Lower-risk Myelodysplastic Neoplasia 2024

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D·MDS
Deutsche MDS-Studiengruppe

Disclosures

	No, nothing to disclose
X	Yes, please specify:

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other (please specify)
Celgene/BMS	x	X	x					
Novartis	x		x					
Curis			x					
Jazz	x		x					
Amgen			x					

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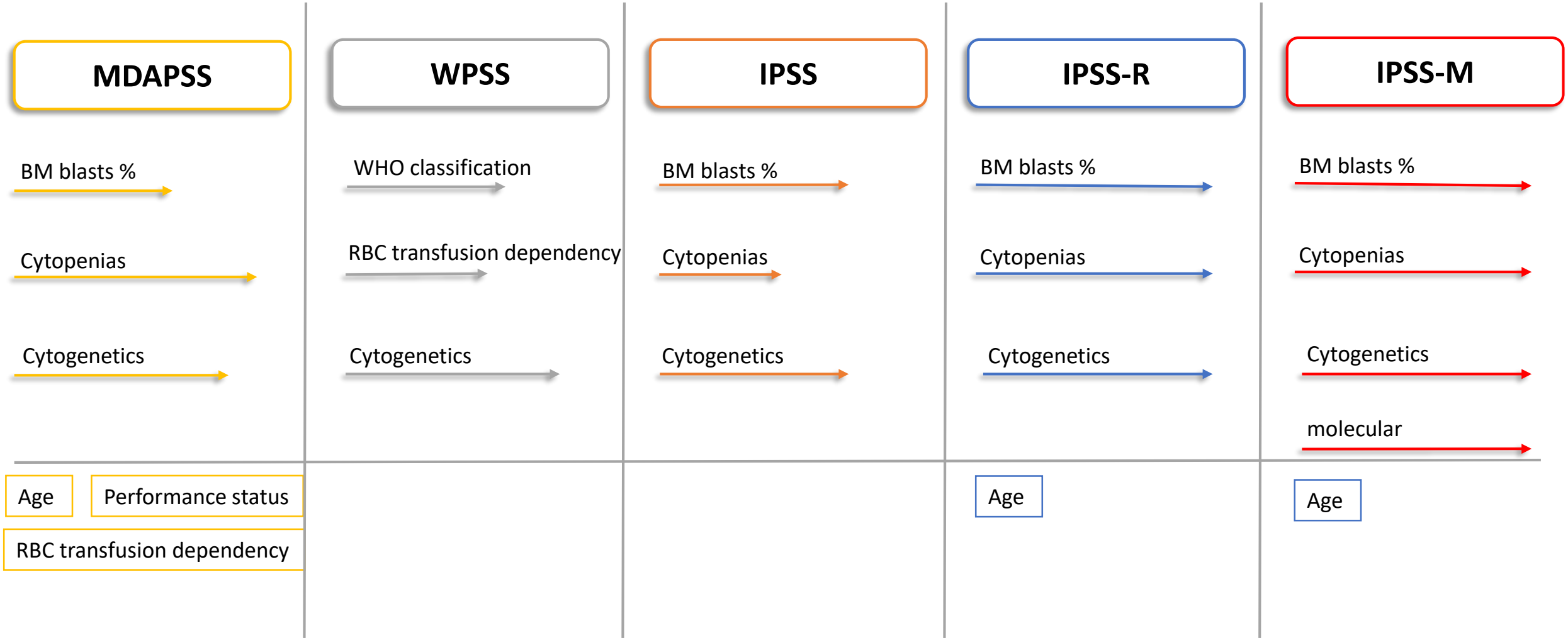
Will you be presenting or referencing off-label or investigational use of a therapeutic product?	
x	Yes (but this will be highlighted)

Current MDS Prognostic Models



Kantarjian H., et al. Cancer, 2008

Malcovati L. et al. J Clin Onc, 2007
Malcovati L. et al. Haematologica, 2011

Greenberg P. et al. Blood, 1997

Greenberg P. et al. Blood, 2012

Bernard et al. NEJM Ev 2022

IPSS-R

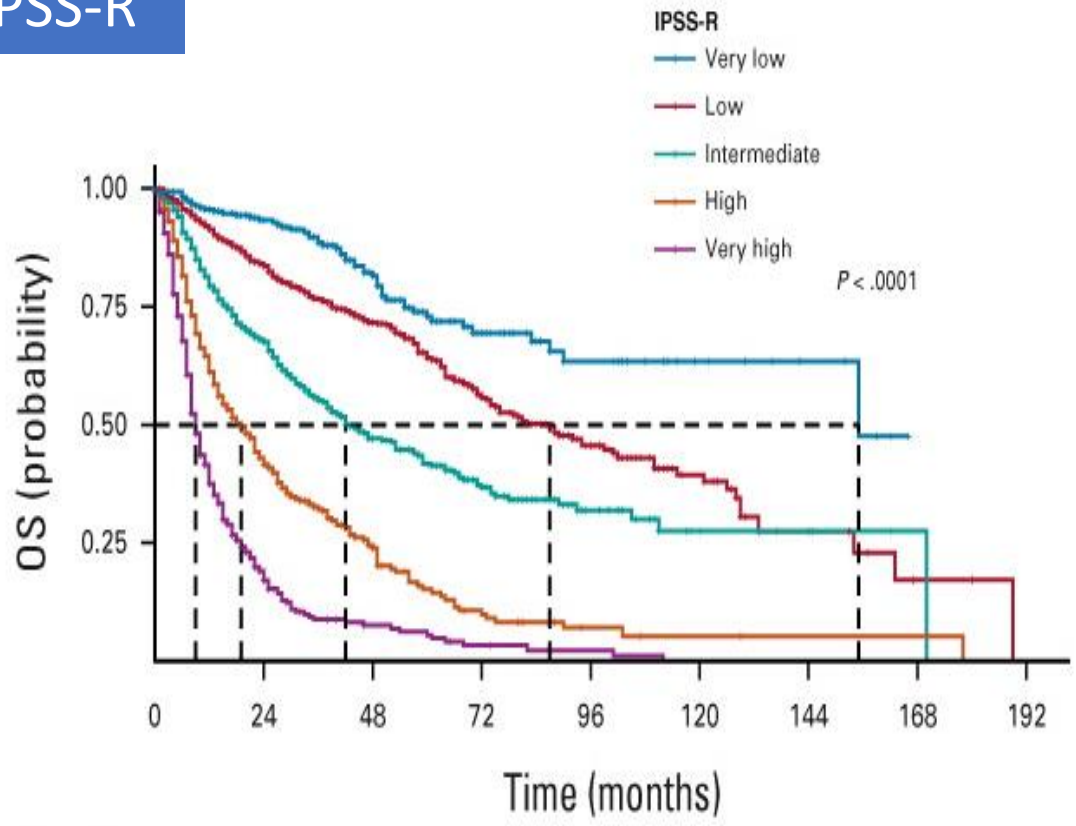
	IPSS-R risk	IPSS-R score	Median OS, years	Median time to 25% AML transformation, years
Lower-risk	Very low	≤1.5	8.8	NR
Lower-risk	Low	>1.5–3	5.3	10.8
Lower-risk / Higher-risk	Intermediate	>3–4.5	3.0	3.2
Higher-risk	High	>4.5–6	1.6	1.4
Higher-risk	Very high	>6	0.8	0.7

AML, acute myeloid leukaemia; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; NR, not reached; OS, overall survival

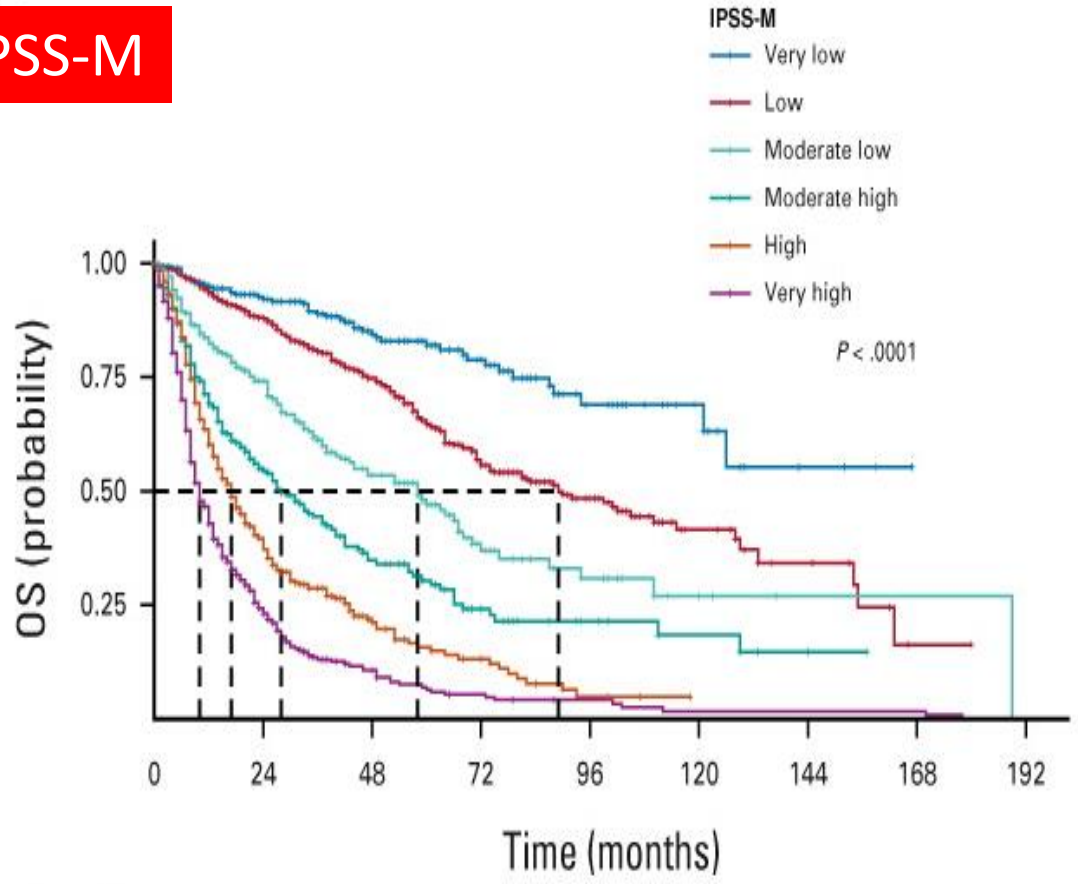
Greenberg et al. Blood 2012

IPSS-R vs. IPSS-M

IPSS-R

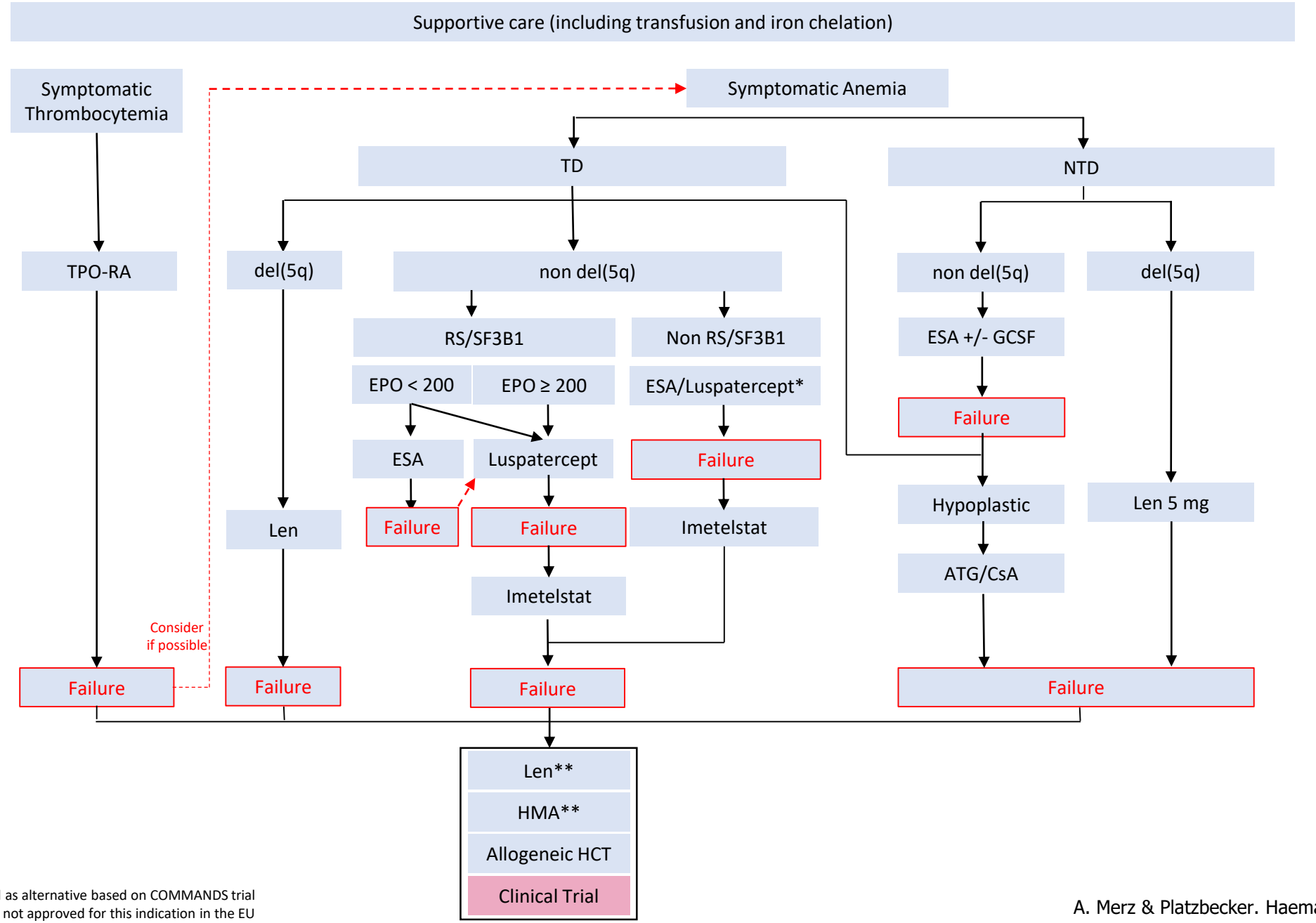


IPSS-M



Sauta et al. JCO 2023

Therapeutic algorithm in LR-MDS



* Luspatercept can be considered as alternative based on COMMANDS trial
** Len/HMA = Lenalidomide/HMA not approved for this indication in the EU

A. Merz & Platzbecker. Haematologica *in press*

Therapeutic algorithm in LR-MDS

Oliva et al. JCO 2023

Kubasch et al. Leukemia 2022

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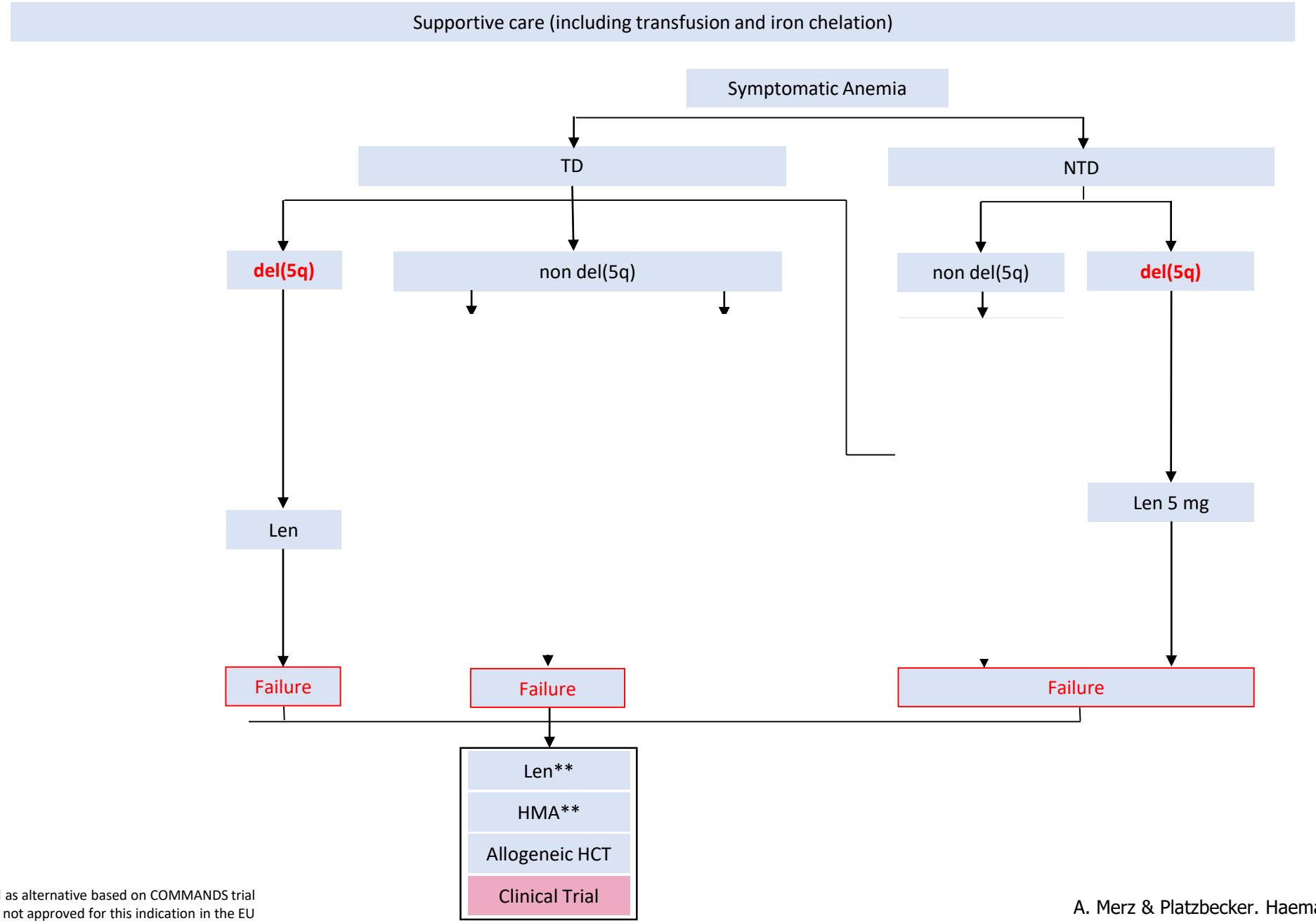

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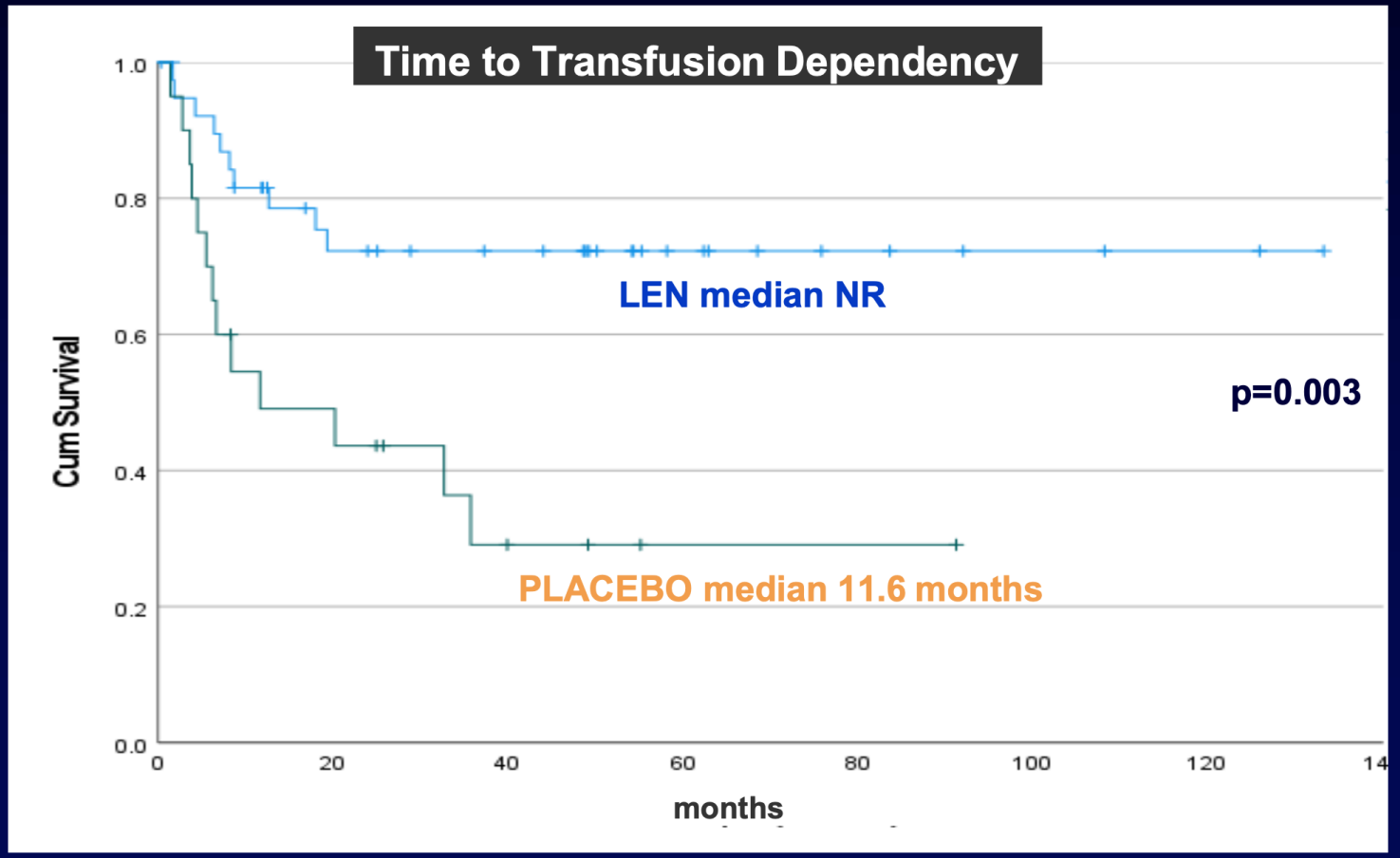
Primary objective: Efficacy (ITT, N=61)

Low doses of Len delayed and decreased transfusion dependency

- TD in 23 patients (38.3%): 10 in Len (25%) vs 13 in placebo (65%)

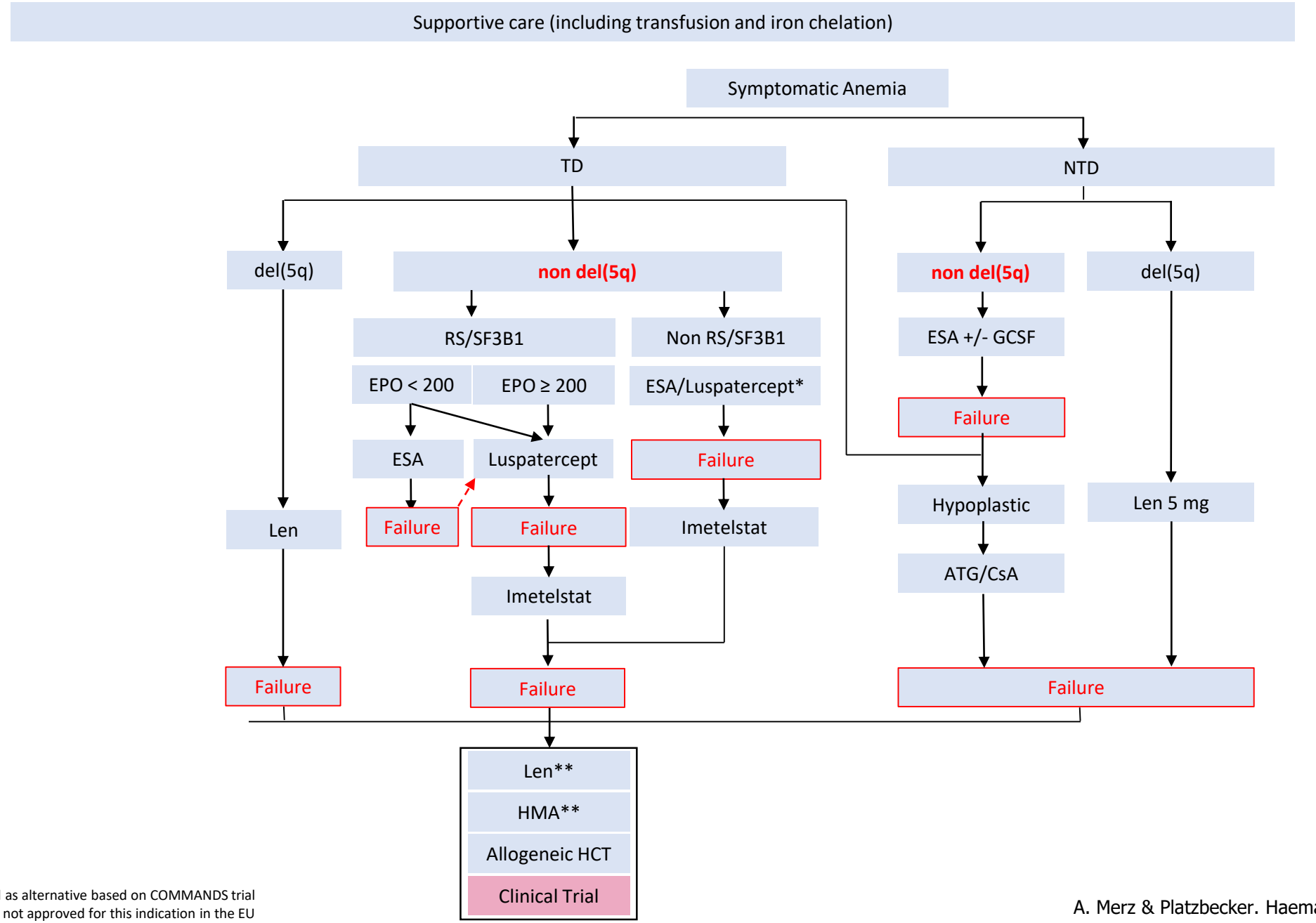
✓ Len decreased in 69.8% the risk of TD: HR 0.302 (0.132-0.692), p=0.005



Median follow up 5.05y (0.3-11): 5.2 vs 4.85, p=ns

Montero et al. Lancet Haem 2024

Therapeutic algorithm in LR-MDS



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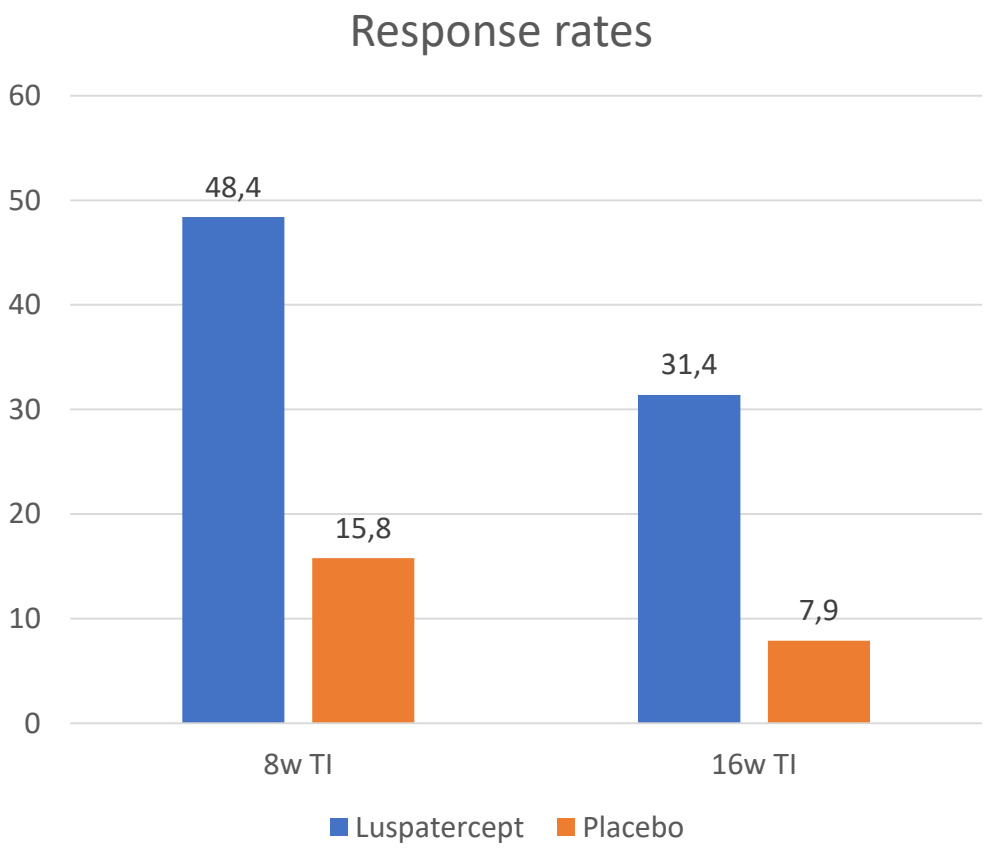
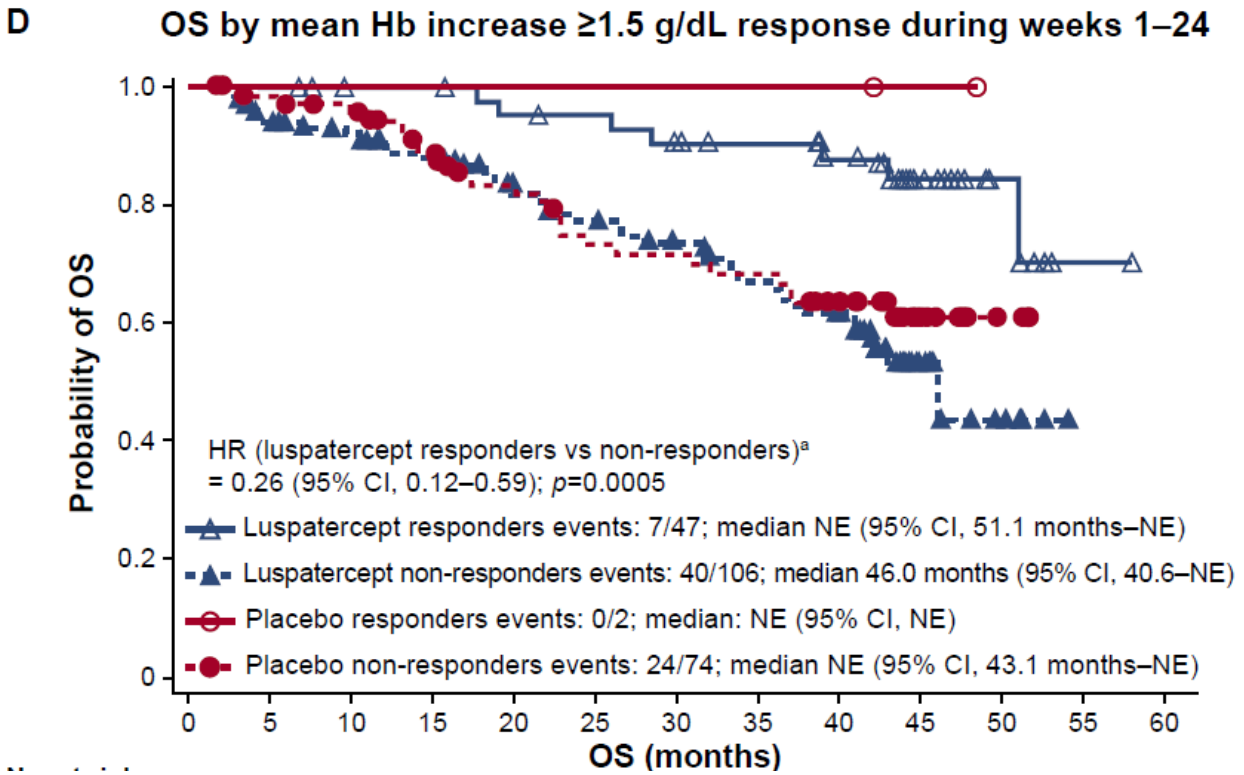
A. Merz & Platzbecker. Haematologica *in press*

MEDALIST Trial

RBC-TI Response by Primary Endpoint long-term follow up





Platzbecker at al. Leukemia 2023

High-dose Luspatercept in TD RS-MDS

LR/HR	Acronym	Full title	IMP	Countries	Target sample	Current status
LR	**LUSPLUS**	*A phase IIIb, open-label, single arm study to evaluate the efficacy and safety of Luspatercept in patients with lower-risk MDS and ring-sideroblastic phenotype (MDS-RS)*	Luspatercept		N=70 (single arm)	Recruiting

Main IN

- LR MDS (IPSS-R very low-, low-, or intermediate-risk)
- RS ≥ 15% in BM or ≥ 5% if SF3B1 mutation is present
- Less than 5% blasts in BM
- Refractory to prior ESA treatment ***or***
- Intolerant to prior ESA treatment ***or***
- ESA ineligible ***or***
- Refractory to- /relapsed after prior HMA or LEN treatment

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PACE Trial

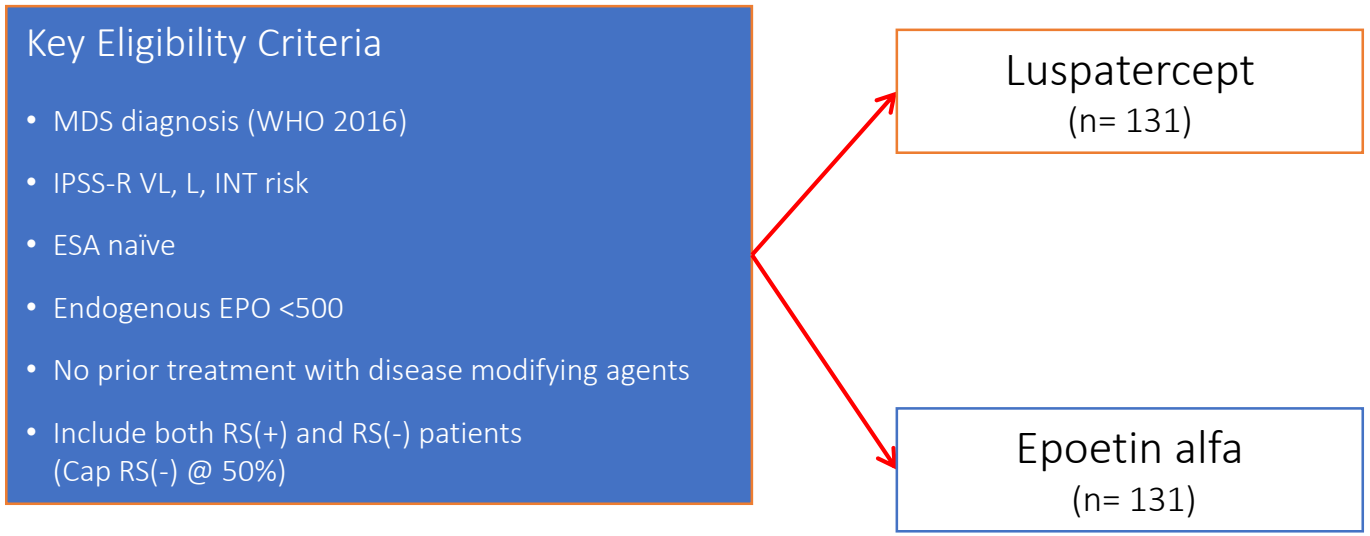
Response by Subgroup

Parameter	Overall	NTD	LTB	HTB
Subgroup	(N = 108)	(n = 34)	(n = 29)	(n = 45)
Category	n (%)	n (%)	n (%)	n (%)
RS status				
RS	42/62 (67.7)	17/19 (89.5)	7/16 (43.8)	18/27 (66.7)
Non-RS	16/44 (36.4)	7/15 (46.7)	3/13 (23.1)	6/16 (37.5)
SF3B1 mutation status				
Mutated	35/47 (74.5)	14/15 (93.3)	6/10 (60.0)	15/22 (68.2)
Wild-type	19/49 (38.8)	8/17 (47.1)	4/16 (25.0)	7/16 (43.8)

Platzbecker et al. JCO 2022

COMMANDS Trial

Luspatercept vs EPO in RS+/RS- MDS



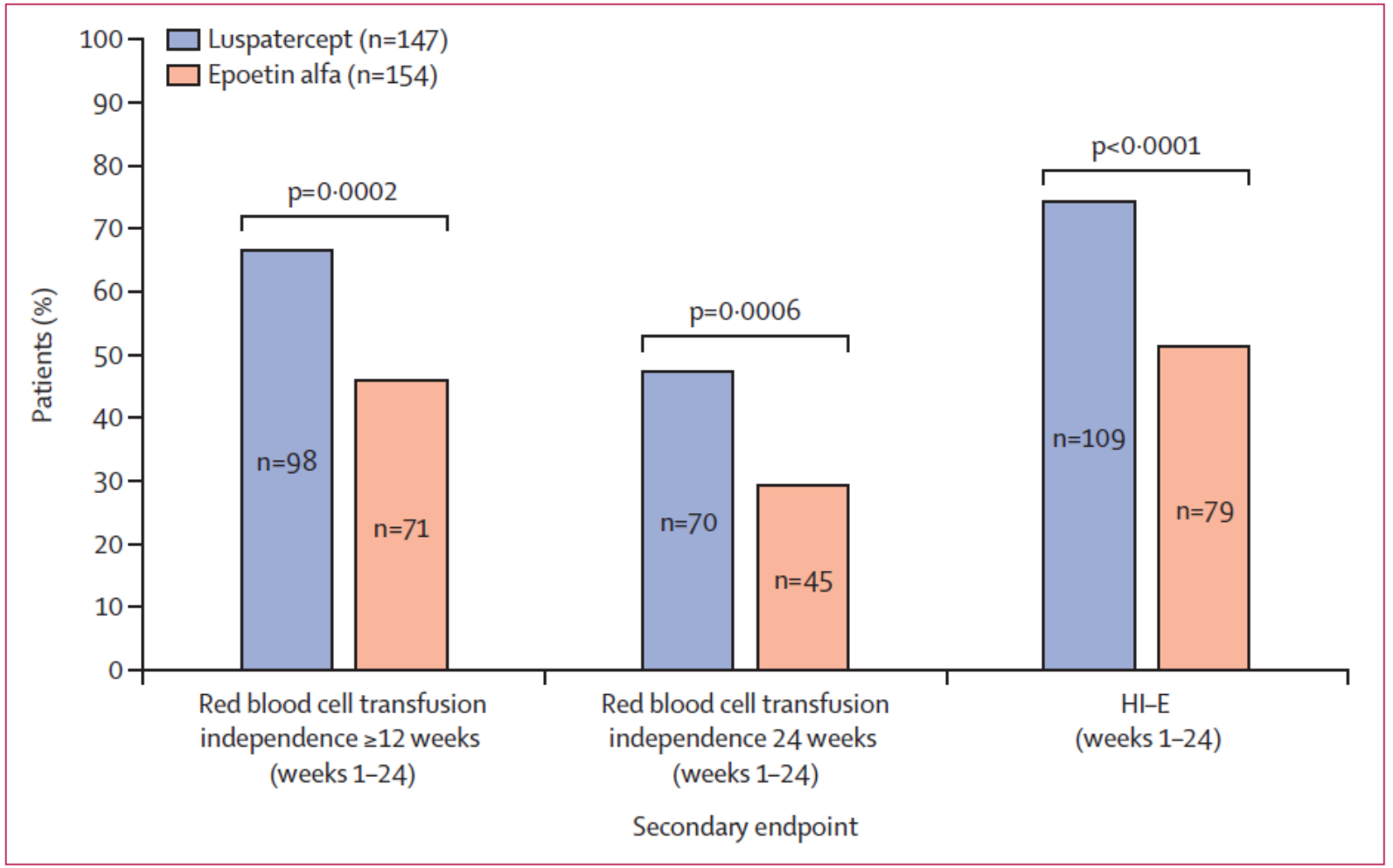
www.clinicaltrials.gov NCT03682536

Patient demographics and disease characteristics at baseline

	Luspatercept (n=178)	Epoetin alfa (n=178)	Total (n=356)
IPSS-R myelodysplastic syndromes risk category			
Very low	16 (9%)	17 (10%)	33 (9%)
Low	126 (71%)	131 (74%)	257 (72%)
Intermediate	34 (19%)	28 (16%)	62 (17%)
High‡	1 (1%)	0	1 (<1%)†
Missing§	1 (1%)	2 (1%)	3 (1%)
Serum erythropoietin concentration, U/L	78·7 (41·7–185·3)	85·9 (40·5–177·8)	84·5 (40·9–179·1)
Serum erythropoietin category, U/L			
≤200	141 (79%)	141 (79%)	282 (79%)
≤100	100 (56%)	103 (58%)	203 (57%)
>100 and ≤200	41 (23%)	38 (21%)	79 (22%)
>200 and <500	37 (21%)	37 (21%)	74 (21%)
Ring sideroblasts¶	130/178 (73%)	128/177 (72%)	258/355 (73%)
Mutated *SF3B1*‖	111/176 (63%)	99/171 (58%)	210/347 (61%)
Red blood cell transfusion burden, units per 8 weeks**	3 (2–4)	3 (2–4)	3 (2–4)
Red blood cell transfusion burden category			
<4 units per 8 weeks	114 (64%)	109 (61%)	223 (63%)
2 units per 8 weeks	80 (45%)	79 (44%)	159 (45%)
≥4 units per 8 weeks	64 (36%)	69 (39%)	133 (37%)
Pretransfusion haemoglobin concentration, g/dL	7·8 (7–8)	7·8 (7–8)	7·8 (7–8)
Haemoglobin category			
<8 g/dL	107 (60%)	106 (60%)	213 (60%)
≥8 g/dL	71 (40%)	72 (40%)	143 (40%)
Platelet count, 10^9/L	230 (155–304)	235 (140–324)	232 (144–310)

Platzbecker et al. Lancet 2023

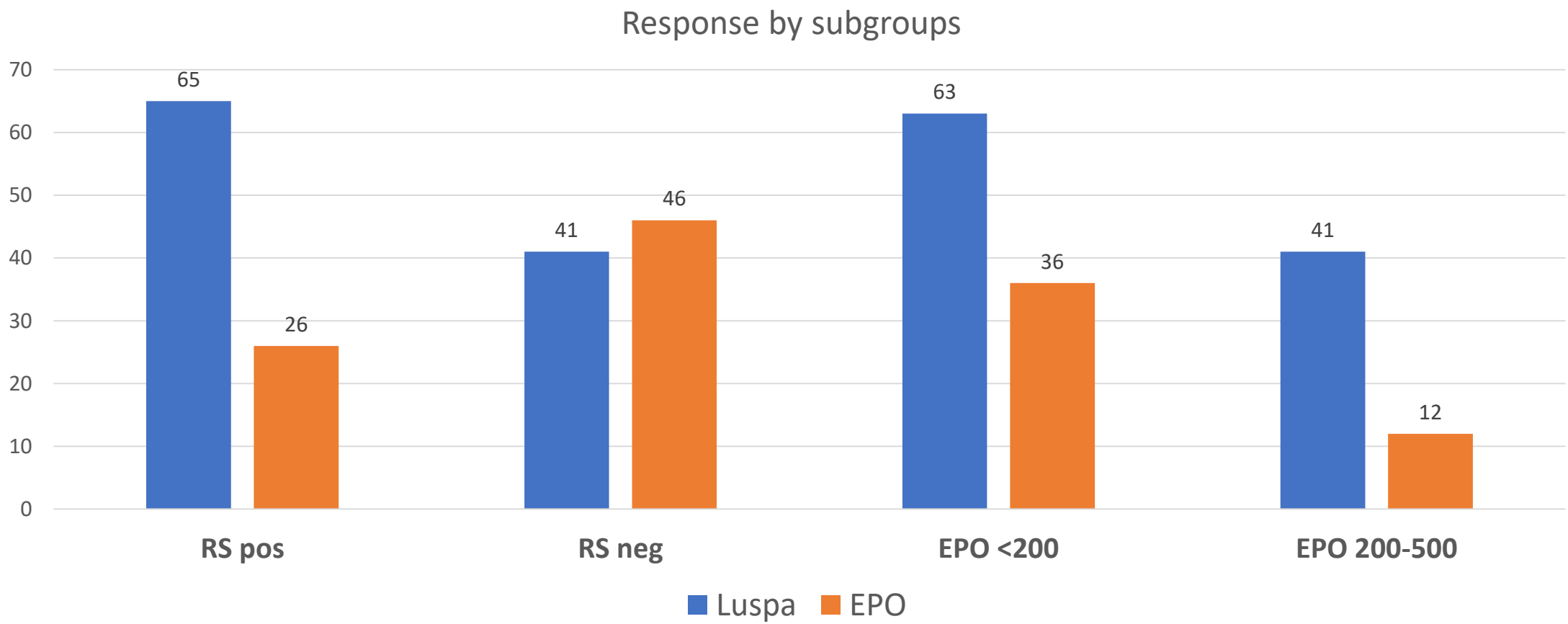
RBC-TI for ≥12 weeks and HI-E response during weeks 1–24



Only patients who received their first dose of treatment at least 24 weeks (169 days) before the data cutoff (Aug 31, 2022), including those who discontinued treatment, were included in the analysis. HI–E=haematological improvement–erythroid.

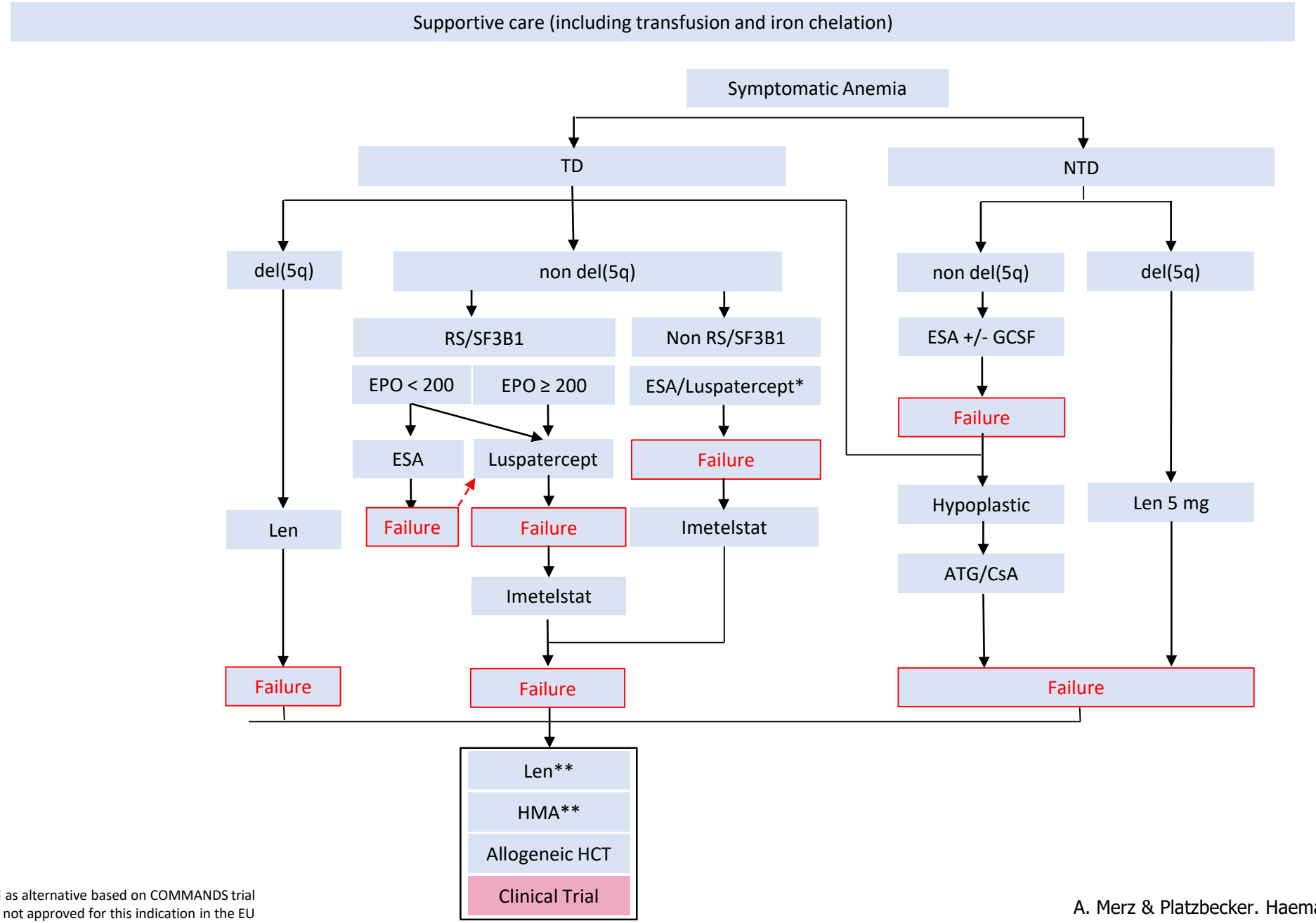
Platzbecker et al. Lancet 2023

RBC-TI for ≥12 weeks and HI-E response during weeks 1–24



Platzbecker et al. Lancet 2023

Therapeutic algorithm in LR-MDS



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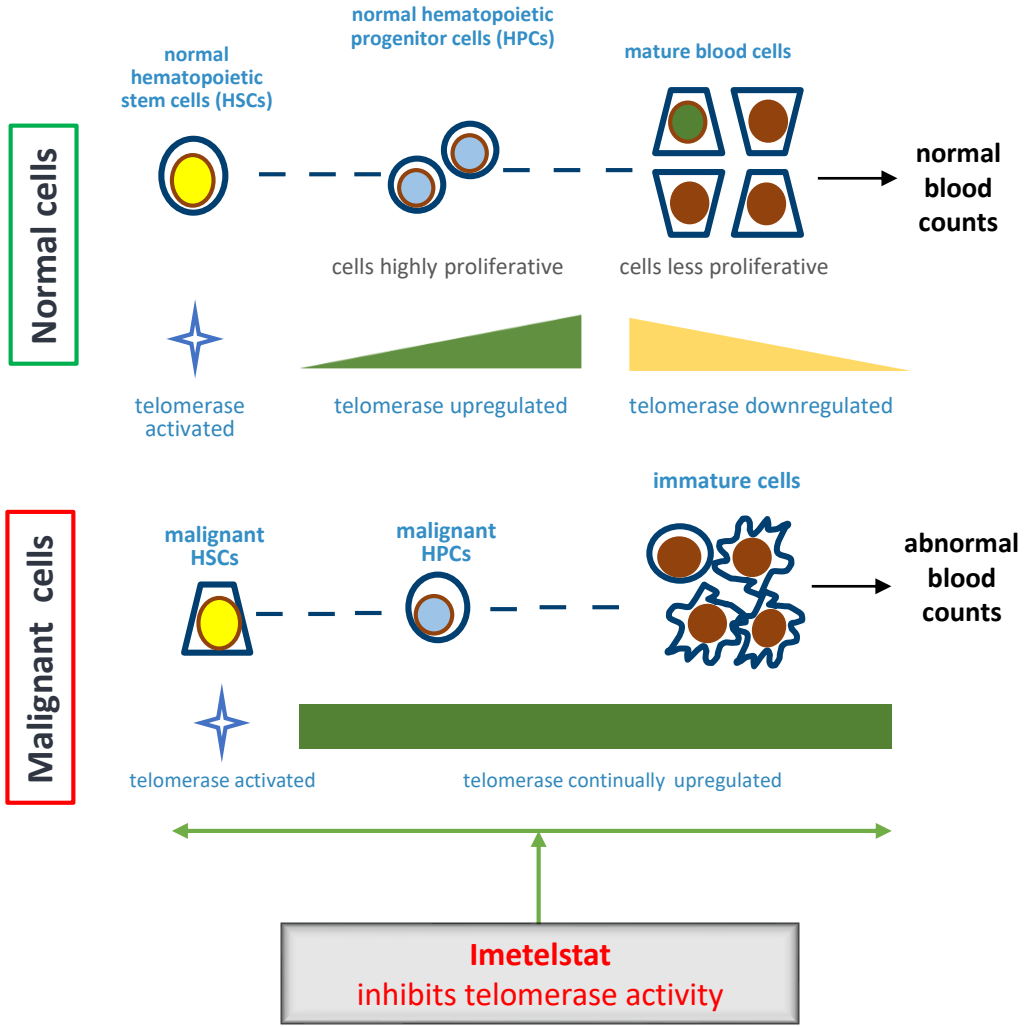
A. Merz & Platzbecker. Haematologica *in press*

Telomerase as a molecular target in oncology



- **Telomeres:**
  - Essential genetic elements
  - TTAGGG repeats, cap chromosome ends
  - Shorten without telomerase
  - Accelerated loss under stress
- **Telomerase:**
  - Synthesizes telomeric DNA
  - Required for cell immortality
  - Not active in somatic cells; transiently upregulated in normal hematopoietic progenitor cells to support controlled proliferation
  - **Highly upregulated in malignant stem/progenitor cells, enabling continued and uncontrolled proliferation**

IMerge (MDS3001; NCT02598661) Phase 2/3 Study Design

Part 1[1,2]
Phase 2, single-arm, open-label
Overall N=57

Target population of non-del(5q)/len/HMA-naive
N=38
Enrollment Complete

Imetelstat
7.5 mg/kg IV q4w

Part 2
Phase 3, randomized, double-blind, placebo-controlled
N=170
Enrollment complete; Top line results early Jan 2023

Stratification: transfusion burden (≤6 vs >6 units); IPSS risk group (low vs intermediate-1)

- **Patients with LR-MDS**[1,2]
  - IPSS low or intermediate-1
  - Relapsed/refractory to ESA or sEPO >500 mU/mL
  - Transfusion dependent: ≥4 units RBC/8 weeks over the 16-week prestudy period
  - Non-del5(q), len/HMA-naive
- **Primary endpoint**: ≥8-week RBC TI
- **Key secondary endpoints**: safety, ≥24-week TI rate, HI-E, OS, PFS, and time to progression to AML

Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent
Pre-medication: diphenhydramine, hydrocortisone 100-200mg (or equivalent)
Supportive care: transfusions, myeloid growth factors per local guidelines

AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IV, intravenous; len, lenalidomide; LR, lower-risk; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; q4w, every 4 weeks; RBC, red blood cell; sEPO, serum erythropoietin; TI, transfusion independence.

1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 3113., www.geron.com

Patient demographics and disease characteristics at baseline

Characteristic	Imetelstat (N=118)	Placebo (N=60)	Total (N=178)
Median age (IQR), year	72 (65-75)	73 (69-78)	72 (66-77)
Male sex, n (%)	71 (60)	40 (66)	111 (62)
Median time since original diagnosis of MDS (IQR), year	3·5 (1·9-6·3)	2·8 (1·3-5·4)	3·3 (1·7-6·0)
Ring sideroblast status, n (%)			
With ring sideroblasts	73 (62)	37 (62)	110 (62)
Without ring sideroblasts	44 (37)	23 (38)	67 (38)
IPSS category†			
Low	80 (68)	39 (65)	119 (67)
Intermediate-1	38 (32)	21 (35)	59 (33)
IPSS-R prognostic risk category, n (%)‡			
Very Low	3 (3)	2 (3)	5 (3)
Low	87 (74)	46 (77)	133 (75)
Intermediate	20 (17)	8 (13)	28 (16)
High	1 (1)	0	1 (1)
Very High	0	0	0
Median prior RBC transfusion burden, RBC units/8 weeks, n (IQR)	6 (6·0-8·0)	6 (5·0-8·5)	6 (6·0-8·0)
Prior RBC transfusion burden, n (%)†			
≥4 to ≤6 units	62 (53)	33 (55)	95 (53)
>6 units	56 (48)	27 (45)	83 (47)
Median pre-treatment haemoglobin level (IQR), g/dL‡	7·9 (7·3-8·3)	7·8 (7·4-8·4)	7·9 (7·4-8·3)
Prior erythropoiesis stimulating agents use, n (%)	108 (92)	52 (87)	160 (90)
Median serum erythropoietin level (IQR), mU/mL	174·9 (76·8-455·0)	277·0 (72·0-621·0)	184·1 (74·9-551·2)
≤500, n (%), mU/mL	87 (74)	36 (60)	123 (69)
>500, n (%), mU/mL	26 (22)	22 (37)	48 (27)
Prior luspatercept, n (%)§	7 (6)	4 (7)	11 (6)

Platzbecker et al. Lancet 2024

Patient demographics and disease characteristics at baseline

Characteristic	Imetelstat (N=118)	Placebo (N=60)	Total (N=178)
Median local neutrophils (IQR), $\times 10^9$/L	2·6 (2·0-3·6)	2·7 (2·0-4·0)	2·6 (2·0-3·8)
Median local platelets (IQR), $\times 10^9$/L	230·0 (168·0-305·0)	229·5 (152·0-303·5)	230·0 (166·0-305·0)

	Imetelstat (N=103)	Placebo (N=52)	Total (N=155)
IPSS-M, n (%)			
Very low	4 (4)	0	4 (3)
Low	65 (63)	33 (64)	98 (63)
Moderate low	22 (21)	10 (19)	32 (21)
Moderate high	7 (7)	6 (12)	13 (8)
High	4 (4)	3 (6)	7 (5)
Very high	1 (1)	0	1 (1)

Platzbecker et al. Lancet 2024

Cytopenias

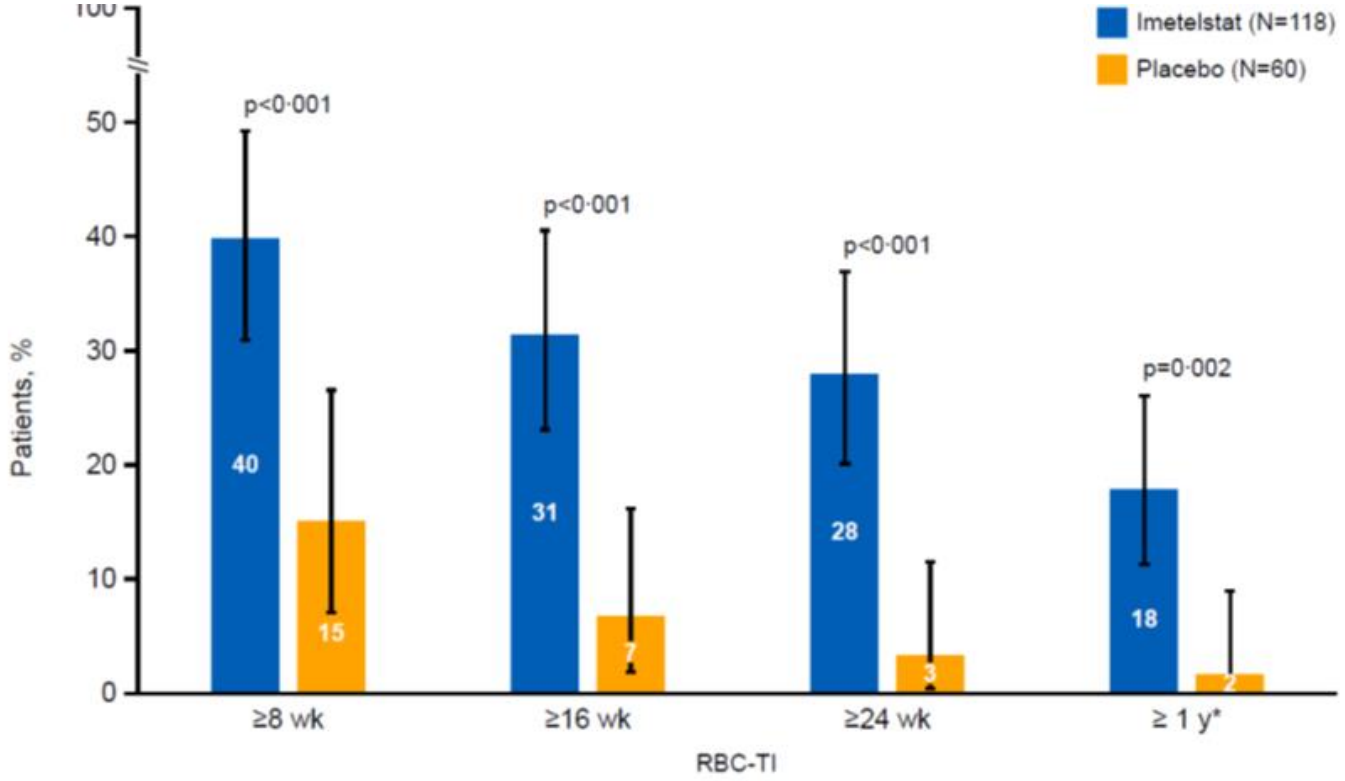
Clinical consequences of cytopenias

Event, n (%)	Imetelstat (N=118)	Placebo (N=59)
Grade ≥3 bleeding events*	3 (3)	1 (2)
Grade ≥3 infections†	13 (11)	8 (14)
Grade 3 febrile‡ neutropenia	1 (1)	0

*No ≥Grade 3 bleeding events in the setting of Grade 3/4 thrombocytopenia; on imetelstat: 2 patients with Grade 4 gastrointestinal bleeding, unrelated and resolved and 1 Grade 3 haematuria, unrelated and resolved.
†On imetelstat: 3 patients with Grade 3/4 infections in setting of Grade 3/4 neutropenia; all 3 were sepsis and resolved with only 1 considered related
‡Occurred at day 33, lasted 8 days; assessed by investigator as possibly related to imetelstat; patient subsequently achieved TI >40 weeks and remains on treatment at data cut-off. TI=transfusion independence.

Platzbecker et al. Lancet 2024

RBC-TI response

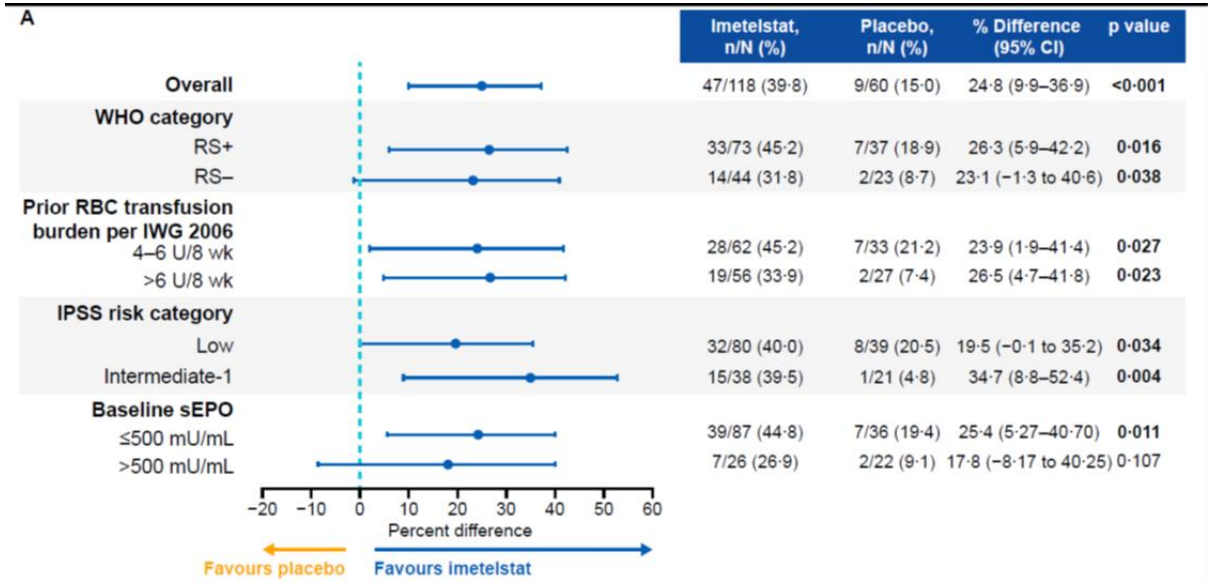


Patients with response, n (% [95% CI])				
Imetelstat	47 (40 [31–50])	37 (31 [23–41])	33 (28 [20–37])	21 (18 [11–26])
Placebo	9 (15 [7–27])	4 (7 [2–16])	2 (3 [0·4–12])	1 (2 [0·04–9])

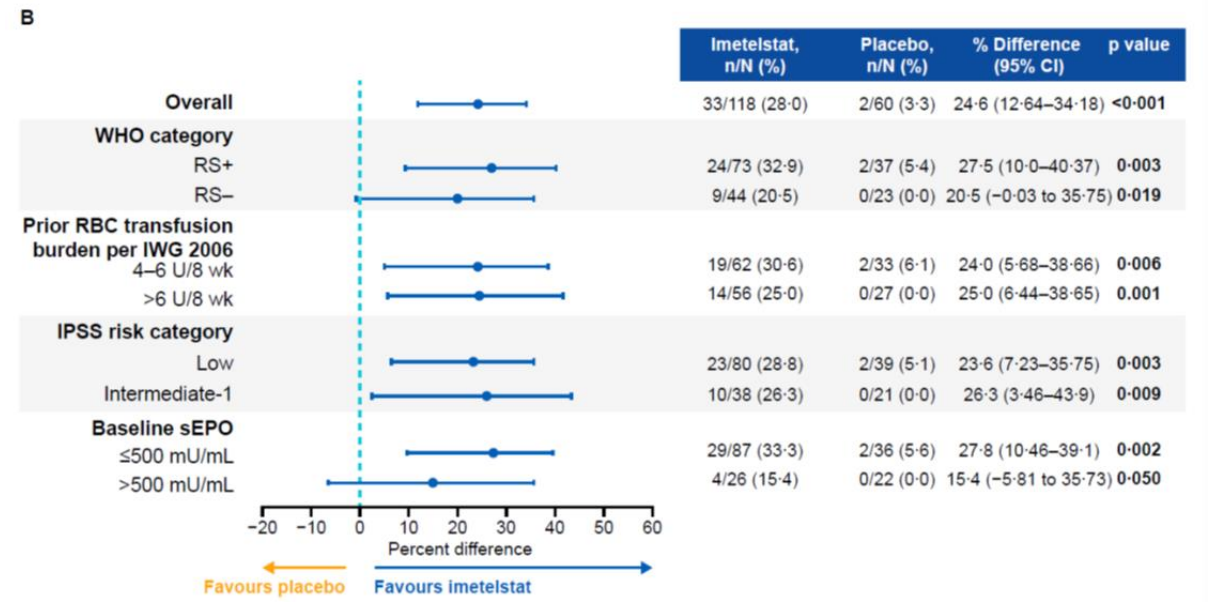
Platzbecker et al. Lancet 2024

Comparison of primary endpoint clinical benefit across clinical subgroups

8w TI

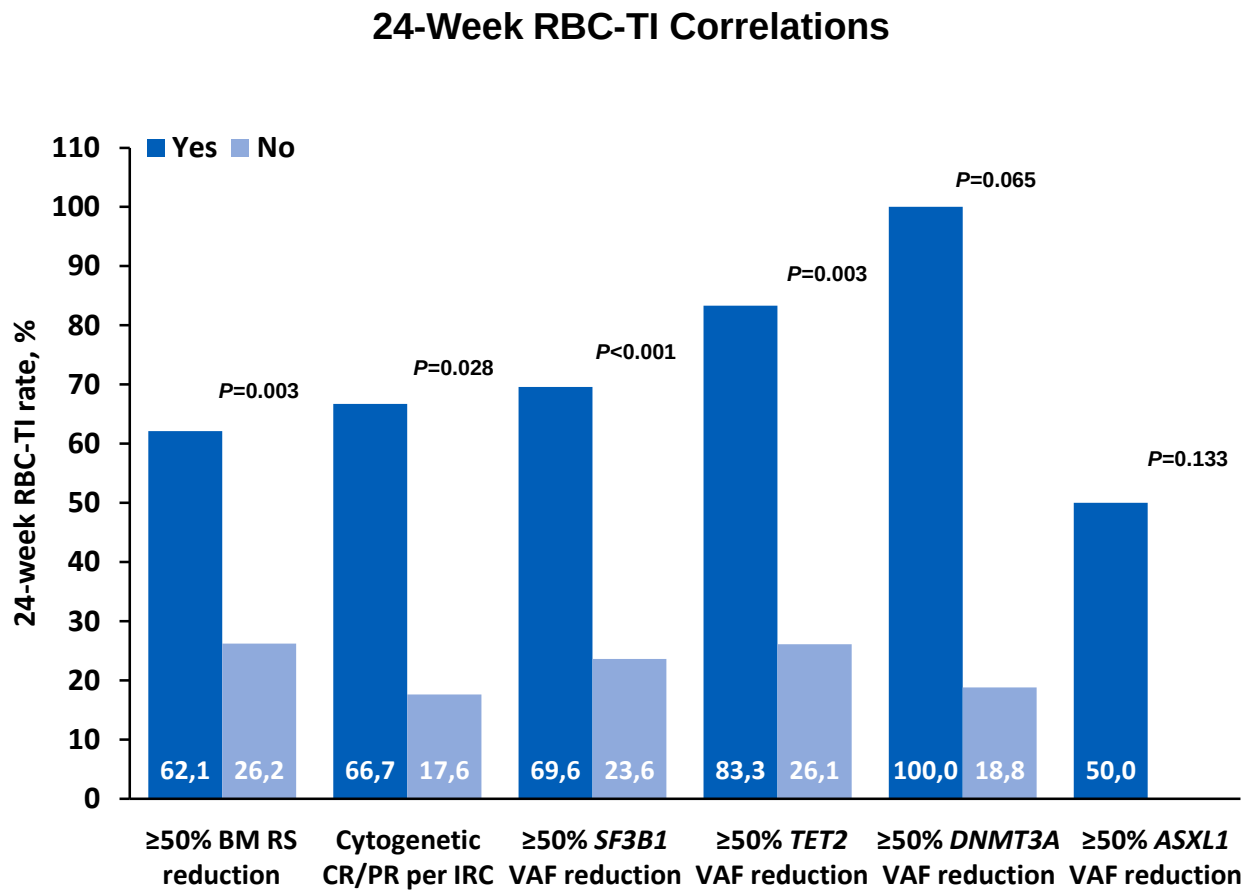


24w TI



Platzbecker et al. Lancet 2024

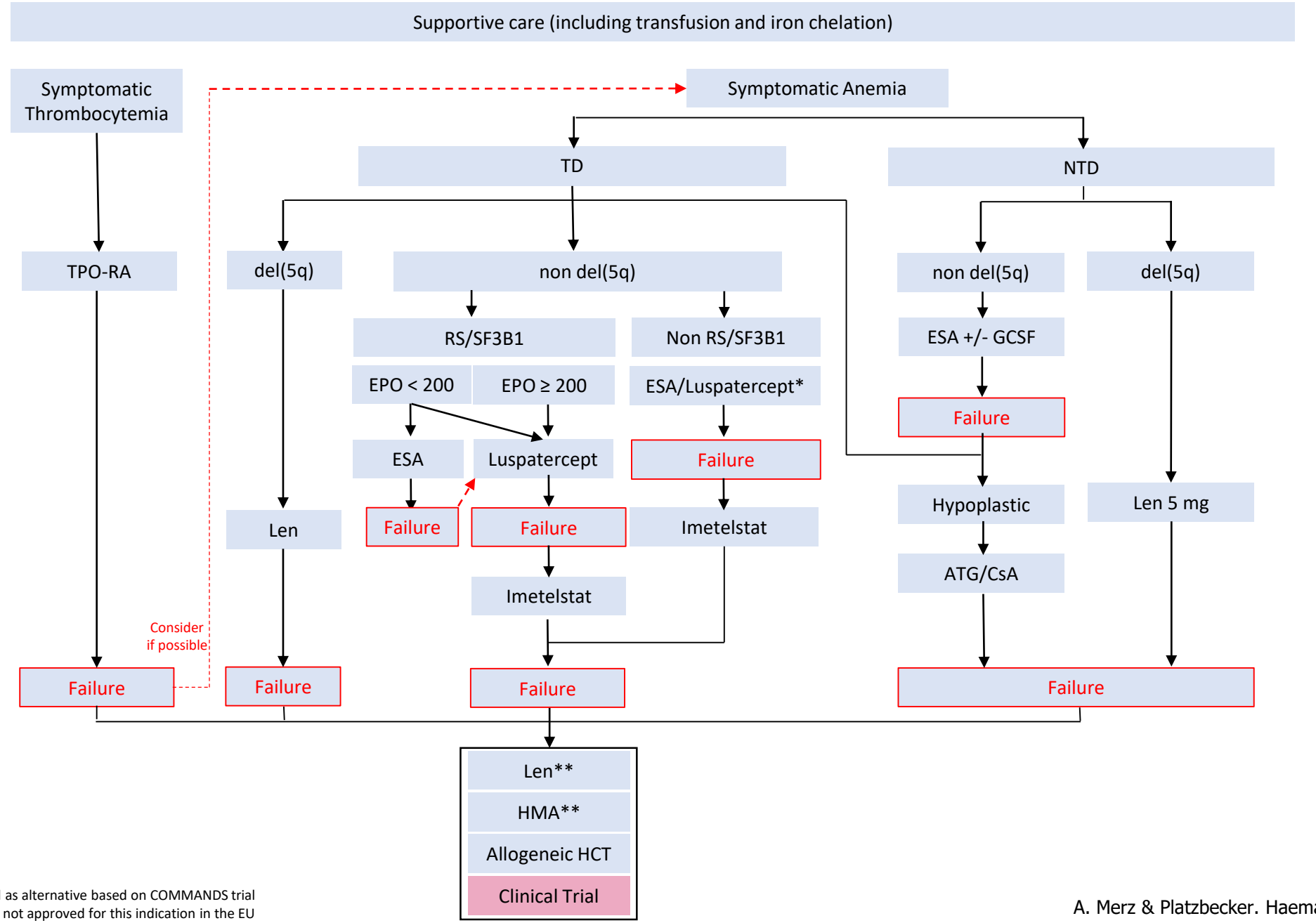
8-Week and 24-Week RBC-TI Correlated With Reduction in RS+ Cells, Cytogenetic Responses, and VAF Reduction in Patients Treated With Imetelstat



Note: *P* value calculated using Fisher exact test between yes vs no in each outcome.
ASXL1, additional sex combs like-1; BM, bone marrow; CR, complete response; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; IRC, independent review committee; PR, partial response; RBC, red blood cell; RS, ring sideroblasts; TET2, Tet methylcytosine dioxygenase 2; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence; VAF, variant allele frequency.

Santini et al. EHA 2023

Therapeutic algorithm in LR-MDS



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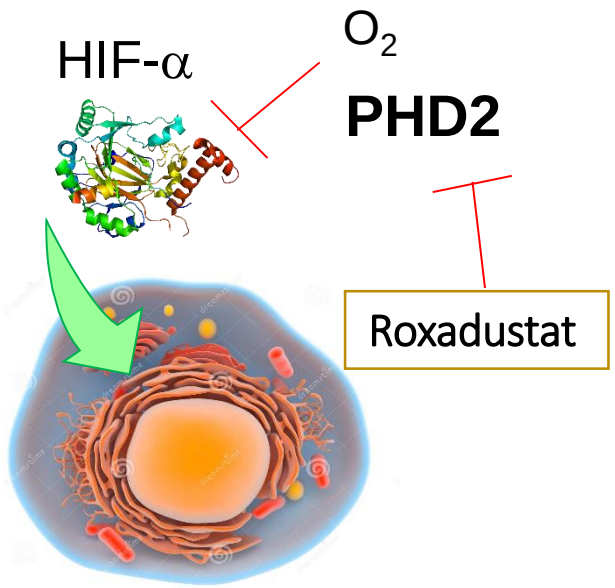
A. Merz & Platzbecker. Haematologica *in press*

Roxadustat in MDS

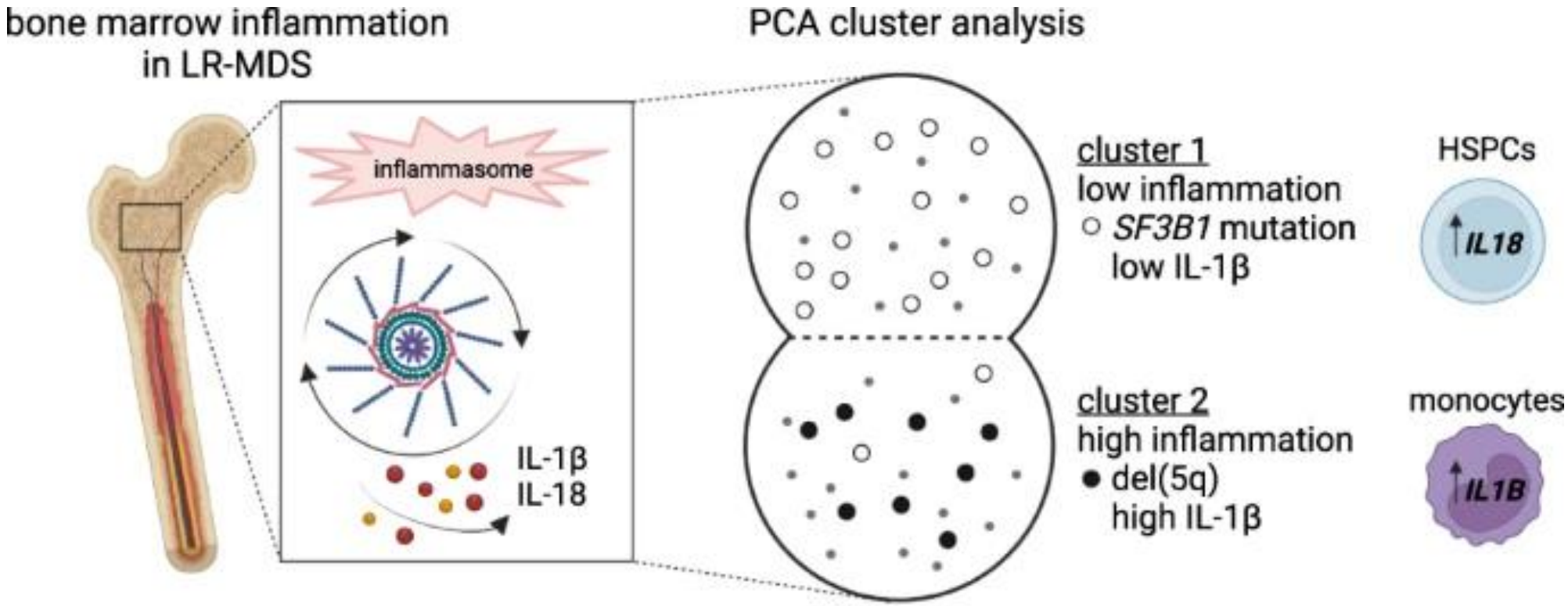
Not better than Placebo



„Inhibiting the inhibition“

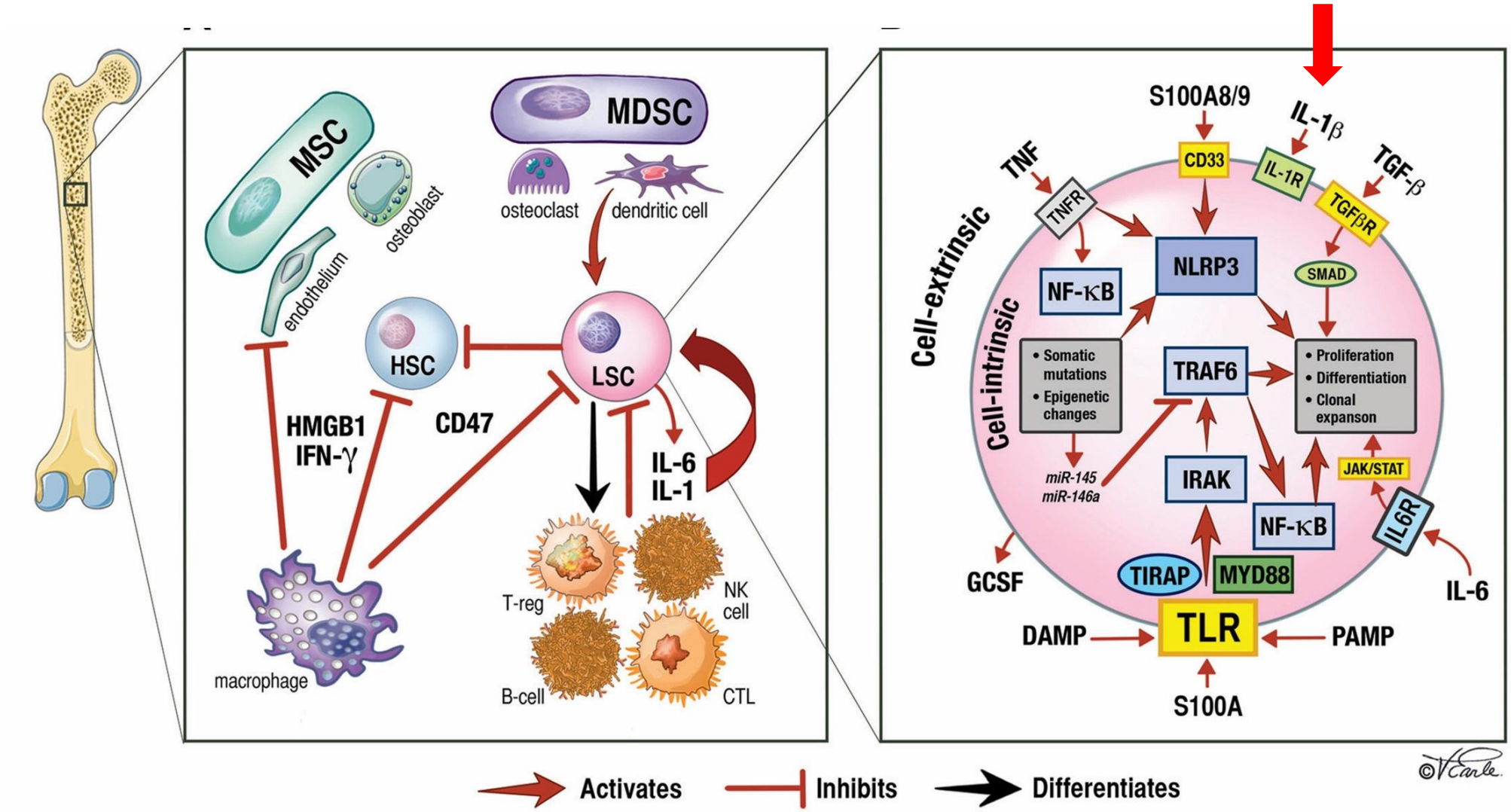
Mittelman et al. AJH 2024

Increased inflammation in LR-MDS patients and type of genetics



Schneider et al. Leukemia 2023

Druggable targets ? – IL-1b



Stubbins, Platzbecker, Karsan. Blood 2022

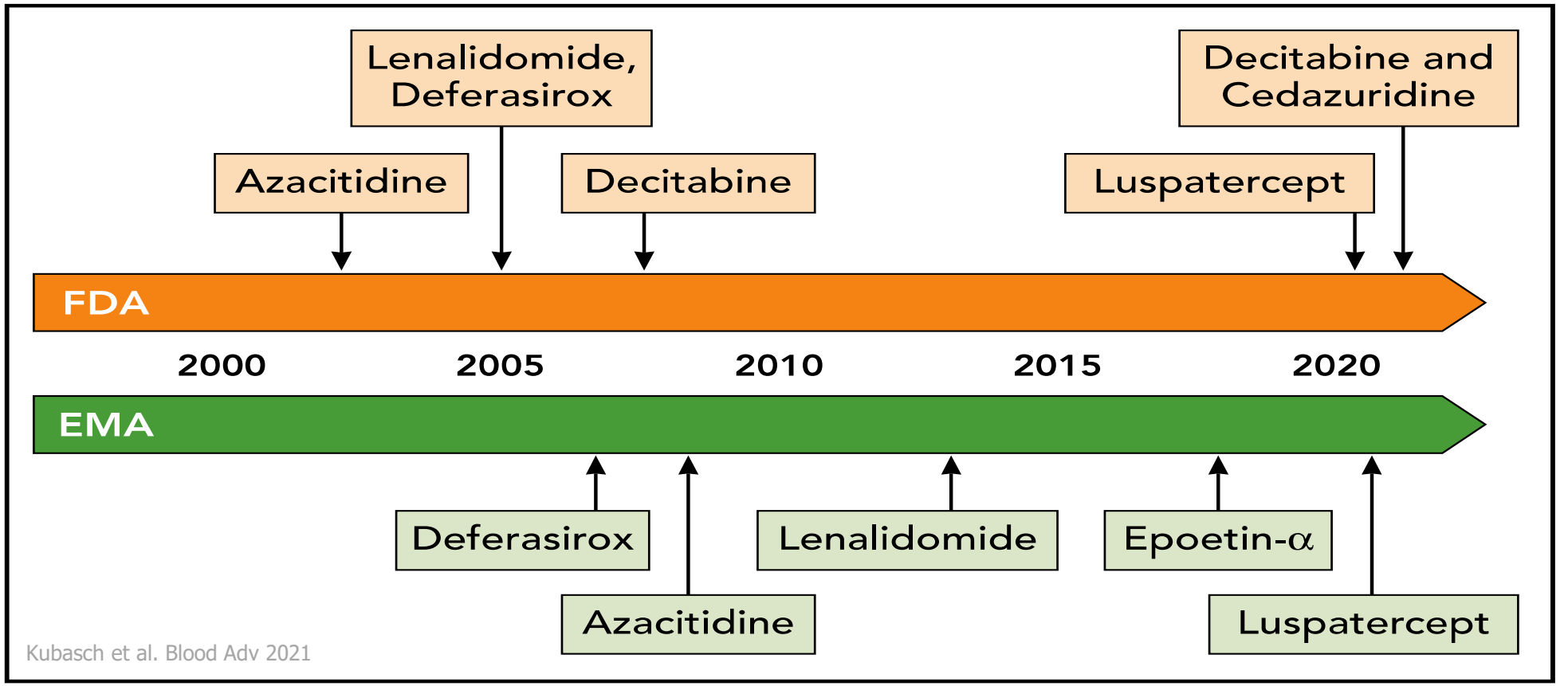
Allo Tregs to target inflammation

- Phase 1 dose-escalation study of CK0801 Treg cells

- Safety and efficacy of this treatment for bone marrow failure syndromes

Kadia et al. NEJM Ev 2024

REMARK Trial by EMSCO



„Our hearts are big, but the possibilities are limited“

Grazie

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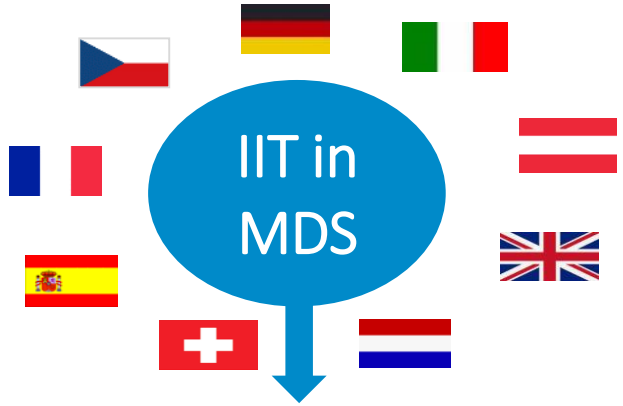

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