# Review Article

# Resistance Mechanisms to Hormonal Therapy in Endometrial Cancer: A Comprehensive Review

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## ABSTRACT

**Background:** Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries, with its incidence rising globally in parallel with obesity and metabolic syndrome. Hormonal therapy, principally progestins and selective oestrogen receptor modulators, represents an essential, fertility-sparing treatment strategy in early-stage, low-grade disease and an alternative systemic option in advanced or recurrent settings. However, a substantial proportion of patients exhibit primary or acquired resistance to hormonal agents, resulting in treatment failure and disease progression. **Objectives:** This review systematically evaluates the molecular and cellular mechanisms underpinning resistance to hormonal therapy in endometrial cancer, with particular emphasis on receptor-level alterations, intracellular signalling dysregulation, epigenetic modifications, the tumour microenvironment, and emerging biomarkers of resistance. **Methods:** A comprehensive search of PubMed, Scopus, and Web of Science databases was conducted for original research articles, systematic reviews, and clinical trials published from 2015 to 2025. Search terms included 'endometrial cancer', 'hormonal therapy resistance', 'progestin resistance', 'progesterone receptor', 'PI3K/AKT/mTOR', 'PTEN', 'microsatellite instability', and related terms. **Results:** Resistance to hormonal therapy in endometrial cancer is multifactorial. Key mechanisms include loss or downregulation of progesterone receptor (PR) and oestrogen receptor (ER) expression, PTEN loss and PI3K/AKT/mTOR pathway hyperactivation, KRAS and CTNNB1 mutations, epigenetic silencing of hormone receptors, altered tumour microenvironment, and upregulation of drug efflux transporters. Emerging evidence implicates mismatch repair deficiency, POLE mutations, and HER2 amplification as modulators of both hormonal responsiveness and therapeutic targetability. **Conclusion:** A mechanistic understanding of hormonal therapy resistance is critical for optimising patient selection, developing combination strategies, and integrating novel targeted agents and immunotherapy into management algorithms for endometrial cancer. Prospective biomarker-driven clinical trials are urgently needed.

***Key words:*** Endometrial neoplasms; hormonal therapy resistance, progestin resistance, progesterone receptors, estrogen receptors, molecular targeted therapy, immunotherapy, epigenetic regulation.

Endometrial cancer (EC) is the most prevalent gynaecological malignancy in high-income countries and ranks sixth among all cancers affecting women globally [1,2]. The American Cancer Society projected approximately 67,880 new cases and 13,250 deaths in the United States in 2024 [3]. Epidemiological trends indicate a rising incidence, largely attributable to the global increase in obesity, type 2 diabetes mellitus, and sedentary lifestyles, key components of metabolic syndrome, all of which promote excess endogenous oestrogen exposure and endometrial proliferation [4,5]. Endometrial cancer is broadly classified into two clinicopathological subtypes. Type I tumours, comprising approximately 80% of cases, are oestrogen-dependent, endometrioid-type, low-grade adenocarcinomas typically harbouring PTEN, PIK3CA, KRAS, and CTNNB1 mutations, along with microsatellite instability [6,7].

Type II tumours, including high-grade serous, clear cell, and carcinosarcoma subtypes, are oestrogen-independent, biologically aggressive, and associated with TP53 mutations and chromosomal instability [8]. The Cancer Genome Atlas (TCGA) Research Network has further refined EC molecular classification into four prognostic subgroups: POLE ultramutated, microsatellite instability-high (MSI-H), copy-number low (endometrioid), and copy-number high (serous-like) [9]. The cornerstone of hormonal therapy in EC relies upon the rationale that endometrioid tumours, which

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frequently express oestrogen receptors (ER) and progesterone receptors (PR), respond to progestational agents through PR-mediated anti-proliferative, pro-differentiating, and pro-apoptotic mechanisms [10,11].

Progestins, including medroxyprogesterone acetate (MPA) and megestrol acetate (MA), remain the most widely used hormonal agents, particularly for fertility preservation in young patients with grade 1 endometrioid EC and for systemic palliation in metastatic disease [12]. Other hormonal agents, including levonorgestrel intrauterine systems, selective oestrogen receptor modulators (SERMs) such as tamoxifen, aromatase inhibitors, and fulvestrant, have also been evaluated, largely in recurrent or advanced settings [13,14]. Despite initial tumour response rates of 25–80% with progestin-based regimens in well-selected patient populations, a significant proportion of patients either do not respond to hormonal therapy (primary resistance) or develop resistance following an initial response (acquired resistance) [15,16].

This treatment failure represents a critical clinical challenge, particularly in patients who are not surgical candidates or who wish to preserve fertility. Understanding the molecular basis of hormonal therapy resistance in EC is therefore essential to guide therapeutic decision-making, identify predictive biomarkers, and inform the rational design of combination strategies. This review comprehensively examines the established and emerging mechanisms of resistance to hormonal therapy in endometrial cancer, with emphasis on receptor-level alterations, downstream signalling pathway dysregulation, epigenetic modifications, the tumour microenvironment, and clinically actionable targets. We further discuss current and investigational strategies to overcome resistance, including targeted agents, immunotherapy, and combination approaches.

## 2. HORMONAL THERAPY IN ENDOMETRIAL CANCER: AN OVERVIEW

### 2.1 Biological Rationale and Receptor Biology

The biological rationale for hormonal therapy in endometrial cancer is grounded in the fundamental role of the oestrogen–progesterone axis in normal endometrial physiology. Oestrogen, acting through ERα and ERβ, promotes endometrial proliferation, whereas progesterone, acting via PR-A and PR-B isoforms, opposes this effect by inducing differentiation, secretory transformation, and ultimately decidualisation or apoptosis [10,17]. Both PR isoforms are encoded by the PGR gene and arise from distinct promoters; PR-B is considered the primary transcriptional activator, while PR-A can act as a dominant repressor of PR-B and steroid receptor activity [18]. The ratio of PR-A to PR-B, as well as total PR expression, are recognised determinants of progestin responsiveness in EC [19].

ER and PR expression, quantified by immunohistochemistry, is routinely assessed in EC to guide treatment decisions. Well-differentiated (grade 1) endometrioid carcinomas demonstrate high rates of ER/PR positivity (>75%), whereas poorly differentiated (grade 3) tumours, serous, and clear cell carcinomas exhibit markedly reduced or absent receptor expression, correlating with diminished hormonal responsiveness [20,21]. Co-expression of both receptors portends a more favourable response to progestin therapy than expression of ER alone [21].

### 2.2 Classes of Hormonal Agents and Clinical Applications

Progestins constitute the primary class of hormonal therapy for EC. Medroxyprogesterone acetate and megestrol acetate are the most extensively studied agents, with reported response rates of 11–56% in early-stage fertility-preservation studies and 9–34% in advanced or recurrent disease [12,15]. The levonorgestrel-releasing intrauterine system (LNG-IUS) provides high local progestin concentrations and is increasingly used in young women with grade 1 EC or atypical endometrial hyperplasia seeking fertility preservation, with pathological complete response rates of 50–90% [22,23].

Aromatase inhibitors (AIs), including letrozole, anastrozole, and exemestane, reduce endogenous oestrogen synthesis in postmenopausal women and have demonstrated modest efficacy in EC, particularly as second-line therapy [24]. Selective oestrogen receptor modulators, notably tamoxifen, paradoxically exert partial oestrogenic agonism on the endometrium and have generally been combined with progestins in alternating regimens; however, clinical benefit has been limited and their role remains investigational [25]. Fulvestrant, a selective oestrogen receptor degrader (SERD), has been evaluated in EC with limited single-agent efficacy but potential synergy with CDK4/6 inhibitors [26,27].

### 2.3 Definitions and Classification of Hormonal Therapy Resistance

For this review, resistance to hormonal therapy in EC is defined as follows: primary (intrinsic) resistance refers to a failure to achieve any objective tumour response after a minimum adequate trial of hormonal therapy (typically ≥3 months); acquired (secondary) resistance refers to the development of tumour progression following an initial objective response or period of stable disease [28]. This distinction is clinically meaningful, as the underlying molecular mechanisms driving primary versus acquired resistance may differ substantially, with implications for subsequent therapeutic strategies.

## 3. MOLECULAR MECHANISMS OF RESISTANCE TO HORMONAL THERAPY

### 3.1 Loss and Downregulation of Hormone Receptors

#### 3.1.1 Progesterone Receptor Loss

Loss or marked downregulation of PR expression constitutes the most well-characterised mechanism of progestin resistance in endometrial cancer [28,29]. PR negativity is observed in up

to 50% of recurrent ECs and is strongly associated with tumour grade, deep myometrial invasion, and lymphovascular space invasion [20,21]. The mechanisms underlying PR loss are multifactorial and include transcriptional repression, post-translational modifications, and epigenetic silencing.

Transcriptional repression of the PGR promoter by oestrogen receptor coactivators, including steroid receptor coactivator (SRC)-1 and SRC-3, and by oncoproteins such as FGFR2, contributes to reduced PR expression in the context of activated growth-factor signalling [30]. Specifically, a shift towards PR-A predominance has also been implicated in progestin resistance, as high PR-A: PR-B ratios suppress PR-B-mediated transcriptional activation of target genes involved in cell cycle arrest and apoptosis [18,19].

#### 3.1.2 Oestrogen Receptor Alterations

Alterations in ER expression and activity represent an additional, though less extensively characterised, mechanism of hormonal therapy resistance in EC. Reduced or absent ERα expression, observed in higher-grade and non-endometrioid tumours, limits EC responsiveness to oestrogen-targeting agents such as AIs and SERDs [21]. ERα gene (ESR1) mutations, which have been extensively studied as mechanisms of AI resistance in breast cancer, have been reported in a subset of EC cases, particularly in the context of prior oestrogen-based therapy, and may confer ligand-independent ER activity [31,32].

ERβ expression in EC is complex and context-dependent: some studies suggest that high ERβ expression correlates with improved prognosis and enhanced progestin responsiveness, while others report paradoxical pro-proliferative effects of ERβ-selective signalling, possibly reflecting ligand- and isoform-specific differences [33]. The clinical implications of ERβ alterations in EC hormonal therapy resistance require further elucidation.

### 3.2 PI3K/AKT/mTOR Pathway Hyperactivation

#### 3.2.1 PTEN Loss and PIK3CA Mutations

Hyperactivation of the phosphatidylinositol 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) signalling pathway represents the most common molecular alteration in endometrioid EC, occurring in 70–93% of cases [6,34,35]. This pathway is activated principally through: (i) loss-of-function mutations or deletions of the tumour suppressor gene PTEN (phosphatase and tensin homologue), present in 50–80% of endometrioid ECs; (ii) activating mutations in PIK3CA, encoding the catalytic p110α subunit of PI3K class IA, detected in 30–50%; and (iii) PIK3R1 mutations affecting the regulatory p85α subunit, present in 30–40% [6,36].

PTEN loss is mechanistically pivotal in hormonal therapy resistance. Under physiological conditions, PTEN dephosphorylates phosphatidylinositol-3,4,5-trisphosphate (PIP3), thereby limiting AKT activation. PTEN loss leads to constitutive PIP3 accumulation, AKT hyperactivation, and subsequent mTOR complex 1 (mTORC1) stimulation, driving cell proliferation, survival, and metabolic reprogramming [35]. Critically, activated AKT directly phosphorylates PR at serine 294, promoting its ubiquitination and proteasomal degradation, thereby reducing PR availability and attenuating progestin responsiveness [37,38]. This mechanistic link between PTEN loss, PI3K/AKT activation, and PR downregulation establishes a direct molecular basis for the association between PTEN mutations and progestin resistance observed clinically [39].

#### 3.2.2 mTOR Pathway and Downstream Effectors

mTOR exists in two functionally distinct complexes: mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin-insensitive). mTORC1 promotes protein synthesis and cell growth via phosphorylation of S6K1 and 4E-BP1, while mTORC2 phosphorylates AKT at serine 473, stabilising its active conformation [35,40]. In EC, mTORC1 hyperactivation also suppresses IRS-1 (insulin receptor substrate-1) through S6K1-mediated negative feedback, paradoxically activating upstream receptor tyrosine kinase (RTK) signalling, a mechanism implicated in resistance to rapamycin analogues (rapalogs) [40,41]. The clinical implication is that mTORC1 inhibition with rapalogs alone may be insufficient to achieve durable antitumour responses in EC, as upstream RTK activation and mTORC2-dependent AKT phosphorylation remain intact.

### 3.3 KRAS and MAPK Pathway Alterations

Activating mutations in KRAS, detected in 15–30% of endometrioid ECs, constitutively activate the RAS/RAF/MEK/ERK mitogen-activated protein kinase (MAPK) pathway, promoting cell proliferation and survival independent of hormonal input [6,42]. KRAS mutations have been associated with reduced PR expression and diminished progestin responsiveness in preclinical models of EC [43]. Cross-talk between the MAPK and PI3K/AKT pathways further amplifies oncogenic signalling and may contribute to the limited efficacy of single-pathway inhibition strategies. BRAF mutations are rare in EC but have been reported in select cases [6].

### 3.4 WNT/β-Catenin Pathway Dysregulation

Activating mutations in CTNNB1, encoding β-catenin, are detected in 20–40% of endometrioid ECs [6,44]. β-Catenin nuclear accumulation drives transcription of WNT target genes, including cyclin D1, c-Myc, and survivin, that promote cell cycle progression and inhibit apoptosis. WNT/β-catenin signalling interacts with the PR pathway: β-catenin can act as a PR coactivator under progestin stimulation, but constitutively activating CTNNB1 mutations may redirect β-catenin from PR-mediated signalling towards autonomous WNT target gene activation, thereby diminishing progestin

responsiveness [44,45]. Additionally, elevated cyclin D1 expression driven by CTNNB1 mutations may sequester CDK4/6 and thereby circumvent progestin-induced G1 cell cycle arrest [45].

### 3.5 FGFR2 and Growth Factor Receptor Signalling

Fibroblast growth factor receptor 2 (FGFR2) activating mutations are present in approximately 10–15% of endometrioid ECs [46]. FGFR2 activation promotes downstream PI3K/AKT and MAPK signalling and has been shown to transcriptionally suppress PR expression via recruitment of the corepressor NRSF/REST to the PGR promoter [30,46]. Moreover, activated FGFR2 promotes epithelial-mesenchymal transition (EMT), further impairing progestin responsiveness. Other growth factor receptors implicated in hormonal resistance include EGFR (overexpressed in 40–60% of ECs) and HER2/neu (amplified in 20–30% of serous ECs), both of which activate PI3K/AKT and MAPK pathways independently of hormonal stimuli [47,48].

### 3.6 Epigenetic Mechanisms of Resistance

#### 3.6.1 DNA Methylation of Hormone Receptor Gene Promoters

Epigenetic silencing through CpG island hypermethylation of the PGR promoter is a well-established mechanism of PR downregulation in EC [49,50]. Studies have demonstrated that PR-B promoter methylation is significantly more prevalent in PR-negative than PR-positive EC specimens, and that demethylating agents such as 5-azacytidine can restore PR expression in PR-negative EC cell lines [50]. Similarly, ESR1 promoter methylation has been reported as a contributor to ER loss in a subset of ECs [49]. The potential reversibility of epigenetic PR silencing has generated interest in demethylating agent progestin combination strategies as a means to overcome epigenetic resistance.

#### 3.6.2 Histone Modifications and Chromatin Remodelling

Beyond DNA methylation, histone modifications, including histone deacetylation by histone deacetylase (HDAC) enzymes and polycomb repressive complex (PRC)-mediated H3K27 trimethylation, contribute to transcriptional silencing of hormone receptor genes and PR target genes in EC [51,52]. Histone deacetylase inhibitors (HDACi), such as vorinostat and entinostat, have been shown to restore PR expression and enhance progestin-induced growth inhibition in preclinical EC models [51]. EZH2, the catalytic subunit of PRC2, is overexpressed in high-grade EC and correlates with reduced PR expression and hormonal therapy resistance [52]. These observations support the rationale for epigenetic-targeted therapy combinations in overcoming hormonal resistance.

#### 3.6.3 Non-coding RNAs

Dysregulation of non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), has emerged as an important layer of post-transcriptional regulation in EC hormonal therapy resistance [53,54]. miR-21, miR-130a, and miR-181a have been reported to target PTEN, PR, or downstream effectors, thereby modulating progestin responsiveness [53]. The lncRNA HOTAIR promotes EZH2-mediated PR silencing and has been associated with aggressive EC behaviour and reduced hormonal sensitivity [54]. Comprehensive characterisation of the EC non-coding transcriptome may identify novel biomarkers and therapeutic targets in the context of hormonal resistance.

### 3.7 Tumour Microenvironment and Immune Evasion

The tumour microenvironment (TME) in EC is increasingly recognised as a determinant of hormonal therapy responsiveness [55,56]. Immunosuppressive cell populations, including regulatory T cells (Tregs), tumour-associated macrophages (TAMs) with M2 polarisation, and myeloid-derived suppressor cells (MDSCs)- create a permissive milieu for tumour proliferation and may attenuate PR-mediated growth inhibition [55]. Progesterone has documented immunomodulatory properties; however, in the context of a suppressed immune microenvironment, these may be insufficient to mount an effective anti-tumour response.

Cancer-associated fibroblasts (CAFs) in the EC stroma produce paracrine growth factors, including hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF-1), and fibroblast growth factor (FGF), that activate RTK signalling and confer progestin resistance on adjacent tumour cells through mechanisms including AKT activation and PR downregulation [56,57]. Furthermore, tumour hypoxia, driven by inadequate vascularization, activates hypoxia-inducible factor 1α (HIF-1α), which cross-talks with ER signalling and promotes oestrogen-independent cell survival under progestin therapy [58].

### 3.8 Drug Efflux and Pharmacological Resistance

Overexpression of ATP-binding cassette (ABC) transporters, particularly P-glycoprotein (ABCB1/MDR1), breast cancer resistance protein (BCRP/ABCG2), and multidrug resistance-associated protein 1 (MRP1/ABCC1), has been reported in a subset of hormone-resistant EC tumours [59]. These transmembrane efflux pumps reduce intracellular accumulation of progestins and other hormonal agents, contributing to pharmacological resistance. Tumour heterogeneity, including the emergence of resistant subclones harbouring distinct molecular alterations, further complicates the durability of hormonal therapy responses [60] (Table 1).

**Table 1. Summary of Key Molecular Mechanisms of Hormonal Therapy Resistance in Endometrial Cancer**

| Mechanism | Molecular Alteration | Frequency in EC | Clinical/Preclinical Evidence |
|---|---|---|---|
| PR loss/downregulation | PGR mutation; PR-A: PR-B imbalance; promoter | ~50% of recurrent EC | Strongly associated with progestin resistance |

| | | | |
|---|---|---|---|
| | methylation | | [28,29]; reversible with demethylating agents [50] |
| PI3K/AKT/mTOR activation | PTEN loss; PIK3CA mutation; PIK3R1 mutation | PTEN: 50–80%; PIK3CA: 30–50% | AKT phosphorylates PR→proteasomal degradation [37,38]; rapalog combinations under trial [67,68] |
| KRAS/MAPK activation | KRAS activating mutation | 15–30% | Reduced PR expression in preclinical EC models [43] |
| WNT/β-catenin activation | CTNNB1 exon 3 mutation | 20–40% | Cyclin D1 overexpression; reduced progestin-induced G1 arrest [44,45] |
| Epigenetic silencing | PGR/ESR1 promoter hypermethylation; EZH2 overexpression | Variable: EZH2 is high in grade 3 | HDACi/DNMTi restore PR expression [50,51,52] |
| Non-coding RNA dysregulation | miR-21, miR-130a, HOTAIR lncRNA | Under investigation | Post-transcriptional repression of PTEN and PR [53,54] |
| Tumour microenvironment | Tregs, M2 TAMs, CAF paracrine signalling | Prevalent in high-grade EC | Immunosuppression attenuates PR-mediated growth inhibition [55,56] |
| Drug efflux transporters | ABCB1/MDR1; ABCG2/BCRP overexpression | Subset of resistant cases | Reduced intracellular progestin accumulation [59] |
| HER2/growth factor RTK | HER2 amplification; EGFR overexpression; FGFR2 mutation | HER2: 20–30% serous EC | PI3K/MAPK cross-activation; PR transcriptional suppression [47,48] |
| ESR1 mutations | Ligand-binding domain mutations | Rare post-AI therapy | Ligand-independent ER activation [31,32] |

## 4. MOLECULAR CLASSIFICATION AND PREDICTIVE BIOMARKERS OF HORMONAL THERAPY RESISTANCE

### 4.1 TCGA/ProMisE Molecular Subtypes and Hormonal Responsiveness

The TCGA-derived molecular classification, validated in clinical practice through the ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) algorithm and incorporated into the 2023 WHO Classification of Tumours of the Female Genital Tract, identifies four EC molecular subgroups with distinct clinical behaviours and potentially different responses to hormonal therapy [9,61,62]. POLE-ultramutated (POLEmut) tumours carry an excellent prognosis and may not require adjuvant therapy; their responsiveness to hormonal agents in the metastatic setting is not well characterised. MSI-H/mismatch repair-deficient (dMMR) tumours demonstrate intermediate prognosis and high immunotherapy sensitivity, suggesting that hormonal therapy alone may be suboptimal [61,62]. Copy-number-low endometrioid tumors, typically ER/PR-positive, are the most likely to benefit from hormonal therapy. Copy-number-high (p53-abnormal) tumours, which include most serous and dedifferentiated carcinomas, are generally ER/PR-negative and unresponsive to hormonal agents.

### 4.2 Predictive Biomarkers of Progestin Response

Multiple biomarkers have been evaluated as predictors of progestin responsiveness in EC. Immunohistochemical PR expression remains the most widely used clinical biomarker; however, PR positivity alone has limited positive predictive value for treatment response [21,63]. The Allred score and H-score methodologies for quantifying PR expression offer greater reproducibility than binary positive/negative classifications and may improve predictive accuracy [63]. PTEN protein expression by immunohistochemistry, PTEN mutation status, and PIK3CA mutation status have been proposed as negative predictive biomarkers of progestin response, as they reflect PI3K/AKT pathway activation and associated PR downregulation [39,64].

Emerging biomarkers include ARID1A mutation status (associated with dMMR and potential immunotherapy benefit), L1CAM overexpression (associated with poor prognosis and reduced hormonal sensitivity), and CTNNB1 exon 3 mutations (associated with intermediate risk and potential WNT pathway targetability) [62,65]. Serum progesterone receptor levels and circulating tumour DNA (ctDNA) monitoring of specific mutations (PTEN, PIK3CA, KRAS) are under investigation as liquid biopsy-based biomarkers for monitoring treatment response and early detection of acquired resistance [66].

## 5. STRATEGIES TO OVERCOME HORMONAL THERAPY RESISTANCE

### 5.1 Targeting the PI3K/AKT/mTOR Pathway

Given the central role of PI3K/AKT/mTOR pathway activation in hormonal therapy resistance, pharmacological inhibition of this pathway represents a rational therapeutic strategy [35,40]. mTOR inhibitors, specifically everolimus and temsirolimus (rapalogs), have been evaluated in EC as single agents and in combination with hormonal therapy. The MANGO trial (NCIC CTG IND.192) demonstrated a disease control rate of 40% for single-agent temsirolimus in EC [67]. The combination of everolimus with letrozole showed a 32% clinical benefit rate and was further explored in the PEARL trial [68]. The EFFORT trial evaluated everolimus plus letrozole with or without metformin, demonstrating that the addition of metformin did not significantly improve outcomes [69].

Pan-PI3K inhibitors (e.g., copanlisib, buparlisib) and dual PI3K/mTOR inhibitors (e.g., gedatolisib, omipalisib) are under investigation in EC clinical trials, with the hypothesis

that dual pathway blockade may overcome the mTORC2-mediated AKT reactivation observed with rapalogs [34,70]. AKT inhibitors, including capivasertib and ipatasertib, have shown promise in early-phase trials in PIK3CA/AKT/PTEN-altered tumours across cancer types and are being evaluated in EC [71]. The identification of predictive biomarkers for PI3K pathway inhibitor response, particularly PTEN loss and PIK3CA mutation status, is critical for patient enrichment in ongoing trials.

### 5.2 CDK4/6 Inhibitors in Hormone Receptor-Positive EC

CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, have transformed the treatment landscape of hormone receptor-positive breast cancer and are being actively investigated in EC, where cyclin D1 overexpression is common (present in 30–50% of cases) [45,72]. By inhibiting CDK4/6-mediated phosphorylation of the retinoblastoma protein (Rb), these agents restore G1 cell cycle arrest, a key mechanism through which progestins exert anti-proliferative effects. Preclinical studies in EC cell lines demonstrate synergistic growth inhibition when CDK4/6 inhibitors are combined with progestins, particularly in tumours with CTNNB1 mutations and cyclin D1 overexpression [45]. Phase II clinical trials evaluating palbociclib combined with letrozole (GOG-3027) and abemaciclib in recurrent EC are ongoing or have recently reported [72,73].

### 5.3 Immune Checkpoint Inhibitors and Immunotherapy

The discovery that dMMR/MSI-H EC tumours exhibit high tumour mutational burden (TMB-H) and an inflamed immune phenotype has led to the regulatory approval of pembrolizumab (anti-PD-1) for dMMR solid tumours, including EC [74,75]. In the pivotal KEYNOTE-158 trial, pembrolizumab achieved an objective response rate (ORR) of 57.1% in dMMR EC patients with prior platinum-based chemotherapy [74]. The KEYNOTE-775 trial demonstrated that pembrolizumab combined with lenvatinib significantly improved progression-free survival (PFS) and overall survival (OS) compared with chemotherapy in previously treated advanced EC, regardless of MMR status [75]. This lenvatinib–pembrolizumab combination has received FDA and EMA approval for this indication.

In the context of hormonal therapy resistance, the intersection of immunotherapy and hormonal pathways is particularly relevant: progestins possess immunomodulatory properties that may influence the tumour immune microenvironment, and conversely, the immune status of the TME may influence PR signalling and progestin responsiveness [55,76]. Whether hormonal therapy–immunotherapy combinations offer synergistic benefit in specific EC molecular subgroups warrants prospective investigation. Ongoing trials exploring immune checkpoint inhibitors combined with progestins, AIs, or CDK4/6 inhibitors in EC are anticipated to provide important data.

### 5.4 HER2-Targeted Therapy

HER2/neu amplification or protein overexpression is present in approximately 20–30% of uterine serous carcinomas and a smaller proportion of endometrioid tumours [48,77]. In HER2-positive advanced or recurrent uterine serous carcinoma, trastuzumab added to carboplatin–paclitaxel chemotherapy demonstrated significantly improved PFS and OS in the randomised Phase II trial by Fader et al. [77]. Trastuzumab deruxtecan (T-DXd), an antibody–drug conjugate, has shown substantial activity in HER2-positive EC in early-phase trials and is under further evaluation [78]. HER2-targeted strategies may be relevant to hormonal therapy resistance, as HER2 signalling activates PI3K/AKT and MAPK pathways, which in turn suppress PR expression and progestin responsiveness [47,48].

### 5.5 Epigenetic Targeting

Preclinical evidence supporting the reversibility of epigenetic PR silencing has motivated the investigation of epigenetic-targeted agents in combination with progestins. HDAC inhibitors, including vorinostat and entinostat, restore PR expression and enhance progestin-induced apoptosis in PR-negative EC cell lines [51]. DNA methyltransferase inhibitors (DNMTi), particularly 5-azacytidine and decitabine, demethylate the PGR promoter and re-express PR in epigenetically silenced EC cells [50]. EZH2 inhibitors, such as tazemetostat, reverse PRC2-mediated PR silencing and are under early-phase clinical investigation in EC [52,79]. The optimal sequencing and combination of epigenetic agents with hormonal therapy requires further clinical validation.

### 5.6 Fertility-Sparing Strategies and Combination Progestin Approaches

For young patients with grade 1 endometrioid EC or atypical endometrial hyperplasia who desire fertility preservation, optimising hormonal therapy efficacy is particularly important. Combination strategies incorporating the LNG-IUS with systemic oral progestins, GnRH agonists, metformin, or aromatase inhibitors have been explored to improve response rates and reduce recurrence [22,23,80]. Metformin, an AMPK activator that inhibits mTORC1 indirectly, has demonstrated preclinical anti-endometrial cancer activity and modest clinical benefit in combination with hormonal therapy in several pilot studies, although Phase III data are awaited [80]. Promising response rates of 75–90% have been reported in selected series with LNG-IUS plus systemic progestin combinations, though long-term oncological safety data remain limited (Table 2).

**Table 2. Selected Clinical Trials Evaluating Strategies to Overcome Hormonal Therapy Resistance in Endometrial Cancer**

| Trial / Phase | Intervention | Population | Key Endpoint / Result |
|---|---|---|---|
| MANGO / Phase II | Temsirolimus monotherapy | Recurrent EC, unselected | DCR 40%; ORR 14% [67] |
| PEARL / Phase II | Everolimus + letrozole | Recurrent EC | CBR 32% [68] |
| EFFORT / Phase II | Everolimus + letrozole ± metformin | Recurrent EC | Metformin did not improve PFS [69] |
| GOG-3027 / Phase II | Palbociclib + letrozole | ER+ recurrent EC | Ongoing; preliminary data awaited |
| KEYNOTE-158 / Phase II | Pembrolizumab | dMMR EC (cohort D) | ORR 57.1%; DoR not reached [74] |
| KEYNOTE-775 / Phase III | Pembrolizumab + lenvatinib | Previously treated advanced EC | Improved PFS and OS vs chemotherapy [75] |
| Fader et al. Phase II | Trastuzumab + carboplatin–paclitaxel | HER2+ uterine serous carcinoma | Improved PFS (12.9 vs 8.0 mo) [77] |
| LNG-IUS + systemic progestin | LNG-IUS + MPA/MA | Grade 1 EC, fertility-sparing | pCR 75–90% in selected series [22,23] |
| Metformin + progestin pilot | Metformin + MPA | Grade 1 EC, fertility-sparing | Promising; Phase III ongoing [80] |
| EZH2 inhibitor (tazemetostat) / Phase I–II | Tazemetostat ± progestin | EC with EZH2 overexpression | Early phase; results pending [52,79] |

## 6. FUTURE DIRECTIONS AND TRANSLATIONAL PERSPECTIVES

A comprehensive understanding of the molecular heterogeneity underlying hormonal therapy resistance in EC is rapidly reshaping the clinical management of this disease. Several important translational priorities are emerging from current research. The integration of molecular profiling into treatment algorithms for EC is imperative. Beyond IHC-based ER/PR quantification, comprehensive genomic profiling, including next-generation sequencing (NGS) for PTEN, PIK3CA, KRAS, CTNNB1, POLE, and MMR gene mutations, as well as HER2 amplification testing, should be incorporated into the standard work-up of patients being considered for hormonal therapy, particularly in the recurrent or advanced setting. ProMisE-based molecular classification should guide not only adjuvant treatment decisions but also hormonal therapy selection [62].

The development of liquid biopsy approaches for serial monitoring of ctDNA in EC patients receiving hormonal therapy represents a promising avenue for early detection of acquired resistance mutations and real-time treatment adaptation. Proof-of-concept studies have demonstrated the feasibility of ctDNA monitoring in EC using digital droplet PCR and ultra-deep NGS platforms [66]. Rational combination strategies, specifically, progestin or AI combined with PI3K/AKT/mTOR inhibitors, CDK4/6 inhibitors, or epigenetic agents, represent the most scientifically grounded approach to overcoming molecular resistance mechanisms identified in individual patients. Biomarker-enriched adaptive clinical trial designs, including platform trials and umbrella protocols, are needed to efficiently test these combinations [71,73].

The tumour immune microenvironment in EC is increasingly tractable as a therapeutic target. Characterisation of the immune phenotype of hormonal therapy-resistant EC, including quantification of TILs, PD-L1 expression, TMB, and dMMR status, may identify patients who are candidates for hormonal therapy–immunotherapy combinations [55,76]. The emerging concept of 'endocrine immune crosstalk' in EC warrants dedicated mechanistic investigation. The development of patient-derived organoid (PDO) models and patient-derived xenograft (PDX) models of EC is providing unprecedented platforms for mechanistic studies of hormonal therapy resistance, drug sensitivity testing, and biomarker discovery [79,80]. These models retain the genetic and phenotypic heterogeneity of primary tumours and offer a valuable bridge between basic research and clinical translation.

## CONCLUSION

Resistance to hormonal therapy in endometrial cancer is a multifaceted phenomenon arising from the interplay of receptor-level alterations, oncogenic pathway hyperactivation, epigenetic silencing, tumour microenvironmental influences, and pharmacological mechanisms. Loss or downregulation of PR expression, driven by PI3K/AKT-mediated proteasomal degradation, epigenetic silencing, or isoform imbalance, represents the most central mechanism of progestin resistance. Concurrent activation of the PI3K/AKT/mTOR, MAPK, WNT/β-catenin, and growth factor receptor pathways sustains oestrogen-independent tumour proliferation and survival, further eroding hormonal therapy efficacy.

The integration of TCGA-based molecular classification into EC management has identified biologically distinct subgroups with differential hormonal therapy responsiveness and amenability to targeted interventions. Ongoing and planned clinical trials are evaluating rational combinations of progestins and aromatase inhibitors with PI3K/mTOR inhibitors, CDK4/6 inhibitors, epigenetic agents, and immune checkpoint inhibitors in molecularly selected patient populations. Translation of these mechanistic insights into biomarker-driven, personalised treatment strategies represents the most promising path forward for patients with hormonal therapy-resistant endometrial cancer. Collaborative, multi-institutional prospective trials incorporating comprehensive tumour molecular profiling, serial ctDNA monitoring, and adaptive design principles are urgently needed to validate emerging combination strategies and improve outcomes in this challenging disease setting.

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