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TIME for Endometrial Cancer: Advancements and challenges in therapeutic targets for the endometrial cancer Tumor Immune MicroEnvironment

Margaret R. Pruitt[1], **Kellsye P. Fabian**[1], **Jung-Min Lee**[2], **James W. Hodge**[1,*]

[1]Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

[2]Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Abstract

Endometrial cancer (EC) is the sixth most common cancer in women worldwide and the fourth most common cancer in women in the United States (U.S.). In the U.S., its incidence and mortality rates have continued to increase since the late 1990s. EC comprises most uterine corpus carcinomas (UCCs) and represents a heterogeneous group of cancers varying in pathology, histology, molecular biology, immunogenicity, and prognosis. Recently, the advancement of molecular classification and subsequent clinical trials have led to new FDA approvals for using immune checkpoint inhibitors in EC. However, recurrent and advanced stage EC continues to demonstrate high morbidity and mortality, denoting an unmet need for innovative immunotherapeutic strategies. This review explores current concepts in the EC tumor immune microenvironment (TIME), comparing antigenicity, immunosurveillance, and immunoregulation among molecular and histologic subtypes and providing insight into which subtypes may be particularly responsive to immunotherapy. Novel immunotherapeutic strategies targeting cancer antigens, emerging immune checkpoints, immunomodulatory cytokines, and tumor-infiltrating immune cells are described and corresponding clinical trials presented. Integrated approaches such as immunogenic modulation—enhancing tumor susceptibility to immune attack—and immune subset conditioning—modifying suppressive immune components within the TIME—are presented as promising avenues to render "cold" tumors responsive. Together, the immunotherapies reviewed here offer potential strategies for treating patients with advanced or refractory EC.

Keywords

Endometrial Cancer; Uterine Corpus Carcinoma; Immunotherapy Combinations; Tumor Immune Microenvironment; Tumor Microenvironment; Molecular Subtypes

*Corresponding author Dr. James W. Hodge, jh241d@nih.gov, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bldg. 10, Rm 8B13, 9000 Rockville Pike, Bethesda, MD 20879.

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Introduction

Endometrial cancer (EC) collectively refers to a group of histologically and molecularly heterogeneous tumors that represent over 90% of uterine corpus carcinomas (UCCs) (1–3). In 2025, UCCs are projected to account for 16,120 or 7% of all new cancer cases in women and 13,860 deaths or 5% of all cancer deaths in women (2). EC is the most common gynecologic cancer in the U.S. and the increasing incidence of ECs contributes to its rank as the fourth most common cancer overall for women in the U.S and the sixth most common cancer globally (1,4–8). Incidence and mortality rates are highest amongst non-Hispanic African American women and the rates of increasing incidence and mortality are higher for non-white racial and ethnic minority groups than white women (8). A retrospective cohort study conducted in a U.S. population between 2010 and 2017 reported a 1.8% increase per year in the age-adjusted mortality rate of UCC and a 2.7% increase per year in the hysterectomy-corrected mortality rate of aggressive subtypes (9). Ten to15% of patients present with advanced-stage disease, which portends a worse prognosis and is not curable (5). One retrospective cohort study of predominantly early-stage patients measured a median time to recurrence of 16 months in the 17% of EC patients who recurred after primary surgery (10). A separate study estimated the median survival for metastatic/recurrent EC to be only 12 to 15 months in patients with measurable disease (5). The increasing incidence and mortality rates and poor prognosis represent an unmet need in EC for treatment of advanced-stage disease.

Histologically, EC is subdivided into two categories: endometrioid (type I) and non-endometrioid (type II). Endometrioid EC (type I) accounts for 80% of EC world-wide and is associated with pathophysiologic states of unopposed estrogen and has a more favorable prognosis. Non-endometrioid EC (type II) makes up 10 to 20% of EC world-wide, is not related to hormonal exposure, and includes the more aggressive EC subtypes, *e.g.,* serous, clear cell, carcinosarcoma, and undifferentiated, that are associated with a worse prognosis (11,12). More recently, with the innovation of genomic analyses and next-generation sequencing, subcategorization of ECs has been resolved to a molecular level (13). The Cancer Genome Atlas (TCGA), the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMise), and the Translational Research in Post-Operative Radiation Therapy in EC (TransPORTEC) are three seminal, large-scale studies that collectively led to the definition of four EC molecular subtypes and their relative prognoses: polymerase ε (POLE) mutated (best prognosis); microsatellite instability high (MSI-H)/ deficient mismatch Repair (dMMR) (intermediate prognosis); copy number low (CNL)/ tumor protein 53 wild type (p53wt) (intermediate prognosis); and copy number high (CNH)/abnormal p53 (p53abn) (worst prognosis) (Fig. 1A) (14–18). CNH/p53abn tumors account for the vast majority of non-endometrioid, high-risk ECs (Fig. 1A) (17,19).

Treatment of inoperable primary and recurrent advanced-stage EC

Management of EC relies primarily on a multimodal approach involving diagnostic and cytoreductive surgery with or without adjuvant radiation, chemotherapy, or both. The specific treatment is guided by stage, risk of recurrence, and operability. The nuanced management of EC is beyond the scope of this review and has previously been discussed

comprehensively (13). The American Joint Committee on Cancer (AJCC) tumor (T), node (N), metastases (M) system defines advanced-stage disease as starting with a tumor that involves the serosa, adnexa, vagina, or parametrium (T3N0M0); this corresponds to International Federation of Gynecology and Obstetrics (FIGO) Stage III disease, demarcating disease with a worse prognosis (20–22). Metastatic disease (FIGO Stage IV) is defined by a tumor that invades the bladder or bowel mucosa (T4, any N, M0) or any distant metastases (any T, any N, M1), which commonly involve the inguinal lymph nodes, peritoneum, lung, and liver, and is generally considered inoperable and incurable (22,23). A platinum-based chemotherapy doublet that often includes four to six cycles of carboplatin plus paclitaxel provides the backbone for first-line systemic therapy and is associated with a median overall survival (OS) of 37 months and median progression-free survival (PFS) of 13 months (24). With the introduction of molecular classification and the subsequent rapid development of clinical trials that investigated targeted immunotherapies, the Food and Drug Administration (FDA) has recently approved several immunotherapies in EC (Fig. 1B). The current National Comprehensive Cancer Network (NCCN) guidelines recommend consideration of molecular testing using a result-based algorithm that incorporates *POLE* sequencing, MMR immunohistochemistry (IHC) or MSI testing, and p53 IHC to guide prognostication (23). Human Epidermal Growth Factor Receptor 2 (HER2) IHC is recommended for all p53 abnormal tumors irrespective of histology (23). While testing recommendations are starting to be reflected in clinical practice, the role of molecular testing in treatment decisions continues to evolve (13,23,25). Currently, the NCCN guidelines for first-line treatment of inoperable primary or recurrent advanced-stage disease recommend the addition of immune checkpoint inhibitors (ICIs) to chemotherapy, e.g., durvalumab, a programmed death-ligand 1 (PD-L1) inhibitor, for dMMR/MSI-H tumors based on the DUO-E trial; pembrolizumab, a PD-1 inhibitor, irrespective of dMMR/MSI status and excluding carcinosarcoma based on the NRG-GY018 trial; and dostarlimab, a PD-1 inhibitor, irrespective of dMMR/MSI status based on the RUBY trial (Table 1). Additionally, HER2-targeted therapy with the antibody–drug conjugate (ADC), trastuzumab deruxtecan, is indicated in recurrent disease with HER2 3+ or 2+ expression by IHC based on the DESTINYPanTumor02 trial (Table 1). Second-line treatment after previous platinum-based chemotherapy and in the absence of a dMMR/MSI-H phenotype can involve pembrolizumab plus lenvatinib based on the KEYNOTE-775 trial (Table 1).

The tumor immune microenvironment (TIME) in EC and immunotherapeutic targets

EC antigenicity: Tumor antigenicity refers to the capacity of cancer cells to generate genomic products and peptide sequences that are recognized by the immune system (26). Cancer antigens can be used to train the immune system to recognize and kill EC cells with the help of cancer vaccines (Table 2) (27–29). Similarly, cytotoxic effector immune cells expressing chimeric antigen receptors (CARs) can be designed to target gynecologic cancer antigens (Table 2) (30–34). Tumor antigens can also guide targeted cytotoxic drug delivery using ADCs (Table 2) (35).

EC antigenicity is highly variable across histologic and molecular subtypes. Generally, a high tumor mutational burden (TMB) in EC is correlated with tumor antigenicity and

improved prognosis and response to PD-1/PD-L1 blockade (36–38). In a computational analysis of genomic and exome sequences from 30 different cancer types, UCCs collectively had the eleventh highest median number of somatic mutations (39). However, in this study the prevalence of somatic mutations varied widely within UCC, ranging from one to over 400 mutations per megabase, an upper limit that is comparable to the mutational burden in colorectal carcinoma, non-small cell lung cancer, and melanoma, all of which are cancers that tend to be responsive to immunotherapy. When subdivided by histology, endometrioid uterine adenocarcinoma displays a higher median TMB and a greater frequency of high TMB cases than carcinosarcoma, which in turn has a higher median TMB than serous adenocarcinoma (38,40). Among molecular phenotypes, dMMR/MSI-H tumors often but not always have high TMB and POLE mutated tumors tend to have very high TMB (28,37,40,41). CNL/p53wt and CNH/p53abn tumors are associated with low TMB (42). Variability in TMB in EC underscores the importance of interpreting its prognostic and predictive potential in the context of the molecular and histologic subtype.

Antigen production is driven by the specific mutational processes of the tumor. A computational analysis by the International Cancer Genome Consortium (ICGC) and TCGA revealed 23 mutational signatures that were frequently reproduced in UCC and associated with mutational processes involving deamination of 5-methylcytosine, expression of Apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like protein (APOBEC), deficiency of DNA MMR proteins, mutations involving POLE, and abnormal non-homologous end-joining (NHEJ), among others (43). Defective DNA replication and DNA damage repair can result in non-synonymous substitutions that translate into cancer-specific proteins or insertions and deletions that generate cancer-specific frameshift peptides, collectively termed neoantigens, *e.g.* mutant epidermal growth factor receptor (EGFR), tumor protein 53 (TP53), and Kirsten rat sarcoma viral oncogene homolog (KRAS) (Table 2) (44). TMB directly correlates with the number of T-cell clonotypes, reflecting the applicability of TMB as a proxy for neoepitope production (45). Additionally, global hypomethylation can lead to the aberrant expression of cancer/testis (CT) antigens, such as the Melanoma-Associate Antigen (MAGE) family and Preferentially Expressed Antigen in Melanoma (PRAME), during oncogenesis (46,47). A comprehensive proteogenomic study of 95 endometrioid and serous EC tumors identified evidence of neoantigen or CT antigen expression in 78% of tumors (48). Serous histology was associated with zero or one predicted neoantigen per sample and high levels of CT antigen expression. Endometrioid histology was associated with both a high frequency of predicted neoantigens as well as heterogeneous CT antigen expression. In this analysis, CT antigen expression did not correlate with POLE or MSI status, whereas the first and second highest neoantigen number per sample mapped to POLE mutated and MSI tumors, respectively. Of the hypo-mutated ECs, CN-low/endometrioid and CN-high/serous tumors display a comparable number of predicted neoantigens that is overall less than that of hypermutated ECs (49,50). Interestingly, while tumors that are CN-high with a low predicted neoantigen load and a non-hyper-mutated genotype correlate with worse PFS and are expected to be less responsive to immunotherapy, they likely have overexpression of specific genomic alterations that can be therapeutically targeted for more effective treatment combinations with immunotherapy (49). Collectively, researchers have repeatedly demonstrated an

increase in neoantigen production in POLE mutated and MSI-H/dMMR ECs in accordance with TMB.

The CT antigens, MAGE-3, MAGE-4, and PRAME are overexpressed in EC. Positive expression for MAGE-3 and MAGE-4 was demonstrated in 15% and 20% of ECs, respectively, and most often associated with serous histology and high tumor grade (51). Reports describe PRAME overexpression in 82–88% of endometrioid, 82–95% of serous, 50% of clear cell, and 60% of carcinosarcoma ECs irrespective of grade and stage (52,53).

In addition to neoantigens and CT antigens, natural surface antigen overexpression can also be used to differentially target cancer cells. HER2, Trophoblast cell-surface antigen 2 (TROP2), and Folate Receptor alpha (FRα) have emerged as highly studied, targetable biomarkers for EC treatment due in large part to their use in FDA-approved ADCs for other solid tumors (Table 2) (35,54–56). HER3, Mucin 1 (MUC1), mesothelin, and protein tyrosine kinase 7 (PTK7) represent additional overexpressed antigens that are the focus of ongoing clinical trials (Table 2).

Immunosurveillance and memory in the EC TIME: Tumor immunosurveillance generally refers to the concept of tumor growth suppression by immune cells that detect tumor antigen and home to sites of malignant cells (26). In EC, the prognostic significance of tumor-infiltrating lymphocytes (TILs) is well established (36). However, the therapeutic use of TILs, bispecific T-cell engagers (BiTEs), and engineered myeloid immune cells remains in early development (Table 2) (57,58). BiTEs are joined antibodies with two binding sites, one for a tumor-cell antigen and another for a T-cell factor, and function to physically bring activated, cytotoxic T cells closer to tumor cells for targeted kill. BiTEs have received FDA approvals in hematologic malignancies, including multiple myeloma.

Infiltration of ECs by innate immune cells is a developing area of study and has been previously summarized (14,59). A single-cell RNA sequencing and mass spectrometry analysis of primary EC tumors and corresponding peripheral blood mononuclear cells (PBMCs) demonstrated that, aside from T cells, natural killer (NK) cells represented the second most dominant population and this population comprised three distinct subsets with varied antitumor cytotoxic potential (60). Another RNA sequencing and proteogenomic analysis of endometrioid and serous EC demonstrated high variability in the representation of antigen presenting cells (APCs), including macrophages, neutrophils, dendritic cells (DCs), and NK cells between the two histologies, as well as between POLE and MSI-H phenotypes (48). Antigen presentation through Major Histocompatibility Complex (MHC) Class I and Class II provides a necessary link between EC antigen expression and expansion of adaptive cytotoxic cells (45,48,61,62). Future studies are needed to further validate the presence of myeloid cells among various EC subtypes, including rare histologies. Additionally, functional studies that evaluate how the EC TIME processes antigens and regulates the development of tolerance to antigen presentation may identify novel therapeutic targets.

BiTEs provide a therapeutic approach that circumvents the requirement for APC interaction (Fig. 2). BiTEs targeting receptor tyrosine kinase like orphan receptor 1 (ROR1), Claudin-6,

and Mucin 16 are currently under investigation in early phase clinical trials (Table 2). Claudin-6 (*CLDN6*), an integral membrane protein component of tight junctions, tends to have higher expression in endometrioid EC as compared to non-endometrioid histologies and is independently associated with worse OS in EC (63). Mucin 16 (*MUC16*), a large transmembrane glycoprotein that is frequently mutated in EC, tends to have lower expression in endometrioid adenocarcinoma than normal endometrium but *MUC16* mutations have been implicated in antitumor immunity and improved prognosis (64,65). The secreted component, CA-125, is elevated in the serum of ~20–25% of all ECs based on various studies that mainly included early-stage cancers; is reported to be elevated in 50–80% of Stage III/IV patients and when present portends a worse prognosis (66,67).

The extent of cytotoxic adaptive immune-cell infiltration into a tumor varies among ECs. POLE mutated and MSI-H/dMMR tumors are known to have a more robust antigenic footprint and also tend to have greater intratumoral $CD8^+$ TIL densities, suggesting that these molecular subtypes may be more susceptible to TIL therapy (28,50,68,69). Sporadic or hereditary origin of a tumor also influences the TIME and may impact the efficacy of various immunotherapeutic approaches (70). The number of activated cytotoxic T cells ($CD8^+$granzyme B^+) infiltrating the stroma is significantly increased in Lynch Syndrome MSI-H samples compared to sporadic MSI-H samples, whereas the number of activated cytotoxic T cells infiltrating the tumor is similar between the two groups (71). While the percentage of tumor-associated $CD8^+$ T cells is not significantly different among EC molecular subtypes, the percentage of tumor reactive $CD8^+$ T cells expressing CD39, a marker of T-cell exhaustion, is significantly higher in POLE mutated and dMMR/MSI-H EC compared to CN high EC (62). Expression of the integrin subunit, CD103, on resident memory T cells (T_{RM}) is stimulated by TGFβ and T-cell receptor (TCR) engagement and comparable among endometrioid, serous, and clear cell EC (72–75). Co-expression of CD39, CD103, and CD8 identifies tumor-reactive T_{RM}, is associated with increased MHC-I–dependent tumor-specific cytotoxicity in gynecologic cancers, and likely displays a distinct transcriptional profile in high-grade EC (73,74). A study of endometrioid EC demonstrated heterogeneous MHC Human Leukocyte Antigen (HLA) I and MHC HLA-II expression between samples and increased neoantigen-specific cytotoxic $CD4^+$ T cells expressing intracellular granzyme B and secreting IFNγ (61). Understanding the functional contribution of these cytotoxic T-cell subsets to malignant cell proliferation, death, and therapeutic resistance will enhance the development of antitumor immunotherapies.

The humoral adaptive immune response in EC has also been characterized. Endometrioid ECs demonstrate a significantly higher $CD4^+$ T-cell density than non-endometrioid histologies, collectively (76). When stratified by molecular subtype, researchers have found no significant difference in the number of tumor-infiltrating or tumor-associated $CD4^+$ T cells using immunohistochemistry and flow cytometry (62,69). Similarly, the prevalence of tumor-infiltrating CD20+ B cells is not significantly different between POLE mutated/MSI-H EC and MSS EC despite the significantly increased expression of chemokines, including chemokine [C-X-C motif] ligand 13 (CXCL13) which is a B-cell chemoattractant that is secreted by $CD4^+$ and $CD8^+$ TILs and required for tertiary lymphoid structure (TLS) formation (61,62,69,75). TLS are detected in 19–78% of ECs, depending on the surface marker expression pattern used and stratification by molecular or histologic subtype

(77–79). However, within the context of EC, whether TLS serve as a sink to sequester tumor-reactive immune cells or a reservoir for antitumor immune cell–activating interactions and antibody production remains unclear.

In EC, the prognostic validity of tumor-associated immune cells depends on several factors. The independent association of increased intratumoral $CD8^+$ TILs with improved OS and disease-free survival (DFS) across molecular and histologic subtypes has been consistently and enduringly demonstrated using IHC (68,76,80,81). However, when tumor-associated immune cells are detected by flow cytometry or in the context of TLS, the association with survival becomes less consistent (62,77–79). High density of $CD4^+$ TILs is an independent prognostic indicator of improved OS (76). Regulatory T cells (Tregs, $FoxP3^+CD4^+$) are not associated with DFS when stratified by high and low infiltrating density but a high ratio of $CD8^+$/FoxP3 and high numbers of $CD8^+$ T cells are associated with improved DFS (72,80). High numbers of $CD8^+$ T cells and $CD45R0^+$ memory cells correlate with significantly improved OS (80). Additional subpopulations of $CD8^+$ T cells expressing CD39 (exhaustion phenotype), CD103 (resident memory phenotype), and/or CXCL13 (B cell–chemokine phenotype) are emerging as favorable prognostic biomarkers (62,72,75). The gamut of studies investigating the prognostic potential of various tumor-infiltrating cell subsets demonstrates variability among tissue compartments (e.g., intraepithelial, peritumoral, stromal), cutoffs for high densities, methods of measurement (e.g., flow cytometry, IHC), and the detection of intracellular versus extracellular markers to name a few, underscoring the importance of interpreting TIL prognostic data in the correct context and with adequate sample size. Still, the identification of prognostically favorable immune cellular subsets can further optimize TIL therapy. Furthermore, investigations into TIL subpopulations and response to immunotherapy can elucidate potential predictive biomarkers (36).

In summary, the variable TIME among EC molecular and histologic subtypes impacts prognosis and response to immunotherapy. POLE mutated and MSI-H/dMMR tumors can be described as immune-included given their association with antigenicity and immune-cell infiltration. In contrast, CN low and CN high tumors align more with an immune excluded phenotype based on limited TMB/neoantigen burden and relatively low immune-cell infiltration. Both immune-included and immune-excluded tumors are susceptible to molecular and cellular immunoregulation that further impacts the overall immunogenicity of the cancer.

EC immunoregulation: While tumor antigenicity and immune-cell infiltration are integral components of an antitumor immune response, they alone are inadequate to ensure sufficient effector function for the elimination of malignant cells. Ultimately, antitumor effector function results from the summation of innumerable inhibitory, activating, and costimulatory signals orchestrated by innate and adaptive immune cells as well as stromal cells (26). Generally, ECs display an immunosuppressive phenotype and employ multiple mechanisms to evade the immune system (59). The PD-1 and PD-L1 axis is the most heavily studied mechanism of immune evasion in EC and represents the first class of ICIs to receive FDA approval in EC (Fig. 1B) (59,82). Beyond the PD-1/PD-L1 immune checkpoint axis, B7 Homolog 4 (B7-H4), Lymphocyte-activation gene 3 (LAG-3), T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT),

and poliovirus receptor-related immunoglobulin domain-containing (PVRIG) protein are emerging immunosuppressive immune checkpoint receptors expressed in EC and are the target of multiple ongoing clinical trials (Table 2) (36,83–86). Given the association of immunosuppressive macrophages and Tregs with worse prognosis and features of tumor aggressiveness in EC, both cell types represent prime therapeutic targets as well (14,59).

Similar to PD-L1, B7-H4 is a member of the B7 family of immune checkpoints that is expressed on tumor cells and antigen-presenting cells (APCs) and has been shown to suppress $CD4^+$ and $CD8^+$ T-cell function by reducing cytokine production and cytolytic activity, inducing T cell cycle arrest, stimulating the differentiation of $CD4^+$ T cells into Tregs, and activating the suppressive function of Tregs(36,86). However, as a novel biomarker, several aspects of B7-H4 biology in EC remain unclear. The prevalence of B7-H4 positivity or overexpression ranges from 71.5 −100% in ECs, depending on the clonal antibody used for detection and cutoffs for positivity (36,86). Conclusions on the prognostic potential of B7-H4 vary among studies, likely owing to differences in patient population and number, primary or metastatic site, cutoffs for positivity, and median follow-up. An early study of 86 patients with uterine endometrioid histology found no relationship between B7-H4 positivity and DFS (87). More recently, a study of 63 patient samples correlated low B7-H4 expression with improved OS and five-year survival without significance as an independent prognostic marker in multivariate analysis (88). Still, a larger study of 664 patients showed that positive B7-H4 expression was a positive independent predictor of disease-specific survival in multivariate analysis (89). Importantly, the B7-H4 ligand on T cells has not yet been identified and research studies have produced conflicting data on the association between B7-H4 expression and TILs (36,86,87,89). Based on IHC detection of B7-H4 expression, most studies report no significant differences between MSI-H and MSS tumors, histologic subtypes, lymph node metastases, myometrial invasion, and stage (87–90). Interestingly, non-specific molecular profile (NSMP) and p53 mutant ECs both displayed higher percentages of B7-H4 positivity than POLE mutated and dMMR tumors, and positive B7-H4 status independently predicts disease-specific survival in NSMP tumors, suggesting B7-H4 targeting therapeutics may be effective options for otherwise high risk EC that is resistant to immunotherapy (89). Future investigations into the mechanism of B7-H4 immunosuppression in EC will benefit from standardized immunoreactivity scoring and cutoffs for positivity.

LAG-3 is a member of the immunoglobulin (Ig) superfamily and is mainly expressed on activated T and NK cells (36). Whereas engagement of MHC-II by LAG-3 inhibits $CD4^+$ T-cell activity, LAG3 binding to fibrinogen-like protein 1 on cancer cells has been demonstrated to inhibit antigen-specific IL-2 secretion in a murine T-cell line, suggesting that the specific binding partner mediates the effect of LAG-3 immunosuppression (36,91,92). Using IHC analysis of 421 patients, immune cells positive for LAG-3 expression were evident in 24% of ECs and tumor cells positive for LAG-3 expression were present in 31.6% of ECs (93). Expression is not associated with specific parameters of tumor aggressiveness, including extent of myometrial invasion, stage, and presence of lymph node metastases (93,94). However, depending on the pattern of LAG-3 expression, studies have shown conflicting correlation with LAG-3 expression and high-grade tumors as well as LAG-3 expression and histology (93,94). LAG-3 expression is significantly increased in

POLE mutated and dMMR tumors and associated with increased cytotoxic TILs (93–95). While LAG-3 expression correlates with improved recurrence-free survival, PFS, and OS, multivariate analyses have failed to produce LAG-3 expression as an independent prognostic marker (93–95). Additional studies aimed at characterizing the expression of LAG-3 binding partners, including fibrinogen-like protein 1, in EC may clarify the mechanism of LAG-3-mediated immunosuppression and define tumor subtypes that could benefit from immunotherapies targeting LAG-3.

TIGIT and PVRIG are distinct inhibitory receptors within the nectin and nectin-like family whose expression has collectively been described on $CD4^+$ and $CD8^+$ T cells, $CD8^+CD103^+$ memory T cells, $CD14^+$ tumor-associated macrophages (TAMs), and $CD56^+$ NK cells in EC (96–98). While both TIGIT and PVRIG have been shown to have multiple binding partners, TIGIT binds the poliovirus receptor (PVR, CD155) expressed on myeloid-derived suppressor cells with strongest affinity and PVRIG binds the poliovirus receptor ligand 2 (PVRL2, CD112) expressed on malignant epithelial cells, endothelial cells, and fibroblasts with greatest affinity (97). Multiple studies link TIGIT and PVRIG expression to an exhausted lymphocyte phenotype (73,96,98,99). TIGIT and PVRIG signaling mechanisms are non-redundant but ultimately reduce chemokine and cytokine production and directly inhibit T-cell activation and proliferation (96,97,100). Increased TIGIT expression on EC-associated NK cells is associated with reduced secretion of IFN-γ, TNF-α, granzyme-B, and degranulation, measured by CD107 release, compared to normal adjacent tissue (69). ECs are ranked within the top five solid tumors with the highest levels of PVRIG and TIGIT expression on $CD4^+$ and $CD8^+$ T cells from the primary tumor and TIGIT or PVRIG expression tends to be higher than their respective ligands (96,99). Although data on expression patterns within EC subtypes is limited, one study demonstrated TIGIT expression in a cohort of serous ECs with varying characteristics of tumor aggressiveness and determined that high TIGIT expression is a significant independent prognostic marker of OS in multivariate analysis (95). PVRIG blockade has been shown to increase TIGIT expression and dual TIGIT and PVRIG blockade in pancreatic and colon cancer preclinical models leads to increased T-cell activation, proliferation, and cytokine release (96,99). Additional studies on expression patterns of the TIGIT/PVRIG axis within EC molecular and histologic subtypes and the impact of dual PVRIG/TIGIT blockade on immune checkpoint expression in NK, TAM, T, and stromal cells will provide insight into potential resistance mechanisms.

In summary, the EC TIME represents a complex and dynamic interplay among cellular and chemical factors. Tumor antigenicity, immune surveillance, and immunoregulation form the foundation of the EC TIME and vary among histologic and molecular subtypes, suggesting inherently different pathophysiology of these tumors. These three foundational components of the TIME are the focus of targeted antitumor immunity–enhancing therapies that are FDA approved and/or in ongoing clinical investigation (Fig. 2).

On the horizon: emerging concepts of immunogenic modulation and immune subset conditioning for the treatment of EC

The mechanistic impact of cancer treatment on the TIME can be encompassed within two broad domains: *immunogenic modulation* and *immune-subset conditioning*. Immunogenic

cell death (ICD) refers to a type of target cell demise induced by an immune reaction. Immunogenic modulation elucidates how anticancer treatments modify the TIME and impact the susceptibility of surviving tumor cells to immune-mediated destruction (101). Immunogenic modulation is distinct from immunoregulation, which describes dynamic processes that stimulate or suppress an immune response. Immune-subset conditioning describes how therapeutic interventions create a more conducive environment for immune-cell infiltration and antitumor activity within the tumor as well as the periphery (102). Insight into the mechanisms of immunogenic modulation and immune-subset conditioning offers a rationale for optimized immunotherapeutic strategies that target the immunosuppressive TIME and ultimately improve outcomes in EC.

Immunogenic modulation: standard-of-care plus experimental combination therapies to sensitize malignant cells to immune-mediated killing: Conventional chemotherapies were originally developed to preferentially and negatively impact rapidly dividing malignant cells. Typically, these therapeutic regimens induce DNA damage, disrupt DNA repair, or impair cell division, resulting in tumor cell death and cancer lesion debulking (103). In addition to these cytotoxic and cytostatic agents, some standard-of-care therapies such as radiotherapy and small molecule inhibitors (SMIs) also induce cell stress that results in immunogenic modulation and ICD (101). ICD, wherein dying cells release signals that prompt DCs to present tumor antigens to T cells, culminates in the activation and development of immunological memory (104,105). If the therapy-induced cell stress does not result in cell death, the surviving tumor cells may be sensitized to immune-cell targeting via immunogenic modulation, which includes upregulated antigen presentation, pro-apoptotic signaling molecules, and immune cell–engaging molecules (101). Exposure of tumor cells to nonlethal/sublethal doses of standard-of-care therapies can render the surviving tumor cells more sensitive to immune-mediated killing (Fig. 3A). Combining standard-of-care therapies known to induce immunogenic modulation with immunotherapy provides an opportunity to sensitize patients' tumors to immunotherapy with drugs that are already FDA approved and that display well-known safety profiles. Our group and others have previously shown immunogenic modulation with several standard-of-care therapies (Fig. 3A), including (a) taxanes (*e.g.* docetaxel, paclitaxel, nab-paclitaxel) (106,107); (b) platinum-based chemotherapy (*e.g.* cisplatin/5-FU, cisplatin/vinorelbine) (108–111); (c) radiation (*e.g.* external-beam, proton, brachytherapy, radioantibody, nuclide chelate, radiofrequency) (108,112–129); d) PARP inhibitors (*e.g.* olaparib, niraparib) (130–133); tyrosine kinase inhibitors (*e.g.* sunitinib/sorafenib/cabozantinib) (134–136); (e) histone deacetylase (HDAC) inhibitors (*e.g.* vorinostat, entinostat) (137–139); and (f) endocrine therapy (*e.g.* tamoxifen, fulvestrant, aromatase inhibitors) (140–143). Prospective clinical trials and translational studies are needed to identify subgroups of EC patients who may benefit from these combination therapies.

Immune-subset conditioning: experimental therapies that counteract the immunosuppressive TIME: Generally, immunotherapy aims to both induce robust antitumor effector cell populations and create a more immune-permissive TIME. Immune-subset conditioning involves three distinct mechanisms. One mechanism involves the establishment of effector cells, which relies on antigen cascade signaling. The antigen

cascade describes pathways by which antigen presentation ultimately leads to effector cell recognition and can be mimicked or enhanced therapeutically with standard-of-care treatments, vaccines, and/or adoptive transfer of NK cells (Fig. 3B). A second mechanism involves the activation and preservation of effector function and this can be achieved therapeutically with synthetic cytokines and/or costimulatory agonist antibodies (Fig. 3B). Lastly, a third mechanism involves the reduction of negative regulatory elements that release the suppression of effector function and can be done through therapies that target M2 macrophages, Tregs, and myeloid-derived suppressor cells (MDSCs) (Fig. 3B). These therapeutic strategies are described below in the context of non-EC solid malignancies and have not yet been tested in EC.

Establish effector cells: vaccine, chemotherapy, modified NK cells: Cancer vaccines are designed to display tumor antigen and are often coupled with stimulatory agents to augment the expansion of tumor-specific, cytotoxic effector cells. Cancer vaccines can be designed using peptide sequence, nucleic acids, cells (*e.g.* DCs), or vectors, each with varying degrees of efficacy. Vaccines that target CT antigens overexpressed in EC, *e.g.* MAGE-3 and PRAME, have been tested in non-EC clinical settings (144,145). Vaccines targeting natural surface antigens overexpressed in EC, *e.g.* HER2, TROP2, and FRα, are also undergoing evaluation (55,146,147). Lastly, TriAdeno is a novel approach that combines three adenovirus vector–based vaccines each targeting antigens implicated in EC: MUC1, carcinoembryonic antigen (CEA), and brachyury, and has been tested in pre-clinical models and Phase I studies (148,149).

Modified NK cells can be employed to directly increase effector cell infiltration into a tumor. PD-L1 t-haNK cells are allogeneic NK cells engineered to express the NK activating signal, CD16, and a high-affinity PD-L1 CAR and retain the expression of endogenous NK receptors (150,151). These cells do not require recipient matching and can be cultivated at large scale for adoptive transfer. Early signs of efficacy of this approach have been reported in small case studies and PD-L1 t-haNK cells are currently under investigation as part of combination immunotherapy in a phase 2 clinical trial involving patients with head and neck squamous cell carcinoma (NCT06239220) (152,153). Memory-like NK cells (m-CENK) are haploidentical NK cells purified by expression of the NK-cell marker, CD56, and further enriched with the stimulatory cytokines, IL-15, IL-12, and IL-18. This approach was recently tested in a first-in-human phase I trial that demonstrated the safety of m-CENK in combination with the IL-15:IL-15 receptor α superagonist, N-803, and ipilimumab, a cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor (154).

Enhance effector function: cytokines and second-generation costimulatory molecules: Therapeutic cytokines directly promote effector cell activity and inhibit suppressive cells when used in combination immunotherapies. The tumor necrosis factor receptors (TNFRs), OX40, 4–1BB, CD40, and glucocorticoid-induced TNFR-related protein (GITR), potentiate the efficacy of cancer vaccines by inhibiting Tregs and providing necessary costimulatory signals for T-cell activation and immune cell memory (155,156). The superagonist, N-803, augments NK-cell and memory $CD8^+$ T-cell proliferation (157–159). N-803 (as Anktiva®) was FDA approved in 2024 for non-invasive bladder carcinoma.

A first-in-class, recombinant protein, NHS-IL12, combines a human monoclonal antibody against DNA exposed at sites of tumor necrosis with two heterodimers of IL-12 (160). NHS-IL12 thereby accumulates intratumorally and induces $CD4^+$ T-cell differentiation, IFN-γ release, and $CD8^+$ T-cell and NK-cell recruitment. The safety of NHS-IL12 has been validated in multiple early phase trials (161,162). A similar agent, aluminum-anchored IL-12 (Alum-IL12), can remain in the TIME for up to thirty days without signs of toxicity and stimulates the differentiation of suppressive M2 macrophages into proinflammatory M1 macrophages in preclinical models (163). The tolerability and biologic activity of Alum-IL12 have been demonstrated in a first-in-human phase 1 trial (164).

STAR0602 represents a second-generation costimulatory molecule. STAR0602 is a first-in-class bifunctional antibody designed by fusing an IL-2 molecule with an antibody that specifically targets T cells expressing variable beta 6 and beta 10 (Vβ6/Vβ10) regions of the T cell receptor and thereby directly stimulates the activation and proliferation of tumor-associated Vβ6/Vβ10 T cells (165). The safety and clinical activity of STAR0602 is being investigated in ongoing early phase clinical trials of patients with anti-PD-L1 resistant solid tumors (166).

Release suppression: inhibitory signaling antagonists: Inhibitory signals can be antagonized therapeutically to release immunosuppression in the TIME. The transforming growth factor-beta (TGF-b) cytokine family promotes the activation of M2 macrophages, Tregs, and MDSCs and several classes of drugs have been designed to selectively counteract TGF-β activity (167). However, collectively, TGF-β antagonists have demonstrated limited clinical benefit and require further optimization. Chemokine receptors 1 and 2 (CXCR1 and CXCR2) regulate MDSC migration and blockade of this axis with the small molecule, SX-682, can reduce tumor-associated MDSCs and potentiate the cytotoxic effects of immunotherapy or chemotherapy (168,169). As a first-in-class oral antagonist, SX-682 is currently undergoing evaluation in phase I clinical trials including patients who progressed on anti-PD-1 treatment (170). Similarly, colony-stimulating factor 1 (CSF1) is a chemokine required for the differentiation and proliferation of TAMs and correlates with worse prognosis, invasiveness, and metastasis in solid tumors, including ovarian carcinomas (171). Blockade of the CSF1/CSF1 receptor (CSFR1) axis results in decreased TAMs and increased tumor-infiltrating $CD8^+$ T cells, providing a preclinical rationale for CSF1/CSFR1 blockade in combination with cancer vaccines. However, currently, clinical trials are investigating the safety and efficacy of small molecule inhibitors and antibodies against CSF1/CSFR1.

A synthesis: rationale for multi-agent immunotherapy combinations: The optimization of systemic antitumor treatment in EC may ultimately require a multi-drug regimen due to the complexity of the immune-excluded TIME and pleiotropic effects of individual immunologic agents. Theoretically, this integrated approach would include agents that concertedly establish effector immune cells, stimulate their proliferation, differentiation, and migration, and sustain their activation. A preclinical study demonstrated the efficacy of a pentatherapy that combined a cancer vaccine, N-803, OX40, GITR, and an indoleamine 2,3-dioxygenase inhibitor (IDOi) (172). In this study, pentatherapy resulted

in increased tumor-associated $CD4^+$ and $CD8^+$ T-cell activity, reduced Treg infiltration, greater reduction in tumor growth, and protection during tumor rechallenge as compared to various monotherapy and dual therapy variations. A second preclinical study compared the efficacy of a hexatherapy combination in a “warm” tumor model and a “cold” tumor model and concluded that the “cold” tumor model required all six agents to reduce tumor size, whereas the “warm” tumor model demonstrated moderate efficacy with monotherapy alone (173). Given the novelty of rationally designed, comprehensive multi-agent combination immunotherapies, the clinical benefit of such an approach has not been established. Early phase clinical trials are ongoing and have demonstrated the safety of multi-drug regimens as well as their ability to expand immune cell subsets in patients (NCT04390399) (154).

Conclusions and future considerations

The TIME represents dynamic cellular and molecular interactions that summate tumor antigenicity, immune-cell infiltration, and immunoregulation. The study of factors affecting the TIME is vast and includes hormone secretion, microbiome growth, and microRNA production in addition to the factors addressed in this review. While collectively ECs present an immunosuppressed TIME, POLE-mutated, MSI-H/dMMR, and endometrioid tumors tend to be immune-included demonstrating high antigenicity and immune cell infiltration and CNL/p53wt, CNH/p53abn, and non-endometrioid tumors tend to be immune-excluded with low TMB and restricted immune-cell infiltration.

Understanding these distinctions among EC subtypes is important for optimal precision therapy, especially in the mitigation of worse clinical outcomes among racial and ethnic minority groups. Non-Hispanic African American (AA) patients are more likely to be diagnosed with aggressive, non-endometrioid histologies (8,174). Researchers have reported conflicting results on ethnic and racial differences in genomic alterations and molecular phenotypes that impact the TIME, including MSI-H, CNH, TP53 mutation, and PD-L1 expression (174–176). Importantly, the interpretation of these studies is often complicated by small patient numbers, the use of self-reported race rather than genetic ethnic ancestry, and the lack of analyses that control for confounding factors related to social determinants of health and comorbid biologic factors.

The integration of therapeutic approaches that exploit immunogenic modulation and immune subset conditioning offers emerging opportunities to augment existing antitumor treatments and further tailor treatment to EC subtype. Effective therapies balance tumor cell killing with immunogenic modulation, two factors that are essential for tumor debulking and malignant cell eradiation but often counterbalanced in the TIME. While radiation and systemic therapy–mediated cell killing initially increase the dying fraction of a tumor and thereby tumor antigen exposure, eventually they remove the source of antigen that is required to educate and activate the immune system. Additionally, antitumor treatment can modify the physiology of antitumor immune cells and exert off-target cytotoxicity on immune cells. These inherent and unintended consequences in turn limit the synergy of innate, cellular, and humoral immune factors that lead to long-term antitumor memory and sustained malignant cell clearance. Importantly, pre-clinical animal modeling and clinical

studies are necessary to optimize therapeutic dosing and sequence for an effective balance of anti-tumor effect and immunogenic modulation.

Additionally, studies using IHC, multiplexed immunofluorescence, flow cytometry, and single-cell RNA sequencing of primary and metastatic EC tumors are needed to thoroughly characterize the immunologic and stromal landscape of EC subtypes, validate computational analyses of the TIME, and support efforts to rationally design combination immunotherapeutic regimens. Further investigation into the effects of treatment on the TIME can elucidate mechanisms of primary and secondary resistance to immunotherapy and guide the development of strategies that sensitize poorly responsive tumors to immunotherapy. Lastly, mechanistic studies aimed at understanding the complexity of interactions among subpopulations of innate and adaptive immune cells can provide detailed insight into how to harness antitumor activity for a durable, curative effect. The development of immune-intact preclinical models is needed to address these mechanistic questions and EC patient-derived organoids (PDOs) are emerging as one alternative to animal models (177–179). EC PDO co-culture experiments can be designed to elucidate the juxtaposition of antitumor effect with immunogenic modulation by observing the effects of immunotherapy on immune cells and tumor cells, separately and together. Predictive computational models may also prove to be a useful preclinical tool in the study of EC, especially rare subtypes. Together, these efforts can build on the current momentum of recently FDA approved immunotherapies in EC and transform the treatment outlook for high morbidity and high mortality EC.

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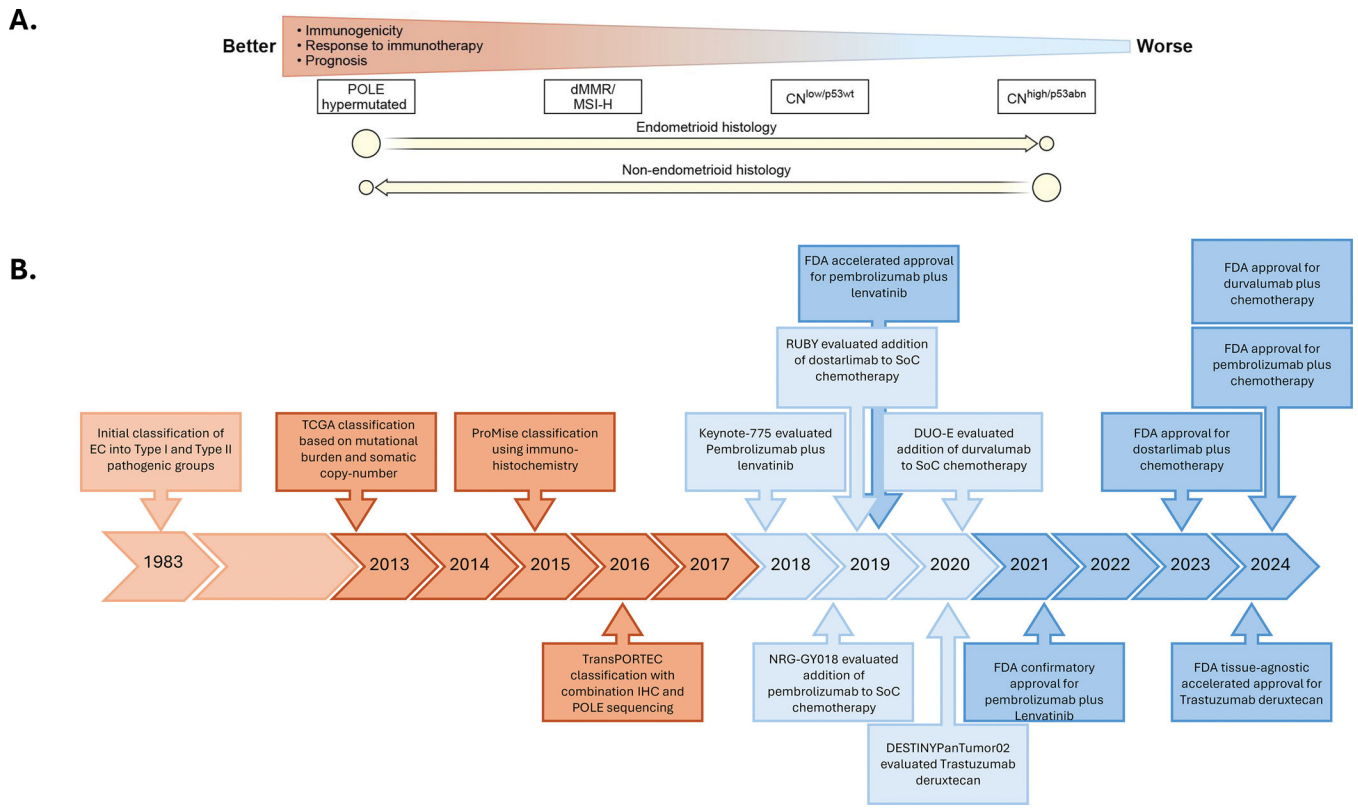

Figure 1.

A. Schematic to depict the gradation of immunoreactivity, susceptibility to immunotherapy, and overall prognosis among the different types of endometrial cancers. **B.** Timeline of diagnostic and immunotherapeutic advancements in endometrial cancer. This timeline highlights advancements in the diagnostic classification of endometrial cancer and Food and Drug Administration (FDA) approvals for the treatment of endometrial cancer. Manuscript dates are based on the year of publication. Clinical trial dates are based on the year the trial opened. TCGA, The Cancer Genome Atlas; SoC, Standard of Care; ECs, Endometrial Cancers.

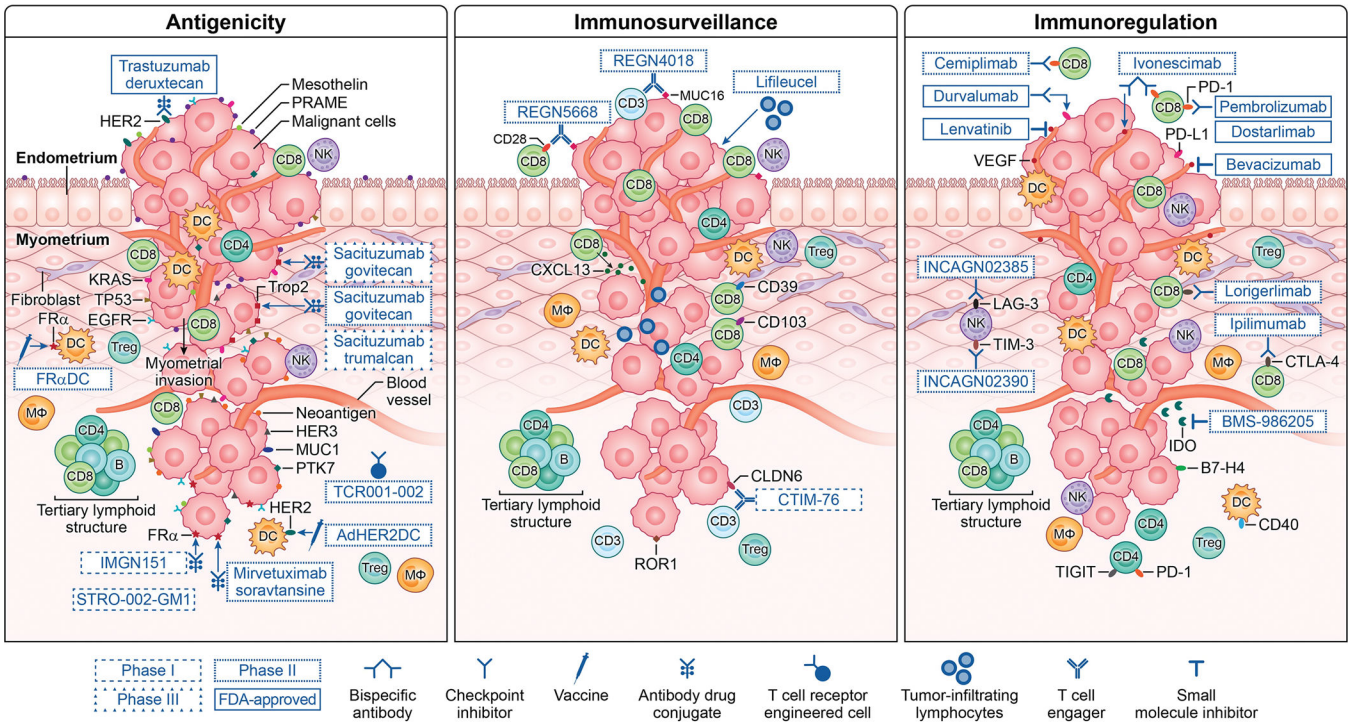

Figure 2.

Immunotherapeutic targets within the endometrial cancer TIME. Each panel illustrates therapeutic targets and corresponding therapies that are under clinical investigation in gynecologic malignancies or FDA-approved for treatment in endometrial cancer. The first panel focuses on the antigenicity of the EC TIME. The second panel focuses on factors involved in immunosurveillance in the EC TIME. The third panel focuses on immunoregulation in the EC TIME.

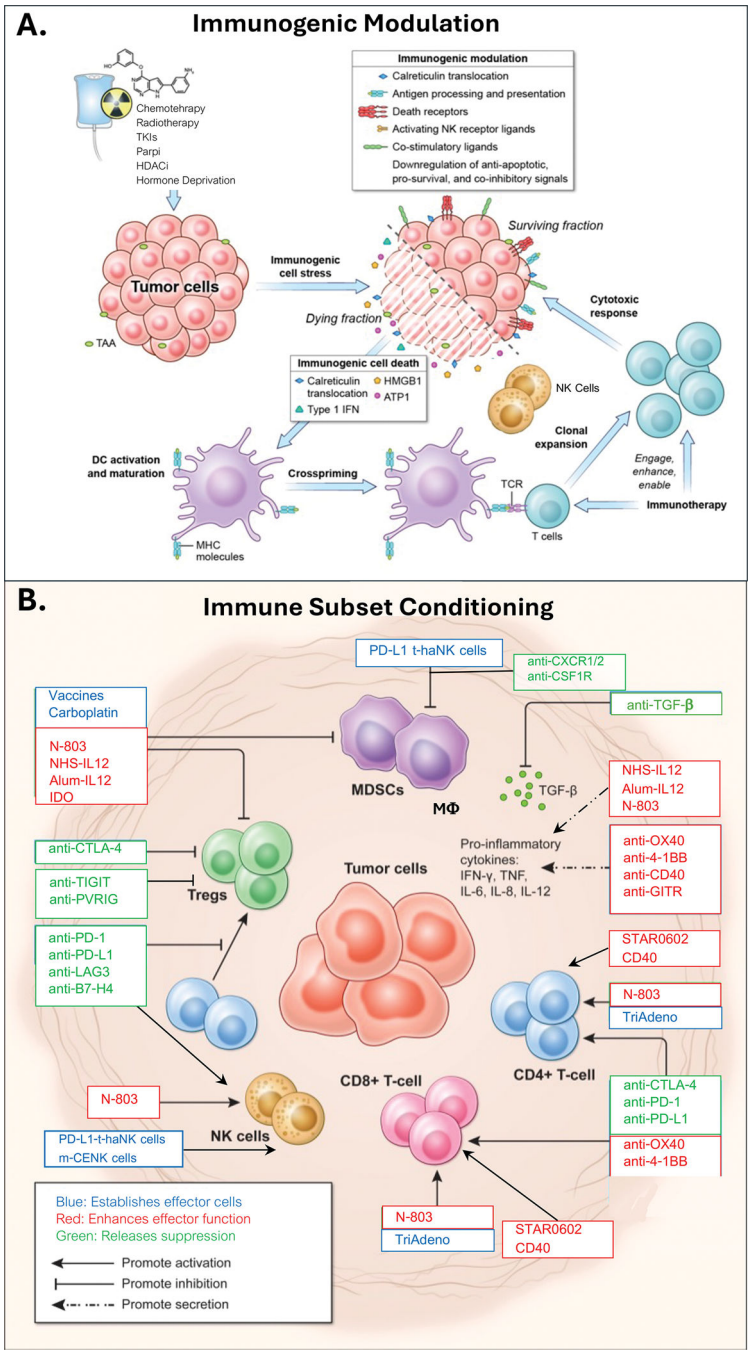

Figure 3.

Targeted approaches that overcome immune suppression in the TIME. Modified from (101,102). **A.** Depicts the concept of immunogenic modulation whereby anticancer treatments alter or kill tumor cells and enhance antitumor immune responses. **B.** Displays immunotherapeutic targets and their corresponding immunotherapy within the concept of immune subset conditioning whereby therapeutic products are used to mediate immune cell function and enhance antitumor immunity.

Table 1.

Clinical Trials that Led to the Approval of Treatments for Endometrial Cancer

NCT Number	Common Name	Phase	Treatment	Patient Population	Outcome	Current Status	Expected Completion Year	Ref
NCT04482309	DPTO2	2	Trastuzumab deruxtecan	HER2 expressing/ amplified solid tumors including EC	ORR HER2 IHC 3+: 61.3% (95% CI, 49.4 to 72.4) Overall: 37.1% (95% CI, 31.3 to 43.2) DOR HER2 IHC 3+: 22.1 months (95% CI, 9.6 to not reached) Overall: 11.3 months (95% CI, 9.6 to 17.8) PFS HER2 IHC 3+: 11.9 months (95% CI, 8.2 to 13.0) Overall: 6.9 months (95% CI, 5.6 to 8.0) OS HER2 IHC 3+: 21.1 months (95% CI, 15.3 to 29.6) Overall: 13.4 months (95% CI, 11.9 to 15.5) Grade ≥3 TEAE = 40.8%	Recruiting	2027	(180)
NCT03981796	RUBY	3	Carboplatin/ paclitaxel with or without Dostarlimab, carboplatin/ paclitaxel with dostarlimab with or without niraparib	Recurrent or Primary Advanced EC	PFS at 24 months (treatment vs placebo) dMMR–MSI-H population: 61.4% (95% CI, 46.3 to 73.4) vs 15.7% (95% CI, 7.2 to 27.0; HR, 0.28; 95% CI, 0.16 to 0.50; P<0.001) overall: 36.1% vs 18.1% OS 24 months (treatment vs placebo) 71.3% (95% CI, 29.3 to 42.9) vs 56.0% (95% CI, 13.0 to 23.9; HR, 0.64; 95% CI, 0.51 to 0.80; P<0.001)	Active, not recruiting	2026	(181)
NCT03914612	NRG-GY018	3	Carboplatin/ paclitaxel with or without Pembrolizumab	Stage III, IV, or Recurrent EC or UCC	PFS (treatment vs control) at 12 months in dMMR: 74% vs 38% (HR, 0.30; 95% CI, 0.19 to 0.48; P<0.001), in pMMR cohort: 13.1 months vs 8.7 months (HR, 0.54; 95% CI, 0.41 to 0.71; P<0.001)	Active, not recruiting	2022	(182)
NCT03517449	KEYNOTE-s775	3	Pembrolizumab plus lenvantinib compared to physician's choice	Advanced, recurrent, metastatic EC	PFS (combo vs chemo) pMMR population: 6.6 vs. 3.8 months (HR, 0.60; 95% CI, 0.50 to 0.72; P<0.001) overall: 7.2 vs. 3.8 months (HR, 0.56; 95% CI, 0.47 to 0.66; P<0.001) OS (combo vs chemo) pMMR population: 17.4 vs. 12.0 months (HR for death, 0.68; 95% CI, 0.56 to 0.84; P<0.001) overall: 18.3 vs. 11.4 months (0.62; 95% CI, 0.51 to 0.75; P<0.001) Grade ≥ 3 AEs (combo vs chemo) 88.9% vs 72.7%	Active, not recruiting	2000	(183)
NCT02715284	Garnet	1	Dostarlimab monotherapy	Part 2B Cohort A1: dMMR/MSI-H EC Part 2B Cohort A2: pMMR/MSS EC	ORR for dMMR population: 44.0% (95% CI, 38.6% to 49.6%) DOR: not reached (range, ≥1.18 to ≥47.21 months) Response lasting ≥ 12 months: 72.2 of responders PFS: 6.9 months (95% CI, 4.2 to 13.6 months) PFS at 24 months: 40.6% (95% CI, 35.0% to 46.1%) OS: not reached (95% CI, 31.6 months to not reached)	Recruiting	2026	(184)

NCT Number	Common Name	Phase	Treatment	Patient Population	Outcome	Current Status	Expected Completion Year	Ref
NCT02628067	KEYNOTE-158	2	Pembrolizumab monotherapy	Advanced, recurrent solid tumors, including EC	ORR: 30.8% (95% CI 25.8% to 36.2%) DOR: 47.5 months range, 2.1+ to 51.1+ months, '+' indicates no progressive disease by the time of last disease assessment) PFS: 3.5 months (95% CI 2.3–4.2 months) OS: 20.1 months (95% CI 14.1–27.1 months) TEAE: 64.7%	Recruiting	2027	(185)
NCT01367002	n/a	2	Carboplatin/ paclitaxel with or without trastuzumab	Uterine Serous Papillary Carcinoma overexpressing HER2	PFS (treatment vs placebo) overall: 12.9 vs 8 months (HR = 0.46; 90% CI, 0.28–0.76; $P = 0.005$) stage III/IV disease: 17.7 vs 9.3 months HR, 0.44; 90% CI, 0.23–0.83; $P = 0.015$) recurrent disease: 9.2 vs 7 months (HR, 0.12; 90% CI, 0.03–0.48; $P = 0.004$) OS (treatment vs placebo): overall: 29.6 versus 24.4 months (HR, 0.58; 90% CI, 0.34–0.99; $P = 0.046$) stage III/IV disease: not reached vs 24.4 (HR, 0.49; 90% CI, 0.25–0.97; $P = 0.041$)	Completed	2022	(186)
NCT04269200	DUO-E	3	Carboplatin/ paclitaxel plus durvalumab followed by maintenance durvalumab with or without olaparib	Advanced or recurrent EC	PFS (durvalumab plus chemo vs. control) ITT: 10.2 vs. 9.6 months (HR= 0.71; 90% CI, 0.57 – 0.89; $P = 0.003$) PFS (durvalumab plus olaparib vs. control) ITT: 15.1 vs. 9.6 months (HR= 0.55; 90% CI, 0.43 – 0.69, $P < 0.0001$) OS – not matured	Active, not recruiting	2027	(132)

HER, human epidermal growth factor receptor; EC, endometrial cancer; IHC, immunohistochemistry; HR; hazard ratio; CI, confidence interval; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; TEAE; treatment emergent adverse event; *dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; UCC, uterine corpus carcinoma; pMMR, proficient mismatch repair; AE, adverse event; MSS*, microsatellite stable; ITT, intention-to-treat

Table 2.

Ongoing Clinic Trials on Endometrial Cancer

	NCT Number	Phases	Treatment	Patient Population	Primary Endpoint	Current Status	Expected Completion
ADC	NCT06242470	1	B7-H3-directed ADC with topoisomerase I inhibitor	Unresectable, locally advanced or metastatic solid tumors including EC	Number of participants with AEs and SAEs	Recruiting	2028
	NCT06330064	2	B7-H3-directed ADC with topoisomerase I inhibitor	Recurrent or metastatic solid tumors including EC that has progressed after systemic platinum-based chemotherapy and ICI therapy	ORR, Number of participants with DLTs and AEs	Recruiting	2028
	NCT06774963	1	B7-H4-directed ADC with MMAE	Advanced unresectable and/or metastatic solid tumors including EC	Safety and tolerability, RP2D	Recruiting	2026
	NCT05123482	1|2	B7-H4-directed ADC with topoisomerase I inhibitor	Solid tumors including metastatic or locally advanced/recurrent EC	Number of participants with DLTs, AEs, and changes from baseline laboratory findings	Recruiting	2027
	NCT03832361	2	FRα-directed ADC with maytansinoid payload	FRα+ persistent or recurrent EC with ≤ 3 prior lines of therapy	ORR	Recruiting	2025
	NCT06400472	1	FRα-directed ADC with topoisomerase I inhibitor, anti-VEGF mAb, carboplatin	FRα+ advanced solid tumors including EC	Number of participants with DLTs, determine RP2D, ORR	Recruiting	2027
	NCT05527184	1	FRα-directed ADC with maytansinoid payload	Recurrent EC with 1–3 prior lines of therapy.	Number of participants with DLT, AEs, and SAEs, RP2D	Recruiting	2027
	NCT05579366	1|2	FRα-directed ADC with topoisomerase I inhibitor	Solid tumors including advanced and/or metastatic EC	Incidence of TEAEs, proportion of participants with DLT, ORR	Recruiting	2027
	NCT05377996	1	HER-2-directed ADC with Auristatin F hydroxypropylamide	Solid tumors including refractory/ relapsed EC with least 1 prior SoC treatment	Frequency and incidence of AEs, ORR	Recruiting	2026
	NCT06003231	2	HER-2-directed ADC with MMAE	HER2+ solid tumors including unresectable locally-advanced or metastatic EC that relapsed/ progressed after at least one prior platinum-based chemotherapy	ORR	Active, not Recruiting	2026
	NCT05150691	1|2	HER2-directed ADC with topoisomerase I inhibitor	HER2+ solid tumors including EC	Percentage of particicpatns with DLT and AEs, MTD, RP2D, ORR, pharmakokinetics	Recruiting	2026
	NCT06293898	1	HER2-directed ADC with topoisomerase I inhibitor	HER2+ advanced solid tumors including EC	Safety, MTD/MAD, RDE	Recruiting	2025
	NCT06172478	2	HER3-directed ADC with topoisomerase I inhibitor	Advanced solid tumors including recurrent/persistent endometrial cancer that has progressed after systemic platinum-based	ORR	Recruiting	2025

	NCT Number	Phases	Treatment	Patient Population	Primary Endpoint	Current Status	Expected Completion
				chemotherapy and anti-PD-1/PD-L1 therapy			
	NCT06751329	1	HER3/MUC1 bispecific ADC with MMAE	Advanced solid tumors including EC	DLTs, MTD	Recruiting	2027
	NCT06466187	1	MSLN-directed ADC with topoisomerase I inhibitor	Metastatic or locally advanced unresectable solid tumors including EC that has progressed after standard cytotoxic therapies	Number of participants with AEs and DLTs	Recruiting	2028
	NCT06171789	1|2	PTK7-directed ADC with MMAE	Advanced solid tumors including EC	Number of participants with AEs and DLTs	Recruiting	2028
	NCT06865677	2	Trop-2-directed ADC with topoisomerase I inhibitor	Recurrent/refractory EC with prior anti-PD-1/PD-L1-based therapy or not eligible for anti-PD-1/PD-L1-based therapy	ORR	Suspended, pending revision	2027
	NCT06486441	3	Trop-2-directed ADC with topoisomerase I inhibitor, doxorubicin, paclitaxel	Recurrent/persistent endometrial cancer that has progressed after systemic platinum-based chemotherapy and anti-PD-1/PD-L1 therapy	PFS, OS	Recruiting	2029
	NCT05489211	2	Trop-2-directed ADC with topoisomerase I inhibitor, capecitabine, 5-FU, prednisolone, carboplatin, cisplatin, anti-VEGF, folinic acid, PD-1/CTLA-4 bispecific antibody, PD-1/TIGIT bispecific antibody	Solid tumors including EC	ORR, number of participants with AEs and SAEs	Recruiting	2026
	NCT06040970	1|2	Trop-2-directed ADC with topoisomerase I inhibitor, cisplatin	Gynecological cancers including platinum sensitive recurrent EC	DLT rate, ORR	Recruiting	2026
	NCT06132958	3	Trop-2-directed ADC with topoisomerase I inhibitor, doxorubucin, paclitaxel	EC with prior systemic platinum-based chemotherapy and anti-PD-1/PD-L1 therapy	PFS, OS	Recruiting	2028
	NCT05941507	1|2	Trop-2-directed mAb linked to MMAE	Advanced solid tumors including EC	Incidence and severity of AEs and SAEs, R2PD, ORR, PFS, OS	Recruiting	2027
	NCT04251416	2	Trop-2-directed ADC with topoisomerase I inhibitor	Recurrent or persistent EC	ORR	Recruiting	2025
T cell engager	NCT05180474	1|2	B7-H4/CD3 bispecific T cell engaging antibody	Solid tumors including EC that progressed after SoC	Number of participants with DLTs and TEAEs	Active, not Recruiting	2027
	NCT06239194	1|2	c-MET/TROP2/CD3/CD28 T cell engaging tetraspecific antibody	Advanced solid tumors including EC	AEs, R2PD, ORR	Recruiting	2028

	NCT Number	Phases	Treatment	Patient Population	Primary Endpoint	Current Status	Expected Completion
	NCT06276491	1	CLDN6/CD3 T cell engaging bispecific antibody	CLDN6+ locally advanced, recurrent, or metastatic gynecological tumors including EC	Incidence of AEs, DLTs, and CRS	Recruiting	2027
	NCT06515613	1	CLDN6/CD3 T cell engaging bispecific antibody	Platinum resistant/refractory EC	Incidence of DLTs, ORR	Recruiting	2027
	NCT04590326	1|2	MUC16/CD28 bispecific T cell engaging antibody, MUC16/CD3 bispecific T cell engaging antibody, anti-PD-1, anti-IL-6 receptor	Progressive or recurrent EC with prior anti- PD-1 therapy and platinum-based chemotherapy	Incidence of DLTs and TEAEs, incidence of deaths, ORR	Recruiting	2027
	NCT03564340	1|2	MUC16/CD3 bispecific T cell engaging antibody, anti-IL6 receptor, anti-PD-1 mAb	MUC16+ progressive or recurrent EC with prior anti- PD-1 therapy and platinum-based chemotherapy	Number of participants DLTs, TEAEs and SAEs, number of deaths, number of participants with laboratory abnormalities, number of participants with laboratory abnormalities, ORR	Recruiting	2026
Immune agonist	NCT05231122	2	anti-CD40 agonist mAb, anti-VEGF, anti-PD-1	Recurrent EC	Incidence of AEs, ORR	Recruiting	2026
T cell activator	NCT05592626	1|2	anti-TCR Vb6/Vb10 antibody fused with IL-2	Solid tumors including unresectable, locally advanced, or metastatic EC	Number of participants with DLTs, AEs, and SAEs, ORR	Recruiting	2026
Adoptive T cell therapy	NCT06218914	1	TCR engineered T cell	Advanced solid tumors including EC with KRAS G12D variant mutation and subject must be HLA-C*08:02 positive	Incidence of DLTs and AEs	Active, not Recruiting	2027
	NCT06481592	2	Adoptive cell therapy with TILs	Recurrent/persistent EC that has progressed after systemic platinum-based chemotherapy and anti-PD-1/PD-L1 therapy	ORR	Recruiting	2028
	NCT05194735	1|2	Neoantigen-specific TCR T-cell therapy	Solid tumors including EC that progressed after at least one line of standard systemic therapy	DLT, MTD, RP2D, ORR, AEs	Active, not Recruiting	2024
CAR therapy	NCT04660929	1	HER2-targeting CAR macrophage, anti-PD-1	HER2+ solid tumors including EC	Frequency and severity of adverse events	Active, not Recruiting	2024
Cancer vaccine combination	NCT06253494	1|2	HER-2 DC vaccine, anti-PD-1, IL-15, TKI	HER2+ EC that progressed after systemic therapy	Number of DLT, R2PD, preliminary efficacy (time from start of treatment to time of progression, death or 6 months)	Recruiting	2026
	NCT06639074	2	Multi-epitope folate receptor alpha-loaded dendritic cell vaccine	Advanced gynecological cancers	RFS	Recruiting	2027
	NCT05269381	1|2	cyclophosphamide, personalized neoantigen vaccine, anti-PD-1, GMCSF	Solid tumors including locally advanced, metastatic, or unresectable EC	Incidence of AEs	Recruiting	2025

	NCT Number	Phases	Treatment	Patient Population	Primary Endpoint	Current Status	Expected Completion
Checkpoint beyond anti-PD-1	NCT04463771	2	anti-PD-1 mAb, IDOi, TKI, anti-LAG-3 mAb, anti-TIM-3	Advanced or metastatic endometrial cancer with disease progression platinum-containing regimen	ORR	Active, not Recruiting	2025
	NCT05112601	2	anti-PD-1 mAb, anti-CTLA-4 mAb	dMMR recurrent EC with 1–2 prior lines of systemic therapy	PFS	Recruiting	2026
	NCT05277051	1	anti-PVRIG mAb, anti-PD-1, anti-CD96	Solid tumors including recurrent or metastatic EC	Number of participants with DLTs, AEs, and SAEs	Recruiting	2028
	NCT05572684	1|2	anti-LAIR-2 Fc fusion protein, anti-PD-1	Solid tumors including EC that progressed on treatment with an anti-PD1/L1 antibody therapy	Number of participants with TEAEs, RP2D	Active, not Recruiting	2025
	NCT05669430	1|2	anti-IGSF8, anti-PD-1	Advanced and/or refractory Solid Tumors including EC	ORR	Recruiting	2026
	NCT06036836	2	anti-PD-1 mAb, anti-LAG-3 mAb	Solid tumors including stage IVb, recurrent, or metastatic pMMR EC	Clinical benefit rate, ORR	Active, not Recruiting	2027
	NCT06730347	2	anti-PD-1/anti-CTLA-4 bispecific DART®	Persistent or recurrent gynecological cancers	ORR	Recruiting	2027
	NCT05032040	2	PD-1/CTLA-4 bispecific mAb	Urogenital cancers including chemotherapy relapsed/refractory, ICI refractory, MSS, pMMR EC	ORR	Active, not Recruiting	2025
Bispecific antibody	NCT05123482	1/2	PD-1/TIGIT bispecific Ab	Solid tumors including EC	Number of participants with DLTs, AEs, and SAEs	Recruiting	2027
	NCT06695845	2	HER-2 bispecific Ab	HER2+ locally advanced, unresectable, or metastatic solid tumors including EC	ORR	Recruiting	2026
	NCT06925724	2	anti-PD-1/anti-VEGF bispecific mAb	Metastatic/recurrent EC that has progressed after treatment with at least one platinum-based regimen	ORR	Recruiting	2027
PD-1 + small molecule inhibitor	NCT04106414	2	IDOi, anti-PD-1	Recurrent or persistent EC with one prior platinum-based chemotherapy	ORR	Active, not Recruiting	2025

ADC, antibody drug conjugate; EC, endometrial cancer; AE, adverse event; SAE, serious adverse event; DLT, Dose limiting toxicity; ICI, immune checkpoint inhibitor; ORR, objective response rate; MMAE, Monomethyl auristatin E; RP2D, recommended phase 2 dose; FRα, folate receptor alpha; VEGF, vascular endothelial growth factor; mAb, monoclonal antibody; TEAE; treatment emergent adverse event; HER, human epidermal growth factor receptor; SoC, standard of care; MTD, maximum tolerated dose; MAD; multiple ascending dose; RDE, recommended dose expansion; PD-1, programmed cell death-1 ; PD-L1, program death ligand 1 ; MUC, mucin; MSLN, mesothelin; PTK7, protein tyrosine kinase 7; Trop-2, Trophoblast surface antigen 2; 5-FU, Fluorouracil; CTLA-4, Cytotoxic T-lymphocyte associated protein 4; TIGIT, T cell immunoreceptor with Ig and ITIM domains; PFS, progression-free survival; OS, overall survival; CD, cluster of differentiation; CLDN6, claudin 6; CRS, cytokine release syndrome; ROR, *receptor tyrosine kinase-like orphan receptor, HSA*, human serum albumin; TCR, T cell receptor; HLA, human leukocyte antigen; TIL, tumor infiltrating lymphocyte; IL, interleukin; TKI, tyrosine kinase inhibitor; RFS, relapse-free survival; GMCSF, *Granulocyte-macrophage colony-stimulating factor; IDOi, indoleamine 2,3-dioxygenase-1 inhibitor; LAG-3*, lymphocyte activation gene 3; TIM-3, *T-cell immunoglobulin and mucin domain 3; dMMR, deficient mismatch repair; PVRIG, poliovirus receptor related immunoglobulin domain-containing;* LAIR-2, Leukocyte-associated immunoglobulin-like receptor 1; IGSF8, immunoglobulin superfamily member 8; KIR3DL3, killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 3; *pMMR, proficient mismatch repair;* MSS, microsatellite stable