FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

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

IPSS-M e modelli predittivi di risposta ad ESAs e Luspatercept nelle MDS a basso rischio

Marco Gabriele Raddi, MD
MDS Unit, Haematology,
Department of experimental and clinical medicine,
University of Florence, Florence, Italy

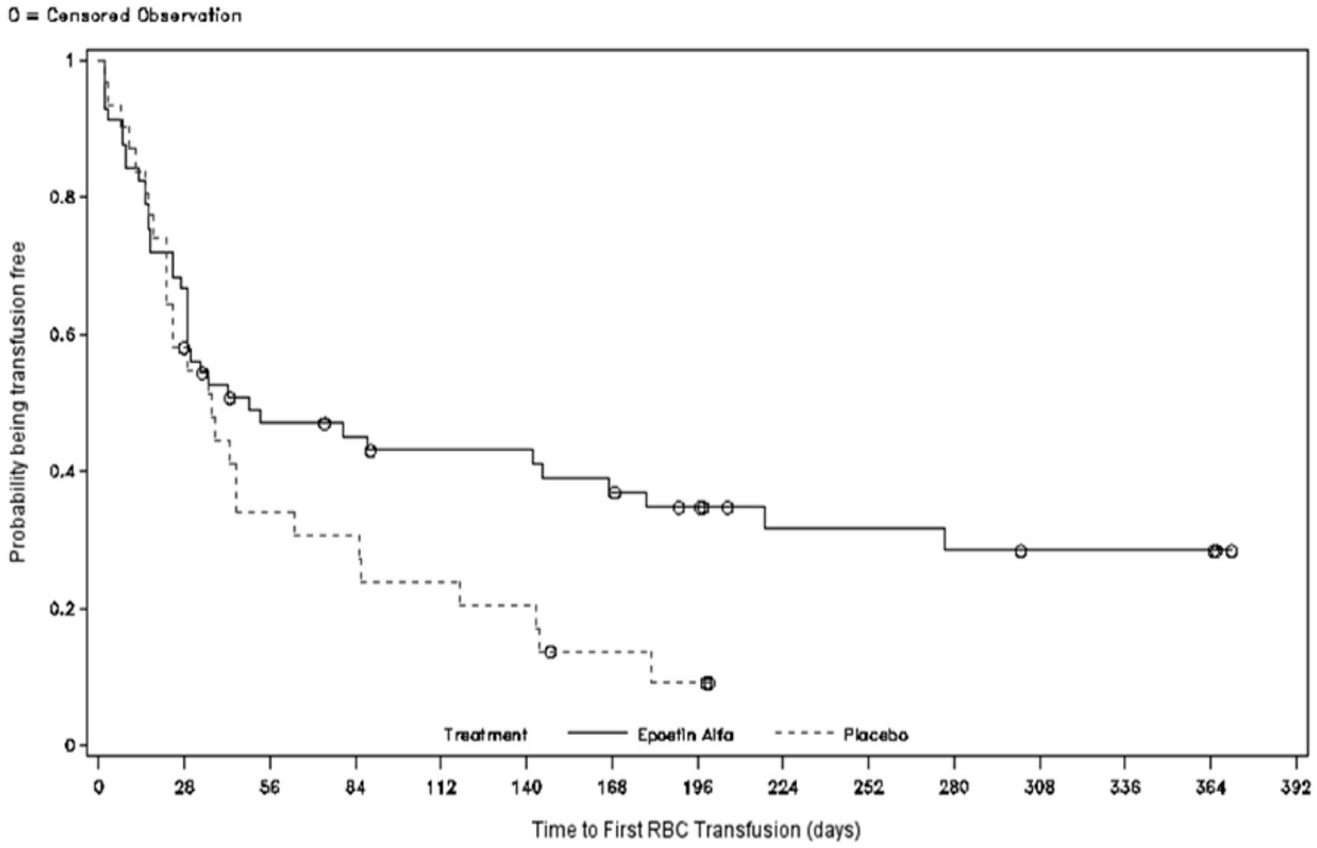
UNIVERSITÀ DEGLI STUDI FIRENZE

Disclosures of Marco Gabriele Raddi

I have no financial interests or relationships to disclose

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

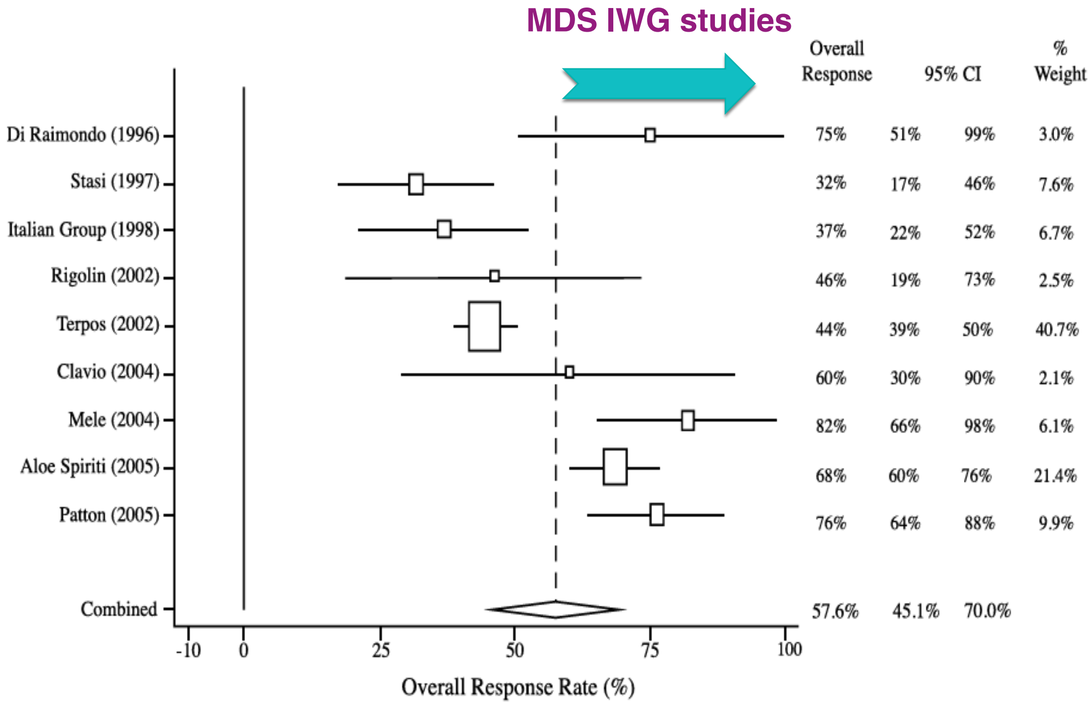
Use of Erythropoiesis stimulating agents (ESAs) in anemic patients with LR-MDS



ER	miTT analysis	
	Placebo $n = 45$	Epoetin-α $n = 85$
Patients with erythroid response[a] at any time during the first 24 weeks of the study	2 (4.4%)	27 (31.8%)
P value[b]		<0.001
Patients with erythroid response by stratification group		
No transfusion and serum erythropoietin level less than 200 mU/mL[c]	1 (4.8%)	20 (50.0%)
Transfusion and serum erythropoietin level less than 200 mU/mL[c]	1 (5.6%)	7 (22.6%)
No transfusion and serum erythropoietin level at least 200 mU/mL	0	0
Transfusion and serum erythropoietin level at least 200 mU/mL	0	0
P value[d]		<0.001
Patients with erythroid response by IPSS risk category		
Low = 0[e]	2 (8.7%)	16 (45.7%)
Intermediate-1 = 0.5–1.0[e]	0	10 (20.4%)
Intermediate-2 = 1.5–2.0	0	0
High = ≥ 2.5	0	0
No IPSS at screening	0	1
P value[d]		<0.001
Percentage of patients with erythroid response at any time during the first 24 weeks of study for evaluable patients[f]	2 (4.4%)	27 (32.9%)

Fenaux, P., *et al. Leukemia* 32, 2648–2658 (2018).

The selection of LR-MDS patients with **sEPO ≤200 U/L** and **≤2 RBC-U/4 weeks** + the use of **optimal dosage** increases the rate of the erythroid response



ESA type	Dosing schedule	Efficacy (response rate), %	Limitations	Comparison and combination studies
Epoetin alfa	30 000–40 000 IU SC weekly	~40–60	Lower response in patients with high endogenous EPO (>500 U/L)	The EPOANE3021 trial showed significant efficacy over placebo (31.8% vs. 4.4%)
Epoetin beta	30 000–60 000 IU SC weekly	~40–60	Requires frequent administration	A randomized study showed that adding G-CSF improved response rates (33.3% vs. 62.5%, $p = 0.03$)
Darbepoetin alfa	150–300 µg SC every 2–3 weeks	~50–70	More expensive than epoetin; response duration varies	The ARCADE trial showed superior transfusion reduction over placebo (36.1% vs. 59.2%)
Methoxy polyethylene glycol-epoetin beta (CERA)	360 µg SC every 3–4 weeks	~40–60	Less commonly used in MDS; limited comparative data	Not widely studied in MDS, but long-acting profile offers potential benefits
Erythropoietin-zeta	40 000–80 000 IU SC weekly	~50–55	Less commonly used in MDS; limited comparative data	Not widely studied in MDS, but is a valid and safe alternative

Pere Gascón, et al. Leukemia Research, 2019,

V. Santini and A. Consagra, BJHem 207:15-26 (2025).

Primary selection for ESA therapy

	Nordic (1997) (Hellstrom-Lindberg [39])	European (2013) (Santini [56])	MDS-CAN ESA (2017) (Houston [61])	ITACA (2017) (Buckstein [60])
Predictive factor (score adjustment)	(n = 63)	(n = 465)	(n = 208)	(n = 463 + 462)
sEPO, IU/L	< 100 (+ 2) 100–500 (+ 1) > 500 (− 3)	> 200 (+ 1)	< 100 (+ 2)	< 100 (+ 1)
RBC transfusion need, units/month	< 2 (+2) ≥ 2 (− 2)	–	–	0 (+ 1)
IPSS	–	–	Low (+1)	Low (+ 1)
IPSS-R		Low (+ 1) Int (+ 2) High (+ 3)	–	–
Serum ferritin, ng/mL	–	> 350 (+ 1)	–	–
Predictive scores (% of patients achieving a response)				
Best to worst	> 1 (74) ± 1 (23) <− 1 (7) (*P* = NR)	0 (85) 1 (80) 2 (64) 3 (40) 4 (20) (*P* = NR)	3 (81) 2 (55) 1 (30) 0 (17) (*P* < 0.0001)	3 (85) 2 (67) 1 (43) 0 (23) (*P* < 0.0001)

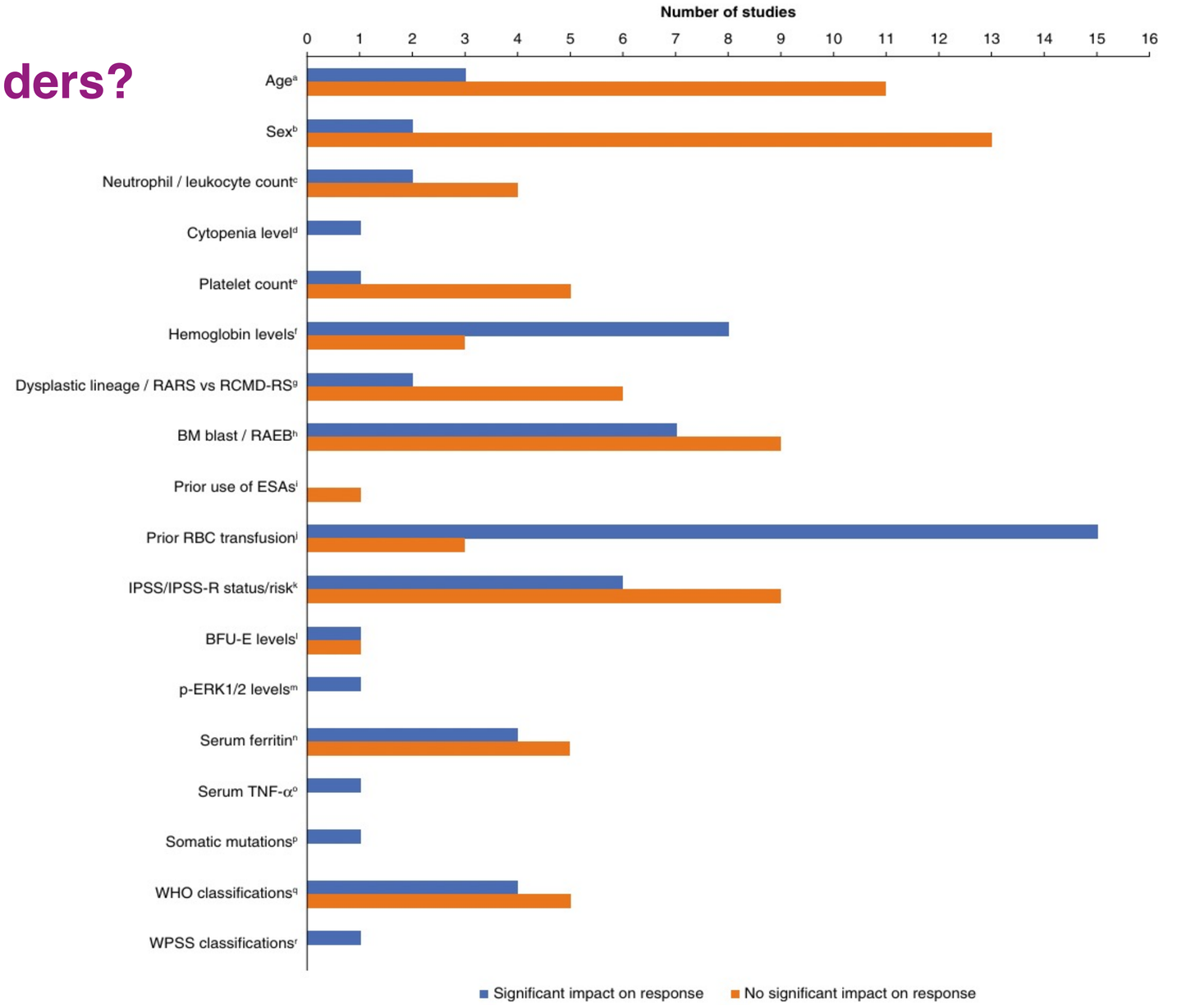
ESA erythropoiesis-stimulating agent, *Int* intermediate, *IPSS* International Prognostic Scoring System, *IPSS-R* revised International Prognostic Scoring System, *ITACA* Italy-Canada, *IU* international unit, *MDS* myelodysplastic syndromes, *MDS-CAN ESA* myelodysplastic syndromes-Canada erythropoiesis–stimulating agent, *NR* not reported, *sEPO* serum erythropoietin

Park S, et al Ann Hematol. 2020 Jan;99(1):7-19

Who are those ∽40% ESA non-responders?

sEPO levels and **transfusion burden** remain the most robust predictors, but…

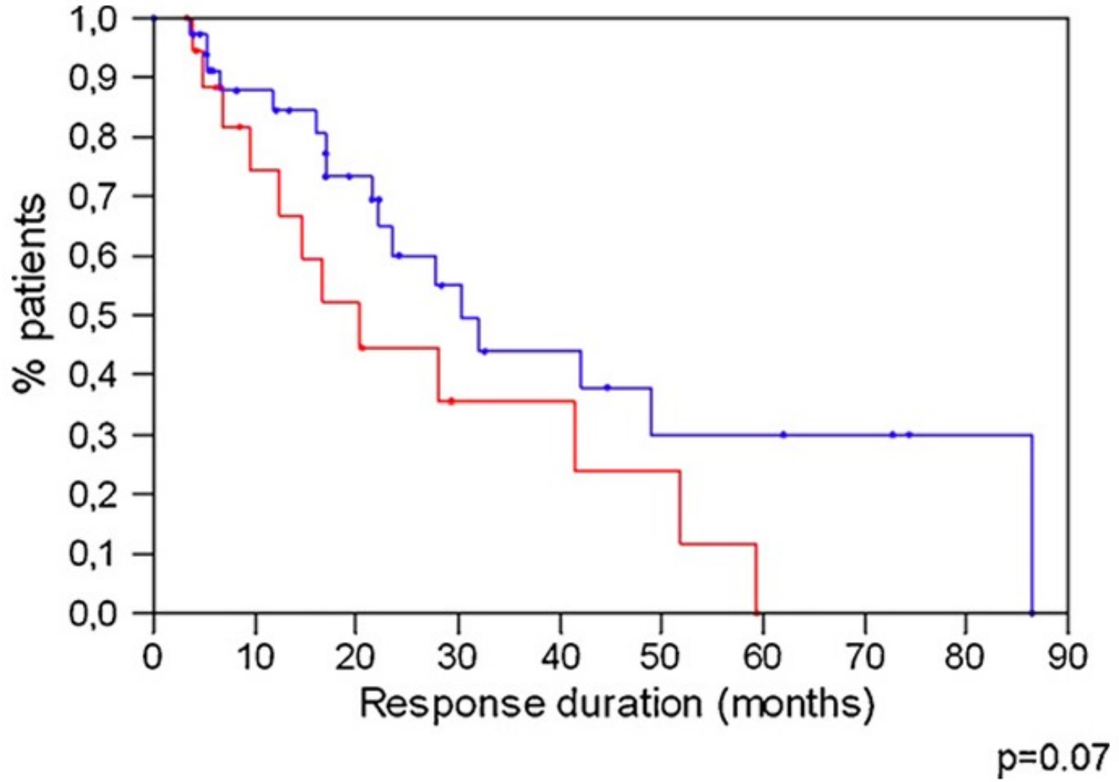
…Novel biomarkers are needed!!

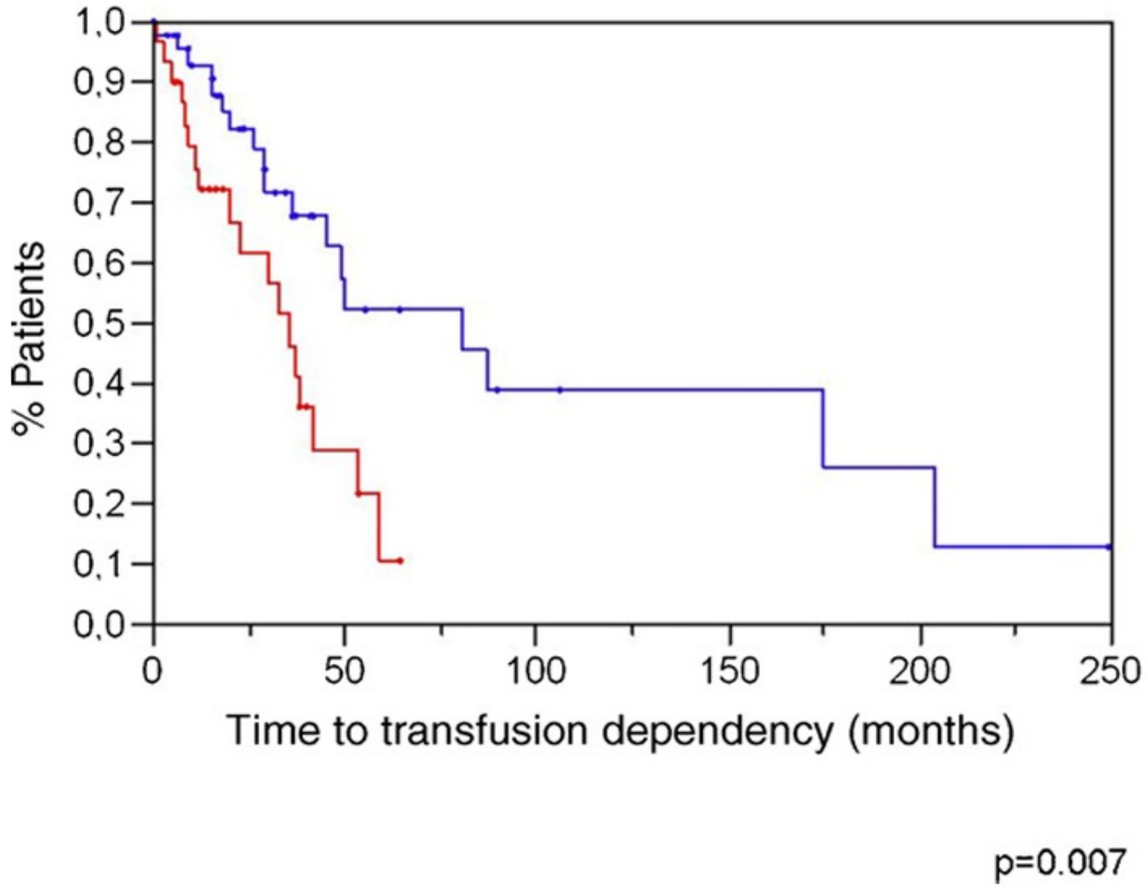


Park S, et al Ann Hematol. 2020 Jan;99(1):7-19

The earlier the better!!

ESA start <6 months from diagnosis
ESA start ≥6 months from diagnosis





Park S, et al. Leuk Res. 2010;34(11):1430-1436 , Park S, Abstract #349 Presented at the ASH Annual Meeting; December 7-10, 2024; San Diego, California

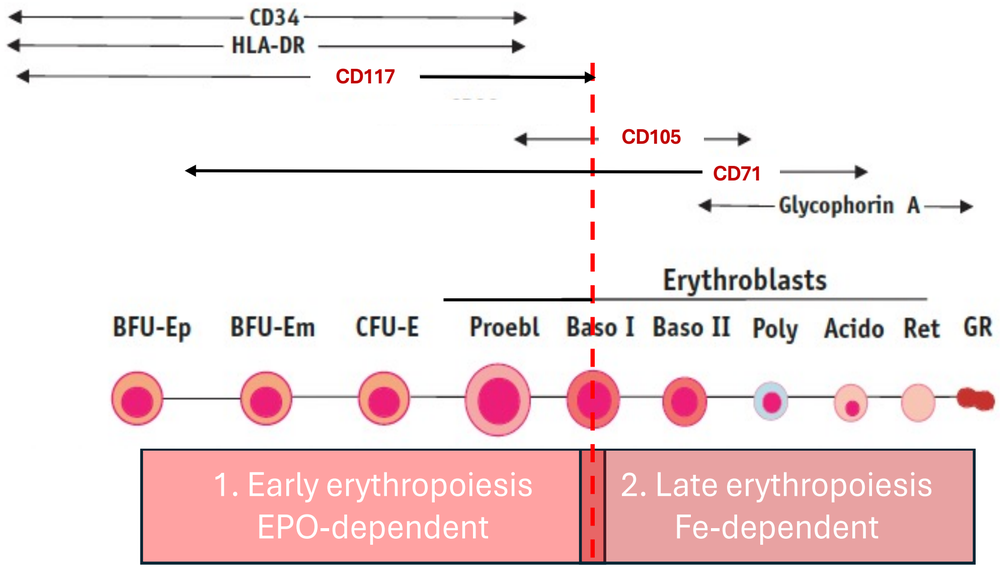
Immature erythroid cells are increased in ESA-sensitive LR-MDS patients

Blood Cancer Journal www.nature.com/bcj

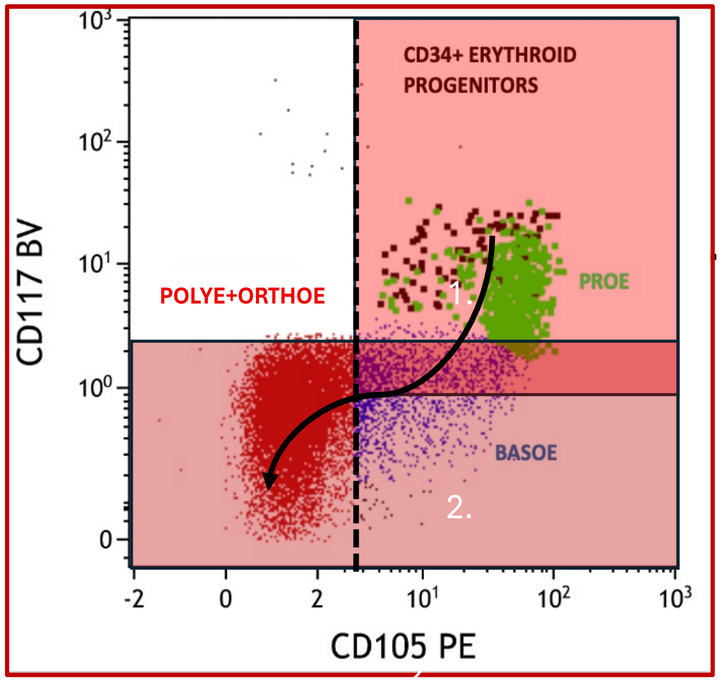
CORRESPONDENCE OPEN

Check for updates

Flow cytometric analysis of erythroid precursors and mutational signatures of lower risk myelodysplastic syndromes identify responders to erythroid stimulating agents



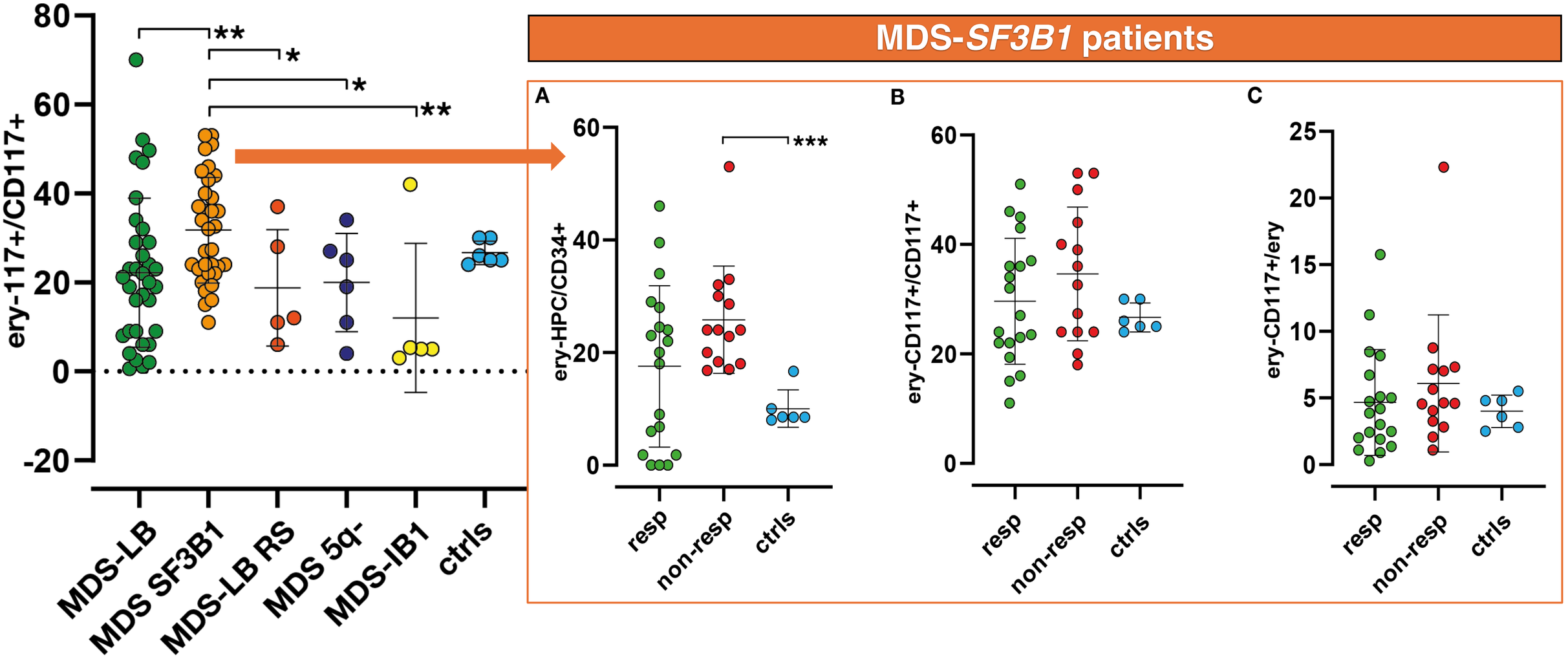
Flow cytometric analysis of erythroid maturation



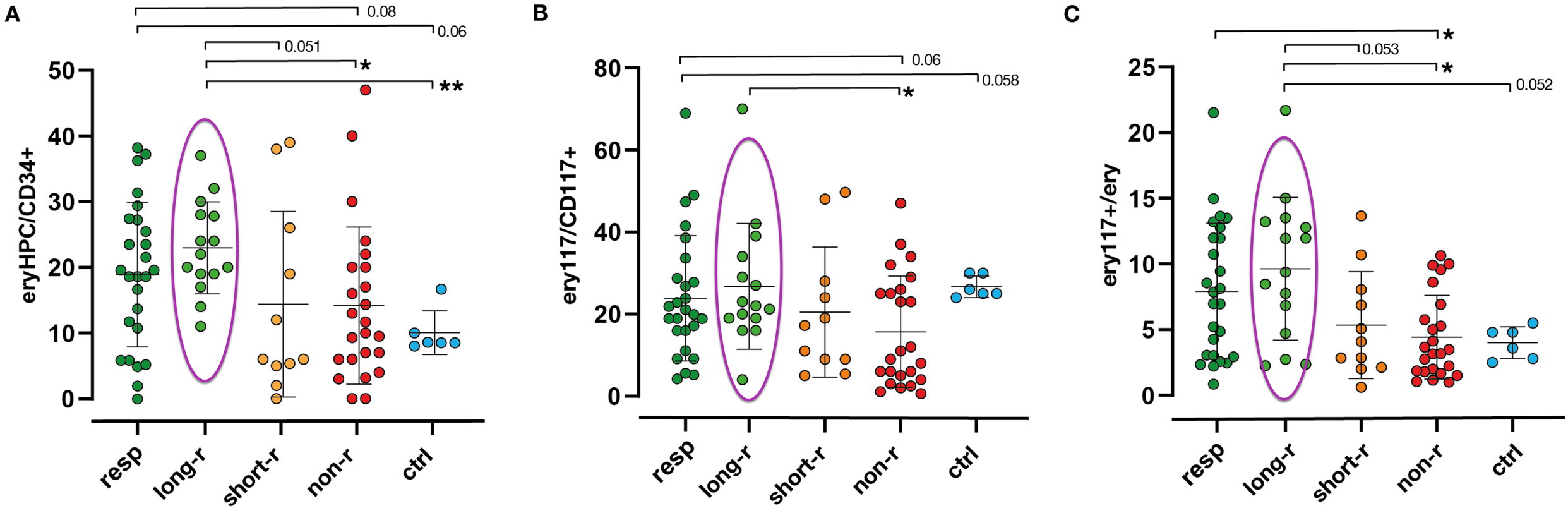
Raddi et al. *Blood Cancer Journal* (2024)

Demographic	Learning cohort (n=97)
Median age (years)	75 (41-92)
Male %(n)	62,8 (61)
Female %(n)	37,2 (36)
Hematological	**Mean (range)**
Hb g/dL	9,67 (7,1-12,5)
sEPO mU/mL	235,22 (7,2-737, n=90)
Ferritin ng/mL	628 (7-7544)
TD %(n)	8,7 (9)
RBC U/8 weeks median (range)	2 (0-4)
WHO 2022	**%(n) n=83**
MDS-LB	40,9 (34)
MDS-*SF3B1*	39,8 (33)
MDS-LB RS	6 (5)
MDS del(5)q	7,3 (6)
MDS-IB1	6 (5)
IPSS-M Category	**%(n) n=83**
Very low	18,3 (15)
Low	46,9 (39)
Moderate low	10,8 (9)
Moderate high	12 (10)
High and Very high	12 (10)
ESA response (HI-E - IWG 2018[1])	**%(n)**
Non-responders	46,6 (48)
Short responders (≤24 months)	25,2 (26)
Long responders (>24 months)	28,1 (29)
Median DOR (months)	23 (10-78)

Patterns of dyserythropoiesis according to MDS subtype

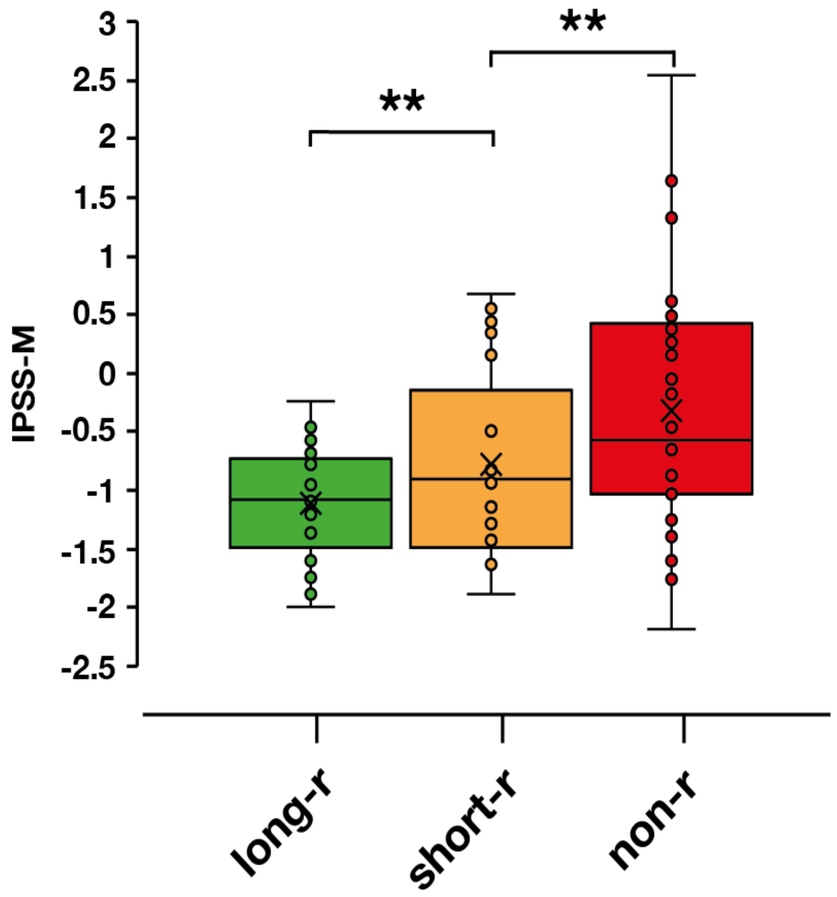


CD34+ and CD117+ erythroid precursors are increased in *SF3B1*^{WT} LR-MDS patients with long (>24 months) ESA response

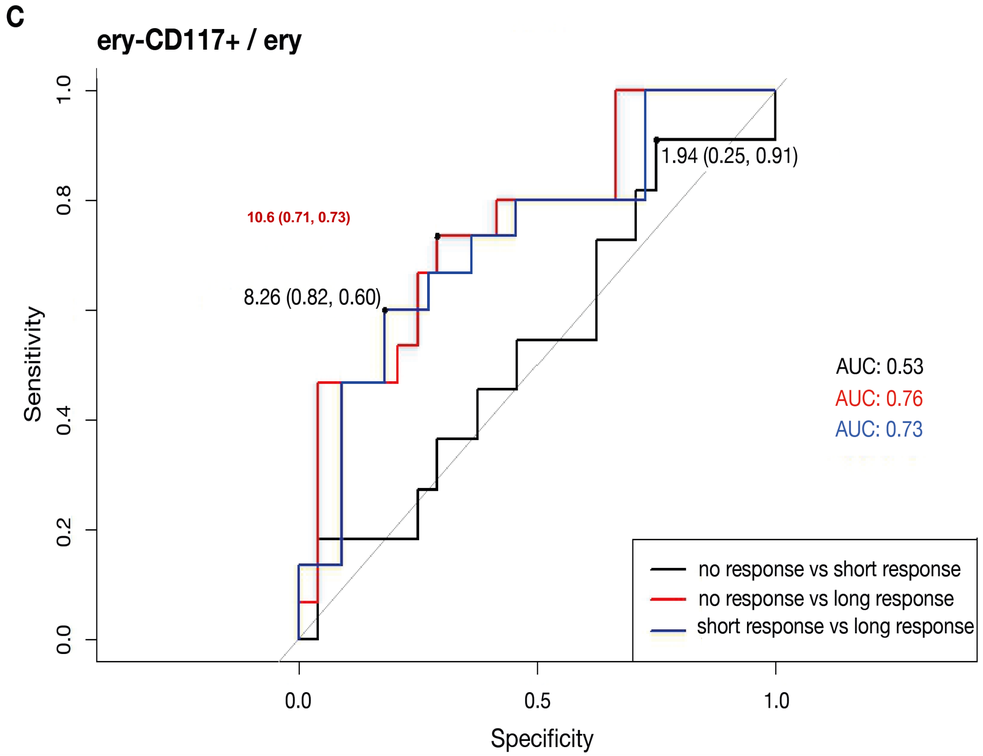


Raddi et al. *Blood Cancer Journal* (2024)

IPSS-M scores and ESA response



SF3B1^{WT} LR-MDS patients

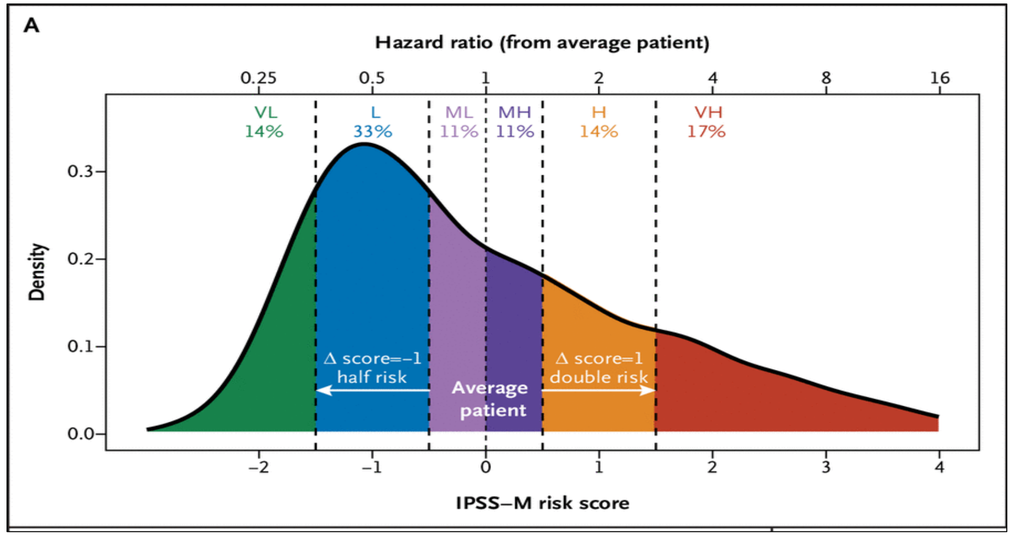


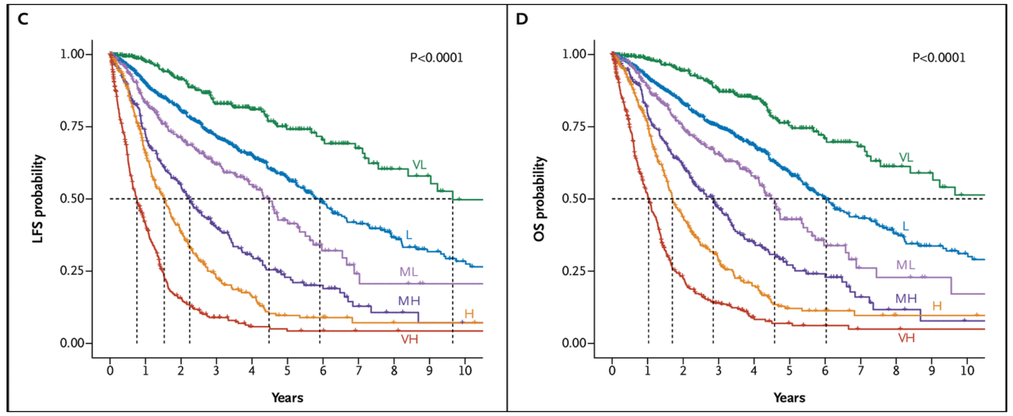
- **Ery-CD117^{+}/ery >10.6%**
- **IPSS-M score <0.25**

Independently from **sEPO** and **TD**

What About Single MDS-Related Somatic Mutations?

IPSS-M score integrates 17 (main) + 15 (residual) prognostically relevant gene mutations





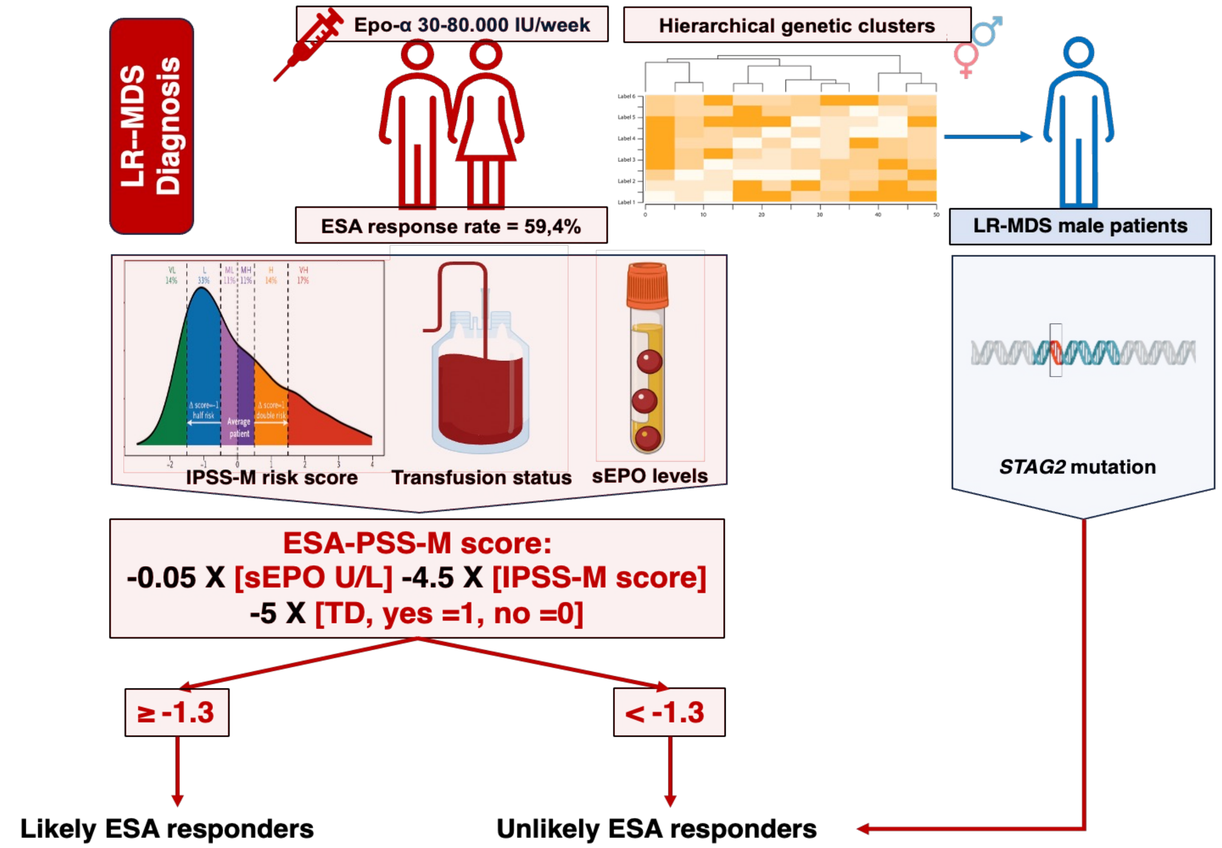
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{5q}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1$^{\alpha}$	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

E. Bernard et al. NEJM, 2022

blood® Regular Article

MYELOID NEOPLASIA

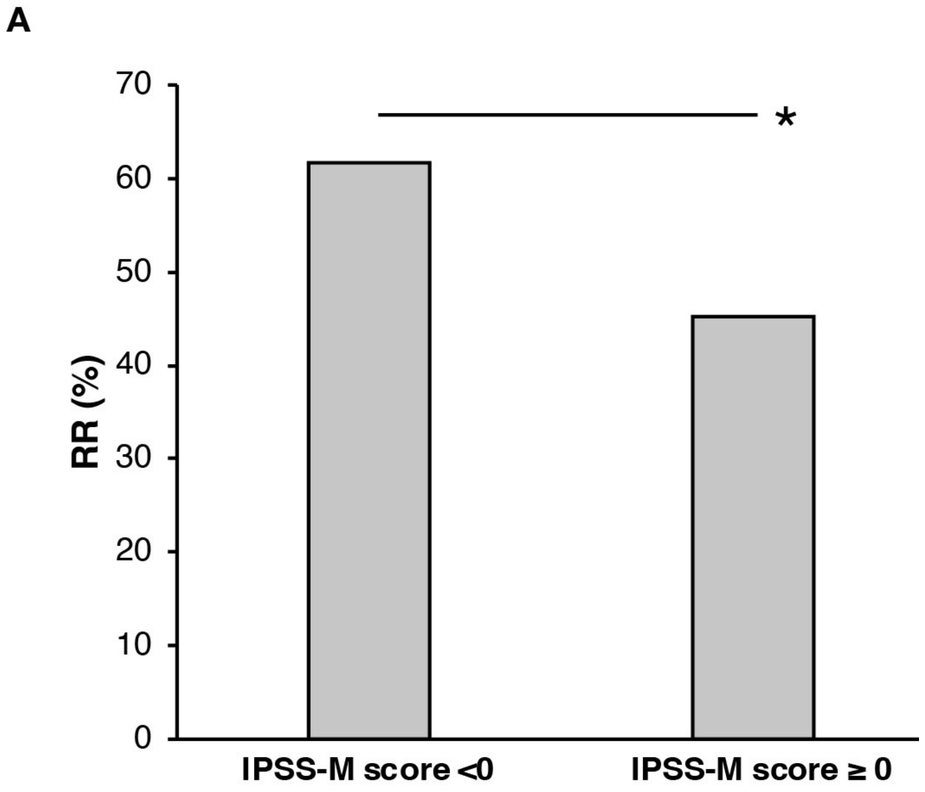
IPSS-M risk and specific sex-associated somatic mutations predict response to ESA therapy in LR-MDS: building a new score



Learning cohort (n = 535)	Mean ± SD (min-max)
Age (years)	74,2 ± 11,8 (18-96)
M:F ratio	1,15
IPSS-R and IPSS-M	**Mean ± SD (min-max)**
IPSS-R score	2,28 ± 0,9 (0-4,5)
IPSS-M score	-0,74 ± 0,82
WHO 2022	**% (n)**
MDS-LB	40 (215)
MDS-*SF3B1*	37,4 (200)
MDS-LB RS	5,2 (28)
MDS *biTP53*	1,1 (6)
MDS 5q-	7,8 (42)
MDS-IB1	7,8 (42)
MDS/MPN-*SF3B1*-T	0,4 (2)
ESA predictors	**Mean ± SD (min-max)**
Hb (g/dL)	9,6 ± 1,34 (5,9 – 15,4)
RBC/8 weeks[1] (n=96)	2,9 ± 1,8 (0-8)
TD rate[1] (%,n)	45,6 (177)
sEPO U/L	99,5 ± 112,8 (4-849)
sEPO < 200 U/L (%)	86,2
ESA Response	**Mean ± SD (min-max)**
HI-E[2] RR (%,n)	59,4 (318)
DOR months	24 ± 26,5 (2-148)

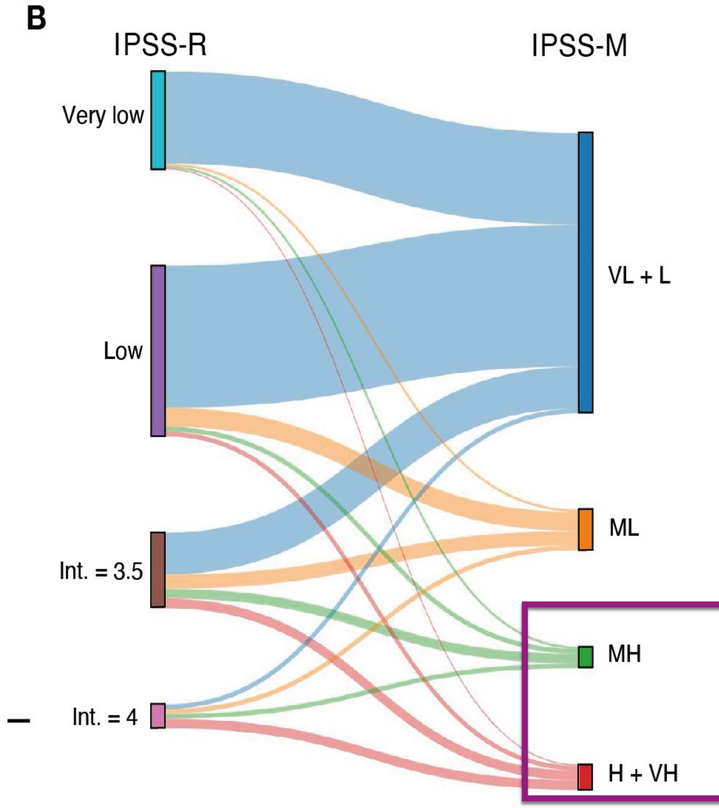
Raddi et al,. *Blood* (2025)

Entire Cohort

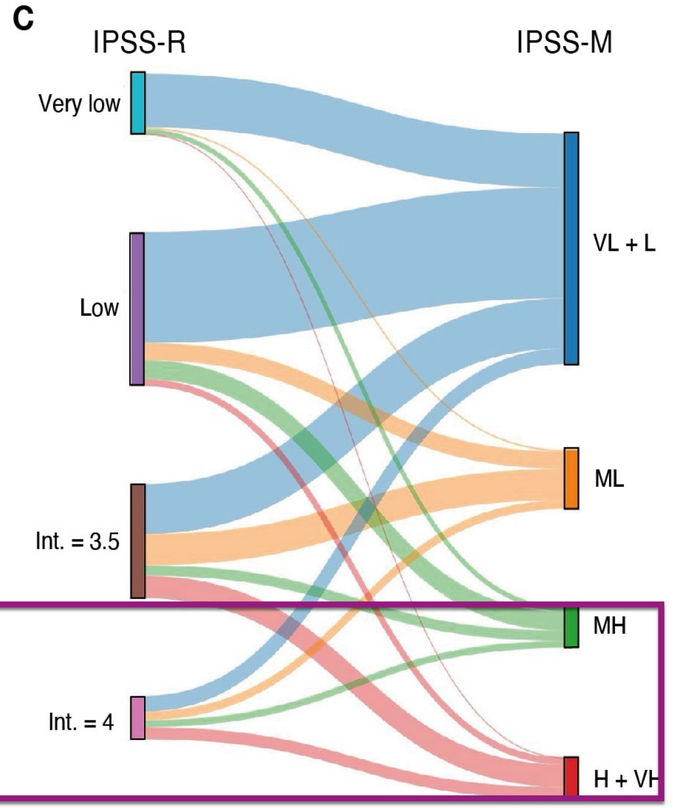


IPSS-R to IPSS-M	n (%)	RR (%)	p
IPSS-M score < 0	445 (83,1)	61,7	0,0048
IPSS-M score ≥ 0	90 (16,9)	45,3	

ESA responders

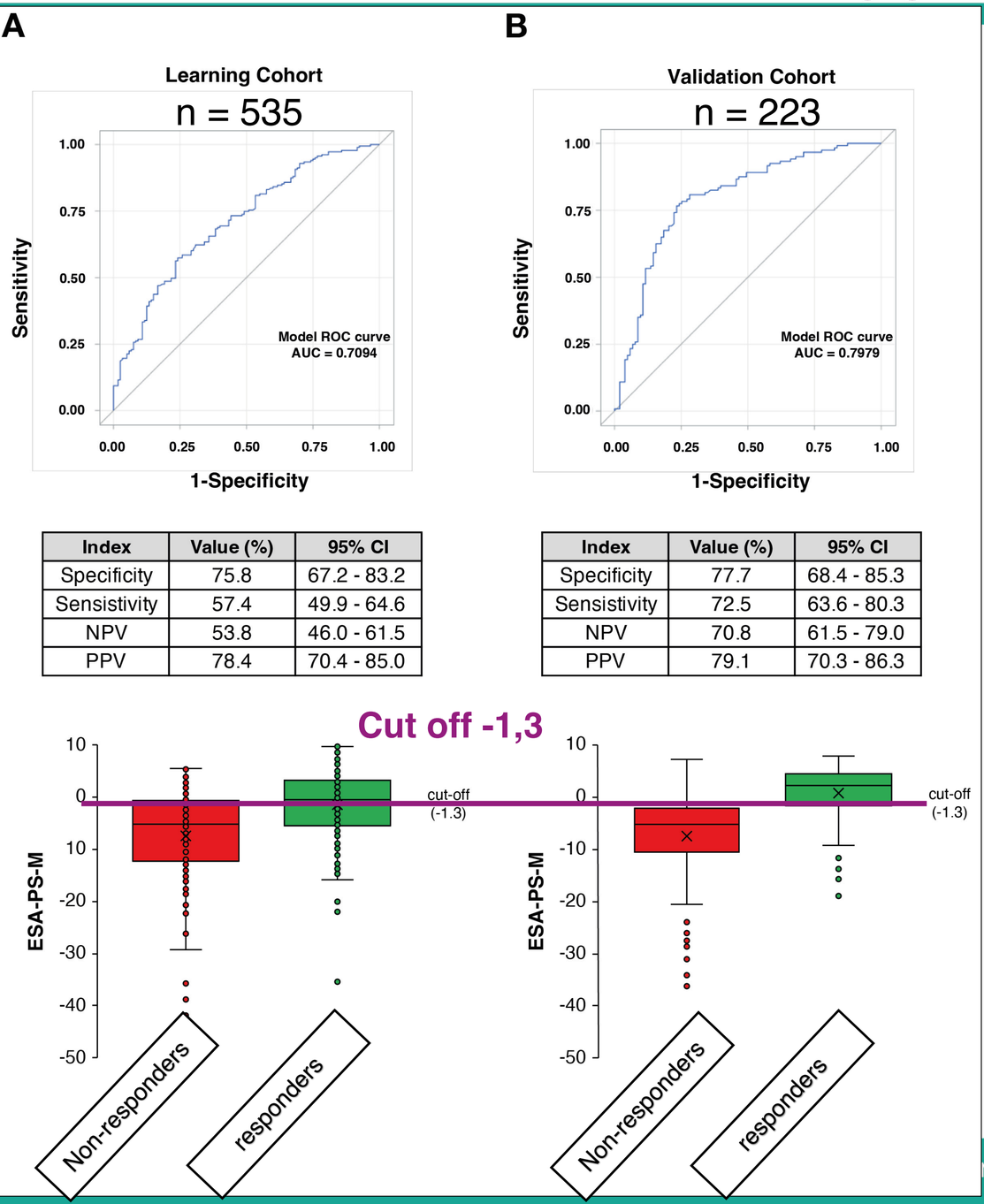


ESA non-responders



Parameter	Responders	Non-responders	p
Hb, dx (g/dL, mean ±SD)	9,7 ±1,3	9,4 ±1,3	0,042
TD (%)	37,5	58,3	0,0001
IPSS-R score (mean ±SD)	2,12 ±0,92	2,53 ±0,93	<0,0001
sEPO (U/L, mean ±SD)	77,3 ±148,1	133,2 ±202,4	<0,0001
n° mutation/patient	1,9	2,1	ns
IPSS-M score	-0,88 ±0,8	-0,54 ±1,1	<0,0001

Raddi et al. *Blood* (2025)



Index	Value (%)	95% CI
Specificity	75.8	67.2 - 83.2
Sensitivity	57.4	49.9 - 64.6
NPV	53.8	46.0 - 61.5
PPV	78.4	70.4 - 85.0

Index	Value (%)	95% CI
Specificity	77.7	68.4 - 85.3
Sensitivity	72.5	63.6 - 80.3
NPV	70.8	61.5 - 79.0
PPV	79.1	70.3 - 86.3

ESA-PSS-M

(molecular predictive scoring system for ESA)

A multivariable weighted score including baseline IPSS-M from IPSS-R LR-MDS patients to predict ESA response

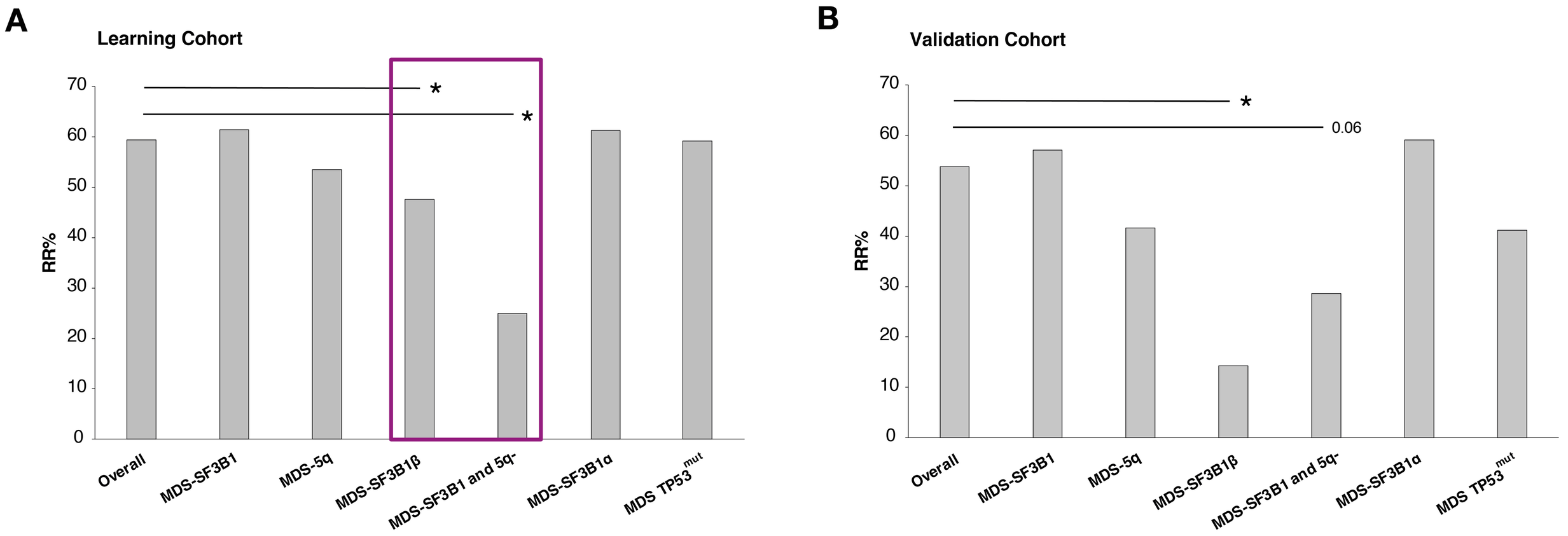
sEPO (U/L)
TD (y/n)
IPSS-M score

-0.05*[sEPO U/L] -4.5*[IPSS-M score] -5*[TD[a]]

[a]yes =1; no =0

Raddi et al. *Blood* (2025)

Not all MDS-*SF3B1* respond the same to ESAs

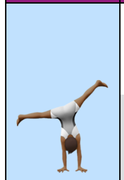


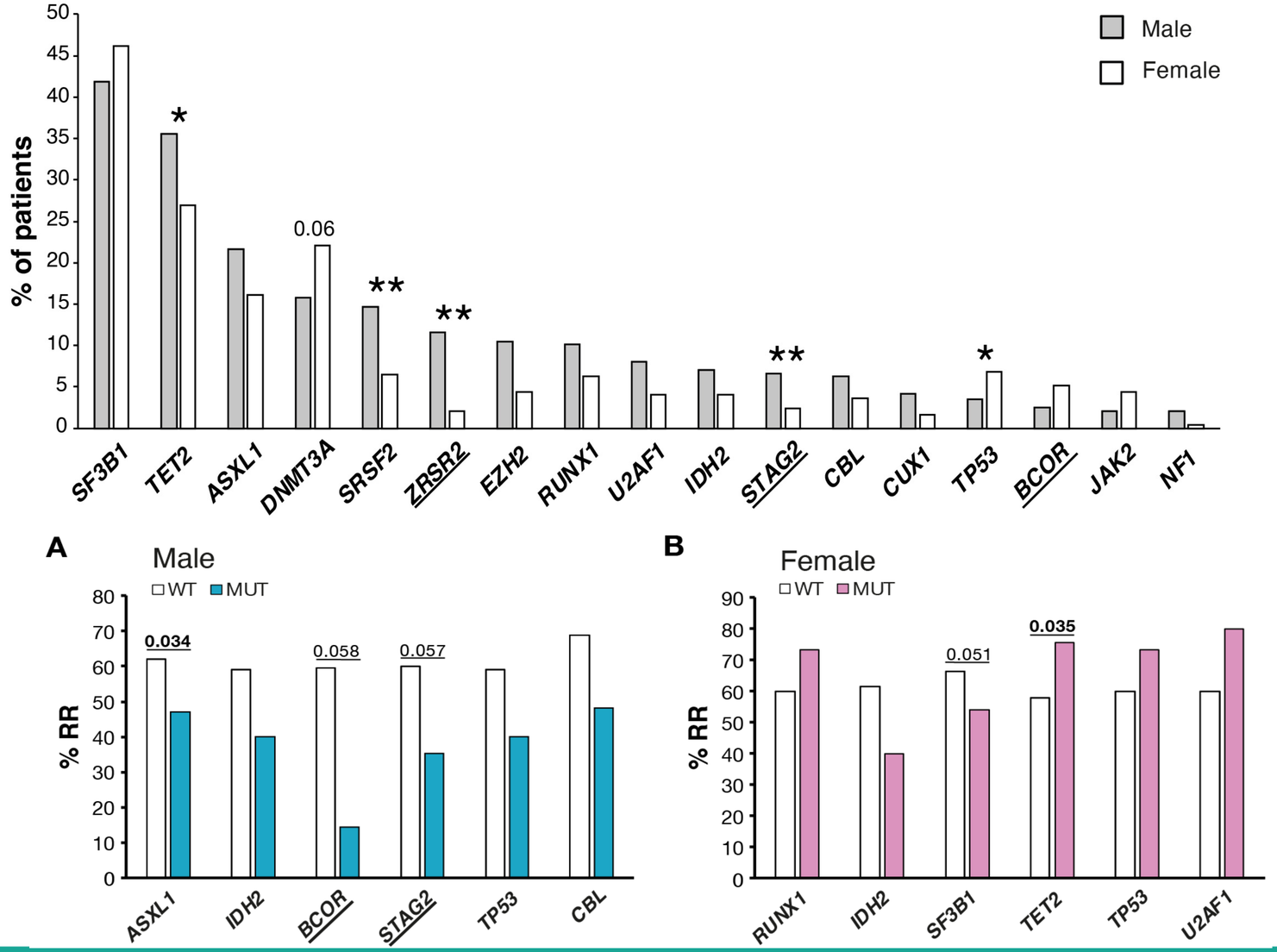
SF3B1β* = SF3B1+ *BCOR, BCORL1, RUNX1, NRAS,* ***STAG2*** or *SRSF2*
**as per IPSS-M*

Raddi et al. *Blood* (2025)

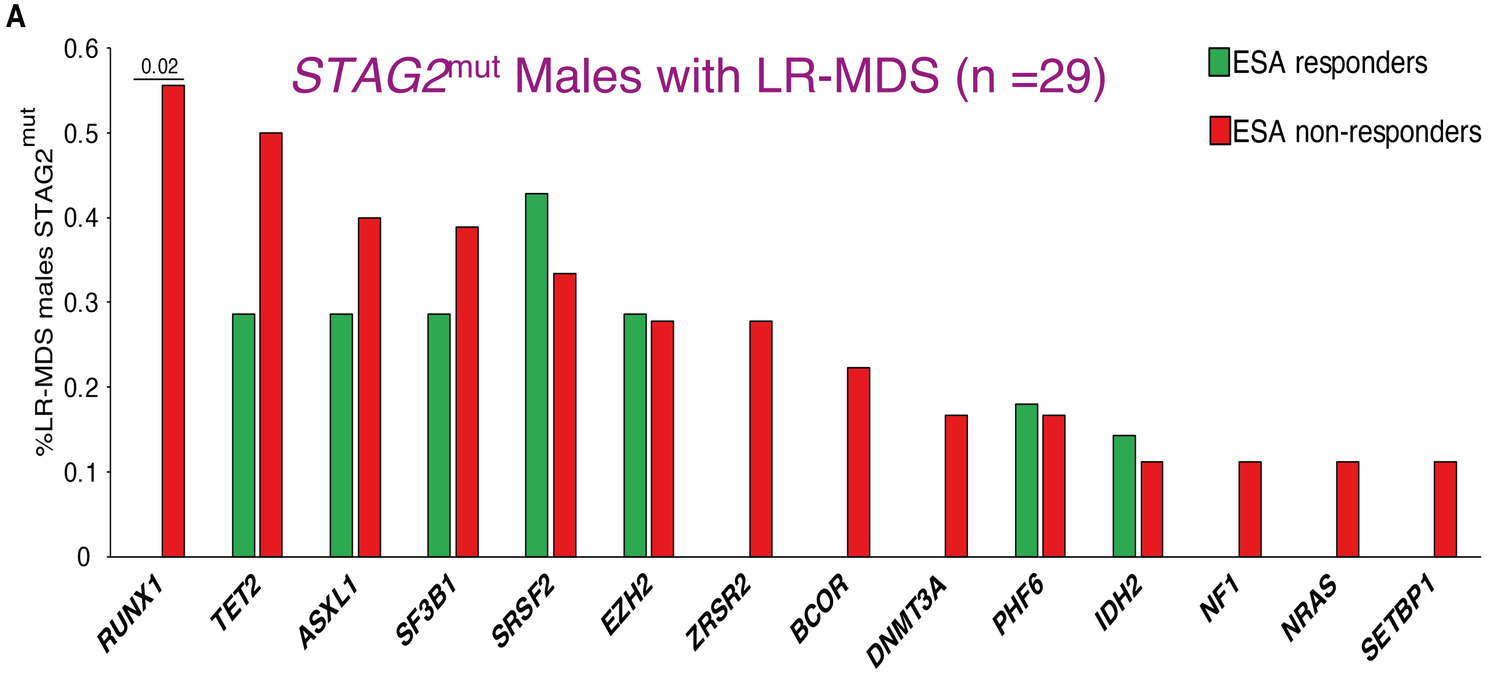
Sex-based differences in mutational landscape and ESA response

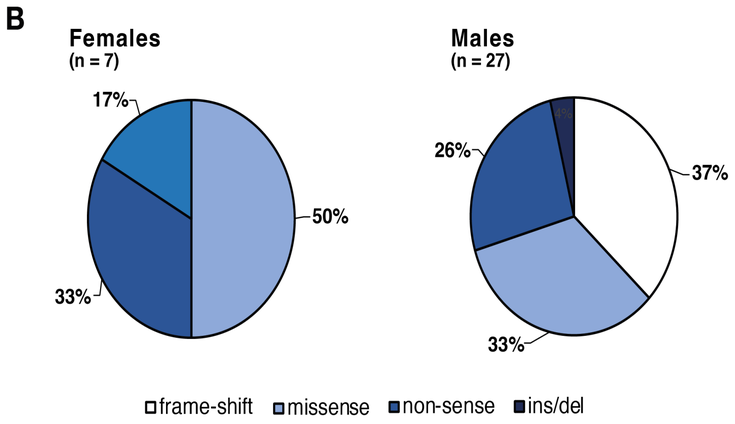
Increased number of somatic mutations in males vs. females

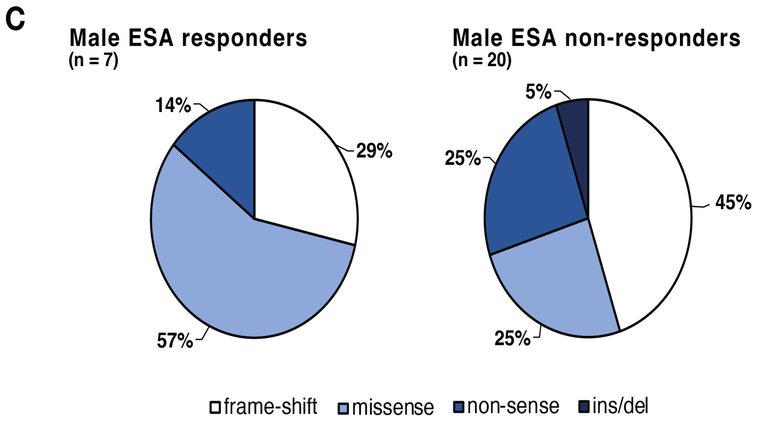
	Parameters	OR (95% CI)	*p*
	sEPO	0.994 (0.991 - 0.998)	0.0007
	STAG2	0.129 (0.033 - 0.507)	0.003
	TD	0.484 (0.247 - 0.947)	0.034
	sEPO	0.996 (0.993 - 1.000)	0.06
	IPSS-M score	0.556 (0.339 - 0.909)	0.019
	TD	0.528 (0.245 - 1.139)	0.1

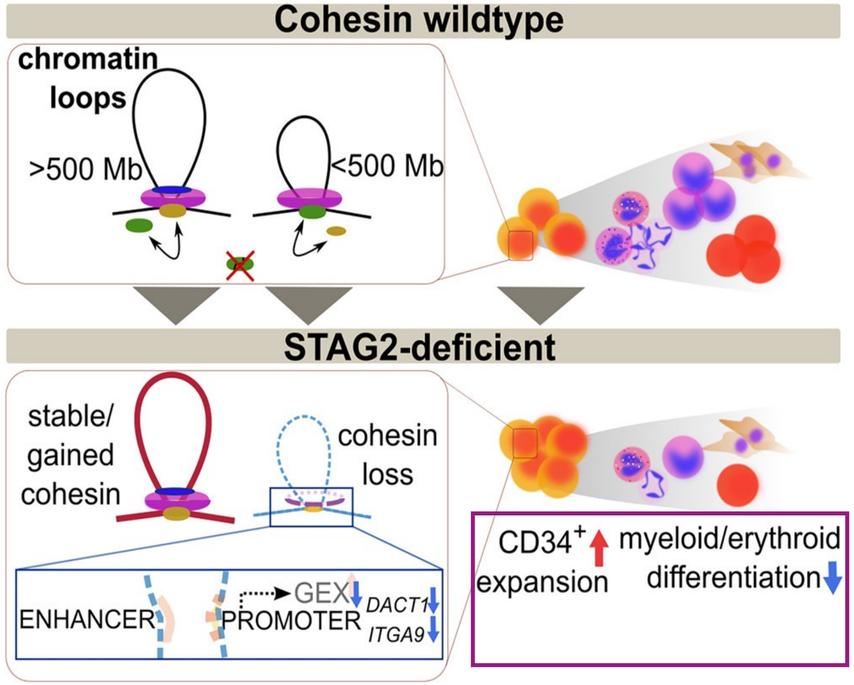


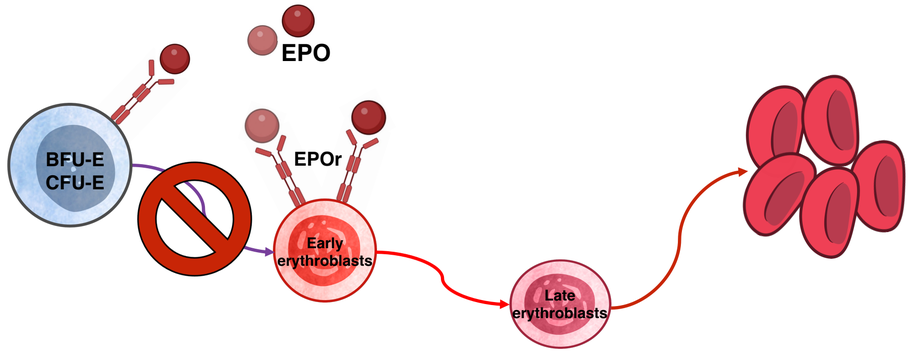
Don't ***STAG(2)*** Me Now!



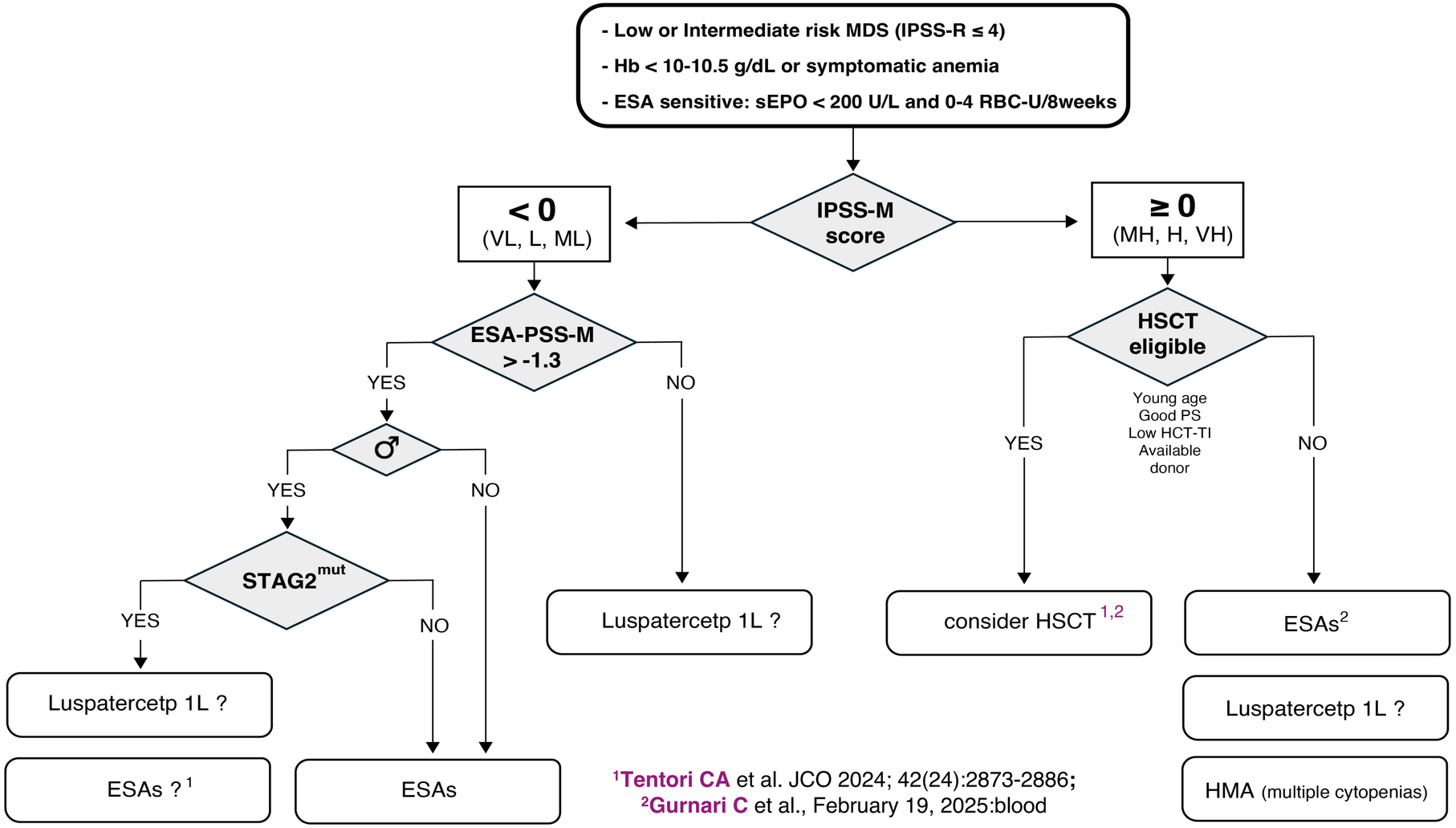








Proposed Algorithm to refine selection for **ESA therapy** integrating **IPSS-M score** and **sex-specific somatic mutations**



[1]**Tentori CA** et al. JCO 2024; 42(24):2873-2886;
[2]**Gurnari C** et al., February 19, 2025:blood

- IPSS-R score ≤ 3.5
- Hb <10g/dL
- Early initiation
- Adequate dosage

Erythroid Response ↑ ↓

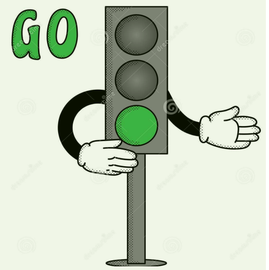
Clinical predictors

Molecular and phenotypic predictors

OPTIMAL SELECTION

sEPO levels ≤ 200 U/L
Transfusion independence

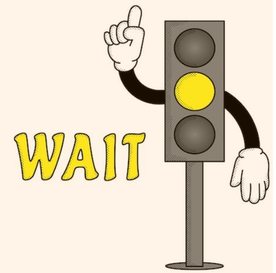
IPSS-M score < 0
ESA-PSS-M score ≥ -1,3
STAG2^{WT} males
Ery-CD117^{+} > 10.6%



SUBOPTIMAL SELECTION

sEPO levels 200 - 500 U/L
RBC-T 1-3 in 8 weeks

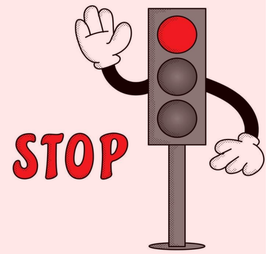
IPSS-M score ≥ 0
ESA-PSS-M score < -1,3
STAG2^{MUT} males
Ery-CD117^{+} ≤10.6%



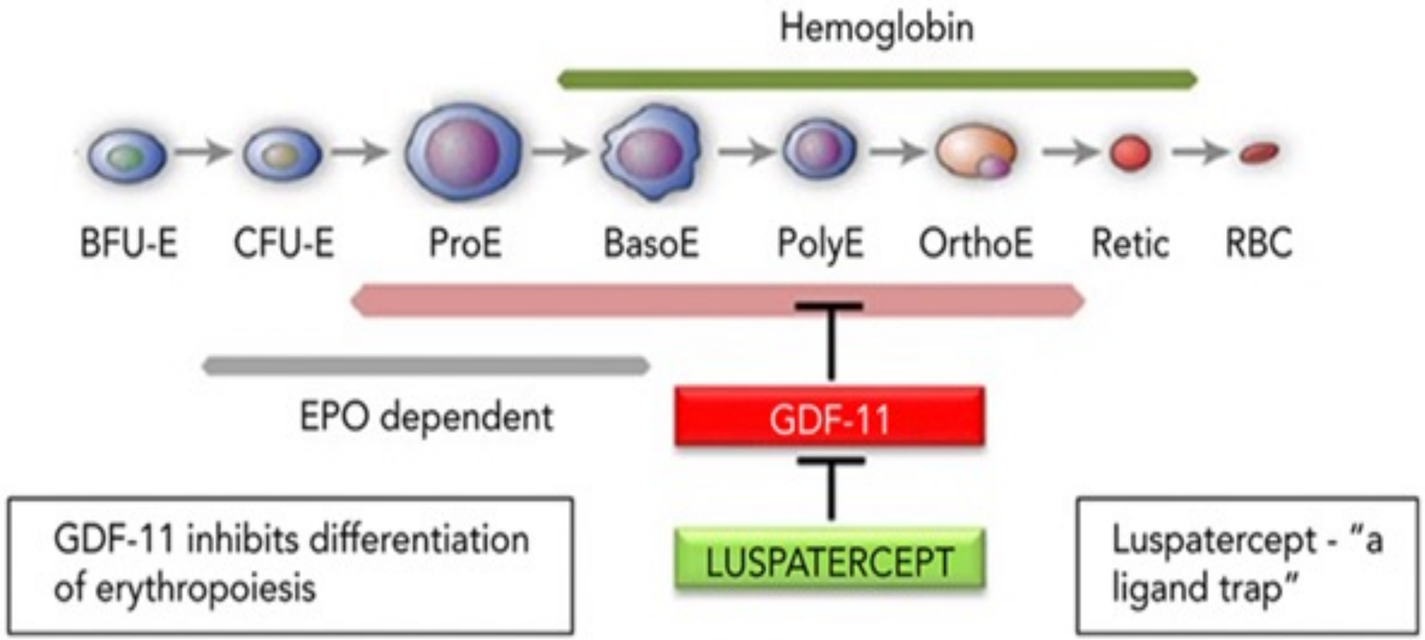
RESISTANCE

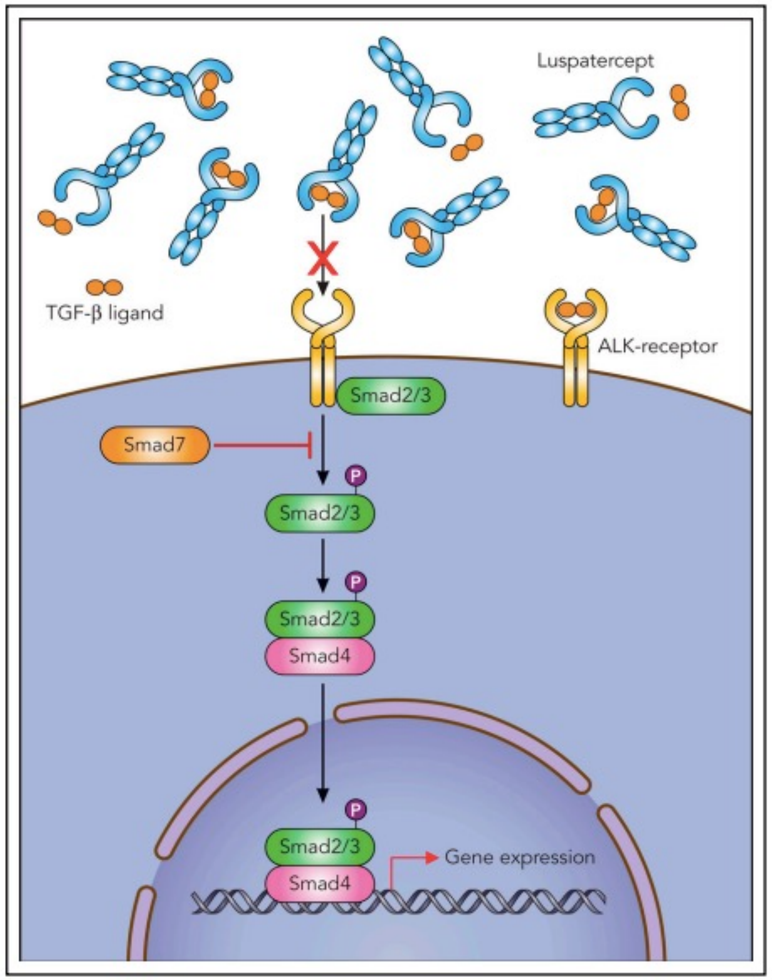
sEPO levels > 500 U/L
RBC-T >3 in 8 weeks

IPSS-M score ≥ 0
ESA-PSS-M score < -1,3
STAG2,^{MUT} males
Ery-CD117^{+} ≤ 10.6%



Mechanism of action of Luspatercept: Erythroid Maturating Agent (EMA)





In a phase II study (PACE) **Luspatercept** demonstrated higher activity in **MDS-RS (67.7% vs 36.4%)**

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

Fenaux P et al. Blood, 2019

Kubash A.S. et al Blood. Advances (2021)

clinical trial updates

Long-Term Efficacy and Safety of Luspatercept for Anemia Treatment in Patients With Lower-Risk Myelodysplastic Syndromes: The Phase II PACE-MDS Study

Uwe Platzbecker, MD[1]; Katharina S. Götze, MD[2]; Philipp Kiewe, MD[3]; Ulrich Germing, MD[4]; Karin Mayer, MD[5]; Markus Radsak, MD[6]; Thomas Wolff, MD[7]; Joerg Chromik, MD[8]; Katja Sockel, MD[9]; Uta Oelschlägel, PhD[9]; Detlef Haase, PhD[10]; Thomas Illmer, MD[11]; Haifa Kathrin Al-Ali, MD[12,13]; Gerda Silling, MD[14]; Joseph G. Reynolds, PhD[15]; Xiaosha Zhang, PhD[15]; Kenneth M. Attie, MD[15]; Jeevan K. Shetty, MD[16]; and Aristoteles Giagounidis, MD[17]

Patient Group	RBC-TI ≥ 8 Weeks[a]	HI-E[b]
All patients, No./total No. (%) [95% CI]	32/73 (43.8) [32.2 to 56.0]	58/108 (53.7) [43.8 to 63.3]
RS status, No./total No. (%) [95% CI]		
RS	22/42 (52.4) [36.4 to 68.0]	42/62 (67.7) [54.7 to 79.1]
Non-RS	10/29 (34.5) [17.9 to 54.3]	16/44 (36.4) [22.4 to 52.2]
Mutation status, No./total No. (%) [95% CI]		
SF3B1 mutation	16/31 (51.6) [33.1 to 69.8]	35/47 (74.5) [59.7 to 86.1]
SF3B1 wild-type	15/32 (46.9) [29.1 to 65.3]	19/49 (38.8) [25.2 to 53.8]
Non-*SF3B1* splicing factor mutation	10/13 (76.9) [46.2 to 95.0]	6/18 (33.3) [13.3 to 59.0]
Any splicing factor mutation	26/44 (59.1) [43.2 to 73.7]	41/65 (63.1) [50.2 to 74.7]
Any splicing factor wild-type	5/19 (26.3) [9.1 to 51.2]	13/31 (41.9) [24.5 to 60.9]
Transfusion burden, No./total No. (%) [95% CI]		
NTD (0 RBC units/8 weeks)	NA	24/34 (70.6) [52.5 to 84.9]
LTB (< 4 RBC units/8 weeks)	20/28 (71.4) [51.3 to 86.8]	10/29 (34.5) [17.9 to 54.3]
HTB (≥ 4 RBC units/8 weeks)	12/45 (26.7) [14.6 to 41.9]	24/45 (53.3) [37.9 to 68.3]

Median Change From Baseline to EOT (Range)

	Overall (N = 51)			RS (n = 32)			Non-RS (n = 19)		
Parameter	**Responder (n = 31)**	**Nonresponder (n = 20)**	***P***	**Responder (n = 23)**	**Nonresponder (n = 9)**	***P***	**Responder (n = 8)**	**Nonresponder (n = 11)**	***P***
BM erythroid progenitor cells,[a,b,c] %	5 (−23 to 35)	0 (−37 to 29)	.267	5 (−23 to 35)	5 (−8 to 26)	.933	13.5 (−6 to 33)	−2 (−37 to 29)	.083
Late to early progenitor cell ratio[a,c]	2.91 (−7.00 to 50.00)	−0.39 (−29.36 to 6.44)	.006	4.02 (−6.99 to 50.00)	−0.45 (−3.36 to 3.56)	.072	1.99 (−2.09 to 8.12)	−0.32 (−29.36 to 6.44)	.029
Myeloid to erythroid ratio[a]	−0.16 (−10.06 to 0.91)	−0.23 (−6 to 26.19)	.412	−0.12 (−1.21 to 0.91)	−0.26 (−1.87 to 0.28)	.586	−1.25 (−10.06 to 0.18)	0.11 (−6.00 to 26.19)	.107
EPO, IU/L	27.7 (−169.4 to 1,121.0)	278.5 (−132.9 to 62,140.6)	.002	12 (−169.4 to 1,121.0)	146.9 (−132.9 to 545.3)	.249	43.7 (−130.6 to 131.9)	1,700.0 (−59.8 to 62,140.6)	.010
sTfR1, nM	18.4 (−21.2 to 111.9)	12.8 (−7.5 to 52)	.458	18.3 (−21.2 to 111.9)	15.35 (2.9-52)	.946	19.6 (−14.9 to 45.3)	5.8 (−7.5 to 40.6)	.525
Absolute reticulocytes, No.	14.42 (−57 to 89)	−13 (13.92 to 38.4)	.454	9 (−29.28 to 62.00)	10.34 (−13.92 to 38.40)	.855	35.42 (−57.00 to 89.00)	13 (−9.24 to 38.37)	.138

DOI: 10.1002/hem3.70086

ARTICLE

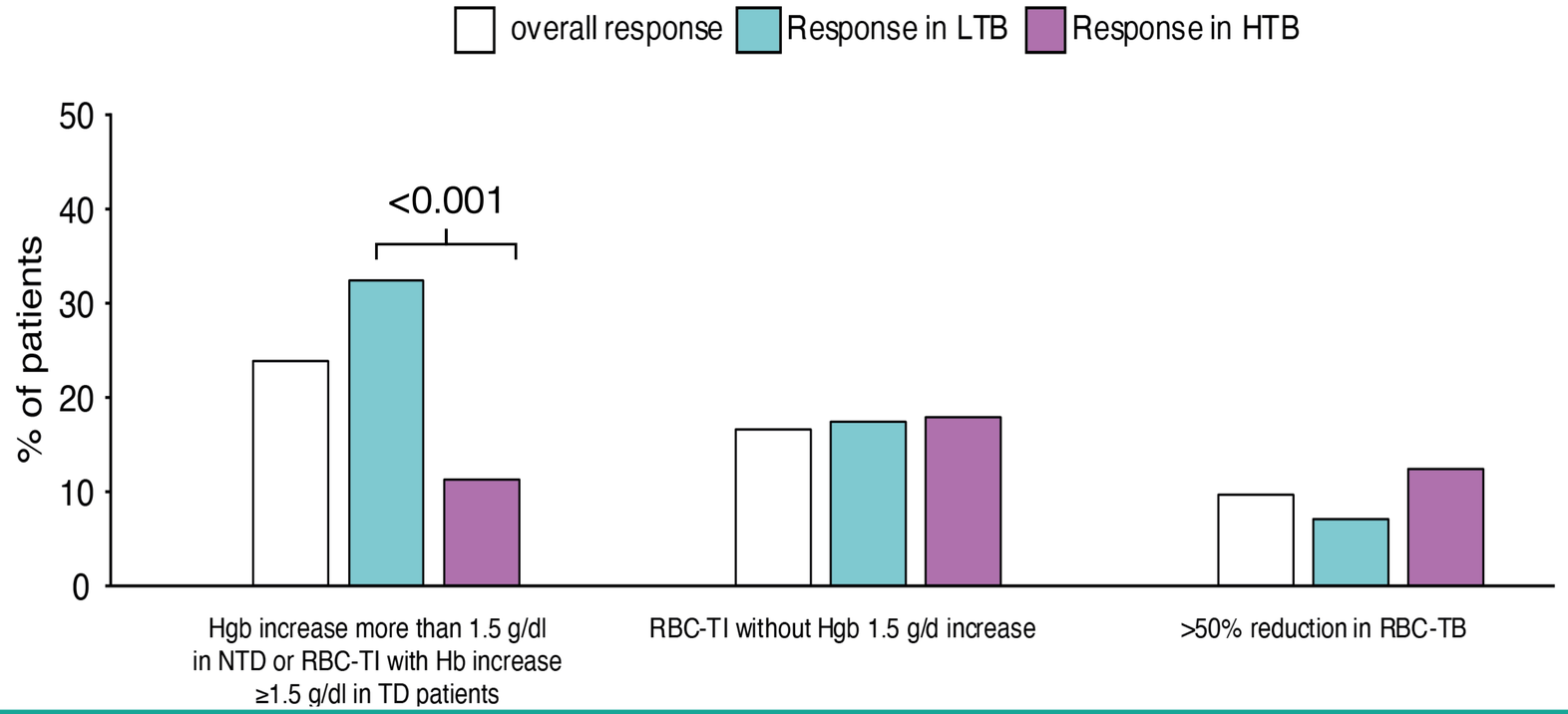
HemaSphere eha

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

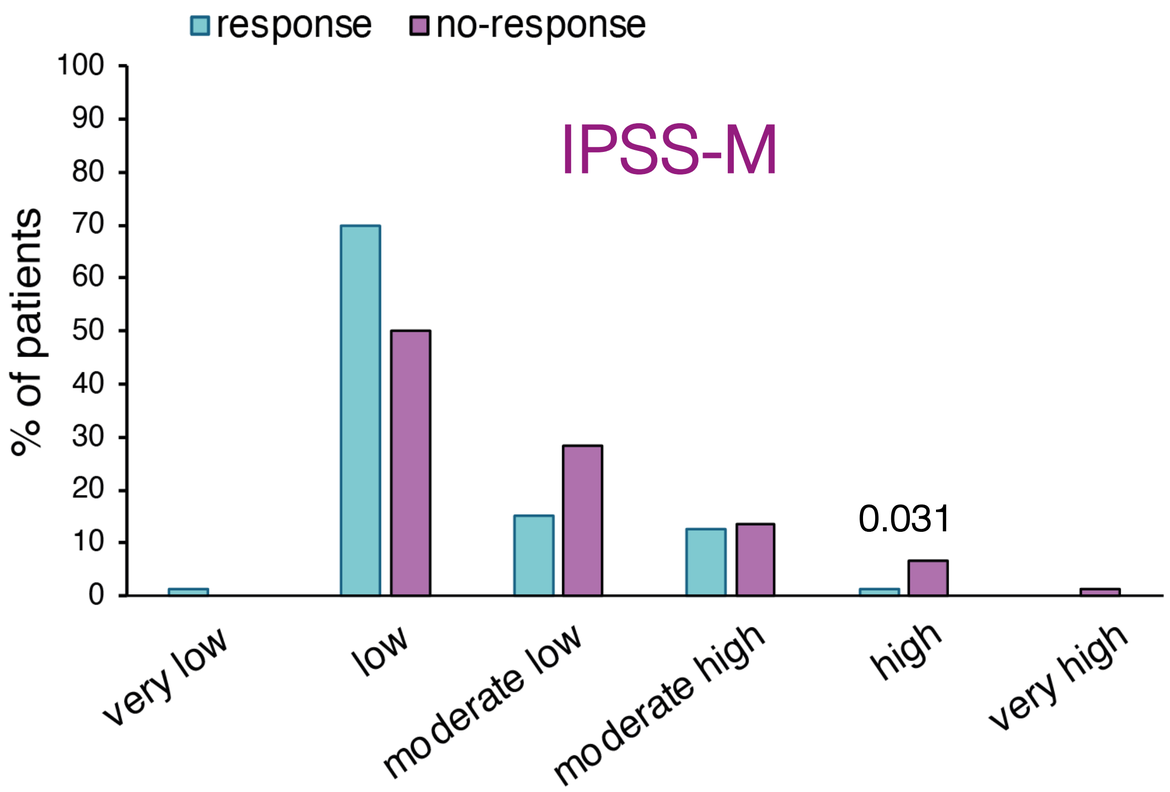
Overall HI-E rate of 50.2% (n = 166/331)

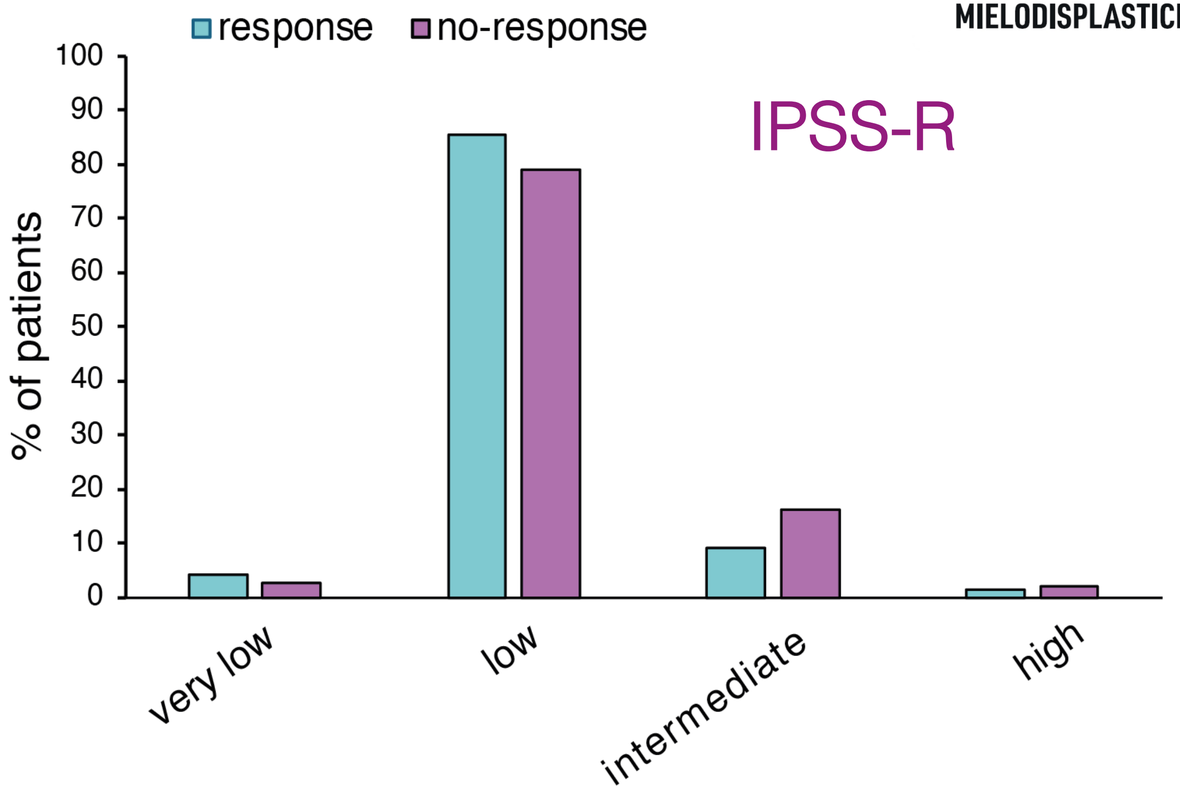
RR was significantly higher in NTD and LTB patients compared to HTB patients

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



Distribution of response by IPSS-M and IPSS-R



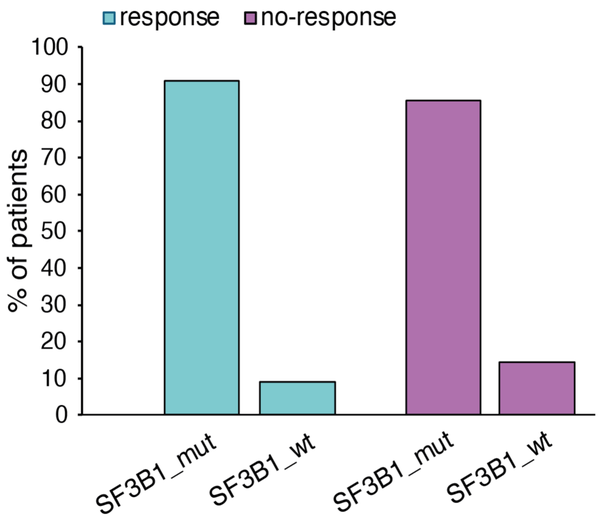


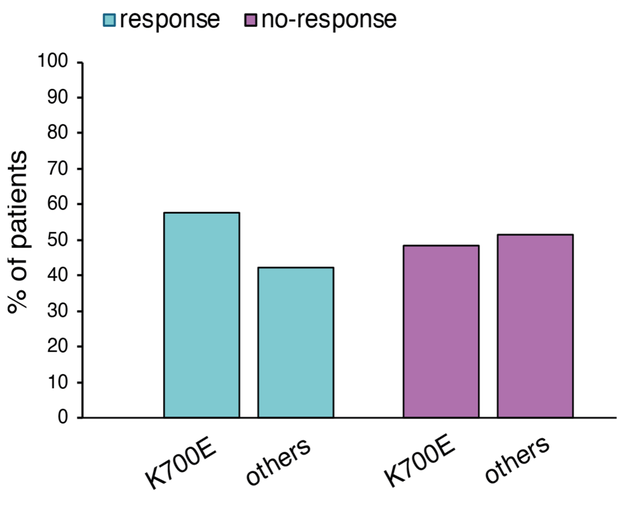
For 154/331 patients with calculated baseline IPSS-M score, response to Luspatercept correlated with molecular risk, while IPSS-R score did not (*p=0.247*).
Cases with >2 somatic mutations showed lower response rate

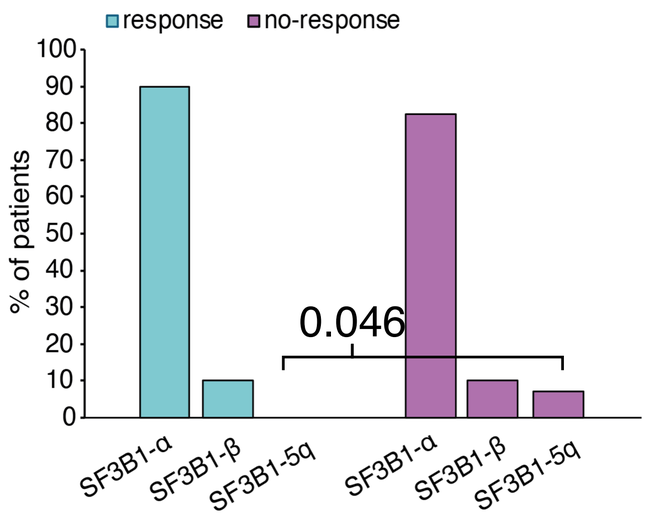
Response to Luspatercept across genetic subtypes

Similar HI-E rates in *SF3B1*^{MT} (53.8%) vs *SF3B1*^{WT} (40.1%, p=0.267) irrespective of *SF3B1* VAF (median 38%)

Among *SF3B1*^{MUT} cases, *SF3B1*$^{\beta}$ and *SF3B1*$^{\alpha}$ obtained superior HI-E rates vs. *SF3B1*^{5q} (p=0.046)







Patients with age-adjusted **hypercellular BM** had higher responses to luspatercept compared with the **hypo- and normocellular groups**

(p=.005, OR1.5, CI 0.27-8.48)

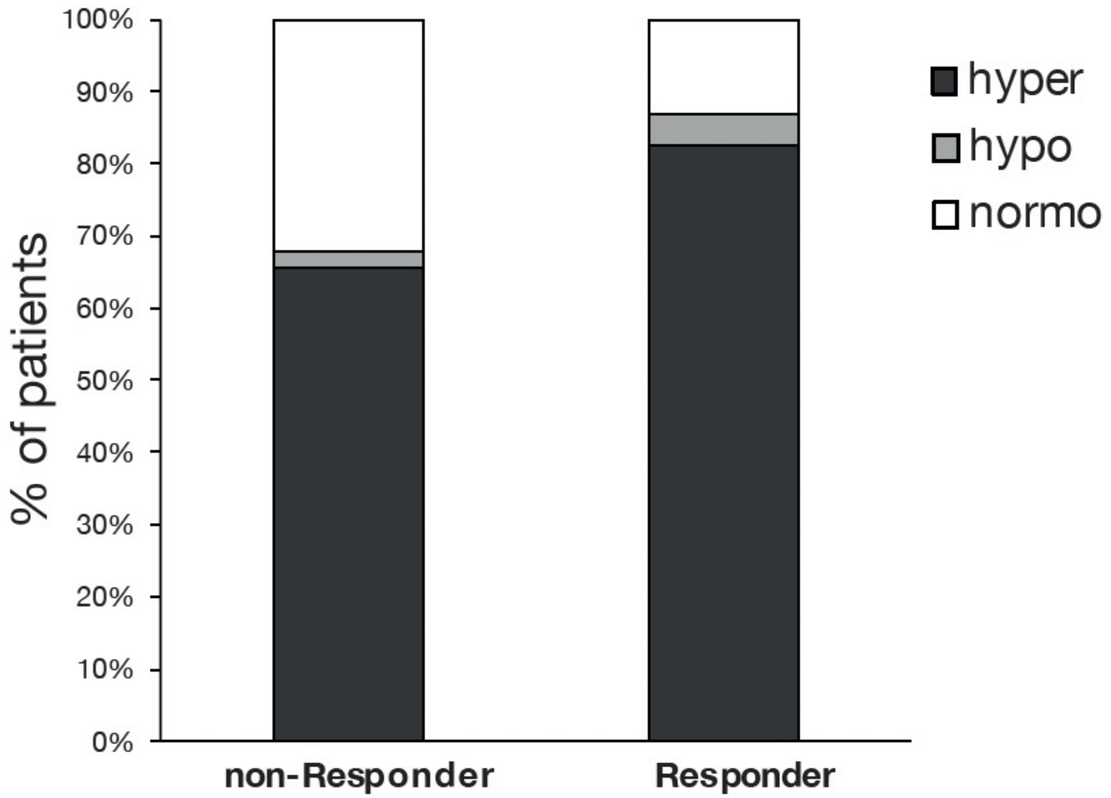
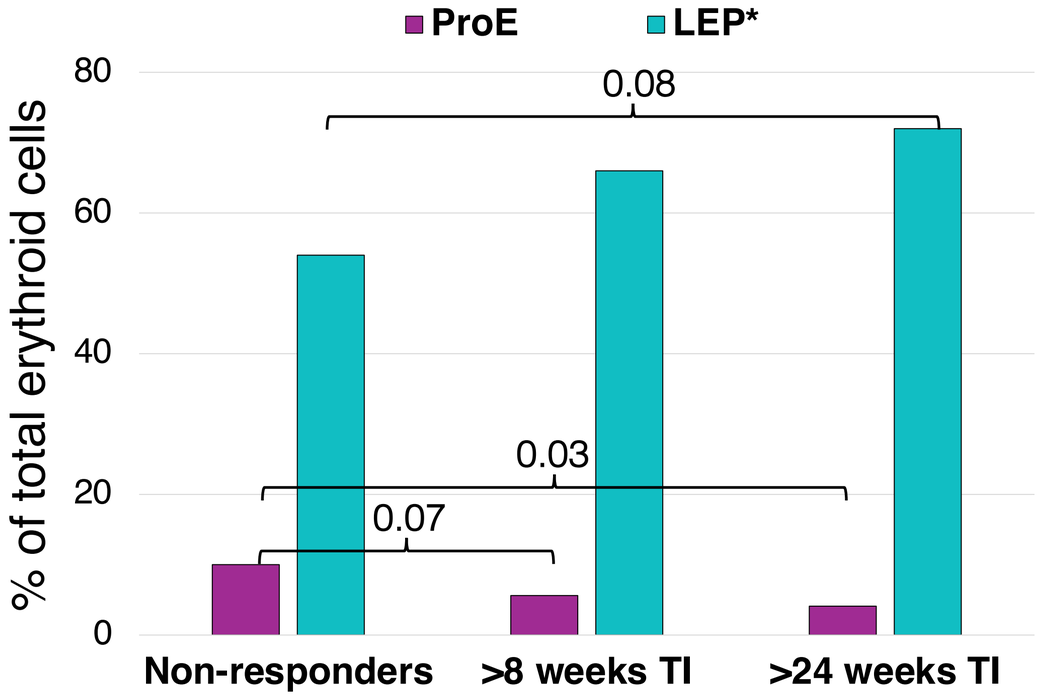


Figure 1 : Response to Luspatercept according to cellularity of Bone Marrow biopsy.

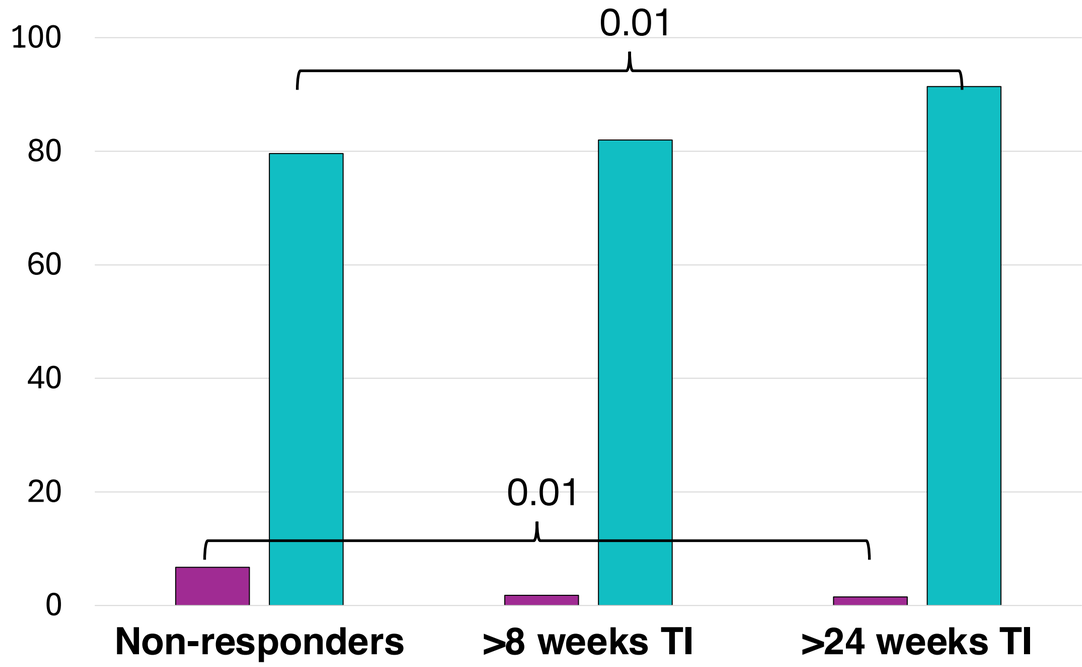
Late to early erythroid ratio correlates with clinically meaningful response to Luspatercept

n = 37 (33/37 received ESAs)
TI >8 weeks 40%
TI >24 weeks 35%

Baseline: pre-Luspatercept



Baseline: pre-ESAs (n =16/33)



*LEP = late erythroid precursors

Boyer T., et al, MDS Foundation - Guided Poster. Leukemia Research,2025,

Why Improve Prediction to Therapies for Anemic Patients with LR-MDS?

Optimized patient selection for therapy in LR-MDS translates into higher and longer responses, freedom from RBC transfusion and improved quality of life.

Effective treatment depends on early initiation with adequate dosing in patients characterized by low serum EPO levels and transfusion burden

Molecular and phenotypic profiling—including IPSS-M risk score, specific genetic signatures (e.g. *SF3B1* molecular subgroups and *STAG2* in male patients), BM cellularity and erythroid precursors quantification—enhances response prediction and underscores the need for closer monitoring in higher-risk subsets (**IPSS-M > 0**).

Pro-inflammatory cytokines? Epigenetics?

Thank you for your attention!!!

MDS Unit, DMSC,
University of Florence

Valeria Santini, MD
Marco Gabriele Raddi, MD
Giorgio Mattiuz, PhD
Elena Tofacchi, PhD
Sven De Pourcq, PhD
Angela Consagra, MD
Luca Rigodanza, MD
Gloria Andreossi, MD
Alessandro Sanna, MD
Cristina Amato, SN
Barbara Caciagli, PhD

aouc Azienda Ospedaliero Universitaria Careggi

AIRC