Tumor angiogenesis, an important step in breast cancer development, invasion, progression, and metastasis, is regulated by the expression of proangiogenic factors such as vascular endothelial growth factor (VEGF). Higher levels of VEGF expression are associated with poor clinical outcomes and decreased survival in patients with breast cancer.

Bevacizumab (Avastin), is a humanized anti-VEGF antibody that is approved by the US Food and Drug Administration for the first-line treatment of metastatic HER2-negative, breast cancer in combination with paclitaxel. In this review, we will discuss the development of bevacizumab and the data pertaining to its use in the treatment of advanced breast cancer.

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Bevacizumab in Combination With Chemotherapy
Bevacizumab demonstrated modest clinical benefit as monotherapy. It is thought that anti-VEGF agents may act to normalize tortuous tumor vasculature, thereby reducing interstitial fluid pressure.
and facilitating drug delivery to solid tumors.[20] A number of preclinical studies have suggested synergy between antiangiogenic therapy and chemotherapy. Here, we review the large, randomized, phase III trials and select phase II studies that test bevacizumab-chemotherapy combinations.

**Capecitabine and Bevacizumab in MBC**—In the first published randomized phase III trial of bevacizumab, 462 eligible patients had anthracycline- and taxane-resistant disease, and progression or recurrence of disease after at least one chemotherapy regimen.[21] Capecitabine (Xeloda) was administered at the same dose and schedule for both treatment arms (2,500 mg/m²/d twice daily for 2 of 3 weeks). Patients randomized to the combination arm received bevacizumab at 15 mg/kg IV every 3 weeks. The primary endpoint of the trial was progression-free survival (PFS). The addition of bevacizumab to capecitabine increased the response rate from 9.1% to 19.8% (P = .001). However, the combination did not significantly increase PFS when compared to capecitabine monotherapy (4.86 vs 4.17 months, hazard ratio = 0.98, 95% confidence interval = 0.77-1.25; P = .857). The bevacizumab combination was well tolerated and did not appear to worsen capecitabine-related toxicity for this pretreated population. Bevacizumab-related toxicities included hypertension (grade 3: 17.9% vs 0.5% for single-agent capecitabine), thromboembolic events (grades 2-4: 6.9% vs 5.6%), proteinuria (grades 1-4: 22.3% vs 7.4%), and minor bleeding. Nine patients developed grade 3/4 CHF or cardiomyopathy: seven in the combination arm (3.1%) and two in the single-agent capecitabine arm (0.9%). Grade 3 or serious bleeding was uncommon and did not differ between therapies.

It was suggested that the activity of bevacizumab may have been obfuscated by the degree of prior therapy in this patient population with refractory disease. Advanced stages of cancer may have redundant angiogenic pathways, making the inhibition of a single receptor pathway inadequate for significant clinical benefit.

A multicenter, phase II study (XCALIBr: Xeloda in Combination with Avastin as first-Line treatment for HER2-negative metastatic Breast cancer) subsequently tested the combination of bevacizumab (15 mg/kg every 3 weeks) with capecitabine (1,000 mg/m² twice daily for 2 of 3 weeks) as first-line treatment for 106 patients with metastatic breast cancer.[22] This trial met its primary endpoint, an increase in time to progression from 4 months (capecitabine monotherapy) to 5.7 months (capecitabine and bevacizumab). The combination also demonstrated improved response rate compared to capecitabine monotherapy. An unplanned, subset analysis of efficacy based on hormone receptor status suggested greater activity in patients with estrogen receptor-positive disease. This finding is hypothesis-generating and will be studied further, as there is no ready explanation for this observation.

**Paclitaxel and Bevacizumab in MBC**—The Eastern Cooperative Oncology Group (ECOG) trial 2100 randomized patients to weekly paclitaxel, with or without bevacizumab, as first-line therapy for locally recurrent breast cancer or MBC.[23] Evidence has suggested that taxanes have antiangiogenic activity when administered at a low weekly dose.[24,25] Therefore, the combination of weekly paclitaxel and bevacizumab was selected for its dual antiangiogenic inhibition. A total of 722 patients were enrolled on this trial. Paclitaxel was given at 90 mg/m² weekly for 3 of 4 weeks. Patients who were randomized to the combination arm received bevacizumab at 10 mg/kg every 2 weeks. Patients with HER2-positive breast cancer were excluded from this trial, unless they had been previously treated with trastuzumab (Herceptin). Pertinent exclusion criteria included the presence of brain metastases and significant underlying heart disease. Patients were permitted to have received adjuvant taxane therapy if a disease-free interval of > 12 months had elapsed. (Two-thirds of patients had received prior adjuvant therapy, and approximately 20% had previous taxane exposure.) Patients were stratified according to prognostic factors such as disease-free interval, number of metastatic sites, prior adjuvant therapy, and hormone receptor status. PFS was the primary endpoint.

Patients receiving paclitaxel with bevacizumab showed a significant improvement in PFS compared with those receiving paclitaxel alone (median = 11.8 vs 5.9 months; hazard ratio for progression = 0.60; P < .001). Similarly, the combination arm demonstrated a higher overall response rate than the single-agent arm (36.9% vs 21.2%, P < .001). The overall survival rate, however, was similar in the two groups (median = 26.7 vs 25.2 months; hazard ratio = 0.88; P = .16).[23] ECOG 2100 demonstrated the efficacy of bevacizumab in combination with paclitaxel, and provided additional safety data. Patients in the combination arm experienced more grade 3/4 hypertension (14.8% vs 0%; P < .001), proteinuria (3.6% vs 0%; P < .001), headache (2.2% vs 0.0%, P = .008), and cerebrovascular ischemia (1.9% vs 0.0%, P = .02) than patients in the single-agent arm. The investigators observed no increased thromboembolic events or episodes of CHF in the combination arm. Quality-of-life measures using the Functional Assessment of Cancer Therapy (FACT)-Breast
Cancer and FACT-General surveys were not different between treatment arms or time points.

**Docetaxel and Bevacizumab in MBC**—Docetaxel is a commonly used taxane with efficacy against breast cancer. The AVADO (AVastin And Docetaxel) trial was a randomized, double-blind, placebo-controlled, phase III study comparing the efficacy of docetaxel with or without bevacizumab for the treatment of patients with locally recurrent or MBC.[26] Patients were randomized to one of three treatment arms: (1) docetaxel at 100 mg/m² every 3 weeks, (2) docetaxel plus bevacizumab at 15 mg/kg every 3 weeks, and (3) docetaxel plus bevacizumab at 7.5 mg/kg every 3 weeks. Patients received a maximum of nine cycles of chemotherapy, but earlier discontinuation was permitted—a noteworthy design difference from ECOG 2100. Placebo or bevacizumab was continued until disease progression. All patients had the option of receiving bevacizumab in combination with their second-line chemotherapy.

The primary study endpoint was PFS, and the protocol-specified primary analysis was an unstratified comparison of PFS between each of the bevacizumab-containing arms and the control arm. The study was not powered to detect a difference between the two bevacizumab doses.

A total of 736 patients were randomized for treatment on study. After a median of 10.2 months, in the unstratified analysis, patients receiving bevacizumab had a significantly longer PFS compared with the docetaxel monotherapy group (bevacizumab at 7.5 mg/kg: median PFS = 8.7 vs 8.0 months, hazard ratio = 0.79, P = .0318; bevacizumab at 15 mg/kg: median PFS = 8.8 vs 8.0 months, hazard ratio = 0.72, P = .0099). The combination therapy also improved response rates compared to docetaxel monotherapy (bevacizumab at 7.5 mg/kg: 55% vs 44%, P = .0295; bevacizumab at 15 mg/kg: 63% vs 44%, P = .0001). The study was not powered to detect differences in overall survival, and any potential differences may be masked by the prespecified crossover to bevacizumab permitted upon progression.[26]

No new safety concerns were raised with regard to bevacizumab-associated toxicity in this study. Nearly every patient experienced at least one adverse event, with no difference between treatment arms. Many of these events could be attributed to the difficulty in delivering docetaxel at 100 mg/m². The rates of greater than grade 3 hypertension associated with bevacizumab (7.5 mg/kg/15 mg/kg) were quite low (0.4%/3.2%) compared to prior reports in the literature. The investigators found no increased arterial or venous thromboembolic events in the bevacizumab-containing arms. Proteinuria rates have not been reported. The incidence of febrile neutropenia was higher for combination therapy.[26]

While this study met its primary endpoint, finding a statistically significant improvement in PFS with the addition of bevacizumab to docetaxel, it may be questioned whether the 0.7- to 0.8-month improvement in median PFS is clinically significant. Although cross-study comparisons are fraught with limitations and pitfalls, it would seem that the median PFS for the combination of paclitaxel and bevacizumab (ECOG 2100) was longer than that seen with the docetaxel/bevacizumab combination. **Other Chemotherapy and Bevacizumab**—While we await longer follow-up of the AVADO data, it becomes apparent that there are many unanswered questions about the optimal chemotherapy with which to combine bevacizumab. Perhaps the differences observed in efficacy may be attributed to drug-specific synergy.

Preliminary data from the RIBBON-1 (Regimens in Bevacizumab for Breast Oncology) trial are anticipated soon. In this multicenter, international, placebo-controlled, randomized, phase III study, patients with metastatic, HER2-negative breast cancer seeking first-line treatment were assigned to two study groups. In the first study group, patients received either bevacizumab or placebo in combination with a taxane (paclitaxel or docetaxel) or anthracycline-based chemotherapy. In the second study group, patients received either bevacizumab or placebo in combination with capecitabine chemotherapy. A preliminary report by Genentech indicates that the primary endpoint of improved PFS was met for the bevacizumab-combinations in both study groups; however, details have not been publically presented for review by the scientific community.[27]

Several phase II trials are exploring the feasibility and efficacy of bevacizumab in combination with other chemotherapy agents. For example, when administered with vinorelbine, bevacizumab demonstrates tolerability and possibly greater efficacy in less refractory patients. [28] A randomized, phase II trial is testing the combination of paclitaxel and bevacizumab, with or without gemcitabine (Gemzar), in MBC. Several studies with nanoparticle albumin-bound (nab)-paclitaxel (Abraxane) are currently accruing patients; other trials are exploring the combination of bevacizumab with nab-paclitaxel and carboplatin,[29] or nab-paclitaxel and gemcitabine.[30] Low-dose, repetitive, “metronomic” chemotherapy with oral cyclophosphamide and methotrexate, with or without bevacizumab, has also been studied in a randomized phase II trial.[31] Preliminary data from all of...
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these trials suggest that bevacizumab combinations are feasible and worthy of further efficacy trials.

Bevacizumab Combined With Other Targeted Therapies

Clinical data for bevacizumab in advanced breast cancer have revealed that angiogenic processes are likely more complicated than initially believed, as patients with metastatic disease are rarely, if ever, cured of their breast cancer. Redundancy at the level of VEGF, VEGF receptor (VEGFR), and countless other signal transduction pathways may explain resistance to monotherapy and argue for combinations of targeted drug therapies.

Perhaps the oldest “targeted” therapy in the treatment of breast cancer is endocrine therapy directed at reducing the impact of estrogen binding to the estrogen receptor. Unfortunately, despite
an initial response to hormone therapies, most patients with breast cancer become refractory to endocrine manipulation in the metastatic setting.[32] Estrogen modulates angiogenesis and has been shown to directly influence neovascularization through effects on endothelial cells in physiologic and pathologic conditions.[33-36] Therapy directed against VEGF may delay resistance to endocrine therapy in the subset of patients with hormone-sensitive breast cancer.

A phase II, multicenter trial of letrozole (Femara) with bevacizumab found this combination feasible for the treatment of patients with hormone receptor–positive MBC.[37] The hypothesis that anti-VEGF therapy can delay resistance to endocrine therapy is being tested in an ongoing proof-of-efficacy phase III Cancer and Leukemia Group B (CALGB)-led multicenter randomized placebo-controlled trial (CALGB 40503). This study is enrolling patients with hormone receptor–positive MBC to first-line endocrine therapy (letrozole or tamoxifen) with or without bevacizumab. Although the primary endpoint is PFS, secondary endpoints will address toxicity, including hypertension, proteinuria, and arterial and venous thromboembolic events. Other endocrine therapy–bevacizumab studies are ongoing, such as a feasibility study of fulvestrant (Faslodex) or anastrozole (Arimidex) plus bevacizumab in MBC.[38]

Several other ongoing trials are exploring the use of novel agents that target signal transduction pathways together with bevacizumab. These studies share the hypothesis that inhibiting multiple targets may be of greater clinical benefit and overcome resistance to monotherapy due to redundancy among and crosstalk between signaling pathways. Bevacizumab doublets under investigation include bevacizumab with trastuzumab, pertuzumab (Omnitarg), lapatinib (Tykerb), and vorinostat (Zolinza) to name just a few. As drug development creates multiple targeted therapeutics, it will be important to determine the safety, efficacy, and role of these therapies, so that they can be incorporated into our treatment algorithms.

**Future Directions**

The benefits of bevacizumab for the treatment of advanced breast cancer have led to the study of its use in combination with chemotherapy for the treatment of early stage disease. The safety and feasibility of bevacizumab in combination with dose-dense doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) has been demonstrated in patients with early-stage, lymph node–positive, HER2-negative breast cancer.[39] and several phase II trials have tested bevacizumab with other adjuvant chemotherapy regimens. ECOG 5103 is a large, multicenter, placebo-controlled, randomized phase III trial comparing the efficacy of adjuvant AC→T with concurrent bevacizumab or with both concurrent and “maintenance” bevacizumab for 1 year. The BEATRICE (BEvacizumab Adjuvant therapy in TRiple negative breast Cancer) and BETH (Bevacizumab and Trastuzumab adjuvant treatment in HER2+ Breast Cancer) trials are additional ongoing large, multicenter studies that will hopefully clarify the potential role for bevacizumab in our adjuvant treatment paradigm. Bevacizumab is also being studied as adjuvant therapy for patients with residual disease following neoadjuvant chemotherapy. The results of these adjuvant/neoadjuvant trials must be considered before bevacizumab can be incorporated into the treatment of early-stage disease.

Several markers being explored may predict or indicate which patients may benefit from the use of bevacizumab or experience greater toxicity. The identification of such predictive markers would be a step closer to personalized medicine, with targeted therapies chosen based on the biology of an individual patient’s tumor. Circulating endothelial and tumor cells have been under investigation in this regard.[40] Recently, germline polymorphisms in the VEGF and VEGFR-2 genes were analyzed in the phase III trial of paclitaxel plus bevacizumab in MBC. In this trial, 14.8% and 3.5% of patients in the bevacizumab-containing arm experienced grade 3/4 hypertension and proteinuria, respectively. Two variant VEGF genotypes (VEGF-1498 TT and VEGF-634 CC) were associated with lower rates of grade 3/4 hypertension in the bevacizumab-containing arm (P = .022 and P = .005, respectively).[41] Interestingly, the bevacizumab-treated patients who experienced hypertension had a longer median survival compared with bevacizumab-treated patients with no hypertension (38.7 vs 25.3 months; P = .002). It is conceivable that unique pharmacogenetics may contribute to differing rates of toxicity and efficacy for patients receiving VEGF-targeted therapy.

**Conclusions**

The success of antiangiogenic therapy is a fine example of the bench-to-bedside paradigm. The addition of bevacizumab to our treatment armamentarium has led to improved clinical outcomes for patients with advanced breast cancer. Further studies are needed to clarify the potential for this active agent’s role more broadly, such as beyond first-line chemotherapy combinations and in the neoadjuvant or adjuvant settings. With validation of VEGF as a therapeutic target, drug development continues with the study of tyrosine kinase inhibitors of the VEGF-receptor and VEGF decoys such as...
VEGF-trap.

This article is reviewed at the following links:
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**References:**