UC San Diego
Moores Cancer Center

mds foundation
the myelodysplastic syndromes foundation, inc.

Treatment of Lower Risk Myelodysplastic Syndromes

MDS Patient and Family Forum
June 29, 2024

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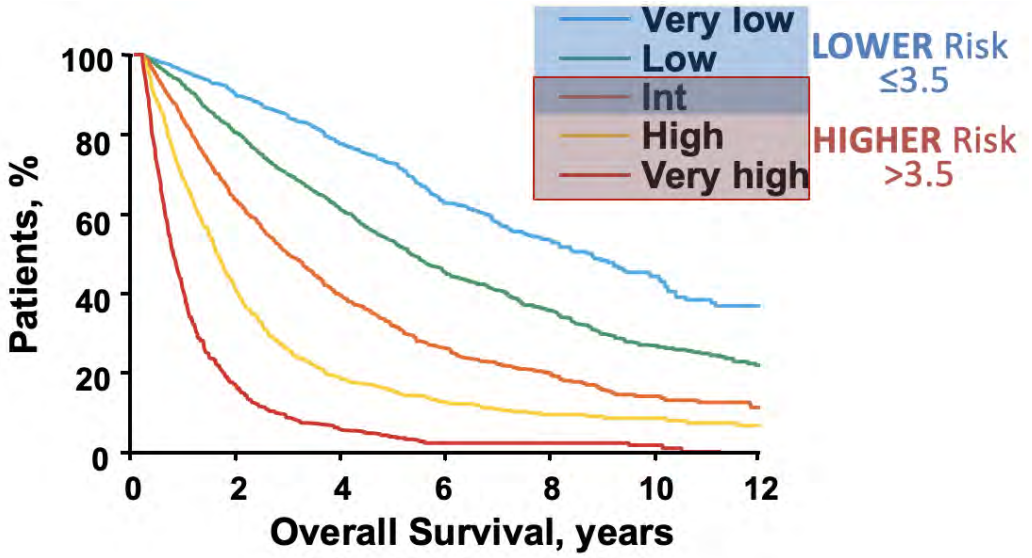
OUTLINE

- Review of risk stratification
- Treatment goals in lower risk MDS
- Treatment of anemia
- Treatment of thrombocytopenia
- Treatment of multilineage dysplasia
- Emerging therapies

IPSS-R Risk Stratification

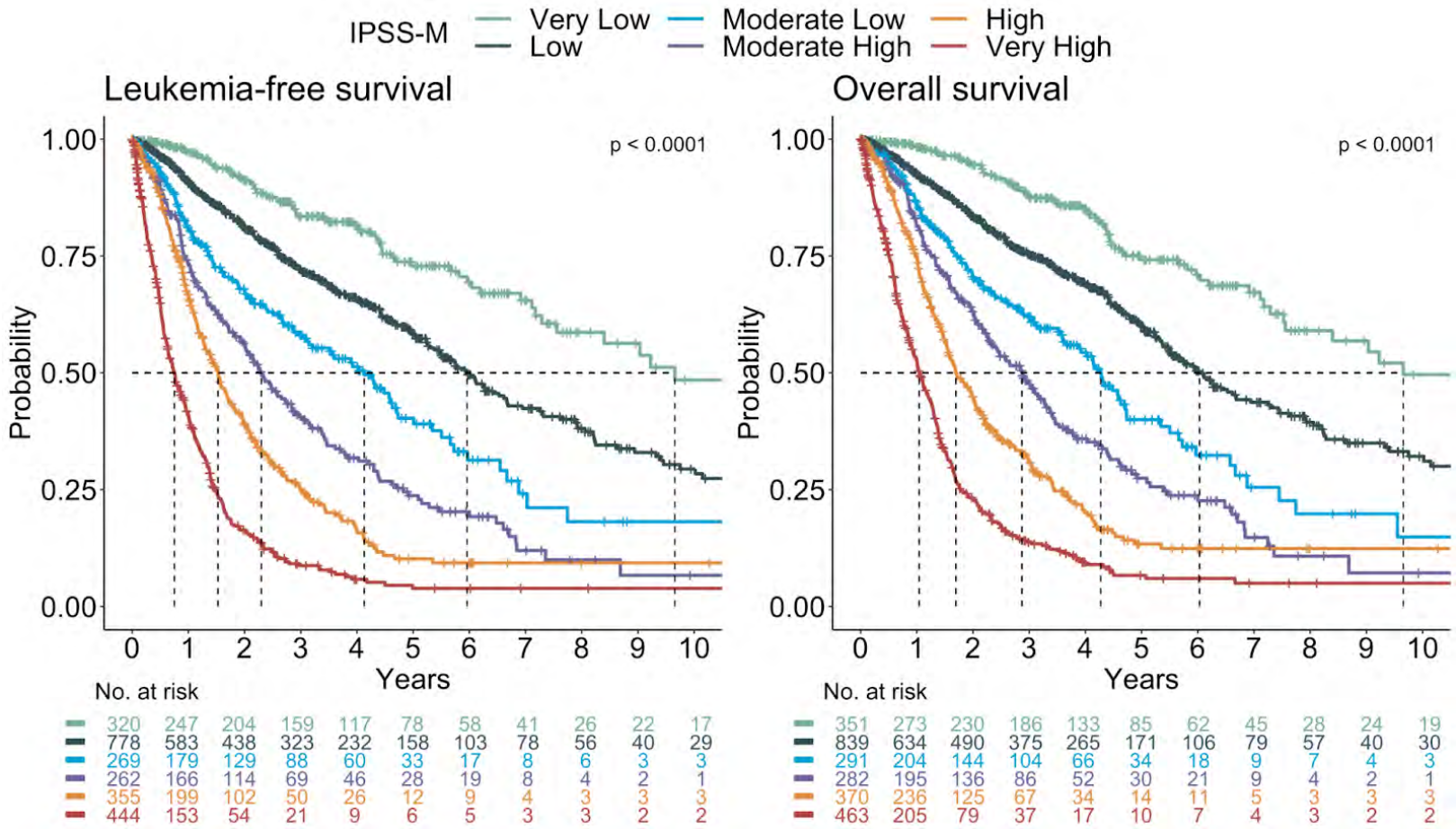
Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Abs. neutrophil count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤ 1.5	19 %	8.8	Not reached
Low	> 1.5 – 3	38 %	5.3	10.8
Intermediate	> 3 – 4.5	20 %	3.0	3.2
High	> 4.5 – 6	13 %	1.6	1.4
Very High	> 6	10 %	0.8	0.73



Greenberg et al, *Blood* 2012

IPSS-M Risk Stratification



Very Low | Low | Moderate Low | Moderate High | High | Very High

Prognostic separation of the IPSS-M risk categories

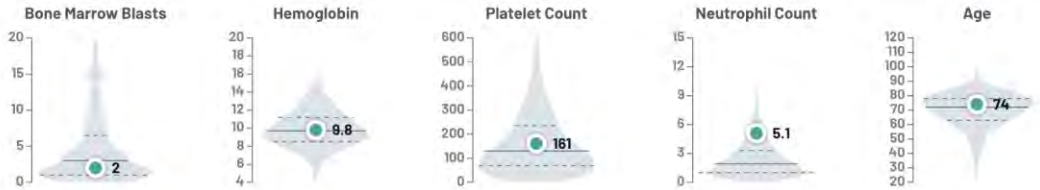
PATIENT SUMMARY

Bone Marrow Blasts:	Hemoglobin:	Platelet Count:	Neutrophil Count:	Age:
2 %	**9.8** g/dL	**161** 1e9/L	**5.1** 1e9/L	**74** years

Cytogenetics Category:	TP53 Mutation Count:	TP53 Maximum VAF:	TP53 locus LOH:
Good	**0**	**N/A**	**No**

Mutated Genes:	Missing Genes:
ASXL1, RUNX1, SRSF2	**0**

Cohort Clinical Distributions (n=2957)



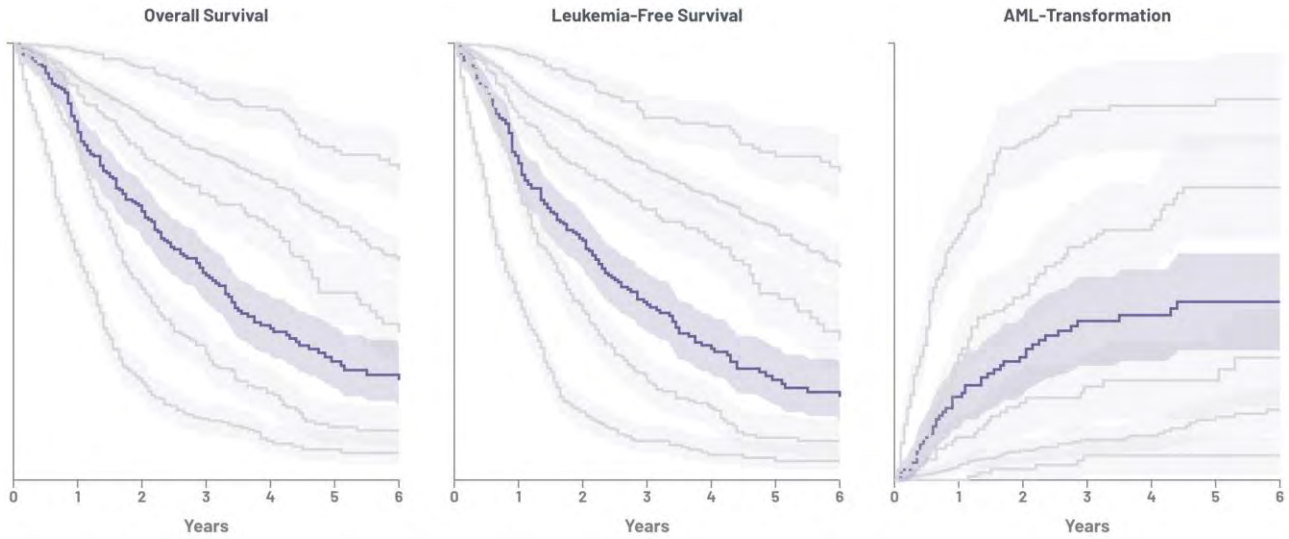
STRATIFICATION RESULTS

IPSS-M Score:	IPSS-R Score:	IPSS-R Score (Age-adjusted):
0.10 MODERATE HIGH	**2.00** LOW	**2.16** LOW

ENDPOINTS

Leukemia-Free Survival (IPSS-M):	Overall Survival (IPSS-M):	AML Transformation (IPSS-M):
2.3 years median	**2.8 years** median	**9.5%** by 1 year
0.91-4.7 years, 25%-75% range	1.2-5.5 years, 25%-75% range	18.9% by 4 years

By IPSS-M | By IPSS-R



mds-risk-model.com

Treatment goals in lower risk MDS

Primary Goal = To improve (or maintain) **QUALITY OF LIFE**

Other Goals:

- Establish an appropriate monitoring plan
- Improve blood counts/decrease transfusion needs
- Lower risk of transformation to leukemia
- *Maximize benefit while minimizing risk*

Treatment goals in lower risk MDS

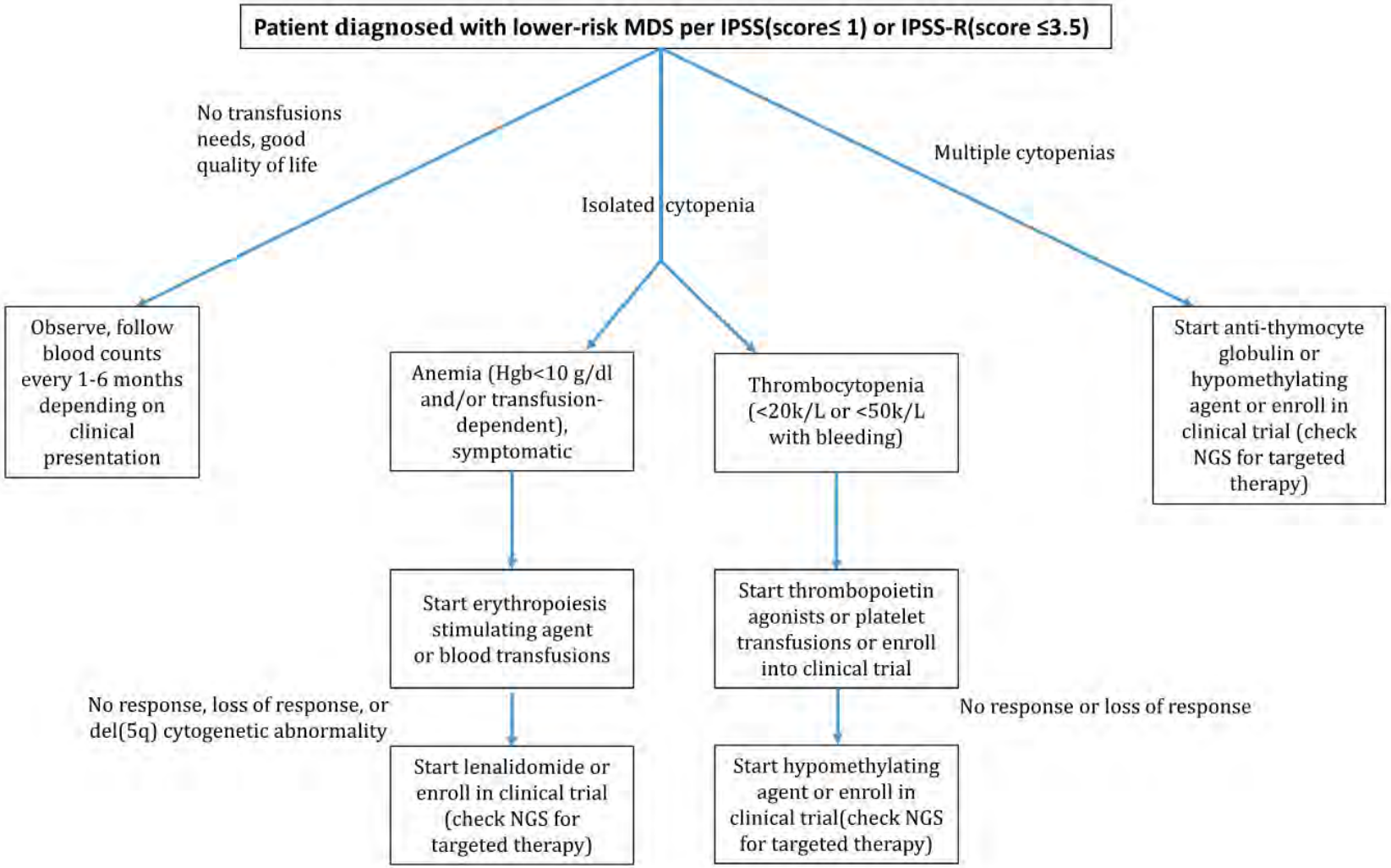
1. Do I need to treat at all?

    - No advantage to early aggressive treatment
    - Observation is often the best approach

2. Are transfusions treatment?

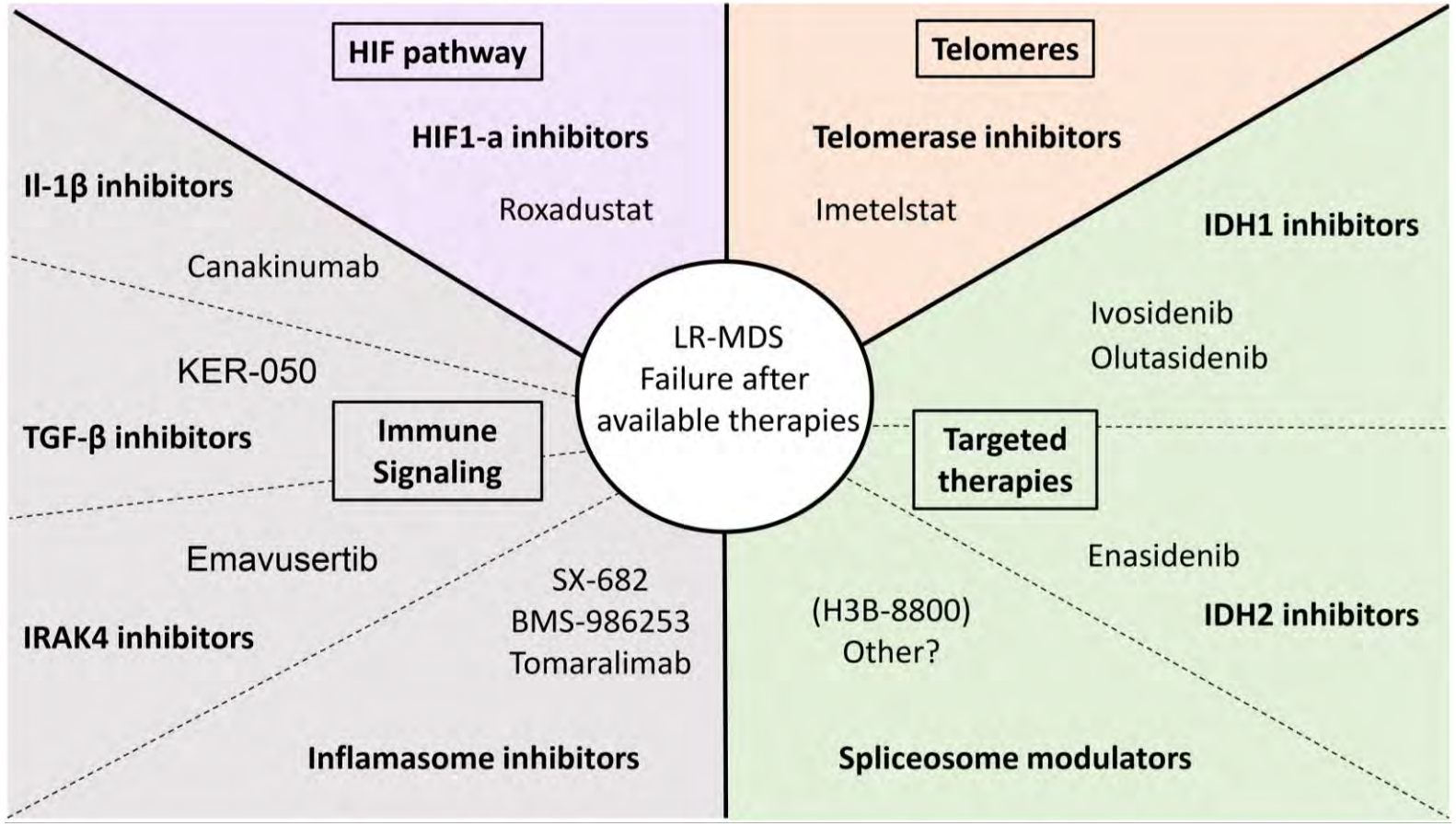
    - No! They are a sign that treatment is needed.

Treatment algorithm for lower risk MDS



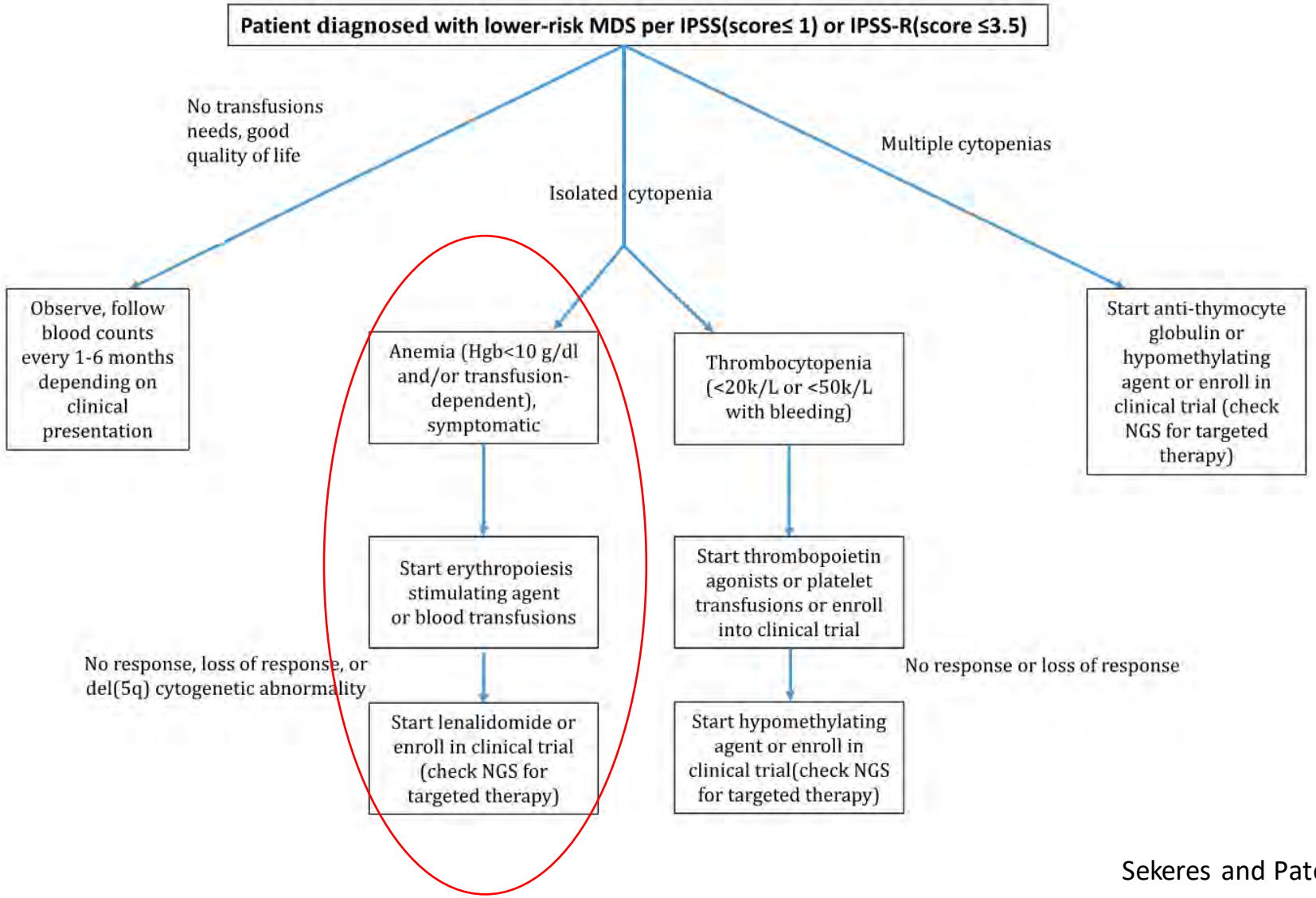
Sekeres and Patel, *ASH Educ Series 2019*

Emerging therapy for lower risk MDS



Sebert, *ASH Educ Series 2023*

Treatment algorithm for lower risk MDS



Sekeres and Patel, *ASH Educ Series 2019*

Erythropoiesis Stimulating Agents (ESAs)

What are erythropoiesis stimulating agents?

- Recombinant growth factors that mimic the effects of the body's endogenous hormone **erythropoietin**
- Given as subcutaneous injections
- Examples include:
  Epoetin (aka Epogen, Procrit, Retacrit)
  Darbepoietin (longer half-life so dosed less frequently)
- Used in multiple other indications (kidney disease/dialysis, chemotherapy-induced anemia, etc)

Treatment of anemia: ESAs

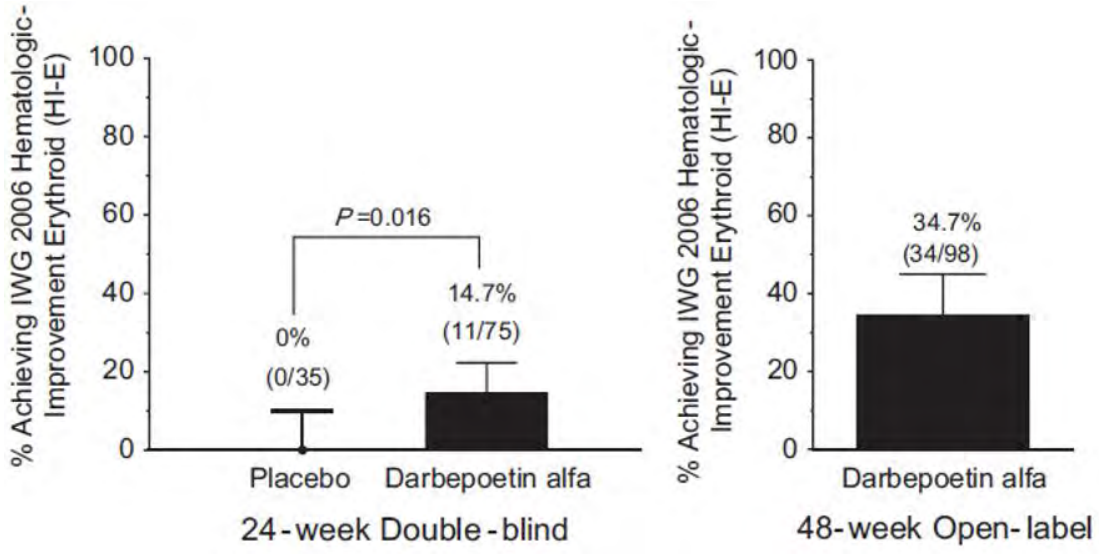
Table II. Response results.

	Patients (%)	Response rate
Growth factors	100	39·5
EPO	57·3	39·4
EPO + GCSF	23·4	47·8
GMCSF	6·2	37·8
EPO + GMCSF	5·8	33·7
GCSF	3·0	47·9
IL3	3·0	17·0
IL6	1·3	38·1

N = 1587

Golshayan, *Br J Haematol* 2007

ESA response rate ~15-40%



Platzbecker et al, *Leukemia* 2017

Treatment of anemia: ESAs

Serum EPO level (U/L)	RBC transfusion requirement
<100 = *+2 pts*	<2 Units / month = *+2 pts*
100-500 = *+1 pt*	≥2 Units / month = *-2 pts*
>500 = *-3 pts*	

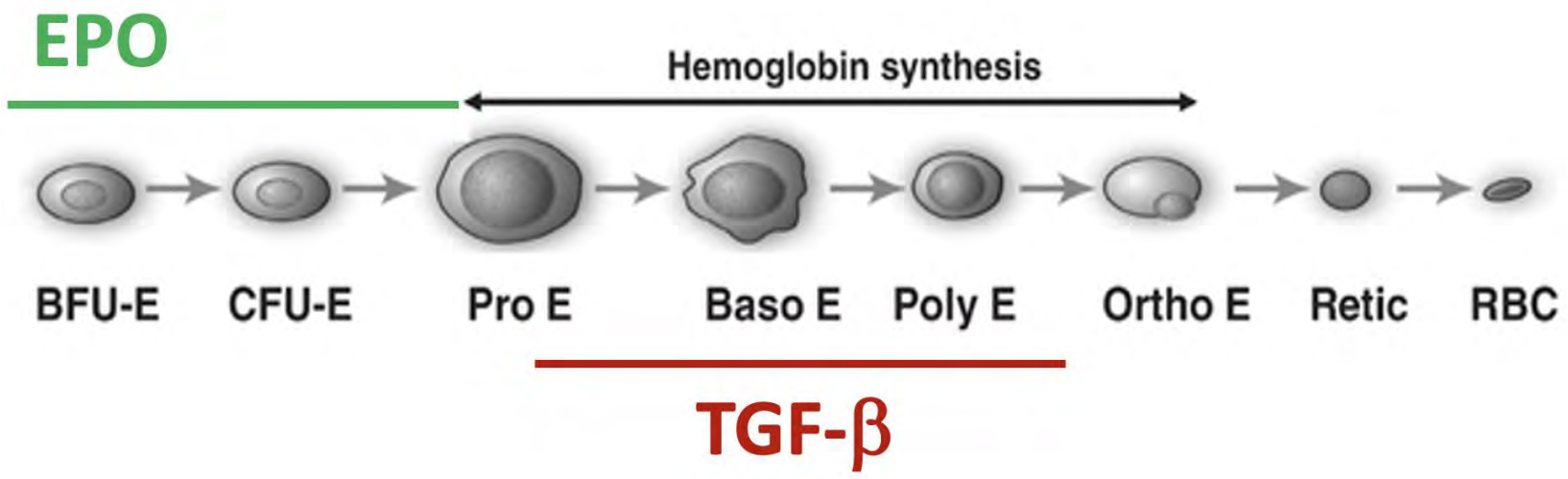
Total Score	Response Rate
High likelihood of response: > +1	**74%** (n=34)
Intermediate likelihood: -1 to +1	**23%** (n=31)
Low likelihood of response: < -1	**7%** (n=39)

Hellstrom-Lindberg E et al, *Br J Haem* 2003

Luspatercept

What is luspatercept?

“Erythroid maturation agent”: Binds to TGF-beta proteins to restore late-stage RBC maturation



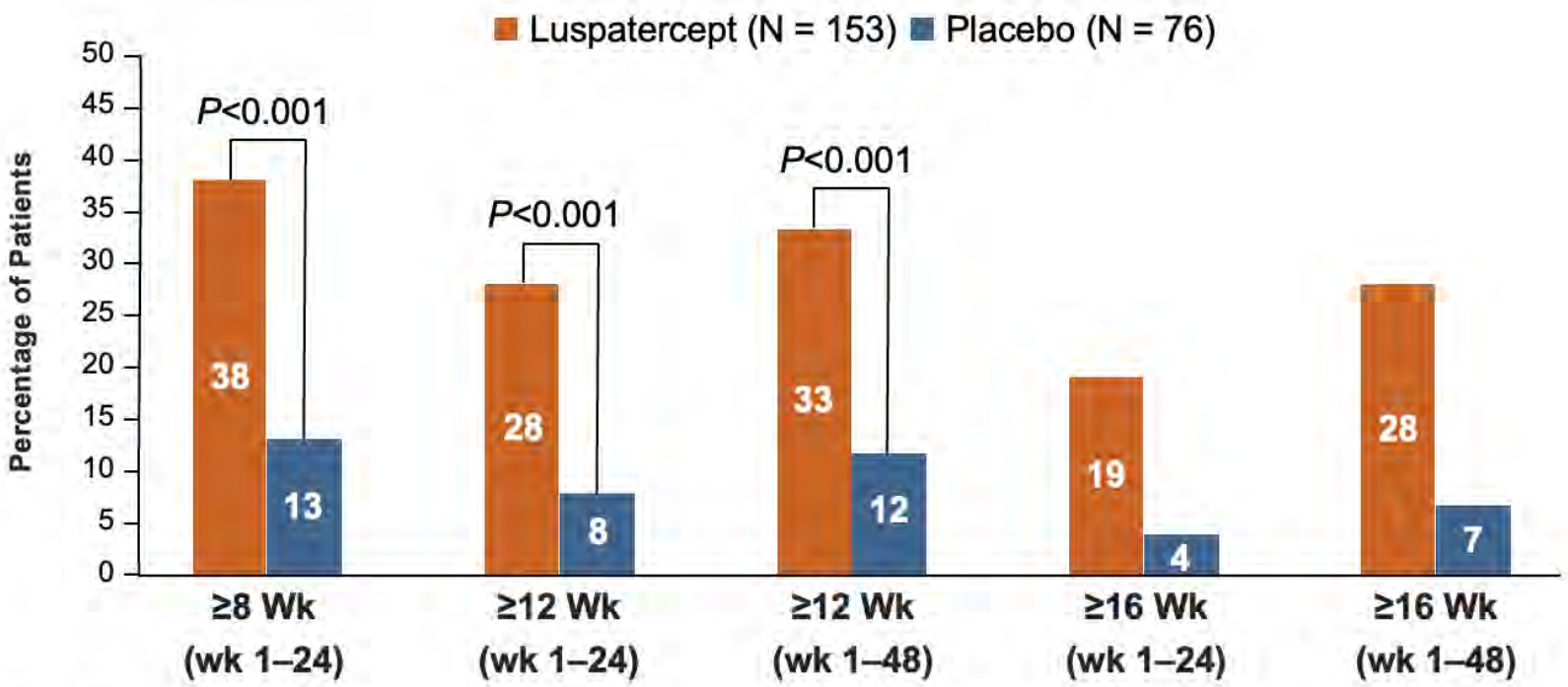
Luspatercept vs Placebo in MDS (MEDALIST): Demographics and Disease Characteristics

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)**
Time since original MDS diagnosis, median (range), months	**44.0 (3–421)**	**36.1 (4–193)**
WHO classification		
• RCMD-RS, n (%)	**145 (94.8)**	**74 (97.4)**
RBC transfusion burden, median (range), units/8 weeks[a]	5 (1–15)	5 (2–20)
• ≥ 6 units/8 weeks, n (%)	**66 (43.1)**	**33 (43.4)**
• < 6 units/8 weeks, n (%)	87 (56.9)	43 (56.6)
Pre-transfusion Hb, median (range), g/dL	**7.6 (6–10)**	**7.6 (5–9)**
IPSS-R risk category		
• Very Low, Low, n (%)	127 (83.0)	63 (82.9)
• Intermediate, n (%)	25 (16.3)	13 (17.1)
SF3B1 mutation, n (%)	**138 (93)**	**64 (86)[c]**
Serum EPO		
• < 200 U/L, n (%)	88 (57.5)[c]	50 (65.8)
• ≥ 200 U/L, n (%)	64 (41.8)[c]	26 (34.2)

[a] In the 16 weeks prior to randomization. [b] 1 (0.7%) patient in the luspatercept arm was classified as IPSS-R High-risk. [c] Data were missing for 1 patient.
RCMD-RS, refractory cytopenia with multilineage dysplasia with RS.

Fenaux et al. *NEJM 2020*

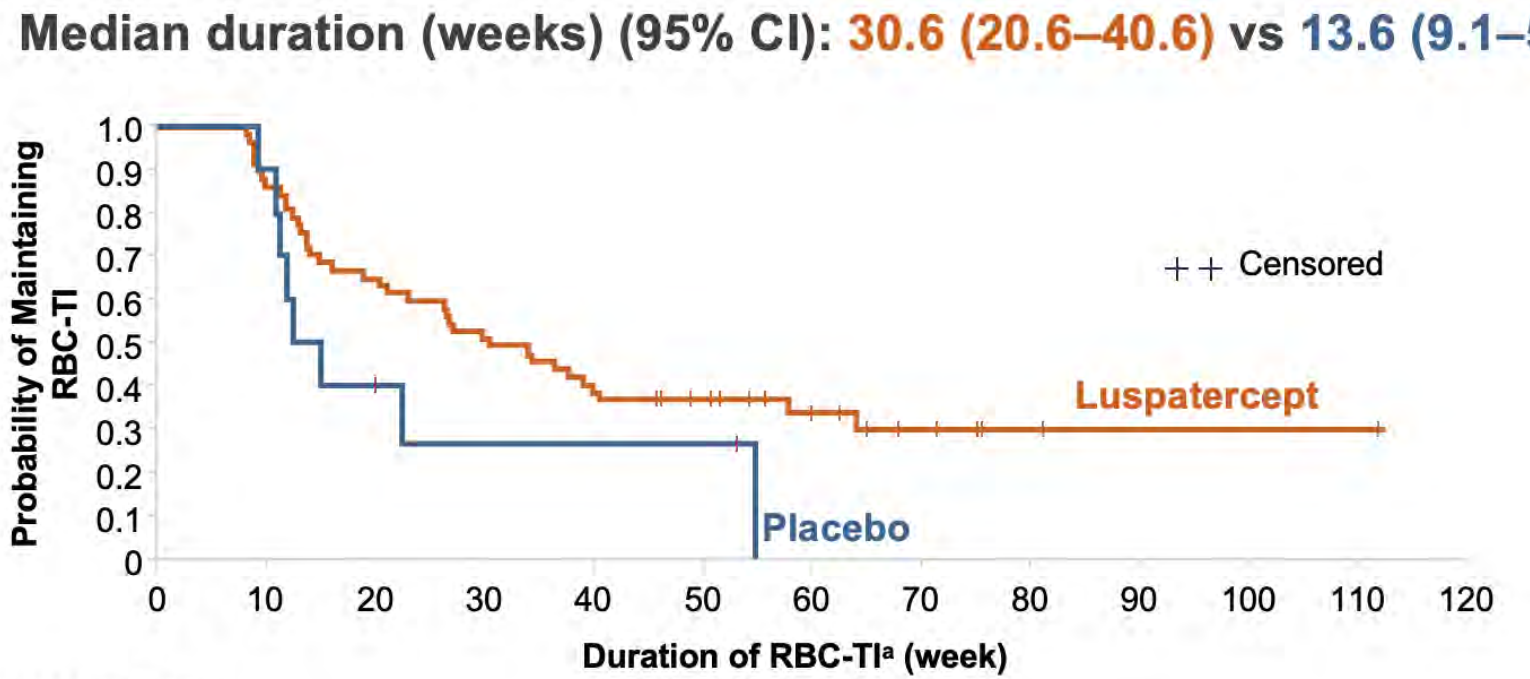
Luspatercept vs Placebo in MDS (MEDALIST): Red Blood Cell Transfusion Independence



No. of patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Fenaux et al. *NEJM 2020*

Luspatercept vs Placebo in MDS (MEDALIST): Duration of Transfusion-Independence in Responders

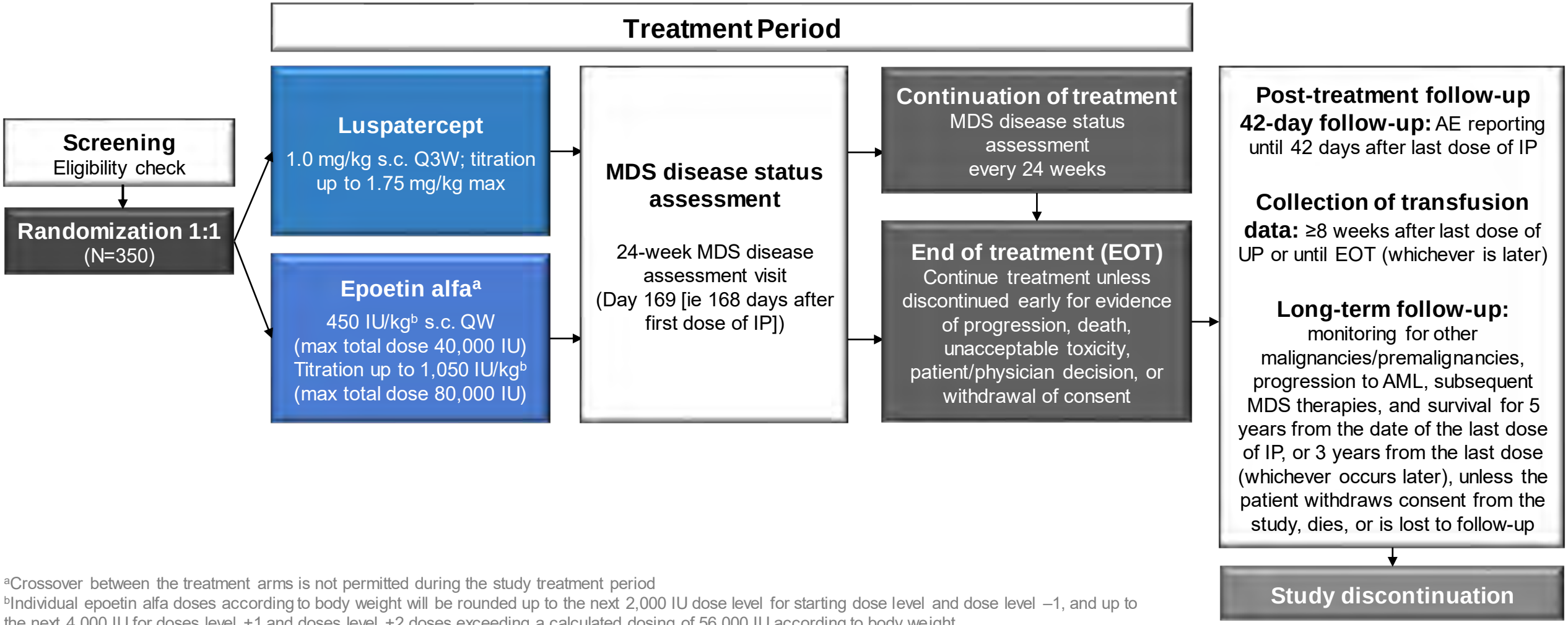


[a] During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.

Fenaux et al. *NEJM 2020*

COMMANDS Trial: Study Design

Randomized Phase 3 Trial of Luspatercept vs Epoetin Alfa for Anemia Due to IPSS-R Very Low-, Low-, or Intermediate-Risk MDS in ESA-Naive Patients Who Require RBC Transfusions



[a]Crossover between the treatment arms is not permitted during the study treatment period

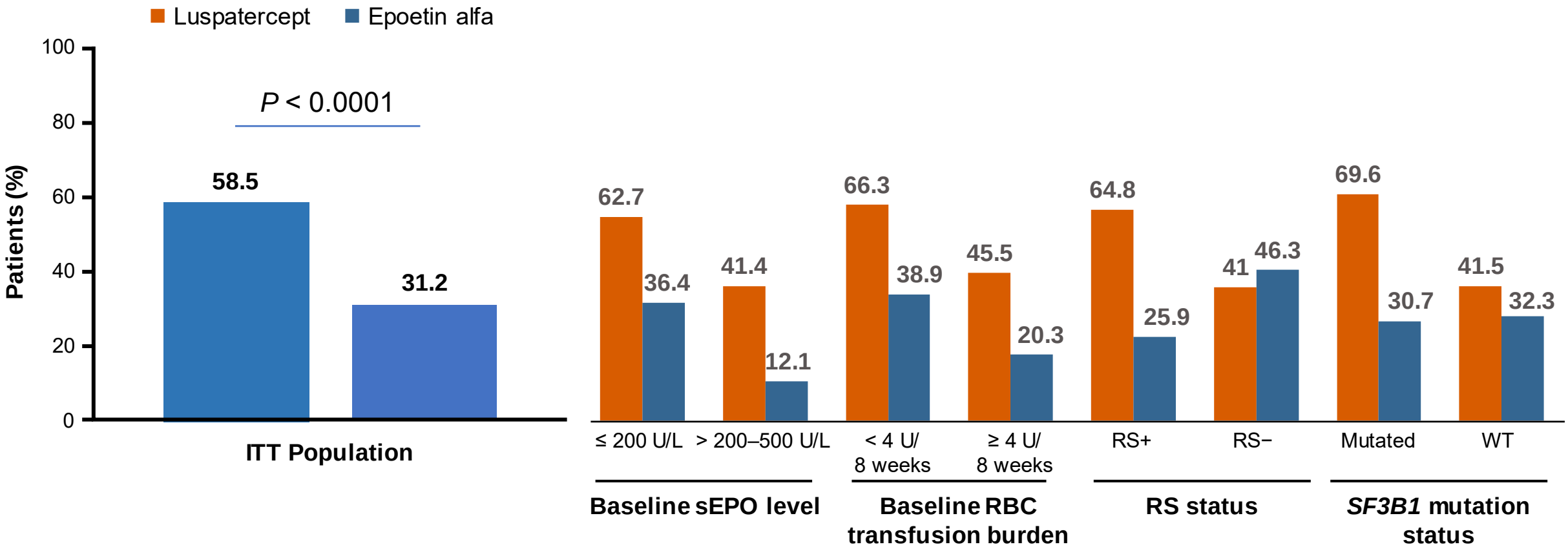
[b]Individual epoetin alfa doses according to body weight will be rounded up to the next 2,000 IU dose level for starting dose level and dose level –1, and up to the next 4,000 IU for doses level +1 and doses level +2 doses exceeding a calculated dosing of 56,000 IU according to body weight.

NCT05035823

COMMANDS Trial

Achievement of Primary Endpoint in Different Patient Subgroups

Primary endpoint: RBC-TI ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL (weeks 1–24)

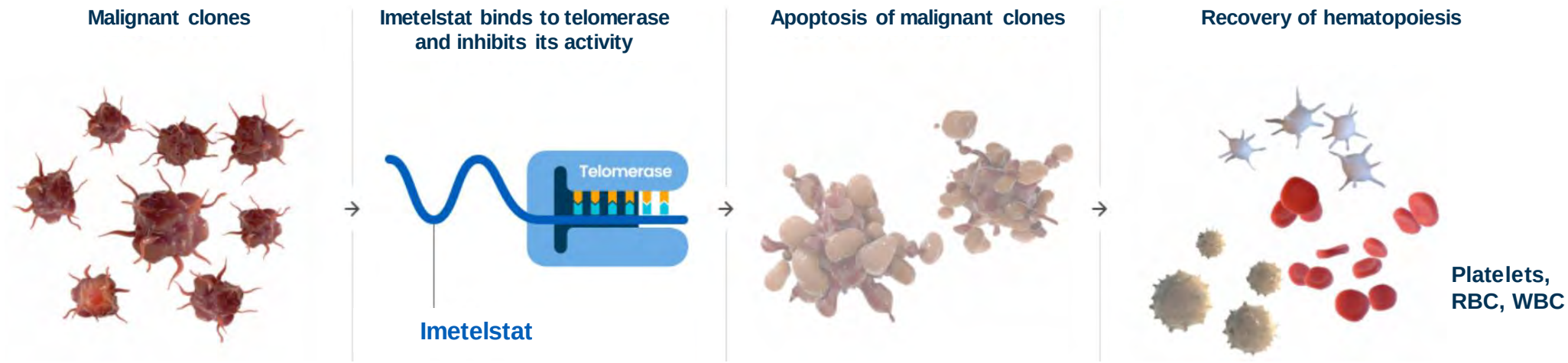


RS status, baseline sEPO level, and baseline RBC transfusion burden were prespecified factors for randomization. *SF3B1* mutation status was a post hoc subgroup analysis. WT, wild type.

Guillermo Garcia-Manero, et al. Presented at ASCO 2023: Abstract 7003.

Imetelstat

What is imetelstat?



Imetelstat is a first-in-class direct and competitive inhibitor of telomerase activity that specifically targets malignant clones with abnormally high telomerase activity, enabling the recovery of effective hematopoiesis[1-4]

Imetelstat has received FDA Fast Track designation for adult patients with transfusion-dependent anemia due to LR-MDS that is not associated with del(5q) who are refractory or resistant to an ESA

ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; LR-MDS, lower risk myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence; WBC, white blood cell.

1. Asai A. *Cancer Res.* 2003;63(14):3931-3939; 2. Herbert B-Sl. *Oncogene.* 2005;24(33):5262-5268; 3. Mosoyan Gl. *Leukemia.* 2017;31(11):2458-2467; 4. Wang X. *Blood Adv.* 2018;2(18):2378-2388; 5. Steensma DP. *J Clin Oncol.* 2021;39(1):48-56; 6. Platzbecker U. *EHA*. 2023. Oral presentation S165.

IMerge (MDS3001; NCT02598661): Study Design

Phase 2/3 Study Assessing Imetelstat in Patients With LR-MDS

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

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

RANDOMIZE 2:1

- **Imetelstat** (n=118)
- **Placebo** (n=60)

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

Primary Endpoint

- ≥8-week RBC TI

Key Secondary Endpoints

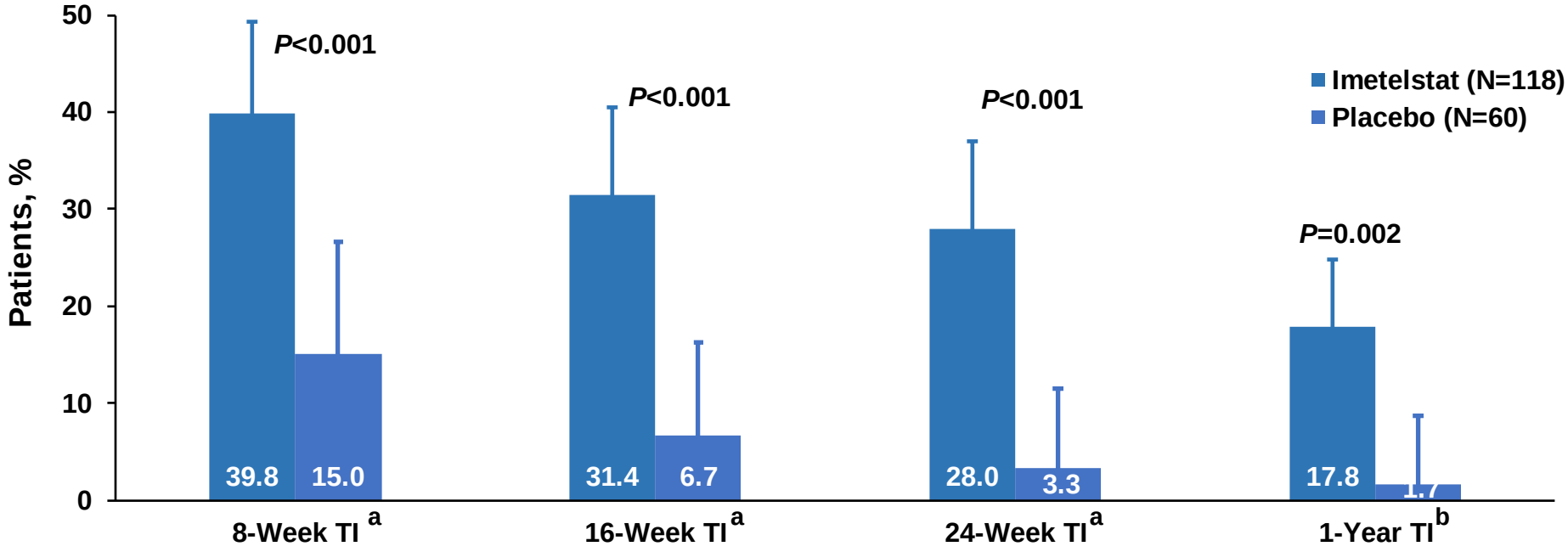
- Safety
- ≥24-week TI rate
- HI-E
- OS
- PFS
- Time to progression to AML

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

Platzbecker et al, *Lancet* 2023

IMerge Trial

Primary End Point of 8-Week RBC-TI Rate Was Significantly Higher With Imetelstat vs Placebo



Patients with response, n (%) 95% CI	8-Week TI[a]	16-Week TI[a]	24-Week TI[a]	1-Year TI[b]
Imetelstat	47 (39.8) 30.9–49.3	37 (31.4) 23.1–40.5	33 (28.0) 20.1–37.0	21 (17.8) 11.4–25.9
Placebo	9 (15.0) 7.1–26.6	4 (6.7) 1.9–16.2	2 (3.3) 0.4–11.5	1 (1.7) 0.0–8.9

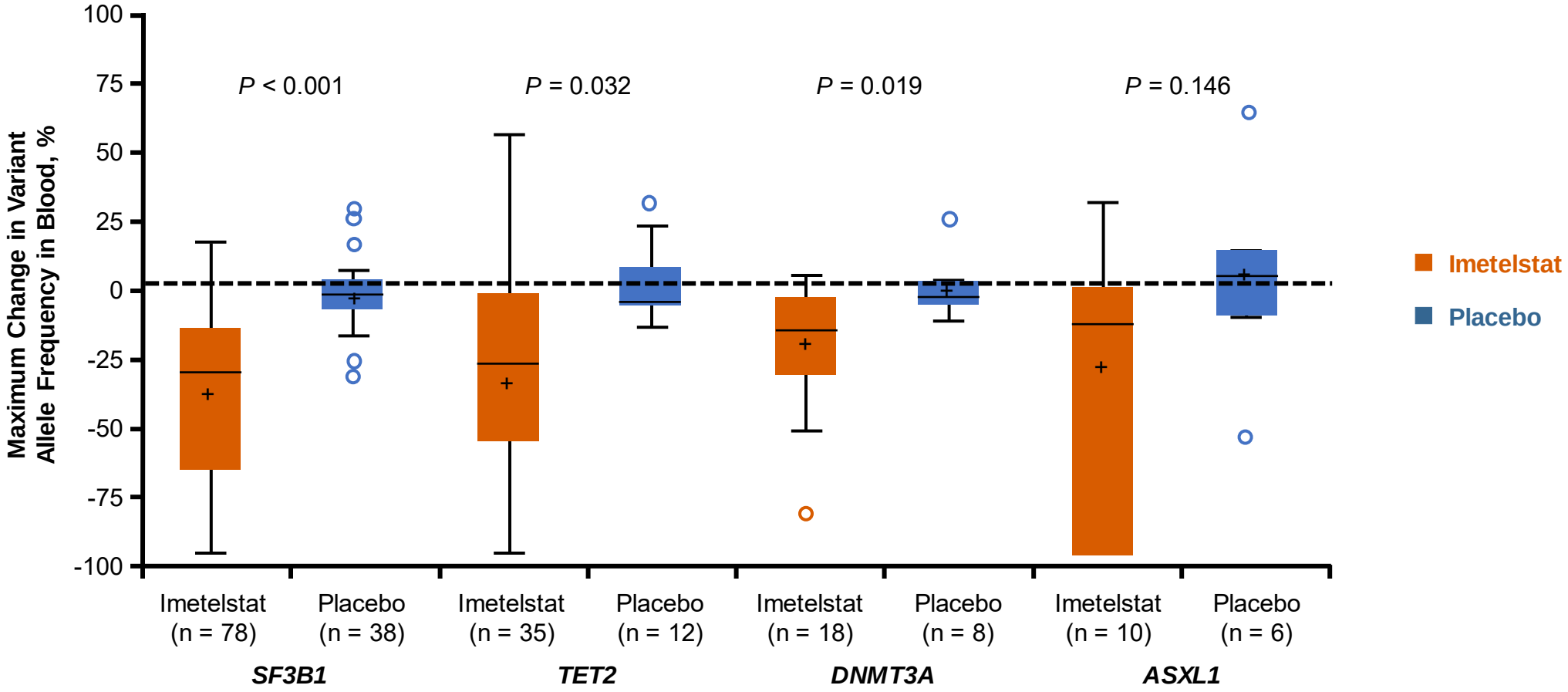
[a]Data cutoff: October 13, 2022. [b]Data cutoff: January 13, 2023.

Note: Primary end point 8-week TI and the first secondary end point 24-week TI were statistically significant by the study prespecified gate-keeping testing procedure. *P* value determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC units/8 weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs intermediate-1) applied to randomization.

Platzbecker et al *Blood*. 2022;140 (Supplement 1): 1106–1108. Platzbecker U et al. Lancet. 2023 Dec 1 [Epub ahead of print].
Press release update https://ir.geron.com/investors/press-releases/press-release-details/2023/Geron-Announces-Positive-Top-Line-Results-from-IMerge-Phase-3-Trial-of-Imetelstat-in-Lower-Risk-MDS/default.aspx

IMerge Trial

Reduction in VAF with Imetelstat Therapy Correlated With Longer Duration on TI and Increased Hb



Platzbecker U, et al. *Lancet*. 2023 Dec 1 [Epub ahead of print].

IMerge Trial

Most Common Adverse Events Were Hematologic

- Median duration of grade 3–4 thrombocytopenia and neutropenia was <2 weeks and >80% of events were reversible to grade ≤2 within 4 weeks
- Clinical consequences of grade 3–4 infection and bleeding were low and similar for imetelstat and placebo

Hematologic AE (≥10% of patients), n (%)	Imetelstat (n=118)		Placebo (n=59)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Thrombocytopenia	89 (75)	73 (62)	6 (10)	5 (8)
Neutropenia	87 (74)	80 (68)	4 (7)	2 (3)
Anemia	24 (20)	23 (19)	6 (10)	4 (7)
Leukopenia	12 (10)	9 (8)	1 (2)	0

Grade 3–4 cytopenias (per lab value)	Imetelstat (n=118)	Placebo (n=59)
Thrombocytopenia events		
Median duration, weeks (range)	1.4 (0.1–12.6)	2.0 (0.3–11.6)
Resolved within 4 weeks, %	86.3	44.4
Neutropenia events		
Median duration, weeks (range)	1.9 (0–15.9)	2.2 (1.0–4.6)
Resolved within 4 weeks, %	81.0	50.0

Platzbecker et al *Blood*. 2022;140 (Supplement 1): 1106–1108.
Press release update https://ir.geron.com/investors/press-releases/press-release-details/2023/Geron-Announces-Positive-Top-Line-Results-from-IMerge-Phase-3-Trial-of-Imetelstat-in-Lower-Risk-MDS/default.aspx

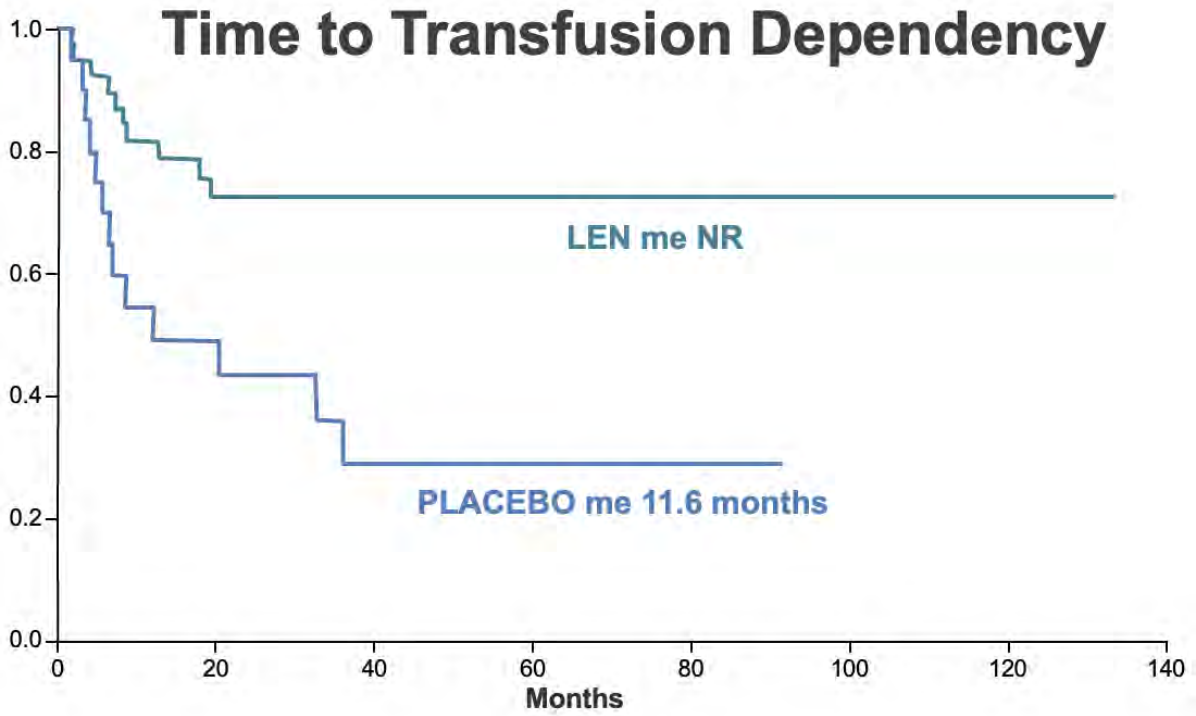
Lenalidomide

What is lenalidomide?

- Immune modulatory drug that has been in use for many years in various hematologic malignancies, particularly multiple myeloma
- Given orally
- Can cause thrombocytopenia and neutropenia

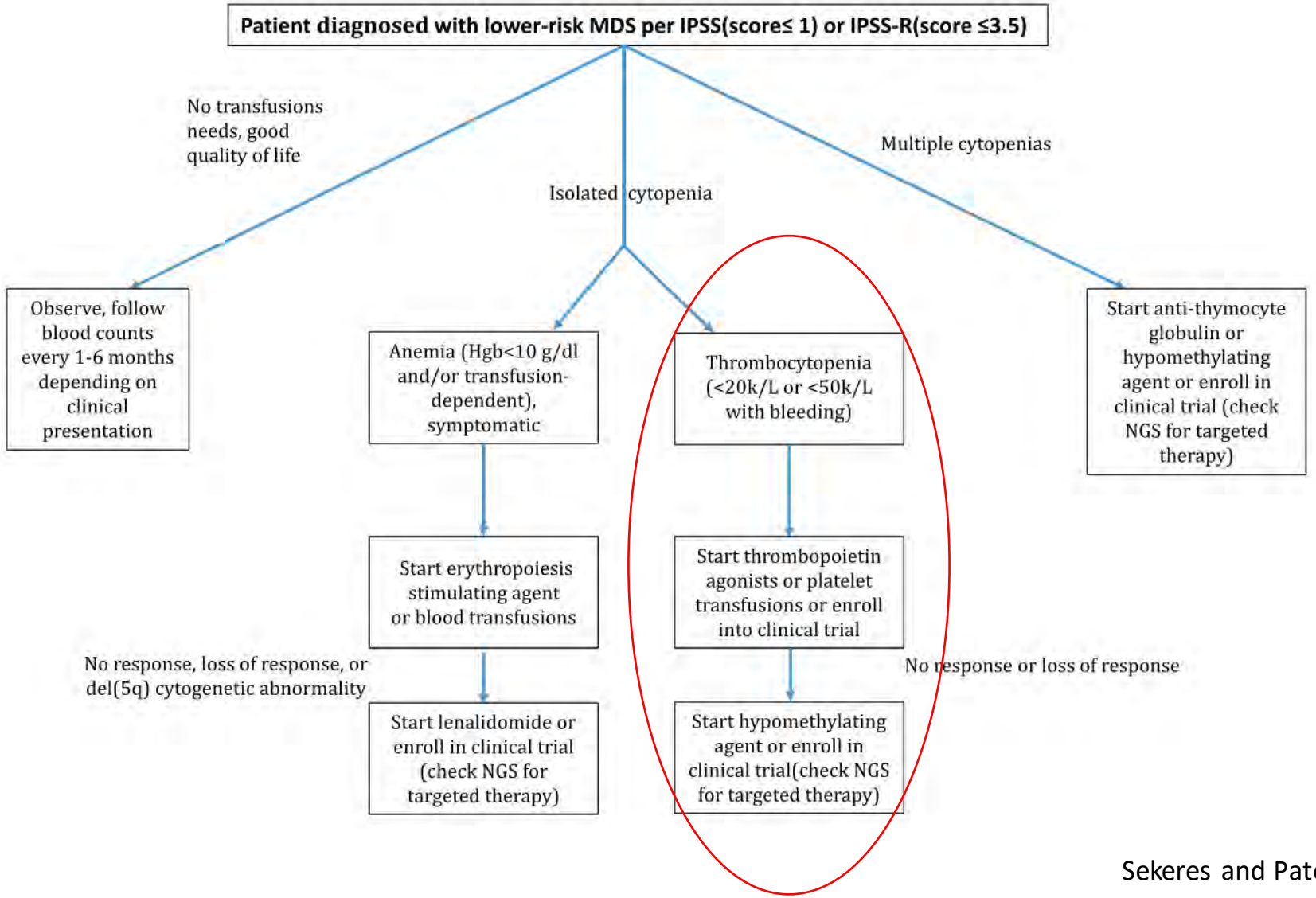
Treatment of anemia: Lenalidomide

- In del(5q) – response rates are high:
  - 50%-70% respond to treatment
  - Median 2 years transfusion free!
- More recently, the “Sintra-Rev” trial showed that low dose LEN can also delay transfusion dependency in del(5q)



Cadenas FL, et al. Presented at ASH 2022. Abstract 46.

Treatment algorithm for lower risk MDS



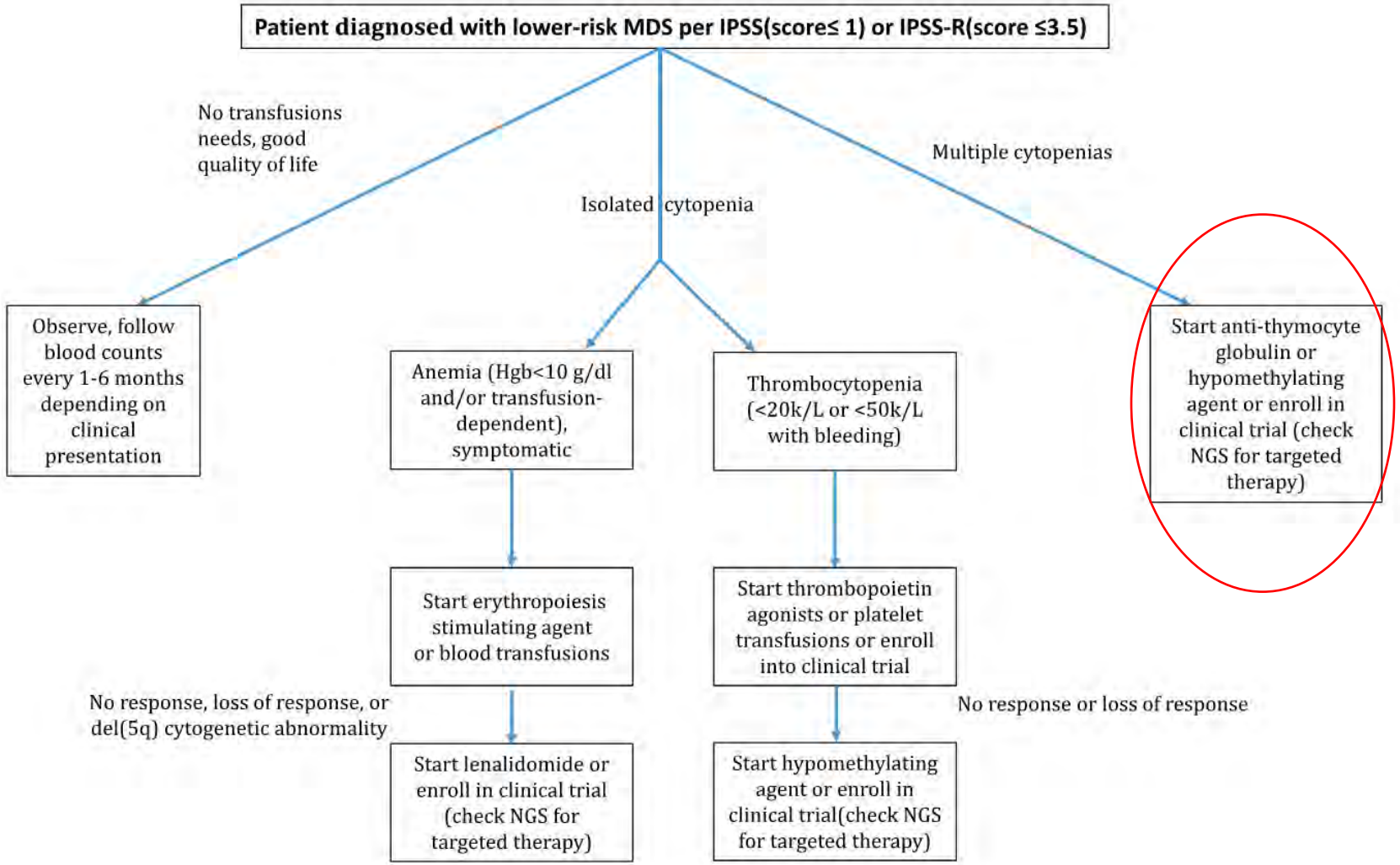
Sekeres and Patel, *ASH Educ Series 2019*

Thrombopoietin Receptor Agonists (TPO-RAs)

Treatment of thrombocytopenia: TPO-RAs

- Growth factors that bind to the thrombopoietin receptor thereby stimulating the development of platelets
- Romiplostim (weekly injection) and Eltrombopag (oral) are FDA approved though not specifically for the indication of MDS
- Can be used in lower risk MDS with isolated or predominant thrombocytopenia (platelets <20k or <50k with bleeding/bruising)
- Generally avoided in patients with higher risk MDS (esp blasts > 5%) due to concern for accelerated transformation to leukemia

Treatment algorithm for lower risk MDS

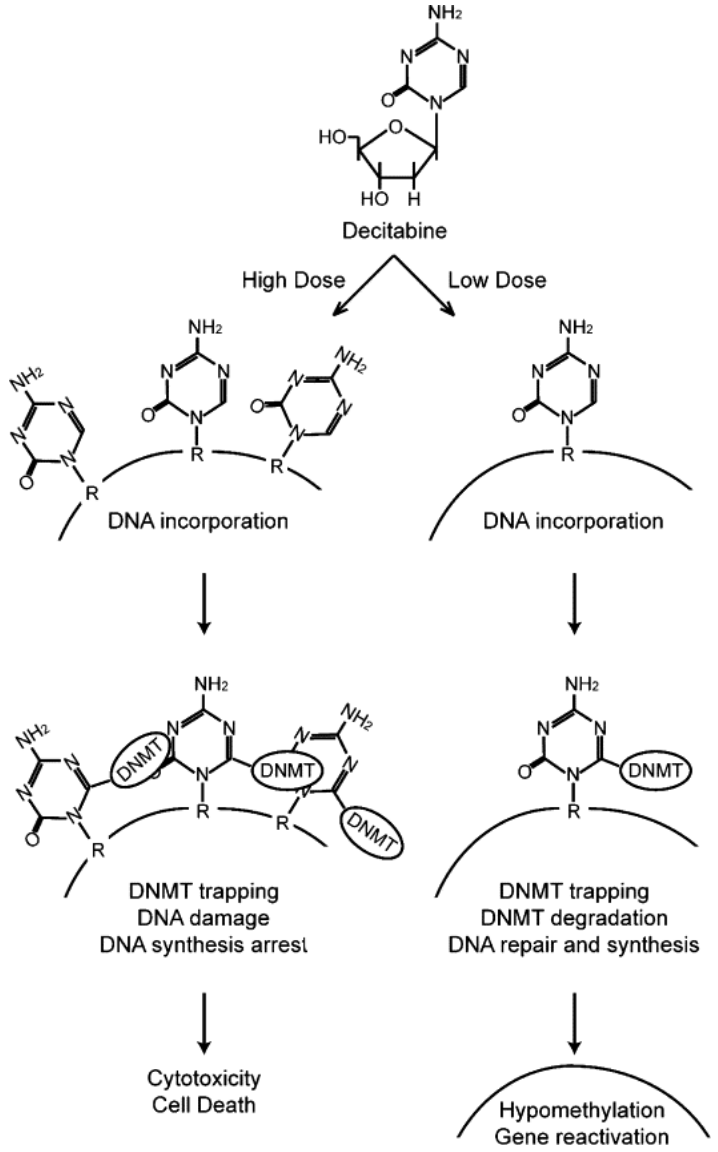


Sekeres and Patel, *ASH Educ Series 2019*

Hypomethylating Agents (HMAs): Azacitidine and Decitabine

What are hypomethylating agents?

- Analogs of the naturally occurring DNA base “cytidine”
- Incorporate into DNA, inducing cell death at high doses, and deplete DNA methyltransferase enzymes at low doses – which affects the expression of various genes
- Azacitidine was approved for the treatment of MDS in 2004 and Decitabine in 2006

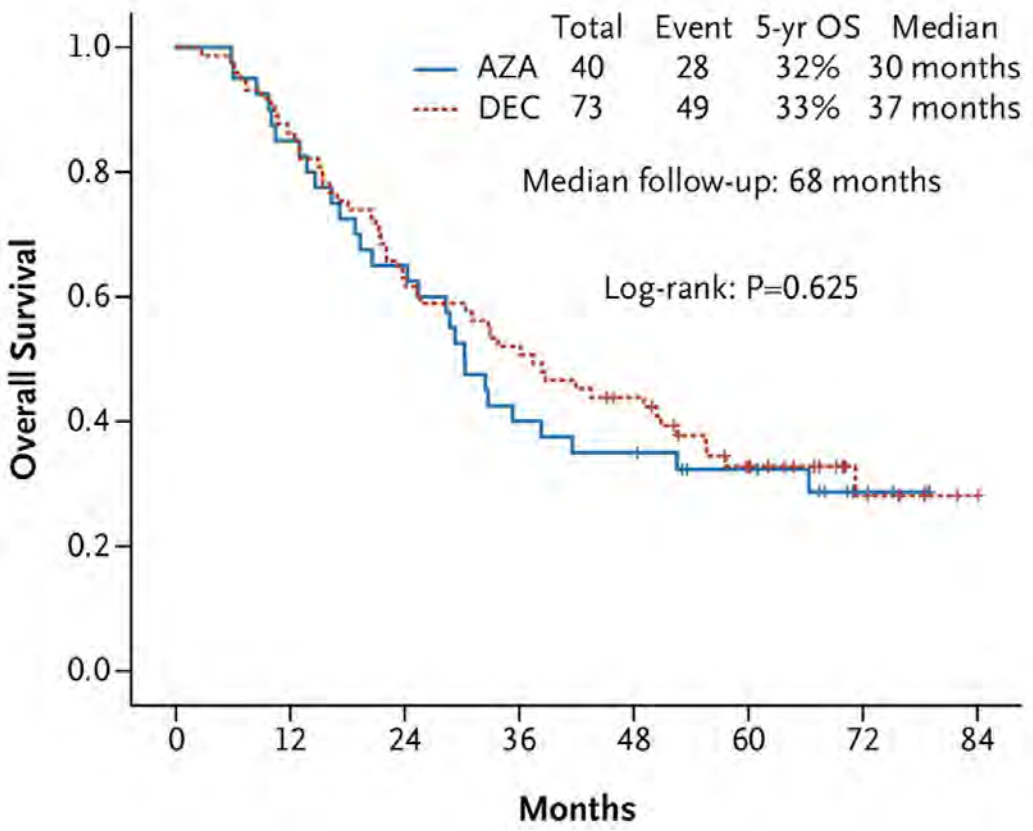


Crit Rev Oncol Hematol. 2007

Treatment of multilineage dysplasia: HMAs

- Sasaki et al (2022) randomized 113 pts with LR-MDS to receive low dose HMA
  - Azacitidine 75mg/m^2 for 3 days every 4 weeks
  - Decitabine 20mg/m^2 for 3 days every 4 weeks

- ORR = 54% (67% with DEC and 48% with AZA)
- Transfusion independence achieved in 32% (duration of response = 22 months)
- Median OS = 33 months



Sasaki et al, *NEJM* 2022

Treatment of multilineage dysplasia: Immunosuppressive therapy

- Higher chance of success in certain MDS patients that have features of immune-mediated disease such as:
  - Hypoplastic bone marrow (too few cells)
  - PNH clones (cells that lack CD55 and CD59 markers)
  - Certain immune receptor types (HLA-DR15)

- Options include:
  - ATG
  - Cyclosporine
  - Steroids
  - Tacrolimus
  - Etanercept

Guidelines for treatment of lower risk MDS

- Primary Goal: to improve **QUALITY OF LIFE**

1. Do I need to treat? - symptomatic cytopenias
2. Is LEN likely to work? - del(5q) or after ESA
3. Is LUSPATERCEPT an option? - Mainly in LR-MDS-RS
4. Are ESA likely to work? - Serum EPO < 500
5. Is IST likely to work? - hypocellular, DR15, PNH
6. Think about iron! - 20 or more transfusions
7. Consider AZA/DEC or clinical trial

Emerging therapy for lower risk MDS

Agent	Mechanism of action	Phase	Population	Identifier	Ref.
Ivosidenib	IDH1 inhibitor	2	Treatment-naive HR-MDS R/R (HMA) HR-MDS R/R (ESA) LR-MDS with anemia All with IDH1m	NCT03503409	20
Enasidenib	IDH2 inhibitor	2	Treatment-naive HR-MDS R/R (HMA) HR-MDS R/R (ESA) LR-MDS with anemia All with IDH2m	NCT03744390	21
		2, with AZA	MDS, excess blats, AML, CMML with IDH2m	NCT03383575	
Olutasidenib (FT-2102)	IDH1 inhibitor	2, with/without AZA/L-DAC	SMD and AML with IDH1m	NCT02719574	
H3B-8800	Splicing modulator	1	SMD, AML, CMML	NCT02841540	24
Roxadustat	HIF inhibitor	3	LR-MDS with anemia, low transfusion burden	NCT03263091	29
		2/3	LR-MDS with anemia	NCT03263091	
Imetelstat	Telomerase inhibitor	2/3	R/R (ESA) LR-MDS	NCT02598661	25
KER-050	TGF-β inhibitor	2	R/R (ESA) LR-MDS	NCT04419649	
Canakinumab	Il-1β inhibitor	1/2, with darbepoietin	R/R (ESA) LR-MDS	NCT04798339	
		2	R/R (ESA) LR-MDS	NCT05237713	
		2	R/R (ESA/HMA) LR-MDS/CMML	NCT04239157	
Emavusertib (CA-4948)	IRAK4 inhibitor	2	Treatment-naive and R/R (ESA) LR-MDS	NCT05178342	
BMS-986253	IL-8 inhibitor	1/2, with/without DEC/cedazuridine	R/R (HMA) HR-MDS R/R (ESA/LEN/Luspa) LR-MDS	NCT05148234	
SX-682	CXCR1 and CXCR2 inhibitor	1	R/R (ESA/LEN) LR-MDS	NCT04245397	
Tomaralimab	TLR2 inhibitor	1/2	R/R (ESA/LEN) LR-MDS	NCT02363491	

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Thank you!

- Rafael Bejar
- MDS Center of Excellence at UC San Diego
- Hematology and BMT faculty
- Our patients!!