

Randomized Phase III Trial of Capecitabine Compared With Bevacizumab Plus Capecitabine in Patients With Previously Treated Metastatic Breast Cancer

Kathy D. Miller, Linnea I. Chap, Frankie A. Holmes, Melody A. Cobleigh, P. Kelly Marcom, Louis Fehrenbacher, Maura Dickler, Beth A. Overmoyer, James D. Reimann, Amy P. Sing, Virginia Langmuir, and Hope S. Rugo

From the Indiana University, Indianapolis, IN; University of California Los Angeles, Los Angeles; Kaiser Northern California, Vallejo; Genentech Inc, South San Francisco; University of California San Francisco, San Francisco, CA; US Oncology, Houston, TX; Rush-Presbyterian-St Luke's Medical Center, Chicago, IL; Duke University, Durham, NC; Memorial Sloan Kettering Cancer Center, New York, NY; Case Western University, Cleveland, OH.

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Kathy D. Miller, MD, Indiana University Cancer Pavilion, 535 Barnhill Dr, RT-473, Indianapolis, IN 46202; e-mail: kathmill@iupui.edu.

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ABSTRACT

Purpose

This randomized phase III trial compared the efficacy and safety of capecitabine with or without bevacizumab, a monoclonal antibody to vascular endothelial growth factor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane.

Patients and Methods

Patients were randomly assigned to receive capecitabine (2,500 mg/m²/d) twice daily on day 1 through 14 every 3 weeks, alone or in combination with bevacizumab (15 mg/kg) on day 1. The primary end point was progression-free survival (PFS), as determined by an independent review facility.

Results

From November 2000 to March 2002, 462 patients were enrolled. Treatment arms were balanced. No significant differences were found in the incidence of diarrhea, hand-foot syndrome, thromboembolic events, or serious bleeding episodes between treatment groups. Of other grade 3 or 4 adverse events, only hypertension requiring treatment (17.9% v 0.5%) was more frequent in patients receiving bevacizumab. Combination therapy significantly increased the response rates (19.8% v 9.1%; $P = .001$); however, this did not result in a longer PFS (4.86 v 4.17 months; hazard ratio = 0.98). Overall survival (15.1 v 14.5 months) and time to deterioration in quality of life as measured by the Functional Assessment Of Cancer Treatment—Breast were comparable in both treatment groups.

Conclusion

Bevacizumab was well tolerated in this heavily pretreated patient population. Although the addition of bevacizumab to capecitabine produced a significant increase in response rates, this did not translate into improved PFS or overall survival.

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INTRODUCTION

Metastatic breast cancer (MBC) remains a devastating disease, claiming the lives of more than 40,000 women in the United States each year.¹ Though an expanding array of active agents has become available for the treatment of metastatic disease, overall survival has changed little in the last half century.² While response rates $\geq 30\%$ are routinely achieved in previ-

ously untreated patients, response rates decrease significantly in patients previously exposed to chemotherapy.³

Further therapeutic advances require new strategies that are based on an understanding of breast cancer biology. Invasion and metastasis of breast cancer depends on angiogenesis, the formation of new blood vessels that nourish the tumor.^{5,6} Extensive laboratory data suggest that angiogenesis plays an essential role in breast cancer

development, invasion, and metastasis.⁷⁻¹⁰ Clinicopathologic correlations confirm this role. Breast cancer vascularity, quantified by tumor microvessel density, predicts tumor shedding at the time of surgery,¹¹ bone marrow micrometastases,¹² recurrence, and overall survival.¹³⁻¹⁵ This nascent vascular network provides a unique opportunity for therapeutic intervention.

Vascular endothelial growth factor (VEGF) is among the most potent stimulators of angiogenesis. In addition to endothelial cell mitogenesis and migration, VEGF inhibits endothelial cell apoptosis and supports maintenance of the newly formed tumor vasculature. VEGF produces other biologic effects, including induction of proteinases that remodel extracellular matrix, increased vascular permeability, vasodilation, and inhibition of antigen-presenting dendritic cells.¹⁶

Bevacizumab (Avastin; Genentech, South San Francisco, CA), a humanized monoclonal antibody (mAb) directed against all isoforms of VEGF-A, inhibits growth of human tumors in animal models.¹⁷ A phase II study of bevacizumab monotherapy in 75 patients with previously treated MBC reported a 9.3% objective response rate, with 17% of patients responding or stable at 22 weeks; four patients continued therapy without progression for more than 12 months.¹⁸ Bevacizumab, alone and in combination with chemotherapy, was well tolerated, with hypertension, proteinuria, thrombosis, and bleeding being the most commonly reported toxicities.¹⁹⁻²² Given the efficacy and minimal toxicity in the phase II studies, this randomized phase III study was initiated to compare capecitabine monotherapy with the combination of capecitabine plus bevacizumab in patients with previously treated MBC.

PATIENTS AND METHODS

Patient Eligibility

Women with histologically or cytologically confirmed MBC were eligible if they had received prior therapy with both an anthracycline and a taxane, and at least one, but no more than two, prior chemotherapy regimens for metastatic disease. If relapse occurred within 12 months of completing adjuvant anthracycline and taxane therapy, patients were eligible without intervening chemotherapy. Patients with HER2-positive disease (3+ protein expression by immunohistochemistry or gene amplification by fluorescence in situ hybridization) must have progressed following trastuzumab. Additional inclusion criteria included bidimensionally measurable disease with at least one lesion measuring ≥ 2 cm; Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate renal, hepatic, and hematologic function.

Patients were excluded if they had any history or radiographic evidence of CNS disease; screening head computed tomography or brain magnetic resonance image was required. Patients could not have other primary malignancy except basal cell carcinoma of the skin or in situ cervical cancer within 5 years, major surgery within 4 weeks, other antitumor therapy within 21 days, nonhealing wound or fracture, infection requiring parenteral

antibiotics, or clinically significant cardiovascular disease. Therapeutic anticoagulation, regular nonsteroidal anti-inflammatory medication, and aspirin (> 325 mg/d) were prohibited, but prophylactic anticoagulants to maintain a vascular access device were permitted. Concurrent administration of bisphosphonates was allowed if initiated at least 21 days before study entry. Women of reproductive potential were required to use effective contraception.

Local institutional review boards approved the protocol, and patients provided written informed consent before screening.

Treatment Plan

All patients received capecitabine 2,500 mg/m²/d (1,875 mg/m²/d if creatinine clearance 30 to 50 mL/min), orally twice daily for 14 days followed by a 7-day rest period. Capecitabine was interrupted for grade 2 or 3 toxicity and resumed at a reduced dose (75% starting dose for first occurrence, 50% at second occurrence) on resolution to less than grade 2. Capecitabine was discontinued if toxicity $\geq$ grade 2 recurred after two dose reductions, and for grade 4 toxicity.

Patients randomized to the combination arm received bevacizumab (15 mg/kg) intravenously on day 1 of each 3-week cycle. Initially, bevacizumab was infused over 90 minutes. If no infusion-related reactions occurred, subsequent infusions were reduced to 60, then 30 minutes. Premedication was optional. Treatment was interrupted for proteinuria $\geq 2,000$ mg per 24 hours and resumed on resolution to less than 2,000 mg per 24 hours. Blood pressure was monitored before and immediately after each bevacizumab infusion; antihypertensive therapy was given at the investigator's discretion. Bevacizumab therapy was not withheld or discontinued for capecitabine-related toxicities.

Patients continued therapy for a maximum of 35 cycles or until disease progression or prohibitive toxicity. Patients without progression at the completion of 35 cycles could continue the same treatment on an extension study. Patients randomized to the combination arm could continue bevacizumab, either alone or with other therapies, after initial disease progression. Patients randomly assigned to capecitabine monotherapy could not receive bevacizumab at any time.

Safety and Efficacy Assessments

Patients were evaluated before each treatment cycle. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Disease status was assessed at baseline, every 6 weeks until 24 weeks, then every 9 weeks until progression. Contrast-enhanced spiral computed tomography of the chest, abdomen, and pelvis was required at each evaluation. In patients with known bone involvement, bone scans were performed at baseline and were repeated as clinically indicated. Visible cutaneous lesions were photographed. All images and clinical information were forwarded to an independent review facility (IRF; RadPharm, Princeton, NJ) for evaluation by radiologists and oncologists blinded to treatment assignment and local response designation. Response was characterized according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria,²³ with the following minor modifications: target lesions were required to be ≥ 2 cm in diameter; unequivocal progression of nontarget lesions required the lesion to be measured at baseline when possible; if measurable, the lesion diameter must have doubled to at least 2 cm; target lesions measured by physical examination had to be clearly visible in good-quality photographs containing a ruler. All patients were monitored for survival every 4 months.

Pharmacokinetics

Pharmacokinetics (PK) were assessed in a subset of patients. For patients in the combination arm, serum samples measured bevacizumab during cycles 1, 3, 5, 7, and 9 (predose and 10 minutes following completion of infusion). Samples to measure capecitabine and its metabolites 5'-deoxy-5-fluorouridine (5-DFUR) and fluorouracil (FU) were drawn during cycles 1 and 3 (predose and 90, 150, and 240 minutes postdose). Exposure to chemotherapy (area under the curve [AUC], 0 to 240 minutes) was assessed for each of the three analytes (capecitabine, FU, and 5-DFUR) and was normalized to capecitabine dose.

Quality of Life

Quality of life (QOL) was assessed using the Functional Assessment Of Cancer Treatment—Breast (FACT-B) questionnaire at baseline, every 6 weeks until 24 weeks, and then every 9 weeks. Time to deterioration in QOL (TDQ) as measured by the Trial Outcome Index (TOI; the sum of the physical well-being, functional well-being, and breast cancer-specific questions in the FACT-B) was the primary end point.²⁴ A decline in TOI of more than five points from baseline, disease progression, or death was considered a clinically meaningful deterioration in QOL. Formal comparison of TDQ used the unstratified log-rank test.

Statistical Analysis

The primary end points were progression-free survival (PFS) as determined by the IRF, and safety of the combination in this patient population. PFS was defined as time from randomization to the date of IRF-documented disease progression or death. The investigator (INV) assessment was used for three patients lacking an IRF assessment. Patients without an event were treated as censored at the time of the last tumor assessment. Secondary end points included PFS based on INV assessment, objective response rate and duration as determined by both IRF and INV, and QOL and survival.

Sample size calculations assumed a two-sided log-rank test, 90% power at the 5% significance level, a hazard ratio of bevacizumab versus control of 0.667 (improvement in median PFS from 4 to 6 months), and one interim analysis at 50% information time, which required 265 events. Enrollment of 400 patients would allow analysis when 66% of patients had progressed. The study would stop at the interim analysis if the hazard ratio for PFS was less than 0.5 (1-sided $P < .0001$) or greater than 1, corresponding to an asymmetric stopping boundary (the efficacy interim analysis was later cancelled due to delayed availability of IRF assessments). An independent data monitoring committee reviewed all deaths, and serious and targeted adverse events (grade 3 and 4 diarrhea, grade 3 hand-foot syndrome, grade 3 and 4 bleeding, and any thrombosis) monthly until December 2001. The protocol was extended to enroll approximately 50 additional patients for PK assessment. Data cutoff for this analysis was 28 June 2002—3 months after the last patient was randomly assigned.

Random assignment was stratified for Eastern Cooperative Oncology Group performance status (0 or 1), number of prior chemotherapy regimens for metastatic disease (0 or ≥ 1), and study site. All randomly assigned patients were included in the efficacy (intent-to-treat) analysis. Safety analyses included only treated patients (analyzed as treated). A two-sided stratified log-rank test was performed at the 0.0498 level to determine whether PFS was prolonged for the bevacizumab plus capecitabine group compared with the capecitabine-alone group (type I error of 0.01% was allocated for both the safety and can-

celled efficacy interim analyses). An estimate of the hazard ratio $\lambda_{\text{bevacizumab} + \text{capecitabine}} / \lambda_{\text{capecitabine}}$ with 95% CIs was determined using a stratified Cox regression model with an indicator variable for treatment group. Median PFS in each treatment group was estimated using the Kaplan-Meier method. Because patients in the bevacizumab treatment arm were permitted to remain on study if capecitabine was discontinued for toxicity, tumor assessments more than 42 days after discontinuation of capecitabine were censored. Objective response rates were compared using the χ^2 test; overall survival comparisons used an unstratified log-rank test. Exploratory analyses to gauge the impact of potential prognostic factors on PFS were conducted using Cox regression to estimate treatment effect within various subgroups.

RESULTS

Patient Population

A total of 462 patients were randomly assigned between November 2000 and March 2002 at 96 US centers: 230 to capecitabine alone and 232 to combination treatment. Fifteen patients randomly assigned to capecitabine alone and three patients randomized to combination treatment never received study treatment and were not included in the safety analysis. Overall, 93 (20%) of the treated patients failed to meet one or more of the eligibility criteria; major reasons for ineligibility included prior therapy within 21 days ($n = 27$), more than two regimens for metastatic disease ($n = 19$), CNS involvement ($n = 10$), laboratory values out of range ($n = 10$), no chemotherapy for metastatic disease with relapse more than 12 months from adjuvant therapy ($n = 4$), and no prior anthracycline or taxane ($n = 3$). Analysis of major end points excluding ineligible patients did not affect the outcome (data not shown); therefore, results presented include all randomized patients. Baseline demographic and tumor characteristics were well balanced between treatment groups (Table 1).

Efficacy

The objective response rate (ORR) significantly improved with addition of bevacizumab, as determined by both the IRF (19.8% [95% CI, 14.7% to 25.0%]) ν 9.1% [95% CI, 5.4% to 12.9%]; $P = .001$) and the investigators (30.2% [95% CI, 24.3% to 36.1%]) ν 19.1% [95% CI, 14.1% to 24.2%]; $P = .006$). The IRF and investigator disagreed on disease progression in 105 patients (22.7%); investigator-determined progression was not confirmed by the IRF in 79 patients, most commonly when progression was determined by physical examination. In 26 patients, progression was determined by IRF review but not investigator review. The combination of capecitabine and bevacizumab did not increase PFS as determined by the IRF (hazard ratio, 0.98 [95% CI, 0.77 to 1.25]; $P = .857$; Figure 1A) or the investigator (data not shown). The median duration of response and the proportion of subjects with responses of

Table 1. Patient Characteristics

Characteristic	Capecitabine (n = 230)		Capecitabine + Bevacizumab (n = 232)	
	No.	%	No.	%
Age, years				
Mean	52		51	
Range	30-77		29-78	
Race				
Black	25	10.9	30	12.9
White	185	80.4	187	80.6
Other	20	8.7	15	6.5
ECOG PS				
0	115	50.0	117	50.4
1	115	50.0	114	49.1
2	0	0	1	0.4
Estrogen receptor-positive	119	51.7	97	41.8
Progesterone receptor-positive	96	41.7	75	32.3
HER2-positive*	47	20.4	61	26.3
Duration of metastatic disease, years				
Median	1.3		1.0	
Range	0-19.3		0-13.2	
Visceral disease	184	80.0	180	77.6
≥ 3 sites of disease	116	50.4	114	49.1
Prior chemotherapy regimens for MBC				
0	37	16.1	35	15.1
1	98	42.6	107	46.1
2	87	37.8	79	34.1
3-5	8	3.5	11	4.7

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MBC, metastatic breast cancer.

*HER2-positive = 3+ by immunohistochemistry or amplification by fluorescence in situ hybridization.

more than 4 months' duration were similar in the two treatment groups (Fig 1B).

At data cutoff, 38% of patients had died. The majority of deaths (95.2%) were due to progressive disease. Two patients in the capecitabine-alone group died while on therapy: one patient suffered a cardiopulmonary arrest shortly after initiating treatment, and a second died from a presumed pulmonary embolus during cycle 2. No treatment-related deaths occurred during initial therapy in the combination arm. Median overall survival was similar in the two treatment groups (Fig 1C).

Safety

The addition of bevacizumab did not affect the frequency or severity of capecitabine toxicities (Table 2). Diarrhea (grade 3; 10.7% in the capecitabine-alone treatment group v 11.8% in the capecitabine plus bevacizumab treatment group), hand-foot syndrome (grade 3; 24.2% in the capecitabine alone v 27.5% in the combination therapy group), and need for dose modifications were similar in the two treatment groups. The mean delivered dose-intensity for capecitabine (80%) was similar to the combination therapy of capecitabine plus bevacizumab (75%). A total of 140 (65%) of

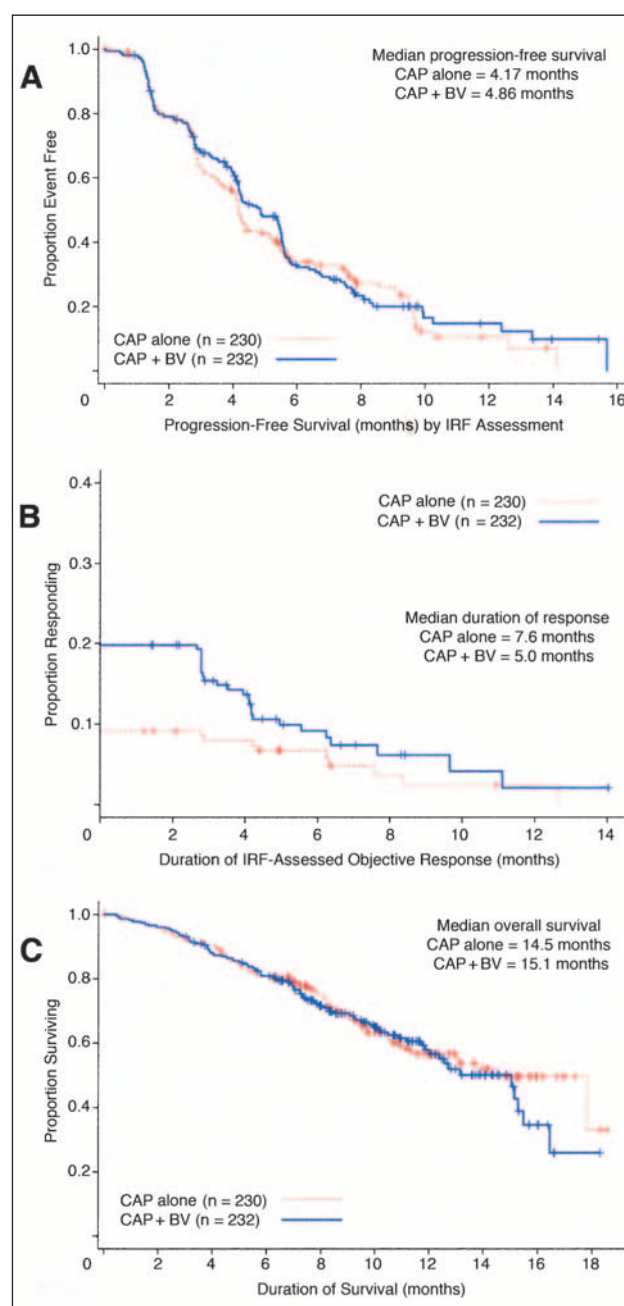


Fig 1. (A) The median progression-free survival by independent review facility (IRF) assessment, (B) median duration of IRF-assessed objective response, and (C) median duration of overall survival in both treatment groups. The investigator assessment was used for three patients lacking an IRF assessment. CAP, capecitabine; BV, bevacizumab.

215 patients in the capecitabine group required drug dose reduction, while 181 (79%) of 229 patients in the combination therapy group had their drug dose lowered. Twenty-nine patients (12.6%) in the capecitabine group and 28 patients (12.2%) in the combination group discontinued treatment due to toxicity. Eleven patients (4.8%) in the combination arm discontinued capecitabine but continued bevacizumab alone

Table 2. Common Capecitabine Toxicities

Toxicity	Capecitabine (n = 215)						Capecitabine + Bevacizumab (n = 229)					
	Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Diarrhea	34	15.8	23	10.7	0	0	37	16.2	27	11.8	0	0
Stomatitis	11	5.1	0	0	1	0.5	16	7.0	4	1.7	0	0
Hand-foot syndrome	77	35.8	52	24.2	0	0	97	42.4	63	27.5	0	0

NOTE. National Cancer Institute Common Toxicity Criteria worst grade experienced per patient.

for at least two cycles. There were no clinically significant infusion reactions.

Hypertension was more common in the combination arm but was generally managed with medical therapy; no patient experienced grade 4 hypertension (Table 3). Four patients discontinued bevacizumab because of hypertension. Changes in preinfusion mean systolic and diastolic blood pressure were -2.6 and -0.7 mmHg, respectively, in the capecitabine alone group, compared with $+5.5$ and $+4.6$ mmHg in the combination group. The risk for developing hypertension correlated only with bevacizumab treatment; no relationship was observed with duration of therapy or pre-existing hypertension.

Proteinuria was more common in patients receiving combination therapy but was rarely clinically significant. Two patients discontinued treatment because of grade 3 proteinuria. One patient subsequently developed nephrotic syndrome; renal biopsy revealed collapsing glomerulopathy. She had mild renal insufficiency at baseline (creatinine clearance 41 mL/min) and had received pamidronate, a drug known to be associated with collapsing glomerulopathy,^{25,26} for nearly 2 years. The incidence of proteinuria in patients receiving concurrent bevacizumab and pamidronate was 33.9%, compared with 18.5% in patients receiving bevacizumab without pamidronate ($P = .026$). Additionally, patients on the combination arm with proteinuria were more likely to report hypertension (47.1% ν 16.9%). Proteinuria was rare in patients receiving capecitabine monotherapy, and there was no increase with pamidronate treatment.

abine monotherapy, and there was no increase with pamidronate treatment.

Bevacizumab clearly increased minor mucosal bleeding. There were no grade 3 or 4 episodes of epistaxis in either patient group. However, a difference between treatment arms did occur for grades 1 or 2 epistaxis, with three events (1.4%) in the capecitabine treatment arm and 36 events (15.7%) in the capecitabine plus bevacizumab arm. Grade 3 or serious bleeding was rare and not different between treatment groups. Grade 4 hemorrhage was not reported. The incidence of thromboembolic events was infrequent and similar in the two treatment groups.

Nine patients in the study developed grade 3 or 4 congestive heart failure or cardiomyopathy: two in the capecitabine-alone group and seven in the combination group (Table 4). Baseline left ventricular ejection fraction (LVEF) was measured in 418 patients. Mean LVEF and number of patients with baseline LVEF less than 50% (14.9% capecitabine alone ν 12.2% combination) were similar in the two treatment groups. LVEF was less than 50% at baseline in three of six bevacizumab-treated patients who developed congestive heart failure or cardiomyopathy (baseline LVEF not measured in one), and in one of two control patients. Cardiac symptoms improved with medical management in all but one patient. Two of seven affected patients continued to receive bevacizumab therapy.

Seventy patients continued bevacizumab, either alone or in combination with other therapies, after initial pro-

Table 3. Common Bevacizumab Toxicities

Toxicity	Capecitabine (n = 215)								Capecitabine + Bevacizumab (n = 229)							
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hypertension	4	1.9	0	0	1	0.5	0	0	9	3.9	4	1.7	41	17.9	0	0
Proteinuria	14	6.5	2	0.9	0	0	0	0	42	18.3	7	3.1	2	0.9	0	0
Bleeding	19	8.8	4	1.9	1	0.5	0	0	60	26.2	5	2.2	1	0.4	0	0
Thrombotic event	0	0	4	1.9	5	2.3	3	1.4	1	0.4	3	1.3	9	3.9	4	1.7
Pulmonary embolism	0	0	0	0	0	0	3	1.4	0	0	0	0	0	0	3	1.3

NOTE. National Cancer Institute Common Toxicity Criteria worst grade experienced per patient.

Table 4. Other Common Toxicities

Toxicity	Capecitabine (n = 215)						Capecitabine + Bevacizumab (n = 229)					
	Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematologic												
Anemia	8	3.7	1	0.5	0	0	12	5.2	4	1.7	0	0
Leukopenia	10	4.7	3	1.4	3	1.4	15	6.6	6	2.6	0	0
Thrombocytopenia	2	0.9	1	0.5	0	0	4	1.7	3	1.3	1	0.4
Gastrointestinal												
Nausea	30	14.0	4	1.9	0	0	33	14.4	6	2.6	0	0
Anorexia	17	7.9	5	2.3	0	0	25	10.9	2	0.9	0	0
Constipation	11	5.1	0	0	0	0	14	6.1	1	0.4	0	0
Cardiac												
Congestive heart failure	0	0	0	0	1	0.5	0	0	5	2.2	0	0
Cardiomyopathy	0	0	0	0	1	0.5	0	0	1	0.4	1	0.4
Infectious												
Infection	24	11.2	1	0.5	0	0	27	11.8	2	0.9	0	0
Fever	6	2.8	2	0.9	0	0	3	1.3	1	0.4	0	0
Miscellaneous												
Asthenia	35	16.3	10	4.7	4	1.9	58	25.3	14	6.1	3	1.3
Headache	9	4.2	1	0.5	0	0	26	11.4	4	1.7	0	0
Pain	20	9.3	4	1.9	0	0	24	10.5	7	3.1	0	0

NOTE. National Cancer Institute Common Toxicity Criteria worst grade experienced per patient.

gression. There were no new toxicities observed or safety issues that emerged in any of the patients.

PK

Bevacizumab PK parameters were estimated in 35 patients. Consistent with prior studies, bevacizumab had a long terminal half-life (23.1 day) and a mean clearance value of 2.08 mL/kg/d. Concentration increased with multiple doses and reached steady-state by week 18. Capecitabine AUC was determined in approximately 20 patients per arm. Dose-normalized AUCs for the three capecitabine-related moieties were similar in the two groups.

QOL

A total of 370 subjects completed baseline, and at least one subsequent QOL assessment (176 controls, 194 combination therapy subjects). Time to deterioration in QOL did not differ between treatment groups (2.86 v 2.92 months; $P = .633$). Detailed QOL analysis will be reported separately.

DISCUSSION

We report the first completed phase III trial of antiangiogenic therapy in patients with MBC. The patients enrolled had received prior anthracycline and taxane therapy; most had visceral involvement. Treatment was based on capecitabine, the only US Food and Drug Administration–approved chemotherapeutic in this refractory population.

The addition of bevacizumab to capecitabine therapy was generally well tolerated, with no significant increase in capecitabine-related toxicities. Though the majority of patients required capecitabine dose modification, excellent dose-intensity was maintained. The incidence of grade 3 hand-foot syndrome in our study (approximately 25%) is higher than in previous reports (approximately 10% to 13%).^{4,27} This difference may be attributed to increased investigator awareness of hand-foot syndrome and the different toxicity grading scales used. We assessed toxicity according to NCI-CTC criteria, which defines skin changes with pain interfering with function as a grade 3 toxicity. In contrast, previous studies used the NCIC-CTC (National Cancer Institute of Canada CTC) scale, which defines pain interfering with function as a grade 2 toxicity.

Bevacizumab-associated toxicities were well predicted by the phase II experience and rarely limited therapy.^{18,22,28} Hypertension requiring initiation or adjustment of prior antihypertensive therapy occurred in 18% of patients. Proteinuria developed in 22% of patients (predominantly grade 1). An apparent association between hypertension and proteinuria was noted in the combination arm: patients with proteinuria were more likely to develop hypertension (47.1% v 16.9%; $P < .001$) than patients who did not develop proteinuria. Thromboembolic events were infrequent and similar in the two treatment arms. Bleeding was primarily limited to minor mucosal oozing that did not require medical

intervention; serious hemorrhage was rare and was not increased in bevacizumab-treated patients.

An apparent increase (two v seven cases) in congestive heart failure and cardiomyopathy occurred in the bevacizumab-treatment arm, but the small number of events makes this association uncertain. All patients had prior anthracycline exposure, three of seven had received left chest wall radiation, and three had an LVEF less than 50% at study entry. In a previous phase II study, two of 75 breast cancer patients treated with bevacizumab monotherapy also developed congestive heart failure. Both had received prior anthracyclines and chest wall radiation; one had metastatic involvement of the pericardium.¹⁸ The association between the cardiac dysfunction, prior anthracycline exposure, and bevacizumab therapy is unclear.

The addition of bevacizumab to capecitabine clearly increased response rates, whether assessed by the IRF or the investigators, without significantly adding to the overall toxicity of the treatment regimen. Despite improvement in ORR, the duration of the responses was short with respect to PFS, and the proportion of long-term responders was similar in the two groups. The challenge now is to better understand how to exploit this activity. While it is possible that a negative interaction occurred between bevacizumab and capecitabine, the increased ORR and absence of augmented capecitabine toxicity makes this an unlikely explanation.

There are several possible explanations why the study did not meet its primary end point. This study used bevacizumab as a general therapy given on a population basis, rather than as a targeted therapy given to patients with a specific molecular phenotype. Methods to select those patients most likely to benefit from VEGF-directed therapies need to be developed. Analysis of primary tumor samples for pathologic factors correlating with response to bevacizumab is ongoing. Initial results were limited by the small number of patients contributing samples, and did not clearly identify a patient subset more likely to benefit from combined therapy.²⁹ Full results of correlative pathology studies will be reported separately.

The results of this study suggest that the optimal time to intervene with an antiangiogenic agent may be earlier in the course of disease. Angiogenic pathways become more numerous and redundant as breast cancer progresses.³⁰ Thus, 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. It is

also unlikely that advanced breast cancer is VEGF-independent, but increased expression of other angiogenic factors render VEGF less critical for continued tumor growth. As such, future trials should focus on patients with less advanced disease when fewer redundant angiogenic pathways exist. In a recently completed study, addition of bevacizumab to first-line chemotherapy (irinotecan, FU/leucovorin) in patients with metastatic colorectal cancer increased ORR, extended the duration of response, and prolonged PFS and overall survival.³¹ The increased ORR in our study and the results of the metastatic colorectal cancer trial further support the investigation of bevacizumab in patients with less refractory breast cancer. A phase III trial evaluating bevacizumab in combination with paclitaxel in chemo-naïve MBC patients (E2100) completed accrual in May 2004.

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Authors' Disclosures of Potential Conflicts of Interest

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