A comprehensive analysis of immunotherapy in advanced endometrial cancer (Review)

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Abstract. The morbidity and mortality rates of endometrial cancer (EC) are increasing yearly. Early-stage EC can be effectively treated through surgery or surgery combined with radiotherapy and chemotherapy. Advanced and recurrent EC is treated with chemotherapy and comprehensive treatment; however, the prognosis for patients at this disease stage is poor. Consequently, novel and effective treatment strategies are urgently required for these patients. Breakthrough progress has been made with the use of immunosuppressants in the treatment of EC, which have been included in treatment guidelines. In the present review, the etiology and classification of EC was outlined and the relevant scientific basis for the application of immunosuppressants in advanced and recurrent EC was discussed. The relevant published and ongoing clinical trials are also summarized. As such, the present review aimed to provide a scientific summary of immunotherapy of EC.

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Abbreviations: EC, endometrial cancer; TCGA, The Cancer Genome Atlas; POLE, polymerase ε; MSI-H, microsatellite instability-high; dMMR, mismatch repair deficient; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand 1; TMB, tumor mutation burden; pMMR, mismatch repair proficient; ORR, overall response rate; mPFS, median progression-free survival; PR, partial response; CR, complete response; SD, stable disease; NCCN, The National Comprehensive Cancer Network; AEs, adverse events; PFS6, PFS rate at 6 months; IV, intravenous; MSS, microsatellite stability; ORR_{Wk24}, ORR at 24 weeks; mOS, median overall survival

Key words: endometrial cancer, risk factors, classification, immune checkpoint inhibitors, programmed cell death protein 1, programmed cell death ligand 1

Contents

1. Background

Endometrial cancer (EC) is one of the three most common malignant tumors of the female reproductive system and it ranks sixth in incidence among female malignant tumors globally (1). The morbidity and mortality rates of EC in developed countries are higher compared with those in developing countries (2). Furthermore, 66,570 new cases of EC and 12,940 EC-related deaths in the US were estimated for 2021 (3). In China, the incidence and mortality rates of EC are also exhibiting gradual increases. Data from the China Cancer Statistics Report indicated that in 2022, there were 84,520 new cases and 17,543 deaths from cancer in corpus uteri in China (4). In total, ~80% of EC cases are limited to the uterus at the initial diagnosis and these patients have a relatively good prognosis with a 5-year survival rate of >95% (5,6). However, in cases with regional or distant metastasis, the prognosis is significantly worse (68 and 17%, respectively) (6,7). Paclitaxel plus carboplatin is the standard first-line treatment for patients with advanced, recurrent or metastatic EC (8). However, the effective rate of this treatment is limited and ranges from 7-14%, with a median overall survival (mOS) time of <1 year (9-12). Therefore, it is necessary to explore new treatment methods in order to prolong the survival time of patients with EC.

2. High-risk factors for EC

At present, the cause of EC remains unknown, but the related high-risk factors may be divided into several categories, including reproductive factors, hormonal use, metabolic syndromes and genetic factors (13). Reproductive risk factors include nulliparity, early menarche, late menopause, infertility and anovulatory menstrual cycles (13). There is evidence that, compared with non-parturient women, the incidence of EC in

postpartum women is reduced by 40% (14). Furthermore, a large-scale meta-analysis reported that parity (the number of births after ≥24 weeks of pregnancy) may be associated with a reduced risk of EC, since the relative risk (RR) of EC decreased when the parity number increased (15). This outcome may be related to the protection of progesterone on the endometrium during pregnancy. EC is a hormone-driven type of cancer and ~80% of EC cases may be caused by excessive estrogen or lack of progesterone (16). Long-term continuous estrogen stimulation, including endogenous and exogenous, increases the risk of hormone-responsive EC. These sources of stimulation include using only estrogen in women with an intact uterus, selective estrogen receptor modulators (such as tamoxifen and raloxifene) and polycystic ovary syndrome (13).

The International Agency for Research on Cancer suggests that obesity is also a risk factor of EC (17). Furthermore, a Mendelian randomization study reported that an increase in BMI had a direct impact on EC risk and the overall impact of SNP alleles associated with an increase in BMI on EC risk exceeded their predicted impact on the BMI (18,19). The association of obesity with EC may be related to elevated estrogen levels, hyperinsulinemia and chronic inflammation (16,20,21). There is also evidence that diabetes increases the risk of EC (14). In a meta-analysis by Tsilidis *et al* (22), it was reported that the overall random impact on the incidence rate of EC in patients with diabetes was 1.97. EC is also associated with certain genetic factors. For instance, white women were reported to have a higher incidence of EC than women of other ethnicities in the US (23); however, this may also be due to the socio-economic differences and requires further study. An Italian study showed that ~5% of patients with EC have a family history of the disease in a first-degree relative (24). In addition, there are two genetic syndromes associated with EC, Lynch syndrome and Cowden syndrome (25-27), with Lynch syndrome (also known as hereditary non-polyposis colorectal cancer) being the most common (25,26). It is estimated that up to 70% of women with Lynch syndrome will develop EC, which is typically hormone-responsive (25,26).

Certain studies have demonstrated that smoking reduces the risk of EC (28) and, compared with non-smokers, current or former smokers have a lower risk of EC (29,30). This reduced risk may be due to the mechanistic link between the anti-estrogen effects of smoking and the risk of EC (14,31). Of note, a study by Aune *et al* (32) reported that body height is significantly associated with the risk of EC [RR, 1.15; 95% confidence interval (CI), 1.09-1.22]. In summary, obesity is the main risk factor for EC and therefore, the importance of weight control to reduce the incidence of EC should be highlighted. However, additional risk factors such as diabetes, smoking and body height require further study.

3. Classification of EC

The classification of cancer is important, since different classifications may result in different treatment methods and prognoses. Based on clinical pathology and molecular characteristics, EC has historically been classified into two categories of Bokhman histopathology: Type I and type II (33). Type I (endometrioid carcinoma) is the most common type and accounts for 60-70% of EC cases, is graded 1 or 2 and exhibits high hormone receptor expression (33). These tumors are more likely to be detected at an early stage due to symptoms such as bleeding and patients with this type have a good prognosis. Type II accounts for 30-40% of all EC cases, typically includes high-grade endometrioid carcinoma and other histological types, such as serous or clear cell carcinoma, and is estrogen-independent (33). Type II is more invasive than type I and, even with an early diagnosis, the prognosis of type II is poor (34). However, the traditional pathological classification has certain limitations. For instance, certain high-level (grade 3) endometrial carcinoma and serous carcinoma are not easily distinguishable in terms of morphology. Furthermore, this classification cannot provide clear targets to assist in selecting new treatment methods or drugs.

In 2013, The Cancer Genome Atlas (TCGA) research network introduced a molecular classification system based on new advances in the understanding of the EC genome landscape (35). TCGA described the four molecular subgroups of EC as follows (35): i) Polymerase-ε (POLE) ultra-mutated, which is characterized by somatic mutations in the exonuclease domain of the DNA replication enzyme POLE and patients with this subtype have an excellent prognosis; ii) microsatellite instability hypermutated (MSI-H), which is characterized by high mutation rates in both sporadic and hereditary EC that are associated with changes in the mismatch repair (MMR) system genes, MLH1, MSH2, MSH6 and post-meiotic segregation 1 homolog 2 (PMS2) and the prognosis of patients with this subtype is intermediate; iii) copy-number low, which is characterized by a low mutational load and an intermediate prognosis, this subtype includes most EC cases and is often associated with gene mutations in phosphate and tension homology deleted on chromsome 10, catenin-β1, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic α subunit, AT-rich interactive domain-containing protein 1A and KRAS; and iv) copy-number high, which includes serous tumors and 25% of high-grade EC cases, patients with this subtype have a poor prognosis and the mutation rate of this subtype is the lowest, but TP53 mutations are frequent. A study of 50 patients with high-grade endometrial adenocarcinoma demonstrated that the clinical prognosis of each subgroup was different (36). At 48 months, the cancer-specific/disease-specific survival rate in the POLE mutation group was 100%, that in the MSI group was 82%, that in the copy-number low group was 77.8% and that in the copy-number high group was 42.9%. Therefore, this classification method reflects that these subgroups not only have different molecular and pathological characteristics, but also exhibit significant differences in clinical outcomes (35,37). This classification is also an example of tumor precision treatment. However, molecular subtyping is based on high-throughput deep sequencing, which is both costly and time-consuming and may limit the wider clinical application.

Talhouk *et al* (38) proposed a simple and economical molecular classification method to replace high-throughput sequencing (Fig. 1). This method used immunohistochemistry to detect the expression of the MMR proteins MSH6 and PMS2 to determine the type of MMR deficiency (dMMR). Sequencing of the exonuclease domain of the catalytic subunit of POLE was then conducted to determine the type of POLE mutant. Finally, cases were divided into p53 mutant-type

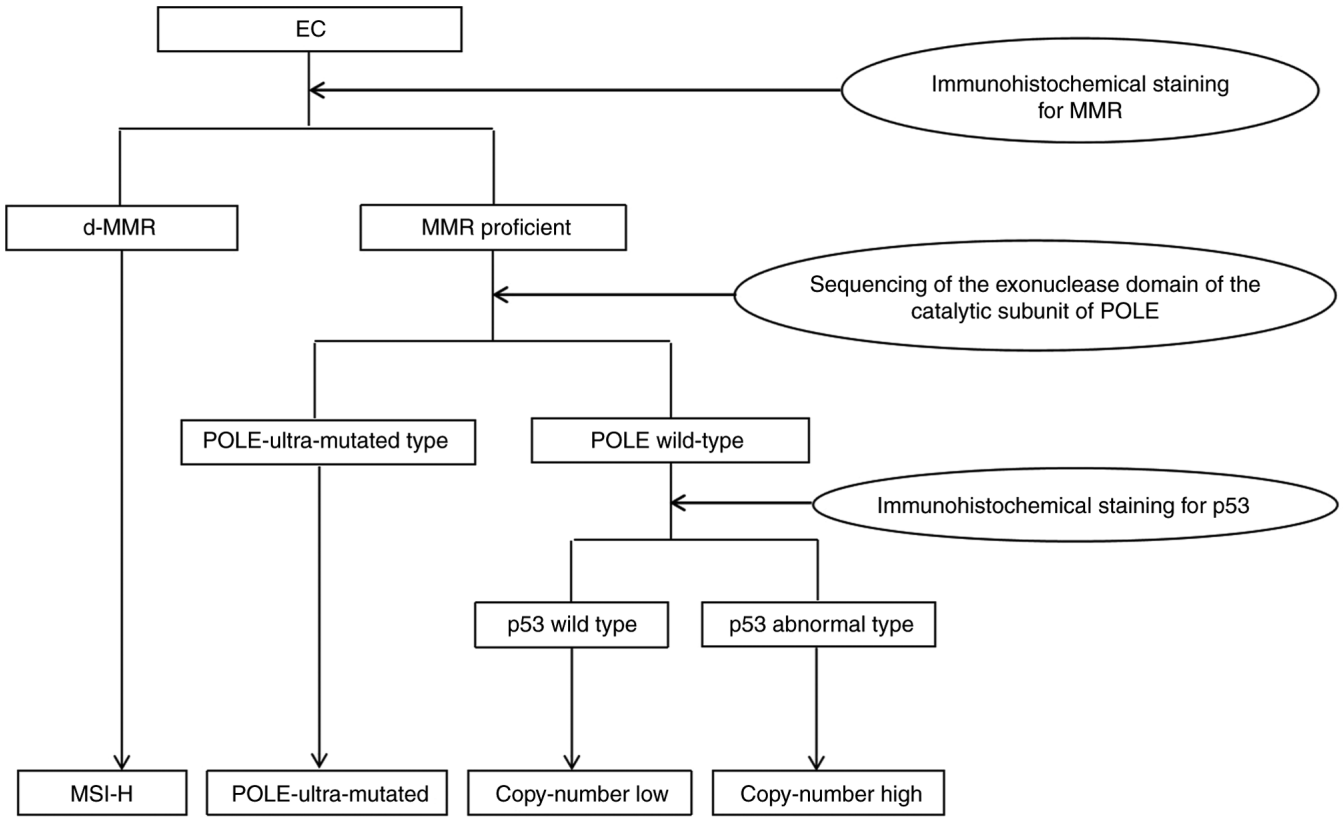

Figure 1. Simple model for the molecular classification of EC. Through sequencing of the exonuclease domain of the catalytic subunit of POLE and immunohistochemical staining for MMRs and p53, EC can be divided into the dMMR type, POLE-ultra-mutated type, p53 wild type and p53 abnormal type, respectively replacing MSI-H, POLE ultramutated, copy-number low type and copy-number high type in the The Cancer Genome Atlas Program classification (38). MMR, mismatch repair proteins; POLE, polymerase epsilon; dMMR, deficient mismatch repair; MSI-H, microsatellite instability hypermutated; EC, endometrial cancer.

according to the p53 immunohistochemistry staining results (staining 2^+ or 0) or p53 wild-type (staining 1^+). By this method, EC was then finally divided into dMMR, POLE ultra-mutated, p53 wild-type or p53 abnormal type, respectively replacing MSI-H, POLE ultra-mutated, copy-number low or copy-number high type. Although this new grouping is not completely equivalent to the TCGA classification, the four survival curves of the groupings were similar to those of the TCGA classification (38). The authors of the aforementioned study suggested that this simple method may be used on a large scale in the clinic, which is of great significance for guiding the molecular classification, risk grading and treatment of EC.

4. Mechanism and application of immunotherapy

Programmed cell death protein 1 (PD-1) was first reported by Ishida *et al* (39) in apoptotic T cells in mice. PD-1 belongs to the CD28 family of proteins and is mainly expressed on the surface of immune cells, such as activated T cells, B cells and natural killer cells (40,41). The most notable ligand of PD-1, PD-1 ligand 1 (PD-L1), is frequently expressed in various types of tumor cell (42). Tumor cells activate the inhibitory signaling pathway of PD-1/PD-L1, inhibit the activation of T cells and finally form an immune microenvironment suitable for tumor cell growth (43,44). Therefore, immunosuppressive agents against PD-1 or PD-L1 restore the immune activity of T cells, enhance the immune response and improve the ability of the immune system to kill tumor cells. This has been a major breakthrough in the field of tumor treatment in recent years (45). At present, PD-1 inhibitors that are effective in cancer treatment include nivolumab, pembrolizumab and cemiplimab, while PD-L1 inhibitors include atezolizumab, avelumab and durvalumab (45). Markers related to the efficacy of immune checkpoint inhibitors include PD-L1, MSI-H or dMMR tumor mutation burden (TMB). A study by Mo *et al* (46) demonstrated that 61.3% of patients with EC expressed PD-L1 in their tumor tissues. Furthermore, the degree of tissue differentiation was negatively associated with PD-L1 expression levels (46). Another previous study has also shown that 25-30% of EC cases have MSI-H or dMMR (47). A study by Kautto *et al* (48) demonstrated that, compared with proficient MMR (pMMR) tumors, dMMR tumors had more somatic mutations and produced more neoantigens. Furthermore, the efficacy of pembrolizumab against dMMR tumors was significantly higher compared to pMMR tumors (48). The therapeutic effect of PD-1/PD-L1 inhibitors is related to the TMB, as PD-1/PD-L1 inhibitors are more effective against tumors with a high TMB (35). Among the four molecular subtypes of EC, the TMB of MSI-H and POLE ultra-mutated subtypes was determined to be higher compared with that of the other groups (35). In addition, a previous study reported that the expression rates of PD-1 in POLE-mutant and MSI-H EC tissues were 73 and 69%, respectively, and that the expression rates of PD-L1 were 100 and 71%, respectively (49).

Another feature of the MSI-H and POLE ultra-mutated subtypes is that they are rich in tumor-infiltrating lymphocytes and $CD3^+$ and $CD8^+$ T lymphocytes (50). Therefore, this suggests that there are active immune responses in the local microenvironment of MSI-H and POLE ultra-mutated tumors and that blocking PD-1/PD-L1 may induce an effective antitumor immune response (51). As such, the MSI-H and POLE ultra-mutated subtypes are most likely to benefit from PD-1/PD-L1 inhibitory therapy.

5. Application of immunosuppressive agents in EC

Until now, the first-line treatment for advanced EC was carboplatin and paclitaxel combined chemotherapy, with an overall response rate (ORR) of 50-60% and a median progression-free survival (mPFS) time of 1 year (52,53). After platinum treatment failed, conventional single drug chemotherapy was administered, but the outcome was poor. For instance, doxorubicin and paclitaxel are the most commonly used second-line treatments for EC and can only provide an mPFS time of 4 months and an mOS time of 1 year (54). Therefore, the exploration of new therapies to improve the prognosis of patients with advanced EC is urgently needed. In previous years, there have been a number of clinical research studies regarding immune checkpoint inhibitors in EC, which have provided a comprehensive scientific basis for drug research and development for the treatment of advanced EC (Table I).

Immune checkpoint inhibitors in monotherapy

Anti-PD-1. Pembrolizumab. In 2015, Le *et al* (55) demonstrated the efficacy of the anti-PD-1 monoclonal antibody pembrolizumab against EC, which provided the first evidence for the administration of immunotherapy in advanced EC. The aforementioned study conducted a phase II clinical trial of 41 patients with metastatic cancer with or without dMMR, including 2 patients with EC. The 2 patients with EC achieved partial response (PR) and the ORR and PFS rates were 71 and 67%, respectively. In addition, >5% of patients experienced adverse events (AEs), including rash or itching (24%), thyroiditis, hypothyroidism or hypophysitis (10%) and asymptomatic pancreatitis (15%). To our knowledge, this study was the first to report the relationship between the tumor microenvironment, genotype and response to checkpoint inhibitors, which are critical for identifying predictors of response to immune checkpoint inhibitor therapy.

In 2016, Mehnert *et al* (56) reported on a 53-year-old patient with high-grade metastatic endometrial adenocarcinoma who received 10 mg/kg pembrolizumab treatment every 2 weeks and ultimately achieved a rapid and sustained (>14 months) clinical response.

In 2017, Le *et al* (57) published the results of a phase II clinical trial (NCT01876511) of pembrolizumab as a single-agent treatment for patients with the dMMR tumor subtype. An ORR of 53% (46 patients) was observed in the 86 patients enrolled and 21% of patients reached complete response (CR; 18 patients). The 15-patient EC cohort also exhibited an ORR of 53% (8 patients) and the disease control rate was 73.3% (11 patients). Throughout the study, 74% of patients experienced adverse reactions, but the majority had low-grade reactions. Endocrine disorders, mainly hypothyroidism, occur in 21% of patients and may be easily treated by thyroid hormone replacement therapy (57). This study further supported the hypothesis that dMMR tumors are sensitive to immunosuppressive agents, regardless of the location of the primary tumor. In the same year, the results of a phase IB trial, KEYNOTE-028 (NCT02054806), were also published (58). The 24 subjects of this study had advanced or metastatic $PD\text{-}L1^+$ EC. Patients who progressed after standard treatment received 10 mg/kg intravenous (IV) pembrolizumab every 2 weeks for up to 24 months or until the disease progressed or the toxicity was intolerable. Among them, 3 patients achieved PR and 2 patients maintained stable disease (SD). The ORR was 13% and the 6-month PFS and OS rates were 19.0 and 68.8%, respectively. As for toxicity, minor adverse reactions were observed in 54.2% of patients, including fatigue, itching, fever and anorexia. Based on the aforementioned results, the US Food and Drug Administration (FDA) approved pembrolizumab for the treatment of solid tumors with MSI-H/dMMR in May 2017. This was the first antitumor drug approved following a diagnosis by biomarker rather than tissue type. In 2019, pembrolizumab was added to The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for EC, stating that pembrolizumab can be used for the treatment of EC when accompanied by MSI-H/dMMR recurrence or metastasis that has not responded to previous treatment (8).

In January 2020, phase II clinical trial (KEYNOTE-158) results were published involving 27 cases of advanced MSI-H or dMMR solid tumors, which were consistent with the results of NCT01876511 (59). Among the 233 patients enrolled, 49 had EC. The ORR of the patients with EC was 57.1%, of which 16% (8 patients) had a CR and 41% (20 patients) had a PR. The mPFS time was 25.7 months. Of the 233 enrolled patients, 151 (64.8%) had treatment-related AEs, of which 34 (14.6%) had grade 3-5 AEs. The most common toxicities were fatigue (14.6%), itching (12.9%), diarrhea (12.0%) and weakness (10.7%). Due to these AEs, 22 patients (9.4%) had to stop treatment.

Nivolumab. Nivolumab is also an anti-PD-1 immunosuppressant. In 2016, Santin *et al* (60) reported on 2 patients with recurrent POLE ultra-mutated and MSH6 hypermutated EC tumors who were unresponsive to conventional surgery and chemotherapy. During the treatment of these 2 patients, nivolumab was administered as a single IV drug at a dose of 3 mg/kg once every 2 weeks. Following computed tomography scanning over several months, it was confirmed that the patients demonstrated a sustained clinical reaction to nivolumab and reported no severe toxicity. In addition, results from a multicenter, open-label nivolumab phase II clinical trial were released in 2019 (61). The 22 patients in this study with advanced/recurrent uterine cancer received 240 mg nivolumab every 2 weeks. The primary endpoint was the ORR and the secondary endpoints included OS, PFS and safety. The resulting ORR was 23%, the mPFS time was 3.4 months and the 6-month OS rate was 73%. In the uterine cancer cohort, the most common treatment-related adverse event was pruritus, which was mostly mild.

Dostarlimab. Dostarlimab (TSR-042) is an effective, selective and humanized anti-PD-1 immunoglobulin G4 monoclonal antibody, which has a high affinity for the PD-1 receptor and can effectively block the binding of PD-1 and

Table I. Published clinical studies with results available.

First author, year	Drug	Target	Trial identifier	Phase	Patient population, number of patients (n)	Treatment	Findings	Adverse reactions	(Refs.)
Le *et al*, 2015	Pembrolizumab	PD-1	NCT01876511	II	Pts with metastatic cancer with or without dMMR (n=41), including pts with EC (n=2)	Pembrolizumab 10 mg/kg IV every 14 days	In pts with dMMR, CRC; ORR, 40.0% (4/10); 20-week PFS, 77.8% (7/9). In pts with pMMR, CRC; ORR, 0% (0/18); 20-week PFS, 11.1% (2/18). In pts with dMMR, non-CRC; ORR, 71.4% (5/7); 20-week PFS, 66.7% (4/6)	Rash, itching, thyroiditis, hypothyroidism, hypophysitis and asymptomatic pancreatitis	(55)
Le *et al*, 2017	Pembrolizumab	PD-1	NCT01876511	II	Pts with 12 dMMR tumor types (n=86), including pts with EC (n=15)	Pembrolizumab 10 mg/kg IV every 14 days	In pts with dMMR ORR, 53.5% (46/86); DCR, 76.7% (66/86) In pts with dMMR of EC ORR, 53.3% (8/15); DCR, 73.3% (11/15)	Hypothyroidism	(57)
Ott *et al*, 2017	Pembrolizumab	PD-1	NCT02054806 (KEYNOTE-028)	Ib	Pts with locally advanced or metastatic PD-L1-positive EC (n=24)	Pembrolizumab 10 mg/kg IV every 2 weeks	ORR, 13.0% (3/23); PFS, 1.8 months; 6-month PFS, 19%; 12-month PFS, 14.3%; 6-month OS, 67%; 12-month OS, 51%	Fatigue, itching, fever and anorexia	(58)
Marabelle *et al*, 2020	Pembrolizumab	PD-1	NCT02628067 (KEYNOTE-158)	II	Pts with advanced MSI-H or dMMR solid tumors (n=233), including pts with EC (n=49)	Pembrolizumab 200 mg IV once every 3 weeks	ORR, 57.1% (28/49); PFS, 25.7 months	Fatigue, itching, diarrhea and weakness	(59)
Tamura *et al*, 2019	Nivolumab	PD-1	JapicCTI-163212	II	Pts with advanced/ recurrent uterine cervical cancer (n=20), uterine corpus cancer (n=23) and soft tissue sarcoma (n=21)	Nivolumab 240 mg IV every 2 weeks	In pts with EC (n=22): ORR, 22.7% (5/22); DCR, 68.2% (15/22); mPFS, 3.4 months; mOS, 8.7 months	Pruritus	(61)
Oaknin *et al*, 2020	Dostarlimab	PD-1	NCT02715284 (GARNET trial)	I	Pts with defective mismatch mutation repair EC (n=104)	Dostarlimab 500 mg IV once every 3 weeks for 4 doses, then 1,000 mg once every 6 weeks	ORR, 42.3% (30/71); DCR, 57.7% (41/71)	Anemia, colitis and diarrhea	(63)

Table I. Continued.

First author, year	Drug	Target	Trial identifier	Phase	Patient population, number of patients (n)	Treatment	Findings	Adverse reactions	(Refs.)
Liu *et al*, 2019	Atezolizumab	PD-L1	NCT01375842	I	Pts with advanced/ recurrent epithelial ovarian (n=12) and uterine cancers (n=15)	In the dose-expansion phase, atezolizumab 15 mg/kg or 1,200 mg IV every 3 weeks for 16 cycles or 1 year of treatment, whichever occurred first	ORR, 13.3% (2/15); mPFS, 1.4 months	Diarrhea and fatigue	(64)
Konstantinopoulos *et al*, 2019	Avelumab	PD-L1	NCT02912572	II	Pts with dMMR (n=15) and pMMR (n=16) recurrent/persistent EC	Avelumab 10 mg/kg IV every 2 weeks	In pts with dMMR (n=15): ORR, 26.7% (4/15); PFS6 rate, 40%. In pts with pMMR/ non-POLE (n=16): ORR, 6.25% (1/16); PFS6 rate, 6.25%	Fatigue and nausea	(65)
Antill *et al*, 2021	Durvalumab	PD-L1	NCT03015129	II	Pts with advanced mismatch repair-deficient (n=36) and repair-proficient (n=31) EC	Durvalumab 1,500 mg IV every 4 weeks	In pts with dMMR (n=36): ORR, 47% (17/36); mPFS, 8.3 months. In pts with pMMR (n=31): ORR, 3% (1/16); mPFS, 1.8 months	Hyperthyroidism and hypothyroidism	(66)
Makker *et al*, 2020	Pembrolizumab + lenvatinib	PD-L1	NCT02501096 (KEYNOTE-146)	II	Pts with previously treated EC (n=108)	Lenvatinib 20 mg once daily orally plus pembrolizumab 200 mg IV once every 3 weeks, in 3-week cycles	ORR_{Wk24}, 38% (41/108); ORR, 38.9% (42/108); mDOR, 21.2 months; mPFS, 7.4 months; mOS, 16.7 months. In pts with MSI-H/dMMR at 24 weeks (n=11): ORR, 63.6% (7/11); in pts with MSS/pMMR at 24 weeks (n=94): ORR, 36.2% (34/94)	Hypertension, diarrhea, fatigue, decreased appetite, hypothyroidism and nausea	(71)

Pts, patients; n, number; EC, endometrial cancer; DCR, disease control rate; dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; mPFS, median progression-free survival; PFS6, PFS rate at 6 months; IV, intravenous; ORR, overall response rate; mOS, median overall survival; MSI-H, microsatellite instability-high; ORR_{Wk24}, overall response rate at 24 weeks; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand 1; POLE, polymerase ε; MSS, microsatellite stability; CRC, colorectal cancer; mDOR, median duration of response.

PD-L1 (62). To date, the GARNET trial (NCT02715284) is the only published study to evaluate the curative effect of dostarlimab in EC and is the largest single study of an anti-PD-1 monotherapy for advanced or relapsed EC (63). As of the data cut-off point, 104 patients with dMMR EC were enrolled and received dostarlimab treatment. Among these patients, 71 with measurable lesions at baseline and a follow-up of ≥6 months were ultimately included in the analysis. The results indicated an ORR of 42.3% (30 patients), a CR rate of 12.7% (9 patients) and a PR rate of 29.6% (21 patients). The treatment response to dostarlimab was long-lasting and the adverse reactions were reported to be tolerable. The most common treatment-related AEs at level 3 or above were anemia (2.9%), colitis (1.9%) and diarrhea (1.9%).

Anti-PD-L1.

Atezolizumab. The NCT01375842 study by Liu *et al* (64) was the first to detail the use of atezolizumab as a single drug treatment for gynecological cancer. In the aforementioned study, all 15 patients with EC were treated with atezolizumab in the dose-expansion phase of the study (15 mg/kg atezolizumab, n=1; 1,200 mg atezolizumab, n=14). As of December 31, 2016, 2 patients showed a PR, 2 patients maintained SD, 9 patients had progressive disease and 2 patients were not evaluable. The ORR was 13.3% [95% CI, 1.7-40.5%]. However, all patients experienced ≥1 AE and 7 patients (46.7%) in the uterine cancer cohort developed treatment-related AEs. In the uterine cancer cohort, the most common treatment-related AEs of any grade were diarrhea (20.0%) and fatigue (13.3%), with no occurrence of treatment-related grade 4 or 5 AEs. It can therefore be suggested that atezolizumab is safe for patients with advanced EC and it may have certain clinical benefits in some patients.

Avelumab. Avelumab, another anti-PD-L1 immunosuppressant, has also shown promising activity in patients with dMMR EC. Konstantinopoulos *et al* (65) published the results of a phase II clinical trial (NCT02912572) with 33 patients that were divided into two cohorts, dMMR and pMMR. The co-primary endpoints were the ORR and PFS rate at 6 months (PFS6). The ORR in the dMMR and pMMR/non-POLE cohorts was 26.7 and 6.25%, respectively. In the dMMR cohort, there were 4 patients with objective responses (1 withCR and 3 with PR). The PFS6 was 40.0% in the dMMR cohort and 6.25% in the pMMR/non-POLE cohort. Of the 31 patients who started the regimen, 22 (71%) had treatment-related AEs of any grade, but there were no grade 4 and 5 treatment-related AEs in any cohort. The most common adverse reactions were fatigue (35.5%) and nausea (16.1%).

Durvalumab. Durvalumab is an IgG1 κ monoclonal antibody that binds to PD-L1 on tumor cells, blocking the interaction with PD-1 on T cells and antigen-presenting cells, thereby alleviating PD-1/PD-L1-mediated immunosuppression and allowing T cells to attack tumor cells (66). Results from the PHAEDRA study demonstrating the activity of durvalumab as a single agent in a dMMR and pMMR EC cohort were published in 2021 (66). The study included 71 patients with advanced EC, of which 36 were dMMR and 35 were pMMR. All patients received IV durvalumab at a dose of 1,500 mg every 4 weeks. The ORR of patients with dMMR was 47% (6 cases of CR and 11 cases of PR), while the ORR of patients with pMMR was 3% (1 case of PR). Furthermore, the mPFS time was 8.3 months in the dMMR cohort, while it was only 1.8 months in the pMMR cohort. A total of 14 patients reported immune-related AEs, most of which were grade 1 or 2, including hyperthyroidism, hypothyroidism, pneumonia and hepatitis.

In summary, the reported efficacy of immune checkpoint inhibitors as monotherapies in treating EC is considerable. However, the results of the aforementioned PD-1 and PD-L1 immunosuppressive drug clinical trials are different, which may be related to various factors, including the size of the samples, the genotype of the subjects and the choice of observation indicators. Therefore, if a large-scale clinical study on PD-1 and PD-L1 immunosuppressive drugs was conducted through a multi-center collaboration that followed a unified research scheme, jointly collecting study subjects and conducting an overall analysis, the clinical trial results would be more robust and reliable.

Immune checkpoint inhibitor-based drug combinations. As mentioned above, the use of immune checkpoint inhibitor monotherapy in EC is mainly limited to patients with dMMR or MSI-H mutations. However, patients with MSI-H/dMMR only account for 25-30% of cases and 70-75% of patients have microsatellite stability (MSS)/pMMR (47). The efficacy of single immune checkpoint inhibitor treatment in patients with MSS/pMMR is not optimal. Furthermore, with the increasingly widespread application of immunosuppressants and the complexity of immune response activation, immunosuppressive drug resistance is gradually increasing. Therefore, finding an improved treatment plan for patients with MSS/pMMR is required and researchers have adopted a joint strategy in the hope of achieving synergistic benefits and reducing the occurrence of primary or secondary drug resistance.

Immune checkpoint inhibitors and angiogenesis inhibitors. Lenvatinib is a kinase inhibitor against VEGFR1-3 and a small molecule targeted drug against angiogenesis (67). In a preclinical model, lenvatinib reduced the number of tumor-associated macrophages and increased the proportion of $CD8^+$ T cells, thereby inducing immune activation (67). In multiple mouse xenograft models, the combination of anti-PD-1 monoclonal antibody and levatinib had a more optimal antitumor activity compared with monotherapy using either drug (68). Therefore, pembrolizumab combined with lenvatinib was hypothesized to be an effective antitumor strategy and as such, KEYNOTE-146 (NCT02501096) aimed to study the safety and initial efficacy of the combined drugs in the treatment of a variety of advanced solid tumors (69). The phase IB component of the study established that the maximum tolerated dose and the recommended phase II dose was 20 mg levatinib orally once a day combined with 200 mg pembrolizumab intravenously every 3 weeks (69). A multi-center, open-label, single-arm, phase II trial further investigated the efficacy of lenvatinib plus pembrolizumab in patients with primary advanced or recurrent EC (70). Between September 10, 2015 and July 24, 2017, 53 patients were included in the analysis. Of these patients, 39.6% (21/53) reported an objective response at week 24 and 30% (16/53) experienced serious treatment-related AEs. In the final efficacy analysis, the median follow-up time for 108 patients was 18.7 months at the time of data cut-off (71). The resulting ORR at week 24

(ORR_{WK24}) of the 108 patients was 38% (41/108). Among these patients, 3 achieved CR and 38 achieved PR at week 24. In the subgroup analysis, the ORR_{WK24} of patients with MSS/pMMR (n=94) and MSI-H/dMMR (n=11) was 36.2% (95% CI, 26.5-46.7%) and 63.6% (95% CI, 30.8-89.1%), respectively. Regardless of the MSI status of the tumor, the median response-duration was 21.2 months, the mPFS time was 7.4 months and the mOS time was 16.7 months. Furthermore, 83/124 (66.9%) patients experienced grade 3 or 4 treatment-related AEs. The most common adverse reactions were hypertension, diarrhea, fatigue, decreased appetite, hypothyroidism and nausea. Based on the aforementioned studies, lenvatinib combined with pambrolizumab was approved by the FDA for the treatment of advanced EC that was not MSI-H/dMMR and had progressed following prior therapy.

A 2:1 randomized phase II clinical trial (NCT03367741) compared the efficacy of a cabozantinib and nivolumab combination (arm A) vs. nivolumab (arm B) in the treatment of recurrent EC (72). The primary endpoint of the study was PFS. The results demonstrated that the mPFS of arms A and B were 5.3 months (95% CI, 3.5-9.5) and 1.9 months (95% CI, 1.6-3.8), respectively. Furthermore, the ORR was 25% in arm A and 16.7% in arm B and the SD rate was 44.4 and 11.1%, respectively. Furthermore, the clinical benefit in arm A was significantly higher compared with that in arm B ($P<0.001$). The most common AEs in arm A were diarrhea (47.2%), elevated liver enzymes (44.4%), fatigue (38.9%), anorexia, hypertension and nausea (30.6%), which were mainly grade 1 or 2.

Further single arm phase II trials (NCT04042116 and NCT04157491) of anti-PD-1 drugs combined with other angiogenesis inhibitors (lucinib and anlotinib) for the treatment of EC are also under investigation at present (73).

Combination immunotherapy. Since any treatment may eventually result in drug resistance, there are ongoing efforts to study combined immunotherapy, which is a combination of immunosuppressive agents with different mechanisms.

A phase II study by Fumet *et al* (74) was the first trial to study a combination of olaparib and dual immunotherapy based on molecular screening. The study will aim to evaluate the effectiveness and safety of an olaparib/durvalumab/tremelimumab combination in patients with several types of solid cancer (n=213) that have at least one homologous repair gene mutation. Patients initially receive 300 mg olaparib twice per day. If there is no progress after receiving olaparib for 6 weeks, the patients receive olaparib and durvalumab (1,500 mg every 4 weeks) and tremelimumab (75 mg IV every 4 weeks) immunotherapy within 4 months. Patients are further administered durvalumab alone until the disease progresses, or patient death or intolerable toxicity occur or the patient/researcher decides to stop treatment.

There are currently additional early trials, such as the combination of nivolumab and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4; NCT03508570 and NCT02982486), for the treatment of advanced EC (75) and the combination or non-combination of nivolumab and indoleamine 2,3-dioxygenase inhibitors (BMS-986205; NCT04106414) (75).

Immune checkpoint inhibitors and chemotherapy. Preclinical studies have indicated that chemotherapy may generate immune stimulation, enhance the presentation of tumor cell-specific antigens and lead to cancer cells triggering immune responses or increasing their susceptibility to immune system attack (76,77). These mechanisms lay the biological foundation for the later clinical research design of using a combination of chemotherapy and immunotherapy to treat cancer. At present, there are a number of phase III trials of immunosuppressive agents combined with carboplatin and paclitaxel for the treatment of patients with advanced or recurrent EC, such as dostarlimab (RUBY; NCT03981796), atezolizumab (AtTEnd; NCT03603184) and pembrolizumab (GY018; NCT02549209) (75). Although these studies do not consider the MMR status when recruiting patients, differences will be assessed in a subgroup analysis of patients with MSI-H and MSS tumors. In addition, a phase III trial of lenvatinib with pembrolizumab vs. doxorubicin or weekly paclitaxel (NCT03517449) in the treatment of advanced EC and a first-line lenvatinib with pembrolizumab vs. carboplatin and paclitaxel chemotherapy (NCT03884101) trial are currently ongoing (75). To the best of our knowledge, there are currently no preliminary data reported on the efficacy of immunotherapy combined with chemotherapy in advanced EC. However, it is esteemed that their combination provides promising results for patients with advanced EC.

Other combinations. Radiotherapy is also an important means to treat malignant tumors. A number of clinical studies have reported that radiotherapy combined with immunotherapy has an acceptable toxicity (78) and enhances the immune response at the irradiated site (79,80). The PRIMMO study (NCT04214067) is an ongoing randomized phase II trial evaluating the efficacy of pembrolizumab combined with low-fraction radiotherapy and immunomodulatory mixtures (vitamin D, curcumin, lansoprazole, aspirin and low-dose cyclophosphamide) in patients with pretreated advanced uterine tumors (cervical or endometrial carcinoma and uterine sarcoma) (81). The main endpoint of the study is the ORR at week 26.

Netrin-1, a protein upregulated in >80% of uterine tumors, serves an important role in cancer progression by regulating cell apoptosis (82). NP137 is a monoclonal antibody targeting netrin-1 that may reduce resistance to chemotherapy (83). A phase IB/II clinical trial (NCT04652076) evaluating the combination of NP137 with pembrolizumab and/or chemotherapy in the treatment of locally advanced/metastatic endometrial or cervical cancer has recently been initiated (73).

6. Conclusions and perspectives

In previous years, immunotherapy has received increasing attention in antitumor therapy. When the immune function of the body functions in a healthy manner, cancerous cells can be eliminated by the immune response in time and most individuals do not develop any tumors. When cancerous cells evade surveillance and elimination by immune cells due to certain changes, tumors may occur (84). Immunotherapy is aimed at all aspects of tumor immunity, using the immune response of the patient to treat tumors, which is safer and more efficient than other treatment methods and may potentially become a new method for the

treatment of EC (85). However, following in-depth research on tumor immunotherapy, its drawbacks have also attracted attention. Indeed, an excessively enhanced immune response may damage normal tissues. For example, the gastrointestinal tract, endocrine glands, skin and liver are the organs most prone to immune-related AEs, while the central nervous system and cardiovascular, lung, musculoskeletal and blood systems are less involved (6). In addition, immune cells recognize tumor cells with a single target, low specificity and a weak killing effect. In previous studies, it was reported that immunosuppressive drug monotherapy has certain effects in the treatment of advanced EC, but the efficacy is not optimal (55-66). Therefore, the ongoing combined strategies of targeted therapy, other immunotherapeutic agents, chemotherapy and radiotherapy may change the therapeutic prospects of advanced EC. In addition, antiangiogenic agents and poly(ADP-ribose) polymerase, PI3K/AKT/mTOR, EGFR, MEK, cyclin-dependent kinase and Wee1 inhibitors have all demonstrated certain activities, generating promising preliminary data (86) and are therefore research areas requiring closer attention.

The prognosis of patients with late-stage recurrent EC is poor. Currently, the NCCN guidelines still consider the chemotherapy regimen of carboplatin combined with paclitaxel as the first-line treatment for recurrent disease (87). Pembrolizumab is also listed as a class 1 treatment option for MSI-H/dMMR endometrial tumors and it is recommended that MSI-H or dMMR testing are performed for recurrent endometrial tumors, if not previously tested. As aforementioned, the effective rate of traditional chemotherapy, such as paclitaxel and carboplatin in the treatment of patients with advanced EC, ranges from 7-14% (9-12), while PD-1/PD-L1 inhibitors have a significant therapeutic effect on MSI-H/dMMR ECs, with an ORR of ~50% (57,59). Therefore, after the patients are fully informed of the efficacy, adverse reactions, medical expenses of immunotherapy and other related content and agree to the application, the markers related to the immunotherapy of the patient (including MSI, MMR, TMB and POLE mutations) can be determined and finally, the most suitable individualized treatment plan for the patient can be chosen. In addition, further research is required to elucidate the resistance mechanism of immunotherapy and for the implementation of immunotherapy early in the first-line treatment of tumors. In summary, it is esteemed that immunotherapy can play an increasingly important role in the treatment of EC and act in combination with various treatment methods to prolong the survival period and improve the quality of life of patients.

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LW collected and analyzed data and drafted the original manuscript. LL analyzed the data and made modifications to the article. DH collected and analyzed data. YZ edited, reviewed and revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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