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New Targeted Agents in Endometrial Cancer: Are We Really Making Progress?

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Abstract Endometrial cancer is the most common gynecological malignancy in Europe and North America. Metastatic and recurrent disease is generally incurable with poor prognosis. Recent advances in molecular profiling of endometrial cancer have elucidated four distinct molecular subtypes with different biology and prognosis which should facilitate the development of treatments tailored to disease-specific subgroups. To date, some molecular-targeted agents have shown interesting clinical activity in the recurrent setting, but no targeted therapies are approved for endometrial cancer. Novel pan-PI3K, AKT, and dual PI3K–mTOR inhibitors are being investigated with early signs of activity, but there are concerns about tolerability and toxicity in this often elderly patient population with comorbidities. The development of anti-angiogenic therapies, PARP inhibitors, and immunotherapies, alone or in combinations, appear to be promising strategies. This paper will describe the current evidence supporting the efficacy of molecular-targeted agents already tested in the treatment of metastatic and recurrent EC, and provide some insights on emerging data related to novel-targeted therapies.

Keywords Cancer · Endometrium · Endometrial cancer · Chemotherapy · Targeted therapy · Molecular targets

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Abbreviations

EC	Endometrial cancer
FIGO	International Federation of Gynecology and Obstetrics
OS	Overall survival
TCGA	The Cancer Genome Atlas
MSI	Microsatellite instable
ORR	Overall response rate
PFS	Progression free survival
SD	Stable disease
MAPK	Mitogen-activated protein kinase
GOG	Gynecologic Oncology Group
CBR	Clinical benefit rate
HR	Homologous repair
VEGF	Vascular endothelial growth factor
PDGF	Derived growth factor
FGF	Fibroblast growth factor
TKI	Tyrosine kinase inhibitor
NCI	National Cancer Institute
PDGFR	Platelet-derived growth factor
FGFR	Fibroblast growth factor receptor
EGFR	Epidermal growth factor receptor
IHC	Immunohistochemistry
FISH	Fluorescence in situ hybridization
TIL	Tumor-infiltrating lymphocyte
PARP	Poly adenosine diphosphate ribose polymerase
IGF	Insulin-like growth factor

Introduction

Endometrial cancer (EC) is the most common gynecological malignant disease in developed countries and the fourth most common cancer in European and North American among women, accounting for the 6 % of new cancer cases and

3 % of cancer deaths per year [1, 2]. Furthermore, with an increasing aging population, the prevalence of EC continues to rise steadily [3], and the greater overall prevalence of obesity and metabolic syndromes in developed countries are significant contributing factors [4]. As EC is frequently symptomatic at presentation, approximately 75 % of women are diagnosed in the early stages (International Federation of Gynecology and Obstetrics [FIGO] stages I or II), in which historically, standard treatment consists of hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection followed by adjuvant therapy tailored on the basis of prognostic factors in the final histology. While the 5-year overall survival (OS) for early-stage EC patients range between 75 and 91 %, the prognosis of advanced and recurrent EC remains poor, overall survival (OS) of 20–26 % at 5 years [5].

The traditional Bokhman's dualistic model [6] is conceptually useful with Type I (estrogen-dependent) with generally good prognosis, and type 2 (non-estrogen-dependent, including clear cell and serous papillary histology) with poorer prognosis was based on clinical and epidemiological characteristics of women with EC in the former Soviet Union more than 30 years ago. Since then, evidence from next-generation sequencing studies and the most recent comprehensive analysis performed by The Cancer Genome Atlas consortium (TCGA) [7•] has expanded our knowledge of recurrently altered signaling pathways in EC. Although, according to the Bokhman's dualistic model, the mutational landscape differs from type I and type II tumors, TCGA data showed a substantial overlap in genetic alterations between both subtypes and strong evidence of the heterogeneity of EC with respect to their biological, genetic, and pathological features [7•]. The TCGA revealed four genomic tumor prognostic subgroups: (1) DNA polymerase epsilon (POLE) ultramutated group, characterized by very high mutation rates and hotspot mutations in the exonuclease domain of POLE58, few copy-number aberrations, mutations in PTEN, PIK3R1, PIK3CA, FBXW7, and KRAS, and favorable outcome; (2) microsatellite instable (MSI) hypermutated group, characterized by microsatellite instability due to MLH1 promoter methylation, high mutation rates, few copy-number aberrations, recurrent RPL22 frameshift deletions, and KRAS and PTEN mutations; (3) copy-number low (endometrioid), comprising microsatellite-stable grade 1 and 2 endometrioid cancers with low mutation rates, characterized by frequent CTNNB1 mutations; and (4) copy-number high (serous-like), characterized by extensive copy number aberrations and low mutation rates, recurrent TP53, FBXW7, and PPP2R1A mutations, infrequent PTEN and KRAS mutations, and poor outcome (Table 1). A number of recent studies are beginning to associate these molecular subtypes and markers with prognosis, and studies are integrating these markers with established clinical and pathological parameters to provide prognostic and predictive information.

Table 1 Characteristics of four genomic classes of endometrioid and serous carcinomas defined by the TGCA

	POLE (ultramutated)	MSI (hypermutated)	Copy-number low (endometriod)	Copy-number high (serous-like)
Copy-number alterations	Low	Low	Low	High
MSI/MLH1 methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Mutation rate	Very high (232×10^4 mutations/Mb)	High (18×10^4 mutations/Mb)	Low (2.09×10^4 mutations/Mb)	Low (2.3×10^4 mutations/Mb)
Molecular profile	POLE (100 %) PTEN (94 %) PIK3CA (71 %) PIK3R1 (65 %) FBXW7 (82 %) ARID1A (76 %) KRAS (53 %) ARID5b (47 %) PD1/PD-L1 overexpression	PTEN (88 %) RPL22 (37 %) KRAS (35) PIK3CA (54 %) PIK3R1 (40 %) ARID1A (37 %) PD1/PD-L1 overexpression	PTEN (77 %) CTNNB1 (52 %) PIK3CA (53 %) PIK3R1 (33 %) ARID1A (42 %) FGFR2 (10.9 %)	TP53 (92 %) PPP2R1A (22 %) FBXW7 (22 %) PIK3CA (47 %) PTEN (11 %) FGFR amplifications and mutations (7 %) HER2 amplified 25 %
Histological type	Endometrioid	Endometrioid	Endometrioid	Serous, Endometrioid, and mixed serous and endometrioid
Tumor grade	Mixed (grades 1–3)	Mixed (grades 1–3)	Grade 1–2	Grade 3
Prognostic	Good	Intermediate	Intermediate	Poor
Potential drugs	PI3K/PTEN/AKT/mTOR pathway inhibitors PARP inhibitors Anti-PD1/PD-L1 inhibitors HDAC inhibitors (against FBXW7 mutations) Hormonal therapies	PI3K/PTEN/AKT/mTOR pathway inhibitors PARP inhibitors Anti-PD1/PD-L1 inhibitors Hormonal therapies	PI3K/PTEN/AKT/mTOR pathway inhibitors PARP inhibitors Hormonal therapies FGFR inhibitors	HER2 targeted inhibitors PI3K inhibitors PARP inhibitors Wee-1 inhibitors HDAC inhibitors (against FBXW7 mutations) FGFR inhibitors

Mb megabase, *MSI* microsatellite instability, *HDAC* Histone deacetylases

For women with relapsed EC and disease that is not amenable to local therapy, the standard first-line approaches remain including chemotherapy and/or hormonal therapy. To date, the doxorubicin/cisplatin/paclitaxel with G-CSF (TAP) regimen is the only combination regimen associated with significant improvement over doxorubicin/cisplatin in overall response rate (ORR) (57 vs 34 %), median progression-free survival (PFS) (median 8.3 vs 5.3 months), and OS (median 15.3 vs 12.3 months). TAP is associated with significant toxicity and a recent equivalence trial, and for many years, carboplatin–paclitaxel combination was an effective and community-accepted therapeutic alternative, achieving an ORR of 40 to 50 % in chemotherapy-naive patients, and with lower toxicity than the three-drug combination. Carboplatin and paclitaxel has been recognized standard first-line approach for metastatic or relapsed EC [8]. The GOG 209 trial was launched to assess whether carboplatin plus paclitaxel was non-inferior in survival to doxorubicin/cisplatin/paclitaxel regimen. Completed in 2009, preliminary study results did not reveal significant differences between the two regimens in either PFS (HR = 1.03) or OS (HR = 1.01), and support the use of carboplatin–paclitaxel for the first-line treatment of EC [9].

Hormonal therapy strategies have been also developed for advanced stage disease with a better activity profile for advanced tumors with hormono-receptor status positive and low-grade histologies; ORR range from 20 to 30 % [10]. Unfortunately, women with advanced EC for whom treatment failed with first-line therapy have few treatment options, including taxanes and doxorubicin, with moderate activity including ORR of 20 % [11]. Treatment options and early phase clinical trial development in EC lag behind other cancer types despite a desperate need for effective therapies and the potential for continued increases in incidence due to dietary lifestyle. Several phase II trials have been conducted in the second-line setting, but only few of them have demonstrated some degree of activity that warranted further investigation in EC [12], and not surprisingly, no novel targeted agents have been approved for treatment of EC. Although retrospective in nature and focused on endometrioid, serous, and mixed carcinomas, the TCGA study has revealed several promising druggable molecular aberrations in all tumors subgroups, including alterations in PI3K-PTEN-mTOR signaling pathway, RAS/β-catenin pathway, FBXW7, FGFR2, and HER2 [7•].

This manuscript will review and discuss progress in advancing targeted therapies in EC and provide the rationale and essential components of future targeted treatment strategies.

PI3K/PTEN/AKT/mTOR Pathway Inhibitors in Endometrial Cancer

Single Agent mTOR Inhibitors

EC demonstrates the highest rate of PI3K pathway alterations of all solid tumors [13]. These alterations affect the full range of histologic variants in EC according to TCGA data, in which gain-of-function mutations in catalytic subunit of PIK3CA, PIK3R1, and mutations in PTEN were commonly identified in the POLE tumors at 71, 65, and 94 %, respectively [7•]. Activation of the PI3K pathway through PTEN loss of function—a tumor suppressor gene responsible for regulating cell growth and proliferation through the mTOR pathway—ranges from 30 to 60 % of all ECs, primarily affecting endometrioid histologies [13]. Amplifications in the PIK3CA gene in almost 40 % of ECs have been also described [13]. The activation of the PI3K pathway related to these molecular alterations seems to be associated with an aggressive phenotype in early-stage ECs, but their prognostic role in advanced stages remains unclear [14].

Most of the published experience utilizing PI3K pathway inhibitors in EC has been based on the use of mTOR inhibitors, including temsirolimus, everolimus, and ridaforolimus. Several phase II clinical trials have investigated the use of rapalogs as a single agent in recurrent EC (Table 2), demonstrating moderate and reproducible activity across histology subtypes in all the studies. The ORR obtained from mTOR therapies ranges from 4 to 25 %, with a higher ORR in patients who had not been heavily pretreated with chemotherapy. Inhibition of mTOR may provide clinically significant with prolonged stable disease (SD) [15–19, 20•]. mTOR inhibitors have shown a tolerable toxicity profile, which includes asthenia, diarrhea, rash, thrombocytopenia, anemia, and metabolic abnormalities such as hyperglycemia, hyperlipidemia, and interstitial pneumonitis. Results from a recent open-label, randomized phase II trial of orally administered ridaforolimus compared with progestin or chemotherapy in second-line treatment of advanced EC patients showed higher stable disease (SD) rates in the ridaforolimus group (35 vs 17 %, $p = .021$) and longer PFS; the study primary end point (3.6 vs 1.9 months, HR = 0.53; 95 % CI 0.31–0.90; $p = 0.008$), however, showed no difference in OS (10 vs 9.6 months, HR = 1.06; 95 % CI 0.70–1.59; $p = .604$) [20•]. This provides some objective evidence for the option of mTOR inhibitors as a potential treatment choice in this setting. To date, despite optimistic clinical data, neither molecular factors nor tumor histology from prospective trials have been predictive for outcome [21].

In order to explain the modest activity shown with the use of mTOR inhibitors as single agents, several potential mechanisms have been suggested including intra- or inter-pathway feedback loops, such as the mTORC2-mediated activation of

Table 2 Completed clinical trials of PI3K/PTEN/AKT/mTOR pathway inhibitors in endometrial cancer

	Phase	Delivery	Selection of patients	Previous chemotherapy	Activity	Candidate biomarkers identified
Ridaforolimus[18]	2	intravenous	No	1–2	ORR 11 % CBR 29 % 6 months PFS: 18 %	None
Ridaforolimus[19]	2	oral	No	Adjuvant only	ORR 8.8 % SD: 52.9 % for a median duration of 6.6 months	No correlation between response and PTEN loss or AKT or PIK3 mutations
Ridaforolimus vs progrestin or chemotherapy[20]	2	oral	No	1–2	ORR 0 % PFS rate 48 % at 16 weeks SD 35 % mPFS 3.6 months (comparator 1.9 months)	None
Everolimus[15]	2	oral	No	1–2	ORR % SD 43 % CBR at 20 weeks 20 %	None
Everolimus[17]	2	oral	No	1–2	ORR 9 % SD 27 % mPFS 2.8 months	No correlation between PTEN or status or PIK3CA mutations
Everolimus plus letrozol[25]	2	oral	No	1–2	ORR 32 % (9 CR) CBR 40 %	Yes (endometrioid histology and CTNNB1 mutations)
Temsirolimus[16]	2	intravenous	No	Chemotherapy- naïve (CN) and chemotherapy treated(CT)	CN: ORR 24 % SD ≥ 8 weeks 69 % mPFS 7.33 months CT: ORR 4 % SD ≥ 8 weeks 46 % mPFS 3.25 months	none
Temsirolimus vs Temsirolimus + megestrol acetate alternating with tamoxifen[24]	2	intravenous	No	0–1	ORR 14 % Excess toxicity	none
Temsirolimus plus bevacizumab[26]	2	intravenous	No	1–2	ORR 24.5 % 6-month PFS 46.9 % mPFS 5.6 months mOS 16.9 months	none
Temsirolimus plus bevacizumab[27]	2	intravenous	No	Adjuvant only	ORR 20 % 6-month PFS 48 %	none
Pilaralisib[29]	2	Oral	No	1–2	ORR 6 % PFS > 6 months 11.9 %	none
BKM120 (NCT01289041)	2	Oral	No	1	Halted for toxic effects	none
Dual PI3K/mTOR inhibitors						
GDC0980[31]	2	Oral	No	1–2	ORR 9 % mPFS 3.5 months	none
AKT inhibitors						
MK2206[33] (NCT01307631)	2	Oral	PIK3CA mutation stratified	1–2	ORR 5.4 %	none

ORR overall response rate, *CBR* clinical benefit rate, *SD* stable disease, *CR* complete response, *mPFS* median progression free survival, *CN* chemotherapy naïve, *CT* chemotherapy treated, *mOS* median overall survival

AKT and mitogen-activated protein kinase (MAPK) pathway, and crosstalk pathways that circumvent dependence on single pathway inhibition [22]. PI3K pathway inhibition has also been shown to modulate sensitivity to hormonal therapies in breast and endometrial cancer cell lines [23]. Therefore, different therapeutic strategies have been explored within the context of EC clinical trials, including the following: next-generation mTORC1/mTORC2 inhibitors, pan-PI3K or AKT inhibitors, and combinations such as dual blockade with mTORs inhibitors and antihormonal treatment or mTOR inhibition and anti-angiogenic therapy.

mTOR Inhibitors and Hormonal Therapy

Preclinical and clinical synergy obtained with the combination of mTOR inhibitors and hormonal therapy in advanced estrogen receptor-positive breast cancer [24] has led to the development of several clinical trials in recurrent EC. GOG-0248 randomized women to temsirolimus alone or temsirolimus with the combination of megestrol acetate alternating with tamoxifen. This study was discontinued early due to an excess of venous thrombosis and no evidence of improved efficacy [25]. More recently, promising clinical activity has been reported with the combination of everolimus and letrozole in a heavily pretreated population. Treatment combination in 35 patients with one to two prior chemotherapy regimens showed a clinical benefit rate (CBR) of 42 % at 16 weeks and 32 % ORR [26]. Endometrioid histology and mutations in CTNNB1 seemed to correlate with outcome. Currently, multiple trials are investigating mTOR inhibitors in combination with hormonal therapy (NCT02228681, NCT02188550, NCT02283658) and the addition of metformin to this treatment combination (NCT01797523).

mTOR Inhibitors and Anti-angiogenic Therapy

The pairing of mTOR inhibitors with anti-angiogenic agents has also been investigated in EC. Temsirolimus in combination with bevacizumab (10 mg/kg every 2 weeks) in pretreated advanced EC demonstrated a promising 25 % ORR and a PFS at 6 months of 47 % [27]; however, almost 39 % of patients discontinued treatment due to toxicity. Data showed significant toxicity including two gastrointestinal–vaginal fistulas, two intestinal perforations, one grade 4 thrombosis, and three possible treatment-related deaths from 49 evaluable patients. The combination of temsirolimus and bevacizumab in 26 women who had received previous adjuvant chemotherapy was associated with partial response in 20 % (PR) and 48 % 6 months PFS rates; however, this did not meet the prespecified efficacy criteria. One duodenal perforation was reported, remaining a challenge the safety profile of this approach [28].

mTOR Inhibitors and Chemotherapy

The combination of temsirolimus with paclitaxel and carboplatin demonstrated good tolerability in a phase I trial led by NCIC CTG [29], and subsequently, the effectiveness of this approach has been recently assessed in the GOG-86P trial [30•]. The GOG-86P is a randomized phase II study compared in 349 EC patients; the following three approaches for the first-line treatment of advanced EC patients were explored: carboplatin/paclitaxel/temsirolimus, paclitaxel/carboplatin/bevacizumab, and ixabepilone/carboplatin/bevacizumab, followed by temsirolimus or bevacizumab as maintenance. The primary end point, PFS of each arm individually compared with historical controls (carboplatin/paclitaxel arm from GOG209 study [9]), did not show significant differences (HR = 1.222; 92.2 % CI 0.961–1.554 vs. HR = 0.85; 92.2 % CI 0.633–1.023 vs. HR = 0.871; 92.2 % CI 0.685–1.107, respectively). Interestingly, differences in OS were shown, favoring paclitaxel/carboplatin/bevacizumab arm with a median OS of 34 months ($p < 0.039$), compared to 25 months for carboplatin/paclitaxel/temsirolimus arm, 25.2 months for ixabepilone/carboplatin/bevacizumab, and 22.7 months from GOG 209 control arm [30•]. These findings warrant further investigation in randomized clinical trials and results from integrative translational studies with clinical endpoints are awaited.

PI3K Inhibitors

Pilaralisib (XL147), an orally bioavailable selective and reversible PI3K inhibitor, showed minimal antitumor activity in a single-arm phase II study, with an ORR of 6.0 %, with no relationship between molecular alterations and clinical activity noted [31]. The oral pan-PI3K, BKM120, has recently demonstrated minimal antitumor activity in monotherapy in 40 recurrent EC patients (4.5 months median PFS and no objective responses) associated to an unfavorable safety profile, including high rate of grade 3/4 toxicities (cutaneous rash (54 %) and depressive events (47 %), and anxiety (40 %) [32].

Dual PI3K Inhibitors/mTOR

Accumulating preclinical evidence suggests that activation of PI3K signaling may sensitize tumors to mTOR inhibition, primarily by the activation of PIK3CA mutations [33]. Administering PI3K inhibitors in combination with mTOR inhibitors may create the opportunity for synergy, thus increasing clinical response to therapy. Recently, the activity of GDC-0980, a dual PI3K/mTOR inhibitor was evaluated in a single arm, phase II study in EC patients treated with one or two prior lines of chemotherapy but no prior PI3K/mTOR inhibitor. At 6 months, 20 % of patients were progression free, with an ORR that was 9 % and a median PFS

of 3.5 months [34]. Interestingly, 44/56 enrolled patients had evaluable archival tumor samples, and 52 % of patients had at least one alteration in PIK3CA, PTEN, or AKT1. All three responder patients had at least one alteration in a PI3K pathway gene, suggesting that patients with a PI3K pathway mutation may have derived enhanced benefit from GDC-0980. Study findings also warn of the significant frequency of grade 3/4 related adverse events observed with hyperglycemia (46 %), rash (30 %), colitis (5 %), and pneumonitis (4 %). Several phase I trials across cancer disease sites, and specifically in EC, are being conducted to more specifically target this pathway by dual inhibition. A phase II non-comparative study of newer dual PI3K/mTOR inhibitors, PF-04691502 (oral) and Gedatolisib (PF-05212384; intravenous), in patients with recurrent EC has been completed, and preliminary results shown are pending (NCT01420081).

AKT Inhibitors

In contrast to mTORC1, evidence suggests that mTORC2, a component of the mTOR complex, is not sensitive to inhibition by rapamycin and its analogs [35]. Therefore, upon selective mTORC1 inhibition, there is positive feedback on AKT, promoting cell proliferation and survival by AKT phosphorylation, and subsequent full AKT activation [35]. Therefore, second-generation mTOR inhibitors which inhibit both mTORC1 and mTORC2 components and AKT inhibitors are being developed in clinical trials. Results from a phase II study of MK-2206, an allosteric AKT inhibitor, in which patients were prospectively stratified for PIK3CA mutation, showed modest clinical activity (two PRs and four patients were on treatment for >6 months) and no correlation between mutational status (9/36 had PIK3CA mutation) and clinical benefit [36]. Interestingly, the greatest benefit was seen in patients with serous histology; a histology subtype usually associated with worse OS. Furthermore, another trial is enrolling only gynecological cancer patients with a PIK3CA or AKT mutation onto a single-agent AKT inhibitor (AZD5363). Promising clinical activity has been reported among the heavily pretreated AKT1 E17K mutant patients, and remarkably, 9/11 evaluable gynecological patients demonstrated target lesion shrinkage, including three confirmed PRs (NCT01226316) [37].

PI3K and PARP Inhibitors

Studies suggest that direct PI3K inhibition leads to defects in specific DNA repair mechanisms, particularly homologous repair (HR) process [38, 39]. PTEN loss of function results not only in the activation of the PI3K pathway but also to dysfunctional homologous recombination (HR) repair of DNA double-strand breaks [40]. Therefore, the possibility that a PI3K inhibitor could be paired with a PARP inhibitor recapitulating the synthetic lethality observed upon PARP inhibition for homozygous *BRCA1*/*BRCA2* mutated tumors is being tested in patients with triple negative breast and ovarian cancer (NCT01623349). The frequency of PI3K pathway activation and the high prevalence of PTEN loss in EC represent a promising strategy toward improving clinical outcomes and also suggest a "new use" of PI3K pathway inhibitors as sensitizers to alternate therapies.

mTOR Inhibitors and Immunotherapies

Recent evidence has demonstrated a critical role for mTOR in the optimization of the response of innate immune cells [41]. Activation of innate immune cells via pattern recognition receptors or growth factor receptors triggers the mTOR signaling pathway that integrates the environmental and intracellular metabolism, guiding the effector response [42]. Preclinical studies have shown that mTORC1 is intimately involved in antigen presentation by dendritic cells and thereby able to modulate their T cell-stimulatory capacity [43]. In addition, inhibition of mTOR promotes the expression of the T-cell co-stimulatory molecule CD86, whereas expression of the T-cell-inhibitory molecule PD-L1 is decreased [44]. Novel phase I trials will examine the effects of vaccine therapy with or without mTOR inhibitors in patients with tumor-associated antigens NY-ESO-1 (NCT01536054, NCT01522820).

Anti-angiogenic Therapies in Endometrial Cancer

Angiogenesis has an important role in the growth in various cancer types, including endometrial cancer. The expression of vascular endothelial growth factor (VEGF) is correlated with microvessel density, vascular proliferation and poor prognosis in EC, and therefore, targeting VEGF has been investigated as a promising therapeutic target [45]. Several phase II trials investigating the role of antiangiogenic agents used in second- or later-line therapy of recurrent EC patients consistently provided some degree of clinical activity, but no antiangiogenic agents have been approved for the treatment of EC.

Bevacizumab

The use of bevacizumab, a recombinant humanized monoclonal antibody against VEGF-A, as single agent, demonstrated promising results in 52 advanced EC patients enrolled in the GOG 229-E study [46]. In this trial, bevacizumab (15 mg/kg IV every 3 weeks until progression or toxicity) administration showed a 13.5 % ORR and a 6-month PFS rate of 40.4 %. Interestingly, the association between elevated VEGF in plasma and poor outcomes was reported. The toxicity profile was tolerable, and no gastrointestinal perforations or fistulae were

seen, suggesting that single-agent bevacizumab may have a promising role in the treatment of recurrent EC.

The role of bevacizumab in combination with chemotherapy in first-line, as well as maintenance with bevacizumab (15 mg/kg/21 days for 16 cycles) in patients with complete response after 6–8 cycles of chemotherapy was initially evaluated by Simpkins et al. [47] in a small phase II that closed early due to initiation of the GOG 86P study, previously discussed [30•]. Furthermore, a randomized phase II trial has compared carboplatin/paclitaxel to carboplatin/paclitaxel/bevacizumab in first-line treatment for advanced or recurrent EC [48]. Remarkably, in a total of 108 enrolled patients, the addition of bevacizumab to carboplatin/paclitaxel significantly increased PFS from 8.7 to 13 months (HR = 0.57; 95 % CI 0.34–0.96) and also favored the ORR (54.7 vs 72.7 %; $p = 0.065$). Grade 3 cardiovascular toxicity was significantly found and should be carefully evaluated in a population with preexisting cardiovascular risk factors, as a total of six thromboembolic events, two intracardiac thrombus, and one cerebrovascular accident were reported in the experimental arm. The combination of temsirolimus (mTOR inhibitor) with bevacizumab has been developed in recurrent EC showing moderate activity, but significant related toxicity [27, 28].

The role of concurrent bevacizumab with either radiation or chemoradition has also recently been investigated. The use of bevacizumab with concurrent radiation in patients with recurrent EC with gross disease involving the vaginal cuff and/or pelvic and/or para-aortic lymph nodes showed 1- and 3-year PFS of 80 and 67 %, respectively, and warrant further investigation in future trials [49]. The use of concurrent bevacizumab and chemoradiotherapy, followed by adjuvant chemotherapy, has also been studied in those patients with high-risk EC. A tolerable toxicity profile was reported as well as promising outcome results at the 1-year interim analysis (100 % OS and 90 % PFS rates, with 3.5 % pelvic and 7 % distant failure rates) [50].

Aflibercept

GOG 229G investigated the safety and activity of aflibercept, a VEGFR-2 ligand-binding fusion protein, also called "VEGF Trap," in 24 advanced EC patients. Although the study met its primary endpoint with a PFS at 6 months of 23 %, the ORR was 6.7 % and significant grade 3/4 adverse events were reported; including 23 % of G3 cardiovascular events, two cases of reverse posterior leukoencephalopathy and up to 32 % of enrolled patients were removed due to toxicity [51].

Multi-Target Tyrosine Kinase Inhibitors

Although inhibition of the VEGF pathway has shown clinical activity in EC, resistance to anti-angiogenic therapy may be related to the activation of several pathways, including those involving platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). Several multi-target tyrosine kinase inhibitors (TKIs) have been evaluated in phase II trials in chemotherapy-exposed advanced EC patients. Sorafenib, evaluated in 56 EC patients (including carcinosarcoma histology) showed minimal activity with 5 % ORR and 42.5 % SD rate [52]. Sunitinib demonstrated promising signs of activity with an ORR of 15 % and a median OS of 19.4 months in a phase II trial of 34 patients with recurrent or advanced EC; however, almost 60 % of patients required a dose reduction [53]. Currently, sunitinib is being compared with temsirolimus in an ongoing National Cancer Institute (NCI) trial (NCT01396408). In addition, the GOG 229 K study exploring the activity of nintedanib, an inhibitor of not only VEGF but also platelet-derived growth factor (PDGFR) and fibroblast growth factor receptor (FGFR), did not demonstrate sufficient clinical efficacy to warrant further single-agent investigations (ORR 9.4 % and an 21.9 PFS rate at 6 months) and closed after the first stage of accrual [54]. Unfortunately, due to modest impact in patient outcomes, toxicity profile, as well as the lack of defined biomarker studies associated with treatment benefit in either of these trials, resulted in a departure from future clinical implementation.

More recently, advances in the molecular profiling of EC have led to the identification of novel predictive biomarkers of interest, such as (FGFR)-2 amplifications or activating mutations, and clinical trials using newer oral TKIs with integrated correlatives studies have been developed. Single agent Brivanib (BMS-582664), a potent dual VEGFR/ FGFR TKI, showed a PFS rate at 6 months of 30.2 % (90 % CI 18.9–43.9) and median OS of 10.7 months in GOG 229I study [55]. Of note, only three patients had FGFR2 mutations. Lenvatinib, an oral TKI targeting VEGFR1-3, FGF1-4, RET, KIT, and PDGFR-b, demonstrated an ORR of 14.3 % and a median PFS of 5.4 months [56]. Analysis of cytokine analysis in pretreatment and posttreatment plasma samples and molecular and gene expression profile was integrated. Seven baseline angiogenic factors correlated with prognosis (survival), such as Ang-2, Il-8, HGR, VEGFA, PIGF, Tie-2, and TNF-a. Among them, only baseline Ag-2, using a defined cut-off value (>2082), correlated with maximum tumor shrinkage, ORR (61 % vs 18 %), median PFS (9.5 vs 3.7 months), and median OS (23 vs 8.9 months). Although patients with PIK3CA mutations showed a trend to worse outcomes, no significant correlations were observed. Gene expression profiling suggested that MAPK and PI3K signaling pathways were involved in lenvatinib resistance and identified that approximately 90 genes correlated with clinical outcomes, including Ang-2 [57]. In addition, dovitinib (TKI258), a potent TKI of FGFR1-3, VEGFR1-3, PDGFR-β, and c-KIT, induces dose-dependent growth inhibition of FGFR2-mutated and FGFR2-nonmutated endometrial xenografts and has been evaluated in second-line therapy for advanced the activity of

dovitinib EC [58]. Dovitinib showed clinical activity regardless FGFR mutational status, suggesting that the activity of this agent in patients with FGFR2-nonmutated tumors might be reflective of the anti-angiogenic effects of dovitinib. Interestingly, dovitinib showed a promising 52 % CBR in the FGFR2-nonmutated group, and about a third of FGFR2 mutated patients were progression-free at 18 weeks. Ultimately, the study did not meet the predefined statistical 40 % threshold and did not continue to stage two raising the question as to whether testing for FGFR2 mutations is a useful enrichment strategy for the development of subsequent FGFR inhibitors. The safety profile as expected consisted of gastrointestinal (diarrhea, vomiting, and nausea) mild to moderate adverse events [58]. Finally, cabozantinib, a c-Met and VEGFR2, RET, KIT, and AXL TKI, is being investigated in patients with metastatic EC (NCT01935934). This trial will integrate a baseline analysis of the molecular status of archival tumor, looking for hepatocyte growth factor receptor amplification and mutation status.

EGFR Pathway Inhibitors in Endometrial Cancer

Epidermal growth factor receptor (EGFR) overexpression is common in EC and its expression has been correlated with poor prognosis [59]. Despite the success of EGFR inhibitors in other malignancies, discouraging results have been observed in EC. Gefitinib and erlotonib, orally available TKI, demonstrated as single agents to be tolerable but did not show sufficient evidence of activity in small phase II studies [60, 61]. While gefitinib demonstrated a 3.8 % ORR and a PFS at 6 months of 15.3 % [60], erlotinib, in chemotherapy naive EC patients, showed a greater but still insufficient 12.5 % ORR, with no correlation with EGFR status [61]. Of note, precycle 1 serum EGFR level was favorably associated with OS (HR = 0.33; 95 % CI 0.13–0.84) and gefitinib treatment, but this association needs to be validated in future clinical trials [60]. In addition, a phase II study investigating the activity of single agent cetuximab, a monoclonal antibody targeted against EGFR, has been completed and results are awaited (NCT00392769).

EGFR type 2 (HER-2)-related inhibitors have been investigated in EC due to HER-2 overexpression in advanced EC (10–30 % of type I and 40–80 % of type II- serous, EC) and its association with poor prognosis [62]. Trastuzumab, a monoclonal antibody that interferes with the HER2, demonstrated a lack of activity in a small phase II study in which 45 % of patients showed HER-2 expression defined by either immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) amplification. There was no evidence to suggest that HER2 overexpression or amplification was associated with ORR, PFS, or OS, and the trial closed early due to poor accrual [63]. In addition, a randomized phase II study of carboplatin and paclitaxel with or without trastuzumab in HER2-positive (3+ by IHC or FISH) serous EC is ongoing (NCT01367002). In the GOG-229D study, Lapatinib, a dual inhibitor of EGFR and HER-2, demonstrated insufficient activity in an unselected EC patient population (only 8 % HER-2 expression). Out of 30 evaluable patients, the PFS at 6 months was 10 % and the ORR 3.3 %. Interestingly, the only achieved response was seen in an EGFR-mutated patient, and this may lead the way toward conducting future trials [64].

Metformin in EC: Old Drug New Indication?

Metformin, an oral biguanide classically known for its role in the management of diabetes, has a renewed interest as a novel strategy in EC. Metformin has demonstrated inhibition of proliferation and induction of apoptosis of EC cell lines, and these effects are associated with both direct insulin-independent and indirect insulin-dependent actions of the drug [65]. Moreover, metformin has shown reduction in cellular proliferation based on ki67 proliferation index reduction in a preoperative study conducted in obese patients with EC [66]. Clinically, two retrospective studies have suggested that metformin is associated with improved OS in patients with diabetes who have EC; however, these correlations vary between studies, and as the primary endpoint was all-cause mortality, the effect of metformin on EC-related death should be interpreted with caution [67, 68].

The therapeutic role of metformin in EC is being investigated in different disease settings, including as neoadjuvant use (NCT01877564), in combination with standard chemotherapy for first-line setting in a phase II/III study conducted by the GOG (NCT02065687), and in the recurrent setting in combination with hormonal and mTOR agents (NCT01797523). Indirect evidence from previous studies has analyzed the activity of mTOR inhibitors and may suggest a trend to better outcomes in patients who received metformin. Slomovitz et al. [26] noted that the nine patients who received metformin during treatment with everolimus and letrozole had an objective RR of 56 %. Furthermore, in a compilation of up to 94 recurrent EC patients who participated in three phase II clinical trials investigating single-agent mTOR inhibitors, 17 patients were receiving metformin while participating in these trials, and although no statistically significant association with clinical outcomes was seen, the results showed a numerically lower proportion of metformin users versus nonusers with a best response of progression (11.8 vs 32.5 %, respectively) [21].

Immunotherapies in Endometrial Cancer

Presently, there are limited clinical data of immunotherapy strategies in EC. As such, significant advances in our understanding of the influence of the microenvironment and

immune system in EC are needed to lead to the development-specific clinical trials for this disease. Recently, tumor-infiltrating lymphocytes (TILs) counts and peritumoral lymphocytes have been described as independent predictors for MSI high-status group in EC [69]. In addition, almost 80 % of EC express high levels of PD-1, or its ligand, PD-L1, providing strong rationale to further develop immunostrategies in EC, including anti-PD-1/PD-L1 antibodies and immune checkpoint regulators [70]. Of relevance, POLE-mutated or MSI EC subgroups are known to harbor high mutation load, which has been correlated with increased PD-1 expression [71]. Data from a recently published phase 2 trial of pembrolizumab (MK3475, anti-PD-1 inhibitor) supports the hypothesis that mismatch repair-deficient tumors, including EC, are highly responsive to immune checkpoint blockade. Of note, 1 CR and 1 PR were observed among the 2 EC enrolled patients [72].

Poly ADP-Ribose Polymerase (PARP) Inhibitors in Endometrial Cancer

Given the impact on clinical outcomes of PARP inhibitors in *BRCA1/2* wild-type high-grade serous ovarian cancer patients [73], the development of PARP inhibitors in diseases with similar hallmarks of DNA repair deficiencies, such as EC, is particularly necessary. Serous EC is characterized by genomically unstable, copy-number-high tumors, similar to triple-negative breast and high-grade serous ovarian cancers, which may therefore also predict for defects in HR that sensitize to PARP inhibition [7•]. Preclinical evidence has shown that loss of PTEN function and microsatellite unstable EC models may predict sensitivity to PARP due to a synthetic lethality process, particularly in a low-estrogenic hormonal setting [74–77]. Currently, a phase II trial of the PARP inhibitor BMN673 is underway in patients with relapsed EC (NCT02127151). In addition, a phase I study is exploring the role of another PARP inhibitor, olaparib, in combination with the mTORC1/2 inhibitor, AZD2014, or the AKT inhibitor, AZD5363, for gynecological cancers, including ECs (NCT02208375).

Targeted Chemotherapy

Epothilones

The epothilones, a novel class of microtubule-stabilizing agents with similar but distinct behaviors to the taxane class of drugs, have preclinical evidence suggesting they retain activity in taxane-resistant tumors [78]. The activity of ixabepilone, a semisynthetic analog of epothilone B, indicated for the treatment of metastatic or locally advanced breast cancer, has been investigated in EC [79]. Ixabepilone in the second-line treatment of EC was initially evaluated in the phase II GOG trial 129-P and showed an ORR of 12 % and an 8-week SD of 60 %. Unfortunately, a phase III trial comparing ixabepilone to the standard second-line treatments (paclitaxel or doxorubicin) showed no benefit with the use of ixabepilone, resulting in shorter OS (10.9 vs 12.3 months; HR = 1.3; 95 % CI 1.0–1.7) and similar PFS (3.4 vs 4 months; HR = 1.0; 95 % CI 0.8–1.3) [80]. In addition, as previously discussed, the GOG 86-P includes one arm testing the combination of carboplatin, ixabepilone, and bevacizumab, which demonstrated an ORR of 53 % and no statistically significant differences in PFS of each arm individually compared to historical controls [30•].

LHRH-Cytotoxic Conjugate

Luteinising-hormone-releasing hormone (LHRH) receptors are expressed in 80 % of ECs, and recently, LHRH receptors have been used for the development of targeted chemotherapy [81]. AEZS-108—an LHRH-cytotoxic conjugate to doxorubicin via a protease-cleavable linker—was shown to bind with high-affinity to LHRH-specific receptors on EC cell lines and upon internalization, and AEZS-108 induces apoptosis in EC cell lines [82]. In a phase II trial, AEZS-108 demonstrated a 31 % ORR in 44 recurrent EC patients, with a safe toxicity profile [83]. A randomized phase III trial comparing doxorubicin to AEZS-108 is ongoing (NCT01767155) in the second-line disease setting.

MEK Inhibitors

MEK is a critical kinase in the MAPK signal transduction pathway for many growth factor receptors, including EGFR, insulin-like growth factor (IGF)-1 receptor and PDGFR, playing an essential role in cell survival, proliferation, and differentiation. Alterations in MAPK signaling, such as activating mutations in IGF1-Receptor/FGFR2, RAS were described in the TCGA report [7•]. Selumetinib, a selective, orally-available, small molecule inhibitor of the MEK-1/2 [84], has been investigated in phase II, single-arm, open-label study conducted in 54 recurrent EC patients, previously treated with one to two cytotoxic regimens [85]. Unfortunately, selumetinib demonstrated minimal activity in EC, with an ORR of 6 % and median PFS of 2.3 months. Presently, it is not clear whether identifiable MAPK alterations are sufficient or necessary for clinical response with MEK inhibitors in EC. An ongoing randomized trial in EC (GOG-229O) is investigating the activity of a MEK inhibitor (trametinib) versus MEK/AKT inhibition with GSK2141795, stratifying by KRAS mutation status, allowing for crossover from trametinib to the combination upon progression (NCT01935973).

Conclusions

Chemotherapy strategies for advanced and recurrent EC patients show activity, but prognosis remains poor. EC has characteristic molecular profile and biology which makes it an attractive setting for target-specific precision therapy. However, this is in a context of a patient population that is older with comorbidities, and toxicity has been a challenging limitation in many trials and challenged development despite encouraging clinical activity.

Considered as the first targeted therapy for the management of advanced EC, combinations with mTOR inhibitors suggest increased sensitivity to hormonal therapy; however, the inability to predict which patients will benefit, and significant associated toxicities reported remain a concern. Future trials should integrate correlative studies to optimize therapeutic approach. As single agents, the use of mTOR inhibitors has shown reasonable tolerability and promising activity as a non-chemotherapy approach for EC patients. Phase III studies should be conducted to confirm the level of activity of these agents when compared to standard chemotherapy, incorporating patient-reported outcomes, allowing for the possibility of their incorporation into clinical practice. Elucidation of a predictive biomarker of response to mTOR inhibition remains an outstanding research and clinical objective. To date, the majority of correlative studies have been performed in archival tumor samples from the time of diagnosis, and future translational research should incorporate paired biopsies from recurrent disease to survey for treatment-induced mutations or other indicators of molecular aberrations. Furthermore, the interplay between intracellular signaling pathways and potential feedback mechanisms may be responsible for the lack of response to PI3K/AKT/mTOR pathway inhibition. Newer therapeutics are under development for the treatment of advanced EC and include pan-PI3K inhibitors, dual mTOR/PI3K inhibitors, AKT inhibitors, or treatment combinations to counteract this emergent resistance.

Targeting angiogenesis has shown to be promising therapeutic approach in EC, with early evidence suggesting a role for bevacizumab in combination with either standard chemotherapy or targeted therapies, such as mTOR inhibitors. Future trials must define the timing and role of angiogenic agents in EC. The use of well-tolerated maintenance therapy should also be considered in the design of future clinical trials. Several multi-TKIs with antiangiogenic effect have demonstrated moderate activity in the second-line treatment of EC patients. While there is excitement in developing newer multi-TKIs that act on multiple pathways—such as PDGFR and FGFR, or treatment combinations—a major limitation remains overlapping toxicity and the lack of validated predictive biomarkers. Incorporation of well-designed correlative studies into future studies is mandatory in order to accurately tailor the specific patient subpopulations that may obtain benefit from anti-angiogenic therapies. Exploration of the role of metformin, immunotherapies, and PARP inhibition represents the most promising strategies in EC. International collaboration will be crucial to ensure the future drug development in EC.

Compliance with Ethical Standards

Conflict of Interest Victor Rodriguez-Freixinos, Katherine Karakasis, and Amit M. Oza declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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