Cancer Treatment Reviews 129 (2024) 102790

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Locally advanced and metastatic endometrial cancer: Current and emerging therapies

Alixe Salmon [a,1], Alizée Lebeau [a,b,1], Sylvie Streel [a], Adriane Dheur [b], Sophie Schoenen [b], Frédéric Goffin [b], Elodie Gonne [a], Frédéric Kridelka [b], Athanasios Kakkos [b,2], Christine Gennigens [a,*,2]

[a] Department of Medical Oncology, CHU Liège, Liège, Belgium
[b] Department of Gynecology and Obstetrics, CHU Liège, Liège, Belgium

ARTICLE INFO

Keywords:
Endometrial cancer
Advanced disease
Metastatic
Targeted therapy
Personalized treatment

ABSTRACT

Until recently, patients diagnosed with locally advanced and metastatic endometrial cancer faced significant challenges in their treatment due to limited options and poor prognostic outcomes. The sequencing of tumors has been a major advancement in its management. It has led to The Cancer Genome Atlas classification currently used in clinical practice and the initiation of several clinical trials for innovative treatments targeting principally signaling pathways, immune checkpoints, DNA integrity, growth factors, hormonal signaling, and metabolism. Numerous clinical trials are investigating a combinatorial approach of these targeted therapies to counter tumoral resistance, cellular compensatory mechanisms, and tumor polyclonality. This review provides a comprehensive overview of historical, current, and promising therapies in advanced and metastatic endometrial cancer. It particularly highlights clinical research on targeted and hormonal therapies, but also immunotherapy, reflecting the evolving landscape of treatment modalities for this disease.

Introduction

Endometrial cancer (EC) is the sixth most prevalent cancer among women, with 417,000 new cases reported annually worldwide [1]. The global incidence of EC has risen by 21% since 2008, attributed to extended life expectancy and the increasing prevalence of obesity [2]. The majority of patients are diagnosed at an early stage and their standard treatment involves surgical intervention, with or without adjuvant radiotherapy and/or chemotherapy, tailored to the assessed risk of disease recurrence [3].

However, approximately 15 % of patients are diagnosed at advanced stages, exhibiting a five-year overall survival (OS) rate of 40–65 % and 15–17 % for International Federation of Gynecology and Obstetrics (FIGO) stages III and IVA-B respectively. Until recently, women with recurrent or metastatic (FIGO IVC) disease faced limited therapeutic alternatives, primarily restricted to chemotherapy, which exhibits reduced effectiveness after first-line treatment. Based on comprehensive genomic analyses, The Cancer Genome Atlas (TCGA) classification has revolutionized the management of EC, enabling the development of innovative therapies. Inspired by TCGA, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) uses cost-effective methods, and clinically practical techniques (such as immunohistochemistry and Polymerase Chain Reaction) to classify EC into four subgroups: (i) POLε mutated; (ii) mismatch repair deficiency (MMRd); (iii) abnormal p53; and (iv) no specific molecular profile (NSMP). This review examines current and emerging treatments for advanced/recurrent EC, focusing on targeted treatments tailored to ProMisE subgroups and therapies aimed at specific targets which play a crucial role in tumor biology. This approach offers a comprehensive perspective on the therapeutic strategies being explored for advanced/recurrent EC.

Targeted treatments tailored to ProMisE subgroups

POLε mutated (7–10 % of EC)

The POLε gene encodes DNA polymerase ε, which is involved in DNA

* Corresponding author.
E-mail address: christine.gennigens@chuliege.be (C. Gennigens).
[1] Joint first co-authors.
[2] Joint last co-authors.

https://doi.org/10.1016/j.ctrv.2024.102790
Received 27 April 2024; Received in revised form 18 June 2024; Accepted 19 June 2024
Available online 22 June 2024

replication and replication fidelity. Tumors with mutations in the exonuclease domain of POLε (POLEmut) are associated with a high tumor mutational burden (TMB). Despite their hypermutated profile, the prognosis for these tumors is favorable (early stage, low recurrence rate). The high TMB generates abnormal proteins on the surface of tumor cells, making them more visible to the immune system and leading to a significant number of tumor-infiltrating lymphocytes. For advanced/recurrent EC, immune checkpoint inhibitors (ICIs) are promising, with ongoing studies [4,5].

MMRd/MicroSatellite Instability High (MSI-H) profile (25–30 % of EC)

Immunotherapy, notably ICIs, represents a major improvement in the treatment of advanced/recurrent EC, particularly in this subgroup. MMRd tumors are deficient in the DNA mismatch repair system, leading to a high TMB and overexpression of the Programmed Death-Ligand 1 (PD-L1) protein. Several clinical trials have demonstrated significant efficacy in the first and second treatment lines (Table 1).

Second-line treatment in metastatic disease

The single-arm phase II study, **KEYNOTE-158**, evaluated pembrolizumab in 90 patients with MMRd advanced/recurrent EC progressing after a first-line of chemotherapy. The results showed a promising overall response rate (ORR) of 48 %, with a progression free survival (PFS) of 13.1 months and a complete response (CR) rate of 14 %. The median duration of response (mDoR) (2.9–49.7+) and OS (27.2-NR) were not reached. Among the 90 patients, 76 % experienced treatment-related adverse events, with 12 % being grade ≥ 3, and 7 % leading to treatment discontinuation. In 2022, pembrolizumab has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) as a single agent for patients with advanced MMRd or MSI-H EC who have disease progression following prior systemic therapy in any setting.

The single-arm phase I trial, **GARNET**, evaluated dostarlimab in two cohorts: MMRd (n = 108) and Mismatch Repair proficient (MMRp) (n = 156). The ORR was 45.5 and 15.4 % in MMRd and MMRp cohorts respectively. TMB is more frequent in MMRd population (86.5 % vs. 7.2 % in MMRp), while the Combined Positive Score (CPS) > 1 is frequent in both cohorts (71.9 % in MMRd vs. 57.7 % in MMRp). Surprisingly, among patients with high TMB and CPS > 1, ORRs were remarkably similar regardless of MMR status (60.4 % in MMRd and 66.7 % in MMRp). Patients with low TMB and CPS < 1 exhibited lower ORRs to dostarlimab (20 % in MMRd and 7.1 % in MMRp) [6,7]. Based on these results, dostarlimab was approved by FDA for MMRd advanced solid tumors and by EMA for MMRd–MSI-H advanced/recurrent EC.

In phase I **POD1UM-101** trial, the efficacy and safety of retifanlimab

Table 1
Clinical trials of targeted treatments tailored to MMRd/MicroSatellite Instability High (MSI-H) profile.

Targets		Trial	Phase	Number of patients	Therapy	Main results
PD-1	Monoclonal Antibody anti PD-1	NRG-GY018	III	816	standard CT ± pembrolizumab, followed by maintenance pembrolizumab vs. placebo (1st line)	MMRd: 74% 12months PFS MMRp: mPFS 13.1 months
	Monoclonal Antibody anti PD-1	RUBY Part 1	III	494	standard CT ± dostarlimab, followed by maintenance dostarlimab vs. placebo (1st line)	Overall population: OS benefit (HR:0.69, 95% CI 0.54-0.89) MMRd: OS benefit (HR: 0.32, 95% CI 0.17-0.63)
		RUBY Part 2	III	291	standard CT ± dostarlimab, followed by maintenance dostarlimab +niraparib vs. placebo (1st line)	Overall population: PFS benefit (HR:0.60, 95%CI 0.43-0.82) MMRd: PFS benefit (HR 0.48, 95% CI 0.24-0.96)
	Monoclonal Antibody anti PD-1	KEYNOTE-158	II	90	pembrolizumab monotherapy	ORR: 48% PFS: 13.1months DOR and OS: NR
	Monoclonal Antibody anti PD-1	GARNET	I	290	dostarlimab monotherapy	MMRd population: ORR: 43.5% DCR: 55.6%
	Monoclonal Antibody anti PD-1	PODIUM-101	I	44	retifanlimab monotherapy	ORR: 43.3% mDOR: NR
PD-L1	Monoclonal Antibody anti-PD-L1	AtTEND	III	671	standard CT ± atezolizumab, followed by maintenance atezolizumab vs. placebo (1st line)	MMRd: PFS benefit (HR: 0.36, 95% CI 0.23-0.57) MMRp: PFS (HR:0.92, 95% CI 0.73-1.16)
	Monoclonal Antibody anti-PD-L1	DUO-E	III	718	Arm 1 : standard CT followed by placebo Arm 2 : standard CT + durvalumab followed by durvalumab Arm 3 : standard CT + durvalumab followed by durvalumab+olaparib (1st line)	Improvement of PFS in durvalumab alone and durvalumab + olaparib arms (in MMRd, MMRp and PDL-1+ cohorts)

CT, chemotherapy; MMRd, mismatch repair deficient; HR, hazard ratio; MMRp, mismatch repair proficient; mPFS, median progression-free survival; pCR, pathological complete response; DOR, duration of response; NR, not reached; DCR, disease control rate; mDOR, median DOR. In green, phase III trial; in red, phase II; in yellow, phase I.

(a PD1-inhibitor) were evaluated in recurrent MMRd EC, after one to five prior lines of treatment (ICI-naïve). The authors showed an ORR of 43.3 %, with 14.5 % CR and 28.9 % partial responses (PR). Out of them, 75.8 % had DoR lasting more than 6 months [8,9].

The ongoing umbrella phase II **POD1UM-204** study is assessing the efficacy of retifanlimab alone, or in combination with other immunotherapy or targeted agents such as epacadostat, an Indoleamine 2,3-DiOxygenase 1 (IDO1) inhibitor [10].

These results offer a therapeutic approach for patient refractory to chemotherapy, with high responses in MMRd tumors. The use of immunotherapy has been extended to first-line treatment combined with chemotherapy.

First-line treatment in advanced/recurrent disease: chemotherapy + ICI

The phase III, double-blind and randomized, **RUBY part 1** trial evaluated the efficacy of adding dostarlimab to standard chemotherapy in 494 EC patients (23.9 % had MMRd tumors). Patients received dostarlimab or placebo, in combination with chemotherapy and in maintenance. In the MMRd cohort, the dostarlimab arm was associated with a 72 % lower risk of progression than the placebo arm (HR: 0.28, 95 % CI: 0.16–0.50). The 2-year PFS rate was 61.4 % and 15.7 % in the dostarlimab and in the placebo arm respectively. This benefit was also observed in the overall population, with a 36 % lower risk of progression. The OS benefit with dostarlimab was statistically significant either in the overall (HR: 0.69, 95 % CI: 0.54–0.89) or in the MMRd populations (HR: 0.32, 95 % CI: 0.17–0.63) [11]. Dostarlimab with carboplatin and paclitaxel followed by single-agent dostarlimab received FDA and EMA approvals in 2023 for primary advanced or recurrent MMRd/MSI-H EC.

The randomized phase III **NRG-GY018**trial assessed the efficacy of adding pembrolizumab to standard chemotherapy. The 816 patients were randomly assigned to receive chemotherapy with pembrolizumab or placebo following by maintenance. In the MMRd cohort (n = 225), pembrolizumab reduced the risk of disease progression by 70 % compared to the control arm, with a 12-month PFS of 74 % and 38 %, respectively (HR: 0.30, 95 % CI: 0.19–0.48). In the MMRp group (n = 591), the median PFS (mPFS) was 13.1 months with pembrolizumab and 8.7 months with placebo (HR: 0.54, 95 % CI: 0.41–0.71). The benefit of pembrolizumab in the MMRd cohort was observed regardless of the mechanism of MMR loss (MLH1 hypermethylation or Lynch syndrome). The safety profile was favorable in both cohorts, with similar frequencies of severe adverse events (AEs) [12].

AtTEND is a phase III, randomized and double-blind trial, including 551 patients, investigating the efficacy of adding atezolizumab to standard chemotherapy. These patients were randomly assigned to receive atezolizumab or placebo with chemotherapy followed by maintenance therapy with atezolizumab or placebo until disease progression. After a median follow-up of 26.2months, the atezolizumab group showed a significant benefit in the MMRd group (HR: 0.36, 95 % CI: 0.23–0.57) with a 2-year PFS of 50.4 % in the atezolizumab vs. 16.0 % in the placebo cohorts. A statistically significant benefit was also demonstrated in the overall population (HR: 0.74, 95 % CI: 0.61–0.91).

First-line treatment in advanced/recurrent disease: chemotherapy + ICI + poly(ADP-ribose) polymerase inhibitors (PARPi)

DUO-E is a double-blind phase III trial investigating the efficacy and safety of durvalumab and olaparib in combination with standard chemotherapy. This trial includes three arms: chemotherapy (Arm A, n = 241), chemotherapy + durvalumab followed by durvalumab + placebo (Arm B, n = 238), chemotherapy + durvalumab followed by durvalumab + olaparib (Arm C, n = 239). The results indicate a statistically significant PFS benefit for arm B (HR: 0.71, 95 % CI: 0.57–0.89) compared to arm A, and for arm C compared to arm A (HR: 0.55, 95 % CI: 0.43–0.69). The addition of olaparib to durvalumab could enhance the PFS benefit in the MMRp group. However, the study was not designed to compare arms B and C. Conversely, addition of durvalumab alone is sufficient in the MMRd population [13].

The **RUBY part 2** trial includes 291 patients and evaluates standard chemotherapy with dostarlimab or placebo, followed by dostarlimab + niraparib or placebo maintenance therapy for up to 3 years. A significant PFS benefit for dostarlimab + niraparib was observed in the overall (HR: 0.60, 95 % CI: 0.43–0.82), in the MMRd (HR: 0.48, 95 % CI: 0.24–0.96) but also in the MMRp cohorts (HR: 0.63, 95 % CI: 0.44–0.91) [14].

Except for dostarlimab evaluated in the RUBY part I trial, the other studies evaluating ICIs in the first-line are not yet mature for OS.

p53 abnormal (15–20 % of EC)

TP53 gene mutations and/or p53 abnormal expression strongly predict a worse prognosis [15,16]. Several clinical studies have focused on the abnormal p53 profile in EC (Table 2). Cancers with TP53 gene mutations are typically dysregulated at the G1/S phase checkpoint, rendering them more vulnerable to Wee1 protein inhibition. The phase IIb ADAGIO study demonstrated clinical activity of adavosertib (Wee1 inhibitor) monotherapy in 109 patients with recurrent serous carcinoma who had received at least one prior line of platinum-based chemotherapy. The authors reported an ORR of 26 % with 1 CR and 26 PR [17]. Its limitation appears to be the toxicity profile. Recently, a new selective small molecule called ZN-c3 has exhibited greater selectivity and improved safety profiles compared to adavosertib [18].

Moreover, the exact impact of immunotherapy necessitates further investigations in terms of sensitivity and resistance. Indeed, the RUBY Part I study demonstrated significant improvement with dostarlimab in OS (HR: 0.41, 95 % CI: 0.2–0.82) and PFS (HR: 0.55, 95 % CI: 0.30–0.99) in this population. The RUBY Part II study confirmed these data with the association of niraparib and dostarlimab. The genotoxic stress and DNA damage lead to an increase of PD-L1 expression in a p53-dependent manner, resulting in modulation of the tumor immune response [19]. Conversely, the phase II randomized MITO-END3 study evaluating the efficacy of avelumab (anti PD-L1), demonstrated efficacy in the MMRd cohort but resulted in worse outcomes in patients harboring p53 mutations [20]. These findings suggest that TP53 mutations may confer resistance to immunotherapy, through mechanisms such as hyperprogression and immune microenvironment escape. However, the sample size (n = 88 in RUBY trial and n = 47 for MITO-END3) is too small to reach definitive conclusions [21,22].

A non-replicative adenovirus vector for p53 gene transfer (Ad5CMV-p53) combined with radiotherapy has improved survival rates in cervical cancer patients as demonstrated in a meta-analysis [23,24]. These findings could pave the way for novel gene therapies targeting p53 in gynecological malignancies, including EC.

NSMP (40–45 % of EC)

This group is heterogeneous and characterized by a low copy number alteration. Clinical studies specifically targeted proteins or signaling pathway deregulations (Table 3).

Hormonal receptors

Hormonal therapy (HT) has long been a treatment modality in the management of EC, specifically for patients with low-grade, estro-progestative receptor-positive and indolent tumors [25].

Progestin agents, such as megestrol acetate (MA) and medroxyprogesterone acetate (MPA), are commonly used (ORR: 15–25 % and mPFS around 3 months). Tamoxifen can be used alone or in combination with progestins (mPFS of 10 months). Aromatase inhibitors, including anastrozole and letrozole, are another HT showing modest activity (ORR: 10 %).

Aromatase inhibitors associated with mTOR inhibitors, such as everolimus or vistusertib, have been studied to enhance responses to HT, yielding promising results in terms of ORR and PFS. A recent phase I/II study assessed vistusertib with anastrozole in 49 pretreated patients,

Table 2
Clinical trials of targeted treatments tailored to p53 abnormal profile.

Targets		Trial	Phase	Number of patients	Therapy	Main results
PD-1	Monoclonal Antibody anti PD-1	RUBY Part 1	III	494	standard CT ± dostarlimab, followed by maintenance dostarlimab vs. placebo (1st line)	P53mut population (n=88) OS HR: 0.41, 95% CI: 0.2-0.82 PFS HR: 0.55, 95% CI: 0.30-0.99
		RUBY Part 2	III	291	standard CT ± dostarlimab, followed by maintenance dostarlimab +niraparib vs. placebo (1st line)	P53mut population (n=49) PFS HR: 0.29, 95% CI: 0.13-0.63
PD-L1	Monoclonal Antibody anti-PD-L1	MITO-END3	II	125	standard CT ± avelumab, followed by maintenance avelumab vs. placebo (1st line)	P53mut population (n=47) vs P53wt OS HR: 2.32, 95% CI: 1.14-4.71 PFS HR: 2.16, 95% CI: 1.34-3.47
p53	WEE1 inhibitor	ADAGIO	II	109	Adavosertib monotherapy	ORR: 26% (1 CR and 26 PR)

CT, chemotherapy; ORR, overall response rate; OS, Overall survival; PFS, progression-free survival; HR, hazard ratio; CI, Confidence Interval; CR, Complete response; PR, Partial response. In green, phase III trial; in red, phase II.

reporting an ORR of 24.5 % compared to 17.4 % for anastrozole alone, with a mPFS of 5.2 vs. 1.9 months [26].

Activation of the estrogen receptor (ER) is a major driver of cyclin D1-CDK4/6 upregulation. The combination of letrozole with CDK4/6 inhibitors such as palbociclib, ribociclib, or abemaciclib, has been investigated in several phase II trials in advanced/recurrent EC. In the PALEO study, which tested patients treated with letrozole and palbociclib, a significant improvement in PFS was observed (8.3 vs. 3.0 months with letrozole alone) [27]. Similarly, the NCT02657928 trial evaluating letrozole combined with ribociclib demonstrated promising clinical activity, with a 12 and 24-month PFS of 55 % and 20 %, respectively [28]. Another study (NCT03675893) investigating letrozole in combination with abemaciclib reported an ORR of 30 % [29]. Unfortunately, the phase III study evaluating the combination of letrozole with lerociclib was aborted (due to strategies changes within the company).

Exportin 1

Selinexor is an oral specific Exportin 1 (XPO1) inhibitor that activates tumor suppressor proteins (including p53) via nuclear retention. The phase III **SIENDO** trial evaluated its efficacy as maintenance therapy in advanced/recurrent EC. In the overall population, selinexor exhibits a mPFS of 5.7 months versus 3.8 months with placebo. This treatment seems to be more efficient in the TP53 wild-type (TP53wt) cohort with a PFS of 28.4 vs. 5.2 months with placebo (HR: 0.41; 95 % CI: 0.25–0.69) [30,31]. Furthermore, the benefit of selinexor was observed regardless the MMR status (TP53wt/pMMR: 39.5 vs. 4.9 months and TP53wt/dMMR : 13.1 vs. 3.7 months) [32]. The ongoing phase III **ENGOT-EN20/GOG-3083/xport-EC-042 study**, is evaluating selinexor as maintenance therapy specifically in the TP53wt population [33].

B-catenin/Wnt (CTNNB1 mutations in 30 % of EC)

Emerging evidence highlights the crucial role of β-catenin-dependent signaling in the progression of endometrioid EC. CTNNB1 mutations are generally associated with good prognosis but surprisingly with a PFS decreased [34].

DKN-01 is a monoclonal antibody targeting Dickkopf-1 (DKK-1), a negative regulator of the Wnt signaling pathway. A phase II study (NCT03395080) evaluated the efficacy of DKN-01 as monotherapy or in combination with paclitaxel in 124 patients with recurrent EC or platinum-resistant/refractory epithelial ovarian cancer [35]. The authors demonstrated promising clinical activity in EC patients with high tumoral DKK1 expression, frequently corresponding to the presence of a Wnt-activating mutation.

Another approach evaluated Porcupine (PORCN) activity inhibition, a protein involved in post-translational modifications of Wnt [36]. NCT02521844 is a clinical trial investigating the safety and tolerability of ETC-159 (PORCN inhibitor), alone or in combination with pembrolizumab, in advanced solid tumors. LGK974 is another PORCN inhibitor which is undergoing clinical evaluation in solid malignancies.

Targeted treatments not tailored to ProMisE classification

In addition to treatments evaluated across different ProMisE subgroups, some targeted strategies focus on specific various proteins.

Growth factor receptor family

Angiogenesis and proliferation are key factors in EC progression. Elevated levels of Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF) and Human Epidermal Growth Factor Receptor are correlated with poor prognosis [37]. Consequently, clinical trials targeting these VEGF/FGF/EGF pathways have been conducted (Table 4).

VEGF receptors

Bevacizumab is a recombinant monoclonal antibody which specifically binds to the VEGF. It demonstrated promising results in a phase II trial with 52 patients with advanced/recurrent EC, reporting an ORR of 13.5 %, mDoR of 6 months, mPFS of 4.17 months, and mOS of 10.55 months [38]. In the GOG209 trial including 15 patients, adding bevacizumab to chemotherapy resulted in a mPFS of 18 months, a mOS of 58 months, and an ORR of 73 % [39].

In a phase II trial, Aflibercept (VEGF Trap) demonstrated a 6-month PFS rate of 41 % in 44 patients with advanced/recurrent EC. The mPFS and mOS were 2.9 and 14.5 months, respectively [40]. However, the unfavorable toxicity profile discouraged further investigations.

Trebananib, a peptibody inhibiting the Tie2 receptor, showed minimal activity in a phase II trial (n = 32; ORR: 3.1 %) [41]. Cediranib, another Tyrosine Kinase Inhibitor (TKI) targeting VEGFR-1/− 2/− 3 and c-Kit reported a mPFS of 3.6 months and a mOS of 12.5 months in

Table 3
Clinical trials of targeted treatments tailored to NSMP profile.

Targets		Trial	Phase	Number of patients	Therapy	Main results
Exportin 1						
XPO1	XPO1 inhibitor	SIENDO	III	113	standard CT followed by maintenance by Selinexor vs. placebo	overall population: mPFS 5.7 months (HR:0.76, 95%CI 0.54-1.08) p53wt: mPFS 28.4 months
Hormonal receptors						
Estrogen	Selective estrogen receptor modulators		II		Tamoxifen	ORR: 10% mPFS: 1.9 months mOS: 8.8 months
	Competitive estrogen receptor antagonist		II		Fulvestrant	ORR: 9.4% and 11.4% (2 studies)
Progestogen	Progestin agents	GOG81	II	145	MPA	Low/High-dose regimen ORR: 25/15% mPFS: 3.2/2.5 months mOS: 11.1/7 months
	Progestin agent + selective estrogen receptor modulator	GOG119	II	61	MPA + Tamoxifen	mPFS: 3 months mOS: 13 months
	Progestin agent + selective estrogen receptor modulator	GOG153	II	61	MA alternated with Tamoxifen	ORR: 27% CRR: 21%
Aromatase + mTOR	Aromatase inhibitor + mTOR inhibitor	NCT01068249	II	38	Letrozole + Everolimus	ORR: 32% CBR: 40% Patients with CTNNB1 mutations responded well
	Aromatase inhibitor + mTOR inhibitor	NCT02730923/ VICTORIA	I /II	75	Anastrozole + Vistusertib	ORR: 24.5% mPFS: 5.2 months
Aromatase + CDK4/6	Aromatase inhibitor + CDK4/6 inhibitor	NSGO-PALEO/ENGOT-EN3	II	73	Letrozole + Palbociclib	mPFS: 8.3 months DCR: 64%
	Aromatase inhibitor + CDK4/6 inhibitor	NCT02657928	II	40	Letrozole + Ribociclib	PFS12: 55% PFS24: 35%
	Aromatase inhibitor + CDK4/6 inhibitor	NCT03675893	II	30	Letrozole + Abemaciclib	mPFS : 9.1 months PFS6: 55.6%
β-catenin / Wnt pathway						
DKK-1	Monoclonal Ab anti DKK-1	NCT03395080	II	62	DKN-01	DKK1 high/low expression ORR: 25/0% mPFS: 4.3/1.8 months mOS: 11.0/8.2 months
PORCN	Porcupine activity inhibition + monoclonal Ab anti PD-1	NCT02521844	IB	20 solid tumors	PORCN + Pembrolizumab	dose escalation: well-tolerated

HR, hazard ratio; CI, Confidence Interval; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival; MPA, medroxyprogesterone acetate; MA, megestrol acetate; CRR, complete response rate; CBR, clinical benefit rate; DCR, disease control rate; PFS12, progression-free survival at 12 months; PFS24, progression-free survival at 24 months; PFS6, progression-free survival at 6 months. PORCN, Porcupine; DKK-1, Dickkopf-1. In green, phase III trial; in red, phase II; in yellow, phase I.

the GOG 229 trial [42]. Pazopanib, a multi-targeted TKI (VEGFR 1/2/3, PDGFR −α/-β, c-Kit), has shown negligible benefit in endometrial carcinosarcoma patients (ORR: 15.8 % at 6 months) [43]. Sunitinib showed an ORR of 18.1 % and a 6-month DCR of 30 % [44].

A randomized phase II trial comparing cabozantinib plus nivolumab (anti PD-1) versus nivolumab alone has demonstrated improved ORR and PFS in the combination arm (ORR: 25 % vs. 16 %, PFS: 5.3 vs. 1.9 months, respectively) [45].

FGF Receptors (Activating FGFR2 mutations: 16 % of EC)

The crosstalk between FGFR and VEGFR pathways in tumor angiogenesis implies that elevated FGF or FGFR expression could contribute to resistance against VEGF-targeting therapies. The treatments used to inhibit its activity are multi-targeted TKIs. TKI targeting FGFR notably

Table 4
Clinical trials of agents targeting growth factor receptors.

Targets		Trial	Phase	Number of patients	Therapy	Main results
VEGFR	Monoclonal Ab anti VEGF-A + CT	GOGO209	III	1381	Bevacizumab + Carboplatin/Paclitaxel	ORR: 73% mPFS: 18 months mOS: 58 months
	TKI of VEGFR 1-2-3 / PDGFR--α/-β / c-Kit	EORTC	II	10	Pazopanib	mPFS: 2 months mOS: 8.7 months
	Monoclonal antibody anti-VEGF-A	GOG229E	II	52	Bevacizumab monotherapy	ORR: 13.5% mPFS: 4.17 months mOS: 10.6 months
	Monoclonal Ab anti VEGF-A + mTOR inhibitor		II	53	Bevacizumab + Temsirolimus	ORR: 24.5 % mPFS: 5.6 months mOS: 16.9 months
	VEGF Trap	NCT00462826	II	49	Aflibercept	mPFS: 2.9 months mOS: 14 months
	TKI of VEGFR + Ab anti-PD-1		II	76	Cabozantinib + Nivolumab	ORR: 25% mPFS: 5.3 months
	Tie Receptor + Angiopoietin 1-2 Interaction inhibition	AMG 386	II	32	Trebananib	ORR: 3.1% mPFS: 1.97 months mOS: 6.6 months
	TKI of VEGFR 1-2-3	GOG229J	II	43	Cediranib	mPFS: 3.6 months mOS: 12.5 months
	TKI of VEGFR 1-2-3 / PDGFR--α/-β		II	34	Sunitinib	ORR: 18.1 % mPFS: 3 months mOS: 19.4 months
	Multi TKI + Anti PD-1	KEYNOTE-775	III	827	Lenvatinib + Pembrolizumab vs. standard CT	Overall population - mPFS: 7.2 months / mOS: 18.3 months MMRp - mPFS: 6.6 months / mOS: 17.4 months
	Multi TKI + Anti PD-1	LEAP-001	III	842	Lenvatinib + Pembrolizumab vs. standard CT (1st line)	MMRp population: OS (HR 1.02) PFS(HR 0.99) MMRd population: ORR 72% PFS 31.8 months (HR 0.61)
FGFR	Multi TKI targeting FGFR	NCT00888173	II	43	Brivanib	ORR: 19% mPFS: 3.3 months mOS: 10.7 months
	Multi TKI targeting FGFR	NCT01225887	II	32	Nintedanib	ORR: 9% mPFS: 3.3 months mOS: 10.1 months
	Multi TKI targeting FGFR	NCT01379534	II	248	Dovitinib	mPFS mutFGFR2/wtFGFR2: 4.1 vs. 2.7 months mOS mutFGFR2/wtFGFR2: 20.2 vs. 9.3 months
	Multi TKI targeting VEGFR 1-3, FGFR1-4, PDGFRalpha, RET and KIT	NCT01111461	II	133	Lenvatinib	mPFS: 5.4 months mOS: 10.6 months
	Multi TKI + Anti PD-1	KEYNOTE-146	Ib/II	108	Lenvatinib + Pembrolizumab	MMRp - ORR: 37.2% / mPFS: 7.4 months MMRd - ORR: 63.6% / mPFS: 18.9 months
HER2	Monoclonal Ab anti HER2 + CT	NCT01367002	II	61	Trastuzumab + CT	mPFS: 12.9 months mOS: 29.6 months
	HER2-ADC (topoisomerase I inhibitor)	NCCH1615/STATICE	II	32	T-DXd	HER2 high/HER2 low group ORR: 54.5/70% mPFS: 6.2/6.7 months mOS: 13.3 months/NR
	HER2-ADC (topoisomerase I inhibitor	DESTINY-PanTumor02	II	40	T-DXd	ORR: 57.5%
	HER2-ADC (duocarmazine)	NCT04205630	II	60	SYD985 (trastuzumab duocarmazine)	mPFS: 4.3 months
	HER2-ADC (duocarmazine) + PARP inhibitor	NCT04235101	I		SYD985 + niraparib	Ongoing
	HER2-ADC (topoisomerase I inhibitor	NCT05150691	I/IIa	631 all solid tumors included	DB-1303	Ongoing

ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival; Ab, antibody; TKI, tyrosine kinase inhibitor; FGFR2mut, FGFR2 mutated; FGFR2wt, FGFR2 wild-type; MMRp, mismatch repair proficient; MMRd, mismatch repair deficient; CT, chemotherapy; T-DXd, trastuzumab deruxtecan; NR, not reached. In green, phase III trial; in red, phase II; in yellow, phase I.

such as brivanib (NCT00888173), nintedanib (NCT01225887), or dovitinib (NCT01379534) have exhibited mPFS ranging from 2.7 to 4.1 months and mOS from 9.3 to 20.2 months, with more promising results in FGFR2-mutated tumors [46–48].

The efficacy of lenvatinib, a TKI targeting VEGF1-3, FGFR1-4, PDGFRα, RET and KIT, was evaluated in several phase I-III trials in patients with advanced/recurrent EC experiencing disease progression after prior systemic treatment [49]. The phase Ib/II KEYNOTE-146/Study 111 [50] investigating pembrolizumab and lenvatinib (87 % MMRp and 10.2 % MMRd) showed ORR of 37.2 % and 63.6 % for MMRp and MMRd patients, respectively. The mPFS in the MMRp and MMRd groups was 7.4 and 18.9 months. Of note, a reduced lenvatinib dose (14 mg) showed similar efficacy.

The phase III KEYNOTE 775/Study 309 compared pembrolizumab and lenvatinib versus chemotherapy in patients with advanced EC, who had undergone at least one prior platinum-based chemotherapy. The combination demonstrated a significant increased mPFS (7.2 vs. 3.8 months) and mOS (18.3 vs. 11.4 months) in the all-comer population. The benefits were also observed in the MMRp group, with a mPFS of 6.6 months and mOS of 17.4 months. The phase III LEAP-001 study compared the combination of lenvatinib and pembrolizumab versus standard chemotherapy as first-line treatment in advanced/recurrent EC. This association did not improve PFS or OS sufficiently to meet the endpoints [51].

In 2021, FDA approved lenvatinib + pembrolizumab in MMRp metastatic EC only, after prior systemic therapy. On the other hand, EMA has also granted approval for the combination regardless of MMR status.

HER2/EGF receptors

EGFR overexpression has been detected in 50–80 % of EC patients, correlating with adverse clinical prognosis. Cetuximab (monoclonal antibody specifically directed against EGFR), lapatinib (dual reversible TKI of EGFR and HER2), gefitinib and erlotinib (EGFR TKIs) have shown good tolerance but limited clinical benefit when used as monotherapy in advanced/recurrent EC [52–55].

HER2 is a transmembrane receptor belonging to the EGFR family, playing a crucial role in regulating tumor cell proliferation, differentiation, and apoptosis; it is also linked to advanced stages [56].

A phase II trial (NCT01367002) combining chemotherapy and trastuzumab significantly improved PFS (12.9 vs. 8.0 months) and OS (29.6 vs. 24.4 months) compared to chemotherapy alone in advanced/recurrent HER2-positive serous EC [57]. Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate (ADC) selectively targets HER2, inducing cell death through topoisomerase I inhibition, with potent cytotoxic effects on neighboring cells regardless of HER2 expression [58]. In the phase II STATICE study, T-DXd showed promising efficacy in HER2-expressing uterine carcinosarcoma patients who received prior standard chemotherapy. The ORRs were 54.5 % and 70.0 % in the HER2-high and HER2-low groups, respectively, and mPFS of 6.2 and 6.7 months. In the phase II DESTINY-PanTumor02 (NCT04482309) trial, preliminary results have shown a particularly high response rate of 57.5 % in EC (84.6 % in HER2 3 + and 47.1 % in HER2 2 +) [59].

Trastuzumab duocarmazine is a novel ADC targeting HER2 combining trastuzumab with duocarmazine, a DNA alkylating agent. In a dose-expansion phase I study, 13 patients with EC were included. Among them, five exhibited a PR (39 %) with a PFS of 4.3 months [60]. Several phase I-II trials are currently underway to assess its efficacy in advanced/recurrent EC and/or solid tumors (NCT04205630 and NCT04235101). A phase I trial is also ongoing to investigate the combination of trastuzumab duocarmazine with niraparib in HER2-positive solid tumors (NCT04235101). DB-1303, an ADC combining an anti-HER2 antibody with a DNA topoisomerase I inhibitor, is currently being evaluated, notably in EC, within a phase I/IIa study.

Signaling pathways

PI3K/AKT/mTOR

Loss of Phosphatase and Tensin Homolog (PTEN) and activation of PIK3CA are the most common alterations in EC, leading to constant AKT activation and mammalian target of rapamycin (mTOR) overexpression, promoting cell proliferation, survival, and tumor progression. Targeting the three pivotal components, mTOR, AKT, and PI3K, either individually or through combined inhibition, is promising [61] (Table 5).

Inhibitors targeting the PI3K/AKT/mTOR signaling pathway were initially tested as monotherapy in recurrent/metastatic EC.

PIK3CA (pilaralisib, apitolisib, and BKM120) [62–64], AKT (MK2206) [65], and mTOR (ridaforolimus and sapanisertib) inhibitors [66–68] did not achieve their objectives, either due to limited antitumor activity or to an unmanageable toxicity profile. Only everolimus, an oral rapamycin analog, showed promising results in phase II studies [69], attributable to its selectivity for mTORC1 and low affinity for mTORC2, resulting in fewer adverse effects, a higher tolerable dose, and extended treatment duration.

Dual inhibitors (LY3023414 and gedatolisib) [70,71] target the signaling pathway at two levels, upstream (PI3K) and downstream (mTOR), but exhibited modest effects with a manageable safety profile in phase II trials.

Subsequently, these inhibitors have been tested in combination with other treatments.

The mTOR pathway plays a role in regulating angiogenesis by upregulating hypoxic stress response genes such as VEGF. However, the combination of bevacizumab and temsirolimus (mTOR inhibitor) reported modest efficacy and significant toxicity [72].

Overactivation of the mTOR pathway can induce tumor cell resistance to HT [73]. Two studies investigated the effect of MA with or without tamoxifen in combination with temsirolimus and AKT inhibitor (ipatasertib). Both were discontinued due to safety concerns. The combination of everolimus, letrozole, and metformin (antidiabetic agent with mTOR inhibitory activity) showed significant clinical benefit (50 %) and ORR (28 %) in women with advanced/recurrent EC [74,75].

There is a crosstalk between the mTOR and Ras/MEK/ERK signaling pathways that allows compensation for the inactivation of one pathway by the activation of the other [76]. The combination of AKT (uprosertib) and MEK (trametinib) inhibitors showed low clinical activity at tolerable doses [77].

In vitro studies suggest PI3K inhibition may sensitize PTEN mutated cells to PARPi. Ongoing trials in recurrent EC explore the combination of AKT inhibitors (vistusertib or capivasertib) with PARPi (olaparib), but also another PARPi (niraparib) with a PIK3CA inhibitor (copanlisib) in [78].

A phase III study evaluating the efficacy of the chemotherapy/metformin combination is currently ongoing.

KRAS (mutations in 10–30 % of EC)

KRAS mutations are found close to areas of endometrial hyperplasia, suggesting their role in early tumorigenesis/progression [79].

CodeBreaK 101 (NCT04185883) is an ongoing phase Ib/II study evaluating safety and efficacy of sotorasib (KRAS p.G12C covalent inhibitor) in monotherapy or combination with other antitumoral therapies in advanced solid tumors harboring this KRAS mutation. Sotorasib has demonstrated encouraging results in a heavily pretreated population with two EC patients included [80] (Table 5).

NCT01935934 is a single-arm trial testing cabozantinib, a multiple TKI (VEGFR2, c-MET, and RET), in 102 women with pretreated recurrent/metastatic EC. In the endometrioid/serous cohorts, the ORR, 12-week PFS, and mPFS were 14/12 %, 67/56 %, and 4.8/4 months, respectively. The benefits increased in patients with concurrent KRAS and PTEN or PIK3CA mutations (ORR of 25 % and 12-week PFS of 83 %) [81] (Table5).

Table 5
Clinical trials of signaling pathway and synthetic lethality targeting agents.

Targets		Trial	Phase	Number of patients	Therapy	Main results
Signaling pathway						
mTOR	mTOR inhibitor rapamycin	NCT00739830	II	130	Ridaforolimus	16-week PFS: 48% 24-week PFS: 38% mPFS: 3.6 months
	mTOR inhibitor rapamycin	AGO-GYN8	II	22	Temsirolimus	PFS6: 33.4% mPFS: 3 months OS: 21.3 months
	mTORC1/2 inhibitor + CT	NCT02725268	II	180	Sapanisertib + Paclitaxel	mPFS: 5.6 months mFU: 17.2 months
AKT	Allosteric inhibitor of AKT1, 2 and 3	NCT03043001	II	14	MK2206	With/without PIK3CA mutation mPFS: 1.7/2.5 months mOS: 8.4/11.1 months
	AKT inhibitor GSK2141795 + MEK inhibitor		I	22	Uprosertib + Trametinib	High level of toxicity = STOP
	Oral Akt inhibitor + Progestagen	NRG-GY028	IB/II	Target: 96	Ipatasertib + MA	Suspended
PI3K	PI3K inhibitor (SAR245408; XL147)		II	67	Pilaralisib	PFS>6 months: 11.9% Minimal antitumor activity Favorable safety profile
	Pure PI3K inhibitor		II	40	BKM120	Minimal antitumor activity Unfavorable safety profile
PI3K / mTOR	Dual PI3K/mTOR inhibitor	MAGGIE	II	56	Apitolisib	Poor tolerability, especially in diabetic patients
KRAS pathway	Multiple tyrosine kinase inhibitor	NCT01935934	II	102	Cabozantinib	KRASmut Endometrioid histology 12-week PFS: 67% mPFS: 4.8 months KRASmut Serous histology 12-week PFS: 56% mPFS: 4.0 months
	KRAS p.G12C inhibitor	CodeBreak 101	IB/II	129 (2 EC)	Sotorasib	All solid cancers combned : In 1st line setting ORR 73% In 2nd line setting ORR 55%
Synthetic Lethality						
HRD	HRD	UTOLA	IIb	147	Olaparib as maintenance vs. placebo	mPFS: 5.4 vs. 3.6 months (HR: 0.59, p = 0.02)
ARID1A	ARID1A	ATARI	II	Min 40 Max 115	Olaparib	On going
	ATR inhibitor	NCT05523440	Ib		Tuvusertib	On going
PTEN	PTEN mutated	ENDOLA	I/II	35	Olaparib + metronomic cyclophosphamide + metformin	mPFS : 8 months

PFS, progression-free survival; mFU, median follow-up; mPFS, median progression-free survival; PFS6, progression-free survival at 6 months; mOS, median overall survival; MA, megestrol acetate; ORR, overall response rate; CT, chemotherapy. In red, phase II trial; in yellow, phase I.

Synthetic lethality

Tumor progression is generally influenced by DNA damage that can be generated by endogenous and exogenous factors. Cells possess multiple DNA repair mechanisms that can be compromised in tumor cells. Increasingly, cancer therapies are being developed based on the principle of synthetic lethality, where the combination of two genetic alterations, typically tolerable individually, becomes lethal for the cell when both alterations occur simultaneously [i.e: use of PARPi in Homologous Recombination Deficiency (HRD) tumor] (Table 5).

HRD

HRD is a defect in the DNA repair process which causes a high degree of genomic instability. HR repair uses the complementary DNA strands of the nearby sister chromatid to repair double-strand breaks with high fidelity [82]. **UTOLA** is a phase IIb, randomized, double-blind trial which assessed the efficacy of olaparib or placebo as maintenance therapy after platinum-based chemotherapy in 147 patients with advanced/recurrent EC. In the HRD-positive tumors (52 %), mPFS was statistically higher with olaparib: 5.4 vs. 3.6 months with placebo (HR: 0.59, p = 0.02) regardless of p53 status. For the 46 patients with CR to previous chemotherapy, mPFS reached 8.8 months in the olaparib vs. 3.8 months in the placebo arms.

AT rich interactive domain 1A (ARID1A) (mutations in 46 % of EC)

ARID1A gene encodes the BAF250a protein, a subunit of the SWItch/Sucrose Non Fermentable protein complex involved in chromatin structure modification and gene expression regulation [83,84].

Despite the observed synthetic lethality between dasatinib (targeting signaling pathways such as c-kit, Bcr-Abl, src, and PDGFR) and ARID1A mutations in ovarian clear cell carcinomas (CCC), dasatinib monotherapy has failed to demonstrate efficacy in the treatment of ARID1A-mutant ovarian and endometrial CCC [85].

Recent studies have shown that ARID1A is implicated in DNA repair via HR. Inhibition of key players such as EZH2, PARP, ATR and cell cycle modulators is being explored as potential innovative options [86].

Hence, clinical studies assessing the efficacy of rucaparib (PARPi), in combination with bevacizumab, has exhibited clinical benefit for cancer patients with ARID1A mutations [87]. Another ongoing phase II trial is investigating the efficacy of niraparib alone or combined with bevacizumab in recurrent EC and/or ovarian cancer carrying ARID1A mutations (NCT05523440).

The phase II ATARI study evaluated the efficacy and tolerability of ceralasertib, an ATR inhibitor, in patients with CCC (endometrial and ovarian). Grade 3 + toxicities were reported in approximately 45 % of patients but leading to treatment discontinuation in less than 10 %. Preliminary results demonstrated a relevant efficacy of ceralasertib regardless of ARID1A status [88]. A phase 1b study (NCT05950464) is underway to assess the safety and optimal dosage of tuvusertib, an ATR-related inhibitor (M1774), in combination with the bromo- and extra-terminal domain (BET) inhibitor (ZEN00-3694).

PTEN

PTEN plays a role in DNA repair by interacting with proteins like ATM, BRCA1, and Rad51, ensuring genome integrity. Understanding its DNA repair function has prompted research into PARPi for PTEN loss tumors. However, several phases Ib-II trials testing PARPis and ICI combinations failed to meet their efficacy threshold [89,90].

In contrast, the phase I/II ENDOLA trial evaluating the triple combination of olaparib, metronomic cyclophosphamide, and metformin exhibited a safety profile and demonstrated a non-progression rate of 61.5 % at 10 weeks and a mPFS of 5.1 months [91].

While there is currently limited retrospective data available for EC, and rigorous patient selection criteria in clinical studies remain imperative, synthetic lethality emerges as a promising approach. Its expanding investigation across various malignancies, including breast, ovarian, and prostate cancers, underscores its potential. Notably, its selective mechanism offers the advantage of mitigating adverse effects, while its combinatory potential with adjunctive therapies presents a strategy to circumvent resistance mechanisms.

Metabolism pathways

Tryptophan catabolism (increased expression of IDO1, decreased levels of tryptophan, and tryptophan metabolites) exerts an immunosuppressive effect. Three enzymes IDO1, IDO2, and tryptophan 2,3-dioxygenase (TDO)—are involved in the degradation of tryptophan into downstream metabolites [92].

Thus, IDO1 represents an attractive target in solid tumors. A phase I/II trial (ECHO-202/KEYNOTE-037, NCT02178722) investigated tolerability and efficacy of pembrolizumab and epacadostat—an IDO1 inhibitor—in selected advanced cancers, including EC. Preliminary results indicated encouraging antitumor activity [93]. Another phase II trial (NCT04106414) evaluated the benefits of nivolumab with or without linrodostat, another IDO1 inhibitor, but the trial was closed due to futility [94]. Finally, in the PODIUM-204 trial, as previously mentioned, the efficacy of retifanlimab is being assessed in combination with epacadostat [10].

Folate (vitamin B9) plays an essential role in cellular metabolism and proliferation. Inhibition of its receptor, the folate receptor (FRα), is an increasingly studied approach in oncology. Many cancers overexpress FRα, including EC (40–90 % overexpression) [95]. A phase I/II study is underway to evaluate the effectiveness of the anti-FRα rinatabart sesutecan, coupled with a topoisomerase 1 inhibitor, in patients with locally advanced and/or metastatic solid tumors. Of the 10 patients already included, two had EC [96]. Mirvetuximab soravtansine (MIRV), an innovative ADC targeting FRα coupled with DM4 (a potent derivative of Maytansine with anti-microtubule activity), could be a promising therapeutic option [97]. Preclinical evidence has shown that MIRV can induce infiltration of T cells within the tumor, thereby enhancing the effectiveness of immunotherapy. A single-arm trial is investigating the combination of MIRV and pembrolizumab with promising results (6.3 % CR and 31.3 % PR).

Conclusion

In the past, patients with advanced/recurrent EC faced limited therapeutic options. The emergence of targeted therapies, HT and immunotherapies indicates significant progresses.

Numerous targeted therapies have been tested in EC, providing a comprehensive catalog of molecules to use according to ProMisE subgroups or tumor protein expression patterns. Precise patient selection based on the molecular profile of the tumor is a crucial element for optimizing the clinical efficacy of treatments, reducing side effects and sample heterogeneity. Clinical studies have failed to meet their objectives due to inadequate patient selection as well as the polyclonal nature of tumors, resulting in resistance and compensatory mechanisms. To counteract this, an increasing number of studies are now opting to combine multiple treatments.

Among the clinical trials, several promising therapies distinguish themselves due to their efficacy. MMRd tumors respond significantly to immunotherapy. Pooled data from the 4 studies (RUBY, DUO-E, AtTEND, and NRG-GY018) involving 2320 patients confirm a significant improvement in survival outcomes when immunotherapy is combined with chemotherapy in first-line treatments. The MMRd subgroup exhibits a pronounced PFS benefits (n = 560; HR 0.33), but it is also evident in the MMRp group (n = 1757; HR 0.74) [98]. The addition of PARPi to immunotherapy and chemotherapy showed significant benefit in the all-comer population, raising the question of its role in MMRp population. This group is highly heterogeneous; thus, it would be interesting to analyze and determine whether a particular subgroup stands out and responds effectively to immunotherapy. Other questions, including who are the 10 % of patients progressing during chemotherapy + immunotherapy, who are the 30–40 % of patients progressing within 12 months even in MMRd population but also the optimal duration of immunotherapy, remain unanswered.

In summary, a comprehensive understanding of the molecular patterns of origin, relapse, and resistance of EC is expected to lead to personalized treatment. The ProMisE classification supports the use of immunotherapy monotherapy (MMRd), immunotherapy in combination with PARPi (MMRp/p53abn), treatment de-escalation (POLEmut), selinexor (p53wt) and combination of hormonal therapy and CDK4/6 inhibitors (NSMP tumors with hormonal receptors). The MMRp

population is heterogeneous and further histological and molecular analyses will enable tumor characterization and specific targeting, either as monotherapy or in combination with other treatments.

EC is also characterized by a high TMB, and therefore, an altered protein expression profile. Protein overexpression could be an interesting target for the use of ADC as trastuzumab deruxtecan (HER2). New ADCs are currently being tested in EC, such as in IMMU-132 or MK-2870–005 studies, which evaluate the efficacy of sacituzumab govitecan, an anti-Trop-2 ADC conjugated to SN-38, the active metabolite of irinotecan.

CRediT authorship contribution statement

Alixe Salmon & Alizée Lebeau: Conceptualization, Investigation, Formal analysis, Methodology, Visualization, Validation, Writing - original draft, Writing - review & editing. **Sylvie Streel:** Conceptualization, Investigation, Formal analysis, Methodology, Validation, Writing - original draft, Writing - review & editing. **Adriane Dheur, Sophie Schoenen, Frédéric Goffin, Elodie Gonne, Frédéric Kridelka:** Resources, Validation, Writing – editing. **Athanasios Kakkos & Christine Gennigens:** Conceptualization, Formal analysis, Methodology, Validation, Resources, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christine Gennigens = All support for the present manuscrit: no disclosures. Grant/contracts: Astra-Zeneca, GSK, Deciphera. Consulting fees: Ipsen, GSK, MSD. Honoraria for lectures: MSD, BMS, Ipsen, Pfizer, Pharmamar, Astra-Zeneca, GSK. Support for meetings and/or travel: Ipsen, Pharmamar, Pfizer, MSD, GSK, Astra-Zeneca. Participation on a data safety monitoring board or advisory board: MSD, BMS, Ipsen, Astra-Zeneca. GSK, Eisai. Others authors – No conflict of interest.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin mai 2021;71(3):209–49.

[2] Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D, et al. Endometrial cancer. Nat Rev Dis Primer 2021;7(1):88.

[3] Restaino S, Paglietti C, Arcieri M, Biasioli A, Della Martina M, Mariuzzi L, et al. Management of patients diagnosed with endometrial cancer: comparison of guidelines. Cancers 2023;15(4):1091.

[4] Garmezy B, Gheeya J, Lin HY, Huang Y, Kim T, Jiang X, et al. Clinical and molecular characterization of POLE mutations as predictive biomarkers of response to immune checkpoint inhibitors in advanced cancers. JCO Precis Oncol déc 2022; 6:e2100267.

[5] Wang F, Zhao Q, Wang YN, Jin Y, He MM, Liu ZX, et al. Evaluation of POLE and POLD1 mutations as biomarkers for immunotherapy outcomes across multiple cancer types. JAMA Oncol Oct 2019;5(10):1504–6.

[6] Oaknin A, Gladieff L, Martínez-García J, Villacampa G, Takekuma M, Giorgi UD, et al. Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial. Lancet 6 janv 2024;403(10421):31–43.

[7] Oaknin A, Gilbert L, Tinker AV, Brown J, Mathews C, Press J, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET—a phase I, single-arm study. J Immunother Cancer 21 janv 2022;;10(1): e003777.

[8] Lakhani N, Cosman R, Banerji U, Rasco D, Tomaszewska-Kiecana M, Garralda E, et al. A first-in-human phase I study of the PD-1 inhibitor, retifanlimab (INCMGA00012), in patients with advanced solid tumors (POD1UM-101). ESMO Open 21 févr 2024;9(4):102254.

[9] Berton D, Pautier P, Lorusso D, Gennigens C, Gladieff L, Kryzhanivska A, et al. Antitumor activity and safety of the PD-1 inhibitor retifanlimab in patients with recurrent microsatellite instability-high or deficient mismatch repair endometrial cancer: Final safety and efficacy results from cohort H of the POD1UM-101 phase I study. Gynecol Oncol 2024;186:191-8.

[10] Slomovitz B, Monk B, Moxley K, Ghali N, Sokol JF, Tian C, et al. A phase 2 umbrella study of retifanlimab (INCMGA00012) alone or in combination with other therapies in patients with advanced or metastatic endometrial cancer (POD1UM-204, GOG 3038, ENGOT-en12/NOGGO). J Immunother Cancer [Internet]. 1 nov 2020 [cité 19 avr 2024];8(Suppl 3). Disponible sur: https://jitc.bmj.com/content/8/Suppl_3/A212.

[11] Powell MA, Bjørge L, Willmott L, Novák Z, Black D, Gilbert L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Ann Oncol Off J Eur Soc Med Oncol 2024;10. S0923–7534(24)00721-X.

[12] Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. N Engl J Med 8 juin 2023;388(23):2159–70.

[13] Westin SN, Moore K, Chon HS, Lee JY, Thomes Pepin J, Sundborg M, et al. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the phase III DUO-E trial. J Clin Oncol 20 janv 2024;42(3):283–99.

[14] Mirza MR, Coleman RL, Hanker L, Slomovitz B, Valabrega G, DeMars L, et al. ENGOT-EN6/GOG-3031/NSGO-CTU-RUBY part 2: A phase III, randomized, double-blind, study of dostarlimab + carboplatin-paclitaxel followed by dostarlimab + niraparib versus placebo (PBO) + carboplatin-paclitaxel followed by PBO in recurrent or advanced endometrial cancer (EC). Ann Oncol. 1 sept 2021; 32:S770-1.

[15] Garg K, Leitao MM, Wynveen CA, Sica GL, Shia J, Shi W, et al. p53 overexpression in morphologically ambiguous endometrial carcinomas correlates with adverse clinical outcomes. Mod Pathol janv 2010;23(1):80–92.

[16] Tresa A, Sambasivan S, Rema P, Dinesh D, Sivaranjith J, Nair SP, et al. Clinical profile and survival outcome of endometrial cancer with p53 mutation. Indian J Surg Oncol sept 2022;13(3):580–6.

[17] Liu J, Oza AM, Colombo N, Oaknin A. ADAGIO: a phase IIb international study of the Wee1 inhibitor adavosertib in women with recurrent or persistent uterine serous carcinoma. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc 2022;32(1): 89–92.

[18] Meric-Bernstam F, Chalsani P, Mamdani H, Zheng C, Viana M, Lambersky R, et al. Abstract CT029: Safety and clinical activity of single-agent ZN-c3, an oral WEE1 inhibitor, in a phase 1 trial in subjects with recurrent or advanced uterine serous carcinoma (USC). Cancer Res 2022;82(12_Supplement):CT029.

[19] Muñoz-Fontela C, Mandinova A, Aaronson SA, Lee SW. Emerging roles of p53 and other tumour-suppressor genes in immune regulation. Nat Rev Immunol 2016;16 (12):741–50.

[20] Pignata S, Califano D, Lorusso D, Arenare L, Bartoletti M, De Giorgi U, et al. MITO END-3: efficacy of avelumab immunotherapy according to molecular profiling in first-line endometrial cancer therapy. Ann Oncol [Internet]. 3 mai 2024 [cité 14 juin 2024]; Disponible sur: https://www.sciencedirect.com/science/article/pii/S0923753424001285.

[21] Li L, Ng DSW, Mah WC, Almeida FF, Rahmat SA, Rao VK, et al. A unique role for p53 in the regulation of M2 macrophage polarization. Cell Death Differ 2015;22 (7):1081–93.

[22] Wellenstein MD, Coffelt SB, Duits DEM, van Miltenburg MH, Slagter M, de Rink I, et al. Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis. Nature 2019;572(7770):538–42.

[23] Zhang WW, Li L, Li D, Liu J, Li X, Li W, et al. The first approved gene therapy product for cancer Ad-p53 (Gendicine): 12 years in the clinic. Hum Gene Ther févr 2018;29(2):160–79.

[24] Su X, Chen WJ, Xiao SW, Li XF, Xu G, Pan JJ, et al. Effect and safety of recombinant adenovirus-p53 transfer combined with radiotherapy on long-term survival of locally advanced cervical cancer. Hum Gene Ther 2016;27(12):1008–14.

[25] Ray-Coquard I, Monk BJ, Lorusso D, Mahdi H, Upadhyay V, Graul R, et al. The promise of combining CDK4/6 inhibition with hormonal therapy in the first-line treatment setting for metastatic or recurrent endometrial adenocarcinoma. Int J Gynecol Cancer 2023;33(12):1943–9.

[26] Heudel P, Frenel JS, Dalban C, Bazan F, Joly F, Arnaud A, et al. Safety and efficacy of the mTOR inhibitor, vistusertib, combined with anastrozole in patients with hormone receptor-positive recurrent or metastatic endometrial cancer: The VICTORIA Multicenter, Open-label, Phase 1/2 Randomized Clinical Trial. JAMA Oncol 2022;8(7):1001-9.

[27] Mirza MR, Bjørge L, Marmé F, Christensen RD, Gil-Martin M, Auranen A, et al. A randomised double-blind placebo-controlled phase II trial of palbociclib combined with letrozole (L) in patients (pts) with oestrogen receptor-positive (ER +) advanced/recurrent endometrial cancer (EC): ESMO Virtual Congress 2020. Ann Oncol 2020;31(Suppl. 4):S1160.

[28] Colon-Otero G, Zanfagnin V, Hou X, Foster NR, Asmus EJ, Wahner Hendrickson A, et al. Phase II trial of ribociclib and letrozole in patients with relapsed oestrogen receptor-positive ovarian or endometrial cancers. ESMO Open Oct 2020;5(5): e000926.

[29] Konstantinopoulos PA, Lee EK, Xiong N, Krasner C, Campos S, Kolin DL, et al. A phase II, two-stage study of letrozole and abemaciclib in estrogen receptor-positive recurrent endometrial cancer. J Clin Oncol Off J Am Soc Clin Oncol 2023; 41(3):599–608.

[30] Bogani G, Monk BJ, Coleman RL, Vergote I, Oakin A, Ray-Coquard I, et al. Selinexor in patients with advanced and recurrent endometrial cancer. Curr Probl Cancer 2023;47(6):100963.

[31] Makker V, Perez-Fidalgo JA, Bergamini A, Spitz DL, Van Gorp T, Sehouli J, et al. Randomized phase III study of maintenance selinexor versus placebo in endometrial cancer (ENGOT-EN5/GOG-3055/SIENDO): Impact of subgroup analysis and molecular classification. J Clin Oncol 2022;40(16_suppl):5511.

[32] Makker V, Perez-Fidalgo JA, Valabrega G, Hamilton E, Gorp TV, Sehouli J, et al. Long-term follow-up of efficacy and safety of selinexor maintenance treatment in

patients with TP53wt advanced or recurrent endometrial cancer: A subgroup analysis of the ENGOT-EN5/GOG-3055/SIENDO study. Gynecol Oncol 2024;185:202-11.
[33] Vergote I, Mirza MR, Coleman RL, Perez-Fidalgo JA, Monk BJ, Valabrega G, et al. ENGOT-EN20/GOG-3083/xport-EC-042: A phase 3, randomized, placebo-controlled, double-blind, multicenter trial of selinexor in maintenance therapy after systemic therapy for patients with P53 wild-type, advanced or recurrent endometrial carcinoma. J Clin Oncol 2023;41(16_suppl):TPS5627-TPS5627.
[34] Yoon H, Suh DH, Kim K, No JH, Kim YB, Kim H. Evaluation of prognostic potential of β-catenin and L1CAM expression according to endometrial cancer risk group. Gynecol Oncol 2024;184:132-8.
[35] Arend R, Dholakia J, Castro C, Matulonis U, Hamilton E, Jackson CG, et al. DKK1 is a predictive biomarker for response to DKN-01: Results of a phase 2 basket study in women with recurrent endometrial carcinoma. Gynecol Oncol 2023;172:82-91.
[36] Madan B, Ke Z, Harmston N, Ho SY, Frois AO, Alam J, et al. Wnt addiction of genetically defined cancers reversed by PORCN inhibition. Oncogene 2016;35(17):2197-207.
[37] Roškar L, Roškar I, Rižner TL, Smrkolj Š. Diagnostic and therapeutic values of angiogenic factors in endometrial cancer. Biomolecules 2022;12(1):7.
[38] Aghajanian C, Sill MW, Darcy KM, Greer B, McMeekin DS, Rose PG, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol Off J Am Soc Clin Oncol 2011;29(16):2259-65.
[39] Simpkins F, Drake R, Escobar PF, Nutter B, Rasool N, Rose PG. A phase II trial of paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma (EMCA). Gynecol Oncol 2015;136(2):240–5.
[40] Coleman RL, Sill MW, Lankes HA, Fader AN, Finkler NJ, Hoffman JS, et al. A phase II evaluation of aflibercept in the treatment of recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2012;127(3):538–43.
[41] Moore KN, Sill MW, Tenney ME, Darus CJ, Griffin D, Werner TL, et al. A phase II trial of trebananib (AMG 386; IND#111071), a selective angiopoietin 1/2 neutralizing peptibody, in patients with persistent/recurrent carcinoma of the endometrium: An NRG/Gynecologic Oncology Group trial. Gynecol Oncol 2015;138(3):513–8.
[42] Bender D, Sill MW, Lankes HA, Reyes HD, Darus CJ, Delmore JE, et al. A phase II evaluation of cediranib in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol 2015;138(3):507–12.
[43] Campos SM, Brady WE, Moxley KM, O'Cearbhaill RE, Lee PS, DiSilvestro PA, et al. A phase II evaluation of pazopanib in the treatment of recurrent or persistent carcinosarcoma of the uterus: a gynecologic oncology group study. Gynecol Oncol 2014;133(3):537–41.
[44] Castonguay V, Lheureux S, Welch S, Mackay HJ, Hirte H, Fleming G, et al. A phase II trial of sunitinib in women with metastatic or recurrent endometrial carcinoma: a study of the Princess Margaret, Chicago and California Consortia. Gynecol Oncol 2014;134(2):274–80.
[45] Lheureux S, Matei D, Konstantinopoulos PA, Block MS, Jewell A, Gaillard S, et al. A randomized phase II study of cabozantinib and nivolumab versus nivolumab in recurrent endometrial cancer. J Clin Oncol 2020;38(15_suppl):6010.
[46] Powell MA, Sill MW, Goodfellow PJ, Benbrook DM, Lankes HA, Leslie KK, et al. A phase II trial of brivanib in recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study. Gynecol Oncol Oct 2014;135(1):38–43.
[47] Dizon DS, Sill MW, Schilder JM, McGonigle KF, Rahman Z, Miller DS, et al. A phase II evaluation of nintedanib (BIBF-1120) in the treatment of recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study. Gynecol Oncol 2014;135(3):441–5.
[48] Konecny GE, Finkler N, Garcia AA, Lorusso D, Lee PS, Rocconi RP, et al. Second-line dovitinib (TKI258) in patients with FGFR2-mutated or FGFR2-non-mutated advanced or metastatic endometrial cancer: a non-randomised, open-label, two-group, two-stage, phase 2 study. Lancet Oncol 2015;16(6):686–94.
[49] Vergote I, Powell MA, Teneriello MG, Miller DS, Garcia AA, Mikheeva ON, et al. Second-line lenvatinib in patients with recurrent endometrial cancer. Gynecol Oncol 2020;156(3):575–82.
[50] Makker V, Aghajanian C, Cohn AL, Romeo M, Bratos R, Brose MS, et al. A phase Ib/II study of lenvatinib and pembrolizumab in advanced endometrial carcinoma (Study 111/KEYNOTE-146): long-term efficacy and safety update. J Clin Oncol Off J Am Soc Clin Oncol 2023;41(5):974-9.
[51] Marth C, Tarnawski R, Tyulyandina A, Pignata S, Gilbert L, Kaen D, et al. Phase 3, randomized, open-label study of pembrolizumab plus lenvatinib versus chemotherapy for first-line treatment of advanced or recurrent endometrial cancer: ENGOT-en9/LEAP-001. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc 2022;32(1):93–100.
[52] Slomovitz BM, Chelariu-Raicu A, Schmeler KM, Lu KH, Gershenson DM, Wolf J, et al. Phase 2 study of cetuximab (Erbitux) in patients with progressive or recurrent endometrial cancer. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc Nov 2020;30(11):1733–7.
[53] Leslie KK, Sill MW, Lankes HA, Fischer EG, Godwin AK, Gray H, et al. Lapatinib and potential prognostic value of EGFR mutations in a Gynecologic Oncology Group phase II trial of persistent or recurrent endometrial cancer. Gynecol Oncol Nov 2012;127(2):345–50.
[54] Leslie KK, Sill MW, Fischer E, Darcy KM, Mannel RS, Tewari KS, et al. A phase II evaluation of gefitinib in the treatment of persistent or recurrent endometrial cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2013;129(3):486–94.
[55] Oza AM, Eisenhauer EA, Elit L, Cutz JC, Sakurada A, Tsao MS, et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. J Clin Oncol Off J Am Soc Clin Oncol 2008;26(26):4319-25.
[56] Morrison C, Zanagnolo V, Ramirez N, Cohn DE, Kelbick N, Copeland L, et al. HER-2 is an independent prognostic factor in endometrial cancer: association with outcome in a large cohort of surgically staged patients. J Clin Oncol Off J Am Soc Clin Oncol 2006;24(15):2376-85.
[57] Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (Stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis. Clin Cancer Res Off J Am Assoc Cancer Res 2020;26(15):3928-35.
[58] Nishikawa T, Hasegawa K, Matsumoto K, Mori M, Hirashima Y, Takehara K, et al. Trastuzumab deruxtecan for human epidermal growth factor receptor 2-expressing advanced or recurrent uterine carcinosarcoma (NCCH1615): the STATICE trial. J Clin Oncol Off J Am Soc Clin Oncol 2023;41(15):2789-99.
[59] Meric-Bernstam F, Makker V, Oaknin A, Oh DY, Banerjee S, González-Martín A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol Off J Am Soc Clin Oncol 2024;42(1):47-58.
[60] Banerji U, van Herpen CML, Saura C, Thistlethwaite F, Lord S, Moreno V, et al. Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study. Lancet Oncol 2019;20(8):1124–35.
[61] Slomovitz BM, Coleman RL. The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. Clin Cancer Res Off J Am Assoc Cancer Res 2012;18(21):5856-64.
[62] Matulonis U, Vergote I, Backes F, Martin LP, McMeekin S, Birrer M, et al. Phase II study of the PI3K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma. Gynecol Oncol févr 2015;136(2):246–53.
[63] Makker V, Recio FO, Ma L, Matulonis U, Lauchle JO, Parmar H, et al. A Multicenter, single-arm, open-label, phase 2 study of apitolisib (GDC-0980) for the treatment of recurrent or persistent endometrial carcinoma (MAGGIE study). Cancer 2016;122(22):3519-28.
[64] Heudel PE, Fabbro M, Roemer-Becuwe C, Kaminsky MC, Arnaud A, Joly F, et al. Phase II study of the PI3K inhibitor BKM120 in patients with advanced or recurrent endometrial carcinoma: a stratified type I–type II study from the GINECO group. Br J Cancer 2017;116(3):303-9.
[65] Myers AP, Konstantinopoulos PA, Barry WT, Luo W, Broaddus RR, Makker V, et al. Phase II, 2-Stage, 2-Arm, PIK3CA mutation stratified trial of MK-2206 in recurrent endometrial cancer. Int J Cancer 2020;147(2):413-22.
[66] Oza AM, Pignata S, Poveda A, McCormack M, Clamp A, Schwartz B, et al. Randomized phase II trial of ridaforolimus in advanced endometrial carcinoma. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(31):3576-82.
[67] Tsoref D, Welch S, Lau S, Biagi J, Tonkin K, Martin LA, et al. Phase II study of oral ridaforolimus in women with recurrent or metastatic endometrial cancer. Gynecol Oncol Nov 2014;135(2):184–9.
[68] Han SN, Oza A, Colombo N, Oaknin A, Raspagliesi F, Wenham RM, et al. A randomized phase 2 study of sapanisertib in combination with paclitaxel versus paclitaxel alone in women with advanced, recurrent, or persistent endometrial cancer. Gynecol Oncol Nov 2023;178:110–8.
[69] Slomovitz BM, Lu KH, Johnston T, Coleman RL, Munsell M, Broaddus RR, et al. A Phase II study of oral mammalian target of rapamycin (mTOR) inhibitor, everolimus, in patients with recurrent endometrial carcinoma. Cancer 2010;116(23):5415-9.
[70] Rubinstein MM, Hyman DM, Caird I, Won H, Soldan K, Seier K, et al. Phase 2 study of LY3023414 in patients with advanced endometrial cancer harboring activating mutations in the PI3K pathway. Cancer 2020;126(6):1274-82.
[71] Del Campo JM, Birrer M, Davis C, Fujiwara K, Gollerkeri A, Gore M, et al. A randomized phase II non-comparative study of PF-04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer. Gynecol Oncol 2016;142(1):62–9.
[72] Alvarez EA, Brady WE, Walker JL, Rotmensch J, Zhou XC, Kendrick JE, et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2013;129(1):22–7.
[73] Stringer EM, Fleming GF. Hormone therapy plus mTOR inhibitors in the treatment of endometrial carcinoma. Oncol Hematol Rev 2013;9(1):41–4.
[74] Slomovitz BM, Filiaci VL, Walker JL, Taub MC, Finkelstein KA, Moroney JW, et al. A randomized phase II trial of everolimus and letrozole or hormonal therapy in women with advanced, persistent or recurrent endometrial carcinoma: A GOG Foundation study. Gynecol Oncol 2022;164(3):481–91.
[75] Soliman PT, Westin SN, Iglesias DA, Fellman BM, Yuan Y, Zhang Q, et al. Everolimus, Letrozole, and Metformin in women with advanced or recurrent endometrioid endometrial cancer: a multi-center, single arm, phase II study. Clin Cancer Res Off J Am Assoc Cancer Res 2020;26(3):581-7.
[76] Panwar V, Singh A, Bhatt M, Tonk RK, Azizov S, Raza AS, et al. Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. Signal Transduct Target Ther 2023;8(1):1-25.
[77] Safety Lead-In of the MEK Inhibitor Trametinib in Combination with GSK2141795, an AKT Inhibitor, in Patients with Recurrent Endometrial Cancer: An NRG Oncology/GOG Study - PMC [Internet]. [cité 5 avr 2024]. Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6922584/.
[78] Santin AD, Filiaci V, Bellone S, Ratner ES, Mathews CA, Cantuaria G, et al. Phase II evaluation of copanlisib, a selective inhibitor of Pi3kca, in patients with persistent

or recurrent endometrial carcinoma harboring PIK3CA hotspot mutations: An NRG Oncology study (NRG-GY008). Gynecol Oncol Rep 2020;31:100532.
[79] Sideris M, Emin EI, Abdullah Z, Hanrahan J, Stefatou KM, Sevas V, et al. The Role of KRAS in Endometrial Cancer: A Mini-Review. Anticancer Res 2019;39(2):533–9.
[80] Hong DS, Fakih MG, Strickler JH, Desai J, Durm GA, Shapiro GI, et al. KRASG12C inhibition with sotorasib in advanced solid tumors. N Engl J Med 2020;383(13): 1207-17.
[81] Dhani NC, Hirte HW, Wang L, Burnier JV, Jain A, Butler MO, et al. Phase II trial of cabozantinib in recurrent/metastatic endometrial cancer: a study of the princess margaret, Chicago, and California Consortia (NCI9322/PHL86). Clin Cancer Res Off J Am Assoc Cancer Res 2020;26(11):2477-86.
[82] Doig KD, Fellowes AP, Fox SB. Homologous recombination repair deficiency: an overview for pathologists. Mod Pathol Off J U S Can Acad Pathol Inc 2023;36(3): 100049.
[83] Guan B, Wang TL, Shih IM. ARID1A, a factor that promotes formation of SWI/SNF-mediated chromatin remodeling, is a tumor suppressor in gynecologic cancers. Cancer Res 2011;71(21):6718-27.
[84] Mullen J, Kato S, Sicklick JK, Kurzrock R. Targeting ARID1A mutations in cancer. Cancer Treat Rev Nov 2021;100:102287.
[85] Miller RE, Brough R, Bajrami I, Williamson CT, McDade S, Campbell J, et al. Synthetic lethal targeting of ARID1A-mutant ovarian clear cell tumors with dasatinib. Mol Cancer Ther 2016;15(7):1472–84.
[86] Mandal J, Mandal P, Wang TL, Shih IM. Treating ARID1A mutated cancers by harnessing synthetic lethality and DNA damage response. J Biomed Sci. 2022;29 (1):71.
[87] Jackson CG, Moore KN, Cantrell L, Erickson BK, Duska LR, Richardson DL, et al. A phase II trial of bevacizumab and rucaparib in recurrent carcinoma of the cervix or endometrium. Gynecol Oncol 2022;166(1):44–9.
[88] Banerjee S, Leary A, Stewart JR, Dewan M, Lheureux S, Clamp AR, et al. 34O ATR inhibitor alone (ceralasertib) or in combination with olaparib in gynaecological cancers with ARID1A loss or no loss: Results from the ENGOT/GYN1/NCRI ATARI trial. ESMO Open 2023;8(1):100814.
[89] Post CCB, Westermann AM, Boere IA, Witteveen PO, Ottevanger PB, Sonke GS, et al. Efficacy and safety of durvalumab with olaparib in metastatic or recurrent endometrial cancer (phase II DOMEC trial). Gynecol Oncol 2022;165(2):223-9.
[90] Madariaga A, Garg S, Tchrakian N, Dhani NC, Jimenez W, Welch S, et al. Clinical outcome and biomarker assessments of a multi-centre phase II trial assessing niraparib with or without dostarlimab in recurrent endometrial carcinoma. Nat Commun 2023;14(1):1452.
[91] You B, Leary A, Rodrigues M, Follana P, Abdeddaim C, Joly F, et al. Abstract CT005: Safety and efficacy of olaparib combined to metronomic cyclophosphamide and metformin in recurrent advanced/metastatic endometrial cancer patients: ENDOLA trial. Cancer Res 2022;82(12_Supplement):CT005.
[92] Fujiwara Y, Kato S, Nesline MK, Conroy JM, DePietro P, Pabla S, et al. Indoleamine 2,3-dioxygenase (IDO) inhibitors and cancer immunotherapy. Cancer Treat Rev 2022;110:102461.
[93] Mitchell TC, Hamid O, Smith DC, Bauer TM, Wasser JS, Olszanski AJ, et al. Epacadostat Plus Pembrolizumab in Patients With Advanced Solid Tumors: Phase I Results From a Multicenter, Open-Label Phase I/II Trial (ECHO-202/KEYNOTE-037). J Clin Oncol Off J Am Soc Clin Oncol 2018;36(32):3223-30.
[94] Kyi C, Rubinstein MM, Shah P, Zhou Q, Iasonos A, Liu Y, et al. A phase II trial of IDO-inhibitor, BMS-986205 (IDO), and PD-1 inhibitor, nivolumab (NIVO), in recurrent or persistent endometrial cancer (EC; CA017-056). J Clin Oncol 2022;40 (16_suppl):5589.
[95] Scaranti M, Cojocaru E, Banerjee S, Banerji U. Exploiting the folate receptor α in oncology. Nat Rev Clin Oncol 2020;17(6):349–59.
[96] Call JA, Anderson I, Winer I, Orr D, Yeku O, Richardson DL, et al. 708 A phase 1/2 study of rinatabart sesutecan (PRO1184), a novel folate receptor alpha-directed antibody-drug conjugate, in patients with locally advanced and/or metastatic solid tumors. J Immunother Cancer [Internet]. 1 nov 2023 [cité 5 avr 2024];11(Suppl 1). Disponible sur: https://jitc.bmj.com/content/11/Suppl_1/A803.
[97] Moore KN, Angelergues A, Konecny GE, García Y, Banerjee S, Lorusso D, et al. Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer. N Engl J Med 2023;389(23):2162-74.
[98] Bogani G, Monk BJ, Powell MA, Westin SN, Slomovitz B, Moore KN, et al. Adding immunotherapy to first-line treatment of advanced and metastatic endometrial cancer. Ann Oncol. 2024;35(5):414–28.