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REVIEW

Immune checkpoint blockades in gynecological cancers: A review of clinical trials

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Abstract

Advanced and recurrent gynecological cancers are associated with a poor prognosis and there is still a lack of effective treatments. Immune checkpoint blockade (ICB) therapy is an important element of cancer-targeted therapy and immunotherapy. The programed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathways are the two main targets of ICB. In this study, we provide a comprehensive review of clinical evidence concerning ICB therapy in gynecological cancers and discuss future implications. All clinical trials of ICB therapy in gynecological cancers were reviewed. We searched ClinicalTrials.gov to collect data from completed and ongoing clinical trials. The clinical evidence regarding the efficacy of ICB agents in gynecological cancers were discussed. Six phase III clinical trials have reported their results of primary outcomes, and a total of 25 phase II clinical trials have been completed. As revealed in phase III trials, pembrolizumab (a PD-1 antibody) improved the overall survival and progression-free survival in endometrial cancer patients with mismatch repair deficiency and cervical cancer patients with expressions of PD-L1. Based on these findings, pembrolizumab was approved by the Food and Drug Administration and European Medicines Agency as a cancer medication used to treat certain patients with endometrial cancer or cervical cancer. Other PD-1 antibodies, including dostarlimab and cemiplimab, also showed antitumor efficacy in clinical trials. Dostarlimab treatment showed an encouraging response rate in endometrial cancer patients with mismatch repair deficiency. Cemiplimab treatment led to a longer overall survival and a lower risk of death than chemotherapy among patients with recurrent cervical cancer. Three completed phase III trials investigated anti-PD-L1 agents (atezolizumab and avelumab) in the treatment of ovarian cancer. The results were not encouraging. Other strategies of ICB therapy which had showed potential clinical benefit in the treatment of gynecological cancers in early-phase trials need to be further evaluated in late-stage trials. The antitumor efficacy of ICB therapy is

Abbreviations: CPS, combined positive score; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; dMMR, deficient mismatch repair; FDA, Food and Drug Administration; HPV, human papillomavirus; ICB, immune checkpoint blockade; MMR, mismatch repair; MSI-H, microsatellite instability hypermutated; ORR, objective response rate; OS, overall survival; PARPi, poly adenosine diphosphate-ribose polymerase inhibitor; PD-1, programed death protein 1; PD-L1, programed death protein ligand 1; PFS, progression-free survival; POLE, polymerase epsilon.

promising, and the key to making further progress in the treatment of gynecological cancers is to identify more biomarkers and explore innovative combination treatments with other targeted therapies.

KEYWORDS
cervical cancer, clinical trials, endometrial cancer, immune checkpoint blockades, ovarian cancer

1 | INTRODUCTION

In the discipline of gynecological oncology, endometrial cancer, cervical cancer and ovarian cancer are the three main malignant diseases, widely affecting the health of women around the world. Despite advances in conventional treatments (eg curative surgery, chemotherapy and radiotherapy), the prognosis is still very poor in patients with advanced-stage or recurrent gynecological cancers. Nevertheless, the use of targeted therapies has provided new therapeutic opportunities for these patients.

The immune checkpoint blockade (ICB) is an important class of targeted therapy and immunotherapy. Immune checkpoint molecules are inhibitory receptors that are expressed on the membranes of immune cells. The expression of immune checkpoint receptors works on the negative regulation of immune response, which is an essential mechanism to maintain self-tolerance and prevent autoimmunity under physiological conditions. However, in the tumor microenvironment, the expression of immune checkpoint receptors is dysregulated to evade antitumor immune response.[1] The immunotherapeutic mechanism of ICB as a promising cancer therapy is demonstrated in Figure 1.

ICBs are agents (mainly antibodies) that target and block immune checkpoint molecules. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody is the first of this class of immunotherapeutics to be approved for clinical use in the treatment of melanoma.[2] CTLA-4 is an inhibitory receptor expressed on T cells that counteracts the activity of CD28, which is a co-stimulatory receptor of T cells. Thus, the expression of CTLA-4 inhibits the activation of T cells.[3] Conversely, the blockade of CTLA-4 enhances the activation of T cells, as well as the immune response.[4] Programed cell death protein 1 (PD-1) is another immune checkpoint receptor expressed on T cells. There are two main ligands for PD-1: PD-1 ligand 1 (PD-L1) and PD-L2, both of which are members of the B7 family.[5] In several different human tumors, PD-1 is expressed on tumor-infiltrating lymphocytes, and the PD-1 ligands are upregulated on the tumor cell surface.[6] The PD-1 pathway plays an important role in immune resistance within the tumor microenvironment, thus the blockade of the PD-1 pathway may enhance antitumor response.[7]

Numerous clinical trials have investigated the antitumor efficacy of ICBs in gynecological cancers. Based on existing clinical evidence, several ICB drugs have been approved as cancer medications to treat patients with certain forms of gynecological cancer. This review summarizes important clinical evidence concerning ICBs in the treatment of gynecological cancers and discusses the future development of ICB therapy.

Key message

This review provides a comprehensive clinical evidence concerning immune checkpoint blockades in the treatment of gynecological cancers and discusses future implications.

A literature search was performed on PubMed, including articles and reviews of clinical trials. We also searched ClinicalTrials.gov to collect data regarding all completed and ongoing clinical trials. The websites of the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) were queried for information concerning each approved drug. Search terms included "gynecological cancers", "endometrial cancer", "cervical cancer", "ovarian cancer", "immune checkpoint blockade", "PD-1", "PD-L1", "PD-L2", "CTLA-4", and each name of the ICB agents (eg "pembrolizumab", "nivolumab", and "ipilimumab"). We also visited the websites of the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) to extract preliminary results from ongoing trials. All of the searches were performed up to February 28, 2022. All studies identified by the search strategy were assessed separately by two authors. The qualities of randomized controlled trials (RCTs) were evaluated using the Jadad scale.

Table 1 provides a summary of currently approved ICBs in the treatment of gynecological cancers. Six phase III clinical trials have reported primary outcomes (Table 2); a total of 25 phase II trials have been completed (Table 3). All phase III studies involved were RCTs with high quality. According to ClinicalTrials.gov, there are a further 19 ongoing phase III trials (Table 4) and dozens of ongoing phase II trials. The study design and status of the ongoing phase II trials are listed in the Tables S1 and S2.

2 | ENDOMETRIAL CANCER

Endometrial cancer is categorized into four separate molecular subtypes according to The Cancer Genome Atlas (TCGA), as follows: polymerase epsilon (POLE) ultra-mutated, microsatellite instability hypermutated (MSI-H), copy-number low and copy-number high, each with a distinct prognosis.[8] MSI-H is a phenotype of the

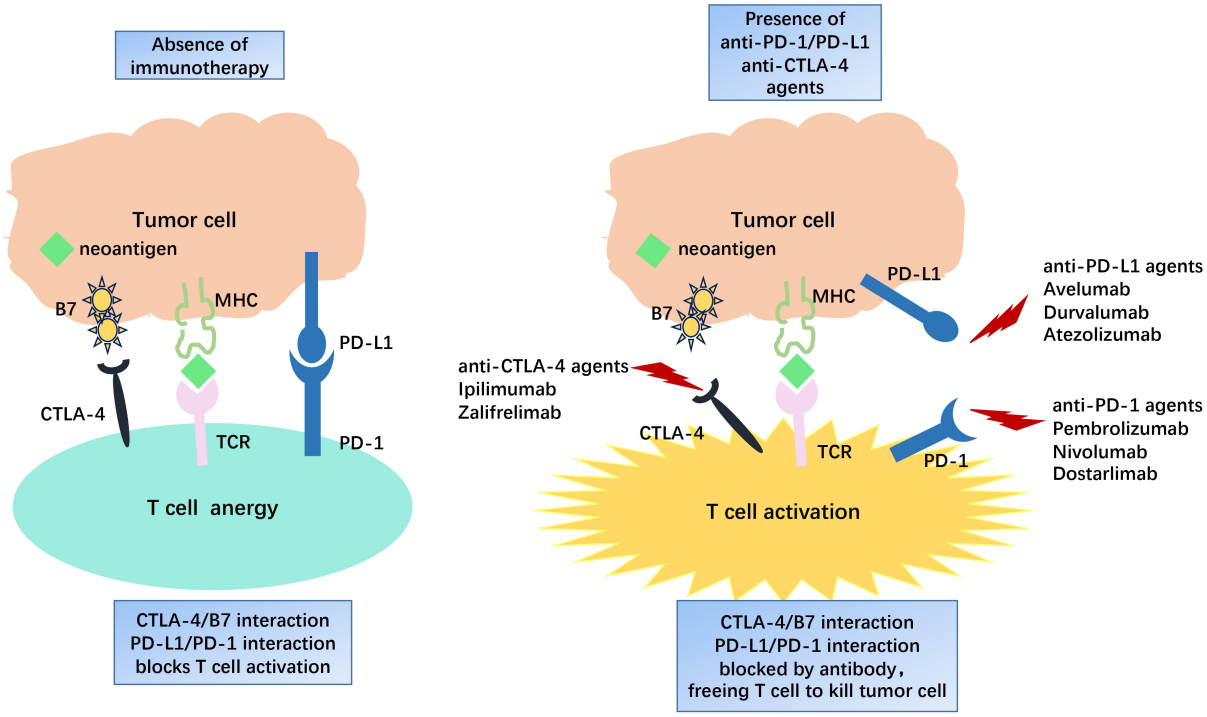

FIGURE 1 The mechanism of immune checkpoint blockade therapy.

deficient mismatch repair (dMMR) pathway, which accelerates the accumulation of DNA mutations. ICB therapy has shown particular efficacy in solid tumors with MSI-H, dMMR and/or high concentrations of tumor-infiltrating lymphocytes.

Pembrolizumab is a humanized monoclonal IgG4 antibody and is a well-known PD-1 inhibitor.[9] In May 2017, the FDA granted accelerated approval of pembrolizumab for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors. The recommended dose is 200 mg intravenously every 3 weeks or 400 mg every 6 weeks. This approval was based on the findings of five clinical trials (KEYNOTE-016, KEYNOTE-164, KEYNOTE-012, KEYNOTE-028 and KEYNOTE-158), which included endometrial cancer patients with MSI-H and/or dMMR.[10] This was the first time that the FDA had approved a cancer treatment based on a common biomarker rather than the origin of the tumor. For patients with advanced endometrial cancer that is not of the MSI-H or dMMR type, the FDA granted accelerated approval of pembrolizumab combined with lenvatinib, a multikinase inhibitor, in September 2019, based on the findings from a phase II study (KEYNOTE-146).[11] The goal of a phase III study (KEYNOTE-775) was to verify the clinical benefits of this accelerated approval. The results of KEYNOTE-775 demonstrated that endometrial cancer patients receiving pembrolizumab plus lenvatinib after chemotherapy exhibited 2.8 months longer progression-free survival (PFS), 5.4 months longer overall survival (OS) and 15% higher objective response rate (ORR; the proportion of patients who had a partial or complete response to therapy) than those receiving chemotherapy alone ($p < 0.001$).[12] Based on these results, the FDA granted full approval to pembrolizumab plus lenvatinib for cases of advanced endometrial cancer in July 2021. Two other phase II trials evaluated the antitumor activity of pembrolizumab in endometrial cancer patients and provided updated results. The first study investigated pembrolizumab as a monotherapy in recurrent cases with dMMR and/or MSI-H. The median follow-up time was 25.8 months with an ORR of 58%. Notably, in patients with Lynch-like syndrome (LLS), the ORR was 100%.[13] The other study explored the addition of pembrolizumab to chemotherapy for advanced or recurrent disease. Results indicated an ORR of 77.8%, with a median PFS of 10.55 months.[14] In addition, three ongoing phase III clinical trials are evaluating the role of pembrolizumab in the treatment of endometrial cancer. Two studies aim to compare the efficacy of pembrolizumab plus lenvatinib in patients with advanced or recurrent endometrial cancer. It is hypothesized that the combination of pembrolizumab and lenvatinib is superior to chemotherapy alone. The other study (Keynote-B21) is investigating the effect of pembrolizumab plus chemotherapy in newly diagnosed endometrial cancer after curative surgery.

Dostarlimab (TSR-042) is another PD-1 monoclonal IgG4 antibody. In April 2021, the FDA granted accelerated approval to dostarlimab for adult patients with recurrent or advanced dMMR endometrial cancer. This approval was based on results from cohort A1 in the GARNET trial, which included 71 patients with dMMR whose cancer had progressed during or after platinum-containing chemotherapy. The confirmed ORR was 42.3%, the complete response rate was 12.7%, and the partial response rate was 29.6%.[15] An ongoing phase III trial (RUBY) is assessing the efficacy of adding dostarlimab to chemotherapy in patients with advanced or recurrent endometrial cancer. This study is expected to report long-term data in 2026.

TABLE 1 Approval anti-PD-1 targeted drugs for gynecological cancers

Target	Drug	Approval year	Approval	Indication		Administration
Anti-PD-1	**Pembrolizumab (Keytruda, Merck)**	**2015**	**EMA**	**EC**	**Endometrial carcinoma**	**200 mg IV every 3 weeks or 400 mg every 6 weeks**
Anti-PD-1	Pembrolizumab (Keytruda, Merck)	2017	FDA	EC	Unresectable or metastatic EC, with a biomarker as MSI-H or dMMR	200 mg IV every 3 weeks or 400 mg every 6 weeks
Anti-PD-1 + VEGFi	Pembrolizumab (Keytruda, Merck) + lenvatinib (Lenvima, Eisai)	2021	FDA/EMA	EC	Advanced EC cases who have disease progression following prior systemic therapy but who are not candidates for curative surgery or radiation	Lenvatinib 20 mg orally once daily with pembrolizumab 200 mg IV every 3 weeks
Anti-PD-1	Pembrolizumab (Keytruda, Merck)	2021	FDA	CC	Persistent, recurrent or metastatic CC cases whose tumors express PD-L1 (CPS≥1)	200 mg IV every 3 weeks or 400 mg every 6 weeks
Anti-PD-1	Dostarlimab (Jemperli, Glaxo Smith Kline)	2021[a]	FDA/EMA	EC	Recurrent or advanced EC, with a biomarker as dMMR	500 mg IV, 4 doses every 3 weeks followed by 1000 mg IV every 6 weeks

Abbreviations: CC, cervical cancer; CPS, combined positive score; dMMR, deficient mismatch repair; EC, endometrial cancer; EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous infusion; MSI-H, microsatellite instability high; PD-1, programed death protein 1; VEGFi, vascular endothelial growth factor inhibitor.

[a]Accelerated approval.

Atezolizumab is a PD-L1 blocking IgG1 antibody that is used in the treatment of urothelial carcinoma, non-small cell lung cancer and triple-negative breast cancer. For endometrial cancer, atezolizumab monotherapy in recurrent disease had an ORR of 13% in a phase Ia study, demonstrating durable clinical benefits.[16] Furthermore, an ongoing phase III trial (AtTEnd/ENGOT-en7) is currently recruiting women to assess atezolizumab combined with chemotherapy in the treatment of advanced or recurrent endometrial cancer.

Besides atezolizumab, avelumab is another PD-L1 blocking IgG1 antibody that is used to treat certain types of cancers such as urothelial carcinoma and renal cell carcinoma. For endometrial cancer, a phase II trial for avelumab showed an ORR of 6.25% in patients with microsatellite stable disease and an ORR of 26.7% in patients with MSI or POLE mutated disease.[17] Microsatellite and POLE status appeared to be correlated with avelumab response, even in PD-L1-negative patients. An ongoing phase II trial (MITO END-3) aims to evaluate the activity of avelumab in combination with chemotherapy in patients with advanced or recurrent endometrial cancer. Another phase II trial exploring the efficacy of avelumab combined with talazoparib (a poly [ADP-ribose] polymerase inhibitor, PARPi) in recurrent endometrial cancer is currently recruiting patients.

Ipilimumab is a CTLA-4 blocking IgG1 antibody used for the treatment of melanoma and renal cell carcinoma. CTLA-4 and PD-1 are two different pathways that regulate the activation of T cells. A combined blockade of CTLA-4 and PD-1 has been reported to amplify antitumor T-cell response and provide synergistic activity. This combination therapy has been investigated in phase III clinical trials for cancer treatment.[18] In July 2018, the FDA granted accelerated approval to the combined use of ipilimumab and nivolumab for the treatment of MSI-H or dMMR metastatic colorectal cancer based on the CHECKMATE 142 study.[19] This combination of PD-1 and CTLA-4 blocking is also being investigated regarding gynecological cancers. In addition, two ongoing phase II trials (NCT05112601, NCT02982486) are focusing on the efficacy of this combination in the treatment of recurrent endometrial cancer with dMMR.

3 | CERVICAL CANCER

Cervical cancer is one of the most common gynecological malignancies among women, and persistent human papillomavirus (HPV) infection is involved in its development. Despite significant advances in early detection and prophylactic vaccinations, the poor prognosis for patients with advanced, recurrent or metastasized disease remains a major issue. ICBs are one of the most prominent representatives of novel therapeutics that are being extensively researched in the treatment of cervical cancer.

Pembrolizumab is currently the only FDA-approved drug for the treatment of cervical cancer. KEYNOTE-158 is a phase II basket study that investigated the antitumor activity of pembrolizumab in multiple cancer types. The results of this trial showed durable antitumor activity in patients with previously treated advanced cervical cancer.[20] Based on these results, in 2018 the FDA granted

TABLE 2 Completed phase III trials of anti-PD-1/PD-L1 agents in gynecological cancers

ID	Cancer/condition	No.	Intervention	mOS (months)	mPFS (months)	SAEs (%)	Refs
NCT03517449 KEYNOTE-775	EC/dMMR	827	1) Physician's choice 2) Pembrolizumab + lenvatinib	12.0 17.4, $p<0.01$	3.8 7.2, $p<0.01$	73 89	[12]
NCT03635567 KEYNOTE-826	CC/persistent, recurrent, or metastatic	548	1) Pembrolizumab + chemotherapy 2) Placebo + chemotherapy	24-month OS: 53.0% 24-month OS: 41.7%, $p<0.001$	10.4 8.1, $p<0.001$	42 36	[21]
NCT03257267	CC/recurrent	608	1) Celiplimab 2 Single-agent chemotherapy	12.0 8.5, $p<0.001$	2.8 2.9, $p<0.001$	45 53	[22]
NCT02580058 JAVELIN Ovarian 200	OC/platinum-resistant, or -refractory recurrent	361	1) Avelumab 2) Avelumab + PLD 3) PLD	18.2 18.4 17.4, $p>0.1$	1.9 3.7 3.5, $p>0.99$	28 36 19	[37]
NCT03038100 IMagyn050	OC/stage III-IV	1300	1) Atezolizumab + PC + bevacizumab 2) Placebo + PC + bevacizumab	– –	19.5 18.4, $p=0.038$	51 52	[35]
NCT02718417 JAVELIN Ovarian 100	OC/untreated	988	1) PC 2) PC+ avelumab, avelumab maintenance 3) PC, avelumab maintenance	Terminated due to the futility of efficacy			[36]

Abbreviations: CC, cervical cancer; dMMR, mismatch repair deficient; EC, endometrial cancer; mOS, median overall survival; mPFS, median progression-free survival; No., number of participants; OC, ovarian cancer; OS, overall survival; PC, paclitaxel + carboplatin; PLD, pegylated liposomal doxorubicin; Refs, references; SAEs, serious adverse events.

accelerated approval of pembrolizumab for patients with advanced PD-L1-positive cervical cancer. In September 2021, the results of the KEYNOTE-826 phase III trial were published.[21] That trial assessed the relative benefits of adding pembrolizumab to chemotherapy with or without bevacizumab, a well-known antiangiogenic agent, among patients with persistent, recurrent or metastatic cervical cancer. The PFS and OS rates increased significantly in the pembrolizumab group, not only in the PD-L1-positive group but also among the intention-to-treat population. In the pembrolizumab group, PFS was 2.2 months longer ($p<0.001$) than in the placebo group among the PD-L1-positive population. Moreover, OS at 24 months was 53.0% with pembrolizumab vs 41.7% without ($p<0.001$).[21] Based on these promising results, in October 2021 the FDA approved pembrolizumab combined with chemotherapy for patients with persistent, recurrent or metastatic cervical cancer, whose tumors expressed PD-L1 with a combined positive score (CPS) of 1 or more. The CPS is defined as the number of PD-L1-positive cells divided by the number of viable tumor cells, multiplied by 100.[21] One ongoing phase III trial (Keynote-A18) is exploring the efficacy of adding pembrolizumab to concurrent chemoradiotherapy in patients with newly diagnosed locally advanced cervical cancer.

Cemiplimab is a high-affinity PD-1-blocking monoclonal IgG4 antibody approved to treat lung and skin cancers, which showed antitumor activity in cervical cancer as well. A phase III trial (EMPOWER-Cervical 1) revealed that cemiplimab treatment led to a 3.5-month longer OS ($p<0.001$) than chemotherapy among patients with recurrent cervical cancer who had had disease progression after first-line chemotherapy. As compared with chemotherapy, cemiplimab treatment resulted in a 31% lower risk of death in the overall population.[22]

Another anti-PD-1 IgG4 antibody, nivolumab, has also been assessed for the treatment of cervical cancer. The CheckMate 358 trial is a phase I/II study that assessed nivolumab monotherapy in patients with virus-associated tumors. The results of that study in patients with recurrent or metastatic cervical cancer were promising, with an ORR of 26.3% and a median OS of 21.9 months.[23] However, another phase II trial revealed that nivolumab monotherapy exhibited low antitumor activity in persistent or recurrent cervical cancer, with an ORR of only 4% and a median duration of stable disease of 5.7 months.[24]

At present, there is limited clinical evidence for using anti-PD-L1 agents in the treatment of cervical cancer. Atezolizumab, avelumab and durvalumab are three anti-PD-L1 agents that are currently undergoing clinical trials. A phase II trial (NCT02921269) investigated the combined activity of atezolizumab and bevacizumab in the treatment of advanced cervical cancer. However, the combination of bevacizumab and atezolizumab did not meet the predefined efficacy endpoint, with an ORR of 0%.[25] One ongoing phase III trial (NCT0355683) is recruiting patients to determine whether the addition of atezolizumab to front-line treatments could improve oncological outcomes in patients with metastatic, recurrent or persistent cervical cancer. This study is expected to report mature data in 2023. Another phase II trial (NCT03260023) is evaluating the activity of

TABLE 3 Completed phase II trials of anti-PD-1/PDL-1 agents in gynecological cancers

ID	Cancer/condition	No.	Intervention	ORR (%)	mPFS (months)	mOS (months)	Conclusion	Refs
NCT02501096 KEYNOTE146	EC/advanced	54	Pembrolizumab + lenvatinib	39.6	7.4	—	Benefited	[11]
NCT02899793	EC/recurrent, dMMR	25	Pembrolizumab: 1. In Lynch-like patients 2. In sporadic patients	100 44.0	3-year PFS: 100% 30%	3-year OS: 100% 43%	Benefited	[13]
NCT02549209	EC/recurrent	46	Pembrolizumab + PC	77.8	10.55		Benefited	[14]
NCT03276013 TOPIC	EC/advanced, recurrent or metastatic	51	Pembrolizumab + doxorubicin	32.0	6.5	18.5	Benefited	[42]
NCT03192059 PRIMMO	CC or EC	43	Pembrolizumab	—	—	—	—	No data, unpublished
NCT02628067 KEYNOTE158	CC/advanced	98	Pembrolizumab	12.2	—	—	Benefited	[20]
NCT02674061 KEYNOTE100	OC/advanced or recurrent	376	Pembrolizumab	8.0	2.1	17.6	—	[30]
NCT02537444 KEYNOTE191	OC/recurrent	78	Pembrolizumab + ACP-196	2.9 9.1	—	—	—	Unpublished
NCT02440425	OC/platinum-resistant	37	Pembrolizumab + paclitaxel	51.4	—	26.3	—	Unpublished
NCT02608684 PemCiGem	OC/platinum-resistant	24	Pembrolizumab + standard treatment	60.0	6.2	11.3	Not benefited	[31]
NCT02865811	OC/platinum-resistant	26	Pembrolizumab + doxorubicin	26.1	8.1	13.8	Benefited	[43]
NCT02901899	OC/recurrent	38	Pembrolizumab + gemcitabine	27.0	—	—	Modest activity	[44]
NCT02853318	OC/recurrent	40	Pembrolizumab + bevacizumab + cyclophosphamide	47.5	10	—	Benefited	Unpublished
NCT02900560	OC/platinum-resistant	34	Pembrolizumab + azacytidine vs pembrolizumab	—	—	—	—	No data, unpublished
NCT03367741	EC/recurrent	76	1)Nivolumab + cabozantinib 2)Nivolumab	25.0 16.7	5.3 1.9	—	Benefited	[45]
NCT02488759 CheckMate 358 trial	CC/recurrent or metastatic	19	Nivolumab	26.0	—	21.9	Benefited	[23]
NCT02498600	OC/persistent or recurrent	49 51	1)Nivolumab 2)Nivolumab + ipilimumab (anti-CTLA-4)	12.2 31.4	2 3.9	—	Benefited	[38]
NCT02873962	OC/recurrent	38	Nivolumab + bevacizumab	28.9	8.1		Benefited	[34]
NCT02431559	OC/platinum-resistant	40	Durvalumab + PLD	15.0	5.5	—	Benefited	[46]
NCT02811497	OC/advanced	28	Durvalumab + DNA hypomethylating agent	7.2	1.9	5.0	Not benefited	[47]

TABLE 3 (Continued)

ID	Cancer/condition	No.	Intervention	ORR (%)	mPFS (months)	mOS (months)	Conclusion	Refs
NCT03899610	OC/advanced	23	Durvalumab + tremelimumab + chemotherapy	100.0	–	–	Benefited	[39]
NCT02912572	EC/recurrent or persistent	33	Avelumab	26.7	–	–	Benefited	[48]
NCT02921269	CC/recurrent	22	Atezolizumab + bevacizumab	0	2.9	8.9	Not benefited	[25]
NCT03816553	CC/recurrent, persistent, or metastatic	45	Camrelizumab + apatinib	55.6	8.8	–	Benefited	[49]
NCT03574779 OPAL	OC/recurrent	41	Dostarlimab + niraparib + bevacizumab	17.9	7.6	–	Benefited	[33]

Abbreviations: CC, cervical cancer; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; dMMR, deficient mismatch repair; EC, endometrial cancer; mOS, median overall survival; mPFS, median progression-free survival; No., number of participants; OC, ovarian cancer; PC, paclitaxel + carboplatin; PLD, pegylated liposomal doxorubicin; Refs, references.

avelumab combined with TG4001 (an HPV vaccine) in a group of patients with recurrent or metastatic HPV-16-positive advanced malignancies. Although durable responses have been observed,[26] patient follow-up is still ongoing. Durvalumab is a selective, high-affinity IgG1 monoclonal antibody blocking PD-L1 that was given accelerated approval by the FDA for treating urothelial carcinoma. Furthermore, a phase III trial (CALLA; NCT03830866) is evaluating the efficacy of adding durvalumab to concurrent chemoradiotherapy in locally advanced cervical cancer.

Concerning anti-CTLA-4 agents, a phase I study (GOG-9929) examined the efficacy of ipilimumab following chemoradiotherapy for newly diagnosed node-positive HPV-related disease.[27] Results revealed an increased expression of activation markers on T cells after ipilimumab treatment. The 12-month OS was 90% and the 12-month PFS was 81%.[28] These findings suggest that the use of immunotherapy after chemoradiotherapy is effective. A phase II trial (NCT01693783) is in progress to assess the safety of ipilimumab in eligible patients with recurrent or metastatic cervical cancer. Zalifrelimab is a new checkpoint inhibitor (anti-CTLA-4) that has emerged as an investigational agent for the treatment of cervical cancer. In addition, a phase II study (GOG-3028) is evaluating balstilimab (anti-PD-1) combined with zalifrelimab in patients with advanced cervical cancer whose condition progressed after first-line chemotherapy. Initial data from this study demonstrated an ORR of 26.5%.[29]

4 | OVARIAN CANCER

Ovarian cancer has the highest mortality rate of all gynecological malignancies, and the majority of women with ovarian cancer (more than 70%) are diagnosed at an advanced stage. Moreover, fewer than 30% of these patients will not experience disease recurrence. Furthermore, there is a high frequency of resistance to current treatments among patients with recurrent disease. Although there have been a series of developments in the treatment of ovarian cancer since the approval of PARPi, research into immunotherapy for ovarian cancer is still in its infancy.

As shown by the results of clinical trials, the antitumor activity of anti-PD-1 agents has been less satisfactory than expected. In a phase II study (KEYNOTE-100), pembrolizumab monotherapy did not show any advantage over chemotherapy in advanced and recurrent ovarian cancer.[30] In this study, the ORR was 8% in the pembrolizumab group. However, higher PD-L1 expression was correlated with a higher response rate, since the ORR was 17.1% in patients with PD-L1 and CPS ≥10. Another phase II study evaluated the addition of pembrolizumab to chemotherapy in platinum-resistant recurrent ovarian cancer.[31] That trial was abandoned when researchers discovered that pembrolizumab did not provide better clinical results than chemotherapy alone. Despite the failure of pembrolizumab monotherapy in ovarian cancer, several studies have explored the combination therapy of pembrolizumab with other targeted therapies. For example, the preliminary results of

TABLE 4 Ongoing phase III trials of anti-PD-1/PD-L1 in gynecological cancers

ID	Cancer/condition	No.	Start date	Targeting	Intervention	Status
NCT03884101 ENGOT-en9	EC/recurrent or stage III-IV	720	2019.4	PD-1 + VEGF	1) Pembrolizumab + lenvatinib 2) Chemotherapy	Recruiting
NCT03914612	EC/advanced or recurrent	810	2019.7	PD-1	1) Pembrolizumab + PC 2) Placebo + PC	Recruiting
NCT04634877 Keynote-B21	EC/high risk	990	2020.11	PD-1	1. Pembrolizumab + chemoradiotherapy 2. Pembrolizumab + chemotherapy	Recruiting
NCT04865289 China extension study	EC/ recurrent or stage III-IV	875	2021.4	PD-1 + VEGF	1) Pembrolizumab + lenvatinib 2) Chemotherapy	Recruiting
NCT05173987 ENGOT-en15	EC/dMMR, advanced or recurrent	350	2022.2	PD-1	1) Pembrolizumab 2) Chemotherapy	Recruiting
NCT04221945 Keynote-A18	CC/advanced	980	2020.1	PD-1	1. Pembrolizumab + chemoradiotherapy 2. Chemoradiotherapy	Recruiting
NCT03740165 KEYLYNK-001/ ENGOT-ov43	OC/fist-line treatment	1086	2018.12	PD-1 + PARP	1) Pembrolizumab + olaparib 2) Pembrolizumab + placebo 3) Placebo + PC + bevacizumab	Recruiting
NCT05092360	OC/platinum-resistant	376	2021.10	PD-1 + IL-2	1) Pembrolizumab + nemvaleukin 2) Pembrolizumab 3) Nemvaleukin	Not recruiting
NCT04679064	OC/recurrent	427	2020.12	PD-1 + PARP	1) Pembrolizumab + niraparib 2) PC + bevacizumab	Recruiting
NCT03522246 ATHENA	OC/stage III-IV	1012	2018.5	PD-1 + PARP	1) Nivolumab + rucaparib 2) Rucaparib + placebo 3) Nivolumab + placebo 4) Placebo	Recruiting
NCT03353831	OC/platinum-resistant	664	2018.9	PD-L1	1) Atezolizumab 2) Placebo + paclitaxel or PLD	Recruiting
NCT03556839	CC/stage IVb	404	2018.9	PD-L1	1) Atezolizumab 2) Placebo + PC+ bevacizumab	Recruiting
NCT03603184 AtTEnd	EC/advanced	550	2018.10	PD-L1	1) Atezolizumab 2) Placebo + PC	Recruiting
NCT03737643 DUO-O	OC/stage III-IV	1056	2019.1	PD-L1 + PARP	1) Durvalumab + olaparib 2) Durvalumab + placebo 3) Placebo + PC + bevacizumab	Recruiting
NCT03830866 CALLA	CC/locally advanced	714	2019.2	PD-L1	1) Durvalumab 2) Placebo + chemoradiation	Recruiting
NCT03981796 RUBY	EC/recurrent or stage III-IV	470	2019.7	PD-1 + PARP	1) Dostarlimab 2) Placebo + PC	Recruiting
NCT03602859 ENGOT-0 V44 /FIRST	OC/stage III-IV	912	2018.10	PD-1 + PARP	1. Dostarlimab + niraparib 2. Niraparib + placebo 3. Placebo	Recruiting
NCT03806049 NSGO/ AVANOVA-Triplet	OC/platinum-sensitive	337	2019.6	PD-1 + VEGF + PARP	1) Dostarlimab + niraparib+ bevacizumab 2) Niraparib + bevacizumab 3) Chemotherapy	Withdrawn
NCT05201547 DOMENICA	EC/dMMR	142	2022.1	PD-1	1. Dostarlimab 2. PC	Not recruiting
NCT03912415 FERMATA	CC/advanced	316	2019.9	PD-1	1. Prolgolimab 2. Placebo + PC + bevacizumab	Recruiting

Abbreviations: CC, cervical cancer; dMMR, mismatch repair deficient; EC, endometrial cancer; No., number of participants; OC, ovarian cancer; PARPi, poly adenosine diphosphate-ribose polymerase inhibitor; PC, paclitaxel + carboplatin; PD-1, programed death protein 1; PD-L1, programed death protein ligand 1; PLD, pegylated liposomal doxorubicin; Refs, references; VEGFi, vascular endothelial growth factor inhibitor.

the TOPACIO study showed that a combination of pembrolizumab and niraparib (a PARPi) displayed promising antitumor activity for patients with recurrent ovarian cancer who had limited treatment options. These positive results applied to all patients, regardless of platinum status, biomarker status or prior bevacizumab treatment, thus advocating further investigations.[32] The phase III trial of pembrolizumab plus niraparib in the treatment of recurrent ovarian cancer (NCT04679064) is currently enlisting patients. Another phase III trial (NCT05092360) is investigating the efficacy of pembrolizumab plus nemvaleukin, a novel engineered interleukin-2 variant immunotherapy, in patients with platinum-resistant ovarian cancer.

Other anti-PD-1 agents, such as dostarlimab and nivolumab, have shown clinical benefits in early phase trials for the treatment of ovarian cancer. A phase II trial assessed the triple therapy effect of dostarlimab, niraparib and bevacizumab in patients with platinum-resistant ovarian cancer, achieving an ORR of 17.9% and a median PFS of 7.6 months.[33] A further phase III trial (NCT03603859) aims to evaluate first-line treatment combined with niraparib plus dostarlimab in ovarian cancer. As for nivolumab, a phase II trial assessed its role in the treatment of recurrent ovarian cancer, and the results revealed that the ORR was 28.9% in patients who received combined nivolumab and bevacizumab treatment.[34] This combination treatment had an even higher ORR (40%) in platinum-sensitive patients. An ongoing phase III trial (NCT03522246) is evaluating nivolumab plus rucaparib (a PARPi) as maintenance treatment following a response to front-line treatment in newly diagnosed cases of advanced ovarian cancer.

The clinical findings of anti-PD-L1 agents in the treatment of ovarian cancer are not encouraging. A phase III trial (IMagyn050) evaluated the addition of atezolizumab to chemotherapy plus bevacizumab in newly diagnosed cases of advanced ovarian cancer. The median PFS was 19.5 months with atezolizumab vs 18.4 months without ($p = 0.28$). Therefore, this result did not support the use of atezolizumab in newly diagnosed patients.[35] Currently, there are two ongoing phase III trials (NCT02891824 and NCT03353831) investigating the role of atezolizumab in instances of recurrent disease. A phase III study of avelumab combined with chemotherapy for previously untreated disease (JAVELIN Ovarian 100) was terminated in 2018 due to a lack of efficacy.[36] This result does not support the use of avelumab in newly diagnosed cases of ovarian cancer. Another phase III trial (JAVELIN Ovarian 200) focused on avelumab for platinum-resistant/refractory recurrent disease. Patients were placed in randomized groups to receive treatment with avelumab, avelumab plus pegylated liposomal doxorubicin (PLD), or PLD alone. Results indicated ORR values of 14.3%, 5.6% and 0%, respectively.[37] Thus, this trial did not meet its primary endpoint. A phase II trial (NCT02431559) revealed that the combination of durvalumab and doxorubicin was associated with an ORR of 15% in platinum-resistant recurrent ovarian cancer. There are also two phase III trials currently investigating durvalumab in gynecological cancers, one of which (DUO-O; NCT03737643) is exploring the combined treatment of chemotherapy, bevacizumab, durvalumab and a olaparib in ovarian cancer.

The combination therapy of anti-CTLA-4 agents with anti-PD-1/PD-L1 agents is also being investigated in clinical trials as a potential treatment strategy for ovarian cancer. A phase II study allocated 100 patients with recurrent or persistent disease to receive either nivolumab or nivolumab plus ipilimumab.[38] Compared with nivolumab alone, the combination treatment resulted in a superior response rate and longer PFS (3.9 vs 2.0 months). Tremelimumab is a monoclonal IgG2 antibody that targets CTLA-4; a phase II study assessed neoadjuvant chemotherapy plus durvalumab and tremelimumab in the treatment of advanced-stage ovarian cancer.[39] A complete response to treatment was achieved in 13% of patients, and 87% experienced a partial response. These data highlight the clinical activity of this combination therapy in the treatment of ovarian cancer.

5 | SAFETY

Since these anti-immune agents target immunity, they may result in abnormal immune reactions and generate toxicity that affects the skin, gut, lung, liver and other tissues. Data from one meta-analysis showed that the most common immune-related adverse events for pembrolizumab are arthralgia, pneumonitis and hepatic toxicities, for nivolumab they are endocrine toxicities, for atezolizumab they are hypothyroidism, and for ipilimumab they are dermatological, gastrointestinal and renal toxicities.[40] ICBs were discontinued because of adverse reactions in 10% of patients with pembrolizumab and 8.7% of patients with cemipilimab.[12,22] However, adverse events that are mostly transient and mild, and do not translate into clinically meaningful differences in health-related quality of life. The incidence of severe adverse events due to the combination of anti-CTLA-4 and anti-PD-1 agents is reported to be 55%,[41] which is significantly higher than either agent individually and leads to discontinuation of treatment in one-third of patients. Nevertheless, more preclinical and clinical investigations are required to elucidate the key mechanisms and predictive biomarkers of the efficacy and safety of these agents and to limit the risk of adverse reaction.

6 | CONCLUSIONS

Considering the immune landscape of cervical cancer and the molecular indicators identified in endometrial cancer, we anticipate that ICB therapy will play an important role in the treatment of certain patients. The distinct outcomes among patients with different MMR or PD-L1 statuses suggest that the key to making progress in ICB therapies is to identify more biomarkers. With the development of HPV therapeutic vaccines, a combination of vaccines and ICBs may be a prospective strategy for treating cervival cancer. Currently, however, the clinical outcomes of ICBs as a primary treatment for ovarian cancer are not promising. Given that PARPi has been a remarkable breakthrough in the treatment of ovarian cancer and is a synergistic partner for ICBs, future clinical trials regarding ovarian cancer should focus on combining ICBs

with PARPi therapy and determining the role of ICBs in the treatment of platinum-resistant recurrent disease. However, the safety profile of these combination therapies represents a new concern that will have to be considered.

AUTHORS' CONTRIBUTIONS

QW and HP did the literature searching and screening. HP drafted the manuscript. QW and XH reviewed and revised the draft. All authors approved the final manuscript.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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