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Development of targeted therapy in uterine serous carcinoma, a biologically aggressive variant of endometrial cancer

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Abstract

Endometrial cancer (EC) is the most common female genital malignancy in the USA. Most carcinomas arising from the uterus are estrogen dependent and are associated with obesity and hypertension. They are designated type I ECs and typically, due to their early diagnosis secondary to postmenopausal bleeding, have a good prognosis. By contrast, type II ECs develop in older patients, are not hormone dependent and are responsible for most recurrences and deaths from EC. Uterine serous cancer constitutes up to 10% of all endometrial tumors, and represents the most biologically aggressive variant of type II EC. This article will describe the most salient molecular markers that have been identified in uterine serous cancer, thus far with emphasis on the use of erbB2 (HER2/neu) as the first of a series of therapeutic markers for the treatment of this highly-aggressive subset of ECs.

Keywords

endometrial cancer; erbB2; hRS7; molecular markers; MT-201; patupilone; pertuzumab; targeted therapy; trastuzumab; uterine serous cancer

Endometrial cancer (EC) is the most common female genital tract malignancy in the USA, with an incidence of 40,000 cases and 7000 deaths annually [1]. It is classified, based on the clinical picture and histopathological pattern, into type I and type II disease [2–4]. Type I disease includes grade 1 and 2 endometrioid histology, is estrogen dependent and usually preceded by endometrial hyperplasia. This cancer typically occurs in obese patients and is associated with diabetes and hypertension. Most patients are typically diagnosed at an early stage, secondary to postmenopausal bleeding, and have a good prognosis [5]. By contrast, type II EC, which includes uterine serous cancer (USC), clear cell cancer and grade 3 endometrioid carcinoma, typically occurs in older, thinner patients and is not hormone dependent. These tumors are generally more aggressive and have a worse prognosis than type I EC [5,6].

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Uterine serous cancer

USC is the most biologically aggressive variant of type II EC, and constitutes approximately 10% of all EC cases [3,7]. It has been associated with women of African–American ethnicity [8,9], tamoxifen use [10] and *BRCA* gene mutations [11]. In a Yale, series the mean BMI of patients with EC was 39, the mean parity was three, 40% had hypertension and 18% had diabetes mellitus [12].

USC is a clinically aggressive disease that has an early predilection for deep myometrial invasion, lymph-vascular space invasion, and intra-abdominal, as well as distant, spread [13]. It was associated with a 50% relapse rate and had a 5-year survival of 18–27% [14]. In another study, it was found to be responsible for 39% of EC related deaths, despite comprising only 10% of EC cases [7]. Surgical staging remains the mainstay of treatment of USC, as the majority of patients with disease clinically confined to the uterus will be upstaged (57–70%) [5]. A Gynecologic Oncology Group trial (GOG 94) reported a 35% 5-year disease-free survival when 31 women with stage I and II USC received adjuvant postoperative whole-abdomen radiation therapy. Others have not found radiation therapy to be effective [12,15,16]. Platinum-based chemotherapy is an established therapy in advanced-stage USC. Conflicting data exist regarding early-stage disease. Data from a Yale series suggest that the combination of carboplatin, paclitaxel and vaginal apex radiation should be routinely used in stage I USC [12]. Only one out of 29 stage IA–IC patients (3.4%) who received platinum-based chemotherapy recurred, whereas 20 out of 32 (62.5%) who did not receive this chemotherapy recurred [12]. Recently, a study of 25 stage I–II USC patients treated at the Memorial Sloan–Kettering Cancer Center (NY, USA) with the combination of carboplatin and paclitaxel and vaginal brachytherapy found comparable results [17]. The overall survival of women with USC, however, remains approximately 30%. The survival of women with stage I–II USC is 35–50% and for stage III–IV USC is 0–15% [14]. These figures illustrate the dire need for a deeper understanding of the molecular pathways active in USC, as well as the necessity to develop novel and more effective therapeutic modalities against recurrent chemotherapy-resistant disease [18].

Histopathology of USC

The endometrial epithelium in USC is composed of stratified tumor cells with a complex growth of short, blunt, stromaless cellular papilla or cellular buds. The proliferating cells show significant cytomegaly and pleomorphism. What distinguishes a serous carcinoma from other types of ECs is uniformly marked cytologic atypia (grade 3 nuclei). The nuclei vary in size by five- to ten-fold, and the nuclear-tocytoplasmic ratio is drastically increased. The chromatin is markedly hyperchromatic and coarse. USC can be of either pure or mixed histologic forms. The mixed forms are associated with either endometrioid carcinomas or clear cell elements [19]. A Yale University (CT, USA) study revealed that there was no difference in survival for stage I patients in whom the USC made up 10–50% of the tumor and those where USC made up >50% of the tumor [12]. Immunohistochemically, the tumor cells of USC are strongly and diffusely positive for p53, p16 and mib-1. Estrogen receptor and progesterone receptor are usually negative or weakly patchy-positive [20]. WT-1 nuclear staining can be seen in a subset of the tumor and is not a reliable marker for distinguishing from an ovarian primary serous carcinoma [20].

Molecular pathology of USC

Moreno-Bueno *et al.* [21] and Risinger *et al.* [22] have used DNA microarrays in an attempt to define the genetic fingerprint of EC. Most of the preferentially expressed genes in Type I EC included those genes that were under cyclic hormonal regulation and those essential for endometrial homeostasis (i.e., *MGB2, LTF, END1* and *MMP11*). On the other hand, genes

expressed in type II tumors were those involved in mitotic spindle regulation and associated with aneuploid and aggressive behavior (i.e., *STK15*, *BUB1* and *CCNB2*) [21]. Santin *et al.* used oligonucleotide micro-arrays that interrogate the expression of some 10,000 known genes to profile ten primary USC cultures and five normal endometrium cultures [23]. Analysis of mRNA fingerprints identified 139 genes that exhibited a fivefold upregulation, and 390 genes that were downregulated by a similar magnitude in USC cell lines compared with endometrial cells. Upregulated genes in USC included oncogenes and genes that encoded for adhesion molecules and secreted proteins [23]. The most salient molecular markers, as well as molecular objects for targeted therapy, will be discussed below. In additional genomic studies comparing the gene-expression profiling of high-grade ovarian serous papillary cancer (OSPC) and USC (i.e., two histologically similar malignancies characterized by markedly different response to chemotherapy), hierarchical cluster analysis of gene expression identified 116 genes that exhibited >twofold differences ($p < 0.05$) and that readily distinguished OSPC from USC [24]. *PAI-2* was the most highly overexpressed gene in OSPC when compared to USC, while *c-erbB2* was the most strikingly overexpressed gene in USC when compared to OSPC. In this study, overexpression of the *c-erbB2* gene and its expression product (i.e., HER2/neu receptor) was validated by quantitative real-time PCR (RT-PCR), as well as by flow cytometry, on primary USC and OSPC, respectively. Immunohistochemical staining of serous tumor samples from which primary OSPC and USC cultures were derived, as well as from an independent set of 20 clinical tissue samples (i.e., ten OSPC and ten USC) further confirmed HER2/neu as a novel molecular diagnostic and therapeutic marker for USC. In addition, this gene-expression profiling study demonstrated for the first time the potential to predict the anatomical site of tumor origin, and readily identified the biologically more aggressive USC from OSPC. More importantly, as emphasized below, this report further supported the hypothesis that a therapeutic strategy targeting HER2/neu may be beneficial in patients harboring chemotherapy-resistant USC [18,24].

Molecular markers in USC

CDKN2A

CDKN2A was found to be the most highly differentially expressed gene in USC with over 101-fold upregulation relative to normal endometrial cells [23]. This is a putative oncosuppressor gene encoding p16, which regulates pRb-G1 arrest, and p14ARF, which blocks MDM2-induced p53 degradation, resulting in an increase in p53 levels and consequent cell cycle arrest [23]. These results suggest that in most USC the marked overexpression of the *CDKN2A* gene may be attributable to a consistent genetic anomaly secondary to an autoregulatory feedback loop, owing to disruption of both the p16-CDK4/cyclin D1-pRb pathway and the p14ARF–MDM2–p53 pathway.

p53

p53 is a tumor suppressor gene that plays an important role in DNA repair [25]. Mutations in *p53* are the most common gene mutations associated with USC and have been reported in 90% of USC specimens [26]. Overexpression of p53 correlates with a mutation of the *p53* gene [23–25]. *p53* gene mutation is known to enhance the aggressiveness of the disease in USC by modulating pathways of proliferation and apoptosis [27]. In one study, 7% of high grade endometrioid adenocarcinomas overexpressed p53 and this was found to independently correlate with poor prognosis in this subset [26].

CA125

CA125 is an immunohistochemical marker that correlates well with disease stage, response to therapy and disease recurrence [28]. The potential for monitoring CA125 level's response

to therapy and/or early detection of disease recurrence needs further validation in prospective randomized studies. Nevertheless, CA125 remains the most common serum tumor marker used in managing patients with USC [5].

Serum amyloid A

Our research group at Yale has recently investigated the expression of serum amyloid A (SAA), an acute-phase reactant known to have a major role as a modulator of inflammation and in the metabolism and transport of cholesterol in USC patients, and evaluated its potential as a serum biomarker [29]. Serum SAA concentration was evaluated in 30 USC patients, 42 patients with benign uterine disease and 51 healthy volunteers. In addition, we evaluated the intracellular levels of SAA in cell cultures, as well as the active secretion of SAA in culture media. In addition to finding significantly higher levels of SAA both intracellularly, and in culture media, SAA concentrations were found to be significantly higher in the serum of USC patients compared with patients with benign uterine disease, as well as healthy volunteers. These studies demonstrated, for the first time, that SAA is not secreted exclusively by the liver, but also by USC. SAA may, hence, represent a new biomarker that may be used in preoperative staging and in monitoring response to therapy and disease recurrence [29].

erbB2

The *c-erbB2* gene encodes for erbB2 (HER2/neu), a member of the erbB receptor tyrosine kinase family. This is a family of four transmembrane glycoproteins (erbB1, erbB2, erbB3 and erbB4) that are expressed on epithelial, mesenchymal and neuronal cells. Ligand binding results in dimerization of the receptor either with a twin receptor (homodimerization) or with one of its siblings (heterodimerization) [30]. This leads to phosphorylation of intracellular tyrosine kinase residues that serve as docking sites for various effectors and transcription factors that ultimately modulate various biological responses, such as proliferation, survival, migration and differentiation. It is noteworthy that the erbB2 heterodimer is characterized by a stronger, and more diverse, signaling potential than other erbB dimers [30]. Importantly, erbB2 overexpression has been previously reported to be associated with cancer cell proliferation, poor survival and resistance to therapy in multiple human tumors [18,31–34].

The frequency of erbB2 overexpression in USC is approximately 20% in Caucasians and 50% in African–Americans [18,35–37]. In an early study by Santin *et al.* the authors tested ten fresh paraffin-embedded USC specimens by immunohistochemistry (IHC) and found that eight out of ten (80%) specimens stained heavily (2+, 3+) for erbB2 [35]. Flow cytometry was used to confirm these findings in three primary USC cell lines, and found that USC expresses significantly more erbB2 receptor (tenfold greater, on average) compared with erbB2-positive primary or established, breast and ovarian cancer cell lines ($p < 0.001$). The authors also demonstrated that cell cultures that overexpressed erbB2 were highly sensitive to trastuzumab-mediated antibody-dependent cellular cytotoxity (ADCC) *in vitro* [35]. erbB2 overexpression in USC was thereafter reported in several studies. The reported frequency ranged from 18–80%, and overwhelmingly, erbB2 overexpression was associated with a poorer prognosis [18,36–41]. A higher frequency in African–Americans (67%) compared with Caucasians (33%) was confirmed by FISH analysis [36]. African–Americans were found to have a significantly higher *erbB2* gene mean copy number and a worse overall survival compared to Caucasians who overexpress erbB2 [36]. erbB2 receptor over-expression was correlated with *c-erbB2* gene amplification [38,41]. The concordance between gene amplification by FISH compared with heavy (3+) and moderate (2+) staining intensity by IHC was 100 and 29%, respectively [38]. A moderate (2+) staining intensity by IHC must therefore be confirmed by FISH if targeted therapy is contemplated [38].

Trastuzumab

Twenty five to 30% of breast cancers overexpress the erbB2 receptor. Trastuzumab (Herceptin®, Hoffman La-Roche, Basel, Switzerland), a humanized monoclonal antibody of the IgG1 family, is approved by the US FDA for treatment of breast cancer. In combination with chemotherapy, trastuzumab reduces the risk of death by 20 and 33% in metastatic and primary breast cancer, respectively [42]. Whereas trastuzumab is alleged to inhibit downstream signal transduction, ultimately modulating proliferation and apoptosis, its principal mechanism of action is believed to be through recruiting host immune cells (natural killer cells), and setting off an ADCC process [43–45].

In vitro studies of trastuzumab in USC

Our group has evaluated the sensitivity of highly aggressive chemoresistant USC primary cell lines to trastuzumab *in vitro* [35]. Upon challenging USC tumor cells that highly express erbB2 with autologous, as well as heterologous, effector cells (natural killer cells) in the presence of trastuzumab, in a standard 5-h chromium release assay, it was found that trastuzumab was able to mediate significant ADCC in those tumor cells (range of killing: 25–60%). Notably, no cytotoxic effect was recorded when tumor cells were incubated with effector cells in the absence of trastuzumab, or in the presence of rituximab, a control antibody. We also demonstrated a significant increase in ADCC after exposure of effector cells from healthy donors to low levels of IL-2, suggesting that nontoxic doses of this cytokine may potentiate the effects of trastuzumab *in vivo*. Importantly, the addition of physiological concentrations of human serum IgG did not inhibit trastuzumab-mediated ADCC against USC. Finally, trastuzumab also inhibited the proliferation of USC cell lines, which overexpress erbB2, in culture. The percentage of proliferation inhibition ranged from 30 to 62% when compared with control or to rituximab.

Pertuzumab (Omnitarg®, Hoffman La-Roche) the first of a new class of agents designated HER dimerization inhibitors, is a humanized IgG1 monoclonal antibody that sterically binds domain II of the erbB2 receptor preventing heterodimerization and signal transduction. Whereas trastuzumab is alleged to inhibit downstream signal transduction, ultimately modulating proliferation and apoptosis, its principal mechanism of action is believed to be through recruiting host immune cells (natural killer cells), and setting off an ADCC process [37,42]. This is dependent on receptor overexpression. Pertuzumab, on the other hand, is believed to inhibit a wider array of downstream signal transduction pathways through inhibition of lateral signal transduction (i.e., heterodimerization). This was studied on several solid tumors *in vitro*, as well as in xenografts [46–48]. Our group evaluated the pertuzumab activity individually and in combination with trastuzumab against primary USC cell lines expressing different levels of erbB2 [37]. The two antibodies were similarly effective in inducing strong ADCC (killing range: from 44.7 to 67.3%) in USC cells expressing high levels of erbB2. Trastuzumab was more potent than pertuzumab in inducing ADCC in low erbB2 expressors. More importantly, however, the combination of the two antibodies significantly increased trastuzumab-induced ADCC ($p = 0.02$). Pertuzumab induced a significant inhibition of proliferation in all USC cell lines irrespective of their erbB2 expression. This synergistic effect, also witnessed in other studies, is believed to be due to the different, but complementary, mechanisms of action of the two antibodies [37,49,50].

In vivo studies of trastuzumab in USC

A Phase II study of single-agent trastuzumab in advanced/recurrent EC patients of any histology has recently been reported from the GOG [51]. This study was not able to demonstrate single-agent activity of trastuzumab against endometrial carcinoma patients

harboring tumors with erbB2 overexpression. Such results, however, have recently been challenged owing to the many shortcomings in the design of the GOG 181b study [52]. Moreover, evidence of trastuzumab-clinical activity in a handful of heavily pretreated endometrial carcinoma patients has been recently reported as case reports in the medical literature [53–55]. Consistent with this view, we reported on two EC patients treated with trastuzumab. The first case had a stage IIIA, platinum refractory grade 3 endometrioid tumor with IHC 3+ erbB2 overexpression. The second case had a stage IIIC USC that persisted after surgery and adjuvant pelvic, as well as extended field, radiation. This patient had an IHC 2+ erbB2 overexpression. Both cases received salvage treatment with trastuzumab, with chemotherapy in the former, and as a single agent in the latter. Both cases achieved significant partial responses and a substantial sustained decrease in CA125 [53]. In another case report Jewell *et al*. reported similar success with trastuzumab therapy in combination with chemotherapy in a 72-year old with stage IIIA grade 2 endometrioid adenocarcinoma that recurred after surgery and adjuvant radiation therapy. The tumor showed IHC 3+ erbB2 overexpression [55]. Finally, Villella *et al*. reported on two recurrent USC patients with advanced disease and 3+ staining by IHC. When treated with trastuzumab, one patient achieved a complete response, and the other had stable disease [54]. In breast cancer, combination therapy with trastuzumab, pertuzumab and chemotherapy is currently being evaluated in a large trial multinational prospective randomized controlled trial [56].

Epithelial cell adhesion molecule

Our group at Yale has recently evaluated the expression of epithelial cell adhesion molecule (EpCAM) and the potential of MT201 (adecatumumab), a human monoclonal antibody against EpCAM, in USC [57]. By IHC, EpCAM expression was found in 96% (26 out of 27) of USC samples and high surface expression of EpCAM was found in 83% (five out of six) of the USC cell lines tested by flow cytometry. Importantly, EpCAM-positive cell lines were found to be highly sensitive to MT201-mediated antibody-dependent cellular cytotoxicity *in vitro*, whereas primary USC cell lines were resistant to natural killer cell-dependent cytotoxicity. These results support the view that MT201 might represent a novel therapeutic strategy in patients harboring advanced/recurrent or metastatic USC refractory to standard treatment modalities [57].

Claudin-3 & -4

Genes encoding tight junction proteins claudin-3 and -4 have recently been discovered as two of the most highly upregulated genes in USC, with over eight- and 12-fold upregulation, respectively, relative to normal endometrial cells [23]. Although the exact function of those proteins in USC is unclear, they have been shown to represent the epithelial receptors for *Clostridium perfringens* enterotoxin (CPE), a potent cytolytic toxin [58]. Because CPE may trigger lysis of mammalian epithelial cells through interactions with claudin-3 and -4 receptors while cells that do not express CPE receptors (i.e., mesothelial cells and most healthy human tissues) are protected from the lethal effects of CPE, overexpression of claudin-3 and -4 tight junction proteins may lead to the development of a novel cytotoxic therapy for USC patients. Consistent with this view, in a recent report we have shown that *in vivo* intratumoral injections of well-tolerated doses of CPE in large subcutaneous USC xenografts may lead to large areas of tumor cell necrosis and tumor disappearance in all the treated animals, whereas sublethal intraperitoneal injections of CPE have a significant inhibitory effect on tumor progression, with extended survival of animals harboring chemotherapy-resistant intra-abdominal USC carcinomatosis [59].

Kallikrein-6 & -10

The kallikrein family consists of 15 genes that encode for trypsin-like or chemotrypsin-like serine proteases. Serine proteases play a well defined role in several cell activities such as blood coagulation, wound healing, digestion, immune response, as well as tumor invasion and metastasis. Secreted serine proteases such as prostate-specific antigen and kallikrein-2 have a clinical application as prostate cancer biomarkers. Kallikrein-6 and -10 were shown to be present in high levels in the circulation of a cohort of ovarian cancer patients, and to correlate with chemoresistance and poor prognosis [60]. In studies by Santin *et al.*, kallikrein-6 and -10 were both found to be highly expressed genes in USC [23,61,62]. It is therefore possible that kallikrein-6 and -10 may serve as markers for early detection and/or monitoring of USC, as well as potential immunotherapeutic targets of vaccination strategies against recurrent/refractory serous gynecologic cancers [61,62].

Patupilone

The *in vitro* sensitivity/resistance to patupilone (i.e., a macrocyclic polyketide member of the epothilone class, a group of micro-tubule-stabilizing agents) versus paclitaxel in USC with high versus low erbB2 expression has recently been reported [63]. Cell lines overexpressing erbB2 showed higher proliferation when compared to low erbB2-expressing cell lines. Compared to low expressing cell lines, high erbB2 expressors were significantly more sensitive to patupilone than to paclitaxel ($p < 0.0002$). By contrast, there was no appreciable difference in sensitivity to patupilone versus paclitaxel in primary USC cell lines with low erbB2 expression. Higher levels of TUBB3 and ABCB1 were detected in USC cell lines with high versus low erbB2 expression ($p < 0.05$). Taken together these studies demonstrated that USCs overexpressing erbB2 display greater *in vitro* sensitivity to patupilone and higher levels of the patupilone molecular target TUBB3 when compared with low erbB2 expressors. Owing to the adverse prognosis associated with erbB2 overexpression in USC patients, patupilone may represent a promising novel drug to combine to platinum compounds in this subset of aggressive endometrial tumors [63].

Sensitivity to platinum-based chemotherapy

Multiple clinical studies have reported on the high resistance of USC to platinum-based chemotherapy [3–6]. Thus, to identify effective chemotherapy regimens against USC, six primary tumor cell lines, half of which overexpress HER2/neu at 3+ level, have recently been evaluated for their *in vitro* sensitivity to 14 single-agent chemotherapies and five combinations by ChemoFx® (Precision Therapeutics Inc., PA, USA) [64]. Cell lines overexpressing HER2/neu showed higher proliferation when compared with low HER2/neu-expressing cell lines and a lower IC_{50} when exposed to the majority of single-agent chemotherapies. Surprisingly, high HER2/neu expressors were found to be more sensitive to platinum compounds, manifesting a 5.22-fold decrease in carboplatin IC_{50} ($p = 0.005$) and a 5.37-fold decrease in cisplatin IC_{50} ($p = 0.02$). These data suggest that the apparent lack of response to chemotherapy among patients with HER2/neu-positive tumors seen in clinical trials may be due to rapid tumor regrowth of surviving tumor cells following initial response to chemotherapy, rather than intrinsic chemotherapeutic drug resistance at the time of chemotherapy treatment [64].

Human immunoconjugate molecule

Human immunoconjugate molecule (hI-con1) is an antibody-like molecule that targets tissue factor (TF). It is composed of a targeting domain (i.e., two human factor VII) fused to an effector domain (IgG1 Fc domain). Our group has recently evaluated the activity of hI-con1 against primary chemotherapy-resistant USC. Immunohistochemical analysis demonstrated

TF expression in the cytoplasm and/or the cell membrane of 100% (16 out of 16) of the USC samples tested. In addition, three out of six cell lines in culture were found to be high expressors of TF when tested by flow cytometry and RT-PCR, compared with normal endometrial cells ($p < 0.001$). In a 5-h chromium release cytotoxicity assay, USC cell lines overexpressing TF, irrespective of erbB2 expression, were highly sensitive to hI-con1-dependent cell-mediated cytotoxicity ($p < 0.001$), while negligible cytotoxicity was seen in the absence of hI-con1 or in the presence of rituximab control antibody.

hI-con1 may hence represent a new therapeutic agent for the treatment of patients with advanced or recurrent USC refractory to standard treatment modalities [65].

IL-6

IL-6 activates the p38 mitogen-activated protein kinase signaling pathway leading to the development of chemotherapy resistance in cancer cells [66]. Interestingly, erbB2 expression facilitates the IL-6-induced mitogen-activated protein kinase signaling pathway. Thus, high levels of IL-6 gene expression and protein secretion may be associated with the erbB2 signaling cascade, promoting resistance to chemotherapeutic agents. IL-6 was found to be highly upregulated in USC [23,66]. Overexpression of IL-6 in USC could potentially lead to a role for drugs that inhibit IL-6 activity in the future management of this disease [66].

αv-integrins

Recently, our group has evaluated the surface expression of integrins belonging to the αV-family, including αVβ3, αVβ5 and αVβ6, in multiple primary USC cell lines using flow cytometry analysis [67]. In addition, we have tested the ability of intetumumab (CNTO 95), a fully human monoclonal antibody against αV-integrins, to inhibit USC cell adhesion and migration. We found high expression of the αV-subunit on the cell surface of all six primary USC cell lines tested (100% positive cells; mean fluorescence intensity range: 13.1–39.5). When the expression of single heterodimeric integrins was evaluated, αVβ3, αVβ5 and αVβ6 were expressed on 37.5, 32.0 and 16.3% of cells (mean fluorescence intensity range: 6.5–16.2, 9.2–32.5 and 6.2–11.5, respectively). Importantly, in functional assays, low doses of intetumumab were effective in inhibiting adhesion (0.15 μg/ml; $p = 0.003$) and migration (1.25 μg/ml; $p = 0.02$) of primary USC cell lines. We concluded that αV-integrins are overexpressed on the cell surface of primary USC cell lines. Intetumumab may significantly inhibit USC cell adhesion and migration pathways and may therefore represent a novel treatment option for patients harboring this rare, but highly aggressive, variant of EC [67].

Extracellular HER2/neu domain

The potential shedding of EGF type-II receptor (HER2/neu) extracellular domain (ECD) in primary USC cell lines and in the serum of USC patients and its biological effects in experiments of trastuzumab-induced cytotoxicity *in vitro* has recently been reported [68]. In this study, HER2/neu expression was evaluated by IHC, RT-PCR and flow-cytometry while *c-erbB2* gene-amplification was assessed using FISH. HER2/neu-ECD levels in the supernatants of USC cell lines and in the serum of 38 USC patients and 19 controls were tested using ELISA. The biologic effect of HER2/neu-ECD on trastuzumab-induced ADCC was evaluated in 5-h chromium-release assays. High levels of HER2/neu-ECD were found in supernatants of all FISH-positive tumors. By contrast, FISH-negative USCs were negative for HER2/neu-ECD shedding. Serum HER2/neu-ECD levels in patients harboring 3+HER2/neu tumors were higher than those found in healthy women ($p = 0.02$) or USC patients with 2+ or 1+/negative HER2/neu expression ($p = 0.02$). In cytotoxicity experiments, trastuzumab-mediated ADCC was significantly decreased by the addition of HER2/neu-

ECD-containing supernatants ($p = 0.01$). We concluded that FISH-positive *c-erbB2* USC cell lines shed high levels of HER2/neu-ECD. High levels of HER2/neu-ECD in USC patients may reduce trastuzumab-mediated ADCC *in vitro* and potentially reduce its therapeutic effect *in vivo*.

Trophoblast cell-surface marker

Our research group has recently evaluated the expression of human trophoblast cell-surface marker (Trop-2) and the potential of hRS7, a humanized anti-Trop-2 monoclonal antibody, as a novel therapeutic strategy against USC [69]. In this study, Trop-2 expression was evaluated by IHC in a total of 23 USC. Six primary USPC cell lines were assessed by flow cytometry and RT-PCR for Trop-2 expression. Sensitivity to hRS7 (Immunomedics, Inc., NJ, USA) ADCC and complement-dependent cytotoxicity was tested in standard 5-h Cr-release assays against primary USC cell lines [51]. Expression of Trop-2 was found in 15 out of 23 (65%) of the tumor tissues tested by IHC and in 50% (three out of six) of the USC cell lines tested by RT-PCR and flow-cytometry (Trop-2 expression in USC versus normal endometrial cells; $p < 0.005$). USC cell lines overexpressing Trop-2, regardless of their intrinsic resistance to natural killer cytotoxicity, were highly sensitive to hRS7-mediated ADCC *in vitro* (range of killing: 28.2–64.4%; $p < 0.001$). Negligible cytotoxicity against USC was seen in the absence of hRS7 or in the presence of rituximab control antibody (range of killing: 1.1–12.4%). Incubation with IL-2 (50 IU/ml) in addition to hRS7 further increased the cytotoxic activity against USPC cell lines overexpressing Trop-2 ($p = 0.008$). We concluded that Trop-2 was highly expressed in USC at mRNA and protein levels and that primary USC cell lines are highly sensitive to hRS7-mediated cytotoxicity *in vitro*. hRS7 may represent a novel therapeutic agent for USC refractory to standard treatment modalities.

Expert commentary

USC is an aggressive variant of EC characterized by a high-grade, complex histology. Although USC accounts for less than 10% of all endometrial tumors, it accounts for a disproportionate number of relapses and EC-related deaths. Type I and II ECs appear to have a different pattern of molecular alterations that underlie pathogenesis and progression. While endometrioid carcinomas tend to have alterations in the tumor suppressor gene, *PTEN*, these are uncommon in USC, with *p53* mutations and erbB2 expression occurring more commonly in this tumor subtype. Both early-stage (stage I/II with disease confined to the uterus) and advanced disease states (stage III/IV with metastases present outside of the uterus) behave aggressively. USC has a tendency to invade the lymphatic and vascular spaces and lymph nodes and to microscopically or macroscopically involve other intraperitoneal structures, particularly the omentum, despite minimal or no invasion present within the uterus. These tumor characteristics lead to high recurrence rates and a poor prognosis for these patients.

Because of poor results with surgery alone, both radiation therapy and chemotherapy have been added postoperatively in an effort to improve outcomes. However, the benefit of these modalities, as well as the optimal treatment for each disease stage remains unclear. Recurrence rates in women diagnosed with advanced-stage disease are much higher than for early-stage disease, with rates of 50–90% reported in published studies. These recurrences are often extrapelvic and largely unsalvageable and highlight the need for novel and effective systemic therapy in the treatment of this disease.

Targeted therapy may represent a reasonable and innovative approach for the treatment of USC refractory to standard treatment modalities. In pursuit of our goal to develop

innovative, highly effective therapeutic strategies for patients with chemotherapy-resistant USC, we searched for potential molecular targets by using high-throughput technologies to compare genetic finger-prints of USC samples with those of healthy endometrial tissue samples [23,24]. Our recent studies have identified a large number of differentially expressed genes, some of which are discussed in this review article, that are known to contribute to USC transformation and tumorigenesis and that may represent ideal targets for the development of novel treatment modalities. Consistent with this view, the HER2/neu, which is targeted by the anti-HER2 monoclonal antibody trastuzumab (i.e., Herceptin), may represent the first of a series of novel diagnostic and therapeutic markers, including but not limited to, EpCAM, kallikrein-6 and -10, TROP-2, claudin-3 and -4, SAA, αV-integrins, IL-6 and hI-con1, endowed with significant therapeutic potential in USC patients harboring advanced and/or recurrent disease.

Five-year view

In 2002, we reported for the first time high erbB2 expression in USC specimens and high sensitivity of USC primary cell lines to trastuzumab antibody-dependent cytotoxicity *in vitro* [34]. IHC data from other research groups, including GOG, and gene-expression profiling results of biologically aggressive USC have recently confirmed overexpression of erbB2 in a large number of USC patients [23,39,40]. On the basis of these results, trastuzumab may very well be an attractive and viable treatment option for advanced-stage USC tumors that overexpress the erbB2 receptor. Consistent with these data, a multi-institutional randomized Phase II trial is currently enrolling patients in the USA (ClinicalTrials identifier: NCT01367002) [101]. The primary objective of this Phase II study is to evaluate whether the addition of trastuzumab to paclitaxel and carboplatin chemotherapy improves progression-free survival when compared to paclitaxel and carboplatin alone in stages III–IV and recurrent USC patients overexpressing erbB2 at 3+ level by IHC or positive by FISH. The secondary objectives of the study include: assess objective response rate; assess overall survival and assess the safety profile of trastuzumab in USC patients. The exploratory/correlative objectives of the study include: determine peripheral blood NK cell numbers and activity in erbB2+ USC patients to provide a basis for assessing the possible therapeutic contributions of immune mechanisms of action of trastuzumab; study erbB2 extracellular domain (ECD) circulating levels in the plasma of USC patients overexpressing erbB2 before, during and after treatment to elucidate whether changes in erbB2 ECD would predict response to trastuzumab; and determine whether CA-125 levels correlate with disease activity in advanced and/or recurrent disease. The results of this trial will be very helpful in determining whether there is a role for trastuzumab in the management of this disease.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010; 60(5):277–300. [PubMed: 20610543]

2. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983; 15:10–17. [PubMed: 6822361]

3••. Fader AN, Boruta D, Olawaiye AB, Gehrig PA. Uterine papillary serous carcinoma: epidemiology, pathogenesis and management. Curr Opin Obstet Gynecol. 2010; 22(1):21–29. Excellent review of uterine serous cancer (USC) with special emphasis on current treatment strategies based on the best evidence available. [PubMed: 19952744]

4. Rose PG. Endometrial carcinoma. N Engl J Med. 1996; 335(9):640–649. [PubMed: 8692240]

5••. Schwartz PE. The management of serous papillary uterine cancer. Curr Opin Oncol. 2006; 18(5): 494–499. Thorough review of the best published literature on USC in 2005. The manuscript thoroughly describes all aspects of diagnosis and management. [PubMed: 16894299]

6. Goff BA. Uterine papillary serous carcinoma: what have we learned over the past quarter century? Gynecol Oncol. 2005; 98(3):341–343. [PubMed: 16111527]

7. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006; 94(5):642–646. [PubMed: 16495918]

8. Maxwell GL, Tian C, Risinger J, et al. Racial disparity in survival among patients with advanced/recurrent endometrial adenocarcinoma: a gynecologic oncology group study. Cancer. 2006; 107(9): 2197–2205. [PubMed: 17001661]

9. Sherman ME, Devesa SS. Analysis of racial differences in incidence, survival, and mortality for malignant tumors of the uterine corpus. Cancer. 2003; 98(1):176–186. [PubMed: 12833470]

10. Marchesoni D, Driul L, Mozzanega B, Nardelli GB, Parenti A. Intraepithelial G3 adenocarcinoma of the endometrium after tamoxifen treatment. Arch Gyneco Obstet. 2005; 271(1):62–65.

11. Biron-Shental T, Drucker L, Altaras M, Bernheim J, Fishman A. High incidence of BRCA1-2 germline mutations, previous breast cancer and familial cancer history in Jewish patients with uterine serous papillary carcinoma. Eur J Surg Oncol. 2006; 32(10):1097–1100. [PubMed: 16650962]

12•. Kelly MG, O'Malley DM, Hui P, et al. Improved survival in surgical stage I patients with uterine papillary serous carcinoma (UPSC) treated with adjuvant platinum-based chemotherapy. Gynecol Oncol. 98(3):353–359.2005; [PubMed: 16005947] Large retrospective series of patients with surgical stage I USC. The manuscript emphasizes the importance of adjuvant chemotherapy in this disease

13. Ueda SM, Kapp DS, Cheung MK, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol. 2008; 198(2):218.e1–218.e6. [PubMed: 18226630]

14. Acharya S, Hensley ML, Montag AC, Fleming GF. Rare uterine cancers. [Erratum in *Lancet Oncol* 7(2), 105 (2006)]. Lancet Oncol. 2005; 6(12):961–971. [PubMed: 16321764]

15. Hamilton CA, Liou WS, Osann K, et al. Impact of adjuvant therapy on survival of patients with early-stage uterine papillary serous carcinoma. Int J Radiat Oncol Biol Phys. 2005; 63(3):839–844. [PubMed: 16199314]

16. Martin JD, Gilks B, Lim P. Papillary serous carcinoma – a less radio-sensitive subtype of endometrial cancer. Gynecol Oncol. 2005; 98(2):299–303. [PubMed: 15964062]

17. Alektiar KM, Makker V, Abu-Rustum NR, et al. Concurrent carboplatin/paclitaxel and intravaginal radiation in surgical stage I–II serous endometrial cancer. Gynecol Oncol. 2009; 112(1):142–145. [PubMed: 19019418]

18••. Santin AD, Bellone S, Van Stedum S, et al. Amplification of c-erbB2 oncogene: a major prognostic indicator in uterine serous papillary carcinoma. Cancer. 2005; 104(7):1391–1397. Retrospective study of 30 cases of USC. The authors evaluate *erbB2* gene amplification by FISH, and its clinical implications both in African Americans and aucasians. [PubMed: 16116605]

19. Sherman ME, Bitterman P, Rosenshein NB, Delgado G, Kurman RJ. Uterine serous carcinoma. A morphologically diverse neoplasm with unifying clinicopathologic features. Am J Surg Pathol. 1992; 16(6):600–610. [PubMed: 1599038]

20. Egan JA, Ionescu MC, Eapen E, Jones JG, Marshall DS. Differential expression of WT1 and p53 in serous and endometrioid carcinomas of the endometrium. Int J Gynecol Pathol. 2004; 23(2): 119–122. [PubMed: 15084839]

21. Moreno-Bueno G, Sanchez-Estevez C, Cassia R, et al. Differential gene expression profile in endometrioid and nonendometrioid endometrial carcinoma: STK15 is frequently overexpressed and amplified in nonendometrioid carcinomas. Cancer Res. 2003; 63(18):5697–5702. [PubMed: 14522886]

22. Risinger JI, Maxwell GL, Chandramouli GV, et al. Microarray analysis reveals distinct gene expression profiles among different histologic types of endometrial cancer. Cancer Res. 2003; 63(1):6–11. [PubMed: 12517768]

23••. Santin AD, Zhan F, Cane' S, et al. Gene expression fingerprint of uterine serous papillary carcinoma: identification of novel molecular markers for uterine serous cancer diagnosis and therapy. Br J Cancer. 2005; 92(8):1561–1573. Using microarray technology, the authors profile reveal the gene expression of USC. Several genes and the proteins they encode are later evaluated for a potential role in targeted therapy. [PubMed: 15785748]

24. Santin AD, Zhan F, Bellone S, et al. Discrimination between uterine serous papillary carcinomas and ovarian serous papillary tumours by gene expression profiling. Br J Cancer. 2004; 90(9): 1814–1824. [PubMed: 15208622]

25. Ragni N, Ferrero S, Prefumo F, et al. The association between p53 expression, stage and histological features in endometrial cancer. Eur J Obstet Gynecol Reprod Biol. 2005; 123(1):111–116. [PubMed: 15894417]

26. Jongen VH, Briet JM, de Jong RA, et al. Aromatase, cyclooxygenase 2, HER-2/neu, and p53 as prognostic factors in endometrioid endometrial cancer. Int J Gynecol Cancer. 2009; 19(4):670–676. [PubMed: 19509570]

27. Lax SF. Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypical to a molecular-based classification. Virchows Archiv. 2004; 444(3):213–223. [PubMed: 14747944]

28. Shedden KA, Kshirsagar MP, Schwartz DR, et al. Histologic type, organ of origin, and wnt pathway status: effect on gene expression in ovarian and uterine carcinomas. Clin Cancer Res. 2005; 11(6):2123–2131. [PubMed: 15788657]

29. Cocco E, Bellone S, El-Sahwi K, et al. Serum amyloid A (SAA): a novel biomarker for uterine serous papillary cancer. Br J Cancer. 2009; 101(2):335–341. [PubMed: 19536090]

30. Yarden Y, Sliwkowski MX. Untangling the erbB signalling network. Nature Rev Mol Cell Biol. 2001; 2(2):127–137. [PubMed: 11252954]

31. Berchuck A, Kamel A, Whitaker R, et al. Overexpression of HER-2/neu is associated with poor survival in advanced epithelial ovarian cancer. Cancer Res. 1990; 50(13):4087–4091. [PubMed: 1972347]

32. Berchuck A, Rodriguez G, Kinney RB, et al. Overexpression of HER-2/neu in endometrial cancer is associated with advanced stage disease. Am J Obstet Gynecol. 1991; 164(1 Pt 1):15–21. [PubMed: 1670908]

33. Hetzel DJ, Wilson TO, Keeney GL. HER-2/neu expression: a major prognostic factor in endometrial cancer. Gynecol Oncol. 1992; 47(2):179–185. [PubMed: 1361478]

34. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987; 235(4785):177–182. [PubMed: 3798106]

35•. Santin AD, Bellone S, Gokden M, et al. Overexpression of HER-2/neu in uterine serous papillary cancer. Clin Cancer Res. 2002; 8(5):1271–1279. First study to report on erbB2 overexpression in USC, and demonstrate the sensitivity of USC cell lines that overexpress erbB2 to trastuzumab-mediated cellular cytotoxicity. [PubMed: 12006548]

36•. Santin AD, Bellone S, Siegel ER, et al. Racial differences in the overexpression of epidermal growth factor type II receptor (HER2/neu): a major prognostic indicator in uterine serous papillary cancer. Am J Obstet Gynecol. 2005; 192(3):813–818. The racial difference in erbB2 expression may, in part, explain the disparity of outcome between African American and Caucasian women with USC. [PubMed: 15746676]

37•. El-Sahwi K, Bellone S, Cocco E, et al. *In vitro* activity of pertuzumab in combination with trastuzumab in uterine serous papillary adenocarcinoma. Br J Cancer. 2010; 102(1):134–143. First published study evaluating the activity of petuzumab in combination with trastuzumab on USC cell lines in culture. The combination produces significantly more cell-mediated cytotoxicity in cell lines that express low levels of erbB2. [PubMed: 19920829]

38. Santin AD, Bellone S, Van Stedum S, et al. Determination of HER2/neu status in uterine serous papillary carcinoma: comparative analysis of immunohistochemistry and fluorescence *in situ* hybridization. Gynecol Oncol. 2005; 98(1):24–30. [PubMed: 15894362]

39. Diaz-Montes TP, Ji H, Smith Sehdev AE, et al. Clinical significance of Her-2/neu overexpression in uterine serous carcinoma. Gynecol Oncol. 2006; 100(1):139–144. [PubMed: 16182348]

40. Grushko TA, Filiaci VL, Mundt AJ, et al. An exploratory analysis of HER-2 amplification and overexpression in advanced endometrial carcinoma: a gynecologic oncology group study. Gynecol Oncol. 2008; 108(1):3–9. [PubMed: 17945336]

41. Odicino FE, Bignotti E, Rossi E, et al. HER-2/neu overexpression and amplification in uterine serous papillary carcinoma: comparative analysis of immunohistochemistry, real-time reverse transcription-polymerase chain reaction, and fluorescence in situ hybridization. Int J Gynecol Cancer. 2008; 18(1):14–21. [PubMed: 17451461]

42. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001; 344(11):783–792. [PubMed: 11248153]

43. Arnould L, Gelly M, Penault-Llorca F, et al. Trastuzumab-based treatment of HER2-positive breast cancer: an antibody-dependent cellular cytotoxicity mechanism? Br J Cancer. 2006; 94(2):259–267. [PubMed: 16404427]

44. Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory fc receptors modulate *in vivo* cytoxicity against tumor targets. Nat Med. 2000; 6(4):443–446. [PubMed: 10742152]

45. Gennari R, Menard S, Fagnoni F, et al. Pilot study of the mechanism of action of preoperative trastuzumab in patients with primary operable breast tumors overexpressing HER2. Clin Cancer Res. 2004; 10(17):5650–5655. [PubMed: 15355889]

46. Agus DB, Akita RW, Fox WD, et al. Targeting ligand-activated erbB2 signaling inhibits breast and prostate tumor growth. Cancer Cell. 2002; 2(2):127–137. [PubMed: 12204533]

47. Agus DB, Gordon MS, Taylor C, et al. Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. J Clin Oncol. 2005; 23(11):2534–2543. [PubMed: 15699478]

48. Mullen P, Cameron DA, Hasmann M, Smyth JF, Langdon SP. Sensitivity to pertuzumab (2C4) in ovarian cancer models: cross-talk with estrogen receptor signaling. Mol Cancer Ther. 2007; 6(1): 93–100. [PubMed: 17237269]

49. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. Cancer Res. 2004; 64(7):2343–2346. [PubMed: 15059883]

50. Scheuer W, Friess T, Burtscher H, Bossenmaier B, Endl J, Hasmann M. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. Cancer Res. 2009; 69(24):9330–9336. [PubMed: 19934333]

51. 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. [PubMed: 19840887]

52. Santin AD. Letter to the editor referring to the manuscript entitled: 'Phase II trial of trastuzumab in women with advanced or recurrent HER-positive endometrial carcinoma: a gynecologic oncology group study' recently reported by Fleming *et al*(*Gynecol Oncol*., 116, 15–20 (2010)). Gynecol Oncol. 2010; 118(1):95–96. [PubMed: 20172595]

53. Santin AD, Bellone S, Roman JJ, McKenney JK, Pecorelli S. Trastuzumab treatment in patients with advanced or recurrent endometrial carcinoma overexpressing HER2/neu. Int J Gynaecol Obstet. 2008; 102(2):128–131. [PubMed: 18555254]

54. Villella JA, Cohen S, Smith DH, Hibshoosh H, Hershman D. HER-2/neu overexpression in uterine papillary serous cancers and its possible therapeutic implications. Int J Gynecol Cancer. 2006; 16(5):1897–1902. [PubMed: 17009989]

55. Jewell E, Secord AA, Brotherton T, Berchuck A. Use of trastuzumab in the treatment of metastatic endometrial cancer. Int J Gynecol Cancer. 2006; 16(3):1370–1373. [PubMed: 16803532]

56••. Baselga J, Swain SM. CLEOPATRA: a Phase III evaluation of pertuzumab and trastuzumab for HER2-positive metastatic breast cancer. Clin Breast Cancer. 2010; 10(6):489–491. Results of this

large multinational randomized controlled trial will shed somemuch anticipated light on the potential benefit ofcombining pertuzumab and trastuzumab (plus docetaxel) in early and metastatic breast cancer patients with high erbB2 expression. [PubMed: 21147694]

57•. El-Sahwi K, Bellone S, Cocco E, et al. Overexpression of EpCAM in uterine serous papillary carcinoma: Implications for EpCAM-specific immunotherapy with human monoclonal antibody adecatumumab (MT201). Mol Cancer Ther. 2010; 9(1):57–66. First report of epithelial cell adhesion molecule (EpCAM) expression in USC. The study demonstrates a high frequency of EpCAM expression and an exquisite sensitivity to a monoclonal antibody (MT201) known to have a favorable toxicity profile. [PubMed: 20053761]

58. Katahira J, Sugiyama H, Inoue N, Horiguchi Y, Matsuda M, Sugimoto N. *Clostridium perfringens* enterotoxin utilizes two structurally related membrane proteins as functional receptors *in vivo*. J Biol Chem. 1997; 272(42):26652–26658. [PubMed: 9334247]

59. Santin AD, Bellone S, Marizzoni M, et al. Overexpression of claudin-3 and claudin-4 receptors in uterine serous papillary carcinoma: novel targets for a type-specific therapy using *Clostridium perfringens* enterotoxin (CPE). Cancer. 2007; 109(7):1312–1322. [PubMed: 17326053]

60. Diamandis EP, Scorilas A, Fracchioli S, et al. Human kallikrein 6 (hK6): a new potential serum biomarker for diagnosis and prognosis of ovarian carcinoma. J Clin Oncol. 2003; 21(6):1035–1043. [PubMed: 12637468]

61. Santin AD, Diamandis EP, Bellone S, et al. Human kallikrein 6: a new potential serum biomarker for uterine serous papillary cancer. Clin Cancer Res. 2005; 11(9):3320–3325. [PubMed: 15867230]

62. Santin AD, Diamandis EP, Bellone S, et al. Overexpression of kallikrein 10 (hK10) in uterine serous papillary carcinomas. Am J Obstet Gynecol. 2006; 194(5):1296–1302. [PubMed: 16647913]

63. Paik D, Cocco E, Bellone S, et al. Higher sensitivity to patupilone versus paclitaxel chemotherapy in primary uterine serous papillary carcinoma cell lines with high versus low HER-2/neu expression *in vitro*. Gynecol Oncol. 2010; 119(1):140–145. [PubMed: 20673976]

64. Cross SN, Cocco E, Bellone S, et al. Differential sensitivity to platinum-based chemotherapy in primary uterine serous papillary carcinoma cell lines with high vs low HER-2/neu expression*in vitro*. Am J Obstet Gynecol. 2010; 203(2):162.e1–8. [PubMed: 20417484]

65. Cocco E, Hu Z, Richter CE, et al. hI-con1, a factor VII-IgGFc chimeric protein targeting tissue factor for immunotherapy of uterine serous papillary carcinoma. Br J Cancer. 2010; 103(6):812–819. [PubMed: 20700124]

66. Bellone S, Watts K, Cane' S, et al. High serum levels of interleukin-6 in endometrial carcinoma are associated with uterine serous papillary histology, a highly aggressive and chemotherapy-resistant variant of endometrial cancer. Gynecol Oncol. 2005; 98(1):92–98. [PubMed: 15904949]

67. Bellone M, Cocco E, Varughese J, et al. Expression of alphaV-integrins in uterine serous papillary carcinomas; implications for targeted therapy with intetumumab (CNTO 95), a fully human antagonist anti-alphaV-integrin antibody. Int J Gynecol Cancer. 2011; 21(6):1084–1090. [PubMed: 21633302]

68. Todeschini P, Cocco E, Bellone S, et al. Her2/neu extracellular domain shedding in uterine serous carcinoma; implications for immunotherapy with trastuzumab. Br J Cancer. 2011; 105(8):1176–1182. [PubMed: 21915118]

69. Varughese J, Cocco E, Bellone S, et al. Uterine serous papillary carcinomas overexpress human trophoblast-cell-surface marker (trop-2) and are highly sensitive to immunotherapy with hRS7, a humanized anti-trop-2 monoclonal antibody. Cancer. 2011; 117(14):3163–3172. [PubMed: 21246534]

Website

101. Evaluation of Carboplatin/Paclitaxel with and Without Trastuzumab (Herceptin) in Uterine Serous Cancer. http://clinicaltrials.gov/ct2/results?term=NCT01367002

Key issues

- Uterine serous cancer (USC) is a highly aggressive variant of endometrial cancer.
- USC is resistant to cytotoxic chemotherapy and is responsible for most recurrences and deaths from endometrial cancer.
- USC has a unique gene expression profile.
- Molecular markers can aid in diagnosis and in monitoring response to therapy in USC.
- Multiple potential molecular markers for targeted therapy in USC are being studied.
- erbB2 is overexpressed in 20–50% of USC patients.
- erbB2 is more frequently overexpressed in African–American patients where it confers a dire prognosis.
- Targeted therapy with trastuzumab is promising and must be widely studied in advanced and recurrent erbB2-expressing USCs.