Current State of MDS in 2026

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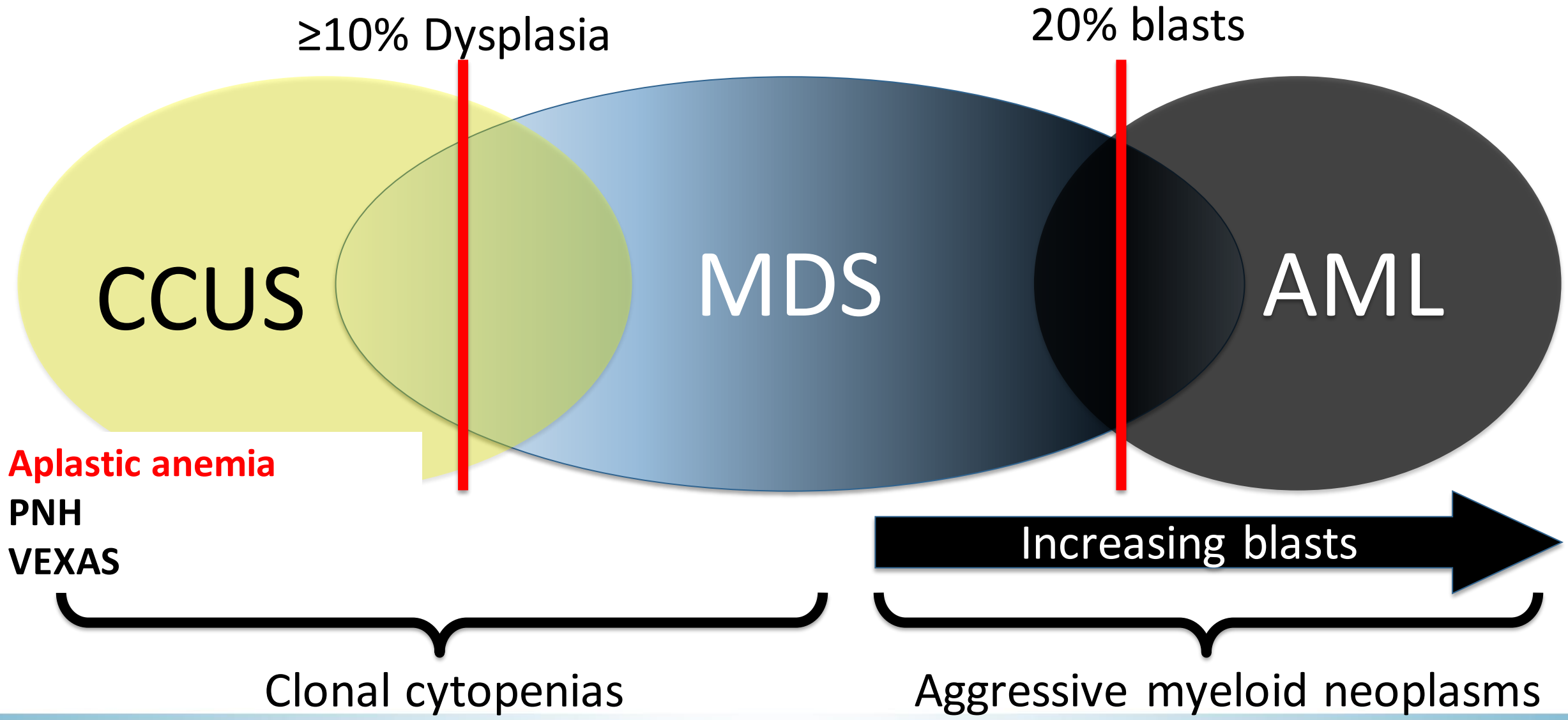
Objectives

- To contextualize MDS as a disease in 2026
  - From precursor states to higher risk disease and back

- To frame current MDS approaches for study and therapy
  - To stimulate discussion and thoughts to improve care/ outcomes for patients with MDS
  - We need MORE (earlier and later)

The borders of MDS

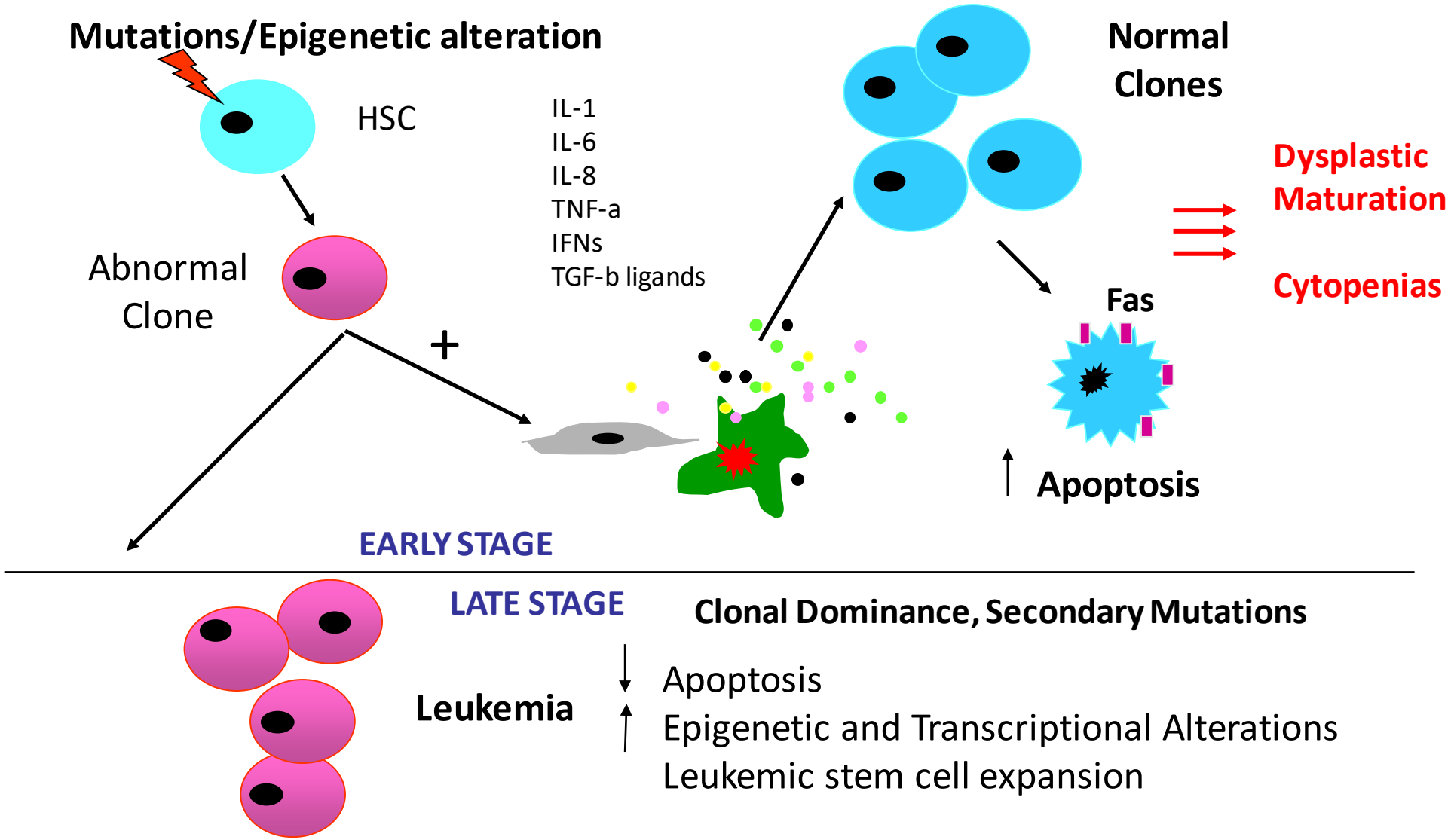


Therapeutic Goals Are Constant for MDS Patients

- Decrease disease burden (transfusions in LR and blasts in HR; clonal burden in all)
- Stabilize marrow function
- Gain trilineage improvement
- Lower risk of transformation to proliferative (high count) AML
- Move to definitive therapy or *Maximize benefit*

EXPECTATION MANAGEMENT

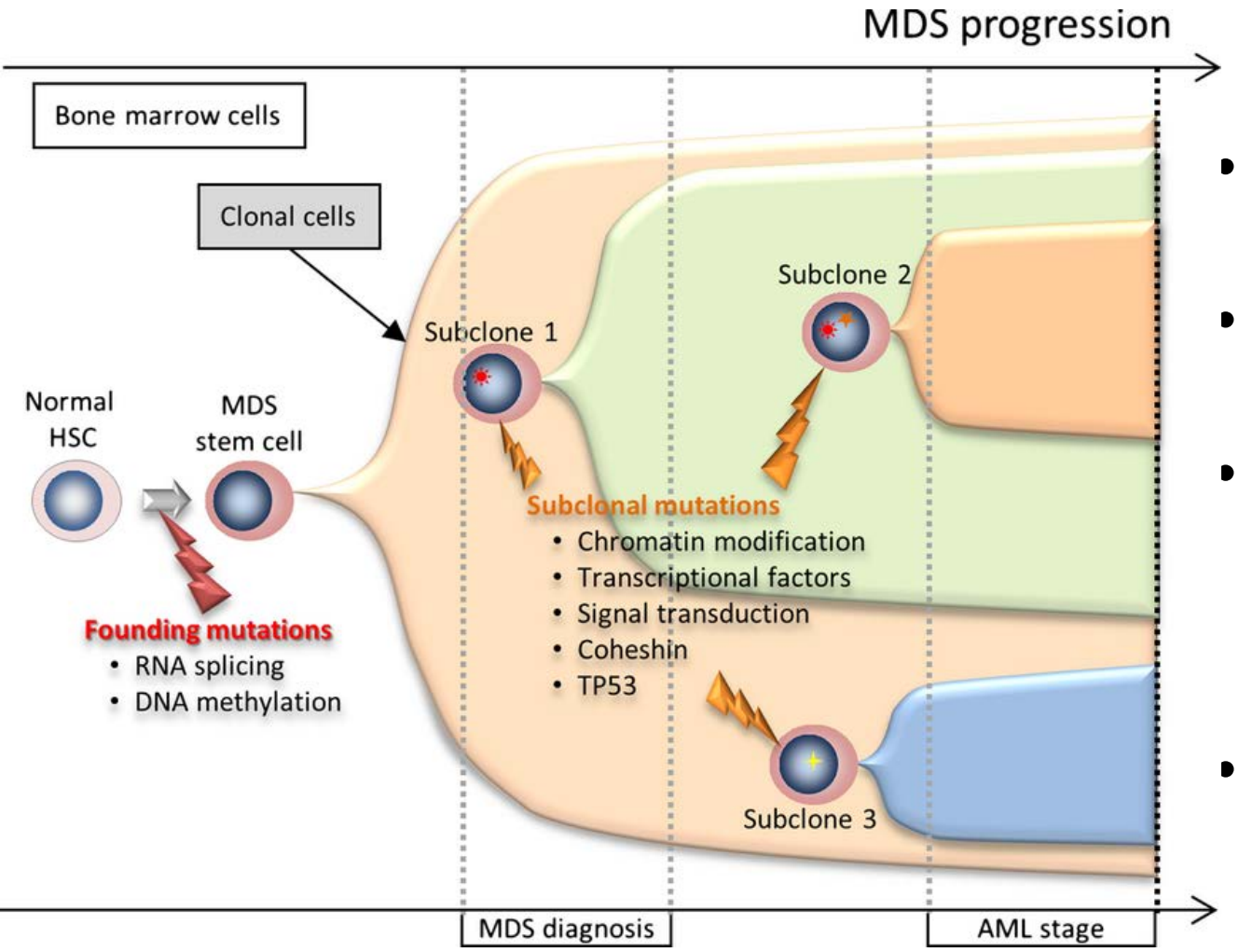
Pathogenesis of MDS is complex



Adapted from Amit Verma, MD

Sallman et al, Blood, 2019; Zhang TY et al, Sci TM, 2020 Carey et al, Cell Reports 2017

The Challenge in MDS is Genetic and Clinical Heterogeneity



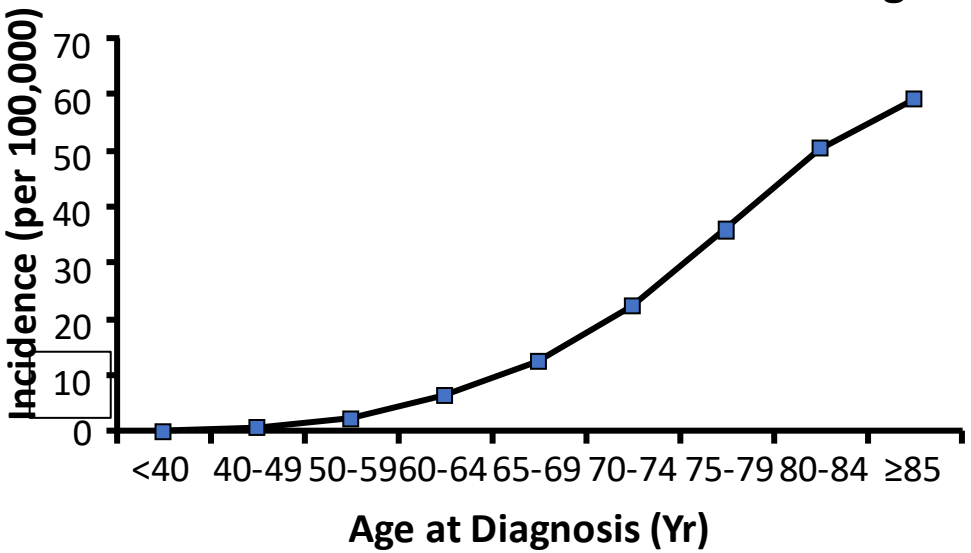
- Aberrant hematopoiesis causing BMF also keeps patients going
- NGS identifies relationships between gene mutations and clinical phenotypes
- Clonal evolution is common through course of disease
  - Founding mutations and subclonal mutations
- Few gain-of-function mutations in MDS→ less amenable to targeted inhibition

Cancer Sci. 2015 Apr;106(4):329-36.
N Engl J Med 2012;366:1090-1098

MDS Epidemiology

- **Overall incidence:** 3.7-4.8/100,000
- **In US:** ≈37,000-48,000
- **Median age:** 70 yr

Incidence Rates of MDS Increase With Age



More than 86% of patients were diagnosed at age ≥60 yr

Epidemiology of Hematologic and Nonhematologic Malignancies in the US (SEER Database, 2012-2018)	Incidence*	5-Yr OS (2012-2018), %
Hematologic malignancies		
Hodgkin's lymphoma	2.6	89.1
MDS	**4.0**	**36.9**
Myeloma	7.1	57.9
Leukemia	14.1	65.7
Non-Hodgkin's lymphoma	19.0	73.8
Selected nonhematologic malignancies		
Lung and bronchus	52.0	22.9
Colon and rectum	37.7	65.1
Breast	128.3	90.6

*Age-adjusted incidence rate per 100,000 men and women per yr between 2012 and 2108.

•Zeidan. Blood Rev. 2019;34:1. seer.cancer.gov/statistics-network. Ma. Am J Med. 2012;125:S2.

MDS Minimal Diagnostic Criteria

Prerequisite criteria: *both 1 and 2 must be fulfilled*

1. Persistent cytopenia(s)

- Hb <12 (women) or 13 (men) g/dL, *or*
- ANC <1800/µL, *or*
- Platelets <150 x 10^9/L

2. EXCLUDE other causes of cytopenias and morphological changes:

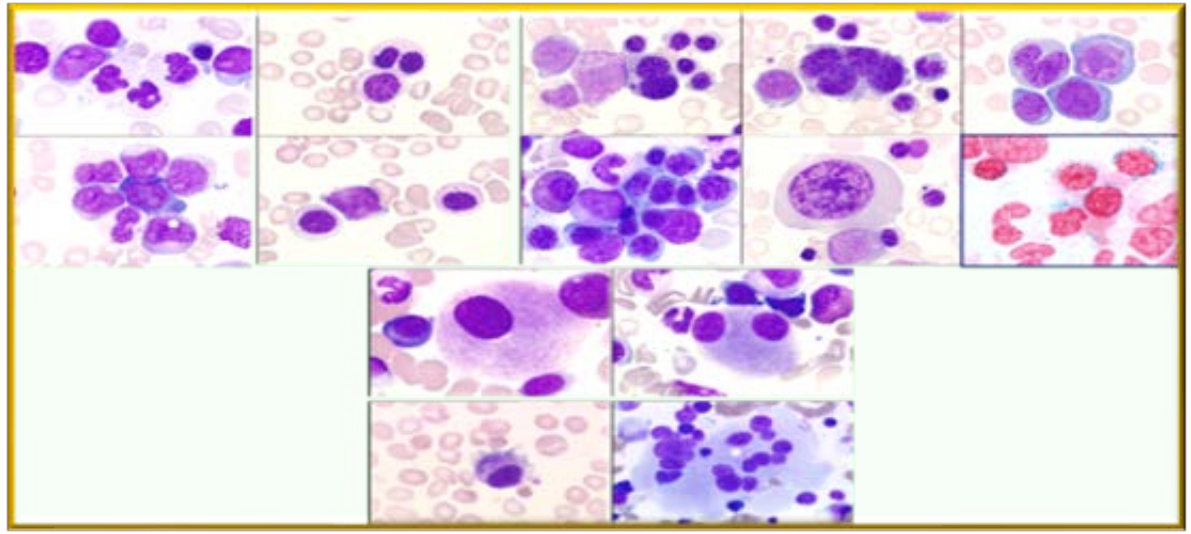
- Vitamin B12/folate/copper deficiency
- HIV or other infections
- Alcohol abuse
- Medications (esp. methotrexate, azathioprine, recent chemotherapy)
- Autoimmune conditions (RA, SLE, etc.)
- Hereditary BMF syndromes (Fanconi anemia, etc)
- Other hematological disorders (aplastic anemia, LGL MPN, etc)

+

MDS major criteria

i. Dysplasia of ≥10% of cells in 1 or more major BM lineage(s) (erythroid, neutrophilic, megakaryocytic) or an increase in RS of ≥15% (or ≥5% in the presence of a *SF3B1* mutation)
ii. An increase in myeloblasts of 5%-19% in dysplastic BM smears or 2%-19% myeloblasts in peripheral blood smears
iii. An MDS-related (5q-, -7, complex…) karyotype

At least 1 of these major MDS criteria has to be met (together with prerequisite criteria) to diagnose MDS



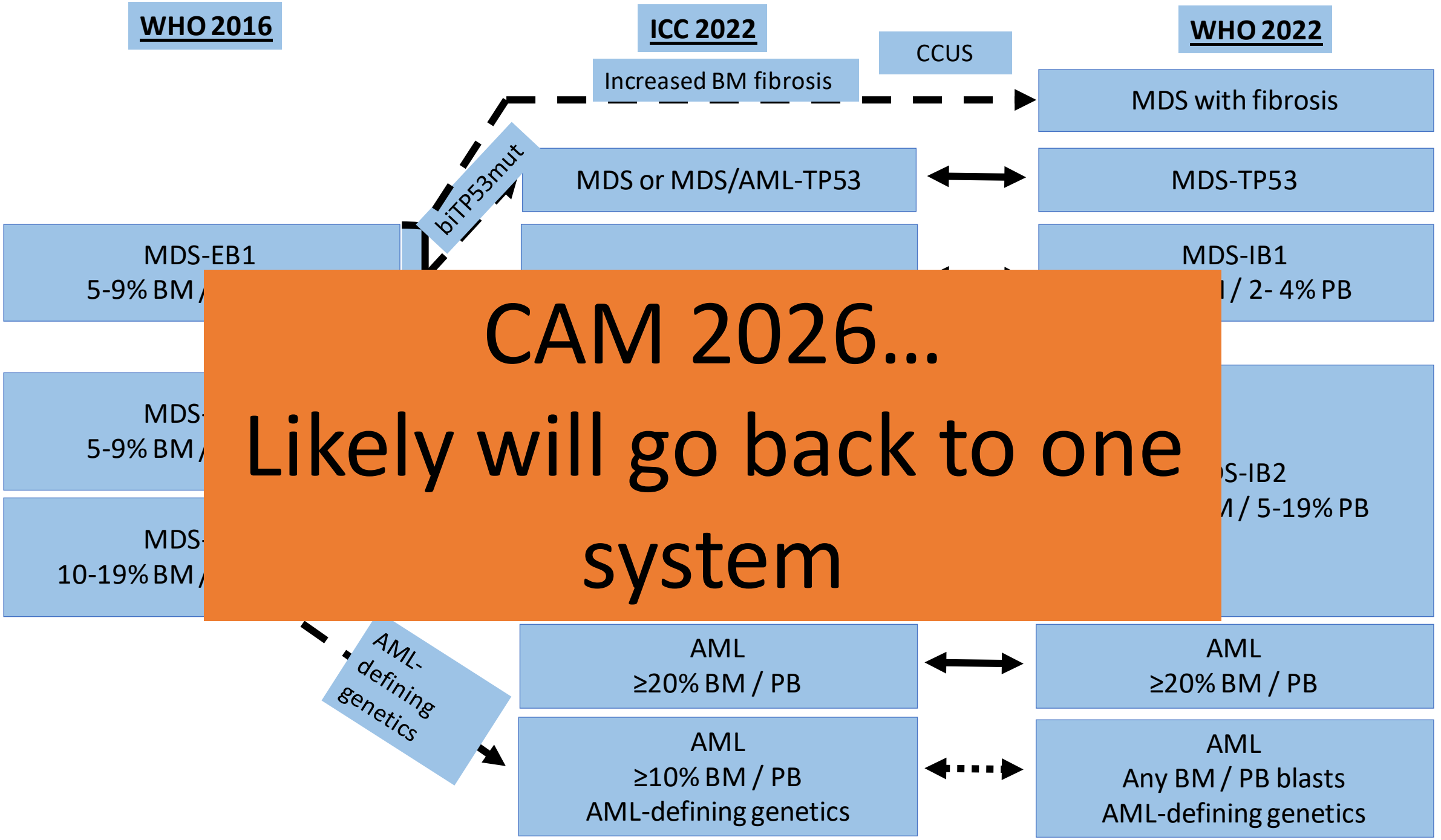
Valent P, et al. *Oncotarget*. 2017;8(43):73483-73500. Greenberg PL, et al. *J Natl Compr Canc Netw*. 2022;20(2):106-117.

Genetic Abnormalities in MDS

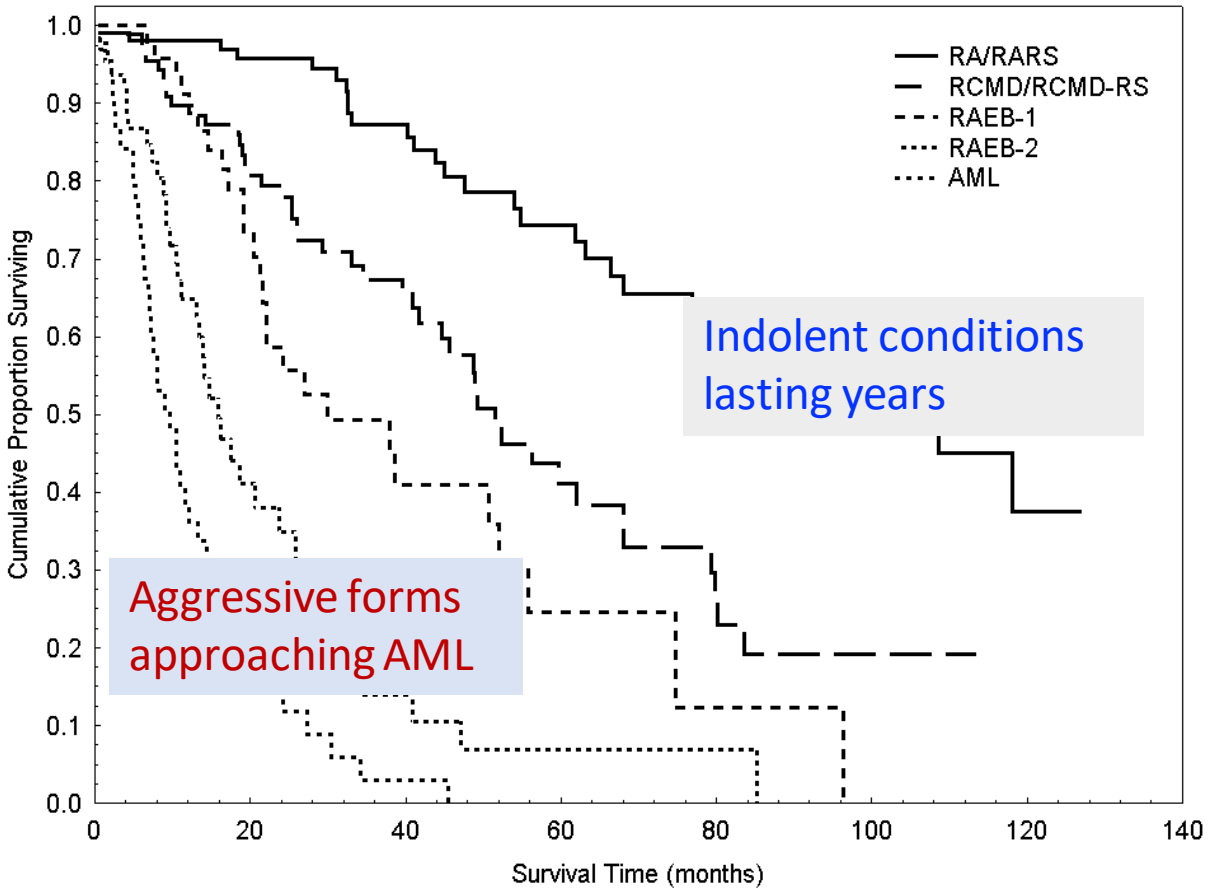
Translocations/ Rearrangements	Uniparental Disomy/ Microdeletions	Copy Number Change	Point Mutations
Rare in MDS	Rare; often at sites of point mutations	~50% of cases	Most common
t(6;9) i(17q) t(1;7) t(3;?) t(11;?) inv(3) idic(X)(q13)	4q - TET2 7q - EZH2 11q - CBL 17p - TP53	del(5q) -7/del(7q) del(20q) del(17p) del(11q) +8 -Y	Likely in all cases ~80% of cases have mutations in a known gene
Karyotype	**Array CGH SNP Array**	**Karyotype/FISH**	**Genotyping Sequencing**

Observed Frequency in MDS

Vardiman. Blood. 2009;114:937. Tiu. Blood. 2011;117:4552. Schanz. J Clin Oncol. 2011;29:1963.
Bejar. NEJM. 2011;364:2496. Bejar. J Clin Oncol. 2012;30:3376.


WHO 2016
ICC 2022
WHO 2022
CCUS
Increased BM fibrosis
MDS with fibrosis
biTP53mut
MDS or MDS/AML-TP53
MDS-TP53
MDS-EB1
5-9% BM /
MDS-IB1
/ 2- 4% PB
MDS-
5-9% BM /
S-IB2
/ 5-19% PB
MDS-
10-19% BM /
CAM 2026…
Likely will go back to one system
AML-defining genetics
AML
≥20% BM / PB
AML
≥20% BM / PB
AML
≥10% BM / PB
AML-defining genetics
AML
Any BM / PB blasts
AML-defining genetics

The Clinical Biology of MDS Can Vary Widely



Malcovati et al. J Clin Oncol. 2005 Oct 20;23(30):7594-603

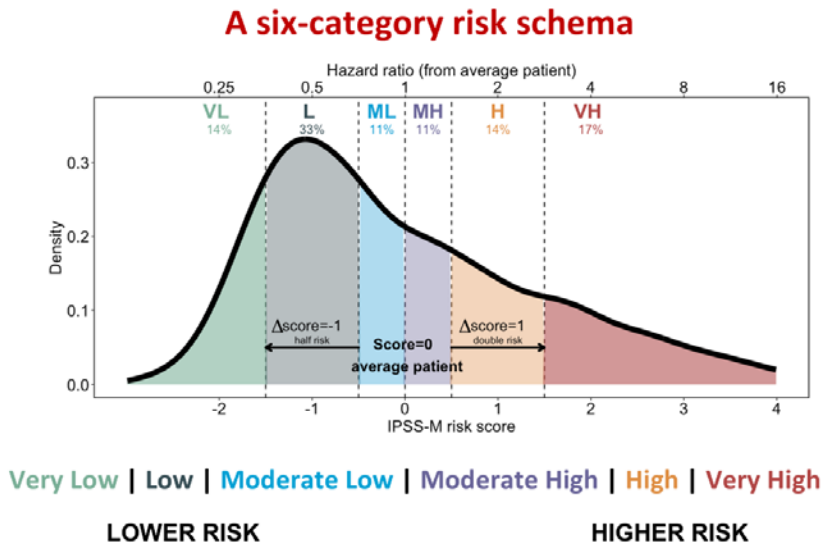
The IPSS-M Improves Risk Stratification over the IPSS-R!

- Retains the cytogenetic risk groups from the IPSS-R
- Clinical variables are continuous for greater accuracy
- 17 main genetic features and 15 residual aggregate features
- A score of 0 is median risk and +1 point is double the LFS-risk
- Valid with t-MDS, low blast AML, and in treated MDS patients

https://mds-risk-model.com/

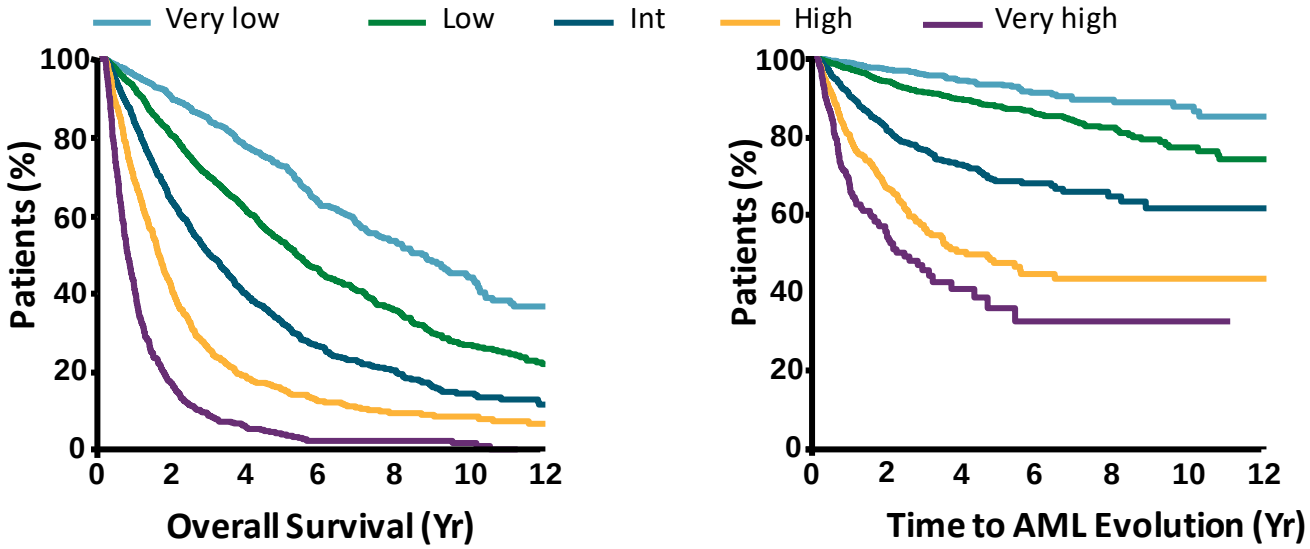
- BUT… we do not use it in trials fully due to caveats

The IPSS-M Risk Score



Risk Groups for the IPSS-R

Risk Group	Points	% of Patients	Median Survival, Yr	Time Until 25% of Patients Develop AML, Yr
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



Bejar. Haematologica. 2014;99:956.; Adapted from Greenberg PL, et al. Blood. 1997;89:2079.

Treatment

BMT is the path to cure for MDS…
Historically even HR MDS Patients Do Not Go to BMT

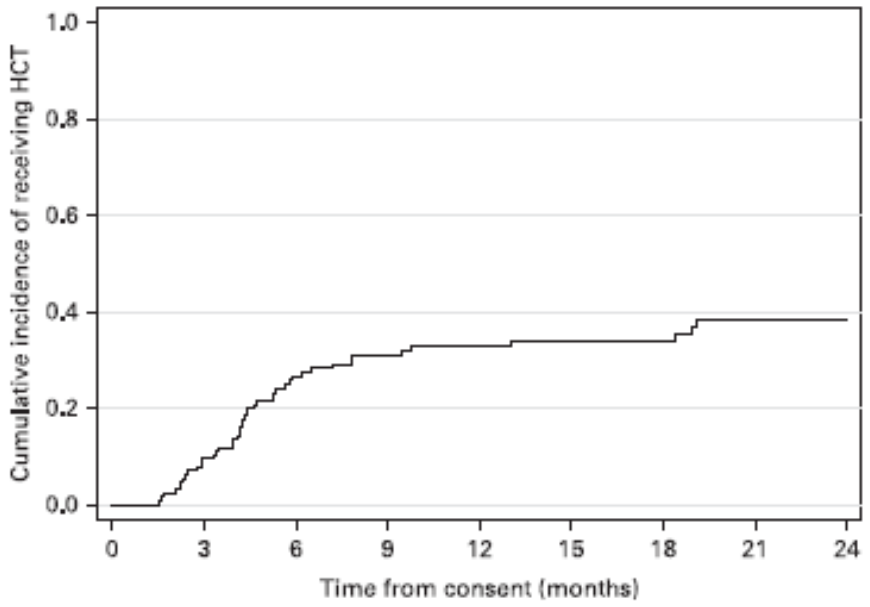


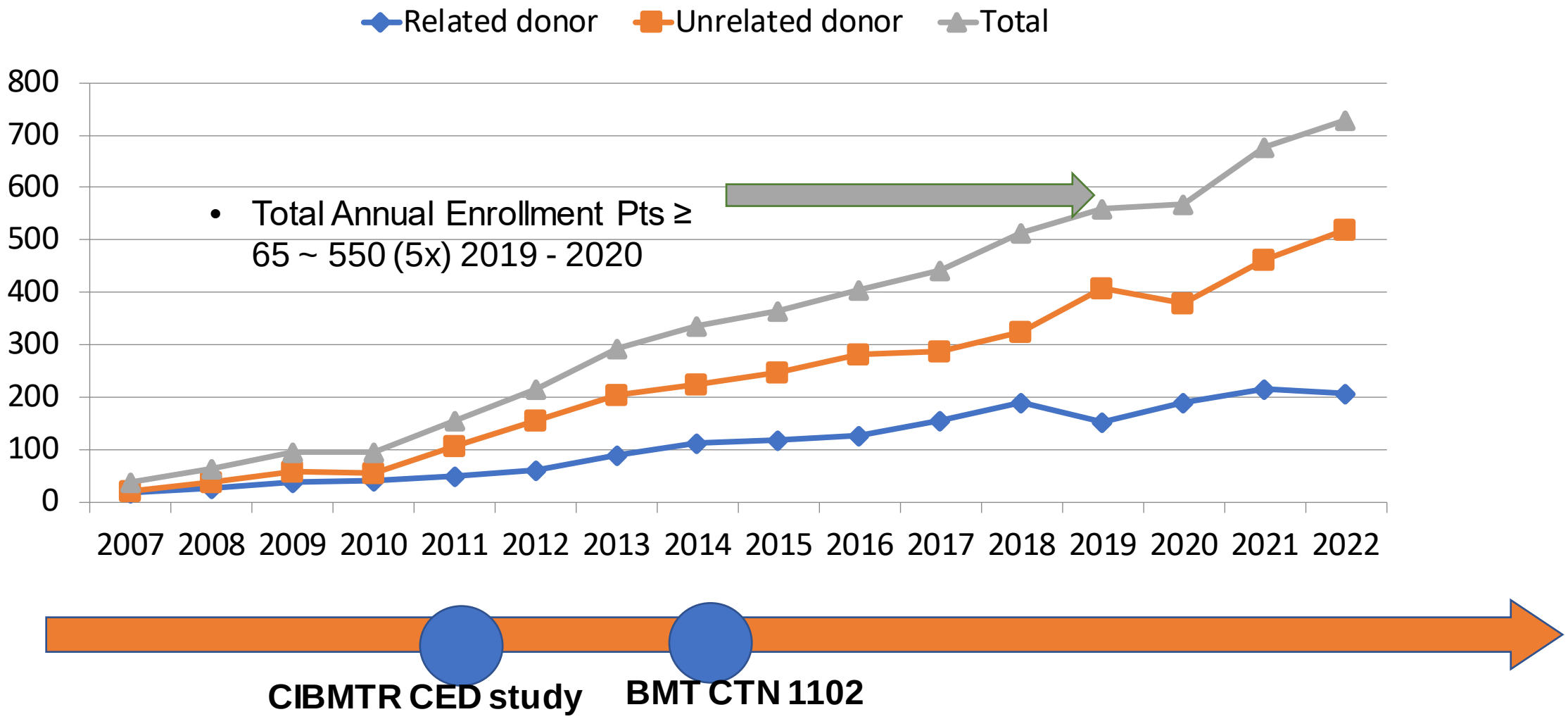
Figure 2. Cumulative incidence of receiving HCT, using a competing risk framework reflecting death without HCT as a competing event.

Factors to Consider

	Effect on non-HCT outcome	Effect on HCT outcome
High IPSS-R or Mol	+++	+
Therapy-related MDS	++++	++
Hypomethylating Failure	++++	+
Molecular Abnormalities >3	+++	++
High HCT-CI (>3)	++	++++
Low Karnofsky score (<80)	++	++++
Geriatric assessment	++	++++
HCT Prognostic Score	++	++++

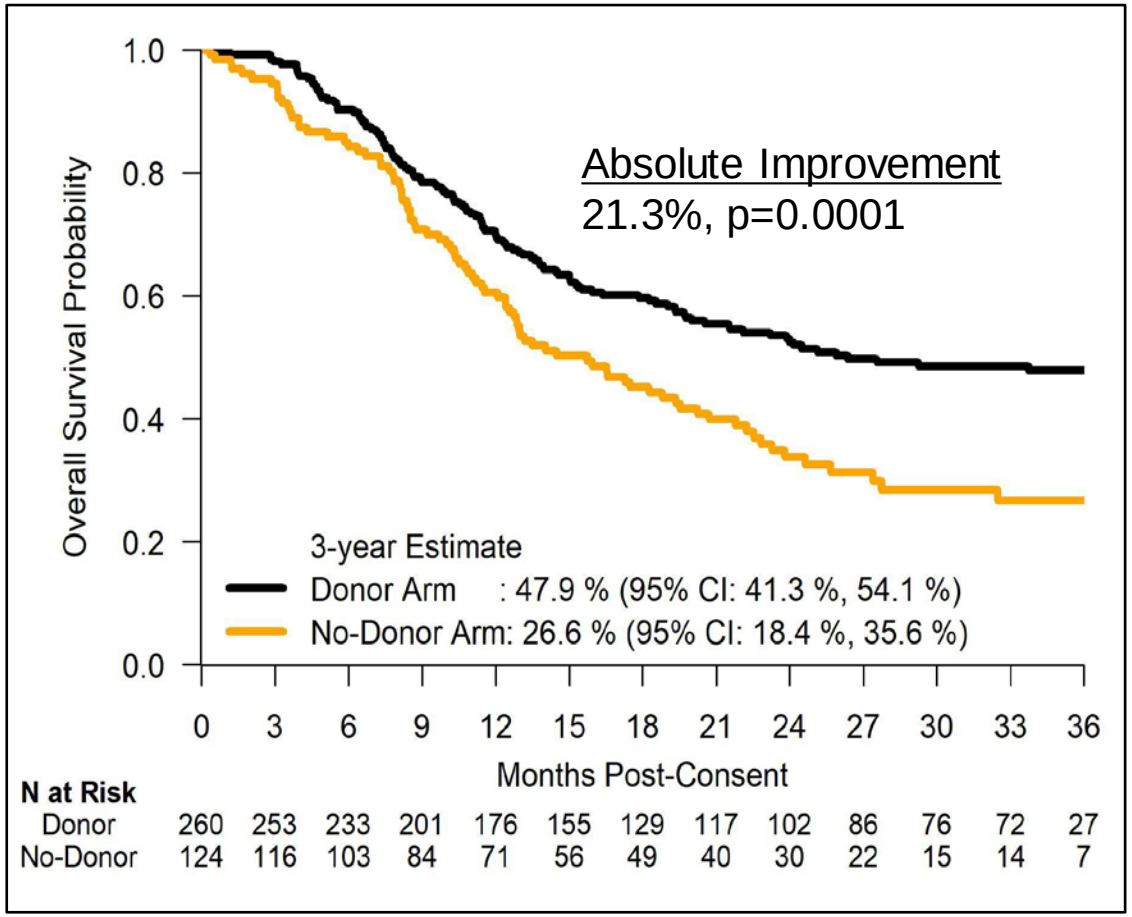
Transplantation trends in patients ≥65 years with MDS

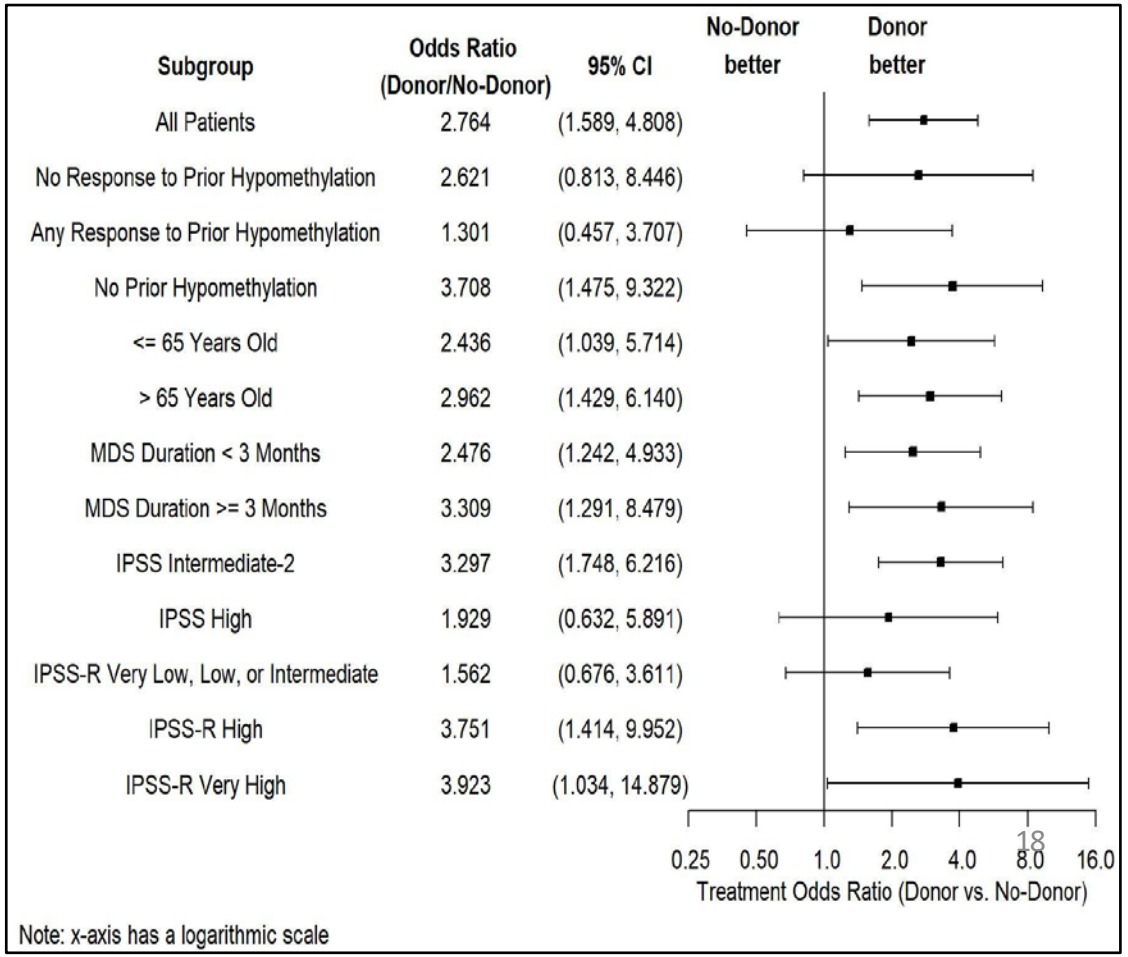
Figure Courtesy: Doug Rizzo, MD, MS



BMT CTN 1102 helped establish role in high-risk MDS

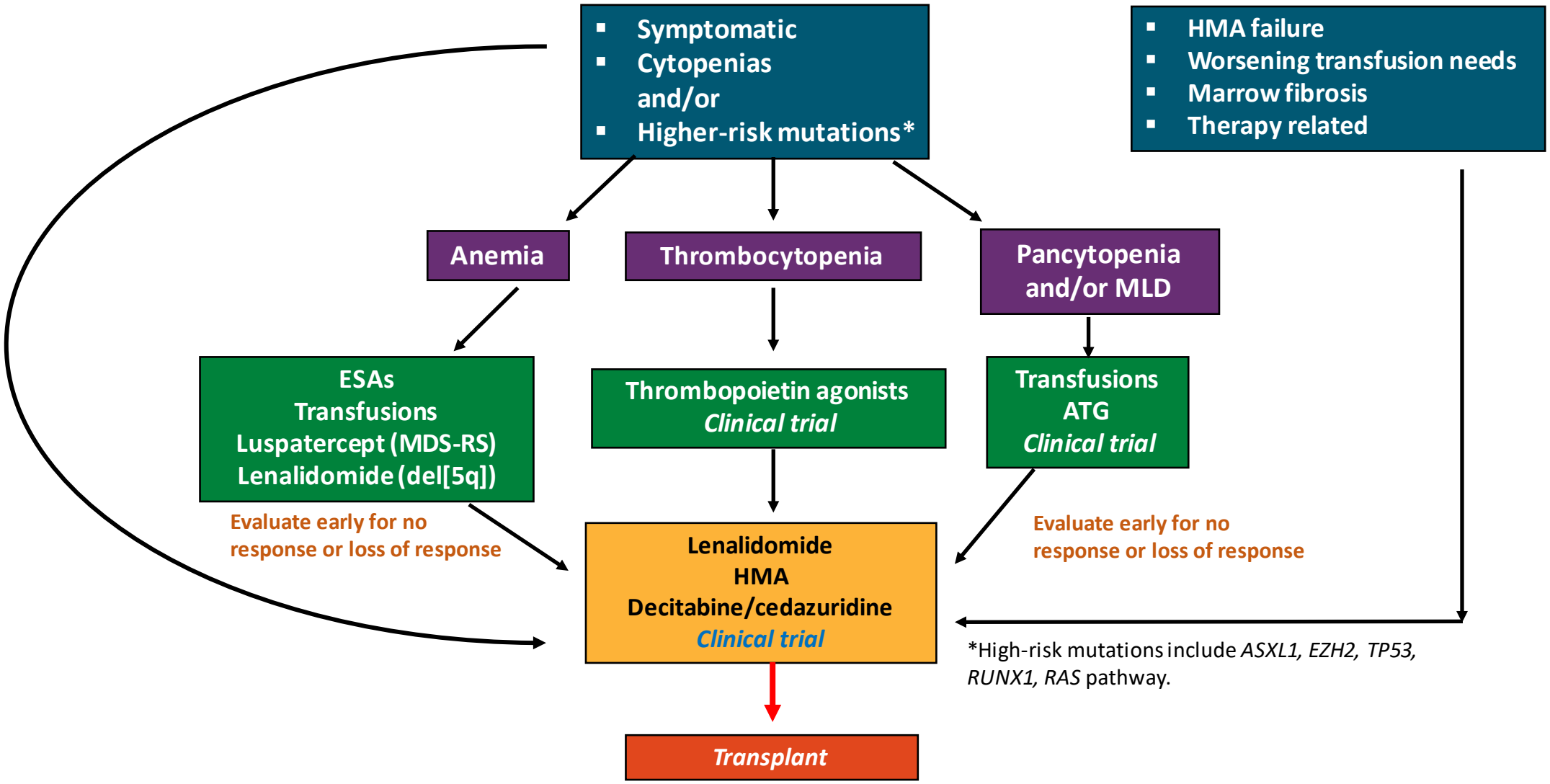
(and only positive trial in 2 decades in HR MDS)





Nakamura et al. J Clin Onc 2021

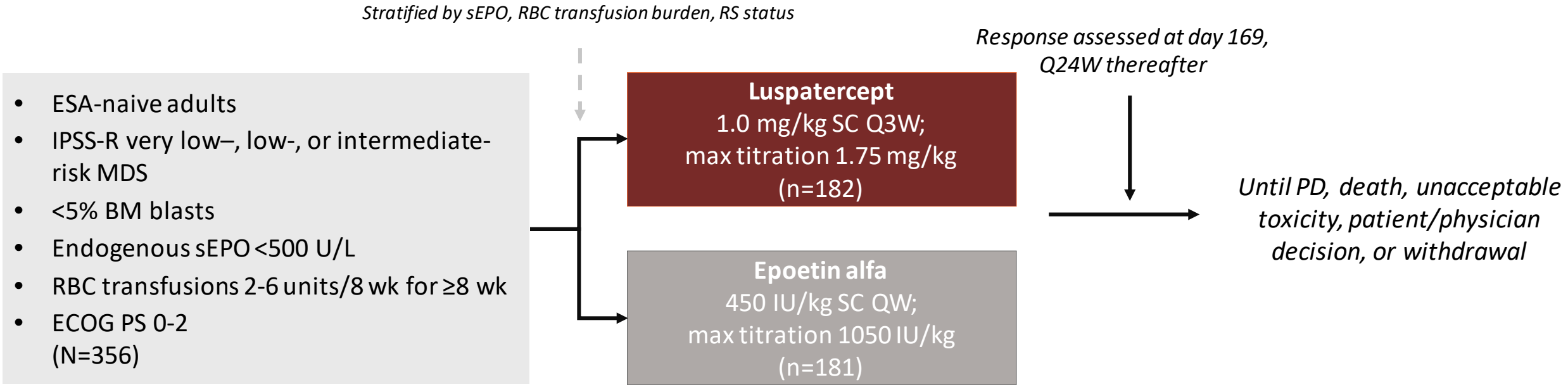
Lower-Risk MDS Treatment Paradigm Considerations



Jain. Biol Blood Marrow Transplant. 2020;26:e263.

COMMANDS Study Design: Luspatercept vs Epoetin Alfa in Frontline LR-MDS

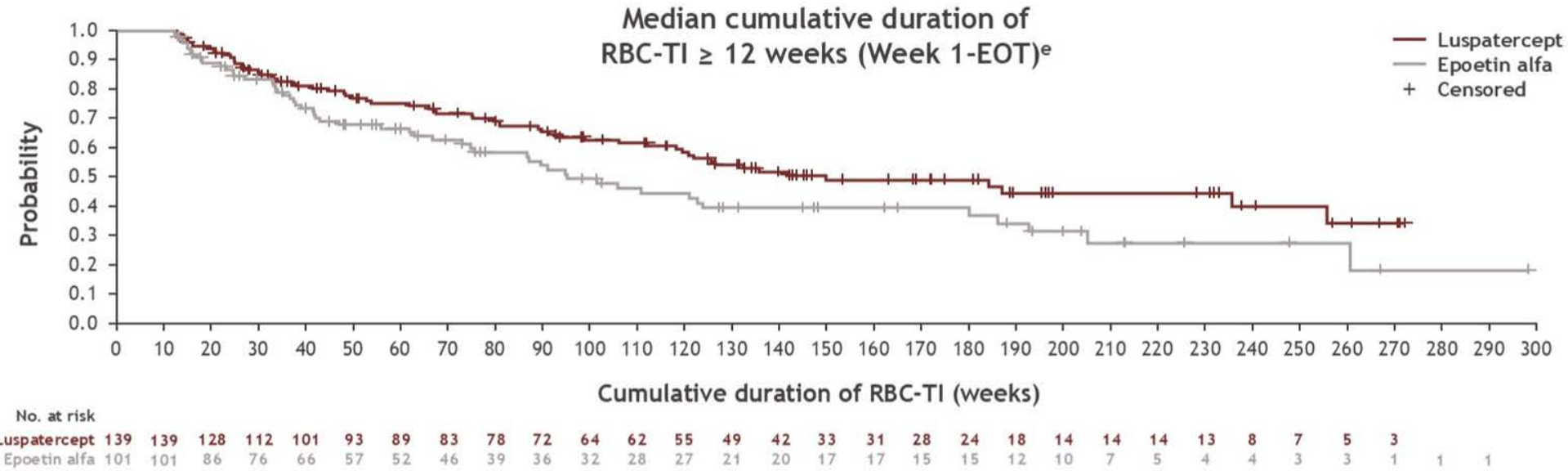
- Global, open-label, randomized phase 3 trial



- **Primary endpoint:** RBC-TI ≥12 weeks **with concurrent mean Hb** increase ≥1.5 g/dL
- **Key secondary endpoints:** HI-E ≥8 weeks per IWG criteria, RBC-TI for 24 weeks, RBC-TI ≥12 weeks, time to first RBC transfusion, safety

Della Porta MG, et al. *Lancet Haematol.* 2024;11(9):e646-e658.

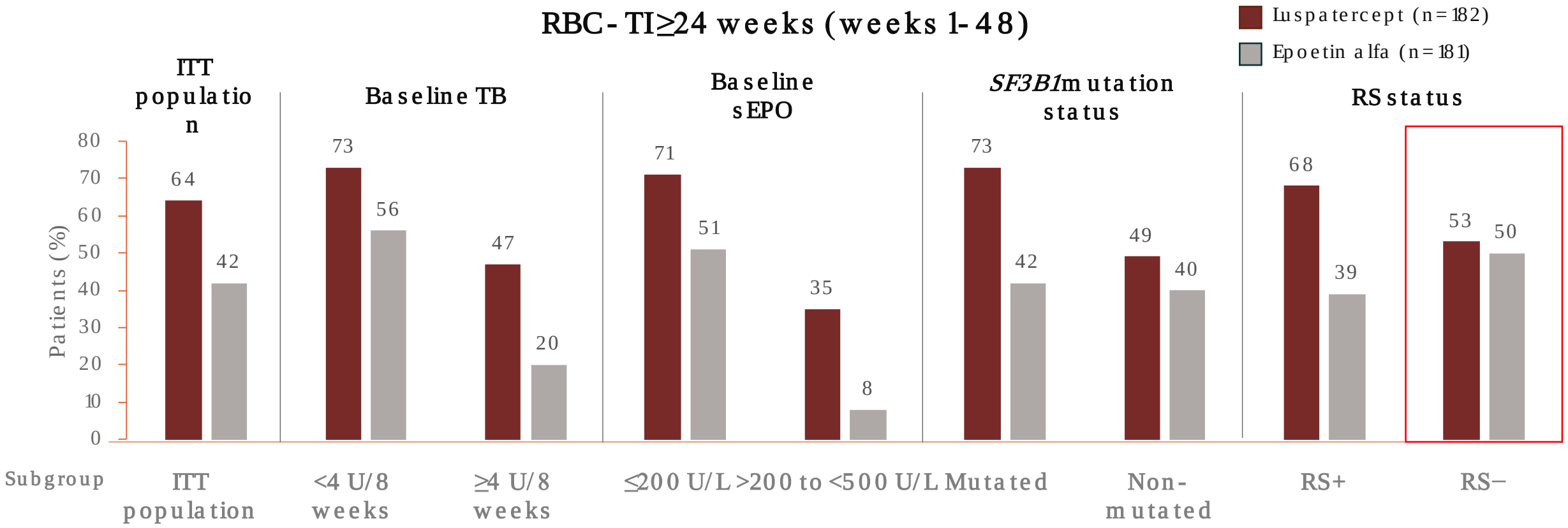
COMMANDS 2.5-year Follow-up: RBC-TI≥12 Wk



	Luspatercept	Epoetin alfa	OR[a]/HR[d] (95% CI)
RBC-TI ≥ 12 weeks (Week 1–EOT) response rate, % (n/N)	76.4 (139/182)	55.8 (101/181)	OR,[a] 2.8 (1.7–4.5) *P*< 0.0001
Median (95% CI) duration of longest RBC-TI ≥12-week period (Week 1–EOT),[b,c] weeks	126.6 (81.0–154.1)	86.7 (55.9–105.9)	HR,[d] 0.632 (0.434–0.919) *P*= 0.0156
Median (95% CI) cumulative duration of RBC-TI ≥12 weeks (Week 1–EOT),[c,e] weeks	150.0 (119.6–256.0)	95.1 (74.9–180.1)	HR,[d] 0.523 (0.353-0.777) *P*= 0.0011

Garcia-Manero G, et al. ASH 2024. Abstr 350.

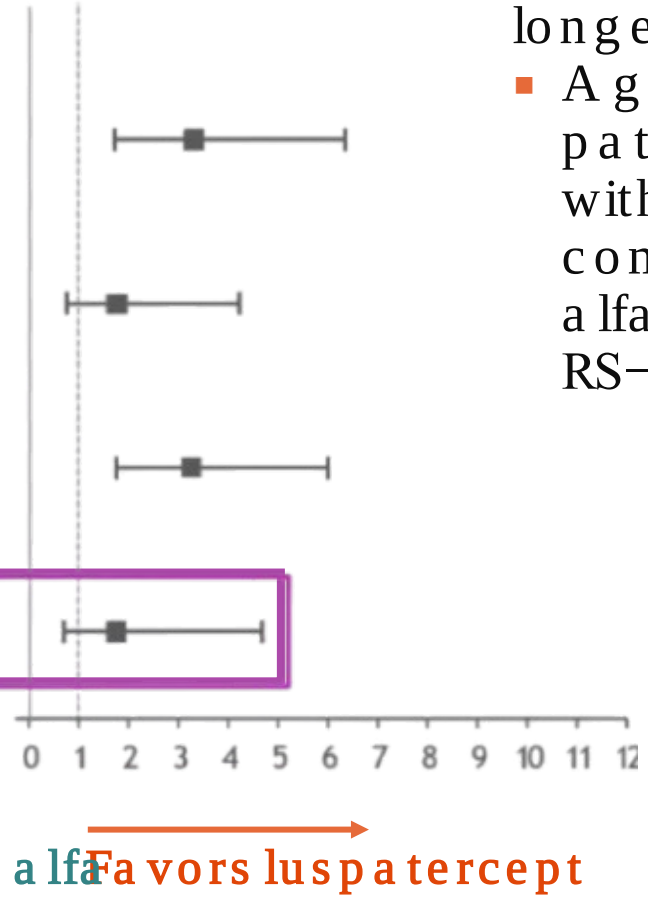
COMMANDS: RBC-TI≥24 Wk



Della Porta MG, et al. *Lancet Haematol.* 2024;11(9):e646-e658.

COMMANDS 21.4-month mF/u: Continuous RBC-TI ≥1.5 Years[a] Across Patient Subgroups

	Luspatercept n/N (%) [95% CI]	Epoetin alfa n/N (%) [95% CI]
***SF3B1* status**		
Mutated	41/114 (36%) [27.2-45.5]	15/101 (14.9%) [8.6-23.3]
Non-mutated	14/65 (21.5%) [12.3-33.5]	10/72 (13.9%) [6.9-24.1]
RS status		
RS+	43/133 (32.3%) [24.5-41]	17/130 (13.1%) [7.8-20.1]
RS−	12/49 (24.5%) [13.3-38.9]	8/50 (16%) [7.2-29.1]



Of patients who had RBC-TI for 1.5 years or longer:

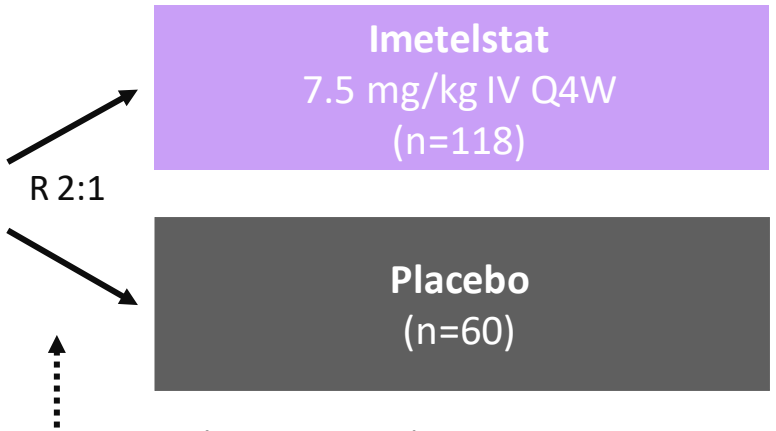
- A greater proportion of patients achieved this with luspatercept compared with epoetin alfa, including among RS− patients

Garcia-Manero G, et al. ASH 2024. Abstr 350.

IMerge: Imetelstat vs Placebo for TD LR-MDS Relapsed/Refractory to ESAs[1,2]

- International, double-blind, randomized phase 3 trial

- Patients with IPSS-R low-risk or intermediate-1–risk non-del(5q) MDS
- R/R to ESA or EPO >500 mU/mL (ESA ineligible)
- RBC transfusion dependent **(≥4 U/8 weeks over 16 weeks before study)**
- No prior lenalidomide or HMAs



Stratified by transfusion burden (4-6 U vs >6 U) and IPSS-R category (low vs intermediate-1)

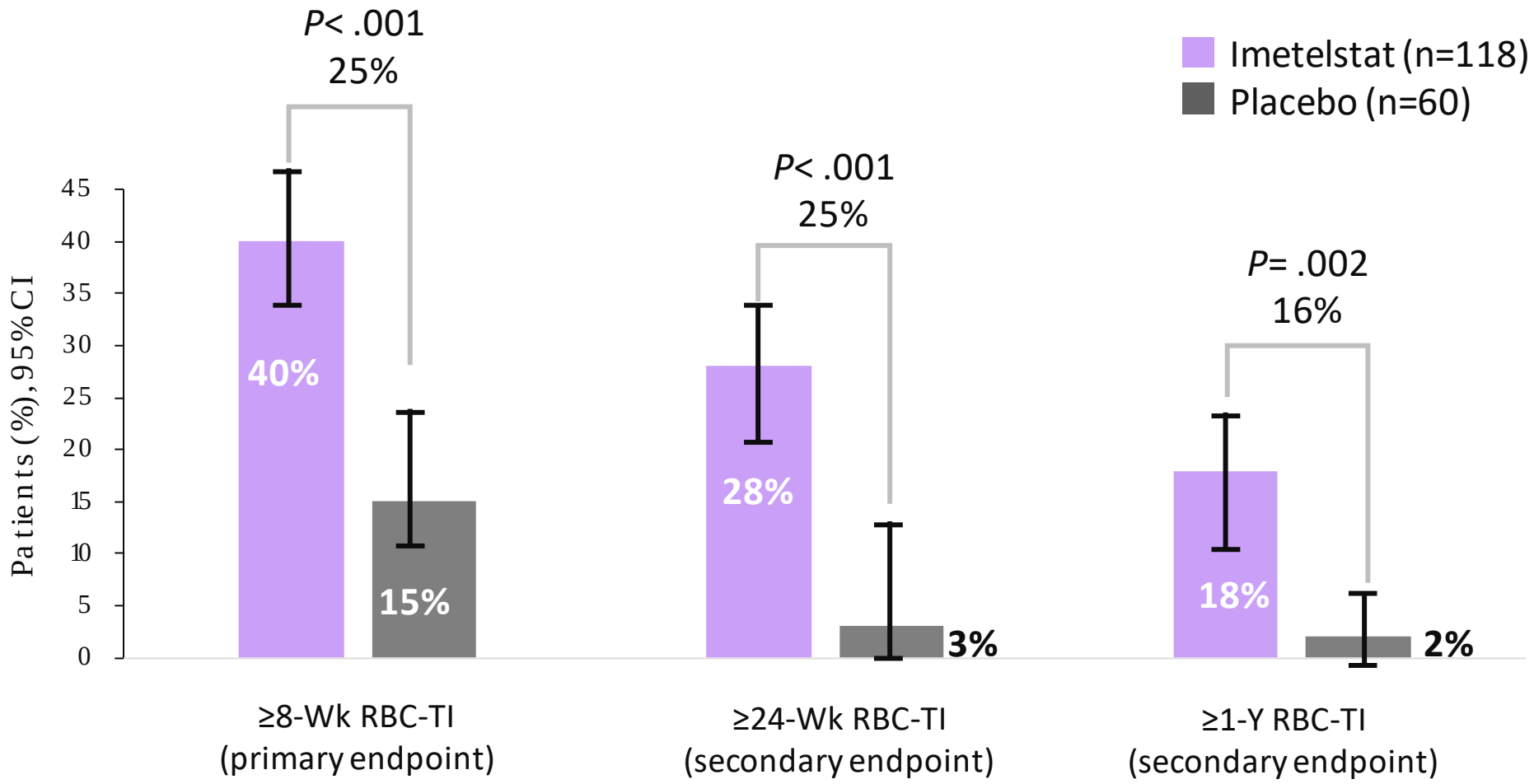
Supportive care
RBC and platelet transfusions, myeloid growth factors (eg, G-CSF), and iron chelation therapy as needed at discretion of investigator

Median age was ≈72 years, 62% had ring sideroblasts, ≈90% had received prior ESA, and <10% had received previous luspatercept

Primary endpoint: 8-week RBC-TI
Secondary endpoints: 24-week RBC-TI, TI duration, HI-E, safety

Subgroup analysis: rates of RBC-TI for imetelstat vs placebo in absence of platelet transfusion or myeloid growth factors

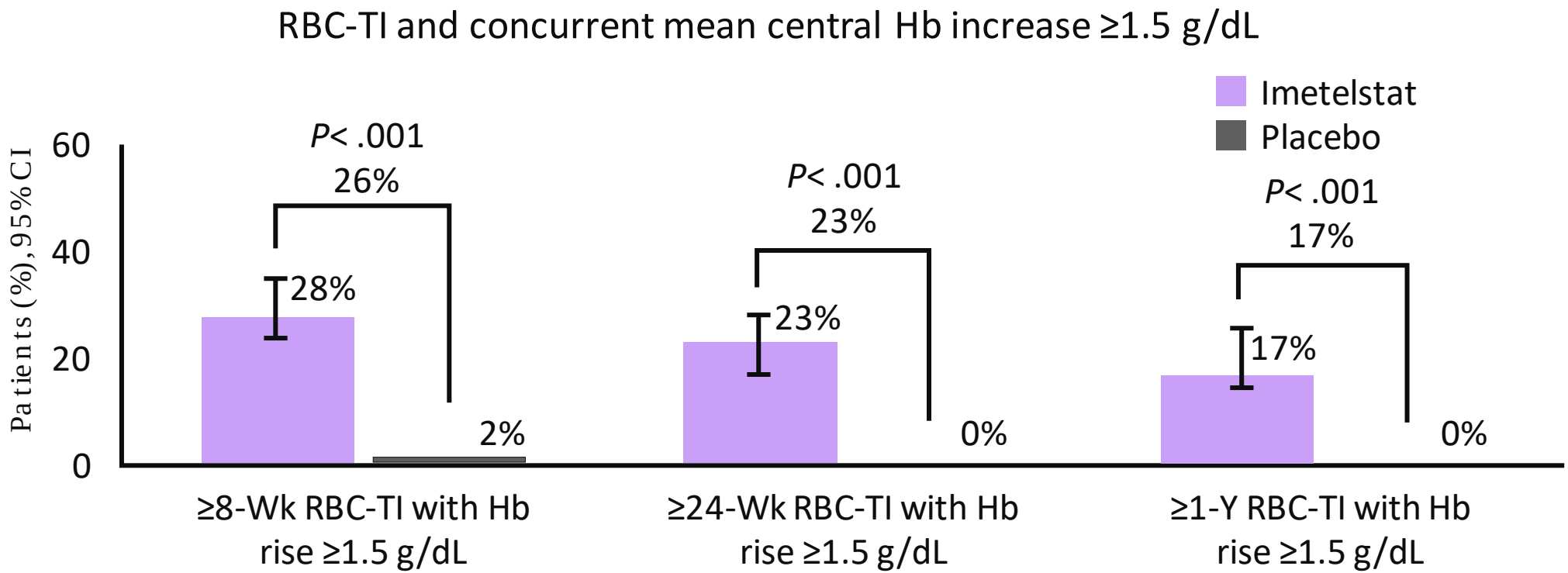
IMerge: Overall RBC-TI



- Among imetelstat responders, RBC-TI could last for extended durations, >1y

Zeidan AM, et al. ASCO 2024. Abstr 6566.

IMerge: Duration of RBC-TI and Concurrent Hb Increase ≥1.5 g/dL



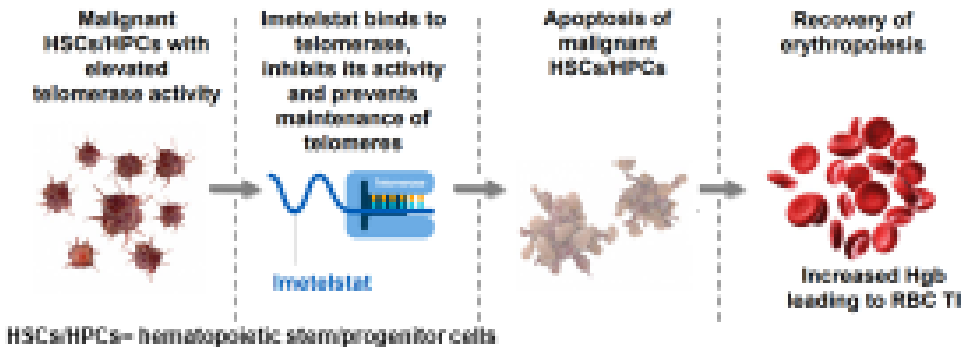
- A greater number of imetelstat-treated patients achieved ≥8-week, ≥24-week, and ≥1-year RBC-TI and concomitant Hb increase of ≥1.5 g/dL

Hb, hemoglobin; RBC-TI, red blood cell transfusion independence.

Zeidan AM, et al. ASCO 2024. Abstr 6566.

Imetelstat: Latest Addition to the Therapeutic Landscape of Lower-Risk Myelodysplastic Syndromes (MDS)

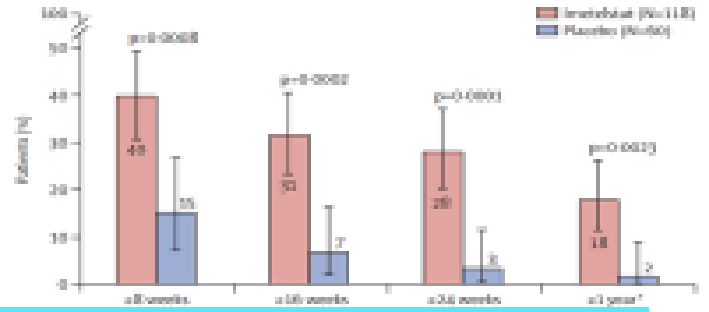
Mechanism of Action:



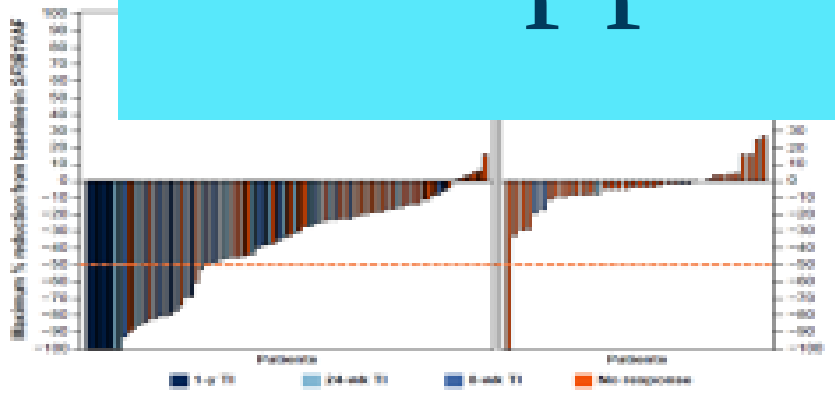
HSCs/HPCs= hematopoietic stem/progenitor cells

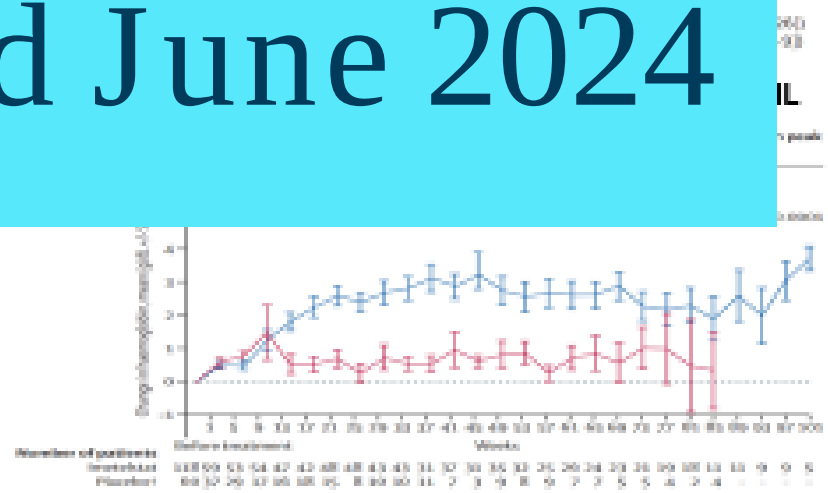
Clinical efficacy:

- Durable 8-week RBC-TI achieved with imetelstat vs placebo



Disease Modi
mutated gene



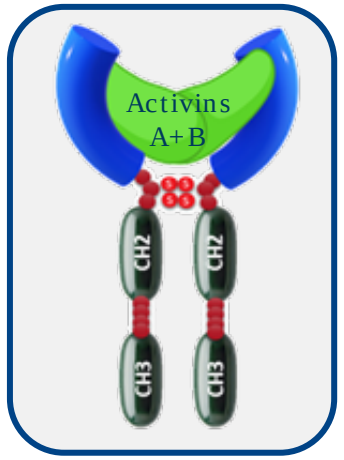


FDAapproved June 2024

Conclusions: Imetelstat has been demonstrated to induce transfusion independence and a significant improvement in Hb level in patients with non-del(5q) lower-risk MDS and transfusion-dependent anemia who have failed or are ineligible for erythropoiesis-stimulating agents.

Abaza & DeZern. DOI: 10.xxxx/blood.2024xxxxxx

KER-050 (elritercept) is Designed to Target Bone Marrow Disorders of Ineffective Hematopoiesis Including MDS



KER-050 (elritercept)

- Designed to inhibit select TGF-beta ligands, including Activin A, which has bee
  ineffective her
  disease patho
  progression[1,2]

- Preclinical data showed that **KER-050 (elritercept) acts on early and late stages of hematopoiesis**, supporting a differentiated MOA[3]

PHASE 3 in 2025-6

potential to:

range of patients with lower-

l benefit beyond improving
s (Chee, et al. ASH 2023 Poster
#1089)

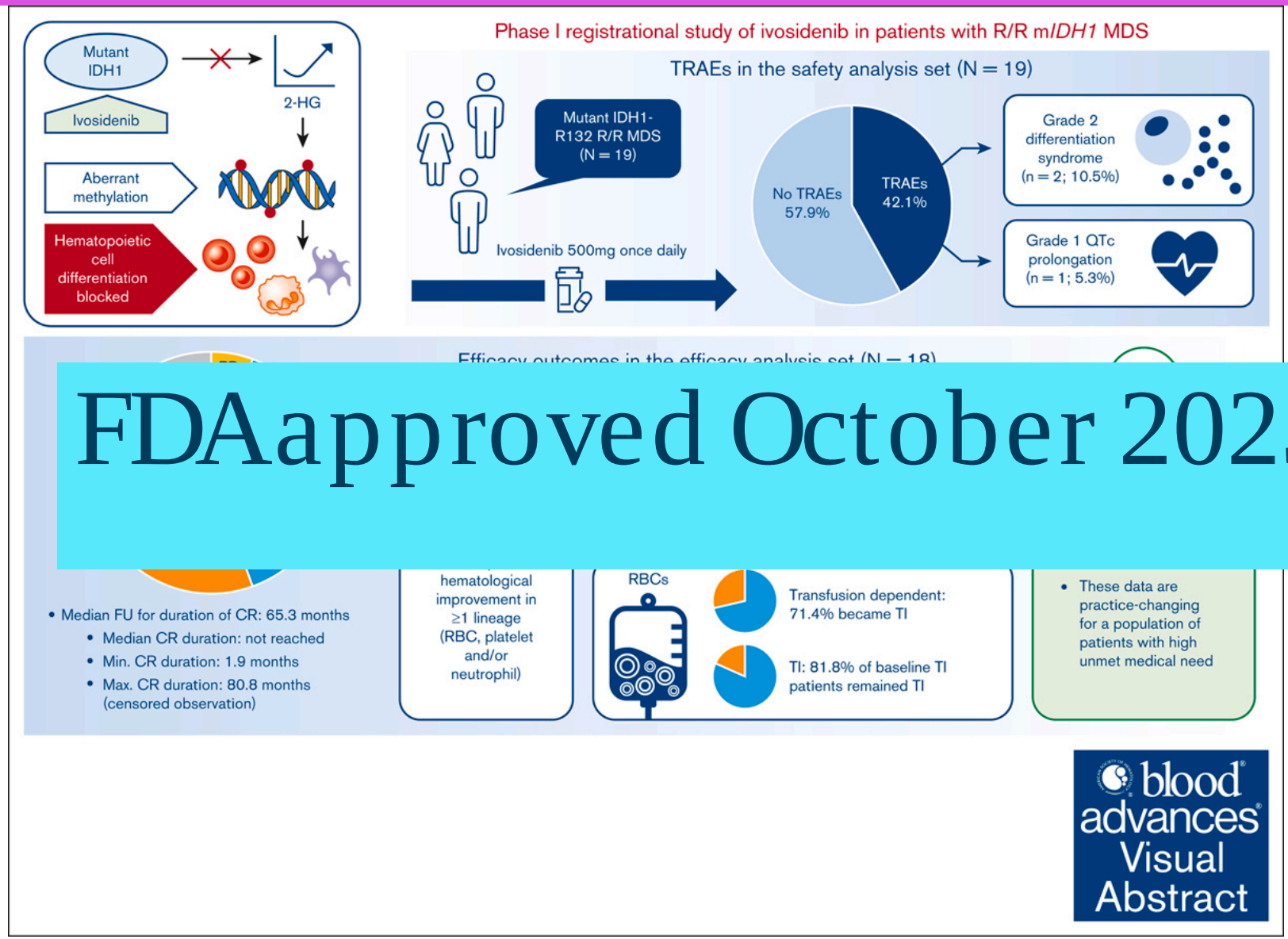
Domain	E
Erythropoiesis	ALL stages of d maturation
Thrombopoiesis	ALL stages of differentiation and maturation
Bone	Increased bone formation
Iron Metabolism	Improved iron utilization

Preliminary results available from an ongoing open-label Phase 2 trial evaluating KER-050 (elritercept) in participants with LR-MDS

[1]Verma A, et al. J Clin Inv 2020; [2]Portale F, et al., Haematologica. 2019; [3]Feigenson, Met al. European Hematology Association. 2021

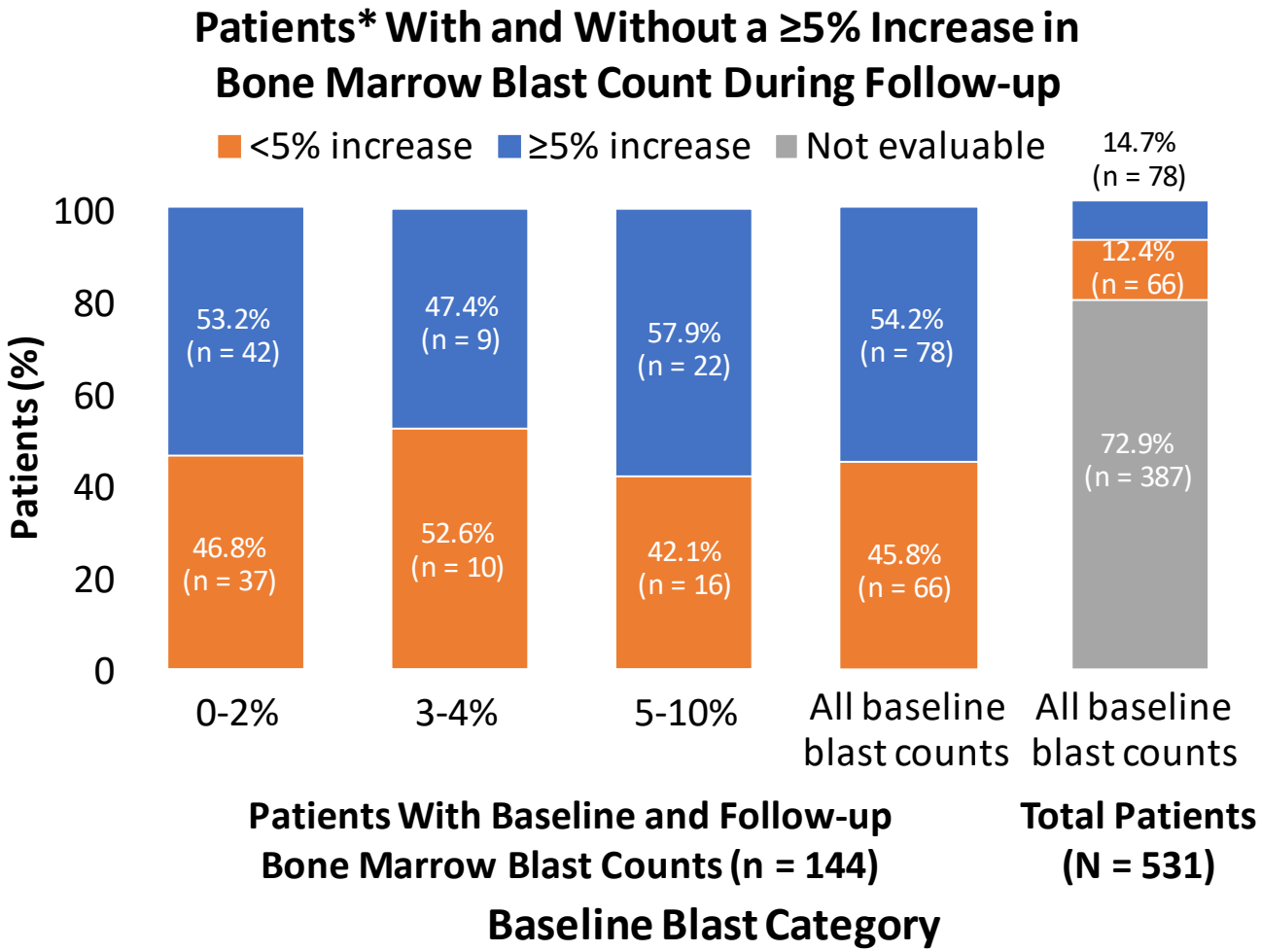
EMA = erythroid maturation agents; ESA = erythropoiesis stimulating agents; LR-MDS = lower-risk myelodysplastic syndrome; MOA =

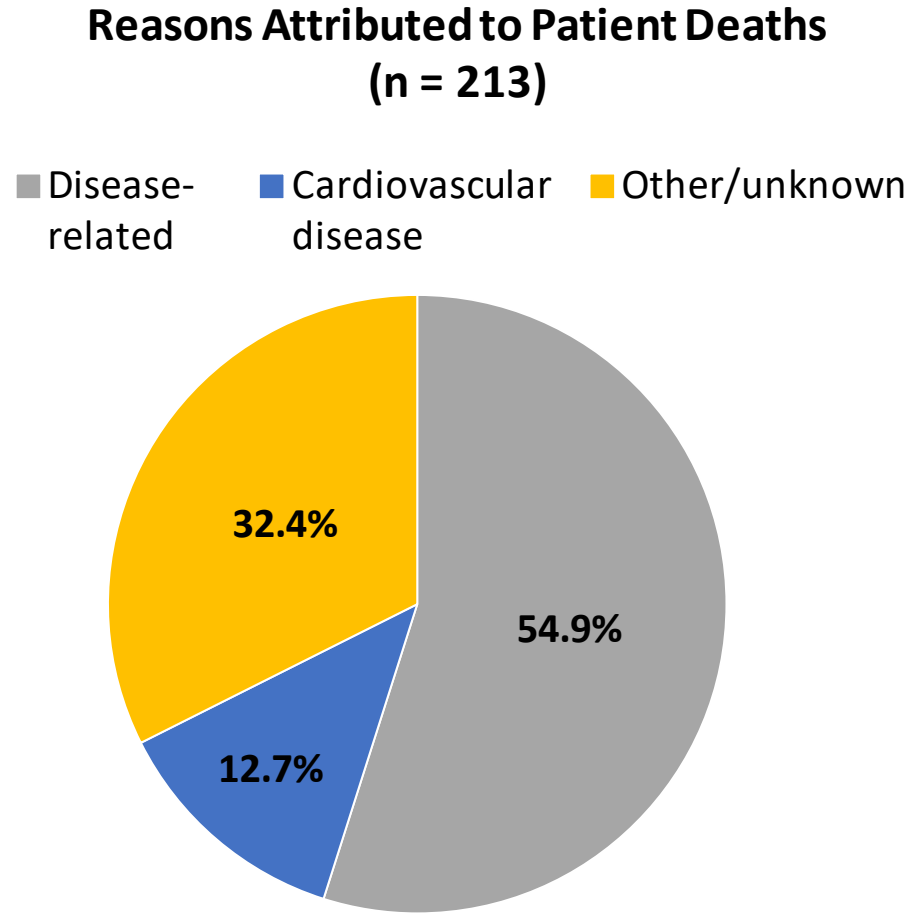
Ivosidenib for mIDH1 relapsed/refractory MDS



FDAapproved October 2023

Treatment Patterns in LR-MDS: Disease Progression and Causes of Death



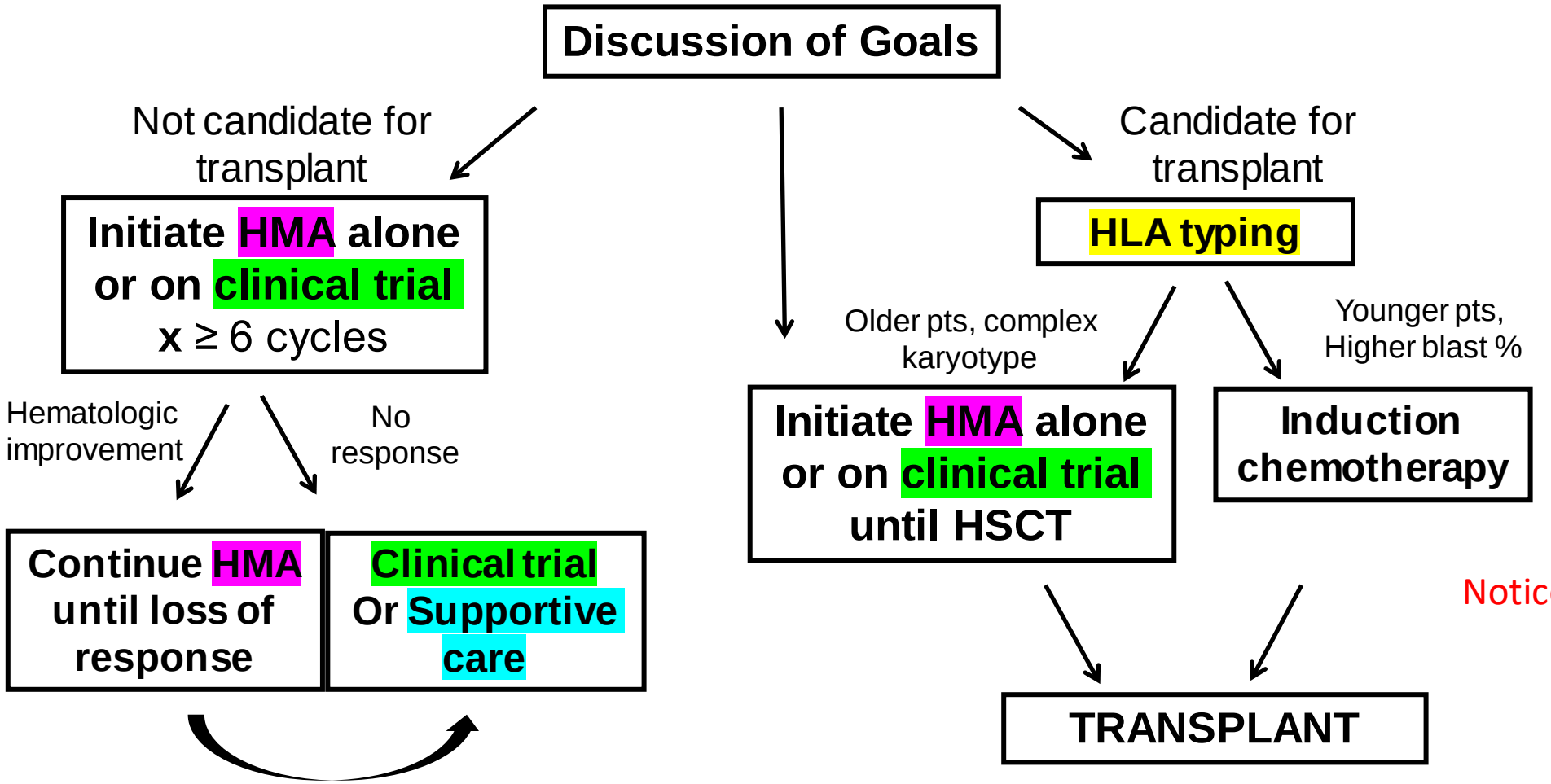


*409 patients (77.0%) had only a baseline bone marrow blast count; 144 patients (27.1%) had both baseline and follow-up bone marrow blast counts.

Komrokji. ASH 2021. Abstr 3686.

Higher-Risk MDS [IPSS-R score ≥4.5; IPSS-M score > 0]

Treatment Paradigm - 2026



Notice VEN is not here

Current Issues in the Treatment of HR-MDS

- Hypomethylating agents only moderately improve survival (~18 months)
- Prognosis after HMA failure is poor (<6 months)
- Patients with complex karyotype/ unfavorable molecular genetics have very poor outcomes (even with BMT)
- No animal models
- We do not understand how to improve NORMAL hematopoiesis
- ***STILL TOO FEW THERAPIES***

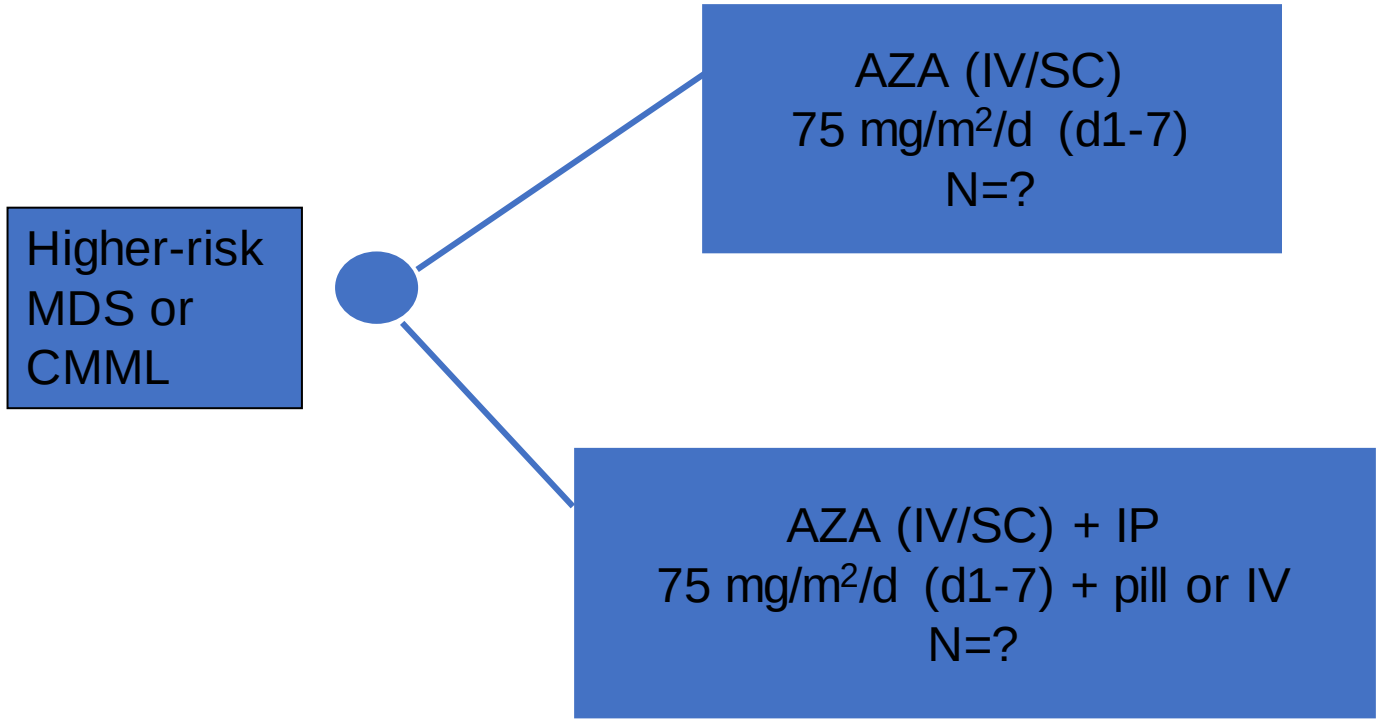
Hypomethylating agents (HMAs) = DNMT-inh have been mainstay of therapy for decades

We are not really making great strides to date…

- AZA = azacitidine = 5-azacytidine= Vidaza
  - IV, SQ (oral aza is Onureg NOT for MDS)

- DEC = DAC = decitabine – Dacogen and Inqovi
  - IV (SQ), oral

Phase 3 CLINICAL TRIALS in Higher RISK MDS

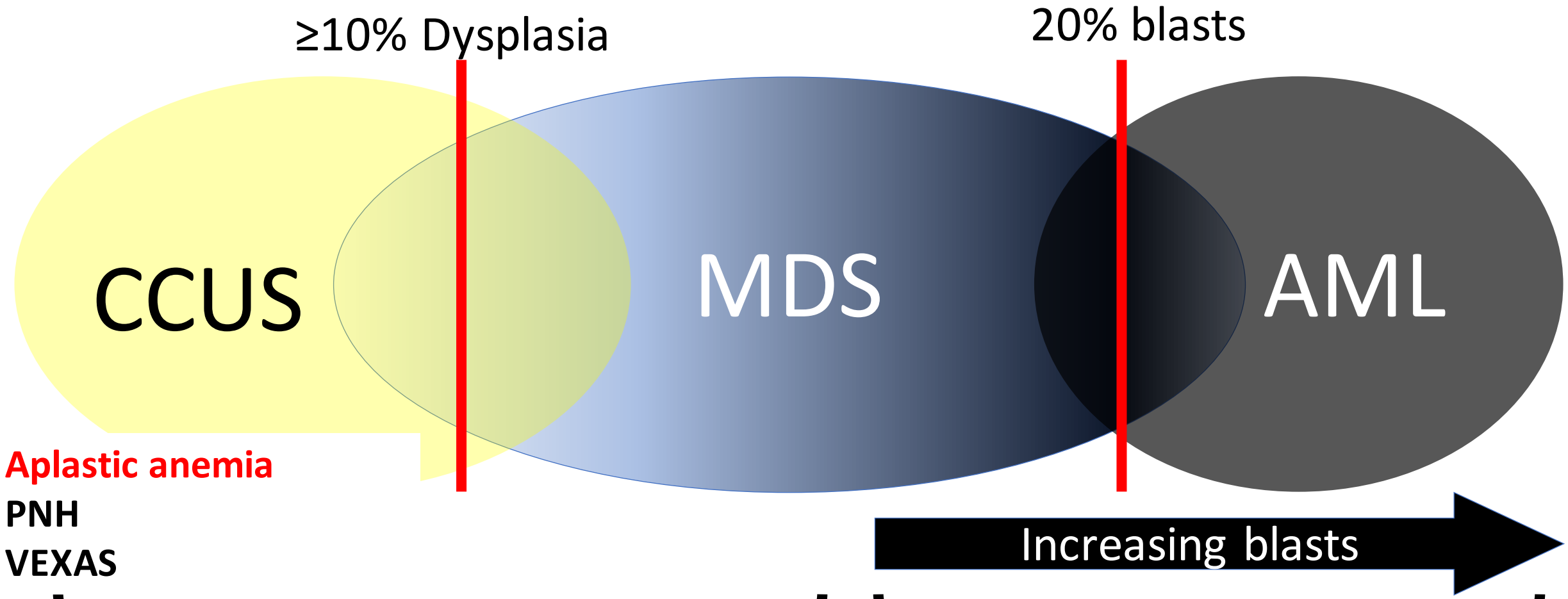


Recent P3 trials in HR MDS

	Pevonedistat NEDD8 inhibitor	Eprenepopt TP53	Sabatolimab TIM3 Inhibitor	Magrolimab CD47mAb	Venetoclax Bcl2-inhibitor	Syros SY-1425 selective RARα agonist= Tamibarotene
Phase progress	III	III	Phase III completed accrual	Phase III completed accrual	Phase III completed	Phase III ongoing
Population						
Planned "n"						
Randomization						
Dosing of IP (with SOC AZA)	IV q4 weeks	IV q2 weeks	IV q4 weeks	C1:D1,4,8,11,15, 22 C2: D1, 8, 15, 22 ≥C3 Q2W	Oral D1-14	Oral D8-28
Endpoint	SO	OS	OS	CR and OS	CR and OS	CR and OS
Trial published	Sekeres et al BA 2024	Sallman et al pending	Zeidan et al LH 2024	Sallman et al pending	Garcia et al pending	DeZern et al BA 2025

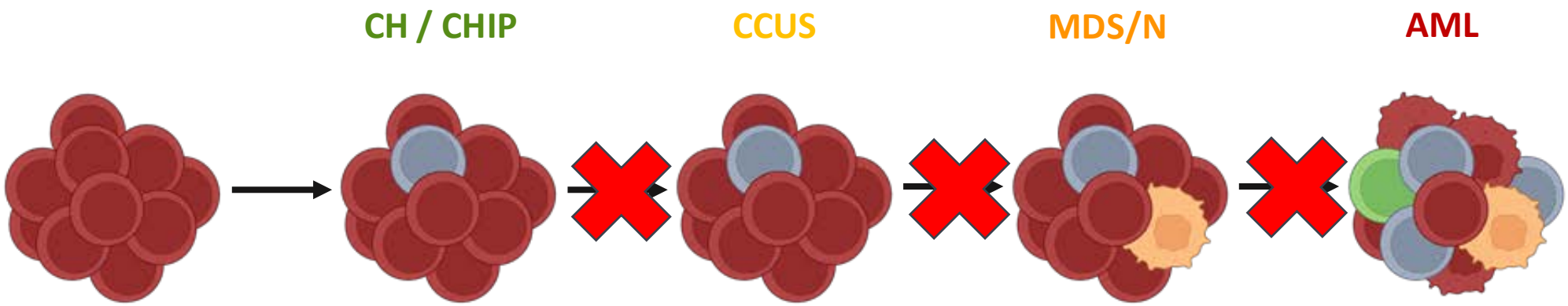
What else/ what next?!?

The borders of MDS



MDS but not… CH! CHIP! CCUS!

Goal: Prevent myeloid-related morbidity and mortality



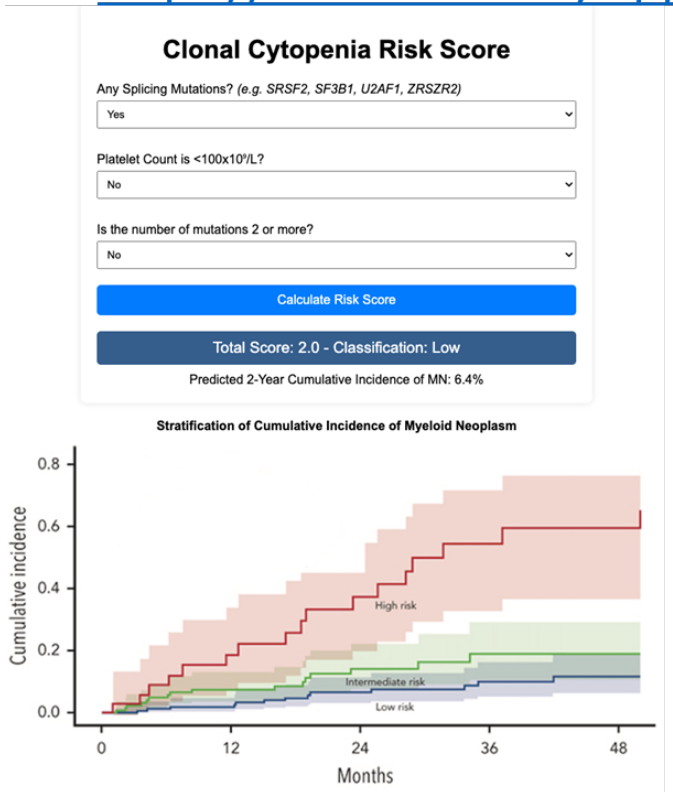
	Healthy / "Normal"	Clonal Hematopoiesis	Clonal Cytopenias	Myelodysplastic Syndromes	Acute Myeloid Leukemia
Mutation	No	**Yes**	**Yes**	**Yes**	**Yes**
Cytopenia	No	No	**Yes**	**Yes**	**Yes**
Dysplasia	No	No	No	**Yes**	**Yes**
Blasts	< 5%	< 5%	< 5%	< 5 – 19%	**> 20%**
5-yr survival	**88%**	**< 88%**	**62%**	**38%** (≥65y 35%)	**32%** (≥65y 11%)

Risk

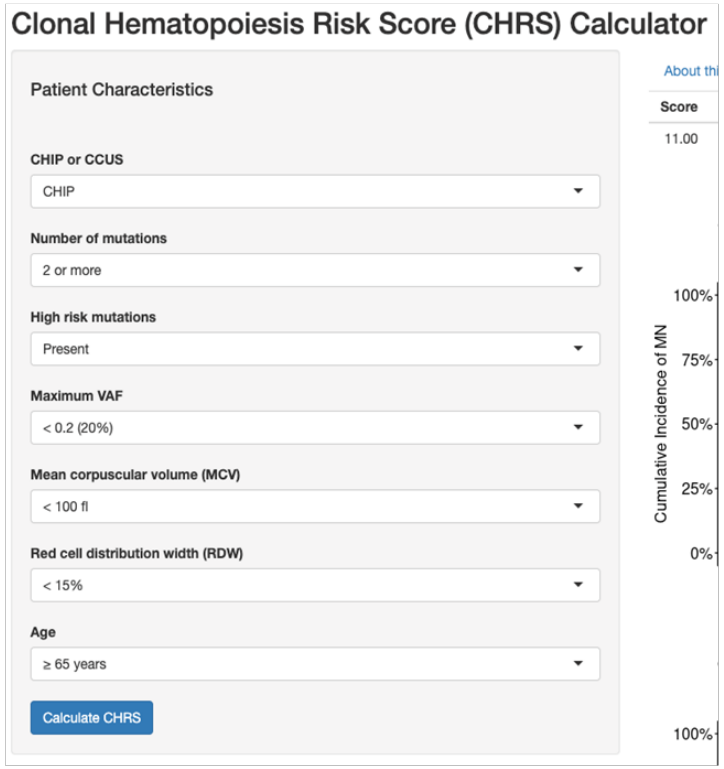
Fried et al. *JAMA* 1998; Træden et al. *Blood* 2023; SEER MDS 2014-2020; SEER AML 2014-2020

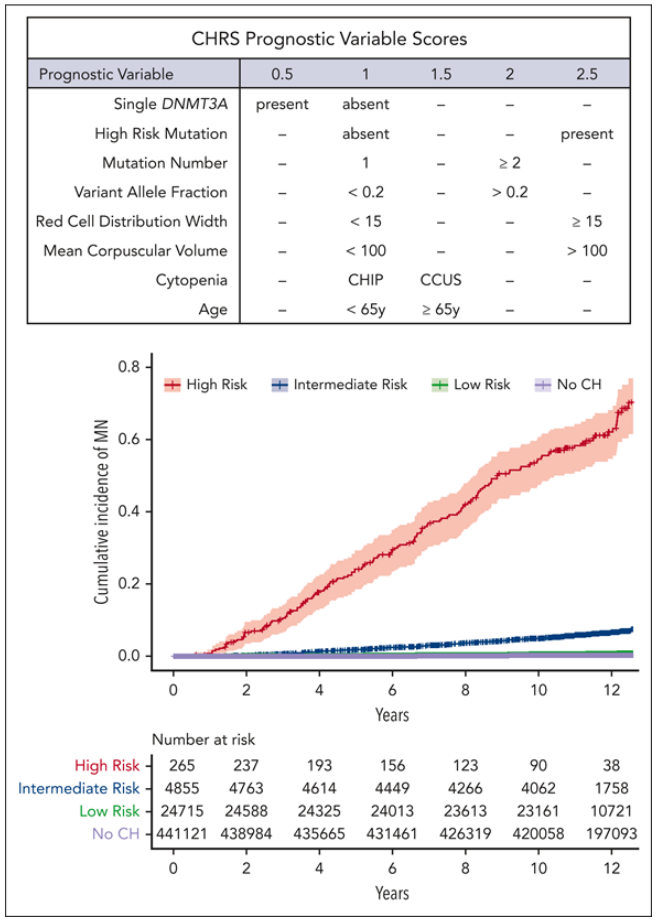
Prognostication require further validation but decent framework

https://ccrscalc.netlify.app/



http://www.chrsapp.com/





CHRS Prognostic Variable Scores

Prognostic Variable	0.5	1	1.5	2	2.5
Single *DNMT3A*	present	absent	–	–	–
High Risk Mutation	–	absent	–	–	present
Mutation Number	–	1	–	≥ 2	–
Variant Allele Fraction	–	< 0.2	–	> 0.2	–
Red Cell Distribution Width	–	< 15	–	–	≥ 15
Mean Corpuscular Volume	–	< 100	–	–	> 100
Cytopenia	–	CHIP	CCUS	–	–
Age	–	< 65y	≥ 65y	–	–

The National Myelodysplastic Syndromes Natural History Study

Sponsored by the National Heart, Lung, and Blood Institute
in collaboration with the National Cancer Institute

THE NATIONAL MDS STUDY & AT-RISK FOR MDS

CLINICALTRIALS.GOV
NCT 02775383

STUDY WEBSITE
HTTPS://THENATIONALMDSSTUDY.NET

CLINICAL TRIALS SUPPORT UNIT
NHLBI-MDS

NHLBI Contracts: CL/B HHSN268201400003I; DCC HHSN268201400002I

Robust biorepository with clinical annotation

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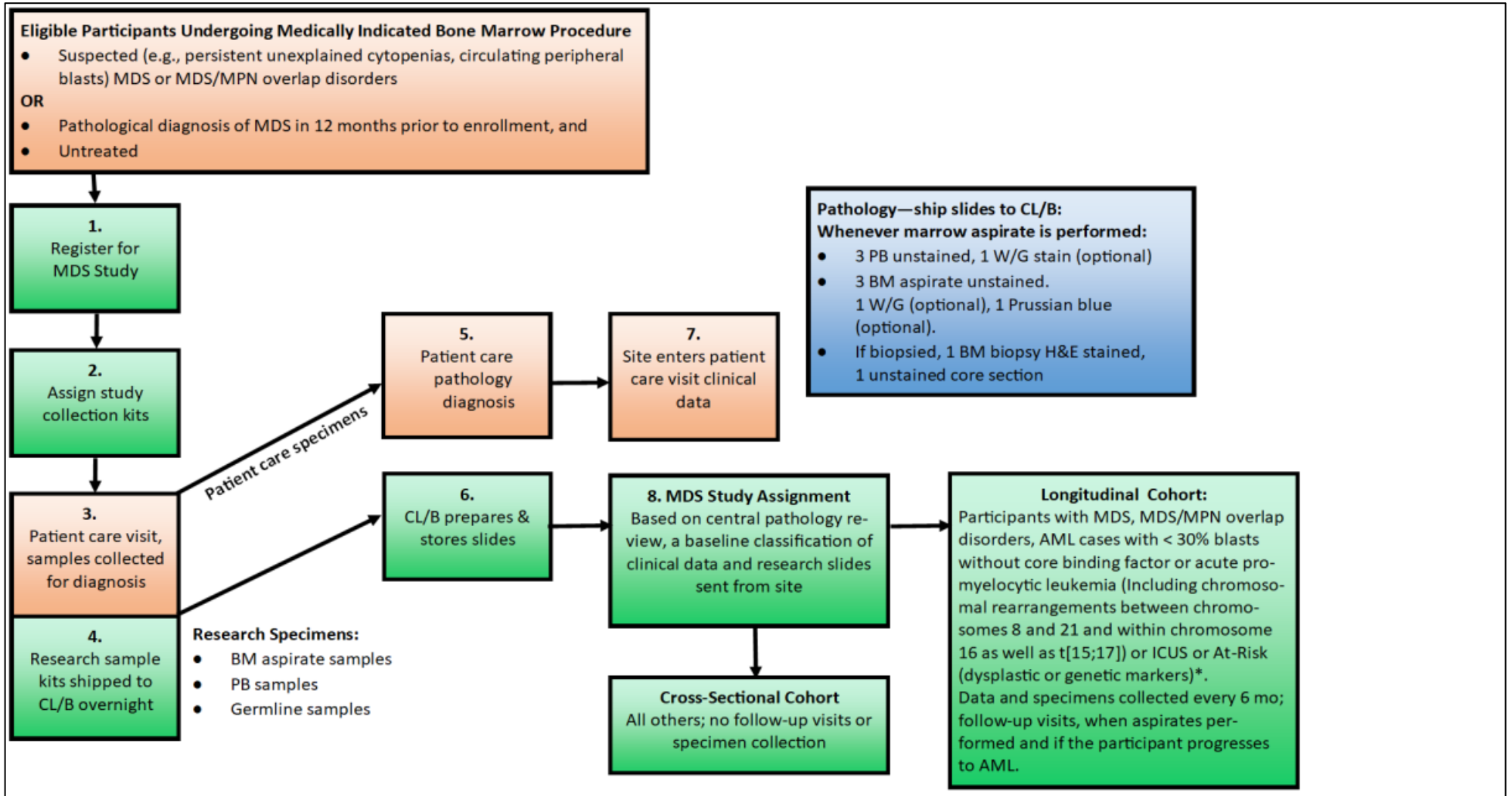

*Cases with local or central pathology assessments of dysplasia in baseline bone marrow aspirate; select karyotype abnormalities; locally or centrally detected genetic mutations meeting minimally acceptable criteria for allelic variant presence.

AML = acute myeloid leukemia; BM = bone marrow; CL/B = central laboratory/biorepository; H&E =hematoxylin and eosin; ICUS = idiopathic cytopenia of undetermined significance; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm; PB = peripheral blood; W/G = wright-giemsa.

Real World Cohort

Characteristic	All MDS (N=613)	ICUS/IDUS (N=264)	CCUS (N=300)	P-value	LR-MDS (N=330)	HR-MDS (N=159)	UNK-MDS (N=124)	P-value
Sex - no. (%)								0.018
Female	178 (30%)	123 (50%)	82 (29%)		94 (30%)	56 (38%)	28 (23%)	
	407 (70%)	124 (50%)	197 (71%)		221 (70%)	93 (62%)	93 (77%)	
AGE - no. (%)				<0.001				0.090
<60	44 (8%)	63 (26%)	19 (7%)		24 (8%)	17 (11%)	3 (2%)	
60-69	116 (20%)	66 (27%)	54 (19%)		63 (20%)	33 (22%)	20 (17%)	
70-79	274 (47%)	80 (32%)	119 (43%)		142 (45%)	69 (46%)	63 (52%)	
80-89	131 (22%)	37 (15%)	80 (29%)		75 (24%)	26 (17%)	30 (25%)	
90+	20 (3%)	1 (0%)	7 (3%)		11 (3%)	4 (3%)	5 (4%)	
Race - no. (%)				0.020				0.648
Asian	4 (1%)	7 (3%)	5 (2%)		1 (0%)	1 (1%)	2 (2%)	
Black or African American	26 (4%)	16 (6%)	6 (2%)		12 (4%)	7 (5%)	7 (6%)	
White	539 (92%)	211 (85%)	256 (92%)		293 (93%)	135 (91%)	111 (92%)	
Other	3 (1%)	4 (2%)	2 (1%)		2 (1%)	1 (1%)	0 (0%)	
Unknown/Not Reported	13 (2%)	9 (4%)	10 (4%)		7 (2%)	5 (3%)	1 (1%)	
Ethnicity - no. (%)				0.027				0.366
Hispanic or Latino	22 (4%)	18 (7%)	9 (3%)		13 (4%)	3 (2%)	6 (5%)	
Not Hispanic or Latino	544 (93%)	218 (88%)	256 (92%)		290 (92%)	141 (95%)	113 (93%)	
Unknown/Not Reported	19 (3%)	11 (4%)	14 (5%)		12 (4%)	5 (3%)	2 (2%)	
Smoking History - no. (%)				<0.001				0.118
Never Smoked	250 (43%)	139 (56%)	122 (44%)		145 (46%)	52 (35%)	53 (44%)	
Smoker	334 (57%)	108 (44%)	157 (56%)		170 (54%)	96 (65%)	68 (56%)	
Prior Cancer - no. (%)				0.082				0.830
No Prior Cancers	412 (70%)	195 (79%)	199 (71%)		225 (71%)	101 (68%)	86 (71%)	
Prior Cancers (1 or more)	173 (30%)	52 (21%)	80 (29%)		90 (29%)	48 (32%)	35 (29%)	
Laboratory Values								
Hemoglobin, g/dL - median (IQR)	10.1 (8.7 - 11.5)	11.9 (10.0 - 13.6)	11.9 (10.3 - 13.5)	<0.001	10.5 (9.1 - 11.8)	9.1 (8.0 - 10.2)	10.1 (8.9 - 11.8)	<0.001
Platelets, $x10^9$/L - median (IQR)	125 (79 - 219)	167 (1034 - 248)	138 (96 - 195)	<0.001	139 (91 - 237)	84 (53 - 143)	135 (82 - 247)	<0.001
ANC, $x10^9$/L - median (IQR)	1.9 (1.1 - 3.1)	2.6 (1.6 - 4.1)	2.9 (1.8 - 4.1)	<0.001	2.1 (1.3 - 3.2)	1.1 (0.7 - 2.0)	2.2 (1.4 - 3.9)	<0.001
Follow-up Time, years - median (IQR)	1.6 (0.7 - 3.0)	1.8 (1.1 - 3.0)	1.8 (0.9 - 3.3)	0.054	2.0 (1.0 - 3.9)	0.9 (0.4 - 1.8)	1.3 (0.6 - 2.2)	<0.001

Central Classification Helpful

The National Myelodysplastic Syndromes Natural History Study

Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

Local vs. Central Pathology Study Assignment

Original (Local) Diagnosis	Final Study Diagnosis							
	MDS	MDS/MPN overlap	ICUS	AML <30% Blasts*	Other AML	Other Malignancy	Other	Total
MDS	193	12	8	3	1	7	40	264
MDS/MPN overlap	3	9	0	0	0	3	0	15
ICUS	9	2	20	0	0	4	27	62
AML <30% Blasts	0	0	0	0	0	0	0	0
Other AML	4	0	0	10	32	0	0	46
Other Malignancy	3	8	0	0	2	26	10	49
Other	54	14	21	2	3	53	335	482
~~Total~~	~~266~~	~~45~~	~~49~~	~~15~~	~~38~~	~~93~~	~~412~~	~~918~~
Agreement Rate	193/266 (73%)	9/45 (20%)	20/49 (41%)	0/15 (0%)	32/38 (84%)	26/93 (28%)	335/412 (81%)	615/918 (67%)
Kappa (95% CI)								0.54 (0.49, 0.59)

Gorak et al. Blood Advances 2023;7:6120-9. Sekeres WSJ August 25, 2023

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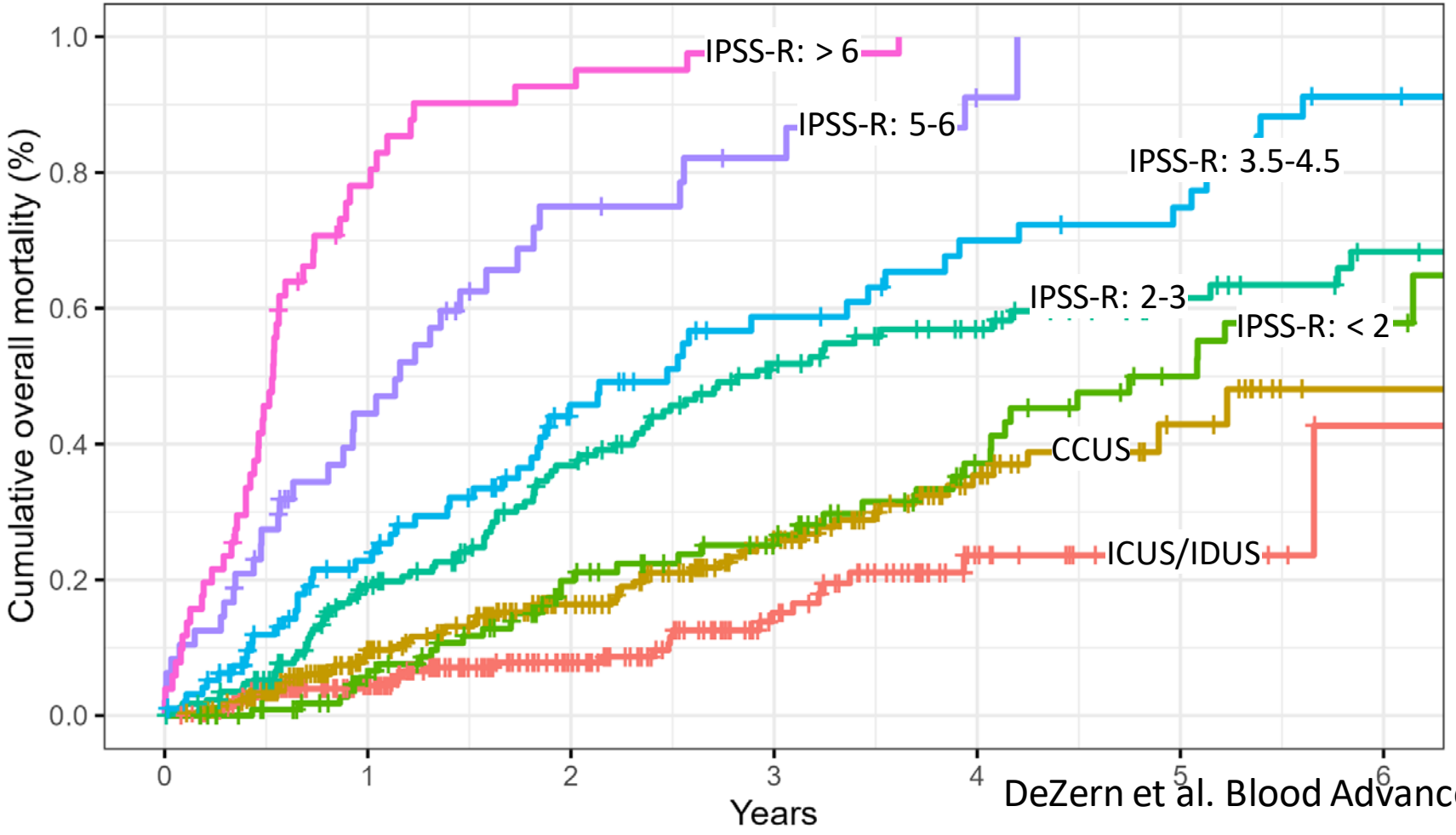
Platelets, $x10^9$/L - median (IQR)	125 (79 - 219)	167 (1034 - 248)	138 (96 - 195)	<0.001	139 (91 - 237)	84 (53 - 143)	135 (82 - 247)	<0.001
ANC, $x10^9$/L - median (IQR)	1.9 (1.1 - 3.1)	2.6 (1.6 - 4.1)	2.9 (1.8 - 4.1)	<0.001	2.1 (1.3 - 3.2)	1.1 (0.7 - 2.0)	2.2 (1.4 - 3.9)	<0.001
Fo **FOLLOW UP TIME** R)	1.6 (0.7 - 3.0)	1.8 (1.1 - 3.0)	1.8 (0.9 - 3.3)	0.054	2.0 (1.0 - 3.9)	0.9 (0.4 - 1.8)	1.3 (0.6 - 2.2)	<0.001

Overall mortality for MDS by IPSS-R, CCUS and ICUS/IDUS



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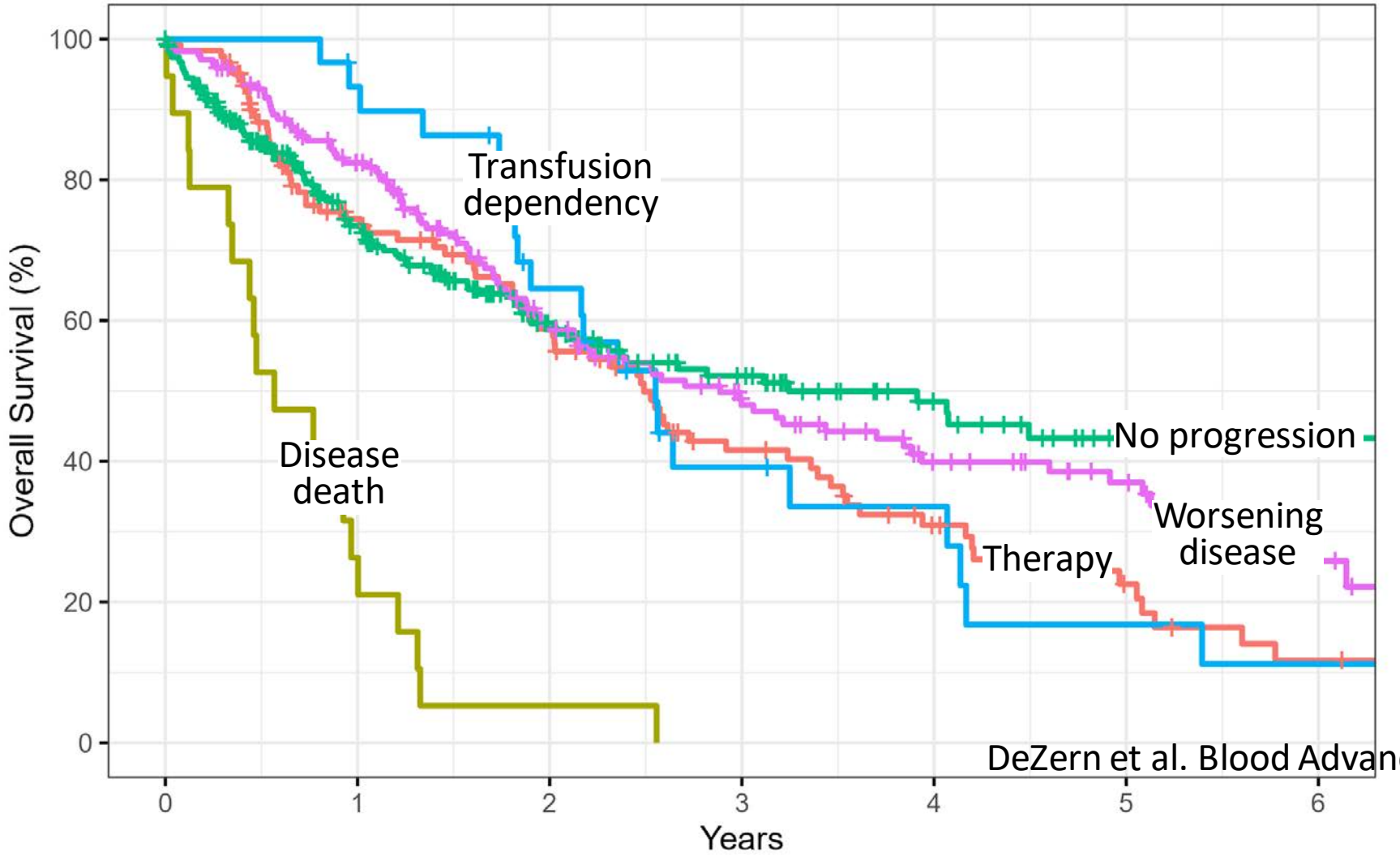
Overall survival for MDS by progression category



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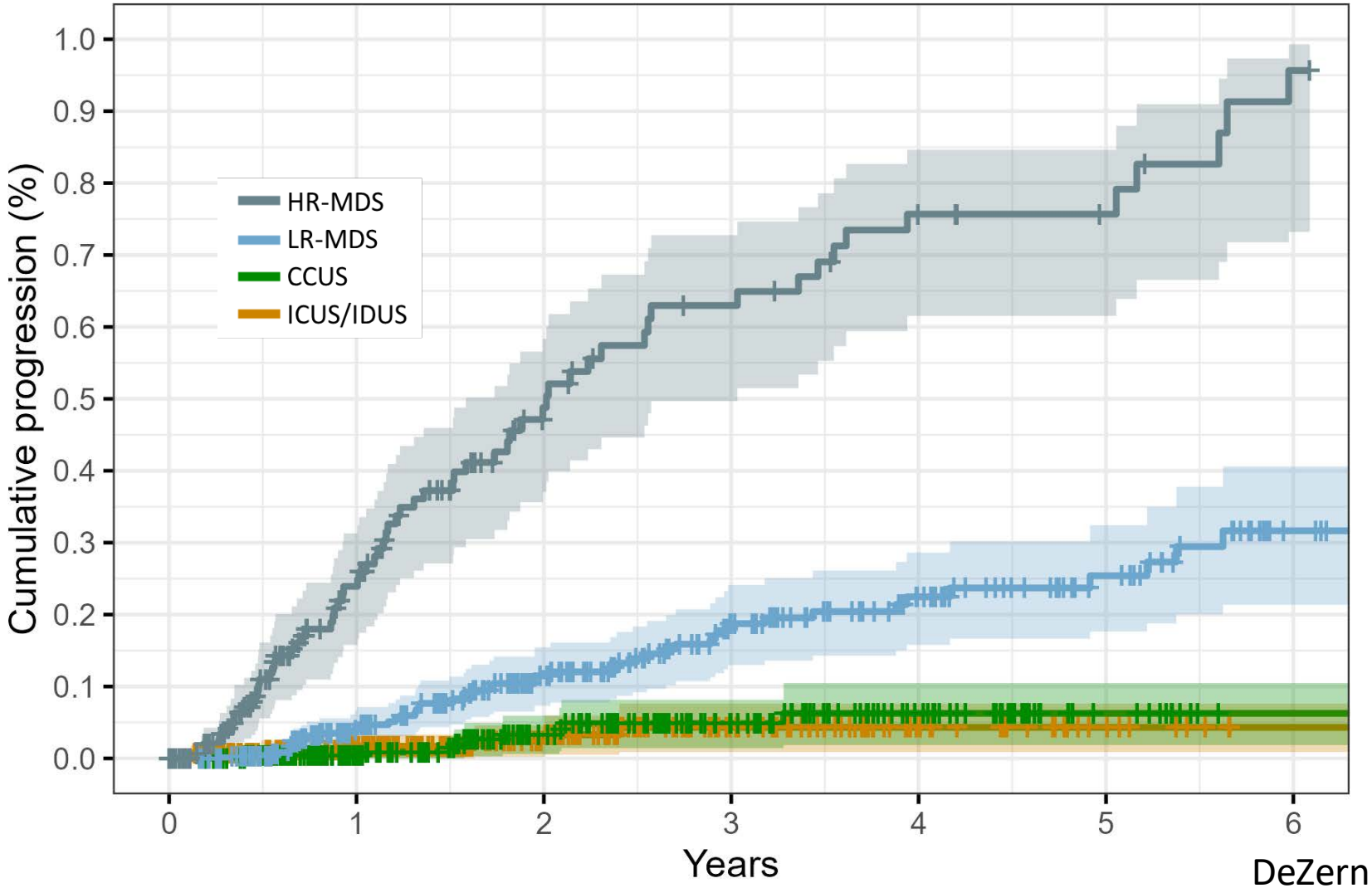
Observed 6-year progression rates for MDS, CCUS and ICUS/IDUS.
Progression defined as as follow-up re-diagnosis of worsening disease (including progression to AML) or MDS/AML-related death.



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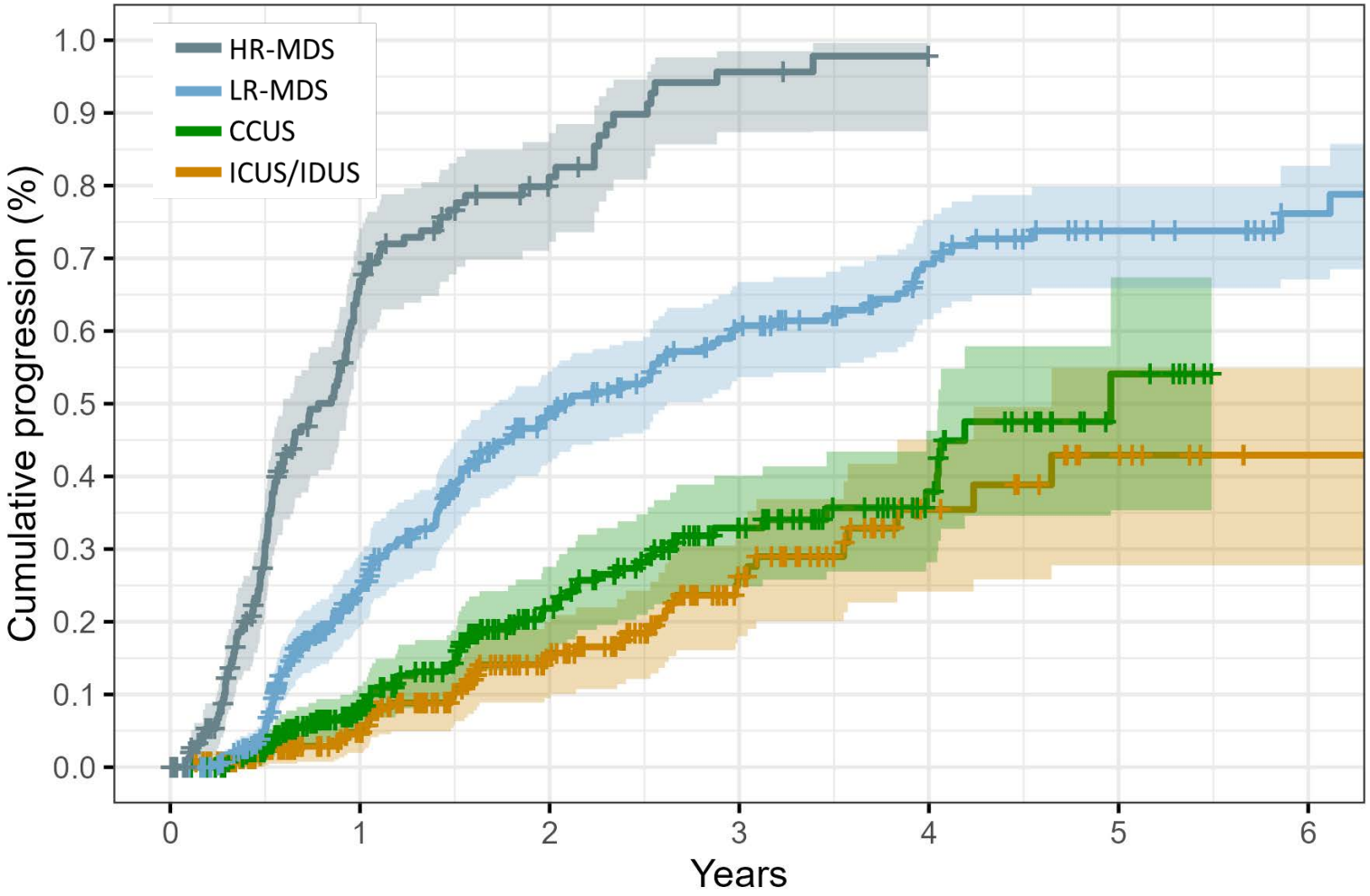
Observed 6-year progression rates for MDS, CCUS and ICUS/IDUS

expanded progression definition: features of worsening disease, increasing transfusion dependency, changes in disease-directed therapy, and MDS/AML-related death



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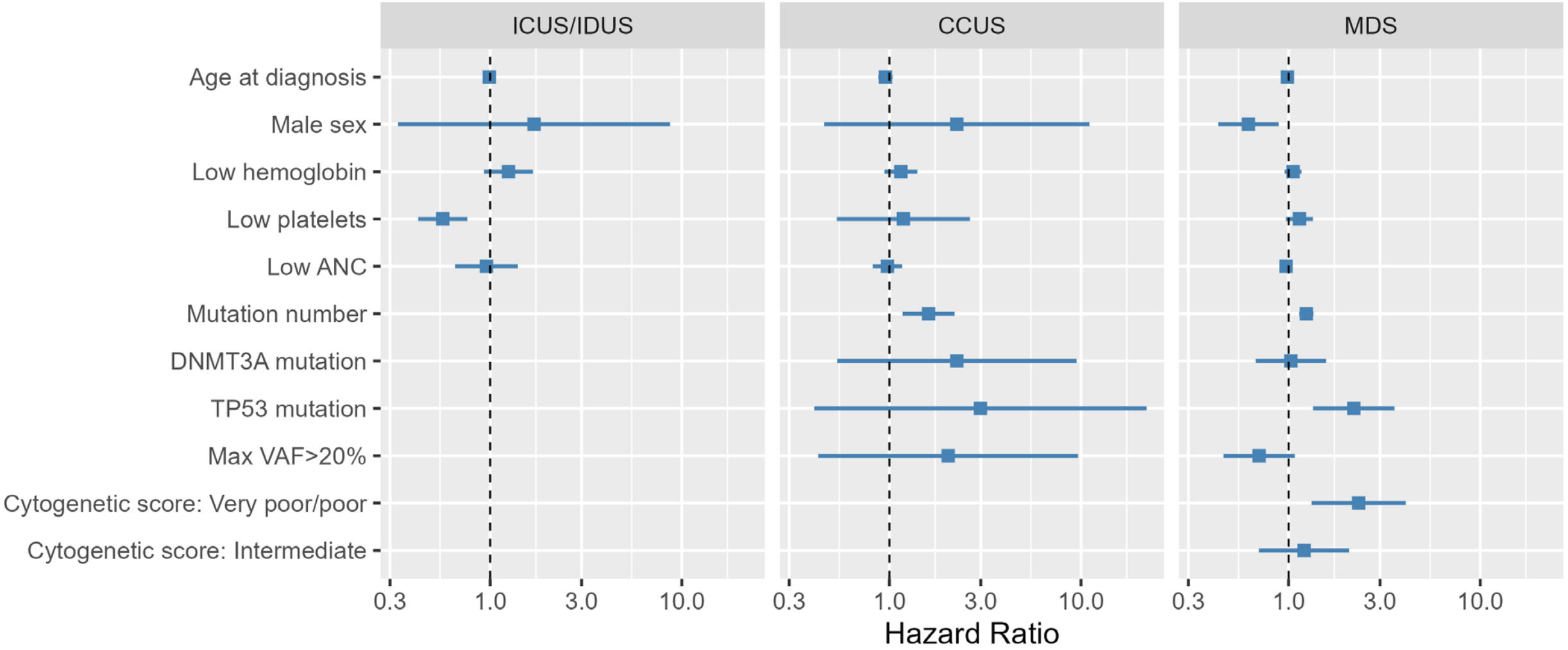
Effect plots for predictors of progression among ICUS/IDUS, CCUS and MDS



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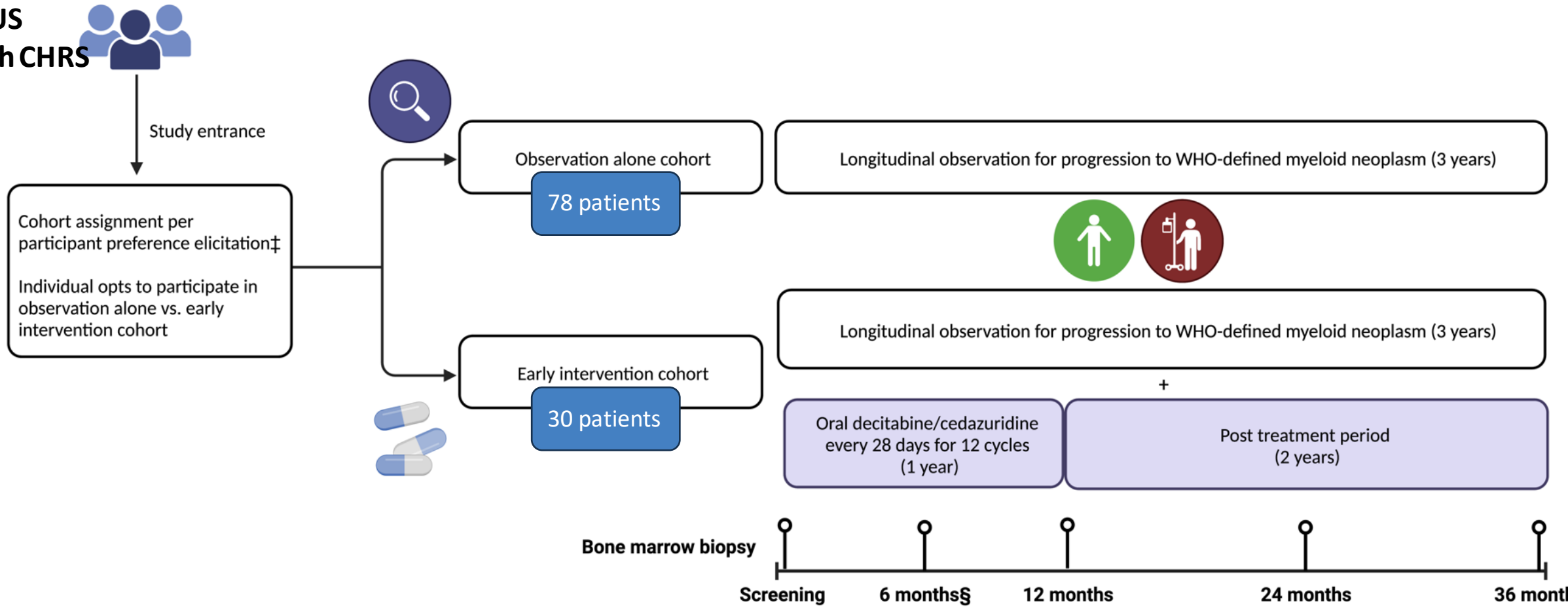
Intervening now… Trial Schema

Study population:

- **CCUS**
- **High CHRS**



<u>Intervention arm. Low dose decitabine/cedazuridine:</u>
1 table torally once daily on Days 1-5 of each 28-day cycle

Current active CCUS clinical trials (N=7)

Trial	Study Title	Population(s)	Intervention	Phase	Location	Status
NCT05641831	Canakinumab in CCUS	High risk	Canakinumab q2m for 2 years	II	US, multicenter	Recruiting
NCT03418038	Ascorbic Acid for the Treatment of CCUS	TET2 mutation(s).	High dose of ascorbic acid 1g/kg 3 times a week for 12 weeks	II	US, single center	Completed
NCT05030441	Ivosidenib for Patients with CCUS and Mutations in IDH1	IDH1 mutation.	Ivosidenib 500 mg daily for up to 17 months	II	US, multicenter	Recruiting
NCT05102370	A Study of Enasidenib in People with CCUS and Mutations in IDH2	IDH2 mutation.	Enasidenib 100 mg daily for 18 months	I	US, multicenter	Recruiting
NCT04741945	Repurposing Metformin as a Leukemia-preventive Drug in CCUS and LR-MDS	CCUS and LR-MDS	Metformin 2000 mg/daily for 12 months	II	Denmark, multicenter	Recruiting
	Statins in Patients With CCUS and MDS	CCUS and MDS	Atorvastatin dosing starts at 80 mg once daily for up to 12 month	II	US, single center	Not yet recruiting
NCT 03682029	Epigenetics, Oral Vitamin C, and Abnormal Blood Cell Formation - Vitamin C in CCUS and LR MDS	CCUS, Low-Risk MDS, and CMML-0/1	Vitamin C 500 mg/capsule. Ingestion of 2 capsules (1000 mg) daily for 12 months.	II	Denmark, Multicenter	Active, not Recruiting

2026 MDS SUMMARY: Asking the relevant questions going forward

- **Options increasing in LR MDS; less so in HR MDS**
- **Biology and prognostication matter**
- **Consider both SOC and trial options**
  - **Continue to seek approval of drugs with novel MOAs**
- **TREAT Earlier? At HR CCUS ?? (where most emphasis may stay)**
- **Refer for HLA typing earlier to plan, extend survival**

MANY THANKS

Happy for questions!
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All patients and families

US MDS CRC

BMT CTN

Hematology & Heme Malignancies group

Clinical Research Staff

HLA lab

NIH National Heart, Lung, and Blood Institute

TEDCO

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

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