Results from a phase 3, randomized, double-blind, placebo-controlled study of darbepoetin alfa for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy

Background: Patients with cancer, not receiving chemotherapy or radiotherapy, often develop anemia as a result of the disease itself. A phase 2 study demonstrated that darbepoetin alfa 6.75 mcg/kg administered once every 4 weeks (Q4W) was effective and well-tolerated in patients with non-myeloid malignancies who were not receiving concomitant chemotherapy (Gordon et al., 2006). We therefore conducted a randomized, double-blind, placebo-controlled phase 3 study to evaluate the efficacy and safety of this regimen for the treatment of anemia of cancer (AoC).

Methods: Patient eligibility included: ≥ 18 years, non-myeloid malignancy (with active disease), ECOG status of 0 to 2, hemoglobin ≤ 11 g/dL, and no chemotherapy or myelosuppressive radiotherapy (ie, pelvic/spinal irradiation) within 4 weeks of screening or planned during the study. Patients were randomized 1:1 to receive either darbepoetin alfa 6.75 mcg/kg Q4W or placebo, until, after a blinded review of the data, 145 patients had experienced at least one red blood cell transfusion from study day 29 to week 17. Additional patients enrolled were to be randomized 9:1 to receive either darbepoetin alfa or placebo until 500 darbepoetin alfa patients were enrolled. There was a 16 week treatment period, with an end of study visit at week 19, and 2 years of follow up to evaluate survival. Patients were stratified at randomization by screening hemoglobin (< 10 g/dL or ≥ 10 g/dL), geographic region (Europe vs Rest of World), red blood cell transfusion in the prior 12 weeks, tumor type/treatment (specifically, diagnoses of chronic lymphocytic leukemia or low grade lymphoma, ongoing hormonal or antibody therapy, vs all other eligible patients), and ECOG status (0-1, 2). Darbepoetin alfa

dosing was withheld if hemoglobin increased to > 13 g/dL and reinstated at a 25% dose reduction once hemoglobin was < 12 g/dL; if hemoglobin increased by more than 1 g/dL in any 2 week period (in the absence of a transfusion within the previous 14 days) or if hemoglobin exceeded 12 g/dL, the dose was reduced by 25%.

The primary endpoint was all occurrences of transfusion from week 5 to 17. Secondary endpoints were: first occurrence of a transfusion from week 5 to 17, change in hemoglobin from baseline to week 17, and safety. Supportive, or tertiary, endpoints included hemoglobin response (≥ 2 g/dL increase in hemoglobin concentration from baseline) at any time from study day 1 to week 17, in the absence of RBC transfusions in the preceding 28 days; hemoglobin correction (hemoglobin concentration ≥ 12 g/dL) at any time from study day 1 to week 17, in the absence of red blood cell transfusions in the preceding 28 days; and hematopoietic response (increase in hemoglobin concentration ≥ 2 g/dL from baseline or achieving a hemoglobin concentration ≥ 12 g/dL, ie, hemoglobin response *or* hemoglobin correction) at any time from study day 1 to week 17, in the absence of red blood cell transfusions in the preceding 28 days.

Results: Patients were enrolled at 144 sites across multiple regions including Western Europe, North America, Australia, and Central and Eastern Europe; the majority (60%) were from Central and Eastern Europe. A total of 1473 subjects were screened for the study, of whom 989 were randomized, and 985 received study drug (darbepoetin alfa or placebo). Approximately 52% of subjects completed the study; the most common reasons for premature study discontinuation were death (20%), consent withdrawn (10%), and disease progression (9%).

The efficacy analysis set consisted of all subjects who received at least 1 dose of investigational product and were randomized during the period of 1:1 randomization (n = 459 darbepoetin alfa, 463 placebo). The analysis of the primary endpoint included

subjects in the efficacy analysis set who completed at least 4 weeks of the study (primary transfusion analysis set; n = 419 darbepoetin alfa, 432 placebo), and analyses of hemoglobin endpoints included subjects in the efficacy analysis set who had a baseline and at least 1 post-baseline hemoglobin value (hemoglobin analysis set; n = 437 darbepoetin alfa, 447 placebo). The safety analysis set included all subjects who received at least 1 dose of investigational product (n = 515 darbepoetin alfa, 470 placebo).

Demographics were broadly similar between the groups (**Table 1**): mean (SD) age was 64.1 (11.6) years; the most common cancers were non-small cell lung (18%), breast (13%), and prostate (11%); most patients had disease stage III or IV (82%) and an ECOG status of 0 or 1 (72%); baseline hemoglobin was 9.5 g/dL in each group. However, there were more men in the darbepoetin alfa group (56% vs 47% in placebo), and more patients received prior chemotherapy in the darbepoetin alfa group (73% vs 66% in placebo). The mean (SD) number of days between prior chemotherapy and first study drug dose was 262 (572) days for the darbepoetin alfa group vs 315 (660) for placebo. The mean (SD) weekly dose of darbepoetin alfa was 98.2 (25.6) mcg/week.

Transfusion occurrences from weeks 5 to 17 favored darbepoetin alfa but were not significantly different between the groups (hazard ratio: 0.85, p = 0.32). Although the Kaplan-Meier proportion of patients who received a red blood cell transfusion from weeks 5 to 17 was lower in the darbepoetin alfa group compared with placebo, this difference was not significant. However, a pre-specified sensitivity analysis of the first occurrence of either a transfusion or hemoglobin value ≤ 8 g/dL found a statistically significant difference favoring darbepoetin alfa (p = 0.02). Among those receiving darbepoetin alfa, there was a significantly higher proportion of patients with hemoglobin

response ($p<0.001$), hemoglobin correction ($p<0.001$), and hematopoietic response ($p=0.002$) compared with placebo.

The adverse event rate was similar between the groups. However, the overall number of deaths among the 985 subjects who received study drug was greater in the darbepoetin alfa group (48.5% vs 46% in placebo; hazard ratio: 1.29; $p=0.006$). In post-hoc survival analyses adjusting for stratification factors at randomization, there remained a significant difference in survival between the groups, but hazard ratios and statistical significance diminished when the analysis was further adjusted for baseline imbalances. Detailed efficacy and safety data are shown in **Table 2 and Table 3, respectively**.

Conclusions: This study did not meet its primary endpoint of reducing transfusions in the darbepoetin alfa treatment group. A prespecified sensitivity analysis of the first occurrence of either a red blood cell transfusion or a hemoglobin concentration ≤ 8 g/dL yielded a statistically significant difference between treatment groups favoring darbepoetin alfa, suggesting that investigator compliance with the transfusion rules may have affected these results. An increase in hemoglobin from baseline to the end of the treatment period was noted in the darbepoetin alfa group; however, there was also a moderate hemoglobin increase in the placebo group. Significantly more deaths occurred in the darbepoetin alfa vs. placebo group. Post-hoc analyses indicated that baseline imbalances and prognostic factors may have contributed to the treatment difference. Based on the observed results and additional analyses, the risk/benefit profile of darbepoetin alfa in anemic patients with cancer not receiving myelosuppressive chemotherapy is at best neutral and possibly negative. Results of long-term follow up are awaited.

TABLE 1: BASELINE DEMOGRAPHICS

(Efficacy analysis set)

	Placebo (N=463)	Darbepoetin alfa (N=459)	Total (N=922)
Sex - n (%)			
Male	216 (46.7)	256 (55.8)	472 (51.2)
Race - n (%)			
White	437 (94.4)	440 (95.9)	877 (95.1)
Other	26 (5.6)	19 (4.1)	45 (4.9)
Mean (SD) Age, years	64.4 (11.4)	63.8 (11.8)	64.1 (11.6)
Tumor Type			
Non-small cell lung	81 (17.5)	86 (18.7)	167 (18.1)
Hematologic[a]	66 (14.3)	63 (13.7)	129 (14.0)
Breast	61 (13.2)	60 (13.1)	121 (13.1)
Prostate	48 (10.4)	50 (10.9)	98 (10.6)
Other[b]	207 (44.7)	200 (43.6)	407 (44.1)
Current disease stage - n (%)			
I to II	53 (11.4)	43 (9.4)	96 (10.4)
III to IV	372 (80.3)	380 (82.8)	752 (81.6)
ECOG performance status - n (%)			
0	85 (18.4)	73 (15.9)	158 (17.1)
1	252 (54.4)	252 (54.9)	504 (54.7)
2	125 (27.0)	133 (29.0)	258 (28.0)
Received prior cytotoxic chemotherapy? - n (%)			
Yes	307 (66.3)	337 (73.4)	644 (69.8)
Days since last prior cytotoxic chemotherapy and first dose			
n	285	324	609
Mean (SD)	314.7 (660.2)	262.0 (572.2)	286.6 (615.0)
Mean (SD) Hemoglobin (g/dL)	9.49 (1.14)	9.47 (1.23)	9.48 (1.19)

[a] Hematologic cancers included chronic lymphocytic leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and other hematological malignancy

[b] Other tumor types included large intestine, kidney, ovarian, cervix, other solid tumor, stomach, head and neck, pancreas, small cell lung, soft tissue sarcoma, bladder, melanoma, endometrial, oral, unknown primary, esophagus, testicular, uterus, and ureter.

TABLE 2: EFFICACY

Efficacy Endpoints	Placebo (n = 432)	Darbepoetin alfa (n = 419)	Statistical Tests
All occurrences of transfusions from weeks 5 to 17	215	176	Hazard Ratio: 0.85 (95% CI: 0.62 to 1.17) (p = 0.320 for DA vs placebo)
KM% (95% CI) for first RBC transfusion from weeks 5 to 17	24.0 (20.1 to 27.8)	19.1 (15.4 to 22.8)	(p = 0.064 for DA-placebo)
KM% (95% CI) for first RBC transfusion from weeks 5 to 17 or Hb ≤ 8 g/dL[a]	33.5 (29.3 to 37.6)	26.9 (22.8 to 31.0)	(p = 0.022 for DA-placebo)
Hb analysis set	**Placebo (n = 447)**	**Darbepoetin alfa (n = 437)**	
Mean change (95% CI) in Hb (baseline to end of treatment period)	0.28 g/dL (0.13 to 0.44)	0.72 g/dL (0.57 to 0.88)	(p<0.0001 for DA-placebo)
KM% (95% CI) for Hb response	28.7 (22.5, 34.9)	48.4 (43.1, 53.8)	(p<0.001 for DA-placebo)
KM% (95% CI) for Hb correction	26.7 (21.0, 32.4)	41.6 (35.9, 47.2)	(p<0.001 for DA-placebo)
KM% (95% CI) for hematopoietic response	37.5 (30.1, 44.9)	52.2 (47.0, 57.5)	(p = 0.002 for DA-placebo)

[a]A prespecified sensitivity analysis was conducted to include as transfused those pts (n=75) whose Hb fell below 8 g /dL, but who were not transfused as recommended in the protocol.
KM = Kaplan-Meier; RBC = red blood cell; Hb = hemoglobin

TABLE 3: SAFETY

Safety endpoints, n (%)	Placebo (n = 470)	Darbepoetin alfa (n = 515)	Statistical tests
Adverse events	359 (76.4)	399 (77.5)	
Severe, life-threatening or fatal adverse events	192 (40.9)	245 (47.6)	
Serious adverse events	159 (33.8)	210 (40.8)	
Treatment related adverse events	16 (3.4)	11 (2.1)	
Severe, life-threatening or fatal adverse events	6 (1.3)	6 (1.2)	
Serious adverse events	5 (1.1)	6 (1.2)	
Cardiovascular and thromboembolic events	36 (7.7)	50 (9.7)	
Deaths on study	94 (20.0)	136 (26.4)	
Deaths due to cardiovascular and thromboembolic events	8 (1.7)	10 (1.9)	
Deaths due to disease progression	77 (16.4)	113 (21.9)	
Deaths on study and during long-term follow-up[a]	216 (46.0)	250 (48.5)	**Hazard ratio for time to death (DA vs placebo):** Stratified for factors at randomization: 1.29 (95% CI: 1.08 to 1.55), p=0.006 Adjusted for stratification factors at randomization: 1.23 (95% CI: 1.02 to 1.48), p=0.031 Adjusted for stratification factors at randomization and sex, stage IV disease, prior chemotherapy use, and prior radiotherapy use: 1.18 (95% CI: 0.98 to 1.42), p=0.082 Adjusted for known prognostic factors (Baseline ECOG, tumor type, tumor stage, baseline FACT-F cutoff at median, baseline Hb): 1.17 (95% CI: 0.97 to 1.42), p=0.11

[a]Median duration of long-term follow up was 20 weeks for placebo and 18 weeks for darbepoetin alfa