



REVIEW ARTICLE

Emerging molecular-targeted therapies—the challenging case of endometrial cancer

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Abstract: Endometrial cancer newly affects an estimated 54,870 women in the United States, being responsible for an estimated 10,170 deaths in 2015. It has demonstrated to harbor a complex carcinogenesis process, with limited treatment options for advanced or persistent disease. Identification and targeting of genetic alterations that lead to progressive disease and therapy resistance is not only challenging, but also often does not correlate with a clinical benefit. Targeted maintenance therapies in endometrial cancer have been largely disappointing. Nonetheless, targeted personalized treatment should be the main goal of treatment of advanced disease in the future. Due to the high variety of drugs being tested in early clinical trials, it is hard to keep pace with the latest developments and ongoing trials. This review aims to summarize the latest published and ongoing trials on targeted therapies in endometrial cancer.

Keywords: endometrial cancer; targeted-therapy; PIK3/AKT/mTOR; ErbB; VEGF

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Endometrial cancer newly affects an estimated 54,870 women in the United States, being responsible for an estimated 10,170 deaths in 2015^[1]. It has been classically classified as estrogen-dependent endometrioid carcinoma (type I, 80%) and estrogen-independent non-endometrioid carcinoma (type II, 20%), including serous, clear cell carcinoma, carcinosarcoma, mucinous adenocarcinoma, squamous cell carcinoma and mixed adenocarcinoma.

Despite this classification, and the fact that each type correlates with characteristic genetic alterations, the PI3K/AKT/mTOR-PTEN pathway appears highly dysregulated in both type I and type II endometrial cancer types, but particularly in type I cancers (>90%). On the other hand, the most commonly described genomic changes in the rarer and more aggressive type II tumors are the amplification of the *HER2* gene (17%–30%)^[2] and mutation of the *TP53* gene (~90%)^[3]. Furthermore, the recent integrated genomic characterization of endometrial cancer was able to identify four categories:

POLE (polymerase epsilon gene) ultramutated, microsatellite instability (MSI) hypermutated, low copy number (CN) and high CN^[4].

Endometrial cancer survival has not changed in the last decade. We have thoroughly explored the sequencing and dosing of standard cytotoxic drugs and have probably maximized, or nearly maximized, their benefits. The standard treatment of endometrial cancer remained similar in the last 20 years, with endocrine therapy and chemotherapy having shown only limited efficacy. Therefore we should be looking for potential targets for consolidation therapies, which will help patients remaining in remission. Novel antitumor agents are currently being evaluated in early clinical trials for endometrial cancer. This review summarizes the most recent early clinical trials evaluating the use of targeted agents in endometrial cancer. The main focus is trials with available results, although the most important ongoing early clinical trials will be as mentioned. *Table 1* summarizes completed trials and their respective overall response

rates (ORR), while *Table 2* summarizes currently ongoing trials.

Table 1 Summarizes completed trials and their respective overall response rates (ORR)

Drug	N	% ORR (CR + PR)
PIK3/AKT/mTOR inhibitors		
XL-147	64	6.0
PF-05212384	38	39.5
PF-04691502	Discontinued	
GDC-0980	Results not published	
AZD6244	54	6.0
Everolimus		
Letrozol	38	32
alone	44	21
alone	35	21
Temsirolimus		
Megestrol	71	14
alone	50	22
Bevacizumab	53	24.5
Chemotherapy	33	14
Chemotherapy-naive	27	4
Ridaforolimus	64	4
	34	8.8
	34	29
HER2 directed therapies		
Tyrosine kinase inhibitor		
Erlotinib	34	12.5
Lapatinib	30	3.3
Monoclonal antibodies		
Trastuzumab	34	0
Cetuximab	23	5.0
VEGF directed therapies		
TKI258 (dovitinib)		
FGFR2(mut)	22	5
FGFR2(WT)	31	16
Aflibercept	49	7
	19	0
Bevacizumab		
Chemotherapy	15	73
Temsirolimus	53	24.5
alone	56	13.5
Brivanib	46	13.8
Nintedanib	37	9.4
Sunitinib	34	18.1

Table 2 Summarizes currently ongoing trials

Drug	Trial number	Population and type of treatment combination
PIK3/AKT/mTOR inhibitors		
MK-2206	NCT01307631	Recurrent or advanced endometrial cancer
ARQ 092	NCT02476955	ARQ 092 in combination with carboplatin plus paclitaxel in selected solid tumors
	NCT01473095	ARQ 092 in adult subjects with advanced solid tumors
GSK2141895	NCT01935973	Trametinib with or without GSK2141795 in treating patients with recurrent or persistent endometrial cancer
Everolimus	NCT02397083	Everolimus and levonorgestrel IUD in the treatment of endometrial hyperplasia and/or early-stage endometrial cancer
	NCT01068249	Letrozole and everolimus in patients with advanced or recurrent endometrial cancer
	NCT02188550	Everolimus and letrozole in platinum resistant relapse or refractory or resistant endometrial cancer
	NCT01797523	Everolimus, letrozole, and metformin in patients with advanced or recurrent endometrial cancer
	NCT02228681	Everolimus and letrozole or tamoxifen/medroxyprogesterone acetate in advanced, recurrent, or persistent endometrial carcinoma.
	NCT00977574	Paclitaxel, carboplatin, and bevacizumab or paclitaxel, carboplatin, and temsirolimus or ixabepilone, carboplatin, and bevacizumab to see how well they work in treating patients with stage III, stage IV, or recurrent endometrial cancer
	NCT01460979	Activity, tolerability, safety of temsirolimus in women with advanced endometrial carcinoma
	NCT01010126	Temsirolimus and bevacizumab in patients with advanced endometrial
	NCT00723255	Bevacizumab and temsirolimus in treating patients with recurrent or persistent endometrial cancer
	NCT02093598	POEM STUDY: a Phase IIa trial in endometrial carcinoma with temsirolimus
NCT01155258	Temsirolimus and vinorelbine ditartrate in patients with unresectable or metastatic solid tumors	
NCT01065662	AZD2171 and temsirolimus in patients with advanced gynecological malignancies	

(Table 2 continued on next page)

(Table 2 Continued)

Drug	Trial number	Population and type of treatment combination
Ridaforolimus	NCT01256268	Carboplatin/taxol/ridaforolimus in endometrial, ovarian and solid tumors
HER2 directed therapies		
Lapatinib	NCT01454479	Recurrent or persistent endometrial carcinoma (per invitation)
Trastuzumab	NCT01367002	Carboplatin/paclitaxel with and without trastuzumab in endometrial cancer
VEGF directed therapies		
	NCT00977574	(see above under temsirolimus)
Bevacizumab	NCT01770171	Carboplatin-paclitaxel ± bevacizumab in advanced (stage III-IV) or recurrent endometrial cancer (MITOBEVAEND2)
	NCT01010126	(see above under temsirolimus)
	NCT02142803	TORC1/2 inhibitor MLN0128 and bevacizumab in treating patients with advanced solid tumors
Brivanib	NCT00888173	Brivanib in patients with recurrent or persistent endometrial cancer
Nintedanib	NCT01225887	Patients with recurrent or persistent endometrial cancer
E7090	NCT02501096	Lenvatinib (E7080) plus pembrolizumab in subjects with selected solid tumors
	NCT01111461	Patients with advanced endometrial cancer and disease progression
Sunitinib	NCT00478426	Patients with recurrent or metastatic endometrial cancer
Cabozantinib	NCT01935934	Patients with recurrent or metastatic endometrial cancer

The PI3K/AKT/mTOR pathway

Mutations in the PI3K/AKT/mTOR pathway have been shown in the vast majority of type I endometrial carcinomas and in a likewise high-proportion of type II tumors. In fact, of all the cancer types studied by the Cancer Genome Atlas, endometrial cancer is the type that shows the highest incidence of mutations in this pathway. It is currently believed that PTEN loss is responsible for the pathogenesis of type I tumors, and mTOR is mainly involved in type II tumors^[5].

PI3K directed therapies

The below-described drugs are oral bioavailable specific

inhibitors of the pan-class PI3K family of lipid kinases with potential antineoplastic activity. They inhibit class I PIK3 in either an ATP-competitive or ATP-independent manner, thereby inhibiting the production of the secondary messenger PIP3 and activation of the PI3K signaling pathway.

BKM-120 (Buparlisib)

BKM-120 has shown a lack of activity in PI3K activated endometrial cancer. NCT01289041 evaluated the use of BKM-120 in endometrial cancer and included 70 patients, of which 49 showed PI3K activated pathway, one showed a complete response, and none showed a partial response. A median progression free survival (PFS) of 1.9 months was shown and an overall survival (OS) of 8.9 months was achieved for patients with PI3K-activated pathway undergoing treatment with BKM-120 (results available at clinicaltrials.gov, non-published). Pre-clinical models show that independent of PIK3CA gene mutation, BKM-120 mediated inhibition of the PI3K/AKT/mTOR pathway in endometrial tumors preclude tumor growth in a primary xenograft model. While a pattern of resistance did emerge, the effect appeared to be mitigated by the addition of conventional cytotoxic chemotherapy^[6].

XL-147 (Pilaralisib)

XL-147 showed minimal antitumor activity in advanced or recurrent endometrial carcinoma in a Phase II trial. XL-147 was administered to patients with endometrial carcinoma who progressed after first-line chemotherapy. Of the 67 enrolled patients, complete or partial tumor responses occurred in 4 patients (overall response rate (ORR) of 6.0%)^[7].

AKT directed therapies

AKT directed drugs are orally bioavailable inhibitors of AKT (protein kinase B) with potential antineoplastic activity. They bind to and inhibit the activity of AKT in either an ATP or a non-ATP competitive manner, resulting in the inhibition of the PI3K/AKT signaling pathway.

MK-2206

NCT01307631 is the sole ongoing trial on MK-2206 in endometrial cancer and has finished accrual. It aims to assess the activity of MK-2206 in patients with recurrent or persistent endometrial cancer classified by PIK3CA mutation. Results are expected in January 2016.

AZD6244 (Selumetinib)

AZD6244 constitutes another drug that did not meet

pre-trial specifications for clinical efficacy. The sole Phase II study enrolled 54 patients and reported an ORR of 6%^[8].

ARQ 092

ARQ 092 in combination with carboplatin plus paclitaxel was tested in a Phase Ib open-label clinical trial in selected solid tumors, including endometrial cancer (NCT02476955). The trial started recruiting in June 2015. A second open-label, Phase I, dose escalation study of oral ARQ 092 administered to subjects with advanced solid tumors and recurrent malignant lymphoma is currently recruiting (NCT01473095).

GSK2141795

Trametinib with or without GSK2141795 is currently being tested in patients with recurrent or persistent endometrial cancer (NCT01935973). The Phase II clinical trial is currently recruiting.

mTOR directed therapies

Newer drugs, such as PF-04691502, PF-05212384 and GDC-0989, target the phosphatidylinositol 3 kinase (PI3K) and mammalian target of rapamycin (mTOR) in the PI3K/mTOR signaling pathway, with potential antineoplastic activity. They inhibit both PI3K and mTOR kinases dually, which may result in a more potent apoptosis induction and growth inhibition of cancer cells overexpressing PI3K/mTOR.

The other types of drugs targeting mTOR are rapalogs (rapamycin derivatives, including everolimus, temsirolimus and ridaforolimus). These are small molecule inhibitors, which bind to the cytosolic protein FK-binding protein 12 resulting in mTOR inhibition, by directly binding to mTOR complex 1 (mTORC1).

PF-04691502

The only Phase II trial investigating the role of PF-04691502 in endometrial cancer was discontinued (NCT01420081, information available online at www.clinicaltrials.gov, not published).

PF-05212384

This is the mTOR inhibitor which showed the most promising results, till date, in a Phase II trial, having enrolled 38 patients and reporting 39.5% of patients showing clinical benefit, 52.6% in the PI3K basal sub-group.

The results were reported online at ClinicalTrials.gov (www.clinicaltrials.gov), and the official report is eagerly awaited.

GDC-0980

GDC-0980 was evaluated in uterine serous cancer cell lines. GDC-0980 caused a strong differential growth inhibition in FISH+ cell lines when compared with FISH-. FISH+ cell lines harboring PIK3CA mutations were significantly more sensitive to GDC-0980 exposure when compared with cell lines harboring wild-type PIK3CA. Oncogenic PIK3CA mutations and *c-erbB2* gene amplification may represent biomarkers to identify patients who may benefit most from the use of GDC-0980^[9]. A study on the use of GDC-0980 was completed in 2013 (NCT01455493) but the results were not published.

Everolimus (RAD-001)

Everolimus has been thoroughly studied in patients with endometrial cancer, with several Phase II trials available and another few recruiting. The most recent clinical Phase II trial, analyzing the combination of everolimus with letrozol, published in March 2015, enrolled 38 patients, with a clinical benefit rate of 40% (14 of 35 patients) and a confirmed objective response rate of 32% (11 of 35 patients). In this trial, serous histology was the best predictor of lack of response. Patients with endometrioid histology and CTNBN1 showed the best response rates^[10]. Analysis from clinical trial specimens determined that S6rp phosphorylation, loss of PTEN expression, and presence of KRAS mutations alone did not correlate with response to everolimus. However, positive pS6rp staining combined with KRAS mutation performed with 100% positive predictive value and specificity to predict nonresponse^[11]. Another Phase II trial, enrolling 44 patients, showed at 20 weeks, a confirmed clinical benefit rate, defined as CR, PR or SD of ≥ 8 weeks in duration, of 21%^[12]. The third Phase II trial enrolled 35 patients. Of the 28 patients available for response analysis, 6 (21%) showed a clinical benefit at 20 weeks of therapy^[13]. There are also two smaller Phase I trials published^[14,15]. A Phase II trial of everolimus in combination with letrozol has finished recruiting and results are expected in April 2016 (NCT01068249). A single arm trial of everolimus and letrozole in platinum resistant relapse or refractory or resistant endometrial cancer (NCT02188550) is currently recruiting. A trial on everolimus and levonorgestrel IUD in the treatment of

endometrial hyperplasia and/or early-stage endometrial cancer is ongoing but has not started accrual yet (NCT02397083). In another Phase II, single-arm, trial everolimus, letrozole, and metformin are being evaluated in patients with advanced or recurrent endometrial cancer. The trial is currently recruiting (NCT01797523). The Gynecologic Oncology Group (GOG) is also recruiting for a randomized Phase II trial of everolimus and letrozole or tamoxifen/medroxyprogesterone acetate in advanced, recurrent, or persistent endometrial carcinoma (NCT02228681).

Temsirolimus (CCI-779)

Temsirolimus is the most extensively studied rapalog in the context of endometrial cancer (*Table 1*). The most recent Phase II trial examined the use of temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: the combination arm was closed early because of an excess of venous thrombosis. Adding the combination of megestrol acetate and tamoxifen to temsirolimus therapy did not enhance activity and the combination was associated with an unacceptable rate of venous thrombosis^[16]. Another Phase II trial evaluated the combination of bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial cancer but was associated with significant toxicity, with 3 treatment-associated patient deaths^[17]. The first Phase II trial on temsirolimus evaluated the single-agent activity of temsirolimus in women with recurrent or metastatic chemotherapy-naïve or chemotherapy-treated endometrial cancer. Temsirolimus showed encouraging single-agent activity in endometrial cancer, which was higher in chemotherapy-naïve patients than in chemotherapy-treated patients and independent of PTEN status^[18]. There were further two Phase I trials evaluating temsirolimus with topotecan and with carboplatin-paclitaxel^[19,20].

A Phase II trial evaluating paclitaxel, carboplatin, and bevacizumab or paclitaxel, carboplatin, and temsirolimus or ixabepilone, carboplatin, and bevacizumab in patients with stage III, stage IV, or recurrent endometrial cancer has finished recruiting and results are eagerly expected (NCT00977574). Equally awaited are the results of the POEM study (NCT00659568). A number of trials evaluating temsirolimus in combination with other drugs are currently ongoing (*Table 2*).

Ridaforolimus (AP23573)

Ridaforolimus is likewise a thoroughly studied rapalog. The latest Phase II trial enrolled 130 patients, of which

64 received ridaforolimus. Treatment discontinuation as a result of adverse events was 33%. Median PFS at the protocol prespecified interim analysis was 3.6 months for ridaforolimus and 1.9 months for the comparator. Oral ridaforolimus showed encouraging activity in advanced endometrial cancer but was associated with significant toxicity^[21]. A second Phase II trial enrolled 34 patients and registered an ORR of 8.8%. No correlation was found between response and mutation status^[22]. Another single-arm Phase II trial enrolled 45 patients. A clinical benefit was achieved in 29% of the patients and was generally well tolerated^[23]. Apart from a trial evaluating carboplatin/taxol/ridaforolimus in endometrial, ovarian and solid tumors, which has finished accrual, there are no other ongoing trials.

Other agents that target the PI3K/AKT/mTOR pathway are currently being developed, including the small molecule bisindolylmaleimide MKC-1 and suberoylanilide hydroxamic acid (SAHA). Their efficacy may later eventually be evaluated in endometrial cancer.

The epidermal growth factor receptor (EGFR or ErbB) family

The EGFR or ErbB family consists of four distinct tyrosine kinases cell surface receptors (ErbB or HER 1-4) that are expressed in the normal endometrium and overexpressed in endometrial cancers, particularly type II cancers. When activated, ErbB dimerizes and induces signal transduction through the PI3K signaling pathway promoting carcinogenesis. As previously mentioned, it is one of the most frequent amplified genes in type II endometrial cancer. Two classes of targeted therapies exist: tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (MoAbs).

EGFR-specific tyrosine kinase inhibitors (TKIs)

TKIs are small molecules to inhibit the cytoplasmic side of the EGFR tyrosine kinase domain, leading to EGFR inactivation. This leads to a halt in signaling the cascade of cells that rely on this pathway for growth, resulting in potential anti-tumor activity.

Gefitinib

There were 2 Phase II trials evaluating the efficacy of gefitinib in recurrent metastatic endometrial cancer, however, they showed that it lacked sufficient efficacy to warrant further evaluation^[24,25]. One of the trials enrolled

29 patients, of which one had a complete response, however, it was not associated with an ErbB mutation^[24]. The other enrolled 24 patients and no clinical responses were observed^[25]. There are currently no ongoing trials.

Erlotinib

The results of the existing Phase II trial were not promising^[26] with 4 partial responses out of 34 enrolled patients. There are currently no ongoing trials.

Lapatinib

Lapatinib is a dual EGFR and ErbB2 inhibitor. A Phase I study of lapatinib plus ixabepilone as second-line treatment for patients with HER2 overexpressed recurrent or persistent endometrial carcinoma (NCT01454479) is enrolling patients by invitation. A Phase II trial exploring the use of lapatinib in women with persistent or recurrent previously treated endometrial cancer showed modest activity of this compound. However, a newly identified mutation in exon 18, E690K, occurred in a patient with a partial response and progression-free survival extending for the past 6 months, so further exploration of this mutation may establish the role, if any, of lapatinib in endometrial cancer^[27].

Monoclonal antibodies

Trastuzumab

Trastuzumab binds to the extracellular segment of the HER2 receptor. Cells treated with trastuzumab undergo arrest during the G1 phase of the cell cycle. It induces downregulation of HER2 leading to disruption of receptor dimerization and signaling through the downstream PI3K cascade. Trastuzumab as a single agent did not demonstrate activity against endometrial carcinomas with HER2 overexpression or HER2 amplification^[28]. There is one ongoing trial (NCT01367002) evaluating the role of carboplatin/paclitaxel with and without trastuzumab in endometrial cancer.

Cetuximab

Cetuximab is a chimeric (mouse/human) monoclonal antibody that binds to EGFR. However, if the KRAS protein is mutated, cetuximab has been found not to work. Cetuximab was equally inactive in endometrial cancer, showing an ORR of 5% in a Phase II trial including 23 patients. The results were not published but the abstract was presented at Society of Gynecological Oncology (SGO) in 2010.

The vascular endothelial growth factor receptor (VEGFR) family

Vascular endothelial growth factor (VEGF) is an important signaling protein involved in angiogenesis. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors on the cell surface, the vascular endothelial growth factor receptor (VEGFR).

TKI258 (Dovitinib)

TKI258 is an orally bioavailable lactate salt of a benzimidazole-quinolinone compound that strongly binds to several members of the receptor tyrosine kinase superfamily (RTK). It binds to the fibroblast growth factor receptor 1, 2 and 3 (FGFR-1, FGFR-2 and FGFR-3), VEGF, platelet-derived growth factor receptor type 3 (PDGFR-3), FMS-like tyrosine kinase 3, stem cell factor receptor (c-Kit) and colony-stimulating factor receptor 1 (CSFR-1). It has been evaluated in the treatment of patients with FGFR2 mutated (mut) or wild-type (WT) advanced and/or metastatic endometrial cancer. Second-line dovitinib in FGFR2 (mut) and FGFR2 (WT) advanced or metastatic endometrial cancer had single-agent activity, but it did not reach the pre-specified study criteria. Of 248 patients with FGFR2 prescreening results, 27 (11%) had FGFR2 (mut) endometrial cancer, of which 22 patients FGFR2 (mut) and 31 patients FGFR2 (WT) were recruited. Seven (31.8%) FGFR2 (mut) patients and nine (29.0%) FGFR2 (WT) patients were progression-free at 18 weeks. On the basis of pre-defined criteria, neither group continued to stage two of the trial^[29].

Aflibercept

Aflibercept binds to circulating VEGFs and acts like a “VEGF trap”, it is a soluble recombinant decoy VEGF receptor that is biologically engineered to bind to all forms of this growth factor. There are two published trials on endometrial cancer. One Phase II trial enrolled 49 patients, of which 7% had a partial response, while there were no complete responders. Of note, 10 patients (23%) met the PFS at 6 months endpoint without starting a subsequent therapy; the remaining 8 patients discontinued therapy for toxicity. Aflibercept met pre-trial activity parameters, but was associated with significant toxicity at this dose and schedule in this population^[30]. The second Phase II trial enrolled 19 patients with endometrial carcinosarcoma and it showed only minor activity, with

one patient presenting stable disease for more than 24 weeks but no objective response^[31]. There are currently no ongoing trials.

Bevacizumab

Bevacizumab has been the most extensively evaluated VEGFR targeted therapy in endometrial cancer. It is a monoclonal antibody directed at the cytokine (VEGF) and has showed very good activity in ovarian and metastatic breast cancer. There are three Phase II and two Phase I trials, which are published. The most recent Phase II trial evaluated the effect of adding bevacizumab to adjuvant paclitaxel and carboplatin and further as maintenance on PFS in advanced or recurrent endometrial carcinoma. It enrolled 15 patients on protocol when accrual to the study was discontinued due to the initiation of a national randomized Phase II trial. One patient suffered a bowel perforation, while five complete responses and six partial responses were seen for an overall response rate of 73%, so the results of the National Trial (NCT00977574) are eagerly awaited. The second Phase II trial evaluated the combination of bevacizumab with temsirolimus and enrolled 53 patients, resulting in three treatment-related patient deaths and clinical responses from 12 patients (24.5%). Although an active combination, it was associated with significant treatment associated toxicity^[17]. The first Phase II trial on bevacizumab evaluated its efficacy in patients with persistent disease after cytotoxic treatment and enrolled 56 patients, with only seven patients (13.5%) showing clinical responses^[32]. NCT01005329 evaluated intensity-modulated radiation therapy, cisplatin, and bevacizumab followed by carboplatin and paclitaxel enrolled 32 patients but reported an unacceptable percentage of treatment-related, grade 3+, non-hematologic adverse events of 23.3%, no results (available from www.clinicaltrials.gov).

MITOBEVAEND2 (carboplatin-paclitaxel ± bevacizumab in stage III–IV or recurrent endometrial cancer, NCT01770171) is currently recruiting and results are eagerly awaited, as they may prove to be practice-changing. Temsirolimus and bevacizumab, in treating patients with advanced endometrial cancer (NCT01010126) is ongoing, but has finished accrual. The combination trial of the mTORC1/2 inhibitor, MLN0128 and bevacizumab in patients with advanced solid tumors (NCT02142803), is currently recruiting.

Brivanib (BMS-582664)

Brivanib is an alaninate salt of a VEGFR-2 inhibitor and is hydrolyzed to an active moiety *in vivo*. It works as a

TKI, strongly binding to and inhibiting VEGFR-2, a tyrosine kinase receptor expressed almost exclusively on vascular endothelial cells. The only published Phase II single-arm trial enrolled 45 and reported 8 (18.6%) responses^[33]. There is one ongoing trial that has finished accrual, (NCT00888173) evaluating single-agent brivanib in patients with recurrent or persistent endometrial cancer.

Nintedanib (BIBF 1120)

Nintedanib is an orally bioavailable, indolinone-derived, RTK inhibitor. This multi-targeted TKI, selectively binds to and inhibits VEGFR, FGFR and PDGFR, which may result in a reduction of the tumor vasculature. There is one published Phase II trial, enrolling 37 patients, reporting three (9.4%) partial responses. Nintedanib lacked sufficient activity as a single agent to warrant enrollment to second stage^[33]. There is one ongoing trial on Nintedanib in patients with recurrent or persistent endometrial cancer that has finished accrual (NCT01225887).

Lenvatinib (E7080)

Lenvatinib is a synthetic, orally available, inhibitor of VEGFR2. Lenvatinib acts as a TKI, blocking the VEGFR2 TK, resulting in inhibition of the VEGF receptor signal transduction pathway, decreased vascular endothelial cell migration and proliferation, and vascular endothelial cell apoptosis. There are currently two ongoing trials on E7080 in endometrial cancer. NCT0111461 has finished accrual and NCT02501096 has not started accrual yet (*Table 2*).

Sunitinib

Sunitinib (SU11248) is a small-molecule, multi-targeted receptor TKI. Its targets include all TK receptors for PDGFR and VEGFR. There is one published Phase II trial on sunitinib, enrolling 34 women, of which six (18.1%) had a partial response. Toxicity was seen frequently but was manageable^[34]. There is one ongoing trial on sunitinib in patients with recurrent or metastatic endometrial cancer that has already finished accrual (NCT00478426).

Cabozantinib (XL184)

Cabozantinib (INN) is a small molecule inhibitor of the TKs c-Met and VEGFR. There is one ongoing trial on cabozantinib-s-malate in the treatment of patients with recurrent or metastatic endometrial cancer, currently recruiting participants (NCT01935934).

Discussion

Endometrial cancer has fallen behind, in terms of molecular characterization and development of molecular-targeted therapies, when compared to other disease sites. While in the adjuvant setting, a combination approach including chemotherapy and radiation therapy is likely to yield the best control rates for the patients, the current research focus should be maintenance therapy that helps patients to remain in remission. “Older” clinical trials have included women with type-I and type-II endometrial cancers, known to represent different disease entities. Unfortunately, only a few molecular-targeted agents have shown significant response rates in clinical trials in endometrial cancer. Many drugs that revealed antitumor activity in preclinical studies were unsuccessful when tested in the clinical setting. We have come to understand that identifying and targeting a mutation does not always result in a clinical response. Further challenging has been the unacceptable toxicity reported in some clinical trials, such as with aflibercept, temsirolimus and ridaforolimus.

Mutation and loss of PTEN function with overexpression of mTOR signaling pathway are involved in the pathogenesis of endometrial cancer, with endometrial cancer being the cancer type that shows the highest incidence of mutations in this pathway. Therefore, the PIK3/AKT/mTOR pathway is a particularly attractive target in endometrial cancer. mTOR inhibitors have shown therapeutic efficacy alone or in combination therapy, regardless of the status of PTEN mutation. The results of the Phase II trial evaluating PF-05212384 are eagerly awaited, as are the results of the Phase II trial evaluating paclitaxel, carboplatin, and bevacizumab or paclitaxel, carboplatin, and temsirolimus or ixabepilone, carboplatin, and bevacizumab (NCT00977574). The dual blockade of mTOR and VEGF by combination with bevacizumab appears particularly attractive. Everolimus, PF-05212384 and temsirolimus showed promising ORR above 20%, either alone or in combination. Although ridaforolimus and temsirolimus show promising anti-tumor activity, they require caution due to a high-toxicity profile.

HER2 amplification is present in a significant proportion of high-grade endometrial tumors at high risk of progression, recurrence, and decreased survival. While HER2-targeted therapies have been practice-changing in breast cancer treatment, HER2 directed therapies in endometrial cancer settings have been frustrating, to say the least. Clinical trials testing HER2-targeted therapies in endometrial cancer have shown minimal clinical benefit due resistance mechanisms that are poorly understood.

These therapies have failed to show adequate response rates in recurrent HER overexpressing endometrial cancer, suggesting that these tumors may possess resistance mechanisms.

Attempts to block the VEGFR family have likewise shown good results in other cancer types, but efforts to block VEGF in endometrial cancer have obtained disappointing results. The timing and role of angiogenic agents remains unclear. Extrapolating from other cancer types, the combined use with chemotherapeutic agents at recurrence could be beneficial. Bevacizumab is the only agent that has consistently shown activity in endometrial cancer, particularly when used in combination with chemotherapy. Another interesting approach appears to be the combination with mTOR inhibitors such as temsirolimus (NCT00977574 and NCT01010126), whose trials results are eagerly awaited.

Conclusion

Endometrial cancer has demonstrated to harbor a complex carcinogenesis process. Even with largely disappointing results obtained this far, targeted personalized treatment should be the main goal of treatment of advanced disease in the future. Better characterization of molecular subtypes is needed to optimize patient selection in future clinical trials.

Conflict of Interest

The author declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

References

1. National Cancer Institute. SEER Cancer Statistics Review (CSR) 1975–2012 [Internet]. 2015 [cited April 2015]. Available from: http://seer.cancer.gov/csr/1975_2012/.
2. Growdon WB, Roussel BN, Scialabba VL, et al. Tissue-specific signatures of activating PIK3CA and RAS mutations in carcinosarcomas of gynecologic origin. *Gynecol Oncol* 2011; 121(1): 212–217.
3. Dedes KJ, Wetterskog D, Ashworth A, et al. Emerging therapeutic targets in endometrial cancer. *Nat Rev Clin Oncol* 2011; 8(5):261–271.
4. Kandath C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. *Nature* 2013; 497(7447): 67–73.
5. Peiro G, Peiro FM, Ortiz-Martinez F, et al. Association of mammalian target of rapamycin with aggressive type II endometrial carcinomas and poor outcome: a potential

- target treatment. *Hum Pathol* 2013; 44(2): 218–225.
6. Bradford LS, Rauh-Hain A, Clark RM, et al. Assessing the efficacy of targeting the phosphatidylinositol 3-kinase/AKT/mTOR signaling pathway in endometrial cancer. *Gynecol Oncol* 2014; 133(2): 346–352.
 7. Matulonis U, Vergote I, Backes F, et al. Phase II study of the PI3K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma. *Gynecol Oncol* 2015; 136(2): 246–253.
 8. Coleman RL, Sill MW, Thaker PH, et al. A phase II evaluation of selumetinib (AZD6244, ARRY-142886), a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol* 2015; 138(1): 30–35.
 9. English DP, Bellone S, Cocco E, et al. Oncogenic PIK3CA gene mutations and HER2/neu gene amplifications determine the sensitivity of uterine serous carcinoma cell lines to GDC-0980, a selective inhibitor of Class I PI3 kinase and mTOR kinase (TORC1/2). *Am J Obstet Gynecol* 2013; 209(5):465.e1–465.e9.
 10. Slomovitz BM, Jiang Y, Yates MS, et al. Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. *J Clin Oncol* 2015; 33(8): 930–936.
 11. Meyer LA, Slomovitz BM, Djordjevic B, et al. The search continues: looking for predictive biomarkers for response to mammalian target of rapamycin inhibition in endometrial cancer. *Int J Gynecol Cancer* 2014; 24(4): 713–717.
 12. Ray-Coquard I, Favier L, Weber B, et al. Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO. *Br J Cancer* 2013; 108(9): 1771–1777.
 13. Slomovitz BM, Lu KH, Johnston T, et al. A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. *Cancer* 2010; 116(23): 5415–5419.
 14. Acevedo-Gadea C, Santin AD, Higgins SA, et al. Phase I clinical trial of the mammalian target of rapamycin inhibitor everolimus in combination with oral topotecan for recurrent and advanced endometrial cancer. *Int J Gynecol Cancer* 2014; 24(3): 528–533.
 15. Vlahovic G, Meadows KL, Uronis HE, et al. A phase I study of bevacizumab, everolimus and panitumumab in advanced solid tumors. *Cancer Chemother Pharmacol* 2012; 70(1): 95–102.
 16. Fleming GF, Filiaci VL, Marzullo B, et al. Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: a gynecologic oncology group study. *Gynecol Oncol* 2014; 132(3): 585–592.
 17. Alvarez EA, Brady WE, Walker JL, 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): 22–27.
 18. Oza AM, Elit L, Tsao MS, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol* 2011; 29(24): 3278–3285.
 19. Temkin SM, Yamada SD, Fleming GF. A phase I study of weekly temsirolimus and topotecan in the treatment of advanced and/or recurrent gynecologic malignancies. *Gynecol Oncol* 2010; 117(3): 473–476.
 20. Kollmannsberger C, Hirte H, Siu LL, et al. Temsirolimus in combination with carboplatin and paclitaxel in patients with advanced solid tumors: a NCIC-CTG, phase I, open-label dose-escalation study (IND 179). *Ann Oncol* 2012; 23(1): 238–244.
 21. Oza AM, Pignata S, Poveda A, et al. Randomized Phase II Trial of Ridaforolimus in Advanced Endometrial Carcinoma. *J Clin Oncol* 2015.
 22. Tsoref D, Welch S, Lau S, et al. Phase II study of oral ridaforolimus in women with recurrent or metastatic endometrial cancer. *Gynecol Oncol* 2014; 135(2): 184–189.
 23. Colombo N, McMeekin DS, Schwartz PE, et al. Ridaforolimus as a single agent in advanced endometrial cancer: results of a single-arm, phase 2 trial. *Br J Cancer* 2013; 108(5): 1021–1026.
 24. Leslie KK, Sill MW, Fischer E, 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): 486–494.
 25. Posadas EM, Liel MS, Kwitkowski V, et al. A phase II and pharmacodynamic study of gefitinib in patients with refractory or recurrent epithelial ovarian cancer. *Cancer* 2007; 109(7): 1323–1330.
 26. Oza AM, Eisenhauer EA, Elit L, et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. *J Clin Oncol* 2008; 26(26): 4319–4325.
 27. Leslie KK, Sill MW, Lankes HA, 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* 2012; 127(2): 345–350.
 28. Fleming GF, Sill MW, Darcy KM, et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2010; 116(1): 15–20.
 29. Konecny GE, Finkler N, Garcia AA, 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): 686–694.
30. Coleman RL, Sill MW, Lankes HA, 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): 538–543.
 31. Mackay HJ, Buckanovich RJ, Hirte H, et al. A Phase II study single agent of aflibercept (VEGF Trap) in patients with recurrent or metastatic gynecologic carcinomas and uterine leiomyosarcoma. A trial of the Princess Margaret Hospital, Chicago and California Cancer Phase II Consortia. *Gynecol Oncol* 2012; 125(1): 136–140.
 32. Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2011; 29(16): 2259–2265.
 33. Dizon DS, Sill MW, Schilder JM, 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): 441–445.
 34. Castonguay V, Lheureux S, Welch S, 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): 274–280.