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ORIGINAL ARTICLE



## Achievement of red blood cell transfusion independence in red blood cell transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes correlates with serum erythropoietin levels

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### ABSTRACT

In the randomized, phase 3, MDS-005 study (NCT01029262), lenalidomide-induced red blood cell transfusion independence (RBC-TI) in 27% of transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes (MDS) ineligible for or refractory to erythropoiesis-stimulating agents. To determine the influence of erythropoietin (EPO) level on response, 155 patients treated with lenalidomide in MDS-005 were categorized into four groups by baseline EPO level. The EPO >500 mU/mL group had higher RBC transfusion burden and the lowest proportion of patients with ring sideroblasts ≥15% versus lower EPO groups. Achievement of RBC-TI ≥8 weeks inversely correlated with EPO level, ranging from 42.5 to 15.5%. EPO level did not affect erythroid hematologic improvement response (36.2–44.4%). This analysis suggests patients with lower EPO levels experience the strongest benefit from lenalidomide. Although meaningful improvements were observed in some patients with EPO level >500 mU/mL, new treatments are needed for this population.

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Erythropoietin; lenalidomide; myelodysplastic syndromes

### Introduction


Myelodysplastic syndromes (MDS) are a group of malignant bone marrow disorders that primarily affect older adults and are characterized by anemia and other cytopenias and an increased risk of transformation to acute myeloid leukemia [1]. Marked disease heterogeneity with regard to bone marrow morphologic features as well as molecular and genetic characteristics contributes to a highly variable natural history. Risk stratification systems have been developed that help identify lower-risk patients with a relatively good prognosis as well as higher-risk patients for whom treatment with disease-modifying agents, such as azacitidine and decitabine, may be warranted [2–4]. Anemia is the most common cause of symptoms in patients with lower-risk MDS. However, the underlying pathophysiology of anemia has not been completely clarified, especially in characterizing the abnormalities in the different MDS subtypes. To date,

the development of effective therapies for anemia in MDS is still proceeding at a relatively slow pace.

For patients with lower-risk MDS, erythropoiesis-stimulating agents (ESAs) are the first-line therapy, provided that the serum erythropoietin (EPO) level is ≤500 mU/mL [5,6]. With this approach, reported rates of erythroid hematologic improvement (HI-E) achievement range from 15 to 63% [7–9] and median durations of response range from 7 to 28 months [7,9]. Use of luspatercept in patients with transfusion-dependent lower-risk non-del(5q) MDS and prior ESA therapy has been assessed [10,11]. In a phase 3 placebo-controlled trial, 38% of patients treated with luspatercept achieved red blood cell transfusion independence (RBC-TI) ≥8 weeks [11]. In patients with lower-risk del(5q) MDS receiving 10 mg lenalidomide, 56% achieved RBC-TI [12].

In a randomized, placebo-controlled, phase 3 study (MDS-005), the efficacy and safety of lenalidomide (10 mg) was evaluated in RBC transfusion-dependent

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 Supplemental data for this article can be accessed [here](#).

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(RBC-TD) patients with lower-risk non-del(5q) MDS who were ineligible for or refractory to ESAs [13]. A significantly higher proportion of patients treated with lenalidomide achieved RBC-TI lasting  $\geq 8$  weeks compared with placebo (26.9 versus 2.5%;  $p < .001$ ). Factors that predicted response to lenalidomide included low baseline EPO level ( $\leq 500$  mU/mL), prior ESA use, and low transfusion burden ( $< 4$  RBC units/28 days). Consistent with these results were those of a study conducted in a comparable cohort of patients with lower-risk MDS who were treated with the combination of EPO and lenalidomide after having lost response to ESAs alone [14].

In an effort to better characterize which non-del(5q) patients are most likely to benefit from lenalidomide therapy, we further explored the impact of clinical characteristics, especially baseline EPO levels, on response in patients treated with lenalidomide in the MDS-005 study. These responses were then compared with those reported in a previous randomized study of patients with lower-risk MDS and del(5q) (MDS-004).

## Methods

### Study design and treatment

Methodologies of the MDS-005 (NCT01029262) and MDS-004 (NCT00179621) trials have been described in detail elsewhere [12,13]. Briefly, MDS-005 was a randomized, placebo-controlled, phase 3 study of lenalidomide in RBC-TD patients with International Prognostic Scoring System (IPSS) Low- or Intermediate-1-risk MDS without del(5q) who were ineligible for or refractory to ESAs [13]. Patients were randomized 2:1 to oral lenalidomide 10 mg once daily or matching placebo once daily (both on 28-day cycles); patients with creatinine clearance 40–60 mL/min received lenalidomide 5 mg once daily. If patients achieved RBC-TI  $\geq 8$  weeks or erythroid response by week 24, double-blind treatment continued until erythroid relapse, disease progression, unacceptable toxicity, or consent withdrawal. MDS-004 was a randomized, placebo-controlled, phase 3 study of lenalidomide (10 or 5 mg/day) in RBC-TD patients with IPSS Low- or Intermediate-1-risk MDS and del(5q) [12].

### Statistical analysis

The current analyses were based on patients who were randomized to lenalidomide and received at least one dose of study treatment. EPO levels were measured prior to randomization by a central

laboratory, and patients with missing baseline EPO data were excluded from the analysis. Baseline characteristics and efficacy endpoints were analyzed according to baseline EPO level. For MDS-005, the following baseline EPO level groups were analyzed:  $\leq 100$ ,  $> 100$  to  $\leq 200$ ,  $> 200$  to  $\leq 500$ , and  $> 500$  mU/mL. These were referred to as the EPO  $\leq 100$ , EPO 100–200, EPO 200–500, and EPO  $> 500$  groups, respectively. For MDS-004, the following baseline EPO level groups were analyzed:  $\leq 200$ ,  $> 200$  to  $\leq 500$ , and  $> 500$  mU/mL; the lower end cutoff of 200 rather than 100 mU/mL was used due to the relatively small number of patients with EPO  $\leq 100$ . Demographic and baseline characteristics were summarized using summary statistics. For continuous variables, summary statistics included number, mean, standard deviation, median, minimum, and maximum. For categorical variables, number and percentage were calculated.

Univariate and multivariate analyses were performed for clinical characteristics predictive of response. Efficacy endpoints were summarized using summary statistics. For MDS-005, efficacy endpoints included rate of RBC-TI  $\geq 8$  weeks (primary endpoint); rate of RBC-TI  $\geq 24$  weeks; duration of RBC-TI; rate of HI-E using International Working Group (IWG) 2006 criteria [15]; rate of  $\geq 4$  RBC units transfusion reduction (based on 8-week and 16-week assessment periods); rate of  $\geq 50\%$  reduction in RBC units transfused; and cytogenetic response. HI-E was defined as a hemoglobin increase by  $\geq 1.5$  g/dL or reduction in transfusion of  $\geq 4$  RBC units over 8 weeks versus pretreatment. Cytogenetic response was evaluated by conventional metaphase cytogenetic analysis according to IWG 2006 criteria [15]. For MDS-004, efficacy endpoints included rate of RBC-TI  $\geq 26$  weeks (primary endpoint); time to RBC-TI  $\geq 26$  weeks; duration of RBC-TI; rate of HI-E using IWG 2000 criteria [16]; time to HI-E; and duration of HI-E.

The data cutoff for inclusion in this analysis was March 17, 2014.

## Results

### Baseline characteristics

Of the 160 patients randomized to lenalidomide in MDS-005, 155 (96.9%) had baseline EPO data available and were included in the analysis. The number of patients in the EPO  $\leq 100$ , 100–200, 200–500, and  $> 500$  groups were 40 (25.8%), 27 (17.4%), 30 (19.4%), and 58 (37.4%), respectively. Baseline demographics and disease characteristics according to EPO level are shown in Table 1. Median age was 71 years overall

**Table 1.** Patient baseline characteristics according to baseline EPO level in lenalidomide-treated patients with lower-risk non-del(5q) MDS.

| Characteristic <sup>a</sup>                        | EPO level (mU/mL)  |                          |                          |                    |
|--|--------------------|--------------------------|--------------------------|--------------------|
|  | ≤100<br>(n = 40)   | >100 to ≤200<br>(n = 27) | >200 to ≤500<br>(n = 30) | >500<br>(n = 58)   |
| Age, years   |                    |                          |                          |                    |
| Mean (SD)  | 73.1 (8.06)        | 70.3 (6.87)              | 70.2 (8.46)              | 67.7 (7.83)        |
| Median (range)                                     | 75.0 (53.0–86.0)   | 70.0 (55.0–83.0)         | 72.0 (46.0–85.0)         | 68.0 (53.0–81.0)   |
| Male, n (%)  | 18 (45.0)          | 17 (63.0)                | 22 (73.3)                | 48 (82.8)          |
| Time since diagnosis, years                        |                    |                          |                          |                    |
| Mean (SD)  | 5.8 (5.47)         | 4.4 (3.83)               | 4.7 (4.65)               | 2.8 (4.07)         |
| Median (range)                                     | 4.3 (0.6–24.2)     | 2.6 (0.8–13.9)           | 4.4 (0.5–23.9)           | 2.2 (0.1–29.6)     |
| RBC transfusion burden, units/28 days              |                    |                          |                          |                    |
| Mean (SD)  | 3.0 (0.99)         | 3.2 (1.12)               | 3.1 (0.91)               | 3.9 (1.44)         |
| Median (range)                                     | 2.8 (1.8–6.5)      | 3.0 (1.8–6.3)            | 3.0 (2.0–5.8)            | 3.8 (1.8–8.8)      |
| IPSS risk category, n (%)                          |                    |                          |                          |                    |
| Low  | 19 (47.5)          | 20 (74.1)                | 12 (40.0)                | 32 (55.2)          |
| Intermediate-1                                     | 21 (52.5)          | 7 (25.9)                 | 18 (60.0)                | 26 (44.8)          |
| IPSS karyotype, n (%)                              |                    |                          |                          |                    |
| Good   | 32 (80.0)          | 23 (85.2)                | 25 (83.3)                | 48 (82.8)          |
| Intermediate                                       | 8 (20.0)           | 4 (14.8)                 | 4 (13.3)                 | 10 (17.2)          |
| Missing  | 0                  | 0                        | 1 (3.3)                  | 0                  |
| WHO 2008 classification, n (%)                     |                    |                          |                          |                    |
| RA   | 0                  | 0                        | 1 (3.3)                  | 5 (8.6)            |
| RARS   | 2 (5.0)            | 2 (7.4)                  | 4 (13.3)                 | 3 (5.2)            |
| RCMD   | 32 (80.0)          | 24 (88.9)                | 19 (63.3)                | 37 (63.8)          |
| RAEB-1   | 6 (15.0)           | 1 (3.7)                  | 6 (20.0)                 | 13 (22.4)          |
| Time from last ESAs to start of lenalidomide, days | n = 17             | n = 13                   | n = 11                   | n = 10             |
| Mean (SD)  | 803.3 (1208.3)     | 517.6 (911.3)            | 444.3 (631.9)            | 229.3 (123.7)      |
| Median (range)                                     | 276.0 (63.0–4850)  | 114.0 (58.0–3314)        | 255.0 (49.0–2216)        | 232.0 (56.0–452.0) |
| Prior MDS therapy, n (%)                           | 40 (100)           | 27 (100)                 | 28 (93.3)                | 35 (60.3)          |
| Prior ESA treatment, n (%)                         | 40 (100)           | 27 (100)                 | 27 (90.0)                | 26 (44.8)          |
| Prior G-CSF use, n (%)                             | 8 (20.0)           | 6 (22.2)                 | 7 (23.3)                 | 3 (5.2)            |
| Number of cytopenias, n (%)                        |                    |                          |                          |                    |
| 0–1  | 28 (70.0)          | 17 (63.0)                | 16 (53.3)                | 36 (62.1)          |
| 2–3  | 12 (30.0)          | 10 (37.0)                | 14 (46.7)                | 22 (37.9)          |
| Serum EPO level at screening, mU/mL                |                    |                          |                          |                    |
| Mean (SD)  | 52.8 (25.43)       | 143.1 (27.95)            | 326.6 (82.06)            | 1835 (1658.6)      |
| Median (range)                                     | 52.5 (6.0–95.0)    | 147.0 (102.0–193.0)      | 309.5 (206.0–495.0)      | 1166 (521.0–7600)  |
| Ring sideroblast status, n (%)                     |                    |                          |                          |                    |
| <15%   | 5 (12.5)           | 2 (7.4)                  | 8 (26.7)                 | 38 (65.5)          |
| ≥15% (RARS and RCMD)                               | 35 (87.5)          | 25 (92.6)                | 22 (73.3)                | 20 (34.5)          |
| Bone marrow blast percentage                       |                    |                          |                          |                    |
| Mean (SD)  | 3.1 (1.85)         | 2.2 (1.55)               | 3.1 (2.20)               | 3.3 (1.99)         |
| Median (range)                                     | 2.8 (0.5–8.5)      | 2.0 (0.0–5.0)            | 3.0 (0.0–9.5)            | 3.3 (0.0–8.5)      |
| Bone marrow blast count, n (%)                     |                    |                          |                          |                    |
| <5%  | 34 (85.0)          | 26 (96.3)                | 24 (80.0)                | 45 (77.6)          |
| ≥5%  | 6 (15.0)           | 1 (3.7)                  | 6 (20.0)                 | 13 (22.4)          |
| ANC, × 10 <sup>9</sup> /L                          |                    |                          |                          |                    |
| Mean (SD)  | 2.7 (1.42)         | 2.6 (1.31)               | 2.5 (2.20)               | 2.6 (1.65)         |
| Median (range)                                     | 2.5 (0.6–6.4)      | 2.5 (0.5–6.8)            | 2.3 (0.6–12.2)           | 2.4 (0.5–7.7)      |
| Platelet count, × 10 <sup>9</sup> /L               |                    |                          |                          |                    |
| Mean (SD)  | 260.1 (123.94)     | 291.8 (113.20)           | 246.4 (118.66)           | 240.6 (154.48)     |
| Median (range)                                     | 227.5 (69.0–579.0) | 286.0 (63.0–588.0)       | 246.5 (51.0–496.0)       | 205.5 (43.0–746.0) |
| Hemoglobin, g/dL                                   |                    |                          |                          |                    |
| Mean (SD)  | 8.9 (1.08)         | 9.1 (1.10)               | 8.7 (1.25)               | 8.4 (1.36)         |
| Median (range)                                     | 8.6 (7.3–12.3)     | 9.0 (7.3–11.7)           | 8.8 (6.1–11.1)           | 8.2 (5.5–11.3)     |
| Creatinine clearance, mL/min                       |                    |                          |                          |                    |
| Mean (SD)  | 69.2 (23.73)       | 81.1 (24.34)             | 82.7 (25.05)             | 89.8 (28.46)       |
| Median (range)                                     | 61.3 (37.8–130.4)  | 82.0 (40.9–141.5)        | 79.0 (45.0–156.3)        | 88.1 (41.9–189.3)  |
| Creatinine, mg/dL                                  |                    |                          |                          |                    |
| Mean (SD)  | 0.9 (0.22)         | 0.9 (0.28)               | 0.9 (0.29)               | 0.9 (0.24)         |
| Median (range)                                     | 0.9 (0.5–1.5)      | 0.9 (0.6–1.6)            | 0.8 (0.5–1.6)            | 0.9 (0.4–1.6)      |
| Serum bilirubin, μmol/L                            |                    |                          |                          |                    |
| Mean (SD)  | 20.1 (13.92)       | 20.8 (15.54)             | 16.5 (6.95)              | 14.4 (9.57)        |
| Median (range)                                     | 17.0 (3.0–62.0)    | 15.0 (7.0–70.0)          | 16.0 (5.0–33.0)          | 12.0 (4.0–57.0)    |
| LDH, mg/dL   |                    |                          |                          |                    |
| Mean (SD)  | 191.2 (84.39)      | 200.2 (72.45)            | 203.9 (75.98)            | 195.0 (67.79)      |
| Median (range)                                     | 180.0 (86.0–568.0) | 190.0 (88.0–347.0)       | 199.0 (86.0–395.0)       | 190.5 (92.0–508.0) |

ANC: absolute neutrophil count; del(5q): deletion 5q; EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; G-CSF: granulocyte colony-stimulating factor; IPSS: International Prognostic Scoring System; LDH: lactate dehydrogenase; MDS: myelodysplastic syndromes; RBC: red blood cell; RA: refractory anemia; RAEB: refractory anemia with excess blasts; RARS: RA with ring sideroblasts; RCMD: refractory cytopenia with multilineage dysplasia; SD: standard deviation; WHO: World Health Organization.

<sup>a</sup>Percentages do not always add up to 100% due to rounding off.

and ranged from 68 years in the EPO >500 group to 75 years in the EPO ≤100 group. The proportion of patients who were male was 45% in the EPO ≤100 group, compared with 82.8% in the EPO >500 group. Median creatinine clearance was 61.3 mL/min in the EPO ≤100 group, rising to 88.1 mL/min in the EPO >500 group; ANOVA revealed that this difference was statistically significant ( $p = .0002$ ).

Data regarding the time from the last dose of ESA to start of lenalidomide therapy were available for 17, 13, 11, and 10 patients in the EPO ≤100, 100–200, 200–500, and >500 groups, respectively. The median time from last ESA dose to start of lenalidomide was longest in the EPO ≤100 group (276 days); median time in the EPO 100–200, 200–500, and >500 groups was 114, 255, and 232 days, respectively (Table 1). Notably, the MDS-005 study included a washout phase of ≥56 days before the start of lenalidomide to minimize the effects of ESAs during lenalidomide treatment.

The EPO >500 group generally had poorer disease characteristics at baseline. The median EPO level was high (1166 mU/mL; range 521–7600 mU/mL) and compared with other EPO groups, the EPO >500 group had higher RBC transfusion burden (Table 1). The EPO >500 group also had the shortest median time since diagnosis (2.2 [range 0.1–29.6] versus 4.3 years [0.6–24.2] in the EPO ≤100 group [ $p = .0013$ ; ANOVA test]), and the lowest proportion of patients with ring sideroblasts (RS) ≥15%, at 34.5% of patients. Patients with RS were those with the World Health Organization (WHO)-defined MDS subtypes refractory

anemia with ring sideroblasts (RARS) or refractory cytopenia with multilineage dysplasia (RCMD) who had RS ≥15%.

### Duration of lenalidomide treatment

The median duration of lenalidomide treatment was comparable among EPO groups (Table 2) and ranged from 151 days in the EPO 200–500 group to 169 days in the EPO 100–200 group.

### Response to lenalidomide

Achievement of RBC-TI ≥8 weeks inversely correlated with baseline EPO level, from 42.5% in the EPO ≤100 group to 15.5% in the EPO >500 group (Table 2; Figure 1(A)). Notably, all patients who achieved RBC-TI ≥8 weeks had received prior ESAs, with the exception of three patients in the EPO >500 group. Median duration of RBC-TI ≥8 weeks was longest in the EPO ≤100 group (326 days), compared with the EPO 100–200, 200–500, and >500 groups (145, 153, and 207 days, respectively; Table 2). However, 14 patients with available baseline EPO data continue to receive lenalidomide as of the cutoff date and data collection for these patients is ongoing. Of these 14 patients, five are baseline EPO ≤100, three are EPO 100–200, two are EPO 200–500, and four are EPO >500.

Univariate and multivariate analysis of predictive factors for RBC-TI ≥8 weeks are presented in Table 3. As previously assessed in the primary MDS-005 study

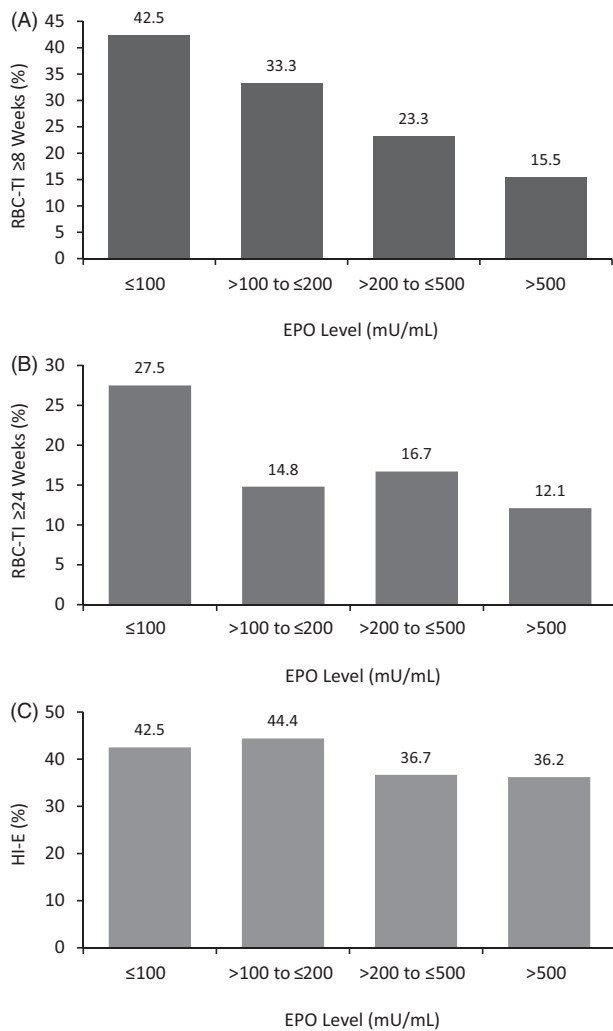
**Table 2.** Response according to baseline EPO level in lenalidomide-treated patients with lower-risk non-del(5q) MDS.

| Response   | EPO level (mU/mL) |                          |                          |                   |
|--|-------------------|--------------------------|--------------------------|-------------------|
|  | ≤100<br>(n = 40)  | >100 to ≤200<br>(n = 27) | >200 to ≤500<br>(n = 30) | >500<br>(n = 58)  |
| RBC-TI ≥8 weeks, n (%)   | 17 (42.5)         | 9 (33.3)                 | 7 (23.3)                 | 9 (15.5)          |
| Duration of RBC-TI, days <sup>a</sup>                          | 326               | 145                      | 153                      | 207               |
| RBC-TI ≥8 weeks by ring sideroblast status, n/N (%)            |                   |                          |                          |                   |
| <15%   | 4/5 (80.0)        | 1/2 (50.0)               | 1/8 (12.5)               | 5/38 (13.2)       |
| ≥15%   | 13/35 (37.1)      | 8/25 (32.0)              | 6/22 (27.3)              | 4/20 (20.0)       |
| RBC-TI ≥8 weeks by sex, n/N (%)                                |                   |                          |                          |                   |
| Female   | 8/22 (36.4)       | 5/10 (50.0)              | 4/8 (50.0)               | 2/10 (20.0)       |
| Male   | 9/18 (50.0)       | 4/17 (23.5)              | 3/22 (13.6)              | 7/48 (14.6)       |
| RBC-TI ≥24 weeks, n (%)  | 11 (27.5)         | 4 (14.8)                 | 5 (16.7)                 | 7 (12.1)          |
| Cytogenetic response (IWG 2006), n (%)                         | n = 6             | n = 3                    | n = 7                    | n = 10            |
| Complete response  | 1 (16.7)          | 1 (33.3)                 | 3 (42.9)                 | 0                 |
| Partial response   | 2 (33.3)          | 0                        | 0                        | 2 (20.0)          |
| HI-E (IWG 2006), n (%)   | 17 (42.5)         | 12 (44.4)                | 11 (36.7)                | 21 (36.2)         |
| ≥50% reduction in RBC units transfused, n (%)                  | 17 (42.5)         | 11 (40.7)                | 10 (33.3)                | 21 (36.2)         |
| ≥4 RBC units transfusion reduction (8-week assessment), n (%)  | 16 (40.0)         | 10 (37.0)                | 10 (33.3)                | 20 (34.5)         |
| ≥4 RBC units transfusion reduction (16-week assessment), n (%) | 10 (25.0)         | 6 (22.2)                 | 6 (20.0)                 | 11 (19.0)         |
| Duration of treatment, days                                    |                   |                          |                          |                   |
| Mean (SD)  | 250.2 (265.54)    | 194.2 (142.37)           | 193.1 (186.96)           | 191.2 (210.34)    |
| Median (range)   | 151.5 (14.0–1158) | 169.0 (28.0–564.0)       | 151.0 (7.0–813.0)        | 162.0 (12.0–1101) |

del(5q): deletion 5q; EPO: erythropoietin; HI-E: erythroid hematologic improvement; IWG: International Working Group; MDS: myelodysplastic syndromes; RBC: red blood cell; RBC-TI: RBC transfusion independence; SD: standard deviation.

<sup>a</sup>Responding patients only, median duration of RBC-TI was estimated using Kaplan–Meier analysis.





**Figure 1.** Rates of RBC-TI  $\geq 8$  weeks (A), RBC-TI  $\geq 24$  weeks (B), and HI-E (C) according to baseline EPO level in lenalidomide-treated patients with lower-risk non-del(5q) MDS. EPO: erythropoietin; HI-E: erythroid hematologic improvement; MDS: myelodysplastic syndromes; RBC-TI: red blood cell transfusion independence.

[13], the rate of RBC-TI  $\geq 8$  weeks was higher in women than men, at 38.0 versus 21.9% (OR 0.432 [95% CI, 0.210 to 0.893;  $p = .023$ ]).

The rate of RBC-TI  $\geq 8$  weeks was also higher in patients with RS  $\geq 15\%$  than in those with RS  $< 15\%$  (30.4 [31/102] versus 20.8% [11/53]), although no statistical comparison was made for these subgroups. For patients with RS  $\geq 15\%$ , consistent rates of RBC-TI  $\geq 8$  weeks (20.0–37.1%) were seen across the EPO groups; however, response rates varied considerably in patients with RS  $< 15\%$  and no clear pattern emerged when analyzed according to baseline EPO level (Figure 2(A)). This may have been due to the limited number of patients in each EPO subgroup.

A plateau was seen regarding the relationship between baseline EPO level and RBC-TI  $\geq 24$  weeks (Table 2; Figure 1(B)). The response rate was highest in patients with baseline EPO  $\leq 100$  (27.5%) and was roughly flat across other EPO groups, ranging from 12.1 to 16.7%. There was no direct correlation between EPO baseline level and achievement of HI-E. Rates of HI-E, as defined by IWG 2006 criteria, were high overall, ranging from 36.2% in the EPO  $> 500$  group to 44.4% in the EPO 100–200 group (Table 2; Figure 1(C)). Similarly, no association between baseline EPO level and achievement of HI-E was observed when analyzed according to RS status (Figure 2(B)).

Cytogenetic response was evaluated in 6, 3, 7, and 10 patients in the EPO  $\leq 100$ , 100–200, 200–500, and  $> 500$  groups, respectively. There was no discernible pattern in response rates according to EPO level, possibly due to the small number of evaluable patients in each subgroup. Complete cytogenetic response was reported in 16.7% (1/6), 33.3% (1/3),

**Table 3.** Univariate and multivariate logistic regression analysis for RBC-TI  $\geq 8$  weeks in lenalidomide-treated patients with lower-risk non-del(5q) MDS ( $N = 160$ ).

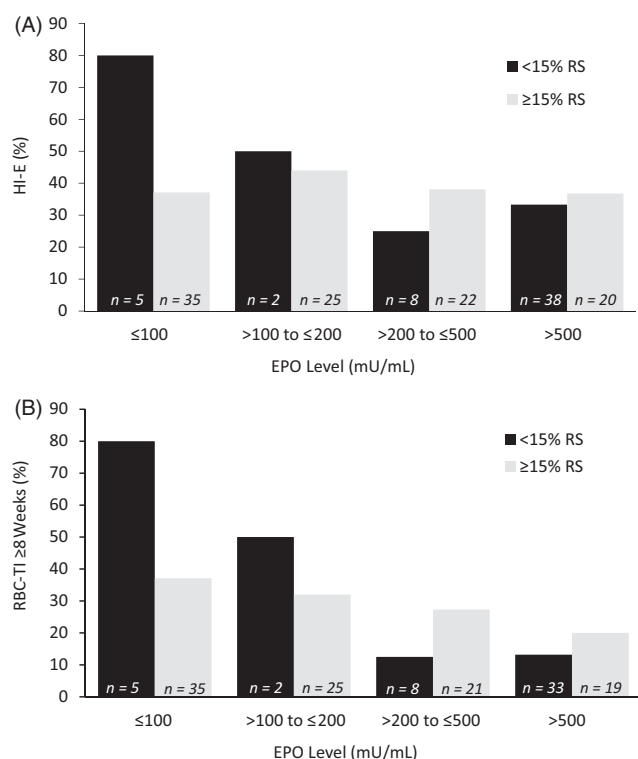
| Variable  | Univariate model    |                 | Multivariate model <sup>a</sup> |                 | Final model <sup>a</sup> |                 |
|---|---------------------|-----------------|---------------------------------|-----------------|--------------------------|-----------------|
|   | Odds ratio (95% CI) | <i>p</i> -value | Odds ratio (95% CI)             | <i>p</i> -value | Odds ratio (95% CI)      | <i>p</i> -value |
| Age ( $\leq 65$ versus $> 65$ years)                            | 1.29 (0.58–2.86)    | .53             | 1.86 (0.74–4.67)                | .19             | –                        | –               |
| Sex (male versus female)  | 0.43 (0.21–0.89)    | .02             | 0.77 (0.33–1.80)                | .55             | –                        | –               |
| Time since MDS diagnosis ( $< 2$ versus $\geq 2$ years)         | 0.86 (0.41–1.81)    | .69             | 1.05 (0.46–2.40)                | .90             | –                        | –               |
| Mean baseline transfusion burden (low versus high) <sup>b</sup> | 2.99 (1.08–8.24)    | .03             | 2.72 (0.91–8.16)                | .07             | 2.59 (0.91–7.36)         | .07             |
| Bone marrow blast count ( $< 5$ versus $\geq 5\%$ )             | 0.85 (0.34–2.11)    | .72             | 0.87 (0.30–2.59)                | .81             | –                        | –               |
| IPSS risk <sup>c</sup> (Int-1 versus Low)                       | 1.44 (0.71–2.90)    | .31             | 1.44 (0.64–3.24)                | .38             | –                        | –               |
| Prior G-CSF use (yes versus no)                                 | 2.17 (0.91–5.2)     | .08             | 2.22 (0.82–6.02)                | .12             | –                        | –               |
| Serum EPO level, mU/mL  |                     |                 |                                 |                 |                          |                 |
| $\leq 100$ versus $> 500$ <sup>a</sup>                          | 4.02 (1.56–10.38)   | .02             | 3.34 (1.11–10.04)               | .07             | 3.53 (1.35–9.24)         | .04             |
| $> 100$ –200 versus $> 500$                                     | 2.72 (0.93–7.94)    | .42             | 2.61 (0.80–8.53)                | .34             | 2.52 (0.85–7.44)         | .43             |
| $> 200$ –500 versus $> 500$                                     | 1.66 (0.55–5.00)    | .54             | 1.25 (0.38–4.09)                | .33             | 1.49 (0.49–4.55)         | .49             |

CI: confidence interval; del(5q): deletion 5q; EPO: erythropoietin; G-CSF: granulocyte colony stimulating factor; Int: Intermediate; IPSS: International Prognostic Scoring System; MDS: myelodysplastic syndromes; RBC-TI: red blood cell transfusion independence.

<sup>a</sup> $N = 155$  patients.

<sup>b</sup>For the European Union, Australia, and United States, Low is defined as  $< 4$  units/28 days and high as  $\geq 4$  units/28 days. For Japan, Low is defined as  $< 8$  units/28 days and high as  $\geq 8$  units/28 days.

<sup>c</sup>Investigator-assessed IPSS risk.



**Figure 2.** Rates of RBC-TI  $\geq 8$  weeks (A) and HI-E (B) by ring sideroblast status according to baseline EPO level in lenalidomide-treated patients with lower-risk non-del(5q) MDS. EPO: erythropoietin; HI-E: erythroid hematologic improvement; MDS: myelodysplastic syndromes; RBC-TI: red blood cell transfusion independence; RS: ring sideroblast.

42.9% (3/7), and 0% (0/10) of patients in the EPO  $\leq 100$ , 100–200, 200–500, and  $>500$  groups, respectively. Partial cytogenetic response was seen in 33.3% (2/6), 0% (0/3), 0% (0/7), and 20.0% (2/10) of patients, respectively.

### **Influence of EPO level in patients with del(5q)**

The relationship between baseline EPO level and response to lenalidomide was also analyzed in a population of patients with lower-risk del(5q) MDS, using data from the MDS-004 study. In the MDS-004 study, the median baseline EPO level of del(5q) patients treated with lenalidomide was 902 mU/mL (range 59.4–6113.0), compared with 297.0 mU/mL (range 6.0–7600.0) for the non-del(5q) patients in MDS-005. Of the 138 patients randomized to lenalidomide in MDS-004, 73 (52.9%) had baseline EPO data available and were included in the analysis. The number of patients in the EPO  $\leq 200$ , 200–500, and  $>500$  groups was 15 (20.5%), 12 (16.4%), and 46 (63.0%), respectively. Baseline demographics and disease characteristics according to EPO level are shown in Table S1. The proportion of patients who were male was comparable

among EPO groups and ranged from 16.7% in the EPO 200–500 group to 26.7% in the EPO  $\leq 200$  group. Median creatinine clearance was 92.8 mL/min in the EPO  $\leq 200$  group, compared with 70.8 mL/min in the EPO  $>500$  group.

No association between baseline EPO level and response to lenalidomide was observed in patients with del(5q) MDS (Supplementary Table S2); there were low numbers of del(5q) patients in the EPO  $\leq 200$  and  $>200$  to  $\leq 500$  groups.

### **Discussion**

The MDS-005 trial is the first randomized trial to evaluate lenalidomide in RBC-TD patients with lower-risk, non-del(5q) MDS who were ineligible for or refractory to ESAs. Results of this analysis indicate that patients with lower EPO levels at baseline were more likely to benefit from lenalidomide treatment, with 42.5% of patients with EPO  $\leq 100$  mU/mL achieving RBC-TI  $\geq 8$  weeks. A higher baseline EPO level did not completely preclude a response: among patients with the highest EPO levels ( $>500$  mU/mL), 15.5% achieved RBC-TI  $\geq 8$  weeks. Furthermore, nearly all patients who achieved RBC-TI  $\geq 8$  weeks had received prior ESAs. Benefit in terms of HI-E was observed irrespective of baseline EPO level.

Rates of RBC-TI  $\geq 8$  weeks were higher in patients with RS  $\geq 15\%$  versus those with RS  $<15\%$ , although no statistical comparison was made for these subgroups. Whereas RBC-TI  $\geq 8$  weeks response rates varied considerably among patients with RS  $<15\%$ , response rates were consistent across EPO groups for patients with RS  $\geq 15\%$ . The significance of these findings are limited by the relatively small number of patients with RS  $<15\%$  in each EPO subgroup. It is to be noted that, because of their good prognosis and long overall survival without progression, MDS-RS patients who have lost response to ESAs tend to be present in high numbers in experimental studies and their ineffective erythropoiesis may be responsive to certain erythropoietic stimulating agents; however, these observations may warrant further investigation.

Baseline EPO level  $>500$  mU/mL was associated with several factors linked to poor outcome, including higher RBC transfusion burden and a lower proportion of patients with RS  $\geq 15\%$ . Patients with EPO  $>500$  mU/mL also had a shorter time since diagnosis, likely due to their ineligibility for ESA treatment [17]. Recently, a higher EPO level at baseline was also associated with a lower probability of RBC-TI response to luspatercept [10], and it has been suggested that failure of ESA therapy is a marker of more aggressive

**Table 4.** Summary overview of published lower-risk non-del(5q) MDS trials.<sup>a</sup>

| Study                                  | MDS-005 phase 3<br>(N = 239)  |                     | GFM phase 2b<br>(N = 131) [14]  |                                |
|--|---|---------------------|---|--------------------------------|
| Treatment                              | LEN (10 mg/day × 28d q4w) <sup>b</sup> versus placebo   |                     | LEN (10 mg/day × 21d q4w) versus LEN + rhEPO (60,000 units/week)              |                                |
| Patients                               | IPSS Low- or Intermediate-1-risk, non-del(5q) MDS, RBC-TD, ineligible for or refractory to ESAs |                     | IPSS Low- or Intermediate-1-risk, non-del(5q) MDS, RBC-TD, refractory to ESAs |                                |
| Primary endpoint                       | RBC-TI ≥ 8 weeks  |                     | HI-E (IWG 2006) after 4 treatment cycles                                      |                                |
| RBC-TI                                 | 8-week: 26.9% versus 2.5%; <i>p</i> < .001<br>24-week: 17.5% versus 0%; <i>p</i> < .001         |                     | 8-week: LEN 13.8% versus LEN + EPO 24.2%; <i>p</i> = .13                      |                                |
| HI-E                                   | 21.8% versus 0% <sup>c</sup>  |                     | 23.1% versus 39.4%; <i>p</i> = .044   |                                |
| Response by baseline EPO level (mU/mL) | RBC-TI ≥ 8 weeks:   | HI-E (IWG 2006):    | RBC-TI:   | HI-E (IWG 2006) <sup>d</sup> : |
|  | ≤100: 42.5%   | ≤100: 42.5%         | N/R   | <100: 47.1%                    |
|  | >100 to ≤200: 33.3%   | >100 to ≤200: 44.4% |   | ≥100: 21.4%                    |
|  | >200 to ≤500: 23.3%   | >200 to ≤500: 36.7% |   |                                |
|  | >500: 15.5%   | >500: 36.2%         |   |                                |

del(5q): deletion 5q; ESA: erythropoiesis-stimulating agent; EPO: erythropoietin; GFM: Groupe Français des Myélodysplasies; HI-E: erythroid hematologic improvement; LEN: lenalidomide; IPSS: International Prognostic Scoring System; IWG: International Working Group; MDS: myelodysplastic syndromes; q4w: every 4 weeks; RBC: red blood cell; RBC-TD: RBC transfusion dependence; RBC-TI: RBC transfusion independence; rhEPO: recombinant human EPO.

<sup>a</sup>Cross-trial comparisons are limited by differences in baseline characteristics and patient eligibility criteria.

<sup>b</sup>LEN 5 mg for patients with creatinine clearance 40–60 mL/min.

<sup>c</sup>≥4 RBC units reduction based on a 16-week assessment period.

<sup>d</sup>Analysis was based on the combined LEN and LEN + EPO groups.

disease that defines a population of patients with poor prognosis [18,19]. Use of ESAs is not recommended for patients with EPO >500 mU/mL due to reduced frequency of response [17,20]. For these patients, very limited treatment options are available [5]. Based on the current study wherein responses did occur with lenalidomide therapy in a small population of patients with EPO levels >500 mU/mL, this recommendation may not necessarily encompass all non-del(5q) patients with high EPO levels. Unfortunately, the current study does not allow for further interrogation of the data to establish signals that would predetermine possible responders.

HI-E was achieved in 36–44% of patients treated with lenalidomide, and the probability of attaining HI-E appeared to be independent of EPO level. In the EPO >500 group, 36.2% achieved HI-E but only 15.5% achieved RBC-TI ≥8 weeks; this discrepancy may reflect the challenge of achieving a stringent clinical trial endpoint, such as RBC-TI ≥8 weeks, in patients with a high transfusion requirement and low hemoglobin level at baseline. It is therefore important to consider various measures of efficacy and response in addition to RBC-TI when making therapeutic decisions in these patients with limited treatment options. RBC-TI ≥8 weeks was independent from EPO levels at baseline in patients who achieved transfusion independence on lenalidomide treatment (Table 2).

The inverse correlation between baseline EPO level and achievement of RBC-TI ≥8 weeks observed in patients treated with lenalidomide is consistent with findings from other studies (Table 4). In a phase 2b study evaluating the combination of lenalidomide and EPO in 131 patients with ESA-refractory lower-risk

non-del(5q) MDS, baseline EPO <100 U/L was significantly associated with achieving HI-E (47 versus 21% for patients with EPO ≥100 U/L) [14]. Similarly, responders to lenalidomide monotherapy had a lower baseline EPO level than nonresponders (255 mU/mL versus 870 mU/mL; although not statistically significant) in a study of 39 patients with lower-risk MDS who had failed prior ESA therapy or had EPO >500 mU/mL [21]. Differences in patient populations and trial design preclude direct comparison of response rates achieved in various studies. These findings suggest that the block in erythropoiesis may be present at various levels of differentiation and that stimulation and restoration of erythroid differentiation in MDS may therefore be obtained *via* modulation of different signaling pathways.

The activity of lenalidomide in patients with non-del(5q) MDS is not fully understood but may be due in part to enhancement of the EPO receptor signaling pathway. MDS clones are characterized by impaired EPO receptor signaling despite normal EPO receptor membrane density [22]. A key determinant of EPO receptor signaling capacity is the location of the EPO receptor within lipid membrane rafts [23], which have been shown to be deficient in MDS clones [24]. Exposure of erythroid progenitor cells to lenalidomide enhanced lipid raft formation *ex vivo*, and this was accompanied by accumulation of signaling-competent JAK2/EPO receptor complexes and exclusion of the phosphatase CD45 in the lipid raft fractions [24,25]. Lenalidomide has also been shown to inhibit CD45, a negative regulator of EPO receptor signaling, which may further potentiate EPO receptor signaling [24,26]. In patients with higher EPO levels, marked intrinsic



defects in the EPO receptor signaling pathway may explain why they are less responsive to lenalidomide. Anemia may arise from defects in early or late-stage erythropoiesis, the latter being EPO-independent [27,28]. Patients whose anemia is caused by defects in late-stage erythropoiesis may be less sensitive to the erythropoietic-promoting effects of lenalidomide.

Correlation of response to lenalidomide with endogenous EPO levels was assessed across all MDS subtypes. No association between baseline EPO level and response to lenalidomide was observed in patients with del(5q). The del(5q) and non-del(5q) subtypes represent genetically and phenotypically different forms of MDS; the molecular mechanism underlying the perturbation of erythropoiesis in del(5q) MDS is profoundly different from that in non-del(5q) MDS [29]. Responses to ESA therapy are more likely to occur in non-del(5q) patients than del(5q) patients; moreover, responses are likely to be of a longer duration in the former group [30]. Ineffective erythropoiesis in del(5q) MDS arises from allelic deletion of a number of genes within the commonly deleted region of chromosome 5q that play critical roles in cell replication [31,32]. Clones with del(5q) are particularly susceptible to the cytotoxic effects of lenalidomide arising from cereblon-dependent degradation of haplodeficient proteins [33].

The effects of lenalidomide on the EPO receptor signaling provide a rationale for combining lenalidomide with ESAs. Clinical data indicate that lenalidomide may restore sensitivity to recombinant human EPO (rhEPO) in EPO-refractory non-del(5q) patients. In a recent phase 3 trial conducted by the ECOG-ACRIN Cancer Research Group evaluating lenalidomide with or without rhEPO in patients with lower-risk non-del(5q) MDS refractory to rhEPO, combination therapy induced a major erythroid response in 25.6% of patients, compared with 9.9% with lenalidomide alone ( $p = .015$ ) [34]. Notably, CD45 isoform distribution was a significant predictor of response to combination therapy ( $p = .04$ ).

Our results should be balanced against the inherent limitations of the analysis, such as its post hoc nature and the relatively small number of patients in each subgroup based on EPO level. Despite its limitations, this analysis provides some important insights on which patients with transfusion-dependent, lower-risk, non-del(5q) MDS who were ineligible for or refractory to ESAs are most likely to respond to lenalidomide therapy. We demonstrated an inverse correlation between baseline EPO level and achievement of RBC-TI  $\geq 8$  weeks. The relationship between EPO level and

HI-E requires further exploration in future studies. For patients with EPO  $>500$  mU/mL, responses to lenalidomide were observed (15.5% achieved RBC-TI  $\geq 8$  weeks and 36.2% achieved HI-E); however, more effective treatment strategies for these patients remains an important unmet medical need.

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## Disclosure statement

VS: Amgen, Astex, Celgene, Janssen, Novartis, Takeda – honoraria. AA: Alexion, Bristol-Myers Squibb, Shire – speakers bureau; Celgene Corporation – consultancy, research funding, speakers bureau; Novartis – consultancy, speakers bureau. AG: Celgene Corporation – consultancy. BS, CLB, and JW: Celgene Corporation – employment, equity ownership. NT: Celgene Corporation – formerly employment, equity ownership. PF: Astex, Janssen – research funding; Celgene Corporation, Novartis, Teva Pharmaceutical Industries – research funding, honoraria.

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