Review

Targeted therapy for high-risk endometrial carcinoma

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Practice Points

- Endometrial cancers can be broadly dichotomized into two types based on histopathologic, clinical and molecular features.
- Type II endometrial cancers constitute a minority of cases but a disproportionate number of deaths and are typified by serous, clear cell or grade 3 endometrioid histology.
- Immunotherapeutic targets for these high-risk endometrial cancers include Her2/Neu, VEGF receptor, epithelial cell adhesion molecule (Ep-CAM), trophoblast cell surface marker (Trop-2), tissue factor (TF) and α_v-integrins.
- Immunotherapies may be enhanced by modulation of membrane-bound complement regulatory proteins or costimulation with IL-2.
- Inhibitors of the EGF receptor, FGF receptor and the PTEN/PI3KCA/AKT/mTOR pathway have an emerging role in the treatment of high-risk endometrial cancers.
- Chemoresistance is multifactorial and attributable to a rapid cellular proliferation rate, autocrine secretion of IL-6, as well as upregulation of tubulin-β-III, among other processes.
- Claudin-3 and -4, natural receptors for *Clostridium perfringens*, may represent an innovative mechanism for targeted drug delivery against chemotherapy-resistant cells and cancer progenitors.
- Epothilones are novel microtubule-stabilizing agents with activity in paclitaxel-resistant disease under clinical investigation for high-risk endometrial cancers.

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SUMMARY Type II endometrial cancers exhibit distinct histopathology, underlying pathogenesis and clinical behavior. These high-risk cancers are associated with an aggressive clinical course and a relatively poor prognosis that underscores the need for the development of novel rational therapeutic strategies that exploit their distinct underlying molecular pathway alterations. In this review, we describe the extent of disease burden and molecular characterization of type II endometrial cancers, summarize the historical development to support current standards of care and delineate the most recent preclinical and clinical advances in immunotherapy, cytotoxic agents and small-molecule inhibitors for this disease.

Disease burden & classification of endometrial cancers

Endometrial cancer is the most common gynecologic malignancy in developed countries, with 47,130 new cases and 8010 deaths projected in the USA alone for 2012 [1]. In total 90% of endometrial cancers arise purely from epithelial glands (adenocarcinomas) [2]. In 8% of cases, malignancy develops from either mesodermal components (leiomyosarcoma or endometrial stromal sarcoma) or both mesodermal and epithelial elements (carcinosarcoma) [3]. Endometrial carcinomas may be broadly dichotomized into two classes with distinct underlying molecular pathogenesis, clinical behavior and histopathology [4].

Type I endometrial cancers comprise 80% of cases and are associated with endometrioid histology (grade 1 or 2) [5,6], a history of exposure to unopposed estrogen with retention of estrogen receptor (ER)/progestin receptor (PR) status [7], and younger age at onset (mean age: 63 years) [8]; deleterious mutations in *k-Ras*, *PTEN* or mismatch repair mechanisms predominate [9,10]. Hyperplasia is a common precursor.

Type II endometrial cancers constitute a minority of cases and characterized by serous, clear cell or grade 3 endometrioid histology [11,12], the absence of an antecedent history of unopposed estrogen, higher frequency in black patients, later stage and age at initial presentation [13]; loss of ER/PR [14] as well as E-cadherin [15], aneuploidy, mutations in p53 and HER2/Neu overexpression are common [7,16–18]. Recently, loss of BAF250a, the protein encoded by the chromatin remodeling tumor suppressor gene *ARID1A*, was implicated in 39% of grade 3 endometrioid, 26% of clear cell and 18% of high-grade serous cancers of the endometrium as examined by immunohistochemistry (IHC) [19] and has been associated with advanced stage [20]. PPP2R1A, the scaffolding subunit of PP2A holoenzyme, is frequently mutated in uterine serous carcinomas (USCs) [21]. Intraepithelial carcinoma is a recognized precursor. Of note, unlike serous cancers of the endometrium, which demonstrate a genetic signature distinct from serous cancers of the ovary, clear cell carcinomas show remarkable similarity regardless of the organ of origin [22].

Type II endometrial cancers are characterized by an aggressive clinical course with relatively poor prognosis. Though serous, clear cell and grade 3 endometrioid cancers collectively constitute <30% of uterine cancers, they account for 74% of deaths; 5-year disease-specific survival rates for USC, clear cell and grade 3 endometrioid carcinomas are 55, 68 and 77%, respectively [23]. This compares unfavorably to the rate of 89% for grade 1/2 endometrioid cancers [8].

Current standard of care

Treatment for high-risk type II endometrial cancers begins with complete surgical staging with intent for cytoreduction to no residual disease followed by platinum-based combination chemotherapy for advanced disease [24]. Staging should consist of total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic/para-aortic lymphadenectomy, omentectomy and peritoneal washings with biopsies [25,26] given that patients with type II disease will exhibit extrauterine spread at the time of initial surgery in 52–70% of instances [26,27] and have a much higher likelihood of positive para-aortic lymph node involvement compared with the rate of 4.6% observed in low-grade tumors [28]. CA-125 is the most commonly used clinical biomarker for serous cancers [25] as elevations reflect disease status by means of advanced stage, omental metastases and lymphatic spread, although preoperative levels do not serve as an independent predictor

for recurrence [29]. The acute-phase reactant serum amyloid A has also been proposed as a novel biomarker given that higher expression is found intracellularly and as a secreted product *in vitro* in USC cell lines compared with B-cell and cervical cancer controls, as well as in serum of patients with USC compared with healthy volunteers and patients who underwent hysterectomy for benign indications [30]. Also of interest are the trypsin-like serine proteases belonging to the human kallikrein and kallikrien-related peptidase family, which have established clinicopathologic correlations in prostate cancer [31,32]. Human kallikrein 6 and 10 appear to be secreted at higher levels by serous gynecologic tumor cells relative to endometrioid tumor cells *in vitro*; accordingly, higher plasma levels discriminate patients with USC from patients undergoing hysterectomy for benign indications [33,34].

Modern management algorithms for advanced disease draw largely upon the cumulative experience from five large Phase III studies conducted by the Gynecologic Oncology Group (GOG), each of which enrolled patients with both type I and II disease [35–39]. Historically, GOG 177 established paclitaxel/doxorubicin/cisplatin (TAP) as standard of care for advanced or recurrent endometrial cancers [36]. GOG 184 subsequently demonstrated equivalent hazard ratios for recurrence or death in patients who received postoperative radiation followed by doxorubicin/cisplatin/paclitaxel versus doxorubicin/cisplatin (0.90; 95% CI: 0.69–1.17, p = 0.21), although there was a 50% reduction in risk of relapse or death with the former regimen in patients with residual disease after debulking at the expense of increased hematologic toxicity [39]. Preliminary analyses of GOG 209 now suggest the noninferiority and favorable side-effect profile of carboplatin/paclitaxel over TAP [40]; this regimen appears to have utility in high-risk disease [41] and is regarded by most as the standard of care.

Fewer data exist regarding treatment of high-risk early-stage disease. Whole-abdominal radiation is of little benefit (GOG–94) [42]. Adjuvant carboplatin/paclitaxel clearly improve recurrence rates, overall survival and progression-free survival [43]. In uterine serous cancers, there is evidence to support the use of vaginal cuff brachytherapy in conjunction with platinum-based chemotherapy. In a retrospective review of 74 patients with stage I uterine serous cancers, no local recurrences occurred in patients who received vaginal cuff brachytherapy, but were diagnosed in six of the 31 patients (19%) who did not. Furthermore, recurrences were far more common in the absence of adjuvant chemotherapy: 6/14 versus 0/7 in stage IA, 10/13 versus 0/15 in stage IB, 4/5 versus 1/7 in stage IC disease [44]. In a similar single-institution review of stage I/II serous cancers, a regimen consisting of six cycles of carboplatin/paclitaxel with vaginal cuff brachytherapy was very well-tolerated and resulted in 5-year progression-free and overall survival rates of 88% [45]. Additionally, there is growing interest in exploring sandwich techniques [46,47].

Data among clear cell cancers is very scant due to the rarity of this entity; even in advanced or recurrent disease, no single Phase III GOG study has enrolled sufficient cases to evaluate the importance of histology [48]. Barney and colleagues published a series of 103 patients with stage I clear cell (pure, n = 21; mixed, n = 8) or serous (n = 74) uterine cancers who received vaginal brachytherapy; approximately 33% also received chemotherapy [49]. Local, regional and locoregional recurrence rates were 5, 7 and 10%, respectively at 5 years. While some pooled analyses suggest that clear cell or serous histologies have similar initial responses to cytotoxic agents compared with endometrioid cancers, clear cell and serous histology are independent predictors of overall survival; clear cell histology also predicts poorer progression-free survival [50].

Optimal therapy for invasive grade 3 endometrioid carcinoma confined to the uterus is the subject of an ongoing trial (PORTEC-3; NCT00411138) [201]. Alektiar and colleagues found equivalent clinical outcomes in a study of 41 patients with stage I or occult stage II grade 3 endometrioid histology compared with 42 patients with USC or clear cell carcinoma, all of whom received intravaginal brachytherapy after surgical staging and underwent external beam radiotherapy in balanced fashion [51]. Over a median follow-up of 46 months, locoregional control rates were 97 vs 90% (p = 0.2), respectively. 5-year disease-free survival was 79 vs 78% (p = 0.3); 5-year overall survival was 71 vs 79% (p = 0.3). Siow and colleagues reported institutional outcomes of 18 patients with grade 3 endometrioid and ten with grade 3 endometrioid stage IC (according to International Federation of Gynecology and Obstetrics 1988 staging) who underwent total hysterectomy, bilateral

salpingo-oophorectomy and pelvic lymph node dissection (76%) or external beam radiotherapy (24%) [52]. All except one patient received vaginal brachytherapy and eight out of ten patients with endometrioid histology received platinum-based adjuvant chemotherapy. Over a median follow-up of 50.1 months, there were five systemic relapses (17.9%) and one pelvic recurrence (3.6%). The authors concluded that vaginal vault brachytherapy was effective in preventing locoregional recurrences, but argued for consideration for adjuvant chemotherapy in these patients given the high rate of systemic relapse.

Such findings truly underscore the need for development of rational therapeutic strategies that exploit the distinct molecular pathway alterations that underlie these clinically aggressive entities.

Immunotherapy for type II endometrial cancers: basis & rationale

Targeted immunotherapy represents a promising strategy for type II endometrial cancers. Monoclonal antibodies result in tumor lysis through antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Both pathways begin with recognition and binding of the monoclonal antibodies to tumor antigen. The F_c region may then be recognized by F_c receptors located on natural killer cells, monocytes, macrophages or granulocytes to initiate ADCC or by C1 (the first component of the complement cascade) to activate the classic pathway of CDC ending in osmotic lysis through the membrane-attack complex.

Immunotherapy for type II endometrial cancers: Phase I/II data

HER2/Neu (ErbB2)

The human EGF receptor (EGFR) family consists of four members: EGFR (*ErbB1*), HER2/Neu (*ErbB2*), HER-3 (*ErbB3*) and HER-4 (*ErbB4*). Ligand binding induces hetero- or homo-dimerization and subsequent activation of pathways integral to proliferation pathways [53]. Amplification of HER2/Neu has been documented in 26–62% of USC cases [17,54–58] and as many as 38% of clear cell endometrial carcinomas [59]; positivity by FISH in grade 3 endometrioid endometrial cancers is far less common (3–8%) [60,61]. Overexpression has been linked to poor prognosis not only in endometrial [17,62] but ovarian [63] and breast [64] cancers. Molecular profiling studies have demonstrated *ErbB2* to be one of the most overexpressed genes to distinguish uterine serous from ovarian serous tumors [65].

Trastuzumab (Herceptin®, Genentech, CA, USA) is a humanized monoclonal IgG1 antibody that works both through recruitment of natural killer cells and initiation of ADCC as well as abrogation of downstream effectors [66]. It is FDA-approved as an adjunct to cyclophosphamide, paclitaxel and doxorubicin in the treatment of early-stage HER2/Neu-positive, node-positive breast cancer and as a single agent for adjuvant treatment of early-stage, HER2/Neu-positive, high-risk ER/PR-negative breast cancers following multi-modality anthracycline-based therapy [67,202]. Based on sound biologic plausibility, there is considerable interest in applications for endometrial cancers. As assessed by standard ^{51}Cr-release assays, trastuzumab results in ADCC in the range of 25–60% against USC that overexpress HER2/Neu; this can be augmented with both IL-2 and simultaneous administration of the heterodimerization inhibitor pertuzumab (Omnitarg®, Genentech)[68,69]. Despite encouraging case reports **(Table 1)** [70–72], when evaluated as a single-agent, trastuzumab 4 mg/kg in week 1 then 2 mg/kg weekly until disease progression in stage III/IV or recurrent endometrial cancers at the Phase II level in GOG-181B failed to demonstrate significant activity [59]. Interestingly, a large number of clear cell carcinomas in this study overexpressed HER2/Neu. These findings have been criticized as inconclusive given that 45.5% of treated patients did not have definitive HER2/Neu amplification and on the basis of slow accrual leading to premature closure [73]. It has been proposed that inter-individual variation in trastuzumab efficacy may also reflect variable amounts of HER2/Neu extracellular domain (ECD) shedding [74]. In a study of 38 USC patients versus 19 controls, serum concentrations of HER2/Neu ECD were higher in patients with tumors expressing HER2/Neu at 3+ by IHC ($p = 0.02$). HER2/Neu positive primary cell lines also secreted HER2/Neu ECD *in vitro*; addition of HER2/Neu ECD-containing supernatants decreased ADCC ($p = 0.01$). A Phase II study of carboplatin/paclitaxel with or without trastuzumab in patients with advanced or recurrent uterine papillary serous carcinoma designated HER2/Neu-positive by 3+ IHC or FISH is currently underway (NCT01367002) [203].

Table 1. Summary of case reports of clinical activity of trastuzumab in heavily pretreated patients with uterine serous carcinomas.

Author	Age (years)	Stage	Histology	Initial treatment	IHC	FISH	Additional regimens	Response	Ref.
Jewell *et al.* (2006)	72	IIIA	Endometrioid grade 2	Surgical staging, whole pelvic RT and vaginal brachytherapy	3+	NR	1st recurrence (pulmonary metastases) at 10 months: weekly paclitaxel then single-agent trastuzumab 100 mg iv. weekly for 7 months 2nd recurrence: weekly paclitaxel and trastuzumab for 2 months then single-agent trastuzumab for 9 months Disease progression: addition of docetaxel 40 mg/m^2 iv.	Partial response for 6 months Stable disease for 11 months Stable disease for 15 weeks	[71]
Villela *et al.* (2006)	NR	IVB	USC	NR	3+	+ (>10)	4 mg/kg iv. once, then 2 mg/kg iv. weekly until progression	Complete response for 6 months	[72]
	NR	IIIC	USC	NR	3+	+ (>10)	4 mg/kg iv. once then 2 mg/kg iv. weekly until progression	Stable disease for 3 months	
Santin *et al.* (2008)	66	IIIA	Endometrioid FIGO grade 3	Surgical staging, whole pelvic radiation, doxorubicin 45 mg/m^2 iv. + cisplatin 50 mg/m^2 + paclitaxel 160 mg/m^2	3+	+ (2.18)	1st recurrence (pelvic lymphadenopathy); whole pelvic radiation Paclitaxel 175 mg/m^2 iv. every 21 days + carboplatin AUC 5 iv. every 21 days + trastuzumab 4 mg/kg iv. once, then 2 mg/kg iv. weekly × 6 then trastuzumab 2 mg/kg iv. weekly + carboplatin AUC 5 every 5 weeks × 8	Persistent disease Partial response	[70]
	63	IIIC	USC	Surgical staging, whole pelvic/ extended-field radiation	2+	+ (3.1)	1st recurrence at 3 months (vaginal cuff); patient declined cytotoxic chemotherapy; trastuzumab 4 mg/kg loading dose then 4 mg/kg biweekly	Partial response for 7 months	

AUC: Area under the curve; FIGO: International Federation of Gynecology and Obstetrics; IHC: Immunohistochemistry; iv.: Intravenous; NR: Not reported; RT: Radiation therapy; USC: Uterine serous carcinoma.

VEGF–A

VEGF–A induces pathologic neoangiogenesis in a variety of human cancers [75]. VEGF is a homodimeric glycoprotein that exists in at least four isoforms due to alternative splicing of the primary messenger RNA transcript [76], the most common of which is VEGF-A. In endometrial cancers, VEGF-A expression has been associated with high grade, lymphovascular space invasion, lymphatogenous spread, poor prognosis [77,78] and p53 upregulation [79]. Bevacizumab (Avastin®, Genentech) is a recombinant human monoclonal IgG1 antibody that neutralizes all isoforms of VEGF [80]. In a Phase II study of recurrent endometrial cancer (GOG 229E) [81], bevacizumab 15 mg/kg every 3 weeks produced clinical response rate of 13.5%, including one complete and six partial responses. Median progression-free and overall survival rates were 4.2 and 10.5 months, respectively. Notably, despite representing only 27% of the study population, serous histology was observed in 100% of complete responses and 50% of partial responses. Presently, bevacizumab in combination with paclitaxel and carboplatin is under study for advanced endometrial cancer (NCT00513786) [204]. Another three-arm Phase II trial is investigating carboplatin/paclitaxel/bevacizumab, carboboplatin/paclitaxel/temsirolimus and carboplatin/ixabepilone/bevacizumab (NCT00977574) [205]. VEGF Trap (Afibercept®, Sanofi-Aventis, Paris, France), a fusion protein containing receptor components and fully human immunoglobulin constant region, is also under evaluation (NCT00462826) [206].

■ Immunotherapy for type II endometrial cancers: preclinical data

Recently the author's group has reported the *in vitro* data to support the candidacy of multiple antigens originally discovered through comparative oligonucleotide microarrays contrasting ten primary USC and five normal endometrial cell lines for targeted immunotherapy [82].

Epithelial cell adhesion molecule (Ep-CAM, also known as Trop-1, TACSTD1, 17-1A, GA733-2, KSA, KS1/4, 323/A3 and CD326) is a calcium-independent homophilic type I transmembrane glycoprotein molecule of 39–42 kDa, expressed at low levels on most surface epithelial cells. Using IHC and flow cytometry, Ep-CAM can be detected in as many as 96% of USC tissues and expressed superficially in 83% of cell lines [83]. Adecatumumab (MT201; Micromet AG, Munich, Germany), a human monoclonal antibody against Ep-CAM, produced mean ADCC of 33%, despite resistance of these cells to CDC. MT201 has been evaluated at the Phase II level in colorectal carcinoma after complete resection of liver metastases alone and in combination with FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) (NCT00866944) [207], as monotherapy in metastatic breast cancer [84], and prostate cancer [85]. It has also been evaluated at the Phase IB level in conjunction with docetaxel in breast cancer [86], but not in gynecologic malignancies.

Trophoblast cell-surface marker (Trop-2, also known as GA733-1, M1S1 and EGP-1) is 35-kDa transmembrane glycoprotein encoded by the gene *TACSTD2* of chromosome 1p32. Trop-2 was originally identified in human trophoblasts [87] and has since been shown to be upregulated relative to normal tissue in both type I [Bignotti *et al.*, Trop-2 protein overexpression as an independent prognostic marker in endometrioid endometrial carcinoma (2012), Submitted] and type II endometrial cancers [88,89], as well as other gynecologic malignancies [90–92]. The human monoclonal antibody hRS7 (Immunomedics, Inc., NJ, USA) produces ADCC in the range of 28.2–64.4% in USC [88] and 33.9–50.6% in grade 3 endometrioid cell lines [89]. hRS7 is scheduled to enter clinical testing in solid tumors in late 2012 [208].

Tissue factor (TF) is a transmembrane receptor for coagulation factor VII/VIIa (fVII) that is aberrantly expressed in urogenital, gastrointestinal, hematologic, breast and lung cancers (reviewed by van den Berg *et al.* [93]). TF overexpression can be observed in 50% of USC cell lines (three of six) as assessed by real-time PCR and flow cytometry; cytoplasmic and/or membrane staining can be documented in 100% (16 out of 16) of tissue specimens analyzed by IHC [94]. Accordingly, in ^{51}Cr-release assays hI-CON-1 (Iconic Therapeutics, Inc., GA, USA), a fusion protein containing a targeting domain against TF and a functional domain consisting of IgG1 F_c, resulted in mean ADCC of 65.6% (range: 57.5–77.0%) in USC cell lines that overexpress TF and was augmented with IL-2. TF overexpression, at least in part, underlies the association of thrombogenesis and cancer (Trousseau's phenomenon). As clear cell carcinomas are particularly thrombogenic and expression in ovarian clear cell carcinomas appears to exceed that of endometrioid and undifferentiated tumors [95], hI-CON-1 may have therapeutic relevance for clear cell carcinomas of the endometrium. Phase I studies of hI-CON-1 are ongoing for macular degeneration (NCT01485588) [209].

Integrins are glycoproteins that exist in at least 24 unique permutations of heterodimers consisting of one α and one β subunit, allowing for functional variation. Integrins contribute to invasion and metastasis in a variety of human carcinomas including melanoma, breast, prostate [96], oral squamous cell [97] and USC [98]. The α_V integrins serve as known receptors for extracellular matrix proteins including vitronectin, tenascin and fibronectin [99]. Of six USC cell lines assessed, 100% expressed at least one isoform of α_V integrin, the most common of which were $\alpha_V\beta_3$ (37.5% of cells, mean fluorescence intensity: 12.3 ± 4.02) and $\alpha_V\beta_5$ (32.0% cells, mean fluorescence intensity: 17.5 ± 9.23). The human monoclonal antibody intetumumab (formerly CNTO-95, Centocor, Inc., PA, USA) targets α_V-integrins and inhibited migration by 17–27% and adhesion by 30–65% at doses of 1.25 µg/ml up to 20 µg/ml when compared with control cells with no monoclonal antibodies added ($p < 0.03$). Intetumumab has been evaluated at the Phase II level in advanced melanoma [100] and hormone-refractory prostate cancer (NCT00537381) [210], but not yet in gynecologic malignancies.

Immunotherapy for type II endometrial cancers: modulation through membrane-bound complement regulatory proteins

Despite encouraging preclinical activity, targeted immunotherapies often fail in the clinical arena. Prior chemotherapy and radiation might lead to immunocompromise and limit efficacy in heavily pretreated patient populations [101]. Tumors also evade immune surveillance through antigen evolution and upregulation of

membrane-bound complement regulatory proteins (mCRPs) that may hinder complement-dependent pathways [102]. The mCRPs CD46 (membrane cofactor protein), CD55 (decay-accelerating factor) and CD59 (protectin) have been shown to be upregulated in colorectal, cervical, prostate and renal cell carcinomas [103–106]; these lead to inactivation of C4b/C3b, dissociation of C3/C5-convertases and prevention of membrane-attack complex assembly, respectively [107,108]. Inhibition of mCRPs using bispecific antibodies results in enhanced CDC in rat models of metastatic colorectal carcinoma [109]. Recently, this group has shown that USC also overexpress CD46, 55 and 59 relative to normal endometrial cells; knockdown via siRNAs of CD55 and CD59 but not CD46 significantly sensitized USC to CDC (from ~6.8 to 11%) and ADCC (from ~48 to >60%) [110]. Inhibition of mCRPs is thus an innovative strategy for treatment of type II endometrial cancers.

Novel cytotoxic chemotherapies

Over the past quarter of a century, the GOG has evaluated over 25 novel cytotoxic agents at the Phase II level for use in endometrial cancers, and exceedingly few of these have proceeded to Phase III testing [50]. Due to low expression of ER/PR, hormonal modulation is often of little benefit in high-risk endometrial cancers, leaving even fewer options for management. In GOG-81, a study of 299 patients with advanced or recurrent endometrial cancer, Thigpen and colleagues witnessed a response rate of only 8–9% if PR levels were <50 fmol/mg cytosolic protein, compared with 37% in receptor-positive patients [111]. The development of novel cytotoxic chemotherapeutic strategies for recurrent or progressive disease therefore remains tantamount, especially for type II cancers. Several recent promising advances are summarized below.

■ Claudin-3 & -4

Claudins are tight junction proteins that regulate paracellular transport and provide cell polarity. In cancer cells, claudin family proteins may contribute to the capacity for invasion and metastasis [112]. While present in few normal tissues, USC [113], as well as prostate cancer cells [114], overexpress claudin-3 and -4; chemotherapy-resistant ovarian cancer cells over-express claudin-4 [115]. These proteins simultaneously serve as low- and high-affinity natural receptors for *Clostridium perfringens* entertoxin, the binding of which results in rapid osmolysis, and therefore serve as attractive targets for selective drug delivery [116,117]. In ovarian cancer xenografts, intraperitoneal administration of *C. perfringens* entertoxin 7.5–8.5 µg in 500 µl of sterile saline every 72–96 h for a total of eight injections beginning 1 week after tumor establishment prevented detectable tumor growth entirely in ≥60% of mice and resulted in statistically significant increases in survival compared with untreated mice who demonstrated hemorrhagic ascites with peritoneal studding by 2–3 weeks and expired within 9 weeks [116].

Although chemotherapy kills the majority of tumor bulk, chemoresistant cancer stem cells frequently remain and contribute to tumor propagation and recurrence [118]. Interestingly, claudin-4 is overexpressed in $CD44^+$/$MyD88^+$ ovarian cancer stem cells. With growing interest in characterization of stem cells within the basalis of the endometrium, which contribute to regeneration across 400 cycles in a typical reproductive lifespan, and cancer stem cells in endometrial cancers [119]. It is conceivable that *C. perfringens* entertoxin-based therapies may represent a strategy for destruction of this population in high-risk endometrial cancers as well [120].

■ Paclitaxel resistance: IL–6, tubulin-β III & epothilones

Type II endometrial cancers are relatively chemoresistant and any observed responses are generally nondurable [121]. Resistance to cytotoxic chemotherapies appears to be multifactorial. First, a brisk growth rate permits rapid tumor regrowth despite initial intrinsic sensitivity to chemotherapeutic agents [122]. Second, these tumors are associated with a distinct milieu of autocrine factors such as IL-6, which has been shown to prognosticate poor outcome and confer resistance to paclitaxel and cisplatin in gynecologic malignancies [123]. Accordingly, using ELISAs, secreted IL-6 expression was found to be higher in USC compared with endometrioid carcinoma cell lines (mean: 3121 pg/ml, range: 1099–5017 pg/ml/105 cells/48 h vs mean: 88 pg/ml, range: 19–112 pg/ml/105 cells/48 h; $p < 0.01$) and in the serum from 13 patients with USC compared with 19 women with endometrioid carcinoma (6.1-fold, $p < 0.03$). By real-time PCR, mean copy number in USC fresh frozen tissues also exceeded that of endometrioid

carcinomas (313 ± 55 vs 53 ± 11, p < 0.01) [124]. IL-6 inhibition thus represents an attractive target for high-risk endometrial cancers. IL-6 inhibitors are currently marketed for the treatment of rheumatoid arthritis. Interestingly, tocilizumab (Actemra®, Hoffmann-La Roche Ltd, Basel, Switzerland), a humanized monoclonal antibody against the IL-6 receptor, has been shown to reduce *in vivo* growth of squamous cell carcinomas [125] and gliomas [126], but has not yet been tested in gynecologic malignancies. Third, resistance to paclitaxel has been tied to overexpression of the class III β isotype of tubulin [127] given the preferential binding of paclitaxel to β-I tubulin isoforms [128] and by means of diminished microtubule assembly [129]. Class III tubulin differs from class I tubulin at paclitaxel binding sites involving amino acid positions 175 (Ser→Ala) and 364–365 (Ala-Val→Ser-Ser) [130]. β-III tubulin overexpression correlates with poor clinical outcome in a variety of human cancers, including ovarian [131], lung [132], and breast [133].

Epothilones are novel microtubule-stabilizing macrolides isolated from *Sorangium cellulosum* [134] with activity in paclitaxel-resistant malignancies, preoverlapping mechanisms of resistance [135], and the unique ability to bind class I and III isoforms with at least equal affinity [128]. Patupilone (Novartis, Basel, Switzerland) and ixabepilone (Ixempra®, BMS-247550; Bristol-Meyers-Squibb, NJ, USA) are notable members of this group.

In vitro, patupilone is highly effective relative to paclitaxel against USC cell lines that express high levels of both tubulin-β-III and HER2/Neu [136], a known poor prognostic factor [17,54]. Patupilone also has activity in clear cell carcinomas of the ovary [Roque et al., Unpublished Data]. This drug has been studied at the Phase I, II and III level in ovarian but not in endometrial carcinomas [137–140,211].

In parallel, ixabepilone has been FDA-approved for treatment of locally advanced/metastatic breast cancer with capecitabine after failure of anthracycline/taxane therapy or as monotherapy after failure of anthracyclines, taxanes and capecitabine. In GOG-126M, an overall response rate of 14.3% and disease stabilization rate of 40.8% was achieved in 49 patients with platinum/taxane-resistant recurrent ovarian cancer using 20 mg/m^2 on days 1, 8 and 15 of a 28 day cycle [141]. GOG-129P evaluated 50 patients with recurrent or persistent endometrial cancer who received one prior line of taxane-based chemotherapy including 40% with serous and 2% with clear cell histology. An

Table 2. Selected studies of small-molecule tyrosine kinase inhibitors in patients with persistent/recurrent endometrial cancer.

Study	Drug	Target	Study	Dose	Clinical outcome	Translational end points	Ref.
Gehrig and Bae-Jump (2010)	Lapatinib (Tykerb®, GlaxoSmithKline, PA, USA)	EGFR and HER2/Neu	GOG-229D (NCT00096447), Phase II	1500 mg p.o. daily	Failed to open to second stage of accrual	None	[75]
Leslie *et al.* (2009)	Gefitinib (Iressa®, AstraZeneca, DE, USA)	EGFR	GOG-229C (NCT00027690), Phase II	500 mg p.o. daily	Of 26 evaluable patients: one complete response; seven with disease stabilization; insufficient efficacy to continue evaluation	High serum EGFR was associated with overall survival	[143]
Oza *et al.* (2008)	Erlotinib (Tarceva®, Genentech, CA, USA)	EGFR	NCIC IN-148, Phase II	150 mg p.o. daily	Of 32 evaluable patients: four partial responses; 15 with disease stabilization	No correlation of response with EGFR mutation or gene amplification by FISH	[144]
Slomovitz *et al.* (2007)	Imatinib (Gleevac®, Novartis, Basel, Switzerland)	C–kit, Abl, PDGF receptor B	Phase I, restricted to USC	400 mg p.o. daily in combination with paclitaxel 175 mg/m^2 every 21 days	Of 11 evaluable patients, dose-limiting toxicities: rash, neutropenia and fatigue	None	[145]

EGFR: EGF receptor; p.o.: Orally; USC: Uterine serous carcinoma.

Table 3. Selected studies of PI3K/AKT/mTOR pathway inhibitors in patients with persistent/recurrent endometrial cancer.

Authors	Drug	Target	Study	Dose	Clinical outcome	Translational end points	Ref.
Oza *et al.* (2006); Oza *et al.* (2008)	Temsirolimus (Torisel®, CCI-779, Wyeth/Pfizer, NY, USA)	mTOR	NCIC CTG IND 160b, including eight USC and one clear cell carcinoma	25 mg iv. weekly	Of 25 evaluable patients: two partial responses; 12 with disease stabilization	Responses independent of PTEN status	[152,153]
Fleming *et al.* (2011)	Temsirolimus	mTOR	GOG-248	25 mg iv. weekly + megestrol acetate 80 mg p.o. bid × 3 weeks alternating with tamoxifen 20 mg p.o. bid × 3 weeks	Closed prematurely due to excessive venous thromboembolic events		[154]
Alvarez *et al.* (2012)	Temsirolimus	mTOR	GOG-229G	25 mg iv. weekly + bevacizumab 10 mg/kg every other week	Of 49 evaluable patients: one complete response; 11 partial responses; median PFS and OS 5.6 and 16.9 months, respectively		[155]
Mackay *et al.* (2011)	Ridaforolimus (previously deforolimus, ARIAD-Merck, NJ, USA)	mTOR	NCIC CTG IND 192, including four USC and two mixed histology	40 mg p.o. daily × 5 days per week of 4-week cycle	Of 33 evaluable patients: two partial responses; 15 with disease stabilization	PTEN/PI3K mutation studies underway	[156]
Oza *et al.* (2011)	Ridaforolimus	mTOR	NCT00739830	40 mg p.o. every day × 5 days per week vs medroxyprogesterone acetate 200 mg p.o. daily or megestrol acetate 40 mg q.i.d. or chemotherapy (carboplatin, paclitaxel, doxorubicin, pegylated liposomal doxorubicin, topotecan single-agent or doublet)	Of 114 patients included in interim analysis: median PFS 3.6 vs 1.9 months for ridaforolimus compared with hormone therapy or chemotherapy		[157]
Slomovitz *et al.* (2011)	Everolimus (Affinitor®, RAD-001, Novartis, Basel, Switzerland)	mTOR	NCT01068249	10 mg p.o. daily with letrozole 2.5 mg p.o. daily in 28-day cycles	Of 19 evaluable patients: one complete response; three partial responses; four with disease stabilization		[158]

iv.: Intravenous; OS: Overall survival; PFS: Progression-free survival; p.o.: Orally; q.i.d.: Four-times a day; USC: Uterine serous carcinoma.

overall response rate of 12% was achieved using 40 mg/m^2 every 21 days; disease stabilization for at least 8 weeks occurred in 60%. Median progression-free and overall survival was 2.9 months and 8.7 months, respectively [142]. Ixabepilone is currently under evaluation investigation as first-line therapy with carboplatin and bevacizumab in stage III/IV primary or recurrent endometrial cancers (GOG–86P; [204]).

Small-molecule tyrosine kinase inhibitors & mTOR inhibitors

Small-molecule inhibitors occupy binding pockets in order to block intracellular signaling pathways important to differentiation and proliferation among tumor cells. Tyrosine kinase inhibitors (TKIs) against EGFR have been developed and are under evaluation for efficacy in endometrial cancer (reviewed by Gehrig and Bae Jump [75]) **(Table 2)** [143–145]. At least in some instances, the dampered response to EGFR inhibitors may relate to overexpression of MDM2, a key inhibitor of the EGFR pathway, and p53, which is commonly mutated in type II cancers and responsible for arrest at the G_1/S or G_2/M transitions of the cell cycle [146]. TKIs against FGF receptor also show promise. This family consists of four tyrosine kinase receptors and 18 ligands [147], mutations

of which occur in conjunction with PTEN alterations but appear to be mutually exclusive with KRAS variants [148]. FGFR mutations have proven to be oncogenic in endometrial cancers [149], but in other contexts may exert tumor suppressive effects [147]. *In vitro* inhibition with pan-FGFR inhibitors results in selective death of endometrial cancer cells that carry activating mutations [148]. Various FGFR inhibitors have entered study at the Phase II level in endometrial cancers (TKI258, NCT01379534 [212]) and at the Phase I level in other solid malignancies (E–3810, NCT01283945 [213]; BGJ398, NCT01004224 [214]; AZD4547, NCT00979134 [215]).

The PTEN–PI3KCA–AKT–mTOR pathway is also of significance for treatment of type II endometrial cancers. PIK3CA, downstream of EGFR and FGFR, encodes the catalytic p110-α subunit of PI3K, which phosphorylates phosphatidylinositol-3,4-diphosphate to generate phosphatidylinositol-3,4,5-triphosphate. This subsequently activates the AKT–mTOR oncogenic pathway [150]. PIK3CA mutations promote oncogenesis [151] and have been observed in as many as 15% of USCs [142]. Inhibitors of mTOR, mammalian target of rapamycin, are under evaluation in the treatment of endometrial cancers **(Table 3)** [152–158]. Surprisingly, responses do not correlate with PTEN status [152] or AKT/mTOR levels [159], and most studies find responses across varied histologies including type II disease.

Conclusion & future perspective

Elucidation of the molecular pathogenesis underlying endometrial cancers remains key in fueling drug discovery. In the near future, whole-genome sequencing will play an increasingly pivotal role in the identification of tumor-specific somatic mutations. A deeper understanding of the mechanisms by which to exploit and augment host immune responses should permit immunotherapy to achieve its intended potential. Tumor-specific drug delivery, small molecule and mTOR inhibitors, and novel cytotoxic agents such as the epothilones are among the most promising developments for this disease and the mature data from their clinical study is eagerly awaited. With growing recognition of the importance of individual tumor biology, in the next 5–10 years we hope that targeted therapies will allow for the genuine practice of personalized molecular medicine.

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