

Darbepoetin Alfa for the Treatment of Anemia in Patients With Active Cancer Not Receiving Chemotherapy or Radiotherapy: Results of a Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Purpose

The efficacy and safety of darbepoetin alfa (DA) for treating patients with active cancer and anemia not receiving or planning to receive cytotoxic chemotherapy or myelosuppressive radiotherapy was evaluated.

Patients and Methods

Patients with active cancer and anemia not receiving or planning to receive chemotherapy or radiotherapy were enrolled onto a phase III, multicenter, randomized, placebo-controlled study and administered placebo or DA 6.75 $\mu\text{g}/\text{kg}$ every 4 weeks (Q4W) for up to 16 weeks with a 2-year follow-up for survival. Patients who completed 16 weeks of treatment could receive the same treatment as randomized Q4W for an additional 16 weeks. The primary end point was all occurrences of transfusions from weeks 5 through 17; safety end points included incidence of adverse events and survival.

Results

The incidence of transfusions between weeks 5 and 17 was lower in the DA group but was not statistically significantly different from that of placebo. DA was associated with an increased incidence of cardiovascular and thromboembolic events and more deaths during the initial 16-week treatment period. Long-term survival data demonstrated statistically significantly poorer survival in patients treated with DA versus placebo ($P = .022$). This effect varied by baseline covariates including, sex, tumor type, and geographic region; statistical significance diminished ($P = .12$) when the analysis was adjusted for baseline imbalances or known prognostic factors.

Conclusion

DA was not associated with a statistically significant reduction in transfusions. Shorter survival was observed in the DA arm; thus, this study does not support the use of erythropoiesis-stimulating agents in this subset of patients with anemia of cancer.

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INTRODUCTION

Anemia is common in patients with cancer and may be caused by the treatment or the disease itself.¹⁻⁴

The pathogenesis of anemia of cancer (AoC) in patients not receiving cancer therapy is poorly defined and may be due to various factors, including inflammatory cytokines, marrow infiltration, and residual marrow impairment from treatment.^{2,5-7}

Anemia is associated with a number of debilitating symptoms that may negatively impact patients' quality of life^{8,9} and may also be an independent prognostic factor for survival.¹⁰ Current therapies for AoC include RBC transfusions and erythropoiesis-stimulating agents (ESAs). Transfusions are associ-

ated with risks, including immunosuppression, hemolytic reactions, iron overload, and disease transmission.^{5,11-13} A limited number of clinical trials have evaluated the efficacy and safety of ESAs in patients with AoC and demonstrated increased hemoglobin levels, reduced transfusion incidence, and improved quality of life.¹⁴⁻²² Although ESAs are approved by the United States Food and Drug Administration and/or the European Agency for the Evaluation of Medicinal Products for the treatment of patients with chemotherapy-induced anemia,²³⁻²⁵ none are approved for use in patients with AoC.

A previous dose- and schedule-finding study suggested that the ESA darbepoetin alfa (DA) was

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well tolerated and effective in patients with AoC and that less-frequent (every 4 weeks; Q4W) DA may benefit patients not receiving cancer treatment.²¹ Here we present results from a large, phase III, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of DA administered 6.75 $\mu\text{g}/\text{kg}$ Q4W for treating the subset of patients with active cancer and anemia who are not receiving or planning to receive cytotoxic chemotherapy or myelosuppressive radiotherapy.

PATIENTS AND METHODS

Patient Population

Study protocols were approved by the institutional review board at each study site, and written informed consent was obtained before study-related procedures were begun.

Patients eligible for the initial 16 weeks of treatment were ≥ 18 years of age, had nonmyeloid malignancies, anemia (hemoglobin ≤ 11 g/dL), Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , ≥ 4 -month life expectancy, and adequate folate, vitamin B12, renal, and liver function. Exclusion criteria included chronic myeloid or acute leukemia; Burkitt's or lymphoblastic lymphoma; receiving or planning to receive cytotoxic chemotherapy, myelosuppressive radiotherapy, or ESAs within 4 weeks before randomization; complete remission; history of pure red cell aplasia; seizures; cardiac conditions; uncontrolled hypertension; infection or chronic inflammatory disease; iron deficiency; known HIV infection; neutralizing antibodies to ESAs; use of drugs or devices not approved by the United States Food and Drug Administration for any indication within 30 days of screening; pregnancy or lactation; and hypersensitivity to mammalian-derived products.

Patients were eligible to receive a further 16 weeks of treatment if they completed 16 weeks of treatment and met certain eligibility criteria (Fig 1).

Study Design

This study was conducted in Europe, North America, and Australia. Patients received up to 16 weeks of treatment followed by an end-of-study visit at week 19 and 2 years of follow-up for survival. Patients who completed 16 weeks of treatment could receive the same blinded treatment Q4W for a further 16 weeks with an end-of-study visit at week 35.

Patients were randomly allocated 1:1 in the initial protocol to receive either DA 6.75 $\mu\text{g}/\text{kg}$ or placebo subcutaneously Q4W until 145 patients had received one or more transfusions between weeks 5 and 17. Additional patients were randomly assigned 9:1 (DA:placebo) until 500 patients were enrolled onto the DA group (for safety evaluation). Randomization was stratified by geographic region (Europe *v* rest of world), baseline hemoglobin (< 10 *v* ≥ 10 g/dL), transfusion status in the previous 12 weeks (yes *v* no), ECOG status (0 to 1 *v* 2), and tumor type/treatment categories (chronic lymphocytic leukemia or low-grade lymphoma *v* hormonal or antibody therapy *v* all other tumor types and therapies¹).

Treatment was withheld when hemoglobin was greater than 13 g/dL and reinstated with a 25% reduction when hemoglobin reached 12 g/dL. Treatment was reduced by 25% if hemoglobin was greater than 12 g/dL or increased greater than 1 g/dL in 14 days.

Patients could receive noncytotoxic antineoplastic therapy or nonmyelosuppressive radiation at the discretion of the investigator.

Study End Points

The primary end point was all occurrences of transfusions from weeks 5 through 17. Secondary end points were incidence of transfusions from weeks 5 through 17; change in hemoglobin concentration from baseline to end of treatment; and hemoglobin response (≥ 2 g/dL increase from baseline), hemoglobin correction (hemoglobin ≥ 12 g/dL), and hematopoietic response (hemoglobin response or correction), within 17 weeks. Change in Functional Assessment of Cancer Therapy (FACT)-Fatigue scores from baseline to week 17 was estimated.

Safety end points included adverse events, serious adverse events, and deaths (during the treatment phase and 2-year follow-up period). Adverse

events were assigned a preferred term using the Medical Dictionary for Regulatory Activities (version 9.0) and grouped by system organ class. The presence of neutralizing antibodies to DA was assessed at baseline and end of treatment.

Statistical Analysis

Analyses were done using SAS version 8.2 (SAS Institute, Cary, NC). The study had 90% power to detect a 40% relative difference in the incidence of transfusions (20% placebo; 12% for DA) with a significance level of 5% (two-sided) and an assumed drop-out rate of 20% using a log-rank test and required approximately 145 patients to have one or more transfusion during weeks 5 through 17. The sample size was approximately 1,000 patients.

Continuous end points were summarized as mean and standard deviation (SD), discrete data as frequency and percent.

All occurrences of transfusions between weeks 5 and 17 (primary end point) were determined in patients who were randomly assigned 1:1, received one or more dose of study drug, and completed ≥ 4 weeks of study. The Anderson-Gill time-to-event model²⁶ estimated the hazard ratio and 95% CI.

The Kaplan-Meier method was used to estimate the incidences of first transfusion, first transfusion or hemoglobin ≤ 8 g/dL from weeks 5 through 17, and hemoglobin end points. Differences between the two groups were assessed by comparing the Kaplan-Meier percents at the last noncensored time point and using Cox proportional hazards models. Hemoglobin end points (in the absence of transfusions in the preceding 28 days) were determined in patients who were randomly assigned 1:1, received one or more dose of study drug, and had a baseline and one or more postbaseline hemoglobin value. The incidence of a ≥ 1 -g/dL hemoglobin increase in 14 days and hemoglobin ≥ 13 g/dL in the absence of a transfusion within 28 days were also summarized.

An analysis of covariance model was used to compare the adjusted means of the treatment groups for changes in hemoglobin concentration and FACT-Fatigue scores from baseline to end of treatment period. Missing hemoglobin values at the end of treatment were imputed using the last postbaseline hemoglobin measurement not within 28 days after a transfusion; missing FACT-Fatigue scores at the end of treatment were imputed using the last observation carried forward. All analyses were stratified or adjusted for stratification variables at randomization (hemoglobin at screening, region, prior transfusion, tumor type/treatment, and ECOG status).

Kaplan-Meier survival curves were plotted for time to all deaths, including those from the long-term follow-up period. Cox proportional hazards models were fit: (1) adjusted for stratification factors at randomization; (2) adjusted for stratification factors at randomization and enrollment status (as a time-dependent covariate indicating use of DA or placebo for up to 32 weeks); and (3) adjusted for stratification factors at randomization, enrollment status, and prognostic factors at baseline (sex, baseline disease stage, prior cytotoxic chemotherapy, and prior radiotherapy). Time to death was also summarized by tumor type, sex, geographic region, screening hemoglobin, prior transfusions, and ECOG status. *P* values for tests of homogeneity of treatment differences for each subgroup are provided.

Cox regression analyses, adjusted for baseline covariates, evaluated the association between survival during the initial 16-week treatment period and three time-dependent covariates: achieving hemoglobin greater than 12 g/dL, having a more than 1-g/dL increase in hemoglobin in 14 days, or having a transfusion.

RESULTS

Patient Characteristics

Patients were enrolled between April 15, 2004, and May 23, 2006, at 144 sites in Europe, Australia, and North America; most patients (75%) were from Europe. A total of 1,473 patients were screened, 989 were randomly assigned to receive either placebo ($n = 472$) or DA ($n = 517$). Two patients per group never received investigational drug. The randomization of the last 64 patients 9:1 (darbepoetin:placebo) resulted in more patients in the DA group. Approximately 52%

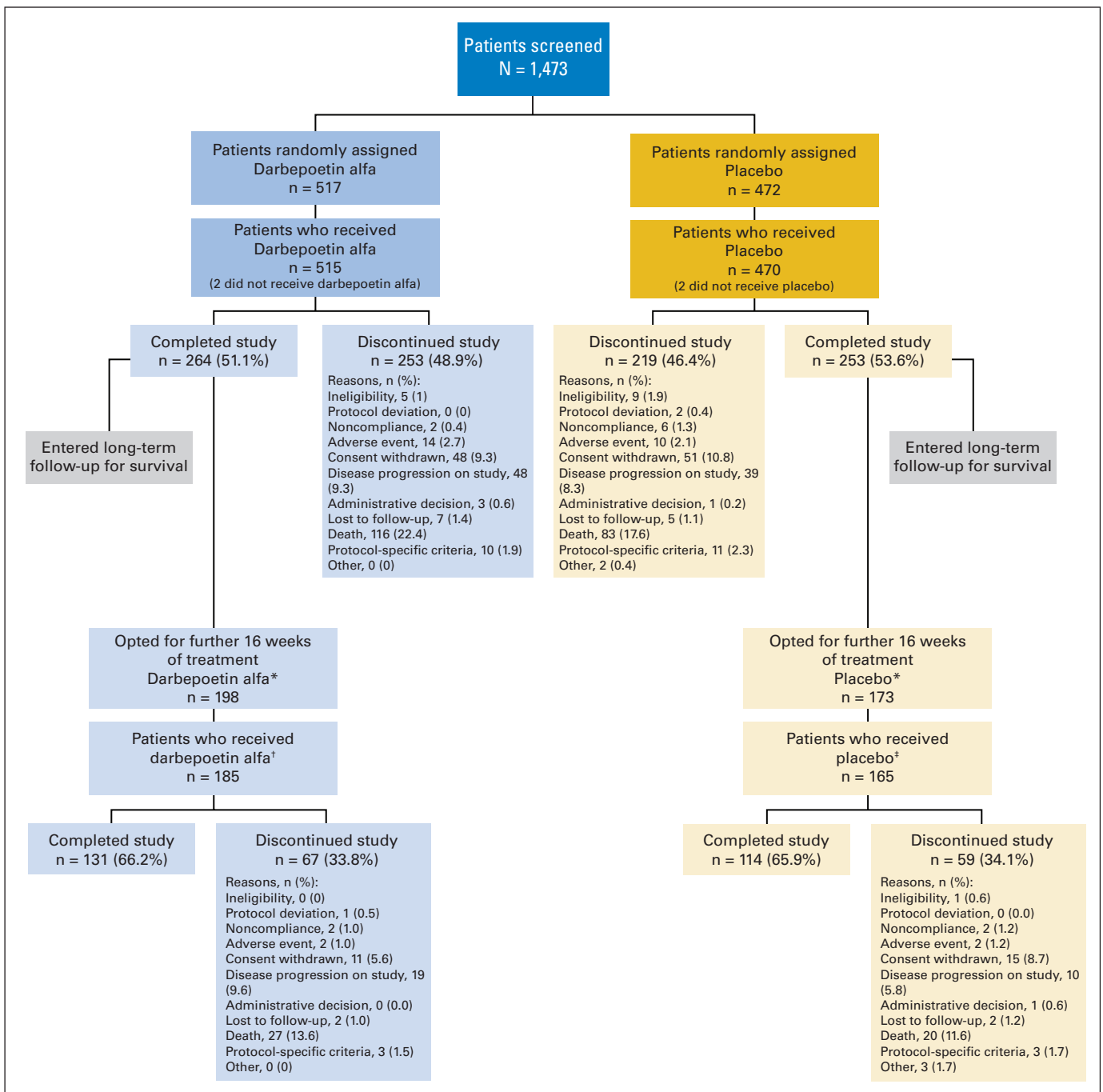


Fig 1. CONSORT diagram. *Inclusion criteria included: completion of 16 weeks of treatment; not receiving or planning to receive cytotoxic chemotherapy or myelosuppressive radiotherapy; no history of seizures; no cardiac conditions, uncontrolled hypertension, or infection or chronic inflammatory disease. †Two patients in the darbepoetin alfa group received placebo but remained in the darbepoetin alfa group for survival analysis. ‡One patient in the placebo group received one dose of darbepoetin alfa and was included in the darbepoetin alfa group for survival analysis.

(n = 517) completed the 16-week treatment period. Of these, 371 opted to continue in the study for a further 16 weeks: 173 patients receiving placebo and 198 patients receiving DA; 66% (n = 245) completed the additional 16-week treatment period (Consort diagram; Fig 1).

Patient demographics were broadly similar between the groups (Table 1). However, the DA group had more men (55.3%, DA; 46.8%, placebo), more patients with stage IV disease, more who had received

prior chemotherapy, and a shorter time from prior chemotherapy to first dose of study drug. Most cancers were solid tumors; the most frequent were non-small-cell lung, breast, prostate, colorectal, and kidney. The most common hematologic malignancies were multiple myeloma and non-Hodgkin's lymphoma; a higher proportion of patients in the DA group had aggressive non-Hodgkin's lymphoma and stage III multiple myeloma. On-study antineoplastic therapies were well balanced between the treatment groups (Table A1, online only).

Table 1. Patient Demographics, Disease Characteristics, and Baseline Laboratory Values*

Characteristic	Placebo (n = 470)		Darbepoetin Alfa 6.75 µg/kg Every 4 Weeks (n = 515)		Total (N = 985)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Male sex	220	46.8	285	55.3	505	51.3
Race/ethnicity						
White	444	94.5	493	95.7	937	95.1
Black	21	4.5	18	3.5	39	4.0
Hispanic	2	0.4	3	0.6	5	0.5
Asian	3	0.6	1	0.2	4	0.4
Age, years						
Mean	64.3		64.0		64.1	
SD	11.4		11.8		11.6	
Older age group						
≥ 65 to < 75 years	162	34.5	163	31.7	325	33.0
≥ 75 years	95	20.2	105	20.4	200	20.3
Solid tumor type						
Non-small-cell lung	83	17.7	97	18.8	180	18.3
Breast	62	13.2	66	12.8	128	13.0
Prostate	49	10.4	54	10.5	103	10.5
Colon	29	6.2	45	8.7	74	7.5
Kidney	28	6.0	22	4.3	50	5.1
Cervix	21	4.5	19	3.7	40	4.1
Ovarian	22	4.7	17	3.3	39	4.0
Stomach	18	3.8	19	3.7	37	3.8
Head and neck†	15	3.2	15	2.9	30	3.0
Small-cell lung	10	2.1	15	2.9	25	2.5
Pancreas	13	2.8	10	1.9	23	2.3
Soft tissue sarcoma	9	1.9	10	1.9	19	1.9
Bladder	10	2.1	8	1.6	18	1.8
Other‡	30	7.5	42	8.2	77	7.8
Disease stage, solid tumors						
I	11	2.3	10	1.9	21	2.1
II	42	8.9	38	7.4	80	8.1
III	104	22.1	115	22.3	219	22.2
IV	275	58.5	311	60.4	586	59.5
Unknown	38	8.1	41	7.9	79	8.0
Patients with extensive small-cell lung cancers§	7	70.0	11	73.3	18	72.0
Hematologic tumor type						
Multiple myeloma	38	8.1	33	6.4	71	7.2
Stage I	3	7.9	2	6.1	5	7.0
Stage II	8	21.1	3	9.1	11	15.5
Stage III	16	42.1	22	66.7	38	53.5
Unknown	11	28.9	6	18.2	17	23.9
Non-Hodgkin's lymphoma	15	3.2	21	4.1	36	3.7
Indolent¶	12	80.0	13	61.9	25	69.4
Aggressive¶	3	20.0	8	38.1	11	30.6
Chronic lymphocytic leukemia	10	2.1	10	1.9	20	2.0
Hodgkin's disease	1	0.2	6	1.2	7	0.7
Other hematologic malignancy	2	0.4	6	1.2	8	0.8
ECOG performance status						
0	87	18.5	85	16.5	172	17.5
1	254	54.0	280	54.4	534	54.2
2	128	27.2	149	28.9	277	28.1
3	1	0.2	0	0.0	1	0.1
Missing	0	0.0	1	0.2	1	0.1
Prior treatment						
Stem-cell/bone marrow transplantation	17	3.6	17	3.3	34	3.5
ESA therapy	80	17.0	84	16.3	164	16.6
Cytotoxic chemotherapy**	310	66.0	381	74.0	691	70.2

(continued on next page)

Darbepoetin Alfa in Patients Not Receiving Chemotherapy or RT

Table 1. Patient Demographics, Disease Characteristics, and Baseline Laboratory Values* (continued)

Characteristic	Placebo (n = 470)		Darbepoetin Alfa 6.75 µg/kg Every 4 Weeks (n = 515)		Total (N = 985)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
No. of days between prior chemotherapy and first dose of study drug						
Mean	312.6		257.7		281.9	
SD	657.2		547.0		598.2	
No. of patients	288		365		653	
Radiotherapy within the last 4 weeks	33	7.0	24	4.7	57	5.8
Baseline laboratory values						
Hemoglobin, g/dL						
Mean	9.49		9.49		9.49	
SD	1.13		1.22		1.18	
No. of patients	470		515		985	
Serum iron, µmol/L						
Mean	9.69		10.13		9.92	
SD	6.95		8.37		7.72	
No. of patients	469		515		984	
Total iron-binding capacity, µmol/L						
Mean	44.85		45.19		45.03	
SD	11.43		11.89		11.67	
No. of patients	468		512		980	
Transferrin Saturation, %						
Mean	21.9		22.4		22.2	
SD	15.7		17.0		16.4	
No. of patients	469		512		981	
Ferritin, µg/L						
Mean	604.2		642.4		624.2	
SD	949.8		1044.4		1000.1	
No. of patients	469		515		984	
Serum endogenous EPO, mU/mL						
Mean	94.59		137.29		117.11	
SD	249.59		535.33		425.22	
No. of patients	407		454		861	
Platelets, × 10 ⁹ /L						
Mean	302.4		292.9		297.4	
SD	165.1		157.6		161.2	
No. of patients	470		515		985	
Absolute neutrophil count, × 10 ⁹ /L						
Mean	5.23		5.12		5.18	
SD	3.55		4.60		4.13	
No. of patients	462		508		970	
Soluble transferrin receptor level, nmol/L††						
Mean	36.10		36.28		36.20	
SD	23.30		18.48		20.86	
No. of patients	373		425		798	

NOTE. Two patients in the darbepoetin alfa group received placebo in the roll-over study but remained in the darbepoetin alfa group for survival analysis; one patient in the placebo group received one dose of darbepoetin alfa in the roll-over study and was included in the darbepoetin alfa group for survival analysis. Baseline characteristics of the transfusion and hemoglobin analysis sets were similar to the safety analysis set.

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; ESA, erythropoiesis-stimulating agent; EPO, erythropoietin.

*Including all patients who received one or more dose of investigational product.

†Includes head and neck and oral.

‡Includes uterus, melanoma, endometrial, esophagus, testicular, ureter, carcinoma of unknown primary, and other solid tumor.

§Of patients with small-cell lung cancer.

||Includes both Durie-Salmon and ISS staging systems.

¶Of patients with non-Hodgkin's lymphoma.

**Patients were required to complete prior cytotoxic chemotherapy 4 weeks before randomization.

††Selected study sites.

Transfusions

All occurrences of transfusions between weeks 5 and 17 were lower in the DA group but were not significantly different from pla-

cebo (Table 2). However, the incidence of transfusions and the incidence of transfusions or hemoglobin ≤ 8 g/dL were statistically significant, favoring DA ($P = .046$ and $P = .009$, respectively; Table 2).

Table 2. Transfusion and Hemoglobin End Points

End Point	Placebo		Darbeoetin Alfa 6.75 μ g/kg Every 4 Weeks		Statistical Test Comparing Darbeoetin Alfa and Placebo			Hazard Ratio	95% CI	P
	%	95% CI	%	95% CI	Difference*		P			
Transfusion end points,† n		432		419						
All occurrences of transfusions from weeks 5 to 17, No. of transfusions		215		176				0.85	0.62 to 1.16	.312
Incidence* of transfusions from weeks 5 to 17	23.9	20.0 to 27.7	19.1	15.4 to 22.8	-5.0	-10.4 to 0.4	.068	0.74	0.55 to 0.99	.046
No. of transfusions		102		77						
No. of patients		432		419						
Europe	23.1	18.2 to 28.1	18.7	14.1 to 23.4	-4.4	-11.2 to 2.4				
No. of transfusions		66		52						
No. of patients		318		310						
Rest of world	33.0	24.1 to 41.8	24.5	16.2 to 32.9	-8.4	-20.6 to 3.8				
No. of transfusions		36		25						
No. of patients		114		109						
Incidence* of transfusions from weeks 5 to 17 or hemoglobin \leq 8 g/dL	33.4	29.2 to 37.5	26.9	22.8 to 31.0	-6.8	-12.7 to -0.9	.024	0.72	0.56 to 0.92	.009
No. of transfusions		144		110						
No. of patients		432		419						
Hemoglobin end points,† n		447		437						
Baseline hemoglobin, g/dL										
Mean		9.52		9.49						
SD		1.11		1.21						
Change in hemoglobin from baseline to EOTP, g/dL§										
Mean		0.29		0.79	0.44	0.22 to 0.66	< .0001			
95% CI		0.03 to 0.55		0.46 to 0.99						
Hemoglobin response*	28.7	22.5 to 34.9	48.4	43.1 to 53.8	19.7	11.4 to 28.1	< .001			
No.		96		184						
Hemoglobin correction*	26.7	21.0 to 32.4	41.6	35.9 to 47.2	15.1	7.1 to 23.2	< .001			
No.		92		160						
Hematopoietic response*	37.5	30.1 to 44.9	52.2	47.0 to 57.5						
No.		123		201	14.7	5.5 to 24.0	.002			

Abbreviations: EOTP, end of treatment period; SD, standard deviation.

*Kaplan-Meier percent at the last non-censored time point.

†Includes patients who were randomly assigned 1:1, received one or more doses of study drug, and completed \geq 4 weeks of study drug.

‡Includes patients who were randomly assigned 1:1, received one or more doses of study drug, and had a baseline and one or more postbaseline hemoglobin values.

§Hemoglobin values that were missing or within 28 days of a transfusion were replaced with the last value not within 28 days of a transfusion. Patients without a transfusion between weeks 5 and 17 were censored at the end of week 17 or on the date recorded in the last follow-up record, whichever was earlier.

The incidence of transfusions among the European study sites was lower than that of the rest of the world (Table 2); among the 75 patients (42 patients receiving placebo; 33 patients receiving DA) whose hemoglobin decreased \leq 8 g/dL but were not transfused, 71 patients (95%) were from Eastern Europe.

Hemoglobin End Points

Mean change in hemoglobin from baseline, hemoglobin response, hemoglobin correction, and hematopoietic response were all statistically significantly higher for the DA group than for the placebo group (Fig 2; Table 2).

Patient-Reported Quality of Life

No significant improvement or worsening of FACT-Fatigue scores was observed in the DA and placebo groups (Table A2, online only).

Exposure to Study Drug

The mean (\pm SD) number of doses received by the placebo and DA groups was 3.2 ± 1.1 and 2.9 ± 1.1 , and the mean duration of treatment was 13.8 ± 4.3 versus 12.9 ± 4.4 weeks, respectively. One

or more doses of DA were withheld in 18.4% of patients, and 39.6% of patients had one or more dose of DA reduced. The mean (\pm SD) weekly dose of DA was $98.2 \pm 25.6 \mu$ g. Of patients who entered the roll-over study, 37.7% had one or more dose of DA withheld, and 66.3% had one or more dose reduced. The mean (\pm SD) weekly dose of DA in the roll-over study was $85.1 \pm 33.5 \mu$ g. Generally, doses were reduced because hemoglobin increased more than 12 g/dL or more than 1 g/dL in 14 days, and doses were withheld because hemoglobin increased more than 13 g/dL.

Safety

Adverse events during the treatment phase. Similar proportions of patients in each treatment group experienced one or more adverse event during treatment; however, patients receiving DA experienced a higher incidence of serious and fatal adverse events than those receiving placebo (Table 3). The incidence of treatment-related adverse events was low in each treatment group but was slightly higher for placebo. The incidence of cardiovascular and thromboembolic events was moderately higher in the DA group (Table 3).

Darbepoetin Alfa in Patients Not Receiving Chemotherapy or RT

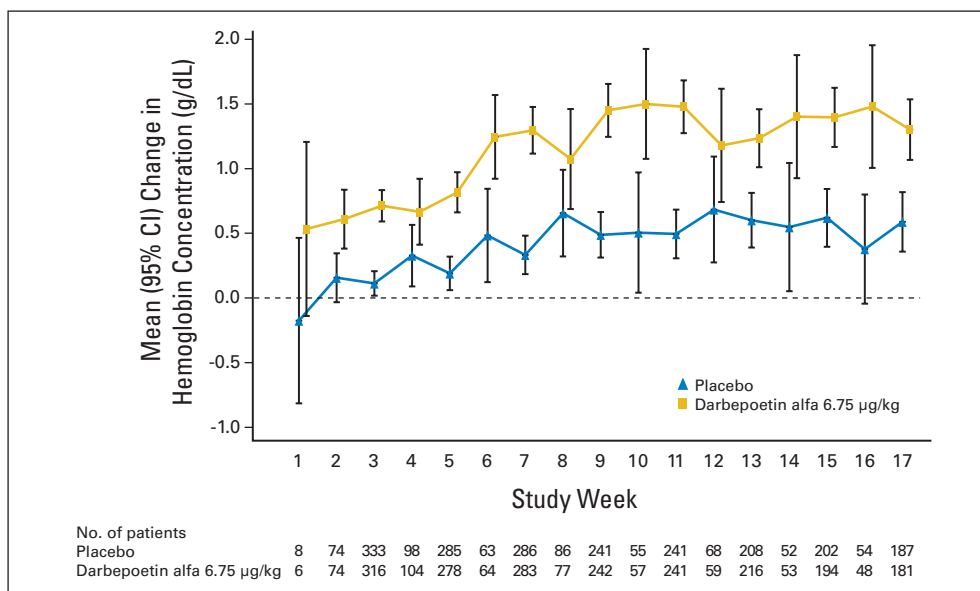


Fig 2. Change in hemoglobin concentration over the treatment period. Available data; bars represent 95% CIs.

During treatment, 113 patients (21.9%) receiving DA compared with 35 patients (7.4%) receiving placebo exceeded a hemoglobin of 13 g/dL, and 217 patients (42.1%) receiving DA compared with 126

patients (26.8%) receiving placebo had a greater than 1-g/dL increase in hemoglobin in 14 days (all unrelated to transfusions). Cardiovascular and thromboembolic events did not seem to occur more

Table 3. Safety*

Parameter	Placebo (n = 470)		Darbepoetin Alfa 6.75 µg/kg Every 4 Weeks (n = 515)	
	No.	%	No.	%
During treatment period				
Adverse events				
Patients with any adverse events	359	76.4	399	77.5
Severe, life-threatening or fatal adverse events	192	40.9	245	47.6
Serious adverse events	159	33.8	210	40.8
Patients with treatment-related adverse events	16	3.4	11	2.1
Severe, life-threatening or fatal adverse events	6	1.3	6	1.2
Serious adverse events	5	1.1	6	1.2
Adverse events leading to study discontinuation†	43	9.1	51	9.9
Adverse events of interest				
Cardiovascular and thromboembolic events	36	7.7	50	9.7
Arrhythmia	17	3.6	21	4.1
Congestive heart failure	13	2.8	12	2.3
Cerebrovascular accident	4	0.9	7	1.4
Myocardial infarction/coronary artery disorders	2	0.4	3	0.6
Embolism/thrombosis (arterial and venous)	7	1.5	12	2.3
Seizure	6	1.3	3	0.6
Hypertension	12	2.6	8	1.6
Pure red cell aplasia	0	0.0	0	0.0
Immune system disorder	1	0.2	0	0.0
Neoplasms benign, malignant, and unspecified (include cysts and polyps)	158	33.6	199	38.6
Death on study‡ (any reason)	96	20.4	138	26.8
Deaths from cancer	77	16.4	113	21.9
Combined safety analysis§				
		n = 469	n = 516	
Deaths during combined treatment period‡	117	24.9	165	32.0
Deaths during combined treatment period and long-term follow-up	240	51.2	280	54.3

*Including all patients who received one or more dose of investigational product.

†Excludes fatal adverse events.

‡Either during treatment or within 6 weeks after the last dose of study drug.

§Two patients in the darbepoetin alfa group received placebo in the roll-over study but remained in the darbepoetin alfa group for safety and survival analyses; one patient in the placebo group received one dose of darbepoetin alfa in the roll-over study and was included in the darbepoetin alfa group for safety and survival analysis.

||Median duration of long-term follow-up was 29.4 weeks for the placebo group and 25.9 weeks for the darbepoetin alfa group.

frequently in patients exceeding hemoglobin 13 g/dL compared with those who did not (hazard ratio [HR] = 0.43; 95% CI, 0.13 to 1.41) nor with those with a greater than 1-g/dL increase in hemoglobin in 14 days compared with those who did not (HR = 0.81; 95% CI, 0.45 to 1.44). No neutralizing antibodies to DA were detected.

Survival. A total of 234 patients died while enrolled in the study (either during treatment or within 6 weeks after the last dose of study drug); 138 patients (26.8%) in the DA group died versus 96 patients (20.4%) in the placebo group. More deaths in the DA group were attributed by the investigators to cancer (Table 3). Including patients who opted to continue participating in the study for a further 16 weeks, deaths while enrolled in the study were 165 patients (32.0%) for DA and 117 patients (24.9%) for placebo.

Significantly more patients receiving DA versus placebo died during treatment and long-term follow-up. The median time to death was estimated at 37 weeks versus 47 weeks, respectively, with median follow-up times of 25.9 and 29.4 weeks. There was a significant difference in survival between the two groups that favored placebo (HR = 1.22; 95% CI, 1.03 to 1.45; $P = .022$); however, the HRs and statistical significance diminished when posthoc analyses were further adjusted for baseline imbalances or known prognostic factors (Fig 3).

The observed effect of treatment on overall survival during treatment and follow-up varied by tumor type. When treated with DA, patients with kidney, non-small-cell lung, prostate, or stomach cancers, non-Hodgkin's lymphoma, or multiple myeloma seemed to have worse survival outcomes (although this only seemed significant in patients with multiple myeloma); the opposite was observed for patients with breast, colon, ovarian, or cervical cancer (Fig 4A). Men, patients from Western Europe, or those with screening hemoglobin ≥ 10 g/dL also seemed to have worse survival outcomes when treated with DA (Fig 4A). However, none of the P values for testing of homogeneity of treatment differences among subgroups was less than .05.

Interestingly, during the initial 16-week treatment period, survival outcomes seemed to be better after achieving hemoglobin greater than 12 g/dL and were neutral after having a more than 1-g/dL increase in hemoglobin in 14 days (Fig 4B). Survival outcomes seemed to be worse after having a transfusion for patients receiving either DA or placebo (HR = 2.55; Fig 4C).

DISCUSSION

This is the largest randomized trial to date in which an ESA was used to treat anemia in the subset of patients with active cancer not receiving or planning to receive cytotoxic chemotherapy or myelosuppressive radiotherapy. Results of previous trials suggested that treatment with ESAs in this setting reduced transfusion risk; however, in two published placebo-controlled studies, this difference was not statistically significant.^{15,21} Likewise, our trial did not demonstrate a statistically significant reduction in all occurrences of transfusions with DA treatment, although therapy was associated with increased hemoglobin concentration. Our failure to demonstrate a statistically significant reduction in occurrences of transfusions may be attributed to insufficient power resulting from a lower-than-predicted transfusion rate (including the failure to administer transfusion for 75 patients at recommended hemoglobin levels) and a greater-than-expected mean hemoglobin increase in the placebo group (0.5 g/dL); DA was associ-

ated with a significant reduction in transfusion incidence when the analysis included patients who should have undergone transfusion.

Our data did not show improved quality of life associated with DA therapy, possibly owing to the high proportion of patients with advanced disease receiving palliative care.

The safety of DA in this subset of patients with AoC is an important issue. Although the incidence of serious adverse events was greater in patients receiving DA, the incidence of serious adverse events attributed to DA was not higher in these patients. Only cardiovascular and thromboembolic events were observed with a higher frequency in patients receiving DA; this is reflected in the product label, and recent meta-analyses of published trials have documented similar or greater incidences of thromboembolic events associated with ESA treatment versus controls in patients with chemotherapy-induced anemia.^{13,27,28}

Previous controlled trials of DA in the AoC setting did not demonstrate a detrimental effect on survival.^{21,22} Also, published meta-analyses demonstrated no reduced survival outcomes in patients with chemotherapy-induced anemia treated with ESAs.^{13,27,28} Thus the significantly higher proportion of deaths in the DA group in the present trial was unexpected. It is important to note that survival was not an end point of this trial, and appropriate stratification factors were not used to ensure balance in baseline-prognostic factors for survival between the two treatment groups. Posthoc analyses accounting for these factors reduced the observed survival difference and diminished statistical significance. Although the test for interaction failed to reach significance at a $P = .066$, it is noteworthy that the HR was 0.95 for female patients compared with 1.32 for male patients, a somewhat surprising difference with no clear explanation. Although more deaths on study were attributed to the underlying malignancy in the DA arm, interpretation of this observation is difficult because assessment of tumor progression was not performed, and cause of death was not reported.

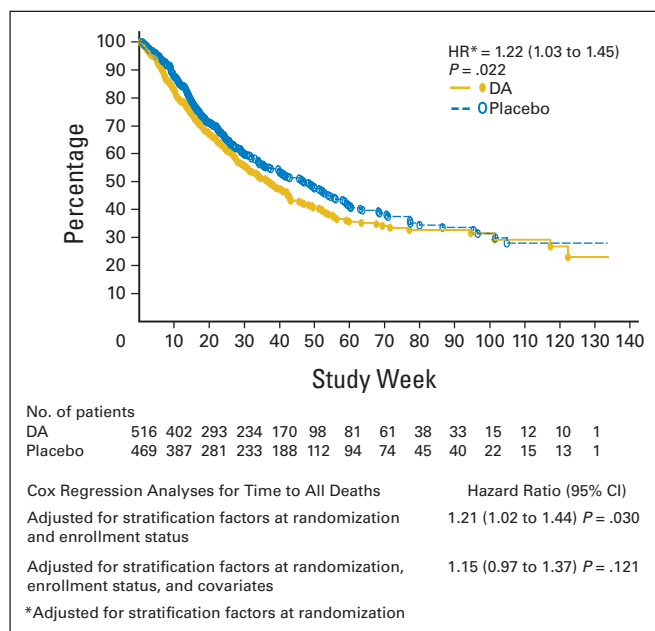


Fig 3. Kaplan-Meier curves of time to all deaths during combined treatment period and long-term follow-up. Hazard ratios for time to all deaths were calculated from Cox proportional hazards models adjusted for stratification factors at randomization and further adjusted for enrollment status and prognostic factors at baseline.

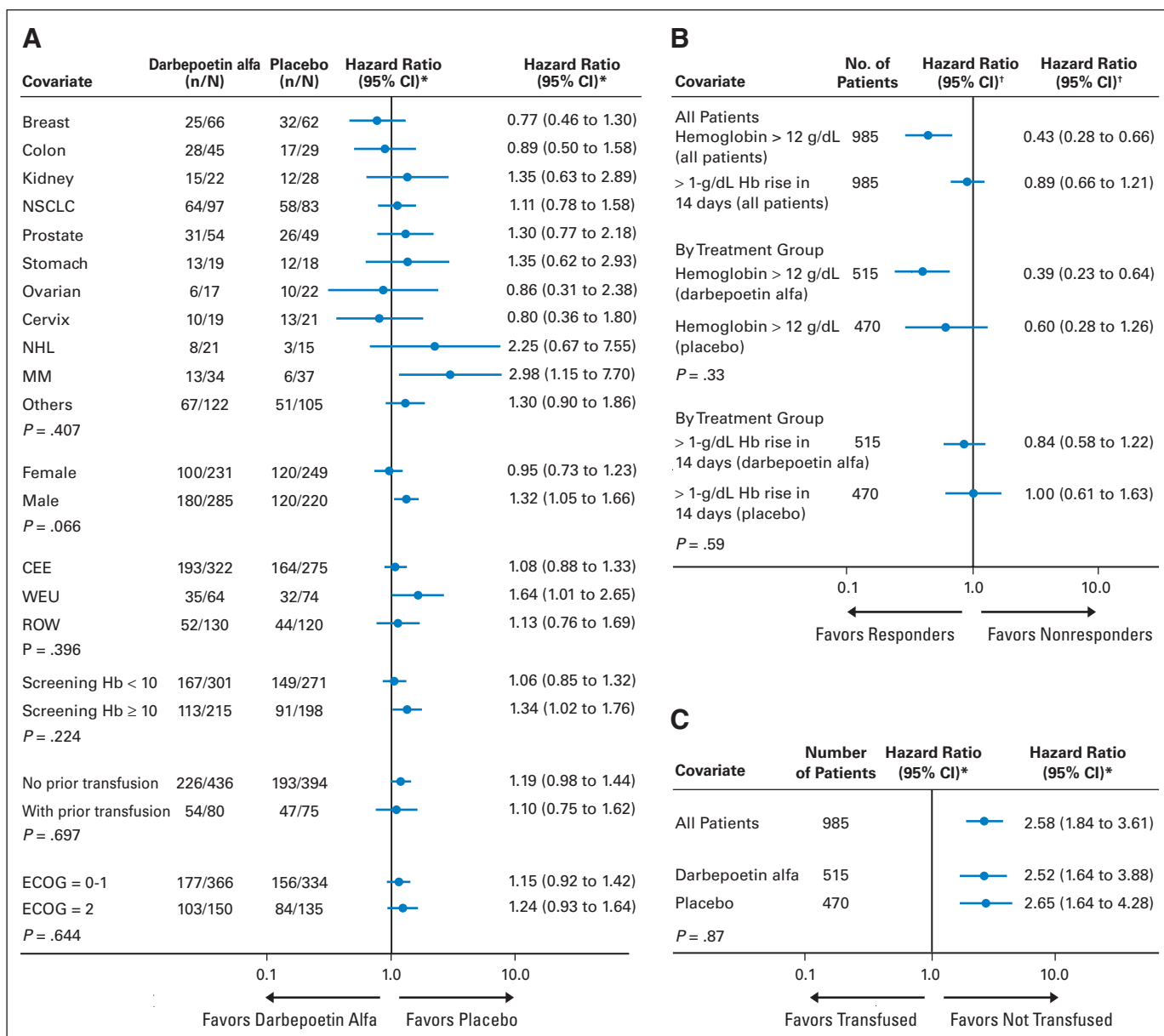


Fig 4. Hazard ratios (95% CI) for time to all deaths. (A) For baseline subgroups (unadjusted). (B) During the initial 16-week treatment period by whether or not patients achieved hemoglobin greater than 12 g/dL or a greater than 1-g/dL increase in hemoglobin in 14 days (adjusted). (C) During the initial 16-week treatment period by whether or not patients received transfusions (adjusted). NSCLC, non-small-cell lung cancer; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; CEE, Central and Eastern Europe; WEU, Western Europe; ROW, rest of world; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin. *During treatment period and long-term follow-up. †During treatment period. *P* values indicate test for interaction.

Several hypotheses have been proposed to account for adverse outcomes observed in other studies with ESAs in oncology populations.^{29,30} These include the effects of high-target hemoglobin levels on cardiovascular and thromboembolic events (for which oncology patients are at increased risk), a putative role for the erythropoietin receptor (EpoR) in tumor progression (however, the anti-EpoR antibodies used to identify EpoR in tissue samples are nonspecific^{31,32}), and direct effects of ESAs on either promoting tumor vascularization or increasing risk for cardiovascular and thromboembolic events.

Although a higher incidence of cardiovascular and thromboembolic events was observed in the DA group, deaths attributed to

these events were balanced between the two groups. Cause of death was not adjudicated in this study; thus deaths from cardiovascular and thromboembolic disease may have been under reported. Interestingly, although this study did not target high hemoglobin levels, neither a greater than 1 g-dL increase in hemoglobin in 14 days nor an increase to more than 12 g/dL seemed to be associated with decreased survival, arguing against a detrimental effect of either higher or rapidly achieved hemoglobin levels. In contrast, transfusion, a potential marker of lack of response to therapy and poorer health, seemed to be associated with worse survival outcomes. No formal data on disease progression were collected, thus no conclusions on an effect of ESA on tumor progression can be

made. Importantly, breast cancer patients did not experience an adverse outcome with respect to mortality, and this result is in contrast to a previous study of anemia prevention in breast cancer patients with chemotherapy-induced anemia.²⁹ Therefore, the data from the present study do not allow an explanation for the observed adverse mortality outcome: there is no support for either increased thrombotic risk or effects of high hemoglobin levels as possible explanations.

In conclusion, in this trial of DA to treat anemia in patients with active cancer not receiving or planning to receive cytotoxic chemotherapy or myelosuppressive radiotherapy, we did not observe a statistically significant reduction in transfusions and cannot exclude a negative impact on survival. Thus this study does not support the use of ESAs in these patients. It is unknown whether these findings can be generalized to the broader AoC population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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

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Appendix

Table A1. Patients Who Received On-Study Antineoplastic Therapy

On-Study Therapy	Placebo (n = 470)		Darbepoetin Alfa 6.75 µg/kg Every 4 Weeks (n = 515)		All Patients (n = 985)	
	No.	%	No.	%	No.	%
Any therapy	175	37.2	199	38.6	374	38.0
Hormonal therapy	90	19.1	94	18.3	184	18.7
Bisphosphonates	79	16.8	86	16.7	165	16.8
Small molecule	27	5.7	28	5.4	55	5.6
Glucocorticoids	19	4.0	26	5.0	45	4.6
Chemotherapy	15	3.2	15	2.9	30	3.0
Interferon	10	2.1	13	2.5	23	2.3
Monoclonal antibody	9	1.9	10	1.9	19	1.9
None of above	5	1.1	2	0.4	7	0.7

NOTE. A patient may have received more than one type of therapy. The investigator determined whether or not a cancer therapy was cytotoxic.

Table A2. Change in FACT-F Subscale Score From Baseline to EOTP

	Placebo (n = 362)	Darbepoetin Alfa 6.75 µg/kg Every 4 Weeks (n = 345)	Difference (darbepoetin alfa-placebo)
Baseline FACT-F score			
Mean	28.46	29.22	
SD	11.47	11.70	
EOTP* FACT-F score			
Mean	28.98	29.24	
SD	12.54	13.13	
Change in FACT-F score from baseline to EOTP			
Mean	0.52	-0.02	
SD	10.41	11.83	
n	362	343	
ANCOVA results†			
LS Mean	0.58	0.33	-0.25
95% CI	-1.20 to 2.36	-1.50 to 2.16	-1.78 to 1.27

Abbreviations: FACT-F, Functional Analysis of Cancer Treatment-Fatigue; EOTP, end of treatment period; SD, standard deviation; ANCOVA, analysis of covariance; LS, least squares.
 *EOTP defined as the earlier of day 119 or end of study. Analysis uses the last value before EOTP.
 †Analysis of covariance including stratification factors at randomization.