Current status and targeted therapies in endometrial cancer: Molecular classification-driven treatment strategies (Review)

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Abstract. Endometrial cancer (EC) is one of the most common gynecological malignancies worldwide. Although numerous patients are diagnosed at an early stage with favorable outcomes, advanced and metastatic disease remains associated with limited therapeutic options and poor prognosis. Advances in molecular characterization have reshaped the understanding of EC pathogenesis and enabled the development of classification-driven treatment strategies. The present review summarized current standard therapies, including surgery, chemotherapy and radiotherapy, and highlighted the growing role of molecularly targeted treatments. The integration of pathogenetic, histopathological and molecular classifications provides a framework for identifying actionable alterations. Key oncogenic signaling pathways, including PI3K/AKT/mTOR and RAS/RAF/MEK/ERK, were discussed in the context of therapeutic targeting and precision medicine. In addition, emerging strategies, particularly immunotherapy and combination approaches, were addressed. A deeper understanding of molecular heterogeneity may facilitate individualized treatment selection and improve clinical outcomes in patients with EC.

Contents

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1. Introduction

Cancer remains a major public health challenge worldwide and is the second leading cause of death in the United States, ranking as the leading cause among individuals aged <85 years old (1). Endometrial cancer (EC) is currently the sixth most commonly diagnosed cancer in women, with its incidence to rise by ~1% annually since the mid-2000s (1-4). Due to the tumor metastasis and recurrence, there is a marked discrepancy in survival rates between women diagnosed with early and late-stage disease.

EC is one of the most common gynecological malignancies and the pathogenesis is complex. Polycystic ovary syndrome, diabetes, obesity, nulliparity, metabolic syndrome, and advanced age are established risk factors of EC (5-7). It typically presents at an early stage with postmenopausal abnormal uterine bleeding noted in ~90% patients (4,8). At present, the treatment of EC is mainly based on surgery, including hysterectomy and bilateral salpingo-oophorectomy (9,10). However surgical treatment is not an ideal option for numerous patients as it may be hazardous and lead to infertility young women. In the younger population, the incidence of EC is unabatedly increasing, with one study demonstrating that <10% of young women have ovarian conservation with type I (11). With the increasing incidence and mortality of EC, it is important to elucidate the pathogenesis of EC at the molecular level and propose novel therapeutic targets, especially since patients with advanced/recurrent EC are unlikely to be cured by surgery, conventional chemotherapy, radiotherapy or a combination of these treatments (12,13). Molecular targeted therapy has long been considered a valuable treatment modality in oncology due to its small size, selective binding to various extracellular and intracellular targets, superiority to cytotoxic chemotherapy and minimal side effects (14).

Several previous reviews have summarized important advances in EC molecular classification, FIGO staging, targeted therapy, immunotherapy, and treatment strategies for advanced

or recurrent disease (15-19). However, most existing reviews have primarily focused on either molecular classification and prognosis, recent FIGO staging updates, general therapeutic advances, or systemic treatment for advanced/recurrent EC. Compared with these reviews, the present review provides a more integrated molecular subtype-based framework. Specifically, it links each major molecular subtype with signaling pathway status, therapeutic vulnerabilities, clinical efficacy of pathway targeting, limitations of failed or modest-efficacy clinical studies, immunotherapy responsiveness, guideline and regulatory implications, and emerging preclinical or early-stage therapeutic concepts. Therefore, the present review aims to provide a subtype-centered translational perspective that connects molecular classification with current and future treatment decision-making in EC.

The present review aimed to provide a comprehensive and up-to-date overview of the current landscape of EC treatment from a molecular classification-driven perspective. First, The Cancer Genome Atlas (TCGA) and traditional-based classification systems were summarized, emphasizing their clinical relevance and limitations. In addition, conventional treatment approaches, including surgery, radiotherapy, chemotherapy and hormonal therapy, were outlined, and their differential efficacy across molecular subtypes were discussed.

Furthermore, the present review focused on key oncogenic signaling pathways implicated in EC, such as the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR), RAS-RAF-MEK-ERK, transforming growth factor-β (TGF-β), and nuclear factor-κB (NF-κB) pathways, highlighting their molecular alterations, therapeutic targets and associated clinical evidence (17). Special attention was also given to the role of immunotherapy, in particular immune checkpoint inhibitors (ICIs), and their application in molecularly defined subgroups. Finally, current challenges and future directions in EC management, including treatment-related toxicities, resistance mechanisms, and emerging personalized therapeutic strategies, were explored. By integrating molecular classification with targeted and immune-based therapies, the present review aimed to provide insights that may facilitate the development of more precise and effective treatment paradigms for EC.

2. Classification systems of EC

Traditional pathogenetic and histopathological classification. EC has previously been classified according to the dualistic model proposed by Bokhman in 1983, which distinguishes between type I (estrogen-dependent) and type II (non-estrogen-dependent) tumors (20-23). This framework has long guided clinical decision-making. However, it does not fully capture the molecular heterogeneity of EC.

Histopathologically, EC includes several subtypes, among which endometrioid carcinoma (24), serous carcinoma (25-27), and clear cell carcinoma are the most common, while rarer entities include uterine carcinosarcoma and mixed histologies. Endometrioid carcinoma accounts for ~80% of EC cases and is typically associated with estrogen exposure, obesity and favorable prognosis. These tumors are often low- to intermediate-grade and may arise from atypical endometrial hyperplasia (28,29). By contrast, serous carcinoma represents a highly aggressive subtype, accounting for 3-10% of cases, and is frequently characterized by TP53 mutations and poor clinical outcomes (22). It typically arises in an atrophic endometrium and is independent of estrogen stimulation. Clear cell carcinoma is a rare but aggressive subtype with unclear molecular origins, sharing features with both endometrioid and serous carcinomas (22,24). Uterine carcinosarcoma, a biphasic tumor containing both epithelial and mesenchymal components, is highly aggressive and associated with poor prognosis (30,31). Although histopathological classification provides important diagnostic and prognostic information, its ability to guide targeted therapy remains limited, highlighting the need for molecular classification systems. The traditional pathogenetic and histopathological classification of EC is summarized in Fig. 1.

TCGA-based molecular classification and clinical implications. TCGA project has redefined EC classification based on genomic and molecular features, enabling a more precise stratification of patients and providing a framework for personalized therapy (28,32). EC is classified into four molecular subtypes: (i) POLE ultra-mutated; (ii) microsatellite instability-high (MSI-H/dMMR); (iii) NSMP; and (iv) CN-high. In Table I, the key features of each EC subtype were summarized, demonstrating the variation in mutated genes and tumor immunity in EC.

The POLE ultra-mutated subtype is characterized by notably high tumor mutational burden (TMB) due to mutations in the exonuclease domain of the POLE gene. These tumors exhibit abundant tumor-infiltrating lymphocytes (TILs) and are associated with favorable prognosis, suggesting strong immunogenicity and potential responsiveness to immunotherapy (33-36). The MSI-H/dMMR subtype results from defects in DNA mismatch repair and is associated with elevated immune infiltration and high PD-1/PD-L1 expression (37). These features provide a clear rationale for immune checkpoint blockade in this subgroup. The CN-low subtype, also referred to as microsatellite stable, typically shows lower mutation rates but frequent alterations in genes such as PTEN and PIK3CA (21). These tumors are often associated with endometrioid histology and may be amenable to targeted therapies involving the PI3K/AKT/mTOR pathway. The CN-high subtype is characterized by extensive copy-number alterations and a high prevalence of TP53 mutations (21). This group is associated with serous histology, aggressive clinical behavior and poor prognosis (38,39), often requiring intensive multimodal treatment strategies. Overall, the TCGA classification provides critical insights into tumor biology and establishes a foundation for molecularly guided therapeutic strategies in EC.

Molecular classification and therapeutic implications. The integration of molecular classification into clinical practice has notably improved the understanding of therapeutic vulnerabilities in EC. Each molecular subtype exhibits distinct genomic alterations, tumor microenvironment (TME) characteristics and treatment sensitivities, providing a rationale for precision medicine approaches.

POLE ultra-mutated tumors, characterized by notably high TMB, demonstrate strong immunogenicity and favorable prognosis. Although these patients often have optimal outcomes with conventional therapy, emerging evidence suggests that

Table I. Molecular characteristics and clinical relevance of TCGA-based subtypes in EC (8,17,34).

Feature	POLE ultra-mutated	MSI-H/dMMR	NSMP (CN-low)	CN-high (p53-abn)
Key mutations	POLE	MMR genes	PTEN, PIK3CA	TP53
PTEN mutation	~94%	~88%	~77%	~2%
TP53 mutation	~35%	~5%	~1%	~92%
PIK3CA mutation	~71%	~54%	~53%	~47%
KRAS mutation	~53%	~35%	Low	Rare
ARID1A mutation	~76%	~37%	42%	Rare
CTNNB1 mutation	Rare	Rare	52%	Rare
Tumor mutational burden	Very high	High	Low	Low
Tumor infiltrating lymphocytes	High	High	Low-moderate	Low
PD-L1 expression	High	High	Variable	Low
Clinical behavior	Excellent prognosis	Intermediate prognosis	Intermediate prognosis	Poor prognosis
Therapeutic implications	Strong response to immunotherapy	Responsive to immunotherapy	May benefit from targeted therapy	Limited response; aggressive management

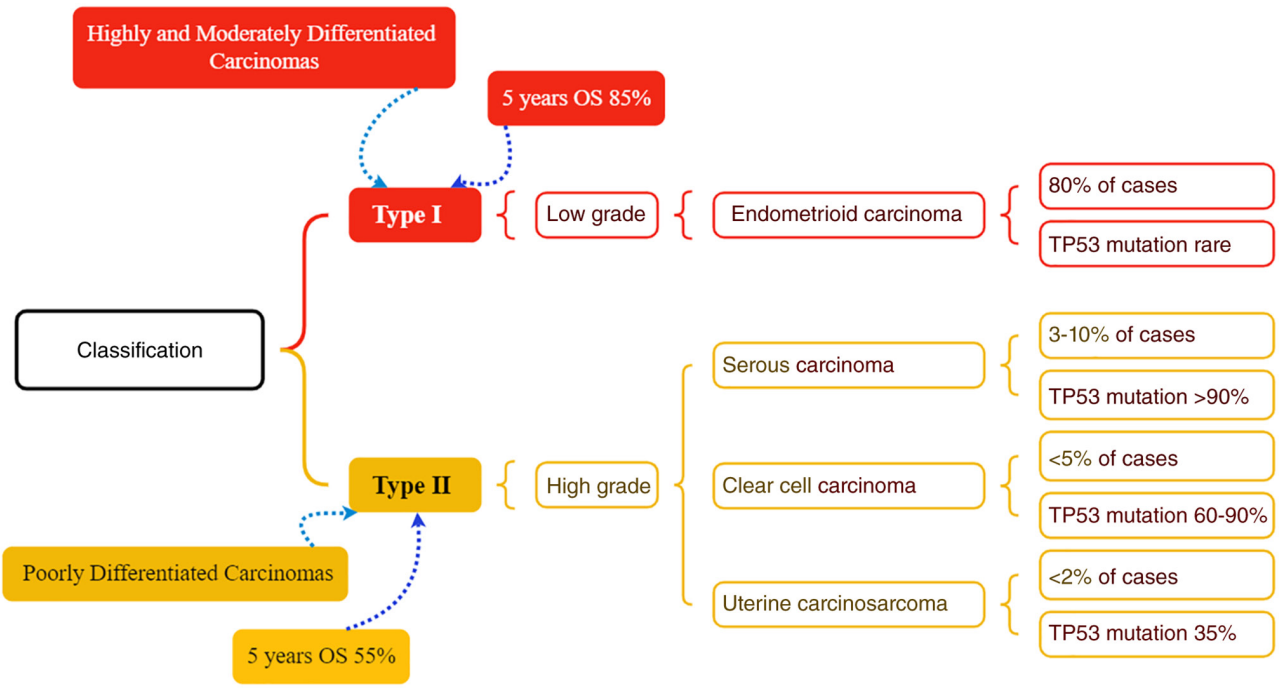

Figure 1. Pathogenetic and histopathological classification of endometrial cancer.

immunotherapy may further enhance disease control in selected cases. MSI-H/dMMR tumors exhibit high levels of immune infiltration and increased expression of immune checkpoint molecules such as PD-1 and PD-L1. These features make them particularly responsive to ICIs, which have become a standard treatment option for advanced or recurrent disease in this subgroup. CN-low tumors frequently harbor mutations in PTEN, PIK3CA and other components of the PI3K/AKT/mTOR pathway. These molecular alterations provide opportunities for targeted therapy, particularly with PI3K, AKT or mTOR inhibitors, either as monotherapy or in combination with hormonal or immune-based approaches. CN-high tumors are characterized by TP53 mutations, genomic instability and aggressive clinical behavior. These tumors are less immunogenic and often exhibit resistance to conventional therapies, necessitating combined treatment strategies, including chemotherapy, targeted agents and emerging immunotherapeutic approaches. Taken together, these findings highlight that molecular classification not only refines prognostic stratification but also serves as a critical framework for guiding individualized therapeutic strategies in EC.

3. Conventional treatment approaches

Surgery as a primary treatment modality. EC is one of the most common gynecological malignancies in women (2).

Current management strategies for EC include surgery as the cornerstone of treatment, often combined with adjuvant radiotherapy, chemotherapy, hormonal therapy or targeted therapy depending on disease stage and risk stratification (40). For the majority of patients, surgical intervention remains the primary and most effective therapeutic approach.

A total of ~90% of endometrial tumors are amenable to surgical resection, which typically consists of total hysterectomy with bilateral salpingo-oophorectomy, with or without pelvic and para-aortic lymph node assessment (4,41). A recent clinical review emphasized that surgery remains the cornerstone of EC management and outline its role relative to evolving systemic therapies (42). In recent years, minimally invasive techniques have increasingly replaced open abdominal procedures. Laparoscopic hysterectomy has demonstrated comparable overall survival outcomes to abdominal hysterectomy while offering notable advantages, including reduced intraoperative blood loss, shorter hospitalization times and lower postoperative morbidity. Consequently, minimally invasive surgery is currently considered the preferred approach for patients with early-stage EC (4,43,44).

The inclusion of oophorectomy in standard surgical management is primarily based on the risk of synchronous ovarian malignancy, occult ovarian metastasis and the role of the ovaries as a major source of estrogen, which may promote tumor growth in hormone-dependent EC (11,45,46). However, bilateral oophorectomy induces premature menopause, which is associated with vasomotor symptoms, reduced quality of life and an increased risk of long-term metabolic complications (11,45,47). Emerging evidence suggests that in carefully selected premenopausal patients with clearly defined early-stage, low-risk disease, ovarian preservation may be a feasible option without compromising oncologic outcomes, while potentially improving long-term quality of life (4,11).

Despite the effectiveness of surgery in early-stage EC, its therapeutic benefit is limited in patients with advanced, recurrent or metastatic disease. In these settings, radical surgical resection is often not feasible, and survival outcomes remain poor. Therefore, adjuvant radiotherapy and/or systemic chemotherapy are commonly required to reduce the risk of disease recurrence and to improve disease control in high-risk patients (48,49). These limitations of surgery underscore the need for integrated multimodal treatment strategies, including systemic therapies, which are discussed in the following sections.

Adjuvant treatment

Radiotherapy. Radiotherapy plays an established role in improving local disease control, particularly tailored based on histopathological risk factors (49,50). Given the limited efficacy of cytotoxic chemotherapy and hormonal therapy in preventing locoregional recurrence in certain patient populations, radiotherapy is frequently incorporated as an adjuvant treatment modality for patients with adverse prognostic factors, including deep myometrial invasion, lymphovascular space invasion and advanced stage disease (9).

Recent clinical trials (49,50) continue to explore optimal radiotherapy strategies and their integration with systemic therapy. An ongoing clinical trial (trial no. NCT05691010) is evaluating the efficacy of short-course radiotherapy combined with chemotherapy in patients with stage III EC, with particular attention to therapeutic outcomes across different molecular subtypes, including CN-low and CN-high tumors. This trial reflects the growing interest in tailoring adjuvant treatment strategies based on molecular classification.

Evidence from large, randomized studies suggests that the benefit of combined chemoradiotherapy may be primarily attributable to improved local control rather than an extension of relapse-free survival (RFS). In a study conducted by Matei *et al* (51), RFS was analyzed in 736 patients with stage III or IVA EC, of whom 707 were randomized to receive either combined chemoradiotherapy or chemotherapy alone. At a median follow-up of 60 months, the proportion of patients who were alive and relapse-free was similar between the two groups (59 vs. 58%). Although the combination regimen did not demonstrate superiority in prolonging RFS, it was associated with a lower incidence of locoregional recurrence. Notably, higher rates of grade 4 or greater acute adverse events were observed in the chemotherapy-alone group compared with the combined treatment group, highlighting the need to balance efficacy and toxicity when selecting adjuvant therapies.

Consistent with the ESGO/ESTRO/ESP 2025 guideline update, adjuvant treatment selection in EC should increasingly be guided by an integrated assessment of anatomical stage, histological features, lymphovascular space invasion and molecular classification. In particular, POLE-mutated, MMRd, NSMP and p53-abnormal status refine prognostic risk grouping and may influence the intensity of adjuvant and systemic treatment (52).

Chemotherapy. Systemic chemotherapy remains a key component of adjuvant and palliative treatment for EC, particularly in patients with high-risk early-stage disease, advanced-stage tumors or recurrent disease (53,54). The American Society of Clinical Oncology Endorsement Panel recommends chemotherapy as an important therapeutic option for women with high-risk early-stage or advanced EC, reflecting its role in reducing the risk of distant metastasis and improving disease control (55). Platinum-based regimens combined with taxanes, most commonly carboplatin plus paclitaxel, are currently considered the standard first-line chemotherapy for EC (12,56,57). While these regimens provide clinical benefit in a substantial proportion of patients, their long-term effectiveness is limited by cumulative toxicity and the development of chemotherapy resistance, particularly in recurrent or metastatic settings. These limitations underscore the unmet need for more effective systemic therapies.

In recent years, the integration of immunotherapy into chemotherapy-based regimens has emerged as a promising strategy for advanced and recurrent EC. In February 2024, pembrolizumab (Keytruda) received priority review from the U.S. Food and Drug Administration (FDA) for use in combination with carboplatin and paclitaxel as first-line treatment for patients with primary advanced or recurrent endometrial carcinoma. This milestone reflects a paradigm shift toward combined systemic approaches and further supports the transition from conventional cytotoxic therapy to molecularly informed treatment strategies, which are discussed in detail in subsequent sections.

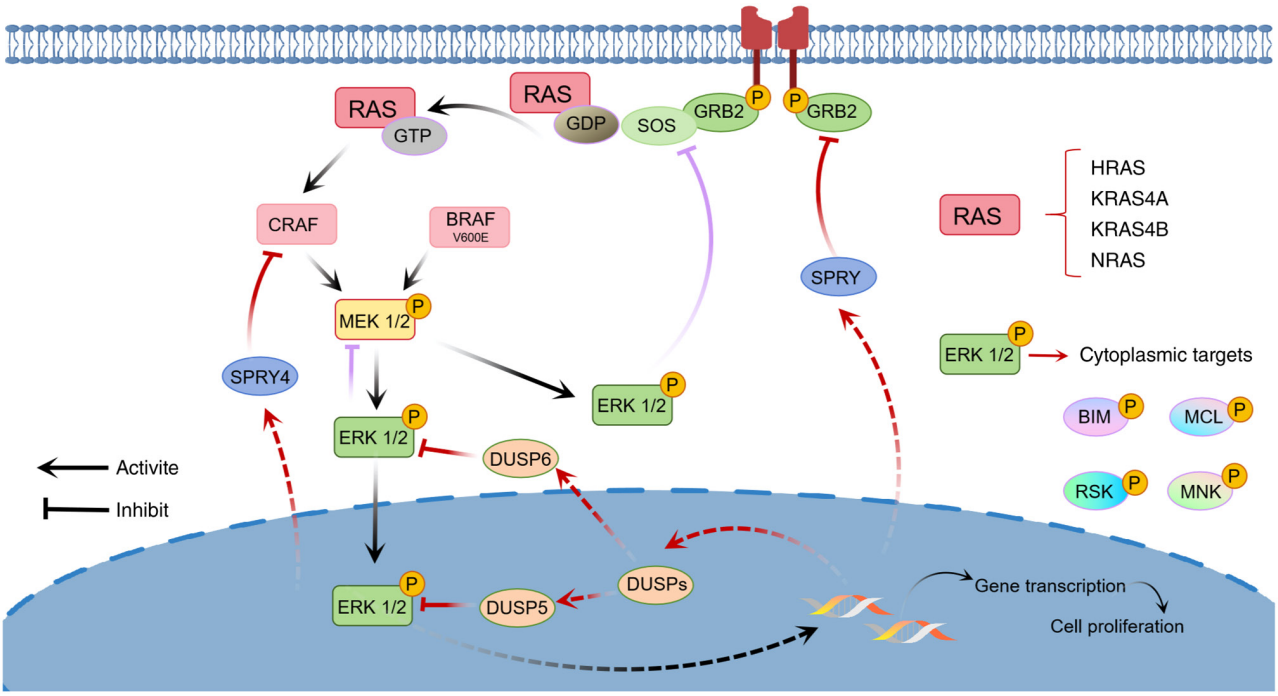

Figure 2. RAS/RAF/MEK/ERK signaling pathway. Activation of receptor tyrosine kinases recruits the GRB2-SOS complex, promoting RAS activation and subsequent RAF, MEK and ERK phosphorylation. This pathway regulates cell proliferation and survival and is tightly controlled by feedback mechanisms, including DUSP and SPRY proteins.

4. Molecular subtype-based signaling pathways and targeted therapeutic strategies in EC

Molecular classification provides a critical framework for understanding the biological heterogeneity of EC and for guiding therapeutic decision-making. Distinct molecular subtypes are defined by specific genomic alterations and signaling dependencies, which influence their responses to targeted therapies and immunotherapy. Rather than acting as isolated mechanisms, key oncogenic pathways, including PI3K/AKT/mTOR, RAS/RAF/MEK/ERK, TGF-β and NF-κB are differentially activated across EC subtypes and contribute to tumor initiation, progression and therapeutic resistance (42). Therefore, the clinical relevance of these pathways should be interpreted in the context of molecular subtype.

In this section, the major signaling pathways and pathway-targeted therapeutic strategies are discussed according to the four major molecular subtypes of EC: POLE-mutated, MSI-H/dMMR, NSMP/CN-low and CN-high/p53-abnormal tumors. For each subtype, pathway activation status, therapeutic vulnerabilities, current efficacy of pathway targeting, and major limitations of available evidence, were summarized. Established therapeutic strategies, investigational approaches and emerging concepts were distinguished between, where appropriate.

In addition, failed or limited-efficacy clinical studies are discussed where relevant, particularly for single-agent pathway inhibitors whose clinical benefits have been constrained by toxicity, compensatory signaling, lack of subtype-specific patient selection, or insufficient biomarker validation.

POLE-mutated EC

Signaling pathway status in POLE-mutated EC. POLE-mutated EC is characterized by an ultramutated genotype, high TMB and strong immunogenicity. Although this subtype generally has a favorable prognosis, signaling pathway alterations may still contribute to tumor growth, immune modulation and therapeutic resistance in selected cases. Among the pathways discussed in this review, RAS/RAF/MEK/ERK signaling is particularly relevant in POLE-mutated tumors, as KRAS mutations are frequently observed in POLE-mutated and MSI-H/dMMR EC (Table I). These alterations suggest that MAPK signaling may act as a context-dependent oncogenic driver in this subtype.

The RAS-RAF-MEK-ERK signaling pathway is a classical MAPK cascade that regulates cell proliferation, survival and differentiation (Fig. 2) (58). Upon activation, RAS recruits RAF kinases, leading to sequential activation of MEK1/2 and ERK1/2, thereby promoting tumor growth and survival (59,60). In EC, aberrant MAPK activation is primarily driven by KRAS mutations, whereas BRAF mutations are rare (61). In addition, crosstalk between MAPK and PI3K/AKT/mTOR pathways may contribute to tumor progression, metabolic reprogramming and therapeutic resistance (62).

POLE-mutated tumors are also characterized by immune activation and inflammatory signaling. In this context, NF-κB-related inflammatory pathways may participate in cytokine production, immune-cell recruitment and tumor-immune microenvironment (TIME) interactions. However, the clinical significance of directly targeting NF-κB or other inflammatory pathways in POLE-mutated EC remains insufficiently defined.

Therapeutic implications and efficacy of pathway targeting. Although MAPK pathway activation provides a

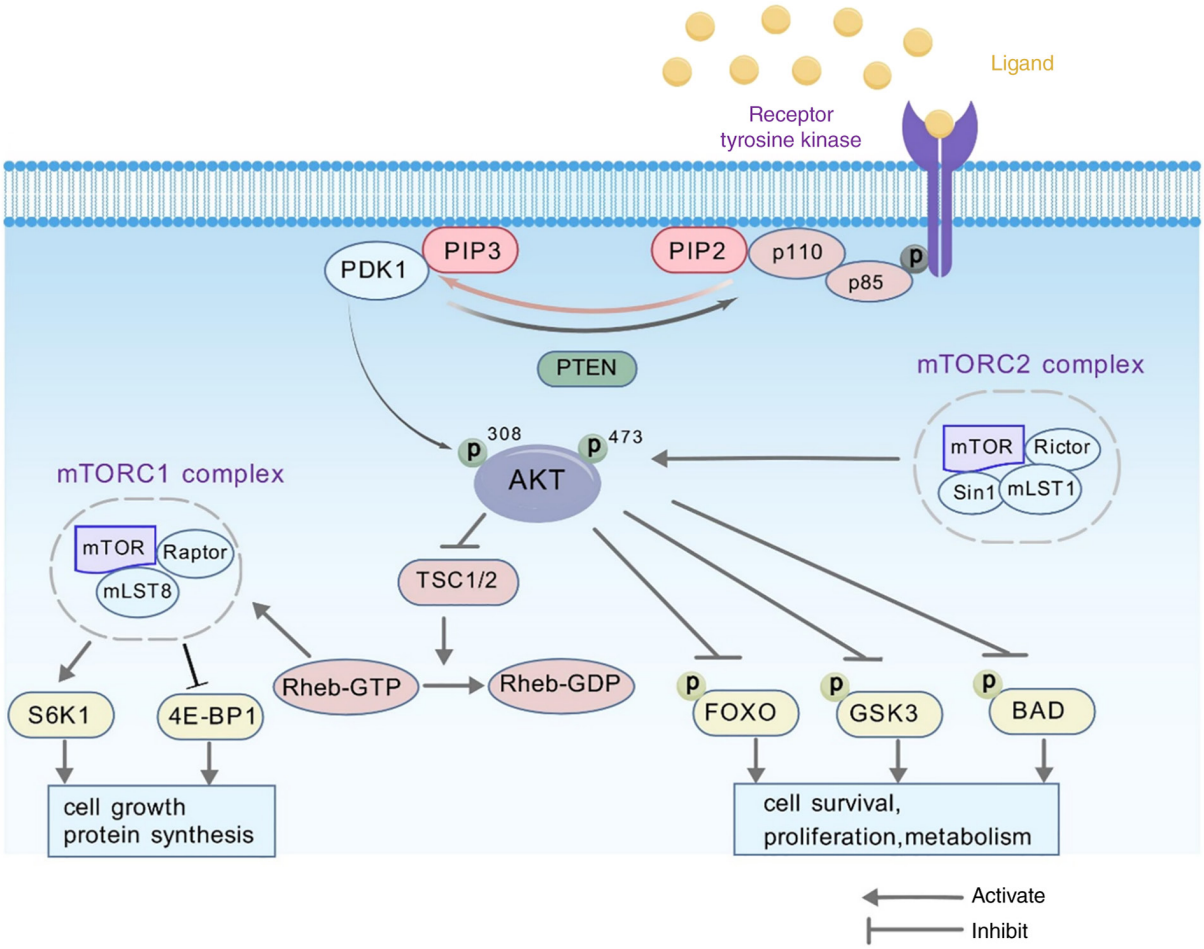

Figure 3. PI3K-AKT-mTOR signaling pathway. Activation of receptor tyrosine kinases triggers PI3K activation and downstream AKT phosphorylation, leading to mTORC1 activation. This pathway regulates cell proliferation, metabolism and survival, and its dysregulation contributes to tumor progression and therapeutic resistance in endometrial cancer.

biological rationale for pathway-directed therapy in selected POLE-mutated tumors, the clinical efficacy of targeting this pathway in POLE-mutated EC has not been firmly established. MEK inhibitors may be relevant in KRAS-mutant tumors, and Preclinical studies have shown that MEK inhibition can exert cytotoxic effects and enhances sensitivity to chemotherapy, such as paclitaxel (63). However, durable clinical benefit in molecularly selected EC populations remains uncertain.

Combination strategies targeting both MAPK and PI3K pathways have demonstrated synergistic effects. For example, trametinib (MEK inhibitor) combined with the AKT inhibitor GSK2141795 has shown enhanced activity in EC models (64), while cobimetinib, alone or in combination with PI3K inhibitors, has shown activity in KRAS-mutant or PTEN-intact tumors (61). These findings support the rationale for combined pathway inhibition, but clinical validation in POLE-mutated EC remains limited.

Although actionable BRAF V600E mutations are rare in EC, BRAF inhibitors such as dabrafenib have shown clinical benefit in selected patients (65-67). In addition, the pan-RAF inhibitors including lifirafenib (BGB-283), have demonstrated activity in early-phase clinical studies involving BRAF- or RAS-mutant solid tumors, supporting further investigation in molecularly selected patients with EC patients (68,69). Nevertheless, because POLE-mutated EC usually has favorable clinical outcomes and strong immunogenicity, pathway-targeted therapies are currently more relevant as investigational or salvage approaches rather than standard treatment strategies. Future studies should clarify whether MAPK-targeted therapy may benefit selected POLE-mutated tumors with actionable RAS/RAF alterations or acquired treatment resistance.

MSI-H/dMMR EC

Signaling pathway status in MSI-H/dMMR EC. MSI-H/dMMR EC is characterized by mismatch repair deficiency, microsatellite instability, increased mutational burden and immune activation. In addition to its immunogenic features, this subtype frequently harbors alterations in oncogenic signaling pathways, particularly PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways. These pathway alterations provide potential therapeutic vulnerabilities but also contribute to pathway redundancy and treatment resistance.

The PI3K/AKT/mTOR pathway is a central regulator of cell growth, metabolism and survival and represents one of the most frequently dysregulated pathways in EC (24,70-72) Its activation is observed across multiple histological and molecular subtypes (Fig. 3), but it is particularly enriched in NSMP and MSI-H/dMMR tumors, where alterations in PTEN, PIK3CA and PIK3R1 are commonly observed.

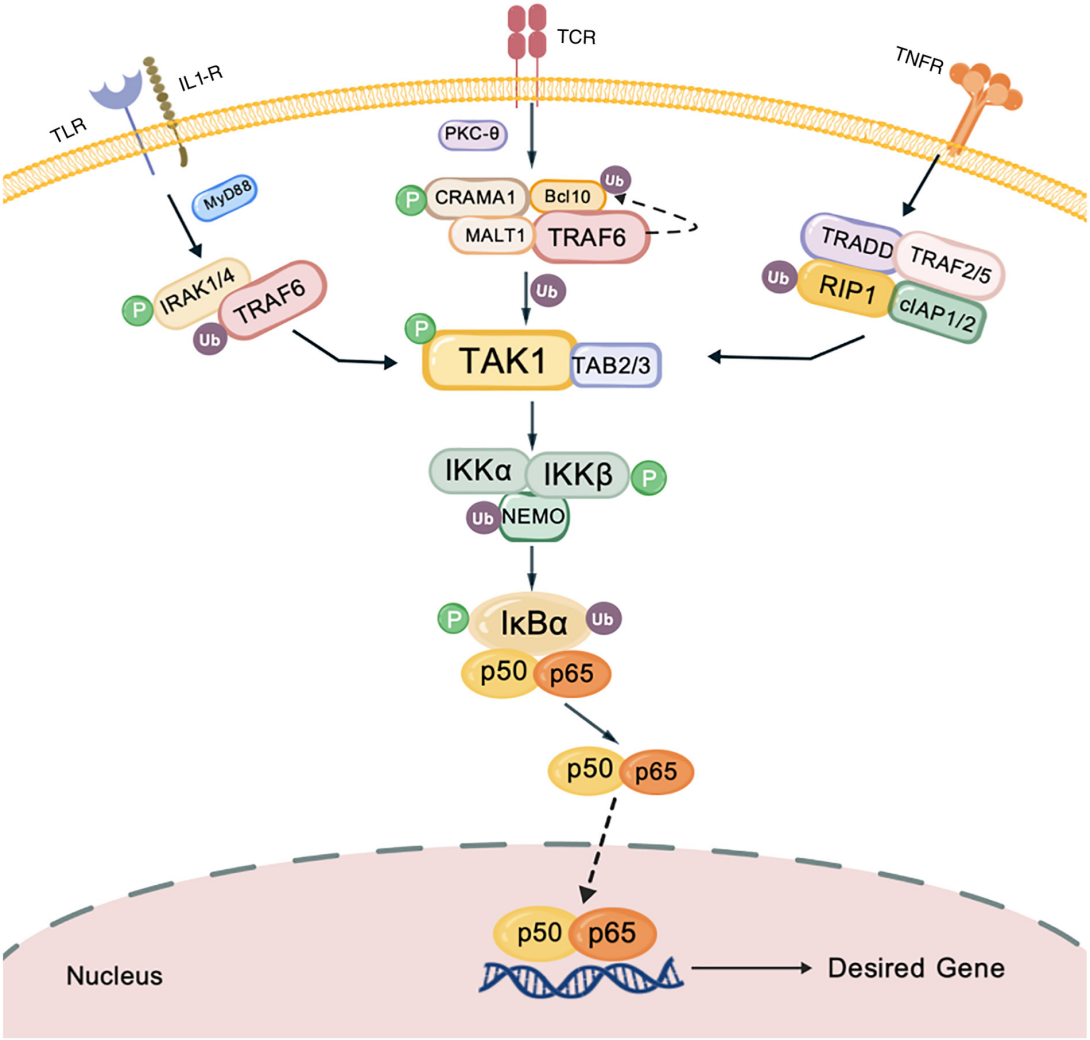

Figure 4. NF-κB signaling pathway. Activation of TNFR, TCR, or TLR/IL-1RI leads to TAK1-IKK complex activation, resulting in IκBα degradation and nuclear translocation of NF-κB dimers (p50/p65). NF-κB regulates transcription of genes involved in inflammation, survival, and tumor progression.

Class I PI3Ks are heterodimeric lipid kinases composed of a catalytic subunit (p110) and a regulatory subunit (p85) and are activated downstream of receptor tyrosine kinases or G protein-coupled receptors (73). AKT, phosphorylates multiple substrates involved in cell survival, proliferation and metabolic regulation (74), while mTOR functions through two distinct complexes, mTORC1 and mTORC2 (75). Dysregulation of this pathway is frequently driven by loss of PTEN function or activating mutations in PIK3CA and PIK3R1, resulting to sustained pathway activation and tumor progression (28,76-78).

MAPK pathway activation is also relevant in MSI-H/dMMR tumors. KRAS mutations occur frequently in POLE-mutated and MSI-H/dMMR subtypes (Table I), supporting the role of MAPK signaling as a subtype-associated oncogenic pathway (61). Moreover, crosstalk between MAPK and PI3K/AKT/mTOR signaling may promote adaptive resistance following single-pathway inhibition (62).

NF-κB signaling is another pathway with subtype-associated relevance in MSI-H/dMMR EC. NF-κB is a key transcription factor regulating cell proliferation, apoptosis, migration and inflammatory responses (79). It is activated through canonical and noncanonical pathways that converge on the IκB kinase complex, leading to nuclear translocation and transcription of pro-inflammatory cytokines, chemokines and survival-related genes (Fig. 4) (80-84). In MSI-H/dMMR and immune-enriched tumors, NF-κB activation is associated with increased immune infiltration, cytokine production and inflammatory amplification.

Therapeutic implications and efficacy of pathway targeting. Given the frequent activation of PI3K/AKT/mTOR signaling in MSI-H/dMMR EC, this pathway has been explored as a therapeutic target. Multiple classes of inhibitors have been developed, including PI3K, AKT, mTOR and dual PI3K/mTOR inhibitors (85). However, despite strong biological rationale, clinical responses to PI3K/AKT/mTOR pathway inhibition remain variable and are often limited by pathway redundancy, compensatory activation and tumor heterogeneity.

Isoform-selective PI3K inhibitors, such as alpelisib (BYL719), have shown clinical activity in PIK3CA-mutant endometrioid EC, supporting a subtype-directed therapeutic approach (86-88). However, pan-PI3K inhibitors have demonstrated limited clinical utility due to toxicity. AKT inhibitors, including ipatasertib and afuresertib, have shown promising

activity in preclinical and early-phase clinical studies, and are being evaluated in combination strategies (89,90). mTOR inhibitors, such as temsirolimus and everolimus, have demonstrated modest activity as monotherapies, partly due to feedback activation of AKT signaling (91). Consequently, next-generation inhibitors targeting both mTORC1 and mTORC2, as well as dual PI3K/mTOR inhibitors (such as dactolisib and samotolisib), are under investigation (92,93).

In MSI-H/dMMR tumors, the integration of pathway inhibition with immune-based therapy may be particularly relevant because of the immunogenic TME. Increasingly, combination strategies integrating PI3K/AKT/mTOR or MAPK pathway inhibition with immune checkpoint blockade are being explored to improve therapeutic outcomes (Table II). Nevertheless, the efficacy of pathway-targeted therapy in MSI-H/dMMR EC remains incompletely established, and predictive biomarkers beyond MSI/MMR status are needed.

Several pathway-targeted approaches in EC have shown only limited or inconsistent clinical efficacy despite strong biological rationale. In particular, single-agent PI3K/AKT/mTOR pathway inhibitors have generally produced modest responses, partly because MSI-H/dMMR status alone does not identify tumors that are dependent on this pathway. Moreover, compensatory activation of MAPK signaling and tumor heterogeneity may reduce the durability of response. These findings suggest that future trials in MSI-H/dMMR EC should incorporate additional pathway biomarkers and should distinguish between preclinical rationale, early-phase activity and clinically validated benefit.

Therapeutic inhibition of MAPK signaling may also be relevant in KRAS-mutant MSI-H/dMMR tumors. MEK inhibition has demonstrated antitumor activity in preclinical EC models and may enhance chemotherapy sensitivity (63). However, monotherapy approaches are often insufficient due to compensatory signaling and pathway crosstalk. Therefore, combined MAPK and PI3K pathway inhibition may represent a rational strategy, although its clinical benefit in MSI-H/dMMR EC remains to be fully validated.

NSMP/CN-low EC

Signaling pathway status in NSMP/CN-low EC. NSMP/CN-low EC is a heterogeneous subtype that often overlaps with endometrioid, hormone-driven tumors and frequently harbors alterations in the PI3K/AKT/mTOR pathway. Among all molecular subtypes, NSMP/CN-low tumors are particularly relevant to PI3K/AKT/mTOR-directed and endocrine-based therapeutic strategies. Alterations in PTEN, PIK3CA and PIK3R1 are commonly observed and contribute to sustained pathway activation, tumor growth, metabolic reprogramming and treatment resistance (28,76-78).

Beyond canonical PI3K/AKT/mTOR pathway components, additional regulators have been identified as potential therapeutic targets. Proteins such as TPX2, SGK1 and MELK have been implicated in pathway activation and tumor progression (94-97). In addition, cytoskeletal-associated proteins and regulatory microRNAs have been shown to modulate pathway activity and contribute to tumor progression and metastasis (98-102). These findings suggest that PI3K/AKT signaling extends beyond canonical oncogenic drivers and involves broader regulatory networks.

MAPK signaling is also relevant in selected NSMP/CN-low tumors, particularly in hormone-resistant or KRAS-mutant contexts. Several metabolic and hormone-related regulators influence MAPK activation. Visfatin promotes tumor proliferation through concurrent activation of PI3K/AKT and MAPK pathways, linking metabolic dysregulation to oncogenic signaling (103). Similarly, CNR1 contributes to progesterone resistance by enhancing ERK signaling, whereas loss of MIG-6 leads to sustained ERBB2-ERK activation and tumor progression (104,105).

TGF-β signaling may retain tumor-suppressive functions in early-stage or CN-low tumors by regulating cell cycle arrest and apoptosis (106,107). However, disruption of SMAD signaling and crosstalk with PI3K/AKT may alter these tumor-suppressive effects and contribute to progression (108,109). NF-κB signaling is also relevant in hormone-resistant NSMP/CN-low tumors, as metabolic and inflammatory regulators can promote survival signaling and progesterone resistance.

Therapeutic implications and efficacy of pathway targeting. Because PI3K/AKT/mTOR alterations are common in NSMP/CN-low EC, this subtype provides a strong biological rationale for pathway-directed treatment. PI3K inhibitors, AKT inhibitors, mTOR inhibitors and dual PI3K/mTOR inhibitors have all been evaluated in EC (85). However, the clinical efficacy of single-agent pathway inhibition has generally been modest and variable.

This limited efficacy is particularly evident for single-agent PI3K/AKT/mTOR pathway inhibition. Although PI3K pathway alterations are common in NSMP/CN-low EC, clinical responses to PI3K, AKT and mTOR inhibitors have often been modest and not durable. Pan-PI3K inhibitors have been limited by toxicity, whereas mTOR inhibitors may induce feedback activation of AKT signaling, reducing their long-term antitumor activity. These limitations indicate that the presence of pathway alterations alone is insufficient to predict clinical benefit and that subtype-specific biomarkers are required for more precise patient selection.

Isoform-selective PI3K inhibitors, such as alpelisib (BYL719), have shown clinical activity in PIK3CA-mutant endometrioid EC, supporting a subtype-directed therapeutic approach. AKT inhibitors including ipatasertib and afuresertib (89,90), have shown promising activity in preclinical and early-phase clinical studies, but their efficacy requires further validation (86-88). mTOR inhibitors, such as temsirolimus and everolimus, have demonstrated modest activity as monotherapies, partly due to feedback activation of AKT signaling (91). Therefore, mTOR inhibitors may be more useful in combination regimens, particularly in hormone-driven EC.

Combination strategies integrating PI3K/AKT/mTOR inhibition with hormonal therapy represent a clinically relevant approach for NSMP/CN-low and hormone receptor-positive endometrioid EC. These strategies may improve endocrine sensitivity and overcome hormone resistance. However, clinical responses remain variable, and durable benefit is limited to selected patients. Therefore, predictive biomarkers are needed to identify patients most likely to benefit from endocrine-targeted or pathway-directed combinations.

Table II. Target inhibitors of the PI3K-AKT-mTOR pathway in clinical trials for EC.

A, PI3K inhibitors (primarily active in NSMP and MSI-H/dMMR EC with PI3K pathway alterations; modest clinical efficacy, with limited durability of response)

First author/s, year	Therapy	Target	Subtype relevance	Clinical setting	Evidence stage/Phase	Key outcomes	(Refs.)
Duggan and Al-Salama, 2023	Copanlisib (BAY 80-6946)	PI3Kα/δ	NSMP; MSI-H/dMMR (PI3K-altered EC)	Persistent/recurrent EC	II	Modest efficacy (ORR, PFS); manageable toxicity	(87)
Matulonis *et al*, 2015	Pilaralisib (XL-147)	Pan- PI3K	NSMP (PI3K pathway-driven EC)	Advanced/recurrent EC	II	Limited efficacy; modest response rates	(155)
Heudel *et al*, 2017	Buparlisib (BKM120)	Pan- PI3K	NSMP	Advanced/recurrent EC	II	Modest efficacy; PFS benefit limited	(156)

B, AKT inhibitors (most relevant in PI3K/AKT pathway-altered EC, particularly NSMP; preliminary clinical activity, with efficacy requiring further validation)

First author/s, year	Therapy	Target	Subtype relevance	Clinical setting	Evidence stage/Phase	Key outcomes	(Refs.)
Myers *et al*, 2020	MK2206	AKT	PI3K/AKT-altered EC; NSMP	Advanced/recurrent EC	II	Modest activity; limited clinical benefit	(157)
Rodon *et al*, 2022	Pifusertib (TAS-117)	AKT	PTEN-deficient EC; NSMP	Advanced/metastatic Solid tumors with Germline PTEN Inactivating Mutations	II	Early-phase data; efficacy not well established	(158)
Smyth *et al*, 2020	Capivasertib (AZD5363)	AKT	PI3K/AKT pathway-altered EC	Advanced Solid Malignancy (EC)	I	Preliminary activity observed; further validation needed	(159)
Aghajanian *et al*, 2018	Uprosertib (GSK2141795)	AKT	Advanced/ recurrent EC (PI3K/AKT axis)	Recurrent/ metastatic EC	I	Safety and PK characterized; efficacy data limited	(160)

C, mTOR inhibitors (primarily active in NSMP and hormone-driven EC; modest clinical efficacy, with greater benefit observed in combination strategies)

First author/s, year	Therapy	Target	Subtype relevance	Clinical setting	Evidence stage/Phase	Key outcomes	(Refs.)
Colombo *et al*, 2013	Ridaforolimus (AP23573)	mTORC1	NSMP; PI3K pathway-activated EC	Persistent/recurrent EC	II	Disease stabilization observed (PFS benefit)	(161)
Oza *et al*, 2011	Temsirolimus (CCI-779)	mTORC1	NSMP	Advanced/metastatic EC	II	Modest activity; limited ORR	(162)
	Everolimus (RAD001)	mTORC1	Hormone-driven EC; NSMP	Recurrent EC	II	Improved outcomes in combination therapy	

Table II. Continued.

C, mTOR inhibitors (primarily active in NSMP and hormone-driven EC; modest clinical efficacy, with greater benefit observed in combination strategies)

First author/s, year	Therapy	Target	Subtype relevance	Clinical setting	Evidence stage/Phase	Key outcomes	(Refs.)
Voss *et al*, 2020	Sapanisertib (TAK-228)	mTORC1/2	PI3K/mTOR-altered EC	Advanced EC	I	Early signals of activity; limited clinical data	(163)

D, Dual PI3K and mTOR inhibitors

First author/s, year	Therapy	Target	Subtype relevance	Clinical setting	Evidence stage/Phase	Key outcomes	(Refs.)
Rubinstein *et al*, 2020	Samotolisib (LY3023414)	Pan-PI3K mTORC1/2	NSMP; PI3K-driven EC	Persistent/recurrent EC	II	Limited efficacy; combination strategies needed	(164)
Makker *et al*, 2016	Apitolisib (GDC-0980)	Pan-PI3K mTORC1/2	NSMP	Persistent/recurrent EC	II	Modest activity; toxicity concerns	(165)
Del Campo *et al*, 2016	Gedatolisib (PF-05212384) PF-04691502	Pan-PI3K mTORC1/2	PI3K/mTOR-altered EC	Recurrent EC	II	Promising early activity; needs validation	(166)

E, Combination

First author/s, year	Therapy	Target	Subtype relevance	Clinical setting	Evidence stage/Phase	Key outcomes	(Refs.)
Gaillard *et al*, 2024	Alpelisib (BYL719) and Fulvestrant (ICI 182780)	PI3Kα and Estrogen receptor	ER+ endometrioid EC; NSMP	ER-positive endometrioid EC	II	Improved endocrine sensitivity; combination benefit	(167)
Heudel *et al*, 2022	Vistusertib (AZD2014) and Anastrozole	mTORC1/2 and aromatase	Hormone receptor-positive EC; NSMP	Hormone receptor positive EC	I/II	Limited efficacy; modest endocrine enhancement	(168)
	ATG 008 and ATG 010	mTORC1/2 and XPO1	Advanced EC (mTOR-driven)	Recurrent or Metastatic EC	II	Early-phase; efficacy not yet defined	
	Ipatasertib (GDC0068) and Megestrol Acetate	AKT and Progesterone receptor	Hormone-driven EC; NSMP	Recurrent/ metastatic EC	Ib/II	Potential benefit in combination; data limited	

Subtype classification is based on TCGA molecular subtypes (POLE, MSI-H/dMMR, NSMP, CN-high). Evidence stage was categorized according to available data, including preclinical evidence, phase I, phase II, phase III and approved clinical use where applicable. CBR, clinical benefit rate; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; ORR, overall response rate; PD, progressive disease; AE, adverse event.

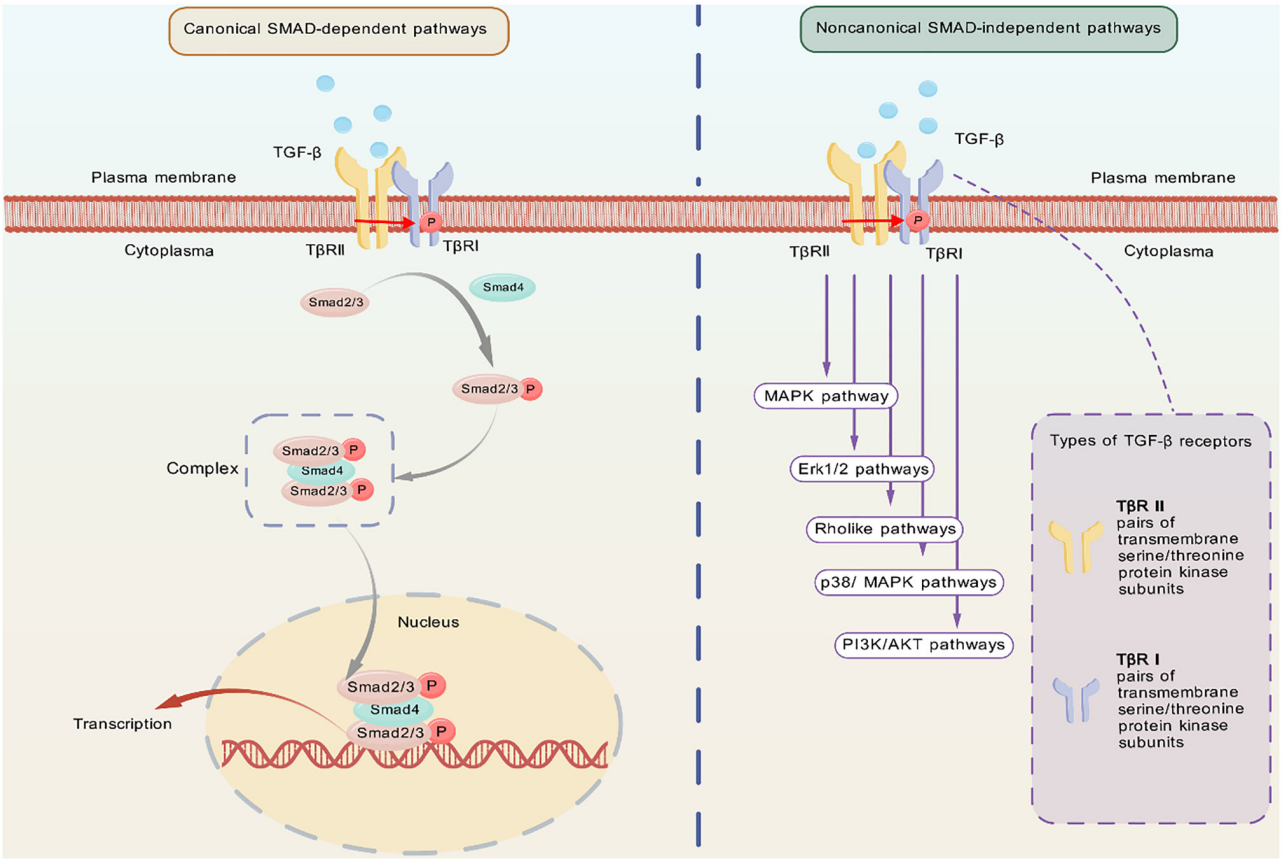

Figure 5. TGF-β signaling pathway. TGF-β binds to type II and type I serine/threonine kinase receptors, with beta-glycan acting as a co-receptor. This activates canonical SMAD2/3-SMAD4 signaling and non-SMAD pathways, including MAPK, PI3K/AKT. These signaling cascades regulate gene expression, cell differentiation, and tumor progression.

MAPK pathway inhibition may also be relevant in selected NSMP/CN-low tumors, particularly those with KRAS activation, PTEN-intact status or hormone resistance. Cobimetinib, alone or in combination with PI3K inhibitors, has shown activity in KRAS-mutant or PTEN-intact tumors (61). In addition, combined MEK and AKT inhibition has shown enhanced activity in EC models (64). However, clinical outcomes remain inconsistent due to adaptive resistance and pathway crosstalk.

Targeting TGF-β or NF-κB signaling in NSMP/CN-low EC remains largely preclinical. Metformin may restore TGF-β-mediated apoptotic signaling through AMPK activation, particularly in PTEN- or SMAD-deficient contexts (110). In hormone-resistant tumors, sterol regulatory element-binding protein 1 promotes proliferation and progesterone resistance through NF-κB signaling, and its inhibition by fatostatin suppresses NF-κB activity and partially restores hormone sensitivity (111-113). These findings support further investigation of subtype-specific combination strategies but require clinical validation.

Overall, NSMP/CN-low EC represents the subtype most closely linked to PI3K/AKT/mTOR and endocrine-related therapeutic strategies. However, single-pathway inhibition is often insufficient due to pathway redundancy, compensatory signaling and intratumoral heterogeneity. Future research should focus on identifying robust biomarkers and optimizing rational combination regimens in molecularly selected patients.

CN-high/p53-abnormal EC

Signaling pathway status in CN-high/p53-abnormal EC. CN-high/p53-abnormal EC is characterized by extensive copy-number alterations, TP53 abnormalities, aggressive clinical behavior and poor prognosis. Compared with POLE-mutated and MSI-H/dMMR tumors, CN-high tumors are generally less immunogenic and more strongly associated with genomic instability, cell-cycle dysregulation, invasive behavior and treatment resistance. In this subtype, the clinical relevance of signaling pathways lies not only in their oncogenic activation but also in their contribution to aggressive tumor biology and therapeutic failure.

TGF-β signaling is particularly relevant in aggressive and advanced EC. The human endometrium undergoes cyclical remodeling regulated by estrogen and progesterone, involving proliferation, differentiation and repair (114). The TGF-β superfamily, including TGF-β1-3, bone morphogenetic proteins, growth and differentiation factors (GDFs), and activins/inhibins, plays a central role in embryonic development and tissue homeostasis (Fig. 5) (115). In EC, TGF-β signaling exhibits a context-dependent. In early-stage or CN-low tumors, it may retain tumor-suppressive functions by regulating cell cycle arrest and apoptosis (106,107). By contrast, in advanced or CN-high tumors, TGF-β signaling is associated with EMT, invasion and metastasis, indicating a shift toward tumor-promoting activity (108).

NF-κB signaling is also relevant in CN-high/p53-abnormal EC. Persistent NF-κB activation promotes chronic inflammation and a pro-tumorigenic microenvironment. In CN-high or hormone-resistant tumors, NF-κB enhances tumor aggressiveness by promoting survival signaling, inflammatory amplification and immune evasion (79-84). Furthermore, interaction between NF-κB signaling, cell-cycle dysregulation and PTEN loss may accelerate tumor progression. For example, cyclin D1, a regulatory subunit of CDK4/6, interacts with NF-κB signaling. The cyclin D1T286A mutation, particularly in the context of PTEN loss, accelerates tumor progression and enhances NF-κB-mediated inflammatory signaling (116,117).

PI3K/AKT/mTOR and MAPK pathway crosstalk may also contribute to tumor progression and therapeutic resistance in CN-high tumors. Although these pathways are not defining molecular features of CN-high/p53-abnormal EC, their interaction with inflammatory, TGF-β and cell-cycle-related pathways may promote aggressive behavior and resistance to therapy.

Therapeutic implications and efficacy of pathway targeting. Therapeutic targeting of the TGF-β signaling in CN-high or advanced EC requires careful consideration of tumor subtype and disease stage. In aggressive tumors, inhibition of TGF-β signaling may help suppress EMT and metastatic progression. Current approaches include neutralizing antibodies, antisense oligonucleotides and small-molecule inhibitors targeting TGF-β receptor I kinase (118). Several repurposed agents and natural compounds have also shown modulatory effects in EC models. Withaferin A inhibits EC cell proliferation through suppression of SMAD2 phosphorylation (119,120), while isoliqueritigenin induces apoptosis and inhibits EMT by downregulating TGF-β/SMAD signaling. Similarly, the bisphenol A derivative BHPF reduces p-SMAD2/3 levels and suppresses metastatic signaling (121). These findings suggest that TGF-β inhibition may be relevant in molecularly defined EC subsets characterized by enhanced EMT and invasive potential.

Additional regulators interacting with TGF-β signaling contribute to EC progression. Loss of PTEN alters SMAD2/3 nuclear localization and may attenuate tumor-suppressive signaling, highlighting crosstalk between PI3K/AKT and TGF-β pathways (109). PDIA6, CD73 and LPCAT1, modulate TGF-β signaling and influence tumor proliferation, metastasis and EMT-related process (122-125). GDF-15 is associated with EMT, chemoresistance and poor prognosis (126,127). Activin signaling also exhibits context-dependent effects, with activin A suppressing proliferation in some settings, whereas activin B promotes invasion and is linked to poor survival in type II EC (128,129).

Despite these biological findings, TGF-β-directed therapies in EC remain largely preclinical, and their clinical efficacy has not yet been clearly established. The dual tumor-suppressive and tumor-promoting roles of TGF-β signaling complicate clinical translation. Therefore, future studies should identify the specific molecular contexts in which TGF-β inhibition may provide therapeutic benefit, particularly in CN-high or invasive tumors.

Direct targeting of NF-κB signaling remains challenging due to its essential role in normal immune function and the lack of highly selective inhibitors. However, indirect targeting approaches may have therapeutic potential. ERK5, a MAPK family member, regulates survival, invasion and autophagy (130-132). Alterations in the MEK5-ERK5 pathway are observed in a substantial proportion of patients with EC (133). Pharmacological inhibition of ERK5 (such as JWG-071) suppresses NF-κB activation and reduces EC cell proliferation, supporting the ERK5/NF-κB axis as a potential therapeutic target.

Metabolic regulation also contributes to NF-κB activation. Sterol regulatory element-binding protein 1 is overexpressed in EC and promotes proliferation and progesterone resistance through NF-κB signaling (111-113). Inhibition of this pathway by fatostatin suppresses NF-κB activity and partially restores hormone sensitivity, linking metabolic reprogramming to inflammation-driven tumor progression. Nevertheless, the clinical utility of NF-κB-directed strategies in CN-high/p53-abnormal EC remains insufficiently validated.

Overall, failed or limited-efficacy experiences in aggressive EC subtypes suggest that targeting a single signaling pathway is unlikely to be sufficient for CN-high/p53-abnormal tumors. Although TGF-β-, NF-κB-, PI3K/MAPK- and cell-cycle-related pathways provide biological rationale for therapeutic intervention, most corresponding strategies remain preclinical or early-phase clinical approaches. Their clinical efficacy has not yet been validated in molecularly stratified EC trials, highlighting the need for subtype-specific trial design and combination regimens.

Overall, CN-high/p53-abnormal EC remains a clinically aggressive subtype with limited efficacy from currently established pathway-targeted strategies. Targeting TGF-β, NF-κB, PI3K/MAPK crosstalk and cell-cycle-related pathways may provide therapeutic opportunities, but most available evidence remains preclinical or early-stage. Therefore, rational combination strategies and subtype-specific clinical trials are needed.

Cross-subtype pathway crosstalk and therapeutic evidence gaps. Although the PI3K-AKT-mTOR, RAS-RAF-MEK-ERK, TGF-β and NF-κB pathways are often described as independent cascades, increasing evidence indicates that they function as an interconnected regulatory network in EC (134). Crosstalk among these pathways coordinates tumor cell proliferation, metabolic reprogramming, immune modulation, EMT and therapeutic resistance. Importantly, the pattern and functional impact of pathway crosstalk differ across molecular subtypes.

In POLE-mutated and MSI-H/dMMR tumors, pathway interactions are frequently linked to immune activation, inflammatory responses and TIME regulation. In NSMP/CN-low tumors, crosstalk between PI3K/AKT/mTOR, MAPK and hormone-related signaling contributes to endocrine resistance and variable responses to targeted therapy. In CN-high/p53-abnormal tumors, integration of PI3K, MAPK, TGF-β and NF-κB pathways contributes to aggressive tumor behavior, invasion and therapy resistance.

A key interaction occurs between the PI3K-AKT-mTOR and RAS-RAF-MEK-ERK pathways (135). RAS can directly activate PI3K, while AKT and ERK share downstream targets regulating cell cycle progression and survival. Reciprocal feedback activation between these pathways following single-agent inhibition represents a key mechanism of adaptive resistance,

supporting the rationale for combined PI3K/MAPK-targeted therapies. However, combination strategies are often limited by toxicity, compensatory pathway activation and lack of validated predictive biomarkers.

The TGF-β pathway further integrates with PI3K/MAPK and NF-κB signaling (134). While TGF-β exerts tumor-suppressive effects during early tumorigenesis, it promotes EMT, invasion and stemness in advanced EC through cooperation with these pathways. In addition, TGF-β-induced cytokines can activate NF-κB, forming a feed-forward loop that sustains a pro-tumorigenic microenvironment.

NF-κB functions as a central inflammatory hub linking oncogenic signaling to the TME (136). Activation of MAPK signaling, metabolic regulators such as SREBPs, or PTEN loss can enhance NF-κB activity, amplifying cytokine production and immune cell recruitment. This inflammatory amplification contributes not only to tumor progression but also to hormone resistance and immune evasion.

Lessons from limited-efficacy clinical studies further support the importance of pathway crosstalk. Many targeted therapies have shown encouraging preclinical activity but only modest clinical benefit when evaluated as single agents. Potential explanations include compensatory activation of parallel pathways, insufficient molecular selection, intratumoral heterogeneity and dose-limiting toxicity. Therefore, future clinical trials should classify therapeutic strategies according to evidence stage, including preclinical, phase I, phase II, phase III and approved settings, and should incorporate molecular subtype-based stratification from the design stage.

Collectively, these findings indicate that signaling pathways in EC operate as an integrated and dynamic network rather than isolated cascades. However, the therapeutic implications of pathway crosstalk remain incompletely understood. Current treatment strategies largely rely on single-pathway inhibition, which may be insufficient to overcome adaptive resistance. Future research should focus on defining subtype-specific pathway interactions and developing rational co-targeting strategies to improve clinical outcomes.

5. Molecular subtype-guided immunotherapy in EC

Immune landscapes and rationale for ICIs in molecularly defined EC. EC is a heterogeneous malignancy characterized by distinct molecular subtypes with divergent immunogenicity and therapeutic responses. These subtype-specific differences in tumor antigenicity and immune microenvironment provide a critical foundation for immunotherapy-based treatment strategies (137). In this context, ICIs have emerged as an effective approach, particularly in advanced and recurrent EC.

From a molecular classification perspective, POLE-mutated and MSI-H/dMMR tumors represent highly immunogenic subtypes. These tumors exhibit high TMB, increased neoantigen load and abundant TILs, along with elevated expression of immune checkpoint molecules such as PD-1 and PD-L1. These features collectively confer strong sensitivity to PD-1/PD-L1 blockade. By contrast, p53-abnormal (CN-high) tumors are typically associated with an immunosuppressive microenvironment, characterized by increased macrophage infiltration and heterogeneous PD-L1 expression, whereas NSMP tumors generally display intermediate immune activation profiles (34). These subtype-specific immune landscapes partially explain the variability in response to immune checkpoint inhibition.

Recent transcriptomic and spatial profiling studies further refine this landscape, demonstrating that immune cell spatial distribution, interferon-γ signaling signatures and the presence of tertiary lymphoid structures are more predictive of immunotherapy responses than PD-L1 expression alone. In addition to PD-1/PD-L1, other immune checkpoints-including CTLA-4, LAG-3, TIM-3, B7-H4 and IDO1-also contribute to immune evasion in EC, supporting the development of combination immunotherapeutic strategies. (21,34,138-140).

Collectively, these findings indicate that immunogenic subtypes (particularly POLE-mutated and MSI-H/dMMR EC) are optimal candidates for immune checkpoint blockade, whereas immunologically 'cold' tumors (such as CN-high or NSMP) may require combination approaches to enhance immune activation and overcome resistance. However, molecular subtype alone is insufficient to fully predict immunotherapy benefit. Although POLE-mutated and MSI-H/dMMR tumors are generally more responsive to ICIs, primary and acquired resistance can still occur. Conversely, pMMR, NSMP/CN-low and p53-abnormal/CN-high tumors often exhibit immune-excluded or immunosuppressive phenotypes, which may limit the efficacy of single-agent immune checkpoint blockade.

Clinical application, evidence stage and subtype-specific outcomes. Clinically, ICIs targeting the PD-1/PD-L1 axis have reshaped the therapeutic landscape of advanced and recurrent EC. Pembrolizumab was approved for patients with advanced MSI-H/dMMR EC who progressed after prior systemic therapy and were not candidates for curative surgery or radiotherapy (141,142). Dostarlimab-gxly was subsequently approved in combination with carboplatin and paclitaxel, followed by dostarlimab maintenance, for primary advanced or recurrent MSI-H/dMMR EC, and this indication was later expanded to a broader population of adult patients with primary advanced or recurrent EC (141,143). More recently, pembrolizumab combined with carboplatin and paclitaxel, followed by pembrolizumab maintenance, was approved for adult patients with primary advanced or recurrent EC (144,145). These approvals indicate that immunotherapy has moved from a biomarker-selected salvage strategy toward a frontline component of treatment for advanced or recurrent EC.

Clinical outcomes of ICIs in EC are strongly influenced by molecular subtype. Patients with dMMR/MSI-H tumors demonstrate the most robust and durable responses, consistent with their high TMB and immunogenic TME. By contrast, pMMR tumors, including NSMP/CN-low and p53-abnormal/CN-high subtypes, exhibit more variable and generally lower response rates, reflecting their relatively immunologically 'cold' phenotype. Large phase III trials reported in recent years further demonstrated that the addition of PD-1/PD-L1 blockade to platinum-based chemotherapy significantly improves progression-free survival across both dMMR and pMMR populations. However, the magnitude of benefit remains notably greater in dMMR tumors, underscoring

the importance of molecular stratification in guiding treatment decisions and optimizing therapeutic outcomes.

Therefore, immunotherapeutic strategies in EC should be interpreted according to evidence stage. Approved or phase III-supported strategies include PD-1/PD-L1 blockade alone or in combination with platinum-based chemotherapy in selected clinical settings. By contrast, dual checkpoint blockade, ICIs combined with anti-angiogenic agents, PI3K/AKT/mTOR inhibitors, antibody-drug conjugates (ADCs) or other immune modulators remain investigational and are mainly supported by phase I, phase II or ongoing clinical trial evidence. Preclinical immune-sensitizing concepts, including modulation of tumor-associated macrophages, metabolic regulators or novel immune checkpoints, require further validation before routine clinical application.

Failed or limited responses and resistance to immunotherapy across molecular subtypes. Although ICIs have substantially improved the treatment landscape of EC, failed or limited responses remain important clinical challenges. The benefit of ICIs is most evident in POLE-mutated and MSI-H/dMMR tumors; however, durable responses are not universal even in these immunogenic subtypes. Primary or acquired resistance may result from defective antigen presentation, impaired interferon signaling, immune editing, T-cell exhaustion and myeloid-driven immunosuppression. These mechanisms may allow tumors to escape immune surveillance despite high neoantigen burden and apparent baseline immunogenicity.

By contrast, pMMR, NSMP/CN-low and p53-abnormal/CN-high tumors generally show lower response rates to single-agent immune checkpoint blockade. These tumors frequently exhibit immune-excluded or immunosuppressive microenvironments, which may limit T-cell infiltration and reduce sensitivity to ICIs. Therefore, single-agent immunotherapy has limited efficacy in these molecular contexts, and combination strategies are usually required.

The phase III chemo-immunotherapy studies also highlight an important limitation: clinical benefit is not uniform across molecular subtypes. Although benefit is observed in both dMMR and pMMR populations, responses in pMMR, NSMP/CN-low and p53-abnormal/CN-high tumors are more heterogeneous and generally less pronounced than those in dMMR/MSI-H tumors. This suggests that non-stratified immunotherapy-based combinations may be insufficient for less immunogenic EC subtypes and that additional biomarkers are required to identify patients most likely to benefit.

Another important limitation is the lack of sufficiently accurate predictive biomarkers. PD-L1 expression and TMB do not fully explain response heterogeneity across molecular subtypes. Emerging biomarkers, including spatial immune architecture, interferon-γ signaling signatures, tertiary lymphoid structures and myeloid composition, may better reflect therapeutic response, but these remain largely investigational. Therefore, ongoing clinical trials should be interpreted according to both molecular subtype and evidence stage, including phase I, phase II, phase III and approved clinical settings. Future studies should incorporate subtype-stratified endpoints and biomarker-defined patient selection to improve the clinical translation of immunotherapy.

Investigational combination strategies and future directions. To address the limited efficacy of single-agent ICIs in less immunogenic EC subtypes, ongoing clinical studies are evaluating rational combination strategies. Representative ongoing clinical trials and emerging immunotherapy strategies in EC are summarized in Table III. These include dual immune checkpoint inhibition, such as PD-1 plus CTLA-4 blockade, combinations with anti-angiogenic agents, PI3K/AKT/mTOR inhibitors, ADCs and emerging immune modulators. These approaches are intended to enhance tumor antigen presentation, increase T-cell infiltration, remodel the immunosuppressive TME and overcome adaptive resistance to PD-1/PD-L1 blockade.

However, most of these strategies remain under clinical investigation, and their efficacy across distinct molecular subtypes has not yet been fully established. Some chemo-immunotherapy regimens are supported by phase III clinical evidence or regulatory approval, whereas many dual-checkpoint, targeted therapy-based or ADC-based combinations remain investigational and are currently supported mainly by phase I/II trials or preclinical rationale. Therefore, future studies should avoid grouping all immunotherapy-based strategies together and instead classify them according to evidence stage, molecular subtype and biomarker-defined population.

Overall, immune checkpoint inhibition has become a cornerstone therapy for molecularly defined EC, particularly in dMMR/MSI-H subtypes. However, its broader clinical applicability remains constrained by resistance mechanisms, heterogeneous benefit in pMMR and p53-abnormal/CN-high tumors, and insufficient biomarker precision. Future progress will depend on biomarker-driven selection, optimized combination strategies and deeper characterization of the TIME to extend durable benefit to less immunogenic EC subtypes.

6. Future directions and novel approaches according to molecular subtype

Despite notable advances in molecular stratification and immune checkpoint blockade, durable disease control in EC remains uneven across molecular subgroups. Therapeutic resistance, including both intrinsic and acquired resistance, continues to limit long-term benefit across chemotherapy, endocrine therapy, targeted agents and immunotherapy. Importantly, these limitations exhibit clear molecular subtype-dependent patterns. Therefore, future therapeutic innovation in EC should move beyond a uniform treatment model and instead focus on molecular subtype-specific vulnerabilities, resistance mechanisms, treatment sequencing and biomarker-guided clinical translation.

POLE-mutated EC. POLE-mutated EC is characterized by an ultramutated genotype, high TMB, strong immune infiltration and generally favorable prognosis. These biological features provide a strong rationale for immune-based approaches and, in selected early-stage patients, potential treatment de-escalation. However, although POLE-mutated tumors are usually associated with excellent outcomes, durable responses are not universal in advanced or recurrent settings, and the mechanisms underlying immune escape in this subtype remain incompletely understood.

Table III. Ongoing clinical trials and emerging immunotherapy strategies in EC.

Therapy	Phase	Trial ID	Registration year	Subtype relevance
Avutometinib + Defactinib + Everolimus	I	NCT07318324	January 2026	RAS-muntant; NSMP
EIK1005 (WRN inhibitor)	I/II	NCT07262619	November 2025	MSI-H/dMMR
Bevacizumab + Chemotherapy + Pembrolizumab	III	NCT07198074	September 2025	pMMR, CN-high (TP53-abnormal)
Fruquintinib + Chemotherapy	II	NCT07170982	September 2025	pMMR; NSMP
AZD8205	III	NCT07044336	September 2025	Unselected EC (all subtypes)
TER-2013	I/II	NCT07109726	July 2025	PI3K/AKT pathway-altered EC; NSMP; MSI-H
TQB2450 + Progestin	II	NCT06914297	March 2025	MSI-H/dMMR EC (fertility-sparing)
NKT3447 (CDK2 Inhibitor)	I	NCT06264921	February 2024	Proliferative EC; NSMP
Dostarlimab	II	NCT06278857	January 2024	MSI-H/dMMR
PRO1107 (PTK7)	I/II	NCT06171789	November 2023	Unselected EC (all subtypes)
MK-2870 (TROP2 ADC)	III	NCT06132958	November 2023	pMMR EC (Post-immunotherapy setting)
AO-252 (TACC3 PPI Inhibitor)	I	NCT06136884	November 2023	Serous EC; CN-high
Sacituzumab Govitecan (TROP2 ADC)	I/II	NCT06040970	September 2023	Broad EC; post-chemotherapy
MK-4280A (Favezelimab + Pembrolizumab	II	NCT06036836	August 2023	pMMR EC
HS-20089 (B7-H4 ADC)	II	NCT06014190	August 2023	B7-H4-high EC; often pMMR
M1774 + ZEN-3694 (ATR)	I	NCT05950464	July 2023	CN-high (TP53-abnormal)
ILB2109 + Toripalimab (A2aR)	I/II	NCT05955105	July 2023	Immunosuppressive EC; pMMR
BBI-355 (CHK1 Inhibitor)	I	NCT05827614	March 2023	DNA damage-altered EC; CN-high (TP53-abnormal)
Navtemadlin (MDM2 inhibitor)	II/III	NCT05797831	March 2023	CN-high (TP53-abnormal); NSMP
DKN-01 + Pembrolizumab	II	NCT05761951	February 2023	Immune-resistant EC; pMMR
Narazaciclib + Letrozole	I/II	NCT05705505	January 2023	Hormone-driven EC; NSMP
APG-1252 (Bcl-2/Bcl-xl inhibitor)	I	NCT05691504	January 2023	Apoptosis-resistant EC; broad

Subtype relevance is defined based on molecular classification (POLE, MSI-H/dMMR, NSMP, CN-high). CDK2, cyclin-dependent kinase 2; PD-1, programmed cell death protein 1; PTK7, protein tyrosine kinase 7; TROP2, tumor-associated calcium signal transducer 2; TACC3, transforming acidic coiled-coil-containing protein 3; LAF3, lymphocyte-activation gene 3; B7-H4, B7 homolog 4; ATR, ataxia telangiectasia and Rad3-related protein; A2aR, adenosine A2a receptor; CHK1, checkpoint kinase 1; MDM2, mouse double minute 2 homolog; DKK1, Dickkopf-related protein 1; Bcl-2/Bcl-xl, B-cell lymphoma 2/B-cell lymphoma-extra-large.

For this subtype, one important future direction is to avoid overtreatment while maintaining oncologic safety. Molecular classification has already reshaped risk assessment by identifying POLE-mutated tumors as a favorable-risk group, suggesting that some patients may benefit from reduced treatment intensity when supported by clinicopathological features and guideline-based assessment (52,146). However, prospective evidence is still needed before broad treatment de-escalation can be routinely applied.

In advanced or recurrent POLE-mutated EC, ICIs may have therapeutic relevance because of the high neoantigen burden and immunogenic TME. Nevertheless, resistance can still occur through defective antigen presentation, attenuation of interferon signaling, T-cell exhaustion and myeloid-driven immunosuppression (147). Therefore, future studies should investigate whether combination strategies targeting alternative immune checkpoints, tumor-associated macrophages or metabolic regulators can overcome resistance in this subtype.

Personalized immunotherapeutic strategies, including neoantigen-based vaccines and adoptive cellular therapies, may be particularly relevant for POLE-mutated tumors because of their high mutational burden. However, these approaches remain largely preclinical or early-stage clinical concepts and require further validation before routine clinical application.

MSI-H/dMMR EC. MSI-H/dMMR EC is characterized by mismatch repair deficiency, microsatellite instability, increased mutational burden and immune activation. This subtype generally shows high sensitivity to immune checkpoint blockade, and chemo-immunotherapy has redefined frontline management in advanced or recurrent disease. Phase III clinical evidence has shown that adding PD-1/PD-L1 blockade to platinum-based chemotherapy improves clinical outcomes, with particularly strong benefit observed in dMMR/MSI-H tumors (145,148,149).

Despite these advances, not all patients with MSI-H/dMMR EC achieve durable disease control. Primary and acquired resistance remain important clinical challenges. Mechanistically, defective antigen presentation, impaired interferon-γ signaling, immune-editing, T-cell exhaustion and myeloid-driven immunosuppression may contribute to checkpoint inhibitor failure across EC subtypes (147). However, the relative contribution of these mechanisms in MSI-H/dMMR tumors has not yet been fully defined.

Future therapeutic strategies for MSI-H/dMMR EC should focus on overcoming immune resistance and optimizing combination therapy. Strategies targeting alternative immune checkpoints (such as LAG-3 and TIM-3), metabolic regulators and tumor-associated macrophages aim to restore effective antitumor immunity (150,151). These strategies are currently investigational and remain mostly in preclinical, phase I or early-phase clinical development. In addition, integration of ICIs with targeted therapies, anti-angiogenic agents or PI3K/AKT/mTOR pathway inhibitors may help overcome immune resistance, but optimal sequencing and patient selection remain unclear.

A major translational gap lies in biomarker precision. Although MSI-H/dMMR status is clinically useful, it does not fully capture response heterogeneity. Currently used biomarkers such as PD-L1 expression and TMB, are insufficient to predict durable benefit across all patients. Emerging evidence suggests that spatial immune architecture, interferon-γ signaling signatures and myeloid composition may more accurately reflect therapeutic response, However, these biomarkers remain largely investigational (152).

NSMP/CN-low EC. NSMP/CN-low EC represents a heterogeneous molecular subgroup that frequently overlaps with hormone-driven endometrioid tumors. Compared with POLE-mutated and MSI-H/dMMR tumors, NSMP/CN-low tumors often show lower immunogenicity and more heterogeneous responses to single-agent ICIs. Therefore, future strategies for this subtype should focus on endocrine-based combinations, PI3K/AKT/mTOR pathway targeting, immune-sensitizing approaches and biomarker refinement.

In NSMP/CN-low EC, endocrine therapy remains clinically relevant, particularly in hormone receptor-positive tumors. However, endocrine resistance is common and may be driven by PI3K/AKT/mTOR activation, MAPK signaling, epigenetic plasticity and TME remodeling. Combination strategies integrating hormonal therapy with PI3K/AKT/mTOR inhibitors, mTOR inhibitors or other targeted agents may improve endocrine sensitivity. Nevertheless, clinical efficacy remains variable, and predictive biomarkers are needed to identify patients most likely to benefit from these approaches.

For immunologically 'cold' NSMP/CN-low tumors, emerging strategies aim to enhance immune responsiveness through rational combinations. These include co-targeting angiogenesis, PI3K/AKT/mTOR signaling and other tumor-intrinsic pathways that modulate the TME. Although these approaches have biological rationale, their clinical efficacy varies across molecular subtypes, and optimal treatment sequencing remains unclear.

ADCs represent another emerging therapeutic strategy for recurrent or treatment-resistant EC. By enabling selective cytotoxic delivery through tumor-associated antigens such as Trop-2, ADCs may help overcome resistance after chemotherapy or immunotherapy and expand treatment options beyond conventional cytotoxic therapy (153). However, most ADC-based approaches in EC remain under investigation, with limited phase III evidence, and their long-term efficacy and subtype-specific benefit have yet to be fully established.

Future progress in NSMP/CN-low EC will depend on improved molecular stratification within this heterogeneous subgroup. Integration of multi-omic profiling, spatial immunogenomics and circulating tumor DNA-based monitoring may refine patient selection and enable adaptive treatment decisions. However, these technologies remain limited by cost, standardization and accessibility challenges.

CN-high/p53-abnormal EC. CN-high/p53-abnormal EC is characterized by extensive copy-number alterations, TP53 abnormalities, aggressive clinical behavior and poor prognosis. This subtype frequently demonstrates immune-excluded or immunosuppressive phenotypes and is often less responsive to single-agent ICIs than MSI-H/dMMR tumors. Therefore, future strategies for CN-high/p53-abnormal EC should focus on intensified combination therapy, antibody-drug conjugates, HER2-targeted therapy, DNA damage response targeting, cell-cycle-directed approaches and TME modulation.

Although chemo-immunotherapy has improved the treatment landscape of advanced or recurrent EC, the magnitude of benefit in pMMR, NSMP and CN-high tumors is generally more heterogeneous than in MSI-H/dMMR tumors (145,148,149). Therefore, additional biomarkers are needed to identify which patients with CN-high/p53-abnormal EC are most likely to benefit from immune-based combinations. In this subtype, immune resistance may be mediated by tumor-intrinsic genomic instability, defective antigen presentation, immunosuppressive myeloid infiltration and inflammatory pathway activation.

ADCs may be particularly relevant for aggressive or recurrent CN-high/p53-abnormal tumors, especially when conventional chemotherapy has failed. Agents targeting Trop-2, B7-H4 or other tumor-associated antigens may provide subtype-relevant therapeutic opportunities. However, these strategies remain investigational, and their efficacy across molecularly defined subgroups has not yet been clearly established.

HER2-targeted therapy may also be clinically relevant in selected serous or p53-abnormal EC with HER2 overexpression or amplification. In addition, DNA damage response inhibitors, PARP inhibitor-based combinations and cell-cycle-directed strategies are being explored in tumors characterized by genomic instability. These approaches

provide a rational direction for CN-high/p53-abnormal EC, but most remain in preclinical, phase I or phase II development and require validation in subtype-stratified clinical trials.

Modulation of the immunosuppressive TME is another important direction for this subtype. Strategies targeting alternative immune checkpoints, macrophage-mediated immunosuppression, metabolic regulators or inflammatory pathways may help convert immune-excluded tumors into more immune-responsive tumors (150,151). However, these approaches remain in early clinical development, and their ability to consistently overcome immune resistance has not yet been established.

Impact of molecular classification on clinical guidelines and regulatory decision-making. Molecular classification has increasingly shifted EC management from a histology-based model toward an integrated clinicopathological and molecular framework. This shift has important implications for diagnosis, risk stratification, adjuvant treatment selection, systemic therapy and regulatory decision-making. The 2025 ESGO/ESTRO/ESP guideline update further reinforces this transition by incorporating the revised 2023 FIGO staging system and newly available clinical evidence into EC management.

First, molecular classification has been incorporated into modern staging and risk assessment systems. The 2023 FIGO staging system integrates molecular features into EC staging and recognizes POLE-mutated, MMRd, p53-abnormal and NSMP as clinically relevant molecular categories (146). This represents an important step toward molecularly informed staging, as POLE-mutated status is associated with favorable prognosis, whereas p53-abnormal status is associated with aggressive biology and poorer outcomes. The 2025 ESGO/ESTRO/ESP guidelines further strengthen this approach by recommending molecular classification based on POLE mutation analysis and immunohistochemical assessment of MMR and p53 status, thereby defining POLE-mutated, MMRd, NSMP and p53-abnormal tumors as clinically relevant categories for risk allocation and treatment planning (52).

Second, the ESGO 2025 update refines prognostic risk grouping by integrating anatomical stage, histological features, lymphovascular space invasion, estrogen receptor status and molecular subtype. When molecular classification is available, FIGO staging can be reported with molecular annotation. For example, molecularly defined categories such as stage IAm POLE-mutated and stage IICm p53-abnormal highlight the distinct prognostic implications of POLE mutation and p53 abnormality in early-stage disease (52,146). In the 2025 ESGO/ESTRO/ESP framework, several POLE-mutated early-stage tumors are classified as low risk, and no adjuvant therapy is recommended for low-risk EC. By contrast, p53-abnormal tumors are more frequently assigned to high-risk categories, supporting more intensive adjuvant or systemic treatment strategies (52).

Third, molecular classification has influenced clinical treatment guidelines by improving patient selection for adjuvant and systemic therapy. POLE-mutated tumors may support treatment de-escalation in appropriate clinical contexts, whereas p53-abnormal tumors often support treatment de-escalation in selected clinical contexts, whereas p53-abnormal tumors often support treatment intensification because of their aggressive biology. MSI-H/dMMR status has become clinically important for identifying patients likely to benefit from immune checkpoint blockade. NSMP/CN-low tumors require further refinement because this group remains biologically heterogeneous and may require additional biomarkers, such as hormone receptor status, CTNNB1 mutation, PI3K pathway alterations or immune microenvironment features.

Fourth, the ESGO 2025 update has important implications for systemic therapy in advanced or recurrent EC. For MMRd tumors with unresectable stage III/IV or recurrent disease, ICIs, such as dostarlimab, durvalumab or pembrolizumab, in combination with carboplatin-paclitaxel chemotherapy followed by immune checkpoint inhibitor maintenance, are recommended as part of first-line treatment (52). For non-MMRd tumors, carboplatin-paclitaxel chemotherapy remains important, particularly in rapidly progressive or symptomatic disease; however, immune checkpoint inhibitor-based combinations and maintenance strategies may be considered in selected patients according to clinical context and available evidence (52). In the second-line setting, treatment is also guided by MMR status, and repeated MMR testing on relapsed tumor tissue may be considered when feasible to guide treatment selection (52).

Fifth, molecular classification has directly influenced regulatory approvals and drug development. Regulatory decisions increasingly rely on biomarker-defined subgroups and molecularly stratified clinical trial outcomes. In 2024, pembrolizumab combined with carboplatin and paclitaxel, followed by pembrolizumab maintenance, was approved for adult patients with primary advanced or recurrent EC (144,148,154). Dostarlimab combined with carboplatin and paclitaxel, followed by dostarlimab maintenance, was also approved and subsequently expanded for adult patients with primary advanced or recurrent EC, including a previous approval for dMMR/MSI-H disease and later expansion to a broader population (154). These approvals illustrate how molecular classification and biomarker-defined trial analyses have accelerated the incorporation of ICIs into standard EC treatment.

Finally, molecular classification has reshaped clinical trial design. Modern EC trials increasingly stratify patients according to MMR/MSI status, p53 status, POLE mutation status and other molecular or immune biomarkers. This enables more precise evaluation of treatment efficacy across subgroups and helps identify populations that may require intensified treatment, combination therapy or de-escalation. Future regulatory decisions will likely depend increasingly on molecularly stratified endpoints, adaptive trial designs and companion biomarker development. Overall, the ESGO 2025 update supports the central concept of this review: molecular classification is no longer only a prognostic tool, but has become an essential framework for risk-adapted, biomarker-guided and subtype-specific treatment of EC.

Lessons from failed or limited-efficacy clinical studies. Failed or limited-efficacy clinical studies provide important lessons for future EC drug development. Across molecular

Table IV. Preclinical and emerging therapeutic concepts according to molecular subtype in EC.

Molecular subtype	Biological vulnerability	Preclinical or emerging strategy	Evidence stage	Translational challenge
POLE-mutated EC	Ultra-mutated genotype, high TMB, high neoantigen burden, strong immune infiltration	Neoantigen-based vaccines; adoptive cellular therapy; alternative immune checkpoint targeting; treatment de-escalation strategies	Preclinical/early clinical concept	Most patients have favorable prognosis; optimal candidates for escalation or de-escalation remain undefined; prospective validation is required
MSI-H/dMMR EC	Mismatch repair deficiency, microsatellite instability, high TMB, immune-active tumor microenvironment	Strategies to overcome ICI resistance, including LAG-3/TIM-3 targeting, tumor-associated macrophage modulation, metabolic immune regulation and ICI-based combinations	Preclinical/phase I-II/ongoing clinical studies	Primary and acquired resistance remain incompletely understood; biomarkers beyond MSI/MMR status are needed
NSMP/CN-low EC	Hormone-driven biology, PI3K/AKT/mTOR pathway alterations, heterogeneous immune activation	Endocrine therapy combined with PI3K/AKT/mTOR inhibitors; immune-sensitizing combinations; Wnt/β-catenin- or CTNNB1-related strategies; ctDNA-guided treatment adaptation	Preclinical/phase I-II/ ongoing clinical studies	This subtype is biologically heterogeneous; predictive biomarkers for endocrine sensitivity, pathway dependence and immunotherapy benefit remain insufficient
CN-high/p53-abnormal EC	TP53 abnormality, copy-number instability, aggressive biology, immune-excluded or immunosuppressive phenotype	HER2-targeted therapy in HER2-positive serous-like tumors; ADCs targeting Trop-2 or B7-H4; DNA damage response inhibitors; PARP inhibitor-based combinations; cell-cycle-directed strategies	Preclinical/phase I-II/ ongoing clinical studies	Clinical benefit remains variable; molecular selection and biomarker-defined trial design are required
Cross-subtype strategies	Pathway crosstalk, tumor heterogeneity, adaptive resistance and tumor-immune microenvironment remodeling	Multi-omic profiling; spatial immunogenomics; circulating tumor DNA monitoring; rational co-targeting of PI3K/MAPK/immune pathways	Emerging translational concept	Cost, standardization, accessibility and prospective clinical validation remain major barriers

ADCs, antibody-drug conjugates; CTNNB1, catenin beta 1; ctDNA, circulating tumor DNA; dMMR, mismatch repair deficient; EC, endometrial cancer; ICIs, immune checkpoint inhibitors; MSI-H, microsatellite instability-high; NSMP, no specific molecular profile; PARP, poly(ADP-ribose) polymerase; TMB, tumor mutational burden.

subtypes, one recurring limitation is that biological pathway activation does not always translate into clinical dependence on that pathway. For example, PI3K/AKT/mTOR pathway alterations are frequent in EC, particularly in NSMP/CN-low and MSI-H/dMMR tumors, but single-agent PI3K, AKT and mTOR inhibitors have generally produced modest and variable clinical responses. Toxicity associated with some pan-PI3K inhibitors, feedback activation after mTOR inhibition and compensatory MAPK signaling may partly explain these limited outcomes.

Similarly, MAPK-, TGF-β- and NF-κB-directed strategies have strong mechanistic rationale but remain insufficiently

validated in EC. Many of these approaches are still in the preclinical, phase I or phase II stage, and their benefit in molecularly defined EC populations has not been clearly established. These findings indicate that future studies should not rely solely on pathway presence but should incorporate functional biomarkers, subtype-specific stratification and rational combination strategies.

In immunotherapy, the most robust benefit has been observed in MSI-H/dMMR and POLE-mutated tumors, whereas pMMR, NSMP/CN-low and CN-high/p53-abnormal tumors show more heterogeneous or limited responses to single-agent immune checkpoint blockade. Even in immunogenic tumors, primary and acquired resistance may occur. Therefore, future immunotherapy trials should distinguish approved phase III-supported strategies from investigational phase I/II combinations and preclinical immune-sensitizing concepts.

These lessons support a more rigorous evidence-stage framework for EC treatment development. Ongoing and emerging strategies should be categorized as preclinical concepts, phase I safety studies, phase II efficacy studies, phase III confirmatory trials or approved clinical strategies. Such classification may help readers better interpret the maturity of current evidence and may facilitate the design of subtype-stratified clinical trials.

Integrated future perspective. Overall, future EC management will likely evolve from static molecular classification toward adaptive, subtype-guided combination strategies. While current molecular classification provides a strong biological and clinical framework, it does not fully capture intratumoral heterogeneity, temporal evolution or treatment-induced resistance. Therefore, integration of multi-omic profiling, spatial immunogenomics, circulating tumor DNA monitoring and real-world clinical data may enable more dynamic treatment adaptation. Representative preclinical and emerging therapeutic concepts according to molecular subtype are summarized in Table IV. This table highlights subtype-specific biological vulnerabilities, candidate therapeutic strategies, evidence stage and major translational challenges.

While emerging strategies show promise, their clinical applicability remains limited by the lack of validated predictive biomarkers. Moreover, the translational relevance of numerous emerging targets remains to be established in large-scale clinical studies. Future progress will depend on rigorous subtype-stratified clinical validation to translate emerging strategies into clinically meaningful benefit. Ultimately, a deeper understanding of pathway crosstalk and TIME interactions will be essential for transitioning from subtype-based treatment toward fully individualized precision oncology in EC, with the goal of extending long-term survival across all molecular subgroups.

7. Conclusion

EC has evolved from a histopathology-defined entity into a molecularly stratified disease in which genomic alterations, signaling pathway dysregulation and immune contexture collectively determine clinical behavior and therapeutic response. The integration of molecular classification has not only refined prognostic assessment but also established a framework for subtype-guided therapeutic strategies.

Distinct molecular subtypes exhibit divergent biological features and treatment sensitivities. Hypermutated tumors, including POLE-mutated and MSI-H/dMMR EC, demonstrate strong immunogenicity and favorable responses to immune checkpoint blockade, whereas NSMP and p53-abnormal (CN-high) subtypes often display limited responsiveness and require combination strategies targeting oncogenic signaling and the TME.

The incorporation of ICIs and rational combination approaches has notably reshaped the management of advanced EC. However, therapeutic resistance, tumor heterogeneity, and the limited predictive accuracy of current biomarkers continue to restrict durable benefit across broader patient populations.

Future progress will depend on integrating multi-omic profiling, spatial immune characterization and real-time disease monitoring to refine patient stratification and enable adaptive therapeutic strategies. Ultimately, a deeper understanding of pathway crosstalk and tumor-immune microenvironment interactions will be essential for transitioning from subtype-based treatment toward fully individualized precision oncology in EC, with the goal of extending long-term survival across all molecular subgroups.

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Competing interests

The authors declare that they have no competing interests.

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