MDS:
Opzioni per il paziente Low-Risk

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Treatment of LR-MDS

National Comprehensive Cancer Network®

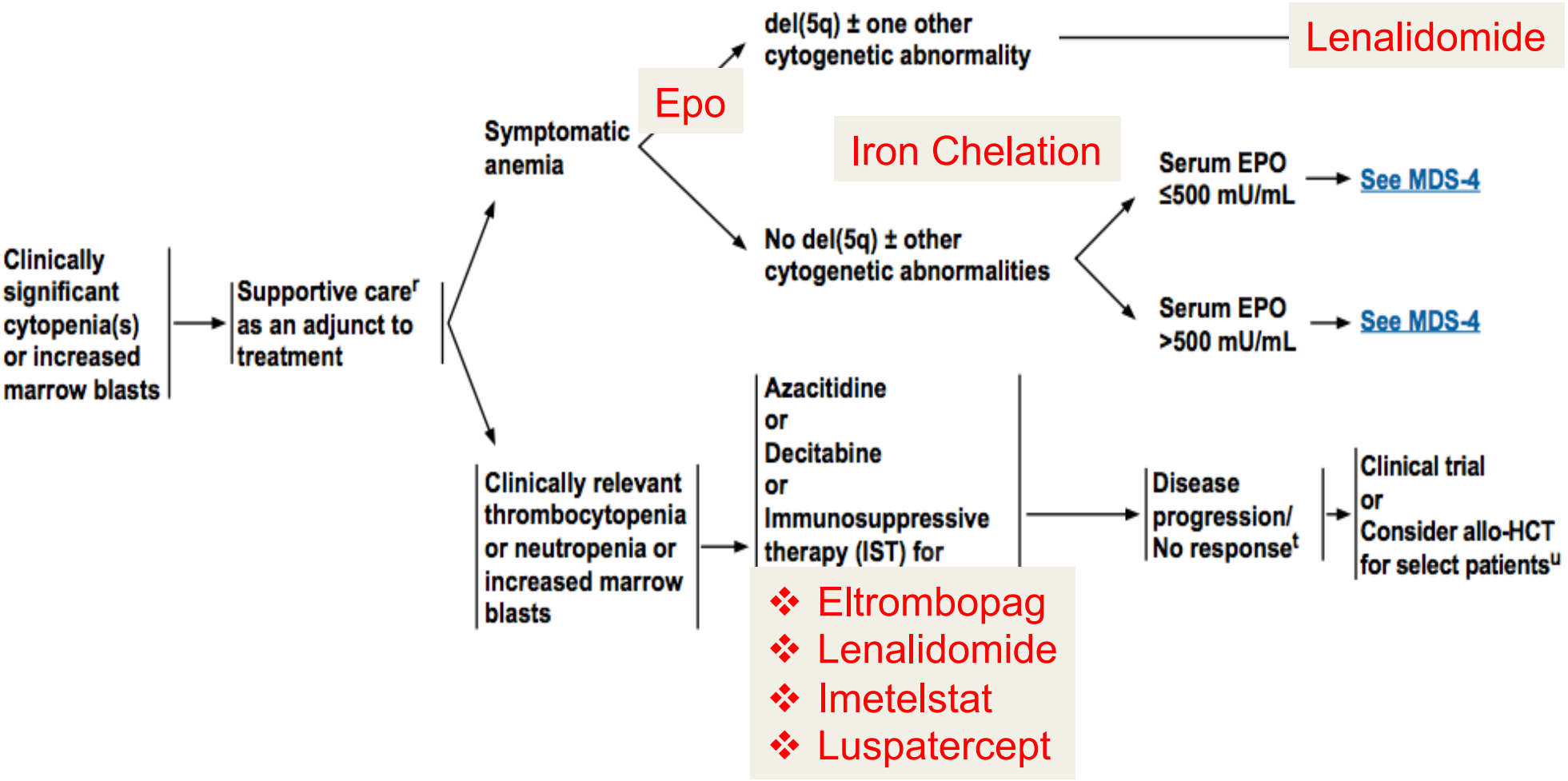
NCCN Guidelines Version 1.2017
Myelodysplastic Syndromes

NCCN Guidelines Index
Table of Contents
Discussion

PROGNOSTIC CATEGORY[o]
IPSS: Low/Intermediate-1
IPSS-R: Very Low, Low, Intermedia
WPSS: Very Low, Low, Intermediate

TREATMENT

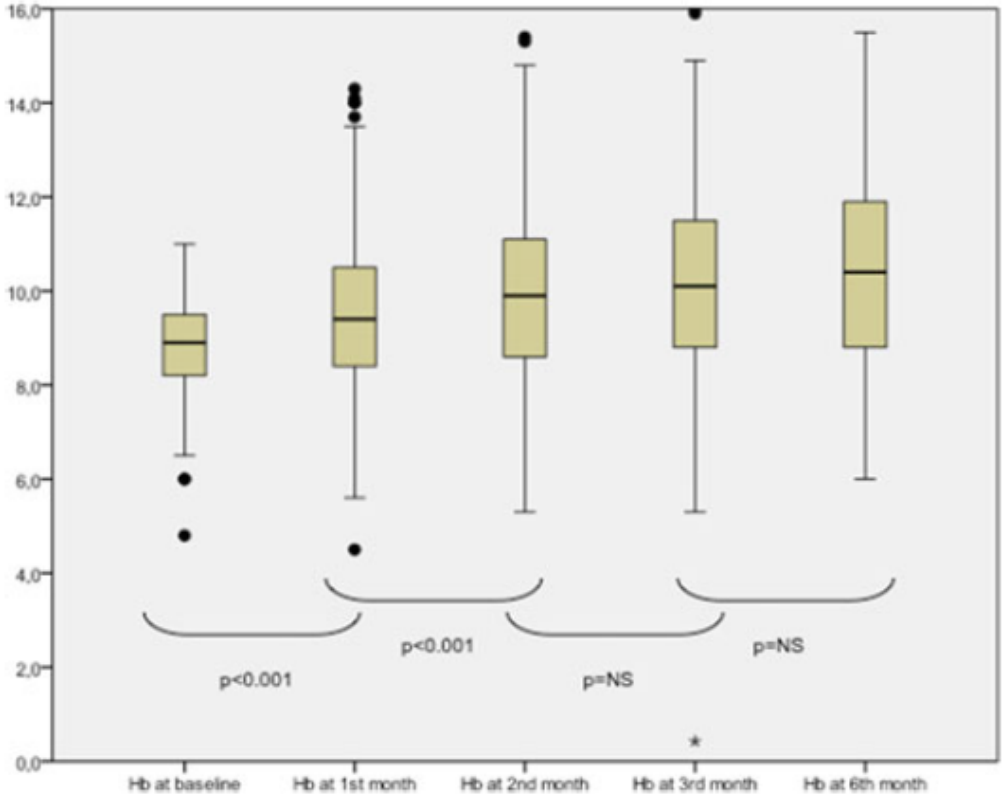
Intermediate: if managed as LR and fails, move to HR-treatment



Real-life use of erythropoiesis-stimulating agents in myelodysplastic syndromes: a "Gruppo Romano Mielodisplasie (GROM)" multicenter study

Francesco Buccisano[1,2] · Anna Lina Piccioni[3] · Carolina Nobile[4] · Marianna Criscuolo[5] · Pasquale Niscola[6] · Caterina Tatarelli[7,8] · Luana Fianchi[5] · Nicoletta Villivà[9] · Benedetta Neri[6] · Ida Carmosino[10] · Svitlana Gumenyuk[11] · Stefano Mancini[12] · Maria Teresa Voso[1] · Luca Maurillo[1] · Massimo Breccia[10] · Gina Zini[5] · Adriano Venditti[1] · Susanna Fenu[13] · Maria Antonietta Aloe Spiriti[7] · Roberto Latagliata[10] · on behalf of GROM (Gruppo Romano Mielodisplasie)

- 543 patients, DG between 2002-2010
- Median age : 75 yrs (69-80yrs)
- IPSS: low 46%
  int-1 43%
  Int-2 10%
  High 1%
- α-Epo: 62%, β-Epo: 35%, Darb: 3%
- High-dose: 33.5%, SD-dose: 66.5%
- Erythroid R: in 326 of 543 (60%) at a median of 3 months of TH (1.8-5.7)

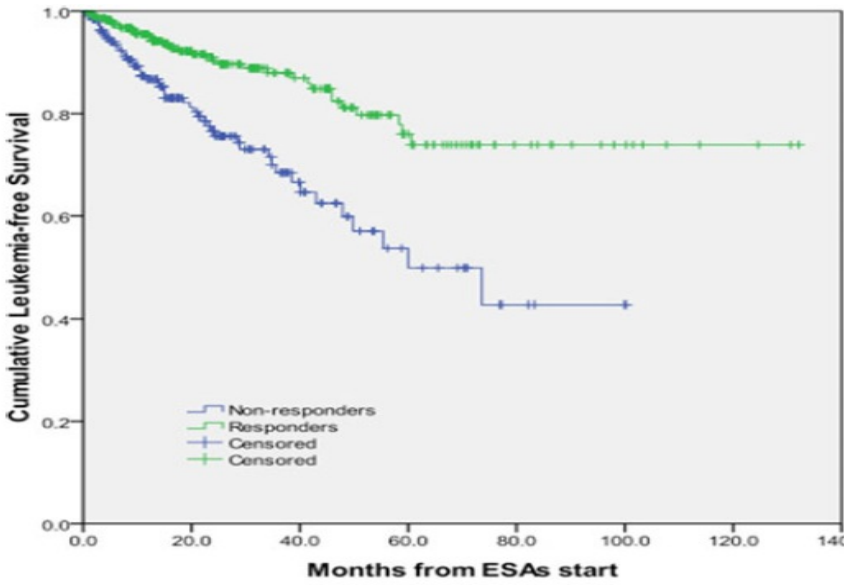


Ann Hematol 2016

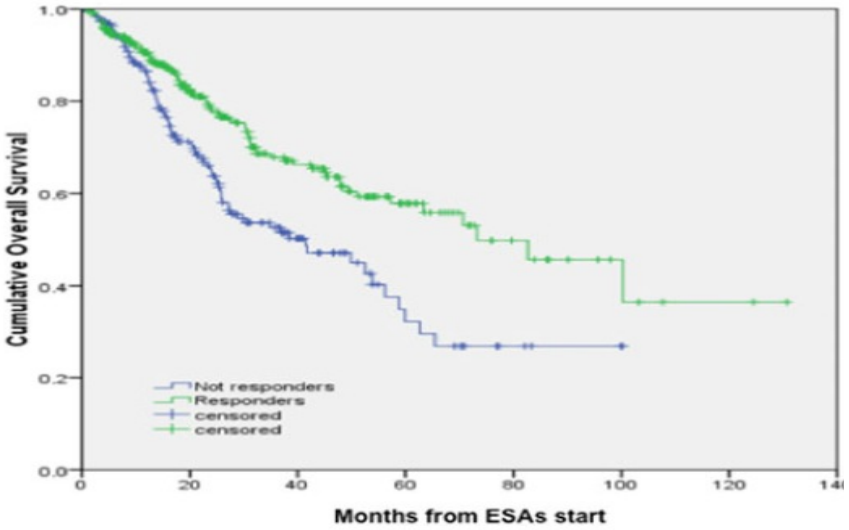
Multivariable Analysis

	p	Odds rati
Overall survival		
Transfusion requirement (no vs. yes)	<0.001	0.453
Sex (female vs. male)	0.001	1.927
IPSS (low/int-1 vs. int-2/high)	0.008	0.458
Response (responders vs. non-responders)	0.023	1.576
Leukemia-free survival		
BM blasts (>5 vs. <5 %)	<0.001	0.357
Response (responders vs. non-responders)	0.001	2.445
Response to ESAs		
Creatinine level (normal vs. abnormal)	<0.001	5.976
Transfusion requirement (no vs. yes)	<0.001	4.077
Endogenous EPO levels (<250 vs. >250 mcg/ml)	0.002	2.416
ESA initial dose (high vs. standard)	0.005	2.377

Leukemia-free Survival



Overall Survival



Buccisano et al, Ann Hematol 2016

Eltrombopag for the Treatment of Thrombocytopenia of Low and Intermediate-1 IPSS Risk MDS: Phase II multicenter, prospective, placebo-controlled single-blind study

	Eltrombopag	Romiplostim
Molecule	Oral, non-peptide agonist	Peptide s.c. agonist
Binding site	Transmembrane domain of the TPOR and of c-MPL different from TPO binding site	Extracellular domain, same as endogeneous TPO binding site
Endogenous TPO competitor	No	yes
Signal transduction	Different than that of endogenous TPO	Similar pathway of endogenous TPO

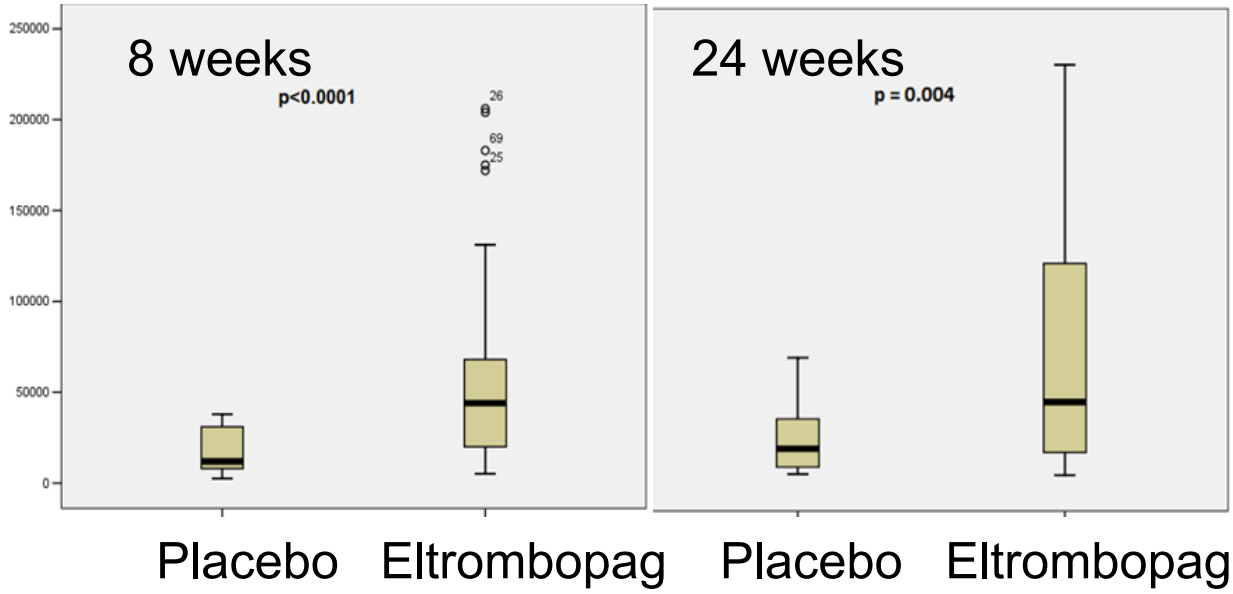
Oliva et al, Oral Abs: Eltrombopag for the Treatment of Thrombocytopenia of Low and Intermediate-1 IPSS Risk Myelodysplastic Syndromes: Interim Results on Efficacy, Safety and Quality of Life of an International, Multicenter Prospective, Randomized, Trial

Study design

EQoL MDS

- Low/Int-1 MDS, PLT count <30 Gi/L
- Ineligible or relapsed or refractory to receive other treatment options
- ESAs or G-CSF allowed during the study as per accepted standards.
- ECOG Performance Status 0-3
- Adequate baseline organ function
- Dose start: 50 mg with increases every 2 weeks up to 300 mg daily
- Random: Eltrombopag vs BSC, 2:1

Platelet Response



Oliva E. et al, submitted

Platelet Response at 8 and 24 Weeks

Response	8 weeks Elt 41:placebo 17	24 weeks Elt 24:Placebo11
R, n	12 : 0	5 : 3
CR, n	9 : 0	8 : 0
NR	20 : 17	11 : 8
Total responses, n	21 : 0	13 : 3
WHO bleeding grade ≥ 2, events	1 : 2	3 : 1

Time to Response (TTR) :
Eltrombopag : median 14 (IQR 8-39) days
Placebo: median 85 (IQR 41-193) days (p =0.023) *
Median daily eltrombopag dose at response: 50 (IQR 50-150) mg.

Other Responses

Response	8 weeks, Elt n=41 : Plac=17	24 weeks, Elt n=24: Plac=11
Erythroid response	4 : 0	4 : 0
Neutrophil response	4 : 1	1 : 1

Lenalidomide in del(5q) LR-MDS

- Long-term outcomes (median follow-up 3.2 years) in 148 patients with del(5q) LR-MDS treated with lenalidomide in the MDS-003 trial.

- RBC-TI > 8 weeks: 65%

- Median time to RBC-TI: 1.3 months (1.1-1.5)

RBC-TI:	IPSS	Low-risk:	69%
		Int-1:	68%
		Int-2/high:	33%
RBC-TI:	Baseline K:	Isolated del(5q)	71%
		Del(5q) plus 1 abn.	48 %
		Del(5q) plus 2 abn	58%
Cytogenetic response:			
		Complete	45.5%
		Partial	26%

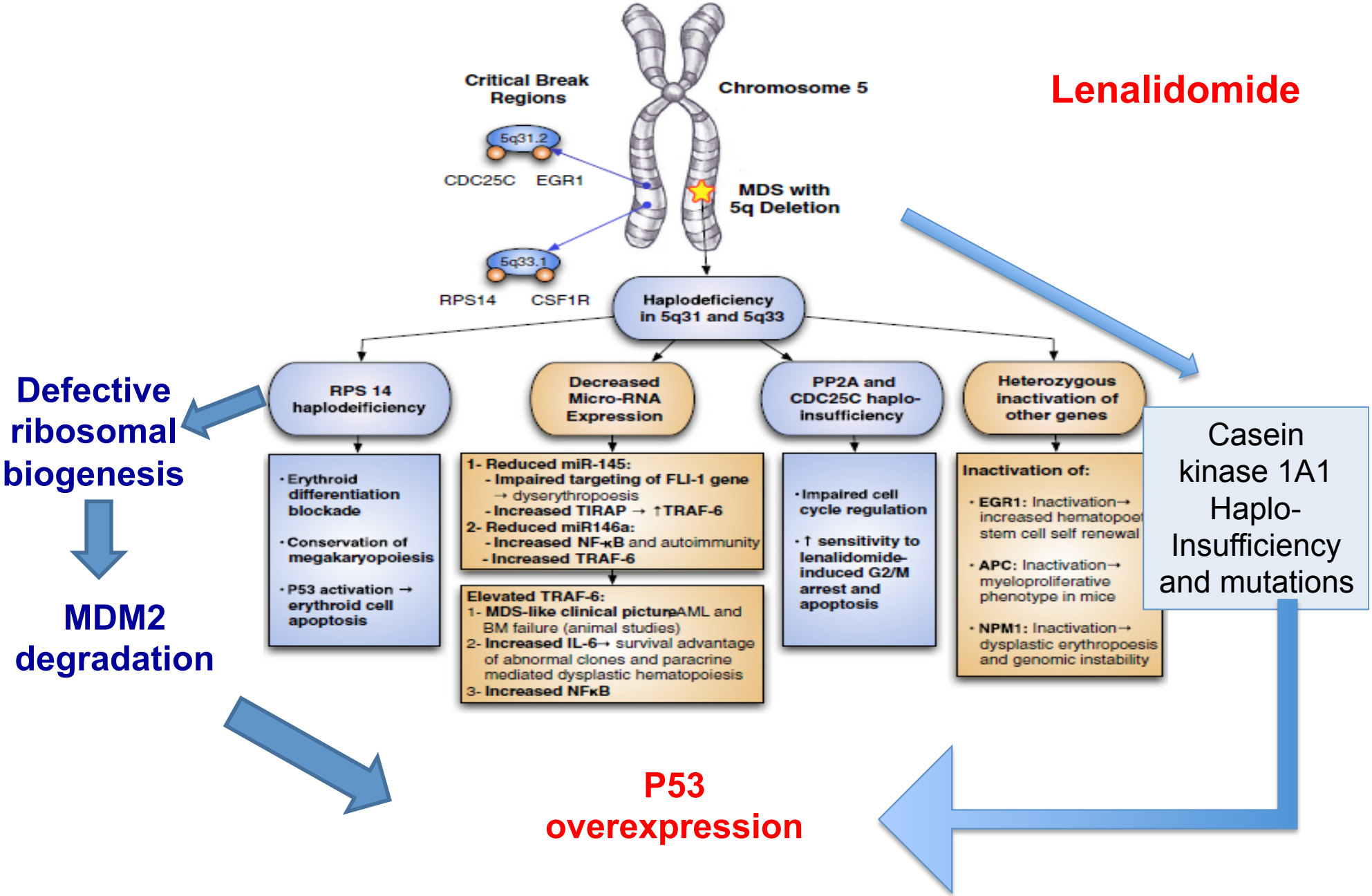
List et al, Leukemia 2014

Prognostic factors for LEN response in 5q- MDS

	Transfusion independence	Overall Survival	AML progression
Isolated del(5q) vs >1 abn	√	√	√
Complete Citogenetic Response	√	√	√
Transf-independence			√

List et al, Leukemia 2014

5q- MDS



From Gaballa and Mesa, Ann Hematol 2014

Lenalidomide in TD non-del(5q) LR-MDS (MDS-005 Trial)

- 239 patients were randomly assigned (2:1) to treatment with 10 or 5 mg lenalidomide (n = 160) or placebo (n = 79) once per day (on 28-day cycles)
- RBC-TI >8 weeks was achieved in 26.9% and 2.5% of patients in the lenalidomide and placebo groups, respectively (p: 0,001). Ninety percent of patients achieving RBC-TI responded within 16 weeks of treatment.
- Median duration of RBC-TI with lenalidomide was 30.9 weeks (95% CI, 20.7-59.1).
- At week 12, mean changes in HRQoL scores from baseline did not differ between treatment groups, which suggests that lenalidomide did not adversely affect HRQoL.
- The most common treatment-emergent adverse events were neutropenia and thrombocytopenia.

Santini et al, J Clin Oncol 2016

Iron Chelation Therapy

Deferasirox for transfusion-dependent patients with myelodysplastic syndromes: safety, efficacy, and beyond (GIMEMA MDS0306 Trial)

Emanuele Angelucci[1], Valeria Santini[2], Anna Angela Di Tucci[1], Giulia Quaresmini[3], Carlo Finelli[4], Antonio Volpe[5], Giovanni Quarta[6], Flavia Rivellini[7], Grazia Sanpaolo[8], Daniela Cilloni[9], Flavia Salvi[10], Giovanni Caocci[11], Alfredo Molteni[12], Daniele Vallisa[13], Maria Teresa Voso[14], Susanna Fenu[15], Lorenza Borin[16], Giancarlo Latte[17], Giuliana Alimena[18], Sergio Storti[19], Alfonso Piciocchi[20], Paola Fazi[20], Marco Vignetti[20], Sante Tura[21]

- Multicenter study
- 152 transfusion-dependent patients with MDS (62 low-IPSS, 90 int-1)
- 96 males, 56 females, median age 72 years
- EXJADE starting dose: 20 mg/kg/die
- **Transfusion-independence:** al least 3 consecutive months without transfusion support and stable Hb 9 g/dl.
- Patients receiving other MDS treatment were excluded from the study

Significant reduction of median ferritin levels
from 1966 ng/ml to 1475 ng/ml, p< 0.0001.

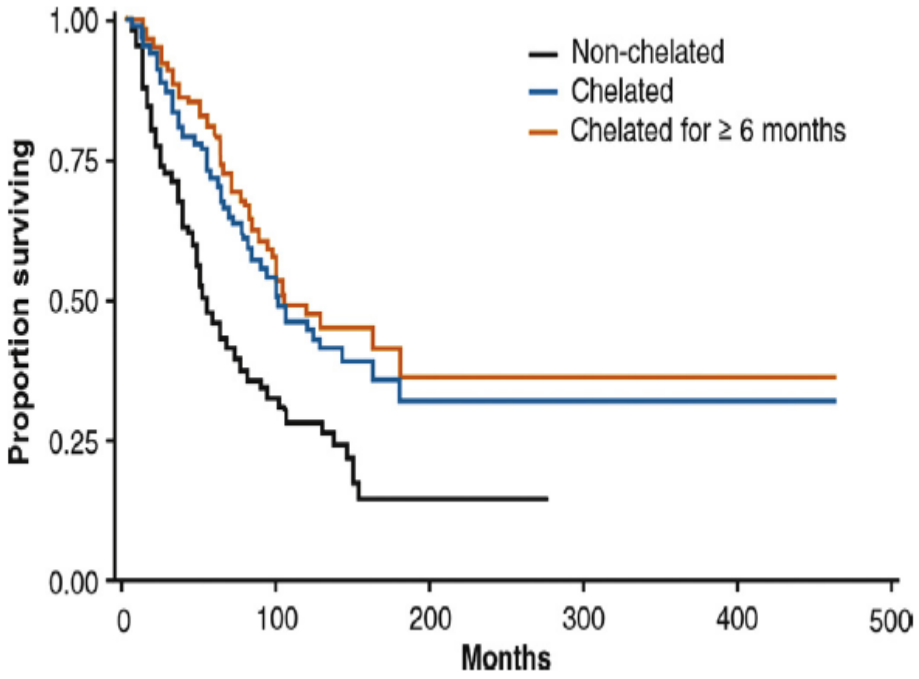
Angelucci et al, EJH 2014

Comparison of 24-month outcomes in chelated and non-chelated lower-risk patients with myelodysplastic syndromes in a prospective registry

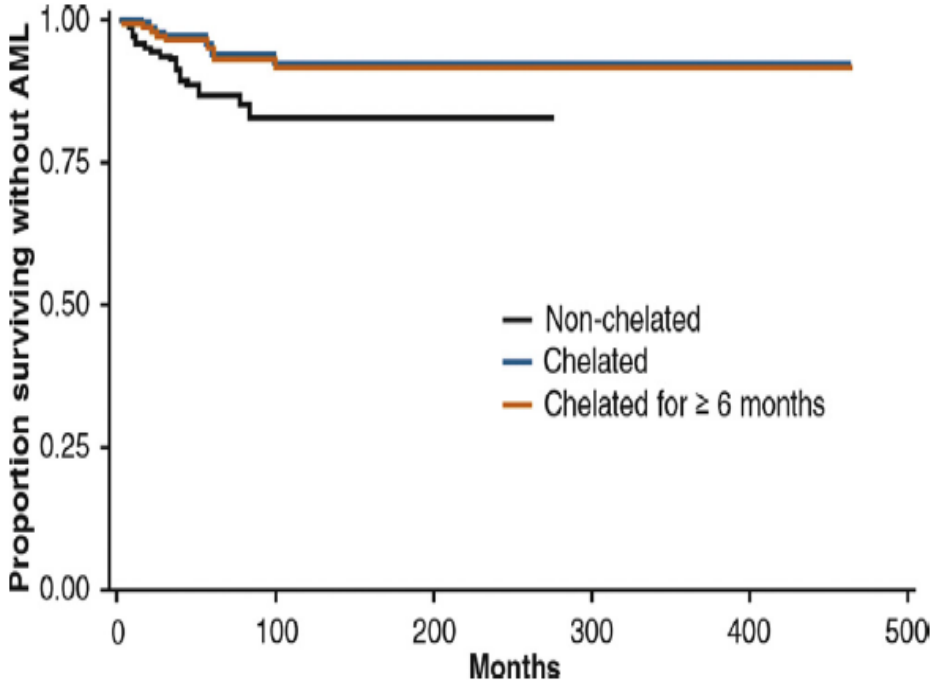
Roger M. Lyons[a,b,*], Billie J. Marek[b,c], Carole Paley[d], Jason Esposito[d], Lawrence Garbo[b,e], Nicholas DiBella[b,f], Guillermo Garcia-Manero[g]

- 600 lower-risk MDS patients with transfusional iron overload
- At baseline, cardiovascular comorbidities were more common in non-chelated pts and MDS therapy was more common in chelated patients

Overall Survival

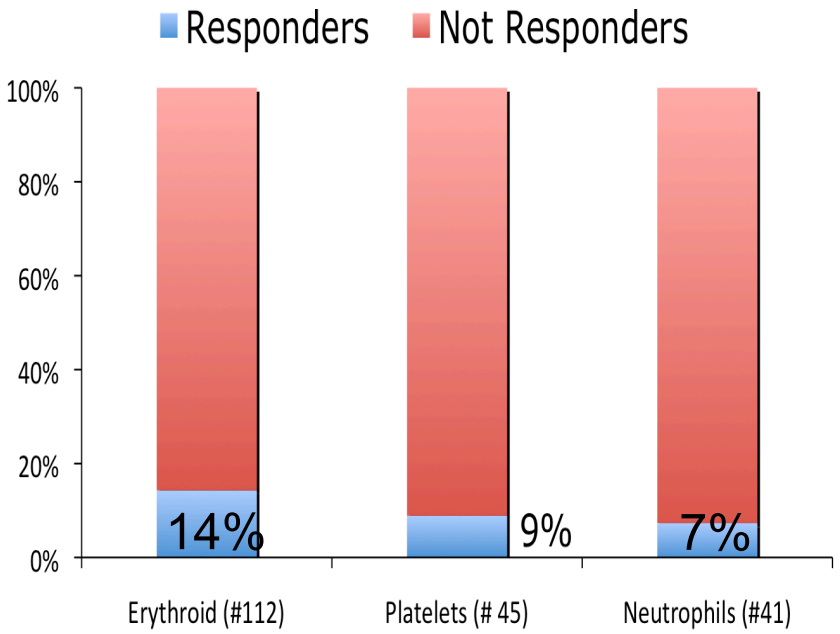


Leukemia-free Survival

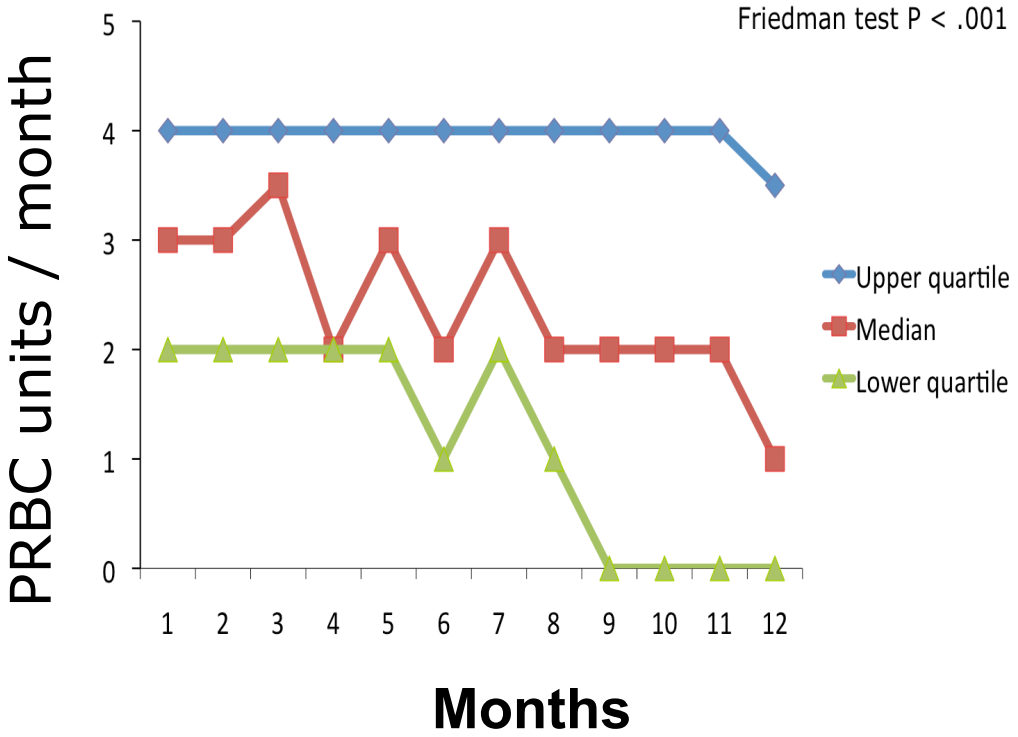


Leukemia Research 2014

Hematologic Response



RBC Units
In 68 pts after 1 year



Months

- Reduction of transfusion needs from 3 (2-5) median PRBC/month to 1 (0-4) after 1 year (P= 0.0001)

- 22 pts obtained TI: probability 5.5%, 15.7% and 19.7% at 6, 9 and 12 months

Angelucci et al, EJH 2014

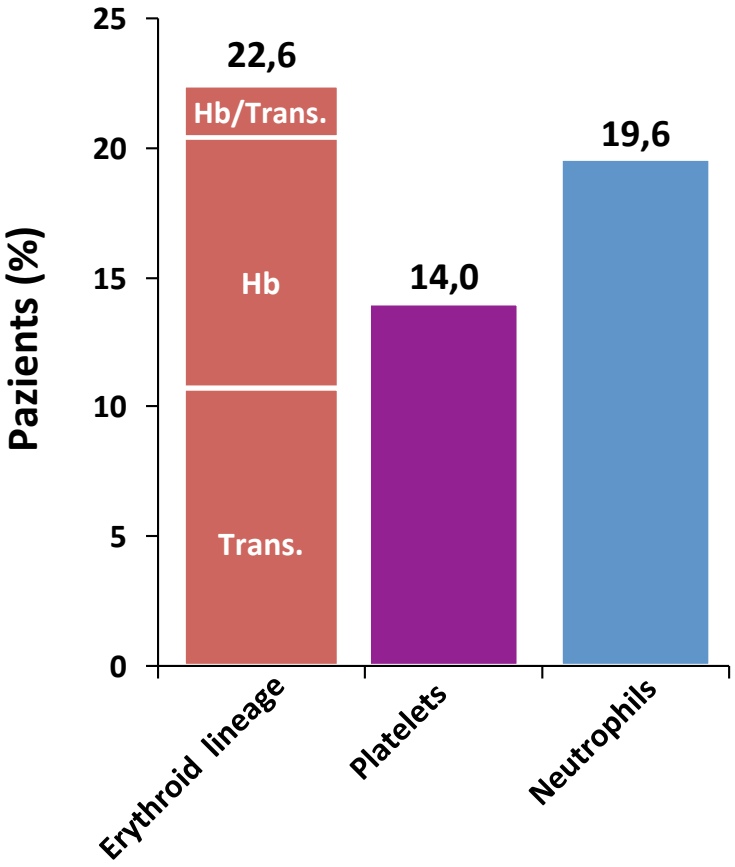
Table 1 Major features indicated in the clinical studies reporting hematologic improvement (HI) during deferasirox treatment

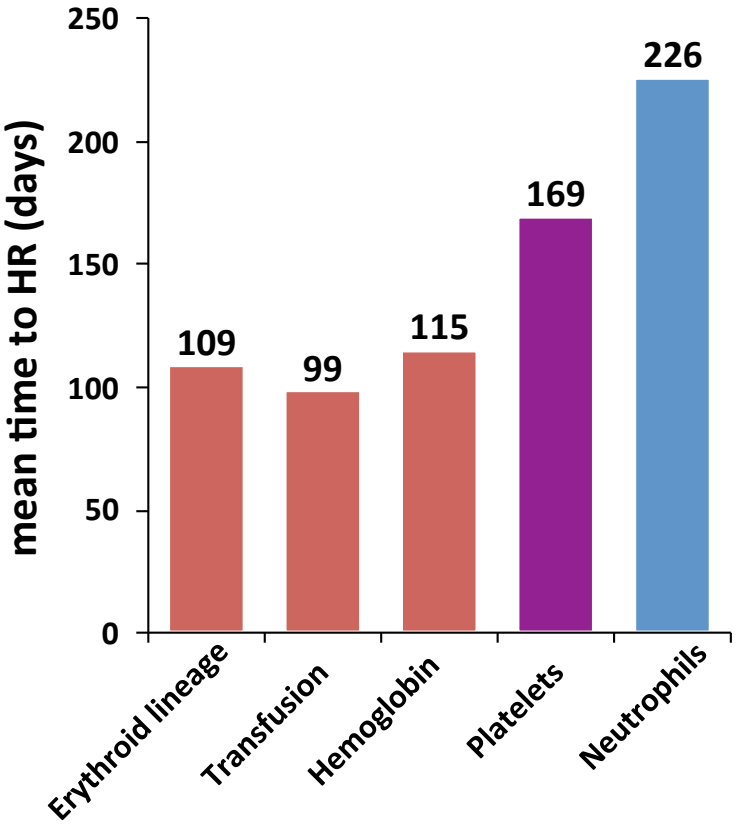
Reference	No. pts	HI-E	HI-plts	HI-PMN	Biological parameters
EPIC [22]	247	53 (21.7 %) 11.8 % TI 8.9 % ↑ Hb	13 (13 %)	50 (22 %)	No significant changes in SF and LIP between responders and non-responders
US03 [23]	173	26 (15 %)	17/77 (22 %)	8/52 (15 %)	No significant changes in SF and LIP between responders and non-responders
German [24]	50	2/33 (6 %)	3/10 (30 %)	–	–
GIMEMA [25]	152	16/152 (11 %)	18/125 (15 %)	1/41 (3 %)	No significant changes in SF between responders and non-responders
Italian cooperative group [26]	105	41/105 (44.5 %)	nr	nr	HI not related to SF changes
REL [27]	53	19 (35.1 %)	8/13 (61 %)	13/17 (76.4 %)	No correlations
GROM Maurillo et al, EJH 2015	118	15 (17.6%) (TI n:6, 7.1%)	5.9%	7.1%	Correlations to higher DFO dose

Modified from Breccia, et al. Ann Hematol 2015

Hematologic Response
EPIC Study

Time to Hematologic Response

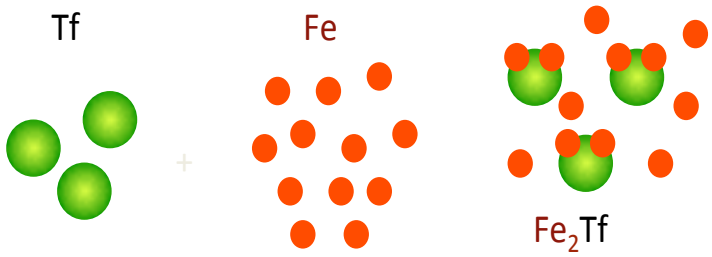




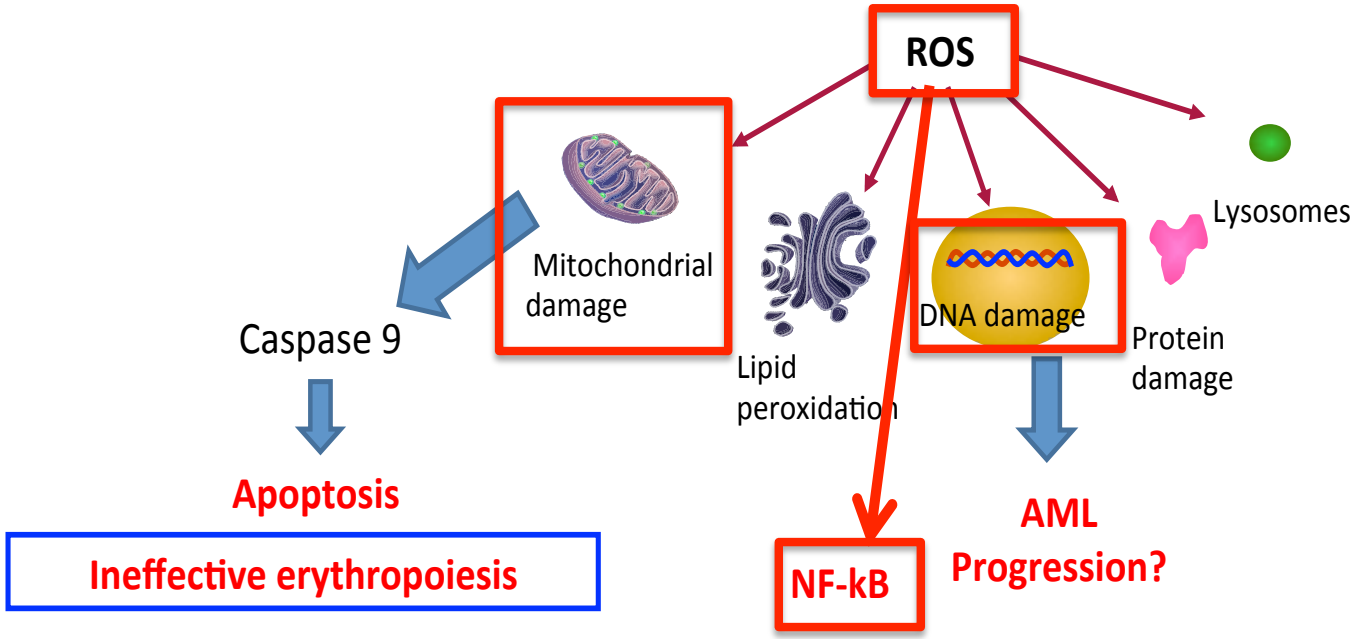
Gattermann, et al. Haematologica 2012

Damage due to Iron Overload: 1. Iron-dependent

Non-transferrin-bound iron (NTBI) induces generation of ROS



NTBI appears in plasma when transferrin is almost completely saturated (saturation > 60–70%); it is taken up by cells* and is highly toxic



* Through L-type calcium-dependent channels.

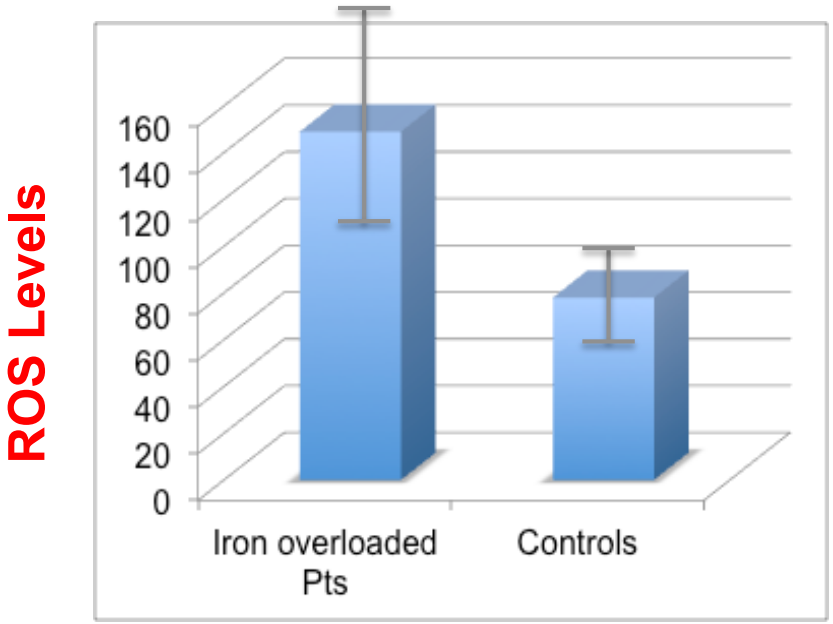
Tf = transferrin.

Cabantchik ZI, et al. Best Pract Res Clin Haematol. 2005;18:277-87.

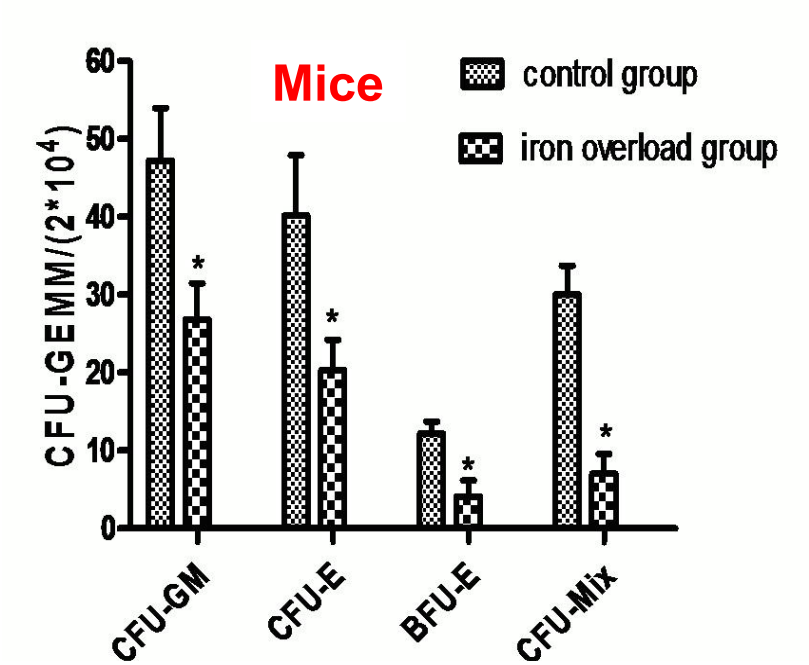
Zuo Y, et al. Cell Res. 2009;19:449-57.

Damage due to Iron Overload:
1. Iron-dependent

NTBI induces generation of ROS



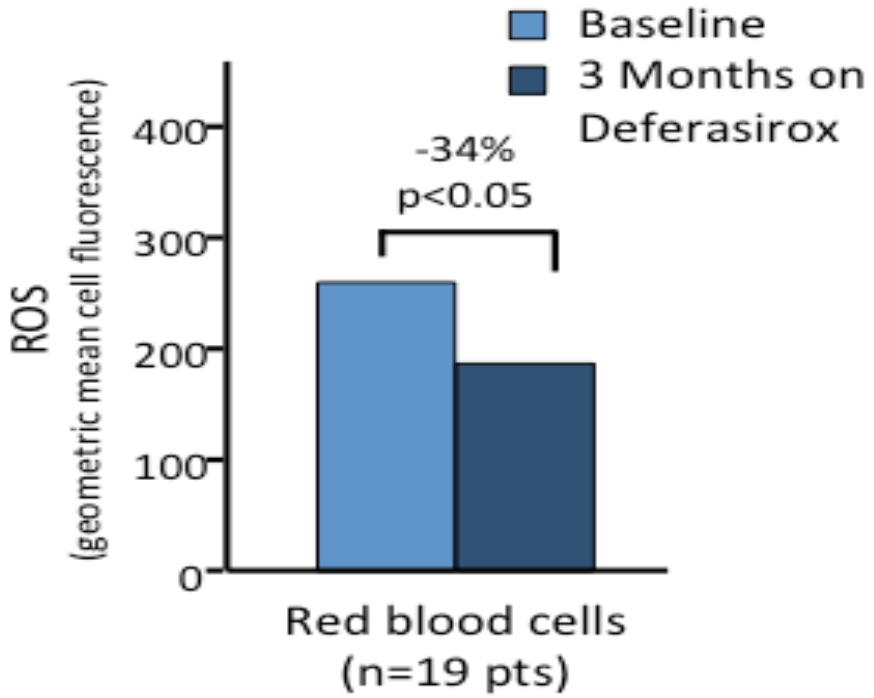
Lu et al, Eur J Hematol 2013



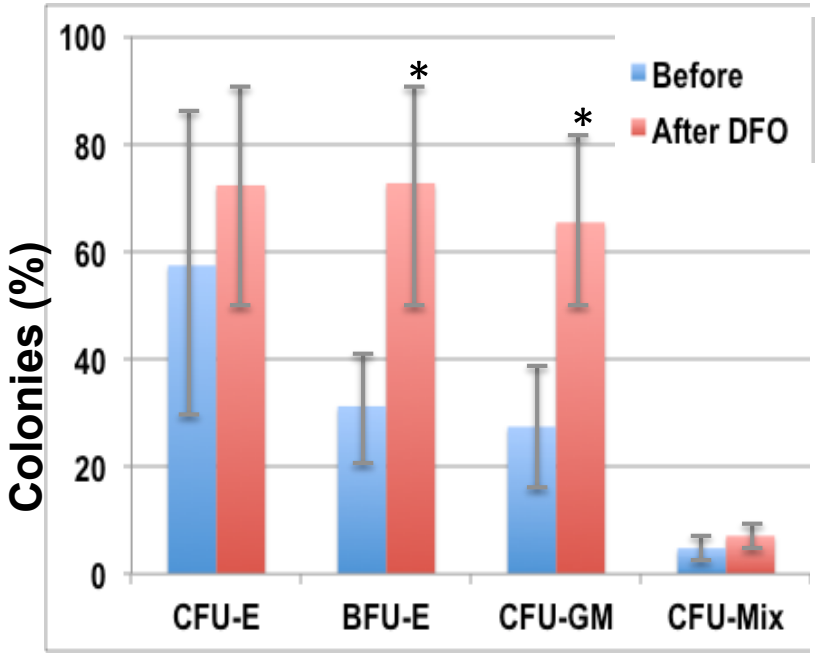
Chai et al, Blood 2013

✓ Iron overload is associated to higher ROS levels and to reduced CFU capacity

Iron Chelation and Inhibition of ROS Production



Ghoti et al, Hematologica 2010

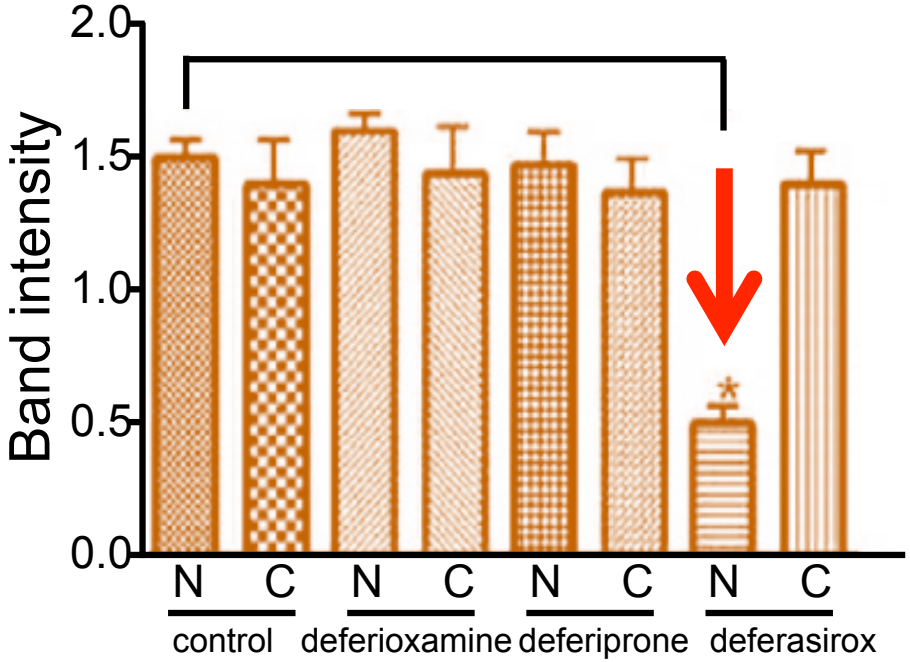


Lu et al, Eur J Hematol 2013

✓ Iron chelation decreases ROS levels and increases CFU capacity

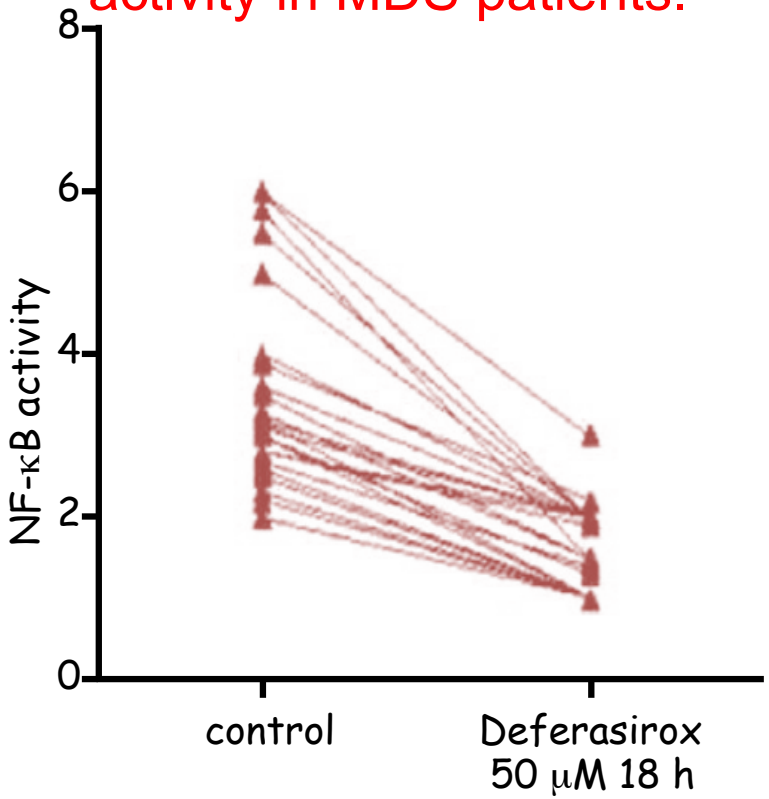
Damage due to Iron Overload:
2. Iron-independent:
NF-KB inhibition, damage to Chromosomal DNA

Deferasirox decreases localization of NF-kB to the nucleus, thus inhibiting NF-kB signaling.



Western blot using NF-kB antibody for the detection of proteins in either nuclear (N) or cytoplasmic (C) extracts in K562 cells.

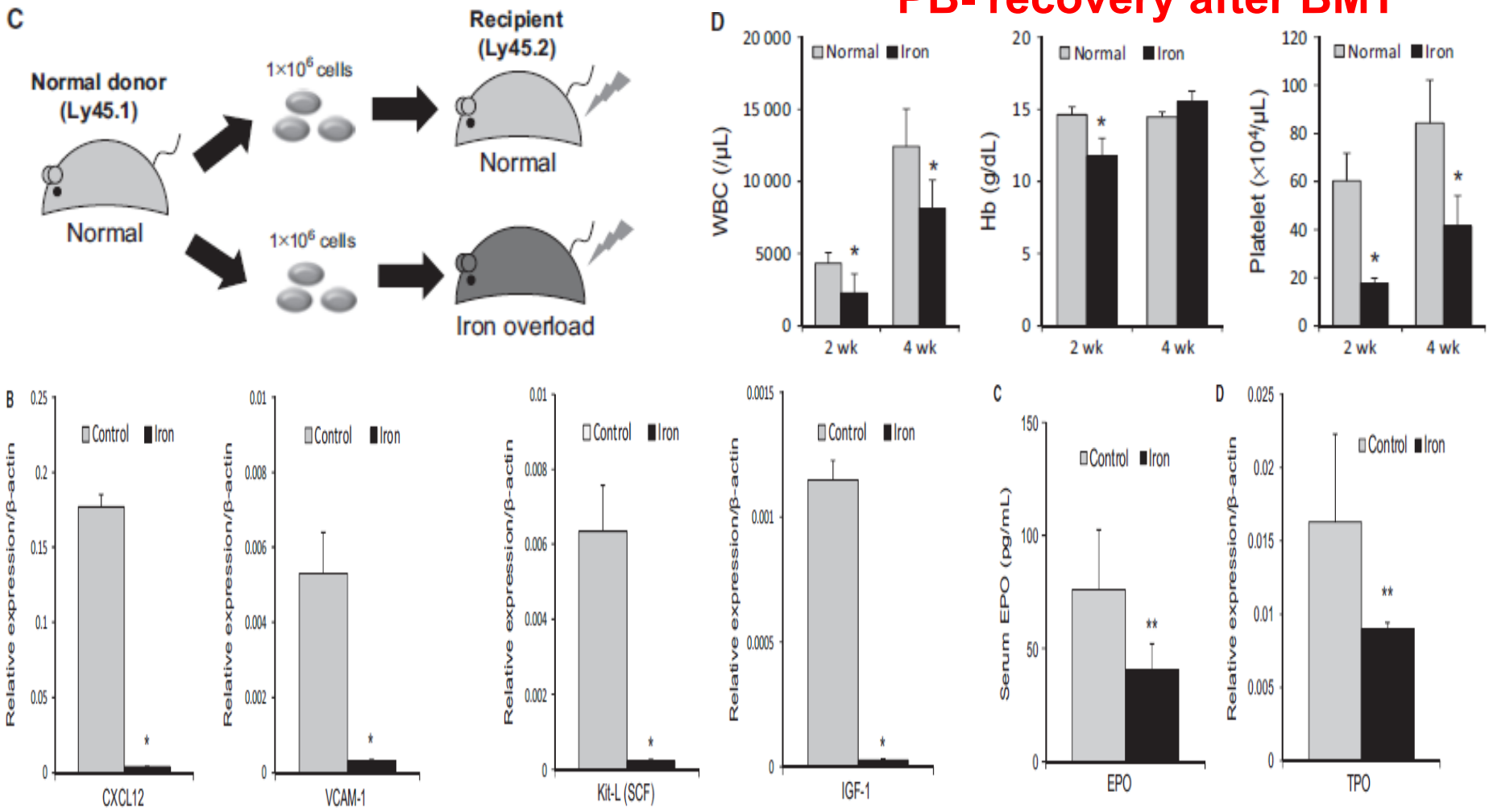
Deferasirox inhibits NF-κB activity in MDS patients.



Messa et al, Haematologica 2010

Damage due to Iron Overload:
3. Damage to the microenvironment

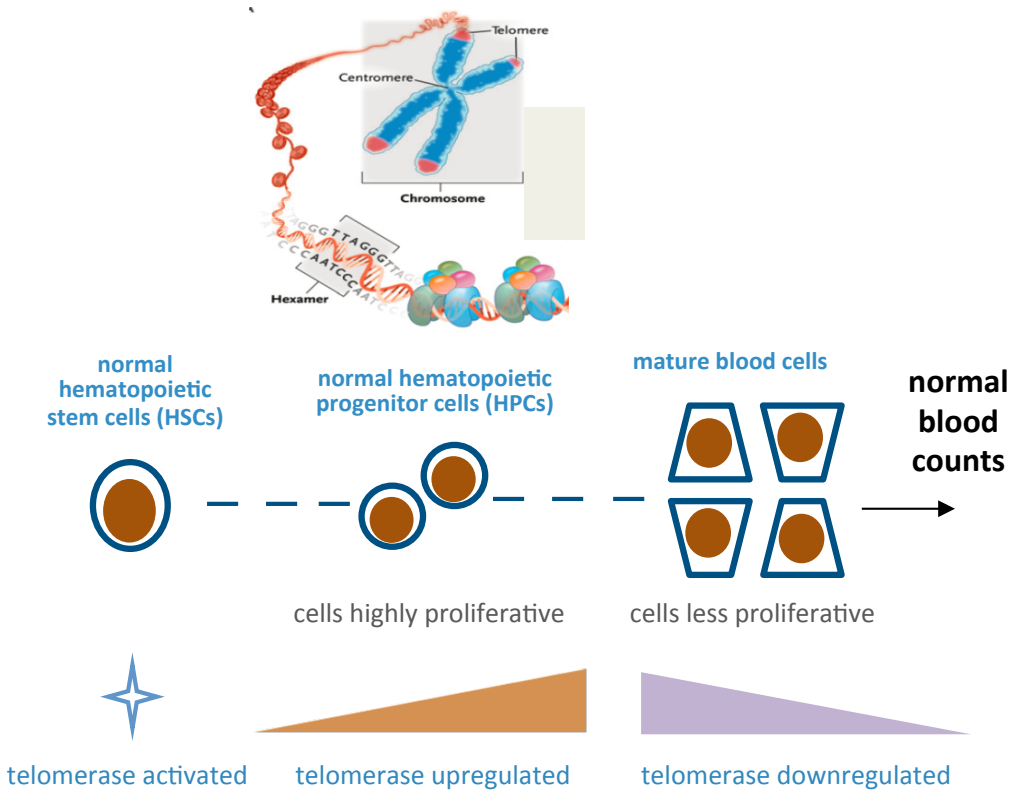
PB- recovery after BMT



- ✓ Iron overloaded mice have delayed reconstitution after SCT
- ✓ And reduced production of cytokines

Okabe et al, Europ J Hematol 2014

Telomerase and Imetelstat

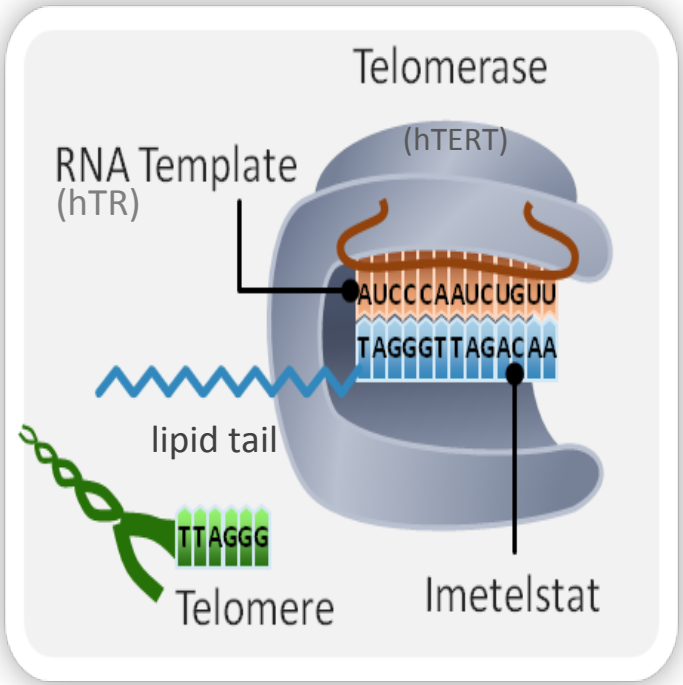


Telomerase enzyme:

- Reverse transcriptase comprised of an RNA component (hTR) and a reverse transcriptase catalytic protein subunit (hTERT)
- Binds to the 3' strand of DNA and adds TTAGGG nucleotide repeats to offset the loss of telomeric DNA occurring with each replication cycle
- Not active in somatic cells; transiently upregulated in normal hematopoietic progenitor cells to support controlled proliferation
- Highly upregulated in malignant progenitor cells, enabling continued and uncontrolled proliferation

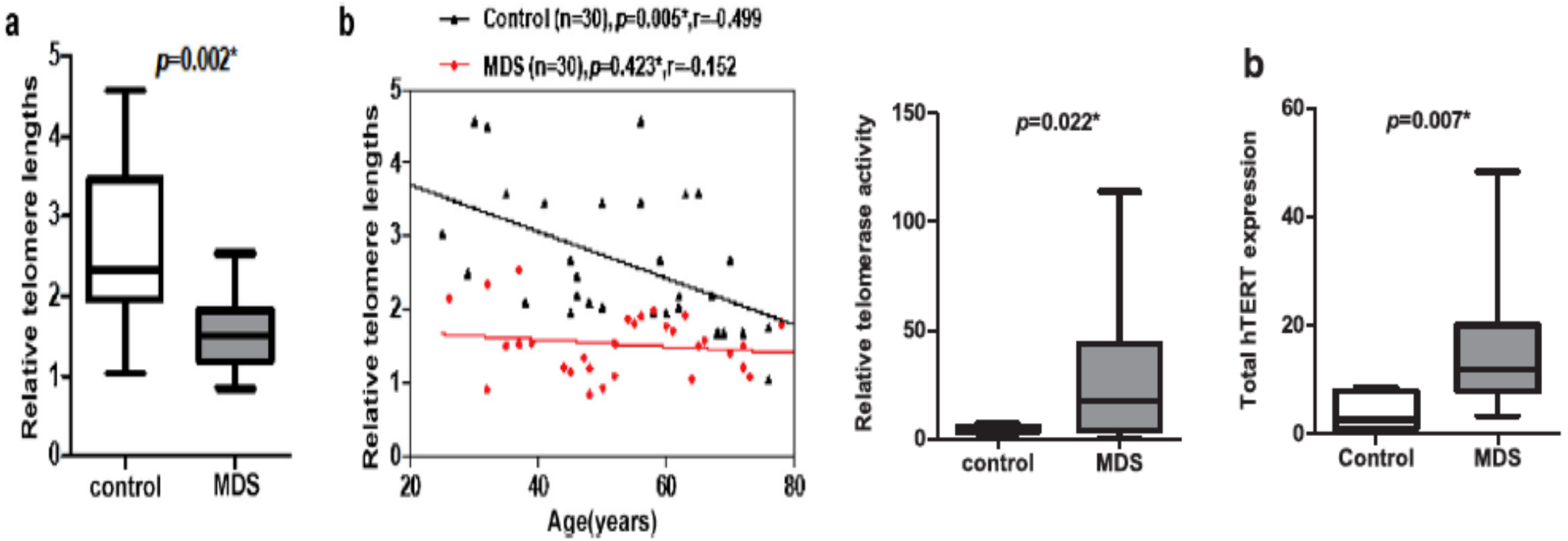
IMETELSTAT
A Telomerase Inhibitor

Imetelstat binds to RNA template preventing maintenance of telomeres



- **Proprietary:** 13-mer thio-phosphoramidate oligonucleotide complementary to hTR, with covalently-bound lipid tail to increase cell permeability/tissue distribution
- **Long half-life** in bone marrow, spleen, liver (estimated human t½ = 41 hr with doses 7.5 – 11.7 mg/kg);
- **Potent competitive inhibitor of telomerase**: IC50 = 0.5-10 nM (cell-free)

Telomerase Activity and Telomers in MDS



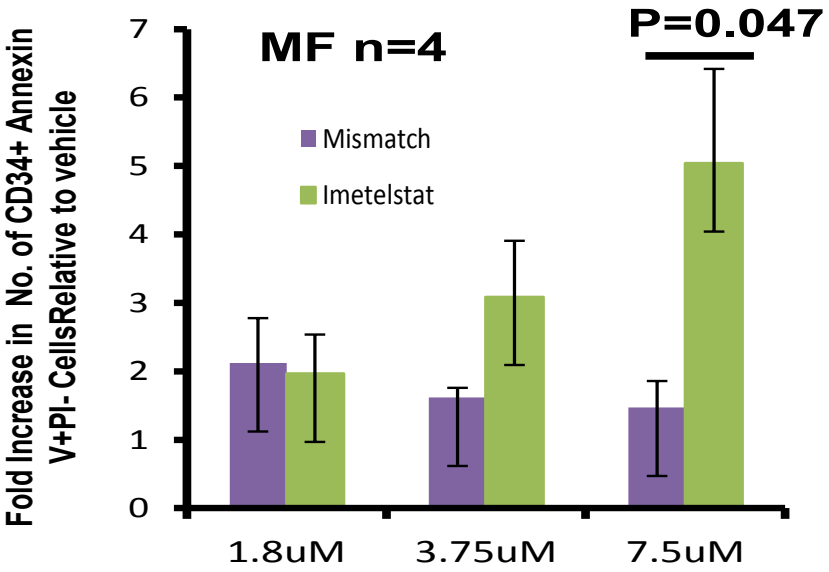
Telomerase activity increased in MDS, independent of

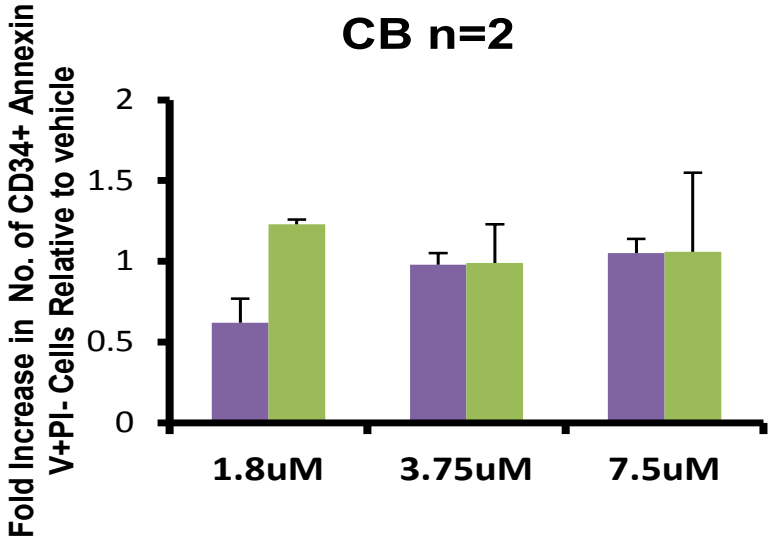
- ✓ IPSS
- ✓ Cytogenetics
- ✓ WHO subtype

Dong et al, Leuk Res 2014

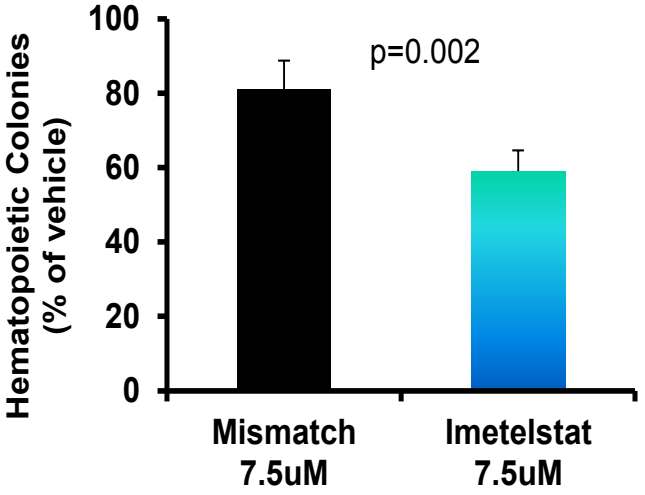
Differential effects of Imetelstat on hematopoietic progenitor cells from MF patients and normal cord blood

Imetelstat Induces Apoptosis of MF but not CB CD34+ Cells





Imetelstat Inhibits Hematopoietic Colony Formation by MF CD34+ Cells



Wang et.al, 2014 ASH abstract # 1879

Imetelstat in MDS (n=9)
7.5mg/kg 2 hr i.v D1 of every 28-day cycle

	MDS (n=9)
Median Age (range; yrs)	70 (54-93)
Male	7 (77.8%)
Transfusion dependent	8 (88.9%)
Median Hb (range; g/dL)	8.4 (6.7-9.8)
IPSS Risk Category	
INT-1	7 (77.8%)
INT-2	2 (22.2%)
Previously treated	7 (77.8%)
Median # of Prior Treatments (range)	3 (1-4)
Prior ESA	6 (66.7%)
Prior Lenalidomide	3 (33.3%)
Abnormal Karyotype	2 (22.2%)

Median duration of treatment = 49 wks (25-77 wks)

4 patients remain on treatment

TI response: 3/8 = 37.5%

Median TI duration in 3 pts: 24 wks (9-28)

Hematologic Toxicity	Worst Grade	MDS: #pts (%)
Anemia	3	6 (66.7%)
	4	–
Neutropenia	3	4 (44.4%)
	4	2 (22.2%)
Thrombocytopenia	3	2 (22.2%)
	4	1 (11.1%)

Grade ≥3 Non-Hematologic AEs

	MDS (n=9)
Fatigue	1 (11.1%)
Lung infection	0
Hyperkalemia	0
Atrial fibrillation	0
Heart failure	1 (11.1%)
Hypotension	1 (11.1%)
Dyspnea	0
Febrile neutropenia	0
Hyperuricemia	0
Hyponatremia	0
Sepsis	0
Abdominal pain	0
aPTT prolonged	0
Cardiac arrest	1 (11.1%)
GGT increased	0
Hyperglycemia	1 (11.1%)
Hypokalemia	0
Hypoxia	0
Lipase increased	0

Worst post-baseline CTC Grade (MDS, n=9)

	Any Worsening	1	2
ALT	5 (55.6%)	4 (44.4%)	1 (11.1%)
AST	5 (55.6%)	4 (44.4%)	1 (11.1%)
Alkaline Phosphatase	3 (33.3%)	3 (33.3%)	0
Total Bilirubin	0	0	0

Worsening defined as CTC grade elevated after baseline OR baseline result > ULN and result >= 1.5xbaseline.

iMERGE
Study Design

N~200

Part 1
Phase 2, single arm, open label
n up to 30

Imetelstat
7.5 mg/kg IV q4w; after 3 cycles escalate to 9.4 mg/kg IV q4w

Ongoing Data Review:
- Futility: ≤4 pts achieve TI
- Other clinical evidence of activity

Part 2
Phase 3, randomized, double-blind, placebo-controlled
n~170

RANDOMIZE

2:1

Imetelstat (n~115)

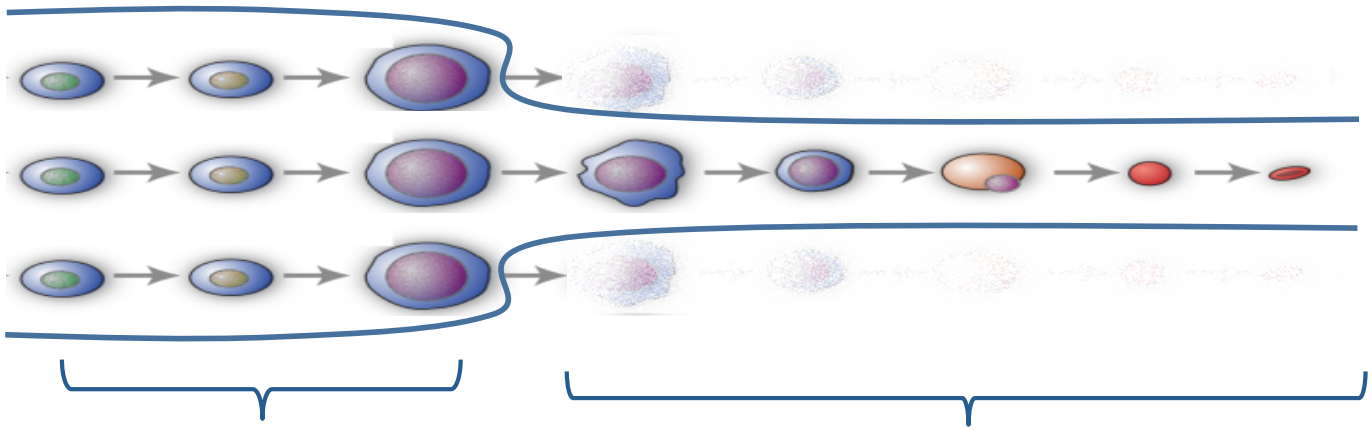
Placebo (n~55)

Stratification:
- Transfusion burden (4 / >4 units)
- Prior lenalidomide (yes / no)

Pre-medication: diphenhydramine, hydrocortisone 100-200mg (or equiv)
Supportive care: RBC transfusions, myeloid growth factors per local guidelines

IMerge
63935937MDS3001

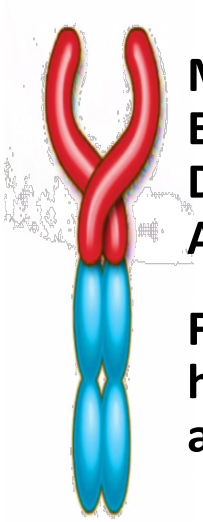
Ineffective Erythropoiesis in LR-MDS



EPO drives proliferation

Excessive GDF-induced Smad2/3 signaling inhibits RBC maturation

Luspatercept



Modified Extracellular Domain of ActRIIB receptor

Fc domain of human IgG_1 antibody

- Luspatercept (ACE-536), a modified activin receptor type IIB (ActRIIB) fusion protein, acts as a ligand trap for GDF11 and other TGF-β family ligands to suppress Smad2/3 activation;
- increased Hb in healthy volunteers
- In a murine model of MDS, murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia and increased Hb

Courtesy of U. Platzbecker

Luspatercept in Low/Int-1-Risk MDS
TD, Refractory or relapsing after ESA, ECOG 0-2

- Subcutaneous (SC) injection every 3 weeks
- **Base study (Phase II, n=58):** 3 months of treatment
  - ✓ Dose escalation phase (n=27): 0.125, 0.25, 0.5, 0.75, 1.0, 1.33, 1.75 mg/kg
  - ✓ 1st Expansion cohort (n=31): starting dose 1.0, titration up to 1.25 mg/kg

- **Extension study (n=32):** additional 24 months of treatment (ongoing)
  - ✓ Starting dose 1.0 mg/kg or current dose, titration up to 1.25 mg/kg

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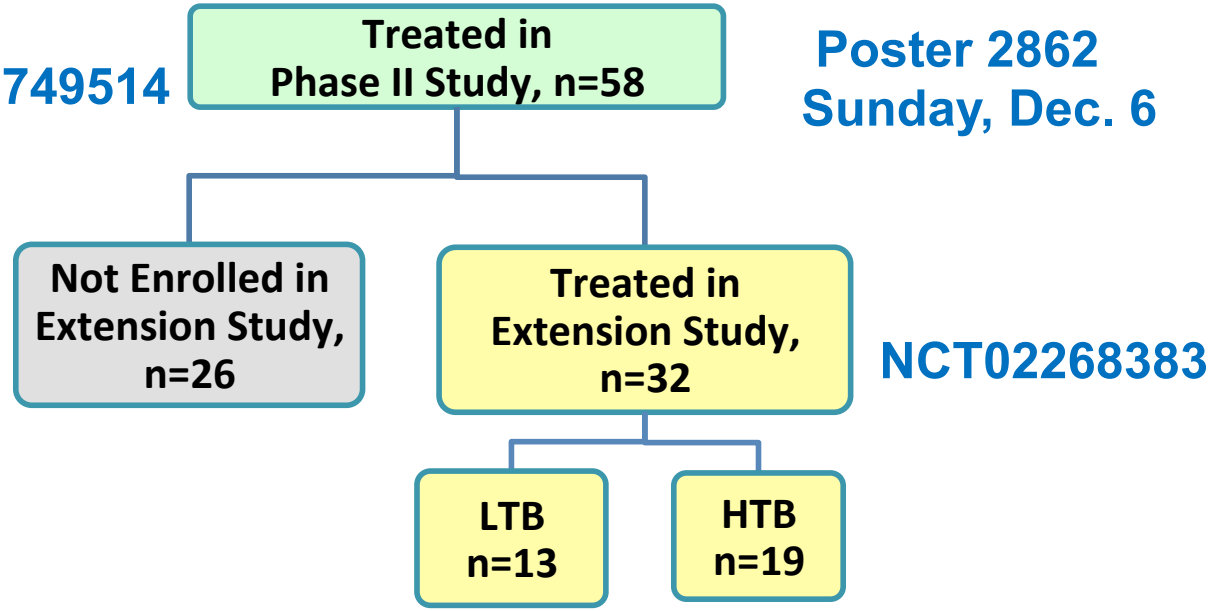


Poster 2862
Sunday, Dec. 6

NCT02268383

Courtesy of U. Platzbecker

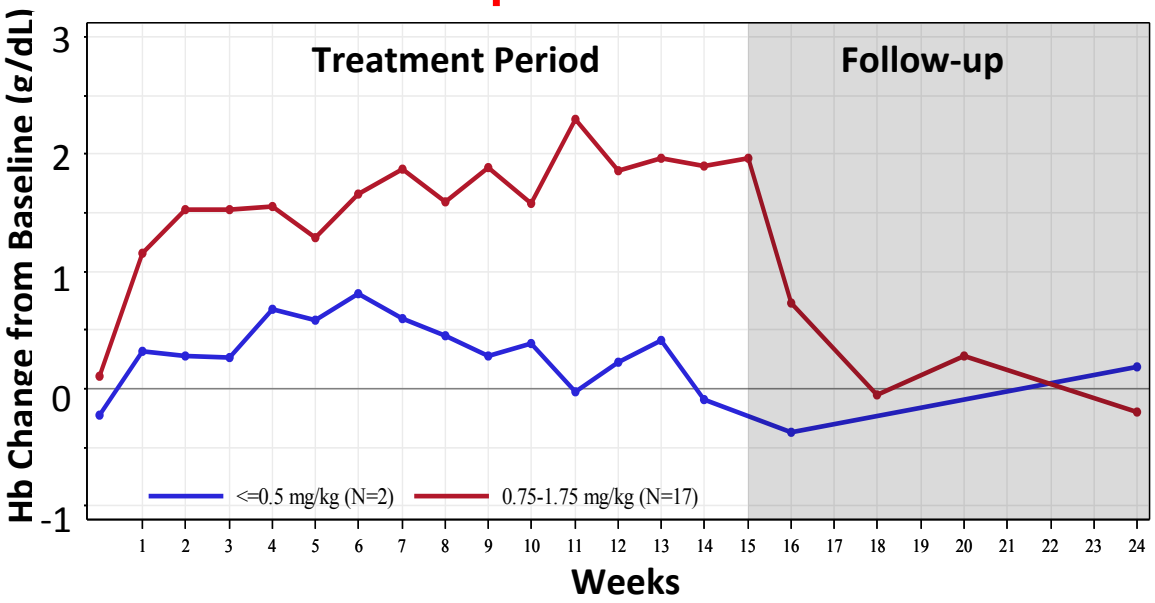
Phase II study (n=58): 3 months of treatment

Category n (%)	Overall N=58
WHO Subtypes	
RARS	11 (19%)
RCMD-RS	29 (50%)
RCMD	6 (10%)
RAEB-1	8 (14%)
Other (RAEB-2, del(5q), MDS/MPN)	4 (7%)
IPSS	
Low	27 (47%)
Int-1	30 (52%)
Int-2	1 (2%)
IPSS-R	
Very Low	2 (3%)
Low	31 (53%)
Intermediate	21 (36%)
High	3 (5%)
Very High	1 (2%)

Responses (over 8 weeks)	0.125-0.5 mg N=9, n (%)	0.75-1.75 mg N=49, n (%)
Low Transf. Burden (< 4U/8wk)		
IWG HI-E, Hb increased ≥ 1.5 g/dL	0/2 (0%)	8/17 (47%)
RBC TI	0/0 (0%)	6/8 (75%)
High Transf. Burden (≥ 4U/8wk)		
IWG HI-E (≥ 4U reduction)	2/7 (29%)	16/32 (50%)
RBC TI	1/7 (14%)	8/32 (25%)

Neutrophil responses (IWG HI-N) in 4 of 8 (50%) patients with baseline neutrophil count < 1.0 X 10^9/L

LTB patients



Platzbecker et al, Poster 2862

Extension study (n=32)

✓ Starting dose 1.0 mg/kg or current dose,
titration up to 1.25 mg/kg, additional 24 months

Category	N=32 n (%)
WHO Subtypes	
RARS	8 (25%)
RCMD-RS	19 (59%)
RCMD	2 (6%)
RAEB-1	3 (9%)
IPSS	
Low	22 (69%)
Int-1	10 (31%)
IPSS-R	
Very Low	9 (28%)
Low	14 (44%)
Intermediate	8 (25%)
High	1 (3%)

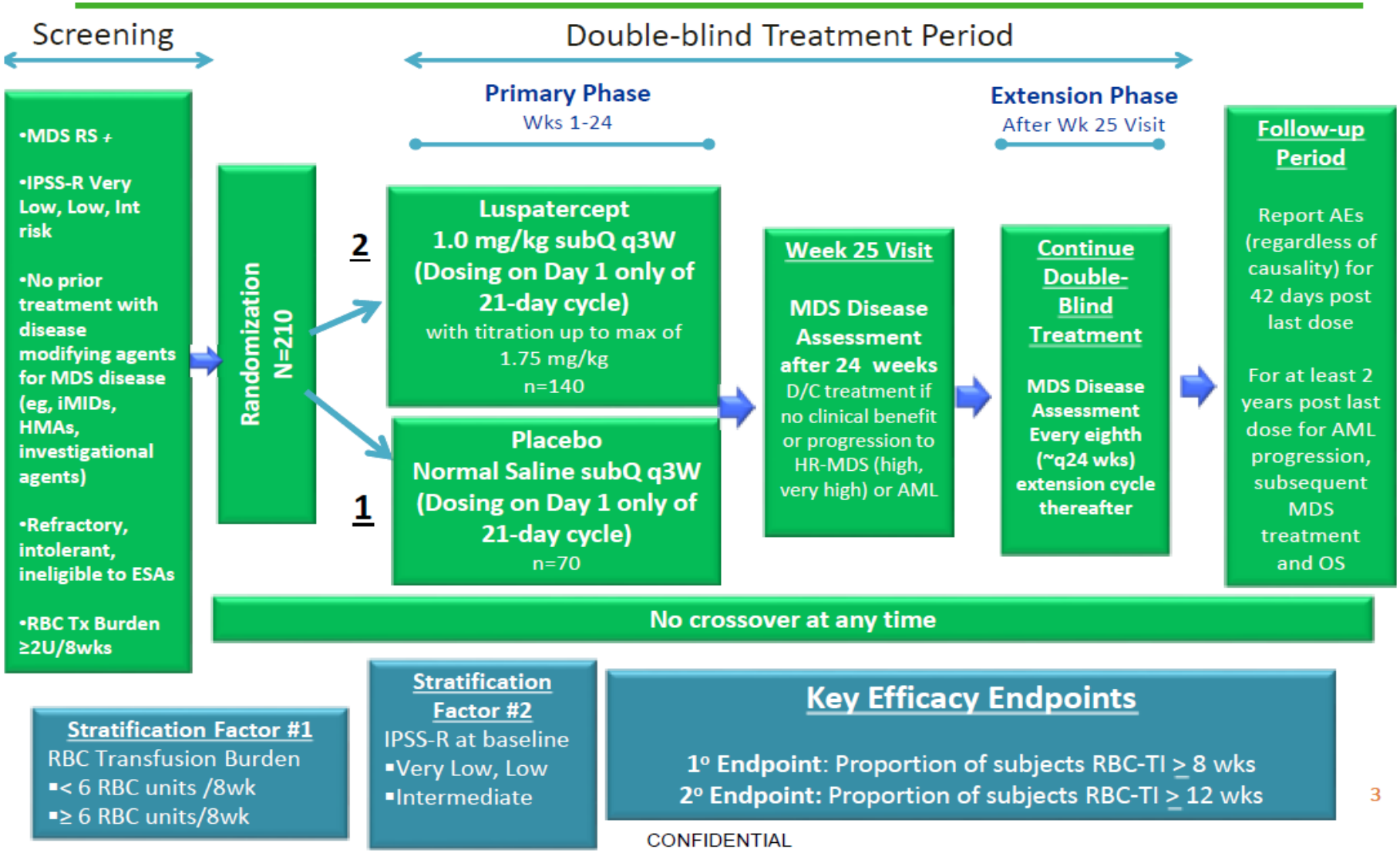
n (%)	IWG HI-E N=32	RBC-TI* N=22
All Patients	22/32 (69%)	11/22 (50%)
RS positive	21/29 (72%)	10/19 (53%)
Baseline EPO		
< 200 U/L	16/20 (80%)	7/13 (54%)
200-500 U/L	5/7 (71%)	2/4 (50%)
> 500 U/L	1/5 (20%)	2/5 (40%)
Prior ESA Treatment		
Yes	12/19 (63%)	7/14 (50%)
No	10/13 (77%)	4/8 (50%)

Giagounidis et al, Oral Abs: Luspatercept Treatment Leads to Long Term Increases in Hemoglobin and Reductions in Transfusion Burden in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS): Preliminary Results from the Phase 2 PACE-MDS Extension Study

Celgene ACE536-MDS-001
The Medalist Trial

MEDALIST: Study Design

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



Summary

- Most LR-MDS respond to EPO, which still represents the first treatment choice in LR-MDS with anemia
- Lenalidomide has high efficacy in patients with isolated del(5q), who often achieve TI and cytogenetic response, indicating the complex mechanism of action of the drug on the 5q- clone
- Iron chelation improves survival and induces hematologic response, due both to iron-dependent and iron-independent mechanisms (probably)
- New drugs will be soon available