A Randomized, Double-Blind, Placebo-Controlled, Phase III Noninferiority Study of the Long-Term Safety and Efficacy of Darbepoetin alfa for Chemotherapy-Induced Anemia in Patients With Advanced Non-Small Cell Lung Cancer

Pere Gascón, Rajnish Nagarkar, Martin Šmakal, Konstantinos N. Syrigos, Carlos H. Barrios, Jesús Cárdenas Sánchez, Li Zhang, David H. Henry, David Gordon, Vera Hirsh, Kaoru Kubota, Sergey Orlov, Gary Thomas, Tilman Steinmetz, Jin-Hyoung Kang, Dianne K. Tomita, Alexander N. Fleishman, Joseph K. Park, Cisio De Oliveira Brandao

PII: S1556-0864(19)33563-4

DOI: https://doi.org/10.1016/j.jtho.2019.10.005

Reference: JTHO 1613

To appear in: *Journal of Thoracic Oncology*

Received Date: 10 July 2019

Revised Date: 30 September 2019

Accepted Date: 3 October 2019

Please cite this article as: Gascón P, Nagarkar R, Šmakal M, Syrigos KN, Barrios CH, Sánchez JC, Zhang L, Henry DH, Gordon D, Hirsh V, Kubota K, Orlov S, Thomas G, Steinmetz T, Kang J-H, Tomita DK, Fleishman AN, Park JK, De Oliveira Brandao C, A Randomized, Double-Blind, Placebo-Controlled, Phase III Noninferiority Study of the Long-Term Safety and Efficacy of Darbepoetin alfa for Chemotherapy-Induced Anemia in Patients With Advanced Non-Small Cell Lung Cancer, *Journal of Thoracic Oncology* (2019), doi: https://doi.org/10.1016/j.jtho.2019.10.005.

A Randomized, Double-Blind, Placebo-Controlled, Phase III Noninferiority Study of the Long-Term Safety and Efficacy of Darbepoetin alfa for Chemotherapy-Induced Anemia in Patients With Advanced Non-Small Cell Lung Cancer

Authors: Pere Gascón,[a] Rajnish Nagarkar,[b] Martin Šmakal,[c] Konstantinos N. Syrigos,[d] Carlos H. Barrios,[e] Jesús Cárdenas Sánchez,[f] Li Zhang,[g] David H. Henry,[h] David Gordon,[i] Vera Hirsh,[j] Kaoru Kubota,[k] Sergey Orlov,[l] Gary Thomas,[m] Tilman Steinmetz,[n] Jin-Hyoung Kang,[o] Dianne K. Tomita,[p] Alexander N. Fleishman,[p] Joseph K. Park,[p] and Cisio De Oliveira Brandao[p]

Affiliations: [a]Department of Hematology-Oncology, Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain; [b]Curie Manavata Cancer Center, Nashik, India; [c]Nemocnice Hořovice, NH Hospital a.s., Hořovice, Czech Republic; [d]3rd Department of Medicine, Athens Medical School, Athens, Greece; [e]Centro de Pesquisa em Oncologia, PUCRS, Porto Alegre, Brazil; [f]Centro Medico de Colima, Colima, Mexico; [g]Sun Yat-Sen University Cancer Center, East Guangzhou, China; [h]University of Pennsylvania, Philadelphia, PA, USA; [i]Cancer Care Centers of South Texas and US Oncology Research Network, San Antonio, TX, USA; [j]MUHC Royal Victoria Hospital, Montreal, QC, Canada; [k]Nippon Medical School, Tokyo, Japan; [l]Saint Petersburg State Medical University, Saint Petersburg, Russian Federation; [m]South Carolina Cancer Specialists, Hilton Head Island, SC, USA; [n]Gemeinschaftspraxis für Hämatologie und Onkologie,

Köln, Germany; [o]The Catholic University of Korea, Seoul, South Korea; [p]Amgen Inc., Thousand Oaks, CA, USA

Research support: The study was funded by Amgen Inc.

Corresponding Author: Pere Gascón, MD, PhD
Department of Hematology-Oncology
Hospital Clínic de Barcelona, University of Barcelona C/Casanova 143, 08036
Barcelona, Spain
Tel. (34) 932275400 ext. 4829
E-mail: gascon@clinic.cat

Running Title: Darbepoetin alfa for Chemotherapy-Induced Anemia in NSCLC

Previous presentations: International Association for the Study of Lung Cancer (IASLC) 19th World Conference on Lung Cancer, Toronto, Canada, September 23–26, 2018; European Society for Medical Oncology (ESMO) 2018 Congress, Munich, Germany, October 19–23, 2018.

Potential Conflicts of Interest:

Pere Gascón has received honoraria from Amgen Inc., Sandoz, and Hospira (Pfizer); has received fees for a consulting or advisory role from Sandoz and Hospira (Pfizer); and has participated in speakers' bureaus with Amgen Inc., Sandoz, and Hospira (Pfizer). Konstantinos N. Syrigos has received honoraria from Bristol-Myers Squibb, Pfizer, and Roche; and discloses travel, accommodations, and expenses from Merck Sharp & Dohme (MSD). Carlos H. Barrios has stock/other ownership interests with Biomarker, MedSIR, and Tummi; has received honoraria from Boehringer Ingelheim, Eisai, GlaxoSmithKline, Novartis, Pfizer, Roche/Genentech, and Sanofi; has received fees for a consulting or advisory role from AstraZeneca, Boehringer Ingelheim, Eisai, GlaxoSmithKline, Libbs, MSD Oncology, Novartis, Pfizer, Roche/Genentech, and United Medical; has received research funding from AB Science,

AbbVie, Abraxis BioScience, Amgen Inc., Asana BioSciences, Astellas Pharma, AstraZeneca, Atlantis Clinica, BioMarin, Boehringer Ingelheim, Bristol-Myers Squibb (BMS), Celgene, Covance, Daiichi Sankyo, Exelixis, GlaxoSmithKline, Halozyme, ImClone Systems, INC Research, inVentiv Health, Janssen, LEO Pharma, Lilly, Medivation, Merck, Merrimack, Millennium, Mylan, Novartis, Pfizer, Roche/Genentech, Sanofi, and Taiho Pharmaceutical; and discloses travel, accommodations, and expenses from AstraZeneca, BMS Brazil, MSD Oncology, Novartis, Pfizer, and Roche/Genentech. Jesús Cárdenas Sánchez has received research funding from Amgen Inc. and Roche. Li Zhang's institution has received research funding from AstraZeneca, Bristol-Myers Squibb, and Pfizer. David H. Henry has received honoraria, fees for a consulting or advisory role, research funding, and discloses travel, accommodations, and expenses from Amgen Inc. David Gordon has stock/other ownership interests with Amgen Inc. (held by a charitable trust), Johnson & Johnson, and Gilead; and discloses travel, accommodations, and expenses from Amgen Inc. Vera Hirsh has received fees for a consulting or advisory role from Amgen Inc., AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Pfizer, and Roche. Kaoru Kubota has received honoraria from AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Kyowa Hakko Kirin, MSD, ONO, Sumitomo Dainippon, and Taiho; has received consulting fees from Taiho; and has received research funding from Boehringer Ingelheim, ONO, and Taiho. Gary Thomas has received consulting fees from AbbVie, Aptitude Health, Cardinal Health, Celgene, and Gilead Sciences; and has received research funding from Amgen Inc., Celgene, Cell Therapeutics, Incyte, Luitpold Pharmaceuticals, Puma Biotechnology, and Pharmacyclics. Tilman Steinmetz has received consulting fees from Amgen Inc., Alexion, ARIAD, Bristol-Myers Squibb, Celgene, Novartis, Janssen-Cilag, Pfizer, and Sanofi; has participated in speakers' bureaus for Amgen Inc., Celgene, and Novartis; has received research funding from Amgen Inc., Celgene, and Novartis; and discloses travel, accommodations, and expenses from Alexion, Amgen Inc., Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Janssen-Cilag, Novartis, Omnicare, and

Sanofi. Dianne K. Tomita, Alexander N. Fleishman, Joseph K. Park, and Cisio De Oliveira Brandao are employees of and hold stocks in Amgen Inc. Rajnish Nagarkar, Martin Šmakal, Sergey Orlov, and Jin-Hyoung Kang have nothing to disclose.

Abstract

Introduction: This study evaluated noninferiority of darbepoetin alfa versus placebo for overall survival (OS) and progression-free survival (PFS) in anemic patients with non-small cell lung cancer (NSCLC) treated to a 12.0-g/dL hemoglobin (Hb) ceiling.

Methods: Adults with stage IV NSCLC expected to receive ≥2 cycles of myelosuppressive chemotherapy and Hb≤11.0 g/dL were randomized 2:1 to blinded 500 µg darbepoetin alfa or placebo Q3W. The primary endpoint was OS; a stratified Cox proportional hazards model was used to evaluate noninferiority (upper confidence limit for hazard ratio [HR] <1.15). Secondary endpoints were PFS and incidence of transfusions or Hb≤8.0 g/dL from week 5 to end of the efficacy treatment period (EOETP).

Results: The primary analysis set included 2516 patients: 1680 randomized to darbepoetin alfa; 836 to placebo. The study was stopped early per independent Data Monitoring Committee recommendation after the primary endpoint was met with no new safety concerns. Darbepoetin alfa was noninferior to placebo for OS (stratified HR=0.92; 95%CI, 0.83–1.01) and PFS (stratified HR=0.95; 95%CI, 0.87–1.04). Darbepoetin alfa was superior to placebo for transfusion or Hb ≤8.0 g/dL from week 5 to EOETP (stratified OR=0.70; 95%CI, 0.57–0.86; *P*<.001). Objective tumor response was similar between the arms (darbepoetin alfa, 36.4%; placebo, 32.6%). Incidence of serious adverse events (AEs) was 31.1% in both arms. No unexpected AEs were observed.

Conclusions: Darbepoetin alfa dosed to a 12.0-g/dL Hb ceiling was noninferior to placebo for OS and PFS and significantly reduced odds of transfusion or Hb≤8.0 g/dL in anemic patients with NSCLC receiving myelosuppressive chemotherapy.

Keywords: darbepoetin alfa, chemotherapy-induced anemia, hemoglobin, lung cancer

Abbreviations: AE, adverse event; APPRISE, Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs; CI, confidence interval; CIA, chemotherapy-induced anemia; CRF, case report form; CTCAE, Common Terminology Criteria for Adverse Events; DMC, Data Monitoring Committee; EOETP, end of the efficacy treatment period; ESA, erythropoiesis-stimulating agents; FDA, Food and Drug Administration; Hb, hemoglobin; HR, hazard ratio; HRQOL, health-related quality of life; IVRS/IWRS, Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS); MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; OR, odds ratio; OS, overall survival; PFS, progression-free survival; PRCA, pure red cell aplasia; Q3W, every 3 weeks; RBCs, red blood cells; REMS, Risk Evaluation and Mitigation Strategy; SOC, standard of care; VTE, venous thromboembolic events.

Introduction

Chemotherapy-induced anemia (CIA) occurs frequently in patients with non-small cell lung cancer (NSCLC) receiving myelosuppressive chemotherapy.[1,2] Erythropoiesis-stimulating agents (ESAs) enhance production of red blood cells (RBCs) by activating the erythropoietin receptor on RBC progenitors.[3] Darbepoetin alfa is a long-acting ESA approved by regulatory authorities in many countries for the treatment of anemia in adult patients with nonmyeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy.[4-6]

Results from several studies in patients with breast and other types of tumors raised concerns regarding an increased risk of mortality and tumor progression with ESAs.[5-14] This study (ClinicalTrials.gov identifier, NCT00858364), along with the Risk Evaluation and Mitigation Strategy (REMS; implemented in 2011), was requested by the US Food and Drug Administration (FDA) and the European Medicines Agency to ensure that the benefits of ESAs for the treatment of CIA outweigh their risks. The REMS/APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) program was discontinued in 2017 after it was determined to no longer be necessary.[15] This placebo-controlled noninferiority study was initiated in 2009 and terminated in 2017. The primary objective was to demonstrate noninferiority of overall survival (OS) when comparing patients on darbepoetin alfa treated to a hemoglobin (Hb) ceiling of 12.0 g/dL to patients treated with placebo. Secondary objectives were to demonstrate noninferiority of progression-free survival (PFS), to demonstrate superiority in reducing the incidence of RBC transfusions or Hb ≤8.0 g/dL, and to assess other safety and

efficacy parameters, all in patients on darbepoetin alfa treated to a Hb ceiling of 12.0 g/dL compared with patients treated with placebo.

Patients and Methods

Patients

Adults included in the study had stage IV NSCLC (not recurrent or restaged) and were expected to receive at least 2 additional cycles (≥6 total weeks) of first-line myelosuppressive cyclic chemotherapy after randomization, an Eastern Cooperative Oncology Group performance status of 0 or 1 within the 21 days before randomization, a life expectancy >6 months, and Hb ≤11.0 g/dL as assessed by the local laboratory (sample obtained within the 7 days before randomization). Patients could receive chemotherapy in combination with other targeted therapy considered standard first-line therapy for NSCLC. Patients were excluded if they had a known primary benign or malignant hematologic disorder that could cause anemia; brain metastases; current active or prior cancer other than NSCLC; prior adjuvant or neoadjuvant therapy for NSCLC; or received an ESA or RBC transfusion within 28 days before randomization. Full inclusion and exclusion criteria are provided (**Supplemental Protocol**). All patients provided written informed consent.

Study Design

This randomized, double-blind, placebo-controlled, phase III, noninferiority study in anemic patients receiving multicycle chemotherapy for the treatment of stage IV NSCLC was conducted at 371 centers in Europe, Latin America, Asia, India, North America, Israel, and South Africa (**Supplemental Table 1**). The investigational products were darbepoetin alfa and placebo. This study was conducted in compliance with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and all applicable regulations/guidelines. Investigators obtained written

approval from local independent ethics committees or institutional review boards. The study consisted of a screening period, treatment period, and long-term follow-up period. Patients were randomized 2:1 to receive darbepoetin alfa 500 µg to a Hb ceiling of 12.0 g/dL or placebo every 3 weeks (Q3W; **Supplemental Figure 1**); randomization was stratified by geographic region, histology, and screening Hb (**Supplemental Table 2**). Randomization was based on a schedule generated before the study start and was centrally executed by an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

Blinding

Darbepoetin alfa was provided as a clear, colorless, sterile, preservative-free protein solution containing 100 µg, 200 µg, 300 µg, and 500 µg of darbepoetin alfa per mL in 1-mL, single-dose vials. Darbepoetin alfa and placebo were provided in similar containers, packaged and stored in the same manner, and identified by a unique box number for assignment via IVRS/IWRS. Darbepoetin alfa and placebo were administered subcutaneously Q3W to a Hb ceiling of 12.0 g/dL and were discontinued within 3 weeks after the last dose of chemotherapy, or upon disease progression, whichever occurred first. The IVRS/IWRS instructed investigators to withhold or reduce the dose of the investigational product (darbepoetin alfa or placebo), including for nonresponsiveness, rapid rate of Hb rise, and high Hb values. Information about dose adjustments and missed or delayed doses is provided (**Supplemental Protocol**). Patients, site personnel, and Amgen study personnel and designees were blinded to the randomized treatment group intervention.

Study Oversight, Interim Analyses, and Early Stopping Criteria

An independent Data Monitoring Committee (DMC) of external experts assessed safety throughout the study and could recommend modifying or stopping treatment or suspending randomization. An independent statistician also performed 5 planned interim analyses and provided interim results to the DMC.

Investigators could prescribe any therapy deemed necessary to provide adequate supportive care except an ESA other than darbepoetin alfa or other investigational drugs. Patients could also receive RBC transfusion, and supplementation with iron, folate, and vitamin B12 (**Supplemental Protocol**). Patients could withdraw from the study at any time and for any reason without prejudice to their medical care.

Endpoints

The primary endpoint was OS, measured from randomization to death from any cause; patients last known to be alive were censored from the last date of contact. Secondary endpoints were PFS and incidence of ≥1 RBC transfusion or Hb ≤ 8.0 g/dL from week 5 (day 29) to the end of the efficacy treatment period (EOETP). PFS was measured from randomization to disease progression or death from any cause; patients who did not die or progress were censored at their last disease assessment date. The EOETP was defined as 21 days after either the last dose of investigational product (darbepoetin alfa or placebo) or the last dose of chemotherapy, whichever was later. Other safety endpoints were the incidence of adverse events (AEs) such as thrombovascular events, venous thromboembolic events (VTEs), and AEs associated with RBC transfusions. The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 was used to code all treatment-emergent AEs to a system organ class and preferred term. The Common Terminology Criteria for Adverse Events (CTCAE) was used to grade AEs.

Objective tumor response (assessed using the version of Response Evaluation Criteria In Solid Tumors specified in the protocol at the time of patient enrollment using investigator-assessed scans) and the incidence of neutralizing antibody formation to darbepoetin alfa were other safety endpoints. Other efficacy endpoints were the incidence of ≥1 RBC transfusion or Hb ≤ 8.0 g/dL from study day 1 to EOETP and the change in Hb from baseline to EOETP.

Statistical Analysis

The primary hypothesis was that the OS of patients treated with darbepoetin alfa would not be worse than the OS of patients treated with placebo. A noninferiority design was used to test this hypothesis using an upper 95% confidence limit of the hazard ratio (HR; darbepoetin alfa to placebo) of 1.15 as the noninferiority margin. Originally, 3000 patients were planned to be enrolled to observe 2700 deaths, providing 93% power to demonstrate noninferiority (see **Supplemental Protocol** for a complete description of sample size considerations). To preserve the overall significance level, statistical testing was hierarchical: noninferiority for OS was tested first, followed by noninferiority for PFS, and then superiority of darbepoetin alfa for incidence of RBC transfusions or Hb ≤ 8.0 g/dL. If all three tests were affirmative, then superiority of darbepoetin alfa was tested for both OS and PFS using the Hochberg procedure. For other endpoints, *P* values were considered descriptive, and no adjustments were made for multiplicity.

The primary analysis set for OS included all randomized patients with NSCLC who received ≥1 dose of darbepoetin alfa or placebo. The analysis set for PFS included patients in the primary analysis who did not have disease progression before randomization; the analysis set for the incidence of transfusion or Hb ≤8.0 g/dL from day 29 to EOETP included patients in the primary analysis whose EOETP was at least day

29; and the analysis set for safety included all randomized patients who received ≥1 dose of darbepoetin alfa or placebo, analyzed according to investigational product received. For OS and PFS, HR and 95% confidence intervals (CI) were calculated using a Cox proportional hazards model, stratified by the stratification factors at randomization, with treatment group as the only covariate. Kaplan-Meier curves, percentages at select time points, and medians were also estimated. The treatment effect for dichotomous endpoints (eg, the incidence of RBC transfusions or Hb ≤ 8.0 g/dL) was tested, if appropriate, using a two-sided Cochran-Mantel-Haenszel test adjusted for stratification factors at randomization at a significance level of 0.05 and summarized with a Mantel-Haenszel common odds ratio and 95% CI summarized over the stratification factors. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Starting on July 17, 2009 until June 7, 2017, a total of 4161 patients were screened and 2549 were randomized to receive darbepoetin alfa (n=1703) or placebo (n=846; **Figure 1**). The target sample size of 3000 patients was not reached because the study was terminated early after the independent DMC concluded that the primary objective of noninferiority for OS had been met with no new safety concerns and recommended that enrollment be stopped. Patient disposition is summarized in **Supplemental Table 3**. The primary analysis set included 2516 patients: 1680 who received darbepoetin alfa and 836 who received placebo. The safety analysis set included 2518 patients: 1685 who received darbepoetin alfa and 833 who received placebo. Reasons for discontinuing treatment are included in **Figure 1**. Most patients discontinued treatment because of protocol-specified criteria, including radiographic disease progression (28% darbepoetin alfa, 30% placebo) and ending chemotherapy (36% darbepoetin alfa, 34% placebo). Median duration of follow-up was measured as the Kaplan-Meier time to censoring. For OS, the duration was 30.36 months for darbepoetin alfa and 33.18 months for placebo; for PFS, the duration was 39.36 months for darbepoetin alfa and 55.79 months for placebo. The median (range) weight-adjusted average weekly dose was 3.0 (0.3–16.7) µg/kg/week for patients who received darbepoetin alfa.

Baseline demographic and disease characteristics are listed in **Table 1**. Overall, patient characteristics were largely balanced between treatment arms. The majority of patients (66%) were men and white/Caucasian (48%) or Asian (43%); the median age was 62 years. The majority (68%) had previous chemotherapy for NSCLC and 32% had no previous treatment for NSCLC. Median baseline Hb was 10.1 g/dL.

A total of 99.7% and 100% of patients in the darbepoetin alfa and placebo groups, respectively, received concomitant medications during the study. Concomitant medications reported for >25% of the patients in the groups were consistent with those expected for patients with advanced NSCLC receiving multicycle chemotherapy and included carboplatin (66.8% darbepoetin alfa, 69.1% placebo), dexamethasone (68.3%, 67.8%), ondansetron (39.8%, 40.9%), paclitaxel (38.6%, 39.5%), and cisplatin (28.2%, 26.5%).

Primary Endpoint

In the primary analysis set, 1269 of 1680 patients (75.5%) in the darbepoetin alfa group and 660 of 836 patients (78.9%) in the placebo group died during the study (**Supplemental Table 4**). Darbepoetin alfa demonstrated noninferiority to placebo for OS; the upper confidence limit of 1.01 was less than the prespecified noninferiority margin of 1.15 (stratified HR=0.92; 95% CI, 0.83–1.01; **Figure 2A**). Median OS was 9.46 months in the darbepoetin alfa group and 9.26 months in the placebo group. OS assessed by stratification variables is shown in **Figure 2B**. In analyses evaluating the treatment effect on OS by variables of interest, the unstratified HR was <1 for all subgroups evaluated, except for patients with a history of VTE (HR=1.13; 95% CI, 0.73–1.77; **Figure 2C**).

Secondary Endpoints

After noninferiority of darbepoetin alfa to placebo for OS was established, noninferiority of darbepoetin alfa to placebo for PFS was formally evaluated. In the radiographic endpoint primary analysis set, 1396 of 1631 patients (85.6%) in the darbepoetin alfa group and 725 of 818 patients (88.6%) in the placebo group progressed or died during the study (**Supplemental Table 5**). Darbepoetin alfa demonstrated noninferiority to

placebo for PFS; the upper confidence limit of 1.04 was less than the prespecified noninferiority margin of 1.15 (stratified HR=0.95; 95% CI, 0.87–1.04; **Figure 3A**). The median PFS was 4.44 months in the darbepoetin alfa group and 4.27 months in the placebo group. PFS assessed by stratification variables is shown in **Figure 3B**. The treatment effect on PFS by factors of interest is shown in **Figure 3C**.

Subsequently, the superiority of darbepoetin alfa in reducing the incidence of RBC transfusion or Hb ≤8.0 g/dL from week 5 to EOETP was formally tested. In the darbepoetin alfa group, 342 patients (22.5%) had an RBC transfusion or Hb ≤8.0 g/dL compared with 223 patients (29.2%) in the placebo group (**Supplemental Table 6**). Darbepoetin alfa demonstrated superiority to placebo for RBC transfusions or Hb ≤8.0 g/dL (stratified odds ratio=0.70; 95% CI, 0.57–0.86; *P*=.0008). Additional transfusion results are provided in **Supplemental Tables 6** and **7**.

After superiority of darbepoetin alfa for the above endpoint was shown, superiority for OS and PFS was tested. Superiority of darbepoetin alfa to placebo with respect to OS (stratified log-rank *P*=.07) and PFS (stratified log-rank *P*=.26) was not demonstrated (**Supplemental Tables 4** and **5**).

Objective tumor response was observed in 593 patients (36.4%) receiving darbepoetin alfa and 267 patients (32.6%) receiving placebo; approximately 1% of patients in each group had a complete response. The stratified odds ratio was 1.18 (95% CI, 0.99–1.41) in favor of darbepoetin alfa.

The mean change in Hb from baseline to the EOETP was 0.42 (95% CI, 0.33–0.51) g/dL in the darbepoetin alfa group and −0.12 (95% CI, −0.25 to −0.00) g/dL in the placebo group.

A total of 1508 patients in the darbepoetin alfa group and 761 patients in the placebo group had a predose antibody result; 1606 patients and 803 patients, respectively, had a postbaseline antibody result. Although some patients developed darbepoetin alfa–binding antibodies during the study (3.1% darbepoetin alfa, 2.4% placebo), no patients developed neutralizing antibodies.

Adverse Events

Overall, 84.5% and 86.3% of patients in the darbepoetin alfa and placebo groups, respectively, experienced treatment-emergent AEs (**Table 2**). The most frequently reported AEs were anemia, neutropenia, nausea, asthenia, and thrombocytopenia. No event occurred with a >5% higher patient incidence among patients receiving darbepoetin alfa compared with placebo. Percentages of patients with AEs that were grade ≥3 or ≥4 were similar between treatment groups (**Table 2**). A total of 205 patients (12.2%) in the darbepoetin alfa group and 113 patients (13.6%) in the placebo group had fatal AEs during the study (**Supplemental Table 8**).

The most frequent AEs of interest were hypersensitivity (10.6% darbepoetin alfa, 9.0% placebo) and embolic and thrombotic events (5.3% darbepoetin alfa, 4.1% placebo; **Table 2**). The most frequently reported AEs in the hypersensitivity, hypertension, and severe cutaneous reaction categories are listed in **Supplemental Table 9**.

The most frequently reported AEs in the embolic and thrombotic events category were pulmonary embolism (1.6% darbepoetin alfa, 1.0% placebo) and deep vein thrombosis (1.1% darbepoetin alfa, 1.1% placebo). All other AEs of interest in the embolic and thrombotic events category were reported for <1.0% of patients in either treatment group. Serious embolic and thrombotic AEs were reported more frequently for

darbepoetin alfa than for placebo. The most frequently reported serious AE in this category was pulmonary embolism. In a separate prespecified analysis, the incidence of VTEs was 2.8% in the darbepoetin alfa group and 2.3% in the placebo group; the incidence of VTEs confirmed by imaging was 1.8% in each treatment group (**Table 3**).

Because pure red cell aplasia (PRCA) is a rare event, a broad search strategy of seven different preferred terms was used to avoid missing potential cases (**Table 2** and footnote). The only preferred term in the antibody-mediated PRCA category was bone marrow failure; no cases of antibody-mediated PRCA were identified for any patient.

Additional Analyses

Following the submission of the results of this trial to the FDA in a prior approval supplement, the FDA requested that additional analyses be performed. These analyses included a summary of OS using the full analysis set (including data collected by sites after consent was withdrawn) and case report form (CRF) values for the stratified analyses rather than IVRS/IWRS values (**Supplemental Table 10**). The FDA also requested a summary of PFS using the full analysis set (including data collected by sites after consent was withdrawn), excluding patients with progression dates prior to randomization, and using CRF values for the stratified analyses rather than IVRS/IWRS values (**Supplemental Table 11**). The results of these ad hoc analyses were consistent with the primary analyses, and they are included in United States Package Insert.[5]

Discussion

In this phase III, randomized, double-blind, placebo-controlled, noninferiority study in patients with advanced NSCLC receiving multicycle chemotherapy, darbepoetin alfa demonstrated noninferiority to placebo for OS and PFS. Darbepoetin alfa also demonstrated superiority to placebo in reducing the incidence of RBC transfusions or Hb ≤ 8.0 g/dL from week 5 to EOETP. This result is clinically significant because reducing the need for transfusions may diminish transfusion-associated risks.[16] AEs were consistent with the known safety profile of darbepoetin alfa. VTEs occurred in 2.8% of patients in the darbepoetin alfa group and 2.3% in the placebo group. The results of this study contribute new important information to longstanding discussions about the safety of darbepoetin alfa, and they may impact clinical practice.

Like the current trial, the EPO-ANE-3010 study (ClinicalTrials.gov identifier, NCT00338286) was conducted following an FDA postmarketing request.[17] EPO-ANE-3010 was an open-label, noninferiority study designed to examine the effect of epoetin alfa on outcomes compared with best standard of care (SOC) in 2098 women undergoing chemotherapy for metastatic breast cancer.[17] In contrast to our study, the primary endpoint of EPO-ANE-3010 was PFS, and noninferiority of epoetin alfa to best SOC was not demonstrated (HR=1.094; 95% CI, 0.996–1.201) because the upper limit exceeded 1.150.[17,18] In the final analysis of EPO-ANE-3010, PFS and OS were further assessed by an independent review committee.[18] Median PFS was the same for each group (7.6 months), and although a 3% risk increase in the epoetin alfa plus SOC group was observed, the noninferiority criteria were met (HR=1.028; 95% CI, 0.922–1.146).[18] In the final analysis of OS, median OS was 17.8 months in the epoetin alfa plus SOC group and 18.0 months in the SOC group.[18] A 7% risk increase in the epoetin alfa plus

SOC was observed and noninferiority criteria were not met (HR=1.073; 95% CI, 0.974–1.182).[18] Point estimates for median PFS and OS in the EPO-ANE-3010 study were therefore very similar between the arms. The median duration of ESA treatment was <3 months and the PFS and OS curves only differed after 12 months.[17,18]

There are multiple differences between the EPO-ANE-3010 study and the current study that may help explain why the EPO-ANE-3010 study did not meet its primary endpoint of PFS while this study met its primary endpoint of OS. Differences included the ESA examined (epoetin alfa versus darbepoetin alfa), tumor types (breast versus NSCLC), patient populations (women versus 66% men, median age 52 versus 62 years), lines of therapy (first and second versus first only), and chemotherapy regimens. The EPO-ANE-3010 trial was designed to provide more than 80% power to exclude an HR of 1.15 with a 1-sided significance level of 0.025 against SOC treatment; the present study was designed to provide more than 90% power to exclude the same HR and significance level against patients given blinded placebo.

The present study is consistent with the results of several studies, including meta-analyses, which have concluded that ESAs increase Hb and reduce the need for transfusions[19] without increasing mortality or disease progression in patients with lung or other cancers undergoing chemotherapy.[20-24] Other studies showed a negative effect on OS and/or PFS in patients who received ESAs.[10-14] Many of these studies included patients who received ESAs outside of the current indication; for example, patients were not receiving chemotherapy or were treated to a Hb target greater than that used in this study.[10-14] In the present study, the point estimate of the HR for OS was higher in patients with a history of VTEs than in patients without a history of VTEs. The risk of

VTEs should be weighed against the benefits to be derived from treatment with darbepoetin alfa in the studied NSCLC population.

This study has several strengths. The study design, including Hb initiation and ceiling levels, was intended to allow sufficient exposure to the study drug to evaluate safety outcomes while minimizing risks and maintaining potential benefits. Additional ad hoc analyses of OS and PFS in broader patient populations that were requested by the FDA gave results consistent with those of the prespecified analyses.

This study also has potential limitations. Darbepoetin alfa was the only ESA examined. Furthermore, health-related quality of life (HRQOL) was not examined, although HRQOL improvement has been shown in patients with a variety of tumor types, including NSCLC, treated with darbepoetin alfa for CIA.[25] This study did not include patients who received chemotherapy in combination with the latest checkpoint inhibitors; nonetheless, the results remain relevant to current practice, because newer immuno-oncology agents are used in combination with myelosuppressive chemotherapy.

Conclusion

In this large, randomized, double-blind, placebo-controlled, multicenter, global study of patients with stage IV NSCLC and CIA, darbepoetin alfa was noninferior to placebo for OS and PFS and superior to placebo for RBC transfusion or Hb ≤8.0 g/dL. Safety findings were consistent with the known safety profile of darbepoetin alfa. In light of the results of this study, darbepoetin alfa should be considered for patients with stage IV NSCLC and anemia concomitant with chemotherapy.

Acknowledgments

The authors acknowledge Miranda Tradewell, PhD, and James Balwit, MS, CMPP (from Complete Healthcare Communications, LLC, an ICON plc company, North Wales, PA, USA), whose work was funded by Amgen Inc., and Micah Robinson of Amgen Inc. for assistance in writing this manuscript. Sharon Hunter, MS, provided biostatistical support (funded by Amgen). The authors would also like to acknowledge the patients and their families and Global Clinical Trials Manager Natasha Gicanov of Amgen Inc.

Data Sharing

There is a plan to share data. This may include de-identified individual patient data for variables necessary to address the specific research question in an approved data sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and 1) this product and indication (or other new use) have been granted marketing authorization in both the US and Europe, or 2) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labelling. A committee of internal advisors reviews requests. If not approved, requests may be further arbitrated by a Data Sharing

Independent Review Panel. Requests that pose a potential conflict of interest or an actual or potential competitive risk may be declined at Amgen's sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available at the following: https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/.

List of Supplemental Materials

Supplemental Protocol.pdf

Supplemental Table 1.pdf

Supplemental Table 2.pdf

Supplemental Table 3.pdf

Supplemental Table 4.pdf

Supplemental Table 5.pdf

Supplemental Table 6.pdf

Supplemental Table 7.pdf

Supplemental Table 8.pdf

Supplemental Table 9.pdf

Supplemental Table 10.pdf

Supplemental Table 11.pdf

Supplemental Figure 1.pdf

References

1. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst* 1999;91:1616-1634.
2. Ludwig H, Aapro M, Bokemeyer C, et al. Treatment patterns and outcomes in the management of anaemia in cancer patients in Europe: findings from the Anaemia Cancer Treatment (ACT) study. *Eur J Cancer* 2009;45:1603-1615.
3. Elliott S, Pham E, Macdougall IC. Erythropoietins: a common mechanism of action. *Exp Hematol* 2008;36:1573-1584.
4. Egrie JC, Dwyer E, Browne JK, Hitz A, Lykos MA. Darbepoetin alfa has a longer circulating half-life and greater in vivo potency than recombinant human erythropoietin. *Exp Hematol* 2003;31:290-299.
5. Aranesp® (darbepoetin alfa). Full Prescribing Information, Amgen Inc., Thousand Oaks, CA, 2019.
6. European Medicines Agency. Aranesp: EPAR - Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000332/WC500026149.pdf. Accessed December 11, 2018.
7. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA* 2008;299:914-924.
8. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst* 2006;98:708-714.

9. Bohlius J, Langensiepen S, Schwarzer G, et al. Recombinant human erythropoietin and overall survival in cancer patients: results of a comprehensive meta-analysis. *J Natl Cancer Inst* 2005;97:489-498.

10. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005;23:5960-5972.

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

12. Smith RE, Jr., Aapro MS, Ludwig H, et al. Darbepoetin alpha for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Oncol* 2008;26:1040-1050.

13. Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol* 2008;108:317-325.

14. Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* 2007;25:1027-1032.

15. US Food and Drug Administration. Information on erythropoiesis-stimulating agents (ESA) epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp). Available at: https://www.fda.gov/Drugs/DrugSafety/ucm109375.htm. Accessed October 22, 2018.

16. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Cancer- and chemotherapy-induced anemia - version 3.2018. Accessed November 20, 2018.

17. Leyland-Jones B, Bondarenko I, Nemsadze G, et al. A Randomized, Open-Label, Multicenter, Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy. *J Clin Oncol* 2016;34:1197-1207.

18. Leyland-Jones B, Bondarenko I, Nemsadze G, et al. Abstract P1-14-01: Final analysis of overall survival (OS) for the epoetin alfa (EPO) phase 3 study, EPO-ANE-3010, of EPO plus standard supportive care (SOC) versus SOC in anemic patients with metastatic breast cancer (MBC) receiving standard chemotherapy. *Cancer Res* 2018;78:P1-14-01.

19. Boccia RV, Henry DH, Belton L, Bohac C, Ghazal HH. Efficacy and safety of darbepoetin alfa initiated at hemoglobin ≤10 g/dL in patients with stage IV cancer and chemotherapy-induced anemia. *Cancer Med* 2016;5:3445-3453.

20. Vansteenkiste J, Glaspy J, Henry D, et al. Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: study-level and patient-level meta-analyses. *Lung Cancer* 2012;76:478-485.

21. Ludwig H, Crawford J, Osterborg A, et al. Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. *J Clin Oncol* 2009;27:2838-2847.

22. Tsuboi M, Ezaki K, Tobinai K, Ohashi Y, Saijo N. Weekly administration of epoetin beta for chemotherapy-induced anemia in cancer patients: results of a multicenter, phase III, randomized, double-blind, placebo-controlled study. *Jpn J Clin Oncol* 2009;39:163-168.

23. Fonseca PJ, Esteban E, de Vicente P, et al. Impact of erythropoietin on the reduction of blood transfusions and on survival of lung cancer patients receiving first-line chemotherapy. *Clin Transl Oncol* 2008;10:426-432.

24. Glaspy J, Crawford J, Vansteenkiste J, et al. Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. *Br J Cancer* 2010;102:301-315.

25. Mouysset JL, Freier B, van den Bosch J, et al. Hemoglobin levels and quality of life in patients with symptomatic chemotherapy-induced anemia: the eAQUA study. *Cancer Manag Res* 2016;8:1-10.

Figure Legends

Figure 1. CONSORT diagram. IVRS/IWRS, Interactive Voice Response System/Interactive Web Response System. [a]2 patients allocated to darbepoetin alfa only received placebo and 6 patients allocated to placebo received at least 1 dose of darbepoetin alfa; thus, 1685 and 833 patients were included in the safety analyses for the darbepoetin alfa and placebo treatment groups, respectively.

Figure 2. Overall survival. (A) Kaplan-Meier estimates of OS in the primary analysis set. The stratified HR and 95% CI were obtained from the Cox proportional hazards model. Stratification factors were geographic region, histology, and screening Hb. (B) OS assessed by stratification variables comparing darbepoetin alfa and placebo. (C) Unstratified HR for darbepoetin alfa versus placebo forest plot of OS by covariates of interest in the primary analysis set. EGFR, epidermal growth factor receptor; EPO, erythropoietin; Hb, hemoglobin; HR, hazard ratio; OS, overall survival; VTE, venous thromboembolic event.

Figure 3. Progression-free survival. (A) Kaplan-Meier estimates of PFS in the primary analysis set. The stratified HR and 95% CI were obtained from the Cox proportional hazards model. Stratification factors were geographic region, histology, and screening Hb. (B) PFS assessed by stratification variables comparing darbepoetin alfa and placebo. (C) Unstratified HR for darbepoetin alfa versus placebo forest plot of PFS by

covariates of interest in the radiographic endpoint primary analysis set. EGFR, epidermal growth factor receptor; EPO, erythropoietin; Hb, hemoglobin; HR, hazard ratio; PFS, progression-free survival; VTE, venous thromboembolic event.

Table 1. Baseline Demographics and Disease Characteristics in the Primary Analysis Set[a]

Characteristic	Darbepoetin alfa (n=1680)	Placebo (n=836)	Total (N=2516)
Sex, n (%)			
Male,	1103 (65.7)	557 (66.6)	1660 (66.0)
Female	577 (34.3)	279 (33.4)	856 (34.0)
Race, n (%)			
White or Caucasian	796 (47.4)	400 (47.8)	1196 (47.5)
Black or African American	44 (2.6)	26 (3.1)	70 (2.8)
Asian	734 (43.7)	352 (42.1)	1086 (43.2)
Japanese	12 (0.7)	7 (0.8)	19 (0.8)
Other	14 (0.8)	6 (0.7)	20 (0.8)
Median (range) age, y	62.0 (26–88)	63.0 (27–88)	62.0 (26–88)
Median (range) weight, kg	61.0 (24.0–143.6)	60.1 (29.6–151.0)	60.9 (24.0–151.0)
ECOG performance status, n (%)			
0	366 (21.8)	173 (20.7)	539 (21.4)
1	1307 (77.8)	658 (78.7)	1965 (78.1)
2	7 (0.4)	5 (0.6)	12 (0.5)
Histology, n (%)			
Squamous	593 (35.3)	287 (34.3)	880 (35.0)
All other	1087 (64.7)	549 (65.7)	1636 (65.0)
Prior treatment for NSCLC before randomization, n (%)			
Chemotherapy	1151 (68.5)	565 (67.6)	1716 (68.2)
Platinum-containing	1118 (66.5)	548 (65.6)	1666 (66.2)
Other	562 (33.5)	288 (34.4)	850 (33.8)
Immunotherapy	6 (0.4)	1 (0.1)	7 (0.3)
Hormonal therapy	0 (0)	0 (0)	0 (0)
Targeted biologics	61 (3.6)	22 (2.6)	83 (3.3)
Targeted small molecules	7 (0.4)	2 (0.2)	9 (0.4)
Other	9 (0.5)	5 (0.6)	14 (0.6)

None	529 (31.5)	271 (32.4)	800 (31.8)
Prior anticancer surgery for NSCLC, n (%)	22 (1.3)	14 (1.7)	36 (1.4)
Median (range) baseline Hb[b,c], g/dL	10.20 (3.8–14.8)	10.10 (6.0–15.6)	10.10 (3.8–15.6)
Baseline Hb group (g/dL)[b,c], n (%)			
<10	722 (43.2)	388 (46.9)	1110 (44.4)
≥10–11	561(33.6)	237 (28.7)	798 (31.9)
≥11	389 (23.3)	202 (24.4)	591 (23.6)
Median (range) erythropoietin, U/L	38.26 (5.0–2828.1)	39.11 (5.0–2126.0)	38.52 (5.0–2828.1)
Median (range) platelets, 10^9/L	311.0 (9–1086)	304.5 (25–1460)	309.0 (9–1460)
Median (range) ferritin, µg/L	346.75 (10.3–8989.5)	334.25 (3.1–4914.0)	342.95 (3.1–8989.5)
Median (range) transferrin saturation, %	21.0 (3.0–95.0)	20.0 (4.0–97.0)	20.0 (3.0–97.0)
Median (range) iron, µg/dL	47.0 (7.0–366.0)	47.0 (6.0–368.0)	47.0 (6.0–368.0)
History of venous thromboembolic events[d], n (%)	84 (5.0)	44 (5.3)	128 (5.1)
History of arterial thromboembolic events[e], n (%)	51 (3.0)	30 (3.6)	81 (3.2)

ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; NSCLC, non-small cell lung cancer.

[a]The primary analysis set included all randomized patients with non-small cell lung cancer who provided informed consent and received ≥1 dose of investigational product.

[b]Baseline is defined as study day 1. If Hb on study day 1 was not available, the closest central Hb within 7 days before randomization/study day 1 was used.

[c]Eligibility and randomization strata were determined based on study entry Hb, which was assessed by a local laboratory in a sample obtained within 7 days before randomization. Of the 2516 patients included in the primary analysis set, 2510 patients had Hb ≤11.0 g/dL at study entry.

[d]Includes thromboembolic events, cerebrovascular accidents, and transient ischemic events.

[e]Includes cerebrovascular accidents and transient ischemic events.

Table 2. Summary of Patient Incidence of Treatment-Emergent Adverse Events in the Safety Analysis Set[a]

Adverse event, n (%)	Darbepoetin alfa (n=1685)	Placebo (n=833)
All treatment-emergent adverse event[b]	1424 (84.5)	719 (86.3)
Serious adverse events	524 (31.1)	259 (31.1)
Leading to discontinuation of investigational product	48 (2.8)	35 (4.2)
Fatal adverse events	205 (12.2)	113 (13.6)
Grade ≥ 3 in any system organ class	831 (49.3)	440 (52.8)
Grade ≥ 4 in any system organ class	354 (21.0)	178 (21.4)
Treatment-emergent adverse events[b] occurring in ≥ 5% of all patients		
Anemia	485 (28.8)	273 (32.8)
Neutropenia	215 (12.8)	84 (10.1)
Nausea	190 (11.3)	103 (12.4)
Asthenia	168 (10.0)	97 (11.6)
Thrombocytopenia	177 (10.5)	78 (9.4)
Dyspnea	132 (7.8)	82 (9.8)
Cough	150 (8.9)	53 (6.4)
White blood cell count decreased	138 (8.2)	65 (7.8)
Decreased appetite	139 (8.2)	63 (7.6)
Platelet count decreased	135 (8.0)	67 (8.0)
Alopecia	125 (7.4)	70 (8.4)
Fatigue	117 (6.9)	70 (8.4)
Vomiting	125 (7.4)	58 (7.0)
Pyrexia	121 (7.2)	60 (7.2)
Constipation	110 (6.5)	56 (6.7)
Diarrhea	116 (6.9)	50 (6.0)
Leukopenia	105 (6.2)	41 (4.9)
Neutrophil count decreased	95 (5.6)	47 (5.6)
Treatment-emergent adverse events of interest[b]		
Hypersensitivity (SMQ)	178 (10.6)	75 (9.0)
Embolic and thrombotic events (SMQ)	89 (5.3)	34 (4.1)

Embolic and thrombotic events, venous (SMQ)	51 (3.0)	23 (2.8)
Antibody-mediated pure red cell aplasia (EOI)[c]	51 (3.0)	20 (2.4)
Hypertension (SMQ)	41 (2.4)	26 (3.1)
Malignancies (SMQ)	38 (2.3)	16 (1.9)
Severe cutaneous adverse reactions (SMQ)	35 (2.1)	11 (1.3)
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)	26 (1.5)	10 (1.2)
Central nervous system vascular disorders (SMQ)	25 (1.5)	8 (1.0)
Ischemic heart disease (SMQ)	23 (1.4)	9 (1.1)
Embolic and thrombotic events, arterial (SMQ)	19 (1.1)	6 (0.7)
Cardiac failure (SMQ)	12 (0.7)	7 (0.8)
Convulsions (SMQ)	9 (0.5)	8 (1.0)

EOI, event of interest; SMQ, standardized MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities.

[a]The safety analysis set included all randomized patients who provided informed consent and received ≥1 dose of investigational product analyzed by actual treatment group.

[b]Treatment-emergent adverse events included all adverse events that began between the first administration of study treatment and 30 days after the last administration of study treatment.

[c]The preferred terms used in the broad search strategy included anti-erythropoietin antibody positive, aplasia pure red cell, aspiration bone marrow abnormal, bone marrow disorder, bone marrow failure, drug-specific antibody present, and neutralizing antibodies positive. The only preferred term with reported events in this broad search was bone marrow failure; no cases of antibody-mediated pure red cell aplasia were identified for any patient.

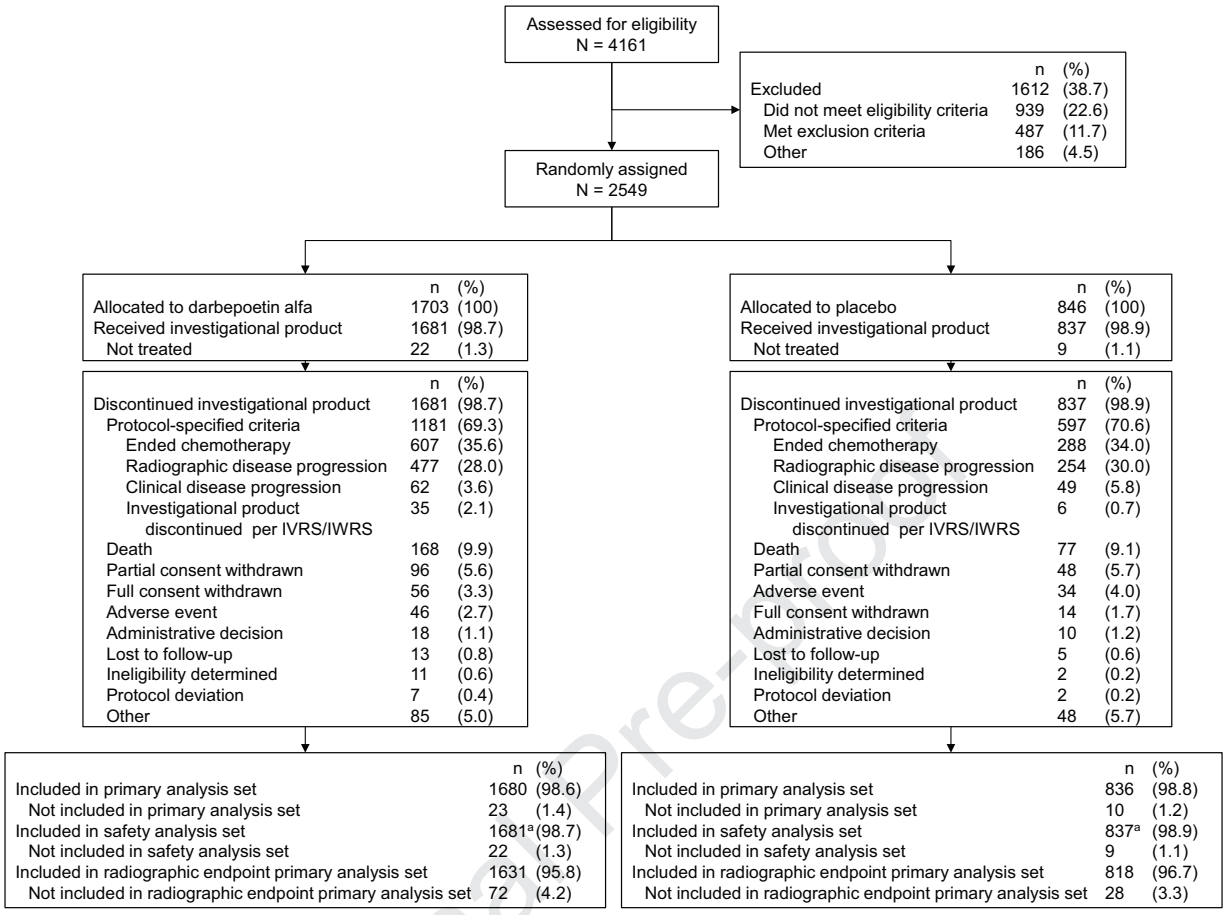
Table 3. Thrombovascular Events in the Safety Analysis Set[a]

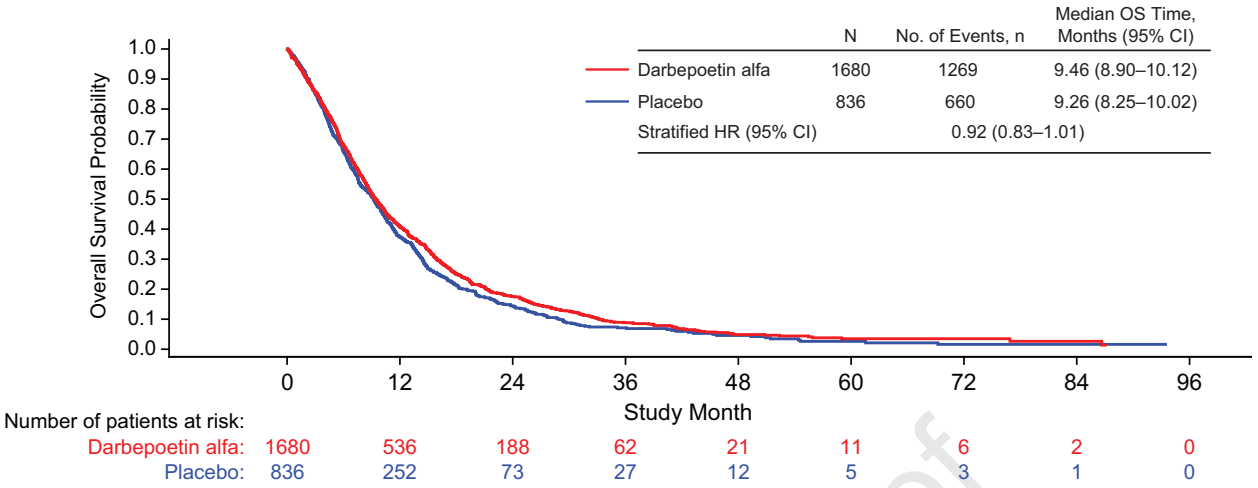
	Darbepoetin alfa (n=1685) n (%)	Placebo (n=833) n (%)
Reported embolic and thrombotic events		
VTE	48 (2.8)	19 (2.3)
CTCAE grade 4 events	4 (0.2)	4 (0.5)
Fatal (grade 5) events	10 (0.6)	3 (0.4)
Was VTE confirmed by imaging?		
Yes	31 (1.8)	15 (1.8)
No	17 (1.0)	4 (0.5)
If yes, specify imaging modality		
Computed tomography	17 (1.0)	6 (0.7)
Magnetic resonance imaging	0 (0)	0 (0)
Duplex Doppler	13 (0.8)	3 (0.4)
Venography	0 (0)	0 (0)
Angiography	2 (0.1)	0 (0)
Ventilation perfusion lung scan	0 (0)	0 (0)
Other	4 (0.2)	6 (0.7)

CTCAE, Common Terminology Criteria for Adverse Events; VTE, venous thromboembolic event.

[a]The safety analysis set included all randomized patients who provided informed consent and received ≥1 dose of investigational product analyzed by actual treatment.

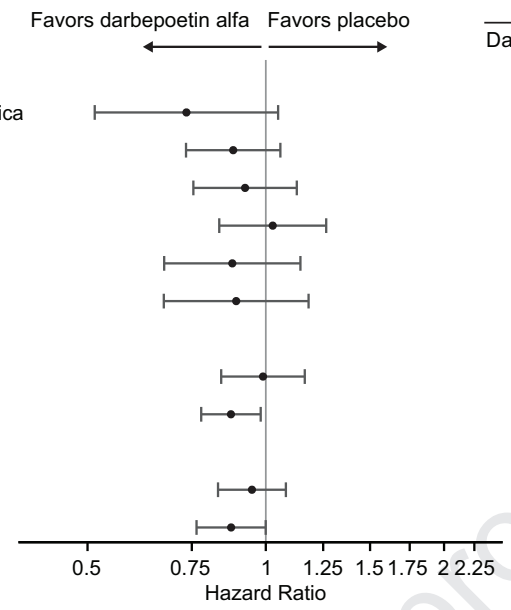
Only includes patients who reported a VTE on the VTE or serious VTE case report form pages.



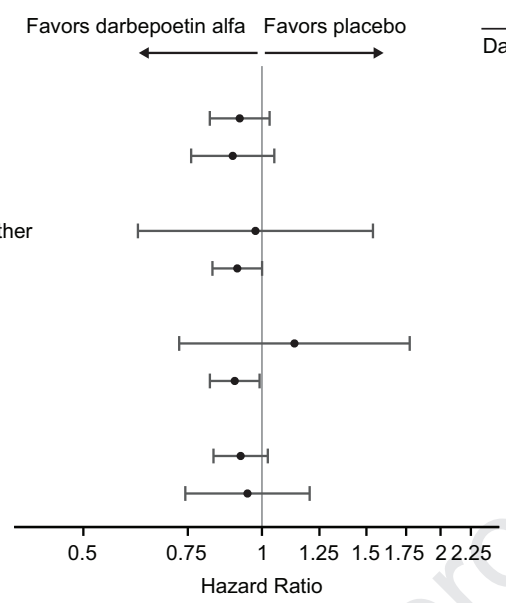


Number of patients at risk:

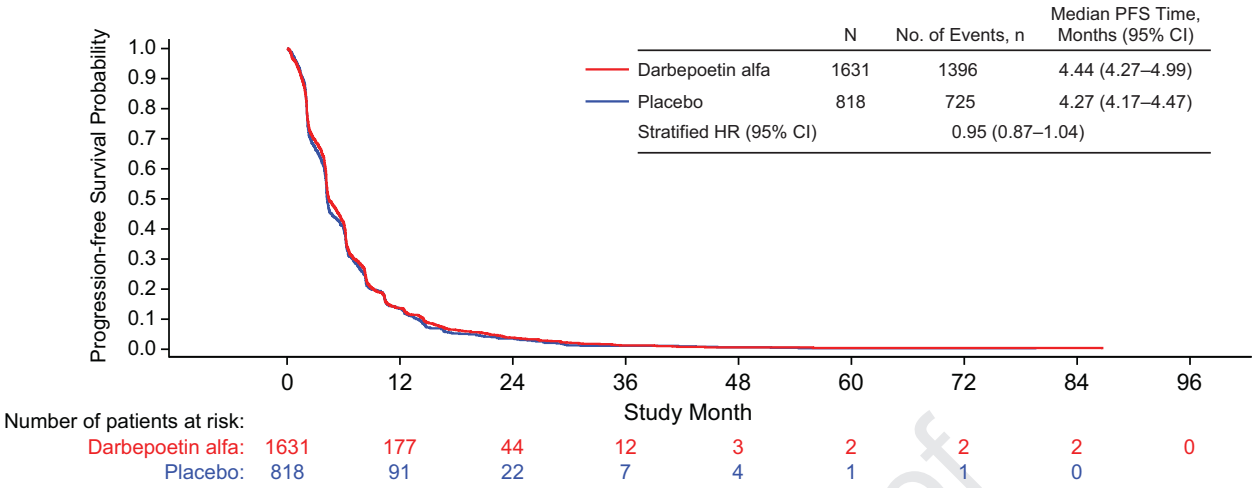
Darbepoetin alfa:	1680	536	188	62	21	11	6	2	0
Placebo:	836	252	73	27	12	5	3	1	0

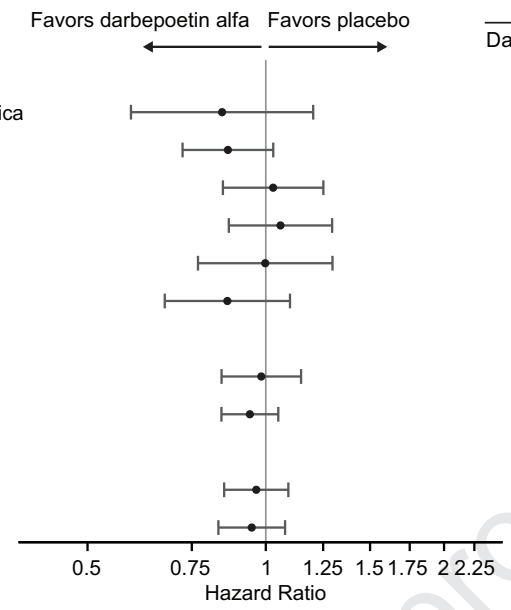


	No. of Events		
	Darbepoetin alfa	Placebo	HR (95% CI)
Geographic Region:			
Western Europe, Israel, & South Africa	108	54	0.73 (0.51–1.05)
Central and Eastern Europe	451	220	0.88 (0.73–1.06)
Latin America and Asia	347	172	0.92 (0.75–1.13)
India	339	168	1.03 (0.83–1.26)
North America	192	99	0.88 (0.67–1.14)
China	243	123	0.89 (0.67–1.18)
Histology:			
Squamous	589	289	0.99 (0.84–1.16)
Nonsquamous	1091	547	0.87 (0.78–0.98)
Screening Hb:			
<10 g/dL	870	433	0.95 (0.83–1.08)
≥10 g/dL	810	403	0.87 (0.76–1.00)

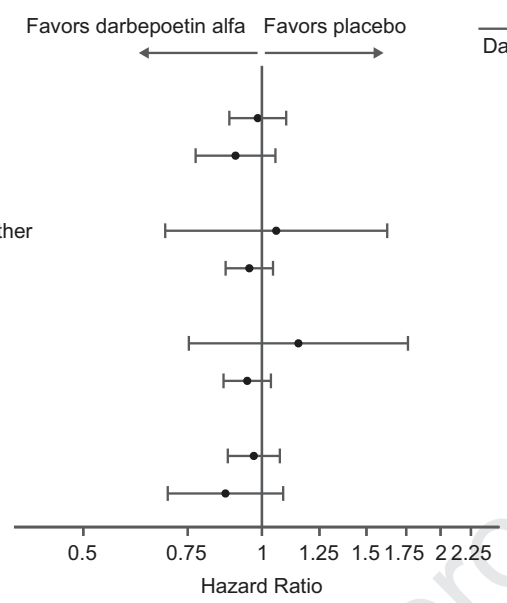


	No. of Events		
	Darbepoetin alfa	Placebo	HR (95% CI)
Chemotherapy type:			
Platinum-based	1118	549	0.92 (0.82–1.03)
Other	562	287	0.89 (0.76–1.05)
Targeted therapy:			
Anti-EGFR or anti-angiogenics or other	101	33	0.98 (0.62–1.54)
No targeted therapy	1579	803	0.91 (0.83–1.00)
History of VTE:			
Yes	84	44	1.13 (0.73–1.77)
No	1596	792	0.90 (0.82–0.99)
Baseline serum EPO:			
≤100 mU/mL	1324	668	0.92 (0.83–1.02)
>100 mU/mL	264	132	0.95 (0.74–1.20)





	No. of Events		
	Darbepoetin alfa	Placebo	HR (95% CI)
Geographic Region:			
Western Europe, Israel, & South Africa	102	52	0.84 (0.59–1.20)
Central and Eastern Europe	443	218	0.86 (0.72–1.03)
Latin America and Asia	326	167	1.03 (0.85–1.25)
India	337	166	1.06 (0.87–1.29)
North America	180	93	1.00 (0.77–1.30)
China	243	122	0.86 (0.68–1.10)
Histology:			
Squamous	571	283	0.98 (0.84–1.15)
Nonsquamous	1060	535	0.94 (0.84–1.05)
Screening Hb:			
<10 g/dL	848	427	0.96 (0.85–1.09)
≥10 g/dL	783	391	0.95 (0.83–1.08)



	No. of Events		
	Darbepoetin alfa	Placebo	HR (95% CI)
Chemotherapy type:			
Platinum-based	1072	533	0.98 (0.88–1.10)
Other	559	285	0.90 (0.77–1.05)
Targeted therapy:			
Anti-EGFR or anti-angiogenics or other	98	31	1.06 (0.69–1.63)
No targeted therapy	1533	787	0.95 (0.87–1.04)
History of VTE:			
Yes	80	40	1.15 (0.75–1.76)
No	1551	778	0.94 (0.86–1.04)
Baseline serum EPO:			
≤100 mU/mL	1288	655	0.97 (0.88–1.07)
>100 mU/mL	258	130	0.87 (0.69–1.09)