

ORIGINAL ARTICLE

## Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer

Alan Sandler, M.D., Robert Gray, Ph.D., Michael C. Perry, M.D., Julie Brahmer, M.D., Joan H. Schiller, M.D., Afshin Dowlati, M.D., Rogerio Lilenbaum, M.D., and David H. Johnson, M.D.

### ABSTRACT

#### BACKGROUND

From Vanderbilt University, Nashville (A.S., D.H.J.); the Dana–Farber Cancer Institute, Boston (R.G.); the Ellis Fischel Cancer Center, University of Missouri, Columbia (M.C.P.); Johns Hopkins University, Baltimore (J.B.); the University of Wisconsin, Madison (J.H.S.); University Hospitals of Cleveland, Cleveland (A.D.); and Mount Sinai Hospital, Miami (R.L.). Address reprint requests to Dr. Sandler at the Vanderbilt–Ingram Cancer Center, 2220 Pierce Ave., Nashville, TN 37232, or at alan.sandler@vanderbilt.edu.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has been shown to benefit patients with a variety of cancers.

#### METHODS

Between July 2001 and April 2004, the Eastern Cooperative Oncology Group (ECOG) conducted a randomized study in which 878 patients with recurrent or advanced non–small-cell lung cancer (stage IIIB or IV) were assigned to chemotherapy with paclitaxel and carboplatin alone (444) or paclitaxel and carboplatin plus bevacizumab (434). Chemotherapy was administered every 3 weeks for six cycles, and bevacizumab was administered every 3 weeks until disease progression was evident or toxic effects were intolerable. Patients with squamous-cell tumors, brain metastases, clinically significant hemoptysis, or inadequate organ function or performance status (ECOG performance status, >1) were excluded. The primary end point was overall survival.

#### RESULTS

The median survival was 12.3 months in the group assigned to chemotherapy plus bevacizumab, as compared with 10.3 months in the chemotherapy-alone group (hazard ratio for death, 0.79;  $P=0.003$ ). The median progression-free survival in the two groups was 6.2 and 4.5 months, respectively (hazard ratio for disease progression, 0.66;  $P<0.001$ ), with corresponding response rates of 35% and 15% ( $P<0.001$ ). Rates of clinically significant bleeding were 4.4% and 0.7%, respectively ( $P<0.001$ ). There were 15 treatment-related deaths in the chemotherapy-plus-bevacizumab group, including 5 from pulmonary hemorrhage.

#### CONCLUSIONS

The addition of bevacizumab to paclitaxel plus carboplatin in the treatment of selected patients with non–small-cell lung cancer has a significant survival benefit with the risk of increased treatment-related deaths. (ClinicalTrials.gov number, NCT00021060.)

N Engl J Med 2006;355:2542-50.  
Copyright © 2006 Massachusetts Medical Society.

**I**N THE UNITED STATES, LUNG CANCER AFFECTS approximately 171,000 people annually and is the leading cause of cancer-related deaths.<sup>1</sup> Approximately 85% of these patients have non-small-cell lung cancer. The Eastern Cooperative Oncology Group (ECOG) conducted a randomized clinical trial comparing four platin-based, two-drug chemotherapy regimens in more than 1100 patients.<sup>2</sup> The median survival was 8 months, with no significant differences in overall survival among the groups. Although modest progress has been made with the use of chemotherapy in patients with metastatic non-small-cell lung cancer, additional treatment options are needed.

Angiogenesis is one of the hallmarks of cancer.<sup>3</sup> Vascular endothelial growth factor (VEGF), an endothelial-cell-specific mitogen, is the major regulator of angiogenesis in normal and malignant tissue.<sup>4,5</sup> Increased expression of VEGF has been found in most tumors in humans, including non-small-cell lung cancers, and in many instances, it is associated with increased risks of recurrence, metastasis, and death.<sup>6-9</sup> Preclinical studies have shown that a murine monoclonal antibody against VEGF can inhibit the growth of human tumor xenografts when given alone or with chemotherapy.<sup>10-13</sup> A humanized variant of this antibody (bevacizumab [Avastin, Genentech]) has clinical activity in human cancer and increases survival when added to standard chemotherapy in metastatic colon cancer.<sup>14</sup>

A randomized phase 2 study, involving patients with advanced non-small-cell lung cancer who had not previously received chemotherapy, compared paclitaxel and carboplatin alone with paclitaxel and carboplatin plus bevacizumab, with bevacizumab at a dose of 7.5 mg or 15 mg per kilogram of body weight intravenously every 3 weeks.<sup>15</sup> In the group receiving the higher dose of bevacizumab, as compared with the two other groups, the median time to disease progression was significantly longer. However, of the 66 patients who received bevacizumab, life-threatening pulmonary hemorrhage occurred in 6, including four fatal events. Serious hemorrhagic events appeared to be more common among patients with predominantly squamous-cell carcinomas. These preliminary results prompted the present phase 3 study, which was designed to investigate whether the addition of bevacizumab to paclitaxel and carboplatin improves survival in patients with metastatic non-squamous-cell, non-small-cell lung cancer.

METHODS

PATIENTS

Between July 2001 and April 2004, we conducted a randomized study in which 878 patients with recurrent or advanced non-small-cell lung cancer (stage IIIB or IV) were assigned to paclitaxel and carboplatin chemotherapy alone (paclitaxel-carboplatin group) (444 patients) or paclitaxel and carboplatin plus bevacizumab (paclitaxel-carboplatin-bevacizumab group) (434 patients). Eligible patients were required to have histologically or cytologically confirmed, newly diagnosed stage IIIB (malignant pleural effusion) or stage IV cancer or recurrent non-small-cell lung cancer for which they had not received chemotherapy. Other inclusion criteria were measurable or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST),<sup>16</sup> an ECOG performance status of 0 or 1, and adequate hematologic, hepatic, and renal function (including urinary excretion of  $\leq 500$  mg of protein per day).

Exclusion criteria were histologic evidence of predominantly squamous-cell cancer; hemoptysis ( $\frac{1}{2}$  tsp or more per event — a criterion added after a grade 5 pulmonary hemorrhage occurred in a patient with pretreatment hemoptysis); central nervous system (CNS) metastases (to reduce concern about possible CNS hemorrhage); pregnancy or lactation; a history of documented hemorrhagic diathesis or coagulopathy; therapeutic anticoagulation; regular use of aspirin ( $>325$  mg per day), nonsteroidal antiinflammatory agents, or other agents known to inhibit platelet function; radiation therapy within 21 days before enrollment or major surgery within 28 days before enrollment; clinically significant cardiovascular disease; and medically uncontrolled hypertension.

LABORATORY CORRELATES

Plasma VEGF levels were measured at baseline in the initial 166 consecutive patients (79 in the paclitaxel-carboplatin group and 87 in the paclitaxel-carboplatin-bevacizumab group) by means of an enzyme-linked immunosorbent assay. Each sample was assayed in duplicate.

STUDY DESIGN

Treatment assignments were designed to achieve a balance between the two study groups in permuted blocks with stratification according to measurable versus nonmeasurable disease, prior radiation

therapy versus no prior radiation therapy, prior weight loss of less than 5% versus 5% or more, and non–small-cell lung cancer, stage IIIB, with pleural effusion versus stage IV or recurrent disease. The primary end point was overall survival. Prespecified stopping rules were based on toxic effects.

Patients were randomly assigned to receive paclitaxel at a dose of 200 mg per square meter of body-surface area and carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 mg per milliliter per minute, administered intravenously on day 1, or paclitaxel and carboplatin plus bevacizumab at a dose of 15 mg per kilogram given intravenously on day 1.<sup>15</sup> Chemotherapy was repeated every 21 days for a total of six cycles unless there was evidence of disease progression or intolerance of the study treatment. Patients in the paclitaxel–carboplatin–bevacizumab group continued to receive bevacizumab monotherapy every 3 weeks until evidence of disease progression or unacceptable toxic effects developed.

The protocol was approved by the institutional review boards of all participating institutions and was carried out in accordance with the Declaration of Helsinki, current Food and Drug Administration Good Clinical Practices, and local ethical and legal requirements. ECOG designed and coordinated the study and was responsible for all aspects of the data collection and analysis; the authors made the decision to publish the data. The authors assume responsibility for the overall content and integrity of the manuscript and vouch for the accuracy and completeness of the reported data; their views do not necessarily represent the official views of the National Cancer Institute (NCI). Bevacizumab (Cancer Chemotherapy National Service Center code 704865) was provided by Genentech and distributed by the NCI.

#### ASSESSMENTS

After the baseline evaluation, tumor status was assessed every 6 weeks for 24 weeks, then every 9 weeks for the remainder of the treatment period, and then every 12 weeks after the completion of treatment. Responses were assessed using RECIST and required confirmation at least 4 weeks after initial documentation.

Assessments of toxic effects were made according to the common toxicity criteria (version 2) of the NCI. Because of concern about pulmonary

hemorrhage, any serious bleeding event (grade 3 or higher) was reported to ECOG and the study chairman within 24 hours after its occurrence.

#### STATISTICAL ANALYSIS

The original study design called for the enrollment of a total of 640 patients, with the final analyses to be performed after 500 deaths had occurred. The design included two planned suspensions of recruitment for the safety analysis after a total of 112 patients had been enrolled and then after a total of 336 patients had been enrolled and planned interim analyses of survival after 218 and 350 deaths had occurred. The plan to suspend recruitment after enrollment of 336 patients was eliminated in August 2003, on the basis of the recommendation by the data monitoring committee; in January 2004, the planned enrollment was increased to 842 patients, with a planned final analysis after 650 deaths had occurred, to target a smaller treatment effect than that in the original study design. The increase in accrual was based on a recommendation by the ECOG Lung Committee, which was unaware of the results of the efficacy analysis. The revised design yielded an 80.5% power of the study to detect a hazard ratio for death of 0.80 in the group treated with chemotherapy plus bevacizumab, with the use of a one-sided test and an overall type I error of 2.5%.

The design specified interim analyses after 286 deaths had occurred (44%) and after 455 deaths had occurred (70%), with stopping rules both for a demonstrated difference between the study groups and for a demonstrated lack of benefit on the basis of the confidence intervals (CIs) for the hazard ratio,<sup>17</sup> estimated by means of a stratified partial-likelihood test with the use of an O'Brien–Fleming boundary. The study was continuously monitored for rates of grades 4 and 5 bleeding events, with early stopping if the rate among the first 336 patients enrolled was significantly higher in the paclitaxel–carboplatin–bevacizumab group than in the paclitaxel–carboplatin group, as calculated with the use of Fisher's exact test.

All efficacy analyses were based on a comparison of the assigned treatments. The primary analysis excluded patients deemed to be ineligible on central review of the submitted data. However, an intention-to-treat analysis of all patients showed similar results ( $P=0.005$  for survival). Survival was defined as the time from randomization to death

from any cause, and progression-free survival as the time from randomization to documented disease progression (according to RECIST) or death. Event-time distributions were estimated by the Kaplan-Meier method. Cox proportional-hazards models, stratified according to the measurability of disease, disease stage, presence or absence of prior radiation therapy, and amount of prior weight loss, were used to estimate the hazard ratios and to test for significance of the timing of events. All reported P values are two-sided, and CIs are at the 95% level. Adverse events were compared with the use of Fisher's exact test.

RESULTS

After the second planned interim analysis, the independent data monitoring committee recommended the release of the study results in March 2005, since the criteria for significance prespecified in the protocol had been met (Wald statistic, 2.67; O'Brien-Fleming boundary, at 72.2% information, 2.41). The results reported here include follow-up through October 2005 (median, 19 months; minimum time from study entry to the cutoff point for the primary analysis, 18 months).

BASELINE CHARACTERISTICS OF THE PATIENTS

Between July 19, 2001, and April 27, 2004, including a prespecified suspension between February and August 2002, a total of 878 patients were enrolled, of whom 444 were assigned to treatment with paclitaxel and carboplatin alone and 434 to paclitaxel and carboplatin plus bevacizumab. Twenty-eight patients were excluded from the primary analysis because of eligibility violations or inadequate data (nine patients because of incorrect disease stage, six because of receipt of radiation therapy within three weeks before entry into the study, four because of histologic findings of squamous-cell cancer, and nine for other reasons) (Fig. 1). Table 1 shows the baseline characteristics of eligible patients. The two groups were well balanced, except for a difference in distribution according to sex (men accounted for 58% of patients in the paclitaxel-carboplatin group and 50% of those in the paclitaxel-carboplatin-bevacizumab group; P=0.03, with Fisher's exact test).

TREATMENT

The median number of cycles of therapy was five in the paclitaxel-carboplatin group and seven in

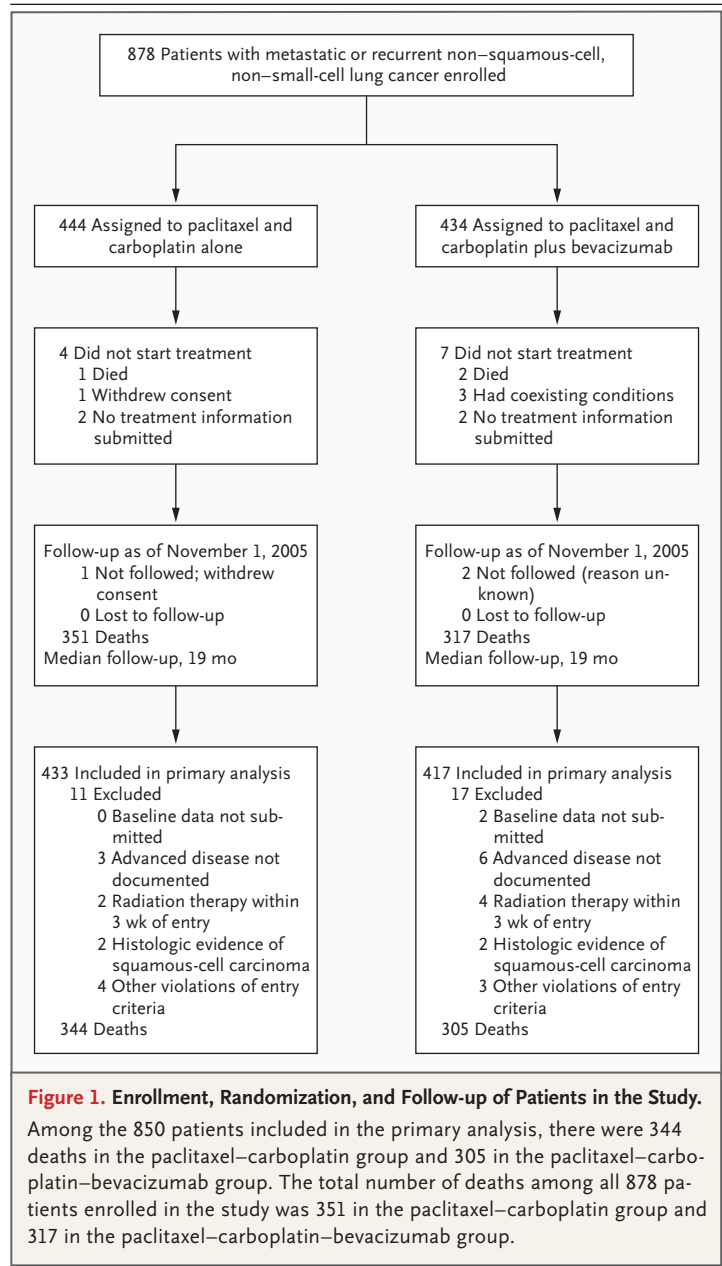


Figure 1. Enrollment, Randomization, and Follow-up of Patients in the Study.

Among the 850 patients included in the primary analysis, there were 344 deaths in the paclitaxel-carboplatin group and 305 in the paclitaxel-carboplatin-bevacizumab group. The total number of deaths among all 878 patients enrolled in the study was 351 in the paclitaxel-carboplatin group and 317 in the paclitaxel-carboplatin-bevacizumab group.

the paclitaxel-carboplatin-bevacizumab group (including the cycles of bevacizumab monotherapy). Of the 407 patients starting treatment with paclitaxel and carboplatin plus bevacizumab for whom we had adequate information on the duration of treatment, 215 (53%) continued with bevacizumab monotherapy, and of these, 107 (50%) received more than five cycles of monotherapy. Information on treatment at the time of disease progression was available for 528 of the 850 patients included in the primary analysis. Chemo-

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Paclitaxel– Carboplatin Group (N=433)	Paclitaxel–Carboplatin– Bevacizumab Group (N=417)
	no. (%)	
Sex†		
Male	253 (58)	210 (50)
Female	180 (42)	207 (50)
Age ≥65 yr	189 (44)	177 (42)
Race‡		
White	378 (91)	352 (90)
Black	23 (6)	22 (6)
Other	14 (3)	17 (4)
ECOG performance status§		
0	170 (40)	167 (40)
1	260 (60)	247 (60)
Measurable disease	392 (91)	381 (91)
Prior weight loss (≥5%)	121 (28)	117 (28)
Stage IIIB	55 (13)	50 (12)
Stage IV	337 (78)	310 (74)
Recurrent disease	40 (9)	57 (14)
Prior radiation therapy	37 (9)	33 (8)
Adenocarcinoma or not other- wise specified	380 (88)	366 (88)
Large-cell cancer	29 (7)	17 (4)
Bronchioloalveolar carcinoma	11 (3)	12 (3)
Other histologic findings	11 (3)	22 (5)
>2 Sites involved	229 (53)	216 (52)
Pleura involved	111 (26)	112 (27)
Liver involved	73 (17)	90 (22)
Bone involved	149 (34)	118 (28)
Adrenal glands involved	72 (17)	53 (13)

\* Because of rounding, percentages may not total 100.

† P=0.03 by Fisher's exact test.

‡ Data on race were not available for 44 patients: 18 in the paclitaxel–carboplatin group and 26 in the paclitaxel–carboplatin–bevacizumab group. Race was determined on the basis of data in hospital records.

§ ECOG performance status was not available for six patients: three in the paclitaxel–carboplatin group and three in the paclitaxel–carboplatin–bevacizumab group.

therapy was given to 200 patients in the paclitaxel–carboplatin group (including 87 of 180 women [48%]) at the time of disease progression, as compared with 180 patients in the paclitaxel–carboplatin–bevacizumab group (82 of 207 women [40%]). In addition, more women in the paclitaxel–carboplatin group received second-line chemotherapy: 48% (87 of 180) as compared with 40% (82 of 207) in the paclitaxel–carboplatin–bevacizumab group.

However, there was no significant difference in the number of women who subsequently received epidermal growth factor–tyrosine kinase inhibitors (32 of 180 in the paclitaxel–carboplatin group and 34 of 207 in the paclitaxel–carboplatin–bevacizumab group).

#### EFFICACY ANALYSIS

The median overall survival was 12.3 months in the paclitaxel–carboplatin–bevacizumab group, as compared with 10.3 months in the paclitaxel–carboplatin group (hazard ratio for death, 0.79; 95% CI, 0.67 to 0.92; P=0.003) (Fig. 2A). Survival rates were 51% in the paclitaxel–carboplatin–bevacizumab group, as compared with 44% in the paclitaxel–carboplatin group, at 1 year and 23%, as compared with 15%, respectively, at 2 years. The median progression-free survival was also significantly improved in the paclitaxel–carboplatin–bevacizumab group (6.2 months, as compared with 4.5 in the paclitaxel–carboplatin group), for a hazard ratio for disease progression of 0.66 (95% CI, 0.57 to 0.77; P<0.001) (Fig. 2B). Among 773 patients with measurable disease, the addition of bevacizumab to paclitaxel and carboplatin improved the response rate; 59 of 392 patients (15%) in the paclitaxel–carboplatin group had a response, as compared with 133 of 381 patients (35%) in the paclitaxel–carboplatin–bevacizumab group (P<0.001).

The effects of bevacizumab on survival and progression-free survival were consistent among the four subgroups, stratified according to whether patients had measurable or nonmeasurable disease, prior radiation therapy or no prior radiation therapy, a weight loss of 5% or more or a loss of less than 5%, and stage IIIB disease (pleural effusion) or stage IV disease, or recurrent disease (Fig. 3).

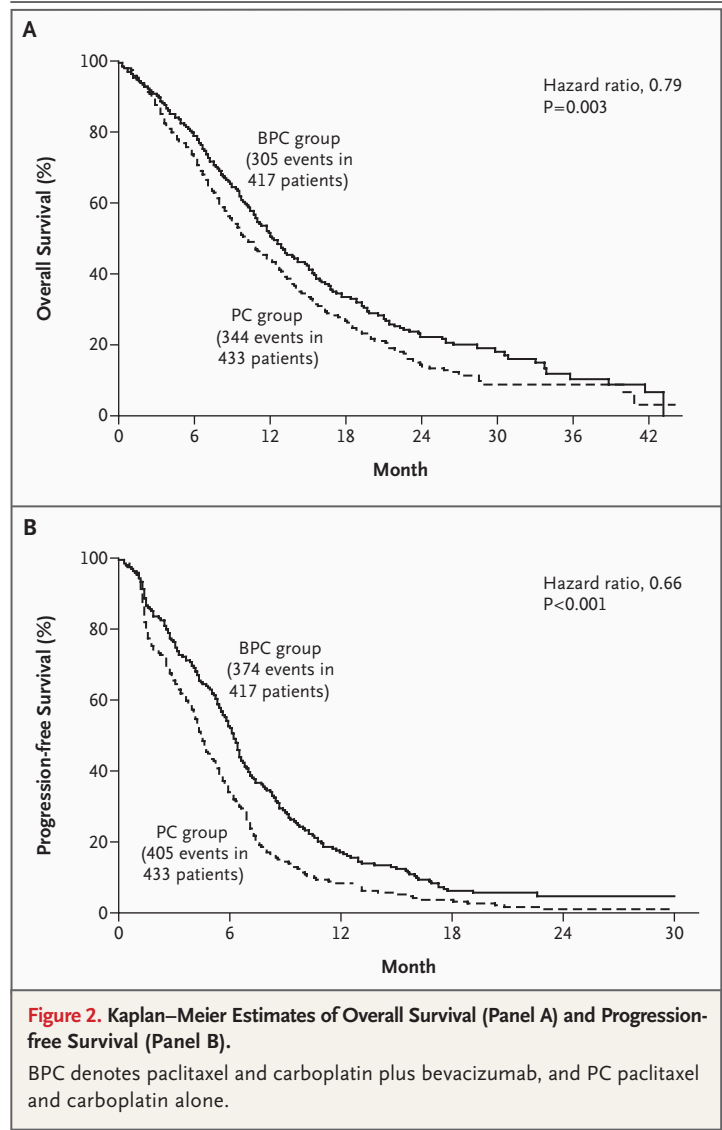
#### VEGF LEVELS

Baseline VEGF levels in 166 patients did not differ significantly according to treatment (P=0.13, calculated by the Wilcoxon rank-sum test) or sex (P=0.67) (median VEGF level, 38.7 ng per milliliter in the paclitaxel–carboplatin group and 33.7 ng per milliliter in the paclitaxel–carboplatin–bevacizumab group; 36.7 ng per milliliter in men and 33.7 ng per milliliter in women; range, 12.5 to 445 in all subgroups). VEGF levels before treatment did not correlate with overall survival (P=0.15).

**SAFETY**

All patients known to have received the study treatment (440 patients in the paclitaxel-carboplatin group and 427 in the paclitaxel-carboplatin-bevacizumab group) were included in the analysis of toxic effects. Reporting was limited to hematologic events of grade 4 or higher and all nonhematologic adverse events of grade 3 or higher. Table 2 lists rates of adverse events in each treatment group. The treating physician's attribution of the adverse event to the treatment or to another cause was not considered in this analysis. The rates of hypertension, proteinuria, bleeding, neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, rash, and headache were significantly higher in the paclitaxel-carboplatin-bevacizumab group than in the paclitaxel-carboplatin group ( $P < 0.05$ ). The difference between the groups appeared during the third cycle; during the first three cycles, events occurred in 57 of the 440 patients in the paclitaxel-carboplatin group (13%) and in 76 of the 427 patients in the paclitaxel-carboplatin-bevacizumab group (18%).

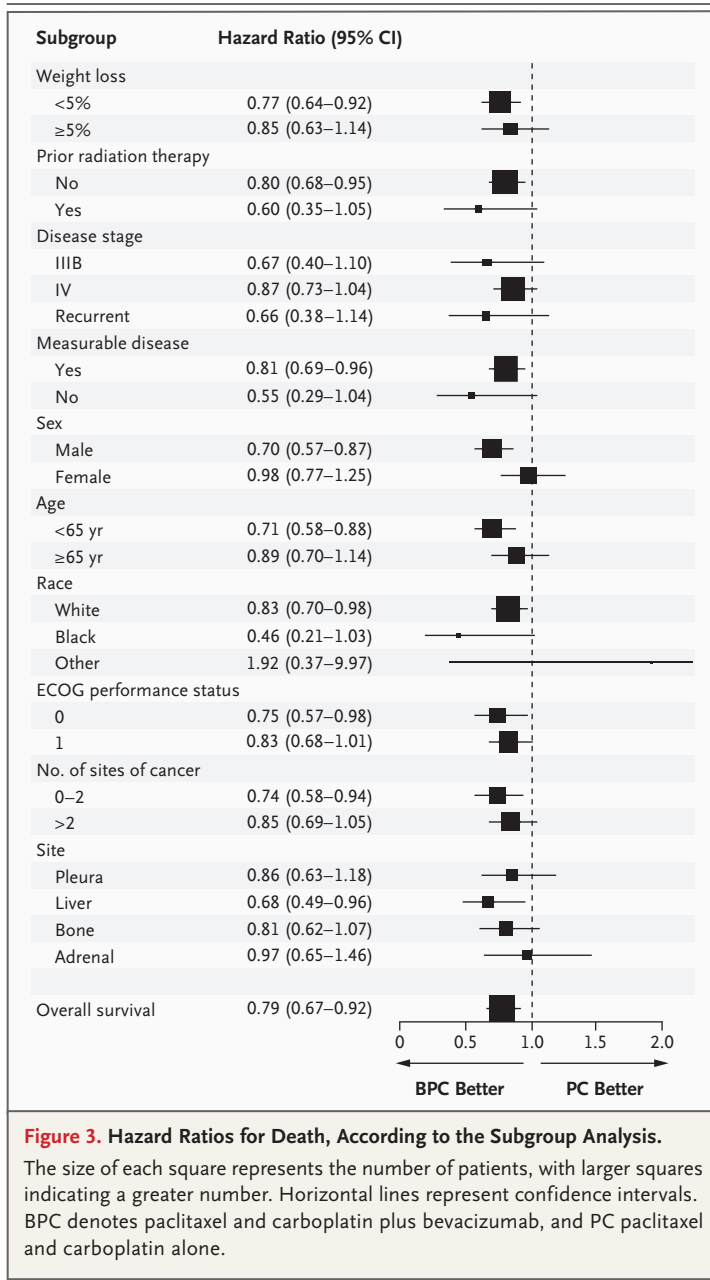
Table 3 lists all causes of death. There were 17 deaths related to toxic effects of the treatment. Two deaths (from gastrointestinal hemorrhage and febrile neutropenia) occurred in patients in the paclitaxel-carboplatin group and 15 occurred in the paclitaxel-carboplatin-bevacizumab group; the difference between the groups was significant ( $P = 0.001$ ). Of the 15 deaths in the paclitaxel-carboplatin-bevacizumab group, 5 were attributed to pulmonary hemorrhage, 5 to complications of febrile neutropenia, 2 each to a cerebrovascular event or gastrointestinal hemorrhage, and 1 to a probable pulmonary embolus. Most of the deaths occurred during the first two cycles of therapy. Three patients in the paclitaxel-carboplatin-bevacizumab group died of cardiac events that were not considered to be related to the treatment: a myocardial infarction 40 days after the last dose of bevacizumab, a sudden death (no autopsy) during the 18th cycle of treatment, and cardiac arrest with bradycardia after the third cycle (no autopsy). Among the 215 patients receiving bevacizumab monotherapy, the most common grade 3 or 4 toxic effects were hypertension (in 12 patients [5.6%]), proteinuria (in 9 patients [4.2%]), fatigue (in 11 patients [5.1%]), and dyspnea (in 12 patients [5.6%]).



**DISCUSSION**

We found that the addition of bevacizumab to a standard, platin-based chemotherapy regimen improved overall survival in patients with advanced non-squamous-cell, non-small-cell lung cancer and a good ECOG performance status. In addition, bevacizumab prolonged progression-free survival and improved the response rate.

The improvement in the response rate was not anticipated a priori, since antiangiogenic drugs were not considered to have a cytotoxic effect.<sup>3</sup> Initially, it was thought that the predominant ef-



fect of antiangiogenic agents was the prevention of the development of new blood vessels, and that in this way these agents inhibit tumor growth. Jain reported that elevated VEGF levels cause a disorganized and “leaky” vasculature within the tumor; this effect elevates interstitial pressure and thus decreases delivery of chemotherapy to the tumor.<sup>18</sup> Subsequently, Willett et al. found that bevacizumab increases drug delivery to the tumor.<sup>19</sup> The significant improvement in the re-

sponse rate in our study and in previous randomized studies of chemotherapy with or without bevacizumab supports the hypothesis that bevacizumab improves drug delivery to the tumor.<sup>14,20,21</sup>

In the phase 2 study that served as the impetus for our trial, an unexpectedly high rate of life-threatening and fatal pulmonary hemorrhages was associated with bevacizumab treatment, particularly in patients with squamous-cell lung cancer.<sup>15</sup> These results led us to exclude patients with predominantly squamous-cell carcinoma, hemoptysis, or both. With these exclusions, the incidence of life-threatening pulmonary hemorrhage was 1.9% (fatal hemorrhage, 1.2%), whereas in the phase 2 study, in which hemoptysis and predominantly squamous-cell carcinoma were not exclusion criteria, the incidence of this complication was 9.1%. Among the five patients who died from pulmonary hemorrhage in our study, one had hemoptysis before entry into the study (before the amendment to exclude patients with hemoptysis of ½ tsp or more at baseline), and hemoptysis developed in another patient during the first cycle of therapy. This second patient continued in the study and had a fatal event during the second cycle of treatment. Clearly, in retrospect, this patient should not have continued to receive bevacizumab. Among the 10 other deaths considered to be related to treatment, 5 were due to complications of febrile neutropenia, 2 to cerebrovascular events, and 2 to gastrointestinal hemorrhage; 1 was thought to be due to a pulmonary embolus.

Neutropenia has not been associated with bevacizumab, yet five patients in the paclitaxel-carboplatin-bevacizumab group had grade 5 febrile neutropenia. Other investigators have reported increased rates of neutropenia when bevacizumab was combined with chemotherapy.<sup>22</sup> The hypertension, proteinuria, and headache observed in this study are adverse events that had previously been associated with bevacizumab. They were generally manageable and did not require permanent discontinuation of bevacizumab.

The benefits of bevacizumab were consistent among all prespecified stratification groups. Exploratory analyses of the treatment groups according to baseline characteristics showed that bevacizumab was beneficial in all the subgroups assessed, with the possible exception of survival among women. The median overall survival in the paclitaxel-carboplatin group and the paclitaxel-carboplatin-bevacizumab group was 8.7 and 11.7

**Table 2. Adverse Events, According to Treatment.\***

Adverse Event	Paclitaxel-Carboplatin Group (N=440)			Paclitaxel-Carboplatin-Bevacizumab Group (N=427)			P Value
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5†	
	<i>number of patients (percent)</i>						
Neutropenia		74 (16.8)			109 (25.5)		0.002
Thrombocytopenia		1 (0.2)			7 (1.6)		0.04
Anemia		4 (0.9)			0		NS
Febrile neutropenia	8 (1.8)		1 (0.2)	17 (4.0)		5 (1.2)	0.02
Hyponatremia	4 (0.9)	1 (0.2)		11 (2.6)	4 (0.9)		0.02
Hypertension	2 (0.5)	1 (0.2)		29 (6.8)	1 (0.2)		<0.001
Proteinuria				11 (2.6)	2 (0.5)		<0.001
Headache	2 (0.5)			13 (3.0)			0.003
Rash or desquamation	2 (0.5)			10 (2.3)			0.02
Bleeding events (all)	3 (0.7)			19 (4.4)			<0.001
Central nervous system hemorrhage					3 (0.7)		
Epistaxis	1 (0.2)			3 (0.7)			
Hematemesis						2 (0.5)	
Hemoptysis	1 (0.2)			2 (0.5)	1 (0.2)	5 (1.2)	
Melena or gastrointestinal bleeding	1 (0.2)		1 (0.2)	3 (0.7)	1 (0.2)		
Other hemorrhage				1 (0.2)	1 (0.2)		

\* Values are unadjusted between-group differences. For hematologic adverse events, only data on grades 4 and 5 events were reported. NS denotes not significant (P>0.05).

† Three other grade 5 adverse events occurred in the paclitaxel-carboplatin-bevacizumab group: two patients had cerebrovascular events and one had a pulmonary embolus.

months, respectively, among men and 13.1 and 13.3 months, respectively, among women. Possible explanations for this finding include imbalances between the two groups with respect to known or unknown baseline prognostic factors, imbalances in the use of second- and third-line therapies, statistical chance, or a true sex-based difference. More women in the paclitaxel-carboplatin group received second-line chemotherapy than in the paclitaxel-carboplatin-bevacizumab group. However, there was no significant difference between the two groups in the number of women who subsequently received epidermal growth factor-tyrosine kinase inhibitors.

Although it has been postulated that baseline VEGF levels correlate with the clinical outcome with bevacizumab treatment, in this trial, the baseline plasma VEGF levels did not correlate with survival. The absence of a correlation was also reported in a trial of first-line therapy with irinotecan, fluorouracil, and leucovorin with or

**Table 3. Causes of Death.**

Variable	Paclitaxel-Carboplatin Group	Paclitaxel-Carboplatin-Bevacizumab Group
	<i>number of patients</i>	
Total deaths	344	305
Cause		
Lung cancer	309	260
Toxic effects	2	14*
Coexisting conditions	16	16
Unknown cause	17	15

\* One patient in the paclitaxel-carboplatin-bevacizumab group who had a grade 5 adverse event was considered to be ineligible because of undocumented advanced disease; data on this patient are not included in the table (but were included in the analysis of adverse events).

without bevacizumab in patients with colorectal cancer.<sup>23</sup>

In summary, the addition of bevacizumab to a standard, platin-based, two-agent chemothera-

py regimen conferred a significant improvement in overall survival, progression-free survival, and response rate in patients with non-squamous-cell carcinoma and a good performance status. Increased toxic effects, particularly febrile neutropenia and pulmonary hemorrhage, were associated with the addition of bevacizumab. These risks must be considered within the context of the survival benefit conferred by the addition of bevacizumab to standard treatment for non-small-cell lung cancer.

Supported in part by grants from the Department of Health and Human Services and the National Institutes of Health (CA23318 to the ECOG statistical center, CA66636 to the ECOG data management center, CA21115 to the ECOG coordinating center and operations office, CA49957 to Dr. Sandler, CA21076 to Dr. Schiller, CA14548 to Dr. Dowlati, CA12046 and CA31946 to Dr. Perry, and CA16116 to Dr. Brahmer).

Presented in part in abstract form at the annual meeting of the American Society of Clinical Oncology (ASCO), Orlando, FL,

May 13–17, 2005, and in part in updated form at the annual meeting of ASCO, Atlanta, June 2–6, 2006.

Dr. Sandler reports receiving grant support from Genentech, OSI, Pfizer, Eli Lilly, Sunesis, Novartis, and Wyeth, lecture fees from Genentech and Bristol-Myers Squibb, and consulting fees from Genentech, OSI, Bristol-Myers Squibb, Eli Lilly, Sanofi-Aventis, Pfizer, Bayer, AstraZeneca, Novartis, Wyeth, Amgen, and Cyclacel; Dr. Gray, receiving grant support from Bayer, Bristol-Myers Squibb, Genentech, Schering-Plough, Berlex, Sanofi-Aventis, Pfizer, Eli Lilly, and Ortho-Biotech; Dr. Perry, holding equity ownership in Genentech; Dr. Brahmer, receiving grant support from Merck, Pfizer, Mederex, and Wyeth, consulting fees from Glaxo-SmithKline and Genentech, and lecture fees from Sanofi-Aventis; Dr. Schiller, receiving grant support from Genentech, GlaxoSmithKline, Cell Pathways, Immunex, Eli Lilly, Abbott, Millennium, Sanofi-Aventis, Novartis, Pfizer, Cell Genesys, Amgen, AstraZeneca, Battelle, and Zivena, and consulting fees from Genentech, AstraZeneca, and Pfizer and serving on an advisory board of EMD Pharmaceuticals; Dr. Dowlati, receiving lecture fees from Genentech; Dr. Lilenbaum, receiving grant support from Genentech, consulting fees from Genentech, Sanofi-Aventis, and AstraZeneca and lecture fees from Eli Lilly; and Dr. Johnson, receiving consulting fees from Merck and Genentech. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin* 2005;55:10-30. [Erratum, *CA Cancer J Clin* 2005;55:259.]
2. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92-8.
3. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100:57-70.
4. Folkman J. What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst* 1990;82:4-6.
5. Ferrara N. The role of vascular endothelial growth factor in pathological angiogenesis. *Breast Cancer Res Treat* 1995;36:127-37.
6. Mattern J, Koomagi R, Volm M. Association of vascular endothelial growth factor expression with intratumoral microvessel density and tumour cell proliferation in human epidermoid lung carcinoma. *Br J Cancer* 1996;73:931-4.
7. Brown LE, Berse B, Jackman RW, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in adenocarcinomas of the gastrointestinal tract. *Cancer Res* 1993;53:4727-35.
8. Brown LE, Berse B, Jackman RW, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in breast cancer. *Hum Pathol* 1995;26:86-91.
9. Seto T, Higashiyama M, Funai H, et al. Prognostic value of expression of vascular endothelial growth factor and its flt-1 and KDR receptors in stage I non-small-cell lung cancer. *Lung Cancer* 2006;53:91-6.
10. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003;9:669-76.
11. Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature* 1993;362:841-4.
12. Kabbinavar FF, Wong JT, Ayala RE, Wintroub AB, Kim KJ, Ferrara N. The effect of antibody to vascular endothelial growth factor and cisplatin on the growth of lung tumors in nude mice. *Proc Am Assoc Cancer Res* 1995;36:488.
13. Borgstrom P, Gold DP, Hillan KJ, Ferrara N. Importance of VEGF for breast cancer angiogenesis in vivo: implications from intravital microscopy of combination treatments with an anti-VEGF neutralizing monoclonal antibody and doxorubicin. *Anticancer Res* 1999;19:4203-14.
14. 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.
15. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184-91.
16. James K, Eisenhauer E, Christian M, et al. Measuring response in solid tumors: unidimensional versus bidimensional measurement. *J Natl Cancer Inst* 1999;91:523-8.
17. Jennison C, Turnbull BW. Interim analyses: the repeated confidence interval approach. *J R Stat Soc [B]* 1989;51:305-61.
18. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med* 2001;7:987-9.
19. Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med* 2004;10:145-7. [Erratum, *Nat Med* 2004;10:649.]
20. Giantonio BJ, Catalano PJ, Meropol NJ, et al. High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: results from the Eastern Cooperative Oncology Group (ECOG) study E3200. *J Clin Oncol* 2005;23:Suppl:16S. abstract.
21. Miller KD, Wang W, Gralow J, et al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). *Breast Cancer Res Treat* 2005;94:Suppl 1:S6. abstract.
22. Kozloff M, Cohn A, Christiansen N, et al. Safety of bevacizumab among patients receiving first-line chemotherapy for metastatic colorectal cancer: preliminary results from a larger registry in the U.S. *J Clin Oncol* 2005;23:Suppl:16S. abstract.
23. Jubb AM, Hurwitz HI, Bai W, et al. Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. *J Clin Oncol* 2006;24:217-27.

Copyright © 2006 Massachusetts Medical Society.