clinical trial updates

Long-Term Efficacy and Safety of Luspatercept for Anemia Treatment in Patients With Lower-Risk Myelodysplastic Syndromes: The Phase II PACE-MDS Study

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abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

Luspatercept has high clinical activity in patients with transfusion-dependent lower-risk myelodysplastic syndromes (LR-MDS) and ring sideroblasts (RS) relapsed or refractory to erythropoietin. We report long-term luspatercept safety and efficacy in 108 patients with LR-MDS in the PACE-MDS study, including 44 non-RS and 34 non–transfusion-dependent or previously untreated patients. The primary end point was safety. Secondary end points included rates of hematologic improvement (HI) erythroid (HI-E), HI neutrophil, and HI platelet. Exploratory end points included erythropoiesis biomarker quantitation and mutation data. Median duration of luspatercept exposure was 315 days (range, 21-1,934 days). No new safety signals emerged. HI-E was observed in 53.7% of patients, including 36.4% of non-RS and 70.6% of non–transfusion-dependent patients. HI neutrophil and HI platelet were observed in 33.3% and 9.5% of patients, respectively. An almost three-fold increase in bone marrow late to early progenitor cell ratio accompanied HI-E response, irrespective of RS status. Lower baseline erythropoietin levels in non-RS patients (69.6 *v* 623.3 IU/L; $P = .0077$) and higher late to early erythroid progenitor cell ratio (10.44 *v* 4.48; $P = .0106$) in RS patients were associated with HI-E. This study highlights luspatercept's effects across LR-MDS subtypes, including untreated MDS-RS, serving as a platform for future trials.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are characterized by ineffective erythropoiesis[1,2]; reducing transfusion burden (TB) and anemia are major treatment aims in lower-risk (LR) MDS.[3]

Luspatercept (ACE-536), a first-in-class erythroid-maturation agent, binds transforming growth factor-β superfamily ligands, diminishing Smad2/3 signaling and enhancing late-stage erythropoiesis.[4-6] The phase II, multicenter, PACE-MDS (ClinicalTrials.gov identifiers: NCT01749514/NCT02268383) study enrolled patients with LR-MDS irrespective of ring sideroblasts (RS), TB, or prior erythropoiesis-stimulating agent (ESA) exposure. International Working Group 2006–defined hematologic improvement (HI) erythroid (HI-E) response was observed in 32/51 (63%) of luspatercept-treated patients; RBC transfusion-independence (RBC-TI) ≥ 8 weeks was observed in 16/42 (38%) transfusion-dependent (TD) patients.[7] Luspatercept is approved for LR-MDS-RS treatment on the basis of the phase III trial (MEDALIST; ClinicalTrials.gov identifier: NCT02631070).[8-10] However, 70%-80% of patients with MDS are non-RS, representing an unmet need, particularly after ESA failure.[11-15]

PATIENTS AND METHODS

The PACE-MDS study evaluated luspatercept for anemia in patients with LR-MDS, including non-RS and non-TD (NTD) patients, up to 5 years. We report long-term luspatercept safety and efficacy data in patients with LR-MDS from PACE-MDS across subtypes, including the largest non-RS group to date. PACE-MDS was approved by each institution's institutional review board and was conducted according to

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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the Declaration of Helsinki. All patients provided written informed consent.

RESULTS AND DISCUSSION

Table 1 shows baseline characteristics for the evaluable cohort. Rates of related treatment-emergent adverse events for RS and non-RS patients were 30/62 (48.4%) and 16/44 (36.4%), respectively ($P = .11$). The most common related treatment-emergent adverse events in RS patients were fatigue (9.7%), hypertension and diarrhea (6.5% each); headache (11.4%), and hypertension and bone pain (6.8% each) in non-RS patients (Data Supplement, online only). One RS patient progressed to acute myeloid leukemia. This confirms the overall safety of luspatercept exposure $\geq$ 2 years.

Although the study sample size was small, and thus the study underpowered for many of the following comparisons, novel trends emerge that require confirmation. RBC-TI $\geq$ 8 weeks was observed in 22/42 (52.4%) RS patients, 10/29 (34.5%) non-RS patients ($P = .139$), and by 32/73 (43.8%) TD patients. RBC-TI $\geq$ 8 weeks was also observed in 20/28 (71.4%) low TB (LTB) and 12/45 (26.7%) high TB (HTB) patients ($P < .001$); 15/32 (46.9%) and 16/31 (51.6%) patients with wild-type *SF3B1* and *SF3B1* mutations ($P = .710$), respectively; and 10/13 (76.9%) with non-*SF3B1* splicing factor mutations ($P = .026$) and 5/19 (23.6%) with no splicing factor mutations ($P = .018$; Table 2).

International Working Group HI-E,[16] was observed in 58/108 (53.7%) patients including 42/62 (67.7%) RS patients, 16/44 (36.4%) non-RS patients ($P = .002$), 24/34 (70.6%) NTD patients, and 17/19 (89.5%) RS NTD patients. Overall, HI-E was observed in 10/29 (34.5%) LTB and 24/45 (53.3%) HTB patients ($P = .115$; Table 2), and 7/15 (46.7%) non-RS NTD, 3/13 (23.1%) non-RS LTB, and 6/16 (37.5%) non-RS HTB patients (Data Supplement). HI-E was observed in 35/47 (74.5%) patients with *SF3B1* mutations versus 19/49 (38.8%) with wild-type *SF3B1* ($P < .001$), and 6/18 (33.3%) with non-*SF3B1* splicing factor mutations versus 13/31 (41.9%) with no splicing factor mutations ($P = .031$; Table 2). A further analysis of splicing factor mutations and HI-E response across LR-MDS subtypes is provided in the Data Supplement.

HI-E was associated with a significantly increased bone marrow (BM) late to early progenitor cell ratio (baseline to end of treatment [EOT]) overall (mean increase in responders *v* nonresponders, 2.91 [range, −7.00 to 50.00] *v* −0.39 [range, −29.36 to 6.44]; $P = .006$) and in non-RS patients (responders *v* nonresponders: 1.99 [range, −2.09 to 8.12] *v* −0.32 [range, −29.36 to 6.44]; $P = .029$). Median erythropoietin (EPO) level increase from baseline to EOT was lower in HI-E responders than in nonresponders overall (27.7 IU/L [range, −169.4 to 1,121.0] *v* 278.5 IU/L [range, −132.9 to 62,140.6]; $P = .002$) and in non-RS patients (43.7 IU/L [range, −130.6 to 131.9] *v* 1,700.0 IU/L [range, −59.8 to 62,140.6]; $P = .010$; Table 3). RBC-TI was associated with lower increase in EPO level versus nonresponders (26.7 IU/L [range, −132.9 to 1,700.0] *v* 229.4 IU/L [range, −59.8 to 62,140.6]; $P = .038$; Data Supplement).

HI neutrophil (HI-N) was observed in 8/24 (33.3%) patients overall, including 4/16 (25.0%) non-RS, 6/13 (46.2%) HTB, 4/5 (80.0%) patients with *SF3B1* mutations versus 6/14 (42.9%) with wild-type *SF3B1* ($P = .224$); and 1/3 (33.3%) with non-*SF3B1* splicing factor mutations versus 5/11 (45.5%) with wild-type copies of any splicing factor gene ($P = .894$). HI platelet (HI-P) was observed in 2/21 (9.5%) patients overall, 1/5 (20.0%) patients with *SF3B1* mutations versus 4/12 (33.3%) with wild-type *SF3B1* ($P = .509$), and 2/4 (50.0%) with non-*SF3B1* splicing factor mutations versus 2/8 (25.0%) with wild-type copies of any splicing factor gene ($P = .418$; Table 2).

Clinically meaningful responses were observed irrespective of RS or *SF3B1*-mutation status, baseline TB, or EPO levels. The 90% response rate in NTD or untreated patients (Data Supplement) with MDS-RS is higher than reported for ESAs (erythroid response: ESA-naive, 45%-73%; prior ESA, 25%-75%).[17] Luspatercept promotes erythroid progenitor differentiation into late-stage erythroid precursors or normoblasts in the BM, whereas ESAs promote early erythroid progenitor proliferation and survival, suggesting possible benefit in combination with or after ESA failure.

Preclinical data suggest a synergistic effect of luspatercept with EPO.[5] We observed increased EPO levels irrespective of RS status (Data Supplement), which, together with late-stage maturation changes, are suggestive of the egress of late-stage progenitors into peripheral blood with compensatory early progenitor cell production demand in BM triggered by supraphysiologic EPO levels. Serum EPO levels increased irrespective of HI-E response. Indirect interference of EPO signaling by luspatercept is also possible.[18]

RBC-TI $\geq$ 8 weeks was observed in over one quarter of non-RS patients and HI-E in one third, including almost half of the NTD non-RS patients, an outcome being explored in the phase III COMMANDS trial (ClinicalTrials.gov identifier: NCT03682536).

Low rates of HI-P were observed; however, HI-N was observed in one third of patients, including one quarter of non-RS patients. Although a small number of patients were evaluated for HI-N and HI-P, this suggests the potential expansion of trilineage activity of luspatercept to non-RS patients,[19] and modulation of the functional capacities of stromal cells as mediating the improvement of inefficient hematopoiesis in MDS.[20] Notably, patient numbers with pre-existing severe thrombocytopenia or neutropenia were low. HI-E response was associated with lower baseline EPO levels in non-RS but not RS patients, further highlighting

TABLE 1. Patient Demographics and Disease Characteristics

Characteristic	Total (N = 108)	RS (n = 62)	Non-RS (n = 44)	NTD (n = 34)	LTB (n = 29)	HTB (n = 45)
Median age, years (range)	72.5 (29-90)	72.0 (29-86)	74.0 (52-90)	72.0 (30-86)	74.0 (52-90)	71.0 (29-84)
Sex, No. (%)						
Female	36 (33.3)	22 (35.5)	14 (31.8)	13 (38.2)	11 (37.9)	12 (26.7)
Male	72 (66.7)	40 (64.5)	30 (68.2)	21 (61.8)	18 (62.1)	33 (73.3)
Median time since original diagnosis of MDS, months (range)	1.62 (0.04-13.62)	2.34 (0.08-13.62)	1.07 (0.04-10.05)	1.01 (0.04-10.78)	1.82 (0.14-10.05)	2.24 (0.08-13.62)
Median baseline transfusion amount for patients with ≥ 2 RBC units transfusion at baseline, RBC units/8 weeks (range)[a]	4.0 (2.0-18.0)	4.0 (2.0-18.0)	4.0 (2.0-8.0)	NA	2.0 (2.0-3.0)	6.0 (4.0-18.0)
Baseline transfusion status, No. (%)						
NTD[b]	34 (31.5)	19 (30.6)	15 (34.1)	34 (100)	0	0
LTB[c]	29 (26.9)	15 (24.2)	13 (29.5)	0	29 (100)	0
HTB[d]	45 (41.7)	27 (43.5)	16 (36.4)	0	0	45 (100)
Median baseline Hb, g/dL (range)	NA	NA	NA	8.6 (6.7-10.1)	8.7 (6.2-10.1)	NA
Median baseline platelet count, × 10^9/L (range)	179.5 (32.0-1,471.0)	247.0 (42.0-1,471.0)	139.5 (32.0-418.0)	204.5 (48.0-558.0)	174.0 (54.0-1,471.0)	179.0 (32.0-612.0)
Median baseline EPO, IU/L (range)	163.1 (0.3-2,433.0)	132.3 (9.8-2,032.0)	286.1 (0.3-1,960.0)	128.9 (22.3-976.0)	186.8 (27.1-1,960.0)	269 (0.3-2,433.0)
Baseline EPO category, No. (%)						
< 100	39 (36.1)	26 (41.9)	13 (29.5)	14 (41.2)	11 (37.9)	14 (31.1)
100 to < 200	19 (17.6)	13 (21.0)	6 (13.6)	9 (26.5)	4 (13.8)	6 (13.3)
200 to < 500	26 (24.1)	15 (24.2)	11 (25.0)	8 (23.5)	6 (20.7)	12 (26.7)
≥ 500	24 (22.2)	8 (12.9)	14 (31.8)	3 (8.8)	8 (27.6)	13 (28.9)
Median baseline SF, μg/L (range)	1,100.0 (42.4-4,438.0)	1,227.0 (83.9-4,438.0)	753.0 (42.4-4,152.0)	562.8 (125.3-2,532.0)	940.9 (42.4-2,508.0)	1,610.0 (83.9-4,438.0)
Baseline SF category, No. (%)						
< 300 ng/mL	12 (11.1)	1 (1.6)	11 (25.0)	7 (20.6)	4 (13.8)	1 (2.2)
300-1,000 ng/mL	41 (38.0)	24 (38.7)	17 (38.6)	18 (52.9)	12 (41.4)	11 (24.4)
> 1,000 ng/mL	55 (50.9)	37 (59.7)	16 (36.4)	9 (26.5)	13 (44.8)	33 (73.3)
RS status, No. (%)						
Positive	62 (57.4)	62 (100)	0	19 (55.9)	16 (55.2)	27 (60.0)
Negative	44 (40.7)	0	44 (100)	15 (44.1)	13 (44.8)	16 (35.6)
Gene mutations, No. (%)						
SF3B1	47 (43.5)	46 (74.2)	1 (2.3)	15 (44.1)	10 (34.5)	22 (48.9)
SRSF2	12 (11.1)	4 (6.5)	8 (18.1)	3 (8.8)	6 (20.7)	3 (6.7)
U2AF1	4 (3.7)	1 (1.6)	3 (6.8)	1 (2.9)	2 (6.9)	1 (2.2)
ZRSR2	5 (4.6)	0	5 (11.4)	3 (8.8)	0	2 (4.4)

(continued on following page)

TABLE 1. Patient Demographics and Disease Characteristics (continued)

Characteristic	Total (N = 108)	RS (n = 62)	Non-RS (n = 44)	NTD (n = 34)	LTB (n = 29)	HTB (n = 45)
WHO subtypes,[e] No. (%)						
EB-1	12 (11.1)	6 (9.7)	5 (11.4)	2 (5.9)	0	10 (22.2)
MDS-RS	18 (16.7)	18 (29.0)	0	10 (29.4)	2 (6.9)	6 (13.3)
MDS-MLD	24 (22.2)	1 (1.6)	23 (52.3)	7 (20.6)	9 (31.0)	8 (17.8)
MDS-RS-MLD	36 (33.3)	36 (58.1)	0	9 (26.5)	13 (44.8)	14 (31.1)
Other	17 (15.7)	1 (1.6)	15 (34.1)	6 (17.6)	5 (17.2)	6 (13.3)
Missing	1 (0.9)	0	1 (2.3)	0	0	1 (2.2)
IPSS classification, No. (%)						
Low	42 (38.9)	34 (54.8)	8 (18.2)	19 (55.9)	10 (34.5)	13 (28.9)
Intermediate-1	63 (58.3)	28 (45.2)	34 (77.3)	14 (41.2)	18 (62.1)	31 (68.9)
Intermediate-2	3 (2.8)	0	2 (4.5)	1 (2.9)	1 (3.4)	1 (2.2)
IPSS-R risk category, No. (%)						
Very low	5 (4.6)	1 (1.6)	4 (9.1)	0	4 (13.8)	1 (2.2)
Low	59 (54.6)	43 (69.4)	16 (36.4)	25 (73.5)	20 (69.0)	14 (31.1)
Intermediate	34 (31.5)	17 (27.4)	16 (36.4)	6 (17.6)	4 (13.8)	24 (53.3)
High	9 (8.3)	1 (1.6)	8 (18.2)	3 (8.8)	1 (3.4)	5 (11.1)
Very high	1 (0.9)	0	0	0	0	1 (2.2)
Previous therapy, No. (%)						
Lenalidomide	8 (7.4)	7 (11.3)	1 (2.3)	1 (2.9)	1 (3.4)	6 (13.3)
Iron chelation therapy[f]	32 (29.6)	23 (37.1)	8 (18.2)	1 (2.9)	5 (17.2)	26 (57.8)
ESA	48 (44.4)	32 (51.6)	16 (36.4)	10 (29.4)	11 (37.9)	27 (60.0)

Abbreviations: C1D1, cycle 1 day 1; EB-1, excess blasts; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; LTB, low transfusion burden; MDS, myelodysplastic syndromes; MDS-MLD, MDS with multilineage dysplasia; MDS-RS, MDS with ring sideroblasts; MDS-RS-MLD, MDS with MLD with RS; NA, not applicable; NTD, non–transfusion-dependent; RCMD-RS, refractory cytopenia with multilineage dysplasia with RS; RS, ring sideroblasts; SF, serum ferritin.

[a]Total amount of RBC transfusions over the 8 weeks before C1D1.

[b]NTD patients are defined as those who did not receive RBC transfusions within 8 weeks before C1D1.

[c]LTB patients are defined as those who received < 4 RBC units within 8 weeks before C1D1.

[d]HTB patients are defined as those who required ≥ 4 RBC units within 8 weeks before C1D1 ($-55 \leq$ day ≤ 1).

[e]If a patient is categorized as having RCMD-RS and another subtype, and has $\geq 15\%$ RS, then RCMD-RS is used.

[f]Iron chelation therapy used within the window of -84 days to C1D1 or after C1D1.

TABLE 2. RBC-TI, HI-E, HI-P, and HI-N Response Rates Overall and by RS Status, Mutation Status, and Baseline Transfusion Burden

Patient Group	RBC-TI ≥ 8 Weeks[a]	HI-E[b]	HI-P[c]	HI-N[d]
All patients, No./total No. (%) [95% CI]	32/73 (43.8) [32.2 to 56.0]	58/108 (53.7) [43.8 to 63.3]	2/21 (9.5) [1.2 to 30.4]	8/24 (33.3) [15.6 to 55.3]
RS status, No./total No. (%) [95% CI]				
RS	22/42 (52.4) [36.4 to 68.0]	42/62 (67.7) [54.7 to 79.1]	1/7 (14.3) [0.4 to 57.9]	4/7 (57.1) [18.4 to 90.1]
Non-RS	10/29 (34.5) [17.9 to 54.3]	16/44 (36.4) [22.4 to 52.2]	1/13 (7.7) [0.2 to 36.0]	4/16 (25.0) [7.3 to 52.4]
Mutation status, No./total No. (%) [95% CI]				
SF3B1 mutation	16/31 (51.6) [33.1 to 69.8]	35/47 (74.5) [59.7 to 86.1]	1/5 (20.0) [0.5 to 71.6]	4/5 (80.0) [28.4 to 99.5]
SF3B1 wild-type	15/32 (46.9) [29.1 to 65.3]	19/49 (38.8) [25.2 to 53.8]	4/12 (33.3) [9.9 to 65.1]	6/14 (42.9) [17.7 to 71.7]
Non-*SF3B1* splicing factor mutation	10/13 (76.9) [46.2 to 95.0]	6/18 (33.3) [13.3 to 59.0]	2/4 (50.0) [6.8 to 93.2]	1/3 (33.3) [0.8 to 90.6]
Any splicing factor mutation	26/44 (59.1) [43.2 to 73.7]	41/65 (63.1) [50.2 to 74.7]	3/9 (33.3) [7.5 to 70.1]	5/8 (62.5) [24.5 to 91.5]
Any splicing factor wild-type	5/19 (26.3) [9.1 to 51.2]	13/31 (41.9) [24.5 to 60.9]	2/8 (25.0) [3.2 to 65.1]	5/11 (45.5) [16.7 to 76.7]
Transfusion burden, No./total No. (%) [95% CI]				
NTD (0 RBC units/8 weeks)	NA	24/34 (70.6) [52.5 to 84.9]	1/4 (25.0) [0.6 to 80.6]	1/6 (16.7) [0.4 to 64.1]
LTB (< 4 RBC units/8 weeks)	20/28 (71.4) [51.3 to 86.8]	10/29 (34.5) [17.9 to 54.3]	0 [0 to 52.2]	1/5 (20.0) [0.5 to 71.6]
HTB (≥ 4 RBC units/8 weeks)	12/45 (26.7) [14.6 to 41.9]	24/45 (53.3) [37.9 to 68.3]	1/12 (8.3) [0.2 to 38.5]	6/13 (46.2) [19.2 to 74.9]

Abbreviations: HI-E, hematologic improvement erythroid; HI-N, HI neutrophil; HI-P, HI platelet; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; NA, not applicable; NTD, non–transfusion-dependent; RBC-TI, RBC transfusion independence; RS, ring sideroblasts.

[a]Patients with a baseline transfusion burden of ≥ 2 RBC units/8 weeks were included in the RBC-TI-evaluable population.

[b]IWG HI-E is defined as the proportion of patients for whom all hemoglobin values increased by ≥ 1.5 g/dL from baseline during any rolling 8-week period in the absence of transfusion for NTD and LTB patients, or a reduction of ≥ 4 RBC units over any rolling 8-week period for HTB patients.

[c]For patients with a baseline value ≥ 20×10^9/L, response is defined as the mean platelet increase in any rolling 8 weeks ≥ 30×10^9. For patients with a baseline value < 20×10^9/L, response is defined as the mean platelet increase in any rolling 8 weeks > 20×10^9/L, with a mean increase of at least 100%.

[d]Response is defined as the mean of neutrophil increase in any rolling 8 weeks of at least 100% and an absolute mean increase > 0.5×10^9/L.

TABLE 3. Change in Erythropoiesis Biomarkers From Baseline to EOT for IWG HI-E Responders Versus Nonresponders for All Patients and by RS Status

	Median Change From Baseline to EOT (Range)								
	Overall (N = 51)			RS (n = 32)			Non-RS (n = 19)		
Parameter	Responder (n = 31)	Nonresponder (n = 20)	*P*	Responder (n = 23)	Nonresponder (n = 9)	*P*	Responder (n = 8)	Nonresponder (n = 11)	*P*
BM erythroid progenitor cells,[a,b,c] %	5 (−23 to 35)	0 (−37 to 29)	.267	5 (−23 to 35)	5 (−8 to 26)	.933	13.5 (−6 to 33)	−2 (−37 to 29)	.083
Late to early progenitor cell ratio[a,c]	2.91 (−7.00 to 50.00)	−0.39 (−29.36 to 6.44)	.006	4.02 (−6.99 to 50.00)	−0.45 (−3.36 to 3.56)	.072	1.99 (−2.09 to 8.12)	−0.32 (−29.36 to 6.44)	.029
Myeloid to erythroid ratio[a]	−0.16 (−10.06 to 0.91)	−0.23 (−6 to 26.19)	.412	−0.12 (−1.21 to 0.91)	−0.26 (−1.87 to 0.28)	.586	−1.25 (−10.06 to 0.18)	0.11 (−6.00 to 26.19)	.107
EPO, IU/L	27.7 (−169.4 to 1,121.0)	278.5 (−132.9 to 62,140.6)	.002	12 (−169.4 to 1,121.0)	146.9 (−132.9 to 545.3)	.249	43.7 (−130.6 to 131.9)	1,700.0 (−59.8 to 62,140.6)	.010
sTfR1, nM	18.4 (−21.2 to 111.9)	12.8 (−7.5 to 52)	.458	18.3 (−21.2 to 111.9)	15.35 (2.9-52)	.946	19.6 (−14.9 to 45.3)	5.8 (−7.5 to 40.6)	.525
Absolute reticulocytes, No.	14.42 (−57 to 89)	−13 (13.92 to 38.4)	.454	9 (−29.28 to 62.00)	10.34 (−13.92 to 38.40)	.855	35.42 (−57.00 to 89.00)	13 (−9.24 to 38.37)	.138

Abbreviations: BM, bone marrow; EOT, end of treatment; EPO, erythropoietin; HI-E, hematologic improvement erythroid; IWG, International Working Group; RS, ring sideroblasts; sTfR1, soluble transferrin receptor 1.

[a]Baseline values come from screening visit only in the base study.

[b]BM erythroid progenitor cells as a percentage of nucleated cells.

[c]Measured by flow cytometry.

the differences between these populations. All patients achieving long-term HI-E, including non-RS patients, had significant changes from baseline to EOT in late-stage erythropoiesis measures, consistent with the putative mechanism of luspatercept in MDS. Late-stage progenitor maturation arrest, their expansion, and missing egress from BM are observed, possibly mediated by negative regulators of erythropoiesis, eg, transforming growth factor-β superfamily ligands. Accordingly, higher responses were observed in patients with a higher late to early erythroid cell ratio. Responders displayed higher late to early erythroid cell baseline ratio, which increased with treatment, suggesting that the terminal differentiation block was not alleviated completely with luspatercept response. However, late-stage progenitor cell accumulation is consistent with accelerated differentiation and maturation process of dysplastic erythroid progenitors, suggesting that the mechanism of luspatercept in LR-MDS is RS status-independent.

In conclusion, luspatercept demonstrated long-term clinical efficacy and safety comparable with previous reports,[7] in patients with LR-MDS irrespective of subtype, particularly in untreated patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Efficacy and Safety of Luspatercept for Anemia Treatment in Patients With Lower-Risk Myelodysplastic Syndromes: The Phase II PACE-MDS Study

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