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Targeting Angiogenesis in Gynecologic Cancers

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Introduction

Gynecologic malignancies including cancers of the uterus, ovaries, cervix, fallopian tubes, vagina, and vulva carry an estimated incidence of 83,750 cases per year, and estimated mortality rate of over 27,000 women per yeargresset[1]. Endometrial cancer is the most common gynecologic malignancy. However, ovarian cancer remains the most common cause of mortality from a gynecologic cancer. The reason for this is attributed to the advanced stage of ovarian cancer at the time of diagnosis, frequent recurrences, and the emergence of drug resistance. Advances in surgery, chemotherapy, and patient care have improved outcomes for gynecologic malignancies, but overall survival rates appear to have plateaued.[2] Therefore, new therapies and therapeutic approaches are needed to improve the outlook for women with gynecologic cancers. Recent insights at the molecular and cellular levels are paving the way for a more directed approach to target mechanisms driving tumorigenesis, such as angiogenesis. This article reviews the roles of new and emerging anti-angiogenesis drugs; summarizes the data obtained from clinical trials of anti-angiogenic agents and discusses future trials underway to address the role of such strategies in gynecologic cancers.

I. Angiogenesis

Development of new blood supply is essential for the development and maintenance of any tissue or organ[3,4]. For cancer to grow beyond 1 mm^3 in size, it is necessary for the tumor to develop a sufficient blood supply[4] _ENREF_4_ENREF_4. Over the last several years, it has become apparent that neovascularization of tumors is a highly complex and regulated process. Classically, there are two distinct types of angiogenesis that have been described. The first is sprouting, which involves branching of new blood vessels from pre-existing blood vessels. The second type is splitting or non-sprouting angiogenesis, which involves the splitting of a lumen of an existing vessel. Unlike physiologic angiogenesis, tumor angiogenesis involves endothelial cells that fail to become quiescent[5]. These cells proliferate

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and grow uncontrollably and have a different phenotype than physiologic vasculature. Morphologically, the tumor vasculature is characterized by irregularly shaped vessels, which are dilated, tortuous, and disorganized[6,7].

Recently, other mechanisms of tumor vascularization have been discovered. These include the recruitment of endothelial progenitor cells (EPC's), vessel co-option, vasculogenic mimicry and lymphangiogenesis. EPCs are circulating cells in the blood that can form new blood vessels. The mobilization and recruitment of EPCs is promoted by several growth factors, chemokines and cytokines produced during tumor growth[8]. Vessel co-option is a process whereby tumor cells can grow along existing blood vessels without evoking an angiogenic response in such vascular places such as the brain or lungs[9]. Vasculogenic mimicry is the process of tumor cell plasticity, mainly in aggressive tumors, in which tumor cells dedifferentiate to an endothelial phenotype and make tube-like structures[9]. This mechanism provides an alternate route for tumor vascularization that may be independent of traditional angiogenesis processes. However, the majority of anti-angiogenesis treatments are currently tailored toward the sprouting biology of angiogenesis.

The establishment of angiogenesis relies on several pro-angiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), ephrins and their receptors. Tumor cells can produce pro-angiogenic factors for vessel formation. The vessel density and circulating tumor levels of pro-angiogenic factors VEGF and PDGF are poor prognostic indicators for many solid tumors including ovarian, endometrial and cervical carcinomas[10–12]. Due to their critical role in angiogenesis, pro-angiogenic factors are attractive therapeutic targets and highly studied in the area of cancer therapeutics.

II. Bevacizumab

VEGF is a major and one of the best characterized pro-angiogenic factors. It consists of family proteins of which VEGFA (synonymously called “VEGF”) is the dominant angiogenic factor[13]. It was originally known as vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) and its mechanism in angiogenesis at that time was unclear[14]. Significant progress in angiogenesis research has elucidated the fact that there are three VEGF receptors, with VEGFR2 being most significant for angiogenesis in most solid tumors[13]. Upon VEGF binding to its receptor on endothelial cells, a cascade of signaling events is activated that results in transcriptional activation of genes responsible for endothelial cell growth. Moreover, activated endothelial cells produce matrix metalloproteinases (MMPs), which break down the extracellular matrix to allow migration of endothelial cells for new blood vessel formation[15,16].

Among the various strategies for targeting VEGF, perhaps the most advanced is the monoclonal antibody bevacizumab. Bevacizumab is a humanized monoclonal antibody directed against human VEGF. It binds to VEGF to block its interaction with VEGF receptors (VEGFR-1 and VEGFR-2), with resultant inhibition of angiogenesis and endothelial cell proliferation[17]. It was the first drug the US Food and Drug Administration (FDA) approved for targeting tumor angiogenesis. Currently, bevacizumab is approved for a variety of solid tumors (e.g. colorectal, renal cell, non squamous non small cell lung cancers, and glioblastoma)[18].

Based on encouraging preclinical results, bevacizumab has been investigated clinically in ovarian cancer patients, both in frontline and recurrent disease settings. Response rates among women with recurrent disease ranged from 16–24% in the initial phase II trials, with median survival of 10.7 to 17 months when administered either as a single agent or in combination with cyclophosphamide[19–21]. In a phase II study of recurrent ovarian and

primary peritoneal cancer, patients received single agent bevacizumab every 3 weeks until disease progression or significant toxicity. Of the 62 evaluable patients, 21% had a clinical response including two complete responses. Median PFS and overall survival were 4.7 and 17 months, respectively. This regimen was well tolerated, and no association was made between prior platinum sensitivity and hazard to progression or death[19]. In a phase II bevacizumab monotherapy study by Cannistra et al., 44 patients with platinum resistant epithelial ovarian cancer and peritoneal serous cancer received single agent bevacizumab every 3 weeks for 5 cycles. Overall response rate was 16%, and median PFS was 4.4 months. This study was terminated early due to a higher than expected incidence of bowel perforation of 11%. We will address more of the toxicities of bevacizumab in the coming paragraphs. From these above studies, it is apparent that bevacizumab has single agent activity against ovarian cancer[20], and subsequent studies addressed its efficacy in combination with cytotoxic agents.

In a phase II study by Penson et al., sixty-two patients with primary epithelial ovarian, fallopian tube, uterine papillary serous and primary peritoneal cancer were evaluated using carboplatin and paclitaxel in combination with bevacizumab. All three agents were given every 21 days for 6–8 cycles followed by bevacizumab every three weeks for one year. All patients had a computer tomography (CT) scan after surgery and before chemotherapy and 45% of the study population had suboptimal cytoreduction (> 1 cm residual disease). Radiographic responses were documented in 21 (75%) of 28 women with measurable disease, with CA-125 responses in 76% of patients. The median PFS was 29.8 months[22]. These efficacy results were favorable compared to historical controls[23]. Another phase II study of patients with primary advanced stage ovarian, peritoneal, or fallopian tube cancer, used treatment protocol of carboplatin/paclitaxel plus bevacizumab for six cycles, and resulted in an overall 80% response rate. The toxicities were overall well tolerated and no gastrointestinal perforations occurred. Two patients had grade 3 hypertension[24]. However, a recent phase II single institution open label trial of intravenous bevacizumab in combination with intraperitoneal chemotherapy for patients with untreated primary advanced stage ovarian cancer, suggested that bowel toxicity may be exacerbated with this route of administration[25]. Table 1 summarizes selected phase II trials with bevacizumab in gynecologic cancers.

There are several phase III clinical trials underway or recently completed in ovarian cancer. GOG 218 and ICON7 are two randomized phase III studies that include combination chemotherapy with maintenance therapy. In GOG 218, 1,873 women with previously untreated advanced epithelial ovarian, primary peritoneal or fallopian tube carcinoma showed that women who received bevacizumab in combination with paclitaxel and carboplatin, and continued on bevacizumab maintenance therapy for a total duration of 15 months, had a median PFS of 14.1 months compared to 10.3 months in women who received chemotherapy alone (hazard ratio = 0.72, $p<0.0001$)[26]. ICON7 included 1,528 women with previously untreated epithelial ovarian, primary peritoneal or fallopian tube carcinoma. Women who received bevacizumab in combination with paclitaxel and carboplatin, and continued use of bevacizumab maintenance for a total duration of up to 12 months, had a median PFS of 18.3 months compared to 16 months in women who received chemotherapy alone (hazard ratio = 0.79, $p = 0.001$)[27]

Several studies were also launched in the setting of relapsed ovarian cancer. GOG 213 and OCEANS study are evaluating chemotherapy and bevacizumab combinations (paclitaxel/carboplatin and gemcitabine/carboplatin, respectively) in patients with recurrent platinum sensitive disease. The OCEANS study recently reported safety and efficacy data in 484 patients stratified by length of platinum-free interval and performance of secondary surgery[28]. Unique in this design was the ability to maintain bevacizumab therapy to

progression after 6 to 10 cycles of concomitant therapy with gemcitabine and carboplatin. No gastrointestinal perforations were observed on either arm of this placebo-controlled trial. Grade 3 hypertension and proteinuria were more frequently observed in the bevacizumab arm. However, the median PFS of the experimental arm was 12.4 months and favorably compared to 8.4 months in the control arm (HR: 0.484, 95% CI: 0.39–0.61, $p < 0.0001$). OS was immature at this report. The AURELIA trial is evaluating the addition of bevacizumab to paclitaxel, topotecan, and liposomal doxorubicin in patients with platinum resistant ovarian cancer. Table 2 shows the completed, ongoing and future phase III trials of bevacizumab in gynecologic cancers.

Phase II studies have also reported some response with use of bevacizumab alone in the setting of persistent or recurrent endometrial and cervical cancer. In patients with recurrent endometrial cancer, bevacizumab treatment resulted in a response rate of 13.5% (one complete response and 7 partial responses) with a median PFS of 3.4 months and OS of 7.29 months[29]. In patients with persistent or recurrent squamous cell carcinoma of the cervix, 23.9% had progression free interval disease for 6 months and 10.9% had a partial response. The median PFS was 3.40 months and OS of 7.29 months. This compared favorably with historical GOG phase II trials in this setting[30]. Table 1 provides a summary of selected phase II trials with bevacizumab in gynecologic cancers.

While anti-VEGF treatments show some promise, there are concerns related to toxicity. The toxicities associated with bevacizumab have been documented from various trials and include hypertension, proteinuria, hemorrhage, neutropenia, venous thromboembolism, pulmonary embolus, congestive heart failure, myocardial infarction, and cerebrovascular ischemia. Hypertension is one the most common side effects of bevacizumab. The pathogenesis of bevacizumab induced hypertension is not thoroughly understood. It is thought that VEGF antagonism can cause a decrease in nitric-oxide production by inhibition of nitric oxide synthase. Suppression of nitric oxide leads to vasoconstriction and decreased sodium ion renal excretion leading to high blood pressure[31]. The occurrence of hypertension is dose-dependent. For example, the overall incidence of hypertension in patients receiving low dose (3, 5, or 7.5 mg/kg/dose) versus higher dose (10 or 15 mg/kg/dose) single agent bevacizumab is 2.7–32% and 17.6–36%, respectively[32]_ENREF_32. Interestingly, this bevacizumab toxicity may be useful as a clinical response parameter in patients. Among breast non-small cell lung, or colorectal cancer patients treated with bevacizumab, those with grade 2–4 hypertension had longer median survival compared to those without such elevation in blood pressure[33–35]. Scartozzi et al. showed that in metastatic colorectal patients treated with bevacizumab, the median PFS was 14.5 months for patients showing bevacizumab-related hypertension, while it was 3.1 months in those without hypertension ($p = 0.04$)[35]_ENREF_27. Although hypertension may be a good clinical measure of treatment response, bevacizumab-induced hypertension must be treated in order to avoid cardiovascular injury. Furthermore, permanent discontinuation of bevacizumab is recommended in patients who have hypertensive crisis[36].

Proteinuria in response to bevacizumab can occur as a result of interference with VEGF-dependent glomerular endothelial injury[37]. It can also occur due to thrombotic microangiopathy. The proteinuria is typically asymptomatic and detected incidentally. Monitoring by use of regular urine dipstick should be considered. Those with dipstick reading of 2 grams or more should undergo 24-hour urine total protein collection. Bevacizumab should be stopped if the patient is excreting at least 2 grams of protein in a 24-hour period. Treatment may resume if the patient recovers within 3 weeks and has no sign of nephrotic syndrome[36].

There is evidence of increased risk of arterial thromboembolic events (ATE) associated with bevacizumab therapy. In a pooled data analysis of 1745 patient with metastatic colorectal cancer, non-small-cell lung cancer (NSCLC) or breast cancer from five randomized trials, the addition of bevacizumab to chemotherapy was associated with increased risk of ATE (overall incidence was 3.8% with bevacizumab vs. 1.7% with chemotherapy). There was no difference with regard to venous thromboembolic events between the two groups[38].

One of the most worrisome complications of bevacizumab in the setting of gynecologic cancers is intestinal perforation. Two phase II trials of bevacizumab in the treatment of ovarian cancer were stopped early due to a high rate of intestinal perforation (11–15%)[20,39]. Other studies have shown smaller incidence of intestinal perforation of around 4–5% in ovarian cancer[40,41]. Perforations are thought to be more prevalent in those with acute diverticulitis, intra-abdominal abscess, gastrointestinal obstruction, tumor at perforation site, abdominal carcinomatosis, and previous abdominal or pelvic radiotherapy[42,43]. Therefore, careful patient selection to reduce risk should be considered by limiting or excluding bevacizumab treatment in patients with clinical symptoms of bowel obstruction, rectosigmoid involvement on exam physical exam, and bowel involvement on CT[44]. There is an increased risk of wound healing complications in patients receiving bevacizumab. It is recommended that there be a 30 day window between discontinuation of bevacizumab and major surgery to lower the risk of surgical wound or bowel anastomosis complications[36].

III. VEGF Trap (aflibercept)

VEGF Trap or aflibercept is a protein that contains the VEGF binding regions of VEGFR-1 and 2 fused to the Fc portion of human IgG1. It acts as a high affinity soluble VEGFR decoy receptor and therefore inhibits the activity of VEGF[45]. Aflibercept is entirely human protein sequence and has a higher affinity to VEGF than bevacizumab. Furthermore, it can bind to placental growth factor (PIGF). The interactions between PIGF and neuropilin-1 and neuropilin-2 provide additional regulation of tumor associated vasculature[46]. Two randomized phase 2 studies were done in patients with recurrent ovarian cancer[47,48]. Results of these studies showed that in heavily pretreated patients, single agent aflibercept could induce tumor response, delay progression, prevent reaccumulation of ascites, and prolong the time for the need for a paracentesis.

Coleman et al. recently reported a combined phase I/II trial of docetaxel plus aflibercept in patients with recurrent ovarian, primary peritoneal or fallopian tube cancer. In the phase II portion, patients were given aflibercept (6 mg/kg) and docetaxel (75 mg/m^2) every 3 weeks. Forty-six patients were enrolled in the phase II trial; among these, 33 patients had platinum resistant disease and 13 were platinum sensitive. Of the 46 patients enrolled in the phase II trial, 11 (24%) had a complete response, 14 had a partial response (30%), and 11(24%) had stable disease. Median PFS was 6.4 months, and median OS was 26.6 months[49]. Similar to bevacizumab, aflibercept treatment was also associated with fatigue, hypertension, and proteinuria.

IV. Small molecule tyrosine kinase inhibitors (SMTKI)

Tyrosine kinases are widely considered to be of therapeutic interest because of their role in growth factor signaling. SMTKIs inhibit VEFGRs directly rather than binding the VEGF ligand like bevacizumab.

a. Sorafenib—Sorafenib is an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, platelet derived growth factor receptor (PDGFR-β), and Raf-1 tyrosine kinase activity[50]. It is currently FDA approved for treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma[51,52]. Matei et al. evaluated sorafenib alone (400 mg orally

twice daily) in patients with recurrent ovarian cancer or primary peritoneal cancer. Twenty four percent of the patients had stable disease for 6 months with 3.4% of patients with a partial response. This modest response was further hindered by substantial toxicity. These included significant grade 3 or 4 toxicities such as rash, hand-foot syndrome, metabolic, GI, cardiovascular, and pulmonary toxicities. These investigators did not recommended continuation of monotherapy with sorafenib for recurrent ovarian and primary peritoneal cancer[53]. Sorafenib has been evaluated in a phase II trial in combination with gemcitabine in recurrent ovarian cancer, and found to have a rate of stable disease at 60% with a 4.7% partial response rate. The median time to progression was 5.4 months, and the median overall survival was 13.0 months[54]. To determine the efficacy and toxicity of sorafenib and topotecan combination in platinum resistant ovarian cancer, a combined analysis of phase I/II showed a partial responses rate of 16.7%, however, only one patient (7%) had a partial response in the phase II portion. The overall stable disease rate was 46.7%. The median PFS was 3.7 months (95% C.I., 3.0–5.5) and median OS was 14.0 months[55]. Currently, a phase II trial of sorafenib in combination with carboplatin/paclitaxel for first line treatment of ovarian cancer is underway[56].

Nimeri et al. evaluated patients with advanced uterine carcinoma and carcinosarcoma in phase II trial with sorafenib (400 mg orally twice daily). The results were modest, showing a partial response rate of 5% and 42.5% achieved stable disease. The 6-month PFS rate was 29%, and the median overall survival was 11.4 months[57].

b. Sunitinib—Sunitinib, also a multi-kinase inhibitor, blocks VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, and RET[58]. It is currently FDA approved for advanced renal cell carcinoma and gastrointestinal stromal tumors (GIST)[58]. A phase II trial of patients with recurrent epithelial ovarian and primary peritoneal cancer using monotherapy sunitinib resulted in a partial response rate of 3.3%. Fifty-three percent of patients had stable disease. Overall median progression-free survival was 4.1 months. Common adverse events included fatigue, gastrointestinal symptoms, hand-foot syndrome and hypertension[59].

A multi-center phase II study was performed to evaluate the activity of sunitinib in women with locally advanced or metastatic cervical cancer. Sunitinib 50 mg/day was administered in 6-week cycles (4 weeks on followed by 2 weeks off treatment). About 84% of patients had stable disease, and the median time to progression was 3.5 months. Fatigue, diarrhea, nausea, taste alteration, hypertension, mucositis and heartburn were the most common non-hematological adverse events. Hematological toxicity was mostly grade 1 or 2 although grade 3 lymphopenia was reported in seven patients and grade 4 in one. The biggest concern in this study was a high fistula rate of 26.3%, which included rectovaginal, enterocutaneous, and bladder-peritoneal. The authors did not recommend continuation of sunitinib monotherapy in this clinical setting for a phase III trial[60]. In phase II studies of patients with recurrent uterine leiomyosarcoma, sunitinib monotherapy resulted in a partial response rate 8.7%. The PFS rate at 6 months was 17.4%. The Median PFS was 1.5 months and the trial failed to meet the objective response[61].

Overall the side effect profile of sorafenib and sunitinib seem similar to bevacizumab. One notable additional side effect seen with these SMTKI's is hand-foot syndrome. Combination of anti-angiogenic agents has been shown to improve efficacy, however, it comes at an added cost of increased toxicity. In a study of combined sorafenib and bevacizumab, there was a 43% response rate in ovarian cancer patients. However, the combination therapy increased toxicity, necessitating the need for dose reduction of sorafenib[62].

C. Cediranib—Cediranib is a tyrosine kinase inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR-α, and c-kit. In a phase II study of cediranib monotherapy for recurrent ovarian

cancer, peritoneal, and fallopian tube cancer, there was a partial response rate of 17%, 13% stable disease, and no complete responses. Median PFS was 5.2 months, and 17% were free of progression at 6 months. Eleven patients (23%) were removed from study because of toxicities before two cycles. Grade 3 toxicities (> 20% of patients) included hypertension (46%), fatigue (24%), and diarrhea (13%). Grade 2 hypothyroidism occurred in 43% of patients. Grade 4 toxicities included CNS hemorrhage (n = 1), hypertriglyceridemia/hypercholesterolemia (n = 1), and dehydration/elevated creatinine (n = 1). No bowel perforations or fistulas occurred[63]. Currently, the International Collaboration for Ovarian Neoplasia 6 (ICON6) study is investigating the role of combination daily cediranib with carboplatin/paclitaxel or carboplatin/gemcitabine for six cycles followed by at least 18 months or until progression of daily cediranib for recurrent platinum sensitive ovarian cancer in a phase III trial[64].

D. Pazopanib—Pazopanib is an inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR-α, PDGFR-β, and c-kit. Pazopanib is FDA approved for the treatment of patients with advanced renal cell carcinoma. In a phase II trial of recurrent ovarian, fallopian tube, and primary peritoneal cancer, the CA-125 response rate was 31%. No patients with measureable disease had a partial or complete response. The progression-free survival at 6 months was 17%. The most common side effects were diarrhea, fatigue, and nausea. The most common adverse events leading to discontinuation of study drug were grade 3 ALT (8%) and AST (8%) elevation. Only 1 grade 4 toxicity (peripheral edema) was reported[65]. Currently, pazopanib is being investigated as maintenance therapy in a double blind, placebo controlled phase III clinical study in women who have achieved a partial or complete response to primary platinum based adjuvant chemotherapy in ovarian cancer (NCT00866697).

In advanced and recurrent cervical cancer, a phase II trial evaluated the combination of daily oral pazopanib and oral lapatinib (dual anti-EGFR and anti-HER2/neu tyrosine kinase inhibitor) *versus* daily oral pazopanib or daily oral lapatinib monotherapy. Randomization of 228 patients resulted in 78 patients (34%) being assigned to the lapatinib arm, 74 patients (33%) to the pazopanib arm, and 76 patients (33%) to the combination arm. However, combination therapy arm was discontinued due to higher rate of toxicity and discontinuation of drugs. Also, the futility boundary was crossed for combination therapy *versus* lapatinib monotherapy. PFS improved with pazopanib over lapatinib (median PFS, 17.1 weeks *versus* 18.1 weeks; HR, 0.66; 90% CI, 0.48 to 0.91; $p < .013$). Overall survival was 11.6 weeks longer in the pazopanib arm compared with the lapatinib arm (median OS, 50.7 weeks *versus* 39.1 weeks; HR, 0.67; 90% CI, 0.46 to 0.99; $p = .045$)[66].

E. BIBF-1120—BIBF-1120 is a potent inhibitor of VEGFR, as well as platelet-derived growth factor receptor and fibroblast growth factor receptor. In a randomized phase II-placebo controlled trial, patients who had just completed chemotherapy for relapsed ovarian cancer, with evidence of response, but at high risk of further early recurrence were treated with BIBF-1120. Study drug was taken continuously (28-day cycles) for nine cycles (36 weeks) or until disease progression or patient withdrawal. Thirty-six-week PFS rates were 16.3% and 5.0% in the BIBF 1120 and placebo groups, respectively (hazard ratio, 0.65; 95% CI, 0.42 to 1.02; $P = .06$). Toxicity was also well tolerated[67]. This has prompted a phase III trial (NCT01015118) where BIBF-1120 will be combined with carboplatin/paclitaxel as front-line chemotherapy in ovarian cancer. A summary of studies involving these small molecule tyrosine kinase inhibitors can be found in Table 3.

V. Epidermal growth factor receptor (EGFR) antibodies and tyrosine kinase inhibitors

Given the heterogeneity, the redundancy of aberrant pathways, and contribution of microenvironment to the survival, growth, and metastasis of solid tumors; it would be attractive to target multiple pathways that can contribute to angiogenesis[68]. Experimental evidence has shown that these pathways are functionally linked and has demonstrated a role for VEGF in the acquired resistance to anti-EGFR drugs when these re_ENREF_64ceptors are pharmacologically blocked[69]. Combined inhibition of EGFR and VEGF signaling interferes with a molecular feedback loop responsible for acquired resistance to anti-ERBB agents and promotes apoptosis while ablating tumor-induced angiogenesis[68,70].

Like VEGFR, EGFR is a tyrosine kinase receptor in the cell membrane. EGFR is in a family of four members: EGFR (Her1), ErbB2 (Her2), ErbB3 (Her3), and ErbB4 (Her4)[71]. The ligand, epidermal growth factor (EGF) and transforming growth factor α (TGF- α), binds to EGFR which then dimerizes the receptor and turns on the signaling cascade pathways to cause cellular proliferation, motility, invasion, apoptosis and angiogenesis. EGFR family members can also be activated by other signaling proteins independent of exogenous EGF ligands. These include other receptor tyrosine kinases such as insulin-like growth factor-1 receptor (IGF-1R)[72]. EGFR is overexpressed in 60% of ovarian cancer, 60–80% of endometrial cancers, 73% of cervical carcinomas, and 68% of vulvar malignancies. It has been shown to be associated with advanced cancer stage and poorer prognosis[73–77] _ENREF_61. Tumor associated endothelial cells can express EGFR and EGFR expression can induce VEGF expression in cancer cells[78]. *In vivo* studies of EGFR have shown increased sensitivity of tumors to chemotherapy and radiation therapy[79,80]. EGFR and ErbB2 generally induce cytostatic effects *in vitro* and rarely cause apoptosis[81,82] However, *in vivo* studies show anti-EGFR treatment leads to tumor regression[5], likely due to EFGR affecting host-tumor reactions leading to cell death. For the strategy to block EGFR activity, two types of inhibitors are currently used: (1) monoclonal antibodies, and (2) EGFR tyrosine kinase inhibitors.

a. Monoclonal antibodies—Cetuximab is a monoclonal antibody against EGFR and has shown improved survival in patients with head/neck and colorectal carcinoma[83,84]. In a phase II trial of relapsed platinum sensitive ovarian cancer who underwent combination therapy of cetuximab and carboplatin, 26 (92.9%) patients had EGFR-positive tumors and the response rate in this group included 9 patients that demonstrated an objective response (3 complete responses; 6 partial responses) and 8 had stable disease. The response rate did not meet criteria for opening second stage of accrual[85]. In a phase II trial of frontline treatment for advanced ovarian cancer, cetuximab was combined with carboplatin and paclitaxel. The median PFS was 14.4 months, and PFS at 18 months was 38.8%. This combination did not demonstrate prolongation of PFS when compared to historical data[86]. Finally, cetuximab monotherapy was evaluated in a phase II trial of recurrent/persistent ovarian cancer where minimal activity was found with this strategy. One of 25 patients achieved partial remission and 9 patients had stable disease. The median progression free survival was 2.1 months[87].

In cervical cancer, cetuximab therapy has had minimal to no effect in recent phase II clinical trials. In a phase II trial of advanced squamous cell or adenocarcinoma of the cervix, cetuximab was combined with cisplatin and topotecan chemotherapy. There were no complete responses, and the partial response and stable disease rate was 32%. This study was stopped due to excess toxicity from the treatments[88]. In another phase II study in advanced cervical cancer, cetuximab was combined with cisplatin. There was a 29.6% partial response rate and 4.8% complete response rate. Based on these results, phase III development was not recommended as there was no additional benefit with cetuximab therapy[89]. Using cetuximab as monotherapy was largely ineffective in advanced cervical

cancer. In a phase II trial of squamous and non-squamous cell recurrent cervical cancer, there were no partial or complete responses with cetuximab monotherapy[90].

Two other EGFR monoclonal antibodies studied in gynecologic cancers are matuzumab and trastuzumab. Matuzumab monotherapy was evaluated in a phase II trial of recurrent platinum refractory ovarian cancer or primary peritoneal cancer. In this study, there were no partial or complete responses. The stable disease rate was 16.2%, and median PFS was 1.9 months[91]. In 2008, matuzumab was discontinued due to poor efficacy in clinical trials[18]. Trastuzumab is an anti-Her2 antibody and has been studied in phase II trials in ovarian and endometrial cancers. Her2 gene amplification has been found to directly correlate with poor clinical outcomes in many malignancies including breast cancer[92]. Data regarding Her2 overexpression and its association with prognosis in ovarian cancer have been controversial. Early studies suggested that Her2 overexpression in ovarian cancer was a frequent event; however, subsequent studies using techniques for validation suggested that Her2 overexpression and amplification frequency in ovarian cancer is a much rarer event[93]. Furthermore, overexpression of Her2 has been associated with a worse prognosis in some studies, but not others[94,95]. In a phase II trial of persistent or refractory ovarian cancer, one patient had a complete response and 2 patients had a partial response. Furthermore, immunohistochemistry, revealed only 11.4% had Her2 positive cancers[96]. In a prospective cohort study of mucinous ovarian cancers, Her2 amplification is present in 18.2% of patients although not of prognostic significance[95]. In endometrial cancer, Her2 overexpression via immunohistochemistry is reported to be 44%, and 12% amplification via fluorescence in situ hybridization[97]. However, the results of trastuzumab in endometrial cancer have been disappointing. In a phase II trial of advanced or recurrent Her2 positive endometrial cancer, trastuzumab treatment resulted in no objective responses and the trial was stopped early due to poor accrual[98].

b. EGFR tyrosine kinase inhibitors (TKI)—EGFR TKIs act intracellularly by competing with ATP binding in the catalytic region of the kinase domain, thereby inhibiting enzymatic activity and its downstream effects[72]. While these tyrosine kinase inhibitors can target EGFR, many can also target mutant receptors like EGFRvIII that lack the critical extracellular regulatory region targeted by some of the antibodies[72].

Gefitinib (Iressa or ZD1839) has been evaluated in several phase II trials in gynecologic cancers. Posadas et al. evaluated 24 patients with platinum refractory ovarian cancer. No objective responses occurred. Approximately 37% of patients had stable disease for greater than 2 months[99]. A phase II trial of persistent or recurrent ovarian cancer with gefitinib showed a partial response of 3.7%. In a phase II trial of recurrent or metastatic cervical cancer, gefitinib monotherapy was evaluated. The majority (86.7%) of patient biopsies expressed high levels of EGFR (2+ or 3+ staining intensity). No patients had an objective response from treatment, and 20% of patients had stable disease. The most common drug-related side effects were diarrhea, acne, vomiting, and nausea[100].

Another EGFR TKI is erlotinib and has shown minimal activity in gynecologic cancers. In a phase II trial of recurrent or progressive ovarian cancer positive for EGFR, no complete responses and 6% partial response rate occurred with erlotinib therapy[36]. In a phase II trial of recurrent or refractory ovarian cancer, erlotinib and bevacizumab combination therapy was evaluated. The complete response rate and partial response rate with this combination was 7.7% each. Due to the lack of improvement over bevacizumab therapy alone and two incidents of fatal gastric perforations, the study was stopped[39]. In a phase II trial of recurrent cervical cancer patients treated with erlotinib, there were no objective responses with four (16%) achieving stable disease; only one patient had a PFS ≥ 6 months (4%). Erlotinib was well tolerated with the most common drug-related adverse events being gastrointestinal

toxicities, fatigue and rash[101]. A summary of clinical trials in gynecologic cancers with EGFR inhibition can found in Table 4.

In summary, clinical trials using anti-EGFR therapy have shown limited activity in gynecologic cancers. Given the high expression of EGFR in gynecologic malignancies, future studies using it in combination with cytotoxic therapy may be beneficial. Furthermore, determining reliable biomarkers to assess patient responsiveness can help monitor EGFR dependent malignancies.

VI. Alternative targets and strategies

Although the above studies have revealed an arsenal of molecular drugs that can target angiogenesis, tumor progression eventually occurs and no difference in overall survival has been accomplished with current clinical trials in anti-angiogenesis drugs. Therefore, the need for different strategies and targets for angiogenesis are desperately needed. One strategy that may hold promise to fight tumor progression includes agents that target components of the tumor microenvironment. For example, pericytes are cells surrounding endothelial cells and are required for microvascular stability and function. On the basis of the known role of platelet-derived growth factor (PDGF)-BB/PDGF receptor (PDGFR) β in pericyte regulation, highly specific inhibitors against PDGF-B were tested in ovarian cancer models with the agent AX102. Combination of bevacizumab plus AX102 was more effective than bevacizumab alone, and resulted in 76–88% inhibition of tumor growth[102]. Therefore, dual targeting of endothelial cells and pericytes holds potential as an anti-vascular therapeutic approach in ovarian carcinoma.

Other targets identified in the tumor vasculature include EZH2 and focal adhesion kinase (FAK). EZH2 has been identified as a key regulator of tumor angiogenesis. EZH2 silencing in the tumor-associated endothelial cells using siRNA resulted in significant growth inhibition in an orthotopic ovarian cancer model. EZH2 silencing in tumor endothelial cells also resulted in decreased angiogenesis[103]. FAK plays a critical role in ovarian cancer cell survival and in various steps in the metastatic cascade. Treatment with FAK siRNA-DOPC plus docetaxel resulted in decreased microvessel density, decreased expression of VEGF and matrix metalloproteinase-9, and increased apoptosis of tumor-associated endothelial cells and tumor cells[104]. As research into the field of angiogenesis continues to rapidly advance, more molecular targets will be identified and new anti-angiogenesis targets will be available to combat tumor growth.

AMG 386 is an investigational, angiopoietin antagonist peptide-Fc fusion protein that selectively binds Ang1 and Ang2, prevents their interaction with Tie2 and inhibits tumor endothelial cell proliferation and tumor growth[105]. Results from a randomized, double blind, placebo-controlled Phase II study to evaluate the safety and tolerability of AMG 386 (3 or 10 mg/kg i.v., weekly) in combination with paclitaxel (80 mg/m^2 i.v., weekly (3 weeks on/1 week off)) in patients with advanced recurrent epithelial ovarian, primary peritoneal or fallopian tube cancer were recently presented at the ASCO 2010 annual meeting. The addition of AMG 386 to paclitaxel demonstrated dose–responsive improvements in PFS together with a manageable safety profile distinct from that of VEGF inhibition[106]. Cabozantinib (XL-184) is an oral, potent inhibitor of MET and VEGFR2. MET over-expression has been observed in variety of solid tumors including advanced ovarian cancer[107]. MET drives more invasive and aggressive behavior of tumor cells, resulting in metastasis[107,108] ENREF 108. MET is further upregulated by the hypoxic conditions created by VEGF pathway inhibitors, which leads to promotion of metastasis[107,108]. Results from a phase II trial of cabozantinib (100 mg/daily orally over 12 weeks) with advanced progressive epithelial ovarian cancer showed a high clinical response (overall 24%)[109]. Due to these promising results, AMG 386 and cabozantinib are entering phase III trials.

Conclusion

Anti-angiogenic drugs have shown promise for treatment of gynecological cancers in phase II and phase III trials. A number of targets in angiogenesis pathways have been identified and drugs targeting these areas have been and are under evaluation. Currently, bevacizumab especially in ovarian cancer seems to hold the most promising results. Whether other agents such as aflibercept or small molecule tyrosine kinase inhibitors will have similar or better success requires additional work.

Unfortunately, the clinical responses to anti-angiogenesis drugs have been transitory, followed by progressive disease. This is likely due to inherent or acquired resistance to such drugs[110]. Therefore, an important area of ongoing research involves identification of reliable predictive markers and understanding the mechanisms of resistance to anti-angiogenesis agents[108,111,112]. We expect that a deeper understanding of such biology will result in better therapeutic approaches that can improve the outcome of patients suffering from gynecologic or other malignancies.

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- Recent insights at the molecular and cellular levels are paving the way for a more directed approach to target mechanisms driving tumorigenesis, such as angiogenesis.
- Anti-angiogenic drugs have shown promise for treatment of gynecological cancers in phase II and phase III trials.
- Clinical responses to anti-angiogenesis drugs have been transitory, followed by progressive disease likely due to acquired resistance to such drugs.

Table 1

Phase II trials of bevacizumab in gynecologic cancers

Study	Therapy	# of patients	Selection Criteria	SD (%)	PR (%)	CR (%)	Median PFS (months) / Median OS (months)
Monk et al.[30]	Bev	46	Recur CxCa	N/A	10.9	0	3.40/7.29
Burger et al.[19]	Bev	62	Recur OvCa	51.6	17.7	3.2	4.7/16.9
Cannistra et al.[20]	Bev	44	Ovaca	61.4	15.9	0	4.4/10.7
Aghajanian et al.[29]	Bev	52	Recur EndoCa	N/A	1.9	11.5	4.2/10.6
Micha et al.[24]	CPB/PTX+ bev	20	OvaCa	5	50	30	N/A / N/A
Penson et al.[22]	CPB/PTX + bev	62	OvCa	21	55	21	29.8/ N/A
Garcia et al.[21]	Cyclo + bev	70	Recur OvCa	63	24	0	7.2/16.9
Konner et al.[25]	IV/IP PTX + IP CDDP + bev	41	OvCa	N/A	N/A	N/A	28.6/ N/A

Abbreviations: bev - bevacizumab; CPB - carboplatin PTX - paclitaxel, CDDP- cisplatin, cyclo-cyclophosphamide, OvaCa - epithelial ovarian cancer, CxCa - cervical cancer, EndoCa -endometrial cancer, Recur - recurrent disease, IV – intravenous, IP - intraperitoneal

Table 2

Phase III trials of bevacizumab in gynecologic cancers

Trial	Site of Disease	Drug Regimens	Date
GOG 218	OvaCa	CPB + PTX vs CBP +PTX + bev vs CBP + PTX + bev then maintenance bev	Sept 2005 to Oct 2008
ICON-7	OvaCa	CBP + PTX with and without bev then maintenance bev	Opened Apr 2006
GOG 252	OvaCa	IV vs IP platinum + PTX with IV bev then maintenance bev	Opened Aug 2009
GOG 262	OvaCa	Dose dense PTX with bev	Awaiting NCI clearance
GOG 213	Platinum-sensitive recur OvaCa	CBP + PTX with and without bev then maintenance bev	Opened Dec 2007
OCEANS	Platinum-sensitive recur OvaCa	CBP + GCB with and without bev	2007–2011
AURELIA	Platinum-resistant OvaCa	PTX + TPT + LD with and without bev	Opened Oct 2009
GCIG	Stage II–IV or recur MucOvaCa	CBP + PTX with and without bev then maintenance bev vs OX + CAP with and without bev then maintenance bev	Opened Jan 2010
GOG 240	Stage IVB, recur CxCa	CDDP + PTX with and without bev vs TPT/PTX with and without bev	Opened Apr 2009

Abbreviations: CBP- carboplatin; PTX-paclitaxel; bev- bevacizumab; GCB- gemcitabine; TPT- topotecan; LD- liposomal doxorubicin; IV- intravenous; IP- intraperitoneal; CDDP- cisplatin; OX- oxiplatin; CAP- capecitabine; OvaCa - epithelial ovarian cancer, CxCa - cervical cancer, EndoCa -endometrial cancer, MucOvaCa – mucinous ovarian cancer, Recur - recurrent disease

Table 3

Clinical trials of SMTKIs

Study	Therapy	# of patients	Selection Criteria	SD (%)	PR (%)	CR (%)	Median PFS (months)/ Median OS (months)
Matei et al.[53]	Sora	71	Recur OvaCa	33.9	3.4	0	2.1/ 16.33
Nimeri et al.[57]	Sora	56	Recur UC or UCS	42.5† 25‡	5† 0‡	0† 0‡	3.2/ 11.4† 1.8/ 5.0‡
Welch et al.[54]	Sora + GCB	33	Recur OvaCa	23.3	4.7	0	5.4/13.0
Rammsubbaiah et al.**55**	Sora + TPT	30	Recur OvaCa	46.7	16.7	0	3.7/14.0
Mackay et al.[60]	Suni	19	LACC or MCC	84	0	0	3.5/ N/A
Biagi et al.[59]	Suni	30	Recur OvaCa	36.7	3.3	0	4.1/ N/A
Matulonis et al.[63]	Cedi	46	Recur OvaCa	13	17	0	5.2/ N/A
Friedlander et al.[65]	Pazo	17	Recur OvaCa	18	18	0	N/A N/A
Monk et al.[66]	Pazo vs.Lap	Pazo = 74 Lap = 78	LACC and Recur cervix	43 44	8 4	1 1	18.1/ 50.7 17.1/ 39.1

Abbreviations: Sora – sorafenib, Suni – sunitinib, Cedi – cediranib, Pazo – pazopanib, Lap – lapatinib, GCB – gemcitabine, Recur – recurrent disease, OvaCa – epithelial ovarian cancer, UC – uterine carcinoma, UCS – uterine carcinosarcoma, LACC – locally advanced cervical cancer, MCC – metastatic cervical cancer, N/A – not available

† = uterine carcinoma;

‡ = uterine carcinosarcoma;

Table 4

Phase II clinical Trials of EGFR inhibitors in gynecologic cancers

Study	Therapy	# of patients	Selection Criteria	SD (%)	PR (%)	CR (%)	Median PFS/ Median OS	Comments
Schilder et al.[87] ENREF 80	Cetux	25	Recur OvaCa	36	4	0	1.8/13	
Santin et al.[90]	Cetux.	35	Recur CxCa	31.4	0	0	1.97/6.7	
Secord et al.[85]	Cetux + CBP	26	Recur, platinum-sensitive OvaCa	11.5	23	11.5	9.4/N/A	32% acniform rash, 18% grade 3–4 hypersensitivity reaction
Konner et al.[86]	Cetux + PTX + CBP	40	OvaCa	N/A	N/A	N/A	14.4/NA	Did not demonstrate prolongation of PFS when compared to historical data.
Kurtz et al.[88]	CSP + TPT + cetux	19	Advance CxCa	32	32	0	5.7/7.2	Study stopped due to excess toxicity (myelosuppression)
Farley et al.[89]	CSP+ cetux	27	Advanced or recur CxCa	N/A	29.6	3.7	3.91/8.77	No additional benefit compared to cisplatin alone
Seiden et al.[91]	Matzu.	37	Recur platinum refractory OvaCa	16.2	0	0	1.9/10.3	
Fleming et al.[98]	Matzu.	33	Advanced or recur EndoCa	36.3	0	0	1.81–1.84/6.8–7.85	
Posadas et al.[99]	Gefi.	24	Platinum-refractory OvCa	37	0	0	N/A / N/A	
Schilder et al.[87]	Gefi.	27	Recur OvaCa	36	0	0	1.87/13	
Goncalves et al.[100]	Gefi.	28	Recur or met CxCa	20	0	0	1.22 / 3.51	
Gordon et al.[113]	Erlo.	34	Recur OvaCa	44	6	0	4.58/8.00	
Nimeri al.[39]	Erlo. + bev	13	Recur OvaCa	54	7.7	7.7	4.1/11.0	
Schilder et al.[101] ENREF 101	Erlo.	28	Recur CxCa	16	0	0	1.87/ 4.96	

Abbreviations: Cetux - cetuximab, Matzu – matuzumab, , Gefi- gefitinib, Erlo – Erlotinib, Recur – recurrent disease, OvaCa – epithelial ovarian cancer, CxCa- cervical cancer, N/A – not available CSP- cisplatin, CBP- carboplatin, PTX-paclitaxel