ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List

ABSTRACT

BACKGROUND

Patients with anemia and lower-risk myelodysplastic syndromes in whom erythropoiesis-stimulating agent therapy is not effective generally become dependent on red-cell transfusions. Luspatercept, a recombinant fusion protein that binds transforming growth factor β superfamily ligands to reduce SMAD2 and SMAD3 signaling, showed promising results in a phase 2 study.

METHODS

In a double-blind, placebo-controlled, phase 3 trial, we randomly assigned patients with very-low-risk, low-risk, or intermediate-risk myelodysplastic syndromes (defined according to the Revised International Prognostic Scoring System) with ring sideroblasts who had been receiving regular red-cell transfusions to receive either luspatercept (at a dose of 1.0 up to 1.75 mg per kilogram of body weight) or placebo, administered subcutaneously every 3 weeks. The primary end point was transfusion independence for 8 weeks or longer during weeks 1 through 24, and the key secondary end point was transfusion independence for 12 weeks or longer, assessed during both weeks 1 through 24 and weeks 1 through 48.

RESULTS

Of the 229 patients enrolled, 153 were randomly assigned to receive luspatercept and 76 to receive placebo; the baseline characteristics of the patients were balanced. Transfusion independence for 8 weeks or longer was observed in 38% of the patients in the luspatercept group, as compared with 13% of those in the placebo group (P<0.001). A higher percentage of patients in the luspatercept group than in the placebo group met the key secondary end point (28% vs. 8% for weeks 1 through 24, and 33% vs. 12% for weeks 1 through 48; P<0.001 for both comparisons). The most common luspatercept-associated adverse events (of any grade) included fatigue, diarrhea, asthenia, nausea, and dizziness. The incidence of adverse events decreased over time.

CONCLUSIONS

Luspatercept reduced the severity of anemia in patients with lower-risk myelodysplastic syndromes with ring sideroblasts who had been receiving regular red-cell transfusions and who had disease that was refractory to or unlikely to respond to erythropoiesis-stimulating agents or who had discontinued such agents owing to an adverse event. (Funded by Celgene and Acceleron Pharma; MEDALIST ClinicalTrials.gov number, NCT02631070; EudraCT number, 2015-003454-41.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Fenaux at Hôpital Saint-Louis, 1 Ave. Claude Vellefaux, 75475 Paris, France, or at pierre.fenaux@aphp.fr; or to Dr. Platzbecker at Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, Leipzig University Hospital, Johannisallee 32 A, 04103 Leipzig, Germany, or at uwe.platzbecker@medizin.uni-leipzig.de.

Drs. Fenaux and Platzbecker and Drs. Komrokji and List contributed equally to this article.

N Engl J Med 2020;382:140-51.
DOI: 10.1056/NEJMoa1908892

Myelodysplastic syndromes are acquired bone marrow disorders predominating in the elderly and are characterized by ineffective hematopoiesis, progressive cytopenias, and risk of progression to acute myeloid leukemia.[1] Lower-risk myelodysplastic syndromes most commonly manifest with symptomatic anemia. (Lower-risk myelodysplastic syndromes are defined according to the International Prognostic Scoring System [IPSS][2] as being of low or intermediate 1 risk or according to the Revised IPSS [IPSS-R] as being of very low, low, or intermediate risk; see the protocol and the Supplementary Methods section in the Supplementary Appendix, both available with the full text of this article at NEJM.org.) In elderly persons, chronic anemia is associated with multiple complications, including cardiovascular complications, increased risks of falls and bone fracture, and shorter survival.[3-5] A high proportion of patients with lower-risk myelodysplastic syndromes eventually become dependent on red-cell transfusions, a situation that is associated with reduced quality of life and overall survival.[5-12]

Treatment goals for patients with lower-risk myelodysplastic syndromes include transfusion independence, improvement in hemoglobin levels, and maintenance of or improvement in quality of life.[5,13,14] Erythropoiesis-stimulating agents are a first-line treatment for lower-risk myelodysplastic syndromes,[1,5] targeting early stages of erythropoiesis by inhibiting apoptosis and stimulating erythropoietin-responsive erythroid precursor proliferation.[15,16] Patients who are dependent on transfusions[5,17-21] or who have serum erythropoietin levels above 200 U per liter[5,18,20-22] are less likely to have a response to erythropoiesis-stimulating agents than are patients who are not dependent on transfusions or who have serum erythropoietin levels below 200 U per liter; patients with myelodysplastic syndromes with ring sideroblasts have a shorter median duration of response to erythropoiesis-stimulating agents than those who do not have ring sideroblasts.[1,5,17,22,23] Although lenalidomide is an established treatment for patients with lower-risk myelodysplastic syndromes with chromosome 5q deletion (del[5q]) who are dependent on transfusions, regardless of previous treatment with erythropoiesis-stimulating agents,[5,24] only 39% of other patients with lower-risk myelodysplastic syndromes receive second-line therapy aside from ongoing red-cell transfusions.[22] Given the limited number of approved and effective treatments, new treatment strategies are needed for patients with non-del(5q) lower-risk myelodysplastic syndromes who are dependent on transfusions.[1,5]

Signaling by means of the SMAD2–SMAD3 pathway is constitutively increased in the bone marrow cells of patients with myelodysplastic syndromes and in disease models with ineffective erythropoiesis, including β-thalassemia.[25-27] SMAD2 and SMAD3 signaling exerts an inhibitory effect on red-cell maturation. Luspatercept is a recombinant fusion protein that binds select transforming growth factor β superfamily ligands to decrease SMAD2 and SMAD3 signaling, thereby enabling erythroid maturation by means of late-stage erythroblast differentiation.[28,29] In mouse models of myelodysplastic syndromes and β-thalassemia, luspatercept decreased SMAD2 and SMAD3 signaling, reduced erythroid hyperplasia, enhanced erythroid maturation, and increased hemoglobin levels.[27,28] Luspatercept consists of a modified extracellular domain of the human activin receptor type IIB linked to the human IgG1 Fc domain,[28] which eliminates activin A binding to minimize nonhematologic effects.

In a phase 2 study involving patients with lower-risk myelodysplastic syndromes, 63% of luspatercept-treated patients had an erythroid response (also called hematologic improvement–erythroid; defined according to the International Working Group [IWG] 2006 criteria[14] as a reduction in red-cell transfusions of ≥4 units per 8 weeks in patients with a baseline transfusion burden of ≥4 units per 8 weeks or as an increase in the hemoglobin level of ≥1.5 g per deciliter over a period of 8 weeks in patients with a baseline transfusion burden of <4 units per 8 weeks) and 38% had transfusion independence for 8 weeks or longer.[30] The overall erythroid response rate was higher among patients with ring sideroblasts (≥15% ring sideroblasts) than among patients with other subtypes of lower-risk myelodysplastic syndromes. MEDALIST was a phase 3 trial evaluating the safety and efficacy of luspatercept in patients with IPSS-R–defined lower-risk myelodysplastic syndromes with ring sideroblasts who had been receiving regular red-cell transfusions and had disease that was refractory to or unlikely to respond to erythropoiesis-stimulating agents or who had discontinued such agents owing to an adverse event.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this randomized, double-blind, placebo-controlled trial at 65 sites in 11 countries (see the Supplementary Appendix). Investigators conducted the trial according to institutional and CONSORT (Consolidated Standards of Reporting Trials) guidelines and in accordance with the laws of applicable authorities. Institutional review boards or ethics committees at each site approved the protocol. All the patients provided written informed consent. The primary sponsor (Celgene), the authors, and the investigators designed the trial in collaboration with the external steering committee; an independent data and safety monitoring board monitored the trial. Acceleron Pharma collaborates with Celgene in the development of luspatercept for the treatment of chronic anemia in patients with myelodysplastic syndromes. Acceleron Pharma provided guidance in the development of the trial design and assessment of data collection. Authors who are employees of Acceleron Pharma provided critical review and modifications to the manuscript, as well as approving the final version of the manuscript.

The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. Editorial and writing assistance was provided by a medical writer, funded by Celgene.

PATIENTS

Eligible patients were 18 years of age or older and had a myelodysplastic syndrome with ring sideroblasts according to World Health Organization criteria (i.e., with either ≥15% ring sideroblasts or ≥5% ring sideroblasts if an *SF3B1* mutation was present, and with <5% bone marrow blasts)[31,32]; had disease that was defined according to the IPSS-R as being of very low, low, or intermediate risk; had been receiving regular red-cell transfusions (≥2 units per 8 weeks during the 16 weeks before randomization); and had disease that was refractory to or was unlikely to respond to erythropoiesis-stimulating agents (owing to an endogenous erythropoietin level of >200 U per liter in those who had not previously been treated with erythropoiesis-stimulating agents) or had discontinued such agents owing to an adverse event. Additional eligibility and exclusion criteria are listed in the Supplementary Appendix.

TRIAL DESIGN

In the double-blind primary phase of the trial, patients were randomly assigned in a 2:1 ratio to receive luspatercept or placebo, administered subcutaneously every 3 weeks for 24 weeks; no crossover was allowed. The starting dose of luspatercept was 1.0 mg per kilogram of body weight. If a new transfusion was deemed to be necessary after the patient was considered to have transfusion independence, patients could continue receiving luspatercept, with adjustment to a dose of 1.33 mg per kilogram and then to 1.75 mg per kilogram (Table S1 in the Supplementary Appendix).

Disease assessment occurred at week 25. Patients without clinical benefit (as assessed by the investigators) discontinued receiving luspatercept or placebo and entered follow-up. Patients who had clinical benefit without disease progression (according to IWG 2006 criteria[14]) could enter the extension phase and continue receiving luspatercept or placebo (in a double-blind fashion) until they had unacceptable toxic effects or disease progression, withdrew consent, or met discontinuation criteria. (The trial design is shown in Fig. S1.)

END-POINT MEASURES

The primary end point was transfusion independence for 8 weeks or longer during weeks 1 through 24; this period of time (1 through 24 weeks) was chosen to reduce potential bias due to loss of patients receiving placebo without an early response. The key secondary end point was transfusion independence for 12 weeks or longer, assessed during both weeks 1 through 48 and weeks 1 through 24. Other secondary end points included erythroid response (also called hematologic response–erythroid; defined by the IWG 2006 criteria[14]), longest duration of primary response, mean increase in hemoglobin levels of at least 1.0 g per deciliter, progression to acute myeloid leukemia, mean change in the serum ferritin level, and safety analyses. Subgroup analyses were performed as exploratory end points. Transfusion independence for 16 weeks or longer (during weeks 1 through 24 and weeks 1 through 48) was also evaluated. Safety laboratory analyses and assessments were performed centrally, whenever possible. All the primary and secondary end points are listed in Table S2.

STATISTICAL ANALYSIS

The data-cutoff date was May 8, 2018. All the efficacy analyses were conducted in the intention-to-treat population. Patients who did not have transfusion independence for 8 weeks or longer by week 24 were considered not to have had a response with regard to the primary end point. The percentages of patients with a response regarding the primary and key secondary end points were compared with the use of a Cochran–Mantel–Haenszel test at a two-sided significance level of 0.05 and with randomization factors as strata: average baseline transfusion burden (≥6 units per 8 weeks vs. <6 units per 8 weeks) and baseline IPSS-R category (very low or low risk vs. intermediate risk). A sequential gatekeeping approach was used for the primary and key secondary end points, which were tested sequentially in the prespecified order (stated above). The duration of transfusion independence of 8 weeks or longer was estimated with the use of Kaplan–Meier analysis of the longest period of response at any dose. Safety analyses were conducted in the safety population (all the patients who received ≥1 dose of luspatercept or placebo). (Additional statistical methods are presented in the Supplementary Methods section in the Supplementary Appendix.)

RESULTS

BASELINE CHARACTERISTICS OF THE PATIENTS

Overall, 229 patients were enrolled (from March 2016 through June 2017); 153 patients were randomly assigned to receive luspatercept, and 76 to receive placebo. The baseline characteristics of the patients were well balanced between the groups (Table 1 and Table S3). The median age of the patients was 71 years (range, 26 to 95), and 63% of the patients were men. With regard to the IPSS-R categories, 10%, 72%, and 17% of the patients had a myelodysplastic syndrome defined as being of very low risk, low risk, and intermediate risk, respectively.

The baseline serum erythropoietin levels were less than 100 U per liter, 100 to less than 200 U per liter, 200 to 500 U per liter, and more than 500 U per liter in 36%, 24%, 25%, and 14% of the patients, respectively. The baseline transfusion burden was at least 6 units per 8 weeks in 43% of the patients and less than 6 units per 8 weeks in 57%; 29% had a baseline burden of less than 4 units per 8 weeks. *SF3B1* mutations were detected in 93% of the patients in the luspatercept group (138 of 148 patients) and in 86% of those in the placebo group (64 of 74) (assessed on the basis of mutation profiles from bone marrow mononuclear cells obtained at baseline). Somatic mutations were distributed similarly in the two groups (Fig. S2 and Table S4).

Overall, the median transfusion burden over an 8-week period during the 16 weeks before treatment was 5 units per 8 weeks (range, 1 to 20). A total of 95% of the patients had received erythropoiesis-stimulating agents previously, and 48% had received iron chelation therapy previously.

PRIMARY END POINT

During the first 24 weeks of the trial, 58 patients (38%) in the luspatercept group had transfusion independence for 8 weeks or longer, as compared with 10 (13%) in the placebo group ($P<0.001$) (Fig. 1). With regard to the primary end point, the majority (62% [36 of 58]) of patients in the luspatercept group who had a response had at least two response intervals of transfusion independence lasting 8 weeks or longer during treatment, whereas all the patients with a response in the placebo group had two or fewer response intervals (Table S5). Although most patients in the luspatercept group who had a response (90% [52 of 58]) had their first response at the starting dose (1.0 mg per kilogram), 7% had their first response after dose increases (2 patients each at the doses of 1.33 mg per kilogram and 1.75 mg per kilogram). Among these 58 patients, 15 (26%) had an initial response at the 1.0 mg per kilogram dose and 14 (24%) had subsequent response intervals at the same or higher doses (Table S6).

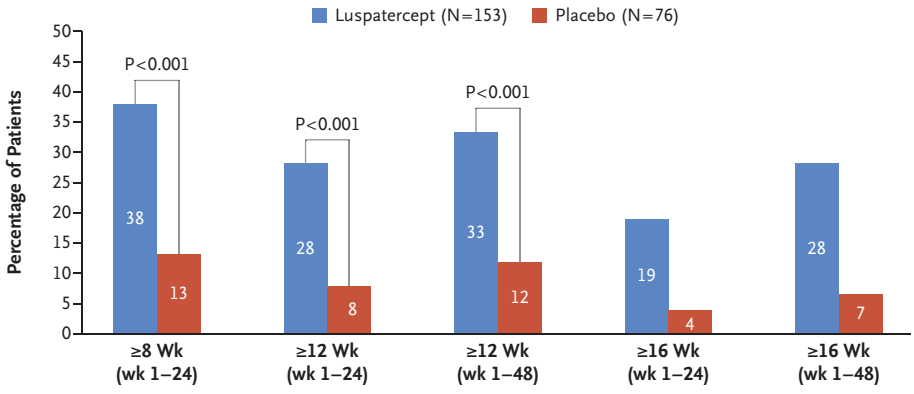
When evaluated according to the baseline transfusion burden, transfusion independence for 8 weeks or longer in the luspatercept group occurred in 80% of the patients (37 of 46) who had been receiving less than 4 units per 8 weeks, in 37% of those (15 of 41) who had been receiving 4 to less than 6 units per 8 weeks, and in 9% of those (6 of 66) who had been receiving at least 6 units per 8 weeks; the corresponding values in the placebo group were 40% (8 of 20 patients), 4% (1 of 23), and 3% (1 of 33). Among patients with a baseline serum erythropoietin level of 200 to 500 U per liter, 40% of patients in the luspatercept group had a response (Fig. S3).

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Luspatercept (N=153)	Placebo (N=76)	Total (N=229)
Median age (range) — yr	71 (40–95)	72 (26–91)	71 (26–95)
Male sex — no. (%)	94 (61)	50 (66)	144 (63)
Median time since original diagnosis of MDS (range) — mo	44.0 (3–421)	36.1 (4–193)	41.8 (3–421)
WHO classification of MDS — no. (%)†			
MDS with refractory anemia with ring sideroblasts	7 (5)	2 (3)	9 (4)
MDS with refractory cytopenia with multilineage dysplasia‡	145 (95)	74 (97)	219 (96)
IPSS-R risk category — no. (%)§			
Very low	18 (12)	6 (8)	24 (10)
Low	109 (71)	57 (75)	166 (72)
Intermediate	25 (16)	13 (17)	38 (17)
Median serum erythropoietin level (range) — U/liter¶	156.9 (12–2454)	130.8 (29–2760)	153.2 (12–2760)
Serum erythropoietin level category — no. (%)			
<100 U/liter	51 (33)	31 (41)	82 (36)
100 to <200 U/liter	37 (24)	19 (25)	56 (24)
200 to 500 U/liter	43 (28)	15 (20)	58 (25)
>500 U/liter	21 (14)	11 (14)	32 (14)
Missing data	1 (1)	0	1 (<1)
Mutated *SF3B1* — no./total no. (%)‖	138/148 (93)	64/74 (86)	202/222 (91)
Median red-cell transfusion burden (range) — no. of units/8 wk over period of 16 wk**	5 (1–15)	5 (2–20)	5 (1–20)
Red-cell transfusion-burden category — no. (%)			
≥6 units/8 wk	66 (43)	33 (43)	99 (43)
4 to <6 units/8 wk	41 (27)	23 (30)	64 (28)
<4 units/8 wk	46 (30)	20 (26)	66 (29)
Median pretransfusion hemoglobin level (range) — g/dl††	7.6 (6–10)	7.6 (5–9)	7.6 (5–10)
Received ESA previously — no. (%)	148 (97)	70 (92)	218 (95)
Disease refractory to ESA — no./total no. (%)	144/148 (97)	69/70 (99)	213/218 (98)
Discontinued previous ESA-containing regimen owing to an adverse event — no./total no. (%)	4/148 (3)	1/70 (1)	5/218 (2)
Previous iron chelation therapy — no. (%)	71 (46)	40 (53)	111 (48)
Median platelet count (range) — 10^{-9}/liter	235.0 (59–892)	222.5 (60–689)	234.0 (59–892)

* Percentages may not total 100 because of rounding. ESA denotes erythropoiesis-stimulating agent, IPSS-R Revised International Prognostic Scoring System, MDS myelodysplastic syndrome, and WHO World Health Organization.
† One patient in the luspatercept group had locally diagnosed MDS with ring sideroblasts with multilineage dysplasia.
‡ All the patients were classified as having refractory cytopenia with multilineage dysplasia with ring sideroblasts because they were required to have ring sideroblasts according to the inclusion criteria.
§ MDS in one patient (1%) in the luspatercept group was classified as IPSS-R high-risk. This case was a protocol violation, and the patient entered the trial in error.
¶ The baseline erythropoietin level was defined as the highest erythropoietin value within 35 days before the first dose.
‖ The analysis included only patients with available baseline gene mutation data.
** The analysis included data only within the 16 weeks before randomization.
†† The pretransfusion hemoglobin level was defined as the last value measured on or before the date and time of the first dose.

The percentages of patients with a response were similar regardless of *SF3B1* allelic burden (data not shown) and the total number of baseline somatic mutations. In the luspatercept group, transfusion independence for 8 weeks or longer was observed in 36%, 35%, 42%, and 33% of patients who had one baseline mutation, two mutations, three mutations, and four or five mutations, respectively (Fig. S4).



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Figure 1. Independence from Red-Cell Transfusion.

Shown are the percentages of patients who had independence from red-cell transfusion (defined as the absence of a red-cell transfusion) for the indicated time periods in each trial group. In the analysis of the primary end point (transfusion independence for ≥8 weeks during weeks 1 through 24), the odds ratio for luspatercept as compared with placebo was 5.07 (95% confidence interval [CI], 2.28 to 11.26). For the key secondary end point of transfusion independence for 12 weeks or longer, the odds ratio was 5.07 (95% CI, 2.00 to 12.84) for the analysis period of weeks 1 through 24 and 4.05 (95% CI, 1.83 to 8.96) for the analysis period of weeks 1 through 48. P values were determined with the use of a Cochran–Mantel–Haenszel test with stratification for average baseline red-cell transfusion burden (≥6 units per 8 weeks vs. <6 units per 8 weeks) and baseline Revised International Prognostic Scoring System score (very low or low risk vs. intermediate risk). An analysis that applied the new International Working Group 2018 response criteria[33] with transfusion independence for 16 weeks or longer was also conducted.

KEY SECONDARY END POINT AND ADDITIONAL SECONDARY END POINTS

During the first 24 weeks, 43 patients (28%) in the luspatercept group had transfusion independence for 12 weeks or longer, as compared with 6 (8%) in the placebo group, and the corresponding values during weeks 1 through 48 were 51 patients (33%) and 9 (12%) (P<0.001 for both comparisons) (Fig. 1). In addition, in the analysis that applied the new IWG 2018 response criteria,[33] a greater percentage of patients in the luspatercept group than in the placebo group had transfusion independence for 16 weeks or longer (19% vs. 4% during weeks 1 through 24, and 28% vs. 7% during weeks 1 through 48) (Fig. 1).

At the data cutoff, the median duration of the longest single period of transfusion independence (in patients who met the primary end point) was 30.6 weeks in the luspatercept group and 13.6 weeks in the placebo group (Table S7); 22 patients (14%) in the luspatercept group had the response (independence from red-cell transfusions for ≥8 weeks, with the criterion met during weeks 1 through 24) maintained at 1 year (data not shown). Overall, at the data cutoff, 46% of the patients were continuing to receive luspatercept and 8% were continuing to receive placebo (Table S8). Treatment exposure is discussed further in the Supplementary Appendix.

During weeks 1 through 24, an erythroid response occurred in 81 patients (53%) in the luspatercept group, as compared with 9 (12%) in the placebo group. During weeks 1 through 48, a total of 90 patients (59%) in the luspatercept group had an erythroid response, as compared with 13 (17%) in the placebo group (Table 2). No significant changes in neutrophil or platelet counts were observed during the double-blind period.

During weeks 1 through 24, a mean increase in the hemoglobin level of at least 1.0 g per deciliter occurred in 54 patients (35%) in the luspatercept group and in 6 (8%) in the placebo group; during weeks 1 through 48, the increases occurred in 63 patients (41%) and 8 patients (11%), respectively (Table 2). Over time, patients in the luspatercept group had greater mean hemoglobin levels than those in the placebo group (Fig. 2A). In the luspatercept group, increases in the hemo-

Table 2. Erythroid Response and Increase in Mean Hemoglobin Levels.

End Point	Luspatercept (N=153)	Placebo (N=76)
Erythroid response during wk 1–24*		
No. of patients (% [95% CI])	81 (53 [45–61])	9 (12 [6–21])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	52/107 (49)	8/56 (14)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	29/46 (63)	1/20 (5)
Erythroid response during wk 1–48*		
No. of patients (% [95% CI])	90 (59 [51–67])	13 (17 [9–27])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	58/107 (54)	12/56 (21)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	32/46 (70)	1/20 (5)
Mean increase in hemoglobin level of ≥1.0 g/dl — no. (% [95% CI])§		
During wk 1–24	54 (35 [28–43])	6 (8 [3–16])
During wk 1–48	63 (41 [33–49])	8 (11 [5–20])

* Analysis was based on the proportion of patients meeting the modified criteria for erythroid response (also called hematologic improvement–erythroid) according to International Working Group 2006 criteria[14] sustained over a consecutive 56-day period during the indicated treatment period: for patients with baseline red-cell transfusion burden of at least 4 units per 8 weeks, a transfusion reduction of at least 4 red-cell units per 8 weeks; and for patients with baseline red-cell transfusion burden of less than 4 units per 8 weeks, a mean increase of hemoglobin of at least 1.5 g per deciliter.
† Analysis was based on the number of patients with baseline red-cell transfusion burden of at least 4 units per 8 weeks.
‡ Analysis was based on the number of patients with baseline red-cell transfusion burden of less than 4 units per 8 weeks.
§ Analysis was based on the proportion of patients with an increase from baseline of at least 1 g per deciliter (>14 days after the last red-cell transfusion or within 3 days before the next red-cell transfusion) that was sustained over any consecutive 56-day period in the absence of red-cell transfusions.

globin level were greater over time among patients who had a response regarding transfusion independence than among those who did not have a response (Fig. 2B), regardless of baseline transfusion burden. Among patients in the luspatercept group who had a response, the median peak increase in the hemoglobin level was 2.55 g per deciliter (range, 1.0 to 4.1).

Patients in the luspatercept group had greater reductions from baseline than those in the placebo group in the mean serum ferritin level, averaged over weeks 9 through 24. The least-squares mean difference (luspatercept vs. placebo) was –229.1 μg per liter (Table S9).

SAFETY

The most frequently reported adverse events during the trial (of any grade and occurring in ≥10% of patients) with luspatercept or placebo were as follows: fatigue (in 27% and 13%, respectively), diarrhea (in 22% and 9%), asthenia (in 20% and 12%), nausea (in 20% and 8%), dizziness (in 20% and 5%), and back pain (in 19% and 7%) (Table 3). Overall, 65 patients (42%) receiving luspatercept and 34 (45%) receiving placebo had adverse events of grade 3 or 4 during the trial (Table S10; specific grade 3 or 4 adverse events are listed in Table S11). A total of 48 patients (31%) receiving luspatercept had at least one serious adverse event, as compared with 23 (30%) receiving placebo.

Seven patients (5%) receiving luspatercept and none of the patients in the placebo group had a dose reduction due to adverse events (Table S12). Overall, 13 patients (8%) receiving luspatercept and 6 (8%) receiving placebo discontinued the trial regimen because of adverse events. Adverse events leading to the discontinuation of luspatercept therapy included fatigue (in 1% of patients) and headache (in 1%) (data not shown). Adverse events occurring more frequently during cycles 1 through 4 of luspatercept treatment included fatigue, diarrhea, asthenia, and dizziness; the incidence declined thereafter and was not associated with dose adjustment (Table S13 and data not shown). Three patients receiving luspatercept had dose reductions per protocol owing to increases in the hemoglobin level of 2.0 g per deciliter or more (Table S14).

One patient in each group had progression to higher-risk myelodysplastic syndromes, and acute myeloid leukemia developed in 4 patients (3 pa-

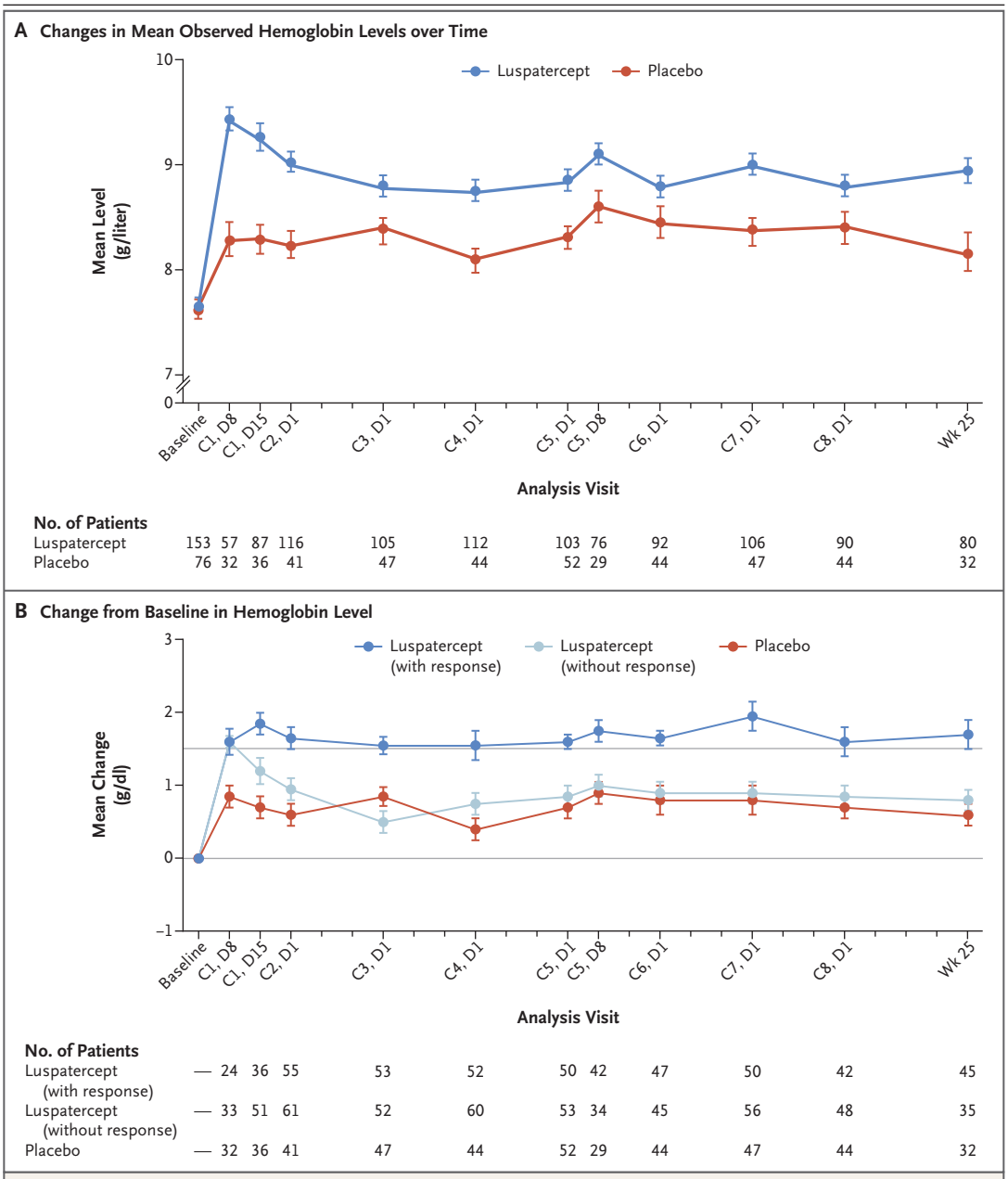


Figure 2. Changes in Mean Hemoglobin Levels over Time.

Panel A shows the mean observed hemoglobin values over time (baseline through week 25) for each trial group. The baseline value was defined as the lowest of the pretreatment or baseline values from the central or local laboratory or the lowest pretransfusion hemoglobin value from transfusion records that were within 35 days before the first dose of luspatercept or placebo. Panel B shows the mean change in hemoglobin level over time in patients in the luspatercept group who had a response with regard to the primary end point and in those in the luspatercept group who did not have a response, as compared with patients who received placebo (baseline through week 25). (At baseline, there were 153 patients in the overall luspatercept group and 76 in the placebo group.) The least-squares mean difference among patients in the luspatercept group who had a response, as compared with patients in the placebo group, was 1.08 (95% CI, 0.84 to 1.31). The median peak improvement in hemoglobin level in patients in the luspatercept group who had a response was 2.55 g per deciliter (range, 1.0 to 4.1). The mean values and standard errors were not calculated if the number of patients was less than 8 in the luspatercept group of patients without a response or if the number was less than 4 in the placebo group. Hemoglobin values that were obtained within 14 days after a red-cell transfusion were censored from these analyses unless they also were within 3 days before receipt of another red-cell transfusion. In both panels, I bars indicate the standard error. Analysis visits are shown according to cycle (C) and day (D).

Table 3. Adverse Events Occurring in at Least 10% of Patients.*

Event	Luspatercept (N=153)		Placebo (N=76)	
	Any Grade	Grade 3	Any Grade	Grade 3
	number of patients with event (percent)			
General disorder or administration-site condition				
Fatigue	41 (27)	7 (5)	10 (13)	2 (3)
Asthenia	31 (20)	4 (3)	9 (12)	0
Peripheral edema	25 (16)	0	13 (17)	1 (1)
Gastrointestinal disorder				
Diarrhea	34 (22)	0	7 (9)	0
Nausea†	31 (20)	1 (1)	6 (8)	0
Constipation	17 (11)	0	7 (9)	0
Nervous system disorder				
Dizziness	30 (20)	0	4 (5)	0
Headache	24 (16)	1 (1)	5 (7)	0
Musculoskeletal or connective-tissue disorder				
Back pain†	29 (19)	3 (2)	5 (7)	0
Arthralgia	8 (5)	1 (1)	9 (12)	2 (3)
Respiratory, thoracic, or mediastinal disorder				
Dyspnea†	23 (15)	1 (1)	5 (7)	0
Cough	27 (18)	0	10 (13)	0
Infection or infestation				
Bronchitis†	17 (11)	1 (1)	1 (1)	0
Urinary tract infection†	17 (11)	2 (1)	4 (5)	3 (4)
Injury, poisoning, or procedural complication: fall	15 (10)	7 (5)	9 (12)	2 (3)

* Adverse events during the trial were not adjusted for treatment exposure.
† At least one serious adverse event occurred: nausea (in one patient receiving luspatercept), back pain (in three receiving luspatercept), dyspnea (in one receiving luspatercept), bronchitis (in one receiving luspatercept), and urinary tract infection (in one receiving placebo).

tients [2%] receiving luspatercept and 1 [1%] receiving placebo). A total of 21 patients died during the trial: 12 patients (8%) in the luspatercept group and 9 (12%) in the placebo group (data not shown). Overall, 5 patients (3%) receiving luspatercept and 4 (5%) receiving placebo died owing to adverse events during the double-blind period or within 6 weeks thereafter; investigators judged the deaths to be unrelated to luspatercept or placebo.

DISCUSSION

In this phase 3 trial involving patients with lower-risk myelodysplastic syndromes with ring sideroblasts who had been receiving regular red-cell transfusions and had disease that was refractory to or unlikely to respond to erythropoiesis-stimulating agents or who had discontinued such agents owing to an adverse event, 38% of the patients in the luspatercept group met the primary end point of transfusion independence for 8 weeks or longer, as compared with 13% of those in the placebo group (P<0.001). The median duration of the longest single continuous period of response to luspatercept was 30.6 weeks. Among patients who had a baseline transfusion burden of 4 to less than 6 units per 8 weeks, 37% of those in the luspatercept group and 4% of those in the placebo group had a response. This finding was consistent with the results of the phase 2 study, which included patients without ring sideroblasts and in which 38% of the patients in the luspatercept group had a response.[30] Although the precise mechanism of action of luspatercept on SMAD2 and SMAD3 signaling remains incompletely understood,[34,35] the rapid onset of treatment effect, extended duration of transfusion

independence, erythroid response, and increased hemoglobin levels suggest that luspatercept had useful clinical effects in these patients.

Luspatercept was associated with mainly low-grade toxic effects that seldom led to the discontinuation of treatment. The incidence of adverse effects generally decreased over time among luspatercept-treated patients. Although the trial was underpowered for the systematic analysis of progression to acute myeloid leukemia, the incidence was low in both groups and consistent with the natural history of lower-risk myelodysplastic syndromes with ring sideroblasts; long-term follow-up is ongoing, and data from the phase 2 study showed no increased risk of progression to acute myeloid leukemia.[30]

The MEDALIST trial focused on patients with lower-risk myelodysplastic syndromes with ring sideroblasts because this is the largest subgroup of patients with myelodysplastic syndromes who have a low risk of progression to acute myeloid leukemia as well as prolonged survival, and therefore the treatment of anemia is particularly important in these patients. The COMMANDS trial (ClinicalTrials.gov number, NCT03682536) is evaluating the efficacy of luspatercept in other subgroups of patients with myelodysplastic syndromes.

Although there were potential differences in the criteria for response assessment between our trial and previous studies,[36-38] luspatercept resulted in a higher percentage of patients with a response or a better safety profile (or both) than were seen with previously evaluated treatments in patients with disease that was refractory or resistant to erythropoiesis-stimulating agents who had non-del(5q) transfusion-dependent lower-risk myelodysplastic syndromes. In a randomized, placebo-controlled trial of lenalidomide in such patients, transfusion independence for 8 weeks or longer was observed in 26.9% of lenalidomide-treated patients (vs. 2.5% of those receiving placebo); among patients with ring sideroblasts (70.3% of all patients), 30.6% of patients in the lenalidomide group had a response.[36] When our analysis was restricted to patients who had a response with regard to the primary end point and who had a similar red-cell transfusion burden as in the lenalidomide trial (≥4 units per 8 weeks), the percentage of patients with a response to luspatercept was similar to that with lenalidomide.[36] However, in contrast to the current trial, grade 3 or 4 neutropenia and thrombocytopenia were reported in 61.9% and 35.6% of the lenalidomide-treated patients, respectively.[36] In a randomized, phase 3 trial comparing lenalidomide with lenalidomide plus epoetin beta in patients with myelodysplastic syndromes that were resistant to erythropoiesis-stimulating agents and were defined as being of low or intermediate 1 risk (according to IPSS) with transfusion dependence, 61.8% of the patients had ring sideroblasts.[37] Overall, 13.8% of the patients in the lenalidomide group and 24.2% of those in the group that received lenalidomide plus epoetin beta had transfusion independence for 8 weeks or longer.[37] Moreover, in a phase 2 study evaluating azacitidine with or without erythropoietin in patients with erythropoiesis-stimulating agent–resistant, transfusion-dependent, lower-risk myelodysplastic syndromes, transfusion independence for 8 weeks or longer was observed in 14.3% of patients receiving azacitidine plus erythropoietin and in 16.3% of those receiving azacitidine; myelosuppression was also observed, a finding similar to other trials of azacitidine.[38,39]

Patients with lower-risk myelodysplastic syndromes with ring sideroblasts for whom erythropoiesis-stimulating agents are not effective or are not an option have limited treatment options available beyond continued transfusions. Luspatercept significantly reduced the transfusion burden in a substantial proportion of these patients and was associated with mainly low-grade toxic effects.

Supported by Celgene in collaboration with Acceleron Pharma.

Dr. Fenaux reports receiving consulting fees from Celgene; Dr. Platzbecker, receiving grant support, paid to GWT-TUD, from Amgen, lecture fees, grant support, paid to the University of Leipzig, fees for serving on a steering committee, consulting fees, and travel support from Celgene, grant support, paid to GWT-TUD, from Janssen Biotech, grant support, paid to University Dresden, from Merck and Novartis, and lecture fees from Novartis; Dr. Mufti, receiving grant support from Celgene and Cellectis; Dr. Garcia-Manero, receiving grant support from AbbVie, Amphivena Therapeutics, Astex Pharmaceuticals, Celgene, H3 Biomedicine, Helsinn Healthcare, Merck, Novartis, and Onconova Therapeutics; Dr. Buckstein, receiving grant support, paid to Sunnybrook Health Sciences Centre, from Celgene and Takeda Oncology and advisory board fees from Celgene; Dr. Santini, receiving fees for serving on an end-point review committee from Amgen, advisory board fees and lecture fees from Celgene, travel support from Janssen Biotech, and advisory board fees from Novartis and Takeda Oncology; Dr. Díez-Campelo, receiving consulting fees from Celgene and Novartis; Dr. Finelli, receiving grant support, paid to S. Orsola-Malpighi University Hospital, from Celgene and advisory board fees from Celgene, Janssen Pharmaceuticals, and Novartis; Dr. Ilhan, receiving grant support from Celgene; Dr. Sekeres, receiving consulting fees from Celgene, Pfizer, Syros Pharmaceuticals, and Takeda Oncology; Dr. Giai, receiving consulting fees from Novartis and fees for serving as an expert witness on treatment for acute myeloid leukemia from Celgene; Dr. Vyas, receiving grant support from Celgene; Dr. Bowen, receiving grant support, paid to Leeds Teaching Hospitals, from Celgene; Dr. Selleslag, receiving consulting

fees from Amgen, Celgene, Daiichi Sankyo, Janssen Pharmaceuticals, Novartis, and Pfizer; Dr. Jurcic, receiving grant support, paid to Columbia University, advisory board fees, and travel support from AbbVie, grant support, paid to Columbia University, from Actinium Pharmaceuticals, grant support, paid to Columbia University, and travel support from Arog Pharmaceuticals, grant support, paid to Columbia University, from Astellas Pharma, advisory board fees from AstraZeneca, grant support, paid to Columbia University, advisory board fees, and travel support from Celgene, grant support, paid to Columbia University, and consulting fees from Daiichi Sankyo, grant support, paid to Columbia University, from Forma Therapeutics, Genentech USA, Kura Oncology, PTC Therapeutics, Seattle Genetics, and Syros Pharmaceuticals, advisory board fees from Incyte and Novartis, and fees for serving on an end-point committee from Novartis; Dr. Germing, receiving consulting fees from Celgene and lecture fees from Novartis; Dr. Götze, receiving lecture fees from Celgene; Dr. Quesnel, receiving travel support from AbbVie, Amgen, Celgene, Daiichi Sankyo, and Teva Pharmaceutical Industries, grant support, paid to Centre Hospitalier Universitaire (CHU) de Lille, from Celgene, and grant support, paid to Service des Maladies du Sang, CHU Lille, from Celgene; Dr. Cluzeau, receiving consulting fees from Menarini International Foundation and Jazz Pharmaceuticals; Dr. Voso, receiving fees for serving on a speakers bureau from Celgene; Dr. Greenberg, receiving grant support, paid to Stanford University, from Celgene; Dr. Zeidan, receiving consulting fees and advisory board fees from Acceleron Pharma and Celgene; Dr. Adès, receiving grant support, paid to Groupe Francophone des Myelodysplasies, from Celgene; Dr. Verma, receiving advisory board fees from Acceleron Pharma, grant support from Bristol-Myers Squibb, Celgene, and Eli Lilly, and receiving consulting fees from and holding stock options in Stelexis; Dr. Savona, receiving fees for serving on a steering committee and fees for serving on a data and safety monitoring board from Celgene; Dr. Laadem, being employed by Celgene; Dr. Benzohra, being formerly employed by and formerly holding stock in Celgene; Ms. Zhang, being employed by and holding stock and stock options in Celgene; Ms. Rampersad, being employed by Celgene; Dr. Dunshee, being employed by and holding stock options in Celgene; Dr. Linde, being employed by Acceleron Pharma and holding stock in Abbott Laboratories, Acceleron Pharma, and FibroGen; Dr. Sherman, being employed by and receiving consulting fees from Acceleron Pharma and Deciphera Pharmaceuticals, receiving consulting fees from Fusion Pharma and Mersana Therapeutics, receiving fees for serving as a board member for NewLink Genetics, Pieris Pharmaceuticals, and Pulmatrix, and holding a patent (10,093,707) on antagonists of activin-ActRIIa and uses for increasing red-cell levels, licensed to Acceleron Pharma, holding a patent (7,988,973) on activin-ActRIIA antagonists and uses for increasing red-cell levels, licensed to Acceleron Pharma, holding a patent (8,895,016) on antagonists of activin-ActRIIA and uses for increasing red-cell levels, licensed to Acceleron Pharma, and holding a patent (8,007,809) on activin-ActRII antagonists and uses for increasing red-cell levels, licensed to Acceleron Pharma; Dr. Komrokji, receiving advisory board fees from Agios Pharmaceuticals, Daiichi Sankyo, Janssen Biotech, Jazz Pharmaceuticals, Novartis, and Pfizer, fees for serving on a speakers bureau from Alexion Pharmaceuticals, grant support, paid to the Moffitt Cancer Center, advisory board fees, and lecture fees from Celgene, and fees for serving on a speakers bureau from Jazz Pharmaceuticals and Novartis; and Dr. List, receiving fees for serving on a data and safety monitoring board from Celgene. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the patients and families who participated in the trial; the staff of Acceleron Pharma, including Kenneth M. Attie, Xiaosha Zhang, Carolyn J. Barron, Joseph G. Reynolds, John Oram, and Tad Akers; and Emily Poulin, of Excerpta Medica, for editorial and writing assistance with earlier versions of the manuscript (including the first draft), funded by Celgene.

APPENDIX

The authors' full names and academic degrees are as follows: Pierre Fenaux, M.D., Ph.D., Uwe Platzbecker, M.D., Ghulam J. Mufti, F.R.C.P., Guillermo Garcia-Manero, M.D., Rena Buckstein, M.D., Valeria Santini, M.D., María Díez-Campelo, M.D., Ph.D., Carlo Finelli, M.D., Mario Cazzola, M.D., Osman Ilhan, M.D., Mikkael A. Sekeres, M.D., José F. Falantes, M.D., Beatriz Arrizabalaga, M.D., Flavia Salvi, M.D., Valentina Giai, M.D., Ph.D., Paresh Vyas, B.Ch., B.M., David Bowen, M.D., Dominik Selleslag, M.D., Amy E. DeZern, M.D., Joseph G. Jurcic, M.D., Ulrich Germing, M.D., Katharina S. Götze, M.D., Bruno Quesnel, M.D., Ph.D., Odile Beyne-Rauzy, M.D., Thomas Cluzeau, M.D., Maria-Teresa Voso, M.D., Dominiek Mazure, M.D., Edo Vellenga, M.D., Ph.D., Peter L. Greenberg, M.D., Eva Hellström-Lindberg, M.D., Amer M. Zeidan, M.B., B.S., M.H.S., Lionel Adès, M.D., Amit Verma, M.D., Michael R. Savona, M.D., Abderrahmane Laadem, M.D., Aziz Benzohra, M.D., Jennie Zhang, M.S., Anita Rampersad, B.A., Diana R. Dunshee, Ph.D., Peter G. Linde, M.D., Matthew L. Sherman, M.D., Rami S. Komrokji, M.D., and Alan F. List, M.D.

The authors' affiliations are as follows: Service d'Hématologie Séniors, Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris and Université Paris 7, Paris (P.F., L.A.), Service des Maladies du Sang, Hôpital Huriez, Centre Hospitalier Universitaire (CHU) de Lille, Lille (B.Q.), the Department of Internal Medicine, CHU Toulouse, Institut Universitaire du Cancer de Toulouse, Toulouse (O.B.-R.), and Université Cote d'Azur, Département d'Hématologie Clinique, CHU Nice, Nice (T.C.) — all in France; Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, Leipzig University Hospital, Leipzig (U.P.), Klinik für Hämatologie, Onkologie, and Klinische Immunologie, Universitätsklinik Düsseldorf, Düsseldorf (U.G.), and Klinik und Poliklinik für Innere Medizin III, Technische Universität München, Munich (K.S.G.) — all in Germany; the Department of Haemato-Oncology, King's College London, London (G.J.M.), Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford (P.V.), and the Department of Haematology, Leeds Teaching Hospitals NHS Trust, Leeds (D.B.) — all in the United Kingdom; the Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston (G.G.-M.); Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto (R.B.); MDS Unit, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence (V.S.), the Department of Oncology and Hematology, S. Orsola-Malpighi University Hospital, Bologna (C.F.), the University of Pavia, Fondazione IRCCS Policlinico S. Matteo, Pavia (M.C.), the Hematology Unit, Santi Antonio e Biagio e Cesare Arrigo Hospital, Alessandria (F.S., V.G.), and Dipartimento Biomedicina e Prevenzione, University of Rome Tor Vergata, Rome (M.-T.V.) — all in Italy; the Hematology Department, University Hospital of Salamanca, Institute of Biomedical Research of Salamanca, Salamanca (M.D.-C.), Unidad de Hematología, Hospital Universitario Virgen del Rocío, Seville (J.F.F.), and the Department of Hematology, Hospital Universitario Cruces, Vizcaya (B.A.) — all in Spain; the Department of Hematology Science, School of Medicine, Ankara University, Ankara, Turkey (O.I.); the Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland (M.A.S.); the Department of Hematology, Algemeen Ziekenhuis Sint-Jan, Bruges (D.S.), and Universitair Ziekenhuis Gent, Ghent (D.M.) — both in Belgium; the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore (A.E.D.); the Division of Hematology–Oncology, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center (J.G.J.), and Albert Einstein College of Medicine (A.V.) — both in New York; the Department of Hematology, University Medical Center of Groningen, University of Groningen, Groningen, the Netherlands (E.V.); Stanford University Cancer Center, Stanford, CA (P.L.G.);

the Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institutet, Stockholm (E.H.-L.); the Department of Internal Medicine, Yale School of Medicine, Yale University, New Haven, CT (A.M.Z.); Vanderbilt University School of Medicine, Vanderbilt–Ingram Cancer Center, Nashville (M.R.S.); Celgene, Summit, NJ (A.L., J.Z., A.R., D.R.D.); Celgene International, Boudry, Switzerland (A.B.); Acceleron Pharma, Cambridge, MA (P.G.L., M.L.S.); and Moffitt Cancer Center, Tampa, FL (R.S.K., A.F.L.).

REFERENCES

1. Adès L, Itzykson R, Fenaux P. Myelodysplastic syndromes. Lancet 2014;383:2239-52.
2. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-88.
3. Oliva EN, Schey C, Hutchings AS. A review of anemia as a cardiovascular risk factor in patients with myelodysplastic syndromes. Am J Blood Res 2011;1:160-6.
4. Stauder R, Valent P, Theurl I. Anemia at older age: etiologies, clinical implications, and management. Blood 2018;131:505-14.
5. Fenaux P, Adès L. How we treat lower-risk myelodysplastic syndromes. Blood 2013;121:4280-6.
6. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. Blood 2012;120:2454-65.
7. Hiwase DK, Kutyna MM, Chhetri R, et al. Transfusion dependency is associated with inferior survival even in very low and low risk IPSS-R patients. Blood 2013;122:1518.
8. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol 2005;23:7594-603.
9. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol 2007;25:3503-10.
10. Malcovati L. Red blood cell transfusion therapy and iron chelation in patients with myelodysplastic syndromes. Clin Lymphoma Myeloma 2009;9:Suppl 3:S305-S311.
11. Malcovati L, Hellström-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood 2013;122:2943-64.
12. Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. Haematologica 2006;91:1588-90.
13. Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood 2000;96:3671-4.
14. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-25.
15. Tehranchi R, Fadeel B, Forsblom AM, et al. Granulocyte colony-stimulating factor inhibits spontaneous cytochrome C release and mitochondria-dependent apoptosis of myelodysplastic syndrome hematopoietic progenitors. Blood 2003;101:1080-6.
16. Tehranchi R, Invernizzi R, Grandien A, et al. Aberrant mitochondrial iron distribution and maturation arrest characterize early erythroid precursors in low-risk myelodysplastic syndromes. Blood 2005;106:247-53.
17. Hellström-Lindberg E. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. Br J Haematol 1995;89:67-71.
18. Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood 2008;111:574-82.
19. Kelaidi C, Park S, Sapena R, et al. Long-term outcome of anemic lower-risk myelodysplastic syndromes without 5q deletion refractory to or relapsing after erythropoiesis-stimulating agents. Leukemia 2013;27:1283-90.
20. Fenaux P, Santini V, Spiriti MAA, et al. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS. Leukemia 2018;32:2648-58.
21. Platzbecker U. Treatment of MDS. Blood 2019;133:1096-107.
22. Park S, Hamel JF, Toma A, et al. Outcome of lower-risk patients with myelodysplastic syndromes without 5q deletion after failure of erythropoiesis-stimulating agents. J Clin Oncol 2017;35:1591-7.
23. Talati C, Sallman D, List A. Lenalidomide: myelodysplastic syndromes with del(5q) and beyond. Semin Hematol 2017;54:159-66.
24. Santini V, Schemenau J, Levis A, et al. Can the revised IPSS predict response to erythropoietic-stimulating agents in patients with classical IPSS low or intermediate-1 MDS? Blood 2013;122:2286-8.
25. Zhou L, Nguyen AN, Sohal D, et al. Inhibition of the TGF-beta receptor I kinase promotes hematopoiesis in MDS. Blood 2008;112:3434-43.
26. Bataller A, Montalban-Bravo G, Soltysiak KA, Garcia-Manero G. The role of TGFβ in hematopoiesis and myeloid disorders. Leukemia 2019;33:1076-89.
27. Suragani RN, Cawley SM, Li R, et al. Modified activin receptor IIB ligand trap mitigates ineffective erythropoiesis and disease complications in murine β-thalassemia. Blood 2014;123:3864-72.
28. Suragani RN, Cadena SM, Cawley SM, et al. Transforming growth factor-β superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. Nat Med 2014;20:408-14.
29. Fenaux P, Kiladjian JJ, Platzbecker U. Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis. Blood 2019;133:790-4.
30. Platzbecker U, Germing U, Götze KS, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol 2017;18:1338-47.
31. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114:937-51.
32. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-405.
33. Platzbecker U, Fenaux P, Adès L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood 2019;133:1020-30.
34. Guerra A, Oikonomidou PR, Sinha S, et al. Lack of *Gdf11* does not improve anemia or prevent the activity of RAP-536 in a mouse model of β-thalassemia. Blood 2019;134:568-72.
35. Camaschella C. GDF11 is not the target of luspatercept. Blood 2019;134:500-1.
36. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol 2016;34:2988-96.
37. Toma A, Kosmider O, Chevret S, et al. Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion. Leukemia 2016;30:897-905.
38. Thépot S, Ben Abdelali R, Chevret S, et al. A randomized phase II trial of azacitidine +/- epoetin-β in lower-risk myelodysplastic syndromes resistant to erythropoietic stimulating agents. Haematologica 2016;101:918-25.
39. Tobiasson M, Dybedahl I, Holm MS, et al. Limited clinical efficacy of azacitidine in transfusion-dependent, growth factor-resistant, low- and Int-1-risk MDS: results from the nordic NMDSG08A phase II trial. Blood Cancer J 2014;4(3):e189.