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SPECIAL ARTICLE

Evolution of Systemic Therapies in Endometrial Cancer: From Cytotoxic Chemotherapy to Immunotherapy, Targeted Therapies, and Antibody–Drug Conjugates

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ABSTRACT

Molecular classification in endometrial cancer (EMC) has become central to treatment decision-making. An advance in molecular classification has transformed the therapeutic landscape of EMC, particularly in patients with high-risk, advanced, or metastatic disease. This coincided with a new era of personalized treatment with targeted therapies, immunotherapy in particular, immune checkpoint inhibitors (ICIs). Several studies have demonstrated the benefits of combination strategies incorporating chemotherapy, targeted therapies, and ICIs with or without tyrosine kinase inhibitor, followed by maintenance therapy. This approach has resulted in clinically meaningful improvements in progression-free survival and, in selected populations, overall survival, with the most pronounced benefit observed in mismatch repair (MMR)–deficient tumors. This review summarizes current evidence from pivotal phase II-III trials evaluating ICIs combined with chemotherapy, ICIs with poly adenosine diphosphate ribose polymerase inhibitors, and targeted agents including trastuzumab, bevacizumab, and selinexor as first- and second-line treatment for EMC. Studies of antibody-drug conjugates, novel therapeutic agents designed to selectively deliver cytotoxic drugs and thereby reduce the systemic toxicity associated with chemotherapy, were also included. Treatment recommendations are summarized within the context of MMR status, p53 abnormalities, human epidermal growth factor receptor 2/neu expression, and other emerging molecular biomarkers.

Keywords: antibody–drug conjugates, endometrial cancer, immunotherapy, precision oncology, targeted therapy

INTRODUCTION

Endometrial cancer (EMC) is the most common gynecologic cancer in developed countries and second most common gynecologic cancer in Thailand.[1] Most patients seek medical consultation in early-stage disease due to abnormal uterine bleeding which is the most common symptom. Early-stage disease is often curable with surgery. If indicated with risk features, radiation therapy is the mainstay of adjuvant treatment.

Chemotherapy either in combination with radiation therapy or chemotherapy alone is considered for the patients with higher risk. For advanced and recurrent diseases, systemic treatment is generally required and relied primarily on chemotherapy, most commonly platinum- and taxane-based regimens.[2] However, chemotherapy offered only limited durability of response and poor outcomes for patients with high-risk, advanced, or recurrent disease.

Over the past decade, advances in molecular classification and tumor biology of EMC have been demonstrated. The Cancer Genome Atlas (TCGA) Research Network reported a biologically heterogeneous nature and a broad spectrum of clinical behavior of many cancers including EMC.[3] Molecular classification has fundamentally altered the understanding of EMC biology and subsequent refinement into clinically applicable molecular subgroups. This has also transformed the therapeutic landscape from generalized systemic treatment with chemotherapy to personalized therapy with targeted therapies, immune checkpoint inhibitors (ICIs), and antibody–drug conjugates (ADCs).

Targeted therapies focus on tailoring treatment according to specific molecular abnormalities of cancer, thereby increasing specificity and reducing damage to normal tissues. Immunotherapy, on the other hand, enhances the function of the immune system in controlling and eliminating cancer cells in appropriately selected patients. ADCs represent a new frontier in EMC treatment by combining precise molecular targeting with potent cytotoxic payloads, aiming to improve the efficiency of cancer cell eradication while minimizing effects on normal cells.

The integration of these novel agents has led to meaningful improvements in progression-free survival (PFS) and, in selected populations, overall survival (OS). This review summarizes the evolution of systemic therapy in EMC, from traditional chemotherapy to biomarker-driven precision medicine.

We discuss pivotal clinical trials supporting first-line and subsequent-line use of targeted agents, ICIs, and ADCs, with emphasis on molecular stratification, clinical outcomes, and future directions. A detailed critical appraisal of each studies/ trials is beyond the scope of this review and will be addressed in our upcoming work.

CONTENT OF REVIEW

Chemotherapy for EMC

Initial systemic therapy for advanced or recurrent EMC was based on single-agent chemotherapy, particularly doxorubicin, which showed modest activity in early Gynecologic Oncology Group (GOG) studies during the 1980s–1990s.[4] Efforts to improve outcomes led to evaluation of combination regimens. GOG-122 demonstrated that doxorubicin plus cisplatin chemotherapy significantly improved PFS and OS compared with whole abdominal irradiation in advanced-stage disease, establishing combination chemotherapy as standard treatment.[5] Subsequent intensification with the triplet regimen of paclitaxel, doxorubicin, and cisplatin (TAP) in GOG-177 resulted in superior objective response rate (ORR), PFS and OS compared with doxorubicin–cisplatin, but at the cost of substantial neurotoxicity.[6] Subsequent trial GOG-209 showed that carboplatin plus paclitaxel was non-inferior to TAP in OS with significantly reduced toxicity.[7] This benchmark trial has led carboplatin plus paclitaxel as the preferred first-line chemotherapy regimen for advanced or recurrent EMC.

Molecular classification and risk stratification of EMC

Based on the TCGA findings of biologic molecular characteristics, genomic alterations, and gene mutations, EMC is classified into four molecular subgroups. These are: *Polymerase Epsilon (POLE)*-mutated, mismatch repair–deficient (MMRd), p53-abnormal, and no specific molecular profile (NSMP). These subtypes have distinct immunogenicity and prognostic outcomes. Notably, because *POLE* mutation acts as a driver mutation, multiple molecular abnormalities (multiple classifiers) may coexist. *POLE* mutation may be found together with MMRd and/or *TP53* mutation (p53abn) in approximately 10-20% of cases. In such cases, prognosis should be determined by the presence of *POLE* mutation. MMRd may also coexist with *TP53* mutation; although data remain limited, prognosis should be determined according to MMRd status.[8]

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Both the International Federation of Gynaecology and Obstetrics (FIGO)8 and the European Society of Gynaecological Oncology (ESGO)/ the European Society for Radiotherapy and Oncology (ESTRO)/ the European Society of Pathology (ESP) guidelines[2] recommend molecular testing as an adjunct to standard histopathologic evaluation whenever feasible. Molecular testing can be performed on preoperative biopsy/ curettage specimens or on hysterectomy specimens.

In early-stage EMC, *POLE*-mutated and p53-abnormal statuses are to be annotated and modify the anatomical stage.[8] Molecular classification is particularly important in high-grade endometrioid carcinoma (grade 3) which exhibits significant heterogeneity in clinical behavior and molecular characteristics. Early-stage tumors with *POLE* mutation have an excellent prognosis, whereas tumors with p53abn or NSMP tumors that are estrogen receptor (ER)–negative are associated with poor prognosis.[9,10]

In advanced stage or recurrent disease, the expression of MMRd and p53-abnormal certainly impact the therapeutic intervention. MMRd tumors exhibit high neoantigen load and immune infiltration, rendering them highly sensitive to ICIs, whereas p53-abnormal tumors often benefit from antiangiogenic or human epidermal growth factor receptor 2 (HER2)-targeted approaches.

ESGO, ESTRO, ESP have jointly made a recommendation of EMC treatment based on prognostic risk group incorporating FIGO staging, location of cancer, surgical pathological and molecular features.[2]

Targeted therapies, immunotherapy, ADCs for EMC

Targeted therapies and ICIs with or without poly adenosine diphosphate ribose polymerase (PARP) inhibitors have been tested in many clinical trials as first- or second-line of treatment for EMC. As first-line treatment, the drugs were combined with chemotherapy, mainly paclitaxel and carboplatin, followed by maintenance therapy after completion of chemotherapy. Tyrosine kinase inhibitors were also tested in combination with ICIs, substituting for the original chemotherapy. These agents were also included in many trials as second-line of EMC treatment.

I. First-line targeted therapy and immunotherapy in EMC patients

Clinical studies evaluating these agents as first-line treatment are summarized in Table 1 and discussed below.

1. ICIs combined with chemotherapy followed by ICI with or without PARP inhibitor maintenance

Four main randomized phase III trials—RUBY, NRG-GY018, AtTEnd, and durvalumab and olaparib (DUO-E)—have evaluated ICIs combined with carboplatin–paclitaxel as first-line therapy in high-risk, advanced, or metastatic EMC, including carcinosarcoma. Collectively, the studies support the use of ICIs combined with carboplatin–paclitaxel followed by ICIs maintenance as first-line treatment in high-risk, advanced, or metastatic EMC—particularly in MMRd tumors, where substantial PFS and emerging OS benefits are observed (e.g., RUBY PFS at 24 months: 61.4% vs. 15.7%; hazard ratio (HR) 0.28). In mismatch repair-proficient (MMRp) tumors, ICIs provide consistent PFS benefit, though OS benefit remains less clear. PD-L1 inhibitors such as atezolizumab improve PFS (especially in MMRd disease), but OS benefit has not been clearly demonstrated. Details are as follows:

1.1 Dostarlimab (RUBY Part 1 / European Gynecological Oncology Trial (ENGOT)-EN6-NSGO / GOG-3031)

The RUBY trial comprised two parts. Part 1 evaluated immunotherapy alone and has been published,[11,12] while Part 2 evaluates immunotherapy combined with a PARP inhibitor. Part 1 study randomized 494 patients with stage III–IV or first recurrent EMC to receive dostarlimab 500 mg or placebo intravenously, in combination with carboplatin–paclitaxel every 3 weeks for 6 cycles.[11,12] This was followed by maintenance treatment with dostarlimab 1000 mg or placebo every 6 weeks for up to 3 years.

The results showed significantly improved PFS at 24 months and OS at 36 months in the patients who had dostarlimab compared to placebo: 36.1% vs. 18.1% (HR 0.64) and 54.9% vs. 42.9% (HR 0.69), respectively. The survival benefits with dostarlimab were evidenced regardless of MMR/ microsatellite stable (MSS) status, albeit lower extent of benefits in the MMRp/MSS group. The greatest benefit was observed in patients with MMRd/high microsatellite instability (MSI-H) tumors, with the PFS at 24 months and OS at 36 months of 61.4% vs. 15.7% (HR 0.28) and 78.0% vs. 46.0% (HR 0.32), respectively. The outcomes for the patients with MMRp/MSS tumors

Table 1 Studies Evaluating ICIs and Targeted Therapies as First-Line Treatment for EMC

Study (ref)	Patient	Biomarker Status	Treatment	Outcome (study vs. control) Data presented as median unless specified otherwise
RUBY part1/ ENGOT-EN6-NSGO/ GOG-3031 (part 1) phase III trial (NCT03981796)[11,12]	N = 494 Measurable stage III-IVA, stage IVB, or RR-EC/CS (CT-free ≥ 6 m) 1L for stage III-IV 1L/2L for RR	MMRd/ MSI-H vs. MMRp/MSS	1) TC Q3W x 6 cycles with Dos 500 mg IV Q3W x 6 cycles then Dos 1000 mg IV Q6W to 3 yrs or until PD/ toxicity 2) TC (as arm 1)	All: 24-m PFS 36.1 vs. 18.1% (HR 0.64, 95% CI 0.51-0.80, p < 0.001) 36-m OS 54.9 vs. 42.9% (HR 0.69, 95% CI 0.54-0.89, p = 0.002) MMRd/MSI-H: 24-m PFS 61.4 vs. 15.7% (HR 0.28, 95% CI 0.16-0.50, p < 0.001) 36-m OS 78.0 vs. 46.0% (HR 0.32, 95% CI 0.17-0.63, p < 0.001) MMRp/MSS: 24-m PFS 28.4 vs. 18.8% (HR 0.76, 95% CI 0.59-0.98) 36-m OS 48.6 vs. 41.9% (HR 0.79, 95% CI 0.60-1.40, p = 0.049)
KEYNOTE-868/ NRG-GY018 phase III trial (NCT03914612)[13]	N = 816 Measurable stage III- IVB, RR-EC (CT-free ≥ 12 m) 1L for stage III-IV 1L/ 2L for RR	MMRd vs. MMRp	1) TC Q3W x 6-8 cycles with Pembro 200 mg IV Q3W x 6-8 cycles, then Pembro 400 mg IV Q6W x 14 cycles 2) TC (as arm 1)	MMRd: 12-m PFS 74% (NA) vs. 38% (median 7.6 m) (HR 0.30, 95% CI 0.19-0.48, p < 0.001) MMRp: PFS 13.1 m vs. 8.7 m (HR 0.54, 95% CI 0.41-0.71, p < 0.001)
KEYNOTE-B21/ ENGOT-en11/ GOG-3053 (NCT04634877)[14]	N = 1095 Stage I, II, non-endometrioid with MI or Stage I, II, abnormal p53/TP53 with MI or Stage III or IVA, any histology	MMRd vs. MMRp	1) TC Q3W x 6 cycles with Pembro 200 mg IV Q3W x 6-8 cycles, then Pembro 400 mg IV Q6W x 6 cycles vs. 2) TC (as arm 1)	All: PFS NR (22%) vs. NR (22%) (HR 1.02, 95% CI 0.79-1.32, p = 0.570) MMRd: PFS NR vs. NR (HR 0.31, 95% CI 0.14-0.69) MMRp: PFS NR vs. NR (HR 1.20, 95% CI 0.91-1.57)
AtTEnd/ENGOT-en7 phase III trial (NCT03603184)[15]	N = 551 Measurable stage III-IV or RR-EC/CS • 1L for all	MMRd vs. MMRp	1) TC Q3W x 6-8 cycles with Atezolizumab 1200 mg IV Q3W x 6-8 cycles then Atezolizumab 1200 mg IV Q3W until PD or toxicity vs. 2) TC (as arm 1)	All: PFS 10.1 vs. 8.9 m (HR 0.74, 95% CI 0.61-0.91, p = 0.022) OS 38.7 vs. 30.2 m (HR 0.82, 95% CI 0.63-1.07, p = 0.048) MMRd: PFS NA vs. 6.9 m (HR 0.36, 95% CI 0.23-0.57, p < 0.001) OS NA vs. 25.7 m (HR 0.41, 95% CI 0.22-0.76) MMRp: PFS 9.5 vs. 9.2 m (HR 0.92, 95% CI 0.73-1.1.6) OS 31.5 vs. 28.6 m (HR 1.00, 95% CI 0.74-1.35)

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Table 1 Studies Evaluating ICIs and Targeted Therapies as First-Line Treatment for EMC (cont.)

Study (ref)	Patient	Biomarker Status	Treatment	Outcome (study vs. control) Data presented as median unless specified otherwise
DUO-E phase III trial (NCT04269200)[16,17]	N = 718 Measurable stage III or IV or RR-EC/CS (CT-free > 12 m), 1L for stage III-IV 1L/2L for RR	MMRd vs. MMRp	1) TC Q3W x 6-8 cycles (**Control**) vs. 2) TC (as I) + Du 1,120 mg IV Q3W x 6-8 cycles, then Du 1,500 mg IV Q4W until PD or toxicity (**Du**) vs. 3) TC (as I) + Du 1,120 mg IV Q3W x 6-8 cycles, then Du 1,500 mg IV Q4W + Olaparib 300 mg tablets bid until PD or toxicity (**DO**)	All: 12-m PFS 61.5% vs. 48.5% vs. 41.1% DuO vs. Control: HR 0.55, 95% CI 0.43-0.69, p < 0.0001 Du vs. Control: HR 0.71, 95% CI 0.57-0.89, p = 0.003 12-m OS 87.7% vs. 84.2% vs. 79.7% DuO vs. Control: HR 0.59, 95% CI 0.42-0.83, p = 0.003 Du vs. Control: HR 0.77, 95% CI 0.56-1.07, p = 0.120) MMRd: 12-m PFS 70.0% vs. 67.9% vs. 43.3% DuO vs. Control: HR 0.41, 95% CI 0.21-0.75 Dur vs. Control: HR 0.42, 95% CI 0.22-0.80 12-m OS 89.2% vs. 91.2% vs. 74.4% DuO vs. Control: HR 0.28 95% CI 0.10-0.68 Du vs. Control: HR 0.34 95% CI 0.13-0.79 MMRp: 12-m PFS 59.4% vs. 44.4% vs. 40.8% DuO vs. Control: HR 0.57, 95% CI 0.44-0.73 Dur vs. Control: HR 0.77, 95% CI 0.60-0.97 12-m OS 87.3% vs. 82.5% vs. 81.0% DuO vs. Control: HR 0.69 95% CI 0.47-1.00 Du vs. Control: HR 0.91 95% CI 0.64-1.30
LEAP-001/EN-GOT-en9 phase III trial (NCT03884101)[20]	N = 842 Stage III-IV or RR-EC (CT-free ≥ 6 m) 1L for stage III-IV, 1L/2L for RR	MMRp	1) TC Q3W x 6-8 cycles vs. 2) Lenva 20 mg oral OD + Pembro 200 mg IV Q3W until PD or toxicity	All: PFS 12.5 vs. 10.2 m (HR 0.91, 95% CI 0.76-1.09) OS 37.7 vs. 32.1 m (HR 0.93, 95% CI 0.77-1.12) MMRp: PFS 9.6 vs. 10.2 m (HR 0.99, 95% CI 0.82-1.21) OS 30.9 vs. 29.4 m (HR 1.02, 95% CI 0.83-1.26)
Fader et al. (Phase II)[21, 22]	N = 61 Stage III-IV or RR-EC 1L for all	HER2/neu	TC Q3W x 6 cycles + Trastuzumab 6 mg/kg IV (8 mg/kg first cycle) Q3W until PD or toxicity vs.TC (as arm 1)	PFS 12.9 vs. 8.0 m (HR 0.46, 90% CI 0.28-0.76, p = 0.005) OS 29.6 vs. 24.4 m (HR 0.58, 90% CI 0.34-0.99, p = 0.046).
GOG-86P (NCT00977574)[31]	N = 494 Measurable stage III-IVA or stage IVB or RR-EC (CT-free ≥ 6 m) 1L for all	p53abn	1) Bev IV and TC IV Q3W x 6 cycles, then Bev IV Q3W until PD or toxicity 2) Temsirolimus IV Day1 and 8 + TC IV Q3W x 6 cycles then Temsirolimus IV Day 1, 8, and 15 Q3W until PD or toxicity 3) Bev IV + IxaC IV Q3W x 6 cycles, then Bev IV Q3W until PD or toxicity	PFS Bev* vs. Temsirolimus: 12.5 vs. 8.2 m; HR 0.48, 95% CI 0.31-0.75) Bev/TC vs. Temsirolimus/TC: HR 0.55, 95% CI 0.32-0.94) Bev/IxaC vs. Temsirolimus/TC: HR 0.43, 95% CI 0.26-0.71) OS Bev* vs. Temsirolimus: HR 0.61, 95% CI 0.38-0.98 *Bev referred to data from both arm 1 and arm 3.

Table 1 Studies Evaluating ICIs and Targeted Therapies as First-Line Treatment for EMC (cont.)

Study (ref)	Patient	Biomarker Status	Treatment	Outcome (study vs control) Data presented as median unless specified otherwise
SIENDO/EN-GOT-EN5/GOG-3055 Phase III trial[25,26]	N = 263 Stage IV or RR-EC completed > 12 w of taxane-platinum, with PR/CR 1L for stage IV 1L/2L for RR	p53wt MMRd/ MMRp	Selinexor 80 mg or placebo oral once weekly (2:1)	All: PFS 5.7 vs. 3.8 m (HR 0.76, 95% CI 0.54-1.08, p = 0.126) p53wt: PFS 28.4 vs. 5.2 m (HR 0.44, 95% CI 0.27-0.73) p53wt/MMRp: PFS 39.5 vs. 4.9 m (HR 0.36, 95% CI 0.19-0.71) p53wt/MMRd: PFS 13.1 vs. 3.7 m (HR 0.49, 95% CI 0.18-1.34)

Abbreviations: 1L, first-line; 2L, second-line; Bev, bevacizumab; CI, confidence interval; CT, chemotherapy; CS, carcinosarcoma; Dur, durvalumab; DuO, durvalumab and olaparib; Dos, dostarlimab; ENGOT, European Gynecological Oncology Trial; EMC, endometrial cancer; HR, hazard ratio; IxaC, ixabepilone and carboplatin; Lenva, lenvatinib; MMRd, mismatched repair deficient; MMRp, mismatched repair proficient; MI, myometrial invasion; NSMP; NA, not available; NR, not reach, NSMP, no specific molecular profile; OS, overall survival; p53wt, p53 wild type; pembro, pembrolizumab; PD, progressive disease; PFS, progression-free survival; PR/CR, partial response/complete response; RR, recurrence; TC, paclitaxel and carboplatin

were also improved, albeit more modest, with the corresponding PFS and OS of 28.4% vs. 18.8% (HR 0.76) and 48.6% vs. 41.9% (HR 0.79), respectively.

1.2 Pembrolizumab

1) KEYNOTE-868 / NRG-GY018

This phase III trial enrolled 816 patients with advanced EMC (stage III–IVA with measurable disease, stage IVB, or recurrent disease with or without measurable disease). This is the only first-line chemoimmunotherapy trial which excluded subjects with uterine carcinosarcomas. Patients were stratified into MMRd (n = 225) and MMRp (n = 591) cohorts.[13] The patients were randomized 1:1 to receive pembrolizumab 200 mg or placebo with carboplatin–paclitaxel every 3 weeks for 6 cycles (up to 10 cycles in selected patients), followed by maintenance treatment with pembrolizumab 400 mg or placebo every 6 weeks for up to 2 years.

Significantly improved PFS benefits from pembrolizumab over chemotherapy alone were demonstrated regardless of MMR status. Among the patients with MMRp tumors, median PFS of the patients who received pembrolizumab was significantly longer vs. control: 13.1 vs. 8.7 months; HR 0.54. Higher degree of benefits was found in those with MMRd tumors, the corresponding 12-month PFS were 74% vs. 38%. Median PFS was not reached in the pembrolizumab group versus 7.6 months in the control group (HR 0.30).

2) KEYNOTE-B21 / ENGOT-en11 / GOG-3053

This phase III trial enrolled 1,095 patients with stage I–II disease with myometrial invasion and non-endometrioid histology or p53/TP53 abnormalities, or stage III–IVA disease with no residual disease after surgery.[14]

The patients were randomized to receive pembrolizumab or placebo, with carboplatin–paclitaxel for 6 cycles, followed by pembrolizumab or placebo every 6 weeks for 6 additional cycles. No difference in PFS was observed overall (22% in both arms). However, prespecified subgroup analysis demonstrated improved PFS in the MMRd subgroup treated with pembrolizumab (HR 0.31), reinforcing the clinical benefit of ICIs in MMRd EMC. Longer follow-up is ongoing to further clarify the benefits.

1.3 Atezolizumab (AtTEnd / ENGOT-en7)

In this trial, 551 patients with advanced (stage III–IV) or first recurrent EMC were randomized 2:1 to receive atezolizumab 1200 mg or placebo with carboplatin–paclitaxel every 3 weeks for 6-8 cycles, followed by maintenance atezolizumab or placebo every 3 weeks until disease progression.[15]

No difference in ORR was observed (75% vs. 74.6%). Nevertheless, the median PFS and OS of all populations were significantly longer with atezolizumab: 10.1 vs. 8.9 months; HR 0.74 for PFS and 38.7 vs. 30.2 months; HR 0.82 for OS. The benefits were observed only in the MMRd group, with median PFS and median OS not reached in those receiving atezolizumab vs. 6.9 months (HR 0.36) and 25.7 months (HR 0.41) in the placebo group. No statistically significant differences in PFS or OS of the patients with MMRp tumors were observed.

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1.4 DUO-E / GOG-3041 / ENGOT-EN10

This phase III trial randomized 718 patients with advanced or first recurrent EMC to receive carboplatin–paclitaxel alone or added with durvalumab 1120 mg every 3 weeks for 6 cycles before durvalumab maintenance 1500 mg every 4 weeks or added with durvalumab before durvalumab and olaparib 300 mg tablets twice daily maintenance.[16,17]

The results of all population showed 12-month PFS was significantly higher in all patients who had durvalumab than chemotherapy alone: 48.5% vs. 41.1% (HR 0.71). The benefits were observed in both MMRp subgroup (modest improvement of 12-month PFS: 44.4% vs. 40.8%; HR 0.77) and especially in MMRd subgroup (12-month PFS of 67.9% vs. 43.3%; HR 0.42).

2. ICIs combined with chemotherapy followed by ICIs plus PARP inhibitor maintenance Therapy

Advanced and metastatic EMC frequently harbors mutations in *PTEN*, *TP53*, and other genes involved in homologous recombination DNA repair (HRD). Recent studies, including DUO-E and RUBY Part 2, have evaluated the role of PARP inhibitors combination with ICIs as maintenance therapy following ICIs combined with chemotherapy in EMC.

2.1 DUO-E / GOG-3041 / ENGOT-EN10

The DUO-E trial also explored whether adding olaparib to durvalumab as maintenance therapy could further improve outcomes beyond those described in Section 1.4.

In patients receiving durvalumab plus olaparib as maintenance therapy, both PFS and OS were significantly improved compared with chemotherapy alone (HR 0.55). When comparing maintenance strategies following chemotherapy plus durvalumab by MMR status, both durvalumab alone and durvalumab plus olaparib demonstrated closely align PFS benefits, although direct statistical comparison was not performed (HR 0.42 vs. HR 0.41, respectively) in the MMRd subgroup. However, in MMRp subgroup, there was a trend toward improved PFS (HR 0.57) from durvalumab plus olaparib compared with durvalumab alone (HR 0.77).

Post hoc analyses evaluating the highly heterogeneous MMRp subgroup—characterized by overlapping biomarker expression (67% PD-L1 positive, 59% *TP53* mutation, 21% HRD, 8% *BRCA* mutation, and 27% serous carcinoma)—demonstrated that durvalumab plus olaparib combined with chemotherapy improved PFS compared with chemotherapy alone across all biomarker-defined subgroups.[18]

2.2 Dostarlimab plus niraparib (RUBY Part 2 / ENGOT-EN6-NSGO / GOG-3031)

This study compared dostarlimab plus chemotherapy followed by maintenance dostarlimab plus niraparib compared to placebo plus chemotherapy followed by placebo. The experimental arm was associated with longer PFS in the intention-to-treat population (median 14.5 vs. 8.3 months; HR 0.60) and the MMRp/MSS cohort (median 14.3 vs. 8.3 months; HR 0.63).[19]

3. ICIs combined with tyrosine kinase inhibitors

3.1 Pembrolizumab plus Lenvatinib (LEAP-001 / ENGOT-en9)

This phase III trial randomized 842 patients with advanced (stage III–IV) or first recurrent EMC who had not previously received first-line chemotherapy to have pembrolizumab 200 mg intravenously every 3 weeks plus lenvatinib 20 mg orally once daily until disease progression vs. carboplatin–paclitaxel chemotherapy every 3 weeks for up to 7 cycles.[20]

After a median follow-up of approximately 38 months, no significant differences in PFS or OS were observed in the overall population. However, in the MMRd subgroup (n = 200), median PFS was significantly longer with pembrolizumab plus lenvatinib (31.8 vs. 9.0 months; HR 0.62).

4. Targeted therapies combined with chemotherapy followed by targeted maintenance

4.1 Trastuzumab (NCT01367002)

Serous carcinoma and carcinosarcoma of the endometrium frequently overexpress HER2/neu, providing a rationale for treatment with trastuzumab, a monoclonal antibody targeting the extracellular domain of HER2/neu.

A randomized phase II trial in patients with advanced-stage or first recurrent with HER2/neu-positive uterine serous carcinoma compared carboplatin–paclitaxel plus trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks intravenously) to carboplatin–paclitaxel alone.[21,22] Treatments continued until disease progression.

The study found an addition of trastuzumab significantly improved both PFS (12.9 vs. 8.0 months; HR 0.46) and OS (29.6 vs. 24.4 months; HR 0.58). Trastuzumab combined with chemotherapy was well tolerated, with manageable toxicity.

4.2 Bevacizumab (GOG-86P)

A phase II trial evaluated bevacizumab in patients with advanced (stage III–IV) or recurrent EMC who had not previously received chemotherapy.[23] Patients were assigned into 3 arms of treatment:

1) Paclitaxel/carboplatin/bevacizumab 2) Paclitaxel/carboplatin/temsirolimus, and 3) Ixabepilone/carboplatin/ bevacizumab. Bevacizumab (arms 1 and 3) or temsirolimus (arm 2) was continued as maintenance therapy.

The ORRs were similar across all three arms. However, OS in the patients who had paclitaxel/carboplatin/bevacizumab (arm 1 and arm 3) were superior compared with temsirolimus (and compared with historical controls from GOG-209). Subsequent analyses focusing on *TP53* mutation status demonstrated that among patients with p53-abnormal tumors (n = 108), bevacizumab significantly improved with HR of 0.48 for PFS and HR of 0.61 for OS compared to the patients who had temsirolimus. No significant survival benefit was observed in patients with *TP53* wild-type tumors.[24]

4.3 Selinexor (SIENDO / ENGOT-EN5 / GOG-3055)

Selinexor is a targeted Exportin 1 (XPO1) inhibitor that blocks nuclear export of tumor suppressor proteins, including p53, thereby promoting selective apoptosis and inhibiting DNA damage repair mechanisms.

The SIENDO phase III trial[25] randomized 263 patients with metastatic (stage IV) or recurrent EMC to receive selinexor or placebo following platinum-based chemotherapy. In the overall population, selinexor did not significantly improve outcomes. However, in patients with p53 wild-type tumors, median PFS was significantly prolonged with selinexor (39.5 vs. 4.9 months; HR 0.36).[26]

An additional phase III trial (ENGOT-EN20/GOG-3083/ XPORT-EC-042) is currently ongoing to further evaluate selinexor in p53 wild-type EMC.

5. ADCs

Until now, there are no studies using ADCs in first-line treatment. An ongoing clinical study is evaluating the investigational anti–trophoblast cell surface antigen 2 (Trop-2) antibody–drug conjugate sacituzumab tirumotecan (Sac-TMT; SKB264/MK-2870) in combination with immunotherapy as first-line maintenance therapy for patients with MMRp EMC (NCT06952504), with enrollment initiated in May 2025.[27]

Summary of first-line targeted therapies and immunotherapy

The integration of immunotherapy and targeted therapies into first-line treatment has significantly improved outcomes for patients with advanced EMC. Molecular profiling is essential for optimizing treatment selection. Treatment selection should be guided by clinical risk and molecular classification2:

1) **Low-risk and intermediate-risk disease:** Surgery alone; no adjuvant immunotherapy or targeted therapy required.

2) **High-risk disease:** Chemotherapy with consideration of combination of ICIs (e.g., dostarlimab, pembrolizumab), followed by ICI maintenance, with or without radiotherapy.

3) **Advanced, metastatic, or unresectable disease:** Treatment should be guided primarily by MMR status and molecular features:

- *MMRd tumors:* ICIs (dostarlimab, pembrolizumab, or durvalumab) plus carboplatin–paclitaxel followed by ICI maintenance.
- *MMRp tumors:* ICIs plus carboplatin–paclitaxel followed by ICI with/without PARP inhibitor maintenance (e.g. dostarlimab, pembrolizumab, atezolizumab, or durvalumab, durvalumab + olaparib)
- *HER2/neu-positive tumors:* Carboplatin–paclitaxel plus trastuzumab, followed by trastuzumab maintenance.
- *p53-abnormal tumors:* Consider bevacizumab-containing regimens.
- *TP53 wild-type tumors:* Consider XPO1 inhibitors (Selinexor) as maintenance therapy.

Ongoing trials investigating novel combinations and biomarkers will further refine personalized therapeutic strategies in this disease.

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II. Second-line targeted therapies and immunotherapy in EMC patients

Immunotherapy is now recognized as the standard first-line treatment for patients with EMC, and its utilization continues to increase. The role of these agents in patients with recurrent or progressive disease as second-line treatment had also been studied. Single-agent ICIs are effective in MSI-H/MMRd tumors, while the combination of pembrolizumab and lenvatinib has become a standard option for MMR-proficient disease after platinum failure. The indication for such therapy, however, should be reconsidered in the context of the patient's prior first-line treatment, which will be discussed in subsequent sections.

Patients with no prior immunotherapy

Whenever feasible, debulking of newly developed lesions or biopsy is recommended to reassess the current microenvironment tumor. In cases where re-biopsy is not possible, archival primary tumor tissue or prior pathological results may serve as alternative sources to guide treatment selection. Table 2 shows specific therapeutic agents and corresponding clinical studies and are detailed below.

1. ICIs monotherapy

1.1 Pembrolizumab (KEYNOTE-158)

This was a phase II trial involving multiple types of solid tumors in patients who had previously received at least one line of chemotherapy. Participants were administered pembrolizumab (200 mg intravenously every 3 weeks) and continued treatment until disease progression or completion of a maximum of 35 cycles. The key findings related to EMC are as follows:

1) KEYNOTE-158 (Cohort D, K)

The cohorts relevant to EMC included Cohort D (EMC) and Cohort K Data from 94 patients with advanced or recurrent EMC from Cohorts D (EMC) and Cohort K (Other Advanced Solid Tumors, excluding Colorectal Cancer, with MSI-H status) with MMRd or MSI-H tumors, and 96 patients from Cohort D with MMRp/MSS tumors.[28,29] The two groups were not directly compared. The results demonstrated the efficacy of pembrolizumab in patients with advanced or recurrent EMC who were positive for MMRd protein or MSI-H following disease progression after prior chemotherapy, and who are not candidates for curative treatment with surgery or radiation. The ORR was 50%, with a median PFS of 13.1 months and a median OS of 65.4 months among those with MMRd/MSI-H group, and 7%, with a median PFS of 2.1 months, and a median OS of 11.1 months among those with MMRp/MSS group.

Adverse events of Grade 3 or higher were observed in 14% of the MSI-H/MMRd population, with no incidence of Grade 5 adverse events.

2) KEYNOTE-158 high tumor mutational burden (TMB-high) subgroup

This prespecified analysis used data from 1,066 solid tumors in patients with progressive disease from prior treatment, comprising 102 with high tumor mutational burden (TMB-high) and 688 with non-TMB-high.[30] This included 15 TMB-high and 67 non-TMB-high EMC patients.

The study showed TMB-high cancers had a favorable ORR to pembrolizumab (29%) compared to the non-TMB-high group (6%). However, no statistical comparison was made. Adverse events of Grade 3 or higher were observed in 13% and Grade 5 in 1% of the total population.

1.2 Dostarlimab (GARNET trial)

This phase I/II trial included patients with advanced or recurrent EMC who had previously received at least one platinum-containing chemotherapy regimen.[31] A total of 314 patients were enrolled (161 patients in the MMRp/MSS group and 153 patients in the MMRd/MSI-H group). Patients were treated with Dostarlimab (500 mg intravenously (IV) every 3 weeks for 4 cycles, followed by 1000 mg IV every 6 weeks) and continued treatment until disease progression. The ORR were 45.5% for MMR/MSI-H group and 15.4% for MMRp/MSS group.

Adverse events of Grade 3 or higher were observed in 17.6% of the MMRd/MSI-H group and 20.5% of the MMRp/MSS group. No incidence of Grade 5 adverse events was reported.

2. Tyrosine kinase inhibitor monotherapy (Lenvatinib)

This phase II trial investigated Lenvatinib in 133 patients with advanced or recurrent EMC who had previously received at least one platinum-containing chemotherapy regimen.[32] Patients in the study received Lenvatinib at a dose of 24 mg orally once daily. The ORR for the entire study population was 14.3%, showing little difference between the endometrioid subtype (15%) and the non-endometrioid subtype (14%). Key efficacy metrics included a duration of response lasting greater than or equal to 23 weeks in 37.6% of patients, a mean PFS of 5.6 months, and a median OS of 10.6 months. Regarding

Table 2 Studies Evaluating ICIs, Antibody-Drug Conjugates, and Targeted Therapies as Second-Line or Later Treatment for EMC

Study (ref)	Patient (all had advanced or recurrent EC)	Biomarker status	Treatment	Outcome (study +/- control) (PFS and OS presented as median unless specified otherwise)
KEYNOTE-158 (Phase II)[28-30]	N = 94 progressed after standard Rx	MMRd/ MSI-H	Pembro 200 mg Q3W up to 35 cycles	MMRd: ORR 50% (95% CI, 40-61) PFS 13.1 m (95% CI, 4.3-25.7) OS 65.4 m (95% CI, 29.5-NR)
	N = 1066	TMB-high	Pembro 200 mg Q3W up to 35 cycles	TMB-high: ORR 29% (95% CI, 21-39)
GARNET (Phase I/II)[31]	N = 314 progressed after standard Rx	MMRd/ MMRp	Dos 500 mg Q3W x 4 cycles then 1000 mg Q6W until PD	MMRp/MSS: ORR 15.4% (95% CI, 10.1-22) MMRd/MSI-H: ORR 45.5% (95% CI, 37.1-54)
Vergote et al. (Phase II)[32]	N = 133 prior 1 platinum-based CT	All population	Lenva 24 mg OD in a 28-day cycle	ORR 14.3% (95% CI: 8.8-21.4) SD: ≥ 23 weeks: 23.3% Clinical benefit: 37.6% (95% CI: 29.3-46.4) PFS: 5.6 m (95% CI: 3.7-6.3) OS: 10.6 m (95% CI: 8.9-14.9)
Study 309/ KEYNOTE-775 (Phase III)[33]	N = 827 prior ≥ 1 platinum-based CT	MMRd/ MMRp	Pembro 200 mg Q3W + Lenva 20 mg QD until PD (Pembro up to 35 cycles) Doxo 60 mg/m2 q 3 weeks, or paclitaxel 80 mg mg/m2 IV q wk (1 week off)	MMRp: PFS 6.7 vs. 3.8 m; HR 0.60 (95% CI, 0.50-0.72) OS 18.0 vs. 12.2 m; HR 0.70 (95% CI, 0.58-0.83) ORR 32.4% vs. 15.1% All comers: PFS 7.3 vs. 3.8 m; HR 0.56 (95% CI, 0.48-0.66) OS 18.7 vs. 11.9 m; HR 0.65 (95% CI, 0.55-0.77) ORR 33.8% vs. 14.7% MMRd: PFS 10.7 vs. 3.7 m; HR 0.39 (95% CI, 0.25-0.60) OS 31.9 vs. 8.6 m; HR 0.43 (95% CI, 0.28-0.68)
DESTINY-PanTumor02 (Phase II)[35]	N= 267 prior ≥ 1 systemic treatment or no satisfactory alternative options	HER2 IHC	Trastuzumab deruxtecan 5.4 mg/kg Q3W until PD	EMC: ORR 57.5% (95% CI, 40.9-73.0) PFS 11.1 m (95% CI, 7.1-NR) All cancersFer: ORR 37.1% (95% CI, 31.3-43.2) PFS 6.9 m (95% CI, 5.6-8)

Abbreviations: 1L, first-line; 2L, second-line; Bev, bevacizumab; CI, confidence interval; CMT, chemotherapy; CS, carcinosarcoma; Dos, dostarlimab; HR, hazard ratio; Lenva, lenvatinib; MMRd, mismatched repair deficient; MMRp, mismatched repair proficient; MSI-H, high microsatellite instability; MSS, microsatellite stable; NR, not reached; ORR, overall response rate; OS, overall survival; p53wt, p53 wild type; Pembro, pembrolizumab; PD, progressive disease; PFS, progression-free survival; TMB, tumor mutational burden

safety, a high incidence of adverse events of Grade 3 or higher occurring in 59% of patients were reported.

3. ICIs combination with tyrosine kinase inhibitor

3.1 Pembrolizumab and lenvatinib (Study 309 / KEYNOTE-775)

This phase III trial randomized 827 patients with advanced or recurrent EMC, previously treated with at least one platinum-based chemotherapy regimen, in a 1:1 ratio to receive either Lenvatinib (20 mg orally once daily) plus Pembrolizumab (200 mg IV every 3 weeks, up to 35 cycles) vs. investigator's choice chemotherapy (Doxorubicin or Paclitaxel).[33]

The study found that patients treated with Lenvatinib combined with Pembrolizumab showed superior efficacy over chemotherapy for advanced

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EMC patients previously treated with platinum. In overall population, median PFS and OS were longer compared to the chemotherapy group: 7.3 months vs. 3.8 months (HR = 0.56) for PFS, and 18.7 months vs. 11.9 months (HR = 0.65) for OS across the entire population. Among the patients with MMRp tumor, longer PFS with Lenvatinib + Pembrolizumab (6.7 months) compared to chemotherapy (3.8 months, HR = 0.60), and significantly longer OS (18 months vs. 12.2 months, HR = 0.70). A more substantial benefit was demonstrated in those with MMRd tumor: significantly longer PFS (10.7 months vs. 3.7 months, HR = 0.39) and dramatically longer OS (31.9 months vs. 8.6 months, HR = 0.43) with Lenvatinib + Pembrolizumab compared to chemotherapy. Adverse events of Grade > 3 were high in both arms, with 90.1% in the combination arm and 73.7% in the chemotherapy arm, and Grade 5 AEs occurred in 6.4% and 5.2%, respectively.

An exploratory analysis[34] in the subset of 71 patients who completed the full 35 cycles of combination therapy and continued Lenvatinib monotherapy after the completion of Pembrolizumab therapy. The analysis revealed continuous treatment provided sustained clinical benefit. For the entire cohort (30 MMRp and 41 MMRd patients), median PFS was 34.1 months, with 2-year and 3-year PFS of 68.3% and 49.3% respectively. The corresponding 2-year and 3-year OS rates were 100% and 89%. The benefit was also demonstrated among the patients with MMRp tumor: median PFS was 34.1 months, with 2-year and 3-year PFS of 66.7% and 46.2% respectively. The corresponding 2-year and 3-year OS were 100% and 84.3%. However, the safety profile showed that Grade > 3 AEs occurred in 80.5% of the total patients who continued Lenvatinib monotherapy. This exploratory data supports the concept of ongoing clinical benefit when continuing Lenvatinib.

4. ADCs

4.1 DESTINY-PanTumor 02

This phase II trial evaluated trastuzumab deruxtecan (T-DXd) in 267 patients, including 40 EMC patients, with HER2-expressing solid tumors (according to 2016 CAP/ASCP/ACSO guidelines for HER2 scoring in gastric cancer) who had received at least one prior chemotherapy regimen.[35] Patients received T-DXd at a dose of 5.4 mg/kg intravenously every 3 weeks until disease progression was detected.

The study demonstrated a favorable ORR across all solid tumors with HER2 expression (immunohistochemistry (IHC) 3+/2+), with particularly high benefit observed in endometrial, ovarian, cervical, bladder, and biliary tract cancers. Across all solid tumor types, the ORR was 37.1%, and the median PFS was 6.9 months. In the EMC group, the ORR was 57.5%. Specifically, within this population, the ORR for HER2 IHC 3+ patients was 84.6%, and the median PFS was 11.1 months.

Regarding safety, the incidence of Grade > 3 adverse events was 40.8% of the total population. An adverse event of special interest was interstitial lung disease or pneumonitis, which occurred in 10.5% of all patients, with a 1.1% incidence of death related to this adverse event.

4.2 Other ADCs

Clinical activity has also been reported with other Trop-2 ADCs. Datopotamab deruxtecan (Dato-DXd) demonstrated antitumor activity in patients with advanced solid tumors, including EMC, in the phase II TROPION-PanTumor03 study.36 In addition, sacituzumab govitecan showed clinical efficacy in heavily pretreated EMC in the phase II basket trial TROPiCS-03.[37]

Ongoing phase III trials are expected to further define the role of Trop-2 ADCs in this disease, including the ASCENT-GYN-01 study evaluating sacituzumab govitecan (NCT06486441) and trials investigating sacituzumab tirumotecan (MK-2870), such as MK-2870-020/TroFuse-020/GOG-3101/ENGOT-cx20 (NCT06459180).

5. Targeted therapies combined with hormonal treatments

Other treatment approaches in EMC include an emerging subgroup of ER–positive disease, which may be amenable to hormonal therapy. Although hormonal treatments are not the primary focus of this review, several phase II studies have explored the combination of endocrine therapy with targeted agents. In the randomized phase II PALEO trial, the cyclin D kinase 4 (CDK4)/6 inhibitor palbociclib combined with endocrine therapy was evaluated in patients with ER-positive endometrioid EMC that was either primary metastatic or relapsed after at least one prior systemic therapy. With a median follow-up of 21.9 months, the median PFS was 8.3 months in the combination arm compared with 3.1 months with endocrine therapy alone.[38]

Similarly, a single-arm phase II study evaluated

abemaciclib plus letrozole in recurrent ER-positive EMC, demonstrating an ORR of 30% and a median PFS of 9.1 months.[39] In addition to CDK4/6 inhibition, targeting the PI3K pathway has also been explored. A phase II study combining the mTOR inhibitor everolimus with letrozole reported an ORR of 32%, with particularly favorable responses observed in patients with endometrioid histology and catenin beta 1 mutations.[40]

Despite these encouraging results, there remains a clear need for phase III validation to define the role of combined hormonal and targeted therapies in EMC, particularly in the context of evolving treatment paradigms and increasing incorporation of molecular classification into clinical decision-making.

Patients with prior immunotherapy

The hypothesized mechanisms of resistance to immunotherapy include genetic alterations, such as beta-2 microglobulin or Janus kinases1/2, changes in the tumor microenvironment characterized by increased vascular endothelial growth factor (VEGF) activity, and an escalation of T-cell inhibitory pathways.

Treatment strategies to address immunotherapy resistance include the use of new agents, such as Werner syndrome helicase (WRN) inhibitors, which are designed to exploit the vulnerability of MMRd cancer cells by inhibiting the WRN protein (crucial for DNA repair), leading to an accumulation of DNA damage and replication stress, while MSS cells are not sensitive to this effect. Other strategies involve combination therapies (ICI + others), such as combining a PD-1 inhibitor with an anti-VEGF agent or a PARP inhibitor, using dual checkpoint blockade, or performing immunotherapy re-challenge (re-use of the same ICI), especially if the patient previously responded well and treatment was discontinued for more than 6 months.[41]

Clinical evidence for rechallenge comes from two retrospective studies. One report involved 8 patients with advanced MMRd EMC who progressed after first-line Pembrolizumab, where second-line treatment with Pembrolizumab plus Lenvatinib achieved an ORR of 75% (CR 12.5%, PR 62.5%).[42] Another study of 11 EMC patients (8 MMRd, 3 MMRp) previously treated with an ICI showed an ORR of 54.6% when given a second-line ICI-based regimen.[43]

Despite these encouraging efficacy signals, safety data for second-line immunotherapy after prior ICI remains limited, as studies on rechallenge have reported severe (grade 3-4) immune-related adverse events, including endocrine AEs and colitis. Consequently, implementing immunotherapy in this patient cohort requires careful consideration of the current limitations in the existing literature. Treatment initiation should be guided by a thorough, individualized assessment of each patient's risk-benefit profile, ideally taking into account putative biomarkers which predict responsiveness to immunotherapy rechallenge.

Summary of second-line targeted therapies, immunotherapy, and ADCs

Treatment is tailored according to molecular features; hence, molecular study should be performed if not prior available.

- MSI-H/MMRd: Consider ICIs e.g. Dostarlimab, Pembrolizumab
- TMB-H: Consider ICI (Pembrolizumab)
- MMRp: Consider Pembrolizumab and Lenvatinib
- HER2 (IHC 3+): Consider HER2-directed ADC i.e. Trastuzumab deruxtecan

To date, no solid evidence from clinical trial to test the role of immunotherapy rechallenge.

CONCLUSION

Systemic therapy for EMC has evolved from uniform chemotherapy to a precision-based approach integrating targeted agents, immunotherapy, PARP inhibitors, tyrosine kinase inhibitors, and ADCs. Molecular classification now underpins therapeutic decision-making and has led to substantial improvements in outcomes for patients with advanced disease. Continued translational research and well-designed clinical trials will further advance personalized care in this rapidly evolving field.

Conflict of Interest

All authors declare no conflicts of interest.

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