VOLUME 23 · NUMBER 25 · SEPTEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study

Brian Leyland-Jones, Vladimir Semiglazov, Marek Pawlicki, Tadeusz Pienkowski, Sergei Tjulandin, George Manikhas, Antoly Makhson, Anton Roth, David Dodwell, Jose Baselga, Mikhail Biakhov, Konstantinas Valuckas, Edouard Voznyi, Xiangyang Liu, and Els Vercammen

From the Department of Medical Oncology, McGill University, Montreal, Canada; N.N. Petrov Research Institute of Oncology; City Oncology Dispensary, St Petersburg; Cancer Research Center; Semashko Central Clinical Hospital; Russian Scientific Center of Radiology, Moscow; City Clinical Hospital, Moscow Region, Russia; Klinika Chemioterapii Centrum Onkologii, Krakov; Klinika Nowotworów Sutka Centrum Onkologii Instytut, Warsaw, Poland; Klinika za Tumore, Zagreb, Croatia; Johnson & Johnson Pharmaceutical Research & Development, High Wycombe, Bucks, United Kingdom; Lithuanian Oncology Centre, Vilnius, Lithuania; and Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ.

Submitted June 22, 2004; accepted April 4, 2005.

Supported by a research grant from Johnson & Johnson Pharmaceutical Research and Development LLC, Raritan, NJ. B.L.-J. was the principal investigator.

Portions of this study were reported previously in Leyland-Jones B, and the BEST Investigators and Study Group: Breast cancer trial with erythropoietin terminated unexpectedly. Lancet Oncol 4:459-460, 2003.

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

Address reprint requests to and address for reprints: Brian Leyland-Jones, MD, Department of Oncology, McGill University, 546 Pine Avenue W, Montreal, Quebec, Canada H2W 1S6; e-mail: brian.leyland-jones@mcgill.ca.

0732-183X/05/2325-5960/$20.00

DOI: 10.1200/JCO.2005.06.150

ABSTRACT

Purpose
To evaluate the effect on survival and quality of life of maintaining hemoglobin (Hb) in the range of 12 to 14 g/dL with epoetin alfa versus placebo in women with metastatic breast cancer (MBC) receiving first-line chemotherapy.

Patients and Methods
Eligible patients were randomly assigned to receive epoetin alfa 40,000 U once weekly or placebo for 12 months. Study drug was initiated if baseline Hb was ≤ 13 g/dL or when Hb decreased to ≤ 13g/dL during the study. The primary end point was 12-month overall survival (OS).

Results
The study drug administration was stopped early in accordance with a recommendation from the Independent Data Monitoring Committee because of higher mortality in the group treated with epoetin alfa. Enrollment had been completed, with 939 patients enrolled (epoetin alfa, n = 469; placebo, n = 470). Most patients had Hb more than 12 g/dL at baseline (median Hb, 12.8 g/dL) or during the study. From the final analysis, 12-month OS was 70% for epoetin alfa recipients and 76% for placebo recipients ($P = .01$). Optimal tumor response and time to disease progression were similar between groups. The reason for the difference in mortality between groups could not be determined from additional subsequent analyses involving both study data and chart review.

Conclusion
In this trial, the use of epoetin alfa to maintain high Hb targets in women with MBC, most of whom did not have anemia at the start of treatment, was associated with decreased survival. Additional research is required to clarify the potential impact of erythropoietic agents on survival when the Hb target range is 10 to 12 g/dL.

J Clin Oncol 23:5960-5972. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Clinical studies in patients with cancer and anemia receiving platinum- or nonplatinum-based chemotherapy have shown that epoetin alfa significantly increases hemoglobin (Hb); decreases transfusion requirements; and improves levels of energy, activity, and overall quality of life (QOL).[1-3] Large community-based studies enrolling thousands of patients support these results.[4-6] Decreased fatigue associated with epoetin alfa is well established,

clinically important,[7,8] and significantly correlated with increased Hb,[1,4-6] even after adjusting for the effects of disease progression and other potential confounding factors on QOL.[9]

Anemia in patients with cancer is also an independent prognostic factor for survival, associated with shorter survival.[10] Anemia correction and enhanced tumor oxygenation are associated with improved survival in patients with various malignancies.[11-20] A potential survival benefit has been reported in patients with cancer receiving epoetin alfa. In a randomized, double-blind, placebo-controlled trial in 375 patients with cancer and anemia receiving nonplatinum chemotherapy, there was a trend in overall 12-month survival favoring epoetin alfa over placebo (overall survival, 37% *v* 33%; median survival time, 17 *v* 11 months, respectively; $P = .13$, log-rank test), although the study was not powered for survival as an end point.[1] In a retrospective review, anemic patients with squamous cell carcinoma of the oral cavity and oropharynx treated with epoetin alfa to maintain Hb survived longer than those not treated with epoetin alfa.[15] Despite these reports, a link has yet to be established between correction of anemia or maintenance of Hb with epoetin alfa and improved survival from an appropriately powered study with survival as the primary end point. This report presents the results from a large, multicenter, double-blind, randomized, placebo-controlled clinical trial to determine whether early intervention with epoetin alfa in mainly nonanemic women receiving first-line chemotherapy, and maintenance of Hb between 12 and 14 g/dL, could improve 12-month overall survival (OS).

PATIENTS AND METHODS

Study Objective

The primary objective of the Breast Cancer Erythropoietin Survival Trial (BEST) was to determine the effect of maintaining Hb 12 to 14 g/dL with epoetin alfa (Eprex; Johnson & Johnson, Raritan, NJ) versus placebo on 12-month OS. Additional efficacy variables included change in Hb level from baseline to study completion, proportion of patients receiving RBC transfusion, tumor response rate, change in QOL, and time to disease progression (TTP).

Patients and Study Design

This double-blind, randomized, placebo-controlled, multicenter study was conducted at 139 sites in 20 countries in Europe, Canada, South Africa, and Australia. The study protocol and amendments were reviewed by an Independent Ethics Committee, and the study was conducted in accordance with the Declaration of Helsinki. Patients or their legal representatives provided written consent to participate in the study. The study was conducted between June 2000 and April 2002, when study drug administration was stopped early in accordance with a recommendation from the Independent Data Monitoring Committee because of higher mortality in the epoetin alfa group. Blinded follow-up of enrolled patients continued until July 2002. Women ≥ 18 years of age who provided written informed consent were enrolled if they met the following criteria: confirmed diagnosis of stage IV metastatic breast cancer (MBC), scheduled to receive first-line chemotherapy (prior hormonal therapy for metastatic disease or cytotoxic therapy in the adjuvant setting was permitted), Hb of any level (no upper or lower limit for inclusion), body weight ≥ 40 kg, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, and life expectancy ≥ 6 months. Concurrent radiotherapy and hormonal therapy were permitted.

Patients were excluded if they had anemia resulting from factors other than cancer or its treatment (eg, hemolysis, GI bleeding), untreated folate or vitamin B_{12} deficiency, pregnancy, history of thrombovascular events (TVEs) in the preceding 6 months, uncontrolled hypertension (ie, diastolic blood pressure > 95 mmHg), current dose-intensification chemotherapy for bone marrow or stem-cell transplant, or treatment with epoetin alfa or other erythropoiesis-stimulating agents in the preceding 4 weeks. Patients were also ineligible if they had brain metastases, any active second primary malignancy within the last 3 years, a major infection requiring hospitalization and antibiotics within 14 days of randomization, or any other clinically significant disease or dysfunction not attributable to underlying malignancy or chemotherapy.

Eligible patients were randomly assigned within 5 days before the first chemotherapy cycle to receive epoetin alfa 40,000 U subcutaneously (SC) once weekly or placebo for 12 months, regardless of tumor progression and corresponding change in chemotherapy regimen. Randomization was stratified by metastatic category (bone metastases only versus other measurable metastatic lesions versus other nonmeasurable metastatic lesions). Hb level and reticulocyte count were assessed at randomization and weekly thereafter to determine when to begin study drug administration (permitted when Hb reached ≤ 13 g/dL). These values were then monitored weekly for 4 weeks of therapy to determine whether dose adjustments were necessary. After 4 weeks of therapy, Hb and reticulocyte counts were monitored every 3 to 4 weeks for the remainder of the double-blind treatment phase. During study drug administration, Hb was to be maintained between 12 and 14 g/dL. Epoetin alfa dose adjustments were permitted (Fig 1). RBC transfusions were allowed if clinically indicated. Oral iron supplementation was administered to support erythropoiesis (200 mg/d elemental iron) if transferrin saturation was less than 20%.

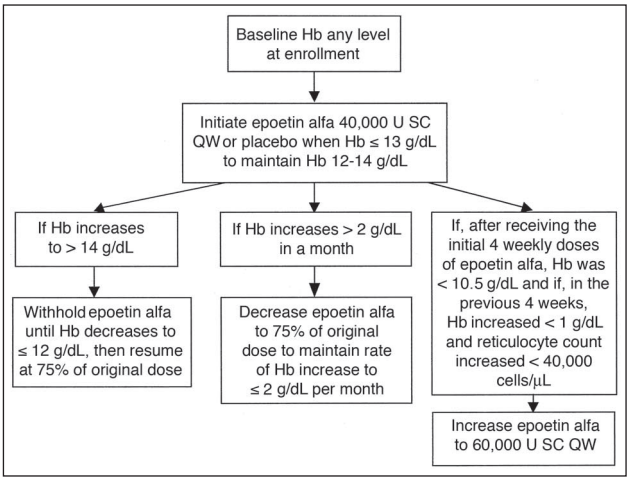

Fig 1. Epoetin alfa dose adjustments. Hb, hemoglobin; SC, subcutaneously; QW, once weekly.

Assessments

Before random assignment, patients were screened through collection of demographic data; history of malignancy; medical history; complete physical examination; clinical laboratory tests (CBC, serum chemistry, iron status, serum folate and vitamin B_{12}, urinalysis, pregnancy test); current therapy; and ECOG performance status. On randomization, an additional CBC was obtained to determine whether study drug administration could begin simultaneously with the first chemotherapy cycle. Baseline QOL was evaluated using the Functional Assessment of Cancer Therapy–General (FACT-G) Total; FACT-Anemia Fatigue and FACT-Anemia Nonfatigue; and the Cancer Linear Analog Scale (CLAS) for Energy, Activity, and Overall QOL. At the end of every chemotherapy cycle, the following were recorded: vital signs, CBC, study drug administration, RBC transfusion use, chemotherapy and radiotherapy details, and adverse events (AEs). In addition, at the end of every even-numbered cycle, QOL assessments were performed and iron status was determined. After the last chemotherapy cycle or at TTP, whichever occurred first, and at study completion (at 12 months or early withdrawal), all assessments were again undertaken: tumor response was assessed by WHO criteria[21] and serum chemistry was assessed by laboratory assessments. Limited data were collected beyond withdrawal, but included a determination of whether the patient was still alive at 12 months or, if not, the date of death, even for patients who withdrew early. At the end of the 12-month double-blind study period, all patients (including placebo recipients) had the option to receive epoetin alfa in an open-label extension phase.

Safety was evaluated by AE reporting and clinical laboratory tests according to the schedule outlined previously. Safety variables were analyzed using the safety population (all randomly assigned patients who had at least one safety assessment) and a modified safety population (all randomly assigned patients who received $\geq$ one dose of study drug and had at least one safety assessment). Any clinically significant abnormalities at study end were observed until resolution or until clinically stable. TVEs were compiled by medical monitors at Johnson & Johnson Pharmaceutical Research Division, based on WHO Adverse Reaction Terms 97 Q4.

Statistics

Efficacy analyses were performed using the intent-to-treat (ITT) population, comprising all randomly assigned patients. Kaplan-Meier estimates of 12-month OS were calculated by treatment group. The primary treatment comparison was based on a log-rank test stratified by metastatic category. Hazard ratios (HRs), 95% CIs, and *P* values were calculated, and Cox model regression analysis was conducted with covariates including age, menopausal status, measurable or nonmeasurable metastatic lesions, estrogen receptor–positive or –negative status, and whether the patient received prior chemotherapy. TTP with the first chemotherapy regimen was analyzed similarly.

QOL data were analyzed using longitudinal techniques. Analyses of area under the curve from randomization to month 12 formed the main QOL end points. Sensitivity analyses were conducted based on different assumptions regarding any missing data mechanism. All *P* values generated from QOL data were adjusted for multiple comparisons using the Bonferroni procedure. The relationship between change in Hb and QOL was examined by correlational techniques, also controlling for multiple comparisons. The statistical analyses were conducted by the study sponsor with input from the study investigators.

Chart Review

After the study was stopped early, a comprehensive chart review was conducted for all patients. Separate report forms were completed by investigators blinded to treatment. Charts for all but two patients (both placebo recipients) were located and additional data were collected and analyzed. Of particular interest were additional data that would permit a better assessment of survival prognosis, including disease site, initial prognosis and assessment of previous tumor response to chemotherapy, systematic assessment of tumor response at predefined intervals, dose and duration of adjuvant chemotherapy, and data regarding cause of death.

RESULTS

Patient Disposition

Nine hundred thirty-nine women with MBC were enrolled (ITT population), with 469 randomly assigned to receive epoetin alfa and 470 randomly assigned to receive placebo (Fig 2). When study treatment was stopped, enrollment was already complete, and 12% of the patients were still receiving study drug; double-blind follow-up through month 12 was continued for the remaining patients. Thirty-five patients were randomly assigned to treatment but did not receive study drug, 14 (3%) in the placebo group, and 21 (4%) in the epoetin alfa group. Four percent of patients in each group deviated from the protocol by beginning treatment with the study drug when their Hb level was more than 13 g/dL. A total of 221 patients withdrew prematurely from the double-blind phase (108 [23%] in the epoetin alfa

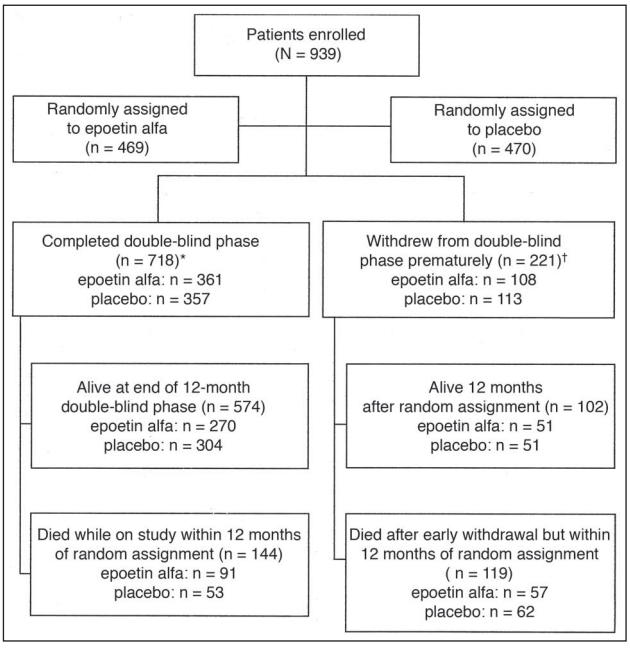

Fig 2. Patient disposition (intent-to-treat [ITT] population, N = 939). (*) Completers are defined as patients who completed the double-blind phase or who died with a date of death no later than the double-blind completion/withdrawal date. (†) Withdrawals are defined as patients who withdrew prematurely from the double-blind study.

group; 113 [24%] in the placebo group). The most common reasons for early withdrawal were patient choice (9% of patients in each group) and "other reason," which was most often disease related (8% and 9% of epoetin alfa and placebo recipients, respectively).

Demographics, Clinical, and Baseline Characteristics

Patient demographics and malignancy characteristics were generally similar between groups (Table 1). However, there were notable differences between groups in baseline ECOG performance status (poorer in the epoetin alfa group), time since initial diagnosis (shorter for the epoetin alfa group), and length of disease-free interval (shorter for the epoetin alfa group). Baseline hematologic assessments were generally similar between groups, but more patients in the epoetin alfa group (14%) than in the placebo group (11%) were anemic (Hb ≤ 10.5 g/dL) at baseline. The most common prestudy chemotherapeutic regimens and hormonal agents are shown in Table 2, and were similar between groups.

Table 1. Patient Demographics and Baseline Characteristics (ITT population, N = 939)

Characteristic	Epoetin Alfa (n = 469) No. of Patients	%	Placebo (n = 470) No. of Patients	%
Age, years				
Mean	55.8		55.1	
SD	11.1		10.5	
Range	24-83		30-84	
Race				
White	459	98	465	99
Black	4	1		0
Asian	3	1	3	1
Other	3	1	2	< 1
Postmenopausal				
No	109	23	110	23
Yes	360	77	359	76
Missing	0		1	< 1
ECOG PS*				
0		42		47
1		46		42
2		12		10
Hb, g/dL				
Mean	12.5		12.5	
SD	1.8		1.7	
RBC	469		468	
Mean	4.3		4.3	
SD	0.6		0.5	
Absolute reticulocyte count, × 10^9/L	440		447	
Mean	62.3		59.4	
SD	61.1		46.7	
Serum iron, μg/dL	456		459	
Mean	79.1		76.0	
SD	43.0		37.3	
TSAT	406		415	
Mean, %	25.0		23.8	
SD, %	14.4		13.1	

Abbreviations: ITT, intent-to-treat; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; RBC, red blood cells; TSAT, transferrin saturation.
*Total does not equal 100% because of rounding.

First-Line Chemotherapy

The most frequently administered first-line chemotherapy regimens were anthracyclines, taxanes, and cyclophosphamide plus methotrexate plus fluorouracil (Table 3). The mean duration of first-line chemotherapy and the overall use of hormonal therapy concurrent with first-line chemotherapy were similar between groups. One hundred thirty-two (28%) patients in each treatment group received radiation therapy on study, including radiation given during and after first-line chemotherapy. There were no notable differences between groups with respect to other concomitant medications.

Study Drug Administration

The median time from random assignment to the start of study drug administration (after Hb decreased to ≤ 13 g/dL) was 4.0 days (range, 0 to 286 days) for the epoetin alfa group and 4.0 days (range, 0 to 265 days) for the placebo group. Dose reductions and withheld doses, largely based on achieving or exceeding target Hb levels, were more common in the epoetin alfa group than in the placebo group. Among patients with available postbaseline Hb levels, 353 of 459 patients (77%) had at least one Hb value more than 14 g/dL in the epoetin alfa group, compared with 157 of 467 (34%) patients in the placebo group.

Survival

An analysis of interim data at the time of study cessation and discontinuation of study drug showed that 249 patients (138 [28%] in the epoetin alfa group; 111 [23%] in the placebo group) died within 12 months of random assignment ($P = .02$ between groups). The final analysis of the 12-month OS rate for the ITT population, based on Kaplan-Meier estimates, showed a lower 12-month OS in the epoetin alfa group (70%) than in the placebo group (76%; HR = 1.37; $P = .01$; Fig 3). Primary causes of death within 12 months attributed by the investigator were disease progression (27% for epoetin alfa *v* 22% for placebo), chemotherapy toxicity (1.7% for epoetin alfa *v* 0.2% for placebo), and TVEs (1.3% for epoetin alfa *v* 0.6% for placebo). Most of the survival difference observed at 12 months was already present at 4 months. After 12 months, the survival curves showed convergence before overlapping at month 19 (Fig 3).

A Cox model regression analysis was performed to estimate the treatment effect after adjusting for demographic and prognostic factors, including the differences noted above. The analysis showed that the HR for 12-month survival remained significant (HR = 1.36; 95% CI,

Table 2. Baseline Disease Characteristics and Prestudy Chemotherapy and Hormonal Therapy (ITT population, n = 939)

Characteristic	Epoetin Alfa (n = 469)		Placebo (n = 470)	
	No. of Patients	%	No. of Patients	%
Age at initial diagnosis, years				
Mean	52.1		51.0	
SD	11.0		10.8	
Time since initial diagnosis, months				
Mean	44.1		49.1	
SD	46.1		53.3	
Time since metastatic diagnosis, months				
Mean	6.6		6.3	
SD	16.5		14.3	
Disease-free interval, months				
Mean	37.6		42.8	
SD	41.3		49.6	
Time from end of adjuvant chemotherapy to diagnosis of metastases, months				
Mean	17.0		19.8	
SD	28.0		35.9	
Median	3.9		3.1	
Range	0-285		0-206	
Disease stage at diagnosis				
I	59	13	68	14
II	205	44	223	47
III	105	22	95	20
IV	96	20	81	17
Missing	4	1	3	1
Type of metastases				
Bone only	66	14	73	16
Other	403	86	397	84
Estrogen receptor status				
Negative	126	27	131	28
Positive	226	48	232	49
Not determined	117	25	107	23
Ascites				
No	458	98	453	96
Yes	9	2	17	4
Missing	2	< 1	0	
Pleural effusion				
No	389	83	396	84
Yes	78	17	74	16
Missing	2	< 1	0	
Prestudy chemotherapy	229	49	233	50
Anthracycline based	212	45	204	43
CMF	97	21	107	23
Prestudy radiotherapy	275	59	296	63
Adjuvant radiotherapy + adjuvant chemotherapy	157	33	170	36
Prestudy hormonal therapy				
Tamoxifen	266	57	250	53
Anastrozole	58	12	47	10
Letrozole	49	10	41	9

Abbreviations: ITT, intent-to-treat; SD, standard deviation; CMF, cyclophosphamide, methotrexate, and fluorouracil.

1.053 to 1.753; $P = .02$), with patients in the epoetin alfa group at higher risk. Another Cox model regression analysis examined the homogeneity of treatment effect by incorporating two-way interaction terms between treatment and other prognostic variables in the model. Several factors were found to be associated with the difference in 12-month survival between treatment groups: baseline body mass index ($P = .01$), baseline CLAS activity score ($P = .02$), baseline CLAS overall QOL score ($P = .01$), and age ($P < .05$). However, none of these significant terms would

Table 3. First-Line Chemotherapy and Concomitant Cancer Therapy (ITT population, n = 939)

Treatment Received	Epoetin Alfa (n = 469) No. of Patients	%	Placebo (n = 470) No. of Patients	%
First-line chemotherapy				
Anthracyclines	234	50	207	44
Taxanes	122	26	129	27
CMF	59	13	64	14
Other*	49	10	67	14
Not recorded†	5	1	3	1
Concomitant therapy				
Hormonal therapy	65	14	69	15
Tamoxifen	31	7	33	7
Letrozole	14	3	13	3
Anastrozole	12	3	12	3

Abbreviations: ITT, intent-to-treat; CMF, cyclophosphamide/methotrexate/5-fluorouracil.
*Includes anthracenediones, vinca alkaloids, trastuzumab, capecitabine, gemcitabine, other single agents, and other combinations.
†Patients withdrew from the study before information was obtained.

alter the direction of the treatment effect in the range of data as seen in this trial. Subgroup analyses on various patient and baseline disease characteristics did not convincingly identify any subgroup that could account for the difference in 12-month mortality between groups.

Four-Month Survival. A treatment group difference in mortality was evident by the first 4 months of therapy, so characteristics of patients who experienced early death were compared between groups. There were 41 (8.7%) early deaths in the epoetin alfa group and 16 (3.4%) in the placebo group. Among patients who died within 4 months of random assignment, the primary cause attributed by the investigators was disease progression (28 [6.0%] epoetin alfa patients and 13 [2.8%] placebo patients; Table 4). In a similar result to the analysis of 12-month results, examination of various patient and baseline disease characteristics for patients who died within 4 months did not identify any characteristics that could account for the mortality difference between treatment groups.

Hemoglobin Maintenance

Target Hb of 12 to 14 g/dL was maintained for 59% of patient-weeks in the epoetin alfa group and for 45% of patient-weeks in the placebo group ($P < .001$ between groups). After week 4, mean Hb increased in the epoetin alfa group and was maintained at or above baseline for the remainder of the study. In contrast, mean Hb declined in the placebo group through week 20, after which the improvement in Hb possibly was related to the end of first-line chemotherapy (Fig 4). Patients who died within 12 months of random assignment, regardless of treatment group, had lower mean baseline Hb and generally lower mean Hb throughout the study compared with patients alive at 12 months (Fig 4).

Transfusion Use

For the ITT population, fewer epoetin alfa than placebo recipients received transfusions on study (10% *v* 14%, respectively; $P = .06$). Median pretransfusion Hb was 8.3 g/dL in both groups.

Tumor Response and Disease Progression

Optimal tumor response (best overall response during first-line chemotherapy) was similar between groups. The objective response rate (complete response + partial response) for the ITT population was 45% in the epoetin alfa group and 46% in the placebo group (Table 5). The objective response rate was also similar between treatment groups both at the end of first-line chemotherapy and at final assessment.

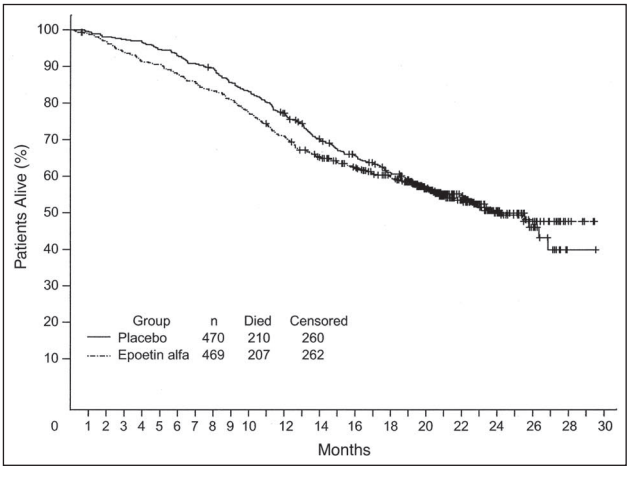

Fig 3. Kaplan-Meier estimate of long-term survival, with convergence of lines about 19 months after randomization (as of January 4, 2003; intent-to-treat [ITT] population, N = 939).

Table 4. Causes of Death Among Patients Who Died Within 4 Months of Random Assignment (ITT population, N = 939)

Outcome	Epoetin Alfa (n = 469) No. of Patients	%	Placebo (n = 470) No. of Patients	%
Alive at 4 months	428	91.3	454	96.6
Died within 4 months	41	8.7	16	3.4
Cause of death within 4 months				
Disease progression	28	6.0	13	2.8
Chemotherapy toxicity	3	0.6	1	0.2
TVE	5	1.1	1	0.2
Other*	4	0.9	1	0.2
Missing	1†	0.2	0	0

Abbreviations: ITT, intent-to-treat; TVE, thrombovascular event.
*Includes fatty embolism, ischemic colon perforation, pulmonary edema, unknown.
†Cause of death unknown.

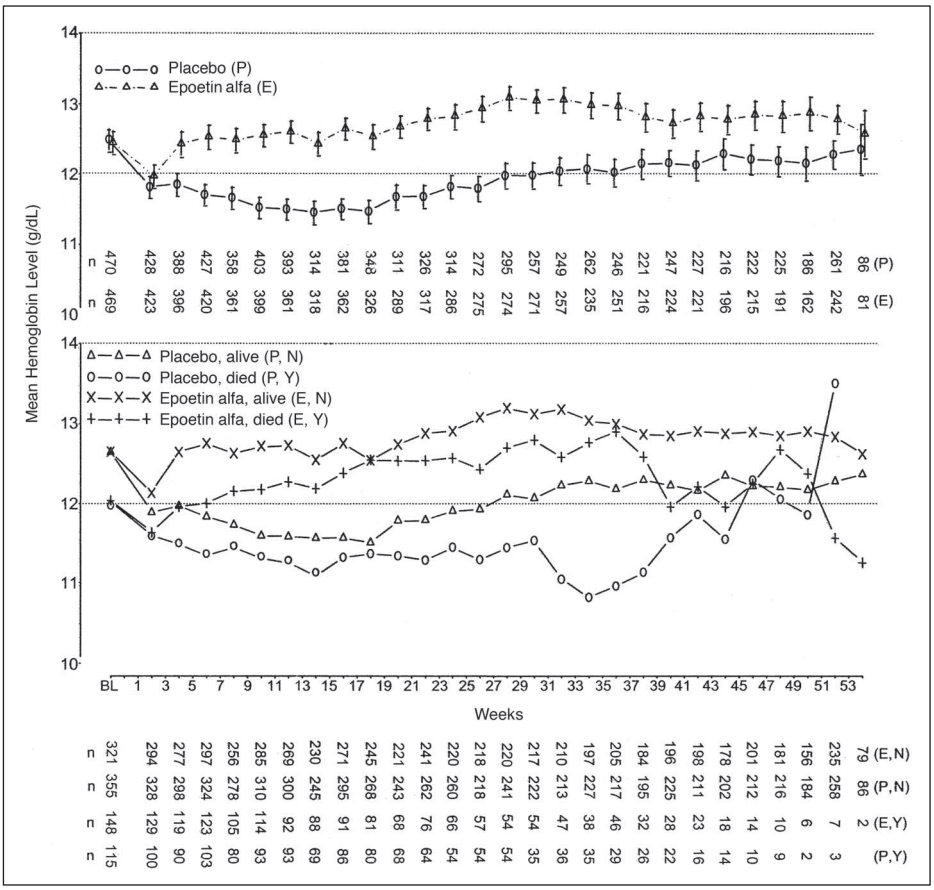

Fig 4. Mean hemoglobin level (95% CI) over time overall and by 12-month survival status (intent-to-treat [ITT] population, N = 939).

TTP with first-line chemotherapy was also similar between groups (Fig 5). On the basis of Kaplan-Meier estimates, 41% of patients receiving epoetin alfa and 43% of patients receiving placebo had evidence of progressive disease by month 12. The duration of progression-free survival was similar between groups (HR = 1.00; $P = .98$).

QOL

No significant differences in QOL were noted between groups for the six primary QOL analyses conducted (all $P \geq 0.16$). However, change in Hb was strongly associated with changes in all three CLAS parameters and with FACT-Anemia Fatigue scores using a piecewise mixed-effects linear model ($P < .05$, after adjusting for multiple testing [Hochberg method]).

Safety

The overall incidence of serious AEs, including deaths, was 42% in the epoetin alfa group and 34% in the placebo group ($P = .02$). In the epoetin alfa group, 5% of serious AEs were considered related to the study drug *v* 2% in the placebo group. The difference was primarily attributable to a higher proportion of patients in the epoetin alfa versus placebo group with extracardiac vascular disorders (3% *v* 1%); RBC disorders (4% *v* 1%); and platelet, bleeding, and clotting disorders (5% *v* 3%). Thirty-seven patients discontinued the study because of AEs (21 [5%] epoetin alfa recipients; 16 [4%] placebo recipients). The types and incidences of AEs leading to early discontinuation were similar between groups.

The overall incidence of TVEs was slightly higher in the epoetin alfa group (16%) than in the placebo group (14%), approximately 70% of which were considered not related to the study drug. Six epoetin alfa patients and two placebo patients who received at least one dose of study drug died as a result of a TVE. The fatal TVE was a pulmonary embolism in six of these eight patients (five patients, epoetin alfa; one patient, placebo) and an acute myocardial infarction in the other two patients (one patient, epoetin alfa; one patient, placebo).

Chart Review

Results from the chart review generally confirmed the data obtained from the clinical trial. Within 12 months of random assignment, there were 18 fatal TVEs: 14 in the epoetin alfa group and four in the placebo group. This was higher than the five versus one death in epoetin alfa- and placebo-treated patients, respectively, attributed to TVE on the case report form. Results of regression analyses incorporating the additional data obtained from the chart review

Table 5. Tumor Response in All Patients (ITT population, N = 939)

Response	Epoetin Alfa (n = 469)		Placebo (n = 470)	
	No. of Patients	%	No. of Patients	%
Overall tumor response				
CR	55	12	45	10
PR	154	33	170	36
ORR (CR + PR)	209*	45	215	46
Tumor response: end of first-line CT				
CR	49	10	41	9
PR	115	25	127	27
ORR (CR + PR)	164	35	168	36
PD	125	27	123	26
New lesions in patients with PD	86	69	101	82
Tumor response: final assessment				
CR	44	9	34	7
PR	45	10	66	14
ORR (CR + PR)	89	19	100	21
PD	195	42	216	46
New lesions in patients with PD	140	72	177	82

Abbreviations: ITT, intent-to-treat; CR, complete response; PR, partial response; ORR, objective response rate; CT, chemotherapy; PD, progressive disease.
*P = .62 between groups, based on the Cochran-Mantel-Haenszel test for ORR.

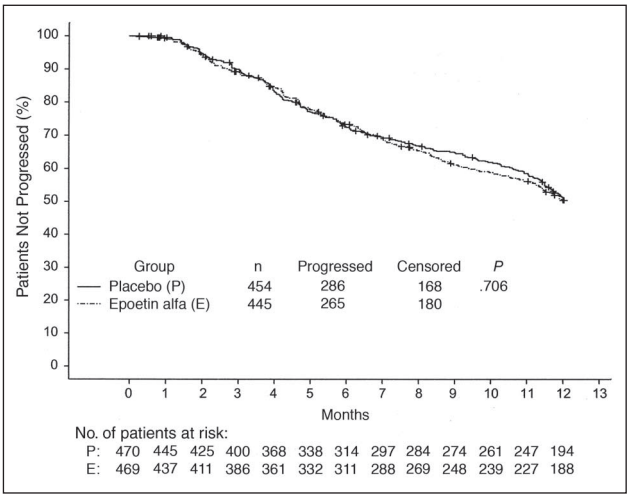

Fig 5. Time to disease progression (intent-to-treat population, N = 939). Forty patients were not assessable.

did not provide an explanation for the survival imbalance. However, caution must be used in interpreting the results of these additional regression analyses, given that not all data requested in the expanded case report form used in the chart review were available from patients' charts. Of note, 28% of the patients' records did not include complete imaging of lung, liver, and bone. Five percent were missing more than one of these assessments. The chart review revealed that due diligence was exercised in the conduct of the study and collection of required baseline data, and nearly all patients enrolled onto the study were both fully eligible for the study (97%), including documentation of metastasis, and received standard of care (SOC) first-line chemotherapy according to the reviewer (96%).

DISCUSSION

The investigational use of epoetin alfa to maintain Hb 12 to 14 g/dL in patients with MBC receiving first-line chemotherapy showed a 6% difference between groups in survival at 12 months favoring placebo (HR = 1.37; P = .01). After adjusting for known prognostic factors, the lower 12-month survival rate in the epoetin alfa group remained significant (HR = 1.36; P = .02). The result also remained significant after using additional data collected through chart review to do additional adjustment for prognostic and demographic factors. The difference in survival as a result of modification of tumor response was not confirmed by a difference in other disease outcomes such as TTP or response rates.

The increased number of TVE-related deaths in the epoetin alfa group explained some, but not all, of the excess deaths in the epoetin alfa group. It is possible that additional fatal TVEs may have occurred during the study that were attributed to disease progression by the investigator. In fact, some studies in patients with cancer in which the cause of death was obtained by autopsy confirm a higher rate of TVEs than reported during this and other trials of epoetin alfa.[22,23]

In a recently published study of epoetin beta for maintenance of normal Hb in patients with head and neck cancer undergoing radiotherapy, increased locoregional progression and lower survival were reported for epoetin beta compared with placebo.[24] In this double-blind, randomized, placebo-controlled trial, patients with baseline Hb $<$ 120 g/L (women) or $<$ 130 g/L (men) received epoetin beta 300 U/kg SC three times a week or placebo to attain a target Hb of $\geq$ 140 g/L (women) or $\geq$ 150 g/L (men). More than 80% of epoetin beta recipients achieved target Hb compared with 15% of placebo recipients. Epoetin beta patients had an adjusted relative risk of locoregional tumor progression of 1.69 (95% CI, 1.16 to 2.47; P = .01) and an adjusted relative risk of death of 1.39 (95% CI, 1.05 to 1.84; P = .02) compared with placebo patients. The investigational design of the study allowed treatment of patients with essentially normal Hb to a high target Hb (mean Hb at week 9, 15.4 g/dL), and Hb increases of up to 2 g/dL in a 1-week period. The number of patients who achieved this rapid increase in Hb was not reported. The high target Hb level and rapid increases in Hb may account for the adverse survival outcome. In addition, differences in baseline factors between groups may have contributed to the survival differences.

Patients in the current epoetin alfa study were treated to a target Hb of 12 to 14 g/dL, higher than that recommended and used for the correction of anemia. Lower 12-month survival in the epoetin alfa group did not appear to be related to elevated mean Hb levels, given that mean Hb was essentially unchanged from baseline (mean increase, 0.1 g/dL). The difference in mean Hb between groups at any time during the study was also relatively small, possibly because a large proportion of patients (45%) did not receive second-line chemotherapy or because of the low incidence of anemia in women with breast cancer. Hb was better maintained at 12 to 14 g/dL with epoetin alfa than with placebo, but most patients in both groups were not and did not become anemic. Patients who died within 12 months of random assignment tended to have lower Hb throughout the study. Lower baseline Hb was associated with a worse prognosis for survival, but maintenance of Hb with epoetin alfa did not improve survival.

Despite most evidence to date supporting the hypothesis that patients with cancer and anemia have poorer outcomes than nonanemic patients, results from the recent survival studies have given rise to debate about whether erythropoietic agents may negatively affect survival, especially at high Hb levels. In the current study, almost twice as many patients in the epoetin alfa group than the placebo group exceeded the target Hb range (Hb $>$ 14 g/dL) at some point during the study. Although speculative, it may be that the relationship between Hb and survival is a U-shaped curve, with increased risks at more extreme Hb levels. It has been suggested that, in certain tumor cell lines and xenografts that express both erythropoietin and its receptor, erythropoietin signaling may promote cancer progression[25-27]; several investigators have suggested a link between erythropoietin receptor expression and tumor proliferation.[25,26,28-30] However, many studies showing such signaling required supratherapeutic concentrations of erythropoietic agents to obtain the response,[25,31] and most in vitro studies have shown no such relationship.[32-35] No causal relationship between epoetin alfa and cancer progression in humans has been shown.[36,37]

Despite the results of our study, the safety and efficacy of epoetin alfa therapy for patients with cancer who are or become anemic while receiving chemotherapy are well established, and epoetin alfa therapy remains appropriate within its approved indications. Guidelines from the American Society of Clinical Oncology and the American Society of Hematology for epoetin alfa use in patients with cancer recommend epoetin alfa as a treatment option for patients with Hb $\leq$ 10 g/dL receiving chemotherapy, and suggest that treatment may be useful for symptomatic or at-risk patients with Hb 10 to 12 g/dL.[38] The National Comprehensive Cancer Network guidelines recommend erythropoietic agents for the treatment of cancer-related or treatment-related anemia in patients with Hb $\leq$ 11 g/dL.[39]

Additional data supporting the use of erythropoietic agents in patients with cancer and anemia are results from an open-label, randomized trial of epoetin alfa in women with breast cancer and mild anemia. In this study, 354 patients with breast cancer undergoing chemotherapy were randomly assigned to early intervention with epoetin alfa 40,000 U SC every week or SOC (efficacy population, n = 175 in each group) for up to 28 weeks or 4 weeks after the last cycle of chemotherapy was complete (whichever was longer).[40] Patients were enrolled when Hb was $\leq$ 15 g/dL and randomly assigned when Hb was $\leq$ 12 g/dL. Mean baseline Hb for the epoetin alfa and SOC groups was lower than in the current study (11.2 and 11.3 g/dL, respectively). Nineteen patients (10.8%) in the epoetin alfa group experienced TVEs; these were attributable to epoetin alfa therapy in seven patients. Fourteen patients (7.9%) in the SOC group experienced TVEs. At the time of writing, 24 patients in the epoetin alfa group and 27 patients in the SOC group had died. These data suggest that differences in study design or selected patients may play an important role in influencing study outcomes.

Unfortunately, because of drawbacks in the design of the current study, a possible imbalance between groups for various risk factors, and the unanticipated Hb outcomes of the trial (ie, the small difference in Hb level between groups), these survival results have been difficult to explain. Nevertheless, because there are now discouraging data from two studies in different tumor types in which treatment to high Hb levels was one of the major design differences from past studies, treatment of nonanemic patients or treatment to high Hb targets is discouraged, and is not approved for any of the erythropoietic agents. Although it is still possible that correction of anemia in patients with cancer may confer a survival benefit, a trial to test this hypothesis has yet to be performed.

Appendix

The following Breast Cancer Erythropoietin Survival Trial (BEST) Investigators participated in this study:

Australia: David Bell, MB, BS; F. Boyle, MB, BS, PhD; J. Levi, MB, BS; H. Wheeler, MB, BS; St. Leonards, NSW; Michael Byrne, MB, BS; M. Buck, MB, BS; J. Dewar, MB, BS; G. van Hazel, MB, BS; Nedlands, WA; John B. Grygiel, Pharm, MB, BS, Associate Prof; D. Dalley, MB, BS; R. Ward, MB, BS, PhD; Darlinghurst, NSW; Tim Price, MB, BS; K. Patterson, MB, BS; K. Pittman, MB, BS; Woodville, SA; Raymond Snyder, MB, BS; W. Burns, MB, BS; A. Dowling, MB, BS; P. Francis, MB, BS; S. McLachan, MB, BS; A. Wirth, MB, BS; Fitzroy, Vic; Robert Stanley, MB, BS; P. Briggs, MB, BS; V. Ganju, MB, BS; J. Griffiths, MB, BS; G. Richardson, MB, BS; East Bentleigh, Vic; John Stewart, MB, BS; S. Ackland, MB, BS; T. Bonaventura, MB, BS; Waratah, NSW; Nicolas Wilcken, MB, BS, PhD; H. Gurney, MB, BS; P.

Harnett, MB, BS; R. Hui, MB, BS; R. Kefford, MB, BS, PhD, Prof; Westmead, NSW.

Austria: Gerhard Baumgartner, MD; Sylvia Marca, MID; Julius Salamon, MID; Wien, Wien; Karlheinz Haberteuer, MD; V. Buxhofer, MD; H. Vedovelli, MD; M. Vynalik, MD; M. Winter; Wien, Wien; Jörg Keckstein, MD; M. Ertl; Frank Tuttlies, MD; Klaus Unterrieder, MD; Villach, Karnten; Ernst Kubista, MD; Arik Galid, MD; Michael Seifert, MD, Prof; Wien, Wien; Heinz Ludwig, MD; I. Assmann; K. Kirchbacher, MD; J. Schuster, MD; K. Strasser, MD; A. Weissmann, MD; Wien, Wien; Markus Raderer, MD; W. Fiebiger, MD; W. Scheithauer, MD, Prof; Wien, Wien; Paul Sevelda, MD; J.L. Baumann, MD; M. Picher, MD; Wien, Wien; Christoph Zielinski, MD; W. Köstler, MD; S. Tomek, MD; Wien, Wien.

Belgium: Vincent Brichard, MD; Yves Humblet, MD; Nathalie Blondeel; Véronique D'Hondt, MD; Yves Humblet, PhD; Jean Pascal Machiels, MD; Brussel, Brabant; Veronique Cocuyt, MD; Annie De Gussem; Simon Van Belle, MD, PhD; Gent, Oost-Vlaanderen; Jacques De Greve, MD, PhD; Ann Blank; Christel Fontaine, MD; Bart Neyns, MD; Brussel, Brabant; Robert Paridaens, MD, PhD; Nicole Mallaerts; Johan Wildiers, MD; Leuven, Brabant.

Bulgaria: Assen Dudov, MD; S. Atanssova-Gancheva, MD; Sofia; Constanta Timcheva, MD, PhD, Associate Prof; S. Hristova, MD; V. Koleva, MD; G. Kurteva, MD, PhD; E. Stefanova; A. Todorova; Sofia; Valentina Tzekova, MD, PhD, Associate Prof; I. Azmanova; S. Djeneva; S. Ignatova; K. Koinov, MD; R. Krasteva, MD; F. Marinov, MD; Sofia.

Canada: Brian Findlay, MD; J. Becevel; J. Giesbrecht, MD; P. Hughe, MD; L. Illes; St. Catharines, ON; Stefan Glück, MD; B. Gore-Hickman, MD; J. Greene; P. Herbert, MD; C. Mohan; S. Paterson, MD; D. Ruether, MD; D. Stewart, MD; Calgary, AB; Rakesh Goel, MD; K. DeJong; S. Gertler, MD; A. Haq, MD; D. Robins; R. Sagal-Nadler, MD; E. Tomiak, MD; S. Verma, MD; J. Yau, MD; V. Young, MD; Ottawa, ON; Paul Goss, MD; H. Gotthardt; T. Marr; Toronto, ON; Hal Hirté, MD; E. Chouinard, MD; T. de Gelder, MD; A. Jecoducci; M. Levine, MD; P. Major, MD; R. Tozer, MD; Hamilton, ON; Kathleen Prichard, MD; S. Berry, MD; L. Bordeleau, MD; M. Miller; C. Sawka, MD; A. Seidenfeld, MD; J. Slinerland, MD; M. Trudeau, MD; E. Warner, MD; N. Wolf; Toronto, ON; Yasmin Rahim, MD; V. Buttu; J. Meharchand, MD; Toronto, ON; Leonard Reyno, MD; B. Colwell, MD; M. Davis, MD; M. Dorreen, MD; M. Goodyear, MD; S. Hebb; D. Rayson, MD; Halifax, NS; Michael Smylie, MD; D. Au, MD; H. Au, MD; S. Koski, MD; J. Mackey, MD; L. Tkachuk; K. Tonkin, MD; Edmonton, AB; Michael Thirwell, MD; P. Ahlgren, MD; S. Burdette-Radoux, MD; Helen Charamis; Bev DeSallis; Cathy Galina; I. Hings, MD; A. Langleben, MD; C. Legler, MD; Cathy Meany; D. Melnychuk, MD; W. Miller, MD; L. Panasci, MD; F. Patenaude, MD; J. Prchal, MD; D. Stern, MD; M. Trudeau, MD; J. Zidulka, MD; Montréal, PQ; Christopher Williams, MD; Burnsteen, MD; C. Lockhart; F. Souliere, MD; Nanaimo, BC; Scott Young, MD; P. Cano, MD; S. Cecchetto; C. Germond, MD; J. Herst, MD; Andrew Knight, P. Lopez, MD; J. Noble, MD; A. Wilson; Sudbury, ON.

Croatia: A. Juretic, MD, PhD, Prof; T. Oresic, MD; R. Petrinovic, MSc; D. Sesek; D. Velimir-Vrdoljak, MD; D. Vukas, MD; D. Zupanc, MD, Consultant; Zagreb, Grad Zagreb.

Czech Republic: Eva Helmichova, MD, PhD; M. Køečková; B. Konopásek, MD, PhD; Praguea; Vladimir Spurny, MD, PhD; L. Pohloa, MD; D. Šnýdrová; Brno, Chechia; Vodvarka Pavel, MD; Z. Bravencova, MD; J. Hudečková; Ostrava-Potruba; Katerina Vondrackova, MD; E. Pavlíková, MD; M. Preusslerová; Pardubice; Jan Vydra, MD; A. Aschermanova, MD; M. Smakal, MD; M. Storkán; Nova Ves pod Plesi.

France: Sylvie Block, MD; S. Lecomte, MD; Valenciennes Cedex; Jacques Bonneterre, Prof, PhD; M. Bonneterre, MD; C. Muriel; V. Servant, MD; L. Vanlemmens, MD; P. Vennin, MD; Lille; Philippe Bougnoux, Prof, PhD, MD; L. Alcaraz, MD; G. Calais, MD; S. Chapet, MD; M. Ferrasson; O. Le Floch, MD; A. Reynaud-Bougnoux, MD; Tours; Laurent Cals, MD; I. Chabber, MD; L. Merad, MD; X. Tchiknavorian, MD; Toulon; Hervé Curé, Prof, PhD, MD; P. Chollet, MD; N. Martineau; Cedex; Dominique Eychenne, MD; M. Benhaddou, MD; S. Chaib-Rassou, MD; C. Ciupea; Troyes; Michel Finck, MD; C. Domicent; Croix; Faress Husseini, MD; Colmar; Moise Namer, Prof, PhD; Y. Chateau; J. Ferrerro, MD; R. Largillier, MD; Nice; Daniel Serin, MD; C. David; Y. Goubely, MD; S. Kirscher, MD; S. Nahon, MD; N. Viellard; Avignon; Dominique Spaeth, MD; C. Laurent; E. Luporsi, MD; M. Rios, MD; B. Weber, MD; Vandoeuvre Les Nancy.

Germany: Andreas Ammon, MD; Hosius, MD; Meyer, MD; Göttingen; Martin Becker, MD; Hermeling; Kreisel-Büstgens, MD; Minden; Lothar Böning, MD; Sommerfeld; München; Barbara Brückner, MD; Dibelius, MD; K. Henning; K. Riehm; Bonn-Venusberg; Christian Falge, MD; Boissevain, MD; Bruntsch, MD; Weigang-Köhler, MD; K. Westphal; Nürnberg; Wolfgang Gaede, MD; Lücking; Hannover; Kay Goerke, MD; Fischer, MD; Marburg; Gerald Gitsch, Prof, MD; Schanze; Woll, MD; Freiburg; Klaus Höffken, Prof, MD; Herr Schmügger; Wedding, MD; Jena; Walter Jonat, Prof, MD; Eidtmann, MD; Mai; Vanhecke, MD; Vespermann; Kiel; Manfred Kindler, MD; Bürger, MD; Frahm; Berlin; Udo Kleeberg, Prof, MD; Von Staden, MD; Hamburg; Heinz Kölbl, Prof, MD; Gräber; Labau; Lebrecht, MD; Ulbrich; Halle; Rolf Kreienberg, Prof, MD; Heillmann, MD; Herroeder, MD; Ulm; Norbert Marschner, MD; Fuxius; Lindl; Rauch; Rees; Freiburg; Dieter Mink, MD; Dörr; Renner, MD; Homburg/Saar; Gerd Müller, MD; R. Uhle, MD; Magdeburg; Michael Schaefer, MD; H. Quabeck, MD; M. Strelow, MD; Duisburg; Tilman Steinmetz; H. Schmitz, MD; Köln; Augustinus Harjanto Tulusan, Prof, MD; Euler, MD; H. Feltman, MD; J. Tio; Bayreuth; Udo Vanhoefer, MD; Welt,

MD; Essen; Manfred Welslau, MD; Streitenberger; Aschaffenburg; Hartmund Wolter, MD; Bonn.

Greece: Athanasios Dimopoulos, MD, PhD; E. Efstathiou, MD; Ch. Kiamouris, MD; Athens; Charalambos Kalofonos, MD, PhD; N. Ioannidou; A. Koutra, MD; Rio, Patras; Demosthenis Skarlos, MD, PhD; Ch. Christodoulou, MD, PhD; G. Klouvas, MD, PhD; M. Mitropoulou; Athens.

Hungary: György Bodoky, Prof, PhD, MD; T. Nagy, MD; K. Tamás, MD; Budapest; Magdolina Dank, PhD, MD; E. Palócz, MD; Budapest; Tamas Magyar, Prof, PhD, MD; M. Vas, MD; Budapest; Tamas Nagykalnai, MD; L. Landherr, MD; Budapest; Istvan Szakolczay, MD; Budapest; László Thurzó, Prof, PhD, MD; E. Valicsek, MD; Szeged.

Italy: Francesco Boccardo, PhD; D. Amoroso, MD; R. Murialdo, MD; Genova Cesare Bumma, PhD; R. Berardo, MD; A. Crova, MD; Torino; Maria Tagliaventi, MD; Augusto Baldoni; Terni; Luca Gianni, MD; G. Citterio, MD; P. Mariani, MD; A. Moliterni, MD; M. Zambetti, MD; Milano; Piero Sismondi, PhD; E. Jacomuzzi, MD; P. Spanu, MD; Torino; Maurizio Tonato, PhD; R. Cherubini, MD; S. Sorbolini, MD; Perugia.

Lithuania: Elona Juozaityte, MD, PhD, Prof; Jurate Grabauskiene; Dariush Norkus, MD; Kaunas; Sigitas Stonkus, MD, PhD; Alvydas Cesas, MD; Laima Grakaviniene; Jurate Pauliukoniene, MD; Klaipeda; Eduardas Aleknavicius, MD, PhD; Audrone Ciceniene, MD; Violeta Garjoniene; Danguole Lankeliene; Ausrine Peciulyte; Terese Pipiriene Zelviene, MD; Joana Rutkauskiene, MD; Janina Strimatiene, MD; Zita Triskute; Rita Verbickaite; Tatjana Vinceliene, MD; Vita Zagrakalyte; Vilnius.

The Netherlands: Robert S. De Jong, PhD; S. Bong; G. Dijkinga; J. Engel; H. Piersma; Groningen; Frans L.G. Erdkamp, MD; H. Bron; C. Erdkamp-Sijbers; F. Peters; Sittard; Jacques A.M.J. Wils, PhD; Giok S. Liem, MD; M. Den Boer; C. Kleijne; L. Ruijters; R. Smits; Roermond; Ron C. Rietbroek, PhD; Le Beverwijk; Harm P. Sleeboon, PhD; Den Haag; Gerd A. Van Deyk, PhD; Lia Rosier; Den Haag.

Poland: Malgorzata Suszko-Kazarnowicz, MD; Olsztyn; Emilia Filipczyk-Cisarz, MD, PhD; P. Katarzyna, MD; P. Malgorzata, MD; M. Pudelko, MD; B. Zurakowska, MD; Wroclaw; Bozenna Karczmarek-Borowska, MD, PhD; A. Czerepińska, MD; B. Kukiela-Budny, MD; G. Stopyra, MD; Lublin; Piotr Korelewski, MD, PhD; Z. Bernaś; M. Urbańska-Gasiorowska, MD; Kraków; E. Glinka-Malaúnicka, MD; Sudol Katarzyna, MD; R. Sienkiewicz-Kozlowska, MD; A. Walaszkowska-Czyż, MD; Warszawa; Cezary Szczylik, MD, PhD; R. Duchnowska, MD; M. Lisik, MD; G. Weislo, MD, PhD; Warszawa; Beata Utracka-Hutka, MD, PhD; E. Nowara, MD; J. Rogozinaska, MD; Gliwice; Marek Wojtukiewicz, MD, PhD; M. Elwira, MD; S. Zbigniew, MD; Bialystok.

Russia: I. Ivanchenko, MD; I. Kucheriavaya; I. Selezneva, MD; Moscow; David Korman, MD, PhD; L. Boronovskaya, MD; I. Maslova, MD; Moscow; E. Anokhina, MD; W. Gerasev, MD, PhD; V. Lebedeva, MD; N. Zabaznyi, MD; Krasnogorsky area, Moscow region; T. Kotkova, MD; M. Mishukova; N. Vinocurova, MD; St. Petersburg; Sergey Odintsov, MD, PhD; S. Apolosova; E. Fedoseeva, MD; V. Kalistov, MD, PhD; M. Sapunov, MD; E. Sharshatkina, MD; E. Tupikova, MD; Moscow; O. Arkhipchenko, MD; A. Bogok, MD, PhD; O. Ivanova, MD, PhD; P. Krivorotko, MD; St. Petersburg; R. Nasysova, MD, PhD; L. Osmanova, MD, PhD; N. Siderova; M. Stenina, MD, PhD; N. Yakovleva; Moscow; T. Barannikova, MD; A. Belonogov, MD; S. Bolshakova, MD; N. Dobrovolskaya, MD, PhD; N. Rumiantseva; E. Shirinskaya; Moscow.

Slovak Republic: Vladimir Goc, MD; V. Slaba; V. Tkacova, MD; Presov; Milan Jurga Ludovit, Prof, MD, PhD; Andrea Doczeova, MD; Anna Novakova, MD; Zuzana Spirkova, MD; Ariana Vopatova, MD; Ttnava; Samuel Klenovsky, MD; A. Lesova, MD; V. Lorinczova; Nitra; Eva Kothajova, MD; M. Kurakova; A. Martinkova, MD; E. Misurova, MD; S. Okapec, MD; V. Zabkova, MD; Banska Bystrica; Ivan Koza, Prof, MD, PhD; L. Bohunicky, MD; Z. Sycova-Mila, MD; Z. Thalmeinerova, MD; Bratislava; Ludmilla Sevcikova, Prof, MD, PhD; M. Chorvath, MD; Z. Pinakova, MD; M. Skultetyova, MD; Bratislava.

South Africa: Bernardo Rapoport, MD; Rabia B. Mahomed, B Pharm; A. Uys, BSc; Saxonwald, Johannesburg; Coenraad Slabber, MD; Robert M.R. Chasen, MD; G.L. Cohen, MD; R. W. Eek, MD; Zelda Herbst, RN; Nicky Martin, RN; Pretoria.

Spain: Vicente Alberola, MD, PhD; V. Carañana, MD; Valencia; Enrique Alés, MD, PhD; P. Aramburo, MD, PhD; C. Erustes, MD; Madrid; Castenon X. Carbonell, MD; B. Queralt, MD; Barcelona; Pere Gascon, MD, PhD; M. Bellet, MD; M. Fontanillas, MD; M. Martin, MD; Barcelona; Jose López, MD, PhD; A. de Juan, MD; Santander; Miguel Martin, MD, PhD; A. Casado, MD; Madrid.

UK: David Cameron, MD; J. Afseth; D.R. Camidge, PhD; M. Davidson; S. Douglas; G. McIntyre; E. Skwarski, Dr, MBChB; D. Storey, Dr, BM, BS, BmedSc; Edinburgh; Stephen Chau, MD; A. Divgi, MRCP; N.S. Ravi, MRCP; B. Scothern; C. Walker; W. Woodward; Nottingham; John Dewar, MD; J.E. Roberts; Dundee; J. Adlard, D, MRCP, FRCR; E. Charles; G.D. Hall, Dr, PhD, MRCP; J. Joseph, Dr; Kwok, Dr; J. Lowes; B. Workman; Leeds; Jonathon Joffe, MD; H. Aram; M.J. Cannon; B. Crosse, Dr, Mmed, Sc; E. Etherington; A. Protheroe, Dr, MB, BS, MCRP; G. Velikova, Dr, BMBS; Huddersfield; Jane Maher, MD; R. Lucy; R. Ng, MD; A. Taylor, Dr; Middlesex; Tariq Mughal, MD; B. Hefferon; T. Parkinson; J. Pearson; Preston; Andrew Wardley, MD; S. Danson, BmedSci, MRCP; A. Griffiths; J. Hassan, MRCP; A. Howell, Prof; V. Lau; J. Livsey, FRCR; M. Middleton, MRCP; H. Mitchell; A. Stewart, Dr, MD; P. Taylor, Dr, FRACP; S.A. Waine; S. Woolley; Manchester; Robert Frederick Leonard, Prof; L. Bastin; J. Ellis-Clarke; Swansea; C.R.J. Twelves, MD; Glasgow.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Brian Leyland-Jones	Johnson & Johnson		Johnson & Johnson (B)		Johnson & Johnson (A)	Johnson & Johnson (C)		
Vladimir Semiglazov								
Marek Pawlicki						Johnson & Johnson (B)		
Tadeusz Pienkowski						Johnson & Johnson (A); Aventis (B)		
Sergei Tjulandin					Aventis (A); Zeneca (A); Eli Lilly (A)	Aventis (B); Roche (B); Jansen Pharma (B)		
George Manikhas						Johnson & Johnson (B)		
Antoly Makhson						Johnson & Johnson (B)		
Anton Roth					Johnson & Johnson (A)			
David Dodwell								
Jose Baselga			Bristol-Myers Squibb (A); Novartis (A); Roche (A)					
Mikhail Biakhov						Johnson & Johnson (B)		
Konstantinas Valuckus						Johnson & Johnson (A)		
Edouard Voznyi						Johnson & Johnson (B)		
Xiangyang Liu	Johnson & Johnson			Johnson & Johnson (A)				
Els Vercammen	Johnson & Johnson			Johnson & Johnson (B)				

Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required

REFERENCES

1. Littlewood TJ, Bajetta E, Nortier JWR, et al, for the Epoetin Alfa Study Group: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving non-platinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 19:2865-2874, 2001

2. Dammacco F, Castoldi G, Rödjer S: Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. Br J Haematol 113:172-179, 2001

3. Abels RI: Recombinant human erythropoietin in the treatment of anaemia of cancer. Acta Haematol 87:4-11, 1992 (suppl 1)

4. Demetri GD, Kris M, Wade J, et al, for the Procrit Study Group: Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: Results from a prospective community oncology study. J Clin Oncol 16:3412-3425, 1998

5. Gabrilove JL, Cleeland CS, Livingston RB, et al: Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: Improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol 19:2875-2882, 2001

6. Glaspy J, Bukowski R, Steinberg D, et al, for the Procrit Study Group: Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. J Clin Oncol 15:1218-1234, 1997

7. Cella D, Zagari MJ, Vandoros C, et al: Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. J Clin Oncol 21:366-373, 2003

8. Patrick DL, Gagnon DD, Zagari MJ, et al, for the Epoetin Alfa Study Group: Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients receiving epoetin alfa. Eur J Cancer 39:335-345, 2003

9. Fallowfield L, Gagnon D, Zagari M, et al, for the Epoetin Alfa Study Group: Multivariate regression analyses of data from a randomized, double-blind, placebo-controlled study confirm quality of life benefit of epoetin alfa in patients receiving non-platinum chemotherapy. Br J Cancer 87:1341-1353, 2002

10. Caro JJ, Salas M, Ward A, et al: Anemia as an independent prognostic factor for survival in patients with cancer: A systemic, quantitative review. Cancer 91:2214-2221, 2001

11. Albain KS, Crowley JJ, LeBlanc M, et al: Survival determinants in extensive-stage non-small-cell lung cancer: The Southwest Oncology Group experience. J Clin Oncol 9:1618-1626, 1991

12. Bokemeyer C, Oechsle K, Hartmann JT, et al: Treatment-induced anaemia and its potential clinical impact in patients receiving sequential high dose chemotherapy for metastatic testicular cancer. Br J Cancer 87:1066-1071, 2002

13. Casas F, Viñolas N, Ferrer F, et al: Improvement in performance status after erythropoietin treatment in lung cancer patients

undergoing concurrent chemoradiotherapy. Int J Radiat Oncol Biol Phys 55:116-124, 2003

14. Fein DA, Lee WR, Hanlon AL, et al: Pretreatment hemoglobin level influences local control and survival of T1–T2 squamous cell carcinomas of the glottic larynx. J Clin Oncol 13:2077-2083, 1995

15. Glaser CM, Millesi W, Kornek GV, et al: Impact of hemoglobin level and use of recombinant erythropoietin on efficacy of preoperative chemoradiation therapy for squamous cell carcinoma of the oral cavity and oropharynx. Int J Radiat Oncol Biol Phys 50:705-715, 2001

16. Grogan M, Thomas GM, Melamed I, et al: The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer 86:1528-1536, 1999

17. MacRae R, Shyr Y, Johnson D, et al: Declining hemoglobin during chemoradiotherapy for locally advanced non-small cell lung cancer is significant. Radiother Oncol 64:37-40, 2002

18. Schafer U, Micke O, Muller SB, et al: Hemoglobin as an independent prognostic factor in the radiotherapy of head and neck tumors. Strahlenther Onkol 179:527-534, 2003

19. Munstedt K, Kovacic M, Zygmunt M, et al: Impact of hemoglobin levels before and during chemotherapy on survival of patients with ovarian cancer. Int J Oncol 23:837-843, 2003

20. Dunst J, Kuhnt T, Strauss HG, et al: Anemia in cervical cancers: Impact on survival, patterns of relapse, and association with hypoxia and angiogenesis. Int J Radiat Oncol Biol Phys 56:778-787, 2003

21. Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treatment. Cancer 47:207-214, 1981

22. Rickels FR, Falanga A: Molecular basis for the relationship between thrombosis and cancer. Thromb Res 102:V215-V224, 2001

23. Sallah S, Wan JY, Nguyen NP: Venous thrombosis in patients with solid tumors: Determination of frequency and characteristics. Thromb Haemost 87:575-579, 2002

24. Henke M, Laszig R, Rübe C, et al: Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. Lancet 362:1255-1260, 2003

25. Acs G, Acs P, Beckwith SM, et al: Erythropoietin and erythropoietin receptor expression in human cancer. Cancer Res 61:3561-3565, 2001

26. Arcasoy MO, Amin K, Karayal AF, et al: Functional significance of erythropoietin receptor expression in breast cancer. Lab Invest 82:911-918, 2002

27. Yasuda Y, Fujita Y, Masuda S, et al: Erythropoietin is involved in growth and angiogenesis in malignant tumours of female reproductive organs. Carcinogenesis 23:1797-1805, 2002

28. McBroom JW, Aes G, Rose GS, et al: Erythopoetin receptor function and expression in epithelial ovarian carcinoma. Gynecol Oncol July 25, 2005 (epub ahead of print)

29. Westenfelder C, Baranowski RL: Erythropoietin stimulates proliferation of human renal cell carcinoma cells. Kidney Int 58:647-657, 2000

30. Acs G, Zhang PJ, Rebbeck TR, et al: Immunohistochemical expression of erythropoietin and erythropoietin receptor in breast carcinoma. Cancer 95:969-981, 2002

31. Batra S, Perelman N, Luck LR, et al: Pediatric tumor cells express erythropoietin and a functional erythropoietin receptor that promotes angiogenesis and tumor cell survival. Lab Invest 83:1477-1487, 2003

32. Dillard DG, Venkatraman G, Cohen C, et al: Immunolocalization of erythropoietin and erythropoietin receptor in vestibular schwannoma. Acta Otolaryngol 121:149-152, 2001

33. Selzer E, Wacheck V, Kodym R, et al: Erythropoietin receptor expression in human melanoma cells. Melanoma Res 10:421-426, 2000

34. Westphal G, Niederberger E, Blum C, et al: Erythropoietin and G-CSF receptors in human tumor cells: Expression and aspects regarding functionality. Tumori 88:150-159, 2002

35. Pajonk F, Sommer A, Weil A, et al: Activation of the erythropoietin-receptor pathway does not affect chemo- or radiosensitivity of EpoR expressing cancer cells. Breast Cancer Res Treat 76: S81, 2002 (abstr 286; suppl 1)

36. Olujohungbe A, Handa S, Holmes J: Does erythropoietin accelerate malignant transformation in multiple myeloma? Postgrad Med J 73: 163-164, 1997

37. Falcioni M, Taibah A, De Donato G, et al: Fast-growing vestibular schwannoma. Skull Base Surg 10:95-99, 2000

38. Rizzo D, Lichtin AE, Woolf SH, et al: Use of epoetin in patients with cancer: Evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol 20:4083-4107, 2002

39. Sabbatini P, Cella D, Chanan-Khan A, et al: Cancer and treatment-related anemia. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, v. 1.2004. Rockledge, PA: National Comprehensive Cancer Network Inc, January 2004

40. Chang J, Couture F, Young S: Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. J Clin Oncol 23:2597-2605, 2005