Overall survival and duration of red blood cell-transfusion independence for erythropoiesis-stimulating agent-naive patients with lower-risk myelodysplastic syndromes treated with luspatercept versus epoetin alfa in the COMMANDS trial

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*At the time of study.

Introduction

- Luspatercept is an erythroid-maturation agent that improves erythropoiesis[1,2]
- The primary analysis of the phase 3 COMMANDS trial (NCT03682536) showed superior efficacy of luspatercept versus epoetin alfa, with sustained and durable clinical benefit for the treatment of anemia among erythropoiesis-stimulating agent (ESA)-naive patients with transfusion-dependent lower-risk myelodysplastic syndromes (LR-MDS)[3,4]
- The results of the COMMANDS trial led to the approval of luspatercept for the treatment of anemia in ESA-naive patients with LR-MDS who may require transfusions[5]

Objective

- To report, for the first time, overall survival (OS) and updated long-term duration of response and safety results from the COMMANDS trial, with a median follow-up of > 2.5 years

Methods

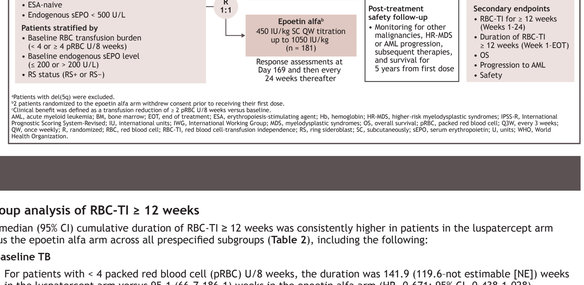
Study design

- COMMANDS is a global, phase 3, open-label, randomized controlled trial
- Study design and key eligibility criteria are presented in **Figure 1**
- Patients were randomly assigned to receive treatment with luspatercept or epoetin alfa

Endpoints (data cutoff: February 7, 2025)

- Red blood cell-transfusion independence (RBC-TI) for ≥ 12 weeks (Weeks 1-24)
- Duration of RBC-TI ≥ 12 weeks (Week 1-end of treatment [EOT])
- OS
- Progression to acute myeloid leukemia (AML)
- Safety

Figure 1. COMMANDS study design



[a]Patients with del(5q) were excluded.
[b]3 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose.
[c]Clinical benefit was defined as a transfusion reduction of ≥ 2 pRBC U/8 weeks versus baseline.
AML, acute myeloid leukemia; BM, bone marrow; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HR-MDS, higher-risk myelodysplastic syndromes; IPSS-R, International Prognostic Scoring System-Revised; IU, International units; IWG, International Working Group; MDS, myelodysplastic syndromes; OS, overall survival; pRBC, packed red blood cell; Q2W, every 2 weeks; QW, once weekly; R, randomized; RBC, red blood cell; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast; SC, subcutaneously; sEPO, serum erythropoietin; U, units; WHO, World Health Organization.

Results

Patients

- As of the data cutoff, 182 patients and 181 patients were randomly assigned to receive luspatercept and epoetin alfa, respectively
  - 154 patients in the luspatercept arm and 149 patients in the epoetin alfa arm had ≥ 1 dose escalation
- Baseline patient characteristics are shown in **Table 1**
- The median follow-up duration was > 2.5 years (30.6 months for the luspatercept arm and 28.8 months for the epoetin alfa arm)
  - The median treatment duration was 71.5 weeks and 44.0 weeks, respectively
  - As of the data cutoff, 41 and 18 patients were still on their respective treatments

Table 1. Baseline characteristics

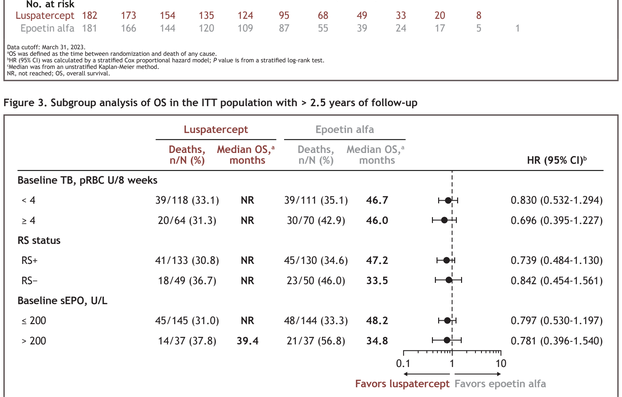
	Luspatercept (n = 182)	Epoetin alfa (n = 181)
Median age (IQR), years	74.0 (68-80)	74.0 (69-80)
Sex, n (%)		
Male	109 (59.9)	92 (50.8)
Female	73 (40.1)	89 (49.2)
Median Hb (IQR), g/dL	7.8 (7.1-8.2)	7.8 (7.1-8.3)
Median TB (IQR), RBC U/8 weeks	3.0 (2.0-4.0)	3.0 (2.0-4.0)
TB category, n (%)		
< 4 RBC U/8 weeks	118 (64.8)	111 (61.3)
≥ 4 RBC U/8 weeks	64 (35.2)	70 (38.7)
Median time since original MDS diagnosis (IQR),[a] months	8.0 (2.0-28.8)	5.1 (1.6-16.8)
sEPO category, n (%)		
≤ 200 U/L	145 (79.7)	144 (79.6)
> 200 to < 500 U/L	37 (20.3)	37 (20.4)
***SF3B1* mutation status, n (%)**		
Mutated	114 (62.6)	101 (55.8)
Non-mutated	65 (35.7)	72 (39.8)
RS status, n (%)		
RS+	133 (73.1)	130 (71.8)
RS−	49 (26.9)	50 (27.6)
Charlson Comorbidity Index,[b,c] mean (SD)	1.2 (1.0)	1.1 (1.2)

Data cutoff: March 31, 2023.
[a]Time since diagnosis of MDS was defined as the number of months from the date of diagnosis to the date of informed consent for the trial.
[b]Derived from medical history data.
[c]Data cutoff: February 7, 2025.
Hb, hemoglobin; MDS, myelodysplastic syndromes; RS, ring sideroblast; sEPO, serum erythropoietin; TB, transfusion burden; U, units.

Overall survival

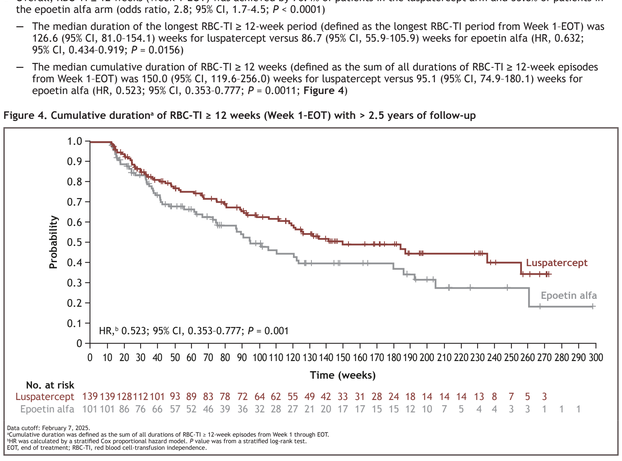
- Median OS was not reached in the luspatercept arm versus 46.0 months in the epoetin alfa arm (HR, 0.805; 95% CI, 0.565-1.146; **Figure 2**)
  - Similar trends in OS were observed in stratification subgroups, including those with high baseline transfusion burden (TB), ring sideroblast-negative (RS−) status, and low baseline serum erythropoietin (sEPO; **Figure 3**)

Figure 2. OS[a] in the ITT population with > 2.5 years of follow-up



Data cutoff: March 31, 2023.
[a]OS was defined as the time between randomization and death of any cause.
[b]HR (95% CI) was calculated by a stratified Cox proportional hazard model; *P* value is from a stratified log-rank test.
[c]Median was from an unstratified Kaplan-Meier method.
NR, not reached; OS, overall survival.

Figure 3. Subgroup analysis of OS in the ITT population with > 2.5 years of follow-up



Data cutoff: February 7, 2025.
[a]Median was from an unstratified Kaplan-Meier method.
[b]HR was calculated by an unstratified Cox proportional hazard model.
NR, not reached; OS, overall survival; pRBC, packed red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; TB, transfusion burden; U, units.

RBC-TI ≥ 12 weeks

- Overall, RBC-TI ≥ 12 weeks (Week 1-EOT) was achieved by 76.4% of patients in the luspatercept arm and 55.8% of patients in the epoetin alfa arm (odds ratio, 2.8; 95% CI, 1.7-4.5; *P* < 0.0001)
  - The median duration of the longest RBC-TI ≥ 12-week period (defined as the longest RBC-TI period from Week 1-EOT) was 126.6 (95% CI, 81.0-154.1) weeks for luspatercept versus 86.7 (95% CI, 55.9-105.9) weeks for epoetin alfa (HR, 0.632; 95% CI, 0.434-0.919; *P* = 0.0156)
  - The median cumulative duration of RBC-TI ≥ 12 weeks (defined as the sum of all durations of RBC-TI ≥ 12-week episodes from Week 1-EOT) was 150.0 (95% CI, 119.6-256.0) weeks for luspatercept versus 95.1 (95% CI, 74.9-180.1) weeks for epoetin alfa (HR, 0.523; 95% CI, 0.353-0.777; *P* = 0.0011; **Figure 4**)

Figure 4. Cumulative duration[a] of RBC-TI ≥ 12 weeks (Week 1-EOT) with > 2.5 years of follow-up

Data cutoff: February 7, 2025.
[a]Cumulative duration was defined as the sum of all durations of RBC-TI ≥ 12-week episodes from Week 1 through EOT.
[b]HR was calculated by a stratified Cox proportional hazard model. *P* value was from a stratified log-rank test.
EOT, end of treatment; RBC-TI, red blood cell-transfusion independence.

Subgroup analysis of RBC-TI ≥ 12 weeks

- The median (95% CI) cumulative duration of RBC-TI ≥ 12 weeks was consistently higher in patients in the luspatercept arm versus the epoetin alfa arm across all prespecified subgroups (**Table 2**), including the following:
  - **Baseline TB**
    - For patients with < 4 packed red blood cell (pRBC) U/8 weeks, the duration was 141.9 (119.6-not estimable [NE]) weeks in the luspatercept arm versus 95.1 (66.7-186.1) weeks in the epoetin alfa arm (HR, 0.671; 95% CI, 0.438-1.028)
    - For patients with ≥ 4 pRBC U/8 weeks, the duration was 184.4 (66.9-NE) weeks versus 110.9 (33.9-NE) weeks (HR, 0.687; 95% CI, 0.332-1.421)
  - **RS status**
    - For patients with RS-positive status, the duration was 126.6 (93.0-235.9) weeks in the luspatercept arm versus 73.1 (41.6-110.9) weeks in the epoetin alfa arm (HR, 0.614; 95% CI, 0.413-0.914)
    - For patients with RS− status, the duration was NE (135.9-NE) versus 205.1 (95.1-NE) weeks (HR, 0.531; 95% CI, 0.184-1.530)
  - **Baseline sEPO**
    - For patients with sEPO ≤ 200 U/L, the duration was 187.3 (125.7-NE) weeks in the luspatercept arm versus 101.4 (74.9-180.1) weeks in the epoetin alfa arm (HR, 0.621; 95% CI, 0.417-0.924)
    - For patients with sEPO > 200 U/L, the duration was 48.3 (26.3-132.6) weeks versus 24.6 (14.9-NE) weeks (HR, 0.804; 95% CI, 0.286-2.265)

Table 2. Subgroup analysis of cumulative duration[a] of RBC-TI ≥ 12 weeks (Week 1-EOT) with > 2.5 years of follow-up

Median duration (95% CI), weeks	Luspatercept	Epoetin alfa	HR (95% CI)[b]
Baseline TB, pRBC U/8 weeks			
< 4	141.9 (119.6-NE)	95.1 (66.7-186.1)	0.671 (0.438-1.028)
≥ 4	184.4 (66.9-NE)	110.9 (33.9-NE)	0.687 (0.332-1.421)
RS status			
RS+	126.6 (93.0-235.9)	73.1 (41.6-110.9)	0.614 (0.413-0.914)
RS−	NE (135.9-NE)	205.1 (95.1-NE)	0.531 (0.184-1.530)
Baseline sEPO, U/L			
≤ 200	187.3 (125.7-NE)	101.4 (74.9-180.1)	0.621 (0.417-0.924)
> 200	48.3 (26.3-132.6)	24.6 (14.9-NE)	0.804 (0.286-2.265)

Data cutoff: February 7, 2025.
[a]Cumulative duration was defined as the sum of all durations of RBC-TI ≥ 12-week episodes from Week 1 through EOT.
[b]HR was calculated by an unstratified Cox proportional hazard model.
EOT, end of treatment; NE, not estimable; pRBC, packed red blood cell; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast; sEPO, serum erythropoietin; TB, transfusion burden; U, units.

Safety and disease progression

- The safety of luspatercept was consistent with previous MDS studies, including the COMMANDS primary analysis[3] (**Table 3**)
- Overall, 2.2% of patients in the luspatercept arm and 5.6% of patients in the epoetin alfa arm experienced disease progression to higher-risk MDS (HR-MDS; **Table 4**)
  - 4.9% versus 4.4% of patients experienced disease progression to AML
- The total number of deaths on and post treatment from all patients who received ≥ 1 dose were 59 (32.4%) in the luspatercept arm and 69 (38.5%) in the epoetin alfa arm

Table 3. Summary of safety with > 2.5 years of follow-up

	Luspatercept (n = 182)		Epoetin alfa (n = 179)	
	n (%)	EAIR/100 PY[b]	n (%)	EAIR/100 PY[b]
Patients with ≥ 1 treatment-emergent EOI[b]	125 (68.7)	73.7	97 (54.2)	69.6
Asthenia (including fatigue, malaise, and lethargy)	63 (34.6)	25.9	48 (26.8)	27.1
Hypertension	32 (17.6)	11.8	19 (10.6)	9.6
Malignancies	22 (12.1)	7.1	16 (8.9)	7.8
Fractures	20 (11.0)	6.7	23 (12.8)	11.2
Kidney toxicity	20 (11.0)	6.7	13 (7.3)	6.4
Premalignant disorders	13 (7.1)	4.1	14 (7.8)	6.5
Immunogenicity hypersensitivity type reactions	10 (5.5)	3.2	3 (1.7)	1.4
Liver toxicity	7 (3.8)	2.2	6 (3.4)	2.8
Immunogenicity injection local type reactions	5 (2.7)	1.6	1 (0.6)	0.5
EMH masses	1 (0.5)	0.3	0	0

Data cutoff: February 7, 2025.
[a]EAIR/100 PY is the average number of patients with the specific treatment-emergent EOI divided by the total exposure time (in years) to the event. Exposure time was the overall treatment exposure for patients without the event and was the time from event start date for patients with the event.
[b]Among the safety population, defined as all randomized patients who received ≥ 1 dose of study treatment (and by treatment received).
EAIR, exposure-adjusted incidence rate; EMH, extramedullary hematopoiesis; EOI, event of interest; PY, person-year.

Table 4. Summary of disease progression with > 2.5 years of follow-up

	Luspatercept (n = 182)	Epoetin alfa (n = 179)
Progression to HR-MDS,[a] n (%)	4 (2.2)	10 (5.6)
HR-MDS incidence rate per 100 PY[b] (95% CI)	0.85 (0.32-2.26)	2.41 (1.30-4.48)
HR (95% CI)[c]	0.388 (0.120-1.250); *P* = 0.1003	
Median time to HR-MDS progression from treatment start date (95% CI), months	NE (NE-NE)	NE (NE-NE)
Progression to AML,[d] n (%)	9 (4.9)	8 (4.4)
AML incidence rate per 100 PY[b] (95% CI)	1.91 (1.00-3.68)	1.91 (0.95-3.81)
HR (95% CI)[c]	1.110 (0.420-2.932); *P* = 0.8326	
Median time to AML progression from initial MDS diagnosis (95% CI), months	NE (132.1-NE)	NE (NE-NE)

Data cutoff: February 7, 2025.
[a]Higher-risk category comprises high- and very high-risk categories per IPSS-R.
[b]PY was calculated from the treatment start date to the HR-MDS onset date or from the randomization date to AML onset date, or to the last follow-up date for patients without progression to HR-MDS or AML.
[c]HR (95% CI) was calculated by a stratified Cox proportional hazard model; *P* value was calculated from a stratified log-rank test.
[d]Based on the ITT population (luspatercept, n = 182; epoetin alfa, n = 181).
AML, acute myeloid leukemia; HR-MDS, higher-risk myelodysplastic syndromes; IPSS-R, International Prognostic Scoring System-Revised; MDS, myelodysplastic syndromes; NE, not estimable; PY, person-year.

Conclusions

- In this first report of OS for the COMMANDS trial, patients who received luspatercept showed a trend for improved survival versus those who received epoetin alfa, with median OS not reached for luspatercept and with a 20% lower risk of death compared with patients treated with epoetin alfa
  - The positive OS trend with luspatercept was observed across prespecified subgroups, including high baseline TB, RS−, and low sEPO populations
  - Extended follow-up is ongoing
- At a median follow-up of > 2.5 years, luspatercept continued to improve response rate and offered a longer duration of response versus epoetin alfa
  - Significantly more patients achieved RBC-TI ≥ 12 weeks with luspatercept versus epoetin alfa
  - Median cumulative duration of RBC-TI ≥ 12 weeks was ~1 year longer with luspatercept versus epoetin alfa
- Safety results remained consistent with the known safety profile of luspatercept in MDS
  - Fewer patients in the luspatercept arm progressed to HR-MDS compared with epoetin alfa
- Luspatercept provided prolonged responses and the potential for extended survival, supporting a new standard of care for anemia in LR-MDS

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