Thursdays Webinars

EuroBloodNet

Patient stratification in MDS

Uwe Platzbecker
Medizinische Klinik und Poliklinik 1
Hämatologie und Zelltherapie, Hämostaseologie
Universitätsklinikum Leipzig

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the Health Programme
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European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Conflict of Interest Declaration

- Honoraria and research funding:
  - Novartis
  - Amgen
  - Celgene/BMS
  - Jazz Pharmaceuticals

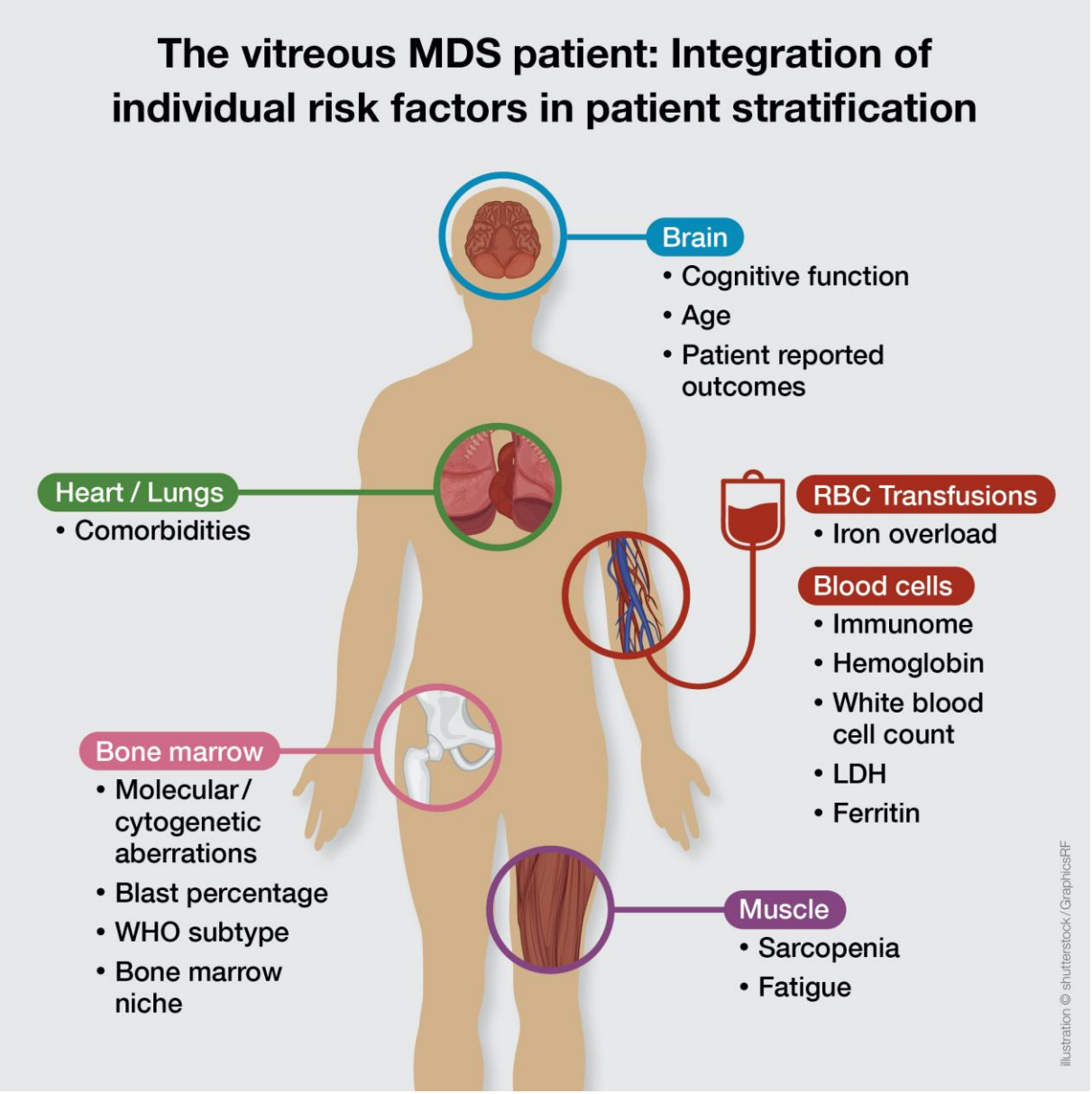
Practical issues before starting

- ✓ 30-35min presentation (30 slides max) + 15 min Q&A session
- ✓ Microphones will be muted by host to avoid back noise
- ✓ Please, stop your video to improve internet conexion
- ✓ Send your questions during the presentation through the chat, they will be gathered and answered after the presentations.

Learning objectives of the webinar

1. Understand current classification in MDS
2. Insights into novel biomarkers of prognosis and therapy
3. Understand treatment strategies

MDS Patient



Kubasch & Platzbecker. unpublished

European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

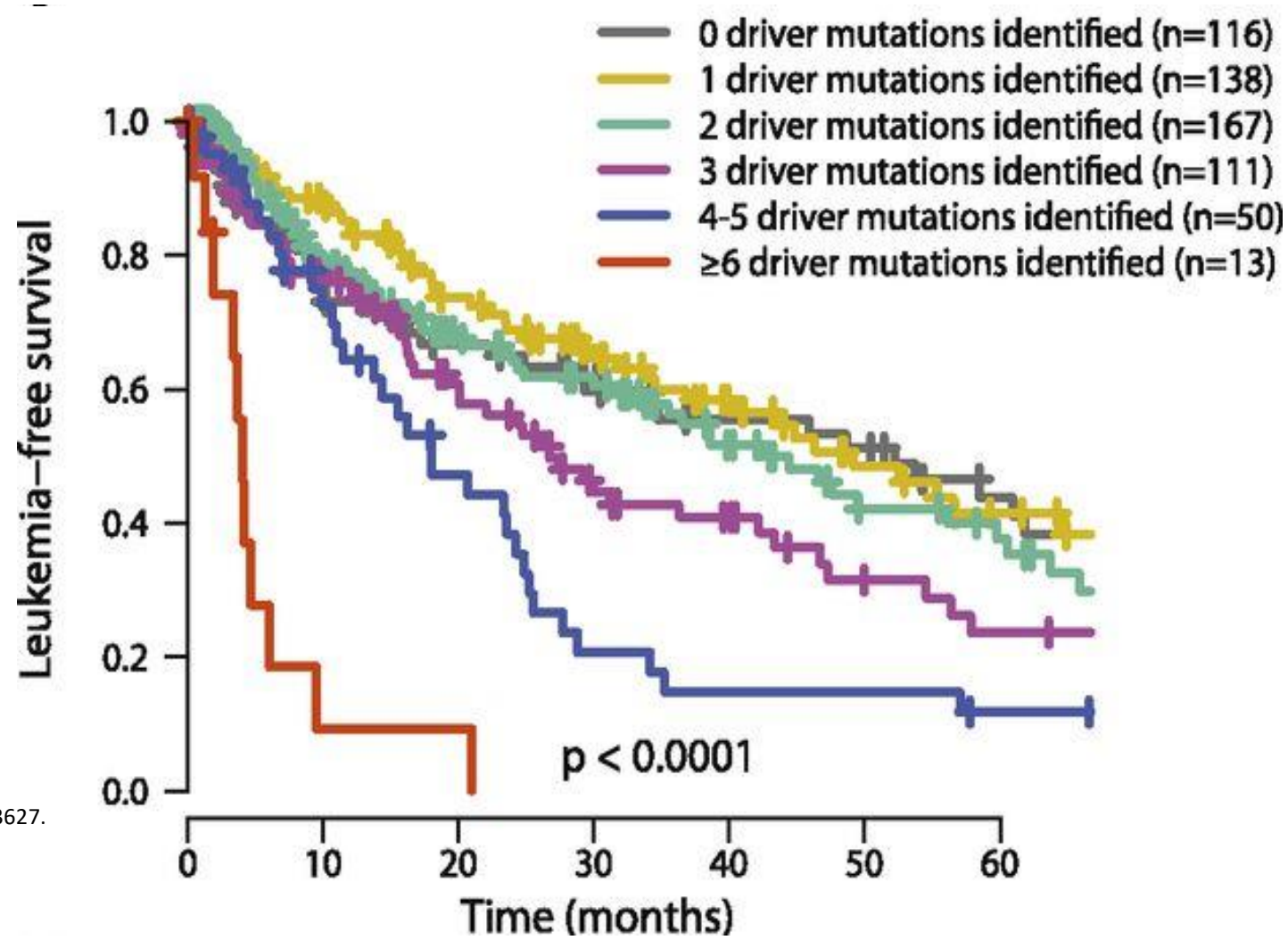
Thursdays Webinars

IPSS-group	Med. OS (years)	
Low	5,7	Low R
Int-1	3,5	
Int-2	1,2	High R
High	0,4	

IPSS-R group	Med. OS (years)	
Very Low	8,8	Low R
Low	5,3	
Intermediate	3,0	High R
High	1,6	
Very High	0,8	

Greenberg et al. Blood 1997 and 2012.

- Heterogenous and largest group of MDS patients
- Life exptecancy mostly „years“ with BSC only
- IPSS: low/int-1 or IPSS-R up to int
- Goal: improvement of QoL
- Challenge: emerging molecular data



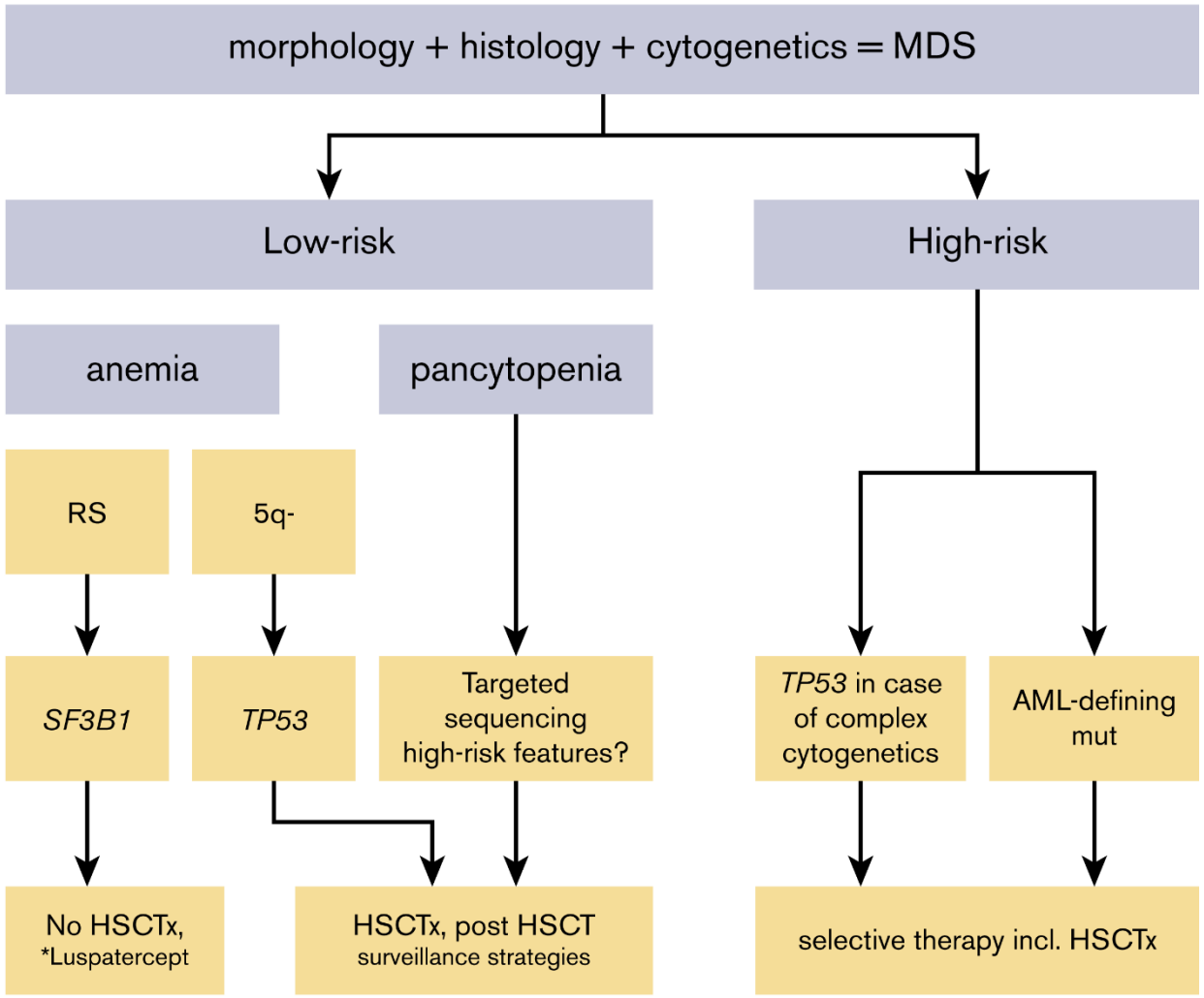
Papaemmanuil E et al. Blood 2013;122:3616-3627.

Blasts	WHO 2016
< 5%	MDS-del(5q) +/-1 except Chr7
< 5%	**MDS-RS with single lineage dysplasia (MDS-RS-SLD)**
< 5%	MDS with single lineage dysplasia (MDS-SLD)
< 5%	MDS with multilineage dysplasia (MDS-MLD) **MDS with RS and multilineage dysplasia (MDS-RS-MLD)**
5-9%	MDS with excess blasts (MDS-EB1)
10-19%	MDS with excess blasts (MDS-EB2)

MDS-RS: 5-14% RS und SF3B1 mut.

Arber et al. Blood 2016.

NGS work-up in a case of "confirmed MDS" by conventional techniques



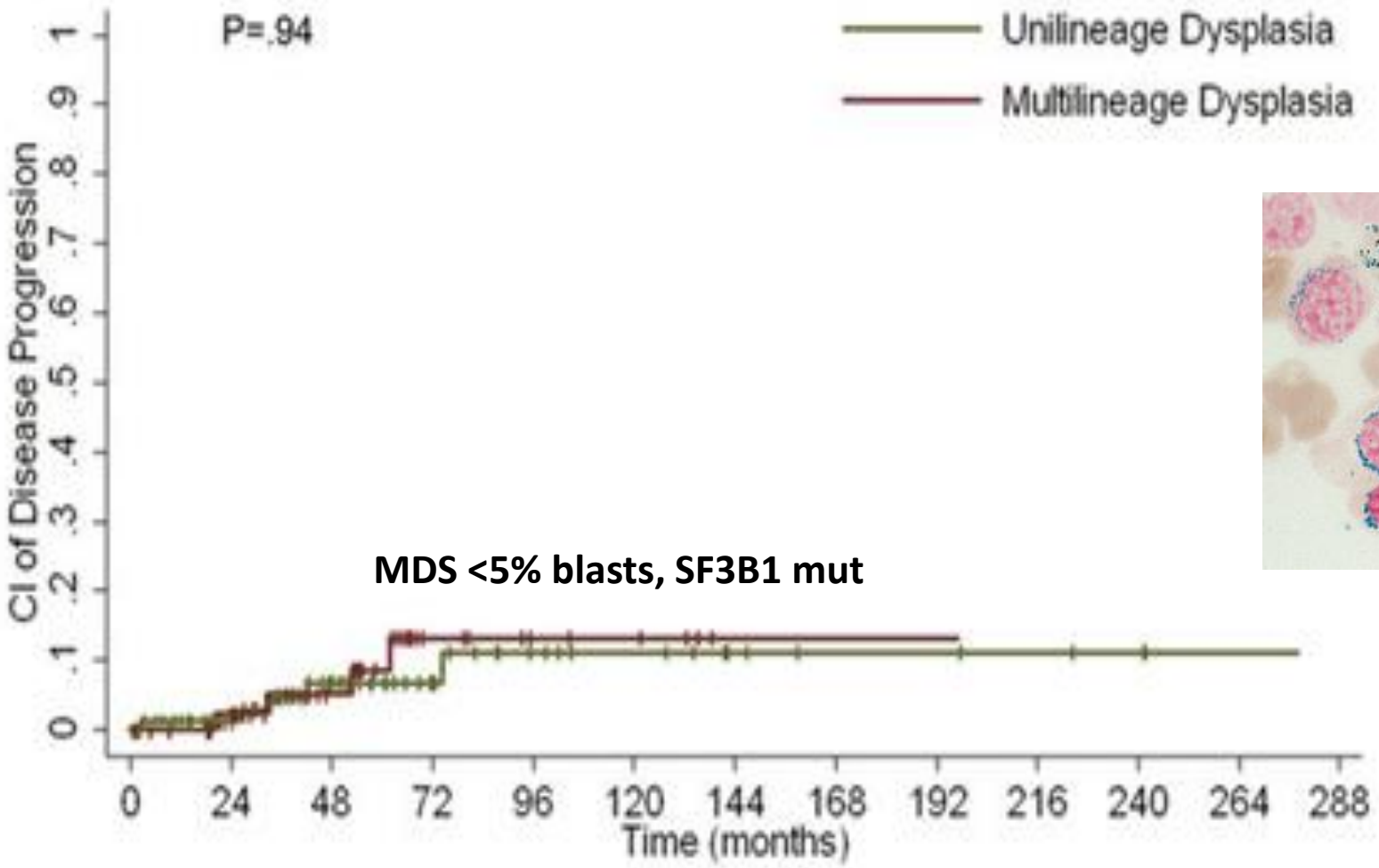
F. Thol, U. Platzbecker, Blood Adv 2019.

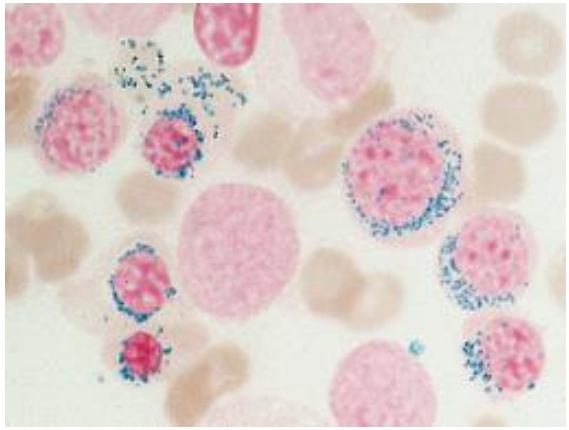
„Some workers restrict the use of the term ‘sideroblastic anaemia’ to those cases of anaemia with high serum iron, a hyperplastic bone marrow with erythroblastic preponderance, and increased numbers of ‘ring form’ sideroblasts.“

„Whether the attempt to identify this disorder on the basis of a single morphological feature is a wise one is to be questioned.“

Damashek et al. BJH 1965

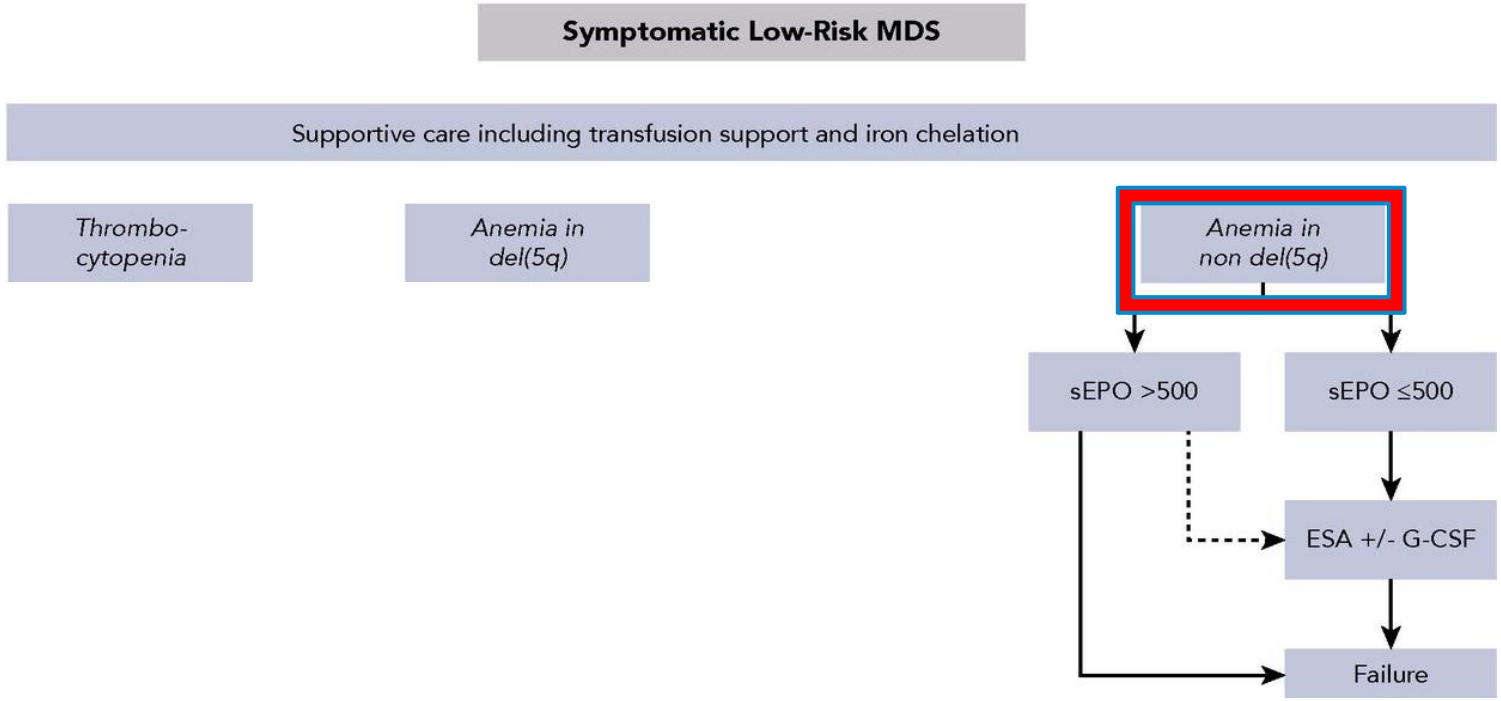
	CASE 1	CASE 2
HB LEVEL	8.5 g/dl	7.9 g/dl
PLT LEVEL	250 x10^9/L	192 x10^9/L
ANC COUNT	2.5 x10^9/L	2.7 x10^9/L
BM BLAST COUNT	3%	2%
CYTOGENETIC ANALYSIS	+19	+19
MOLECULAR ANALYSIS	TET2 (VAF) 35%) DNMT3A (VAF 25%) SF3B1 (VAF 22%)	ASXL1 (VAF 28%) ETV6 (VAF 32%) U2AF1(VAF 22%)
MDS WHO SUBTYP	MDS-RS-SLD	MDS-RS-SLD
IPSS	0.5 (int-1)	0.5 (int-1)
IPSS-R	4.0 (int)	3.5 (int)





MDS <5% blasts, SF3B1 mut

Malcovati et al. Blood 2015

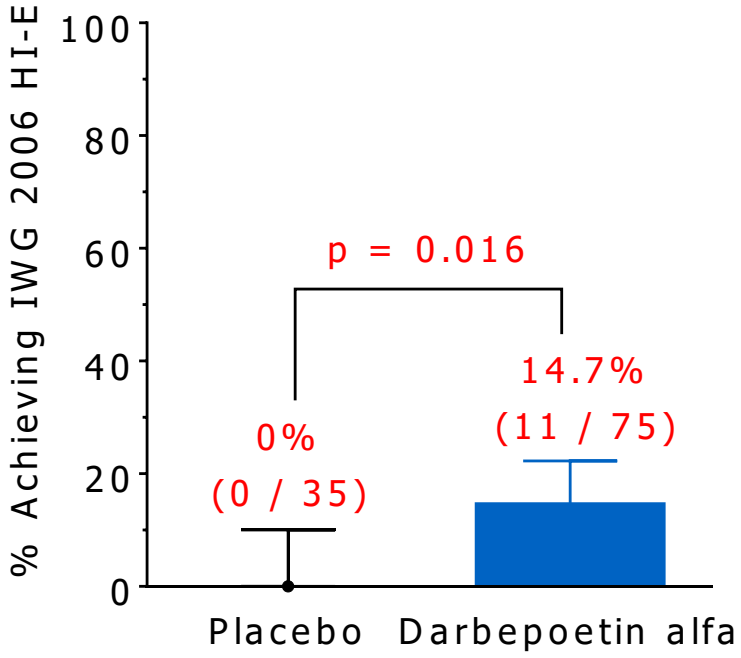


Blood 2019;133:1096-1107.

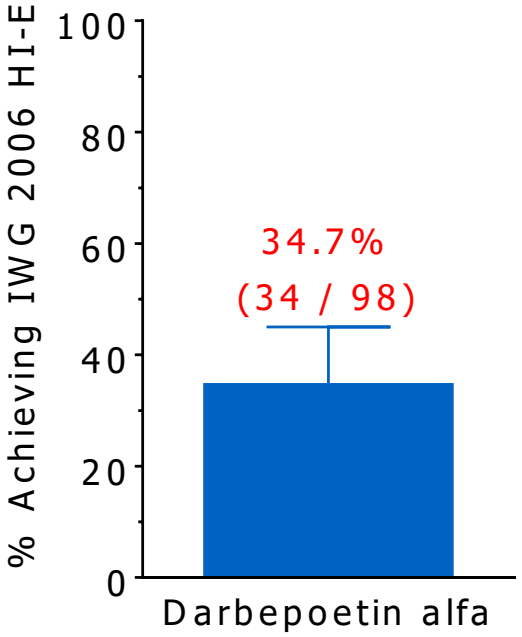
	Placebo n=45	Epoetin alfa n=85	p
Subjects achieving erythroid response (primary endpoint)	2 (4.4%)	27 (31.8%)	<0.001
Subjects with erythroid response at any time during the first 24 weeks*	2 (4.4%)	39 (45.9%)	<0.001

**Ad hoc* analysis.

Fenaux et al. Leukemia 2018.



24-week Double-blind



48-week Open-label

Platzbecker et al. Leukemia 2017.

- n=1698 IPSS low/int-1
- 34% primary ESA resistance
- 61.5% responded to ESAs, median duration 17 months

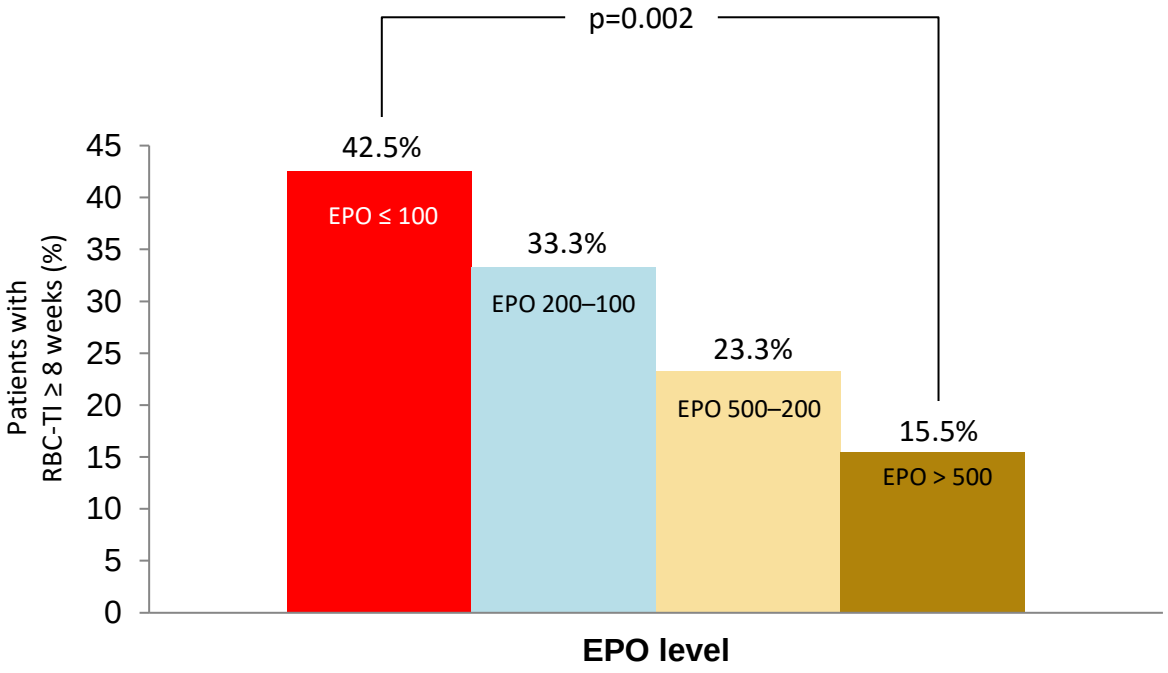
Park et al. JCO 2017.

ark et al. JCO 2017

Characteristic	No. (%)		
	Persisting Response (n = 551)	Relapse (n = 494)	Primary Resistance (n = 653)
Age, years			
Median	76	74	72
Q1-Q3	71-83	68-81	66-80
Female sex	275 (50)	200 (40)	226 (35)
WHO classification at ESA initiation			
RA without excess of blasts	343 (38)	239 (27)	309 (34)
MDS with ringed sideroblasts	130 (25)	191 (36)	207 (39)
RAEB-1	47 (31)	34 (22)	70 (46)
RCUD or MDS-U	31 (24)	30 (23)	67 (52)
HgB at ESA initiation, g/dl			
Median	9.4	9.2	9.0
Q1-Q3	8.8-10.0	8.5-9.9	8.2-9.7
IPSS-R score at ESA initiation			
Very low	126 (45)	77 (27)	80 (28)
Low	305 (32)	292(31)	352 (37)
Intermediate	46 (20)	61 (26)	126 (54)
High	4 (100)	0	0
Not evaluable*	70 (30)	64 (28)	95 (41)
Serum ferritin, μg/L			
Median	426	506	578
Q1-Q3	126-552	188-620	220-740
Serum EPO level, mU/mL			
Median	60	183	245
Q1-Q3	21-75	38-323	49-260

Park et al. JCO 2017.

RBC-TI ≥ 8 weeks according to baseline EPO level groups in patients with prior ESA therapy:



Santini et al. JCO 2016.

How to make ESA better?


- COMMUNICATION -
HOW ARE YOU?
WIE GEHTS?
PEHEA KOE?
你好嗎？
COMMENT ALLEZ-VOUS?
designed by freepik.com

Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials

U. Platzbecker,[1-3,*] P. Fenaux,[3-5,*] L. Adès,[3-5] A. Giagounidis,[3,6] V. Santini,[3,7] A. A. van de Loosdrecht,[3,8] D. Bowen,[9] T. de Witte,[10]
G. Garcia-Manero,[11] E. Hellström-Lindberg,[12] U. Germing,[3,13] R. Stauder,[14] L. Malcovati,[15] M. Sekeres,[16] D. P. Steensma,[17] and S. Gloaguen[3]

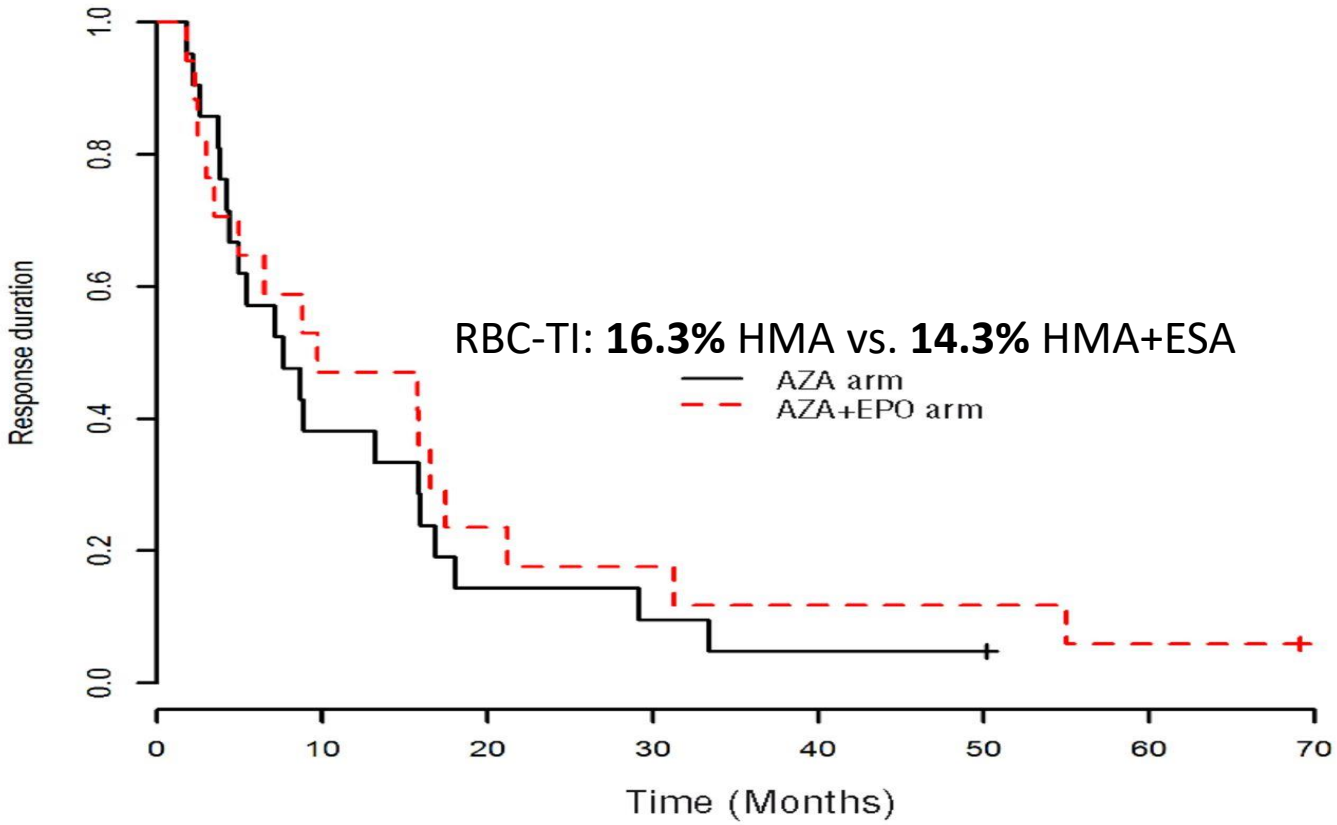
Item	Suggested IWG 2018 criteria	IWG 2006 criteria
Baseline criteria		
Definition of transfusion-burden categories	3 groups: NTD (0 RBCs in 16 wk)* LTB (3-7 RBCs in 16 wk in at least 2 transfusion episodes, maximum 3 in 8 wk)* HTB (≥8 RBCs in 16 wk, ≥4 in 8 wk)	2 groups: TD (at least 4 U of RBC with 8 wk for Hb < 9 g/dL) TID (<4 U of RBC with 8 wk for Hb < 9 g/dL)
Pretreatment RBC transfusion policy	Transfusion policy for the individual patient prior to therapy should be maintained on treatment†	Transfusion threshold of 9 g/dL, no exception for clinical indication

Platzbecker & Fenaux et al. Blood 2019;133:1020-1030.

Combine it

	L arm (N=65)	LE arm (N=66)	P-value
HI-E, IWG 2006 criteria	**23.1%**	**39.4%**	0.044
RBC-TI	13.8%	24.2%	NS
Median duration in months	18.1	15.1	NS

Toma et al. Leukemia 2016.



Thépot et al. Haematologica 2016.

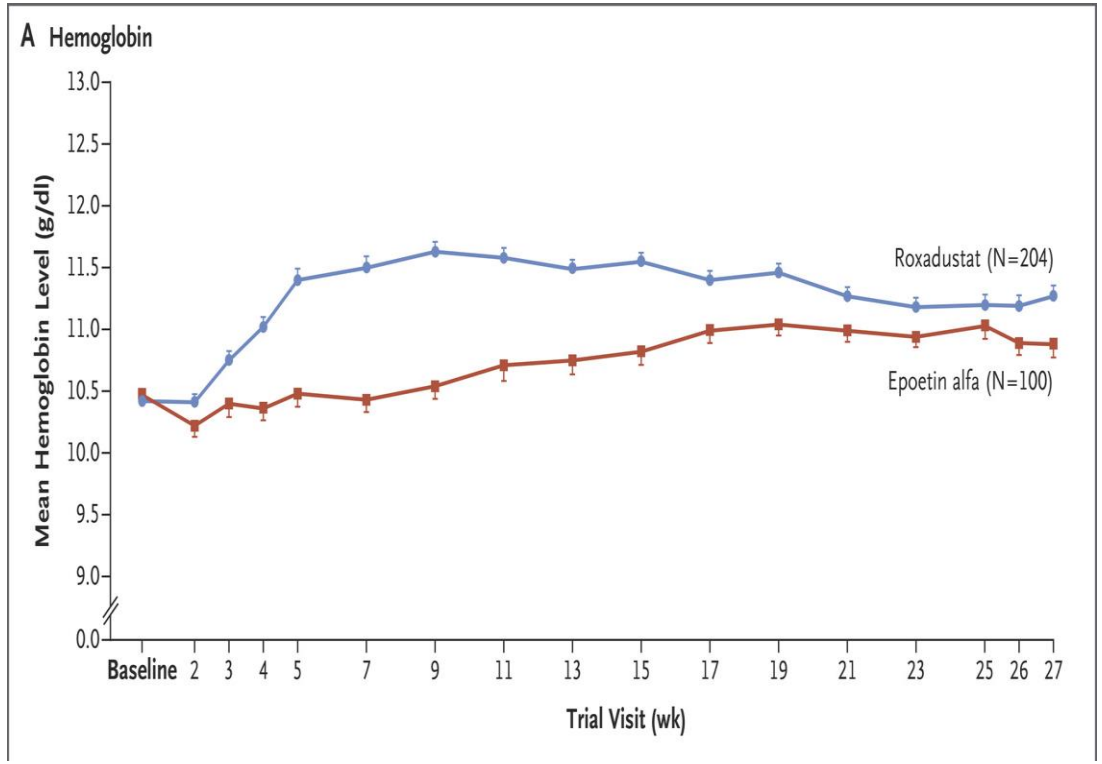
Select patients

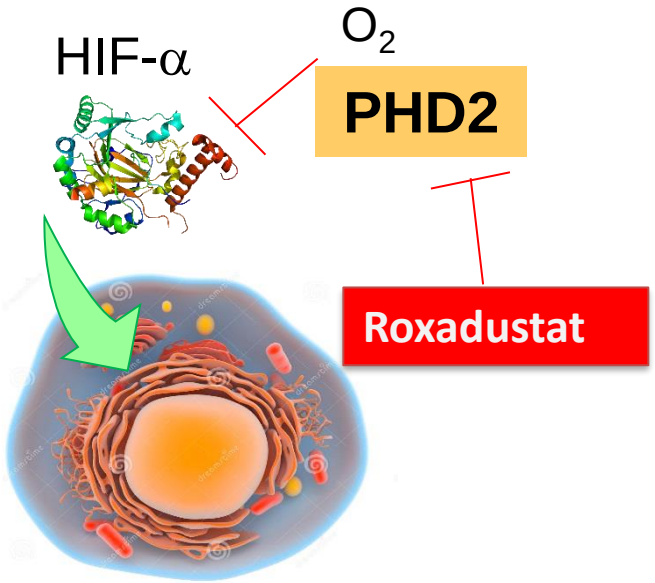
Number of Mutations	HI-E (%)
0	73
1	71
2	79
3	47
4	38

Presence of >2 mutations predicted worse HI-E to ESA in lower risk MDS.
≤2 mutations: 74%, vs > 2 mutations: 46% (p=0.01)

Kosmider et al. Haematologica 2016.

Make endogenous EPO great again





„Inhibiting the inhibition“

Chen et al. NEJM 2019.

Other Approaches

3d DAC vs. 3d AZA q4w

- N=113
- 85% INT-1 IPSS-R
- 19% ESA pre-treatment
- Median time from diagnosis: 5 weeks

- **HI: 18%**
- Median response duration: 18 months

Jabbour et al. Blood 2017.

- CC-486 vs placebo
- LR-MDS, RBC-transfusion dependent anemia and thrombocytopenia (n=216)

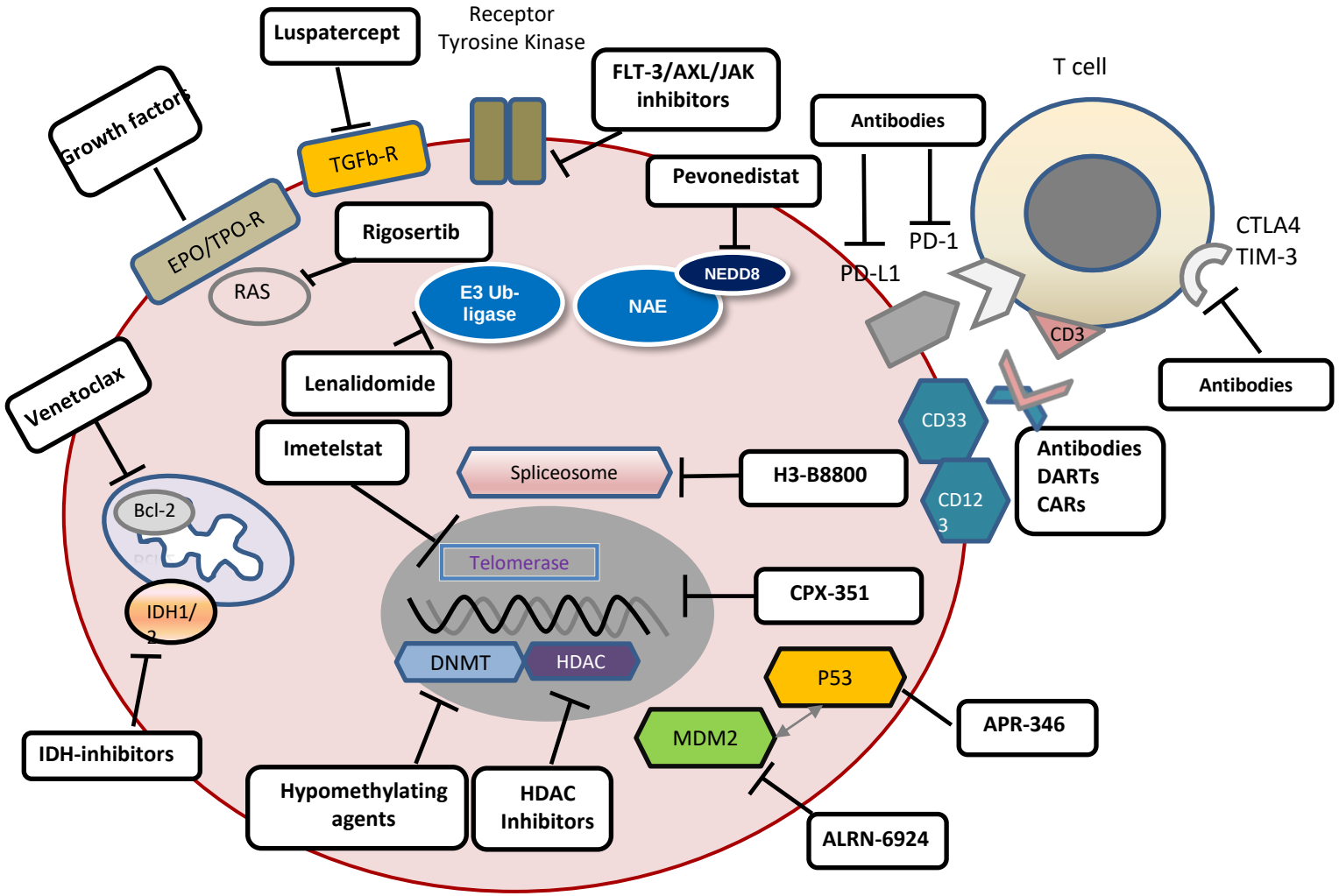
- CC-486 vs placebo:
  - RBC-TI (≥8 weeks) = 31% vs 11%; median duration = 11.1 vs 5.0 months
  - PLT-TI (≥8 weeks) = 17% vs 14%; median duration = 12.1 vs 4.4 months
- HI-E rates were comparable; HI-P rate was significantly higher in the CC-486 arm
- Most common AEs were grade 1–2 GI events; AEs were more frequent with CC-486

- Study met the primary endpoint of RBC-TI and induced durable bilineage Hb and PLT improvements
- AEs were more frequent with CC-486; patients with severe neutropenia are at higher risk for hematologic toxicity during early treatment

Garcia-Manero et al. EHA 2020

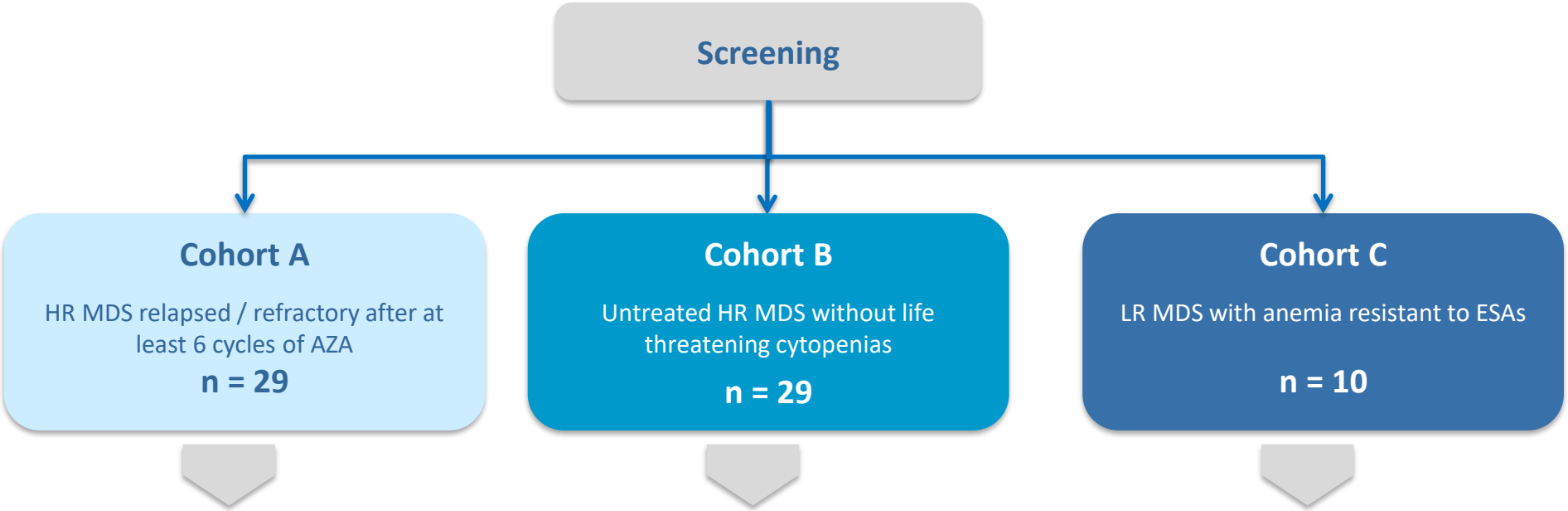
Other (Better) Approaches

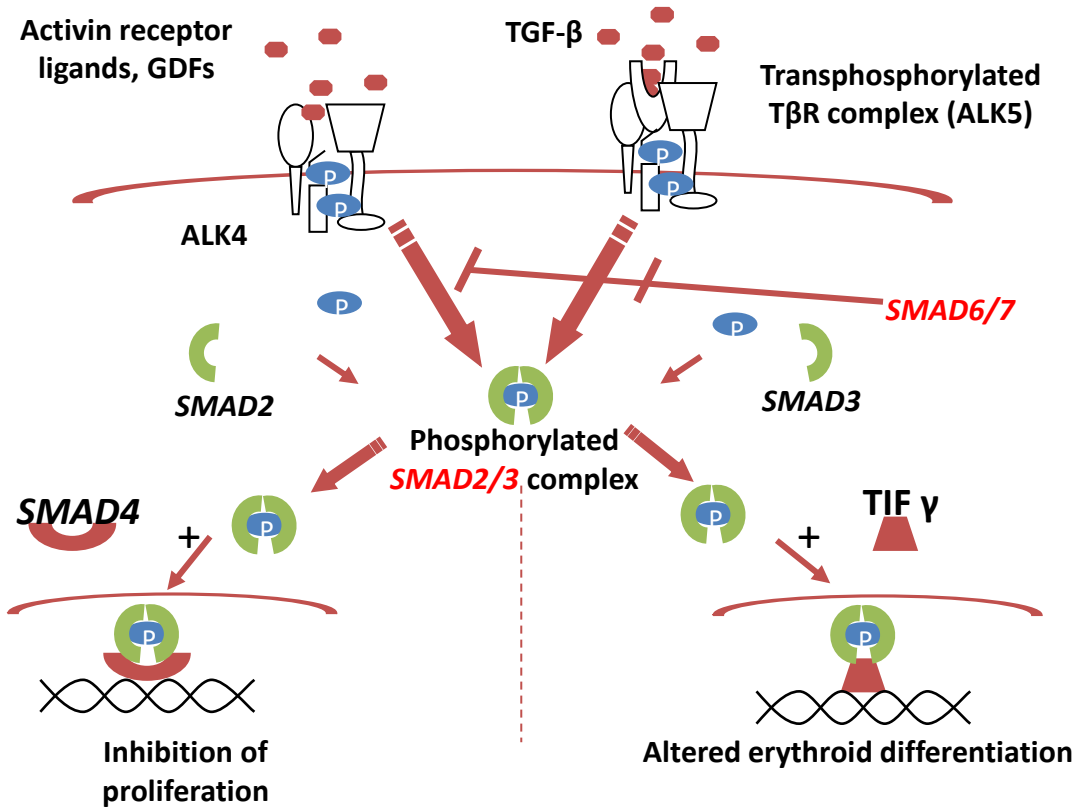
Which target ?



U. Platzbecker. Blood 2019

IDEAL – trial design

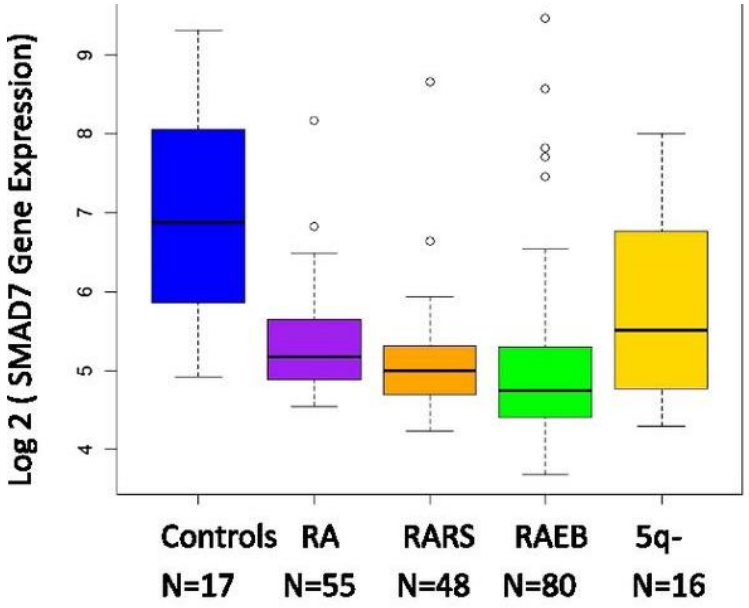




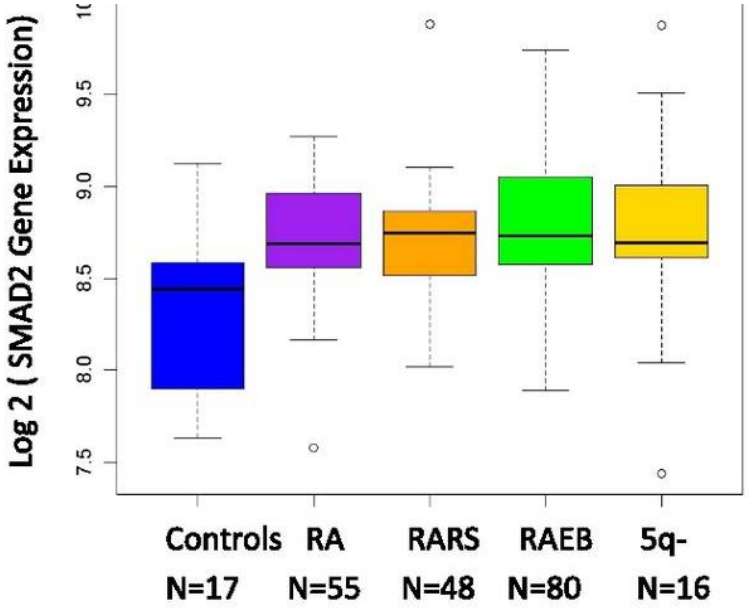
ALK, activin-like kinase receptor; GDF, growth differentiation factor; TGF-β, transforming growth factor β.

Figure provided courtesy of Amit Verma.

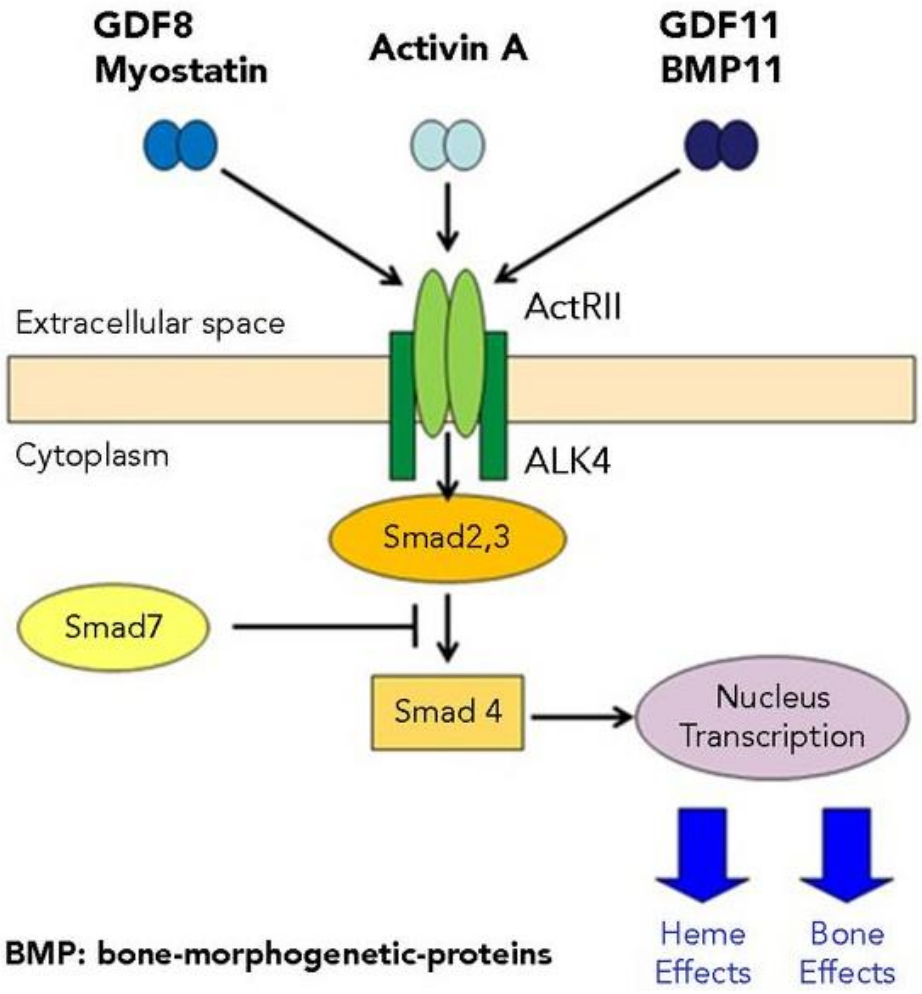
SMAD7



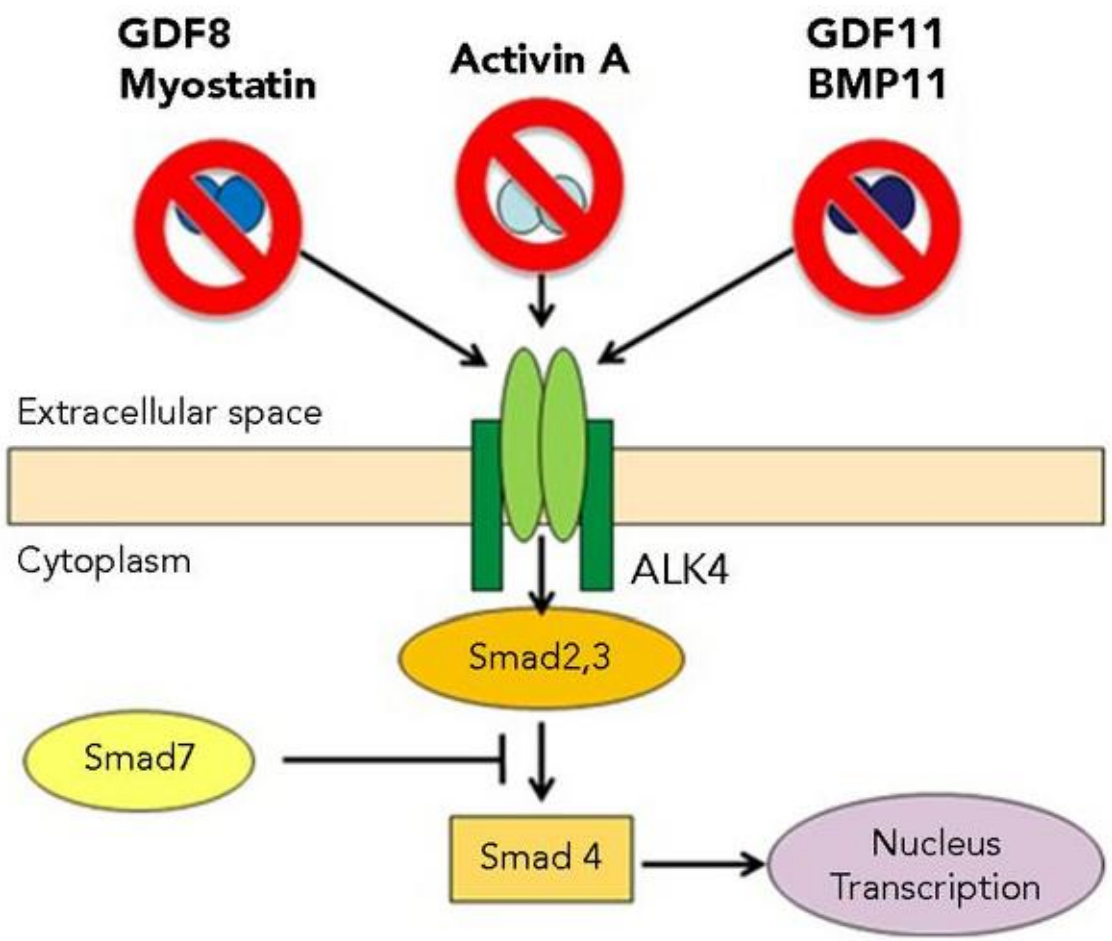
SMAD2 (effector of SMAD7)



Bhagat TD, et al. Blood 2013;121:2875–81.



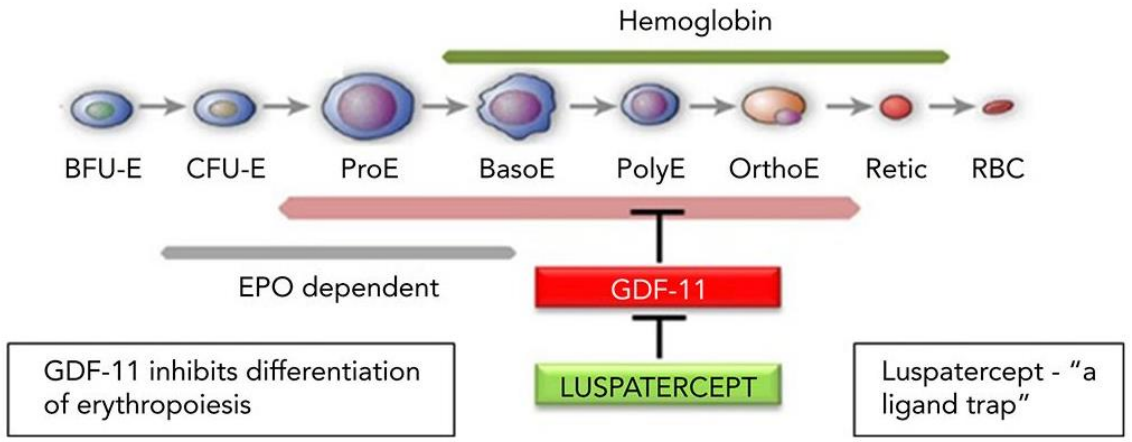
Fenaux, Kiladjan, Platzbecker. Blood 2019;133:790-794.



Fenaux, Kiladjan, Platzbecker. Blood 2019;133:790-794.

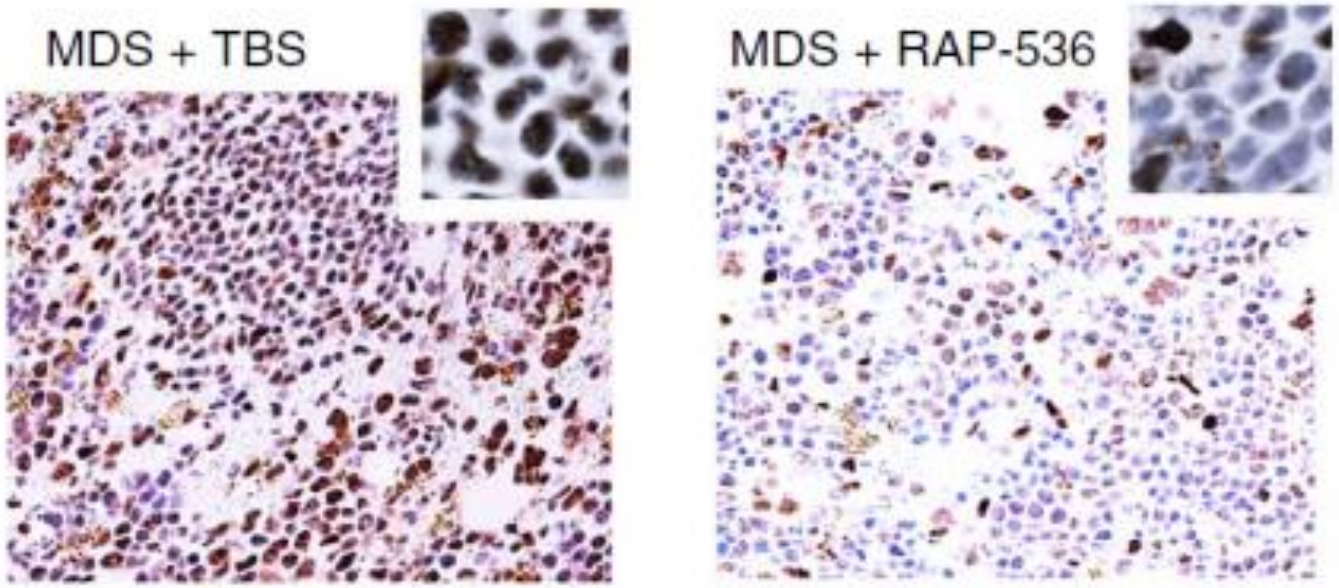
	(ACE-536) **Luspatercept**	(ACE-011) **Sotatercept**
	Modified Extracellular Domain of **ActRIIB** Fc Domain of human IgG_1 Antibody	Extracellular Domain of **ActRIIA** Fc Domain of human IgG_1 Antibody
Activin A Binding	**No**	**Yes**
Bone Increase	**No**	**Yes**
RBC Increase	**Yes**	**Yes**

Mechanism of action of Luspatercept



Fenaux, Kiladjan, Platzbecker. Blood 2019;133:790-794.

Inhibits Smad2/3 Signaling



Studies using RAP-536, murine analog of luspatercept.

Suragani R et al., Nature Med 2014.

RED CELLS, IRON, AND ERYTHROPOIESIS

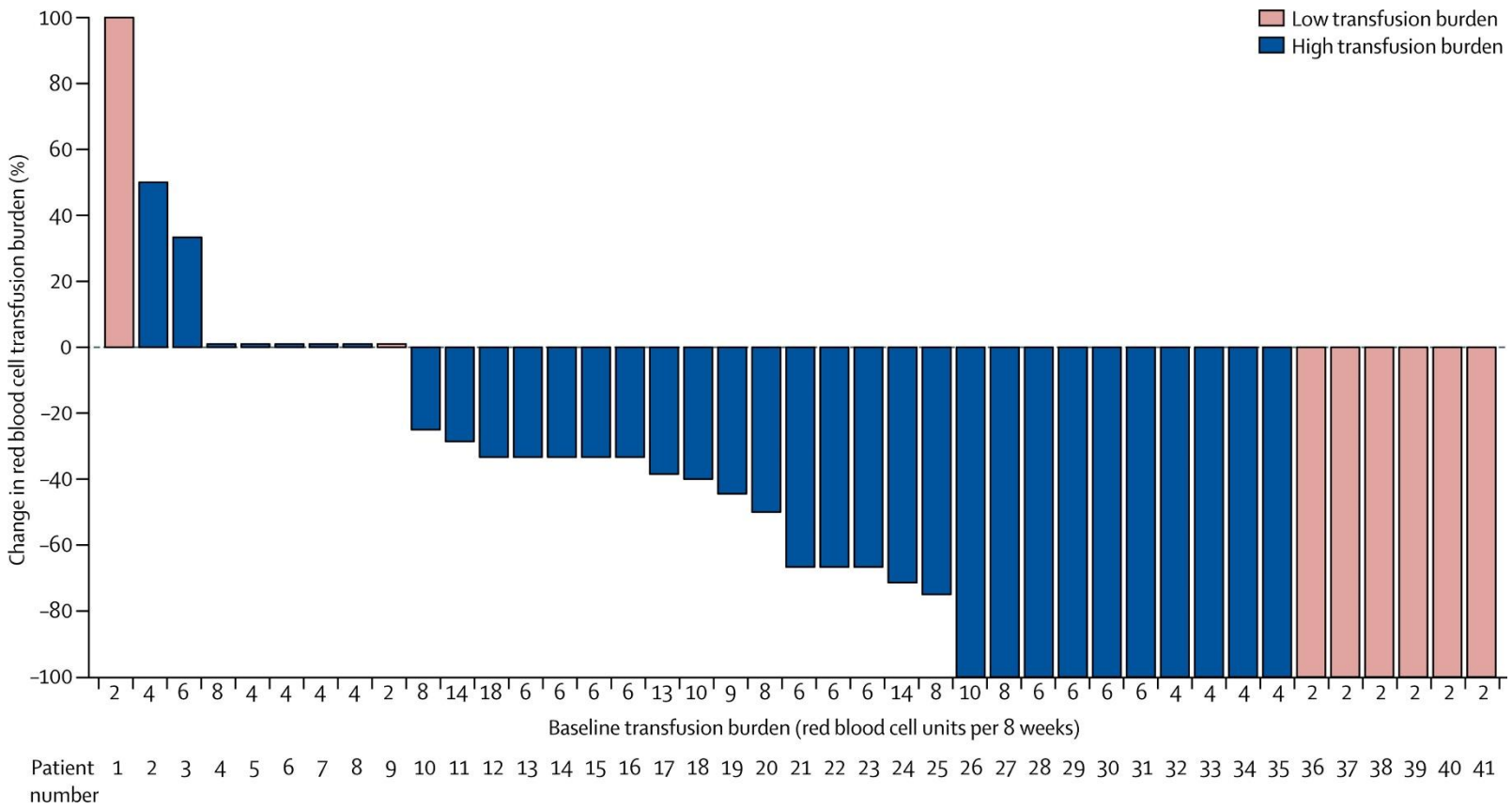
Comment on Guerra et al, page 568

GDF11 is not the target of luspatercept

Clara Camaschella | San Raffaele Scientific Institute

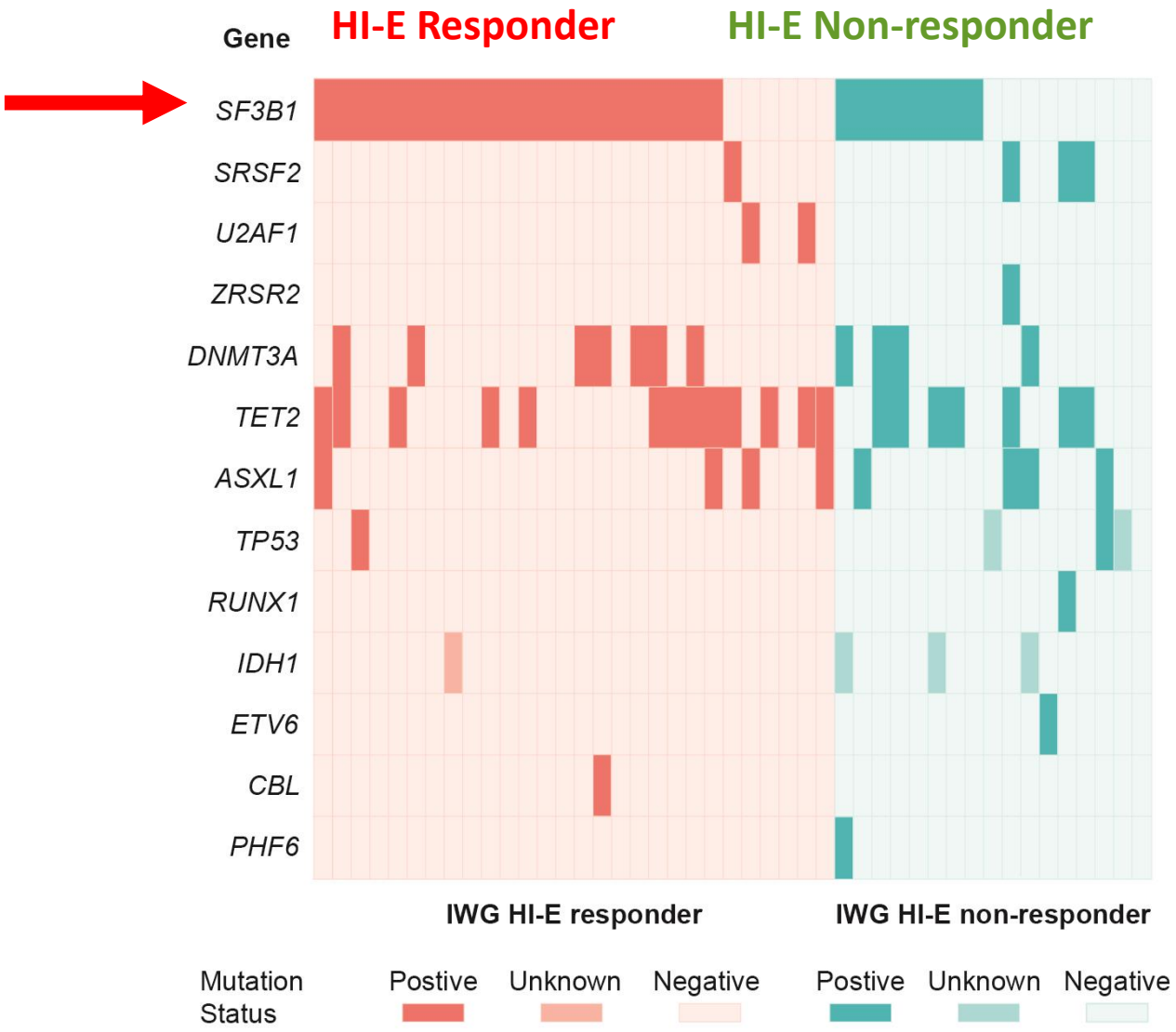
In this issue of *Blood*, Guerra et al have excluded that growth differentiation factor 11 (GDF11) is the target of luspatercept, a novel drug that promotes differentiation of terminal erythropoiesis and is under evaluation for treatment of β-thalassemia and low-risk myelodysplastic syndromes (MDSs).[1]

Blood 2019.



Platzbecker et al. Lancet Oncology 2017.

Erythroid Response with Luspatercept by Mutation



Patient Population

- < 5% blasts in bone marrow
- No 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 units/8 weeks
- No prior treatment with disease-modifying agents (e.g. iMIDs, HMAs)

Randomize 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 21 days
n = 76

Data cutoff: May 8, 2018 Includes last subject randomized + 48 weeks.

EPO, erythropoietin; HMA, hypomethylating agent; iMID, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

Fenaux & Platzbecker et al. NEJM 2020.

MEDALIST Trial

Luspatercept in RS+MDS

RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**37.9**	**13.2**
P value[a]	< 0.0001	

Fenaux & Platzbecker et al. NEJM 2020.

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IWG 2018: 19.0% vs. 3.9%, weeks 1–24

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for rare or low prevalence complex diseases

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Fenaux & Platzbecker et al. NEJM 2020.

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MEDALIST Trial

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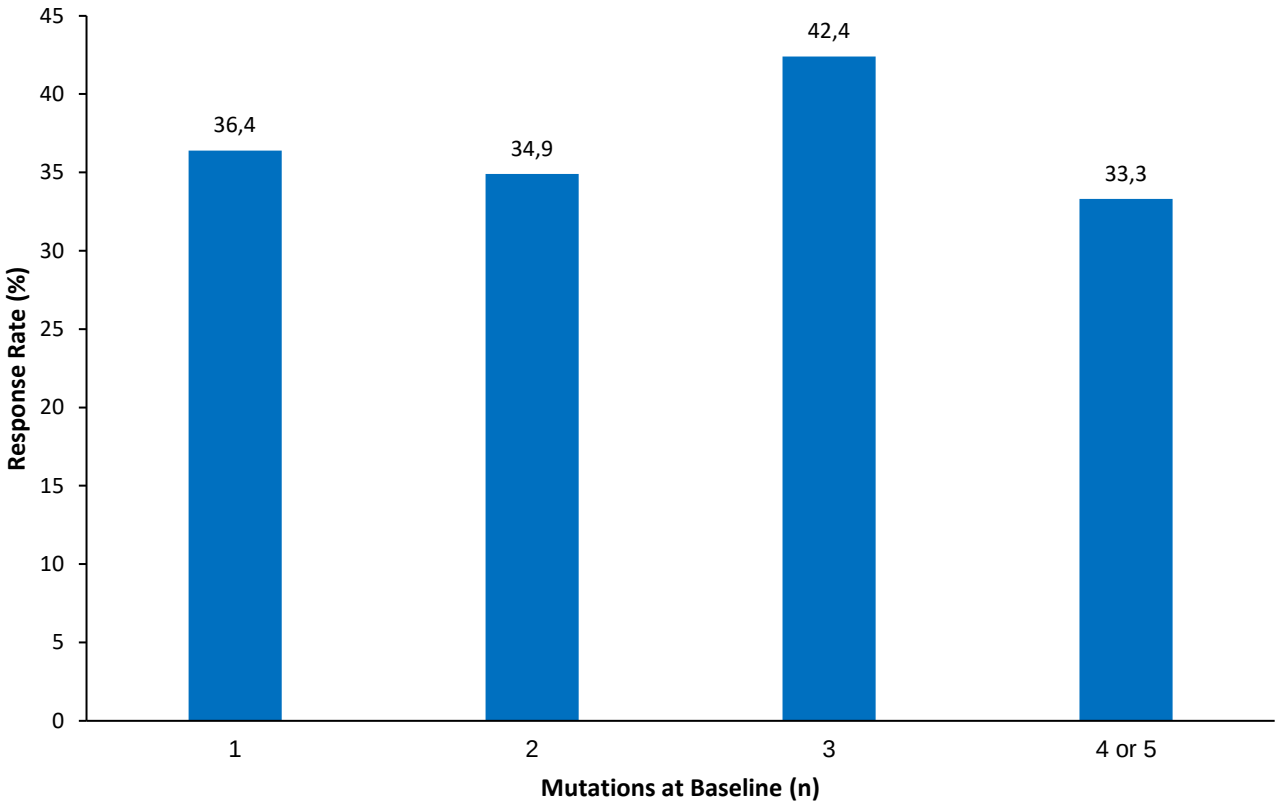
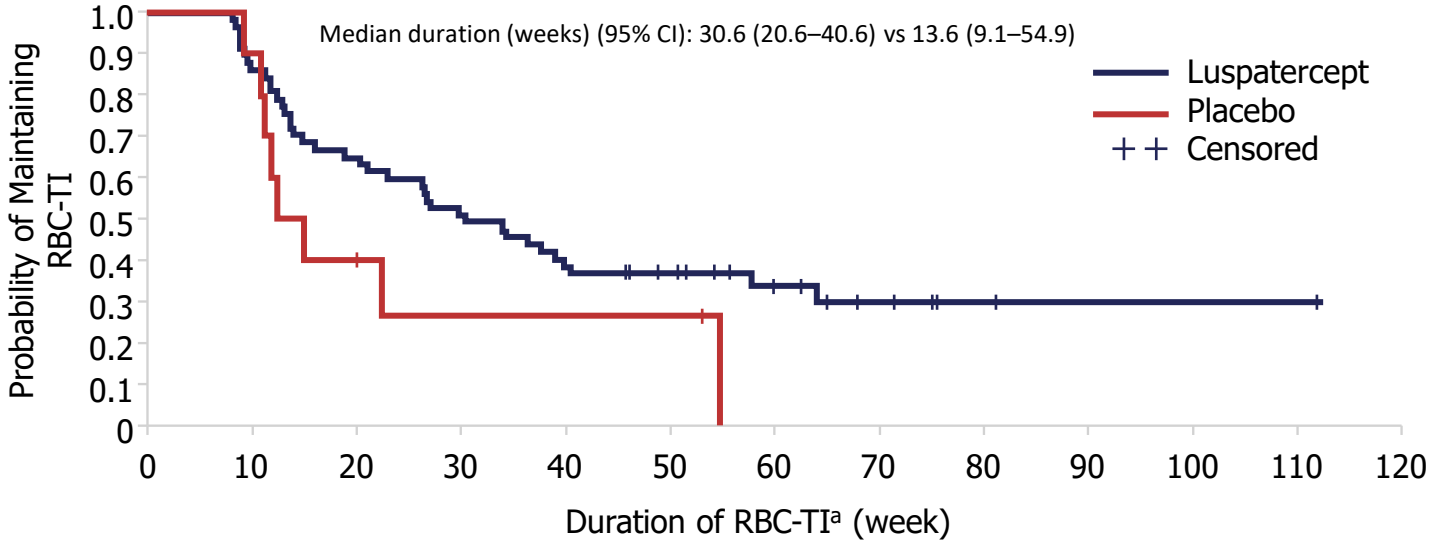


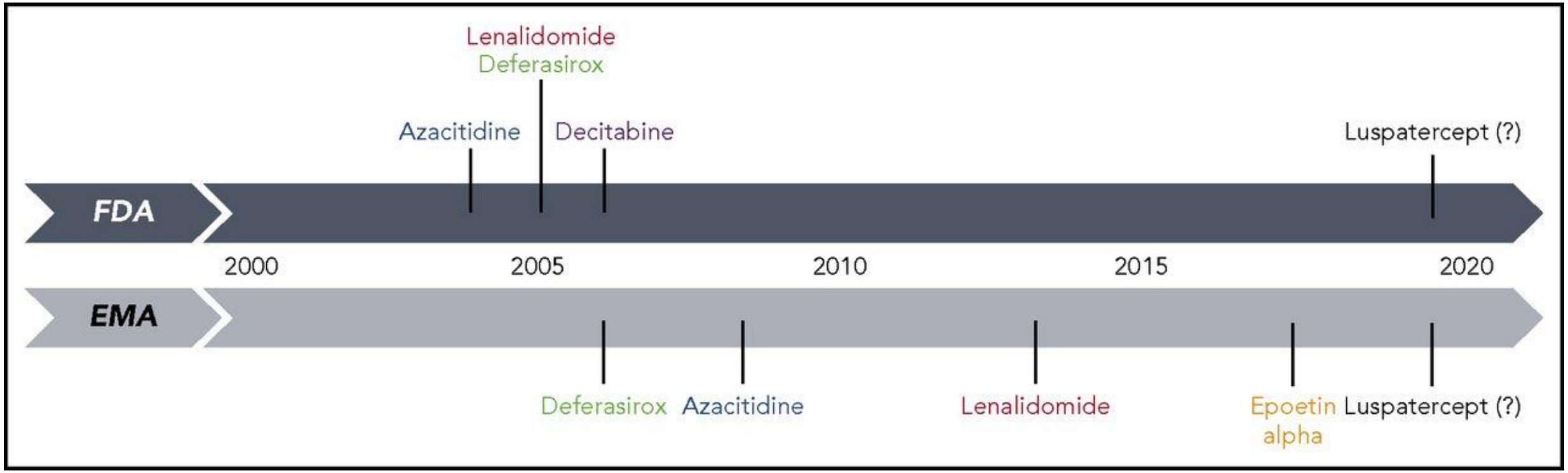
Fenaux & Platzbecker et al. NEJM 2020.



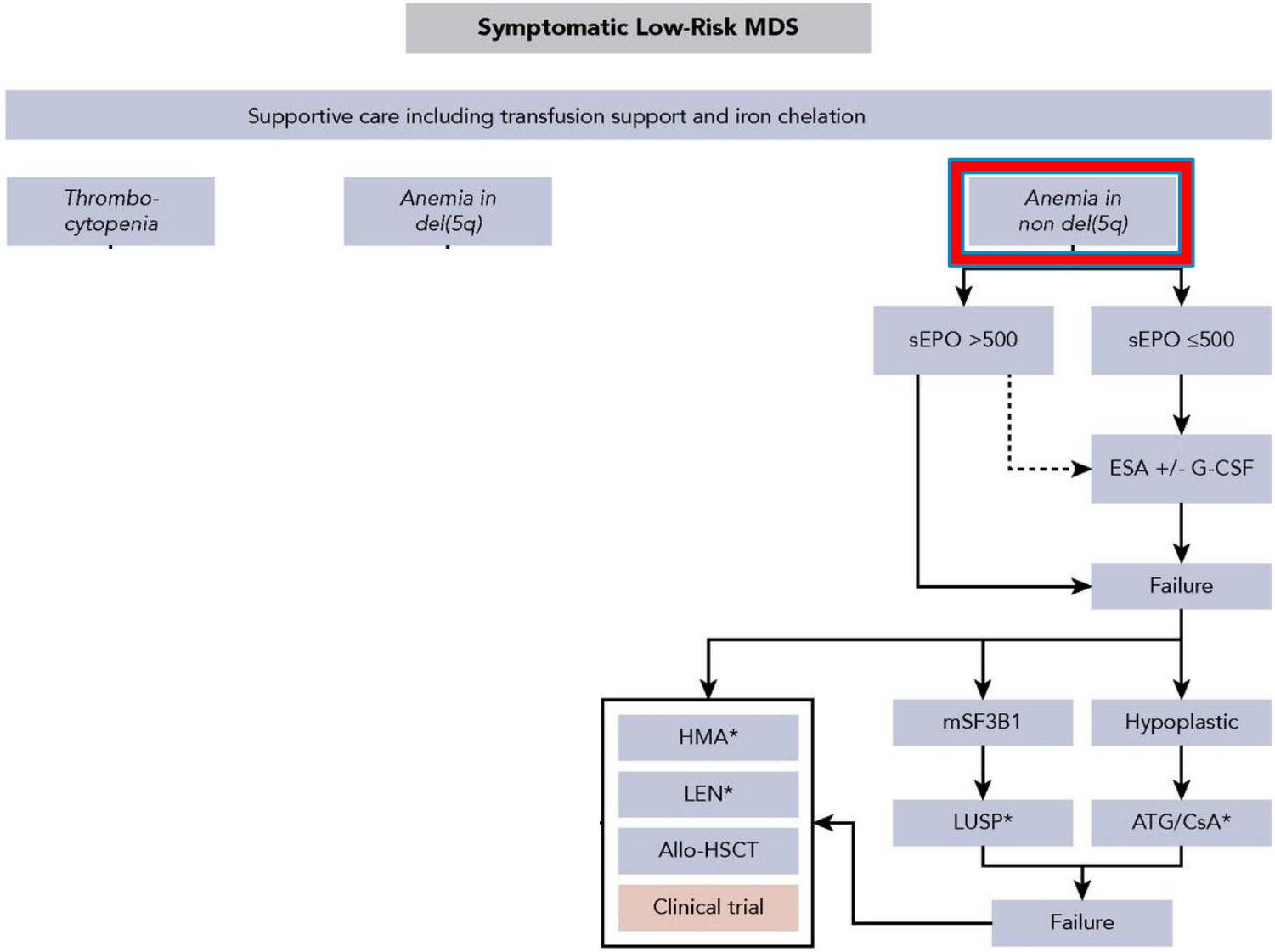
Number of patients													
Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

[a] During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.

Fenaux & Platzbecker et al. NEJM 2020.



U. Platzbecker. Blood 2019;133:1096-1107.



U. Platzbecker. Blood 2019;133:1096-1107.

Response Rates	IWG-HI-E, n/N (%) (N=99)	RBC-TI, n/N (%) (N=67)
All patients	52/99 (52.5)	29/67 (43.3)
ESA-naïve	28/53 (52.8)	17/31 (54.8)
ESA-exposed	24/46 (52.2)	12/36 (33.3)
RS Status		
RS+	40/60 (66.7)	20/40 (50.0)
Non-RS	10/31 (32.3)	7/22 (31.8)
Unknown	2/8 (25.0)	2/5 (40.0)

Platzbecker et al. ASH 2017.

Key Eligibility Criteria

- MDS diagnosis (WHO 2016)
- IPSS-R VL, L, INT risk
- No del5q MDS
- Requiring RBC transfusions while Hgb **≤ 9 g/dL**
- **≥ 2 – 6** units of RBCs within the 8 weeks prior to randomization
- **ESA naïve**
- **Endogenous EPO <500**
- No prior treatment with disease modifying agents
- **Include both RS(+) and RS(-) patients**
  (Cap RS(-) @ 50%)

Stratification:

RBC Transfusion Burden
- 2-3 / 4-6 units

RS status:
- RS(+) / RS(-)

EPO level:
- < 200 / <500

Luspatercept (ACE-536)
1.0 mg/kg q3W
with titration up to max 1.75 mg/kg
(n= 131)

Epoetin alfa
450 IU/kg s.c. weekly (max. total dose 40K IU) titration up to 1050 IU/kg
(max. total dose 80K IU
(n= 131))

MDS Disease Assessment after 24 wks and q6months thereafter
D/C treatment if no clinical benefit, progression to HR-MDS (high, very high) or AML

Follow-Up
subjects for ≥ 3 years post last dose for AML progression, subsequent MDS treatment and OS

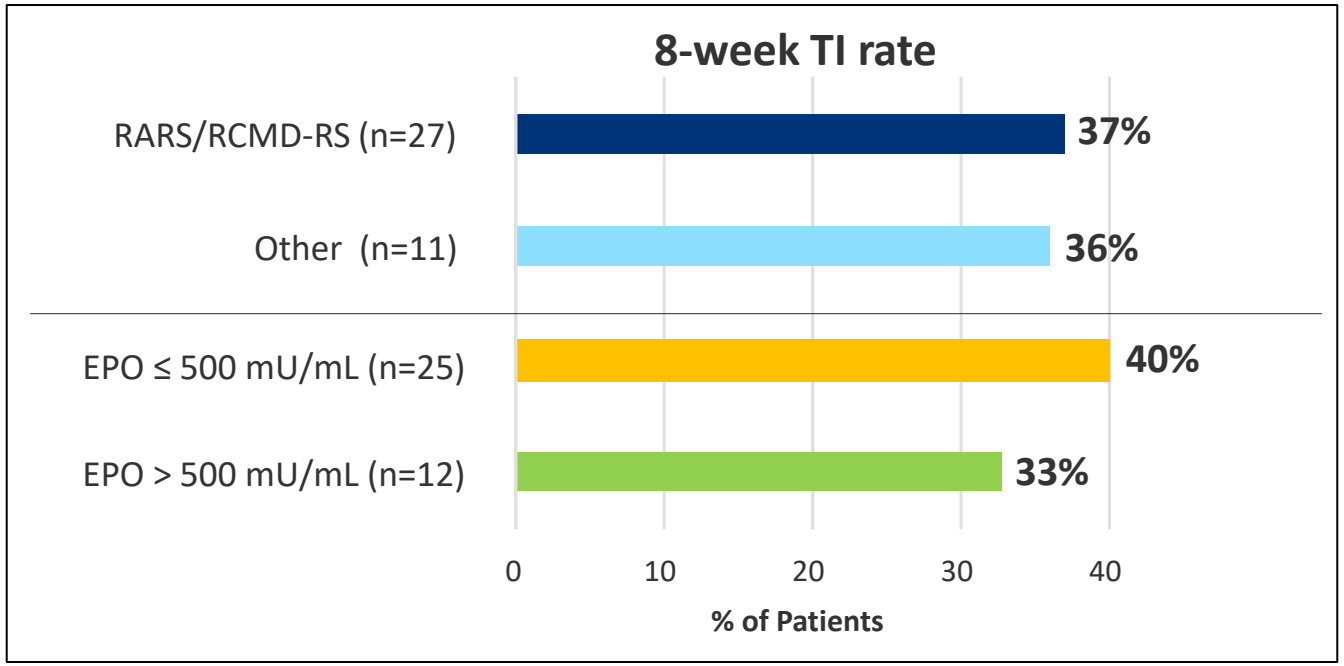
- 1:1 randomization
- Open label with blinded IRAC
- 262 subjects planned
  (TI 45% → 65% Power 90%)

- **1° Endpoint:** RBC-TI for the first 24 weeks from randomization
- **2° Endpoints (Key):**
  - HI-E per IWG (Cheson, 2006): Proportion of subjects achieving HI-E over any consecutive 56-day period in absence of transfusions
  - Mean hemoglobin increase ≥ 1.5 g/dL:
    Proportion of subjects achieving ≥ 1.5 g/dL mean increase in Hgb over a consecutive 24-week period in the absence of RBC transfusions

ClinicalTrials.gov Identifier: NCT03682536.

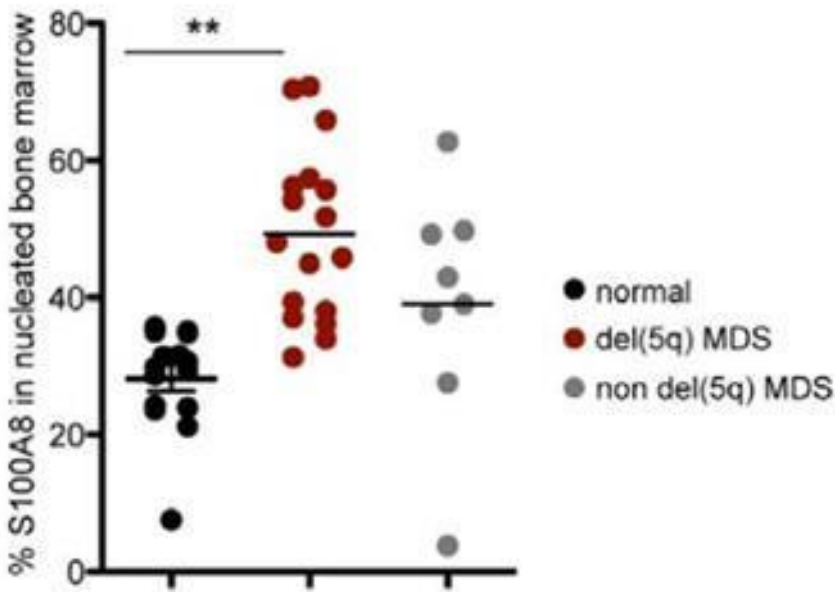
Other (Better?) Concepts

Parameters	N=38
Rate of 8-week TI, n (%)	14 (37)
Rate of 24-week TI, n (%)	10 (26)
Median time to onset of TI (range), weeks	8.1 (0.1-33.1)
Median duration of TI (range), weeks	NE (17.0-NE)



Steensma et al. ASH 2018.

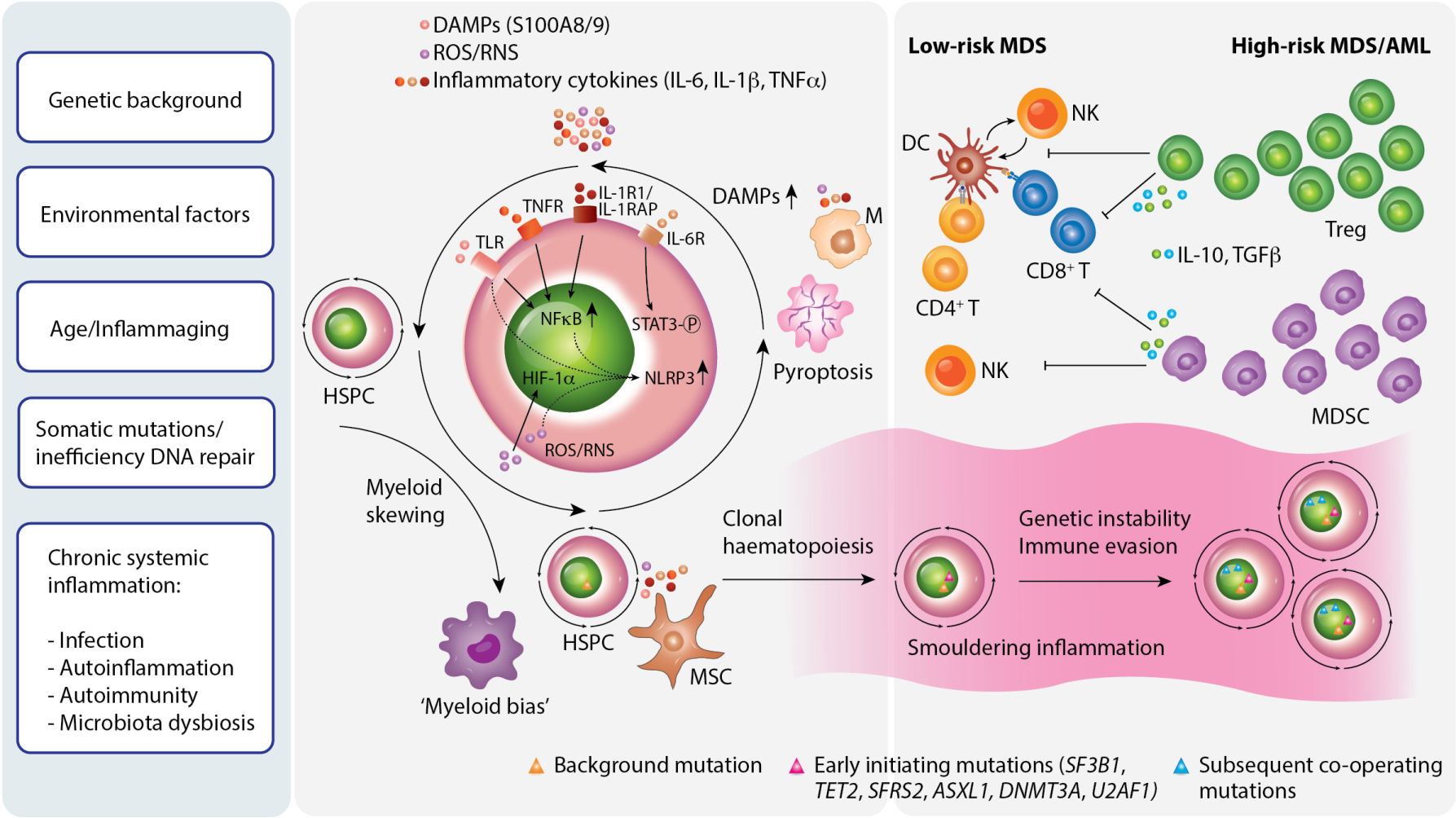
S100A



S100A8/S100A9 is induced during inflammatory processes including MDS

Schneider RK, et al. Nat Med 2016;22:288–97.

The immune contexture in myelodysplastic syndromes



Winter, Shoale, Kordasti & Platzbecker. Journal Clinical Oncology 2020

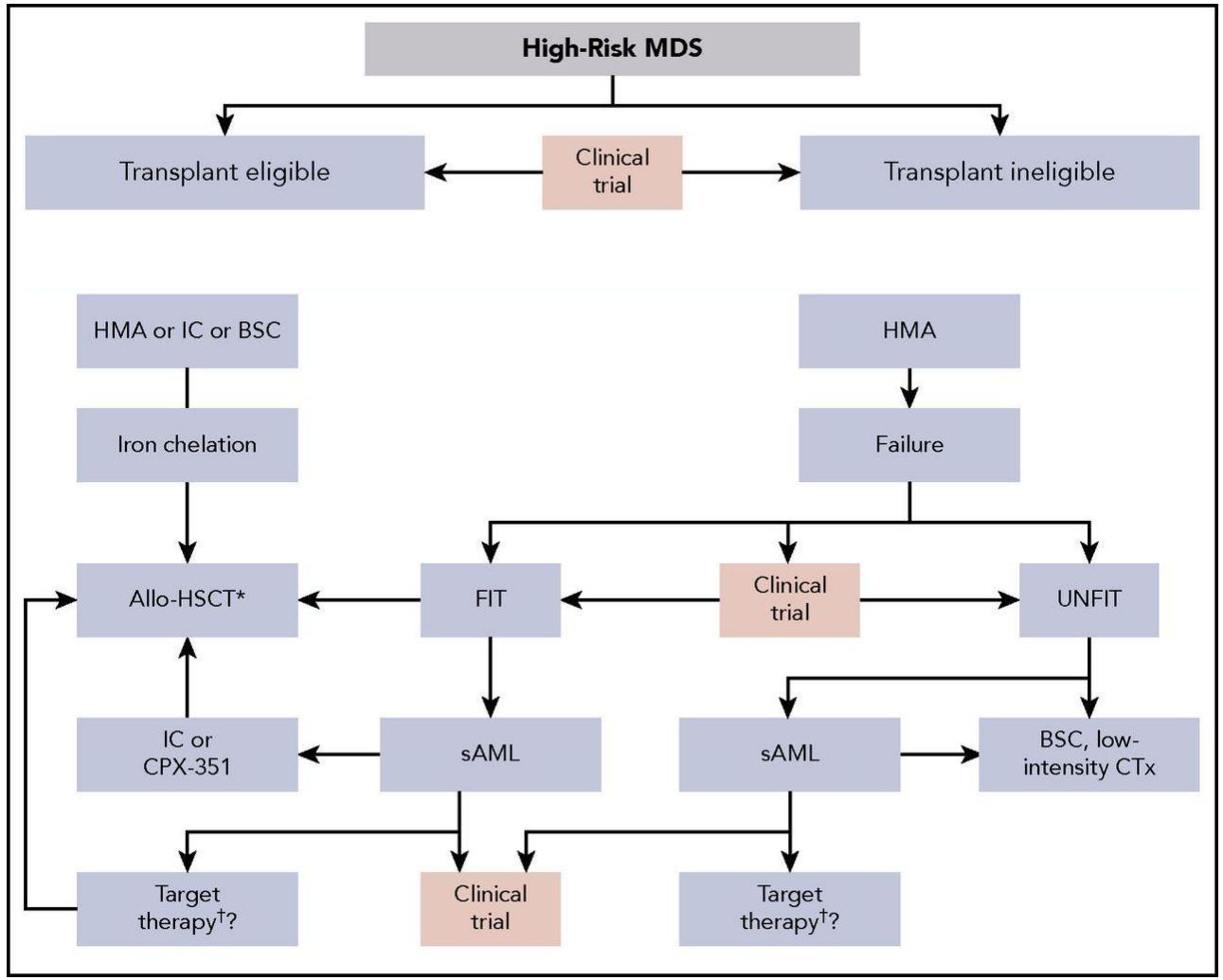
Novel therapeutic agents evaluating immune targets in MDS

TABLE 1. Novel Therapeutic Agents Evaluating Immune Targets in MDS

Class	Drug	Target	Patient Group	Clinical Trial	Reference
TLR inhibition	OPN-305 (mAb)	TLR2	HMA failure lower-risk MDS	NCT02363491: phase I-II, completed	155
	IRAK-1/4 inhibitor	IRAK-1/4	N/A	Preclinical	28
	Bortezomib	NF-κB pathway, TRAF6 inhibition	Lower-risk MDS with p65 activation	NCT01891968: phase II, completed	156
NLRP3 inhibition	Ibrutinib	BTK inhibitor, regulator of NLRP3 inflammasome	Higher-risk MDS	Phase I, recruiting; in combination with Len (NCT03359460) or Aza (NCT02553941)	
Cytokine inhibition	Luspatercept (ACE-536)	TGF-β superfamily ligands	Lower-risk MDS	NCT02631070: phase III, active, not recruiting and NCT03682536: phase III, recruiting; luspatercept *v* epoetin alpha	157,158
Checkpoint inhibitors	Ipilimumab/ nivolumab	CTLA-4/PD-1	Untreated MDS, post–HMA failure	NCT02530463: phase II, recruiting; alone or in combination with Aza	93
	Durvalumab	PD-L1	Untreated higher-risk MDS, AML	NCT02775903: phase II, active, not recruiting; in combination with Aza	
	Atezolizumab	PD-L1	HMA R/R MDS, HMA-naïve MDS	NCT02508870: phase I, suspended; alone or in combination with Aza	
	Pembrolizumab	PD-1	IPSS int-1 or higher (HMA-naïve and HMA failure)	NCT03094637: phase II, recruiting; in combination with Aza	159
	Hu5F9-G4 (5F9)	CD47	R/R AML or MDS, treatment-naïve unfit AML or higher-risk MDS	NCT03248479: phase IB, recruiting; alone or in combination with Aza	100
NK therapies	CD16/IL-15/CD33 TRIKE	CD16/CD33	High-risk MDS, R/R AML, CD33 hematologic malignancies	NCT03214666: phase I/II, not yet recruiting	69
	Lirilumab	KIR2DL1/2L3	Lower-risk and higher-risk MDS without prior HMA therapy	NCT02599649: phase II, completed; alone or in combination with Aza/nivolumab	
MDSC elimination	BI 836858	CD33	R/R lower-risk MDS (HMA-naïve and HMA failure)	NCT02240706: phase I-II, recruiting	91
Vaccine therapies	DEC-205/NY-ESO-1 fusion protein CDX-1401	—	IPSS (int-1, int-2, high), AML	NCT03358719: phase I, recruiting	90
	Potential neoantigen-based vaccine approach	MDS cells expressing defined neoantigens	MDS or CCUS	NCT03072498: sample collection, recruiting	
CAR T cells	CM-CS1 T-cell infusion	NKG2D	MDS-EB, AML, MM	NCT02203825: phase I, completed	

Winter, Shoale, Kordasti & Platzbecker. Journal Clinical Oncology 2020

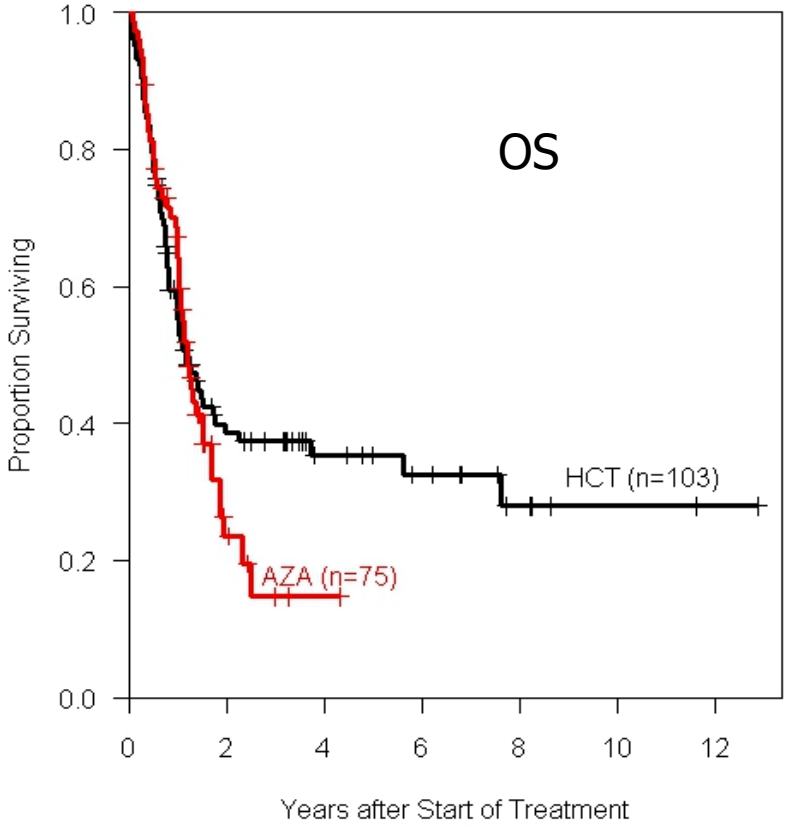
Therapeutic algorithm in HR-MDS patients

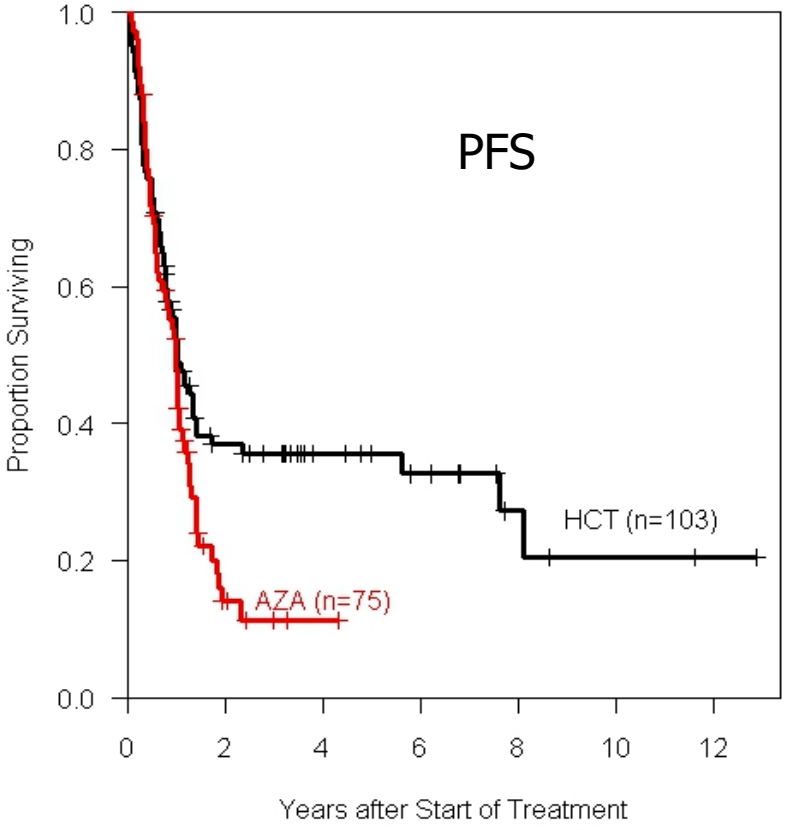


Blood 2019;133:1096-1107

Allogeneic SCT vs. AZA in HR-MDS

retrospective analysis age 60-70 years



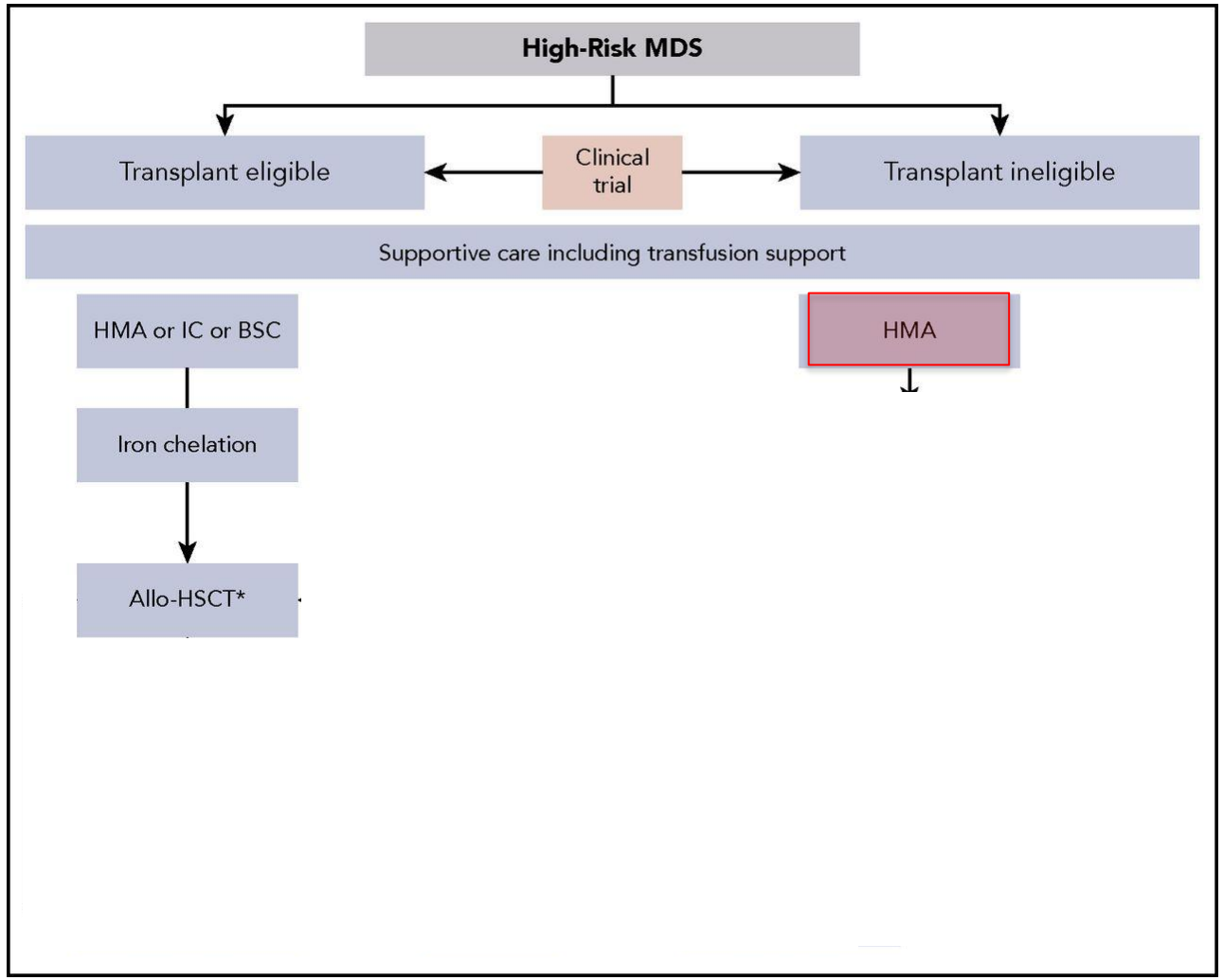


European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

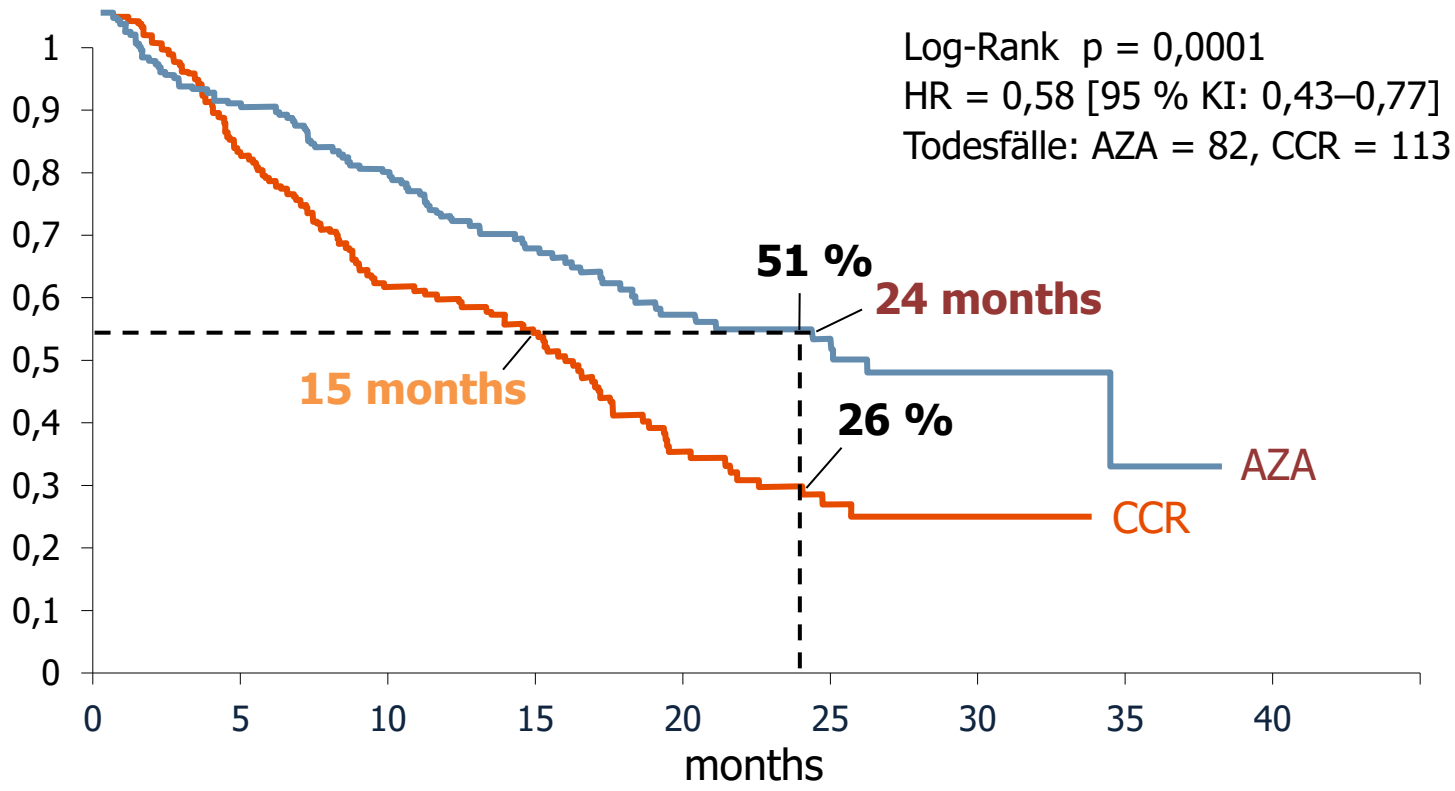
BBMT 2012

Therapeutic algorithm in HR-MDS patients



AZA in HR-MDS

up to 30% blasts



CCR = Conventional Care Regime

Fenaux P et al. Lancet Oncol 2009

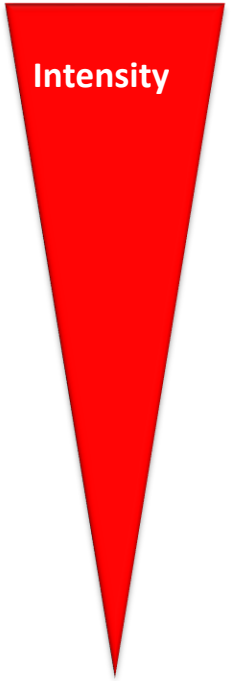
HMA + VENETOCLAX > HMA

1st line elderly AML

	DAC	AZA
	Group A (n=23)	Group B (n=22)
Complete remission	8 (35%)	6 (27%)
CRi	6 (26%)	7 (32%)
Partial remission	1 (4%)	0
MLFS*	2 (9%)	5 (23%)
Resistant disease	3 (13%)	2 (9%)
Non-evaluable†	3 (13%)	2 (9%)
Complete remission and CRi	14 (61%)	13 (59%)
Overall response‡	15 (65%)	13 (59%)
Overall outcome§	17 (74%)	18 (82%)

DiNardo et al. Lancet Oncology 2018

HMA Failure



Subsequent therapy	N (%)	Median survival
Allogeneic transplant	37 (9%)	19.5 months
Investigational therapy (e.g. IMiD, HDACi, other)	44 (10%)	13.2 months
Intensive cytotoxic therapy (e.g., 3&7)	35 (8%)	8.9 months
Low-dose chemotherapy (e.g. LDAC, 6-MP)	32 (7%)	7.3 months
Palliative / supportive care	122 (28%)	4.1 months
Subsequent therapy unknown	165 (38%)	3.6 months

Prébet T et al J Clin Oncol 2011; 29:3322-7
Jabbour E et al Cancer 2010;116(16):3830-4

VARIABLE	GRADING	POTENTIAL CLINICAL CONSEQUENCE
PROGNOSTIC SCORING SYSTEMS (E.G. IPSS-R)	Good risk Poor risk	Standard therapy or supportive care only Hypomethylating agents, allo-HCT
PERFORMANCE STATUS	Good Poor	Standard therapy including allo-HCT Supportive care or low intensive therapy
EPO LEVEL	Low High	Treatment with ESA in case of anemia No ESA
FERRITIN LEVEL	High	Treatment with iron chelation
GENETICS	Del(5q) Good risk Poor risk	Targeted treatment with Lenalidomide Standard therapy or supportive care only Intensified surveillance strategy, Allo-HCT, Clinical Trial
DRUGGABLE MOLECULAR TARGETS	SF3B1 mutation TP53 mutation WT TP53 IDH1/2 mutation Spliceosome mutations	Treatment with Luspatercept Treatment with TP53 modulators Treatment with Nutlins Treatment with IDH inhibitors Treatment with Spliceosome modulators