Update on the Chemotherapeutic Management of Endometrial Cancer

Amy Bregar, MD, Katina Robison, MD, and Don S. Dizon, MD

Dr Bregar is a fourth-year resident in obstetrics and gynecology at Women & Infants Hospital/Warren Alpert Medical School of Brown University in Providence, Rhode Island. Dr Robison is a gynecologic oncologist at Women & Infants Hospital and an assistant professor at the Warren Alpert Medical School of Brown University in Providence, Rhode Island. Dr Dizon is a medical oncologist at the Massachusetts General Hospital Cancer Center and Harvard Medical School in Boston, Massachusetts.

Address correspondence to:
Don S. Dizon, MD
55 Fruit Street
Boston, MA 02114
Tel: 617-724-4800
Fax: 888-922-8041
E-mail: ddizon@partners.org
Twitter: @drdonsdizon

Keywords
Chemotherapy, endometrial cancer, epothilones, mTOR inhibitors, tyrosine kinase inhibitors

Abstract: Endometrial cancer is the most common gynecologic cancer in the United States and the fourth most common cancer in women. Although endometrial cancer most often presents at an early stage, when surgical treatment is effective, chemotherapy has become a critical component in the treatment of advanced or recurrent endometrial cancer. The use of chemotherapy has evolved and is now often administered to women with early-stage disease in the presence of high-risk features (eg, clear cell or serous histology), or in the adjuvant setting for women with advanced disease that has been surgically cytoreduced. There are no agents approved by the US Food and Drug Administration for second-line or later use in the setting of endometrial cancer. Options for women whose disease progresses after adjuvant chemotherapy have varying success. Therapies that target specific molecular pathways have emerged as promising treatments for endometrial cancer. Given the poor response rates for systemic chemotherapy in patients with advanced or recurrent disease, these novel agents have great potential to influence our care for women with endometrial cancer. In this article, we review the role of chemotherapy in the treatment of endometrial cancer, with an emphasis on first- and second-line treatment and novel agents in clinical trials.

Introduction

Endometrial cancer is the most common gynecologic cancer in the United States and the fourth most common cancer in women, surpassed only by breast, lung, and colon cancer. The American Cancer Society estimates that in 2014, there will be approximately 52,630 new cases of uterine cancer and 8590 women will die of their disease.[1] The median age of diagnosis is 61 years, with the majority of endometrial cancers presenting between ages 50 and 60 years.[2] Incidence varies by race. Although the incidence of uterine cancer has stabilized in white women, it has increased by approximately 2% per year since 2004 for African American women.[3] African American women also are more likely to die of their disease compared with white women, independent of risk factors.[4]

Prognosis depends on many factors including stage, grade, histologic type, depth of myometrial invasion, lymphovascular space invasion, and the presence of distant disease.[5-8] Although endometrial cancer is most often diagnosed at an early stage owing to symptoms such as vaginal bleeding and bloating,[2] some women present with advanced or metastatic disease. In aggregate, patients who present with early-stage, localized disease have 5-year survival rates approaching 90%, whereas patients with distant disease at the time of diagnosis have a dismal 5-year survival rate of approximately 16%.[3]

Endometrial cancer is surgically staged according to the 2009 Federation of Gynecologists and Obstetricians (FIGO) staging system.[9] Most endometrial cancers are adenocarcinomas and can be classified into 2 types based on clinical, pathologic, and molecular data (Table 1).[10] Grade 3 endometrioid adenocarcinomas tend to behave similarly to more aggressive type 2 tumors, raising questions about the appropriateness of their classification as type 1 tumors.[11]

In this report we provide an overview of the role of chemotherapy in this disease, with an emphasis on the first- and second-line treatment and novel agents in clinical trials. Owing to space limitations, adjuvant treatment for early-stage, high-risk endometrial carcinoma and the role of endocrine therapy for this disease are not covered.

Table 1. Characteristics of Type 1 and Type 2 Endometrial Cancer

	Type 1	Type 2
Histology	Endometrioid	Serous or clear cell
Grade	Low	High
Precursor	Hyperplasia	Atrophy
Distribution	85%	15%
Hormonal impact	Estrogen dependent	Estrogen independent
Body habitus	Obese	Thin
Age	Perimenopausal	Postmenopausal
Risk factors	Diabetes, PCOS, nulliparity, late menopause	None
Genetic mutations	PTEN inactivation, *KRAS* mutation, microsatellite instability	*P53* mutation, *P16* mutation, HER2 overexpression
Prognosis	Better prognosis	More aggressive, generally higher mortality

HER2, human epidermal growth factor receptor 2; PCOS, polycystic ovary syndrome; PTEN, phosphatase and tensin homolog.

Data from Lewin SN. *Clin Obstet Gynecol.* 2011;54(2):215-218.[9]

First-line Chemotherapy in Endometrial Cancer

The use of chemotherapy has evolved and chemotherapy is now often administered to women with early-stage disease in the presence of high-risk features (clear cell or serous histologies) or in the adjuvant setting for women with advanced disease that has been surgically cytoreduced. This precedent was initially established from trials, including Gynecologic Oncology Group (GOG) 122, which randomly assigned 396 women with surgically cytoreduced stage III and IV endometrial cancer to whole abdominal radiation therapy (RT) or doxorubicin and cisplatin (AP) chemotherapy.[12] Compared with whole abdominal RT, AP improved progression-free survival (PFS) (hazard ratio [HR] for progression, 0.71 [95% CI, 0.55-0.91]) and overall survival (stage-adjusted death HR, 0.68 [95% CI, 0.52-0.89]). The most common grade 3 and 4 toxicities were hematologic (RT vs AP: leukopenia, 4% vs 6%; neutropenia, <1% vs 85%; thrombocytopenia, 3% vs 21%) and gastrointestinal (RT vs AP: 13% vs 20%).[12] Results of the subsequent GOG 177 trial suggested that the addition of paclitaxel (taxane, anthracycline, and platinum; TAP) might produce a greater benefit when administered with AP[13]; a subsequent phase 3 trial of TAP vs AP, GOG 184, found that paclitaxel was not associated with a survival advantage and that it caused an increase in toxicity.[14]

Given the toxicities associated with TAP, a subsequent randomized trial evaluated the efficacy of carboplatin and paclitaxel, which is a more common and less toxic regimen. In GOG 209, over 1300 women were randomly assigned to receive either carboplatin plus paclitaxel or TAP. Preliminary results, which were presented at the 2012 Society of Gynecologic Oncology Annual Meeting on Women's Cancer, showed that carboplatin plus paclitaxel resulted in equivalent PFS compared with TAP (median, 14 months in both arms; HR, 1.03) and similar overall survival (median, 32 months vs 38 months; HR, 1.01).[15]

Second-line Chemotherapy Options for Endometrial Cancer

There are no US Food and Drug Administration–approved agents for second-line or later treatment of endometrial cancer. Options for women whose disease progresses after receiving adjuvant chemotherapy have varying success (Table 2). Limited data suggest that a better response to initial chemotherapy portends a better outcome with additional chemotherapy. A retrospective pooled analysis of 5 phase 3 GOG protocols demonstrated that the progression-free interval (PFI; the time between the end of initial adjuvant chemotherapy and the diagnosis of relapse) was the most significant factor predictive of

Table 2. GOG Phase 2 Trials of Single-Agent Chemotherapy in Second-line Treatment of Advanced or Recurrent Endometrial Cancer

GOG Protocol	N	Drug	RR, %
86-I Sutton et al, 1996[38]	33	Ifosfamide	24.3
86-M Homesley, 2005[39]	52	Liposomal doxorubicin	11.4
129-C Lincoln et al, 2003[40]	44[a,b]	Paclitaxel	27.3
129-E Moore et al, 1999[41]	25[a]	Dactinomycin	12
129-H Muggia et al, 2002[42]	42[a]	Liposomal doxorubicin	9.5
129-J Miller et al, 2002[43]	28[a]	Topotecan	9
129-K Fracasso et al, 2006[44]	52[a]	Oxaliplatin	13.5
129-N Garcia et al, 2008[45]	26[a]	Docetaxel (weekly)	7.7
129-P Dizon et al, 2009[20]	50[a]	Ixabepilone	12

GOG, Gynecologic Oncology Group; RR, response rate.

[a] Prior chemotherapy.

[b] Paclitaxel-naive.

survival after second-line chemotherapy. Compared with an initial PFI of less than 6 months, a PFI of greater than 6 months resulted in a 30% reduction in the risk of death (HR, 0.70 [95% CI, 0.59-0.84]) and an improvement in median overall survival (10 months vs 5 months) after second-line chemotherapy.[16]

These results are in line with data from a Japanese study that evaluated the platinum-free interval among women treated with a platinum-based combination as second-line therapy after prior receipt of first-line platinum-based treatment (n=56) and a separate cohort receiving first-line platinum-based chemotherapy for advanced or recurrent disease (n=21).[17] Among those receiving platinum-based treatment in the second-line setting, a platinum-free interval of greater than 12 months was associated with an improvement in both response and overall survival. For those being treated with first-line platinum-based treatment, a platinum-free interval of less than 3 months was associated with worse outcomes. These data require prospective validation, but for women who are chemotherapy-naive or have a long platinum-free interval at the time of recurrence or metastatic disease, treatment with carboplatin and paclitaxel would be a reasonable option. However, given the limited data available, we advocate for participation in well-designed clinical trials.

Novel Agents for Endometrial Cancer

Therapies targeting specific molecular pathways have emerged as promising treatments for endometrial cancer. Given the poor response rates with systemic chemotherapy in patients with advanced or recurrent disease, these novel agents have great potential to influence our care for women with endometrial cancer. Completed studies have evaluated a novel microtubule-stabilizing agent (ixabepilone [Ixempra, Bristol-Myers Squibb]), agents that inhibit mammalian target of rapamycin (mTOR; temsirolimus [Torisel, Wyeth], everolimus [Afinitor, Novartis], ridaforolimus), agents that target epidermal growth factor receptor (erlotinib [Tarceva, Genentech/Astellas], gefitinib, cetuximab [Erbitux, Bristol-Myers Squibb/Lilly), an agent that targets human epidermal growth factor receptor 2 (trastuzumab [Herceptin, Genentech]), and antiangiogenesis agents (bevacizumab [Avastin, Genentech], ziv-aflibercept [Zaltrap, Sanofi/Regeneron], brivanib).

Epothilones

The epothilones are a novel class of microtubule-stabilizing agents with a mechanism of action similar to that of the taxanes. While epothilones and taxanes bind to the same site on β-tubulin, epothilones bind in a different manner. The benefit of epothilones is that they appear to retain activity in taxane-resistant tumors, theoretically owing to their differing binding technique. In addition, they act synergistically in combination with other agents, including bevacizumab and sunitinib (Sutent, Pfizer), based on preclinical activity in breast, lung, and colon cell lines.[18,19] Ixabepilone, a semisynthetic epothilone, has been approved for the treatment of metastatic breast cancer and is now being investigated in the treatment of advanced and recurrent endometrial cancer.

In GOG trial 129-P, 50 patients with persistent or recurrent endometrial cancer who had received prior taxane chemotherapy were administered ixabepilone (40 mg/m^2 over 3 hours on day 1 of a 21-day cycle) until disease progression or intolerable toxicity occurred.[20] Patients received a total of 224 cycles and a median of 4 cycles. The overall response rate was 12%; 1 patient experienced a complete response (2%) and 5 patients demonstrated a partial response (10%). Stable disease for 8 weeks was noted in 30 patients (60%). The major toxicities (grades 3 to 4) were neutropenia (52%), leukopenia (48%), gastrointestinal toxicity (24%), neurologic toxicity (18%), infection (16%), and anemia (14%).[20] Unfortunately, a phase 3 trial comparing ixabepilone to a community standard (paclitaxel or doxorubicin) as second-line therapy for advanced and metastatic endometrial cancer showed no benefit with the use of ixabepilone.[21] Compared with the use of paclitaxel or

doxorubicin, ixabepilone resulted in shorter overall survival (10.9 months vs 12.3 months; HR, 1.3 [95% CI, 1.0-1.7]) and similar PFS (3.4 months vs 4 months; HR, 1.0 [95% CI, 0.8-1.3]). There was also no difference in the overall response rate (15% in both groups).[21]

The role of ixabepilone in the treatment of endometrial cancer remains undefined. However, it is being evaluated as part of a randomized phase 2 trial conducted by the GOG. In GOG 86-P (NCT00977574), patients were randomly assigned to treatment in 1 of 3 arms: (1) carboplatin, paclitaxel, and bevacizumab; (2) carboplatin, paclitaxel, and temsirolimus; or (3) carboplatin, ixabepilone, and bevacizumab. This study has completed accrual and results are eagerly anticipated.[22]

mTOR Inhibitors

Mammalian target of rapamycin (mTOR) is an intracellular serine-threonine kinase that has a role in the regulation of cell growth, proliferation, and survival.[23] A mutation of *PTEN*, a tumor-suppressor gene, is common in endometrial cancer and results in increased activation of the phosphoinositide 3-kinase/Akt pathway. Downstream effects include upregulation of mTOR and, accordingly, decreased regulation of cell cycle control.

The first-generation mTOR inhibitors include everolimus (Afinitor, Novartis), temsirolimus, and ridaforolimus (AP23573 or MK-8669). Early phase 2 trials of these mTOR inhibitors demonstrated promising results and established the basis for their continued investigation in the treatment of endometrial cancer.[24-26] It remains unclear, however, which patients are most likely to benefit from treatment. As an example, in one trial temsirolimus was administered to women who had previously received chemotherapy (n=25) and a separate cohort of women who were chemotherapy-naive (n=29). The response rates were 4% and 14%, respectively, with stable disease in 48% and 69%. In addition, median overall survival was longer when temsirolimus was administered to women who were chemotherapy-naive than to those who were previously treated (9.7 months vs 5.1 months).[27]

Recent phase 2 studies have utilized mTOR inhibitors in combination with other agents with the goal of achieving better response rates. GOG 229-G combined temsirolimus (25 mg intravenously [IV] weekly) with bevacizumab, a monoclonal vascular endothelial growth factor (VEGF) inhibitor (10 mg/kg given every other week), in women with persistent or recurrent disease after 1 or 2 prior cytotoxic chemotherapies. Twelve of 49 evaluable patients achieved a clinical response, for a response rate of 24.5%, and 23 patients (46.9%) survived progression-free for at least 6 months. Despite these promising results, significant toxicities occurred: 2 patients experienced gastrointestinal-vaginal fistulas, 2 patients experienced intestinal perforations, 1 patient had a grade 3 hemorrhage while receiving warfarin, and 1 patient experienced a grade 4 thrombotic event. Three possible treatment-related deaths were also noted.[28] GOG 248 randomly assigned patients to temsirolimus (25 mg IV weekly) vs the combination of weekly temsirolimus with a regimen of megestrol acetate 80 mg twice a day for 3 weeks, alternating with tamoxifen 20 mg twice a day for 3 weeks, in women with recurrent or metastatic endometrial carcinoma. The combination arm was closed early owing to an excess of venous thrombosis (5 deep venous thromboses and 2 pulmonary emboli); however, a response rate of 14% was noted in the 21 patients who received combination treatment. A total of 50 evaluable patients were treated in the single-agent arm and a response rate of 22% was noted.[29]

Table 3. Recent Phase 2 Trials of Targeted Therapies in Second-line Treatment of Advanced or Recurrent Endometrial Cancer

Reference	N[a]	Drug	RR, %
mTOR inhibitors			
Slomovitz et al, 2010[46]	28[b]	Everolimus	21 (CBR)
Oza et al, 2011[27]	29(25[b])	Temsirolimus	14(4)
Angiogenesis inhibitors			
Correa et al, 2010[34]	20(12[b])	Sunitinib	15
Nimeiri et al, 2010[35]	40[a]	Sorafenib	5
Aghajanian et al, 2011[31]	52[a]	Bevacizumab	13.5
Coleman et al, 2012[32]	44[a]	Aflibercept	6.7
Powell et al, 2012[33]	43[a]	Brivanib	18.6
Dizon et al,[36] 2014	32	Nintedanib	9.4
EGFR inhibitors			
Oza et al, 2008[47]	32	Erlotinib	12.5
Slomovitz et al, 2010[48]	23[a]	Cetuximab	5
Fleming et al, 2010[49]	33(25[b])	Trastuzumab	0
Leslie et al, 2012[50]	30[b]	Lapatinib	3
Leslie et al, 2013[51]	26[b]	Gefitinib	4
Combined therapies			
Alvarez et al, 2013[28]	49[b]	Temsirolimus + bevacizumab	24.5
Fleming et al, 2014[29]	20[b]/50[b]	Temsirolimus +/– megestrol acetate/tamoxifen	14/22

CBR, clinical benefit response: confirmed complete response, partial response, or stable disease at 20 months; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; RR, response rate.

[a] Slashes differentiate between groups and parentheses represent a subset.

[b] Prior chemotherapy exposure.

In summary, while mTOR inhibitors hold promise for the treatment of endometrial cancer, the results from trials have been fairly disappointing. Subsequent studies should concentrate on identifying patients who are most likely to benefit from therapy. Unfortunately, alterations in *PTEN* or *PIK3CA* appear to be unreliable biomarkers for drug activity, though the presence of a *KRAS* mutation might predict inactivity of these agents. In addition, data reviewed by Myers suggest that not all alterations result in a similar cellular impact, which suggests that future work should specify the mutational features associated with potential drug activity.[30] As noted above, the role of temsirolimus in the first-line treatment of endometrial cancer is being investigated in the recently completed GOG 86-P trial and results are anticipated.

Angiogenesis Inhibitors

Angiogenesis is an essential component of tumor growth, proliferation, and metastasis and its inhibition is an attractive anticancer strategy that has been widely employed in cancer treatment. Angiogenesis has been inhibited primarily in 2 fashions: either by targeting the growth factors or by targeting the growth factor receptors.

Bevacizumab is a monoclonal antibody against VEGF-A. VEGF is essential for normal angiogenesis and its expression is upregulated in cancer cells. GOG 229E investigated the activity of single-agent bevacizumab (15 mg/kg IV every 3 weeks until progression or toxicity) in 52 women with persistent or recurrent endometrial cancer treated with up to 2 prior cytotoxic chemotherapeutic regimens. The overall response rate with bevacizumab was 13.5% and included 1 complete response and 6 partial responses. The 6-month PFS rate was 40.4%. No gastrointestinal perforations or fistulae were seen, and the primary grade 3 and 4 toxicities were hypertension (4), pain (4), musculoskeletal (3), hemorrhage (2), thrombosis/embolism (2), proteinuria (2), and constitutional (2). Only 6% of women discontinued therapy prior to progression.[31] These results suggest that single-agent bevacizumab may have a promising role in the treatment of recurrent endometrial cancer.

Aflibercept is a protein that binds to VEGF-A, VEGF-B, and placental growth factor, thus exhibiting a unique method of antiangiogenesis. A phase 2 trial of aflibercept (4 mg/kg IV every 14 days in 28-day cycles) in 24 patients with recurrent endometrial cancer demonstrated a response rate of 6.7% (0 complete responses and 3 partial responses) and 18 patients (41%) had PFS of 6 months. However, 8 of the 18 patients had to discontinue therapy owing to toxicity and began receiving another therapy before reaching 6 months. Significant grade 3 and 4 toxicities included cardiovascular (23%/5%), constitutional (7%/0%), hemorrhagic (2%/5%), metabolic (7%/2%), and pain (18%/0%). Two treatment-related deaths also were noted, 1 caused by gastrointestinal perforation and 1 caused by arterial rupture. While aflibercept achieved pretrial activity parameters, significant toxicity at the prescribed dose and schedule is likely prohibitive and more research is needed.[32] We await the results of GOG 86P to define the activity of bevacizumab when combined with chemotherapy (carboplatin with either paclitaxel or ixabepilone) as a first-line treatment for endometrial cancer.

Multitargeted Receptor Tyrosine Kinase Inhibitors

Another class of agents is receptor tyrosine kinase inhibitors that target multiple pathways, and several have undergone evaluation in uterine carcinoma. Brivanib (BMS-582664) is a dual tyrosine kinase inhibitor of VEGF receptors (VEGFR2 and VEGFR3) and fibroblast growth factor receptors (FGFR1, FGFR2, and FGFR3). Brivanib was investigated in GOG 229-I, which demonstrated a response rate of 19% in women with recurrent or advanced endometrial cancer; 30% of patients were progression-free at 6 months.[33]

Sunitinib is a tyrosine kinase inhibitor against multiple VEGF receptors that was investigated in a phase 2 trial of 34 patients with recurrent or advanced endometrial cancer. Women received 50 mg of oral sunitinib daily for 4 consecutive weeks followed by 2 weeks without treatment. Of the 20 patients evaluable for response, 3 patients (15%) achieved a partial response. Five patients had a best response of stable disease, 4 of them remaining progression-free for greater than 6 months.[34] Sorafenib is a multitargeting drug that also has a role in the inhibition of VEGF receptors. A multicenter phase 2 study that included 40 patients with recurrent or advanced endometrial carcinoma demonstrated a partial response rate of only 5% and a stable disease rate of 42.5%.[35]

Finally, nintedanib, a potent oral tyrosine kinase inhibitor against platelet-derived growth factor receptors, FGF receptors, and VEGF receptors was evaluated in GOG 229-K. Of 32 eligible patients, 3 partial responders were recorded (overall response rate, 9.4%) and the event-free survival rate at 6 months was 22%.[36] Although this study closed after the first stage of accrual owing to a lack of activity, preclinical data suggest that endometrial cancers with a loss of function mutation of *P53* may be highly susceptible to nintedanib when combined with paclitaxel.[37] These data lend support to a potential phase 2 randomized trial, stratified by *P53* status. Such a trial is under consideration in the cooperative group system.

Conclusion

Despite endometrial cancer being the most common gynecologic malignancy, increasing evidence suggests that

endometrial cancer is a heterogeneous disease, divisible into categories based on not only histology and stage but also grade, prior treatment efforts, genetic mutations, and alterations in molecular pathways. Although our armamentarium of chemotherapeutic and biologic agents continues to grow, we have yet to achieve significant improvement in meaningful clinical outcomes such as improved survival or disease stability in patients with recurrent or persistent disease. Cytotoxic chemotherapy remains the primary treatment in patients with advanced or metastatic disease, and carboplatin plus paclitaxel is the regimen of choice. No second-line chemotherapeutic option has demonstrated clear superiority, and the prognosis for such patients remains poor. More evidence is needed to guide our use of chemotherapy in high-risk patients with early-stage disease, especially in our patients with the highest-risk histologic subtypes. Continued attention to combination therapy utilizing both chemotherapy and promising novel agents, such as mTOR inhibitors and anti-VEGF agents, has potential to capitalize on synergistic treatment effects that might be more beneficial than any one treatment modality alone.

References

1. Endometrial (uterine) cancer. American Cancer Society. http://www.cancer.org/cancer/endometrialcancer/detailedguide/endometrial-uterine-cancer-key-statistics. Updated February 3, 2014. Accessed July 5, 2014.
2. Sorosky JI. Endometrial cancer. *Obstet Gynecol*. 2012;120(2 pt 1):383-397.
3. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2011. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2011/. Based on November 2013 SEER data submission. Updated May 12, 2014. Accessed July 5, 2014.
4. Maxwell GL, Tian C, Risinger J, et al; Gynecologic Oncology Group study. Racial disparity in survival among patients with advanced/recurrent endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Cancer*. 2006;107(9):2197-2205.
5. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1991;40(1):55-65.
6. Kodama S, Kase H, Tanaka K, Matsui K. Multivariate analysis of prognostic factors in patients with endometrial cancer. *Int J Gynaecol Obstet*. 1996;53(1):23-30.
7. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet*. 2006;95(suppl 1):S105-S143.
8. Lewin SN, Herzog TJ, Barrena Medel NI, et al. Comparative performance of the 2009 International Federation of Gynecology and Obstetrics' staging system for uterine corpus cancer. *Obstet Gynecol*. 2010;116(5):1141-1149.
9. Lewin SN. Revised FIGO staging system for endometrial cancer. *Clin Obstet Gynecol*. 2011;54(2):215-218.
10. McMeekin DS, Yashar C, Campos SM, Zaino RJ. Corpus: epithelial tumors. In: Barakat RR, Berchuck A, Markman M, Randall ME, editors. *Principles and Practice of Gynecologic Oncology*. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2013;661-714.
11. Voss MA, Ganesan R, Ludeman L, et al. Should grade 3 endometrioid endometrial carcinoma be considered a type 2 cancer—a clinical and pathological evaluation. *Gynecol Oncol*. 2012;124(1):15-20.
12. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2006;24(1):36-44.
13. Fleming GF, Filiaci VL, Bentley RC, et al. Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study. *Ann Oncol*. 2004;15(8):1173-1178.
14. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2009;112(3):543-552.
15. Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study [SGO abstract LBA-1]. *Gynecol Oncol*. 2012;125(3):771-773.
16. Moore KN, Tian C, McMeekin DS, Thigpen JT, Randall ME, Gallion HH. Does the progression-free interval after primary chemotherapy predict survival after salvage chemotherapy in advanced and recurrent endometrial cancer?: a Gynecologic Oncology Group ancillary data analysis. *Cancer*. 2010;116(23):5407-5414.
17. Matoda M, Omatsu K, Yamamoto A, et al. Importance of platinum-free interval in second-line chemotherapy for advanced or recurrent endometrial cancer. *Eur J Gynaecol Oncol*. 2014;35(3):224-229.
18. Lee FY, Covello KL, Castaneda S, et al. Synergistic antitumor activity of ixabepilone (BMS-247550) plus bevacizumab in multiple in vivo tumor models. *Clin Cancer Res*. 2008;14(24):8123-8131.
19. Lee F, Jure-Kunkel MN, Salvati ME. Synergistic activity of ixabepilone plus other anticancer agents: preclinical and clinical evidence. *Ther Adv Med Oncol*. 2011;3(1):11-25.
20. Dizon DS, Blessing JA, McMeekin DS, Sharma SK, DiSilvestro P, Alvarez RD. Phase II trial of ixabepilone as second-line treatment in advanced endometrial cancer: Gynecologic Oncology Group trial 129-P. *J Clin Oncol*. 2009;27(19):3104-3108.
21. ClinicalTrials.gov. A study of ixabepilone as second line therapy for locally advanced, recurrent, or metastatic endometrial cancer (IXAMPLE2). http://clinicaltrials.gov/ct2/show/NCT00883116?term=NCT00883116. Identifier NCT00883116. Accessed July 14, 2014.
22. ClinicalTrials.gov. 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. http://clinicaltrials.gov/show/NCT00977574. Identifier NCT00977574. Accessed July 15, 2014.
23. Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. *J Clin Oncol*. 2006;24(29):4783-4791.
24. Colombo N, McMeekin S, Schwartz P, et al. A phase II trial of the mTOR inhibitor AP23573 as a single agent in advanced endometrial cancer [ASCO abstract 5516]. *J Clin Oncol*. 2007;25(18S)(suppl).
25. Oza AM, Elit L, Provencher D, et al. 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 160b [ASCO abstract 5516]. *J Clin Oncol*. 2008;26(15S)(suppl):296s.
26. Slomovitz BM, Lu KH, Johnston T, et al. A phase II study of oral mammalian target of rapamycin mTOR inhibitor, RAD001 (everolimus), in patients with recurrent endometrial carcinoma (EC) [ASCO abstract 5502]. *J Clin Oncol*. 2008;26(15S)(suppl):293s.
27. Oza AM, Elit L, Tsao MS, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol*. 2011;29(24):3278-3285.
28. Alvarez EA, Brady WE, Walker JL, et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2013;129(1):22-27.
29. Fleming GF, Filiaci VL, Marzullo B, et al. Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: a gynecologic oncology group study. *Gynecol Oncol*. 2014;132(3):585-592.
30. Myers AP. New strategies in endometrial cancer: targeting the PI3K/mTOR pathway--the devil is in the details. *Clin Cancer Res*. 2013;19(19):5264-5274.
31. Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2011;29(16):2259-2265.
32. Coleman RL, Sill MW, Lankes HA, et al. A phase II evaluation of aflibercept in the treatment of recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2012;127(3):538-543.
33. Powell MA, Sill MW, Goodfellow PJ, et al. A phase II trial of brivanib in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *Int J Gynecol Cancer*. 2012;22(suppl 3):E115.
34. Correa R, Mackay H, Hirte HW, et al. A phase II study of sunitinib in recurrent or metastatic endometrial carcinoma: a trial of the Princess Margaret Hospital, The University of Chicago, and California Cancer Phase II Consortia [ASCO abstract 5038]. *J Clin Oncol* 2010;28:15S(suppl).
35. Nimeiri HS, Oza AM, Morgan RJ, et al. A phase II study of sorafenib in advanced uterine carcinoma/carcinosarcoma: a trial of the Chicago, PMH, and California Phase II Consortia. *Gynecol Oncol*. 2010;117(1):37-40.

36. Dizon DS, Sill M, Schilder JM, et al. Results of Gynecologic Oncology Group (GOG) 229 K: a phase II trial of BIBF-1120 for women with advanced, recurrent, or metastatic endometrial carcinoma [SGO abstract 133]. *Gynecol Oncol*. 2014;133:55.
37. Meng X, Dizon DS, Yang S, et al. Strategies for molecularly enhanced chemotherapy to achieve synthetic lethality in endometrial tumors with mutant p53 [published online December 7, 2013]. *Obstet Gynecol Int*. doi:10.1155/2013/828165.
38. Sutton GP, Blessing JA, DeMars LR, Moore D, Burke TW, Grendys EC. A phase II Gynecologic Oncology Group trial of ifosfamide and mesna in advanced or recurrent adenocarcinoma of the endometrium. *Gynecol Oncol*. 1996;63(1):25-27.
39. Homesley HD, Blessing JA, Sorosky J, Reid G, Look KY. Phase II trial of liposomal doxorubicin at 40 mg/m(2) every 4 weeks in endometrial carcinoma: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 2005;98(2):294-298.
40. Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2003;88(3):277-281.
41. Moore DH, Blessing JA, Dunton C, Buller RE, Reid GC. Dactinomycin in the treatment of recurrent or persistent endometrial carcinoma: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol*. 1999;75(3):473-475.
42. Muggia FM, Blessing JA, Sorosky J, Reid GC. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2002;20(9):2360-2364.
43. Miller DS, Blessing JA, Lentz SS, Waggoner S. A phase II trial of topotecan in patients with advanced, persistent, or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2002;87(3):247-251.
44. Fracasso PM, Blessing JA, Molpus KL, Adler LM, Sorosky JI, Rose PG. Phase II study of oxaliplatin as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2006;103(2):523-526.
45. Garcia AA, Blessing JA, Nolte S, Mannel RS; Gynecologic Oncology Group. A phase II evaluation of weekly docetaxel in the treatment of recurrent or persistent endometrial carcinoma: a study by the Gynecologic Oncology Group. *Gynecol Oncol*. 2008;111(1):22-26.
46. Slomovitz BM, Lu KH, Johnston T, et al. A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. *Cancer*. 2010;116(23):5415-5419.
47. Oza AM, Eisenhauer EA, Elit L, et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. *J Clin Oncol*. 2008;26(26):4319-4325.
48. Slomovitz B, Schmeler K, Miller D, et al. Phase II study of cetuximab (erbitux) in patients with progressive or recurrent endometrial cancer [SGO abstract 13]. *Gynecol Oncol*. 2010;116(13)(suppl 1).
49. Fleming GF, Sill MW, Darcy KM, et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2010;116(1):15-20.
50. Leslie KK, Sill MW, Lankes HA, et al. Lapatinib and potential prognostic value of EGFR mutations in a Gynecologic Oncology Group phase II trial of persistent or recurrent endometrial cancer. *Gynecol Oncol*. 2012;127(2):345-350.
51. Leslie KK, Sill MW, Fischer E, et al. A phase II evaluation of gefitinib in the treatment of persistent or recurrent endometrial cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2013;129(3):486-494.