

Endometrial Carcinoma: A Review of Chemotherapy, Drug Resistance, and the Search for New Agents

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The article discusses epothilones in the context of endometrial cancer, for which they are not approved.

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ABSTRACT

Adenocarcinoma of the endometrium represents the most common gynecologic malignancy in developed countries. Although early-stage cancers are effectively treated surgically, commonly without adjuvant therapy, the treatment of high-risk and advanced disease is more complex. Chemotherapy has evolved into an important modality in high-risk early-stage and advanced-stage disease, and in recurrent endometrial cancer. Taxane-based therapy consistently demonstrates the highest response rates in the first-line and salvage settings of endometrial cancer. Unfortunately, response to chemotherapy is modest and strategies are needed to predict chemotherapy-responsive and chemotherapy-

resistant populations. Chemotherapy resistance mediated by overexpression of drug efflux pump proteins and mutations in β -tubulin isoforms in both primary and recurrent disease represent unique treatment challenges and highlight the need for new agents that are less susceptible to these known resistance pathways. Epothilone B analogs are novel cytotoxic agents with activity in solid tumors, including advanced/recurrent endometrial carcinoma, and may have unique properties that can overcome resistance in some settings. These agents alone and in combination represent a new therapeutic opportunity in endometrial carcinoma. *The Oncologist* 2010;15:1026–1033

A BRIEF OVERVIEW OF ENDOMETRIAL CARCINOMA

Endometrial carcinoma is the most common gynecologic malignancy in the U.S. It was estimated that 42,000 new cases would be diagnosed and 7,700 endometrial carcinoma-related deaths would occur in 2009 [1]. This corresponds to a lifetime risk of 2.6% for women living in developed nations [2], with a median age at diagnosis of

61 years [3]. The epidemiology of endometrial cancer is multifactorial. Most cases are sporadic and develop in postmenopausal women. Approximately 2%–5% of endometrial carcinomas are associated with a hereditary gene alteration, nonpolyposis colorectal cancer syndrome, which is associated with germline mutations to DNA mismatch repair genes [4]. The most common risk factors associated with the development of endometrial carcinoma are unop-

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Table 1. Endometrial cancer patient survival rate according to International Federation of Gynecology and Obstetrics stage

Stage I	Stage II	Stage III	Stage IV
A, 89%	A, 80%	A, 63%	A, 20%
B, 90%	B, 72%	B, 39%	B, 17%
C, 81%	C, 51%		

Data from Creasman WT, Odicino F, Maisonneuve P et al. Carcinoma of the corpus uteri. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006;95(suppl 1): S105–S143.

posed estrogen exposure and obesity (type I cancers) [5]. Unopposed estrogen replacement therapy and the use of tamoxifen are the most common sources of exogenous estrogen [6], whereas endogenous sources such as obesity, cirrhosis, estrogen-producing tumors, and reproductive factors such as anovulation are also associated with the development of endometrial carcinoma [3, 7]. A smaller subset of sporadic cancers is associated with aging and unique genetic/molecular changes, producing a more aggressive variant, serous/clear cell type (type II cancers).

Most cancers of the endometrium are of endometrioid histology, followed by the serous and clear cell types [3, 8]. In a prospective surgical series of >2,600 patients with clinically early-stage disease, 78% had endometrioid, 11% had serous, and 1.6% had clear cell tumor types [9]. Uterine sarcomas represent 3%–5% of all uterine cancers. Tumor stage is determined according to the International Federation of Gynecology and Obstetrics (FIGO) staging system and is based on the surgically determined extent of disease spread. The majority of endometrial cancers are diagnosed at an early stage, with approximately 72% stage I, 12% stage II, 13% stage III, and 3% stage IV. FIGO has announced a revised staging system for 2009 [10]. Whereas early-stage disease is associated with a favorable prognosis, mortality rates increase with advancing stage of disease (Table 1) [11].

EVOLUTION OF CHEMOTHERAPY IN THE MANAGEMENT OF ENDOMETRIAL CANCER

Of all the gynecologic malignancies, the management of endometrial cancer has undergone the most dramatic shift in recent years. There has been an introduction and acceptance of minimally invasive surgical techniques, more common use of surgical staging with pelvic and para-aortic lymphadenectomy, and greater consideration to remove or debulk i.p. metastases (akin to ovarian cancer debulking surgery). A better understanding of uterine factors, includ-

Table 2. Response rate to single-agent chemotherapy in chemotherapy-naïve endometrial carcinoma patients

Drug	Dose and schedule	Response rate
Doxorubicin	50–60 mg/m ² every 3 wks	17%–37%
Paclitaxel	250 mg/m ² over 24 hours every 3 wks	36%
Cisplatin	50–100 mg/m ² every 3 wks	20%–42%
Carboplatin	360–400 mg/m ² every 4 wks	24%–33%

Data adapted from Fleming GF. Systematic chemotherapy for uterine carcinoma: Metastatic and adjuvant. *J Clin Oncol* 2007;25:2983–2990.

ing tumor grade, depth of invasion, lymph vascular space invasion, and cervical involvement, and how surgical staging can define risk strata have altered the use of adjuvant therapy. Today, there is less use of pelvic radiation therapy, and when radiation is used a substitution to vaginal cuff brachytherapy is more common. Most dramatic has been the introduction of chemotherapy into the first-line management of patients with high-risk disease. Chemotherapy was traditionally reserved to treat incurable patients with disseminated or recurrent endometrial cancer, often after the failure of hormonal therapy.

Phase II trials have identified doxorubicin, paclitaxel, and the platinum agents cisplatin and carboplatin as the most active agents in patients with persistent or recurrent disease (Table 2) [12]. Two studies demonstrated a higher response rate (RR) with the combination of cisplatin and doxorubicin, albeit with a lesser effect on progression-free survival (PFS) and overall survival (OS) than with single-agent doxorubicin. The Gynecologic Oncology Group (GOG) study 107 showed a doubling of the complete RR (19% versus 8%) and a longer PFS interval (median, 5.7 months versus 3.8 months; hazard ratio [HR], 0.736; confidence interval [CI], 0.577–0.939; $p = .014$) with the combination [13]. The European Organization for Research and Treatment of Cancer similarly showed a higher RR (43% versus 17%) and modestly better survival favoring the combination [14]. As a result of these studies, the doublet regimen became a standard for advancement in many future phase III studies.

Paclitaxel as a single agent has been evaluated in advanced/recurrent disease patients, showing RRs of 37% (no prior therapy) and 25% (one prior chemotherapy, 40 of 44 patients treated with doxorubicin–platinum chemotherapy), making this agent the most active reported in phase II studies [15, 16]. The GOG subsequently compared doxorubicin–cisplatin with doxorubicin–paclitaxel, and demonstrated nearly identical RRs, PFS intervals, and OS times in

patients with advanced/recurrent disease [17]. In the GOG 177 study, a phase III trial comparing doxorubicin–cisplatin alone with doxorubicin–cisplatin plus paclitaxel, for the first time, a significantly greater RR (57% versus 34%), PFS interval (median, 8.3 months versus 5.3 months), and OS time (median, 15.3 months versus 12.3 months) with combination chemotherapy using the three-drug paclitaxel–doxorubicin–cisplatin (TAP) regimen were observed [18]. Despite the superior outcomes noted with the three-drug TAP regimen, neurotoxicity and a 3-day schedule have limited enthusiasm for its use. The GOG recently completed a ~1,300 patient trial (GOG 209) comparing TAP with paclitaxel–carboplatin in patients with advanced/recurrent measurable disease or those with advanced disease treated in an adjuvant setting. The results of the GOG 209 trial, which completed enrollment in April 2009, are maturing.

In all, the GOG has published four phase III trials in patients with advanced/recurrent disease including >1,200 patients. RRs of 25%–57%, with the best complete RR of only 22%, were reported [19]. The population of patients with advanced or recurrent, measurable disease included in those trials was relatively heterogeneous and included patients with stage III, stage IV, and recurrent disease and all tumor grades and histologic types, and 55% had received prior radiation therapy. Factors independently associated with longer survival included white/Hispanic race, better performance status, stage III disease, no prior radiation therapy, and endometrioid tumor histology [17].

POSTOPERATIVE CHEMOTHERAPY VERSUS RADIATION THERAPY

There has been a fundamental paradigm shift to incorporate chemotherapy into the first-line management of patients with endometrial cancer. In the GOG 122 study, doxorubicin–cisplatin was compared with whole abdominal radiation therapy in patients with small-volume residual stage III–IV disease [20]. A significantly greater PFS rate (at 60 months, 50% versus 38%) and survival rate (at 60 months, 55% versus 42%) were seen in the chemotherapy arm, with an HR for death of 0.68 (CI, 0.52–0.89; $p = .004$). Despite the improvement associated with chemotherapy, however, nearly 50% of patients in either arm recurred, showing the profound need for continued improvement.

Two additional studies compared cyclophosphamide–cisplatin–doxorubicin (CAP) with pelvic radiation therapy and demonstrated comparable outcomes in patients with less advanced disease. In a study conducted by the Japanese GOG, with predominantly early-stage patients (75% stage I–II), there was no difference between treatment arms in PFS or OS for all enrolled patients [21]. However, for a higher risk group IC (stage I with >50% myometrial inva-

sion, with grade 3 tumors or age >70, stage II–IIIa), both the PFS and OS times were significantly longer in patients treated with chemotherapy. In a similar study by Maggi and colleagues, with predominantly higher stage patients (62% stage IIIa/c), no differences in PFS or OS were seen between patients treated with CAP and those treated with pelvic radiation [22]. In both studies, the frequency of disease recurrence at a distant site with chemotherapy was 16%–21%, versus 13%–26% with pelvic radiation, indicating that distant disease control with chemotherapy is perhaps surprisingly modest. At present, it is unclear how to best define which patient populations may derive the most benefit from chemotherapy. Uterine factors (grade, depth of invasion, histology, lymphovascular space invasion) and patient age have been used to define risk strata for early-stage patients, but they have not been used to predict which patients will respond to chemotherapy [23, 24].

CHEMOTHERAPY PLUS RADIATION

Sequential use of chemotherapy and radiation was also evaluated in two prospective studies. In the GOG 184 study, patients with stage III disease received volume-directed radiation followed by doxorubicin–cisplatin with or without paclitaxel. No difference in the 36-month PFS rate was seen between the arms, and distant sites of failure, even with the use of chemotherapy, were recorded in 28% of patients [25]. The Norwegian Society of Gynecologic Oncology reported preliminary findings of a randomized trial including patients at risk for micrometastases (78% stage IB–C), comparing pelvic radiation alone with pelvic radiation plus chemotherapy [26]. A variety of chemotherapy regimens were permitted and chemotherapy could have been administered before or after radiation. The results showed longer PFS and cancer-specific survival times favoring the inclusion of chemotherapy. Patterns of failure showed that 16% of radiation patients had recurrences outside the radiated field, compared with 10% when chemotherapy was added. The Radiation Therapy Oncology Group reported a small, phase II trial evaluating concurrent cisplatin with pelvic radiation followed by four cycles of paclitaxel–cisplatin chemotherapy in 46 patients with high-risk disease [27]. That report showed excellent local control, with 2% of patients experiencing pelvic failures, but 19% had a distant recurrence. The trial was the basis for one of the treatment arms in the ongoing GOG 258 trial (six cycles paclitaxel–carboplatin versus concurrent cisplatin and pelvic radiation followed by four cycles paclitaxel–carboplatin) in patients with optimally resected stage III endometrial cancer.

Table 3. Response rate for endometrial carcinoma patients treated with second-line chemotherapy

Drug	Dose and schedule	Response rate
Cisplatin	50 mg/m ² every 3 wks	4%
Docetaxel	36 mg/m ² every wk	7.7%
Pegylated liposomal doxorubicin	50 mg/m ² every 4 wks	9.5%
Ixabepilone	40 mg/m ² every 3 wks	12%
Oxaliplatin	130 mg/m ² every 3 wks	13.5%
Ifosfamide	1.2 mg/m ² (5 days) every 4 wks	15%
Paclitaxel	110–200 mg/m ² (over 3 hours) every 3 wks	27.3%

Data adapted from Dizon DS, Blessing JA, McMeekin DS et al. Phase II trial of ixabepilone as second-line treatment in advanced endometrial cancer: Gynecologic Oncology Group trial 129-P. *J Clin Oncol* 2009;27:3104–3108.

SECOND-LINE CHEMOTHERAPY EXPERIENCE

Although chemotherapy has shown an important role in high-risk disease, substantial room for improvement exists. Combination regimens are the most active, but in measurable disease populations responses are observed in only ~50% of patients, and a complete response is infrequently observed. Both the PFS and survival times have been improved, yet the 5-year survival rate for patients with advanced/recurrent measurable disease patients is <10%, and for those with stage III disease it is typically around 50%–60% [19, 20, 22, 25]. After primary therapy with combination regimens, the efficacy of second-line chemotherapy is particularly limited (Table 3). Antimicrotubule agents have shown the most promise. In a population in which 91% had received doxorubicin–platinum chemotherapy, paclitaxel produced a RR of 25%; the epothilone B analog ixabepilone produced an RR of 12% in a population in which 94% had received prior paclitaxel [16, 28]. Interestingly, docetaxel, which had shown activity in paclitaxel-treated breast and ovarian cancer patients, produced an RR of only 8% (80% had received prior paclitaxel) in patients with advanced/recurrent endometrial cancer [29]. After failure of primary chemotherapy, there is no established active second-line agent in this disease. Understanding the processes by which tumors develop resistance is critical, and defining which patients have the best chance to respond to established or novel therapies is our greatest challenge.

ENDOMETRIAL CARCINOMA AND DRUG RESISTANCE

As discussed, combination chemotherapy is increasingly being used in the first-line treatment of endometrial carcinoma patients; however, the low initial complete response rate and the high rate of eventual recurrence or progression suggest de novo and/or rapidly developing resistance.

Given the initial activity seen in at least some patients, identifying ways to target cytotoxic agents to tumor susceptibility or to avoid agents that will not have activity would be an important advancement. The underlying causes of drug resistance in malignancies are multifactorial. Resistance to antimicrotubule agents such as paclitaxel is particularly challenging given the importance of these agents in a variety of tumor types. Tumor cells in general may develop resistance to paclitaxel by overexpression of the multidrug-resistance gene (*MDR-1*), which encodes P-glycoprotein (P-gp), an efflux pump that prevents accumulation of a variety of natural product–based chemotherapeutic agents [30, 31]. Point mutations in tubulin-binding sites, where paclitaxel binds and promotes assembly and stabilization, have also been identified [32, 33]. Clinically, these two mechanisms of resistance seem to be less relevant, however [34].

An additional mechanism of taxane resistance is through selective overexpression of β -tubulin subtypes such as β -tubulin III (β -III) and β -V [34, 35]. The presence of β -III subunits inhibits the assembly of β subunits promoted by taxanes [36]. In tumor cell lines derived from lung, ovarian, prostate, and breast cancers, high levels of β -III were associated with taxane resistance [37–39]. This mechanism may be particularly important because it may be predictive of taxane response and prognostic for outcome [34]. In ovarian cancer, high β -III expression was associated with a shorter PFS duration and was independently associated with poorer survival [40]. In another report, immunohistochemical staining for β -III showed higher expression in histologic types commonly associated with a poorer response (clear cell, mucinous), and tumors with high β -III levels had no response to standard chemotherapy [41]. Data relating to β -III and resistance in endometrial cancer are limited. However, findings from one study show that β -III expression is common in endometrial cancer and is not correlated with histologic type or grade, stage, depth of myometrial infiltration, or lymph node invasion. The authors proposed that this lack of correlation between β -III expression and various histologic features may account for the relative insensitivity of endometrial cancer to chemotherapy [42]. In another study, a β -III–expressing aggressive type II endometrial cell line was shown to be resistant to taxanes, but sensitive to epothilone B. However, downregulation of β -III correlated with greater sensitivity to taxanes [43]. It has been suggested that drugs such as epothilone analogs, which selectively target β -III tubulin, may be active in taxane-resistant tumors [34, 44]. To date,

no data demonstrating relationships between β -III tubulin expression and outcome have been reported in endometrial cancer.

In endometrial cancer specifically, other proposed mechanisms of resistance include inhibition of apoptosis via alterations in both the extrinsic apoptosis pathway (Fas proteins) and the intrinsic pathway [inhibitor of apoptosis proteins (IAP) and Bcl-2], alterations in the phosphatidylinositol 3' kinase (PI3K)–Akt pathway, and *p53* mutation [43, 45–47]. However, no clinical reports validating these models have been reported. Phase II studies of mammalian target of rapamycin (mTOR) inhibitors, which have effects downstream to the PI3K–Akt pathway, appear to hold promise in endometrial cancer. It is interesting to note that, in the small series so far conducted, responses appear to be related by extent of prior therapy with chemotherapy. For example, in the phase II study of temsirolimus, including a population of patients who had not been previously treated, the RR was 26% [48]. Three subsequent trials in patients who had previously been treated with chemotherapy showed RRs of 0%–9% using mTOR inhibitors, although stable disease was common [48–50]. This is somewhat different from what was observed with hormonal therapy, for which prior exposure to either progestins or chemotherapy was not thought to alter the other agent's responsiveness. To what extent these findings are a result of the different agents used versus the extent of pretreatment remains to be explored.

RATIONALE FOR EPOTHILONES IN ENDOMETRIAL CARCINOMA

The epothilones, a new class of tubulin-polymerization agents, are macrolide antibiotics obtained from the fermentation of the mycobacterium *Sorangium cellulosum*. They were originally recognized by the National Cancer Institute as potent cytotoxic agents in 1994, and include naturally occurring epothilones A–F as well as synthetic derivatives such as ixabepilone [51–53]. The epothilones have a mechanism of action similar to that of the taxanes and bind microtubules near the paclitaxel-binding site, promoting microtubule stabilization and inducing cell-cycle arrest at the G₂/M checkpoint with subsequent apoptosis. Microtubule inhibitors, such as the taxanes, have demonstrated efficacy in endometrial carcinoma; however, the hydrophobic nature of paclitaxel makes it highly susceptible to the multidrug resistance protein (MRP), which facilitates cellular efflux of the drug and limits cytotoxicity. Unlike the taxanes, epothilones and their synthetic derivatives demonstrate potent activity in multidrug-resistant cell lines. Not only are these agents able to overcome drug resistance, but they do not readily induce the overexpression of MRP-1 or

P-gp resistance mechanisms in epithelial tumor cells [54, 55].

Ixabepilone, a semisynthetic lactam derivative of epothilone B, is a metabolically stable form of this agent. Ixabepilone has demonstrated preclinical efficacy across a broad range of cancer models with 50 inhibitory concentrations in the low nanomolar range. Importantly, preclinical data have demonstrated significant antitumor activity in clinically derived paclitaxel-resistant carcinomatous cell lines [56]. Synergistic antitumor activity was demonstrated in vivo when ixabepilone was used in conjunction with commonly used cytotoxic and biologic agents such as cisplatin, capecitabine, bevacizumab, sunitinib, cetuximab, and trastuzumab [55, 57, 58]. Preclinical data have also demonstrated that ixabepilone has antitumor activity in paclitaxel-resistant cell lines overexpressing β -III. Given these findings, the development of ixabepilone advanced into clinical studies as a potential treatment in patients with heavily pretreated or chemotherapy-resistant malignancies [55].

Phase II and phase III clinical trials demonstrated the antitumor activity of ixabepilone in solid tumors of the ovary, uterine cervix, pancreas, breast, and lung (non-small cell), as well as in non-Hodgkin's lymphoma [56]. Recent findings from a phase II trial of ixabepilone in patients with recurrent or persistent platinum- or taxane-resistant ovarian or peritoneal cancer showed a response rate of 14.3% and an acceptable safety profile [59]. Ixabepilone as a single agent is approved for use in breast cancer that has progressed following therapy with a taxane, an anthracycline, and capecitabine, and in combination with capecitabine in patients with metastatic or locally advanced disease that has progressed after taxane and anthracycline therapy. Dose-limiting toxicities consist of neutropenia, peripheral neuropathy, and fatigue, which are lower with a 3-hour infusion of 40 mg/m². Other toxicities include hypersensitivity requiring premedication, myalgia, arthralgia, alopecia, nausea/vomiting, anorexia, and stomatitis, with a safety profile that is similar across trials in a variety of solid tumors [54].

THE FUTURE OF THE EPOTHILONES IN ENDOMETRIAL CARCINOMA

Given the propensity of endometrial carcinomas to possess inherent resistance to current cytotoxic agents or develop broad resistance following first-line therapy, epothilone analogs such as ixabepilone should be further evaluated. Particularly exciting are the demonstrated properties in vitro, showing activity against multidrug-resistant metastatic breast cancer, and in clinical practice, showing activity against taxane-resistant breast and endometrial cancers. At the present time, translational and clinical data are lacking

on their activity in endometrial carcinomas with β -III expression. An ongoing phase III trial in recurrent/persistent endometrial carcinoma patients previously treated with chemotherapy (Clinical Protocol CA136196) is comparing ixabepilone with paclitaxel or doxorubicin and includes the collection of pathologic materials for translational research to validate the hypothesis that ixabepilone may have a unique role in β -III-expressing tumors. Interestingly, a retrospective analysis of data from a clinical trial of neoadjuvant ixabepilone showed that patients with triple-negative breast cancer had higher β -III expression levels, and suggested that β -III expression may predict response to ixabepilone [60].

Whereas single-agent ixabepilone therapy has demonstrated activity in resistant solid tumors *in vivo* and *in vitro*, synergistic antitumor activity was also demonstrated *in vivo* with the combination of ixabepilone and bevacizumab. Cell models derived from breast, colon, lung, and kidney carcinomas have been evaluated and clinical trials are now being conducted to assess this specific drug combination. Initial data from a randomized, phase II study of ixabepilone and bevacizumab for the first-line treatment of metastatic breast cancer have shown encouraging clinical activity and a safety profile similar to that of bevacizumab-paclitaxel [61]. Based on promising results supporting combination regimens with cytotoxic and targeted agents, the GOG recently opened a randomized phase II clinical trial using these agents in combination. This three-armed trial is randomizing stage III/IV patients at primary diagnosis and patients with disease recurrence who have received no prior chemotherapy to receive either paclitaxel-carbo-

platin-bevacizumab or paclitaxel-carboplatin-temsirolimus or ixabepilone-carboplatin-bevacizumab every 21 days. That trial is early in patient accrual, but is representative of the current treatment strategies using epothilones for endometrial carcinomas.

SUMMARY

Advanced and recurrent endometrial carcinomas remain a challenging group of tumors that are only modestly responsive to first-line chemotherapy and demonstrate high rates of multifactorial chemotherapy resistance. Ixabepilone and the other epothilones offer better efficacy against such tumors because of their lesser susceptibility to known tumor resistance mechanisms, such as drug efflux pumps and β -tubulin mutations. The rationale for using epothilones alone and in combination in patients with this high-risk malignancy is scientifically sound and warrants future exploration.

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REFERENCES

- American Cancer Society. Estimated new cancer cases and deaths by sex, US, 2009. Available at <http://www.cancer.org/acs/groups/content/@nho/documents/document/500809webpdf.pdf>, page 4, accessed September 7, 2010.
- Jemal A, Siegel R, Ward E et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
- Creasman WT, Odicino F, Maisonneuve P et al. Carcinoma of the corpus uteri. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006;95(suppl 1):S105–S143.
- McMeekin DS, Alektiar KM, Sabbatini PJ et al. Corpus: Epithelial tumors. In Barakat RR, Markman M, Randall ME, eds. *Principles and Practice of Gynecologic Oncology*. Philadelphia: Lipponcott, 2009:683–732.
- Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: Results from the Netherlands Cohort Study. *J Natl Cancer Inst* 2004;96:1635–1638.
- Fisher B, Costantino JP, Wickerham DL et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90:1371–1388.
- Brinton LA, Berman ML, Mortel R et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: Results from a case-control study. *Am J Obstet Gynecol* 1992;167:1317–1325.
- Baekelandt MM, Castiglione M; ESMO Guidelines Working Group. Endometrial carcinoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2008;19(suppl 2):ii19–ii20.
- Walker JL, Piedmonte MR, Spirtos NM et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group study LAP2. *J Clin Oncol* 2009;27:5331–5336.
- Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 2009;105:103–104.
- Sorosky JI. Endometrial cancer. *Obstet Gynecol* 2008;111:436–447.
- Fleming GF. Systematic chemotherapy for uterine carcinoma: Metastatic and adjuvant. *J Clin Oncol* 2007;25:2983–2990.
- Thigpen JT, Brady MF, Homesley HD et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 2004;22:3902–3908.
- Aapro MS, van Wijk FH, Bolis G et al. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: Definitive results of a randomized

- study (55872) by the EORTC Gynecological Cancer Group. *Ann Oncol* 2003;14:441–448.
- 15 Ball HG, Blessing JA, Lentz SS et al. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: A Gynecologic Oncology Group study. *Gynecol Oncol* 1996;62:278–281.
 - 16 Lincoln S, Blessing JA, Lee RB et al. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol* 2003;88:277–281.
 - 17 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;15:1173–1178.
 - 18 Fleming GF, Brunetto VL, Cella D et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 2004;22:2159–2166.
 - 19 McMeekin DS, Filiaci VL, Thigpen JT et al. The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: A Gynecologic Oncology Group study. *Gynecol Oncol* 2007;106:16–22.
 - 20 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;24:36–44.
 - 21 Susumu N, Sague S, Udagawa Y et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: A Japanese Gynecologic Oncology Group study. *Gynecol Oncol* 2008;108:226–233.
 - 22 Maggi R, Lissoni A, Spina F et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: Results of a randomised trial. *Br J Cancer* 2006;95:266–271.
 - 23 Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol* 2004;92:744–751.
 - 24 Creutzberg CL, van Putten WL, Koper PC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-I endometrial carcinoma: Multicentre randomised trial. PORTEC Study Group. *Post Operative Radiation Therapy in Endometrial Carcinoma*. *Lancet* 2000;355:1404–1411.
 - 25 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;112:543–552.
 - 26 Hogberg T, Rosenberg P, Kristensen G et al. A randomized phase III study on adjuvant treatment with radiation +/- chemotherapy in early stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991) [abstract 5503]. *J Clin Oncol* 2007;25(18 suppl):274s.
 - 27 Greven K, Winter K, Underhill K et al. Final analysis of RTOG 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. *Gynecol Oncol* 2006;103:155–159.
 - 28 Dizon DS, Blessing JA, McMeekin DS et al. Phase II trial of ixabepilone as second-line treatment in advanced endometrial cancer: Gynecologic Oncology Group trial 129-P. *J Clin Oncol* 2009;27:3104–3108.
 - 29 Garcia AA, Blessing JA, Nolte S et al. 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;111:22–26.
 - 30 Schneider J, Efferth T, Centeno MM et al. High rate of expression of multidrug resistance-associated P-glycoprotein in human endometrial carcinoma and normal endometrial tissue. *Eur J Cancer* 1993;29A:554–558.
 - 31 Esteller M, Martinez-Palones JM, Garcia A et al. High rate of MDR-1 and heterogeneous pattern of MRP expression without gene amplification in endometrial cancer. *Int J Cancer* 1995;63:798–803.
 - 32 Giannakakou P, Sackett DL, Kang YK et al. Paclitaxel-resistant human ovarian cancer cells have mutant beta-tubulins that exhibit impaired paclitaxel-driven polymerization. *J Biol Chem* 1997;272:17118–17125.
 - 33 Monzó M, Rosell R, Sánchez JJ et al. Paclitaxel resistance in non-small-cell lung cancer associated with beta-tubulin gene mutations. *J Clin Oncol* 1999;17:1786–1793.
 - 34 Dumontet C, Jordan MA, Lee FF. Ixabepilone: Targeting β III-tubulin expression in taxane-resistant malignancies. *Mol Cancer Ther* 2009;8:17–25.
 - 35 Bhattacharya R, Cabral F. Molecular basis for class V β -tubulin effects on microtubule assembly and paclitaxel resistance. *J Biol Chem* 2009;284:13023–13032.
 - 36 Lu Q, Luduena RF. Removal of β III isotype enhances Taxol induced microtubule assembly. *Cell Struct Funct* 1993;18:173–182.
 - 37 Kavallaris M, Kuo DY, Burkhart CA et al. Taxol-resistant epithelial ovarian tumors are associated with altered expression of specific β -tubulin isoforms. *J Clin Invest* 1997;100:1282–1293.
 - 38 Burkhart CA, Kavallaris M, Band Horwitz S. The role of beta-tubulin isoforms in resistance to antimetabolic drugs. *Biochim Biophys Acta* 2001;1471:O1–O9.
 - 39 Liu B, Staren ED, Iwamura T et al. Mechanisms of Taxotere-related drug resistance in pancreatic carcinoma. *J Surg Res* 2001;99:179–186.
 - 40 Ferrandina G, Zannoni GF, Martinelli E et al. Class III beta-tubulin overexpression is a marker of poor clinical outcome in advanced ovarian cancer patients. *Clin Cancer Res* 2006;12:2774–2779.
 - 41 Umezū T, Shibata K, Kajiyama H et al. Taxol resistance among the different histological subtypes of ovarian cancer may be associated with the expression of class III beta-tubulin. *Int J Gynecol Pathol* 2008;27:207–212.
 - 42 Zhu C, Luo J, Shi H et al. Expression of tubulin, p53, ki67, receptors for estrogen, and progesterone in endometrial cancer. *Eur J Gynaecol Oncol* 2009;30:514–517.
 - 43 Cochrane DR, Spoelstra NS, Howe EN et al. MicroRNA-200c mitigates invasiveness and restores sensitivity to microtubule-targeting chemotherapeutic agents. *Mol Cancer Ther* 2009;8:1055–1066.
 - 44 Mozzetti S, Iantomasi R, De Maria I et al. Molecular mechanisms of paclitaxel resistance. *Cancer Res* 2008;68:10197–10204.
 - 45 Chaudhry P, Asselin E. Resistance to chemotherapy and hormone therapy in endometrial cancer. *Endocr Relat Cancer* 2009;16:363–380.
 - 46 Gagnon V, Van Themsche C, Turner S et al. Akt and XIAP regulate the sensitivity of human uterine cancer cells to cisplatin, doxorubicin and taxol. *Apoptosis* 2008;13:259–271.
 - 47 Esteller M, Xercavins J, Reventos J. Advances in the molecular genetics of endometrial cancer (review). *Oncol Rep* 1999;6:1377–1382.
 - 48 Oza AM, Elit L, Biagi J et al. Molecular correlates associated with a phase II study of temsirolimus (CCI-779) in patients with metastatic or recurrent endometrial cancer—NCIC IND 160 [abstract 3003]. *J Clin Oncol* 2006;24(18 suppl):121s.
 - 49 Slomovitz BM, Lu KH, Johnston T et al. A phase II study of oral mammalian target of rapamycin (mTOR) inhibitor, RAD001 (everolimus) in pa-

- tients with recurrent endometrial carcinoma (EC) [abstract 5502]. *J Clin Oncol* 2008;26(5 suppl):293s.
- 50 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 [abstract 5516]. *J Clin Oncol* 2007;25(18 suppl):278s.
- 51 Holfe G, Berdorf N, Steinmetz H et al. Epothilone A and B—novel 16-membered macrolides with cytotoxic activity: Isolation, crystal structure and conformation in solution. *Angew Chem Int Engl* 1996;35:1567–1569.
- 52 Bollag DM, McQueney PA, Zhu J et al. Epothilones, a new class of microtubule-stabilizing agents with a Taxol-like mechanism of action. *Cancer Res* 1995;55:2325–2333.
- 53 Kowalski RJ, Giannakakou P, Hamel E. Activities of the microtubule-stabilizing agents epothilones A and B with purified tubulin and in cells resistant to paclitaxel (Taxol®). *J Biol Chem* 1997;272:2534–2541.
- 54 Rivera E, Lee J, Davies A. Clinical development of ixabepilone and other epothilones in patients with advanced solid tumors. *The Oncologist* 2008;13:1207–1223.
- 55 Lee FY, Borzilleri R, Fairchild CR et al. Preclinical discovery of ixabepilone, a highly active antineoplastic agent. *Cancer Chemother Pharmacol* 2008;63:157–166.
- 56 Steinberg M. Ixabepilone: A novel microtubule inhibitor for the treatment of locally advanced or metastatic breast cancer. *Clin Ther* 2008;30:1590–1617.
- 57 Lee FY, Casteneda S, Hawken D et al. Bevacizumab/ixabepilone (BMS-247550) combination produces synergistic antitumor efficacy in multiple tumor models in vivo and is superior to bevacizumab/paclitaxel combination [abstract B246]. In: AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Philadelphia: AACR-NCI-EORTC, 2005:9093s.
- 58 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;14:8123–8131.
- 59 De Geest K, Blessing JA, Morris RT et al. Phase II clinical trial of ixabepilone in patients with recurrent or persistent platinum- and taxane-resistant ovarian or primary peritoneal cancer: A Gynecologic Oncology Group study. *J Clin Oncol* 2010;28:149–153.
- 60 Horak CE, Lee FY, Xu L et al. High β III tubulin expression in triple negative (TN) breast cancer (BC) subtype and correlation to ixabepilone response: A retrospective analysis [abstract 3587]. *J Clin Oncol* 2009;27(15 suppl):167s.
- 61 Rugo HS, Campone M, Amadori D et al. Randomized phase II study of weekly versus every-3-week ixabepilone plus bevacizumab (ixa/bev) versus paclitaxel plus bev (pac/bev) as first-line therapy for metastatic breast cancer (MBC) [abstract 1029]. *J Clin Oncol* 2009;27(15 suppl):47s.