Progetto Ematologia-Romagna

RAVENNA, 5 MAGGIO 2018

AULA MAGNA – Casa Matha

LE MIELODISPLASIE, OGGI: Spunti terapeutici della quota di eritropoiesi inefficace

Carlo Finelli

Istituto di Ematologia.

Policlinico S. Orsola-Malpighi. Bologna

CLASSIFICAZIONE PATOGENETICA DELLE ANEMIE

a) ridotta formazione di eritroblasti (I gruppo) (Aplasia)

b) ridotta formazione di eritrociti (II gruppo) (Eritropoiesi inefficace)

c) ridotta sintesi di emoglobina (III gruppo)

d) ridotta sopravvivenza degli eritrociti (IV gruppo) (Emolisi)

ANEMIE DEL II GRUPPO

- Sono caratterizzate prevalentemente da una ridotta formazione di eritrociti, spesso più grandi del normale (macrociti o megalociti). Il numero dei reticolociti è molto basso; a differenza di quanto avviene nel I gruppo, la biopsia midollare mostra un'enorme iperplasia eritroblastica: gli eritroblasti «affluiscono» a legioni dai pools staminali, ma proliferano e maturano difettosamente, morendo in gran parte prima di diventare eritrociti **(eritropoiesi inefficace)**.

JCI The Journal of Clinical Investigation

THE QUANTITATIVE DETERMINATION OF IRON KINETICS AND HEMOGLOBIN SYNTHESIS IN HUMAN SUBJECTS

Myron Pollycove, Robert Mortimer

J Clin Invest. 1961;40(5):753-782. https://doi.org/10.1172/JCI104310.

Research Article

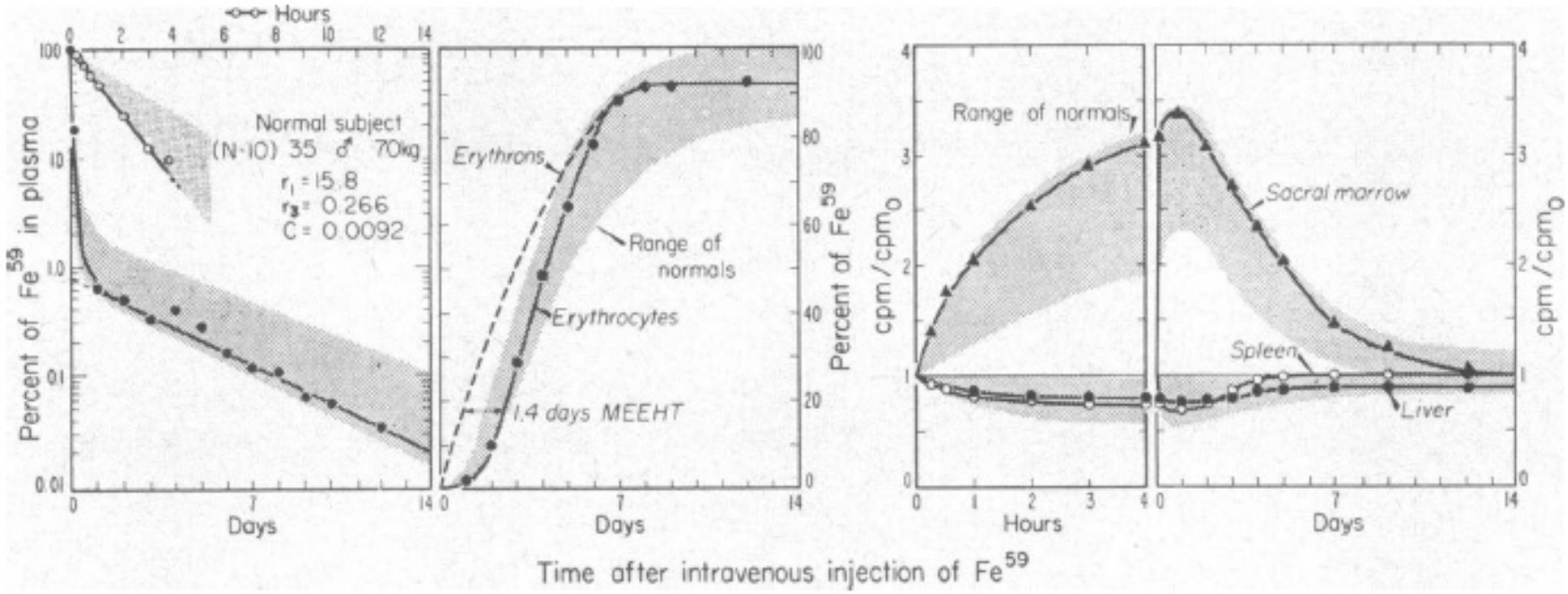


FIG. 1. RADIOIRON IN PLASMA AND ERYTHROCYTES, AND SURFACE RADIOACTIVITY IN A NORMAL SUBJECT. The interrupted curve, showing cumulative fixation of radioiron in erythrons, and the mean effective erythron hemoglobinization time (MEEHT) are calculated as shown in Appendices C and D.

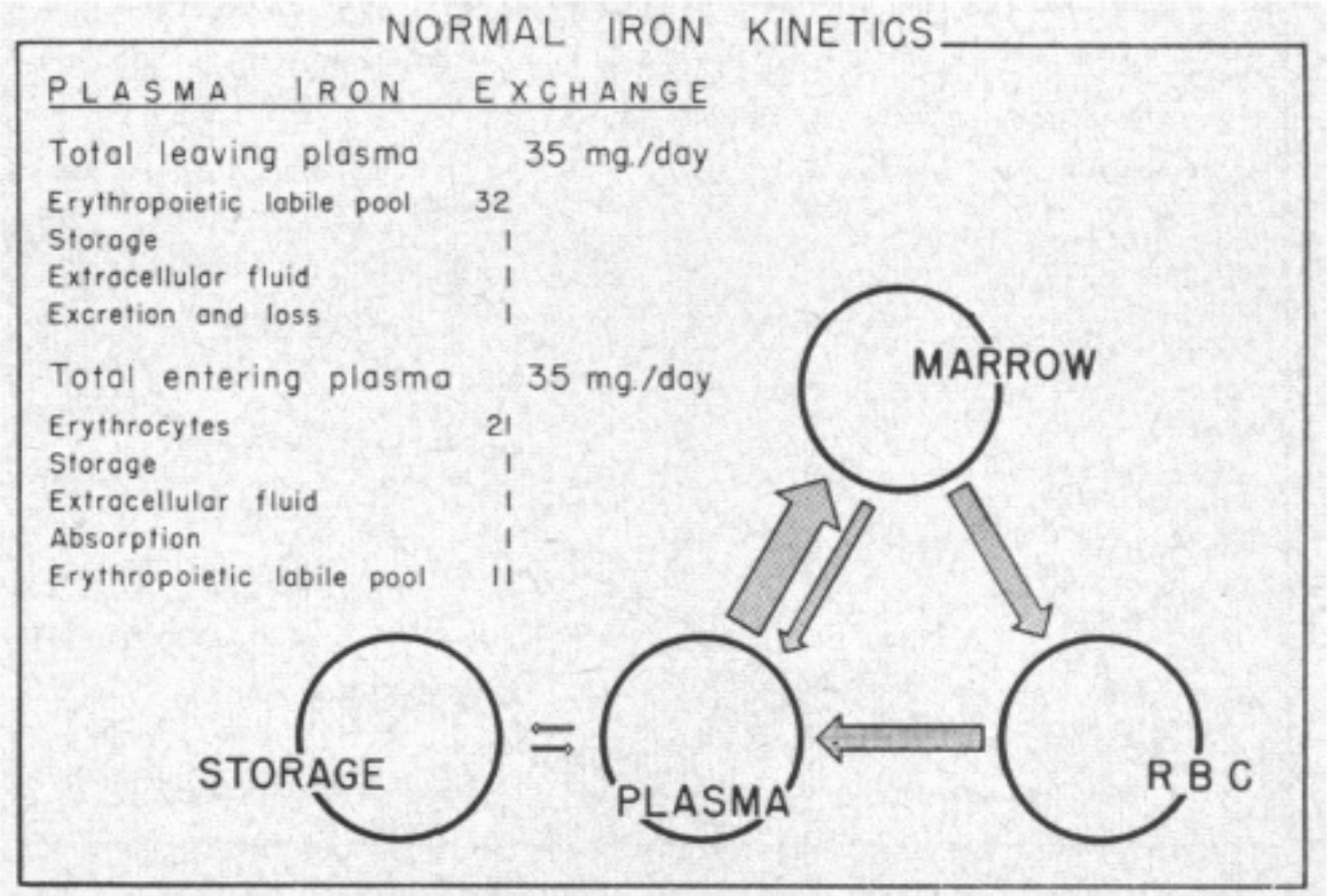


FIG. 17. QUANTITATIVE ASPECTS OF NORMAL IRON KINETICS.

TURA, S., ***BACCARANI***, M., ***RICCI***, P., ZACCARIA, A., MULLERBÉRAT, C.N.: ***Anemia diseritropoietica idiopatica acquisita***. Proc. XXIV Congresso Nazionale della ***Societa Italiana di Ematologia***, September 1973, Salice Terme (Pavia), p. 1–72.

SINDROMI MIELODISPLASTICHE (MDS)

Gruppo eterogeneo di malattie, caratterizzate da:

1) citopenia periferica

2) dismielopoiesi, con midollo più spesso normo-ipercellulato, più raramente ipocellulato, con o senza incremento della quota blastica (comunque < 20%)

3) aumentato rischio di evoluzione in leucemia acuta mieloide (AML)

Specificity of dysplastic findings

Morphological abnormalities[a]	*Cutoff values*[b]	*AUC*	*Cohen's K-coefficient (inter-observer agreement)*[c]
Erythroid lineage			
Megaloblastoid changes	>5%	0.814, $P<0.001$	0.83
Bi- or multinuclearity	>3%	0.679, $P<0.001$	0.87
	>5%	0.698, $P<0.001$	
Nuclear lobulation or irregular contours	>3%	0.674, $P<0.001$	0.84
Pyknosis	>5%	0.677, $P<0.001$	0.81
Cytoplasmic fraying	⩾7%	0.602, $P<0.001$	0.82
Ring sideroblasts	>5%	0.650, $P<0.001$	0.95
	⩾15%	0.719, $P<0.001$	
Ferritin sideroblasts	⩾30%	0.670, $P<0.001$	0.92
Granulocytic lineage			
Myeloblasts	>3%	0.777, $P<0.001$	0.92
	>5%	0.723, $P<0.001$	
Auer rods	⩾1%	0.524, $P=0.001$	0.90
Pseudo Pelger–Hüet anomaly	>3%	0.714, $P<0.001$	0.87
	>5%	0.814, $P<0.001$	
Abnormal nuclear shape	⩾7%	0.700, $P<0.001$	0.86
Neutrophil hypogranulation	>3%	0.791, $P<0.001$	0.81
	>5%	0.821, $P<0.001$	
Megakaryocytic lineage			
Micromegakaryocytes	>5%	0.916, $P<0.001$	0.88
Small binucleated megakaryocytes	>5%	0.845, $P=0.001$	0.81
Megakaryocytes with multiple separated nuclei	>5%	0.750, $P<0.001$	0.84
Hypolobated or monolobar megakaryocytes	>5%	0.646, $P<0.001$	0.86

9% false positive

5% false positive

11% false positive

30% cutoff better than 10%

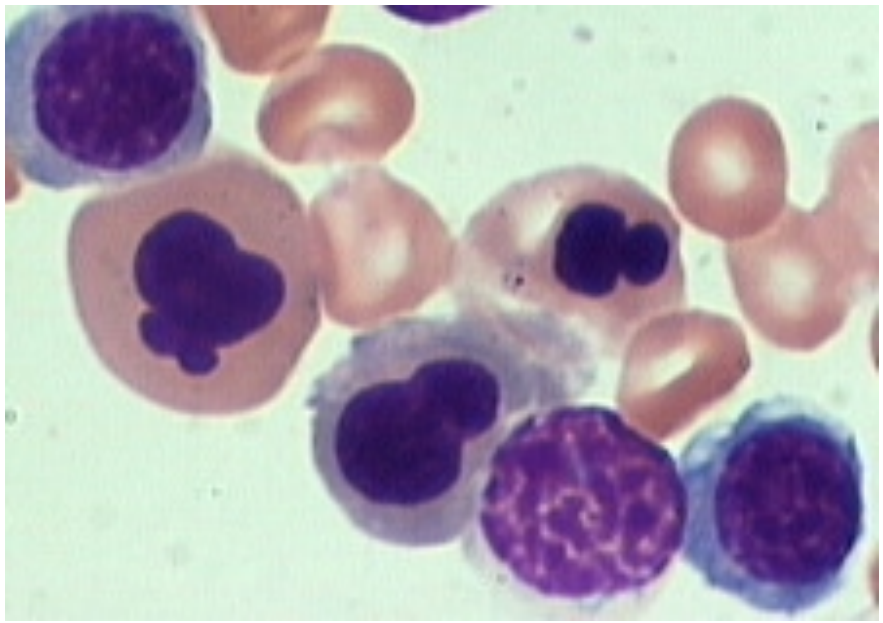
Della Porta MG et al. Leukemia 2015;29:66

MDS classification: new terminology

WHO 2016	WHO 2008
• MDS with single lineage dysplasia (MDS-SLD)	Refractory cytopenia with unilineage dysplasia (RCUD)
• MDS with multilineage dysplasia (MDS-MLD)	Refractory cytopenia with multilineage dysplasia (RCMD)
• MDS with ring sideroblasts – MDS-RS with single lineage dysplasia (MDS-RS-SLD) – MDS-RS with multilineage dysplasia (MDS-RS-MLD)	Refractory anemia with ring sideroblasts (RARS) Refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS)
• MDS with isolated del(5q)	MDS with isolated del(5q)
• MDS, unclassifiable (MDS,U)	MDS, unclassifiable (MDS,U)
• MDS with excess blasts (MDS-EB)	Refractory anemia excess blasts (RAEB)
• *Refractory cytopenia of childhood (RCC)(provisional)*	*Refractory cytopenia of childhood (RCC)(provisional)*

ANEMIA in MDS

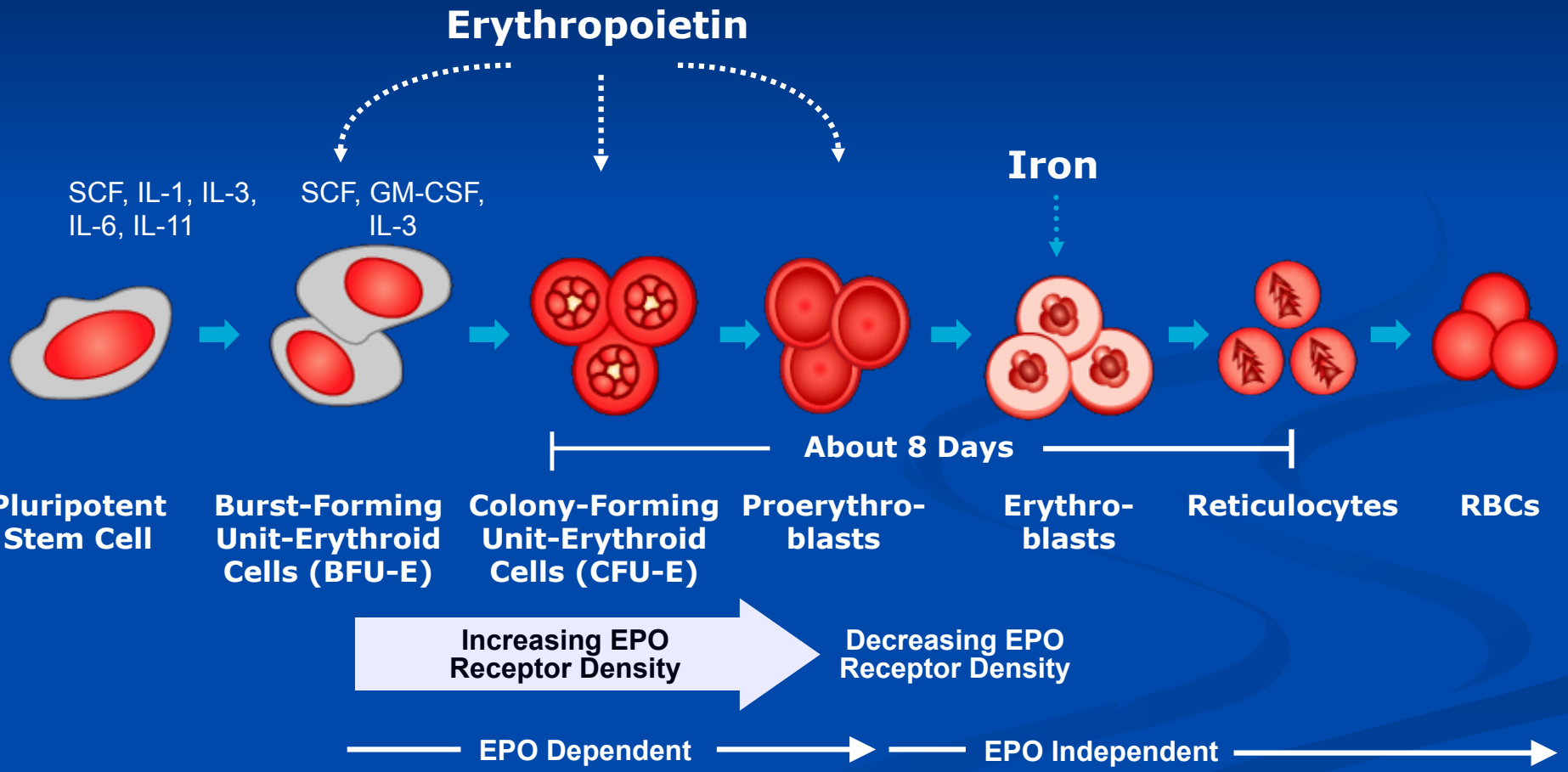
- More than 50% of patients show anemia (Hb < 10 g/dl) at diagnosis
- More than 90% become anemic during the course of the disease
- More than 80% require red-cell transfusion



New IWG criteria (Hematological Erythroid Improvement for Hb < 11 g/dl) Blood 2006

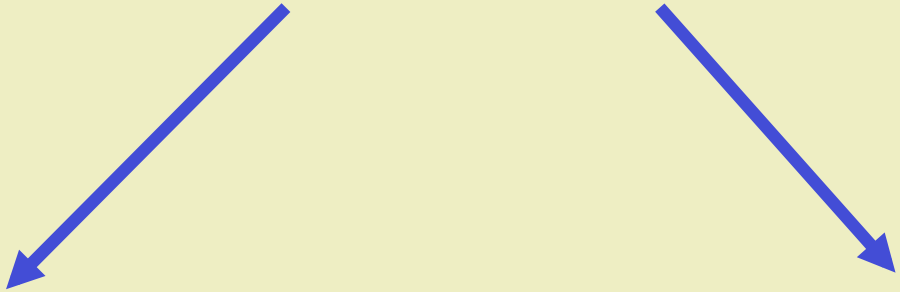
- Hb increase by > 1.5 g/dl
- Reduction of transfusion by an absolute number of at least 4 RBC trasfusions/8 weeks compared to pre-treatment transfusion number in the previous 8 weeks (Hb < 9 g/dl)
- Responses must last > 8 weeks

Erythropoietin is Essential for Key Steps in Erythropoiesis



Papayannopoulou T, et al. In: Hoffman R, et al., ed. *Hematology: Basic Principles and Practice*. 4th ed. 2005;267-288.

ACTIVITY OF r-EPO IN MDS



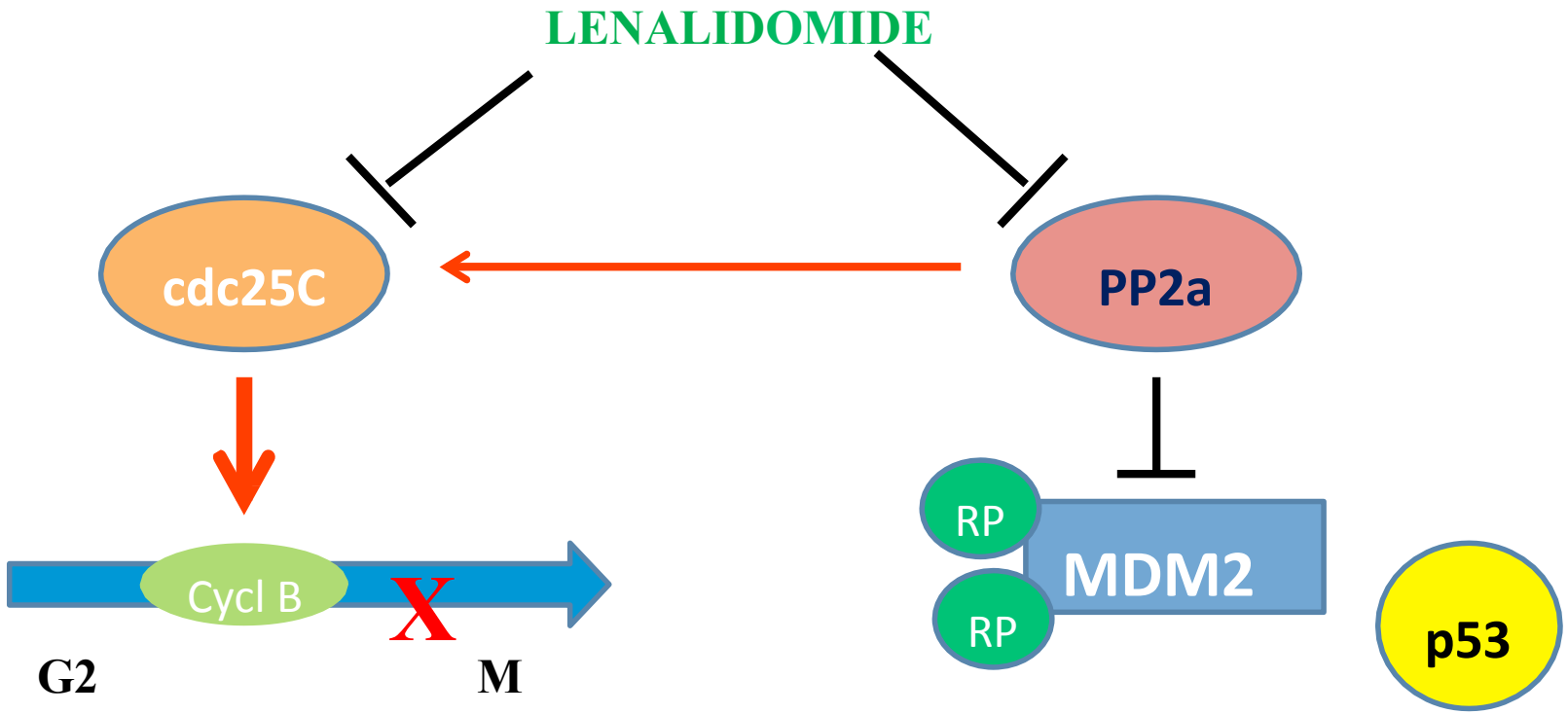
STIMULATION OF NORMAL OR CLONAL ERYTHROID PRECURSORS

Merchav 1990; Aoki, 1992, Rigolin et al, 2002 and 2004

INHIBITION OF PREMATURE APOPTOSIS

Aoki et al, 1992; Tehranchi et al, 2003; Rigolin et al, 2004; Stasi et al, 2004

MDS CON DELEZIONE 5q:
ECCANISMO DI AZIONE DELLA LENALIDOMIDE

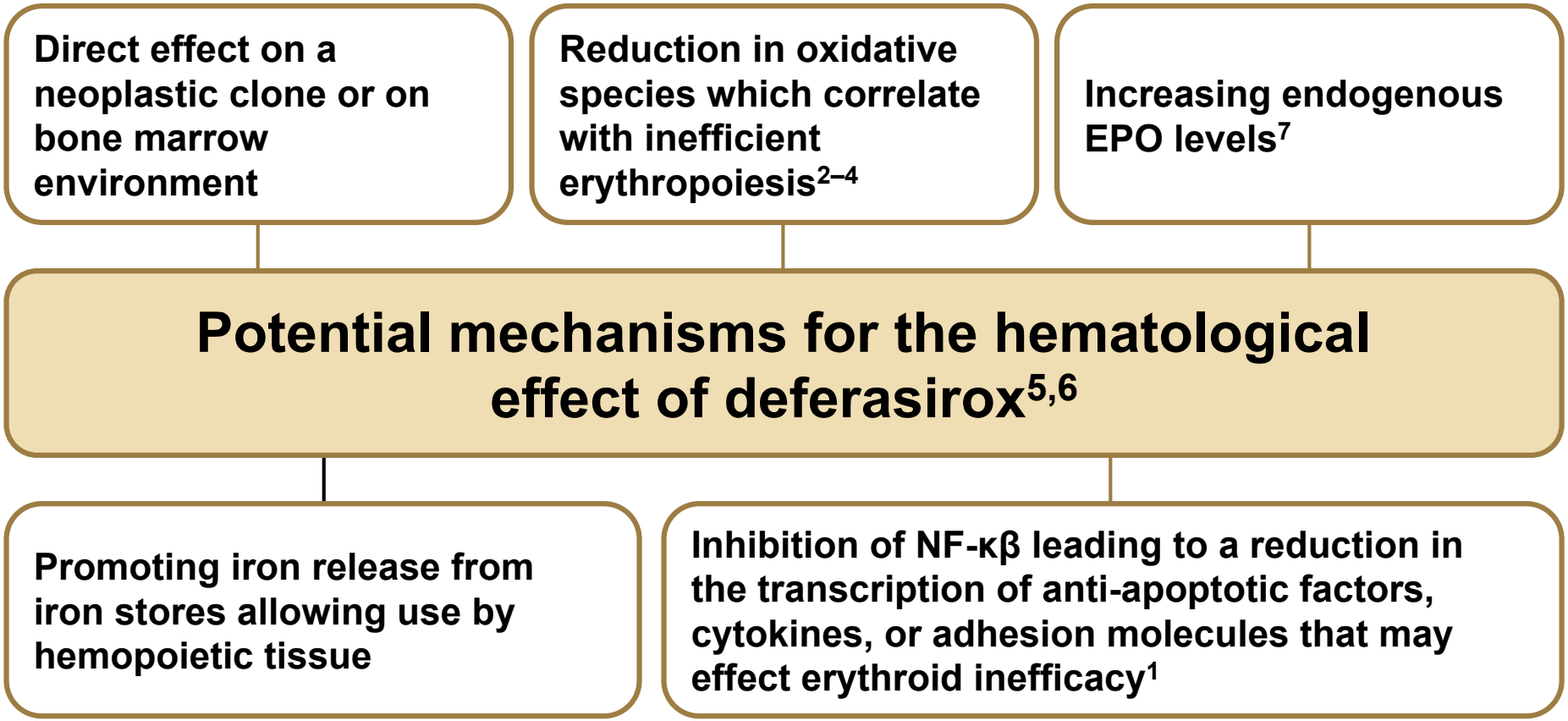


Arresto in G2
ed apoptosi del clone 5q-

Riduzione di p53
e ripristino dell'eritropoiesi

Sallman DA et al, Front Oncol 2014;4:264-9

Potential Mechanisms for the Hematologic Effect of Deferasirox



1. Messa E, et al. *Haematologica*. 2010;95:1308-16. 2. Ghoti H, et al. *Eur J Haematol*. 2007;79:463-7.
3. Hartmann J, et al. *Blood*. 2008;112:[abstract 2694]. 4. Chan LSA, et al. *Blood*. 2008;112:[abstract 2685].
5. Breccia M, et al. *Acta Haematol*. 2010;124:46-8. 6. Guariglia R, et al. *Leuk Res*. 2011;35:566-70.
7. Ren X, et al. *J Appl Physiol*. 2000;89(2):680-6.

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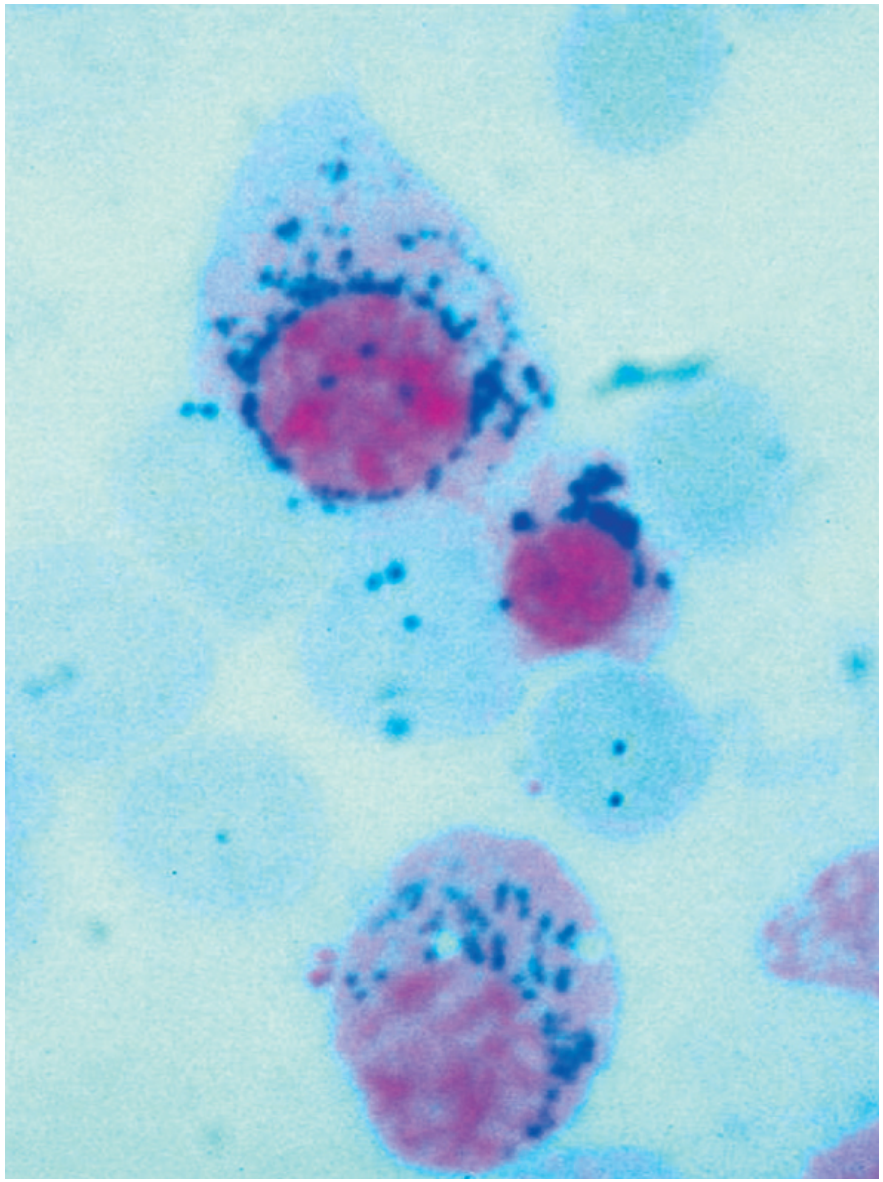
DISERITROPOIESI: SIDEROBLASTI AD ANELLO

(da Liso V., in: "Sindromi Mielodisplastiche. Dalla teoria alla pratica clinica" Elsevier Masson, 2008)



DEFINIZIONE DI SIDEROBLASTI

- tipo 1: < 5 granuli siderotici
- tipo 2: ≥ 5 granuli siderotici (non perinucleari
- ad anello: ≥ 5 granuli perinucleari (solitamente ma non necessariamente ≥ 1/3 della rima nucleare)
- RARS o RCMD-RS: sideroblasti ad anello ≥ 15%

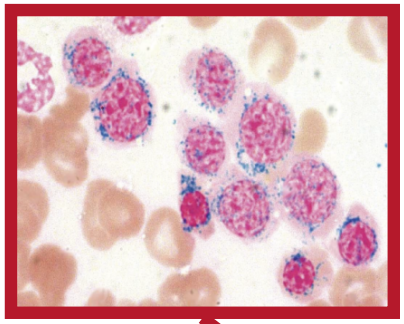
Pathophysiology of ring sideroblasts

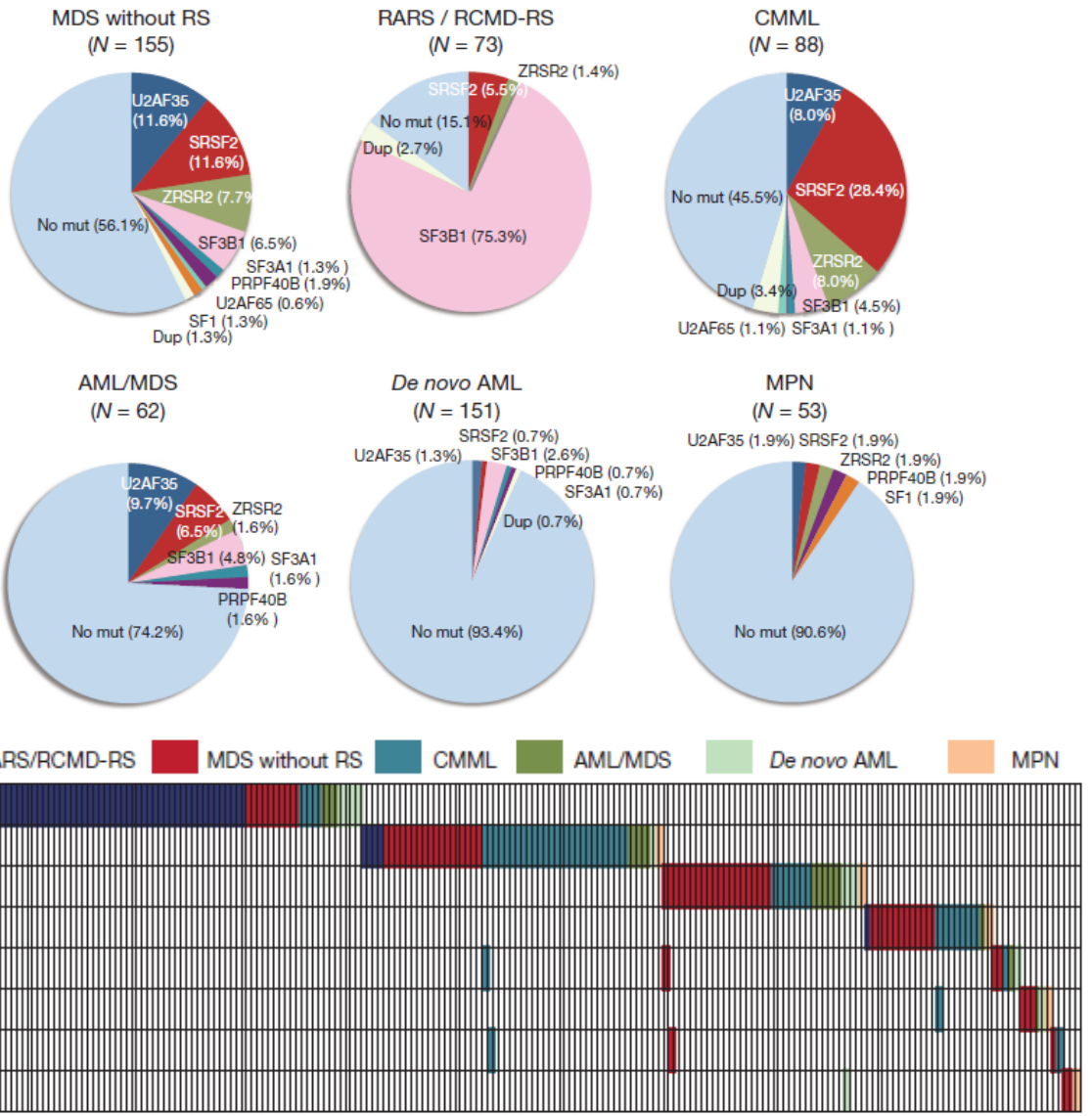
- The excess iron in the mitochondria of ring sideroblasts is stored in the form of mitochondrial ferritin, a ferritin isoform encoded by an intronless gene mapped on chromosome 5q23.1 (Levi et al, 2001; Cazzola et al, 2003). Mitochondrial ferritin has ferroxidase activity, and is therefore likely to sequester potentially harmful free iron (Corsi et al, 2002; Drysdale et al, 2002), and in human tissues has a highly restricted expression in erythroid cells and testis (Santambrogio et al, 2007; Arosio & Levi, 2010).

Frequent Mutations in MDS-Associated Genes Likely to Indicate Clonal Hematopoiesis

Mutated Gene[†]	Typical Somatic Mutation Type and Locations[‡‡]	Overall Incidence	Clinical Significance
TET2	Nonsense or Frameshift Missense: any in codons 1134–1444 or 1842–1921	20%–25%	Associated with normal karyotypes. More frequent in CMML (40%–60%).
DNMT3A	Nonsense or Frameshift Missense in codon R882	12%–18%	Associated with a poor prognosis.
TP53	Nonsense or Frameshift Missense: any codon ***except*** P47S and P72R	8%–12%	Independently associated with a poor prognosis. More frequent with complex karyotypes (50%) and del(5q) (15%–20%). May predict resistance or relapse to lenalidomide.
SF3B1	Missense: E622, Y623, R625, N626, H662, T663, K666, K700E, I704, G740, G742, D781	18%–30%	Strongly associated with ring sideroblasts and more frequent in RARS (80%). Associated with a more favorable prognosis.
SRSF2	Missense: P95	10%–15%	More frequent in CMML (40%–50%) and associated with a poor prognosis.
U2AF1	Missense: S34, Q157	8%–12%	Associated with a poor prognosis.
ZRSR2	Nonsense or Frameshift	5%–10%	Associated with a poor prognosis.
ASXL1	Nonsense or Frameshift	15%–25%	Independently associated with a poor prognosis in MDS and CMML. More frequent in CMML (40%–50%).
RUNX1	Nonsense or Frameshift Missense: any in codons 100–210	10%–15%	Independently associated with a poor prognosis in MDS. May be familial in very rare cases.
EZH2	Nonsense or Frameshift Missense: any in codons 622–732 (***except*** Y646)	5%–10%	Independently associated with a poor prognosis in MDS and MDS/MPN. More frequent in CMML (12%).
NRAS	Missense: G12, G13, Q61	5%–10%	Associated with a poor prognosis, particularly in patients predicted to have lower-risk MDS. More frequent in CMML and JMML (~15%).
CBL	Missense: any in codons 366-420	<5%	More frequent in CMML (10%–20%) and JMML (15%).
JAK2	Missense: V617F	<5%	More frequent in RARS-T (50%).
SETBP1	Missense: E858, D868, S869, G870, I871, D880	<5%	Associated with disease progression. More frequent in CMML (5%–10%) and JMML (7%).
IDH1	Missense: R132	<5%	More frequent in AML.
IDH2	Missense: R140Q, R172	<5%	More frequent in AML.
ETV6	Nonsense or Frameshift	<5%	Independently associated with a poor prognosis.

Frequent pathway mutations of splicing machinery in myelodysplasia

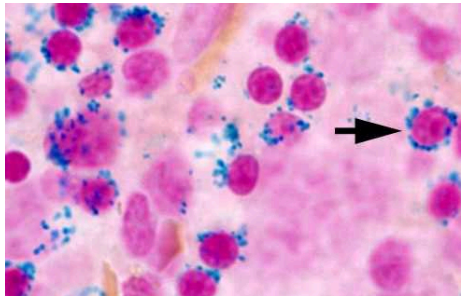




Nature. 2011 Sep 11;478(7367):64-9

SPLICING

- ***splicing*** Processo di trasformazione (maturazione) di una molecola di RNA mediato dalla rimozione di alcune sequenze (introni) e dall'unione di quelle rimanenti con formazione di un RNA maturo per le successive funzioni (in partic., per la traduzione, nel caso dell'mRNA). Lo s. riguarda sia i tRNA, sia gli rRNA che, soprattutto, gli mRNA. Il trascritto primario di ogni gene che codifica una proteina (pre-mRNA) ha infatti la stessa organizzazione del gene stesso. Esso contiene brevi tratti di RNA codificanti i polipeptidi (esoni) intervallati da lunghe regioni, spesso con funzione regolativa, non codificanti (introni). Un tipico gene di mammifero è distribuito su 16 kb di cui solo una piccola parte codificante; a seguito della rimozione degli introni, l'mRNA ha una lunghezza media di circa 2,2 kb. Lo s., insieme ad altre modificazioni degli RNA di nuova sintesi, ha luogo nel nucleo della cellula.



Mutations of SF3B1 (25-30% of MDS)

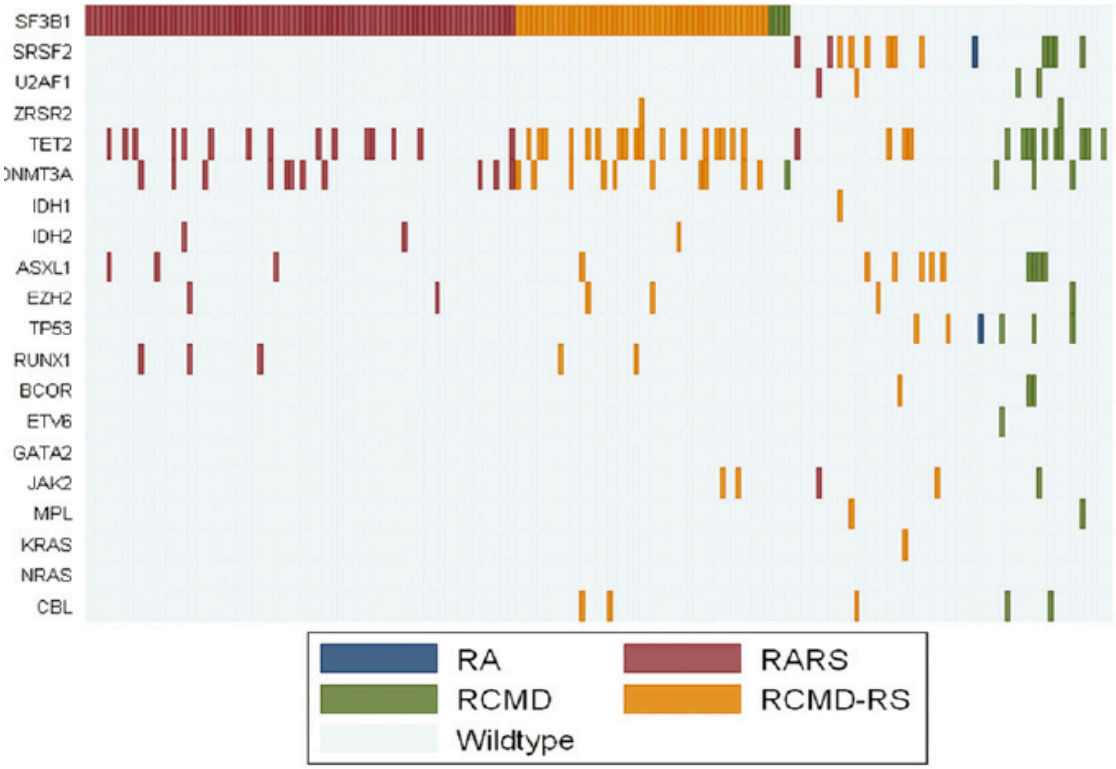
***SF3B1*, a gene encoding a core component of RNA splicing machinery**

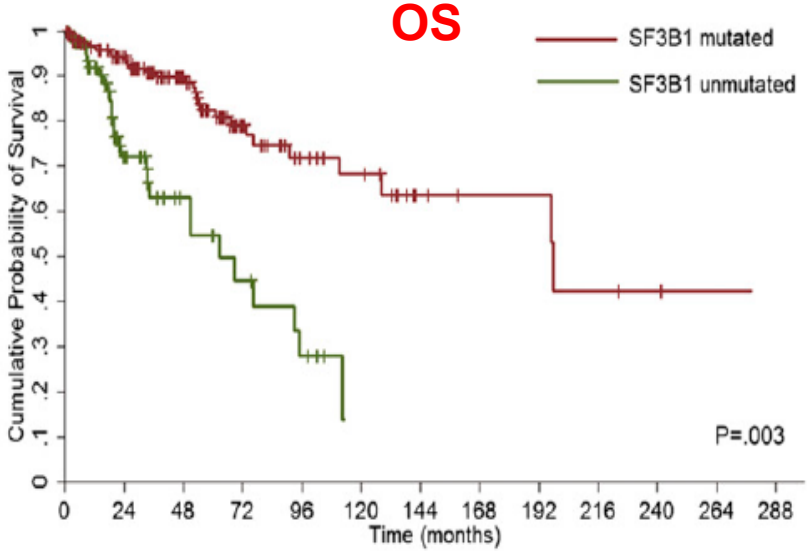
Subtype	N. pts	SF3B1 mutation (%)
Myelodysplastic syndromes		
RA	122	14 (11.5%)
RARS	105	83 (79.0%)
RCMD	96	6 (6.3%)
RCMD-RS	52	30 (57.7%)
RAEB-1	83	7 (8.4%)
RAEB-2	53	6 (11.3%)
MDS del(5q)	22	4 (18.2%)
Myelodysplastic/myeloproliferative neoplasms		
CMML	62	4 (6.5%)
RARS-T	18	12 (66.7%)
MDS/MPN-U	3	0

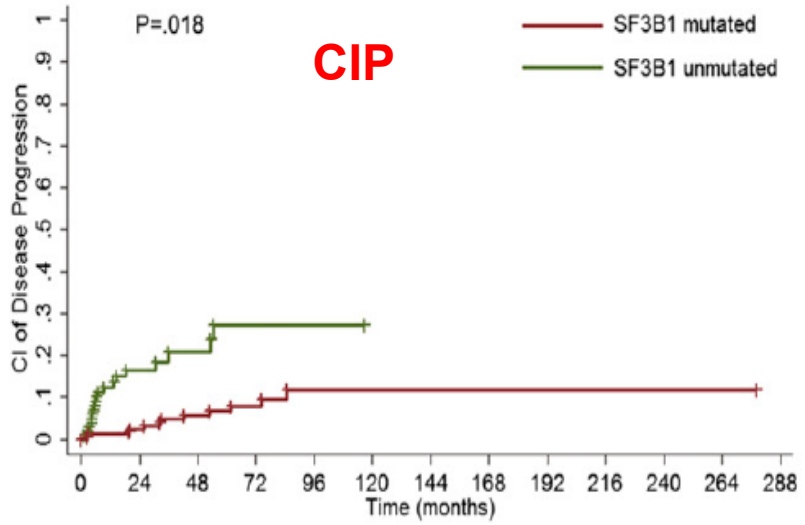
Malcovati et al, Blood 2011

MDS con Mutazione di SF3B1

- n=293 pazienti con neoplasie mieloidi e >1% sideroblasti ad anello (RS)
- SF3B1 mutata nell'81% delle RARS o RCMD-RS







- Le MDS con RS non-mutate per SF3B1 presentano displasia multilineare e prognosi sfavorevole

Malcovati E et al. Blood 2015

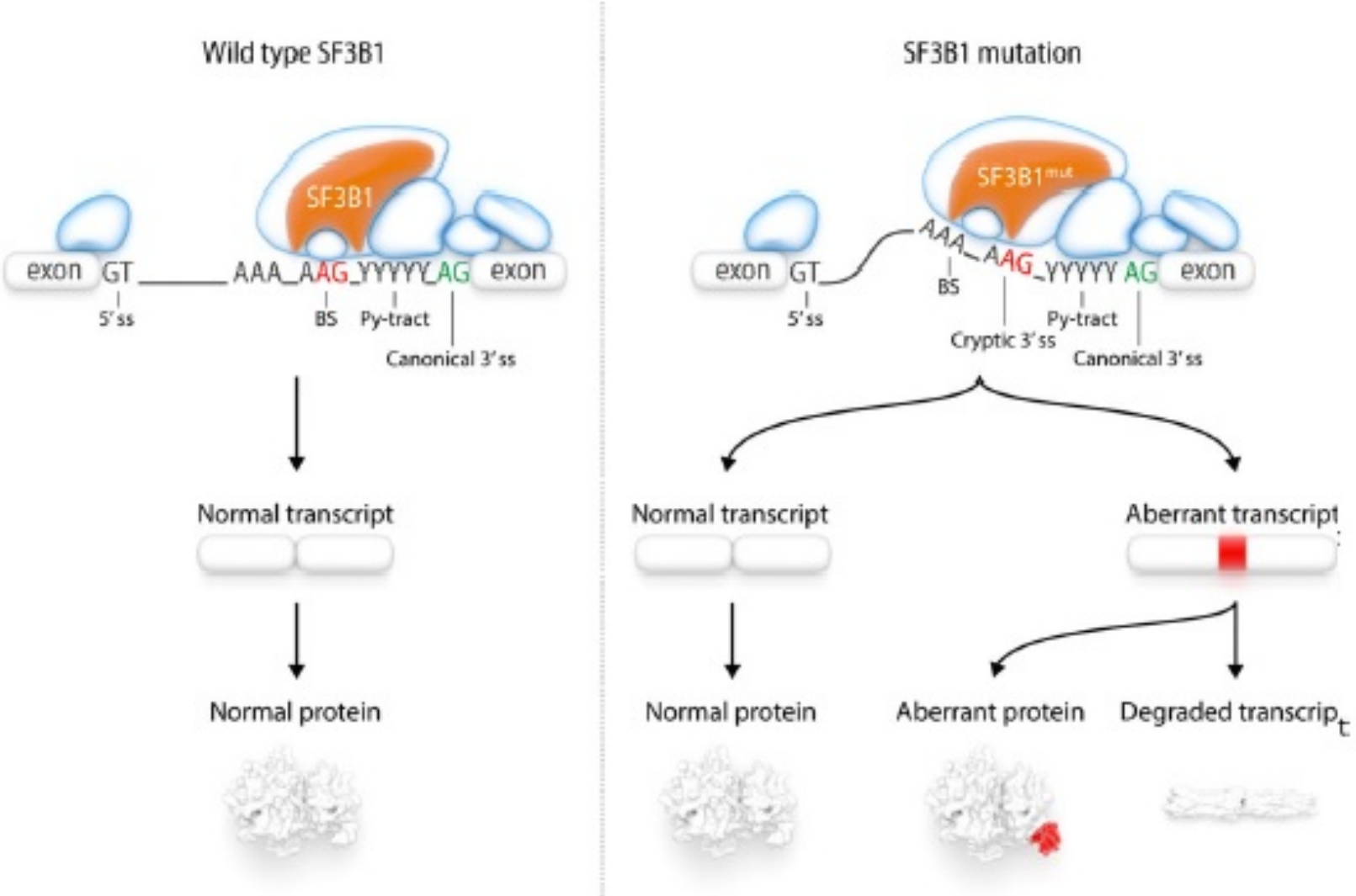


Fig 2. Schematic representation of RNA splicing in wild type and mutant SF3B1 cells. (A) The SF3B1 protein is a core component of the U_{12} small nuclear ribonucleoprotein, involved in the recognition of the branch point sequence during selection of the 3′ splice site in RNA splicing. (B) *SF3B1* mutations result in misrecognition of 3′ splice sites, by utilizing a cryptic AG sequence. Based on the position of premature termination codons, aberrant mRNA transcripts that contain premature stop codons are then subjected to degradation by NMD pathway.

British Journal of Haematology, 1982, **50**, 55–62

Quantitative evaluation of erythropoietic activity in dysmyelopoietic syndromes

M. CAZZOLA, G. BAROSI,* C. BERZUINI,† M. DACCO', ESTER ORLANDI,* M. STEFANELLI† AND E. ASCARI *Istituto di Patologica Medica, * Clinica Medica I 'A. Ferrata', and †Istituto di Informatica e Sistemistica, University of Pavia, Pavia, Italy*

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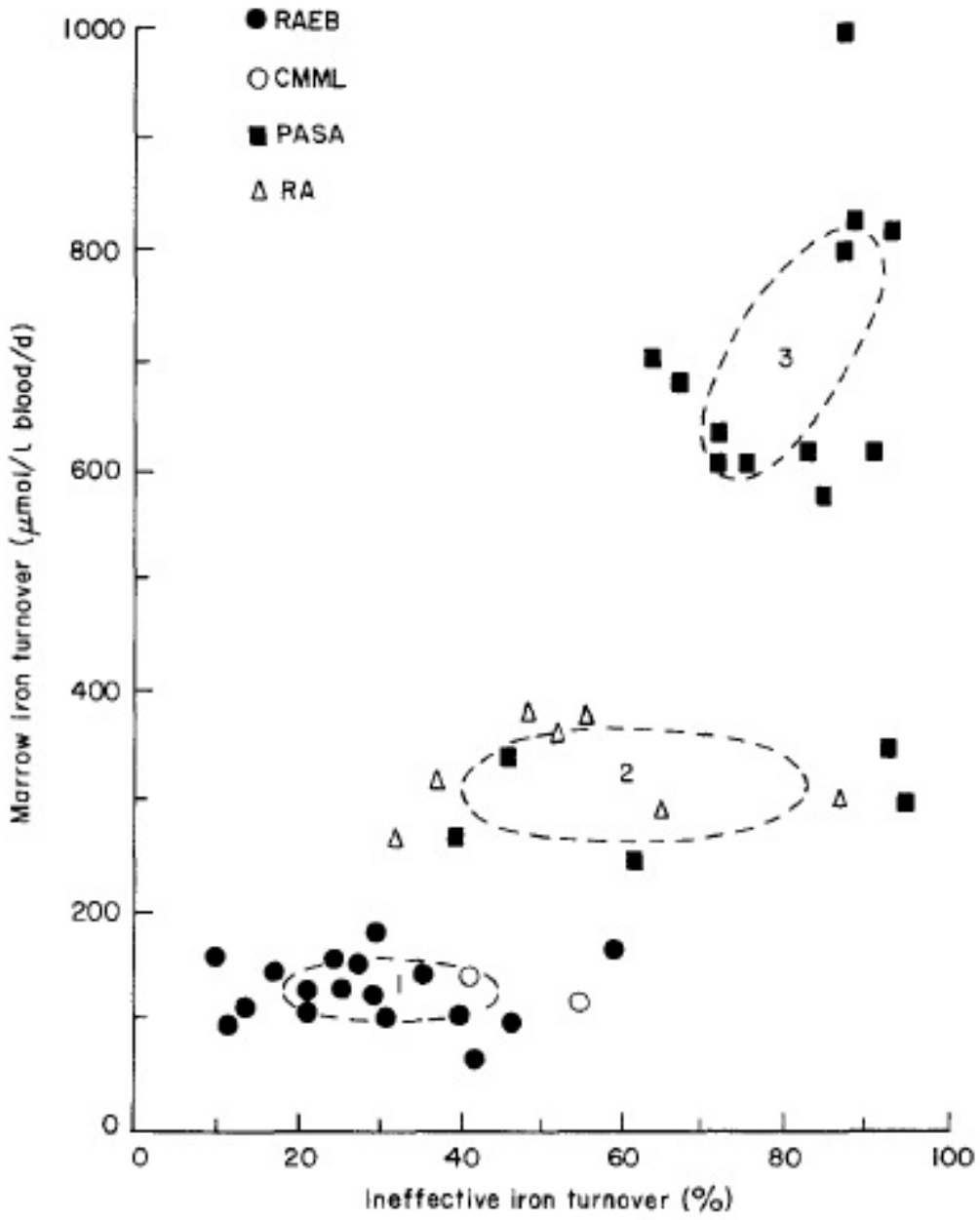
RAEB
CMML
PASA
RA
1000
800
600
400
200
0
0
20
40
60
80
100
Marrow iron turnover (μmol/l blood/d)
Ineffective iron turnover (%)
1
2
3

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SF3B1-mutated myelodysplastic syndrome with ring sideroblasts harbors more severe iron overload and corresponding over-erythropoiesis

Yang Zhu, Xiao Li*, Chunkang Chang, Feng Xu, Qi He, Juan Guo, Ying Tao, Yizhi Liu, Li Liu, Wenhui Shi

Department of Haematology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

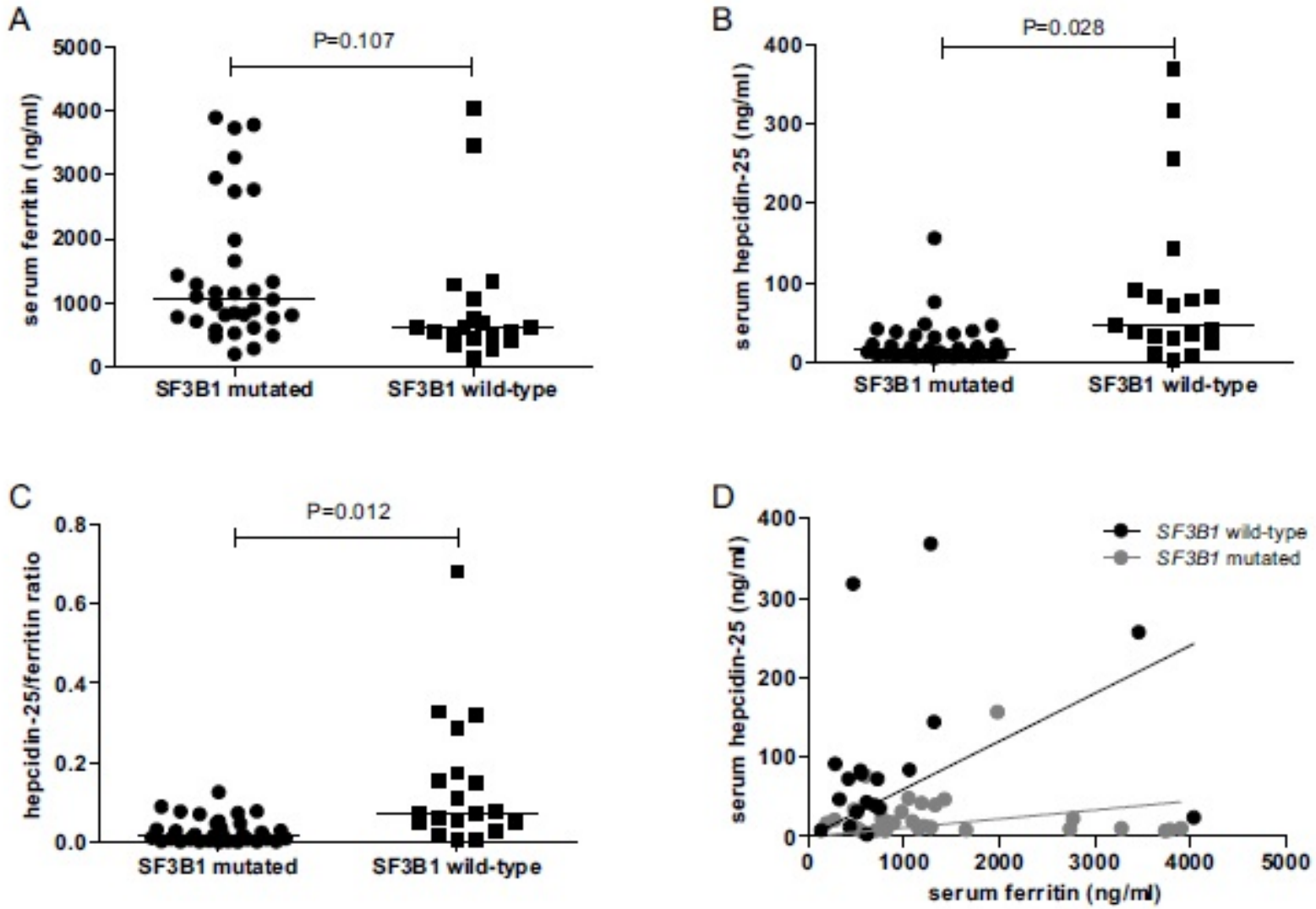


Fig. 4. Serum ferritin and hepcidin-25 levels in MDS-RS patients.
(A) Comparison of serum ferritin according to *SF3B1* mutational status ($P = 0.107$).
(B) Comparison of serum hepcidin-25 concentration according to *SF3B1* mutational status ($P = 0.028$).
(C) Comparison of serum hepcidin-25/ferritin ratio according to *SF3B1* mutational status ($P = 0.012$).
(D) Linear correlation between hepcidin and serum ferritin according to *SF3B1* mutational status in patients with MDS-RS.

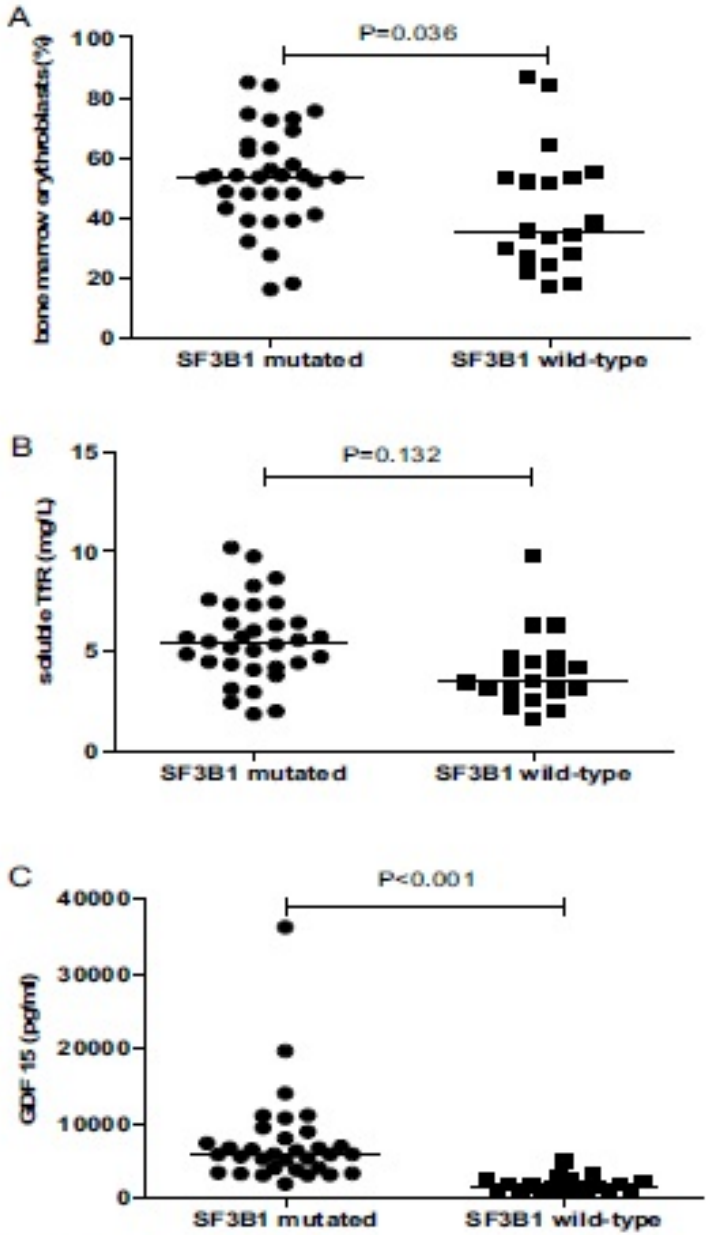
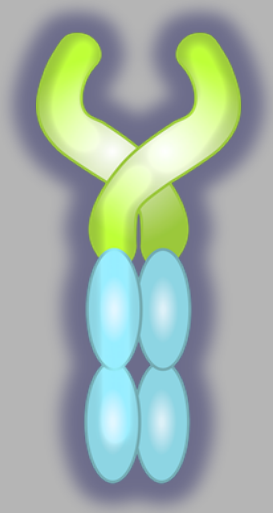
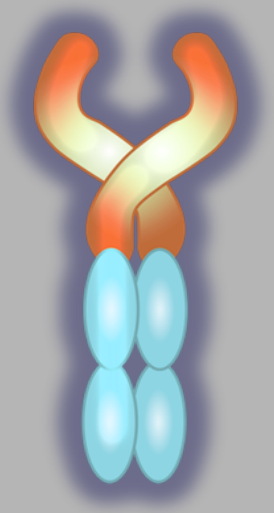


Fig. 5. Indicators related with erythropoietic activity in MDS-RS patients.
(A) Comparison of the percentage of BM erythroblasts according to *SF3B1* mutational status ($P = 0.036$).
(B) Comparison of soluble transferring receptor level according to *SF3B1* mutational status ($P = 0.132$).
(C) Comparison of serum GDF-15 concentration according to *SF3B1* mutational status ($P < 0.001$).

Sotatercept and Luspatercept: Novel Ligand Traps for TGF-β Superfamily Ligands

	Sotatercept[1,2]	Luspatercept[3,4]
Fusion proteinS with ligand trap activity toward the activin type 2 receptors[2,3]	Extracellular domain of **ActRIIA**	Modified extracellular domain of **ActRIIB**
Do not bind EPO receptors[2,3]	Fc domain of human IgG_1 antibody	Fc domain of human IgG_1 antibody
Heme effect[2,3]	+	+
Bone effect[5]	+	–





1. Komrokji R, et al. *Blood.* 2014;124(21) [poster presentation; abstract 3251]. 2. Carrancio S, et al. *Br J Haematol.* 2014;165(6):870-882. 3. Suragani R, et al. *Nat Med*. 2014;20(4):408-414. 4. Platzbecker U, et al. *Blood.* 2014;124(21) [oral presentation; abstract 411]. 5. Iancu-Rubin C, et al. *Exp Hematol*. 2013;41(12):155-166.e17.

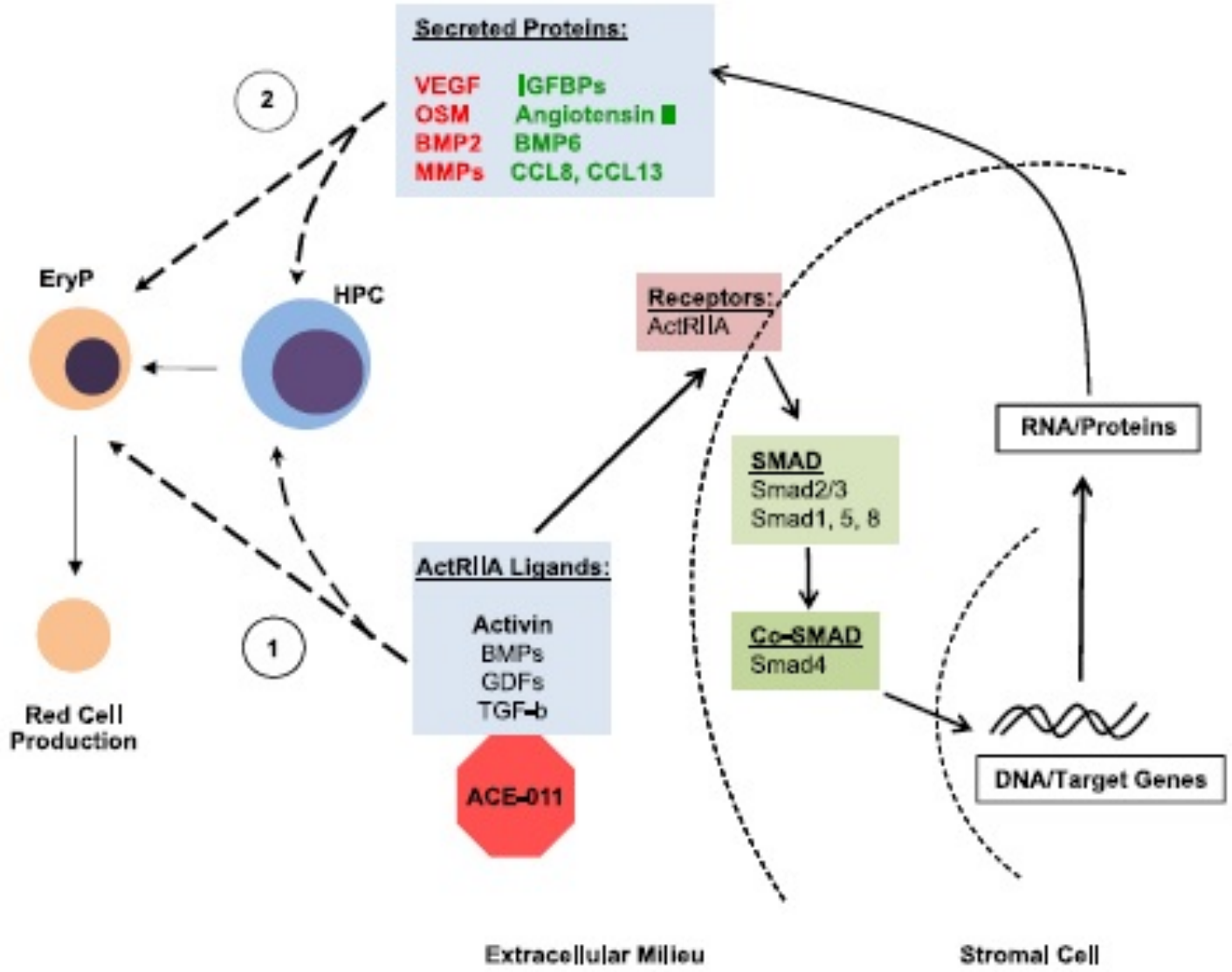
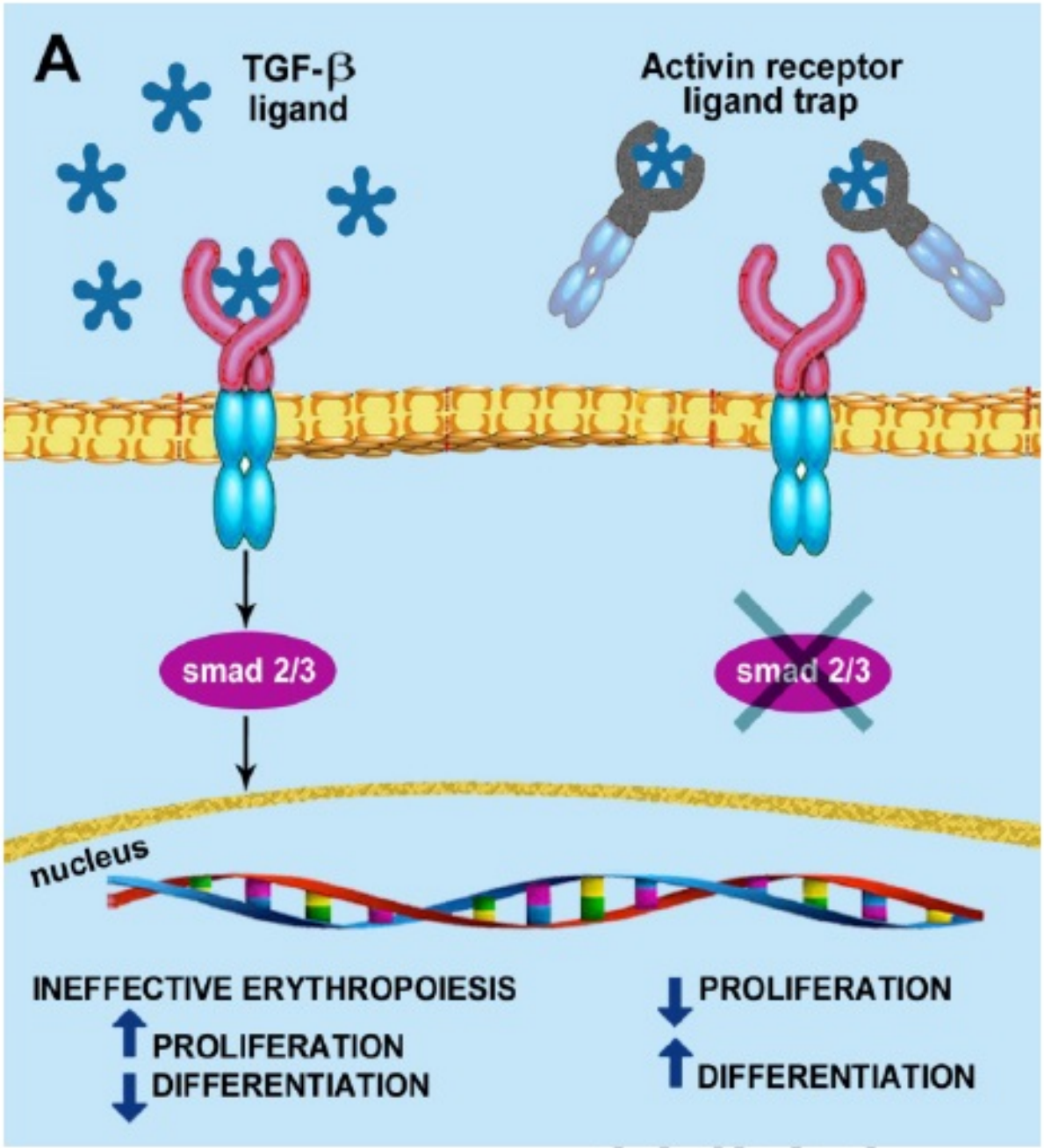


Figure 5. Schematic representation of the potential mechanisms underlying ACE-011 effects on erythropoiesis. (1) By binding ActIIA ligands, ACE-011 can modulate their direct or indirect functions in erythroid development. (2) By neutralizing TGF-β family members, ACE-011 can modulate the SMAD intracellular signaling pathway, which can result in changes in the transcription of SMAD target genes that encode secreted proteins with inhibitory or stimulatory roles at different stages of erythropoiesis. ActIIRA = activin receptor type IIA; BMPs = bone morphogenetic proteins; CCL = chemokine (C-C motif) ligand; EryP = erythroid precursors; GDF = growth differentiation factor; HPC = hematopoietic progenitor cells; IGFBP = insulin growth factor binding protein; OSM = oncostatin M; MMP = matrix metalloproteinase; TGF-β = transforming growth factor beta; VEGF = vascular endothelial growth factor.


A
TGF-β ligand
Activin receptor ligand trap
smad 2/3
smad 2/3
nucleus
INEFFECTIVE ERYTHROPOIESIS
PROLIFERATION
DIFFERENTIATION
PROLIFERATION
DIFFERENTIATION

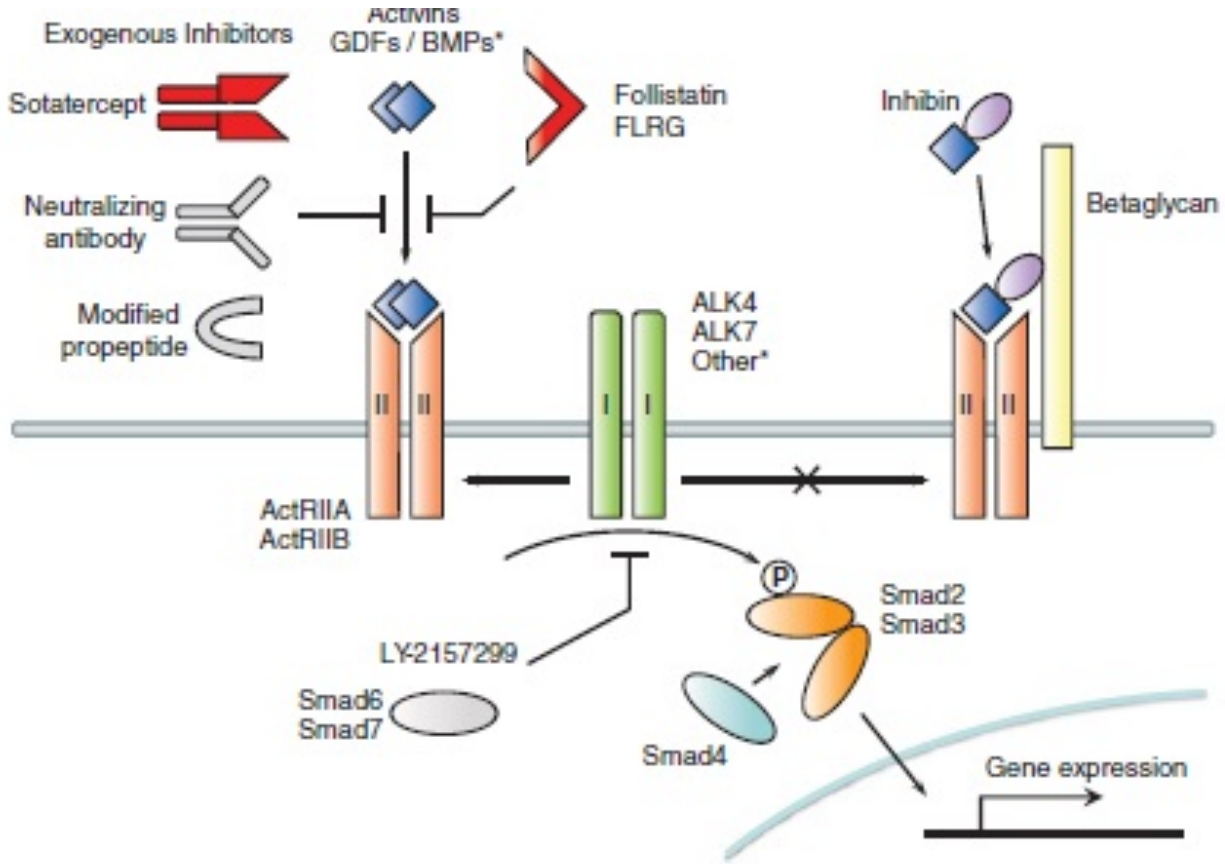
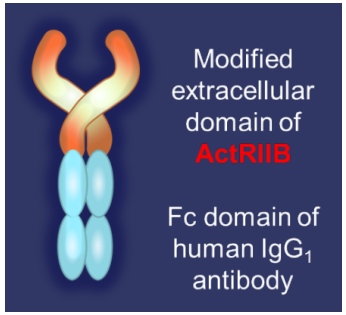


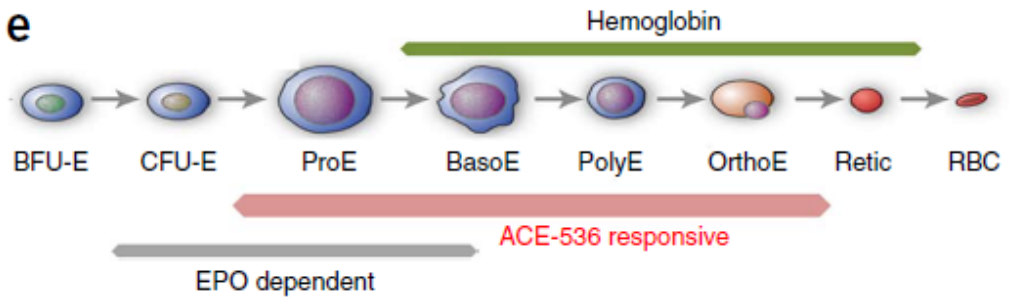
Figure 2. Activin receptor signaling pathway and exogenous inhibitors. Activins and some GDFs bind type II receptor (e.g., ActRIIA) with high affinity and trigger formation of a ternary complex with type I receptor (e.g., ALK4). Activated type I receptor then phosphorylates Smad2/3 (regulatory Smads), which form a heteromeric complex with Smad4 (co-Smad) that translocates to the nucleus and regulates gene expression. Smad6/7 (inhibitory Smads) mediate feedback on kinase activity of type I receptors, and small molecule inhibitors (e.g., LY-2157299) also target this activity in ALK4, ALK7, and ALK5. Sotatercept is an ActRIIA fusion protein that sequesters activins and related ligands in a manner similar to that of the endogenous traps follistatin and FLRG. Inhibins competitively inhibit binding of activins and BMPs to type II receptor (facilitated by betaglycan) and thereby prevent assembly of active ternary complex. Neither neutralizing antibodies nor modified propeptide domains related to this pathway have reached a clinical stage of development.

*ActRIIA/ActRIIB may mediate BMP signaling via the Smad1/5/8 pathway under some conditions.

ActRII: Activin receptor type II; ALK: Activin receptor-like kinase; BMP: Bone morphogenetic protein; FLRG: Follistatin-related gene; GDF: Growth and differentiation factor; Smad: Protein homolog of SMA (small body size) in *C. elegans* and MAD (mothers against decapentaplegic) in *Drosophila*.

Luspatercept-ACE536

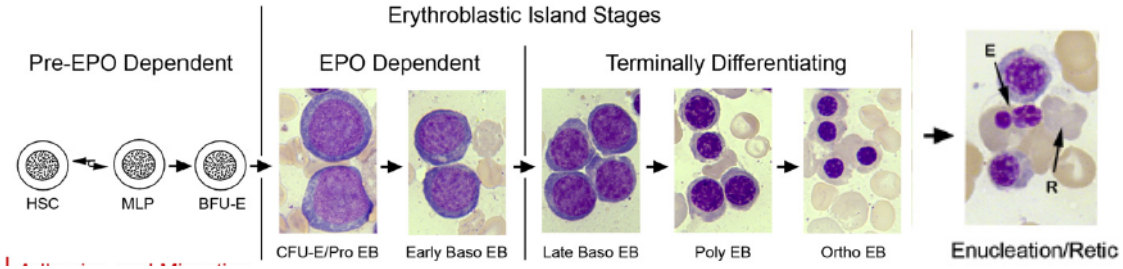




- È una proteina di fusione tra dominio extracellulare modificato del recettore di tipo IIB dell'activina *(ActRIIB)* e la porzione Fc dell'IgG umana

- Agisce come *ligand trap di vari ligandi di TGF-β.*

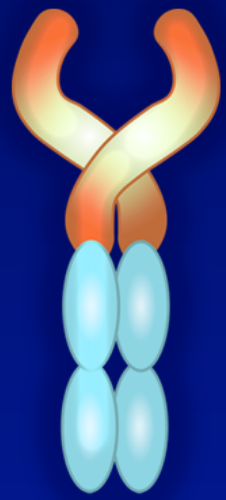
- *tra cui* GDF11, regolatore negativo degli stadi tardivi della differenziazione eritroide →da cui l'**inibizione del signaling Smad2/3**



1.Attie, K et al Am J Hematol 2014;89:766
2.Suragani R, et al. *Nat Med.* 2014;20(4):408-414.

Luspatercept: Overview

- Modified extracellular domain of activin receptor type IIB (ActRIIB) linked to the Fc protein of human IgG
  - Modified to decrease binding to activin A
- Binds to ligands in the TGF-β superfamily (GDF11) **that regulate late-stage erythropoiesis** and inhibits Smad2/3 signaling
- SMAD2/3 is constitutively activated in the hematopoietic progenitors, resulting in ineffective erythropoiesis[1]

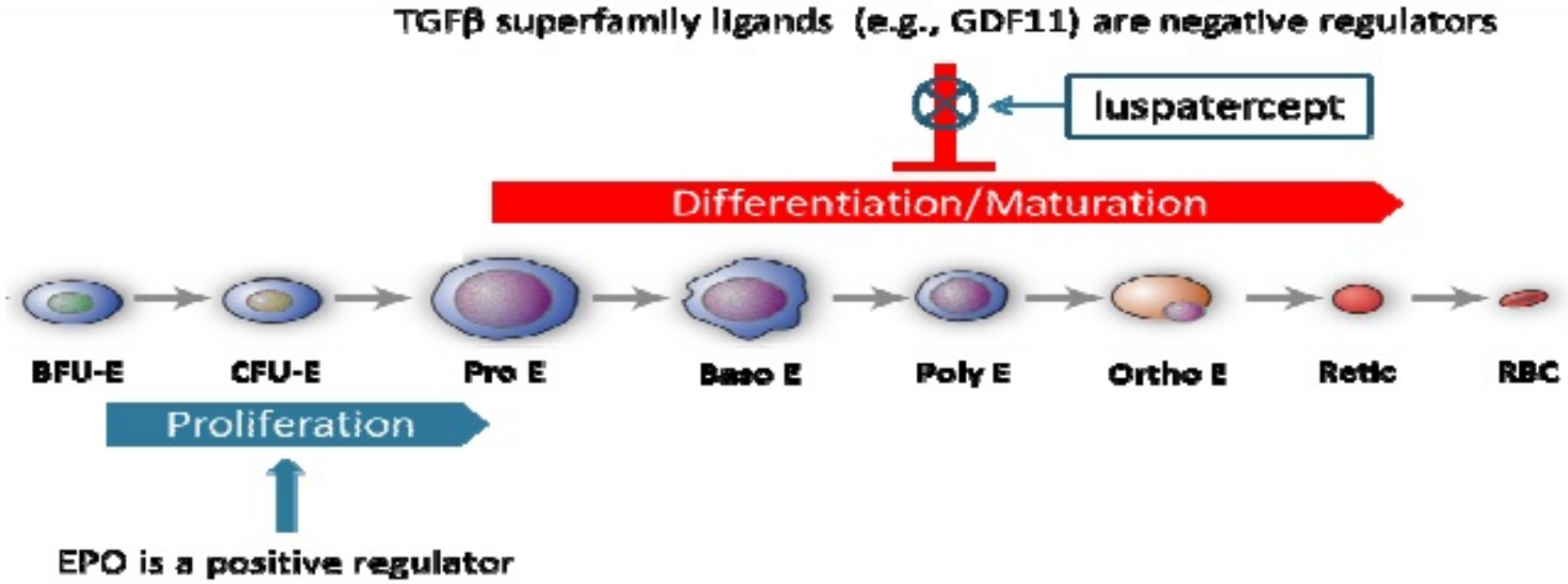


Modified extracellular domain of **ActRIIB**

Fc domain of human IgG_1 antibody

Suragani R, et al. *Nat Med.* 2014;20:408-414.

Mechanism of Action of Luspatercept

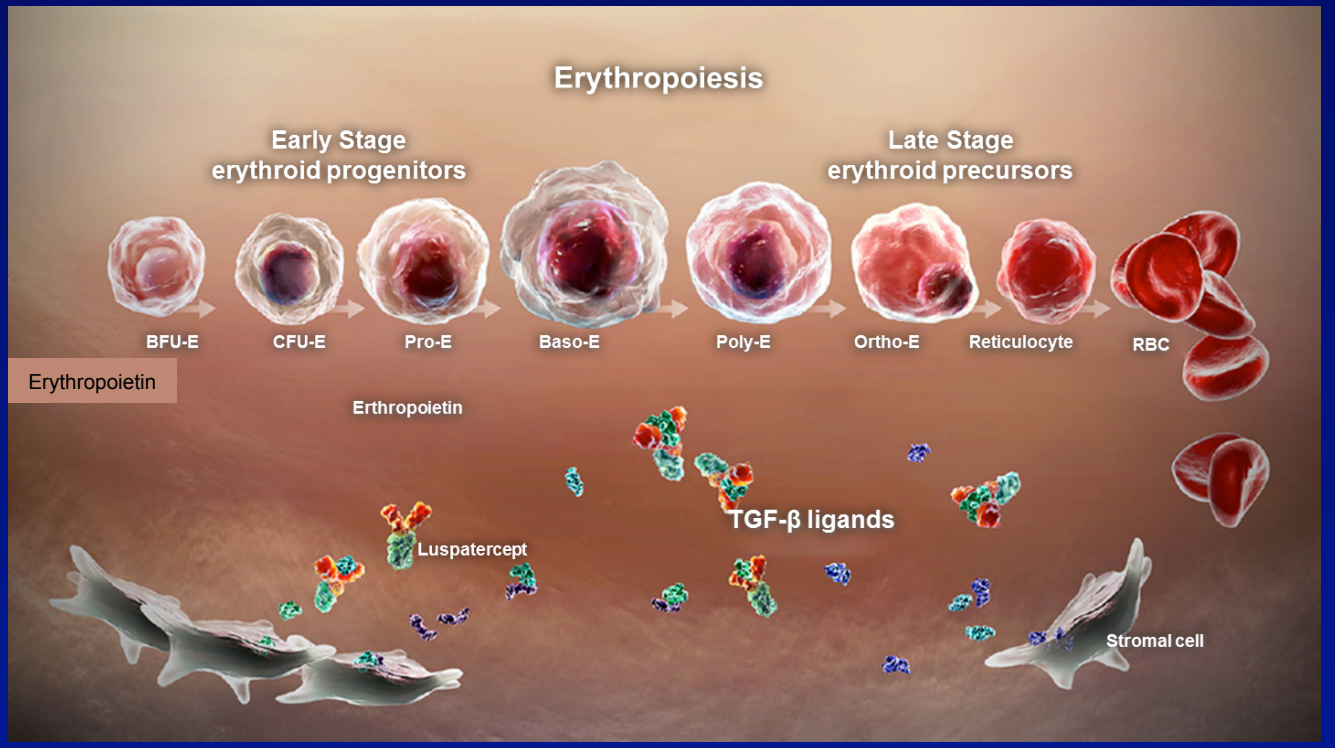


- Novel mechanism of action on endogenous inhibitors of late stage erythropoiesis to increase release of mature erythrocytes
- EPO stimulates proliferation and differentiation of early erythroid progenitors and ACE-536 promotes erythrocyte maturation which acts during the later stages of erythropoiesis
- The increase in RBC occurs without affecting the populations of EPO-responsive cells (BFU-E and CFU-E).

Suragani R et al., Nature Med 2014

Luspatercept: Hypothesized Mechanism of Action

- In preclinical murine models, luspatercept[2]:
  - **Promoted maturation of late-stage erythroid precursors in vivo**
  - **Increased RBC, hematocrit, and Hb levels in a dose-dependent manner**
- In a phase I clinical trial in healthy post-menopausal women[4]:
  Luspatercept stimulated RBC production and increased Hb levels at effective dose levels



JOURNAL OF BONE AND MINERAL RESEARCH
Volume 24, Number 4, 2009
Published online on December 1, 2008; doi: 10.1359/JBMR.081208

Single-Dose, Randomized, Double-Blind, Placebo-Controlled Study of ACE-011 (ActRIIA-IgG1) in Postmenopausal Women*

Jon Ruckle,[1] Mark Jacobs,[1] William Kramer,[2] Amelia E Pearsall,[3] Ravindra Kumar,[3] Kathryn W Underwood,[3] Jasbir Seehra,[3] Yijun Yang,[3] Carolyn H Condon,[3] and Matthew L Sherman[3]

ABSTRACT: The effects of ACE-011 on safety, pharmacokinetics, and bone biomarkers were evaluated in healthy, postmenopausal women. Our data indicate that ACE-011 results in a sustained increase in biomarkers of bone formation and reduction in markers of bone resorption. The activin type IIA receptor (ActRIIA) is the high-affinity receptor for activin. ACE-011 is a dimeric fusion protein consisting of the extracellular domain of the human ActRIIA linked to the Fc portion of human IgG1. ACE-011 binds to activin, preventing activin from binding endogenous receptors. A randomized, double-blind, placebo-controlled study was conducted to evaluate the safety and tolerability of ACE-011. Forty-eight healthy, postmenopausal women were randomized to receive either a single dose of ACE-011 or placebo and were followed for 4 mo. Dose levels ranged from 0.01 to 3.0 mg/kg intravenously and from 0.03 to 0.1 mg/kg subcutaneously. Safety and pharmacokinetic (PK) analyses and the biological activity of ACE-011, as assessed by markers of bone turnover, and follicle stimulating hormone (FSH) levels were measured. No serious adverse events (AEs) were reported. AEs were generally mild and transient. The PK of ACE-011 was linear over the dose range studied, with a mean half-life of 24–32 days. The absorption after subcutaneous dosing was essentially complete. ACE-011 caused a rapid and sustained dose-dependent increase in serum levels of bone-specific alkaline phosphatase (BSALP) and a dose-dependent decrease in C-terminal type 1 collagen telopeptide (CTX) and TRACP-5b levels. There was also a dose-dependent decrease in serum FSH levels consistent with inhibition of activin. ACE-011 is a novel agent with biological evidence of both an increase in bone formation and a decrease in bone resorption. ACE-011 may be an effective therapy in a variety of diseases involving bone loss.
J Bone Miner Res 2009;24:744–752. Published online on December 1, 2008; doi: 10.1359/JBMR.081208

Key words: ACE-011, activin, anabolic, osteoporosis, bone biomarkers

The Journal of Clinical Pharmacology
53(11) 1121–1130

DOI: 10.1002/jcph.160

Multiple-Dose, Safety, Pharmacokinetic, and Pharmacodynamic Study of Sotatercept (ActRIIA-IgG1), a Novel Erythropoietic Agent, in Healthy Postmenopausal Women

Matthew L. Sherman, MD[1], Niels G. Borgstein, MD[1], Louisa Mook, MD[1], Dawn Wilson, BS[1], Yijun Yang, ScD[1], Nianhang Chen, PhD[2], Ravindra Kumar, PhD[1], Kenneth Kim, MD[3], and Abderrahmane Laadem, MD[2]

Abstract

Ligands of the transforming growth factor-beta superfamily and activin-receptor signaling play an important role in erythropoiesis. Sotatercept, an activin receptor type IIA (ActRIIA) ligand trap, is a novel, recombinant, fusion protein comprising the extracellular domain of human ActRIIA linked to the Fc portion of human immunoglobulin G1. Sotatercept, originally developed to increase bone mineral density, was noted to have robust effects on erythropoiesis. Here, we evaluated the safety, pharmacokinetic properties, and pharmacodynamic effects of sotatercept in 31 healthy postmenopausal women. Sotatercept was administered at dose level 0.1, 0.3, or 1 mg/kg every 28 days subcutaneously for up to four doses. Sotatercept was generally safe and well tolerated, and elicited clinically significant, dose-dependent increases in hemoglobin, hematocrit, and red blood cell counts that persisted for up to 4 months. The effect of sotatercept on hemoglobin was dose-limiting. Sotatercept also increased bone mineral density and biomarkers of bone formation. The sotatercept serum exposure–dose relationship was linear, with a mean terminal half-life of approximately 23 days. ActRIIA ligands are important regulators of erythrocyte production in healthy individuals. Clinical studies are ongoing to explore the potential of sotatercept to treat anemia and diseases of ineffective erythropoiesis as well as an agent to increase bone mineral density.

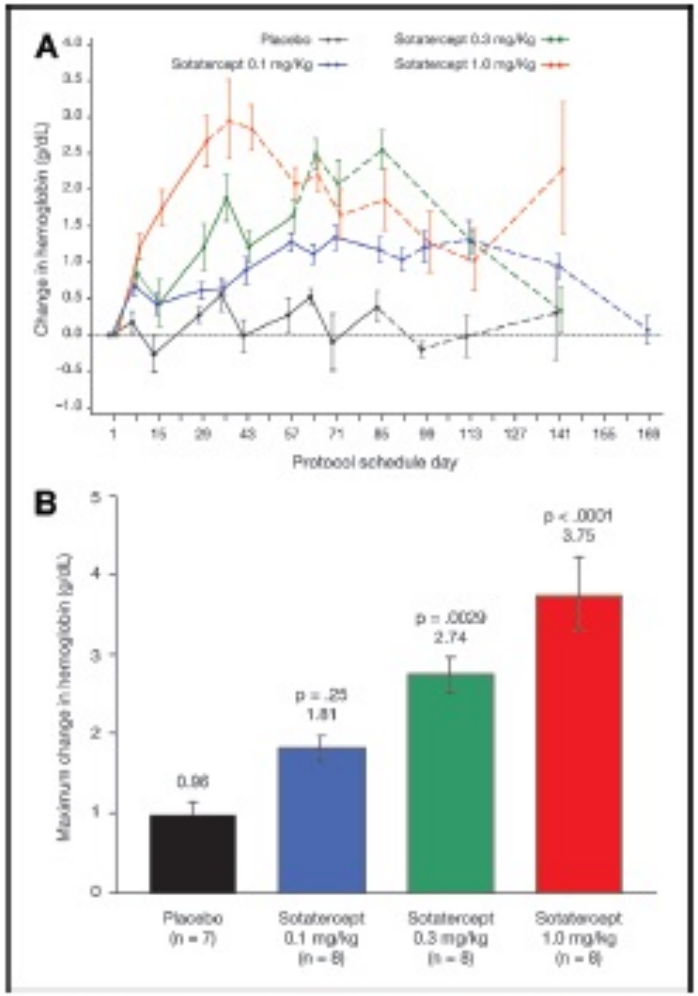


Figure 2. Effects of sotatercept on hemoglobin levels and red blood cell counts. (A) Mean change in hemoglobin levels from baseline over time (days post-first dose) by treatment group. For each dose, the solid line represents the dosing period, and the dashed line represents the follow-up period (i.e., visits after the last dose). The last dose of 0.1 mg/kg (four doses), 0.3 mg/kg (three doses), and 1 mg/kg sotatercept (two doses) was administered on study days 85, 57, and 29, respectively. Error bars show standard error of the mean (SEM). (B) Mean maximum change in hemoglobin from baseline after the initial dose by treatment group. Error bars indicate SEM. p-values show differences compared with placebo.

The elevated hemoglobin levels returned toward

A phase 1 study of ACE-536, a regulator of erythroid differentiation, in healthy volunteers

Kenneth M. Attie,[1]* Mark J. Allison,[2] Ty McClure,[1] Ingrid E. Boyd,[1] Dawn M. Wilson,[1] Amelia E. Pearsall,[1] and Matthew L. Sherman[1]

ACE-536, a recombinant protein containing a modified activin receptor type IIB, is being developed for the treatment of anemias caused by ineffective erythropoiesis, such as thalassemias and myelodysplastic syndromes. ACE-536 acts through a mechanism distinct from erythropoiesis-stimulating agents to promote late-stage erythroid differentiation by binding to transforming growth factor-β superfamily ligands and inhibiting signaling through transcription factors Smad 2/3. The goal of this Phase 1 study was to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of ascending dose levels of ACE-536 in healthy volunteers. Thirty-two postmenopausal women were randomized in sequential cohorts of eight subjects each to receive up to two doses of either ACE-536 (0.0625–0.25 mg/kg) or placebo (3:1 randomization) given subcutaneously every 2 weeks. Mean baseline age was 59.4 years, and hemoglobin was 13.2 g/dL. ACE-536 was well tolerated at dose levels up to 0.25 mg/kg over the 1-month treatment period. There were no serious or severe adverse events, nor clinically meaningful changes in safety laboratory measures or vital signs. Mean ACE-536 AUC_{0-14d} and C_{max} increased proportionally after first dose; mean $t_{1/2}$ was 15–16 days. Dose-dependent increases in hemoglobin concentration were observed, beginning 7 days after initiation of treatment and maintained for several weeks following treatment. The proportion of subjects with a hemoglobin increase ≥1.0 g/dL increased in a dose-dependent manner to 83.3% of subjects in the highest dose group, 0.25 mg/kg. ACE-536 was well tolerated and resulted in sustained increases in hemoglobin levels in healthy postmenopausal women.

Am. J. Hematol. 89:766–770, 2014.

bjh research paper

Sotatercept in patients with osteolytic lesions of multiple myeloma

Kudrat M. Abdulkadyrov,[1] Galina N. Salogub,[2] Nuriet K. Khuazheva,[3] Matthew L. Sherman,[4] Abderrahmane Laadem,[5] Rachel Barger,[4] Robert Knight,[5] Shankar Srinivasan[5] and Evangelos Terpos[6]

[1]Russian Research Institute of Haematology and Blood Transfusion, [2]St Petersburg Pavlov State Medical University n.a. I.P. Pavlov, St Petersburg, [3]Municipal Clinical Hospital n.a. S.P., Moscow, Russia, [4]Acceleron Pharma Inc., Cambridge, MA, [5]Celgene Corporation, Summit, NJ, USA and [6]Department of Clinical Therapeutics, University of Athens School of Medicine, Alexandra General Hospital, Athens, Greece

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Correspondence: Evangelos Terpos, Department of Clinical Therapeutics, University of Athens School of Medicine, Alexandra General Hospital, 80 Vas. Sofias Av., 11528 Athens, Greece

Summary

This phase IIa study evaluated the safety and tolerability of sotatercept, and its effects on bone metabolism and haematopoiesis in newly diagnosed and relapsed multiple myeloma (MM) patients. Patients were randomized (4:1) to receive four 28-d cycles of sotatercept (0·1, 0·3, or 0·5 mg/kg) or placebo. Patients also received six cycles of combination oral melphalan, prednisolone, and thalidomide (MPT). Thirty patients were enrolled; six received placebo and 24 received sotatercept. Overall, 25% of patients received all four sotatercept doses; 71% of sotatercept-treated patients had ≥1 dose interruption mainly due to increases in haemoglobin levels. Grade ≥3 adverse events (AEs) were reported in 17% of patients receiving placebo and 58% receiving sotatercept. Grade 4 AEs in sotatercept-treated patients were neutropenia, granulocytopenia, and atrial fibrillation (one patient each). In patients without bisphosphonate use, anabolic improvements in bone mineral density and in bone formation relative to placebo occurred, whereas bone resorption was minimally affected. Increases in haemoglobin levels, *versus* baseline, and the duration of the increases, were higher in the sotatercept-treated patients, with a trend suggesting a dose-related effect. Multiple doses of sotatercept plus MPT appear to be safe and generally well-tolerated in MM patients.

Sotatercept in patients with osteolytic lesions of multiple myeloma (Abdulkadyrov KM, Br J Haematol 2014)

- Phase IIa study: 30 newly diagnosed and relapsed multiple myeloma (MM) pts (6 placebo, 24 sotatercept); all pts: six cycles of combination oral melphalan, prednisolone, and thalidomide (MPT)
- Evaluation of bone metabolism and haematopoiesis
- In patients without bisphosphonate use, anabolic improvements in bone mineral density and in bone formation relative to placebo occurred, whereas bone resorption was minimally affected.
- Increases in haemoglobin levels, versus baseline, and the duration of the increases, were higher in the sotatercept-treated patients, with a trend suggesting a dose-related effect.
- 25% of patients received all four sotatercept doses; 71% of sotatercept-treated patients had ≥1 dose interruption mainly due to increases in haemoglobin levels. Grade ≥3 adverse events (AEs): 17% of pts receiving placebo and 58% receiving sotatercept. Grade 4 AEs in sotatercept-treated patients were neutropenia, granulocytopenia, and atrial fibrillation (one patient each).

Sotatercept (ACE-011) for the treatment of chemotherapy-induced anemia in patients with metastatic breast cancer or advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens: results from two phase 2 studies

Haralambos Raftopoulos[1] · Abderrahmane Laadem[2] · Paul J. Hesketh[3] · Jerome Goldschmidt[4] · Nashat Gabrail[5] · Cynthia Osborne[6] · Muhammad Ali[7] · Matthew L. Sherman[8] · Ding Wang[9] · John A. Glaspy[10] · Marie Puccio-Pick[2] · Jun Zou[2] · Jeffrey Crawford[11]

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Sotatercept (ACE-011) for the treatment of chemotherapy-induced anemia in patients with metastatic breast cancer or advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens: results from two phase 2 studies (Raftopoulos H, Support Care Cancer 2016)

- In study A011-08, pts with metastatic breast cancer were randomized to 2:2:2:1 to receive sotatercept 0.1, 0.3, or 0.5 mg/kg, or placebo, respectively, every 28 days. In study ACE-011-NSCL-001, pts with solid tumors treated with platinum-based chemotherapy received sotatercept 15 or 30 mg every 42 days
- In the A011- 08 and ACE-011-NSCL-001 studies, more pts achieved a mean Hb increase of ≥1 g/dL in the combined sotatercept 0.3 mg/kg and 15 mg (66.7 %) group and sotatercept 0.5 mg/kg and 30 mg (38.9 %) group versus the sotatercept 0.1 mg/kg (0 %) group. No patients achieved a mean Hb increase of ≥1 g/dL in the placebo group.
- The incidence of treatment-related adverse events (AEs) was low in both studies, and treatment discontinuations due to AEs were uncommon

An activin receptor IIA ligand trap corrects ineffective erythropoiesis in β-thalassemia

Michael Dussiot[1–5,13], Thiago T Maciel[1–5,13], Aurélie Fricot[1–5], Céline Chartier[1–5], Olivier Negre[6,7], Joel Veiga[4], Damien Grapton[1–5], Etienne Paubelle[1–5], Emmanuel Payen[6,7], Yves Beuzard[6,7], Philippe Leboulch[6,7], Jean-Antoine Ribeil[1–4,8], Jean-Benoit Arlet[1–4], Francine Coté[1–4], Geneviève Courtois[1–4], Yelena Z Ginzburg[9], Thomas O Daniel[10], Rajesh Chopra[10], Victoria Sung[11], Olivier Hermine[1–4,12] & Ivan C Moura[1–5]

The pathophysiology of ineffective erythropoiesis in β-thalassemia is poorly understood. We report that RAP-011, an activin receptor IIA (ActRIIA) ligand trap, improved ineffective erythropoiesis, corrected anemia and limited iron overload in a mouse model of β-thalassemia intermedia. Expression of growth differentiation factor 11 (GDF11), an ActRIIA ligand, was increased in splenic erythroblasts from thalassemic mice and in erythroblasts and sera from subjects with β-thalassemia. Inactivation of GDF11 decreased oxidative stress and the amount of α-globin membrane precipitates, resulting in increased terminal erythroid differentiation. Abnormal GDF11 expression was dependent on reactive oxygen species, suggesting the existence of an autocrine amplification loop in β-thalassemia. GDF11 inactivation also corrected the abnormal ratio of immature/mature erythroblasts by inducing apoptosis of immature erythroblasts through the Fas–Fas ligand pathway. Taken together, these observations suggest that ActRIIA ligand traps may have therapeutic relevance in β-thalassemia by suppressing the deleterious effects of GDF11, a cytokine which blocks terminal erythroid maturation through an autocrine amplification loop involving oxidative stress and α-globin precipitation.

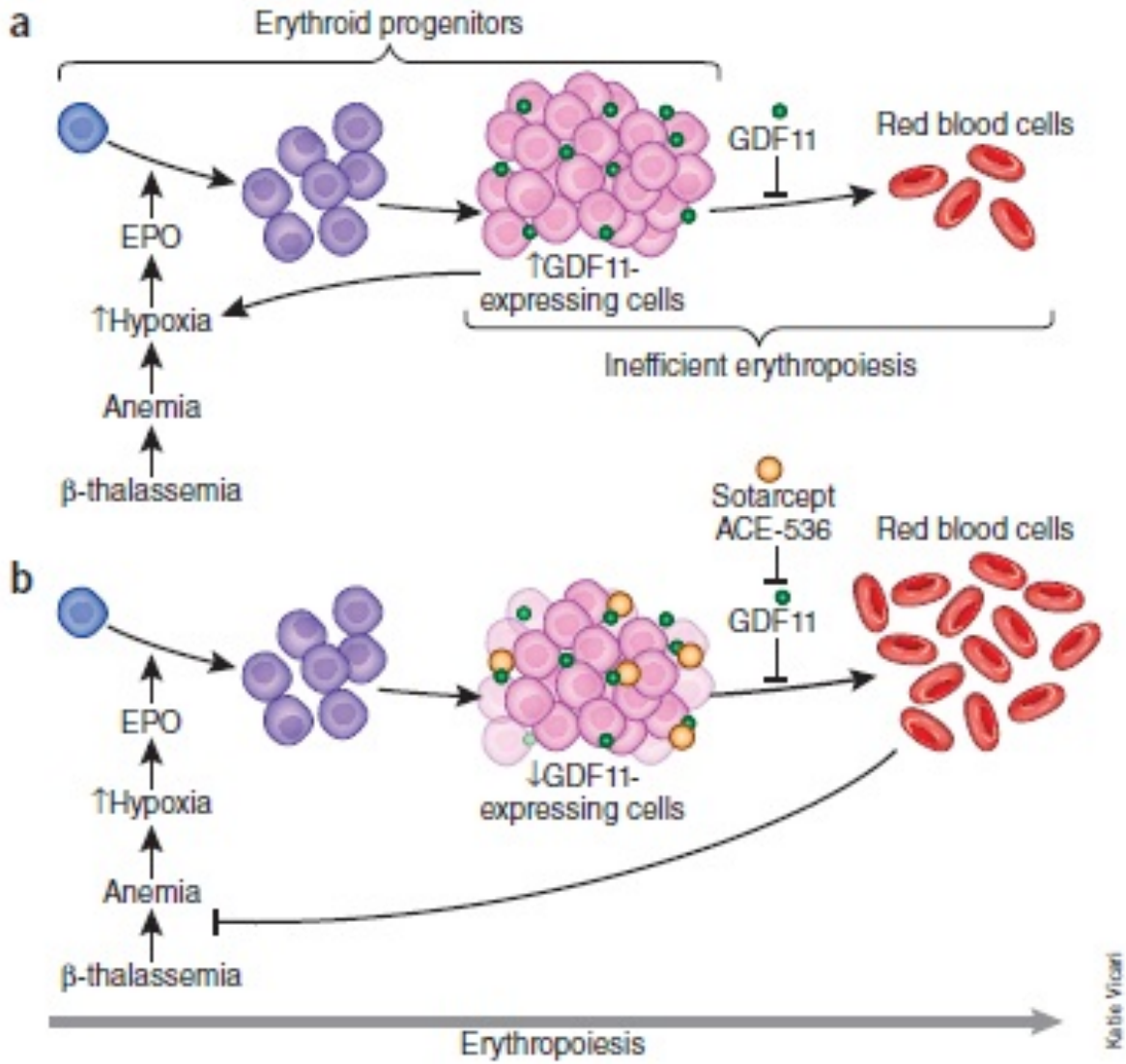

Figure 1 Relieving ineffective hematopoiesis with TGF-β ligand traps. (**a**) In β-thalassemia or MDS, defects in erythroid differentiation cause anemia leading to tissue hypoxia, which promotes the production of the erythroid differentiation hormone EPO. Defective erythroid differentiation in these syndromes results in an accumulation of GDF11-expressing erythroid progenitors. GDF11 maintains the survival of these progenitors and inhibits further differentiation, which further aggravates the ineffective erythropoiesis. (**b**) Dussiot *et al.*[3] and Suragani *et al.*[4] find that inhibiting GDF11 signaling with sotatercept or ACE-536 induces apoptosis of GDF11-expressing erythroid progenitors, restoring their ability to differentiate and, hence, alleviating the anemia.

Drug Trial name	Trial Number	Phase	Disease	N. of patients	Primary end-point	Status
Luspatercept [22,23]	NCT01749540/ Extension NCT02268409	Phase II Open-label, ascending dose study to evaluate the effects	TD and NTDT	64 (30 TD, 34 NTDT)	Proportion of patients who have an erythroid response: Hb increase of ≥ 1.5 g/dL from baseline for ≥ 14 days (in the absence of RBCs transfusions) in NTDT patients, or ≥ 20% reduction in RBC transfusion burden compared to pretreatment in TDT patients	Completed/ Active, not recruiting
Luspatercept BELIEVE study [27]	NCT02604433	Phase III Double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety plus BSC versus placebo plus BSC	TD	300	Proportion of subjects with hematological improvement from Week 13 to Week 24 compared to 12-week prior to randomization. Hematological improvement: ≥ 33% reduction from baseline in RBCs transfusion burden with a reduction of at least 2 units.	Recruiting
Sotatercept (ACE-011) [24]	NCT01571635	Phase IIA Dose finding study to determine the safety and tolerability	TD and NTDT	46	The PRD is be defined as the highest dose level at which no more than one out of six subjects experiences a DLT. RD is defined based on the review of the efficacy and safety parameters as well as dose modification data.	Active, not recruiting
Ruxolitinib TRUTH study [39]	NCT02049450	Phase II Study of efficacy and safety	TD	30	Percent change in RBC transfusion requirement between week 6 and week 30 and the baseline period between week -24 and the day before first study drug administration.	Completed
DFX in tablets ECLIPSE study [49]	NCT02125877	Phase II A randomized, open-label, multicenter, two arm study to investigate the benefits of an improved DFX formulation	TD	173	The percentage of participants with adverse events, serious adverse events and deaths was assessed. The percentage of participants with post-baseline laboratory values meeting specified criteria for notable/extended range was assessed.	Completed

Table I: Drugs in clinical trial for β-thalassemia. NTDT: non-transfusion dependent thalassemia, TDT: transfusion dependent thalassemia, Hb: hemoglobin, RBCs: red blood cells, BSC Best Supportive Care, PRD: potential recommended dose, RD: actual recommended dose, DLT: dose limiting toxicity, DFX: Deferasirox.

Luspatercept Increases Hemoglobin, Decreases Transfusion Burden and Improves Iron Overload in Adults with Beta-Thalassemia
Piga A et al. Blood 2016 128:851 (ASH 2016)

- 30 TD pts (base study), (24 extension study).
- 20/24 (83%) and 16/24 (67%) TD pts achieved a ≥ 33% and ≥ 50% decrease in transfusion burden over any 12-week period compared to baseline, respectively. Duration of response ranged from 12 to 48+ weeks.
- 34 NTD pts (base study), (27 extension study)
- 21/27 (78%) and 15/27 (56%) NTD pts achieved ≥ 1.0 g/dL and ≥ 1.5 g/dL increases, respectively, in mean Hgb over any 12-week period compared to baseline. Duration of response ranged from 16 to 72+ weeks, with no trend for lower Hgb response over time. 3/5 (60%) pts with baseline LIC ≥ 5 mg/g dw had a decrease in LIC ≥ 2 mg/g dw after at least 6 months of treatment; 8/9 (89%) patients with baseline LIC < 5 mg/g dw maintained LIC < 5 mg/g dw.
- AEs were mostly mild-moderate: bone pain, myalgia, arthralgia, headache, asthenia, and musculoskeletal pain.

INTERIM RESULTS FROM A PHASE 2A, OPEN-LABEL, DOSE-FINDING STUDY OF SOTATERCEPT (ACE-011) IN ADULT PATIENTS (PTS) WITH BETA-THALASSEMIA

M.D. Cappellini et al, Haematologica | 2015; 100(s1) | 17-18 (EHA 2015)

- 30 of 46 pts (65%) in the sotatercept 0.1, 0.3, 0.5, 0.75, and 1.0 mg/kg dose groups were NTD and 16 (35%) were TD).
- Of 30 NTD pts, 6, 6, 6, 7, and 5 were included in the different dose groups.
- Increased exposure was associated with higher mean Hb increases over 9 weeks for NTD pts (r =0.78, *P* <0.0001) and with reduced transfusion burden over 24 weeks for TD pts (r =0.74, *P* <0.01).
- Among TD pts evaluable for efficacy, 8 of 14 pts (57%) showed a ≥20% reduction in transfusion burden on treatment *versus* 6 month transfusion burden at baseline, whereas ≥50% reduction was observed for 1 of 5 pts in the 0.75 mg/kg dose group and 1 of 2 pts in the 1.0 mg/kg dose group.
- Overall, sotatercept was well tolerated and 25 of 46 pts (54%) remain on treatment; 19 (41%) pts have been on treatment for ≥1 year, 8 (17%) for ≥22 months, and 2 (4%) for ≥2 years. Grade ≥3 treatment-related AE leading to discontinuation were seen in 4 pts (worsening bone pain; ventricular extrasystoles ; hypertension)

INTERIM RESULTS FROM A PHASE 2A, OPEN-LABEL, DOSE-FINDING STUDY OF SOTATERCEPT (ACE-011) IN ADULT PATIENTS (PTS) WITH BETA-THALASSEMIA

M.D. Cappellini et al, Haematologica | 2015; 100(s1) | 17-18 (EHA 2015)

Table 1. Rates of Hb response for NTD pts.

	Sotatercept dose					
	0.1 mg/kg (n = 6)	0.3 mg/kg (n = 6)	0.5 mg/kg (n = 6)	0.75 mg/kg (n = 7)	1.0 mg/kg (n = 5)	Total (n = 30)
Hb increase ≥ 1.0 g/dL from baseline sustained for ≥ 12 weeks	0	4 (67)	4 (67)	6 (86)	1 (20)	15 (50)
Hb increase ≥ 1.5 g/dL from baseline sustained for ≥ 12 weeks	0	2 (33)	2 (33)	5 (71)	1 (20)	10 (33)

All values are expressed as n (%)

RAP-011 improves erythropoiesis in zebrafish model of Diamond-Blackfan anemia through antagonizing lefty1

Jason Ear,[1] Haigen Huang,[1] Tianna Wilson,[1] Zahra Tehrani,[1] Anne Lindgren,[1] Victoria Sung,[2] Abderrahmane Laadem,[3] Thomas O. Daniel,[3] Rajesh Chopra,[3] and Shuo Lin[1]

[1]Department of Molecular, Cell and Developmental Biology, University of California Los Angeles, Los Angeles, CA; [2]Celgene Corporation, San Francisco, CA; and [3]Celgene Corporation, Summit, NJ

Key Points

- Ribosome deficiency in zebrafish leads to defects in erythroid maturation and is reversed by RAP-011 treatment.
- Identification of lefty1 as a key mediator of erythropoiesis.

Diamond-Blackfan Anemia (DBA) is a bone marrow failure disorder characterized by low red blood cell count. Mutations in ribosomal protein genes have been identified in approximately half of all DBA cases. Corticosteriod therapy and bone marrow transplantation are common treatment options for patients; however, significant risks and complications are associated with these treatment options. Therefore, novel therapeutic approaches are needed for treating DBA. Sotatercept (ACE-011, and its murine ortholog RAP-011) acts as an activin receptor type IIA ligand trap, increasing hemoglobin and hematocrit in pharmacologic models, in healthy volunteers, and in patients with β-thalassemia, by expanding late-stage erythroblasts through a mechanism distinct from erythropoietin. Here, we evaluated the effects of RAP-011 in zebrafish models of RPL11 ribosome deficiency. Treatment with RAP-011 dramatically restored hemoglobin levels caused by ribosome stress. In zebrafish embryos, RAP-011 likely stimulates erythropoietic activity by sequestering lefty1 from erythroid cells. These findings identify lefty1 as a signaling component in the development of erythroid cells and rationalize the use of sotatercept in DBA patients. (*Blood*. 2015;126(7):880-890)

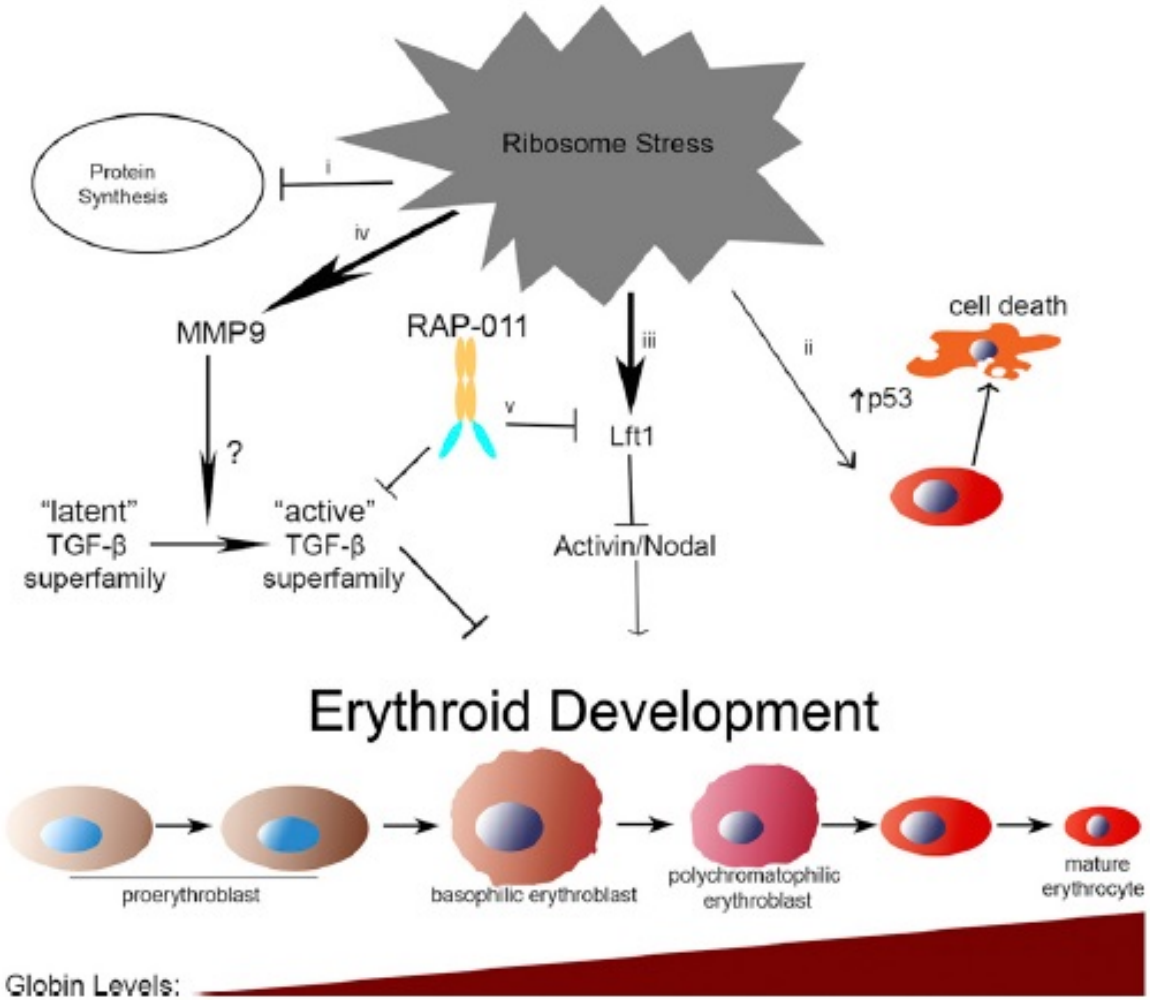

Figure 7. Model of erythroid failure during ribosome stress in zebrafish embryos and rescue with RAP-011. Multiple defects lead to the erythroid failure in zebrafish embryos upon ribosome deficiency. (i) Ribosome stress leads to lower rates of protein synthesis. (ii) Increase in p53 activity in erythroid cells lead to cell-cycle arrest and cell-death after the delay in maturation. (iii) Lft1 blocks the erythroid-promoting activity of activin/nodal signaling. (iv) Elevated MMP9 activity converts latent TGF-β to its active form. Activated TGF-β/TGF-β superfamily members induce cell-cycle arrest in erythroid cells. (v) RAP-011 sequesters and blocks active TGF-β superfamily members and Lft1 from binding to the endogenous receptor.

Inhibition of the TGF-β receptor I kinase promotes hematopoiesis in MDS

Li Zhou,[1] Aaron N. Nguyen,[2] Davendra Sohal,[1] Jing Ying Ma,[2] Perry Pahanish,[1,3] Krishna Gundabolu,[1] Josh Hayman,[1] Adam Chubak,[1] Yongkai Mo,[1] Tushar D. Bhagat,[1] Bhaskar Das,[1] Ann M. Kapoun,[2] Tony A. Navas,[2] Simrit Parmar,[3] Suman Kambhampati,[4] Andrea Pellagatti,[5] Ira Braunchweig,[1] Ying Zhang,[6] Amittha Wickrema,[7] Satyanarayana Medicherla,[2] Jacqueline Boultwood,[5] Leonidas C. Platanias,[8] Linda S. Higgins,[2] Alan F. List,[9] Markus Bitzer,[1] and Amit Verma[1,3]

[1]Albert Einstein College of Medicine, Bronx, NY; [2]Scios, Fremont, CA; [3]University of Texas Southwestern Medical School and Dallas Veterans Affairs Medical Center (VAMC); [4]VAMC, Kansas City, MO; [5]John Radcliffe Hospital, Oxford, United Kingdom; [6]Laboratory of Cellular and Molecular Biology, National Cancer Institute, Bethesda, MD; [7]University of Chicago, IL; [8]Northwestern University Robert H. Lurie Cancer Center, Chicago, IL; and [9]Moffitt Cancer Center, Tampa, FL

MDS is characterized by ineffective hematopoiesis that leads to peripheral cytopenias. Development of effective treatments has been impeded by limited insight into pathogenic pathways governing dysplastic growth of hematopoietic progenitors. We demonstrate that smad2, a downstream mediator of transforming growth factor–β (TGF-β) receptor I kinase (TBRI) activation, is constitutively activated in MDS bone marrow (BM) precursors and is overexpressed in gene expression profiles of MDS CD34+ cells, providing direct evidence of overactivation of TGF-β pathway in this disease. Suppression of the TGF-β signaling by lentiviral shRNA-mediated down-regulation of TBRI leads to in vitro enhancement of hematopoiesis in MDS progenitors. Pharmacologic inhibition of TBRI (alk5) kinase by a small molecule inhibitor, SD-208, inhibits smad2 activation in hematopoietic progenitors, suppresses TGF-β–mediated gene activation in BM stromal cells, and reverses TGF-β–mediated cell-cycle arrest in BM CD34+ cells. Furthermore, SD-208 treatment alleviates anemia and stimulates hematopoiesis in vivo in a novel murine model of bone marrow failure generated by constitutive hepatic expression of TGF-β1. Moreover, in vitro pharmacologic inhibition of TBRI kinase leads to enhancement of hematopoiesis in varied morphologic MDS subtypes. These data directly implicate TGF-β signaling in the pathobiology of ineffective hematopoiesis and identify TBRI as a potential therapeutic target in low-risk MDS. (Blood. 2008;112:3434-3443)

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Reduced SMAD7 leads to overactivation of TGF-beta signaling in MDS that can be reversed by a specific inhibitor of TGF-beta receptor I kinase

L Zhou[1], **C McMahon**[1], **T Bhagat**[1], **C Alencar**[1], **Y Yu**[1], **M Fazzari**[1], **D Sohal**[1], **C Heuck**[1], **K Gundabolu**[1], **C Ng**[1], **Y Mo**[1], **W Shen**[1], **A Wickrema**[2], **G Kong**[1], **E Friedman**[1], **L Sokol**[3], **G Mantzaris**[1], **A Pellagatti**[4], **J Boultwood**[4], **LC. Platanias**[5], **U Steidl**[1], **L Yan**[6], **JM Yingling**[6], **MM Lahn**[6], **A List**[3], **M Bitzer**[7], and **A Verma**[1]

[1]Albert Einstein College of Medicine, Bronx, NY

[2]University of Chicago, Chicago, IL

[3]Moffitt Cancer Center, Tampa, FL

[4]John Radcliffe Hospital, Oxford, UK

[5]Northwestern University Robert H Lurie Cancer Center, Chicago, IL

[6]Eli Lilly

MANUSCRIPT SLIDE DECK

Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study

Uwe Platzbecker[1a], Ulrich Germing[2a], Katherina S. Götze[3a], Philipp Kiewe[4a], Karin Mayer[5a], Jörg Chromik[6a], Markus Radsak[7a], Thomas Wolff[8a], Xiaosha Zhang[9], Abderrahmane Laadem[10], Matthew L. Sherman[9], Kenneth M. Attie[9], and Aristoteles Giagounidis[11a]

[1]Universitätsklinikum "Carl Gustav Carus" der Technischen Universität Dresden, Dresden, Germany; [2]Klinik für Hämatologie, Onkologie und Klinische Immunologie, Universitätsklinikum Düsseldorf, Düsseldorf, Germany; [3]Technische Universität München, Munich, Germany; [4]Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin, Germany; [5]Universitätsklinikum Bonn, Bonn, Germany; [6]Universitätsklinikum Frankfurt, Johann-Wolfgang-Goethe-Universität, Frankfurt, Germany; [7]Johannes Gutenburg-Universität, Mainz, Germany; [8]OncoResearch Lerchenfeld UG, Hamburg, Germany; [9]Acceleron Pharma, Cambridge, MA, USA; [10]Celgene Corporation, Summit, NJ, USA; [11]Marien Hospital Düsseldorf, Düsseldorf, Germany

[a] Affiliated with the German MDS Study Group (D-MDS).

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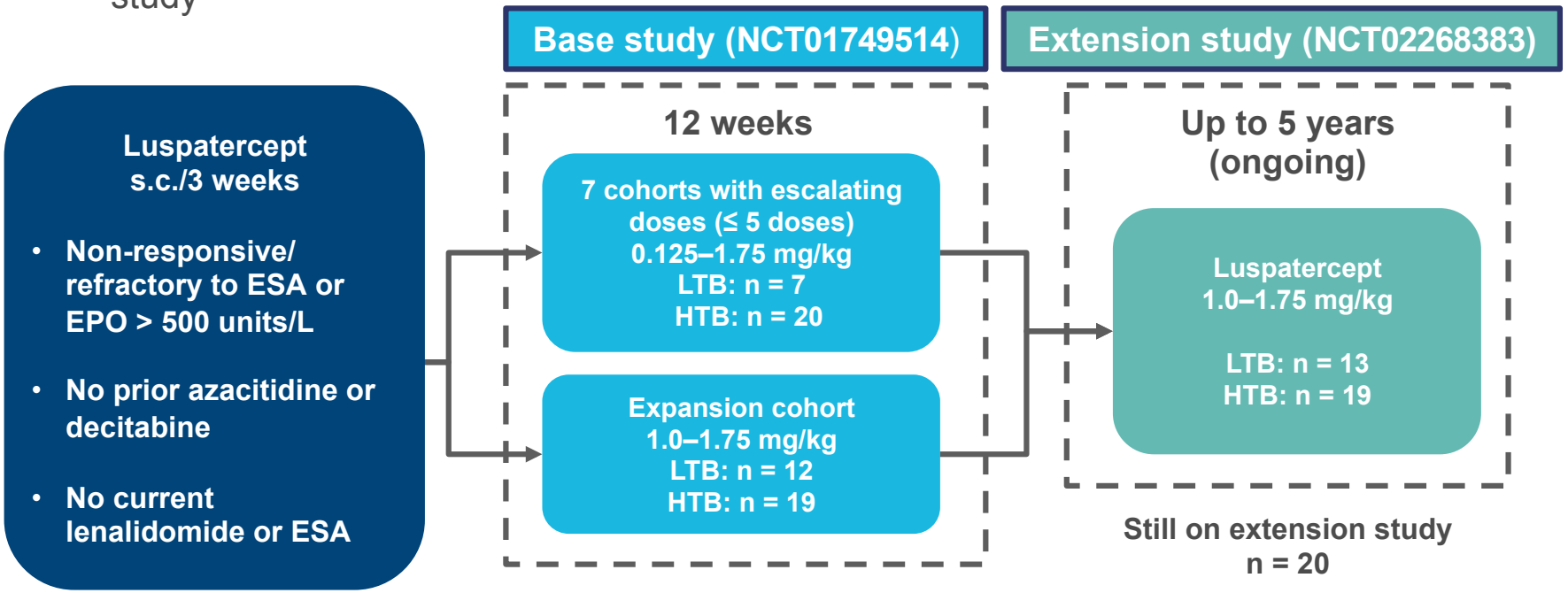
STUDY DESIGN

- The PACE-MDS study is a phase 2, open-label, 3-month dose-escalation study evaluating the efficacy and safety of luspatercept in patients with anemia due to LR MDS
  - Patients who completed the 12-week base study were eligible to enter the 5-year extension study



- The data cutoff for these analyses was March 4, 2016

HTB (≥ 4 units/8 week, Hb < 10 g/dL)
LTB (< 4 units/8 week, Hb < 10 g/dL)

EPO, erythropoietin; HTB, high transfusion burden; LTB, low transfusion burden; LR, lower risk; s.c., subcutaneous.

Platzbecker U, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017. doi: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

KEY BASELINE PATIENT CHARACTERISTICS

	Base Study Dose Level		
	0.125–0.5 mg/kg (n = 9)	0.75–1.75 mg/kg (n = 49)	Total (N = 58)
Median age, years (range)	72 (27–88)	71 (30–90)	71.5 (27–90)
Male sex, n (%)	1 (11)	33 (67)	34 (59)
Median time since diagnosis, years (range)	4.6 (1–10)	2.3 (0–14)	2.4 (0–14)
Transfusion burden			
LTB, n (%)	2 (22)	17 (35)	19 (33)
Median Hb level, g/dL (range)	8.7 (8.3–9.0)	8.7 (6.4–10.1)	8.7 (6.4–10.1)
HTB, n (%)	7 (79)	32 (65)	39 (67)
Median RBC transfusion burden, units/8 weeks (range)	8.0 (4.0–8.0)	6.0 (4.0–18.0)	6.0 (4.0–18.0)
Prior ESA treatment, n (%)	3 (33)	35 (71)	38 (66)
Baseline EPO, n (%)			
< 200 IU/L	3 (33)	25 (51)	28 (48)
200–500 IU/L	2 (22)	11 (22)	13 (22)
> 500 IU/L	4 (44)	13 (27)	17 (29)
RS status, n (%)			
RS+ (RS ≥ 15%)	5 (56)	40 (82)	45 (78)
RS−	3 (33)	7 (14)	10 (17)
Unknown	1 (11)	2 (4)	3 (5)
SF3B1 mutation status, n (%)			
Positive	3 (33)	30 (61)	33 (57)
Negative	5 (56)	15 (31)	20 (35)
Unknown	1 (11)	4 (8)	5 (9)

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HTB, high transfusion burden; LTB, low transfusion burden; RBC, red blood cell; RS, ring sideroblasts.

Platzbecker U, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017. doi: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

RESULTS

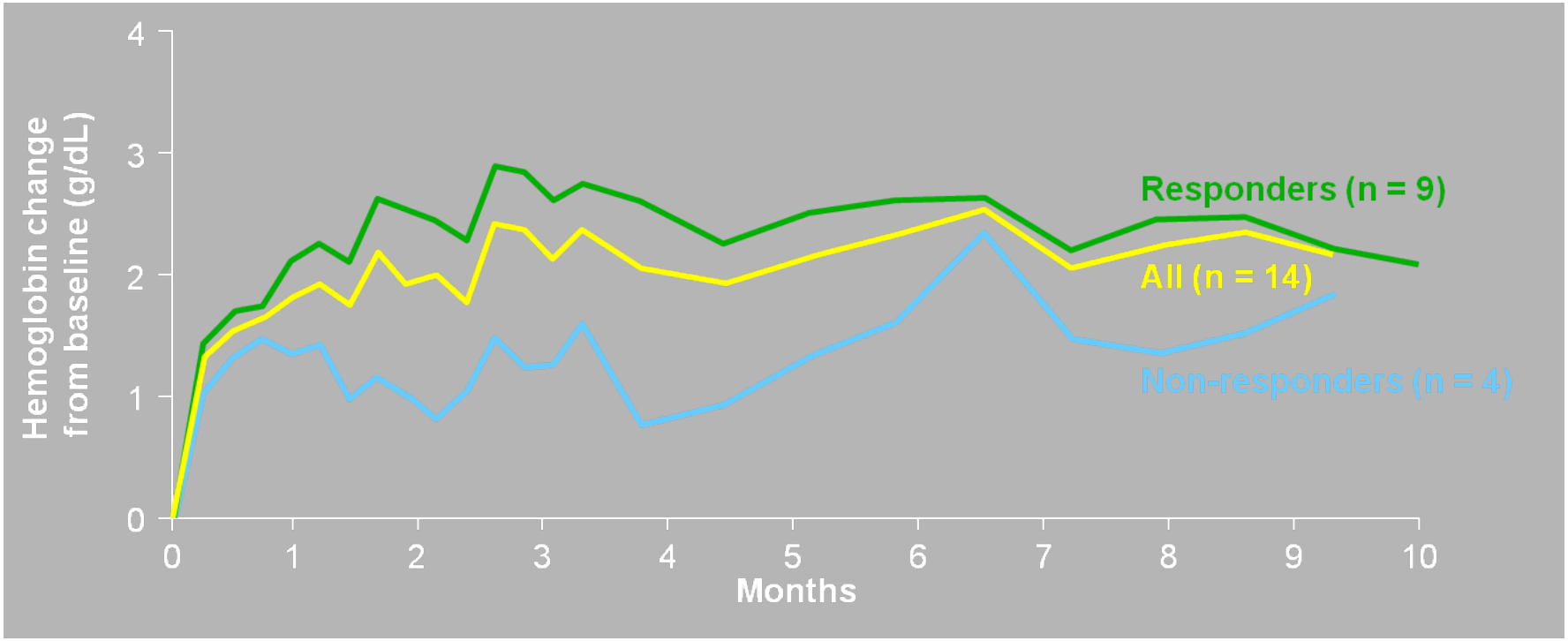
- Median duration of treatment was 6.8 months (range 2.0–19.8)
  - 20 patients ongoing as of the data cutoff[a]
- Median duration of follow-up was 243 days (IQR 304)
- **Of 51 patients treated with 0.75–1.75 mg/kg luspatercept[b], 32 (63% [95% CI 48–76]) achieved HI-E**
  - 21/34 (62%) patients with prior ESA use achieved HI-E, compared with 11/17 (65%) patients without prior ESA use
  - 5/8 (63%) patients who had previously received lenalidomide achieved HI-E, compared with 27/43 patients (63%) who had not previously received lenalidomide
  - 19/25 (76%) patients with baseline EPO < 200 IU/L, 7/12 (58%) with baseline EPO ≥ 200 to ≤ 500 IU/L, and 6/14 (43%) with EPO > 500 IU/L achieved HI-E
  - 29/42 (69%) RS-positive patients achieved HI-E versus 3/7 (43%, *P* = 0.36) RS-negative patients
- **Of 9 patients who received 0.125–0.5 mg/kg luspatercept during the base study, 2 (22% [95% CI 3–60]) achieved HI-E**

[a] Data cutoff was March 4, 2016.
[b] Fifty-one patients received higher dose concentrations during the base and extension study; 2 patients received lower dose concentrations in the base study and higher dose concentrations in the extension study.

CI, confidence interval; IQR, interquartile range.

Platzbecker U, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017. doi: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

A phase 2, multicenter, open-label, 3-month dose-escalation study to determine efficacy and safety of luspatercept in lower-risk MDS, followed by a 24-month extension study



13 of 19 (68%) HTB patients achieved IWG HI-E response for transfusions

8 of 19 (42%) HTB patients achieved RBC-TI

3 of 3 LTB patients with 2U RBC/8 weeks achieved RBC-TI

RESULTS: HI-E AND RBC-TI

Patients Treated with Luspatercept 0.75–1.75 mg/kg Achieving IWG HI-E and RBC-TI Over 8 Weeks in the Base and Extension Studies

n/N (%)	IWG HI-E[a]	RBC-TI[b]
All patients	32/51 (63)	16/42 (38)
Transfusion burden		
LTB (< 4 RBC units/8 weeks)	11/17 (65)	6/8 (75)
HTB (≥ 4 RBC units/8 weeks)	21/34 (62)	10/34 (29)
Prior use of ESAs		
Yes	21/34 (62)	11/29 (38)
No	11/17 (65)	5/13 (39)
Prior use of lenalidomide		
Yes	5/8 (63)	1/8 (13)
No	27/43 (63)	15/34 (44)
Serum erythropoietin level		
< 200 IU/L	19/25 (76)	10/19 (53)
≥ 200 to ≤ 500 IU/L	7/12 (58)	4/9 (44)
> 500 IU/L	6/14 (43)	2/14 (14)
RS status		
Positive (≥ 15% RS)	29/42 (69)	14/33 (42)
Negative (< 15% RS)	3/7 (43)	2/7 (29)
Unknown	0/2	0/2

[a] For LTB patients, IWG HI-E is defined as ≥ 1.5 g/dL Hb increase over 8 weeks; for HTB patients, IWG HI-E is defined as a reduction of ≥ 4 RBC units over 8 weeks;
[b] Patients with a baseline transfusion burden of ≥ 2 RBC units/8 weeks were included in the RBC-TI evaluable population.

Platzbecker U, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017. doi: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

RESULTS: HI-E AND RBC-TI (cont.)

n/N (%)	IWG HI-E[a]	RBC-TI[b]
SF3B1 mutation status		
Positive	24/31 (77)	11/25 (44)
Negative	6/15 (40)	5/13 (39)
Unknown	2/5 (40)	0/4
Any splicing factor[c]		
Positive	27/37 (73)	15/30 (50)
Negative	5/14 (36)	1/12 (8)
IPSS classification		
Low risk	18/23 (78)	7/14 (50)
Intermediate-1 risk	14/27 (52)	9/27 (33)
Intermediate-2 risk	0/1	0/1
IPSS-R classification		
Very Low to Low risk	20/31 (65)	11/23 (48)
Intermediate risk	10/17 (59)	5/16 (31)
High to Very High risk	2/3 (67)	0/3

[a] For LTB patients, IWG HI-E is defined as ≥ 1.5 g/dL Hb increase over 8 weeks; for HTB patients, IWG HI-E is defined as a reduction of ≥ 4 RBC units over 8 weeks.
[b] Patients with a baseline transfusion burden of ≥ 2 RBC units/8 weeks were included in the RBC-TI evaluable population.
[c] Splicing factors assessed were *SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2.*

ESA, erythropoiesis-stimulating agent; HTB, high transfusion burden; HI-E, hematologic improvement–erythroid; IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell; RS, ring sideroblast; TI, transfusion independence.

Platzbecker U, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017. doi: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

RESULTS: FACTORS ASSOCIATED WITH RESPONSE

Factors Associated With IWG HI-E Response

	Estimated Coefficient	*P* Value
Univariate analysis		
IPSS category (Low vs Int-1/Int-2)	1.28	0.04
Baseline EPO (continuous)	−0.00019	0.60
Baseline EPO < 100 vs ≥ 100 IU/L	1.55	0.03
Baseline EPO < 200 vs ≥ 200 IU/L	1.15	0.06
Prior ICT (yes vs no)	0.067	0.91
Prior ESA (yes vs no)	−0.127	0.84
RS ≥ 15% (no vs yes)	−1.09	0.19
Presence of *SF3B1* mutation (yes vs no)	−1.638	0.02
Multivariate analysis		
Baseline EPO < 100 vs ≥ 100 IU/L	1.71	0.04
Presence of *SF3B1* mutation (yes vs no)	−1.96	0.01

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement–erythroid; ICT, iron chelation therapy; Int, Intermediate; IPSS, International Prognostic Scoring System; IWG, International Working Group; RS, ring sideroblast.

Platzbecker U, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017. doi: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

RESULTS: FACTORS ASSOCIATED WITH RESPONSE (cont.)

Factors Associated With RBC-TI

	Estimated Coefficient	*P* Value
Univariate analysis		
IPSS category (Low vs Int-1/Int-2)	0.74	0.27
Baseline EPO (continuous)	−0.0025	0.04
Baseline EPO < 100 vs ≥ 100 IU/L	1.96	0.01
Baseline EPO < 200 vs ≥ 200 IU/L	1.15	0.08
Baseline EPO < 500 vs ≥ 500 IU/L	1.80	0.04
Prior ICT (yes vs no)	−1.73	0.02
Prior ESA (yes vs no)	−0.02	0.97
RS ≥ 15% (no vs yes)	−0.61	0.50
Presence of SF3B1 mutation (yes vs no)	−0.23	0.74
Multivariate analysis		
Baseline EPO < 500 vs ≥ 500 IU/L	2.14	0.02
Prior ICT (yes vs no)	−2.04	0.01

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; ICT, iron chelation therapy; Int, Intermediate; IPSS, International Prognostic Scoring System; IWG, International Working Group; RBC, red blood cell; RS, ring sideroblast ; TI, transfusion independence.

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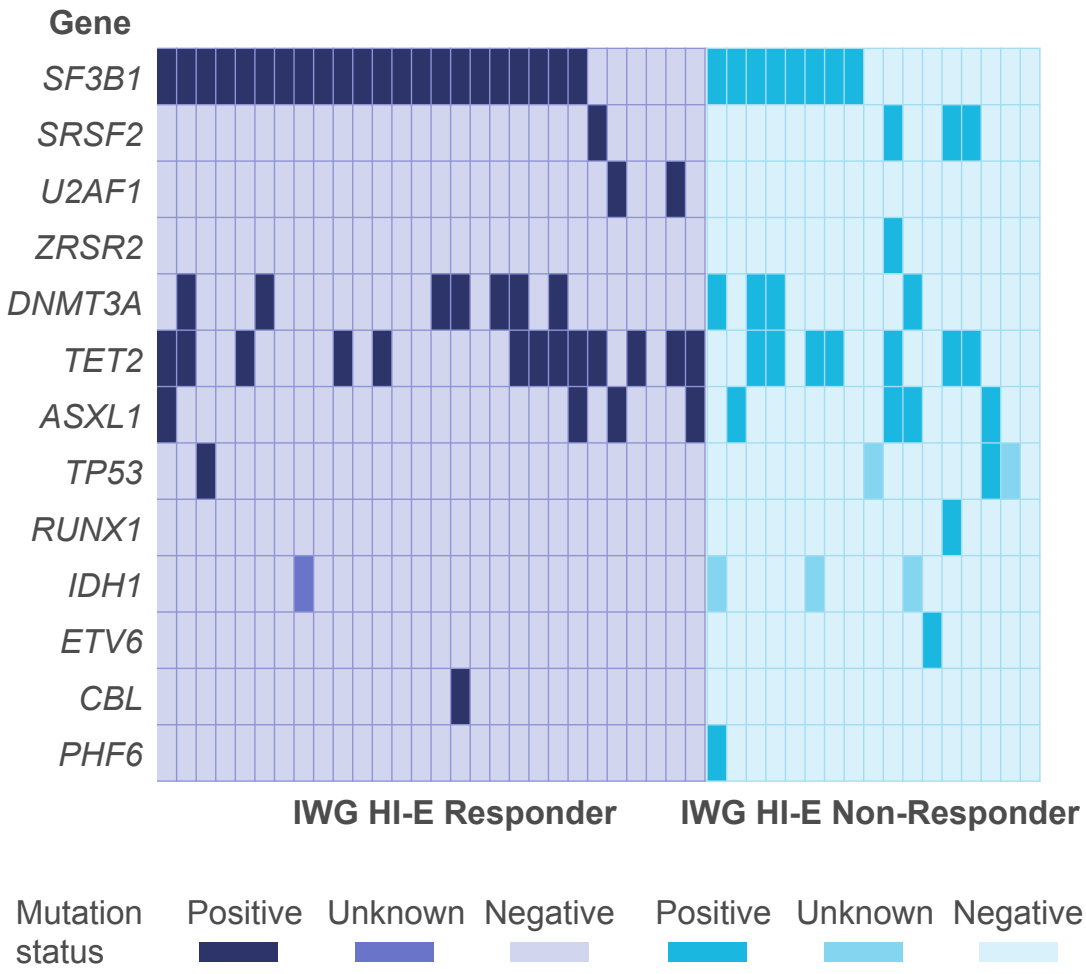
RESULTS: MUTATION ANALYSIS

- 24/31 (77%) *SF3B1* mutation-positive patients achieved HI-E
  - all were RS-positive
- 6/15 (40%) *SF3B1* mutation-negative patients achieved HI-E
  - 3/6 responders (50%) were RS-positive

Mutation Profile of IWG-Defined HI-E Responders Versus Non-Responders



HI-E, hematologic improvement–erythroid; IWG, International Working Group.

Platzbecker U, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017. doi: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

PLATZBECKER ET AL. RESULTS & AUTHORS' CONCLUSIONS

- Of the mutations assessed, patients with *SF3B1* mutations had the highest HI-E response rates (72%)
- The most frequent co-mutations were *SF3B1* and *TET2* (20%) and *SF3B1* and *DNMT3A* (17%)
- IWG HI-E responders had significantly higher bone marrow erythroid cells and precursors (P = 0.0204)

Mutation, n/N (%)	IWG HI-E
SF3B1	33/46 (72%)
TET2	17/29 (59%)
DNMT3A	11/18 (61%)
ASXL1	6/13 (46%)
SRSF2	3/9 (33%)

- Overall, 52 of 99 (53%) patients achieved IWG HI-E
  - 40 of 62 (65%) RS+ patients achieved HI-E versus 12 of 35 (34%) RS− patients
- 29 of 67 (43%) patients receiving luspatercept achieved RBC-TI ≥ 8 weeks
- The majority of AEs reported were grades 1–2
  - 8 possibly related grade 3 AEs and 4 possibly related serious AEs were reported

Patients receiving luspatercept continued to demonstrate sustained improvements in erythroid response, with a high proportion achieving RBC-TI ≥ 8 weeks

Treatment benefit was similar between ESA-naïve and ESA-treated patients

The majority of patients had at least 1 mutation in the genes analyzed

AE, adverse event; ESA, erythropoiesis-stimulating agent; RS, ring sideroblast.

Platzbecker et al. Mutational Profile and Analysis of Lower-Risk Myelodysplastic Syndromes (MDS) Patients Treated With Luspatercept: Phase 2 PACE-MDS Study. Poster presentation at the 59th Annual Meeting of the American Society of Hematology (ASH); December 9–12, 2017; Atlanta, GA, USA. Abstract 2982.

Higher response rates were observed in patients with RS, lower EPO levels, and SF mutations

Subgroup n (%)	IWG HI-E Response Rate	RBC-TI Response Rate
All	**24 of 49 (49)**	**14 of 40 (35)**
RS+	22 of 40 (55)	12 of 31(39)
RS-	2 of 7 (29)	2 of 7(29)
SF3B1 mutation	18 of 30 (60)	9 of 24 (38)
Any SF mutation	20 of 36 (58)	13 of 29 (45)
EPO < 200 U/L	16 of 25 (64)	10 of 18 (56)
EPO 200–500 U/L	4 of 11 (36)	3 of 9 (33)
EPO > 500 U/L	4 of 13 (31)	1 of 13 (8)
Prior ESA	16 of 35 (46)	10 of 29 (35)
ESA naïve	8 of 14 (57)	4 of 11 (36)

EPO, erythropoietin; ESA, erythropoietin stimulating agent ; RS, ring sideroblasts; SF, splicing factor; SF3B1, Splicing Factor 3b, Subunit 1.

Platzbecker U, et al. Biomarkers of Ineffective Erythropoiesis Predict Response to Luspatercept in Patients with Low or Intermediate-1 Risk MDS: Final Results from the Phase 2 PACE-MDS Study. *Poster presented at: Annual Meeting and Exposition of the American Society of Hematology* 2015; December 5–8; Orlando, FL. Abstract 2862.

RESULTS: SAFETY

Related TEAEs Occurring in the Base and Extension Studies

Preferred Term, n (%)	Grade 1–2 TEAEs (N = 58)	Grade 3 TEAEs (N = 58)
Fatigue	4 (7)	0
Bone pain	3 (5)	0
Diarrhoea	3 (5)	0
Myalgia	2 (3)	1 (2)
Headache	2 (3)	0
Hypertension	2 (3)	0
Injection site erythema	2 (3)	0
Increased blast cell count	0	1 (2)
General physical health deterioration	0	1 (2)

- Grade 1−2 TEAEs reported in 1 patient included: arthralgia, chest discomfort, decreased appetite, flatulence, hyperkalemia, hypotonia, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, nausea, peripheral edema, pain in extremity, platelet count increase, pruritis, rash, rash pruritic, tremor, and vomiting
- No related grade 4−5 TEAEs were reported

TEAE, treatment-emergent adverse event.

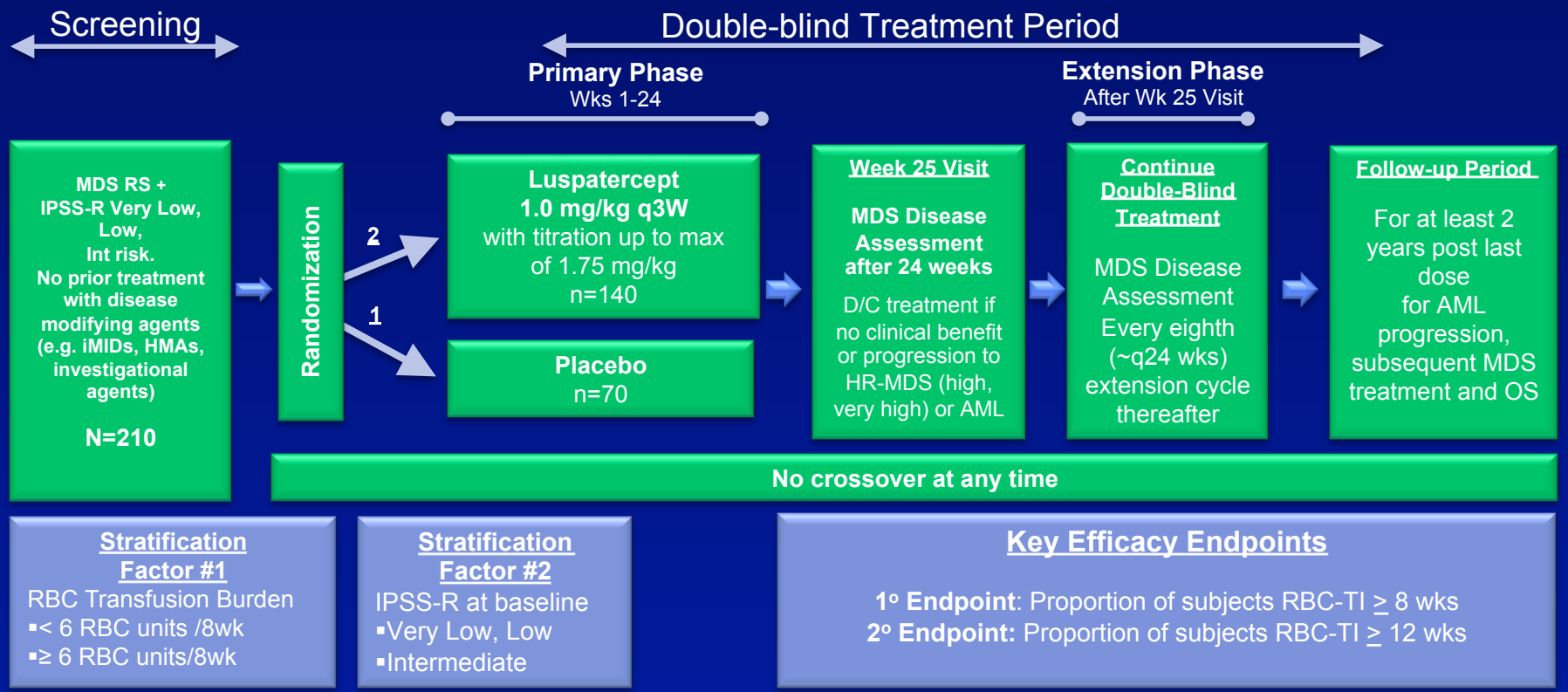
Platzbecker U, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017. doi: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

AUTHORS' CONCLUSIONS

- Higher dose levels of luspatercept induced HI-E in 63% and RBC-TI in 38% of patients with lower-risk MDS and anemia
- RS positivity and *SF3B1* mutations were associated with higher response rates, and may be predictive of response to treatment
- Luspatercept was well tolerated with no cytopenias reported in patients receiving treatment
- Overall, these data support the use of luspatercept in patients with lower-risk MDS and anemia; based on these data, a randomized, placebo-controlled, phase 3 study of luspatercept in patients with lower-risk, RS-positive MDS is currently ongoing

Platzbecker U, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. *Lancet Oncol.* 2017. doi: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

MEDALIST: Study Design
Phase 3 Study Design in RS(+) LR-MDS pts



https://clinicaltrials.gov/ct2/show/NCT02631070?term=medalist+phase+3&rank=1. Accessed April 21, 2017

Sotatercept with long-term extension for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes: a phase 2, dose-ranging trial

Rami Komrokji, Guillermo Garcia-Manero, Lionel Ades, Thomas Prebet, David P Steensma, Joseph G Jurcic, Mikkael A Sekeres, Jesus Berdeja, Michael R Savona, Odile Beyne-Rauzy, Aspasia Stamatoullas, Amy E DeZern, Jacques Delaunay, Gautam Borthakur, Robert Rifkin, Thomas E Boyd, Abderrhamane Laadem, Bond Vo, Jennie Zhang, Marie Puccio-Pick, Kenneth M Attie, Pierre Fenaux, Alan F List**

Summary

Background Myelodysplastic syndromes are characterised by ineffective erythropoiesis leading to anaemia. Sotatercept (ACE-011) is a novel activin receptor type IIA fusion protein that acts as a ligand trap to neutralise negative regulators of late-stage erythropoiesis. The aim of the study was to establish a safe and effective dose of sotatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes.

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Sotatercept with long-term extension for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes: a phase 2, dose-ranging trial (Komrokji et al, Lancet Haematol 2018)

- Open-label, multicentre, dose-ranging, phase 2 trial (11 centres in the USA and France) (eligible pts: IPSS risk low or Int-1; anaemia requiring RBC transfusions; ineligible for, or refractory to ESAs).
- Pts randomly assigned to: either 0·1 or 0·3 mg/kg sotatercept SC, and were assigned to 0·5, 1·0, and 2·0 mg/kg groups in a non-randomised fashion.
- 74 pts enrolled (51 (69%) with ring sideroblasts); (7 to 0·1 mg/kg; 6 to 0·3 mg/kg; 21 to 0·5 mg/kg; 35 to 1·0 mg/kg, and 5 to 2·0 mg/kg).
- 36 (49%; 95% CI 38–60) of 74 pts achieved HI-E; 29 (47%; 95% CI 35–59) of 62 pts with a high transfusion burden achieved HI-E; and 7 (58%; 95% CI 32–81) of 12 pts with a low transfusion burden achieved HI-E
- The proportion of pts who achieved a response was higher in the ring sideroblast-positive pts than the ring sideroblast-negative pts

Sotatercept with long-term extension for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes: a phase 2, dose-ranging trial (Komrokji et al, Lancet Haematol 2018)

- The most commonly reported adverse events were fatigue in 19 (26%) of
- 74 patients and peripheral oedema in 18 (24%) of 74 patients.
- Grade 3–4 treatment-emergent adverse events (TEAEs) were reported in 25 (34%) of 74 pts; 4 (5%) pts had grade 3–4 TEAEs that were considered to be treatment related.
- The most common grade 3–4 TEAEs were lipase increase and anaemia, which each occurred in 3 (4%) of 74 pts.
- 17 (23%) of 74 patients had at least one serious TEAE, and one patient died from a treatment-emergent subdural haematoma due to a fall.
- Luspatercept is derived from the activin receptor type IIB and binds with less affinity to activin A than sotatercept, potentially reducing the risk of off-target adverse events.

FASTTRACK
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Journal of Cellular Biochemistry

Cooperative Effect of Erythropoietin and TGF-β Inhibition on Erythroid Development in Human Pluripotent Stem Cells

Yinliang Xie,[1] Hao Bai,[2] Yanfeng Liu,[2] Dixie L. Hoyle,[2] Tao Cheng,[1] and Zack Z. Wang[2*]

[1] *State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Disease Hospital, Chinese Academy of Medical Sciences, Tianjin, China*

[2] *Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205*

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Research paper

Associations of myeloid hematological diseases of the elderly with osteoporosis: A longitudinal analysis of routine health care data

Thomas Datzmann[a,b,*,1], Freya Trautmann[a,b,1], Falko Tesch[a], Anna Mies[c], Lorenz C. Hofbauer[d,e,f], Uwe Platzbecker[c,f], Jochen Schmitt[a,b]

[a] TU Dresden, Medizinische Fakultät Carl Gustav Carus, Center for Evidence-Based Healthcare, Dresden, Germany
[b] National Center for Tumor Diseases, Dresden, Germany
[c] TU Dresden, Department of Internal Medicine I, Dresden, Germany
[d] TU Dresden, Department of Internal Medicine III, Dresden, Germany
[e] TU Dresden, Center for Healthy Aging, Dresden, Germany
[f] German Cancer Consortium (DKTK), partner site Dresden and German Cancer Research Center (DKFZ), Heidelberg, Germany

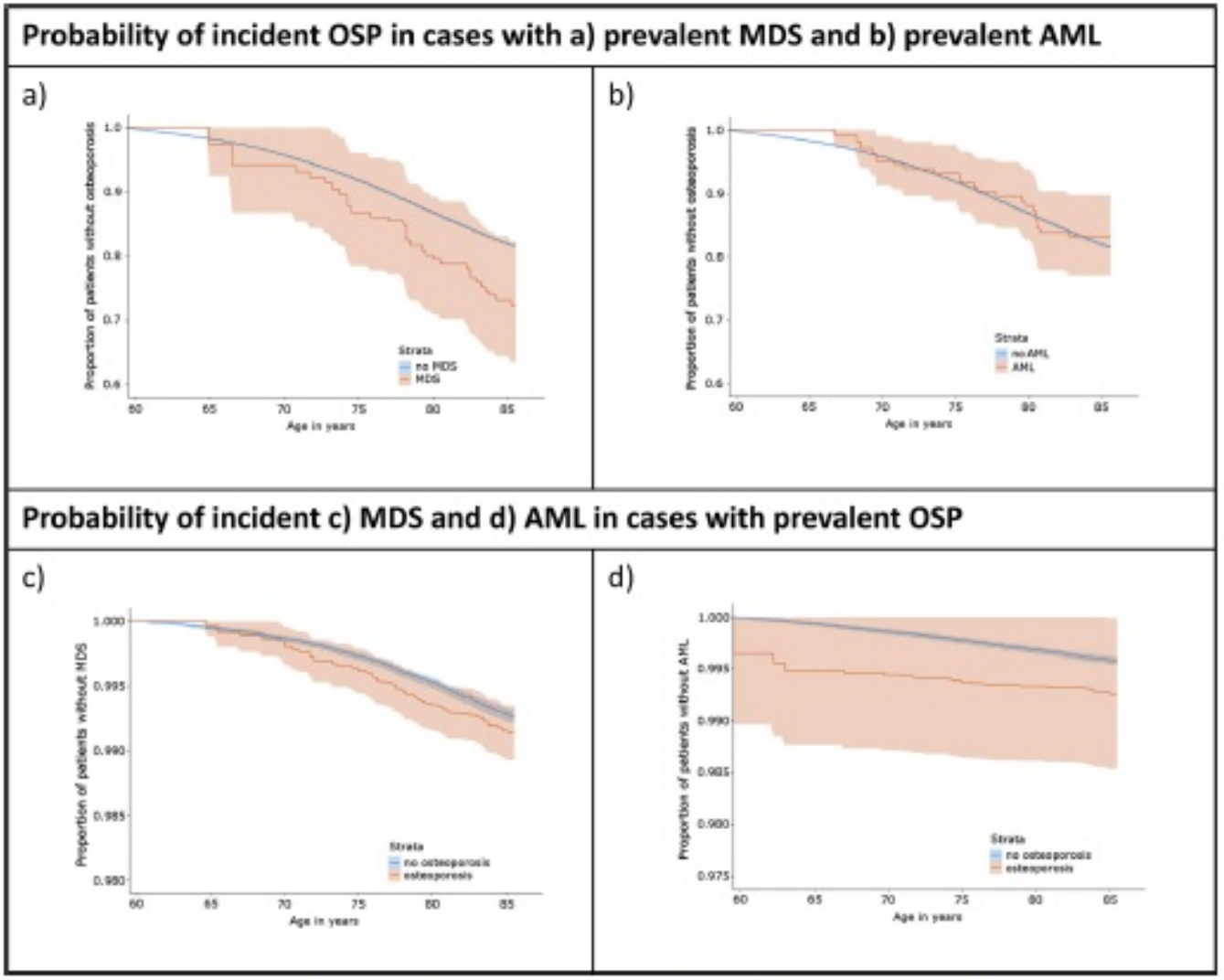

Fig. 1. Kaplan-Meier estimates for associations of OSP, MDS, and AML in the period 2009–2014 with 95% confidence intervals. Top: a) The patient cohort with MDS (red line) aged > 65 years shows a significant higher proportion of OSP cases compared to the *no MDS* cohort (blue line). b) No significant difference in the proportion of OSP cases between the *AML* and *no AML* cohort (both lines overlap). Bottom: c) The patient cohort with OSP (red line) aged > 70 years shows a slightly higher proportion of MDS cases compared to the *no osteoporosis* cohort (blue line), but failed to reach significance in the unadjusted cox model (Table 3). d) Despite no overlap of both curves, the hazard ratio of the corresponding cox model (Table 3) is not significant and therefore no difference can be determined in the proportion of AML cases between the *osteoporosis* and the *no osteoporosis* cohort. Note the enlarged scale of the two images (c,d) below. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)