Cancer Chemother Pharmacol (2015) 76:1–11
DOI 10.1007/s00280-015-2758-z

REVIEW ARTICLE

Endometrial cancer: redefining the molecular-targeted approach

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Received: 13 March 2015 / Accepted: 21 April 2015 / Published online: 3 May 2015

Abstract Endometrial cancer (EC) is the most frequent gynecologic malignancy in the world. Metastatic and recurrent disease confers a worse prognosis, and the side effects of the current cytotoxic agents are the main cause of treatment disruption. Recently, the genetic alterations that facilitate the start, development and progression of EC have been elucidated, reclassifying the disease in distinct subtypes with different mechanisms of carcinogenesis. Targeted therapy aims to interfere specifically these mechanisms causing less toxicity, therefore opening new perspectives for a tailored treatment and improvement of response and survival rates for heavily treated recurrent disease. Treatment with hormone therapy was not addressed in this review because it is an extensively discussed issue and would divert the discussion about molecular-targeted therapy. The purpose of this paper was to review the available literature data regarding the main genetic abnormalities related to the carcinogenesis and evaluate the safety and efficacy of the molecular-targeted agents in the treatment of metastatic and recurrent EC.

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

Abbreviations

EC	Endometrial cancer
GOG	Gynecologic Oncology Group
HNPCC	Hereditary non-polyposis colorectal carcinoma

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Introduction

Among the gynecologic malignancy, endometrial cancer (EC) is the most frequent, with 52,630 estimated new cases and 8590 deaths worldwide for 2014. The lifetime risk for developing this malignancy is approximately 2.7 %, based on 2008–2010 data [1]. Almost 90 % of the cases of EC are sporadic, whereas the remaining are hereditary [2].

Since 1983, according to the Bokhman [3] hypothesis, the sporadic endometrial tumorigenesis is broadly divided into type 1 and type 2. This dualistic model defines these cancers in terms of both histology and clinical behavior. Type 1 tumors are more frequent, approximately 70–80 %. They follow the estrogen-related pathway, arising from a background of unopposed estrogenic stimulation, associated with endometrial hyperplasia, expressing estrogen (ER) and progesterone receptors (PR). Most of the type 1 are low grade and, histologically, shows endometrioid differentiation. Mucinous adenocarcinomas express ER and/or PR, are low grade and are also considered type 1 carcinomas. In general, type 1 EC has a favorable behavior and good response to treatment with hormone therapy in the context of metastatic and recurrent disease.

The frequency of the sporadic type 2 carcinomas ranges from 10 to 20 %. They follow the estrogen-unrelated pathway and arise from the background of an atrophic endometrium. They are usually high-grade carcinomas of non-endometrioid differentiation and have a negative or weakly positive for expression of ER and PR. Type 2 carcinomas occur at an older age than the type 1 tumors [4].

In the last decade, the increasing molecular knowledge of the tumorigenesis pathways has distinguished the EC in different subtypes by genetics alterations. The Cancer Genome Atlas Research Network (TCGA) has reported an important integrated genomic, transcriptomic and

proteomic characterization of 373 EC (307 endometrioid, 53 serous and 13 mixed endometrioid and serous). Considering mutations, copy number aberrations and microsatellite instability status, EC was reclassified into four novel categories that could have immediate therapeutic application: POLE ultramutated, microsatellite instability (MSI) hypermutated, copy number low and copy number high. The POLE subtype occured in 10 % of endometrioid tumors and was characterized by ultrahigh somatic mutation frequency, MSI and newly identified hotspot mutations in the exonuclease domain. All of the endometrial tumors were examined for mRNA expression ($n = 333$), protein expression ($n = 293$), miRNA expression ($n = 367$) and DNA methylation ($n = 373$) [5].

In this genomic data, mutations in PI3K/AKT pathway were more frequent in EC than in any other tumor type studied by TCGA. The endometrioid EC frequently presented POLE mutation, MSI (40 %), KRAS and CTNNB1 activation signaling, showing many characteristics in common with colorectal carcinoma. And similar to basal-like breast cancer and high-grade serous ovarian carcinoma (HGSOCs), the uterine serous carcinomas presented high frequency of non-silent *TP53* and somatic copy number alterations. However, HGSOCs and basal-like breast cancers did not demonstrate high frequency of *PIK3CA*, *FBXW7*, *PPP2R1A* and *ARID1A* mutations as shown in uterine serous carcinomas [5].

One important point of this analysis was that the molecular characterization demonstrated that approximately 25 % of tumors classified as high-grade endometrioid by pathologists have a molecular phenotype similar to uterine serous carcinoma. The TCGA has important limitations: Clear cell histology and carcinosarcoma were not evaluated, and high-grade endometrioid carcinoma classified as being of copy number high subtype might have included mixed tumors in which only endometrioid component was sampled.

Finally, in this context of different sets of genes and molecular alterations, referred as a 'multi-step carcinogenesis,' several novel treatment regimens are being developed based on drugs targeting specifically these pathways, achieving therapeutic effects with fewer side effects [6, 7].

The type I endometrial carcinomas (endometrioid)

The temporal sequence of the large number of mutations that promote the carcinogenesis of type I EC is not known. The most common genetic alterations include microsatellite instability, *PTEN* and β-catenin mutation. There is also evidence for different gene profiles of *EGFR*, *FGFR2* and mTOR pathway [8, 9].

The mismatch repair system (MRS) is composed by the genes MLH and MSH. The MLH1 inactivation is the most common mechanism of tumorigenesis in the endometrium, accomplished by hypermethylation of CpG islands in the promoter, the process of epigenetic silencing. MLH1 is important in repair of short segments (2–4 bases). Since simple repeat sequences are unstable in cells with MSI, the observed mutation may be secondary to the MSI derived from defective *MLH1* expression, differently to colon cancer, where MSI is due to mutations in the *MSH2*, *MLH1* and *MSH6* genes. Inherited or somatically acquired mutations of *MSH6* are also common in patients with MSI EC [10–12].

MSI has been found in a substantial fraction of sporadic endometrial tumors, but data on whether these endometrial tumors differ from their MSI counterparts in clinical characteristics, prognostic variables and survival are still lacking [9, 13]. Basil et al. [14]. demonstrated that only 13 % of MSI (+) endometrial tumors presented with advanced stage III or IV disease compared with 28 % of MSI (−) tumors. This clinical difference regarding stage has not been demonstrated previously in EC. They also suggested that MSI (−) was found to be associated with more aggressive histological subtypes by univariate analysis, but no difference in overall survival (OS) was observed. These findings were different from previous series involving other types of cancer, in which MSI (+) was associated with good behaviors and better prognosis, acting as a marker of aggressiveness [10–12, 15].

Hereditary non-polyposis colorectal carcinoma (HNPCC) is a well-characterized autosomal dominant cancer syndrome associated with tumor MSI, and EC is the second most common malignancy found in these patients [7, 16]. MSI is more frequent in endometrioid than in non-endometrioid tumors [10]. Approximately 12–24 % of sporadic colorectal cancers have MSI positivity, and it is associated with favorable prognosis and improved survival [17, 18]. Otherwise, sporadic endometrioid tumors are positive for MSI in 30 % of the patients [15].

Currently, by non-inferiority analysis, the GOG 209 study has established carboplatin plus paclitaxel as first-line chemotherapy regimen for patients with recurrent EC, demonstrating a better toxicity profile compared with the three-drug regimen paclitaxel, doxorubicin and cisplatin [19]. Prospective trials evaluating the interaction between tumor MSI and response to platinum compound therapy in women with advanced or recurrent EC are necessary to clarify the relationship between mismatch repair and response to chemotherapy.

The *PTEN* gene, located at chromosome 10q23, encodes a protein (phosphatase and tensin homolog, PTEN) with tyrosine kinase function and behaves as a tumor suppressor gene. The inactivation of the *PTEN* tumor suppressor gene is implicated in the carcinogenesis of a large range of human sporadic. This is the most frequent genetic alteration or abnormality (qualquer um dos dois) in endometrioid adenocarcinoma, present in 83 % of the cases. Numerous

mechanisms of inactivation and the pathway downstream that lead to the cancer phenotype have been described. These alterations seem to be conserved in a given histological subtype of adenocarcinoma irrespective of the primary site. For example, endometrioid adenocarcinomas of the ovary and endometrium have similar inactivation patterns associated. On the other hand, the consequences of altered PTEN expressions are different in various tissues [20, 21].

PTEN acts as a gatekeeper for initiation of carcinogenesis in the endometrium from a normal background state, and additional *PTEN* damage accumulates in the transition from premalignant to malignant disease. Thus, immunohistochemically detected PTEN loss expression is an informative biomarker for endometrial neoplasm, including precancerous lesions [22].

One of the most important signaling pathways involved in gynecologic carcinogenesis is the PI3K/AKT/mTOR pathway. Eighty percent of the cases of endometrioid EC have one or more somatic alterations affecting this pathway. Thus, amplifications, mutations and translocations, resulting in aberrant activation of this pathway, occur more frequently than in any other pathway [23, 24].

The primary negative regulator of the PI3K pathway is PTEN. Therefore, PTEN loss may lead to aberrant cell growth and an escape from apoptosis. *PIK3CA*, another gene often mutated in various types of cancer, may also hold a role in the alteration of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway in EC. *PIK3CA* mutations appear in 25–36 % of endometrioid EC and in 15 % of non-endometrioid EC, often coinciding with PTEN mutations [25].

One important study explored whether mutations of the PI3K pathway, apart from *PI3KCA* and *PTEN*, were present in EC [26]. It has been reported by several groups a mutation rate of up to 20 % in *PI3K1*, which is significantly higher than any other lineage, therefore demonstrating a selective target in EC [25, 27, 28]. The *PI3KR1* gene encodes the PI3K regulatory subunit p85a. Several of these mutations are known to phosphorylate AKT, thus activating the downstream signaling pathway. The *PIK3R2* has also been established as a novel cancer gene. The mutation rate for *PIK3R2* has been reported in up to 5 % of EC, and several mutations have shown to exhibit gain of function [25, 27]. Shoji et al. [29] detected the presence of *AKT1* mutations in 2 % of ECs tissue samples, which did not demonstrate other mutations in *PIK3CA*, *PTEN* or *KRAS*. The authors suggested that *AKT1* mutation might be mutually exclusive with other PI3K–AKT activating alterations.

The RAS–RAF–MAPK is another important pathway in a variety of human cancers, interacting with the PI3K pathway through the RAS proteins. This interaction may suggest a cooperation between the two pathways in order to determine functional outcomes. Somatic mutations of the *KRAS* gene are found in 18–28 % of endometrioid EC [30, 31].

Constitutive activating mutations in *KRAS* are more frequently found in tumors with MSI, suggesting that both events may occur simultaneously before clonal expansion [32]. In EC, *KRAS* mutations can coexist with mutations in *PIK3CA*, *PIK3R1* and *PTEN*, suggesting that *KRAS* mutations are not functionally redundant with PI3K pathway mutations [33].

The most common molecular alterations in tumor cells leading to disruption of β-catenin degradation are mutations that inactivate APC or activate β-catenin itself [34]. These alterations produce an accumulation of cytoplasmic β-catenin that translocates into the nucleus, interacts with members of the lymphoid enhancer factor-1/T cell factor and activates the transcription of various genes, such as *cyclin D1* and *MYC*. The APC/β-catenin signaling pathway has mainly been studied in the type 1 of EC. In these tumors, mutations of β-catenin occurred in up to 17 % of cases [35]. E-cadherin is a transmembrane protein with an intracellular domain that connects to the actin cytoskeleton through a complex with cytoplasmic catenin. Decreased expression of E-cadherin is associated with a loss of cell–cell cohesive forces and has been shown to precede tumor cell motility. The mainway that APC protein downregulates β-catenin levels is by cooperating with glycogen 76 synthase kinase 3β (GSK-3β), inducing phosphorylation of serine–threonine residues coded in exon 3 of the β-catenin gene and its degradation through the ubiquitin–proteasome pathway [36, 37]. The β-catenin alterations are almost exclusive and do not coexist with MSI, *PTEN* and *KRAS* mutations. When altered, β-catenin expression changes are usually seen throughout all tumor cells, its changes are present in some premalignant lesions [36]. This suggests that β-catenin mutation is an early step of endometrial tumorigenesis that is clonally represented in all tumor cells. On the other hand, alterations in β-catenin activity probably contribute to later tumor progression targeting the *cyclin D1* gene [38, 39].

Finally, some preclinical studies have addressed great attention in exploring the alterations in the fibroblast growth factor receptor 2 (FGFR2) in EC [40–42]. FGFR2 arose as a possible target for therapeutic approaches, enabling the development of the FGFR inhibitors as novel molecular agents for the treatment of several types of tumors. FGFR2 belongs to fibroblast growth factor receptor (FGFR) tyrosine kinase family that comprises four different transmembrane receptor tyrosine kinases (FGFR1–FGFR4) and their alternative spliced isoforms [42]. They activate downstream pathways such as RAS–RAF–MAPK and differentially respond to FGF ligands. Depending on the type of the cell, *FGFR2* has been shown to play crucial role in many physiological and pathological processes and

is considered as either oncogene or tumor suppressor gene. Several types of molecular alterations have been described, including gene overexpression and point mutation [43].

The type 2 endometrial carcinoma (non-endometrioid)

The background of the non-endometrioid EC (type 2) is fairly different. They are comprised of the high-grade papillary serous and clear cell carcinomas. These tumors arise in relatively older women and are not usually preceded by a history of unopposed estrogen exposure, but rather from a background of atrophic endometrium. They perform an aggressive clinical course, a greater propensity for early spreading and a worse prognosis than the more common endometrioid adenocarcinomas [44, 45].

The most common genetic alteration in type 2 EC occurs in *p53* gene. This tumor suppressor is located on chromosome 17 and is important in preventing the propagation of cells with damaged DNA. Mutations in *p53* are present in nearly 90 % of serous carcinomas. After DNA damage, nuclear p53 accumulates and causes cell cycle arrest by inhibiting cyclin-D1 phosphorylation of the *Rb* gene and thereby promoting apoptosis. Mutations in p53 are present in almost 80 % of endometrial intraepithelial carcinoma lesions, the precursor lesion to serous carcinomas. It is postulated that mutation in one allele occurs early during the development of serous carcinoma, and loss of the second normal allele occurs late in the progression to carcinoma [46].

Inactivation of *p16* and overexpression of HER2/neu are other alterations that occur in type 2 EC. *p16* inactivation was found in approximately 45 % of serous carcinomas and some clear cell cancers. The *p16* tumor suppressor gene is located on chromosome 9p21 and encodes a regulatory protein in the cell cycle. Furthermore, inactivation of *p16* leads to uncontrolled cell growth and tumor progression [47]. HER2/neu overexpression and gene amplification were found in about 45 and 70 % of clear cell and serous carcinomas, respectively. HER2/neu is an oncogene that codes a transmembrane receptor tyrosine kinase involved in cell signaling [48, 49]. Negative and reduced E-cadherin expression occurred in 62 and 87 % of serous and clear cell cancers, respectively. E-cadherin-negative tumors are more likely to be poorly differentiated or non-endometrioid and are associated with poorer prognosis [50, 51].

The hereditary endometrial carcinomas

Comprising the Lynch syndrome, the most common extracolonic malignancy is the EC, developed at a significant earlier age than in the general population. Currently, the most important pathway of HNPCC is the MSI [48, 49, 52, 53]. The EC arising in HNPCC is related to type 1 tumors, since they occur at young age and are histologically of mucinous or endometrioid type, but their pathway is driven by germ line mutations and is, thus, distinctive [54–57].

New approaches for endometrial cancer

In case of recurrent advanced disease, when surgery is not effective in curing and chemotherapy cannot be used to control the disease progression, the median survival among these patients is <1 year. However, the use of the new targeted agents alone or in combination with cytotoxic therapy is emerging as a promise to prolong survival and improve the quality of life. The results and characteristics of the completed trials evaluating the molecular-targeted drugs are summarized in Table 1.

Angiogenesis inhibitors

Bevacizumab, aflibercept and thalidomide are the antiangiogenic agents that have been recently evaluated in the treatment of EC, as well as sunitinib, a multi-targeted agent. Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF)-A. VEGF is a cytokine associated with the promotion of cell division and permeability of vascular endothelial cells, essential for angiogenesis, and is enhanced in cancer cells. In a phase II GOG trial of single-agent bevacizumab in recurrent EC, seven of 52 patients (13.5 %) exhibited a clinical response [one complete response (CR) and six partial responses (PR)] and 21 patients (40.4 %) had a progression-free survival (PFS) of at least 6 months. The median PFS was 4.2 months, and the overall survival (OS) was 10.5 months. The adverse reactions were the same as those seen with conventional bevacizumab therapy, although no perforation of the digestive tract or fistula formation was reported [58]. Results of an ongoing three-arm phase II trial that compares the combination of standard chemotherapy or ixabepilone-containing regime with bevacizumab versus the combination of the standard cytotoxic scheme with temsirolimus are anxiously expected to disclose how well they work in patients with stage III, stage IV and recurrent EC [59].

Aflibercept exhibits high-affinity binding to VEGF-A, VEGF-B and placental growth factor. In a GOG phase II trial, three out of 44 patients (7 %) had PR, and 10 patients (23 %) met the endpoint of 6 months PFS. The median PFS and OS were 2.9 and 14.6 months, respectively. Significant toxicities were uncommon, but there were two treatment-related deaths recorded—one GI perforation and one arterial rupture [60].

Table 1 Clinical trials with target therapy in ovarian cancer

Drug	Class	Phase	Number of patients	Response
Sunitinib monotherapy [62]	TKI multi-targeted inhibitor: VEGFR and PDGFR	II	Chemotherapy treated: 33	PR: 18.1 % SD: 18.1 % PFS > 6 m: 30.3 % PFS: 3 m
Erlotinib monotherapy [63]	TKI EGFR inhibitor	II	Chemotherapy naive: 34	PR: 12.5 % SD: 46.9 %
Gefitinib monotherapy [64]	TKI EGFR inhibitor	II	Chemotherapy treated: 26	CR: 3.8 % SD: 27.2 % PFS ≥ 6 m:15.4 %
Lapatinib monotherapy [70]	TKI HER2 inhibitor	II	Chemotherapy treated: 30	PR:3.3 % SD: 23.3 % PFS > 6 m:10 %
Aflibercept monotherapy [60]	Fusion protein anti-VEGF	II	Chemotherapy treated: 27	PR: 7 % SD: 32 % PFS ≥ 6 m: 41 %
Thalidomide monotherapy [61]	Immunomodulatory agent	II	Chemotherapy treated: 24	PR: 12.5 % SD: 8.3 % PFS: 1.7 m PFS ≥ 6 m: 8.3 %
TEM monotherapy [72]	mTOR inhibitor	II	Chemotherapy naive: 29 Chemotherapy treated: 25	Chemotherapy naive: PR: 14 %; SD: 69 %; PFS: 7.33 m. Chemotherapy treated: PR: 4 %; SD: 48 %; PFS 3.25 m.
Ridaforolimus monotherapy [78]	mTOR inhibitor	II	Chemotherapy treated: 24 Chemotherapy naive: 7	PR: 8.8 % SD: 52.9 %
Bevacizumab monotherapy [58]	Anti-VEGF Mab	II	Chemotherapy treated: 50	CR: 1.9 % PR: 11.5 % PFS ≥ 6 m: 40.4 %
Trastuzumab monotherapy [68]	Anti-HER2 receptor Mab	II	Chemotherapy naive: 8 Chemotherapy treated: 26	PR: 0 % SD: 58.8 % PFS: 1.84 m
Combination of TEM and bevacizumab [74]	mTOR inhibitor and anti-VEGF Mab	II	Chemotherapy treated: 53	CR: 2 % PR: 22.5 % SD: 55.1 % PFS ≥ 6 m: 46.9 % PFS: 5.6 m
Combination of temsirolimus and PLD [75]	mTOR inhibitor and anthracycline	Ib	Chemotherapy treated: 5	PR: 20 % SD: 60 % PFS ≥ 6 m: 80 %

Table 1 continued

Drug	Class	Phase	Number of patients	Response
Dovitinib [89]	TKI FGFR2 inhibitor	II	Mutated: 22 Non-mutated: 31	Mutated: PR: 5 %; SD: 59 %; PFS: 4.1 m; OS: 20.2 m. Non-mutated: PR: 16 %; SD: 35 %; PFS: 2.7 m; OS: 9.3 m
Brivanib [90]	TKI multi-targeted inhibitor: anti-FGFR and anti-VEGF	II	Chemotherapy treated: 43	OS: 10.7 m CR: 2.3 % PR: 16.3 % PFS $\geq$ 6 m: 30.2 % PFS: 3.3 m
Nintedanib [91]	TKI multi-targeted inhibitor: PDGFR, FGFR and VEGFR	II	Chemotherapy treated: 32	OS: 10.1 m PFS > 6 m: 21.9 % CR: 0 % PR: 9.4 %
Pilaralisib [85]	TKI PI3K inhibitor	II	Chemotherapy treated: 67	CR: 3 % PR: 3 % PFS > 6 m: 11.9 %

TKI tyrosine kinase inhibitor, *TEM* temsirolimus, *VEGF* vascular endothelial growth factor, *PDL* pegylated liposomal doxorubicin, *PR* partial response, *SD* stable disease, *PFS* progression-free survival, PFS > 6 m, progression-free survival >6 months

The exact mechanism of angiogenesis inhibition by thalidomide is unknown. The GOG performed a phase II trial evaluating the anti-tumor activity and adverse effects of thalidomide in persistent or recurrent EC. Only three of 24 patients (12.5 %) had PR, two (8.3 %) had stable disease (SD), and 15 (62.5 %) had progressive disease (PD); two patients (8.3 %) remained progression free after 6 months, and the median PFS and OS were 1.7 and 6.3 months, respectively. Thalidomide demonstrated limited ability to reduce angiogenic markers levels and to delay progression [60].

Sunitinib, an oral multi-targeted receptor tyrosine kinase inhibitor with antiangiogenic activity, was evaluated in a Canadian phase II trial, where six (18.1 %) out of 33 women had PR and six (18.1 %) had SD; in total, 10 patients (30.3 %) had disease control for at least 6 months [62].

EGFR inhibitors

The recent attempt to inhibit the EGFR pathway in EC was performed mainly with low molecular weight tyrosine kinase inhibitors (gefitinib, erlotinib) and cetuximab, a monoclonal antibody against EGFR. Amit et al. [63] assessed 32 patients for response to erlotinib in a phase II trial: 12.5 % had PR and 46.8 % had SD. Of the 26 patients evaluable for gefitinib efficacy in other similar phase II trial, four patients experienced PFS more than 6 months, one had CR, and the clinical benefit was 31 % [64].

HER2 inhibitors

Trastuzumab and pertuzumab are monoclonal antibodies that act in different domains of HER2 and are used in the treatment for HER2-enriched breast cancer. Many case reports suggested responses to trastuzumab in patients with recurrent and metastatic EC who had HER2 overexpressed [65–67]. The GOG group performed a phase II trial to evaluate the efficacy of single-agent trastuzumab in advanced or recurrent HER2-positive EC. Even with the amendment to require HER2 amplification by FISH, of the 34 patients enrolled, no major tumor response was observed and 20 patients experienced stable disease [68]. A preclinical study evaluated pertuzumab activity separately or in combination with trastuzumab against primary uterine serous papillary adenocarcinoma cell lines expressing different levels of HER2/neu. The results revealed that pertuzumab significantly increases trastuzumab-induced antibody-dependent cell-mediated cytotoxicity and may represent a new therapeutic option [69]. Lapatinib and neratinib are HER2 and EGFR inhibitors. The GOG 229D was a phase II trial assessing the efficacy of single-agent lapatinib in persistent and recurrent EC. Three out of 30 evaluable patients

had a PFS more than 6 months. Only one had a PR, seven had SD, 21 had PD, and just 8 % was HER2 positive. The study concluded that lapatinib did not have enough activity to be used as a single agent [70]. Data demonstrated that cell lines with HER2 amplification were strongly more sensitive to neratinib compared with non-amplified cell lines; thus, neratinib may be a potential treatment for HER2-amplified EC [71].

mTOR inhibitors

Of particular interest is the PI3K/AKT/mTOR inhibition in the treatment of recurrent or persistent EC, since this pathway is frequently activated. Temsirolimus (TEM), an ester derivative of rapamycin, is the most studied mTOR inhibitor in this context. A phase II study looking at 29 chemotherapy-naive patients showed that 14 % had PR and 69 % had SD as best response. On the other hand, 25 patients were in the chemotherapy-treated group: one (4 %) had PR and 12 (48 %) had SD [72]. A Canadian study concluded that women previously treated with chemotherapy were at 7.3 times greater risk of progression and experienced 20.9 % increased tumor growth when compared to chemotherapy-naive women [73]. The combination of TEM and bevacizumab assessed in previously treated patients showed 24.5 % of clinical responses (CR or PR) and 46.9 % progression free for at least 6 months [74]. A phase Ib trial showed that the combination of TEM and pegylated liposomal doxorubicin (PLD) is safe and manageable [75]. The phase II trial performed by Fleming et al. [76] assessing TEM with megestrol alternating with tamoxifen in women with metastatic and recurrent EC was closed early because of an excess of venous thrombosis and the absence of activity. Ridaforolimus was assessed in two phase II trials. In the first one, Colombo et al. [77] demonstrated that 13 of 45 patients (28.9 %) achieved a clinically beneficial response (CR, PR or SD) for more than 16 weeks. In a most recent trial, the response rate was even higher; Tsoref et al. [78] showed that 21 of 34 patients (61.7 %) had clinical benefit. Recently, the anti-diabetic medication metformin has been demonstrated to exert anti-neoplastic effects in several cancer cell lines, including EC cell lines. Metformin also reduces the AKT activity through inhibition of insulin receptor substrate 1 [79]. A retrospective multi-institutional cohort analysis compared EC patients with diabetes mellitus who used metformin to those who did not use from 2005 to 2010 and concluded that non-metformin users had 1.8 times worse recurrence free survival (95 % CI 1.1–2.9, $p = 0.02$) and 2.3 times worse overall survival (95 % CI 1.3–4.2, $p = 0.005$) [80]. Prospective ongoing trials are evaluating the association of metformin with other therapies. MD Anderson is recruiting patients for a phase II single-arm study to evaluate whether the combination of everolimus, letrozole and metformin can help control recurrent or progressive EC [81]. Also GOG is now conducting a randomized phase II/III two-arm placebo-controlled trial to evaluate the addition of metformin to the cytotoxic regimen paclitaxel and carboplatin in treating patients with EC stage III, IV or recurrent disease [82].

New agents

The phosphatidylinositol 3-kinase (PI3K) pathway, considered an attractive target for therapeutic intervention, is one of the most altered oncogenic pathways in EC. Two phase II trials evaluating the safety and efficacy of the PI3K inhibitors BKM-120 [83] and XL147 [84] for recurrent EC were completed not long ago and are under analysis. A recent phase II multicenter single-arm study evaluated the use of pilaralisib (XL147) in previously treated advanced or recurrent EC. Of the 67 assessed patients, only 6 % presented overall response rate and the rate of PFS >6 months was 11.9 %. There was no association between molecular alterations and clinical activity, and the most commonly reported adverse events grade >3 were rash (9.0 %), diarrhea (4.5 %) and increased alanine aminotransferase (4.5 %) [85].

The inhibition of the AKT pathway could play an important therapeutic role in the treatment of advanced EC. A preclinical analysis has demonstrated specificity of MK-2206, an orally active allosteric inhibitor for AKT. Used in the context of progestin resistance, the MK-2206 stabilized and increased the level of the progesterone receptor B and improved progesterone response in EC cells that have hyperactivated AKT. A phase II investigating the efficacy of the MK-2206 in recurrent EC is ongoing [86]. Others AKT inhibitors (ARQ 092, AZD5363, GDC-0068 and GSK2141795) are being tested in early-stage clinical trials for solid tumors.

The FGFR2 has emerged as a novel target-based therapy for the treatment of EC. A preclinical study explored the anti-tumor activity of the FGFR2 inhibitor dovitinib in EC xenograft models and concluded that its action is beyond the *FGFR2* mutational status [87]. Another preclinical assay demonstrated synergistic antitumor activity combining ponatinib, an oral multi-targeted kinase inhibitor that potently inhibits all four FGFR family members, with ridaforolimus in EC cells [88].

The results of a phase II trial evaluating the efficacy and safety of dovitinib as second-line therapy in mutated and non-mutated patients with advanced EC were recently presented at the ESMO Congress 2014. The median PFS (4.1 versus 2.7 months) and OS (20.2 versus 9.3 months) trended to be higher in the *FGFR2* mutated group; the disease control rate was 64 % (59 % SD, 5 % PR) in the *FGFR2* mutated group and 51 % (35 % SD, 16 % PR) in

the *FGFR2* non-mutated group, respectively. The most common grade 3/4 adverse events were hypertension (17 %) and diarrhea (9 %) [89].

The phase II trial published by Pollock et al. [90] evaluated the efficacy and tolerability of brivanib, an oral multi-targeted inhibitor with anti-VEGF and anti-FGFR activity, as single agent in recurrent or persistent EC. Of the 43 evaluable patients, 18.6 % had response (1 CR and 7 PR) and the median PFS and OS were 3.3 and 10.7 months, respectively. Brivanib was reasonably well tolerated; nine patients had grade 3 hypertension and one experienced grade 4 confusion.

Recently, a GOG single-arm phase II study evaluated nintedanib, a potent small molecule triple receptor tyrosine kinase inhibitor of PDGFR α and β, FGFR 1/3 and VEGFR 1–3, as monotherapy in the treatment of recurrent or persistent EC. Of the 32 eligible patients, there were no CR and only three partial responses with an overall response rate of 9.4 %. The PFS, OS and the PFS at 6 months were, respectively, 3.3, 10.1 months and 21.9 %; gastrointestinal toxicity was the most common serious adverse event (5). Based on the insufficient activity, the enrollment to second stage of the study was not carried out [91].

Theoretically, dual mTOR/PI3K competitive inhibitors attached to the ATP-binding cleft of both class I PI3Ks and mTORC1/2 should suppress more efficiently the PI3K/AKT/mTOR pathway than agents that act at single points of inhibition. Preclinical trials using GDC-0980 and BEZ235 have demonstrated cell growth inhibition in several cancer cell lines and tumor xenograft models [92, 93]. Apparently, the BEZ235 had more anti-tumor activity in tumor cells with PI3K and/or *PTEN* mutations [94]. Recently, GDC-0980 phase II study has been completed, but so far results have not been published [95].

Conclusion

The recent advances in the comprehension of the molecular mechanism of endometrial genetic alterations and pathways that explain the carcinogenesis have led to the development of clinical trials addressing the use of new targeted therapies for EC. Unfortunately, in spite of the efforts of the pharmaceutical industry and academic institutions, only few molecular-targeted agents have shown a significant impact on survival and response in clinical trials. Many agents that demonstrated significant antitumor activity in preclinical studies have failed to reproduce these results when tested in the clinical studies, and most of the patients with advanced disease remain incurable and refractory to conventional therapy.

Among the targeted therapy drugs, as shown in Table 1, the mTOR inhibitors had the highest response rates, reaching considerable PR (14 %), SD (69 %) and median PFS (7.3 months) for the chemotherapy-naive group [72]. The FGFR inhibitors remain a promise for personalized treatment of advanced endometrial disease, but we must wait for unpublished results of recently closed clinical trials. Even more, it has become clear that chemotherapy-naive patients respond better than previously treated patients. Perhaps this fact may be explained by changes in the molecular profile over the course of the disease. However, these outcomes still remains lower in comparison with the results presented by the classical trials that evaluated cytotoxic chemotherapy regime adriamycin and cisplatin where objective responses (CR and PR) reached 60 % in the first trial [96] and 43 % in the EORTC study [97], but with greater toxicity profile.

As exposed above, EC has a heterogeneous complex carcinogenesis process. Several genetic abnormalities accumulate in the cellular machinery affecting components of the same or different pathways. Consequently, there is considerable difficulty in identifying a specific target that, when pharmacologically inhibited, would make the cancer cells susceptible, shifting them toward the mechanism of apoptosis.

In conclusion, even with limited results obtained so far, the personalized approach should be the mainstay for future alternative treatment in metastatic disease with even more specific and less toxic agents.

Conflict of interest None.

References

1. Ries LAG, Melbert D, Krapcho M et al (2014) SEER cancer statistics review, 1975–2014. National Cancer Institute; Bethesda, MD. http://seer.cancer.gov/statfacts/html/corp.html, based on November 2013 SEER data submission, posted to the SEER web site
2. Doll A, Abal M, Rigau M et al (2008) Novel molecular profiles of endometrial cancer new light through hold windows. J Steroid Biochem Mol Biol 108(3–5):221–229
3. Bokhman JV (1983) Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 15(1):10–17
4. Ambros RA, Sherman ME, Zahn CM, Bitterman P, Kurman RJ (1995) Endometrial intraepithelial carcinoma: a distinctive lesion specifically associated with tumors displaying serous differentiation. Hum Pathol 26:1260–1267
5. Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I (2013) Integrated genomic characterization of endometrial carcinoma. Nature 497(7447):67–73
6. Aggarwal P, Kehoe S (2010) Serum tumour markers in gynaecological cancers. Maturitas 67:46–53
7. Hecht Jonathan L, Mutter George L (2006) Molecular and pathologic aspects of endometrial carcinogenesis. J Clin Oncol 24(29):4783–4791
8. Thoury A, Descatoire V, Kotelevets L, Kannengiesser C, Bertrand G, Theou-Anton N, Frey C, Genestie C, Raymond E, Chastre E, Lehy T, Walker F (2014) Evidence for different expression

profiles for c-Met, EGFR, PTEN and the mTOR pathway in low and high grade endometrial carcinomas in a cohort of consecutive women. Occurrence of PIK3CA and K-Ras mutations and microsatellite instability. Histol Histopathol 29(11):1455–1466
9. Heinen CD (2014) Translating mismatch repair mechanism into cancer care. Curr Drug Targ 15:53–64
10. Caduff RF, Johnston CM, Svoboda-Newman SM, Poy EL, Merajver SD, Frank TS (1996) Clinical and pathological significance of microsatellite instability in sporadic endometrial carcinoma. Am J Pathol 148:1671–1678
11. Esteller M, Levine R, Baylin SB, Ellenson LH, Herman JG (1998) MLH1 promoter hypermethylation is associated with the microsatellite instability phenotype in sporadic endometrial carcinomas. Oncogene 17:2413–2417
12. Swisher EM, Mutch DG, Herzog TJ et al (1998) Analysis of MSH3 in endometrial cancers with defective DNA mismatch repair. J Soc Gynecol Investig 5:210–216
13. Bilbao C, Rodrıguez G, Ramırez R, Falcon O, Leon L, Chirino R, Rivero JF et al (2006) The relationship between microsatellite instability and PTEN gene mutations in endometrial cancer. Int J Cancer 119:563–570
14. Cohn DE, Basil JB, Venegoni AR et al (2000) Absence of PTEN repeat tract mutation in endome- microsatellite instability. Gynecol Oncol 79:101–106
15. Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M (1993) Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature 363:558–561
16. Jernvall P, Makinen MJ, Karttunen TJ, Makela J, Vihko P (1999) Microsatellite instability impact on cancer progression in proximal and distal colorectal cancers. Eur J Cancer 35:197–201
17. Johannsdottir JT, Bergthorsson JT, Gretarsdottir S, Kristjans-son AK, Ragnarsson G, Jonasson JG et al (1999) Replication error in colorectal carcinoma: association with loss of heterozygosity at mismatch repair loci and clinicopathological variables. Anticancer Res 19:1821–1826
18. Catasus L, Machin P, Matias-Guiu X, Prat J (1998) Microsatellite instability in endometrial carcinomas: clinicopathologic correlations in a series of 42 cases. Hum Path 29:1160–1164
19. Miller D, Filiaci V, Fleming G et al (2012) Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a gynecologic oncology group study. Gynecol Oncol 125:771–773
20. Mutter GL (2001) PTEN, a protean tumor suppressor. Am J Pathol 158:1895–1898
21. Mutter GL, Lin MC et al (2000) Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Nat Can Inst 92:11
22. Tashiro H, Blazes MS, Wu R, Cho KR, Bose S, Wang SI et al (1997) Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecological malignancies. Cancer Res 57:3935–3940
23. Risinger JI, Hayes AK, Berchuck A, Barrett JC (1997) PTEN/MMAC1 mutations in endometrial cancers. Cancer Res 57:4736–4738
24. Pavlidou A, Vlahos NF (2014) Molecular Alterations of PI3K/Akt/mTOR pathway: a therapeutic target in endometrial cancer. Sci World J, Art id 709736
25. Urick ME, Rudd ML, Godwin AK, Sgroi D, Merino M, Bell DW (2011) PIK3R1 (p85a) is somatically mutated at high frequency in primary endometrial cancer. Can Resear 71(12):4061–4067
26. Cheung LW et al (2011) High frequency of PIK3R1 and PIK3R2 mutations in endometrial cancer elucidates a novel mechanism for regulation of PTEN protein stability. Cancer Discov 2:170–185
27. Slomovitz BM, Lu KH, Johnston T et al (2010) A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. Cancer 116(23):5415–5419
28. Kim DH, Sarbassov DD, Ali SM et al (2002) mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell 110(2):163–175
29. Shoji K, Oda K, Nakagawa S et al (2009) The oncogenic mutation in the pleckstrin homology domain of AKT1 in endometrial carcinomas. Br J Cancer 101(1):145–148
30. Swisher EM, Peiffer-Schneider S, Mutch DG et al (1999) Differences in patterns of TP53 and KRAS2 mutations in a large series of endometrial carcinomas with or without microsatellite instability. Cancer 85:119–126
31. Lax SF, Kendall B, Tashiro H et al (2000) The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. Cancer 88:814–824
32. Lagarda H et al (2001) K-ras mutations in endometrial carcinomas with microsatellite instability. J Path 193(2):193–199
33. Aberle H, Bauer A, Stappert J, Kispert A, Kemler R (1997) beta-catenin is a target for the ubiquitin-proteasome pathway. EMBO J 16(13):3797–3804
34. Bailey T, Biddlestone L, Shepherd N, Barr H, Warner P, Jankowski J (1998) Altered cadherin and catenin complexes in the Barrett's esophagus-dysplasia-adenocarcinoma sequence: correlation with disease progression and dedifferentiation. Am J Pathol 152(1):135–144
35. Wirtz R, Kuhl M, Wedlich D, Birchmeier W (1998) Functional interaction of an axin homolog, conductin, with beta-catenin, APC, and GSK3beta. Science 280:596–599
36. Kim YT, Choi EK, Kim JW et al (2002) Expression of E-cadherin and alpha-, beta-, gamma-catenin proteins in endometrial carcinoma. Yonsei Med J 43:701–711
37. Shih HC, Shiozawa T, Miyamoto T et al (2004) Immunohistochemical expression of E-cadherin and beta-catenin in the normal and malignant human endometrium: an inverse correlation between E-cadherin and nuclear beta-catenin expression. Anticancer Res 24:3843–3850
38. Shtutman M, Zhurinsky J, Simcha I et al (1999) The cyclin D1 gene is a target of the beta-catenin/LEF-1 pathway. Proc Natl Acad Sci USA 96:5522–5527
39. Oehler MK, Brand A, Wain GV (2003) Molecular genetics and endometrial cancer. J Br Menopause 3:27–31
40. Katoh M (2008) Cancer genomics and genetics of FGFR2 (Review). Int J Oncol 33:233–237
41. Byron SA, Gartside MG, Wellens CL et al (2008) Inhibition of activated fibroblast growth factor receptor 2 in endometrial cancer cells induces cell death despite PTEN abrogation. Cancer Res 68:6902
42. Dutt A, Salvesen HB, Chen TH et al (2008) Drug-sensitive FGFR2 mutations in endometrial carcinoma. Proc Natl Acad Sci USA 105:8713
43. Gatius S, Velasco A, Azueta A, Santacana M et al (2011) FGFR2 alterations in endometrial carcinoma. Modern Path 24:1500–1510
44. Macdonald ND, Salvesen HB, Ryan A, Malatos S, Stefansson I, Iversen OE et al (2004) Molecular differences between RER + and RER- sporadic endometrial carcinomas in a large population-based series. Int J Gynecol Cancer 14:957–965
45. Risinger JI, Maxwell GL, Berchuck A, Barrett JC (2003) Promoter hypermethylation as an epigenetic component in Type I and Type II endometrial cancers. Ann N Y Acad Sci 983:208–212
46. Niederacher D, An HX, Cho YJ, Hantschmann P, Bender HG, Beckmann MW (1999) Mutations and amplification of oncogenes in endometrial cancer. Oncology 56:59–65
47. Saffari B, Jones LA, El-Naggar A, Felix JC, George J, Press MF (1995) Amplification and overexpression of HER-2/neu

(c-erbB2) in endome- trial cancers: correlation with overall survival. Cancer Res 55:5693–5698
48. Vasen HF, Watson P, Mecklin JP et al (1994) The epidemiology of endometrial cancer in hereditary nonpolyposis colorectal cancer. Anticancer Res 14:1675–1678
49. Peltomaki P, Vasen HF, The International Collaborative Group on HNPCC (1997) Mutations predisposing to hereditary nonpolyposis colorectal cancer: database and results of a collaborative study. Gastroenterology 113:1146–1158
50. Williams JA Jr, Wang ZR, Parrish RS, Hazlett LJ, Smith ST, Young SR (1999) Fluorescence in situ hybridization analysis of HER-2/neu, c-myc, and p53 in endometrial cancer. Exp Mol Pathol 67:135–143
51. Chon HS, Hu W, Kavanagh JJ (2006) Targeted therapies in gynecologic cancers. Curr Cancer Drug Targets 4:333–363
52. Miyaki M, Konishi M, Tanaka K et al (1997) Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. Nat Genet 17:271–272
53. Schweizer P, Moisio AL, Kuismanen SA et al (2001) Lack of MSH2 and MSH6 characterizes endometrial but not colon carcinomas in hereditary nonpolyposis colorectal cancer. Cancer Res 61:2813–2815
54. Parc YR, Halling KC, Burgart LJ et al (2000) Microsatellite instability and hMLH1/hMSH2 expression in young endometrial carcinoma patients: association with family history and histopathology. Int J Cancer 86:60–66
55. De Leeuw WJ, Dierssen J, Vasen HF et al (2000) Prediction of a mismatch repair gene defect by microsatellite instability and immunohistochemical analysis in endometrial tumors from HNPCC patients. J Pathol 192:328–335
56. Sandles LG (1998) Familial endometrial adenocarcinoma. Clin Obstet Gynecol 41:167–171
57. Ollikainen M, Abdel-Rahman WM, Moisio AL et al (2005) Molecular analysis of familial endometrial carcinoma: a manifestation of hereditary nonpolyposis colorectal cancer or a separate syndrome? J Clin Oncol 23:4609–4616
58. Aghajanian C, Sill MW, Darcy KM et al (2011) Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a gynecologic oncology group study. J Clin Oncol 29:2259–2265
59. National Cancer Institute (2000) Paclitaxel, Carboplatin, and Bevacizumab or Paclitaxel, Carboplatin, and Temsirolimus or Ixabepilone, Carboplatin, and Bevacizumab in treating patients with stage III, Stage IV, or Recurrent Endometrial Cancer. Bethesda (MD): National Library of Medicine (US). http://clinicaltrials.gov/show/NCT00977574 NLM identifier: NCT 00977574
60. Coleman RL, Sill MW, Lankes HA et al (2012) A phase II evaluation of aflibercept in the treatment of recurrent or persistent endometrial cancer: a gynecologic oncology group study. Gynecol Oncol 127:538–543
61. McMeekin DS, Sill MW, Benbrook D et al (2007) A phase II trial of thalidomide in patients with refractory endometrial cancer and correlation with angiogenesis biomarkers: a gynecologic oncology group study. Gynecol Oncol 105:508–516
62. Castonguay V, Lheureux S, Welch S, Mackay HJ et al (2014) 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 134:274–280
63. Oza AM, Eisenhauer EA, Elit L, Cutz JC, Sakurada A et al (2008) Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC-148. J Clin Oncol 26:4319–4432
64. Leslie KK, Sill MW, Darcy KM et al (2009) Efficacy and safety of gefitinib and potential prognostic value of soluble EGFR, EGFR mutations, and tumor markers in a Gynecologic Oncology Group phase II trial of persistent or recurrent endometrial cancer. J Clin Oncol 27:e16542
65. Santin AD, Bellone S, Roman JJ, McKenney JK, Pecorelli S (2008) Trastuzumab treatment in patients with advanced or recurrent endometrial carcinoma overexpressing HER2/neu. Int J Gynaecol Obstet 102(2):128–131
66. Jewell E, Secord AA, Brotherton T, Berchuck A (2006) Use of trastuzumab in the treatment of metastatic endometrial cancer. Int J Gynecol Cancer 16(3):1370–1373
67. Villella JA, Cohen S, Smith DH, Hibshoosh H, Hershman D (2006) HER-2/neu overexpression in uterine papillary serous cancers and its possible therapeutic implications. Int J Gynecol Cancer 16(5):1897–1902
68. Fleming GF, Sill MW, Darcy KM, McMeekin DS, Thigpen JT, Adler LM et al (2010) Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 116(1):15–20
69. El-Sahwi K, Bellone S, Cocco E, Cargnelutti M, Casagrande F, Bellone M et al (2010) In vitro activity of pertuzumab in combination with trastuzumab in uterine serous papillary adenocarcinoma. Br J Cancer 102(1):134–143
70. Leslie KK, Sill MW, Lankes HA, Fischer EG, Godwin AK, Gray H et al (2012) Lapatinib and potential prognostic value of EGFR mutations in a Gynecologic Oncology Groupphase II trial of persistent or recurrent endometrial cancer. Gynecol Oncol 127(2):345–350
71. Schwab CL, English DP, Roque DM, Bellone S et al (2014) Neratinib shows efficacy in the treatment of HER2/neu amplified uterine serous carcinoma in vitro and in vivo. Gynec Oncol 135:142–148
72. Oza AM, Elit L, Provencher D et al (2008) A phase II study of temsirolimus (CCI-779) in patients with metastatic and/or locally advanced recurrent endometrial cancer previously treated with chemotherapy: NCIC CTG IND 160 b. J Clin Oncol 26:e5516
73. Rachel RA, Jamal R, Tu D, Walsh W, Dancey J et al (2013) Clinical and toxicity predictors of response and progression to temsirolimus in women with recurrent or metastatic endometrial cancer. Gynec Oncol 131:315–320
74. Alvarez EA, Brady WE, Walker JL, Rotmensch J, Zhou XC, Kendrick JE (2013) Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a gynecologic oncology group study. Gynecol Oncol 129:22–27
75. Boers-Sonderen MJ, Geus-Oei LF, Desar IME, Van der Graaf WTA, Oyen WJG (2014) Temsirolimus and pegylated liposomal doxorubicin (PLD) combination therapy in breast, endometrial, and ovarian cancer: phase Ib results and prediction of clinical outcome with FDG-PET/CT. Target Oncol 9(4):339–347
76. Fleming GF, Filiaci VL, Marzullo B, Zaino RJ, Davidson AS, Pearl M (2014) Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: a gynecologic oncology group study. Gynec Oncol 132:585–592
77. Colombo N, McMeekin S, Schwartz P et al (2007) A phase II trial of the mTOR inhibitor AP23573 as a single agent in advanced endometrial cancer. J Clin Oncol 25:5516
78. Tsoref D, Welch S, Lau S, Biagi J, Tonkin K, Lee Ann Martin LA (2014) Phase II study of oral ridaforolimus in women with recurrent or metastatic endometrial cancer. Gynecol Oncol 135(2):184–189
79. Zakikhani M, Blouin MJ, Piura E, Pollak MN (2010) Metformin and rapamycin have distinct effects on the AKT pathway and proliferation in breast cancer cells. Breast Cancer Res Treat 123(1):271–279
80. Ko EM, Walter P, Jackson A, Clarkd L, Franasiak J et al (2014) Metformin is associated with improved survival in endometrial cancer. Gynecol Oncol 132:438–442
81. M.D. Anderson Cancer Center (2000) A phase II, single-arm study of RAD001 (Everolimus), Letrozole, and Metformin in

patients with advanced or recurrent endometrial carcinoma. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/study/NCT01797523 NLM identifier: NCT01797523
82. Gynecologic Oncology Group (2000) Paclitaxel and carboplatin with or without metformin hydrochloride in treating patients with stage III, IV, or Recurrent Endometrial Cancer. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/study/NCT02065687 NLM identifier: NCT02065687
83. Novartis Pharmaceuticals (2000) BKM120 as second-line therapy for advanced endometrial cancer. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). http://clinicaltrials.gov/show/NCT01289041 NLM identifier: NCT 01289041
84. Sanofi (2000) Study of XL147 (SAR245408) in Advanced or recurrent endometrial cancer. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). http://clinicaltrials.gov/show/NCT01013324 NLM identifier: NCT 01013324
85. Ursula M, Ignace V, Floor B, Lainie PM, Scott M, Michael B, Frank C, Yi X, Coumaran E, Sharad G (2014) Phase II study of the PI3K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma. Gynecol Oncol. doi:10.1016/j.ygyno.2014.12.019
86. National Cancer Institute (2000) Akt Inhibitor MK2206 in treating patients with recurrent or advanced endometrial cancer. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). http://clinicaltrials.gov/show/NCT01307631 NLM identifier: NCT 01307631
87. Konecny GE, Kolarova T, O'Brien NA, Winterhoff B, Yang G et al (2013) Activity of the fibroblast growth factor receptor inhibitors dovitinib (TKI258) and NVP-BGJ398 in human endometrial cancer cells. Mol Cancer Ther 12(5):632–642
88. Gozgit JM, Squillace RM, Wongchenko MJ, Miller D et al (2013) Combined targeting of FGFR2 and mTOR by ponatinib and ridaforolimus results in synergistic antitumor activity in FGFR2 mutant endometrial cancer models. Cancer Chemother Pharmacol 71:1315–1323
89. Abstract LBA27—Phase 2 study of second-line dovitinib (TKI258) in patients with fibroblast growth factor receptor 2 (FGFR2)-mutated or –non-mutated advanced and/or metastatic endometrial cancer
90. Powell MA, Sill MW, Goodfellow PJ, Benbrook DM, Lankes HA, Leslie KK et al (2014) A phase II trial of brivanib in recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study. Gynecol Oncol 135:38–43
91. Dizon DS, Michael Sill MW, Schilder JM, McGonigle KF, Rahman Z et al (2014) A phase II evaluation of nintedanib (BIBF-1120) in the treatment of recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study. Gynec Oncol 135:441–445
92. Wallin JJ, Edgar KA, Guan J, Berry M, PriorWW Lee L et al (2011) GDC-0980 is a novel class I PI3K/mTOR kinase inhibitor with robust activity in cancer models driven by the PI3K pathway. Mol Cancer Ther 10:2426–2436
93. Maira SM, Stauffer F, Brueggen J, Furet P, Schnell C, Fritsch C et al (2008) Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity. Mol Cancer Ther 7:1851–1863
94. Shoji K, Oda K, Nakagawa S, Ikeda Y, Kuramoto H, Nishida M et al (2010) Activity of dual PI3K/mTOR inhibitor, NVP-BEZ235, and mTOR inhibitor, RAD001 (everolimus), in endometrial cancer cell lines [abstract]. J Clin Oncol 28:15s (supp abstr 5074)
95. Genentech, Inc. (2000) A study of GDC-0980 in the treatment of recurrent or persistent endometrial carcinoma. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). http://clinicaltrials.gov/show/NCT01455493 NLM identifier: NCT01455493
96. Trope C, Johnsson JE, Simonsen E, Christiansen H, Cavallin-Stahl E, Horvath G (1984) Treatment of recurrent endometrial adenocarcinoma with a combination of doxorubicin and cisplatin. Am J Obstet Gynecol 149:379–381
97. Van Wijk FH, Aapro MS, van Wijk FH, Bolis G et al (2003) Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. Ann Oncol 14:441–448