



Marguerite Bride. *Country Farm II*. Watercolor, 10" × 15".

*Systemic treatments for patients with metastatic endometrial cancer are reviewed.*

## Current Treatment of Metastatic Endometrial Cancer

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**Background:** Endometrial cancer is the most common gynecologic malignancy. The majority of patients have disease confined to the uterus and have an excellent overall prognosis. However, subgroups of patients have advanced primary disease or recurrences following primary treatment.

**Methods:** The management of metastatic disease is variable, depending on factors such as comorbidities, tumor grade, performance status, and prior treatments. Management options include hormonal therapy and cytotoxic chemotherapy, as well as targeted therapies that inhibit angiogenesis and the cellular signaling pathways involved in cell growth and proliferation. A comprehensive review of these treatments for metastatic endometrial cancer was conducted and is discussed.

**Results:** Hormonal therapy and cytotoxic chemotherapy have traditionally been used in the treatment of metastatic endometrial cancer. Advances in molecular biology have led to multiple potential targeted therapies to be used in the treatment of metastatic endometrial cancer.

**Conclusions:** While several treatment modalities are now available to treat patients who present with metastatic endometrial cancer, overall prognosis remains poor.

### Introduction

It is estimated that over 40,000 women were diagnosed with cancer of the uterus in 2008.<sup>1</sup> Overall prognosis for these women is excellent as the majority of patients present with early-stage disease that is confined to the uterus at the time of hysterectomy, leading to 5-year sur-

vival rates of greater than 70%. Women who are at high risk for recurrence and/or metastasis include those with deep myometrial invasion, grade 3 disease, or high-risk cellular histologic types such as serous or clear cell.<sup>2</sup> Although serous and clear cell carcinomas of the uterus account for less than 10% of cases of endometrial cancer diagnosed, these tumors tend to be estrogen-independent and clinically aggressive, usually presenting at a high stage and grade, and are frequently refractory to therapies often used to treat type endometrioid endometrial cancers.

A metastatic workup including radiographic imaging by CT scan of the upper abdomen and chest is appropriate following surgical staging that reveals risk factors for metastases. It is also appropriate in unstaged

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*Abbreviations used in this paper:* GOG = Gynecologic Oncology Group, ER = estrogen receptor, PR = progesterone receptor.

patients with high-risk histologic types (grade 3 endometrioid, serous, or clear cell).

A small minority of women with recurrent or advanced-stage disease present with solitary metastatic lesions that are amenable to radiation with or without surgical resection. Women with vaginal recurrences who have not received radiation can be treated with radiation, with complete response rates of 40% to 81%.<sup>3,5</sup> Small central pelvic recurrences within a radiated field may be cured with pelvic exenteration.<sup>6</sup> Multiple reports of women with isolated metastasis to the lung parenchyma, brain, or liver who achieved long-term survival following an excisional surgical procedure have been published.<sup>7,8</sup>

Prognosis is poor for the remainder of patients with metastatic endometrial cancer, with a median survival of only approximately 12 months for women enrolled in clinical trials for recurrent or metastatic endometrial cancer.<sup>9</sup> The mainstay of treatment of recurrent and metastatic endometrial cancer remains systemic therapy in the form of hormonal therapy or cytotoxic chemotherapy. Patients with low-grade disease with estrogen receptor (ER)-positive and progesterone receptor (PR)-positive carcinoma tend to respond as well to hormonal therapy as to cytotoxic chemotherapy, with fewer side effects. Hormonal therapy may also be prioritized in patients with poor performance status and/or multiple medical comorbidities. Cytotoxic chemotherapy may be more appropriate as initial therapy for younger patients with high grade disease.

## Hormonal Therapy

Since the uterus is a sex steroid-responsive target organ, hormonal treatment is a logical option in patients with endometrial cancer. The ER and PR status in metastatic endometrial cancer has predictive value in determining response to hormonal therapy, which supports the use of these assays in the management of patients with metastatic disease. However, they remain imperfect predictors, and up to 10% of women with hormone receptor-negative tumors have been reported to have an objective response to hormonal therapy.<sup>10,11,12</sup> In patients with poor performance status, hormonal treatment provides a therapeutic choice with few side effects and low morbidity.

### Progestins

As early as the 1950s, progestins were reported to have an antiestrogenic effect on the endometrium and to produce marked changes in the glands and stroma. This led to the concept that they might be useful in the treatment of endometrial cancer.<sup>15</sup> Within the glandular epithelium of the endometrium, progesterone primarily acts as an antagonist to estrogen-mediated cell proliferation. Progesterone inhibits ER gene expression and enhances degradation of the ER.<sup>14</sup>

Response rates to progestin therapy of 34%, with progression-free intervals of 16 to 28 months, were initially reported in a retrospective analysis.<sup>15</sup> However, subsequent prospective trials demonstrated overall response rates between 11% and 16% in women treated with medroxyprogesterone acetate or megestrol acetate, with progression-free intervals of only 4 to 6 months.<sup>10,11,16,17</sup> Because progestins paradoxically downregulate the ligand-dependent activation of the PR, long-term continuous exposure to progestins may set the stage for loss of effect within the endometrium.<sup>18</sup>

Low histologic grade, the presence of PR within the tumor, and an extended interval between initial diagnosis and development of metastatic disease have been shown to predict for response to hormonal treatment. Thigpen et al<sup>10</sup> reported a median survival of 18.8 months in progestin-treated patients with grade 1 tumors compared with 6.9 months for patients with grade 3 tumors. Low-grade tumors are more likely than high-grade tumors to express PR. Response rates as high as 37% have been reported in patients with PR-positive disease (measured by immunohistochemistry) compared with a response rate of 8% in women with PR-negative disease.<sup>10,11,12</sup> A recent systematic review addressed the issue of the optimal population among patients with metastatic endometrial cancer to receive treatment with progestin. Patients who were either ER- or PR-positive had high response rates (26% to 89%), while patients whose tumors were PR-negative had lower response rates (8% to 17%).<sup>12</sup> Although patients with low-grade tumors expressing ER and PR are more likely to have meaningful responses to progesterone treatment, receptor-negative status should not be an absolute contraindication to hormonal treatment.

The recommended dose of oral progestin for metastatic endometrial cancer given in the form of megestrol acetate is 200 mg/day. Dose escalation has not been shown to increase efficacy.<sup>11</sup> The major toxic effects of progestins given at doses routinely used in the treatment of endometrial cancer include the development of thrombophlebitis, pulmonary emboli, weight gain, and edema.<sup>10,11</sup>

### Selective Estrogen-Receptor Modulators

Selective estrogen-receptor modulators (SERMs) are compounds that bind to the ER with high affinity and display tissue- and cell type-specific ER agonism or antagonism.

**Tamoxifen:** Tamoxifen, which is widely used to both treat and prevent breast cancer, has been shown to increase the risk of endometrial cancer. It has modest efficacy in the management of metastatic endometrial cancer, with response rates of 10% in phase II studies.<sup>19</sup> As with progestin therapy, low-grade endometrial cancers are more likely than high-grade tumors to respond to treatment with tamoxifen.<sup>19</sup>

**Tamoxifen Combined With Progestins:** The Gynecologic Oncology Group (GOG) conducted two studies that combined progestins with tamoxifen using different schedules. This strategy was chosen to avoid the downregulation of PR that occurs with continuous treatment with progestin alone, the hypothesis being that intermittent treatment with progestin would permit tamoxifen to induce PR and thus enhance the effect of progestin therapy. In the first trial, patients received alternating 3-week courses of megestrol acetate and tamoxifen.<sup>20</sup> The overall response rate was 27%, the median progression-free survival was 2.7 months, and the response rate in patients with grade 1 endometrial cancer was 38%. Patients in the second trial were treated with continuous tamoxifen plus alternating weekly cycles of medroxyprogesterone acetate.<sup>21</sup> The response rate was 33%, with a median progression-free interval of 3 months. Although these response rates are higher than those reported for progestins alone, the progression-free intervals and overall survival rates are similar. A correlative study to this second trial explored the relationship between hormone receptor status and response to the combination of tamoxifen and megestrol. Interestingly, response rates were high even in patients with estrogen- and progesterone-negative tumors (a response rate of 26% for estrogen-negative tumors and 32% for progesterone-negative tumors).<sup>22</sup> The toxicities, which principally were weight gain and thromboembolic events, were tolerable with both regimens of tamoxifen plus progestin.

**Other SERMs:** In two multi-institutional phase II trials using arzoxifene (a nonsteroidal SERM that is not commercially available), response rates were 25% and 31%, with an acceptable toxicity profile.<sup>23,24</sup> The patient populations enrolled onto these trials were selected for low-grade disease and the presence of PR. An ongoing GOG trial is investigating the activity of fulvestrant, a pure ER antagonist that induces degradation of the ER in patients with recurrent/metastatic endometrial carcinoma. Hormone receptor status (estrogen and progesterone) will be correlated with response.

### Aromatase Inhibitors

The results of two phase II studies of aromatase inhibitors in the treatment of advanced endometrial carcinoma have been published. The first trial showed a response rate to anastrozole of only 9% in women without prior cytotoxic chemotherapy.<sup>25</sup> A large percentage of the patients enrolled in this trial had high-grade histology, which may have contributed to the low response rate. In a Canadian phase II study, letrozole 2.5 mg daily was given to 32 postmenopausal women with advanced or recurrent metastatic endometrial cancer. Of the 28 patients evaluable for response, 1 (4%) had a complete response, 2 (7%) had a partial response, and 11 (39%) had stable disease for a median

duration of 6.7 months (range 3.7 to 19.3 months).<sup>26</sup> A correlation between hormone receptor status and response was not found.

### Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone (GnRH) agonists cause an initial increase in pituitary gonadotropins, followed by a profound suppression that results in a decrease of gonadal sex hormones to castrate levels. However, most women with recurrent endometrial cancer are either surgically or naturally postmenopausal; thus these agents have been tested for the potential antagonism of the GnRH receptors on the endometrial cancer itself. Investigation into the activity of GnRH agonists in patients with endometrial cancer has shown rates ranging from 0% to 28%.<sup>27-29</sup> A GOG study of goserelin acetate reported two complete and three partial responses among 40 patients with recurrent disease (18% of whom had received prior progestins), for an overall response rate of 12.5%, a median progression-free survival of 1.9 months, and a median overall survival of 7.3 months.<sup>29</sup> This activity was deemed insufficient to warrant further study of GnRH agonists in the treatment of metastatic endometrial cancer.

### Cytotoxic Chemotherapy

Cytotoxic chemotherapy is the mainstay of therapy for metastatic endometrial carcinoma. Many cytotoxic chemotherapy regimens have demonstrated activity. Response rates, however, are modest, with progression-free intervals of approximately 4 to 6 months and median overall survival in the range of 12 months.<sup>9</sup> Many women with metastatic endometrial cancer are elderly and may have previously undergone pelvic radiation therapy, making them more susceptible to adverse effects of aggressive cytotoxic regimens.

### Single-Agent Chemotherapy

The most active classes of chemotherapy agents in metastatic endometrial cancer are anthracyclines, platinum compounds, and taxanes, all of which produce response rates of greater than 20% (Table 1).<sup>30-48</sup>

**Table 1. — Response Rates of Selected Single-Agent Cytotoxic Chemotherapy in Metastatic Endometrial Cancer Without Prior Chemotherapy**

Single Agent	Dose	Response Rate (%)
Doxorubicin <sup>30-32,43</sup>	50–60 mg/m <sup>2</sup> Q 3 wks	17–37
Epirubicin <sup>33</sup>	80 mg/m <sup>2</sup> Q 3 wks	26
Cisplatin <sup>39-41</sup>	50–100 mg/m <sup>2</sup> Q 3–4 wks	17–42
Carboplatin <sup>35-38</sup>	360–400 mg/m <sup>2</sup> Q 4 wks	24–33
Paclitaxel <sup>44-48</sup>	Various	20–36
Docetaxel <sup>42</sup>	35 mg/m <sup>2</sup> per wk	21
Ifosfamide <sup>34</sup>	5 g/m <sup>2</sup> Q 3 wks	12–25
Etoposide <sup>42</sup>	50 mg/d × 21 days Q 4 wks	14

Anthracyclines have been most extensively studied, with doxorubicin and epirubicin having similar overall response rates between 17% and 37%<sup>30-34,49</sup> and median time to progression of 6 to 9.5 months. Interestingly, pegylated liposomal doxorubicin was shown to have a single-agent response rate of only 9.5%.<sup>50</sup> Thirty-two of 40 of these patients had been previously treated with doxorubicin. This prompted another GOG trial of pegylated liposomal doxorubicin in patients without prior cytotoxic chemotherapy.<sup>51</sup> The response rate was again poor, only 11.5%, possibly because investigators placed patients on this trial whom they deemed could not tolerate more aggressive front-line therapy. However, there is no evidence to support this hypothesis. Cisplatin produces single-agent response rates of 17% to 42% when used in chemotherapy-naïve patients as well as patients with prior regimens.<sup>34,39-41,49,52</sup>

Carboplatin yields similar response rates to cisplatin with less toxicity.<sup>34-38,49,52</sup> Paclitaxel is the third drug that has consistently shown single-agent response rates of greater than 20%, in this case even when administered in patients with prior cytotoxic chemotherapy.<sup>34,44-49,52</sup> No other drug has shown response rates this high in the second-line setting.

Cyclophosphamide, ifosfamide, docetaxel, etoposide, and topotecan have all shown moderate response rates when given as single agents to women with metastatic endometrial cancer.<sup>34,42,52</sup> Gemcitabine has not been tested.

### Combination Chemotherapy

More recent chemotherapy trials investigating the treatment of advanced and metastatic endometrial cancer have focused on the use of cytotoxic chemotherapy in multidrug combinations. Response rates to combinations of cytotoxic chemotherapy range from 33% to 57% (Table 2).<sup>31,32,43,53,54</sup>

The GOG and the European Organisation for Research and Treatment of Cancer (EORTC) Gynaecological Cancer Group conducted two large phase III trials to examine the combination of cisplatin and doxorubicin with doxorubicin alone.<sup>32,43</sup> The GOG trial included 284 eligible patients. The overall response rate was 42% for patients receiving the combination compared with 25% for patients receiving doxorubicin alone ( $P = .004$ ). Median progression-free survival was 5.7 months for the combination regimen and 3.8 months in the single-agent arm.<sup>32</sup> In the EORTC trial, which enrolled 177 patients, the combination arm achieved a significantly higher response rate than the single-agent doxorubicin arm ( $P < .001$ ), with a response rate of 43% in the combination group vs 17% in the group who received doxorubicin alone.<sup>43</sup> Despite longer progression-free intervals in both

of these trials, an overall survival benefit was not seen. The cisplatin and doxorubicin doublet was found to produce similar results to paclitaxel plus doxorubicin in another randomized prospective trial.<sup>53</sup>

The next GOG phase III trial in endometrial cancer compared cisplatin plus doxorubicin to doxorubicin, cisplatin, and paclitaxel with granulocyte colony-stimulating factor (G-CSF) support. The three-drug arm produced more objective responses than the two-drug arm (57% vs 34%,  $P < .01$ ). Progression-free survival was extended to 8.3 months compared with 5.3 months in the control arm ( $P < .01$ ); and overall survival reached a median of 15.3 months compared with 12.3 months ( $P < .037$ ). Patients who received doxorubicin plus cisplatin on this trial were not likely to receive paclitaxel as first salvage therapy, which might account for the survival advantage for the three-drug combination. As seen in previous trials, increasing efficacy with more chemotherapy also led to increasing toxicity; patients receiving the three-drug combination were more likely to suffer thrombocytopenia and grade 3 and 4 neurotoxicity.<sup>54</sup>

The current GOG phase III trial compares the three-drug regimen of cisplatin, doxorubicin, and paclitaxel with G-CSF support to carboplatin combined with paclitaxel. Phase II trials testing the combination of carboplatin and paclitaxel in advanced, recurrent, or metastatic endometrial cancer have shown response rates of 46% to 78%. Oncologists are familiar with this regimen, and it is known to be generally tolerable.<sup>55-57</sup>

A Cochrane review recently attempted to address the issue of whether more chemotherapy is better in the case of treating advanced, recurrent, or metastatic endometrial cancer. Eleven randomized clinical trials were identified that included a total of 2,288 patients. A meta-analysis of six trials showed improved progression-free survival with more intensive chemotherapy

**Table 2. — Randomized Trials of Combination Chemotherapy in Metastatic Endometrial Cancer**

Study and Regimen	No. of Patients	Response Rate (%)	Median Overall Survival (mos)
Thigpen et al <sup>31</sup>	356		
Doxorubicin		22	6.7
Doxorubicin/cyclophosphamide		33	7.3
Aapro et al <sup>43</sup>	177		
Doxorubicin		17	7.0
Doxorubicin/cisplatin		43	9.0
Thigpen et al <sup>32</sup>	281		
Doxorubicin		25	9.2
Doxorubicin/cisplatin		42	9.0
Fleming et al <sup>53</sup>	317		
Doxorubicin/cisplatin		40	12.6
Doxorubicin/paclitaxel		43	13.6
Fleming et al <sup>54</sup>	273		
Doxorubicin/cisplatin		34	12.3
Doxorubicin/cisplatin/paclitaxel		57	15.3

compared with less intense chemotherapy (hazard ratio [HR] = 0.80, 95% confidence interval [CI] = 0.71-0.90;  $P = .004$ ) but a comparable overall survival (HR = 0.90, 95% CI = 0.80-1.03;  $P = .12$ ). Grade 3 and 4 toxicity, particularly in the form of myelosuppression and gastrointestinal toxicity, was higher in patients receiving more intense chemotherapy regimens.<sup>58</sup>

## Targeted Therapy

Recent advances in the understanding of the molecular and genetic basis of cancer have led to the development of targeted therapies that inhibit angiogenesis and the cellular signaling pathways involved in cell growth and proliferation. Several of these targeted agents are currently being investigated in endometrial carcinoma.

### mTOR Inhibitors

Inactivating mutations of phosphatase and tensin homolog (PTEN), a tumor suppressor gene, are found in 40% to 60% of endometrial cancers. As measured by immunohistochemistry, a loss or decrease of PTEN expression was seen in 66% of 61 endometrioid-type cancers, whereas four of five uterine serous carcinomas showed intense PTEN staining. PTEN-deficient cells are sensitive to mammalian target of rapamycin (mTOR) inhibitors in vitro since loss of PTEN leads to constitutive activation of Akt, which in turn upregulates mTOR activity (Figure).<sup>59</sup> Hence, there was interest in testing mTOR inhibitors in the treatment of endometrial cancer.

The National Cancer Institute of Canada reported a preliminary response rate of 26% in chemotherapy-naïve endometrial cancer patients treated with temsirolimus, an mTOR inhibitor.<sup>60</sup> Response in this group of patients was not correlated to PTEN status as evaluated by immunohistochemistry. Preliminary studies of other mTOR inhibitors, everolimus and AP2357, have shown clinical responses mainly in the form of stable disease (8 of 15 and 7 of 19 women, respectively).<sup>61,62</sup> A phase II trial of temsirolimus in heavily pretreated patients with endometrial cancer was recently completed by the NCIC. A 7% partial response rate and a 44% stable disease rate was seen.<sup>63</sup> Combinations of mTOR inhibitors with hormonal therapy, chemotherapy, or other targeted

therapies such as epidermal growth factor receptor (EGFR) inhibitors and antiangiogenic agents have been promising in the preclinical setting, and numerous trials to develop and test such combinations are underway. For example, investigators at the University of Chicago have undertaken a phase I trial of temsirolimus combined with topotecan in women with gynecologic malignancies for further development in ovarian and endometrial cancers. The GOG plans a trial combining bevacizumab and temsirolimus in endometrial cancer and also a trial combining progestin therapy with temsirolimus. In support of the latter combination, it has been shown in endometrial cancer cell lines that exposure to an mTOR inhibitor increases progesterone mRNA expression and inhibits ER mRNA expression.<sup>64</sup>

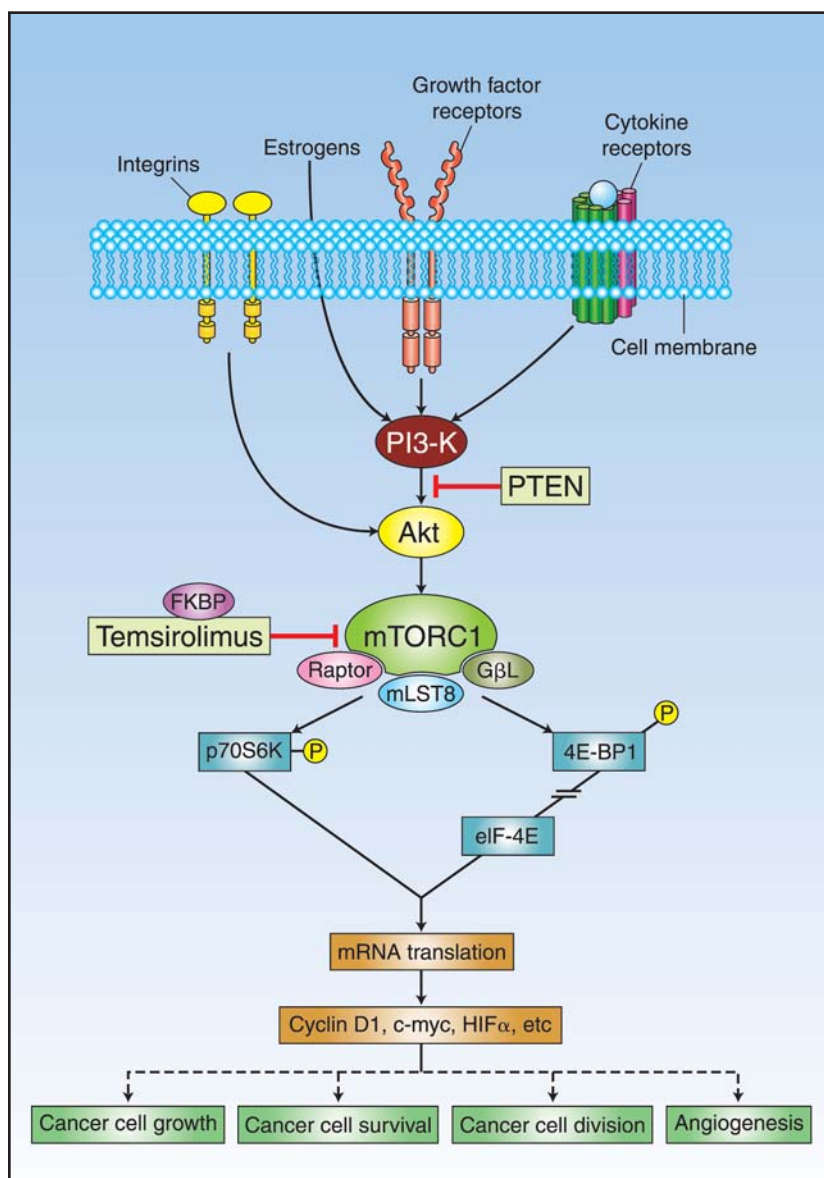


Figure. — Molecular targets in endometrial cancer. From Rini BI. Temsirolimus, an inhibitor of mammalian target of rapamycin. *Clin Cancer Res.* 2008;14(5):1286-1290. © 2008 by the American Association for Cancer Research. Reproduced with permission of the American Association for Cancer Research via the Copyright Clearance Center.

## Antiangiogenics

Bevacizumab is a recombinant humanized immunoglobulin monoclonal antibody to vascular endothelial growth factor (VEGF) that has shown significant activity in a number of malignancies. A small, retrospective review of the use of bevacizumab in recurrent uterine neoplasms showed 2 responses and 3 women with stable disease among 10 evaluable patients.<sup>65</sup> A phase II trial of single-agent bevacizumab in metastatic endometrial cancer has been completed within the GOG, and results should be available soon (GOG 229-E).

VEGF-Trap is a recombinantly produced fusion protein consisting of human VEGF receptor extracellular domains fused to the Fc portion of a human immunoglobulin  $\gamma$  (IgG). It functions as a decoy receptor preventing the VEGF ligand from interacting with its ligand. A GOG phase II trial of VEGF trap in metastatic endometrial cancer is ongoing (GOG 229-F).

A phase II trial of sorafenib, a tyrosine kinase inhibitor with antiangiogenic activity, has been completed in the National Cancer Institute's phase II network. Preliminary results show modest activity. A phase II trial of a second antiangiogenic tyrosine kinase inhibitor, sunitinib, is ongoing.<sup>66</sup>

## Trastuzumab

HER2 overexpression has been demonstrated and linked to prognosis in many cancer types. A recent study of HER-2 expression in banked tissue from patients with endometrial cancer revealed that 104 of 234 patients (44%) showed positive (2+/3+) cellular membrane HER-2 expression on immunohistochemistry (IHC) staining. Uterine serous carcinoma had the highest rate of HER-2 overexpression by IHC (43%) and of gene amplification measured by in situ hybridization (FISH) (29%). IHC and FISH positivity did not lead to an increase in disease specific death.<sup>67</sup> Trastuzumab is a monoclonal antibody to the extracellular domain of the HER-2 protein. Although the HER-2 overexpression seen in serous carcinoma of the uterus provides a strong biologic rationale for the use of trastuzumab in the treatment of this malignancy, a GOG study examining the use of trastuzumab in women with HER-2-positive endometrial cancer did not report any activity.<sup>68</sup>

## EGFR Inhibitors

EGFR is expressed in normal endometrium and is overexpressed in endometrial cancer where it is associated with advanced stage and poor prognosis.<sup>69</sup> Antagonists to EGFR include small molecule tyrosine kinase inhibitors (gefitinib, erlotinib, and lapatinib) and the anti-EGFR monoclonal antibody cetuximab. Erlotinib administration in women with recurrent and metastatic endometrial cancer led to only 1 partial response among 27 women, with 12 patients showing stable disease with a median duration of response of 3.4 months.<sup>70</sup> A phase

II clinical trial of cetuximab in recurrent endometrial cancer is ongoing.

It is hoped that other new therapies such as mismatch repair defects or PIK3CA mutations will be able to target specific known molecular defects in endometrial cancer and will achieve meaningful improvements in the prognosis of women with metastatic disease. Meanwhile, there is no good second-line treatment, and clinical trials should be encouraged.

## Conclusions

Women with metastatic endometrial cancer have an overall poor prognosis, with survival estimates of less than 1 year. Patients who are chemotherapy-naïve with a good performance status should be treated with combination chemotherapy. A combination of paclitaxel, doxorubicin, and cisplatin has shown the highest overall response rates to date. In women with multiple medical comorbidities, single-agent chemotherapy may be better tolerated with acceptable results. Hormonal therapy should be considered in women with low-grade tumors and/or in women with a poor performance status because of the low associated morbidity of treatment.

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