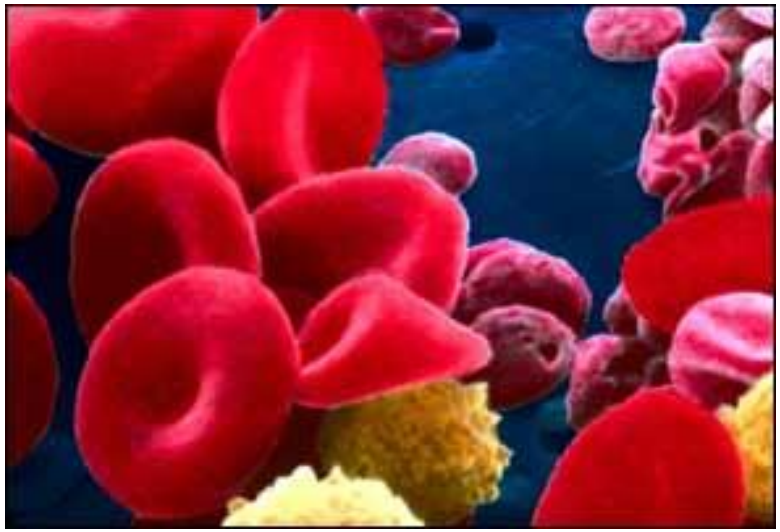
Myelodysplastic syndromes
MDS



Dr. Drorit Merkel
Head of the MDS&BMF center
Chaim Sheba Medical Center

מר אליהו כהן גרוש בן 74. חקלאי
הופנה לבירור ירידה בספירות הדם.
משנת 2003 נצפית ירידה איטית בשלושת השורות.
ללא היסטוריה של שתיית אלכוהול או מחלת כבד. שולל כאבי פרקים.
אושפז לפני 3 שנים בגלל דלקת ריאות.
לאחרונה פטרת בוושט שהודגמה בגסטרוסקופיה.

בבדיקה –א.מ.ל
ספירת הדם-
Hb- 10.5, MCV-99, WBC-1000, NEUT-300.
במשטח דם- לא נראו בלסטים.
בבדיקת מח העצם – נראו שינויים דיספלסטיים בשלושת השורות. ללא ריבוי של בלסטים. ללא סידרובלסטים טבעתיים.
ב-FISH וכרומוזומים נראה -20q.

Myelodysplastic Syndrome - MDS

- A group of clonal bone marrow stem cell disorders,
  - Hyper-cellular marrows
  - Peripheral cytopenias
  - Cytogenetic changes
  - Excess of blasts

- Heterogeneity- highly variable natural history.
- De novo or secondary
- Median age: 74 yr
  - 90% of patients aged > 50 years

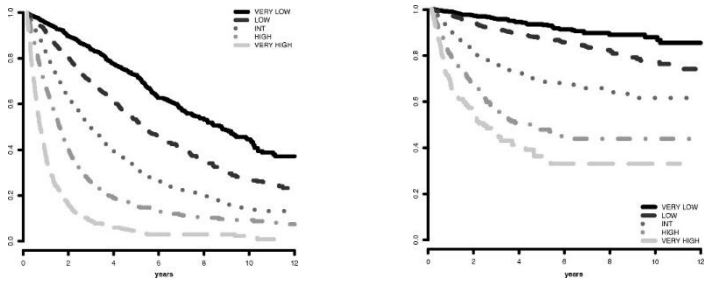
- MDS incidence increases with age (rate per 100,000):
  - ages 60–64 years, 5.4 cases
  - ages 80–84 years, 36.2 cases

- Progression
  - bone marrow failure,
  - conversion to AML (20%-60%).

The most common malignant bone marrow disorders

Annual new MDS diagnoses per 100,000: 3-6 cases

Survival and AML progression based on IPSS-R prognostic risk-based categories.



Peter L. Greenberg et al. Blood 2012;120:2454-2465

Malcovati L, Blood 2013;122:2943; Tefferi A, NEJM 2009; 361: 1872
Ades L, Lancet 2014;383:2293; Rollison DE, Blood 2008; 112: 45
deSwart L BJH 2015;170:372; Mittelman M Is J Med Sci 1990;26:468

Myelodysplastic Syndromes
Classification

Presence of cytopenia
- reduced and possibly dysfunctional circulating WBC, platelets, and RBC

Presence of dysplasia
- alteration in size, shape, and organization of cells
- impaired differentiation of immature precursor cells
- propensity for precursors to accumulate, hypercellular BM

Percentage of blasts

Cytogenetic abnormalities

Molecular abnormalities

Overall survival

Risk of progression to AML and death

WHO – Myelodysplastic Neoplasms

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

ICC- International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Overview of pre-MDS states and major diagnostic features

ICUS idiopathic cytopenia	Peripheral cytopenia(s) , MDS criteria not fulfilled, no MDS-related mutation found, no or only mild (<10%) dysplasia, blast cells <5% [c]
CHIP clonal hematopoiesis	No peripheral cytopenia , MDS criteria not fulfilled, one or more MDS-related mutations found, no or only mild (<10%) dysplasia, blast cells <5% [c]
IDUS idiopathic dysplasia	No peripheral cytopenia , MDS criteria not fulfilled, no MDS-related mutation found, dysplasia in ≥10% of neutrophilic, erythroid, and/or megakaryocytes found, blast cells <5%
CCUS clonal cytopenia	Peripheral cytopenia(s) , MDS criteria not fulfilled, one or more MDS-related mutations found, no or only mild (<10%) dysplasia, blast cells <5%

Cytopenia must persist for at least 4 months.
Mutations - cytogenetics, FISH, or sequencing studies.
In sequencing studies, the variant allele frequency should be **at least 2%** to count as diagnostic.
Flow cytometry studies and/or immunohistochemical studies (% of CD34+ and/or KIT+ cells) can support microscopic examinations.

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***

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

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MDS/AML	Typically ≥1‡	1≤	0	10-19% BM or PB‖	Any, except AML-defining¶	**Any, except *NPM1*, bZIP *CEBPA* or *TP53***

Myeloid neoplasms with mutated *TP53*

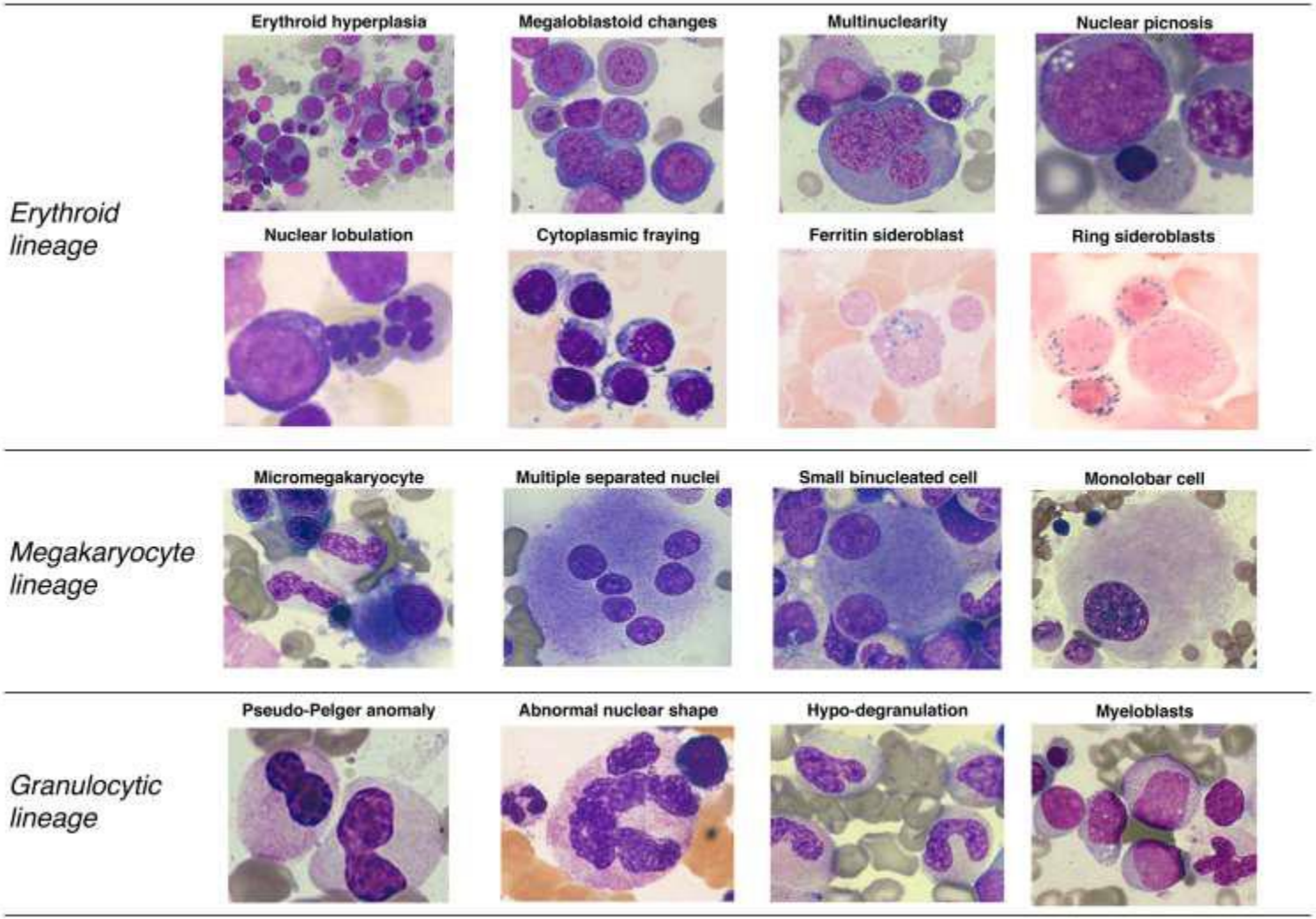
Type .	Cytopenia .	Blasts .	Genetics .
MDS with mutated *TP53*	Any	**0-9%** bone marrow and blood blasts	**Multi-hit** TP53 mutation* or *TP53* mutation (**VAF > 10%**) and **complex karyotype often with loss of 17p†**
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	**Any somatic** *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%)

*** Defined as 2 distinct *TP53* mutations (each VAF > 10%) OR a single *TP53* mutation with (1) 17p deletion on cytogenetics; (2) VAF of > 50%; or (3) Copy-neutral LOH at the 17p *TP53* locus.**
† If *TP53* locus LOH information is not available.

ICC of hematologic neoplasms with germline predisposition

Myeloid neoplasms with germline *CEBPA* mutation
Myeloid or lymphoid neoplasms with germline *DDX41* mutation
Myeloid or lymphoid neoplasms with germline *TP53* mutation
Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder
Myeloid or lymphoid neoplasms with germline *RUNX1* mutation
Myeloid neoplasms with germline *ANKRD26* mutation
Myeloid or lymphoid neoplasms with germline *ETV6* mutation
Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems
Myeloid neoplasms with germline *GATA2* mutation
Myeloid neoplasms with germline *SAMD9* mutation
Myeloid neoplasms with germline *SAMD9L* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
Fanconi anemia
Shwachman-Diamond syndrome
Telomere biology disorders including dyskeratosis congenita
Severe congenital neutropenia
Diamond-Blackfan anemia
JMML associated with neurofibromatosis
JMML associated with Noonan-syndrome-like disorder (CBL-syndrome)
Myeloid or lymphoid neoplasms associated with Down syndrome
Acute lymphoblastic leukemia with germline predisposition*
Acute lymphoblastic leukemia with germline *PAX5* mutation
Acute lymphoblastic leukemia with germline *IKZF1* mutation

Pivotal role of morphology in diagnosis and prognostication of MDS



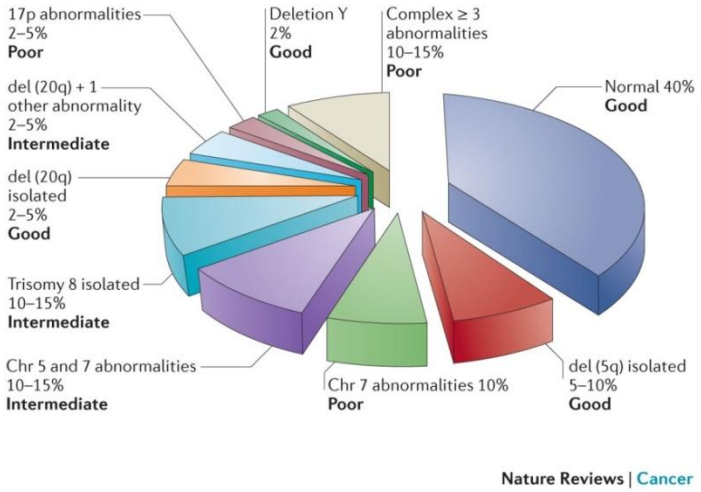
Cazzola et al. Blood. 2013 Dec 12;122(25):4021-3411

IPPS-R: Cytogenetic Prognostic Subgroups

- **Very Good**: del(11q),-Y
- **Good**: Nl, del(20q), del(5q) alone and double, del(12p)
- **Intermediate**: +8, 7q-, i(17q),+19,+21, any othersingle or double, independent clones
- **Poor**: der(3)q21/q26,-7, double including 7q-,Complex (3 abnormalities)
- **Very Poor**: Complex (>3 abnormalities)

	0	1	1.5	1.5	2.5	3.5	5
Cyto	Very Good		Good		Int	Poor	**Very Poor**
Blasts	<5%			5-10%	11-30%		
Hb	≥10		<10				
Plt	≥100		<100				
ANC	**0.8≥**	**<0.8**					

***Regression analysis for survival and AML evolution**



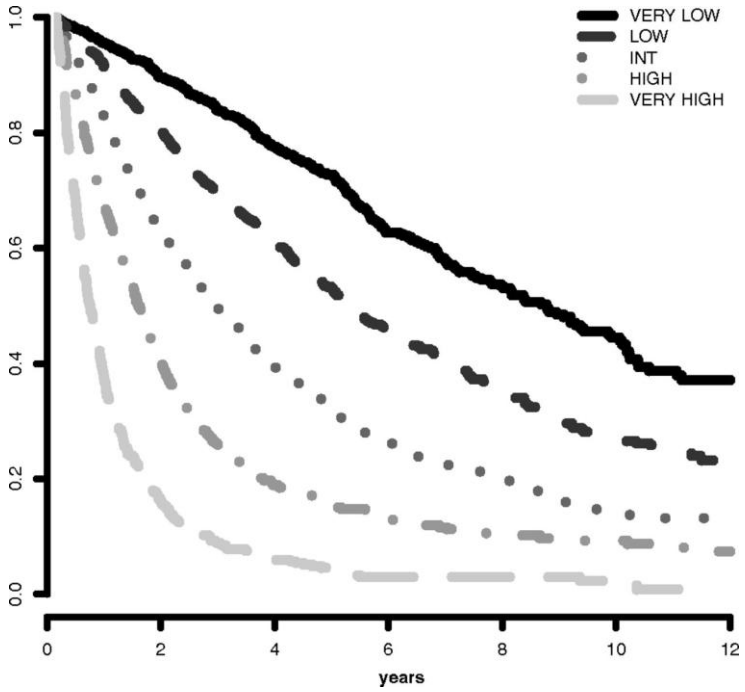
	1 Very Low	2 Good	3 Intermediate	4 Poor	5 Very High
OS	8.7	5.3	3.0	1.6	0.8
AML, 25%	NR	10.7	4.0	1.4	0.8

Prognostic Risk Groups/Scores*

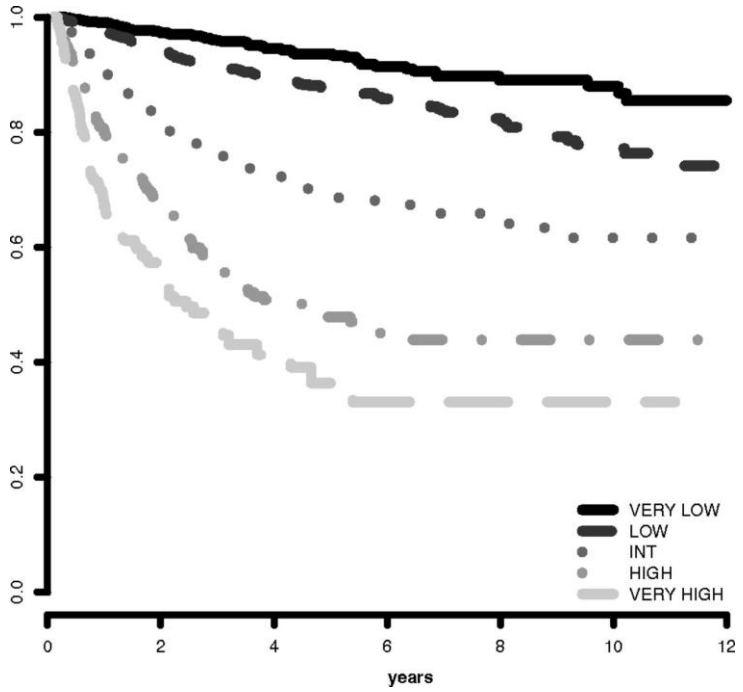
1. Very Low:	**0 - 2**
2. Good:	**>2 - 3.5**
3. Intermediate:	**>3.5 - 5**
4. High:	**>5 - 6**
5. Very High:	**>6**

Schanz et al, J Clin Oncol

Survival based on IPSS-R prognostic risk-based categories.



AML evolution based on IPSS-R prognostic risk-based categories.



Peter L. Greenberg et al. Blood 2012;120:2454-2465

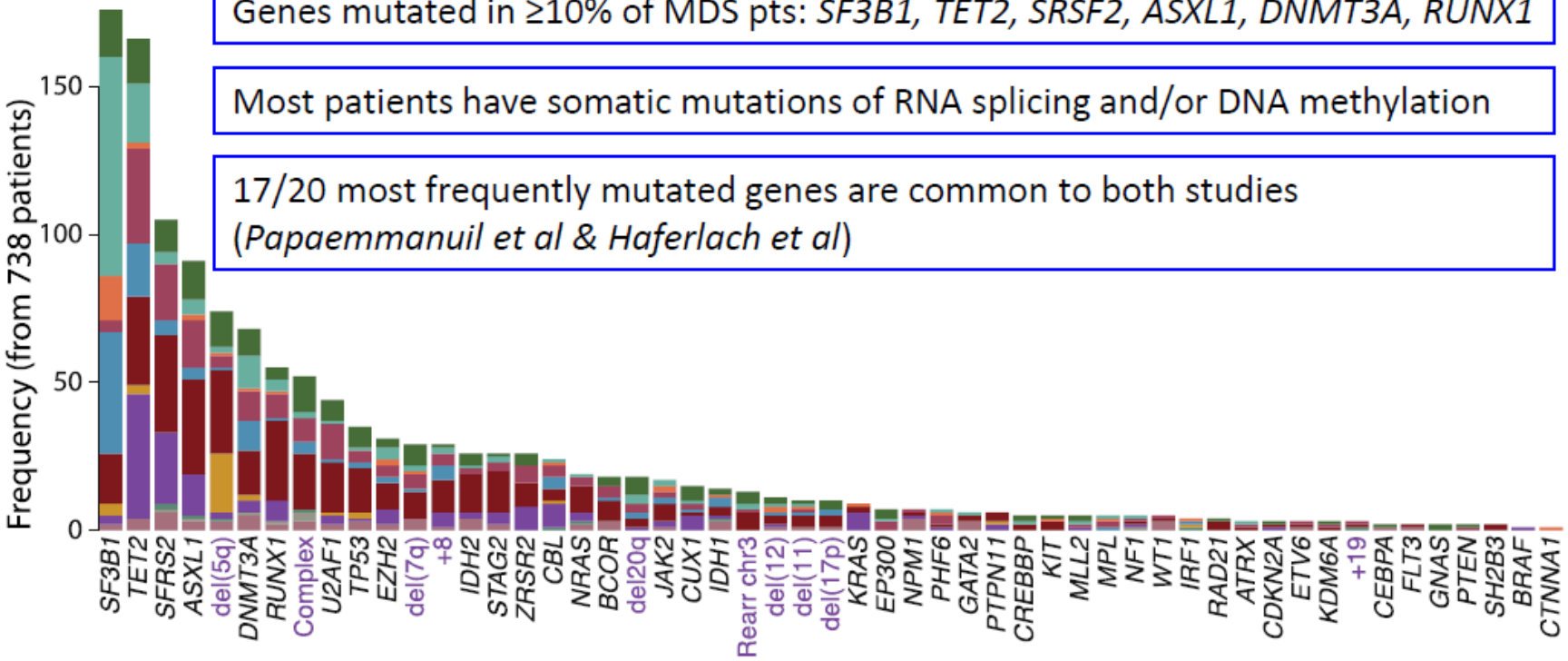
blood

Somatic gene mutations in patients with MDS

Genes mutated in ≥10% of MDS pts: *SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1*

Most patients have somatic mutations of RNA splicing and/or DNA methylation

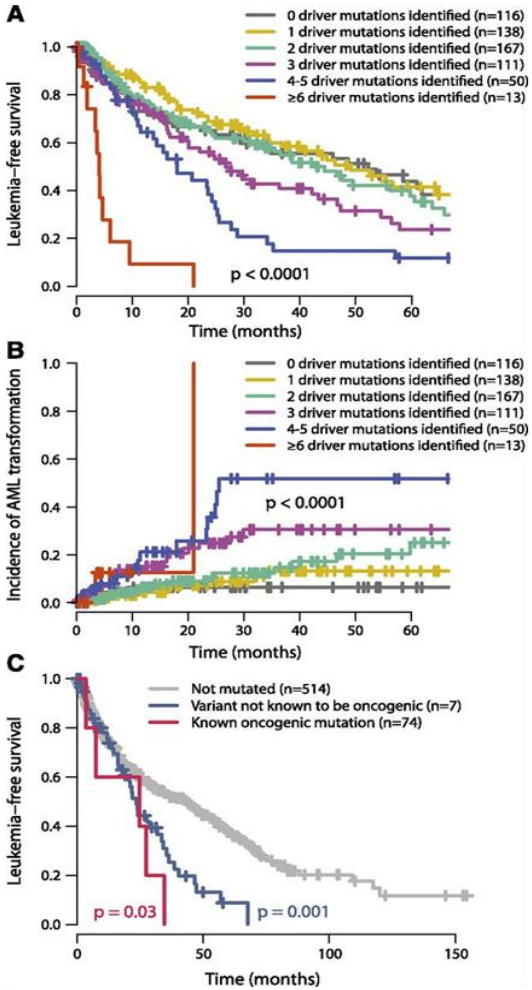
17/20 most frequently mutated genes are common to both studies (*Papaemmanuil et al & Haferlach et al*)



Papaemmanuil et al. Blood. 2013 Nov 21;122(22):3616-27

Haferlach et al. Leukemia. 2014 Feb;28(2):241-7

Relationship between number of oncogenic mutations and outcome.



Elli Papaemmanuil et al. Blood 2013;122:3616-3627

Gene mutations data for MDS patients by genes mutated and biological pathways affected

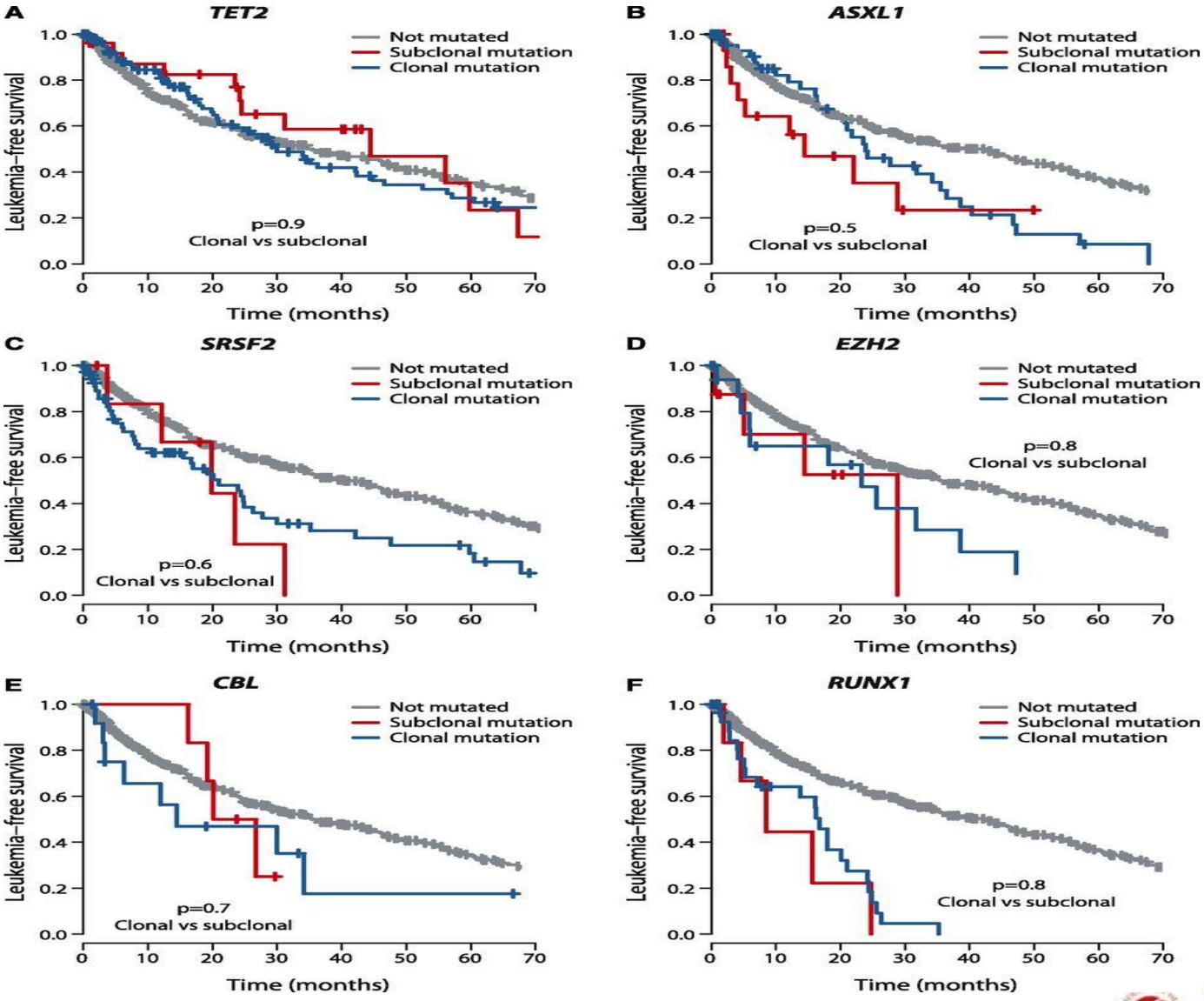
Functional Pathway	Gene	Frequency in MDS	Phenotypic association	Prognostic relevance in isolation	Prognostic impact maintained in large sequencing studies
RNA Splicing	SF3B1	25-30%	MDS with ring sideroblasts	Good risk	Yes
	SRSF2	10-20%	Myelomonocytic (if co-mutated with TET2)	Adverse risk	
	U2AF1	5-10%	-	Adverse risk	
	ZRSR2	~5%	Myelomonocytic (if co-mutated with TET2)	Unclear	
DNA Methylation	TET2	20-30%	Myelomonocytic (if co-mutated with SRSF2/ZRSR2)	None	
	DNMT3A	~10%	-	Adverse risk*	
	IDH1	<5%	-	Adverse risk	
	IDH2	<5%	MDS with excess blasts	Adverse risk	
Chromatin Modification	ASXL1	15-20%	MDS with excess blasts	Adverse risk	Yes
	EZH2	~5%	-	Adverse risk	Yes
Transcription factors	RUNX1	5-10%	MDS with excess blasts	Adverse risk	Yes
	BCOR	<5%	-	Adverse risk	
DNA repair	TP53	~5%	MDS with excess blasts	Adverse risk	Yes
Cell Signalling	NRAS/KRAS	<5%	-	Unclear	
	CBL	<5%	-	Unclear	
Cohesin Complex	STAG2	5-10%	MDS with excess blasts	Adverse risk	Yes
No mutation	-	~10%	MDS with uni- or multilineage dysplasia	Good risk‡	

Seminars in hematology, July 2017, Pages 133-140

שיבא
תל השומר
עיר הבריאות של ישראל

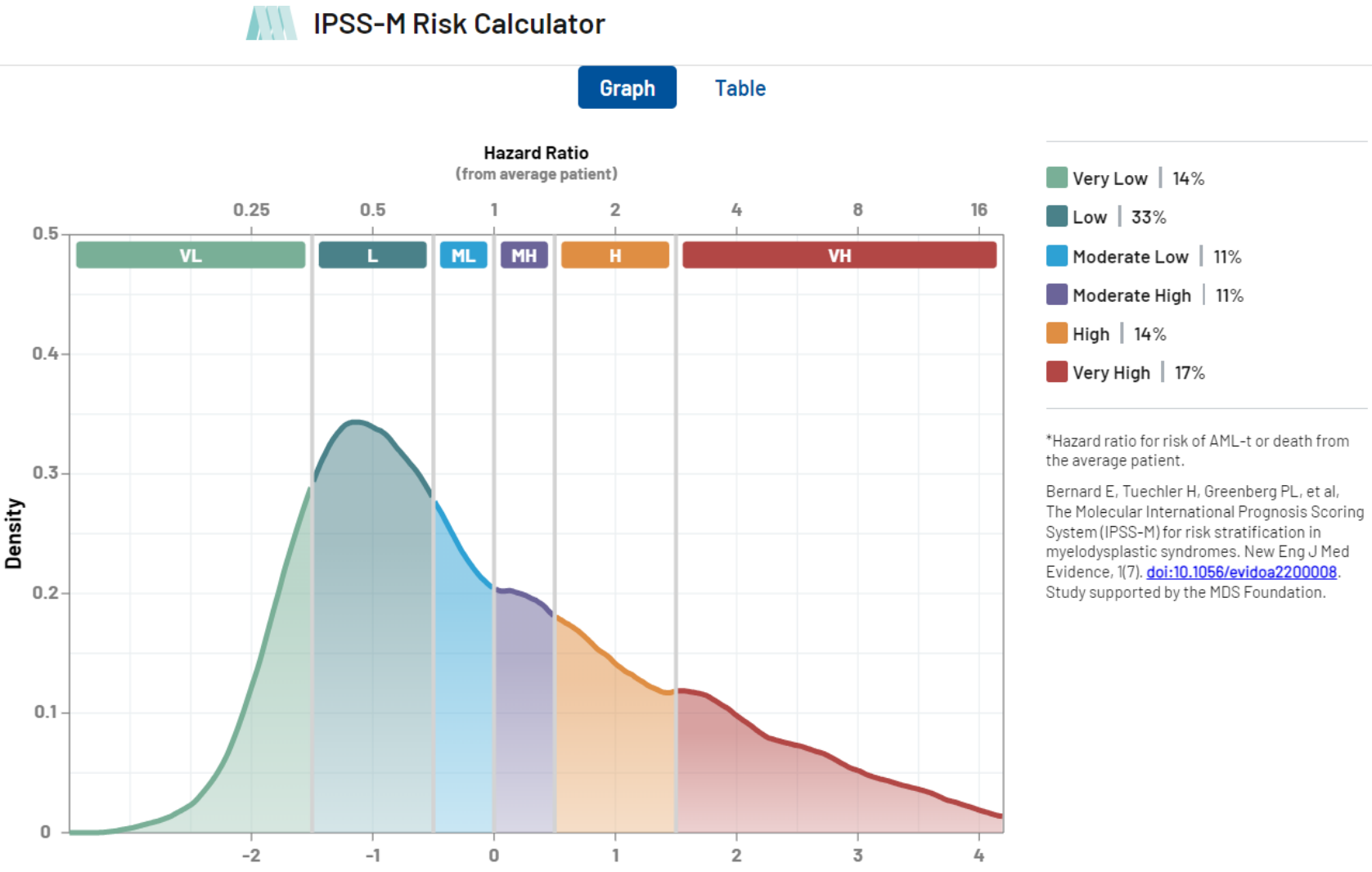
המרכז לתסמונות מיאלודיספלסטיות - MDS

Outcome by whether driver mutations are clonal or subclonal.



Elli Papaemmanuil et al. Blood 2013;122:3616-3627

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



MDS – symptoms & signs

Non-specific symptoms, consequences off cytopenias,

- **Symptoms of anemia**
- **Infections**
- **Bleeding**

Differential diagnosis:

- **Aplastic anemia**
- **Disease accompanied by marrow dysplasia:**
  - **B_{12} and/or folate deficiency**
  - **Exposure to haevy metals,**
  - **Recent cytotoxic therapy**
  - **Inflamation (HIV and chronic liver disease/ethylism)**

Presentation of myelodysplastic syndromes

- Anemia- 60% of patients
  - fatigue, weakness, and dyspnea
- Neutropenia- 50% of
  - frequent infections, mouth sores, or fever.
  - Bacterial infection is a major cause of mortality.
- Thrombocytopenia- 40-60% of patients
  - abnormal bleeding or bruising.
  - Severe thrombocytopenia (platelet count < 20 x 10/9L) is seen in about 18%
  - Thrombocytopenia is usually associated with advanced forms

Predisposition:

Heritable	Acquired
Constitutional genetic disorders	Senescence Mutagen/Genotoxic Stress
Trisomy 8 mosaicism	Therapeutic alkylators, Topo-II agents,
Familial monosomy 7	β-emitters (^{32}P), autoSCT
Neurofibromatosis 1	Environmental/occupational (benzene)
Embryonal dysgenesis (del12p)	Tobacco
Congenital Neutropenia	Aplastic anemia
Kostmann, Schwachman-Diamond	PNH
DNA repair deficiencies	
Fanconi anemia, AT, Bloom syndrome	

List AF, et al. The Myelodysplastic Syndromes. In: Wintrobe's Hematology 2003.

Goals of Therapy in MDS

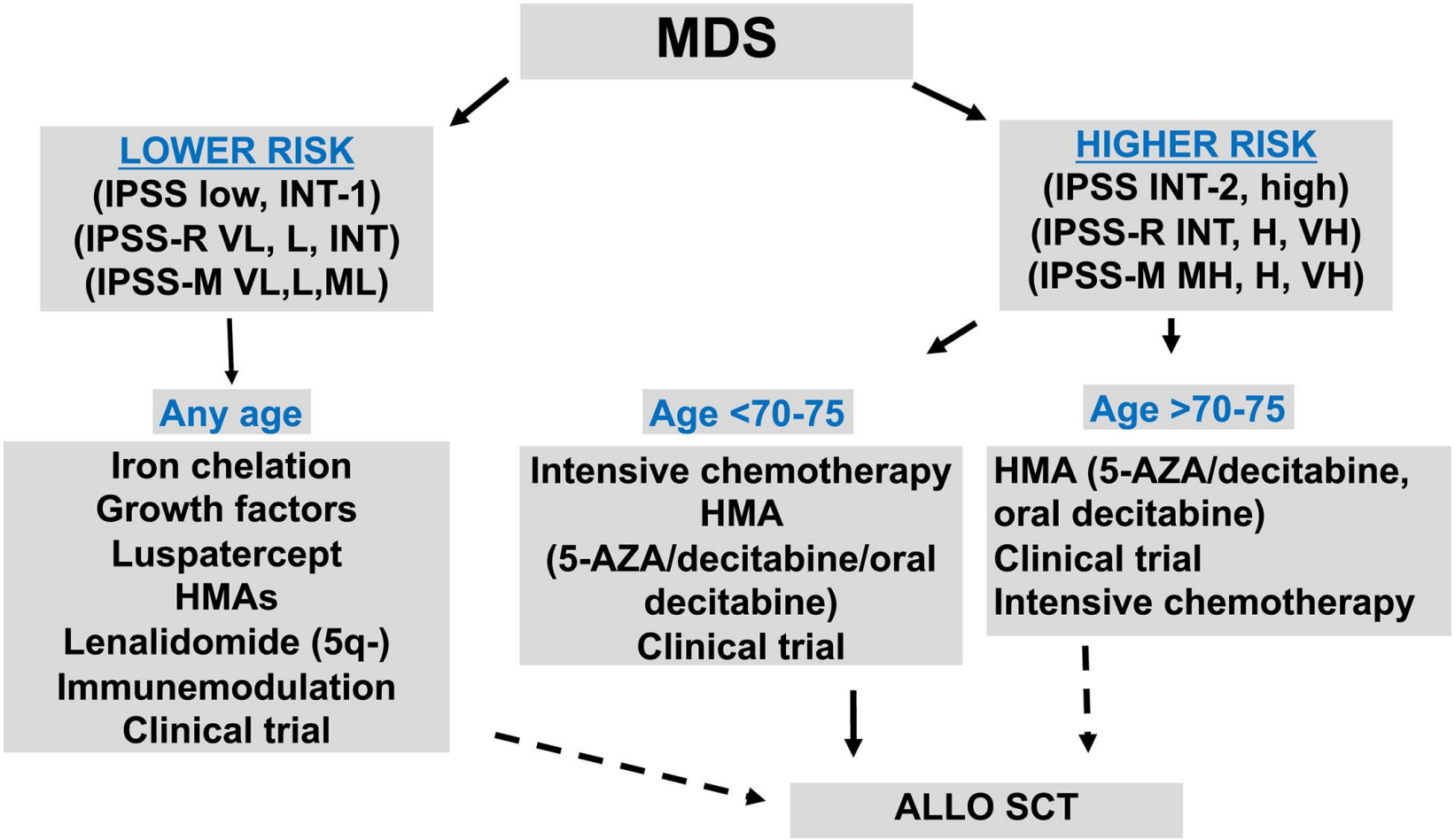
- **Select the therapy best suited for the individual**
  - **Performance status, disease classification, IPSS score (cytogenetics, cytopenias, BM blasts), and treatment tolerance**
- **Low/Int-1 IPSS:**
  - **Improve blood counts (decrease transfusions and infections)**
- **Int-2/high-risk IPSS:**
  - **Prolong survival**
  - **Delay leukemic progression**

Improve quality of life

Possible cure of disease

List AF, et al. *Hematology* (Am Soc Hematol Educ Program). 2004;297-317. Cheson BD, et al. *Blood*. 2000;96:3671.
NCCN Myelodysplastic Panel Members. Available at: http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf

Proposed treatment algorithm for patients with MDS 2023



Guillermo Garcia-Manero

Am J Hematol..1325–98:1307;2023

Transfusion- Anemia

Anemia complicates majority of MDS.

- **Solitary cytopenia in 30%.**
- **Usually low reticulocyte count.**
- **Response to EPO 20-30%; Few transfusion independent.**
- **Response seen in 1-2 months of therapy.**
- **Iron repletion/supplementation should be monitored**

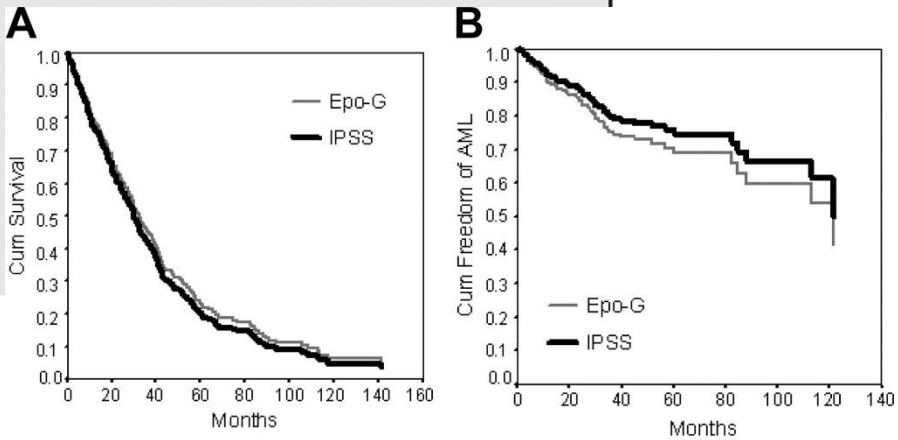
Cheson BD, et al. *Blood* 2000. 96:3671-4.

Predictive variables for ESA response in MDS.

Table 1. Predictive variables for ESA response in MDS

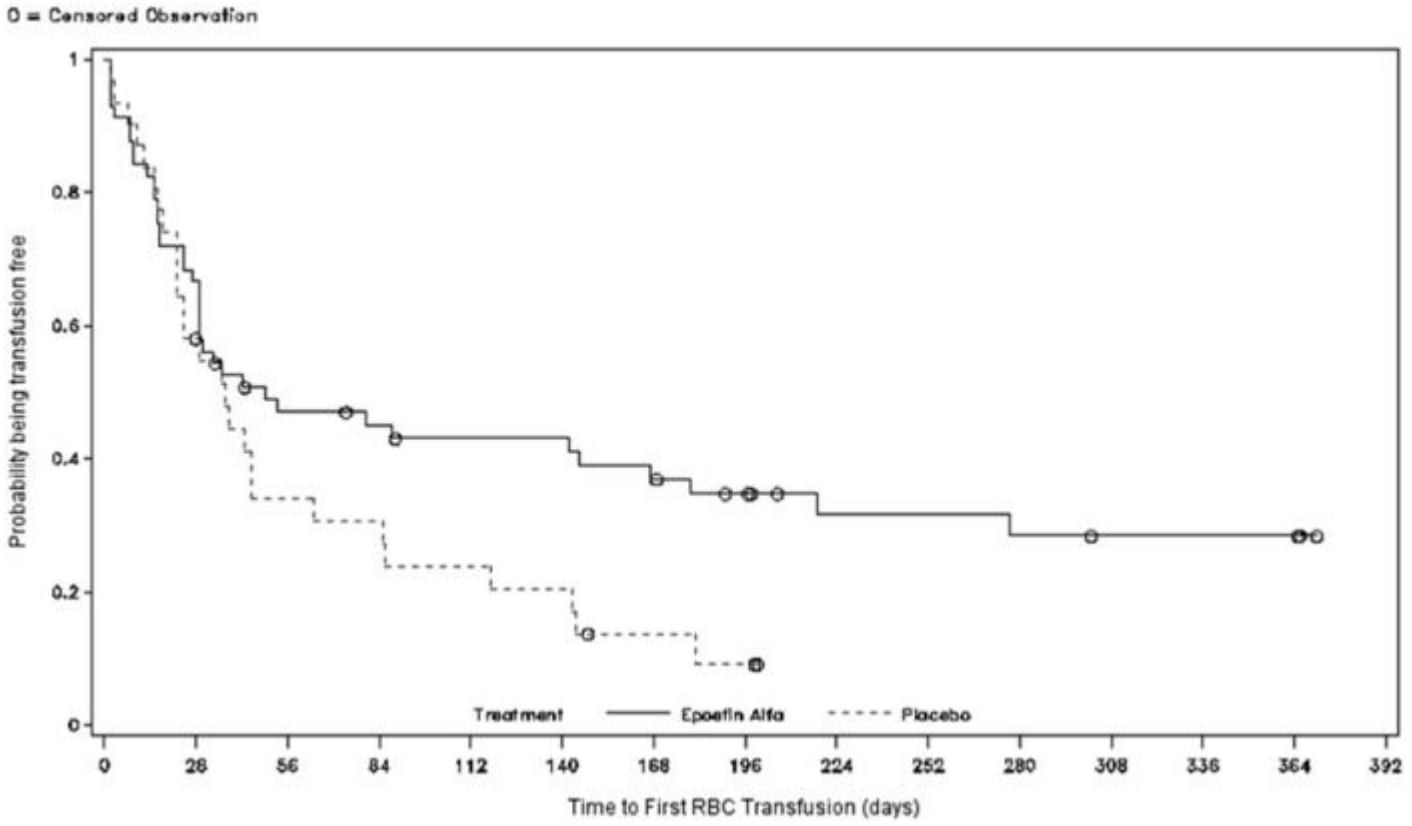
Biological
Endogenous erythropoietin levels <500 U/L
Marrow blast <10%
IPSS low-INT-1
Diagnosis of refractory anemia
Normal karyotype
Clinical
Transfusion independence
Short duration of disease

Abbreviations: ESA, erythropoietic stimulating agents; INT-1, intermediate-1; IPSS, International Prognostic Score System; MDS, myelodysplastic syndromes.



Jadersten, M. et al. Blood 2005;106:803-811

A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS



- Fenaux 2018 Dec;32(12):2648-2658.

Transfusions-PLT

Majority of patients will require transfusion support.

- **Thresholds based on symptoms, co-morbidities:**

  PLTs <10-20K well tolerated in absence of bleeding.

  - Dysfunction may require higher PLT threshold or target HCT.
  - Irradiated only with intensive chemo or transplantation.

Multiple transfusions lead to complications.

- **Allo-sensitization.**
- **Iron overload.**

  Chelation for > 25U pRBC and prolonged life expectancy.

  Iron absorption may be seen in RARS

Cheson BD, et al. *Blood* 2000. 96:3671-4.
Http:// www.NCCN.org MDS Guidelines

Transfusion therapy results in iron overload

80%of MDS patients have HB<10g/dl at diagnosis.
The majority become transfusion-dependent

- **1 blood unit contains 200–250 mg iron**
- **Iron overload occurs after ~ 20 transfusions leading to ferritin levels of about 1,000 μg/L**

2 units/month

24 units/year

≥ 5 g iron/year

Serum ferritin ~ 1,000 μg/L

Normal body iron: 3–4 g
No physiological mechanism to excrete excess of iron

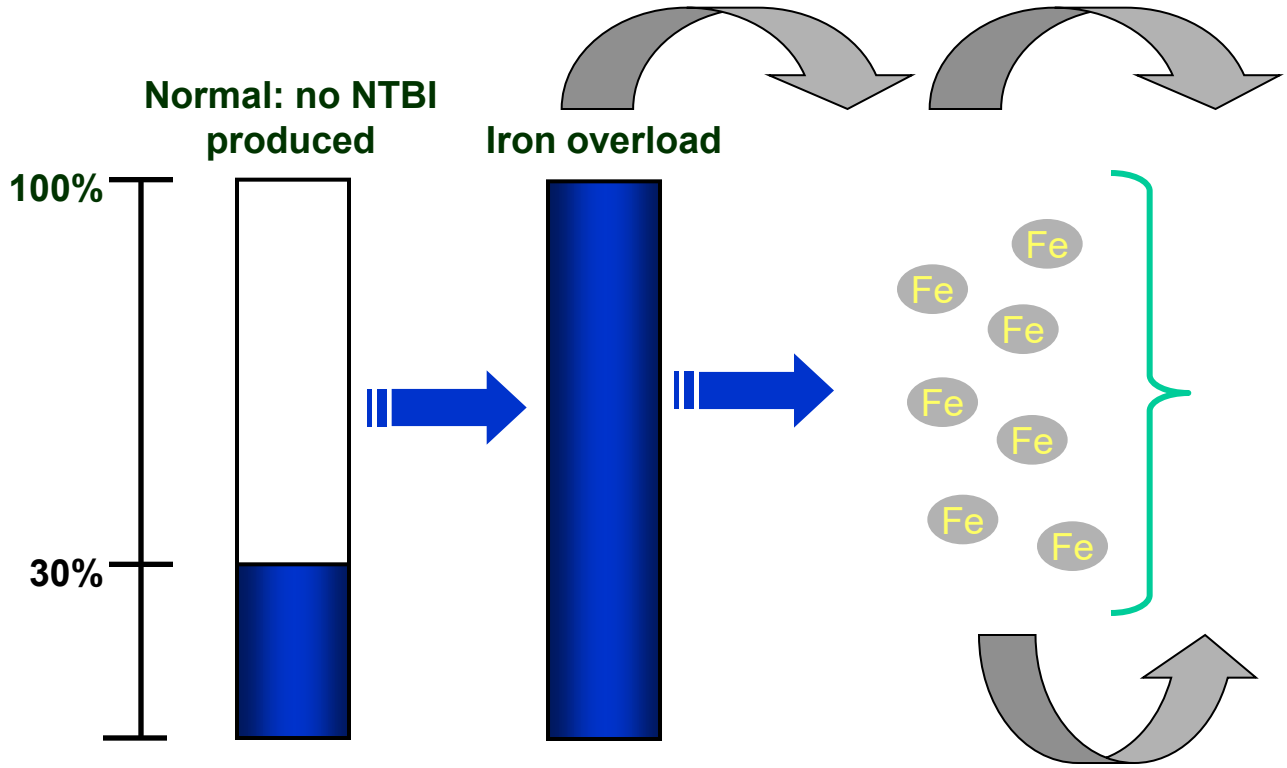
Porter JB. Br J Haematol. 2001;115:239-52.

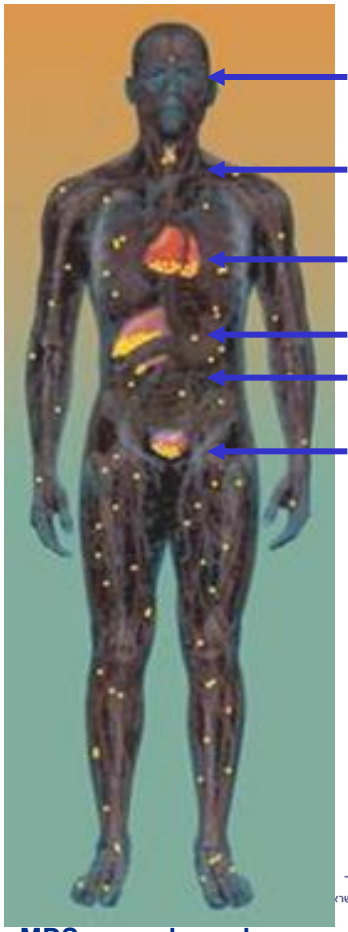
Iron overload and organ loading

Transferrin saturation due to
- **Ineffective erythropoiesis leading to increased iron absorption**
- **Frequent blood transfusions or**

Subsequent formation of NTBI in plasma

Uncontrolled iron loading of organs





Relation between chelation and clinical outcomes in lower-risk patients with myelodysplastic syndromes: Registry analysis at 5 years

Causes of Death for All Enrolled Patients.
Nonchelated - 241 (73.1%),
Chelated - 168 (62.2%),
Chelated ≥6 months 121(59.6%)
(*P* = 0.001 for nonchelated vs chelated ≥6 months).

Figure 2. Overall Survival

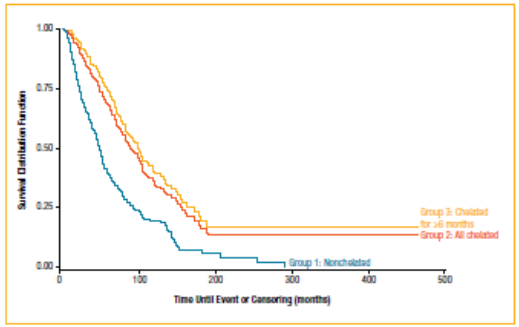
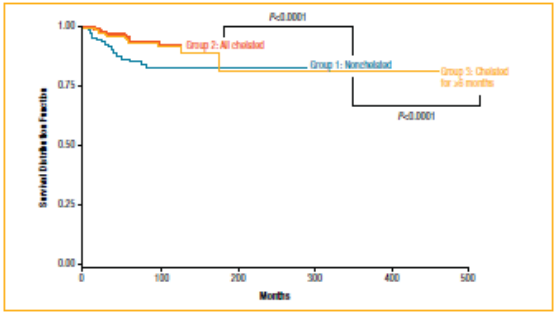
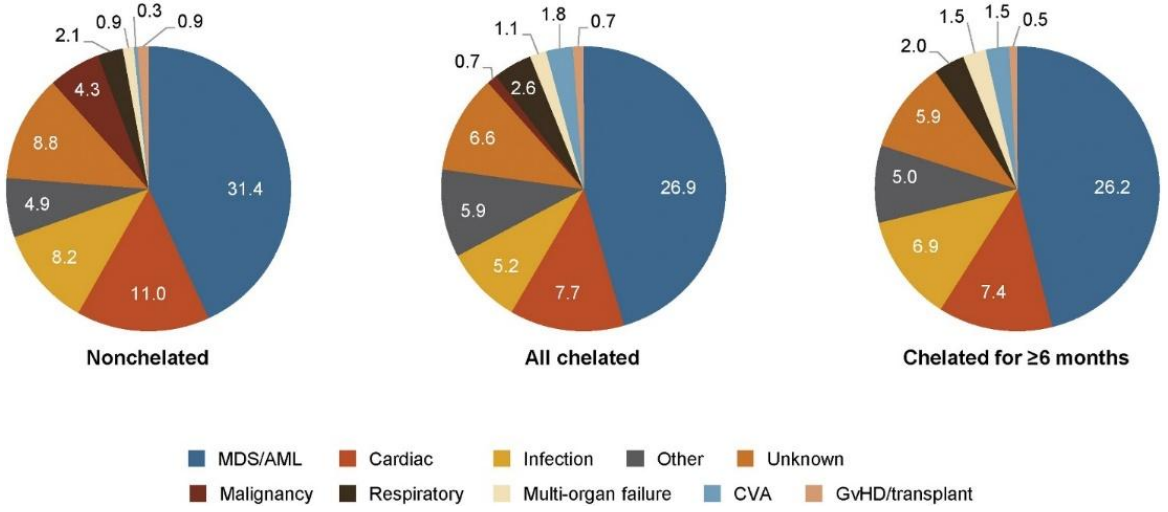


Figure 3. Time to Progression to Acute Myeloid Leukemia



Causes of death due to MDS/AML, infection, and malignancy in the nonchelated group. (*P* = 0.0014),



Volume 56, May 2017, Pages 88-95 LYONS Leukemia Research

Lenalidomide
5q- syndrome Low risk

- **Reduced need for transfusions 76%; (112 of 148 patients)**
- **Among 85 patients who could be evaluated,**
  - **62 had cytogenetic improvement,**
  - **38 of the 62, 61% - had a complete cytogenetic remission.**
- **RBC-TI was durable and was associated with:**
- **- improvement in Hb levels**
- **- improvement in HRQoL**
- **- Reduced risk of death**
- **Lenalidomide was generally well tolerated**

Fenaux P. et al. blood, July 13, 2011

A 78 years old male.

MDS RARS NK IPSSR -2

2012 - ANEMIA
BMB 2015 - Normocellular and distorted bone marrow. The morphological features are not enough for the diagnosis of myelodysplasia.

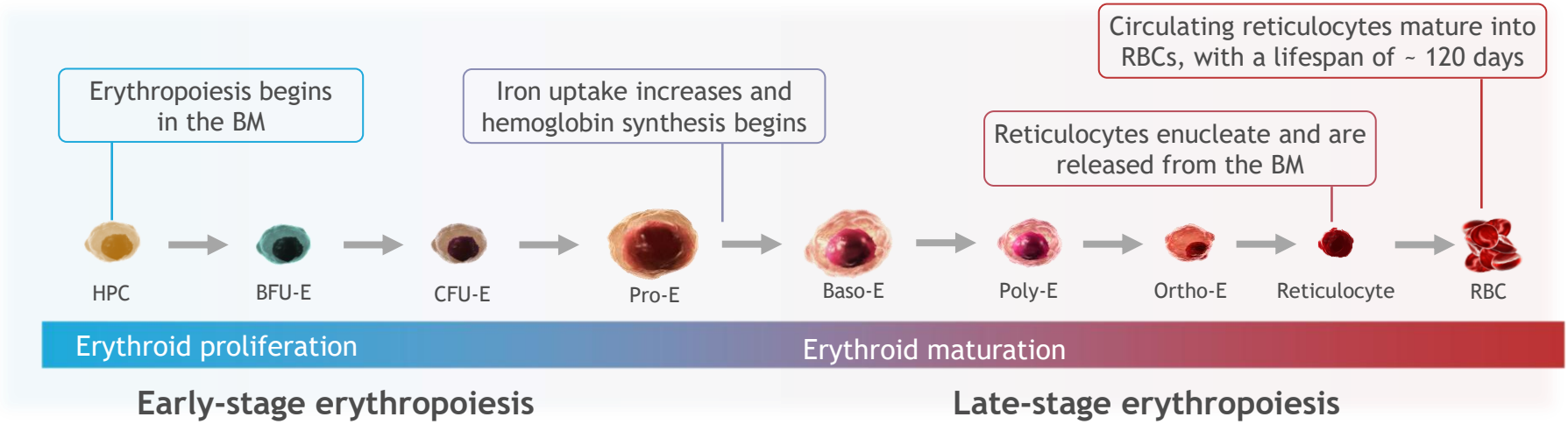
BMB 2017 - Normocellular for age bone marrow (in 40% of the biopsy) showing red cell hyperplasia with occasional immature forms and occasional small hypolobed atypical megakaryocytes. The morphologic changes show mild dysplastic changes but are not sufficient for the diagnosis of myelodysplasia.
BMA – Ring sideroblasts ~ 30%

BMB-2020 Hypercellular bone marrow showing red cell hyperplasia with dyserythropoiesis and dysplasia of the megakaryocytes. Although the morphologic findings are compatible with a multilinear myelodysplastic syndrome (RARS as per clinical information) the marked red cell hyperplasia could be partly secondary to treatment (Epoetin).

2017 – ESA therapy with neupogen
03/2021 – LUSPATERCEPT
12/2022 – transfusion RBC dependent – low intensity still with Luspatercept
2025 – Luspatercept + ESA

NORMAL ERYTHROPOIESIS

- Erythropoiesis is the process by which mature RBCs are produced[1–3]
- Erythropoiesis involves several stages of proliferation in which erythroid precursor cells differentiate and expand[1–3]
- The process is controlled by a network of cytokines and transcription factors[1–3]

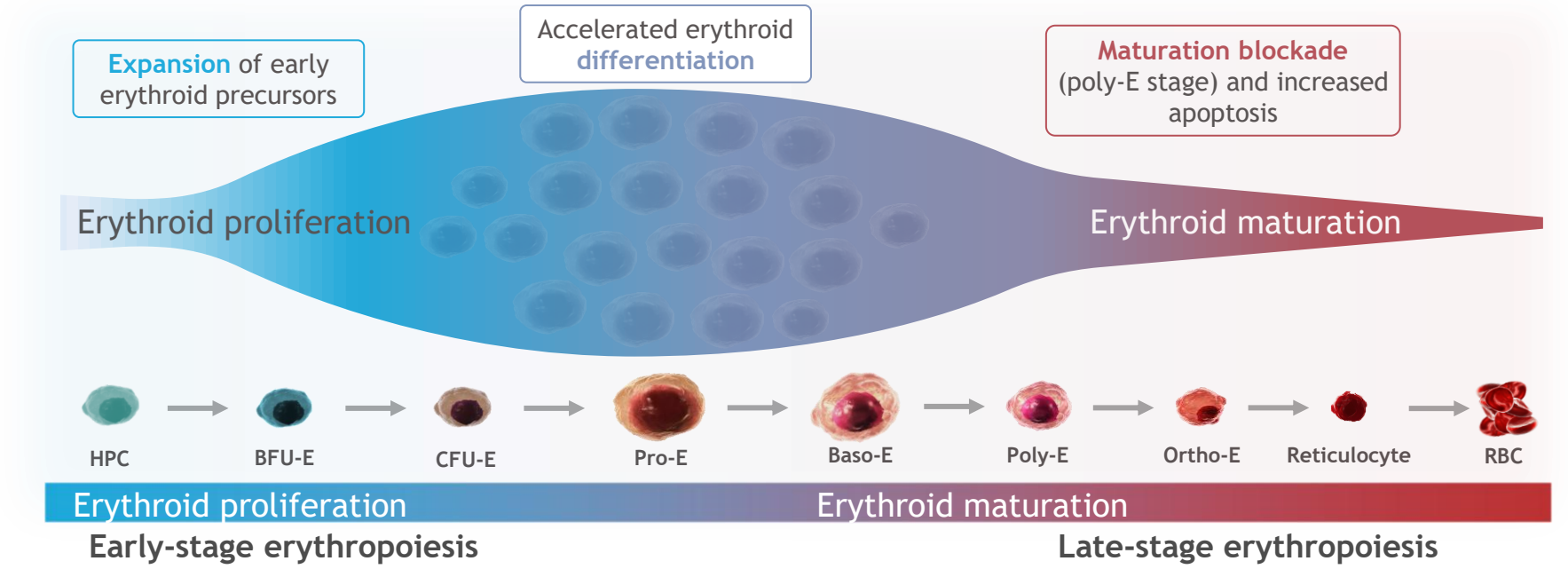


baso-E, basophilic erythroblast; BFU-E, burst-forming unit-erythroid; BM, bone marrow; CFU-E, colony-forming unit-erythroid; HPC, hematopoietic progenitor cell; ortho-E, orthochromatic erythroblast; poly-E, polychromatic erythroblast; pro-E, pro-erythroblast; RBC, red blood cell.

1. Zivot A et al. *Mol Med* 2018;24:11. 2. Valent P et al. *Haematologica* 2018;103:1593–1603. 3. Nandakumar SK et al. *Br J Haematol* 2016;173:206–218.

INEFFECTIVE ERYTHROPOIESIS[1-4]

- Defects in erythropoiesis, as seen with MDS, may lead to accelerated differentiation and apoptosis of erythroid precursors, resulting in decreased RBC output

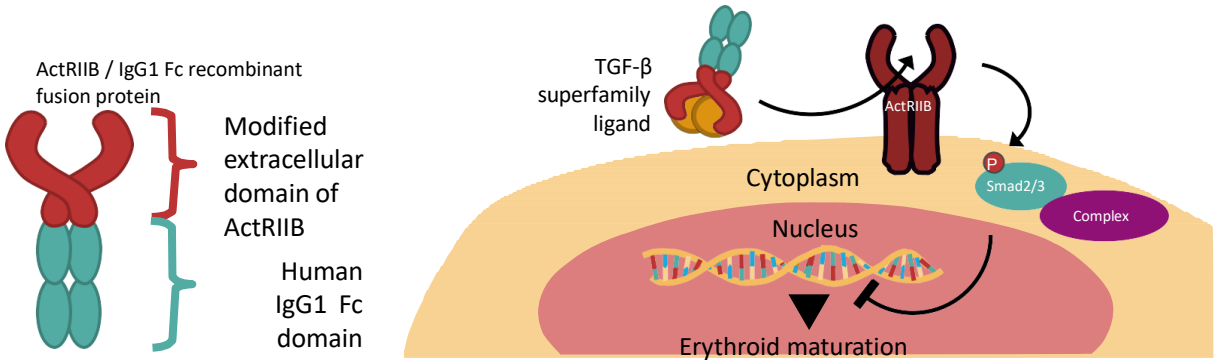


Baso-E, basophilic erythroid; BFU-E, burst-forming unit-erythroid; CFU-E, colony-forming unit-erythroid; HPC, hematopoietic progenitor cell; MDS, myelodysplastic syndromes; Ortho-E, orthochromatophilic erythroblasts; Poly-E, polychromatophilic erythroblasts; Pro-E, proerythroblasts; RBC, red blood cell. 1. Zivot A et al. *Mol Med* 2018;24:11. 2. Valent P et al. *Haematologica* 2018;103:1593–1603. 3. Nandakumar SK et al. *Br J Haematol* 2016;173:206–218. 4. Fontenay-Roupie M et al. *Br J Haematol* 1999;106:464–473.
Included with permissions Zivot A et al, 2018, *Mol Med*.

MEDALIST Trial
Luspatercept

- Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase 2 study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes[2]

Luspatercept



ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-β, transforming growth factor beta.

1. Suragani RN, et al. Nat Med. 2014;20:408-414;
2. Platzbecker U, et. A. Lancet Oncol. 2017; 18:1338.

ActRIIB - -activing receptor type B – receptor of serine/threonine kinase that interacts with multiple ligands of the TGF b superfamily

INEFFECTIVE ERYTHROPOIESIS: ABERRANT SMAD2/3 SIGNALING

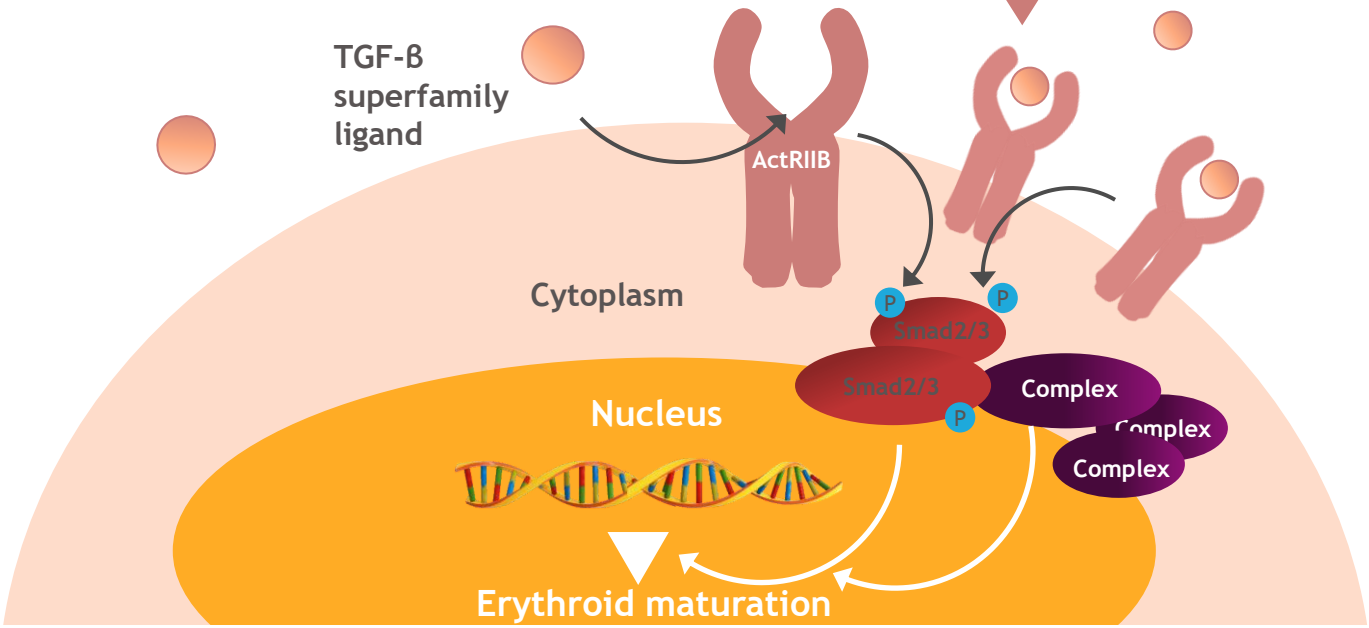
TGF-β superfamily signaling via Smad2/3 regulates erythroid maturation during late-stage erythropoiesis[1]

Select TGF-β superfamily ligands signal via ActRIIB to trigger the Smad2/3 signaling pathway[1-3]

Ligand binding triggers phosphorylation (activation) of Smad2/3, enabling it to form a heteromeric Smad complex[3,4]

The Smad complex translocates to the nucleus, where it modulates transcription of genes involved in erythroid maturation[3-7]

Increased aberrant TGF-β superfamily signaling via the Smad2/3 pathway is a component of **ineffective erythropoiesis** and impaired erythroid maturation[6,7]



Bristol Myers Squibb

ActRIIB, activin receptor type IIB; P, phosphorylation; Smad, small mothers against decapentaplegic; TGF-β, transforming growth factor β.

1. Attie KM et al. *Am J Hematol* 2014;89:766–770. 2. Cappellini MD et al. *Blood Rev* 2018;32:300–311. 3. Blank U, Karlsson S. *Blood* 2015;125:3542–3550. 4. Hata A, Chen YG. *Cold Spring Harb Perspect Biol* 2016;8:a022061. 5. Blank U, Karlsson S. *Leukemia* 2011;25:1379–1388. 6. Suragani RN et al. *Blood* 2014;123:3864–3872. 7. Suragani RN et al. *Nat Med* 2014;20:408–414.

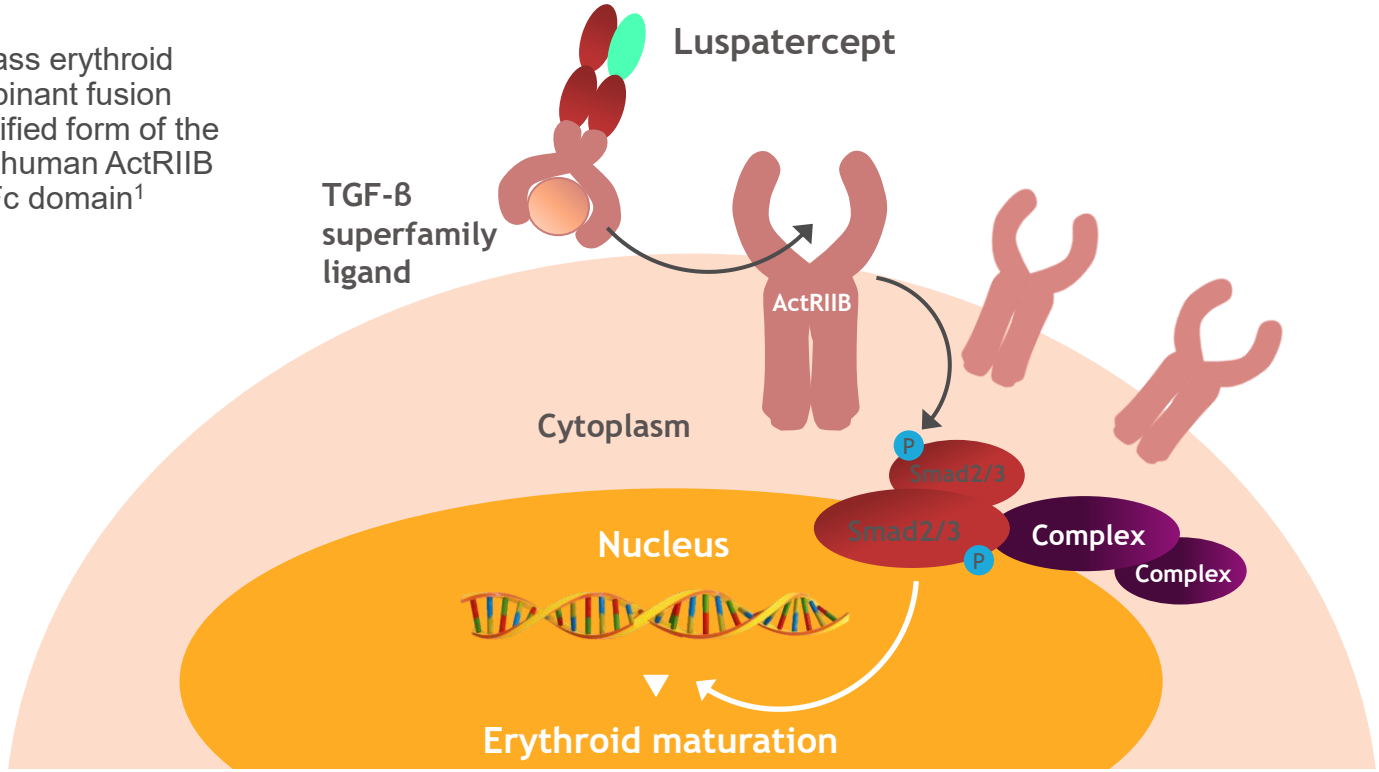
LUSPATERCEPT DECREASES SMAD2/3 SIGNALING

- Luspatercept is a first-in-class erythroid maturation agent: a recombinant fusion protein consisting of a modified form of the extracellular domain of the human ActRIIB linked to the human IgG1 Fc domain[1]

Luspatercept binds to select TGF-β superfamily ligands[2-4]…

… inhibiting ActRIIB activation and decreasing Smad2/3 signaling[2]

Decreasing Smad2/3 signaling enhances erythroid maturation in late-stage erythropoiesis[3]



ActRIIB, activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; P, phosphorylation; Smad, small mothers against decapentaplegic; TGF-β, transforming growth factor β.

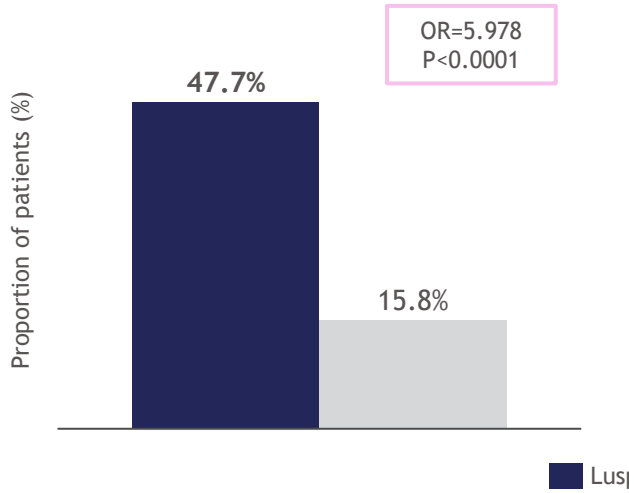
1. Attie KM et al. *Am J Hematol* 2014;89:766–770. 2. Suragani RN et al. *Nat Med* 2014;20:408–414. 3. Suragani RN et al. *Blood* 2014;123:3864–3872. 4. Cappellini MD et al. *Blood* 2018;132:163.

LUSPATERCEPT ENABLES DURABLE TRANSFUSION INDEPENDENCE

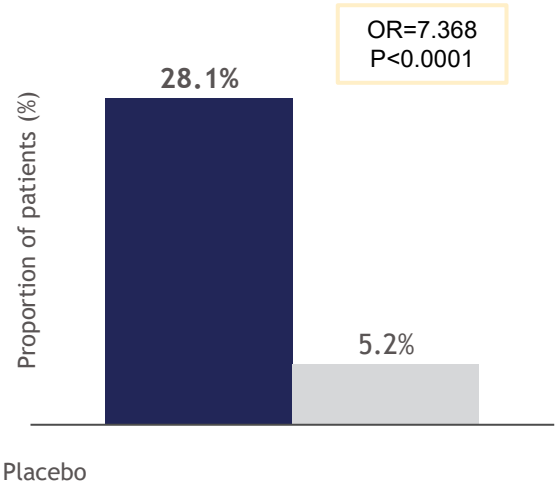
Data cut-off: 01 July 2019

RBC-TI achievement over entire treatment period [1,a]

RBC-TI ≥8 weeks over entire treatment period [1,a]



RBC-TI ≥24 weeks over entire treatment period [2,a]



Luspatercept Placebo

[a] ITT population: luspatercept (n=153) ; placebo (n=76), secondary endpoint

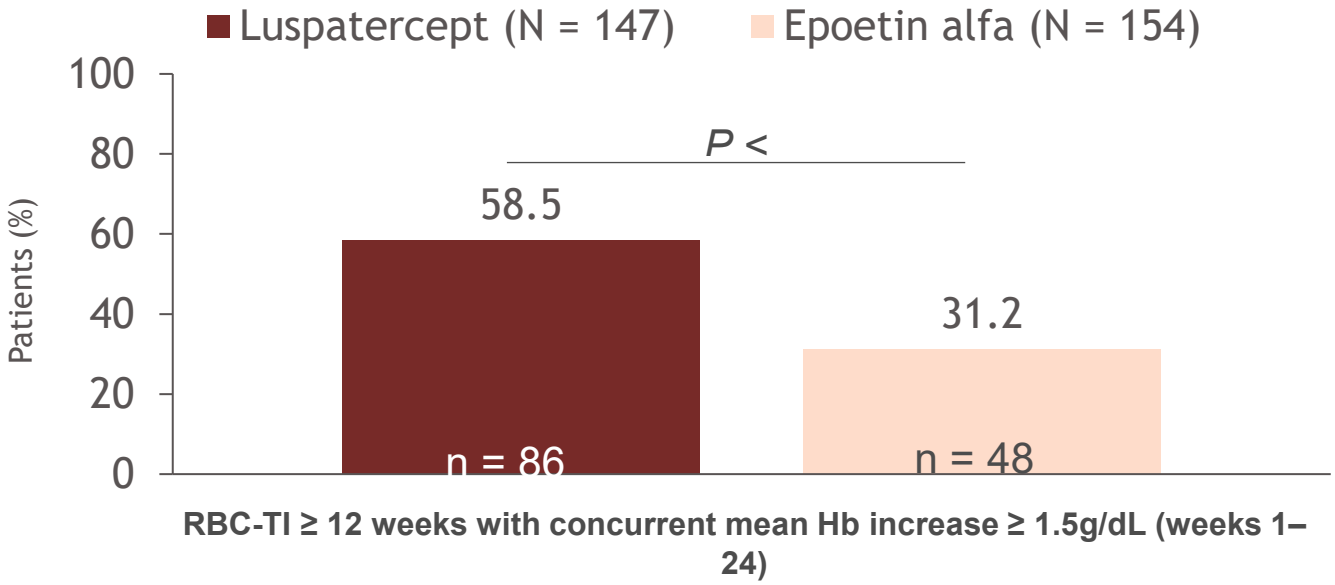
Longer-term analysis of the **MEDALIST study** found **a significantly higher proportion of luspatercept-treated patients achieving RBC-TI** ≥8 weeks compared to placebo

References: 1) Fenaux P, et al. ASH 2019: Oral presentation 2) Celgene internal materials.

ITT: Intention to treat; OR: Odds ratio; RBC-TI: Red blood cell transfusion independent

COMMANDS PRIMARY ENDPOINT: LUSPATERCEPT SUPERIOR TO EPOETIN ALFA

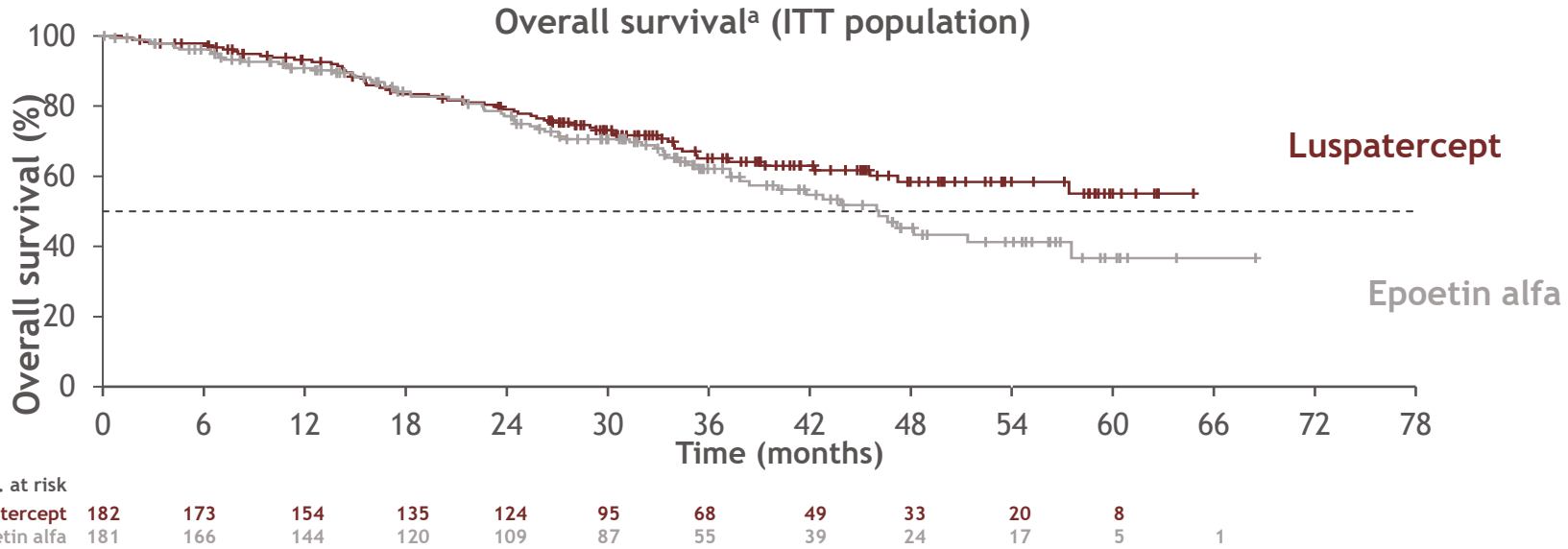
- Of 301 patients included in the efficacy analysis, 86 (58.5%) patients receiving luspatercept and 48 (31.2%) epoetin alfa achieved the primary endpoint



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

Garcia-Manero G, et al. ASCO 2023 [Abstract #7003]

COMMANDS: overall survival with > 2.5 years of follow-up



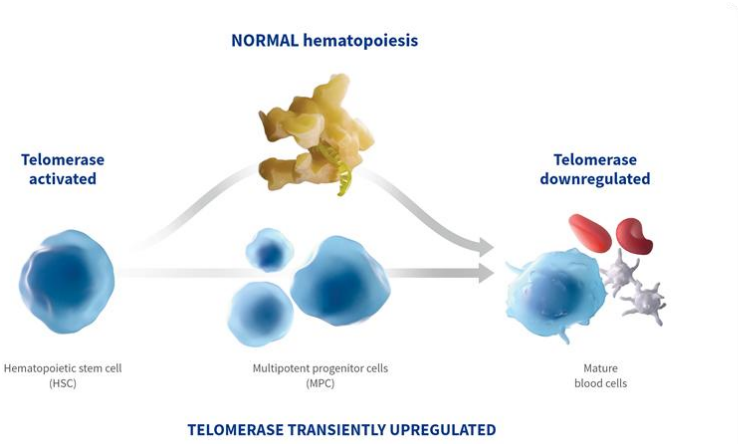
	Luspatercept	Epoetin alfa	HR (95% CI)[b]
Median OS,[c] months	NR	46.0	0.805 (0.565-1.146)
Piecewise analysis Deaths, n/N (%), ≥ 36 months	6/68 (8.8)	15/55 (27.3)	0.330 (0.128-0.853); *P* = 0.0221

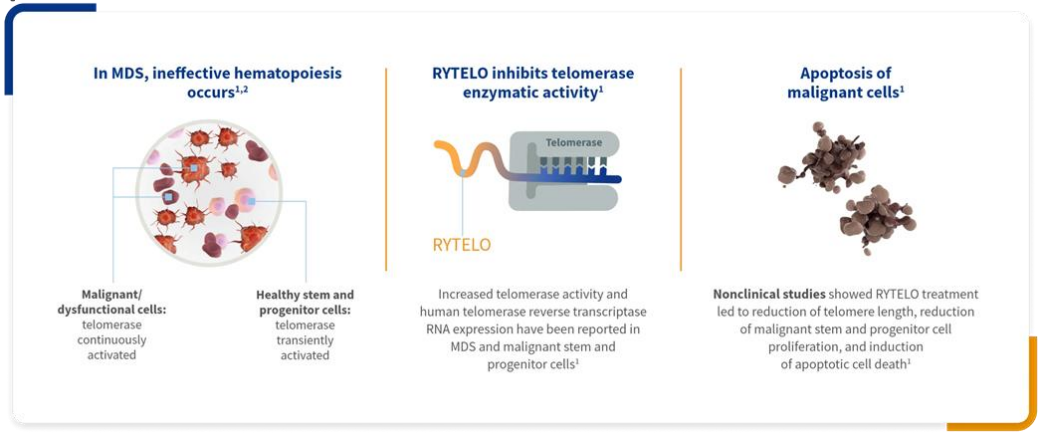
Data cutof
NR, not reached.
[a]Overall survival is defined as the time between randomization and death of any cause. [b]HR (95% CI) is calculated by stratified Cox proportional hazard model; *P* value is from a stratified log-rank test. [c]Median is from an unstratified Kaplan-Meier method.

Guillermo Garcia-Manero, et al, Overall survival and duration of response for transfusion independence in erythropoiesis-stimulating agent-naive patients with very low-, low-, or intermediate-risk myelodysplastic syndromes treated with luspatercept versus epoetin alfa in the COMMANDS trial. ASCO 2025 Abstract number 6512.

IMETELSTAT

- A competitive telomerase inhibitor
- Showed promising results in a phase 2 trial
- In a phase 3 (IMerge), the drug was superior to placebo in ESA-relapsed, ESA-refractory, or ESA-ineligible MDS patients. The response rate was 40% who became transfusion-independent for at least 8 weeks.





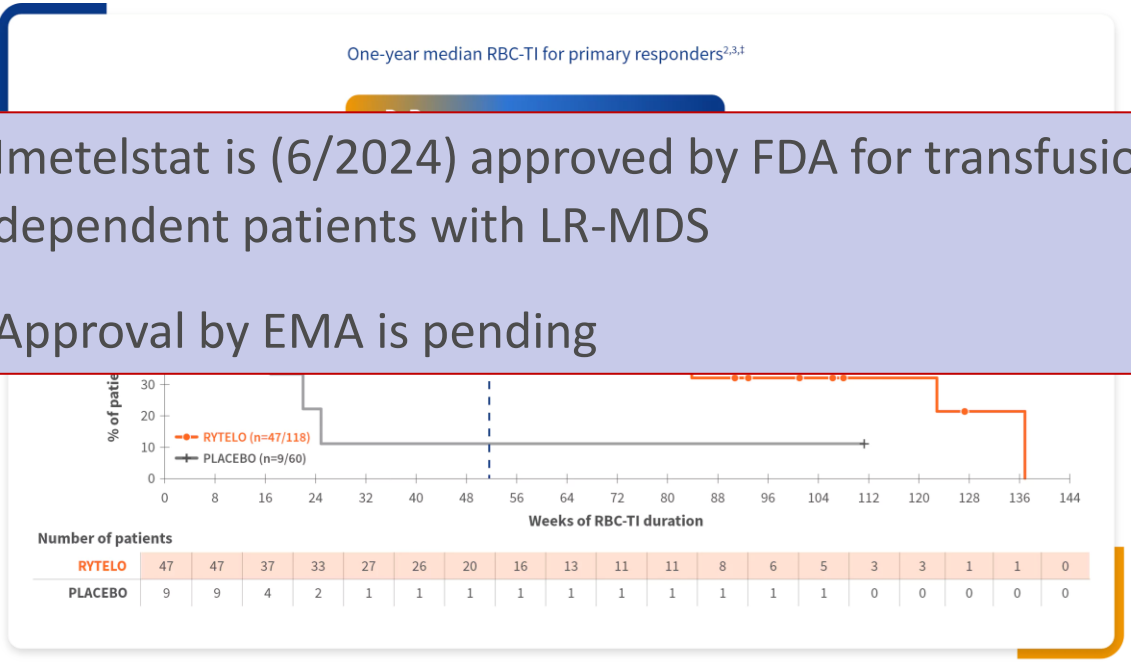
Steensma DP et al. J Clin Oncol. 2021 Jan 1;39(1):48-56; Waksal JA et al. Bl Adv 2023; 7(16): 4302-4314;

Zeidan AM et al. ASCO 2023; Abs # 7004; Platzbecker U et al. Lancet. 2024 Jan 20;403(10423):249-260

The IMerge

Phase 3 clinical trial assessed the safety and efficacy of RYTELO (n=118) vs placebo (n=60) in LR-MDS patients with transfusion-dependent anemia

- Imetelstat is (6/2024) approved by FDA for transfusion-dependent patients with LR-MDS
- Approval by EMA is pending



PRIMARY ENDPOINT:

39.8% of patients treated with RYTELO achieved ≥8-week RBC-TI (95% CI, 30.9-49.3) vs 15% of patients with placebo (95% CI, 7.1-26.6) (*P*<0.001)[1,*]

SECONDARY ENDPOINT:

The median duration of RBC-TI among primary responders was 51.6 weeks vs 13.3 weeks with placebo[2,3,†]

LR-MDS - ANEMIA: NEW AGENTS

- **Luspatercept**
  - Fusion protein, binding TGF-β, reducing SMAD2/3
    - In late erythropoiesis
  - **MEDALIST**: 2nd line
    - Transfusion free: **38%** (vs 13% placebo) ***Fenaux*** *NEJM 2020*

  - **COMMANDS**: 1st line
    - Lus vs ESA: Response **58%** (vs 31%) ***Platzbecker*** *Lancet 2023*
  - A paradigm change ? **Luspatercept first line ?**
- **Imetelstat**
  - Telomerase inhibitor
  - IMerge (Phase 3): 40% (vs 15%) ***Platzbecker*** *Lancet 2023*
  - **Durable**; No prolonged OS ***Santini*** *EHA 2024*

LR-MDS ANEMIA: EXPERIMENTAL (2024)

- **HMA:**
  - Standard like in HR-MDS
  - **Oral Aza**: Quazar (MDS-003), P 3, IT 38%

    Garcia Manero *J Clin Oncol 2021*
- **Imetelstat**
  - Telomerase inhibitor; IMerge (P 3): 40% (vs 15%)

    Platzbecker*, Lancet 2023*
  - Durable; No prolonged OS

    Santini *EHA 2*

- **Ker-050:**
  - Modified activin receptor; P 2 – TI 51%

    Diez-Campleo *ASH 2023*
- **AG-946**
  - Pyruvate kinase activator; Phase 2a/b ?

https://www.pharmaceutical-technology.com/data-insights/ag-946-agios-pharmaceuticals; ***Fattizzo*** *AJH 2024*

Chemotherapy in MDS

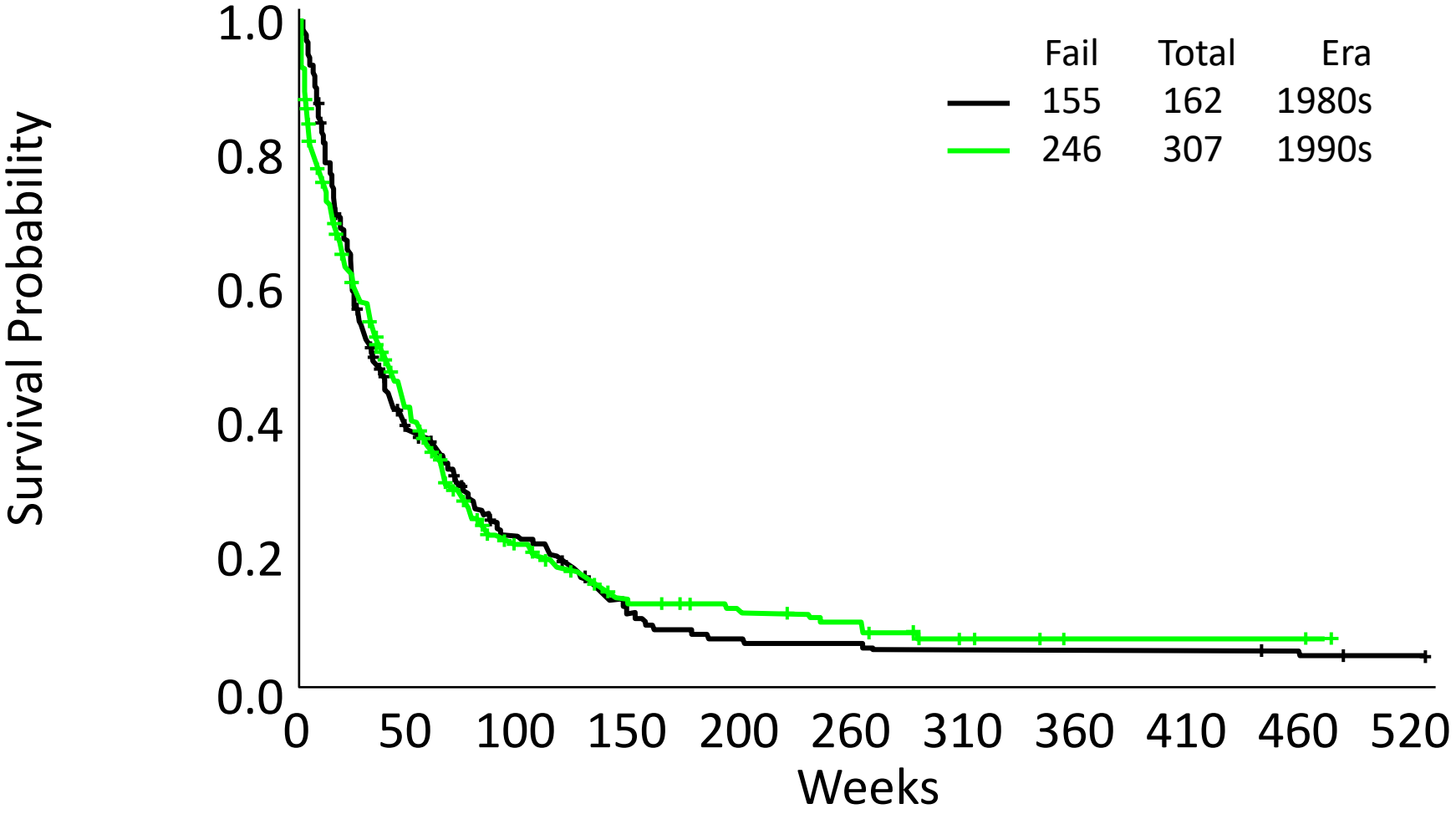
Low-Dose Chemotherapy

- Cytarabine: inhibits DNA synthesis
- Azacitidine & Decitabine: demethylating agents with cytotoxic effects.

High-Dose Chemotherapy

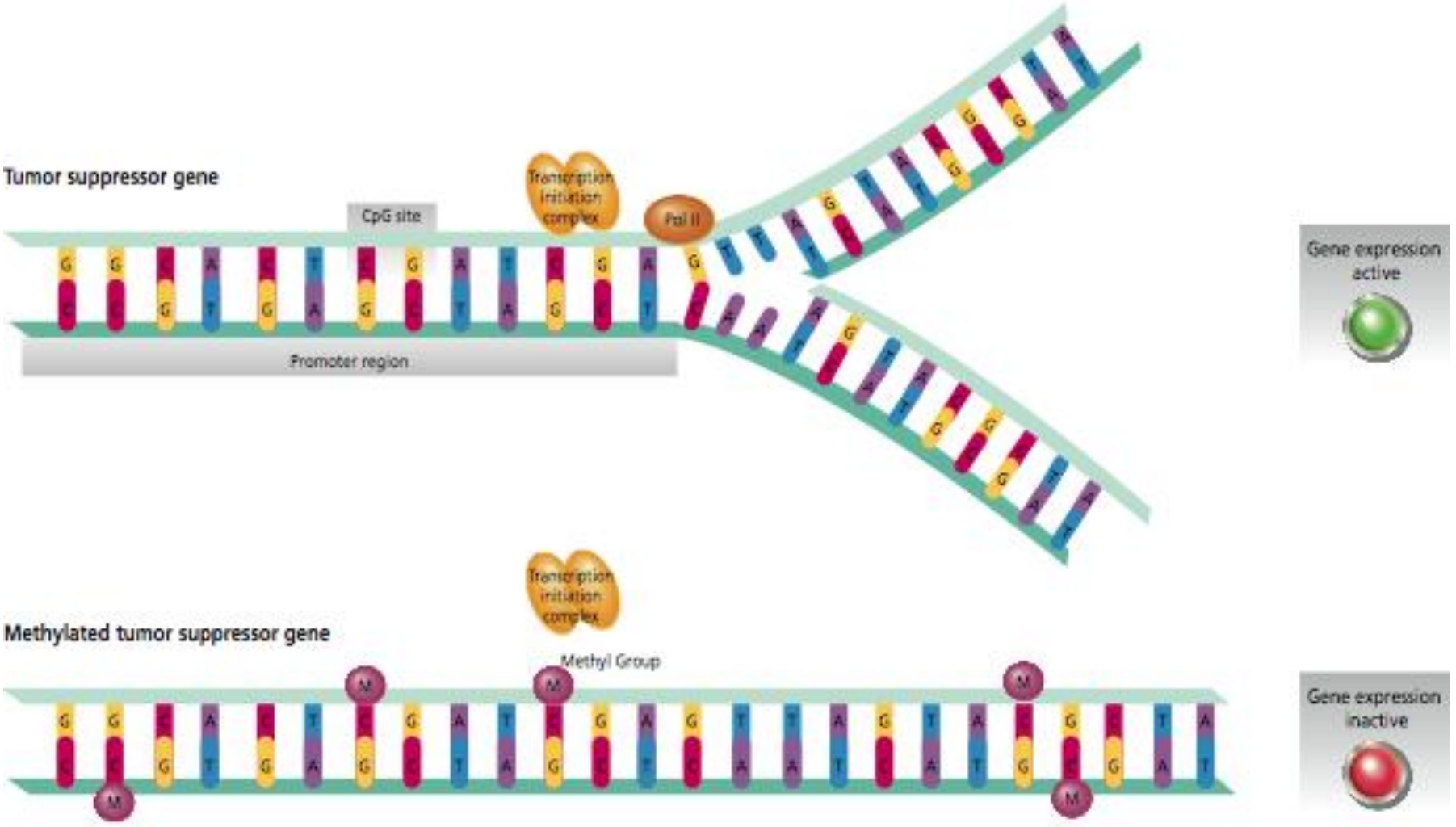
- Cytarabine: inhibits DNA synthesis
- Melphalan: alkylating agents → cell death
- Topotecan: topoisomerase inhibitor → cytotoxic during cell replication

Survival Rates Before (1980s) and After (1990s) the Use of Chemotherapy

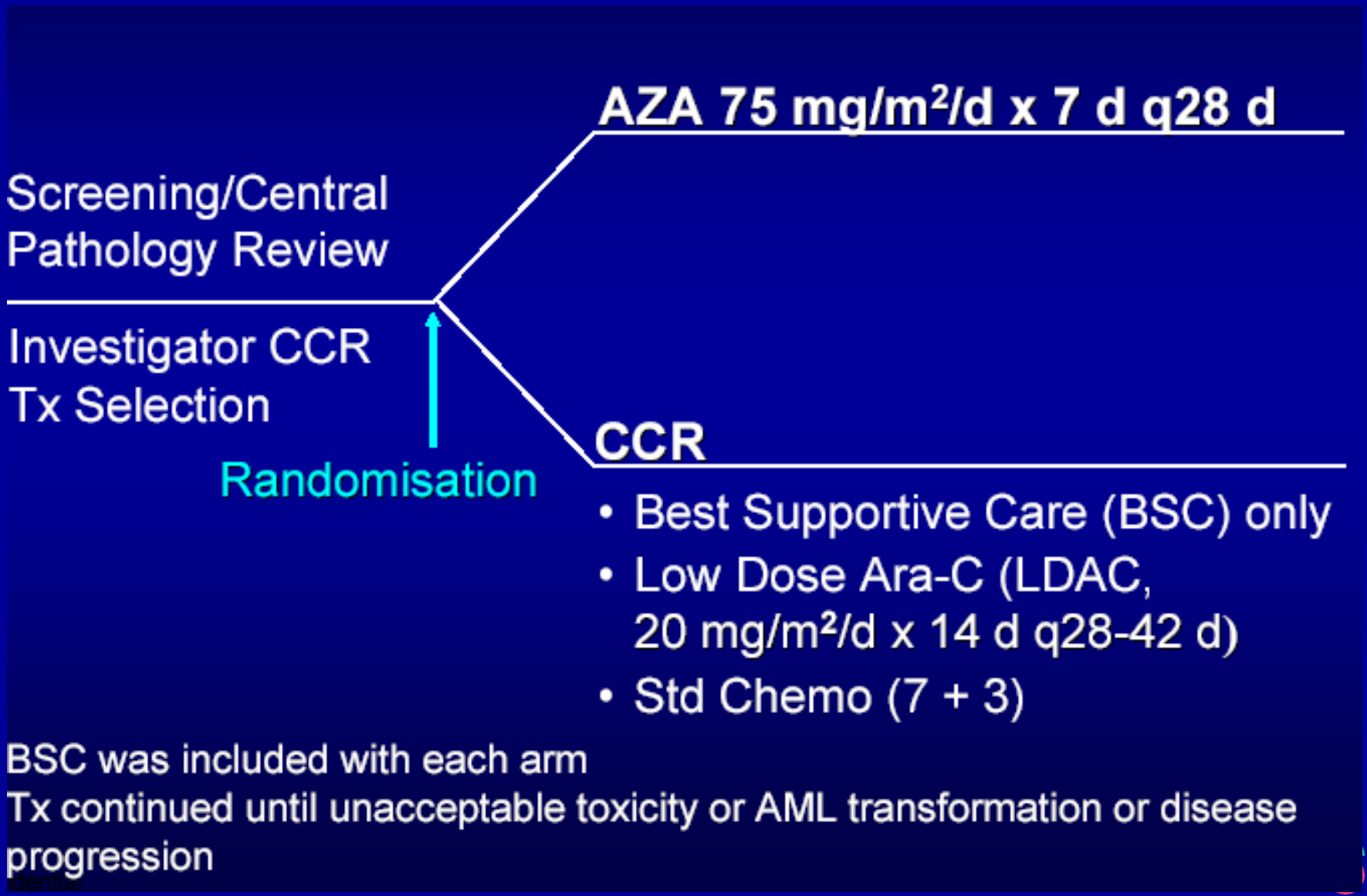


Source: Estey E. MD Anderson Data. Unpublished.

Methylation Inhibits Expression of Genes

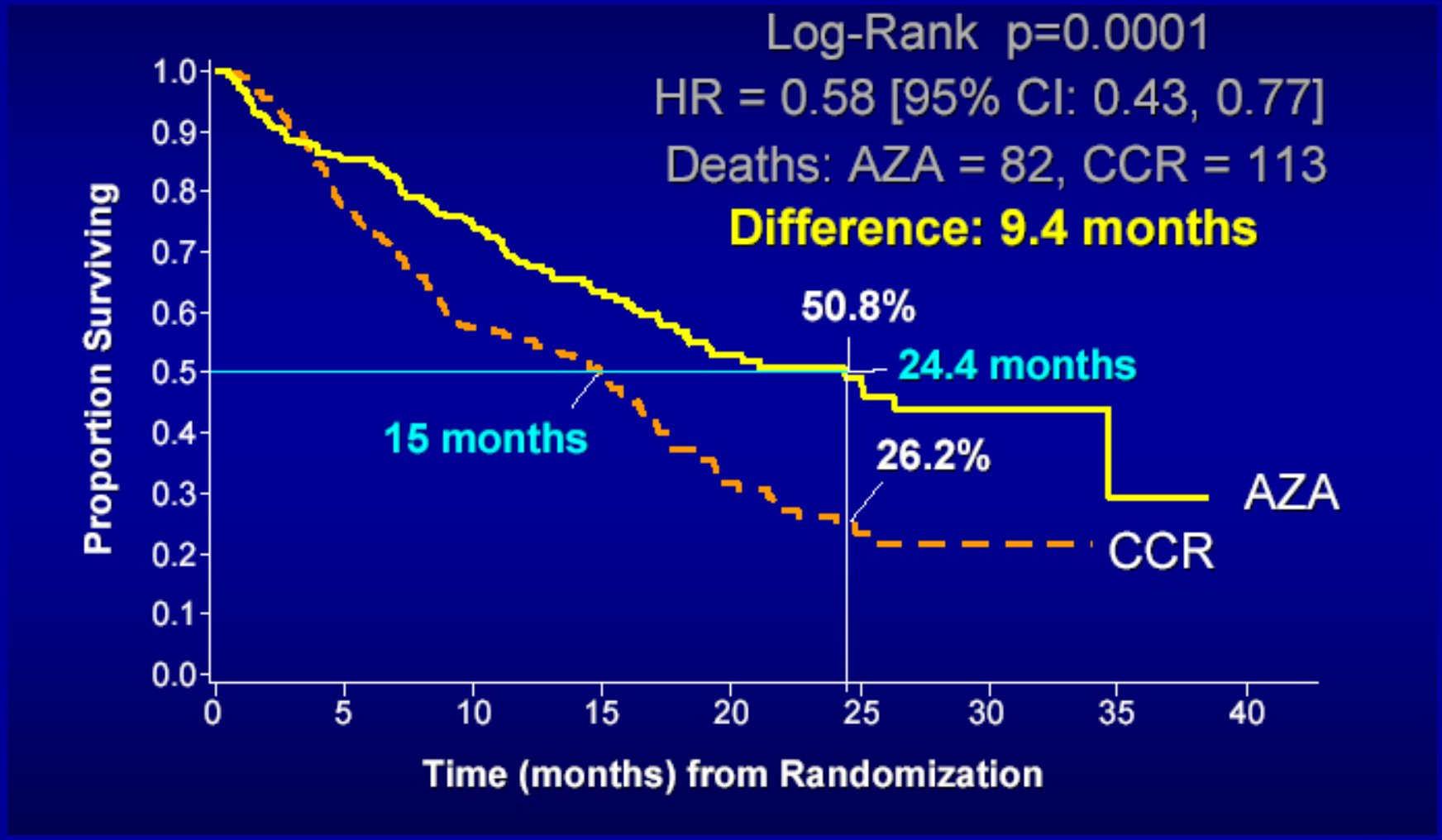


Azacitidine Survival Study



Overall Survival Azacitidine vs CCR

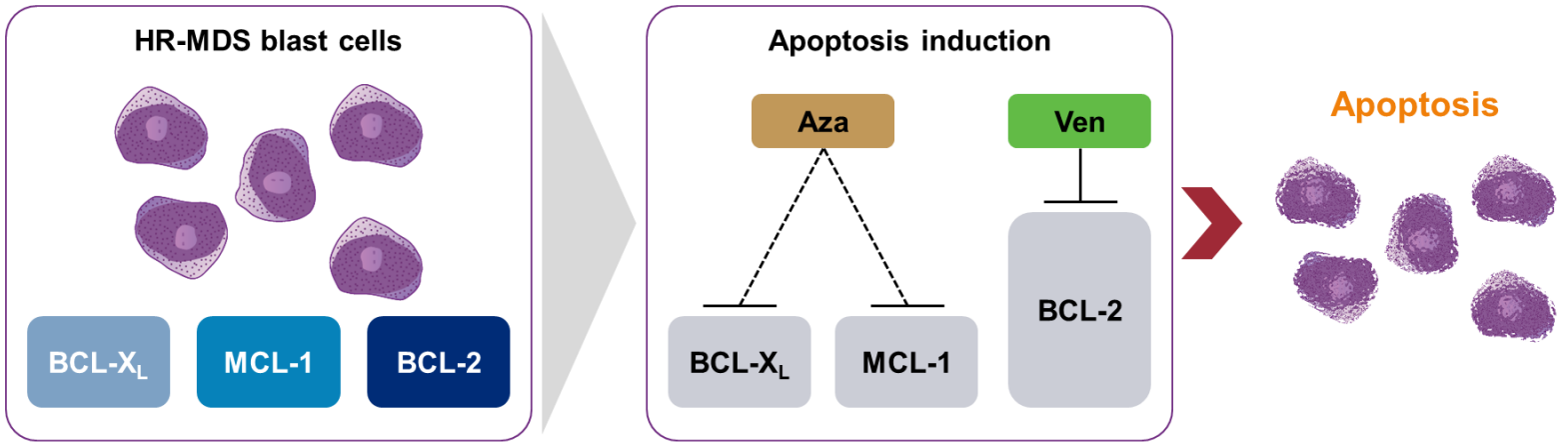
ITT Population



Ven + Aza mechanism of action

– **Venetoclax is a selective, potent, orally bioavailable BCL-2 inhibitor, which has demonstrated synergy with hypomethylating agents in preclinical and clinical studies of myeloid malignancies[1-4]**

Ven + Aza Mechanism of Action



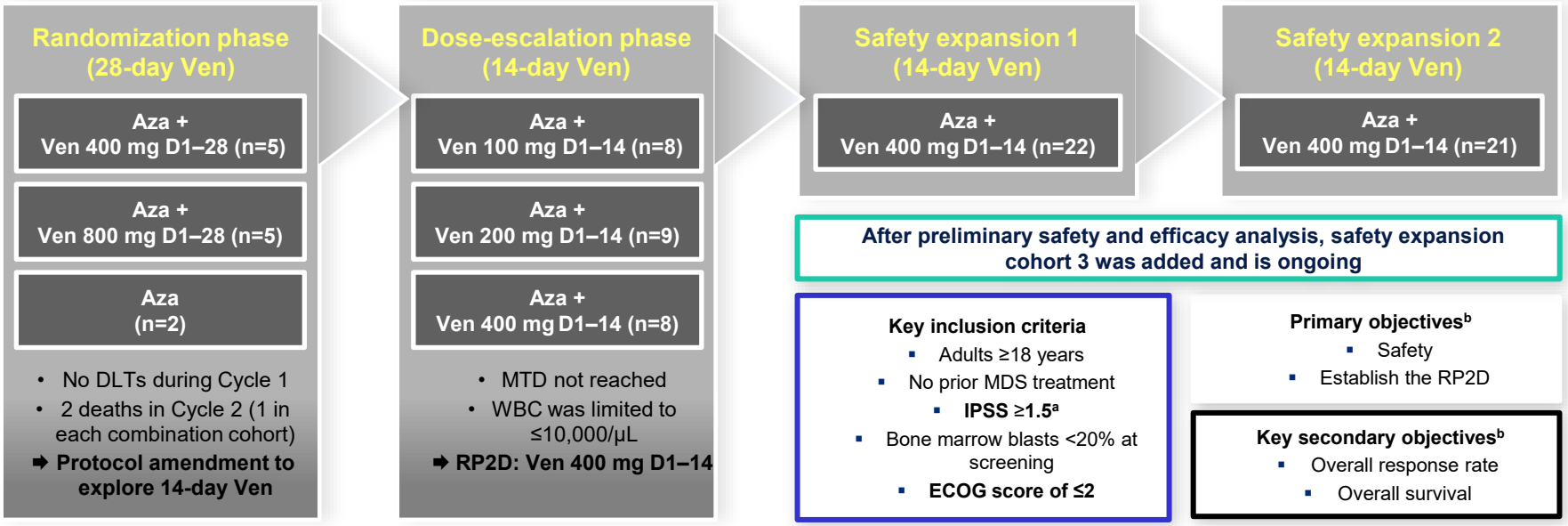
Size of rectangles indicates relative dependency on specific protein for survival
Dotted lines indicate an indirect therapeutic effect on BCL-2 family member dependency

Aza, azacitidine; BCL-2, B-cell lymphoma 2; HR-MDS, higher-risk myelodysplastic syndrome; MCL-1, myeloid cell leukemia 1; Ven, venetoclax.

1. DiNardo CD, et al. *Lancet Oncol.* 2018;19(2):216–28. 2. DiNardo CD, et al. *Am J Hematol.* 2018;93(3):401–7. 3. Jilg S, et al. *Exp Hematol Oncol.* 2019;8:9. 4. Jin S, et al. *Clin Cancer Res.* 2020;26(13):3371–83.

This ongoing Phase 1b study evaluates Ven + Aza for the treatment of patients with treatment-naïve HR-MDS

- We report efficacy among mutationally defined subgroups as well as depth of molecular response at the RP2D of Ven 400 mg D1-14 + Aza
- Treatment cohorts (28-day cycles); Aza 75 mg/m^2 D1–7



NCT02942290

[a]Study protocol has been amended to allow patients with higher-risk IPSS-Revised (intermediate, high, and very high) results and patients planning to undergo allo-HSCT; [b]Safety and efficacy assessments were carried out on all patients who received ≥1 dose of study drug; efficacy endpoints were evaluated according to the 2006 International Working Group response criteria.

allo-HSCT, allogeneic hematopoietic stem cell transplantation; Aza, azacitidine; D, Day; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; HR-MDS, higher-risk myelodysplastic syndrome; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; Ven, venetoclax; WBC, white blood cell.

Baseline Characteristics of 78 patients enrolled

- 51 patients received the RP2D Ven 400 mg D1–14; 9 received Ven 200 mg D1-14, 8 received Ven 100 mg D1-14, 5 received Ven 800 mg D1-28, and 5 received Ven 400 mg D1-28
- At the December 15, 2020 data cutoff, median follow-up time was 23 months (range 0.1–44.2)

Characteristic	N=78
Male, n (%)	56 (72)
Median age, years (range)	70 (26–87)
ECOG performance score, n (%)	
0	33 (42)
1	38 (49)
2	7 (9)
Bone marrow blasts, n (%)	
≤5%	7 (9)
>5% to ≤10%	21 (27)
>10% to ≤20%	49 (63)
>20%	1 (1)
IPSS karyotype risk, n (%)	
Good	31 (40)
Intermediate	16 (20)
Poor	31 (40)

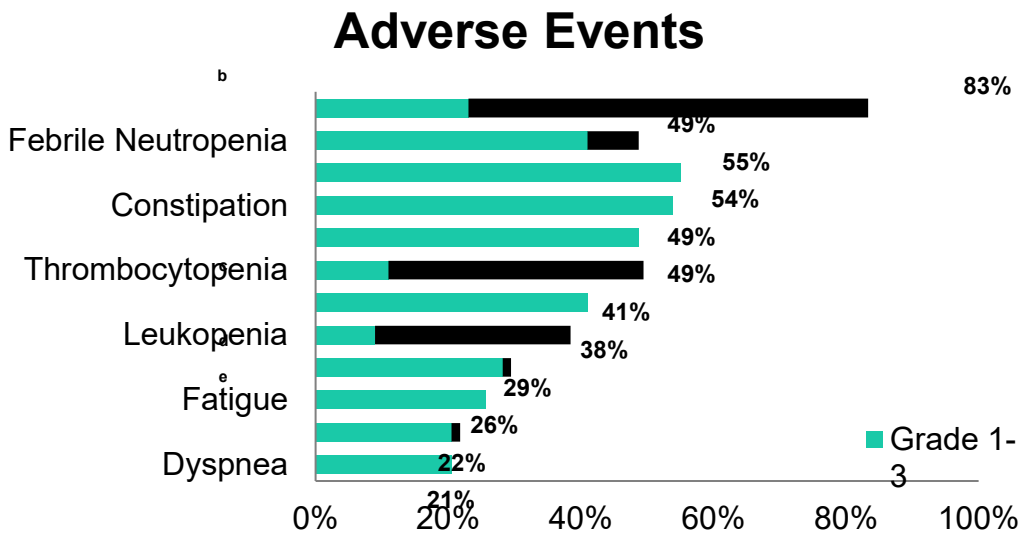
Characteristic, n (%)	N=78	
IPSS risk classification		
Intermediate-2	57 (73)	
High	21 (27)	
IPSS-R risk classification		
Intermediate	14 (18)	
High	16 (20)	
Very high	48 (62)	
Baseline cytopenias	**Grade 3**	**Grade 4**
Neutropenia	24 (31)	22 (28)
Thrombocytopenia	20 (26)	6 (8)
Leukopenia	30 (38)	3 (4)
Anemia	10 (13)	0

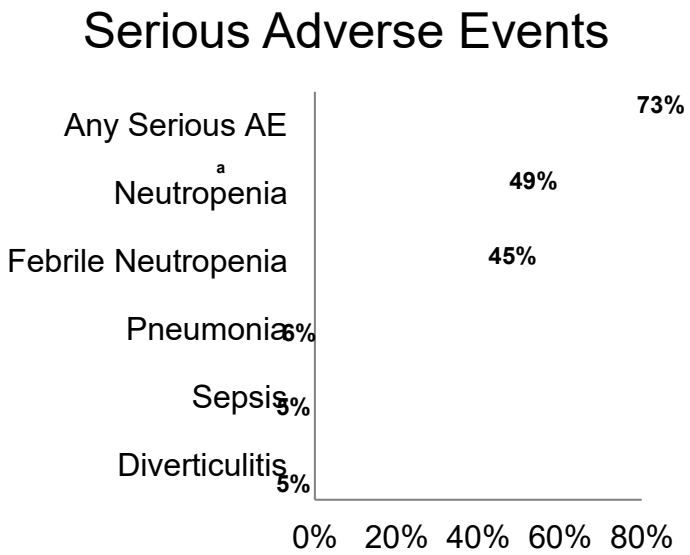
Data cutoff: Dec 15, 2020

Aza, azacitidine; ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System-Revised; RP2D, recommended phase 2 dose; Ven, venetoclax.

– **Median cycles of Aza received: 4 (range 1-27); median cycles of Ven received: 4 (range 1-27)**
– **30-day mortality after first dose was 1%; 7 patients (9%) experienced an AE leading to death[a]**

Summary of Adverse Events in All Patients (N=78)[1]



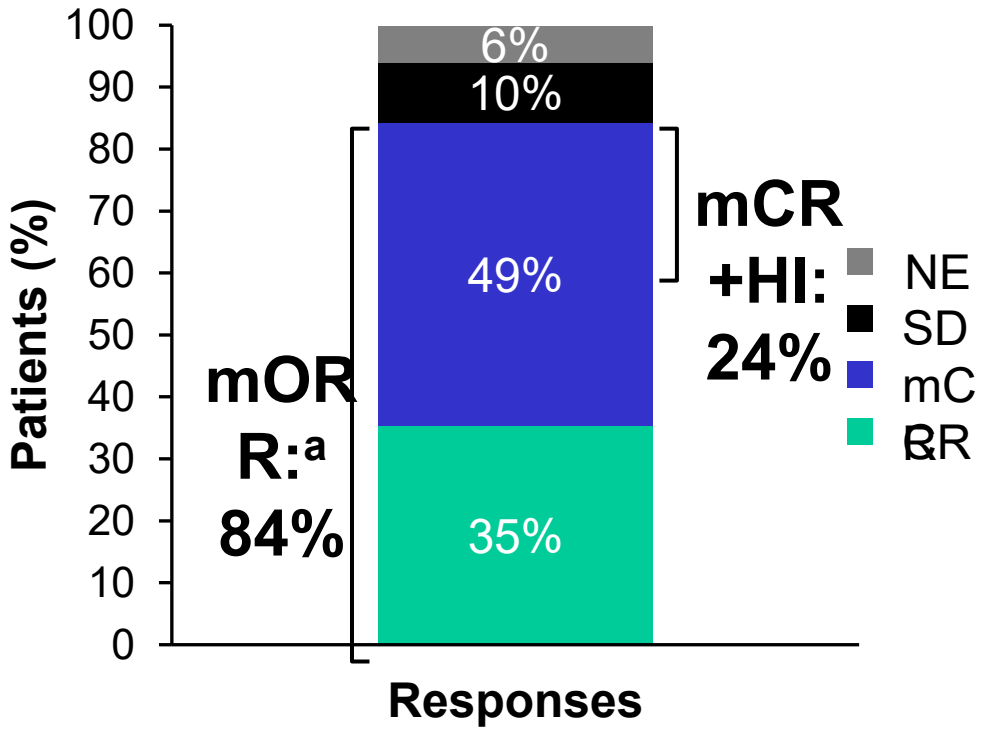


Data cutoff: Dec 15, 2020

1. Wei AH, et al. EHA 2021. Abstract EP917.

AEs reported in ≥20% of patients for any grade. SAEs reported in ≥5% of patients. [a]Grade 5 AEs were general disorders and administration site conditions (n=2), infections (n=4), and respiratory failure (n=1); [b]Includes neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic sepsis, and neutropenic infection; [c]Includes platelet count decreased; [d]Includes white blood cell count decreased; [e]Includes hemoglobin count decreased. AE, adverse event; Aza, azacitidine; HR-MDS, higher-risk myelodysplastic syndrome; Ven, venetoclax.

84% of patients who received RP2D Ven + Aza (N=51) responded to treatment

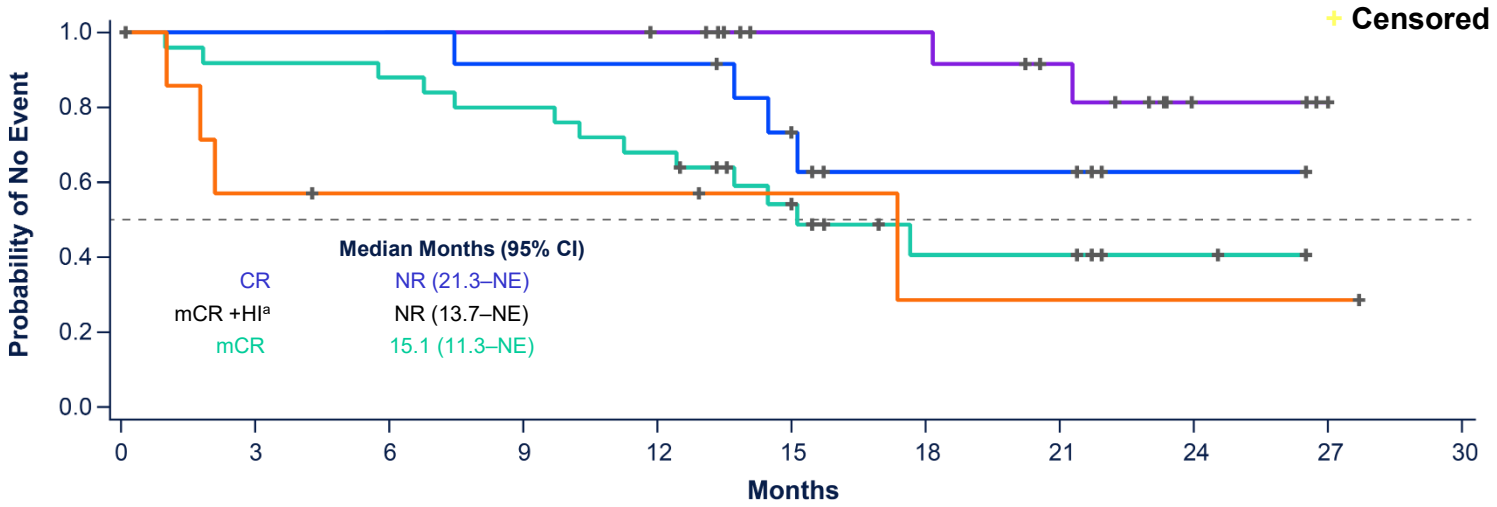


- **Median time to response: 0.9 months (95% CI, 0.7–5.8)**
- **Median duration of response: 12.4 months (95% CI, 9.9–NR)**

Data cutoff: Dec 15, 2020

[a]mORR=CR+mCR+PR; PR, n=0; response rates based on IWG 2006 response criteria.
Aza, azacitidine; CR, complete remission; HI, hematologic improvement; mCR, marrow complete remission; mo, month; mORR, modified overall response rate; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial remission; RP2D, recommended phase 2 dose; SD, stable disease; Ven, venetoclax.

OS by best response among patients who received RP2D Ven + Aza (N=51)

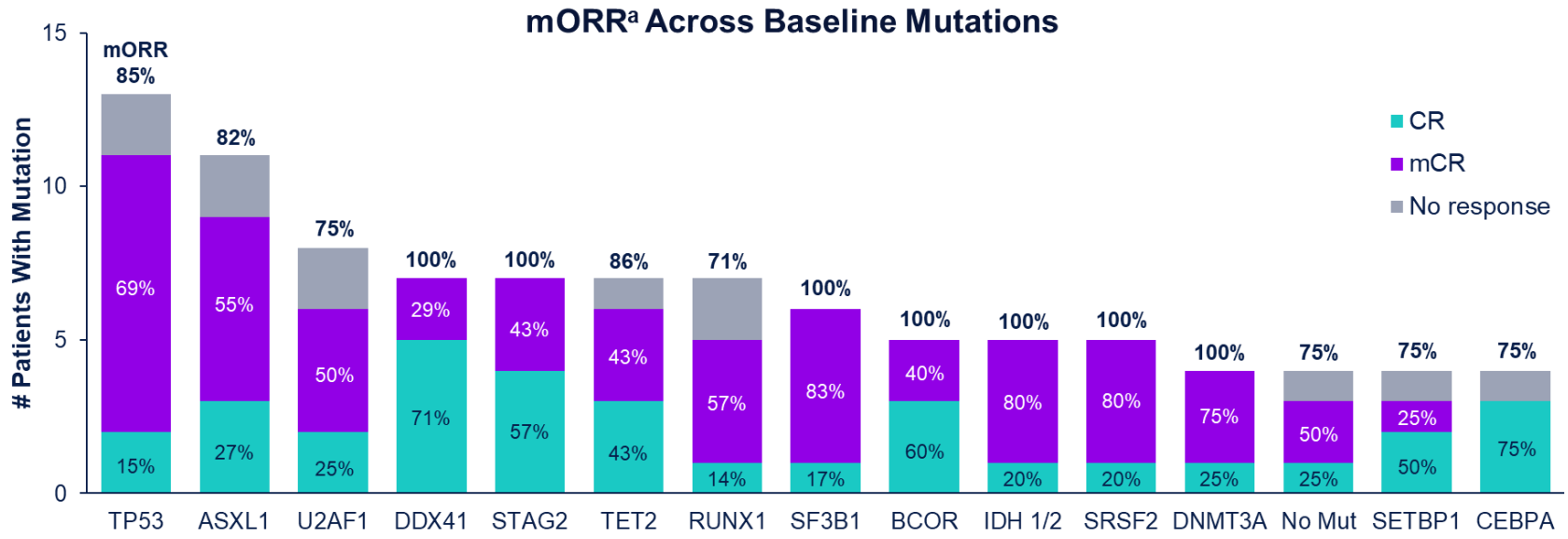


Number at Risk

CR	18	18	18	18	17	12	12	9	3	1	0
mCR +HI[a]	12	12	12	11	11	8	4	4	1	0	
mCR	25	23	22	20	17	11	5	5	2	0	

Data cutoff: Dec 15, 2020

[a]Subset of patients with mCR. Aza, azacitidine; CR, complete remission; HI, hematologic improvement; mCR, marrow complete remission; OS, overall survival; RP2D, recommended phase 2 dose; Ven, venetoclax.



- 7 of 13 patients with *TP53* mutations had multi-hit/bi-allelic *TP53* mutations
- Responses of those with multi-hit/bi-allelic *TP53* were similar to responses in patients with any *TP53* mutation:
  - CR: 28.6% (2/7); mORR: 71.4% (5/7)

Data cutoff: Dec 15, 2020

[a]mORR=CR+mCR+PR; Baseline mutational profiling was available for 49/51 patients who received the RP2D of Ven + Aza. Mutations assessed from BMA at screening using Archer® VariantPlex® Myeloid, or peripheral blood at screening using Illumina TruSight® Myeloid Panel. Response rates based on IWG 2006 response criteria. Analysis of patients receiving RP2D.

Aza, azacitidine; BMA, bone marrow aspirate; CR, complete remission; HR-MDS, higher-risk myelodysplastic syndrome; mCR, marrow complete remission, mORR, modified overall response rate; RP2D, recommended phase 2 dose; Ven, venetoclax.

Conclusions

- Ven + Aza was associated with an acceptable safety profile for patients with HR-MDS
- Patients with HR-MDS treated with Ven (400 mg D1–14) + Aza (75 mg/m^2) had rapid, durable responses and high remission rates
- Patients across key mutational profiles, including those harboring poor prognostic mutations, achieved meaningful clinical and molecular responses

- Aza, azacitidine; D, days; HR-MDS, higher-risk myelodysplastic syndrome; Ven, venetoclax.

Venetoclax and Azacitidine in the Treatment of Patients with Relapsed/Refractory Myelodysplastic Syndrome

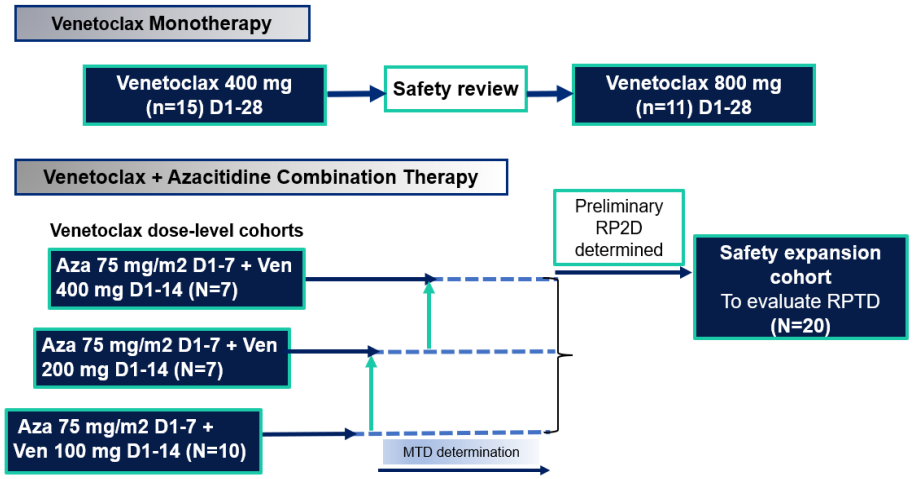
Amer M Zeidan[1], Uma Borate[2], Daniel A Pollyea[3], Andrew M Brunner[4], Fernando Roncolato[5], Jacqueline S Garcia[6], Robin J Filshie[7], Olatoyosi Odenike[8], Anne-Marie Watson[9], Ashish Bajel[10], Kiran Naqvi[11], Jiuhong Zha[12], Leah Hogdal[12], Ying Zhou[12], David Hoffman[12], Steve Kye[12], Guillermo Garcia-Manero[13]

[1] Section of Hematology, Department of Internal Medicine, Yale University and Yale Cancer Center, New Haven, CT, USA; [2] Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [3] Department of Hematology, University of Colorado, Aurora, CO, USA; [4] Center for Leukemia, Massachusetts General Hospital, Boston, MA, USA; [5] Department of Hematology, University of New South Wales, Sydney, Australia; [6] Department of Medicine, Dana-Farber Cancer Institute, Boston, MA, USA; [7] Department of Hematology, St Vincent's Hospital, Melbourne, AUS; [8] University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL, USA; [9] Department of Haematology, Liverpool Hospital, Liverpool, AUS; [10] Department of Clinical Haematology, Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Melbourne, AUS; [11]Genentech, South San Francisco, CA, USA; [12] AbbVie Inc, North Chicago, IL, USA; [13]Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

American Society for Hematology 2021, December 11-14, Atlanta, GA, USA

Ven is an orally available small molecule selective BCL-2 inhibitor evaluated for the treatment of R/R MDS

Study design
NCT02966782



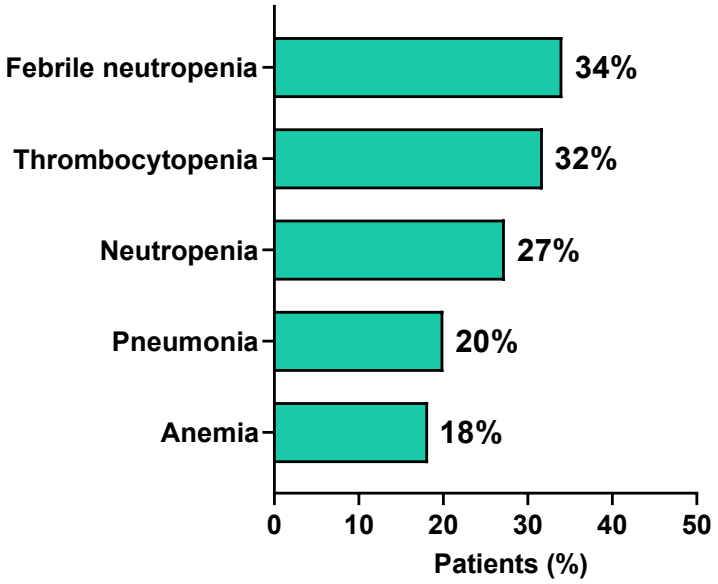
Key endpoints
Safety, objective response rate, hematological improvement and transfusion independence, overall survival, molecular mutation, and patient-reported outcomes

- **Ongoing Phase 1b study in patients with R/R MDS treated with escalating doses Ven+Aza**
- **Responses were assessed per modified International Working Group 2006 criteria[1]**
- **Mutation status was determined in bone marrow mononuclear cells with Archer's VariantPlex Myeloid/Core Myeloid Next-generation sequencing panel and in the peripheral blood with Illumina's TruSight Myeloid panel. The limit of detection for these panels was 1-5%**
- **Baseline %BCL-2+/%BCL-xL blast ratio was determined by flow cytometry[2]**
- **The RPTD of Ven is 400 mg for 14 days for the treatment of R/R MDS**

[1]Cheson BD, et al. Blood. 2006;108(2):419-425.; [2]Konopleva et al., Cancer Discovery, 2016

Aza, azacitidine; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HI, hematological improvement; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; RPTD, recommended phase two dose; R/R MDS, relapsed/refractory myelodysplastic syndrome; TI, transfusion independence; Ven, venetoclax; R/R MDS status was determined by the investigator

Treatment-emergent adverse events among patients treated with Ven+Aza



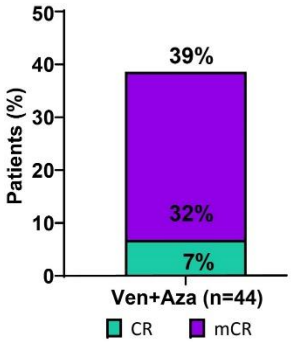
- Patients received a median of 4 cycles (range 1 — 32) of venetoclax and 4 cycles (range 1 — 31) of azacitidine
- All 44 patients (100%) had at least one treatment-emergent adverse event (TEAE) of any grade and 42 (96%) had at least one grade ≥3 TEAE
- Predominant grade ≥ 3 AEs were hematological AEs and infections
- Grade ≥ 3 TEAE related to Ven was reported in 30 (68%) patients
- SAE related to Ven was reported in 10 (23%) patients
- No event of tumor lysis syndrome was reported without ramp up

[a]TEAEs Grade ≥3 with >15% occurrence have been reported; TEAE, treatment-emergent adverse event; SAE, serious adverse event;

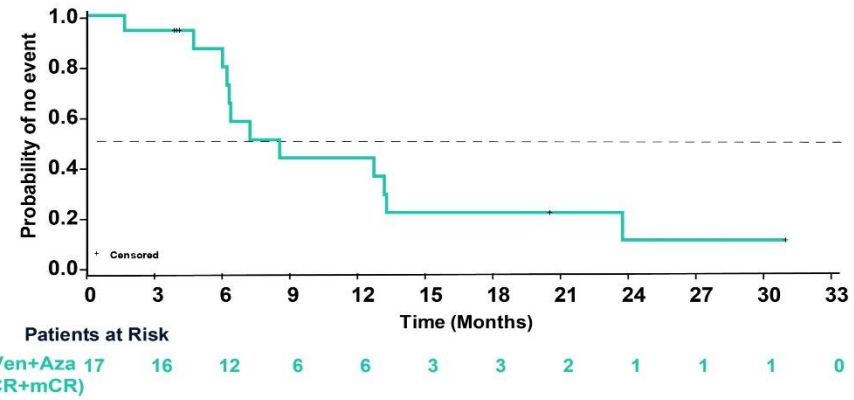
Treatment-emergent adverse events grade≥3[a]

Patients treated with Ven+Aza achieved early and durable responses

CR+mCR



Duration of CR+mCR



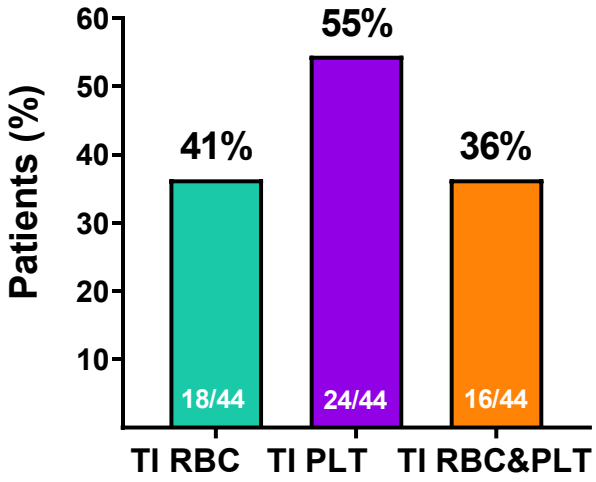
DoR	# of events	12-month, % (95% CI)	24-month, % (95% CI)	Median DoR, months (95% CI)
Ven+Aza (CR+ mCR)	12	43.4 (18.1 – 66.6)	10.9 (0.8 – 35.8)	8.6 (6.0 – 13.3)

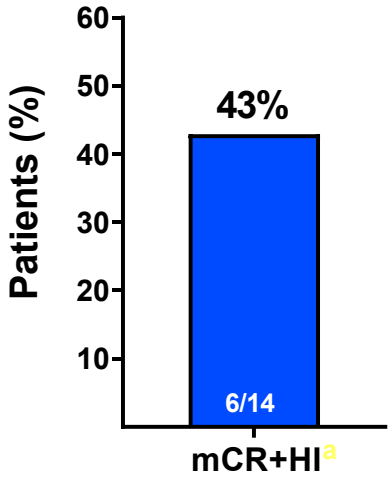
- The median duration of follow up was 21.2 months (range 0.4 – 37.5[a])
- The median DoR for CR+mCR was 8.6 months (95% CI 6.0 – 13.3)
- Median time to first response of CR or mCR was 1.2 months (range 0.7 – 6.3)
- Stable disease was observed in 18 (40.9%) patients and progressive disease in 2 (4.5%) patients [b]

Bone marrow aspirates for response assessments were collected at screening, day 22 of cycle 1 and 2, day 28 at end of cycles 2, 4, 6, and every 3 cycles thereafter

DoR, duration of response; CR, complete remission; mCR, marrow CR; [a]The patient with the longest time on study was censored and not an event; [b]Seven (15.9%) patients were not evaluable for response

Patients treated with Ven+Aza achieved transfusion independence and hematological improvement





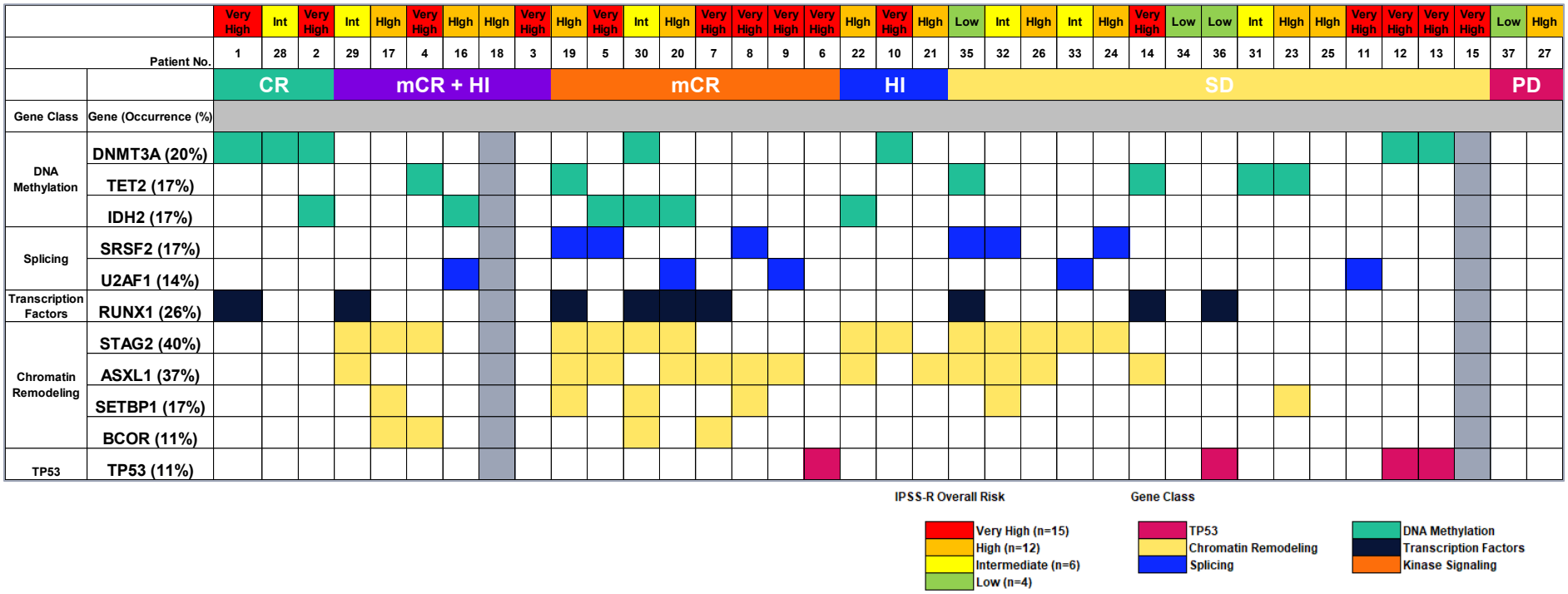
- Post-baseline TI (RBC or PLT) was achieved by 10/32 (31%) patients who were transfusion dependent at baseline
- Median time to next treatment[b] was 5.7 months (95% CI 4.8 – 8.8)
- 9 (21%) patients transformed to AML
- 9 (21%) patients received post-study transplant of which 3 (7%) had bone marrow transplant and 6 (14%) had peripheral blood stem cell transplant

AML, acute myeloid leukemia; HI, hematological independence; mCR, marrow complete remission; PLT, platelet; RBC, red blood cell; TI, transfusion independence; The post-baseline TI was defined as a period of at least 56 days with no transfusion during the evaluation period. The evaluation period for transfusion independence is from the date of the first dose of the study drug to the last dose of the study drug + 30 days or one day before the date of progressive disease from disease response (IWG 2006, Cheson MDS), death or the initiation of post-treatment therapy whichever is earliest;

[a] Patients with mCR who achieved HI;

[b] Time to next treatment was defined as the number of months from the date of the first dose of study drug to the start of new non-protocol specified anti-cancer therapy (Post study treatment systemic cancer therapies or post study transplant) or death of any cause

Responses were observed in most analyzed mutational sub-groups

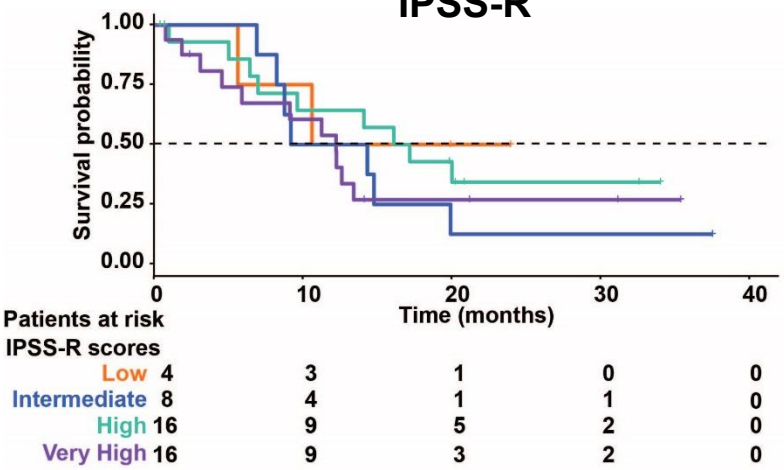


Baseline mutation status was evaluated in 41/44 patients; co-mutations were included in the categorization; CR, complete remission, IPSS-R, International Prognostic Scoring System-Revised ; mCR, marrow complete remission; HI, hematological improvement; PD, progressive disease; SD, stable disease

Note: interpretation of data is limited by the small sample size of each mutant subgroup

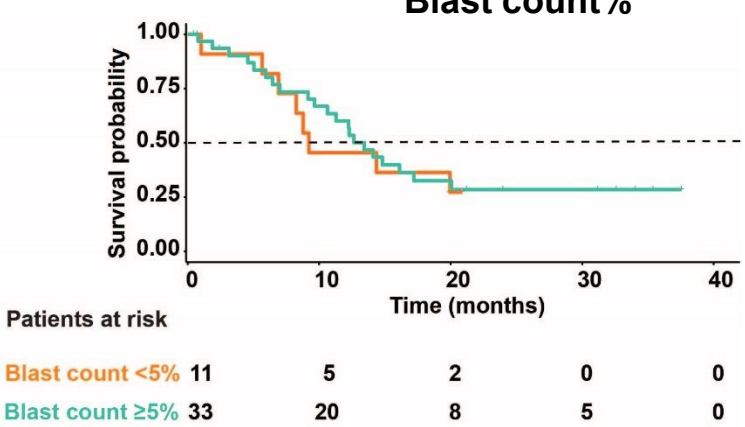
Overall survival was independent of baseline IPSS-R and blast count percent

IPSS-R



IPSS-R	Median OS, months
Low	10.6
Intermediate	11.8
High	16.7
Very high	12.2

Blast count%



Blast count %	Median OS, months
Blast count <5%	9.2
Blast count ≥5%	13.4

IPSS-R, International Prognostic Scoring System-Revised; OS, overall survival; NR, not reached
Note: interpretation of data is limited by the small sample size of each mutant subgroup

Patient-reported outcomes with Ven+Aza treatment

Patient-reported Outcomes (PROs) - EORTC-QLQ-C30

Data collection

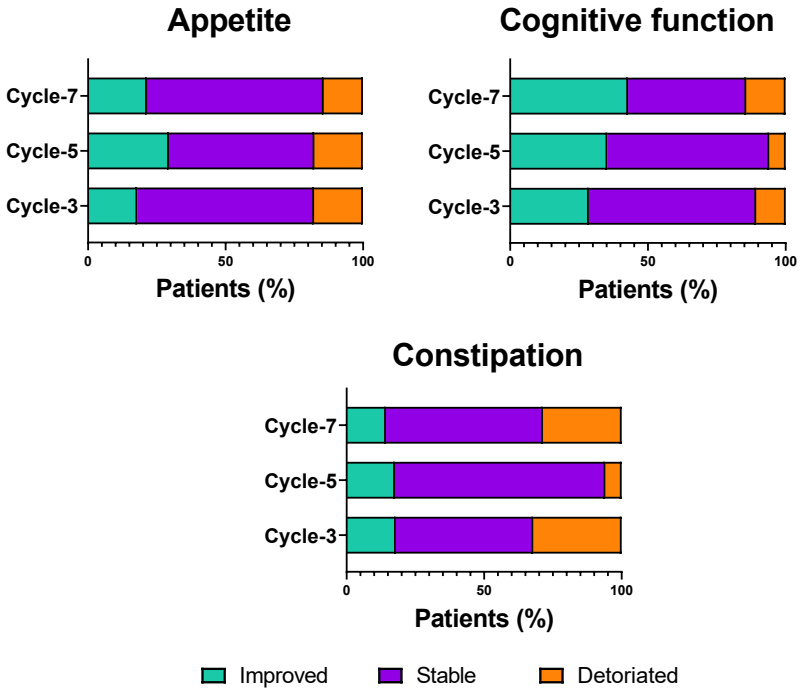
- PRO data was collected at baseline and then on Day 1 of every other treatment cycle through cycle 15

Data analysis

- Proportions of patients whose change in scores indicated meaningful improvement, deterioration, or were stable, were analyzed by cycle
- Differences in proportions were analyzed using the chi-square test
- Due to small sample sizes, data reported here are restricted to the first 3 post-baseline cycles (cycles 3, 5, and 7)

Interpretation of scores

- A threshold of 5 points was used, based upon the lower limit of meaningful change in scores[1]
- A change smaller than 5 points indicated no significant change, and an increase of at least 5 points indicates improvement (better) functioning; a decrease of at least 5 points indicates deterioration (worsening) in symptoms. Stable patients were defined as those with score changes of less than 5 in either direction



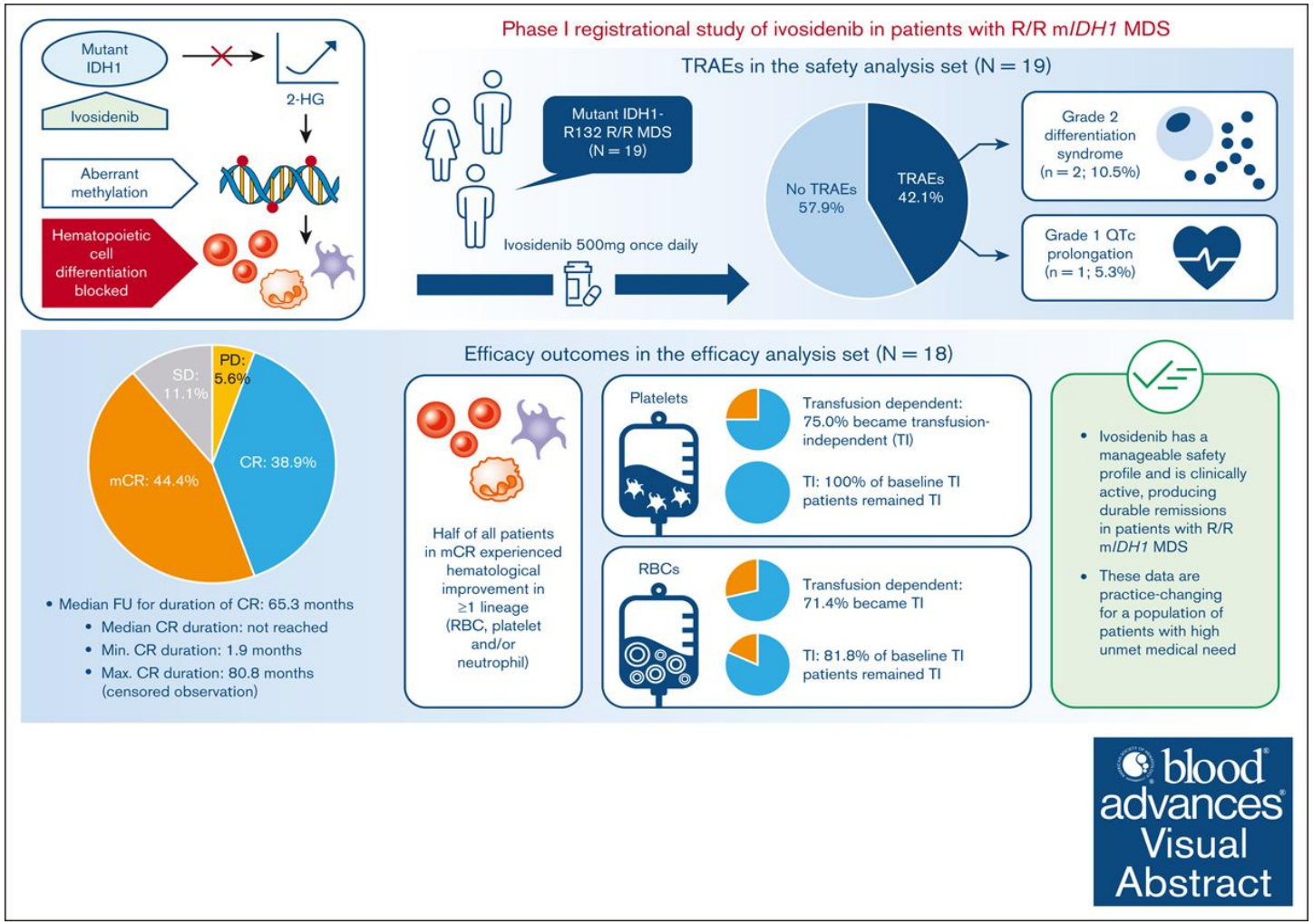
- Clinically meaningful differences in the proportion of patients with improved, stable, and detoriated scores were observed for appetite, cognitive function, and constipation

[1]Cocks et al.; 2012

Phase 3 randomized, controlled VERONA trial, a comparison of oral venetoclax plus azacitidine with placebo plus azacitidine in patients who have newly diagnosed, higher-risk MDS.

The trial has **failed** to meet its primary end point for OS outcomes, having produced a hazard ratio of 0.908 (stratified log-rank, *P*=0.3772).

Final phase 1 results of ivosidenib for patients with mutant *IDH1* relapsed/refractory myelodysplastic syndrome



Phase II study of the IDH2-inhibitor enasidenib in patients with high-risk IDH2-mutated MDS

	RESPONSE EVALUABLE (N = 46)	ARM A (UNTREATED) ENA+AZA (N = 25)	ARM B (HMA-FAILURE) ENA (N = 21)
Overall response rate (ORR), n (%)	(68) 30	(84) 21	(43) 9
Complete remission (CR)	(24) 11	(24) 6	(24) 5
Partial remission (PR)	(7) 3	(8) 2	(5) 1
Marrow CR (mCR)	(26) 12	(44) 11	(5) 1
Hematological improvement (HI) only	(9) 4	(8) 2	(10) 2
No response (NR), n (%)	(35) 16	(16) 4	(57) 12
Stable disease (SD)	(30) 14	(16) 4	(48) 10
Progressive disease (PD)	(4) 2	(0) 0	(10) 2

ALLO-BMT
General Treatment Principles

- **The only known curative modality,**
- **Appropriate/practical only in a small subset.**
- **Individualize therapy (according to risk group, patient preference).**
- **Toxicity**

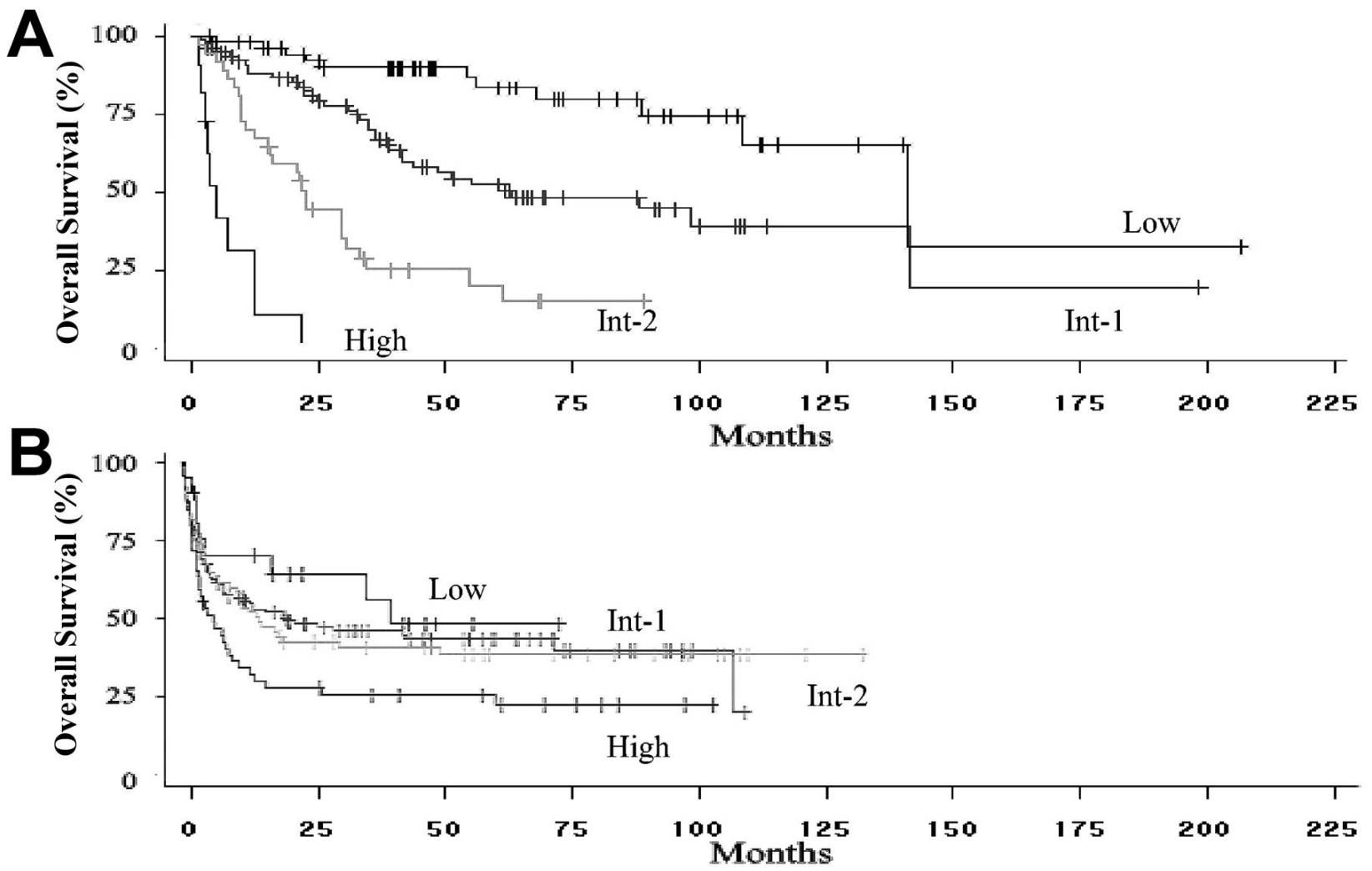
Cheson BD, et al. *Blood* 2000. 96:3671-4.

Risk Factors

Relapse	Procedure Related
• High risk cytogenetics • History of abnormal blood counts • High myeloblast count • FLT3 mutations?? • Severe flow-cytometric aberrancies	• Poor performance status • Older age • Abnormal organ function

E Estey,MD (MD Anderson)Source:
J Deeg,MD (Fred Hutchinson Cancer Center)
April, 2004

Overall survival of patients included in the analysis.

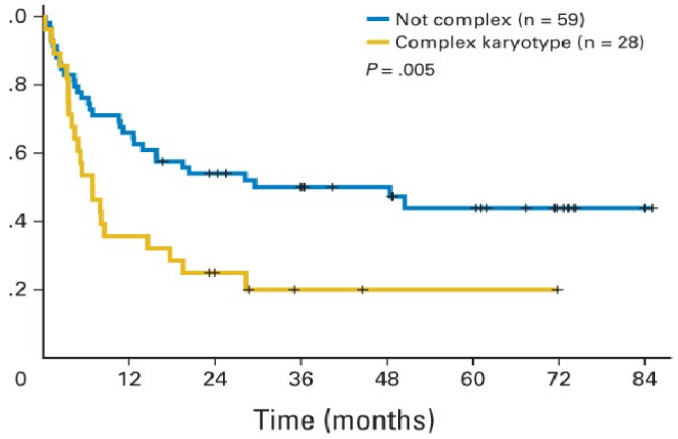


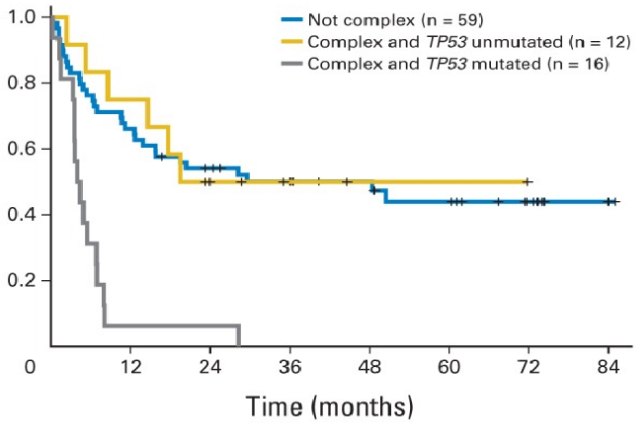
Corey S. Cutler et al. Blood 2004;104:579-585

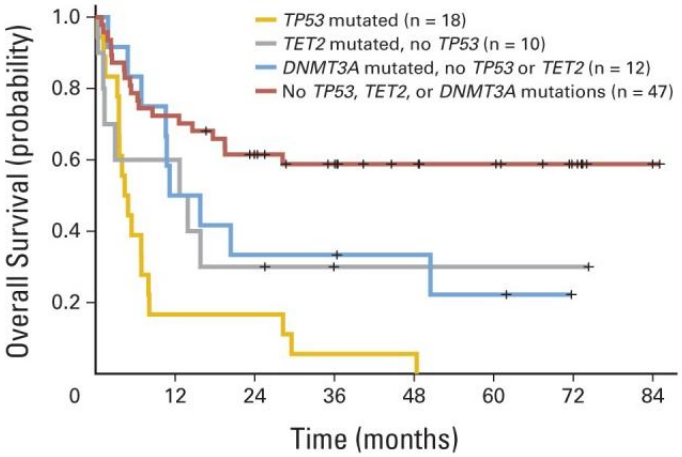
Approximation of Life Expectancy (Years)

	Immediate Transplant	Transplant in 2 Years	Transplant at Progression
Low	6.51	6.86	7.21
Int-1	4.61	4.74	5.16
Int-2	4.93	3.21	2.84
High	3.20	2.75	2.75

Somatic mutations predict poor outcome in patients with MDS after BMT



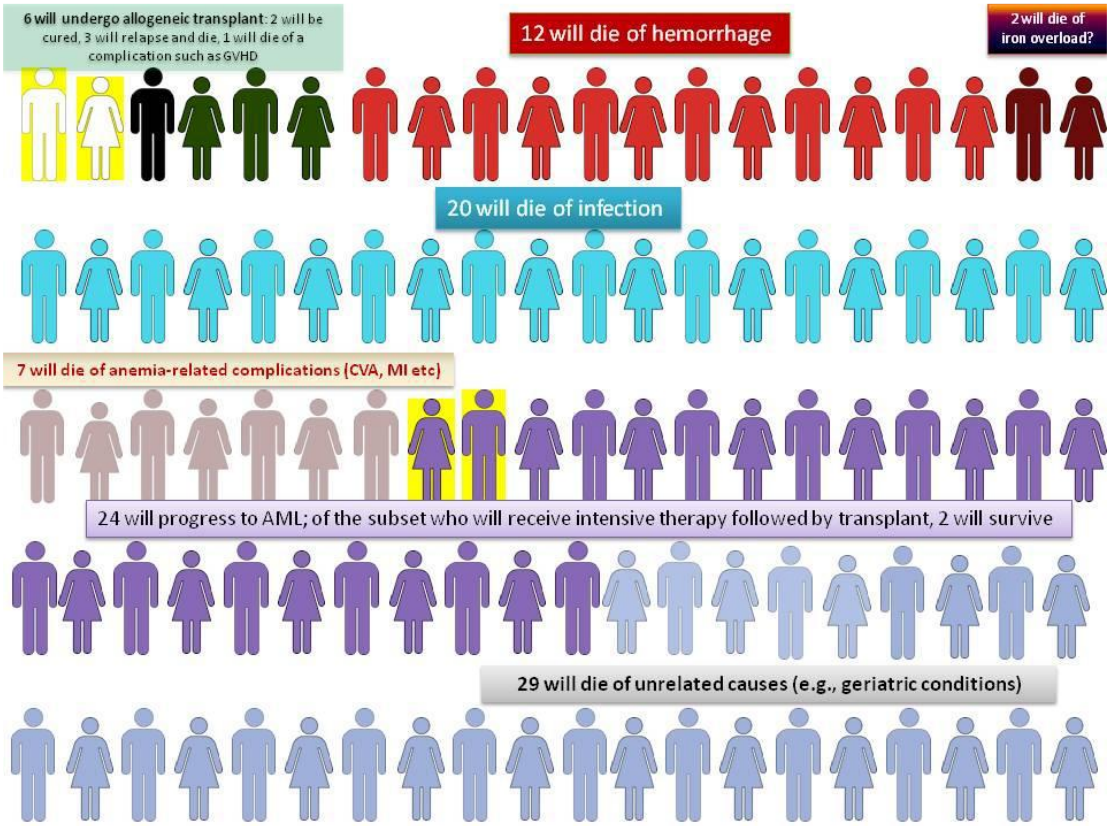




David Steensma Clinic oncology 2014 Sep 1;32(25):2691-8

שיבא
תל השומר
עיר הבריאות של ישראל
המרכז לתסמונות מיאל

Graphical Representation of Clinical Outcomes for Patients with MDS



David P. Steensma
Leukemia & Lymphoma

שיבא
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עיר הבריאות של ישראל

המרכז לתסמונות מיאלודיספלסטיות - MDS