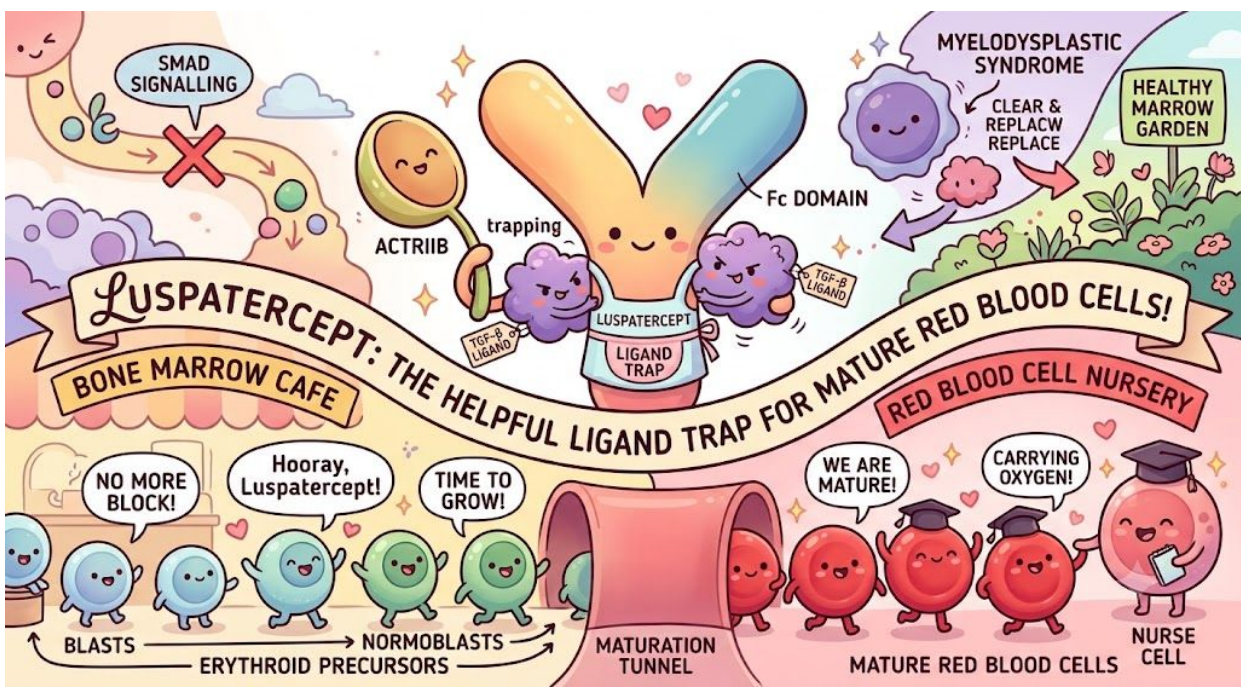


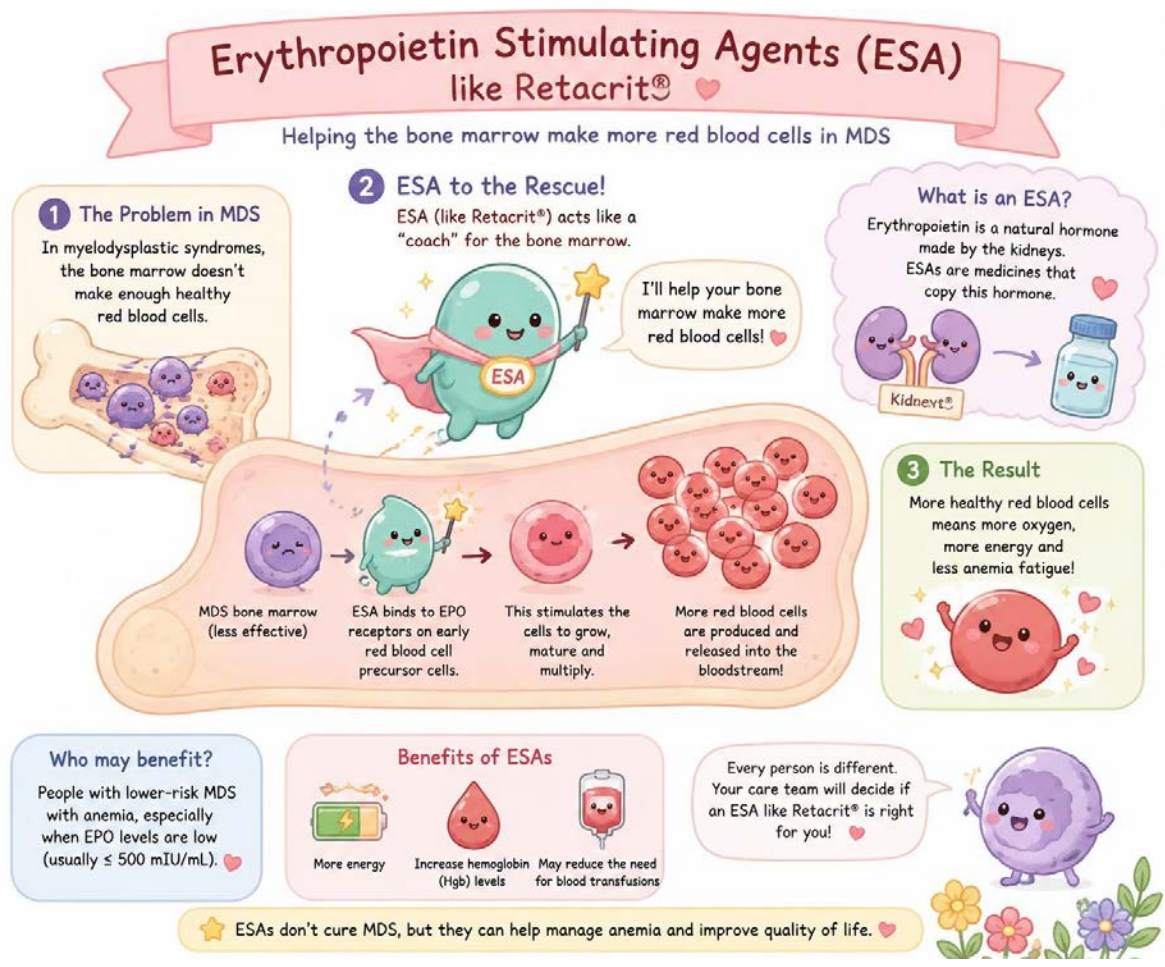
FLASCO MALIGNANT HEMATOLOGY 2026

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

Jonathan Feld, MD



OR





Lower-Risk MDS Summary



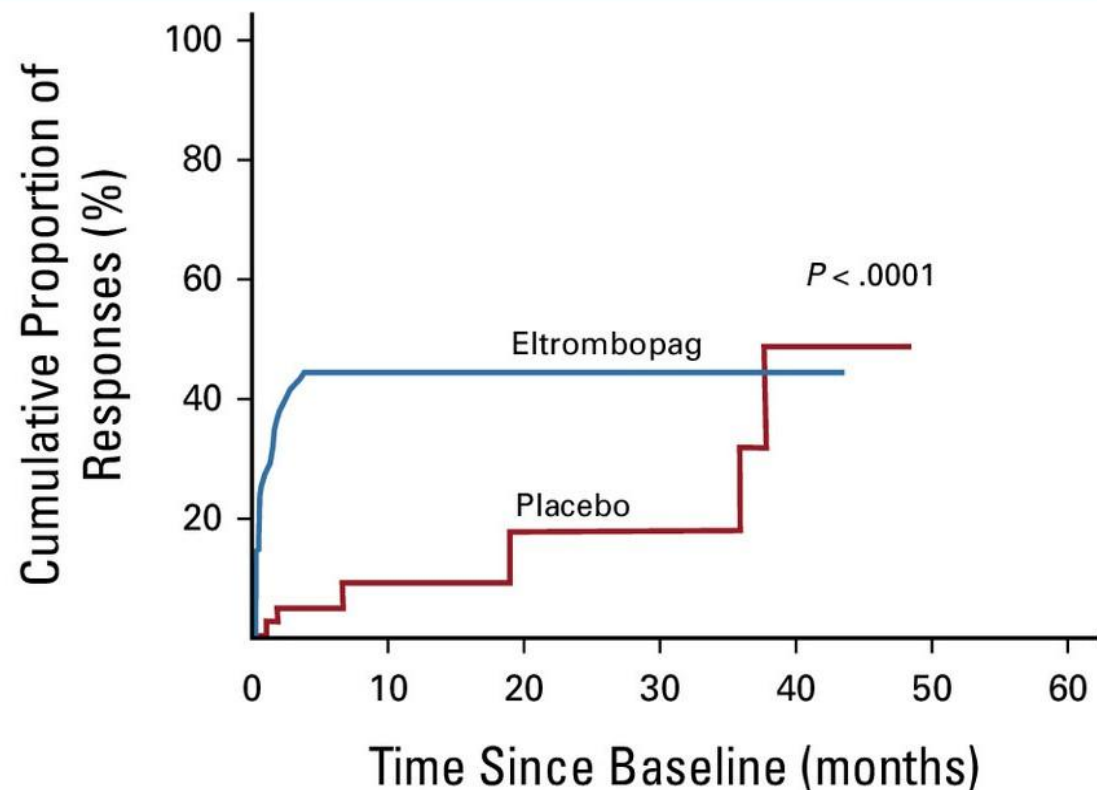
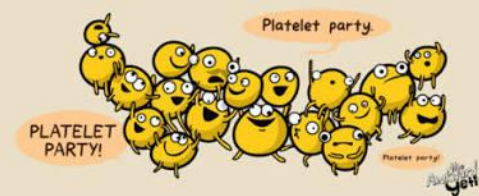
•Lower-Risk MDS

- Thrombocytopenia (without increased blasts) → TPO mimetic
- Neutropenia (without increased blasts) → G-CSF, PPx
- Del5q → ESA / Lenalidomide
- Hypoplastic MDS → IST (ATG + CsA + EPAG)
- Ringed Sideroblast positive → **Luspatercept** / ESA +/- GCSF
- Ringed Sideroblast negative → ESA / **Luspatercept**
- High EPO level → Imetelstat / HMA



• **Lower-Risk MDS**

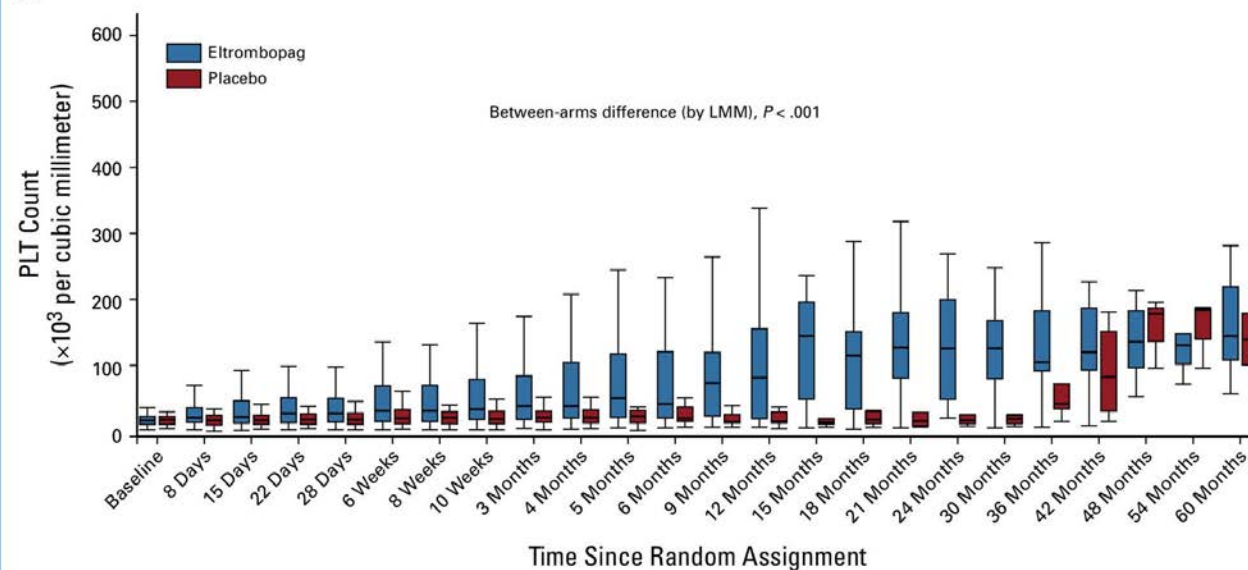
- Thrombocytopenia (without increased blasts) → TPO mimetic
- Neutropenia (without increased blasts) → G-CSF, PPx



No. at risk:

Eltrombopag	111	11	2	1	1	0	0
Placebo	54	13	8	6	2	0	0

A





G-CSF in MDS



NEUTROPHIL



Current Treatment Landscape



•Lower-Risk MDS

- Thrombocytopenia (without increased blasts) → TPO mimetic
- Neutropenia (without increased blasts) → G-CSF, PPx
- Del5q → ESA / Lenalidomide
- Hypoplastic MDS → IST (ATG + CsA + EPAG)

Table 2. Erythroid Response to Lenalidomide.

Variable	Continuous Daily Dosing (N=102)*	21-Day Dosing (N=46)*	All Patients (N=148)
Erythroid response — no. (%)			
Transfusion independence	71 (70)	28 (61)	99 (67)
95% CI			59–74
≥50% decrease in no. of transfusions	8 (8)	5 (11)	13 (9)
95% CI			5–15
Total transfusion response	79 (77)	33 (72)	112 (76)
95% CI			68–82
Time to response — wk			
Median	4.7	4.3	4.6
Range	1–34	1–49	1–49
Hemoglobin — g/dl			
Baseline†			
Median	7.7	8.0	7.8
Range	5.3–10.4	5.6–10.3	5.3–10.4
Response‡			
Median	13.4	13.5	13.4
Range	9.2–18.6	9.3–16.9	9.2–18.6
Increase			
Median	5.4	5.4	5.4
Range	2.2–11.4	1.1–9.1	1.1–11.4

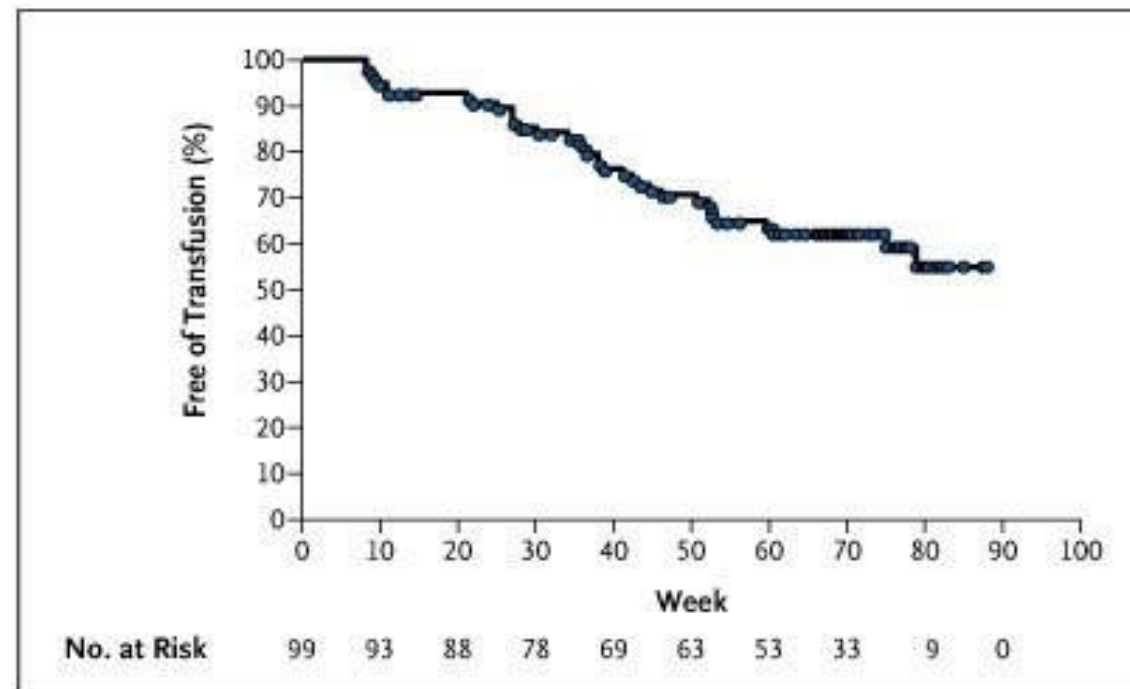


Table 3. Frequency of Cytogenetic Response According to Karyotype Complexity.

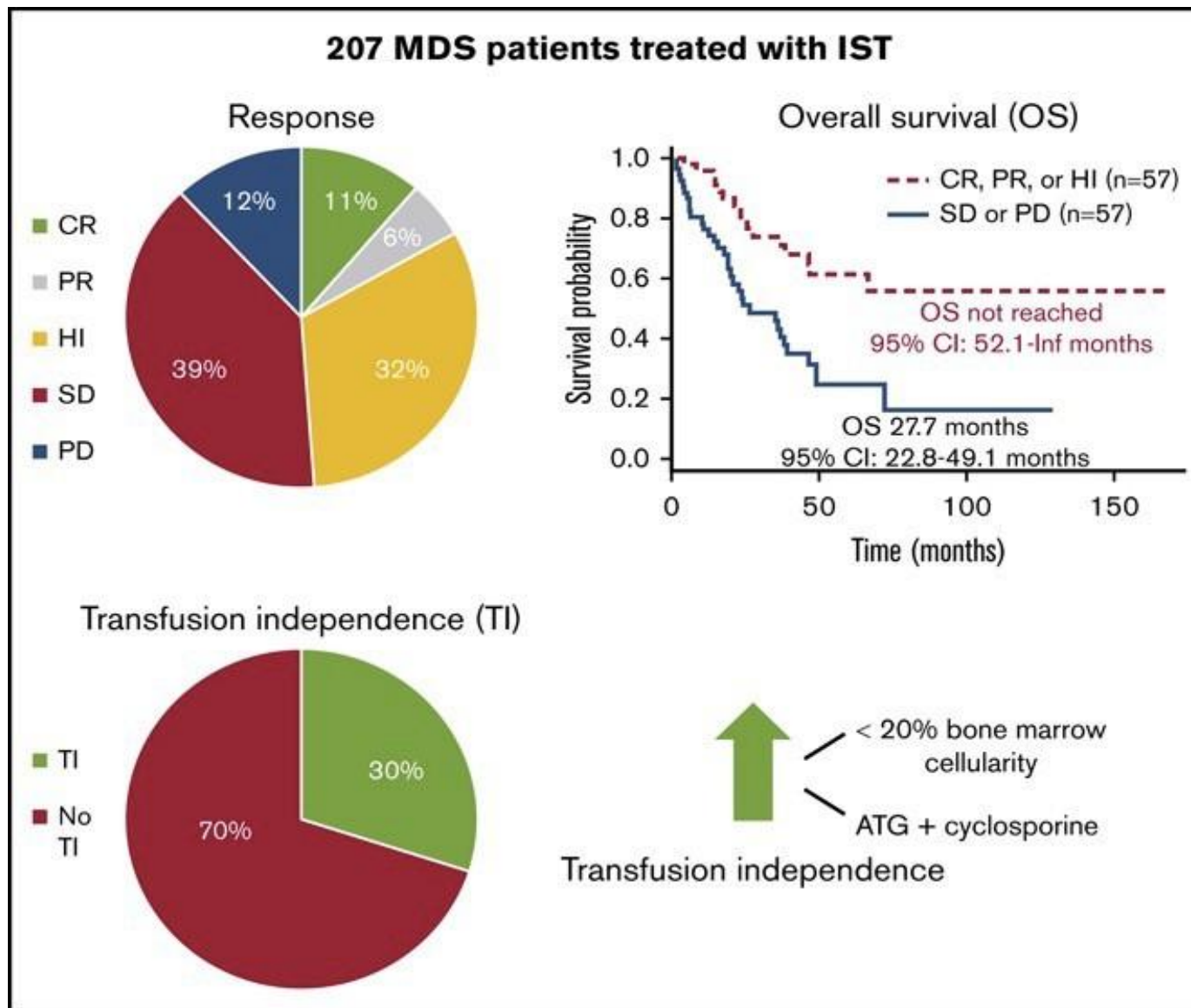
Complexity	Patients Who Could Be Evaluated*	Cytogenetic Response	Complete Cytogenetic Remission
Isolated 5q deletion — no. (%)	64	49 (77)	29 (45)
5q deletion + 1 additional abnormality — no. (%)	15	10 (67)	6 (40)
Complex (≥3 abnormalities) — no. (%)	6	3 (50)	3 (50)
P value		0.27	0.93

* Patients who could be evaluated were those with at least 20 analyzable cells in metaphase at baseline and at least one follow-up assessment. P values are for the association between karyotypic complexity and a cytogenetic response or complete cytogenetic remission.

* The daily dose was 10 mg.

† The baseline hemoglobin concentration was the minimum value during the baseline period.

‡ The response hemoglobin concentration was the maximum value during the transfusion-independent response period.

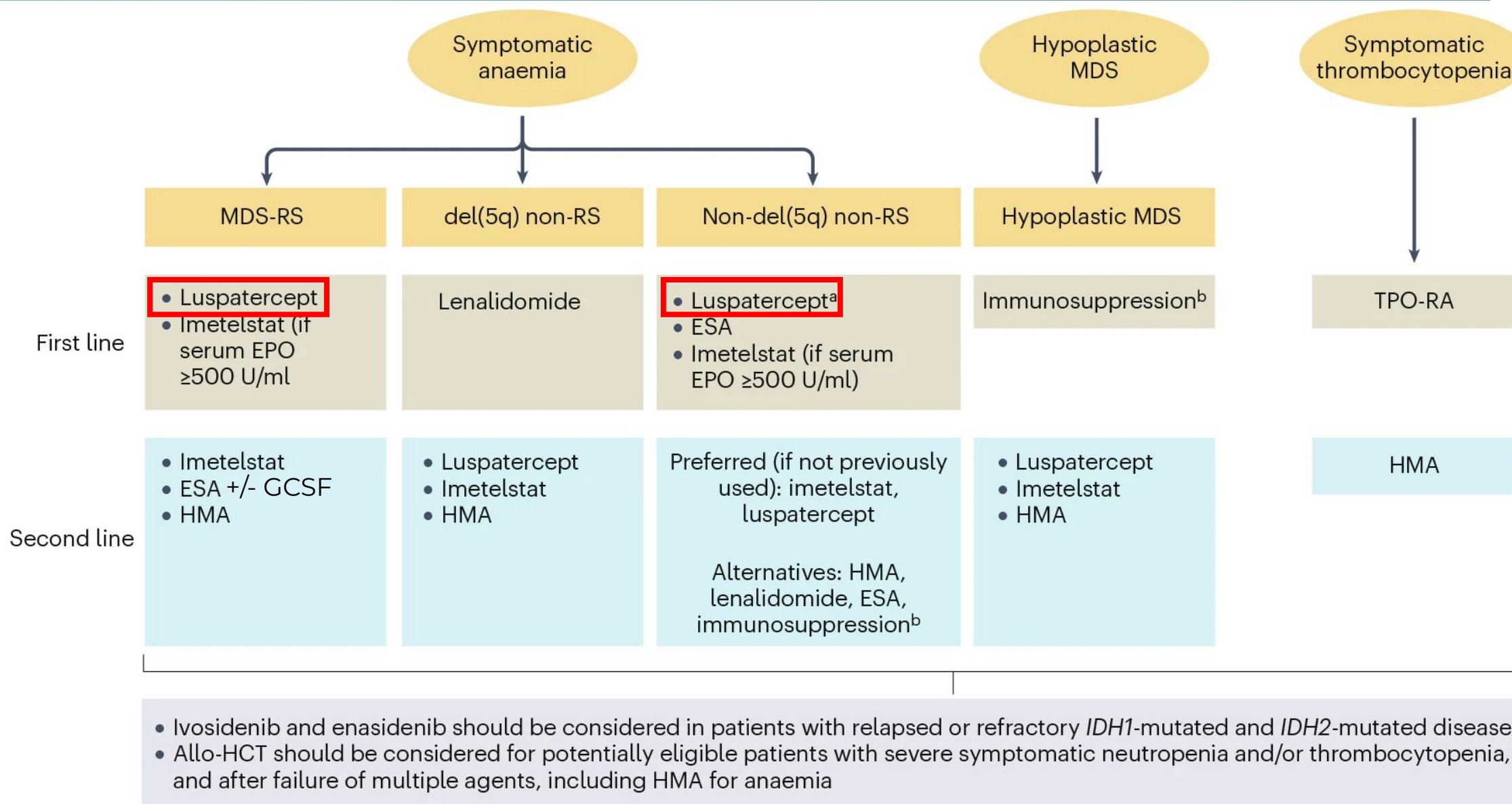
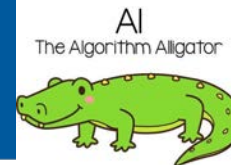




WHAT ABOUT LOWER-RISK ANEMIC MDS PATIENTS?

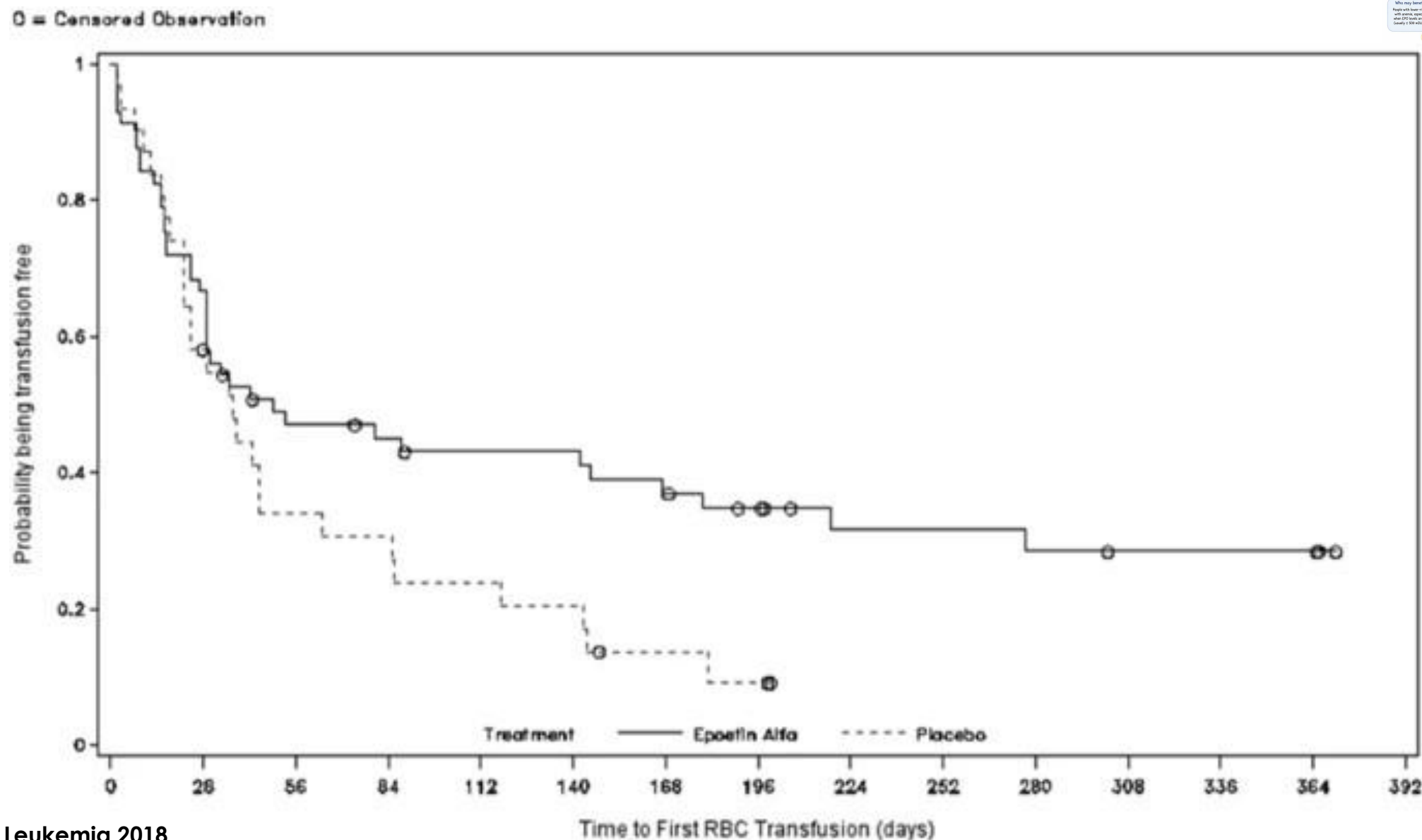
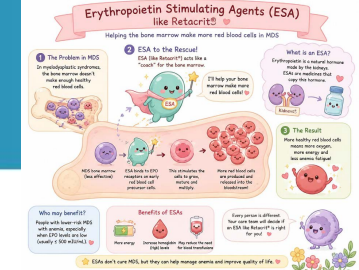


Treatment Algorithm



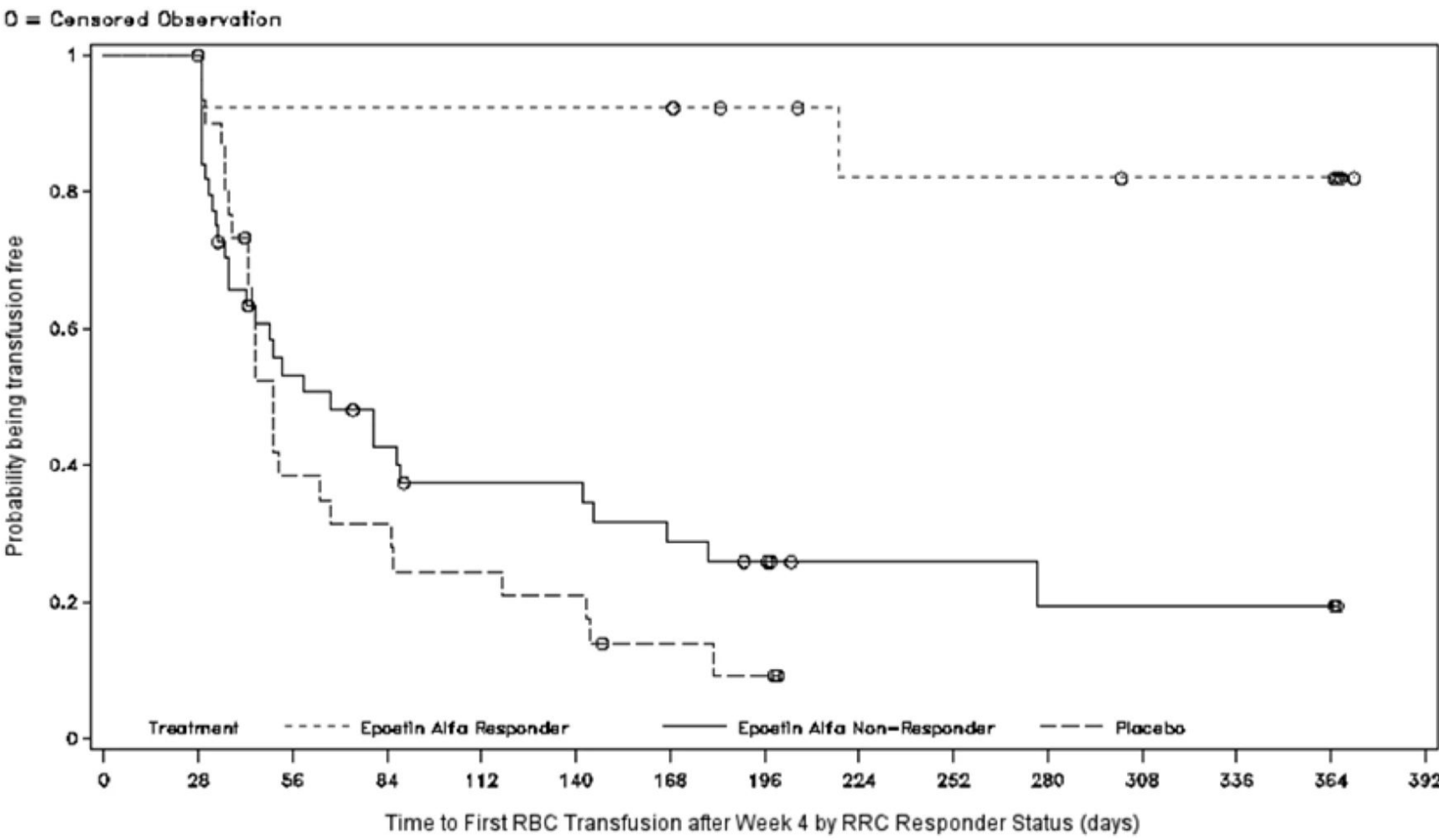
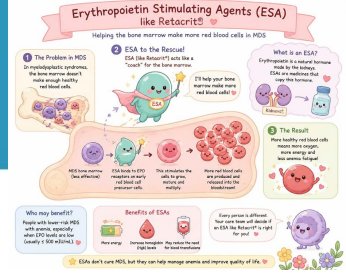


ESA (Retacrit) MDS Phase III





EPO Stimulating Agents





HI Response by EPO Level



	EPO <200 (n=1009)	EPO 200-500 (n=109)	EPO >500 (n=93)	p-value
Age (median, years)	70.6	68.1	67.5	p<0.001
Sex (male)	664 (65.8%)	75 (68.8%)	66 (71.0%)	p=0.457
Race (white)	932 (92.4%)	98 (89.9%)	82 (88.2%)	p=0.435
Median HgB (g/dL)	10.5	9.20	8.50	p<0.001
RBC-TD (%)	144 (14.3%)	46 (42.2%)	59 (63.4%)	p<0.001
Ferritin>1000 (%)	146 (14.9%)	37 (36.3%)	49 (55.1%)	p<0.001
RUNX1 MT	9.9% (84/851)	15.6% (14/90)	20.3% (16/79)	p=0.0076
U2AF1 MT	18.6% (158/851)	29.7% (27/91)	35.4% (28/79)	p<0.001
ZRSR2 MT	11.2% (95/891)	18.7% (17/91)	30.4% (24/79)	p<0.001
EZH2 MT	5.3% (45/851)	11% (10/91)	20.3% (16/79)	p<0.001

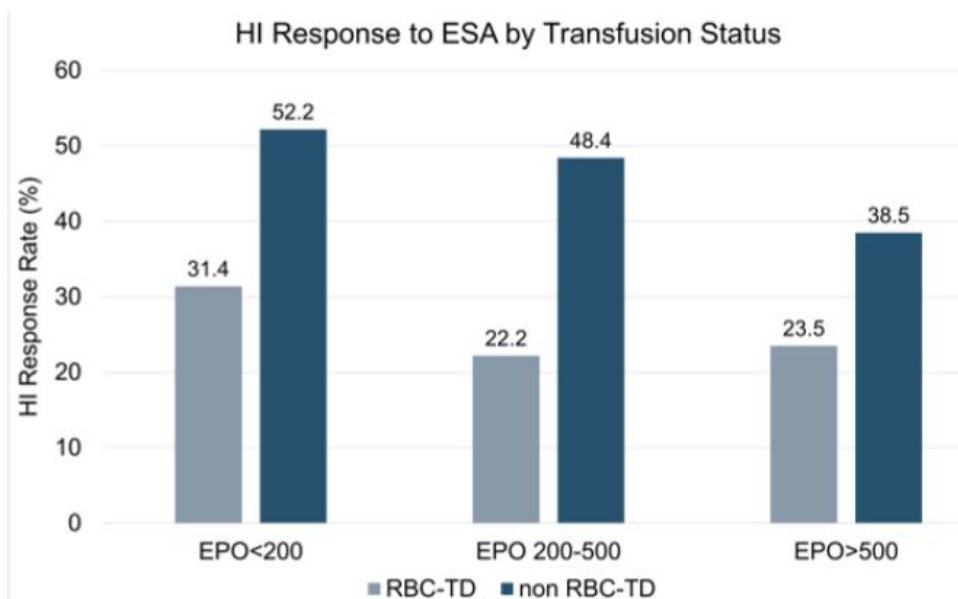


Figure 1: The rate of hematological improvement (HI) (defined as a hemoglobin increase of at least 1.5 g/dL, transfusion independence (RBC-TI) and/or 50% decrease in transfusion burden) in patients with LR-MDS treated with erythroid stimulants (ESA), stratified according to red blood cell transfusion dependency and EPO levels ($p=0.003$ for EPO<200, $p=0.031$ for EPO 200-500, and $p=0.436$ for EPO>500).

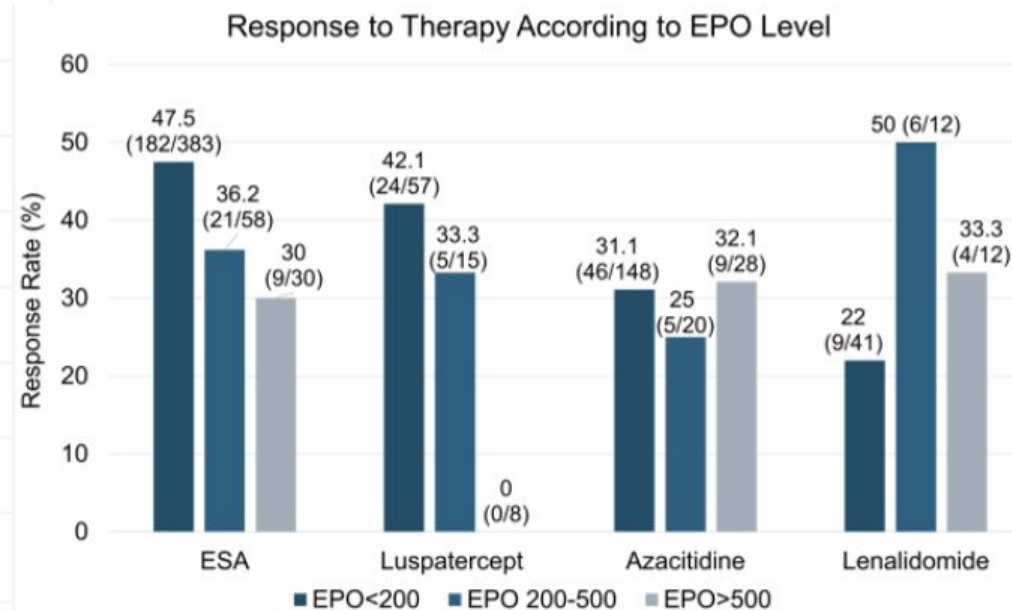
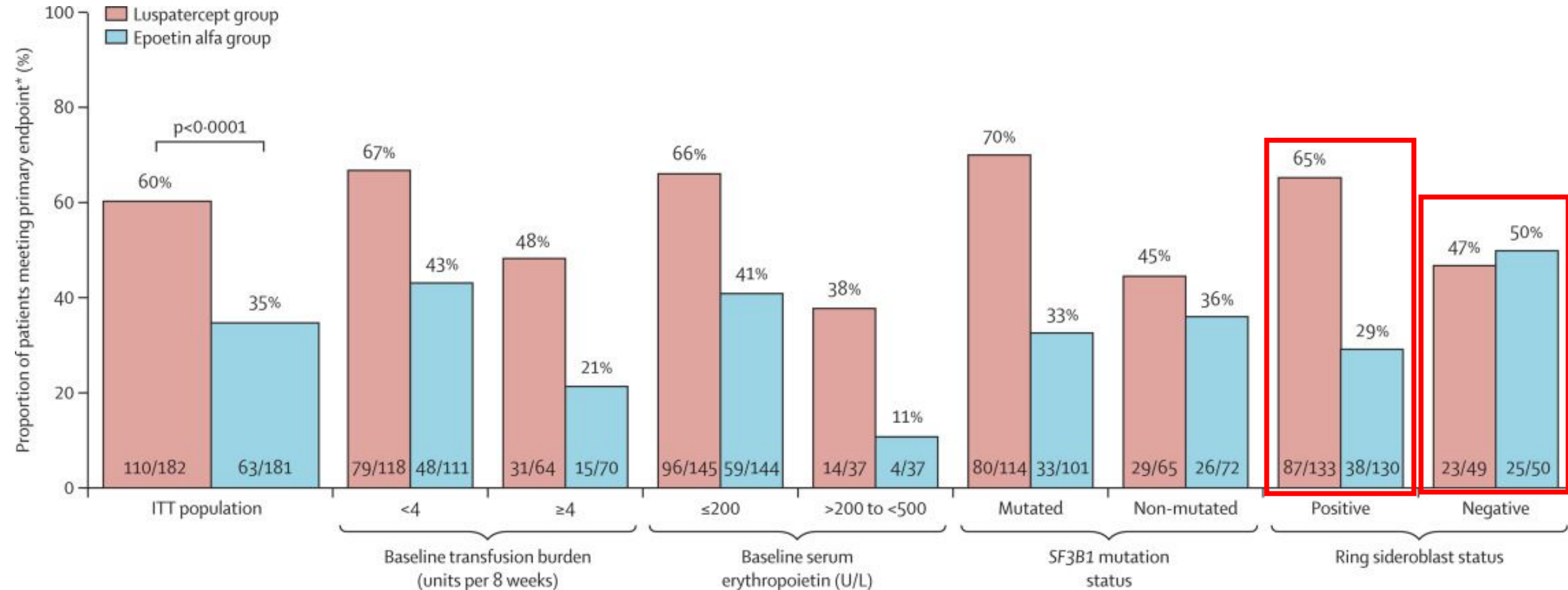


Figure 2: Response rates (defined as hematological improvement or better response) in patients treated with ESA, luspatercept (monotherapy only), azacitidine, or lenalidomide as first-line therapies ($p=0.063$ for ESA, $p=0.028$ for luspatercept, $p=0.84$ for azacitidine, and $p=0.161$ for lenalidomide).



Luspatercept COMMANDS TRIAL

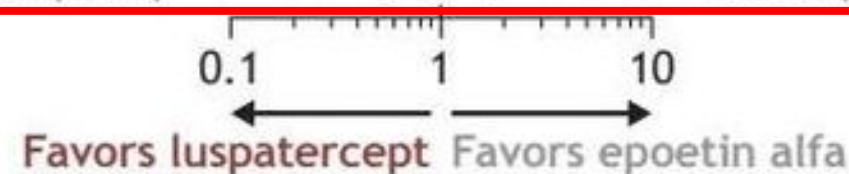




Luspatercept COMMANDS TRIAL



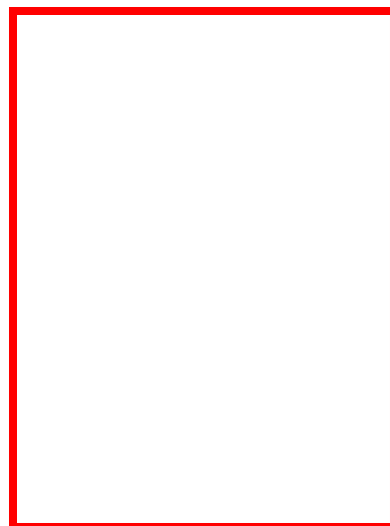
	Luspatercept		Epoetin alfa		HR (95% CI) ^c
	Median OS, months ^b	Deaths, n/N (%)	Median OS, months ^b	Deaths, n/N (%)	
Overall (ITT)	NR	66/182 (36.3)	46.0	77/181 (42.5)	0.781 (0.559-1.092)
Baseline sEPO, U/L					
≤ 200	NR	51/145 (35.2)	51.4	53/144 (36.8)	0.814 (0.554-1.196)
> 200	43.0	15/37 (40.5)	35.4	24/37 (64.9)	0.669 (0.350-1.278)
Baseline TB, pRBC U/8 weeks					
< 4	57.5	43/118 (36.4)	47.2	41/111 (36.9)	0.870 (0.567-1.334)
≥ 4	NR	23/64 (35.9)	39.9	36/70 (51.4)	0.623 (0.369-1.054)
RS status					
Positive	NR	45/133 (33.8)	47.2	52/130 (40.0)	0.698 (0.468-1.040)
Negative	54.8	21/49 (42.9)	46.2	24/50 (48.0)	0.956 (0.531-1.723)



	Retacrit	Luspatercept
Dose	60,000 U weekly	122.5 mg q3 weeks
Approx. cost/dose	\$4,068	\$20,924
Doses over 18 mo	78	26
18-month cost	\$317,341	\$544,019
Difference		+\$226,677



Luspatercept MAXILLUS TRIAL





Luspatercept MAXILLUS TRIAL

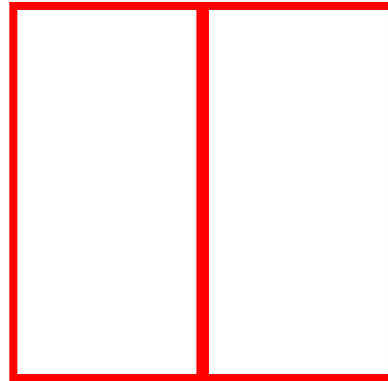
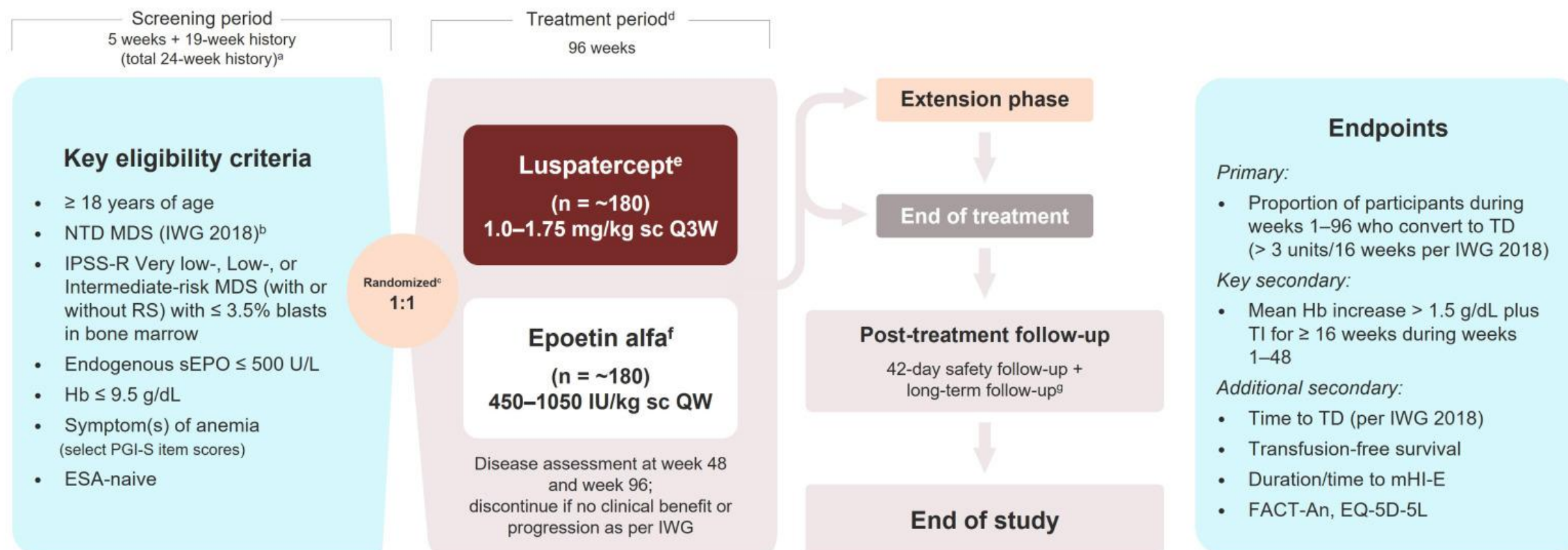




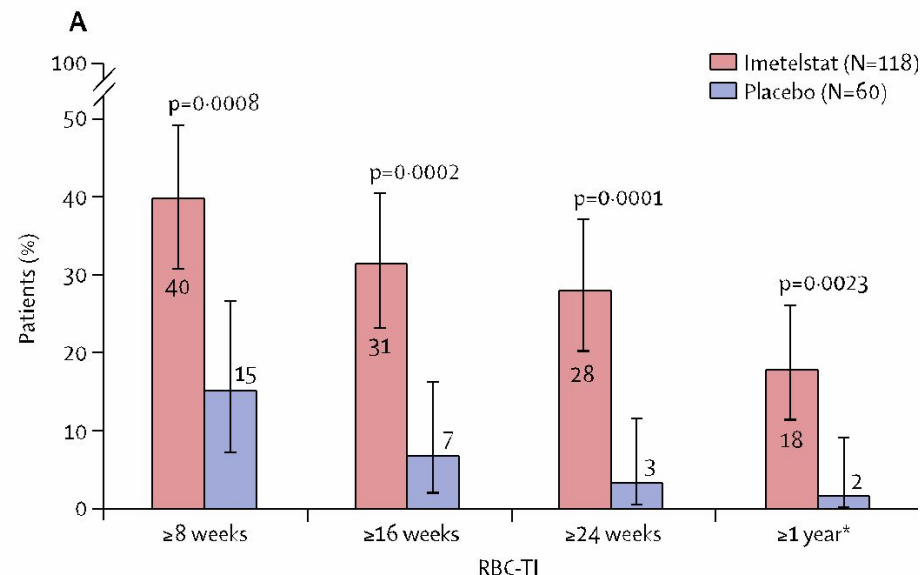
Figure. The ELEMENT-MDS study design



^aRBC transfusion history must be available for ≥ 24 weeks; ^bZero (0) RBC units over 16 weeks prior to randomization; 1–2 RBC units within the 16 weeks prior to enrollment are allowed provided transfusion was administered for an acute event/illness (ie, surgical procedure, bleeding, infection) or presence of comorbidity, and not for the treatment of low Hb (with or without symptoms) alone; ^cStratified by baseline (1) sEPO level: 0–200 vs 200–500; (2) RS status (50% cap for RS negative); (3) IPSS-R Very low-, Low- vs Intermediate-risk; ^dCrossover between the treatment arms is not permitted during the study treatment period; ^eStarting dose 1.0 mg/kg, dose escalation up to 1.75 mg/kg to maintain Hb between 10–11.5 g/dL; ^fStarting dose = 450 IU/kg, dose escalation up to 1050 IU/kg (max 80,000 IU) to maintain Hb between 10–11.5 g/dL; ^g≥ 5 years post 1st dose of IP or 3 years from last dose (whichever occurs later) for AML progression, MDS treatment, OS. Abbreviations: AML, acute myeloid leukemia; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACT-An, Functional Assessment of Cancer Therapy-Anemia; Hb, hemoglobin; IP, investigational product; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; MDS, myelodysplastic syndromes; mHI-E, modified hematologic improvement–erythroid response; NTD, non-transfusion-dependent; OS, overall survival; PGI-S, Patient Global Impression of Severity; QW, every week; Q3W, every 3 weeks; RBC, red blood cell; RS, ring sideroblasts; sc, subcutaneous; sEPO, serum erythropoietin; TD, transfusion dependent; TI, transfusion independent.



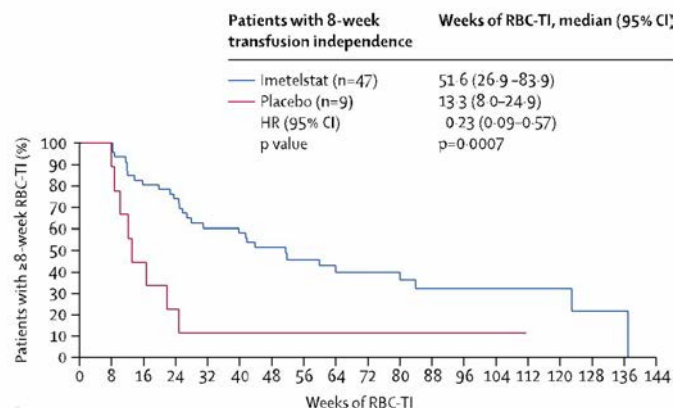
Imetelstat IMERGE



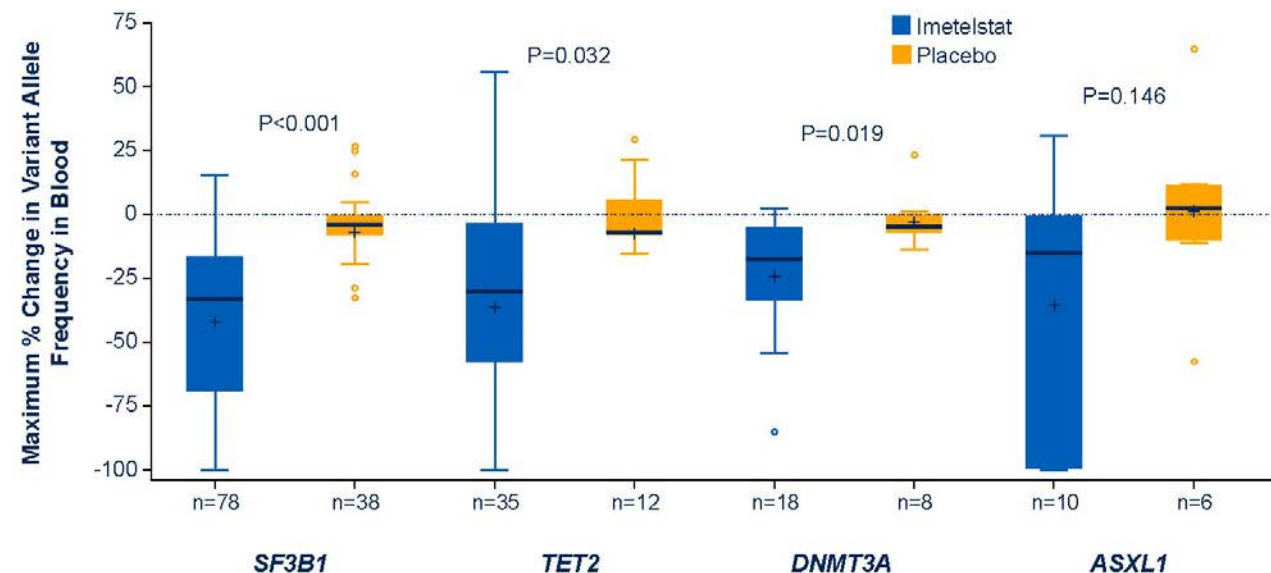
Patients with response, n (% [95% CI])

Imetelstat	47 (40% [31-50])	37 (31% [23-41])	33 (28% [20-37])	21 (18% [11-26])
Placebo	9 (15% [7-27])	4 (7% [2-16])	2 (3% [0.4-12])	1 (2% [0.04-9])

B



Number of patients	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Imetelstat	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0



	Imetelstat, n/N (%)	Placebo, n/N (%)	% Difference (95% CI)	P-Value
Overall	47/118 (39.8)	9/60 (15.0)	24.8 (9.9-36.9)	<0.001
WHO category				
RS+	33/73 (45.2)	7/37 (18.9)	26.3 (5.9-42.2)	0.016
RS-	14/44 (31.8)	2/23 (8.7)	23.1 (-1.3 to 40.6)	0.038
Prior RBC transfusion burden per IWG 2006				
4-6 units/8 weeks	28/62 (45.2)	7/33 (21.2)	23.9 (1.9-41.4)	0.027
>6 units/8 weeks	19/56 (33.9)	2/27 (7.4)	26.5 (4.7-41.8)	0.023
IPSS risk category				
Low	32/80 (40.0)	8/39 (20.5)	19.5 (-0.1 to 35.2)	0.034
Intermediate-1	15/38 (39.5)	1/21 (4.8)	34.7 (8.8-52.4)	0.004
Baseline sEPO				
≤500 mU/mL	39/87 (44.8)	7/36 (19.4)	25.4 (5.3-40.7)	0.011
>500 mU/mL	7/26 (26.9)	2/22 (9.1)	17.8 (-8.2 to 40.3)	0.107



Imetelstat Real World Use





Randomized low-dose HMA in Lower-Risk MDS



Study Design

ABSTRACT #487

Inclusion Criteria

≥18 years with **IPSS low- or intermediate-1-risk** MDS, CMML, or MDS/MPN

ECOG **0 to 3**

Prior hypomethylating agent exposure **excluded**

Cohorts

Transfusion dependent

3-day decitabine, 20 mg/m²
3-day azacitidine, 75 mg/m²
5-day azacitidine, 75 mg/m²

Transfusion independent

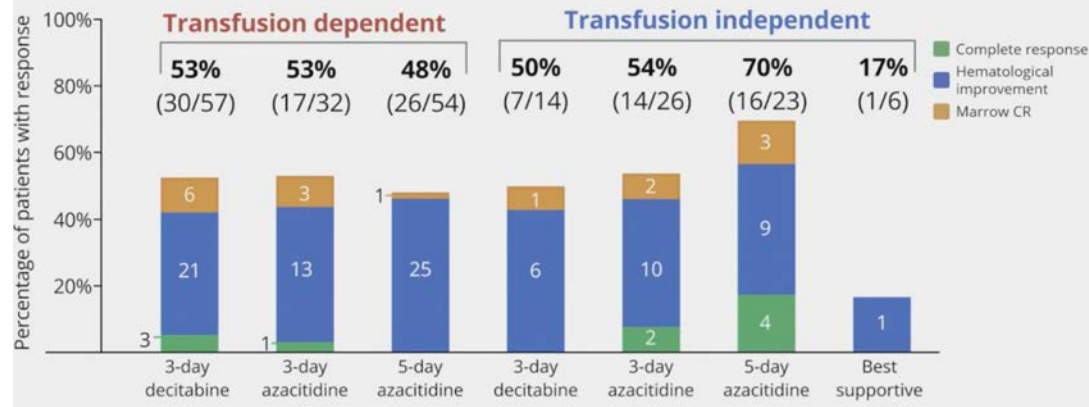
3-day decitabine, 20 mg/m²
3-day azacitidine, 75 mg/m²
5-day azacitidine, 75 mg/m²
Best supportive care

Transfusion dependence was defined as requiring a RBC or platelet transfusion due to MDS **at any point** prior to therapy.

Bayesian randomization assigned patients to the arm with the **best EFS**.

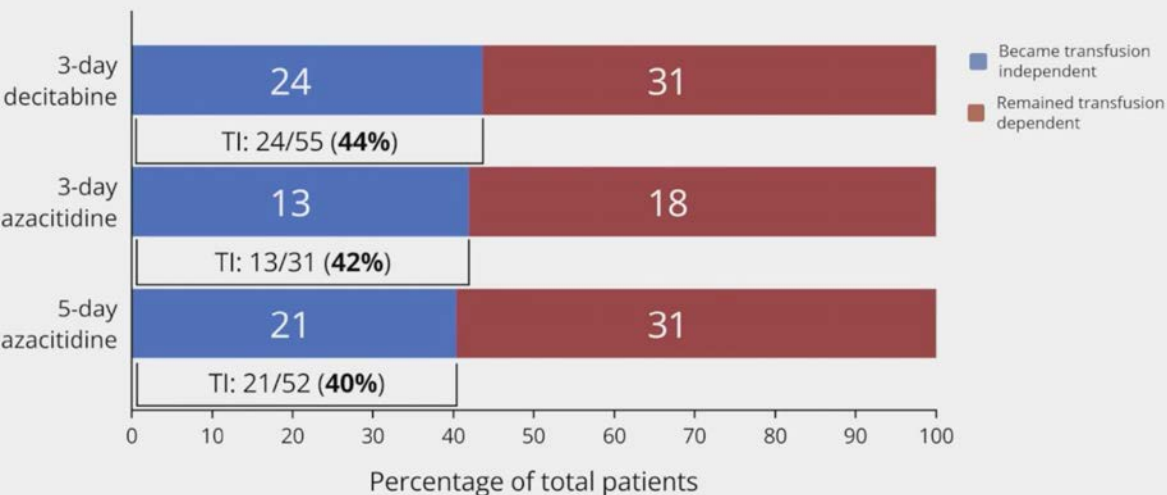
Overall Response Rate

ABSTRACT #487



Transfusion Independence

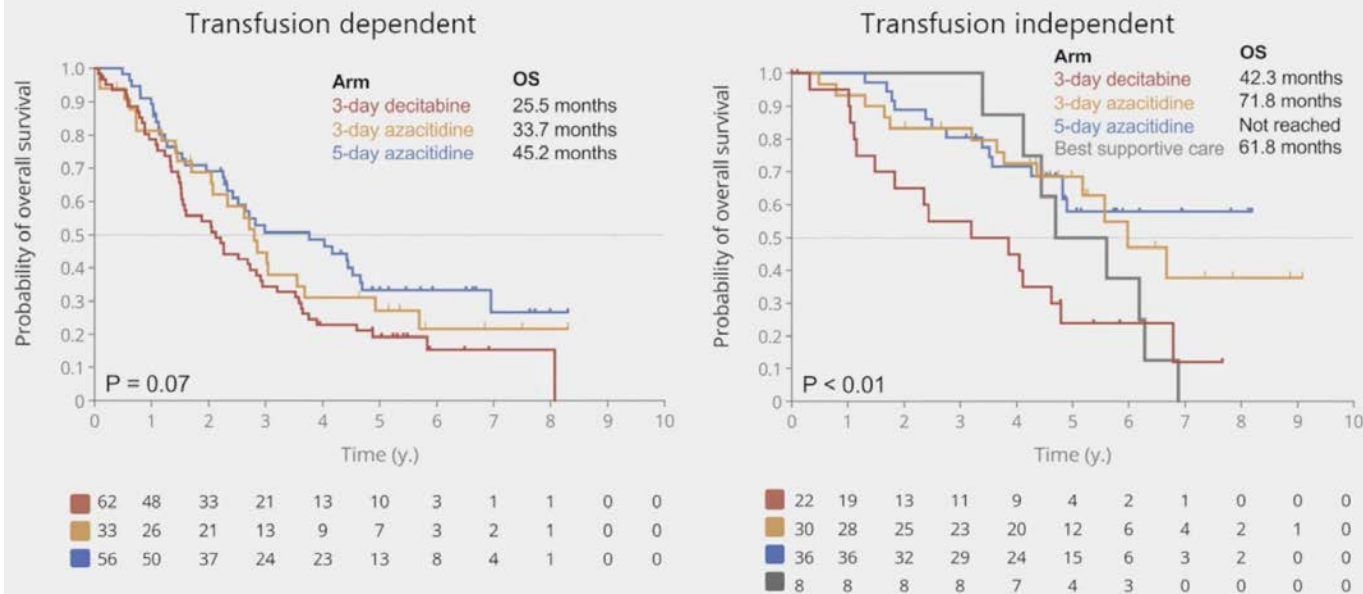
ABSTRACT #487



Transfusion independence: transfusion-free for ≥8 consecutive weeks between the first dose and study treatment discontinuation.

Overall Survival

ABSTRACT #487

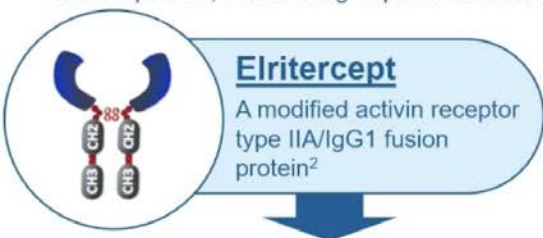




Elritercept



- Dysregulated TGF- β superfamily signaling in LR-MDS suppresses erythroid differentiation and leads to ineffective hematopoiesis, contributing to persistent anemia^{1,2}

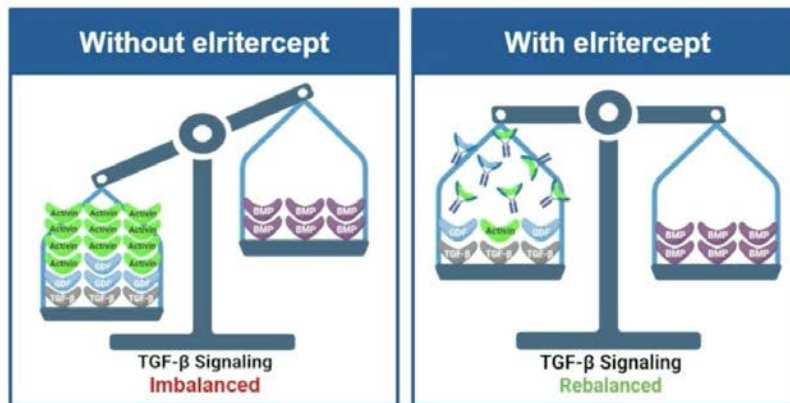


Elritercept

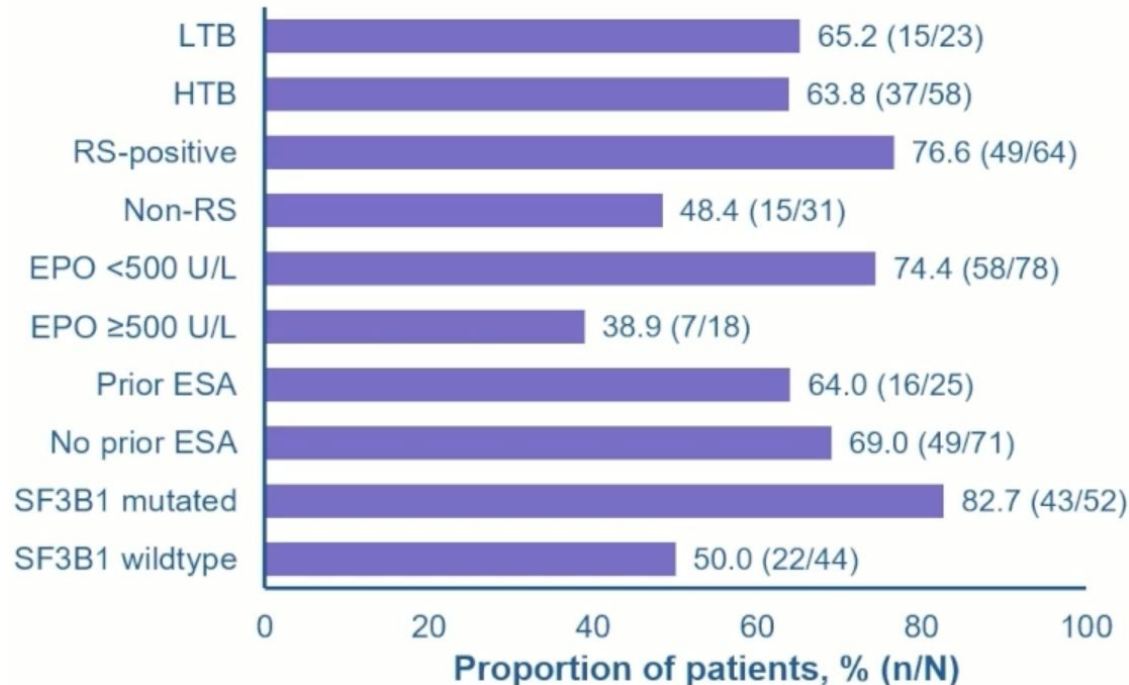
A modified activin receptor type IIA/IgG1 fusion protein²

Elritercept selectively binds and **potently blocks downstream signaling** of the TGF- β superfamily ligands **activin A and B**, and **GDF 8 and 11**^{2,3}

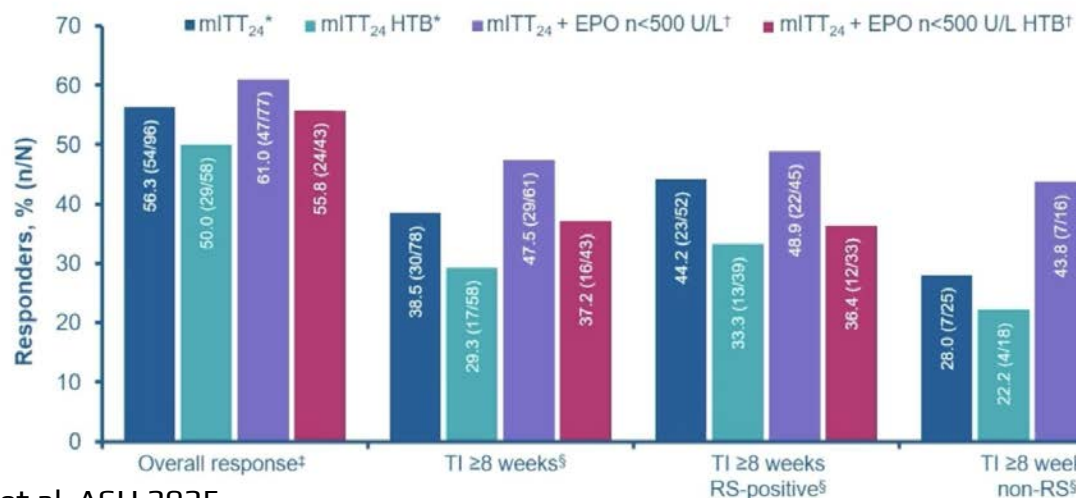
This can potentially provide therapeutic benefit to a broad and heterogeneous subset of patients with MDS^{2,3}



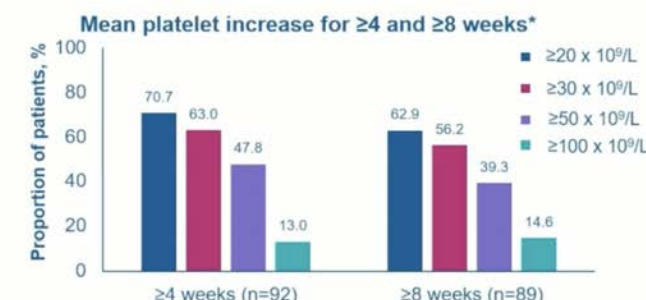
Overall erythroid response across subgroups*†



Transfusion independence for ≥8 weeks was achieved by Week 24 across a range of patient subgroups



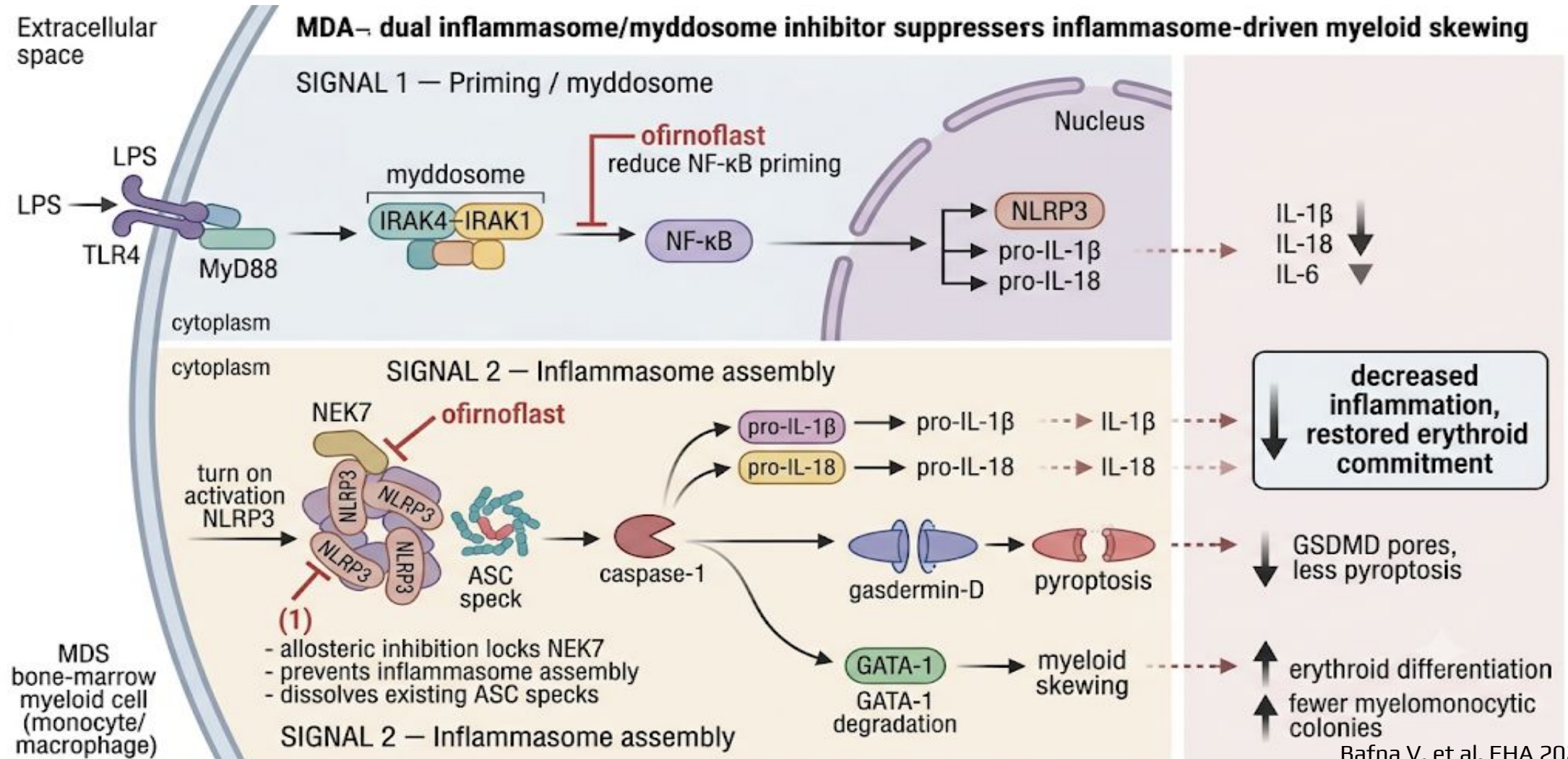
- 7/22 (31.8%) patients with baseline ANC <1.5 x 10⁹/L achieved an ANC ≥1.5 x 10⁹/L (sustained for ≥8 weeks)
- Of three patients with baseline neutrophil count <1.0 x 10⁹/L, one had a sustained modified HI-N response† for ≥4 weeks



- 8/24 (33.3%) patients with baseline platelet count <150 x 10⁹/L achieved a platelet count ≥150 x 10⁹/L (sustained for ≥8 weeks)
- In patients with pretreatment platelets <100 x 10⁹/L, 2/7 (28.6%) achieved a sustained modified HI-P response† for ≥4 weeks and 1/7 (14.3%) had a sustained modified HI-P response for ≥8 weeks

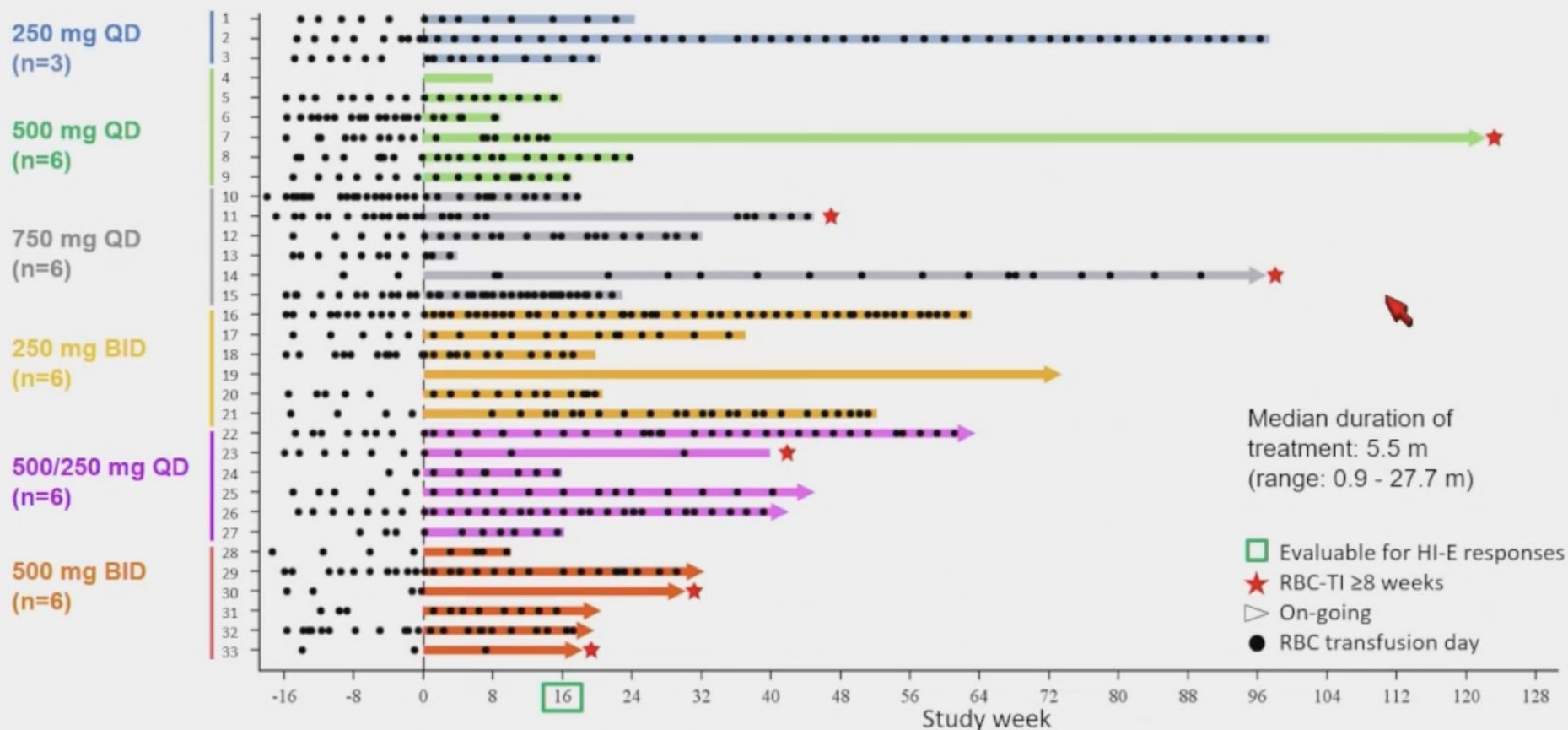


Ofirnoflast Is A Dual Allosteric Modulator Of NEK7/NLRP3 Assembly And Myddosome/NF- κ B Signaling





RBC Transfusion Events by Dose Group



- 6/18 (33%) evaluable TD patients receiving ≥500 mg QD achieved RBC-TI >8 weeks; 4 >16 weeks; 3 >24 weeks
- Median time to onset of RBC-TI: 1.9 months
- Median duration of RBC-TI: 22.9 weeks (9 - 104.3)



Ofirnoflast NEK7 Inhibitor



Majority (67%) Of Patients Had Hematologic Benefit

Hematological improvement based on hematology parameters criteria per IWG 2018

HEMATOLOGIC IMPROVEMENT	TD (HTB and LTB)		NTD		OVERALL	
	Eligible, N	Response Rate (<i>Best on Study</i>) n (%)	Eligible, N	Response Rate (<i>Best on Study</i>) n (%)	Eligible, N	Response Rate (<i>Best on Study</i>) n (%)
	18	10 (55.6)	12	9 (75.0)	30	20 ^[b] (66.7)
LINEAGE						
HI-E ^[c]	18	10 (55.6)	12	9 (75.0)	30	19 (63.3)
HI-P ^[d]	3	1 (33.3)	2	2 (100)	5	3 (60.0)
HI-N ^[e]	4	2 (50.0)	1	1 (100)	5	3 (60.0)

Among 18 TD Patients: 56% and 39% Achieved TI ≥ 8 and 16 Weeks, Respectively

	LTB (N=2)	HTB (N=16)	Overall (N=18)
RBC-TI ≥8 weeks	2/2 (100.0%)	8/16 (50.0%)	10/18 (55.6%)
RBC TI ≥16 weeks	1/2 (50.0%)	6/16 (37.5%)	7/18 (38.9%)
<i>Of patients achieving RBC-TI ≥8 weeks, maintaining TI ≥16 weeks</i>	1/2 (50.0%)	6/8 (75.0%)	7/10 (70%)
TI Duration weeks ^[b] Median (Min, Max)	23.1 (14.1, 34.9)	28.9 (11.3, 32.0)	28.0 (11.3, 34.9)

KEY SAFETY

No Treatment Related Serious Adverse Events

Most common TEAEs

Fatigue (8.1%), Cough (8.1%), Constipation (8.1%), Anemia (5.4%), Leukocytosis (5.4%), Pyrexia (5.4%) and Hyperkalemia (5.4%)

Grade ≥3 TRAEs

hypertension n=1 in a patient with a history of hypertension, leukopenia n=1

Death on Study was not treatment related

Due to febrile neutropenia which PI determined was due to underlying disease.



Lower-Risk MDS Trials



Drug	Trial	Mechanism of Action	Patients	Inclusion Criteria	Endpoints / Outcomes
Elritercept (KER-050, TAK-226)	ELRiSE MDS (Ph3) 	TGF-B ligand trap Randomized to EPO	N=300 ESA/Luspatercept Naive	EPO<500 2-6u RBC/8wk prior	Primary: TI $\geq$ 12wk in 24wk period with concurrent $\geq$ 1.5g Hb increase
	RENEW (Ph3) 	Randomized to Placebo	N=225 R/R ESA	LTB: 4-7u/16 wk HTB: $\geq$ 8u/16wk	Primary: TI $\geq$ 8wk in 24wk period
Roxadustat*	MATTERHORN (Ph3)	HIF-PH Inhibitor Placebo Randomized	N=140 82 Roxadustat 58 Placebo	-No Restriction on Prior ESA use -2-4u pRBC over preceding 8wks	TI $\geq$ 8wks: 47.5% vs 33.3% (p=0.217) In pts with $\geq$ 2u pRBC in 4wk period, TI $\geq$ 8wks: 36.1% (13/36) vs 11.5% (3/26), p=0.047
	Ph3 Trial NCT07722988	Placebo Randomized	N=201	-RR/ESA ineligible - $\geq$ 4u pRBC over 2 consecutive 8wks	Primary: TI $\geq$ 8wk in 24wk period
Momelotinib	MIDAS (Ph 2)	JAK1/JAK2/ACVR1 Inhibitor Randomized to different dose levels	N=80	R/R to ESA or Luspatercept $\geq$ 3u pRBC over preceding 16wks	Primary: TI $\geq$ 12wk in 24wk period
Tebapivat* (AG-946)	Ph 2b	Pyruvate Kinase Inhibitor	N=65	R/R to ESA +/- GCSF and/or Luspatercept LTB: 3-7u/16wk, <4u in 8wk before HTB: $\geq$ 8u/16wk and $\geq$ 4u in 8wk before	Primary: TI $\geq$ 8wk in 24wk period “While tebapivat demonstrated evidence of biological activity, clinical benefit was not observed in a sufficient proportion of patients or subgroup of patients...”

* Completed accrual



THANK YOU!

