Luspatercept versus epoetin alfa for treatment of anemia in patients with erythropoiesis-stimulating agent-naive lower-risk myelodysplastic syndromes requiring red blood cell transfusions: data from the phase 3 COMMANDS study

MDS-157

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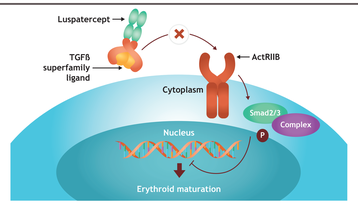
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Introduction

- Luspatercept improves erythropoiesis as shown in the MEDALIST trial[1] (**Figure 1**)
- Patients with lower-risk myelodysplastic syndromes (LR-MDS) without ring sideroblast (RS) with low transfusion burden (TB) can benefit from luspatercept[2,3]
- Luspatercept treatment can result in increased mean platelet and neutrophil counts in patients with LR-MDS[4]
- We present the results of the pre-planned interim analysis of the phase 3 COMMANDS study (NCT03682536) comparing the efficacy and safety of luspatercept versus erythropoiesis-stimulating agents (ESAs) in ESA-naive transfusion-dependent (TD) patients with LR-MDS

Figure 1. Luspatercept mechanism of action



ActRIIB, activin receptor type IIB; P, phosphorylation; TGFβ, transforming growth factor beta.

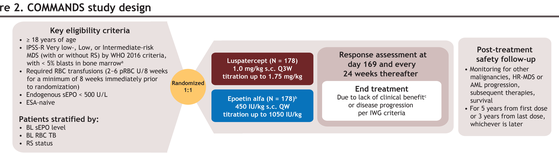
Objective

- To report prespecified interim efficacy and safety data from the phase 3, open-label, randomized COMMANDS study (NCT03682536) comparing luspatercept with epoetin alfa in ESA-naive TD patients with LR-MDS

Methods

- COMMANDS (NCT03682536) 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 red blood cell (RBC) transfusions (**Figure 2**)

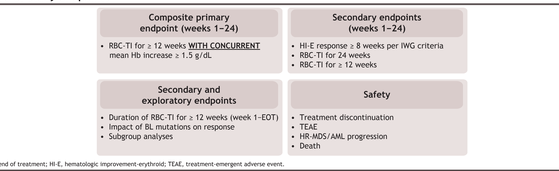
Figure 2. COMMANDS study design



[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, high-risk MDS; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; pRBC, packed RBC; Q2W, every 3 weeks; QW, once weekly; s.c., subcutaneously; sEPO, serum erythropoietin; WHO, World Health Organization.

- The data cutoff date for this planned interim analysis was August 31, 2022
  - This prespecified interim analysis was planned for when ~ 300 patients had either completed 24 weeks of treatment or discontinued prior to completing 24 weeks of treatment (at 85% of information for the primary endpoint)
- The primary endpoint was the achievement of RBC transfusion independence (RBC-TI) ≥ 12 weeks with a concurrent mean hemoglobin (Hb) increase ≥ 1.5 g/dL in weeks 1-24 (**Figure 3**)
- Key secondary endpoints during weeks 1-24 included achievement of RBC-TI ≥ 12 weeks and RBC-TI for 24 weeks, and HI-E ≥ 8 weeks (**Figure 3**)
- Other endpoints included duration of RBC-TI ≥ 12 weeks, progression to AML, and safety (**Figure 3**)

Figure 3. Study endpoints



EOT, end of treatment; HI-E, hematologic improvement-erythroid; TEAE, treatment-emergent adverse event.

Results

- Baseline characteristics were balanced between treatment arms (**Table 1**)

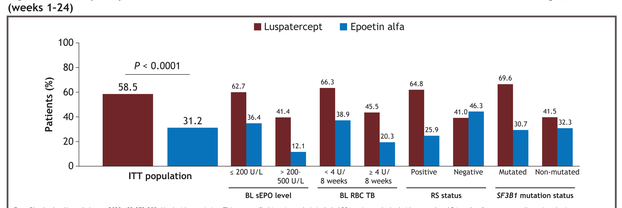
Table 1. Demographics and BL patient characteristics

	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 2 pRBC units ≥ 4 pRBC units	114 (64.0) 80 (44.9) 64 (36.0)	109 (61.2) 79 (44.4) 69 (38.8)
IPSS-R risk classification at BL, n (%) Very low Low Intermediate Other[c] *Missing*[d]	16 (9.0) 126 (70.8) 34 (19.1) 1 (0.6) 1 (0.6)	17 (9.6) 131 (73.6) 28 (15.7) 0 2 (1.1)
RS status, n (%) Positive Negative *Missing*[d]	130 (73.0) 48 (27.0) 0	128 (71.9) 49 (27.5) 1 (0.6)
SF3B1 mutation status, n (%) Mutated Non-mutated *Missing*[d]	111 (62.4) 65 (36.5) 2 (1.1)	99 (55.6) 72 (40.4) 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), × 10^9/L	230.0 (38-770)	234.5 (47-715)
Absolute neutrophil count, median (range), × 10^9/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.

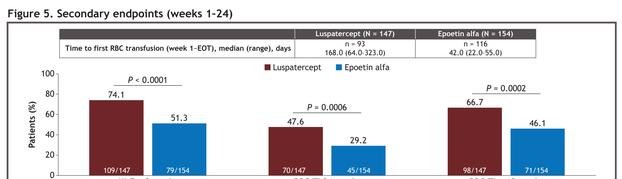
- Achievement of the primary endpoint favored luspatercept or was similar to epoetin alfa for all subgroups analyzed (**Figure 4**)
- Luspatercept treatment favored achievement of HI-E ≥ 8 weeks, RBC-TI 24 weeks, and RBC-TI ≥ 12 weeks during weeks 1-24 (**Figure 5**)

Figure 4. Primary endpoint: achievement of RBC-TI ≥ 12 weeks with a concurrent mean Hb increase ≥ 1.5 g/dL (weeks 1-24)



From Platzbecker U, et al. *Lancet* 2023;402:373-385. Used with permission. This prespecified interim analysis included 301 patients who had either completed 24 weeks of treatment or discontinued prior to completing 24 weeks of treatment. ITT, intent-to-treat.

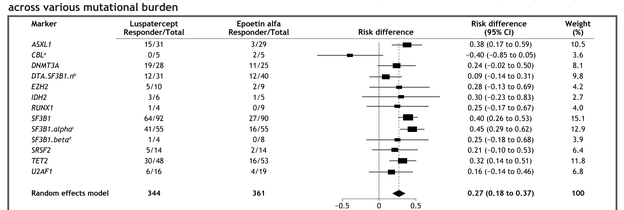
Figure 5. Secondary endpoints (weeks 1-24)



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- Mutation frequency at BL did not differ significantly between the luspatercept and epoetin alfa treatment arms
- BL mutational burden was lower in primary endpoint responders versus non-responders in the epoetin alfa arm and was significantly associated with the achievement of clinical benefit ($P = 0.016$); but not for luspatercept ($P = 0.56$)
- Patients with *SF3B1*, *SF3B1alpha*, *ASXL1*, and *TET2* mutations were associated with favorable clinical benefit with luspatercept versus epoetin alfa (**Figure 6**)
- Luspatercept patients had a higher probability of achieving clinical benefit, regardless of overall mutational burden, versus epoetin alfa

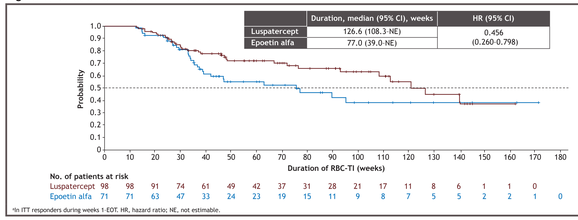
Figure 6. Exploratory endpoints: mutational burden association with response and broad activity of luspatercept across various mutational burden



From Platzbecker U, et al. *Lancet* 2023;402:373-385. Used with permission. [a]Low patient numbers preclude meaningful conclusions at this time; [b]DTA_SF3B1.m is a wild-type *SF3B1* with concomitant mutations in *ASXL1* and/or *TET2* or *DNMT3A*; [c]*SF3B1.alpha* is defined as *SF3B1* mutations with concomitant mutation of *DNMT3A* or *ASXL1* and/or *TET2*; [d]*SF3B1.beta* is defined as mutated *SF3B1* with concomitant mutations in any of the listed genes *BCOR*, *BCORL1*, *NRAS*, *RUNX1*, *SRSF2* or *STAG2*. CI, confidence interval.

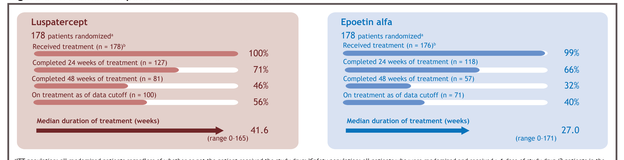
- The median duration of the longest single RBC-TI period for patients who achieved RBC-TI ≥ 12 weeks (week 1 to EOT) was longer in the luspatercept arm than in epoetin alfa arm (**Figure 7**)
- Median duration of treatment was longer with luspatercept compared with epoetin alfa (**Figure 8**)
- The total number of doses received of luspatercept and epoetin alfa is shown in **Table 2**
- Main reasons for treatment discontinuation and key safety findings are presented in **Figures 9** and **10**, respectively

Figure 7. Duration of RBC-TI ≥ 12 weeks[a]



[a]In ITT responders during weeks 1-EOT. HR, hazard ratio; NE, not estimable.

Figure 8. Treatment exposure: duration of treatment

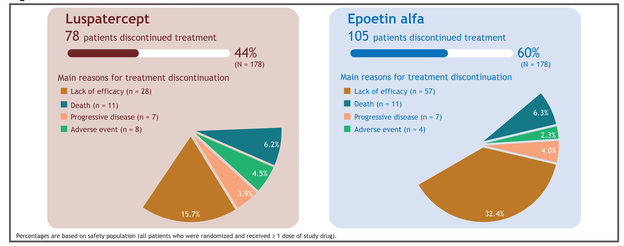


[a]ITT population: all randomized patients regardless of whether or not the patient received the study drug; [b]Safety population: all patients who were randomized and received ≥ 1 dose of study drug (2 patients in the epoetin alfa arm were randomized but not treated due to withdrawal of consent on the date of the first dose).

Table 2. Total number of doses received by dose level

Luspatercept (N = 178)	n/N (%)	Epoetin alfa (N = 176)	n/N (%)
1.0 mg/kg	1139/2950 (39)	337.5 IU/kg	377/6729 (5)
1.33 mg/kg	584/2950 (20)	450 IU/kg	1627/6729 (24)
1.75 mg/kg	1078/2950 (36)	787.5 IU/kg	1519/6729 (23)
0.40-0.80 mg/kg	149/2950 (5)	1050 IU/kg	3206/6729 (48)

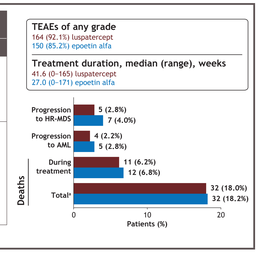
Figure 9. Treatment discontinuation



Percentages are based on safety population (all patients who were randomized and received ≥ 1 dose of study drug).

Figure 10. Key safety findings

Patients, n (%)	Luspatercept (N = 178) Any grade	Luspatercept (N = 178) Grade 3/4	Epoetin alfa (N = 176) Any grade	Epoetin alfa (N = 176) Grade 3/4
Hemo-related TEAEs				
Anemia	17 (9.6)	13 (7.3)	17 (9.7)	12 (6.8)
Thrombocytopenia	11 (6.2)	7 (3.9)	3 (1.7)	1 (0.6)
Neutropenia	9 (5.1)	7 (3.9)	13 (7.4)	10 (5.7)
Leukocytopenia	2 (1.1)	0	3 (1.7)	0
TEAEs of interest				
Fatigue	26 (14.6)	1 (0.6)	12 (6.8)	1 (0.6)
Diarrhea	26 (14.6)	2 (1.1)	20 (11.4)	1 (0.6)
Peripheral edema	23 (12.9)	0	12 (6.8)	0
Asthenia	22 (12.4)	0	25 (14.2)	1 (0.6)
Nausea	21 (11.8)	0	13 (7.4)	0
Dyspnea	21 (11.8)	7 (3.9)	13 (7.4)	2 (1.1)
TEE	8 (4.5)	5 (2.8)	5 (2.8)	1 (0.6)



Safety data are not exposure-adjusted.
[a]Deaths during treatment period and post-treatment period. TEE, thromboembolic event.

Conclusions

- The COMMANDS study achieved its primary endpoint, demonstrating that luspatercept is superior to ESA in ESA-naive TD LR-MDS
  - The primary endpoint was achieved in 59% of patients treated with luspatercept versus 31% with ESA
  - Median duration of response was 127 weeks versus 77 weeks in favor of luspatercept, which is ~ 1 year longer than with ESAs
- Luspatercept provides clinical benefit regardless of subgroups and baseline mutational burden
- Luspatercept has a manageable and predictable safety profile, consistent with previous clinical experience and convenient (Q3W) administration
- Luspatercept is the first and only therapy to demonstrate superiority in a head-to-head study against ESAs and brings a paradigm shift in the treatment of LR-MDS-associated anemia

References

1. Fenaux P, et al. *N Engl J Med* 2020;382:140-151.
2. Platzbecker U, et al. *Lancet Oncol* 2017;18:1338-1347.
3. Platzbecker U, et al. *J Clin Oncol* 2022;40:3800-3807.
4. Garcia-Manero G, et al. *Blood* 2022;139:624-629.

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