ORIGINAL ARTICLE

Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer

Kathy Miller, M.D., Molin Wang, Ph.D., Julie Gralow, M.D., Maura Dickler, M.D., Melody Cobleigh, M.D., Edith A. Perez, M.D., Tamara Shenkier, M.D., David Cella, Ph.D., and Nancy E. Davidson, M.D.

ABSTRACT

BACKGROUND

In an open-label, randomized, phase 3 trial, we compared the efficacy and safety of paclitaxel with that of paclitaxel plus bevacizumab, a monoclonal antibody against vascular endothelial growth factor, as initial treatment for metastatic breast cancer.

METHODS

We randomly assigned patients to receive 90 mg of paclitaxel per square meter of body-surface area on days 1, 8, and 15 every 4 weeks, either alone or with 10 mg of bevacizumab per kilogram of body weight on days 1 and 15. The primary end point was progression-free survival; overall survival was a secondary end point.

RESULTS

From December 2001 through May 2004, a total of 722 patients were enrolled. Paclitaxel plus bevacizumab significantly prolonged progression-free survival as compared with paclitaxel alone (median, 11.8 vs. 5.9 months; hazard ratio for progression, 0.60; P<0.001) and increased the objective response rate (36.9% vs. 21.2%, P<0.001). The overall survival rate, however, was similar in the two groups (median, 26.7 vs. 25.2 months; hazard ratio, 0.88; P=0.16). Grade 3 or 4 hypertension (14.8% vs. 0.0%, P<0.001), proteinuria (3.6% vs. 0.0%, P<0.001), headache (2.2% vs. 0.0%, P=0.008), and cerebrovascular ischemia (1.9% vs. 0.0%, P=0.02) were more frequent in patients receiving paclitaxel plus bevacizumab. Infection was more common in patients receiving paclitaxel plus bevacizumab (9.3% vs. 2.9%, P<0.001), but febrile neutropenia was uncommon (<1% overall).

CONCLUSIONS

Initial therapy of metastatic breast cancer with paclitaxel plus bevacizumab prolongs progression-free survival, but not overall survival, as compared with paclitaxel alone. (ClinicalTrials.gov number, NCT00028990.)

From Indiana University Cancer Center, Indianapolis (K.M.); Dana–Farber Cancer Institute, Boston (M.W.); Puget Sound Oncology Consortium, Seattle (J.G.); Memorial Sloan-Kettering Cancer Center, New York (M.D.); Rush–Presbyterian–St. Luke's Medical Center, Chicago (M.C.); Mayo Clinic, Jacksonville, FL (E.A.P.); British Columbia Cancer Agency–Vancouver Cancer Center, Vancouver, BC, Canada (T.S.); Evanston Northwestern Healthcare and Robert H. Lurie Comprehensive Cancer Center of Northwestern University — both in Evanston, IL (D.C.); and Johns Hopkins Kimmel Comprehensive Cancer Center, Baltimore (N.E.D.). Address reprint requests to Dr. Miller at the Indiana Cancer Pavilion, 535 Barnhill Dr., RT473, Indianapolis, IN 46202, or at kathmill@iupui.edu.

N Engl J Med 2007;357:2666-76.

Laboratory and clinical evidence supports the central role of angiogenesis in the progression of breast cancer.[1,2] Multiple angiogenic factors are commonly expressed by invasive breast cancers; the 121-amino-acid isoform of vascular endothelial growth factor (VEGF) predominates.[3] VEGF stimulates endothelial proliferation and migration, inhibits endothelial apoptosis, induces proteinases that remodel the extracellular matrix, increases vascular permeability and vasodilatation, and inhibits antigen-presenting dendritic cells.[4] Differences in function among the various VEGF isoforms are not well defined, though VEGF-C has a predominant role in lymphangiogenesis, whereas VEGF-A is more potent in inducing vasodilatation and pathologic angiogenesis.[5,6]

Bevacizumab (Avastin, Genentech) is a humanized monoclonal antibody directed against all isoforms of VEGF-A. In a phase 1 and phase 2 study that tested three different doses of bevacizumab monotherapy (3, 10, or 20 mg per kilogram of body weight every 2 weeks) in 75 patients with previously treated metastatic breast cancer, the objective response rate was 9.3%, and 17% of patients had a response or were stable at 22 weeks. The dose of 10 mg per kilogram was suggested for further trials.[7] In a phase 3 trial, the addition of bevacizumab to capecitabine in patients previously treated with anthracyclines and taxanes significantly increased the objective response rate (9.1% vs. 19.8%, $P=0.001$) but not progression-free survival (4.2 vs. 4.9 months; hazard ratio for disease progression, 0.98) or overall survival (15.1 vs. 14.5 months).[8] The present trial (E2100) compared paclitaxel alone with paclitaxel plus bevacizumab as initial therapy for patients with metastatic breast cancer.

METHODS

PATIENT ELIGIBILITY

Patients with histologically or cytologically confirmed metastatic breast cancer were eligible if they had not received previous cytotoxic therapy for metastatic disease. Previous hormonal therapy for metastatic breast cancer or cytotoxic adjuvant chemotherapy was allowed. Patients who had received taxane-based adjuvant therapy were required to have had a disease-free interval of at least 12 months after completion of taxane therapy. Those with human epidermal growth factor receptor type 2 (HER2)–positive breast cancer (graded as 3+ according to immunohistochemical analysis or gene amplification by fluorescence in situ hybridization) were eligible only if they had received trastuzumab. Additional inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate renal, hepatic, and hematologic function. The presence of measurable tumor was not required for inclusion in the trial.

Patients were excluded if they had a history of or radiographic evidence of central nervous system disease; imaging of the central nervous system was required as a screening test. Patients were also excluded if they had had another cancer except basal-cell carcinoma of the skin or in situ cervical cancer within the previous 5 years, major surgery within the previous 4 weeks, or other antitumor therapy within the previous 21 days, or if they currently had a nonhealing wound or fracture, an infection requiring parenteral antibiotics, or clinically significant cardiovascular disease. Patients were excluded if they were currently taking therapeutic anticoagulant agents, nonsteroidal antiinflammatory agents, or more than 325 mg of aspirin daily, but prophylactic low-dose anticoagulant agents were permitted. Concurrent administration of bisphosphonates was allowed.

Local institutional review boards approved the protocol. Written informed consent was required from each patient before screening.

TREATMENT PLAN

All patients received 90 mg of paclitaxel per square meter of body-surface area on days 1, 8, and 15 of every 28-day cycle. The dose was transiently reduced to 65 mg per square meter if any of the following toxic effects occurred: 1000 to 1499 granulocytes per cubic millimeter, 75,000 to 99,999 platelets per cubic millimeter, aspartate transaminase more than 5 but not more than 10 times the upper limit of normal, or 1.6 to 2.5 mg of bilirubin per deciliter (27 to 43 μmol per liter). The dose was permanently reduced to 65 mg per square meter in cases of prolonged granulocytopenia, fever associated with granulocytopenia, bleeding associated with 40,000 or fewer platelets per cubic millimeter, and any platelet count of 20,000 or fewer per cubic millimeter. Paclitaxel was withheld in cases of grade 3 neuropathy and resumed at a reduced dose on resolution to grade

0 or 1. It was permanently discontinued for severe hypersensitivity reactions or for grade 3 or 4 neuropathy lasting more than 3 weeks or recurring after dose reduction.

Patients assigned to combined therapy received 10 mg of bevacizumab per kilogram intravenously on days 1 and 15. Initially, bevacizumab was infused for 90 minutes; subsequent infusions were reduced to 60 minutes and then to 30 minutes, as tolerated. Premedication was optional. Treatment was interrupted for proteinuria (urinary protein excretion, ≥2000 mg per 24 hours). Antihypertensive therapy was administered at the discretion of the investigator. Bevacizumab therapy was not withheld or discontinued for paclitaxel-related toxic effects.

The patients continued therapy until disease progression or prohibitive toxic effects occurred. Patients assigned to combination therapy who discontinued paclitaxel without disease progression (i.e., because of toxic effects or at the discretion of the patient or investigator) could continue bevacizumab monotherapy until disease progression or unacceptable toxic effects occurred. Patients assigned to paclitaxel monotherapy could not receive bevacizumab at any time.

SAFETY AND EFFICACY

Clinical status, liver function, and serum creatinine levels were assessed before each cycle. A complete blood count was obtained before each paclitaxel infusion. Dipstick urinalysis was performed before each bevacizumab infusion; a 24-hour urine sample was obtained for 1+ protein on dipstick testing. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Disease status was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST)[9] at baseline and every 12 weeks until progression. Quality of life was assessed with the use of the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire at baseline, week 17, and week 33.

ROLE OF THE SPONSOR

The E2100 trial was conducted under a corporate research and development agreement between Genentech and the National Cancer Institute. Genentech provided bevacizumab and partial funding but did not participate in the design of the study or data collection. Analysis was conducted by the ECOG. The lead author made the decision to publish and wrote the manuscript, which was reviewed by all authors and submitted to Genentech for comment. The authors vouch for the completeness and accuracy of the data.

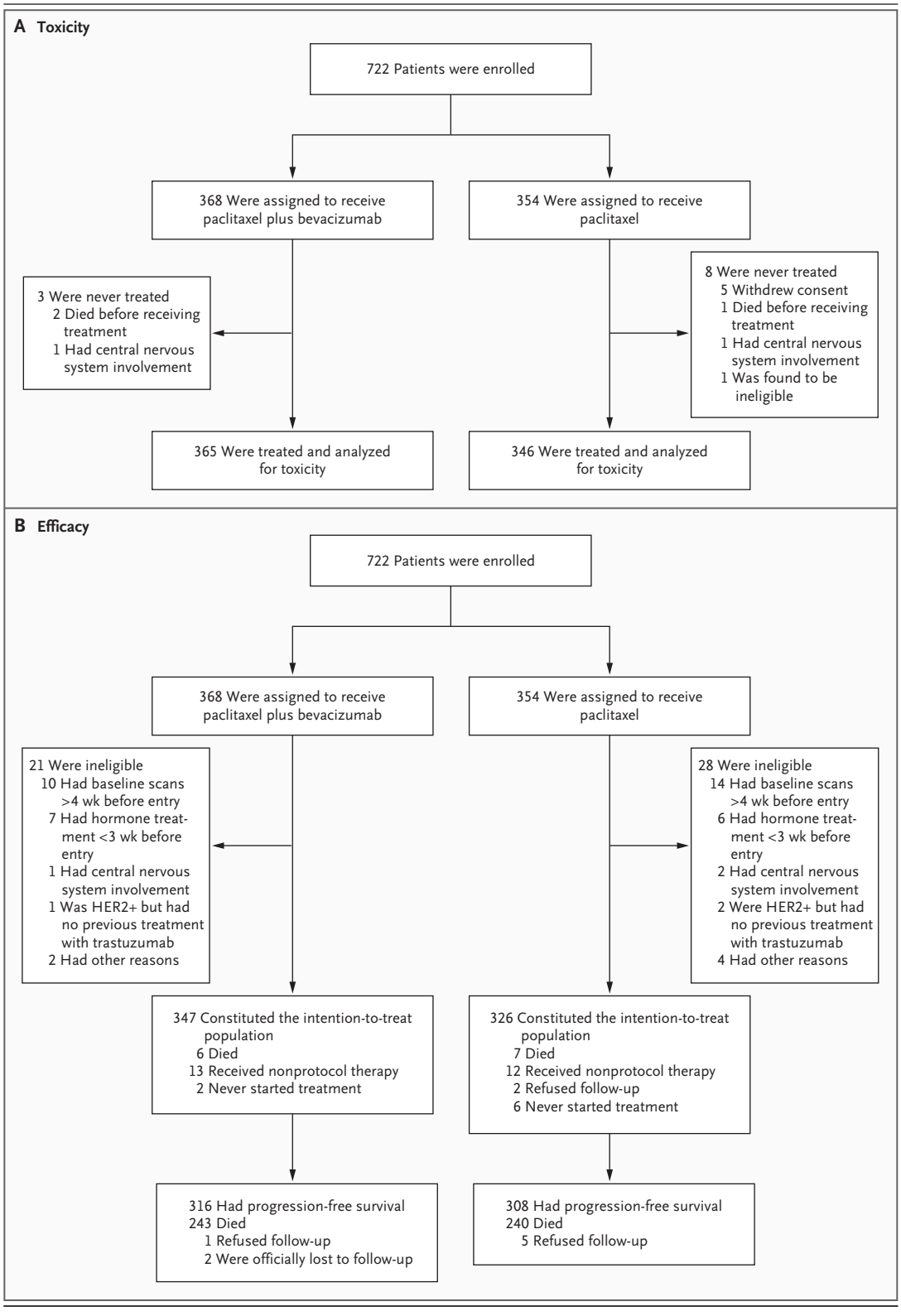
Figure 1 (facing page). Analyses of Toxic Effects and Efficacy.

All treated patients were included in the analyses of toxic effects (Panel A), irrespective of eligibility. All patients meeting eligibility criteria were included in the efficacy analyses (Panel B) according to their randomized treatment assignment. Two eligible patients assigned to paclitaxel plus bevacizumab and six patients assigned to paclitaxel alone never started treatment. Progression-free survival data were censored for patients initiating nonprotocol therapy. CNS denotes central nervous system.

STATISTICAL ANALYSIS

The primary end point was progression-free survival, defined as the time from randomization to disease progression or death from any cause. In patients with measurable disease, progression was determined by RECIST. In patients without measurable lesions, progression was defined as development of new lesions or "unequivocal progression" of existing lesions. Secondary end points included objective response rate, toxic effects, overall survival, and quality of life.

The study design required enrollment of 685 patients to give full information at 546 progression-free survival events. The design yielded an 85% power to detect a 33% improvement in median progression-free survival (from 6 months to 8 months). The trial included prespecified stopping rules based on toxic effects, a prespecified stopping rule based on evaluation of efficacy after 171 progression-free survival events (at 31% information), and two additional planned interim efficacy analyses, at 50% and 78% information. Stopping rules in favor of the alternative hypotheses were obtained by the one-sided Lan–DeMets error spending rate function corresponding to the O'Brien–Fleming boundary[10] with a one-sided type I error of 2.7%; those in favor of the null hypothesis were based on repeated-confidence-intervals methods.[11] With the futility stopping rules taken into account, the overall type I error



was expected to be 2.5% or less. With the use of survival data through June 7, 2007, we report the final analysis of progression-free survival and overall survival.

Treatment assignments were determined with the use of permuted blocks within strata. Stratification factors included disease-free interval (≤24 months vs. ≤24 months), number of metastatic sites (<3 vs. ≥3), previous adjuvant chemotherapy (yes vs. no), and estrogen-receptor status (positive vs. negative vs. unknown). All eligible patients were included in the efficacy analysis according to their treatment assignment. The primary prespecified analysis for progression-free survival and overall survival was stratified with the use of the log-rank test according to previous adjuvant therapy and disease-free interval. All treated patients were included in the analyses of toxic effects (analyzed as treated), regardless of eligibility.

Time-to-event distributions were estimated by Kaplan–Meier analysis. Cox proportional-hazards methods, with data stratified according to previous adjuvant therapy and disease-free interval, were used to estimate hazard ratios and test for the significance of time-to-event variables. The proportionality assumption was tested by the method of Grambsch and Therneau.[12] Both the objective response rate and toxic effects were compared with the use of Fisher's exact test. Change in quality of life was compared with the use of the Wilcoxon rank-sum test. A pattern-mixture model analysis for longitudinal data with nonignorable missing data was also conducted.[13] All P values are two-sided; confidence intervals are at the 95% level.

RESULTS

PATIENT POPULATION

We randomly assigned 722 patients to treatment between December 2001 and May 2004. All 711 treated patients were evaluated for toxic effects (Fig. 1A). Forty-nine enrolled patients (6.8%) did not meet all the eligibility criteria and were excluded from efficacy analyses (Fig. 1B). Six eligible patients assigned to paclitaxel and two assigned to combination therapy were not treated but are included in the efficacy analysis according to their assignment. The two groups of patients were similar at baseline with respect to demographic and tumor characteristics, except that more patients assigned to paclitaxel alone had either measurable disease or visceral involvement (Table 1).

EFFICACY

There were 624 reported events, and paclitaxel plus bevacizumab significantly prolonged progression-free survival as compared with paclitaxel alone (median, 11.8 vs. 5.9 months; hazard ratio for disease progression, 0.60; P<0.001) (Fig. 2A). A Cox regression model including treatment (P<0.001) and the interaction between treatment and time (P<0.001) showed that the effect of treatment declined with time. The addition of bevacizumab to paclitaxel significantly improved the objective response rate in all eligible patients (36.9% vs. 21.2%, P<0.001) and in the subgroup of patients with measurable disease at baseline (49.2% vs. 25.2%, P<0.001). At data cutoff, 483 patients had died, the majority (88.8%) from progressive disease. Combined therapy increased the 1-year survival rate (81.2% vs. 73.4%, P=0.01); however, the median overall survival was similar in the group receiving combined therapy and in the group receiving paclitaxel alone (26.7 months and 25.2 months, respectively; hazard ratio, 0.88; P=0.16) (Fig. 2B).

Proportional-hazards models stratified according to disease-free interval and adjuvant chemotherapy were fitted to investigate the effect of bevacizumab on progression-free survival in clinically relevant subgroups of patients (Fig. 3). The hazard ratios favored combined therapy in all subgroups but did not reach statistical significance in some of the smaller subgroups. The addition of bevacizumab prolonged progression-free survival from 3.0 to 12.0 months (hazard ratio, 0.46; P<0.001) in patients who had received taxane-based adjuvant therapy. The effect of bevacizumab declined significantly with age treated as a continuous variable (P=0.04). There was no significant interaction between treatment and any other patient characteristic.

Slightly more patients with visceral involvement or measurable disease were assigned to paclitaxel monotherapy than to combination therapy. To investigate the influence of this imbalance and other potential prognostic factors on our results, we conducted a multivariate analysis using the proportional-hazards model, with data stratified according to disease-free interval and adjuvant chemotherapy. We considered the follow-

Table 1. Demographic and Disease Characteristics of Eligible Patients.*

Characteristic	Paclitaxel plus Bevacizumab (N=347)	Paclitaxel (N=326)
Years of age — median (range)	56 (29–84)	55 (27–85)
Estrogen-receptor status — no. (%)		
Positive	208 (59.9)	205 (62.9)
Negative	133 (38.3)	118 (36.2)
Unknown	6 (1.7)	3 (0.9)
Progesterone-receptor status — no. (%)		
Positive	155 (44.7)	147 (45.1)
Negative	175 (50.4)	167 (51.2)
Unknown	17 (4.9)	12 (3.7)
HER2 status — no. (%)		
Positive	5 (1.4)	3 (0.9)
Negative	321 (92.5)	293 (89.9)
Unknown	21 (6.1)	30 (9.2)
Previous adjuvant chemotherapy — no. (%)		
None	123 (35.4)	114 (35.0)
Anthracycline	136 (39.2)	133 (40.8)
Taxane	60 (17.3)	48 (14.7)
Disease-free interval — no. (%)		
≤24 mo	144 (41.5)	133 (40.8)
>24 mo	203 (58.5)	193 (59.2)
Extent of disease — no. (%)		
≥3 sites	149 (42.9)	151 (46.3)
<3 sites	198 (57.1)	175 (53.7)
Location of disease — no. (%)		
Viscera†	276 (79.5)	284 (87.1)
Bone only	36 (10.4)	25 (7.7)
Disease evaluation — no. (%)		
Measurable‡	238 (68.6)	254 (77.9)
Nonmeasurable	109 (31.4)	72 (22.1)
Median duration of follow-up — mo	41.6	43.5

* Because of rounding, percentages may not sum to 100. HER2 denotes human epidermal growth factor receptor type 2.
† Fisher's exact test (two-sided) was used for the comparison between the two groups; P=0.009.
‡ Fisher's exact test (two-sided) was used for the comparison between the two groups; P=0.007.

ing covariates: treatment assignment, measurable disease, number of disease sites, estrogen-receptor status, location of disease (visceral only vs. bone only), age (as a continuous variable), race (white vs. other), progesterone-receptor status, menopausal status, and the interactions between treatment assignment and age and time. The final model, which satisfied the Cox model assumption, included treatment assignment (P<0.001), measurable disease (P=0.03), number of disease sites (P=0.003), estrogen-receptor status (P<0.001), age (P=0.02), the interaction between treatment assignment and age (P=0.02), and the interaction between treatment assignment and time (P<0.001).

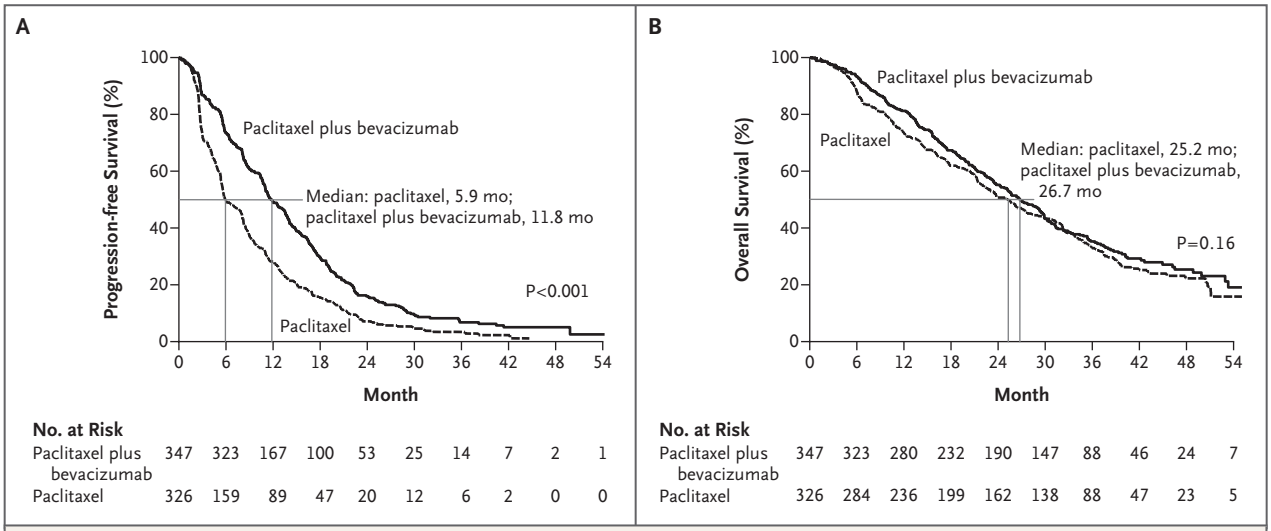


Figure 2. Survival Analyses.

Progression-free survival (Panel A) and overall survival (Panel B) in all eligible patients were analyzed with the use of the Kaplan–Meier method. Analyses including all patients assigned to treatment yielded similar results (data not shown).

To investigate the influence of patient- or investigator-driven ascertainment bias, we compared the distribution of the interval from the last negative disease assessment with the time of documented progression. The median was 2.8 months in both groups (P=0.94 by the Wilcoxon two-sample test). Similarly, we found no difference in the proportion of patients with an interval less than 2.5 months (30.1% vs. 31.7%). Finally, we moved all progression-free survival times forward to the next scheduled assessment and recalculated progression-free survival. The results were similar to those of our original analysis (12.8 vs. 6.2 months; hazard ratio, 0.61; P<0.001).

TOXIC EFFECTS

The addition of bevacizumab had little effect on the frequency or severity of expected paclitaxel-related toxic effects (Table 2). Hematologic, gastrointestinal, and musculoskeletal toxic effects were minimal and similar in both groups. Grade 3 or 4 neuropathy (23.6% vs. 17.6%, P=0.03), infection (9.3% vs. 2.9%, P<0.001) and fatigue (8.5% vs. 4.9%, P=0.04) were more frequent in the combination group. Paclitaxel was discontinued at least 3 weeks before disease progression (or before the last disease assessment for patients without progression) in 117 patients treated with paclitaxel (35.9%) and 178 patients treated with paclitaxel plus bevacizumab (51.3%), most commonly because of cumulative toxic effects. The median duration of paclitaxel treatment was 5.1 months in patients treated with paclitaxel alone and 7.1 months in patients treated with combined therapy. Of the patients in the combination group, 74 (21.3%) continued bevacizumab monotherapy for a median of 3.7 months. The Supplementary Appendix (available with the full text of this article at www.nejm.org) lists the reasons for discontinuation of treatment in both groups.

Hypertension was more common in patients receiving bevacizumab and was managed with medical therapy; grade 4 hypertension developed in only one patient, resulting in discontinuation of bevacizumab. Proteinuria was rarely clinically significant. Grade 3 hemorrhage was uncommon and its frequency did not differ between treatment groups; grade 4 hemorrhage was not reported. Thromboembolic events were infrequent overall, but there was a significant increase in cerebrovascular ischemia among patients receiving combined therapy (1.9% vs. 0.0%, P=0.02). Patients receiving combined therapy were also more likely to report grade 3 or 4 headaches (2.2% vs. 0.0%, P=0.008).

QUALITY OF LIFE

The FACT-B questionnaire was completed by 631 patients at baseline, 488 at 17 weeks, and 368 at 33 weeks. There were no significant differences

Subgroup	No. of Patients	Progression-free Survival (mo)		Hazard Ratio (95% CI)
		Paclitaxel	Paclitaxel plus Bevacizumab	
Hormone-receptor status				
ER–, PR–	233	4.6	8.8	0.53 (0.40–0.70)
ER+, PR–	109	9.3	12.6	0.88 (0.58–1.33)
ER+, PR+	289	8.0	14.4	0.54 (0.44–0.70)
Adjuvant chemotherapy				
None	237	6.5	13.6	0.67 (0.51–0.87)
Nontaxane	328	7.7	10.8	0.59 (0.47–0.75)
Taxane	108	3.0	12.0	0.46 (0.30–0.71)
Anthracycline therapy				
Yes	269	5.6	10.7	0.54 (0.42–0.70)
No	167	8.0	13.2	0.58 (0.42–0.81)
Age				
27–49 yr	220	5.5	12.5	0.50 (0.38–0.67)
50–64 yr	305	6.7	11.3	0.56 (0.44–0.72)
65–85 yr	148	7.9	11.9	0.77 (0.54–1.09)
Disease-free interval				
0–24 mo	277	4.9	10.3	0.60 (0.47–0.77)
>24 mo	396	8.2	14.4	0.59 (0.48–0.73)
No. of sites				
<3	373	7.1	13.8	0.56 (0.45–0.70)
≥3	300	5.6	10.7	0.65 (0.51–0.82)
Visceral disease				
No	113	7.2	15.7	0.63 (0.40–0.97)
Yes	560	5.8	11.0	0.59 (0.49–0.70)
Bone disease only				
No	612	5.7	11.3	0.57 (0.48–0.68)
Yes	61	13.0	19.7	0.61 (0.33–1.11)
Measurable disease				
Yes	492	5.6	11.2	0.55 (0.46–0.67)
No	181	11.4	13.9	0.68 (0.49–0.95)
Overall	673	5.9	11.8	0.60 (0.51–0.70)

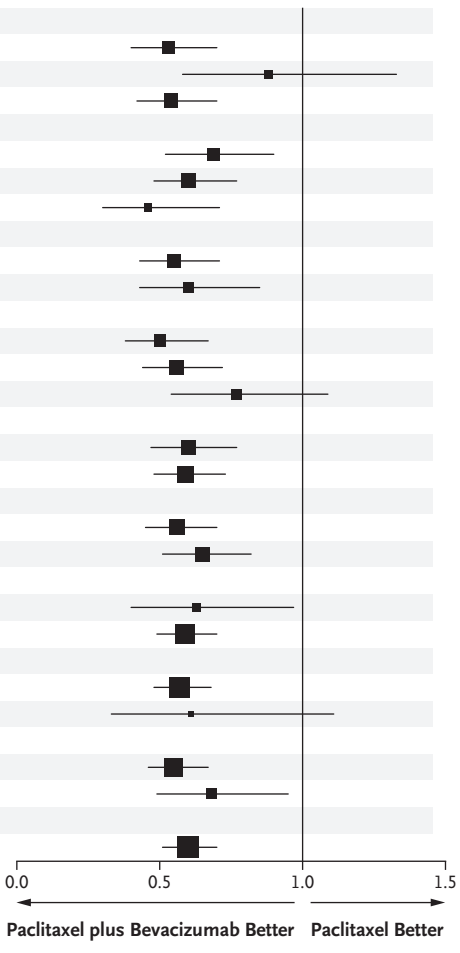


Figure 3. Hazard Ratios for Disease Progression.

Hazard ratios favor the addition of bevacizumab in all clinically relevant patient subgroups. Only the interaction between treatment assignment and age (treated as a continuous variable) was significant (P=0.04), a result indicating that the effect of bevacizumab declined with age. There was no significant interaction between treatment and any other patient characteristic, suggesting that benefit was not limited to any particular subgroup of patients. The size of the squares is proportional to the size of the subgroup. CI denotes confidence interval, ER estrogen-receptor status (positive or negative), and PR progesterone-receptor status (positive or negative).

in the mean change in scores from baseline for the FACT-B, the FACT-B subscale, or the Trial Outcome Index[14,15] (the sum of the physical well-being, functional well-being, and breast cancer–specific questions in the FACT-B) (Fig. 4).

DISCUSSION

In this phase 3 trial of paclitaxel plus bevacizumab as the initial treatment of metastatic breast cancer, the safety profile of the combination was similar to profiles reported in previous randomized trials.[8,16-18] Most toxic effects were minimal, rarely limited therapy, and did not have a detrimental effect on overall quality of life.[15]

We enrolled patients with predominantly HER2-negative breast cancer; no patient received concurrent trastuzumab. Further studies are needed to assess the efficacy of bevacizumab in patients with HER2-positive metastatic breast cancer.[19,20] In our trial, bevacizumab was not given to patients who had a tumor with a specific mo-

Table 2. Treatment-Related Toxic Effects.*

Effect	Paclitaxel plus Bevacizumab (N=365)		Paclitaxel (N=346)		P Value
	Grade 3	Grade 4	Grade 3	Grade 4	
	percent				
Allergic reaction	3.0	0.3	2.6	0.3	
Neutropenia	0	0	0.3	0	
Anemia	0.3	0	0	0	
Thrombocytopenia	0	0	0	0.3	
Febrile neutropenia	0.5	0.3	0	0	
Infection	8.8	0.5	2.9	0	<0.001
Fatigue	8.8	0.3	4.6	0.3	0.04
Nausea	3.3	0	1.2	0	
Vomiting	2.7	0	2.0	0	
Stomatitis	1.1	0	0.3	0.3	
Anorexia	0.5	0.3	0.3	0	
Increased aspartate aminotransferase	1.4	0	0.6	0	
Sensory neuropathy	23.0	0.5	17.1	0.6	0.05
Arthralgia	2.7	0.5	1.4	0	
Myalgia	1.6	0.5	1.2	0	
Hypertension	14.5	0.3	0	0	<0.001
Thrombosis or embolism	1.6	0.5	0.6	0.9	
Cerebrovascular ischemia	0.8	1.1	0	0	0.02
Left ventricular dysfunction	0.8	0	0	0.3	
Hemorrhage	0.5	0	0	0	
Gastrointestinal perforation	0.5	0	0	0	
Headache	2.2	0	0	0	0.008
Proteinuria	2.7	0.8	0	0	<0.001

* Toxic effects are graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. The worst grade considered at least possibly related to treatment is given. The only patients with grade 5 events were one patient in the paclitaxel-plus-bevacizumab group with a ruptured diverticulum, one in the paclitaxel-plus-bevacizumab group with erosion in an area of bowel-wall involvement, and one in the paclitaxel group with left ventricular dysfunction. All three events were considered by the treating investigators to be unrelated to therapy. The P values are for the differences between the treatment groups for grades 3, 4, and 5 combined.

lecular phenotype. Although benefit was seen across a number of clinically important subgroups, our results would be strengthened by the ability to identify patients most likely to benefit from VEGF-directed therapies.

In a previous phase 3 study, the addition of bevacizumab to capecitabine significantly increased the objective response rate but not progression-free survival or overall survival.[8] What might account for the different results in these trials? It seems unlikely that chance could account for the improvement in progression-free survival found in our trial. Investigator or patient bias, always a consideration in open-label studies, is unlikely to explain our results. If such biases had a large role, we would have expected to see a greater improvement in patients with nonmeasurable lesions, where disease assessment is necessarily subjective. Actually, the hazard ratio was more favorable in patients with measurable disease than in those with nonmeasurable disease (0.55 vs. 0.68).

Substantial differences between the patient populations of these studies may account for the disparate results. All patients in the earlier study had received previous anthracycline and taxane

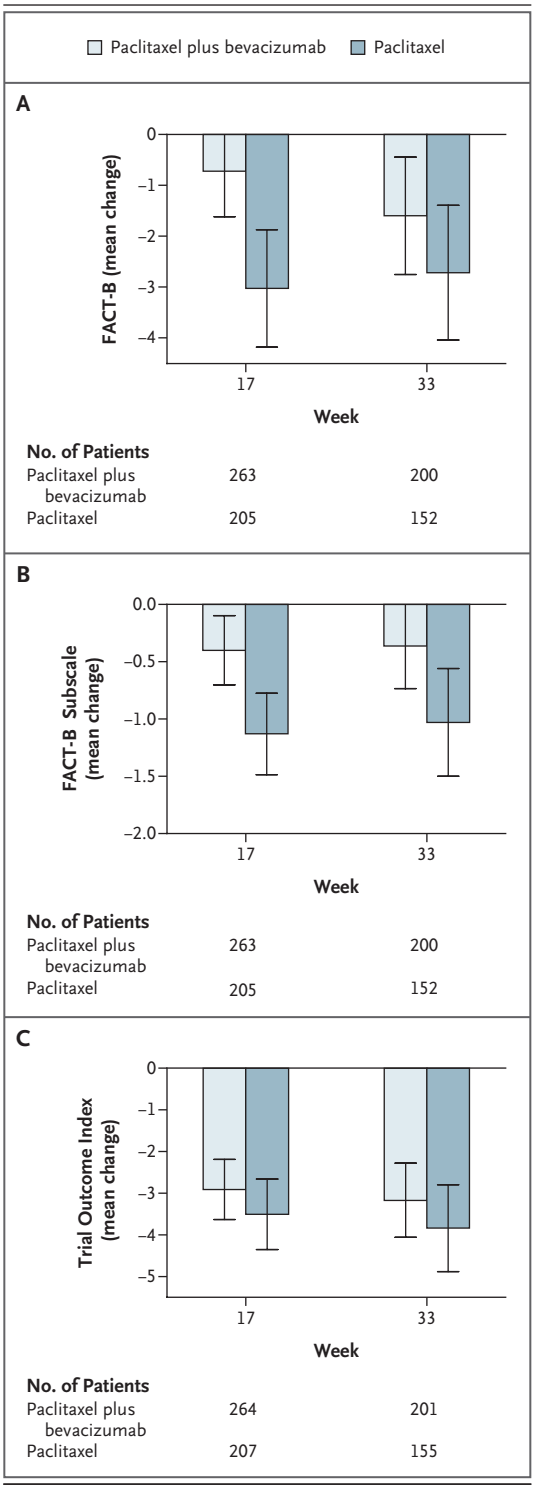


Figure 4. Changes in Quality-of-Life Measures.

The graphs show the mean changes in the scores on the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire (Panel A), the FACT-B subscale (Panel B), and the Trial Outcome Index (Panel C) during treatment. Error bars indicate standard deviations. A decrease in score denotes a decline in health-related quality of life; no significant differences were identified.

therapy, and most (more than 85%) had received chemotherapy for metastatic disease.[8] In contrast, 35.2% of our patients had not received any previous chemotherapy, and only 13.2% had received both an anthracycline and a taxane as adjuvant therapy.

A recent phase 2 trial found a median time to disease progression of only 5.7 months (95% confidence interval, 4.9 to 8.4) with capecitabine plus bevacizumab as initial chemotherapy.[21] Perhaps paclitaxel is uniquely synergistic with bevacizumab. Indeed, the taxanes have distinct antiangiogenic activity.[22] In preclinical studies, VEGF protected endothelial cells from the antiangiogenic properties of docetaxel; bevacizumab overcame this protective effect in vitro and in vivo.[23]

Despite a striking improvement in progression-free survival, the addition of bevacizumab did not prolong overall survival in this study. Patients with metastatic breast cancer frequently receive multiple therapies during the course of their disease. Data on treatment administered after progression were not collected in this trial, precluding an exploratory analysis of the influence of subsequent therapy on overall survival. Though the mechanisms of resistance to bevacizumab are not well defined,[24,25] it is possible that resistance to bevacizumab results in relative resistance to subsequent therapies. Alternatively, rebound increases in VEGF on discontinuation of bevacizumab could result in more aggressive disease. Resistance to paclitaxel, whether mediated by increased expression of the multidrug resistance protein[26] or by microtubule mutations,[27] could also cause resistance to subsequent chemotherapy.

We found that treatment with bevacizumab early in the course of metastatic breast cancer, when angiogenic pathways are less redundant, improved progression-free survival and the objective response rate. Although our patients were receiving their first treatment for metastatic breast cancer, only a third had never received any chemotherapy. More than 80% had overt visceral involvement, presumably with an established vasculature. In short, first-line therapy for metastatic breast cancer is not "early" in the natural history of breast cancer. Recent laboratory studies suggest that the initial events in the development of metastasis are

VEGF-dependent.[28,29] If this is true, the most successful clinical application of angiogenesis inhibitors is likely to be in patients with micrometastatic disease in the adjuvant setting.

Supported in part by Public Health Service Grants CA23318, CA66636, CA21115, CA49883, and CA16116 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by Genentech.

Dr. Miller reports receiving lecture fees and consulting fees for service on breast cancer advisory boards from Roche. Dr. Gralow reports receiving lecture fees and consulting fees for service on breast cancer advisory boards from Genentech and Roche. Dr. Dickler and Dr. Cobleigh report receiving consulting fees from Genentech for service on breast cancer advisory boards. Dr. Cobleigh reports receiving lecture fees from Genentech. Dr. Perez reports receiving consulting fees from Genentech, GlaxoSmithKline, Bristol-Myers Squibb, and Sanofi-Aventis for service on breast cancer advisory boards, as well as grant support for clinical translational studies from Genentech. No other potential conflict of interest relevant to this article was reported.

The views expressed are those of the authors and do not necessarily represent the official views of the National Cancer Institute.

We thank Dr. George Sledge and Dr. Robert Gray for helpful discussions and Carol Chami for providing technical assistance in preparing the manuscript.

REFERENCES

1. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 1990;82:4-6.
2. Gasparini G. Angiogenesis in breast cancer: role in biology, tumor progression, and prognosis. In: Bowcock A, ed. Breast cancer: molecular genetics, pathogenesis, and therapeutics. Totowa, NJ: Humana Press, 1999:347-71.
3. Relf M, LeJeune S, Scott PA, et al. Expression of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor beta-1, platelet-derived endothelial cell growth factor, placenta growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis. Cancer Res 1997;57:963-9.
4. Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. Endocrinol Rev 1997;18:4-25.
5. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol 2002;20:4368-80.
6. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669-76.
7. Cobleigh M, Miller K, Langmuir V, et al. Phase II dose escalation trial of Avastin (bevacizumab) in women with previously treated metastatic breast cancer. Breast Cancer Res Treat 2001;69:301.
8. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005;23:792-9.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-16.
10. O'Brien PC, Fleming T. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
11. Jennison C, Turnbull B. Interim analyses: the repeated confidence interval approach. J R Stat Soc B 1989;51:305-61.
12. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515-26.
13. Fitzmaurice GM, Laird NM, Shneyer L. An alternative parameterization of the general linear mixture model for longitudinal data with non-ignorable drop-outs. Stat Med 2001;20:1009-21.
14. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy–Breast quality-of-life instrument. J Clin Oncol 1997;15:974-86.
15. Wagner L, Wang M, Miller K, et al. Health-related quality of life among patients with metastatic breast cancer receiving paclitaxel versus paclitaxel plus bevacizumab: results from the Eastern Cooperative Oncology Group (ECOG) study E2100. Breast Cancer Res Treat 2006;100:Suppl 1:S239. abstract.
16. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
17. Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 2006;355:2542-50. [Erratum, N Engl J Med 2007;356:318.]
18. Skillings JR, Johnson D, Miller K, et al. Arterial thromboembolic events (ATEs) in a pooled analysis of 5 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy. J Clin Oncol 2005;23:Suppl:196S. abstract.
19. Pegram MD, Reese DM. Combined biological therapy of breast cancer using monoclonal antibodies directed against HER2/neu protein and vascular endothelial growth factor. Semin Oncol 2002;29:Suppl 11:29-37.
20. Pegram M, Chan D, Dichmann RA, et al. Phase II combined biological therapy targeting HER2 proto-oncogene and the vascular endothelial growth factor using trastuzumab (T) and bevacizumab (B) as first line treatment of HER2-amplified breast cancer. Breast Cancer Res Treat 2006;100:Suppl 1:S28. abstract.
21. Sledge G, Miller K, Moisa CG, Gradishar W. Safety and efficacy of capecitabine (C) plus bevacizumab (B) as first-line in metastatic breast cancer (XCALIBr Trial). J Clin Oncol 2007;25:Suppl:18S. abstract.
22. Miller KD, Sweeney CJ, Sledge GW Jr. Redefining the target: chemotherapeutics as antiangiogenics. J Clin Oncol 2001;19:1195-206.
23. Sweeney CJ, Miller KD, Sissons SE, et al. The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. Cancer Res 2001;61:3369-72.
24. Kerbel RS, Yu J, Tran J, et al. Possible mechanisms of acquired resistance to anti-angiogenic drugs: implications for the use of combination therapy approaches. Cancer Metastasis Rev 2001;20:79-86.
25. Miller KD, Sweeney CJ, Sledge GW Jr. The Snark is a Boojum: the continuing problem of drug resistance in the anti-angiogenic era. Ann Oncol 2003;14:20-8.
26. Brouty-Boyé D, Kolonias D, Wu CJ, Savaraj N, Lampidis TJ. Relationship of multidrug resistance to rhodamine-123 selectivity between carcinoma and normal epithelial cells: taxol and vinblastine modulate drug efflux. Cancer Res 1995;55:1633-8.
27. Hari M, Loganzo F, Annable T, et al. Paclitaxel-resistant cells have a mutation in the paclitaxel-binding region of beta-tubulin (Asp26Glu) and less stable microtubules. Mol Cancer Ther 2006;5:270-8.
28. Kaplan RN, Riba RD, Zacharoulis S, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature 2005;438:820-7.
29. Steeg PS. Tumor metastasis: mechanistic insights and clinical challenges. Nat Med 2006;12:895-904.