FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

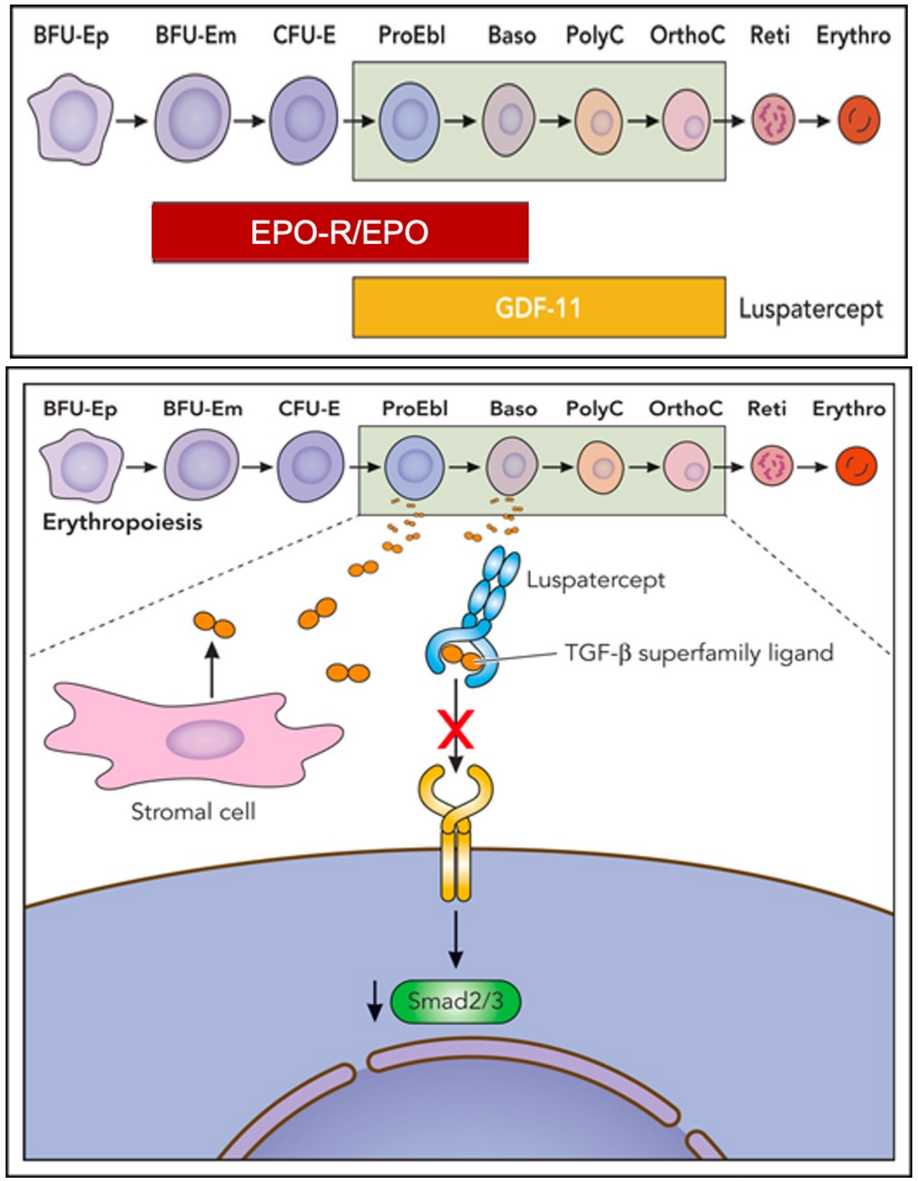
Firenze, CSF Montedomini
"Il Fuligno"
24-25 ottobre 2025

Risultati degli studi clinici e Real World Data con Luspatercept

ANGELA CONSAGRA, MD
MDS-Unit, AOU Careggi, Firenze
SOS Oncoematologia Firenze - Dipartimento Oncologico – USL Toscana Centro

Disclosures of Angela Consagra

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other



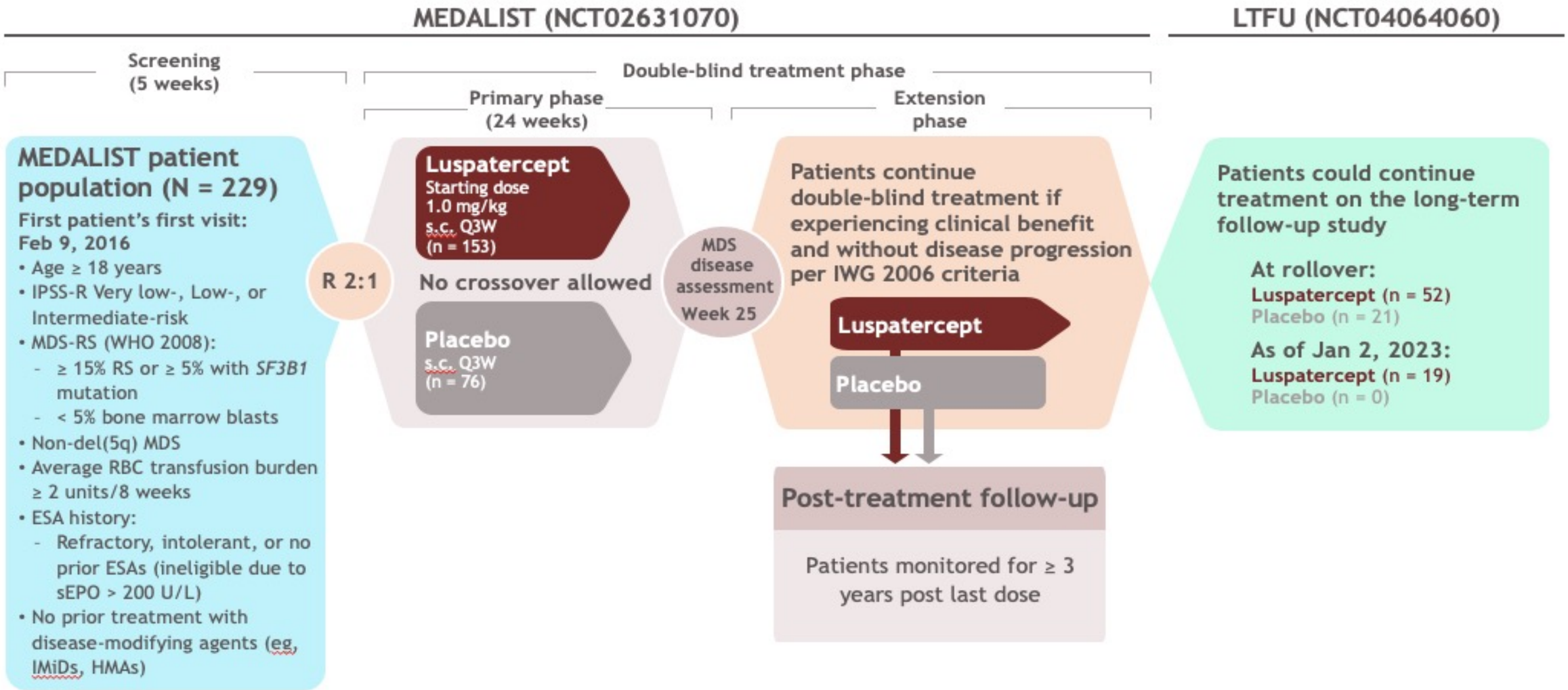
Adapted from A.S. Kubasch et al. Blood adv 2021

Luspatercept is a fusion protein constituted by the modified extracellular domain of human activin receptor type IIB linked to the human IgG1 Fc domain.

In a phase II study (PACE) Luspatercept demonstrated higher activity in MDS-RS vs other types of MDS

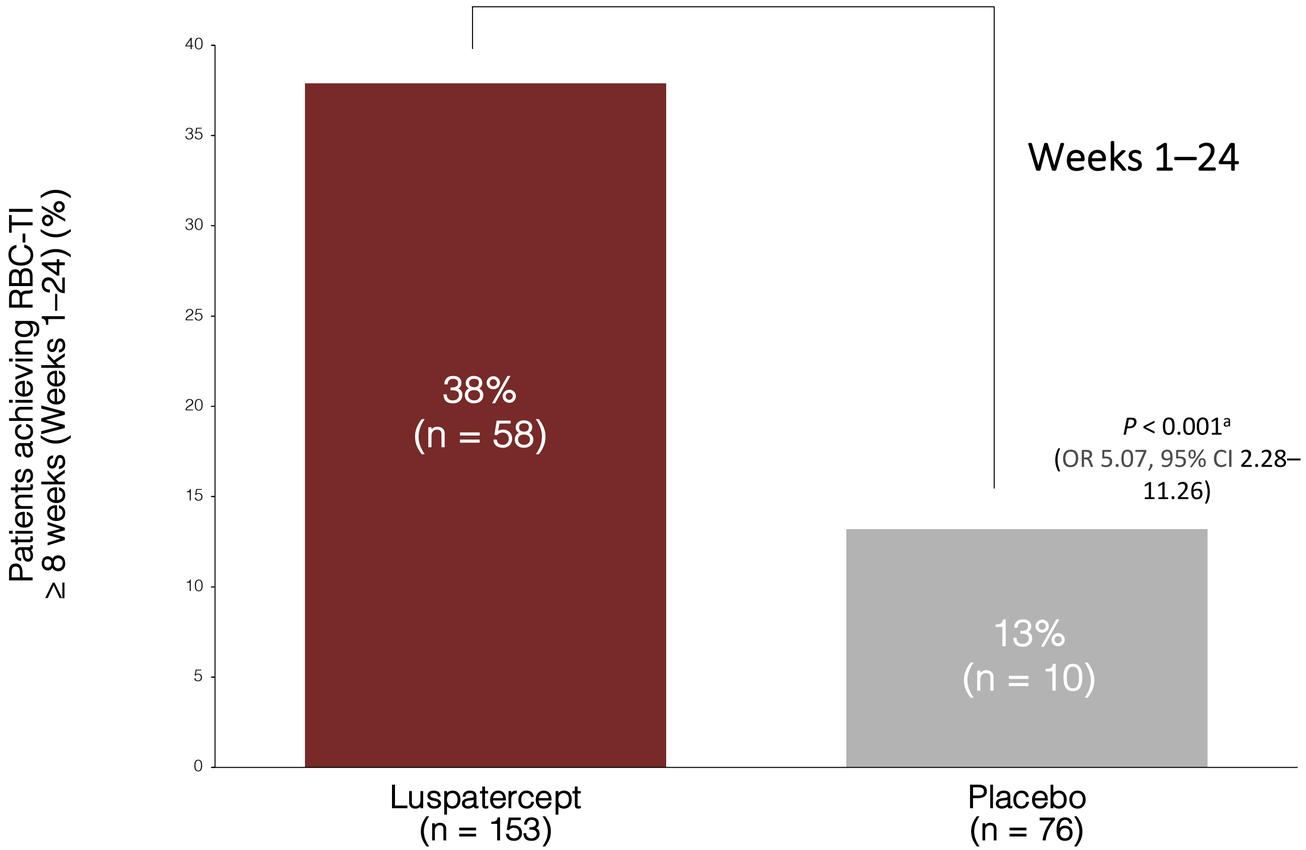
Lancet Oncol. 2017 Oct;18(10):1338-1347

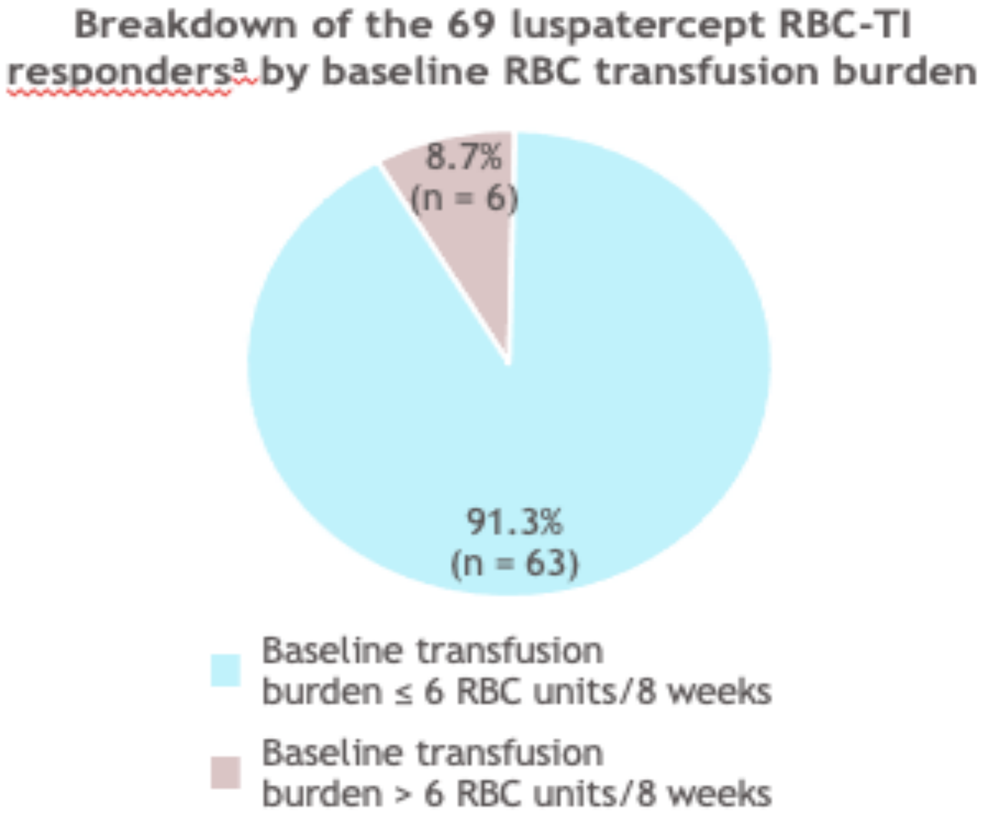
MEDALIST Trial and long term follow up design



Santini V. et al, ASH 2023, abstract #915

MEDALIST Trial: LUSPATERCEPT INDUCES RBC TRANSFUSION INDEPENDENCE ≥ 8W





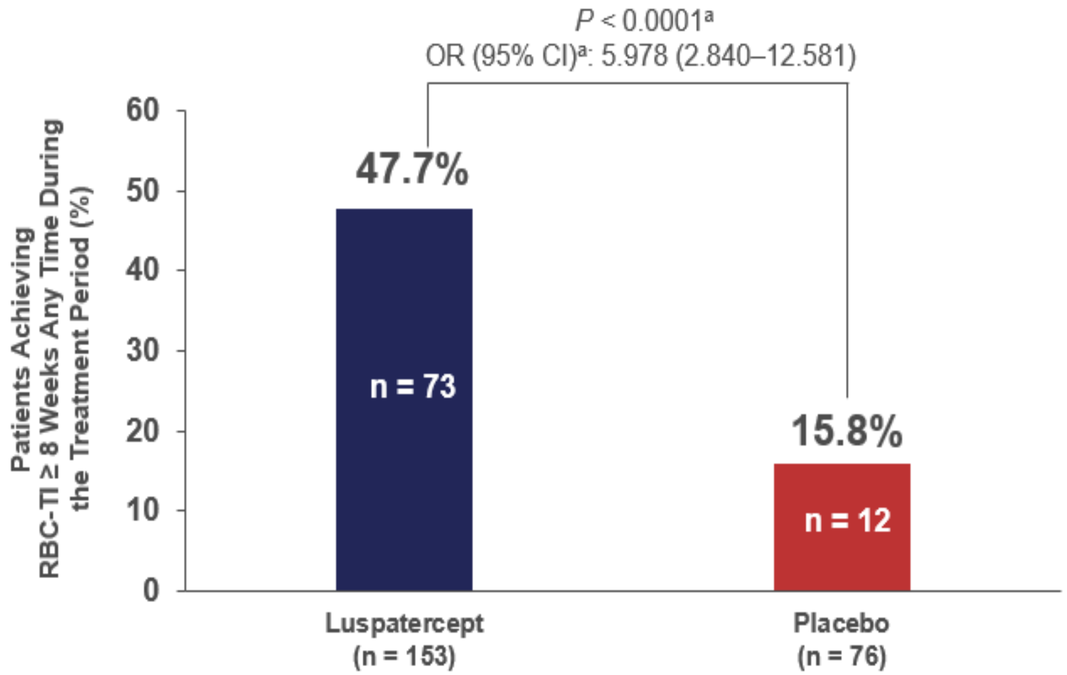
- RR were similar regardless of *SF3B1* allelic burden and total number of baseline somatic mutations

Fenaux et al, N Engl J Med. 2020 Jan 9;382(2):140-151

LUSPATERCEPT INDUCES TRANSFUSION INDEPENDENCE IN RS+ LR MDS

When assessed during the entire treatment period, a greater proportion of luspatercept-treated patients achieved RBC-TI ≥ 8 weeks compared with placebo than previously reported

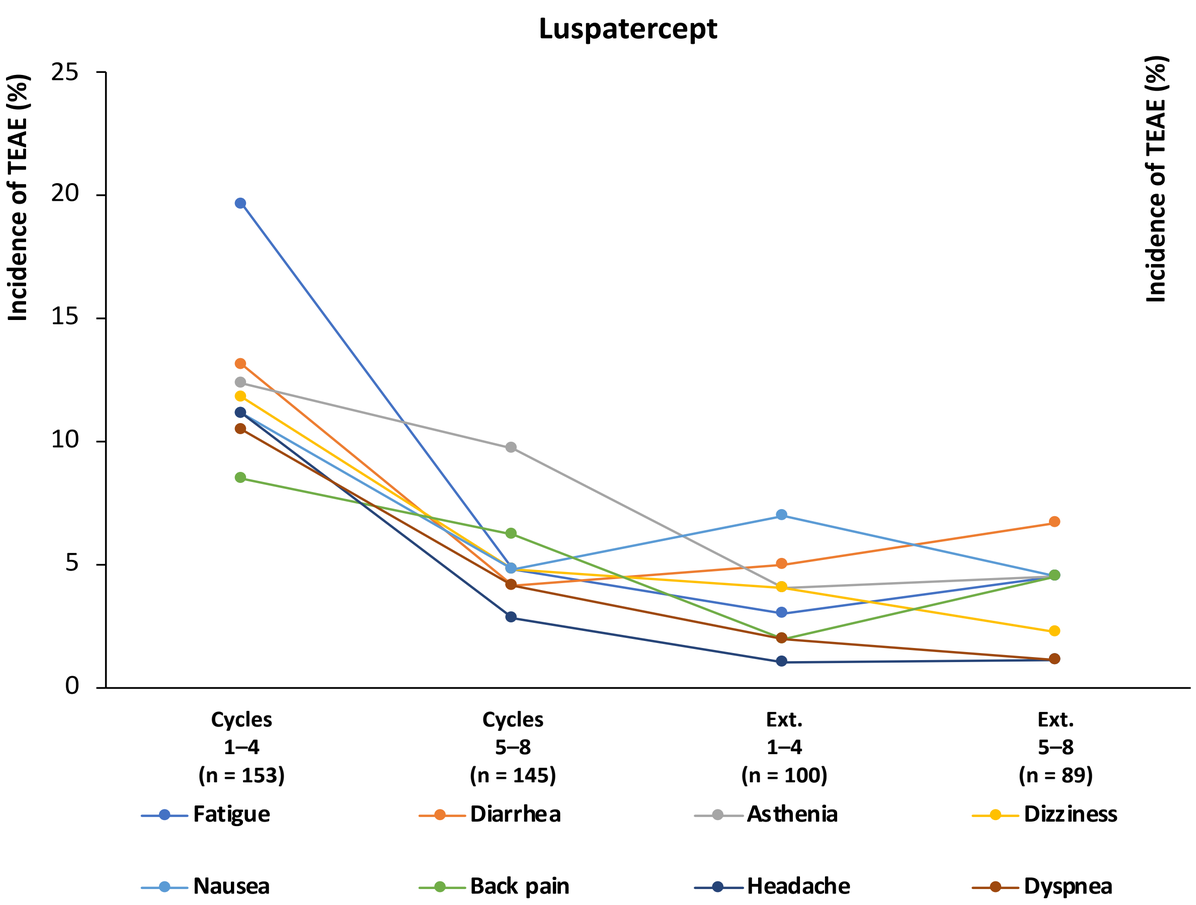
	Luspatercept (N = 153)	Placebo (N = 76)
SF3B1 mutated, n (%)	138/148 (93)	64/74 (86)
Time since MDS diagnosis, months, median (range)	44.0 (3-421)	36.1 (4-193)
Baseline transfusions per 8 weeks over 16 weeks, RBC units, median (range)	5.0 (1-15)	5.0 (2-20)
Transfusion burden at baseline, n (%)		
< 6 RBC units/8 weeks over 16 weeks	87 (56.9)	43 (56.6)
≥ 6 RBC units/8 weeks over 16 weeks	66 (43.1)	33 (43.4)

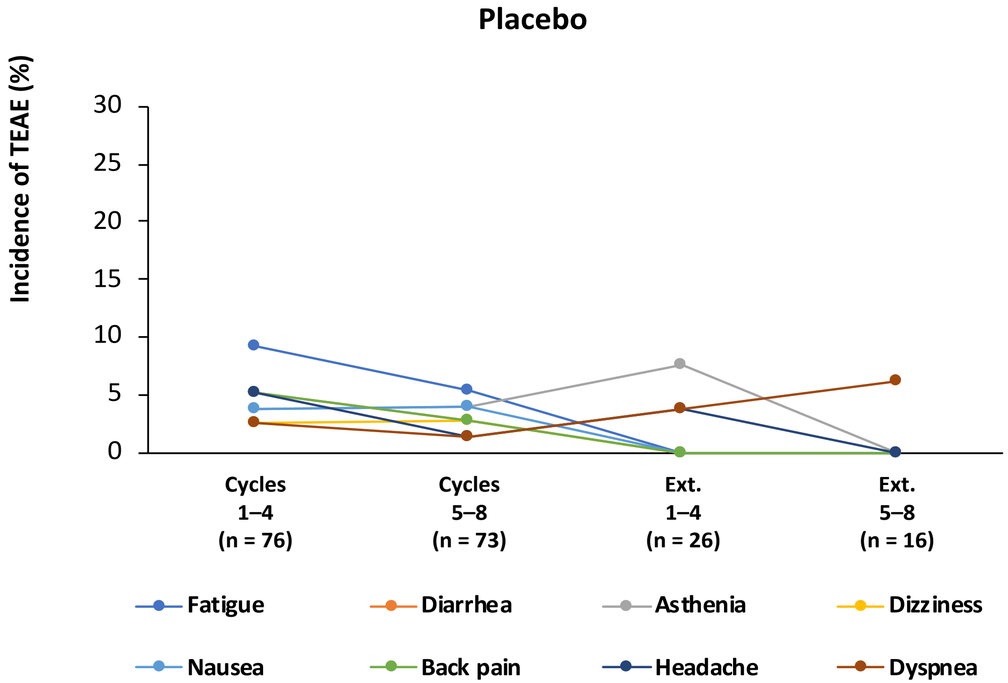


Luspatercept has been approved by FDA and EMA in 2020 for second line therapy in TD MDS-RS after ESAs failure or intolerance
(and also in TD and NTD thalassemia)

Santini V. et al, ASH 2023, abstract #915

SAFETY: FREQUENT TEAEs (ANY GRADE) BY TREATMENT CYCLE





TEAEs generally decreased over time in both treatment arms during the first 24 weeks of the study

Fenaux et al, N Engl J Med. 2020 Jan 9;382(2):140-151

Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive patients with transfusion-dependent lower-risk myelodysplastic syndromes: COMMANDS TRIAL

Key patient eligibility criteria

- ≥ 18 years of age
- IPSS-R Very low-, Low-, or Intermediate-risk MDS (with or without RS) by WHO 2016, with < 5% blasts in bone marrow[a]
- Required RBC transfusions (2–6 pRBC units/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO < 500 U/L
- ESA-naive

Patients stratified by:

- Baseline RBC transfusion burden
- Baseline sEPO level
- RS status

R 1:1

- Luspatercept (N = 182) 1.0 mg/kg s.c. Q3W titration up to 1.75 mg/kg
- Epoetin alfa (N = 181)[b] 450 IU/kg s.c. QW titration up to 1050 IU/kg

Response assessment at day 169 and every 24 weeks thereafter

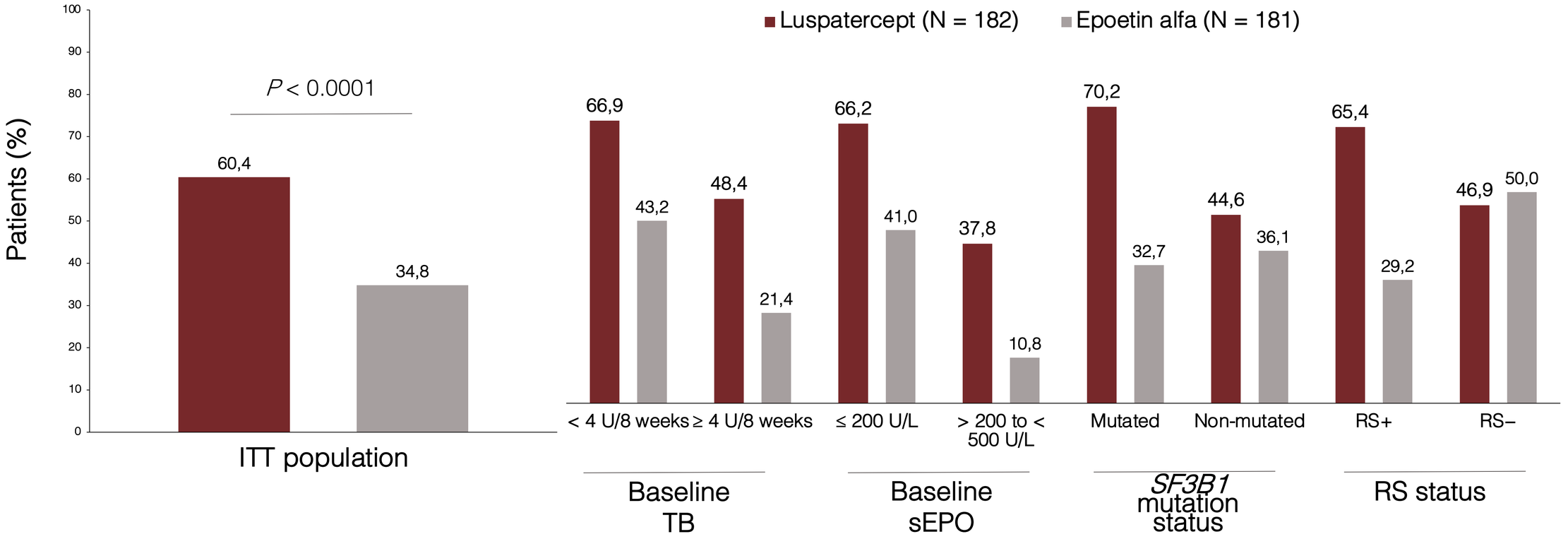
End treatment
Due to lack of clinical benefit[c] or disease progression per IWG 2006 criteria

Post-treatment safety follow-up

- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

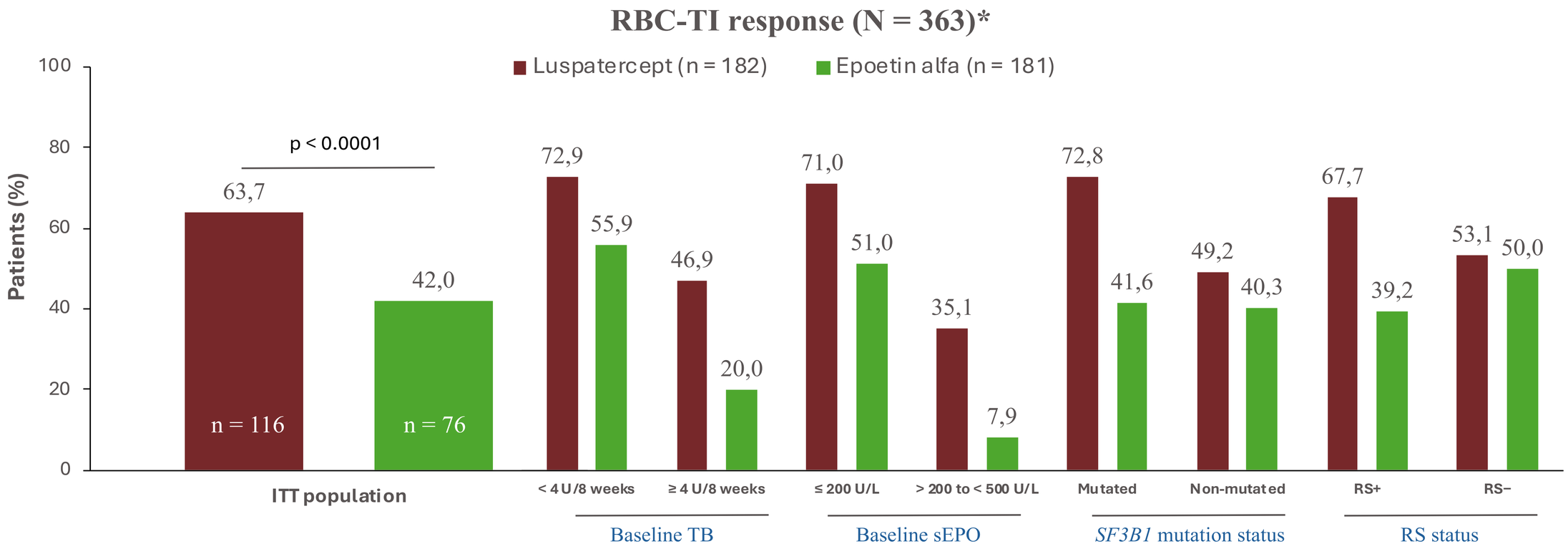
Garcia Manero et al. ASH 2023, Presentation 193

COMMANDS: RBC-TI for ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL



Garcia Manero et al. ASH 2023, Presentation 193

COMMANDS: Preplanned exploratory analysis of RBC-TI for ≥ 24 weeks

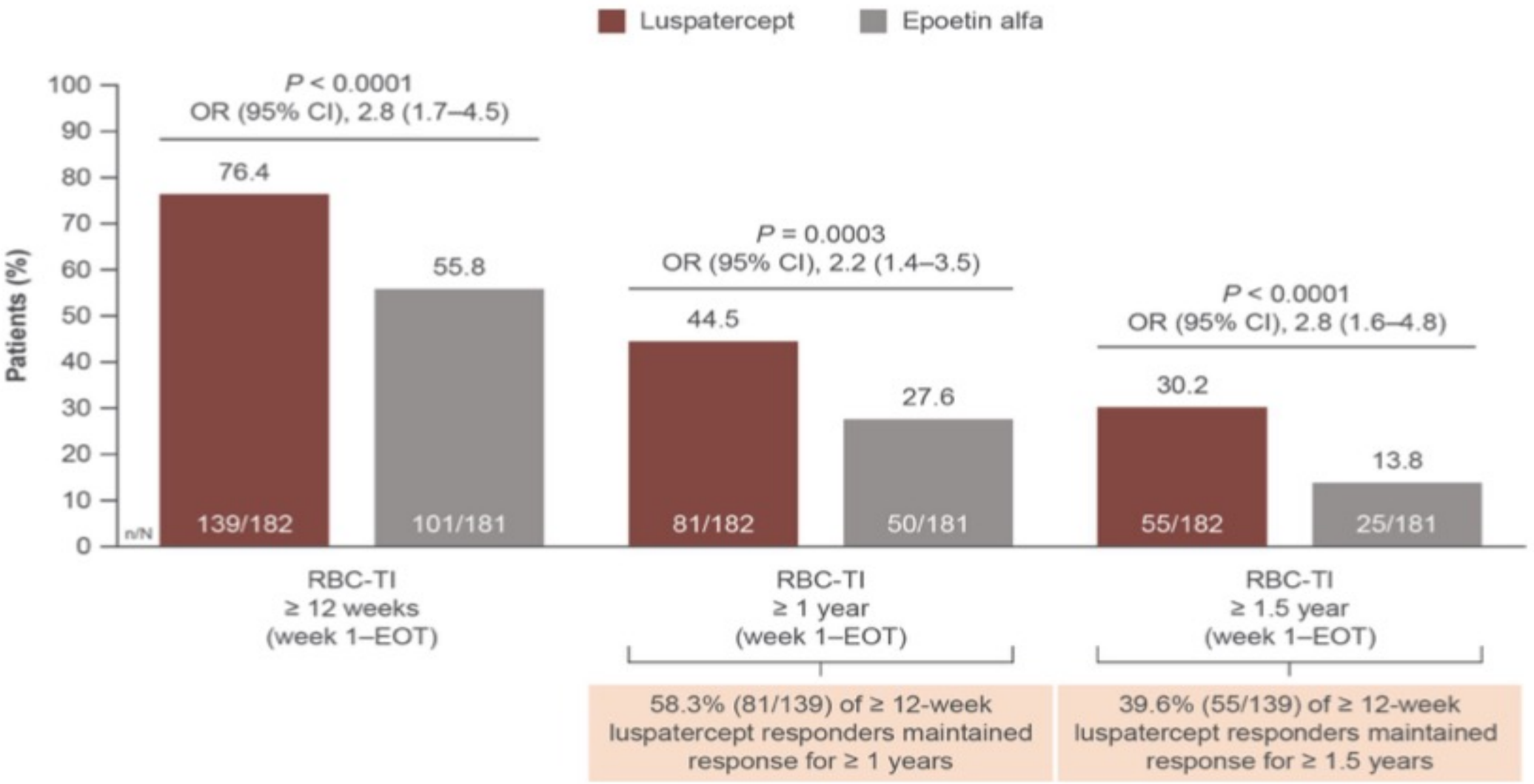


- Response rates of RBC-TI for ≥ 24 weeks (Weeks 1-48) were greater with luspatercept vs. epoetin alfa regardless of baseline TB, sEPO category, or *SF3B1* mutation status

Luspatercept has been approved by FDA and EMA in 2024 in all TD MDS as first-line treatment

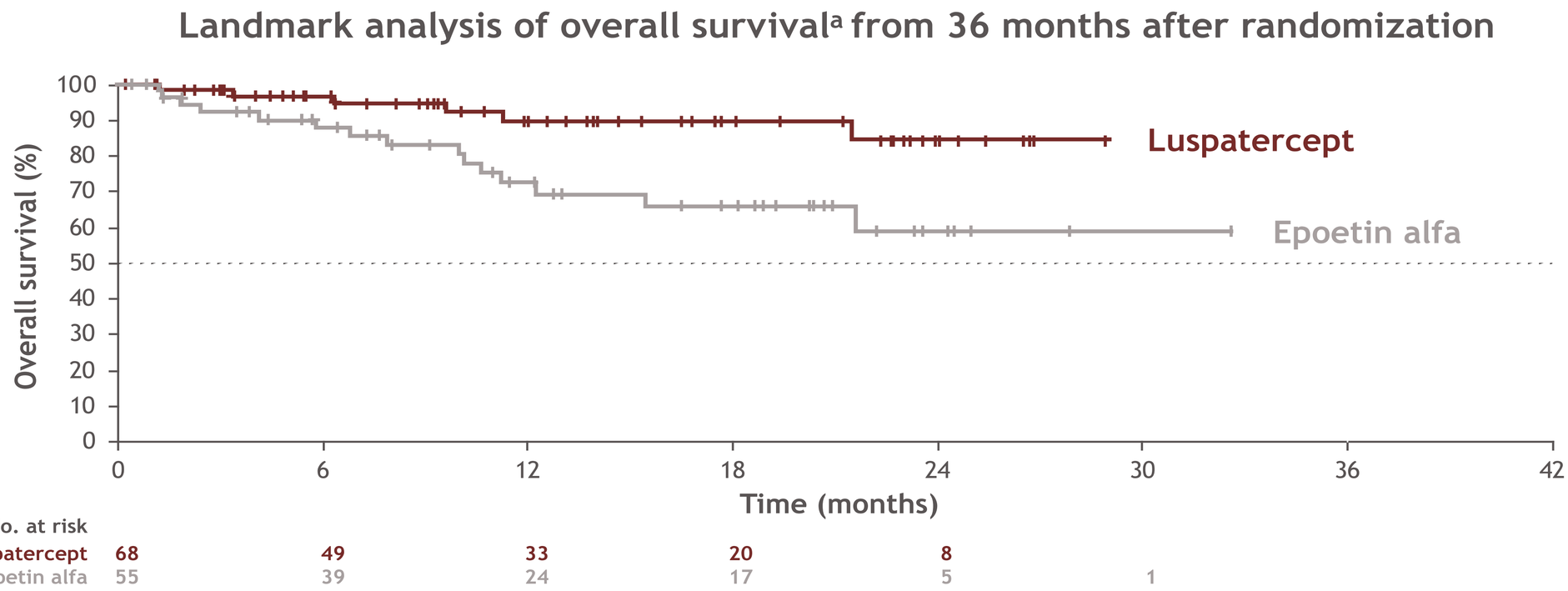
Della Porta MG , Garcia Manero G et al, Lancet Hematol 2024

COMMANDS: LONG TERM RBC-TI RESPONSES



Garcia Manero et al, Adv Ther (2025) 42:3576-3589

COMMANDS: landmark analysis of overall survival (≥ 36 months)



	Luspatercept	Epoetin alfa	HR (95% CI)[b]
Median OS,[c] months	NR	NR	0.330 (0.128-0.852); *P* = 0.0161

Data cutoff: February 7, 2025. Median follow-up (range) 30.6 (1-65) months for luspatercept arm and 28.8 (0-69) months for epoetin alfa.
[a]Overall survival is defined as the time between the landmark (i.e., 36 months after randomization) and death of any cause. [b]HR (95% CI) is calculated by stratified Cox proportional hazard model. *P* value is from stratified log-rank test. [c]Median is from unstratified Kaplan-Meier method.

Santini V, et al. EHA 2025 [Abstract S177]

REAL WORLD DATA OF LR-MDS-RS PATIENTS TREATED WITH LUSPATERCEPT

In April 2023, FISiM published data from a multicenter, observational trial evaluating the efficacy and safety of Luspatercept in a population of adult patients who were treated in expanded access program.

	MEDALIST (n = 153)	EAP (n = 177)	p-value
RBC-TI ≥ 8 weeks during Weeks 1–24, n (%)	**58 (37.9)**	**56 (31.6)**	
Baseline transfusion requirements			
≥6 units/8 weeks, n (%)	6/66 (9.0)	27/112 (23.9)	**<.001**
4 to 5 units/8 weeks, n (%)	15/41 (36.6)	16/48 (34.0)	
<4 units/8 weeks, n (%)	37/46 (80.4)	13/17 (76.4)	
Baseline transfusion requirements			
≥8 units/8 weeks, n (%)	**NR**	14/76 (18.4)	**<.001**
4 to 7 units/8 weeks, n (%)		28/84 (33.3)	
<4 units/8 weeks, n (%)		13/17 (76.4)	

A multiple logistic regression analysis indicated a significant correlation between the initial transfusion burden and the individual probability of achieving transfusion independence (*p<.001*). No correlation was observed with age, gender, IPSS-R risk, time since initial diagnosis, and time since first RBC transfusion.

Lanino L. .et al, Am J Hematol. 2023 Aug;98(8):E204-E208

REAL WORLD DATA OF LR-MDS-RS PATIENTS TREATED WITH LUSPATERCEPT

Received: 23 July 2024 | Accepted: 22 December 2024

DOI: 10.1002/hem3.70086

HemaSphere eha

ARTICLE

Response to luspatercept can be predicted and improves overall survival in the real-life treatment of LR-MDS

Angela Consagra[1,^] | Luca Lanino[2,3,^] | Najla H. Al Ali[4] | Luis Aguirre[5] | Zhuoer Xie[4] | Onyee Chan[4] | Gloria Andreossi[1] | Marco G. Raddi[1,6] | Luca Rigodanza[1] | Alessandro Sanna[1] | Giorgio Mattiuz[1] | Elena Tofacchi[1,6] | Cristina Amato[1] | Michele Tanturli[7] | Sven De Pourcq[1,6] | Alison Walker[4] | Andrew Kuykendall[4] | Jeffrey Lancet[4] | Eric Padron[4] | David A. Sallman[4] | Francesco Restuccia[8] | Alessandra Perego[9] | Marta Ubezio[2,3] | Bruno Fattizzo[10] | Marta Riva[11] | Giulia Maggioni[2,3] | Alessia Campagna[2,3] | Matteo G. Della Porta[2,3] | Valeria Santini[1,^] | Rami S. Komrokji[4,^]

REAL WORLD DATA OF LR-MDS-RS PATIENTS TREATED WITH LUSPATERCEPT AT MOFFIT CANCER CENTER AND FISiM

Baseline RBC transfusion burden (TB) was defined as follows:

- non-transfusion dependent (NTD) → 0 units in 8 weeks prior Luspatercept
- low TB (LTB) → 1-5 units/8 weeks
- high TB (HTB) → ≥ 6 units/8 weeks

An erythroid hematological response (HI-E) was defined as follow:

- an objective Hgb increase of >1.5 g/dl in NTD,
- RBC-TI with Hgb increase of 1.5 g/dl, or RBC-TI without Hgb 1.5 g/dl increase, or >50% reduction in RBC TB among RBC-TD,

Patients who did not reach HI-E > 8 weeks were considered non-responders

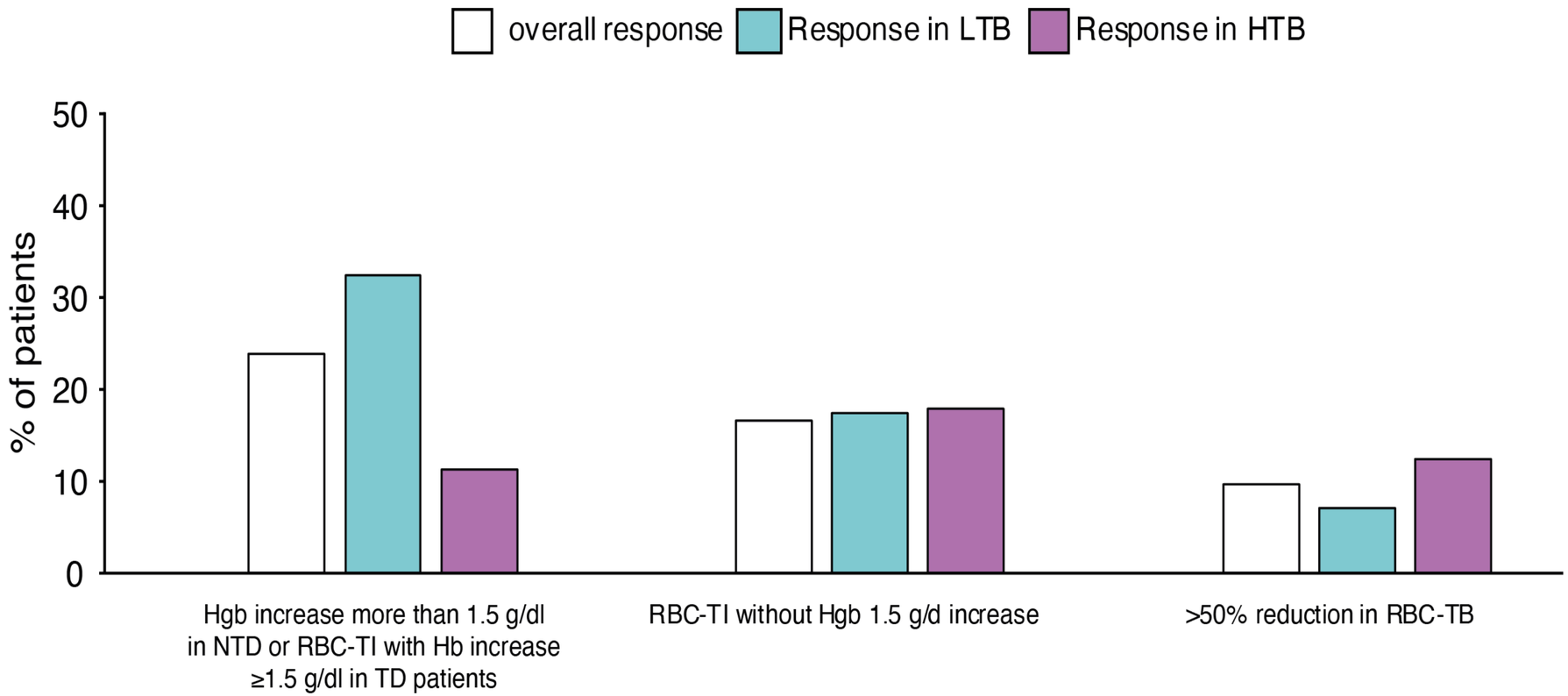
CHARACTERISTICS OF PATIENTS

	MCC-FISIM (n=331)
Age (median)	75 (31-94)
Gender (male)	211 (63.74)
Hb (mean) g/dl	7.97 (5.5-11.5)
PLT (mean) x10^9/L	268.5 (15-1002)
ANC (mean) x10^9/L	2.86 (.38-13.5)
Serum erythropoietin level (median) U/L	60.1 (n=111)
WHO 2016 %(n)	**% (n)**
MDS-RS	96.5 (310)
MDS-del5q	1.5 (5)
MDS-MLD	0.6 (2)
MDS/MPN with RS and thrombocytosis	4.4 (14)
NGS	**% (n)**
SF3B1	93.4 (169/181)
U2AF1	3.5 (6/171)
ZRSR2	4.1 (7/171)
TET-2	33.3 (57/171)
DNMT3A	22.2 (38/171)
ASXL-1	14.6 (25/171)
TP53	6.4 (11/171)
EZH-2	4.7 (8/171)
ETV-6	1.7 (3/171)
SETBP1	5.8 (10/171)
RUNX-1	3.5 (6/171)
CBL	1.1 (2/171)
JAK-2	9.3 (16/171)

	MCC-FISIM (n=331)
IPSS-M (n=154)	**% (n)**
Very Low	.64 (1)
Low	60.38 (93)
Moderate Low	21.42 (33)
Moderate High	12.98 (20)
High	3.89 (6)
Very High	.64 (1)
IPSS-R (n=291)	**% (n)**
Very low	3.43 (10)
Low	82.13 (239)
Intermediate	12.71 (37)
High	1.71 (5)
Very high	-
RBC-Transfusion Burden	% (n)
NTD	6.3 (21)
LTB	38.1 (126)
HTB	55.6 (184)
Prior Treatment	% (n)
ESA	95.77 (317/331)
HMA	15.7 (52/331)
Lenalidomide	11.5 (38/331)

Consagra A et al, Hemasphere. 2025 Feb;9:e70086

OVERALL RESPONSE AND TYPES OF RESPONSE

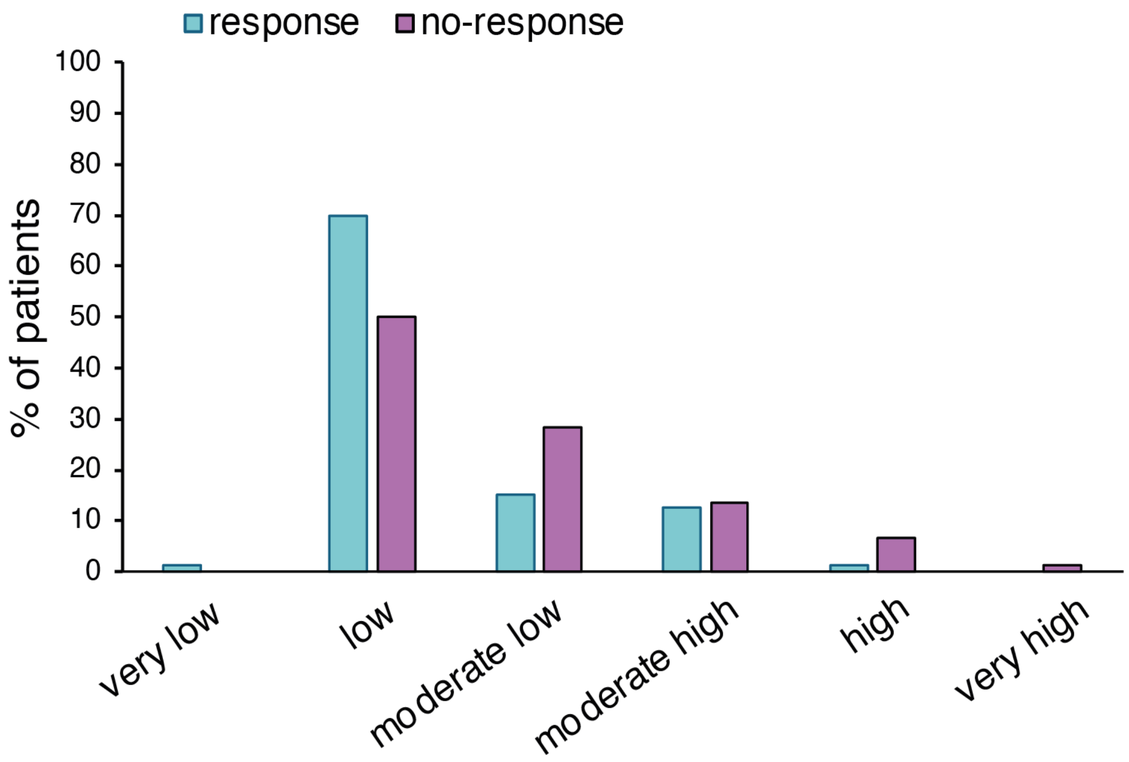


HI-E was observed in 166 patients (50.2%) and was significantly higher in NTD and LTB patients compared to HTB patients ($p<0.001$)

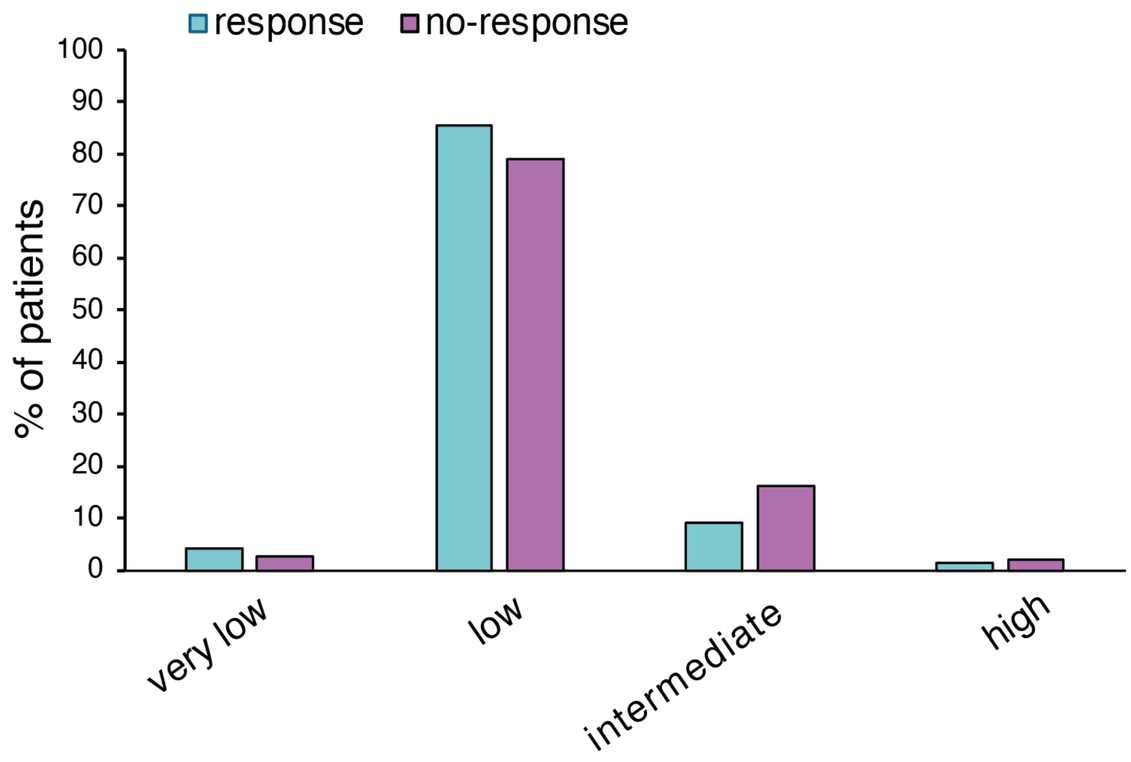
81% (17/21) of NTD patients achieved HI-E

Consagra A et al, Hemasphere. 2025 Feb;9:e70086

DISTRIBUTION OF RESPONSE BY IPSS-M AND IPSS-R



IPSS-M



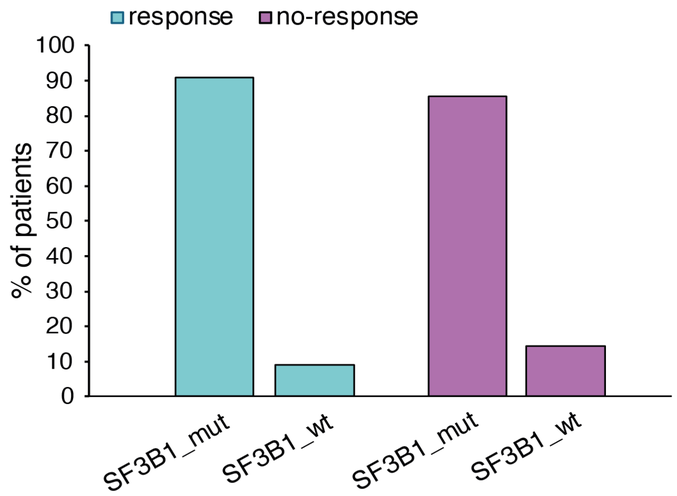
IPSS-R

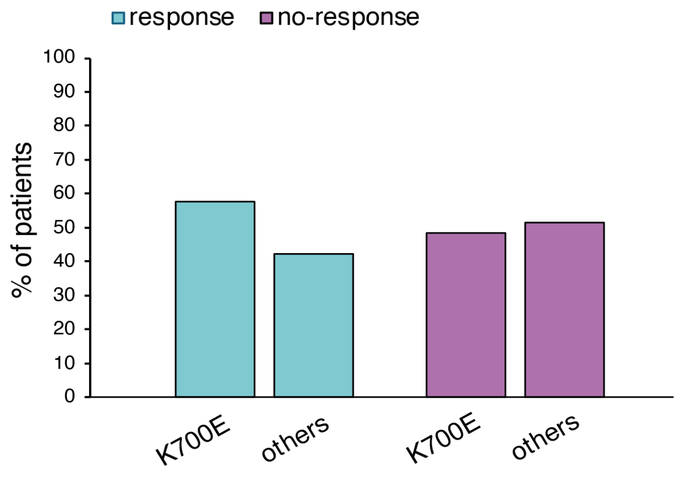
For 154/331 patients with calculated IPSS-M prior to Luspatercept, response was significantly correlated with disease risk (*p=.031*), while IPSS-R score did not correlate with response (*p=.247*).

Consagra A et al, Hemasphere. 2025 Feb;9:e70086

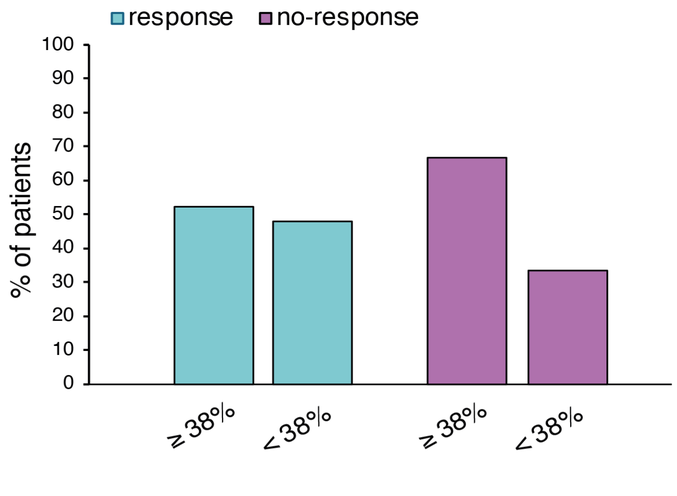
RESPONSE AND MOLECULAR CHARACTERISTICS

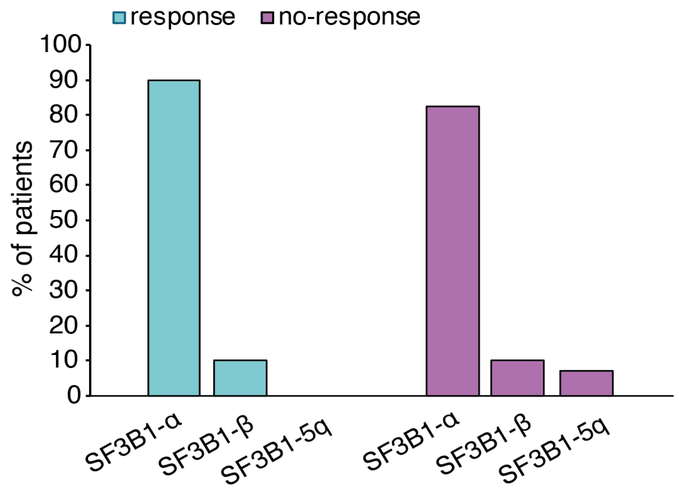
- Similar RR in *SF3B1*-MT pts compared to *SF3B1*-WT, 91/169 (53.8%) vs 9/22(40.1%), *p=.267*





- Segregation of *SF3B1*-MT cases into 3 distinct groups revealed that *SF3B1*$^{\beta}$ and *SF3B1*$^{\alpha}$ obtained superior erythroid improvement rates compared to *SF3B1*^{5q} with a significance of *p=.046*.

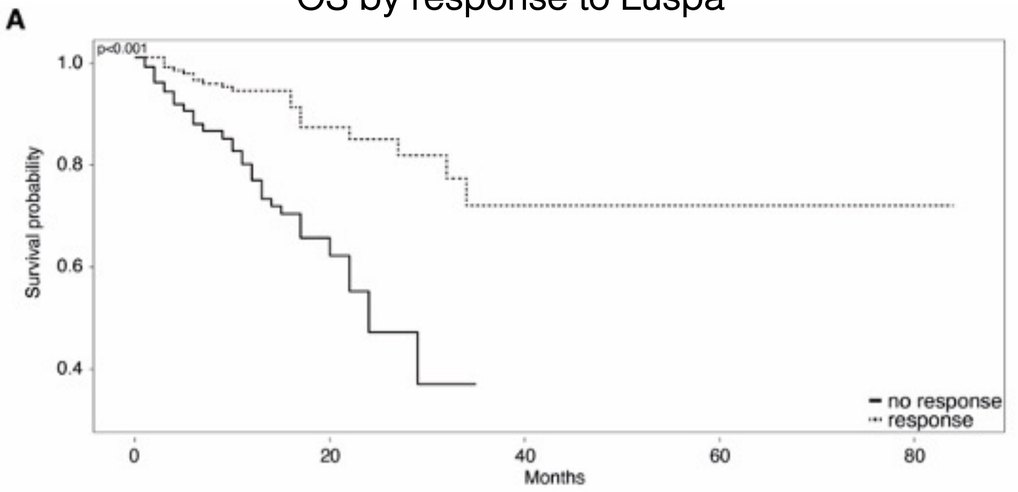




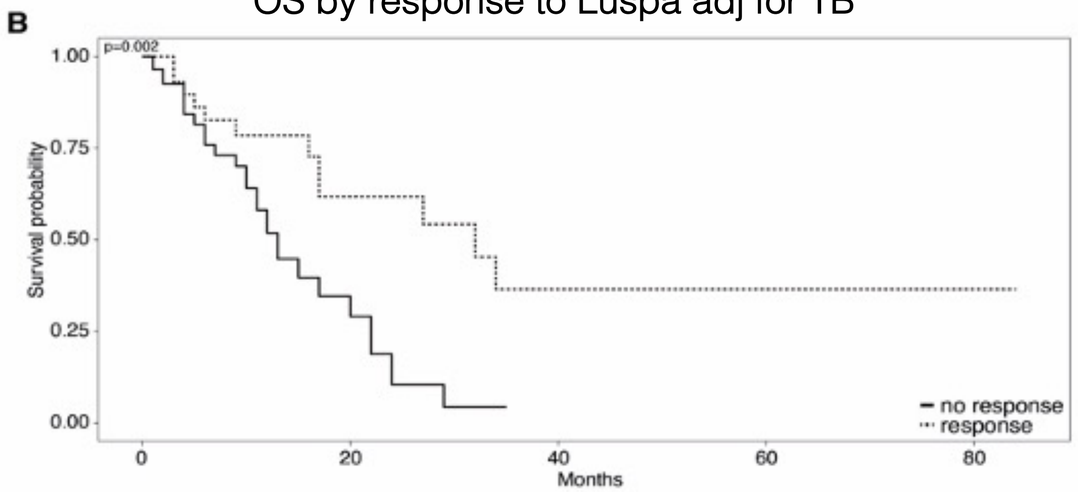
Consagra A et al, Hemasphere. 2025 Feb;9:e70086

OVERALL SURVIVAL BY RESPONSE

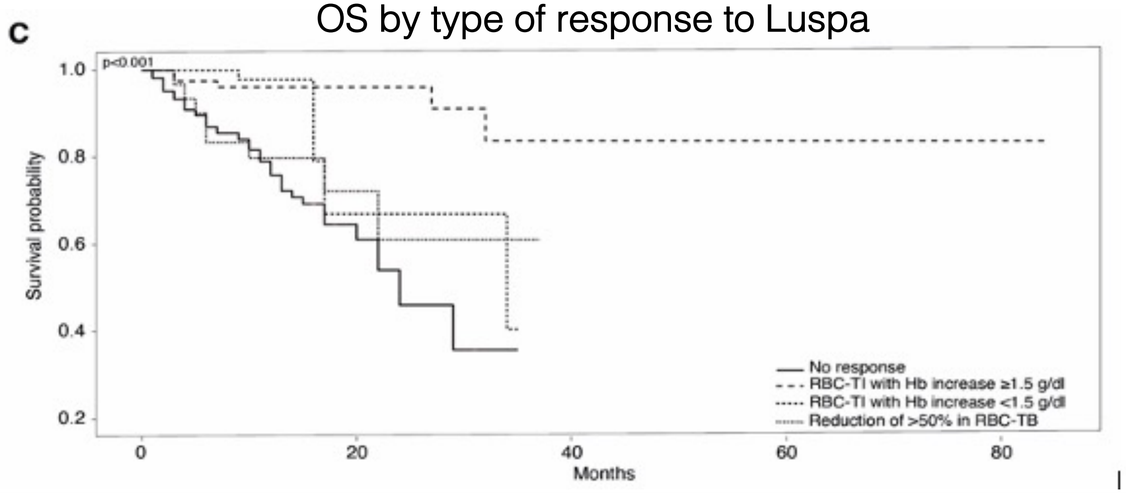
OS by response to Luspa



OS by response to Luspa adj for TB



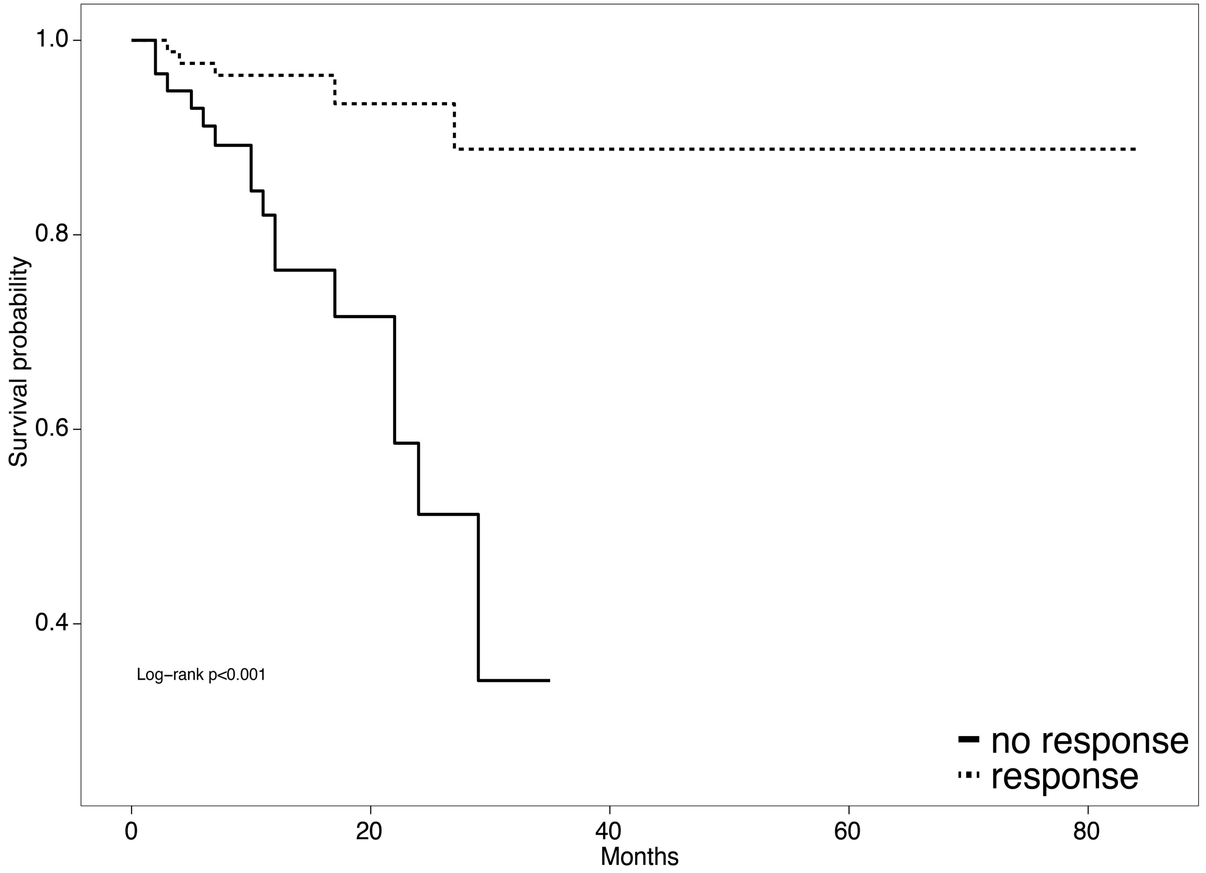
OS by type of response to Luspa



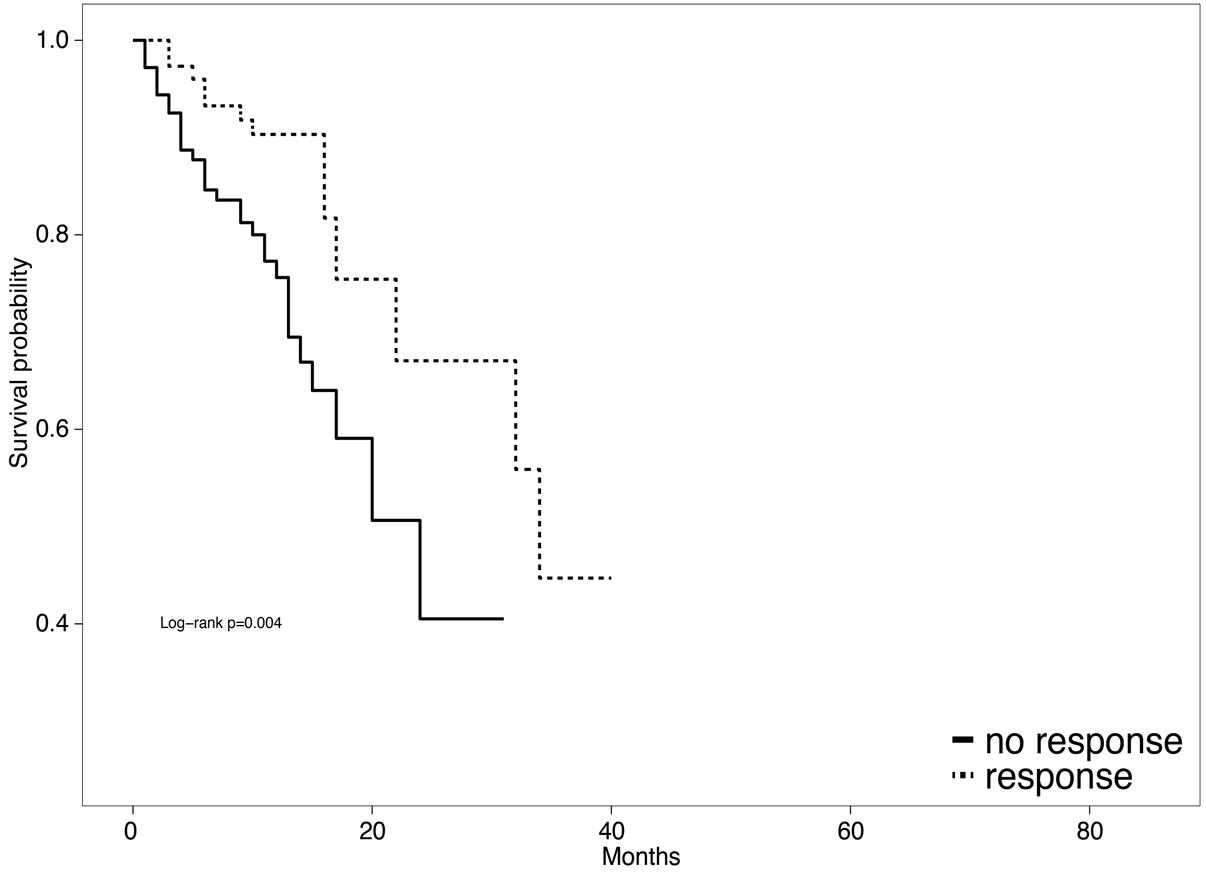
Consagra A et al, Hemasphere. 2025 Feb;9:e70086

OVERALL SURVIVAL BY TRANSFUSION BURDEN

OS by response in NTD/LTB



OS by response in HTB



Consagra A et al, Hemasphere. 2025 Feb;9:e70086

REAL WORLD DATA OF LR-MDS-RS PATIENTS TREATED WITH LUSPATERCEPT

Author (year)	N pts	ORR / HI-E	TI ≥8w	Predictors of response
Farrukh F. (2022)	39	18%	16%	Lower EPO (*p=0.01*); higher ALC (*p=0.05*) and AMC (*p=0.03*)
Mukherjee S. (2022)	76	not reported	>90% in LTB; ↓ burden in moderate TB	LTB associated with TI (*p* not reported)
Heyrman B. (2024)	77	65.8%	43%	No significant baseline predictors identified
Madanat Y.F.(2024)	37	52%	48% (≥16w FU)	Lower EPO (<100 IU/L) associated with HI-E (*p=0.02*)
Memoli M. (2024)	23	63.5% at 24 weeks →56% at one year	35% at 24w →51% at one year	LTB associated with higher TI (*p=0.002*)
Mariani L. (2025)	40	30%	32.5%	LTB associated with higher response (*p* not reported)
Bouchla A. (2025)	98	42.9%	44.3% (≥24 w FU)	≥2 mutations associated with worse OS (*p=0.032*)
Zhang Z. (2025)	60	51%	48% at 8w -> 25.8% at 16 w	Lower EPO (≤500 IU/L) independently associated with response (*p=0.025 uni; p=0.07 multi*)

Luspatercept: Start with maximum approved dose? MAXILUS Phase 3 trial

Key eligibility criteria

- IPSS-R very low-, low- or intermediate-risk MDS (with or without RS)
- **Requiring RBC transfusions** (≥ 1 RBC unit within 8 weeks prior to treatment)
- **Hb ≤ 10 g/dL**
- Endogenous sEPO < 500 U/L for ESA-naïve cohort

Primary phase: Weeks 1–24

Non-randomized 1:1

Cohort 1:
ESA-naïve (n = ~50)
Luspatercept
1.75 mg/kg s.c. Q3W

Cohort 2:
ESA R/R[a] (n = ~50)
Luspatercept
1.75 mg/kg s.c. Q3W

Response evaluation

Extension: Up to 2 years

Discontinue treatment if no clinical benefit or progression

Continue treatment if clinical benefit

End of treatment

Post-treatment follow-up

End of study

Primary endpoint

RBC-TI for ≥ 8 weeks and concurrent Hb increase of ≥ 1 g/dL (weeks 1–24)

Secondary endpoints

RBC-TI over any consecutive 8-/12-/16-/24-week period

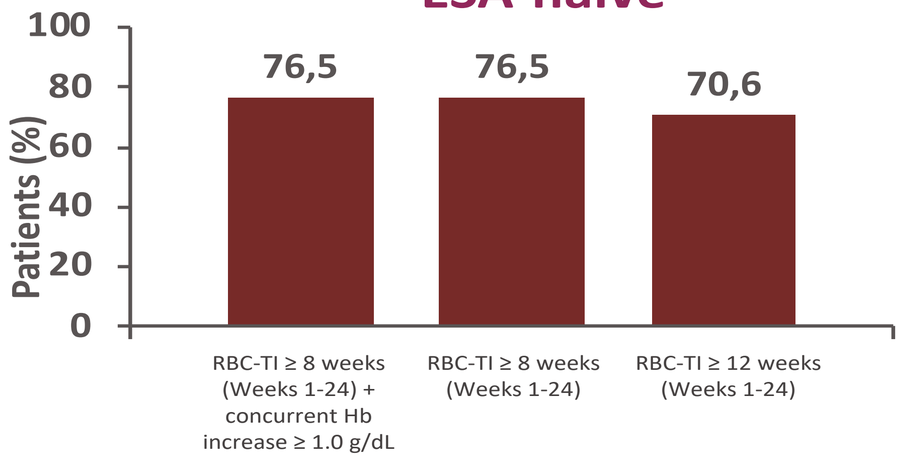
Time to onset and maximum duration of RBC-TI periods

Mean Hb increases (≥ 1 g/dL and ≥ 1.5 g/dL from baseline)

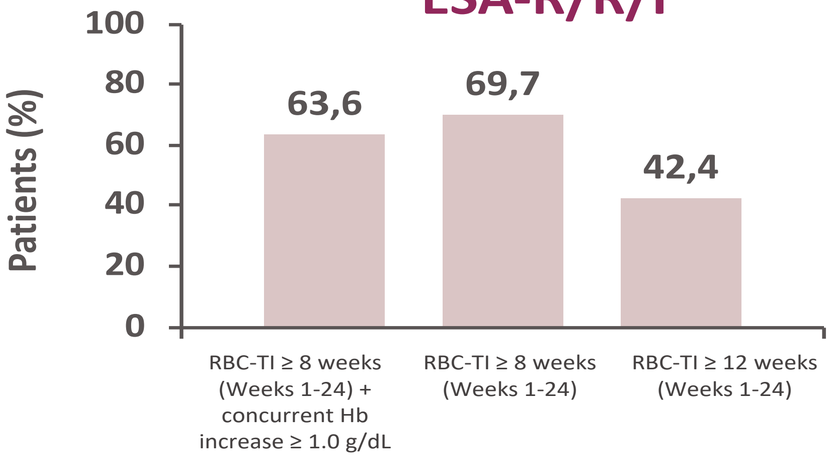
Change in total RBC units transfused over 16 weeks

OS, progression to AML, QoL, safety

ESA-naive

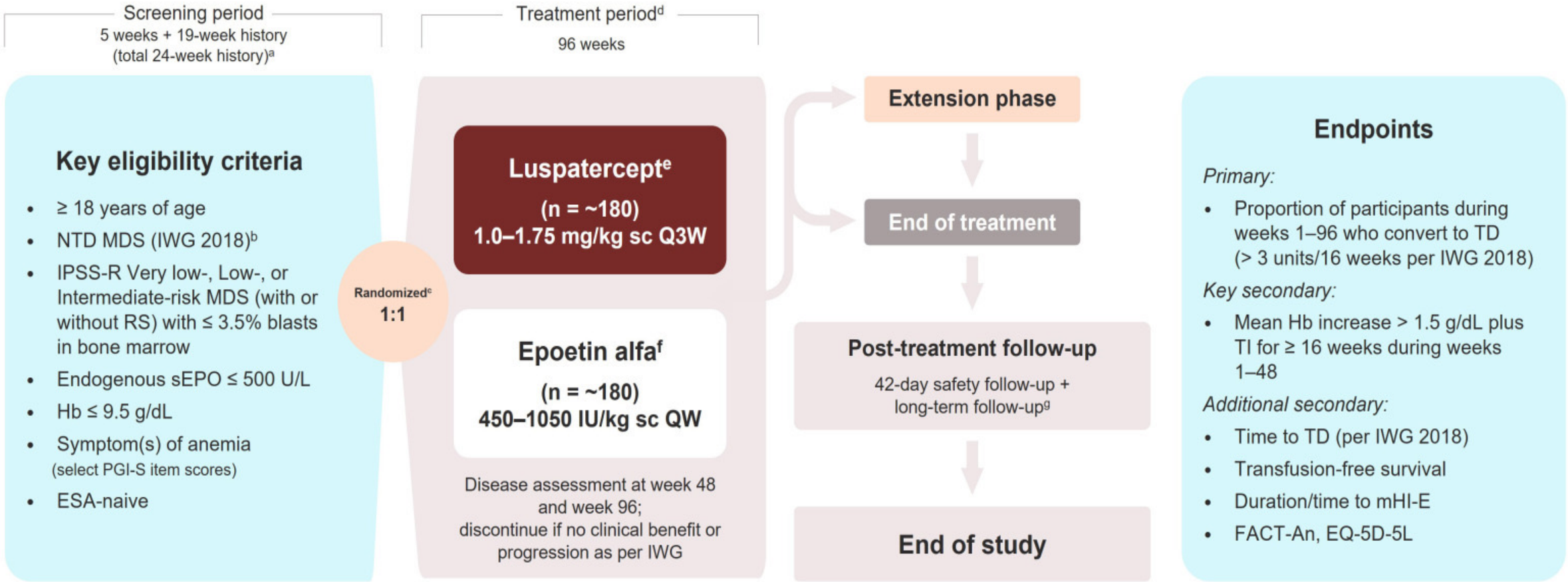


ESA-R/R/I



Zeidan et al, SOHO 2025, Abstract No. MDS-736

CA056-025 (ELEMENT-MDS) Phase 3 Registrational Trial
Luspatercept vs Epoetin Alfa in NTD VL,L,INT-Risk MDS Patients ESA-naive, EPO<500, open label randomized 1:1



Zeidan et al, Blood (2023) 142 (Supplement 1): 6503.

Can ESAs and Luspatercept Be Combined in Non-RS MDS?

N = 24 patients with LR-MDS[1]

- Without RS or del(5q)
- Ineligible or having failed to achieve a response (or subsequently relapsed) after ESA
- No disease progression

Luspatercept SC every 21 days

Doses ranging from 0.8 to 1.75 mg/kg

Epoetin alfa weekly

Dose concentrations 30,000 UI to 60,000 UI

Luspatercept 1.75 mg/kg/21d and EPO 60 000 UI/w, balanced clinical efficacy (including erythroid responses) and safety

Outcome, n (%)	Low Transfusion Burden (n = 6)	High Transfusion Burden (n = 16)	Nontransfusion Dependent (n = 2)	Overall (N = 24)
Erythroid response* at Wk 25	2 (33)	4 (25)	1 (50)	**7 (30)**

Ades L, et al. ASH 2024. Absract 351

CONCLUSIONS

- **Luspatercept** represents a major advancement in the management of TD anemia in **lower-risk MDS**, providing **deeper and more durable responses** compared with ESAs.
- **Real-world data** confirm its **efficacy and safety** even in **older, frailer, and heavily pretreated** patient populations.
- **Transfusion burden and serum EPO levels** remain the main predictors of response.
- Achieving a **deep erythroid response** correlates with **improved overall survival**.
- Ongoing studies aim to **expand luspatercept use as first-line** in TI anemia and explore **novel therapeutic combinations**.

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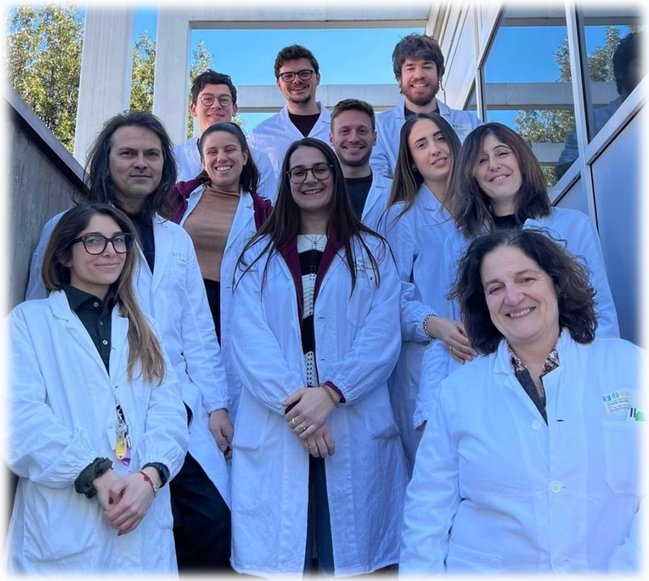

MDS-UNIT (prof.ssa Valeria Santini and collabortators), Careggi Hospital, Florence

Thank's for your attention