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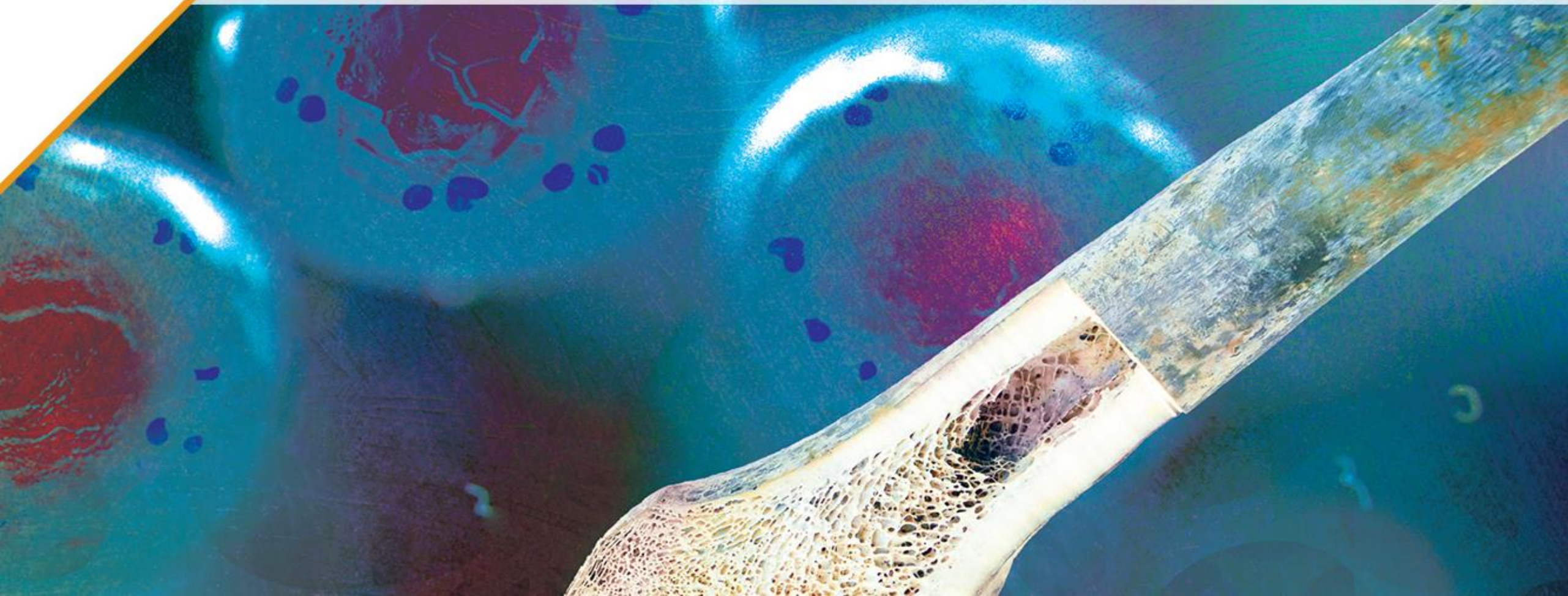
Shifting Paradigms for Assessment and Management of Lower-Risk MDS:

Genomics, Risk Stratification, and Novel Therapies



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Disclosure of Conflicts of Interest

- **Rami Komrokji, MD**, reported a financial interest/relationship or affiliation in the form of *Consultant*: AbbVie; Acceleron Pharma; Bristol-Myers Squibb Co; Celgene Corp; CTI BioPharma Corp; Geron; Innovent; Jazz Pharmaceuticals plc; Novartis Pharmaceuticals Corp; PharmaEssentia; Taiho Pharmaceutical Co, Ltd; and Takeda. *Speaker*: AbbVie, Bristol-Myers Squibb Co, Celgene Corp, Jazz Pharmaceuticals plc, and Servier.

- **Michael R. Savona, MD**, reported a financial interest/relationship or affiliation in the form of *Consultant:* AbbVie; Bristol-Myers Squibb Co; Celgene Corp; CTI BioPharma; Geron; Novartis Pharmaceuticals Corp; Ryvu; Sierra Oncology; Takeda; and TG Therapeutics, Inc. *Research funding:* ALX Oncology; Astex; Incyte; Takeda; and TG Therapeutics, Inc. *Royalty shares:* Boehringer-Ingelheim. *Stocks:* Karyopharm and Ryvu.

- **Jamile M. Shammo, MD, FASCP, FACP** reported a financial interest /relationship or affiliation in the form of *Speakers' bureau:* Alexion, Bristol-Myers Squibb Co, Incyte, and Sanofi. *Research grant*: AbbVie, Alexion, Bristol-Myers Squibb Company, CTI BioPharma, and Kartos Therapeutics. *Data and safety monitoring committee*: Apellis Pharmaceuticals and NS-Pharma. *Stocks*: AbbVie, Baxter, and Takeda Pharmaceutical Co.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Interpret molecular testing and risk stratification to facilitate diagnosis, prognostication, and treatment decision-making
- Formulate an evidence-based treatment plan for patients with lower-risk MDS based on patient- and disease-related factors
- Assess recent and available clinical evidence for novel emerging treatment strategies for managing lower-risk MDS patients
- Employ strategies to mitigate and manage treatment-related adverse events to enhance quality of life for patients with MDS

MDS, myelodysplastic syndrome.

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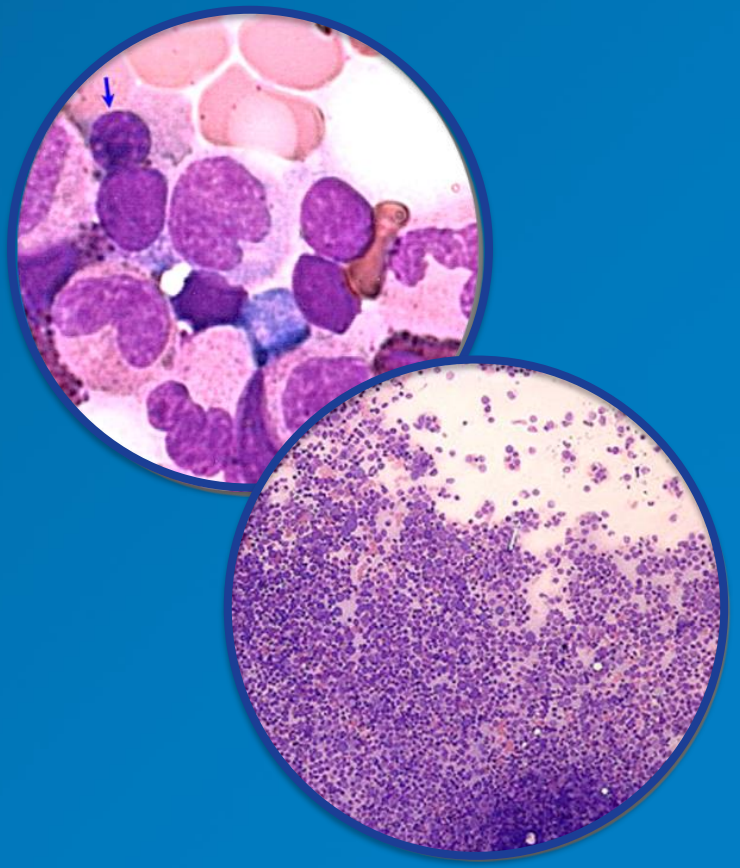
Overview of Low-Risk MDS and Risk For Progression to AML

Myelodysplastic Syndromes

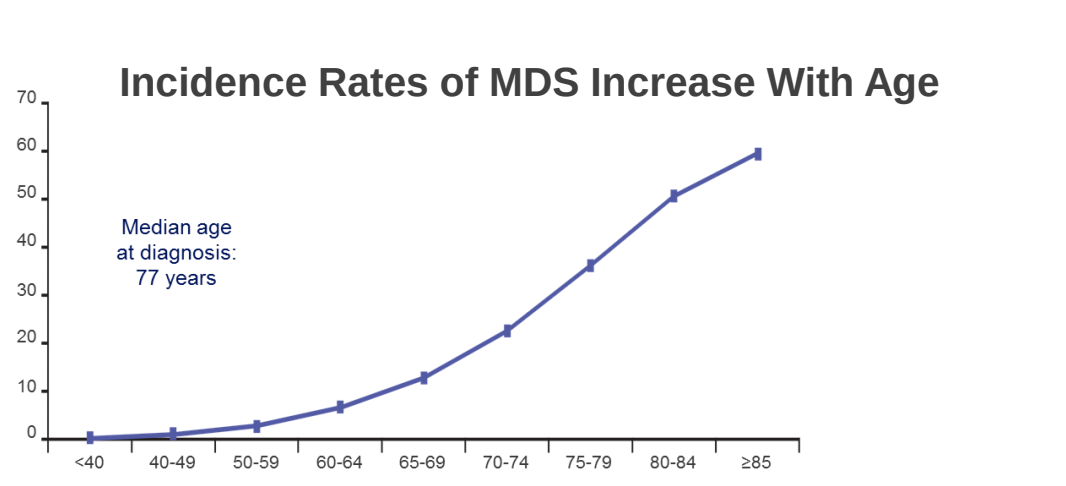
- A group of clonal hematopoietic stem cell disorders characterized by:
  - *Ineffective hematopoiesis/Features of bone marrow failure*
  - *Morphologic dysplasia of hematopoietic lineages*
  - *Acquired cytogenetic abnormalities ~50% of cases*
  - *Clonal hematopoiesis in ~90% of cases*
- Most cases are de novo MDS, a minority are related to toxin exposure (therapy-related)
- Tendency to progress to AML ~ 30% (higher in t-MDS)
- Bone marrow morphology is typically hypercellular for age
- Bone marrow can be hypocellular in ~10% of cases



AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; t-MDS, therapy-related MDS.
Bennett et al. In: Abeloff et al, eds. *Clinical Oncology*. 2004:2849-2881. SEER data. 2000-2009.

MDS Epidemiology

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



More than 86% of patients were diagnosed at age 60 years or older

Epidemiology of Hematologic and Nonhematologic Malignancies in the US (SEER Database, 2016)	Incidence[a]	5-year Overall Survival (2006-2012)
Hematologic malignancies		
Hodgkin lymphoma	2.6	86.2%
MDS	**4.5**	**29%**
Myeloma	6.5	48.5%
Leukemia	13.5	59.7%
Non-Hodgkin lymphoma	19.5	70.7%
Selected nonhematologic malignancies		
Lung and bronchus	57.3	17.7%
Colon and rectum	41.0	65.1%
Breast	124.8	89.7%

[a]Age-adjusted incidence rate per 100,000 men and women per year between 2009 and 2013.
MDS, myelodysplastic syndrome.
Zeidan et al. *Blood Rev.* 2019;34:1-15. SEER Cancer Statistics Review, 1975-2016. Ma. *Am J Med*. 2012;125(7 suppl):S2-S5.

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MDS Minimal Diagnostic Criteria

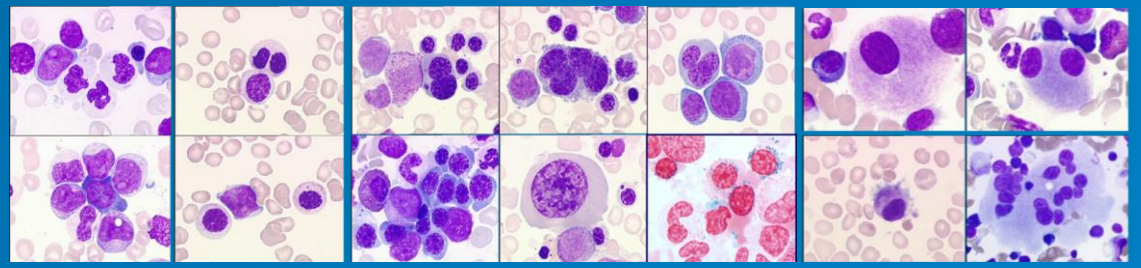
Prerequisite Criteria (Both 1 and 2 must be fulfilled)

1. Cytopenia(s)
   - Hb <10 g/dL, or
   - ANC <1800/µL, or
   - Platelets <100 x 10^9/L
2. EXCLUDE other causes of cytopenias and morphologic changes:
   - Vitamin B12/folate deficiency
   - HIV or other viral infection
   - Copper deficiency
   - Alcohol abuse
   - Medications (esp. methotrexate, azathioprine, recent chemotherapy)
   - Autoimmune conditions (ITP, Felty syndrome, SLE, etc)
   - Hereditary BMF syndromes (Fanconi anemia, etc)
   - Other hematologic disorders (aplastic anemia, LGL disorders, MPN, etc)

MDS Major Criteria

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

At least one of these major MDS criteria has to be met (with prerequisite criteria) to arrive at the diagnosis of MDS



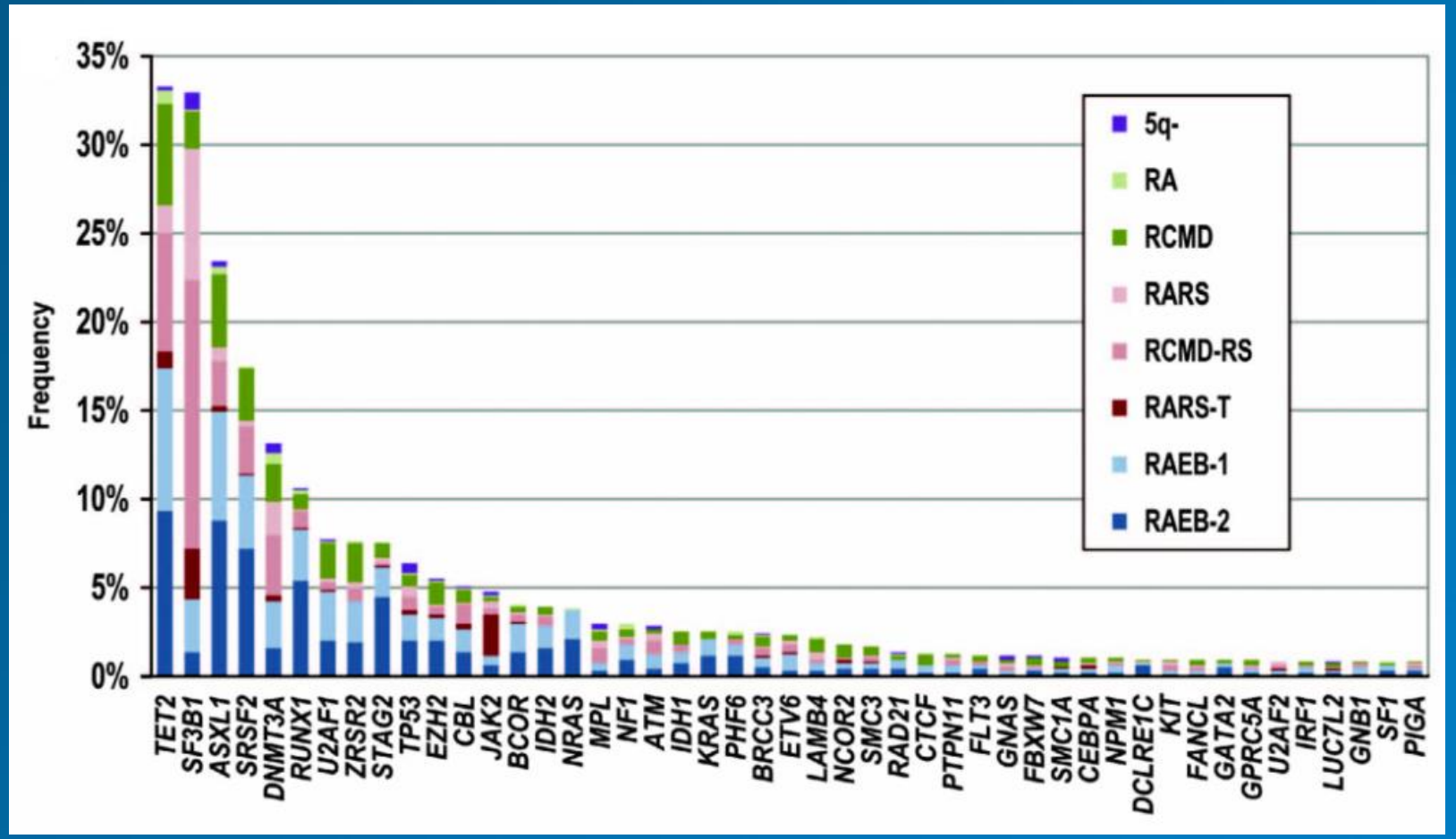
ANC, absolute neutrophil count; BM, bone marrow; BMF, bone marrow failure; Hb, hemoglobin; ITP, immune thrombocytopenia; LGL, large granular lymphocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; SLE, systemic lupus erythematosus.

Valent et al. *Oncotarget* 2017;8(43):73483-73500.

MDS Is a Genetic Disease

Recurrent Genetic Mutations in MDS

~89% of patients had a mutation by NGS



MDS, myelodysplastic syndrome; NGS, next-generation sequencing.

Haferlach et al. *Leukemia* 2014;28:241-247.

Genetic Abnormalities in MDS

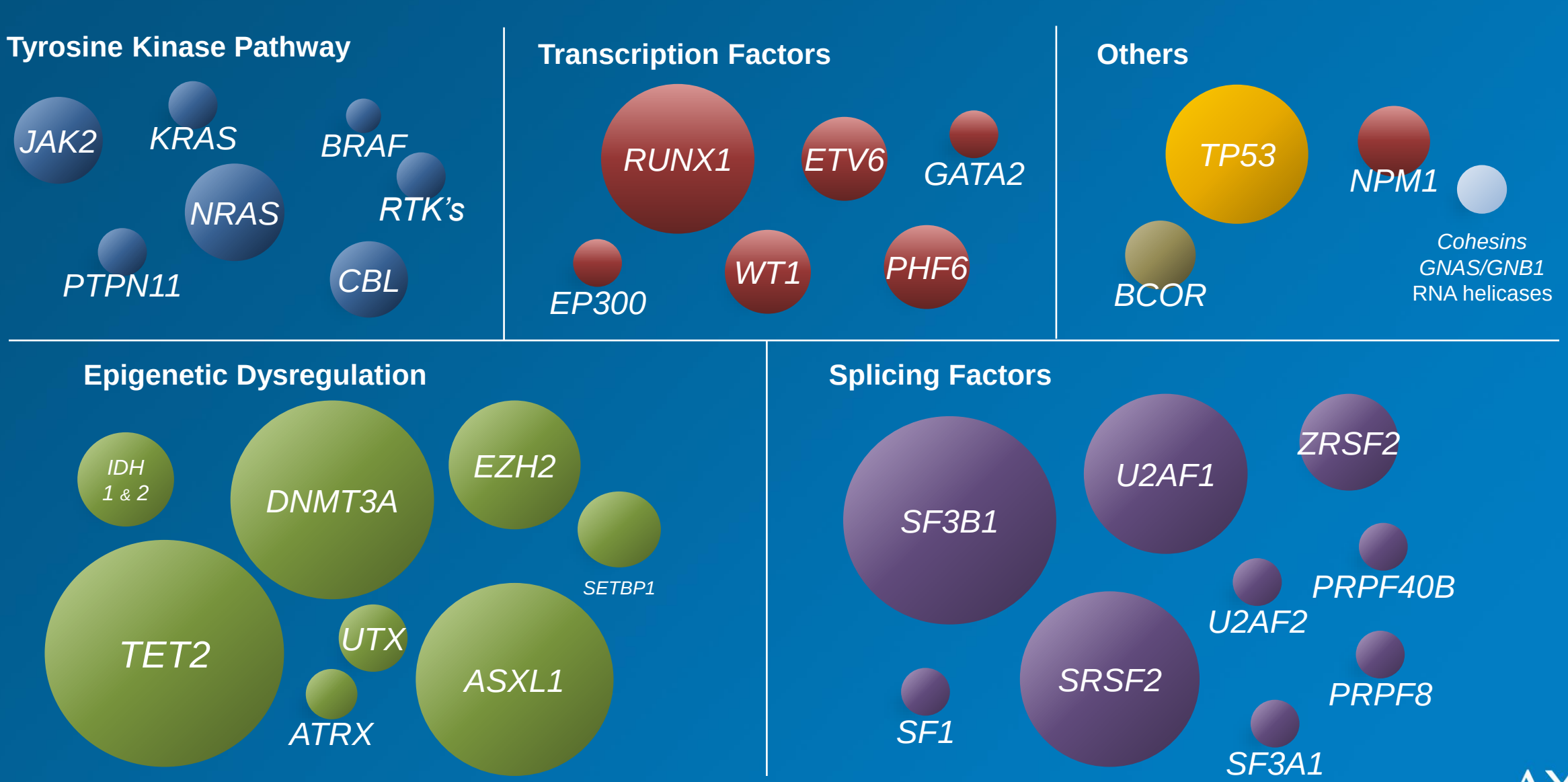
Translocations/ Rearrangements	Uniparental Disomy/ Microdeletions	Copy Number Change	Point Mutations
Rare in MDS	Rare–often at sites of point mutations	About 50% of cases	Most common
t(6;9) i(17q) t(1;7) t(3;?) t(11;?) inv(3) idic(X)(q13)	4q - *TET2* 7q - *EZH2* 11q - *CBL* 17p - *TP53*	del(5q) -7/del(7q) 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

CGH, comparative genomic hybridization; FISH, fluorescence in situ hybridization; MDS, myelodysplastic syndrome; SNP, single nucleotide polymorphism.

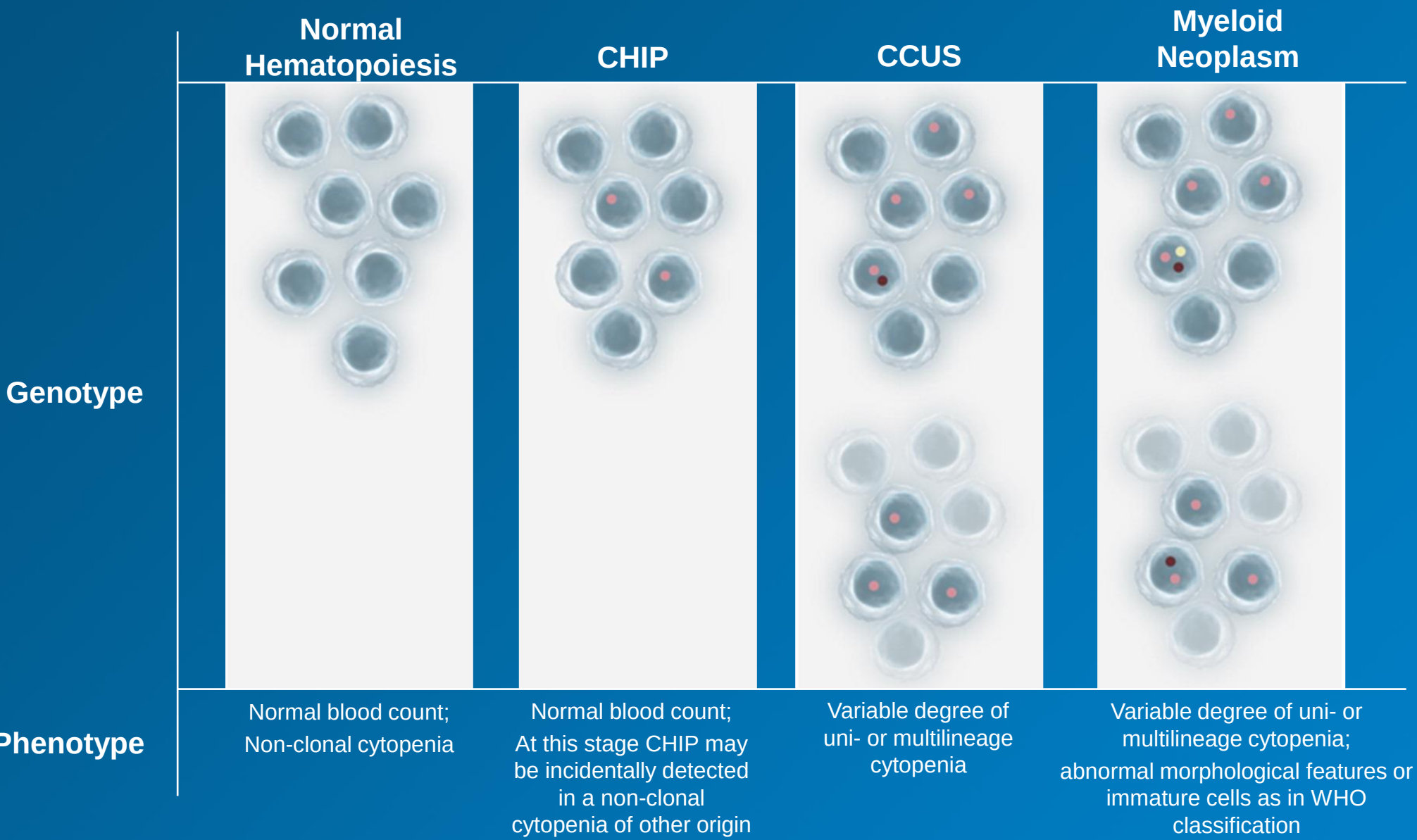
Vardiman et al. *Blood* 2009;114(5):937-951; Tiu et al. *Blood* 2011;117(17):4552-4560; Schanz et al. *J Clin Oncol.* 2011;29(15):1963-1970; Bejar et al. *N Engl J Med.* 2011;364(26):2496-2506; Bejar et al. *J Clin Oncol*. 2012;30(27):3376-3382.

Oncogenic Gene Mutations in MDS



Slide courtesy of D. Steensma (modified)

MDS Precursors States



CCUS, clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; MDS, myelodysplastic syndrome; WHO, World Health Organization.
Adapted from DeZern et al. *Am Soc Clin Oncol Educ Book* 2019;39:400-410.

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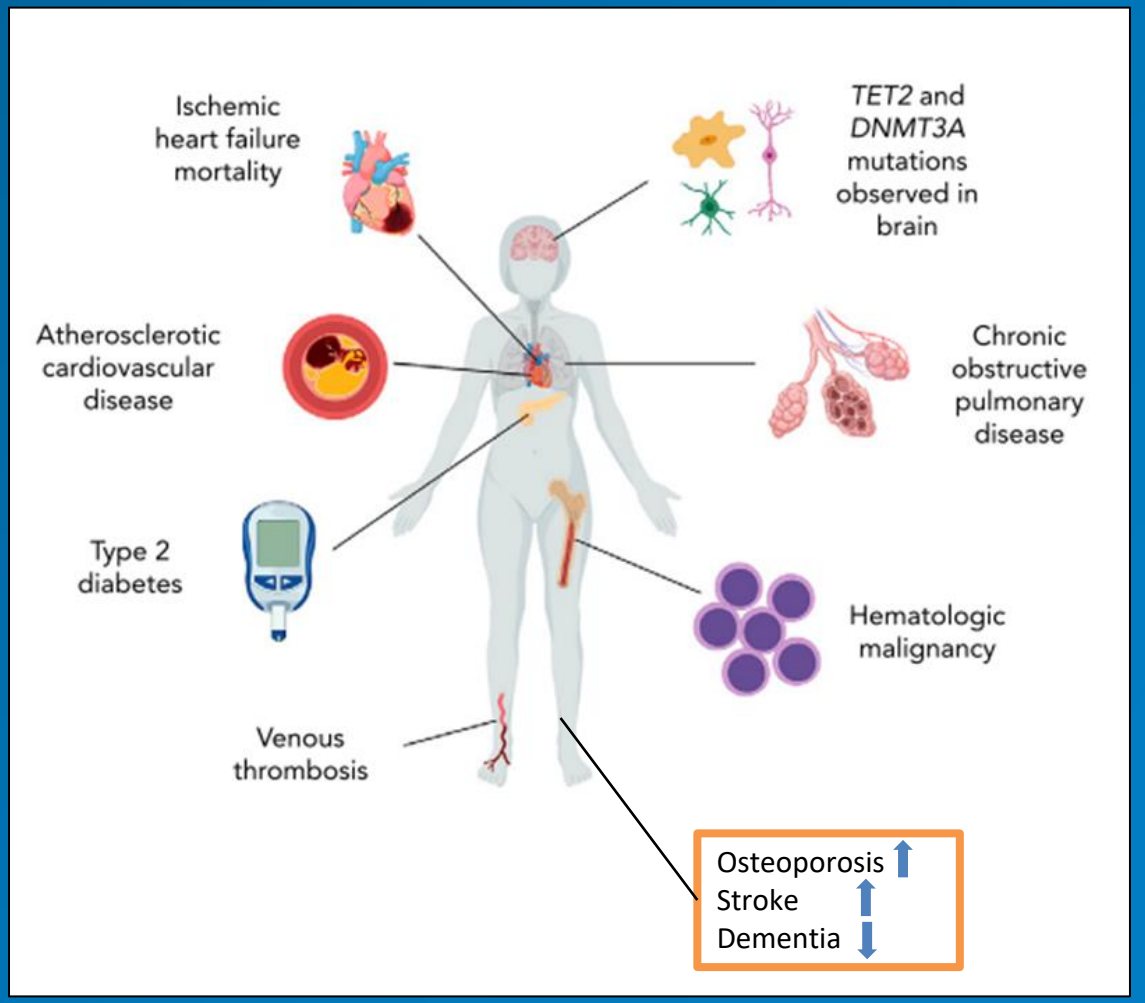
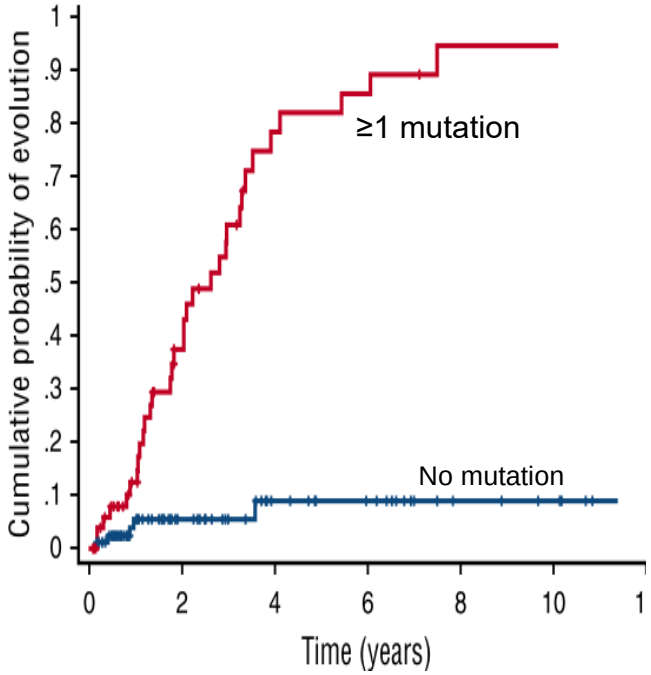
The Consequences of CHIP

- Hematologic malignancies (HR 11-13)
- Increased all-cause mortality (HR 1.4; 95% CI 1.1-1.8)
- Cardiovascular disease (HR 2.0; 95% CI 1.1-1.8)
- Stroke (HR 2.6; 95% CI 1.4 - 4.8)

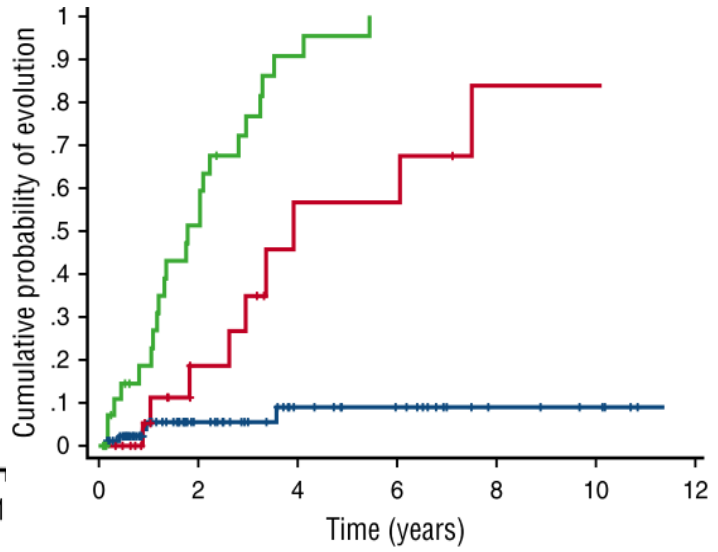


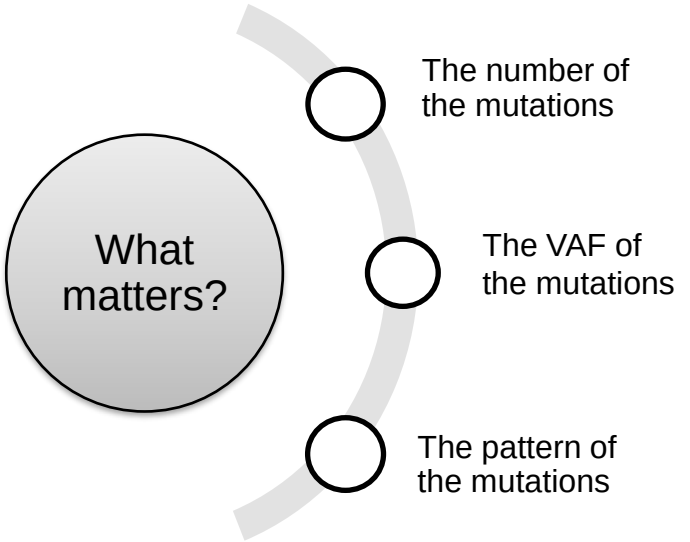
CHIP, clonal hematopoiesis of indeterminate potential.
Jaiswal et al. *N Engl J Med*. 2014;371:2488-2498; Jaiswal et al. *Blood* 2020;136(14):1606-1614.

What Is the True Prognosis of CCUS?



High risk group=
Spliceosome gene;
Co-mutation with *DAT*





CCUS, clonal cytopenia of undetermined significance; *DAT, DNMT3A, ASXL1,* and *TET2*; VAF, variant allele frequency.
Malcovati et al. *Blood* 2017;129(25):3371-3378.

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MDS WHO 2016 Classification

PB and BM Findings and Cytogenetics of MDS					
Name	**Dysplastic lineages**	**Cytopenias***	**Ring sideroblasts as % of marrow erythroid elements**	**BM and PB blasts**	**Cytogenetics by conventional karyotype analysis**
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15% / <5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15% / <5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15% / ≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15% / ≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except –7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19%, no Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 x 10^9/L; and absolute neutrophil count, <1.8 x 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 x 10^9/L.
† if *SF3B1* mutation is present.
‡ One percent PB blasts must be recorded on at least 2 separate occasions.
§ Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.
BM, bone marrow; MDS, myelodysplastic syndrome; PB, peripheral blood; WHO, World Health Organization.
Adapted from Arber et al. *Blood* 2016;127:2391.

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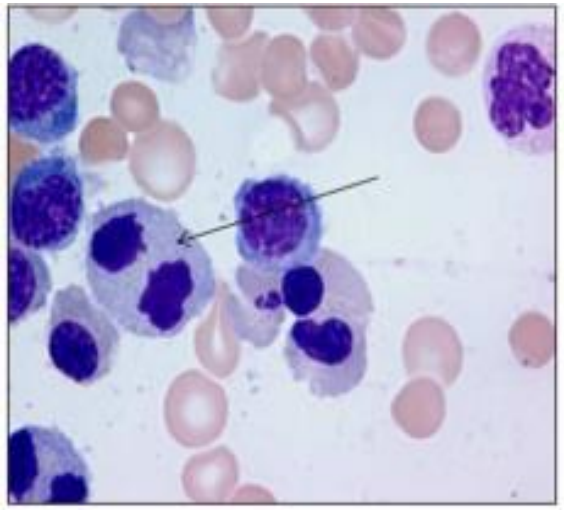
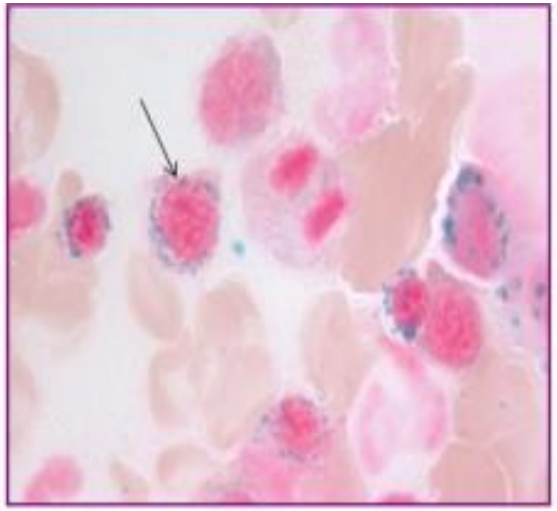
MDS with Ring Sideroblasts



Wright Giemsa stain demonstrating Dyserythropoiesis (arrow)



Prussian blue stain demonstrating Ring sideroblasts (arrow)

- RS are erythroid precursors in which after Prussian blue staining (Perls reaction) there are a minimum of five siderotic granules covering at least a third of the nuclear circumference
- The iron deposited in the perinuclear mitochondria of RS is present in the form of mitochondrial ferritin

MDS, myelodysplastic syndrome; RS, ring sideroblasts.
Patnaik and Tefferi. *Am J Hematol*. 2015;90(6):549-559.

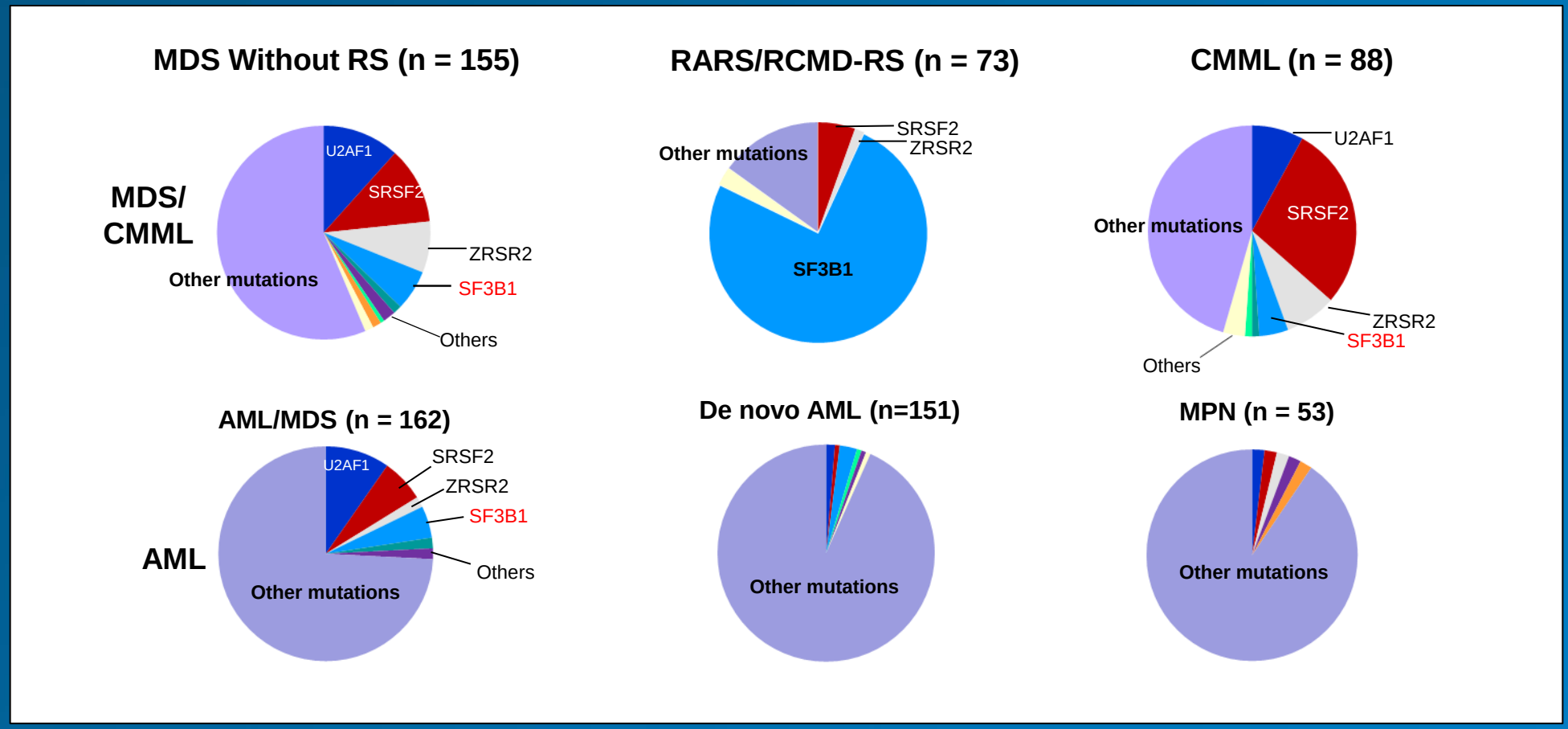
RS and *SF3B1*

- *SF3B1* mutations can be seen in ~80% of RARS cases, with the percentage of BM RS often correlating directly with the *SF3B1* mutant allele burden
- Meayamycin, a pharmacologic inhibitor of SF3B1, can induce RS in healthy in vitro BM cells, and BM RS can be seen in *sf3b1*-heterozygous-knockout mice
- The molecular mechanism behind the development of RS in relation to *SF3B1* mutations is unclear. One hypothesis is that *SF3B1* mutations could alter *ABCB7* gene expression, dysregulating mitochondrial iron homeostasis, resulting in the formation of RS
- *SF3B1* mutations can be seen in a variety of myeloid neoplasms with BM RS such as RARS-T (~80%), RCMD-RS (~30%), PMF~7% , and CMML~6%
- They have also been described in nonmyeloid cancers such as CLL (~15% enriched in patients with del11q) where they are associated with adverse prognosis

BM, bone marrow; CLL, chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; PMF, primary myelofibrosis; RARS, refractory anemia with ring sideroblasts; RARS-T, refractory anemia with ring sideroblasts with thrombocytosis; RCMD, refractory cytopenia with multilineage dysplasia; RS, ring sideroblasts.

Patnaik and Tefferi. *Am J Hematol*. 2015;90(6):549-559.

Spliceosome Mutations Are Enriched in MDS

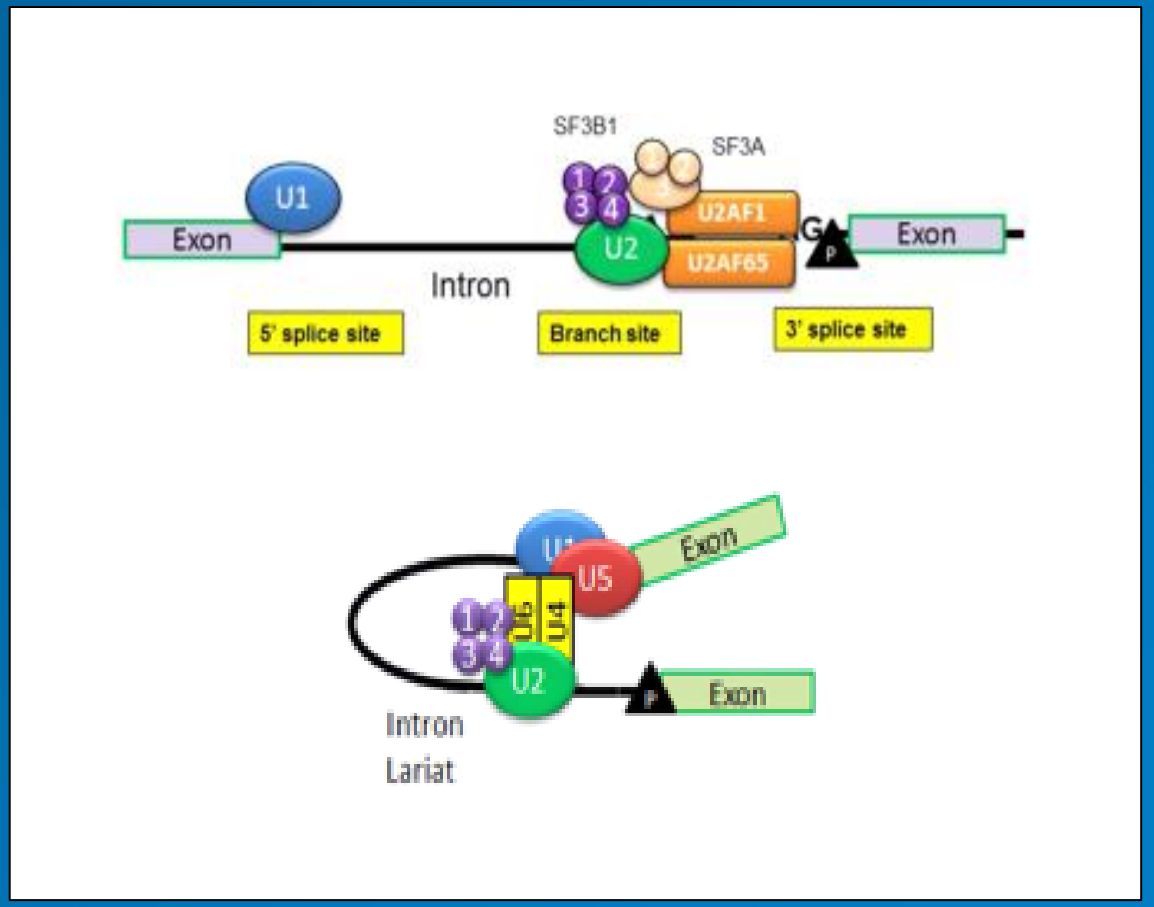


AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RS, ringed sideroblasts.

Yoshida et al. *Nature* 2011;478(7367):64-69.

SF3B1

- SF3 splicing factors help tether the U2 snRNP to the pre-mRNA
  - These factors play an additional role in the formation of the intermolecular helix between the 5’ end of U2 and the 3’ end of U6 snRNAs
- **Splicing Factor 3 Binding Partner 1 – SF3B1** (155kDa) is one of the seven SF3 spliceosome-associated proteins that are incorporated into the spliceosome during the assembly of the pre-splicing complex and become part of the U2 snRNP
- Most mutations in *SF3B1* are **heterozygous** substitutions and tend to cluster in exons 12–16 of the gene (chromosome 2q33.1)
- The *SF3B1* K700E mutation usually accounts for 50% of the variants, with additional codons such as 666, 662, 622, and 625 acting as hot spot sites



snRNP, small nuclear Ribonucleoproteins.
Patnaik and Tefferi. *Am J Hematol*. 2015;90(6):549-559. © 2015 John Wiley & Sons, Inc.

Proposed Diagnostic Criteria MDS With Mutated *SF3B1* 2020

- Cytopenia defined by standard hematologic values
- Somatic *SF3B1* mutation
- Isolated erythroid or multilineage dysplasia*
- Bone marrow blasts <5% and peripheral blood blasts <1%
- WHO criteria for MDS with isolated del(5q), MDS/MPN-RS-T or other MDS/MPNs, and primary myelofibrosis or other MPNs are not met
- Normal karyotype or any cytogenetic abnormality other than del(5q); monosomy 7; inv(3) or abnormal 3q26, complex (≥3)
- Any additional somatically mutated gene other than *RUNX1* and/or *EZH2*†

*RS are not required for the diagnosis.
†Additional *JAK2V617F*, *CALR*, or *MPL* mutations strongly support the diagnosis of MDS/MPN-RS-T.
MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; RS, ring sideroblasts; RS-T, ring sideroblasts with thrombocytosis; WHO, World Health Organization.
Malcovati et al. *Blood* 2020;136(2):157-170.

IPSS-M

Step	Development
Encoding for clinical and molecular variables	• Continuous encoding of clinical variables; linear function for BM blasts, Hg • Platelet values capped at 250 x 10^9/L; ANC not included • Maintained 5 IPSS-R cytogenetic categories • Gene mutations incorporated as binary variables aside from *TP53* allelic state and *SF3B1* subsets accounting for comutations
Determination of independent IPSS-M prognostic variables	• Model fit with a Cox multivariable regression adjusted for confounder variables (age, sex, primary vs therapy-related MDS) • Continuous clinical parameters • IPSS-R cytogenetic categories • 17 genetic variables from 16 main effect genes • 1 genetic variable from 15 residual genes (*BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1*)

ANC, absolute neutrophil count; BM, bone marrow; Hg, hemoglobin; IPSS-M, Molecular International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes.

Bernard. et al. 63rd ASH Annual Meeting & Exposition; 2021. Abstract 61.

IPSS-Revised

	Score Value						
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**3**	**4**
Cytogenetics	Very good	–	Good	–	Intermediate	Poor	Very poor
BM blast, %	≤2	–	>2 - <5	–	5 - 10	>10	–
Hemoglobin, g/dL	≥10	–	8 - <10	<8	–	–	–
Platelets, x10^9/L	≥100	50 - <100	<50	–	–	–	–
ANC, x10^9/L	≥0.8	<0.8	–	—	—	—	—

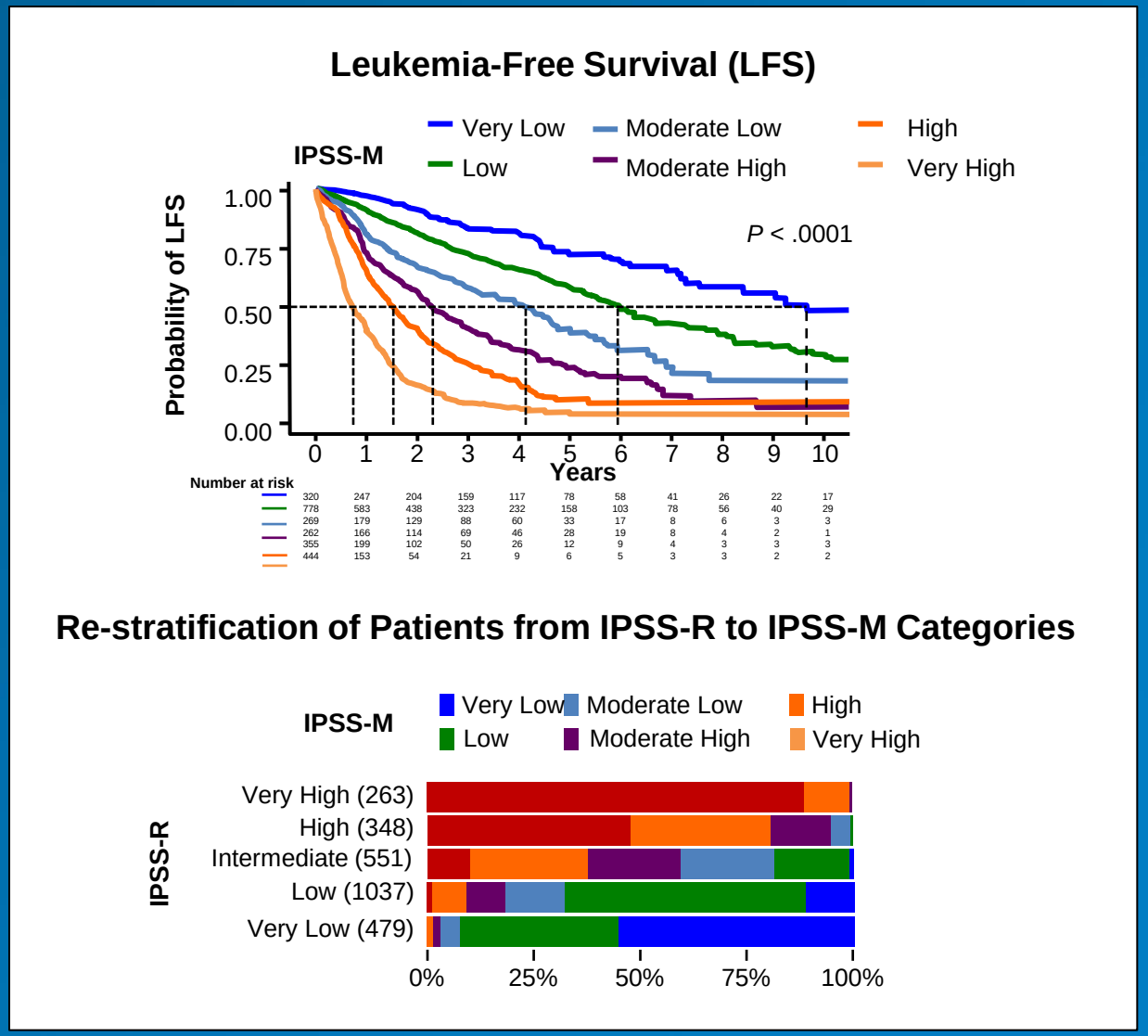
Risk	Score
Very Low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

ANC, absolute neutrophil count; BM, bone marrow; IPSS, International Prognostic Scoring System.
Greenberg et al. *Blood* 2012;120:2454-2465.

Molecular IPSS for MDS

- Diagnostic MDS samples from 2,957 patients with less than 20% blasts and white blood cell count below 13x10^9/L were profiled for mutations in 156 driver genes (discovery cohort)
- Candidate target risk variables consisted of blood counts, blasts, cytogenetics and gene mutations, while patient age, sex and MDS type (de novo or not) were treated as confounders

- 46% (n = 1,223) of patients were re-stratified
- 7% (n = 196) of patients were re-stratified by more than one strata



IPSS, International Prognostic Scoring System; IPSS-M, Molecular IPSS; IPSS-R, Revised IPSS; MDS, myelodysplastic syndrome.
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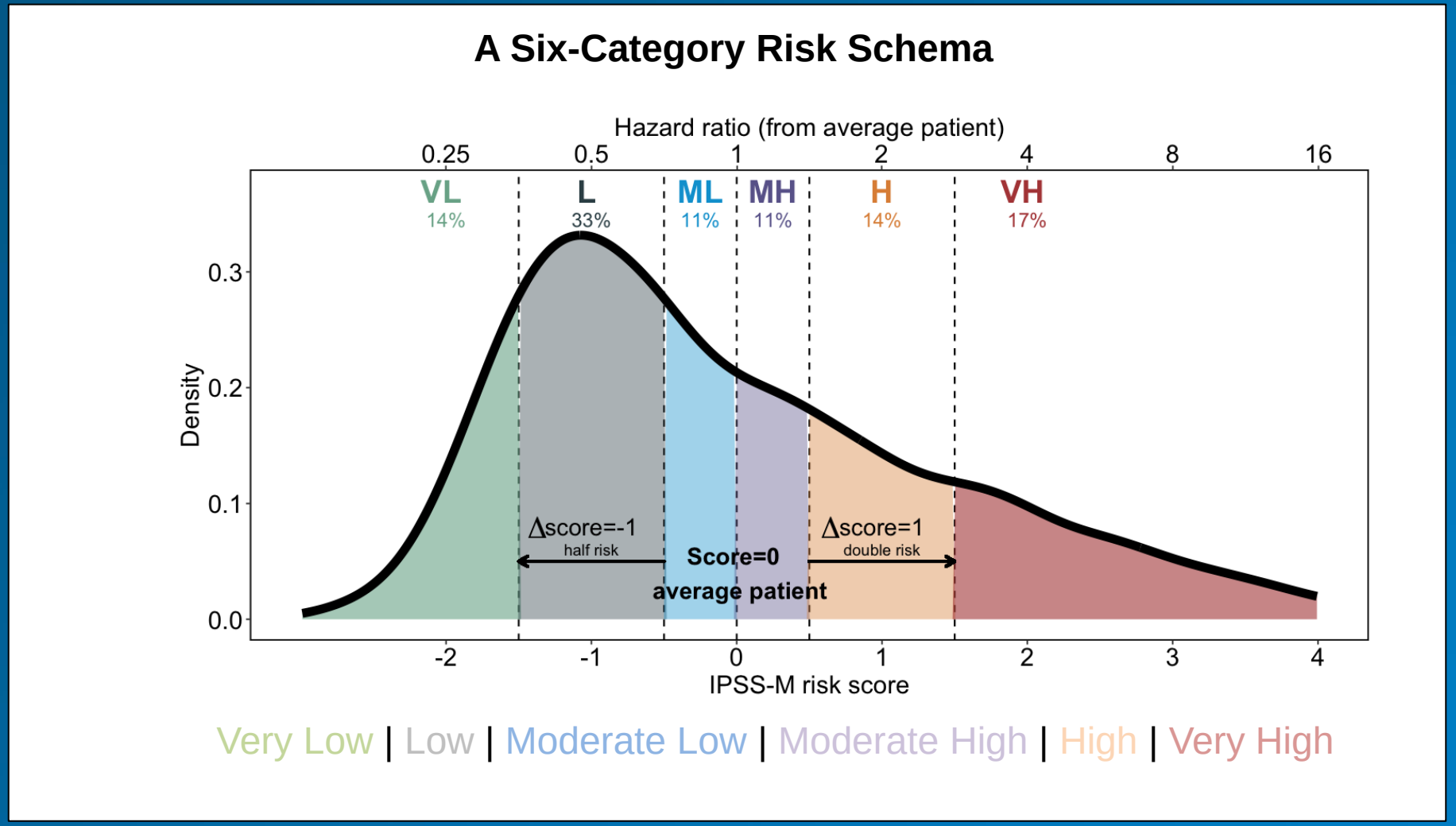
The IPSS-M Risk Categories



IPSS-M, Molecular International Prognostic Scoring System.
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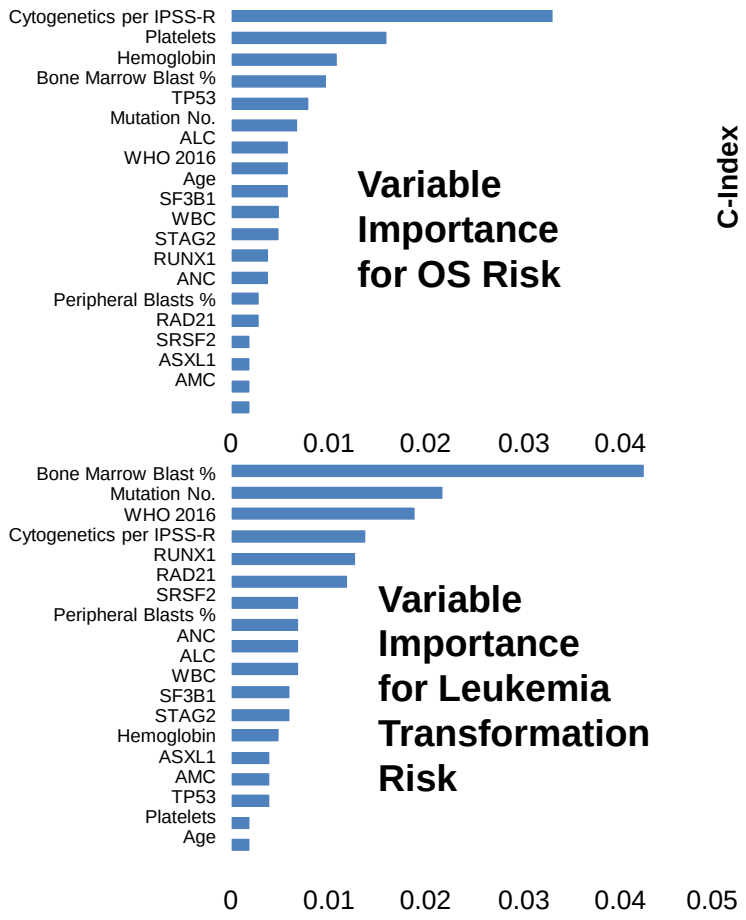
Development of IPSS-M: Association Between Gene Mutations and Clinical Endpoints in Discovery Cohort

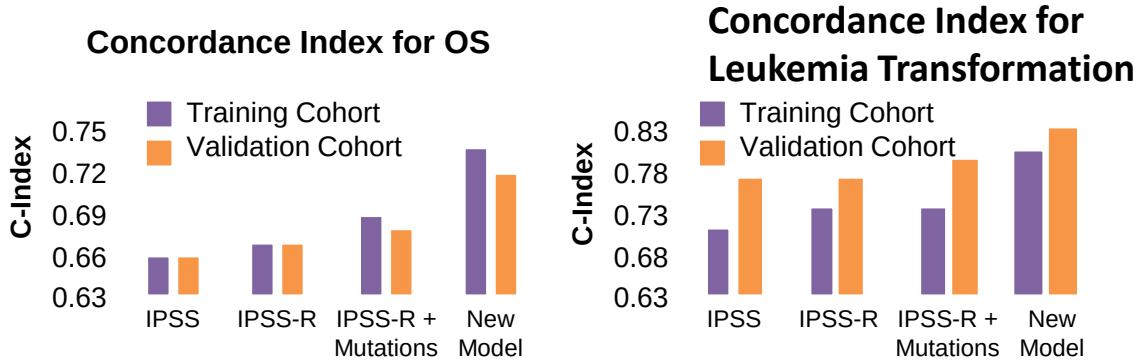
- After adjusting for age, sex, MDS type (primary vs therapy related), and IPSS-R raw score, multiple genes were associated with adverse outcomes including LFS (14 genes), OS (16 genes), and AML transformation (15 genes)
- Strongest associations found with:
  - *TP53* multi-hit (multiple mutations, mutation with deletion or copy-neutral LoH; 7% of patients)
  - *MLL* partial tandem duplication (2.5% of patients)
  - *FLT3* mutations (1.1% of patients)
- *SF3B1* mutations were associated with favorable outcomes, modulated by pattern of co-mutations
  - *SF3B1*^{5q}: concomitant isolated del(5q) (7%)
  - *SF3B1*$^{\beta}$: co-occurrence of mutations in *BCOR, BCORL1, RUNX1, NRAS, STAG2, SRSF2* (15%)
  - *SF3B1*$^{\alpha}$: any other *SF3B1* mutations

AML, acute myeloid leukemia; IPSS-M, Molecular International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; LFS, leukemia-free survival; LoH, loss of heterozygosity; MDS, myelodysplastic syndromes; OS, overall survival.

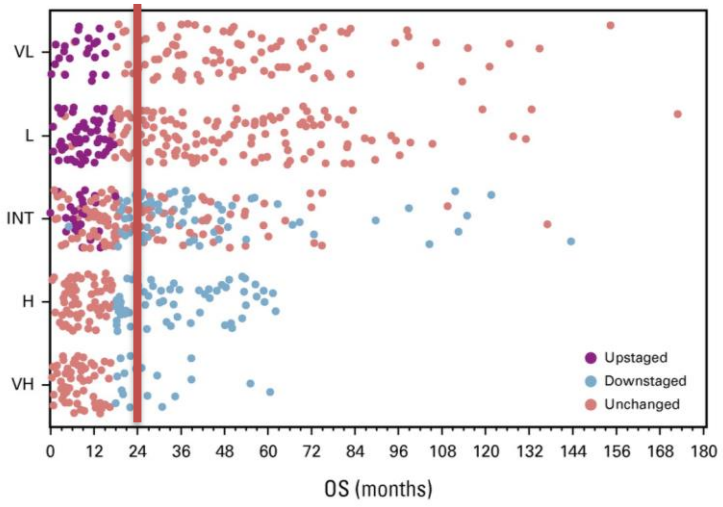
Bernard et al. 63rd ASH Annual Meeting & Exposition; 2021. Abstract 61.

New Personalized Prediction Model to Risk-Stratify Patients With MDS





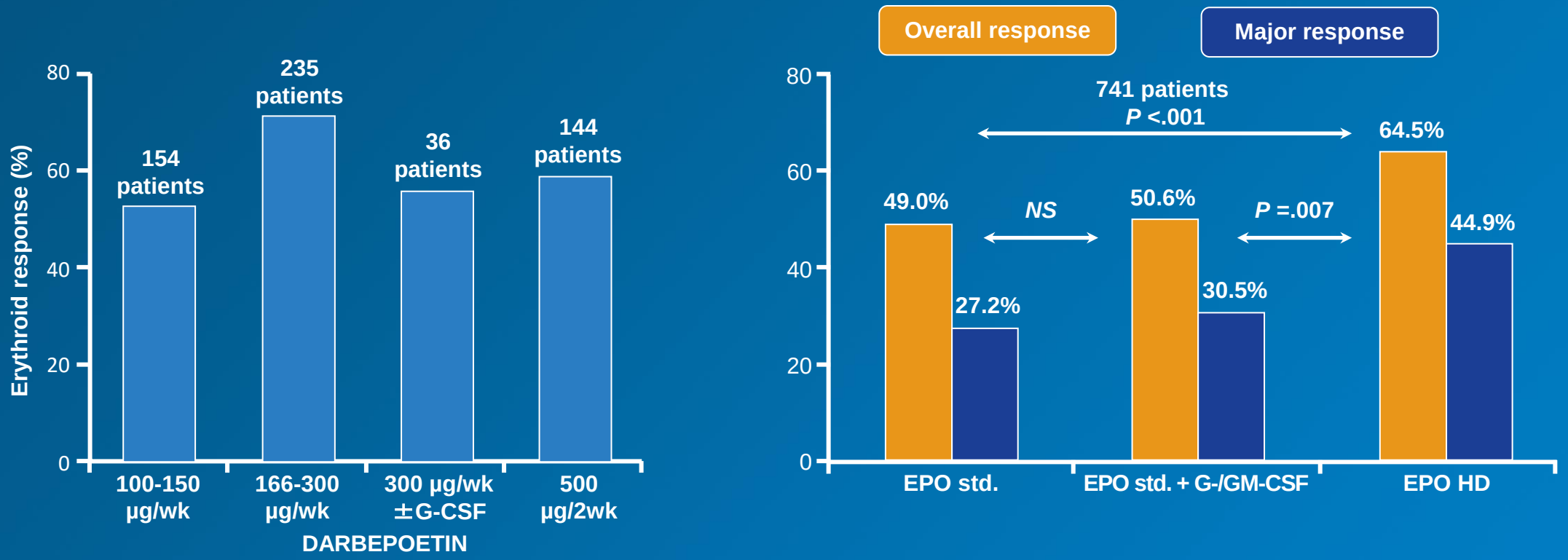
OS Based on IPSS-R Category in Training Cohort With New Model



IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; OS, overall survival.
Adapted from Nazha et al. *J Clin Oncol*. 2021;39:3737.

AXIS Medical Education

Meta-analysis of Erythroid Response to Erythropoietin-Stimulating Agents

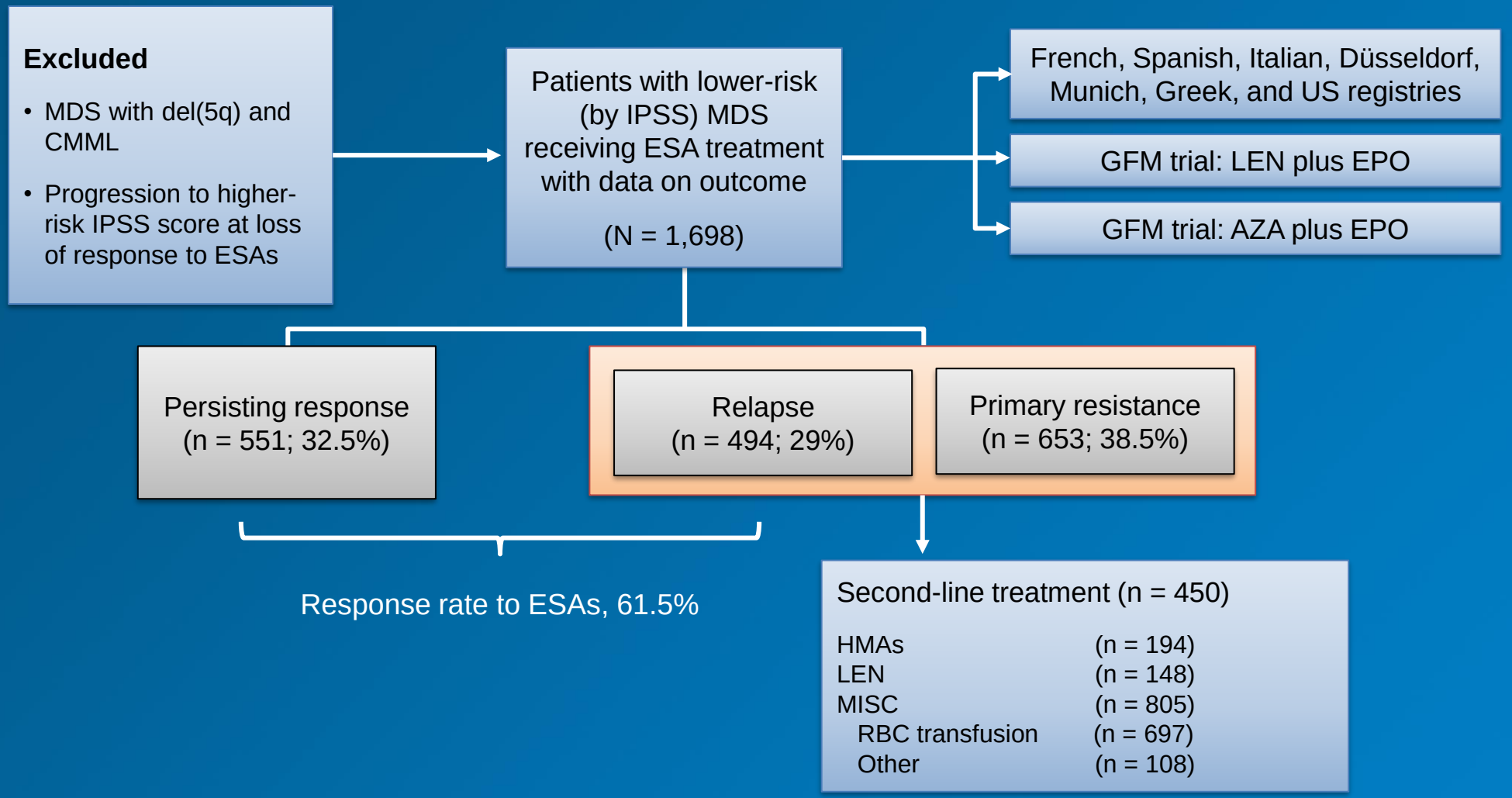


Higher dosing regimens of both epoetin alfa (weekly dose 60-80 K IU) and darbepoetin alfa (weekly dose 150-300 mcg) correlate with higher erythroid response rates

EPO, erythropoietin; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage-colony stimulating factor; HD, high dose; NS, not significant; std, standard.

Moyo et al. *Ann Hematol*. 2008;87:527-536. Mundle et al. *Cancer* 2009;115:706-715. Santini. *Semin Hematol*. 2012;49:295-303. Santini. *Oncologist* 2011;16:35-42. Nilsson-Ehle et al. *Eur J Haematol*. 2011;87:244-252.

Outcome After ESA Failure



CMML, chronic myelomonocytic leukemia; EPO, erythropoietin; ESA, erythropoietin-stimulating agent; HMAs, hypomethylating agents; IPSS, International Prognostic Scoring System; LEN, lenalidomide; MDS, myelodysplastic syndrome; AZA, azacytidine; RBC, red blood cell.

Park et al. *J Clin Oncol*. 2017;35(14):1591-1597.

AXIS Medical Education

Outcome After ESA Failure

Treatments (other than RBC transfusion) Administered After ESA Failure

	Treatment Line (No. of patients)		
Treatment	**Second**	**Third**	**Fourth**
HMAs	194	60	26
LEN	148	139	9
Other*	108	54	26

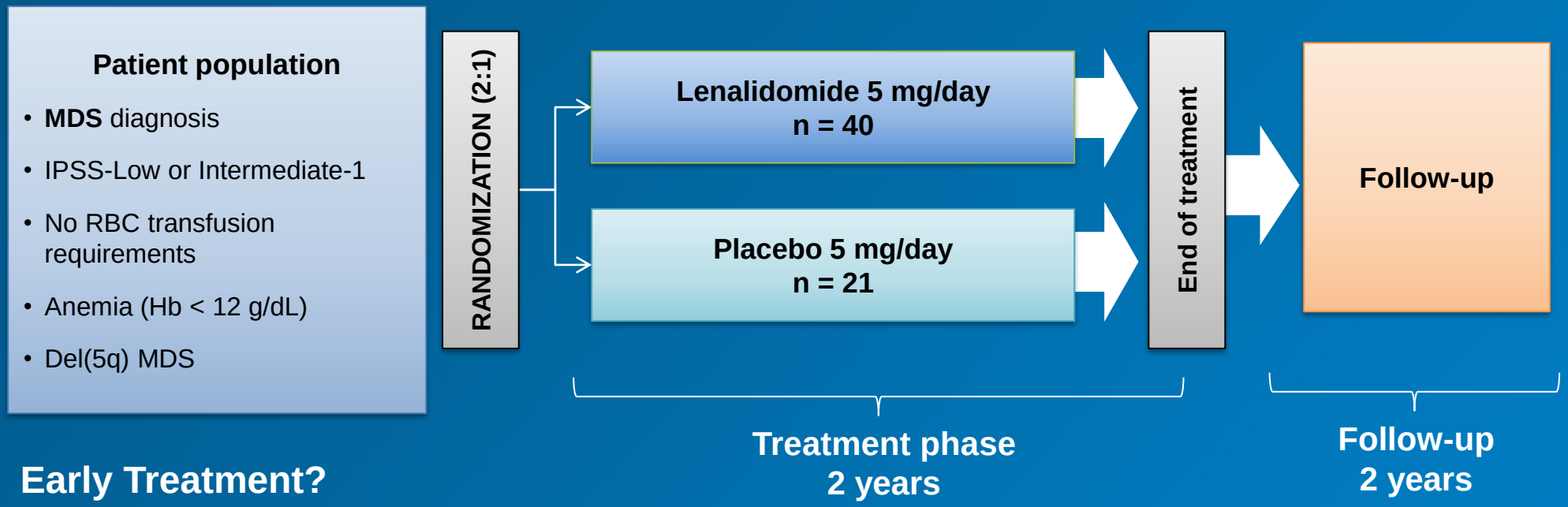
Of the 1,147 patients experiencing primary or secondary ESA failure, 450 (39%) received a second-line treatment other than RBC transfusions

*Valproic acid, ACE-536 or -011, thalidomide, antithymocyte globulin ± ciclosporine, low-dose cytarabine, hydroxyurea, or all-*trans*-retinoic acid.
ESA, erythropoietin-stimulating agent; HMAs, hypomethylating agents; LEN, lenalidomide; MDS, myelodysplastic syndrome; RBC, red blood cell.
Park et al. *J Clin Oncol*. 2017;35(14):1591-1597.

AXIS Medical Education

Sintra-Rev Trial: Efficacy and Safety of Early Intervention

A phase 3, double-blind, randomized, placebo-controlled, multicenter study



Early Treatment?

Primary endpoint: time to TD (transfusion dependence)

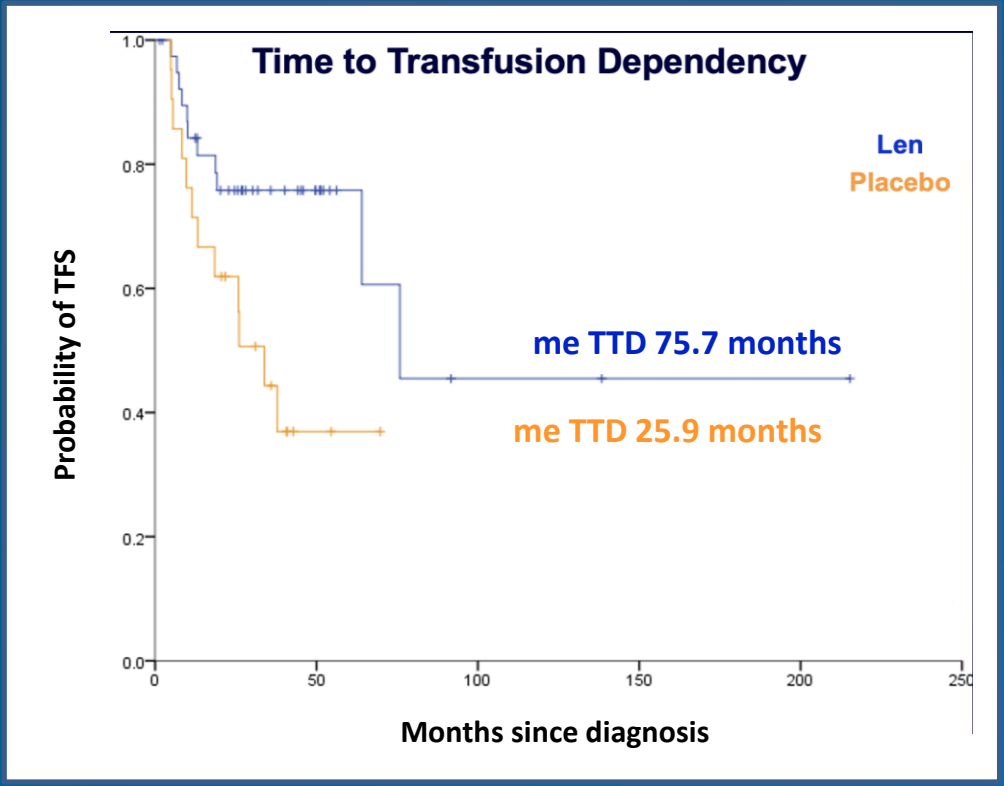
Secondary endpoints included: erythroid (HI-E) and cytogenetic response (CyR) (all according to IWG 2006 criteria), OS, EFS, time to AML and mutational analysis (TP53 and other myeloid mutations)

AML, acute myeloid leukemia; EFS, event-free survival; HI-E, hematologic improvement-erythropoietic; IPSS, International prognostic scoring system; IWG, International Working Group; MDS, myelodysplastic syndrome; OS, overall survival; RBC, red blood cell.

Cadenas et al. *Blood* 2020;136(suppl 1):28-29.

Sintra-Rev Trial: Efficacy and Safety Profiles of Early Intervention

Early treatment in anemic non-TD patients



Patient characteristics:

- 82% females; median age 72 years (range 37-89); median time since diagnosis 3.6 months; median Hb at inclusion 9.8 g/dL (7.1-11.7 g/dL); and 93% of patients had isolated del(5q)

Lenalidomide versus placebo:

- Low doses delay TTD (75.7 vs 25.9 months; $P = .021$)
- ER in 72.5% vs 0.0% of patients ($P < .001$)
- Cytogenetic responses in 80% vs 4.8% ($P < .001$)

Tolerability:

- The number of adverse events reported within both treatment arms were not significantly different
- Lenalidomide had a manageable safety profile

Author's conclusions:

- Low dose lenalidomide (5 mg) in anemic non-TD low-risk MDS del(5q) patients prolongs the period of time to TD, improves Hb levels and induces clonal responses

ER, erythroid response; Hb, hemoglobin; Len, lenalidomide; MDS, myelodysplastic syndrome; TD, transfusion dependent; TTD, time to transfusion dependence; ER, erythroid response.

Cadenas et al. *Blood* 2020;136(suppl 1):28-29.

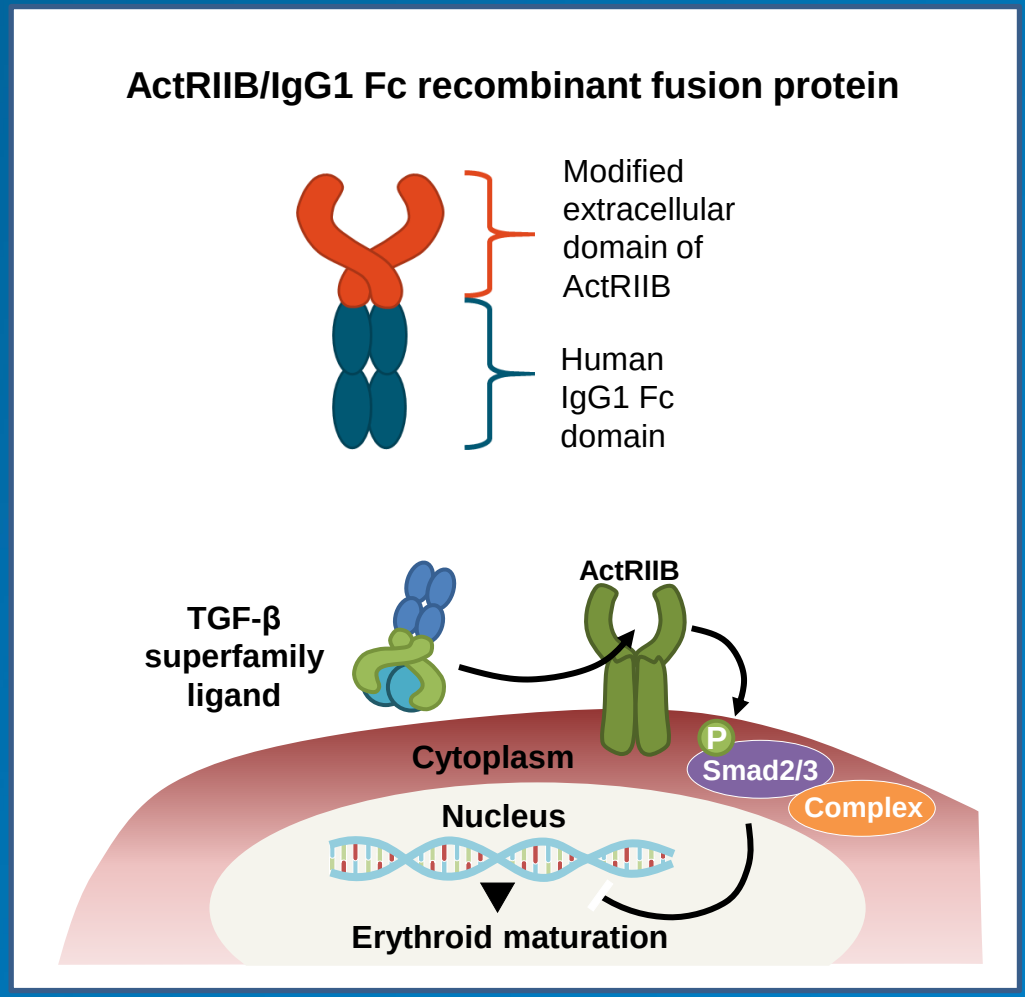
Lenalidomide in MDS

- Lenalidomide is standard of care[1] for lower-risk MDS with del(5q)[2,3]
  - Transfusion independence by IWG (67%)[2,3]
  - Duration of response is approximately 3 years with lenalidomide 10 mg[2]
    - MDS-004 supports 10 mg as appropriate starting dose versus 5 mg[2]
  - Higher TI for 10 mg
  - Greater proportion of cytogenetic responses versus 5 mg (50% vs 25% [*P* = .066])
  - Lenalidomide was generally well tolerated with a manageable safety profile
- MDS-001, MDS-002, and MDS-005 provided evidence that lenalidomide could be a choice for anemia treatment in patients with lower-risk non-del(5q) MDS with adequate platelets and neutrophil count[4,5,6]

1. Prebet et al. *Oncotarget* 2017;8:1936-1935. 2. Fenaux et al. *Blood* 2011;118:3765-3776. 3. List et al. *N Engl J Med*. 2006;355:1456-1465. 4. List et al. *N Engl J Med*. 2005;352:549-557.
5. Raza et al. *Blood* 2008;111:86-93. 6. Sekeres et al. *J Clin Oncol*. 2008;26:5943-5949.
AML, acute myeloid leukemia; IWG, International Working Group; MDS, myelodysplastic syndrome; TI, transfusion independence.

Luspatercept

- First-in-class erythroid maturation agent inhibits abnormal SMAD2/3 signaling by neutralizing select TGF-β superfamily ligands and improves late-stage erythropoiesis in MDS models
- Phase 2 study in patients with Low- or Intermediate-1-risk MDS, luspatercept yielded high frequency of transfusion reduction or RBC-TI in patients with MDS-RS versus other subtypes



Adapted from Fenaux et al. *Blood* 2019;133(8):790-794; Suragani et al. *Nat Med.* 2014;20:408. Platzbecker et al. *Lancet Oncol*. 2017;18:1338-1347.
MDS, myelodysplastic syndrome; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF, tumor growth factor.

MEDALIST Trial: Study Design

A randomized, double-blind, placebo-controlled, Phase 3 study

Patient Population

- MDS-RS (WHO): ≥ 15% RS or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks
- No prior treatment with disease-modifying agents (e.g. iMIDs, HMAs)

RANDOMIZATION (2:1)

Luspatercept 1.0 mg/kg (s.c.) every 21 days
n = 153

Dose titrated up to a maximum of 1.75 mg/kg

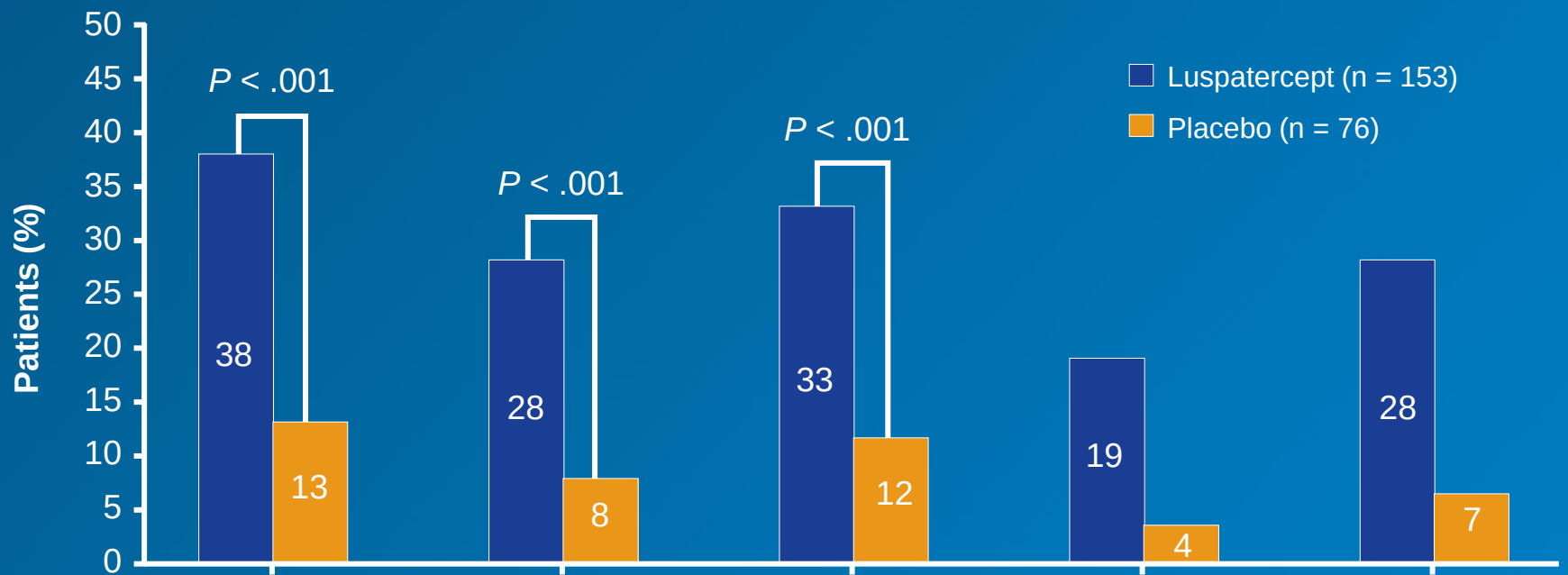
Placebo (s.c.) every 21 days
n = 76

Disease & Response Assessment week 24 & every 6 months
Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; no crossover allowed

Subjects followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment and overall survival

EPO, erythropoietin; ESA, erythropoiesis-simulating agent; HMA, hypomethylating agent; iMID, immunomodulatory drug; IPSS-R, International Prognostic Scoring System-Revised; IWG, International Working Group; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; RBC, red blood cell; WHO, World Health Organization.

MEDALIST: Red Cell Transfusion Independence with Luspatercept in MDS-RS



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 (13 [3-16])	6 (12 [6-21])	3 (4 [1-11])	5 (7 [2-15])

MDS-RS, myelodysplastic syndrome with ring sideroblasts.

Fenaux et al. *N Engl J Med*. 2020;382:140-151.

MEDALIST: RBC-TI ≥8 Weeks

RBC-TI ≥ 8 Weeks Over the Entire Treatment Period	Luspatercept (n = 153)	Placebo (n = 76)	Luspatercept Minus Placebo	
			OR (95%CI)*	*P**
Average baseline RBC transfusion requirement, n/N (%)				
≥ 6 U/8 weeks	14/66 (21.2)	2/33 (6.1)	4.17 (0.89–19.60)	.0547
≥ 4 to < 6 U/8 weeks	20/41 (48.8)	2/23 (8.7)	10.00 (2.07-48.28)	.0013
< 4 U/8 weeks	39/46 (84.8)	8/20 (40.0)	8.36 (2.51-27.83)	.0002

More luspatercept-treated patients achieved RBC-TI ≥ 8 weeks over the entire treatment period compared with those receiving placebo, regardless of baseline transfusion burden

*Determined using a Cochran-Mantel-Haenszel test.
OR, overall response; RBC-TI, red blood cell transfusion independence.
Fenaux et al. *N Engl J Med*. 2020;382:140-151.

MEDALIST: Safety

TEAE of any grade, %	Luspatercept (n = 153)	Placebo (n = 76)
Fatigue	27	13
Diarrhea	22	9
Asthenia	20	12
Nausea*	20	8
Dizziness	20	5
Back pain*	19	7
Cough	18	13
Peripheral edema	16	17
Headache	16	7
Dyspnea*	15	7
Bronchitis	11	1
Constipation	11	9
UTI	11	5
Injury, poisoning, or procedural complication: fall	10	12

TEAE, %	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE	98.0	92.1
≥ 1 serious TEAE	31.4	30.3
≥ 1 Grade 3/4 TEAE	42.5	44.7
TEAEs leading to death	3.3	5.3
≥ TEAE causing discontinuation	8.5	7.0

- Four patients progressed to AML
  - 3 in luspatercept arm
  - 1 in placebo arm
- Most common grade 3/4 TEAEs in luspatercept arm:
  - Anemia (6.5%)
  - Fatigue (4.6%)
  - Fall (4.6%)

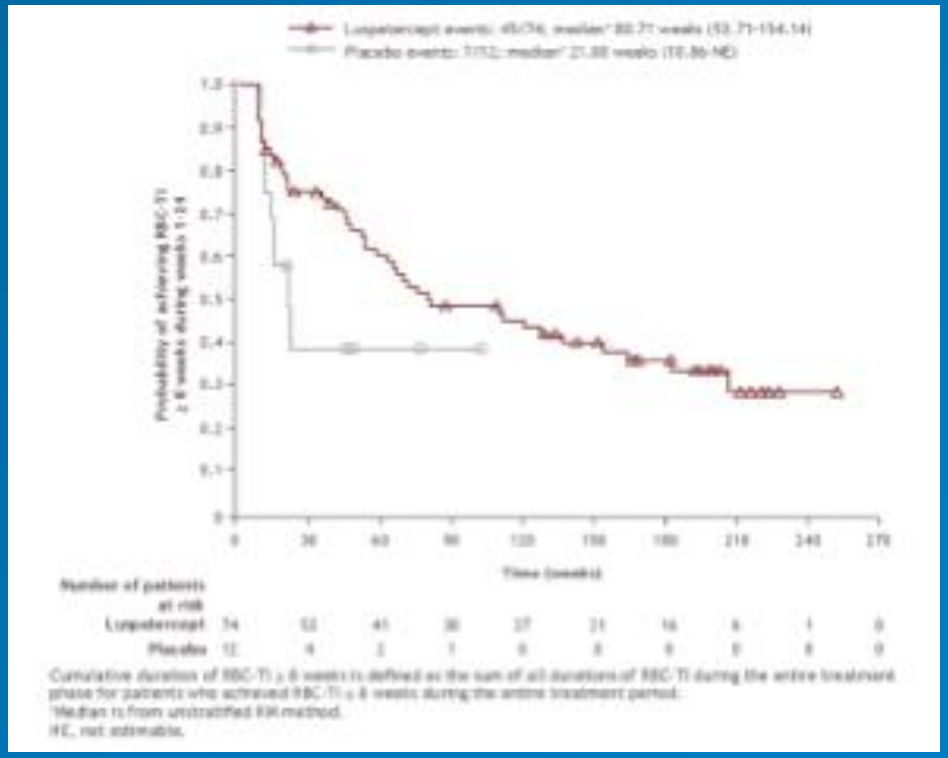
*At least one serious adverse event occurred: nausea (in one patient receiving luspatercept), back pain (in three receiving luspatercept), dyspnea (in one receiving luspatercept), bronchitis (in one receiving luspatercept), and urinary tract infection (in one receiving placebo).
AML, acute myeloid leukemia; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.
Fenaux et al. *N Engl J Med*. 2020;382:140-151.

MEDALIST: Long-Term Response

RBC-TI ≥ 8 weeks and ≥ 16 weeks during the entire treatment period

	Luspatercept (n = 153)	Placebo (n = 76)
Achievement of RBC-T1 ≥ 8 weeks		
Patient, n (%) 95% CI	74 (48.4) 40.22-56.58	12 (15.8) 8.43-25.96
Common risk difference in response rate, % (95% CI)	32.95 (22.07-43.83)	
OR (95% CI)	6.12 (2.91-12.87)	
P	<.0001	
Achievement of RBC-T1 ≥ 16 weeks		
Patient, n (%) 95% CI	48 (31.4) 24.9-39.39	6 (7.9) 2.95-16.40
Common risk difference in response rate, % (95% CI)	23.37 (14.05-32.68)	
OR (95% CI)	5.90 (2.34-14.90)	
P	<.0001	

Cumulative duration of RBC-TI ≥ 8 weeks during the entire treatment period for patients who achieved RBC-TI ≥ 8 weeks during the entire treatment period



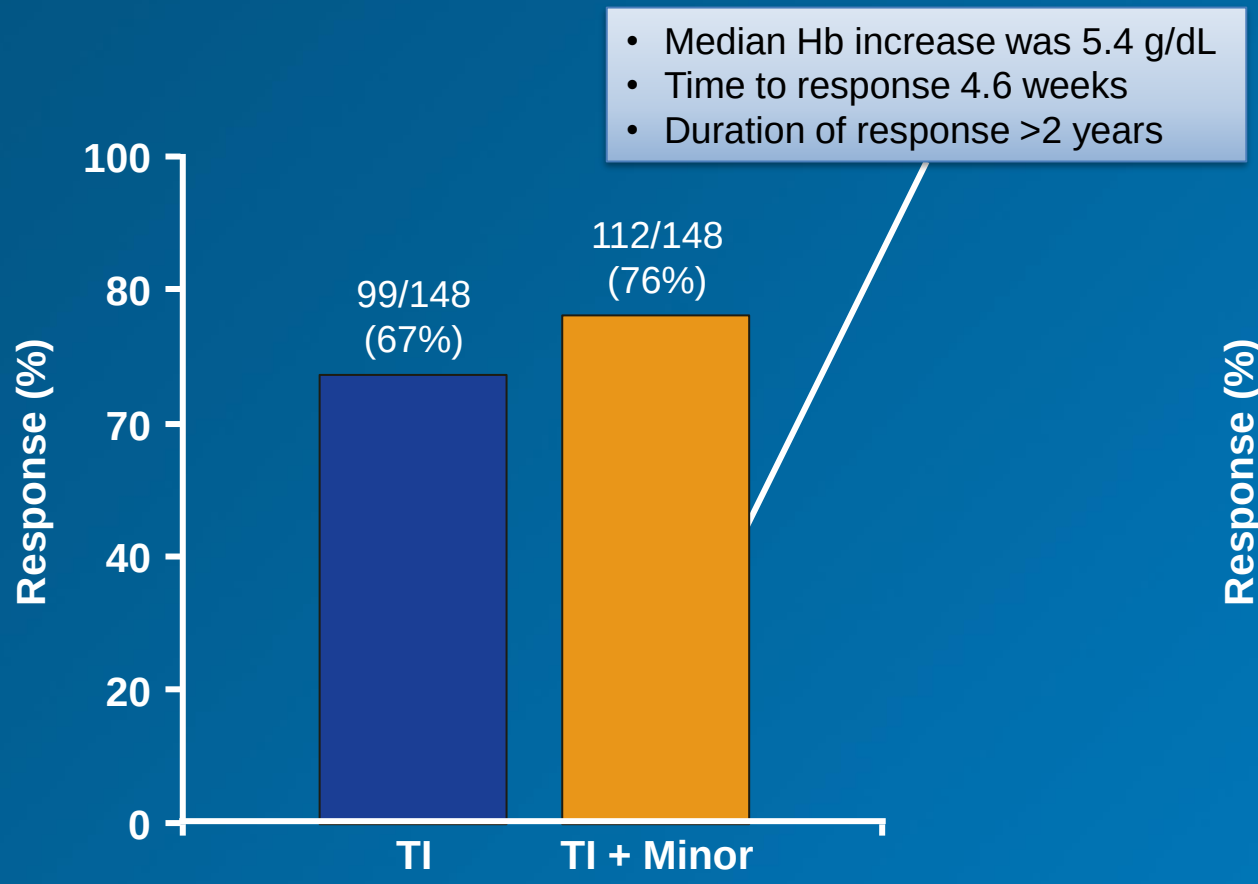
- Patients receiving luspatercept experienced an extended period of RBC-TI compared with those randomized to placebo throughout the entire treatment period
- Patients randomized to luspatercept who achieved RBC-TI ≥8 weeks during the entire treatment period experienced durable clinical responses, with a median cumulative duration of RBC-TI response of approximately 20 months

OR, overall response; RBC-TI, red blood cell transfusion independence.

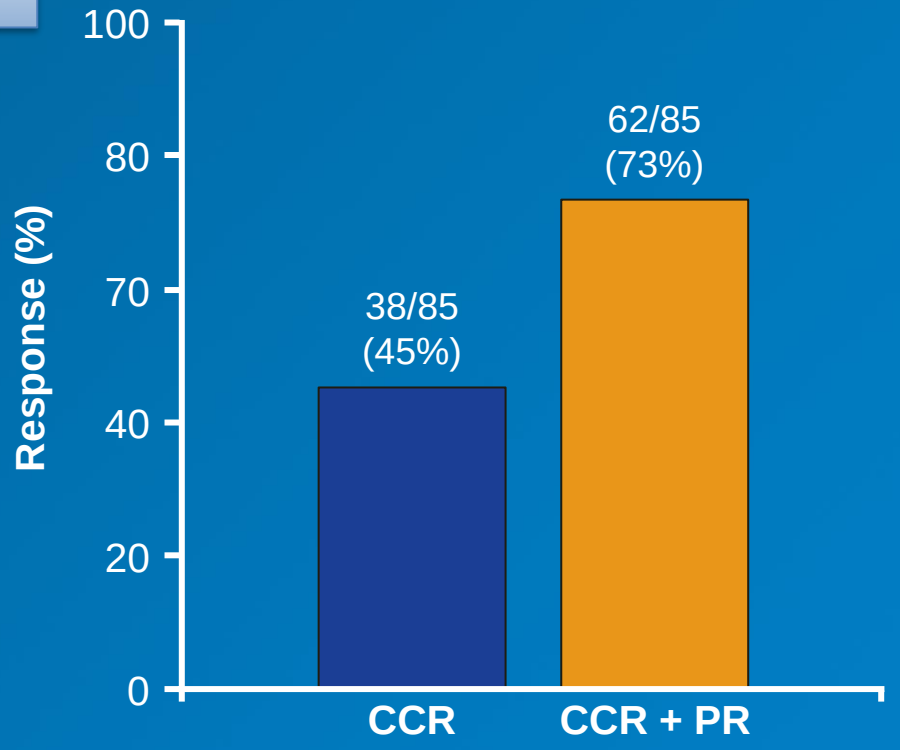
Fenaux et al. *J Clin Oncol*. 2022;40(suppl 16):7056.

MDS-003: Response to Lenalidomide Therapy

Erythroid Response



Cytogenetic Response

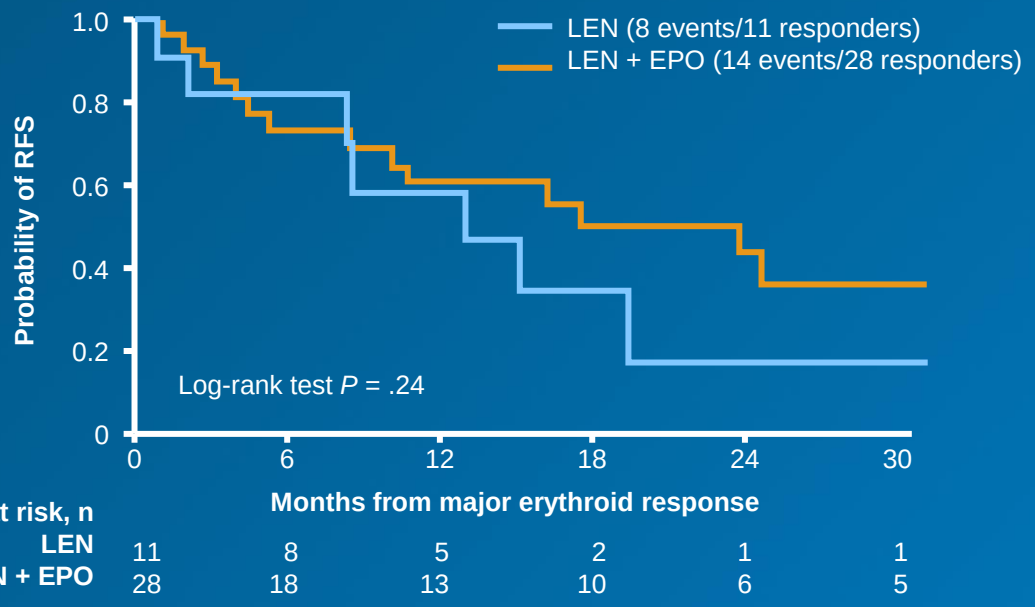


CCR, complete cytogenetic remission; PR, partial response; TI, transfusion independence; Hb, hemoglobin.
List et al. *N Engl J Med*. 2006;355:1456-1465.

AXIS Medical Education

Phase 3 ECOG 2905 Study of Lenalidomide ± EPO Alfa in Lower-risk MDS Non-del(5q) Refractory to Erythropoietin: RFS

Randomized, phase 3 trial of patients with low- or intermediate-1 risk by IPSS; symptomatic anemia either untransfused with hemoglobin <9.5 g/cL or RBC-TD (N = 247; n = 195 evaluable)



- There was no statistically significant difference in the frequency of Grade ≥ 3 non-hematologic AEs between treatment arms
- The toxicity associated with LEN and EPO alfa was similar to treatment with LEN alone

AEs, adverse events; EPO, erythropoietin; IPSS, International Prognostic Scoring System; LEN, lenalidomide; RBC-TD, red blood cell transfusion dependence; RFS, relapse-free survival.
List et al. *J Clin Oncol* .2021;39:1001-1009.

AXIS Medical Education

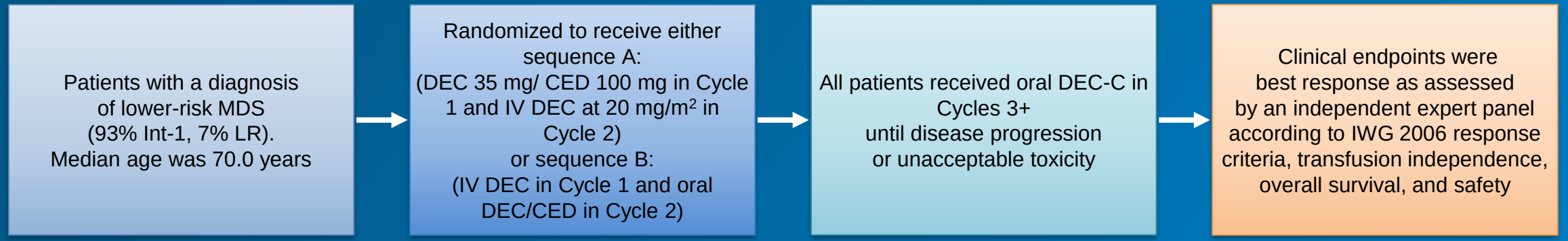
Immunosuppressive Therapy

- One course ATG +/– CSA
- Possible positive variables for IST response[1-4]
  - **Age is the strongest variable for response**
  - HLA-DR15 status
  - Short duration of disease
  - Short duration of red cell transfusion dependence
  - Trisomy 8
  - **Hypoplastic MDS**
  - PNH clone
- Possible negative predictors of response
  - Del(5q)
  - **SB1518**[4]
- Responses were durable and trilineage responses were observed in some patients[2]

ATG, antithymocyte globulin; CSA, cyclosporine; IST, immunosuppressive therapy; MDS, myelodysplastic syndrome; SB1518, pacritinib; PNH, paroxysmal nocturnal hemoglobinuria.

1. Sauntharajah et al. *Blood* 2002;100:1570-1574. 2. Sloand et al. *J Clin Oncol*. 2008;26:2505-2511. 3. Sloand et al. *Blood* 2004;104(11):1431. 4. Komrokji et al. *Blood* 2015;125(17):2649-2655.

ASCERTAIN Study: A Longer-Term Follow-up in LR-MDS



- CR rate was 23% and marrow CR was 26%
  - 13% had hematologic improvement
- ORR was 57%
- Safety profile was consistent with that of decitabine
  - TEAEs of CTCAE ≥ grade 3, included cytopenias (neutropenia [59%], thrombocytopenia [58%], anemia [48%], leukopenia [26%]), febrile neutropenia (32%), and pneumonia (19%)

CED, cedazuridine; CR, complete remission; CTCAE, Common Terminology Criteria for Adverse Events; DEC, decitabine; DEC-C; decitabine/cedazuridine; IWG, International Working Group; Int-1, Intermediate 1 risk; LR-MDS, low-risk myelodysplastic syndrome; ORR, overall response rate; TEAEs, treatment-emergent adverse events.

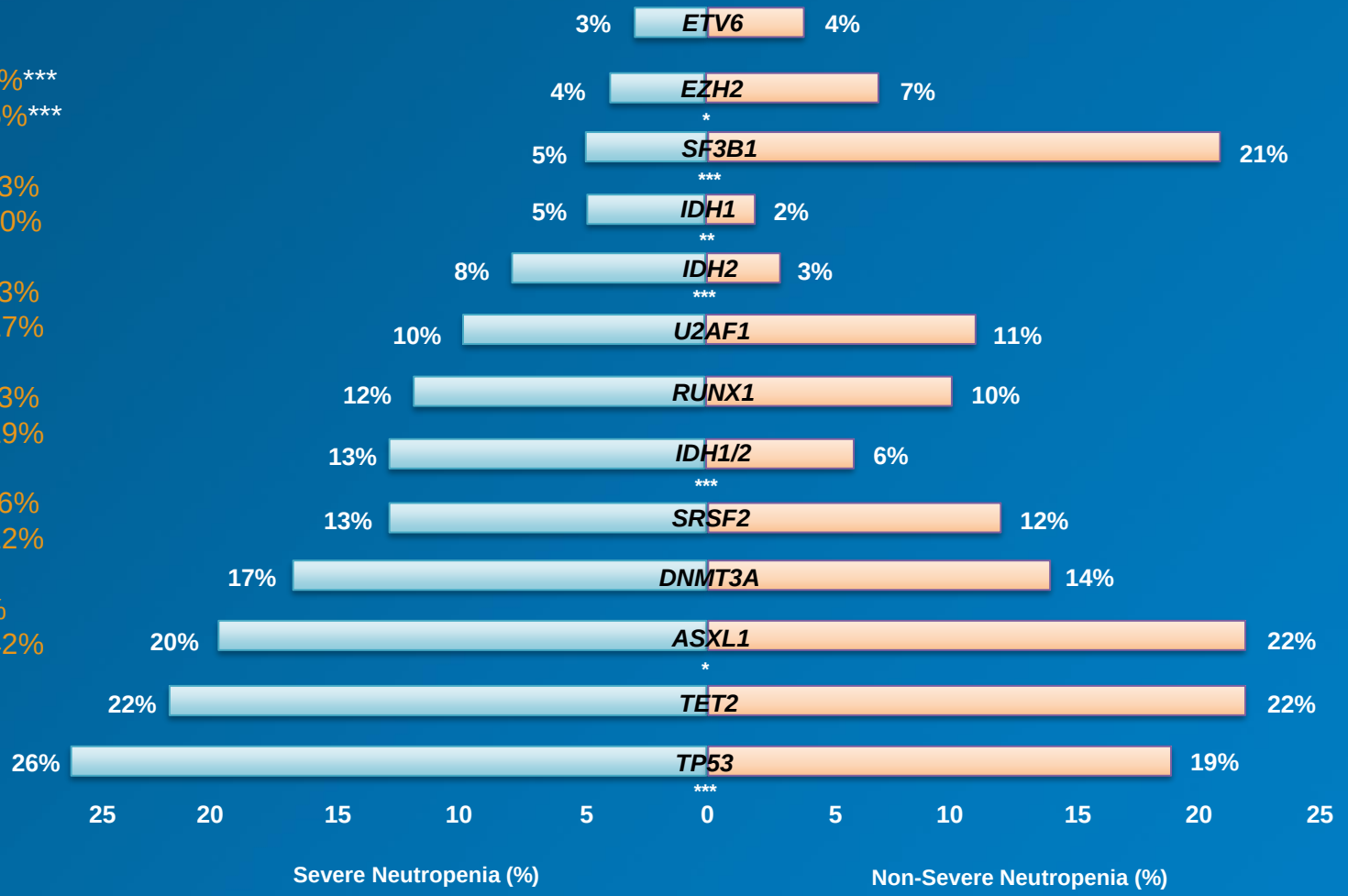
Garcia-Manero et al. *Blood* 2021;138(suppl 1):66.

IDH Mutations Are Enriched in Myelodysplastic Syndrome Patients With Severe Neutropenia: A Potential Targeted Therapy

Percent of Different Mutations in Severe Neutropenia (SN) vs. Non-severe Neutropenia (NSN)

R-IPSS: SN vs. NSN

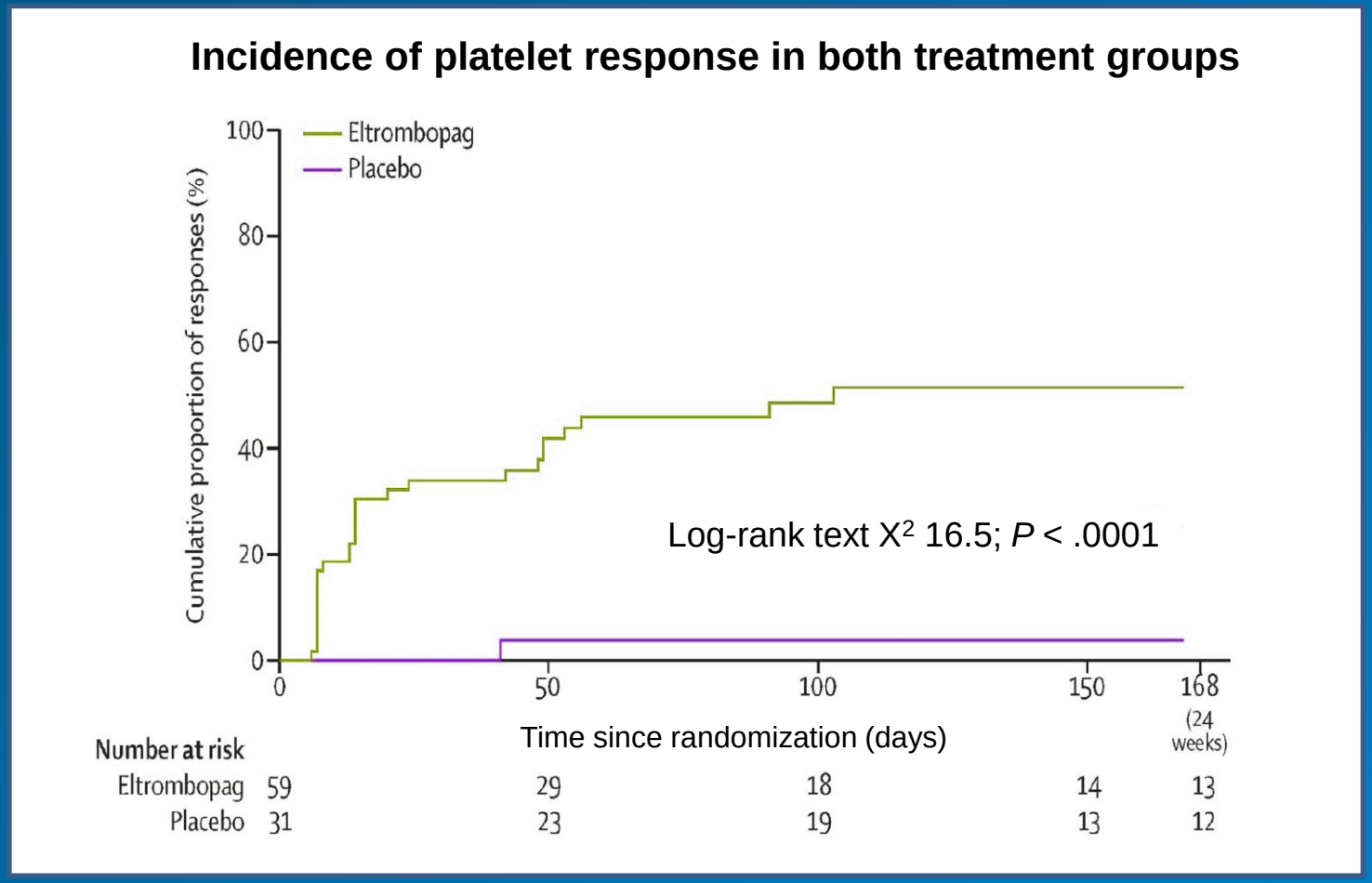
LR 3% vs. 4% HR 3% vs. 5%	LR 14% vs. 6%*** HR 13% vs. 6%***
LR 3% vs. 7% HR 4% vs. 5%	LR 17% vs. 13% HR 11% vs. 10%
LR 8% vs. 28%*** HR 4% vs. 5%	LR 15% vs. 13% HR 18% vs. 17%
LR 6% vs. 2%** HR 5% vs. 3%	LR 25% vs. 23% HR 18% vs. 19%
LR 8% vs. 3%** HR 9% vs. 4%**	LR 29% vs. 26% HR 19% vs. 12%
LR 15% vs. 12% HR 8% vs. 10%	LR 4% vs. 8% HR 36% vs. 42%
LR 11% vs. 10% HR 12% vs. 11%	



Adapted from Komrokji et al. *Blood* 2021;138(suppl 1):1526.

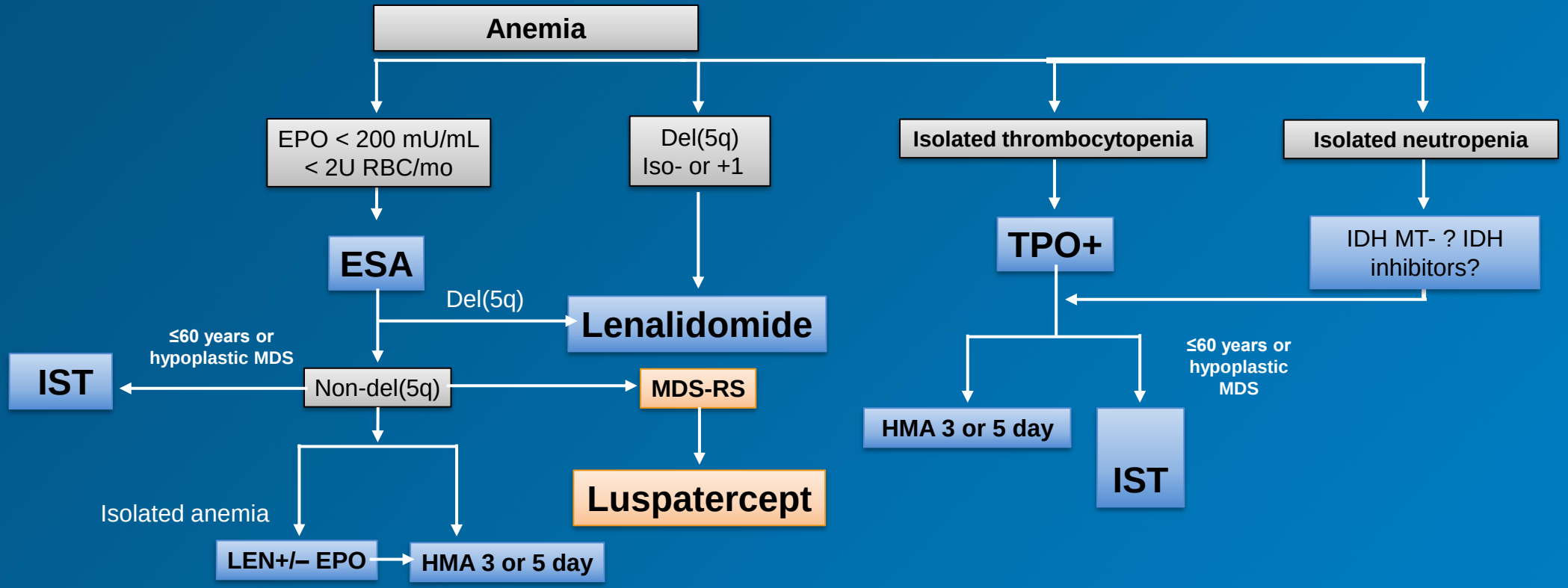
AXIS Medical Education

Eltrombopag for LR-MDS



LR-MDS, low-risk myelodysplastic syndrome.
Adapted from Oliva et al. *Lancet Haematol*. 2017;4(3):e127-e136.

How Do I Manage LR-MDS in 2022



- Allogeneic stem cell transplant maybe considered after standard therapy failure or in younger patients with higher-risk disease features
- Iron chelation should be considered in patients with evidence of iron overload

EPO, erythropoietin; ESA erythropoiesis-stimulating agents; HMA, hypomethylating agent; IST, immunosuppressive therapy; LEN, lenalidomide; LR-MDS, low-risk myelodysplastic syndromes; MDS-RS, myelodysplastic syndromes-ring sideroblasts; RBC, red blood cell; TPO, thrombopoietin; IDH-MT, isocitrate dehydrogenase mutation.
Adapted from Volpe and Komrokji. *Ther Adv Hematol*. 2021;12:1-10.

AXIS Medical Education

Shifting Paradigms for Assessment and Management of Lower-Risk MDS:

Genomics, Risk Stratification, and Novel Therapies