NIH Public Access
Author Manuscript
Clin Breast Cancer. Author manuscript; available in PMC 2012 October 15.

Published in final edited form as:
Clin Breast Cancer. 2010 ; 10(Suppl 1): E23–E31. doi:10.3816/CBC.2010.s.004.

Antiangiogenic Therapies in Early-Stage Breast Cancer

Christina Derleth and **Ingrid A. Mayer**
Department of Medicine and Breast Cancer Research Program, Vanderbilt-Ingram Comprehensive Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

Abstract

Angiogenesis, which is crucial for the growth and spread of cancer cells, has become an important target for antineoplastic therapies in a variety of malignant tumors. Vascular endothelial growth factor and its receptor promote formation of new blood vessels in tumors. Several drugs, most notably the monoclonal antibody bevacizumab, have been developed to inhibit this process. Clinical trials utilizing bevacizumab and other antiangiogenic drugs in metastatic breast cancer have demonstrated enhanced response rates and prolonged progression-free survival, though no overall survival benefit has been seen. Trials are now under way exploring the use of antiangiogenic agents in patients with early stage breast cancer. We performed a comprehensive review of the published literature (English language), US National Institutes of Health clinical trials registry (ClinicalTrials.gov), and established cooperative groups that revealed approximately 75 clinical trials, completed or ongoing, utilizing antiangiogenic drugs in early-stage breast cancer. A number of phase II trials in the neoadjuvant setting have reported preliminary results suggesting response rates similar to those seen with traditional anthracycline-plus-taxane combination regimens. Most of these early trials have not yet met any survival endpoints. Studies are also ongoing in the adjuvant setting, and these have not yet been reported. The toxicities associated with these agents are similar to those that have been reported in the metastatic trials. Most of these side effects are grade 1 or 2 and are easily manageable; however, there remain a small percentage of patients who sustain life-threatening vascular events, bleeding, or wound-healing complications. This number is significantly higher in patients receiving antiangiogenic drugs when compared with controls. While we eagerly await completion and results of this impressive portfolio of studies in early breast cancer with antiangiogenic agents, there is an urgent need for a more rational patient/antiangiogenic therapy selection with greater insight into predictive factors for toxicities, therapy efficacy, and clinical benefit.

Keywords

Angiogenesis; Bevacizumab; Cyclophosphamide; Docetaxel; Neoadjuvant therapy; Paclitaxel

Address for correspondence: Ingrid Mayer, MD, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, 2220 Pierce Avenue, 777 Preston Research Building, Nashville, TN 37232, Fax: 615-343-7602; ingrid.mayer@vanderbilt.edu.

Dr. Derleth has no relevant relationships to disclose.
Dr. Mayer has no relevant relationships to disclose.
This article includes discussion of investigational and/or unlabeled uses of drugs, including the use of bevacizumab in combination with paclitaxel for the treatment of patients with early-stage breast cancer; and sorafenib or bevacizumab monotherapy or in combination with vinorelbine, docetaxel, docetaxel/doxorubicin, docetaxel/trastuzumab, capecitabine, gemcitabine, albumin-bound paclitaxel, letrozole, trastuzumab, lapatinib, carboplatin, cisplatin, doxorubicin/cyclophosphamide, cyclophosphamide/methotrexate, or epirubicin/cyclophosphamide for the treatment of patients with breast cancer.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Introduction

Angiogenesis, the formation and growth of new blood vessels, is crucial for the growth and spread of cancer cells.[1] As a result, angiogenesis has become an important target for antineoplastic therapies in a variety of malignant tumors. Angiogenesis requires stimulation of vascular endothelial cells through the release of angiogenic peptides, of which vascular endothelial growth factor (VEGF) is the most potent. The VEGF/VEGF receptor (VEGFR) complex involves several ligands (VEGF-A, the parent ligand, and VEGF-B, -C, -D, and -E, as well as placental growth factor) and their associated receptors (VEGFR-1/FLT-1, VEGFR-2/KDR, VEGFR-3/FLT-4, and neuropilin-1 and -2).[2] VEGF-A, the single most important angiogenic cytokine, is widely expressed by tumor cells and is central in angiogenesis and tumor progression.[3] The biologic effects of VEGF are mediated through binding to 1 of 3 endothelial surface receptors: VEGFR-1 (FLT-1), VEGFR-2 (FLK-1/KDR), and VEGFR-3; binding to the coreceptor neuropilin enhances signaling.[2] VEGFR activation leads to endothelial cell mitogenesis and migration; induction of proteinases, leading to remodeling of the extracellular matrix; increased vascular permeability and vasodilation; immune modulation via inhibition of antigen-presenting dendritic cells, and maintenance of survival for newly formed blood vessels by inhibiting endothelial cell apoptosis.[2]

Vascular endothelial growth factor is expressed by most tumor types, including breast cancer.[4] In recent years, substantial laboratory and indirect clinical evidence has accumulated to support the central role of angiogenesis in breast cancer development, invasion, and metastasis.[5] Clinical evidence suggests that high microvessel density in premalignant lesions is associated with an increased risk of invasive breast cancer and subsequent relapse.[6] Several studies have found an inverse correlation between VEGF expression and overall survival (OS) in both node-positive and node-negative breast cancer.[7–9] Increased VEGF expression has also been associated with impaired response to tamoxifen or chemotherapy in patients with advanced breast cancer.[10] HER2 gene amplification has been associated with increased VEGF production in breast cancers.[11–15] Treatment of breast cancer cells with the HER2 antibody 4D5 reduces VEGF production,[14] suggesting that HER2 is causally associated with expression and secretion of the angiogenic factor. Vascular endothelial growth factor expression can be quantified via immunohistochemistry in breast cancer tumor specimens, and both expression and intensity of expression were found to correlate with a significantly inferior outcome of breast cancer.[16]

Among the commercially available antiangiogenic agents, bevacizumab (rhuMAb VEGF, Avastin™; Genentech, Inc.; South San Francisco, CA) is the most established in the treatment of breast cancer. Bevacizumab is a humanized monoclonal antibody directed against the VEGF-A ligand and was shown to inhibit the growth of several human tumors in animal models.[17,18] A phase I trial confirmed the safety of bevacizumab and found the expected decrease in circulating VEGF levels.[19] In combination with chemotherapy, bevacizumab appears to be synergistic in terms of normalizing mature microvasculature.[20] Combination therapy can also prevent the regrowth of tumor microvasculature, which might account for extended time to tumor progression that has been observed when compared with chemotherapy alone. Bevacizumab is approved in combination with chemotherapy by the US Food and Drug Administration (FDA) for the first-line treatment of newly diagnosed and relapsed/refractory metastatic colorectal cancer, first-line treatment of advanced nonsquamous non–small-cell lung cancer, metastatic renal cell carcinoma, and metastatic breast cancer (MBC) and as a single agent in glioblastoma. A dual-institution phase II study of single-agent bevacizumab in patients with previously treated MBC showed that 17% of patients had a response or stable disease at 22 weeks; 4 patients continued therapy without

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

progression for over 12 months.[21] Congestive heart failure was reported in 2 of 75 patients (2.7%) enrolled in the phase II study of bevacizumab monotherapy. Both had had previous anthracycline treatment and left chest wall radiation; 1 had concurrent pericardial involvement with metastatic disease.[21,22] Phase II trials also combined bevacizumab with a variety of other agents including vinorelbine[23] and docetaxel[24] in the refractory metastatic setting.

Given the efficacy and limited toxicity, a phase III study (AVF2119g) randomized 462 patients with anthracycline- and taxane-refractory disease to receive capecitabine with or without bevacizumab.[25] Bevacizumab induced hypertension, proteinuria, and minor mucosal bleeding, but these toxicities were rarely severe. Combination therapy significantly increased response rate; nevertheless, progression-free survival (PFS; primary endpoint) was similar in both groups. Seven patients (3.1%) receiving capecitabine plus bevacizumab developed clinically significant congestive heart failure. Cardiac dysfunction has not been reported in bevacizumab-treated patients without previous anthracycline exposure. Though a negative trial, the initial phase III randomized trial represented an important proof of concept.

E2100, a phase III trial that randomized patients to receive weekly paclitaxel with or without bevacizumab as first-line chemotherapy for HER2-negative MBC, enrolled 722 patients.[26] There was a significant improvement in the median PFS from 5.9 months to 11.8 months (hazard ratio [HR], 0.60; 95% CI, 0.51–0.70; $P < .0001$). Furthermore, the addition of bevacizumab to weekly paclitaxel doubled the objective response rate from 25.2% to 49.2% in patients with measurable disease and from 21.2% to 36.9% in all eligible patients. Of note, in subgroup analysis even patients who had previously been treated with taxane therapy benefited from combination treatment with bevacizumab and paclitaxel (HR, 0.46; 95% CI, 0.30–0.71).[26] The most common grade 3 toxicity encountered in the combination arm was hypertension in 15% of patients. Less than 5% of patients experienced grade 3 thromboembolic events, bleeding, or proteinuria. Unfortunately, there was no statistically significant difference in OS. Nevertheless, the results of E2100 lead to the FDA approval of bevacizumab in combination with paclitaxel in the first-line treatment of HER2-negative MBC.[26] AVADO (Avastin and Docetaxel in Metastatic Breast Cancer) was another phase III trial that reported a 2-month improvement in PFS (HR, 0.77; $P = .0061$) with the combination of docetaxel plus bevacizumab in the first-line treatment of MBC.[27] Once again, no difference in OS was seen. Two additional randomized, phase III, placebo-controlled trials, RIBBON-1 and RIBBON-2, are evaluating different chemotherapies in combination with bevacizumab or placebo as first-line treatment (RIBBON-1) or second-line treatment (RIBBON-2) for MBC. RIBBON-1 has completed accrual and evaluated capecitabine, taxane (docetaxel or nanoparticle albumin-bound paclitaxel), or anthracycline-based chemotherapy, determined by physician choice, in combination with either placebo or bevacizumab. Preliminary results demonstrated a prolongation in PFS in all chemotherapy arms combined with bevacizumab. This study has not yet reached 50% of events for its OS analysis.[28] RIBBON-2 evaluated the addition of bevacizumab to different chemotherapy regimens used as second-line treatment for patients with MBC and no previous bevacizumab exposure.[29] In contrast to the AVF2119g study, RIBBON-2 met its primary endpoint of PFS advantage (HR, 0.78; $P = .0072$), but without overall response rate or survival differences seen between the different combination arms of the trial (Table 1).[26–29]

Bevacizumab has also been combined with endocrine therapies. It is known that cyclical neovascularization of the female reproductive tract in premenopausal women is controlled by estrogen. Specifically, preclinical models have demonstrated that estrogen induces endothelial cell proliferation and migration and that estrogen-induced angiogenesis is mediated by VEGF.[30–32] Based on these preclinical results, a phase II feasibility study was

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

performed evaluating the combination of letrozole and bevacizumab. The objective response rate was only 7% (all partial responses [PRs]) for the combination; however, 67% of the patients on the trial had stable disease (SD) for more than 6 months.[33]

Preclinical data supports the use of bevacizumab in combination with trastuzumab in HER2-overexpressing breast cancers. Exposure to trastuzumab significantly decreased VEGF in HER2-overexpressing cells.[34] In vivo experiments have demonstrated reduction in xenograft volume using a combination of trastuzumab and bevacizumab compared with single-agent control.[34] Phase I data suggested that trastuzumab and bevacizumab could be combined relatively safely, and that in at least 1 patient who had progressed on previous trastuzumab, a response was observed.[35] Preliminary results of a phase II study combining trastuzumab and bevacizumab as first-line therapy for MBC evaluated 37 out of a planned 50 patients for response assessment.[36] Of those, 1 patient had a complete response (CR; 2.7%), 19 had a PR (54.1%), 11 had SD (29.7%), and 6 had progressive disease (16.2%). Thirteen patients in this trial developed decreased left ventricular ejection fraction (LVEF), most patients with grade 1 cardiac toxicity and 1 patient with severe congestive heart failure. Whether these patients had received previous anthracycline therapy is not known, and no additional follow-up on the outcome of this trial has been reported. Eastern Cooperative Oncology Group 1105 is a phase III trial that randomized women with untreated HER2-positive MBC to treatment with paclitaxel, carboplatin (optional), and trastuzumab with or without bevacizumab to determine the additional benefit of bevacizumab. GlaxoSmithKline has subsequently conducted a phase II trial combining lapatinib and bevacizumab in patients with advanced or metastatic HER2-positive breast cancer. The results of these trials have not yet been published. In total, there are more than 50 ongoing or completed clinical trials evaluating bevacizumab in combination with other agents under a variety of circumstances in MBC.

A number of additional agents have been developed to target tumor angiogenesis. Antibodies such as ramucirumab, IMC-18F1, and aflibercept, and small molecules including sunitinib, sorafenib, vatalanib (PTK787), pazopanib, vandetanib (ZD6474), motesanib (AMG 706), cediranib (AZD2171), and semaxanib (SU5416) target the VEGF/VEGFR signaling pathway and other related receptor tyrosine kinases.[37–46] Certain newer drugs, including AMG 386, recombinant human endostatin, recombinant human interleukin-12, and tetrathiomolybdate (ATN-224), target angiogenesis via alternative mechanisms.[47–50] Several of these antiangiogenic agents are being studied in the treatment of breast cancer. Sorafenib is an orally administered multikinase inhibitor that inhibits VEGFR and the Raf kinase, the latter of which mediates cell growth and proliferation. Two phase II randomized trials utilizing sorafenib in combination with chemotherapy have recently been reported. The first examined capecitabine with or without sorafenib for the first- or second-line treatment of HER2-negative MBC[51] and demonstrated an improvement in PFS with the addition of sorafenib, albeit at the expense of significant increase in hand-foot syndrome toxicity. The second was a randomized trial combining paclitaxel with sorafenib or placebo as first-line therapy for HER2-negative MBC, in which the addition of sorafenib improved median time to progression and response rate, but not PFS. A 10-fold increase in hand-foot syndrome was seen in the sorafenib group.[52]

Targeting Angiogenesis in Early-Stage Breast Cancer

Angiogenic pathways become more numerous and redundant as breast cancers progress.[53,54] Given such redundancy, it is unlikely that inhibition of a single factor or pathway would produce a sustained clinical effect in patients with previously treated, highly refractory disease. This suggests that earlier initiation of antiangiogenic intervention may be beneficial[55] in those patients who are likely to benefit from angiogenesis inhibition.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

The presumed mechanisms of action of bevacizumab include the increased delivery of cytotoxic drugs into tumors by decreasing intratumoral pressure and normalizing dysfunctional vasculature, and antiangiogenesis by direct action on endothelial cells. Whether these proposed mechanisms play a substantial role in the eradication of micrometastasis is questionable (ie, by definition, micrometastasis is characterized by the absence of supporting blood vessels and clearly does not show increased intratumoral pressure). Nevertheless, in primary human breast cancer, VEGF has been identified as the most abundant of more than 6 vascular growth factors that have been evaluated.[53] VEGF is produced early in breast tumor development and is highly expressed in ductal carcinoma in situ.[56] The correlation between VEGF expression and microvessel density in patients with intermediate- and high-grade ductal carcinoma in situ suggests that angiogenesis occurs before significant fibroblastic stromagenesis in pre-invasive breast lesions.[57] Recent preclinical results support a role for cancer stem cells in the angiogenic drive and the mechanism of antiangiogenic agents.[58] In view of their potent tumorigenic properties, cancer stem cells are more likely to be angiogenesis-dependent, and thus more susceptible to the effects of antiangiogenic agents. Based on these considerations, it is conceivable that the addition of antiangiogenic agents to conventional adjuvant chemotherapy might not lead to increased eradication of micrometastatic tumor cells, but could prevent the formation of macrometastasis, as long as bevacizumab is continued. In this case, an effect on disease-free survival (DFS), but not long-term OS, might be observed in clinical trials.

Many studies are currently evaluating bevacizumab in both the neoadjuvant and adjuvant setting. A comprehensive review of the published literature (English language), US National Institutes of Health clinical trials registry (ClinicalTrials.gov), and established cooperative groups revealed approximately 75 clinical trials, completed or ongoing, utilizing bevacizumab in early-stage breast cancer.

Neoadjuvant Trials

In the past 2 decades, neoadjuvant chemotherapy has become more popular in patients with operable disease in need of chemotherapy.[59] According to National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 results, neoadjuvant chemotherapy yields a survival outcome similar to that obtained with the adjuvant treatment in early breast cancer patients, and allows a significantly higher rate of breast conservation surgery.[60] In addition, it allows the possibility of quickly evaluating treatment activity in vivo. Indeed, the documentation of a pathologic CR (pCR) in the breast and axillary contents at the time of definitive surgery represents a good predictor of long-term survival and cure.[60] Numerous chemotherapy regimens have been tested in the neoadjuvant setting, in which the majority of the regimens tested were based on anthracyclines.[61] Nevertheless, there is evidence in favor of the addition of taxanes in the neoadjuvant setting,[61–63] because taxanes add substantial efficacy to adjuvant chemotherapy. Taxanes are being increasingly used for patients with node-positive breast cancer, with rates of pCR that roughly range from 20% to 30% for non–trastuzumab-containing regimens.[64]

Several pilot and phase II studies utilizing bevacizumab for neoadjuvant treatment of breast cancer have been conducted and reported (Table 2).[65–71] Most of the completed trials were performed in patients with stage II–III, and/or inflammatory, HER2-negative breast cancer, albeit a few were geared toward patients with HER2-positive disease. Wedam et al conducted a single-arm pilot study in which patients with inflammatory or locally-advanced breast cancer received bevacizumab alone, then in combination with chemotherapy (doxorubicin and docetaxel).[72] Of the 21 patients enrolled, 14 patients had a PR, 5 had SD, and 2 progressed on treatment. They observed that the levels of phosphorylated-VEGFR-2 (Y951 and Y996) decreased significantly in patients who achieved a PR or SD, whereas

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

these levels remained high in the 2 patients who progressed on therapy. Also seen, was a significant increase in tumor apoptosis, which persisted with the addition of chemotherapy.

Overall, the addition of bevacizumab to a variety of chemotherapy regimens in the neoadjuvant setting was well tolerated, with an acceptable toxicity profile despite a slight increase in the rates of leukopenia, hypertension, thromboembolic events, and wound complications postoperatively (including infection). A recent report by Golshan et al evaluated the surgical complications of 2 neoadjuvant trials conducted at the Dana-Farber Cancer Institute.[73] Fifty-one patients were treated on a neoadjuvant phase II trial of cisplatin and bevacizumab for stage II–III triple-negative breast cancer. Postoperative complications were reported in 22 patients (43%): 4 patients (8%) required wound debridement and removal of expanders, 8 patients (16%) sustained wound breakdowns, 5 patients (10%) developed hematomas requiring operative intervention, and 5 patients (10%) developed seromas requiring multiple aspirations. In contrast, 28 patients completed neoadjuvant cisplatin single-agent therapy, where postoperative complications were reported in 11 patients (39%): 5 seromas requiring drainage (18%), 2 hematomas (7%), 2 abscesses (7%), and 2 wound breakdowns (7%). No reconstructions were lost, including the 3 expanders and 2 TRAM flaps. Overall, a significant number of postoperative complications were seen in both trials, but the rates of complications between them were not statistically significant. Nevertheless, the use of expanders or implants were problematic for patients treated with bevacizumab, with a trend toward more wound-related events for this group.

Regarding efficacy, the addition of bevacizumab to a variety of chemotherapy regimens yielded rates of pCR ranging from 9% to 33% in patients with HER2-negative breast cancer, and 53%–65% in patients with HER2-positive breast cancer that received chemotherapy, trastuzumab, and bevacizumab as their neoadjuvant treatment (Table 2). These rates of pCR overall do not seem substantially different from the ones seen with anthracycline/taxane chemotherapy regimens with or without trastuzumab.

Table 3 shows ongoing clinical trials with antiangiogenic therapies in the neoadjuvant setting, in which combinations of antiangiogenic agents with endocrine, chemotherapy, or HER2-based regimens are being explored. Studies conducted in the neoadjuvant setting provide a great opportunity to develop insights into the biologic basis for the efficacy of antiangiogenic agents. Reliable immediate endpoints that allow for more rapid evaluation of the potential benefit of antiangiogenic-containing combinations are needed. Several of the ongoing trials include biomarker or tissue correlative studies that will hopefully provide new tools for predicting response to these agents.

Adjuvant Trials

Eastern Cooperative Oncology Group E2104 was a 2-arm non-randomized phase II trial designed to evaluate the safety of incorporating bevacizumab into an anthracycline-containing adjuvant therapy.[74] In addition to dose-dense doxorubicin and cyclophosphamide followed by paclitaxel (ddAC → T), all patients received bevacizumab (10 mg/kg every 2 weeks × 26) either initiated concurrently with AC (arm A: ddBAC → BT → B) or initiated concurrently with paclitaxel (arm B: ddAC → BT → B). The primary endpoint of the trial was the incidence of clinically apparent cardiac dysfunction (CHF). A total of 226 patients were enrolled: 11% experienced grade 3 hypertension, 2% had thrombosis, 1% developed proteinuria, and < 1% sustained a hemorrhage. One patient developed grade 4 cerebrovascular ischemia. Clinical CHF was reported in 2 patients in arm A after cycles 4 and 6; 4 patients had asymptomatic declines in LVEF to < 40% after 4 (n = 1) and 16 cycles (n = 3). Two patients in arm B were reported to have clinical CHF because of diastolic dysfunction (both associated with a decline in LVEF to 40%–50%) after 4 and 9 cycles; 1 patient had asymptomatic decline in LVEF to < 40% after 8 cycles. The authors concluded

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

that the anthracycline-based chemotherapy/bevacizumab combination was overall safe and feasible; hence, a large adjuvant trial named E5103 was activated. E5103 randomizes patients to 1 of 3 arms: arm A will receive anthracycline and taxane-based therapy; arm B will receive this same chemotherapy with concurrent bevacizumab; and arm C will have the same chemotherapy with concurrent bevacizumab and an additional 6 months of maintenance therapy with bevacizumab. A number of other phase II and III clinical trials were launched in the adjuvant setting for patients with HER2-negative and HER2-positive stages II and III breast cancer (Table 4), exploring different combinations of chemotherapy and variable durations of antiangiogenic therapy, aiming for improvement in DFS.

Long-term follow-up of neoadjuvant studies consistently demonstrates significantly improved survival in individuals with pCR, with comparatively inferior outcomes in those with residual disease at surgery.[61–63] Outcomes in the triple-negative breast cancer population tend to be worse, with a rate of distant DFS of 70% at 4 years.[75] It is thought that after receiving an appropriate neoadjuvant regimen, the presence of viable tumor tissue reflects inherent resistance of the tumor to further cytotoxic therapy. Currently, no standard therapy exists in this clinical setting, and there is significant interest in exploring novel biologic therapy as an alternative approach. Dana-Farber Cancer Institute conducted a phase II pilot study exploring a combination of chemotherapy plus anti-angiogenic treatment postoperatively in this patient population.[76] Eighty-one patients with stage II–III breast cancer with residual invasive carcinoma at surgery following anthracycline-containing neoadjuvant chemotherapy received treatment consisting of bevacizumab for 1 year, starting no less than 1 month after surgery or 2 weeks after radiation. Sequential cohorts also received concurrent chemotherapy, either metronomic chemotherapy (cyclophosphamide 50 mg orally daily, and methotrexate 2.5 mg orally days 1 and 2 each week for a total of 6 months), or capecitabine 2000 mg/m^2/day 14 days on/7 days off for 18 weeks. Concurrent endocrine and/or trastuzumab therapy was allowed. At a median on-study follow-up of 7.5 months, 6 patients (7%) had tumor recurrence. Treatment-related toxicities included fatigue (41%), headache (32%), arthralgia (31%), and hypertension (23%). Preliminary analysis suggested that the combination of bevacizumab and metronomic chemotherapy had a more favorable side effect profile, as the combination of capecitabine and bevacizumab led to more diarrhea, hand-foot syndrome, and grade 3/4 toxicity. Nine patients came off of study for toxicity, including 1 patient with heart failure. The planned ABCDE trial (A Phase III Randomized Study of Adjuvant Bevacizumab, Metronomic Chemotherapy, Diet and Exercise after Preoperative Chemotherapy for Breast Cancer) intends to explore the role of antiangiogenic therapy using bevacizumab combined with metronomic cyclophosphamide/methotrexate for 6 months in patients with residual disease after neoadjuvant chemotherapy. Of particular note, single-agent bevacizumab will be continued for a total of 3 years, whereas most other trials have only continued antiangiogenic therapies for up to 1 year. Presumably, this decision was based on the recently presented results of NSABP C-08 (FOLFOX6 with or without bevacizumab for up to 1 year in patients with stage II and III high-risk colon cancer), in which the DFS curves for the control and bevacizumab-containing arms come together after 30 months.[77] ABCDE aims to determine, in a randomized phase III design, the efficacy of these treatments. All patients will also be randomized to 1 of 2 lifestyle interventions to explore the effect of changes in diet and exercise on relevant biomarkers in a breast cancer survivor population. Given the lack of standard options in this clinical setting, it is hoped that the proposed novel biologic therapy will improve breast cancer outcomes in this high-risk patient population.

Discussion

Among a growing arsenal of antiangiogenic agents, bevacizumab remains the most established in the treatment of breast cancer. Despite encouraging results in the metastatic

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

setting, we need to better understand which tumor phenotypes are most sensitive to angiogenic inhibition. Unfortunately, most markers that have shown encouraging results in animal models have not correlated with therapeutic response or resistance in humans. Interestingly, multiple studies suggest that bevacizumab-induced hypertension may be an indicator of increased clinical benefit. Unfortunately, the median time of onset to hypertension is 3 months, making this a difficult marker for response to bevacizumab, particularly in the neoadjuvant setting.[78–80] Recently, genetic variability in VEGF has been studied as a potential predictive biomarker for bevacizumab. The VEGF-1154 AA and -2578 AA genotypes predicted improved median OS, whereas the VEGF-634 CC and -1498 TT genotypes predicted protection from grade 3–4 hypertension in the E2100 trial.[81] If validated, these finding could help direct which subgroup of patients should receive bevacizumab.

The toxicities associated with antiangiogenic therapies, though they compare favorably to chemotherapy in the metastatic setting, have potential serious and/or long-term effects that may be unacceptable in patients with curable diseases. Nearly every study conducted utilizing bevacizumab has described at least 1 serious adverse event related to wound healing, bleeding, or an acute vascular event,[21,25,26,65,82,83] which is particularly relevant to patients receiving antiangiogenic agents in the neoadjuvant setting. Miller et al describe a statistically significant increase in the rate of cerebrovascular ischemia in patients receiving the combination of bevacizumab and paclitaxel (1.9% vs. 0; $P = .02$).[26] Hypertension and proteinuria, though generally mild (grade 1–3), are relatively common.[25,26,82,83] A recent meta-analysis (7 randomized control trials, > 1800 patients) reported a hypertension incidence of 17.6%–36% in the bevacizumab arm in comparison with 1.7% of the non-bevacizumab control arm[78,84,85]; 1 clinical study reported a median time to hypertension onset of 131 days from first treatment.[86] Another meta-analysis (5 randomized control trials, > 1700 patients) reported increased incidence of arterial thromboembolic events (3.8% vs. 1.7%),[87] and a third meta-analysis (15 randomized control trials and almost 8000 patients) reporting a venous thromboembolic events risk of 33% in the bevacizumab arms.[88] It is not yet established whether there are lasting effects on the vasculature and what the implications may be for long-term cancer survivors who receive antiangiogenic agents. With that in mind, we have recently initiated a prospective clinical trial to assess how changes in endothelial function measures (noninvasive finger pulse wave analysis [EndoPAT], and biomarkers such as serum VEGF, PAI-1, tPA; urine prostacyclin [PGI-M] and thromboxane A2 [TxA2]) and bone marrow–derived endothelial progenitor cell levels are associated with bevacizumab-induced hypertension. We believe these measures could prove to be valuable surrogate biomarkers for bevacizumab toxicities and ultimately future cardiovascular events as well.

The higher response rates and higher time to progression seen in the breast cancer trials in the metastatic setting were the basis for the enthusiasm for exploring antiangiogenic drugs in the treatment of early breast cancer. While these studies in MBC have demonstrated that the addition of bevacizumab to traditional chemotherapeutic drugs significantly improved time to progression,[25,26,28,89] no OS advantage has been achieved. Furthermore, as discussed previously, NSABP C-08 did not show improvement in DFS. Patients in this study received either FOLFOX6 alone or in combination with bevacizumab, and single-agent bevacizumab was continued for a total of 1 year. Though the survival curves initially favored the bevacizumab-containing arm, they eventually came together at 3 years.[77]

The reasons for a lack of OS advantage in all of these trials are unknown. Possible explanations include (1) the plethora of active agents available in the metastatic setting, where patients can live many months or even years, sometimes being exposed to 8 or more different therapies before death; (2) resistance to bevacizumab; (3) stimulation of tumor

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

proliferation when the antiangiogenic agent was stopped; and (4) development of more aggressive tumor phenotype over time. Bergers et al recently reviewed 2 general modes of resistance to angiogenesis inhibitors, in particular those targeting the VEGF pathways: first, adaptive (evasive) resistance; and second, intrinsic (preexisting) nonresponsiveness.[90] Adaptive or evasive resistance refers to the ability of a tumor, after an initial response phase, to adapt so as to evade the therapeutic blockade. The tumor accomplishes this by inducing or accentuating mechanisms that enable neovascularization despite the therapeutic blockade, or reduce dependence on such growth of new blood vessels by other means, leading to renewed tumor growth and progression. By contrast, intrinsic nonresponsiveness is a preexisting condition defined by the absence of any (even transitory) beneficial effect of an antiangiogenic therapy, ranging from the inability to shrink or stabilize tumors to the lack of improvement in quality of life. Consequently, tumors grow and progress unabated during the course of antiangiogenic therapy.

Our current inability to identify which patients truly benefit from antiangiogenic agents may be the real reason for the survival outcome of these trials. Thus, we should not have a diminished enthusiasm for conducting trials in the neoadjuvant and adjuvant settings in breast cancer. These studies may offer the best opportunity to better elucidate mechanisms of resistance to antiangiogenic therapies, as well as provide a deeper understanding of the tumor phenotypes that would benefit the most from angiogenic blockade. As we eagerly await completion and results from this impressive portfolio of studies with antiangiogenic agents in early breast cancer, there is an urgent need for a greater insight into predictive factors for toxicities, therapy efficacy, and clinical benefit. Also yet to be determined is the appropriate duration of antiangiogenic therapy in the adjuvant setting. As our oncology patient populations live for a longer period of time, a better understanding of the cardiovascular implications of bevacizumab will become increasingly relevant. Above all, a rational approach to patient/antiangiogenic therapy selection and combination with current therapies may further decrease morbidity and mortality in women with breast cancer.

Acknowledgments

Supported by the Breast Cancer Specialized Program of Research Excellence (SPORE) grant 2P50 CA098131-06.

References

1. Fidler IJ, Ellis LM. The implications of angiogenesis for the biology and therapy of cancer metastasis. Cell. 1994; 79:185–8. [PubMed: 7525076]
2. Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. Endocr Rev. 1997; 18:4–25. [PubMed: 9034784]
3. Ferrara N, Alitalo K. Clinical applications of angiogenic growth factors and their inhibitors. Nat Med. 1999; 5:1359–64. [PubMed: 10581076]
4. Ferrara N. Role of vascular endothelial growth factor in the regulation of angiogenesis. Kidney Int. 1999; 56:794–814. [PubMed: 10469350]
5. Gasparini G. Biological and clinical role of angiogenesis in breast cancer. Breast Cancer Res Treat. 1995; 36:103–7. [PubMed: 8534859]
6. Schneider BP, Miller KD. Angiogenesis of breast cancer. J Clin Oncol. 2005; 23:1782–90. [PubMed: 15755986]
7. Gasparini G. Prognostic value of vascular endothelial growth factor in breast cancer. Oncologist. 2000; 5(suppl 1):37–44. [PubMed: 10804090]
8. Gasparini G. Clinical significance of determination of surrogate markers of angiogenesis in breast cancer. Crit Rev Oncol Hematol. 2001; 37:97–114. [PubMed: 11166583]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

9. Gasparini G, Toi M, Miceli R, et al. Clinical relevance of vascular endothelial growth factor and thymidine phosphorylase in patients with node-positive breast cancer treated with either adjuvant chemotherapy or hormone therapy. Cancer J Sci Am. 1999; 5:101–11. [PubMed: 10198732]
10. Foekens JA, Peters HA, Grebenchtchikov N, et al. High tumor levels of vascular endothelial growth factor predict poor response to systemic therapy in advanced breast cancer. Cancer Res. 2001; 61:5407–14. [PubMed: 11454684]
11. Konecny GE, Meng YG, Untch M, et al. Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients. Clin Cancer Res. 2004; 10:1706–16. [PubMed: 15014023]
12. Linderholm B, Andersson J, Lindh B, et al. Overexpression of c-erbB-2 is related to a higher expression of vascular endothelial growth factor (VEGF) and constitutes an independent prognostic factor in primary node-positive breast cancer after adjuvant systemic treatment. Eur J Cancer. 2004; 40:33–42. [PubMed: 14687787]
13. Pegram MD, Reese DM. Combined biological therapy of breast cancer using monoclonal antibodies directed against HER2/neu protein and vascular endothelial growth factor. Semin Oncol. 2002; 29:29–37. [PubMed: 12138395]
14. Petit AM, Rak J, Hung MC, et al. Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: angiogenic implications for signal transduction therapy of solid tumors. Am J Pathol. 1997; 151:1523–30. [PubMed: 9403702]
15. Yang W, Klos K, Yang Y, et al. ErbB2 overexpression correlates with increased expression of vascular endothelial growth factors A, C, and D in human breast carcinoma. Cancer. 2002; 94:2855–61. [PubMed: 12115372]
16. Ragaz J, Miller K, Badve S. Adverse association of expressed vascular endothelial growth factor (VEGF), Her2, Cox2, uPA and EMSY with long-term outcome of stage I–III breast cancer (BrCa). Results from the British Columbia Tissue Micro-array Project. J Clin Oncol. 2004; 23:8, abstract 524. [PubMed: 15545663]
17. Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature. 1993; 362:841–4. [PubMed: 7683111]
18. Warren RS, Yuan H, Matli MR, et al. Regulation by vascular endothelial growth factor of human colon cancer tumorigenesis in a mouse model of experimental liver metastasis. J Clin Invest. 1995; 95:1789–97. [PubMed: 7535799]
19. Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol. 2001; 19:843–50. [PubMed: 11157038]
20. McDonald DM, Choyke PL. Imaging of angiogenesis: from microscope to clinic. Nat Med. 2003; 9:713–25. [PubMed: 12778170]
21. Cobleigh MA, Langmuir VK, Sledge GW, et al. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol. 2003; 30:117–24. [PubMed: 14613032]
22. Sledge G, Miller K, Novotny WF. A phase II trial of single-agent rhuMab VEGF (recombinant humanized monoclonal antibody to vascular endothelial cell growth factor) in patients with relapsed metastatic breast cancer. Proc Am Soc Clin Oncol. 2000; 19:3a, abstract 5c.
23. Burstein HJ, Parker L, Savoie J. Phase II trial of the anti-VEGF antibody bevacizumab in combination with vinorelbine for refractory advanced breast cancer. Breast Cancer Res Treat. 2002; 76(suppl 1):S115.
24. Ramaswamy B, Elias AD, Kelbick NT, et al. Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients. Clin Cancer Res. 2006; 12:3124–9. [PubMed: 16707611]
25. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005; 23:792–9. [PubMed: 15681523]
26. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007; 357:2666–76. [PubMed: 18160686]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

27. Miles, DW.; Chan, A.; Romieu, G., et al. Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC). Presented at: the 33rd Annual San Antonio Breast Cancer Symposium; December 9–13, 2009; San Antonio, TX. p. Abstract 41
28. Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). J Clin Oncol. 2009; 27(15 suppl): 42s, abstract 1005.
29. Brufsky, A.; Bondarenko, IN.; Smirnov, V., et al. RIBBON-2: A randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of HER2-negative metastatic breast cancer. Presented at: the 33rd Annual San Antonio Breast Cancer Symposium; December 9–13, 2009; San Antonio, TX. p. Abstract 42
30. Heryanto B, Lipson KE, Rogers PA. Effect of angiogenesis inhibitors on oestrogen-mediated endometrial endothelial cell proliferation in the ovariectomized mouse. Reproduction. 2003; 125:337–46. [PubMed: 12611597]
31. Kazi AA, Jones JM, Koos RD. Chromatin immunoprecipitation analysis of gene expression in the rat uterus in vivo: estrogen-induced recruitment of both estrogen receptor alpha and hypoxia-inducible factor 1 to the vascular endothelial growth factor promoter. Mol Endocrinol. 2005; 19:2006–19. [PubMed: 15774498]
32. Soares R, Reis-Filho JS, Gartner F, et al. Vascular endothelial growth factor, transforming growth factor-alpha, and estrogen receptors: possible cross-talks and interactions. Am J Pathol. 2002; 160:381–2. author reply 2–3. [PubMed: 11786431]
33. Traina TA, Rugo HS, Caravelli JF, et al. Feasibility trial of letrozole in combination with bevacizumab in patients with metastatic breast cancer. J Clin Oncol. 2009; 28:628–33. [PubMed: 19841327]
34. Epstein M, Ayala R, Tchekmedyian N. HER2-overexpressing human breast cancer xenografts exhibit increased angiogenic potential mediated by vascular endothelial growth factor (VEGF). Breast Cancer Res Treat. 2002; 76:S143, abstract 570.
35. Pegram MD, Yeon C, Ku NC, et al. Phase I combined biological therapy of breast cancer using two humanized monoclonal antibodies directed against HER2 proto-oncogene and vascular endothelial growth factor (VEGF). Breast Cancer Res Treat. 2004; 88(suppl 1):S124, abstract 3039.
36. Pegram M, Chan D, Dichmann RA. Phase II combined biological therapy targeting the HER2 proto-oncogene and the vascular endothelial growth factor using trastuzumab (T) and bevacizumab (B) as first line treatment of HER2-amplified breast cancer. Breast Cancer Res Treat. 2006; 100(suppl 1):S28, abstract 301.
37. Drevs J, Siegert P, Medinger M, et al. Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. J Clin Oncol. 2007; 25:3045–54. [PubMed: 17634482]
38. Bianchi G, Loibl S, Zamagni C, et al. Phase II multicenter, uncontrolled trial of sorafenib in patients with metastatic breast cancer. Anticancer Drugs. 2009; 20:616–24. [PubMed: 19739318]
39. Moreno-Aspitia A, Morton RF, Hillman DW, et al. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. J Clin Oncol. 2009; 27:11–5. [PubMed: 19047293]
40. Burstein HJ, Elias AD, Rugo HS, et al. Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2008; 26:1810–6. [PubMed: 18347007]
41. Deprimo SE, Friece C, Huang X. Effect of treatment with sunitinib malate, a multitargeted tyrosine kinase inhibitor, on circulating plasma levels of VEGF, soluble VEGF receptors 2 and 3, and soluble KIT in patients with metastatic breast cancer. J Clin Oncol. 2006; 24(18 suppl):22s, abstract 578.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

42. Hurwitz HI, Dowlati A, Saini S, et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res. 2009; 15:4220–7. [PubMed: 19509175]
43. Miller KD, Trigo JM, Wheeler C, et al. A multicenter phase II trial of ZD6474, a vascular endothelial growth factor receptor-2 and epidermal growth factor receptor tyrosine kinase inhibitor, in patients with previously treated metastatic breast cancer. Clin Cancer Res. 2005; 11:3369–76. [PubMed: 15867237]
44. Banerjee S, Zvelebil M, Furet P, et al. The vascular endothelial growth factor receptor inhibitor PTK787/ZK222584 inhibits aromatase. Cancer Res. 2009; 69:4716–23. [PubMed: 19435899]
45. Rosen LS, Kurzrock R, Mulay M, et al. Safety, pharmacokinetics, and efficacy of AMG 706, an oral multikinase inhibitor, in patients with advanced solid tumors. J Clin Oncol. 2007; 25:2369–76. [PubMed: 17557949]
46. O'Donnell A, Padhani A, Hayes C, et al. A Phase I study of the angiogenesis inhibitor SU5416 (semaxanib) in solid tumours, incorporating dynamic contrast MR pharmacodynamic end points. Br J Cancer. 2005; 93:876–83. [PubMed: 16222321]
47. Herbst RS, Hong D, Chap L, et al. Safety, pharmacokinetics, and antitumor activity of AMG 386, a selective angiopoietin inhibitor, in adult patients with advanced solid tumors. J Clin Oncol. 2009; 27:3557–65. [PubMed: 19546406]
48. Bekaii-Saab TS, Roda JM, Guenterberg KD, et al. A phase I trial of paclitaxel and trastuzumab in combination with interleukin-12 in patients with HER2/neu-expressing malignancies. Mol Cancer Ther. 2009; 8:2983–91. [PubMed: 19887543]
49. Lowndes SA, Adams A, Timms A, et al. Phase I study of copper-binding agent ATN-224 in patients with advanced solid tumors. Clin Cancer Res. 2008; 14:7526–34. [PubMed: 19010871]
50. Lu N, Ling Y, Gao Y, et al. Endostar suppresses invasion through downregulating the expression of matrix metalloproteinase-2/9 in MDA-MB-435 human breast cancer cells. Exp Biol Med (Maywood). 2008; 233:1013–20. [PubMed: 18480415]
51. Baselga, J.; Roche, H.; Costa, F., et al. SOLTI-0701: A multinational double-blind, randomized phase 2b study evaluating the efficacy and safety of sorafenib compared to placebo when administered in combination with capecitabine in patients with locally advanced or metastatic breast cancer. Presented at: the 33rd Annual San Antonio Breast Cancer Symposium; December 9–13, 2009; San Antonio, TX. p. Abstract 45
52. Gradishar, WJ.; Kaklamani, V.; Prasad Sahoo, T., et al. A double-blind, randomized, placebo-controlled, phase 2b study evaluating the efficacy and safety of sorafenib (SOR) in combination with paclitaxel (PAC) as a first-line therapy in patients (pts) with locally recurrent or metastatic breast cancer (BC). Presented at: the 33rd Annual San Antonio Breast Cancer Symposium; December 9–13, 2009; San Antonio, TX. p. Abstract 44
53. Relf M, LeJeune S, Scott PA, et al. Expression of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor beta-1, platelet-derived endothelial cell growth factor, placenta growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis. Cancer Res. 1997; 57:963–9. [PubMed: 9041202]
54. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003; 9:669–76. [PubMed: 12778165]
55. Moore A. Breast-cancer therapy–looking back to the future. N Engl J Med. 2007; 357:1547–9. [PubMed: 17928605]
56. Brown LF, Berse B, Jackman RW, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in breast cancer. Hum Pathol. 1995; 26:86–91. [PubMed: 7821921]
57. Pavlakis K, Messini I, Vrekoussis T, et al. The assessment of angiogenesis and fibroblastic stromagenesis in hyperplastic and pre-invasive breast lesions. BMC Cancer. 2008; 8:88. [PubMed: 18384688]
58. Eyler CE, Rich JN. Survival of the Fittest: Cancer Stem Cells in Therapeutic Resistance and Angiogenesis. J Clin Oncol. 2008; 26:2839–45. [PubMed: 18539962]
59. Kaufmann M, von Minckwitz G, Smith R, et al. International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. J Clin Oncol. 2003; 21:2600–8. [PubMed: 12829681]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

60. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997; 15:2483–93. [PubMed: 9215816]
61. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003; 21:4165–74. [PubMed: 14559892]
62. Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol. 2002; 20:1456–66. [PubMed: 11896092]
63. Chakravarthy AB, Kelley MC, McLaren B, et al. Neoadjuvant concurrent paclitaxel and radiation in stage II/III breast cancer. Clin Cancer Res. 2006; 12:1570–6. [PubMed: 16533783]
64. Estévez LG, Gradishar WJ. Evidence-based use of neoadjuvant taxane in operable and inoperable breast cancer. Clin Cancer Res. 2004; 10:3249–61. [PubMed: 15161677]
65. Greil R, Moik M, Reitsamer R, et al. Neoadjuvant bevacizumab, docetaxel and capecitabine combination therapy for HER2/neu-negative invasive breast cancer: Efficacy and safety in a phase II pilot study. Eur J Surg Oncol. 2009; 35:1048–54. [PubMed: 19250795]
66. Balduzzi A, Montagna E, Bagnardi V, et al. Infusional fluorouracil, epirubicin, and cisplatin followed by weekly paclitaxel plus bevacizumab in locally advanced breast cancer with unfavorable prognostic features. Anticancer Drugs. 2009; 20:197–203. [PubMed: 19182679]
67. Rastogi P, Buyse M, Swain SM, et al. Bevacizumab begining concurrently with a sequential regimen of doxorubicin and cyclophosphamide followed by docetaxel and capecitabine as neoadjuvant therapy followed by postoperative bevacizumab alone for woment with HER2-negative locally advanced breast cancer: a phase II trial of the NSABP Foundation Research Group. J Clin Oncol. 2009; 27(15 suppl):27s, abstract 584.
68. Ryan PD, Tung NM, Isakoff SJ, et al. Neoadjuvant cisplatin and bevacizumab in triple negative breast cancer (TNBC): Safety and efficacy. J Clin Oncol. 2009; 27(15 suppl):18s, abstract 551.
69. Makhoul, I.; Vicki, KS.; Kokourian, S., et al. Bevacizumab combined with chemotherapy significantly improves pathologic complete response in patients with operable or locally advanced breast cancer. Presented at: the 32nd Annual San Antonio Breast Cancer Symposium; December 10–14, 2008; San Antonio, TX. p. Abstract 5114
70. Yardley DA, Raefsky E, Castillo R, et al. Results of a multicenter pilot study of weekly nab-paclitaxel, carboplatin with bevacizumab, and trastuzumab as neoadjuvant therapy in HER2+ locally advanced breast cancer with SPARC correlatives. J Clin Oncol. 2009; 27(15 suppl):13s, abstract 527.
71. Smith JW, Buyse M, Rastogi P, et al. Epirubicin plus cyclophosphamide followed by docetaxel plus trastuzumab and bevacizumab as neoadjuvant therapy for HER2-positive locally advanced breast cancer (LABC) or as adjuvant therapy for HER2-positive pathologic stage III breast cancer (PS3BC): A phase II trial of the NSABP Foundation Research Group. J Clin Oncol. 2009; 27(15 suppl):26s, abstract 580.
72. Wedam SB, Low JA, Yang SX, et al. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. J Clin Oncol. 2006; 24:769–77. [PubMed: 16391297]
73. Golshan, M.; Garber, J.; Gelman, R., et al. Surgical complications and the use of bevacizumab. Presented at: the 33rd Annual San Antonio Breast Cancer Symposium; December 9–13, 2009; San Antonio, TX. p. Abstract 43
74. Miller K, O'Neill A, Perez EA, et al. Phase II feasibility trial incorporating bevacizumab into dose dense doxorubicin and cyclophosphamide followed by paclitaxel in patients with lymph node positive breast cancer: a trial of the Eastern Cooperative Oncology Group (E2104). J Clin Oncol. 2008; 26(15 suppl):11s, abstract 520.
75. Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res. 2007; 13:2329–34. [PubMed: 17438091]
76. Mayer EL, Miller K, Rugo H, et al. A pilot study of adjuvant bevacizumab and chemotherapy after neoadjuvant chemotherapy for high-risk breast cancer. J Clin Oncol. 2008; 26(15 suppl):11s, abstract 519.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

77. Wolmark N, Yothers G, O'Connell MJ, et al. A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08. J Clin Oncol. 2009; 27(18 suppl):6s, abstract LBA4.

78. Mir O, Ropert S, Alexandre J, et al. Hypertension as a surrogate marker for the activity of anti-VEGF agents. Ann Oncol. 2009; 20:967–70. [PubMed: 19403940]

79. Scartozzi M, Galizia E, Chiorrini S, et al. Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. Ann Oncol. 2009; 20:227–30. [PubMed: 18842611]

80. Spano JP, Chodkiewicz C, Maurel J, et al. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. Lancet. 2008; 371:2101–8. [PubMed: 18514303]

81. Schneider BP, Radovich M, Miller KD. The role of vascular endothelial growth factor genetic variability in cancer. Clin Cancer Res. 2009; 15:5297–302. [PubMed: 19706811]

82. Allegra CJ, Yothers G, O'Connell MJ, et al. Initial safety report of NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. J Clin Oncol. 2009; 27:3385–90. [PubMed: 19414665]

83. Miles D, Chan A, Romieu G, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. J Clin Oncol. 2008; 26(15 suppl): 1008s, abstract LBA1011.

84. Zhu X, Wu S, Dahut WL, et al. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. Am J Kidney Dis. 2007; 49:186–93. [PubMed: 17261421]

85. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004; 350:2335–42. [PubMed: 15175435]

86. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med. 2003; 349:427–34. [PubMed: 12890841]

87. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst. 2007; 99:1232–9. [PubMed: 17686822]

88. Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA. 2008; 300:2277–85. [PubMed: 19017914]

89. Miles, DW.; Chan, A.; Romieu, G., et al. Final overall survival results from the randomized, double-blind, placebo-controlled, phase III AVADO study of bevacizumab plus docetaxel compared with placebo plus docetaxel for first-line treatment of locally recurrent or metastatic breast cancer. Presented at: the 33rd Annual San Antonio Breast Cancer Symposium; December 9–13, 2009; San Antonio, TX. p. Abstract 41

90. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. Nat Rev Cancer. 2008; 8:592–603. [PubMed: 18650835]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 1

Results From Phase III Trials of Bevacizumab in the Metastatic Setting

Study	Line of Therapy	Placebo Controlled	Chemotherapy	Bevacizumab, mg/kg	Sample Size	Median PFS for Bevacizumab Arms, Months	Median OS for Bevacizumab Arms, Months	ORR, %
E2100[26]	First	No	Paclitaxel	10 every 2 weeks	722	11.8 vs. 5.9 (HR, 0.60; $P = .0001$)	26.7 vs. 25.2 (HR, 0.88; $P = .16$)	36.9 vs. 21.2 ($P < .001$)
AVADO[27]	First	Yes	Docetaxel	7.5 or 15 every 3 weeks	736	Pl: 8.1; 7.5 mg: 9.0 (HR, 0.86; $P = .1163$); 15 mg: 10.0 (HR, 0.77; $P = .0061$)	Pl: 31.9; 7.5 mg: 30.8 (HR 1.05; $P = .7198$); 15 mg: 30.2 (HR 1.03; $P = .8528$)	Pl: 46.4; 7.5 mg: 55.2 ($P = .0739$); 15 mg: 64.1 ($P = .0003$)
RIBBON-1[28]	First	Yes	Capecitabine,[a] taxane,[b] or anthracycline	15 every 3 weeks	1237	C: 8.6 vs. 5.1 (HR, 0.688; $P = .0002$); T/A: 9.2 vs. 8.0 (HR, 0.644; $P < .0001$)	Not reached	C: 35.4 vs. 23.6 ($P = .0097$); T/A: 51.3 vs. 37.9 ($P = .0054$)
RIBBON-2[29]	Second	Yes	Taxane,[c] capecitabine, gemcitabine, or vinorelbine	10 every 2 weeks or 15 every 3 weeks[d]	684	7.2 vs. 5.1 (HR, 0.775; $P = .0072$)	18 vs. 16 ($P = .372$)	39.5 vs. 29.6 ($P = .0193$[e])

[a] Chemotherapy per investigator's choice.

[b] Albumin-bound paclitaxel or docetaxel.

[c] Paclitaxel, albumin-bound paclitaxel, or docetaxel.

[d] Dependent on chemotherapy schedule.

[e] Prespecified $\alpha = 0.01$.

Abbreviations: A = anthracycline; AVADO = Avastin and Docetaxel in Metastatic Breast Cancer; C = capecitabine; HR = hazard ratio; ORR = overall response rate; Pl = placebo; T = taxane

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 2

Results From Phase II Trials of Bevacizumab in the Neoadjuvant Setting

Study	Phase	IHC Status	Neoadjuvant Treatment	N	cCR,[a] %	pCR,[b] %
Balduzzi et al[66]	II	HER2-negative	Epirubicin, cisplatin, infusional 5-FU → paclitaxel + bevacizumab	30	3	33
Rastogi et al[67]	II	HER2-negative	Doxorubicin, cyclophosphamide + bevacizumab → docetaxel + capecitabine + bevacizumab	45	31	9
Ryan et al[68]	II	Triple-negative	Cisplatin + bevacizumab	46	26	15
Makhoul et al[69]	II	Any	Docetaxel, cyclophosphamide + bevacizumab	40	–	33
Greil et al[65]	II	Any	Capecitabine, docetaxel + bevacizumab	18	–	22
Yardley et al[70]	II	HER2-positive	Albumin-bound paclitaxel, carboplatin, trastuzumab + bevacizumab	29	–	65
Smith et al[71]	II	HER2-positive	Epirubicin, cyclophosphamide + bevacizumab → docetaxel + bevacizumab + trastuzumab	75	–	53

[a] Rate of complete clinical response.

[b] Rate of complete pathologic response.

Abbreviations: 5-FU = 5-fluorouracil; IHC = immunohistochemistry

Clin Breast Cancer. Author manuscript; available in PMC 2012 October 15.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 3

Ongoing Multicenter Clinical Trials Utilizing Antiangiogenic Agents in the Neoadjuvant Setting

Trial Sponsor/Number	Title	Phase
HER2-Positive Tumors		
NSABP FB-5	A Phase II Clinical Trial of Epirubicin Plus Cyclophosphamide Followed by Docetaxel Plus Trastuzumab and Bevacizumab Given as Neoadjuvant Therapy for HER2-Positive Locally Advanced Breast Cancer or Given as Adjuvant Therapy for HER2-Positive Pathologic Stage III Breast Cancer	II
Hoffmann-La Roche ML21531	An Open Label Study to Assess the Rate of Pathologic Complete Response in Patients With Primary Inflammatory HER2-positive Breast Cancer Treated With Avastin + Herceptin Based Chemotherapy	II
HER2-Negative		
NSABP FB-4	A Phase II Clinical Trial of Bevacizumab Beginning Concurrently With a Sequential Regimen of Doxorubicin and Cyclophosphamide Followed by Docetaxel and Capecitabine as Neoadjuvant Therapy Followed by Postoperative Bevacizumab Alone for Women With Locally Advanced Breast Cancer	II
NSABP B-40	A Randomized Phase III Trial of Neoadjuvant Therapy in Patients With Palpable and Operable Breast Cancer Evaluating the Effect on Pathologic Complete Response (pCR) of Adding Capecitabine or Gemcitabine to Docetaxel When Administered Before AC With or Without Bevacizumab and Correlative Science Studies Attempting to Identify Predictors of High Likelihood for pCR With Each of the Regimens	III
CALGB-40603	Randomized Phase II 2 × 2 Factorial Trial of the Addition of Carboplatin ± Bevacizumab to Neoadjuvant Weekly Paclitaxel Followed by Dose- Dense AC in Hormone Receptor-Poor/HER2-Negative Resectable Breast Cancer	II
SWOG-S0800	A Randomized Phase II Trial of Weekly Nanoparticle Albumin Bound Paclitaxel (NAB-Paclitaxel) (NSC-736631) with or without bevacizumab, either preceded by or Followed by q 2 week Doxorubicin (A) and Cyclophosphamide (C) Plus Pegfilgrastim (PEG-G) as Neoadjuvant Therapy for Inflammatory and Locally Advanced HER-2/NEU Negative Breast Cancer	II
Hoffmann-La Roche ML19884	An Open Label Neoadjuvant Study to Assess the Effect of Avastin on Tumor Response in Patients With Inflammatory or Locally Advanced Breast Cancer	II
Hoffmann-La Roche ML20561	An Open Label Study to Assess the Effect of Neoadjuvant Treatment With Docetaxel + Xeloda + Avastin on Pathologic Response Rate in Inflammatory or Locally Advanced Breast Cancer	II
Hoffmann-La Roche ML20382	An Open Label Study to Assess the Effect of a Combination of Avastin and Docetaxel and Sequential Chemotherapy on Pathologic Response in Patients With Primary Operable HER2 Negative Breast Cancer	II
Hoffmann-La Roche ML21744	A Multicenter, Randomized, ph II Clinical Trial to Evaluate the Effect of Avastin in Combination With Neoadj Treatment Regimens on the Molecular and Metabolic Characteristics and Changes in the Primary Tumors With Ref to the Obtained Responses in Patients With Large Primary HER2 Neg Breast Cancers	II
TORI B-02	A Multicenter, Placebo-Controlled, Double-Blind Randomized Phase II Trial of Neoadjuvant Treatment With Single-Agent Bevacizumab or Placebo, Followed by Six Cycles of Docetaxel, Doxorubicin, and Cyclophosphamide (TAC), With or Without Bevacizumab in Patients With Stage II or Stage III Breast Cancer	II
German Breast Group GBG 45	Phase II Study of Neoadjuvant Epirubicin, Cyclophosphamide (EC) + Sorafenib Followed by Paclitaxel (P) + Sorafenib in Women With Previously Untreated Primary Breast Cancer (SOFIA)	II
GSK 110264, NSABP FB-6	A Phase II Clinical Trial of Four Cycles of Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel Given Concurrently With Pazopanib as Neoadjuvant Therapy Followed by Postoperative Pazopanib for Women With Locally Advanced Breast Cancer	II
German Breast Group GBG 44	A Phase III Trials Program Exploring the Integration of Bevacizumab, Everolimus (RAD001), and Lapatinib Into Current Neoadjuvant Chemotherapy Regimes for Primary Breast Cancer	III
NCIC Clinical Trials Group CAN-NCIC-MA29	A Feasibility Study of Pre-Operative Sunitinib (SU11248) With Multiple Pharmacodynamic Endpoints in Patients With T1c-T3 Operable Carcinoma of the Breast[a]	II

[a] HER2, ER, or PR status not specified.

Abbreviations: CALGB = Cancer and Leukemia Group B; GSK = GlaxoSmithKline; NCIC = National Cancer Institute of Canada; NSABP = National Surgical Adjuvant Breast and Bowel Project; SWOG = Southwest Oncology Group

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 4

Ongoing Multicenter Phase III Clinical Trials Utilizing Antiangiogenic Agents in the Adjuvant Setting

Trial Sponsor/Number	Official Title	Phase
HER2-Positive		
NSABP B-44-I	BETH Study: A Multicenter Phase III Randomized Trial of Adjuvant Therapy for Patients With HER2-Positive Node-Positive or High Risk Node-Negative Breast Cancer Comparing Chemotherapy Plus Trastuzumab With Chemotherapy Plus Trastuzumab Plus Bevacizumab	III
HER2-Negative		
ECOG 5103	A Double-Blind Phase III Trial of Doxorubicin and Cyclophosphamide Followed by Paclitaxel With Bevacizumab or Placebo in Patients With Lymph Node Positive and High Risk Lymph Node Negative Breast Cancer	III
NSABP B-46-I	A Phase III Clinical Trial Comparing the Combination of TC Plus Bevacizumab to TC Alone and to TAC for Women With Node-Positive or High-Risk Node-Negative, HER2-Negative Breast Cancer	III
Dana Farber 09-134	ABCDE: A Phase III Randomized Study of Adjuvant Bevacizumab, Metronomic Chemotherapy (CM), Diet and Exercise After Preoperative Chemotherapy for Breast Cancer	III
Triple-Negative Tumors		
Hoffmann-La Roche BO20289	An Open Label 2-arm Study to Evaluate the Impact of Adjuvant Bevacizumab on Invasive Disease Free Survival in Triple Negative Breast Cancer	III

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSABP = National Surgical Adjuvant Breast and Bowel Project