Real-world hemoglobin outcomes of patients with lower-risk myelodysplastic syndromes receiving first-line luspatercept or first-line erythropoiesis-stimulating agents in the US

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Introduction

- More than 80% of patients with lower-risk myelodysplastic syndromes (LR-MDS) have anemia, which is associated with a higher risk of cardiac events and deaths and lower quality of life
- The treatment goal for anemic patients with LR-MDS is to maintain a hemoglobin (Hb) level between 10 and 12 g/dL
- While erythropoiesis-stimulating agents (ESAs) have been the mainstay of anemia treatment in LR-MDS, 68% of patients receiving ESAs experience treatment failure[1]
  - Such patients often receive red blood cell (RBC) transfusions for anemia management; however, prolonged RBC-transfusion dependence (RBC-TD) can worsen disease prognosis
- Luspatercept, which stimulates early- and late-stage erythropoiesis, was approved as first-line (1L) anemia treatment for LR-MDS by the US FDA in August 2023 based on data from the COMMANDS trial[2]
- Patients in the COMMANDS trial achieving Hb ≥ 10 g/dL experienced durable RBC-transfusion independence (RBC-TI) and improved quality of life regardless of therapy[3,4]
- Current real-world evidence on Hb outcomes associated with 1L luspatercept treatment among patients with LR-MDS is limited
  - Such data on 1L luspatercept from real-world settings will further contextualize findings from the COMMANDS trial and may help to inform clinical management of LR-MDS

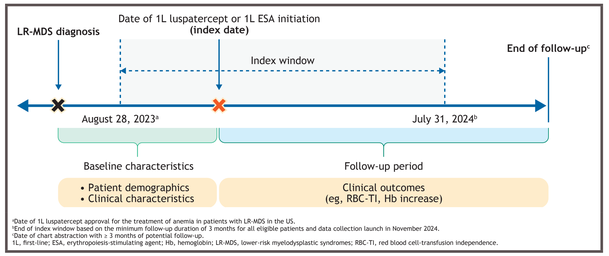
Objective

- To assess Hb and transfusion outcomes of patients with LR-MDS receiving 1L luspatercept or 1L ESAs after 1L luspatercept approval in the US

Methods

- A retrospective observational review of medical records of patients with LR-MDS receiving 1L luspatercept or 1L ESA was conducted (**Figure 1**)
- Physicians were recruited from an anonymized research panel and were required to fulfill the following criteria: (1) be hematologists, hematologist oncologists, or medical oncologists; (2) have been in practice for ≥ 2 years; (3) have treated ≥ 3 patients with myelodysplastic syndromes in the past year; (4) be the main decision-maker regarding patients' myelodysplastic syndromes treatment; and (5) have the right to access patients' medical records
- Data were collected using a customized electronic data collection form between November 2024 and March 2025
- Patient selection criteria are shown in **Table 1**

Figure 1. Study design



[a]Date of 1L luspatercept approval for the treatment of anemia in patients with LR-MDS in the US.
[b]End of index window based on the minimum follow-up duration of 3 months for all eligible patients and data collection launch in November 2024.
[c]Date of chart abstraction with ≥ 3 months of potential follow-up.
1L, first-line; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LR-MDS, lower-risk myelodysplastic syndromes; RBC-TI, red blood cell-transfusion independence.

Table 1. Patient selection criteria

Inclusion criteria	Exclusion criteria
• Documented diagnosis of primary or secondary MDS confirmed through bone marrow testing within -30/+365 days of MDS diagnosis date • Documented determination of LR-MDS as measured by the IPSS or IPSS-R at or before index treatment (ie, 1L luspatercept or 1L ESA) initiation • Received 1L luspatercept or 1L ESA treatment for anemia any time between August 28, 2023, and July 31, 2024 — Combination therapy with ESA (within 7 days before to any time after luspatercept start) was allowed for the 1L luspatercept cohort • ≥ 18 years of age at index date • Known vital status (ie, alive or deceased) • Availability of patient's complete medical record	• History of AML prior to MDS diagnosis • Prior treatment with hypomethylating agents, disease-modifying agents (including lenalidomide), other immunosuppressants/ immunomodulatory agents, or MDS-directed chemotherapy • Participated in a clinical trial for the treatment of MDS before or while on index treatment • Evidence of other malignant neoplasms during the 12 months before diagnosis of MDS • Received stem cell transplant prior to index treatment initiation • Receipt of combination therapy with hypomethylating agents, luspatercept (for 1L ESA cohort), lenalidomide, other immunosuppressants/immunomodulatory agents, or other MDS-directed chemotherapy

1L, first-line; AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System-Revised; LR-MDS, lower-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes.

Study measures and analysis plan

- Study measures included patients' demographic and clinical characteristics, 1L luspatercept and 1L ESA treatment characteristics, and hematological outcomes during the first 6 months of index treatment
- Descriptive statistics were used to summarize study measures
- The primary Hb outcome was achievement of Hb ≥ 10 g/dL during the first 6 months of index treatment
  - The eligible study population for this assessment included patients with baseline Hb < 10 g/dL before 1L treatment initiation and known Hb during the first 6 months of treatment
  - Time to achieving Hb ≥ 10 g/dL was estimated using Kaplan-Meier (KM) analysis
    - Multivariable Cox regression was conducted to compare the likelihood of achieving Hb ≥ 10 g/dL for the 1L luspatercept versus 1L ESA cohorts
  - The proportion of patients achieving Hb ≥ 10 g/dL was also evaluated among key clinical subgroups: patients with (1) baseline Hb < 8 g/dL, (2) ring sideroblast (RS)-negative status, (3) baseline serum erythropoietin (sEPO) < 200 IU/L, and (4) RS-negative status with baseline sEPO < 200 IU/L
- A secondary outcome was assessment of RBC-TI maintenance for ≥ 12 weeks among patients who achieved Hb ≥ 10 g/dL versus those who did not during the first 6 months of index treatment
  - Eligible patients for this assessment included patients with known RBC data during the baseline and follow-up periods and receipt of ≥ 8 weeks of 1L treatment

Results

- A total of 117 physicians contributed data for 418 patients with LR-MDS (1L luspatercept: 213; 1L ESA: 205)
- Physician and patient characteristics are presented in **Table 2** and **Table 3**, respectively

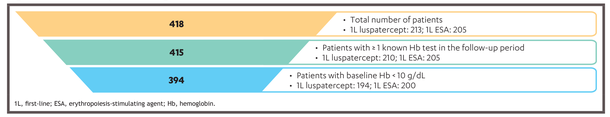
Table 2. Physician characteristics

	Overall (N = 117)	Contributed to 1L luspatercept (n = 78)	Contributed to 1L ESA (n = 70)
Primary medical specialty, n (%)			
Hematologist	3 (2.6)	3 (3.8)	1 (1.4)
Hematologist oncologist	108 (92.3)	72 (92.3)	65 (92.9)
Medical oncologist	6 (5.1)	3 (3.8)	4 (5.7)
Time managing treatment of hematology/oncology patients, median (IQR), years	14.0 (8.0-20.0)	14.0 (8.0-20.0)	14.5 (10.0-20.0)
Patients with MDS treated in past 12 months, median (IQR), n	36.0 (25.0-55.0)	35.5 (25.0-55.0)	34.0 (22.0-55.0)
Primary practice setting, n (%)			
Academic/teaching hospital or medical center	56 (47.9)	40 (51.3)	35 (50.0)
Community/non-academic hospital or medical center	61 (52.1)	38 (48.7)	35 (50.0)
Size of primary practice setting,[a] n (%)			
Individual practice	3 (2.6)	1 (1.3)	2 (2.9)
Small/intermediate practice	41 (35.0)	31 (39.7)	21 (30.0)
Large practice	73 (62.4)	46 (59.0)	47 (67.1)
Geographic region, n (%)			
Northeast	29 (24.8)	18 (23.1)	20 (28.6)
South	48 (41.0)	32 (41.0)	30 (42.9)
Midwest	10 (8.5)	9 (11.5)	5 (7.1)
West	30 (25.6)	19 (24.4)	15 (21.4)
Participated in a clinical trial for MDS treatments, n (%)			
Yes	24 (20.5)	19 (24.4)	12 (17.1)
No	93 (79.5)	59 (75.6)	58 (82.9)

[a]Individual practice defined as 1 hematologist/oncologist in practice; small/intermediate practice defined as 2 to 9 hematologists/oncologists/subspecialists in practice; and large practice defined as ≥ 10 hematologists/oncologists/subspecialists in practice.
1L, first-line; ESA, erythropoiesis-stimulating agent; MDS, myelodysplastic syndromes.

- KM and multivariable analyses were performed among 394 eligible patients with baseline Hb < 10 g/dL and known Hb during the follow-up period (1L luspatercept: 194; 1L ESA: 200; **Figure 2**)
- Among eligible 1L luspatercept patients (n = 194), 22.2% had intermediate-risk status per the International Prognostic Scoring System (IPSS)/International Prognostic Scoring System-Revised (IPSS-R), 30.9% had sEPO < 200 IU/L, 43.3% had RS-negative status, 45.4% had baseline Hb < 8 g/dL, and 22.7% were RBC-TD at baseline (defined as ≥ 2 RBC units/8 weeks)
- Among eligible 1L ESA patients (n = 200), 13.0% had intermediate-risk status per the IPSS/IPSS-R, 54.5% had sEPO < 200 IU/L, 59.0% had RS-negative status, 42.5% had baseline Hb < 8 g/dL, and 17.0% were RBC-TD at baseline

Figure 2. Number of patients eligible for outcome assessment



1L, first-line; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.

- More patients in the 1L luspatercept cohort versus the 1L ESA cohort achieved Hb ≥ 10 g/dL during the first 6 months of treatment (69.6% vs 58.0%) with a quicker response time (KM median [95% CI], 2.3 months [2.1-3.0] vs 5.3 months [3.2-not estimable]; $P = 0.003$)
- The adjusted hazard ratio (aHR) for achieving Hb ≥ 10 g/dL with 1L luspatercept versus 1L ESA was 1.44 (95% CI, 1.05-1.98; $P = 0.023$), indicating that patients receiving 1L luspatercept had a 44% higher chance of achieving Hb ≥ 10 g/dL at any given time versus patients receiving 1L ESA, controlling for other patient characteristics (**Table 4**)
- Patients with baseline Hb ≥ 8 g/dL had a higher chance of achieving Hb ≥ 10 g/dL (aHR, 2.01 [95% CI, 1.51-2.69]; $P < 0.001$); in contrast, patients who were RBC-TD at baseline had a lower chance (aHR, 0.51 [95% CI, 0.33-0.76]; $P = 0.001$; **Table 4**)

Table 4. Key factors associated with achieving Hb ≥ 10 g/dL

Variables[a]	aHR	95% CI	*P* value
Index treatment			
1L ESA	1.00 (Reference)		
1L luspatercept	1.44	1.05-1.98	0.023
Any karyotype/chromosomal abnormality			
Yes	1.00 (Reference)		
No	1.92	1.26-2.91	0.002
Not assessed	2.89	1.24-6.73	0.014
ECOG performance status score at index treatment initiation			
0/1/unknown	1.00 (Reference)		
≥ 2	0.59	0.37-0.92	0.019
Baseline RS status			
RS+	1.00 (Reference)		
RS−	0.70	0.48-1.02	0.067
Unknown	0.50	0.31-0.79	0.003
Baseline sEPO level, IU/L			
< 200	1.00 (Reference)		
≥ 200 to < 500	0.90	0.63-1.30	0.587
≥ 500	0.90	0.58-1.41	0.658
Unknown	1.00	0.66-1.52	0.991
Baseline Hb level, g/dL			
< 8	1.00 (Reference)		
≥ 8	2.01	1.51-2.69	< 0.001
Unknown	1.73	0.97-3.06	0.062
Baseline RBC transfusion burden			
Not RBC-TD (< 2 RBC U/8 weeks)	1.00 (Reference)		
RBC-TD (≥ 2 RBC U/8 weeks)	0.51	0.33-0.76	0.001
Unknown baseline RBC need	1.56	0.88-2.77	0.128

[a]Other variables in the multivariable Cox regression model included age, race, sex, primary health insurance, treatment setting, IPSS/IPSS-R risk status, number of genetic mutations, and *SF3B1* mutation status.
1L, first-line; aHR, adjusted hazard ratio; ECOG, Eastern Cooperative Oncology Group; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System-Revised; RBC, red blood cell; RBC-TD, red blood cell-transfusion dependent; RS, ring sideroblast; sEPO, serum erythropoietin; U, units.

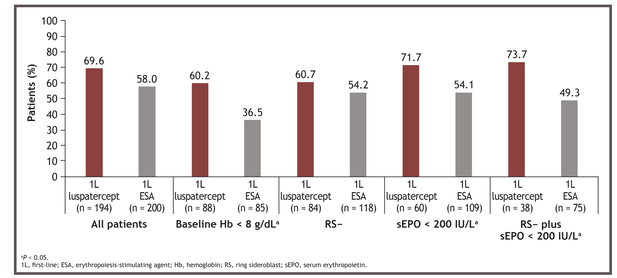
Table 3. Patient characteristics

	1L luspatercept (n = 213)	1L ESA (n = 205)
Age at index treatment initiation, median (IQR), years	68.4 (61.4-74.5)	66.6 (59.6-74.8)
Sex, n (%)	n = 211	n = 204
Male	119 (56.4)	125 (61.3)
Female	92 (43.6)	79 (38.7)
Race,[a] n (%)		
White	146 (68.5)	139 (67.8)
African American/Black	50 (23.5)	48 (23.4)
Other	14 (6.6)	15 (7.3)
Unknown	5 (2.3)	5 (2.4)
Primary insurance at index treatment initiation, n (%)		
Commercial insurance	72 (33.8)	83 (40.5)
Medicare	118 (55.4)	88 (42.9)
Medicaid	7 (3.3)	13 (6.3)
Other/unknown/uninsured	16 (7.5)	21 (10.3)
Treatment setting, n (%)		
Academic/teaching hospital or medical center	115 (54.0)	106 (51.7)
Community/non-academic hospital or medical center	98 (46.0)	99 (48.3)
Geographic region, n (%)		
Northeast	50 (23.5)	58 (28.3)
South	81 (38.0)	100 (48.8)
Midwest	33 (15.5)	11 (5.4)
West	49 (23.0)	36 (17.6)
Total duration of follow-up, median (IQR), months	10.8 (7.2-14.5)	11.2 (6.5-13.7)
Time from MDS diagnosis to index treatment initiation, median (IQR), months	0.9 (0.5-1.9)	0.7 (0.3-1.5)
Year of index treatment initiation, n (%)	n = 209	n = 205
2023	84 (40.2)	107 (52.2)
2024	125 (59.8)	98 (47.8)
Patients receiving concomitant ESA with 1L luspatercept, n (%)	4 (1.9)	-
Observed duration of index treatment, median (IQR), months	8.3 (5.1-12.9)	7.8 (5.2-12.3)
IPSS/IPSS-R risk status at index treatment initiation, n (%)		
Very low/low risk	163 (76.5)	179 (87.3)
Intermediate risk	50 (23.5)	26 (12.7)
Number of genetic mutations, n (%)		
0	69 (32.4)	106 (51.7)
1	100 (46.9)	80 (39.0)
≥ 2	44 (20.7)	19 (9.3)
***SF3B1* mutation status, n (%)**		
Mutated (ie, positive)	100 (46.9)	26 (12.7)
Non-mutated	101 (47.4)	147 (71.7)
Unknown/test not performed	12 (5.6)	32 (15.6)
Any karyotype/chromosomal abnormalities, n (%)	n = 210	n = 194
Yes	41 (19.5)	27 (13.9)
No	169 (80.5)	167 (86.1)
ECOG performance status score at index treatment initiation, n (%)	n = 212	n = 201
0/1	188 (88.7)	167 (83.1)
≥ 2	24 (11.3)	34 (16.9)
RS status[b] at index treatment initiation, n (%)	n = 171	n = 146
RS+	82 (48.0)	27 (18.5)
RS−	89 (52.0)	119 (81.5)
sEPO levels at index treatment initiation, n (%), IU/L	n = 170	n = 150
< 200	63 (37.1)	111 (74.0)
≥ 200 to < 500	54 (31.8)	35 (23.3)
≥ 500	53 (31.2)	4 (2.7)
Hb levels before index treatment initiation	n = 197	n = 192
Median (IQR), g/dL	8.0 (7.1-8.6)	8.0 (7.0-8.9)
Hb level, n (%), g/dL	n = 213	n = 205
< 8	88 (41.3)	85 (41.5)
8 to < 10	93 (43.7)	102 (49.8)
≥ 10	16 (7.5)	5 (2.4)
Baseline RBC transfusion burden,[c] n (%)	n = 201	n = 202
No baseline RBC need (0 RBC U/8 weeks)	106 (52.7)	129 (63.9)
Not RBC-TD (< 2 RBC U/8 weeks)	42 (20.9)	37 (18.3)
RBC-TD (≥ 2 RBC U/8 weeks)	48 (23.9)	34 (16.8)
Unknown baseline RBC need	5 (2.5)	2 (1.0)

[a]Multiple responses were permitted; data may exceed 100%.
[b]RS-positive status was defined as RS levels with a constitution of ≥ 15% erythroid precursors in bone marrow, or RS levels ≥ 5% and < 15% if an *SF3B1* mutation was present; RS-negative status was defined as RS levels < 5% or 5% to 15% with absence of *SF3B1* mutation.
[c]Among patients with known baseline transfusion status.
1L, first-line; ECOG, Eastern Cooperative Oncology Group; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System-Revised; MDS, myelodysplastic syndromes; RBC, red blood cell; RBC-TD, red blood cell-transfusion dependent; RS, ring sideroblast; sEPO, serum erythropoietin; U, units.

- The positive benefit of 1L luspatercept remained when evaluating key subgroups, with statistically significant differences seen among patients with baseline Hb < 8 g/dL, baseline sEPO < 200 IU/L, and RS-negative status with baseline sEPO < 200 IU/L (**Figure 3**)

Figure 3. Proportion of patients achieving Hb ≥ 10 g/dL stratified by treatment cohort and key subgroups



[a]*P* < 0.05.
1L, first-line; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; RS, ring sideroblast; sEPO, serum erythropoietin.

Maintenance of RBC-TI for ≥ 12 weeks

- Among 296 eligible patients, 82.2% of patients who achieved Hb ≥ 10 g/dL also maintained RBC-TI for ≥ 12 weeks during the first 6 months of index treatment (n = 152/185) versus 51.4% of patients who did not achieve Hb ≥ 10 g/dL (n = 57/111)
- Among patients who achieved Hb ≥ 10 g/dL, 90.9% receiving 1L luspatercept maintained RBC-TI for ≥ 12 weeks (n = 90/99) versus 72.1% receiving 1L ESA (n = 62/86; $P < 0.001$)

Limitations

- The population included in this study represents a convenience sample of patients with LR-MDS sourced from physicians willing to participate in the study; hence, the study findings may have limited generalizability
- Data were extracted by the treating physicians or their designated staff and, therefore, may be subject to data entry errors, lack of documentation, and abstraction burden; we anticipate both treatment cohorts to be similarly impacted by these factors
- The RBC transfusion burden and Hb levels were measured during the first 6 months of index treatment; thus, more longitudinal research is necessary to better understand the durability of response for 1L luspatercept and 1L ESA treatment

Conclusions

- During the first 6 months of treatment, patients treated with 1L luspatercept versus 1L ESA showed a greater and faster response rate of achieving Hb ≥ 10 g/dL, demonstrating significant clinical benefit of 1L luspatercept for Hb improvement compared with 1L ESA treatment in patients with LR-MDS
- Controlling for 1L treatment and patient characteristics, a statistically significant higher likelihood of Hb improvement was seen for patients with baseline Hb ≥ 8 g/dL
  - However, patients with baseline RBC-TD had a significantly lower probability of achieving Hb ≥ 10 g/dL
- Positive treatment effect of luspatercept compared with ESA in achieving Hb ≥ 10 g/dL was also seen among key patient subgroups
- Overall, a higher proportion of patients who achieved Hb ≥ 10 g/dL also maintained RBC-TI for ≥ 12 weeks during the first 6 months of treatment, demonstrating the clinical importance of achieving Hb ≥ 10 g/dL
  - This clinical benefit was observed among more patients receiving 1L luspatercept than 1L ESA
- These real-world findings highlight the treatment benefit of 1L luspatercept for Hb improvement and underscore the importance of early anemia treatment initiation in LR-MDS before patients' Hb levels drop below 8 g/dL and/or they become RBC-TD
  - These results complement the findings from the COMMANDS trial[5] and support luspatercept as a preferred 1L therapy for anemia in patients with LR-MDS

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