First-line luspatercept versus erythropoiesis-stimulating agents for anemia in lower-risk myelodysplastic syndromes: a real-world analysis from Florida Cancer Specialists & Research Institute

MDS-1121

Gustavo Fonseca,[1] Amanda K. Warner,[1] Carmelo Alonso,[2] Christian Okitondo,[1] Hannah Dracos,[1] Nisha Singh,[2] Samantha Slaff[2]

[1]Florida Cancer Specialists & Research Institute, Tampa, FL, USA; [2]Bristol Myers Squibb, Lawrenceville, NJ, USA

Introduction

- Anemia is the most common cytopenia in patients with lower-risk myelodysplastic syndromes (LR-MDS), affecting > 80% of patients, and is associated with symptom burden, frequent red blood cell (RBC) transfusion requirements, and reduced health-related quality of life[1,2]
- Historically, erythropoiesis-stimulating agents (ESAs) were the only treatment option for LR-MDS anemia but they are hindered by limited response rates and durability[3,4]
- Luspatercept is a first-in-class erythroid maturation agent that binds to select transforming growth factor-beta superfamily ligands to reduce SMAD2/3 signaling, and it enhances early- and late-stage erythropoiesis and improves iron homeostasis[5]
- Luspatercept was approved for the first-line treatment of anemia in adults with LR-MDS in August 2023 based on its superior efficacy over ESAs in the phase 3 COMMANDS trial[6,7]
- Real-world data on the effectiveness of luspatercept as a first-line treatment remain limited

Objective

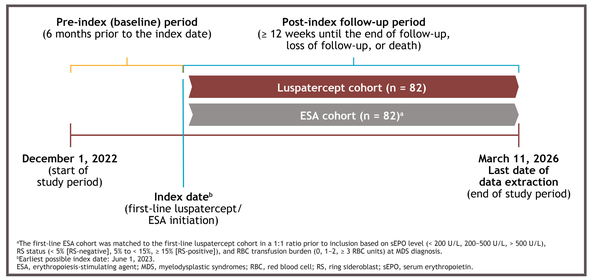
- To evaluate the comparative effectiveness of first-line luspatercept versus ESAs in patients with LR-MDS treated at Florida Cancer Specialists & Research Institute (FCS) community oncology sites

Methods

Study overview

- This was a non-interventional, retrospective review of clinical data from the FCS databases and electronic medical records of patients with LR-MDS (**Figure 1**)
  - The first-line ESA cohort was matched to the first-line luspatercept cohort in a 1:1 ratio prior to inclusion based on serum erythropoietin (sEPO) level (< 200 U/L, 200–500 U/L, > 500 U/L), ring sideroblast (RS) status (< 5% [RS-negative], 5% to < 15%, ≥ 15% [RS-positive]), and RBC transfusion burden (0, 1–2, ≥ 3 RBC units)

Figure 1. Study design



[a]The first-line ESA cohort was matched to the first-line luspatercept cohort in a 1:1 ratio prior to inclusion based on sEPO level (< 200 U/L, 200–500 U/L, > 500 U/L), RS status (< 5% [RS-negative], 5% to < 15%, ≥ 15% [RS-positive]), and RBC transfusion burden (0, 1–2, ≥ 3 RBC units) at MDS diagnosis.
[b]Earliest possible index date: June 1, 2023.
ESA, erythropoiesis-stimulating agent; MDS, myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin.

Patient eligibility criteria

Inclusion criteria	Exclusion criterion
• ≥ 18 years of age • Initial MDS diagnosis at or before luspatercept or ESA initiation • LR-MDS diagnosis[a] • Luspatercept or ESA treatment as first-line therapy[b,c] • ≥ 12 weeks of follow-up data available from luspatercept or ESA initiation[d] • ≥ 6 months of baseline data available	• Participation in a luspatercept or ESA clinical trial at any time prior to luspatercept or ESA receipt

[a]Defined as an IPSS score of low or intermediate-1; IPSS-R score of very low, low, or intermediate; or IPSS-M score of very low, low, or moderate low at the time of diagnosis.
[b]Treatment naive prior to luspatercept or ESA initiation.
[c]Patients who previously used an ESA for chronic kidney disease were not eligible.
[d]Patients who died within this period were included.
ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System; IPSS-M, International Prognostic Scoring System-Molecular; IPSS-R, International Prognostic Scoring System-Revised; LR-MDS, lower-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes.

Study outcomes

- Change from baseline in hemoglobin (Hb) levels at Weeks 12, 16, and 24
  - Hb levels taken > 14 days after a prior infusion or within 3 days before a next transfusion (for patients receiving regular transfusions) were included in these analyses
- Proportion of patients achieving an Hb rise of ≥ 1.5 g/dL from luspatercept or ESA initiation to Week 12
- Proportion of patients achieving RBC-transfusion independence (RBC-TI) for ≥ 12 weeks with a concurrent mean Hb rise of ≥ 1.5 g/dL
- Mean rise in Hb levels from luspatercept or ESA initiation to Week 12 by subgroups, including RS status category (RS-negative, RS-positive), sEPO level category (< 200 U/L), RS status category and sEPO level at diagnosis (RS-negative and sEPO < 200 U/L), and transfusion status (non-transfusion dependent [NTD], transfusion dependent [TD])
- Proportion of patients achieving RBC-TI for ≥ 12 weeks with a concurrent mean Hb rise of ≥ 1.5 g/dL at Week 12 with luspatercept versus ESA by the same subgroups
- Patients were censored from analyses of Hb levels and RBC-TI at the time of treatment discontinuation, at last follow-up, upon starting concurrent treatments that impact Hb levels, or upon starting second-line treatment
- Treatment discontinuation and reasons for discontinuation
- Proportion of patients with progression to acute myeloid leukemia (AML)

Results

Baseline patient characteristics

- The median (interquartile range [IQR]) duration of follow-up from first-line treatment initiation was numerically shorter (52.0 [36.2–84.8] weeks) for luspatercept than for ESA (67.5 [45.4–103.5] weeks) likely due to the delay in first-line luspatercept uptake following approval
- Within the variables matched across the luspatercept and ESA cohorts at diagnosis, 56.1% of patients were RS-negative (RS < 5%), 53.7% had sEPO < 200 U/L, and 79.0% had no RBC transfusions in the prior 8 weeks; other baseline characteristics, including mean Hb (luspatercept, 9.0 g/dL; ESA, 9.1 g/dL), were well balanced (**Table 1**)
- Overall, 79.0% of patients in each cohort had no RBC transfusions in the 8 weeks before treatment initiation

Table 1. Baseline patient characteristics

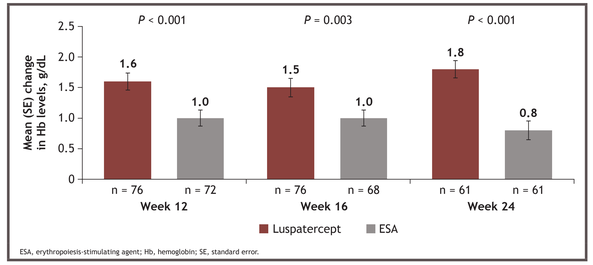
	Luspatercept n = 82	ESA n = 82
Age, median (IQR), years	78 (74–83)	78 (72–84)
Male, n (%)	53 (64.6)	50 (61.0)
Race, n (%)[a]		
White	75 (91.5)	77 (93.9)
Black	3 (3.7)	3 (3.7)
Ethnicity, n (%)[b]		
Not Hispanic/Latino	59 (72.0)	65 (79.3)
Hispanic/Latino	2 (2.4)	6 (7.3)
Duration of follow-up, mean (SD), weeks	59.0 (29.6)	72.9 (36.5)
RS status, n (%)		
< 5% (RS−)	46 (56.1)	46 (56.1)
5% to < 15%	3 (3.7)	3 (3.7)
≥ 15% (RS+)	21 (25.6)	21 (25.6)
Status unknown	4 (4.9)	4 (4.9)
Unavailable	8 (9.8)	8 (9.8)
sEPO level, n (%)		
< 200 U/L	44 (53.7)	44 (53.7)
200–500 U/L	4 (4.9)	4 (4.9)
> 500 U/L	0	0
Unknown	34 (41.5)	34 (41.5)
ECOG PS score, n (%)		
0	23 (28.0)	21 (25.6)
1	43 (52.4)	30 (36.6)
2	8 (9.8)	14 (17.1)
3	0	1 (1.2)
4	0	0
Unknown	8 (9.8)	16 (19.5)
IPSS, n (%)[c]		
Very low	11 (13.4)	17 (20.7)
Low	54 (65.9)	48 (58.5)
Moderate low	1 (1.2)	0
Intermediate	16 (19.5)	17 (20.7)
Hb level, mean (SD), g/dL[d]	9.0 (1.1)[e]	9.1 (1.0)[e]
RBC TD before treatment initiation, n (%)	17 (21.0)[e]	17 (21.0)[e]
Low TB[f]	12 (14.8)	12 (14.8)
High TB[f]	5 (6.2)	5 (6.2)

Note: Baseline characteristics are reported at MDS diagnosis unless specified otherwise.
Purple outlined rows indicate matched characteristics.
[a]Other: luspatercept, 2 (2.4%); ESA, 2 (2.4%); unknown: luspatercept, 2 (2.4%); ESA, 0.
[b]Unknown: luspatercept, 21 (25.6%); ESA, 11 (13.4%).
[c]Includes combined IPSS, IPSS-R, and IPSS-M.
[d]At treatment initiation.
[e]n = 81.
[f]Low TB was defined as 1 to 2 RBC units within 8 weeks prior to luspatercept or ESA initiation; high TB was defined as ≥ 3 RBC units up to 8 weeks prior to luspatercept or ESA initiation.
ECOG PS, European Cooperative Oncology Group performance status; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IPSS, International Prognostic Scoring System; IPSS-M, International Prognostic Scoring System-Molecular; IPSS-R, International Prognostic Scoring System-Revised; IQR, interquartile range; MDS, myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblast; SD, standard deviation; sEPO, serum erythropoietin; TB, transfusion burden; TD, transfusion dependent.

Efficacy outcomes

- The final analytic cohorts included 81 patients per cohort
  - One luspatercept patient who started luspatercept and ESA on the same day was censored from the luspatercept cohort, and the matched patient in the ESA cohort was also censored
- At Week 12, 76 patients in the luspatercept cohort and 72 patients in the ESA cohort were uncensored; at Week 16, 76 and 68 patients were uncensored, respectively; and at Week 24, 61 patients in each cohort were uncensored
- Luspatercept produced significantly greater mean Hb increases versus ESA from treatment initiation at all time points evaluated (**Figure 2**)

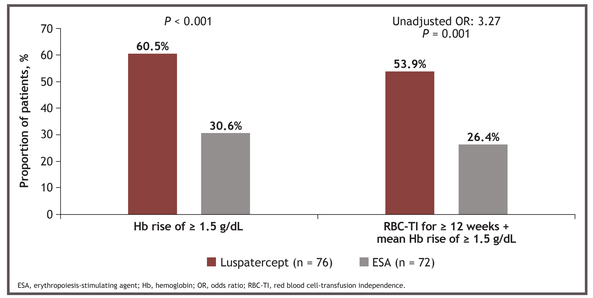
Figure 2. Mean change in Hb levels from treatment initiation through Week 24



ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; SE, standard error.

- Among uncensored patients at Week 12, a significantly greater proportion of luspatercept-treated versus ESA-treated patients achieved an Hb rise of ≥ 1.5 g/dL (60.5% vs 30.6%) and RBC-TI for ≥ 12 weeks with a concurrent mean Hb rise of ≥ 1.5 g/dL (53.9% vs 26.4%; **Figure 3**)
- Median time to an Hb rise of ≥ 1.5 g/dL was 21.0 days with luspatercept and 49.5 days with ESA

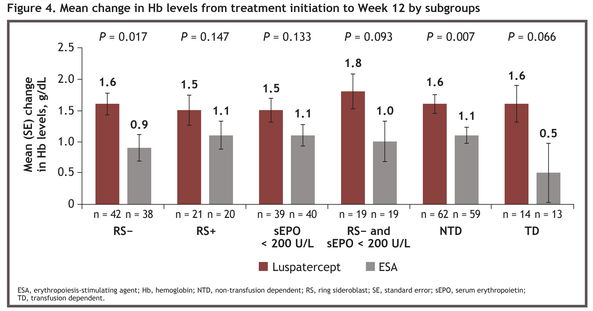
Figure 3. Proportion of patients achieving an Hb rise of ≥ 1.5 g/dL alone and concurrently with RBC-TI for ≥ 12 weeks from treatment initiation to Week 12



ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; OR, odds ratio; RBC-TI, red blood cell-transfusion independence.

- Luspatercept demonstrated consistently greater improvements in mean Hb versus ESA at Week 12 across all assessed subgroups (**Figure 4**)

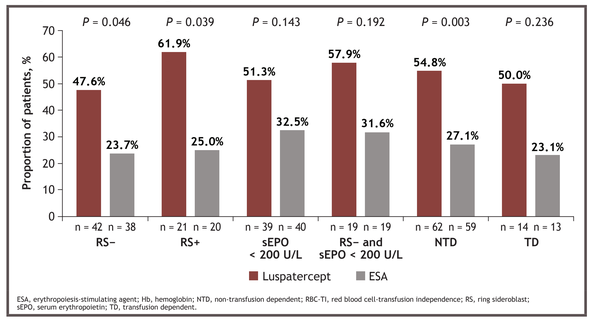
Figure 4. Mean change in Hb levels from treatment initiation to Week 12 by subgroups



ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; NTD, non-transfusion dependent; RS, ring sideroblast; SE, standard error; sEPO, serum erythropoietin; TD, transfusion dependent.

- A greater proportion of patients achieved RBC-TI for ≥ 12 weeks with a concurrent mean Hb rise of ≥ 1.5 g/dL at Week 12 with luspatercept versus ESA across subgroups (**Figure 5**)

Figure 5. Proportion of patients achieving RBC-TI for ≥ 12 weeks with a concurrent mean Hb rise of ≥ 1.5 g/dL at Week 12 by subgroups



ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; NTD, non-transfusion dependent; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast; sEPO, serum erythropoietin; TD, transfusion dependent.

Treatment patterns and AML progression

- The median (IQR) duration of treatment for patients who discontinued treatment was 25.1 (17.0–46.5) weeks for luspatercept and 21.3 (12.5–39.9) weeks for ESA (**Table 2**)
- Of patients discontinuing treatment, fewer luspatercept-treated versus ESA-treated patients discontinued due to suboptimal response (**Table 2**)
- No luspatercept-treated and 2 (2.4%) ESA-treated patients experienced progression to AML

Table 2. Treatment discontinuation summary

	Luspatercept (n = 82)	ESA (n = 82)
Discontinued treatment, n/N (%)	22/82 (26.8)	32/82 (39.0)
Achievement of therapeutic target[a]	4/22 (18.2)	4/32 (12.5)
Secondary/other comorbidities	1/22 (4.5)	2/32 (6.3)
True discontinuations	17/22 (77.3)	26/32 (81.3)
Suboptimal response	4/17 (23.5)	13/26 (50.0)
Hospice	2/17 (11.8)	4/26 (15.4)
MD choice	3/17 (17.6)	4/26 (15.4)
AE or toxicity	5/17 (29.4)	0
AML	0	2/26 (7.7)
Progression to disease[b]	1/17 (5.9)	1/26 (3.8)
Financial/insurance	1/17 (5.9)	1/26 (3.8)
Patient choice	0	1/26 (3.8)
Unknown	1/17 (5.9)	0
Treatment duration for patients who discontinued treatment, median (IQR), weeks	25.1 (17.0–46.5)	21.3 (12.5–39.9)

[a]As documented in electronic medical records to indicate that patients had achieved Hb levels that were considered sufficient and were discontinued from treatment.
[b]Other than AML.
AE, adverse event; AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IQR, interquartile range; MD, medical doctor.

Conclusions

- In this real-world study, patients with LR-MDS-related anemia who received first-line luspatercept treatment demonstrated greater therapeutic benefits than those treated with ESA
  - Outcomes in the overall population were comparable with those reported in the registrational clinical trials,[7,8] but with significant improvements observed with luspatercept versus ESA across subgroups (including RS-negative, sEPO < 200 U/L, and RS-negative with sEPO < 200 U/L subgroups)
- Fewer patients receiving first-line luspatercept discontinued treatment compared with ESA overall (26.8% vs 39%), including roughly half the rate of discontinuation due to suboptimal response among patients with true discontinuations (23.5% vs 50%)
- No AML progression events were observed with luspatercept
- These findings demonstrate the clinical benefits of first-line luspatercept over ESA therapy, supporting its use as a more effective treatment option for patients with LR-MDS-related anemia in real-world clinical practice

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