Effectiveness of Darbepoetin Alfa for Chemotherapy-induced Anemia When Initiated at Hemoglobin ≤10 g/dL

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ABSTRACT

Purpose: Limited data are available to describe the effectiveness of darbepoetin alfa (DA) in terms of hemoglobin (Hb) and transfusion outcomes when initiated at Hb ≤10 g/dL (the threshold specified in the summary of prescribing characteristics). We assessed DA, initiated according to current labeling (Hb ≤10 g/dL), in chemotherapy-induced anemia (CIA).

Methods: Data for patients with cancer and CIA who initiated DA at Hb ≤10 g/dL were extracted from a database of Amgen-sponsored trials. A comparative analysis was limited to randomized, controlled trials in patients treated with DA or control (placebo/best supportive care). Data for the DA arm(s) of randomized, multiple-arm, or prospective, single-arm trials were also extracted (DA-only analysis; non–front-loaded studies only). Outcomes included Hb increase ≥1 g/dL or ≥2 g/dL during the first 12 weeks of treatment. Crude and Kaplan–Meier proportions of patients who experienced each outcome and time (days) to each outcome were summarized by treatment arm. Meta-analysis (fixed-effects inverse-variance method) was performed to compare outcomes for DA with control.

Findings: The comparative analysis included 4 studies (2 in lung cancer, 1 in lymphoproliferative disease, and 1 in non-myeloid malignancy: DA, n = 261; control, n = 273). The DA-only analysis included 15 studies (n = 3768). In comparative analyses, more patients who received DA than placebo achieved Hb increase of ≥1 g/dL (fixed-effects hazard ratio [HR] = 2.07; 95% CI, 1.62–2.63) or ≥2 g/dL (HR = 2.91; 95% CI, 2.09–4.06). Median times to ≥1 g/dL or ≥2 g/dL increase were 43 or 78 days for DA (not evaluable for placebo). Transfusions were less common in patients who received DA (HR = 0.58; 95% CI, 0.44–0.77). Addition of 2 dose-finding studies did not change the findings of the main comparative analysis. Results were similar in the DA-only analyses.

Implications: This is the first patient-level meta-analysis, to our knowledge, to evaluate the efficacy in terms of Hb response of DA treatment when initiated according to current product labeling in patients with CIA. Limitations include the small number of studies and patients eligible for inclusion in the comparative analyses and the absence of non-Amgen trials of DA. The results of the comparative analysis confirm that DA is more effective than placebo at increasing serum Hb levels and at reducing the need for transfusion in patients with CIA when treatment is initiated at Hb ≤10 g/dL, as per current product labeling. (*Clin Ther.* 2016;38:122–135) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: chemotherapy-induced anemia, darbepoetin alfa, hemoglobin, licensed indication, meta-analysis, transfusion.

INTRODUCTION

Chemotherapy-induced anemia (CIA) is common in patients with cancer who are undergoing myelosuppressive chemotherapy.[1] In such patients, anemia has a

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detrimental effect on quality of life and can also negatively affect the patient's prognosis, increasing mortality rates by up to 65%.[2] In particular, anemia can often lead to the need for transfusions, which are associated with a range of issues, including the availability of suitable blood, the checks necessary to ensure the recipient's safety (eg, transfusion-transmitted diseases), the inconvenience to both patients and health care professionals, and the associated costs.[2] Treatments, such as erythropoiesis-stimulating agents (ESAs) that can increase hemoglobin (Hb) concentrations and thereby reduce the need for red blood cell transfusion[2] are therefore of great benefit to patients and health care systems.

In 2008, the summary of product characteristics for the ESA darbepoetin alfa (DA) was updated, decreasing the Hb treatment initiation and discontinuation thresholds to $\leq$10 and $>$12 g/dL, respectively.[3] This was done as a result of data indicating that ESA treatment in patients with cancer was potentially associated with an increased risk of thromboembolic events and mortality, and similar changes were made by the Food and Drug Administration in the United States.[4]

Because most clinical trials that investigated the effectiveness of DA in CIA were started before this update, limited data are available to describe the effectiveness of DA in terms of Hb and transfusion outcomes when initiated at Hb $\leq$10 g/dL. The landmark registration Phase III placebo-controlled trials of DA, for example, included patients when their Hb was $<$11 g/dL, and the dose of blinded study drug was withheld if a patient's Hb concentration increased to $>$15.0 g/dL (for men) or $>$14.0 g/dL (for women).[5,6] After the patient's Hb concentration decreased to 13.0 g/dL, administration of the study drug was reinstated at 50% of the previous dose.

Several meta-analyses and systematic reviews have assessed the safety profile of ESAs in CIA, analyzed results in individual tumor types, and combined data for different ESAs.[7–16] These reviews found that ESA treatment can improve Hb concentrations and/or reduce the need for transfusion in patients with CIA.[10,13–16] Some reviews also suggest that ESA treatment can increase the rate of mortality when used inappropriately in patients with CIA,[7,8,12,15] although others have found no increase in that rate of mortality.[9,11,13,14,16] These reviews have not, however, evaluated the effectiveness of DA in terms of Hb and transfusion outcomes in the subgroup of patients with a baseline Hb $\leq$10 g/dL.

We conducted a pooled analysis and meta-analysis that were based on data from Amgen-sponsored DA trials to assess the effectiveness of DA in CIA in patients who initiated DA at Hb $\leq$10 g/dL.

METHODS

Objectives

The objective of this analysis was to summarize data on the effectiveness of DA when used according to the revised prescribing information and recommendations with an Hb treatment initiation threshold $\leq$10 g/dL for CIA. Effectiveness was assessed in terms of achievement of Hb targets (increase of $\geq$1 g/dL and $\geq$2 g/dL) and transfusion requirements.

Study Design

Data were sourced from a central database of Amgen-sponsored trials of DA in CIA. For comparative analyses, randomized controlled trials of DA in CIA that had at least 1 arm of a prespecified DA regimen versus control (placebo/best supportive care) were eligible for selection. Only data for DA arm(s) of permitted DA regimens and control data were extracted and were limited to patients who initiated DA at $\leq$10 g/L. For supportive analyses (DA-only analyses), randomized multiple-arm or prospective single-arm trials of DA in CIA that had at least 1 arm of a prespecified DA regimen were selected. Again, only data for DA arm(s) of permitted DA regimens were extracted and were limited to patients who initiated DA at $\leq$10 g/dL. Prespecified permitted DA regimens were 6.75 μg/kg (500 μg) every 3 weeks (Q3W), 2.25 μg/kg (150 μg) weekly (QW), 4.5 μg/kg (300 μg) Q3W, any 2-weekly regimen, and the QW 4.5 μg/kg (300 μg) front-loading dose regimen (ie, a high initial dose with the intention of subsequently reducing the dose and/or dose interval). Studies of 4-weekly DA, and all dose-finding studies, were excluded. In the DA-only analysis, data were analyzed separately for front-loading and non–front-loading DA regimens, because front-loading dosing is not licensed for DA. This was not done for the comparative analysis because the number of studies was too small.

Outcomes and Analyses

Outcomes included the percentage of patients with an Hb increase $\geq$1 g/dL or $\geq$2 g/dL, time to first Hb increase $\geq$1 g/dL or $\geq$2 g/dL, the percentage of

Table I. Randomized, controlled studies included in the comparative analysis.

Study	Cancer Population	Treatment Duration (wk)	Screening Hb Concentration for Study Inclusion (g/dL)	Initial DA Dose	Hb Indication for Transfusion (g/dL)	Total Patients Enrolled Who Received Study Drug (n)		Patients with Hb ≤10 g/dL at Baseline (n)		Percentage of Total Patients (%)
						DA	Placebo	DA	Placebo	
Hedenus et al[5]	Lymphoproliferative malignancies	12	<11	2.25 μg/kg/wk	<8*	174	170	107	105	62
Pirker et al[21]	Small-cell lung cancer	18	≤13	300 μg QW	NS	299	289	12	18	5
Hernandez et al[22]	Non-myeloid malignancy	15	<11	300 μg Q3W	≤8†	193	193	85	83	44
Vansteenkiste et al[6]	Lung cancer	12	<11	2.25 μg/kg/wk	≤8*	156	158	57	67	39
	Total (4 studies)					822	810	261	273	33

DA = darbepoetin alfa; Hb = hemoglobin; NS = not specified; QW = every week; Q3W = every 3 weeks.
*Recommended concentration; initiation of transfusion at the discretion of the investigators.
†Transfusions with Hb >8 g/dL were allowed if signs or symptoms of anemia were present.

Table II. Studies with darbepoetin arms included in the darbepoetin alfa-only non–front-loading dose analyses.

Study	Cancer Population	Treatment Duration (wk)	Screening Hb Concentration for Study Inclusion (g/dL)	Initial DA Dose	Hb Indication for Transfusion (g/dL)	Control	Total Patients Enrolled Who Received Study Drug (n)	DA Patients with Hb ≤10g/dL at Baseline (n)	Percentage of Total Patients (%)
Vansteenkiste et al[6]	Lung	12	<11	2.25 μg/kg/wk	≤8*	Placebo	156	57	37
Hedenus et al[19]	Lymphoproliferative malignancy	12	≤11	2.25 μg/kg/wk	≤8*	Placebo	174	107	61
Vadhan-Raj et al[23]	Non-myeloid malignancy	15	≤11	3.0 μg/kg Q2W	As medically needed	None	1173	543	46
Glaspy et al[24]	Non-myeloid malignancy	16	≤11	6.75 μg/kg Q3W	NS	None	81	29	36
Gabrilove et al[25]	Non-myeloid malignancy	26	≤11	200 μg Q2W	As medically needed	None	2401	994	41
Senecal et al[26]	Breast	16	<11	200 μg Q2W	<8*	Epoetin alfa	72	18	25
Schwartzberg et al[27]	Non–small-cell lung cancer	16	≤11	200 μg Q2W	NS	Epoetin alfa	51	13	25
Schwartzberg et al[27]	Gynecologic malignancy	16	≤11	200 μg Q2W	NS	Epoetin alfa	34	16	47
Glaspy et al[28]	Non-myeloid malignancy	16	≤11	200 μg Q2W	≤8†	Epoetin alfa	606	235	39
Boccia et al[29]	Various tumors	13	<11	300 μg Q3W	NS	None	1493	583	39
Canon et al[30]	Non-myeloid malignancy	15	<11	500 μg Q3W 2.25 μg/kg QW	≤8‡	None	705	378	54
Hernandez et al[22]	Non-myeloid malignancy	15	<11	300 μg Q3W	≤8†	Placebo	193	85	44
Bastit et al[31]	Non-myeloid malignancy	16	<11	500 μg Q3W	≤8*	None	396	183	46
Schwartzberg et al[32]	Non-myeloid malignancy	25	<11	150 μg QW 300 μg Q2W 500 μg Q3W	NS	None	752	340	45

(continued)

Table II. (continued).

Study	Cancer Population	Treatment Duration (wk)	Screening Hb Concentration for Study Inclusion (g/dL)	Initial DA Dose	Hb Indication for Transfusion (g/dL)	Control	Total Patients Enrolled Who Received Study Drug (n)	DA Patients with Hb ≤10g/dL at Baseline (n)	Percentage of Total Patients (%)
Auerbach et al[33]	Non-myeloid malignancy	15	≤10	500 μg Q3W 300 μg Q3W 500 μg Q3W 300 μg Q3W	NS	None	238	187	79
	Total (15 studies)						8525	3678	44

DA = darbepoetin alfa; Hb = hemoglobin; NS = not specified; QW = every week; Q2W = every 2 weeks; Q3W = every 3 weeks.
*Recommended concentration; initiation of transfusion at the discretion of the investigators.
†Transfusions with Hb >8 g/dL were allowed if signs or symptoms of anemia were present.
‡Transfusions with Hb >8 g/dL were allowed in symptomatic patients or as recommended by the physician.

patients who received a red blood cell transfusion from the start of week 5 (day 29), and time to first transfusion from day 29. Analyses were limited to data up to 12 weeks after the initiation of DA or control. Outcomes were also analyzed in subgroups of patients with Hb at treatment initiation <9 g/dL versus 9 to ≤10 g/dL.

For the comparative analysis, and separately for the DA-only analysis, study data were pooled to calculate crude and Kaplan–Meier percentages and time to each outcome of interest by treatment arm (DA or placebo for the comparative analysis; DA for the DA-only analysis). Kaplan–Meier plots were used to summarize time to each outcome of interest graphically. Crude percentages were calculated together with a Wilsons 95% CI.[17] The CI for Kaplan–Meier percentages were calculated by taking 1 minus the survivor function at the last noncensored time point (Greenwoods formula[18]).

For the comparative analysis only, meta-analysis techniques were used to calculate treatment effect for DA. An inverse-variance method was used (for both a random [DerSimonian–Laird] and fixed-effect model) on the basis of hazard ratios (HRs). I^2 statistics for heterogeneity were also calculated.

To confirm that exclusion of dose-finding studies in the original study design did not affect the overall findings, sensitivity analyses for the comparative analysis were conducted, including data from 2 DA dose-finding studies.[19,20]

RESULTS

Studies Included

The database review identified 4 studies that met the inclusion and exclusion criteria for the comparative analysis (DA, n = 261; placebo, n = 273) (Table I).[5,6,21,22] All 4 studies were Phase III randomized, double-blind, placebo-controlled trials. In addition, 2 placebo-controlled dose-finding studies were identified that included patients who initiated treatment at Hb ≤10 g/dL. These studies were excluded from the main analysis but were included in a sensitivity analysis. The database review for the DA-only analysis identified 15 relevant non–front-loading studies (n = 3768; Table II)[6,19,23–33] and 6 front-loading studies (n = 901; see Supplemental Table I in the online version at http://dx.doi.org/10.1016/j.clinthera.2015.11.012). Here, we focus on the comparative analysis and non–front-loading DA-only analysis.

Table III. Baseline characteristics of patients in the comparative analysis and the DA-only analysis (non–front-loading).

	Comparative Analysis		DA-Only Analysis (non–front-loading)
	DA (n = 261)	Placebo (n = 273)	DA (n = 3768)
Male sex, n (%)	135 (52)	143 (52)	1489 (40)
Age, y, mean [SD]	64.5 [12]	63.0 [12]	62.2 [13]
Age <65 y, n (%)	115 (44)	139 (51)	2017 (54)
Tumor type, n (%)			
Breast	25 (10)	11 (4)	729 (19)
Gastrointestinal	8 (3)	13 (5)	740 (20)
Genitourinary	7 (3)	4 (2)	200 (5)
Gynecologic	9 (3)	6 (2)	340 (9)
Hematologic	119 (46)	128 (47)	636 (17)
Lung	80 (31)	99 (36)	804 (21)
Other	13 (5)	12 (4)	319 (8)
Disease stage, n (%)			
Stage II or lower/limited	33 (13)	43 (16)	608 (16)
Stage III or higher/extensive	218 (84)	213 (78)	2854 (76)
Missing/other	10 (4)	17 (6)	306 (8)
ECOG performance status, n (%)			
0	53 (20)	44 (16)	1227 (33)
1	121 (46)	131 (48)	2026 (54)
2	44 (17)	54 (20)	370 (10)
3	4 (2)	4 (2)	7 (<1)
Missing	39 (15)	40 (15)	138 (4)
Hemoglobin, g/dL, mean [SD]	9.1 [0.7]	9.1 [0.8]	9.3 [0.6]

DA = darbepoetin alfa, ECOG = Eastern Cooperative Oncology Group.

Baseline characteristics of the included patients are shown in Table III. Hematologic and lung cancers were the most common malignancies in the comparative analysis, and lung, gastrointestinal, breast, and hematologic cancers were most common in the DA-only analysis. Baseline age, disease stage, performance status, and Hb concentrations were similar for the DA and placebo groups of the comparative analysis and the population included in the DA-only analysis; average age across these groups ranged from 62.2 to 64.5 years, >75% of patients had disease stage III or higher (or extensive disease), and most patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. Baseline Hb was 9.1 g/dL in the DA and placebo groups of the comparative analysis and 9.3 g/dL in the DA-only analysis.

Comparative Analysis

Mean Hb concentrations over time are shown in Figure 1. On the basis of crude and Kaplan–Meier percentages, more patients who received DA achieved an increase in Hb of ≥1 g/dL or ≥2 g/dL versus placebo (Table IV). Fixed-effect HRs for patients with an Hb increase of ≥1 g/dL and ≥2 g/dL for DA versus placebo were 2.07 (95% CI, 1.62–2.63) and 2.91 (95% CI, 2.09–4.06), respectively (Figure 2). Median time to a ≥1 g/dL increase was 43 days (95% CI, 37–50 days) for DA and was not evaluable (NE) for placebo (Figure 3**A**). Median time to a ≥2 g/dL increase was 78 days (95% CI, 71–NE days) for DA and was NE for placebo (Figure 3**B**).

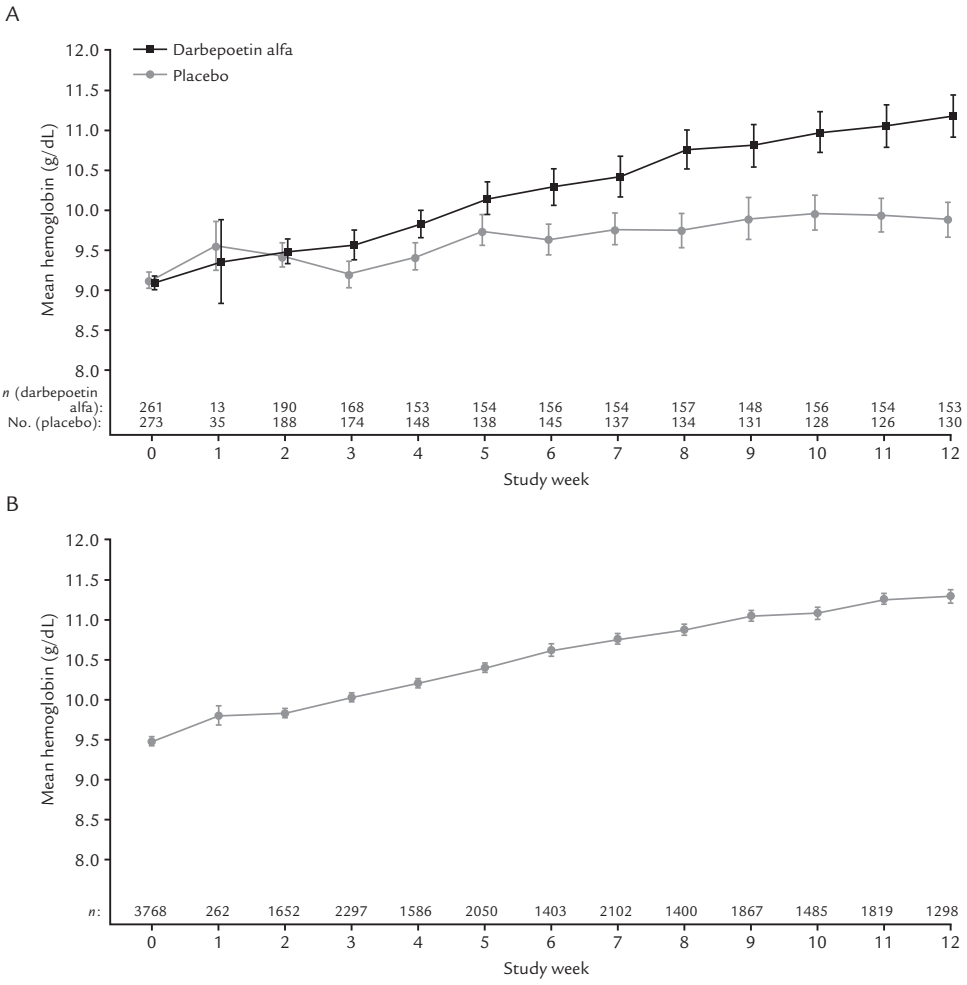

Figure 1. Mean hemoglobin concentrations during the first 12 weeks of treatment in the (A) comparative and (B) darbepoetin alfa-only non–front-loading analyses. Error bars represent 95% CIs.

The crude and Kaplan–Meier percentages of DA-treated patients who achieved Hb increases ≥1 g/dL and ≥2 g/dL were similar in the subgroups of patients with baseline Hb <9 g/dL or Hb 9 to ≤10 g/dL (Table IV). Fixed-effect HRs for an Hb increase of ≥1 g/dL and ≥2 g/dL for DA versus placebo were 1.61 (95% CI, 1.05–2.46) and 1.72 (95% CI, 1.03–2.85), respectively, for the Hb <9 g/dL subgroup, and 2.31 (95% CI, 1.72–3.11) and 3.70 (95% CI, 2.36–5.81) for the Hb 9 to ≤10 g/dL subgroup. In patients with baseline Hb <9 g/dL, median time to a ≥1 g/dL increase was 49 days (95% CI, 43–52 days) for DA and 77 days (95% CI, 57–NE days) for placebo. In patients with baseline Hb 9 to ≤10 g/dL, median time to a ≥1 g/dL increase was 43 days (95% CI, 29–50 days) for DA and NE for placebo.

On the basis of crude and Kaplan–Meier percentages, transfusions were more commonly required between the start of week 5 and end of week 12 in patients who received placebo than in patients who received DA (Table IV). Fixed-effect HR for DA versus placebo was 0.58 (95% CI, 0.44–0.77) (Figure 2C). More patients with a baseline Hb <9 g/dL needed transfusions than patients with a baseline Hb 9 to ≤10 g/dL in both the DA and placebo arms (Table IV).

Table IV. Summary of patients with an increase in Hb ≥1 g/dL or ≥2 g/dL during the first 12 weeks of treatment or who required a transfusion (red blood cell or whole blood) from start of week 5 to end of treatment.

	Crude analysis			Kaplan–Meier Analysis		
	Comparative Analysis		DA-Only Analysis (non–front-loading)	Comparative Analysis		DA-Only Analysis (non–front-loading)
	DA	Placebo		DA	Placebo	
All patients, n	261	273	3768	261	273	3768
Hb ≥1 g/dL	66 (60–71)	40 (35–46)	67 (65–68)	76 (69–83)	48 (40–57)	82 (80–85)
Hb ≥2 g/dL	45 (39–51)	19 (15–24)	43 (42–45)	58 (49–68)	27 (18–37)	60 (57–63)
Transfusion	33 (27–39)	49 (43–55)	23 (22–25)	34 (28–40)	51 (45–57)	25 (23–26)
Baseline Hb <9 g/dL, n	96	80	968	96	80	968
Hb ≥1 g/dL	63 (53–72)	45 (35–56)	66 (63–69)	71 (61–81)	53 (41–66)	81 (77–85)
Hb ≥2 g/dL	47 (37–57)	30 (21–41)	46 (43–49)	59 (46–73)	37 (25–49)	66 (60–72)
Transfusion	43 (33–53)	58 (47–69)	35 (32–38)	44 (34–55)	61 (50–73)	37 (34–41)
Baseline Hb 9–≤10 g/dL, n	165	193	2800	165	193	2800
Hb ≥1 g/dL	68 (60–75)	38 (32–45)	67 (66–69)	79 (69–88)	46 (36–57)	83 (80–85)
Hb ≥2 g/dL	44 (36–51)	15 (10–20)	42 (40–44)	57 (45–69)	24 (12–35)	58 (55–61)
Transfusion	26 (20–34)	45 (38–53)	19 (18–21)	27 (20–35)	47 (40–54)	21 (19–22)

Values are percentage (95% CI), unless otherwise indicated.
DA = darbepoetin alfa; Hb = hemoglobin.

Sensitivity Analyses

The sensitivity analysis included 2 additional randomized, placebo-controlled, dose-finding studies,[19,20] providing an overall total of 598 patients (DA, n = 313; placebo, n = 285). Inclusion of these 2 studies did not change the interpretation of the efficacy findings from the main comparative analysis.

DA-Only Analysis (non–front-loading data)

Mean Hb concentrations over time in the non–front-loading dose analysis are shown in Figure 1B. The crude and Kaplan–Meier percentages of patients who achieved a ≥1 g/dL or ≥2 g/dL increase in Hb were similar to the percentages seen for DA in the comparative analysis (Table IV). Overall, the median time to an Hb increase ≥1 g/dL was 43 days (95% CI, 43–43 days) (Figure 4A), and to an Hb increase of ≥2 g/dL was 78 days (95% CI, 74–78 days) (Figure 4B). Results in patients with baseline Hb <9 g/dL or 9 to ≥10 g/dL were similar to results for the ≤10 g/dL population in terms of crude and Kaplan–Meier percentages of patients who achieved a ≥1 g/dL or ≥2 g/dL increase in Hb (Table IV) and time to Hb increase 1 g/dL or 2 g/dL (data not shown).

The percentages of patients who required a transfusion on the basis of crude and Kaplan–Meier percentages were similar to those in the comparative analysis (Table IV). Again, more patients with a baseline Hb <9 g/dL needed transfusions than patients with a baseline Hb 9 to ≤10 g/dL.

Results in the front-loading studies were similar to those in the non–front-loading studies (see online-only supplement).

DISCUSSION

This is the first patient-level meta-analysis, to our knowledge, to evaluate the efficacy, in terms of Hb response, of DA treatment when initiated according to the current product labeling in patients with CIA.

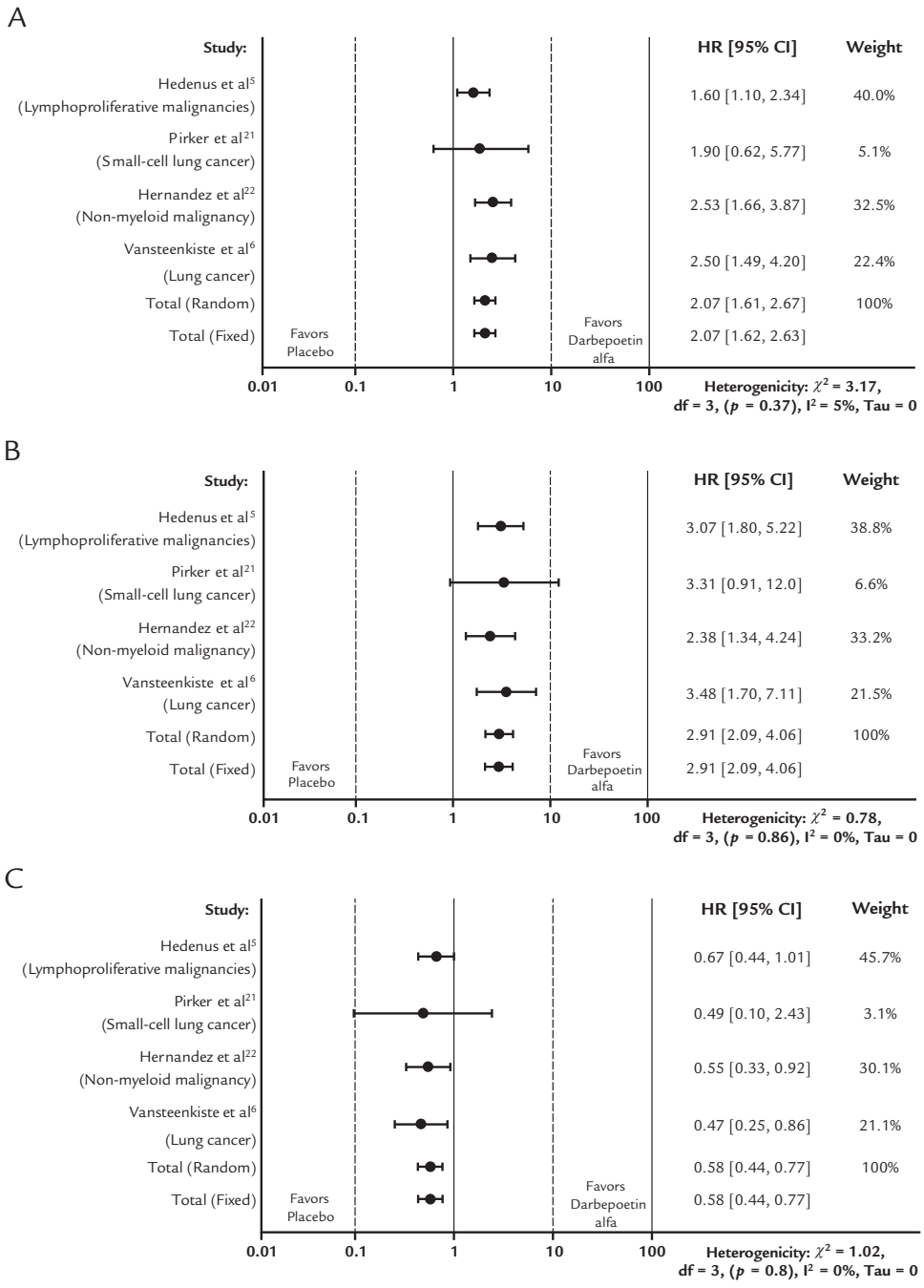

Figure 2. Forest plot shows the meta-analysis results for a hemoglobin increase of (A) ≥1 g/dL or (B) ≥2 g/dL, or (C) transfusion in patients who receive darbepoetin alfa or placebo (comparative analysis). HR = hazard ratio.

The results of the comparative analysis confirm that DA is more effective than placebo at increasing serum Hb concentrations and at reducing the need for transfusion in patients with CIA when treatment is initiated at Hb ≤10 g/dL. Addition of 2 dose-finding studies did not change the findings of the main comparative analysis, and the results were consistent with the DA-only analyses, which included larger patient cohorts.

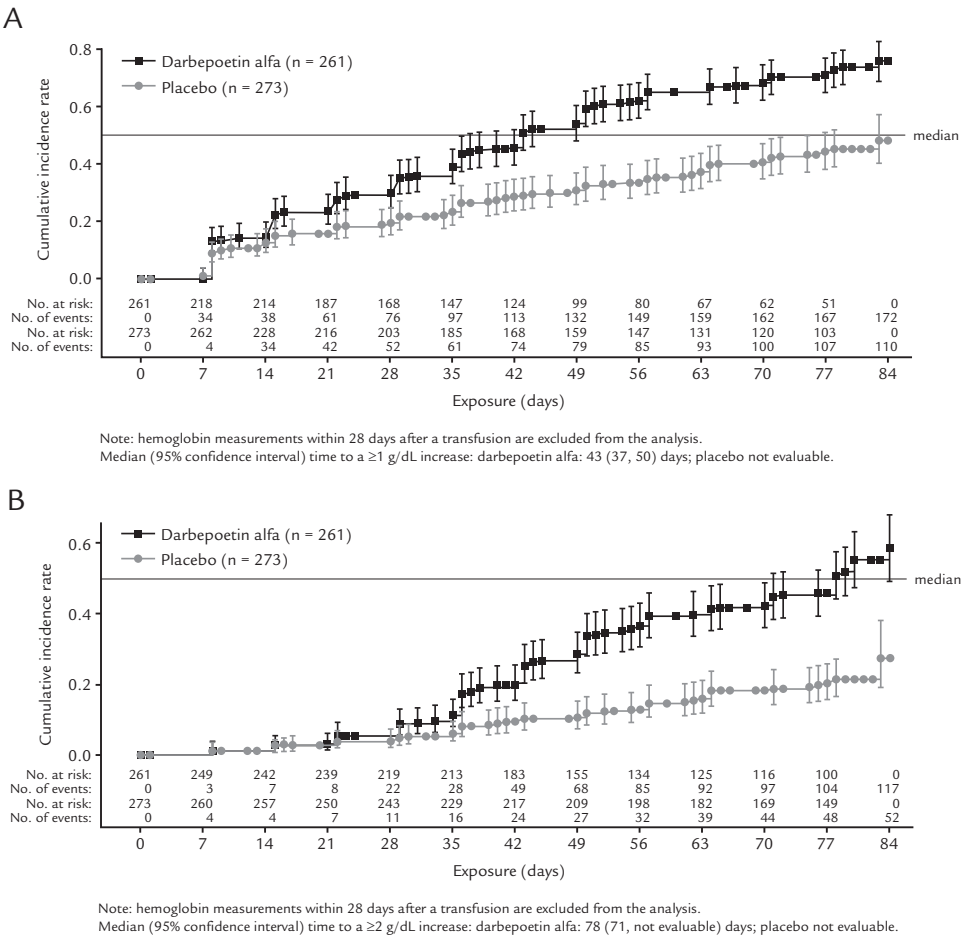

Figure 3. Kaplan–Meier curves for time to (A) increase in hemoglobin of ≥1 g/dL during the first 12 weeks of treatment and (B) increase in hemoglobin of ≥2 g/dL during the first 12 weeks of treatment (comparative analysis).

The results of this analysis are consistent with previously published observational studies, post hoc analyses, chart reviews, and single-center studies of DA, which reported data on the efficacy of DA when initiated at Hb ≤10 g/dL.[34–41] For example, data from the CHOICE observational study in 1887 patients with solid tumors and CIA who received DA for 9 weeks found that 29% of patients who initiated treatment at Hb <9 g/dL and 20% of patients who initiated treatment at Hb 9 to <10 g/dL required a transfusion between the start of week 5 and end of treatment.[39] In a post hoc analysis of a Phase III study in patients with non-myeloid malignancies and CIA, Kaplan–Meier transfusion incidences with Q3W and QW DA were 36% and 41%, respectively, in patients who initiated treatment at Hb <10 g/dL.[40] Similarly, post hoc analysis of an earlier study in patients with lung cancer and CIA found that transfusion incidence with weekly DA was 31%.[40] The results of the present study are also consistent with studies of DA in patients with a broader range of baseline Hb concentrations, including those >10 g/dL.[6,20,22,28,30]

Notably, the present analysis indicates similar efficacy outcomes regardless of whether DA was initiated at Hb concentrations <9 g/dL or 9 to ≤10 g/dL, although the need for transfusions was numerically higher in patients in the lower Hb category. This is consistent with an earlier exploratory

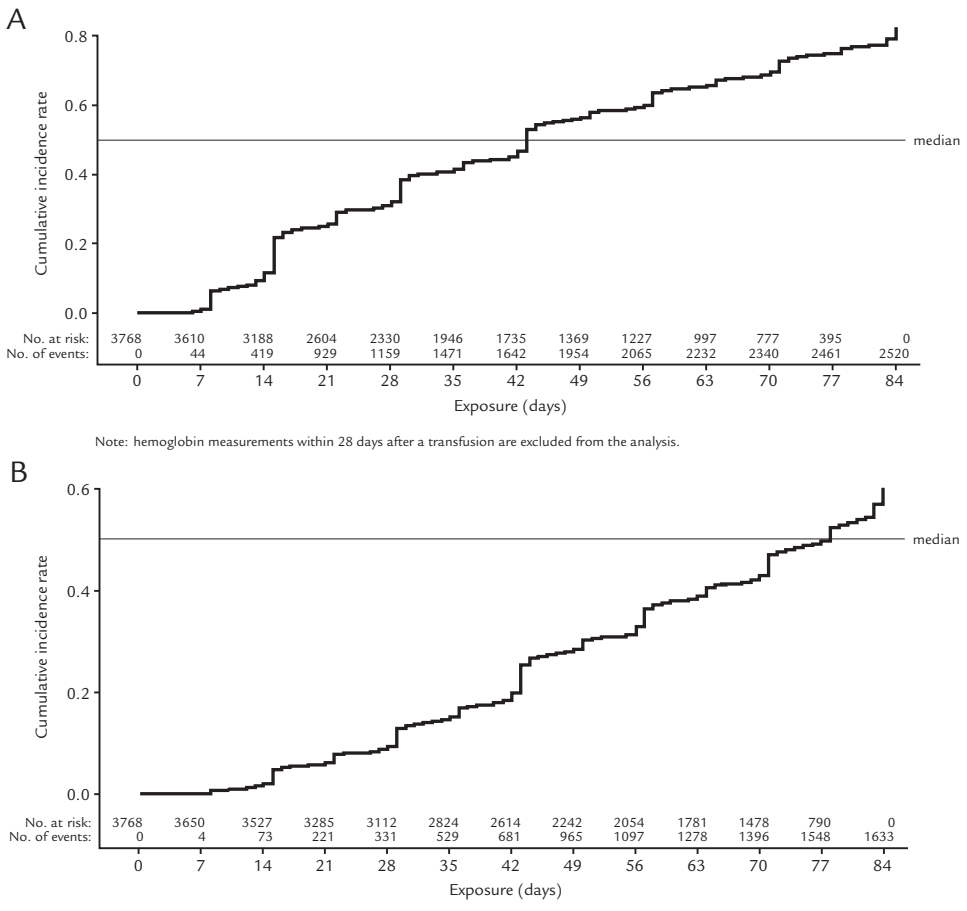

Figure 4. Kaplan–Meier curves for time to (A) increase in hemoglobin of ≥1 g/dL during the first 12 weeks of treatment and (B) increase in hemoglobin of ≥2 g/dL during the first 12 weeks of treatment (darbepoetin alfa-only analysis, non–front-loading).

analysis of data from a 15-week clinical trial by Canon et al[35] in which patients received DA 500 μg Q3W or 2.25 μg/kg QW. Results of that analysis suggested that baseline Hb <9 g/dL (n = 126) was associated with worse outcomes than 9 to ≤10 g/dL (n = 225) in terms of a ≥1 g/dL increase in Hb within 14 days, and for achievement of Hb ≥10 g/dL and need for transfusion. The researchers therefore recommended that treatment be initiated as soon as possible after Hb falls to 10 g/dL.[35]

The strength of the present study is in the pooling of effectiveness data from multiple studies, particularly for the DA-only analyses; we recognize that a limited number of studies and patients were eligible for inclusion in the comparative analyses. Notably, the included studies were designed when DA was generally initiated at a higher Hb threshold, so only those data from the subset of patients who initiated Hb at ≤10 g/dL were extracted. In addition, this analysis of short-term (≤26-week) studies focused on assessing the efficacy of DA specifically in patients whose treatment was initiated at the lower Hb threshold introduced by regulatory bodies in 2008. Analysis of longer-term end points in these patients, including key adverse events and survival, would be of great interest. Finally, it should be noted that non-Amgen trials of DA were not included.

CONCLUSIONS

The results of this pooled analysis suggest that DA is effective at rapidly increasing Hb concentrations and reducing the need for transfusions in patients with CIA when initiated after Hb falls to $\leq$10 g/dL, as per current product labeling.

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CONFLICTS OF INTEREST

This work was supported by Amgen (Europe) GmbH. Amgen sponsored the Phase III DA studies included in these analyses and was involved in the design, data collection, analysis, and data interpretation. Dr. Hedenus has received minor honoraria for temporary advisory boards for Pharmacosmos and Amgen. Dr. Belton is a contractor funded by Amgen (Europe) GmbH. Dr. Terwey is an employee of Amgen Switzerland AG. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTARY INFORMATION

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2015.11.012.

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SUPPLEMENTARY MATERIALS

Darbepoetin-only Front-loading Analyses

The database review for the darbepoetin alfa (DA)-only analysis identified 6 front-loading studies (n=901; Supplementary Table I). Baseline characteristics of the included patients (**Supplementary Table II**) were similar to those in the comparative and non-front-loading DA-only analyses.

Mean hemoglobin (Hb) levels over time are shown in Supplementary Figure 1. In the analysis of front-loading DA doses, the crude and Kaplan–Meier percentages of patients achieving a ≥1 g/dL or ≥2 g/dL increase in Hb were generally similar, or slightly higher than the percentages seen for DA in the comparative and non-front-loading DA-only analyses (Supplementary Table III). Overall, the median (95% confidence interval [CI]) time to an Hb increase ≥1 g/dL was 35 (29–36) days (Supplementary Figure 2a); the median (95% CI) time to an Hb increase ≥2 g/dL was 64 (57–71) days (Supplementary Figure 2b). Results in patients with baseline Hb <9 g/dL or 9–≥10 g/dL were similar to those for the ≤10 g/dL population in terms of crude and Kaplan–Meier percentages of patients achieving a ≥1 g/dL or ≥2 g/dL increase in Hb (Supplementary Table III), and time to Hb increase 1 g/dL or 2 g/dL (data not shown).

The percentages of patients requiring a transfusion based on crude and Kaplan–Meier percentages were similar to those in the comparative and non-front-loading DA only analyses (Supplementary Table III). Again, more patients with a baseline Hb <9 g/dL needed transfusions than those with a baseline Hb 9–≤10 g/dL.

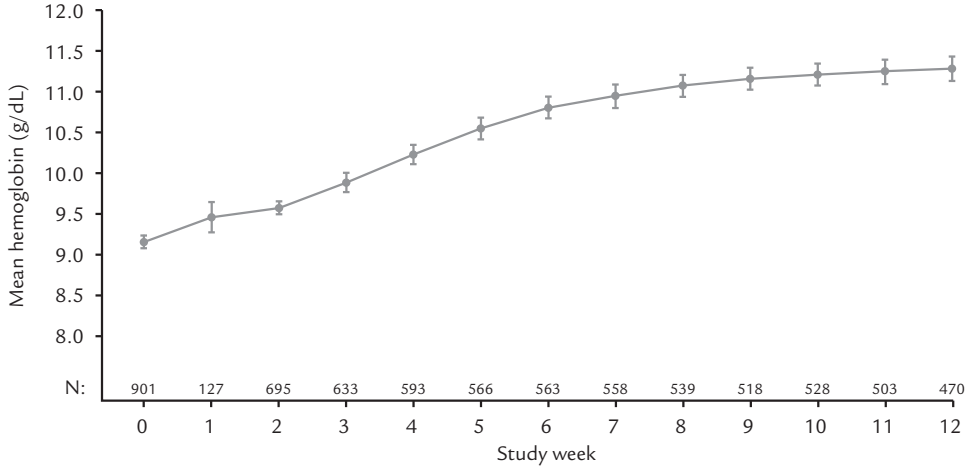

Figure S1. Mean hemoglobin levels during the first 12 weeks of treatment in the darbepoetin-only front-loading analyses. Error bars represent 95% confidence intervals.

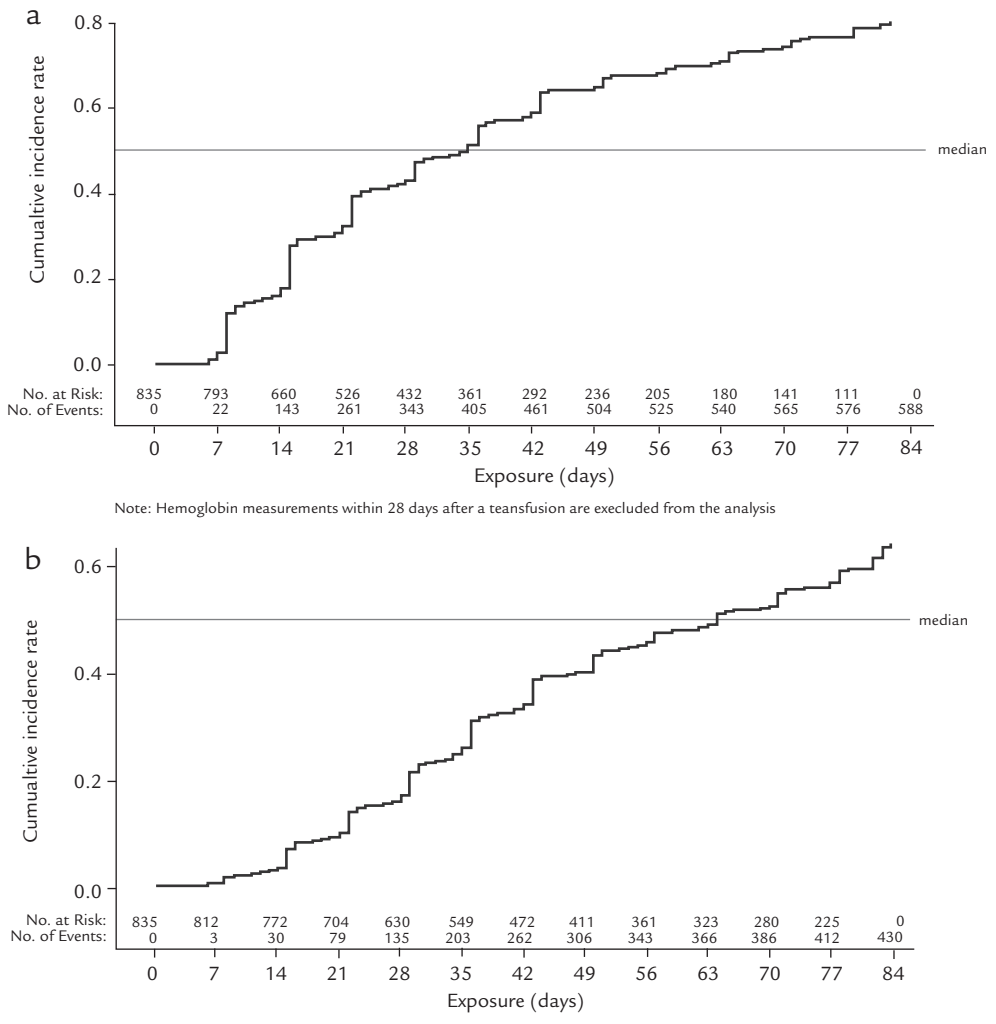

Figure S2. Kaplan–Meier curve for time to a) increase in hemoglobin of ≥ 1 g/dL during the first 12 weeks of treatment, and b) increase in hemoglobin of ≥ 2 g/dL during the first 12 weeks of treatment in patients receiving darbepoetin alfa (darbepoetin-only non-front-loading analysis).

Supplementary Table I. Studies with darbepoetin arms included in the darbepoetin-alfa-only front-loading dose analyses.

Study	Cancer population	Treatment duration (weeks)	Screening Hb level for study inclusion	Initial DA dose	Control	Hb indication for transfusion	Total patients enrolled who received study drug (n)	DA patients with Hb ≤10g/dL at baseline (n)	% of total patients
Glaspy et al. 2003	Solid tumors	12	≤11 g/dL	4.5 μg/kg/week	Epoetin alfa	≤8 g/dL*	92	53	58
ClinicalTrials.gov: NCT00038064	Non-myeloid malignancy	16	≤11 g/dL	4.5 μg/kg/week	Epoetin alfa	NS	353	183	52
Hesketh et al. 2004	Non-myeloid malignancy	16	<11 g/dL	4.5 μg/kg/week 325 μg QW	None	≤8 g/dL†	242	75	31
Pirker et al. 2008	Small-cell lung cancer	18	≤13 g/dL	300 μg QW	Placebo	NS	299	12	4
Kotasek et al. 2007	Non-myeloid malignancy	16	≤11 g/dL	4.5 μg/kg/week 2.25 μg/kg/week	None	≤8 g/dL†	723	439	61
ClinicalTrials.gov: NCT00111137	Non-myeloid malignancy	12	≤11 g/dL	4.5 μg/kg/week	Epoetin alfa	NS	353	139	39
	Total (6 studies)						2062	901	44

DA = darbepoetin alfa; Hb = hemoglobin; QW = every week; Q2W = every 2 weeks; Q3W = every 3 weeks.
*Transfusion with Hb >8 g/dL allowed if medically indicated.
†Recommended level; initiation of transfusion at the discretion of the investigators.

Supplementary Table II. Baseline characteristics of patients included in the darbepoetin-alfa-only front-loading dose analyses.

	Darbepoetin alfa (n = 901)
Male sex, n (%)	374 (42)
Age (years), mean [SD]	62.0 [13]
Age <65 years, n (%)	475 (53)
Tumor type, n (%)	
Breast	139 (15)
Gastrointestinal	173 (19)
Genitourinary	43 (5)
Gynecological	80 (9)
Hematological	222 (25)
Lung	170 (19)
Other	74 (8)
Disease stage, n (%)	
Stage II or lower/limited	91 (10)
Stage III or higher/extensive	729 (81)
Missing/other	81 (9)
ECOG performance status, n (%)	
0	225 (25)
1	400 (44)
2	100 (11)
3	3 (<1)
Missing	173 (19)
Hemoglobin (g/dL), mean [SD]	9.2 [0.7]

ECOG = Eastern Cooperative Oncology Group; SD = standard deviation.

Supplementary Table III. Summary of percentage (95% confidence interval) of patients with an increase in hemoglobin (Hb) ≥1 g/dL or ≥2 g/dL during the first 12 weeks of treatment or requiring a transfusion (red blood cell or whole blood) from start of week 5 to end of treatment in the darbepoetin-alfa-only front-loading dose analyses.

	Crude analysis	Kaplan–Meier analysis
All patients	(n=901)	(n=901)
Hb ≥1 g/dL	70 (67–73)	81 (77–84)
Hb ≥2 g/dL	51 (48–55)	65 (60–70)
Transfusion	26 (24–30)	28 (25–31)
Baseline Hb <9 g/dL	(n=290)	(n=290)
Hb ≥1 g/dL	68 (62–73)	77 (71–83)
Hb ≥2 g/dL	56 (50–62)	69 (61–77)
Transfusion	36 (30–42)	38 (32–44)
Baseline Hb 9–≤10 g/dL	(n=611)	(n=611)
Hb ≥1 g/dL	72 (68–75)	83 (78–87)
Hb ≥2 g/dL	49 (45–54)	63 (56–70)
Transfusion	22 (19–26)	24 (20–27)

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