Clinical benefit of luspatercept in patients with lower-risk myelodysplastic syndromes and high transfusion burden in the phase 3 MEDALIST study

Abstract Number
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Introduction

- Patients with lower-risk myelodysplastic syndromes (LR MDS) develop anemia due to ineffective erythropoiesis, leading to dependence on red blood cell (RBC) transfusions[1,2]
- There is a need for effective therapies to reduce RBC transfusion burden, particularly for those patients who have significant transfusion needs[1,2]
- Luspatercept is a first-in-class erythroid maturation agent that binds to select TGF-β superfamily ligands to diminish Smad2/3 signaling and promote 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 a phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of luspatercept in patients with LR MDS with RS who require RBC transfusions[4]

Objective

- To evaluate the clinical benefit of luspatercept in patients with LR MDS with high transfusion burden (HTB) in the MEDALIST trial

Methods

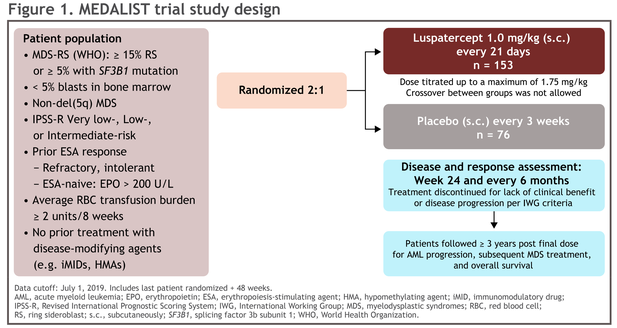
Study design

- MEDALIST is an ongoing phase 3, randomized, double-blind, placebo-controlled trial (NCT02631070)
- Patients were randomized at 65 sites between March 2016 and June 2017
- Eligible patients were:
  - Aged ≥ 18 years
  - 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 (ESAs)
  - Required RBC transfusions
- Patients were randomized 2:1 to receive luspatercept (starting dose 1.0 mg/kg, with titration up to 1.75 mg/kg in patients not achieving RBC transfusion independence) or placebo subcutaneously every 3 weeks for ≥ 24 weeks (**Figure 1**)
- Patients receiving transfusion of ≥ 6 RBC units within 8 weeks prior to study were classed as HTB; patients receiving < 6 RBC units were classed as low transfusion burden (LTB)

Study endpoints

- The primary endpoint was achievement of RBC transfusion independence (TI) ≥ 8 weeks during Weeks 1-24
- The key secondary endpoint was achievement of RBC-TI ≥ 8 weeks during Weeks 1-48
- Additional secondary endpoints included:
  - ≥ 50% and ≥ 75% reduction in RBC units transfused from baseline over at least 24 weeks
  - Achievement of major hematologic improvement-erythroid (HI-E) (per International Working Group [IWG] 2006 criteria[5]) for ≥ 8 weeks, defined as a reduction of ≥ 4 RBC units from baseline (for patients with baseline RBC transfusion burden of ≥ 4 units/8 weeks) or a mean hemoglobin increase of ≥ 1.5 g/dL from baseline (for patients with baseline RBC transfusion burden of < 4 units/8 weeks)

Figure 1. MEDALIST trial study design



Data cutoff: July 1, 2019. Includes last patient randomized + 48 weeks.
AML, acute myeloid leukemia; EPO, erythropoietin; ESAs, 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 to receive luspatercept (n = 153) or placebo (n = 76) (**Table 1**)
  - 99 (43%) were HTB and 130 (57%) were LTB
- 148 (97%) and 70 (92%) patients in the luspatercept and placebo arms, respectively, had received prior ESAs
- The median duration of treatment received on study was 7.6 and 18.6 months for HTB and LTB patients receiving luspatercept, respectively, versus 5.5 and 5.5 months for patients receiving placebo
- The median (range) transfusion burden at baseline for HTB patients in the luspatercept and placebo arms was 7.5 (6-15) and 8.0 (6-20) RBC units over 8 weeks (in the 16 weeks prior to randomization), respectively
- 68.2% and 66.7% of HTB and LTB patients in the luspatercept arm, respectively, received 1.75 mg/kg as their maximum dose level
- As of data cutoff (July 1, 2019), 41 (26.8%) patients continue to receive luspatercept, while all patients receiving placebo discontinued at the end of the treatment phase

Table 1. Baseline characteristics

Characteristic	Luspatercept (N = 153)		Placebo (N = 76)	
	HTB (n = 66)	LTB (n = 87)	HTB (n = 33)	LTB (n = 43)
Age, median (range), years	71.5 (40-85)	71.0 (41-95)	71.0 (37-85)	74.0 (26-91)
Male, n (%)	53 (80.3)	41 (47.1)	23 (69.7)	27 (62.8)
RBC transfusion burden category, n (%)[a]				
≥ 6 U/8 weeks	66 (100)	0	33 (100)	0
≥ 4 to < 6 U/8 weeks	0	41 (47.1)	0	23 (53.5)
< 4 U/8 weeks	0	46 (52.9)	0	20 (46.5)
IPSS-R, n (%)[b]				
Very low	10 (15.2)	8 (9.2)	4 (12.1)	2 (4.7)
Low	43 (65.2)	66 (75.9)	21 (63.6)	36 (83.7)
Intermediate	12 (18.2)	13 (14.9)	8 (24.2)	5 (11.6)
High	1 (1.5)	0	0	0
Baseline Hb, median (range), g/dL[c]	7.6 (6-10)	7.7 (6-10)	7.5 (5-9)	7.8 (6-9)
Baseline EPO level, mean, IU/L	331.94	239.45	407.70	189.98
***SF3B1* mutation, n (%)[d]**	60 (90.9)	81 (93.1)	30 (90.9)	35 (81.4)
Serum EPO, n (%)				
< 200 U/L	36 (54.5)	52 (59.8)	15 (45.5)	35 (81.4)
≥ 200 U/L	30 (45.5)	34 (39.1)	18 (54.5)	8 (18.6)
Missing	0	1 (1.1)	0	0
Prior ESA use, n (%)	63 (95.5)	85 (97.7)	29 (87.9)	41 (95.4)

[a]In the 16 weeks prior to randomization. [b]1 patient in the luspatercept arm was classified as IPSS-R High risk. [c]Baseline Hb was defined as the last value measured on or before the date and time of first dose. [d]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%. EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HTB, high transfusion burden; IPSS-R, Revised International Prognostic Scoring System; LTB, low transfusion burden; RBC, red blood cell; RS, ring sideroblast; *SF3B1*, splicing factor 3b subunit 1.

Achievement of HI-E per IWG 2006 criteria

- In Weeks 1-48, 37 of 66 (56.1%) HTB patients in the luspatercept arm and 9 of 33 (27.3%) HTB patients in the placebo arm achieved HI-E response per IWG 2006 criteria ($P = 0.0071$) (**Figure 2**)

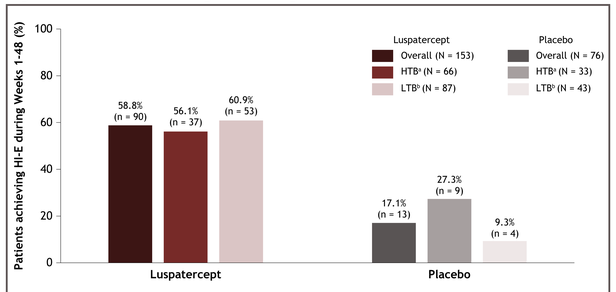
Achievement of RBC-TI

- 6 of 66 (9.1%) luspatercept-treated HTB patients and 1 of 33 (3.0%) placebo-treated HTB patients achieved the primary endpoint of RBC-TI ≥ 8 weeks in Weeks 1-24 ($P = 0.27$)
  - Median time to achieve RBC-TI in HTB patients was 50.0 days (range 1.0-100.0) with luspatercept versus 1.0 day for the 1 patient who achieved RBC-TI with placebo
  - Median duration of RBC-TI in HTB patients was 53.9 weeks (range 8.4-137.1) with luspatercept versus 54.9 weeks for the 1 patient who achieved RBC-TI with placebo
- 12 of 66 (18.2%) luspatercept-treated HTB patients and 2 of 33 (6.1%) placebo-treated HTB patients achieved RBC-TI ≥ 8 weeks in Weeks 1-48 (**Figure 3**)
  - In the placebo arm, as of the data cutoff, all patients had discontinued treatment
- 14 of 66 (21.2%) luspatercept- and 2 of 33 (6.1%) placebo-treated HTB patients achieved RBC-TI ≥ 8 weeks at any point during the entire assessment period

Reduction in transfusion burden

- 23 of 66 (34.8%) and 12 of 66 (18.2%) HTB patients receiving luspatercept achieved ≥ 50% and ≥ 75% reduction in RBC transfusion burden from baseline over at least 24 weeks, respectively (**Figure 4**)
  - Among patients receiving luspatercept, the most common dose level at which a ≥ 50% reduction in RBC transfusion burden over at least 24 weeks was first achieved was 1.0 mg/kg
  - Mean time to first achievement of a ≥ 50% reduction in RBC transfusion burden over at least 24 weeks was 2.7 months for the 23 luspatercept-treated HTB responders and 1.5 months for the 3 placebo-treated HTB responders

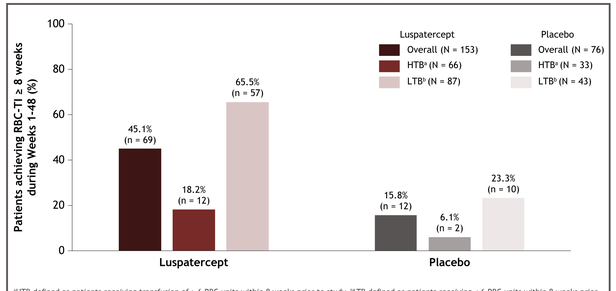
Figure 2. Patients achieving HI-E during Weeks 1-48



[a]HTB defined as patients receiving transfusion of ≥ 6 RBC units within 8 weeks prior to study. [b]LTB defined as patients receiving < 6 RBC units within 8 weeks prior to study. HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; LTB, low transfusion burden; RBC, red blood cell.

- Kaplan-Meier estimate of median longest duration of ≥ 50% reduction in RBC transfusion burden over at least 24 weeks was 72.3 weeks (95% confidence interval [CI] 29.6-not estimable [NE]) for the 23 luspatercept-treated HTB responders and NE (95% CI 27.7-NE) for the 3 placebo-treated HTB responders
- The mean number of transfusion events for HTB patients in Weeks 1-24 was 9.2 and 12.4 in the luspatercept and placebo arms, respectively (hazard ratio 0.794, 95% CI 0.660-0.956)

Figure 3. Patients achieving RBC-TI ≥ 8 weeks during Weeks 1-48

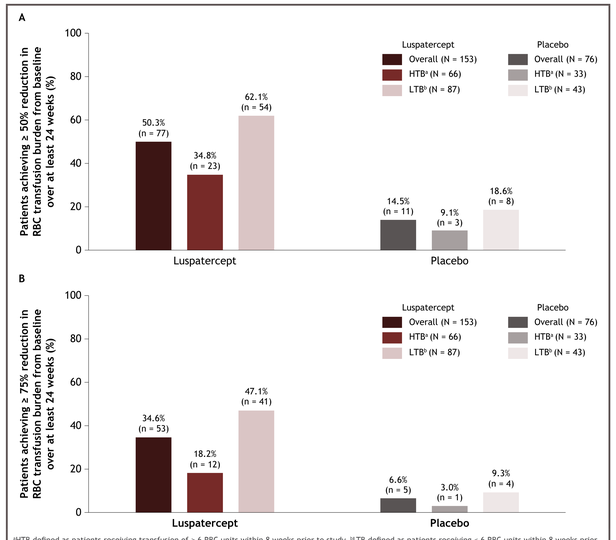


[a]HTB defined as patients receiving transfusion of ≥ 6 RBC units within 8 weeks prior to study. [b]LTB defined as patients receiving < 6 RBC units within 8 weeks prior to study. HTB, high transfusion burden; LTB, low transfusion burden; RBC-TI, red blood cell transfusion independence.

Safety

- The most common treatment-emergent adverse events (TEAEs) of any grade with luspatercept were fatigue (30.1% of patients), diarrhea (28.1%), and asthenia (25.5%)
- 11 of 66 (16.7%) HTB patients receiving luspatercept and 3 of 33 (9.1%) patients receiving placebo reported ≥ 1 TEAE leading to discontinuation
- 35 of 66 (53.0%) HTB patients receiving luspatercept and 18 of 33 (54.5%) patients receiving placebo reported ≥ 1 grade 3-4 TEAE
- 28 of 66 (42.4%) luspatercept-treated HTB patients and 15 of 33 (45.5%) placebo-treated patients reported ≥ 1 serious TEAE
  - 3 (4.5%) patients receiving luspatercept reported ≥ 1 suspected-related serious TEAE
- Of all patients, 3 of 153 (2.0%) receiving luspatercept progressed to acute myeloid leukemia (AML) versus 2 of 76 (2.6%) receiving placebo
  - Of those patients receiving luspatercept who progressed to AML, 2 had HTB
  - Of those receiving placebo who progressed to AML, 0 had HTB
  - Time from MDS diagnosis to AML progression ranged from 57.2-223.6 months in the 3 patients receiving luspatercept versus 30.1-32.7 months in the 2 patients receiving placebo

Figure 4. Patients achieving ≥ 50% (A) and ≥ 75% (B) reduction in RBC transfusion burden from baseline over at least 24 weeks



[a]HTB defined as patients receiving transfusion of ≥ 6 RBC units within 8 weeks prior to study. [b]LTB defined as patients receiving < 6 RBC units within 8 weeks prior to study. HTB, high transfusion burden; LTB, low transfusion burden; RBC, red blood cell.

Conclusions

- In this study of patients with LR MDS with RS, luspatercept treatment resulted in clinically significant reductions in RBC transfusion burden and achievement of HI-E, including in HTB patients
- Although rates of RBC-TI ≥ 8 weeks were low in HTB patients receiving luspatercept, there were reductions in number of transfusion events, and HTB patients had longer periods of transfusion burden reduction

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Disclosures

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