

Lower-Risk MDS: Should All Patients Receive Frontline Luspatercept?

POSITION: Frontline Luspatercept

Namrata S. Chandhok
Associate Professor of Clinical Medicine
Clinical Leader of the Leukemia Site Disease Group
Myeloid Malignancies Program
University of Miami Miller School of Medicine
Sylvester Comprehensive Cancer Center



**Disclaimer: Frontline luspatercept for all
lower-risk MDS ... except isolated del(5q) 😊**

Lenalidomide remains first-line in isolated del(5q). Every other patient is in scope.

Several lines of evidence support frontline luspatercept for all ESA-naïve patients with lower-risk MDS

1

ESAs are an unreliable first-line standard

No FDA indication in MDS, no defined escalation algorithm, and frequent under-dosing. Two-thirds of patients fail.

2

The RS-negative population is where the evidence must be discussed

Guidelines already establish luspatercept as preferred in RS-positive disease. In RS-negative disease, durability and real-world data favor luspatercept.

3

Efficacy is highest when luspatercept is given first and at full dose

Frontline use outperforms post-ESA use, and maximum-dose initiation removes the titration step.

4

Acquisition cost is not the same as total cost of care

Transfusion delivery, clinic time, iron overload and chelation are excluded from the usual comparison.

5

Overall survival trends favor luspatercept

ESAs have no MDS indication and no standardized dosing or escalation algorithm

	Epoetin alfa	Luspatercept
FDA indication in MDS	None — used off-label	Approved, first-line, ESA-naïve
Escalation algorithm	No defined timing, increment or ceiling	1.0 → 1.33 → 1.75 mg/kg, protocol-defined
Response if under-dosed	Falls to 15–25%	Weight-based; under-dosing not a failure mode
Administration interval	Weekly	Every 3 weeks

COMMANDS used protocol-dosed epoetin alfa. Community practice frequently does not, which widens the real-world difference.

Most patients fail first-line ESA therapy and never receive another active treatment

FAIL FIRST-LINE ESA

68%

244 of 359 patients

MEDIAN TIME TO FAILURE

56 days

irrespective of RS status or sEPO

RECEIVE NO SECOND LINE

61%

following ESA failure

Failure rates were 68.0% overall, 68.7% with ring sideroblasts <5%, and 63.3% with sEPO <200 U/L. No second-line therapy given after ESA failure improved overall survival on multivariable analysis.

ESA failure is rarely a transition to second-line therapy; for most patients it is the end of active treatment.

Luspatercept: guideline-preferred first-line therapy for RS+ disease

FDA indication 1.2 requires only ESA-naïve status, very low- to intermediate-risk disease, and transfusion need. Ring sideroblasts appear solely in the second-line indication (1.3), which derives from MEDALIST.

RING SIDEROBLAST-POSITIVE

NCCN Category 1

Preferred first-line option.

RS $\geq 15\%$, or $\geq 5\%$ with SF3B1 mutation.

RING SIDEROBLAST-NEGATIVE

NCCN Category 2A

First-line option, not designated preferred.

The population in which ESA-first is defended.

The argument that follows addresses the RS-negative population specifically.

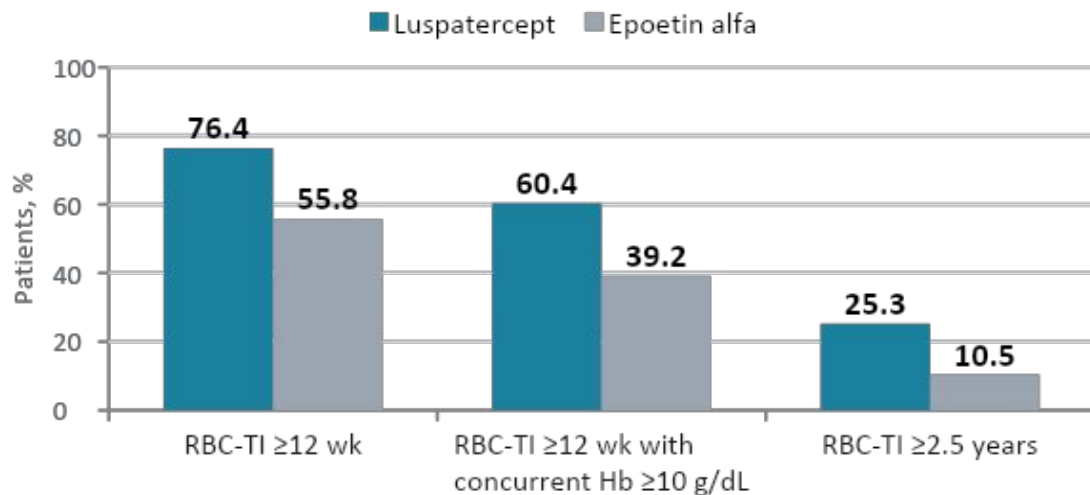
COMMANDS showed superiority over epoetin alfa across all efficacy endpoints

Endpoint (Weeks 1–24)	Luspatercept	Epoetin alfa	Rate difference (95% CI)
RBC-TI ≥ 12 wk + Hb rise ≥ 1.5 g/dL (primary)	58.5%	31.2%	26.6 (15.8, 37.4)
HI-E per IWG ≥ 8 weeks	74.1%	51.3%	22.3 (11.8, 32.8)
Mean Hb increase ≥ 1.5 g/dL	72.1%	48.7%	23.2 (12.2, 34.1)
RBC-TI ≥ 12 weeks	66.7%	46.1%	19.1 (8.6, 29.6)
RBC-TI for 24 weeks	47.6%	29.2%	17.0 (6.7, 27.2)

Every confidence interval excludes zero. Primary endpoint $P < 0.0001$; number needed to treat ≈ 4 . Randomization was stratified by transfusion burden, ring sideroblast status and serum erythropoietin.

This is the evidence base on which the FDA granted a frontline indication with no ring sideroblast restriction.

Transfusion independence lasted twice as long, and progression to higher-risk MDS was halved



Cumulative duration of transfusion independence
184.4 vs 95.1 wk

HR 0.537 (0.362–0.796)

P = 0.0017

Progression to higher-risk MDS

2.2% vs 5.6%

Progression to AML was comparable,
4.9% vs 4.4%.

One in four luspatercept patients maintained transfusion independence for ≥2.5 years, compared with one in ten on epoetin alfa.

Overall survival favors luspatercept — a signal beyond what lower-risk MDS therapy is *historically* expected to deliver

LUSPATERCEPT

Not reached

median overall survival · 66/182 deaths (36.3%)

EPOETIN ALFA

46.0 months

median overall survival · 77/181 deaths (42.5%)

HR 0.781 (95% CI 0.559–1.092), P = 0.1485 — an approximately 20% lower hazard of death that did not reach statistical significance.

Established goals of therapy in lower-risk MDS are transfusion independence, hematologic improvement and quality of life. Luspatercept met all three: RBC-TI ≥ 12 wk 76.4% vs 55.8%, and transfusion independence with a concurrent hemoglobin ≥ 10 g/dL — the threshold associated with improved fatigue, dyspnea and quality of life — in 60.4% vs 39.2%.

Median survival in lower-risk MDS is 3–11 years; no approved therapy has prospectively demonstrated a survival benefit.

Adverse events are comparable to epoetin alfa once treatment exposure is taken into account

	Luspatercept	Epoetin alfa
Median treatment duration	71.5 weeks	44.0 weeks
Events of interest, exposure-adjusted	73.7 / 100 PY	69.6 / 100 PY
Treatment-related serious TEAE	0.5%	2.2%
Treatment-related grade 3/4 TEAE	8.8%	2.8%
Progression to higher-risk MDS	2.2%	5.6%
Progression to AML	4.9%	4.4%

Hypertension was the main excess event of interest: 17.6% versus 10.6% crude, 11.8 versus 9.6 per 100 patient-years exposure-adjusted, and manageable with standard antihypertensives.

Luspatercept patients remained on treatment 62% longer. Exposure-adjusted event rates were 73.7 versus 69.6 per 100 patient-years.

Patients on luspatercept were more than twice as likely to achieve both a clinical and a quality-of-life response

EORTC QLQ-C30 · odds ratio (95% CI)

Global health status / QoL	3.21 (1.95–5.28)
Role functioning	3.17 (1.88–5.35)
Social functioning	3.19 (1.92–5.30)
Physical functioning	2.75 (1.69–4.48)
Fatigue	2.50 (1.53–4.09)
Dyspnea	2.15 (1.33–3.47)

FACT-An · odds ratio (95% CI)

Fatigue subscale	2.51 (1.56–4.03)
Anemia subscale	2.24 (1.40–3.59)
Emotional well-being	3.12 (1.92–5.10)
Physical well-being	2.91 (1.78–4.77)
Trial outcome index	2.47 (1.54–3.97)
Total score	2.12 (1.32–3.40)

Every one of the 15 QLQ-C30 domains and all 10 FACT-An domains favored luspatercept with an odds ratio above 2.

Transfusion independence in this trial came with measurable improvement in how patients felt and functioned.

RS-negative disease carries adverse mutations, and the luspatercept advantage increases with mutational burden

Mutation	RS-positive	RS-negative	Prognostic weight
SF3B1	82%	5%	Favorable
ASXL1	19%	29%	Adverse
U2AF1	7%	22%	Adverse
SRSF2	7%	16%	Adverse

Response advantage by mutational burden

≥2 mutations: +34 points (0.22–0.46)

<2 mutations: +13 points (−0.05–0.30)

Overall survival in ASXL1-mutated patients (n=76)

HR 0.49 (0.27–0.88), P = 0.017 favoring luspatercept

The mutations that define RS-negative disease are those in which luspatercept performs best and ESAs perform worst.

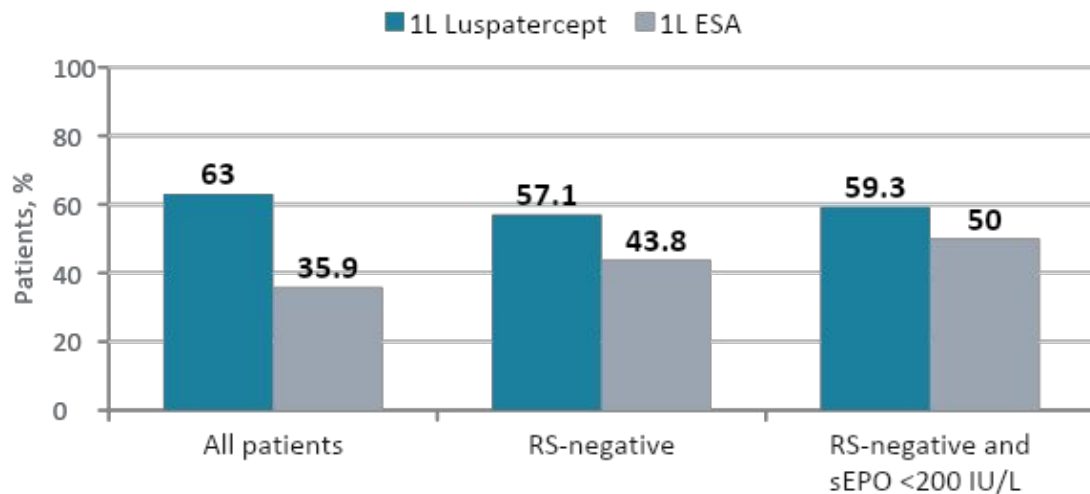
In RS-negative disease only the 24-week response rate is equivalent; all durability endpoints favor luspatercept

RS-negative endpoint	Luspatercept	Epoetin alfa
Week-24 response (risk difference -0.04 , CI -0.20 to 0.11)	Equivalent	Equivalent
RBC-TI ≥ 24 weeks	53% (26/49)	50% (25/50)
RBC-TI ≥ 1.5 years	24.5% (12/49)	16.0% (8/50)
Cumulative duration of RBC-TI ≥ 12 wk (HR 0.538)	Not reached	205.1 weeks
Responders remaining in response at data cutoff	83.3% (25/30)	67.6% (23/34)

For comparison, in SF3B1 wild-type patients RBC-TI ≥ 24 weeks was 49% (32/65) versus 40% (29/72), and RBC-TI ≥ 1.5 years was 21.5% (14/65) versus 13.9% (10/72).

A single equivalent 24-week endpoint is set against four consecutive measures of response duration.

US real-world data confirm superiority of first-line luspatercept in RS-negative patients



Adjusted odds ratio

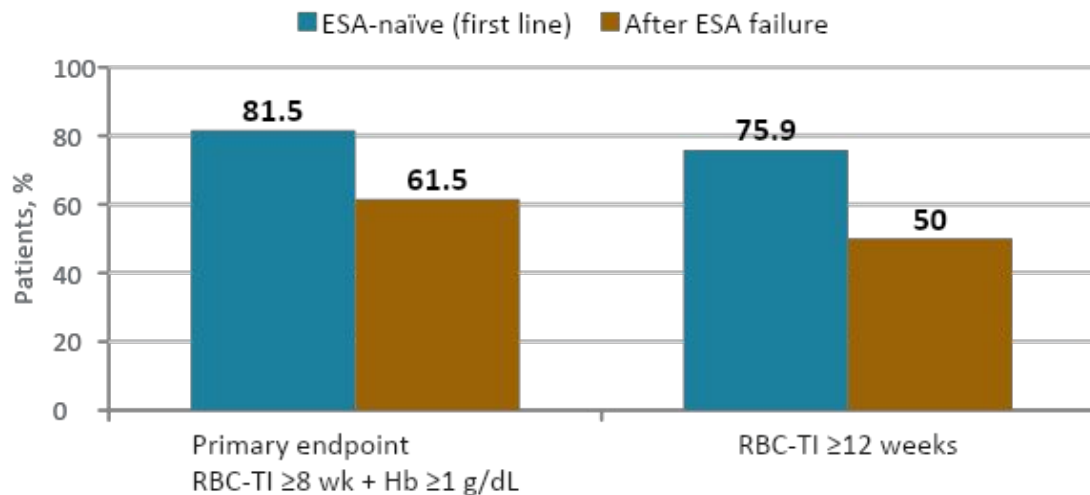
3.26

95% CI 1.73–6.15, P < 0.001

The ESA cohort was enriched for favourable features: 51.1% had sEPO <200 IU/L versus 29.0% of luspatercept patients.

Endpoint: RBC-TI ≥ 12 weeks with concurrent Hb rise ≥ 1.5 g/dL within the first 6 months of therapy.

Luspatercept is more effective given first-line than after ESA failure



Median duration of RBC-TI

Not reached

first line

59.6 weeks

after ESA failure

Median interval from MDS diagnosis to treatment: 2.2 months first line versus 25.2 months after ESA failure.

Deferring luspatercept behind an ESA trial does not preserve its efficacy.

Initiation at the maximum approved dose removes titration and raises frontline response to 81.5%

	COMMANDS (titrated)	MAXILUS (flat 1.75 mg/kg)
Starting dose	1.0 mg/kg	1.75 mg/kg
Dose escalation required	80.2% needed ≥ 1 escalation; 64.8% reached 1.75 mg/kg	None
Primary endpoint, ESA-naïve	58.5%	81.5%
Tolerability	—	11.1% grade 3/4 related; 3.7% stopped for an AE

Dose modifications on flat dosing were predominantly response-driven: 33.3% of delays were for a pre-dose hemoglobin ≥ 12 g/dL and 18.5% of reductions for a hemoglobin rise >2 g/dL.

Fewer titration steps reduce the opportunity for under-treatment, the principal real-world failure mode in MDS anemia therapy.

Simplified dosing standardizes care in the community setting, where most lower-risk MDS is managed

What happens in community practice	Evidence
Only 35.5% of lower-risk MDS patients ever start first-line therapy	US Oncology Network, n = 2,736
ESAs are commonly dosed at CKD rather than MDS levels	Response falls to 15–25%
ESA therapy is often continued despite documented failure	Florida Cancer Specialists, n = 359
Luspatercept at 1.75 mg/kg requires no titration decision	MAXILUS: 81.5% response

Escalation is near-universal when it is required: 80.2% of COMMANDS and 82.6% of INDEPENDENCE patients needed a dose increase. Starting at the maximum approved dose removes a step nearly every patient eventually needs.

A therapy whose success depends on repeated titration decisions performs worst where those decisions are least standardized.

Drug price is one line item; every other cost of care moves in the opposite direction

4.9

**fewer RBC units
by week 96**

≈ \$3,100 in US
per-unit charges

2.9

**fewer transfusion
episodes by week 96**

≈ \$6,900 in US
procedure charges

50%

**fewer admissions
and ER visits**

US claims: 26% fewer inpatient,
31% fewer outpatient visits

\$3–6k

**per month of iron
chelation deferred**

triggered after 20–30
units transfused

≈ \$10,000 per patient in avoided US transfusion charges by week 96

before counting admissions, iron chelation, or clinic time

Published cost analyses are European and Australian. US median charge is \$634 per RBC unit and \$2,388 per transfusion procedure — roughly 11× the cost of the blood product itself.

89 additional weeks of transfusion independence, half the hospital utilization, 35 fewer clinic days per year — every avoided transfusion priced at US rates.

Every objection to frontline luspatercept- answered by the current evidence

Objection	Evidence
<i>“RS-negative patients do not benefit”</i>	One equivalent 24-week endpoint against four durability endpoints, plus 57.1% vs 43.8% in US practice
<i>“There is no survival benefit”</i>	A favorable survival trend; no approved lower-risk MDS therapy has shown more
<i>“The RS-negative OS hazard ratio is 0.96”</i>	99 patients, 45 events, 95% CI 0.53–1.72 — not informative in either direction
<i>“ESA first preserves a second line”</i>	61% of ESA failures have historically received no second line, and none of those therapies improve survival
<i>“ESAs suffice in low-EPO RS-negative disease”</i>	In US practice 1L luspatercept exceeded 1L ESA in that stratum: 59.3% vs 50.0%
<i>“Luspatercept is too expensive”</i>	Account for transfusions, infusion-centre care, time toxicity and iron chelation
Real world: For most patients with lower-risk MDS, the first agent chosen is often the only agent received.	

Thank you for your Attention

Namrata.chandhok@miami.edu



COMMANDS: study design and endpoints

Element	Detail
Design	Phase 3, global, multicentre, open-label, randomized, active-controlled; 1:1
Population	ESA-naïve; IPSS-R very low/low/intermediate-risk MDS (WHO 2016); <5% marrow blasts; with or without ring sideroblasts; del(5q) and MDS-U excluded
Transfusion criterion	2–6 pRBC units/8 weeks for ≥ 8 weeks immediately before randomization
sEPO criterion	Endogenous serum erythropoietin <500 U/L
Treatment	Luspatercept 1.0 mg/kg SC Q3W $\rightarrow$ 1.75 mg/kg vs epoetin alfa 450 IU/kg QW $\rightarrow$ 1050 IU/kg
Primary endpoint	RBC-TI ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL, Weeks 1–24
Stratification	Baseline transfusion burden (<4, ≥ 4 U/8 wk); RS status (+/–); sEPO (≤ 200 , >200 U/L)

COMMANDS: baseline disease characteristics

Characteristic	Luspatercept (N=178)	Epoetin alfa (N=178)
Median age, years	74 (33–93)	74
Median hemoglobin, g/dL	7.80 (4.7–9.2)	7.80 (4.5–10.2)
Median serum EPO, U/L	78.7 (7.8–495.8)	85.9 (4.6–462.5)
IPSS-R very low / low / intermediate	9.0% / 70.8% / 19.1%	9.6% / 73.6% / 15.7%
Ring sideroblast positive	130 (73.0%)	128 (71.9%)
Ring sideroblast negative	48 (27.0%)	49 (27.5%)
SF3B1 mutated	111 (62.4%)	99 (55.6%)
Median transfusion burden, U/8 wk	3.0 (1–10)	3.0 (0–14)

COMMANDS: complete FDA efficacy results

Endpoint (Weeks 1–24)	Luspatercept n (%)	Epoetin alfa n (%)	Rate difference (95% CI)	P
RBC-TI ≥ 12 wk + Hb ≥ 1.5 g/dL	86 (58.5)	48 (31.2)	26.6 (15.8, 37.4)	<0.0001
Mean Hb increase ≥ 1.5 g/dL	106 (72.1)	75 (48.7)	23.2 (12.2, 34.1)	—
HI-E per IWG ≥ 8 weeks	109 (74.1)	79 (51.3)	22.3 (11.8, 32.8)	<0.0001
RBC-TI for 24 weeks	70 (47.6)	45 (29.2)	17.0 (6.7, 27.2)	0.0012
RBC-TI ≥ 12 weeks	98 (66.7)	71 (46.1)	19.1 (8.6, 29.6)	0.0003

95% CI for the primary endpoint: luspatercept 50.1–66.6, epoetin alfa 24.0–39.1. Common rate difference uses Mantel-Haenszel stratum weights. CMH test stratified by baseline transfusion burden, RS status and sEPO level; two-sided P values. Statistical significance threshold at the second interim analysis was two-sided P = 0.03.

COMMANDS: cumulative duration of RBC-TI ≥ 12 weeks by subgroup

Subgroup	Luspatercept median, wk	Epoetin alfa median, wk	HR (95% CI)
Overall (ITT)	184.4	95.1	0.537 (0.362–0.796)
sEPO ≤ 200 U/L	230.4	101.4	0.627 (0.420–0.935)
sEPO > 200 U/L	48.3	24.6	0.804 (0.286–2.265)
Transfusion burden < 4 U/8 wk	144.0	95.1	0.701 (0.458–1.073)
Transfusion burden ≥ 4 U/8 wk	Not reached	110.9	0.688 (0.330–1.433)
Ring sideroblast positive	126.6	73.1	0.612 (0.410–0.914)
Ring sideroblast negative	Not reached	205.1	0.538 (0.187–1.550)

COMMANDS: overall survival, ITT and subgroups

Population	Luspatercept deaths / median OS	Epoetin alfa deaths / median OS	HR (95% CI)
Overall (ITT)	66/182 (36.3%) · NR	77/181 (42.5%) · 46.0 mo	0.781 (0.559–1.092)
sEPO ≤200 U/L	51/145 (35.2%) · NR	53/144 (36.8%) · 51.4 mo	0.814 (0.554–1.196)
sEPO >200 U/L	15/37 (40.5%) · 43.0 mo	24/37 (64.9%) · 35.4 mo	0.669 (0.350–1.278)
Transfusion burden <4 U/8 wk	43/118 (36.4%) · 57.5 mo	41/111 (36.9%) · 47.2 mo	0.870 (0.567–1.334)
Transfusion burden ≥4 U/8 wk	23/64 (35.9%) · NR	36/70 (51.4%) · 39.9 mo	0.623 (0.369–1.054)
Ring sideroblast positive	45/133 (33.8%) · NR	52/130 (40.0%)	0.698 (0.468–1.040)
Ring sideroblast negative	21/49 (42.9%) · 54.8 mo	24/50 (48.0%) · 46.2 mo	0.956 (0.531–1.723)

Data cutoff 6 Oct 2025; median follow-up 35.9 vs 30.8 months. Exploratory subgroup analyses, unstratified hazard ratios.

COMMANDS: distribution of somatic mutations by RS status

Gene	RS-positive	RS-negative	Gene	RS-positive	RS-negative
SF3B1	82%	5%	SRSF2	7%	16%
TET2	38%	26%	EZH2	7%	5%
ASXL1	19%	29%	RUNX1	4%	5%
DNMT3A	16%	18%	STAG2	2%	6%
U2AF1	7%	22%	No panel mutation	3%	24%

Most mutations had a variant allele frequency of 3–50%. RS-negative disease is depleted of SF3B1 and enriched for ASXL1, U2AF1 and SRSF2. Nearly one quarter of RS-negative patients had no detectable panel mutation.

COMMANDS: clinical response by mutation (all patients)

Marker	Luspatercept responders	Epoetin alfa responders	Risk difference (95% CI)
SF3B1	80/114	33/102	0.38 (0.25, 0.50)
SF3B1-alpha (with DTA mutation)	52/69	19/62	0.45 (0.29, 0.60)
TET2	42/63	18/58	0.36 (0.19, 0.52)
ASXL1	21/41	5/34	0.37 (0.17, 0.56)
DNMT3A	21/30	13/29	0.25 (0.01, 0.50)
SRSF2	8/21	2/13	0.23 (-0.06, 0.51)
U2AF1	6/16	6/22	0.10 (-0.20, 0.40)
All markers pooled	445	429	0.25 (0.15, 0.35)

Risk difference in response, luspatercept versus epoetin alfa. Positive values favor luspatercept.

COMMANDS: mutational burden and the ASXL1 survival signal

Baseline mutational burden	Luspatercept	Epoetin alfa	Risk difference (95% CI)
Fewer than 2 mutated genes	37/64	27/60	0.13 (−0.05, 0.30)
2 or more mutated genes	72/115	32/111	0.34 (0.22, 0.46)

Response by number of mutated genes (luspatercept vs epoetin alfa): 0 genes 6/15 vs 8/15 · 1 gene 31/49 vs 19/47 · 2 genes 44/63 vs 16/60 · 3 genes 21/29 vs 12/30 · ≥4 genes 7/18 vs 4/10

Post-hoc OS analysis	n	HR (95% CI)	P
ASXL1 mutation present	76	0.49 (0.27–0.88)	0.017
CBL mutation present	14	7.34 (1.40–38.52)	0.018
SF3B1 mutation present	—	0.70 (0.44–1.12)	0.140

COMMANDS: RS-negative and SF3B1 wild-type outcomes in detail

Endpoint	RS- luspatercept	RS- epoetin alfa	SF3B1-wt luspatercept	SF3B1-wt epoetin alfa
RBC-TI ≥ 24 weeks (Weeks 1–48)	26/49 (53%)	25/50 (50%)	32/65 (49%)	29/72 (40%)
RBC-TI ≥ 1.5 years	12/49 (24.5%)	8/50 (16.0%)	14/65 (21.5%)	10/72 (13.9%)
Cumulative RBC-TI ≥ 12 wk, median	Not reached	205.1 wk	—	—
Responders ongoing at cutoff	25/30 (83.3%)	23/34 (67.6%)	—	—
Overall survival, median	54.8 mo	46.2 mo	—	—

ITT comparators: RBC-TI ≥ 24 weeks 116/182 (64%) vs 76/181 (42%); RBC-TI ≥ 1.5 years 55/182 (30.2%) vs 25/181 (13.8%), $P < 0.0001$. RS-positive: RBC-TI ≥ 24 weeks 90/133 (68%) vs 51/130 (39%); RBC-TI ≥ 1.5 years 43/133 (32.3%) vs 17/130 (13.1%).

Preplanned subgroup analyses of secondary endpoints; not powered for statistical significance.

MAXILUS: design and baseline characteristics

Characteristic	ESA-naïve (n=54)	ESA-R/R/I (n=52)
Median age, years	76.0 (71.0–80.0)	76.0 (70.5–81.5)
Median time since MDS diagnosis, months	2.2 (0.3–9.2)	25.2 (10.0–65.5)
Median transfusion burden, pRBC U/8 wk	2.0 (1.0–4.0)	4.0 (2.0–6.0)
Median hemoglobin, g/dL	8.1 (7.2–8.5)	7.5 (7.0–7.8)
sEPO ≤ 200 IU/L	42 (77.8%)	23 (44.2%)
IPSS-R very low / low / intermediate	3.7% / 68.5% / 25.9%	9.6% / 69.2% / 21.2%
Ring sideroblast negative	23 (42.6%)	19 (36.5%)
Median serum ferritin, $\mu\text{g/L}$	601.5	963.2

MAXILUS: efficacy in both cohorts

Endpoint	ESA-naïve (n=54)	ESA-R/R/I (n=52)
RBC-TI ≥ 8 wk + Hb increase ≥ 1 g/dL (primary)	81.5% (44/54)	61.5% (32/52)
RBC-TI ≥ 8 weeks	83.3% (45/54)	67.3% (35/52)
RBC-TI ≥ 12 weeks	75.9% (41/54)	50.0% (26/52)
RBC-TI ≥ 12 wk + Hb increase ≥ 1.5 g/dL	72.2% (39/54)	40.4% (21/52)
Modified HI-E per IWG 2018	87.0% (47/54)	76.9% (40/52)
RS-negative subgroup, RBC-TI ≥ 12 wk	73.9% (17/23)	36.8% (7/19)
RS-positive subgroup, RBC-TI ≥ 12 wk	77.4% (24/31)	57.6% (19/33)
sEPO ≤ 200 IU/L, RBC-TI ≥ 12 wk	86.0% (37/43)	56.5% (13/23)
Median duration of RBC-TI ≥ 12 weeks	Not reached	59.6 weeks

MAXILUS: treatment exposure and safety

Parameter	ESA-naïve (n=54)	ESA-R/R/I (n=52)
Still on active treatment at cutoff	70.4%	38.5%
Discontinued — lack of efficacy	11.1%	23.1%
Discontinued — adverse event	3.7%	1.9%
≥1 dose delay (pre-dose Hb ≥12 g/dL)	51.9% (33.3%)	42.3% (3.8%)
≥1 dose reduction (Hb rise >2 g/dL)	24.1% (18.5%)	9.6% (3.8%)
Any-grade TEAE / treatment-related	94.4% / 29.6%	100% / 46.2%
Grade 3–4 TEAE / treatment-related	68.5% / 11.1%	53.8% / 7.7%
Grade 5 TEAE / treatment-related	0 / 0	7.7% / 0
Progression to higher-risk MDS / AML	3.7% / 0	3.8% / 0

All-treated population. Data cutoff 1 Oct 2025.

US real-world cohort: baseline and outcomes

Baseline characteristic	1L luspatercept (n=186)	1L ESA (n=174)
Median age at treatment initiation, years	68.3 (61.4–74.3)	65.7 (59.4–74.0)
ECOG performance status 0–1	88.1%	83.5%
SF3B1 mutation	47.8%	13.2%
Ring sideroblast positive	40.3%	13.8%
sEPO <200 IU/L	29.0%	51.1%
RBC-TI ≥12 wk + Hb ≥1.5 g/dL, first 6 months	1L luspatercept	1L ESA
All patients (adjusted OR 3.26, 1.73–6.15, P<0.001)	63.0%	35.9%
Ring sideroblast positive	70.0%	28.6%
Ring sideroblast negative	57.1%	43.8%
RS-negative and sEPO <200 IU/L	59.3%	50.0%

Transfusion dependence as an independent predictor of mortality

Finding	Value	Source
Excess mortality with transfusion dependence	~60% higher risk; pooled HR $\approx$ 0.40 favoring TI	Braga Lemos M, et al. Eur J Haematol 2021;107:3–23
Median OS, transfusion-dependent vs independent	1.7 vs 5.7 years	Same meta-analysis (17 studies)
Effect within IPSS-R Low-risk patients	Independently worse OS; excess deaths non-leukemic	Hiwase DK, et al. Am J Hematol 2017;92:508–514
Prognostic value beyond IPSS-M	TD improves IPSS-M prediction	Creignou M, et al. J Intern Med 2024;296:53–67
Leukemic transformation	OR 1.2	Herrera D, et al. J Clin Oncol 2023;41(suppl):e19075

Cost of transfusion-dependent care: source data

Parameter	Value	Source
True delivered cost per RBC unit (blood product = 59%)	US\$440	Mo A, et al. Br J Haematol 2026;209:275–285
Annual transfusion cost per patient	~US\$6,607	Mo A, et al. 2026
Additional per-unit process cost once alloimmunized	+24%	Mo A, et al. 2026
Total transfusion-related cost, 6 months (France, MDS-RS)	€16,188	Jouzier C, et al. Transfusion 2022;62:961–973
4-year cumulative transfusion cost (Sweden), very low → very high risk	\$8,805 → \$80,106	Zhao J, et al. Vox Sang 2021;116:581–590
Deferasirox	\$3,000–6,000 / month	Leitch HA, Buckstein R. Blood 2025;145:383–396
Iron delivered per RBC unit	200–250 mg	Leitch HA, Buckstein R. 2025

Geography: these analyses derive from European and Australian systems where ESA home administration is available. US delivery adds infusion-centre facility fees, nursing time and travel. Weekly ESA administration requires approximately 52 visits per year versus 17 for every-3-week luspatercept; median age in COMMANDS was 74 years.

Component-cost data from separate published analyses; no incremental cost-effectiveness analysis exists in lower-risk MDS.

Luspatercept: labelled warnings and adverse reactions

Warning / precaution	Detail
Thrombosis / thromboembolism	Reported in 8/223 (3.6%) of REBLOZYL-treated beta thalassemia patients. Consider thromboprophylaxis in patients at increased risk.
Hypertension	Reported in 63/554 (11.4%) of REBLOZYL-treated patients; grade 3–4 incidence 2–9.6% across studies. Monitor blood pressure before each dose.
Extramedullary hematopoietic masses	Increased risk in beta thalassemia; monitor and discontinue for serious complications.
Embryo-fetal toxicity	May cause fetal harm; effective contraception during treatment and for 3 months after the final dose.

ESA-naïve MDS patients: grade ≥ 3 adverse reactions occurring in $\geq 2\%$ were hypertension and dyspnea. Most common ($\geq 10\%$) all-grade reactions were diarrhea, fatigue, hypertension, peripheral edema, nausea and dyspnea. Among ESA-naïve MDS patients with normal baseline blood pressure, 23 (36%) developed systolic BP ≥ 140 mmHg and 11 (6%) diastolic BP ≥ 80 mmHg.

References (1 of 2)

1. REBLOZYL (luspatercept-aamt) for injection. US Prescribing Information. Bristol Myers Squibb; February 2026.
2. Garcia-Manero G, Della Porta MG, Zeidan AM, et al. Updated overall survival and long-term transfusion independence from the phase 3 COMMANDS trial in ESA-naïve patients with lower-risk MDS. ASCO 2026 Abstract 6566 / EHA 2026. Data cutoff 6 Oct 2025.
3. Della Porta MG, Diez Campelo M, Santini V, et al. Luspatercept initiated at the maximum-approved dose in patients with lower-risk MDS who require transfusions: primary analysis from MAXILUS. EHA 2026 Abstract S173. Data cutoff 1 Oct 2025.
4. Amanam I, Agu C, Korgaonkar S, et al. Real-world outcomes of patients with lower-risk MDS receiving first-line luspatercept or first-line ESA in the US. J Clin Oncol 2025;43(suppl 16):6570.
5. Garcia-Manero G, Della Porta MG, Zeidan AM, et al. Overall survival and duration of response for transfusion independence in COMMANDS. J Clin Oncol 2025;43(suppl 16):6512.
6. Della Porta MG, Garcia-Manero G, Santini V, et al. COMMANDS primary analysis. Lancet Haematol 2024;11(9):e646–e658. PMID 39038479.
7. Platzbecker U, Della Porta MG, Santini V, et al. COMMANDS interim analysis. Lancet 2023;402(10399):373–385. PMID 37311468.
8. Garcia-Manero G, Santini V, Zeidan AM, et al. Long-term transfusion independence with luspatercept versus epoetin alfa in COMMANDS. Adv Ther 2025;42(7):3576–3589. PMID 40377899.
9. Komrokji RS, Hayati S, Ugidos M, et al. Impact of mutational landscape and burden on RBC transfusion response in COMMANDS. Am J Hematol 2026;101(3):427–438.
10. NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes, v2.2026.

References (2 of 2)

11. Park S, Hamel JF, Toma A, et al. Outcome of lower-risk MDS without 5q deletion after failure of ESAs. *J Clin Oncol* 2017;35(14):1591–1597. PMID 28350519.
12. Balleari E, Filiberti RA, Salvetti C, et al. Effects of different doses of erythropoietin in patients with MDS: a propensity score-matched analysis. *Cancer Med* 2019;8(18):7567–7576.
13. Mo A, Haysom H, Carrandi A, et al. The true cost of red cell transfusion for patients with myelodysplastic syndromes: a time-driven activity-based costing study. *Br J Haematol* 2026;209(1):275–285.
14. Jouzier C, Cherait A, Cony-Makhoul P, et al. Red blood cell transfusion burden in MDS with ring sideroblasts (GFM). *Transfusion* 2022;62(5):961–973. PMID 35452143.
15. Zhao J, Dahlén T, Edgren G. Costs associated with transfusion therapy in patients with MDS in Sweden. *Vox Sang* 2021;116(5):581–590. PMID 33210286.
16. Leitch HA, Buckstein R. How I treat iron overload in adult MDS. *Blood* 2025;145(4):383–396. PMID 38941618.
17. Braga Lemos M, Rodrigues SR, Schroeder T, et al. Transfusion dependence and burden in MDS: systematic review and meta-analysis. *Eur J Haematol* 2021;107(1):3–23.
18. Hiwase DK, Singhal D, Strupp C, et al. Dynamic assessment of RBC-transfusion dependency improves the prognostic value of the revised IPSS. *Am J Hematol* 2017;92(6):508–514.
19. Creignou M, Bernard E, Gasparini A, et al. Early transfusion patterns improve IPSS-M prediction in MDS. *J Intern Med* 2024;296(1):53–67. PMID 38654517.
20. Platzbecker U, Götze KS, Kiewe P, et al. Long-term efficacy and safety of luspatercept: the phase 2 PACE-MDS study. *J Clin Oncol* 2022;40(33):3800–3807.
21. FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations.

Community practice: where lower-risk MDS anemia is actually managed

Finding	Value	Cohort
Lower-risk MDS patients initiating any 1L therapy	35.5%	US Oncology Network, n = 2,736
Higher-risk MDS patients initiating any 1L therapy	74.2%	Same cohort
Hematologic improvement on ESA in LR-MDS	33.7%	Community practice, n = 359
Reduction in transfusion requirement on ESA	10.3%	Same cohort

ESA response when dosed at CKD rather than MDS levels 15–25% Propensity-matched analysis

Authors of the community ESA cohort concluded that patients in US community oncology settings may continue ESA treatment despite documented failure. Most patients who began first-line therapy discontinued it, and few advanced to second line.

US healthcare resource utilization: luspatercept versus ESA

Healthcare resource utilization versus ESA	Relative reduction with luspatercept
All-cause inpatient visits	26% lower
All-cause outpatient visits	31% lower
MDS-related inpatient visits	25% lower

Median age 77 years (luspatercept) and 78 years (ESA); median follow-up 14.6 and 14.4 months. These are US data and therefore complement the European and Australian cost analyses, which do not capture US infusion-centre facility fees, nursing time or travel.

COMMANDS: cumulative RBC units and transfusion visits

Cumulative burden per patient	Luspatercept	Epoetin alfa	Absolute difference
RBC units, week 24	3.8	5.7	−1.9 units
RBC units, week 96	8.7	13.6	−4.9 units (≈36%)
Transfusion visits, week 24	2.4	3.6	−1.2 visits (≈33%)
Transfusion visits, week 96	5.7	8.6	−2.9 visits (≈33%)

Both RBC units and transfusion visits accumulated more slowly with luspatercept through approximately 1.5 years. The absolute difference was greater among patients entering the trial with a high transfusion burden. At a delivered cost of ~\$440 per unit, 4.9 avoided units corresponds to approximately \$2,150 per patient in product and process cost alone.

Real-world healthcare utilization before and during luspatercept

Utilization measure	Before luspatercept	During luspatercept
Any inpatient admission or ER visit	17.6%	7.3%
Inpatient admission	12.1%	6.1%
Emergency department visit	11.0%	3.7%
Inpatient admissions per 100 patient-years	18.9	8.2
ER visits per 100 patient-years	18.4	4.4

Limitations: convenience sampling, physician-entered records, and events occurring outside the contributing clinician's system may not have been captured. This is a within-patient before-and-after comparison, not a randomized comparison, and regression to the mean cannot be excluded.

Patient and caregiver time burden of chronic transfusion

Measure	Reported burden
Transfusion visits per patient over 4 months	6.3 (≈18.9 per year)
Caregiver hours accompanying patients over 6 months	21.5 hours
Caregiver hours per month on other disease-related tasks	14.7 hours
Caregiver hours per month travelling to transfusion	3.8 hours

Median age in COMMANDS was 74 years. Transfusion-related time falls predominantly on family caregivers and is not captured in drug-acquisition cost comparisons. Weekly ESA administration requires approximately 52 clinic visits per year versus 17 with every-3-week luspatercept.

Formal cost-effectiveness evaluations: Canada and Japan

Evaluation and population	Comparator	Conclusion	ICER
CADTH — RS+, post-ESA / ESA-ineligible	Transfusion-based supportive care	Not cost-effective at C\$50,000/QALY	C\$623,219 / QALY
Japan C2H — ESA-naïve, RS-positive	Darbepoetin ± supportive care	Additional benefit demonstrated	¥27,268,507 / QALY
Japan C2H — ESA-naïve, RS-negative	Darbepoetin ± supportive care	No additional benefit demonstrated	Cost increase
Japan C2H — post-ESA, RS-positive	Transfusion-based supportive care	Additional benefit demonstrated	¥41,138,889 / QALY
Japan C2H — post-ESA, RS-negative	Transfusion-based supportive care	Insufficient evidence	Not estimable

Both evaluations used list prices without confidential rebates, and neither incorporates the October 2025 COMMANDS data cut, MAXILUS, or US real-world outcomes. The Japanese RS-negative determination rests on the week-24 composite endpoint, which is equivalent in that subgroup, and does not incorporate the durability endpoints.

COMMANDS: depth and durability of transfusion independence

Outcome, Week 1 to end of treatment	Luspatercept	Epoetin alfa	Difference
Primary endpoint, Weeks 1–24 (full analysis)	60%	35%	25.4 points, P<0.0001
Any RBC-TI ≥12 weeks	76.4% (139/182)	55.8% (101/181)	20.6 points
RBC-TI maintained ≥1 year	44.5% (81/182)	27.6% (50/181)	16.9 points
RBC-TI maintained ≥1.5 years	30.2% (55/182)	13.8% (25/181)	16.4 points
Median cumulative duration of RBC-TI ≥12 wk	184.4 weeks	95.1 weeks	HR 0.537

Among the 139 luspatercept patients achieving at least a 12-week transfusion-independence response, 58.3% maintained a response for at least one year and 39.6% for at least 1.5 years.

COMMANDS: head-to-head safety in detail

Event	Luspatercept n (%)	EAIR/100 PY	Epoetin alfa n (%)	EAIR/100 PY
Any-grade TEAE	178 (97.8)	599.5	166 (92.7)	409.9
Treatment-related TEAE	64 (35.2)	33.9	37 (20.7)	23.0
Serious TEAE	90 (49.5)	44.2	77 (43.0)	51.1
Treatment-related serious TEAE	1 (0.5)	0.4	4 (2.2)	2.1
Grade 3/4 TEAE	117 (64.3)	73.8	93 (52.0)	68.3
Treatment-related grade 3/4 TEAE	16 (8.8)	6.4	5 (2.8)	2.6
Grade 5 TEAE	17 (9.3)	6.5	17 (9.5)	8.6

Median treatment duration 61.9 vs 44.7 weeks (Sep 2023) and 71.5 vs 44.0 weeks (Feb 2025). Events of interest: 68.7% vs 54.2% crude but 73.7 vs 69.6 per 100 patient-years exposure-adjusted. Thromboembolic events 6.6% vs 3.4% (EAIR 4.7 vs 3.1). Progression to higher-risk MDS 2.2% vs 5.6%, HR 0.388 (0.120–1.250); AML 4.9% vs 4.4%, HR 1.110 (0.42–2.932).

Safety population: luspatercept n=182, epoetin alfa n=179. Data cutoffs 22 Sep 2023 and 7 Feb 2025.

COMMANDS: health-related quality of life, complete domain results

EORTC QLQ-C30 (n = 174 vs 172)

Constipation	3.21
Global health status/QoL	3.21
Social functioning	3.19
Insomnia	3.19
Role functioning	3.17
Pain	2.90
Cognitive functioning	2.84
Emotional functioning	2.81
Physical functioning	2.75
Financial difficulties	2.72
Appetite loss	2.64
Fatigue	2.50
Diarrhea	2.44
Nausea/vomiting	2.34
Dyspnea	2.15

FACT-An (n = 173 vs 173)

Emotional well-being	3.12
Physical well-being	2.91
Social/family well-being	2.80
FACT-G	2.58
Fatigue subscale	2.51
Trial outcome index	2.47
Functional well-being	2.42
Trial outcome index-fatigue	2.29
Anemia subscale	2.24
Total score	2.12

All values are odds ratios favoring luspatercept; every 95% CI excluded 1. Clinical response in the HRQoL population was 61% vs 35%, OR 3.1 (2.0–4.9), $P < 0.001$.

A sensitivity analysis using RBC-TI through week 24 gave the same direction across all domains. Missing HRQoL data were imputed as non-response.

Odds of achieving both the clinical response and maintained/improved HRQoL at week 24. Base-case analysis; nominal P values.

Scope and the second-line landscape

Consideration	Detail
del(5q) excluded from COMMANDS	Lenalidomide remains the preferred first-line option in del(5q) disease. NCCN limits its luspatercept recommendation to patients without del(5q).
Second line now exists after ESA failure	Imetelstat, FDA-approved June 2024 for LR-MDS with transfusion-dependent anemia requiring ≥ 4 units/8 weeks after ESA failure or ineligibility.
IMerge phase 3 results	RBC-TI ≥ 8 weeks 39.8% vs 15.0% placebo ($P < 0.001$); RBC-TI ≥ 24 weeks 28.0% vs 3.3% ($P < 0.001$).
Imetelstat toxicity profile	Grade 3/4 neutropenia 72% and thrombocytopenia 65%; >80% resolved to grade ≤ 2 within 4 weeks.