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ORIGINAL REPORT

Safety and Efficacy of Darbepoetin Alfa in Previously Untreated Extensive-Stage Small-Cell Lung Cancer Treated With Platinum Plus Etoposide

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

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ABSTRACT

Purpose
A placebo-controlled, double-blind, randomized, phase III study was conducted in patients with extensive-stage small-cell lung cancer receiving first-line platinum-containing chemotherapy to determine if increasing or maintaining hemoglobin concentration with darbepoetin alfa could increase patient survival.

Patients and Methods
Darbepoetin alfa (300 μg) or placebo was administered once per week for 4 weeks then every 3 weeks for up to six cycles of chemotherapy (carboplatin plus etoposide or cisplatin plus etoposide) plus 3 weeks after the last dose of chemotherapy. Patients with disease progression were observed until death or until all patients completed their end-of-study visit and 496 deaths had occurred. The two coprimary end points were change in hemoglobin concentration from baseline to the end of the chemotherapy period and overall survival; statistical testing of survival was done if change in hemoglobin was significant at $P < .05$.

Results
The study enrolled 600 patients. Patients' hemoglobin levels dropped due to the myelosuppressive chemotherapy; however, treatment with darbepoetin alfa maintained hemoglobin levels significantly higher than placebo ($P < .001$). There was no statistically significant difference in overall survival between the treatment groups (hazard ratio [HR], 0.93; 95% CI, 0.78 to 1.11; $P = .431$). As expected, darbepoetin alfa was associated with a higher incidence of thromboembolic events (darbepoetin alfa, 9%; placebo, 5%). The transfusion risk was lower in the darbepoetin versus placebo group (HR, 0.40; 95% CI, 0.29 to 0.55).

Conclusion
The results of this study did not demonstrate improved survival after treatment with darbepoetin alfa; however, they reinforce the benefit of erythropoiesis-stimulating agents in reducing transfusions and their neutral impact on survival in patients with chemotherapy-induced anemia.

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INTRODUCTION

Patients with cancer receiving chemotherapy often develop anemia, which is associated with a number of debilitating symptoms that may reduce patients' quality of life.[1] Anemia is also an independent prognostic factor for survival and has been shown to increase the overall risk of death in cancer patients by an estimated 65%.[2]

Darbepoetin alfa is an erythropoiesis-stimulating agent (ESA) that is approved by the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for the treatment of patients with chemotherapy-induced anemia (CIA).[3,4] Darbepoetin alfa increases hemoglobin levels, reduces the incidence of RBC transfusions, and improves health-related quality of life in this patient population.[5-7]

A previous study of patients with lung cancer receiving platinum-containing chemotherapy suggested a potential survival benefit among the subset of patients with small-cell lung cancer (SCLC) who received darbepoetin alfa versus placebo: deaths occurred in 59% of patients who received darbepoetin alfa versus 69% of patients who received placebo, and the median duration of overall survival was 46 weeks in the darbepoetin alfa group and 34 weeks in the placebo group.[5] The hypothesis of a survival benefit associated with darbepoetin alfa treatment was used as the rationale for this study, which was

designed to determine if increasing or maintaining hemoglobin concentrations with darbepoetin alfa could increase survival compared with placebo in patients with extensive-stage SCLC receiving first-line platinum-containing chemotherapy. This placebo-controlled, double-blind, randomized, phase III study had two coprimary end points: change in hemoglobin concentration from baseline to the end of the chemotherapy period and overall survival. Other end points included safety during the treatment period, the incidence of transfusions, and health-related quality-of-life outcomes.

PATIENTS AND METHODS

Patient Population

The study protocol was approved at the institutional review board or independent ethics committee at each site; all patients gave written informed consent before any study-related procedures began. Eligibility criteria included: ≥ 18 years old; pathologically proven but previously untreated extensive-stage SCLC for which chemotherapy was planned every 3 weeks for six cycles; hemoglobin concentration ≥ 9g/dL and ≤ 13g/dL; Eastern Cooperative Oncology Group performance status 0 to 2; life expectancy ≥ 3 months; and adequate renal, liver, and hematopoietic function. Exclusion criteria included: known primary hematologic disorder that could cause anemia; brain metastases; unstable or uncontrolled disease or cardiac condition related to or affecting cardiac function; other known primary malignancies; iron deficiency (serum ferritin < 20 ng/mL and transferrin saturation < 20%); previous chemotherapy or radiation therapy for SCLC; previous ESA therapy; more than 2 units of packed RBCs within 4 weeks of random assignment or any transfusion within 2 weeks of random assignment; pregnancy or breast feeding; HIV positive; and known hypersensitivity to recombinant mammalian-derived products.

Study Drug and Design

Darbepoetin alfa was supplied in 1-mL single-dose vials as a clear, colorless, sterile solution containing 500 μg/mL darbepoetin alfa. Placebo and darbepoetin alfa were supplied in identical vials.

This was a placebo-controlled, double-blind, randomized, multicenter, superiority study comparing the safety and efficacy of darbepoetin alfa with placebo in anemic patients with extensive-stage SCLC. The randomized treatment assignment was obtained from the interactive voice-response system no more than 3 days before the first dose of investigational product. Patients were randomly assigned (1:1) to receive 300 μg darbepoetin alfa or placebo subcutaneously once per week for the first 4 weeks, then every 3 weeks for up to six cycles of chemotherapy plus 3 weeks after the last dose of on-study chemotherapy. The chemotherapy regimen was an IV infusion of either carboplatin plus etoposide or cisplatin plus etoposide administered according to the institutional guidelines. The first dose of darbepoetin alfa was administered on study day 1 immediately before the first cycle of chemotherapy. An additional weekly dose of darbepoetin alfa was administered if a patient's hemoglobin was lower than 11g/dL. Darbepoetin alfa was withheld if hemoglobin was ≥ 14g/dL; once hemoglobin declined to lower than 13g/dL, darbepoetin alfa was reinstated every week (weeks 1 to 4) or every 3 weeks (week 5 to end-of-treatment period).

End-of-treatment visits occurred 8 weeks after completion of on-study chemotherapy. Patients received a chest x-ray or computed tomography scan every 3 months after the end-of-treatment visit until documented disease progression defined by modified Response Evaluation Criteria in Solid Tumors. Patients continued to be observed every 3 months until death or until all patients completed their end-of-study visit and 496 deaths had occurred (approximately 1 year after the last patient was randomly assigned).

End Points

The coprimary end points were: the change in hemoglobin concentration from baseline to end of chemotherapy period; and overall survival. Other efficacy end points included change in Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale scores from baseline to the end of treatment and incidence of transfusions during the treatment phase. Safety end points included the incidence of adverse events, serious adverse events, treatment-related adverse events, adverse events of interest (adverse events identified due to theoretical or known safety concerns), disease progression, and deaths during treatment and long-term follow-up.

Statistical Analyses

A sample size of approximately 600 patients was chosen to provide adequate power to detect significant changes in the coprimary end points of change in hemoglobin and survival (> 95% power to detect a 1-g/dL difference in hemoglobin concentration between groups; 89% power to detect a 25% improvement in survival; hazard ratio [HR], 0.75). Randomization was stratified by region (Western Europe *v* Australia/North America *v* rest of the world); Eastern Cooperative Oncology Group performance status (0 or 1 *v* 2); and levels of lactate dehydrogenase (LDH; below *v* above the upper limit of normal). An independent data-safety monitoring board recommended continuing the study after two separate interim analyses in April and August 2005, after the 165th and 248th deaths, respectively.

A prespecified stepdown procedure allowed for hierarchical statistical testing of survival (nominal $P < .025$ for increased survival; $P < .012$ for decreased survival) only if change in hemoglobin was significant at $P < .05$. Survival for the two treatment groups was compared using a two-sided log-rank test adjusted for stratification factors at random assignment. Hazard ratios and corresponding 95% CIs were calculated using a stratified Cox proportional hazards regression model. Time to disease progression and progression-free survival were evaluated using the same methods.

The mean change in hemoglobin concentration from baseline to the end of chemotherapy period for the two treatment groups was compared using a generalized Cochran-Mantel-Haenszel test adjusted for stratification factors. The difference (95% CI) in the change in hemoglobin between groups was estimated using an analysis of variance model. Change in FACT-F scores from baseline to end of treatment was analyzed by an analysis of covariance model stratified by factors at randomization and baseline FACT-F scores. Incidence of transfusion was calculated as the crude percentage with 95% CI; time to first transfusion was summarized by plotting the Kaplan-Meier estimate.

A posthoc analysis of the incidence of cardiovascular/thromboembolic events was performed using a stratified Cox proportional hazards regression model.

RESULTS

This study was conducted at 69 sites in Europe, Australia, and Canada; 600 patients were enrolled in this study. The study period was December 10, 2002 (date the first patient was randomly assigned), through February 22, 2007 (data cutoff date by which 496 deaths had occurred).

Study Population

The flow of patients through the study is shown in Figure 1. Half of the patients in each group completed the treatment phase of the study. The main reasons for study discontinuation were similar in the two treatment groups (Fig 1).

Baseline demographics and clinical characteristics were similar between the two treatment groups (Table 1). Sixty-five percent of patients were men, 65% were younger than 65 years of age, and the majority of patients smoked while on study.

Hemoglobin During the Treatment Period

As expected, the mean hemoglobin concentration fell in both treatment arms due to the myelosuppressive effects of platinum-containing chemotherapy. However, the coprimary hemoglobin end point was achieved: the mean change in hemoglobin concentration

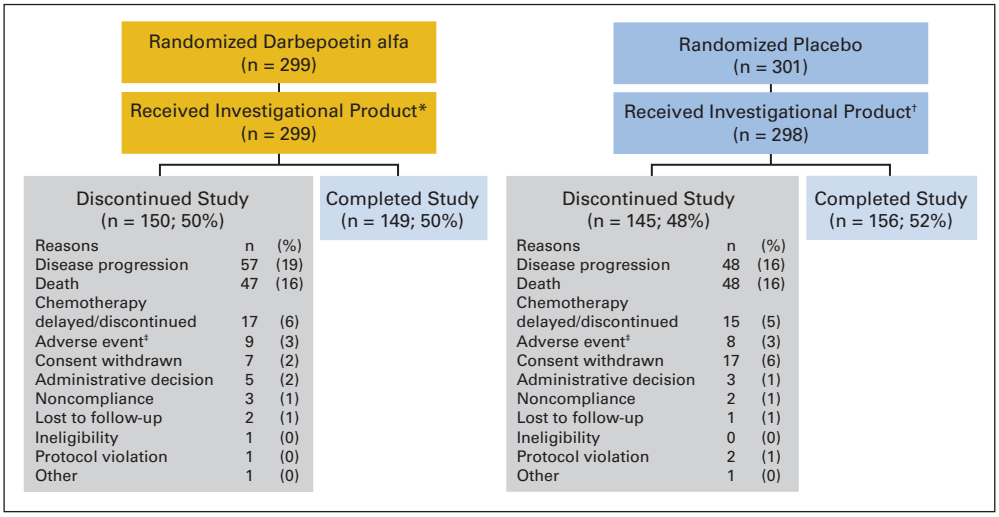

Fig 1. CONSORT diagram. (*) One patient randomly assigned to darbepoetin alfa received investigational product but did not receive the study chemotherapy and was excluded from the efficacy analyses. (†) Two patients randomly assigned to the placebo group received one dose of darbepoetin alfa in error and were included in the darbepoetin alfa group for analysis of safety, two patients did not receive investigational product, and one patient received neither investgational product nor study chemotherapy. (‡) Discontinuation due to adverse event excludes disease progression and death. Percentages are based on randomly assigned patients.

from baseline to the end of chemotherapy period was statistically significantly less ($P < .001$) in the darbepoetin alfa group (−1.13 g/dL; 95% CI, −1.36 to −0.91) compared with the placebo group (−1.98 g/dL; 95% CI, −2.2 to 1.76; Fig 2); the estimated difference was 0.84 g/dL (95% CI, 0.53 to 1.15).

Survival

Overall, 493 of 596 patients (242 in the darbepoetin alfa group [81%] and 251 in the placebo group [84%]) died during treatment and long-term follow-up period. Three additional patients died before receiving any investigational product or chemotherapy and were excluded from the analysis. The coprimary end point of superiority of darbepoetin alfa versus placebo for overall survival was not achieved: there was no statistically significant difference in overall survival between the two treatment groups (HR, 0.93, 95% CI, 0.78 to 1.11; $P = .434$; Table 2; Fig 3). Similarly, there was no significant difference between the two groups with regard to progression-free survival or time to disease progression (Table 2).

Table 1. Baseline Patient Demographics and Disease Characteristics

Characteristic	Darbepoetin Alfa (n = 298)		Placebo (n = 298)		All Patients (N = 596)	
	No.	%	No.	%	No.	%
Sex, male	187	63	198	66	385	65
Race, white	298	100	298	100	596	100
Smoking while on study	268	90	271	91	539	90
Mean age, years	60.6		61.3		61.0	
SD	9.2		8.3		8.8	
≥ 65	106	36	102	34	208	35
ECOG performance status						
0-1	233	78	235	79	468	79
2	65	22	63	21	128	21
Geographic region						
Western Europe	66	22	66	22	132	22
Australia/North America	10	3	9	3	19	3
Rest of the world	222	74	223	75	445	75
Patients with ≥ 1 non-target lesion*	194	65	203	68	397	67
CT scan of target lesion	292		292		584	
Mean sum of index	166.7		165.8		166.3	
SD	94.4		100.1		97.2	
Time since diagnosis, days						
No.	298		296		594	
Mean	17.5		21.6		19.5	
SD	11.6		50.9		36.9	
Mean baseline Hb, g/dL	12.03		11.86		11.94	
SD	1.07		1.03		1.05	
Baseline LDH in normal range	124	42	130	44	254	43

NOTE. Data include all patients who received one or more doses of investigational product and one or more doses of study chemotherapy.
Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; CT, computed tomography; Hb, hemoglobin; LDH, lactate dehydrogenase.
*Patients may be counted in more than one category.

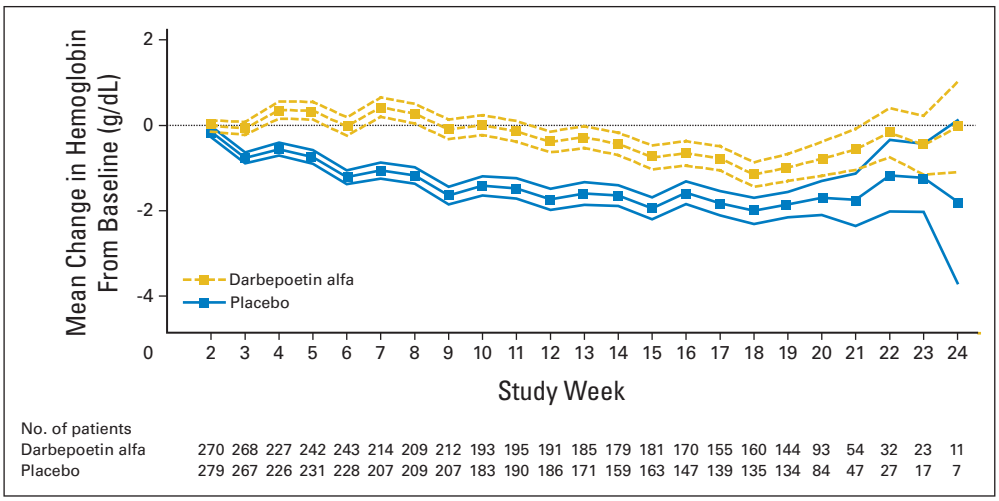

Fig 2. Changes in hemoglobin concentration throughout the study. Data represent mean values of hemoglobin (g/dL). Results exclude hemoglobin assessments within 28 days of a transfusion. Yellow squares indicate patients receiving darbepoetin alfa treatment, and blue squares indicate patients receiving placebo. Lines above and below the data points indicate upper and lower 95% confidence intervals, respectively.

Safety During the Treatment Period

The incidence of all adverse events reported during the treatment period was similar between the two treatment groups (Table 3). The incidence of each adverse event was generally similar between treatment groups with the exception of thrombocytopenia (darbepoetin alfa, 20%; placebo, 13%) and anemia (15% darbepoetin alfa, 29% placebo). The most common adverse events were consistent with a population of SCLC patients receiving chemotherapy and included nausea (darbepoetin alfa, 44%; placebo, 41%), neutropenia (darbepoetin alfa, 37%; placebo, 32%), vomiting (darbepoetin alfa, 29%; placebo, 33%), and alopecia (darbepoetin alfa, 23%; placebo, 23%).

The incidence of all serious adverse events was slightly higher in the darbepoetin alfa group (46%) compared with the placebo group (41%). The most common serious adverse events were febrile neutropenia (darbepoetin alfa, 3%; placebo, 5%), neutropenia (darbepoetin alfa, 3%; placebo, 4%), thrombocytopenia (darbepoetin alfa, 3%; placebo, 1%), fatigue (darbepoetin alfa, 3%; placebo, 1%), pneumonia (darbepoetin alfa, 3%; placebo, 2%), and vomiting (darbepoetin alfa, 2%; placebo, 3%).

Treatment-related serious adverse events were reported for six patients in the darbepoetin alfa group (one staphylococcal infection, one ischemic stroke, one thrombosis, and three patients with pulmonary embolism) and two patients in the placebo group (one patient with vomiting and one with cerebral ischemia, convulsion, and loss of consciousness).

Of adverse events of interest, cardiovascular/thromboembolic adverse events occurred at a marginally statistically significant higher rate in the darbepoetin alfa group (65 [22%] of 301 patients) than in the placebo group (43 [15%] of 296 patients) primarily due to a higher incidence of embolisms/thromboses in the darbepoetin alfa group (Table 3).

Fifty-three patients (18%) in the darbepoetin alfa group and 48 patients (16%) in the placebo group died during the treatment period or within 30 days after the last dose of investigational product (Table 3). Deaths considered associated with fatal adverse events were reported for 48 patients (16%) in the darbepoetin alfa group and 43 patients (15%) in the placebo group. The cause of death for the 10 patients who did not have fatal adverse events was progressive disease (three darbepoetin alfa, four placebo) and unspecified reasons (two darbepoetin alfa, one placebo). There were two deaths in the darbepoetin alfa group that were considered by the investigator to be possibly related to treatment: one patient with pulmonary embolism and one with ischemic stroke. Deaths due to cardiovascular/thromboembolic events were similar between the treatment groups (darbepoetin alfa, 4%; placebo, 3%).

Across both treatment groups, 574 patients (96%) had a predose antibody result and 516 patients (86%) had one or more postdose results. No sample tested positive for neutralizing antibodies to darbepoetin alfa.

Table 2. Survival

Parameter	Darbepoetin Alfa (n = 298) KM Median	Darbepoetin Alfa (n = 298) 95% CI	Placebo (n = 298) KM Median	Placebo (n = 298) 95% CI	*P* for Treatment Comparison Darbepoetin Alfa *v* Placebo*	HR†	95% CI
Overall survival, weeks	40	37 to 44	40	37 to 43	.434	0.93	0.78 to 1.11
Progression-free survival, weeks	24	23 to 25	24	24 to 26	.817	1.02	0.86 to 1.21
Time to progression or death due to progression, weeks	25	24 to 27	25	24 to 27	.765	1.03	0.86 to 1.23

NOTE. Cut-off date was February 22, 2007.
Abbreviations: KM, Kaplan-Meier stratified by treatment; HR, hazard ratio.
**P* value calculated from stratified log-rank test stratified by baseline Eastern Cooperative Oncology Group and baseline lactate dehydrogenase.
†HR (darbepoetin alfa *v* placebo, 95% CI) calculated from a stratified Cox proportional hazards regression model.

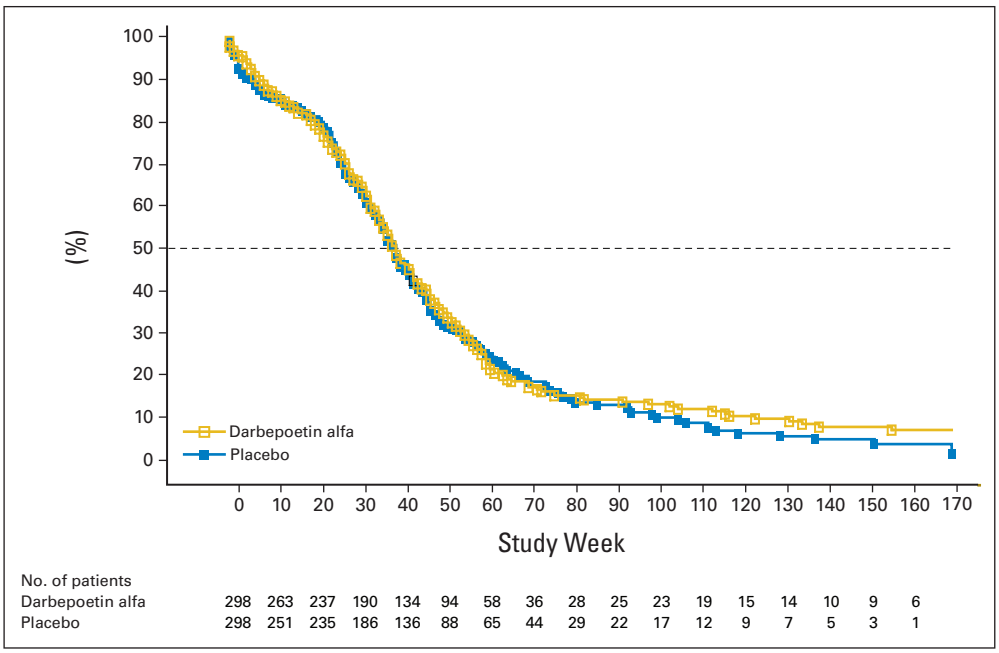

Fig 3. Kaplan-Meier curves of overall survival. Yellow squares indicate patients receiving darbepoetin alfa treatment, and blue squares indicate patients receiving placebo.

Other Efficacy End Points

The unadjusted Kaplan-Meier curves for time to first transfusion are shown in Figure A1 (online only). A total of 52 patients (17%; 95% CI, 13.3 to 22.2) in the darbepoetin alfa group and 116 patients (39%; 95% CI, 33.4 to 44.7) in the placebo group had at least one transfusion during the treatment phase. The risk of receiving a transfusion was significantly lower in the darbepoetin alfa group compared with the placebo group (HR, 0.40; 95% CI, 0.29 to 0.55).

The mean change in FACT-F subscale score from baseline to the end of treatment was approximately two-fold higher in the darbepoetin alfa versus placebo group (Table 4) with an estimated difference of 0.86 points (95% CI, −1.16 to 2.88).

Exposure to Study Drugs

The mean number of doses administered was 9.4 (standard deviation [SD], 4.8) in the darbepoetin alfa group and 12.8 (SD, 6.0) in the placebo group. The average mean weekly dose in the darbepoetin alfa group was 195.2 μg (SD, 66.6). Thirty-nine percent of patients in the darbepoetin alfa group and 5% in the placebo group had $\geq$ 1 dose withheld because their hemoglobin increased to $\geq$ 14g/dL.

Six cycles of chemotherapy were received by 62% and 59% of patients in the darbepoetin alfa and placebo groups, respectively. The mean weekly doses of chemotherapy in the darbepoetin alfa versus placebo groups were: 153 (SD, 32) versus 153 mg/wk (SD, 34) for etoposide; 151 (SD, 41) versus 156 mg/wk (SD, 39) for carboplatin; and 42 (SD, 8) versus 43 mg/wk (SD, 8) for cisplatin.

DISCUSSION

This placebo-controlled, double-blind, randomized, phase III study evaluated the safety and efficacy of darbepoetin alfa to treat previously untreated, extensive-stage SCLC patients receiving platinum-based chemotherapy. The study achieved one of its two coprimary end points: darbepoetin alfa maintained significantly higher hemoglobin concentrations compared with placebo, even though hemoglobin concentrations fell due to the myelosuppressive nature of the chemotherapy. Darbepoetin alfa also significantly reduced the risk of receiving a transfusion but did not improve FACT-F scores in these patients. The latter observation may not be unexpected given the relatively higher mean hemoglobin concentration at entry to this trial. In contrast, the previous trial in lung cancer reported by Vansteenkiste et al[5] did demonstrate an improvement in FACT-F scores in patients receiving darbepoetin alfa compared with placebo.

The second coprimary end point of superiority of darbepoetin alfa versus placebo for overall survival was not achieved: there was no statistically significant difference in overall survival between the two groups (HR, 0.93; 95% CI, 0.78 to 1.11). However, the upper limit of the 95% CI excludes an increase in risk of $\geq$ 11% for patients receiving darbepoetin alfa. There was also no statistically significant difference in progression-free survival and time to disease progression. These data are concordant with a number of other survival studies in CIA patients, in which there was no negative impact of ESAs on survival-related outcomes.[8-10] In addition, three recent meta-analyses of published trials did not demonstrate reduced survival outcomes in CIA patients treated with ESAs.[11-13]

Adverse events reported during the treatment period (nausea, neutropenia, vomiting, and alopecia) were as expected for patients receiving first-line platinum-containing chemotherapy. The incidence of cardiovascular/thromboembolic events was marginally statistically significantly higher in the darbepoetin alfa group ($P = .0495$); however, the incidence in both groups was as expected and is consistent with that reported in meta-analyses and the prescribing information for darbepoetin alfa.[3,11-13]

Table 3. Summary of Adverse Events (safety analysis set)

Adverse Event	Darbepoetin Alfa (n = 301)* No.	%	Placebo (n = 296)* No.	%
All	288	96	289	98
Severe, life-threatening, or fatal	181	60	169	57
Serious	138	46	121	41
Treatment related	15	5	16	5
Severe, life-threatening, or fatal	6	2	1	0
Serious	6	2	2	1
Adverse events of interest	131	44	113	38
Cardiovascular and thromboembolic adverse events†‡	65	22	43	15
Arrhythmia	15	5	14	5
Cerebrovascular accidents	14	5	9	3
Congestive heart failure	7	2	10	3
Myocardial infarction/coronary artery disorders	9	3	4	1
Embolism/thrombosis (arterial and venous)	26	9	15	5
Seizure	4	1	9	3
Hypertension	18	6	15	5
Pure red cell aplasia	0	0	0	0
Immune system disorder	0	0	1	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	58	19	50	17
Discontinuation due to adverse events§	12	4	10	3
Deaths on study (any reason)‖	53	18	48	16

*Two patients randomly assigned to the placebo group received one dose of darbepoetin alfa each in error and were therefore analyzed in the darbepoetin alfa group.
†A patient may have had an event in more than one subcategory.
‡The analysis of incidence of cardiovascular/thromboembolic events based on the stratified Cox model reported a *P* for treatment effect of .0495 and the HR of 1.47 (95% CI, 1.00 to 2.16).
§Includes disease progression and excludes death.
‖Deaths during treatment period or 30 days after the last dose of investigational product.

This study was initiated in 2002, after results from a similarly designed phase III study showed a trend toward improved survival in patients with lung cancer.[5] At that time, the oncology community theorized that tumor oxygenation resulting from increased hemoglobin levels might improve tumor response to chemotherapy and radiation therapy. Therefore, dose withholding in the present study occurred at relatively high hemoglobin levels (≥14g/dL), 2g/dL higher than indicated by the current US Food and Drug Administration-approved product label.[3] Also, darbepoetin alfa treatment was initiated using higher hemoglobin entry critiera (> 9g/dL and < 13g/dL) than in most studies in CIA where treatment is generally initiated when hemoglobin is ≤ 11g/dL.

Despite high hemoglobin concentrations for treatment initiation and dose withholding, there was no adverse impact on outcome in our study. Studies in CIA that used similar hemoglobin concentrations at treatment initiation and dose withholding have yielded conflicting results on survival outcomes: in two studies in women with metastatic breast cancer receiving chemotherapy, one reported negative survival outcomes in the ESA-treated arm,[14] whereas the other reported neutral survival outcomes.[10] In addition, results from a number of other studies have generated concerns relating to decreased survival with ESA use. However, they were in unapproved indications that used ESAs to increase hemoglobin levels higher (up to 15.5g/dL) than those recommended in product labels, to normalize hemoglobin during radiation therapy treatment, or to treat anemia in patients not receiving chemotherapy or radiation therapy.[15-18]

Higher doses of ESAs have also been suggested as potentially causative in adverse outcomes. In the front-loading phase of this study, approximately twice the currently recommended weekly dose of darbepoetin alfa was administered. The average weekly dose of approximately 190 μg is the highest average dose administered in a darbepoetin alfa study in oncology to date; however, there was no adverse impact on the incidence of thromboembolic events, survival, and disease progression.

This study also provides some important data with respect to the speculated role of the erythropoietin receptor (EpoR) in survival outcomes. EpoR has been reported to be expressed in a number of tumor types including SCLC,[19,20] and those observations have been cited as a potential mechanistic explanation for the adverse survival outcomes reported in some studies. It is important to note, however, that the reagents used to identify EpoR have been shown to be nonspecific and unsuitable for immunohistochemstry.[21-25] There was no significant difference in time to disease progression/death due to progression between the two treatment groups in our study; thus, even if the EpoR was expressed in SCLC, our results suggest that it plays no role in tumor growth. This is in line with several other reports that have not observed increased disease progression when using ESAs to treat patients with CIA.[8,10,14,26-28]

The results of our study could not confirm the initial hypothesis of improved survival when using ESAs to treat anemia in SCLC patients receiving platinum-based chemotherapy. However, they are directly relevant to the current debate on ESA safety given the

Table 4. FACT-F Subscale Scores

Parameter	Darbepoetin Alfa (n = 249) No.	Mean	SE	Placebo (n = 240) No.	Mean	SE
Baseline FACT-F subscale score	249	30.60	0.72	240	30.50	0.73
FACT-F subscale score at EOT*	245	32.14	0.75	239	31.24	0.82
Change in FACT-F score from BL to EOT*	245	1.50	0.84	239	0.70	0.86

Abbreviations: FACT-F, Functional Assessment of Cancer Therapy-Fatigue; EOT, end of treatment; BL, baseline.
*Occurred 8 weeks after a patient received the last dose of on-study chemotherapy.

high baseline hemoglobin levels observed, the high hemoglobin-target level employed, and the high-doses of darbepoetin alfa administered. Overall, these data add to the growing body of evidence on ESA safety and reinforce the neutral impact of ESAs on survival in patients with CIA. We believe that darbepoetin alfa is safe and effective when used in approved patient populations in accordance with US Food and Drug Administration and EMEA dosing recommendations. A number of prospectively designed studies are either underway or planned as efforts continue to evaluate long-term survival in anemic cancer patients treated with darbepoetin alfa.

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 Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Irene Ferreira, Amgen Inc (U); Tom Lillie, Amgen (U) **Consultant or Advisory Role:** Robert Pirker, Amgen (C), Roche (C); Rodryg A. Ramlau, Amgen Inc (U) **Stock Ownership:** Irene Ferreira, Amgen; Tom Lillie, Amgen **Honoraria:** Robert Pirker, Amgen, Roche **Research Funding:** Johan F. Vansteenkiste, Amgen **Expert Testimony:** None **Other Remuneration:** None

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

