy was tolerable, and responses in patients without HRD were higher than expected with either agent as monotherapy.143

The FDA-recommended niraparib dose is 300 mg taken orally once daily. The most common serious AEs reported in NOVA and PRIMA were thrombocytopenia, anemia, and neutropenia. Disutility analyses showed no significant QOL impairment associated with these toxic effects.144

Veliparib

Veliparib is a potent small-molecule inhibitor of PARP-1/2.145 Early-phase trials demonstrated activity of veliparib among OC patients with BRCAm to provide rationale for further clinical development.109,146–149 New results from a phase III trial, VELIA/GOG-3005 (NCT02470585), were reported at the ESMO Congress 2019. It assessed the efficacy of veliparib (150 mg orally twice daily) added to first-line chemotherapy and continued as maintenance monotherapy in patients with previously untreated advanced HGSOC. In the BRCAm cohort, the median PFS was 12.7 months longer in the veliparib-throughout arm than in the control arm (P < 0.001). In the HRD cohort, it was 11.4 months longer (P < 0.001). And in the ITT population, the median PFS was 5.2 months longer (P < 0.001). AEs reported with veliparib were predominantly gastrointestinal and hematologic. The most common AE leading to the discontinuation of veliparib was nausea.150

For the treatment of CC, there was a phase I/II trial (NCT01266447) that assessed veliparib in combination with topotecan for patients with recurrent or persistent CC, showing minimal clinical activity with an ORR of 7%.151 Another phase I trial (NCT01281852) investigated veliparib in combination with cisplatin and paclitaxel in patients with recurrent or metastatic CC.152 The results demonstrated an ORR of 34%, illustrating the potential of PARP inhibitors as a combination therapy in CC.

Other PARP inhibitors

Talazoparib is a potent PARP inhibitor showing antitumor cytotoxicity at much lower concentrations than other agents, with an ORR of 42% in early-phase clinical trials for advanced OC with BRCAm.153,154

Pamiparib is a highly selective oral PARP-1/2 inhibitor capable of penetrating the brain.155 In a phase I trial of pamiparib combined with tislelizumab (an immune checkpoint inhibitor) in advanced solid tumors, 9 (26%) of the 34 patients with OC achieved clinical responses.156 A phase II trial (NCT03933761) is assessing the clinical benefit rate of pamiparib in fusion-positive, reverse-reversion-negative HGSOC with BRCAm.

Fluzoparib is a novel PARP inhibitor undergoing clinical trials with potent anticaner activities.157,158 Two ongoing Phase III trials (NCT03519230 and NCT03863860) are investigating the efficacy of pamiparib and fluzoparib as maintenance therapy in recurrent OC, respectively.

In summary, PARP inhibitors are acting as an exciting new option for patients with OC by significantly increasing both PFS and OS, especially for those with HRDs. However, cost effectiveness and drug resistance remain to be improved.159,160 In the future, it is necessary to identify more indications and predictive biomarkers.151,152 Moreover, numerous ongoing clinical trials of novel combination therapies are guiding the future direction of targeted therapy strategies (Tables 13 and 14).163,164
PI3K/AKT/mTOR pathway blockade

The phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling is one of the critical intracellular pathways that regulates important cell activities, such as cell growth, survival, proliferation, differentiation, metabolism, apoptosis, and angiogenesis. PI3K is a plasma membrane-associated lipid kinases, composed of regulatory subunit (PIK3R) and catalytic subunit (PIK3CA) that mediate receptor binding, activation, and localization of the enzyme. In normal conditions, PI3K can be activated by a variety of stimuli, including growth factors, cytokines, and hormones. Activation of AKT regulates a number of downstream targets. mTOR is a serine/threonine protein kinase and the best-described downstream target of AKT, composed of mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). mTORC1 is sensitive to inhibition by rapamycin, and its analogs and mTORC2 exerts a positive feedback activation on AKT. There are also endogenous negative regulators of the PI3K pathway, such as the tumor suppressor—phosphatase and tensin homologue (PTEN). The PI3K/Akt/mTOR pathway is also involved in cross talk with other signaling pathways, including the Ras/Raf/MEK and estrogen receptor (ER) pathways. The overview of the PI3K/AKT/mTOR signaling pathway is included in Fig. 1. In cancer, this pathway can be aberrantly activated via a number of mechanisms, including loss of tumor-suppressor function, exposure to carcinogens, mutations/amplifications of PI3K, and mutations/amplifications of AKT. The deregulation of the PI3K/AKT/mTOR pathway occurs in many cancers. As for gynecological cancers, this pathway is overactivated in OC (~70%), as well as EC and CC. In EC, the mutation rates of PI3K and PTEN were high, especially in the POLE subgroup. In vitro model of CC, mTOR inhibitors markedly reduced the expression level of HPV E7 protein, inducing apoptosis. Based on the preclinical evidence, the PI3K/AKT/mTOR pathway emerges as a potential therapeutic target in cancer, as well as gynecological malignancy. There are many drugs being tested in each part of this pathway: PI3K inhibitors, mTOR inhibitors, AKT inhibitors, and dual inhibitors on PI3K/mTOR or PI3K/AKT. mTOR inhibitors (everolimus and temsirolimus) and PI3K inhibitors (idelalisib, alpelisib and copanlisib) have been FDA-approved to be effective in the advanced cancer treatment, such as breast cancer, renal cell carcinoma, and lymphoma. Despite there are a number of preclinical/clinal data on PI3K/AKT/mTOR pathway inhibitors, currently there is no FDA-approved indication in gynecological cancers.

mTOR inhibitors

The most tested drugs in the PI3K/AKT/mTOR pathway are those blocking mTOR activity. Temsirolimus, everolimus, and ridaforolimus are the most-studied mTOR inhibitors in gynecological cancers. The results of completed clinical trials (phase II) investigating the safety and efficacy of them in gynecological cancers are summarized in Table 7.

Consistent with preclinical findings, clinical trials demonstrated promising activities of mTOR inhibitors in EC. Temsirolimus, an intravenous mTORC1 inhibitor (25 mg weekly), showed efficacy as monotherapy for advanced and recurrent EC with ORRs of 22–25%. Ridaforolimus is another intravenous mTORC1 inhibitor, administered at a dose of 12.5 mg daily for 5 consecutive days every 2 weeks, showing a modest therapeutic efficacy as a single agent. A phase II trial studied the efficacy and tolerability of ridaforolimus in recurrent and advanced EC with an ORR of 8.8% and a SD of 52.9%. Everolimus, an oral mTORC1 inhibitor (10 mg daily), was evaluated in a phase II study (NCT00087685) for the treatment of patients with recurrent or persistent EC, showing an ORR of 0% and a SD of 43%. However, everolimus was reported to have the best effects in recurrent EC when combined with hormonal therapy (e.g., letrozole, an aromatase inhibitor), showing ORRs of 29–32%. Given that mTOR inhibitors are cytostatic cell cycle agents with a benefit mainly in terms of disease stabilization rather than disease response (tumor shrinkage), we found only modest effects of mTOR inhibitors as monotherapy in OC and CC based on current clinical evidence. Reasons to these disappointing results might be: (1) one pathway blockade is insufficient; combined therapies are needed; (2) analogs of rapamycin selectively inhibit mTORC1; the other mTOR complex, mTORC2, is a positive regulator of AKT; (3) predictive biomarkers are required to identify population who can get most benefit from this pathway blockade. Considering the evidence from preclinical studies showing promising activity of mTOR inhibitors in combination with chemotherapy, a number of clinical trials assessed the efficacy of the addition of mTOR to cytotoxic drugs, as well as novel combination of different targeted therapies. A Phase II trial (NCT01031381), evaluating everolimus plus bevacizumab in recurrent OC, reported that 28% patients were progression-free at 6 months. Patients with both platinum-sensitive and -resistant disease showed response. Overall, the regimen was well-tolerated. A randomized Phase II trial (NCT00977574) compared the efficacy of temsirolimus in combination with chemotherapy (carboplatin and paclitaxel) to bevacizumab plus chemotherapy in advanced or recurrent EC. Patients treated by temsirolimus plus chemotherapy had an ORR of 55.3%, and a median OS of 25 months. However, the results reported no improvement in comparison to bevacizumab plus chemotherapy. A phase I trial (NCT02193633) investigated the efficacy of vistusertib (a dual mTORC1/mTORC2 inhibitor) in combination with paclitaxel in OC, showing an ORR of 52% and a median PFS of 5.8 months. Currently, no specific predictive biomarker has been recognized. Tumors with PI3K or PTEN mutations did not necessarily respond to mTOR inhibitors. Common treatment-related AEs of mTOR inhibitors include stomatitis, mucositis, pneumonitis, rash, fatigue, anemia, diarrhea, nausea, vomiting, hyperglycemia, and immunosuppression.

AKT inhibitors

GSK2141795 and MK2206 are inhibitors targeting AKT, acting upstream of mTOR. A phase II trial tested dual inhibition of PI3K and Ras signaling by combining the AKT inhibitor (GSK2141795, 50 mg orally daily) and the MEK inhibitor (trametinib, 1.5 mg orally daily) in recurrent CC, with AEs including gastrointestinal events, fatigue, and rash. One patient had an unconfirmed partial response, with an ORR of 7.1%. Eight patients (57.1%) had stable disease. However, the combination of trametinib and GSK2141795 was shown to have high levels of toxicity in EC at this dose. And the preliminary efficacy is disappointing in another phase II trial (NCT01935973). Moreover, a two-arm, PIK3CA mutation stratified phase II trial (NCT01307631) in recurrent EC demonstrated limited single-agent activity of MK2206 (200 mg orally weekly) in both PIK3CA mutant and wild-type populations. Afuresertib, another AKT inhibitor, combined with chemotherapy showed an acceptable safety profile in patients with platinum-resistance OC in a phase I study. A phase II trial of afuresertib plus weekly paclitaxel in platinum-resistance OC (NCT04374630, PROFECTA-II) is under way.

PI3K inhibitors

BKM120 (buparlisib) is an oral pure PI3K inhibitor. It was shown to have antitumor activity in preclinical and early trials. However, a phase II trial (NCT01397877) demonstrated that the BKM120 (100 mg orally daily) was associated with a minimal antitumor activity as monotherapy in advanced or recurrent EC. Another oral PI3K inhibitor, pilaralisib (600-mg capsules or 400-mg tablets daily), also had minimal success in a phase II trial in advanced or recurrent EC. PF-04691502 and gedatolisib (PF-05212384) are potent, dual PI3K/mTOR inhibitors. A randomized phase II non-comparative trial (NCT01420081) was...
conducted in patients with recurrent EC following platinum-containing chemotherapy. Clinical benefit response criteria were only met in the gedatolisib/stathmin-low arm. Common treatment-related AEs include nausea, mucositis, decreased appetite, diarrhea, fatigue, vomiting, rash, and stomatitis.

In summary, the role of the PI3K/AKT/mTOR pathway inhibitors in gynecological cancers is not yet clear. The reasons for the unsatisfactory results may be related to the feedback loops and compensatory activation of Ras pathway. Even though the presented clinical results are controversial, there are amount of preclinical studies and clinical trials in progress, mainly combining PI3K signaling blockade with other therapies or different targeted agents. For example, a randomized phase II trial (NCT02397083) is designed to study how everolimus works with the levonorgestrel-releasing intrauterine system for early-stage EC. Another phase II trial (NCT03008408) is to learn if the combination of everolimus, letrozole, and ribociclib (a CDK4/6 inhibitor) can help to control recurrent or progressive EC. Dual mTORC inhibition continues to be assessed in advanced or recurrent OC (NCT03648489). Furthermore, for the future of this pathway targeted therapy, studies of predictive biomarkers might be very helpful and important.

### Table 7. Completed phase II trials of PI3K/AKT/mTOR pathway inhibitors in gynecological cancers

| ID          | Cancer/condition          | No. | Intervention                        | ORR (%) | CBR (%) | mPFS (mon.) | mOS (mon.) | SAEs (%) | Refs |
|-------------|---------------------------|-----|-------------------------------------|---------|---------|-------------|------------|----------|------|
| NCT001460979| EC/advanced               | 22  | Temsirolimus                        | 10      | 35      | 3.0         | 21.3       | –        | 415  |
| AGO-GYNB    | EC/advanced               | 22  | Temsirolimus                        | 4.8     | 38.1    | 3.4         | 21.9       |          |      |
| NCT00429793 | OC/recurrent              | 54  | Temsirolimus                        | 9.3     | –       | 3.1         | 11.6       | 9.26     | 416  |
| NCIC IND 160| EC/recurrent or metastatic| 23  | Temsirolimus                        | 26      | 89      | –           | –          | –        | 188  |
| NCT00723255 | EC/recurrent              | 53  | Temsirolimus + bevacizumab          | 24.5    | 40      | 5.6         | 16.9       | 63.27    | 417  |
| NCT00729686 | EC/advanced or recurrent  | 71  | (1) Temsirolimus                    | 22      | 52.4    | 4.9         | 10.8       | 36       | 187  |
|             |                           |     | (2) Temsirolimus + hormone therapy  | 14.3    |         | –           | –          | 61.9     |      |
| NCT00072176 | EC/locally advanced,      | 60  | (1) Temsirolimus + hormone therapy  | 14      | 89      | 7.33        | –          | 33.33    | 418  |
| NCIC CTG    | recurrent, or metastatic  |     | (2) Temsirolimus + chemotherapy     | 4       | 50      | 3.25        | –          | 33.33    |      |
| NCT00977574 | GOG-86P                  | 349 | EC/stage III–IV or recurrent        | (1) Bevacizum + PC | 59.5 | –       | 34         | 42.8      | 36    | 188  |
|             |                           |     | (2) Temsirolimus + PC               | 55.3    |         | 25         | 50.4       |          |      |
|             |                           |     | (3) Bevacizum + IC                  | 52.9    |         | 25.2       | 46.5       |          |      |
| NCT01026792 | CC/advanced or metastatic| 38  | Temsirolimus                        | 3       | 60.6    | 3.52        | –          | 40.5     | 419  |
| NCT00087685 | EC/progressive or recurrent| 35  | Everolimus                          | 21      | 45.1    | –           | –          | –        | 192  |
| NCT01068249 | EC/recurrent              | 38  | Everolimus + letrozole              | 32      | 40      | 3           | 14         | 31.6     | 194  |
| NCT01797523 | EC/recurrent              | 58  | Everolimus + letrozole + metformin  | 29      | 66.7    | –           | –          | –        | 193  |
| NCT02283658 | OC/ER +, recurrent        | 20  | Everolimus + letrozole              | 16      | 37      | 3.9         | 13         | 63       | 420  |
| NCT00739830 | EC/stage III–IV           | 130 | (1) Hormone or chemotherapy         | 4       | 17      | 1.9         | –          | 34       | 421  |
|             |                           |     | (2) Ridaforolimus                   | 0       | 35      | 3.6         | –          | 57       |      |
| NCT00122343 | EC/recurrent              | 45  | Ridaforolimus                       | 11      | 19      | –           | –          | 33       | 422  |
| NCT00770185 | EC/recurrent              | 35  | Ridaforolimus                       | 8.8     | 62      | –           | –          | 37.1     | 423  |
| –           | EC/progressive            | 45  | Ridaforolimus                       | 7.4     | 33      | –           | –          | 35.6     | 424  |
| NCT01935973 | EC/recurrent or persistent| 26  | GSK2141795 + trametinib             | 8.3     | –       | –           | –          | 61       | 203  |
| NCT02538627 | CC/persistent or recurrent| 35  | GSK2141795 + trametinib             | 7.1     | 44      | 3.6         | 14.8       | 57       | 202  |
| NCT01307631 | EC/recurrent              | 37  | MK2206                              | 5.5     | 33      | –           | 8          | 37.8     | 205  |
| NCT01397877 | EC/advanced or recurrent  | 40  | BKM120                              | 0       | 60      | 4.5         | 21         |          | 209  |
| NCT02193633 | OC/HGSOC                 | 27  | Vistusertib + chemotherapy          | 52      | 78      | 5.8         | –          | –        | 198  |
| NCT01587040 | EC/advanced or recurrent  | 67  | Pilaralisib                         | 6       | 13.4    | –           | –          | 52.9     | 210  |
| NCT01420081 | EC/recurrent              | 40  | Gedatalisib                         | 16      | 5       | 3.6         | –          | –        | 212  |

CBR clinical benefit rate = complete response + partial response + stable disease, ER + estrogen receptor positive
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Fig. 3 The HER signal transduction pathway and therapeutic interventions

initiates a cascade of downstream signaling, such as P13K/AKT/ mTOR, Ras/Raf/MAPT (the mitogen-activated protein kinase pathway), and JAK/ STAT (the signal transducer and activation of the transcription pathway), which regulate from cell division to death, motility to adhesion (Fig. 3). Overexpression of EGFR and HER2 protein and amplification of HER2 oncogene play an important role in carcinogenesis, associated with breast, lung, gastric, ovarian, endometrial, and bladder cancer. HER2 is also related to increased recurrence and poor prognosis in some cancers. Thus, EGFR and HER2 are promising targets for treatment of cancer.

HER-targeted drugs include monoclonal antibodies and small-molecule inhibitors. Monoclonal antibodies against the extracellular domain of the HER receptor include cetuximab, nimotuzumab, trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1). Cetuximab and nimotuzumab bind to the extracellular domain of the EGFR. Trastuzumab obstructs HER2 homodimerization. HER2 overexpression is required for trastuzumab to be effective. Pertuzumab inhibits HER2 heterodimerization and does not require HER2 overexpression to be effective. T-DM1 is trastuzumab conjugated to emtansine (a microtubule inhibitor), which inhibits microtubule assembly in the cytoplasm and thus leads to cell death. Small-molecule inhibitors are TKIs including gefitinib, erlotinib, lapatinib, and afatinib against intracellular kinase domain to prevent signaling. Among them, gefitinib and erlotinib are inhibitors selective for EGFR. Lapatinib and afatinib inhibit both EGFR and HER2. Most of them have been approved by FDA as targeted therapies for certain advanced or recurrent cancers with selected biomarkers, such as breast cancer, colorectal cancer and non-small cell lung cancer (NSCLC).

As for gynecological cancers, HER2 is an important oncogene in high grade and stage EC, especially in uterine serous carcinoma. In OC, the rate of HER2 overexpression is highly variable (ranging from 2% to 66%), and the rate of EGFR overexpression is 30–70%. In CC, the rate of EGFR overexpression ranges from 6% to 90%. However, unlike in NSCLC, the clinical significance of EGFR/HER2 gene amplification or protein overexpression and the efficacy of HER-targeted therapy are still controversial in gynecological cancers (Table 8).

Cetuximab
Cetuximab was demonstrated to have no additional benefit beyond chemotherapy in several phase II trials for CC. Moreover, in a phase II trial, the combination of cetuximab and topotecan induced a high rate of serious adverse reactions in the treatment of advanced CC. Another randomized phase II trial, MITO CERV-2 (NCT00997009), studied the efficacy of cetuximab plus carboplatin and paclitaxel in advanced or recurrent CC, showing no significant improvement in either the median PFS or the median OS. For OC, a phase II trial (NCT00086892) demonstrated modest activity of cetuximab in combination with carboplatin in patients with platinum-sensitive recurrent OC with an ORR of 32.1% and an increased incidence of hypersensitivity reactions. There is limited information about the clinical efficacy of cetuximab in EC.

Trastuzumab
Trastuzumab treatment revealed no responses in a phase II trial with HER2-positive EC (NCT00006089). However, another randomized phase II trial (NCT01367002) of paclitaxel and carboplatin with or without trastuzumab in primary stage III or IV or recurrent HER2-positive uterine serous carcinomas showed an improvement in the median PFS in the trastuzumab combination arm (4.6 months longer, P = 0.005). In the population with primary advanced-stage disease, the median PFS was 17.9 months in the trastuzumab combination arm versus 9.3 months in the chemotherapy alone arm. In the population with recurrent disease, the median PFS was 9.2 versus 6 months, respectively. For patients with HER2 overexpression OC, trastuzumab showed modest activity with an ORR of 7.3% in a phase II trial. A clinical study in china demonstrated that the combination of abraxane and trastuzumab might have promising efficacy and adverse reaction in the treatment of recurrent OC, showing a control rate of 86.4%. However, there is limited information about the clinical efficacy of trastuzumab for CC.

Pertuzumab
A randomized phase II trial (NCT00096993) of chemotherapy (gemcitabine) with or without pertuzumab in patients with platinum-resistant OC demonstrated an increased ORR in the pertuzumab combination arm. Furthermore, a phase III trial, PENELOPE (NCT01684878), evaluated the addition of pertuzumab to chemotherapy in patients with platinum-resistant OC with low tumor HER3 mRNA expression. However, the differences in the median PFS and OS were not statistically significant. In unselected patients with platinum-sensitive recurrent OC, a phase II trial (NCT02004093) showed that the addition of pertuzumab to chemotherapy
| ID          | Cancer/condition                  | Phase No. | Intervention                      | ORR (%) | mPFS (mon.) | mOS (mon.) | SAEs (%) | Refs       |
|------------|-----------------------------------|-----------|-----------------------------------|---------|-------------|------------|----------|------------|
| NCT02095119 | CC/recurrent or metastatic        | I/II 17   | Nimotuzumab                       | 0       | 5.43        | 9.9        | –        | 425        |
| NCT00997009 | CC/recurrent                      | II 108    | (1) PC                            | 84.6    | 5.2         | 17.7       | –        | 244        |
|            |                                   |           | (2) PC + cetuximab                | 76.4    | 7.6, P = 0.20 | 17, P = 0.27 | –        |            |
| NCT10101192| CC/advanced, persistent, or recurrent | II 27    | Cetuximab + cisplatin             | 29.6    | 3.91        | 8.77       | –        | 245        |
| NCT00499031| CC/persistent or recurrent        | II 38     | Cetuximab                         | 0       | 1.97        | 6.7        | 42.86    | 246        |
| NCT00086892| OC/platinum-sensitive recurrent   | II 29     | Cetuximab                         | 32.1    | 9.4         | –          | –        | 248        |
| NCT01684878| OC/platinum-resistant, with low tumor | II 156   | (1) Placebo + chemotherapy         | 8.7     | 2.6         | 8.4        | 37.66    | 253,254    |
| PENEOLOPE  | HER3 mRNA expression              | II 149    | (1) Chemotherapy                  | -       | 9.3         | Not reached | 16.2     | *          |
|            |                                   |           | (2) Pertuzumab + chemotherapy      | 9.5     | 8.0, P = 0.3967 | 28.2       | 26.7     |            |
| NCT00096993| OC/platinum-resistant recurrent   | II 103    | (1) Placebo + chemotherapy         | 4.6     | 2.6         | 13.1       | 61.5     | 252        |
|            |                                   |           | (2) Pertuzumab + chemotherapy      | 13.8    | 2.9, P = 0.07 | 13.0, P = 0.65 | 35.38    |            |
| NCT02004093| OC/platinum-sensitive recurrent   | II 149    | (1) PC                            | -       | 9.3         | Not yet estimable | 16.2      | 255        |
|            |                                   |           | (2) PC + pertuzumab                | 8.5     | 8.5         | 28.2       | 26.67    |            |
| NCT00189579| OC/recurrent or refractory, HER2+ | II 41     | Trastuzumab                       | 7.3     | 2.0         | –          | –        | 239        |
| NCT00006089| EC/recurrent or stage III-IV, HER2+ | II 34    | Trastuzumab                       | 0       | 1.8         | 6.8        | –        | 249        |
| NCT01367002| EC/advanced or recurrent, serous  | II 61     | (1) Chemotherapy                  | 75      | 8.0         | –          | 51       | 250        |
|            |                                   |           | (2) Trastuzumab + chemotherapy     | 44      | 12.6, P = 0.005 | –          | –        |            |
| NCT00023699| OC/persistent or recurrent        | II 30     | Gefitinib                         | 0       | 1.23        | 3.7        | –        | 427        |
| NCT00189358| OC/platinum-resistant recurrent   | II 56     | Gefitinib + tamoxifen             | 0       | 1.9         | 8.4        | 3.6      | 248        |
| -          | CC/advanced or metastatic         | II 28     | Gefitinib                         | 0       | 1.2         | 3.6        | –        | 266        |
| NCT00113373| OC/recurrent                      | II 28     | Lapatinib                         | 0       | 8.0         | –          | 40       | 258        |
| NCT00436644| OC/platinum-resistant recurrent   | II 18     | Lapatinib + topotecan             | 5.6     | 3.5         | 15.5       | 22.2     | 260        |
| NCT00888810| OC/recurrent                      | II 39     | Lapatinib + topotecan             | 14      | –           | –          | –        | 259        |
| NCT00096447| EC/persistent or recurrent        | II 30     | Lapatinib                         | 3.3     | 1.82        | 7.33       | 33.3     | 256        |
| NCT00430781| CC/metastatic                     | II 230    | (1) Lapatinib                     | 5       | 4.0         | 9.1        | 28.95    | 257        |
|            |                                   |           | (2) Pazopanib                     | 9       | 4.2, P < 0.013 | 11.8, P = 0.045 | 37.84    |            |
| NCT00263822| OC/no progression after first-line PC | III 835 | (1) Erlotinib                     | –       | 12.7        | 50.8       | 67       | 262        |
|            |                                   |           | (2) Observation                   | 12.4, P = 0.525 | 59.1, P = 0.903 | –        | –        |            |
| NCT00030446| OC/recurrent                      | II 50     | Erlotinib + carboplatin           | 57      | –           | –          | 38       | 429        |
| NCT00126542| OC/recurrent                      | II 13     | Erlotinib + bevacizum             | 15      | 4.1         | 11         | –        | 261        |
| NCT00130520| OC/advanced                       | II 40     | Erlotinib + bevacizum             | 23.1    | 4           | –          | 30       | 398        |
| NCT00059787| OC/advanced                       | II 56     | Erlotinib + chemotherapy          | 29      | 34.3        | –          | –        | 430        |
| NCT00217529| OC/advanced                       | II 159    | Erlotinib + chemotherapy          | Terminated because of gastrointestinal toxicity. | 431        |
| NCT00031993| CC/recurrent or persistent        | II 28     | Erlotinib                         | 0       | Only 1 patient PFS > 6 mths | 432        |

*Unpublished data found in ClinicalTrials.gov
carboplatin-based chemotherapy did not substantially prolong PFS. Also, there is limited information about the clinical efficacy of pertuzumab for EC and CC.

**TKIs**

In clinical trials of small-molecule inhibitors, a phase II trial (NCT00096447) tested the efficacy of lapatinib and explored biological characteristics in persistent or recurrent EC. The analysis demonstrated that lapatinib had limited activity in unselected cases in EC, as well as in OC and CC. A phase II trial assessed the activity and tolerability of the combination of bevacizumab and erlotinib in recurrent OC with an ORR of 15%. Furthermore, a phase III trial (NCT00263822), evaluating the efficacy of maintenance erlotinib in OC patients after first-line chemotherapy, showed no improvement in PFS or OS. Moreover, this study failed to show a consistent correlation between EGFR mutational status/protein expression and clinical outcomes. For CC, a phase II trial evaluated the efficacy of erlotinib combined with chemoradiation in treating patients with locally advanced CC, showing a promising activity with a complete response of 94.4%. Other HER-targeted TKIs (e.g., gefitinib, canertinib, and vandetanib) showed minimal clinical activities in gynecological cancers in current clinical trials.

Even though the present clinical evidences are not very satisfying, HER-targeted therapies continue to be investigated in gynecological cancers for their potent value for biomarker-selected patients (e.g., NCT01388621, NCT01367002, NCT02039791, NCT00292955, NCT03469551, NCT00317772, NCT01953926). Furthermore, preclinical data suggested the potential of novel combination strategies involving HER-targeted therapy, which are also investigated in ongoing clinical trials.

**Other molecular targeted therapies**

**Ras/Raf/MEK.** In the Ras/Raf/MEK signaling pathway, Ras activation is the first process in activation of the mitogen-activated protein kinases (MAPKs) cascade. Upon Ras activation, Raf is recruited to the cell membrane where subsequent changes in Raf phosphorylation status result in activating MEK kinases (MEK1 and MEK2). MEK1 and MEK2 furtherly trigger Erk1 and Erk2. Finally, Erks regulate the activity of several transcription factors that control gene expression. The janus kinase/signal transducer and activator of the transcription pathway has promising potent as an antitumor targeted therapy, the clinical efficacy of this strategy in gynecological cancers is currently limited.

**JAK/STAT.** The janus kinase/signal transducer and activator of the tran-ons (JAK/STAT) pathway has been proved to mediate the action of cytokines, interferons and growth factors, and their control of gene expression. Activation of the JAK/STAT pathway and overexpression of STAT have been seen in many malignancies such as colorectal and breast cancers. Therefore, the JAK/STAT pathway is being focused as a potential target in cancer therapies. Ruxolitinib is an FDA-approved drug of JAK for treatment of patients with polycythemia vera. Preclinical
studies demonstrated that ruxolitinib reduced OC cell viability. It enhanced the sensitivity of OC cells to other anticancer agents, and suppressed ovarian tumor growth in mice. These results supported the clinical investigation of ruxolitinib in OC patients. A phase I/II trial (NCT02713386) is trying to explore the effect of ruxolitinib phosphate when given together with paclitaxel and carboplatin in treating patients with stage III–IV OC.

HGF/c-MET. Tyrosine kinase receptor c-MET (cellular–mesenchymal to epithelial transition factor) is activated by hepatocyte growth factor (HGF) and it can trigger important cellular processes. Upon binding by HGF, MET is dimerized and activates cellular processes through the Ras/Raf/MEK and PI3K/AKT/mTOR pathways (Fig. 4). In a limited number of tumors, MET genetic lesions or mutations lead to the constitutive activation of MET. However, in a majority of malignancies, aberrant MET signaling derives from the upregulation of HGF transcription, leading to receptor and ligand overexpression.

Since the publications of pioneer studies, the HGF/c-MET system has gained growing attention with its role in the pathogenesis of gynecological cancers. In a study analyzing 1115 advanced cancer patients, MET amplification was detected in 2.6% patients with solid tumors. But in OC, MET overexpression was detected in more than 20% (range from 22% to 41%) ovarian clear cell adenocarcinomas. And increased expression of HGF and
c-Met signaling is associated with a poor prognosis of EC patients.\textsuperscript{321} Therefore, targeting the interaction of c-MET and HGF would be beneficial in treating gynecological cancers. Despite there are massive preclinical data on the HGF/c-MET axis, currently there is no FDA-approved indication of this targeted therapy in cancers.

The most tested drugs in HGF/c-MET axis are those blocking c-MET activity. Rilotumumab and cabo-taxinib are the most-studied c-MET inhibitors in gynecological cancers. The results of the completed clinical trials (phase II) investigating the safety and efficacy of them in gynecological cancers are summarized in Table 9. A phase II trial (NCT01039207) evaluated the rilotumumab in the treatment of persistent or recurrent OC. Only 1/31 achieved objective response, and only two patients got 6-month PFS.\textsuperscript{322} A phase II trial (NCT02315340) evaluated cabo-taxinib in treating patient with recurrent clear cell OC with no response.\textsuperscript{323} Another phase II trial (NCT01716715) compared cabo-taxinib versus weekly paclitaxel in treatment of persistent OC, with even worse OS and ORR in cabo-taxinib arm.\textsuperscript{324} These results do not warrant further evaluation of rilotumumab or cabo-taxinib as a single agent in targeted therapy of OC. There is currently limited information of the clinical efficacy of these agents in EC and CC.

**Src.** Sarcoma proto-oncogene tyrosine kinase (Src) is a downstream component of many growth factor receptors, such as VEGFR, EGFR, and c-MET.\textsuperscript{325} Src is thought to increase chemotherapy resistance through activating Ras and AKT.\textsuperscript{326} Preclinical studies showed that inhibiting Src resulted in enhancing apoptosis caused by cytotoxic drugs, such as paclitaxel, carboplatin, and gemcitabine.\textsuperscript{327,328} Src has been found to be overexpressed in gynecological cancers and promote resistance against chemotherapy.\textsuperscript{328,329} Dasatinib and saracatinib are the most-studied highly selective Src inhibitors in gynecological cancers.\textsuperscript{330} In a phase II trial (NCT01196741), it was reported that saracatinib did not improve activity of weekly paclitaxel in platinum-resistant OC.\textsuperscript{331} Another phase II trial (NCT02059265) showed that dasatinib had minimal activity as a single agent in patients with recurrent OC.\textsuperscript{332} Even though no obvious activity has been seen as a single agent, Src inhibitors used in combination with other antitumor agents are promising.

**Notch.** Notch signaling is a primordial, evolutionarily conserved cell-fate determination pathway that has great relevance to multiple aspects of cancer biology, from cancer stem cell to tumor immunity.\textsuperscript{333,334} Previous studies have shown that the Notch pathway is associated with the epithelial–mesenchymal transition (EMT) processes in OC and CC.\textsuperscript{335–338} Currently, several classes of Notch inhibitors have been developed, mainly composed of gamma-secretase inhibitors (GSIs), siRNA, and monoclonal antibodies against Notch pathways.\textsuperscript{339} RO4929097 is a GSI, which had insufficient activity as a single agent in platinum-resistant OC in a phase II clinical trial (NCT01175343).\textsuperscript{339}

**Cell cycle checkpoints.** Wee1 is a kinase controlling G/M and S phase checkpoints via phosphorylation of the cyclin-dependent kinases. Ataxia-telangiectasia-mutated and Rad3 related kinase (ATR) plays an important role in the DNA damage response to replication stress, preventing the entry of cells with damaged DNA into mitosis (e.g., when the cancer cells are challenged by chemotherapy).\textsuperscript{340} These functions of Wee1 and ATR make them potential therapeutic targets. The activities of ATR inhibitors (e.g., AZD6738) and Wee1 inhibitors (e.g., AZD1775) have been investigated in early-phase trials in gynecological cancers.\textsuperscript{341} (Tables 9 and 14).

**Antibody–drug conjugates.** Antibody–drug conjugates (ADCs) are complex engineered molecules composed of a monoclonal antibody conjugated to payload (e.g., cytotoxic drugs) via stable linkers.\textsuperscript{342,343} By binding to the antigens on the tumor cell surface, the ADCs release the drug components intracellularly and lead to the death of tumor cell. This site-selective drug delivery can reduce toxicities for patients by limiting the exposure of normal tissues to the cytotoxic drugs.\textsuperscript{344} Mirvetuximab soravtansine is an ADC for treatment of folate receptor α (FRα)-expressing tumors, comprising a humanized FRα-binding monoclonal antibody, a cytotoxic maytansinoid effector molecule DM4, and a cleavable disulfide linker.\textsuperscript{345–347} The FRα mediates the endocytotic uptake of folate, which has a role in amino acid, DNA and RNA metabolism as well as in methylation reactions.\textsuperscript{348} FRα is overexpressed in several cancers, including ovarian, lung, renal, endometrial, colorectal and breast cancers.\textsuperscript{349–351} Thus, it is a promising target for ADC design. The FRα expression in tumor is a response-predictive biomarker for patient selection. Preclinical studies showed it to have potent antitumor activities in OC xenografts.\textsuperscript{350} Phase I trials of mirvetuximab soravtansine in OC were conducted\textsuperscript{347,351} in a population of patients with FRα-positive and platinum-resistant OC, mirvetuximab soravtansine showed an ORR of 26% and a median PFS of 4.8 months.\textsuperscript{352} However, the phase III FORWARD I trial (NCT02631876), comparing the safety and efficacy of mirvetuximab soravtansine to chemotherapy in platinum-resistant OC, was terminated because it did not meet prespecified primary endpoints. Another newly registered phase III trial (NCT04209855) is going to compare the efficacy chemotherapy in platinum-resistant OC with a high-level of FRα expression.

Tisotumub vedotin is a monoclonal auristatin E (MMAE) bearing ADC conjugated to an anti-tissue factor (TF) monoclonal antibody via a protease cleavable linker. TF is involved with tumor cell signaling and angiogenesis. Ongoing phase II/III trials GEN701/GEN702 (NCT02001623, NCT02552121), investigated tisotumub vedotin in solid tumor, including cervical, ovarian, endometrial, and other solid cancers. In the preliminary data released, 11/34 (32.4%) patients with CC achieved a response.\textsuperscript{353,354} Other ADCs continue to be investigated in a number of ongoing clinical trials (e.g., NCT03748186, NCT03835819, NCT01631552, NCT03657043, NCT03191628, NCT02988817, NCT02751918, NCT02606305, NCT02208375, NCT02996825).

**Programmed death protein-1 pathway blockade.** Another class of novel alternative therapy in cancer treatment is the immunotherapeutic approach, particularly the agent that inhibits the immune checkpoint. Programmed death protein-1 (PD-1) is an immune checkpoint molecule which is more commonly studied in immunotherapy researches of gynecological cancers. It plays an important role in T-cell coinhibition and exhaustion, and subsequently helps tumor cells evade immune surveillance.\textsuperscript{355} Thus, monoclonal antibodies were developed as a promising cancer therapy targeting at blocking the PD-1 pathway in tumor progression. Although immune checkpoint inhibitors do not target to kill tumor cells directly, they play an antitumor role by enhancing T-cell functions (Fig. 5). The expression of immunosuppressive PD-1 ligands (PD-L1 or PD-L2) on the surface of tumor cells is an important predictive biomarker of response to PD-1 blockade.\textsuperscript{356,357} It is also indicated that mismatch repair-deficient (dMMR) tumors, including dMMR EC, are sensitive to PD-1 blockade.\textsuperscript{358} Anti-PD-1 agents (pembrolizumab and nivolumab) and anti-PD-L1 agents (atezolizumab, avelumab, and durvalumab) were FDA-approved drugs for several kinds of advanced-stage cancers, such as melanoma, NSCLC and renal cell carcinoma.\textsuperscript{359–361} In 2017, pembrolizumab was approved by FDA for the treatment of patients with unresectable or metastatic solid tumors with a biomarker referred to as microsatellite instability-high (MSI-H) or dMMR.\textsuperscript{362} These biomarkers are most commonly found in colorectal, gastrointestinal, and endometrial cancers.\textsuperscript{362–364} Successfully, pembrolizumab was approved in certain condition of CC and EC (Table 1), basing on findings from two phase II trials.
(KEYNOTE 158 and KEYNOTE 146).\textsuperscript{365,366} The results of the completed phase I/II trials of anti-PD-1/PD-L1 agents for ovarian, cervical, and endometrial cancers are summarized in Table 10. And other ongoing phase II/III trials investigating anti-PD-1/PD-L1 therapy (not in addition to other targeted agents) in gynecological cancers are listed in Tables 11 and 12.

**Anti-PD-1 agents.** A phase Ib KEYNOTE-028 trial (NCT02054806) of pembrolizumab (10 mg/kg intravenously every 2 weeks) as a treatment of PD-L1–positive solid tumors showed that pembrolizumab was associated with a 17% ORR in CC cohort, a 13% ORR in EC cohort, and a 11.5% ORR in OC cohort, respectively.\textsuperscript{367}–\textsuperscript{369} In KEYNOTE 158 trial (NCT02628067), pembrolizumab was investigated in a single cohort of recurrent or metastatic CC, resulting in an ORR of 12.2%. In the population of patients with PD-L1–positive tumors, the ORR was 14.6%. No response was observed in patients with PD-L1–negative tumors. The median OS was 9.4 months in the total population and 11 months in the PD-L1–positive tumor population.\textsuperscript{365} On the ground of this trial, the FDA-approved pembrolizumab for patients with recurrent or metastatic CC with disease progression on or after chemotherapy whose tumors expressed PD-L1, in 2018. As for EC, a phase II study evaluated the clinical efficacy of pembrolizumab in nine patients with recurrent or persistent EC with dMMR, and the results indicated that the ORR was 56%, the 12-month OS rate was 89%, and the median OS had not been reached.\textsuperscript{370} For EC patients without MSI or PD-L1 expression status, another phase II KEYNOTE 146 trial (NCT02501096) assessed the activity and safety of lenvatinib plus pembrolizumab in patients with biomarker-unselected advanced EC.\textsuperscript{371} Lenvatinib is an oral multikinase inhibitor targeting VEGFR, FGFR, PDGFR, RET, and KIT.\textsuperscript{372} An interim report of KEYNOTE 146 showed this combination of PD-1 blockade and inhibition of angiogenesis (as well as VEGF–mediated immune suppression) was associated with antitumor activity with an ORR of 35.6%.\textsuperscript{366} In September 2019, the FDA granted accelerated approval to the combination of pembrolizumab and lenvatinib for the treatment of patients with advanced EC without MSI-H or dMMR and who have disease progression following prior systemic therapy, but were not candidates for curative surgery or radiation. For patient with recurrent OC, single-agent pembrolizumab showed modest activity in a phase II trial (NCT02674061) with an ORR of 7.4–9.9%.\textsuperscript{373} A phase I/II trial (NCT02657889) demonstrated that niraparib combined with pembrolizumab was tolerable and had promising antitumor activity for platinum-resistant current OC with an ORR of 18% and a disease control rate of 65%.\textsuperscript{143} Furthermore, a recent study identified two determinants of response to the combination of pembrolizumab and niraparib: the presence of mutational signature 3 as a surrogate of HRD and a positive immune score as a surrogate of interferon-primed, CD8–exhausted effector T cells in the tumor microenvironment. Presence of one or both tumor features was associated with significantly prolonged PFS while absence of both was associated with no response.\textsuperscript{374}

Nivolumab is another well-known anti-PD-1 drug. As indicated by a phase I/II trial (NCT02488759), nivolumab had a promising activity in metastatic CC with an ORR of 26%.\textsuperscript{375} However, another phase II trial (NCT02257528) demonstrated that single-agent nivolumab exhibited low antitumor activity in recurrent CC with an ORR of 4% and a SD of 36%.\textsuperscript{376} In patients with platinum-resistant recurrent OC, early-phase trials showed that monotherapy of anti-PD-1 agents had promising activity.\textsuperscript{377,378}

Dostarlimab (TSR-042) is an investigational humanized anti-PD-1 monoclonal antibody. It demonstrated robust clinical activity in patients with previously treated recurrent or advanced EC in both MSI-H and MSS subgroups. It is being evaluated in combination of bevacizumab and niraparib in patients with platinum-resistant OC (NCT03574779).

**Anti-PD-L1 agents.** In a phase la trial (NCT01375842) assessing atezolizumab (10 mg/kg intravenously every 3 weeks) in advanced/recurrent EC, the ORR was 13.3% (2/15) in all populations. Both these two patients were in population with PD-L1 status >5% of tumor-infiltrating immune cells (2/5). Moreover, a trend for higher PFS and OS was noticed with higher PD-L1 expression.\textsuperscript{379} A phase II trial (NCT02912572) of avelumab (10 mg/kg intravenously every 2 weeks) in patients with microsatellite stable (MSS), microsatellite instable (MSI), and POLE-mutated recurrent/persistent EC demonstrated an ORR of 6.25% in the MSS cohort and an ORR of 27.6% in the MSI/POLE cohort.\textsuperscript{380} As demonstrated in these clinical outcomes, PD-L1 status, dMMR, MSI, and POLE mutation were predictive biomarkers to identify the EC population who could benefit from PD-1 blockade. However, in patients with recurrent OC, a single-agent trial of anti-PD-L1 agents demonstrated only modest efficacy.\textsuperscript{381}

Fig. 5 The immune checkpoint blockades. Antigen presenting cells (APC) take up antigen (Ag) released from tumor cells and present it to T cells. PD-1 receptors inhibit immune responses by engagement of PD-L1 and PD-L2. Therefore, monoclonal antibody blocking the PD-1 pathway results in enhancing antitumor immunity.
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Several clinical trials are further conducted to combine chemotherapy or other targeted therapies with anti-PD-1/PD-L1 agents in treatment of gynecological cancers. A phase II trials showed that the combination of durvalumab (10 mg/kg intravenously every 2 weeks) and doxorubicin was associated with an ORR of 15% in platinum-resistant recurrent OC. A great number of agents in treatment of gynecological cancers. A phase II trials are unsatisfying, anti-PD-1/PD-L1 drugs (either used as monotherapy or used in combination with chemotherapy, other immune checkpoint inhibitors, cancer vaccines or other targeted therapies) are still expected to be promising approaches, especially in the treatment of CC and EC.382–384

**Table 10. Completed phase I/II trials of anti-PD-1/PD-L1 in gynecological cancers**

| ID          | Cancer/condition      | Phase | No. | Intervention                          | ORR (%) | mPFS (mon.) | mOS (mon.) | SAEs (%) | Refs |
|-------------|-----------------------|-------|-----|---------------------------------------|---------|-------------|------------|----------|------|
| NCT02573962 | OC/platinum-resistant recurrent | II    | 20  | Nivolumab                             | 15      | 3.5         | 20         | 40       | 378  |
| NCT00279664 | OC/recurrent          | II    | 38  | Nivolumab + bevacizumab               | 21      | 9.4         | –          | –        | 377  |
| NCT02488759 | OC/advanced           | I     | 17  | Nivolumab                             | 5.9     | –           | –          | 5        | 435  |
| NCT02537444 | OC/advanced           | I/II  | 19  | Nivolumab                             | 26      | 21.9        | –          | –        | 375  |
| NCT02257528 | CC/persistent or recurrent | II    | 26  | Nivolumab                             | 4       | –           | –          | 24       | 376  |
| NCT02674062 | OC/advanced or recurrent | II    | 376 | Pembrolizumab                         | 7.4–9.9 | 2.1         | 17.6       | 19.7     | 373  |
| NCT02657889 | OC/recurrent          | I/II  | 62  | Pembrolizumab + niraparib             | 18      | Not reached | –          | –        | 143  |
| NCT02501096 | EC/advanced           | II    | 99  | Pembrolizumab                         | 12.2    | 2.1         | 9          | 12.2     | 365  |
| NCT02054806 | CC/advanced           | II    | 9   | Pembrolizumab                         | 56      | –           | Not reached | 0       | 370  |
| NCT0250146  | EC/advanced           | II    | 54  | Pembrolizumab + lenvatinib            | 39.6    | 7.4         | –          | 30       | 366  |
| NCT02054806 | CC/advanced, PD-L1(+) | lb    | 24  | Pembrolizumab                         | 13      | –           | –          | 16.7     | 367  |
| NCT02054806 | CC/advanced, PD-L1(+) | lb    | 26  | Pembrolizumab                         | 11.5    | 1.9         | 13.8       | 3.8      | 368  |
| NCT02431559 | CC/advanced, PD-L1(+) | lb    | 24  | Pembrolizumab                         | 17      | –           | –          | 21       | 369  |
| NCT02573962 | OC/platinum-resistant recurrent | II    | 40  | Durvalumab + PLD                      | 15      | 5.5         | –          | 57.5     | *    |
| NCT01772004 | Solid Tumor           | Ec/lb | 124 | Avelumab                              | 9.7     | 2.7         | 10.8       | 6.5      | 381  |
| NCT02912572 | EC/MSS                | II    | 33  | Avelumab                              | 27.6    | –           | –          | 19       | 380  |
| NCT01375842 | EC/advanced or recurrent | la   | 15  | Atezolizumab                          | 13.3    | 1.7         | 9.6        | 13.3     | 379  |
| NCT01375842 | OC/advanced           | I     | 12  | Atezolizumab                          | 22.2    | 2.9         | 11.3       | 25.0     | 436  |
| NCT01375842 | OC/advanced           | I     | 15  | Pembrolizumab + lenvatinib            | 13.3    | 1.4         | 9.6        | 43.3     | 437  |

*Unpublished date found in clinicaltrials.gov

**Note:** dMMR mismatch repair-deficient, MSS microsatellite stable, MSI microsatellite unstable, POLE polymerase-ε. 

In EC, type I (endometrioid histologies), the most common type, is associated with an excess estrogen exposure in the absence of counteractive effects of progesterone, mostly with expressing estrogen and/or progesterone receptors (ER/PR).385–387 Hormonal therapy is an alternative treatment to control metastatic or recurrent disease.388,389 In addition to the conventional progestin therapy, inhibition of estrogen-induced proliferation by anti-estrogen agents has been evaluated in EC, including selective estrogen receptor modulators (SERMs) or downregulators (SERDs) and aromatase inhibitors.390,391

Selective estrogen receptor downregulators. In EC, type I (endometrioid histologies), the most common type, is associated with an excess estrogen exposure in the absence of counteractive effects of progesterone, mostly with expressing estrogen and/or progesterone receptors (ER/PR).385–387 Hormonal therapy is an alternative treatment to control metastatic or recurrent disease.388,389 In addition to the conventional progestin therapy, inhibition of estrogen-induced proliferation by anti-estrogen agents has been evaluated in EC, including selective estrogen receptor modulators (SERMs) or downregulators (SERDs) and aromatase inhibitors.390,391

Fulvestrant, the main SERD, has an anti-proliferative effect through down regulation of ER and plays an antitumor role as both hormonal therapy and targeted therapy. Fulvestrant was approved by FDA for the treatment of postmenopausal metastatic ER/PR-positive breast cancer, not yet for gynecological cancers.392–394 A phase II trial (NCT00334295) evaluated the activity and toxicity of fulvestrant, in patients with advanced or recurrent ER/PR-positive EC.394 It demonstrated an ORR of 11.4% in the ITT group, with a median PFS of 2.3 months and a median OS of 13.2 months. However, another phase II trial showed minimal activity of
| ID          | Cancer/condition          | No. | Start date | Intervention                  | Design                  | Status                |
|-------------|---------------------------|-----|------------|-------------------------------|-------------------------|-----------------------|
| NCT02725489 | Women's cancers           | 13  | 2016.6     | Durvalumab                    | Non-randomized parallel | Not yet recruiting    |
| NCT02811497 | OC/platinum-resistant     | 60  | 2016.9     | Durvalumab + azacitidine      | Single group            | Recruiting            |
| NCT03899610 | advanced                 | 24  | 2019.7     | Durvalumab + tremelimumab + chemotherapy | Single group            | Recruiting            |
| NCT03357757 | Virus associated cancer   | 39  | 2018.2     | Avelumab + valproic acid      | Single group            | Recruiting            |
| NCT03503786 | EC/advanced or recurrent  | 120 | 2018.4     | Avelumab + PC vs. avelumab    | Randomized parallel     | Not yet recruiting    |
| NCT02440425 | OC/platinum-resistant     | 43  | 2015.8     | Pembrolizumab + paclitaxel   | Single group            | Active, not recruiting|
| NCT02635360 | CC/advanced               | 88  | 2016.1     | Pembrolizumab maintenance/throughout, plus chemoradiation | Randomized parallel     | Recruiting            |
| NCT02608684 | OC/platinum-resistant     | 21  | 2016.2     | Pembrolizumab + standard treatment | Single group            | Active, not recruiting|
| NCT02530154 | OC/stage II-IV            | 30  | 2016.7     | Pembrolizumab + PC           | Single group            | Recruiting            |
| NCT02899793 | EC/recurrent or metastatic| 25  | 2016.9     | Pembrolizumab                 | Single group            | Recruiting            |
| NCT02865811 | OC/platinum-resistant     | 26  | 2016.9     | Pembrolizumab + doxorubicin   | Single group            | Active, not recruiting|
| NCT02901899 | OC/recurrent              | 38  | 2016.11    | Pembrolizumab + gemcitabine   | Single group            | Recruiting            |
| NCT02900560 | OC/platinum-resistant     | 34  | 2016.12    | Pembrolizumab + azacytidine vs. pembrolizumab | Non-randomized parallel | Active, not recruiting|
| NCT02834975 | OC/advanced               | 40  | 2016.12    | Pembrolizumab + PC           | Single group            | Recruiting            |
| NCT0319209 | CC or EC                 | 43  | 2017.7     | Pembrolizumab                 | Single group            | Recruiting            |
| NCT02549209 | EC/recurrent              | 46  | 2017.8     | Pembrolizumab + PC           | Single group            | Recruiting            |
| NCT03126812 | OC/stage IV               | 15  | 2017.11    | Pembrolizumab as neoadjuvant  | Single group            | Recruiting            |
| NCT03275506 | OC/stage IV               | 45  | 2018.2     | Pembrolizumab + chemotherapy vs. chemotherapy | Non-randomized parallel | Recruiting            |
| NCT03029403 | OC/advanced               | 42  | 2018.2     | Pembrolizumab + DPX-Survivac (vaccine) + cyclophosphamide | Non-randomized parallel | Recruiting            |
| NCT03410784 | OC/advanced               | 72  | 2018.4     | Pembrolizumab + PC           | Single group            | Not yet recruiting    |
| NCT03276013 | TOPIC                     | 51  | 2018.5     | Pembrolizumab + doxorubicin   | Single group            | Recruiting            |
| NCT03539328 | OC/platinum-resistant     | 138 | 2018.6     | Pembrolizumab + chemotherapy vs. chemotherapy | Randomized parallel     | Not yet recruiting    |
| NCT03732950 | OC/recurrent              | 30  | 2019.3     | Pembrolizumab                 | Single group            | Recruiting            |
| NCT03430700 | PROMPT                    | 28  | 2019.5     | Pembrolizumab + paclitaxel   | Single group            | Recruiting            |
| NCT04375956 | OC/platinum-resistant     | 100 | 2020.5     | Pembrolizumab                 | Single group            | Not yet recruiting    |
| NCT04238988 | CC/locally advanced       | 45  | 2020.3     | Pembrolizumab + PC           | Single group            | Not yet recruiting    |
| NCT03340376 | CC/recurrent              | 48  | 2017.8     | Atezolizumab vs. atezolizumab + doxorubicin vs. doxorubicin | Randomized parallel     | Recruiting            |
| NCT03612791 | CC/advanced               | 190 | 2018.6     | Atezolizumab + radiotherapy vs. radiotherapy | Randomized parallel     | Recruiting            |
| NCT03614949 | CC/recurrent, persistent, | 26  | 2019.1     | Atezolizumab                 | Single group            | Recruiting            |
| NCT02498600 | or metastatic             |     |            |                               |                         |                       |
| NCT03241745 | EC/metastatic or recurrent| 40  | 2017.8     | Nivolumab                     | Single group            | Recruiting            |
| NCT03808857 | CC/recurrent or metastatic| 80  | 2019.2     | GB226                         | Single group            | Recruiting            |
| NCT03972722 | CC/recurrent or metastatic| 89  | 2019.5     | GLS-010                       | Single group            | Recruiting            |
| NCT04188860 | CC/recurrent              | 34  | 2019.12    | Camrelizumab + paclitaxel     | Single group            | Recruiting            |
| NCT04368273 | CC/advanced               | 30  | 2020.5     | Toripalimab                   | Single group            | Not yet recruiting    |
| NCT03104699 | CC/advanced               | 211 | 2017.4     | Balstilimab                   | Single group            | Active, not recruiting|
Table 12. Ongoing phase III trials of anti-PD-1/PD-L1 in gynecological cancers (not including novel combination therapy)

| ID             | Cancer/condition                  | No. | Start date | Intervention                          | Status          |
|----------------|-----------------------------------|-----|------------|---------------------------------------|-----------------|
| NCT02580058 JAVELIN Ovarian 200 | OC/platinum-resistant, or refractory recurrent | 566 | 2015.12 | Avelumab + PLD vs. avelumab vs. PLD | Active, not recruiting |
| NCT02891824 ATALANTE      | OC/platinum-sensitive recurrent | 405 | 2016.9 | Atezolizumab vs. placebo, plus PC + bevacizumab | Recruiting |
| NCT03038100 iMagyn050        | OC/stage III–IV                  | 1300 | 2017.3 | Atezolizumab vs. placebo, plus PC + bevacizumab | Active, not recruiting |
| NCT03353831                | OC/platinum-resistant recurrent | 664 | 2018.9 | Atezolizumab vs. placebo, plus Paclitaxel or PLD | Recruiting |
| NCT03556839                | CC/stage IV                      | 404  | 2018.9 | Atezolizumab vs. placebo, plus PC + bevacizumab | Recruiting |
| NCT03603184  AtTeNd         | EC/advanced                      | 550  | 2018.10 | Atezolizumab vs. placebo, plus PC | Recruiting |
| NCT03635567 KEYNOTE-826     | CC/persistent, recurrent, or metastatic | 600  | 2018.10 | Pembrolizumab vs. placebo, plus PC + bevacizumab | Recruiting |
| NCT03914612                | EC/advanced or recurrent         | 810  | 2019.7 | Pembrolizumab vs. placebo, plus PC | Recruiting |
| NCT04221945                | CC/locally advanced              | 980  | 2020.4 | Pembrolizumab vs. placebo, plus chemoiradiation | Recruiting |
| NCT03830866 CALLA          | CC/locally advanced              | 714  | 2019.2 | Durvalumab vs. placebo, plus chemoiradiation | Recruiting |
| NCT03981796 RUBY           | EC/recurrent or stage III–IV     | 470  | 2019.7 | Dostarlimab vs. placebo, plus PC | Recruiting |
| NCT03912415 FERMATA        | CC/advanced                      | 316  | 2019.9 | Prolgolimab vs. placebo, plus PC + bevacizumab | Not yet recruiting |

Table 13. Ongoing phase III trials of novel combination targeted therapy in gynecological cancers

| ID             | Cancer/condition                  | No. | Start date | Target                      | Intervention                                | Status          |
|----------------|-----------------------------------|-----|------------|-----------------------------|---------------------------------------------|-----------------|
| NCT02502266 COCOS | OC/platinum-resistant or refractory recurrent, BRCAm | 680  | 2016.2 | VEGF, PARP                | Cederanib + olaparib vs. cederanib vs. chemotherapy | Recruiting |
| NCT02446600        | OC/platinum-sensitive recurrent   | 549  | 2016.2 | VEGF, PARP                | Cederanib + olaparib vs. olaparib vs. chemotherapy | Active, not recruiting |
| NCT03522246 ATHENA | OC/stage III–IV                 | 1012 | 2018.5 | PARP, PD-1                | Rucaparib + nivolumab vs. rucaparib + placebo vs. nivolumab + placebo vs. placebo | Recruiting |
| NCT03602859 ENGOT-OV44/FIRST | OC/stage III–IV             | 912  | 2018.10 | PARP, PD-1                | Dostarlimab + niraparib vs. niraparib + placebo vs. placebo | Recruiting |
| NCT03884101 ENGOT-en9 | EC/recurrent or stage III–IV   | 720  | 2019.4 | VEGF, PD-1                | Lenvatinib + pembrolizumab vs. chemotherapy | Recruiting |
| NCT0374015 KEYLYNK-001/ENGOT-ov43 | OC/fist-line treatment     | 1086 | 2018.12 | VEGF, PARP, PD-1          | Pembrolizumab + olaparib vs. pembrolizumab + placebo vs. placebo, plus PC + bevacizumab | Recruiting |
| NCT03737643 DUO-O     | OC/stage III–IV                 | 1056 | 2019.1 | VEGF, PARP, PD-1          | Durvalumab + olaparib vs. durvalumab + placebo vs. placebo, plus PC + bevacizumab | Recruiting |
| NCT03806049 NSGO/AVANOVA-Triplet | OC/platinum-sensitive recurrent | 337  | 2019.6 | VEGF, PARP, PD-1          | Niraparib + bevacizumab + dostarlimab vs. niraparib + bevacizumab vs. chemotherapy | Not yet recruiting |

fulvestrant in advanced, recurrent, or persistent EC. No patient demonstrated a complete or partial response in the 22 ER-negative patients, with a stable disease rate of 18% as the best response. The median PFS and OS were 2 and 3 months, respectively. In the 31 ER-positive patients, the ORR and stable disease rate were 16% and 29%, with a median PFS of 10 months and a median OS of 26 months, respectively. As for OC, fulvestrant was associated with a low ORR of 8% and a stable disease rate of 35% in ER-positive, multiply recurrent OC. The effect of anti-estrogenic agents in advanced or recurrent EC needs further investigations. Furthermore, combining hormonal therapy with targeted therapies is a novel strategy in treating certain gynecological cancers, which is being assessed in several ongoing clinical trials (e.g., NCT03643510, NCT03294694, NCT02730923, NCT02476955, and NCT02188550).

**CONCLUSION**

From the large amount of clinical trials on targeted agents and molecular drugs, we can see the great enthusiasm in targeted therapies. Consequently, it has led to significant breakthrough in personalized medicine of antitumor treatment strategy, including gynecological cancers. According to current clinical evidence, PARP inhibitors have made a remarkable progress in treatment of OC depending on the identification of disease with HRD (e.g., BRCAm). As for EC, given the identification of hormone-dependent histological type and POLE/MSI molecular subtypes, the activity of PI3K/AKT/mTOR, PD-1, and hormone receptor-targeted therapies might be promising in treatment of patients with EC. Since CC is mostly associated with persistent infection of virus, immune-targeted therapies (e.g., anti-PD-1/PD-L1 agents) are expected to be prospective treatment strategy. For the future research, as we
| ID           | Cancer/condition                  | No. | Started date | Targets                          | Drugs                                           | Design               | Status               |
|--------------|----------------------------------|-----|--------------|----------------------------------|------------------------------------------------|----------------------|----------------------|
| NCT02345265  | OC/recurrent                      | 70  | 2015.12      | VEGF, PARP                       | Cediranib + olaparib                            | Single group         | Active, not recruiting |
| NCT0250266   | OC/ platinum-resistant recurrent  | 680 | 2016.2       | VEGF, PARP                       | Cediranib + olaparib vs. cediranib vs. olaparib | Randomized parallel  | Recruiting           |
| NCT02889900  | OC/platinum-resistant recurrent   | 62  | 2017.1       | VEGF, PARP                       | Cediranib + olaparib                            | Single group         | Recruiting           |
| NCT03117933  | OCTOVA                            | 138 | 2017.3       | VEGF, PARP                       | Paclitaxel vs. cediranib + paclitaxel vs. cediranib + olaparib | Randomized parallel  | Active, not recruiting |
| NCT0331574   | BARCO                             | 100 | 2017.6       | VEGF, PARP                       | Paclitaxel vs. cediranib + olaparib            | Randomized parallel  | Recruiting           |
| NCT03326193  | OC/advanced                       | 105 | 2018.1       | VEGF, PARP                       | Niraparib + bevacizumab                        | Single group         | Active, not recruiting |
| NCT03462212  | MITO25                            | 234 | 2018.2       | VEGF, PARP                       | Rucaparib + bevacizumab + chemotherapy vs. rucaparib + chemotherapy vs. bevacizumab + chemotherapy | Randomized parallel  | Recruiting           |
| NCT03570437  | COPELIA                           | 129 | 2018.5       | VEGF, PARP                       | Paclitaxel vs. cediranib + paclitaxel vs. cediranib + olaparib | Randomized parallel  | Recruiting           |
| NCT03476798  | CC or EC/recurrent                | 70  | 2018.6       | VEGF, PARP                       | Rucaparib + bevacizumab                        | Single group         | Recruiting           |
| NCT03660826  | EC/recurrent, refractory, or      | 120 | 2018.9       | VEGF, PARP                       | Cediranib vs. olaparib vs. cediranib + olaparib | Randomized parallel  | Active, not recruiting |
| NCT02889900  | CONCERTO                          | 40  | 2019.1       | VEGF, PARP                       | Niraparib + brivanib                           | Single group         | Recruiting           |
| NCT02889900  | OC/platinum-sensitive recurrent   | 40  | 2020.5       | VEGF, PARP                       | Niraparib + anlotinib                         | Single group         | Recruiting           |
| NCT02921269  | CC/recurrent                      | 22  | 2017.3       | VEGF, PD-1                      | Atezolizumab + bevacizumab                     | Single group         | Not yet recruiting    |
| NCT03572478  | EC/metastatic or recurrent        | 60  | 2018.8       | VEGF, PD-1                      | Rucaparib vs. nivolumab vs. rucaparib + nivolumab | Randomized parallel  | Recruiting           |
| NCT03526432  | EC/advanced, recurrent or         | 55  | 2018.8       | VEGF, PD-1                      | Atezolizumab + bevacizumab                     | Single group         | Recruiting           |
| NCT03367871  | CC/recurrent, persistent, or      | 39  | 2018.12      | VEGF, PD-1                      | Pembrolizumab + bevacizumab                    | Single group         | Recruiting           |
| NCT03816553  | CC/recurrent, persistent, or      | 49  | 2019.1       | VEGF, PD-1                      | Camrelizumab + apatinib                       | Single group         | Recruiting           |
| NCT04068974  | OC/platinum-resistant recurrent   | 28  | 2019.8       | VEGF, PD-1                      | Camrelizumab + apatinib                       | Single group         | Not yet recruiting    |
| NCT04197219  | EC/recurrent                      | 26  | 2020.1       | VEGF, PD-1                      | Pembrolizumab + axitinib                      | Single group         | Not yet recruiting    |
| NCT03797326  | Advanced solid tumors            | 180 | 2019.2       | VEGF, PD-1                      | Pembrolizumab + lenvatinib                    | Single group         | Recruiting           |
| NCT04236362  | OC                               | 30  | 2020.1       | EGFR, PD-1                      | TQB2450 + anlotinib                           | Single group         | Not yet recruiting    |
| NCT02571725  | OC/recurrent, BRCAm               | 50  | 2016.2       | PARP, PD-1                      | Olaparib + tremelimumab                       | Single group         | Recruiting           |
| NCT02912572  | EC/recurrent                      | 70  | 2016.12      | PARP, PD-1                      | Talazoparib + avelumab                        | Non-randomized parallel | Recruiting       |
|              |                                  | 242 | 2017.10      | PARP, PD-1                      | Talazoparib + avelumab                        | Recruiting           |                     |
| ID               | Cancer/condition                        | No. | Started date | Targets | Drugs | Design | Status          |
|------------------|----------------------------------------|-----|--------------|---------|-------|--------|-----------------|
| NCT03330405      | Javelin Parp Medley OC/platinum-sensitive recurrent |     | 2018.8       | PARP, PD-1 | Rucaparib + nivolumab vs. nivolumab vs. rucaparib | Non-randomized parallel | Recruiting       |
| NCT03572478      | EC/ metastatic or recurrent             | 60  | 2019.1       | PARP, PD-1 | Niraparib/dostarlimab + niraparib vs. chemotherapy | Randomized parallel | Recruiting       |
| NCT03651206      | ROCSAN OC/recurrent                    | 196 | 2019.5       | PARP, PD-1 | Dostarlimab + niraparib | Single group | Recruiting       |
| NCT03824704      | EC/ metastatic or recurrent             | 139 | 2018.8       | PARP, PD-1 | Rucaparib + nivolumab | Single group | Recruiting       |
| NCT04068753      | STAR OC/recurrent                      | 150 | 2019.10      | PARP, PD-1 | Dostarlimab + niraparib | Single group | Active, not recruiting |
| NCT03951415      | DOMEC EC/recurrent                     | 55  | 2019.7       | PARP, PD-1 | Durvalumab + olaparib | Single group | Recruiting       |
| NCT03955471      | MOONSTONE OC/progressive or recurrent   | 68  | 2019.9       | PARP, PD-1 | Durvalimab + niraparib | Single group | Recruiting       |
| NCT03824704      | OC/HGSOC or endometroid                | 139 | 2019.5       | PARP, PD-1 | Rucaparib + nivolumab | Single group | Recruiting       |
| NCT04068753      | STAR OC/platinum-resistant recurrent   | 150 | 2019.10      | PARP, PD-1 | Dostarlimab + niraparib | Single group | Active, not recruiting |
| NCT03951415      | DOMEC EC/recurrent                     | 55  | 2019.7       | PARP, PD-1 | Durvalumab + olaparib | Single group | Recruiting       |
| NCT03955471      | MOONSTONE OC/progressive or recurrent   | 68  | 2019.9       | PARP, PD-1 | Durvalimab + niraparib | Single group | Recruiting       |
| NCT03824704      | OC/HGSOC or endometroid                | 139 | 2019.5       | PARP, PD-1 | Rucaparib + nivolumab | Single group | Recruiting       |
| NCT04068753      | STAR OC/platinum-resistant recurrent   | 150 | 2019.10      | PARP, PD-1 | Dostarlimab + niraparib | Single group | Active, not recruiting |
| NCT03951415      | DOMEC EC/recurrent                     | 55  | 2019.7       | PARP, PD-1 | Durvalumab + olaparib | Single group | Recruiting       |
| NCT03955471      | MOONSTONE OC/progressive or recurrent   | 68  | 2019.9       | PARP, PD-1 | Durvalimab + niraparib | Single group | Recruiting       |
| ID          | Cancer/condition | No. Started date | Target(s) | Drugs                                      | Design                           | Status       | Acknowledgements |
|------------|------------------|------------------|------------|--------------------------------------------|----------------------------------|--------------|------------------|
| NCT03355976 | OC/advanced, recurrent, or metastatic | 62 2018.4 | PD-1, CTLA-4 | Nivolumab + ipilimumab vs. nivolumab        | Randomized parallel Recruiting   | Recruiting   |                  |
| NCT03894215 | CC/recurrent      | 200 2019.3       | PD-1, CTLA-4 | Balstilimab AGEN 1884                       | Randomized parallel Recruiting   | Recruiting   |                  |
| NCT02734004 | TRU-D OC/stage III IV | 24 2019.7       | PD-1, CTLA-4 | Durvalumab + tremelimumab                  | Single group Recruiting          | Recruiting   |                  |
| NCT03439085 | CC/recurrent or metastatic | 77 2018.11      | PD-1, HPV vaccine | Durvalumab + MEDI0457                        | Single group Recruiting          | Recruiting   |                  |
| NCT04096911 | CC               | 20 2019.7       | PD-1, HPV vaccine | Sintilimab + quadrivalent HPV vaccine        | Single group Recruiting          | Recruiting   |                  |
| NCT03835819 | EC/advanced or recurrent | 35 2019.9      | PD-1, ADC | Pembrolizumab + mirvetuximab soravtansine  | Single group Recruiting          | Recruiting   |                  |
| NCT03113487 | OC/recurrent     | 28 2018.2       | PD-1, p53   | Pembrolizumab + pS3MA W                   | Single group Recruiting          | Recruiting   |                  |

### ACKNOWLEDGEMENTS

This study was supported by National Major Scientific and Technological Project for "Significant New Drugs Development" in China (2018ZX09733001).

### AUTHOR CONTRIBUTIONS

X.Z. substantially contributed to the conception and design of the work. Q.W. and H.L. P. did the literature research and data retrieval. Q.W. drafted the article and revised it. X.R.Q. and M.W. reviewed the draft. All authors approved the submitted version.

### ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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