CLINICAL INVESTIGATION

New advances in the treatment of endometrial cancer

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Endometrial carcinoma is the most common gynecological malignancy. Prognosis is poor following disease recurrence or diagnosis at an advanced stage. In this setting, combination chemotherapy is the hallmark of therapy. However, women who develop recurrence or metastatic disease after initial treatment have limited options for additional therapy. This emphasizes the need for new treatment approaches, many of which are currently under investigation. A literature review was performed to determine current and future treatment options for endometrial cancer. The epothilones, angiogenesis inhibitors and mTOR inhibitors are three emerging second-line agents with promising activity against endometrial cancer. Clinical trials are underway to determine how to best incorporate emerging therapies in the treatment of endometrial carcinoma.

Keywords: advanced endometrial cancer • chemoresistance • epothilone • PTEN • Type I endometrial carcinoma • Type II endometrial carcinoma

Endometrial cancer is the most common gynecological malignancy and the fourth most common malignancy in women in the USA after breast, lung and colon cancers [1]. In 2010, it was estimated that 43,470 women in the USA would be diagnosed with endometrial cancer (6% of new cancer cases) and 7950 women would die of the disease (3% of all cancer deaths) [1]. The incidence of endometrial cancer increases with age. The vast majority of women are diagnosed between the ages of 50 and 60 years and approximately 75% of the patients are diagnosed with early-stage disease [2].

Endometrial cancer can be classified as two different types [3,4]. Type I disease represents the majority of the cases of endometrial cancer and is more common in pre- and peri-menopausal women. It is associated with unopposed estrogen exposure and is associated with endometrial hyperplasia as a precursor lesion. Type I tumors are mostly endometrioid in histology, express both estrogen and progesterone receptors, and are typically of low histologic grade and favorable clinical behavior. Type II tumors represent 10–20% of the sporadic endometrial carcinomas and usually arise in a background of atrophic endometrium via a mechanism unrelated to estrogen. They are more common in postmenopausal women. These tumors consist mostly of serous and clear-cell carcinomas, are typically high-grade, and are characterized by a more aggressive course and poorer prognosis compared with Type I tumors [4].

Beyond this classification, up to 10% of the cases are associated with hereditary predisposition [2]. Up to 5% of the tumors in this subclass are associated with hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) [5]. This syndrome is inherited in an autosomal-dominant fashion and it is also associated with early-onset rectal, ovarian, small bowel and ureter/renal pelvic tumors [6].

In the USA, most cases of endometrial cancer are diagnosed at an early stage. Subsequently, the 5-year relative survival rate for women diagnosed with endometrial carcinoma is 83%. Notably, relative survival in Caucasian women exceeds that for African–American women by more than 8% at each corresponding stage

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of disease [7]. Despite the favorable prognosis associated with early diagnoses, prognosis is poor following recurrence or diagnosis at an advanced stage.

Current treatment of endometrial cancer

The current treatment for endometrial cancer involves the use of surgery, radiation therapy, hormone therapy and chemotherapy either alone or sequentially. The staging and primary surgical treatment for endometrial cancer involves a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) with pelvic and paraaortic lymph node dissection [8]. Although the American Congress of Obstetricians and Gynecologists (ACOG) recommends full surgical staging, including lymph node dissection, for all cases of endometrial cancer [9], this remains controversial. Two recent trials did not show improvement in disease-free or overall survival (OS) after lymphadenectomy in early-stage disease [10,11]. However, the concern exists that omitting lymphadenectomy in patients with grade 1 tumors may lead to inappropriate postoperative treatment [12].

Traditionally, surgical treatment of endometrial cancer has been through laparotomy. Over the last 15 years, however, minimally invasive approaches have gained wide acceptance and are frequently used. The laparoscopic surgical approach involves either laparosocopic-assisted vaginal hysterectomy (LAVH) or total laparoscopic hysterectomy (TLH) [13]. A study conducted by the Gynecologic Oncology Group (GOG) randomized more than 2600 patients with stage I–IIA uterine cancer to laparoscopy or laparotomy [14]. This trial demonstrated that laparoscopic surgery was safe, and patients in the laparoscopy group had significantly less postoperative adverse events. This trial also found that although operative time was longer in the laparoscopy group, duration of hospitalization was significantly shorter and the intraoperative complication rate was similar regardless of the surgical approach [14]. Follow-up of these patients is ongoing to determine whether there are differences in survival and disease recurrence between the two groups. A recent meta-analysis also demonstrated comparable treatment effectiveness between the two surgical approaches with the laparoscopy group having longer operative time but fewer perioperative complications, decreased blood loss, shorter hospital stay and faster return to normal activity [15]. Beyond laparoscopy, there is a considerable amount of literature emerging about robotic-assisted surgical approaches for endometrial cancer staging. In a study comparing laparotomy, laparoscopy and robotic-assisted approaches, the robotic approach resulted in the shortest hospital stay, lowest estimated blood loss and highest lymph node yield [16].

Radiation therapy is used in the adjuvant setting in the treatment of endometrial cancer. The use of radiation in early-stage disease has been evaluated in five major trials. Two of these trials looked specifically at pelvic external beam radiation therapy (EBRT) in the adjuvant setting [17,18], while the trial by Aalders *et al.* as well as the A Study in the Treatment of Endometrial Cancer (ASTEC) trial compared pelvic EBRT in combination with vaginal brachytherapy vs vaginal brachytherapy alone [19,20]. Last, the Postoperative Radiation Therapy in Endometrial Cancer (PORTEC)-2 trial randomized patients to vaginal brachytherapy or pelvic EBRT in the adjuvant setting [21]. All of these studies demonstrated that radiation therapy, regardless of the modality, improved local disease control and recurrence-free survival, but did not decrease the rate of distant metastases or improve OS [17–21]. The GOG trial found that the reduction in recurrence risk was particularly evident in a high–intermediate-risk subgroup of women with three risk factors (grade 2 or 3 tumors, lymphovascular invasion, and invasion of the outer third of the myometrium), those ≥50 years of age with two of these risk factors, and those ≥70 years of age with one risk factor [18]. These risk factors have found their way to both clinical management and in the design of more contemporary endometrial cancer trials; for example, the currently enrolling GOG 249 trial in early endometrial cancer (stage I–II), comparing pelvic radiation to vaginal brachytherapy with chemotherapy, has incorporated these factors as part of its eligibility [101]. The results of this trial will identify if adding chemotherapy to vaginal brachytherapy can replace pelvic radiation among this high–intermediate patient subgroup.

Trials evaluating vaginal brachytherapy (VBT) did not show a difference when combined with EBRT or if used alone [19–21]. However, one of these, the PORTEC-2 trial, demonstrated a reduction in the rate of toxicity in the brachytherapy group [20]. Thus, VBT is now considered an acceptable option in women with early-stage, high–intermediate-risk disease who have undergone complete surgical staging. Radiation therapy also plays a key role in the treatment of local disease recurrence, especially if the patient is not a good surgical candidate or if the lesions cannot be completely resected. The 5-year survival rate may be as high as 75% in women with an isolated vaginal recurrence treated with radiation therapy [22].

Oral or parenteral progesterone may play a role in the conservative management of patients with endometrial cancer, particularly those that are early-stage and well differentiated. In a series of 81 patients with these disease characteristics, 62 (76%) responded to treatment, of which 15 (24%) recurred and ten (67%) of these

ultimately underwent total abdominal hysterectomy. Six of the patients that had a hysterectomy had evidence of persistent grade 1 adenocarcinoma, but none of the patients had extrauterine extension, and no patient in the series died of her disease [23]. Furthermore, 20 of the patients were able to become pregnant at least once after completion of the treatment.

Despite the favorable outcome associated with early-stage disease, the prognosis is poor following disease recurrence (with the exception of local vaginal recurrence) or diagnosis at an advanced stage. Surgical cytoreduction, however, may play a significant role even in the treatment of this cohort of women. In one study, complete resection to no gross disease was associated with an improvement in median survival [24]. However, many of these patients have multiple comorbidities including obesity, diabetes and hypertension, which may render them poor surgical candidates.

Beyond surgery, multiple clinical trials have been conducted addressing the issue of optimal therapy for patients with advanced or recurrent disease. GOG 122 randomly allocated 396 patients with stage III/IV endometrial carcinoma following total abdominal hysterectomy to whole-abdominal radiotherapy (WART) or chemotherapy with doxorubicin and cisplatin (AP). Chemotherapy significantly improved 5-year progression-free survival (PFS; 50 vs 38%), and OS (55 vs 42%) when compared with WART. However, pelvic recurrence rate was slightly higher in the chemotherapy group (18 vs 13%) [25].

The Japanese Gynecologic Oncology Group 2033 trial randomized women to either whole-pelvic radiation versus a combination of cisplatin, doxorubicin and paclitaxel (CAP) [26]. The study population included 25% with stage III disease and 14% with grade 3 histology; the majority had stage IC (61%) and grade 1 tumors (55%). Overall, there was no difference between radiation and chemotherapy in 5-year PFS and OS. In the subgroup analysis, women at high–intermediate risk as defined by stage IC with age >70 years or grade 3 tumors, or by stage II or IIIA with >50% myometrial invasion, had significantly better PFS (84 vs 66%) and OS (90 vs 74%) with chemotherapy than radiation [26].

GOG 184 randomized 552 women with advanced disease who underwent surgical debulking and adjuvant radiation therapy to AP or CAP [27]. At 3 years, recurrence-free survival did not differ between the two groups. In a subgroup analysis, CAP was associated with a 50% reduction in the risk of relapse or death compared with AP in women with gross residual disease at enrollment; however, the CAP regimen was associated with more frequent and severe hematologic toxicity, sensory neuropathy and myalgia.

Based on data from these trials, there is now more frequent use of chemotherapy for the first-line treatment of women with advanced disease. Four active agents have been identified in Phase II trials: doxorubicin, cisplatin, carboplatin and paclitaxel **(Table 1)** [28–37]. Follow-up trials were then focused on combination chemotherapy. An early trial demonstrated that paclitaxel, when used as a single agent, had a response rate of 36% in this patient population [37]. A landmark trial demonstrated an increased response rate as well as a PFS difference of 5.7 versus 3.8 months when using AP versus doxorubicin alone, respectively. However, OS was no different [38]. Using the findings from these two trials, a comparison was made between paclitaxel and doxorubicin versus AP. This trial failed to demonstrate a significant difference in response rate, PFS or OS, and AP remained the standard of care [39]. However, given the high single-agent activity of paclitaxel and cisplatin, a follow-up trial, GOG 177, randomized patients to AP with or without paclitaxel [40]. The triple-agent therapy had an increased response rate as well as PFS and OS [40]. These findings support the results from the subgroup analysis of GOG 184, where treatment with CAP was associated with a 50% reduction in the risk of relapse or death compared with AP in women with gross residual disease at enrollment [27]. The cumulative effect of these studies has been the realization of the important role chemotherapy plays in the management of advanced endometrial cancer, and as a result, the more common utilization of chemotherapy in the postoperative (adjuvant-intent) setting.

However, the combination of chemoradiation has not been completely ruled out as a treatment alternative given the ability of radiotherapy to control loco-regional disease. Some trials have looked at this combination in a sequential approach with patients receiving radiotherapy followed by chemotherapy. In a pooled analysis of two randomized trials, the sequential approach, compared

Table 1. Single-agent activity in endometrial cancer.

Study	Agent	Dose	Response rate		Ref.
			No.	%	
Thigpen *et al.*	Doxorubicin	60 mg/m^2	16/43	37	[28]
Horton *et al.*	Doxorubicin	50 mg/m^2	4/21	19	[29]
Thigpen *et al.*	Doxorubicin	60 mg/m^2	22/97	22	[30]
Thigpen *et al.*	Cisplatin	50 mg/m^2	10/49	20	[31]
Seski *et al.*	Cisplatin	50, 70, 100 mg/m^2	11/26	42	[32]
Tropé *et al.*	Cisplatin	50 mg/m^2	4/11	36	[33]
Deppe *et al.*	Cisplatin	3 mg/kg	4/13	31	[34]
Green *et al.*	Carboplatin	400 mg/m^2	7/23	30	[35]
Long *et al.*	Carboplatin	300–400 mg/m^2	7/25	28	[36]
Ball *et al.*	Paclitaxel	200–250 mg/m^2	10/28	37	[37]

with plain radiotherapy, was associated with a reduced risk for relapse as well as improved cancer-specific survival with hazard ratios of 0.63 and 0.55, respectively. However, OS was not improved [41]. A separate multicenter retrospective analysis evaluated the outcome of different sequential therapy approaches: chemotherapy, followed by radiation, and then further chemotherapy (CRC); radiation followed by chemotherapy (RC); and chemotherapy followed by radiation (CR). Compared to RC and CR, patients treated with CRC had a superior 3-year OS (88%) and PFS (69%) [42]. This 'sandwich' approach has been evaluated in several single-institution trials [43–45]. A retrospective analysis of 23 patients receiving this treatment modality had PFS of 74% and OS of 79% at 5 years [43]. A prospective cohort evaluating carboplatin and paclitaxel interposed with radiation in women with stage III–IV endometrial cancer demonstrated 3-year disease-free survival and OS rates of 53 and 68%, respectively [44]. Last, in our own series of 25 patients treated with six cycles of carboplatin and paclitaxel with radiation (given after the first three cycles), median PFS and OS was not reached with 32-month median follow-up and 96% were able to complete sandwich therapy [45].

Research is ongoing evaluating chemoradiotherapy as a treatment option. The GOG 258 trial, which is currently recruiting, will evaluate carboplatin and paclitaxel given with or without cisplatin-sensitizing radiation therapy in women with stage III or IVA disease [102]. Alongside this paradigm shift in the upfront management where active agents are utilized earlier in the management of this disease, there has been a subsequent change in the management options for women who relapse after first-line therapy and, to date, there are no US FDA-approved agents in this indication. The GOG has conducted multiple Phase II trials of single-agent chemotherapy in this context, but responses are only seen in a limited number of patients and typically last for only several months (Table 2) [46–52]. One of the underlying factors for reduced clinical benefit may be the presence of resistance to the currently available first-line chemotherapy agents. The paclitaxel trial by Lincoln *et al.* showed this agent to have a high response rate as a second-line drug [49]. However, none of the patients enrolled in that study had been previously exposed to taxanes, thus mitigating the role of chemoresistance. By contrast, Garcia *et al.* only achieved a 7% response rate when patients received the taxane docetaxel as a second-line agent; however, 20 of the 26 patients in this trial had been previously exposed to paclitaxel [51]. Interestingly, Dizon *et al.* achieved a 12% response rate with ixabepilone as a second-line single agent, which is noteworthy considering that 94% had previously received a taxane [52].

Hormone therapy is typically reserved for use in advanced or recurrent disease, with the exception of progesterone in early, well-differentiated disease, as discussed earlier. In the setting of advanced disease, progesterone has been used as a first-line agent achieving higher response rates in patients with hormone receptor-positive tumors and increased median survival in patients with low-grade disease [53]. Tamoxifen has also been evaluated in the setting of advanced disease. In a study by the GOG, tamoxifen demonstrated only a 10% overall response rate as a single agent [54]. However, two GOG trials demonstrated response rates of 27 and 33% when tamoxifen was combined with either megestrol acetate or medroxyprogesterone, respectively [55,56]. Yet, whether the combination of tamoxifen and progesterone is more effective than progesterone alone has only been evaluated in a single, randomized Phase II trial that showed no difference between the two treatment arms [57]. Thus, further studies are warranted. Aromatase inhibitors and gonadotropin-releasing hormone (GnRH) agonists have also been used, although the data supporting their activity are relatively sparse.

The poor prognosis of patients with advanced and recurrent endometrial carcinoma emphasizes the need for new treatment approaches. Currently, interest has focused on three classes of agents: epothilones, angiogenesis inhibitors and mTOR inhibitors. These novel therapies, and their rationale for use in endometrial cancer, will be the main focus of the remainder of this review.

Epothilones

The epothilones are a family of new microtubule-stabilizing agents that have received special attention because of their retained activity in taxane-resistant and -refractory tumors. Preclinical studies have also demonstrated that epothilones may not be affected by resistance mechanisms, including P-glycoprotein overexpression. Ixabepilone is the first drug in this class that has been approved by the FDA for use as a second-line agent in patients with metastatic or advanced breast cancer that is refractory to capecitabine, anthracyclines and taxanes [58–60]. Ixabepilone has also shown activity in a variety of other solid cancers in Phase II trials, including prostate, non-small-cell lung, and squamous cell carcinoma of the head and neck [61–65].

The documented activity of ixabepilone in breast cancer and other solid tumors refractory to taxanes prompted a Phase II clinical trial with this agent in patients with recurrent or persistent endometrial carcinoma who had failed one prior chemotherapy regimen [52]. The overall response rate was 12%. Out of the 50 patients that were enrolled in the trial, one patient achieved a complete remission, while five others achieved partial remission lasting between 4.2 and 19.8 months. Stable disease for

Table 2. Single-agent chemotherapy in second-line treatment of advanced or recurrent endometrial cancer.

Study	Agent	Dose	Response rate		Median response duration (months)	Ref.
			No.	%		
Sutton *et al.*	Ifosfamide	1.2 g/m^2/day x 5 days every 4 weeks	6/40	15	3.9	[46]
Miller *et al.*	Topotecan	0.5–1.5 mg/m^2/day x 5 days every 3 weeks	2/22	9	2.1–6.9	[47]
Muggia *et al.*	PLD	50 mg/m^2 over 1 h every 4 weeks	4/42	9	1.1–5.4	[48]
Lincoln *et al.*	Paclitaxel	175–200 mg/m^2 over 3 h every 3 weeks	12/44	27	4.2	[49]
Fracasso *et al.*	Oxaliplatin	130 mg/m^2 over 2 h every 3 weeks	7/52	13	10.9	[50]
Garcia *et al.*	Docetaxel	36 mg/m^2 over 1 h on days 1, 8 and 15 every 4 weeks	2/26	7	2	[51]
Dizon *et al.*	Ixabepilone	40 mg/m^2 as a 3 h infusion on day 1 of a 21-day cycle	6/50	12	2.9	[52]

PLD: Pegylated liposomal doxorubicin.

at least 8 weeks was noted in 30 patients, and the median PFS was 2.9 months, while the 6-month PFS was 20%. The median OS was 8.7 months [52]. The most common side effects were neutropenia and gastrointestinal and constitutional symptoms. While these results are modest, it is important to remember that all patients had been treated with platinum and 94% of the patients had also previously received a taxane. These results provide the background for the Phase III study comparing ixabepilone with paclitaxel or doxorubicin in women with locally advanced, recurrent or metastatic endometrial cancer who progressed after first-line chemotherapy, which is now recruiting [103]. The primary end point is OS and the results of this study will determine whether ixabepilone emerges as the preferred second-line agent for the treatment of recurrent/metastatic disease. This study also represents the first trial aiming for FDA approval as a second-line treatment in this disease. The second study is a three-arm, randomized, Phase II trial sponsored by the GOG. This study is looking at new treatment combinations that may be used in chemotherapy-naive patients with advanced-stage or recurrent endometrial cancer. Two of the treatment arms include two of the standard first-line agents (carboplatin and paclitaxel), while doxorubicin is replaced by bevacizumab or temsirolimus, two of the emerging targeted therapies in the treatment of endometrial cancer. In the third treatment arm, carboplatin remains in addition to bevacizumab but the paclitaxel is replaced by ixabepilone [104]. Therefore, pending the results of this study and follow-up trials, ixabepilone may emerge as a first-line agent in the treatment of endometrial cancer.

mTOR inhibitors

Endometrial carcinomas with endometrioid histology involve mutations in *PTEN*, *K-ras* and β-*catenin*, as well as defects in DNA mismatch repair leading to microsatellite instability [66]. Out of these mutations, the most common is in the PTEN tumor-suppressor gene [67,68]. The protein product of PTEN has several functions including cell-cycle arrest at the G1/S checkpoint and regulation of mechanisms involved in apoptosis. One of the mechanisms through which PTEN regulates apoptosis involves three other gene products PI3K, AKT and mTOR (Figure 1). PI3K, once activated, phosphorylates PI-(4)-phosphate and PI-(4,5)-biphosphate (PIP_2) into PI-(3,4)-biphosphate and PI-(3,4,5)-triphosphate (PIP_3). PIP_3 binds to AKT, which undergoes a conformational change that allows its phosphorylation by PDK1 at Thr308 and at Ser473 by mTOR complex 2. This results in AKT activation. Activated AKT then activates mTOR, a central regulator of cell growth and apoptosis [69]. PTEN opposes the activity of PI3K, and thus controls the levels of phosphorylated AKT.

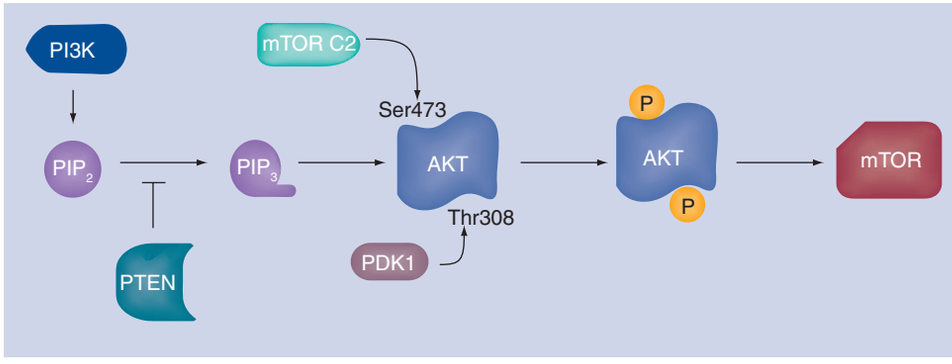

Figure 1. PI3K/AKT/mTOR pathway.
P: Phosphorylation; PDK1: Phosphatidylinositol-dependent kinase 1; PIP_2: Phosphotidylinositol-(4,5)-bisphosphate; PIP_3: Phosphatidylinositol-(3,4,5)-triphosphate; PTEN: Phosphatase with tensin homology.

Once PTEN is mutated or altered, the protein product losses the ability to regulate PI3K and AKT leading to unchecked upregulation of mTOR, ultimately resulting in activation of several transcription factors that drive abnormal cell growth and escape from apoptotic pathways [70,71]. Loss of PTEN is probably an early event in tumorigenesis, as evidenced by its presence in precancerous lesions. The mutation is well documented in endometrial hyperplasia with and without atypia [72].

The high occurrence of PTEN mutation in endometrial cancer and the subsequent upregulation of the PI3K/AKT/mTOR pathway has led to the active investigation of several known mTOR inhibitors as potential second-line therapies for patients with advanced or recurrent disease. The three mTOR inhibitors that are currently being studied are temsirolimus, ridaforolimus (previously known as deforolimus) and everolimus (Table 3) [73–75]. Treatment of 27 women with temsirolimus achieved an 8% partial response rate, and 44% of the patients experienced stable disease [73]. Of the patients, seven developed side effects including pneumonitis, mucositis, gastrointestinal symptoms, fatigue and pain. Ridaforolimus treatment was administered to 45 patients, of whom 34 had received prior chemotherapy. The most common adverse events included fatigue, anemia and hyperglycemia. A total of 18 of the patients that received the treatment discontinued the therapy, primarily due to disease progression. Out of the remaining 27 patients, 28% had either a complete or partial response [74]. Last, everolimus, which is the only oral mTOR inhibitor that has been studied to date, showed a PFS of 4.5 months. The side effects included abdominal pain and nausea/vomiting [75]. Based on these results, mTOR inhibitors exhibit activity against advanced or recurrent endometrial carcinoma and thus, warrant continued evaluation. In addition, in endometrial cancer cell lines, rapamycin has been shown to act synergistically with cisplatin and paclitaxel by inhibiting cellular growth and proliferation as well as by inducing apoptosis [76,77]. Based on these findings, clinical trials are currently evaluating the activity of mTOR inhibitors in combination with chemotherapy. A Phase I trial of everolimus used in combination with topotecan for the treatment of advanced endometrial cancer is currently recruiting [105].

Multiple other agents targeting the PI3K/AKT/mTOR pathway are currently being developed and may eventually warrant investigation in patients with endometrial cancer. Some of these agents include bisindolylmaleimide MKC-1 (formerly known as Ro-31–7453), an orally active, small molecule that reduces phosphorylated AKT; and suberoylanilide hydroxamic acid (SAHA), which was demonstrated to decrease expression of mTOR and one of its downstream targets [78].

Angiogenesis inhibitors

Angiogenesis is integral to the growth and metastasis of many malignancies, including endometrial cancer [78]. High VEGF levels were observed in 56% of 111 endometrioid endometrial carcinomas, and were strongly correlated with angiogenesis and poor patient outcome [79]. Of the agents in this class under investigation, data involving bevacizumab are available. In a retrospective analysis involving nine patients with recurrent disease, bevacizumab was administered with a cytotoxic agent, and the combination showed a partial response in two out of eight evaluable patients and two other women had stable disease [80]. A recent Phase II trial of bevacizumab in patients with recurrent or persistent endometrial cancer after one or two prior chemotherapy regimens showed objective responses in eight out of the 53 patients, one of which had a complete response. In addition, 19 patients were progression free at 6 months. The median PFS and OS were 4.2 and 10.5 months, respectively [79]. Cardiovascular side effects as well as pain were the most common toxicities, with each developing in 7.5% of the patients. These findings indicated that bevacizumab has promising single-agent activity, and as such it is being actively investigated when given in combination with other targeted agents such as temsirolimus or with standard chemotherapeutic agents (carboplatin/paclitaxel) [104,106]. Beyond bevacizumab, sunitinib, a tyrosine kinase inhibitor against multiple VEGF receptors, has also been evaluated in a completed Phase II trial. A Phase II study of 16 patients with recurrent or metastatic endometrial carcinoma who had received one prior chemotherapy regimen produced partial responses in two patients (12.5%) and stable disease in two others. However, the median time to tumor progression was only 2.5 months [81]. It remains

Table 3. Phase II trials of mTOR inhibitors in the treatment of endometrial cancer.

Study	Agent	Dose	Response rate		Stable disease		Ref.
			No.	%	No.	%	
Oza *et al.*	Temsirolimus	25 mg weekly	2/27	7.4	12/25	44	[73]
Colombo *et al.*	Deforolimus	12.5 mg/day x 5 days every other week	2/27	7.4	7/27	26	[74]
Slomovitz *et al.*	Everolimus	10 mg/day	0/29	0	11/29	38	[75]

to be seen whether this agent has a future role in endometrial cancers. Other angiogenesis-directed agents that continue in development through the GOG are aflibercept (VEGF-Trap), the oral angiokinase inhibitor Brivanib and, soon to activate, is the oral triple angiokinase inhibitor, BIBF-1120.

Future perspective

Despite several decades of extensive research and the development of multiple agents with known activity against endometrial cancer, the prognosis and survival rate has not significantly improved. The current and future challenge entails how best to treat women with advanced or recurrent disease; especially those women who relapse after first-line therapy and for whom there is no current standard of care.

Our understanding of the molecular basis of tumorigenesis has grown significantly, and consequently new therapies have been proposed targeting specific molecular alterations such as the mTOR inhibitors and the angiogenesis inhibitors. Our more detailed understanding has also allowed us to understand some of the mechanisms involved in the chemoresistance of first-line agents leading to new drugs, such as the epothilones, which may circumvent some of the known resistance pathways.

Given the paucity of effective second-line agents for the treatment of recurrent or advanced endometrial cancer, current trials are not only focusing on the activity of these novel agents, but also on the maximization of treatment response. Clinical evidence suggests that it may be possible to improve on the activity achieved by these agents when they are given in combination with existing cytotoxic agents or with each other. Testament to this is the three-arm, Phase II GOG trial looking at new treatment combinations that involve carboplatin, paclitaxel, bevacizumab (a VEGF inhibitor), temsirolimus (an mTOR inhibitor) and the epothilone ixabepilone [103]. Results of this trial may redefine first-line therapy for advanced endometrial cancer and are thus eagerly anticipated.

Recently, trastuzumab was shown to have some activity in two patients with advanced endometrial carcinoma expressing HER2/neu [82], a transmembrane receptor that is often present in high-grade tumors [83]. Currently, there are no clinical trials evaluating trastuzumab, but given these findings, upcoming trials may include this agent to evaluate the response in high-grade tumors.

In conclusion, as the results of the clinical trials discussed in this review become available, along with further understanding of the tumorigenesis of endometrial cancer, it will be possible to better define an ideal treatment regimen and sequence for patients with advanced disease.

Disclaimer

The authors take full responsibility for the content of this publication and confirm that it reflects their viewpoint.

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Executive summary

- The current treatment for endometrial cancer involves the use of surgery, radiation therapy, hormone therapy and chemotherapy either alone or sequentially.
- Early-stage disease has a favorable prognosis.
- For women with recurrent or advanced-stage disease, the prognosis is poor and the hallmark of therapy has been chemotherapy.
  - First-line chemotherapy typically consists of a combination regimen using cisplatin/doxorubicin/paclitaxel, followed by treatment with a single agent on disease progression.
  - Currently there is no standard treatment for women who relapse after first-line therapy.
- Ongoing research has focused on three classes of agents: epothilones, angiogenesis inhibitors, and mTOR inhibitors.
  - Epothilones are microtubule-stabilizing agents that have demonstrated retained activity in taxane-resistant and -refractory tumors.
  - The mTOR inhibitors (i.e., temsirolimus) and the VEGF inhibitors (i.e., bevacizumab) have shown promising activity against endometrial carcinoma.
- Clinical trials are underway to determine how to best incorporate these novel therapies in the treatment of endometrial carcinoma.

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- ■■ of considerable interest

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▪▪ **The results of this study will determine if ixabepilone emerges as the preferred second-line agent for the treatment of recurrent/metastatic endometrial carcinoma.**

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▪▪ **The results of this study may redefine the first-line treatment for advanced endometrial cancer.**

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▪▪ **This trial will further evaluate the activity of everolimus, one of the mTOR inhibitors, when given in combination with topotecan. This trial will further help define an ideal treatment regimen and sequence for patients with advanced disease.**

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▪▪ **This trial will evaluate the activity of bevacizumab and temsirolimus when these two agents are given in combination. This trial does not include any cytotoxic agent as part of the treatment regimen, thus highlighting the important role that targeted therapies play in the treatment of endometrial cancer.**