Abstract. Immunotherapy is an emerging clinical approach that has gained traction over the past decade as a novel treatment option for lung cancer and melanoma. Notably, researchers have made marked improvements in the treatment of endometrial cancer (EC), and potential immune responses have been identified in patients with EC, thereby offering the possibility of exploring immunotherapy for EC. Nevertheless, various needs remain unmet, and immunotherapy applications in EC have yielded limited success, as only a minority of patients exhibited a clinical response. Therefore, further understanding of immune dysfunction associated with EC is still required. The present review describes recent findings regarding the immunosuppressive microenvironment of EC, with emphasis on immune evasion mechanisms and immunotherapy in EC.

1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in the developed world. The latest estimates indicated that there were 61,880 new cases and 12,160 EC-related deaths in 2019 in the USA (1). Obesity, hypertension and diabetes are the major risk factors for the development of EC in developed nations (2,3). Furthermore, Lynch syndrome is known to lead to the development of EC (4,5). In 1983, EC was first classified into the type I and II subgroups based on clinicopathological characteristics. Type I EC represents the most common form (70-80%). At least 90% of tumors express estrogen receptor (ER)-α moderately or strongly. By contrast, type II EC is estrogen-independent and predominantly represents serous carcinoma (6-8). However, this histological classification of EC has its limitations, such as poor reproducibility and overlapping morphological and immunohistochemical features (9,10). By performing comprehensive genomic analysis, The Cancer Genome Atlas program, which was first funded by the National Cancer Institute, aimed to classify EC on the basis of survival outcomes. The percentage of cases found for each type were as follows: i) Polymerase ε (POLE) ultramutated, 7%; ii) microsatellite instability (MSI) hypermutated, 30%; iii) copy-number low (microsatellite stable), 65%; and iv) copy-number high
developed a more peripheral blood from patients with endometrioid grade 3 EC, patients with EC than in the endometrium of control subjects. The number of CD8 T cells was lower in the endometrium of patients with EC (24). In another study involving 90 patients with EC, Kondratiev et al (25) demonstrated that an increase in the number of CD8+ T cells at the invasive border of the tumor epithelium is a favorable prognostic factor for patients with EC. Patients with a higher number of intraepithelial CD8+ lymphocytes at the invasive border of the tumor epithelium had improved overall survival (OS) time compared with patients with a lower number of intraepithelial CD8+ lymphocytes. Survival analysis demonstrated that cancer stage, vascular invasion, tumor grade and the number of intraepithelial CD8+ lymphocytes at the invasive border were independent predictors of OS time (25).

Regulatory T cells (Tregs). Chang et al (26) studied 57 patients with stage I-IV EC and observed that the CD4+CD25+ T cell population was considerably larger in tumor-infiltrating lymphocytes (TILs) than that in peripheral blood lymphocytes (PBLs). Correlation analysis suggested that the upregulation of CD4 and CD25 expression in T cells in the cancer microenvironment was positively associated with high tumor grade, stage and myometrium invasion (26). Forkhead box P3 (Foxp3) expression in CD4+CD25+ Tregs is lower in PBLs than in TILs (26). Additionally, both granzyme B and perforin are rarely expressed in peripheral Tregs, but are widespread in Tregs in the tumor milieu (26). However, CD8+ cytotoxic T lymphocytes (CTLs), derived from PBLs, express higher levels of granzyme B and perforin than TILs, and T helper 1 cytokines and cytotoxic molecules are simultaneously increased in CD8+ CTLs, suggesting that, in the EC microenvironment, Tregs restrict CD8+ T cell activity in a granzyme B- and perforin-dependent manner (26). Low levels of both T helper 1 cytokines and cytotoxic enzymes contribute to the Treg-mediated inhibition of tumor clearance (26). Similar results were also obtained by Yamagami et al (27), who reported that the CD4+Foxp3+ cell count and CD4+/CD8+ ratio were novel prognostic factors for EC.

Macrophages. Macrophages, which can be polarized to the M1 (classical) or M2 (alternative) phenotypes, are one of the most abundant stromal immune cell types. In the tumor microenvironment, tumor-associated macrophages (TAMs) polarize to the M2 phenotype, which promotes immunosuppression, tumor progression and metastasis (28-30). The frequency of CD68+ macrophages is higher in the epithelial and stromal cells of type I and II EC than in those of the benign endometrium (31). Furthermore, patients with EC who have high CD68+ macrophage counts in the intra-tumoral border have worse progression-free survival (PFS) and OS time than patients with low CD68+ TAM density (32). Weber et al (33) demonstrated that the density of CD163+ M2 macrophages increased to a high level in the advanced stages of endometrioid adenocarcinoma of the uterus. Consistent with these findings, Kübler et al (34) reported that there is a positive association between the expression of TAMs and advanced stage, higher tumor grade, lymphovascular space invasion and lymph node metastasis (LNM) in type I EC. Furthermore, TAMs are independently associated with recurrence-free survival and OS in type I EC (34).
Natural killer (NK) cells. NK cells are effector cells involved in antitumor and antiviral innate immune responses. NK cell activation is impaired in the tumor microenvironment, including the EC microenvironment. Garzetti et al (35) suggested that locally advanced stage I and II ECs had significantly lower mean values of NK cell activity compared with healthy controls. Furthermore, a decrease in NK cell activity increased the depth of myometrial tumor invasion (35). NK cell activity also diminished with increased nuclear grade in stage I EC. In another study involving 40 patients with stage I EC who underwent radical surgery, NK cell activation was negatively associated with histopathological features of stage I EC, including myometrial tumor invasion and proliferating cell nuclear antigen immunoreactivity (36). Recently, Versluis et al (37) suggested that the upregulation of human leukocyte antigen (HLA)-E predicted improved disease-free survival and disease-specific survival time in EC. The number of NKp46 positive cells predicted a good clinical outcome, when the HLA-E levels were upregulated. However, the prognosis was poor when HLA-E levels were normal (Hazard ratio, 13.4; 95% confidence interval, 1.70-106.14).

Dendritic cells (DCs). DCs are a major part of the tumor microenvironment and serve an essential role in antitumor immunity by processing and presenting antigens to antigen-specific T cells. Disruption of DC activity is associated with EC progression (38). DC invasion has been observed in endometrial endometrioid adenocarcinoma (38). The DC markers S100-DR and HLA-DR have functions related to the delay of tumor progression and LNM in EC. Jia et al (40) reported that the expression levels of CD80, CD86 and CD40 on DCs in the normal human endometrium were significantly higher than those on DCs in endometrioid adenocarcinoma. Morphological differences have also been observed between tumor-infiltrating DCs and those in the normal human endometrium. These findings suggested that the morphological differences and low expression levels of CD80, CD86 and CD40 on DCs could reflect functional changes in tumor-infiltrating DCs, affecting antigen uptake and presentation, thereby possibly promoting tumor immune escape.

B lymphocytes and others. Zinovkin and Pranjol (41) studied 82 patients with endometrioid adenocarcinoma at stages I-III and demonstrated that the downregulation of lineage-specific markers in T lymphocytes (CD3), NK cells (CD57) and macrophages (CD68), and an increased expression of markers for tumor-associated B lymphocytes (CD20) and dendritic cells (S100) are associated with poor survival outcomes in EC.

**Table I. Immunosuppressive microenvironment in EC: Cell-mediated approach.**

| Cell type       | Regulation | Specimen           | Clinical application                                                                                                                                                                                                 | Refs. |
|-----------------|------------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| CD8+ T cells    | Down       | Blood and tumor tissue | The presence of intraepithelial CD8+ lymphocytes at the invasive border are an independent predictor of survival in EC.                                                                                              | (23,24) |
| Treg cells      | Up         | Blood and tumor tissue | The presence of CD4+CD25+ T cells in the EC milieu is associated with the tumor grade, stage and myometrium invasion. CD4+Foxp3+ count and CD4+ Foxp3+/CD8+ ratio are novel prognostic factors for EC. | (25,26) |
| Macrophages     | Up         | Tumor tissue        | Worse PFS and OS time are observed in patients with high CD68+ density at the invasive margin. The number of TAMs strongly correlate with advanced stages, higher tumor grade, LVI and LNM, and are independently associated with recurrence-free survival and OS in type-I EC. | (31-33) |
| NK cells        | Down       | Blood and tumor tissue | Decrease in NK cell activity is associated with the depth of myometrial invasion. NK cell activity is related to myometrial invasion and immunoreactivity of proliferating cell nuclear antigen in stage I EC. The number of NK cells and HLA-E expression are associated with EC survival and prognosis. | (35,36,38) |
| Dendritic cells | Down       | Tumor tissue        | Dendritic cell markers S100 and HLA-DR have functions related to the delay of tumor progression and LNM in EC.                                                                                                                                                       | (39-41) |
| B lymphocytes   | Up         | Tumor tissue        | Low expression levels of markers for tumor-associated T lymphocytes (CD3), NK cells (CD57) and macrophages (CD68), and an increased expression of markers for tumor-associated B lymphocytes (CD20) and dendritic cells (S100) are associated with poor survival outcomes in EC. | (42) |

EC, endometrial cancer; HLA, human leukocyte antigen; PFS, progression-free survival; OS, overall survival; TAMs, tumor associated macrophages; LNM, lymph node metastasis; LVI, lymphovascular space invasion; NK, natural killer.
cancer-associated fibroblasts (42) and adipocytes (43) serve an important role in the genesis of an immunosuppressive microenvironment and in the malignant progression of hyperplasia, their functions in EC need to be studied further in the future. Cell-mediated mechanisms are summarized in Table I.

**Molecular targets**

**Programmed cell death-1 (PD-1)/PD-1 ligand-1 (PD-L1) and PD-L2.** The B7 family of immune checkpoint inhibitors is divided into three subgroups: Group I consists of B7-1, B7-2, CD28, cytotoxic T-lymphocyte-associated protein 4 and B7H, group II includes PD-1/PD-L1/PD-L2, and group III includes B7-H3, B7-H4, HERV-H LTR-associating 2, and transmembrane and immunoglobulin domain-containing protein 2. The members of the B7 family serve a critical role in the immune response (44). PD-1 was first discovered in 1992 and is expressed on the surface of T cells (45). PD-1 has two known ligands, PD-L1 and PD-L2 (46). PD-L1, which has been extensively studied over the last few years, is the most well-known immune checkpoint inhibitor (47). Overall, 67-100% of primary, recurrent and metastatic EC cases express PD-L1 (48). Mo et al (49) suggested that PD-1, PD-L1 and PD-L2 expression in all tumor-infiltrating immune cells is more frequent in moderately and poorly differentiated EC and non-endometrioid EC than in well-differentiated EC and endometrioid EC. Recently, Kim et al (50) proposed the prognostic significance of PD-1 and PD-L1 in patients with EC, and indicated that high PD-L1 levels were an independent adverse prognostic factor for PFS, especially for subgroups of patients with an MSI mutation. Analysis of immune markers suggested that high PD-L1/CD8 and PD-L1/PD-1 ratios were independently positively associated with shorter PFS times.

**B7-H3 and B7-H4.** B7-H3 and B7-H4, two novel members of the B7 family, have been suggested to serve an immune function in the tumor microenvironment (51). Brunner et al (52) studied 99 patients with type I or II primary EC and observed that patients with advanced tumors had markedly higher B7-H3 levels than patients with low-grade tumors. Additionally, expression analysis of B7-H3 in the vascular endothelium of the tumor tissue suggested a positive association with EC grade. Furthermore, there was a strong association between B7-H3 expression in tumor cells and frequency of CD8+ positive TILs. Univariate survival analysis indicated that B7-H3 overexpression in cancer cells was associated with shortened OS time (52). Similarly, B7-H4 was upregulated in hyperplastic and malignant endometrial epithelium, and associated with the frequency of T cells, suggesting that B7-H4 overexpression reflects more aggressive EC, leading to EC tumor cell evasion (53). Additionally, a recent study indicated that B7-H4 expression was consistent across the various molecular subtypes of EC, suggesting that B7-H4 expression is independent of EC grade, histological type and infiltrating-immune cell type (54).

**Indoleamine 2,3-dioxygenase (IDO).** IDO is an enzyme that catalyzes the metabolism of the essential amino acid tryptophan in the initial and rate-limiting steps of the kynurenine pathway (55). Accumulating evidence has indicated that cancer tissue contains higher IDO levels than normal tissue (55). Ino et al (56) reported that high IDO expression in EC cells was present in 37/80 cases and was positively associated with surgical stage, myometrial invasion status, lymphovascular space involvement and LNM, but not with histological grade. Patients with EC expressing high levels of IDO had significantly worse PFS and OS time than patients with EC with low or no IDO expression. Multivariate analysis has suggested that IDO expression is an independent predictor of PFS (56). Furthermore, high levels of IDO in EC correspond to a low density of TILs and NK cells (57,58), and high levels of PD-L1 (59).

**HLA.** The HLA class I system serves an important role in the tumor immune response. This system comprises the classical HLA-A, -B and -C antigens, and the non-classical HLA-E, -F and -G antigens (60). Cancer cells can escape the CTL response by inhibiting HLA class I molecules (61,62). de Jong et al (63) reported the loss of HLA-A and/or HLA-B/C in 41.3% of patients in a study conducted on a cohort of 486 patients with sporadic endometrioid EC. Furthermore, the downregulation of HLA-B/C has been observed to occur more frequently in high-grade EC (63). Barrier et al (64) demonstrated that HLA-G protein was localized in the glandular epithelium and expressed in a substantial proportion of endometrial adenocarcinoma cases. However, overexpression of HLA-G in EC is not associated with clinical variables, disease-free survival or disease-specific survival (65). Non-classical HLA-G comprises four membrane-bound isoforms (HLA-G1 to HLA-G4) and three soluble isoforms (HLA-G5 to HLA-G7) (66). All HLA-G isoforms are detectable in the early and advanced stages of EC (67). The plasma levels of soluble HLA-G are significantly higher in patients with EC compared with that in healthy individuals. Additionally, soluble HLA-G5 molecules are more frequently observed than membrane-bound HLA-G1 molecules in patients with EC (67). Notably, the level of soluble HLA-G is higher in the early stages of EC compared with that in high-grade EC (67).

**Receptor-binding cancer antigen expressed on SiSo cells (RCAS1).** RCAS1 is expressed on immune cells and serves as a ligand for a receptor of RCAS1 present on various human cell lines and normal peripheral lymphocytes such as T, B and NK cells (68,69). In hepatocellular carcinoma and pancreaticobiliary cancers, high levels of RCAS1 result in aggressive tumor behavior in humans, widely invasive type more frequently overexpressed RCAS1 than the minimally invasive type, and the incidences of RCAS1 overexpression increased with carcinoma dedifferentiation (70). Sonoda et al (71) was the first to report that the expression levels of RCAS1 were higher in endometrioid adenocarcinoma than in the normal and hyperplastic endometrium, and that RCAS1 exhibited significantly higher expression in grade III tumors than in grade I or II tumors. By contrast, RCAS1 expression is independent of clinical stage, myometrial invasion status, lymph-vascular space invasion and LNM in EC (71). Subsequently, the same authors (72) studied 147 patients with uterine EC and demonstrated that RCAS1 was expressed in 106 patients. Furthermore, 30/147 patients exhibited RCAS1 overexpression, which was positively associated with age at surgical resection, cancer stage, extent of myometrial invasion and positive peritoneal cytology results. Additionally, RCAS1 expression and metastasis were clinically
significant predictors of OS according to multivariate analysis (72). Recently, Szubert et al (73) suggested that high levels of RCAS1 in post-surgery serum are an independent predictor of shortened OS time in patients with EC.

Cyclooxygenase-2 (COX-2). COX is the rate-limiting enzyme in the synthesis of prostaglandins. COX exists both as a constitutively expressed isoform (COX-1) and a regulated isoform (COX-2) (74). COX-2 enables tumor cells to escape immunological surveillance (75,76). Ohno et al (77) studied 70 patients with EC and proposed that COX-2 overexpression was positively associated with EC stage and myometrial invasion status. There was also an inverse association between the levels of COX-2 and the frequency of CD8+ T cells in tumor cells. Furthermore, univariate analysis indicated that COX-2 levels were predictive of EC recurrence (77). A previous study demonstrated that patients with MSI-positive EC and high COX-2 expression had a worse prognosis than patients with MSI-positive EC and low COX-2 expression (78).

Fas and Fas ligand (FasL). Fas (CD95) and its ligand FasL are expressed in various types of cancer and have been implicated in immune evasion mechanisms in cancer cells (79). In a previous study, Fas mRNA expression was markedly lower in EC tissue, compared with that in normal endometrial tissue. However, no significant difference in FasL mRNA expression was detected (80). Jia et al (81) reported that Fas expression was significantly lower in tumor-infiltrating DCs and significantly higher in endometrioid adenocarcinoma than in the normal endometrium, resulting in tumor immune escape (81).

Survivin. Immune responses to survivin have been described in several types of tumors (82,83). Survivin upregulation in patients with EC leads to the inhibition of apoptotic proteins and promotes multi-drug resistance. High levels of survivin have been suggested to be an independent prognostic factor of EC associated with poor PFS time (84,85). Furthermore, survivin downregulation by curcumin-loaded amphiphilic mixed micelles has been demonstrated to improve immunochemotherapy in EC (86).

Interleukin-6 (IL-6). IL-6 is a pro-inflammatory cytokine that is involved in the modulation of the immune response (87). Bellone et al (88) reported that IL-6 mRNA expression was significantly upregulated in uterine serous papillary carcinoma. Furthermore, IL-6 expression levels were significantly higher in patients with EC and uterine papillary serous carcinoma than in healthy females (88). The molecular targets described in this section are summarized in Table II.

3. Mechanisms of immune evasion in EC

The mechanisms of immune evasion in EC can be broadly grouped into five categories: i) Gene mutations; ii) inhibition of T lymphocyte activity; iii) inhibition of NK cell activity; iv) promotion of PD-L1 protein expression; and v) promotion of EC cell sensitivity to estrogen (Fig. 1). However, the actual mechanisms of immune evasion in EC are likely more complex. The available evidence is reviewed in the following sections.

Gene mutations. Ren et al (89) detected 50 Janus kinase 1 (JAK1)-truncating mutations in 5.67% of gynecological tumors, using the Total Cancer Care® tumor bank resource. Furthermore, frame-shift mutations at K142, P430 and K860 have been suggested to be hotspot mutation sites. Functional
Table II. Immunosuppressive microenvironment in EC: Molecular target approach.

| Molecular target | Regulation | Specimen     | Clinical application                                                                 | Refs. |
|------------------|------------|--------------|--------------------------------------------------------------------------------------|-------|
| PD-1/ PD-L1/ PD-L2 | Up         | Tumor tissue | High PD-L1 is an independent adverse prognostic factor for PFS in all patients and in the MSI subgroup. Immune marker ratios indicate independently shorter PFS times for high PD-L1/CD8 and PD-L1/PD-1 ratios. Therapeutic strategies targeting the immune checkpoint inhibitors PD-1/PD-L1 are in clinical application, and a number of clinical trials are underway. | (47-49) |
| B7-H3/ B7-H4     | Up         | Tumor tissue | B7-H3 expression is associated with EC cells and TILs; overexpression of B7-H3 in EC cells is associated with shortened OS times. B7-H4 expression is independent of grade, histology and immune cell infiltration in EC. Inhibiting B7-H3/B7-H4 represents a promising treatment in EC, and clinical trials targeting B7-H3/B7-H4 are in progress. | (52-54) |
| IDO              | Up         | Tumor tissue | In EC, high IDO expression is positively associated with surgical stage, myometrial invasion, lymph-vascular space involvement and LNM. Patients with high IDO expression have significantly impaired OS and PFS time. IDO expression is an independent prognostic factor for PFS. Inhibiting IDO represents promising treatment in EC, and the clinical trials targeting IDO are in progress. | (56-59) |
| HLA              | HLA-A/B/C, down; HLA-G, up | Blood and tumor tissue | Patients with grade-III EC express more soluble HLA-G than patients with low grade. HLA-G5 is only expressed in high-grade EC as well as in early stages, suggesting that inhibiting HLA-G is a promising treatment in EC, but no clinical trials targeting HLA-G in EC are under investigation. Patient HLA type may influence immunotherapy. | (63-67) |
| RCAS1            | Up         | Blood and tumor tissue | RCAS1 overexpression is associated with age at surgery, stage, extent of myometrial invasion and positive peritoneal cytologic results. RCAS1 expression is a clinically significant prognostic factor for OS. High post-surgery serum RCAS1 levels are an independent indicator of shortened OS time in patients with EC. Inhibiting IDO may be a promising treatment in EC. No clinical trial involving RCAS1 is currently in progress. | (71-73) |
| COX-2            | Up         | Tumor tissue | COX-2 is associated with EC FIGO stage and myometrial invasion, and COX-2 is a significant predictor of disease relapse. The prognosis is poorer in patients with MSI-positive EC with high COX-2 expression, compared with that in those with low COX-2 expression. A clinical trial using the COX-2 inhibitor celecoxib is currently in progress. | (77,78) |
| Fas/FasL         | Fas, down; FasL, up | Tumor tissue | The role of Fas/FasL in tumor immune escape suggests a promising treatment in EC. However, no clinical trial involving Fas/FasL is currently underway. | (80,81) |
| Survivin         | Up         | Tumor tissue | Survivin is an independent prognostic factor in EC, suggesting that the inhibition of survivin could be a promising treatment option for EC. However, no clinical trial investigating survivin in EC is currently underway. | (84-86) |
| IL-6             | Up         | Blood         | IL-6 levels represent a promising marker in tumor immunotherapy, and inhibiting IL-6 provides a promising immunotherapy approach for EC. | (88)   |

EC, endometrial cancer; PFS, progression-free survival; OS, overall survival; HLA-E, human leukocyte antigen E; PD-1, programmed cell death-1; PD-L1/2, PD-1 ligand 1/2; MSI, microsatellite instability; TILs, tumor-infiltrating lymphocytes; IDO, indoleamine 2,3-dioxygenase; RCAS1, receptor-binding cancer antigen expressed on SiSo cells; COX-2, cyclooxygenase 2; FIGO, Federation of Gynecology and Obstetrics; FasL, Fas ligand; IL-6, interleukin 6.
expression (89). Furthermore, the loss of low-molecular weight protein-2 and transporter associated with antigen processing-1 inhibits the presentation of tumor antigens and contributes to tumor immune evasion in EC (89). Recently, Albacker et al (90) demonstrated that JAK1 frameshift mutations were associated with high tumor mutation burden and MSI mutations in EC. Furthermore, endometrial and stomach adenocarcinomas with JAK1 frameshift mutations displayed low interferon response levels and an increase in antitumor immunological reactions. These results suggested that mutations in JAK1 were associated with the loss of interferon response and tumor immune escape in MSI-type EC (90).

Mucin 16, cell surface-associated (MUC16), also known as CA125, is a diagnostic serum marker and an indicator of adverse prognosis in gynecological cancer types (91). Recently, the MUC16 gene was found to be frequently mutated in EC. Patients with EC harboring somatic MUC16 mutations had longer OS times compared with non-MUC16 mutated patients with EC. In addition, MUC16 mutations promoted antitumor immune responses in these patients. Furthermore, the upregulation of the NO2-dependent IL-12 signaling pathway indicated the higher rate of MUC16 mutations in NK cells and some surface proteins in CTLs. These patients also had significantly longer survival times. In addition, patients with EC harboring MUC16 mutations have an elevated level of cytotoxic TILs, thereby rescuing T cell antitumor immunity in the EC microenvironment as well as prolonging OS (92).

MHC I molecules inhibit cancer by activating the immune response, and MHC I inhibition leads to cancer immune evasion (93). Nucleotide oligomerization domain-like receptor (NLR) family, caspase recruitment domain-containing 5 (NLRC5) has recently been recognized as a crucial transcriptional coactivator of MHC I expression (94). Yoshihama et al (95) revealed that copy-number loss-, somatic mutation- and epigenetic alteration-mediated NLRC5 downregulation was associated with the expression of MHC I molecules and cytotoxic T cell markers in uterine cancer. Furthermore, overexpression of NLRC5 contributes to the activation of CD8+ CTLs and patient survival in uterine cancer (95).

Inhibition of T-lymphocyte activity. COX-2 upregulation suppresses antitumor immunity in several types of cancer (96,97). High levels of COX-2 are implicated in immunosuppression in EC. Ohno et al (77) reported that COX-2 attenuated the infiltration of CD8+ T cells into the EC tumor milieu, thereby allowing cancer cells to escape immunosurveillance. St-Germain et al (98) demonstrated that AKT signals induce COX-2 expression via the activation of the NF-κB/IκB signaling pathway in EC (98).

V-domain Ig suppressor of T cell activation (VISTA) is a newly identified immune checkpoint inhibitory molecule. VISTA is overexpressed in EC. Upregulation of VISTA in EC suppresses T cell proliferation and IFN-γ and tumor necrosis factor-α expression in vitro, and reduces the number of tumor-infiltrating CD8+ T cells in vivo (99). Furthermore, treatment with allopurinol-conjugated anti-VISTA antibody prolongs the survival of tumor-bearing mice (99).

TAMs serve an important role in immunosuppression mechanisms in EC (100). A previous study demonstrated that TAMs could mediate immune suppression by inhibiting T-cell activation and promoting the expression of immunosuppressive cytokines, as well as C-C motif chemokines 17 and 22 (101).

Inhibition of NK cell activity. Yoshida et al (102) demonstrated that, in a mouse xenograft model of EC, tumor growth was faster in nude mice bearing IDO-overexpressing xenografts than in control mice. Splenic NK cell counts were lower in mice bearing an IDO-overexpressing xenograft compared with those in control xenografted mice. Furthermore, IDO-overexpressing cell cultures greatly decreased the lytic activity of NK cells in nude mice. Oral administration of the IDO inhibitor 1-methyl-D-tryptophan and paclitaxel to mice bearing an IDO-overexpressing xenograft promoted the antitumor effect of pacltaxel and led to markedly longer survival times. These results indicated that IDO overexpression in human EC cells may lead to tumor development in vivo by restricting NK cell activity (102). In addition, Check and Cohen (103) demonstrated that progesterone-induced blocking factor (PIBF) may be associated with the production of an immunomodulatory protein through the inhibition of NK cell cytotoxicity in cancer (103). Nevertheless, the role of PIBF in EC needs to be studied further.

Promotion of PD-L1 protein expression. Yang et al (104) reported that 17β-estradiol could increase the levels of PD-L1 by activating the PI3K/AKT signaling pathway in ER-α-positive Ishikawa cells. In a co-culture of Ishikawa cells and T cells, the expression levels of interferon-γ and IL-2 were downregulated, and the expression levels of B cell lymphoma 2 were upregulated following treatment with 17β-estradiol, suggesting that ER-α-positive EC cells inhibit T-cell function by promoting PD-L1 expression in the tumor microenvironment (104).

Promotion of EC cell sensitivity to estrogen. Ning et al (105) demonstrated that IL-4- and IL-13-induced CD68+CD163+ macrophages enhance the effects of estradiol on EC cell proliferation by upregulating ER-α. The infiltrating CD68+CD163+ macrophages upregulate the expression levels of inflammatory cytokines, such as IL-17A, through ten-eleven translocation 1-mediated epigenetic modulation. The increased estrogen sensitivity of the EC cells stimulates cancer cell proliferation by activating the PI3K/AKT signaling pathway.

4. Immunotherapy for EC

Based on the findings on the immunosuppressive microenvironment and the mechanisms of immune evasion in EC, several immunotherapeutic strategies were explored in EC. These approaches can be broadly subdivided into three categories: i) Anticancer vaccines; ii) immune checkpoint inhibitors; and iii) immunomodulatory agents (Fig. 2).

Anticancer vaccines. Vaccine-based treatments for cancer are designed with the aim of activating immune responses against tumor antigens. In a phase I trial by Kaumaya et al (106), which enrolled 24 patients with metastatic cancer (5 with breast cancer, 5 with ovarian cancer, 5 with colorectal cancer, 2 with EC, 1 with cervical cancer, 1 with pancreatic cancer, 1 with adrenal cancer, 1 with gastrointestinal stromal cancer,
1 with leiomyosarcoma, 1 with non-small cell lung cancer and 1 with an unspecified squamous cell cancer), a dose escalation (range, 0.5-3.0 mg) study was designed with a combination vaccine. The vaccine was a mixture of two chimeric, human epidermal growth factor receptor 2 B cell epitopes fused to a promiscuous T cell epitope. After receiving three inoculations of the intended dose, 62.5% of patients raised an antibody response with no serious adverse events, autoimmunity disease or cardiotoxicity. These results suggested that the peptide vaccine safely induced the generation of IgG antibodies in a population of patients who have metastatic disease, including EC (106). Nonetheless, to date, immunotherapeutic approaches, such as the use of vaccines in patients with EC (107,108), are largely limited to a handful of patients owing to the prognostic relevance of TILs, data related to TILs remains controversial with a higher level of TILs associated to low grade lesions by some authors (21) and to a high grade by others (22).

**Immunomodulatory agents** (IDO, COX-2, RCAS1, TF, Trop-2, survivin, IL-6, rBBX-01) were administered an intravenous humanized monoclonal antibody targeting PD-1 (pembrolizumab) at 10 mg/kg every 2 weeks for up to 24 months. Among the 24 patients, 3 patients with EC had a partial clinical response, while stable disease was observed in 2 patients with EC. Furthermore, the overall response rate was 13%. The 6-month PFS and OS rates were 19.0 and 68.8%, respectively. Only mild adverse effects, such as fatigue, pruritus, pyrexia and anorexia, were observed in 54.2% of patients (111). In a phase II trial involving pembrolizumab, objective response rates reached 71% in 2 patients with MSI-high EC (112). Recently, Makker et al (113) conducted a study involving 54 patients with EC (unscreened for MSI or PD-L1 expression) and analyzed 53 patients in an open-label, single-arm, phase 2 study (NCT02501096). In this study, 21 patients had an objective response, with an acceptable safety profile at week 24 after they were administered 20 mg oral lenvatinib daily, plus 200 mg intravenous pembrolizumab every 3 weeks. However, an increased frequency of hypothyroidism was observed (113). Other humanized antibodies of checkpoint inhibitors targeting PD-1, such as atezolizumab, durvalumab, tremelimumab, ipilimumab and nivolumab, were also studied in EC with a POLE-ultramutated and MSI-hypermutated phenotype. A significant clinical response was observed in these clinical trials (111,113-116). These clinical trials involving immunotherapy for EC are available at https://clinicaltrials.gov, and are listed in Table III.

Patients with Lynch syndrome-associated MSI-high EC exhibit a lower response rate to single anti-PD-1 or anti-PD-L1 therapy than patients with sporadic MSI-high EC (117). These data suggested that clinical trials assessing the effect of immunotherapy in patients with EC must assess Lynch-related and sporadic MSI-high EC independently (117). However, POLE-ultramutated status has been revealed as an early and, possibly, initiating event in EC (118). These results provide a strong theoretical basis for further research of checkpoint inhibitors in EC with a POLE-ultramutated and MSI-hypermutated phenotype (119). Notably, a recent study by Talhouk et al (120) revealed that TIL-high tumors harbor dense T- and B-lineage infiltrates and multiple immunosuppressive effects.
Table III. Ongoing and completed clinical trials involving immunotherapy in EC.

| Study title                                                                 | Brief study description                                                                                                                                                                                                                                                                                                                                 | Intervention                                      | Phase | Status    | Enrollment, n | NCT number        | Refs. |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------|-----------|---------------|-----------------|-------|
| Safety and immune response to a multi-component immune-based therapy (mke1106-pp) for patients with advanced cancer                                                                 | A dose comparison of a multi-component active immunotherapy designed to stimulate an immune reaction to specific tumor-associated antigens that are highly expressed on a large number of solid tumors                                                                                                            | PSMA/PRAME                                      | I     | Completed  | 12             | NCT00423254     | NA    |
| Screening of biomarkers on endometrial cancers Immunotherapy using TILs for patients with metastatic cancer                                                                                  | To evaluate the role of mesothelin and elucidate the potential of mesothelin as a target antigen for immunotherapy To select a specific subset of white blood cells from the tumor and to test whether selected cells can cause digestive tract, urothelial, breast or ovarian/endometrial tumors to shrink, and to see if this treatment is safe | Surgery                                         | NA    | Unknown   | 250            | NCT00674349     | NA    |
| Tisotumab vedotin (humax®-tf-adc) safety study in patients with solid tumors Study of pembrolizumab (mk-3475) in participants with advanced solid tumors (mk-3475-028/keynote-28) Phase 1b/2 trial of lenvatinib (e7080) plus pembrolizumab in subjects with selected solid tumors Mtk-3475 immunotherapy in endometrial carcinoma Pilot study of durvalumab and Vigil in advanced women's cancers A phase ii of nivolumab plus ipilimumab in non-resectable sarcoma and endometrial carcinoma | To establish the tolerability of Tisotumab vedotin in a mixed population of patients with specified solid tumors To assess the efficacy and safety of pembrolizumab (MK-3475) administered to participants with incurable advanced biomarker-positive solid tumors that have not responded to current therapy or for which current therapy is not appropriate To determine and confirm the maximum tolerated dose for lenvatinib in combination with pembrolizumab in participants with selected solid tumors and evaluate the safety and efficacy of the combination To evaluate the mechanism of action of pembrolizumab (MK-3475) on the endometrial cancer tumor environment To determine the effects of Vigil and durvalumab in advanced women’s cancers To determine whether nivolumab plus ipilimumab are effective and safe in the treatment of sarcoma and endometrial carcinoma patients with somatic deficient MMR as a selection tool | Tisotumab vedotin (HuMax-TF-ADC) Pembrolizumab Lenvatinib + pembrolizumab Pembrolizumab Vigil + durvalumab Ipilimumab + nivolumab | I, II  | Completed  | 195            | NCT02001623     | 116   |
|                                                                           |                                                                                                             |                                                  |       | Recruiting | 332            | NCT01174121     | 115   |
|                                                                           |                                                                                                             |                                                  |       | Recruiting | 360            | NCT02501096     | 114   |
|                                                                           |                                                                                                             |                                                  |       | Recruiting | 477            | NCT02054806     | 112   |
|                                                                           |                                                                                                             |                                                  |       | Recruiting | 30             | NCT02982486     | NA    |
|                                                                           |                                                                                                             |                                                  |       | Recruiting | 15             | NCT02725489     | NA    |
|                                                                           |                                                                                                             |                                                  |       | Recruiting | 60             | NCT02982486     | NA    |
| Study title | Brief study description | Intervention | Phase | Status | Enrollment, n | NCT number | Refs. |
|-------------|-------------------------|--------------|-------|--------|--------------|------------|-------|
| Study of pembrolizumab, radiation and immune modulatory cocktail in cervical/uterine cancer | To discover the antitumor immune response by a combination of PD-1 blockade, radiation and immune/environmental-targeting compounds in cervical and uterine cancer | Pembrolizumab + radiation + vitamin D + aspirin + lansoprazole + cyclophosphamide + curcumin + Durvalumab | II | Recruiting | 43 | NCT03192059 | 117 |
| Durvalumab, radiotherapy in gynecological cancer | To evaluate the safety and efficacy of Durvalumab and Tremelimumab in combination with radiation therapy as a possible treatment for recurrent or metastatic gynecological cancer | Durvalumab + tremelimumab + radiation | I | Recruiting | 32 | NCT03277482 | NA |
| Multiorgan metabolic imaging response assessment of abemaciclib | A screening program for Abemaciclib efficacy in multiple platinum-resistant tumor types by using metabolic imaging (PERCIST) and RECIST v1.1 criteria | Abemaciclib | II | Recruiting | 85 | NCT03339843 | NA |
| Synergy-AI: artificial intelligence-based precision oncology clinical trial matching and registry | To evaluate the feasibility and clinical utility of an Artificial Intelligence-based precision oncology clinical trial matching tool, powered by a virtual tumor boards program, and its clinical impact on patients with advanced cancer to facilitate clinical trial enrollment, as well as the financial impact, and potential outcomes of the intervention | Clinical Trial Matching | NA | Recruiting | 1,500 | NCT03452774 | NA |
| Lenvatinib in combination with pembrolizumab versus treatment of physician’s choice in participants with advanced endometrial cancer (mk-3475-775/e7080-g000-309 per merck standard convention (keynote-775)) | To evaluate the treatment outcome between pembrolizumab (MK-3475) in combination with lenvatinib and doxorubicin or paclitaxel | Pembrolizumab + lenvatinib + paclitaxel + doxorubicin | III | Recruiting | 780 | NCT03517449 | NA |
| Atezolizumab trial in endometrial cancer-attend | To determine the effects of atezolizumab in advanced endometrial cancer | Atezolizumab + placebos + paclitaxel + carboplatin | III | Recruiting | 550 | NCT03603184 | NA |
| Study title                                                                 | Brief study description                                                                                                                                                                                                 | Intervention                  | Phase | Status               | Enrollment, n | NCT number   | Refs. |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------|----------------------|---------------|--------------|-------|
| A study to evaluate the safety and tolerability of immunotherapy combinations in participants with advanced malignancies | To evaluate the safety, tolerability, pharmacokinetic, pharmacodynamic and clinical activity of AB928 in combination with AB122 (an anti-PD-1 antibody) in participants with advanced malignancies | AB928 + AB122                | I     | Recruiting          | 58            | NCT03629756  | NA    |
| A phase 2 study of mirvetuximab soravtansine (INGN853) and pembrolizumab in endometrial cancer | To evaluate Mirvetuximab Soravtansine (IMGN853) and Pembrolizumab in combination as a possible treatment for endometrial cancer                                                                                       | Pembrolizumab + IMGN853      | II    | Not yet recruiting  | 35            | NCT03835819  | NA    |
| Pembrolizumab in addition to paclitaxel and carboplatin for treating patients with stage III-IV or recurrent endometrial cancer | To evaluate how well the combination of pembrolizumab, paclitaxel and carboplatin works compared with paclitaxel and carboplatin alone in treating patients with endometrial cancer that is stage III or IV, or has come back (recurrant) | Carboplatin + paclitaxel + pembrolizumab + placebo | III   | Not yet recruiting  | 810           | NCT03914612  | NA    |
| Frontline immunotherapy combined with radiation and chemotherapy in high-risk endometrial cancer | To evaluate the feasibility of pembrolizumab combined with radiation administered to the upper part of the vagina (vaginal cuff brachytherapy) followed by three cycles of pembrolizumab and chemotherapy in patients with endometrial cancer | Pembrolizumab + radiation     | I     | Not yet recruiting  | 20            | NCT0392409   | NA    |

AB, Arcus Biosciences; EC, endometrial cancer; MMR, mismatch repair; NA, not applicable; NCT, national clinical trial; PSMA, prostate-specific membrane antigen; PRAME, preferentially expressed antigen of melanoma; TIL, tumor-infiltrating lymphocytes.
features, and are more common among the molecular subtypes of EC associated with high mutation load (MMR and POLE) than ECs with a low mutation load (p53 abnormalities and p53 wild-type). Furthermore, TIL<sup>low</sup> tumors are generally devoid of immunological features and are more prevalent in ECs harboring p53 abnormalities and wild-type p53, although they are also seen in MMR and POLE subtypes. Additionally, in multivariate models involving a ProMisE subtype, T-cell markers and TIL clusters, only ProMisE was associated with independent prognostic significance (120). These findings suggested that the assessment of an immune response rather than the molecular subtype may better predict a clinical response to immunotherapy (120,121). Nevertheless, as aforementioned, targeting the PD-1 signaling pathway has great potential in enhancing antitumor immune responses, as accumulating evidence demonstrates that antitumor functions are induced following PD-1 and PD-L1 engagement in cancer cells in vivo (50,112-117). These multifunctional PD-1 signaling pathways need to be made available for the treatment of additional types of cancer.

**Immunomodulatory agents in EC.** Immunomodulatory agents, other than immune checkpoint inhibitors, may emerge as promising therapeutic agents in the future. Mills et al (59) demonstrated that IDO levels were upregulated in endometrial carcinoma and diffuse staining was principally more common in MMR-deficient cancer, particularly Lynch syndrome-associated cases, suggesting that targeting IDO may be a promising treatment approach for MMR-deficient endometrial carcinoma.

Other immunotherapies currently under investigation for the treatment of EC involve immunomodulatory agents, such as COX-2 (122), RCAS1 (123), tissue factor (124), human trophoblast-cell surface marker (125), survivin (126), IL-6 (127) and rBBX-01 (128). These targets are still in preclinical or early clinical development and have achieved promising clinical results, indicating that these immunotherapies are potential strategies in the treatment of EC.

**5. Conclusions and future perspectives**

The aforementioned research efforts, which aimed to investigate the role of the immune response in EC, including the immunosuppressive microenvironment, immune evasion mechanisms and immunotherapy, offer a strong rationale for immunotherapeutic approaches in the treatment of EC. Indeed, the use of checkpoint inhibitors and cancer vaccines for EC treatment has yielded good clinical outcomes. Although key milestones have been reached, numerous efforts have proven ineffective and the efficacy of immunotherapy in EC needs to be further demonstrated in the future.

Firstly, the induced immunosuppressive microenvironment in EC is influenced by multiple factors, including immune cells, immune checkpoint inhibitors, and immunomodulatory agents and their interactions. Therefore, it is necessary to understand the manner in which the tumor immunosuppressive microenvironment can be modulated to enhance the immune response against EC. Furthermore, significant knowledge gaps need to be filled through the use of molecular, cellular and structural biology approaches, in order to identify appropriate targets for immune cells, immune checkpoint inhibitors and immunomodulatory agents in immunotherapeutic applications.

Secondly, the exact immunosuppressive or immune evasion mechanisms involved in EC remain to be determined. Indeed, only a few candidate neoantigens selected by the current neoantigen-prediction algorithms trigger an antitumor response. Mechanisms of immunosuppression and immune evasion proposed on the basis of preclinical studies on immune checkpoint inhibitors and immunomodulatory agents represent a promising clinical application. However, these have yet to be tested on patients in EC, with the results pending for numerous clinical trials.

Lastly, a single immunotherapy approach may be ineffective against advanced metastatic or recurrent EC. Evidence from preclinical research indicates that combinatorial modalities, targeting different facets of the immune response, lead to improved therapeutic efficacy; early clinical studies suggest that such therapeutic approaches can be more effective. However, side effects must be considered when using such combinations. The sequence, timing, dosage and choice of drugs should be designed well to achieve optimal antitumor and minimal off-target side effects. Furthermore, a combinatorial therapy approach may be appropriate to synergize the effects of conventional therapies and immunotherapy against EC.

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Authors’ contributions**

LZ wrote the manuscript and drafted the figures. XL and JZ revised the manuscript. YC and BW reviewed and revised the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.
Competition interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69: 7-34, 2019.
2. Van Arsdale A, Miller DT, Kuo DY, Isani S, Sanchez L and Nevidomsky NS: Association of obesity with survival in patients with endometrial cancer. Gynecol Oncol 154: 156-162, 2019.
3. Yang X and Wang J: The Role of Metabolic Syndrome in Endometrial Cancer: A Review. Front Oncol 9: 744, 2019.
4. Lynch HT, Snyder CL, Shaw TG, Heinen CD and Hitchins MP: Milestones of Lynch syndrome: 1895-2015. Nat Rev Cancer 15: 181-194, 2015.
5. Borett M, Maenhoudt N, Luo X, Hennes A, Boecks B, Bui B, Heremans R, Perneel L, Kobayashi H, Van Zundert I, et al: Patient-derived organoids from endometrial disease capture clinical heterogeneity and are amenable to drug screening. Nat Cell Biol 21: 1041-1051, 2019.
6. Bohkmann JV: Two pathoegenetic types of endometrial carcinoma. Gynecol Oncol 15: 10-17, 1983.
7. Morice P, Leary A, Creutzberg C, Abu‑Rustum N and Darai E: Endometrial cancer, Lancet 387: 1094-1106, 2016.
8. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, Tatebe K and Veneris JL: Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin 69: 258-279, 2019.
9. Han G, Sidhu D, Duggan MA, Arsenneau C, Cesari M, Clement PB, Ewanowich CA, Kalloger SE and Köbel M: Reproducibility of histological cell type in high-grade endometrial cancer. Mod Pathol 26: 1594-1604, 2013.
10. Zannoni GF, Vellone VG, Arena V, Prisco MG, Scambia G, Carbone A and Gallo D: A clin genomic‑based classifier for endometrial carcinoma. Gynecol Oncol 15: 10-17, 2019.
11. Morice P, Leary A, Creutzberg C, Abu‑Rustum N and Darai E: Endometrial cancer, Lancet 387: 1094-1106, 2016.
12. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, Tatebe K and Veneris JL: Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin 69: 258-279, 2019.
13. Han G, Sidhu D, Duggan MA, Arsenneau C, Cesari M, Clement PB, Ewanowich CA, Kalloger SE and Köbel M: Reproducibility of histological cell type in high-grade endometrial cancer. Mod Pathol 26: 1594-1604, 2013.
14. Zannoni GF, Vellone VG, Arena V, Prisco MG, Scambia G, Carbone A and Gallo D: A clin genomic‑based classifier for endometrial carcinoma. Gynecol Oncol 15: 10-17, 2019.
15. References
40. Jia J, Wang Z, Li X, Wang Z and Wang X: Morphological character-istics and co-stimulatory molecule (CD80, CD86, CD40) expression in tumor infiltrating dendritic cells in endometrio-dendritic adenocarcinoma. Eur J Obstet Gynecol Reprod Biol 160: 227-233, 2012.

41. Zinovkin D and Panrjal MZ: Tumor-infiltrated lymphocytes, macrophages, and dendritic cells in endometriod adenocarcinoma of corpus uteri as potential prognostic factors: An immunohistochemical study. Int J Gynecol Cancer 26: 1207-1212, 2016.

42. Inoue T, Kitano T, Kawana K, Taguchi A, Nagamatsu T, Fujimoto A, Tomio K, Yamashita A, Eguchi S, Nishida H et al: Cancer-associated fibroblast suppresses killing activity of natural killer cells through downregulation of poliovirus receptor (PVR/ CD155), a ligand of activating NK receptor. Int J Oncol 49: 1687-1695, 2016.

43. Kerr J, Anderson C and Lippman SM: Physical activity, sedentary behaviour, diet, and cancer: An update and emerging new evidence. Lancet Oncol 18: e457-e471, 2017.

44. Ni L and Dong C: New checkpoints in cancer immunotherapy. Immunol Rev 276: 56-65, 2017.

45. Ishida Y, Agata Y, Shibahara K and Honjo T: Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J 11: 3887-3895, 1992.

46. Curran CS, Gupta S, Sanz I and Sharon E: PD-1 immunobiology in systemic lupus erythematosus. J Autoimmun 97: 1-9, 2019.

47. Jin H-T, Ponnappan R and Okazaki F: Role of PD-1 in regulating T-cell immunity 350: 17-37, 2010.

48. Vanderstraeten A, Luyten C, Verbiest G, Tuytens S and Amanet F: Mapping the immunosuppressive environment in uterine tumors. Implications for immunotherapy. Cancer Immunol Immunother 63: 545-557, 2014.

49. Mo Z, Liu J, Zhang Q, Chen Z, Mei J, Liu L, Yang S, Li H, Zhou L and You Z: Expression of PD-1, PD-L1 and PD-L2 is associated with differentiation status and histological type of endometrial cancer. Oncol Lett 12: 944-950, 2016.

50. Kim J, Kim S, Lee HS, Yang W, Cho H, Choy DB, Choi SJ, Hong S and Kim JH: Prognostic implication of programmed cell death 1 protein and its ligand expressions in endometrial cancer. Gynecol Oncol 149: 381-387, 2019.

51. Janakiram M, Shah UA, Liu W, Zhao A, Schoenberg MP and Zang X: The third group of the B7-CD28 immune checkpoint family: HHLA2, TMIGD2, B7x, and B7-H3. Immunol Rev 276: 26-39, 2017.

52. Brunner A, Hinterholzer S, Riss P, Heinez G and Brustmann H: Immunoexpression of B7-H3 in endometrial cancer: Relation to tumor T-cell infiltration and prognosis. Gynecol Oncol 106: 119-127, 2007.

53. Zang X: The third group of the B7-CD28 immune checkpoint family: HHLA2, TMIGD2, B7x, and B7-H3. Immunol Rev 276: 52-65, 2017.

54. Walker MS, Louie S, Maldonado H and Nijman HW: Loss of HLA class I and mismatch repair protein blockade immunotherapy. Science 359: 582-587, 2018.

55. McGowan R, Boerma A, van den Hoven E, Hollema H and Nijman HW: Loss of HLA class I and mismatch repair protein expression in sporadic endometrial endometrioid carcinomas. Int J Cancer 131: 1828-1836, 2012.

56. Barrier BF, Kendall BS, Sharpe-Timms KL and Kost ER: Characterization of human leukocyte antigen-G (HLA-G) expression in endometrial adenocarcinoma. Gynecol Oncol 103: 25-30, 2006.

57. Bijnen CB, Banetama-Joppe EF, de Jong RA, Leffers N, Mourits MJ, Eggink HF, van der Zee AG, Hollema H, de Bock GH and Nijman HW: The prognostic role of classical and nonclassical MHC class I expression in endometrial cancer. Int J Cancer 126: 1417-1427, 2010.

58. Lin A and Yan WH: Heterogeneity of HLA-G expression in cancers: Facing the challenges. Front Immunol 9: 2164, 2018.

59. Ben Yahia H, Bahay W, Bortolotti D, Boujelbene N, Laaribi AB, Zid H, Kehila M, Chelbi H, Boudabous A, Mrid K, et al: Increased plasmatic soluble HLA-G levels in endometrial cancer. Mol Immunol 99: 82-86, 2018.

60. Sonoda K, Miyamoto S, Hirakawa T, Yagi H, Yotsukumo F, Nakashima M, Watanabe T and Nakano H: Association between RCAS1 expression and microenvironmental immune cell death in uterine cervical cancer. Gynecol Oncol 97: 772-779, 2005.

61. Nakashima M, Sonoda K and Watanabe T: Inhibition of cell growth and induction of apoptotic cell death by the human tumor-associated antigen RCAS1. Nat Med 5: 938-942, 1999.

62. Liu C, Giagounidi P, MacHale S, Beavis P, Bower A, Omote H, Brosens IA, Gluckman EJ, Agarwal D, et al: Genetic models reveal cis and trans immune-regulatory activities of PD-L1. J Autoimmun 97: 1-9, 2019.

63. Kerr J, Anderson C and Lippman SM: Physical activity, sedentary behaviour, diet, and cancer: An update and emerging new evidence. Lancet Oncol 18: e457-e471, 2017.

64. Calviño-Sampedro C, Gomez-Tourino I, Cordero OJ, Reche PA, Gómez-Perozas M, Sánchez-Trincado JL, Rodríguez MA, Saez AM, Vituela JE and Calviño RV: Naturally presented HLA class I-restricted epitopes from the neurotrophic factor B0/SM are targets of the autologous immune response in type 1 diabetes. FASEB J 33: 6390-6401, 2019.

65. Liepe J, Marino F, Sidney J, Jeko A, Bunting DE, Sette A, Klotzelm PM, Stumpf MP, Heck AJ and Mishto M: A large fraction of HLA class I ligands are proteasome-generated spliced peptides. Front Immunol 9: 2236, 2018.

66. Chowell D, Morris LGT, Grigg CM, Weber JK, Samstein RM, Makarov V, Kuo F, Kendall SM, Requena D, Riaz N, et al: Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy. Science 359: 582-587, 2018.

67. Calviño-Sampedro C, Gomez-Tourino I, Cordero OJ, Reche PA, Gómez-Perozas M, Sánchez-Trincado JL, Rodríguez MA, Saez AM, Vituela JE and Calviño RV: Naturally presented HLA class I-restricted epitopes from the neurotrophic factor B0/SM are targets of the autologous immune response in type 1 diabetes. FASEB J 33: 6390-6401, 2019.

68. Li X, Marino F, Sidney J, Jeko A, Bunting DE, Sette A, Klotzelm PM, Stumpf MP, Heck AJ and Mishto M: A large fraction of HLA class I ligands are proteasome-generated spliced peptides. Front Immunol 9: 2236, 2018.

69. Chowell D, Morris LGT, Grigg CM, Weber JK, Samstein RM, Makarov V, Kuo F, Kendall SM, Requena D, Riaz N, et al: Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy. Science 359: 582-587, 2018.

70. Calviño-Sampedro C, Gomez-Tourino I, Cordero OJ, Reche PA, Gómez-Perozas M, Sánchez-Trincado JL, Rodríguez MA, Saez AM, Vituela JE and Calviño RV: Naturally presented HLA class I-restricted epitopes from the neurotrophic factor B0/SM are targets of the autologous immune response in type 1 diabetes. FASEB J 33: 6390-6401, 2019.
80. Das H, Koizumi T, Sugimoto T, Chakraborty S, Ichimura T, Hasegawa K and Nishimura R: Quantitation of Fas and Fas ligand gene expression in human ovarian, cervical and endometrial carcinomas using real-time quantitative RT-PCR. Br J Cancer 82: 1668-1688, 2000.

81. Jia JJ, Wang ZN, Liu GX and Wang ZX: Apoptosis and expression of Fas/FasL in tumor infiltrating dendritic cells in human endometrioid adenocarcinoma. Nan Fang Yi Ke Da Xue Xue Bao 31: 1693-1696, 2011 (In Chinese).

82. Rapoport AL, Aharoni A, Wolfson A, Stelmuerer EA, Vogl DT, Fang HB, Cai L, Janovsky S, Chew A, Storkel A, Akpek G et al: Combination immunotherapy using adoptive T-cell transfer and tumor antigen vaccination on the basis of hTERT and survivin after ASCET for myeloma. Blood 117: 788-797, 2011.

83. Vezzoni F, Morozzi C, Mirjolot A, Collin B, Oudot A, Charon-Barra C, Arnauld L, Niraudoc S and Boidot R: Survivin-3B potentiates immune escape in cancer but also inhibits the toxicity of cancer chemotherapy. Cancer Res 73: 5391-5401, 2013.

84. Wang Z, Liu Y and Liu M: Platelet-rich plasma injection is not more effective than a hypalric acid to treat knee osteoarthritis when using a random-effects model. Br J Sports Med 50: 953-954, 2016.

85. Chuwa AH, Oke K, Idia K, Ikuda F, Wada-Hiraike O, Inaba K, Makki C, Takeuchi M, Oki S, et al: Significance of survivin as a prognostic factor and a therapeutic target in endometrial cancer cells to be explored. Cancer Res 64: 5211-5220, 2005.

86. Kumar A, Sirohi VK, Anum F, Singh PK, Gupta K, Gupta D, Saraf SA, Dwivedi A and Chourasia MK: Enhanced apoptosis, survivin down-regulation and assisted immunochemotherapy by curcumin loaded amipolistic mixed micelles for subjugating endometrial cancer. Eur J Cancer 43: 1933-1943, 2007.

87. Kang S, Tanaka T, Narazaki M and Kishimoto T: Targeting Interleukin-6 Signaling in Clinical. Immunity 50: 1007-1023, 2019.

88. Bellone S, Watts K, Cano S, Palmeri M, Cannon MJ, Burnett A, Roman JJ, Fecorelli S and Santin AD: High serum levels of interleukin-6 in endometrial carcinoma are associated with uterine serous papillary histology, a highly aggressive and chemotherapy-resistant variant of endometrial cancer. Gynecol Oncol 98: 92-98, 2005.

89. Ren Y, Zhang Y, Liu BZ, Fenstermacher DA, Wright KL, Teer JK and Wu J: JAK1 truncating mutations in gynecologic cancer define new role of cancer-associated protein tyrosine kinase aberrations. Sci Rep 3: 3042, 2013.

90. Albacker LA, Wu J, Smith P, Warmuth M, Stephens PJ, Zhu P, Yu L and Chmielecki J: Loss of function JAK1 mutations occur at high frequency in cancers with microsatellite instability and are suggestive of immune evasion. PLoS One 12: e0176181, 2017.

91. Chao A, Tang YH, Lai CH, Chang CJ, Chang SC, Wu TI, Hsueh S, Wang CJ, Choi HH and Chang TC: Potential of an age-stratified CA125 cut-off value to improve the prognostic classification of patients with endometrial cancer. Gynecol Oncol 129: 500-504, 2013.

92. Lu H and Sun J: prognostic factors for patients with advanced endometrial cancer: enhancing the infiltration and antitumor immunity of cytotoxic T lymphocytes in the endometrial cancer microenvironment. OncolImmunology 7: e1487914, 2018.

93. Grotzke JE, Sengupta D, Lu Q and Cresswell P: The ongoing saga of the mechanism(s) of MHC class I-restricted cross-presentation. Curr Opin Immunol 46: 89-96, 2017.

94. Chen Y, Li H, Xiao C, Zeng X, Xiao X, Zhou Q and Xiao P: NLRC5: Potential novel anti-inflammatory biomarker for predicting and reflecting the progression of IgA nephritis. J Transl Med 16: 1139, 2018.

95. Yoshida S, Ino K, Ishida Y, Kajiyama H, Yamamoto E, Shibata K, Terauchi M, Nawa A, Akimoto H, Takikawa O, et al: Overexpression of indoleamine 2,3-dioxygenase in human endometrial carcinoma cells induces rapid tumor growth in a mouse model. Jpn J Cancer Res 99: 589, 2008.

96. Check JW and Cohen B: The role of progestogen and the progesterone receptor in human reproduction and cancer. Expert Rev Endocrinol Metab 8: 469-484, 2013.

97. Yang L, Huang F, Mei J, Wang X, Zhang Q, Wang H, Xi M and You Z: Posttranscriptional control of PD-1 expression by 17β-estradiol via PI3KAkt survival pathway in ERα-positive cancer cell lines. Int J Gynecol Cancer 27: 196-205, 2017.

98. Ning C, Xie B, Zhang L, Li C, Shan W, Yang B, Luo X, Gu C, He Q, Jin H et al: Infiltrating macrophages induce ERα expression through an IL17A-mediated epigenetic mechanism to sensitize endometrial cancer cells to endocrine therapy. Gynecol Oncol 141: 564-569, 2016.

99. Baums KA, Foy KO, Garrett J, Rawale SV, Picari D, Thordrum JM, Lamb T, Mani A, Kane Y, Balint CR, et al: Phase I active immunotherapy with combination of two chimeric, human epidermal growth factor receptor 2, B-cell epitope fusions fused to a promiscuous T-cell epitope. Cancer Immunol Immunother 65: 193-196, 2016.

100. Ohno S, Kyo S, Myoso J, Dohi S, Ishizaki J, Miyamoto K, Morita S, Sakamoto J, Enomoto T, Kimura T, et al: Wilms' tumor 1 (WT1) peptide immunotherapy for gynecological malignancies. Anticancer Res 29: 4779-4784, 2009.

101. Jäger E, Karbach J, Gnjatic S, Neumann A, Bender A, Valmori D, Ayyoub M, Ritter E, Ritter G, Jäger D, et al: Recombinant vaccinia/vpoxv NY-ESO-1 vaccines induce both humoral and cellular NY-ESO-1-specific immune responses in cancer patients. Proc Natl Acad Sci USA 103: 14453-14458, 2006.

102. Howitt BE, Shukla SA, Sholl LM, Ritterhouse LL, Watkins JC, Rodig S, Stover E, Strickland KC, D'Andrea AD, Wu CJ, et al: Association of Polymerase ε-Mutated and Microsatellite-Instable Endometrial Cancers With Neoantigen Load, Number of Tumor-Infiltrating Lymphocytes, and Expression of PD-1 and PD-L1. JAMA Oncol 1: 1319-1323, 2015.

103. Mehnert JM, Panda A, Zhong H, Hirshfeld K, Damare S, Lane K, Sokol L, Stein MN, Rodriguez-Rodriguez L, Kaufman HL, et al: Immune activation and response to pembrolizumab in PDL1-positive advanced endometrial cancer. J Clin Invest 126: 2334-2340, 2016.

104. Oku TA, Bang D, Williams J, Yoon JA, Kiwon MJ, Rugo HS, Puzanov I, Mehnert JM, Aung KL, Lopez J, et al: Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: Results from the KEYNOTE-028 study. J Clin Oncol 35: 2535-2541, 2017.

105. Osterman C, McCarthy MBE, Coté MP, Beitzel K, Bradley J, Polkowski G and Mazzocco AD: Platelet-rich plasma increases anti-inflammatory markers in a human coculture model for osteoarthritis. Am J Sports Med 43: 1474-1484, 2015.

106. Kato M, Sasako T, Vuglia D, Ford J, Mose MS, Cohn AL, Mier J, Di Simone C, Hyman DM, Stoner DE, Dutcus CE, et al: Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: An interim analysis of a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 20: 711-718, 2019.

107. Tran E, Turcotte S, Gros A, Robbins PF, Lu YM, Dudley ME, Wunderlich JR, Somerville RH, Horgan K, Hinrichs CS, et al: Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. Science 344: 641-645, 2014.

108. de Bono JS, Concín N, Hong DS, Thistlethwaite FC, Machiels JP, Arkenau HT, Plummer R, Jones RH, Nielsen D, Windfeld K, et al: Tisotumab vedotin in patients with advanced or metastatic solid tumours (InnovaTV 201): A first-in-human, multicentre, phase 1-2 trial. Lancet Oncol 20: 383-393, 2019.

109. Tuyaerts S, Van Nuffel AMT, Naert E, Van Dam PA, Vuytsleke P, De Caluwe A, Aspeslagh S, Dirix P, Lippens L, De Jaeghere E, et al: OncoImmunology: combining PD-1 blockade, radiation and immunomodulation to tackle cervical and uterine cancer. BMC Cancer 19: 506, 2019.
117. Pakish JB, Zhang Q, Chen Z, Liang H, Chisholm GB, Yuan Y, Mok SC, Broadus RR, Lu KH and Yates MS: Immune microenvironment in microsatellite-instable endometrial cancers: Hereditary or sporadic origin matters. Clin Cancer Res 23: 4473-4481, 2017.

118. Temko D, Van Gool IC, Rayner E, Glaire M, Makino S, Brown M, Chegwidden L, Palles C, Depreeuw J, Beggs A, et al: Somatic POLE exonuclease domain mutations are early events in sporadic endometrial and colorectal carcinogenesis, determining driver mutational landscape, clonal neoantigen burden and immune response. J Pathol 245: 283-296, 2018.

119. Eggink FA, Van Gool IC, Leary A, Pollock PM, Crosbie EJ, Milesklin L, Jordanova ES, Adam J, Freeman-Mills L, Church DN, et al: Immunological profiling of molecularly classified high-risk endometrial cancers identifies POLE-mutant and microsatellite unstable carcinomas as candidates for checkpoint inhibition. OncoImmunology 6: e1264565, 2016.

120. Talhouk A, Derocher H, Schmidt P, Leung S, Milne K, Gilks CB, Anglesio MS, Nelson BH and McAlpine JN: Molecular subtype not immune response drives outcomes in endometrial carcinoma. Clin Cancer Res 25: 2537-2548, 2019.

121. Mullen MM and Mutch DG: Endometrial tumor immune response: Predictive biomarker of response to immunotherapy. Clin Cancer Res 25: 2366-2368, 2019.

122. DeLong P, Tanaka T, Kruklitis R, Henry AC, Kapoor V, Kaiser LR, Sterman DH and Albelda SM: Use of cyclooxygenase-2 inhibition to enhance the efficacy of immunotherapy. Cancer Res 63: 7845-7852, 2003.

123. Han Y, Qin W and Huang G: Knockdown of RCAS1 expression by RNA interference recovers T cell growth and proliferation. Cancer Lett 257: 182-190, 2007.

124. Cocco E, Hu Z, Richter CE, Bellone S, Casagrande F, Bellone M, Todeschini P, Krikun G, Silasi DA, Azodi M, et al: hI-con1, a factor VII-IgGFc chimeric protein targeting tissue factor for immunotherapy of uterine serous papillary carcinoma. Br J Cancer 103: 812-819, 2010.

125. Varughese J, Cocco E, Bellone S, de Leon M, Bellone M, Todeschini P, Schwartz PE, Rutherford TJ, Pecorelli S and Santin AD: Uterine serous papillary carcinomas overexpress human trophoblast-cell-surface marker (Trop-2) and are highly sensitive to immunotherapy with hRS7, a humanized anti-Trop-2 monoclonal antibody. Cancer 117: 3163-3172, 2011.

126. Vanderstraeten A, Everaert T, Van Bree R, Verbist G, Luyten C, Amant F and Tuyaerts S: In vitro validation of survivin as target tumor-associated antigen for immunotherapy in uterine cancer. J Immunother 38: 239-249, 2015.

127. Dijkgraaf EM, Santegoets SJ, Reynolds AK, Goedemanns R, Wouters MC, Kenter GG, van Erkel AR, van Poelgeest MI, Nijman HW, van der Hoeven JJ, et al: A phase I trial combining carboplatin/doxorubicin with tocilizumab, an anti-IL-6R monoclonal antibody, and interferon-α2b in patients with recurrent epithelial ovarian cancer. Ann Oncol 26: 2141-2149, 2015.

128. Rader JS, Aylsworth CF, Juckett DA, Mutch DG, Powell MA, Lippmann L and Dimitrov NV: Phase I study and preliminary pharmacology of the novel innate immune modulator rBBX-01 in gynecologic cancers. Clin Cancer Res 14: 3089-3097, 2008.

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