Assessment of dose-dependent response to luspatercept in patients with lower-risk myelodysplastic syndromes with ring sideroblasts in the phase 3 MEDALIST trial

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Introduction

- Patients with lower-risk myelodysplastic syndromes (LR MDS) develop anemia due to ineffective erythropoiesis, leading to red blood cell (RBC) transfusion dependence[1,2]
- Luspatercept is a first-in-class erythroid maturation agent that binds to select transforming growth factor-B superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis[3]
- MEDALIST is an ongoing phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of luspatercept in patients with LR MDS with ring sideroblasts (RS) who require RBC transfusions
  - The primary results of the MEDALIST trial demonstrated that a significant proportion of luspatercept-treated patients achieved RBC transfusion independence (TI) ≥ 8 weeks during the first 24 weeks of the study[4]
- Luspatercept has been approved by the US Food and Drug Administration for the treatment of anemia in adult patients failing an erythropoiesis-stimulating agent and requiring ≥ 2 RBC units over 8 weeks with Very low- to Intermediate-risk MDS with RS or with myelodysplastic/myeloproliferative neoplasm with RS and thrombocytosis[5]

Objective

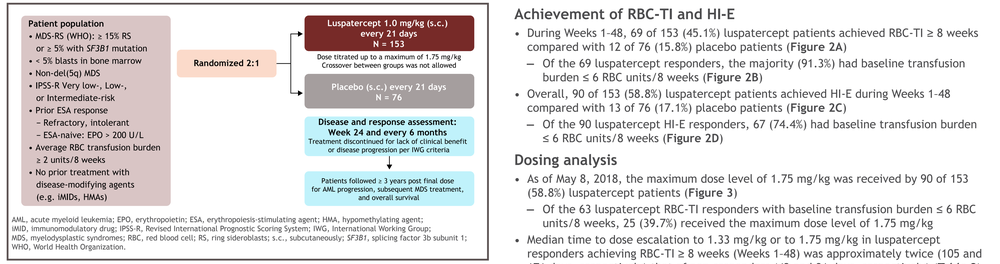
- To evaluate the effect of luspatercept dose on efficacy and treatment-emergent adverse events (TEAEs)

Methods

Study design

- MEDALIST is an ongoing phase 3, randomized, double-blind, placebo-controlled trial (NCT02631070); patients in the luspatercept arm who have not discontinued from treatment continue to receive the study drug
- Patients were randomized at 65 sites between March 2016 and June 2017
- The MEDALIST study design is shown in **Figure 1**
  - Patients were randomized 2:1 to receive luspatercept (starting dose 1.0 mg/kg) or placebo subcutaneously every 21 days for ≥ 24 weeks
  - Dose titration was allowed up to 1.33 mg/kg and then up to 1.75 mg/kg in the absence of RBC-TI after ≥ 2 doses at same dose level
  - Dose reductions or delays were used to manage excessive hemoglobin (Hb) increase and safety
  - Stratification factors were: average baseline RBC transfusion burden (≥ 6 vs < 6 RBC units per 8 weeks) and baseline Revised International Prognostic Scoring System (IPSS-R) score

Figure 1. MEDALIST trial study design



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 sideroblasts; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

RBC-TI, hematologic improvement-erythroid (HI-E), and dosing analyses

- RBC-TI ≥ 8 weeks during Weeks 1-48 was defined as the absence of any RBC transfusion during any consecutive 56-day period during Weeks 1-48
- HI-E during Weeks 1-48 was defined as the proportion of patients who met the modified HI-E criteria per the International Working Group 2006 criteria,[6] sustained over Weeks 1-48
- Dosing analyses presented include:
  - Maximum dose level received
  - Dose escalations, time to dose escalation, and treatment duration by dose
  - Dose at first response: RBC-TI ≥ 8 weeks (Weeks 1-48) and HI-E (Weeks 1-48)
- These responses were measured within the first 48 weeks of the study and are therefore reported as of May 8, 2018
- Baseline RBC transfusion burden subgroups for these analyses include:
  - ≤ 6 RBC units/8 weeks
  - > 6 RBC units/8 weeks

Safety analysis

- Data cutoff for incidence of dose reductions, dose delays, and TEAEs was July 1, 2019

Results

Patients

- 229 patients were randomized and received luspatercept (N = 153) or placebo (N = 76) (**Table 1**)
  - Baseline RBC transfusion burden was ≤ 6 RBC units/8 weeks in 108 of 153 (70.6%) luspatercept patients and in 50 of 76 (65.8%) placebo patients
  - Baseline RBC transfusion burden was > 6 RBC units/8 weeks in 45 of 153 (29.4%) luspatercept patients and in 26 of 76 (34.2%) placebo patients

Table 1. Baseline patient 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, median (range), units/8 weeks[a]	5 (1-15)	5 (2-20)
≤ 6 units/8 weeks, n (%)	108 (70.6)	50 (65.8)
> 6 units/8 weeks, n (%)	45 (29.4)	26 (34.2)
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)	64 (86.5)
Serum EPO, n (%)[d]		
< 200 U/L	88 (57.5)	50 (65.8)
≥ 200 U/L	64 (41.8)	26 (34.2)
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; Hb, hemoglobin; IPSS-R, Revised International Prognostic Scoring System; RBC, red blood cell; RS, ring sideroblasts; SD, standard deviation; *SF3B1*, splicing factor 3b subunit 1.

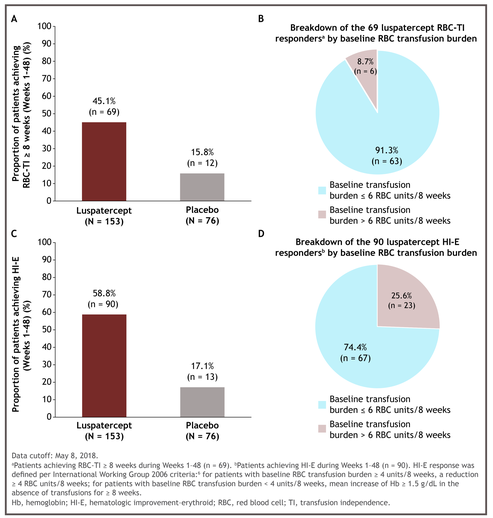
Achievement of RBC-TI and HI-E

- During Weeks 1-48, 69 of 153 (45.1%) luspatercept patients achieved RBC-TI ≥ 8 weeks compared with 12 of 76 (15.8%) placebo patients (**Figure 2A**)
  - Of the 69 luspatercept responders, the majority (91.3%) had baseline transfusion burden ≤ 6 RBC units/8 weeks (**Figure 2B**)
- Overall, 90 of 153 (58.8%) luspatercept patients achieved HI-E during Weeks 1-48 compared with 13 of 76 (17.1%) placebo patients (**Figure 2C**)
  - Of the 90 luspatercept HI-E responders, 67 (74.4%) had baseline transfusion burden ≤ 6 RBC units/8 weeks (**Figure 2D**)

Dosing analysis

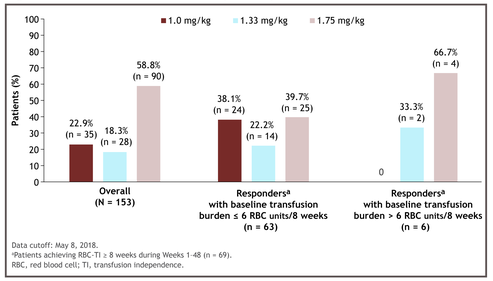
- As of May 8, 2018, the maximum dose level of 1.75 mg/kg was received by 90 of 153 (58.8%) luspatercept patients (**Figure 3**)
  - Of the 63 luspatercept RBC-TI responders with baseline transfusion burden ≤ 6 RBC units/8 weeks, 25 (39.7%) received the maximum dose level of 1.75 mg/kg
- Median time to dose escalation to 1.33 mg/kg or to 1.75 mg/kg in luspatercept responders achieving RBC-TI ≥ 8 weeks (Weeks 1-48) was approximately twice (105 and 171 days, respectively) that of non-responders (43 and 91 days, respectively) (**Table 2**)
  - Dose escalations were seen more frequently in patients with higher erythropoietin levels, IPSS-R Intermediate score, and greater RBC transfusion burden at baseline
- Median (range) duration of treatment at 1.33 mg/kg was 1.4 (0.7-17.5) months in luspatercept patients overall and 3.5 (1.2-17.5) months in luspatercept RBC-TI responders (**Table 2**)
- Median (range) duration of treatment at 1.75 mg/kg was 5.9 (0.7-19.5) months in luspatercept patients overall and 8.5 (0.7-17.5) months in luspatercept RBC-TI responders (**Table 2**)
- The majority of luspatercept RBC-TI responders (47 of 69, 68.1%) achieved their first response at 1.0 mg/kg without requiring dose escalation (**Figure 4A**)
  - Similarly, the majority of luspatercept RBC-TI responders with baseline transfusion burden ≤ 6 RBC units/8 weeks achieved their first response at 1.0 mg/kg
  - Luspatercept RBC-TI responders with baseline transfusion burden > 6 RBC units/8 weeks achieved their first response at doses higher than 1.0 mg/kg

Figure 2. Achievement of RBC-TI ≥ 8 weeks (A and B) and HI-E (C and D) during Weeks 1-48



Data cutoff: May 8, 2018.
[a]Patients achieving RBC-TI ≥ 8 weeks during Weeks 1-48 (n = 69). [b]Patients achieving HI-E during Weeks 1-48 (n = 90). HI-E response was defined per International Working Group 2006 criteria[6] for patients with baseline RBC transfusion burden ≥ 4 units/8 weeks, a reduction ≥ 4 RBC units/8 weeks; for patients with baseline RBC transfusion burden < 4 units/8 weeks, mean increase of Hb ≥ 1.5 g/dL in the absence of transfusions for ≥ 8 weeks.
Hb, hemoglobin; HI-E, hematologic improvement-erythroid; RBC, red blood cell; TI, transfusion independence.

Figure 3. Maximum dose level of luspatercept received



Data cutoff: May 8, 2018.
[a]Patients achieving RBC-TI ≥ 8 weeks during Weeks 1-48 (n = 69).
RBC, red blood cell; TI, transfusion independence.

- Overall, 57 of 90 (63.3%) luspatercept patients who achieved HI-E during Weeks 1-48 achieved their first response at 1.0 mg/kg (**Figure 4B**)
  - 43 of 67 (64.2%) luspatercept HI-E responders with baseline transfusion burden ≤ 6 RBC units/8 weeks achieved their first response at 1.0 mg/kg
  - 14 of 23 (60.9%) luspatercept HI-E responders with baseline transfusion burden > 6 RBC units/8 weeks also achieved their first response at 1.0 mg/kg

Safety

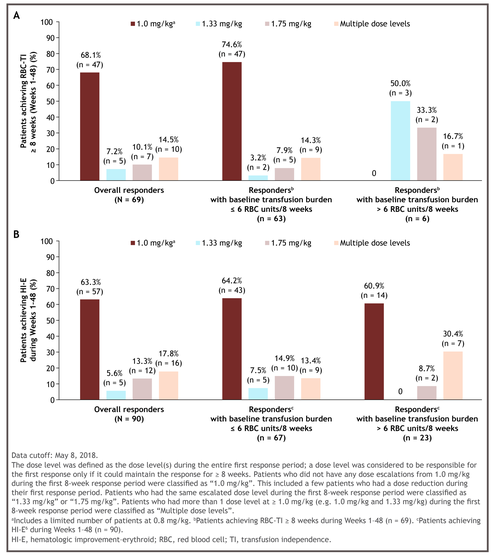
- Of 153 luspatercept-treated patients, 74 (48.4%) and 9 (5.9%) experienced ≥ 1 dose delay and ≥ 1 dose reduction, respectively (**Table 3**)
  - Dose delays due to pre-dose Hb levels ≥ 11.5 g/dL occurred in 13 (8.5%) luspatercept patients
  - Dose reductions due to Hb increase ≥ 2 g/dL versus pre-dose Hb level of prior treatment cycle occurred in 3 (2.0%) luspatercept patients

Table 2. Dose escalations and time to dose escalation by RBC-TI response

Parameter	Luspatercept responders[a] (n = 69)	Luspatercept non-responders[a] (n = 84)	Luspatercept overall (N = 153)
No dose escalation, n (%)	24 (34.8)	11 (13.1)	35 (22.9)
Dose escalation to 1.33 mg/kg, n (%)	45 (65.2)	73 (86.9)	118 (77.1)
Time to dose escalation to 1.33 mg/kg, median (range), days	105 (40-419)	43 (39-258)	63 (39-419)
Duration of treatment at 1.33 mg/kg, median (range), months	3.5 (1.2-17.5)	1.4 (0.7-8.3)	1.4 (0.7-17.5)
In patients with baseline transfusion burden ≤ 6 RBC units/8 weeks	3.5 (1.2-17.5)	1.4 (0.7-8.3)	1.6 (0.7-17.5)
In patients with baseline transfusion burden > 6 RBC units/8 weeks	2.9 (1.3-9.5)	1.4 (0.7-5.1)	1.4 (0.7-9.5)
Dose escalation to 1.75 mg/kg, n (%)	29 (42.0)	61 (72.6)	90 (58.8)
Time to dose escalation to 1.75 mg/kg, median (range), days	171 (81-359)	91 (81-344)	106 (81-359)
Duration of treatment at 1.75 mg/kg, median (range), months	8.5 (0.7-17.5)	2.9 (0.7-19.5)	5.9 (0.7-19.5)
In patients with baseline transfusion burden ≤ 6 RBC units/8 weeks	7.7 (0.7-17.2)	2.8 (0.7-19.5)	6.2 (0.7-19.5)
In patients with baseline transfusion burden > 6 RBC units/8 weeks	13.8 (4.1-17.5)	4.2 (0.7-15.2)	4.3 (0.7-17.5)

Data cutoff: May 8, 2018.
[a]Response was defined as achieving RBC-TI ≥ 8 weeks during Weeks 1-48.
RBC, red blood cell; TI, transfusion independence.

Figure 4. First RBC-TI ≥ 8 weeks (A) and HI-E response (B) during Weeks 1-48 by dose level in patients receiving luspatercept



Data cutoff: May 8, 2018.
The dose level was defined as the dose level(s) during the entire first response period; a dose level was considered to be responsible for the first response only if it could maintain the response for ≥ 8 weeks. Patients who did not have any dose escalations from 1.0 mg/kg during the first 8-week response period were classified as "1.0 mg/kg". This included a few patients who had a dose reduction during their first response period. Patients who had the same escalated dose level during the first 8-week response period were classified as "1.33 mg/kg" or "1.75 mg/kg". Patients who had more than 1 dose level at ≥ 1.0 mg/kg (e.g. 1.0 mg/kg and 1.33 mg/kg) during the first 8-week response period were classified as "Multiple dose levels".
[a]Includes a limited number of patients at 0.8 mg/kg. [b]Patients achieving RBC-TI ≥ 8 weeks during Weeks 1-48 (n = 69). [c]Patients achieving HI-E[6] during Weeks 1-48 (n = 90).
HI-E, hematologic improvement-erythroid; RBC, red blood cell; TI, transfusion independence.

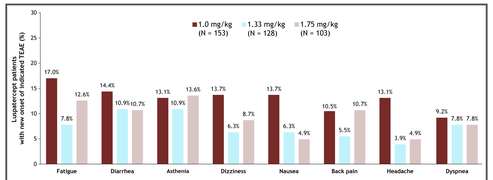
- Dose reductions due to any suspected related grade ≥ 3 adverse event occurred in 5 (3.3%) luspatercept patients
- New onset of TEAEs reported more frequently with luspatercept generally did not increase with dose increases from 1.0 mg/kg to 1.75 mg/kg (**Figure 5**)

Table 3. Dose delays and reductions

Parameter, n (%)	Luspatercept (N = 153)
≥ 1 dose delay	74 (48.4)
Due to pre-dose Hb levels ≥ 11.5 g/dL	13 (8.5)
≥ 1 dose reduction	9 (5.9)
Due to Hb increase ≥ 2 g/dL vs pre-dose Hb level	3 (2.0)
Due to any suspected related grade ≥ 3 AE	5 (3.3)

Data cutoff: July 1, 2019.
AE, adverse event; Hb, hemoglobin.

Figure 5. New onset of TEAEs at each dose level in patients receiving luspatercept



Data cutoff: July 1, 2019.
TEAEs include adverse events that started on or after the date of first dose and on or before 42 days after the date of last dose of study treatment. If a patient experienced multiple events under the same SOC and PT, then the patient is counted only once for that SOC and PT level. All TEAEs regardless of severity are counted.
SOC, System Organ Class; PT, Preferred Term; TEAE, treatment-emergent adverse event.

Conclusions

- The majority of luspatercept patients with baseline transfusion burden ≤ 6 RBC units/8 weeks who achieved RBC-TI ≥ 8 weeks within the first 48 weeks achieved their first response at 1.0 mg/kg
  - An additional 11% of patients in this group (and approximately 17% of responders overall) achieved their first response only with higher doses (1.33 mg/kg and 1.75 mg/kg)
  - Dose escalations contributed to maintenance of RBC-TI ≥ 8 weeks response or achievement of multiple response episodes
  - Although the number of RBC-TI responders with baseline transfusion burden > 6 RBC units/8 weeks was small (n = 6), 50% achieved their first response at 1.33 mg/kg
- The majority of luspatercept patients who achieved HI-E during Weeks 1-48 achieved their first response at 1.0 mg/kg, regardless of baseline transfusion burden
- The luspatercept dose range of 1.0-1.75 mg/kg was well tolerated, without dose-dependent increases in TEAEs

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