Longer-term red blood cell transfusion reduction in the phase 3 MEDALIST study of luspatercept in patients with lower-risk myelodysplastic syndromes with ring sideroblasts

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Rami S. Komrokji,[1] Mikkael A. Sekeres,[2] Amer M. Zeidan,[3] Pierre Fenaux,[4] Uwe Platzbecker,[5] Amy E. DeZern,[6] Peter L. Greenberg,[7] Michael R. Savona,[8] Joseph G. Jurcic,[9] Amit Verma,[10] Ghulam J. Mufti,[11] Rena Buckstein,[12] Valeria Santini,[13] Abderrahmane Laadem,[14] Rodrigo Ito,[14] Jennie Zhang,[14] Chrystal U. Louis,[14] Peter G. Linde,[15] Guillermo Garcia-Manero[16]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; [3]Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; [4]Service d'Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France; [5]Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany; [6]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [7]Stanford University Cancer Center, Stanford, CA, USA; [8]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA; [9]Division of Hematology/Oncology, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, USA; [10]Department of Oncology, Albert Einstein College of Medicine, Montefiore Medical Center, New York, NY, USA; [11]Department of Haemato-Oncology, King's College London, London, UK; [12]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [13]MDS Unit, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]Acceleron Pharma, Cambridge, MA, USA; [16]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Introduction

- Lower-risk myelodysplastic syndromes (LR MDS) are characterized by ineffective erythropoiesis, leading to anemia, red blood cell (RBC) transfusion dependence, and reduced quality of life[1,2]
- There is a need for effective treatments for anemia in transfusion-dependent patients with LR MDS[1,2]
- Luspatercept is a first-in-class erythroid maturation agent that binds to select transforming growth factor-β superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis[3]
  - Luspatercept is indicated for the treatment of anemia in adult patients with LR MDS with ring sideroblasts (RS) who require regular RBC transfusions
- MEDALIST is an ongoing phase 3, randomized, double-blind, placebo-controlled trial (NCT02631070) evaluating the efficacy and safety of luspatercept in patients with LR MDS with RS who require RBC transfusions[4]

Objective

- To evaluate long-term transfusion burden reduction in patients treated with luspatercept in the MEDALIST trial

Methods

Study design

- Patients were randomized at 65 sites between March 2016 and June 2017
- Eligible patients were aged ≥ 18 years and had anemia due to Revised International Prognostic Scoring System-defined Very low-, Low-, or Intermediate-risk MDS with RS; were refractory to, intolerant of, or unlikely to respond to (serum erythropoietin > 200 U/L) erythropoiesis-stimulating agents; and required RBC transfusions
- Patients were randomized 2:1 to receive luspatercept (starting dose 1.0 mg/kg, with titration allowed up to 1.75 mg/kg) or placebo subcutaneously every 21 days for ≥ 24 weeks (**Figure 1**)
- Patients receiving placebo were not allowed to cross over to the luspatercept arm

Endpoints

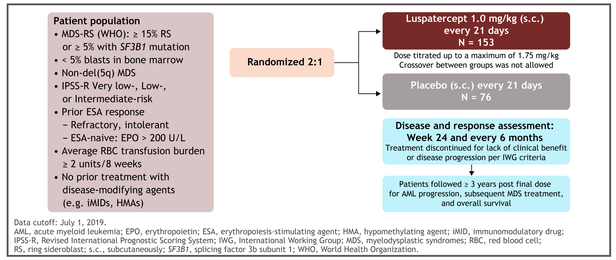
Study endpoints

- Primary endpoint: RBC transfusion independence (RBC-TI) ≥ 8 weeks (Weeks 1–24)
- Key secondary endpoint: RBC-TI ≥ 12 weeks (Weeks 1–24 and Weeks 1–48)

Additional endpoints

- Reduction in RBC units transfused from baseline
- Achievement of modified hematologic improvement-erythroid (HI-E) (per International Working Group [IWG] 2006 criteria[5])
  - Defined as a reduction of ≥ 4 units RBCs from baseline, sustained for ≥ 8 weeks (for patients with baseline RBC transfusion burden of ≥ 4 units/8 weeks) or a mean hemoglobin increase of ≥ 1.5 g/dL from baseline, sustained for ≥ 8 weeks (for patients with baseline RBC transfusion burden of < 4 units/8 weeks)
- Longest duration of primary response
- Change from baseline in number of transfusion visits
- Change in iron parameters

Figure 1. MEDALIST trial study design



Data cutoff: July 1, 2019.
AML, acute myeloid leukemia; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; iMID, immunomodulatory drug; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; MDS, myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblast; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

Results

Patients

- 229 patients were randomized; 153 to receive luspatercept and 76 to receive placebo (**Table 1**)
- As of data cutoff (July 1, 2019), the median follow-up time in the luspatercept and placebo arms was 26.4 and 26.1 months, respectively
- The median (range) transfusion burden at baseline was 5 (1-15) and 5 (2-20) RBC units over 8 weeks in the luspatercept and placebo arms, respectively
- The mean (standard deviation) transfusion burden at baseline was 5.5 (2.76) and 5.8 (2.95) RBC units over 8 weeks in the luspatercept and placebo arms

Table 1. Baseline characteristics

Characteristic	Luspatercept (N = 153)	Placebo (N = 76)
Age, median (range), years	71 (40-95)	72 (26-91)
Male, n (%)	94 (61.4)	50 (65.8)
RBC transfusion burden category, n (%)[a]		
≥ 6 units/8 weeks	66 (43.1)	33 (43.4)
≥ 4 to < 6 units/8 weeks	41 (26.8)	23 (30.3)
< 4 units/8 weeks	46 (30.1)	20 (26.3)
IPSS-R, n (%)[b]		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75.0)
Intermediate	25 (16.3)	13 (17.1)
SF3B1 mutation, n (%)[c]	138 (93.2)[c]	64 (86.5)[c]
Serum EPO, n (%)[d]		
< 200 U/L	88 (57.5)	50 (65.8)
≥ 200 U/L	64 (41.8)	26 (34.2)
Previously received ESAs, n (%)	148 (96.7)	70 (92.1)
Baseline Hb, median (range), g/dL[e]	7.6 (6-10)	7.6 (5-9)
Serum ferritin, mean (SD), μg/L	1,348.0 (971.2)	1,503.8 (1,242.9)

[a]In the 16 weeks prior to randomization. [b]1 patient in the luspatercept arm was classified as IPSS-R High risk. [c]Of patients with available baseline gene mutation data: n = 148 in the luspatercept arm; and n = 74 in the placebo arm; no patients with *SF3B1* mutation had RS <15%. [d]Data were missing for 1 patient in the luspatercept arm. [e]Baseline Hb was defined as the last value measured on or before the date and time of first dose. EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IPSS-R, Revised International Prognostic Scoring System; RBC, red blood cell; RS, ring sideroblast; SD, standard deviation; *SF3B1*, splicing factor 3b subunit 1.

Long-term transfusion burden reduction

- The primary endpoint (RBC-TI ≥ 8 weeks during Weeks 1–24) was achieved by 58 of 153 (37.9%) and 10 of 76 (13.2%) patients receiving luspatercept and placebo, respectively ($P < 0.0001$)
- 73 of 153 (47.7%) and 12 of 76 (15.8%) patients receiving luspatercept and placebo, respectively, achieved RBC-TI ≥ 8 weeks any time during the treatment period ($P < 0.0001$)
- 77 of 153 (50.3%) patients receiving luspatercept and 11 of 76 (14.5%) patients receiving placebo achieved ≥ 50% reduction in RBC transfusion burden from baseline for ≥ 24 weeks ($P < 0.0001$)
  - The median longest episode of RBC transfusion burden reduction ≥ 50% was 131.6 weeks in the luspatercept arm and not estimable in the placebo arm

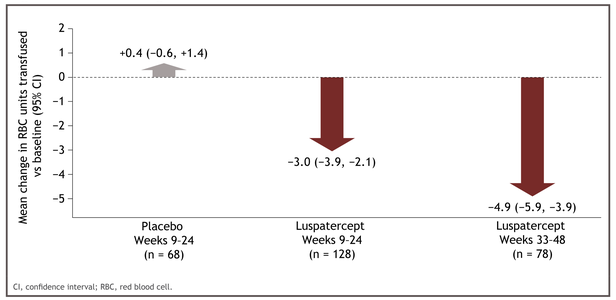
Change in RBC transfusions on treatment

- In Weeks 9–24, mean change from baseline in RBC units transfused was −3.0 (95% confidence interval [CI] −3.9, −2.1) versus +0.4 (95% CI −0.6, +1.4) in the luspatercept versus placebo arms (**Figure 2**)
  - In Weeks 33–48, mean change from baseline in RBC units transfused was −4.9 (95% CI −5.9, −3.9) in patients receiving luspatercept
- In Weeks 1–24, mean number of transfusion visits was 5.9 versus 9.5 in the luspatercept versus placebo arms (**Figure 3**)

Total transfusions over 48 weeks

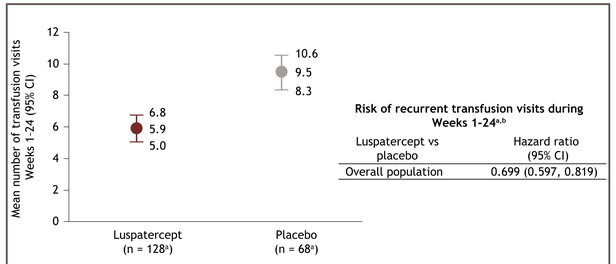
- The mean number of RBC units transfused during Weeks 1–48 was 22.89 versus 35.98 in the luspatercept versus placebo arms ($P < 0.0001$) (**Table 2**)
- The mean number of RBC transfusion visits during Weeks 1–48 was 12.95 versus 19.54 in the luspatercept versus placebo arms ($P < 0.0001$) (**Table 2**)

Figure 2. Mean change from baseline in RBC units transfused



CI, confidence interval; RBC, red blood cell.

Figure 3. Mean number of transfusion visits in Weeks 1–24



Risk of recurrent transfusion visits during Weeks 1-24[a,b]

	Luspatercept vs placebo	Hazard ratio (95% CI)
Overall population		0.699 (0.597, 0.819)

[a]83.7% (128/153) patients treated with luspatercept and 89.5% (68/76) placebo patients completed 24 weeks of treatment and were considered having complete data for this analysis. [b]A Cox model using the Andersen-Gill model[6] to assess the recurrence of transfusion visits during the primary treatment phase (Weeks 1-24). CI, confidence interval.

Table 2. Number of RBC units transfused and transfusion visits over 48 weeks

	Luspatercept (N = 153)	Placebo (N = 76)
Number of RBC units transfused over 48 weeks		
Mean	22.89	35.98
LS mean	23.28	35.20
LS mean difference (95% CI)	−11.92 (−15.55, −8.28)	
P value	< 0.0001	
Number of RBC transfusion visits over 48 weeks		
Mean	12.95	19.54
LS mean	13.14	19.15
LS mean difference (95% CI)	−6.00 (−8.16, −3.85)	
P value	< 0.0001	

CI, confidence interval; LS, least squares; RBC, red blood cell.

Change in serum ferritin

- Least squares (LS) mean change in serum ferritin from baseline to Weeks 9–24 was −2.7 μg/L and +226.5 μg/L in the luspatercept and placebo arms, respectively (LS mean difference −229.1 μg/L; $P = 0.0024$) (**Table 3**)
  - The mean change in serum ferritin in Weeks 33–48 was −72.0 μg/L and +247.4 μg/L in the luspatercept and placebo arms, respectively (LS mean difference −319.5 μg/L; $P = 0.0294$)

Table 3. Mean change from baseline in serum ferritin

	Averaged over Weeks 9–24		Averaged over Weeks 33–48	
	Luspatercept (N = 153)	Placebo (N = 76)	Luspatercept (N = 153)	Placebo (N = 76)
LS mean (SE), μg/L	−2.7 (54.05)	+226.5 (68.02)	−72.0 (74.76)	+247.4 (140.96)
LS mean difference (95% CI), μg/L	−229.1 (74.43)		−319.5 (144.57)	
P value	0.0024		0.0294	

CI, confidence interval; LS, least squares; SE, standard error.

Achievement of HI-E

- In Weeks 1–24, 81 of 153 (52.9%) patients in the luspatercept arm and 9 of 76 (11.8%) patients in the placebo arm achieved modified HI-E response per IWG 2006 criteria

Conclusions

- Luspatercept produced clinically meaningful and durable reductions in RBC transfusions in patients with LR MDS with RS
- Luspatercept also resulted in statistically significant reductions in serum ferritin in patients with LR MDS with RS

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