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Review

Immune microenvironment and molecular mechanisms in endometrial cancer: implications for resistance and innovative treatments

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Abstract
This review provides a systematic overview of the molecular mechanisms of endometrial cancer and its drug resistance, particularly involving the aberrant activation of some key signaling pathways. These molecular mechanisms significantly affect the therapeutic outcome of endometrial cancer by promoting tumor cell proliferation, anti-apoptosis, and drug resistance. The article also analyzes the critical role of the immune microenvironment in cancer drug resistance, focusing on the impact of immune cells, immune checkpoints, and hypoxic metabolic reprogramming on anticancer therapies. In recent years, immunotherapy and individualized therapy have shown promising clinical outcomes, especially in advanced endometrial cancer. This article summarizes recent advances in related therapeutic strategies and proposes emerging therapeutic strategies by targeting key pathways and modulating the immune microenvironment to overcome drug resistance and improve patient prognosis.

Keywords Endometrial cancer · Molecular mechanisms · Drug resistance · Immunotherapy · Tumor microenvironment · Immune checkpoint inhibitors · Precision medicine

1 Introduction

Endometrial cancer represents one of the most prevalent malignant neoplasms within the female reproductive system and is typically classified, based on the histological features, into endometrioid, serous and clear cell carcinomas [1] (Clinical actionability of molecular targets in endometrial cancer). Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) is a novel molecular classifier that combines mutation and protein expression analysis to help assess risk for more precise treatment [2]. Endometrial cancer is the most prevalent cancer in high-income countries with the highest incidence in North America [3]. In China, while the incidence of endometrial cancer remains relatively low, there has been a significant increase in recent years, mainly attributed to an increase in risk factors such as obesity and diabetes mellitus [4].Clinically, patients typically present with abnormal vaginal bleeding and pelvic pain. However, the absence of distinct early symptoms leads to late-stage diagnoses, complicating treatment and affecting survival rates [5].

The treatment of endometrial cancer mainly consists of traditional methods such as surgery, radiotherapy, and chemotherapy [6]. Surgery is usually the treatment of choice for early stage disease, and in recent years, minimally invasive surgery has gained significant prominence in the management of endometrial cancer [7, 8]. However, single surgery such

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as systematic lymphadenectomy is often ineffective in advanced cases, but their importance in diagnosis and staging should not be overlooked [9]. Although radiotherapy and chemotherapy improve patient survival, they are also associated with adverse effects and drug resistance [10]. In recent years, targeted therapies and immunotherapies have gradually become a research hotspot, and immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have demonstrated significant effectiveness in clinical trial [11]. For example, a clinical trial reported a 13% objective response rate (ORR) in patients with advanced endometrial cancer treated with pembrolizumab [12]. These emerging therapies present potential advancements in the prognosis of patients diagnosed with advanced endometrial cancer.

This review aimed to reveal the molecular mechanisms underlying endometrial cancer and the profound impact of the immune microenvironment on disease progression and drug resistance. Recent studies have clearly indicated that various mechanisms are involved in drug resistance among endometrial cancer cells through aberrant activation of key signaling pathways, genetic mutation, and modification of the tumor microenvironment. We explored how these resistance mechanisms affect the efficacy of existing treatments, particularly targeted therapies and immunotherapies. Simultaneously, this study assessed recent advances in relevant therapeutic strategies and suggested the possibility of emerging therapeutic strategies to address the challenges posed by drug resistance. By systematically analyzing the progress of the current research, this study provides a solid theoretical foundation for clinical applications to promote the early diagnosis and individualized treatment of endometrial cancer.

2 Key signaling pathways in drug resistance

2.1 PI3K/Akt/mTOR pathway

The PI3K/Akt/mTOR pathway is crucial for tumor cell proliferation, survival, and resistance to apoptosis and it plays a critical role in drug resistance in endometrial cancer [13]. Mutations in genes, such as PIK3CA, PTEN, and AKT1, can aberrantly activate this pathway, promoting tumor cell resistance to targeted drugs (Fig. 1A).

For example, the mutations in the PIK3CA gene increase the activity of PI3K and result in prolonged activation of the signaling pathways of Akt and mTOR, reinforcing properties of cell viability and anti-apoptotic [14]. In endometrial cancer cells, PIK3CA mutations are commonly associated with resistance to mTOR inhibitors. One study demonstrated that everolimus, a commonly used mTOR inhibitor, was significantly less effective against PIK3CA-mutant endometrial cancer cells and only showed some efficacy when combined with other targeted agents [15].

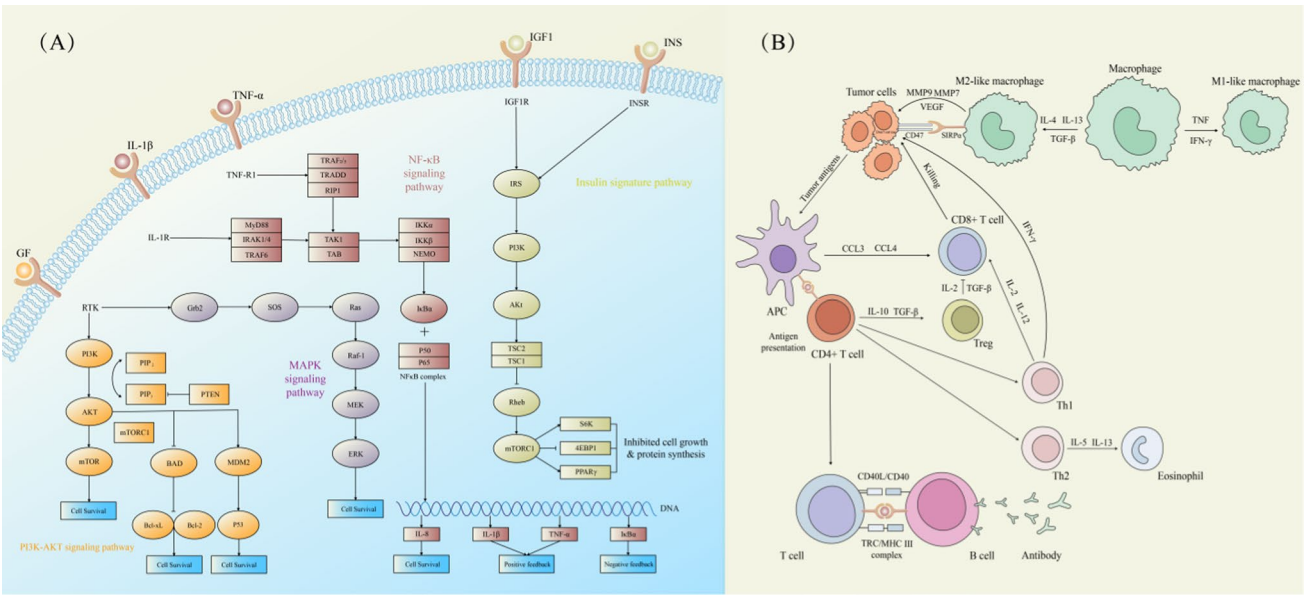

Fig. 1 Tumor molecular mechanisms and immune microenvironment. **A** Highlights the PI3K/Akt/mTOR, MAPK/ERK, NF-κB pathways and Insulin signature pathway, showing their roles in tumor cell survival and resistance. **B** Depicts the tumor immune microenvironment, including CD8 + T cells, Tregs, macrophages, and dendritic cells, and their interactions within the tumor context

PTEN is an oncogene, and its loss of function leads to aberrant activation of the PI3K/Akt/mTOR pathway, enhancing the proliferative capacity and anti-apoptotic properties of cancer cells [16]. PTEN mutations have been widely observed in endometrial cancer and are suggested to be an important factor in the development of resistance to mTOR inhibitors [17]. This overactivation of the PI3K/Akt pathway due to PTEN modification promotes cancer cell resistance to chemotherapy and targeted therapy [18].

Similarly, AKT1 mutations increase pathway activity, causing a conformational change in the Akt protein and resulting in sustained activity that activates downstream mTOR signaling. The response of these mutant endometrial cancer cells reduce their response to PI3K inhibitors is also reduced. For instance, Yu et al. found that ARQ 092 and ARQ 751, two highly potent selective inhibitors, effectively blocked AKT1-E17K phosphorylation [19].

In recent years, combination therapies targeting the PI3K/Akt/mTOR pathway have shown promise for reversing drug resistance. Combining an mTOR inhibitor with a PI3K inhibitor has been effective in reducing the activity of this pathway, thereby decreasing tumor cell resistance to the targeted drug. For example, a study found that LY3484356, a novel oral selective estrogen receptor degrader (SERD), combined with everolimus or alpelisib, significantly inhibited the proliferation and migration of endometrial cancer cells and enhanced drug sensitivity [20].

2.2 MAPK/ERK pathway

The MAPK/ERK signaling pathway is pivotal for cell proliferation and differentiation, and abnormal activation of this pathway is closely associated with drug resistance in many cancers [21]. Activation of the MAPK/ERK pathway significantly enhances the resistance of endometrial cancer cells to common chemotherapeutic drugs such as cisplatin (DDP) and paclitaxel. Paucarmayta et al. found that progesterone-calcitriol enhances cancer cell sensitivity to DDP by inhibiting the MEK/ERK pathway [22]. Additionally, KRAS mutations often result in the abnormal activation of the MAPK/ERK pathway. This mutation is commonly observed in endometrial cancer [23]. Skoulidis et al. found that sotorasib showed notable efficacy in the treatment of KRAS G12C mutant non-small cell lung cancer (NSCLC), with an objective response of 37.1% (95% [CI] 28.6–46.2) [24].

Drug resistance in endometrial cancer can be partially reversed by inhibiting ERK activity. Zhao et al. found that sirtuin 2 decreased the sensitivity of endometrial cancer cells to cisplatin and paclitaxel by activating the MEK/ERK signaling pathway [25]. Kanawat Wiwatchaitawee et al. found that PD98059 (a reversible MEK inhibitor) effectively inhibited ERK signaling and showed good synergy with chemotherapeutic agents in clinical trials [26]. In another study, combination therapy with trametinib (an MEK inhibitor) and dasatinib (an EphA2 inhibitor) significantly inhibited the proliferation of endometrial cancer cells and reduced their drug resistance, showing the potential for treating drug-resistant tumors [27]. Additionally, another study showed that the MEK1/2 inhibitor cobimetinib, in combination with entrectinib (a tropomyosin-related kinase A inhibitor), dramatically enhanced the inhibitory effect of entrectinib on the RAF/MEK/ERK signaling pathway, while also preventing the reactivation of pERK1/2 signaling [28].

2.3 NF-κB signaling pathway

The NF-κB signaling pathway is commonly activated in the inflammatory microenvironment and has been shown to be a key factor in tumor progression and drug resistance in various cancers [29, 30]. Inflammatory factors such as TNF-α and IL-6 activate the NF-κB signaling pathway, which can induce anti-apoptotic gene expression in tumor cells. This enhances the anti-apoptotic ability of tumor cells and makes them resistant to targeted drugs and immunotherapy [31]. Xiaohong Ma et al. found that fatostatin enhances the sensitivity of endometrial cancer cells to progesterone by inhibiting the SREBP1-NF-κB pathway. Additionally, Yiran Liang et al. reported that heat shock protein beta-1 (HSPB1) could inhibit chemotherapy-induced ferroptosis by promoting the activation of NF-κB signaling pathway [30].

Recently, several studies have reported novel strategies to enhance the sensitivity of cancer chemotherapy using NF-κB inhibitors. For example, Gege Chen et al. identified DCZ0415, a small molecule inhibitor that targets TRIP13, which inhibits NF-κB signaling thus overcoming multiple myeloma drug resistance [32]. ChunYu Chen et al. found that Ovatodiolide (OVA) suppressed mechanistic target of rapamycin kinase(mTOR) and NF-κB signaling pathway in endometrial cancer, with good therapeutic efficacy when OVA was used alone or in combination with other drugs [33]. Combining

NF-κB inhibitors with standard chemotherapeutic agents represents a promising therapeutic strategy with significant potential for reversing resistance. These findings provide an important theoretical basis for the development of novel therapeutic strategies.

3 Immune microenvironment and endometrial cancer drug resistance

3.1 Immune cells

The tumor microenvironment (TME) of endometrial cancer is replete with a variety of immune cells, including CD8 + cytotoxic T cells, regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and dendritic cells (DCs), which play complex and pivotal roles in regulation of tumor growth and response to therapy (Fig. 1B).

3.1.1 T cells

CD8 + cytotoxic T cells serve as the core of the antitumor immunity and directly mediate cytotoxic responses by recognizing tumor antigens. Patel et al. found a significant increase in the number of CD8 + T cells in endometrial cancer, with CD103- CD8 + T cells playing a major cytotoxic role [34].This finding conflicts with that of a 2016 study by Workel et al., who found that high infiltration of CD103 + cells contributes to an improved prognosis in patients with endometrial adenocarcinoma. This discrepancy may be related to the infiltration of CD103 + and CD8 + T cells [35]. Additionally, An et al. found that KIF2C was negatively correlated with the level of CD8 + T cells and that treatment combined with an anti-PD1 antibody enhanced the anti-tumor effect of CD8 + T cells, suggesting that KIF2C may be a potential target for EC therapy [36].

In contrast, the function of Tregs is induced in TME is induced by the secretion immunosuppressive factors (e.g., TGF-β and IL-10), which create an immunosuppressive microenvironment conducive to tumor survival [37]. Junxiu Liu et al. found that BCHE is expressed at low levels in endometrial cancer and that Tregs negatively correlate with BCHE expression [38]. This negative correlation suggests that BCHE may have a regulatory role in the development and progression of endometrial cancer and indicates its potential as a novel target for immunotherapy.

A previous study has shown that PTEN deficiency is associated with resistance to Anti-PD-1 Checkpoint Blockade Therapy in cancer [39]. Francisco Exposito et al. further found that tumor cells secrete cytokines such as TGF-β and CXCL10, which promote promote the differentiation of CD4 + T cells to Treg, thus suppressing anti-tumor immunity [40]. Therefore, a combination of therapeutic measures such as TGF-β inhibitors and TLR agonists, might restore the efficacy of PD-1 therapy in Pten-deficient tumors against.

3.1.2 Tumour-associated macrophages

Tumor-associated macrophages, particularly M2-type macrophages, play a crucial roles as tumor supports in the TME by promoting tumor growth and drug resistance. By secreting anti-inflammatory factors such as IL-10 and the angiogenic factor VEGF, M2-type TAMs not only create an environment conducive to tumor cell survival but also significantly affect the efficacy of the anti-angiogenic drug bevacizumab. Notably, the expression of macrophage migration inhibitory factors (MIF) is reduced in bevacizumab-resistant glioblastomas, leading to the accumulation of M2-type tumor-promoting macrophages.Notably, downregulation of MIF expression was realized in bevacizumab-resistant glioblastomas and resulted in the accumulation of M2-type tumor-promoting macrophages [41].These M2 macrophages are localized at tumor margins and enhance tumor angiogenesis and invasiveness, thereby promoting tumor growth. Wang et al. found that silencing BMAL1 promotes the polarization of macrophage from M1-type to M2 by modulating the LDHA/lactate axis, which could enhance GBM sensitivity to bevacizumab [42].

Additionally, in a study on endometrial cancer, Sengal et al. found that the FGFR inhibitor BGJ398 reduced M2 type macrophage infiltration [43]. This supports the clinical use of FGFR inhibitors in the treatment of endometrial cancer. Zhou et al. discovered that the overexpression of the long-chain non-coding RNA NIFK-AS1 regulates macrophage polarization

in the tumor immune microenvironment by downregulating the miR-146a-induced Notch1 signaling pathway [44]. This provides new molecular targets for interventions in tumor progression and for improving the efficacy of immunotherapy.

3.1.3 Dendritic cells

Recent studies have revealed the unique role of DCs in the mechanism of drug resistance in endometrial cancer and that the functional inhibition of DCs impairs the overall anti-tumor immune efficiency. Jia et al. found that the high expression of microRNA-155 (miR-155) reduced the production of the pro-inflammatory factor IL-12 in DCs, which prevented the differentiation of Th1 cells and diminished the anti-tumor response of the immune system [45]. It is evident that targeted inhibitors of miR-155 may serve as an effective immunotherapeutic strategy to further enhance the anti-tumor activity of DCs, thereby improving the therapeutic outcome of endometrial cancer. In addition, a clinical study found that a DC vaccine combined with carboplatin and paclitaxel chemotherapy had a safe profile and immunological efficacy in patients with metastatic endometrial cancer [46]. This suggests that chemotherapy combined with an immunotherapeutic strategy targeting DCs has a positive effect on the reduction of drug-resistant endometrial cancer.

3.2 Immune checkpoints

The PD-1/PD-L1 pathway is one of the most common immune checkpoints in endometrial cancer, allowing cancer cells to evade immune surveillance by inhibiting T cell activity. Gao et al. found that endometrial cancer cells with SPOP mutations were ineffective at degrading IRF1 via the ubiquitin-proteinase pathway, leading to the upregulation of PD-L1. This upregulation inhibits T cell activity and anti-tumor responses [47].

A clinical study by Oaknin et al. found durable anti-tumor activity and a manageable safety profile for dostarlimab in EC patients with DNA mismatch repair defects (dMMR) or microsatellite instability-high (MSI-H). The ORR was 43.5% in dMMR/MSI-H patients and 14.1% in MMRp/MSS patients [48]. Another clinical study showed that pembrolizumab, in combination with carboplatin and paclitaxel, demonstrated significant therapeutic benefits in patients with advanced or recurrent endometrial cancer. The 12-month progression-free survival rate after adding pembrolizumab reached 74%, compared with 38% in the control group (hazard ratio HR = 0.30, 95% CI 0.19–0.48, $P < 0.001$) [49]. This suggests that combination therapy enhances the immune response of patients, thereby improving the efficacy of conventional chemotherapeutic agents and providing new treatment options.

3.3 Hypoxia and metabolic reprogramming

Hypoxia, one of the hallmark features of the TME, plays a crucial role in the drug resistance mechanism in endometrial cancer through the activation of hypoxia-inducible factor (HIF-1α). HIF-1α exhibits increased stability under hypoxic conditions [50], and its activation regulates various pathways, and its activation regulates various cancer cells to adapt to unfavorable microenvironment. Pingping Su et al. found that HIF-1α adapted to the hypoxic environment by interacting with ERRα, which enhanced the anti-apoptotic ability and resistance to chemotherapeutic agents in endometrial cancer cells [51]. Shasha Yin et al. found that hypoxic conditions increase PD-L1 expression through activation of HIF-1α and HIF-2α, which promotes self-renewal and immune escape of endometrial cancer stem cell-like cells (ECSCs) [52]. Moreover, Kyu Kwang Kim et al. discovered that tetrathiomolybdate (TM) increased available cellular oxygen by inhibiting mitochondrial complex IV activity, thereby promoting the degradation of HIF-1α. Additionally, TM decreased the expression of HIF-1α target genes such as PDK1 and GLUT1 and significantly inhibited the secretion of the angiogenic factor VEGF. This suggests a new strategy for inhibiting the HIF-1α pathway to limit tumor angiogenesis [53].

4 Emerging therapeutic strategies

4.1 Histology-based precision therapy

Individualized medicine is becoming a significant focus in the treatment of endometrial cancer, utilizing integrated genomic, proteomic, and metabolomic analyses to develop precise treatment plans. Genomic analyses can identify mutations associated with therapeutic sensitivity and aid in the selection of appropriate targeted drugs. For example, patients with PIK3CA mutations may be more suitable for treatment with PI3K inhibitors [54], and a combination of

everolimus and letrozole may be more suitable for patients with endometrioid EC with CTNNB1 mutations [55]. Additionally, constructing an immune-related risk score model by studying pivotal immune-related genes will be useful for guiding immunotherapy and predicting endometrial cancer prognosis [56–58]. The integration of multi-omics data forms the scientific basis for individualized treatment of endometrial cancer and facilitates the development of more precise and effective treatment strategies.

4.2 Dynamics of new drug development and clinical trials

With a deeper understanding of endometrial cancer, several new drugs and combination therapies are emerging, particularly targeted immunotherapies, which have shown great potential. This study showed that the addition of pembrolizumab to standard chemotherapy was effectively improved the outcomes of patients with advanced or recurrent EC [49]. Additionally, the combination of dostarlimab and carboplatin-paclitaxel significantly prolonged progression-free survival (PFS) in such patients [59]. For patients with advanced EC, combination therapy using lenvatinib and pembrolizumab has become an effective treatment option for patients with advanced EC [60]. For patients with MSI-H/dMMR, pembrolizumab monotherapy demonstrated long-lasting antitumor effects by inhibiting tumor progression [61]. This table summarizes multiple emerging therapies that offer new possibilities for the individualized treatment of patients with EC (Table 1).

5 Discussion

In recent years, significant progress has been made in the study of endometrial cancer, particularly concerning its molecular mechanisms, immune microenvironment, and emerging therapeutic strategies. Through in-depth studies of key signaling pathways (e.g. PI3K/Akt, MAPK and Wnt/β-catenin), researchers have revealed various molecular mechanisms that promote the development of endometrial cancer [67–69]. Moreover, the characteristics of the immune microenvironment have received increasing attention for tumourigenesis, progression, and therapeutic response, and clinical data have shown that the type of immune cells infiltrated by the tumour is closely associated with patient prognosis [70, 71]. Meanwhile, results from clinical trials of novel targeted therapies and immunotherapies have shown promising efficacy, especially in patients with specific molecular markers [72–74]. These studies provide new perspectives and possible solutions to improve the diagnosis, treatment and prognosis of endometrial cancer.

Future studies should explore the interactions between the molecular mechanisms of endometrial cancer and immune microenvironment. Understanding the specific roles of different types of immune cells in the tumor microenvironment and their effects on tumor proliferation, metastasis, and drug resistance will provide an important basis for the development of more effective immunotherapy strategies. Additionally, with advancements in single-cell sequencing technology, researchers can more comprehensively resolve the heterogeneity of the tumor microenvironment, thereby providing a more precise basis for individualized treatment [75–77].At the same time, the importance of rare endometrial cancers, such as EC with IM/diff, in tumor aggressiveness should not be underestimated. Their identification through morphology and immunohistochemistry techniques is particularly vital [78, 79].

Effects of the microbiome on endometrial cancer have only recently been appreciated [80–83]. Moreover, the analysis of the effects of the microbiome on anti-tumor immune responses might also present new perspectives in the development of novel therapeutic strategies [84]. Future studies could integrate multi-omics data to explore the interactions between the microbiome, genome, and immune microenvironment, thereby advancing individualized treatment of endometrial cancer.

Table 1 Endometrial cancer clinical trials

ClinicalTrials.gov number	Trial stage	Number of patients	Treatment programs	Therapeutic effects	References
NCT03517449	Phase III	A total of 155 patients were enrolled in the study, with 66 pMMRs and 11 dMMRs in the lenvatinib + pembrolizumab group; 68 pMMRs and 10 dMMRs in the TPC group	Lenvatinib + Pembrolizumab: lenvatinib 20 mg po qd + pembrolizumab 200 mg IV q3w; TPC: doxorubicin 60 mg/m2 IV q3w or paclitaxel 80 mg/m2 IV qw (3 weeks on/1 week off)	mPFS:lenvatinib + pembrolizumab 7.2 months;TPC 3.7 months; HR 0.64 (95% CI0.44–0.94) mOS: lenvatinib + pembrolizumab 20.6 months; TPC: 12.2 months; HR 0.61 (95% CI 0.41–0.90) ORR: lenvatinib + pembrolizumab 39%; TPC 21%	[62]
NCT03015129	Phase II	A total of 75 recurrent or persistent EC patients were enrolled in the study, 37 in the Durvalumab group and 38 in the Durvalumab + Tremelimumab group	Durvalumab: durvalumab 1500 mg IV q4w Durvalumab + Tremelimumab: Durvalumab 1500 mg IV q4w + 75 mg tremelimumab IV q4w for up to 4 cycles, and then continue durvalumab 1500 mg IV q4w	ORR:Durvalumab 10.8%; Durvalumab + Tremelimumab 13.5% mPFS: Durvalumab 7.4 weeks; Durvalumab + Tremelimumab 7.9 weeks	[63]
NCT02454972	Phase II	A total of 73 patients (regardless of subtype)were enrolled in the study	All patients: lurbinectedin 3.2 mg/m^2 IV q3w	ORR(95%CI) 11.3% (5.0–21.0%) mPFS(95%CI) 2.6 (1.4–4.0)	[64]
NCT04157491	Phase II	A total of 23 recurrent or advanced EC patients were enrolled in the study	All patients: sintilimab 200 mg IV on day 1 q3w and 12 mg anlotinib(Toxicity was managed with interruptions of study drugs or dose reduction of anlotinib) po on days 1–14 q3w	OR(95% CI): (73.9) (51.6–89.8) PFS ≥ 6 months(95% CI):76.7 (52.7–89.6) PFS ≥ 12 months(95% CI): 57.1 (33.6–75.0)	[65]
NCT03192059	Phase II	A total of 25 patients (regardless of subtype)were enrolled in the study	All patients: the immunomodulatory five-drug cocktail (50 mg cyclophosphamide, 325 mg aspirin, 180 mg or 30 mg lansoprazole (dose alternating weekly), 50 µg vitamin D, and 2 g turmeric phytosome qd for 2 weeks) + pembrolizumab(200 mg IV q3w for six cycles) + SBRT [24 Gy was delivered to a single tumor lesion in three fractions over five days during the first cycle of pembrolizumab (study days 15, 17, and 19)]	OR(95% CI) 12.0 (3.4–28.2)	[66]

pMMRs mismatch repair proficient, dMMR mismatch repair deficien, TPC reatment of physician's choice chemotherapy, mPFS median progression-free survival, HR hazard ratios, CI confidence interval, mOS median overall survival, ORR overall response rate, SBRT Stereotactic body radiotherapy

Author contributions YC, LJ, LZ, HC and QW conceived the study. YC, LJ and LZ drafted the manuscript. YC performed the literature search and collected the data. HC and QW helped with the final revision of this manuscript. All authors reviewed and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests Hao Chi has a position on editorial board of Discover Oncology, and was not involved in the review or decisions related to this manuscript. The other authors declare no competing interests.

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