Antiangiogenic agents show promise in extending survival in women with ovarian cancer, but continued study is needed to minimize the side effects of these agents.

**Antiangiogenic Therapies in Epithelial Ovarian Cancer**

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**Background:** Angiogenesis is a critical component of tumor development and proliferation, and increased angiogenesis has been associated with a worse clinical outcome in a number of solid tumors, including ovarian cancer. Therefore, agents that target the angiogenic process are of considerable interest in the treatment of ovarian cancer.

**Methods:** Studies evaluating the efficacy of antiangiogenic agents in ovarian cancer are reported. Antiangiogenic agents examined include vascular endothelial growth factor (VEGF) pathway inhibitors, including monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and a soluble receptor decoy, as well as inhibitors of other angiogenic factors and vascular disrupting agents.

**Results:** The VEGF inhibitor bevacizumab has been shown to have efficacy in ovarian cancer in phase II trials and a progression-free survival advantage in one phase III trial. TKIs block the VEGF receptors and secondary angiogenic pathways and have shown activity in phase I and II trials. Alternative angiogenesis inhibitors include EphA2 inhibitors and a selective angiopoietin 1/2-neutralizing peptibody. Another strategy is to destroy the existing tumor vasculature, and a number of vascular disrupting agents are being studied in preclinical and phase I trials. Antiangiogenic agents have a unique side effect profile, likely due to inhibition of normal physiologic angiogenesis.

**Conclusions:** Phase II and early phase III trials have demonstrated that antiangiogenic therapies have significant activity in ovarian cancer. The results of phase III trials in the front-line and recurrent settings will determine the extent of clinical benefit of antiangiogenic therapies in combination with chemotherapy. Antiangiogenic agents have a distinct side effect profile, and further studies are necessary to evaluate how to minimize the incidence of these events and to identify women most likely to benefit from these therapies.

**Introduction**

In 1971, Folkman proposed that angiogenesis permits rapid expansion of a tumor population and growth beyond a diameter of 1 mm to 2 mm, which is the limit of simple diffusion of nutrients and oxygen. Additionally, he proposed that neovascularization facilitates metastasis, as the leaky basement membrane of immature capillaries allows malignant cells to enter the circulatory system.
is now widely recognized that angiogenesis is a critical component of tumor development and proliferation. Furthermore, increased angiogenesis as manifested by increased tumor microvessel density (MVD) has been associated with a worse clinical outcome in a variety of solid tumors, including ovarian cancers.

**Angiogenesis in Ovarian Cancer**

Epithelial ovarian cancer spreads by local extension and seeding of the peritoneal cavity and invasion through the lymphatic channels, with less common spread by hematogenous routes. However, several authors have reported that MVD has prognostic significance for survival in ovarian cancer.\(^2\)\(^\text{-}\)\(^23\) Specifically, in one study, women whose tumors had high MVD, as determined by immunohistochemistry for von Willebrand factor (vWF) and CD31, had a median survival of 2.7 years compared with 7.9 years in those with low MVD.\(^3\) Overall, the published data indicate that a high degree of tumor angiogenesis is predictive of poor clinical outcome.\(^3\)\(^,\)\(^5\)\(^,\)\(^7\)\(^-\)\(^21\),\(^24\),\(^25\) with only one study finding no association between MVD and survival and three studies reporting that higher MVD is an independent prognostic factor for improved survival in women with advanced ovarian cancer.\(^21\),\(^23\)

While a variety of markers are used to measure MVD — vWF, CD31, and CD34 — these markers are non-specific to endothelial cells and thus their clinical utility may be limited. However, CD105 (endoglin) is expressed almost exclusively on endothelial cells in solid tumors undergoing neoangiogenesis, and it modulates angiogenesis by regulating cellular proliferation, differentiation, and migration. Three ovarian cancer studies investigated CD105 MVD and found it to be an independent predictor of poor survival in two reports.\(^2\),\(^20\) Taskiran et al\(^20\) reported that women whose tumors had the highest CD105 MVD (43 vessels/high power field [HPF]) had a 5-year survival rate of 34% compared with 82% for those whose tumors had the lowest CD105 MVD (12 vessels/HPF; \(P = .01\)). While Rubatt et al\(^25\) found that CD105 was an independent prognostic factor for worse progression-free survival (PFS) after adjusting for clinical covariates. In contrast, Henriksen et al\(^26\) demonstrated longer overall survival (OS) in tumor specimens with positive CD105 expression in tumor-associated blood vessels when compared with specimens with negative CD105 expression in tumor-associated blood vessels. Although the data are conflicting, most reports indicated that a higher degree of angiogenesis, as manifested by a greater MVD using a variety of MVD markers, was a prognostic indicator of worse clinical outcome in women with ovarian cancer.

**The Role of Vascular Endothelial Growth Factors in Ovarian Cancer**

Ovarian tumors, like many malignancies, overexpress pro-angiogenic factors including vascular endothelial growth factors (VEGFs), fibroblast growth factors, angiopoietin, platelet-derived growth factors (PDGFs), and pro-angiogenic cytokines such as tumor necrosis factor alpha and interleukins 6 and 8.\(^27\) Of these, members of the VEGF family are the most potent pro-angiogenic factors. VEGF activation promotes endothelial cell proliferation and migration for the formation of new blood vessels and increases permeability of existing blood vessels to allow for the leakage of multiple plasma proteins, including those playing a role in angiogenesis.\(^28\) Also, VEGF inhibits apoptosis of the newly formed hyperpermeable blood vessels.\(^29\) By this mechanism, VEGF also plays a key role in the formation of ascites and pleural effusions.

Additionally, VEGF plays a significant part in the normal function of the ovary, with serum VEGF levels rising and falling in a predictable pattern during the ovulatory cycle.\(^30\) Therefore, it is not surprising that VEGF plays a role in the biology of ovarian cancer. Preclinical studies have demonstrated that animals inoculated with VEGF/green fluorescent protein (GFP)-positive ID8 in vitro transformed C57BL6 murine ovarian epithelial cells developed diffuse peritoneal carcinomatosis and ascites in a pattern similar to metastatic ovarian cancer.\(^31\)

VEGF expression is higher in ovarian cancers than in normal ovarian tissue or benign ovarian neoplasms, and increasing VEGF expression in either cytosolic fractions derived from ovarian cancers or serum VEGF levels in preoperative serum was associated with advanced stage and worse survival.\(^32\),\(^34\) Even for patients with early-stage disease, cancers with elevated VEGF expression and preoperative serum VEGF levels were associated with a higher risk of disease recurrence and worse overall and disease-free survival.\(^35\),\(^36\) In a study by Paley et al.\(^35\) multivariate analysis showed that increased VEGF transcript expression was the strongest prognostic factor for a worse prognosis compared with other high-risk features such as stage IC-IIIC disease, tumor rupture, poorly differentiated histology, malignant peritoneal cytology, and postoperative adjuvant therapy. For women with advanced-stage cancer, high serum VEGF levels have been associated with a more aggressive disease phenotype and were an independent risk factor for ascites, increased metastases, suboptimal tumor debulking, and decreased survival.\(^34\),\(^36\) The strong association between tumor angiogenesis, VEGF expression and serum levels, and clinical outcome in ovarian cancer makes the VEGF pathway an attractive therapeutic target.

**VEGF Targeting Therapies in Ovarian Cancer**

There are two primary strategies to inhibit the VEGF pathway: (1) inhibition of the VEGF ligand with antibodies or soluble receptors and (2) inhibition of the VEGF receptor (VEGFR) with tyrosine kinase inhibitors (TKIs), or receptor antibodies. Therapies that specifically target the VEGF ligand or its receptors, VEGFR-1 and VEGFR-2, inhibit only the VEGF pathway and therefore inhibit angiogenesis without disrupting "off-target" pathways. In
contrast, TKIs that target the receptor have a wider range of inhibitor effects and may disrupt other secondary pathways that are mediated through receptor kinases. Of the VEGF-targeting therapies, the most experience has been with a monoclonal antibody that binds the VEGF ligand, known as bevacizumab (Avastin).

**Bevacizumab**

Bevacizumab is a 149-kDa recombinant humanized monoclonal IgG1 anti-VEGF antibody. It has been FDA-approved for the treatment of metastatic colorectal, breast, and non–small cell lung cancer and shows promise in the treatment of ovarian cancer.

The efficacy and tolerability of single-agent bevacizumab for the treatment of recurrent epithelial ovarian, peritoneal or fallopian tube cancer have been evaluated in two pivotal phase II trials (Table 1). The overall response rate in these trials was 16% to 21% with an additional 20% to 60% of patients achieving stable disease. OS in these studies was 10 to 17 months, with a PFS of approximately 4.5 months. However, 40% of patients enrolled on the Gynecologic Oncology Group study (GOG 170D) achieved a PFS of greater than 6 months compared with 28% in AVF 2949g conducted by Cannistra et al. Although GOG 170D showed no difference in response to bevacizumab based on platinum resistance, only 58% of patients in the GOG study were considered platinum-resistant, while AVF 2949g was limited to patients with platinum-resistant disease who had also developed progressive disease after treatment with either topotecan or liposomal doxorubicin. Additionally, patients enrolled in the GOG study could not have been treated with more than two previous regimens, while 47.7% of patients on AVF 2949g had been treated with three previous regimens. Due to a higher-than-expected rate of serious adverse events, including 5 gastrointestinal (GI) perforations (11%) accounting for 1 death, the AVF 2949g study was closed to enrollment. Additional adverse events on that study included 4 arterial thromboembolic events in 3 patients, with 1 death resulting from cerebral ischemia and myocardial infarction. Grade 3 hypertension developed in almost 10% of patients in both studies, but an episode of hypertensive encephalopathy contributed to the third treatment-related death in the AVF 2949g study. In contrast, while there were 2 deep venous thromboses and 1 pulmonary embolus observed in the GOG trial, there were no GI perforations, arterial thromboembolic events, or treatment-related deaths.

The number of GI perforations in the AVF 2949g study was higher than previously reported in trials evaluating bevacizumab in other tumor types. Combined data from multiple small studies have demonstrated that the overall risk of GI perforations is higher in bevacizumab-treated ovarian cancer patients (5.4%) than in bevacizumab-treated colorectal cancer patients (2.4%). Several mechanisms have been proposed, including one theory that ovarian cancer cells invade the bowel serosa and that subsequent tumor necrosis after treatment predisposes to bowel perforation. Another theory is that carcinomatosis, a condition frequently seen in ovarian cancer, increases pressure on weakened areas of the bowel, predisposing to microperforations that heal poorly during bevacizumab treatment. A review of events in the AVF 2949g trial revealed that all five of the GI perforations occurred in pa-

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**Table 1. — Summary of Completed Ovarian Cancer Trials With Bevacizumab as a Single Agent or in Combination With Cytotoxic Agents**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>RR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>OS</th>
<th>PFS</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 170D</td>
<td>Recurrent, Bevacizumab 15 mg/kg</td>
<td>21%</td>
<td>3%</td>
<td>18%</td>
<td>63%</td>
<td>16.9 mos</td>
<td>4.7 mos</td>
<td>Grade 3/4 GI events 6.5% (no GIP), Grade 3 hypertension 9.7%, Grade 4 proteinuria (1)</td>
</tr>
<tr>
<td>AVF 2949g</td>
<td>Recurrent, Bevacizumab 15 mg/kg</td>
<td>15.9%</td>
<td></td>
<td></td>
<td>SD</td>
<td>61.4%</td>
<td>10.7 mos</td>
<td>Grade 3/4 GI events 11%, ATE 6.8%, Grade 3 hypertension 9.1%</td>
</tr>
<tr>
<td>NCI 5789</td>
<td>Recurrent, Bevacizumab 10 mg/kg + cyclophosphamide po 50 mg</td>
<td>24%</td>
<td></td>
<td></td>
<td>SD</td>
<td>63%</td>
<td>16.9 mos</td>
<td>PFS 7.2 mos</td>
</tr>
<tr>
<td>TEACO</td>
<td>Primary, Bevacizumab 15 mg/kg + doxorubicin 75 mg/m² + oxaliplatin 85 mg/m²</td>
<td>75%</td>
<td>34.6%</td>
<td>40%</td>
<td>SD</td>
<td>14%</td>
<td>PFS 69.1 wks</td>
<td>Grade 3/4 neutropenia 39%, Grade 3/4 hypertension 8.2%, Grade 3/4 fatigue 7.3%, GIP 1.1%</td>
</tr>
<tr>
<td>Micha et al</td>
<td>Primary, Bevacizumab 15 mg/kg + paclitaxel 175 mg/m² + carboplatin AUC 5</td>
<td>80%</td>
<td>30%</td>
<td>50%</td>
<td></td>
<td></td>
<td></td>
<td>Grade 3/4 neutropenia 48.3%, Grade 3 hypertension 11%, DVT 11%, No GIP</td>
</tr>
</tbody>
</table>

**Notes:** RR = response rate, CR = complete response, PR = partial response, SD = stable disease, OS = median overall survival, PFS = median progression-free survival, GIP = gastrointestinal perforation, ATE = arterial thrombotic event, DVT = deep vein thrombosis.
tients who had received three prior regimens (there were no GI perforations in the 23 patients who had received only two previous regimens), and all had radiologic evidence of bowel involvement at the time of enrollment. Cannistra et al hypothesized that GI perforations may occur at higher rates in heavily pretreated patients with platinum-resistant disease. The incidence of GI perforations has been evaluated in several retrospective multi-institutional studies, including one report published by Wright et al that included 62 patients treated with bevacizumab either as a single agent or in combination with chemotherapy. Analysis of the four GI perforations (6.5%) revealed no statistically significant associations between GI perforations and patient or treatment characteristics. However, all 4 patients had large intra-abdominal tumor volumes and were heavily pretreated, with a median number of prior treatments of 8.5 compared with 5 for the remainder of the cohort. Interestingly, all 4 patients were responding to bevacizumab, as evidenced by decreasing CA-125 levels. In another retrospective cohort study comparing 68 patients treated with bevacizumab with 195 patients treated with cytotoxic chemotherapy without bevacizumab, GI perforation rates were similar in both groups (7.2% in the bevacizumab group and 6.5% in the chemotherapy group). Interestingly, the relative risk of GI perforation in the bevacizumab cohort was not increased (1.09; 95% confidence interval [CI], 0.40–2.96) despite a higher mean number of previous chemotherapy regimens in the bevacizumab cohort (5 vs 3). Perforations occurred more commonly in the small bowel in the bevacizumab cohort (80%), while colonic perforations predominated in the chemotherapy cohort (69%), suggesting a different underlying anatomical or biological etiology of the two types of GI perforations. The authors proposed that impaired healing of microperforations during antiangiogenesis treatment led to perforation of the small bowel in the bevacizumab group, while unresolved colonic obstructions led to perforations in the chemotherapy group. The results of this study indicated that women with recurrent ovarian cancer have a 7% risk of GI perforation and that bevacizumab does not significantly increase that risk compared to standard relapse therapy. However, careful patient selection is warranted, and bevacizumab should be administered with caution or avoided in patients with heavily pretreated disease, symptoms of bowel obstruction, or radiologic evidence of transmural bowel involvement.

Studies in other tumor types have shown limited activity of single-agent bevacizumab but significantly increased activity in combination with cytotoxics. Several hypothetical benefits of combination therapy include (1) independent effects of both agents, (2) improved delivery of chemotherapy to the tumor after treatment with bevacizumab and normalization of the tumor vasculature, (3) sensitization of endothelial cells to chemotherapy, and (4) reduced production of both tumor and endothelial-derived growth factors that promote tumor growth and neovasculature development. Retrospective studies of bevacizumab in combination with various cytotoxic agents for the treatment of recurrent ovarian cancer have demonstrated an acceptable toxicity profile, with 30% to 40% response rates. Results from a phase II trial revealed significant activity of bevacizumab in combination with low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer and demonstrated a response rate of 24% (NCI 5789). Of note, the best response was seen in patients who had clear cell cancers (50% vs 30% in serous, 5% in adenocarcinoma not oth-

Fig 1. — GOG 218 schema. All chemotherapy cycles are administered every 21 days.
Randomized

Paclitaxel 175 mg/m²
+ carboplatin AUC 6
+ bevacizumab 7.5 mg/kg × 6 cycles

Bevacizumab 7.5 mg/kg
× 12 cycles

Primary endpoint: progression-free survival
Secondary endpoint: overall survival

Fig 2 — ICON7 schema. All chemotherapy cycles are administered every 21 days.

erwise specified; \( P = .049 \). The median PFS was 7.2 months, and median OS was 16.9 months. Hematologic toxicities and hypertension accounted for the majority of the grade 3 toxicities. Three patients developed GI perforations, accounting for 1 treatment-related death, and 2 additional treatment-related deaths were caused by pulmonary hypertension. Overall, the combination of bevacizumab and metronomic cyclophosphamide was well tolerated with significant clinical benefit.

Bevacizumab in combination with cytotoxic agents has also been studied in the first-line setting for advanced epithelial ovarian cancer.\(^4^5,4^6\) The TEACO study (Tax-otere, Eloxatin, Avastin in Cancer of the Ovary) is a phase II study of bevacizumab in combination with oxaliplatin and docetaxel for women with stage IB–IV epithelial ovarian, peritoneal, or fallopian tube cancer.\(^4^4\)

Another phase II study, conducted by Micha et al.,\(^4^6\) evaluated bevacizumab in combination with carboplatin and paclitaxel. Overall response rates in the primary setting were 75% to 80%, with preliminary analysis in the TEACO study showing a 1-year probability rate of PFS of 70.1%. Myelosuppression was the major toxicity, with grade 3/4 neutropenia occurring in 39% of the participants in the TEACO study and approximately 50% in the study by Micha et al.\(^4^6\)

The incidence of febrile neutropenia was negligible in both trials. Similar to other studies, approximately 10% of patients developed hypertension, and 1 GI perforation was reported.

Bevacizumab in combination with carboplatin and paclitaxel as primary treatment is being evaluated in two phase III trials, GOG 218 (Fig 1) and the International Collaborative Ovarian Neoplasm trial (ICON7) (Fig 2). GOG 218 completed enrollment in June 2009 and included only women with advanced-stage epithelial ovarian, peritoneal, or fallopian tube carcinomas. In contrast, ICON7, which completed enrollment in February 2009, allowed women with stage IIB–IV disease, as well as those with early-stage high-risk carcinomas (stage I–IIA, grade 3, or clear cell histology) to enroll. After a median follow-up of 17.4 months, preliminary results of 1,873 patients enrolled on GOG 218 showed a 3.8-month improvement in PFS in the maintenance bevacizumab arm (14.1 months) compared to the standard chemotherapy arm (10.3 months), with a hazard of first progression of
The GOG has recently activated a study of adjuvant bevacizumab in combination with intravenous (IV) and intraperitoneal (IP) paclitaxel and platinum-based chemotherapy (Fig 3). The goals of the GOG 252 study are several-fold, including a comparison of IP chemotherapy with either carboplatin or cisplatin to IV therapy (dose-dense weekly IV paclitaxel, IV carboplatin, and IV bevacizumab) and a determination of whether a regimen of IP cisplatin and IV paclitaxel on day 1 of therapy plus IP paclitaxel on day 8 improves PFS compared to IP carboplatin and dose-dense weekly IV paclitaxel. All of the participants receive bevacizumab in the front-line setting as well as 16 cycles of bevacizumab consolidation therapy. Accrual for this study is ongoing.

Second-line studies of bevacizumab in combination with cytotoxic agents are also in progress. GOG 213 is a phase III study evaluating both the roles of secondary debulking and bevacizumab in combination with carboplatin and paclitaxel in the treatment of recurrent, platinum-sensitive epithelial ovarian, peritoneal, or fallopian tube cancer (Fig 4). The Ovarian Cancer Evaluation of Avastin and Safety-AVF4095g trial (OCEANS) is a phase III study designed to compare gemcitabine and carboplatin with or without bevacizumab in patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer (Fig 5). After 6 to 8 cycles of combination therapy, patients continue with bevacizumab or placebo consolidation for up to 51 weeks.

Interestingly, there are conflicting data regarding response to bevacizumab and VEGF levels. In the NCI 5789 study, VEGF levels were assessed both at baseline and during treatment. Median VEGF levels decreased between the first and eighth treatments but varied widely, and there did not appear to be an association between VEGF levels and disease response. Han et al evaluated VEGF and CD31 MVD counts in pretreatment tumor biopsies as well as in plasma and serum VEGF levels obtained from women.
enrolled on GOG 170D. Although a high CD31 MVD count was significantly associated with increased risk for death, there were no significant changes in CD31 MVD, p53, or VEGF tissue levels during the course of therapy. Interestingly, serum but not plasma VEGF levels decreased after bevacizumab treatment. However, levels were not associated with PFS or OS. In contrast, Smerdel et al\textsuperscript{[49]} reported that response to bevacizumab was significantly correlated to baseline serum VEGF levels in 38 patients treated with single-agent bevacizumab. Specifically, patients who had a serum VEGF level of $< 540$ pg/mL had a higher response rate of 60\% compared with 0\% for patients who had a baseline serum VEGF level of $> 540$ pg/mL. Additionally, patients with low baseline serum VEGF levels had significantly better PFS ($P = \text{.047}$) and OS ($P = .01$) compared to those with high VEGF levels. Further evaluation of VEGF levels as well as other biomarkers should be conducted in prospective trials to identify women most likely to benefit from antiangiogenic therapy.

\textbf{VEGF Trap}

VEGF Trap (afilibercept, AVE0005) is a unique fusion protein that combines the Fc portion of human IgG1 with the principal extracellular ligand-binding domains of VEGFR-1 and VEGFR-2. Afilibercept acts as a high-affinity soluble VEGFR decoy, inhibiting VEGF-mediated events. Unlike bevacizumab, afilibercept is composed entirely of human protein sequences, resulting in a higher binding affinity for VEGF and the ability to bind to other VEGF family members, including placental growth factor (PIGF).\textsuperscript{50} Preclinical in vivo studies have demonstrated that treatment with afilibercept decreased tumor burden by 56\% compared to controls and resulted in complete resolution of measurable ascites. Additionally, treatment with afilibercept decreased the density and tortuosity of the vasculature surrounding the tumors.\textsuperscript{51} Tew et al\textsuperscript{[52]} presented the results of a multicenter phase II study of afilibercept in 215 women with recurrent ovarian cancer. Eligibility criteria included a history of 3 to 4 previous treatment regimens and documented platinum-resistance as well as topotecan-and/or liposomal doxorubicin resistance. Participants were randomized to afilibercept at a dose of either 2 mg/kg/IV or 4 mg/kg/IV every 2 weeks. The primary endpoint was response rate. Secondary endpoints included time to progression, PFS, OS, CA-125 response rate, and safety endpoints. Response to treatment was assessed by the clinical investigators and also by an independent review committee (IRC). As assessed by the investigators, objective response rates were 7.3\% and 3.8\% in the 4 mg/kg and 2 mg/kg dose, respectively. However, based on the IRC evaluation, the response rates were 4.6\% and 0.9\% in the 4 mg/kg and 2 mg/kg cohorts, respectively. The study did not achieve its primary endpoint of demonstrating that patients in either arm of the study achieved a RECIST response rate as assessed by the IRC that was statistically significantly greater than 5\%. The CA-125 response rates, which were defined as a reduction in CA-125 protein levels of at least 50\% were approximately 11\% in both arms. Of the 130 patients evaluable for CA-125 response from the combined groups, 18 (13.8\%) had either a RECIST (as assessed by the IRC) or CA-125 response. The median PFS was 13.3 and 13.0 weeks with the 4 mg/kg and 2 mg/kg doses, respectively. The median OS was 49.3 and 55.4 weeks with the 4 mg/kg and 2 mg/kg doses, respectively. Of the 40 patients in both dose groups who had evaluable ascites at baseline, 77.5\% had either a complete disappearance or stabilization of their ascites. The adverse effects of afilibercept were typical of this class of antiangiogenic agents, with hypertension being the most common grade 3/4 adverse event. The incidence of bowel perforations was rare (1.8\%).\textsuperscript{52,53} In a parallel pilot study, 12 patients
with advanced epithelial ovarian cancer and symptomatic ascites requiring frequent paracentesis were treated with aflibercept 4 mg/kg every 2 weeks. After receiving 1 to 13 cycles of aflibercept, 8 of 10 evaluable patients achieved a repeat paracentesis response rate (RPRR), defined as at least a doubling of time to the first paracentesis after initiating therapy compared to a baseline average, with a range of 12 to 205 days. Grade 3/4 adverse events included bowel obstruction (40%), nausea and vomiting (30%), anorexia, edema, general health deterioration (20%), and 1 case of GI perforation.54

Coleman et al55 presented the results of a phase I study of aflibercept in combination with docetaxel. Aflibercept was administered at 2, 4, or 6 mg/kg as a single agent in cycle 0 and in combination with docetaxel 75 mg/m² in subsequent cycles. This study showed that aflibercept could be safely administered at 6 mg/kg with docetaxel. The most common toxicities were headache, hypertension, fatigue and ulceration. One episode of grade 4 neutropenia occurred. Two of 9 patients (22%) discontinued treatment due to toxicity, 1 with hypertension after cycle 4 and 1 with ulceration after cycle 13. The median number of cycles administered was 5 (range 3 to 15), and partial responses were observed in 2 of 9 patients (22%), with a median time to progression of 15 weeks. A phase II study is ongoing.

### Table 2. Summary of Tyrosine Kinase Inhibitors Under Investigation in Solid Tumors, Including Ovarian Cancers

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibits</th>
<th>Development Phase</th>
<th>Outcomes</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cediranib (AZD2171)</td>
<td>VEGFR-1, -2, -3 c-kit</td>
<td>II - Monotherapy, recurrent ovarian cancer</td>
<td>PR 17%, SD 13%, PFS 5.2 mos</td>
<td>Grade 3: hypertension 46%, fatigue 24%, diarrhea 13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS not yet reached</td>
<td>Grade 4: CNS hemorrhage (1), dehydration (1), percholesterolemia (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III - Carboplatin + paclitaxel ± cediranib, recurrent ovarian cancer</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>VEGFR-2, -3 Ras/Raf/Mek/ERK pathways, PDGFR-β</td>
<td>I - Monotherapy, advanced solid tumors</td>
<td>SD 22%, median duration 7.2 mos</td>
<td>Dermatologic changes, fatigue, GI effects (diarrhea, nausea, anorexia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I - Gemcitabine + sorafenib, advanced solid tumors</td>
<td>PR 5%, SD 63.2%, Dose 400 mg bid with gemcitabine 1,000 mg/m² weekly</td>
<td>Grade 3/4: thrombocytopenia (29%), lymphopenia (21%), lipase elevation (19%), neutropenia (17%), fatigue (14%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I - Oxaliplatin + paclitaxel + sorafenib, advanced carcinomatosis</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II - Bevacizumab + sorafenib, recurrent ovarian cancer</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II - Sorafenib ± paclitaxel and carboplatin, recurrent ovarian cancer</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>Sunitinib (SU11248)</td>
<td>VEGFR-1, -2, -3 PDGFR-α, -β</td>
<td>II - Monotherapy, advanced ovarian cancer</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>Pazopanib (Votrient)</td>
<td>VEGFR-1, -2, -3 PDGFR-α, -β c-kit</td>
<td>II - Monotherapy; recurrent ovarian cancer</td>
<td>CA-125 response 47%, SD 27%</td>
<td>Grade 3/4: diarrhea, ALT elevation</td>
</tr>
<tr>
<td>Vatalanib (PTK 787)</td>
<td>VEGFR-1, -2, -3 PDGFR-β c-kit</td>
<td>Ib - Carboplatin + paclitaxel + vatalanib, first-line ovarian cancer</td>
<td>CR + PR 9%, SD 9%, Dose 1,250 mg/day with paclitaxel</td>
<td>Grade 3/4: neutropenia (31%), leukopenia (18%), hypertension (10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I - Carboplatin + paclitaxel + vatalanib</td>
<td>PR 29%, SD 21%, MTD pending</td>
<td>Hyperglycemia (29%), hypertension (7%), diarrhea (7%), transaminitis (7%)</td>
</tr>
</tbody>
</table>

SD = stable disease, CR = complete response, PR = partial response, MTD = maximum tolerated dose, OS = overall survival, PFS = progression-free survival.
**TKIs of VEGF Receptors**

Several TKIs are being investigated that inhibit the VEGFRs directly rather than the binding of the VEGF ligand (Table 2). Cediranib (AZD2171) is an oral TKI that targets all three VEGFRs and c-kit. In a phase II study in women with recurrent epithelial ovarian, peritoneal, or fallopian tube cancer, cediranib demonstrated a significant clinical benefit rate (tumor response, stable disease, or CA-125 nonprogression > 16 weeks) of 30%. Median OS had not been reached after a median follow-up of 10.7 months. Cediranib is being evaluated in combination with carboplatin and paclitaxel in a phase III trial (ICON6) in women with recurrent disease (Fig 6).\(^5^6\)

Sorafenib (Nexavar) is an oral kinase inhibitor that targets the Ras/Raf/Mek/ERK pathways in addition to VEGFR-2 and -3 and PDGF receptor beta (PDGFR-β). It is currently FDA-approved for treatment of advanced renal cell carcinoma and has been evaluated in a phase I study that included 10 women with ovarian cancers for the treatment of advanced, refractory solid tumors.\(^5^7\) GOG 170F is a phase II trial of single-agent sorafenib in patients with recurrent ovarian or primary peritoneal cancer who had progressed within 12 months of platinum-based therapy.\(^5^8\) Preliminary results of 59 patients with measurable disease revealed that 12 had survived progression-free for at least 6 months. Responses in 3 patients have yet to be determined. Two patients had partial responses, 20 had stable disease, and 30 had progressive disease. Significant grade 3/4 toxicities included rash, metabolic disturbances, and GI, cardiovascular, and pulmonary events. No treatment-related deaths were observed.

Sorafenib has also been tested in combination with gemcitabine in a phase I study by Siu et al.\(^5^9\) In this study of 42 patients, 6 patients (14%) had advanced ovarian cancer. There were 2 partial responses in the women with ovarian cancer, and an additional 12 patients overall (63.2%) had disease stabilization. Multiple phase I/II trials are currently being conducted to further evaluate the activity of sorafenib in epithelial ovarian cancer. Additionally, there is a randomized phase II study comparing sorafenib 400 mg twice daily to placebo as maintenance therapy in women with advanced ovarian or primary peritoneal cancer in complete remission following surgery and 1 previous chemotherapy regimen.

Sunitinib (SU11248) is an oral TKI that targets all three VEGFRs as well as PDGFR-α and -β. It is approved by the FDA for the treatment of GI stromal tumors and advanced renal cell carcinomas. PDGF may play a role in ovarian carcinogenesis and progression. Thus, there is strong rationale to assess drugs such as sunitinib and sorafenib, which target both PDGF and VEGF pathways, in the treatment of ovarian cancer. Two active phase II studies of sunitinib are underway for patients with advanced or metastatic epithelial ovarian, peritoneal or fallopian tube cancer.\(^6^0,6^1\)

Pazopanib is an oral TKI that targets all three VEGFRs, both PDGFRs, and c-kit. Preliminary results of a phase II study of patients with recurrent epithelial ovarian, fallopian tube, or peritoneal carcinoma demonstrated a significant CA-125 response, which was the primary endpoint of the study.\(^6^2\) The findings from the first stage of the study met criteria to proceed to the second stage of enrollment.

Vatalanib (PTK 787) is a TKI most selective for VEGFR-2, but it inhibits all known VEGFRs, PDGFR-β, and c-kit. Treatment of an ovarian cancer xenograft with vatalanib significantly inhibited growth of tumor cells and...
Alternative Antiangiogenesis Therapies

While VEGF-induced tumor neovascularization is prominent, angiogenesis is also regulated by multiple redundant pathways, and tumors may activate these secondary pathways to overcome bevacizumab-related VEGF inhibition and tumor growth suppression. Therefore, other antiangiogenic therapeutic strategies have been developed to overcome resistance to VEGF blockade, and several are undergoing clinical evaluation. A thorough review of these additional targets and agents are beyond the scope of this article.

One potential target is EphA2, an oncoprotein and tyrosine kinase receptor that is associated with high MVD. EphA2 is overexpressed in a number of malignancies, including ovarian carcinoma, but it is absent or expressed at low levels in normal epithelial tissue. Preclinical studies show promise for the treatment of ovarian cancer with anti-EphA2 agents. Treatment of mice with orthotopic ovarian tumors with EA5, a monoclonal EphA2-agonist antibody, alone or in combination with paclitaxel, resulted in significant reduction in tumor weight. Additionally, mice treated with combination EA5 and paclitaxel lived significantly longer and had reduced tumor MVD and increased endothelial cell apoptosis. Further EphA2 specificity has been achieved by conjugating an anti-EphA2 monoclonal antibody (1C1) with a chemotherapeutic agent (monomethyl auristatin phenylalanine, MMAF). The 1C1-MMAF conjugate bound to EphA2-positive ovarian cancer cells but not to EphA2-negative cells. In an orthotopic murine model, treatment with 1C1-MMAF significantly inhibited ascites formation in SKOV3 cell lines with high levels of VEGF.`

<table>
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<tr>
<th>Compound</th>
<th>Mechanism</th>
<th>Development Phase</th>
<th>Outcomes</th>
<th>Toxicity</th>
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| Combretastatin (CA4P) | Tubulin depolymerising agent   | I - Monotherapy, advanced solid tumors | CR (1/25)  
SD (3/25)  
Dose ≤ 60 mg/m2 every 3 wks | Tumor pain  
Grade 3 myelosuppression (3/107 courses)  
Grade 1 QTc prolongation (7 episodes) |
| Oxi4503          | Tubulin depolymerising agent   | Preclinical: Colorectal, renal cell, breast and sarcoma xenografts | Reduction of tumor blood vessels and tumor necrosis | N/A                                   |
| ZD6126           | Tubulin depolymerising agent   | I - Monotherapy, advanced solid tumors | SD 22%  
DCE-MRI evidence of decreased tumor blood flow  
Dose 80 mg/m2 every 2-3 wks | Common: Abdominal pain, nausea, constipation, dyspnea  
DLTs (11%): hypotension, abnormal LVEF, myocardial ischemia |
|                  | preclinical: Monotherapy and docetaxel combination in ovarian cancer xenograft | 65% tumor reduction  
86% tumor reduction and improved survival in combination group | N/A |
|                  | I - Monotherapy, advanced malignancies | DCE-MRI evidence of decreased vascular flow  
Dose 30 mg/m2 weekly × 3 wks every 28 days | Asymptomatic systolic hypotension without cardiac compromise |
| AVEB002          | Tubulin depolymerising agent   | III - In development | N/A | N/A |
| ABT751           | Sulfonamide colchicine-binding antimitotic agent | I - Monotherapy, refractory solid tumors | SD (4/39)  
Dose 250 mg po daily × 7 days, then 150 mg bid × 7 days every 21 days | Common: fatigue, asthenia, anorexia, constipation/ileus, peripheral neuropathy, myalgias  
Grade 3/4: neuropathy, nausea, constipation/ileus, abdominal pain, arthralgia/myalgia |

DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging, CR = complete response, SD = stable disease, DLT = dose-limiting toxicity, LVEF = left ventricular ejection fraction.
tumor growth by 85% to 98% and increased survival from a mean of 29.4 days to 60.6 days. A phase I clinical trial is being developed.

AMG 386 is a promising peptide-Fc fusion protein that inhibits angiogenesis by binding angiopoietin-1 and -2 and blocking interaction with the Tie2 receptor. In a phase II trial of weekly paclitaxel with AMG 386 or placebo for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, the side effect profile was acceptable. Grade 3 toxicities included peripheral edema (4%), hypokalemia (12%), and thromboembolic events (arterial 2%, venous 8%). Hypertension was noted in 8% but none was grade 3. PFS for the combination group was 7.2 months compared with 4.6 months for the placebo group in this heavily pretreated group of patients, with a hazard ratio (HR) of 0.76 (95% CI, 0.59–0.98, P = .17). Response rate in patients with measurable disease was 27% in the AMG 386 group compared with 19% in the placebo group, and CA-125 decreased in 100% of patients in the AMG 386 group compared to 63% in the placebo group. Most intriguing is the fact that stratification by platinum-resistance status demonstrated that patients with platinum-resistant or refractory disease had the greatest response to AMG 386, with an HR of < 1.69. Continued studies are warranted to further evaluate the activity of AMG 386 against ovarian cancer and to further optimize the dose.

Vascular Disrupting Agents

One of the most interesting classes of therapies is the group of vascular disrupting agents (VDAs). VDAs destroy existing tumor vasculature rather than merely inhibit the formation of new tumor vasculature. This leads to rapid and extensive decrease in tumor blood flow and to secondary tumor cell death. In a preclinical model, treatment of human clear cell renal carcinoma murine xenografts with bevacizumab alone or in combination with tubulin depolymerizing agents, combretastatin (CA4P) or Oxi4503 (OXiGENE), resulted in significantly greater tumor growth delay than any of the agents alone. A phase I study of CA4P in advanced solid tumors demonstrated an acceptable safety profile and potential antitumor activity with one complete response and stabilization of disease in 3 patients. The predominant adverse effect was tumor pain. Several VDAs are being evaluated in preclinical and phase I studies (Table 3), including Oxi4503, ZD6126, AVE8062, and ABT775. Corollary studies are ongoing to determine the best way to measure disease response, as current disease measurement strategies may not be adequate to assess VDA-induced antitumor activity.

Conclusions

Retrospective studies and phase II trials have indicated that angiogenic agents have promising activity in women with ovarian cancer. It is hoped that the results of landmark phase III clinical trials in both the front-line and recurrent settings will demonstrate that VEGF blockade can enhance survival for women with this disease. However, critical issues remain unresolved, such as (1) the rational identification of women most likely to benefit from antiangiogenic agents, (2) the elucidation of resistance to VEGF blockade and continued development of alternative antiangiogenic strategies, and (3) the development of targeted tumor-specific antiangiogenic therapies in order to avoid adverse events associated with the inhibition of normal physiologic angiogenesis.

References

Anticancer Res. 2006;26(6B):3925-3932.


