Reduction of transfusion burden, hemoglobin increase, and dose titration in the COMMANDS study of luspatercept versus epoetin alfa in erythropoietin-stimulating agent-naive patients with transfusion-dependent lower-risk myelodysplastic syndromes

MDS-234

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Introduction

- Luspatercept is an erythroid maturation agent approved for treatment of anemia in erythropoiesis-stimulating agent (ESA)-refractory adults with lower-risk myelodysplastic syndromes (LR-MDS) with ring sideroblasts (RS) or with myelodysplastic/myeloproliferative neoplasm with RS and thrombocytosis[1,2] who require transfusions of ≥ 2 red blood cell (RBC) units over 8 weeks
- Interim data from the phase 3, open-label COMMANDS study (NCT03682536) investigating the efficacy and safety of luspatercept versus epoetin alfa in ESA-naive patients with transfusion-dependent (TD) LR-MDS with or without RS demonstrated durable improvements in RBC transfusion independence (RBC-TI) with luspatercept[3]

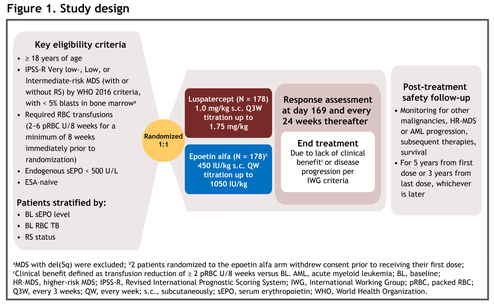
Objective

- To report the clinical benefits of luspatercept beyond RBC-TI and the impact of luspatercept dose escalation on RBC-TI response in patients from the COMMANDS study, stratified by baseline (BL) transfusion burden (TB)

Methods

- COMMANDS is a global, phase 3, open-label, randomized study comparing the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anemia due to LR-MDS in ESA-naive patients who require RBC transfusions (**Figure 1**)
  - Eligible patients were ≥ 18 years of age and TD (requiring 2-6 pRBC U/8 weeks for ≥ 8 weeks immediately preceding randomization)
- Patients were randomized (1:1) to luspatercept or epoetin alfa, and stratified by:
  - TB (< 4 vs ≥ 4 U/8 weeks)
  - sEPO concentration (≤ 200 U/L vs > 200 to < 500 U/L)
  - RS status (RS positive vs RS negative)
- The starting dose of luspatercept was 1.0 mg/kg, with stepwise dose escalation to 1.33 mg/kg and 1.75 mg/kg allowed
- The starting dose of epoetin alfa was 450 IU/kg, with stepwise dose escalation to 787.5 IU/kg and 1050 IU/kg allowed
- Dose escalations were allowed when patients' hemoglobin (Hb) levels were below target range (10-12 g/dL) or Hb level increase compared with previous measurement was ≤ 1 g/dL
- Primary endpoint
  - The primary endpoint was RBC-TI ≥ 12 weeks with a concurrent mean Hb increase of ≥ 1.5 g/dL (weeks 1-24)
- Additional endpoints
  - Achievement of Hb increase ≥ 1.5 g/dL (weeks 1-24)
  - Duration of Hb increase ≥ 1.5 g/dL (week 1 to end of treatment [EOT])
  - Achievement of ≥ 50% reduction in pRBC units for ≥ 12 weeks and ≥ 24 weeks (week 1 to EOT)
  - Duration of ≥ 50% reduction in pRBC units for ≥ 12 weeks and ≥ 24 weeks (week 1 to EOT)
  - Achievement of RBC-TI ≥ 12 weeks response by dose level and TB

Figure 1. Study design



[a]MDS with del(5q) were excluded; [b]2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose; [c]Clinical benefit defined as transfusion reduction of ≥ 2 pRBC U/8 weeks versus BL. AML, acute myeloid leukemia; BL, baseline; HR-MDS, higher-risk MDS; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; pRBC, packed RBC; Q3W, every 3 weeks; QW, every week; s.c., subcutaneously; sEPO, serum erythropoietin; WHO, World Health Organization.

Results

Baseline characteristics

- As of August 31, 2022, 178 patients had been randomized to luspatercept and 178 to epoetin alfa
  - BL characteristics were well balanced between the groups (**Table 1**)

Table 1. Demographics and BL patient characteristics

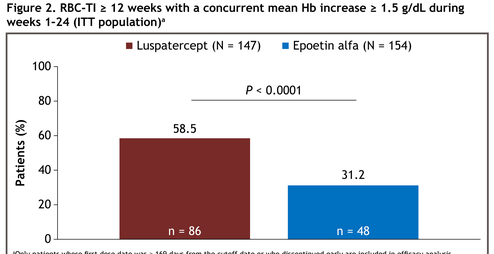
	Luspatercept (N = 178)	Epoetin alfa (N = 178)
Age, median (range), years	74.0 (46.0-93.0)	75.0 (33.0-91.0)
Female, n (%)	71 (39.9)	87 (48.9)
Time since original MDS diagnosis, median (range), months[a]	8.0 (~0.4 to 243.1)	5.2 (~0.3 to 171.6)
BL TB, median (range), pRBC units	3.0 (1-10)	3.0 (0-14)
BL TB category,[b] n (%)		
< 4 pRBC units	114 (64.0)	109 (61.2)
2 pRBC units	80 (44.9)	79 (44.4)
≥ 4 pRBC units	64 (36.0)	69 (38.8)
IPSS-R risk classification at BL, n (%)		
Very low	16 (9.0)	17 (9.6)
Low	126 (70.8)	131 (73.6)
Intermediate	34 (19.1)	28 (15.7)
Other[c]	1 (0.6)	0
Missing[d]	1 (0.6)	2 (1.1)
RS status, n (%)		
Positive	130 (73.0)	128 (71.9)
Negative	48 (27.0)	49 (27.5)
Missing[e]	0	1 (0.6)
***SF3B1* mutation status, n (%)**		
Mutated	111 (62.4)	99 (55.6)
Non-mutated	65 (36.5)	72 (40.4)
Missing[e]	2 (1.1)	7 (3.9)
Hb, median (range), g/dL	7.80 (4.7-9.2)	7.8 (4.5-10.2)
sEPO, median (range), U/L	78.71 (7.8-495.8)	85.9 (4.6-462.5)
Platelet count, median (range), ×10⁹/L	230.0 (38-770)	234.5 (47-715)
Absolute neutrophil count, median (range), ×10⁹/L	2.4 (0.4-9.1)	2.3 (0.5-13.3)
Serum ferritin, median (range), µg/L	626.2 (12.4-3170.0)	651.3 (39.4-6960.5)

[a]Number of months from date of original diagnosis to date of informed consent; [b]BL TB is the number of RBC units received 8 weeks prior to or on the first dose date; [c]The central pathology laboratory confirmed the MDS diagnosis with an IPSS-R score of Intermediate at screening for 1 patient in the luspatercept arm; at the next bone marrow assessment, the central laboratory sent the report with an IPSS-R score of High, confirmed that the score at screening was also High, and acknowledged the mistake; [d]For 3 patients (1 in the luspatercept arm and 2 in the epoetin alfa arm) the risk score could not be calculated; [e]One patient in the epoetin alfa arm had a bone marrow biopsy assessed by the central lab with a diagnosis of MDS with multilineage dysplasia and RS status was not provided.

Primary endpoint

- Of the 301 patients included in this pre-planned efficacy analysis, 86/147 (58.5%) patients receiving luspatercept and 48/154 (31.2%) receiving epoetin alfa achieved the primary endpoint (**Figure 2**)

Figure 2. RBC-TI ≥ 12 weeks with a concurrent mean Hb increase ≥ 1.5 g/dL during weeks 1-24 (ITT population)[a]

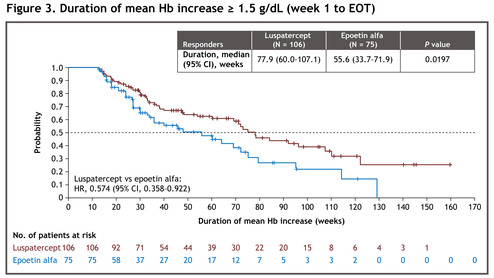


[a]Only patients whose first dose date was ≥ 169 days from the cutoff date or who discontinued early are included in efficacy analysis. ITT, intent-to-treat.

Mean Hb increase ≥ 1.5 g/dL (weeks 1-24)

- Greater proportions of patients treated with luspatercept compared with those treated with epoetin alfa achieved a mean Hb increase ≥ 1.5 g/dL during weeks 1-24 (106 [72.1%] vs 75 [48.7%] patients)
  - Common risk difference (CRD) in response rate was 23.2 (95% confidence interval [CI], 12.2-34.1; *P* < 0.0001)
- In these patients, the median duration of the longest period where the mean Hb increase ≥ 1.5 g/dL was sustained (week 1 to EOT) was longer with luspatercept compared with epoetin alfa (77.9 vs 55.6 weeks, respectively; *P* = 0.0197) (**Figure 3**)

Figure 3. Duration of mean Hb increase ≥ 1.5 g/dL (week 1 to EOT)



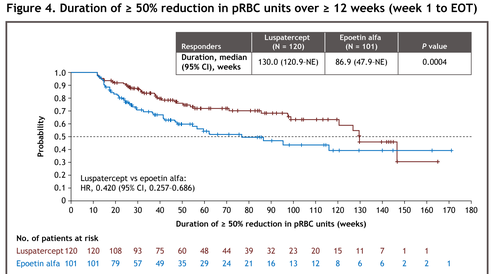
Reduction in pRBC units of ≥ 50% over ≥ 12 and ≥ 24 weeks (week 1 to EOT)

- A significantly greater proportion of patients treated with luspatercept than patients treated with epoetin alfa achieved a ≥ 50% reduction in pRBC units transfused over ≥ 12 and ≥ 24 weeks during the entire treatment period (**Table 2**)
- The median duration of ≥ 50% reduction in pRBC units over ≥ 12 and ≥ 24 weeks in responders was significantly longer in the luspatercept arm than the epoetin alfa arm (**Figures 4** and **5**)

Table 2. Reduction in pRBC units of ≥ 50% over ≥ 12 and ≥ 24 weeks (week 1 to EOT)

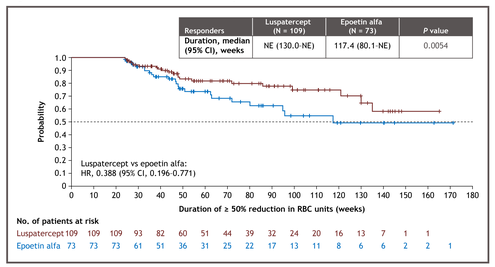
	Luspatercept (N = 147)	Epoetin alfa (N = 154)	CRD
≥ 50% reduction in pRBC units over ≥ 12 weeks (week 1 to EOT), n (%)	120 (81.6)	101 (65.6)	14.5 (95% CI, 4.9-24.2); *P* = 0.0016
≥ 50% reduction in pRBC units over ≥ 24 weeks (week 1 to EOT), n (%)	109 (74.1)	73 (47.4)	25.4 (95% CI, 15.1-35.8); *P* < 0.0001

Figure 4. Duration of ≥ 50% reduction in pRBC units over ≥ 12 weeks (week 1 to EOT)



NE, not evaluable.

Figure 5. Duration of ≥ 50% reduction in pRBC units over ≥ 24 weeks (week 1 to EOT)



Dose escalation during the study

- 70.2% (125/178) of patients treated with luspatercept compared with 74.4% (131/176) of patients treated with epoetin alfa had dose escalations (**Table 3**)

Table 3. Dose escalation (safety population)

n (%)	Luspatercept (N = 178)	Epoetin alfa (N = 176)
Patients with dose escalation	125 (70.2)	131 (74.4)
Dose escalated from 1.0 to 1.33 mg/kg	122 (68.5)	0
Dose escalated from 1.33 to 1.75 mg/kg	88 (49.4)	0
Dose escalated from 450 to 787.5 IU/kg	0	129 (73.3)
Dose escalated from 787.5 to 1050 IU/kg	0	102 (58.0)

- The proportion of patients who achieved their first RBC-TI ≥ 12 weeks response at 1.0, 1.33, and 1.75 mg/kg luspatercept doses was 65.3%, 6.1%, and 5.4%, respectively (**Table 4**)
  - Although > 60% of patients achieved their first response at the 1.0 mg/kg luspatercept dose, dose escalation was needed to maintain this first response or achieve another
- The proportion of patients who achieved their first RBC-TI ≥ 12 weeks response at 450, 787.5, and 1050 IU/kg epoetin alfa doses was 44.2%, 2.6%, and 5.2%, respectively (**Table 4**)

Table 4. Patients who achieved first RBC-TI ≥ 12 weeks (week 1 to EOT) response at different dose levels (ITT population)[a]

Achievement of first RBC-TI ≥ 12 weeks response by dose level, n (%)	Luspatercept (N = 147)	Epoetin alfa (N = 154)
1.0 mg/kg	96 (65.3)	NA
1.33 mg/kg	9 (6.1)	NA
1.75 mg/kg	8 (5.4)	NA
450 IU/kg	NA	68 (44.2)
787.5 IU/kg	NA	4 (2.6)
1050 IU/kg	NA	8 (5.2)

[a]Only patients whose first dose date was ≥ 169 days from the cutoff date or who discontinued early are included in efficacy analysis. NA, not applicable.

Dose escalation during the study by BL TB

- A greater proportion of patients with low TB (LTB) than high TB (HTB) had their first response at luspatercept dose 1.0 mg/kg (77.2% vs 45.5%, respectively) (**Table 5**)
- 10.9% and 5.5% of patients with HTB receiving luspatercept had their first responses at 1.33 mg/kg and 1.75 mg/kg, respectively

Treatment duration and discontinuation

- Median (range) treatment duration was 41.6 (0-165) weeks for luspatercept and 27.0 (0-171) weeks for epoetin alfa
- A lower proportion of patients discontinued luspatercept (n = 78 [43.8%]) compared with epoetin alfa (n = 105 [59.7%])

Table 5. Patients who achieved first RBC-TI ≥ 12 weeks response (week 1 to EOT) at different dose levels by BL TB (ITT population)[a]

Achievement of first RBC-TI ≥ 12 weeks response by dose level, n (%)	Luspatercept		Epoetin alfa	
	LTB[b] (n = 92)	HTB[c] (n = 55)	LTB[b] (n = 90)	HTB[c] (n = 64)
1.0 mg/kg	71 (77.2)	25 (45.5)	NA	NA
1.33 mg/kg	3 (3.3)	6 (10.9)	NA	NA
1.75 mg/kg	5 (5.4)	3 (5.5)	NA	NA
450 IU/kg	NA	NA	52 (57.8)	16 (25.0)
787.5 IU/kg	NA	NA	3 (3.3)	1 (1.6)
1050 IU/kg	NA	NA	4 (4.4)	4 (6.3)

[a]Only patients whose first dose date was ≥ 169 days from the cutoff date or who discontinued early are included in efficacy analysis; [b]LTB defined as < 4 U/8 weeks prior to randomization; [c]HTB defined as ≥ 4 U/8 weeks prior to randomization.

Safety

- A similar proportion of treatment-emergent adverse events (TEAEs) of any grade occurred in the luspatercept (n = 164 [92.1%]) and epoetin alfa arms (n = 150 [85.2%])
- Both luspatercept and epoetin alfa were well tolerated (**Table 6**)

Table 6. Safety

Patients, n (%)	Luspatercept (N = 178)	Epoetin alfa (N = 176)
Hematologic TEAEs (any grade)		
Anemia	17 (9.6)	17 (9.7)
Thrombocytopenia	11 (6.2)	3 (1.7)
Neutropenia	9 (5.1)	13 (7.4)
Leukocytopenia	2 (1.1)	3 (1.7)
TEAEs of interest (event of interest)		
Asthenia	48 (27.0)	38 (21.6)
Hypertension	25 (14.0)	13 (7.4)
Kidney toxicity	14 (7.9)	10 (5.7)
Malignancies	12 (6.7)	9 (5.1)
Thromboembolic event	8 (4.5)	5 (2.8)
Premalignant disorder	8 (4.5)	9 (5.1)
Immunogenicity injection local-type reaction	5 (2.8)	1 (0.6)
Immunogenicity hypersensitivity-type reaction	3 (1.7)	2 (1.1)
Liver toxicity	3 (1.7)	5 (2.8)
Extramedullary hematopoiesis masses	0	0
Progression to HR-MDS	5 (2.8)	7 (4.0)
Progression to AML	4 (2.2)	5 (2.8)

Conclusions

- There is a need for more treatment options that increase the rate and durability of RBC-TI response for patients with TD LR-MDS
- Patients treated with luspatercept experienced clinically meaningful and statistically significant improvements in RBC-TI and erythroid response when compared with epoetin alfa in ESA-naive patients with TD LR-MDS
- The majority of patients treated with luspatercept required dose escalation to maintain or achieve response
- A smaller proportion of patients with HTB achieved a first response at lower luspatercept dose levels compared with patients with LTB, suggesting that earlier dose increases or treatment initiation could be beneficial for this subgroup of patients
- Luspatercept had an acceptable and manageable safety profile that was consistent with previous MDS findings
- Luspatercept represents a new standard of care for ESA-naive TD patients with anemia due to LR-MDS

References

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