Advancements and Novel Options in MDS: What Does the Future Hold for Us?

Advancements in MDS:

What does the Future Hold For us

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November 5th, 2022

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Conflict of interest disclosure

- Consulting/honoraria: BluePrint Medicines, GERON, OncLive

- Advisory board member/honoraria: Sierra Oncology, Stemline Therapeutics, Morphosys, Taiho, and Novartis

- I WILL include discussion of investigational or off-label use of a product in my presentation

Outline

- Definition and Epidemiology of MDS

- Pathogenesis and making a diagnosis of MDS

- 2022 Updates in:
    - MDS subtype / classification
    - Prognostic risk score of MDS

- Approved treatments and Advancements for lower-risk MDS

- Approved treatments and Advancements for higher-risk MDS

How would you define MDS?

- Myelodysplastic syndromes (MDS) comprise a heterogeneous group of malignant clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, dysplastic changes and risk of transformation to acute myeloid leukemia.
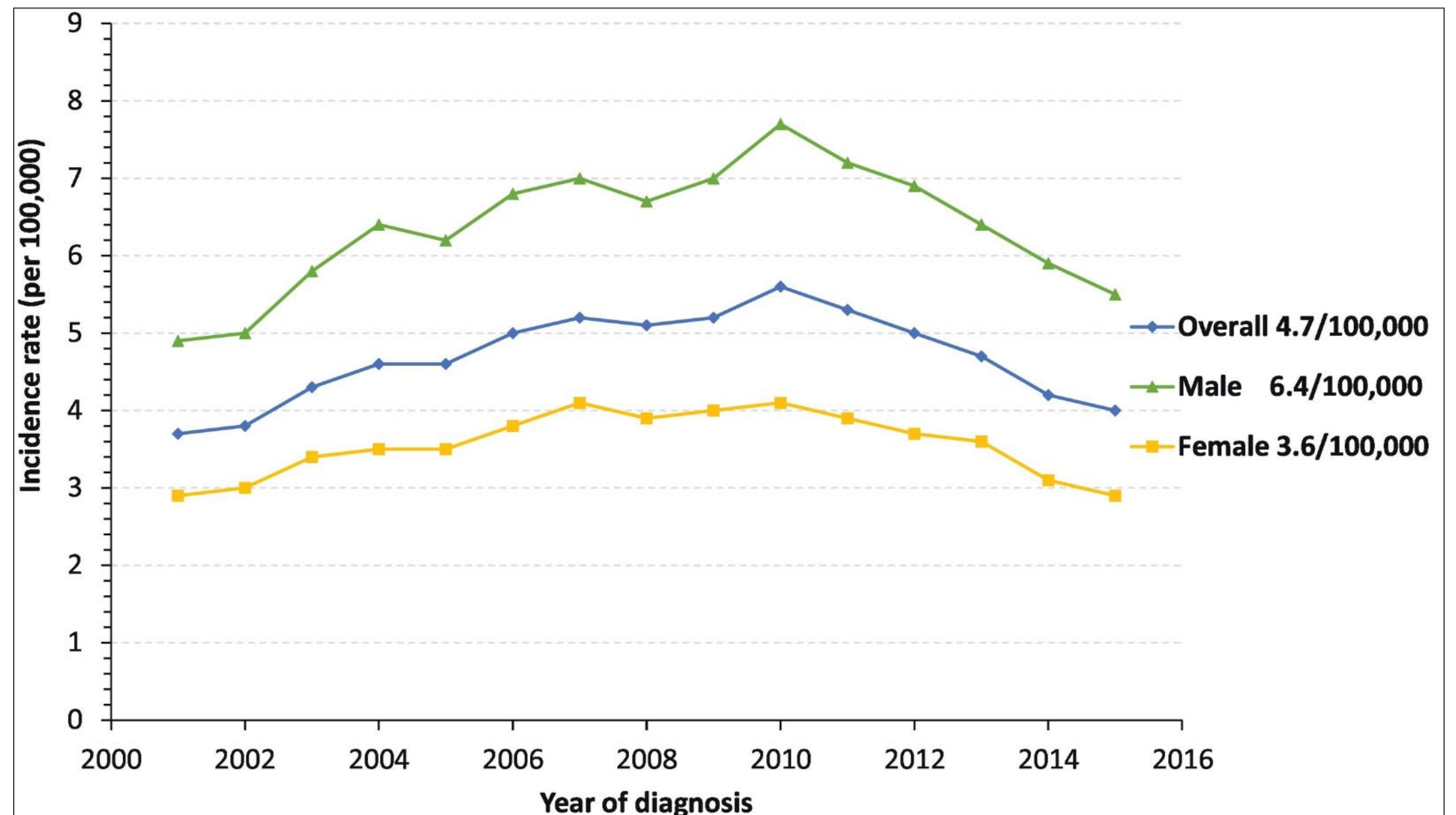
- MDS IS A BONE MARROW CANCER

MYELODYSPLASTIC NEOPLASMS
New terminology and grouping framework
The classification introduces the term *myelodysplastic neoplasms* (abbreviated MDS) to replace myelodysplastic syndromes, underscoring their neoplastic nature and harmonizing terminology with MPN. These clonal haematopoietic neoplasms are defined by
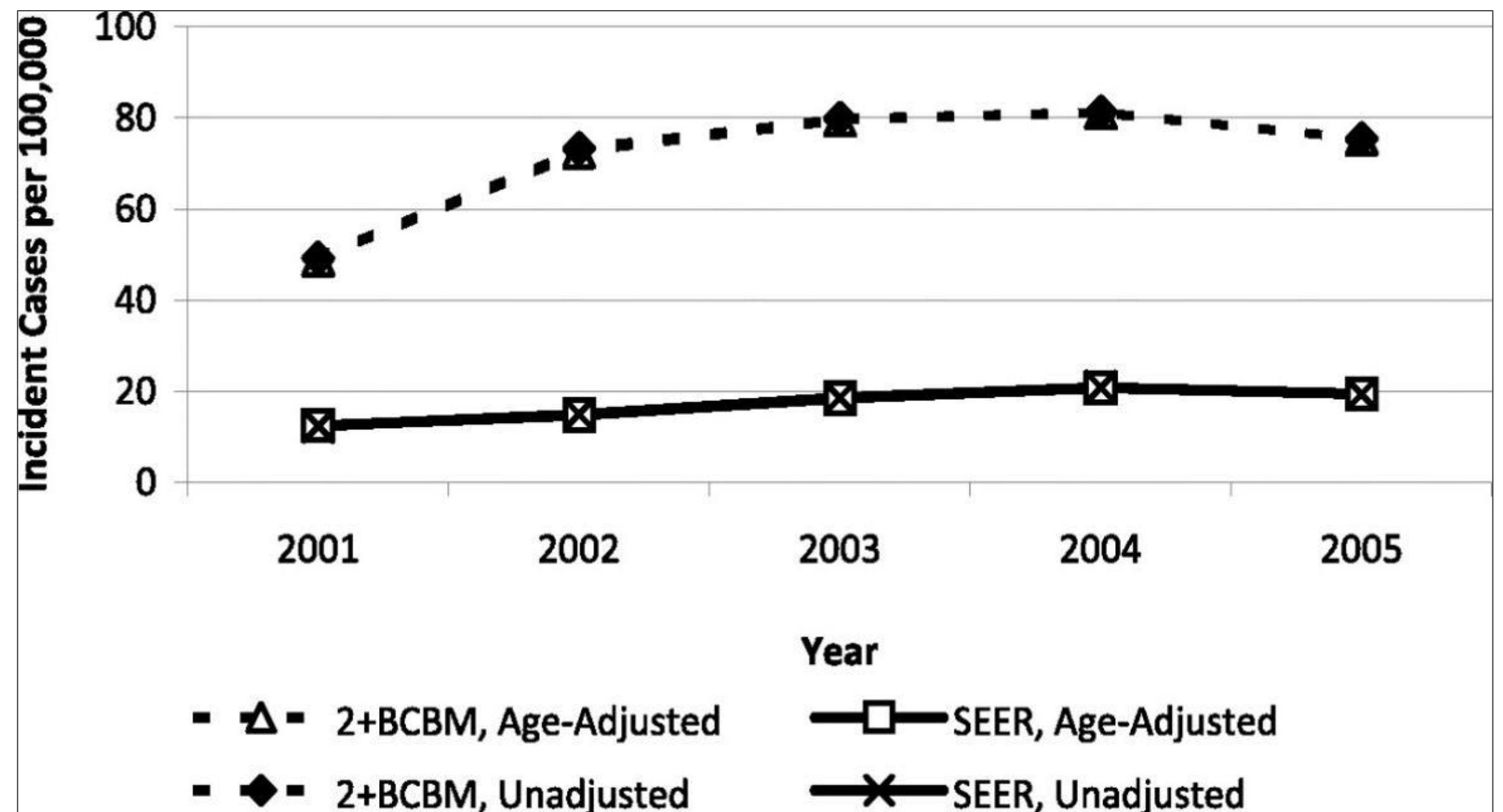
Epidemiology of MDS – SEER DATA

- Captured as "cancer" – 2001

- 13,400 new cases per year

- Incidence Rate 4.7/100,000

- Male preponderance (M:F 1.5-2.0)
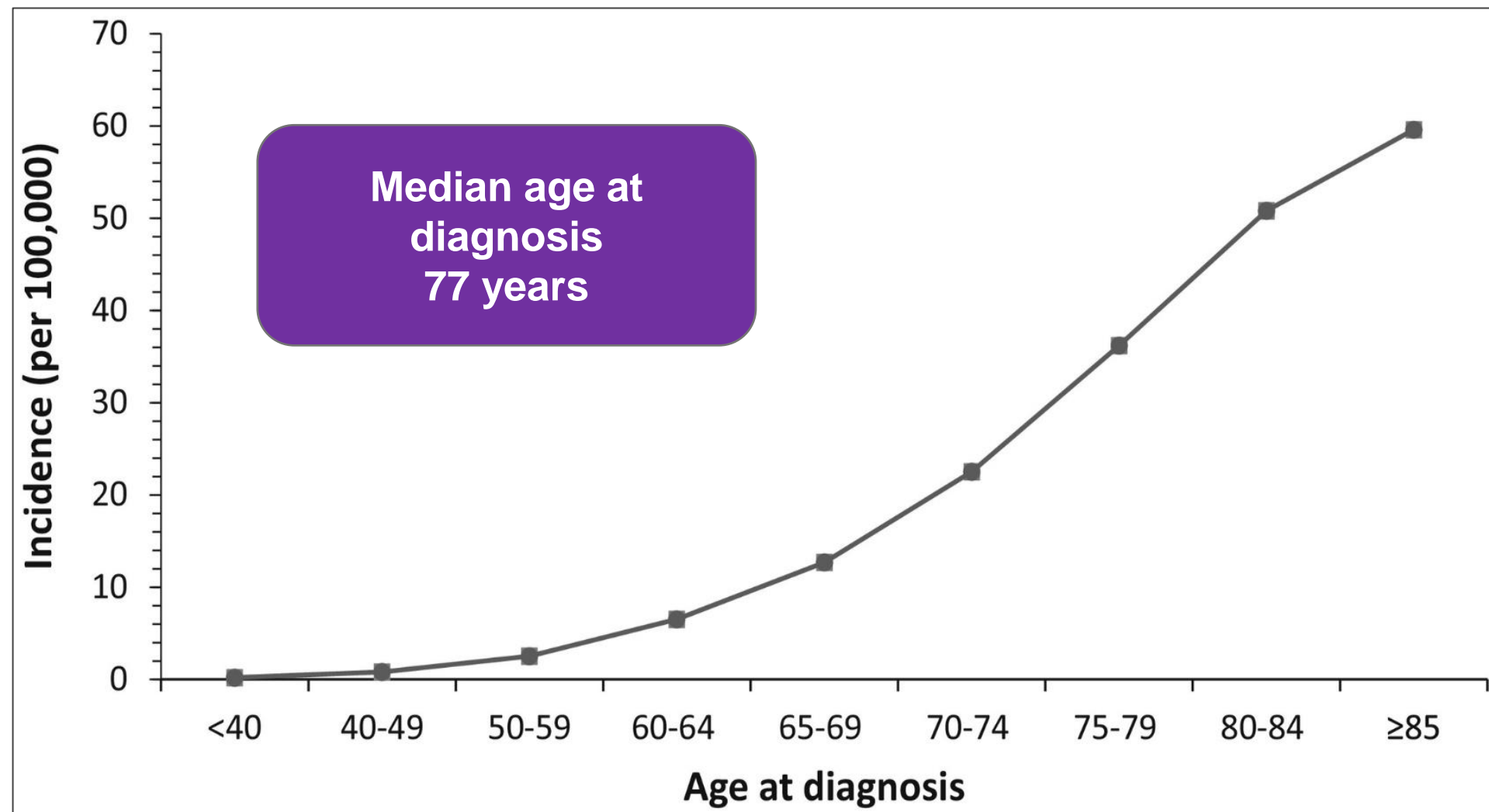
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Incidence Rates Based on a claims-based Algorithm

- Patients ≥65 years

- Incidence of 75/100,000

vs. 20/100,000 reported by SEER

Cogle CR et al. Blood 2011

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Age at diagnosis and Overall Survival

Median age at diagnosis 77 years

5 year overall survival rate in MDS ~ 31%
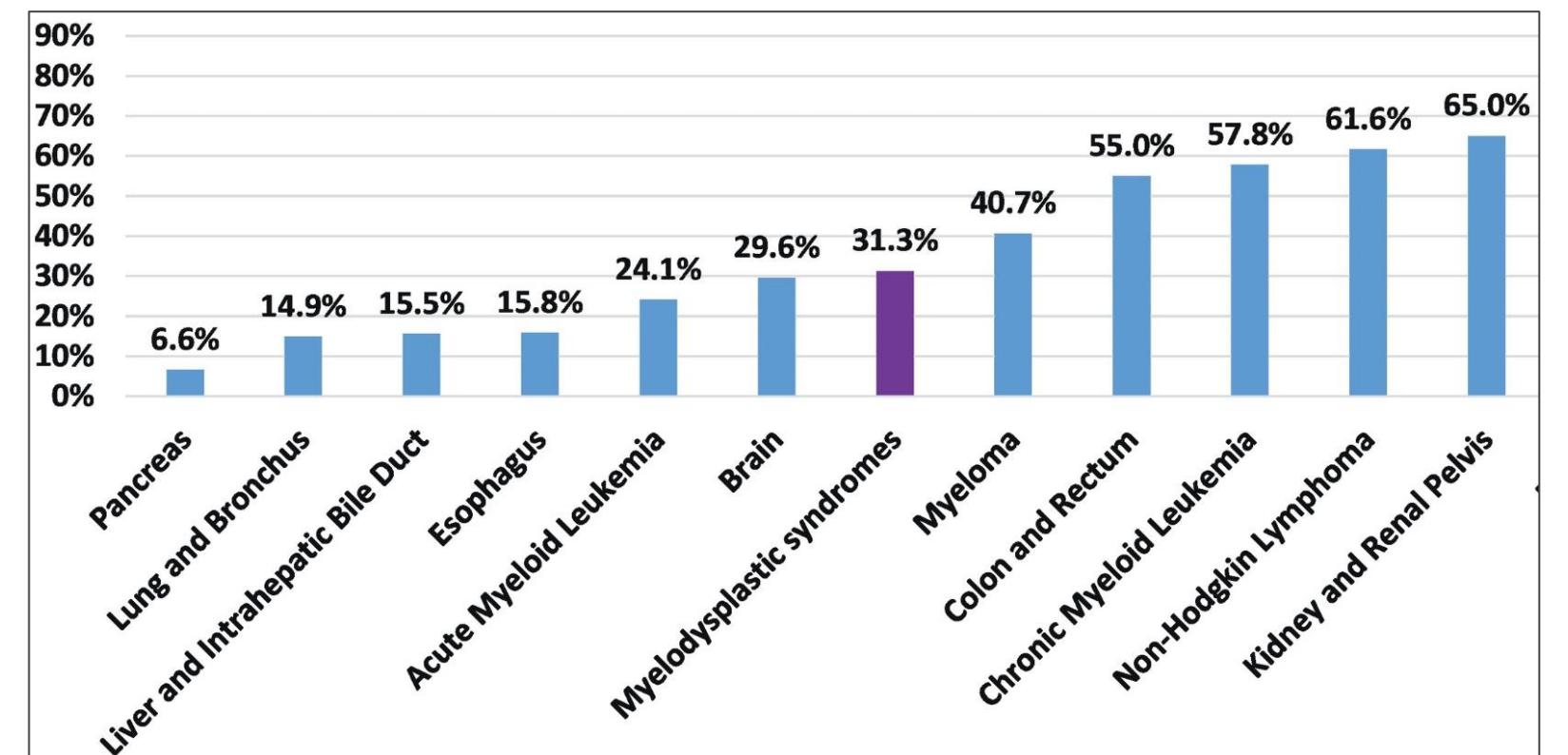
Zeidan AM et al. Blood Rev. 2018 (SEER data, based on the November 2017 submission)

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Hematopoiesis

- Myeloid Family

- Lymphoid Family
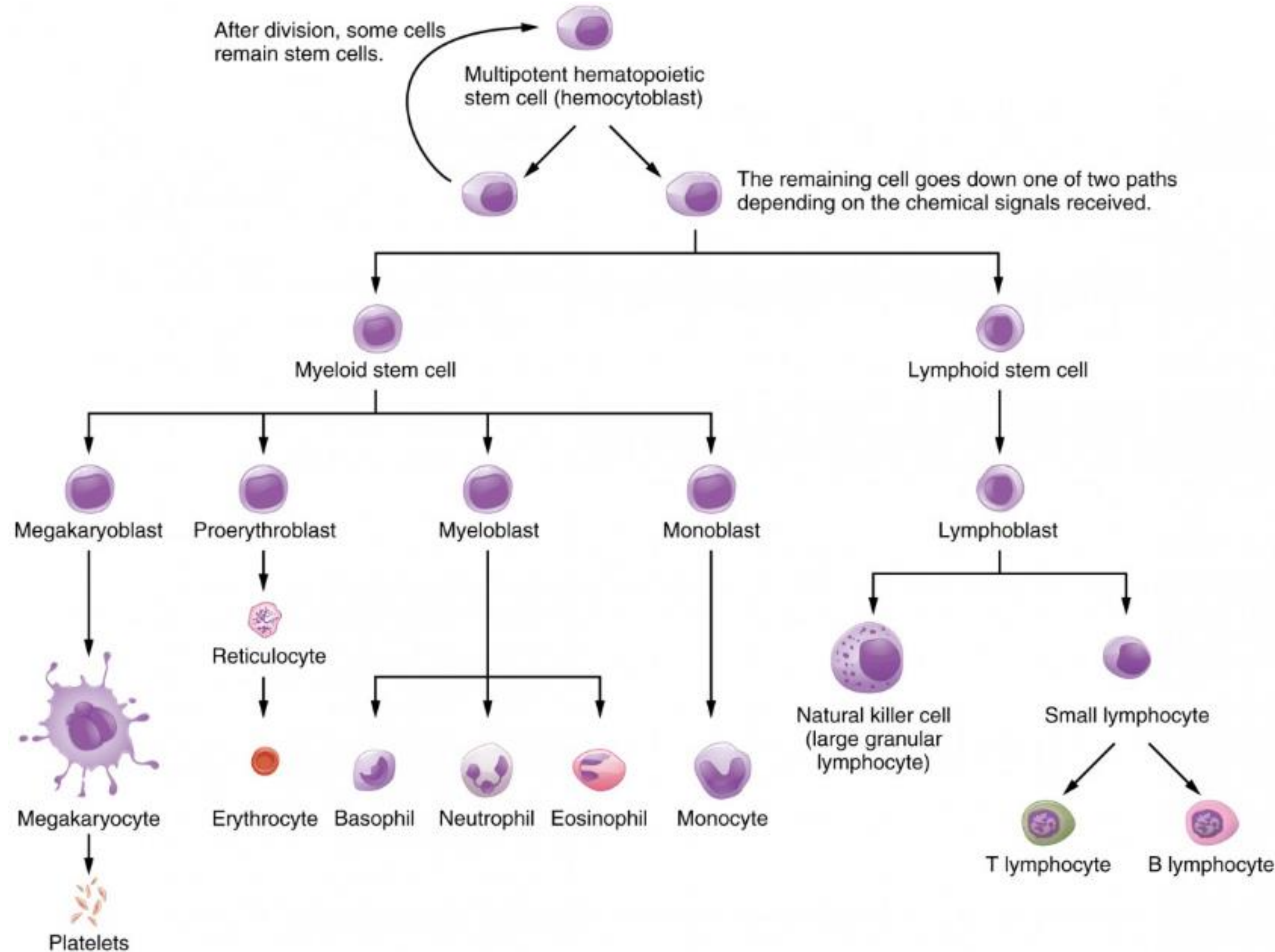
Diagnosis and Marrow Dysplasia

- Dysplastic changes in > 10% of cells
  - ➤ Peripheral cytopenias
  - ➤ Increased blasts
  - ➤ Increased ring sideroblasts

- Defining karyotype/genomic abnormality

- 2022: Defining genetic abnormality

(Gene mutation)
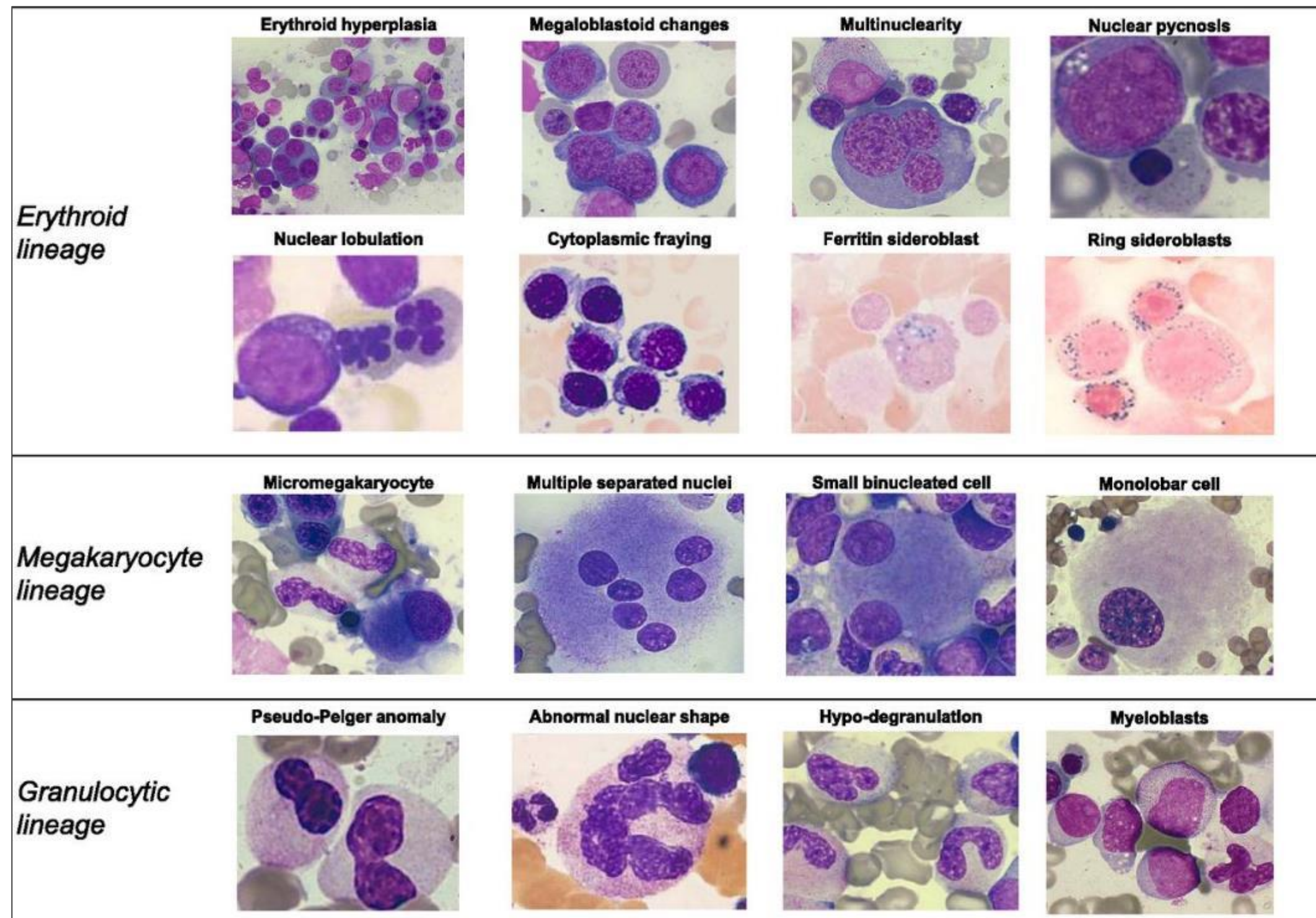
Cazzola M, et al. Blood 2013

What are Chromosomes (DNA/Genetic Material)

Chromosome

p arm (short arm structure)

Centromere (constricted point where the two chromatids are held together)

q arm (long arm structure)

DNA molecule (strands of DNA are formed into compact structures inside of the chromosome by proteins called histones)
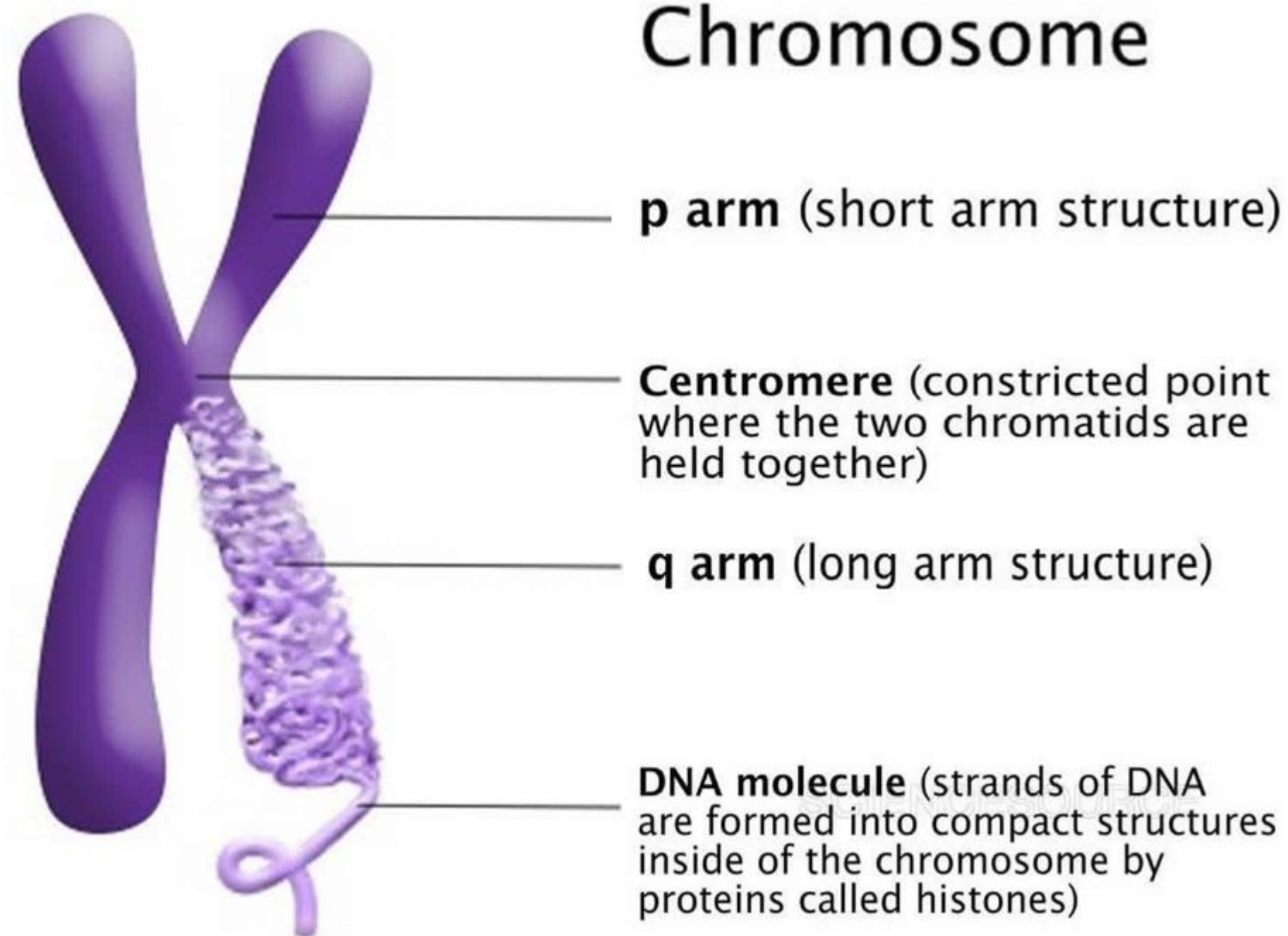
MDS Defining Cytogenetic Abnormalities

A

B

C

D

Table 18. Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes when ≥20% PB or BM blasts are present and prior therapy has been excluded

| Cytogenetic abnormalities |
| --- |
| Complex karyotype (3 or more abnormalities) |
| **Unbalanced abnormalities** |
| −7/del(7q) |
| del(5q)/t(5q) |
| i(17q)/t(17p) |
| −13/del(13q) |
| del(11q) |
| del(12p)/t(12p) |
| idic(X)(q13) |
| **Balanced abnormalities** |
| t(11;16)(q23.3;p13.3) |
| t(3;21)(q26.2;q22.1) |
| t(1;3)(p36.3;q21.2) |
| t(2;11)(p21;q23.3) |
| t(5;12)(q32;p13.2) |
| t(5;7)(q32;q11.2) |
| t(5;17)(q32;p13.2) |
| t(5;10)(q32;q21.2) |
| t(3;5)(q25.3;q35.1) |

Arber D, et al. Blood. 2016

Genomic Landscape of MDS: 944 patients

- 90% had 1 or more driver mutations (median: 3/pt, [0-12])
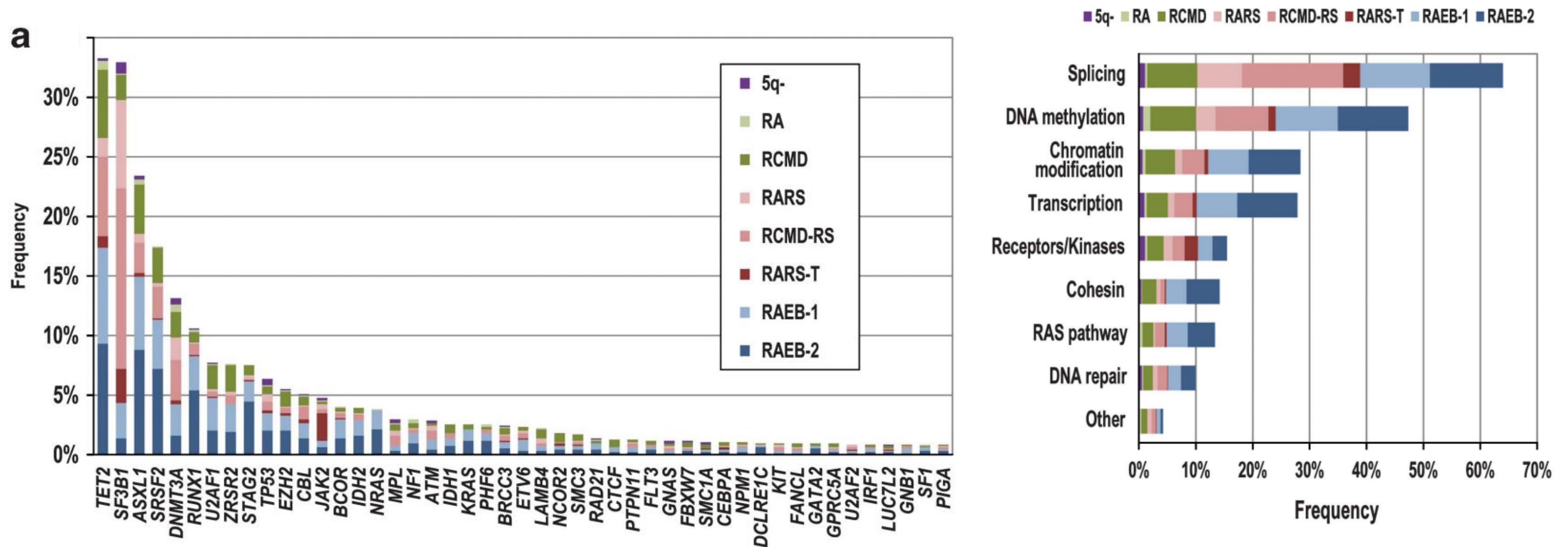
Haferlach et al. Leukemia 2014

I. MDS Subtypes: 2016 WHO Classification of MDS

Category	Abbreviation	Bone Marrow Blast %
MDS with Single-lineage dysplasia	MDS-SLD	<5%
MDS with multi-lineage dysplasia	MDS-MLD	<5%
MDS with ring sideroblasts & Single lineage dysplasia	MDS-RS-SLD	<5%
MDS with ring sideroblasts and multi-lineage dysplasia	MDS-RS-MLD	<5%
MDS with isolated del(5q)	Del(5q) MDS	<5%
MDS with excess blasts -1	MDS-EB1	5-9%
MDS with excess blasts -2	MDS-EB2	10-19%
MDS unclassifiable with 1% PB blasts, SLD with pancytopenia or based on cytogenetic abnormalities	MDS-U	<5%
Refractory cytopenia of childhood	RCC	<5%

Allow for treatment options:
-Presence of *SF3B1* mutation – MDS-Ring Sideroblasts – Luspatercept
-Presence of del(5q) – Lenalidomide

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MDS Subtypes: 2022 WHO and International Consensus Classification of MDS

- What I need to know:

1. Number of dysplastic cell lines (1 or more)

2. Presence of del(5q) as the sole abnormality +- 1 additional abnormality

3. Percentage of blasts

4. Presence of *SF3B1* mutation

5. Presence of TP53 mutation/multiple TP53 mutations

Table 20. Myelodysplastic syndromes (MDS) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics†	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1‡	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), −7/del(7q), abn3q26.2, or complex	*SF3B1* (≥ 10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1‡	≥1	Thrombocytosis allowed	<5% BM <2% PB§	del(5q), with up to 1 additional, except −7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS without dysplasia	0	≥1	0	<5% BM <2% PB§	−7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥ 10% VAF)
MDS, NOS with single lineage dysplasia	1	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*;not meeting criteria for MDS-*SF3B1*
MDS, NOS with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*,; not meeting criteria for MDS-*SF3B1*
MDS with excess blasts (MDS-EB)	Typically ≥1‡	≥1	0	5-9% BM, 2-9% PB§	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1‡	≥1	0	10-19% BM or PB||	Any, except AML-defining¶	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

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Myeloid neoplasms with mutated *TP53* (Table 21)

This disease category encompasses separate diagnoses of MDS, MDS/AML, and AML with mutated *TP53* (including pure erythroid leukemia), according to the blast percentage. These diseases are grouped together because of their overall similar aggressive behavior irrespective of the blast percentage, warranting a more unified treatment strategy across the blast spectrum.[120,127] The presence of multihit *TP53* mutations in

Table 21. Myeloid neoplasms with mutated *TP53*

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF > 10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF > 10%)

Arber et al. Blood. 2022

Prognostic risk score of MDS – Lower-risk *vs* Higher-risk

- **International Prognostic Scoring System (IPSS, 1997)**

- **Revised IPSS (2012)**

- **IPSS-Molecular (IPSS-M) (2022)**

- **4 major elements to calculate risk score:**

    1. **Counts (Absolute neutrophil count/ANC, hemoglobin level, platelet count)**

    2. **Bone marrow blast %**

    3. **Cytogenetics/chromosomal study**

    4. **Genomic abnormalities/Mutations**

International Prognostic Scoring System (IPSS)

	Categories and Associated Scores			
Cytogenetic risk group	Good	Intermediate	Poor	
	0	0.5	1	
Marrow blast proportion	<5%	5%-10%	11- 20%	21-30
	0	0.5	1.5	2
Number of cytopenias	0/1	2/3		
	0	0.5		

** Karyotype definitions:
Good: Normal;-Y; del (5q); del (20q)
Poor: Complex (≥3 abnormalities); abnormal chromosome 7.
Intermediate: All others.

Risk group	Points	Median survival (years)	Time to 25% of patients progressing to AML (years)
Low	0	5.7	9.4
Intermediate-I	0.5-1.0	3.5	3.3
Intermediate-II	1.5-2.0	1.2	1.1
High	2.5-3.5	0.4	0.2

Adapted from: Greenberg P, et al. Blood, 1997

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Revised International Prognostic Scoring System (IPSS-R)

	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	≥10 g/dL	8 - <10 g/dL	<8 g/dL		
	0	1	1.5		
Absolute neutrophil count	≥0.8 x 10^9/L	<0.8 x 10^9/L			
	0	0.5			
Platelet count	≥100 x 10^9/L	50 - 100 x 10^9/L	<50 x 10^9/L		
	0	0.5	1		

Risk group	Points	% patients (n=7,012)	Median survival (years)	Median survival for pts <60 years	Time to 25% of patients progressing to AML (years)
Very low	0-1.5	19%	8.8	Not reached	Not reached
Low	2.0-3.0	38%	5.3	8.8	10.8
Intermediate	3.5-4.5	20%	3.0	5.2	3.2
High	5.0-6.0	13%	1.5	2.1	1.4
Very high	>6.0	10%	0.8	0.9	0.7

Adapted from: Greenberg P, et al. Blood, 2012

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Molecular International Prognostic Scoring System

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

2022 IPSS-M Classification
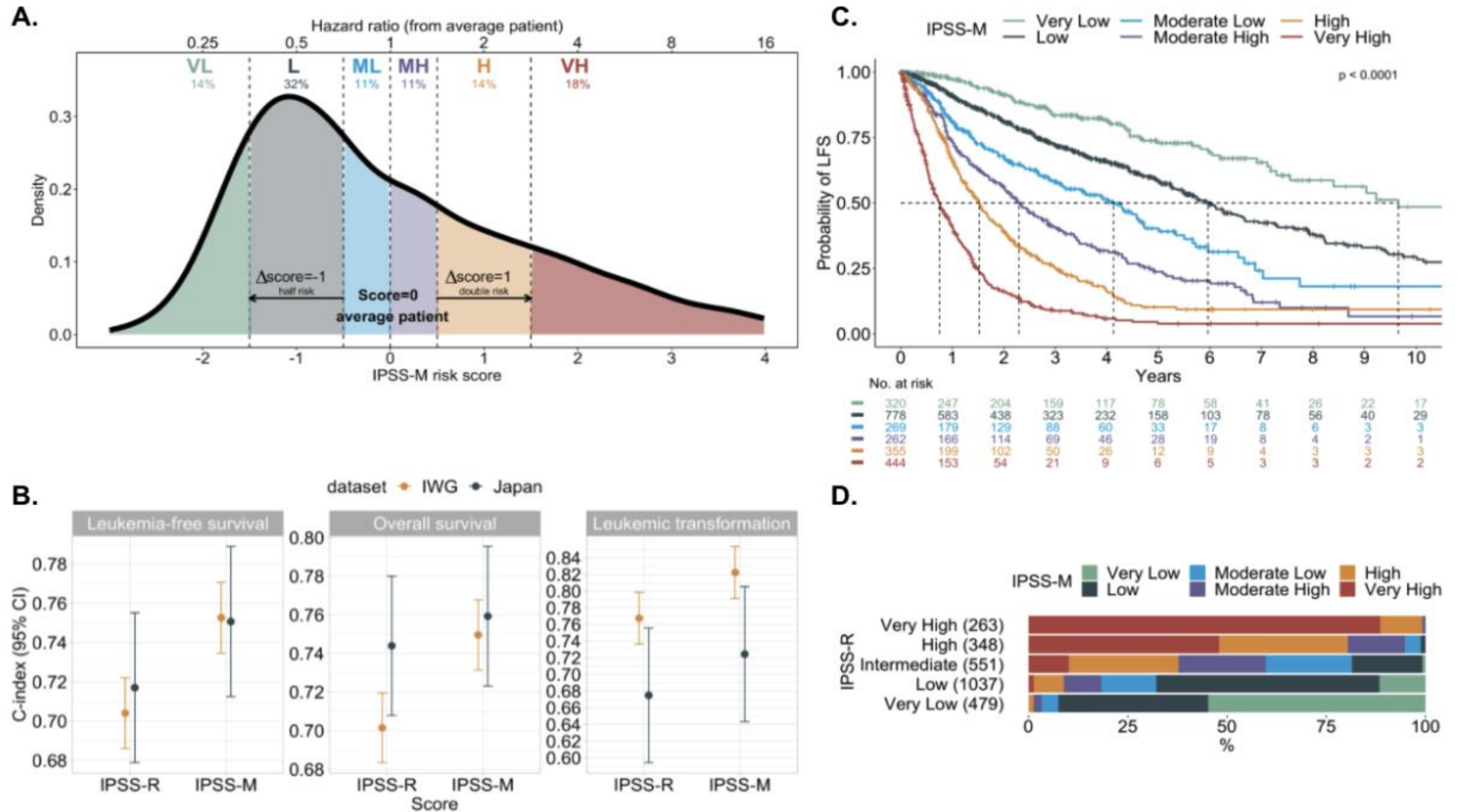
Bernard et al. NEJM Evidence 2022

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Prognostic risk score of MDS: Lower vs. Higher-risk MDS

- **Lower Risk MDS**

  - International prognostic scoring system (IPSS) **Low-risk, Intermediate-1 risk (0-1.0)**

  - Revised-IPSS: **Very low risk, low-risk and intermediate risk (<3.5)**

  - Molecular-IPSS: **Very low, low and Moderate-Low Scores**

  - Morphology: **MDS without excess blasts**

- **Higher Risk MDS**

  - International prognostic scoring system (IPSS) **Int-II, high risk**

  - Revised-IPSS: **Intermediate, High and Very high risk**

  - Molecular IPSS: **Moderately High, High and Very High**

  - Morphology: **MDS-Excess Blasts 1/2**

Treatment Goals and Advancements in Lower-risk MDS

- Improve blood counts and decrease transfusion requirements

- Improve quality of life and symptom burden

- Only curative option is allogeneic hematopoietic cell transplant

- Timing to initiate treatment is key ---- always consider the following 2 factors:

  1. Blood Counts

  2. Patient's Symptom Burden

Treatment Goals in Higher-risk MDS

- Prevent disease progression to acute leukemia

- Prolong survival

- Only curative option is allogeneic hematopoietic cell transplant

Figure 1: U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) drug approvals for Myelodysplastic syndromes
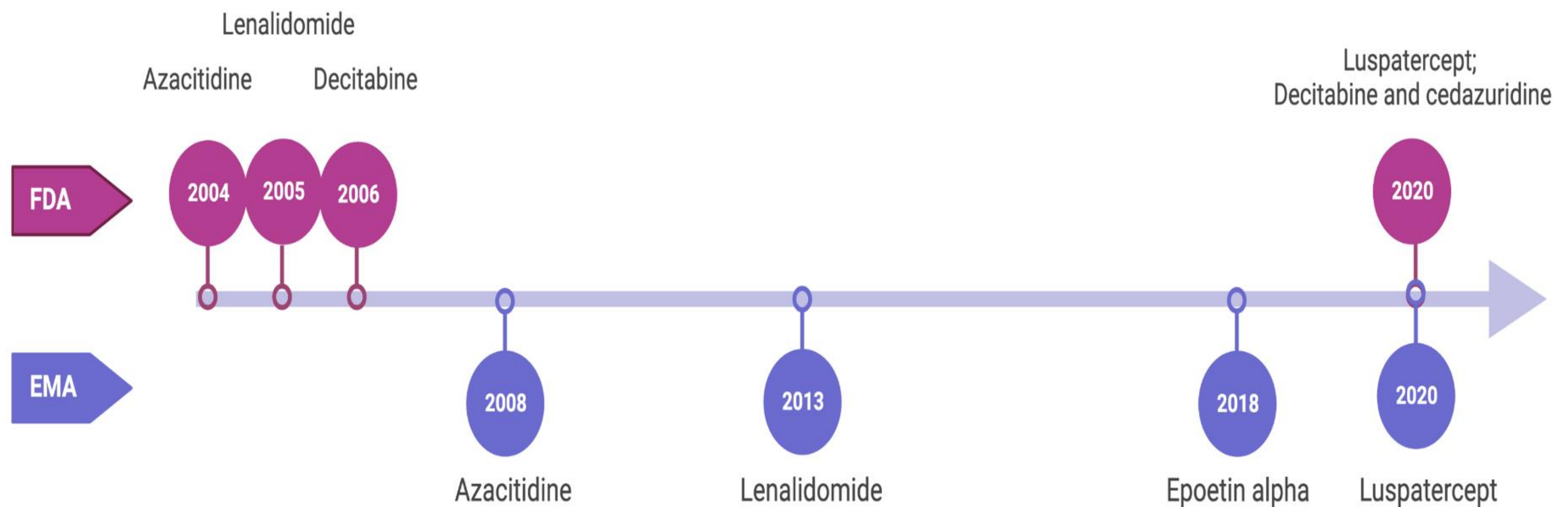
Treatment algorithm for lower-risk MDS
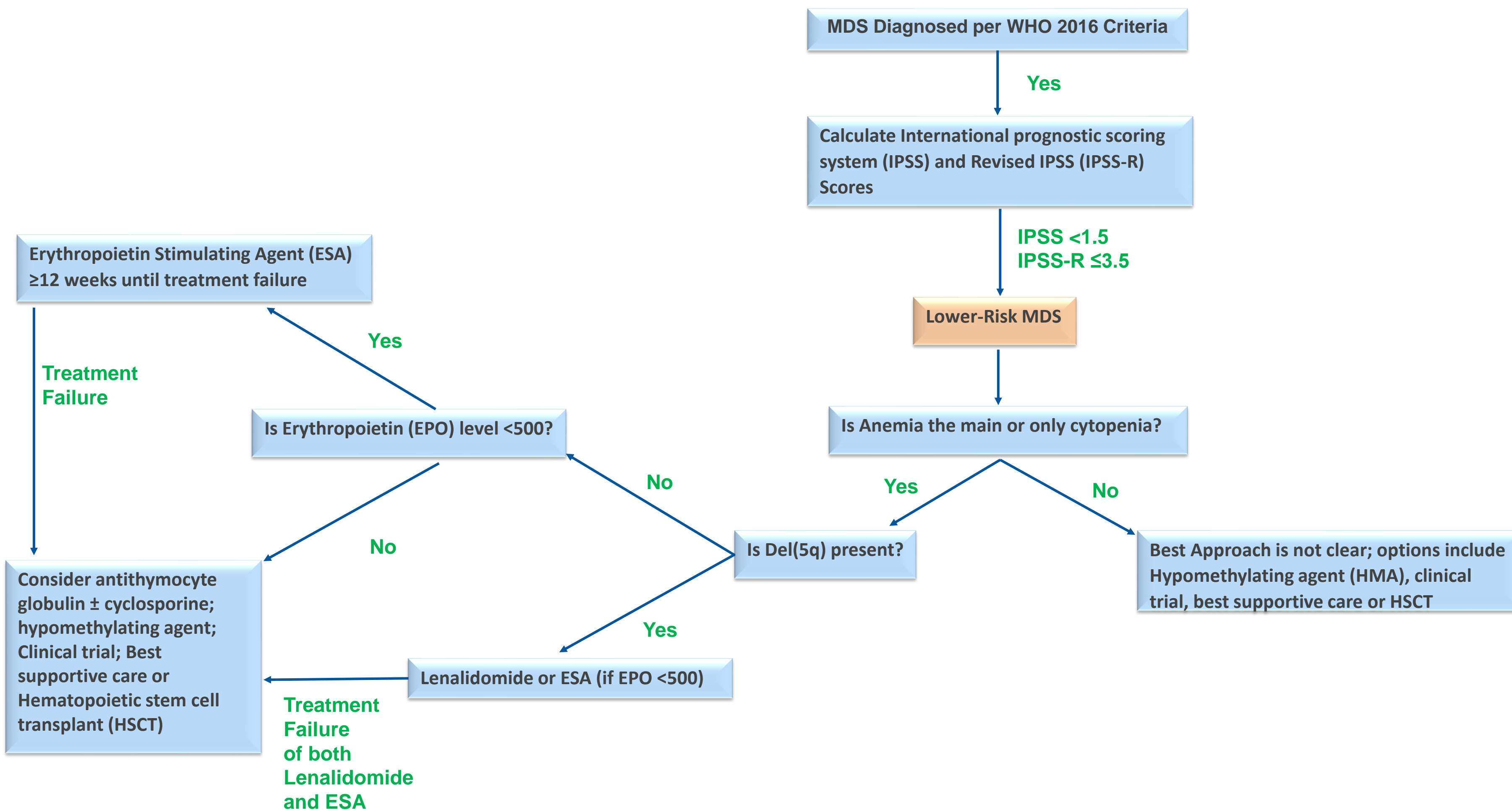
Madanat Y.F., Sekeres M.A. (2019) Myelodysplastic Syndromes (MDS). Concise Guide to Hematology. Springer, Cham

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Figure 2: Novel and Approved therapies for Lower-risk Myelodysplastic Syndromes.
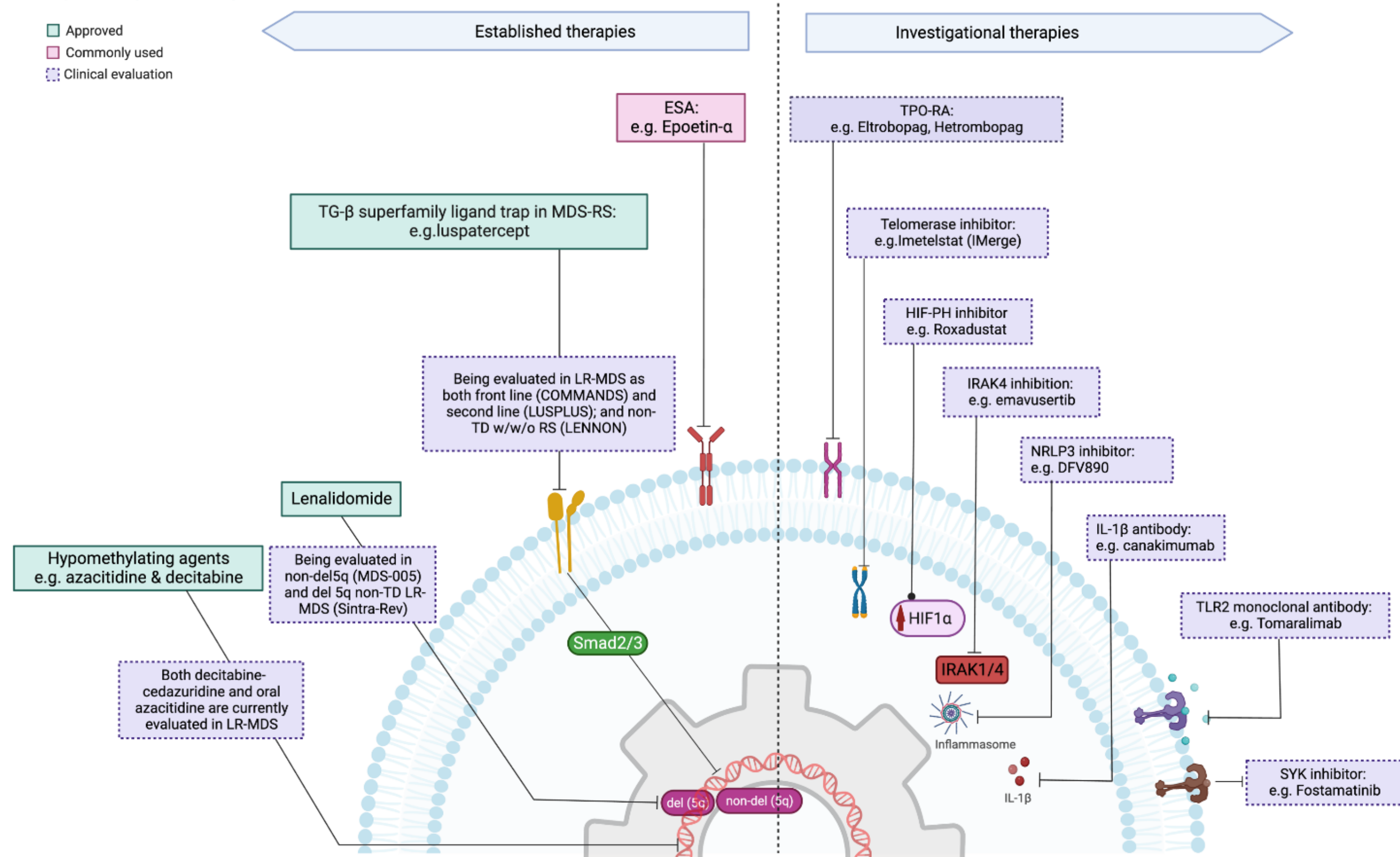
The MEDALIST Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated Anemia With Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

Pierre Fenaux, Uwe Platzbecker, Ghulam J. Mufti, Guillermo Garcia-Manero, Rena Buckstein, Valeria Santini, María Díez-Campelo, Carlo Finelli, Mario Cazzola, Osman Ilhan, Mikkael A. Sekeres, José F. Falantes, Beatriz Arrizabalaga, Flavia Salvi, Valentina Giai, Paresh Vyas, David Bowen, Dominik Selleslag, Amy E. DeZern, Joseph G. Jurcic, Ulrich Germing, Katharina S. Götze, Bruno Quesnel, Odile Beyne-Rauzy, Thomas Cluzeau, Maria Teresa Voso, Dominiek Mazure, Edo Vellenga, Peter L. Greenberg, Eva Hellström-Lindberg, Amer M. Zeidan, Abderrahmane Laadem, Aziz Benzohra, Jennie Zhang, Anita Rampersad, Peter G. Linde, Matthew L. Sherman, Rami S. Komrokji, Alan F. List

MEDALIST Trial
Primary Endpoint: Red Blood Cell Transfusion Independence ≥ 8 Weeks

RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**58 (37.9)**	**10 (13.2)**
95% CI	30.2–46.1	6.5–22.9
P value[a]	< 0.0001	

[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
CI, confidence interval.

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MEDALIST Trial
Duration of RBC-TI Response in Primary Endpoint Responders

Median duration (weeks) (95% CI): 30.6 (20.6–40.6) vs 13.6 (9.1–54.9)

— Luspatercept
— Placebo
++ Censored

- Median DOR luspatercept 30.6 weeks
- Median DOR PL arm was 13.6 weeks

Probability of Maintaining RBC-TI (y-axis)

Duration of RBC-TI[a] (week) (x-axis)

Number of patients
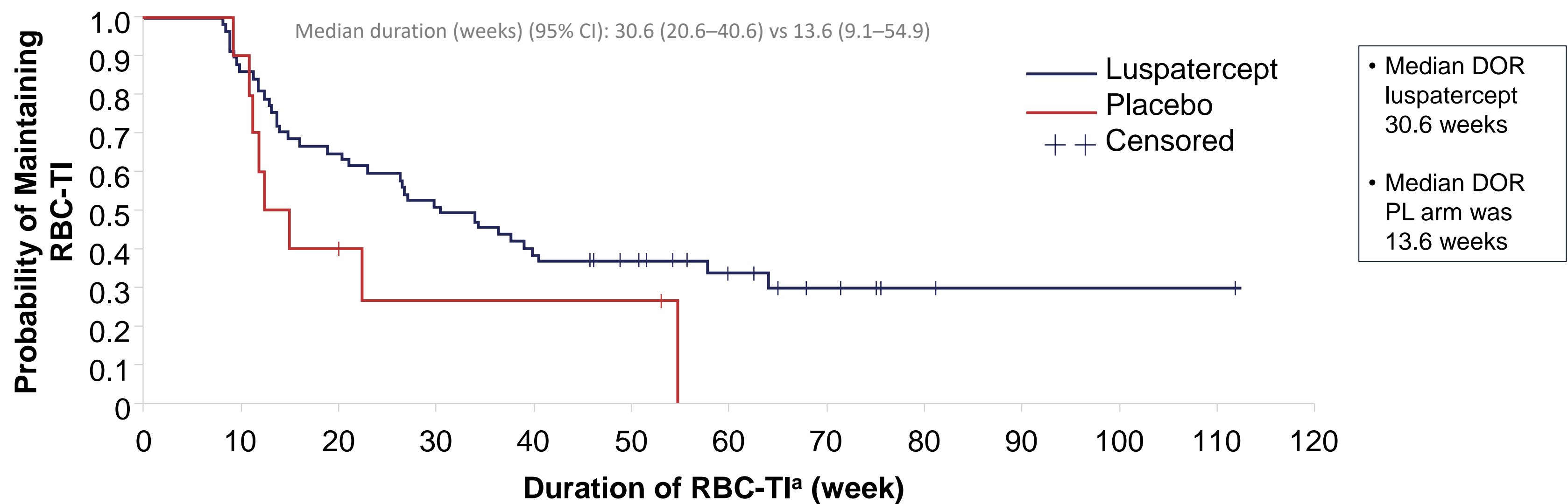
	0	10	20	30	40	50	60	70	80	90	100	110	120
Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

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

American Society of Hematology

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

Place video here

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

Uwe Platzbecker[1], Pierre Fenaux[2], David P. Steensma[3], Koen Van Eygen[4], Azra Raza[5], Ulrich Germing[6], Patricia Font[7], Maria Diez-Campelo[8], Sylvain Thepot[9], Edo Vellenga[10], Mrinal M. Patnaik[11], Jun Ho Jang[12], Helen Varsos[13], Esther Rose[13], Jacqueline Bussolari[13], Fei Huang[14], Laurie Sherman[14], Faye Feller[14], Souria Dougherty[14], Libo Sun[14], Ying Wan[14], Aleksandra Rizo[14], Valeria Santini[15]

[1]University Clinic Leipzig (DE), [2]Hospital Saint-Louis, Universitey Paris Diderot (FR), [3]Dana-Farber Cancer Institute (US), [4]Algemeen Ziekenhuis Groeninge (BE), [5]Columbia University Medical Center (US), [6]Universitätsklinik Düsseldorf, Heinrich-Heine-Universität (DE), [7]Hospital General Universitario Gregorio Marañon (SP), [8]The University Hospital of Salamanca (SP), [9]CHU Angers (FR), [10]University Medical Center Groningen (NE), [11]Mayo Clinic, Rochester (US), [12]Samsung Medical Center, Sungkyunkwan University School of Medicine (KO), [13]Janssen Research & Development, LLC (US), [14]Geron Corporation (US), [15]MOS Unit, AOU Careggi-University of Florence (IT)

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Phase 2/3 Study Design

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Enrollment Complete

Phase 2
single arm, open label
LR MDS R/R to ESA

Imetelstat (n=38)
7.5 mg/kg IV q4w

Currently Enrolling

Phase 3
double-blind, placebo-controlled
N~170

Imetelstat (n~115)
7.5 mg/kg IV q4w

R A N D O M I Z E

2:1

Stratification:
- Transfusion burden (≤6 vs. >6 units)
- IPSS risk category (low vs intermediate-1)

Placebo (n~55)
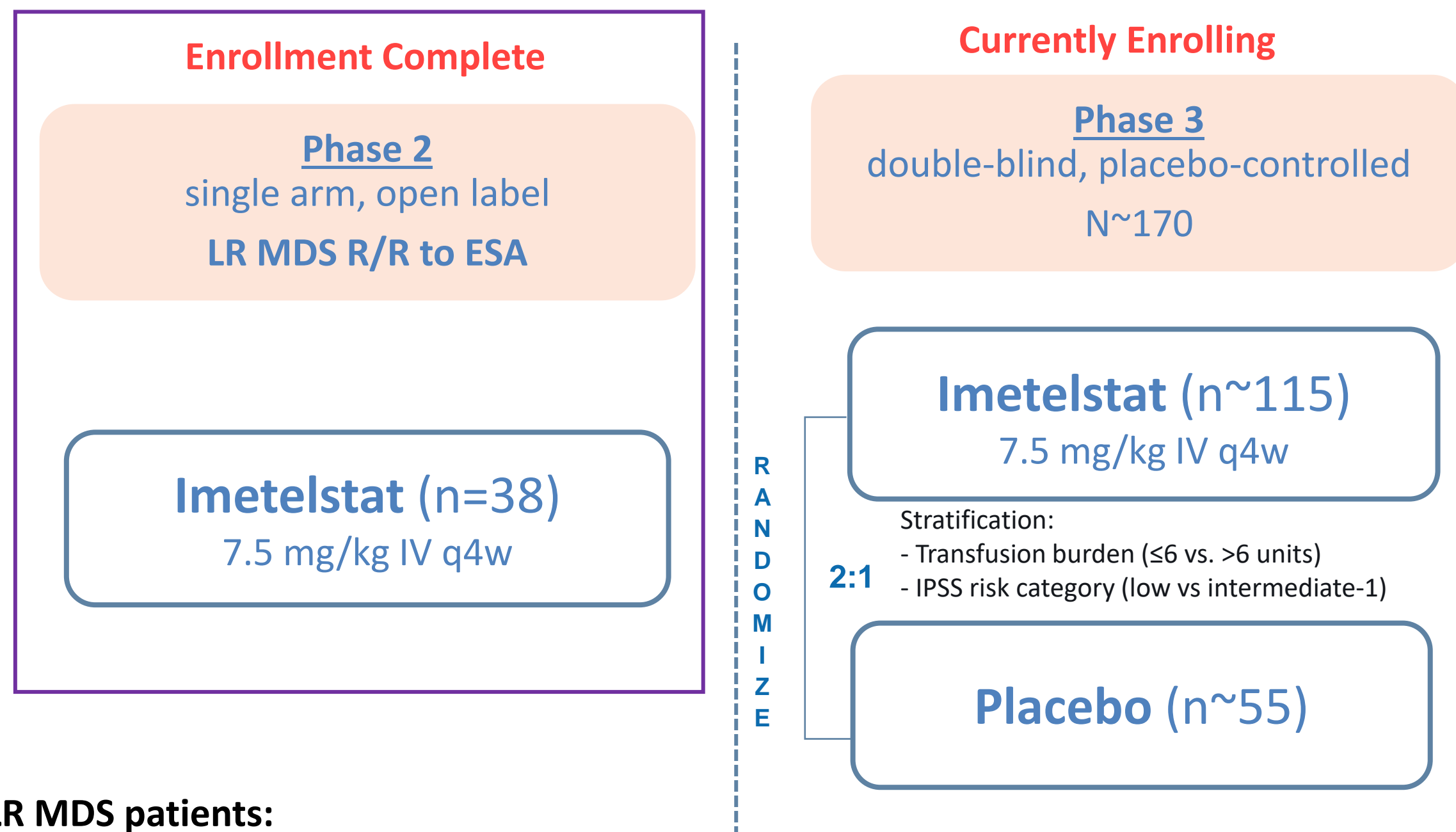
Results from Phase 2 recently published online ahead of print: 2020 Oct 27;JCO2001895

❑ **LR MDS patients:**
  ○ Non-del(5q), IPSS Low or Int-1
  ○ Relapsed/Refractory to ESA or EPO >500 mU/ml; HMA/Len naïve
  ○ Transfusion dependent: ≥ 4 units RBC/8 weeks over 16 week pre-study period
❑ **Primary Endpoint: 8-week RBC Transfusion Independence (TI)**
❑ **Key Secondary Endpoints: 24-week RBC TI/Duration of TI/HI-E**

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agents; IPSS, International Prognostic Scoring System; Len, lenalidomide; LR, low risk; RBC, red blood cell; R/R, relapsed/refractory

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Meaningful and Durable Transfusion Independence (TI) with Imetelstat Treatment

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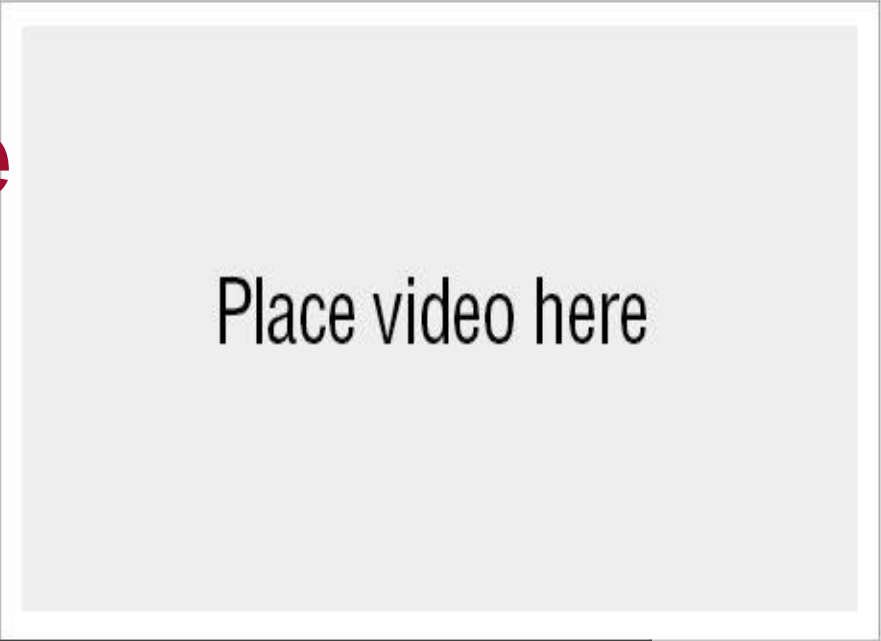
Parameters	N = 38
8-week TI, n (%)	**16 (42)**
Time to onset of 8-week TI, weeks, median (range)	8.3 (0.1-40.7)
Duration of TI, weeks, median (95% CI)[a]	**88.0 (23.1 – 140.9*)**
Cumulative duration of TI ≥ 8 weeks[b], median (95% CI)[a]	92.3 (42.9, 140.9)
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	12 (32)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

[a] Kaplan Meier method; [b] Cumulative Duration of TI ≥ 8 weeks is defined as the sum of all periods of TI ≥ 8 weeks during the treatment; [c] Maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb / 8 weeks).
CI, confidence interval; Hb, hemoglobin

*Longest TI > 2.7 years

Treatment algorithm for Higher-risk MDS

Calculate International prognostic scoring system (IPSS) and Revised IPSS (IPSS-R) Scores

IPSS >1.5
IPSS-R ≥3.5

Higher-Risk MDS

Patient desires and suitable for bone marrow transplant, younger patient with good performance status & available stem cell donor

Yes

No

Initiate bone marrow transplant work up. In the meantime treat with HMA or intensive chemotherapy depending on patient age, bone marrow blast percentage and cytogenetic risk group

Hypomethylating agent (HMA) for ≥6 cycles OR clinical trial option

Clinical Trial option or best supportive care

Madanat Y.F., Sekeres M.A. (2019) Myelodysplastic Syndromes (MDS). Concise Guide to Hematology. Springer, Cham

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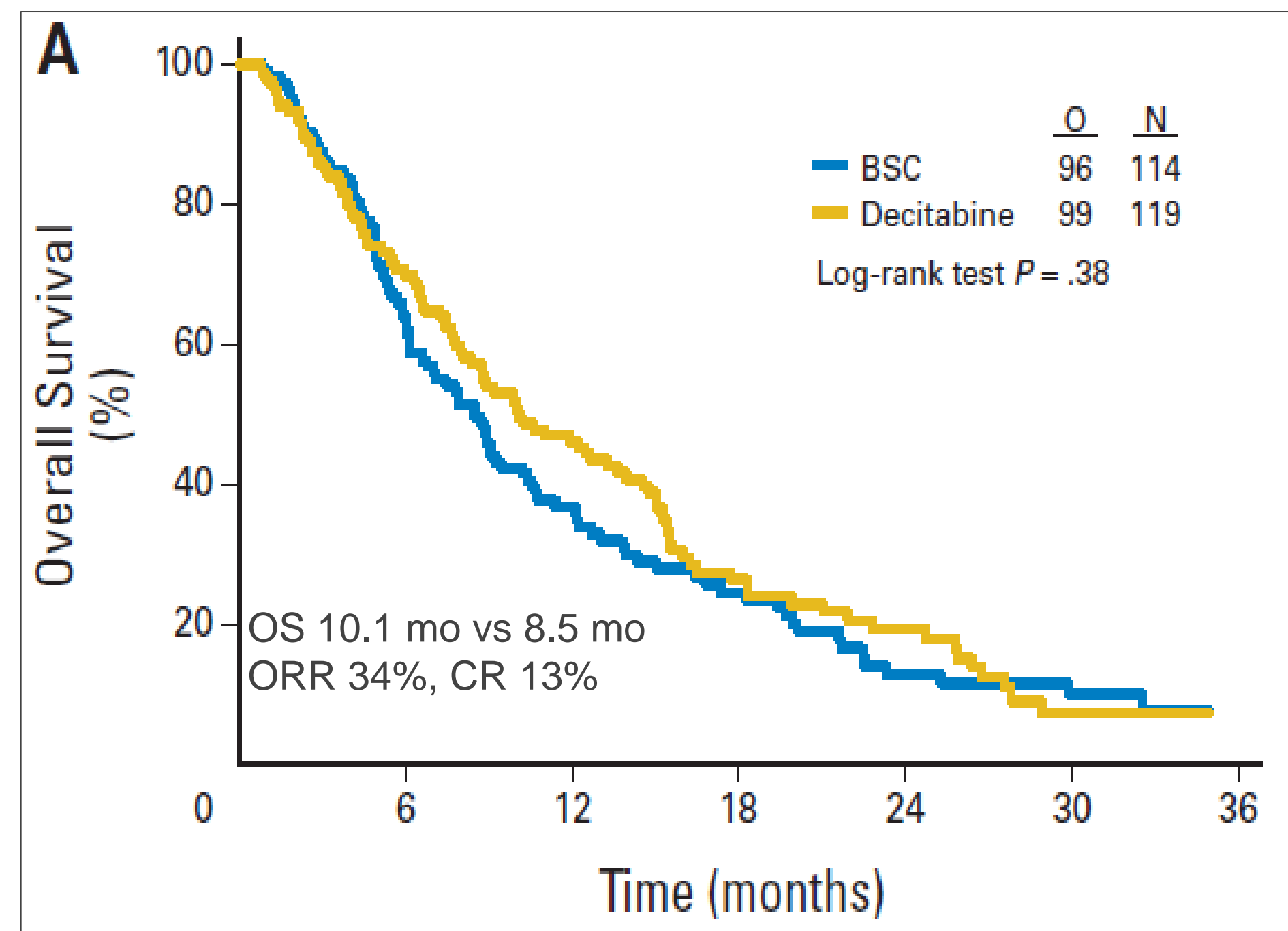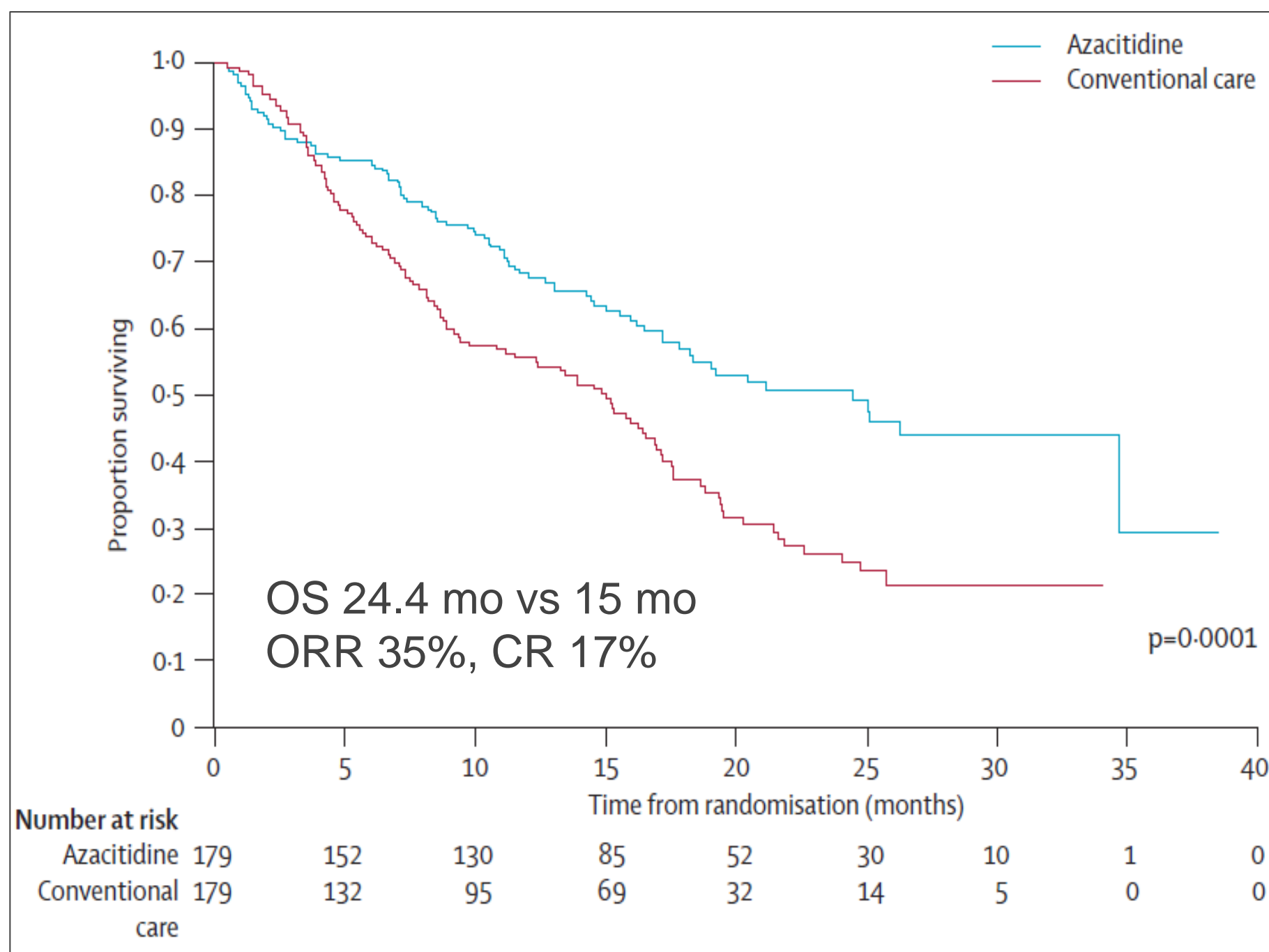# Outcomes of Hypomethylating Therapy in Higher-risk MDS Azacitidine and Decitabine

OS 24.4 mo vs 15 mo
ORR 35%, CR 17%

OS 10.1 mo vs 8.5 mo
ORR 34%, CR 13%
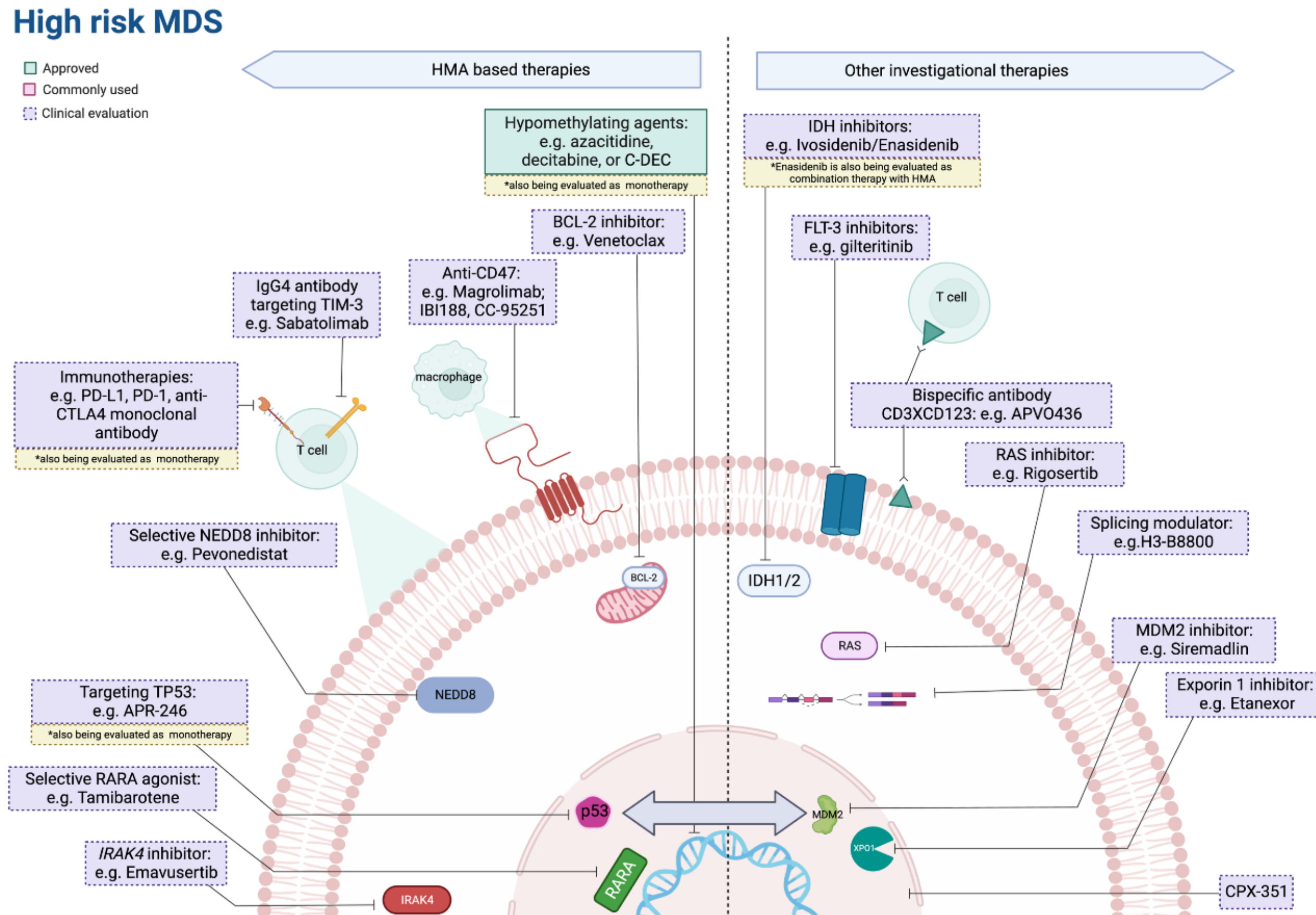
Fenaux P et al. Lancet. 2009

Lubbert et al. JCO. 2011

Figure 3: Novel and Approved Therapies for Higher-Risk Myelodysplastic Syndromes

High risk MDS

- ☐ Approved
- ☐ Commonly used
- ☐ Clinical evaluation

HMA based therapies

Other investigational therapies

Hypomethylating agents: e.g. azacitidine, decitabine, or C-DEC
*also being evaluated as monotherapy

IDH inhibitors: e.g. Ivosidenib/Enasidenib
*Enasidenib is also being evaluated as combination therapy with HMA

BCL-2 inhibitor: e.g. Venetoclax

FLT-3 inhibitors: e.g. gilteritinib

IgG4 antibody targeting TIM-3 e.g. Sabatolimab

Anti-CD47: e.g. Magrolimab; IBI188, CC-95251

T cell

Immunotherapies: e.g. PD-L1, PD-1, anti-CTLA4 monoclonal antibody
*also being evaluated as monotherapy

macrophage

Bispecific antibody CD3XCD123: e.g. APVO436

RAS inhibitor: e.g. Rigosertib

Selective NEDD8 inhibitor: e.g. Pevonedistat

Splicing modulator: e.g.H3-B8800

BCL-2

IDH1/2

RAS

MDM2 inhibitor: e.g. Siremadlin

Targeting TP53: e.g. APR-246
*also being evaluated as monotherapy

NEDD8

Exporin 1 inhibitor: e.g. Etanexor

Selective RARA agonist: e.g. Tamibarotene

p53

MDM2

IRAK4 inhibitor: e.g. Emavusertib

RARA

XPO1

IRAK4

CPX-351

Madanat et al. Expert Review of Hematology, *Submitted Work*, under Review, 2022

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Promising Clinical Trial >> Options – Higher-Risk MDS

- Combination of Magrolimab with azacitidine vs azacitidine alone (completed enrollment, awaiting results)

- Combination of Venetoclax with azacitidine vs azacitidine alone (enrolling)

Magrolimab + Aza in Patients With MDS and AML: Study Design

- **Multicenter, single-arm phase Ib study**

  - Current analysis reports data from expansion phase

Patients with untreated AML ineligible for induction CT or untreated MDS classed intermediate to very high risk by IPSS-R (N = 68)

→

Safety Evaluation

Magrolimab 1, 30 mg/kg QW* +
Aza 75 mg/m^2 Days 1-7
(n = 6)

→

Expansion

Magrolimab 1, 30 mg/kg QW or Q2W* +
Aza 75 mg/m^2 Days 1-7
(n = 68)

*Patients received magrolimab 1 mg/kg priming dose, followed by dose ramp-up to 30 mg/kg by Wk 2, continued thereafter.

- **Primary endpoints: safety, efficacy**

- **Secondary endpoints: magrolimab PK, PD, immunogenicity**

- **Exploratory endpoints: CD47 receptor occupancy, immune activity markers, molecular profiling**

Sallman. ASCO 2020. Abstr 7507.

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Magrolimab + Aza in Patients With MDS and AML: Response

Best Overall Response, n (%)	MDS (n = 33)	AML (n = 25)
ORR	30 (91)	16 (64)
CR	14 (42)	10 (40)
CRi	NA	4 (16)
PR	1 (3)	1 (4)
MLFS/marrow CR	8 (24)*	1 (4)
Hematologic improvement	7 (21)	NA
SD	3 (9)	8 (32)
PD	0	1 (4)

Outcome, n (%)	MDS (n = 33)	AML (n = 25)
RBC transfusion independence	11/19 (58)	9/14 (64)
Complete cytogenetic response	9/26 (35)	6/12 (50)
MRD negativity in responders	6/30 (20)	8/16 (50)
Median DoR, mos	NR (0.03+ to 10.4+)	NR (0.03+ to 15.1+)
Median follow-up, mos (range)	5.8 (2.0 to 15.0)	9.4 (1.9 to 16.9)

*4 patients had marrow CR and hematologic improvement.

- Median TTR: 1.9 mos; median OS: NR (either arm)

- 6-mo CR rate, MDS patients: 56%

- 9 of 58 (16%) patients received alloSCT

Sallman. ASCO 2020. Abstr 7507.

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Magrolimab + Aza in Patients With MDS and AML: Response in Patients With *TP53* Mutation

Outcome	MDS *TP53* Mutant (n = 12)	AML *TP53* Mutant (n = 4)
ORR, n (%)	9 (75)	3 (75)
CR, n (%)	5 (42)	2 (50)
CRi/marrow CR, n (%)	4 (33)	1 (25)
Complete cytogenetic response, n/N (%)*	4/8 (50)	3/3 (100)
MRD negativity in responders, n/N (%)	4/9 (44)	0
Median DoR, mos	NR (0.03+ to 15.1)	NR (0.03+ to 5.2+)
6-mo survival probability, %	91	100
Median follow-up, mos (range)	8.8 (1.9 to 16.9)	7 (4.2 to 12.2)

*Responders with cytogenetic abnormalities at baseline.
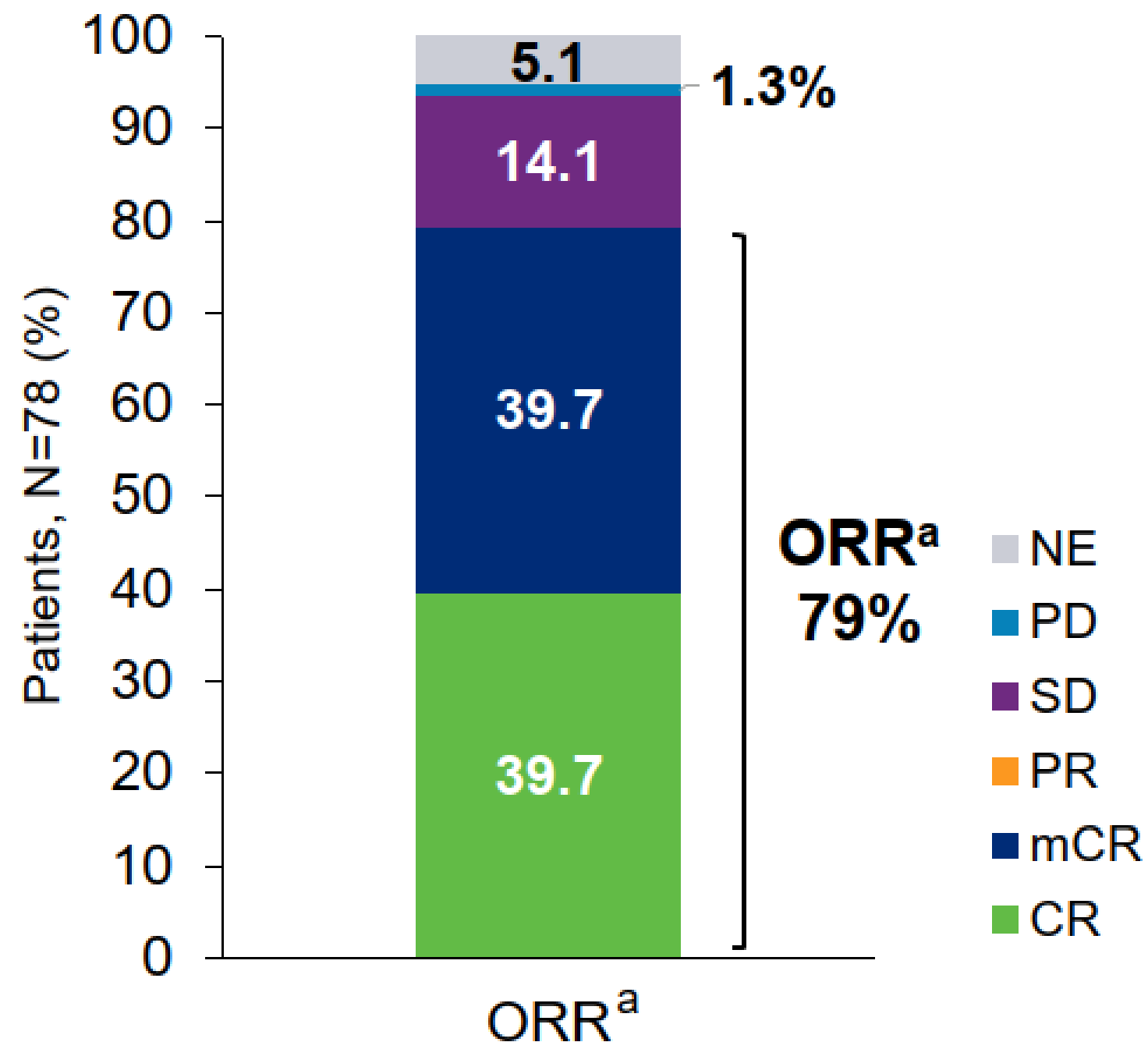
Sallman. ASCO 2020. Abstr 7507.

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Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination With Azacitidine for the Treatment of Patients With Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study

Jacqueline S. Garcia,[1] Andrew H. Wei,[2] Uma Borate,[3] Chun Yew Fong,[4] Maria R. Baer,[5] Florian Nolte,[6] Joseph Jurcic,[7] Meagan A. Jacoby,[8] Wan-Jen Hong,[9] Uwe Platzbecker,[10] Olatoyosi Odenike,[11] Ilona Cunningham,[12] Ying Zhou,[13] Bo Tong,[13] Leah Hogdal,[13] Rajesh Kamalakar,[13] Jessica E. Hutti,[13] Steve Kye,[13] Guillermo Garcia-Manero[14]

Slide Courtesy: Dr. Garcia

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Response Rates and Transfusion Independence

Bar chart (ORR[a]):
- CR: 39.7
- mCR: 39.7
- SD: 14.1
- PD: 1.3%
- NE: 5.1
- ORR[a]: 79%

Legend:
- NE
- PD
- SD
- PR
- mCR
- CR

- Median DoR: 12.9 months (min–max, 12.1–16.8)
- Median DoR after CR: 13.8 months (min–max, 6.5–20.9)
- Median time to CR: 2.6 months (min–max, 1.2–19.6)
- For patients receiving Ven 400 mg (RP2D; n=51)[b]
  - 84% of patients achieved ORR[a]
    - 47% achieved ORR by Cycle 2; 78% achieved ORR by Cycle 3
  - 35% of patients achieved CR

Transfusion independence rate	n (% of N=78)
RBC and platelet	51 (65)
RBC	52 (67)
Platelet	60 (77)

- A total of 16 patients (21%) went on to receive poststudy transplants; 7 received bone marrow transplant; and 9 received stem cell transplant

[a]Excludes patients of Arm C (Aza only); ORR includes CR + mCR + PR; PR n=0; per IWG 2006 (Cheson BD, et al. *Blood*. 2006;108(2):419–25);
[b]Excludes 5 patients from the randomization phase who received 28-day Ven
Aza, azacitidine; CR, complete remission; DoR, duration of response; IWG 2006, International Working Group 2006; mCR, marrow CR; NE, not evaluable; NR, not reported; ORR, objective response rate; PD, disease progression; PR, partial response; RBC, red blood cell; RP2D, recommended phase 2 dose; SD, stable disease; Ven, venetoclax
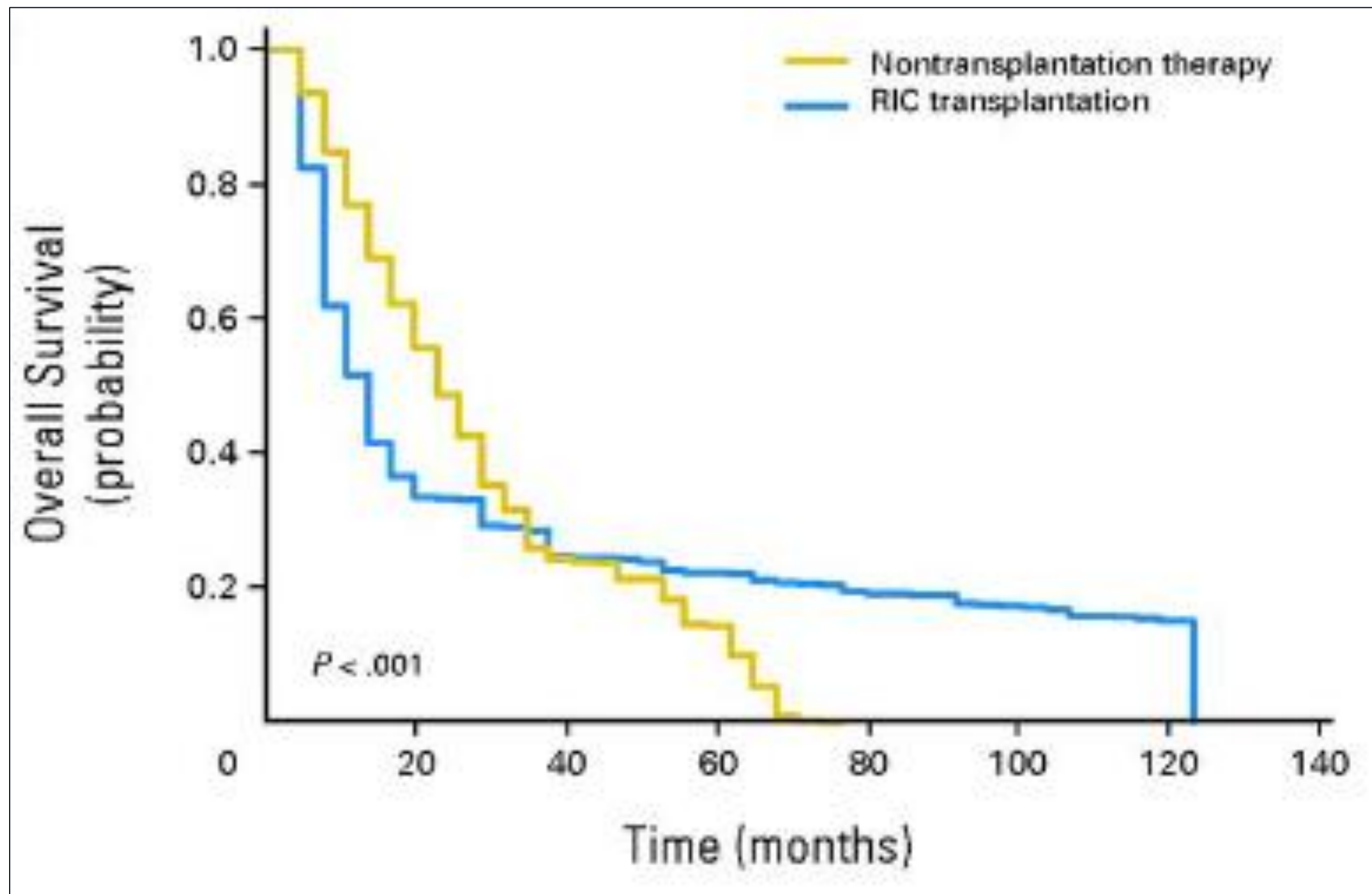
Data cutoff: June 30, 2020

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Slide Courtesy: Dr. Garcia

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Allogeneic Transplant – Lower-Risk MDS Decision Model
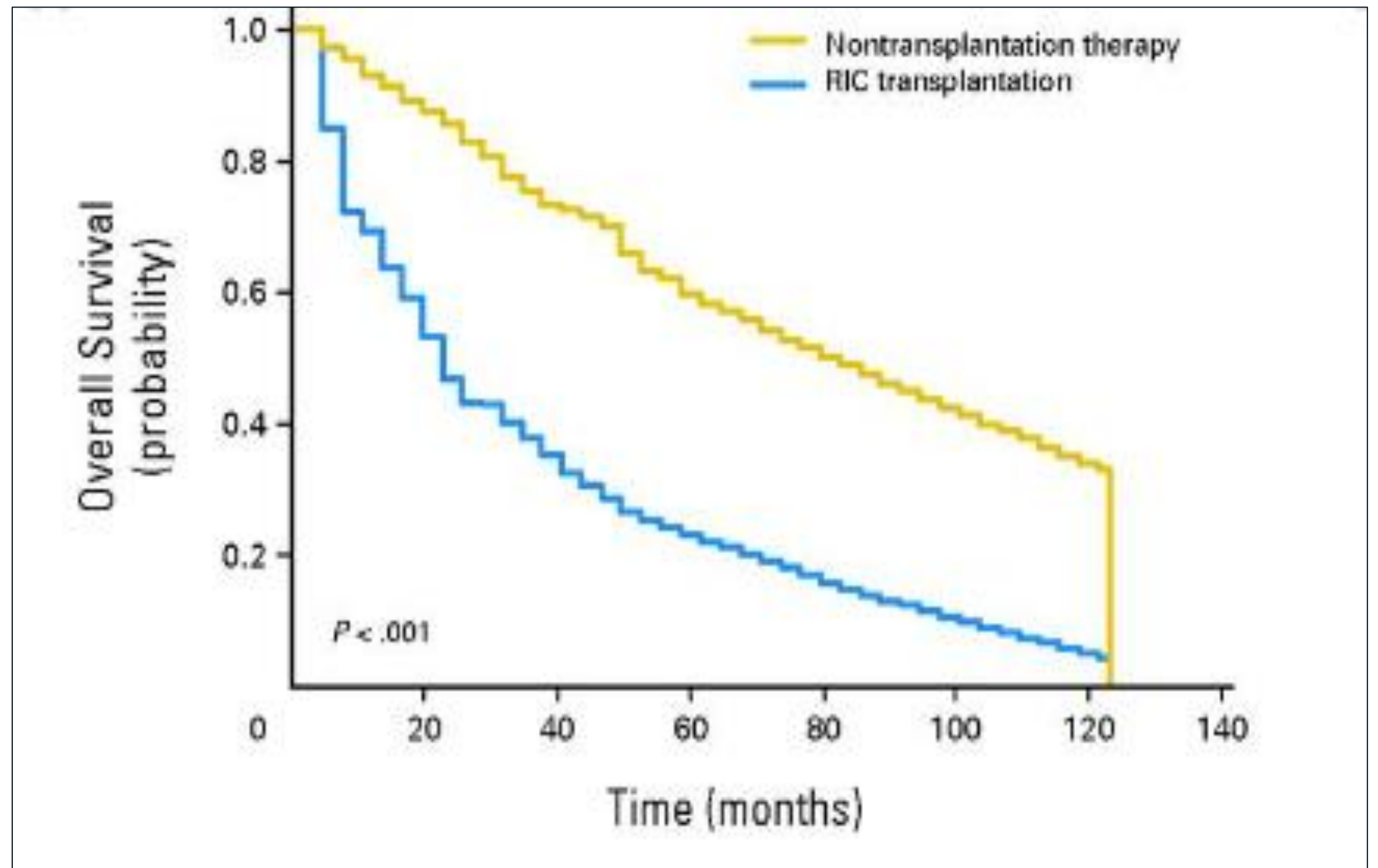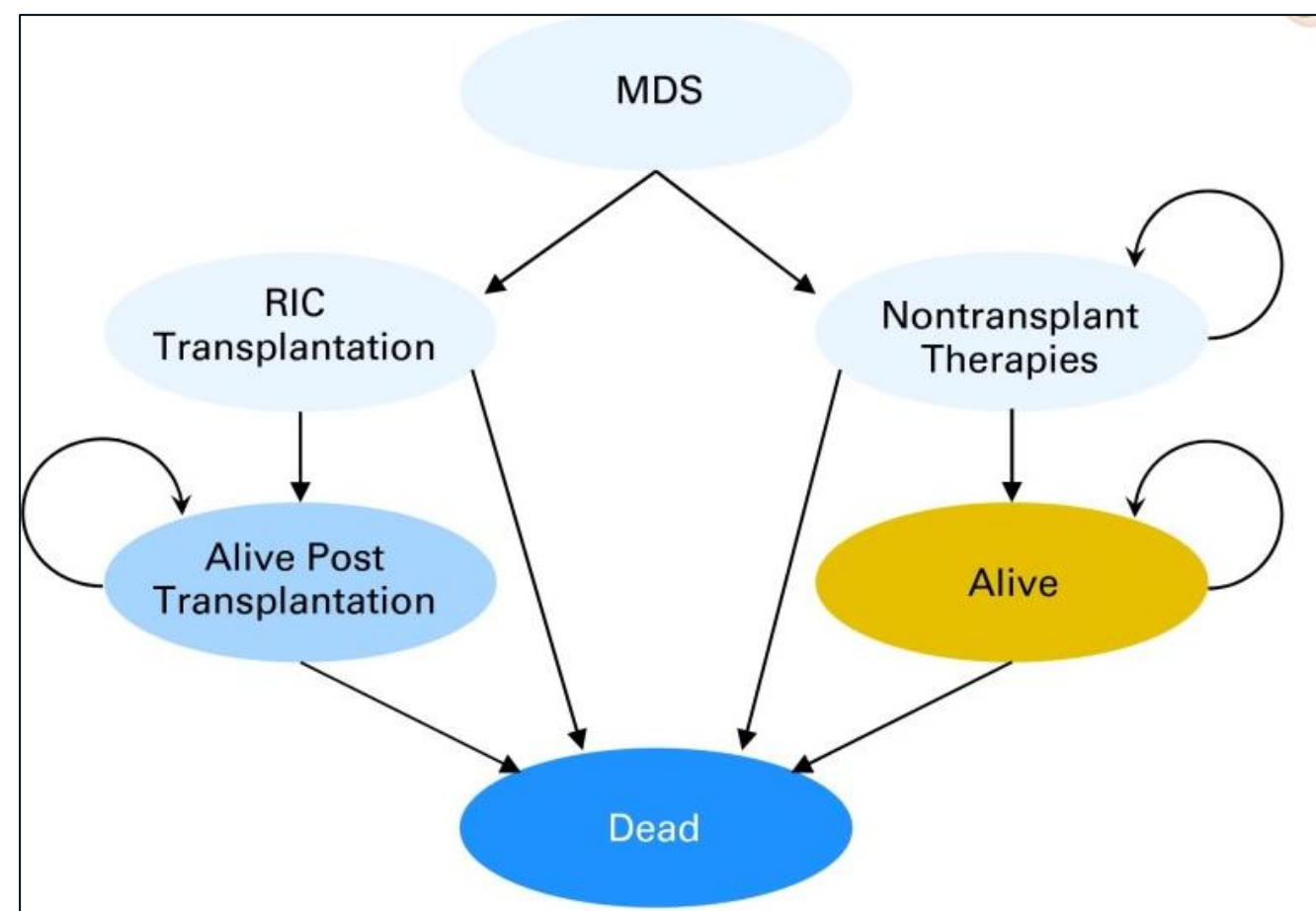
Koreth et al. J Clin Oncol. 2013

Allogeneic Transplant – Higher-Risk MDS Decision Model

Koreth et al. J Clin Oncol. 2013

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Summary FDA Approved treatments in MDS

- Lenalidomide for deletion 5q MDS

- Luspatercept for MDS-RS or MDS/MPN-RS-T

- Hypomethylating agents (Azacitidine, Decitabine, Decitabine-cedazuridine)

- Commonly used off-label:
  - Erythropoietin stimulating agents (erythropoietin and darbepoetin)
  - Lenalidomide for non-del(5q) MDS
  - Immunosuppressive therapy (Antithymocyte globulin (ATG) and cyclosporine)

Putting it all together!

1. Observation	1. For all lower-risk MDS without transfusion needs
2. Transfusion support (best supportive care)	2. ALL patients needing it
3. Erythropoietin Stimulating Agents	3. Lower-risk MDS, with low EPO level (<500) and anemia
4. Lenalidomide	4. Lower-risk MDS, deletion 5q and anemia
5. Luspatercept	5. Lower-risk MDS with ring sideroblasts (SF3B1) and anemia
6. Hypomethylating agents (HMAs): Azacitidine or decitabine	6. ALL Higher-risk MDS (eligible or ineligible for transplant)
7. Allogeneic Stem Cell Transplant	7. High-risk MDS and patient eligible/wanting transplant
8. Clinical Trial Options	8. Always encouraged when available

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Our patients, caregivers and patient advocates

mds foundation
the myelodysplastic syndromes foundation, inc.

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