Real-world treatment patterns and outcomes of first-line luspatercept in patients with myelodysplastic syndromes in the United States

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Introduction

- Patients with lower-risk myelodysplastic syndromes (LR-MDS) often develop anemia, which can lead to transfusion dependency (TD) and highlights the need for strategies to improve quality of life and survival[1,2]
- In August 2023, luspatercept was approved in the United States for the first-line (1L) treatment of anemia in adults with LR-MDS who require red blood cell (RBC) transfusions and are naive to erythropoiesis-stimulating agents (ESAs) based on the phase 3 COMMANDS trial[3,4]
- Since its 2023 approval, real-world evidence on luspatercept as a 1L therapy in LR-MDS remains limited
- Furthermore, the effectiveness of second-line (2L) ESAs following 1L luspatercept discontinuation has not been evaluated in real-world settings

Objective

- To report patient characteristics, clinical outcomes, and treatment patterns of patients with myelodysplastic syndromes (MDS) receiving 1L luspatercept and receiving 2L ESAs following 1L luspatercept discontinuation in a real-world setting

Methods

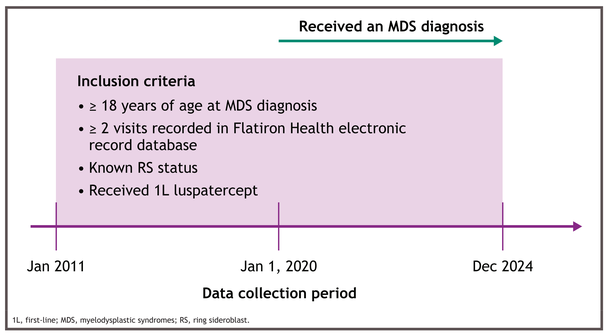
Study design

- This retrospective, observational US cohort study used the Flatiron Health electronic record database
  - Records were retrieved from January 2011 to December 2024
- Eligible patients received an MDS diagnosis after January 1, 2020, were ≥ 18 years of age at diagnosis, had known ring sideroblast (RS) status, and were included in the Flatiron Health electronic record database with ≥ 2 visits (**Figure 1**)

Outcomes

- Achievement of RBC-transfusion independence (RBC-TI; no transfusions for ≥ 12 weeks during Weeks 1-24 of treatment)
- Achievement of modified erythroid hematologic improvement (mHI-E)
  - For non-TD patients: mean increase in hemoglobin of ≥ 1.5 g/dL without RBC transfusions for ≥ 16 weeks during Weeks 1 to 24 of treatment
  - For TD patients: no transfusions for ≥ 16 weeks (for patients with low transfusion burden, defined as those receiving 1 to 7 RBC units during 16 weeks prior to luspatercept initiation) or a ≥ 50% reduction in transfusion burden versus baseline per 16 weeks (for patients with high transfusion burden, defined as those receiving ≥ 8 RBC units during 16 weeks prior to luspatercept initiation) during Weeks 1 to 24 of treatment
- Treatment patterns after failure
  - Dose escalations and treatment discontinuations
  - RBC-TI and mHI-E with 2L ESAs following 1L luspatercept discontinuation

Figure 1. Study design



1L, first-line; MDS, myelodysplastic syndromes; RS, ring sideroblast.

Results

Patients treated with 1L luspatercept

- In total, 320 patients were treated
- Baseline patient demographics and clinical characteristics are shown in **Table 1**
  - Of the patients with available data for each characteristic, 30.0% (96/320) were TD, 27.2% (87/320) had RS-negative status, and 66.5% (115/173) had serum erythropoietin (sEPO) < 200 U/L

Table 1. Baseline characteristics for patients treated with 1L luspatercept

Characteristic	1L luspatercept N = 320
Age, median (95% CI), years	78 (53-85)
Sex, n (%)	
Male	179 (55.9)
Female	141 (44.1)
RS status, n (%)	
RS+	233 (72.8)
RS−	87 (27.2)
Time from diagnosis to treatment initiation, median (range), months	1.6 (0-131.2)
Hb, median (95% CI), g/dL	
NTD	8.7 (6.9-11.1)
TD[a] (up to 16 weeks prior to index)	8.0 (6.5-9.9)
TB, n (%)	
NTD	224 (70.0)
TD[a] (up to 16 weeks prior to index)	96 (30.0)
sEPO levels, n (%), U/L	**n = 173**
< 200	115 (66.5)
≥ 200	58 (33.5)
IPSS-R risk level, n (%)	**n = 154**
High	5 (3.2)
Intermediate	32 (20.8)
Low	100 (64.9)
Very low	17 (11.0)

[a]TD was defined as ≥ 1 RBC unit during 16 weeks prior to luspatercept initiation.
1L, first-line; Hb, hemoglobin; IPSS-R, International Prognostic Scoring System-Revised; NTD, non-transfusion dependent; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; TB, transfusion burden; TD, transfusion dependent; U, units.

Treatment modifications

- Luspatercept was initiated at a 1 mg/kg dose in the majority of patients with a documented initial dose (98.9% [263/266]; **Table 2**)
- Overall, 27.5% of patients (88/320) received a dose escalation
  - Of those, 86.4% (76/88) escalated from 1 to 1.33 mg/kg, and 52.3% (46/88) escalated from 1.33 to 1.75 mg/kg
  - The median time to first dose escalation was 3.5 months
- Luspatercept was discontinued in 28.1% of patients (90/320)
  - Of those, 36.7% (33/90) discontinued before receiving the maximum luspatercept dose (1.75 mg/kg)
  - The primary reason for discontinuation was a lack of response (58.4% among all patients who discontinued [52/90] and 33.3% among patients who discontinued before reaching the maximum dose [11/33])

Achievement of RBC-TI and mHI-E

- At a median follow-up of 8.8 months (~38.2 weeks), RBC-TI for ≥ 12 weeks during Weeks 1 to 24 was achieved in 61.5% of TD patients (59/96; **Figure 2**)
  - Data were consistent across subgroups, with 53.3% of RS-negative patients (16/30) and 69.2% of patients (18/26) with sEPO < 200 U/L achieving RBC-TI
- Of 293 patients with available data for mHI-E response, 50.9% (n = 149) achieved a response for ≥ 16 weeks during Weeks 1 to 24

2L ESA treatment following 1L luspatercept discontinuation

- Following 1L luspatercept discontinuation, 25.6% of patients (23/90) initiated 2L ESA therapy, 13 of whom were TD (**Table 3**)
- At a median follow-up of 5.7 months (~24.8 weeks), RBC-TI for ≥ 8 weeks during Weeks 1 to 24 of treatment was achieved in 38.5% of TD patients (5/13; **Figure 3**), with a median duration of response of 4.1 months (~17.8 weeks)
- Of 19 patients with available data for mHI-E response assessment, 26.3% (n = 5) achieved a response for ≥ 8 weeks during Weeks 1 to 24 (**Figure 3**), with a median duration of response of 4.2 months (~18.2 weeks)

Table 2. Treatment modifications for patients treated with 1L luspatercept

Modification	1L luspatercept N = 320
Luspatercept dose at initiation, n (%)	
0.8 mg/kg	2 (0.6)
1 mg/kg	263 (82.2)
1.33 mg/kg	0
1.75 mg/kg	1 (0.3)
Unknown/not documented	54 (16.9)
Patients receiving dose escalation, n (%)	
No	232 (72.5)
Yes	88 (27.5)
0.8-1 mg/kg	5 (5.7)
1-1.33 mg/kg	76 (86.4)
1-1.75 mg/kg	3 (3.4)
1.33-1.75 mg/kg	46 (52.3)
Luspatercept discontinuation, n (%)	
No	230 (71.9)
Yes	90 (28.1)
Before reaching maximum dose (1.75 mg/kg)	33 (36.7)
Luspatercept dose at discontinuation,[a,b] n (%)	**n = 89**
1 mg/kg	23 (25.8)
1.33 mg/kg	10 (11.2)
1.75 mg/kg	35 (39.3)

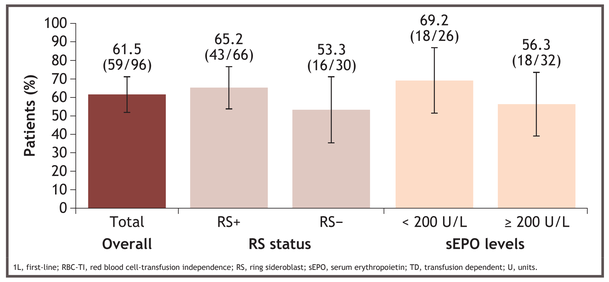
[a]Dose not known or documented for 21 patients.
[b]Dose at discontinuation was assessed among patients who discontinued luspatercept treatment and were alive at the time of discontinuation.
1L, first-line.

Table 3. Baseline characteristics for patients treated with 2L ESAs following 1L luspatercept discontinuation

Characteristic	2L ESAs following 1L luspatercept discontinuation N = 23
Age, median (95% CI), years	79 (60-85)
Sex, n (%)	
Male	12 (52.2)
Female	11 (47.8)
RS status, n (%)	
RS+	18 (78.3)
RS−	5 (21.7)
Hb, median (95% CI), g/dL	9 (6-11)
TB, n (%)	
NTD	10 (43.5)
TD[a] (up to 16 weeks prior to index)	13 (56.5)
sEPO levels, n (%), U/L	**n = 13**
< 200	5 (38.5)
≥ 200	8 (61.5)
IPSS-R risk level, n (%)	**n = 12**
High	1 (8.3)
Intermediate	2 (16.7)
Low	8 (66.7)
Very low	1 (8.3)

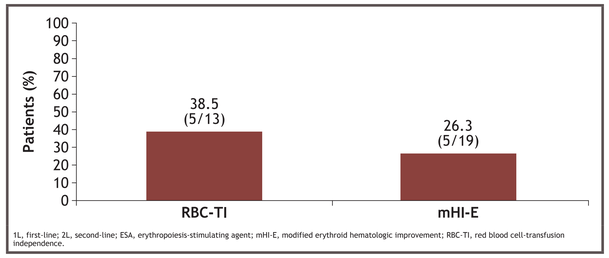
[a]TD was defined as ≥ 1 RBC unit during 16 weeks prior to luspatercept initiation.
1L, first-line; 2L, second-line; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IPSS-R, International Prognostic Scoring System-Revised; NTD, non-transfusion dependent; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; TB, transfusion burden; TD, transfusion dependent; U, units.

Figure 2. Achievement of RBC-TI for ≥ 12 weeks during Weeks 1 to 24 for TD patients treated with 1L luspatercept



1L, first-line; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast; sEPO, serum erythropoietin; TD, transfusion dependent; U, units.

Figure 3. Achievement of RBC-TI and mHI-E for ≥ 8 weeks during Weeks 1 to 24 for all patients treated with 2L ESAs following 1L luspatercept discontinuation



1L, first-line; 2L, second-line; ESA, erythropoiesis-stimulating agent; mHI-E, modified erythroid hematologic improvement; RBC-TI, red blood cell-transfusion independence.

Conclusions

- In real-world practice, among patients with MDS receiving 1L luspatercept who discontinued therapy, 36.7% did so before reaching the maximum dose, often due to perceived lack of response, highlighting the need for education on optimal dosing protocols
- Patients with MDS treated with 1L luspatercept achieved RBC-TI and mHI-E, with response rates comparable to those observed in the registrational clinical trial[4]
- Therapeutic benefits with 1L luspatercept were observed across all subgroups, including RS-negative and sEPO ≥ 200 U/L populations
- 2L ESAs remained an effective treatment following 1L luspatercept discontinuation, with observed responses consistent with the expected efficacy of ESAs in routine clinical care
- These findings highlight the clinical benefit of luspatercept in ESA-naive patients, demonstrating its effectiveness for patients with MDS in a real-world setting

References

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