Darbepoetin alfa 300 or 500 μg once every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia

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This study evaluated efficacy and safety of darbepoetin alfa administered every 3 weeks (Q3W) at fixed doses of 300 or 500 μg with or without intravenous (IV) iron in treating anemia in patients receiving multicycle chemotherapy. This Phase 2, double-blind, 2 × 2 factorial study randomized patients to one of four treatment arms; darbepoetin alfa 300 μg ($n = 62$), darbepoetin alfa 300 μg plus IV iron ($n = 60$), darbepoetin alfa 500 μg ($n = 60$), or darbepoetin alfa 500 μg plus IV iron ($n = 60$). Patients had nonmyeloid malignancies, hemoglobin levels $\leq$10 g dL^{-1}, and no iron deficiency. Primary endpoint was achievement of target hemoglobin ($\geq$11 g dL^{-1}). Secondary endpoints included incidence of transfusions and change in Functional Assessment of Cancer Therapy Fatigue (FACT-F) score from baseline to end of study. Safety was evaluated by incidence of adverse events. No evidence of a statistically significant interaction between darbepoetin alfa dose received and IV iron usage was observed, therefore, results are provided separately comparing darbepoetin alfa doses and comparing IV iron usage groups. Similar proportions of patients receiving darbepoetin alfa 300 or 500 μg achieved target hemoglobin (75 and 78%, respectively); Kaplan–Meier median time to target hemoglobin was 10 and 8 weeks, respectively. More patients receiving IV iron (82%) than not receiving IV iron (72%) achieved hemoglobin target. Adverse events profiles were similar for darbepoetin alfa treatment groups. Transient anaphylactoid reactions were reported in two patients receiving IV iron. Darbepoetin alfa at 300 μg Q3W and 500 μg Q3W showed similar benefit, while added IV iron improved treatment response in these patients. Am. J. Hematol. 85:655–663, 2010. © **2010 Wiley-Liss, Inc.**

Introduction

Darbepoetin alfa is an erythropoiesis-stimulating agent (ESA) used in standard clinical practice for improving hemoglobin levels and reducing red blood cell (RBC) transfusions in patients with chemotherapy-induced anemia (CIA). The recommended starting dose for darbepoetin alfa is 2.25 μg kg^{-1} weekly (QW) or 500 μg every 3 weeks (Q3W) in both the US and Europe [1,2]. Also, darbepoetin alfa at a fixed dose of 300 μg Q3W may be an effective strategy for the treatment of CIA in some patients [3,4]. Further investigation is warranted to determine the lowest darbepoetin alfa dose levels for use in patients to avoid RBC transfusions. This is the first trial comparing the efficacy of darbepoetin alfa at doses of 300 μg versus 500 μg.

In the CIA setting, 50–70% of patients respond to treatment with ESAs as measured by increased hemoglobin levels or decreased RBC transfusion requirements [5–10]. Some patients may have absolute iron deficiency (low iron stores) or functional iron deficiency (normal iron stores with suboptimal iron mobilization) that may contribute to decreased response to ESA treatment [11]. Further, patients who are not iron deficient can develop iron deficiency when they start receiving ESA therapy [12]. ESA labels recommend evaluation of iron status before and during treatment with ESAs and recommend iron supplementation for correction of iron deficiency (serum ferritin levels $<$100 ng mL^{-1} or serum transferrin saturation [Tsat] $<$ 20%) [1,2,13]. The American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) guidelines also recommend iron supplementation in cancer patients with low iron stores receiving ESA therapy [1,2,13–15]. In addition, the National Comprehensive Cancer Network (NCCN) guidelines now recommend intravenous (IV) iron supplementation with low molecular weight (LMW) iron dextran for CIA patients with functional iron deficiency [16].

Several studies have shown that IV iron supplementation during ESA therapy in the CIA setting is well tolerated and increases treatment response [17–21]. In a Phase 3 study in CIA patients receiving darbepoetin alfa 500 μg Q3W, IV iron administered as iron-sucrose increased the hematopoietic response rate (proportion of patients achieving hemoglobin $\geq$12 g dL^{-1} or hemoglobin increase of $\geq$2 g dL^{-1}) and lowered incidence of RBC transfusions [18]. This was the first study to show a statistically significant reduction in RBC transfusion needs for ESA-treated patients receiving IV iron versus ESA-treated patients not receiving IV iron (9% vs. 20%, $P = 0.005$). Iron-sucrose-related adverse events, mostly gastrointestinal in nature, occurred in 3% of patients in the IV iron-treated group. Such gastrointestinal events are rare with LMW iron dextran [22,23]. In another CIA study, a higher proportion of patients receiving darbepoetin alfa with IV iron achieved hematopoietic response than those receiving darbepoetin alfa without IV iron [21]. That study excluded patients with absolute and functional iron deficiency by requiring serum ferritin levels $\geq$100 ng mL^{-1} and Tsat $\geq$20%. In a study of anemic patients with lymphoproliferative malignancies and positive marrow hemosiderin receiving an ESA but not receiving chemother-

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apy (anemia of cancer) [19], increased mean hemoglobin was reported in patients receiving IV iron compared with patients not receiving IV iron.

The administration route of the supplemented iron appears to be important, as demonstrated by greater increases in hemoglobin levels in cancer patients receiving an ESA in combination with IV iron administered either as an IV bolus or total dose infusion compared with patients receiving an ESA with oral iron [17,20]. The important issue of long-term effects of IV iron in combination with an ESA on overall survival and/or disease progression in patients without iron deficiency has not been well studied. However, in a recent study of 127 anemic autologous stem cell transplant patients who received darbepoetin alfa with or without IV iron, no increase in recurrence or decreased survival was seen in the IV iron arm for up to 5 years [24].

This Phase 2 study evaluated the efficacy and safety of darbepoetin alfa administered Q3W at a fixed dose of 300 or 500 μg with or without IV iron in treating anemia in patients with nonmyeloid malignancies receiving multicycle chemotherapy and hemoglobin levels $\leq$10 g dL^{-1}, without iron deficiency.

Methods

Participants. This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines. The institutional review boards of the participating medical centers approved the protocols and all patients gave written informed consent before any study-related procedures were performed.

Eligible patients ($\geq$18 years of age at screening) had active nonmyeloid malignancies, anemia (screening hemoglobin $\leq$10 g dL^{-1}) related to cancer and chemotherapy, $\geq$8 additional weeks of planned chemotherapy, adequate renal and liver function, and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were excluded if they had absolute iron deficiency (Tsat <15% and serum ferritin <10 ng mL^{-1}) at screening or had any known sensitivity to iron administration, history of a hematologic disorder that could cause anemia (other than a nonmyeloid malignancy), unstable or uncontrolled cardiac disease, history of deep vein thrombosis within 6 months prior to screening, and RBC transfusions or erythropoietic therapy or myeloablative radiation therapy within 28 days before randomization and/or screening.

Study drugs. Darbepoetin alfa (Aranesp®, Amgen, Thousand Oaks, CA) was supplied in 1-mL single-dose vials as a clear, colorless, sterile protein solution. In the US, IV iron (provided as INFeD®, Watson Pharma, Morristown, NJ) was supplied by a central pharmacy, Coram Rx (Malvern, PA). In Europe, IV iron (provided as Cosmofer®, Pharmacosmos, Denmark) was supplied via a central interactive voice response system (IVRS). Iron was supplied as a dark brown, slightly viscous sterile liquid in amber vials. Each 1 mL contained the equivalent of 50 mg of elemental iron (as a dextran complex in ferric hydroxide) and ~0.9% sodium chloride in water for injection.

Study design. This was a Phase 2, double-blind, multicenter, 2 × 2 factorial study. The two study factors were dose of darbepoetin alfa (500 μg Q3W versus 300 μg Q3W) and IV iron usage (IV iron versus no IV iron). The study was blinded to the dose of darbepoetin alfa administered and open-label for IV iron administration.

A randomization list was created and maintained by an independent randomization group at the study sponsor using permuted blocks. The randomization list was transmitted to an IVRS vendor for execution. Enrollment and randomization were done by telephone and confirmed by facsimile. Patients were assigned blinded boxes of study medication using box numbers, which were recorded and reconciled. The study was blinded while the study was ongoing and unblinded after all patients completed the study.

In the 15-week study period, the last doses of darbepoetin alfa and iron were given at Week 12, with an end-of-study evaluation 3 weeks after the last dose of study drugs. Eligible patients were randomized in a 1:1:1:1 ratio to one of four treatment arms; darbepoetin alfa 300 μg Q3W, darbepoetin alfa 500 μg Q3W, darbepoetin alfa 300 μg Q3W plus IV iron, and darbepoetin alfa 500 μg Q3W plus IV iron. Randomization was stratified by planned chemotherapy (platinum versus nonplatinum) and geographic region (North America versus Europe). Patients were enrolled from study sites in North America and Europe between December 18, 2006 and August 27, 2007, and the last patient ended the study on December 12, 2007.

Darbepoetin alfa 300 μg or 500 μg was administered Q3W subcutaneously, with no dose escalations allowed. Dose reductions for patients receiving darbepoetin alfa 300 μg Q3W or 500 μg Q3W were allowed as follows: the dose was reduced to 200 μg Q3W or 300 μg Q3W, respectively, if a patient had a hemoglobin level $\geq$12 g dL^{-1} with no other previous dose reductions or if a patient had a rapid rise in hemoglobin (defined as a > 1.5-g dL^{-1} increase in hemoglobin within 21 days). After a second rapid rise in hemoglobin, the darbepoetin alfa dose was reduced to 150 μg Q3W or 250 μg Q3W, respectively, and further reduced to 100 μg Q3W or 200 μg Q3W, respectively, after a third rapid rise in hemoglobin. Thereafter, darbepoetin alfa dose was withheld when a subsequent rapid rise in hemoglobin occurred. Darbepoetin alfa dose was also withheld if a hemoglobin threshold (defined as hemoglobin >13 g dL^{-1}) was reached, and was reinitiated when hemoglobin fell to <12 g dL^{-1}. Dose reduction and dose withholding rules did not apply if the patient had a RBC transfusion within 21 days prior to the next dosing visit.

An IV iron dose of 400 μg was administered over ~30 min after the darbepoetin alfa at each visit. Intravenous iron was given as planned even if the darbepoetin alfa dose was withheld; however, if at any study visit a patient's ferritin level exceeded 1000 ng mL^{-1}, iron supplementation was withheld until the next dosing visit. Intravenous iron could be reinstated at the next dosing visit if the patient's ferritin decreased to $\leq$800 ng mL^{-1}. Patients could receive oral iron if they were not randomized to IV iron treatment.

Endpoints. The primary endpoint was achievement of target hemoglobin ($\geq$11 g dL^{-1}) during the treatment period in the absence of any RBC transfusions in the preceding 28 days. Secondary endpoints included time to achieving target hemoglobin, change in hemoglobin from baseline to end of treatment period (EOTP), proportion of patients with a hematopoietic response (defined as either a 2-g dL^{-1} increase from baseline in hemoglobin or a hemoglobin correction to $\geq$12 g dL^{-1} in the absence of any RBC transfusions in the preceding 28 days), time to hematopoietic response, proportion of patients with $\geq$1 RBC transfusion and proportion of patients with $\geq$1 RBC transfusion or hemoglobin $\leq$8 g dL^{-1} without receiving a transfusion from Week 1 or Week 5 to end of study, change in Functional Assessment of Cancer Therapy Fatigue (FACT-F) subscale score from baseline to end of study, and time to a three-point change in FACT-F subscale score. Exploratory analyses examined efficacy outcomes stratified by baseline serum ferritin (<100 ng mL^{-1} or $\geq$100 ng mL^{-1}) or Tsat levels (< 19% or $\geq$19%).

Safety endpoints included incidence of adverse events, rapid rise in hemoglobin >1.5 g dL^{-1} in a 21-day window, hemoglobin increase >13 g dL^{-1}, and formation of neutralizing antibodies to darbepoetin alfa. Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA), and formation of antibodies to darbepoetin alfa was assessed at the beginning and end of the study.

Statistical analysis. This estimation study tested no formal hypothesis. All statistical analyses were performed using SAS statistical software version 8.2 (SAS Institute, Cary, NC). Baseline demographic and clinical characteristics were summarized by mean and standard deviation (SD) for continuous measures and number and percentage for categorical measures.

The primary efficacy endpoint of proportion of patients achieving target hemoglobin and secondary endpoints of proportion of patients achieving hematopoietic response, time to achieving target hemoglobin, time to hematopoietic response, and proportion receiving $\geq$1 RBC transfusion and proportion receiving $\geq$1 RBC transfusion or had hemoglobin $\leq$8 g dL^{-1} who were not transfused were summarized by both Kaplan–Meier (K-M) estimates and crude percentage with 95% confidence limits (CLs). Logistic regression analysis and Cox proportional hazards models were used to assess whether there was an interaction between darbepoetin alfa dose and IV iron use (stratified by planned chemotherapy type and geographic region). In the absence of evidence of an interaction ($P > 0.1$ for the treatment group by IV iron term), efficacy parameters were prespecified to be estimated by pooling across all patients who received 300 μg Q3W versus all patients who received 500 μg Q3W, regardless of whether patients received IV iron; and by pooling across darbepoetin alfa dose to estimate the effect of IV iron versus no IV iron. If the results showed that an interaction exists, then the factors were not to be pooled for analysis and estimates were to be provided for each of the four treatment arms.

Change in hemoglobin from baseline to EOTP was analyzed using both a last value carried forward (LVCF) imputation approach and an

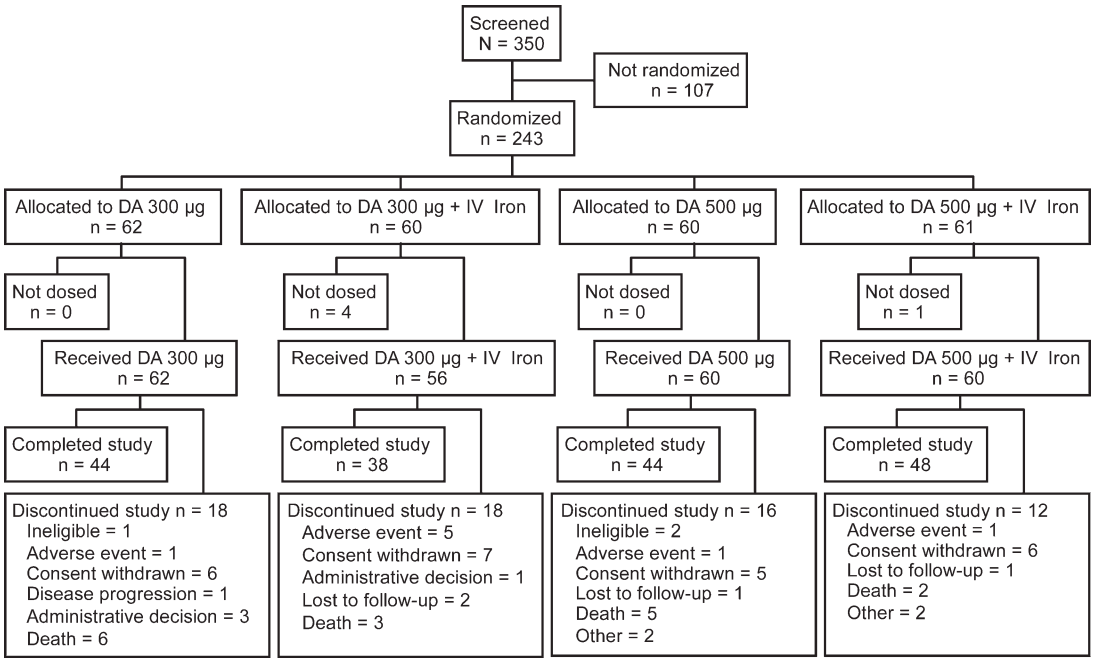

Figure 1. CONSORT diagram of patient flow in the study. DA = darbepoetin alfa; IV = intravenous.

available data approach (no imputation) and summarized using an analysis of covariance (ANCOVA) model. Change in FACT-F subscale score from baseline to EOTP was summarized by an ANCOVA model including randomization strata, treatment group, and baseline score. K–M estimates of the median time to a three-point change in the FACT-F subscale score was also summarized (with 95% rank-based CL).

Results

Participants

The 243 patients enrolled in the study were randomized to a treatment group (see Figure 1). Patients were enrolled from sites in the US ($n = 174$), Romania ($n = 38$), and Russia ($n = 31$). Four patients randomized to receive darbepoetin alfa 300 µg plus IV iron and one patient randomized to receive darbepoetin alfa 500 µg plus IV iron were not dosed. Sixty-four patients (26%) did not complete the study. The most common reasons for early discontinuation were consent withdrawal (10%) and death (7%). Demographics were similar among the treatment groups (Table I). Of the 238 patients dosed, 79% were white, 66% were female and mean age was about 62 years. The most common tumor types were gastrointestinal, breast, and lung. Mean baseline hemoglobin ranged from 9.3 to 9.4 g dL^{-1}, mean baseline serum ferritin levels ranged from 291.3 to 332.6 ng mL^{-1}, and mean baseline Tsat ranged from 25 to 27% among the treatment groups.

Efficacy evaluations

No evidence of a significant interaction between darbepoetin alfa dose received and IV iron usage was observed for the efficacy endpoints evaluated; target hemoglobin (primary efficacy endpoint, $P = 0.53$ by logistic regression model or 0.12 by Cox proportional hazards regression model), hematopoietic response ($P = 0.82$ by logistic regression model or 0.21 by Cox proportional hazards regression model), RBC transfusions ($P > 0.40$ by both logistic regression and Cox proportional hazards regression models), and mean change in FACT-F score ($P = 0.16$ by logistic regression or 0.23 by Cox proportional hazards regression models). Therefore, as prespecified in the statistical analysis plan, efficacy results were pooled and summarized for each of the darbepoetin alfa doses regardless of whether patients received IV iron; efficacy results were also pooled and summarized for IV iron versus no IV iron regardless of darbepoetin alfa dose received.

Similar proportions (K–M estimates) of patients achieved target hemoglobin ($\geq$11 g dL^{-1}) in the darbepoetin alfa 300 and 500 µg groups (75% [95% CL: 65%, 85%] and 78% [95% CL: 70%, 87%], respectively); however, analyzed by IV iron usage, a slightly higher proportion of patients in the IV iron group compared with the no IV iron group achieved target hemoglobin (82% [95% CL: 73%, 90%] versus 72% [95% CL: 62%, 82%]), (Figure 2A). Stratified by baseline serum ferritin level, a higher proportion of patients in the group with baseline serum ferritin $<$100 ng mL^{-1} receiving IV iron achieved target hemoglobin compared with patients in the other treatment groups (Figure 2B). Stratified by baseline Tsat levels, slightly higher proportions of patients with baseline Tsat either $<$ or $\geq$19% who received IV iron achieved target hemoglobin compared with those who did not receive IV iron (Figure 2C). K–M median (95% CL) time to target hemoglobin was 10 (7, 11) weeks in the darbepoetin alfa 300 µg group, 8 (6, 10) weeks in the darbepoetin alfa 500 µg group, 9 (7, 11) weeks in the no IV iron group, and 8 (5, 10) weeks in the IV iron group (see Figure 3).

The K–M proportion of patients achieving hematopoietic response was higher in the darbepoetin alfa 500 µg than the 300 µg group (76% [95% CL: 67%, 85%] versus 69% [95% CL: 59%, 78%]) and higher in the IV iron than the no IV iron group (82% [95% CL: 74%, 90%] versus 63% [95% CL: 53%, 73%]), (Figure 4A). For patients not receiving IV iron supplementation, a substantially higher proportion of patients in the group with baseline serum ferritin $\geq$100 ng mL^{-1} versus the group with baseline serum ferritin $<$100 ng mL^{-1} achieved a hematopoietic response (67% [95% CL: 55%, 79%] versus 22% [95% CL: 7%, 56%]), (Figure 3B). For the groups with baseline serum ferritin $<$100 ng mL^{-1}, a substantially higher proportion of patients receiving IV iron achieved hematopoietic response compared with patients not receiving IV iron (100% [95% CL: not calculable] versus 22% [95% CL: 7%, 56%]), (Figure 4B). For the groups with baseline serum ferritin $\geq$100 ng mL^{-1}, still a

TABLE I. Baseline Demographic and Clinical Characteristics by Darbepoetin Alfa Dose and by IV Iron

	Darbepoetin alfa 300 μg Q3W	Darbepoetin alfa 500 μg Q3W	No IV iron	IV iron
	n = 118	*n* = 120	*n* = 122	*n* = 116
Sex, *n* (%)				
Female	78 (66)	80 (67)	77 (63)	81 (70)
Male	40 (34)	40 (33)	45 (37)	35 (30)
Race, *n* (%)				
White	93 (79)	96 (80)	98 (80)	91 (78)
Black	12 (10)	20 (17)	14 (11)	18 (16)
Hispanic	9 (8)	4 (3)	8 (7)	5 (4)
Other	4 (3)	0 (0)	2 (2)	2 (2)
Age, years				
Mean (SD)	61.7 (13)	64.5 (13)	64.4 (13)	61.8 (13)
Min, Max	27, 97	32, 93	35, 97	27, 93
≥65, *n* (%)	48 (41)	67 (56)	63 (52)	52 (45)
Primary tumor type, *n* (%)				
Gastrointestinal	26 (22)	29 (24)	34 (28)	21 (18)
Breast	25 (21)	15 (13)	21 (17)	19 (16)
Lung	31 (26)	32 (27)	34 (28)	29 (25)
Gynecologic	17 (14)	16 (13)	13 (11)	20 (17)
Genitourinary	7 (6)	2 (2)	2 (2)	7 (6)
Leukemia[a]	2 (2)	3 (3)	3 (2)	2 (2)
Lymphoma/myeloma[b]	5 (4)	14 (12)	12 (10)	7 (6)
Other[c]	5 (4)	9 (8)	3 (2)	11 (9)
Disease stage[d], *n* (%), [*n*]				
I/II	17 (15) [113]	17 (15) [111]	25 (22) [115]	9 (8) [109]
III	39 (35) [113]	39 (35) [111]	43 (37) [115]	35 (32) [109]
IV	51 (45) [113]	47 (42) [111]	40 (35) [115]	58 (53) [109]
Unknown	6 (5) [113]	8 (7) [111]	7 (6) [115]	7 (6) [109]
Disease stage for SCLC, *n* (%), [*n*]				
Limited	3 (60) [5]	5 (56) [9]	4 (57) [7]	4 (57) [7]
Extensive	2 (40) [5]	4 (44) [9]	3 (43) [7]	3 (43) [7]
Patients with any prior chemotherapy, *n* (%)	118 (100)	117 (98)	120 (99)	115 (98)
Platinum	63 (53)	64 (53)	60 (50)	67 (57)
Taxane	36 (31)	34 (28)	37 (31)	33 (28)
Anthracycline	16 (14)	17 (14)	18 (15)	15 (13)
Alkylating agents	22 (19)	23 (19)	24 (20)	21 (18)
Topoisomerase 1 inhibitors	8 (7)	7 (6)	7 (6)	8 (7)
Topoisomerase 2 inhibitors	8 (7)	12 (10)	12 (10)	8 (7)
Alkaloids	11 (9)	22 (18)	19 (16)	14 (12)
Antimetabolites	45 (38)	45 (38)	42 (35)	48 (41)
Monoclonal antibodies	19 (16)	21 (18)	21 (17)	19 (16)
Hormonal therapy	3 (3)	7 (6)	2 (2)	8 (7)
Glucocorticoids	28 (24)	42 (35)	36 (30)	34 (29)
Antineoplastic antibiotics	2 (2)	3 (3)	2 (2)	3 (3)
Other chemotherapy	23 (19)	21 (18)	21 (17)	23 (20)
ECOG status at screening[e], *n* (%)				
0	32 (27)	25 (21)	30 (25)	27 (23)
1	68 (58)	81 (68)	75 (61)	74 (64)
2	11 (9)	12 (10)	10 (8)	13 (11)
Unknown	7 (6)	2 (2)	7 (6)	2 (2)
Baseline hemoglobin[f] (g dL^{-1})				
Mean (SD)	9.4 (1.0)	9.3 (1.1)	9.4 (1.0)	9.3 (1.0)
Baseline hemoglobin category, *n* (%)				
<10 g dL^{-1}	88 (75)	92 (77)	93 (76)	87 (75)
≥10 g dL^{-1}	30 (25)	28 (23)	29 (24)	29 (25)
Serum ferritin (ng mL^{-1})				
Mean (SD) [*n*]	291.3 (240.0) [86]	332.3 (231.9) [92]	322.6 (253.7) [92]	301.8 (216.6) [86]
Tsat, %				
Mean (SD) [*n*]	27.4 (17.8) [118]	25.1 (17.4) [118]	25.5 (17.0) [121]	27.0 (18.3) [115]
Serum erythropoietin (mU mL^{-1})[g]				
Mean (SD) [*n*]	100.1 (154.1) [118]	82.8 (131.3) [119]	90.3 (145.3) [121]	92.5 (141.2) [116]
Baseline FACT-F score				
Mean (SD) [*n*]	29.3 (12.3) [118]	29.4 (11.9) [116]	29.5 (12.2) [119]	29.2 (12.0) [115]

SD = standard deviation; CL = confidence limit; SCLC = small cell lung cancer; ECOG = Eastern Cooperative Oncology Group; FACT-F = Functional Assessment of Cancer Therapy Fatigue; Tsat = transferrin saturation; IV = intravenous; Q3W = every three weeks.

[a] Includes chronic lymphocytic leukemia and acute lymphocytic leukemia.

[b] Includes Hodgkin's disease, non-Hodgkin lymphoma, other lymphoma, and multiple myeloma.

[c] May include bone sarcoma, soft tissue sarcoma, melanoma, and head and neck cancer.

[d] Disease stage for all patients except patients with SCLC.

[e] Denominator for calculating percentages is based on number of patients in the study at that visit.

[f] Last available hemoglobin measurement in the absence of any RBC transfusion within 28 days, from 7 days prior to study Day 1 through study Day 1.

[g] One patient in the darbepoetin alfa 500 μg without IV iron group had a recorded baseline serum erythropoietin of 10,400 mU mL^{-1} that was deemed a data error as it is not a possible value consistent with human life. This patient was excluded from the summary.

higher proportion of patients receiving IV iron achieved hematopoietic response compared with patients not receiving IV iron (75% [95% CL: 63%, 85%] versus 67% [95% CL: 55%, 79%]), (Figure 4B). Stratified by baseline Tsat levels, slightly higher proportions of patients in the IV iron groups versus the no IV iron groups achieved hematopoietic response regardless if baseline Tsat levels were <19% or ≥19% (Figure 3C). The K-M median (95% CL) time to hematopoietic response was 11 (8, 12) weeks in the darbepoetin alfa 300 μg group versus 9 (8, 10) weeks in the

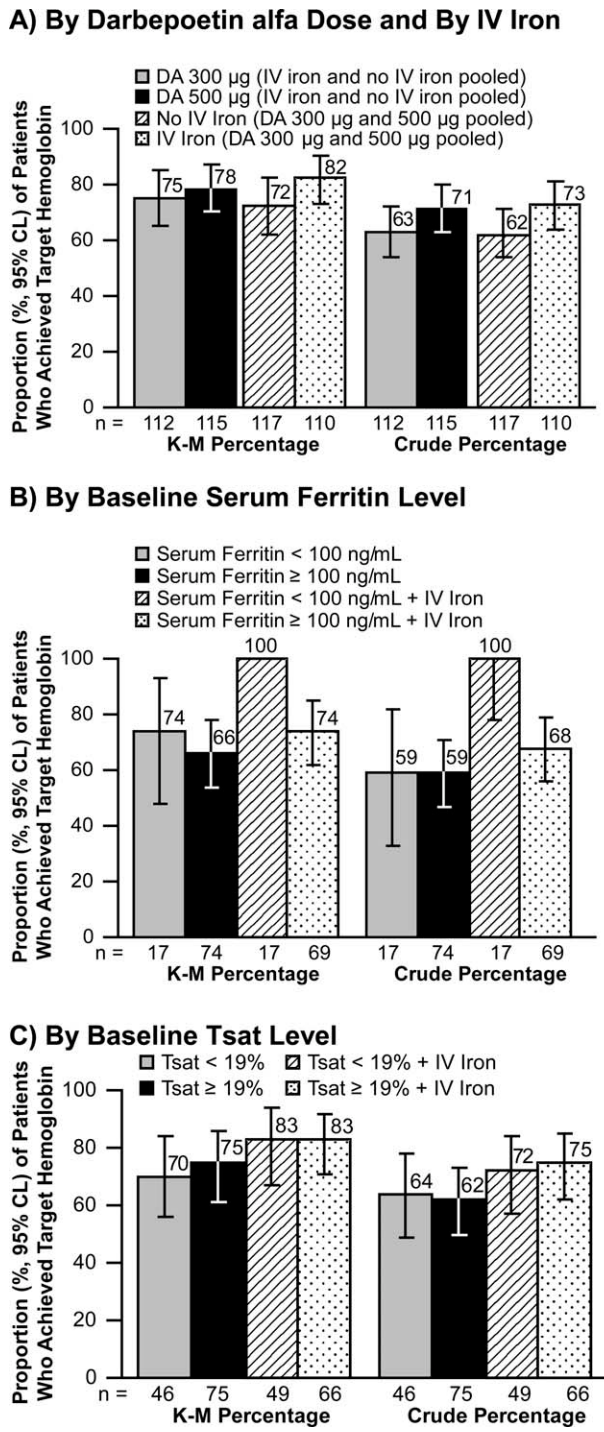

Figure 2. Target hemoglobin. Proportion of patients achieving target hemoglobin stratified by (A) darbepoetin alfa dose and receipt of IV iron; (B) baseline serum ferritin; and (C) baseline Tsat. Bars represent 95% CL. DA = darbepoetin alfa; K–M = Kaplan–Meier; IV = intravenous; Tsat = transferrin saturation; CL = confidence limits.

darbepoetin alfa 500 µg group; and 12 (10, 15) weeks in the no IV iron group versus 8 (7, 9) weeks in the IV iron group (see Figure 5).

Mean change in hemoglobin from baseline to EOTP was similar in the two darbepoetin alfa dose groups and was slightly higher in the IV iron than the no IV iron group (Table II). Mean hemoglobin after achieving target was similar in the two darbepoetin alfa dose groups; and was slightly higher in the IV iron group than the no IV iron group (Table II).

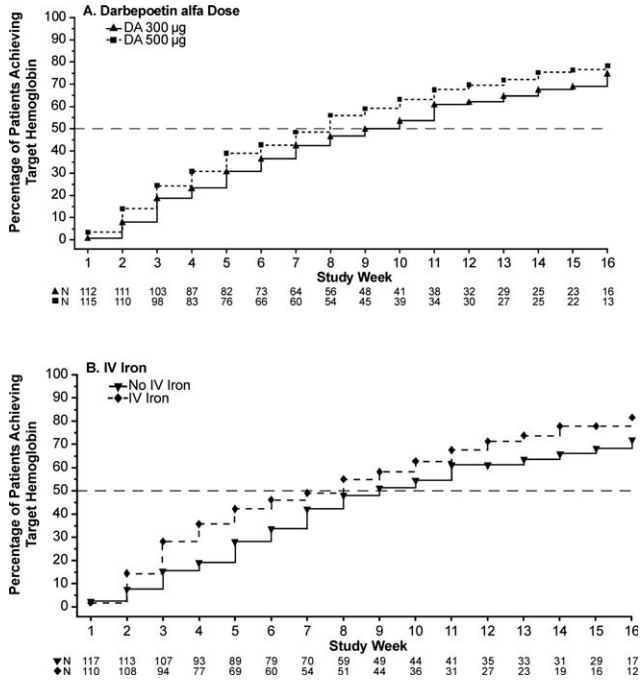

Figure 3. Kaplan–Meier time to target hemoglobin. Proportion of patients achieving target hemoglobin stratified by (A) darbepoetin alfa dose and (B) IV Iron usage. DA = darbepoetin alfa; IV = intravenous.

The K–M proportion (95% CL) of patients with ≥1 RBC transfusion (or hemoglobin ≤8 g dL^{-1} without receiving a transfusion) from Week 1 to end of study was 40% (30%, 49%) and 36% (27%, 49%) in the darbepoetin alfa 300 and 500 µg groups, respectively; and 40% (31%, 49%) and 36% (27%, 44%) in the no IV iron and IV iron groups, respectively (Table III). The proportion of patients with ≥1 RBC transfusion (or hemoglobin ≤8 g dL^{-1} without receiving a transfusion) from Week 5 to end of study was similar in the two darbepoetin alfa dose groups and the two IV iron usage groups (Table III). Excluding patients who had hemoglobin ≤8 g dL^{-1} without receiving a transfusion, the proportion of patients with ≥1 RBC transfusion from Week 1 to end of study and from Week 5 to end of study was similar in the two darbepoetin alfa dose groups and the two IV iron usage groups (Table III).

Mean change from baseline to end of study (95% CL) in serum ferritin was 309.9 (183.0, 436.7) and 271.1 (170.6, 371.6) ng mL^{-1} in patients receiving darbepoetin alfa 300 and 500 µg, respectively, and 49.8 (−48.7, 148.29) and 538.9 (434.5, 643.3) ng mL^{-1} in patients with no IV iron and with IV iron, respectively. Mean change in Tsat from baseline to end of study (95% CL) was 1.8 (−2.6, 6.2) and 4.4 (0.4, 8.4) percent in patients receiving darbepoetin alfa 300 and 500 µg, respectively, and −0.4 (−4.3, 3.5) and 6.7 (2.2, 11.2) in patients with no IV iron and with IV iron, respectively.

Least squares mean [95% CL] change in FACT-F score from baseline to EOTP was higher in the darbepoetin alfa 300 µg group than the darbepoetin alfa 500 µg group (3.7 [1.6, 5.7] versus 1.1 [−1.0, 3.2]); and higher in the IV iron group than the no IV iron group (3.3 [1.3, 5.4] versus 1.5 [−0.6, 3.5]). The K–M proportion (95% CL) of patients who had a clinically significant (≥3 points [25]) increase in FACT-F score was 100% (100%, 100%) for the darbepoetin alfa 300 µg group, 64% (55%, 73%) for the darbepoetin alfa 500 µg group; and 66% (57%, 75%) for the no IV iron group and 100% (100%, 100%) for the IV iron group. K–M median (95% CL) time to three-point increase in FACT-F

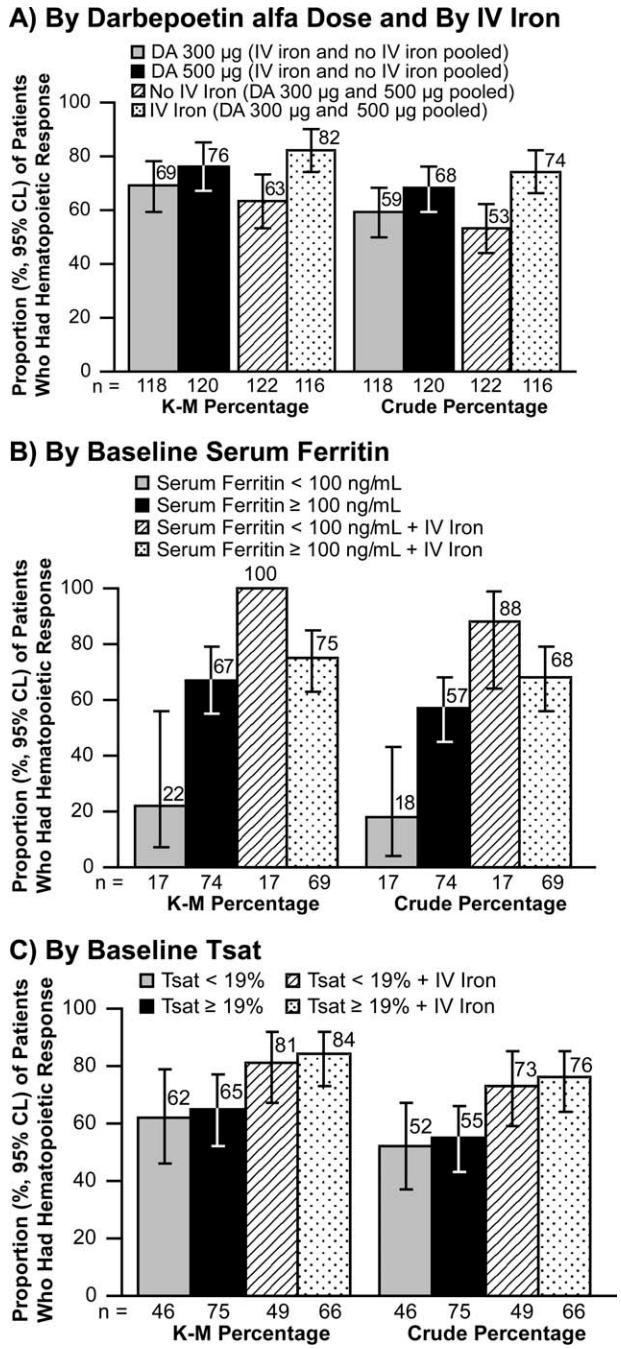

Figure 4. Hematopoietic response. Proportion of patients achieving a hematopietic response stratified by (A) darbepoetin alfa use and receipt of IV iron, (B) baseline serum ferritin, and (C) baseline Tsat. Bars represent 95% CL. DA = darbepoetin alfa; K–M = Kaplan-Meier; IV = intravenous; Tsat = transferrin saturation; CL = confidence limits.

score from baseline to EOTP was similar for the darbepoetin alfa treatment groups; 7 (4, 10) weeks for the darbepoetin alfa 300 µg group and 7 (6, 10) weeks for the darbepoetin alfa 500 µg group. This was shorter in the IV iron group than the no IV iron group; 7 (4, 7) weeks versus 10 (7, 10) weeks.

Safety evaluations

Patients were dosed with darbepoetin alfa for similar periods (11.1 weeks, darbepoetin alfa 300 µg; 11.3 weeks darbepoetin alfa 500 µg) and the mean (SD) average weekly doses were 88.7 (16.6) µg for the darbepoetin alfa 300 µg group and 136.5 (33.9) µg for the 500 µg group. For patients

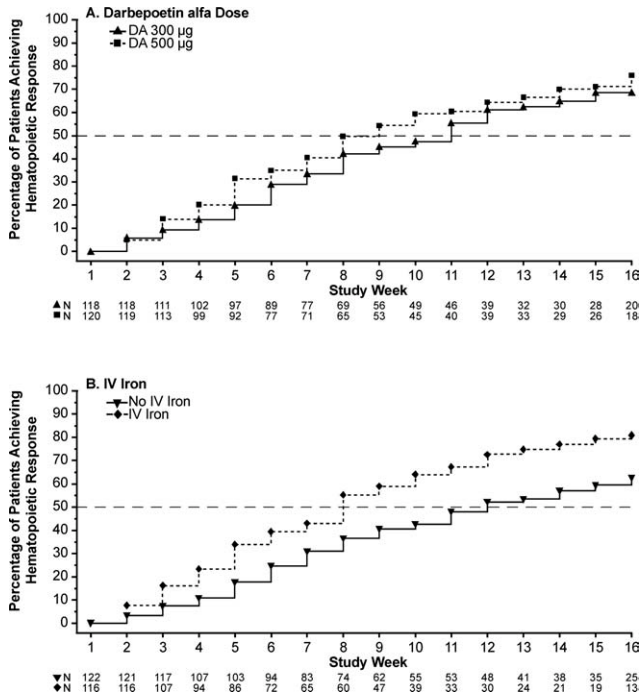

Figure 5. Kaplan–Meier time to hematopoietic response. Proportion of patients achieving hematopoietic response stratified by (A) darbepoetin alfa dose, and (B) IV Iron usage. DA = darbepoetin alfa. IV = intravenous.

who received IV iron, mean (SD) time of iron dosing was 10.6 (3.8) weeks, and the mean (SD) average weekly IV iron dose was 110.3 (36.1) mg. More patients in the darbepoetin alfa 500 µg group than the darbepoetin alfa 300 µg group had ≥1 darbepoetin alfa doses withheld because of hemoglobin levels exceeding threshold (13 g dL^{-1}) (20% vs. 14%) and more had darbepoetin alfa dose decreases (57% vs. 40%). For patients receiving IV iron, 29% had their IV iron dose withheld for reaching ferritin >1000 ng mL^{-1}. Thirty (25%) patients in the no IV iron group received oral iron as permitted in the protocol for patients who were not randomized to IV iron treatment. A summary of darbepoetin alfa and IV iron dosing results is provided in Table IV.

The overall safety profiles were similar between treatment groups, with adverse events as expected for a CIA population (Table V). Two patients had anaphylactoid reactions soon after initiating IV iron therapy, but recovered uneventfully without hospitalization. Similar proportions of patients experienced cardiovascular and thromboembolic events in the darbepoetin alfa treatment groups and the IV iron usage groups. Also, similar rates of deaths were reported and no deaths were deemed treatment-related. A higher proportion of patients in the darbepoetin alfa 500 µg group than the 300 µg group experienced a rapid rise in hemoglobin (63% vs. 54%); similarly, a higher proportion reached hemoglobin threshold (28% vs. 21%). More patients in the IV iron group than the no IV iron group experienced rapid rise in hemoglobin (71% vs. 47%) and more reached hemoglobin threshold (32% vs. 17%). No neutralizing antibodies to darbepoetin alfa were detected.

Discussion

In this study, no evidence of a statistically significant interaction between darbepoetin alfa dose received and IV iron usage was observed for the efficacy endpoints evaluated. Therefore, as prespecified, efficacy results were pooled and summarized for each of the darbepoetin alfa doses regardless of whether patients received IV iron; results were also

TABLE II. Hemoglobin Endpoints

	Darbepoetin alfa 300 μg Q3W	Darbepoetin alfa 500 μg Q3W	No IV iron	IV iron
	n = 118	*n* = 120	*n* = 122	*n* = 116
Change in hemoglobin from baseline to EOTP				
Mean (95% CL) LVCF, g dL^{-1}	1.5 (1.2, 1.8)	1.6 (1.3, 1.9)	1.3 (0.9, 1.6)	1.9 (1.5, 2.2)
LS Mean (95% CL)[a] LVCF, g dL^{-1}	1.6 (1.3, 1.9)	1.6 (1.3, 2.0)	1.3 (1.0, 1.6)	1.9 (1.6, 2.3)
Mean (95% CL) Available data, g dL^{-1}, [*n*]	1.5 (1.2, 1.8) [117]	1.6 (1.3, 1.9) [119]	1.3 (1.0, 1.6) [120]	1.9 (1.5, 2.2) [116]
LS Mean (95% CL)[a] Available data, g dL^{-1}, [*n*]	1.6 (1.3, 1.9) [117]	1.7 (1.3, 2.0) [119]	1.3 (1.0, 1.6) [120]	1.9 (1.6, 2.2) [116]
Mean (95% CL) hemoglobin concentration after achieving target, g dL^{-1}, [*n*][b]	11.7 (11.5, 11.8) [77]	11.6 (11.4, 11.8) [87]	11.5 (11.3, 11.6) [78]	11.8 (11.6, 12.0) [86]
Proportion of patients maintaining mean hemoglobin after achieving target[b,c], *n* (%)				
<11 g dL^{-1}	14 (18)	24 (28)	22 (28)	16 (19)
11 to 13 g dL^{-1}	60 (78)	56 (64)	54 (69)	62 (72)
>13 g dL^{-1}	3 (4)	7 (8)	2 (3)	8 (9)

EOTP = end of treatment period; CL = confidence limits; LS = least squares; Q3W = every three weeks; IV = intravenous; LVCF = last value carried forward.

[a] LS mean and CL computed from an analysis of covariance with baseline hemoglobin as the covariate and adjusting for the treatment and the stratification factor; interaction between treatment factors was not significant ($P > 0$) and was dropped from the model; excludes patients with a missing or nonevaluable baseline hemoglobin.

[b] Including patients who had hemoglobin values ≥11 g dL^{-1} at baseline; but these patients were not counted as having achieved the target hemoglobin level for target hemoglobin response.

[c] Percentages based on the number of patients who achieved the target hemoglobin level or who had hemoglobin values ≥11g dL^{-1} at baseline.

TABLE III. RBC Transfusions

	Darbepoetin alfa 300 μg Q3W	Darbepoetin alfa 500 μg Q3W	No IV iron	IV iron
	n = 118	*n* = 120	*n* = 122	*n* = 116
Patients who had an RBC transfusion or had a hemoglobin value ≤8 g dL^{-1} without receiving a transfusion during the study				
Received ≥1 RBC transfusions from Week 1 to end of study				
K–M percentage mean[a,b] (95% CL)	40 (30, 49)	36 (27, 45)	40 (31, 49)	36 (27, 44)
Crude percentage mean[c] (95% CL)	38 (29, 47)	36 (27, 44)	39 (30, 47)	35 (27, 44)
Received ≥1 RBC transfusions from Week 5 to end of study				
K–M percentage mean[a] (95% CL), [*n*]	29 (20, 37) [116]	29 (20, 37) [116]	29 (20, 37) [117]	28 (20, 37) [115]
Crude percentage mean[c] (95% CL), [*n*]	27 (19, 35) [116]	28 (20, 37) [116]	27 (19, 35) [117]	28 (20, 36) [115]
Patients who had an RBC transfusion				
Received ≥1 RBC transfusions from Week 1 to end of study				
K–M percentage mean[a,b] (95% CL)	28 (20, 37)	30 (23, 40)	30 (23, 39)	28 (20, 37)
Crude percentage mean[c] (95% CL)	26 (18, 34)	30 (22, 38)	29 (21, 37)	28 (19, 36)
Received ≥1 RBC transfusions from Week 5 to end of study				
K-M percentage mean[a] (95% CL), [*n*]	20 (13, 29) [116]	23 (16, 32) [115]	22 (15, 31) [117]	20 (14, 29) [114]
Crude percentage mean[c] (95% CL), [*n*]	18 (11, 25) [116]	22 (15, 30) [115]	21 (13, 28) [117]	20 (13, 27) [114]

CL = confidence limits; K-M = Kaplan-Meier; Q3W = every three weeks; IV = intravenous; RBC = red blood cell.

[a] Determined from the K-M estimate.

[b] One patient in the darbepoetin alfa 500 μg group was excluded from the K-M analysis because of a missing transfusion date.

[c] Binomial proportion with CLs calculated using the normal approximation.

TABLE IV. Darbepoetin Alfa and IV Iron Dosing

	Darbepoetin alfa dosing		IV iron dosing	
	Darbepoetin alfa 300 μg Q3W	Darbepoetin alfa 500 μg Q3W	No IV iron	IV iron
Study drug exposure	*n* = 118	*n* = 120	*n* = 121	*n* = 117
Number of weeks of dosing				
Mean (SD)	11.1 (3.5)	11.3 (3.0)	–	10.6 (3.8)
Min, Max	1, 15	1, 14	–	1, 13
Number of doses received				
Mean (SD)	4.1 (1.2)	4.1 (1.1)	–	3.7 (1.4)
Min, Max	1, 6	1, 6	–	0, 5
Average weekly dose				
Mean (SD)	88.7 (16.6) μg	136.5 (33.9) μg	–	110.3 (36.1) mg
Min, Max	36, 120 μg	53, 200 μg	–	0, 160 mg
Number of patients who had ≥1 dose withheld, *n* (%)	16 (14)	24 (20)	–	34 (29)
Number of patients who had a dose withheld for reaching hemoglobin threshold, *n* (%)	16 (14)	24 (20)	–	–
Number of patients who had a dose withheld for reaching ferritin >1000 ng mL^{-1}, *n* (%)	–	–	–	34 (29)
Number of patients who had a dose increase, *n* (%)	2 (2)	2 (2)	–	4 (3)
Number of patients who had a dose decrease, *n* (%)	47 (40)	68 (57)	–	0 (0)
Number of patients who received oral iron[a], *n* (%)	–	–	30 (25)	6 (5)

[a] The protocol allowed patients to receive oral iron if they were not randomized to the IV iron treatment arm.

Q3W = every three weeks; IV = intravenous.

TABLE V. Overall Summary of Adverse Events

Adverse events, *n* (%)	Darbepoetin alfa 300 μg Q3W *n* = 118	Darbepoetin alfa 500 μg Q3W *n* = 120	No IV iron *n* = 121	IV iron *n* = 117
Patients with any adverse events	105 (89)	109 (91)	110 (91)	104 (89)
Patients with serious adverse events	44 (37)	42 (35)	45 (37)	41 (35)
Patients with treatment-related[a] adverse events	5 (4)	2 (2)	0 (0)	14 (12)
Patients with serious treatment-related[a] adverse events	3 (3)	2 (2)	0 (0)	3 (3)[b]
Patients with adverse events leading to study discontinuation	17 (14)	9 (8)	14 (12)	12 (10)
Patients with adverse events of interest				
Cardiovascular and thromboembolic events	16 (14)	21 (18)	19 (16)	18 (15)
Embolism/thrombosis	8 (7)	10 (8)	10 (8)	8 (7)
Arrhythmias	6 (5)	10 (8)	7 (6)	9 (8)
Congestive heart failure	2 (2)	2 (2)	1 (1)	3 (3)
Myocardial infarction/artery disorders	1 (1)	3 (3)	2 (2)	2 (2)
Cerebrovascular accident	0 (0)	1 (1)	0 (0)	1 (1)
Deaths on study (any reason)[c]	11 (9)	10 (8)	13 (11)	8 (7)

Q3W = every three weeks; IV = intravenous.

[a] For the "Darbepoetin alfa" columns, the adverse events are darbepoetin alfa-related; for the "IV iron usage" columns, the adverse events are IV iron-related.

[b] Episodes of transient anaphylactoid reactions occurred in two patients soon after initiating IV iron, but these patients recovered uneventfully without hospitalization; one patient in this group had enlarged uvula, lip swelling, and dyspnoea (symptoms resolved).

[c] Deaths on study or within 30 days after the last dose of study drug.

pooled and summarized for IV iron usage regardless of darbepoetin alfa dose received as prespecified.

This is the first comparison of fixed doses of darbepoetin alfa at 300 μg Q3W versus 500 μg Q3W. Hemoglobin levels increased in patients receiving darbepoetin alfa Q3W at a dose of either 300 μg or 500 μg. The results suggest that patients receiving darbepoetin alfa 500 μg Q3W may have an earlier hemoglobin response compared with patients receiving darbepoetin alfa 300 μg Q3W. Patients receiving IV iron had larger increases in hemoglobin levels, and hemoglobin response occurred earlier compared with patients not receiving IV iron. This is consistent with findings from other studies that have reported significant improvements in hemoglobin levels for patients receiving ESA therapy in combination with IV iron in the CIA setting [17–21]. In the present study, RBC transfusions were not different for the IV iron usage groups, consistent with findings from most studies evaluating iron usage in CIA patients [17,19–21]. Notably, the study by Bastit et al. [18] showed a significant decrease in number of transfusions in the IV iron group compared with the no IV iron group.

Inconsistent results were observed for achieving target hemoglobin and achieving hematopoietic response when data were stratified by baseline serum ferritin ($<$100 ng mL^{-1} vs. $\geq$100 ng mL^{-1}), reinforcing the observation that serum ferritin is a poor predictor of response to IV iron, as show in previous studies [26]. More patients receiving IV iron than those not receiving IV iron achieved target hemoglobin regardless of baseline Tsat levels.

Even though a statistically significant interaction between darbepoetin alfa dose received and IV iron usage was not observed, exploratory analyses of hematological endpoints by randomized group were done. For the darbepoetin alfa 300 μg Q3W, darbepoetin alfa 300 μg Q3W plus IV iron, darbepoetin alfa 500 μg Q3W, and darbepoetin alfa 500 μg Q3W plus IV iron groups, K–M proportions of patients achieving target hemoglobin were 70, 81, 75, and 82%; and K–M proportions of patients achieving hematopoietic response were 59, 79, 68, and 84%, respectively. The K–M median time to hemoglobin response was 11, 6, 7, and 8 weeks; and K–M median time to hematopoietic response was 14, 8, 9, and 8 weeks, respectively. RBC transfusion requirements (K–M estimates) were 43, 35, 37, and 36% from Week 1 to end of study; and 30, 27, 28, and 30% from Week 5 to end of study, respectively. Clinically significant mean changes in FACT-F score ($\geq$3 points [25]) were 67, 100, 65, and 63%, respectively. These preliminary ad hoc findings appear to suggest that darbepoetin alfa 300 μg Q3W administered in combination with IV iron may enhance treatment response and therefore correct anemia to a similar extent as darbepoetin alfa 500 μg Q3W monotherapy in these CIA patients. These suggestive data warrant further evaluation of the IV iron effect on darbepoetin alfa dose requirements in the CIA setting.

The overall safety profiles were similar between groups, with adverse events as expected for a CIA population. Anaphylactoid reactions were reported in two patients after administration of IV iron, both of whom recovered uneventfully without hospitalization. The report of these anaphylactoid reactions in response to LMW iron is surprising and has not been observed in a number of similar studies [17–19,21,27]. No other safety signal was reported when darbepoetin alfa was dosed concurrently with IV iron in this population. Importantly, the effect of IV iron either alone or in combination with an ESA on overall survival and/or disease progression in oncology patients who are not iron deficient has not yet been studied.

In this exploratory analysis, darbepoetin alfa administered at either 300 μg Q3W or 500 μg Q3W appeared to impact hemoglobin rise and hematopoietic response similarly, while IV iron enhanced these responses. Properly powered Phase 3 studies are needed to establish definitively that IV iron added to darbepoetin alfa Q3W significantly improves treatment response and heightens benefit to the ESA exposure.

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