

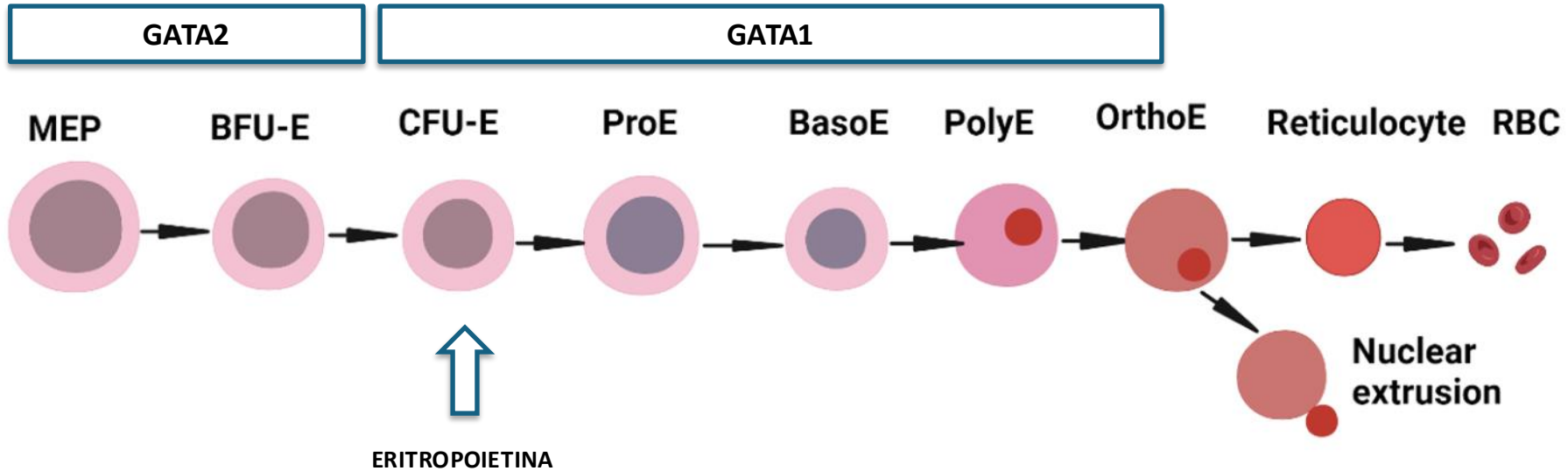
YOUNG SCIENCE FORUM: IL FUTURO NASCE IN LABORATORIO

**Perché bersagliare il pathway TGF- β / SMAD: le basi molecolari
dell'utilizzo di Luspatercept e Momelotinib**

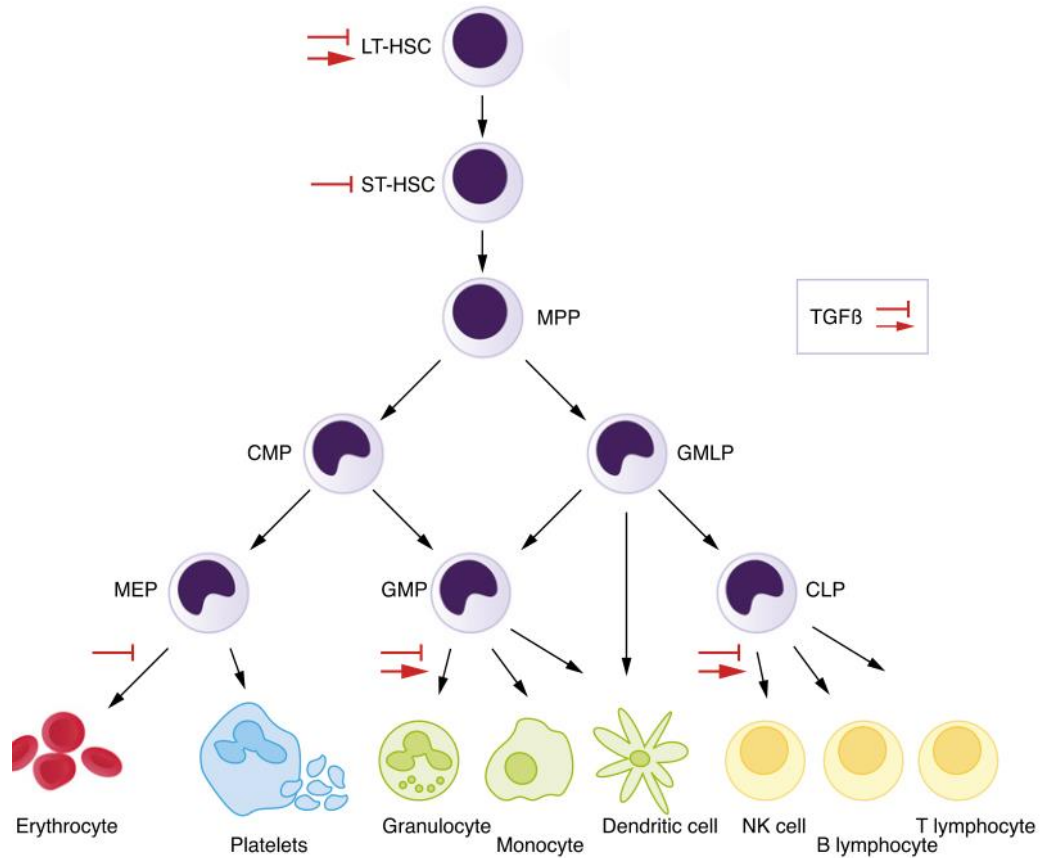
Dr. Antonio Frolli, MD

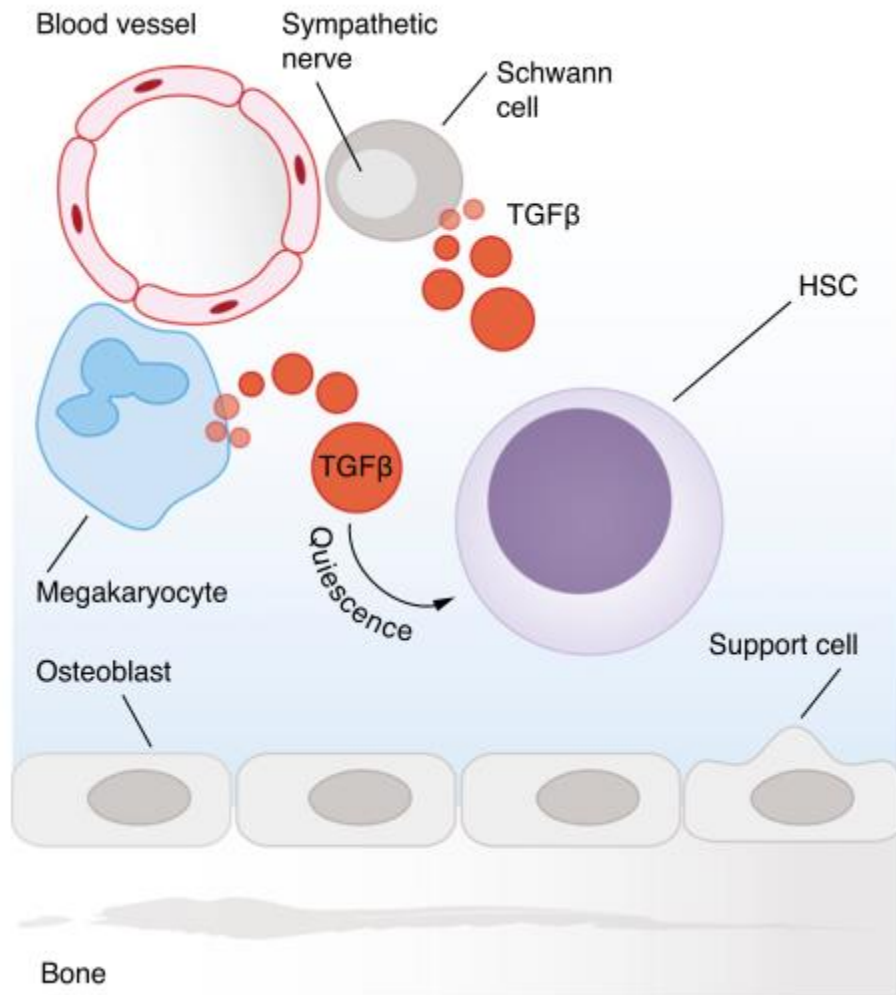
SCDU Ematologia e Terapie Cellulari, AO Ordine Mauriziano di Torino

TORINO, ACCADEMIA DI MEDICINA | 4-5 GIUGNO 2026

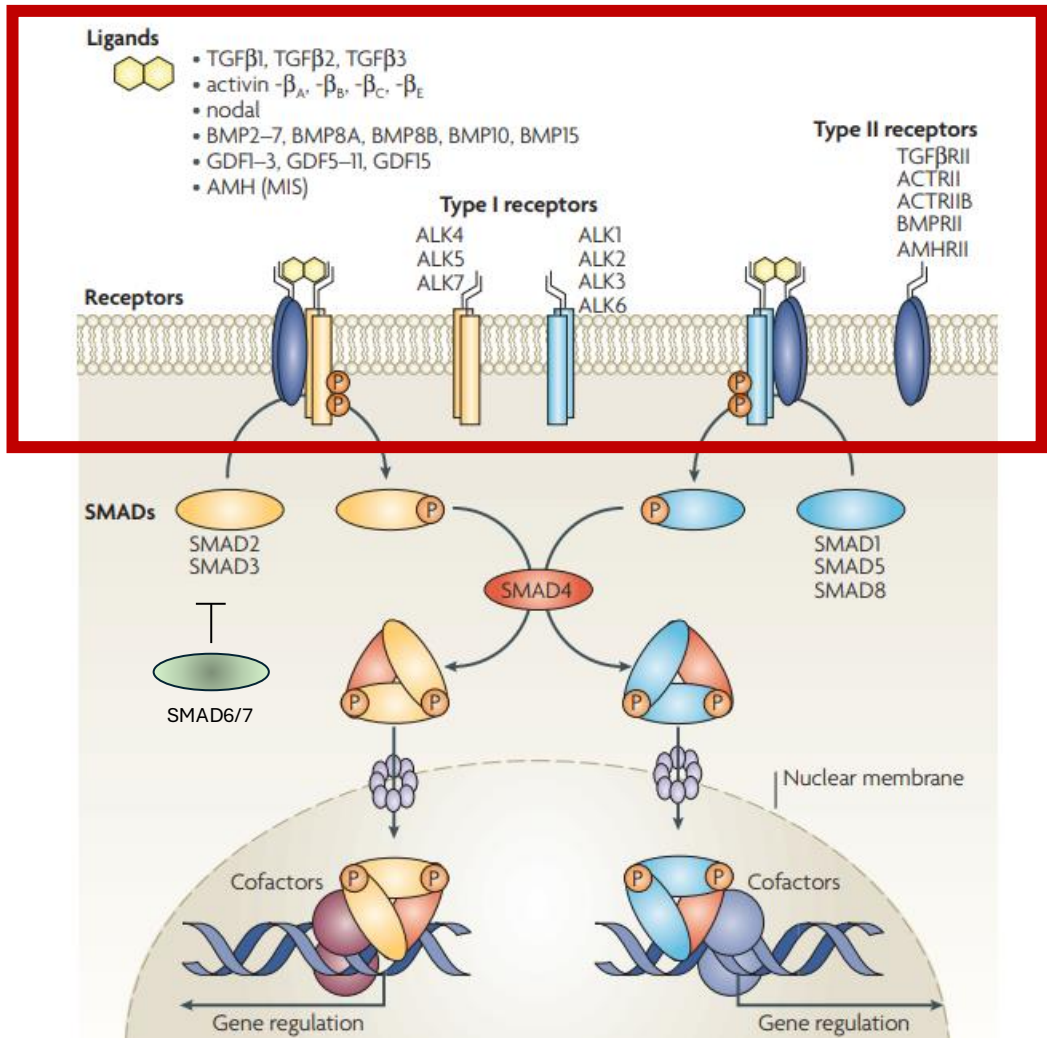


TGF-B?





TGF-B è una
famiglia di ligandi
 e recettori

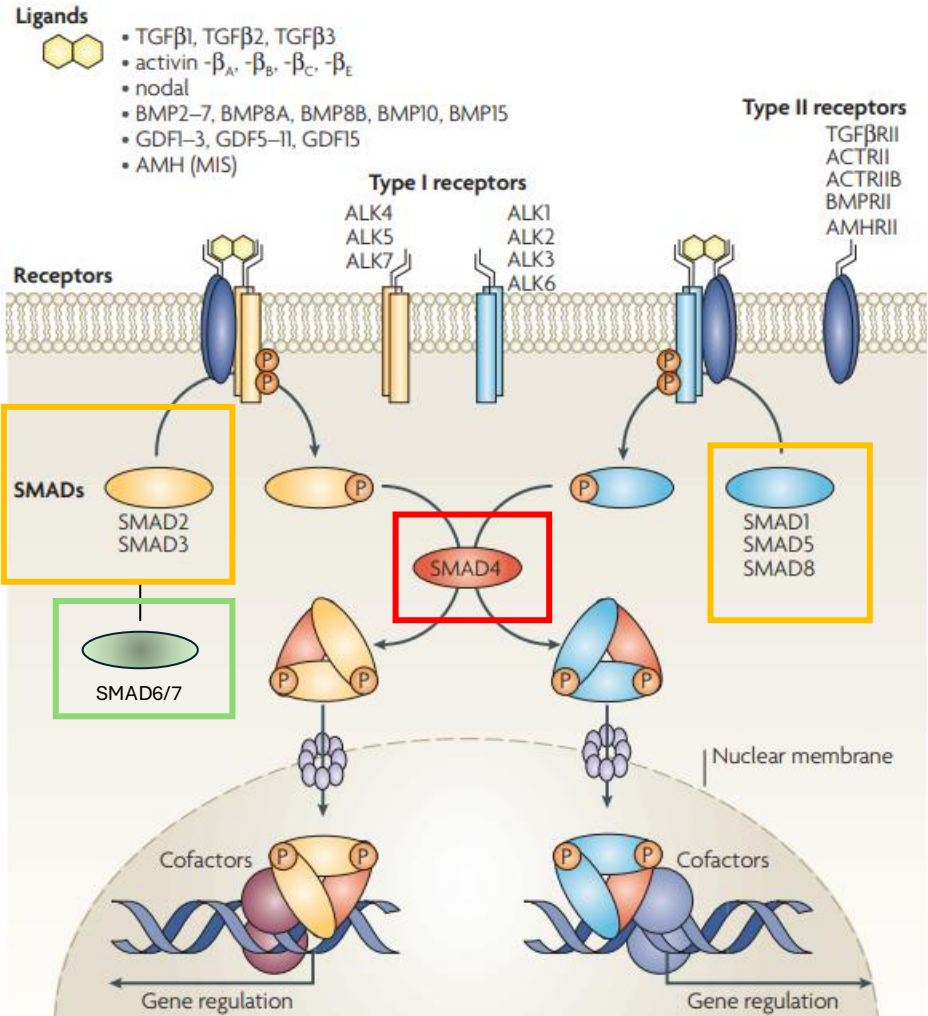


3 TIPI DI SMAD

SMAD receptor regulated

SMAD cofactor

SMAD inhibitor

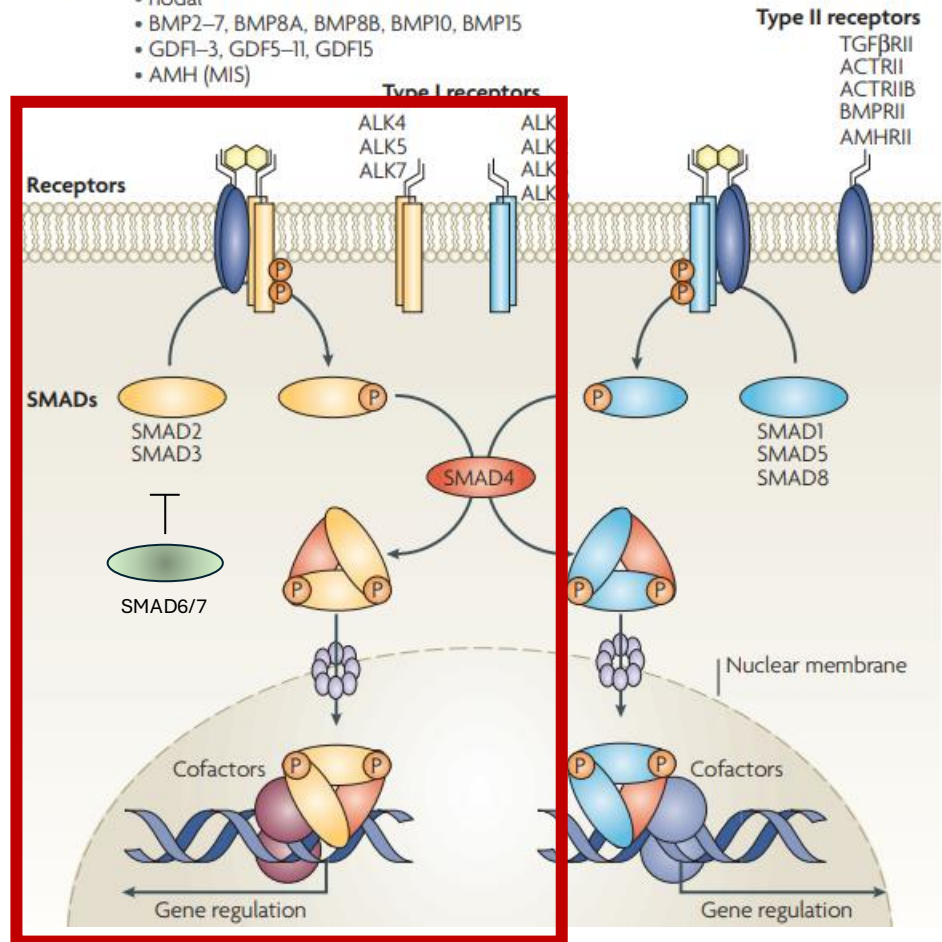


Pathway coinvolta nell'eritropoesi

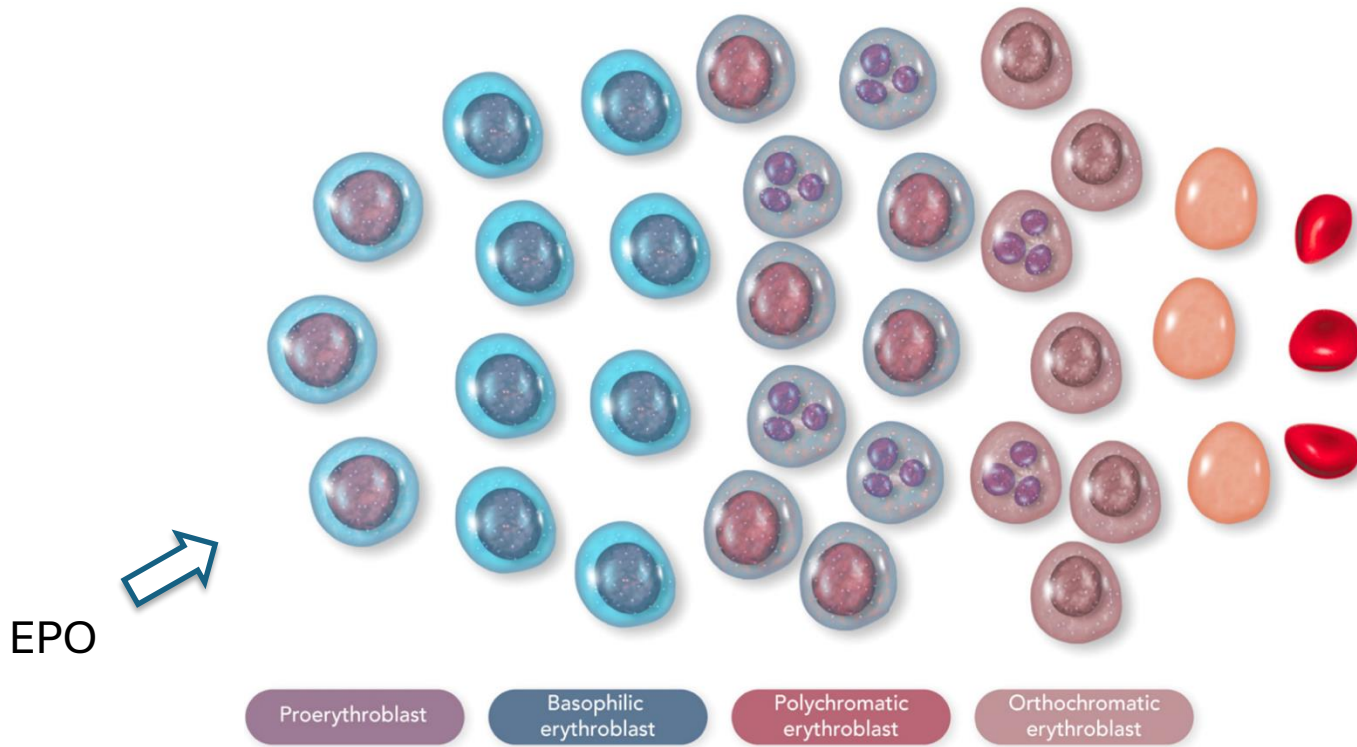
Ligands



- TGF β 1, TGF β 2, TGF β 3
- activin - β_A , - β_B , - β_C , - β_E
- nodal
- BMP2-7, BMP8A, BMP8B, BMP10, BMP15
- GDF1-3, GDF5-11, GDF15
- AMH (MIS)



MDS e ERITROPOIESI INEFFICACE



CONTROLLO DELL'ANEMIA

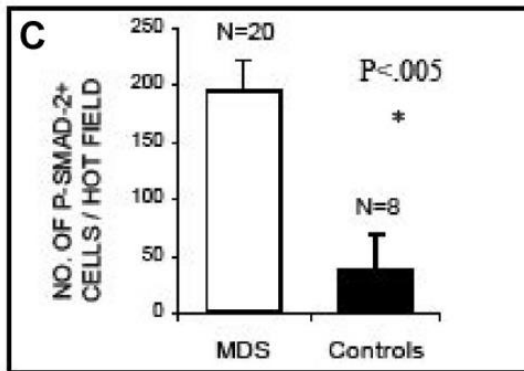
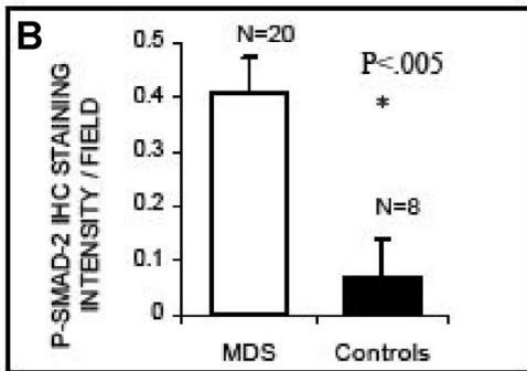
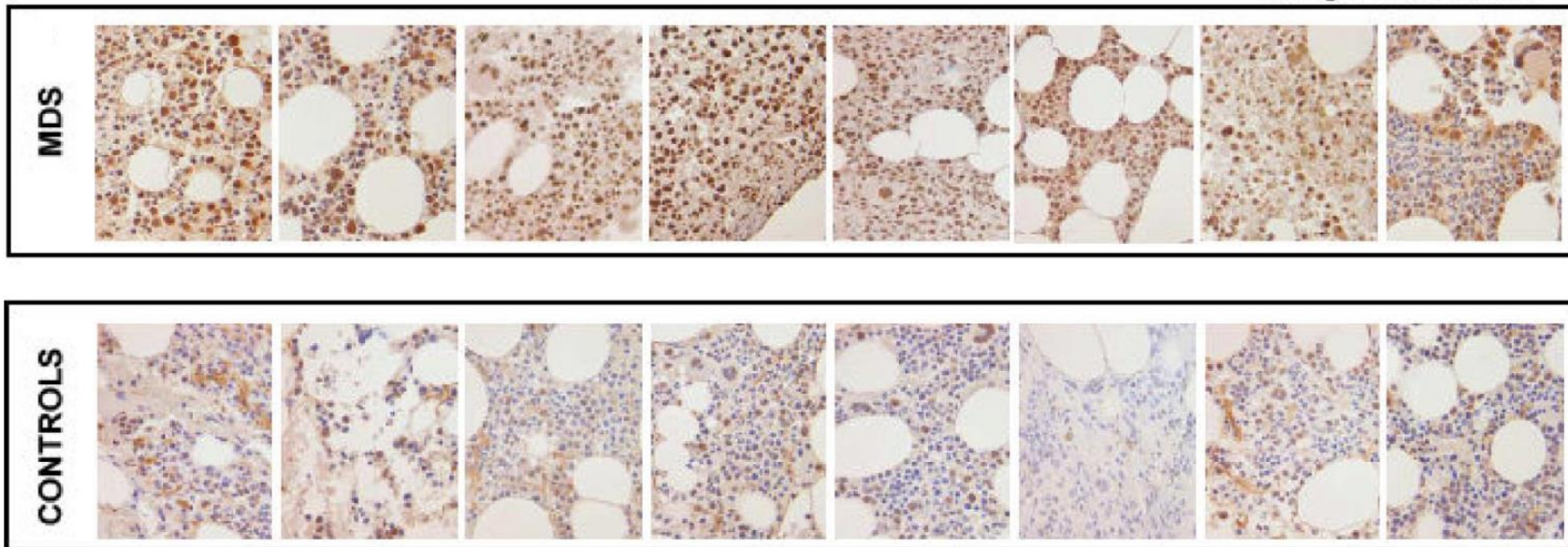


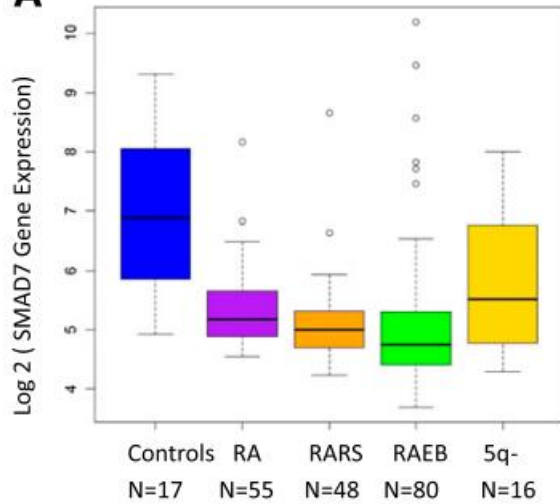
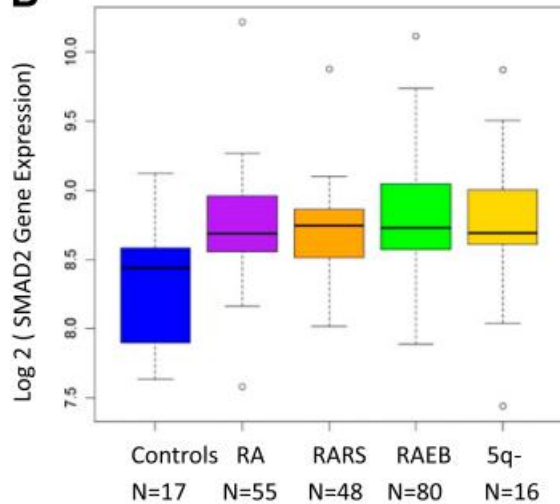
SUPPORTO CON rEPO

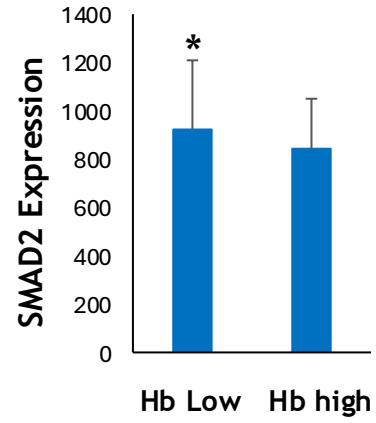
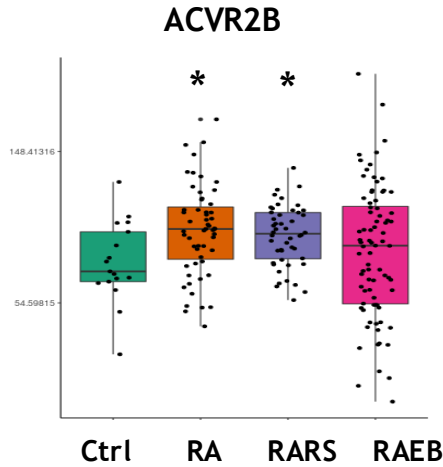
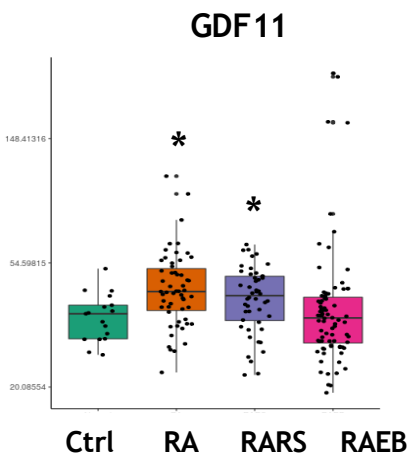
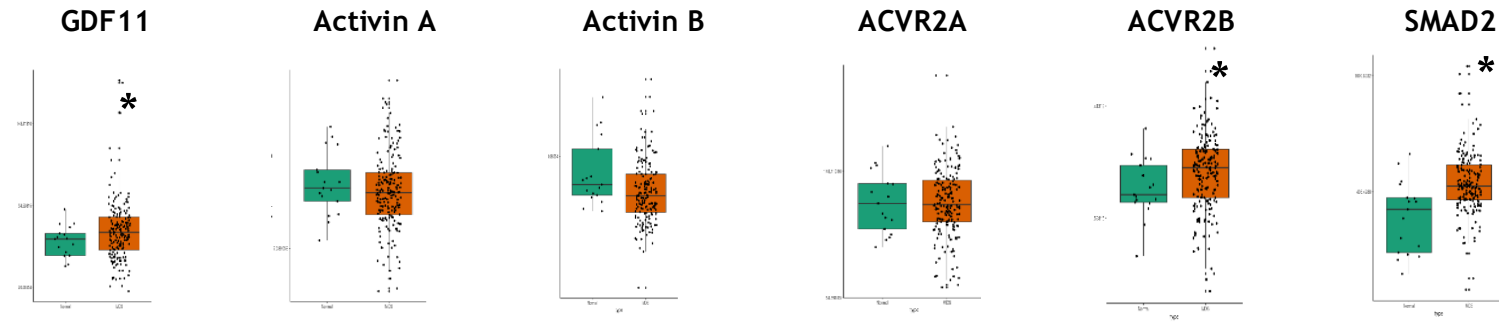
Risposta 30-40%
Durata di risposta 6-24 mesi



Altri target terapeutici?

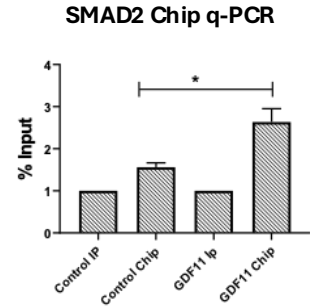
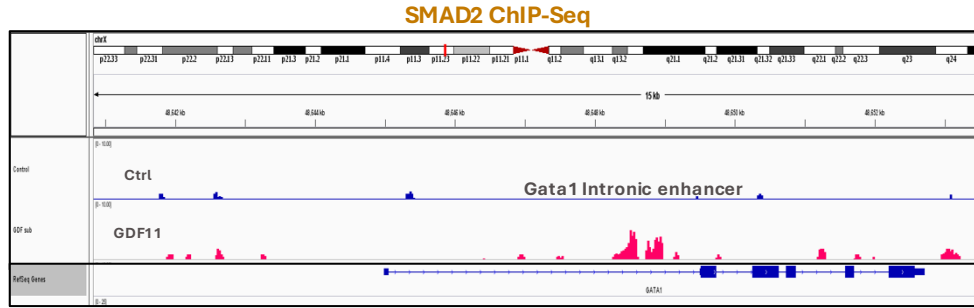
A*Phospho-Smad2 IHC*

A**B**

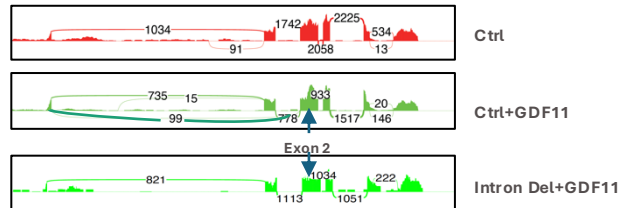


■ Age-matched controls (n = 17)
 ■ MDS patient samples (n = 183)

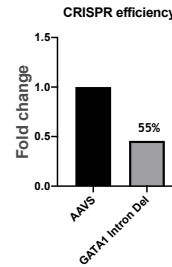
GDF11-driven SMAD2 binds GATA1 intronic region and modulates splicing to produces short isoform



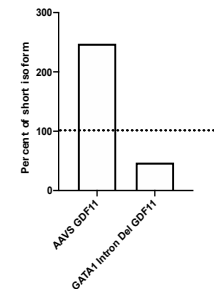
Exon 2 skipping leads to GATA1 short isoform



CRISPR deletion of the intron 2 binding site eliminates GDF11-induced GATA1 short isoform in primary erythroid cells

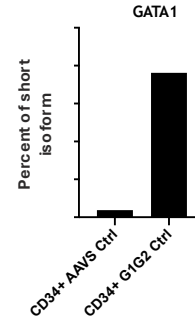
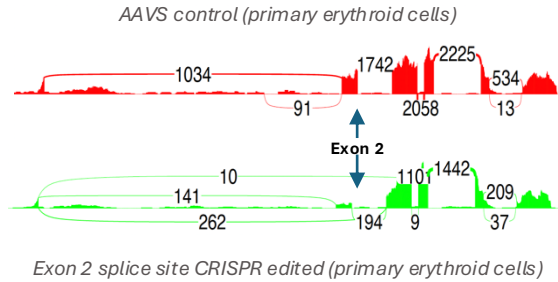
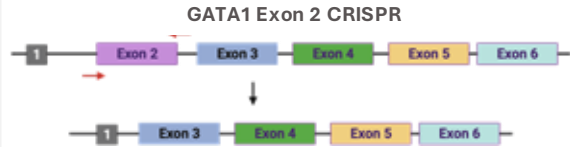


Appearance of GATA1 short isoform

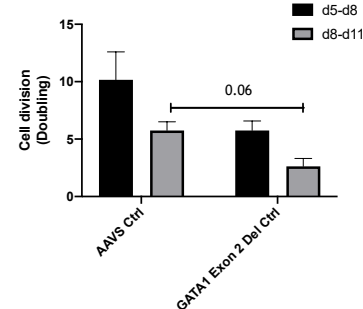
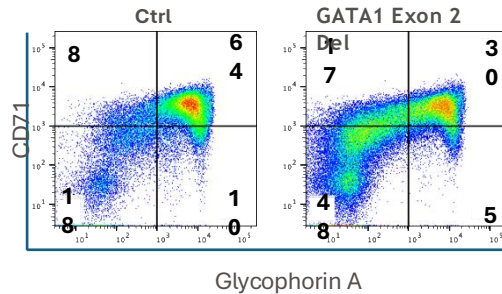


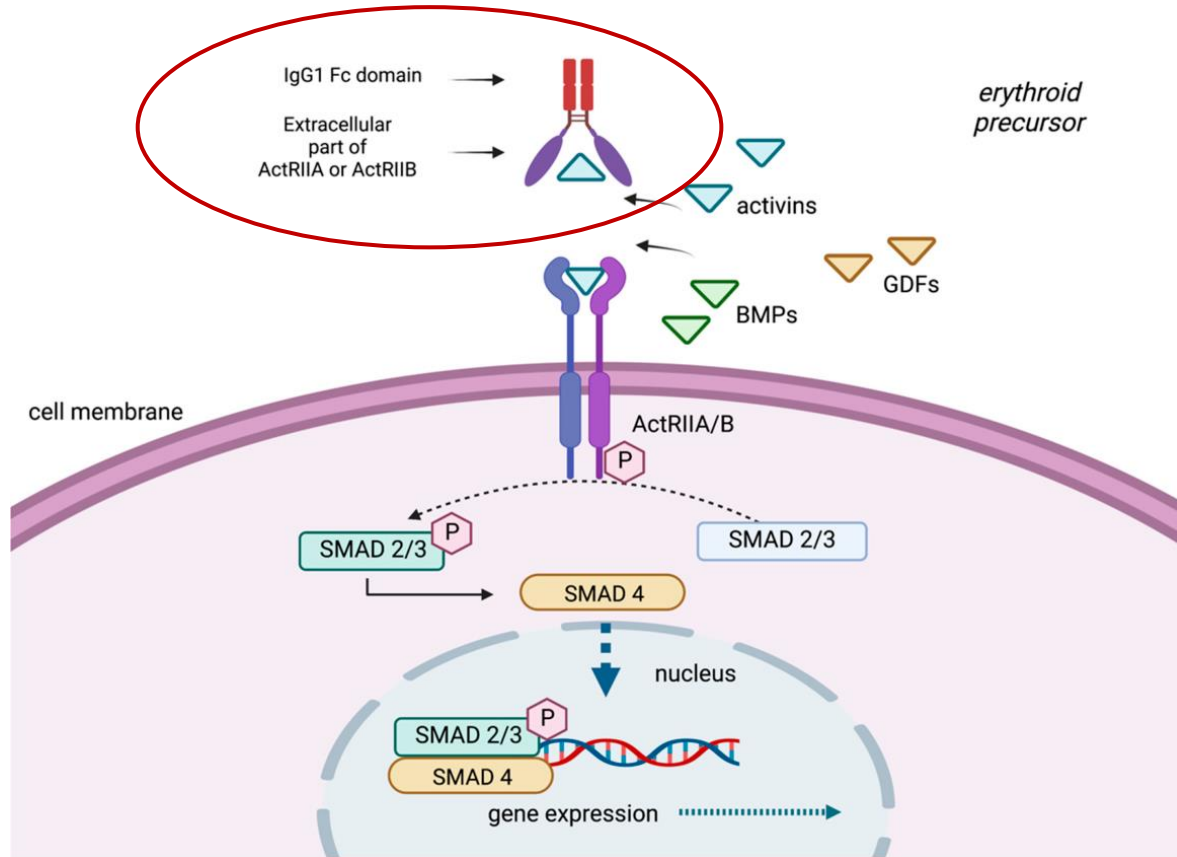
Ctrl, control; GDF11, Growth Differentiation factor 11; q-PCR, quantitative polymerase chain reaction; seq, sequencing.

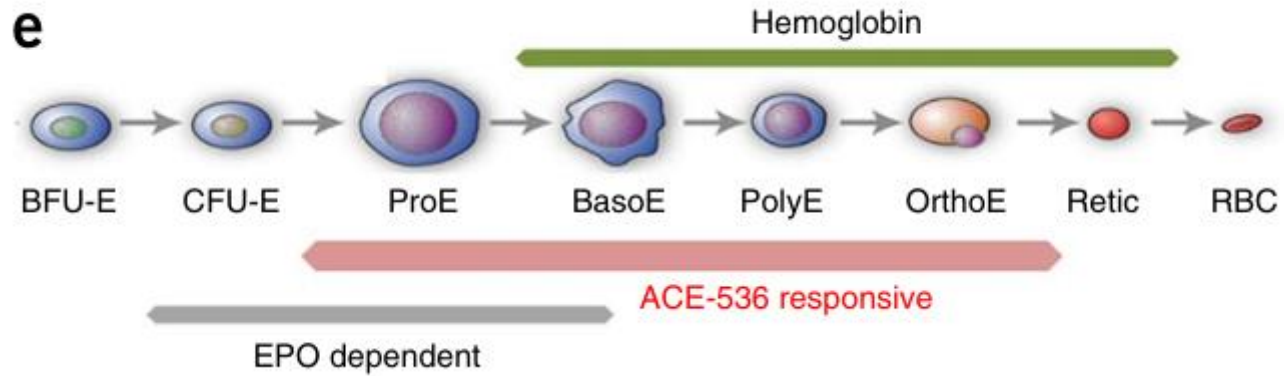
GATA1 short isoform leads to ineffective erythropoiesis



- Skipping of Exon 2 leads to reduced erythropoiesis in primary human CD34⁺ cells

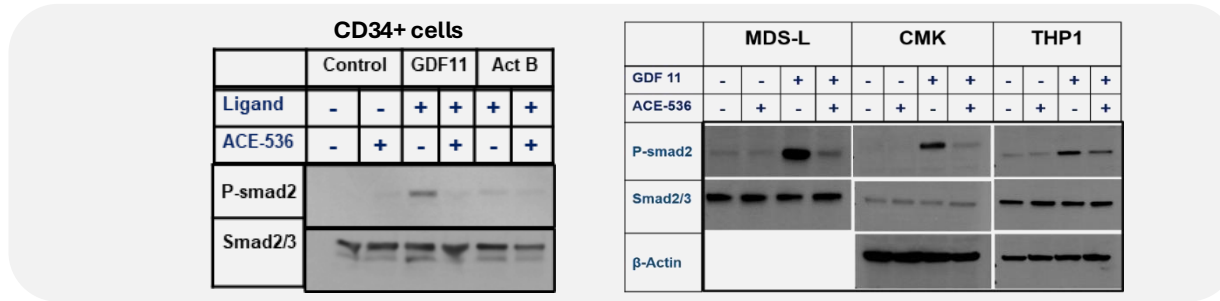




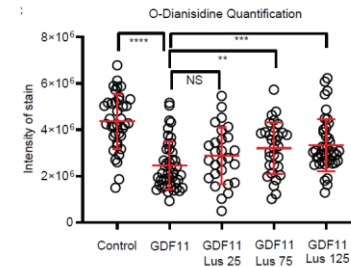
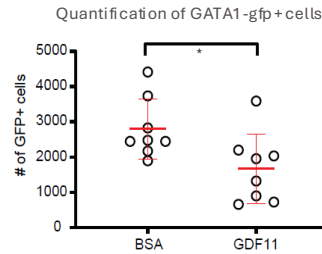
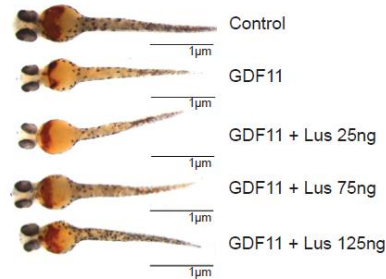


GDF11 induction of anemia in vivo is mitigated by luspatercept

- Luspatercept inhibits GDF11-mediated SMAD2 activation in primary erythroid progenitors



- Luspatercept inhibits GDF11-mediated anemia in zebrafish

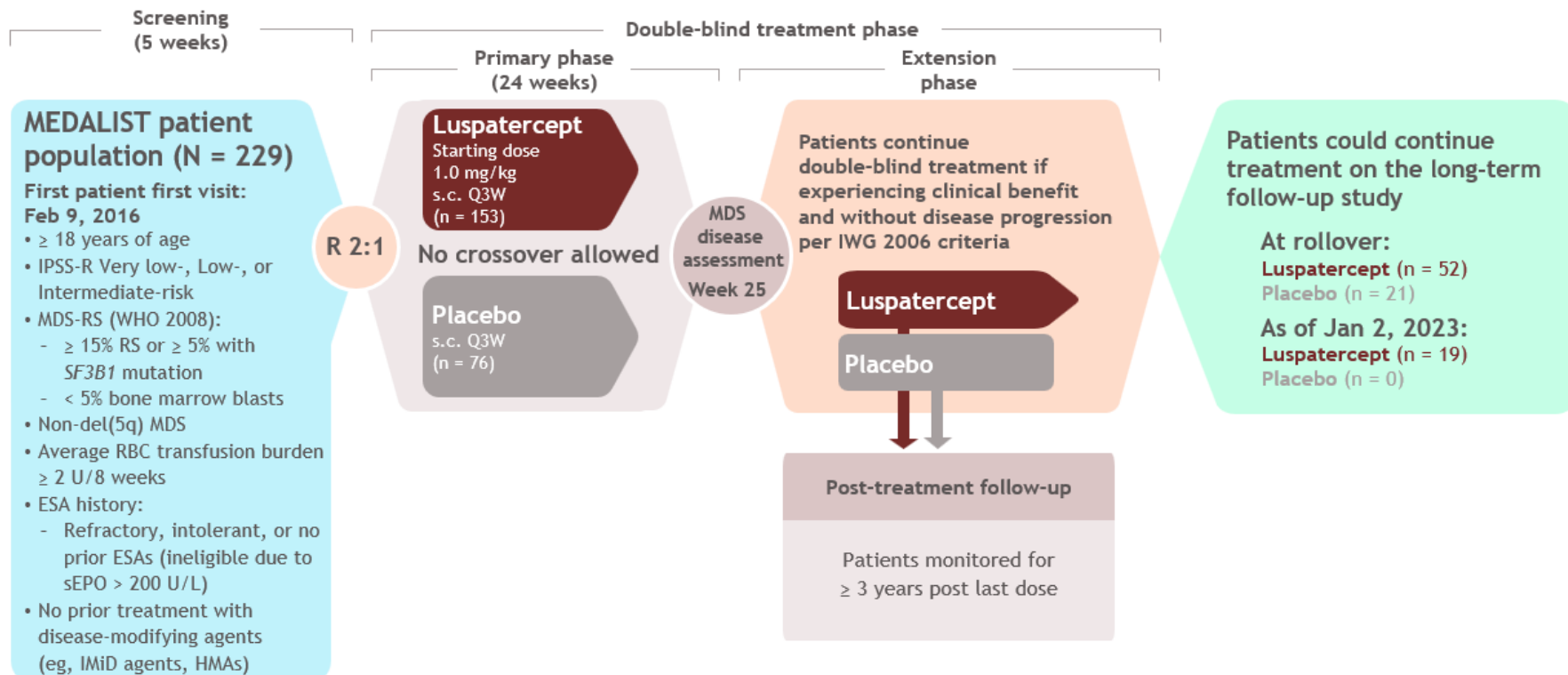


Trial name	Study type	Year of publication	Disease focus	Primary endpoint	Results, % of Luspatercept responders
BEYOND [34]	Phase 2, randomized, double-blind, placebo	2022	Non-transfusion-dependent β -thalassemia	Hb $\uparrow \geq 1$ g/dL from baseline for ≥ 2 weeks during weeks 13–24	77.1% vs. 0% in placebo arm; P < 0.0001
BELIEVE [33]	Phase 3, randomized, double-blind, placebo	2020	Transfusion-dependent β -thalassemia	$\geq 33\%$ reduction in transfusion burden during weeks 13–24 and reduction in ≥ 2 RBC transfusion units	21.4% vs. 4.5% in placebo arm; P < 0.001
PACE-MDS [28]	Phase 2, open-label	2019	Lower-risk MDS (RS and non-RS)	Hematologic improvement–erythroid (HI-E) per IWG 2006 criteria	Non-RS: 36.4%; RS: 67.7%; Overall: 53.7%
MEDALIST [3]	Phase 3, randomized, double-blind, placebo	2020	Lower-risk MDS with ring sideroblasts	≥ 8 weeks of RBC transfusion independence (RBC-TI) during first 24 weeks	38% vs. 13% in placebo arm; P < 0.001
COMMANDS [29–31]	Phase 3, randomized, open-label	2023	ESA-naive, lower-risk MDS	≥ 12 weeks RBC-TI + mean Hb $\uparrow \geq 1.5$ g/dL in weeks 1–24	58.5% (Luspatercept) vs. 31.2% (epoetin alfa); P < 0.0001

MEDALIST study design

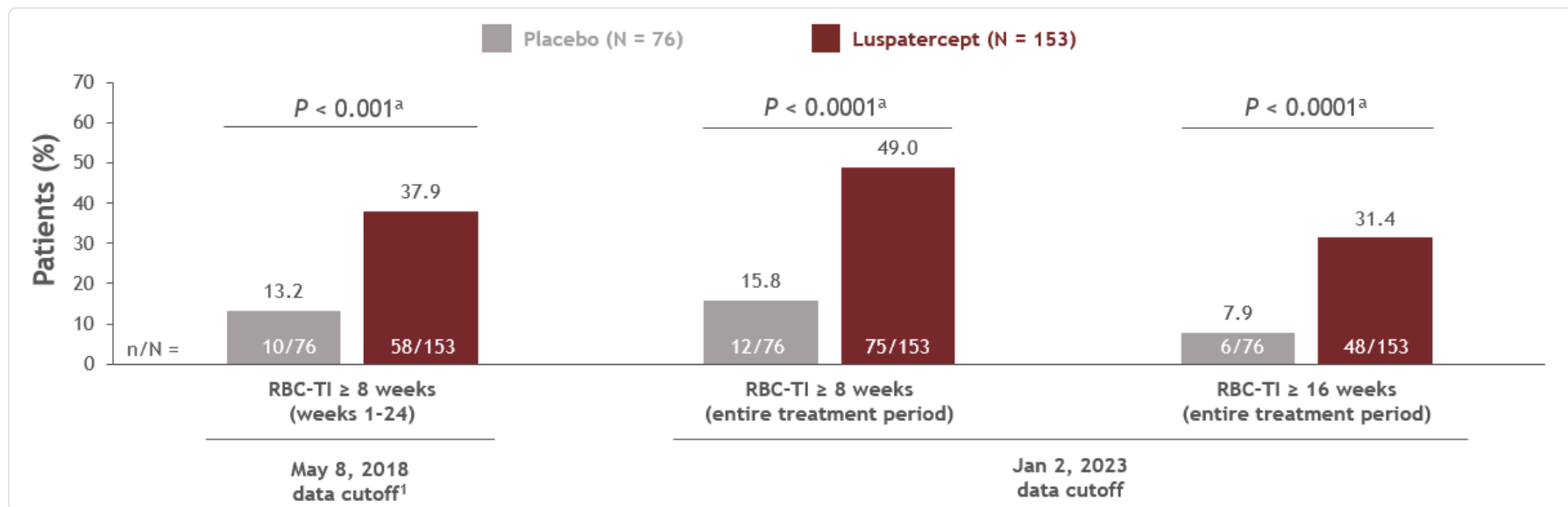
MEDALIST (NCT02631070)

LTFU (NCT04064060)



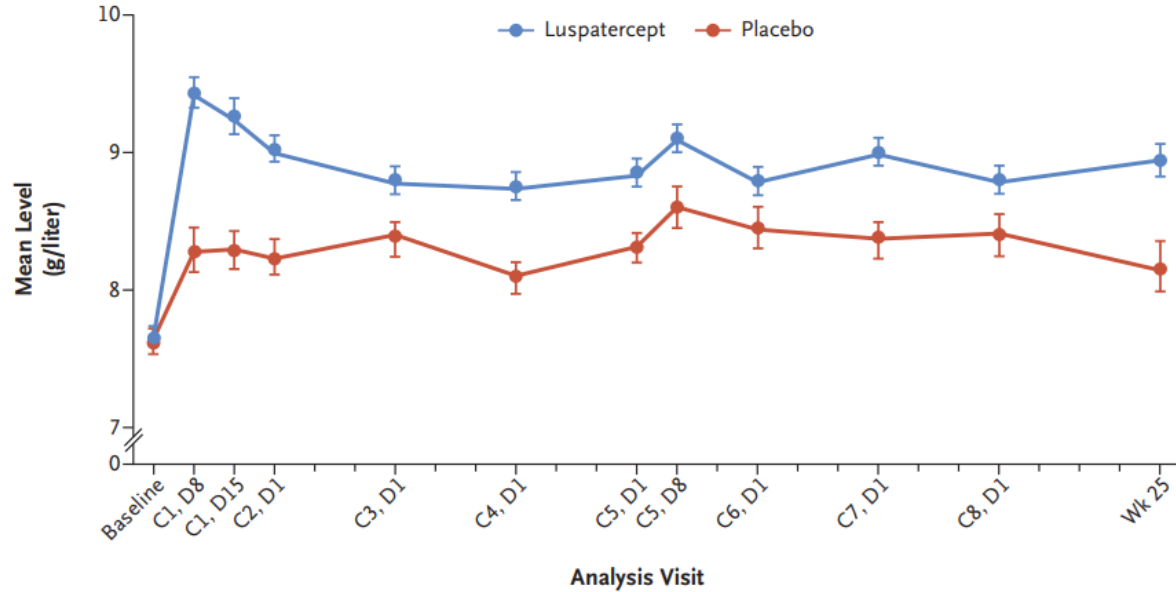
Treatment and follow-up duration and rates of RBC-TI

- As of January 2, 2023, the median (range) duration of:
 - **Treatment** was 50.9 (5.9-332.9) weeks for luspatercept and 24.0 (9.0-103.0) weeks for placebo
 - **Follow-up** was 39.9 (2.8-76.0) months for luspatercept and 38.7 (1.7-68.6) months for placebo



TRIAL MEDALIST – fase III

A Changes in Mean Observed Hemoglobin Levels over Time



No. of Patients

Luspatercept	153	57	87	116	105	112	103	76	92	106	90	80
Placebo	76	32	36	41	47	44	52	29	44	47	44	32

COMMANDS study design

Key eligibility criteria

- Age \geq 18 years
- IPSS-R Very low-, Low-, or Intermediate-risk MDS by WHO 2016 criteria, with $<$ 5% blasts in BM^a
- Required RBC transfusions (2-6 pRBC U/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO $<$ 500 U/L
- ESA-naive

Patients stratified by:

- BL TB ($<$ 4 U/8 weeks vs \geq 4 U/8 weeks)
- BL RS status (RS+ vs RS-)
- BL sEPO level (\leq 200 U/L vs $>$ 200-500 U/L)

R 1:1

Luspatercept (n = 182)
starting at 1.0 mg/kg
s.c. Q3W

Epoetin alfa (n = 181)^b
starting at 450 IU/kg
s.c. QW

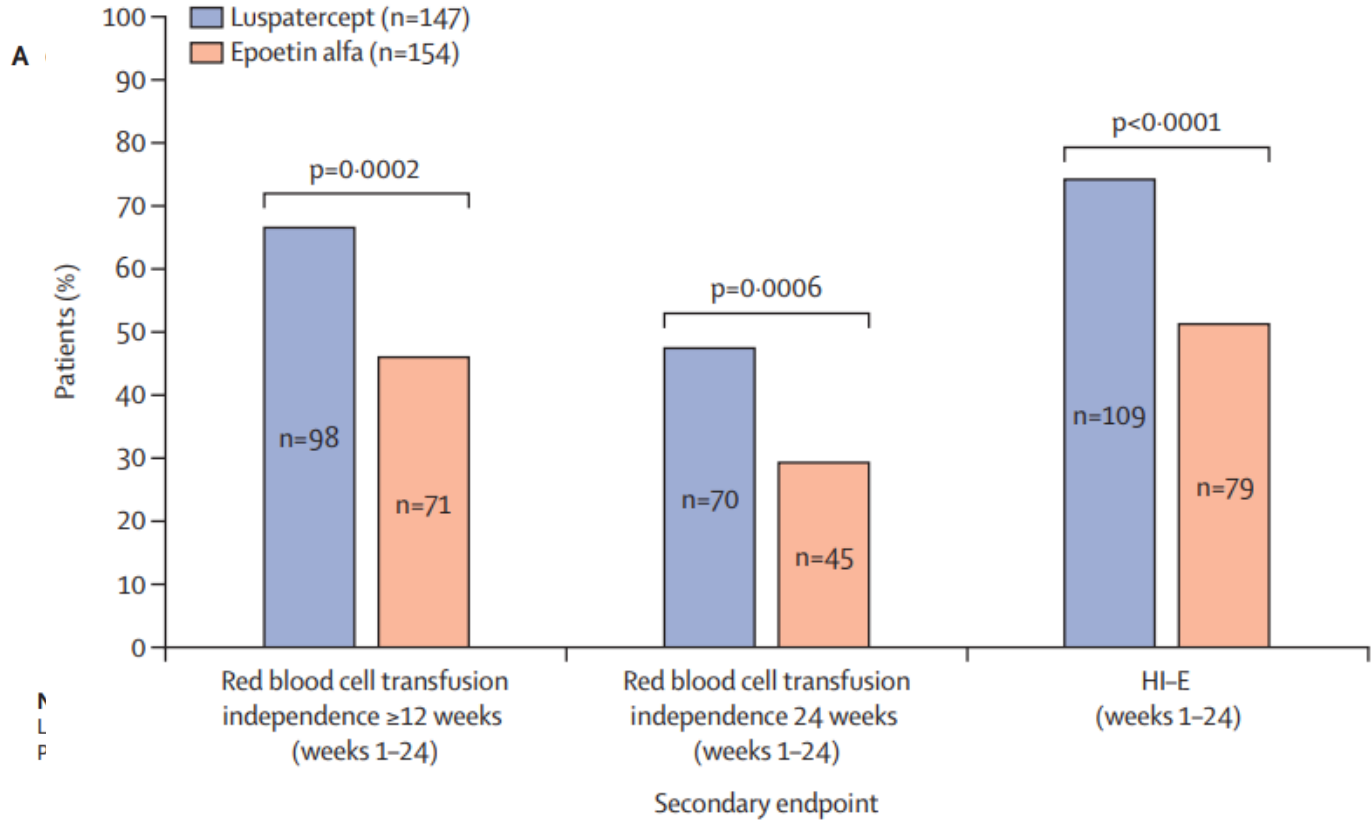
Response assessment at
day 169 and every
24 weeks thereafter

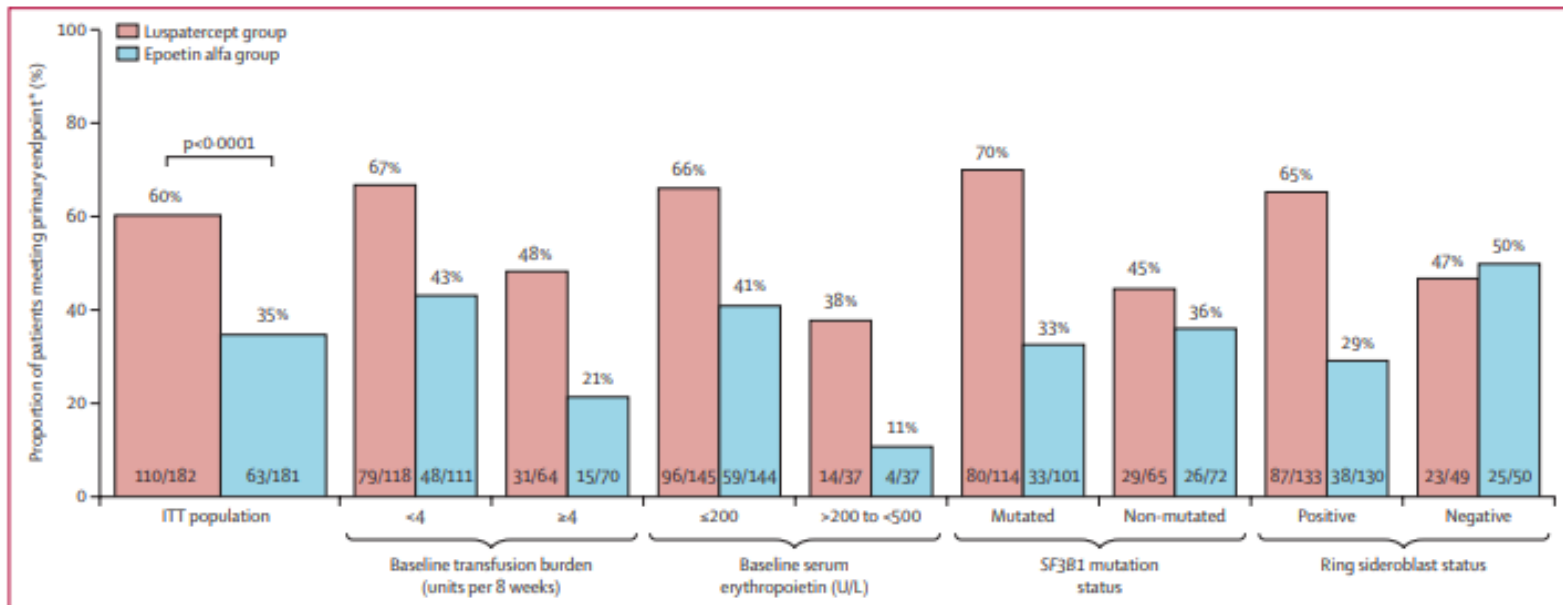
EOT
Due to lack of clinical
benefit^c or disease
progression per IWG criteria

Post-treatment safety follow-up

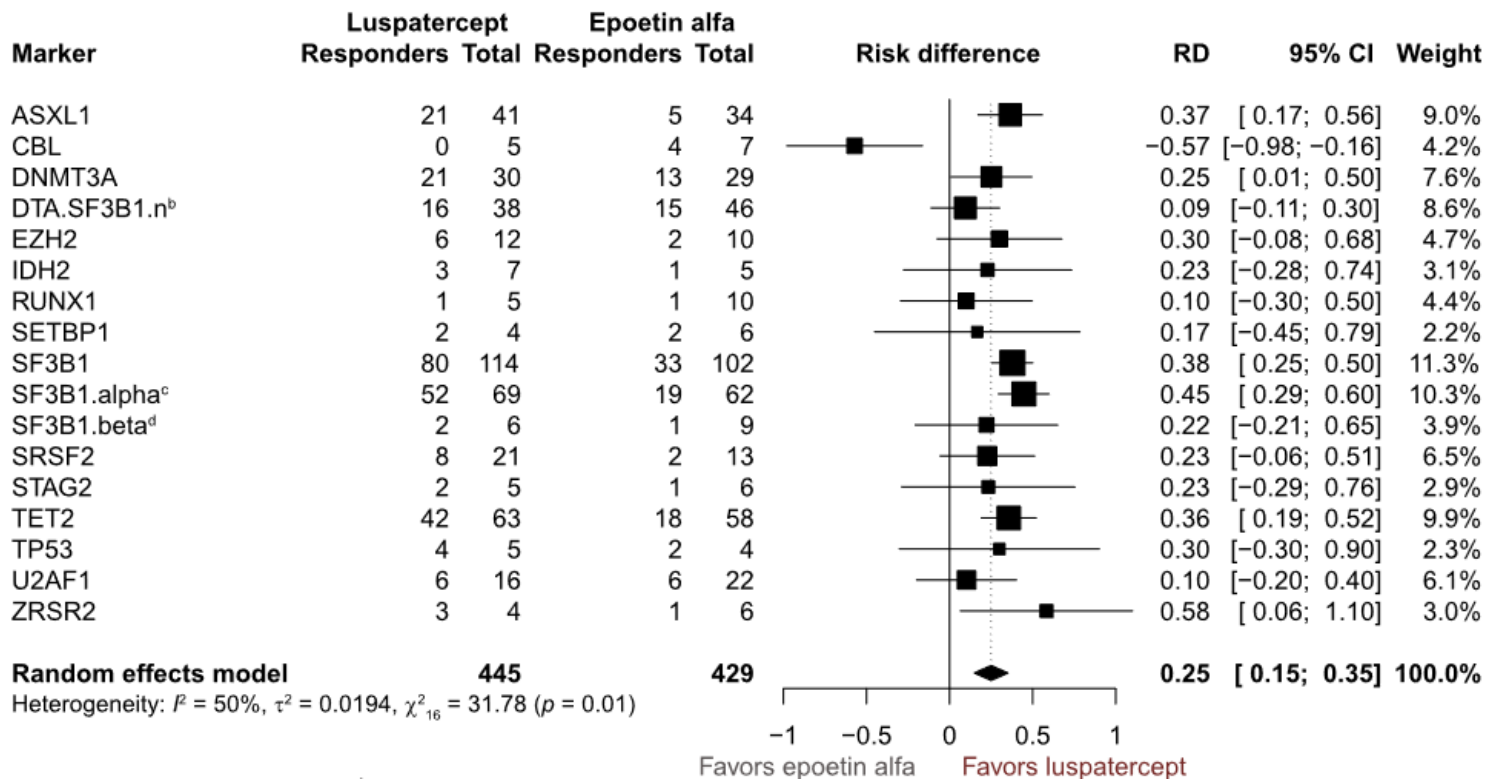
- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

TRIAL COMMANDS – fase III

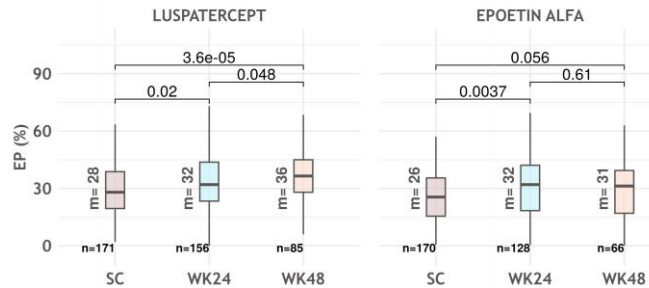
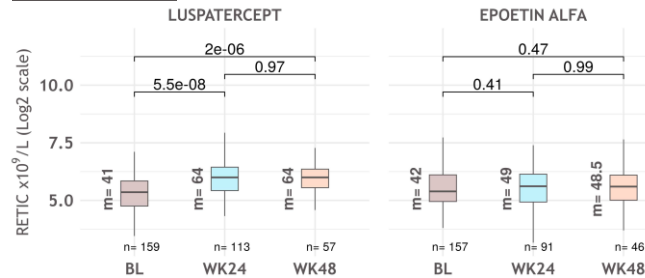
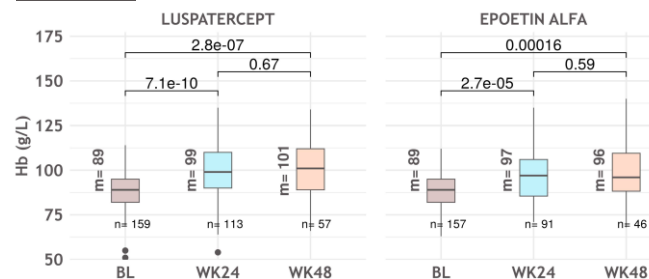




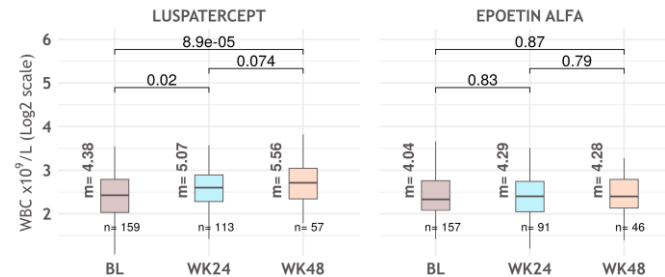
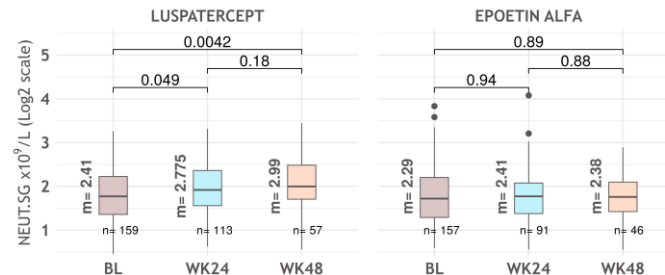
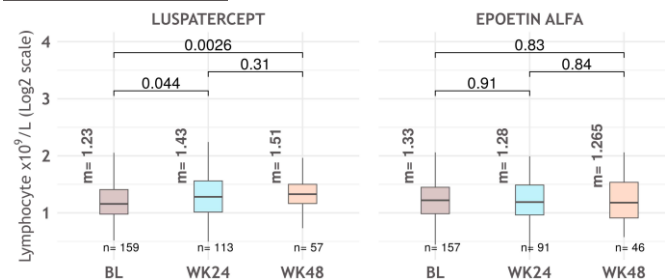
Luspatercept showed broad activity across multiple MDS-associated mutations in the primary analysis of the COMMANDS study^a



A

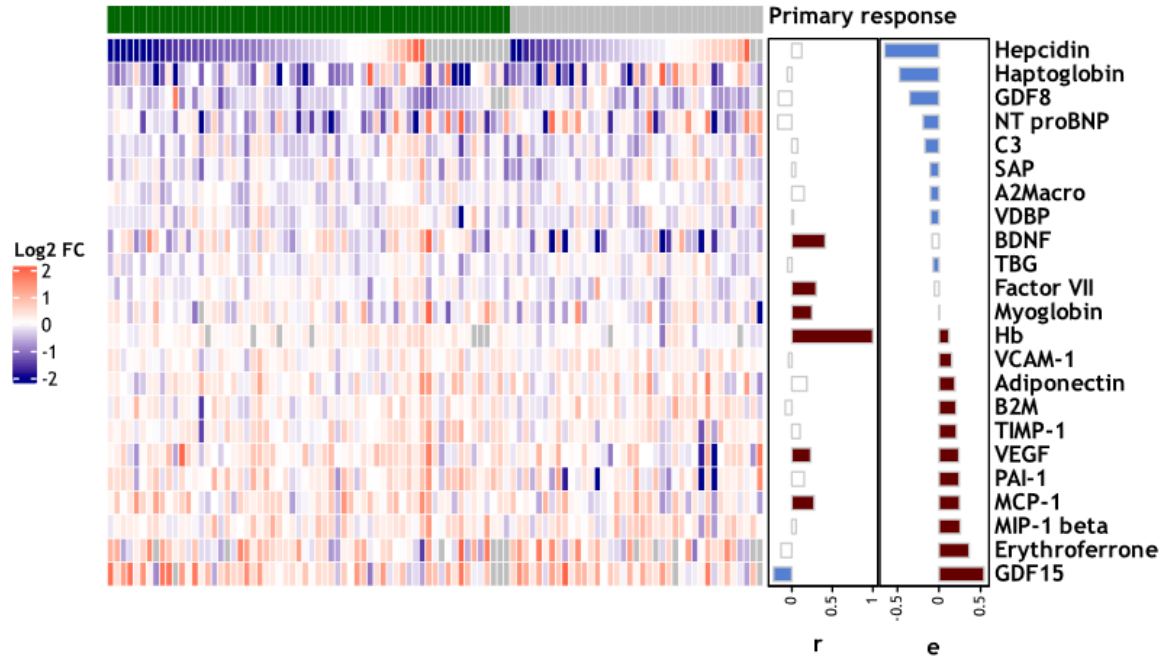
BM erythroid precursors (%)PB reticulocytesHemoglobin

B

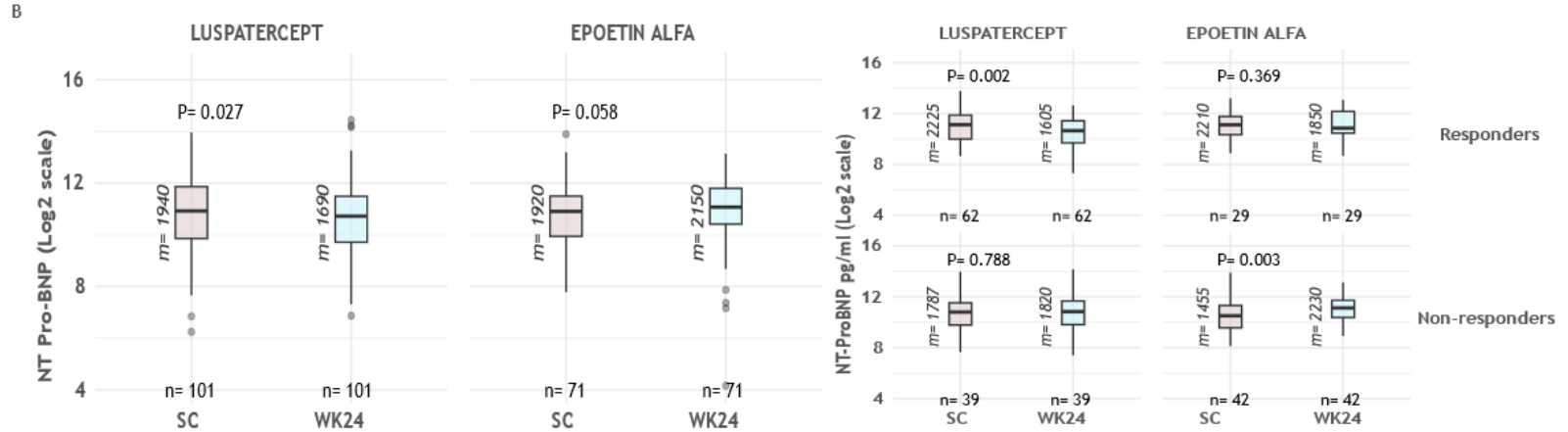
PB white blood cell countsPB segmented neutrophil countPB lymphocyte counts

Cytokines and chemokines modulated by luspatercept

A



Luspatercept alleviates heart failure/cardiac damage markers



Future Directions

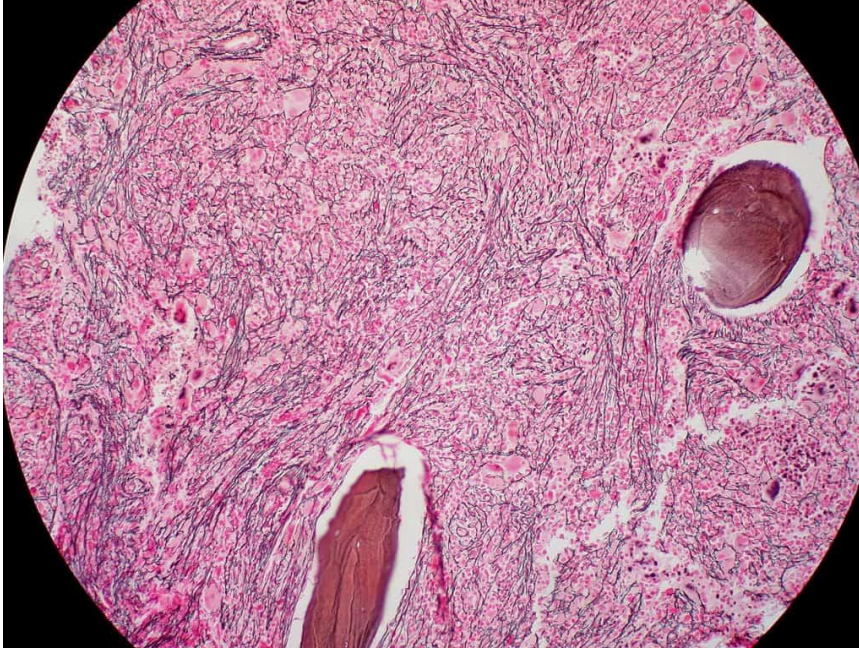
➔ ELEMENTS-MDS Trial

➔ MAXILUS Trial

➔ GFM COMBOLA Trial

TGF- β in altre neoplasie ematologiche?

Mielofibrosi



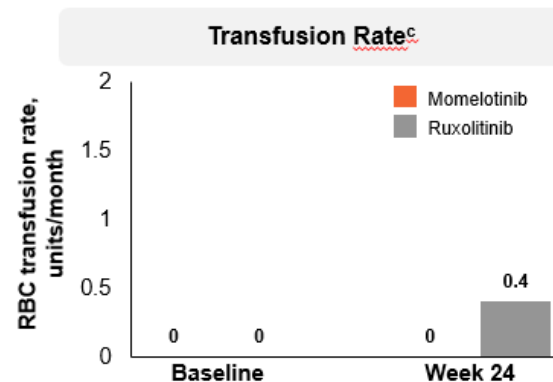
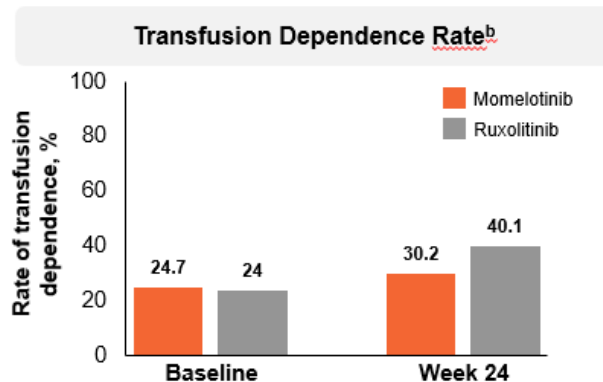
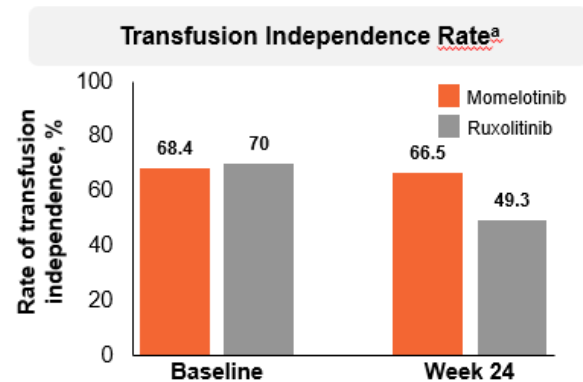
Anemia sintomatica alla
diagnosi 38%

Trasfusione dipendenza
alla diagnosi 24%

Terapia JAKi +/- EPO

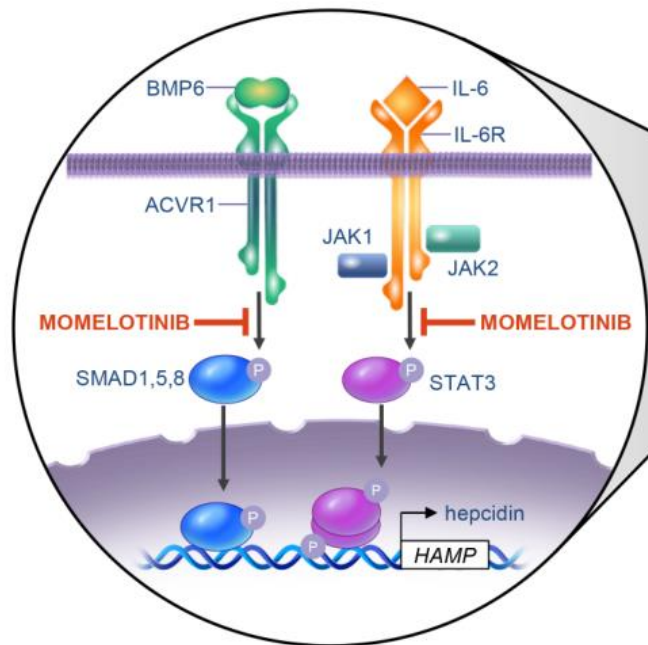
SIMPLIFY-1: Transfusion Requirements at Week 24

Secondary Endpoints

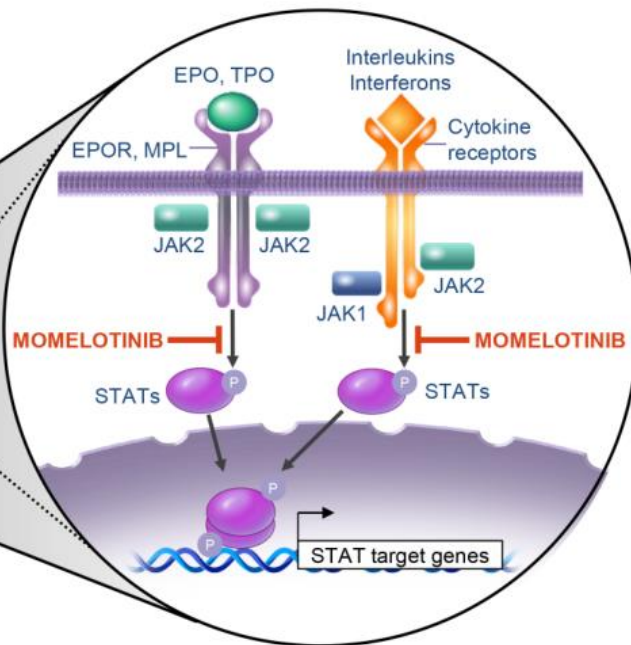
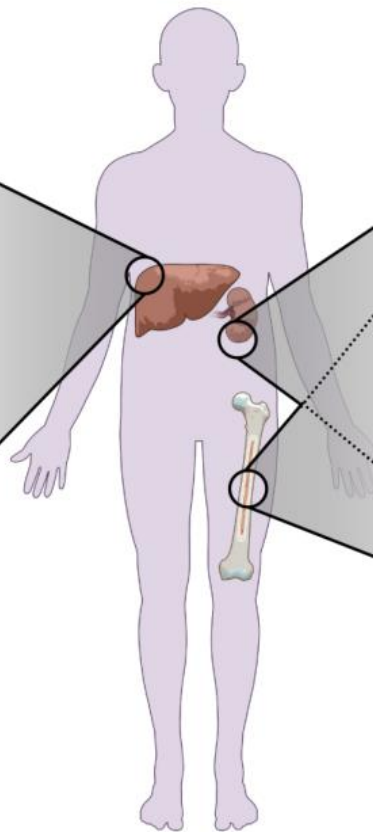


	RBC TI-R at week 24, %	RBC TD rate at week 24, %	RBC transfusion rate, units/month
Momelotinib (n=215)	66.5	30.2	0
Ruxolitinib (n=217)	49.3	40.1	0.4
Nominal <i>P</i>	<.001	.019	<.001

The momelotinib arm had higher RBC transfusion independence response rates vs ruxolitinib at week 24

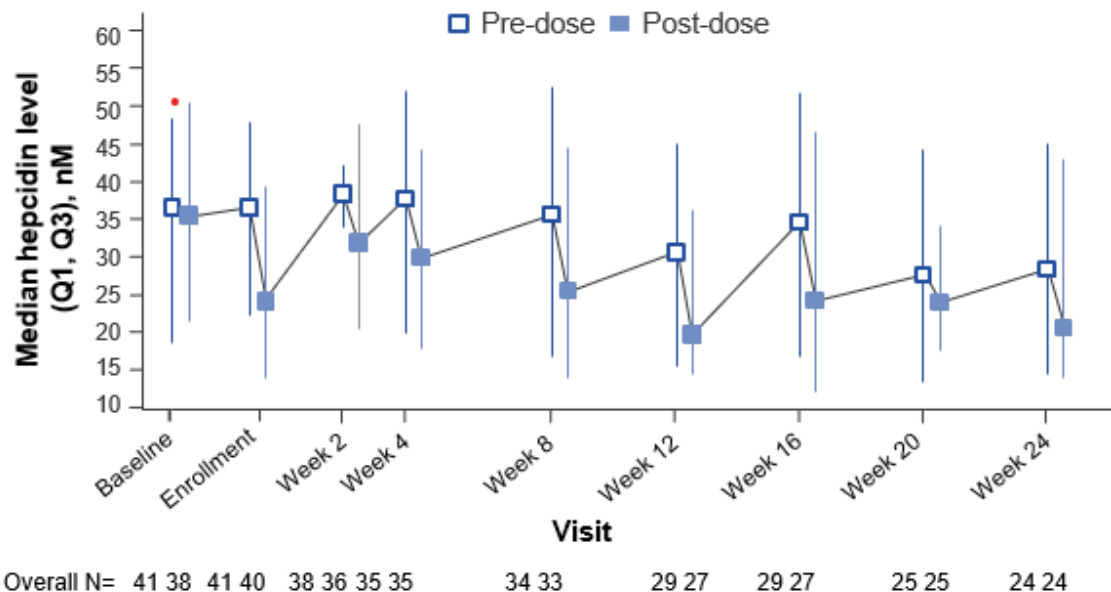


Decreased hepcidin (*HAMP*) transcription restores iron homeostasis and **increases hemoglobin** leading to an improvement in iron-restricted anemia

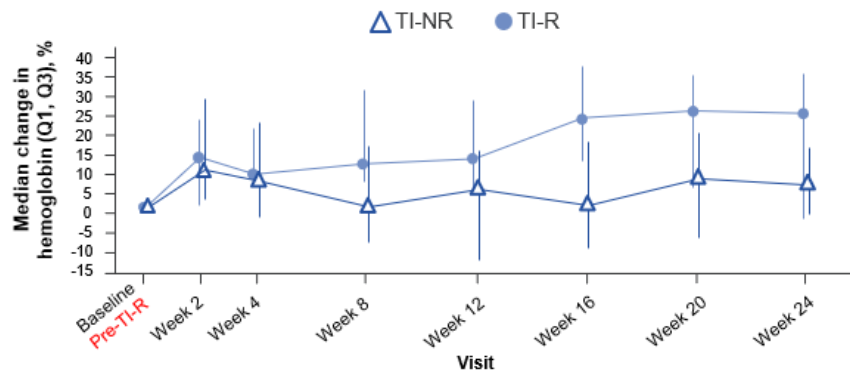


Reduced extramedullary hematopoiesis **improves splenomegaly** Decreased inflammation and aberrant cytokine signaling **reduces constitutional symptoms**

Hepcidin levels (overall population)

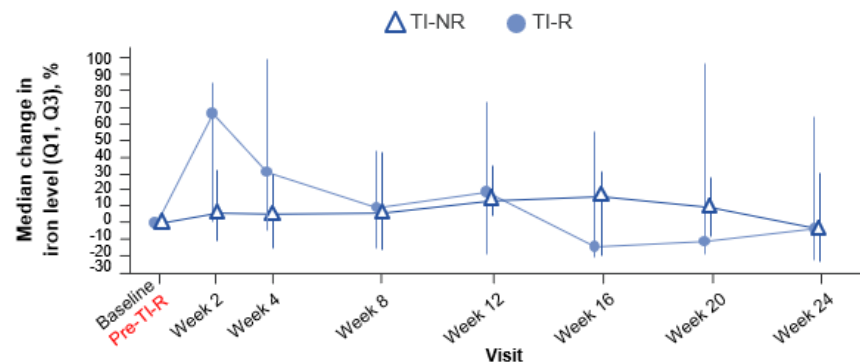


Hemoglobin levels



TI-NR N=	27	26	25	22	20	18	16	16
TI-R N=	14	11	12	14	13	10	10	9

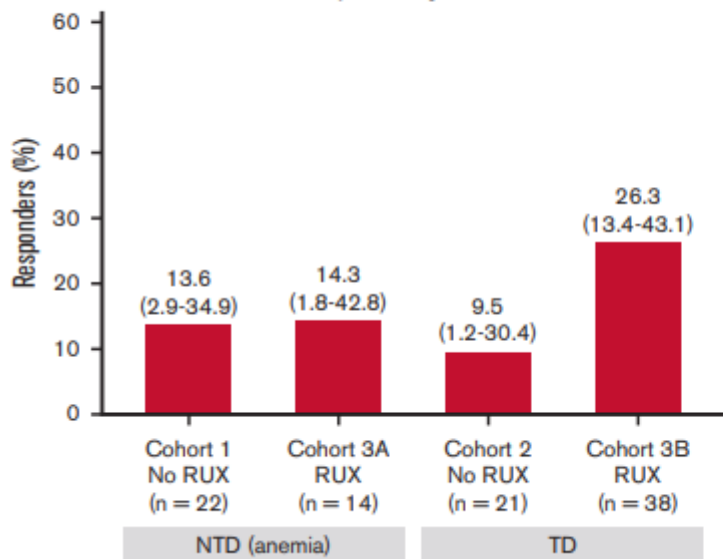
Percentage change in iron levels



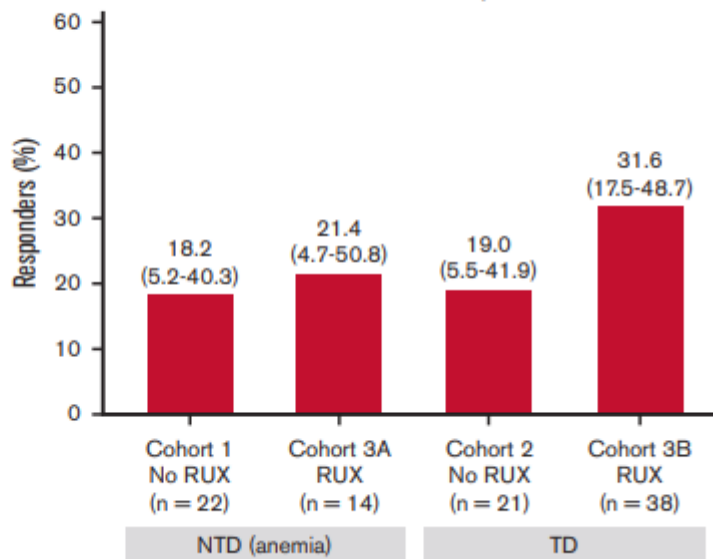
TI-NR N=	27	25	23	20	16	15	13	11
TI-R N=	14	11	12	14	14	10	9	8

Luspatercept in MF

Primary treatment period
(up to day 169)



Entire treatment period



■ Primary endpoint

TD patients:
anemia response defined as 84
consecutive days without RBC
transfusion

NTD patients:
anemia response defined as 84
consecutive days with ≥ 1.5 g/dL
Hgb increase from baseline
without RBC transfusion

Future Directions



INDIPENDENCE Trial



ODYSSEY Trial

SCDU Ematologia AO Mauriziano

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Dott. Guido Parvis

Dott.ssa Daniela Gottardi

Dott.ssa Piera Sivera

Dott. Alessandro Cignetti

Dott.ssa Valentina Gaidano

Dott.ssa Valentina Bonuomo

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Dott.ssa Martina Bullo

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Dott.ssa Rita Vacca

Dott. Simone Rocco

Dott. Afshin Bagherzadehsamarin



GRAZIE!