TO THE EDITOR:

Longer-term benefit of luspatercept in transfusion-dependent lower-risk myelodysplastic syndromes with ring sideroblasts

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Patients with myelodysplastic syndromes (MDS) often develop anemia,[1] which is associated with fatigue, reduced quality of life, and increased hospitalization and mortality.[2-5] Anemia is often managed with red blood cell (RBC) transfusions[1]; ~50% of patients with lower-risk MDS (LR-MDS) require RBC transfusions within 2 years of diagnosis.[6] Chronic RBC transfusions are associated with decreased quality of life,[5,7,8] increased risk of iron overload, and reduced survival[9,10] and come with significant health system costs and strain to the limited space in clinic and infusion areas, which intensified during the coronavirus disease 2019 pandemic.[11,12]

Based on the phase 3, double-blind, MEDALIST study (NCT02631070), luspatercept was approved in the United States and Europe for the treatment of anemia after failure of an erythropoiesis-stimulating agent (ESA; or in patients who are unlikely to respond to ESAs), when ≥2 RBC units are required over 8 weeks in adult patients with revised International Prognostic Scoring System (IPSS-R) very low- to intermediate-risk MDS with ring-sideroblasts (RS), or with MDS/myeloproliferative neoplasm with RS and thrombocytosis.[13,14] Here, we report longer-term results from the MEDALIST trial with double the follow-up time of the primary analysis.[14]
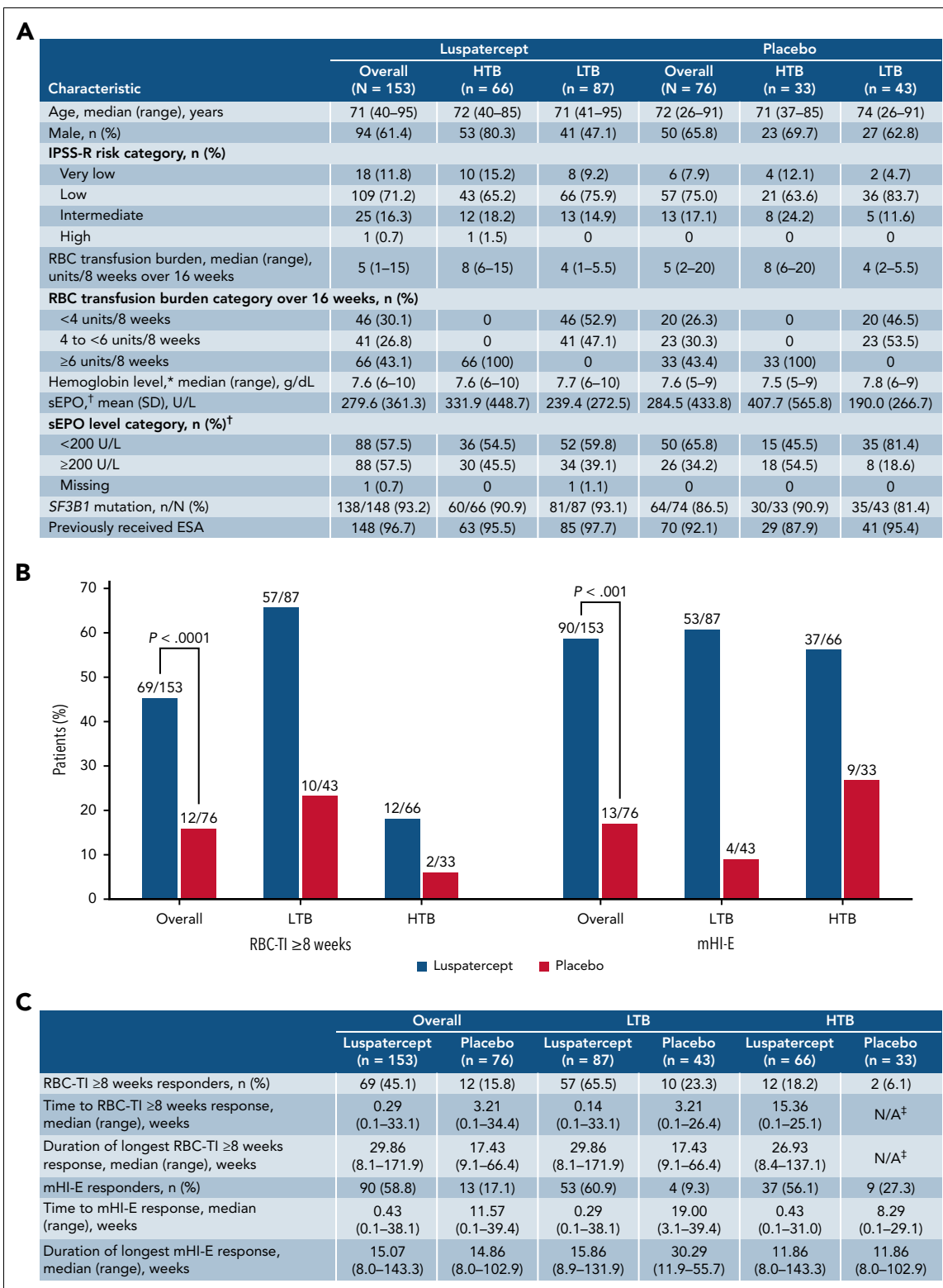
Eligible patients (≥18 years) had anemia owing to LR-MDS-RS (defined as IPSS-R very low, low, or intermediate risk[15,16]); received regular RBC transfusions (≥2 units per 8 weeks during the 16 weeks before randomization); were refractory to, intolerant of, or unlikely to respond to (ie, serum erythropoietin >200 U/L) ESAs; and had not received disease-modifying agents (supplemental Figure 1, available on the *Blood* website). In the primary analysis, baseline transfusion burden was categorized as receiving <4 RBC units per 8 weeks, 4 to <6 RBC units per 8 weeks, or ≥6 RBC units per 8 weeks[14]; therefore, in the current

post hoc analysis, patients receiving ≥6 RBC units within 8 weeks prior to randomization were classified as having high transfusion burden (HTB), whereas those receiving 2 to <6 RBC units were classified as having low transfusion burden (LTB).
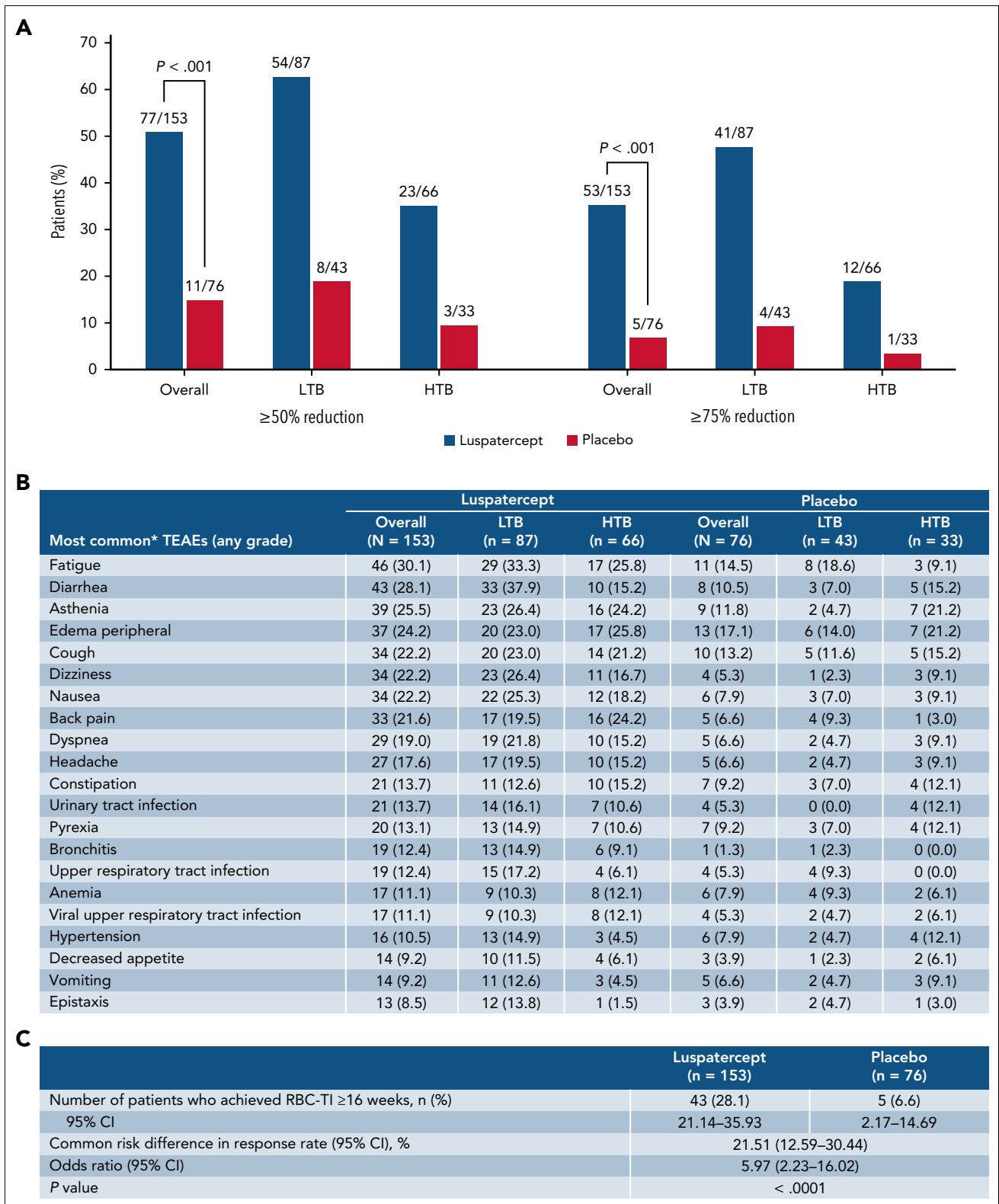
Figure 1A shows baseline characteristics of the 229 randomized patients (luspatercept, N = 153; placebo, N = 76). As of July 1, 2019, 41 patients (26.8%) were still receiving luspatercept after >2 years, with some still on treatment after 3 years, but all patients receiving placebo had discontinued treatment. Median follow-up times for the current analysis were 26.4 and 26.1 months for lusp-atercept and placebo, respectively, compared with 13.9 months and 14.3 months for the primary analysis.

Approximately 3 times as many patients receiving luspatercept vs placebo achieved RBC-transfusion independence (RBC-TI) for ≥8 weeks during weeks 1 to 48 (69/153 [45.1%] vs 12/76 [15.8%]; $P < .0001$; Figure 1B). Forty-six of 73 patients who achieved RBC-TI ≥8 weeks at any time during the entire treatment period were TI at 1 year (supplemental Figure 1). Furthermore, during weeks 1 to 48, RBC-TI ≥16 weeks was achieved by 43/153 (28.1%) and 5/76 (6.6%) patients in the luspatercept and placebo arms, respectively ($P < .0001$; Figure 2C).

During the primary analysis, 37.9% of patients receiving luspatercept achieved RBC-TI for ≥8 weeks during weeks 1 to 24 vs 13.2% for placebo ($P < .001$).[14] The increase from 37.9% to 45.1% among patients receiving luspatercept suggests additional patients would achieve RBC-TI beyond the primary 24-week follow-up period. A similar effect was observed among patients with HTB (12/66 [18.2%] vs 2/33 [6.1%]) and LTB (57/87 [65.5%] vs 10/43 [23.3%]) (Figure 1B). Lower rates of achievement of RBC-TI ≥8 weeks by HTB patients vs LTB patients reflect the difficulty for patients with HTB LR-MDS to achieve TI with any therapy.

A

Characteristic	Luspatercept Overall (N = 153)	HTB (n = 66)	LTB (n = 87)	Placebo Overall (N = 76)	HTB (n = 33)	LTB (n = 43)
Age, median (range), years	71 (40–95)	72 (40–85)	71 (41–95)	72 (26–91)	71 (37–85)	74 (26–91)
Male, n (%)	94 (61.4)	53 (80.3)	41 (47.1)	50 (65.8)	23 (69.7)	27 (62.8)
IPSS-R risk category, n (%)						
Very low	18 (11.8)	10 (15.2)	8 (9.2)	6 (7.9)	4 (12.1)	2 (4.7)
Low	109 (71.2)	43 (65.2)	66 (75.9)	57 (75.0)	21 (63.6)	36 (83.7)
Intermediate	25 (16.3)	12 (18.2)	13 (14.9)	13 (17.1)	8 (24.2)	5 (11.6)
High	1 (0.7)	1 (1.5)	0	0	0	0
RBC transfusion burden, median (range), units/8 weeks over 16 weeks	5 (1–15)	8 (6–15)	4 (1–5.5)	5 (2–20)	8 (6–20)	4 (2–5.5)
RBC transfusion burden category over 16 weeks, n (%)						
<4 units/8 weeks	46 (30.1)	0	46 (52.9)	20 (26.3)	0	20 (46.5)
4 to <6 units/8 weeks	41 (26.8)	0	41 (47.1)	23 (30.3)	0	23 (53.5)
≥6 units/8 weeks	66 (43.1)	66 (100)	0	33 (43.4)	33 (100)	0
Hemoglobin level,* median (range), g/dL	7.6 (6–10)	7.6 (6–10)	7.7 (6–10)	7.6 (5–9)	7.5 (5–9)	7.8 (6–9)
sEPO,† mean (SD), U/L	279.6 (361.3)	331.9 (448.7)	239.4 (272.5)	284.5 (433.8)	407.7 (565.8)	190.0 (266.7)
sEPO level category, n (%)†						
<200 U/L	88 (57.5)	36 (54.5)	52 (59.8)	50 (65.8)	15 (45.5)	35 (81.4)
≥200 U/L	88 (57.5)	30 (45.5)	34 (39.1)	26 (34.2)	18 (54.5)	8 (18.6)
Missing	1 (0.7)	0	1 (1.1)	0	0	0
SF3B1 mutation, n/N (%)	138/148 (93.2)	60/66 (90.9)	81/87 (93.1)	64/74 (86.5)	30/33 (90.9)	35/43 (81.4)
Previously received ESA	148 (96.7)	63 (95.5)	85 (97.7)	70 (92.1)	29 (87.9)	41 (95.4)

B

C

	Overall Luspatercept (n = 153)	Placebo (n = 76)	LTB Luspatercept (n = 87)	Placebo (n = 43)	HTB Luspatercept (n = 66)	Placebo (n = 33)
RBC-TI ≥8 weeks responders, n (%)	69 (45.1)	12 (15.8)	57 (65.5)	10 (23.3)	12 (18.2)	2 (6.1)
Time to RBC-TI ≥8 weeks response, median (range), weeks	0.29 (0.1–33.1)	3.21 (0.1–34.4)	0.14 (0.1–33.1)	3.21 (0.1–26.4)	15.36 (0.1–25.1)	N/A‡
Duration of longest RBC-TI ≥8 weeks response, median (range), weeks	29.86 (8.1–171.9)	17.43 (9.1–66.4)	29.86 (8.1–171.9)	17.43 (9.1–66.4)	26.93 (8.4–137.1)	N/A‡
mHI-E responders, n (%)	90 (58.8)	13 (17.1)	53 (60.9)	4 (9.3)	37 (56.1)	9 (27.3)
Time to mHI-E response, median (range), weeks	0.43 (0.1–38.1)	11.57 (0.1–39.4)	0.29 (0.1–38.1)	19.00 (3.1–39.4)	0.43 (0.1–31.0)	8.29 (0.1–29.1)
Duration of longest mHI-E response, median (range), weeks	15.07 (8.0–143.3)	14.86 (8.0–102.9)	15.86 (8.9–131.9)	30.29 (11.9–55.7)	11.86 (8.0–143.3)	11.86 (8.0–102.9)

Figure 1. Patient baseline characteristics, RBC-TI ≥8 weeks and mHI-E response. Baseline characteristics of patients in the MEDALIST trial by transfusion burden (A). Rates of RBC-TI for ≥8 weeks and mHI-E response during weeks 1 to 48, overall and by transfusion burden (B). Time to first response and duration of RBC-TI ≥8 weeks and mHI-E response (C). mHI-E response was defined according to IWG 2006 criteria[17] as a mean hemoglobin increase ≥1.5 g/dL among patients with a baseline RBC transfusion burden <4 units per 8 weeks or a reduction of ≥4 RBC units among patients with baseline RBC transfusion burden ≥4 units per 8 weeks, sustained over a consecutive 56-day period. *Last value measured on or before the date and time of the first dose of luspatercept per placebo. †Highest value within 35 days before the first dose of luspatercept per placebo. ‡Only 2 patients with HTB who received placebo achieved RBC-TI; therefore, a median duration could not be reliably estimated. IWG, International Working Group; mHI-E, modified hematologic improvement-erythroid; SD, standard deviation; sEPO, serum erythropoietin; SF3B1, splicing factor 3b subunit 1.

A

Patients (%)

≥50% reduction
- Overall: 77/153, 11/76
- LTB: 54/87, 8/43
- HTB: 23/66, 3/33
- Overall *P* < .001

≥75% reduction
- Overall: 53/153, 5/76
- LTB: 41/87, 4/43
- HTB: 12/66, 1/33
- Overall *P* < .001

■ Luspatercept ■ Placebo

B

Most common* TEAEs (any grade)	Luspatercept Overall (N = 153)	Luspatercept LTB (n = 87)	Luspatercept HTB (n = 66)	Placebo Overall (N = 76)	Placebo LTB (n = 43)	Placebo HTB (n = 33)
Fatigue	46 (30.1)	29 (33.3)	17 (25.8)	11 (14.5)	8 (18.6)	3 (9.1)
Diarrhea	43 (28.1)	33 (37.9)	10 (15.2)	8 (10.5)	3 (7.0)	5 (15.2)
Asthenia	39 (25.5)	23 (26.4)	16 (24.2)	9 (11.8)	2 (4.7)	7 (21.2)
Edema peripheral	37 (24.2)	20 (23.0)	17 (25.8)	13 (17.1)	6 (14.0)	7 (21.2)
Cough	34 (22.2)	20 (23.0)	14 (21.2)	10 (13.2)	5 (11.6)	5 (15.2)
Dizziness	34 (22.2)	23 (26.4)	11 (16.7)	4 (5.3)	1 (2.3)	3 (9.1)
Nausea	34 (22.2)	22 (25.3)	12 (18.2)	6 (7.9)	3 (7.0)	3 (9.1)
Back pain	33 (21.6)	17 (19.5)	16 (24.2)	5 (6.6)	4 (9.3)	1 (3.0)
Dyspnea	29 (19.0)	19 (21.8)	10 (15.2)	5 (6.6)	2 (4.7)	3 (9.1)
Headache	27 (17.6)	17 (19.5)	10 (15.2)	5 (6.6)	2 (4.7)	3 (9.1)
Constipation	21 (13.7)	11 (12.6)	10 (15.2)	7 (9.2)	3 (7.0)	4 (12.1)
Urinary tract infection	21 (13.7)	14 (16.1)	7 (10.6)	4 (5.3)	0 (0.0)	4 (12.1)
Pyrexia	20 (13.1)	13 (14.9)	7 (10.6)	7 (9.2)	3 (7.0)	4 (12.1)
Bronchitis	19 (12.4)	13 (14.9)	6 (9.1)	1 (1.3)	1 (2.3)	0 (0.0)
Upper respiratory tract infection	19 (12.4)	15 (17.2)	4 (6.1)	4 (5.3)	4 (9.3)	0 (0.0)
Anemia	17 (11.1)	9 (10.3)	8 (12.1)	6 (7.9)	4 (9.3)	2 (6.1)
Viral upper respiratory tract infection	17 (11.1)	9 (10.3)	8 (12.1)	4 (5.3)	2 (4.7)	2 (6.1)
Hypertension	16 (10.5)	13 (14.9)	3 (4.5)	6 (7.9)	2 (4.7)	4 (12.1)
Decreased appetite	14 (9.2)	10 (11.5)	4 (6.1)	3 (3.9)	1 (2.3)	2 (6.1)
Vomiting	14 (9.2)	11 (12.6)	3 (4.5)	5 (6.6)	2 (4.7)	3 (9.1)
Epistaxis	13 (8.5)	12 (13.8)	1 (1.5)	3 (3.9)	2 (4.7)	1 (3.0)

C

	Luspatercept (n = 153)	Placebo (n = 76)
Number of patients who achieved RBC-TI ≥16 weeks, n (%)	43 (28.1)	5 (6.6)
95% CI	21.14–35.93	2.17–14.69
Common risk difference in response rate (95% CI), %	21.51 (12.59–30.44)	
Odds ratio (95% CI)	5.97 (2.23–16.02)	
P value	< .0001	

Figure 2. Transfusion burden reduction, TEAEs, and RBC-TI ≥16 weeks. Rates of ≥50% and ≥75% reduction in RBC transfusion burden from baseline over ≥24 weeks during the entire treatment phase, overall, and by transfusion burden (A). Summary of TEAEs during the entire treatment period (B). Rates of RBC-TI ≥16 weeks during weeks 1 to 48. Data are n (%). Transfusion events and TEAEs are reported during weeks 1 to 48. *Those occurring in ≥10% in any group. CI, confidence interval; TEAE, treatment emergent.

From weeks 1 to 48, the median (range) hemoglobin levels in HTB patients during the longest period of RBC-TI ≥8 weeks receiving luspatercept and placebo were 98.9 g/dL (85.8-107.5) and 95.3 g/dL (94.8-95.9), respectively, and in LTB patients, they were 92.6 g/dL (74.2-113.4) and 89.8 g/dL (82.9-96.8), respectively.

Overall, the median (range) duration of RBC-TI ≥8 weeks response was 29.9 weeks (8.1-171.9) for patients receiving luspatercept and 17.4 weeks (9.1-66.4) for placebo. The median duration of RBC-TI for the 12/66 (18.2%) HTB patients receiving luspatercept who achieved RBC-TI ≥8 weeks was 26.9 weeks (range, 8.4-137.1). Given only 2/33 (6.1%) HTB patients receiving placebo achieved RBC-TI ≥8 weeks, a median duration of response could not be reliably estimated. For LTB patients, median (range) duration of RBC-TI was 29.9 weeks (8.1-171.9) and 17.4 weeks (9.1-66.4) for patients receiving luspatercept and placebo, respectively (Figure 1C).

Overall, during weeks 1 to 48, 31/153 (20.3%) patients receiving luspatercept achieved >1 period of RBC-TI ≥8 weeks response, including 29/87 (33.3%) LTB and 2/66 (3.0%) HTB patients, compared with 3/76 (3.9%) patients receiving placebo, whom were LTB patients.

During weeks 1 to 48, significantly more patients receiving luspatercept achieved a modified hematologic improvement-erythroid (mHI-E) response (per IWG 2006 criteria[17]) vs placebo (58.8% [95% confidence interval (CI), 50.6-66.7] vs 17.1% [95% CI, 9.4-27.5]; $P < .001$). Rates of mHI-E achievement increased from 52.9% of patients during weeks 1 to 24 in the primary analysis[14] to 58.8% in the current analysis. Rates of mHI-E response were comparable for luspatercept between HTB patients and LTB patients, 56.1% (95% CI, 43.3-68.3) and 60.9% (95% CI, 49.9-71.2), respectively (Figure 1C), as was time to mHI-E (HTB 0.43 weeks vs LTB 0.29 weeks), while duration of mHI-E was slightly longer in LTB patients (HTB 11.9 weeks vs LTB 15.9 weeks).

During the entire treatment phase, a significantly greater proportion of patients receiving luspatercept vs placebo achieved ≥75% reduction in RBC transfusion burden over ≥24 weeks, both overall (34.6% vs 6.6%; $P < .001$) and among patients with HTB (18.2% vs 3.0%) and LTB (47.1% vs 9.3%) (Figure 2A). The clinical benefit of luspatercept to HTB patients is further supported by these data, indicating that focusing exclusively on TI as an outcome can prevent recognition of significant benefits of many therapies, including luspatercept.

Overall, more patients receiving luspatercept reported a serious adverse event of any grade during weeks 1 to 48 vs placebo (46.4% vs 32.0%, respectively), which was higher than the rates for the luspatercept arm in the primary analysis (31% vs 30% for luspatercept vs placebo).[14] Rates were comparable between LTB and HTB patients within the luspatercept arm (47.1% vs 45.5%, respectively). The most common treatment-emergent adverse events (TEAEs) of any grade with luspatercept were fatigue (30.1%) and diarrhea (28.1%) (Figure 2B). Among luspatercept HTB patients, the most common TEAEs were fatigue (25.8%) and peripheral edema (25.8%), whereas among LTB patients, they were diarrhea (37.9%) and fatigue

(33.3%) (Figure 2B). Additional efficacy and safety data are presented in the supplemental material.

One limitation, common to long-term follow-up reports of any randomized trial in which clinical outcomes are improved in the intervention arm, is the higher rate of double-blind treatment discontinuation owing to lower efficacy in the control arm. As time progresses, this causes increasing imbalance and may introduce confounders and bias in interpretation of differences in results between the arms. Despite this limitation, more than a quarter of patients randomized to luspatercept remained on treatment for >2 years, supporting its long-term benefit.

In conclusion, luspatercept had a generally acceptable and predictable safety profile while affording sustained periods of TI and effectively reducing transfusion burden among HTB and LTB patients, contributing to maintaining or improving patient quality of life.[18] These data further support the sustained clinical benefits of luspatercept in patients with LR-MDS-RS compared with outcomes from the primary analysis.[14]

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Authorship

Contribution: A.M.Z., U.P., G.G.-M., M.A.S., P.F., A.E.D., P.L.G., M.R.S., J.G.J., A.K.V., G.J.M., R.B., V.S., and R.S.K. enrolled patients to the study, and collected and interpreted data; J.Z., G.Z., and X.H. analyzed and interpreted data; J.K.S., R.I., and J.T.B. interpreted data; and all authors contributed to drafting the manuscript and provided final approval to submit the manuscript.

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Footnotes

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