2026

DEBATES AND DIDACTICS in Hematology and Oncology

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Sequencing Anemia Therapies in Lower Risk Myelodysplastic Syndromes

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Disclosures

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Agenda

Erythropoiesis Stimulating Agents (ESA) response prediction

Front-line Transfusion Dependent (TD) non-del(5q): COMMANDS and the evolving treatment landscape

Post-ESA and post-luspatercept sequencing

Special genotypes/phenotypes: del(5q), IDH-mutated, mixed cytopenias

Practical algorithm

Anemia in Lower Risk MDS

- *Myelodysplastic syndromes/neoplasms (MDS) are a heterogeneous group of myeloid neoplasms.*

- *Most newly diagnosed MDS cases are classified as lower risk, typically defined as IPSS Low/Intermediate-1, IPSS-R ≤ 3.5 and IPSS-M ≤0. Anemia is the predominant cytopenia affecting patients with lower-risk MDS.*

- *The clinical question has evolved from "ESA versus transfusions?" to how best to sequence available therapies for anemia in lower-risk MDS.*

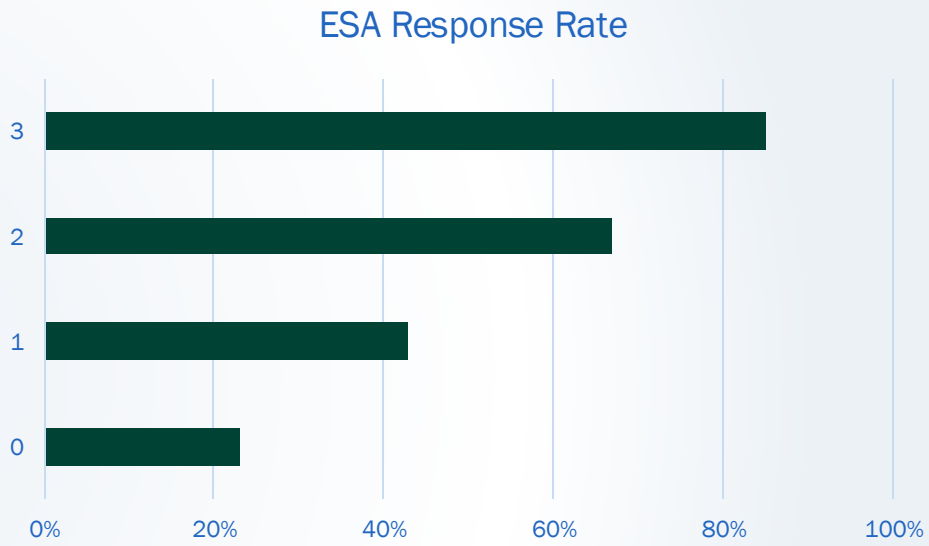
Clinical lymphoma, myeloma & leukemia, 25(11), e933–e941.e2.; Current hematologic malignancy reports, 10(3), 272–281.

1st Line: ESA in lower risk MDS Anemia– The Historical Standard

Erythropoiesis-stimulating agents (ESAs)—including darbepoetin and epoetin—have been used for decades as first-line therapy for anemia in lower-risk MDS, especially in the non–del(5q) MDS setting.

Response prediction tools (Nordic / Hellström-Lindberg score, ITACA, CAN score) consistently identify a common pattern:

Lower baseline serum erythropoietin (EPO) levels, Lower transfusion burden → higher likelihood of response.



ITACA score
1 point for each variable

1) Transfusion independence
2) EPO level < 100 IU/L
3) IPSS low-risk category

Am J Hematol. 2017;92(10):1037-1046.

Redefining 1st Line Standard: COMMANDS Trial

- *R-IPSS up to intermediate risk (and blasts less than 5%)*
- *Transfusion dependency (2-6 units / 8 weeks)*
- *Erythropoietin (EPO) level less than 500 IU/L*
- *NO prior ESA, Luspatercept, Lenalidomide or Hypomethylating Agents.*
- *NO del(5q) MDS*

Randomization / Stratification

- *Baseline transfusion burden (<4 or ≥ 4 units of RBC in preceding 8 weeks).*
- *EPO level (≤200 IU/L vs >200 - 500).*

•Positive for ring sideroblasts (≥15% erythroid precursors or SF3B1 mutated with at least 5% of erythroid precursors) Vs Negative.

Luspatercept (starting dose @ 1 mg/kg; step up to 1.75 mg/kg) every 3 weeks

vs

Epoetin alfa at a starting dose of 450 IU/kg; step up to a maximum of 1050 IU/kg every week.

The Lancet. Haematology, 11(9), e646–e658.

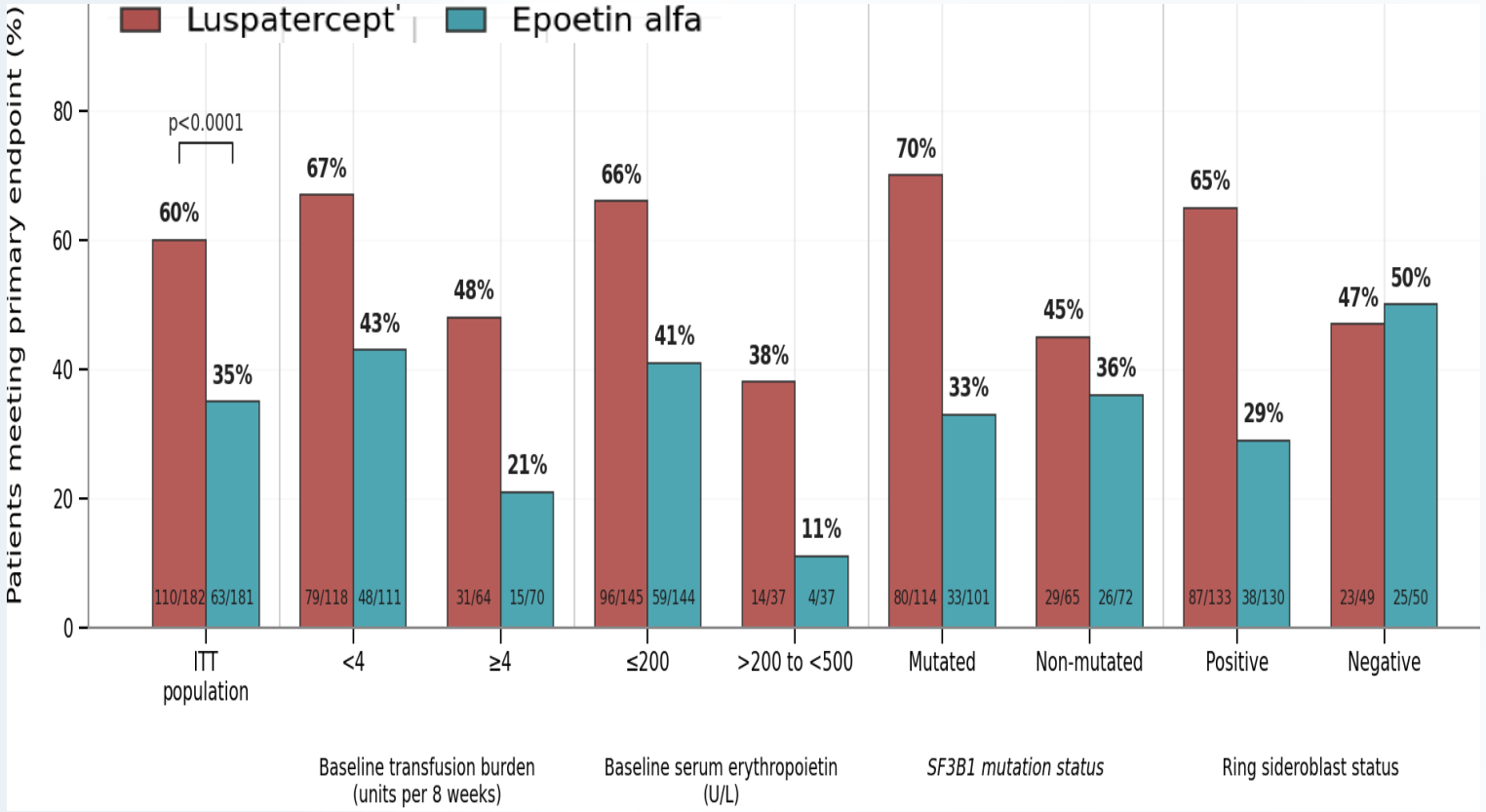
COMMANDS: Baseline Characteristics

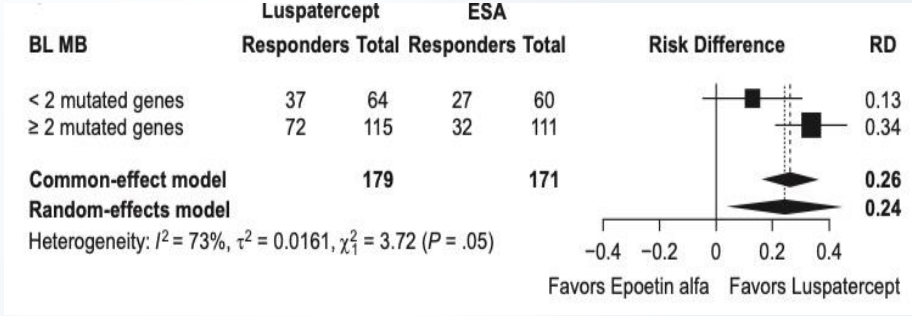
Primary endpoint: Transfusion independence for at least 12 weeks with a concurrent mean Hgb increase of at least 1.5 g/dL during weeks 1–24.

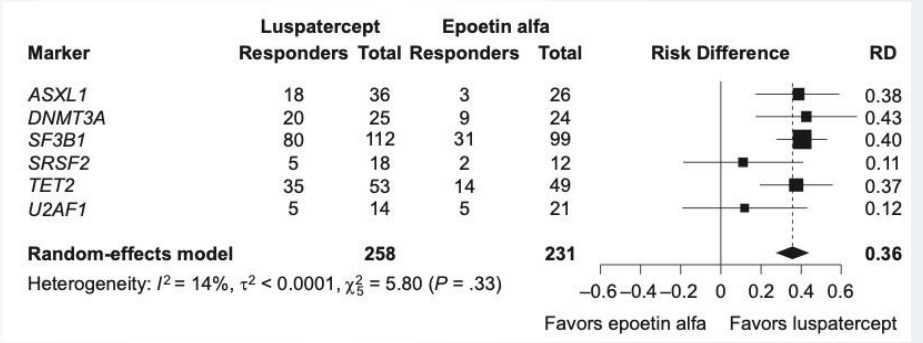
	Luspatercept (n:182)	Epoetin alfa (n:181)
Age (mean)	74	75
Female	40%	49%
Race-White	80%	79%
Race-Black	1%	-
R-IPSS (low)	71%	73%
R-IPSS (intermediate)	19%	16%
EPO (median)	77	85
EPO up to 200 IU/L	80%	80%
+ RS	73%	72%
+ SF3B1	63%	56%
Hgb <8 g/dl	60%	60%
Platelets (median)	230	235

The Lancet. Haematology, 11(9), e646–e658; *Am J Hematol*. 2026;101(3):427-438

COMMANDS: Primary Endpoint

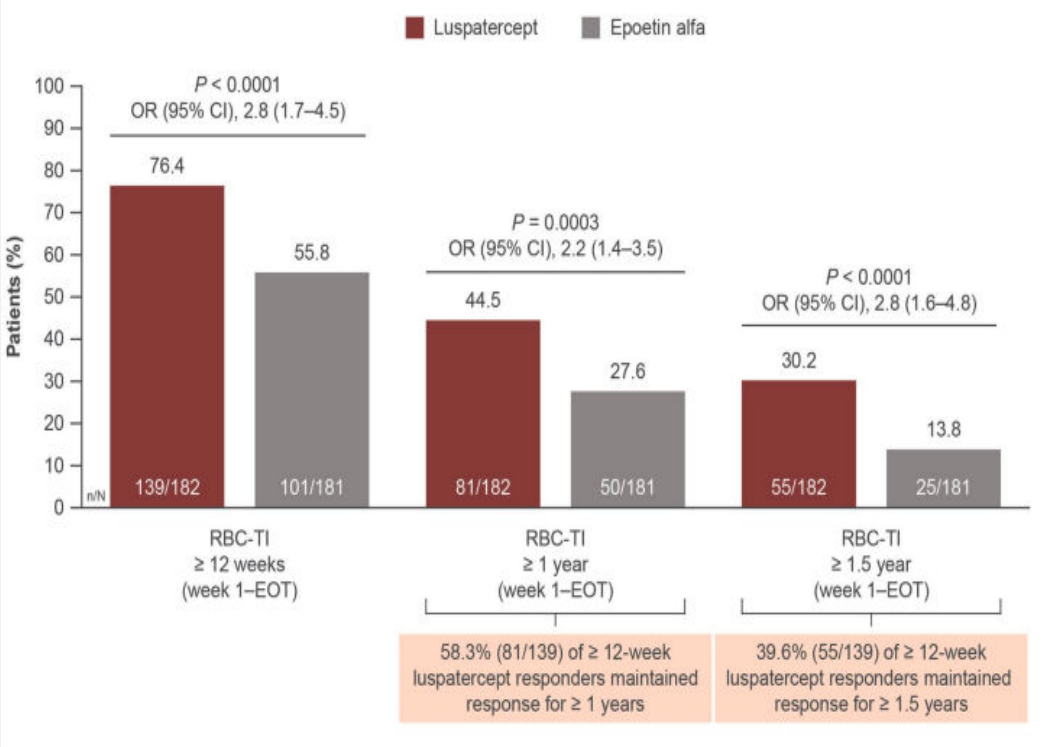


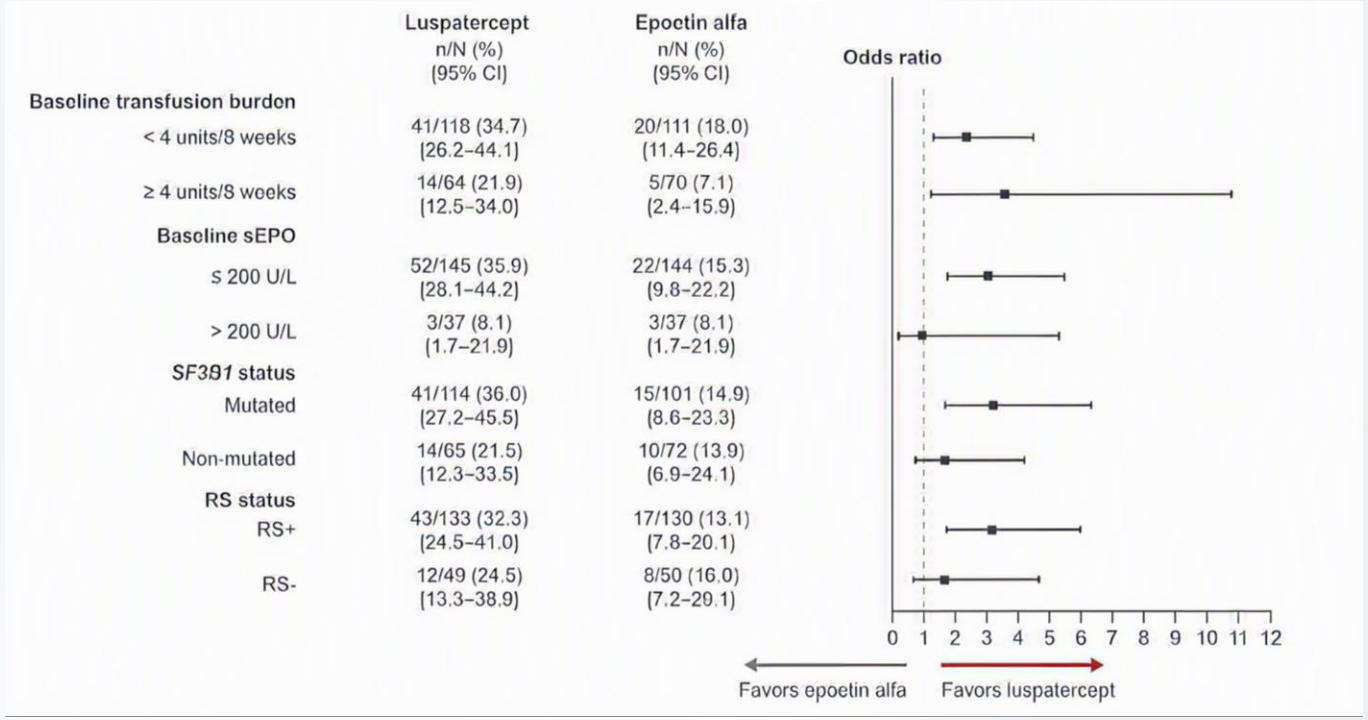




The Lancet. Haematology, 11(9), e646–e658; *Am J Hematol*. 2026;101(3):427-438

COMMANDS: Long Term Transfusion Independence





Adv Ther (2025) 42:3576–3589

COMMANDS: Long Term Outcomes

Endpoint	LUSPATERCEPT	ESA	HR (95% CI)
Median OS	NR	46.0 months	0.78 (0.56–1.09)
RBC-TI ≥12 weeks	76.40%	55.80%	
RBC-TI ≥12 weeks + mean Hb ≥10 g/dL	60.40%	39.20%	
Median cumulative duration of RBC-TI ≥12 weeks (95% CI)	184.4 weeks (118.4–NE)	95.1 weeks (74.9–180.1)	0.54 (0.36–0.80)
RBC-TI ≥2.5 years	25.30%	10.50%	
Mean Hb increase ≥1.5 g/dL	80.20%	58.60%	
Median duration of Hb increase ≥1.5 g/dL (95% CI)	72.9 weeks (53.9–89.9)	47.9 weeks (35.9–60.0)	0.61 (0.44–0.85)
Progression to higher-risk MDS	3.30%	7.30%	
Progression to AML	4.90%	5.50%	
Pts remaining on treatment at cutoff	17.60%	7.80%	
Median follow-up	35.9 months (range 1–73)	30.8 months (range 0–77)	

Abstract: EHA 2026; #3488

Beyond 1st Line: MEDALIST Trial — Phase III Luspatercept in LR-MDS with RS+/SF3B1+

Key Eligibility

- Adults with MDS-RS (≥15% ring sideroblasts, or ≥5% with SF3B1 mutation)
- IPSS-R Very low / Low / Intermediate risk
- RBC transfusion-dependent (≥2 units / 8 weeks)
- ESA-refractory, -intolerant, or unlikely to respond (EPO >200 U/L)
- No prior disease-modifying therapy; no del(5q)

Randomized
2:1
N = 229

Luspatercept (n = 153)

1.0 mg/kg SC every 3 weeks, titrated up to 1.75 mg/kg

Placebo (n = 76)

SC every 3 weeks; supportive care during follow-up

Primary endpoint RBC-TI ≥ 8 weeks (weeks 1–24)

Key Outcomes

Outcome	Lusp	Pbo	P
RBC-TI ≥8 wk, wk 1–24 (primary)	**38%**	13%	<0.001
RBC-TI ≥8 wk, entire tx period	**48%**	16%	<0.0001
RBC-TI ≥16 wk, entire tx period	**31%**	8%	<0.0001
Mean Hb ↑ ≥1.5 g/dL	**42%**	4%	<0.0001
AML progression	**2.6%**	3.9%	—
Alive at last cutoff	**69.3%**	68.4%	NS

OS benefit tied to response: **Luspatercept** wk 1–24 responders had longer OS vs non responders (RBC-TI ≥8 wk HR 0.32; ≥16 wk HR 0.26; mHI-E HR 0.26). Median OS NR (both arms).

Transfusion-dependent, ESA-refractory/intolerant, RS-positive lower-risk MDS (NCT02631070)

N Engl J Med. 2020;382(2):140-151; Leukemia. 2023;37(11):2314-2318

Beyond 1st Line: Imerge Trial

- *IMerge: Randomized, double-blind, placebo-controlled phase III trial evaluating imetelstat in lower-risk MDS*
- *ITT population: N=178; randomized 2:1 to imetelstat (n=118) or placebo (n=60)*
- *Key eligibility: non-del(5q) lower-risk MDS with RBC transfusion dependence (≥4 units/8 weeks)*
- *Patients were ESA-refractory, ESA-relapsed, or ESA-ineligible due to high endogenous EPO*
- *Treatment: imetelstat 7.5 mg/kg IV every 4 weeks versus placebo*

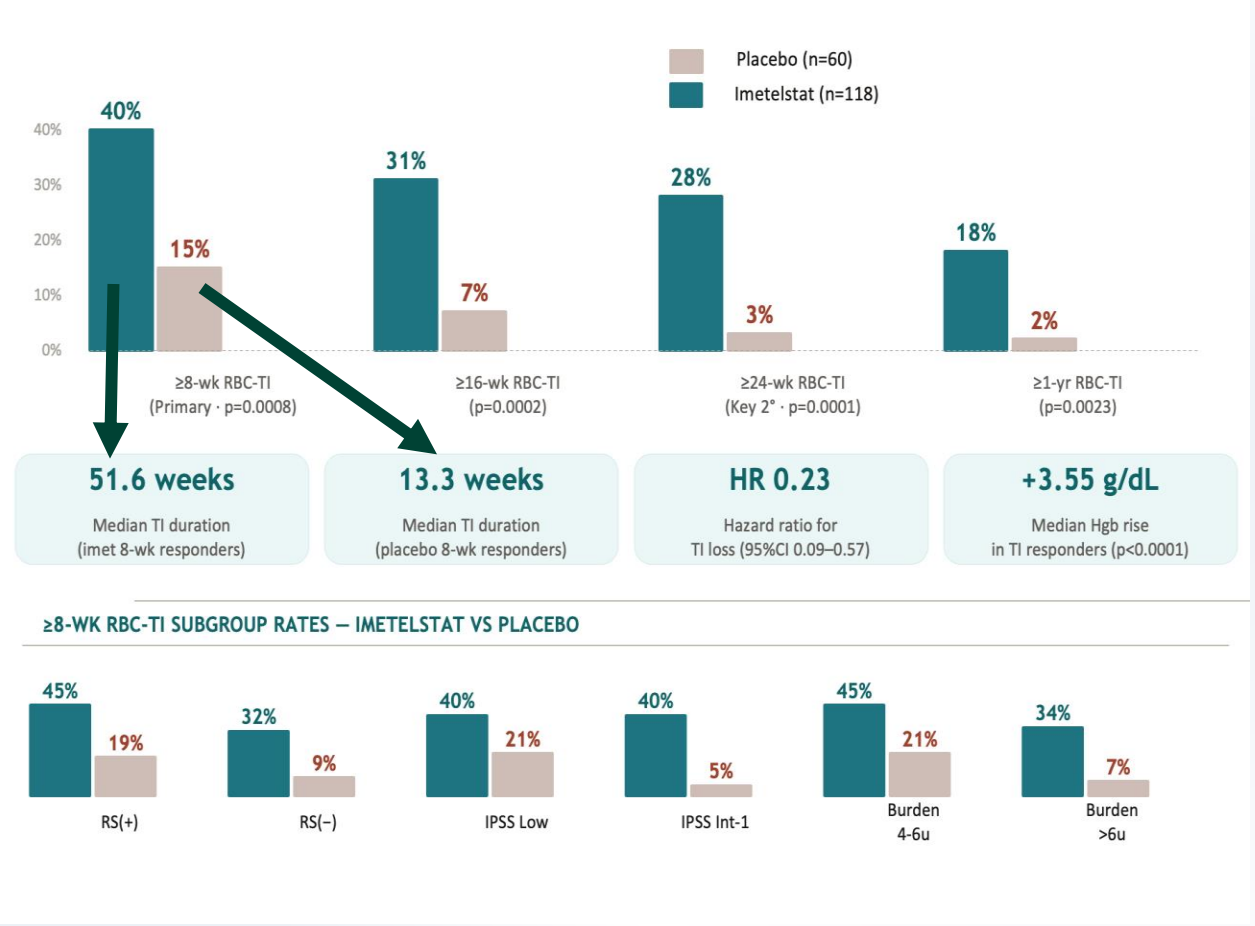
Lancet. 2024;403(10423):249-260

IMerge – Demographic and disease Characteristics

	Imetelstat (n:118)	Placebo (n:60)
Age (median)	72	73
Male	60%	67%
R-IPSS (low)	74%	77%
R-IPSS (intermediate)	17%	13%
pRBC units / 8 weeks (range)	6 (6-8)	6 (5-8.5)
Prior ESA use	108 (92%)	52 (87%)
Serum erythropoietin, median (IQR), mU/mL	174.9 (76.8–455.0)	277.0 (72.0–621.0)
EPO > 500 IU/L	22%	37%

Lancet. 2024;403(10423):249-260

IMerge: Key Outcomes and AE



AE	Imetelstat any	Imetelstat G3/4	Placebo any	Placebo G3/4
Thrombocytopenia	75	62	10	8
Neutropenia	74	68	7	3
Asthenia	19	0	14	0
Diarrhea	12	1	5	0
ALT increase	12	3	7	3

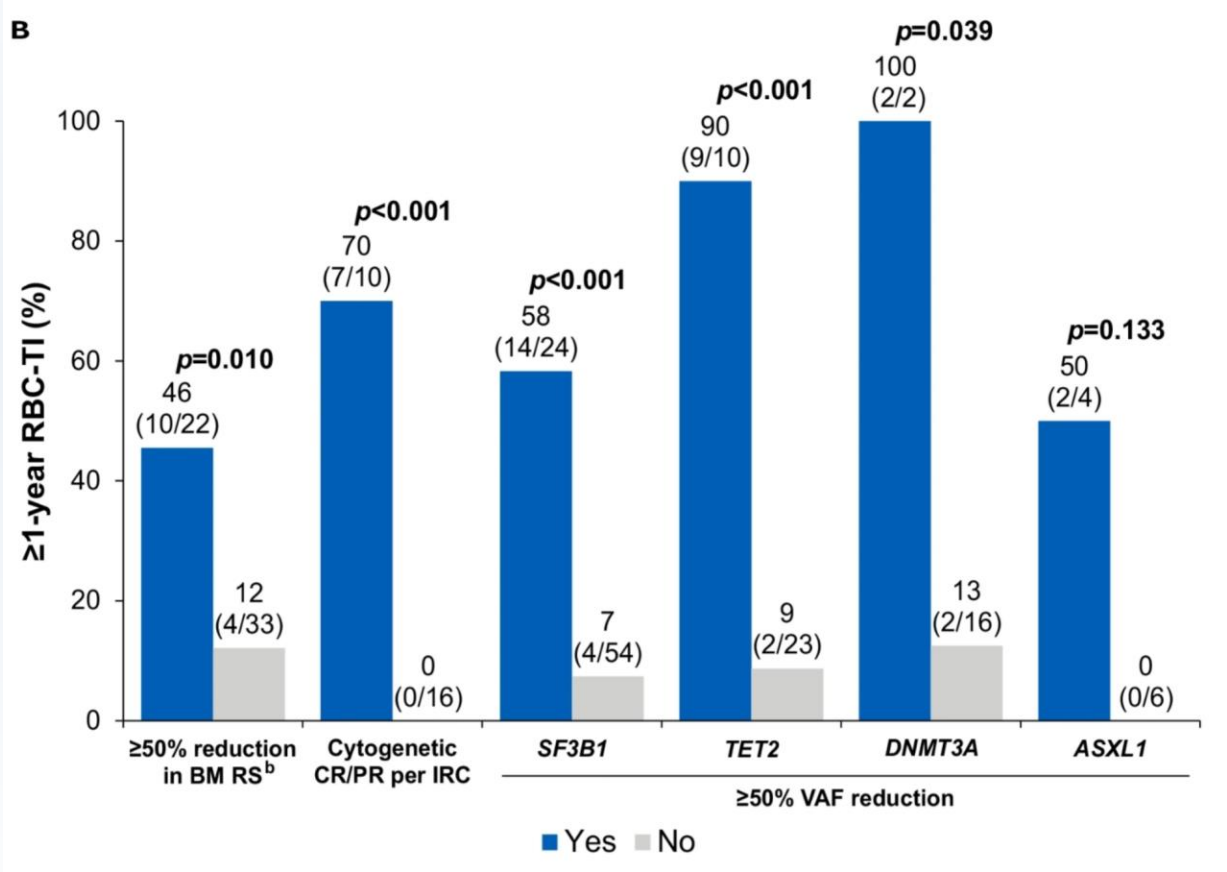
- *49% in the Imetelstat arm vs 7% in placebo arm had dose reductions*
- *16% in the Imetelstat arm vs none in placebo arm discontinued treatment secondary to adverse events*
- *In exploratory /associative analysis, maximum hemoglobin rise was associated with ≥50% maximum platelet reduction and ≥75% maximum neutrophil reduction within the first 2 cycles* **in a pooled analysis** *of Imetelstat studies.*

Lancet. 2024;403(10423):249-260; Blood Cancer J. 2026;16(1):55

IMerge: VAF Changes And Long Term TI

Mean maximum VAF reduction by RBC-TI response (Imetelstat arm)

Response group	SF3B1	TET2	DNMT3A	ASXL1
≥1-year RBC-TI responders	-76%	-77%	-41%	-76%
≥8 weeks to < 1 year RBC-TI	-44%	-29%	-39%	-53%
Non responders	-24%	-6%	-14%	-15%



Exploratory molecular data suggest clonal-burden reduction associated with durable TI.

Leukemia. 2026;40(2):397-409.

Beyond 1st Line: Phase III Trials of Lenalidomide ± ESA in LR Non-del(5q) MDS

Trial & Design	Population	Intervention	Primary Endpoint	Secondary / duration	Biomarkers / predictors
MDS-005 Phase III, randomized, double-blind, placebo-controlled	Non-del(5q), IPSS low/Int-1 MDS; RBC-TD; ESA-refractory or ESA-ineligible. N=239; 2:1 LEN n=160; PBO n=79	LEN 10 mg daily vs placebo 28-day cycles	RBC-TI ≥8 weeks: 26.9% vs 2.5% p<0.001	RBC-TI ≥24 weeks: 17.5% vs 0% Median TI duration (for RBC-TI ≥8 weeks): 30.9 weeks	Exploratory/post hoc: lower EPO enriched for TI with only 15.5% if EPO>500. Later mutation analysis: ASXL1 mutation associated with lower RBC-TI≥8 weeks.
GFM-Len-Epo-08 Phase III randomized	Non-del(5q), lower-risk, ESA-refractory, RBC-TD MDS N=131 LEN+EPO-β n=66; LEN n=65	LEN 10 mg daily, days 1–21 q28d + EPO-β 60,000 U weekly vs LEN alone	HI-E after 4 cycles 39.4% vs 23.1% p=0.044	RBC-TI: ~24% vs ~13% (NS) Median response duration: 15.1 vs 18.1 months p=0.47, NS	Len response was associated in some patients with a decrease in the size of the dominant subclone; the dominant subclone re-expanded upon loss of response or progression to AML

J Clin Oncol. 2016;34(25):2988-2996; Leukemia. 2016;30(4):897-905; Leuk Lymphoma. 2020;61(6):1475-1483; Leukemia. 2021;35(3):897-900; Blood. 2016;127(6):749-760.

Beyond 1st Line: HMA and alloHSCT

Study / Design (N, phase, schedule)	ORR (by arm)	TI / HI-E	mOS	AML / mortality	Notes
N=113 (81% MDS;59 patients TD); phase 2 (Bayesian adaptive) DEC 20 mg/m² IV d1–3 vs AZA 75 mg/m² d1–3, q28 days 68-mo f/u; N=113	*Overall Cohort 60% DEC 67% vs AZA 48% (P=.042)*	**TI 32% (DEC 41% vs AZA 15%; (P=.039); median TI dur 22 mo**	*Overall cohort: 33 months*	*No early death*	*Patients analyzed: TP53 (6.9%); DNMT3A (4.9%); IDH2(4.9%); and JAK2 (2.9%)*
NCT02269280 (ASH 2025 Abstract; EHA 2025 abstract) N=241; phase 2 Bayesian, DEC 20 mg/m² d1–3 AZA 75 mg/m² d1–3 AZA 75 mg/m² d1–5 q28 days 61% TD. TI included BSC arm	*TD ORR: 55 % / 57% / 48% (NS)* *TI ORR: 47% / 56% / 70%; BSC 17%;*	*TD (n=149) TI (n=92)* **TD (RBC/Plt) to TI: 44% / 42% / 40% (NS)**	*TD: 26.5 / 33.7 / 45.2 (P=.09) TD HR 0.56* *TI: 43.5 / 80.1 / NR / 67.2 (P=.01) AZA5>DEC3: HR 0.30*	*EFS primary endpoint; AML transformation included within EFS definition*	*NGS n=224: ASXL1: 31%, RUNX1: 14%, TP53: 8%*
MDS-ALLO-RISK Lower-risk MDS or CMML (10% of patients) w/ high-risk features N=77 (62 donor / 15 no-donor); phase 2, donor-vs-no-donor	*CR: 67.8% (transplanted) vs 21.4% (no-donor)*	—	*3-yr OS 57.6% (donor) vs 64.3% (no-donor) HR 0.75, P=.53 (NS); IPTW confirmed no benefit*	*NRM 24.7% at 36 months; ↑cGVHD, severe infections*	*Study was terminated early. IPSS low/int-1 with high-risk features: intermediate-or-higher IPSS-R, severe cytopenias, or failure of 2 treatment lines*

Blood. 2017;130(13):1514-1522; NEJM Evid. 2022;1(10):EVIDoa2200034.; Blood Adv. 2026;10(2):494-504; Bouligny, EHA 2025

Beyond 1st Line: IDH1/2 Inhibitors in LR MDS with Anemia

- **IDIOME phase II trial — ivosidenib (IDH1 inhibitor)**

  IDIOME phase II ivosidenib trial included a planned LR-MDS cohort after ESA failure; final EHA 2024 report included 3 cohort C patients, with 2 CRs.

- **Ivosidenib phase I sub-study in IDH1-mutated R/R MDS**

  Enrolled predominantly higher-risk / relapsed-refractory MDS patient. Among baseline transfusion-dependent patients, ~67% became transfusion independent for ≥56 days; final analysis reported 71.4% RBC-TD patients became TI.

- **GFM/EMSCO IDEAL phase II trial — enasidenib (IDH2 inhibitor)**

  Cohort C: 11 patients with IDH2-mutated lower-risk MDS after ESA failure. 55% achieved CR with transfusion independence. Median time to response: ~3 cycles. Responses were durable.

Clin Cancer Res. 2025;31(17):3613-3617. *Blood* (2024) 144 (Supplement 1): 1839; Blood Adv. 2024;8(15):4209-4220.

Anemia Management: Focus on Del(5q) MDS

Setting	Trial / Population	Intervention	Key outcomes
RBC transfusion-dependent	*MDS-004* *Phase III, randomized, double-blind* *N=205; IPSS low/Int-1 del(5q) MDS*	*LEN 10 mg d1–21 or 5 mg daily vs placebo*	*Primary endpoint: RBC-TI ≥26 weeks* *• LEN 10 mg: 56.1%* *• LEN 5 mg: 42.6%* *• Placebo: 5.9%* *Cytogenetic response: 50% with LEN 10 mg vs 25% with LEN 5 mg*
Non–transfusion-dependent anemia	*SintraREV* *Phase III, randomized, double-blind* *N=61; low/Int-1 del(5q), ESA-naïve, non-TD anemia*	*LEN 5 mg daily vs placebo up to 2 years*	*Median time to transfusion dependence:* *• LEN: not reached* *• Placebo: 11.6 months*
After LEN failure / progression	*International retrospective cohort N=392. lower-risk MDS (up to Int-1 IPSS) majority with del(5q) /del(5q) with additional chromosomal change.*	*Individualized: clinical trial, HMA, supportive care, or selected allo-HSCT*	*Median survival after LEN failure for del(5q): 24 months.* *HMA associated with relatively prolonged survival; allo-HSCT only for selected patients with progression/high-risk features. ESA responses were diminished.*

Blood. 2011;118(14):3765-3776; Lancet Haematol. 2024;11(9):e659-e670; Oncotarget. 2017;8(47):81926-81935

LR MDS: Clinical Trials Landscape

NCT07422480	*A Study to Compare Elritercept With Epoetin Alfa to Treat Anemia in Adults With Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes (MDS) Who Need Regular Blood Transfusions (ELRiSE MDS)*
NCT06847867	*A Study of Momelotinib in Participants With Low-risk Myelodysplastic Syndrome (MIDAS)*
NCT05320198	*Study of DISC-0974 (RALLY-MF) in Participants With Myelofibrosis or Myelodysplastic Syndrome and Anemia*
NCT05949684	*A Study to Compare the Efficacy and Safety of Luspatercept in Participants With Myelodysplastic Syndrome (MDS) and Anemia Not Receiving Blood Transfusions (ELEMENT-MDS)*
NCT05490446	*A Study of Tebapivat (AG-946) in Participants With Anemia Due to Lower-Risk Myelodysplastic Syndromes (LR-MDS)*
NCT05924100	*Efficacy and Safety of Luspatercept for the Treatment of Anemia Due to MDS With del5q, Refractory/Resistant/Intolerant to Prior Treatments, RBC-TD (Phoenix)*
NCT04245397	*Study of SX-682 Alone and in Combination With Oral or Intravenous Decitabine in Subjects With Myelodysplastic Syndrome*

Symptomatic anemia in LR-MDS

Assess:
- RBC transfusion burden
- Serum EPO
- del(5q)
- RS / SF3B1
- Cellularity
- Cytopenias and progression risk

Clinical trial preferred when feasible.

Non-del(5q), RS− / SF3B1 WT TD, sEPO above 500 IU/L

Minority of cases. ESA benefit is much less likely; consider imetelstat, clinical trial; IST maybe useful in context of hypocellular bone marrowor HMA for multilineage cytopenias/higher risk features. Limited data exist for luspatercept.

Non-del(5q), TD, RS+ / SF3B1+

Luspatercept favored. COMMANDS showed strongest first-line signal in RS/SF3B1-positive disease.

Non-del(5q), TD, RS− / SF3B1 WT, sEPO ≤200 IU/L

ESA or luspatercept. Favor Luspatercept for transfusion burden (especially heavy), increased mutation burden. Luspatercept responses may be more durable.

Non-del(5q), RS− / SF3B1 WT, sEPO >200 - 500 IU/L

ESA benefit less likely; consider luspatercept; subgroup estimates are less robust than RS/SF3B1-positive disease.

Post-ESA failure, TD non-del(5q)

Imetelstat is a key option. COMBOLA trial is investigating role of Luspatercept in this setting.

Post-ESA failure RS+ / SF3B1+

Luspatercept is an option if not previously used. MEDALIST supports use after ESA failure/ineligibility in RS-positive LR-MDS.

Imetelstat has also demonstrated efficacy.

Post-luspatercept failure

Imetelstat is an attractive option; direct prospective sequencing data remain limited.

After second-line failure in non- Del(5q) MDS

Imetelstat preferred if not used before.

Lenalidomide has limited role in patients with isolated anemia. Responses appear diminished after use of HMA in lower risk MDS.

- Low-dose HMA for mixed cytopenias or rising blasts, adverse molecular/cytogenetic evolution.

- Assess for allo-HSCT taking into account fitness, cytopenias, mutational/cytogenetic data and available trial options.

Special phenotypes: when the non-del(5q) anemia algorithm should change

del(5q) MDS

If RBC-TD: lenalidomide is the targeted standard.
Check TP53 allelic state/VAF and monitor cytopenias/clonal evolution.

If RBC-TI: non-TD symptomatic anemia:
Consider early low-dose lenalidomide in selected patients after shared decision-making.

IDH inhibitors may be considered in patients who carry relevant mutations. Data are limited.

Hypoplastic / immune-mediated phenotype

Consider IST in selected patients: hATG + cyclosporine, especially in hypocellular marrow and clinical features resembling immune marrow failure.

del(5q) after lenalidomide failure

Clinical trial preferred.
Consider HMA for progression/mixed cytopenias; allo-HSCT consideration if fit and high-risk / progressive biology.

After IST failure

Reassess diagnosis/risk, cytogenetics, and mutations.
Treat according to dominant phenotype: anemia-directed agent, HMA, trial, or transplant evaluation.