When are erythroid stimulating agents (ESA) effective and what can we offer after their failure?

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DISCLOSURES

- Novartis, Pfizer, Takeda, and BMS (Advisory board and research grants)
- Sandoz (research grant)
- Novartis, Takeda, BMS (Honoraria)

PHASE III trials

EPOANE

- EPO alfa 450UI/kg (30000 IU for 60kg /week) Endpoint : ER at W24
- Same characteristics of patients (IPSS int-1: 49%),
- rate of previous transfusions (38%)
- ER: 31,8% with EPO (45% after response review committee) vs 4,4%
- RBC transfusions at W24: 25% with EPO arm vs 54%
- Flexibility for EPO adjustment, and evaluation of response not only at W24

Fenaux et al, Leukemia 2018

ARCADE

- Darbepoietin 500µg/3w (after 48w: Darbe 500µg/2w): Endpoint ER at W24
- IPSS int-1: 57%
- rate of previous transfusions (27%)
- ER: 14,7% with darbe vs 0%
- RBC transfusions at W24: 36% with Darbe vs 59% in placebo
- Stop of darbepoietin whenever Hb reached 12g/l

Platzbecker and al, Leukemia 2017

EPO alfa: EMA authorization for low risk MDS in 2017

Hb<10g/dl or RBC transfusion dependence
IPSS low risk 0 or 1
% of blasts<10% if karyotype non available

Response rate: between 40 and 60%
Median duration of response 22 months

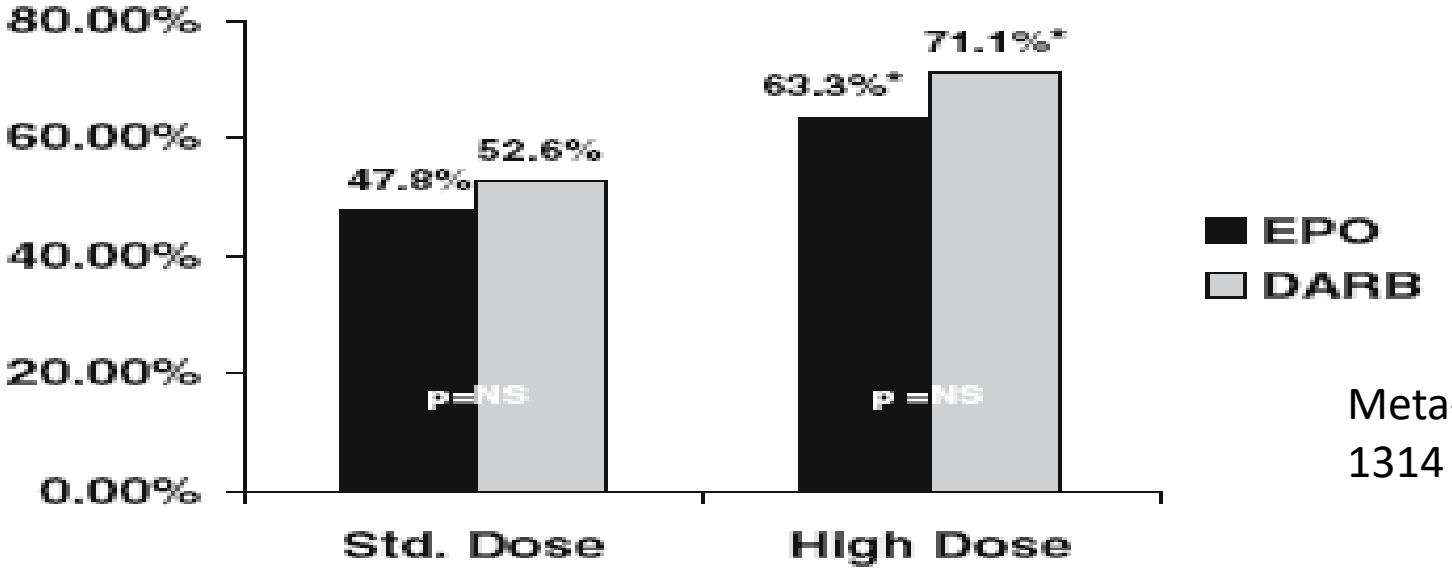
Park s, Blood 1998

No difference between EPOα and darbepoietin

- **No difference between EPO α (n=925) and darbepoetin (n=329)**

=> Overall response rate: 57,6 % vs 59,4% (p =0,828)

Higher response rates with high doses of ESA (p<0,001)



Meta-analysis
1314 patients, 22 studies

30000 to 40000 UI/week
150µg darbe/ 2 week

60000 to 80000 UI/week
300µg darbe/week

Moyo et al, Ann Hematol 2008

Predictive factors of ESA failure

- IPSS-R
- EPO levels
- Gene mutation burden
- Lower serum ferritin level

The role of IPSS-R in assessing erythroid response

(collaborative work of the GFM, the FISM and Düsseldorf registry)

Patients treated with ESA with at least 6 months of follow up

989 pts

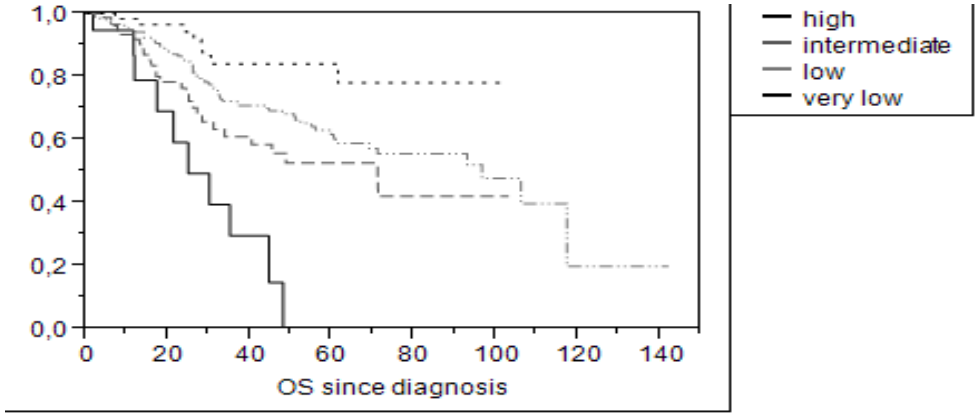
221 pts FISM register
63 pts from Dusseldörf
705 pts from the GFM

exclusion

Hb>10g/dl
Ferritinemia<20
EPO>500
With missing data

456 pts

61% IWG 2006 RR



P<0.0001

V. Santini, U Germing and S Park al, Blood 2013: 122(13):2286-8

The role of IPSS-R, EPO and serum ferritin levels in assessing erythroid response

IPSS	n	% pts	RR (IWG 2006)	univariate	multivariate
low	256	55%	72		
Int-1	210	45%	52	0.001	
IPSS-R					
very low	69	15%	85		
low	281	61%	68		
intermediate	87	19%	48		
high	19	4%	31	<0.0001	<0.0001
EPO, mU/ml					
≤100	306	67%	75		
>100	150	33%	45	<0.0002	
≤200	393	86%	75		
>200	63	13%	31	<0.0001	<0.0001
Serum ferritin, ng/ml					
≤350	224	49%	72		
>350	232	51%	58	0.001	0.002

score

IPSS-R
very low=0
Low=1
Int=2
High=3

EPO>200=1

SF>350=1

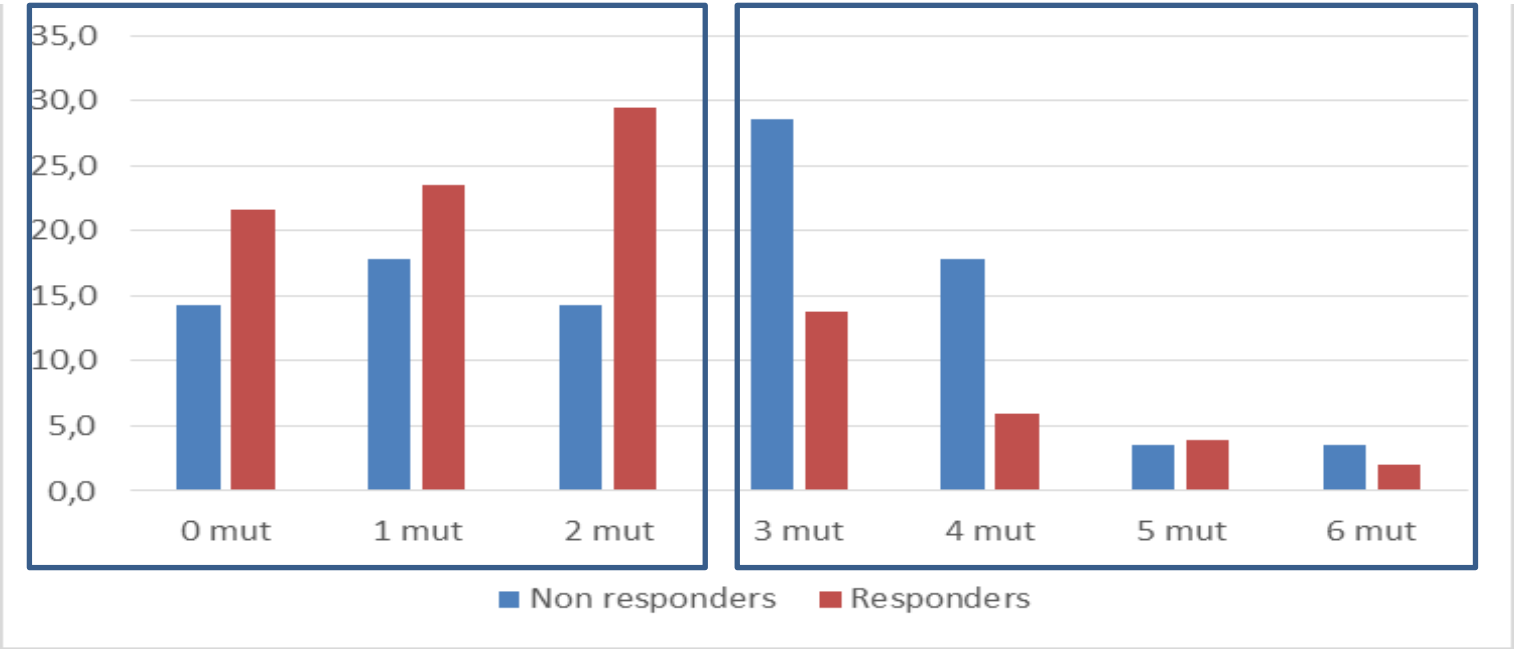
SCORE (n=)	IWG 2006 RESPONSE RATE
0 (n=40)	85
1 (n=115)	80
2 (n=144)	64
3 (n=95)	40
4 (n=64)	20

35%

V. Santini, U Germing and S Park al, Blood 2013

Distribution of the mutations according to response to ESA

N mutations	HI-E (%)
0	73
1	71
2	79
3	47
4	38



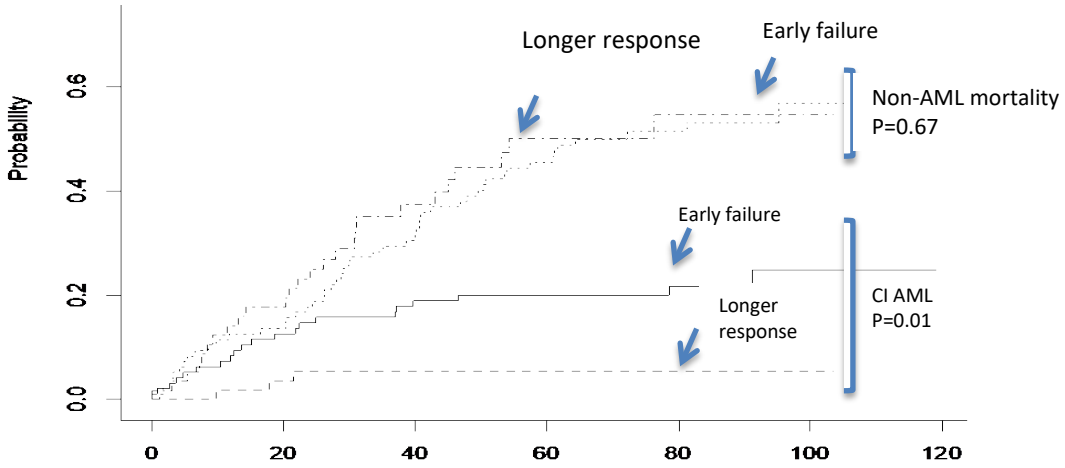
N=79 patients

Presence of >2 mutations predicted worse HI-E to ESA in lower risk MDS.

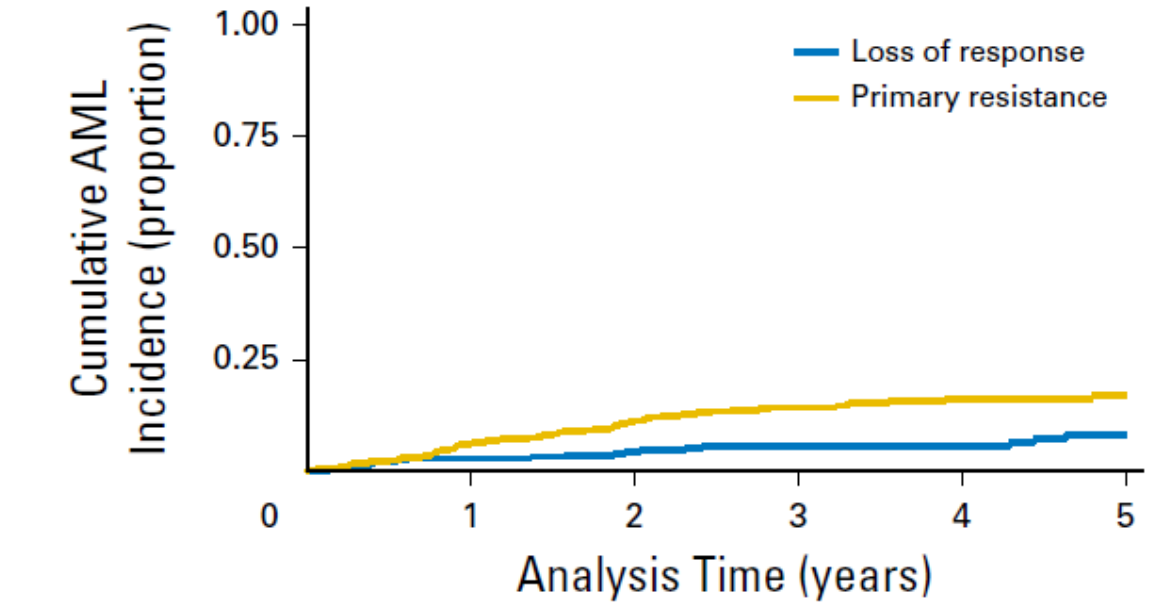
≤2 mutations: 74% vs > 2 mutations: 46% (p=0.01)

O Kosmider, S. Park, Haematologica. 2016 Jul;101(7):e280-3

Early failure to ESA is correlated with higher incidence of AML



C.Kelaidi, Leukemia 2013



No. at risk:						
Loss of response	416	320	239	174	125	86
Primary resistance	592	459	342	253	160	101

S. Park, JCO 2017

NEJM Evidence

Published June 12, 2022

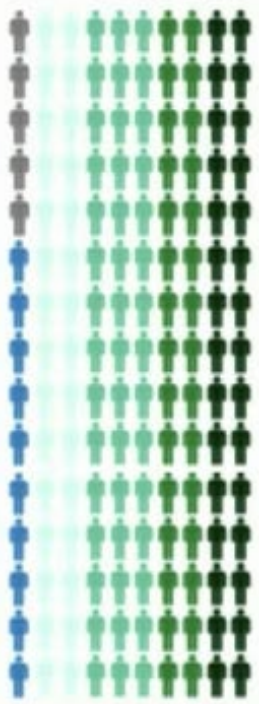
DOI: 10.1056/EVIDoa2200008

ORIGINAL ARTICLE

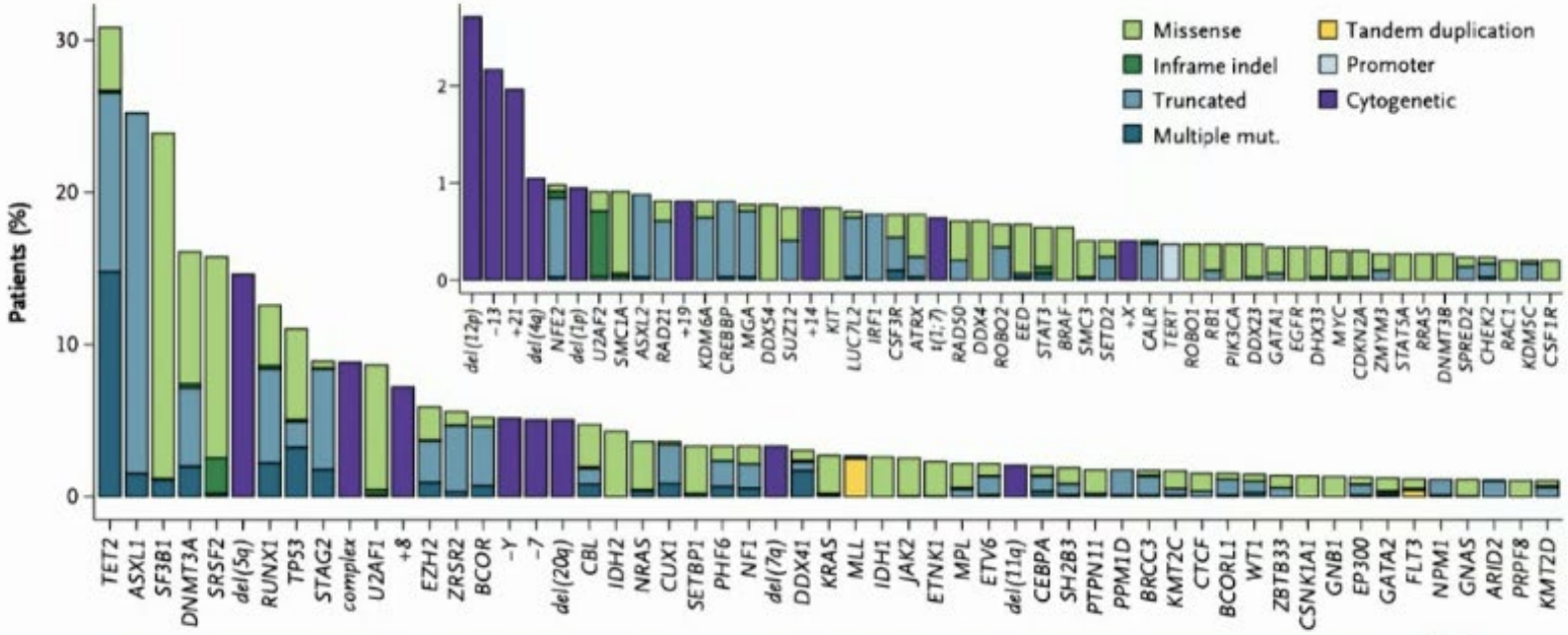
Molecular International Prognostic Scoring System for Myelodysplastic Syndromes

E. Bernard et al, 2022

Comprehensive molecular annotation in MDS



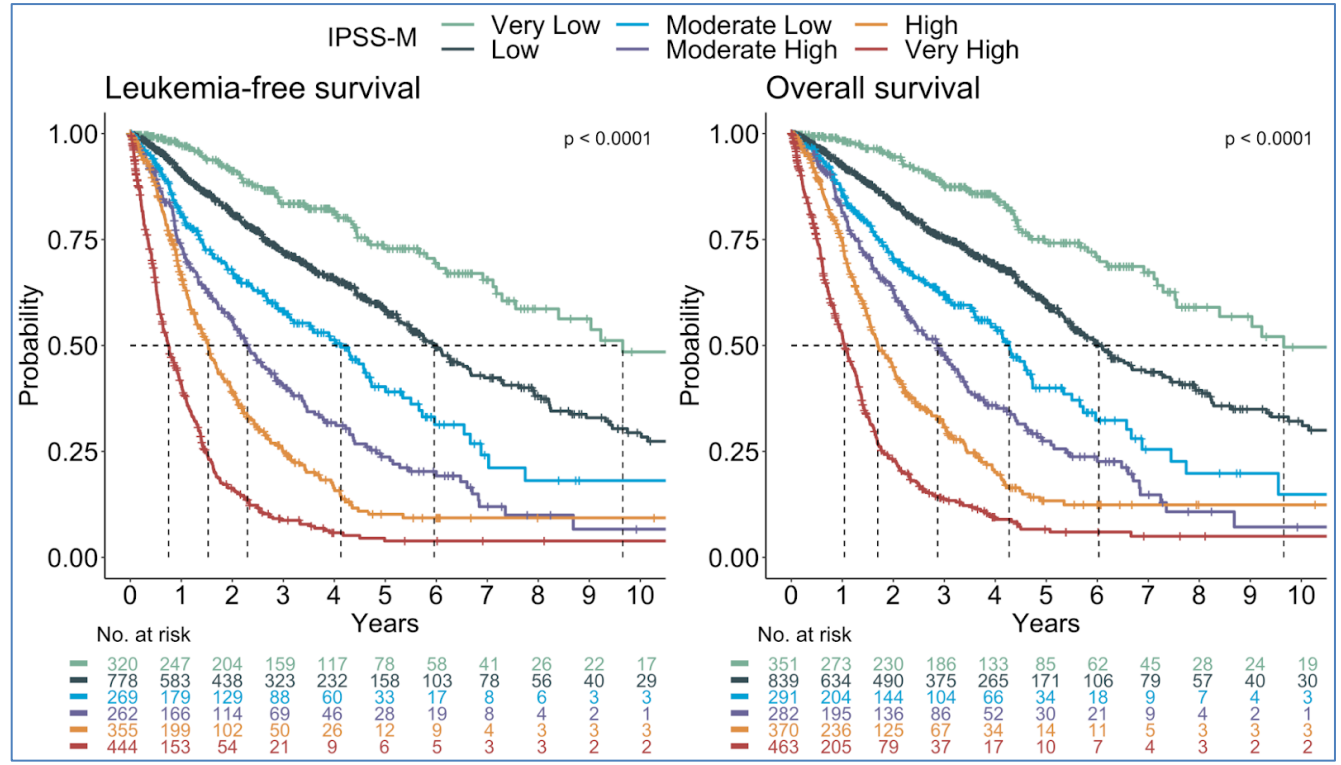
n=2,957



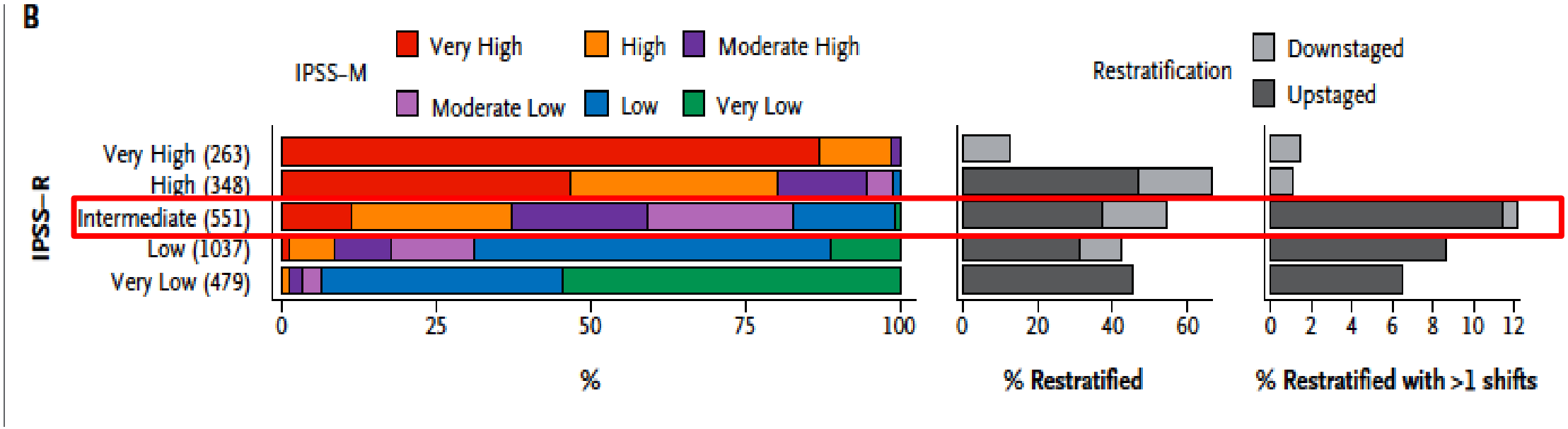
53% gene mutations. 4% cytogenetic alterations. 37% both. 94%

E. Bernard et al, NEJM evidence 2022

Category	Variable	Multivariable model: hazard ratio[#] (95% CI)	Weight w	Scaling x^{mean}
confounder	$^{y}/_{10}$ **Age**, in years	1.23 (1.05 - 1.43)	N/A	N/A
	Sex:Male	1.22 (1.06 - 1.41)	N/A	N/A
	Type:Secondary/Therapy-related	1.36 (1.10 - 1.68)	N/A	N/A
clinical	% **Bone Marrow Blasts**, in %	1.42 (1.30 - 1.55)	0.352	0.922
	$^{y}/_{100}$ min(**Platelets**,250), in x10^{9}/L	0.80 (0.72 - 0.89)	-0.222	1.41
	Hemoglobin, in g/dL	0.84 (0.81 - 0.88)	-0.171	9.87
cytogenetics	**IPSS-R category vector**[&]	1.33 (1.21 - 1.47)	0.287	1.390
gene main effects 17 variables, 16 genes	***TP53***^{multi}	3.27 (2.38 - 4.48)	1.18	0.0710
	MLL^{PTD}	2.22 (1.49 - 3.32)	0.798	0.0247
	FLT3$^{ITD+TKD}$	2.22 (1.11 - 4.45)	0.798	0.0108
	SF3B1^{5q}	1.66 (1.03 - 2.66)	0.504	0.0166
	NPM1	1.54 (0.78 - 3.02)	0.430	0.0112
	RUNX1	1.53 (1.23 - 1.89)	0.423	0.126
	NRAS	1.52 (1.05 - 2.20)	0.417	0.0362
	ETV6	1.48 (0.98 - 2.23)	0.391	0.0216
	IDH2	1.46 (1.05 - 2.02)	0.379	0.0429
	CBL	1.34 (0.99 - 1.82)	0.295	0.0473
	EZH2	1.31 (0.98 - 1.75)	0.270	0.0588
	U2AF1	1.28 (1.01 - 1.61)	0.247	0.0866
	SRSF2	1.27 (1.03 - 1.56)	0.239	0.158
	DNMT3A	1.25 (1.02 - 1.53)	0.221	0.161
	ASXL1	1.24 (1.02 - 1.51)	0.213	0.252
	KRAS	1.22 (0.84 - 1.77)	0.202	0.0271
	SF3B1$^{\alpha}$	0.92 (0.74 - 1.16)	-0.0794	0.186
gene residuals[$] 1 variable, 15 genes	min(**Nres**,2) Possible values are 0,1 or 2	1.26 (1.12 - 1.42)	0.231	0.388



E. Bernard et al, NEJM evidence 2022



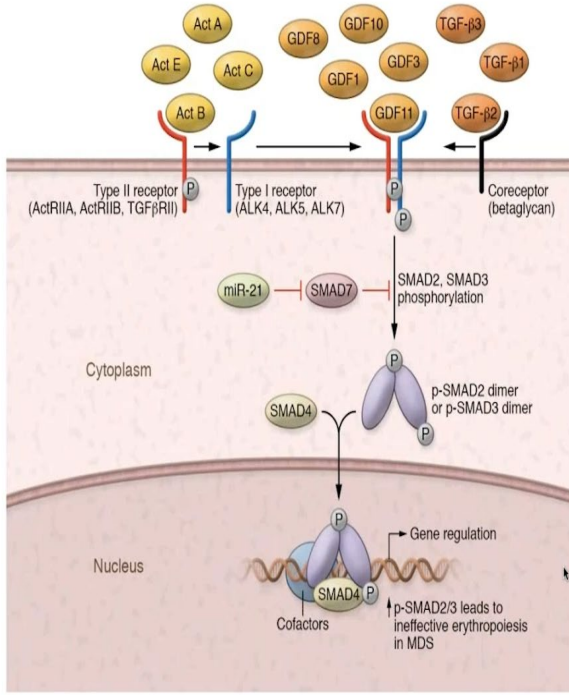
IPSS-R => IPSS-M: 46% of patients shift from a category to another one

Interesting to refine intermediate risk MDS patients?

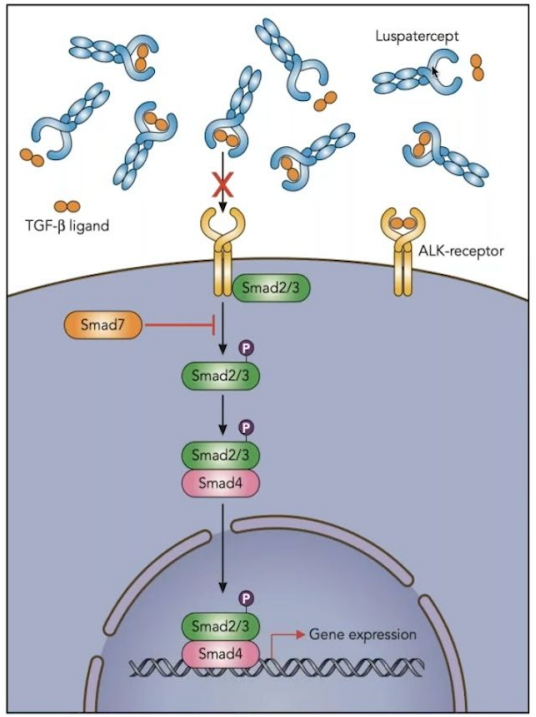
E. Bernard et al, NEJM evidence 2022

How to manage ESA failure?

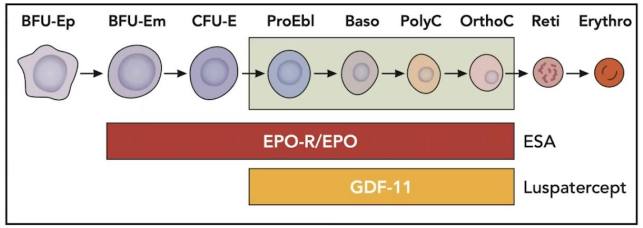
TGF-β superfamily signalling



Effects of a GDF ligand trap



Kubasch, Fenaux, Platzbecker. Blood Adv in press



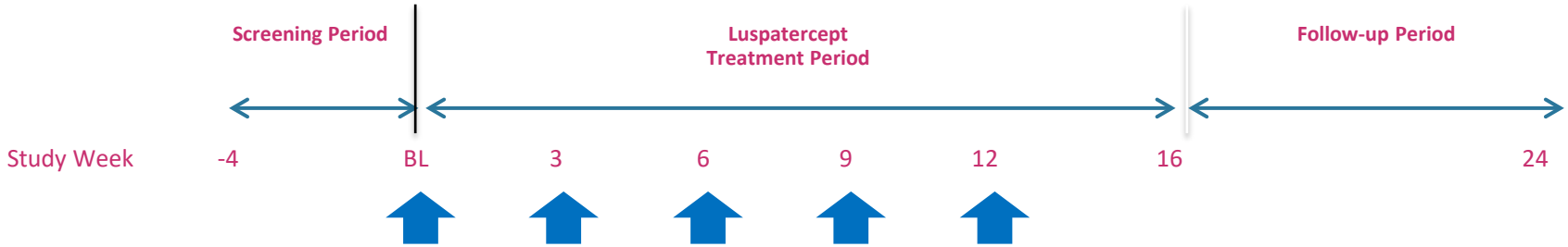
1.Luspatercept and MDS-RS

Luspatercept PACE-MDS Study: LR ESA R/R MDS

- Phase 2, multicenter, open-label, dose-finding study in IPSS low/int-1 MDS
- **Eligibility criteria:** EPO >500 U/L or nonresponsive/refractory to ESA; no prior azacitidine or decitabine; no current lenalidomide, ESA, G-CSF

- **Primary efficacy endpoints**
  - Low Transfusion Burden (LTB, <4U RBC/8 weeks, Hgb <10 g/dL): Hemoglobin increase of ≥ 1.5 g/dL for ≥ 2 weeks
  - High Transfusion Burden (HTB, ≥4U RBC/8 weeks): Reduction of ≥4U or ≥50% units transfused over 8 weeks

- Luspatercept administered SC every 3 weeks for 3 months



NCT01749514, EudraCT 2012-002523-14

Uwe Platzbecker, Lancet Oncology 2017

Hemoglobin and Transfusion Response rates Impact of Dose (Base study) PACE-MDS Study

- **HI-E 63% and RBC TI 38% in all MDS patients**
- **HI-E 43% and RBC TI 29% in MDS without RS patients**

	IWG HI-E*	RBC-TI†
All patients	32/51 (63%)	16/42 (38%)
Transfusion burden		
Low transfusion burden (<4 red blood cell units per 8 weeks)	11/17 (65%)	6/8 (75%)
High transfusion burden (≥4 red blood cell units per 8 weeks)	21/34 (62%)	10/34 (29%)
Previous use of ESAs		
Yes	21/34 (62%)	11/29 (38%)
No	11/17 (65%)	5/13 (39%)
Previous use of lenalidomide		
Yes	5/8 (63%)	1/8 (13%)
No	27/43 (63%)	15/34 (44%)
Serum erythropoietin concentration		
<200 IU/L	19/25 (76%)	10/19 (53%)
≥200 IU/L to ≤500 IU/L	7/12 (58%)	4/9 (44%)
>500 IU/L	6/14 (43%)	2/14 (14%)
Ring sideroblast status		
Positive (≥15% ring sideroblasts)	29/42 (69%)	14/33 (42%)
Negative (<15% ring sideroblasts)	3/7 (43%)	2/7 (29%)
Unknown	0/2	0/2
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‡		
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

Uwe Platzbecker, Lancet Oncology 2017

MEDALIST Study design

Inclusion Criteria

- MDS with RS (WHO): ≥ 15% RS or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- Non-del(5q) MDS
- IPSS-R Very low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 U/8 weeks
- No prior treatment with disease-modifying agents (e.g. IMiD agents, HMAs)

Randomized 2:1

Luspatercept 1.0 mg/kg (s.c.) every 21 days
(n = 153)

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 3 weeks
(n = 76)

Disease and response assessment
Week 24 and every 6 months
Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria

Patients followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment, and overall survival; crossover between groups was not allowed

Fenaux et al, NEJM 2020

Baseline patient characteristics MEDALIST study

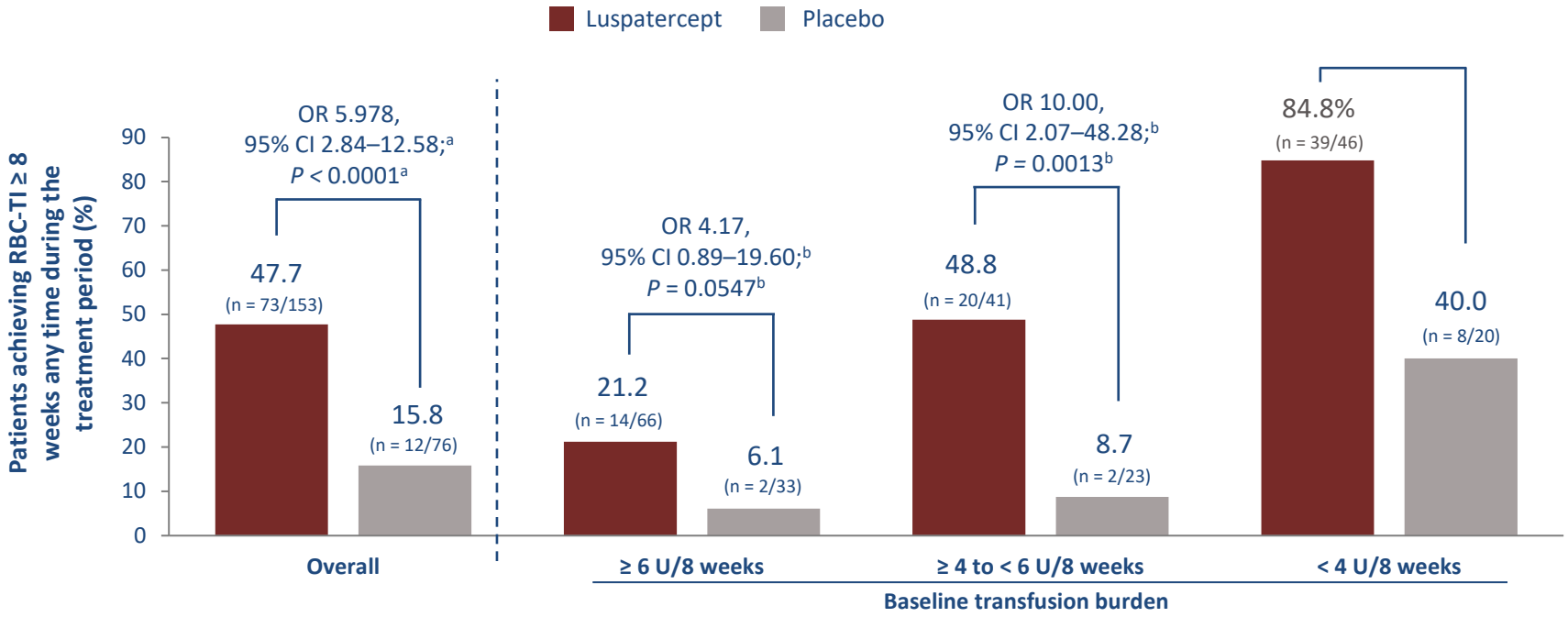
Characteristic	Luspatercept (n = 153)	Placebo (n = 76)
Age, median (range), years	71 (40–95)	72 (26–91)
Male, n (%)	94 (61.4)	50 (65.8)
RBC transfusion burden, median (range), U/8 weeks[a]	5 (1–15)	5 (2–20)
≥ 6 U/8 weeks, n (%)	66 (43.1)	33 (43.4)
≥ 4 to < 6 U/8 weeks, n (%)	41 (26.8)	23 (30.3)
< 4 U/8 weeks, n (%)	46 (30.1)	20 (26.3)
IPSS-R, n (%)[b]		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75.0)
Intermediate	25 (16.3)	13 (17.1)
***SF3B1* mutation, n (%)[c]**	138 (93.2)[c]	64 (86.5)[c]
Serum EPO, n (%)[d]		
< 200 U/L	88 (57.5)	50 (65.8)
≥ 200 U/L	64 (41.8)	26 (34.2)
Baseline hemoglobin, median (range), g/dL[e]	7.6 (6–10)	7.6 (5–9)
Serum ferritin, mean (SD), µg/L	1,348.0 (971.24)	1,503.8 (1,242.94)

[a] In the 16 weeks prior to randomization. [b] 1 patient in the luspatercept arm was classified as IPSS-R High-risk. [c] Of patients with available baseline gene mutation data: n = 148 in the luspatercept arm; and n = 74 in the placebo arm; no patients with *SF3B1* mutation had RS < 15%.[d] Data were missing for 1 patient in the luspatercept arm. [e] Baseline hemoglobin was defined as the last value measured on or before the date and time of first dose.

EPO, erythropoietin; SD, standard deviation.

Fenaux et al,. NEJM 2020

RBC-TI ≥ 8 weeks Achieved any time during treatment period: MEDALIST study



- **Primary endpoint previously reported:** **37.9%** luspatercept versus **13.2%** placebo patients achieved RBC-TI ≥ 8 weeks during Weeks 1–24 (*P* < 0.0001)

Luspatercept:
Good safety profile
FDA and EMA approvals for MDS-RS

Fenaux et al., NEJM 2020

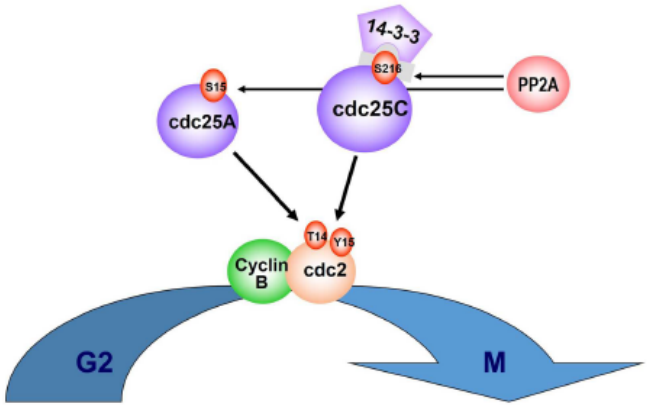
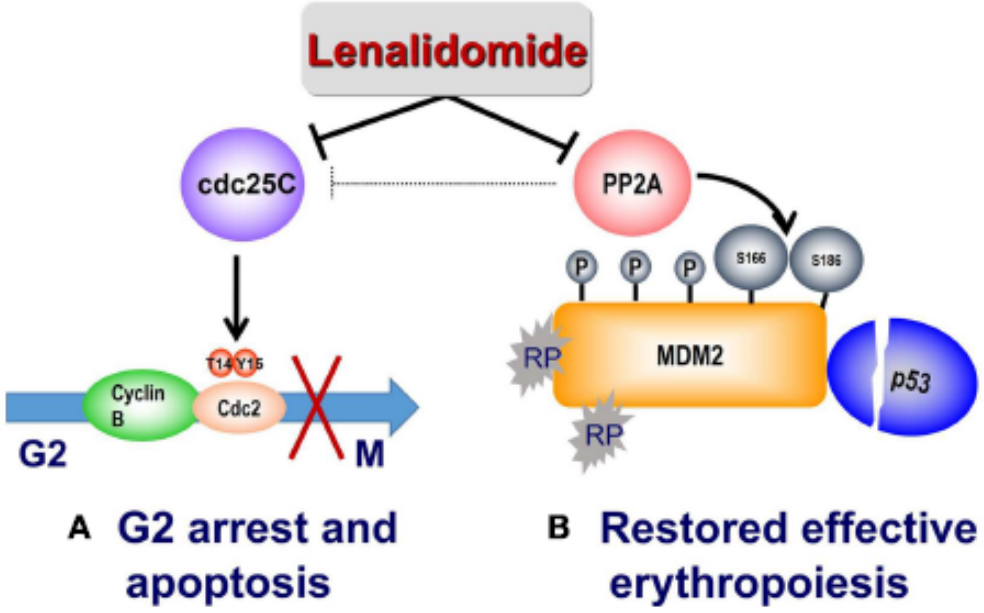


FIGURE 1 | CDC25C and PP2Acα regulatory role on cell cycle. Entry into mitosis is mediated via PP2A dephosphorylation of Cdc25C, at the regulatory serine substrate (Ser[216]), leading to 14-3-3 displacement and nuclear translocation of the CyclinB/cdc2 complex. PP2A also regulates phosphorylation of Cdc25A at Ser[15]. Phosphorylation of tyrosine (Tyr[15]) and threonine (Thr[14]) residues within the ATP binding domain of cyclin-dependent kinase-1 (CDK-1, or cdc2) inhibit CDK-1/Cyclin B complexes and cell-cycle progression from G_2 to M.



Sallman et al, Frontiers in Oncology 2014

2. Lenalidomide and lower risk MDS

Lenalidomide trials

Drug	trial name	type of trial	pts	response	reference
Lenalidomide	MDS003	Phase II trial	148 LR MDS with del 5q, transfusion dependent	TI: 67%, Cy Resp: 70%, Cy CR: 50%	List et al, NEJM 2006
Lenalidomide	MDS004	phase III trial	205 LR-MDS with del 5q, transfusion dependent	TI-182d: 57,4% (10mg, p< 0,0001 vs placebo), 37,2% (5mg, p=0,0001 vs placebo), 2,2% (placebo)	Fenaux et al, Blood 2011
Lenalidomide	MDS005	phase III trial	239 LR –MDS without del 5q	TI>8 weeks 26,9% vs 2,5%, p< 0,001; Hb increase 19,4% vs 2,5%	Santini et al, JCO 2016
LEN EPO vs LEN	GFM LEN EPO	phase III trial	131 LR MDS non del5q ESA resistant or Tdependent	TI and HI-E: 63,6% vs 36,9% LEN-EPO vs LEN alone), HI-E 39,4% vs 23,1%	Toma et al, Leukemia 2016
LEN EPO vs LEN	US intergroup trial	phase III trial	195 pts LR MDS non del5q	Ov ER 46,5% vs 32,3% (LEN-EPO vs LEN alone)	List et al, JCO 2021

Lenalidomide practical recommendations (but not approved by FDA)

- MDS refractory to ESA
- Lenalidomide+ESA
- 10 mg daily
- 3-month trial: response in 40% of patients
- Propose to pts with platelets > 100 G/L and absolute neutrophil count> 1 G/L
- No prior use of HMA

3. Hypomethylating agents trials

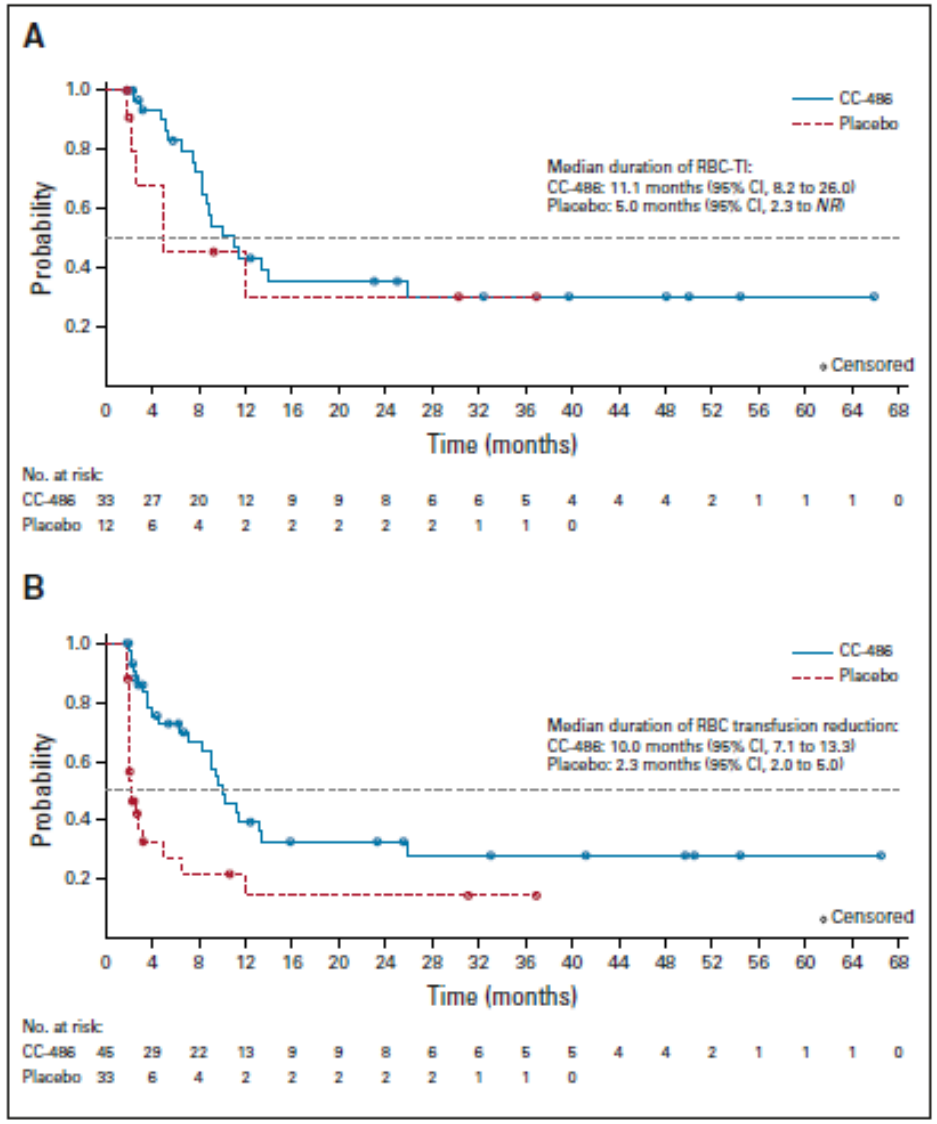
Drug	trial name	type of trial	pts	response	reference
AZA+EPO 5days	NMDSG08A	phase II randomized trial	30 LR MDS ESA resistant or TD	23% and 7% of RR in AZA vs AZA+EPO arms	Tobiasson Blood Cancer J 2014
AZA +EPO vs AZA 5 days SC	AZA EPO	phase II randomized trial	98 LR MDS	TI 16,3% vs 14,3% , HI-E 34,7% vs 24,5% in AZA+EPO vs AZA , p=0,38	Thepot et al, Hematologica 2016
Azacitidine or decitabine 3 days	US MDS	Bayesian response adaptive design	113 LR MDS or MDS/MPN	TI 32% (DEC) vs 16% (AZA), p=0,2	Jabbour et al, Blood 2017
CC-486 21 days/28d vs placebo		phase III	216 LR MDS RCB TD anemia and thrombopenia	31% vs 11% RBC TI (p=0,0002); HI-E 23,4% vs 4,6% (p< 0,0001), grade 3-4 infections in 43% vs 27,5%	Garcia-Manero et al, JCO 2021

Oral azacytidine: CC-486

Characteristic	CC-486 (n = 107)	Placebo (n = 109)	Total (N = 216)
Age, years, median (range)	74.0 (30-89)	73.0 (44-88)	74.0 (30-89)
Age ≥ 65 years, n (%)	91 (85.0)	95 (87.2)	186 (86.1)
Sex, n (%)			
Male	79 (73.8)	79 (72.5)	158 (73.1)
Female	28 (26.2)	30 (27.5)	58 (26.9)
WHO 2008 MDS classification, n (%)			
RCMD	80 (74.8)	73 (67.0)	153 (70.8)
RAEB-1	17 (15.9)	29 (26.6)	46 (21.3)
RA	4 (3.7)	3 (2.8)	7 (3.2)
RARS	3 (2.8)	2 (1.8)	5 (2.3)
MDS-U	2 (1.9)	2 (1.8)	4 (1.9)
RT	1 (0.9)[a]	0 (0.0)	1 (0.5)
IPSS risk, n (%)			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate-1	106 (99.1)	109 (100)	215 (99.5)
Intermediate-2	1 (0.9)	0 (0.0)	1 (0.5)
High	0 (0.0)	0 (0.0)	0 (0.0)
IPSS-R risk, n (%)			
Very low (≤ 1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Low (> 1.5-3)	24 (22.4)	21 (19.3)	45 (20.8)
Intermediate (> 3-4.5)	51 (47.7)	48 (44.0)	99 (45.8)
High (> 4.5-6)	27 (25.2)	33 (30.3)	60 (27.8)
Very high (> 6)	1 (0.9)	0 (0.0)	1 (0.5)
Missing	4 (3.7)	7 (6.4)	11 (5.1)
IPSS cytogenetic risk, n (%)			
Good	87 (81.3)	90 (82.6)	177 (81.9)
Intermediate	17 (15.9)	14 (12.8)	31 (14.4)
Missing[b]	3 (2.8)	5 (4.6)	8 (3.7)
IPSS-R cytogenetic risk, n (%)			
Very good	2 (1.9)	3 (2.8)	5 (2.3)
Good	86 (80.4)	89 (81.7)	175 (81.0)
Intermediate	16 (15.0)	11 (10.1)	27 (12.5)
Missing[b]	3 (2.8)	6 (5.5)	9 (4.2)
Gene mutations,[c] n (%)	n = 102	n = 102	n = 204
ASXL1	29 (28.4)	39 (38.2)	68 (33.3)
TET2	21 (20.6)	23 (22.5)	44 (21.6)
RUNX1	10 (9.8)	23 (22.5)	33 (16.2)
U2AF1	18 (17.6)	15 (14.7)	33 (16.2)
SRSF2	14 (13.7)	16 (15.7)	30 (14.7)
DNMT3A	10 (9.8)	15 (14.7)	25 (12.3)
Months since MDS diagnosis, median (range)	18.9 (0.9-153)	16.1 (0.4-381)	17.5 (0.4-381)
Platelet transfusion–dependent,[d] n (%)	30 (28.0)	35 (32.1)	65 (30.1)
RBC transfusion requirement per 28 days,[e] units, median (range)	3.3 (1.3-10.0)	3.3 (1.3-9.5)	3.3 (1.3-10.0)

RBC-TI 31% vs 11% (p=0,0002)

But more early deaths due to infections



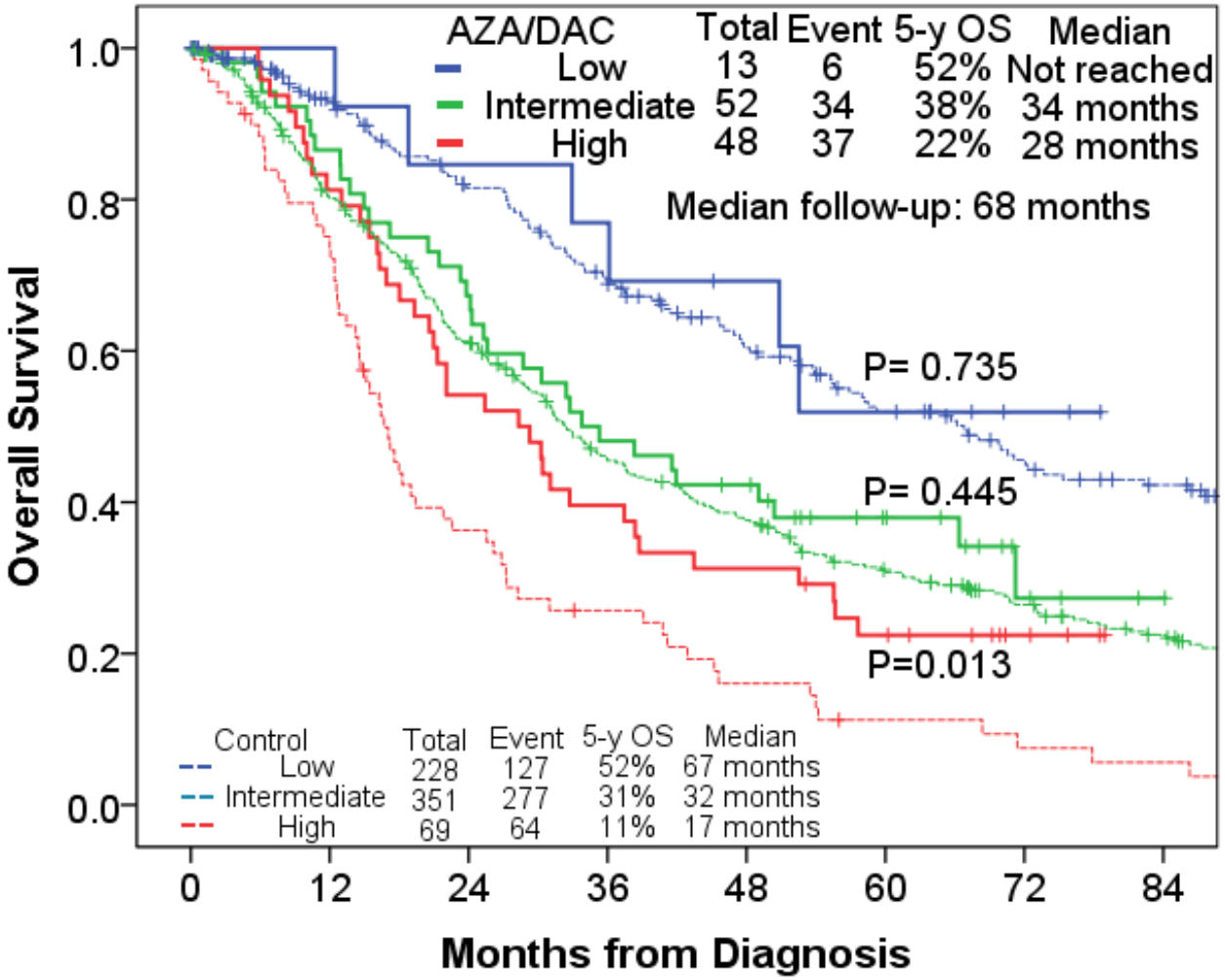
Garcia-Manero, JCO 2021

Phase II trial: Decitabine vs. azacitidine in lower-risk MDS response (IWG): some responses but no impact on OS

Response	Decitabine (N=70) n (%)	Azacitidine (N=39) n (%)	p
CR	26 (37)	14 (36)	0.90
mCR	6 (9)	2 (5)	
HI	17 (24)	3 (8)	
ORR	**49 (70)**	**19 (49)**	**0.03**
SD	18 (26)	17 (44)	
PD	3 (4)	3 (8)	
TI	16/39 (38%)	3/20 (15%)	0.03

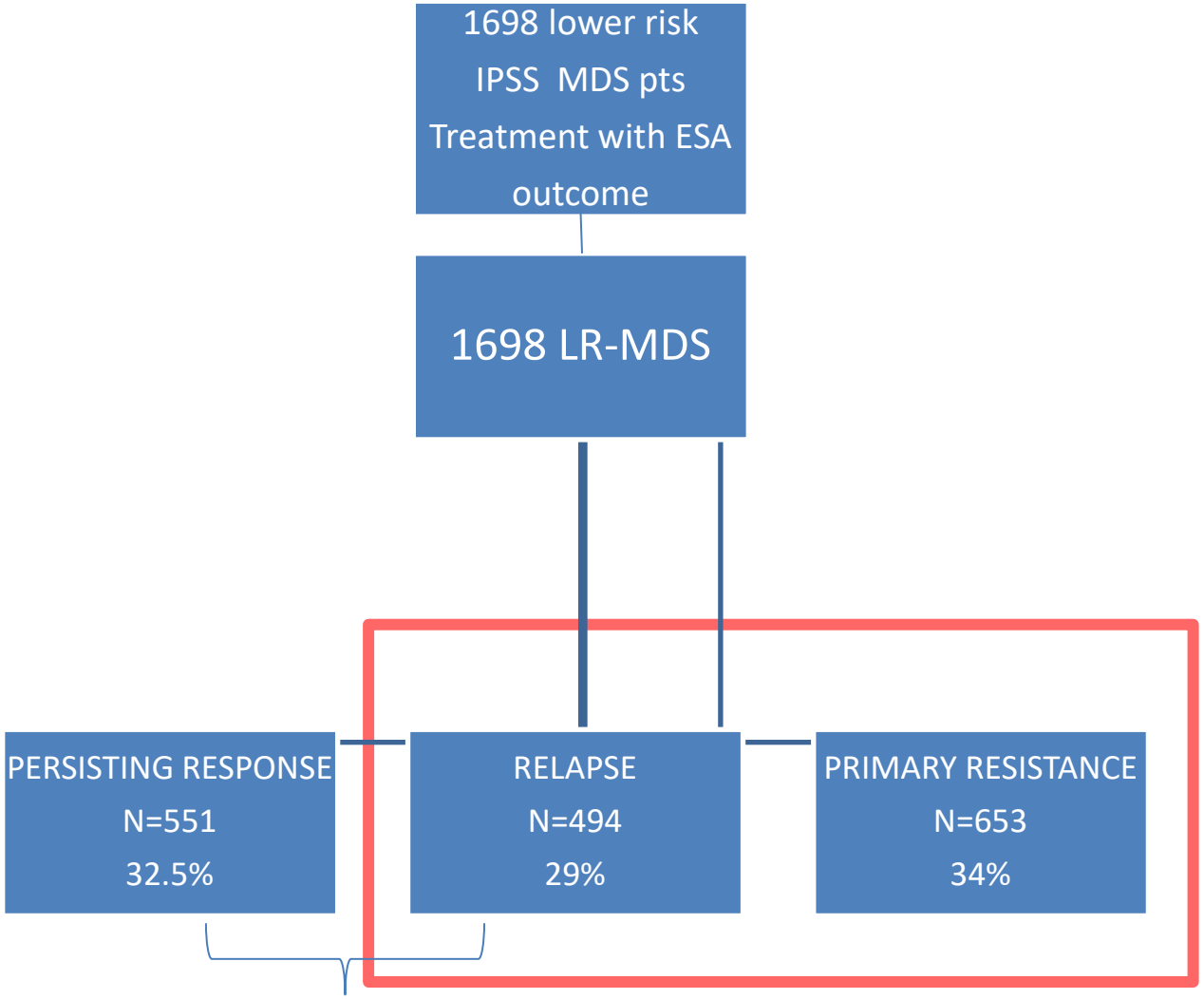
Median number of cycles: 9 (range: 1-41)

CR, complete response; HI, hematologic improvement; IWG, International Working Group; mCR, marrow complete response; MDS, myelodysplastic syndromes; ORR, overall response rate; PD, progressive disease; SD, stable disease.
Jabbour E, et al. *Blood* 2017;130(13):1514-22.



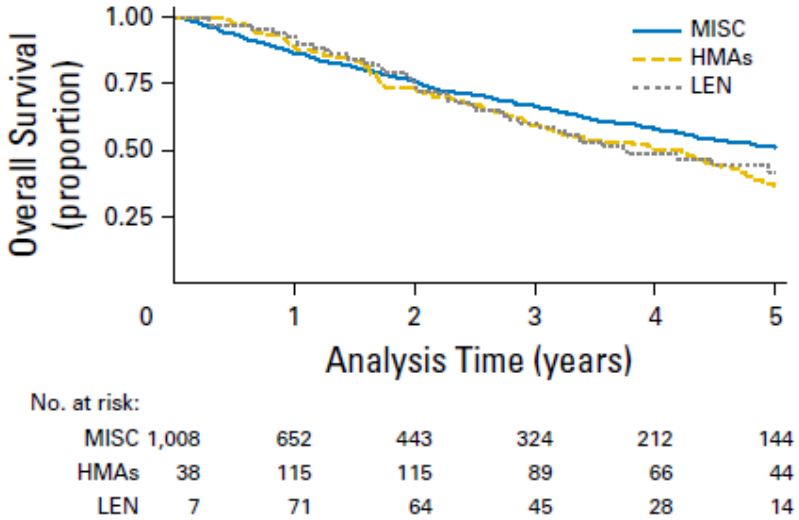
AZA, azacitidine; DAC, decitabine; MDS, myelodysplastic syndromes; OS, overall survival; y, year.
Sasaki K, et al. *NEJM Evidence, 2022*

No impact of LEN or HMA on OS after ESA failure



Response rate of 61.5%

	TX2	TX3	TX4
RR	37.8%	41%	55%
HMA	194 (RR 25%)	60	26
LEN	148 (RR 38%)	139	9
Median duration (mo)	9	5	4

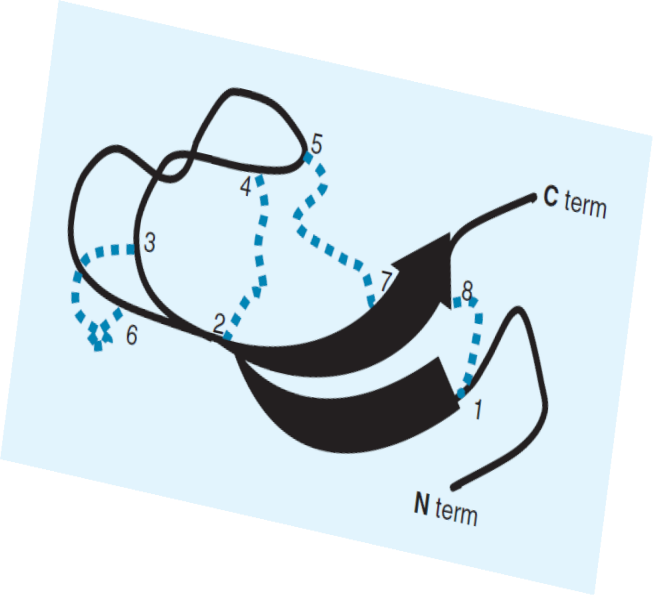


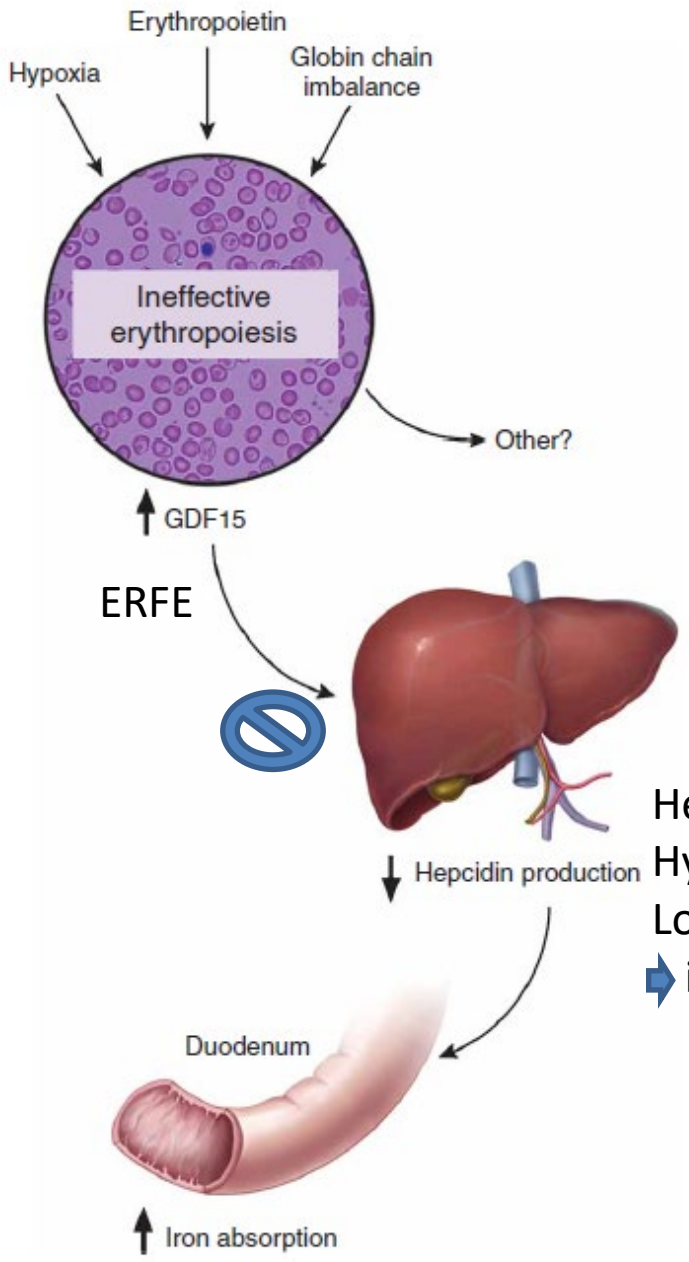
S Park et al, JCO 2017

4. Iron and erythropoiesis: interest of iron modulation?

Hepcidin

25 AA peptid
4 disulfur bonds
Stable Tertiary structure





Hepcidin:
Hyposideremic property
Lowered in dyserythropoiesis
➡ iron overload

Tanno et al, Nat Med 2007
Kautz L, Ganz T., Nat Genet 2014
Bondu et al, Sci T Med 2019

Hepcidin and MDS

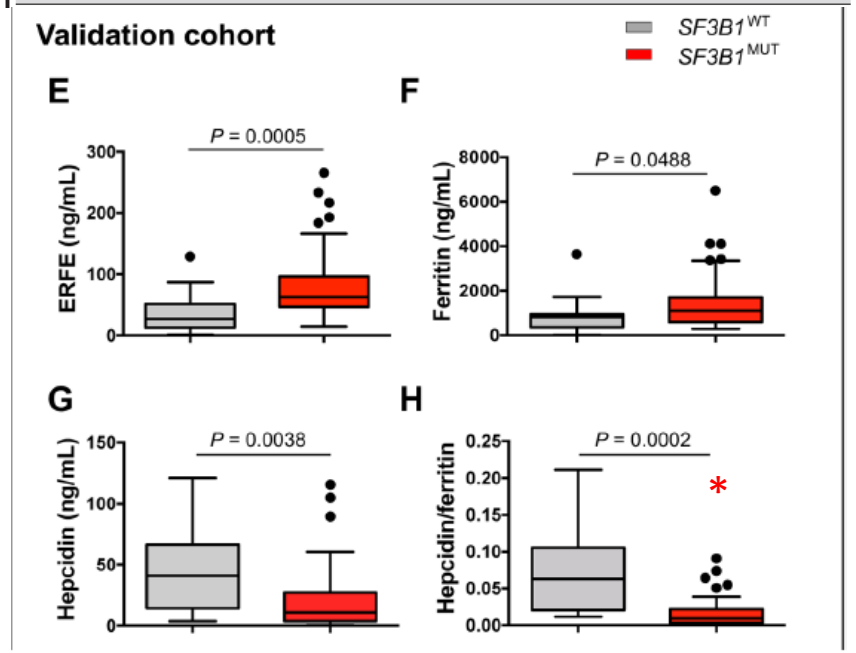
Bondu et al, Sci T Med 2019

	RA (n = 31)	RARS (n = 9)	RCMD (n = 19)	RAEB (n = 32)	5q- syndrome (n = 7)	CMML (n = 7)	Unclass (n = 8)	P°
Age (years)	75.8±10.3	73.4±7.7	73.7±7.1	70.2±7.6	71.4±12.0	73.0±8.2	67.1±13.0	0.163
Male sex (%)	61.3	44.4	73.7	78.1	57.1	85.7	62.5	0.397
CRP* (mg/l)	2.09 (1.07–4.10)	1.46 (0.36–5.56)	3.30 (1.37–7.97)	9.13 (5.41–15.39)	2.21 (0.53–9.13)	5.03 (0.19–129.90)	10.77 (5.16–22.48)	0.008
Ferritin* (μg/l)	368 (231–586)	725 (403–1305)	420 (230–768)	661 (461–947)	1364 (233–8001)	289 (130–646)	580 (135–2493)	0.104
Hepcidin* (nmol/l)	3.46 (2.06–5.81)	1.43 (0.51–4.03)	3.83 (1.85–7.96)	11.31 (7.38–17.32)	6.62 (1.26–34.84)	10.04 (2.10–48.00)	6.06 (1.18–31.27)	0.003
Hepcidin/Ferritin* Ratio (nmol/μg×1000)	9.39 (5.72–15.41)	1.97 (0.86–4.52)	9.13 (3.97–20.95)	16.69 (9.73–28.63)	4.85 (2.63–8.96)	34.68 (6.10–197.22)	10.45 (2.63–41.45)	0.003
Hb (g/dl)	10.62±2.08	10.18±1.00	10.31±1.40	9.07±1.24	10.90±2.30	9.44±1.39	10.39±1.87	0.008
Platelet count (n. cell×10^9/l)	165.35±99.01	411.78±283.70	270.84±641.14	91.53±66.38	122.57±71.82	82.57±63.47	35.86±32.58	0.051
LDH* (U/l)	321 (258–399)	304 (255–362)	371.85 (284–488)	280 (227–346)	283 (243–329)	403 (156–1042)	430 (128–1441)	0.393
NTBI (μM)	0.01±1.15	1.59±1.96	−0.32±1.25	0.03±1.55	0.65±1.82	0.19±1.24	0.60±1.92	0.058
s-Iron (μg/dl)	117±53	153±69	117±55	131±64	159±67	126±55	114±43	0.441
s-Transferrin (g/l)	212±38	180±29	209±46	191±38	191±41	209±28	203±50	0.219
Transferrin saturation (%)	41.7±23.4	68.4±28.6	44.4±23.9	51.9±28.2	71.7±35.2	48.9±26.9	45.7±26.1	0.048
GDF-15* (pg/ml)	3852 (2608–5687)	4793 (2144–10714)	4630 (2408–8904)	4846 (3284–7151)	5636 (1905–16677)	3938 (2225–6972)	3971 (1161–13585)	0.976
EPO* (U/l)	37.50 (14.56–96.54)	134.24 (51.61–349.15)	82.62 (35.96–189.62)	232.87 (149.55–362.64)	187.82 (46.04–766.24)	88.46 (17.75–440.76)	83.89 (11.29–623.34)	0.011
IPSS (%)								
low	63.0	100.0	61.1	0.0	85.7	50.0	33.3	
int-1	33.3	0.0	38.9	34.5	14.3	33.3	33.3	
int-2	3.7	0.0	0.0	51.7	0.0	16.7	33.3	<0.001
high	0.0	0.0	0.0	13.8	0.0	0.0	0.0	
Transfused patients (%)	29.6	33.3	27.8	56.3	33.3	57.1	50.0	0.303

°: by Analysis of Variance (ANOVA) or by χ^2-analysis, when indicated.
*: variables not normally distributed are expressed as geometric means with 95% CIs.
doi:10.1371/journal.pone.0023109.t002

Santini et al, Plos One 2011

	Controls (n = 54)	MDS (n = 113)	P
Age (years)	34.8±15.8	72.8±9.2	<0.001
Male sex (%)	61.1	68.1	0.370
CRP (mg/l)	1.07 (0.93–1.23)	3.81(2.71–5.36)	<0.001
Ferritin* (μg/l)	79 (64–97)	515 (407–652)	<0.001
Hepcidin* (nM/l)	4.20 (3.53–5.00)	5.31 (3.98–7.08)	0.288
Hepcidin/Ferritin Ratio*	52.94 (43.57–64.33)	10.10 (7.53–13.53)	<0.001
s-Iron (μg/dl)	100±28	127±59	<0.001
s-Transferrin (g/l)	2.51±0.37	2.01±0.40	<0.001
Transferrin Saturation (%)	28.9±9.1	49.8±27.4	<0.001



Lower hepcidin/ferritin ratio predicts lower and shorter response rate to ESAs in LR-MDS

Table 2A. Baseline biological markers associated with response to erythropoiesis-stimulating agents.

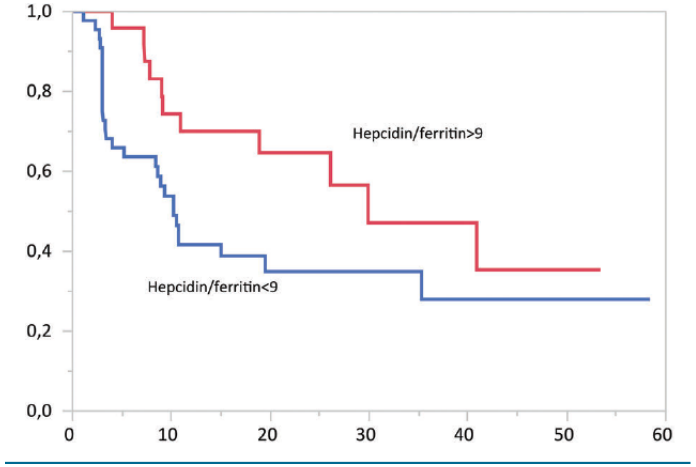
Variables	Responders n=33	Non-responders n=37	Univariate analysis (*P*)
Hb level ng/mL, mean	9.4	9.4	0.37
sEPO level IU/L, mean	65.5	117	0.001
Ferritin (ng/mL), mean	613	618	0.62
Transferrin saturation (%), mean	36.2	50.7	0.04
Hepcidin (ng/mL), mean	39.3	30.2	0.45
Hepcidin/ferritin (x100), mean	9	6	0.04
Patients with hepcidin:ferritin ≤9; n (%)	15 (45%)	27 (73%)	0.006
GDF-15 (pg/mL) mean	1822	2180	0.47
Patients with GDF-15 >2000 pg/mL; n (%)	11 (33%)	20 (54%)	0.046
Ogata score, mean	1.26	1.57	0.4
RED score at T0, mean	4.9	6.2	0.05
Patients with RED score >4; n (%)	15 (45%)	23 (62%)	0.029
RED score+ Ogata score, mean	6.5	7.6	0.15
Patients with >2 mutations; n (%)	7 (21%)	25 (67%)	0.37

Table 2B. Multivariate analysis of predictors of erythroid hematologic improvement (HI-E) to erythropoiesis-stimulating agents.

Variables		OR (95%CI)	*P*
Hepcidin/ferritin (x100)	>9	4.44 [1.23-18.2]	0.02
	≤9 (ref)	1.00	
GDF-15 (pg/mL)	≤2000	2.86 [0.80-11.6]	0.11
	>2000 (ref)	1.00	
RED score at T0	≤4	4.02 [1.0-22.7]	0.05
	>4 (ref)	1	

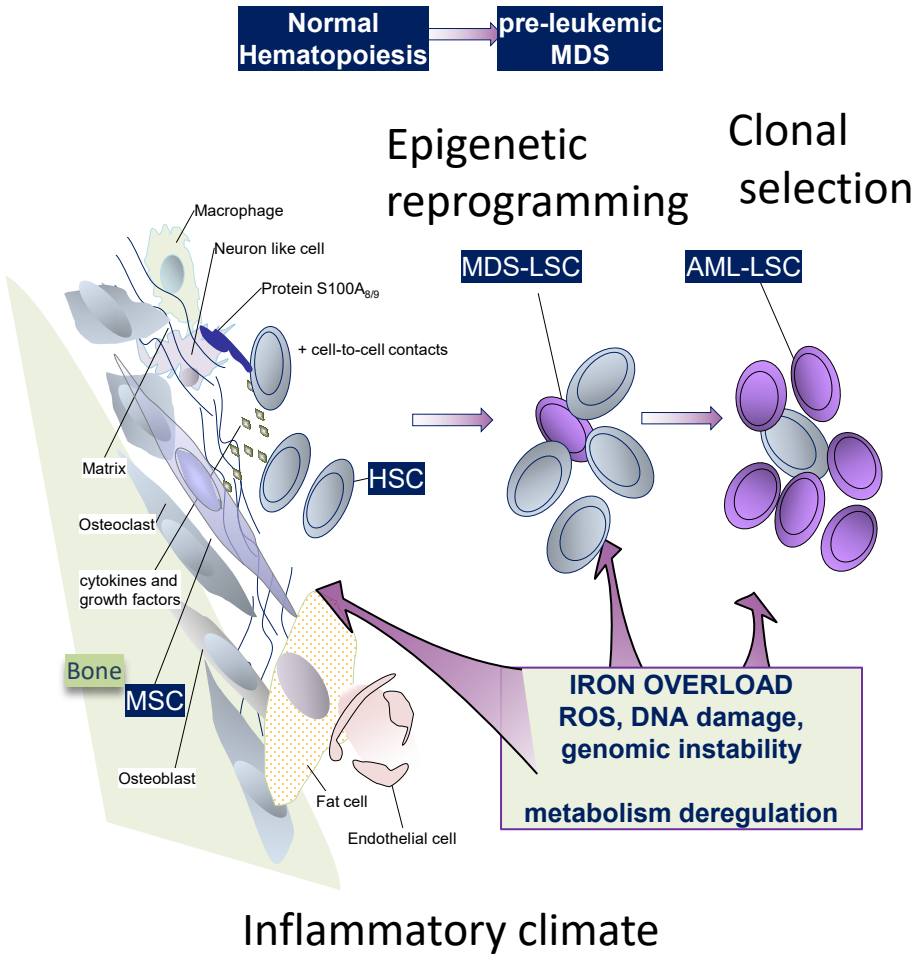
Hb: hemoglobin; sEPO: serum erythropoietin; GDF-15: growth-differentiation factor-15; T0: baseline.

Duration of response to ESAs



Park S, et al., *Haematologica* 2019;104:497–504

Iron overload is damageable to LSC and microenvironment



- In MDS blood, there is excess ROS and downregulation of GSH, and in bone marrow, there is an excess of DNA damage.
- MDS leads to DNA damage in NHD13 mice.

- Iron overload affects the cell viability of HSCs and MSCs in MDS with increased levels of ROS, stimulated p38MAPK, p53.
- Iron overload hinders proliferation of erythroid progenitor cells (BFU-E) in patients with MDS, improvement during iron chelation.

- Transplant of BM from normal donors to recipients with OI showed delayed hematopoietic reconstitution, indicating that excess iron has a negative impact on the hematopoietic microenvironment.

- Free iron catalyzes oxidative damage in vitro on MSCs attenuating hematopoiesis.

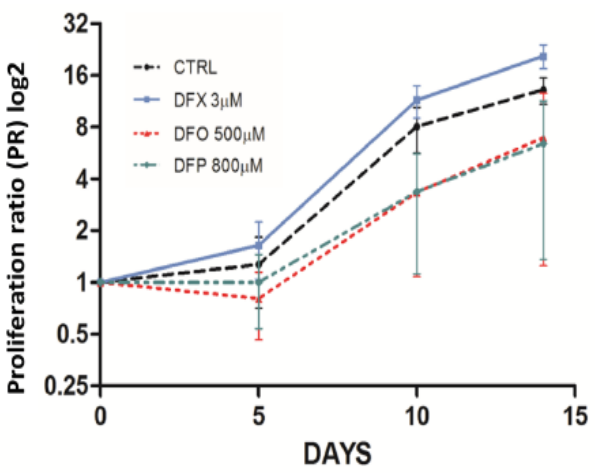
Okabe H, *et al. Eur J Haematol* 2014
Zhang Y, et al. PLoS One. 2015;10:e0120219.
Chung JY, et al. Leuk Res. 2014;38:95-102
Lu et al, Eur J Haematol 2013
Ghoti H, et al. Eur J Haematol. 2007;79:463-7;
Novotna B, et al. Leuk Res. 2009;33:340-3;
Hartmann J, et al. Leuk Res. 2013;37:327-32.

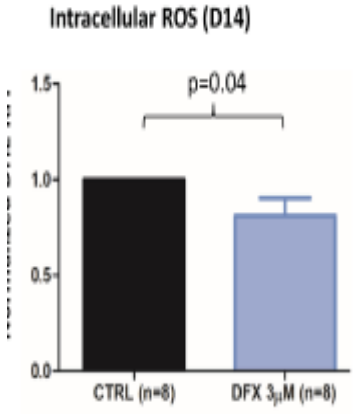
Iron modulation by deferasirox impacts ROS and NF-KB

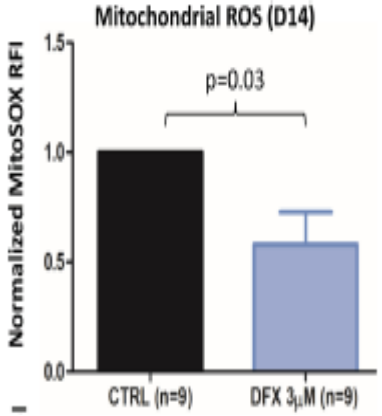
- Low doses of DFX cause an overgrowth of erythroid progenitors.
- The iron chelating properties of low dose DFX did not activate iron regulatory proteins or deplete functional iron.
- Low dose DFX attenuates ROS.
- Low-dose DFX activates the NF-κB pathway in erythroid precursors triggering anti-apoptotic and anti-inflammatory signals.

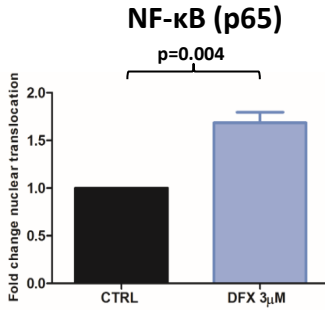
Meunier M, Park S., Oncotarget. 2017

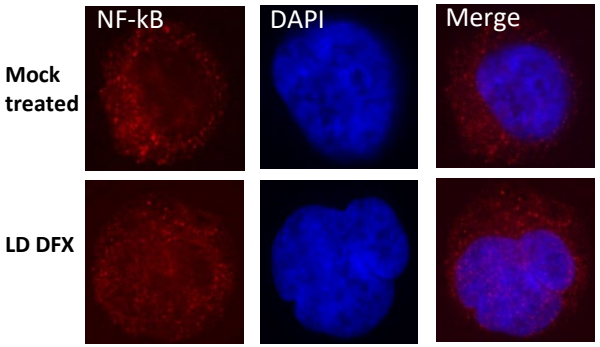
Proliferative effect specific of DFX



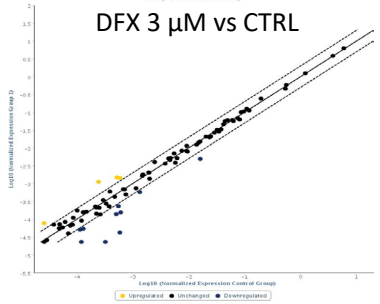




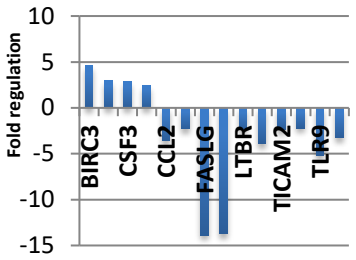




NFκB target genes PCR arrays (n=5)



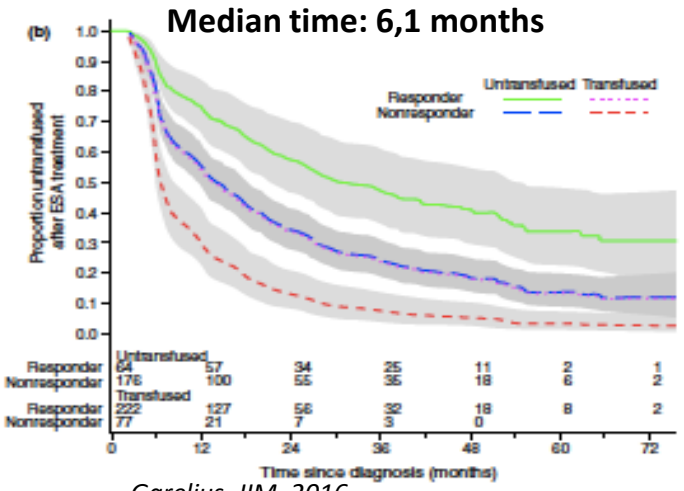
- 4 up-regulated genes
- 10 under-expressed genes



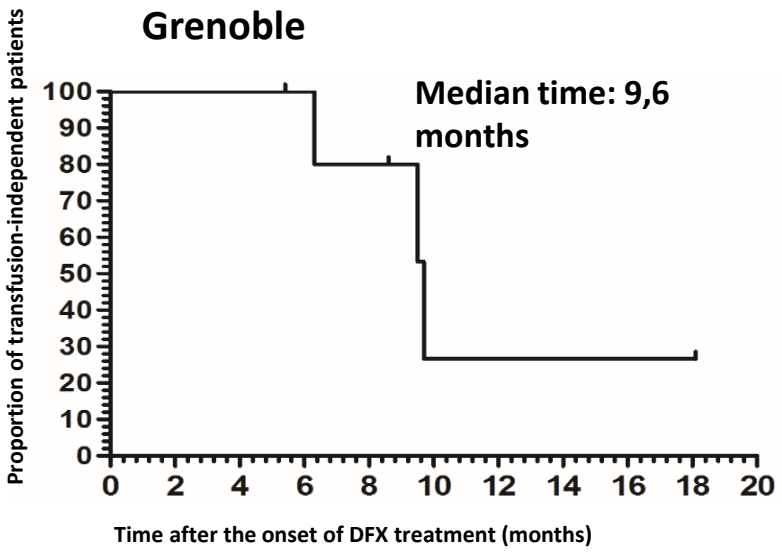
- Anti-apoptotic signal (BIRC3, FASLG)
- Anti-inflammatory signal (TLR4, TLR9, LTBR, TICAM2)

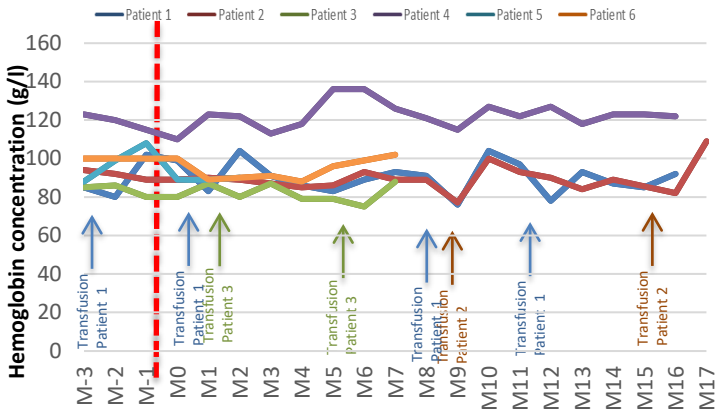
LODEFI TRIAL IN FRANCE

NCT03387475



Garelius, JIM, 2016





LODEFI trial in France , PI: S. PARK

EudraCT n°2017-001258-33,

→

Patients:

Anemic low-risk MDS

ESA refractory or low need of red blood cell transfusions

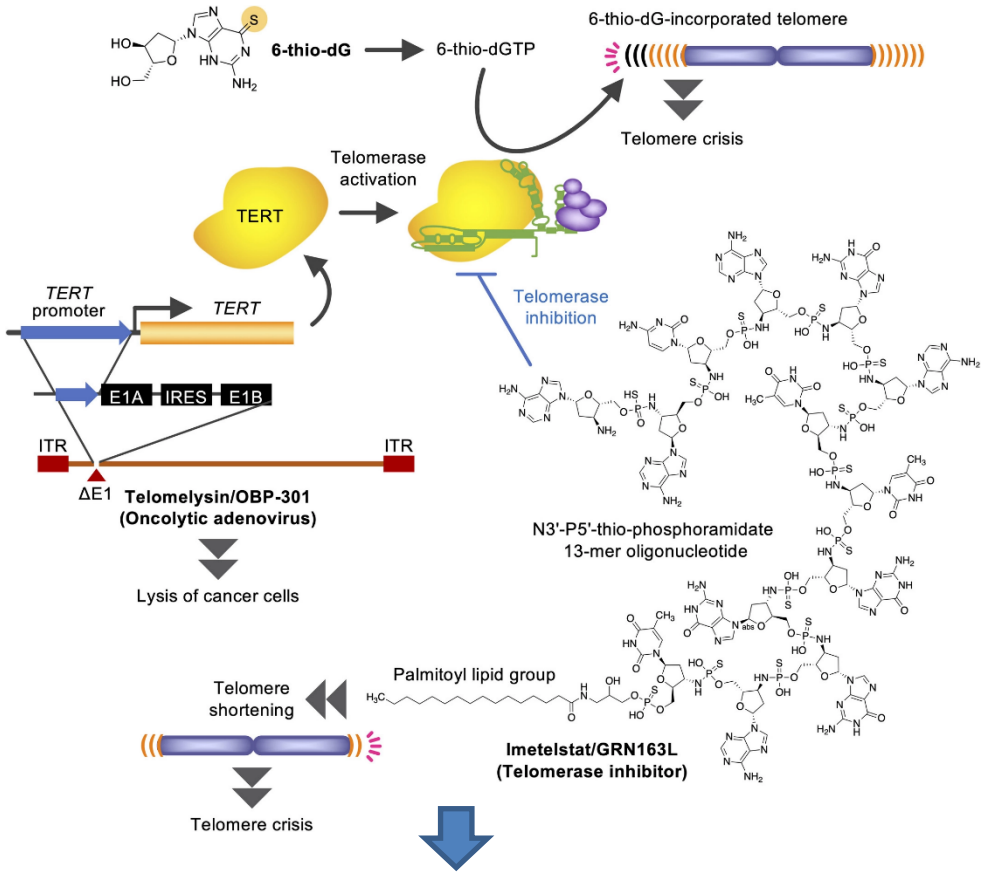
Ongoing….

5. IMETELSTAT
Phase II IN LR ESA R/R MDS

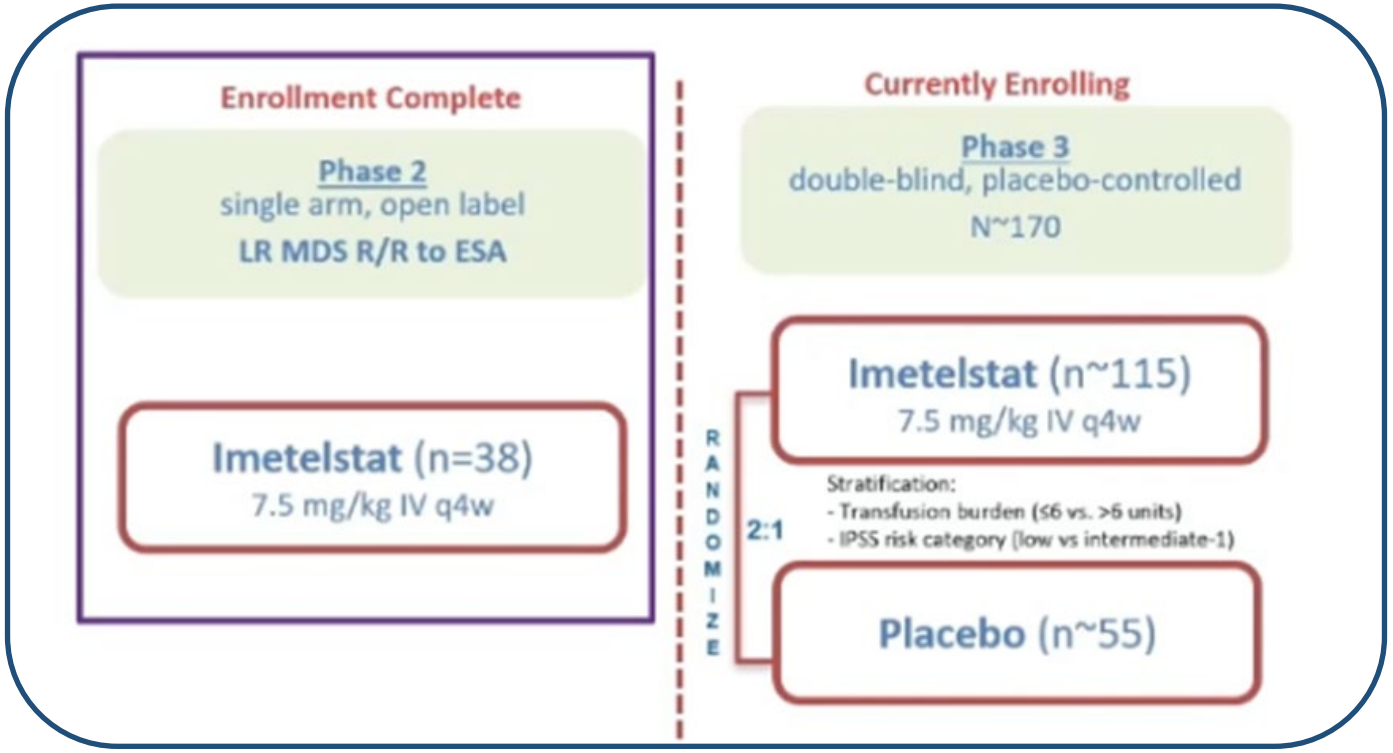
Abs.# 658 ASH 2020

Treatment with Imetelstat Provides Durable Transfusion Independence (TI) in Heavily Transfused Non-Del(5q) Lower Risk MDS (LR-MDS) Relapsed/Refractory (R/R) to Erythropoiesis Stimulating Agents (ESAs)

Increased telomerase activity in MDS



Apoptosis of telomerase positive cancer cells



Steensma DP et al, JCO 2021

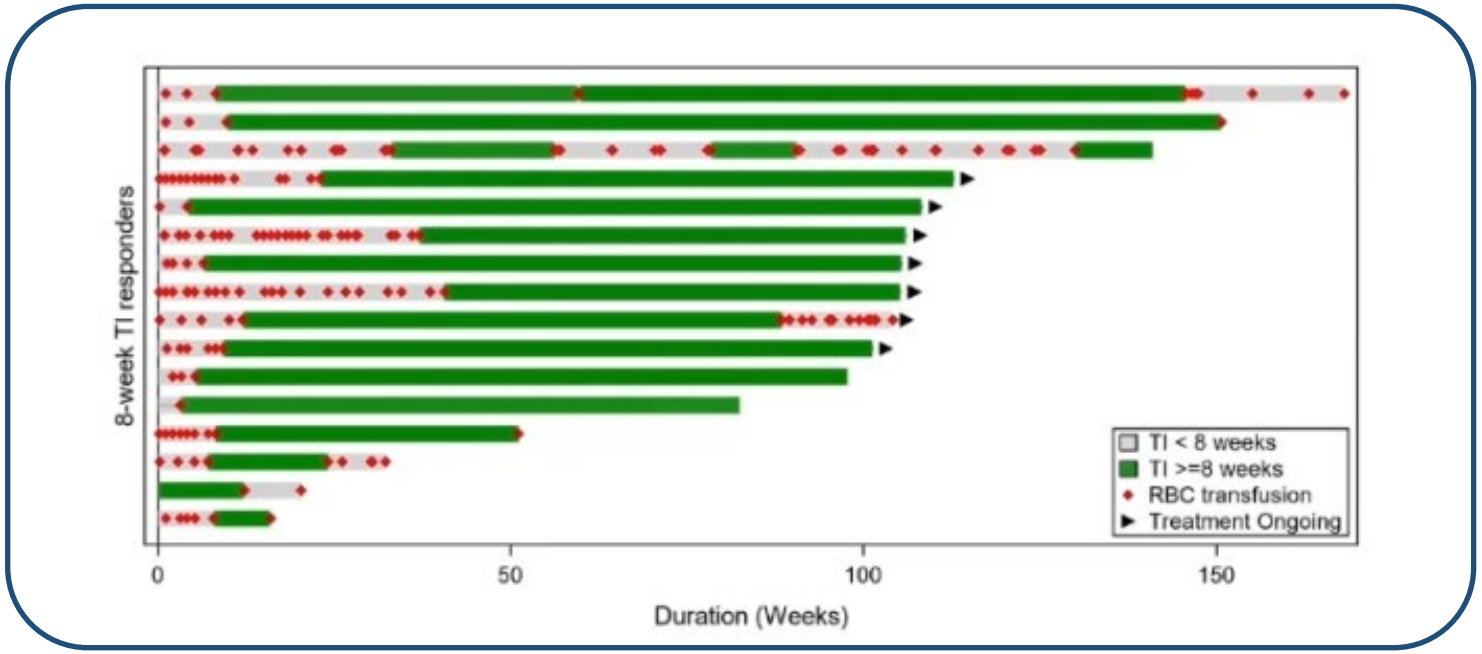
IMETELSTAT

TI at 8 and 24 weeks

Parameters	N = 38
8-week TI, n (%)	**16 (42)**
Time to onset of 8-week TI, weeks, median (range)	8.3 (0.1-40.7)
Duration of TI, weeks, median (95% CI)[a]	**88.0 (23.1 – 140.9*)**
Cumulative duration of TI ≥ 8 weeks[b], median (95% CI)[a]	92.3 (42.9, 140.9)
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	12 (32)
24-week TI, n (%)	**12 (32)**
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	11 (29)
1-year TI, n (%)	**11 (29)**

HI-E

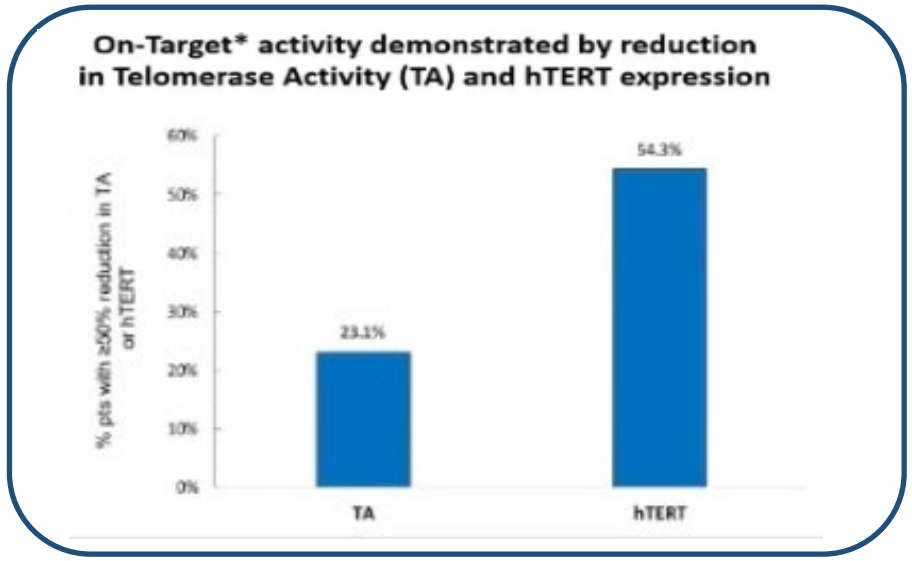
Parameters	N = 38
HI-E per IWG 2006, n (%)	**26 (68)**
≥1.5 g/dL increase in Hb lasting ≥ 8 weeks[a], n (%)	13 (34)
Transfusion reduction by ≥ 4 units/8 weeks, n (%)	26 (68)
Duration of HI-E, weeks, median (95% CI)[b]	**92.7 (37.1, 149.4)**
Major and Minor Response per IWG 2018	
Major response: 16-week TI, n (%)	**14 (37)**
Minor response: ≥ 50% transfusion reduction/16 weeks, n (%)	21 (55)
CR + marrow CR, n (%)	9 (24)
CR, n (%)	4 (11)
marrow CR, n (%)	5 (13)

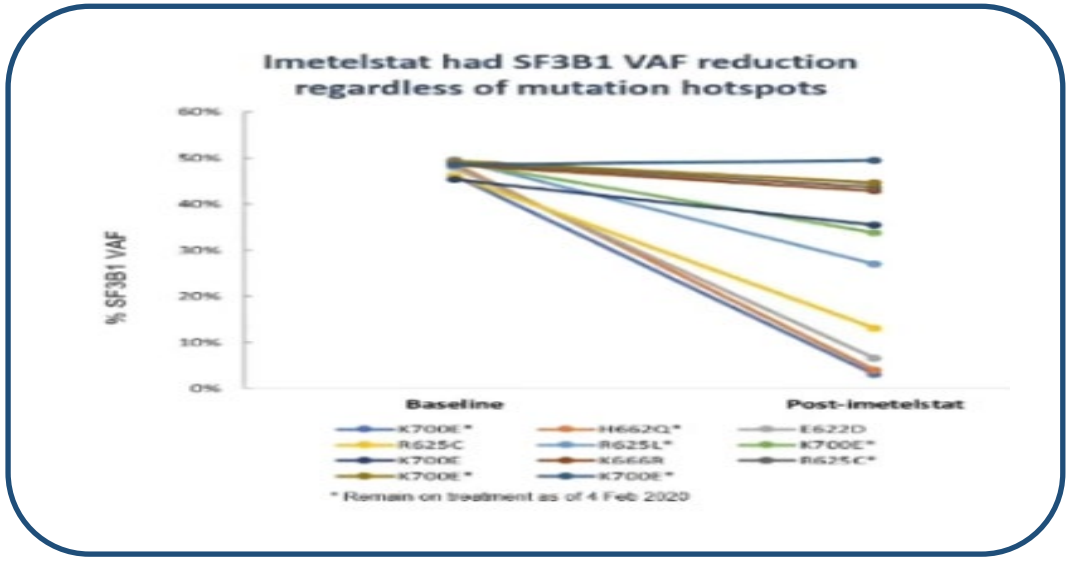


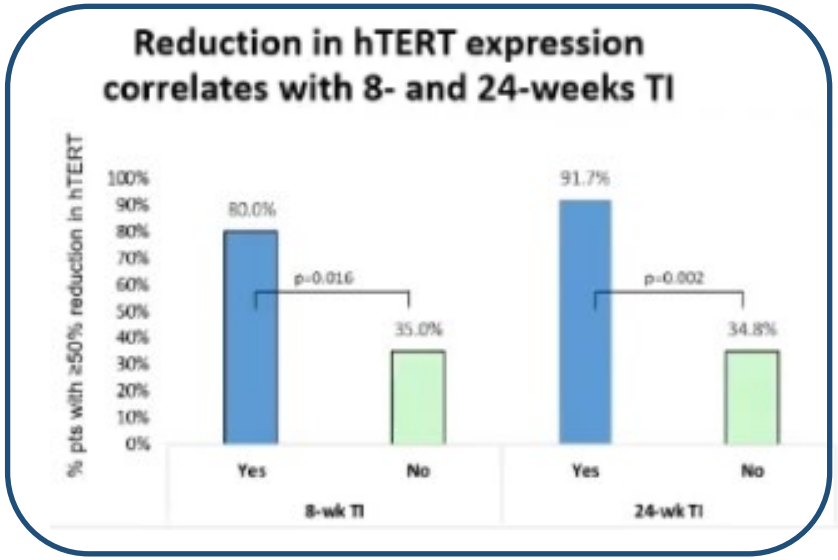
- 29% of the patients transfusion free for at least one year
- Longest transfusion free period 2.7 years

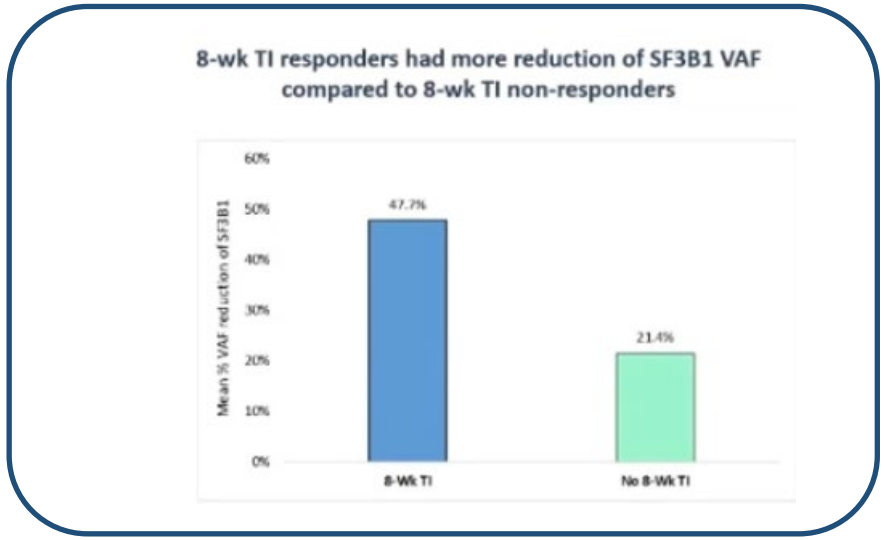
Steensma, JCO 2021

IMETELSTAT
Biomarkers









Phase III in progress

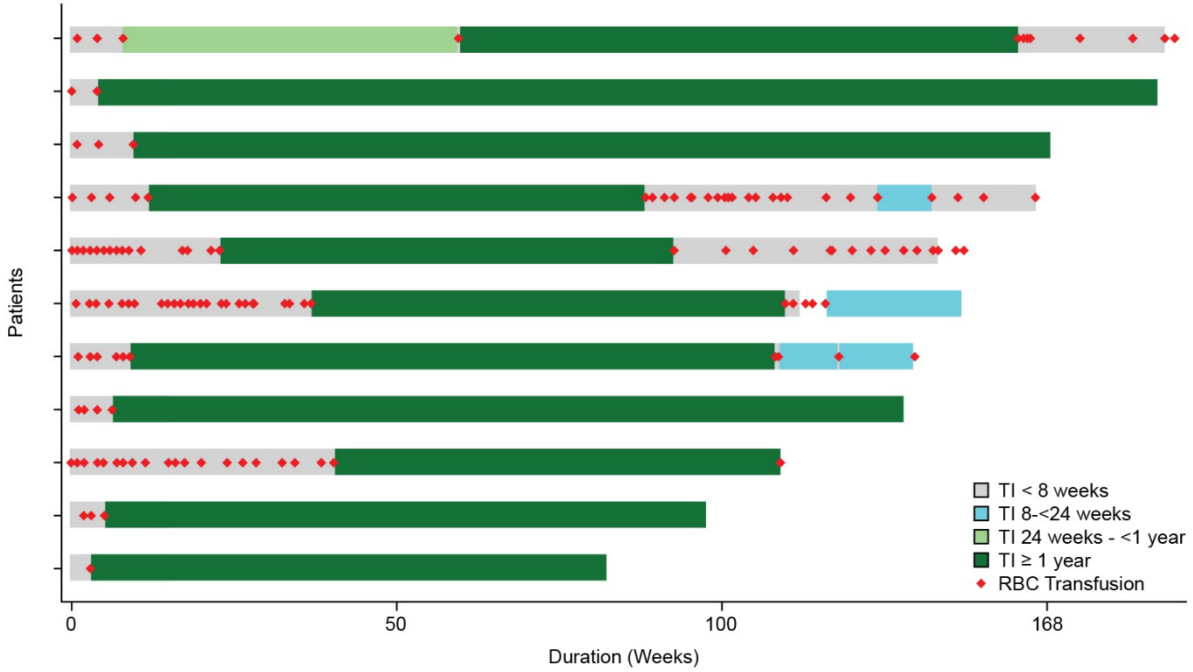
Steensma, JCO 2021

Prolonged transfusion independence> 1 year with Imetelstat

Table. Baseline characteristics of imetelstat-treated LR-MDS patients achieving RBC TI > 1 year

Baseline characteristic	Patients with TI >1 year (n=11)
IPSS category, n (%)	
Low	5 (45.5)
Intermediate-1 risk	6 (54.4)
MDS-RS, n (%)	10 (90.9)
Prior RBC transfusion burden over 8 weeks prior to study treatment, median (range)	6.0 units (4-14)
Prior ESA, n (%)	11 (100)
≥2 years since initial diagnosis, n (%)	10 (90.9)
Normal karyotype, n (%)	7 (63.6)

Figure. Swimmers plot of imetelstat-treated LR-MDS patients achieving RBC TI > 1 year



89% reduction of SF3B1 VAF
56% achieved a > 50% VAF reduction

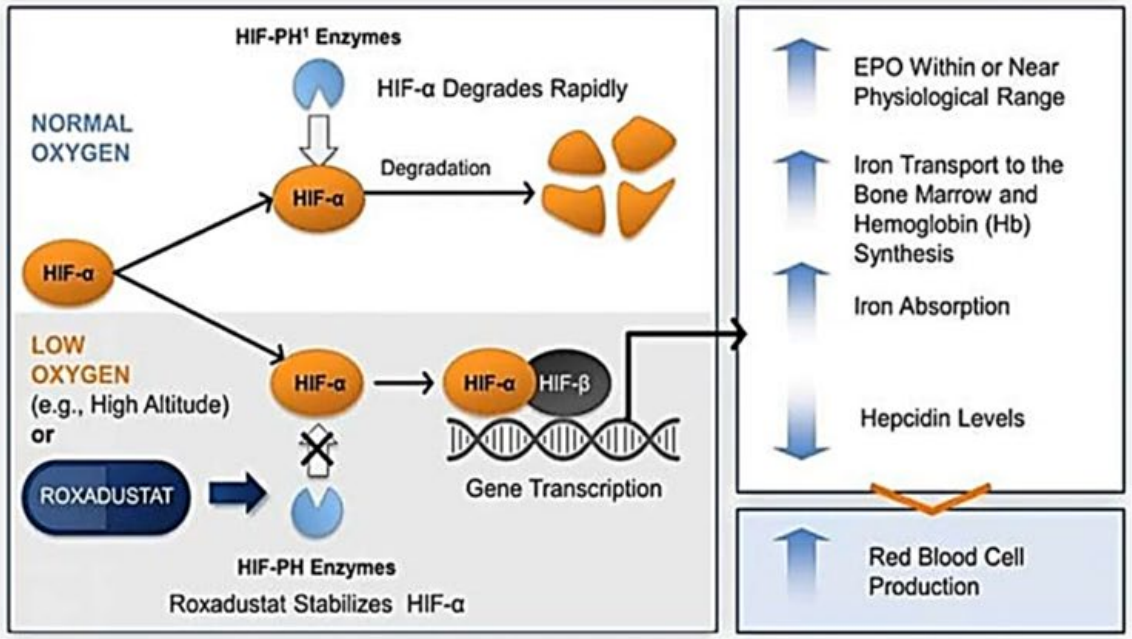
11 pts/16: median number of cycles 27
Median duration of TI : 24 months

Platzbecker U, et al, ASH 2022, #abs 459

6. Roxadustat: HIF stabilizer: EPO increase

Roxadustat*

Oral treatment, three times weekly
Approved by EMA on May 2020 for anemia of CKD



FibroGen, Inc. Available at: https://medicalxpress.com/news/2019-07-drug-trial-efficacy-anemia-chronic.html. Accessed January 2021.

Ongoing Phase III NCT 03263091

- IPSS-R very low, low and intermediate risk MDS
- 5q- excluded
- RBC dependent 2—4 RBC unit/8 weeks
- Prior ESA allowed

Primary endpoint

- RBC-TI ≥8 weeks
- Efficacy in achieving Hb correction and reduction of RBC units
- Transfused in 28 weeks in comparison to baseline

Complete October 2021

*This compound does not have a marketing authorization in this indication

NCT03263091. Available at: https://clinicaltrials.gov/ct2/show/NCT03263091?term=roxadustat&draw=3&rank=13. Accessed 22 December 2020; Henry D, et al. Poster presented at ASH 2020; ePoster #1277.

Henri D et al, ASH 2020, #1277

Roxadustat

Roxadustat*: ongoing Phase III NCT03263091

Study Design

Two-part Study

1. Open-label (OL), 3 sequential starting dose cohorts of 8 patients each (N = 24)
   - Primary objective: identify dose for double-blind study segment and evaluate safety

OL reported here

Open-label lead-in

Screening Period (28 days)	Treatment Period (52 weeks)	
• Lower-risk MDS Patients • Transfusion-dependent (1—4 pRBC over last 8 weeks) • Hb ≤10.0 g/dL	Starting dose: 8 weeks • 1.5 mg/kg TIW • 2.0 mg/kg TIW • 2.5 mg/kg TIW	• Dose adjustment allowed every 8 weeks • Best supportive care allowed, per protocol

Ongoing

2. Randomized, double-blind, placebo-controlled segment (Ongoing) (N = 160, 3:2 randomization)
   - Primary objective: evaluate efficacy (i.e. transfusion independence) and safety

Report on 24 patients in open-label phase of this Phase III study

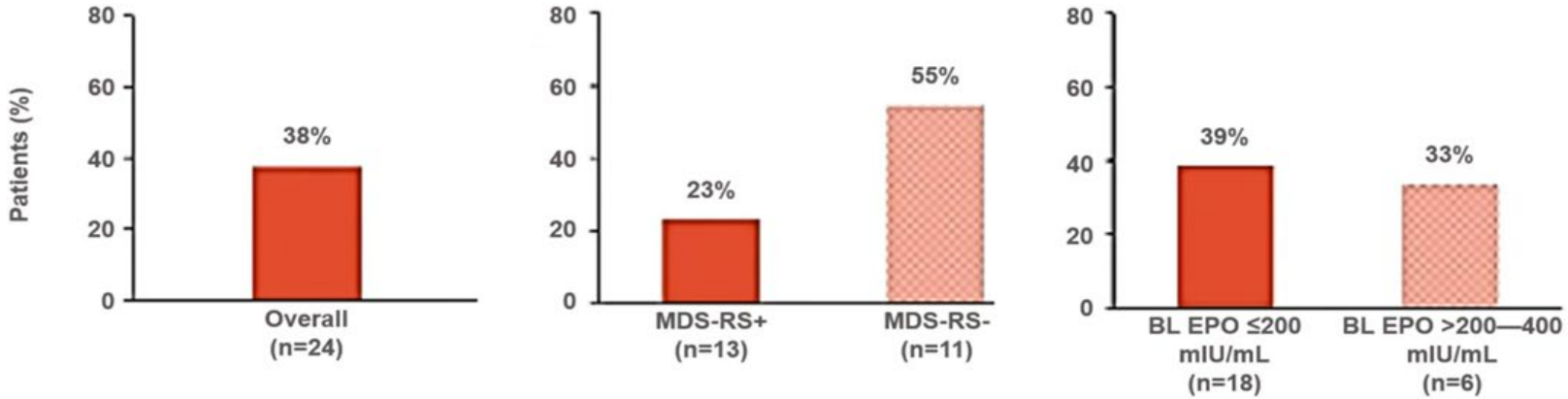
*This compound does not have a marketing authorization in this indication

Henri D et al, ASH 2020, #1277

Roxadustat

Roxadustat*: ongoing Phase III NCT03263091

Primary & exploratory endpoints: RBC-TI ≥8 weeks (during both 28 & 52 Weeks)



- 78% (7 of 9) patients were on 2.5 mg/kg dose at the time of RBC-TI
- During the first 8 weeks FIXED DOSE, RBC-TI was achieved in a small proportion of patients in cohorts 1 (25%) and 3 (50%)

Exploratory endpoint of patients with/without ring sideroblasts (RS) during weeks 1—28 and 1—52

Exploratory endpoint of patients in baseline erythropoietin (BL EPO) categories during weeks 1—28 and 1—52

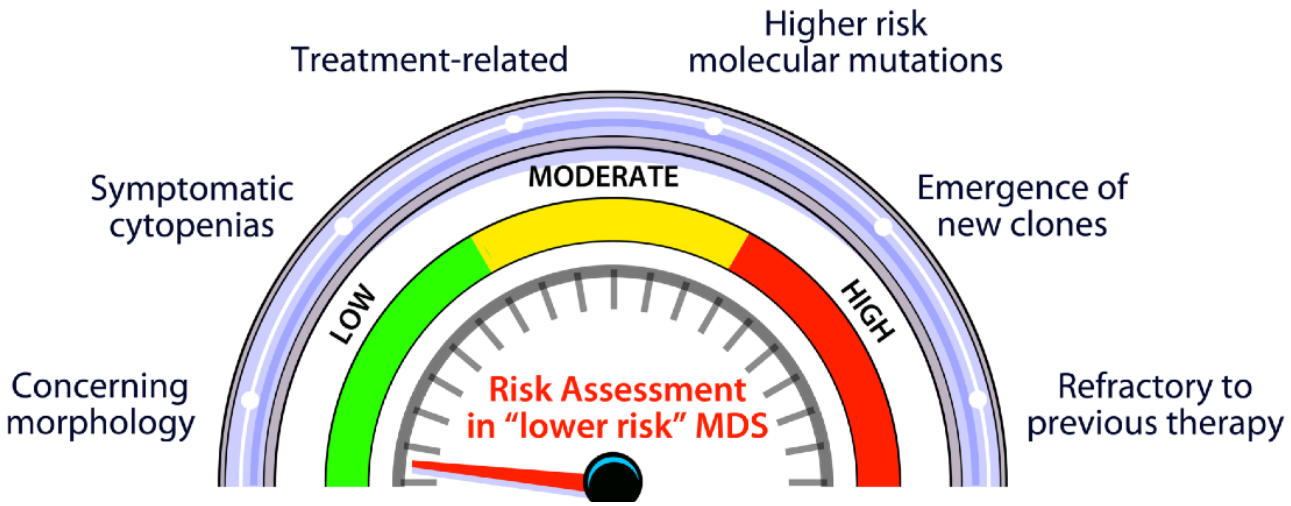
*This compound does not have a marketing authorization in this indication

Henri D et al, Am J Hematology 2022

ALLOGENEIC TRANSPLANTATION

Variable	Poor prognostic feature
R-IPSS	Intermediate High or very high
Treatment outcome Lenalidomide (especially in patients with isolated del 5q) Immunosuppressive therapy Hypomethylating agents	Primary or secondary failure
Somatic mutations	Consistent and increasing TP53 clone Absence of SF3B1 mutation (especially in MDS with ring sideroblasts) RUNX1, ASXL1 mutations Multiple somatic mutations
Etiology of MDS	Therapy-related MDS
Marrow biopsy	grade 2 or higher myelofibrosis
Cytopenia	Profound symptomatic neutropenia or refractory thrombocytopenia
Karyotype	Emergence of unfavorable abnormality (ies)

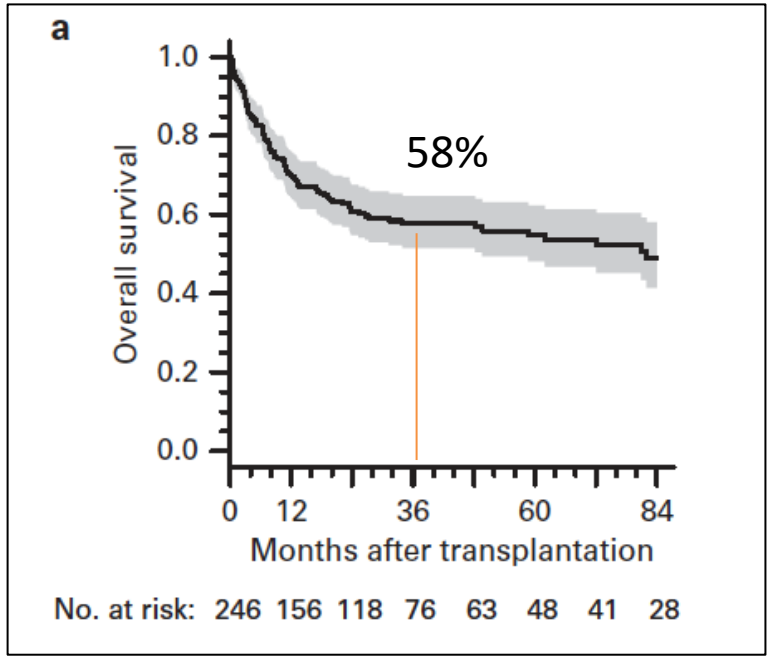
M. Robin, Leukemia, 2020

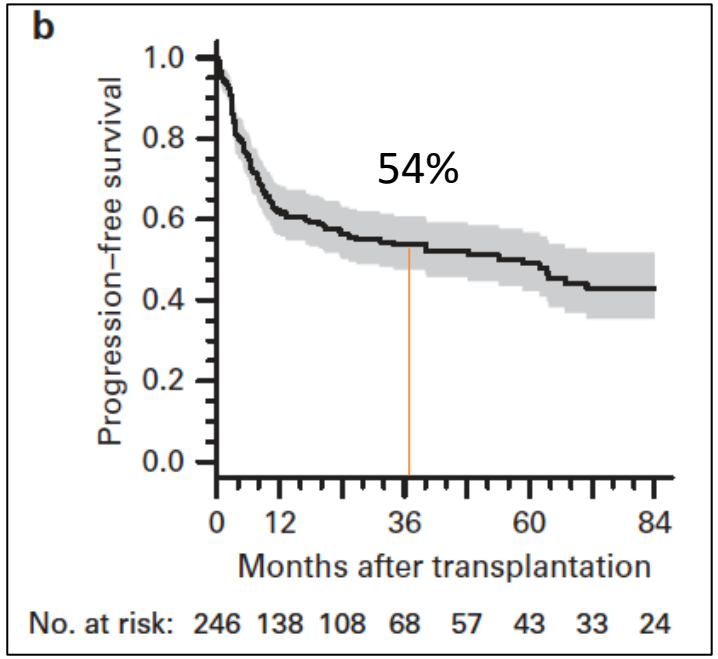


Amy E. DeZern,, Hematology Am Soc Hematol Educ Program, 2021,

ALLOGENEIC TRANSPLANTATION

- Retrospective analysis of 246 MDS patients in the EBMT database who were transplanted for IPSS low or intermediate-1 disease;
- 76% were reclassified as intermediate or higher risk according to R-IPSS;
- In a multivariate analysis, adverse risk factors for PFS were:
  - marrow blast percentage
  - donor/recipient CMV serostatus
  - source of stem cells



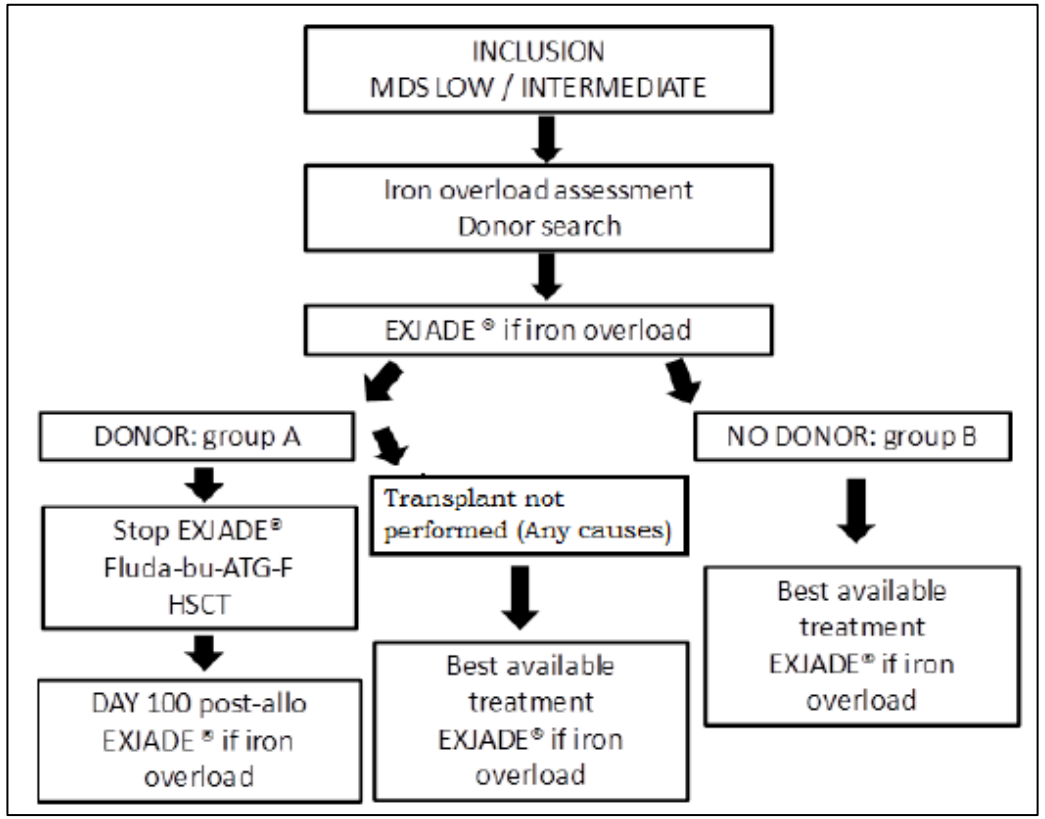


M. Robin, BMT, 2017

- Lower risk MDS patients have better outcome than those with ‘higher risk’ after HSCT,
- Selecting the right source of stem cells, CMV-positive donor for CMV-positive patients and using in vivo T cell depletion results in the best outcome in these patients,
- Need of prospective study

MDS-ALLO-RISK TRIAL

- R-IPSS intermediate or higher
- RBC transfusion dependent anemia and failure to two or more treatments (including EPO, Lenalidomide or HMA);
- Platelets < 20 G/L requiring transfusions
- ANC < 0.5 G/L with severe infection
- No CI to allo HSCT
- Age <70 years
- HLA identical donor (sibling or 10/10 unrelated)



- 79 patients were included, 64 in group A (with donor) and 15 in group B (without donor)
- Three-year OS was 60% (95%CI: 46.9-76.8) in group A and 64.2% (41.3-99.6) in group B (p=NS)

M. Robin, ASH 2021

Targeted options in MDS

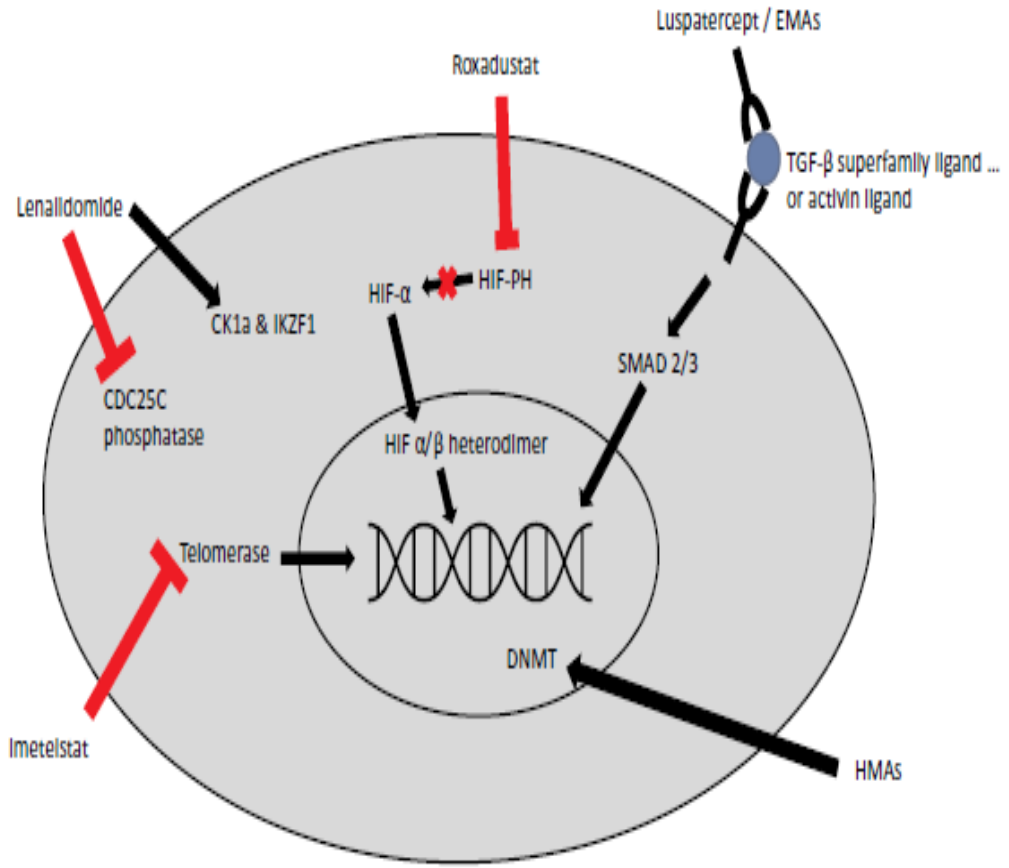
IDH-2 (5-10%): enasidenib
IDH-1 (5%): ivosidenib
CD47: multiple agents
TP53 (10%): APR-246 anti-CD47
NPM1 (1%): ara-C based
TIM-3: multiple agents

This presentation may include information about investigational products and/or uses that are not approved for use in Europe

Conclusion: how to treat anemia after ESA failure?

- Acting via the immunome and the micro-environment: luspatercept and lenalidomide
- Acting on epigenetic deregulation?

- Acting on erythropoiesis: EPO, iron: deferasirox, hepcidin modulators
- Acting on HIF: roxadustat
- Acting on telomerase: imetelstat
- Allogeneic transplantation for intermediate/ high risk MDS



R. Lewis et al, Cancer Manag and Research 2021

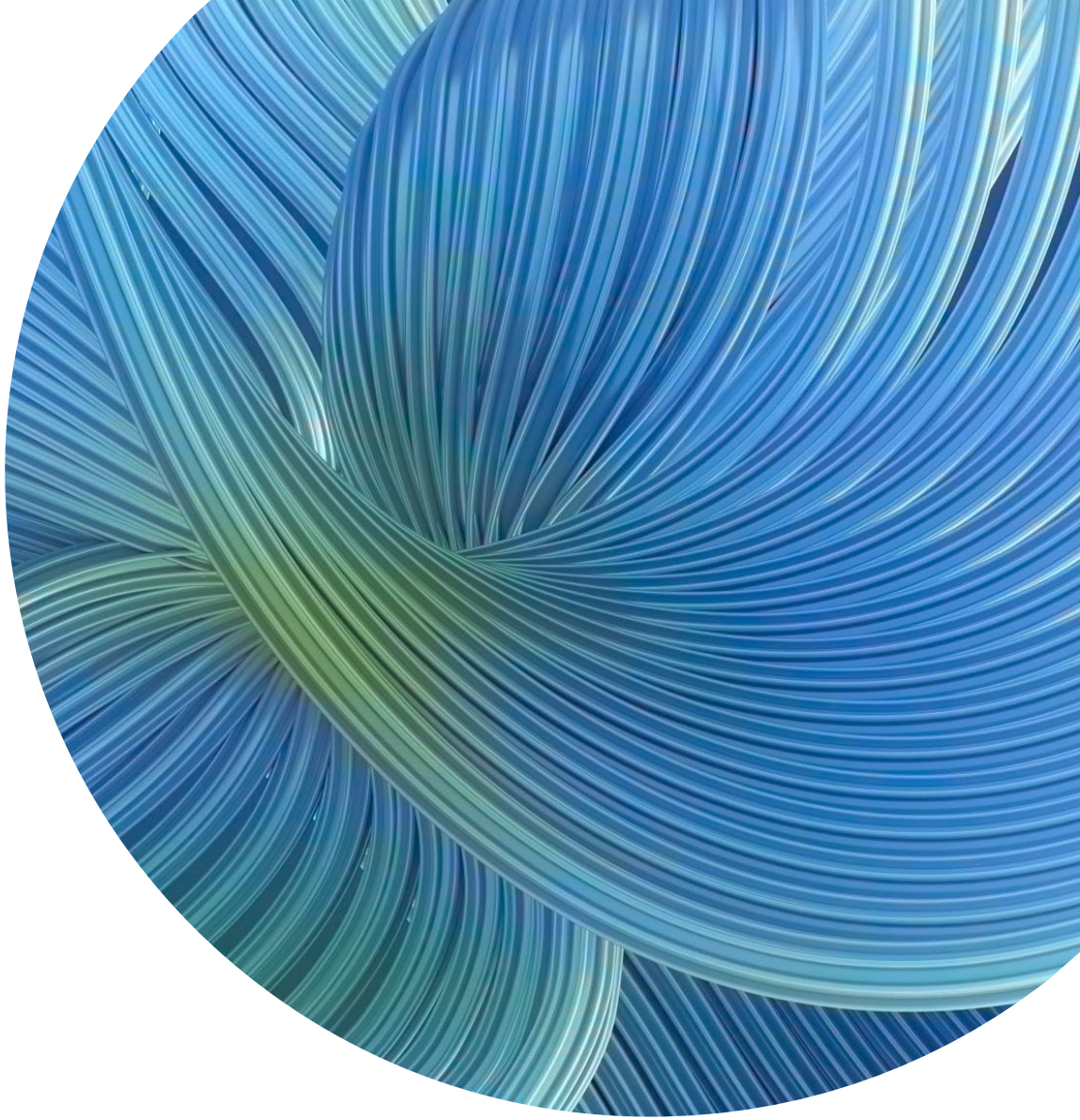
Conclusion
LOWER RISK MDS

Predictive factos of reponse to ESA

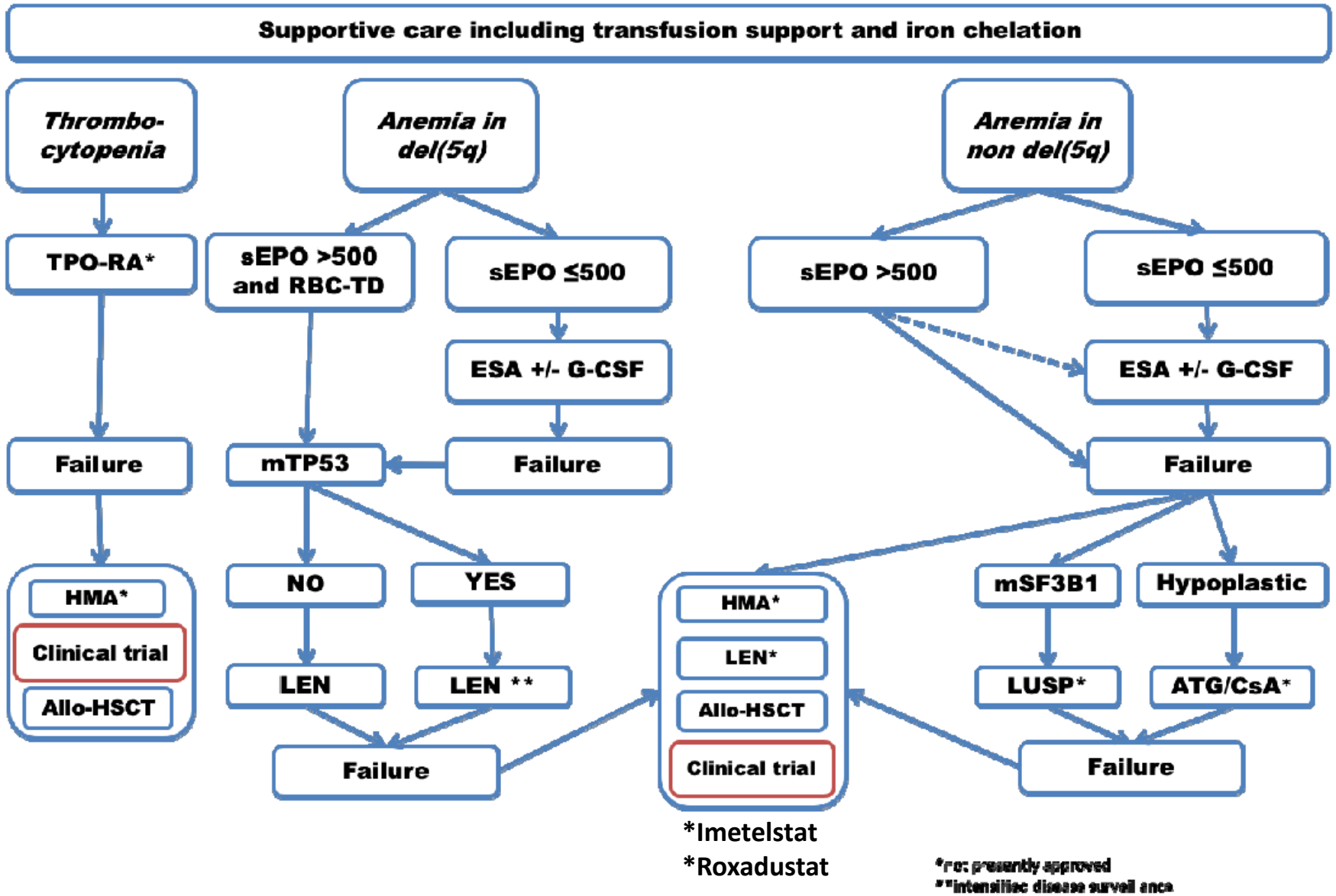
- IPSS-R
- Ferritin
- EPO
- Number of gene mutations
- Hepcidin/ferritin ratio
- Flow cytometry

ESA failure

- Worse prognosis with higher AML incidence
- Use prognostic factors of response to ESA to propose earlier second line therapies?
- 2nd line: Luspatercept in particular in MDS-RS (FDA and EMEA approvals)
- lenalidomide? but outside Marketing Authorization
- Low dose iron chelator in trial, HIF stabilizer, imetelstat
- The challenge: intermediate risk MDS



Symptomatic Low-Risk MDS



Platzbecker U, Blood 2019

THANK YOU FOR YOUR ATTENTION

WELCOME TO GRENOBLE AND THE FRENCH ALPES