Epithelial ovarian cancer (EOC), along with primary peritoneal cancer (PPC), is the fifth leading cause of cancer mortality in women in the United States, with an estimated 15,500 deaths and 22,280 new cases diagnosed in 2012. Localized disease accounts for only 15% of the women diagnosed with ovarian cancer, as they often remain asymptomatic until the disease is well advanced. Conversely, a projected 63% of women diagnosed with ovarian cancer have distant metastases, and the associate 5-year survival rate is an abysmal 27%. Standard therapy for advanced disease has traditionally relied on cytotoxic agents, such as DNA platinating agents, nucleoside analogs, and taxanes, that kill rapidly dividing tumor cells by disrupting DNA or microtubule integrity. Despite the efficacy of cytotoxic agents, the majority of women experience relapse and subsequent progression to treatment-refractory disease. Antiangiogenic agents constitute a new class of drugs employed as treatment for various tumor types. The antitumor activity of these agents is due to their ability to interrupt or mimic cell signals at the molecular level and, ultimately, interfere with tumor angiogenesis and survival. Vascular endothelial growth factor (VEGF), which induces the proliferation and migration of endothelial cells and increases vascular permeability, is a primary mediator of tumor angiogenesis. Hypoxia of the microenvironment enhances expression of VEGF in tumor cells and leads to unregulated new vessel growth (reviewed in 3). Unlike that found in normal tissues, tumor vasculature is highly disorganized and permeable, which perpetuates tumor hypoxia, growth factor expression, and potentially interferes with therapeutic drug delivery.

Antiangiogenic agents function by interrupting a proangiogenic growth factor communication loop between tumor cells and resident endothelial cells (Please refer to the illustration on page 4). In addition to VEGF, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and hepatocyte growth factor (HGF) are able to increase endothelial cell proliferation upon binding with their respective receptors. Angiotensin-1 additionally regulates endothelial cell survival by suppressing apoptosis when VEGF is present, and inducing apoptosis in its absence. Upon VEGF binding its receptor, vascular endothelial growth factor receptor (VEGFR), on the surface of endothelial cells, receptor dimerization leads to phosphorylation of key tyrosine residues of its intracellular tail and activation of numerous downstream signaling pathways. Two activated pathways that play an important role in endothelial and tumor cell growth and survival are the Raf-MEK-Erk and phosphotidylinositol-3-kinase (PI3K)-Akt pathways. Each member of these proangiogenic pathways represents potential targets for drug development and mechanisms of action for the treatment of cancer.

Numerous therapeutic agents that inhibit angiogenesis are being evaluated for activity in the treatment of advanced ovarian cancer. Angiogenesis plays an important role in both the cyclical nature of normal ovarian function and ovarian tumorigenesis. VEGF expression is increased in ovarian tumors compared to normal ovaries, and high VEGF expression in tumors has been linked to poorer prognosis. The effects of VEGF expression on vascular permeability is also thought to be a significant contributor to the development of malignant ascites in ovarian cancer patients. Along these lines, VEGF inhibition in animal models of ovarian cancer dramatically alters tumor vasculature, inhibits ascitic fluid accumulation, and reduces tumor growth.

Over the last decade, numerous antiangiogenic agents with different mechanisms of action have undergone clinical evaluation for use in treating patients with ovarian cancer. This review will update clinical trial data regarding the use antiangiogenic agents for the treatment of platinum-sensitive and platinum-resistant advanced ovarian cancer.

Anti-VEGF Monoclonal Antibody: Bevacizumab

Bevacizumab is a humanized anti-VEGF monoclonal antibody that specifically binds VEGF in the extracellular space and prevents it from complexing with VEGFR. Bevacizumab (BV) has been approved by the FDA, as monotherapy or as part of combination therapy, for the treatment of metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma, and advanced renal cell carcinoma. The activity of BV in the first-line, recurrent/platinum-sensitive, and platinum-resistant therapeutic settings has been evaluated in a number of phase 2 and 3 clinical trials.
Bevacizumab as First-Line Therapy

Two randomized phase 3 trials were conducted to evaluate the addition of BV to standard first-line chemotherapy for advanced ovarian cancer in response to encouraging results from several phase 2 trials that showed treatment with BV could elicit tumor response and delay disease progression.11-13 The activity of BV as front-line therapy was first demonstrated in an open-label phase 2 trial investigating the addition of BV 15 mg/kg q3w to carboplatin AUC 5/paclitaxel 175 mg/m².14 Women with newly diagnosed advanced (stage ≥ IC) epithelial müllerian tumors were enrolled for the study, 79% of which had optimally cytoreduced disease.9 Using combined RECIST and formal Rustin criteria, researchers reported an overall response rate (ORR) of 76%, with complete responses (CR) in 21% of patients. The median progression-free survival (mPFS) was 29.8 months, while median overall survival (OSS) has not yet been reached.

The phase 3 GOG 0218 trial was initiated to evaluate the superiority of adding BV to standard first-line therapy and to compare the effect of longer and shorter periods of VEGF suppression.14 In this double-blind and placebo-controlled trial, a total of 1,873 women with previously untreated advanced (stage III or IV), EOC, PPC, or fallopian tube cancer were randomized to receive 6 cycles of carboplatin AUC 5/paclitaxel 175 mg/m² (chemotherapy), 6 cycles of chemotherapy plus BV 15 mg/kg q3w (BV-initiation), or 6 cycles of chemotherapy plus 22 cycles of BV 15 mg/kg q3w (BV-throughout). Median PFS was significantly prolonged in the BV-throughout arm when compared to the chemotherapy arm (14.1 months vs. 10.3 months, P < .0001), but not in the BV-initiation arm (11.2 months vs. 10.3 months, P = .16). The BV-associated improvement in PFS was seen for all prognostic groups. Median overall survival was similar for chemotherapy, BV-initiation, and the BV-throughout treatment groups (39.3, 38.7, and 39.7 months, respectively), and this was likely due to the confounding effects of post-progression treatment, particularly crossover to antiangiogenic therapy in the management of recurrent disease.

The ICON 7 (International Cooperative Group for Ovarian Neoplasia) phase 3 trial investigated the addition of BV to carboplatin/paclitaxel as first-line therapy for advanced ovarian cancer, but at half the dose intensity used in GOG 0218.15 A total of 1528 women diagnosed with high-risk early stage or advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer were randomized to receive either 6 cycles of carboplatin AUC 5/paclitaxel 175 mg/m² (chemotherapy) or chemotherapy plus concurrent BV 7.5 mg/kg q3w (chemotherapy-BV) for 6 cycles followed by continued BV for 12 additional cycles. The addition of BV to chemotherapy improved median PFS by 1.7 months (19.8 months vs. 17.3, P = .004). The maximum benefit from BV treatment occurred at 12 months, which coincided with the end of BV exposure, and diminished thereafter such that PFS was slightly higher in the chemotherapy group by 24 months. Subgroup analysis showed that the addition of BV to chemotherapy greatly improved the median PFS (16.0 vs. 10.5 months, P = .002) in patients at high risk for progression. Although survival data is not yet mature, the updated analysis also revealed this same subgroup of patients benefitted from BV treatment in terms of median OS (36.6 vs. 28.8 months, P = .002) as well.

Both the GOG 0218 and ICON7 demonstrated that adding BV to carboplatin and paclitaxel standard first-line therapy significantly prolonged PFS in women with advanced ovarian cancer, and ICON7 subgroup analysis revealed a significant BV-associated survival benefit for patients at high risk for progression.

Recurrent, Platinum-Sensitive Disease

Another phase 3 trial, OCEANS, was implemented to assess the efficacy and safety of BV in the treatment of patients with recurrent, platinum-sensitive advanced ovarian cancer.16 Treatment of this patient population with combination therapy with gemcitabine/carboplatin (GC) was approved by the FDA in 2006 after results of a European phase 3 intergroup trial demonstrated its superiority to gemcitabine alone.17 Investigators initiated OCEANS in response to results from a phase 2 trial, the GOG 170D study, which indicated that BV monotherapy had activity in treating patients with platinum-sensitive and platinum-refractory disease after recurrence.16 Of 62 recruited were enrolled in this phase 2 study, 58% had a platinum-free interval (PFI) of less than 6 months and were considered platinum-sensitive. Investigators reported a 21% ORR, which included two CRs and 11 PRs. Median PFS and OS were 4.7 months and 17 months, respectively. Importantly, the investigators reported no significant association of prior platinum sensitivity or number of prior treatments with death, suggesting that BV had enduring activity in recurrent ovarian cancer.

The OCEANS trial, an industry-sponsored, placebo-controlled trial, randomized 484 women with platinum-sensitive ovarian cancer (PFI of at least 6 months) after first-line therapy to treatment with either GC AUC 4/1000 mg/m² plus placebo (GC) or GC plus BV 15 mg/kgq3w; (GC-BV).16 Median PFS was 4 months longer in patients treated with GC-BV compared to those treated with GC (12.4 vs. 8.4 months, P < .0001). The addition of BV to GC was also associated with a statistically significant improvement in the ORR (78.5% vs. 57.4%, P < .0001), of which the majority were partial responses (148 of 242 and 117 of 242, respectively). Survival data is immature, but data with a high degree of censoring yielded median OS of 35.2 months for GC-treated patients and 33.3 months for GC-BV-treated patients. Together with the results of GOG 0218 and ICON7, results from OCEANS suggest that BV improves efficacy in terms of PFS of standard chemotherapy doublets for patients with chemotherapy-naïve platinum-pretreated ovarian cancer.

Platinum-Resistant/Refractory Disease

The platinum-resistant treatment setting for women with advanced ovarian cancer is an important one. Improving outcome in these patients represents an unmet medical need; a high recurrence...
rate and typical survival times of less than 12 months characterize treatment-refractory disease. To assess whether BV could improve outcome in this refractory patient population, investigators initiated the industry-sponsored phase 3 study, AURELIA. This randomized, open-label phase 3 trial compared chemotherapy (investigator’s choice: paclitaxel 80 mg/m² days 1, 8, 15, 22 q4w; topotecan 4 mg/m² days 1, 8, 15 q4w; liposomal doxorubicin 40 mg/m² day 1 q4w) and chemotherapy plus BV 15 mg/kg q3w as salvage therapy in patients with advanced ovarian cancer. Patients were treated to progression or unacceptable toxicity, when they crossed over to treatment with chemotherapy alone (after initial BV exposure) or BV monotherapy (after initial chemotherapy alone). Results of the trial showed that the addition of BV to chemotherapy was associated with an approximate doubling in median PFS (6.7 vs. 3.4 months, P < .001), and was consistent across all subgroups analyzed. Further, over twice as many patients treated with BV experienced an objective response (27.3% vs. 11.8%, P = .001) when compared to those treated with chemotherapy alone. The AURELIA investigators suggested this was likely due to the fact that patients in the BV arm received more cycles of chemotherapy than those in the chemotherapy arm alone. Survival data are not yet mature but are expected in 2013.

Two earlier phase 2 trials evaluated the potential role of BV in the treatment of platinum-resistant ovarian cancer and provided the impetus for phase 3 analysis. In one trial, patients were treated with nab-paclitaxel 100 mg/m² days 1,8,15 and BV 10 mg/kg q2w until disease progression. Approximately 46% patients experienced a partial response and median PFS was 8.3 months. Median OS was 16.5 months. A second phase 2 study conducted in this disease setting assessed the activity of BV 10 mg/kg q2w in combination with topotecan (4 mg/m² days 1, 8, 15 q4w) resulted in comparable measures of efficacy: median PFS was 7.8 months and median OS was 16.6 months. Interestingly, this study suggested that patients who had undergone 2 previous treatment regimens received substantially greater benefit from BV than those who had only received one prior regimen; patients in this subgroup had significantly longer median survival (22.9 vs. 12.8 months, P = .02).

Results of both phase 2 and 3 trials in the platinum-resistant treatment suggest that benefit from BV on outcome is independent of chemotherapy partners, affording flexibility for physicians in choosing appropriate cytotoxic agents for treating patients in the salvage setting.

**Ongoing Trials of Bevacizumab**

Several other phase 3 trials of BV for advanced ovarian cancer are ongoing. The first of these, GOG 0213, seeks to clarify the role of BV in recurrent, platinum-sensitive disease in combination with chemotherapy (carboplatin plus either paclitaxel or docetaxel). The trial’s primary objective is to determine whether a second round of surgical cytoreduction and adjuvant chemotherapy, with or without BV, improves overall survival.

Another phase 3 trial, GOG 0252, compares the safety and efficacy of BV plus I.V. paclitaxel/carboplatin with BV plus intraperitoneal (I.P.) chemotherapy (paclitaxel plus either I.P. carboplatin or I.P. cisplatin) as first-line therapy. This trial is active but no longer recruiting patients.

Further investigating BV in combination with carboplatin and paclitaxel as therapy for patients with advanced ovarian cancer, a phase 3 study has been initiated to assess the safety profile associated with longer exposure to these agents. Patients will be exposed to combination therapy for up to a total of 8 cycles and BV for up to a total of 36 cycles. Secondary outcome measures for the study include PFS and overall response rate.

A multicenter, open-label phase 3 trial is currently recruiting patients with newly diagnosed stage II-IV or recurrent stage I mucinous ovarian cancer to compare the efficacy of first-line treatment with carboplatin/paclitaxel, carboplatin/paclitaxel/BV, oxaliplatin/capecitabine, and oxaliplatin/capecitabine/BV. All patients receive 6 cycles of combination therapy, and then those randomized to BV-containing therapy receive and additional 12 cycles of BV alone. The primary objectives of the study are to determine if capecitabine/oxaliplatin reduces the death rate compared to carboplatin/paclitaxel and if BV reduces the death rate compared to no BV.

A German phase 3 trial (BOOST) has been initiated to evaluate the optimal duration of first-line chemotherapy in patients with BV in combination with paclitaxel and carboplatin (6 cycles). Patients will be randomized to receive BV alone after combination therapy for either an additional 16 or 38 cycles until disease progression or unacceptable toxicity.

**Multitargeted Antiangiogenic Agents**

A major class of antiangiogenic agents is the small molecule receptor tyrosine kinase inhibitors (TKIs). These agents pass freely through cell membranes and disrupt intracellular signaling by preventing phosphorylation of VEGFR (1-3), PDGFR, c-Kit, and FGFR, and subsequent activation of downstream pathways (Please refer to the illustration on page 4).

**In Phase III Clinical Development**

Multitargeted antiangiogenic agents currently in phase 3 clinical development for the treatment of advanced ovarian cancer include pazopanib, BIBF 1120 and AMG 386.

Pazopanib is a multitargeted oral angiogenesis inhibitor that suppresses the signaling function of VEGFR, PDGFR, and c-Kit. Pazopanib was granted FDA approval in October 2009 for the treatment of advanced renal cell carcinoma, and April 2012 for
Targeting Cells and Pathways in Advanced Ovarian Cancer

During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells, which in turn, release growth factors that sustain angiogenesis. Antiangiogenic agents target key pathways in proliferating endothelial cells, pericytes, and tumor cells.

1. **Endothelial Cell**
   - The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGFR-1, VEGFR-2, VEGFR-3, activating signal transduction to promote angiogenesis, vasculogenesis, and lymphangiogenesis.
   - Hypoxia
   - VEGF-B
   - VEGF-A
   - VEGF-C
   - VEGF-D
   - VEGF
   - Paracrine factors
   - PI3K
   - Akt
   - Ras
   - Raf
   - MEK
   - ERK
   - p38MAPK
   - eNOS
   - Caspase-9

2. **Pericyte**
   - Platelet-derived growth factor (PDGF) and its receptor PDGFR-β mediate vessel maturation.
   - Hypoxia
   - PDGF
   - VEGF
   - O2
   - VEGF/other angiogenic growth factors
   - O2

3. **Tumor Cell**
   - Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.
   - Hypoxia
   - HER2
   - Endothelial cell
   - Tumor cell

**Targeted Agents** (Targets shown in diagram above)
- Bevacizumab
- BIBF 1120
- Pazopanib
- Sunitinib
- AMG 386
- VEGF Trap
the treatment of soft tissue sarcoma, due to its ability to delay progression and elicit enduring response in pretreated and treatment-naive patients.

Phase 2 trials of pazopanib have conflicting findings that should be further evaluated. In one trial, pazopanib was evaluated as monotherapy for recurrent ovarian cancer in a non-randomized, open-label phase 2 study. Patients with recurrent ovarian cancer and good performance status (ECOG 0 in 96% of participants) were treated with pazopanib 800 mg QD until progression or unacceptable toxicity. Response to therapy was defined as a ≥ 50% reduction in baseline CA-125. Thirty-one percent of patients experienced a CA-125 response to therapy was defined as a > 50% reduction in baseline with pazopanib 800 mg QD until progression or unacceptable toxicity. Response to therapy was defined as a ≥ 50% reduction in baseline CA-125. Thirty-one percent of patients experienced a CA-125 response

AMG 386 is an antiangiogenic peptide-Fc fusion protein (peptibody) that prevents interaction between the Tie2 receptor on endothelial cells and its ligands, angiopoietin1 and 2 (Ang1, Ang2). Tie2 signaling activity promotes angiogenesis through increased endothelial cell survival, proliferation and migration. Ang2 is consistently overexpressed at sites of active angiogenesis, and functions in distinct yet parallel proangiogenic pathway.

Recently published results from a randomized, placebo controlled phase 2 trial suggested that AMG 386 improved PFS in a dose-dependent manner. Patients with recurrent ovarian cancer were randomized to receive paclitaxel (80 mg/m² QW) in combination with AMG 386 10 mg/kg QW, AMG 386 3 mg/kg QW or placebo QW. Although none of the efficacy measures reached statistical significance, patients treated with higher levels of AMG 386 had a substantially longer median PFS than those who received lower dose AMG 386 (7.2 vs. 5.7 months) or placebo (7.2 vs. 4.6 months). Additionally, the longer PFS associated with the higher dose of AMG 386 treatment leads to a survival benefit compared to lower dose AMG 386 (22.5 vs. 20.4 months) or placebo (22.5 vs. 20.9 months). The ORR reported for this trial was 37%, 19%, and 27%, respectively. CA125 responses were 71% and 28% for the investigational and placebo arms. Pharmacokinetic/pharmacodynamic analysis suggested that maximum PFS benefit may not have been reached with AMG 386 10 mg/kg QW, and investigators suggested AMG 386 15 mg/kg QW for future evaluation.

A phase Ib trial evaluated the efficacy of AMG 386 15 mg/kg QW in combination with paclitaxel 175 mg/m² q3w/carboplatin AUC 6 q3w as first-line therapy in women with high risk early stage and advanced ovarian cancer. After 6 cycles of combination therapy, AMG 386 was continued as maintenance therapy for up to 18 months. The higher dose of AMG 386 was tolerable in combination with cytotoxic chemotherapy.

In response to encouraging phase 2 data, TRINOVA-1 was planned to evaluate the efficacy of paclitaxel plus 3 trial in treating women with recurrent, partially platinum sensitive or resistant advanced EOC, PPC or fallopian tube cancer in a randomized, placebo-controlled phase trial. A second planned phase 3 trial, TRINOVA-2, evaluating the addition of AMG 386 to pegylated liposomal doxorubicin was suspended due to shortages of pegylated liposomal doxorubicin from interruption of manufacturing. And finally, the TRINOVA-3 phase 3 trial planned implemented to evaluate AMG 386 in combination with paclitaxel and carboplatin as first-line therapy for advanced ovarian cancer. Participants will be randomized to treatment with AMG 386 15 mg/kg QW or placebo in combination with standard paclitaxel/carboplatin until progression or unacceptable toxicity. The primary outcome measure for this trial is PFS.

BIBF 1120 is a small molecule tyrosine kinase inhibitor with antiangiogenic activity due to its inhibition of VEGFR, PDGFR and FGFR signaling. The activity of BIBF 1120 as maintenance therapy for recurrent ovarian cancer was investigated in a randomized, placebo controlled phase 2 study. Participants who had responded to their most recent chemotherapy regimen were treated with BIBF 1120 250 mg twice daily or placebo continuously for 36 weeks. Greater than half of the trial participants entered onto the study after at least a third line of therapy. At the end of treatment, PFS rates were 16.3% and 5.0% for BIBF 1120- and placebo-treated patients, respectively. Although the trial was not powered for direct comparison of PFS or OS, the hazard ratio for the two groups was 0.65 and 0.84, respectively.

An ongoing, large phase 3 trial, the AGO-OVAR 12 trial, was initiated to evaluate the role BIBF 1120 in combination with standard frontline chemotherapy in the treatment of advanced ovarian cancer. Planned enrollment is 1,300 patients, and exclusion criteria for the trial include previous exposure to angiogenic inhibition. The primary outcome measure for this trial is PFS.

**Antiangiogenic Agents on the Horizon in Ovarian Cancer**

There are numerous agents in early stages of clinical development that show promise for treating patients with advanced ovarian cancer.
Aflibercept is a soluble VEGFR fusion protein made from the extracellular portions from VEGFR-1 and -2 bound to the Fc portion of IgG1. Aflibercept binds to and prevents proangiogenic signaling by VEGF-A, -B and placental growth factor. Two phase 2 trials conducted in heavily pretreated patients with recurrent malignant ascites demonstrated that treatment with aflibercept extended time to repeat paracentesis. In a randomized phase 2 study, patients received either aflibercept 4 mg/kg q2w or placebo for at least days.31 Patients on this trial had a median of four previous lines of chemotherapy. The mean time to repeat paracentesis was approximately one month longer for patients who received aflibercept (55.1 vs. 23.3 days, P = .0019). A smaller open-label, single arm phase 2 study also found that treatment of women with advanced ovarian cancer and malignant ascites with aflibercept 4 mg/kg q2w led to an increase in time to repeat paracentesis.44

Median time to repeat paracentesis was 76 days, compared to 16.8 days at baseline. Median PFS for treated patients was 59.5 days. An ongoing phase 1/2 trial of aflibercept in combination with docetaxel as therapy for recurrent advanced ovarian cancer is estimated to be completed in 2014.45

MK-2206 is an inhibitor of Akt, which signals downstream of growth factor signaling and promotes cell growth and survival.46 Preclinical studies suggested that MK-2206 could augment the action of cytotoxic agents, such as docetaxel and carboplatin. Results from a dose-finding phase 1 study of MK-2206 in advanced cancer patients suggested that this agent was able to elicit tumor response, including CA-125 response.47,48 A phase 2 study of MK-2206 at the Dana-Farber Cancer Institute in the treatment of platinum-resistant advanced ovarian cancer is currently underway.49

Sunitinib is a small molecule multi-targeted tyrosine kinase inhibitor blocks the signaling activity of the VEGFR1-3, PDGFR, c-KIT, and Flt-3, which play an important role in tumor progression, development, and angiogenesis.50 Sunitinib is FDA approved for the treatment of imatinib-resistant GIST, advanced renal cell carcinoma, and unresectable locally advanced and metastatic pancreatic neuroendocrine tumors. Two phase 2 trials of sunitinib in patients with recurrent advanced ovarian cancer suggested that it has modest activity in this clinical setting. One trial evaluated sunitinib at 2 dose levels in patients with platinum-resistant disease who had failed 3 previous therapies.51 Patients were randomized to two sunitinib treatment schedules: 50 mg daily for four of six weeks, or 37.5 mg daily continuously. The ORR in patients treated with sunitinib 50 mg was 16.7%, compared to 5.4% in those who received sunitinib 37.5 mg. Progression-free (4.8 vs. 2.9 months) and overall survival (13.6 vs. 13.7 months) were comparable between the two treatment groups. A second phase 2 study of sunitinib was conducted in patients with recurrent, platinum-sensitive disease.52 Patients with one or two prior chemotherapies were treated with sunitinib 50 mg daily for four of six weeks, and patients with fluid accumulation during the off-treatment periods changed to continuous treatment with 37.5 mg. One partial response was observed and the median PFS was 4.1 months. Investigators from both trials recommended sunitinib 50 mg four of six schedule for further evaluation.

IMC-3G3 is a fully human IgG1 monoclonal antibody targeting human PDGFR. Its antiangiogenic action comes from blocking the binding of PDGF and PDGFR, and subsequent activation of cell survival and migration signals.53 An ongoing randomized phase 2 trial is evaluating pegylated liposomal doxorubicin in combination with IMC-3G3 for the treatment of platinum-resistant advanced ovarian cancer.54 Data reports are currently awaited, and the estimated study completion date is August 2012.

EMND 2076 is a promiscuous small molecule kinase inhibitor able to suppress angiogenesis and cell proliferation through their selective inhibition Aurora A, VEGFR, FGFR, src, c-KIT, and FAK.55 Preclinical studies showed that EMND 2076 was able to prevent the formation of new blood vessels and regress formed vessels in vivo. During phase 1 trial of EMND-2076 in advanced solid tumors, two patients with platinum-refractory ovarian cancer experienced partial response by RECIST criteria.56 Based on these findings, an open-label phase 2 trial of EMND-2076 was conducted in patients with recurrent/refractory ovarian cancer.57 Patients were initially treated with EMND-2076 325 mg/d, but the dose was reduced to 275 mg/d due to toxicities and treatment delays. The confirmed ORR for this study was 7% and 6-month PFS rate wacal development evaluation of EMND-2076 in ovarian cancer is ongoing.

TRC-105 is a monoclonal antibody that targets CD105, or endoglin, which is an endothelial cell membrane receptor that is highly expressed on developing vessels in tumors but not normal mature vessels.58 Endoglin is essential for angiogenesis and regulates endothelial cell signaling and function. An open-label dose finding study of TRC-105 in was conducted in patients with advanced solid tumors.59 Serum concentrations expected to saturate endoglin-binding sites were achieved continuously at 15 mg/kg q2w. Antitumor activity was noted in patients with prostate cancer, endometrial cancer, colorectal cancer, and ovarian cancer. Based on these results, an open-label, single arm phase 2 trial was initiated in patients with recurrent advanced ovarian cancer.60 The primary outcome measure is 6-month PFS rate and objective response rate by RST criteria.

**Metronomic Chemotherapy**

Another treatment strategy for ovarian cancer that has received more attention recently is the dosing of chemotherapeutic agents to low, repetitive levels that preferentially affect stromal and endothelial cells rather than tumor cells. The maximum tolerated doses (MTDs) were effective in killing endothelial cells, but the scheduled breaks in treatment allow for recovery of the blood vessels and tumors themselves. Several studies of metronomic chemotherapy schedules have been conducted in patients with advanced recurrent ovarian cancer.
A preclinical dose-finding study of topotecan in an orthotopic model of advanced ovarian cancer found that while the MTD of topotecan caused higher morbidity than metronomic topotecan, tumor vascularity was suppressed more in response to metronomic treatment. Compared to controls, metronomic dosing yielded that greatest reduction in vascular density (32-33%, \( P < .01 \)). Another preclinical study assessed the addition of pazopanib to topotecan and found combination therapy superior to metronomic topotecan alone in terms of suppression of tumor cell proliferation (\( P < .01 \)). The investigators recommended pazopanib and metronomic topotecan for clinical development.

After favorable results in a breast cancer trial that demonstrated activity of metronomic chemotherapy in heavily pretreated patients, a phase 2 trial of BV 10 mg/kg q2w in combination with low dose metronomic cyclophosphamide 50 mg/d was conducted in patients with recurrent ovarian cancer. Findings of the trial included a 56% 6-month PFS rate and a partial response rate of 24%. Median time to progression was 7.2 months and median survival was 16.9 months.

### Biomarkers

The emergence of several antiangiogenic agents as efficacious in treating advanced ovarian cancer has provided impetus to identify biomarkers that will reveal mechanisms of action of toxicity or activity to treating physicians. Identification of prognostic and predictive biomarkers that will direct treatment decisions represents the “brass ring” of clinical research in the era of targeted therapy. With the goal of improving efficacy and minimizing toxicity, selecting patients for therapy based on tumor biology and patient characteristics remains a challenge in the majority of tumor types. To date, no reliable and specific biomarkers for angiogenesis and treatment with antiangiogenic agents have been identified.

Despite the lack of validated biomarkers, clinical observations in ovarian cancer provide clues for potential candidate biomarkers. As previously mentioned, high levels of tumor VEGF is associated with poorer prognosis in patients with advanced ovarian cancer. Multivariate analysis of one study showed that VEGF expression in tumors, by immunohistochemistry, and disease stage were independent prognostic indicators of survival (\( P = .008 \) and \( P = .006 \), respectively).

A recently reported study of the loss of heterozygosity (LOH) in the entire genome of ovarian tumors indicated that genomic instability in ovarian cancer is a significant and independent negative prognostic factor for both PFS and OS. Investigators assessed the prevalence of LOH in numerous ovarian tumors using whole genome Single Nucleotide Polymorphism (SNP) arrays and found that the average percentage of the genome with LOH was 35%, and that the fraction of the genome with LOH correlated significantly with OS (\( P = .0000034 \)) and PFS (\( P = .0016 \)). This data, however, requires further validation and evaluation of its clinical utility.

### Safety of Antiangiogenic Therapy for Ovarian Cancer

Antiangiogenic agents, relative to cytotoxic chemotherapy, are well tolerated and associated with fewer treatment interruptions and discontinuations due to toxicities. Nevertheless, VEGF is critical for the health and maintenance of a number of organ systems, and pharmacological disruption of its physiology is associated with a number of distinct class-effect adverse events that require careful monitoring and management. Among the most notable adverse effects associated with VEGF-targeted therapy are hypertension, arterial and venous thromboembolism, impaired wound healing, bleeding, and proteinuria. These class-effect toxicities are related to the targeted action of antiangiogenic agents.

**Hypertension** is a common class-based toxicity of VEGF inhibition and can usually be managed with standard antihypertensive medications. VEGF regulates synthesis of the vasodilator nitric oxide (NO) in vessel walls by upregulating production of endothelial NO synthase (eNOS). Inhibiting VEGF decreases NO production, promoting vasoconstriction, increased peripheral resistance, and elevated blood pressure. Anti-VEGF therapy also induces a functional decrease in the number of arterioles and capillaries, which may also contribute to increased peripheral resistance.

In GOG 0218, the incidence of \( \geq \) grade 2 hypertension increased with exposure to BV, 7.2% in the chemotherapy group, 16.5% in BV-initiation group and 22.9% in the BV-throughout group. This experience was mirrored in the ICON7 trial, where the incidence of \( \geq \) grade 2 hypertension was 18% in BV-treated patients compared to 2% in chemotherapy-treated patients. OCEANS reported an even higher incidence of hypertension, with 17.4% BV-treated patients experiencing \( \geq \) grade 3 hypertension. Exposure time to BV correlates with the rate of hypertension, as BV-treated patients were exposed for over one year in the GOG 0218 trial, and BV exposure was even longer in OCEANS trial. Toxicity profiles for multitargeted angiogenic inhibitors in ovarian cancer, such as pazopanib and sunitinib, also include hypertension.

**Arterial thrombotic events (ATE)** Patients treated with anti-VEGF therapy also experience an increased incidence of ATEs. A pooled analysis of five randomized clinical trials of BV found an incidence of ATE that was roughly doubled in patients who received combination chemotherapy plus BV (3.8%) versus controls (1.7%; \( P < 0.05 \)). This finding was not supported by results of the GOG 0218 trial, as the rate of ATEs across all groups in the study was below 1%. Since the safety of resuming BV therapy in patients with a resolved ATE has not been studied, BV prescribing information states that the agent should be discontinued in patients who experience a severe ATE. A possible association between BV and venous thromboembolism (VTE) is more controversial. Although some studies have reported an increased incidence of VTE with BV therapy, a meta-analysis involving 6,055 patients from 10 randomized phase 2 and 3 BV clinical trials found no overall increased risk from the addition of BV to chemotherapy.
### Select Phase 2 and 3 Clinical Trials of Anti-Angiogenic Agents in Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Treatment</th>
<th>ORR</th>
<th>mPFS</th>
<th>mOS</th>
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<td>Phase 3&lt;sup&gt;14&lt;/sup&gt; (GOG-0218)</td>
<td>First-line therapy of advanced ROC</td>
<td>paclitaxel/carboplatin: +PL +BV 15 mg/kg q3w initial +BV 15 mg/kg q3w throughout</td>
<td>48%</td>
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<td>(P = .45)*</td>
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<tr>
<td>Phase 3&lt;sup&gt;15&lt;/sup&gt; (ICON7)</td>
<td>First-line therapy of high-risk, early stage and advanced ROC</td>
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<td>17.4 months</td>
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<td></td>
<td>78.5%</td>
<td>19.8 months</td>
<td>35.2 months</td>
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<td></td>
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<td></td>
<td>(P &lt; .001)</td>
<td>12.4 months</td>
<td>33.3 months**</td>
</tr>
<tr>
<td>Phase 3&lt;sup&gt;16&lt;/sup&gt; (OCEANS)</td>
<td>Recurrent, platinum-sensitive ROC</td>
<td>Gemcitabine/carboplatin: +PL +BV 15 mg/kg q3w to PD</td>
<td>11.8%</td>
<td>3.4 months</td>
<td>NR (2013)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27.3%</td>
<td>6.7 months</td>
<td>16.9 months</td>
</tr>
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<td></td>
<td>(P = .001)</td>
<td>12.4 months</td>
<td>20.9 months</td>
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<td></td>
<td>(P &lt; .001)</td>
<td>(P = .081)*</td>
</tr>
<tr>
<td>Phase 3&lt;sup&gt;19&lt;/sup&gt; (AURELIA)</td>
<td>Platinum resistant ROC</td>
<td>Chemo (investigators choice): paclitaxel, topotecan or PLD alone +BV 15 mg/kg q3w</td>
<td>75%</td>
<td>22.5 months*</td>
<td>20.4 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>46.1%</td>
<td>16.5 months</td>
<td>13.7 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>37%</td>
<td>20.9 months</td>
<td>13.6 months</td>
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<td></td>
<td></td>
<td></td>
<td>27%</td>
<td>20.9 months</td>
<td>13.6 months</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Recurrent, platinum-refractory EOC PPC</td>
<td>BV 15 mg/kg q3w</td>
<td>21%</td>
<td>4.7 months</td>
<td>17 months</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Platinum-resistant EOC PSC</td>
<td>BV 15 mg/kg q3w</td>
<td>15.9%</td>
<td>4.4 months</td>
<td>10.7 months</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Recurrent, platinum-refractory EOC PPC</td>
<td>Metronomic cyclophosphamide + BV 10 mg/kg q2w</td>
<td>24%</td>
<td>7.2 months (TTP)</td>
<td>16.9 months</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;13&lt;/sup&gt;</td>
<td>First-line/adjuvant therapy of ROC or PSMC</td>
<td>Carboplatin/paclitaxel + BV 15 mg/ml q3w</td>
<td>75%</td>
<td>29.8 months</td>
<td>NR</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Recurrent, platinum-resistant EOC PPC</td>
<td>nab-paclitaxel + BV 15 mg/ml q2w</td>
<td>46.1%</td>
<td>8.3 months</td>
<td>16.5 months</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Recurrent ROC</td>
<td>Paclitaxel + AMG 386 10 mg/kg qw AMG 386 3 mg/kg qw PL qw</td>
<td>37%</td>
<td>7.2 months*</td>
<td>22.5 months*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19%</td>
<td>5.7 months</td>
<td>20.4 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>27%</td>
<td>4.6 months</td>
<td>20.9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(P = .225)*</td>
<td>(P = .081)*</td>
<td>(P = .51)</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Relapsed ROC</td>
<td>BIBF 1120 250 mg twice daily or PL 250 mg twice daily</td>
<td>16.3%</td>
<td>16.3%</td>
<td>16.3%</td>
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<tr>
<td></td>
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<td></td>
<td>5% (PFS rate at 36 wks, P = .06)</td>
<td>5% (PFS rate at 36 wks, P = .06)</td>
<td>5% (PFS rate at 36 wks, P = .06)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(P = .51)</td>
<td>(P = .51)</td>
<td>(P = .51)</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Recurrent ROC</td>
<td>Pazopanib 800 mg daily to PD</td>
<td>4%</td>
<td>18%</td>
<td>4%</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Platinum-resistant ROC</td>
<td>Sunitinib 50 mg daily 4 of 6 weeks, or Sunitinib 37.5 mg daily continuously</td>
<td>16.7%</td>
<td>4.8 months</td>
<td>13.6 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5.4%</td>
<td>2.9 months</td>
<td>13.7 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(P &gt; .11)</td>
<td>13.6 months</td>
<td>13.7 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(P = 3048)</td>
<td>(P = .8380)</td>
<td>(P = .8380)</td>
</tr>
<tr>
<td>Phase 2&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Recurrent, platinum-Resistant ROC with malignant ascites</td>
<td>Aflibercept 4 mg/kg q2w</td>
<td>59.5 days</td>
<td>92 days</td>
<td></td>
</tr>
</tbody>
</table>

**ORR**, objective response rate; **mPFS**, median progression-free survival; **mOS**, median overall survival; **ROC**, epithelial ovarian, primary peritoneal and fallopian tube cancer; **PL**, placebo; **BV**, bevacizumab; **NR**, not reported/reached; **PD**, progressive disease; **PLD**, pegylated liposomal doxorubicin; **EOC**, epithelial ovarian cancer; **PSC**, peritoneal serous cancer; **PPC**, primary peritoneal cancer; **PSMC**, papillary serous mullerian carcinoma;

* as compared with the control group

**data not yet mature
Congestive heart failure (CHF) has been reported sporadically in clinical trials of BV for advanced solid tumors. Both the GOG 0218 and the ICON7 randomized trials found that the incidence of CHF in BV-treated patients was very low. Some patients, however, suffered CHF in trials of multitargeted angiogenic inhibitors in multiple disease settings. Findings of large randomized trials of pazopanib and sunitinib in renal cell carcinoma demonstrated treatment-emergent declines in left ventricular ejection fraction (LVEF). A phase 3 trial of sunitinib in pNET found that 2% of sunitinib-treated patients had cardiac failure leading to death. The prescribing information for pazopanib and sunitinib recommends discontinuation of treatment upon clinical manifestation of CHF and dose reduction for patients with a decline in LVEF from baseline. Phase 2 trials of both sunitinib and pazopanib in ovarian cancer reported no incidence of any-grade CHF.

Bleeding events linked to VEGF-inhibition have been widely reported in clinical trials. Across indications, the incidence of grade ≥ 3 hemorrhagic events in BV-treated patients ranged from 1.2% to 4.6%. Bleeding events are linked to sites of tumor growth; serious pulmonary hemorrhage occurred in 31% of BV-treated patients with non-squamous non-small cell lung cancer, and intracranial hemorrhage occurred in 5% of BV-treated glioblastoma patients. The GOG, ICON7 and OCEANS phase 3 trials in ovarian cancer indicate that BV treatment is associated with a higher incidence of grade ≥ 3 bleeding in this patient population (1.9%, < 1%, and 6.5%, respectively). Fatal bleeding events have been reported for sunitinib and pazopanib (1%) in large clinical trials. Antiangiogenic treatment with BV, sunitinib or pazopanib is not recommended for patients with a recent history of hemoptysis, and discontinuation of therapy is necessary for patients after a bleeding event.

Bowel perforation is an unusual but potentially life-threatening complication of VEGF inhibition and appears to be slightly more prevalent among ovarian cancer patients than other tumor types. Variable rates of bowel perforation have been reported for studies of BV for recurrent ovarian cancer. A study of single-agent BV in recurrent ovarian cancer found a rate of GI bowel perforation of 11.4% (five of 44), which led to early study closure. All five patients had radiographic evidence of bowel involvement in disease at study initiation. Phase 3 trials of BV in patients with ovarian cancer have not produced similar rates of bowel perforation. GOG 0218 reported a rate of 5.4% for all grade ≥ 2 GI events, which included perforation, fistula, necrosis or anastomotic leak. Rates of GI perforation in BV-treated patients reported for the ICON7 and OCEANS trials were 1% and 0, respectively.

A retrospective review of 82 patients with recurrent epithelial ovarian cancer treated with BV at a single institution between 2006 and 2009 identified bowel perforation in 8 patients (9.8%). Among these cases, a history of bowel surgeries (87.5% versus 24.3%; \( P = .0008 \)) and the presence of symptoms of bowel obstruction (100% versus 18.9%; \( P = .0001 \)) were markedly higher in women who developed this complication than in those who did not. A separate retroplysis identified 4 incidents cases of GI bowel perforations (7%) in 62 BV-treated patients, with all occurring in patients with large intra-abdominal tumor burdens who responded to BV treatment.

While the precise mechanisms remain unclear, one hypothesis posits that tumor necrosis and regression coupled with impairment of healing mechanisms during angiogenesis inhibition may weaken segments of the bowel wall already compromised by tumor and obstruction. Patients with bowel involvement by tumor, bowel obstruction, and who have undergone heavy pretreatment (≥ 3 prior regimens) with cytotoxic chemotheraphy may be particularly susceptible to bowel perforation during antiangiogenic therapy.

Proteinuria is one of the most common side effects of anti-VEGF therapy. Rates of grade ≥ 3 proteinuria reported for BV-treated patients in phase 3 trials of advanced ovarian cancer ranged from 1% to 8.5%. Although the precise mechanisms are not fully understood, renal toxicity and proteinuria during anti-VEGF therapy may be the result of dysfunction of the glomerular endothelium and localized thrombotic microangiopathy related to disruption in VEGF supply. These effects appear to be primarily transient, since renal function and proteinuria usually improve when antiangiogenic therapy is withdrawn.

Future Directions

A number of published clinical studies have now validated the role of antiangiogenic therapeutics in the management of advanced ovarian cancer. Both GOG 0218 and ICON7 established that the addition of BV to first-line standard chemotherapy improves PFS in this tumor type. Ongoing studies such as GOG 0252 are exploring whether adding BV to different routes and schedules for administering standard cytotoxic chemotherapy (for example, I.P. and dosedense chemotherapy) can build upon improvements in both disease free and overall survival. Future clinical evaluation of BV should include defining the optimal duration of BV therapy, both pre- and post-progression, and assessing the efficacy and safety monotherapy with an anti-VEGF agent between chemotherapy courses. As new agents representing different components of angiogenesis undergo clinical development, optimal sequencing of agents in the treatment of ovarian cancer must be evaluated. The identification of clinically validated biomarkers will aid in stratifying patients based on their likelihood to respond to angiogenesis inhibitors as well as direct treatment decision across multiple lines of therapy.


Three critical needs have been identified by the Angiogenesis Foundation in regards to ovarian cancer. There is a large amount of new information emerging on ovarian cancer therapies and clinicians do not have enough time to adequately review all of this important information in this rapidly expanding field. Clinicians are not educating patients about the side effects of antiangiogenic therapy and referring patients to specialists to optimize management of side effects and increasing patient outcomes. There are many clinical trials out there researching several new targeted therapies, providing clinicians with this updated information will help increase enrollment in these clinical trials and can lead to an increase in the number of treatment options with fewer side effects.

New treatment approaches are therefore urgently required to improve outcome in this disease and one promising strategy to have emerged has been the study of angiogenesis in ovarian cancer and the role of modulators of angiogenesis in its treatment.

PROGRAM LEARNING OBJECTIVES At the completion of this activity, participants should be able to:

- Describe the role of tumor angiogenesis as both a disease mechanism and therapeutic target in ovarian cancer.
- Explain optimizing combinatorial agent treatment strategies.
- Interpret the outcome data from recent well-designed scientific and clinical studies of protocols studying new-targeted therapies.
- Integrate adverse events management into new therapy settings.
- Assess treatment options, efficacy data, and side effects with members of the cancer treatment team, as well as cancer patients and their family members.

METHOD OF PARTICIPATION

There are no fees for participating in and receiving credit for this online educational activity. The participant should, in order, read the objectives and faculty disclosures, review the educational content, answer the multiple-choice post-test and complete the evaluation. This program is available in PDF format accessible from the Angiogenesis Foundation’s website (http://www.angio.org) in the CME section. A print version is also available; for more information contact outreach@angio.org.

After reviewing the material, CME credits are available through the Angiogenesis Foundation’s website (http://www.cmeonline.org) by selecting the name of the program (registration required). Course code: 2012OVARIAN

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COURSE FACULTY

William Li, MD
Dartmouth Medical College

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William W. Li, M.D., President, the Angiogenesis Foundation, Editor-in-Chief
Dr. Li has no relevant financial relationships to disclose.

Erin Grothey, M.S.
Medical Writer, the Angiogenesis Foundation
Medical Writer has no relevant financial relationships to disclose. Erin Grothey’s spouse received grant/research support from Genentech and Eli Lilly and Company.

DISCUSSION OF UNLABELLED USE

This CME activity contains discussion of published and/or investigational use of: aflibercept, AMG 386, bevacizumab, BIBF 1120, EMNDD 2076, IMC-3G3, MK-2206, pazopanib, sunitinib, and TRC-105

TOPICS AND EDUCATIONAL CONTENT

Antiangiogenic therapy for locally advanced ovarian cancer:

- Mechanisms of action and rationale for antiangiogenic agents for ovarian cancer treatment
- Small molecule angiogenesis inhibitors
- Other investigational treatment strategies
- Side effects
- Conclusions and future directions

SYSTEM REQUIREMENTS

This educational program is available in PDF format. To view and print PDF files, you must have Adobe Reader installed on your computer. Most computers already have this software installed. If yours does not, you can download Adobe Reader free from the Adobe Web site: http://www.adobe.com.

For questions about this program, please contact the Angiogenesis Foundation at 617-401-2779 or outreach@angio.org.