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BRIEF REPORT

Long-Term Transfusion Independence with Luspatercept Versus Epoetin Alfa in Erythropoiesis-Stimulating Agent-Naive, Lower-Risk Myelodysplastic Syndromes in the COMMANDS Trial

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ABSTRACT

Introduction: The efficacy of erythropoiesis-stimulating agents (ESAs) for transfusion-dependent (TD) anemia in lower-risk myelodysplastic syndromes (LR-MDS) is limited. Luspatercept achieved significantly greater rates of red blood cell (RBC) transfusion independence (TI) versus epoetin alfa (an ESA) in the phase 3 COMMANDS trial. This analysis assessed long-term RBC-TI, cumulative response, and safety with luspatercept in COMMANDS.

Methods: Eligible patients aged ≥ 18 years, with ESA-naive, RBC TD LR-MDS were randomized 1:1 to receive luspatercept (1.0 mg/kg, titration to 1.75 mg/kg permitted) or epoetin alfa (450 IU/kg, titration to 1050 IU/kg). Disease assessment was carried out at week 24 (day 169) and every 24 weeks thereafter. Treatment continued until disease progression, lack of clinical benefit, unacceptable toxicity, or consent withdrawal.

Results: At data cutoff (September 22, 2023; median follow-up: luspatercept 21.4 months, epoetin alfa 20.3 months), a greater proportion

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of patients treated with luspatercept (n = 182) versus epoetin alfa (n = 181) achieved a longest single RBC-TI period ≥ 1 year (44.5% vs. 27.6%; P = 0.0003) and ≥ 1.5 years (30.2% vs. 13.8%; P < 0.0001). Higher rates of RBC-TI ≥ 1.5 years with luspatercept over epoetin alfa were consistent across all prespecified subgroups, including patients with ring sideroblast-negative status and low baseline serum erythropoietin. Longer cumulative RBC-TI response [sum of all durations of RBC-TI for ≥ 12 weeks; week 1 to end of treatment (95% CI)] was observed with luspatercept [154.7 weeks (118.4–NR)] versus epoetin alfa [91.1 weeks (73.1–123.9)]. Rates of treatment-emergent adverse events, including asthenia and hypertension, generally decreased over time in both arms. Progression rates to high-risk MDS and acute myeloid leukemia were similarly low (< 5%) in both treatment arms.

Conclusions: These data demonstrated sustained, durable clinical benefit across subgroups and support luspatercept as the treatment of choice for anemia in patients with LR-MDS who are TD and ESA-naive.

Trial Registration Number: NCT03682536.

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PLAIN LANGUAGE SUMMARY

Myelodysplastic syndromes (MDS) are a group of blood disorders, where the bone marrow fails to make enough healthy blood cells. MDS is also considered a blood cancer. Patients who have lower-risk MDS (LR-MDS) have a lower chance of progressing to more serious conditions, like high-risk MDS or acute myeloid leukemia. Most patients with LR-MDS have anemia (low red blood cells [RBC]) and need frequent RBC transfusions. Erythropoiesis-stimulating agents (ESAs), like epoetin alfa, are commonly used to treat anemia. However, ESAs may not be as effective in all patients and the effects may not last as long. The COMMANDS trial looked at patients with LR-MDS and compared 2 treatments, luspatercept and epoetin alfa. The aim was to see which treatment could help patients avoid transfusions for a longer time, or be "transfusion-free." The results showed that there were more patients on luspatercept who were transfusion-free, compared with epoetin alfa, at both the 1-year and the 1.5-year timepoints. These results were similar across different patient subgroups, including patients with specific genetic mutations. Patients treated with luspatercept and epoetin alfa had similar rates of side effects, which decreased over time. Additionally, the risk of progression to more serious conditions was low and similar between the two groups. In conclusion, luspatercept helped patients with LR-MDS avoid transfusions for over 1.5 years. This supports the use of luspatercept as a first-choice treatment in patients with LR-MDS.

Keywords: Anemia; Epoetin alfa; Erythroid-stimulating agents; Luspatercept; Myelodysplastic syndromes; Transfusion-independence

Key Summary Points

Why carry out this study?

Erythropoiesis-stimulating agents (ESAs) are used to reduce chronic anemia and the need for red blood cell transfusions in patients with lower-risk myelodysplastic syndromes (LR-MDS), but these agents have suboptimal efficacy, especially in transfusion-dependent patients, and the duration of response is limited. This extended analysis of the phase 3 COMMANDS trial assessed long-term efficacy of luspatercept compared with epoetin alfa for achieving red blood cell transfusion independence in patients with ESA-naive, transfusion-dependent, lower-risk MDS.

What was learned from this study?

Patients treated with luspatercept had higher rates of red blood cell transfusion independence lasting ≥ 1.5 years, and longer cumulative duration of response compared with epoetin alfa in the intent-to-treat population and across clinically relevant subgroups.

Rates of progression to high-risk MDS and acute myeloid leukemia were low and similar across treatment arms, and rates of adverse events including asthenia and hypertension decreased over time in both arms. These data demonstrate long-lasting clinical benefit with luspatercept and support luspatercept use as a treatment of choice for anemia in transfusion-dependent ESA-naive patients with lower-risk MDS.

INTRODUCTION

Patients with myelodysplastic syndromes (MDS) frequently have chronic anemia and require red blood cell (RBC) transfusions. Transfusion dependence in MDS is associated with reduced overall survival and worse quality of life compared with patients who are transfusion independent (TI), as well as increased healthcare resource utilization [1]. Among patients with lower-risk MDS (LR-MDS), transfusion dependence is also associated with higher incidence of non-leukemic death and acute myeloid leukemia (AML) transformation compared with patients who are RBC-transfusion-independent (RBC-TI) [2]. Erythropoiesis-stimulating agents (ESAs) are an established therapeutic option for anemia in patients with LR-MDS; however, erythroid responses are observed at higher rates in patients who are transfusion-independent compared with those who are transfusion-dependent (TD) [3, 4]. Among both TD and TI patients, duration of response to ESAs ranges from 5–19 months [5–10].

Luspatercept is a recombinant fusion protein that binds endogenous TGF-β superfamily ligands and promotes both early- and late-stage erythroid maturation [11–14]. Luspatercept is approved for the treatment of anemia in patients without previous ESA use in adult patients with very low- to intermediate-risk MDS who may require regular RBC transfusions, and for the treatment of anemia failing ESA treatment and requiring ≥ 2 RBC units over 8 weeks in patients with very low- to intermediate-risk MDS with ring sideroblasts (RS) or MDS/myeloproliferative neoplasms with RS and thrombocytosis (MDS/MPN-RS-T) [15]. The phase 3 COMMANDS trial (NCT03682536) evaluated luspatercept versus epoetin alfa in patients with TD, ESA-naive, LR-MDS. The primary analysis of the COMMANDS trial found that a significantly higher proportion of patients treated with luspatercept compared with epoetin alfa reached the primary endpoint of ≥ 12 weeks RBC-TI with concurrent mean hemoglobin increase ≥ 1.5 g/dL (60% vs. 35%; $P < 0.0001$) at the data cutoff of March 31, 2023.

With approximately 6 additional months of follow-up (data cutoff September 22, 2023), patients treated with luspatercept compared with epoetin alfa achieved longer median duration of RBC-TI lasting ≥ 12 weeks with concurrent mean hemoglobin increase ≥ 1.5 g/dL (128.1 vs. 95.1 weeks, HR 0.709, 95% CI 0.444–1.132, $P = 0.1482$). Patients treated with luspatercept also had longer median duration of RBC-TI ≥ 12 weeks than epoetin alfa (126.6 vs. 89.7 weeks, HR 0.61, 95% CI 0.4–0.95, $P = 0.026$) [16]. Longer durations of RBC-TI lasting ≥ 12 weeks were observed with

luspatercept than epoetin alfa across patient subgroups based on RS status, baseline transfusion burden, serum erythropoietin concentration, and *SF3B1* mutation status; median duration of response was not reached in the luspatercept group for patients with RS-negative (RS–) or *SF3B1* non-mutated status [16].

The aim of this analysis was to assess the long-term clinical benefit of luspatercept versus epoetin alfa in COMMANDS, including extended RBC-TI, cumulative duration of response, and safety after approximately 6 additional months of follow-up from the primary analysis.

METHODS

Study Design and Participants

Full study methods have been published previously [16, 17]. Briefly, COMMANDS was a phase 3, open-label, randomized controlled trial conducted at 142 sites across 26 countries. Eligible patients were aged ≥ 18 years, had a diagnosis of MDS per World Health Organization 2016 classification that met revised International Prognostic Scoring System classification for very low, low, or intermediate risk, had endogenous serum erythropoietin < 500 U/L, were ESA-naive, and required RBC transfusions (2–6 units packed RBC/8 weeks for a minimum of 8 weeks immediately prior to randomization). Patients were randomized 1:1 to receive luspatercept 1.0 mg/kg (titration up to 1.75 mg/kg) subcutaneously once every 3 weeks or epoetin alfa 450 IU/kg (titration up to 1050 IU/kg; maximum total dose 80,000 IU) subcutaneously once weekly (Supplementary Fig. 1). Appropriate dose adjustments to luspatercept and epoetin alfa were permitted from week 7 day 1 to maintain the target hemoglobin range of 10–12 g/dL. Patients may have had luspatercept dose level increased in a stepwise manner beyond the starting dose of 1.0–1.33 mg/kg and up to a maximum of 1.75 mg/kg if, after at least 2 consecutive doses, a patient was not RBC transfusion-free or hemoglobin concentration was less than 10 g/dL, with the hemoglobin increase less than or equal to 1 g/dL since the last dose (Supplementary Table 1).

Randomization was stratified by RBC transfusion burden at baseline (< 4 vs. ≥ 4 packed RBC units per 8 weeks), RS status (positive vs. negative), and endogenous serum erythropoietin at baseline (≤ 200 U/L vs. > 200 U/L). Disease assessment was carried out at week 24 (day 169) and every 24 weeks thereafter. Treatment continued until disease progression per International Working Group (IWG) 2006 criteria [18], lack of clinical benefit, unacceptable toxicity, or withdrawal of consent. Clinical benefit was defined as RBC transfusion reduction of ≥ 2 packed RBC units/8 weeks compared with baseline [for any consecutive 8-week period within the 12 weeks immediately preceding day 169 and every 24 weeks thereafter (i.e., day 337, day 505, etc.)]. Absence of disease progression was defined per IWG 2006 criteria for altering the natural history of MDS based on central morphological assessment of bone marrow, peripheral blood, and cytogenetics results. Both criteria were required to be confirmed for a patient to remain on treatment beyond each 24-week timepoint. For safety, patients were followed for 5 years from first dose or 3 years from last dose, whichever was later.

The trial was performed in accordance with the Declaration of Helsinki and International Council on Harmonisation guidelines, and received review board approval from each participating site's institutional review board/ethics committee. All patients provided written informed consent documentation prior to trial entry.

Outcomes

The primary endpoint of the COMMANDS trial was the proportion of patients with RBC-TI for ≥ 12 weeks with a concurrent mean hemoglobin increase of ≥ 1.5 g/dL during weeks 1–24. Key secondary endpoints assessed during weeks 1–24 included the proportion of patients with hematological improvement-erythroid (HI-E) for ≥ 8 weeks per IWG 2006 criteria [18], RBC-TI for ≥ 12 weeks, and RBC-TI for ≥ 24 weeks. Other secondary endpoints included the proportion

of patients with RBC-TI lasting ≥ 24 weeks (weeks 1–48), duration of RBC-TI lasting ≥ 12 weeks (week 1 to end of treatment), and safety. The long-term clinical benefit assessment described in this report included the proportion of patients who achieved continuous RBC-TI for ≥ 1 and ≥ 1.5 years, as well as duration, timing of, and intervals between RBC-TI responses for individual patients. RBC-TI lasting ≥ 1.5 years was also analyzed in key patient subgroups (baseline transfusion burden, baseline serum erythropoietin, *SF3B1* mutation status, and RS status). Cumulative duration of RBC-TI was defined as the sum of all durations of RBC-TI for ≥ 12 weeks from week 1 to end of treatment.

Adverse event (AE) safety monitoring included adverse events of interest (EOIs) identified based on non-clinical findings or the known safety profile of the study drugs. Preferred terms were coded with the Medical Dictionary for Regulatory Activities (version 26.0). Adverse events were graded based on the patient's symptoms according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Treatment-emergent adverse events (TEAEs) were defined as adverse events that started on or after the first dose of study medication until 42 days after the last dose of any study drug. Exposure-adjusted incidence rates (EAIRs) were calculated per 100 person-years (PY), defined as 100 times the number of patients with the specific treatment-emergent EOI divided by the total exposure time (in years) to the event. Patients were also followed up for progression to high-risk MDS or AML.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Disposition and Baseline Characteristics

At the data cutoff for this analysis (September 22, 2023), 182 patients were randomized to luspatercept and 181 to epoetin alfa. Median (IQR) follow-up was 21.4 (14.2–32.4) months for luspatercept versus 20.3 (12.7–30.9) months

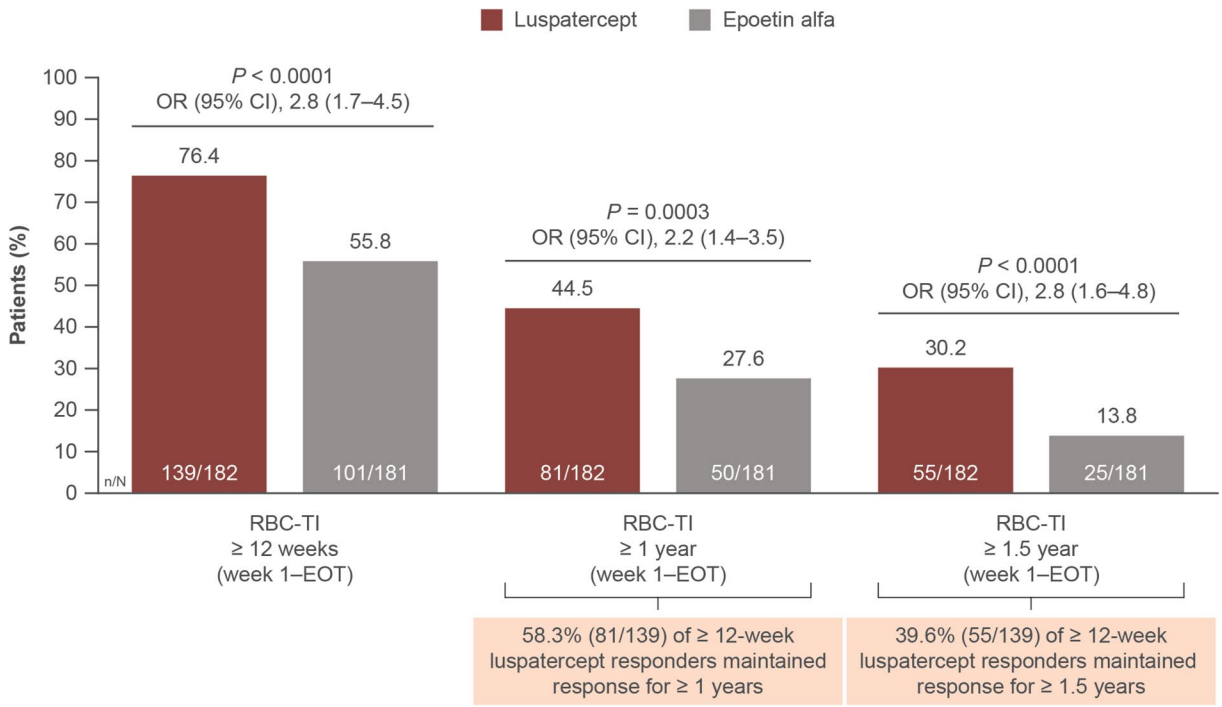


Fig. 1 Long-term RBC-TI responses. *EOT* end of treatment, *RBC-TI* red blood cell transfusion-independent. © American Society of Hematology (2024). Reused with permission

for epoetin alfa. Median treatment exposure was longer with luspatercept (61.9 weeks) than with epoetin alfa (44.7 weeks). Baseline demographics and disease characteristics were similar between luspatercept and epoetin alfa arms and have been reported previously [16, 17].

Red Blood Cell Transfusion Independence

From week 1 to end of treatment, significantly more patients in the luspatercept arm compared with the epoetin alfa arm achieved uninterrupted RBC-TI responses lasting ≥ 12 weeks (76.4% vs. 55.8%; $P < 0.0001$), ≥ 1 year (44.5% vs. 27.6%; $P = 0.0003$), and ≥ 1.5 years (30.2% vs. 13.8%; $P < 0.0001$) (Fig. 1). Among patients who achieved a ≥ 12-week RBC-TI response with luspatercept (n = 139/182), 81/139 (58.3%) maintained their response for ≥ 1 year and 55/139 (39.6%) for ≥ 1.5 years.

Descriptive subgroup analyses showed a trend towards higher rates of RBC-TI ≥ 1.5 years with luspatercept compared with epoetin alfa across prespecified patient subgroups (Fig. 2), including patients with baseline serum erythropoietin ≤ 200 U/L (35.9% vs. 15.3%, odds ratio [OR] 3.10, 95% CI 1.76–5.47), non-mutated *SF3B1* (21.5% vs. 13.9%, OR 1.70, 95% CI 0.70–4.15), and RS– status [24.5% vs. 16.0%, OR 1.70, 95% CI 0.63–4.62]. Luspatercept also demonstrated higher rates of RBC-TI ≥ 1.5 years compared with epoetin alfa in patients with both low (< 4 units/8 weeks, 34.7% vs. 18.0%, OR 2.41, 95% CI 1.31–4.48) and high (≥ 4 units/8 weeks, 21.9% vs. 7.1%, OR 3.64, 95% CI 1.23–10.78) transfusion burden. Patients with high baseline serum erythropoietin (> 200 U/L) had similar response rates across both treatment arms (8.1% vs. 8.1%, OR 1.0, 95% CI 0.19–5.31). Kaplan–Meier estimates of duration of response for patient subgroups have been reported previously [16].

Patients treated with luspatercept tended to have longer lasting periods or multiple periods of response, resulting in longer cumulative response over an extended treatment

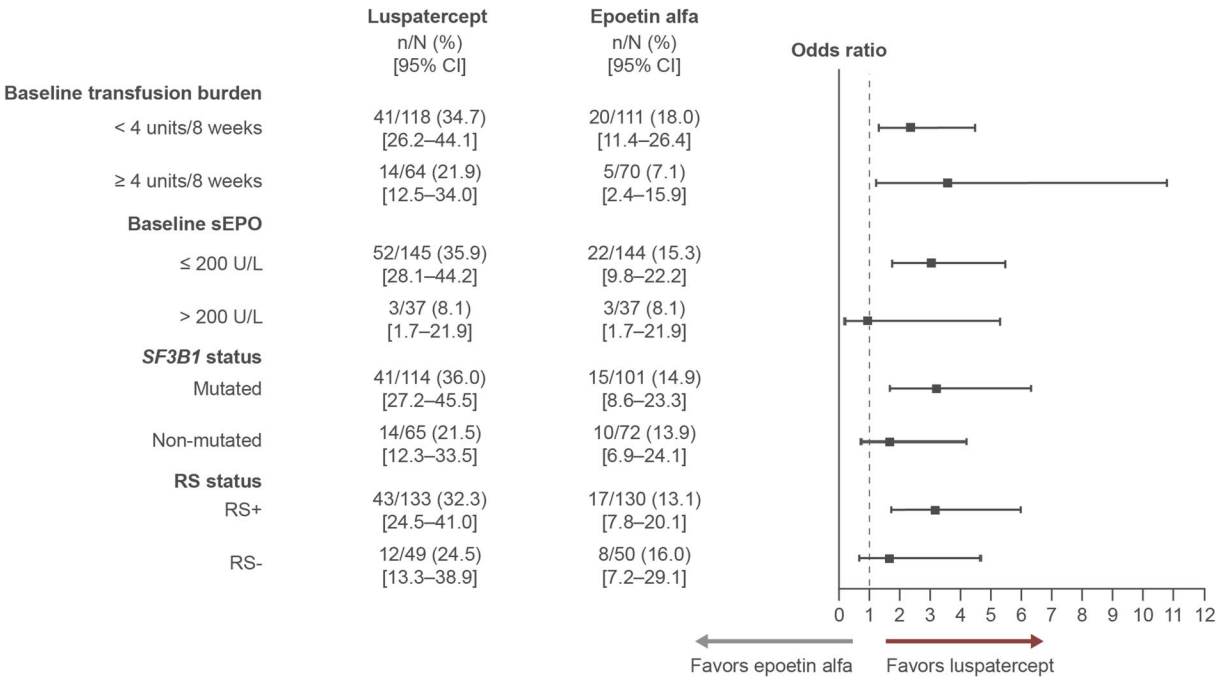


Fig. 2 Continuous RBC-TI ≥ 1.5 years across patient subgroups. Continuous response defined as patients achieving a single, uninterrupted period of RBC-TI for ≥ 1.5 years from week 1 to end of treatment. *CI* confidence interval, *EPO* erythropoietin, *SF3B1* splicing factor 3B subunit 1, *RBC* red blood cell; *RBC-TI* red blood cell transfusion-independence, *RS* ring sideroblast. © American Society of Hematology (2024). Reused with permission

period (Fig. 3). Median cumulative duration of all response episodes was 154.7 weeks (95% CI 118.4–NR) in the luspatercept arm and 91.1 weeks (95% CI 73.1–123.9) in the epoetin alfa arm (P = 0.0016). Among patients with multiple RBC-TI response periods (luspatercept, n = 28; epoetin alfa n = 17) median (IQR) time between multiple response periods was 2 (1–38) days and 19 (1–35) days for luspatercept and epoetin alfa, respectively. Patients received a median of 2 units of RBC transfusions in periods between responses in both arms.

As previously reported in the primary analysis, 80% of patients in the luspatercept group had at least one dose escalation to maintain the target hemoglobin range of 10–12 g/dL or TI. Overall, 78% of patients were titrated from 1.0 to 1.33 mg/kg, and 65% were titrated from 1.33 to 1.75 mg/kg [16].

Safety and MDS Disease Progression

Overall rates of TEAEs, suspected-related TEAEs, grade 3/4 TEAEs, and serious TEAEs were generally similar between treatment arms and decreased from week 1 to 84 (Fig. 4). As previously reported in the primary analysis, treatment-emergent EOIs were reported in 111 (61.0%) and 87 (48.6%) patients receiving luspatercept and epoetin alfa, respectively [16]. The most frequently occurring EOI in both the luspatercept and epoetin alfa arms was asthenia (32.4% and 25.7%, respectively). Rates of asthenia and hypertension generally decreased after the first few weeks of treatment and over time up to week 84 in both arms (Fig. 4). When adjusted for treatment exposure, EOI were broadly similar between luspatercept and epoetin alfa arms, with the exception of hypertension, which had a higher rate in the luspatercept arm (13.7/100 PY vs. 9.4/100 PY).

A total of 4 (2.2%) patients in the luspatercept arm and 6 (3.4%) patients in the epoetin alfa

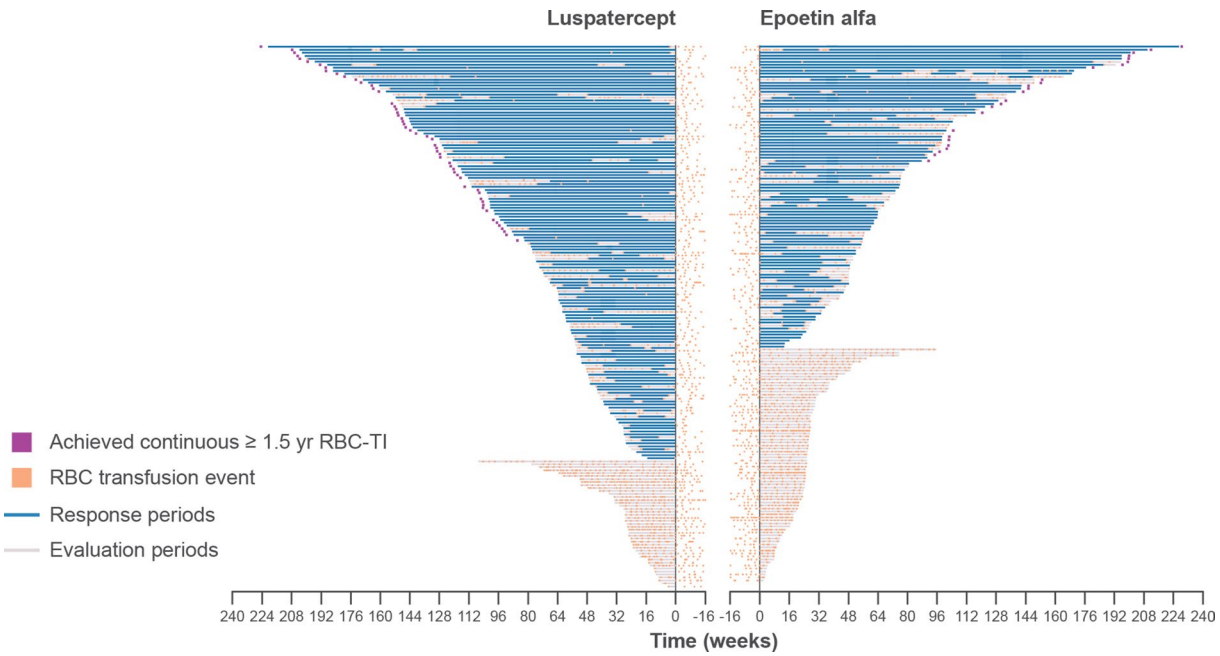
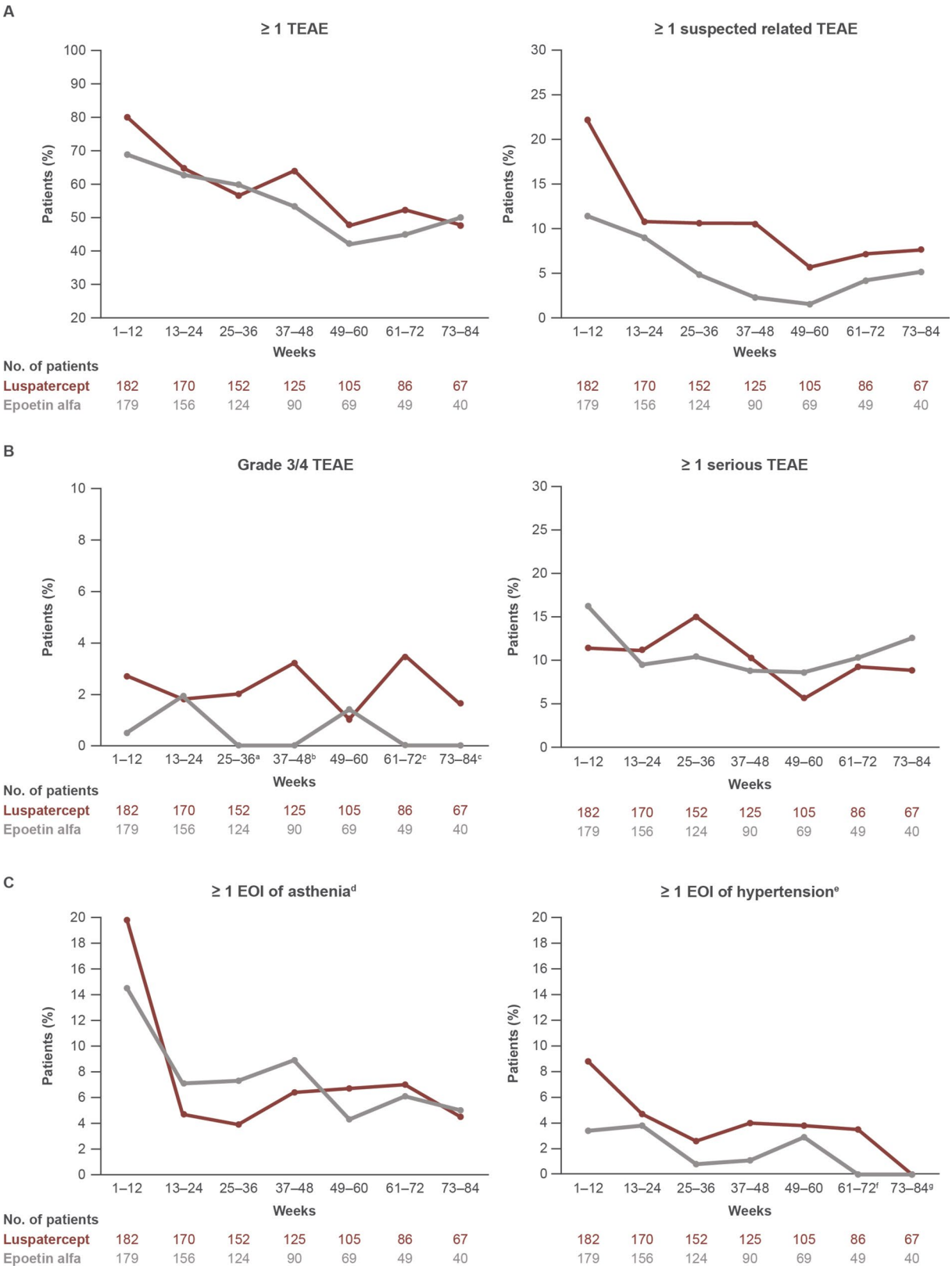


Fig. 3 Patients with multiple consecutive RBC-TI periods. Multiple periods of RBC-TI ≥ 12 weeks for individual patients are shown in the plot interrupted by evaluation periods or RBC transfusion events. Continuous response defined as patients achieving a single, uninterrupted period of RBC-TI for ≥ 1.5 years from week 1 to end of treatment. *RBC* red blood cell, *RBC-TI* red blood cell transfusion-independence. © American Society of Hematology (2024). Reused with permission


A
≥ 1 TEAE
Patients (%)
100
90
80
70
60
50
40
30
20
1–12
13–24
25–36
37–48
49–60
61–72
73–84
Weeks
≥ 1 suspected related TEAE
Patients (%)
30
25
20
15
10
5
0
1–12
13–24
25–36
37–48
49–60
61–72
73–84
Weeks
No. of patients
Luspatercept 182 170 152 125 105 86 67
Epoetin alfa 179 156 124 90 69 49 40
182 170 152 125 105 86 67
179 156 124 90 69 49 40
B
Grade 3/4 TEAE
Patients (%)
10
8
6
4
2
0
1–12
13–24
25–36[a]
37–48[b]
49–60
61–72[c]
73–84[c]
Weeks
≥ 1 serious TEAE
Patients (%)
30
25
20
15
10
5
0
1–12
13–24
25–36
37–48
49–60
61–72
73–84
Weeks
No. of patients
Luspatercept 182 170 152 125 105 86 67
Epoetin alfa 179 156 124 90 69 49 40
182 170 152 125 105 86 67
179 156 124 90 69 49 40
C
≥ 1 EOI of asthenia[d]
Patients (%)
20
18
16
14
12
10
8
6
4
2
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1–12
13–24
25–36
37–48
49–60
61–72
73–84
Weeks
≥ 1 EOI of hypertension[e]
Patients (%)
20
18
16
14
12
10
8
6
4
2
0
1–12
13–24
25–36
37–48
49–60
61–72[f]
73–84[g]
Weeks
No. of patients
Luspatercept 182 170 152 125 105 86 67
Epoetin alfa 179 156 124 90 69 49 40
182 170 152 125 105 86 67
179 156 124 90 69 49 40

◂**Fig. 4** Patients with ≥ 1 TEAE or suspected-related TEAE (**A**), ≥ 1 grade 3/4 TEAE or serious TEAE (**B**), ≥ 1 EOI of asthenia or hypertension (**C**) up to 1.5 years. [a]No reported grade 3/4 TEAEs in weeks 25–36 in the epoetin alfa arm. [b]No reported grade 3/4 TEAEs in weeks 37–48 in the epoetin alfa arm. [c]No reported grade 3/4 TEAEs in weeks 61–84 in the epoetin alfa arm. [d]EOI of asthenia included fatigue, malaise, and lethargy. [e]EOI of hypertension included hypertension, essential hypertension, hypertensive urgency, labile hypertension, and hypertensive nephropathy. [f]No reported EOIs of hypertension in weeks 61–72 in the epoetin alfa arm. [g]No reported EOIs of hypertension in weeks 73–84 in either. *EOI* event of interest, *TEAE* treatment-emergent adverse event. © American Society of Hematology (2024). Reused with permission

arm progressed to high-risk MDS; median time to progression was not reached (Table 1). Progression to AML occurred in 7 (3.8%) patients in the luspatercept arm and 8 (4.4%) patients in the epoetin alfa arm and median time to progression was not reached in both arms.

DISCUSSION

The phase 3 COMMANDS trial showed that patients with ESA-naive TD LR-MDS had significantly higher rates of continuous RBC-TI lasting ≥ 1 year, and ≥ 1.5 years when treated with luspatercept compared with epoetin alfa for an extended period, as well as longer cumulative duration of RBC-TI response with luspatercept. Rates of TEAEs and exposure-adjusted EOI rates were generally similar between treatment arms and decreased over time. Rates of progression to high-risk MDS and AML were low and comparable between treatment arms. This analysis provides important insight into longer-term efficacy and safety of luspatercept in this LR-MDS population.

The difference in response rates between luspatercept and epoetin alfa arms increased over time, with over twice as many patients having a period of continuous RBC-TI lasting ≥ 1.5 years with luspatercept compared with epoetin alfa (30.2% vs. 13.8%). Over the extended treatment period, patients in the luspatercept arm not only had longer lasting continuous periods of response but also longer cumulative duration of all response episodes compared with epoetin alfa (154.7 weeks vs. 91.1 weeks). Previous reports have suggested that for patients with LR-MDS who respond to ESAs, median duration of response lasts between 5 and 19 months [5–10]. Therefore, the data from the COMMANDS analysis support the use of luspatercept as a first-line treatment which could fulfill an unmet need for treatment options and provide longer-lasting RBC-TI response in transfusion-dependent LR-MDS.

The long-term benefit observed with luspatercept in this COMMANDS analysis also aligns with real-world data. In a retrospective US cohort analysis among 32 patients with LR-MDS who were ESA-naive and TD at baseline, 93.8% achieved TI ≥ 12 weeks [19]. With median follow-up of 5.7 months, most (93.9%) ESA-naive patients were still receiving luspatercept at the time of data collection [19]. In a recent US claims database analysis, 53.9% of TD patients (n = 282) treated with luspatercept had rolling 12-week RBC-TI, although this analysis did not evaluate ESA-naive patients separately [20]. Overall, 75.4% of patients were treated with luspatercept for ≥ 6 months and 67.1% of patients were treated with luspatercept for ≥ 12 months [20]. In a US and Italian cohort analysis of 331 patients with anemia and LR-MDS treated with luspatercept, median duration of erythroid response was 65 weeks with 13 months of follow-up.[21]. Although real-world analyses of luspatercept treatment of anemia in MDS for over 1 year are limited due to the relatively recent FDA and EMA approval [15], together these data indicate a pattern of durable response.

This COMMANDS analysis showed a descriptive trend towards higher rates of ≥ 1.5-year RBC-TI with luspatercept over epoetin alfa across prespecified subgroups, including patients with low baseline serum erythropoietin (2.3× greater), non-mutated *SF3B1* (1.5× greater), and RS– status (1.5× greater). Higher rates of RBC-TI ≥ 1.5 years were also observed with luspatercept than epoetin alfa in groups with low and high transfusion burden at baseline. Low baseline serum erythropoietin levels

Table 1 Progression to high-risk MDS and AML

	Luspatercept (*n* = 182)	Epoetin alfa (*n* = 181)
Progression to high-risk MDS, *n* (%)	4 (2.2)	6 (3.4)[a]
High-risk MDS exposure-adjusted incidence rate per 100 person-years[b] (95% CI)	98.52 (36.98–262.49)	117.5 (52.79–261.56)
Median time to high-risk MDS progression from initial MDS diagnosis (95% CI)	NR (NR–NR)	NR (NR–NR)
Progression to AML, *n* (%)	7 (3.8)	8 (4.4)
AML incidence rate per 100 person-years (95% CI)[c]	2.02 (0.96–4.24)	2.48 (1.24–4.97)
Hazard ratio (95% CI)[d]	1.026 (0.360–2.925); *P* = 0.9612	
Median time to AML progression from initial MDS diagnosis (95% CI)	NR (132.1–NR)	NR (NR–NR)

[a]Progression to high-risk MDS assessed among 179 evaluable patients in the epoetin alfa arm

[b]Person-year is the overall treatment exposure for patients without an event and the time from treatment start to the first event for patients with an event

[c]Person-year is calculated from randomization date to AML onset date, or to the last AML follow-up date for subjects without progression to AML

[d]One-sided *P*-value based on log-rank test, derived baseline stratifications are used, hazard ratio is calculated by Cox proportional hazard model

AML acute myeloid leukemia, *CI* confidence interval, *MDS* myelodysplastic syndromes, *NR* not reached

have been previously viewed as predicting a higher likelihood of ESA response in adults with LR-MDS [22]. Mutated *SF3B1* has also been identified as a positive prognostic factor in MDS, whereas RS– patients have a worse prognosis [23, 24]. In the COMMANDS primary analysis, rates of RBC-TI lasting 24 weeks (weeks 1–48) were higher with luspatercept than epoetin alfa for patients with baseline serum epoetin ≤ 200 U/L (71% vs. 51%) and mutated *SF3B1* (73% vs. 42%), but similar for patients with RS– status (53% vs. 50%) [16]. Median duration of RBC-TI ≥ 12 weeks (week 1–EOT) with luspatercept versus epoetin alfa respectively in patients with RS– status was not reached (95% CI 135.9–NR) versus 95.1 weeks (95% CI 74.9–NR); median duration of RBC-TI ≥ 12 weeks was 128.1 weeks (95% CI 112.7–NR) versus 89.7 weeks (95% CI 62.9–157.3) for patients with baseline serum erythropoietin ≤ 200 U/L, and not reached (95% CI 46.0–NR) versus 95.1 weeks (95% CI 63.7–NR) for patients with non-mutated *SF3B1*. The extended analysis shows a potential advantage of luspatercept for durable responses in clinically relevant subgroups ≥ 1.5 years, with emerging benefit for RS– populations. Despite a small sample size of patients with RS– status, benefit for ≥ 1.5 years RBC-TI was observed in this group for the first time in this analysis. Among patients with baseline serum erythropoietin > 200 U/L, the proportion of patients with ≥ 1.5 years RBC-TI was the same in both luspatercept and epoetin alfa arms; however, as reported in the primary analysis, the median duration of response for this subgroup was greater with luspatercept [52.9 weeks (95% CI 26.7–NR)] versus epoetin alfa (23.9 weeks (95% CI 14.9–NR)] at the same data cutoff. Additional studies are needed to assess the impact of luspatercept in patients with higher baseline serum erythropoietin levels, who may be less likely to respond to treatment [25]. While continued investigation is required to confirm these trends, descriptive analyses indicate long-term efficacy of luspatercept in a broad population of

patients with ESA-naive, TD LR-MDS, particularly in patients with RS– status.

The safety profile of luspatercept in this analysis was generally consistent with the known safety profile of luspatercept in MDS indications and with previous trial analyses [15–17, 26]. Asthenia and hypertension decreased in frequency over time with treatment exposure. Rates of progression to high-risk MDS and AML were also low and similar between arms.

Limitations of the COMMANDS trial have been discussed previously [16, 17], and include the open-label design and relatively high proportion of patients with RS+ status (73%) or *SF3B1* mutations (59%) compared with the expected patient population. Subgroup analyses were not powered for statistical significance due to the low numbers of patients in some subgroups, and further investigation is required to confirm findings.

CONCLUSION

In this analysis of long-term responses in the COMMANDS trial, luspatercept continued to demonstrate higher rates of sustained and durable clinical benefit compared with epoetin alfa. This benefit was observed across prespecified clinically relevant subgroups, including patients with RS– status, low baseline serum erythropoietin, and non-mutated *SF3B1*. Luspatercept safety results were consistent with previous MDS studies. These data continue to support luspatercept as the treatment of choice in TD ESA-naive patients with LR-MDS.

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Author Contributions. The study was conceived and designed by Guillermo Garcia-Manero, Barkha Aggarwal, Dimana Miteva, and Uwe Platzbecker. Data acquisition was performed by Guillermo Garcia-Manero, Valeria Santini, Amer Zeidan, Rami Komrokji, Veronika Pozharskaya, Shelonitda Rose, David Valcárcel, Pierre Fenaux, Jake Shortt, Matteo Giovanni Della Porta, and Uwe Platzbecker. Data analysis was performed by Veronika Pozharskaya, Shelonitda Rose, and Yinzhi Lai. Data was interpreted by Guillermo Garcia-Manero, Valeria Santini, Amer M. Zeidan, Rami S. Komrokji, Veronika Pozharskaya, Shelonitda Rose, Karen Keeperman, Yinzhi Lai, Sameer Kalsekar, Barkha Aggarwal, Dimana Miteva, David Valcárcel, Pierre Fenaux, Jake Shortt, Matteo Giovanni Della Porta, and Uwe Platzbecker. All authors contributed to data interpretation and manuscript development. All authors read and approved the final manuscript.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available to protect patient privacy. Data sharing requests for non-identifiable patient-level and study-level clinical data, clinical study reports, and protocols will be considered on a case-by-case basis. Bristol Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

Declarations

Conflicts of Interest. Valeria Santini has been a member of the board of directors or an advisory board for AbbVie, Bristol Myers Squibb/Celgene, CTI, Geron, Jazz, Keros, Novartis, Servier, and Syros. Amer M. Zeidan has consulted for AbbVie, Agios, Akeso Pharma, ALX Oncology, Amgen, Astellas, BeiGene, BioCryst, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Chiesi, Daiichi Sankyo, Epizyme, Faron, Genentech, Geron, Gilead, GlycoMimetics, Hikma, Janssen, Karyopharm, Kura Oncology, Kyowa Kirin, LAVA Therapeutics, Mendus, Notable Labs, Novartis, Orum, Otsuka, Pfizer, Regeneron, Rigel, Schrödinger, Servier, Sumitomo, Syndax, Syros, Taiho, Takeda, Treadwell, Vincerx, and Zentalis; has received research funding from AbbVie, Amgen, Astex, Bristol Myers Squibb, Celgene, Geron, Kura, Novartis, Otsuka, Shattuck Labs, Syros, and Takeda; and has received honoraria from AbbVie, Agios, Akeso Pharma, ALX Oncology, Amgen, Astellas, BeiGene, BioCryst, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Chiesi, Daiichi Sankyo, Epizyme, Faron, Genentech, Geron, Gilead, GlycoMimetics, Hikma, Janssen, Karyopharm, Kura Oncology, Kyowa Kirin, LAVA Therapeutics, Mendus, Notable Labs, Novartis, Orum, Otsuka, Pfizer, Regeneron, Rigel, Schrödinger, Servier, Sumitomo, Syndax, Syros, Taiho, Takeda, Treadwell, Vincerx, and Zentalis. Rami S. Komrokji has participated in advisory boards for Bristol Myers Squibb, Daiichi Sankyo, Jazz, PharmaEssentia, Rigel, Servier, Sobi, and Sumitomo; has received research grants from Bristol Myers Squibb; has consulted for Geron and Genentech; and has participated in speakers' bureaux for PharmaEssentia, Rigel, Servier, and Sobi. Veronika Pozharskaya is an employee of Bristol Myers Squibb and holds stock in Bristol Myers Squibb and Merck. Shelonitda Rose has received travel support from Bristol Myers Squibb and holds stock in Bristol Myers Squibb/Celgene. Yinzhi Lai, Sameer Kalsekar, Barkha Aggarwal, and Karen Keeperman are employees of and hold stock in Bristol Myers Squibb. Dimana Miteva is an employee of Bristol Myers Squibb. David Valcárcel has consulted for Amgen, Astellas, Bristol Myers Squibb/Celgene, Janssen, Jazz, Merck Sharpe & Dohme, Novartis, Pfizer, Sanofi, Sobi, and Takeda; has received honoraria from Amgen, Astellas, Bristol Myers Squibb/Celgene, Janssen, Jazz, Merck Sharpe & Dohme, Novartis, Pfizer, Sanofi, Sobi, and Takeda; and has received meeting and travel support from AbbVie, Bristol Myers Squibb/Celgene, Jazz, Novartis, and Sobi. Pierre Fenaux has received research funding (as the GFM chairperson) from AbbVie, Astex, Bristol Myers Squibb, Novartis, and Servier; and has received honoraria from AbbVie and Bristol Myers Squibb. Jake Shortt has received research funding from Astex/Taiho; has consulted for Astellas, Bristol Myers Squibb, Novartis, Otsuka, and Pfizer; has received honoraria from Novartis and Mundipharma; and has participated on the ELEMENT trial steering committee for Bristol Myers Squibb (paid to institution). Matteo Giovanni Della Porta has received honoraria from and participated on a data safety monitoring or advisory board for Bristol Myers Squibb. Uwe Platzbecker has received grant support (paid to GWT-TUD) from Amgen and Janssen; has received lecture fees and grant support (paid to the University of Leipzig) from Amgen; has received grant support (paid to the University of Dresden) from Merck and Novartis; has consulted for AbbVie, Bristol Myers Squibb, Curis, Geron, and Novartis; has received honoraria from Bristol Myers Squibb; has received travel support from Bristol Myers Squibb; and is a member of the board of directors or an advisory board for the MDS Foundation. Guillermo Garcia-Manero has nothing to disclose.

Ethical Approval. The trial was performed in accordance with the Declaration of Helsinki and International Counsel on Harmonisation guidelines and received review board approval from each participating site's institutional review board/ethics committee. All patients provided written informed consent documentation prior to trial entry.

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