Azienda Ospedaliero Universitaria Careggi

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

UNIVERSITÀ DEGLI STUDI FIRENZE
DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA

CONVEGNO FISiM

Firenze, CSF Montedomini
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STUDI REAL LIFE CON LUSPATERCEPT

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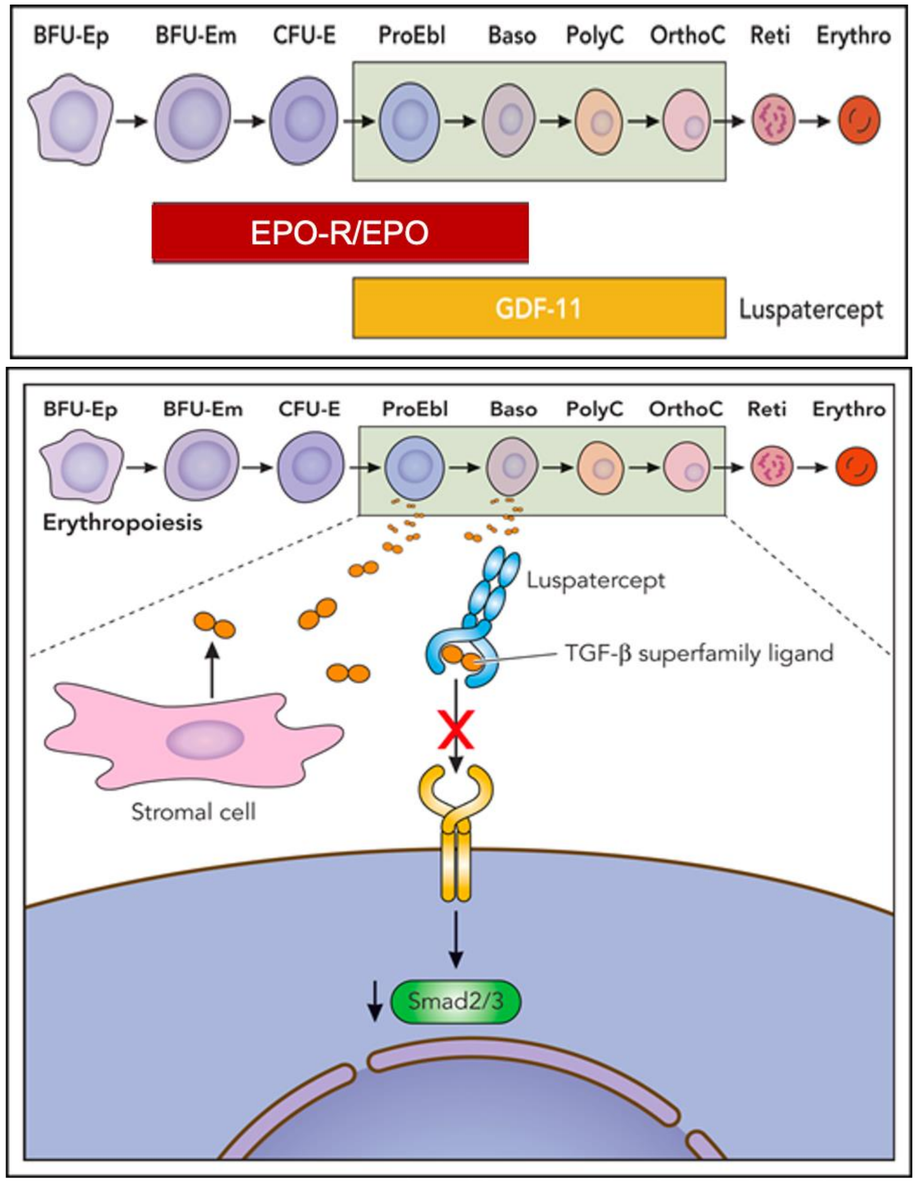


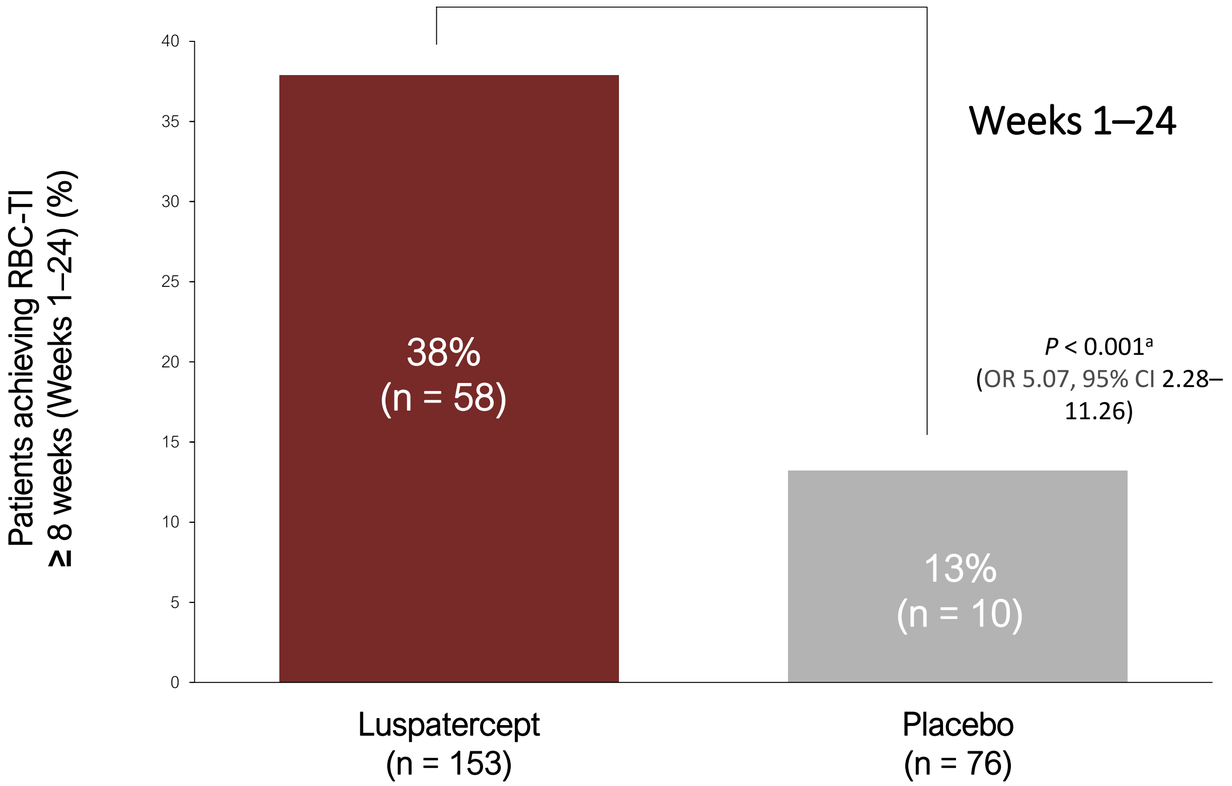
Adapted from A.S. Kubasch et al. Blood adv 2021

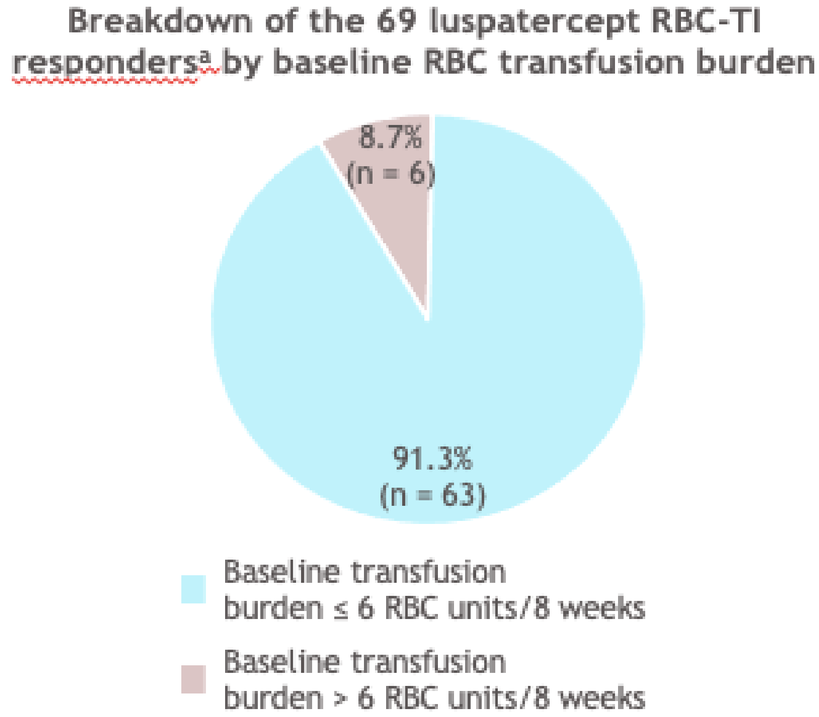
Luspatercept is a fusion protein constituted by the modified extracellular domain of human activin receptor type IIB linked to the human IgG1 Fc domain.

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

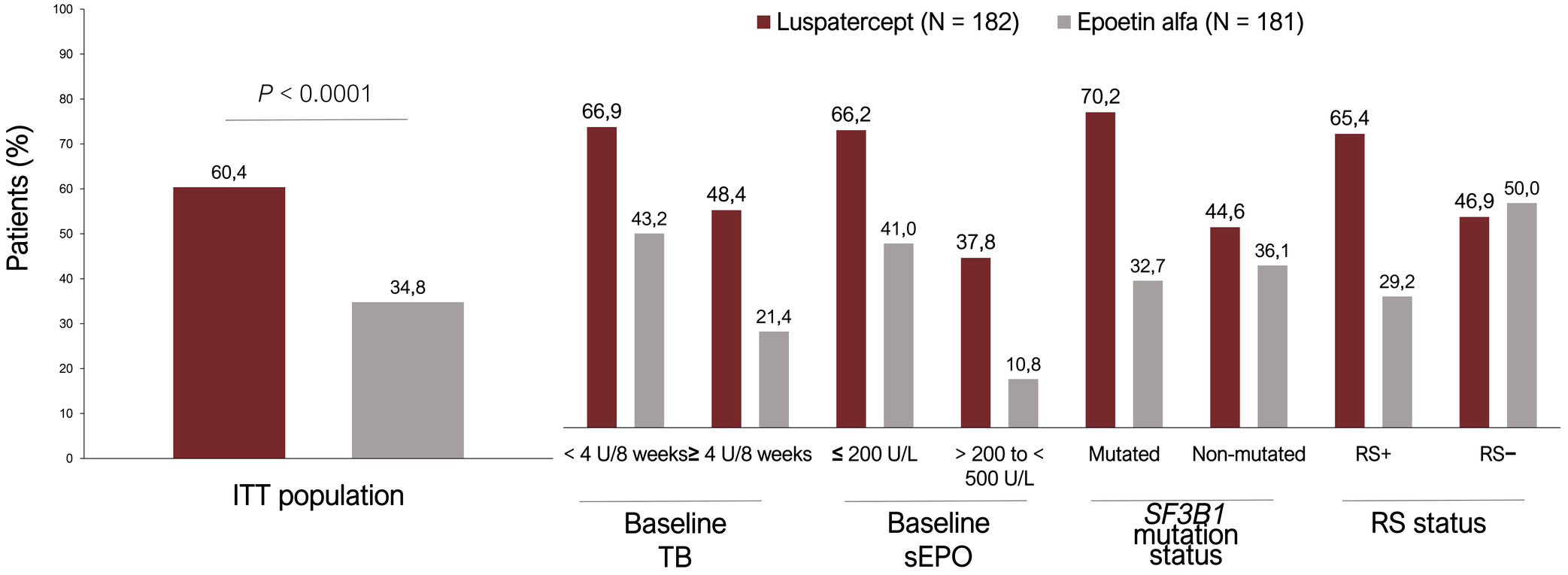




- RR were similar regardless of *SF3B1* allelic burden and total number of baseline somatic mutations
- When assessed during the entire treatment period, a greater proportion of Luspatercept-treated pts achieved RBC-TI ≥ 8 weeks

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

COMMANDS Trial



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

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)	
4 to 5 units/8 weeks, n (%)	15/41 (36.6)	16/48 (34.0)	**<.001**
<4 units/8 weeks, n (%)	37/46 (80.4)	13/17 (76.4)	
Baseline transfusion requirements			
≥8 units/8 weeks, n (%)		14/76 (18.4)	
4 to 7 units/8 weeks, n (%)	**NR**	28/84 (33.3)	**<.001**
<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 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,

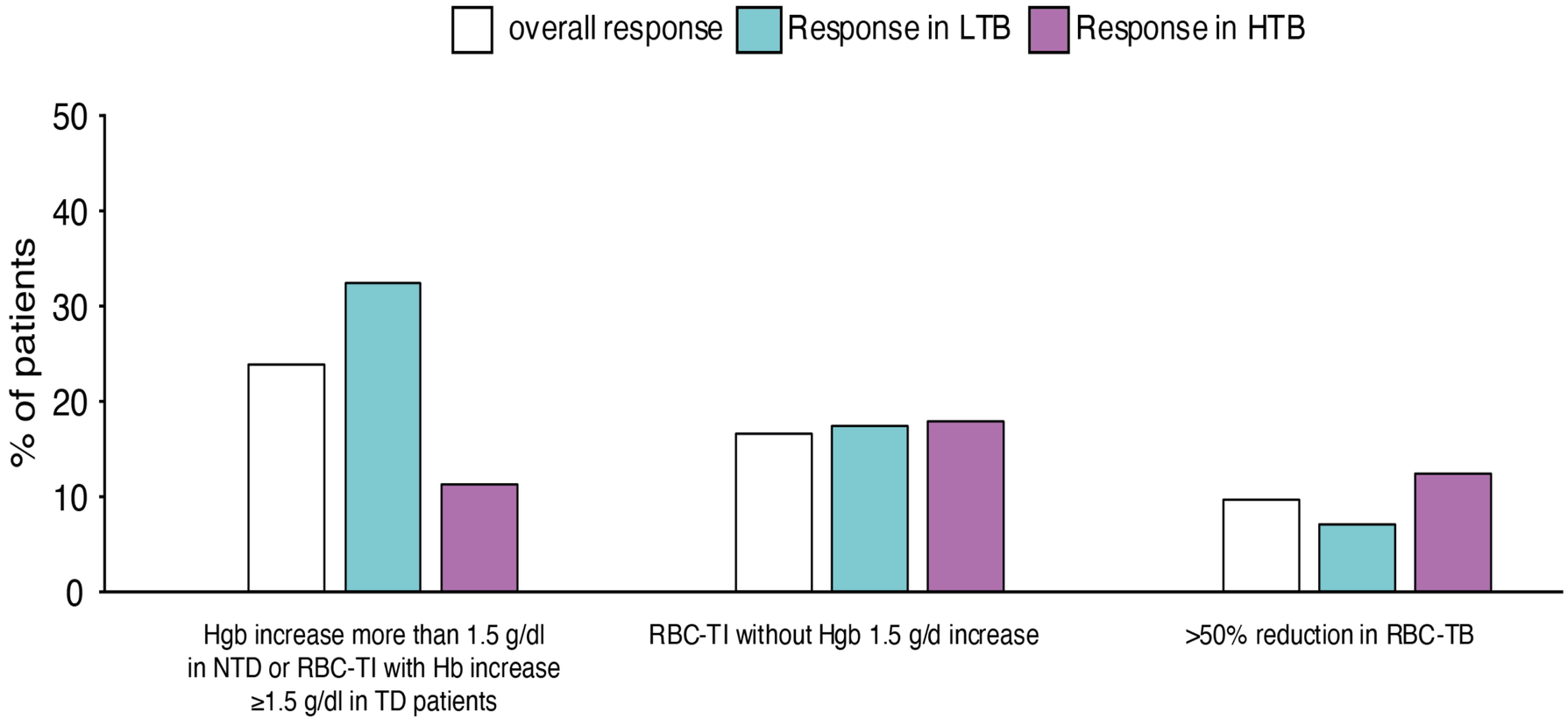
Patients who did not reach HI-E > 8 weeks were considered non-responders

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)

OVERALL RESPONSE AND TYPES OF RESPONSE

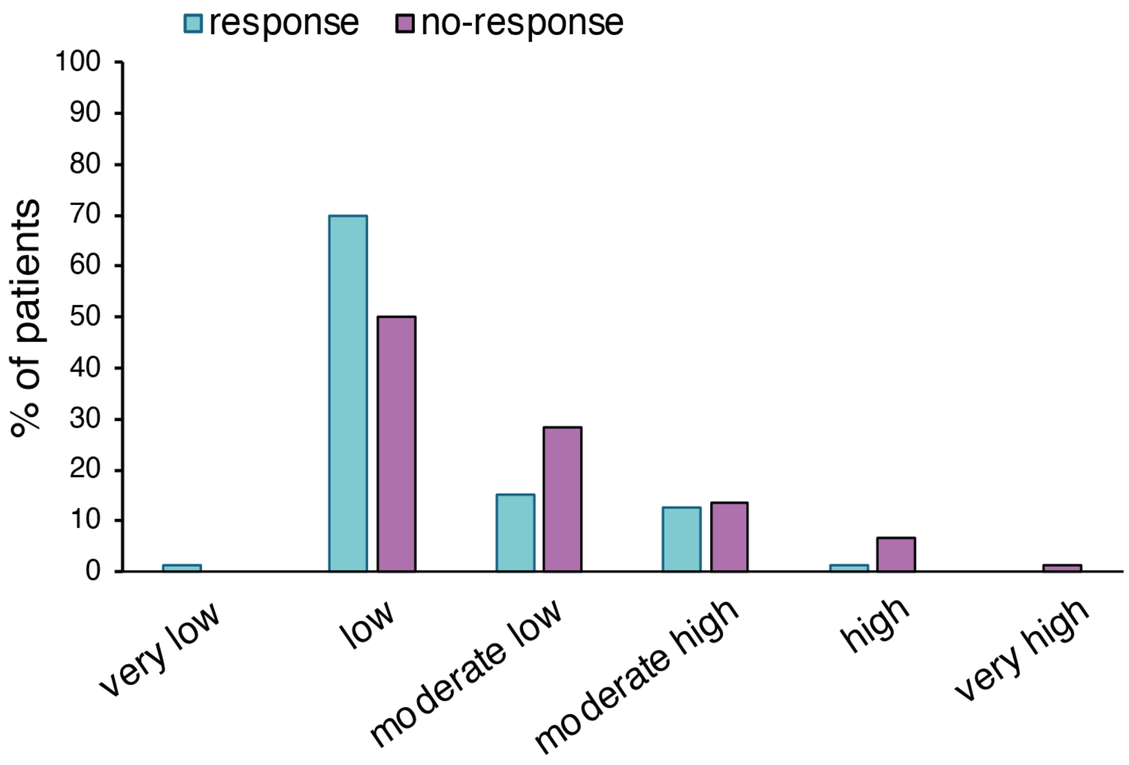


HI-E was observed in 166 patients (50.2%) and was significantly higher in NTD and LTB patients compared to HTB patients ($p<0.001$)

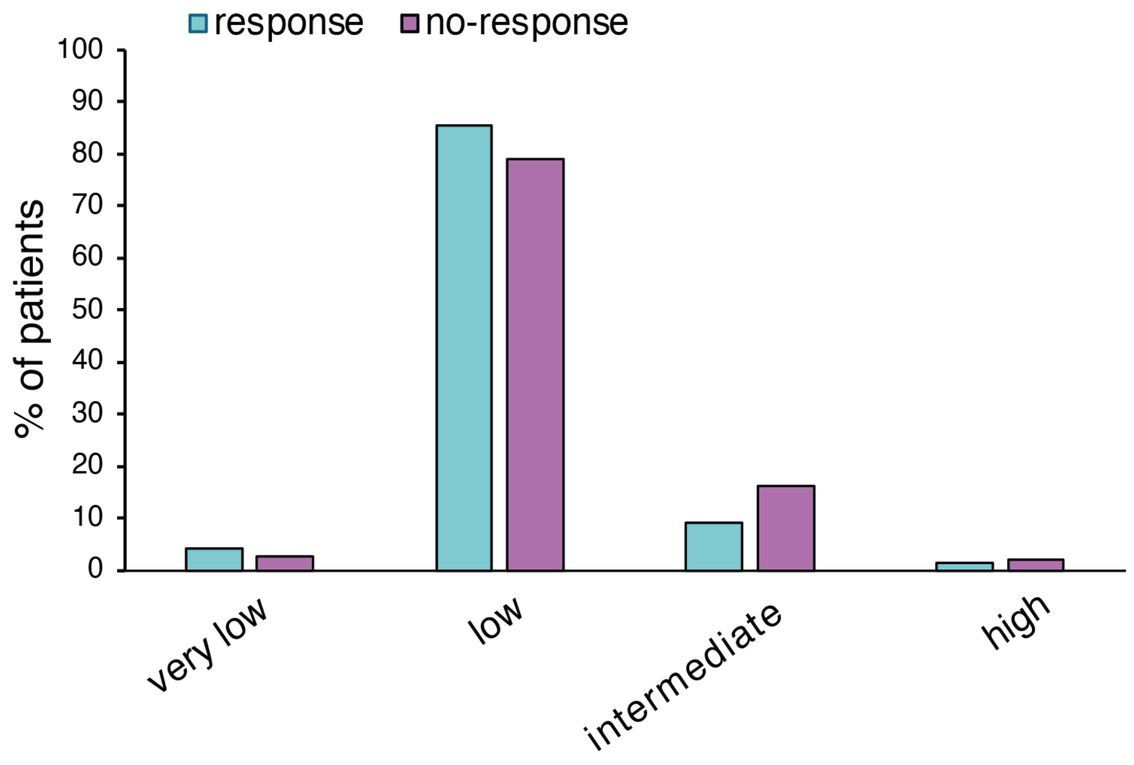
81% (17/21) of NTD patients achieved HI-E

Consagra A et al,, paper accepted by HemaSphere (under revision), please do not share

DISTRIBUTION OF RESPONSE BY IPSS-M AND IPSS-R



IPSS-M



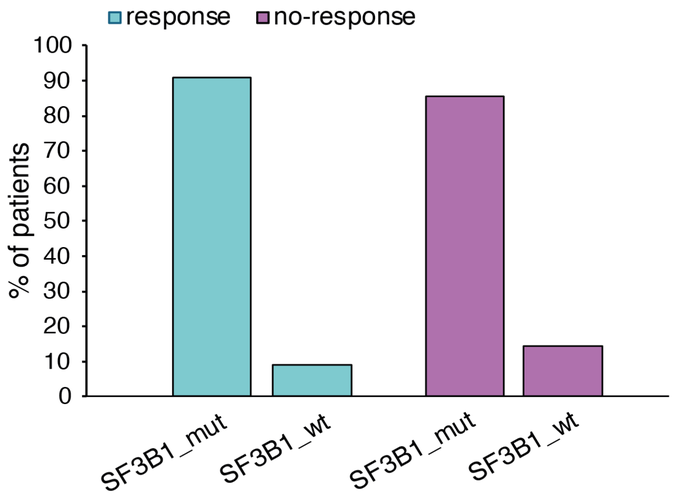
IPSS-R

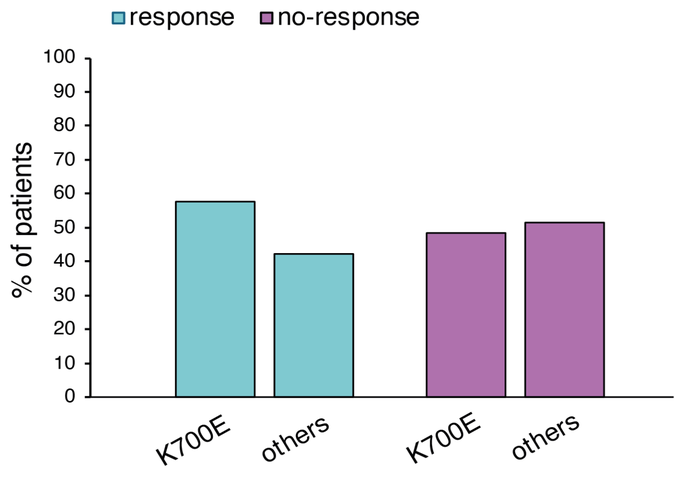
For 154/331 patients with calculated IPSS-M prior to Luspatercept, response was significantly correlated with disease risk (*p=.031*), while IPSS-R score did not correlate with response (*p=.247*).

Consagra A et al,, paper accepted by HemaSphere (under revision), please do not share

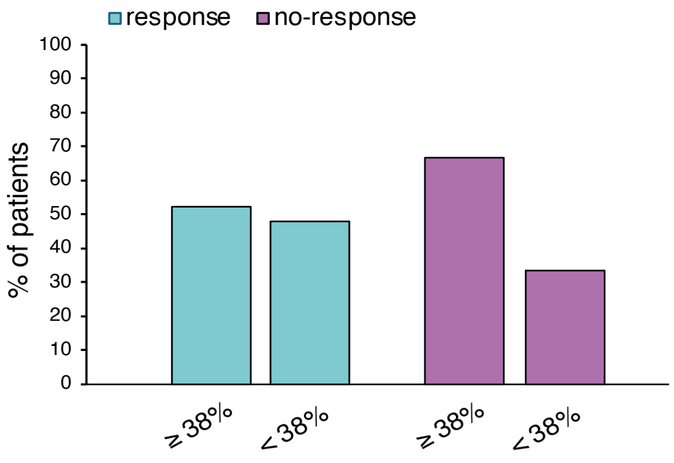
RESPONSE AND MOLECULAR CHARACTERISTICS

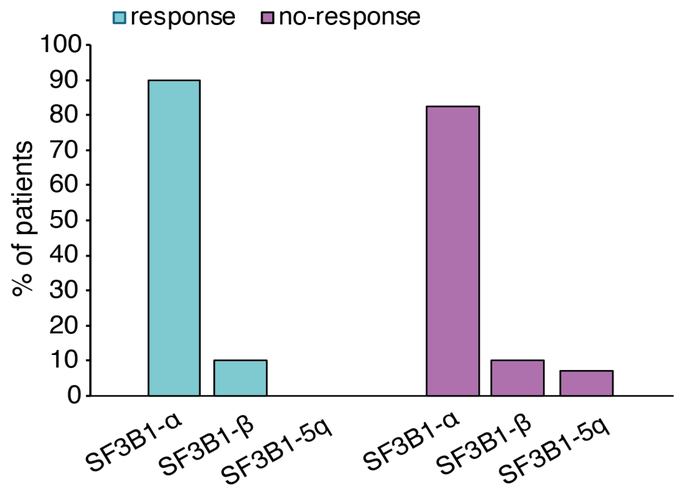
- Similar RR in *SF3B1*-MT pts compared to *SF3B1*-WT, 91/169 (53.8%) vs 9/22(40.1%), *p=.267*





- 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*.





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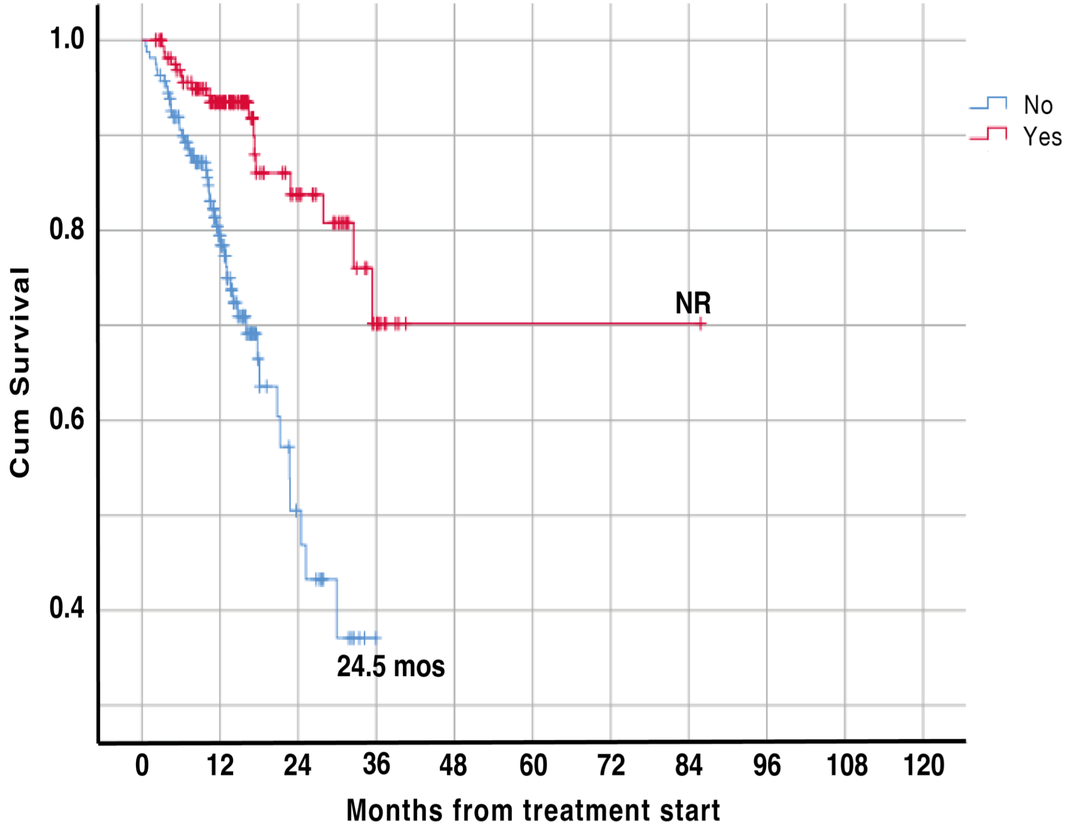
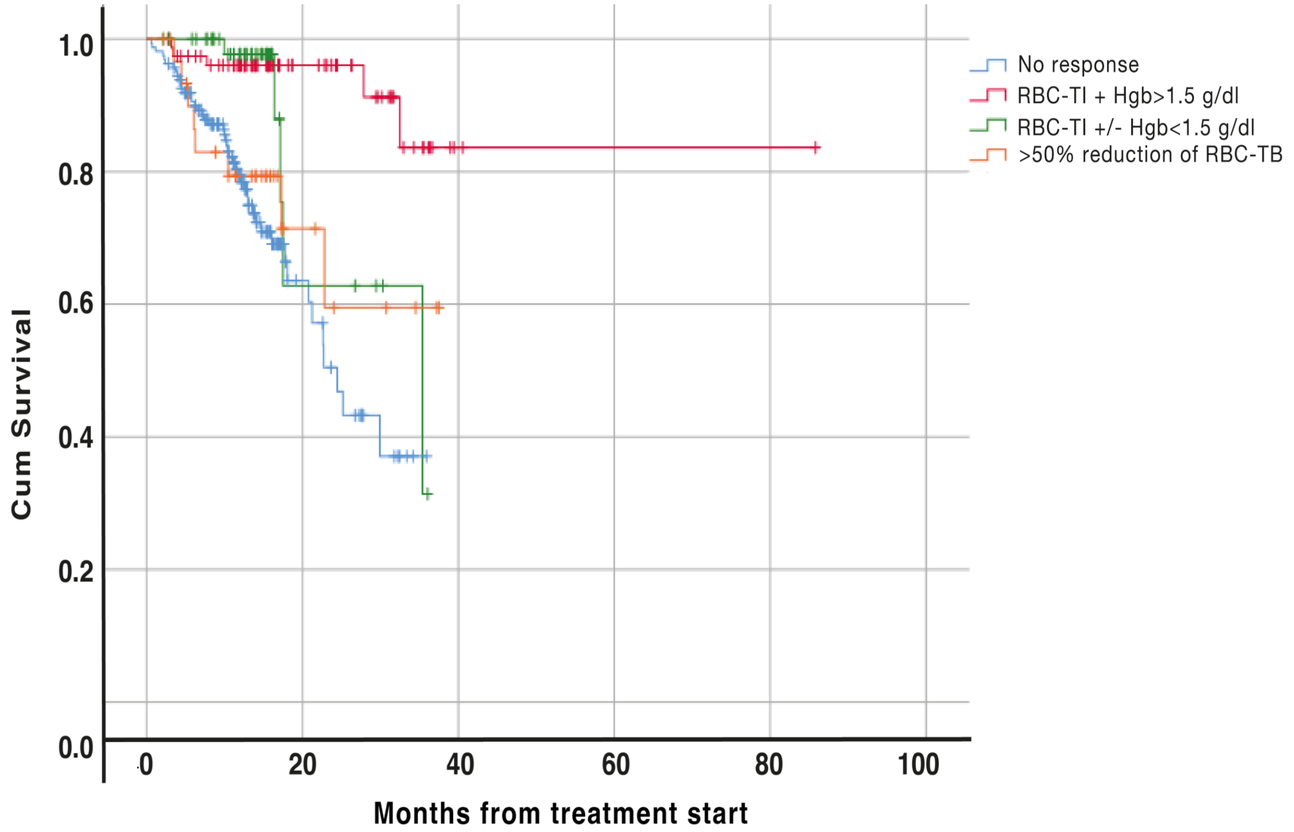
IMPROVED OS AMONG LUSPATERCEPT RESPONDERS

Median OS was significantly longer among patients with RBC-TI > 8 weeks and Hgb ≥1.5 g/dl increase compared with other HI-E and non-responders (p<.000)



OS responders vs non responders



OS according to type of response

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FUTURE DIRECTIONS IN LUSPATERCEPT RESEARCH: REAL-WORLD EVIDENCE AND TRANSLATIONAL MEDICINE APPROACHES

- *Genetic and molecular analysis* → previous investigations into genetic mutations (e.g., *SF3B1*) and molecular profiles have shown potential in predicting response to Luspatercept in MDS patients

- *Flow cytometric analysis of erythroid precursors* → offers a promising avenue for identifying responders to treatment

Raddi M.G. et al, Blood Cancer J, 2024 Aug 7;14(1):127

- *Epigenetic profiling* → explore epigenetic changes and protein expression in erythroid precursors to identify new factors influencing treatment response

- *Inflammation* → evaluate the role of inflammation in the bone marrow microenvironment and whether modulating these responses can enhance Luspatercept efficacy

FUTURE DIRECTIONS IN LUSPATERCEPT RESEARCH: REAL-WORLD EVIDENCE AND TRANSLATIONAL MEDICINE APPROACHES

- *Long-term response* → study factors contributing to the loss of response over time and optimize maintenance strategies
- *Combination with iron chelation therapy* → investigate whether combining Luspatercept with iron chelators could benefit patients with significant iron accumulation from prior transfusions
- *Combination with ESAs* → investigate the potential synergistic effect of combining Luspatercept with ESAs, particularly in patients with suboptimal or declining response to ESAs
- *Non-responder analysis* → investigate the mechanisms behind Luspatercept resistance in some patients and identify alternative therapies or combination strategies for this subgroup

Ongoing Clinical Trials

- **MAXILUS** → the impact of initiating directly at the maximum dose
- **ELEMENT** → first-line treatment in NTD patients

WHO IS THE IDEAL PATIENT FOR LUSPATERCEPT IN 2024?

Reflecting on current evidence

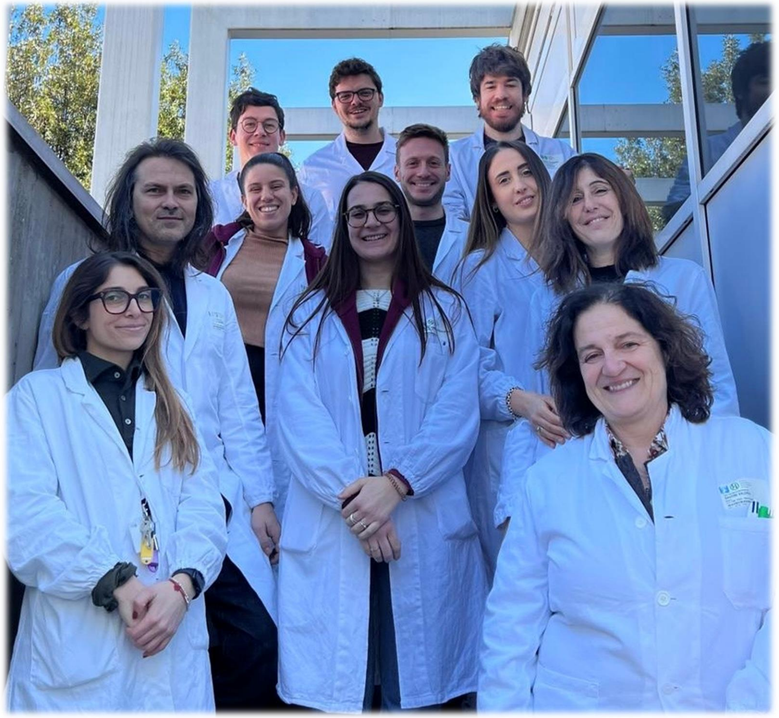
- First line → TD (>4 RBC/8w and long history of TD) LR-MDS, especially if *SF3B1*$^{\alpha}$ MT and sEpo> 200 UI/L

- Second line → after ESAs failure, TD LR-MDS (Imetelstat? Especially if only anemic and > 6 RBC/8w)

- Third line → TD LR-MDS after HMA or lenalidomide failure

Blood ADV 2023 Jul 25; 7(14): 3677–3679
ASH 2023, Abstract 1871 , A. Consagra

MDS-del5q with *SF3B1* mutation do not seem to respond to Luspatercept in second/third line and data on first line therapy with Luspatercept are not available.



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

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Grazie per l'attenzione