Curr Oncol Rep (2012) 14:1–11
DOI 10.1007/s11912-011-0202-z

BREAST CANCER (KR FOX, SECTION EDITOR)

# Bevacizumab in the Treatment of Metastatic Breast Cancer: Friend or Foe?

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Published online: 20 October 2011


**Abstract** Metastatic breast cancer (MBC) is a major cause of death among women worldwide. Progress has been made in treating MBC with the advent of anti-estrogen therapies, potent cytotoxic agents, and monoclonal antibodies. Bevacizumab is a monoclonal antibody against circulating vascular endothelial growth factor (VEGF), which was approved in 2008 by the US Food and Drug Administration (FDA), for first-line treatment of HER-2 negative MBC in combination with paclitaxel. The FDA then reversed this decision in December 2010 by recommending removal of the MBC indication from bevacizumab, citing primarily safety concerns, and that these risks did not outweigh the ability of bevacizumab to significantly prolong progression-free survival. This decision was unexpected in the oncology community and remains controversial. This review looks at all available phase 3 data with bevacizumab in the MBC setting to determine whether the data support this decision by the FDA, and discusses the future of bevacizumab in breast cancer.

**Keywords** Bevacizumab · Metastatic breast cancer · Randomized control (phase 3) trials · Review · Chemotherapy · Anti-angiogenesis

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## Introduction

Bevacizumab is a monoclonal antibody against circulating VEGF (vascular endothelial growth factor), thereby interfering with the process of tumor angiogenesis by preventing this ligand from interacting with its receptor [1]. Bevacizumab was the first anti-angiogenic drug approved for the treatment of cancer with initial approval in the setting of advanced colorectal cancer and later in lung cancer in combination with chemotherapy [2, 3]. Bevacizumab, after results of the E2100 randomized phase 3 trial demonstrated efficacy in breast cancer, was granted "accelerated" approval by the US Food and Drug Administration (FDA) in 2008 in combination with weekly paclitaxel for the first-line treatment of HER2-negative metastatic breast cancer (MBC). The FDA then reversed this decision approximately 2 years later in December 2010, removing the MBC indication from bevacizumab. In its decision, the FDA cited primarily safety concerns and that the risks that bevacizumab presented to patients with MBC outweighed any benefit in prolonging progression-free survival (PFS). This decision was unexpected in the oncology community and has generated a fair amount of controversy. In this article we review the biology of tumor angiogenesis, discuss all available phase 3 data with bevacizumab in MBC, and discuss available cost-effectiveness data. Even more importantly, we will critically evaluate the arguments proffered by the FDA and whether we consider the available data support their decision to remove the MBC indication.

## Tumor Angiogenesis as a Concept of Growth Promotion

The growth of blood vessels (angiogenesis or neovascularization) is essential for organ growth and repair. An

imbalance in this process contributes to numerous malignant, inflammatory, ischemic, infectious, and immune disorders [4]. The observation that malignant tumor growth can be accompanied by increased vascularity was reported over a century ago [5]. In the 1920s and 30s, early angiogenesis investigators hypothesized that tumor growth is dependent on the formation of a neovascular supply and that tumors must secrete soluble substances that promote their own angiogenesis. However, it was not until 1971 that Folkman reported the isolation of such a substance from a carcinoma grown in rats, and called it a "tumor angiogenic factor" (TAF) [6]. He proposed that tumors cannot grow beyond a certain size without inducing angiogenesis and that inhibiting tumor angiogenesis could prevent local tumor growth and the formation of distant metastases [7]. There are many critical growth factors involved in the physiological regulation of blood vessel formation, and the actions of these molecules must be very carefully orchestrated in terms of time, space, and dose so as to form a functioning vascular network [8]. Although the acquisition of angiogenic activity by tumor cells depends on the complex interaction between these growth factors, blockade of even a single growth factor might limit vascular growth, with the most compelling evidence to date supporting blockade of VEGF [8]. One predominant factor that stimulates tumor angiogenesis is vascular endothelial growth factor A (VEGF). In 1989, Leung et al. [9] reported the isolation and sequencing of an endothelial cell mitogen from pituitary cells and called it VEGF which stimulates proliferation and migration of vascular endothelial cells (ECs). It also promotes survival, inhibits apoptosis, and regulates permeability of ECs [10].

The function of VEGF is mediated by binding to the vascular endothelial receptors 1 and 2 (VEGFR1 and VEGFR2). The role of the tyrosine kinase receptor VEGFR1 has not been completely elucidated. However, it is thought to participate in embryonic vessel development, and is proposed to facilitate hematopoiesis and recruitment of endothelial cell progenitors to tumor blood vessels from bone marrow [10]. The second VEGF receptor, VEGFR2, is the key mediator of VEGF-driven angiogenesis. Upon VEGF binding, VEGFR2 undergoes auto-transphosphorylation and downstream effectors including phospholipase C gamma, protein kinase C, Raf, the MAP kinase signaling cascades, and the PI3K and FAK pathways are activated, leading to endothelial cell proliferation, migration, and survival [11, 12].

In recent years, the molecular actions of VEGF and its inhibitors have been better understood. Yet, the way in which anti-angiogenic agents actually work in terms of combating cancer has not been clearly defined. According to the Folkman hypothesis, interference with tumor angiogenesis results in inhibition of new vessel formation or progressive loss of existing vessels. Thus, the result would be an inadequate blood supply slowing and preventing tumor growth [6].

An alternative hypothesis proposed by Jain is based on the fact that tumor vessels are structurally and functionally abnormal, while naïve vessels are tightly associated with stabilizing pericytes and less dependent on VEGF for survival. He asserts that unlike embryogenically derived blood vessels, the majority of tumor blood vessels are tortuous, dilated, and saccular that are poorly organized and hyper-permeable [13]. These characteristics, as well as the compression of rapidly growing cancer cells, lead to poor blood flow. Thus, VEGF inhibition causes these immature blood vessels to be "pruned" leaving a minority of vessels that are, as he called them, "normalized." As a result, the vasculature that remains in the face of anti-VEGF therapy consists of a higher percentage of pericyte-associated blood vessels that are more efficient in function [7]. This leads to a transient improvement of blood flow within the tumor which enhances the delivery of chemotherapy. Additionally, because stable vessels within the tumor are less leaky, interstitial pressure may decrease and thereby facilitate tissue penetration of chemotherapy [13, 14]. Tumor angiogenesis results in abnormal vasculature, leading to increased interstitial pressure and irregular tumor perfusion. Consequently, recent research has indicated that VEGF blockade with bevacizumab or other anti-angiogenic agent may potentiate the anti-tumor effect of chemotherapy. This synergistic effect may be due in part to the transient normalization of tumor vasculature, allowing for the delivery of cytotoxic therapy and thereby overcome factors that interfere with delivery of chemotherapy to tumor, such as impaired blood supply, high interstitial fluid pressure, and hypoxia [15].

## Bevacizumab Background

On the basis of the growing body of evidence for VEGF as a critical mediator of angiogenesis, a murine monoclonal antibody against human VEGF (A.4.6.1) was developed that exerted a potent inhibitory effect on the growth of several tumor cell lines in nude mice [16]. This antibody was later humanized (rhuMab VEGF, or bevacizumab) and was able to bind VEGF with an affinity similar to that of the original antibody, inhibiting tumor growth at relatively low doses in preclinical models. The reliance of tumors on angiogenesis for growth (the central role of VEGF in angiogenesis), the preclinical activity of anti-VEGF antibodies, the negative effect of increased VEGF levels on prognosis, and the potential of VEGF to act synergistically with chemoradiotherapy all provided a strong rationale for

VEGF-based anti-angiogenic approaches in breast cancer therapy. Bevacizumab was first evaluated in a phase 1–2 clinical trial in women with chemotherapy-refractory MBC as monotherapy [1]. In this study, patients ($n$=75) received bevacizumab in different escalating doses intravenously every 2 weeks (3, 10, or 20 mg/kg). ORR was low (ie, 9.3%), with the median duration of response being 5.5 months (range: 2.3–13.7 months). At the final tumor assessment date, on day 154, approximately 12 out of 75 patients (16%) were found to have stable disease or a confirmed continued response. Although this was a small trial, the extended period of stable disease with bevacizumab alone is quite remarkable. A median TTP and OS of 2.4 and 10.2 months, respectively, were reported in this study. Overall, bevacizumab was very well tolerated with a side-effect profile that was clearly distinct from what is typically observed with cytotoxic chemotherapy. These adverse effects, however, were similar to what had been previously reported in metastatic colorectal cancer [1]. In the phase 1 portion of this study, headache was the dose-limiting toxicity for bevacizumab experienced at 20 mg/kg. Four patients that received bevacizumab at 20 mg/kg were discontinued from the study due to the following: hypertensive encephalopathy, nephrotic syndrome, proteinuria, and headache associated with nausea and vomiting. Thrombotic events were observed in three patients. Given the toxicity from bevacizumab at 20 mg/kg, it was concluded that the recommended phase 2 dose should be 10 mg/kg intravenously every 2 weeks for the treatment of MBC.

## Phase 3 Bevacizumab Trials in MBC

The first phase 3 trial exploring the use of bevacizumab in the setting of MBC was the AVF2119g trial (Table 1). This trial evaluated bevacizumab plus capecitabine as second-line therapy versus capecitabine alone in patients with MBC who had previously received anthracyclines and taxanes. In this study, patients ($n$=462) were randomized to receive capecitabine (2500 mg/m$^2$ days 1–14 followed by 1 week rest) with or without bevacizumab (15 mg/kg intravenously) every 3 weeks. Patients either relapsed within 12 months of completing adjuvant therapy or had previously received 1–2 prior lines of therapy for metastatic disease. The primary end point was progression-free survival (PFS). The addition of bevacizumab to capecitabine was not associated with any significant improvement of either median PFS (4.86 vs 4.17 months, $P$=0.857) or median OS (15.1 vs 14.5 months, $P$=0.63). While not the primary end point of this trial, a significant improvement in ORR was observed with patients who received bevacizumab plus capecitabine versus capecitabine alone (19.8% vs 9.1%, $P$=0.001). Moreover, the duration of response was found to be longer in the combination arm (7.5 vs 4.9 months). The addition of bevacizumab did not appear to exacerbate capecitabine-associated toxicities, such as hand-foot syndrome, diarrhea, or mucositis. Bevacizumab-associated toxicities reported in this study that were significantly higher in the combination arm included hypertension and proteinuria, with approximately 18% of the patients in the combination arm having grade 3 hypertension versus 0.5% in patients receiving capecitabine only. Thromboembolic events and serious hemorrhage were distinctly uncommon in this study, and no significant differences between combination and capecitabine alone arms were noted. One of the primary interpretations as to why bevacizumab did not lead to significant improvements in PFS or OS in this trial was due to the fact that the patients enrolled in this study were rather heavily pretreated and perhaps the true anti-tumor benefit of bevacizumab was not seen because of greater resistance to chemotherapy [17].

Consequently in the next randomized MBC phase 3 trial, bevacizumab was evaluated as first-line therapy in combination with weekly paclitaxel (Table 1). In this trial, the Eastern Cooperative Group (ECOG) 2100 trial compared the efficacy and safety of weekly paclitaxel plus bevacizumab to paclitaxel alone as first-line therapy in 722 women with MBC. The primary end point was PFS. Women were randomized to receive either weekly paclitaxel (90 mg/m$^2$) on days 1, 8, and 15 every 4 weeks alone or in combination with bevacizumab (10 mg/kg) on days 1 and 15. In this trial, median PFS was 11.4 months for paclitaxel/bevacizumab versus paclitaxel alone 5.9 months (hazard ratio 0.6; $P$<0.001). Moreover, objective response rates with bevacizumab/paclitaxel were almost twice that observed with paclitaxel (36.9% vs 21.2%; $P$<0.001). However, there was no significant difference in OS between both groups (median, 26.7 vs 25.2 months; hazard ratio, 0.88; $P$=0.16). The overall toxicity profile of bevacizumab when combined with weekly paclitaxel was tolerable. The overall frequencies of grade 3–4 hemorrhagic (0.5%), thromboembolic events (2.1%), or gastrointestinal perforation (0.5%) were quite low with bevacizumab and did not significantly differ between treatment arms. The frequency of grade 3–4 hypertension was significantly higher in patients that were receiving bevacizumab (14.8% vs 0; $P$<0.001); grade 3 proteinuria was also higher, but was observed in only 2.7% of patients (vs 0% for paclitaxel alone; $P$<0.001). When evaluating adverse toxicities typically associated with paclitaxel, in this study the addition of bevacizumab had little effect on the frequency or severity of most paclitaxel-related toxic effects. For instance, hematologic, gastrointestinal, and musculoskeletal toxicities were minimal and similar in both groups, with the exception that grade 3–4 sensory neuropathy (23.5% vs 17.7%, $P$=0.05), infection

**Table 1** Phase 3 trials with bevacizumab-containing regimens in MBC

| Study | Treatment arms | PFS, *months* | ORR,% | OS, *months* |
|---|---|---|---|---|
| First-line studies | | | | |
| E2100 [17, 42] | BV 10 mg/kg every 2 weeks plus paclitaxel 90 mg/m$^2$ on days 1, 8, and 15 of every 4-week ($n$=368) or paclitaxel alone ($n$=354) | 11.3 vs 5.9; HR=0.48; $P$<0.0001 | 48.9 vs 22.2; $P$<0.0001 | 26.7 vs 25.2; HR=0.88; $P$=0.16 |
| AVADO [43] | BV 7.5 mg/kg+docetaxel 100 mg/m$^2$ on day 1 of each 3-week cycle ($n$=248) vs placebo+docetaxel at same dose ($n$=206) | 9.0 vs 8.1; stratified HR=0.8; $P$=0.045 | 55.2 vs 46.4; $P$=0.0739 | 30.8 vs 31.9; HR=1.05; $P$=0.72 |
| | BV 15 mg/kg+docetaxel 100 mg/m$^2$ on day 1 of each 3-week ($n$=247) vs placebo+docetaxel at same dose ($n$=241) | 10.0 vs 8.1; stratified HR=0.67; $P$=0.0002 | 64.1 vs 46.4; $P$=0.0003 | 30.2 vs 31.9; HR=1.03, $P$=0.85 |
| RIBBON-1 [44, 45] | BV 15 mg/kg every 3 weeks+cape 2,000 mg/m$^2$ for 14 days ($n$=409) vs placebo+cape 2,000 mg/m$^2$ for 14 days ($n$=206) | 8.6 vs 5.7; HR=0.688; $P$=0.0002 | 35.4 vs 23.6; $P$=0.0097 | 29.0 vs 21.2; $P$=0.2707 |
| | BV 15 mg/kg every 3 weeks+taxane/anthracycline every 3 weeks ($n$=415) vs placebo+taxane/anthracycline every 3 weeks ($n$=207) | 9.2 vs 8.0; HR=0.644; $P$<0.0001 | 51.3 vs 37.9; $P$=0.0054 | 25.2 vs 23.8; $P$=0.8298 |
| Second-line studies | | | | |
| AVF2119g [46] | BV 15 mg/kg every 3 weeks+Cape 2,500 mg/m$^2$ per day d 1–14 followed by a 1-week rest period (3-week cycle) | 4.86 vs 4.17 month; HR=0.98; $P$=0.857 | 19.8 vs 9.1; $P$=0.001 | 15.1 vs 14.5 month |
| RIBBON-2 [45, 47] | Chemotherapy + BV (10 mg/kg IV every 2 weeks or 15 mg/kg IV every 3 weeks depending on when the accompanying chemotherapy cycle is given) vs chemotherapy+placebo | 7.2 vs 5.1; HR=0.775; $P$<0.0072 | 39.5 vs 29.6; $P$=0.0193 | 18 vs 16.4; $P$=0.372 |

*BV* bevacizumab; *Cape* capecitabine; *HR* hazard ratio; *MBC* metastatic breast cancer; *ORR* objective response rate; *OS* overall survival; *PFS* progression-free survival

(9.3% vs 2.9%, $P$<0.001), and fatigue (9.1% vs 4.9%, $P$=0.04) were more frequent with weekly paclitaxel and bevacizumab. Moreover, no differences in quality of life (QoL) were observed between both groups.

Differences between the patient populations of these studies may account for the former trial (AVF2119g) being negative and the latter (E2100) positive. For example, patients in the AVF2119g study had received previous anthracycline and taxane adjuvant chemotherapy, and most (more than 85%) had received chemotherapy for metastatic disease. In contrast, 35.2% of patients in the E2100 trial had not received any prior adjuvant chemotherapy, and only 13.2% had received both an anthracycline and a taxane as adjuvant therapy [17]. It is of interest that in an exploratory analysis, patients who received prior taxanes in the adjuvant setting also benefitted from the addition of bevacizumab in E2100.

One potential explanation for the rather dramatic difference seen in the E2100 trial between weekly paclitaxel alone and paclitaxel plus bevacizumab, may be that patients in the control arm fared much worse than would be expected (ie, that these results were not typical). If one looks at the recently published CIRG/TORI 010 study, a multinational randomized phase 2 trial, there are major differences in median PFS with the same dose of weekly paclitaxel in a similar patient population as E2100 [18•]. The overall goal of this trial was to compare the effectiveness of motesanib (an oral small-molecule VEGFR tyrosine-kinase inhibitor) to bevacizumab when combined with paclitaxel. This trial enrolled patients with HER-2 negative MBC ($n$=281), randomly assigned in a 1:1:1 ratio to paclitaxel (90 mg/m$^2$ day 1, 8, and 15), plus either motesanib 125 mg orally, bevacizumab, or placebo. In this study, PFS with paclitaxel alone was 9 months versus 11.5 months for paclitaxel/bevacizumab. While the combined bevacizumab/paclitaxel arm had a median PFS that was remarkably similar to E2100, the paclitaxel-alone arm of 9 months in the TORI 010 trial was markedly different from the 5.9 months observed in E2100. A recently presented phase 2 trial with weekly paclitaxel (90 mg/m$^2$) and bevacizumab (10 mg/kg) on days 1 and 15 in Japanese patients with HER-2 negative MBC ($n$=120) reported a median PFS of 12.9 months (95% CI 11.1–18.2) and median OS of 35.8 months (95% CI 26.4–not reached) [19]. Thus, two additional large trials confirm the long PFS seen with the same weekly paclitaxel/bevacizumab combination utilized in the E2100 trial.

The next randomized phase 3 trial performed after E2100 was the AVADO (Avastin and Docetaxel) trial, a double-blind, placebo-controlled trial (Table 1). This trial investigated the efficacy of docetaxel +/− bevacizumab as first-line therapy in patients with HER2-negative MBC breast cancer. It also explored two different dose levels of bevacizumab. The majority of patients (75%) had received prior adjuvant chemotherapy, with anthracycline-based and/or prior taxane therapy. The primary end point in this trial was PFS between control arm and each dose level of

bevacizumab. This study, however, was not powered to detect a difference between both bevacizumab doses. Patients ($n$=736) were randomized to receive docetaxel (100 mg/m$^2$) every 21 days plus either: bevacizumab (7.5 mg/kg), bevacizumab (15 mg/kg), or placebo. Patients were required to receive docetaxel for a maximum of nine cycles or until the development of adverse toxicities or disease progression, whichever came first. This design differs from the E2100 trial where paclitaxel was given to disease progression. By contrast, in the AVADO trial, two dose reductions of docetaxel were permitted in the event of severe toxicities to 75 mg/m$^2$ and/or 60 mg/m$^2$. Patients in this trial were also permitted to continue on bevacizumab or placebo after discontinuation of docetaxel as maintenance therapy until disease progression. At the time of progression, all study participants were given the option to receive bevacizumab in conjunction with second-line chemotherapy. A significant improvement in median PFS was again observed with the addition of bevacizumab at both 7.5 mg/kg (9.0 vs 8.1 months, stratified HR=0.8, $P$=0.045) and 15 mg/kg (10.0 vs 8.1 months, stratified HR=0.67, $P$=0.0002). Significantly higher ORR rates were also observed with both doses of bevacizumab (7.5 mg/kg: 55.2% vs 46.4%, $P$=0.0739; 15 mg/kg: 64.1% vs 46.4%, $P$=0.0003). However, as in the two prior studies, the addition of bevacizumab to cytotoxic chemotherapy was not found to be associated with any significant increase in median OS, either at 7.5 mg/kg (30.8 vs 31.9 months, HR=1.05, $P$=0.72) or 15 mg/kg (30.2 vs 31.9 months, HR=1.03, $P$=0.85). The inclusion of the cross-over design likely also contributed to the absence of an overall survival benefit being observed with the addition of bevacizumab. There were no additional safety concerns in this trial with the addition of bevacizumab to docetaxel. The incidence of severe hemorrhagic or thromboembolic events with both bevacizumab doses was comparable to the prior studies and was not significantly different from what was observed in patients who received docetaxel alone.

The RIBBON trials were essentially two separate randomized placebo-controlled phase 3 trials designed to determine the optimal chemotherapy to combine with bevacizumab. A variety of chemotherapy regimens were combined with bevacizumab as either first-line (RIBBON-1) or second-line (RIBBON-2) therapy in patients with HER-2 negative MBC. These studies essentially addressed the possibility that the anti-tumor activity of bevacizumab is chemotherapy specific and may potentially explain differences noted in previous trials. In RIBBON-1, patients ($n$=1,237) were randomized in a 2:1 ratio to receive chemotherapy with or without bevacizumab (15 mg/kg intravenously) every 3 weeks. The specific type of chemotherapy was at the discretion of the treating oncologist. Patients could be treated with a variety of options, including a taxane (docetaxel or nab-paclitaxel, but not weekly paclitaxel), an anthracycline, or capecitabine. The primary end point was PFS, with OS being a secondary end point. A significant improvement in median PFS was observed with bevacizumab plus a taxane or anthracycline over chemotherapy alone (9.2 vs 8.0 months; $P$<0.0001). Similarly, PFS was significantly improved with bevacizumab/capecitabine over capecitabine alone (8.6 vs 5.7 months; $P$<0.0002). No significant improvement in OS was observed with the bevacizumab-containing arms. For the group of patients who received capecitabine, the estimated hazard ratio for OS was 0.85 (95% CI, 0.63–1.14; $P$=0.27). There was a trend for an improved 1-year survival rate with capecitabine/bevacizumab relative to capecitabine plus placebo (81.0% vs 74.4%, respectively; $P$= 0.076). For patients who received anthracyclines or taxanes (+/− bevacizumab), the stratified HR for OS was 1.03 (95% CI, 0.77–1.38; log-rank $P$=0.83). For patients who received anthracyclines or taxanes alone versus the same chemo plus bevacizumab, 1-year survival rates were 83.2% and 80.7%, respectively ($P$=0.44).

In the RIBBON-2 trial, bevacizumab-naïve patients ($n$=684) were randomized to receive second-line chemotherapy (determined by treating oncologist) with bevacizumab or placebo. Possible chemotherapeutic options were a taxane (weekly paclitaxel or every-3-week paclitaxel, nab-paclitaxel or docetaxel), capecitabine (200 mg/m$^2$ days 1–14 on 3-week cycle), gemcitabine (1,250 mg/m$^2$) on days 1 and 8 every 3 weeks, or vinorelbine (30 mg/m$^2$) weekly. Patients who received second-line cytotoxic chemotherapy plus bevacizumab had significantly longer PFS than patients who received chemotherapy alone (7.2 vs 5.1 months; $P$<0.072). These results were also consistent across all chemotherapy subgroups, except for the vinorelbine subgroup which may have been due to the fact that it included only 76 patients. There was no significant overall survival advantage noted with the addition of bevacizumab to chemotherapy relative to chemotherapy alone.

A recently presented meta-analysis by Valachis et al. [20••] pooled data from E2100, AVADO, and RIBBON-1. It reaffirmed that the addition of bevacizumab to different chemotherapeutic agents in the first-line treatment of MBC significantly improves PFS, with a pooled HR of 0.70 (95% CI, 0.60–0.82; $P$<0.001). This benefit in delay of tumor progression was seen across various subgroups and was independent of dominant sites of metastases, hormone receptor status, or prior adjuvant taxane use. The addition of bevacizumab to cytotoxic chemotherapy was also found to be associated with a significant improvement in overall response rates ($P$<0.001). However, even when data from

these three trials were polled together, no significant improvements in OS were observed with bevacizumab-containing arms as evidenced by a pooled HR of 0.90 (95% CI, 0.80–1.03; $P$=0.119) [20••].

## ATHENA Registry Trial

ATHENA is an open-label single-arm international study involving 2251 MBC patients who received first-line therapy with bevacizumab plus taxane monotherapy or combination chemotherapy [21••]. This study represents the largest study of MBC patients treated with bevacizumab-containing chemotherapy regimens in the context of a general oncology setting. The primary objective of this study was to evaluate the overall safety profile of bevacizumab when combined with chemotherapy in a broader population of patients with MBC that more closely represents a patient population typical of routine clinical oncology practice.

Patients were able to receive (at the discretion of the treating oncologist) bevacizumab 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks in combination with a taxane regimen or any other alternate chemotherapy regimen (excluding anthracyclines). Patients in this study had primarily estrogen receptor–positive breast cancer (66.1%) and had >3 metastatic sites (64%). Most patients received paclitaxel (35%) or docetaxel (33%) alone. Of the patients that received paclitaxel, most received it on a weekly schedule (17%), versus every 3 weeks (13%) or other (6%). The most frequently utilized non-taxane chemotherapy were capecitabine (5%) and vinorelbine (3%). First-line bevacizumab in combination with taxane-based chemotherapy was found to be well tolerated with a low incidence of severe adverse events (SAEs) in a broad group of MBC patients. The incidence of grade 3–4 hypertension was 4.4%, lower than what was reported in E2100 (16%), but similar to AVADO (4.5%). Moreover, other bevacizumab-related SAEs (grade≥3) were uncommon: proteinuria (1.7%), arterial/venous thromboembolism (3.3%), perforation (0.26%), and congestive heart failure (0.44%). The overall efficacy was similar to what has been previously reported in phase 3 trials. The overall response rate (best response) was 52% in the intent-to-treat population, with an additional 33% of patients with stable disease as their best response. The overall median TTP was 9.5 months (95% CI, 9.1–9.9). When evaluating patients who received paclitaxel monotherapy with bevacizumab, the median TTP was 9.8 months (95% CI, 9.1–10.5).

These results are consistent with those from the first-line bevacizumab randomized trials in a patient population that more closely mirrors patients treated in general oncology practice. Interestingly, in the ATHENA trial there were approximately 170 patients who were 70 years of age or older. A subanalysis that was recently published [22••] found the overall incidence of bevacizumab-related serious adverse toxicities were similar to that noted in younger patients (<70 years). For instance, the only grade ≥3 toxicities that were more commonly observed in patients 70 or older included hypertension (6.9% vs 4.2%) and proteinuria (4.0% vs 1.5%). Grade 3 or higher arterial/venous thromboembolic events, CNS hemorrhage, or cardiac events were similar in older and younger patients. Moreover, in this older subset of patients, where approximately half were treated with single-agent paclitaxel plus bevacizumab, the median TTP was 10.4 months.

## Overall Safety Profile with Bevacizumab

In the recent ruling by the FDA in December 2010 to remove the breast cancer indication from bevacizumab, one of the primary reasons for this decision was due to concerns that patients receiving bevacizumab experienced a significant increase in serious side effects [23]. Clearly bevacizumab has a side effect profile that is distinct from that seen with traditional cytotoxic chemotherapy, and appears not to be intrinsic to bevacizumab, but a class-specific effect seen with other anti-angiogenic agents that target VEGF. These toxicities include hypertension, proteinuria, thrombosis, and hemorrhage [24]. There appears to be a significant dose-dependent increase in the risk of proteinuria and hypertension associated with bevacizumab therapy [25]. However, proteinuria and hypertension are fairly uncommon, and, for the most part, manageable. The bevacizumab-expected side effects were remarkably similar across all of these trials and did not really change when combined with several different types of chemotherapy. Moreover, the overall incidence of bevacizumab-related grade 3–5 adverse toxicities in these trials appears to be the same or perhaps even slightly lower than reported levels in the trials that led to FDA approval of bevacizumab in metastatic colon cancer, NSCLC, renal cell carcinoma, or glioblastoma multiforme (Table 2).

Therefore, after reviewing available MBC phase 3 safety (AVF2119g, E2100, AVADO, RIBBON- 1, and RIBBON-2), bevacizumab generally appeared to be well tolerated. There were no new safety signals or additional safety concerns with bevacizumab that were revealed by these trials despite evaluation of several different chemotherapy combinations. Adverse events (AEs) due to bevacizumab are typically mild to moderate and/or manageable with standard medication, and they rarely require discontinuation of therapy. However, some distinctly uncommon AEs, including arterial thrombosis and cardiac toxicity, are more serious and require additional monitoring and awareness.

**Table 2** Grade 3–4 SAEs in bevacizumab phase 3 trials in FDA-approved indications and median PFS and OS

| Cancer type | Grade 3–4 SAEs occurring ≥2% of chemotherapy-alone arms;% absolute increase over control arm | | | | | |
|---|---|---|---|---|---|---|
| | Bleeding | Hypertension | Venous thromboembolism | Proteinuria | Significant improvement median PFS? | Significant improvement median OS? |
| NSCLC [48] | 3.7% | 6.3% | 2% | 3% | Yes (6.2 vs 4.5 month) | Yes (12.3 vs 10.3 month) |
| mCRC [49] | — | 10% | 4% | — | Yes (8.8 vs 6.8 month) | Yes (20.3 vs 15.6 month) |
| MBC [42] | 0.5% | 14.8% | 1.5% | 3% | Yes | No |
| GBM [50] | 1.2% | 4.9% | 6% | — | No | No |
| mRCC [51] | 3% | 3% | 2% | 7% | Yes (10.2 vs 5.4 month) | No |

*GBM* glioblastoma multiforme; *MBC* metastatic breast cancer; *mCRC* metastatic colorectal cancer; *mRCC* metastatic renal cell cancer; *NSCLC* non–small cell lung cancer; *OS* overall survival; *PFS* progression-free survival; *SAE* severe adverse event

## Phase 3 Data with Bevacizumab in MBC: What Have We Learned?

It appears that the safety concerns of bevacizumab that were one of the primary reasons in the FDA's decision to remove the metastatic breast cancer indication are not justified based on the available data. However, two other arguments remain against using bevacizumab in MBC that need to be discussed. The first argument is that bevacizumab does not have sufficient activity to warrant its routine use, as it does not appear to prolong overall survival. The second is an economic one, suggesting that the use of bevacizumab in MBC is not cost-effective and that its significant costs outweigh the modest clinical benefit.

Before we discuss the merits of these arguments, what have we learned from these well-designed phase 3 trials? There are several conclusions that can be made. First, combining bevacizumab with several different chemotherapies as either first-line (all trials) or second-line therapy (one of two trials) significantly delays tumor progression in MBC. When looking at trials separately this effect is likely in the range of 1–3 months over that of standard cytotoxic chemotherapy alone; or when looking at the hazard ratio from the meta-analysis there is an approximate 30% relative improvement in delay of tumor progression over chemotherapy alone. Second, the overall differences between weekly paclitaxel and paclitaxel plus bevacizumab seen in E2100 are likely anomalous, due to aberrantly low median PFS time (5.9 months) observed in the control arm. Moreover, if the median PFS with weekly paclitaxel alone had been similar to that reported in other studies (ie, approximately 9 months as reported in CIRG/TORI 010), then these results would have been in line with the other trials discussed here. What has been consistently shown in three different trials now is that the combination of weekly paclitaxel and bevacizumab is associated with a median PFS of approximately 12 months. Third, a lower bevacizumab dose of 7.5 mg/kg every 3 weeks did not result in inferior PFS or OS than 15 mg/kg dose, when combined with docetaxel (AVADO). Fourth, the overall safety profile of bevacizumab was consistent across all trials and there were no new bevacizumab safety concerns raised in any of these trials. Even when looking at women 70 and older, the use of bevacizumab in a routine clinical practice setting in the ATHENA registry trial appeared to be reasonably safe. Finally, while overall response rates are higher, there appears to be no significant improvement of OS with the addition of bevacizumab to chemotherapy.

This leads to an important, but unanswered question: why was no difference in median OS observed? It is important to note that some trials may not have been sufficiently powered to detect small differences in OS, since the primary end point was PFS. One common explanation is that no OS difference was observed because of the impact of additional lines of therapy after progression of disease. It is clearly true in MBC that the many available therapeutic options could confound detection of differences in OS between two different groups of patients. However, this is not universally true and there have been other trials where OS differences were observed in MBC patients even though they likely received many subsequent lines of therapy after randomization. One example is a recent study with the chemotherapeutic agent eribulin where patients with anthracycline and taxane refractory MBC were randomized to receive either eribulin or single-agent treatment of physician's choice. This trial demonstrated that the median OS of eribulin (13.1 months; 95% CI, 11.8–14.3) was significantly longer ($P$=0.041) than standard single-agent chemotherapy (10.6 months; 95% CI, 9.3–12.5; hazard ratio 0.81; 95% CI, 0.66–0.99) [26, 27].

Most clinical trials do not collect data on post-trial therapy, and without this it would be impossible to determine with any certainty, whether there were any differences in post-trial systemic therapies received by patients in bevacizumab and non-bevacizumab groups [28]. Another explanation for no significant OS difference could be due to a cross-over effect when patients in non-bevacizumab arms are allowed to receive bevacizumab at

the time of progression. There are data to support this hypothesis. Di Leo and colleagues [29] found that when some randomized phase 3 trials were re-analyzed, and patients who crossed-over to receive the experimental agent at time of progression were censored, a significant survival benefit was observed. However, recent data presented in ASCO 2011 by the FDA raise questions about the relationship between PFS and OS. It has been assumed that there is a strong relationship between these two end points. But, when the FDA reviewed phase 3 data from 12 trials that were submitted to support approval in MBC, no significant association between PFS and OS was seen [30]. These data call into the question the notion that drugs that significantly prolong PFS should necessarily also significantly prolong OS.

Another possibility may be that a small percentage of MBC patients derive a meaningful benefit from the addition of bevacizumab to chemotherapy, and therefore the benefit is diluted when the majority of patients don't derive a benefit. A dilution effect, analogous to treating all MBC patients with trastuzumab, and not only those with HER-2 amplified disease, would be addressed by identification of a good predictive marker. It is likely that development of an accurate predictive biomarker for anti-angiogenic therapy would translate into seeing a much larger therapeutic effect of the addition of bevacizumab to cytotoxic chemotherapy. Work has already been done to identify anti-angiogenic markers to measure the biologic effect of bevacizumab, but little has been established in terms of discovering and validating predictive biomarkers.

Some of the surrogate markers that have been explored include vascular imaging or correlating hypertension induced by bevacizumab in certain patients with a favorable clinical response. Thus far, imaging studies have not been found to be very accurate in predicting the efficacy of anti-angiogenic therapy [31]. Induction of hypertension after initiation of bevacizumab, however, has been shown to be associated with a more favorable prognosis. In a retrospective review of patients enrolled in the E2100 study, the presence of grade 3 or 4 hypertension was significantly associated with increased duration of OS, compared with patients who had no hypertension (38.7 vs 25.3 months, $P=0.002$) [32].

Schneider and co-workers [32] investigated five VEGF and two VEGF receptor 2 polymorphisms in retrospective subset analyses of the E2100 trial cohort. Two VEGF genotypes (VEGF-2578AA and VEGF-1154AA) were significantly associated with improved OS in the bevacizumab plus paclitaxel group (interaction for treatment effect $P=0.02$ and $P=0.0049$, respectively). However, the VEGF-2578AA and VEGF-1154AA polymorphisms did not predict PFS benefit (only OS), raising doubts as to the validity of the findings. Other biomarkers have also been investigated. There are data to support further investigation into measurement of intratumoral VEGF levels [33], circulating ICAM-1 levels [34], measurement of circulating endothelial cells [35], as well as baseline CD31, PDGFR-β, and gene ontology (GO) classes for VEGFR activity and mitosis levels [36]. Moreover, markers of possible resistance to anti-VEGF therapies have been identified from preclinical models, including Bv8, platelet-derived growth factor C (PDGF-C), neuropilin-1, and δ-like protein 4 (DLL4) [31, 37]. VEGF polymorphisms are so far the only biomarkers to show potential, but important questions remain about their clinical utility [31].

## Regulatory History of Bevacizumab in MBC: Differences in Data Interpretation Between FDA and EMA

Bevacizumab received its first cancer indication in February 2004 when the FDA approved it for the treatment of metastatic colorectal cancer [2]. This approval was based on data from the E3200 phase 3 randomized trial, which showed that the addition of bevacizumab to oxaliplatin/5-FU–based chemotherapy significantly prolonged median OS from 15.6 to 20.3 months [38]. Subsequent to this, bevacizumab received indications in other solid tumors including non–small cell lung cancer (NSCLC), glioblastoma, and renal cell carcinoma. On March 28, 2007, the European Medicines Agency (EMA) approved bevacizumab in combination with paclitaxel for the first-line treatment of MBC based on E2100 trial results. Approximately 1 year later in March 2008, the FDA granted accelerated approval of bevacizumab in the treatment of MBC, contingent on additional data that confirmed improvement of PFS. On July 20, 2010, after reviewing all available data, including the RIBBON-1 trial, the Oncologic Drugs Advisory Committee, an independent advisory committee composed primarily of oncologists, voted 12–1 to remove the metastatic breast cancer indication from bevacizumab's label. In December 2010, the FDA announced its decision to remove the indication for bevacizumab in MBC based primarily on the finding that the combination of bevacizumab with cytotoxic chemotherapy did not prolong overall survival, nor slowed disease progression sufficiently to warrant the risks that bevacizumab presented to patients [23]. Concerns over the significant increases in serious side effects observed in the phase 3 trials, including bleeding, perforation, and thromboembolic events, were cited despite the fact that the above-discussed phase 3 breast cancer trials did not demonstrate any new safety concerns with bevacizumab, and the overall incidence of these toxicities was no higher than those found in metastatic colorectal cancer trials (Table 2).

On the other hand, European regulatory authorities came to a different conclusion than the FDA, and bevacizumab continues to be an accepted option for MBC. In fact, the EMA's Committee for Medicinal Products for Human Use (CHMP) has given approval for extending the indication of bevacizumab in MBC, and also permitting it to be combined with capecitabine in the first-line setting when a taxane/anthracycline combination cannot be used.

## Is Bevacizumab Cost-Effective in Treating MBC?

Our group recently assessed the cost-effectiveness of bevacizumab in combination with paclitaxel [39]. We developed a decision-analytical model using efficacy and adverse events data from the ECOG 2100 trial. Health utilities were derived from the available literature. Costs were obtained from the Center for Medicare Services Drug Payment Table and Physician Fee Schedule with a payer perspective and are represented in 2010 US dollars. Bevacizumab added 0.49 years of PFS and 0.135 quality-adjusted life-year (QALY) with an incremental cost of $100,300 and therefore a cost of $204,000 per year of PFS gained and an incremental cost-effectiveness ratio (ICER) of $745,000 per QALY. The main drivers of the model were drug acquisition cost, PFS, and health utility values. Using a threshold of $150,000/QALY, drug price would have to be reduced by nearly 80% or alternatively PFS increased by 10 months to make bevacizumab cost-effective. The results of the model were robust in sensitivity analyses. One other evaluation has been published with an assessment of the cost-effectiveness of bevacizumab added to paclitaxel with a Swiss health care system perspective. The authors used a Markov model and also derived the clinical benefits from ECOG 2100 [40]. They showed that bevacizumab cost an additional EUR 40,369 and generated an increment of 0.22 QALY and an ICER of EUR 189,427/QALY. In their probabilistic sensitivity analysis, the willingness to pay threshold of EUR 60,000 was never reached. These results suggest that bevacizumab added to paclitaxel is not cost-effective at currently accepted thresholds in the treatment of metastatic breast cancer.

## Future Directions and Conclusions

Three arguments can be made when deciding whether or not bevacizumab should be used in routine clinical practice to treat MBC: safety, efficacy, and cost. While the FDA cited safety concerns primarily for its reasons to remove bevacizumab's MBC indication, the preponderance of the phase 3 data shows that there were no new safety concerns with bevacizumab compared with other disease settings. Moreover, the data showed that the overall frequencies of bevacizumab-related toxicities were remarkably similar when combined with several different chemotherapeutic agents. When evaluating the efficacy data, there is a clear benefit in the first-line setting in that bevacizumab does prolong PFS. What remains unanswered from the data is whether prolongation of PFS is enough to judge bevacizumab efficacious or does one have to show clear prolongation of OS. If the removal of the breast cancer indication was due to lack of an OS benefit, then this raises the question why the FDA has not also revoked bevacizumab's indication in metastatic renal cell cancer and glioblastoma multiforme since the addition of bevacizumab to interferon and irinotecan, respectively, didn't prolong OS (Table 2). In this light, the decision by the FDA to remove the MBC indication appears rather arbitrary.

Although speculative, the results of breast cancer adjuvant trials with bevacizumab based on the PFS advantage seen in E2100 may be instructive. If these trials are ultimately found to show a survival benefit over non–bevacizumab-containing control arms, it would provide support for the contention that PFS improvements in MBC may translate into significant improvements in OS in the adjuvant setting.

When looking at the cost argument, it seems apparent that bevacizumab is expensive and not cost effective. This is not unique to bevacizumab of course, but is a fact of cancer care in the 21st century. Market-based policy solutions that are most effective in bringing down the cost curve of oncology care go beyond the scope of this review. While the ultimate decisions of the FDA are putatively not based on cost whatsoever, from a societal vantage point physicians who have access to expensive interventions should consider the cost-effectiveness or lack thereof of cancer drugs and be better stewards of finite health care resources [41].

There are many ways that bevacizumab could be utilized in a more cost-effective manner in the setting of MBC. For example, on the efficacy side, identification of robust predictive markers may greatly enhance the efficacy of bevacizumab in MBC since treating only those patients likely to respond would make it more cost effective. On the cost side of the equation, technical advances that reduce the production cost of monoclonal antibodies would have a favorable impact on the cost-effectiveness of bevacizumab.

Bevacizumab is well tolerated in patients and its safety profile in MBC is similar to that seen in other disease-site approved indications. The advantage of bevacizumab in prolonging PFS in patients with MBC has been consistent across several phase 3 randomized trials, but this did not translate into a significant overall survival advantage. The consistent finding of median PFS of approximately 12 months specifically with weekly paclitaxel and bevaci-

zumab in three different trials is especially noteworthy suggesting that the type of chemotherapy bevacizumab is combined with matters in MBC. The debate concerning the relevance of PFS as a study end point remains problematic and unresolved. However, bevacizumab remains an FDA-approved therapy in metastatic renal cell cancer and glioblastoma despite no demonstrable prolongation of OS. Based on all the available evidence, bevacizumab is no foe of patients with metastatic breast cancer from the perspective of safety and efficacy. Until PFS has definitively been shown not to be a valid study end point, a more prudent decision would have been to continue the MBC indication—at least for the combination of weekly paclitaxel and bevacizumab—and allow physicians and patients to draw their own conclusions rather than an apparently arbitrary governmental decision.

**Disclosure** A. J. Montero: none; M. Escobar: none; G. Lopes: honoraria from Roche and Genentech; S. Glück: honoraria from Genentech; C. Vogel: consultant to Genentech, Amgen, Sandoz, and Merck and educational presentations/speakers' bureaus for Amgen, GlaxoSmithKline, GTx, Genentech, and Sanofi.

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