How I Treat Myelodysplastic Syndrome (MDS)

Midwest Leukemia Symposium

August 19, 2022

Marlise R. Luskin, MD MSCE
Adult Leukemia Program
Dana-Farber Cancer Institute and Brigham and Women's Hospital
Assistant Professor, Harvard Medical School

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Marlise R. Luskin, MD MSCE

Titles:
Physician, Division of Leukemia, Dana-Farber Cancer Institute
Assistant Professor, Harvard Medical School
Associate Program Director, DF/MGB Hematology Oncology Fellowship

Education and Training:
Medical School: University of Pennsylvania, Philadelphia, PA

Residency, Internal Medicine: Brigham and Women's Hospital, Boston, MA

Fellowship, Hematology/Oncology: University of Pennsylvania SOM, Philadelphia, PA

Clinical Focus: AML, ALL, CML, MDS, and MPNs
Research Focus: ALL, AYAs, novel therapeutics for acute leukemia.

My Approach to MDS (and outline of this talk…)

- **Make a diagnosis:** *From cytopenias to MDS.*
- **Risk stratification:** *IPSS and beyond.*
- **Treatment decisions:** *Define goals and individualize management.*

How Does MDS Present?

Symptoms: Asymptomatic, fatigue

- **Common: None**, fatigue, weakness, angina, dizziness
- **Less common**: Infection, bruising, bleeding, fever, weight loss, autoimmune phenomena

Lab Work: Cytopenias; dysplasia on blood smear

- **90% anemia** (macrocytic or normocytic, increased RDW)
- 50% leukopenia, 25% thrombocytopenia, 50% pancytopenia
- Isolated neutropenia and thrombocytopenia less common *but possible*

Exam: Benign, or symptomatic anemia

- Pallor, petechiae, purpura
- *Hepatomegaly, splenomegaly, lymphadenopathy rare*
- Sweets syndrome (neutrophilic dermatosis)

Cazzola et al. *N Eng J Med* 2020;383:1358-74

Is pan-cytopenia MDS? Primary vs secondary?

- Do comorbidities account for presence *and degree* of cytopenias??
  - e.g., cirrhosis, CKD, rheumatologic/inflammation, ETOH, medications
- Is the patient acutely ill (septic, infected)? Nutritional deficiencies?
- **Don't blame age**→ evaluate. ***Avoid ER if patient stable…***
- **Warning signs:** Multiple cell lines down; "severe" cytopenias, monocytosi, rapid downward trajectory (situational awareness).
- <u>Pre-referral/First visit work-up (rapid)</u>:
  - *Nutritional*: Iron studies, vitamin B12, folate, copper
  - *Hyperproliferative vs destructive?:* Reticulocytes, LDH, bilirubin haptoglobin/DAT
  - *Comorbidities*: RF, ANA, HIV, hepatitis B/C/HIV, CMP (Cr, LFTs)
  - *Myeloma screen:* SPEP/IFXN, serum FLC
  - *Stable?* Coags/INR/fibrinogen (rule out APL)

Myelodysplastic Syndromes (MDS)

Group of chronic, hematopoietic neoplasms characterized by *ineffective, clonal hematopoiesis*.

Diagnosis: Bone marrow biopsy

1) Cytopenias (Hg <10 g/dL, plts <100 K/uL, ANC <1.8 K/uL)
2) One or more MDS-defining abnormality:

   -Dysplasia (≥10% in 1 or more lineage); or ringed sideroblasts ≥15% (or ≥ in presence of *SF3B1*).

   -MDS-defining cytogenetic abnormality

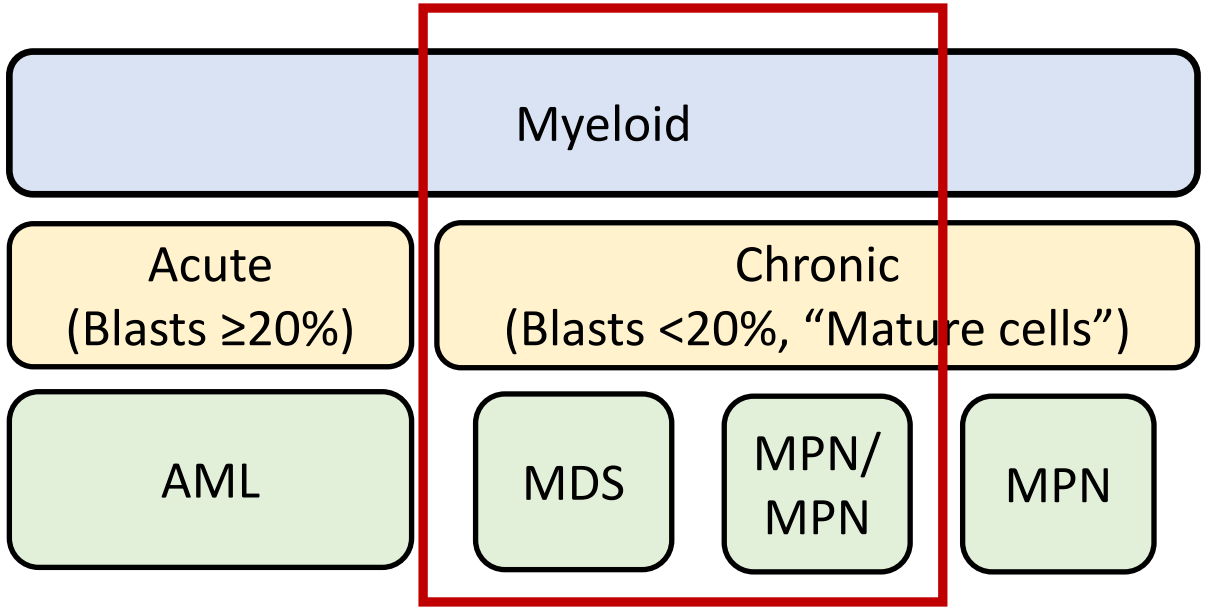
   -Excess blasts: BM (≥5% to <20%) or blood (≥1% - <20%)

Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable

If ONLY dysplasia, make sure to rule out secondary causes of pancytopenia as other etiologies (medications-MTX, illness, age) can cause dysplasia.

Arber et al. *Blood* 2016;127:2391-405 (WHO 2016)

How I Think About Myeloid Leukemias: Simplified



- **Acute leukemia** – Excess of immature cells (blasts). Differentiation impairment.
- **Chronic myeloid leukemias –** No or less impairment of differentiation.
  - **Dysplastic** – bone marrow failure.
  - **Proliferative** – bone marrow over-production.

WHO MDS Classification (2016)

DYSPLASIA
- One or more lineage
- Ringed sideroblasts

Deletion del5q

Excess blasts

MISC

Table 15. 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% or 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

Arber et al. *Blood* 2016;127:2391-405 (WHO 2016)

WHO MDS Classification (2022)

Genetics
- Del5q
- *SF3B1*
- *TP53* biallelic

Morphology
- Low blast
- Low cellularity
- Excess blasts
- Fibrosis

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.

Khoury et al. Leukemia 2022 (WHO 2022)

ICC MDS Classification (2022)

Genetics

SF3B1

Del5q

Morphology

Dysplasia

Blasts

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

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics[b]***	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1[c]	≥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[c]	≥1	Thrombocytosis allowed	<5% BM <2% PB[d]	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[d]	-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[d]	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[d]	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[c]	≥1	0	5-9% BM, 2-9% PB[d]	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1[c]	≥1	0	10-19% BM or PB[e]	Any, except AML-defining[f]	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

Table 21. Myeloid neoplasms with mutated *TP53*

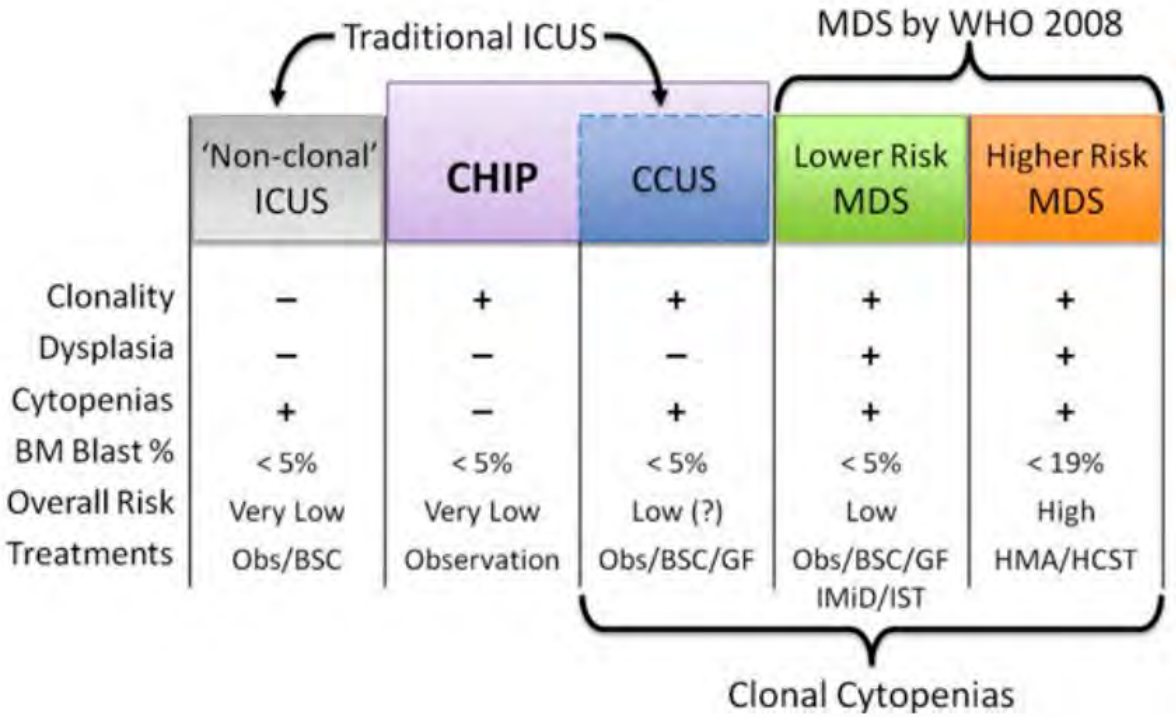
Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation[a], or *TP53* mutation (VAF >10%) and complex karyotype often with loss of 17p[b]
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF >10%)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

TP53 biallelic or high VAF

Arber et al. *Blood* 2022 (ICC 2022)

What is MDS? (the ABCs)

- **Hallmarks of the disease ("the ABCs"):**
  - Risk of progression to **A**ML
  - **B**one marrow failure (progressive cytopenias)
  - **C**lonality indicates **c**ancer (almost all have abnormal karyotype and/or at least one clonal molecular gene mutation)
- ***Note on molecular mutations*:**
  - Diagnostic criteria (*SF3B1, TP53*)
  - Confirm clonality
  - Risk stratification

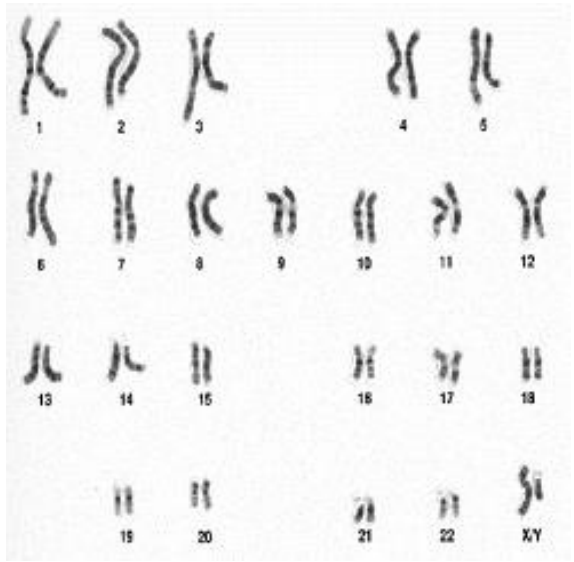


Arber et al. *Blood* 2016;127:2391-405; Khoury et al. Leukemia 2022*; ;* Arber et al. *Blood* 2022*;* Malcovati et al. *Blood* 2017;129:3371-78

Genetics of the Myelodysplastic Syndromes

MDS karyotypes (~50%) disease-defining w/ cytopenia

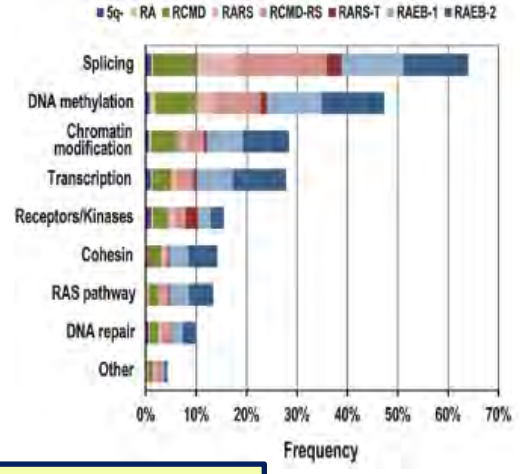
-7/del(7q)
del(5q)
del(11q)
del(12p) or t(12p)
del(9q)
idic(X)(q13)
del(17p)/t(17p)/ i(17q)
t(11;16)(q23.3;p13.3)
t(3;21)(q26.2;q22.1)
t(1;3)(p36.3;q21.3)
t(2;11)(p21;q23.3)
inv(3)(q21.3q26.2)
t(6;9)(p23.3;q34.1)



Somatic molecular mutations: not disease-defining!

mRNA splicing, chromatin modification, transcription, DNA methylation
Present in >90%

SF3B1, TET2, SRSF2
ASXL1, DNMT3A, RUNX1
U2AF1, TP53, EZH2
ETV6, U2AF2, ZRSRS



Very rare to be unable to define a clonal genetic event!

Arber et al. *Blood* 2016;127:2391-405; Khoury et al. Leukemia 2022*;* Arber et al. *Blood* 2022*;* Malcovati et al. *Blood* 2017;129:3371-78; Bejar et al. *N Eng J Med* 2011;364:2496-506; Papaemmanuil et al. *Blood* 2013;122:3616-27; Haferlach T et al. *Leukemia* 2014;28:241-47

A **bone marrow biopsy** is required!

- **Cellularity** (usually hyper cellular; ~10% hypocellular)
- **Dysplasia** (present?, number of lineages?)
- **Blast %** (MDS, MDS/AML, AML)
- **Karyotype**
- **Other findings**
  - Second diagnoses?
  - Fibrosis?

Clonal hematopoieis of indeterminate potential (CHIP) – increases risk for

- All cause mortality
- Leukemia/MDS
- Cardiovascular disease
- Stroke
- COPD
- Gout
- *Standards of care for monitoring and management being defined!*

Jaiswal *N Eng J Med* 2017;377:111-21; Fuster et al. *Science* 2017; Agrawal et al. *Blood* 2022; Bhattacharya et al. *Stroke* 2022;53:788-97; Miller et al. *Blood* 2022;139:357-68

Clonal Progression

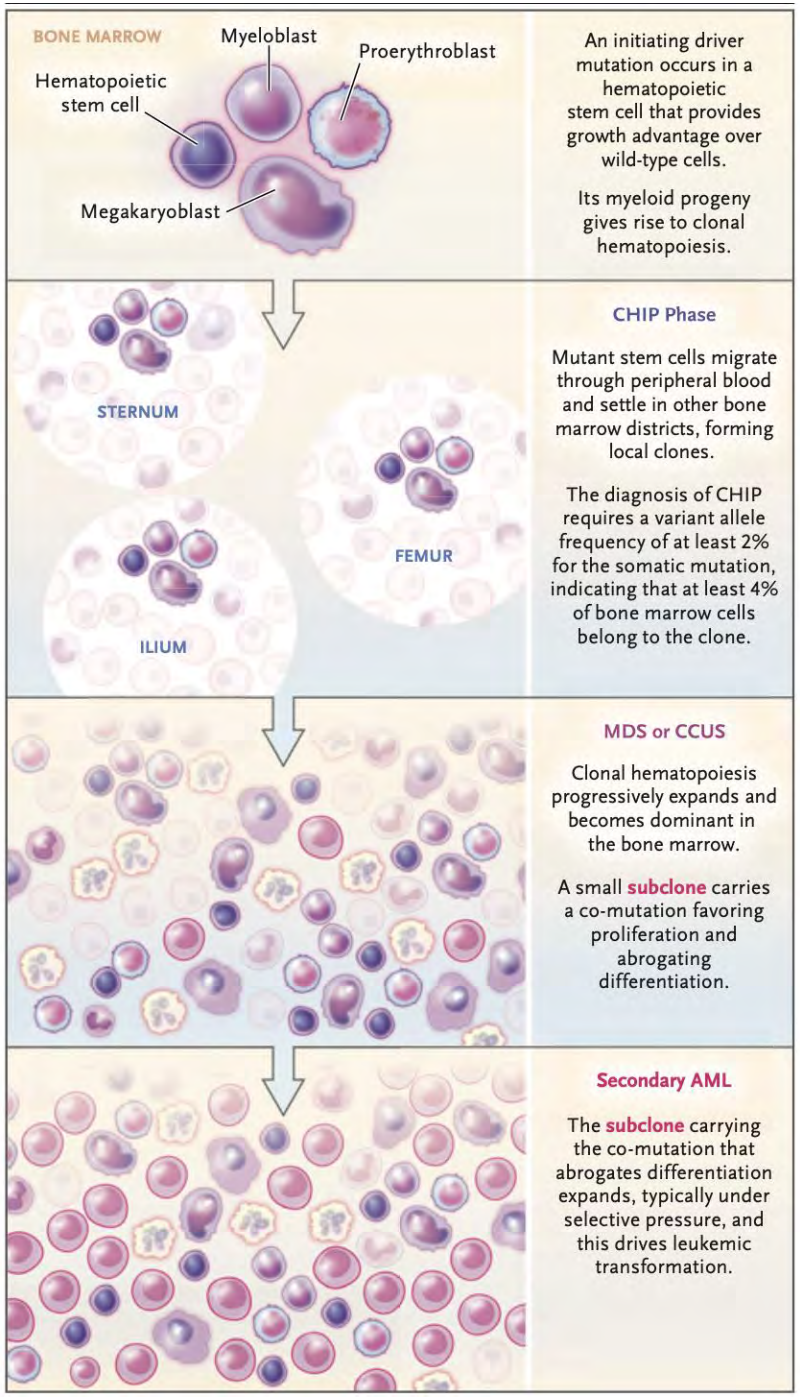
Normal polyclonal hematopoiesis

CHIP

CCUS

MDS

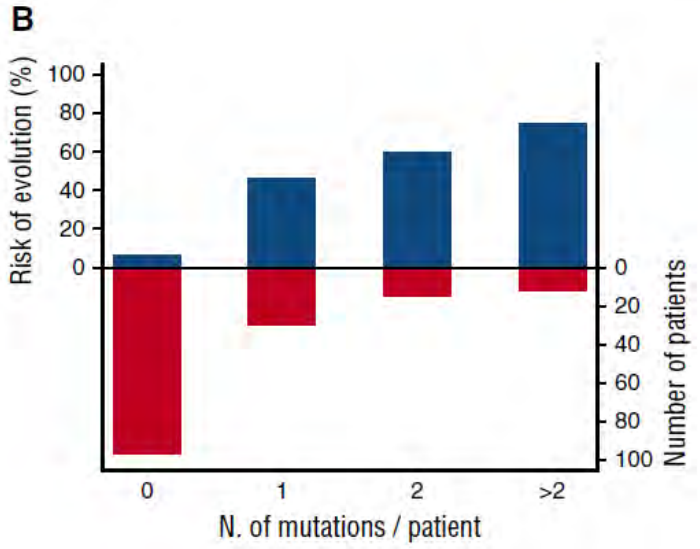
AML

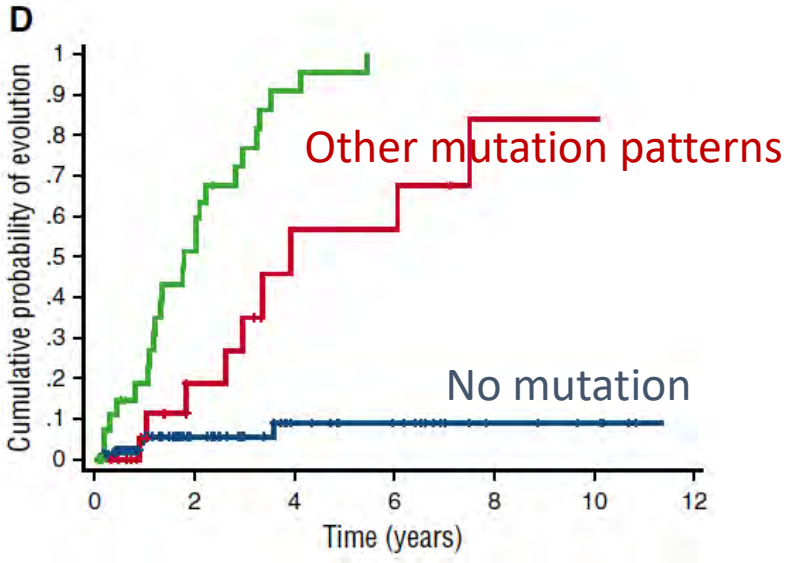


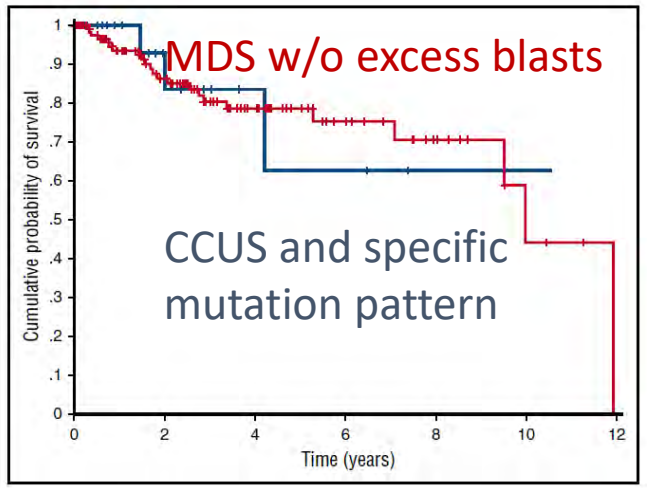
Cazzola et al. *N Eng J Med* 2020;383:1

Cytopenias → Risk Myeloid Neoplasm

Spliceosome mutation and D/A/T mutation w/ add mutations







In patients with cytopenias – molecular mutations help determine risk of evolution

RISK

1) High VAF mutation 2) Multiple mutations 3) Spliceosome mutation

Malcovati et al. *Blood* 2017;129:3371-78

MDS – Epidemiology and Demographics

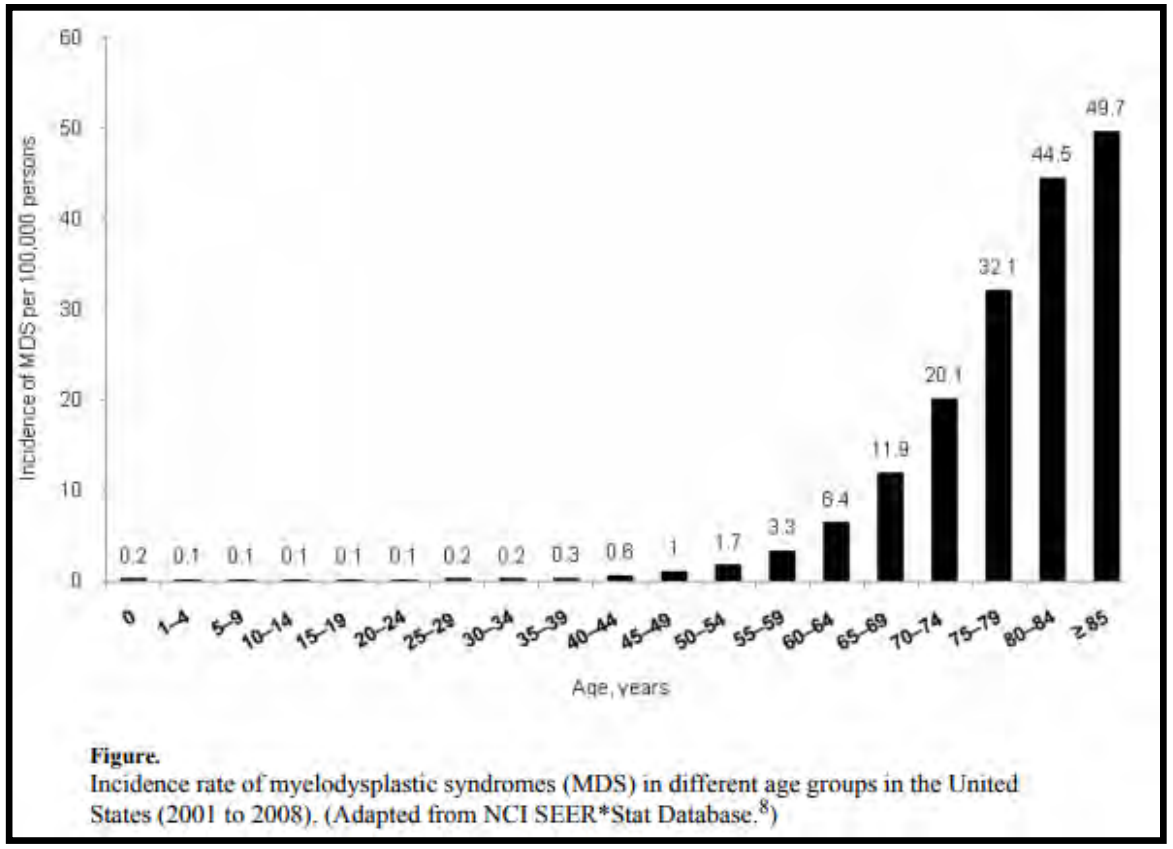


Figure.
Incidence rate of myelodysplastic syndromes (MDS) in different age groups in the United States (2001 to 2008). (Adapted from NCI SEER*Stat Database.[8])

- Median age at diagnosis: ~70-75 years
- Approximately 40,000 cases/year
- Cytopenias in older adults often incompletely evaluated.
- *Risk factors:*
  - Typical: Age, male gender, clonal hematopoiesis, prior chemotherapy/radiation
  - Young onset: aplastic anemia, inherited predisposition syndromes

Ma et al. *Cancer* 2007;109:1536-42; Rollison et al. *Blood* 2008;112:45-52; Goldberg et al. *J Clin Oncol* 2010;28:2847-52; Cogle et al. *Blood* 2011;117:7121-5; Zeiden et al. *Blood Rev* 2019;34:1-15

MDS – Inherited Predisposition

- *DDX41*
- Telomere biology disorders (DKC)
- RUNX1 FPD
- Fanconi anemia
- *GATA2*
- Shwachman-diamond syndrome

Family history?

Comorbid conditions? pulmonary fibrosis, early graying, liver cirrhosis, immune deficiency.

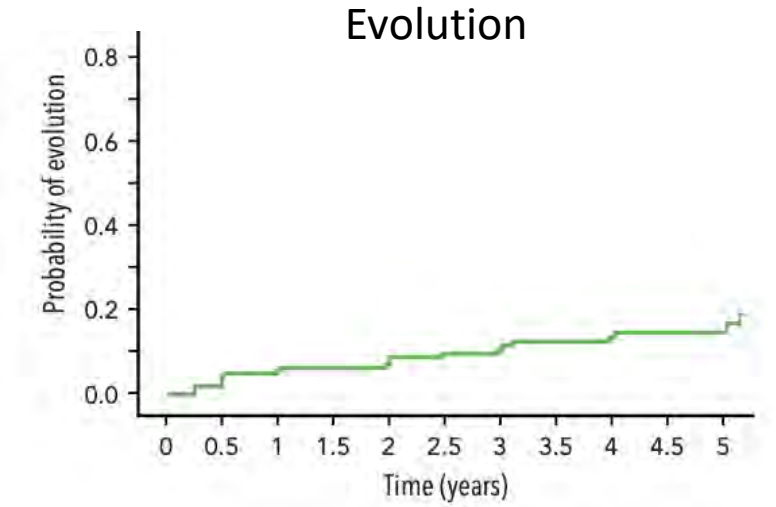
May not have any clues on history of exam!!

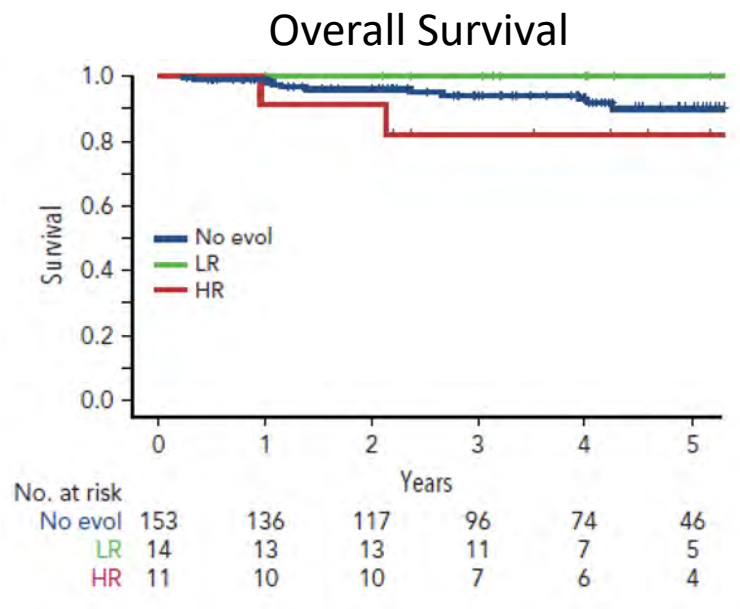
Suggest referral to a specialized center, for genetic testing, recommendations.

Schratz et al. *Blood* 2020; Feurstein et al. *Blood Advances* 2020; Sebert et al. *Blood* 2019;134:1441-44

MDS – Risk in Aplastic Anemia (Watch!)

- Older patients (>40 years) had a significantly higher risk of clonal evolution.
- **High-risk evolution was observed in 5.7% of the EPAG-IST group** and 10.3% of the historic IST group at 4 years.
  - **Median time earlier in EPAG group 186 days** vs 777 days, **~ half within 6 months**.
- **Most chromosome 7 abnormalities**.





Patel et al. *Blood* 2022;139:34-43

How common is MDS?
Will I see this in my practice?

Predisposing factors unknown in vast majority (85% are considered "de novo") – for these AGE is primary risk factor.

- **Risk factors:** chemo (alkylators and topo II inhibitors), ionizing radiation, environment (benzene), history of AA or PNH, familial syndrome.

Median age > 65 years, male predominance

- Unusual < 50 years unless treatment-related, inherited predisposition/aplastic anemia.

Incidence unknown (10-40K new cases/yr; prevalence 60-120K).

- **Incomplete diagnostic evaluation of elderly patients.**
- Underreporting to cancer registries. Claims →higher estimates.

Ma et al. *Cancer* 2007;109:1536-42; Rollison et al. *Blood* 2008;112:45-52;
Goldberg et al. *J Clin Oncol* 2010; 28:2847-52; Cogle et al. *Blood* 2011; 117:7121-5

Predict the future…

MDS – "Staging" (Risk Scores) - IPSS

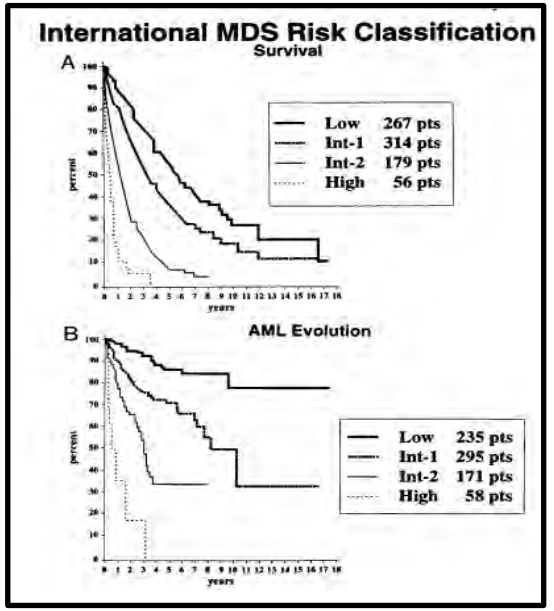
- Do not use typical "staging" (i.e stage I-IV).
- **We want to understand pace of disease worsening:**
  - Further bone marrow failure.
  - Progressive to AML.
- **So IPSS/IPSS-R developed to estimate:**
  - Time to AML progression.
  - Overall survival.
- **Integrate disease features associated with risk:**
  - Number and degree of cytopenias.
  - Presence and degree of excess blasts.
  - Karyotype (cytogenetic risk).
- **International Prognostic Scoring System (IPSS) and Revised IPSS most used historically.**

Table 1. International Prognostic Scoring System (IPSS): prognostic variables

	0	0.5	1.0	1.5	2.0
Marrow blasts, %	<5	5-10	—	11-20	21-30
Karotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3	—	—	—

— indicates not applicable; Good = normal, -y, del(5q), del(20q); Poor = complex (≥3 abnormalities) or chromosome 7 anomalies; and Intermediate = any other abnormalities.

IPSS



Greenberg et al. *Blood* 1997;89:2079-88; Greenberg et al. *Blood* 2012;120:2454-65; Kantarjian et al. *Cancer* 2008;113:1351-61; Della Porta et al. *Leukemia* 2015;29:1502-13

MDS – "Staging" (Risk Scores) – IPSS-R

Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

— indicates not applicable.

IPSS-R → same "variables" but refined categorization.
More weight to cytogenetics and cytopenias.

Table 4. IPSS-R prognostic risk categories/scores

Risk category	Risk score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

IPSS-R

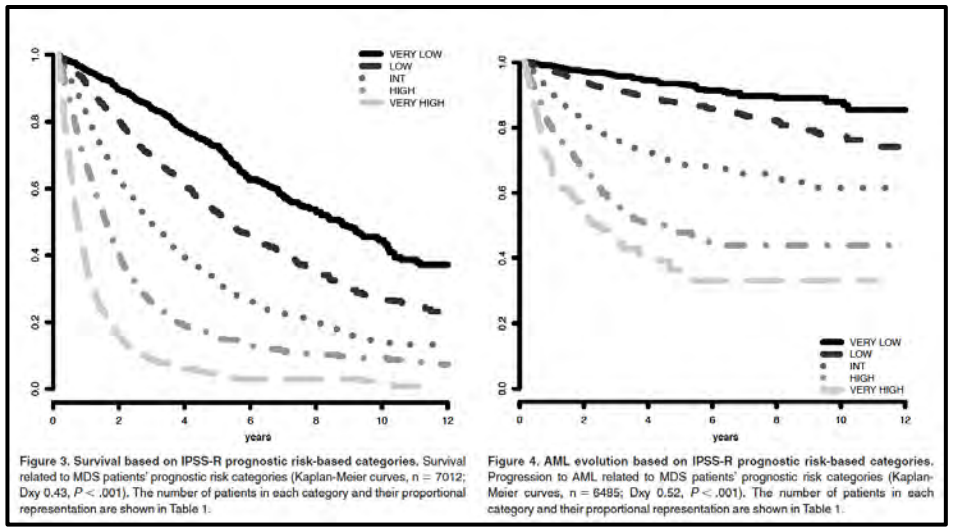


Figure 3. Survival based on IPSS-R prognostic risk-based categories. Survival related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 7012; Dxy 0.43, P < .001). The number of patients in each category and their proportional representation are shown in Table 1.

Figure 4. AML evolution based on IPSS-R prognostic risk-based categories. Progression to AML related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 6485; Dxy 0.52, P < .001). The number of patients in each category and their proportional representation are shown in Table 1.

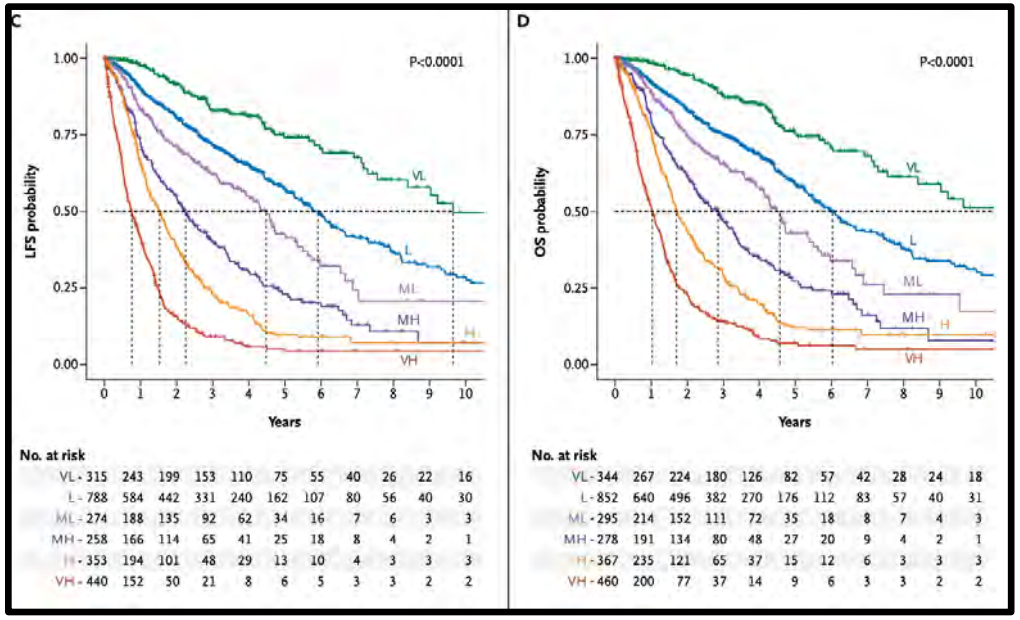
Greenberg et al. *Blood* 1997;89:2079-88; Greenberg et al. *Blood* 2012;120:2454-65;
Kantarjian et al. *Cancer* 2008;113:1351-61; Della Porta et al. *Leukemia* 2015;29:1502-13

MDS – "Staging" (Risk Scores) – IPSS-M

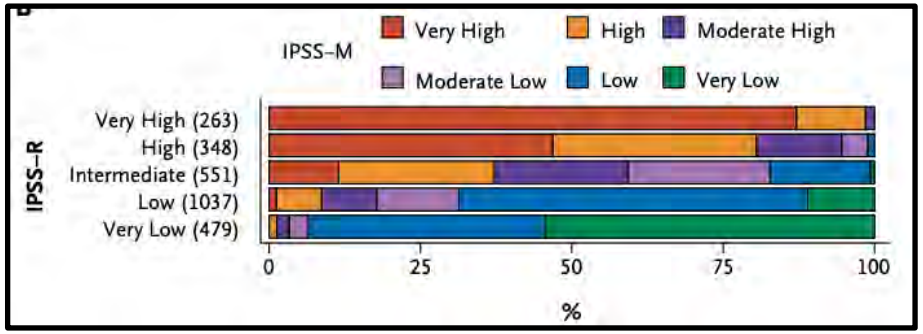
ORIGINAL ARTICLE

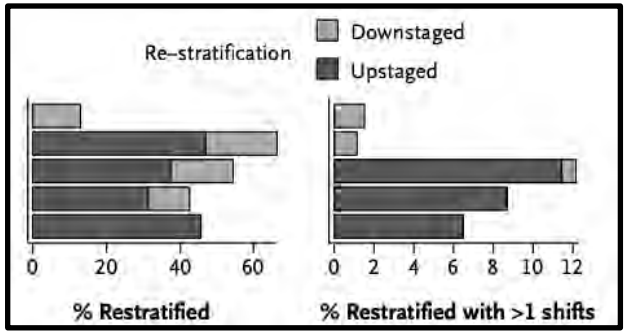
Molecular International Prognostic Scoring System for Myelodysplastic Syndromes

Elsa Bernard, Ph.D.,[1] Heinz Tuechler, Peter L. Greenberg, M.D.,[2] Robert P. Hasserjian, M.D.,[3] Juan E. Arango Ossa, M.S.,[1]



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



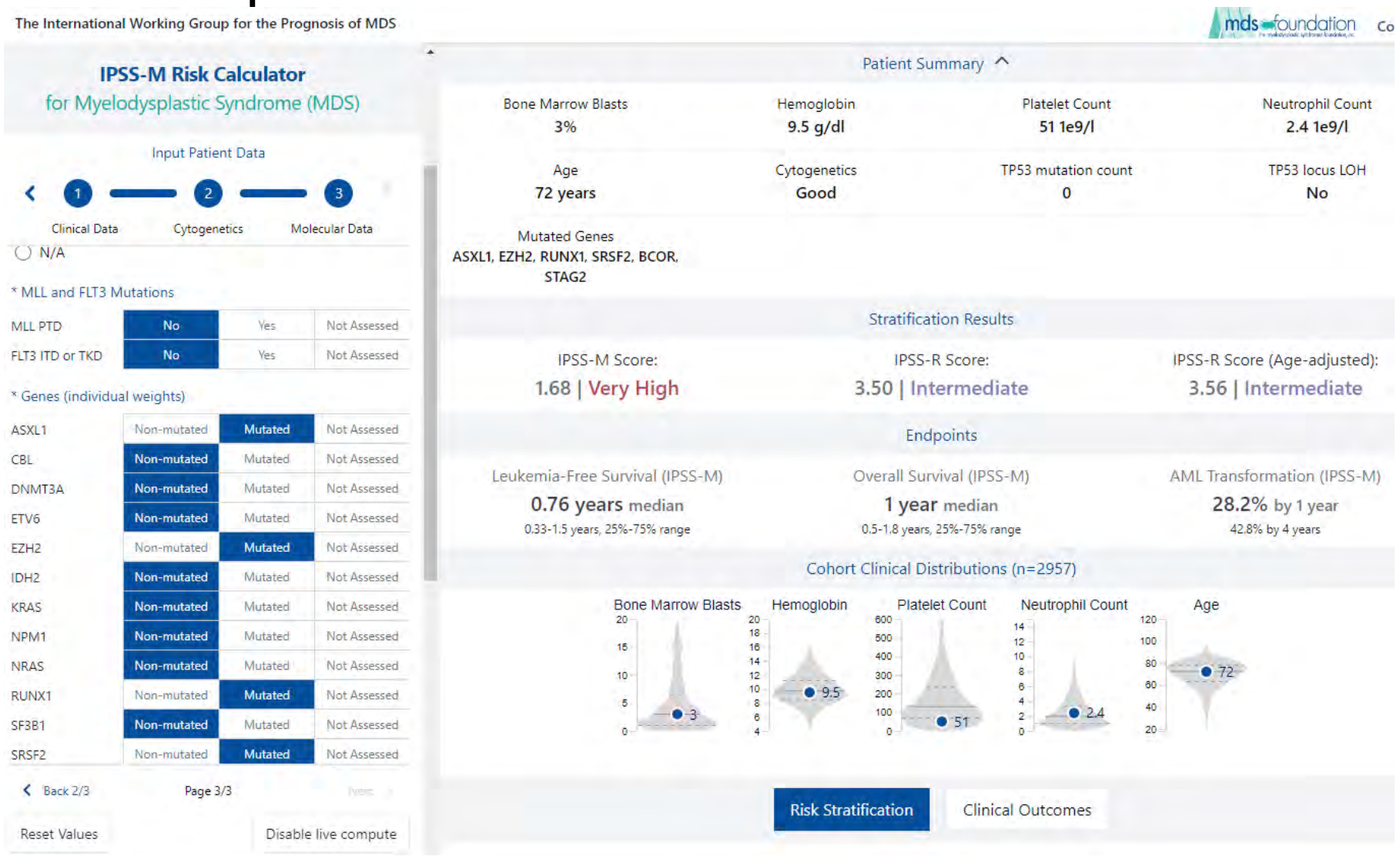


46% of patients were restratified

7% of patients were restratified by more than 1 strata

Bernard et al. *N Eng J Med Evid* 2022; 1 (7)

Example: IPSS-M *versus* IPSS-R



Greenberg et al. *Blood* 2012;120:2454-65; Bernard et al. *N Eng J Med Evid* 2022; 1 (7)

Other Risk Features

- Therapy-related
- Fibrosis
- Neutropenia
- Transfusion dependence, transfusion refractoriness.
- Clonal evolution (cytogenetics, molecular).

Malcovati et al. *J Clin Oncol* 2007;25:3503-10; Della Porta et al. *J Clin Oncol* 2008;27:754-62; Breccia et al. *Leuk Res* 2012;546-7; Cordoba et al. *Leuk Res* 2012;36:287-92; Zeidan et al. *Leukemia* 2017;31:1391-7; Ramos et al. *Oncotarget* 2016;7

Decide on Treatment

Personalized - characteristics of **disease (MDS)** and **patient**.

Disease –

- Current impact – symptomatic cytopenias
- Risk – low versus high

Patient –

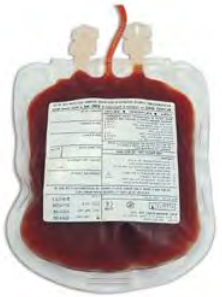
- "Fit" or "Frail"
- Specific comorbidities
- Values/goals

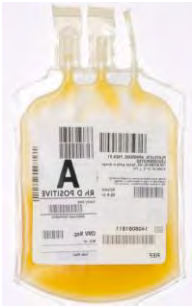
Define goals of therapy

1) Symptom control
2) Lengthen life
3) Cure

Goldberg et al. *J Clin Oncol* 2010;28:2847-52; Wang et al. *Leuk Res* 2009;33:1594-8; Bammer et al. *J Geriatric Oncol* 2014;5:299-306; Abel and Buckstein. *Am Soc Clin Oncol Educ Book*; 2016;35:e337-44; Luskin and Abel *J Geriatr Oncol* 2018;9:302-7.

MDS – Approach to Treatment





Supportive care

- Goal: Improve quality of life.
- Who: Any with symptoms (low and high-risk disease)

- Erythropoietin, TPO mimetics
- Transfusions
- Lenalidomide (esp: *del5q*)
- Luspatercept (*only ringed sideroblasts*)
- Immune suppression *(consider for hypoplastic MDS)*

Ongoing reassessment, education, and counseling!

Disease modifying treatment

- Goal: Lengthen life, ?cure
- Who: High-risk disease.

- Azacitidine and decitabine (chemotherapy)
- Curative: Allogeneic stem cell transplant

Supportive management of cytopenias

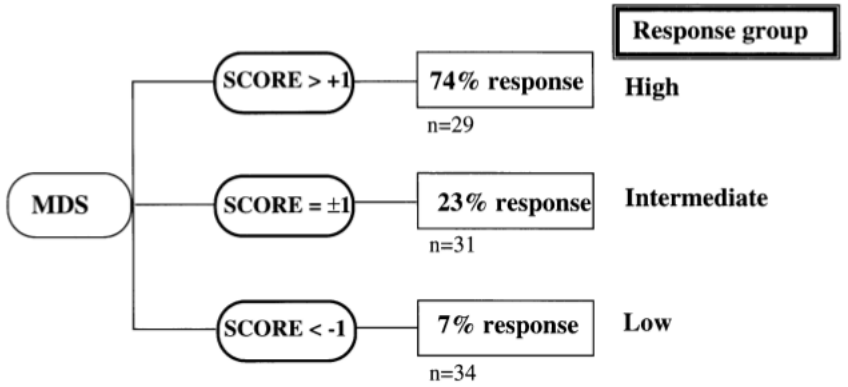
Goals: Decrease transfusions, improve QOL
(Anemia is most common, thrombocytopenia particularly challenging)

Anemia

- Erythropoietin
- Transfusions
- Lenalidomide
- Luspatercept
- Low dose HMA

Thrombocytopenia

- TPO mimetics
- Anti-fibrinolytic agents
- Transfusions
- IST
- Low dose HMA



Scores for predicting response to treatment with G-CSF + EPO

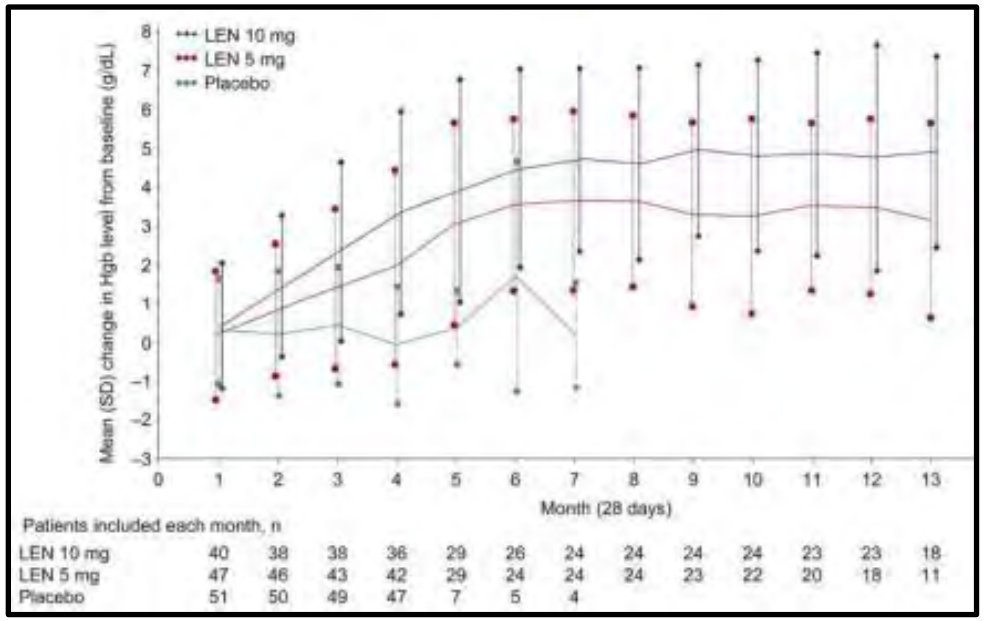
Serum epo U/l	<100	+2
	100-500	+1
	>500	-3
RBC transfusion need	<2 units/mo.	+2
	≥2 units/mo.	-2

Hellstrom-Lindberg et al *Br J Haematol* 1997;99:344-51; Platzbecker et al. *Leukemia* 2017;31:1944-50; Sasaki et al. *NEJM Evi* 2022

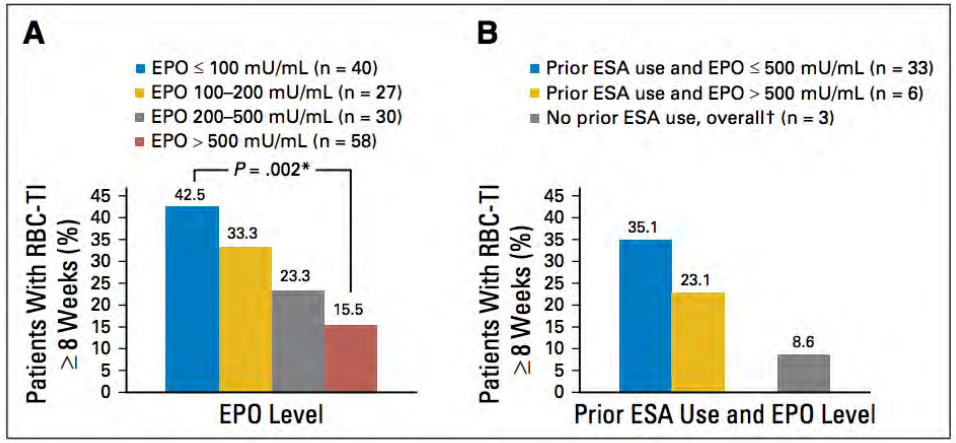
Lenalidomide

- del(5q) → ~70% heme response
  - Median Hg rise 5.4 g/dL
  - Median response duration >2 years.
- Responders → decreased risk of death AML progression
- Cytogenetic responses.

- Present response rate in non-del(5q) but less frequent (~25%), response shorter (<1 year).



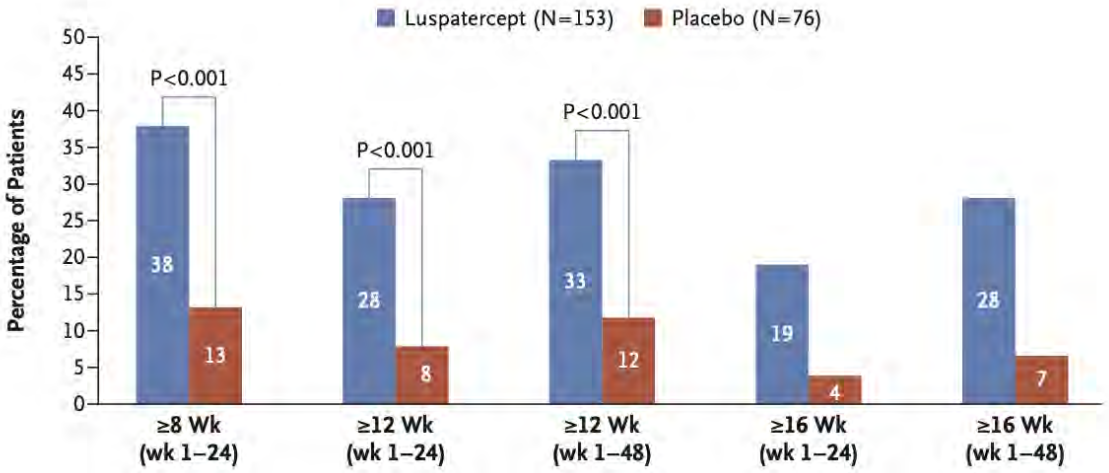
MDS-004



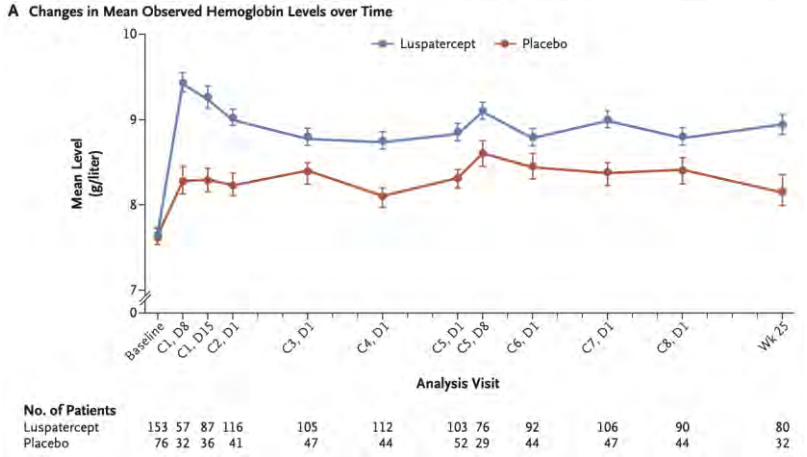
MDS-005

List et al. *N Engl J Med* 2005;352:549-57; List et al. *N Engl J Med* 2006;355: 1456-65; Fenaux et al. *Blood* 2011;118:3765-76; Raza et al. *Blood* 2008;111:86-93; Santini et al. *J Clin Oncol* 2016;34:2988-96

Luspatercept (Medalist Trial)



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



No. of Patients											
Luspatercept	153	57	87	116	105	112	103	76	92	106	90	80
Placebo	76	32	36	41	47	44	52	29	44	47	44	32

Event	Luspatercept (N=153)		Placebo (N=76)	
	Any Grade	Grade 3	Any Grade	Grade 3
	number of patients with event (percent)			
General disorder or administration-site condition				
Fatigue	41 (27)	7 (5)	10 (13)	2 (3)
Asthenia	31 (20)	4 (3)	9 (12)	0
Peripheral edema	25 (16)	0	13 (17)	1 (1)
Gastrointestinal disorder				
Diarrhea	34 (22)	0	7 (9)	0
Nausea†	31 (20)	1 (1)	6 (8)	0
Constipation	17 (11)	0	7 (9)	0
Nervous system disorder				
Dizziness	30 (20)	0	4 (5)	0
Headache	24 (16)	1 (1)	5 (7)	0

Fenaux et al. *N Eng J Med* 2020;382:140

Hypomethylating agents

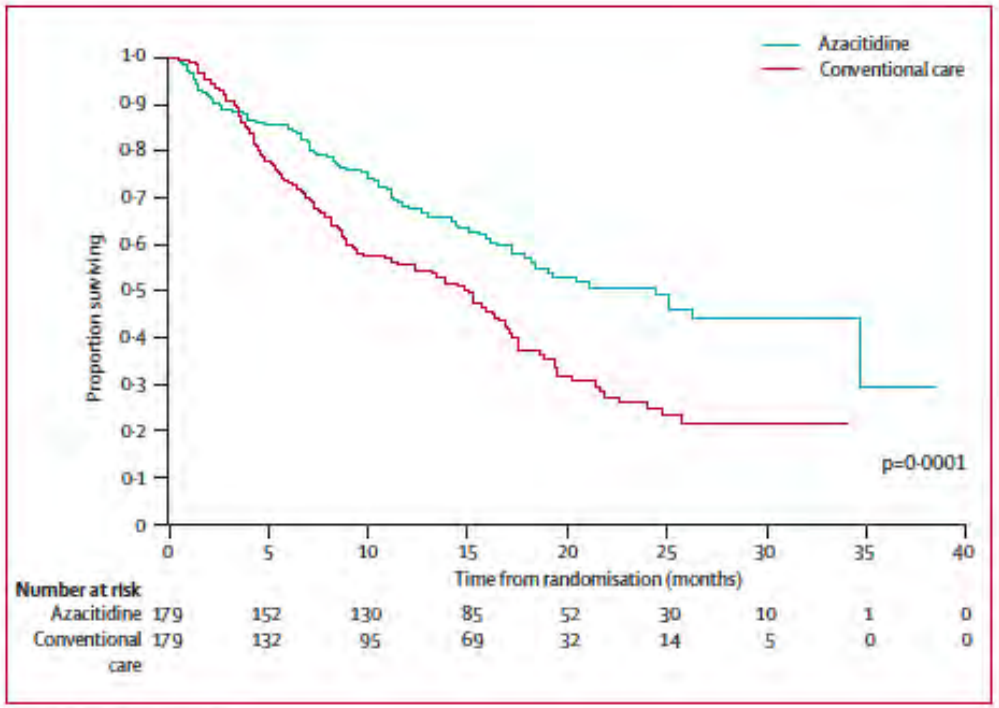


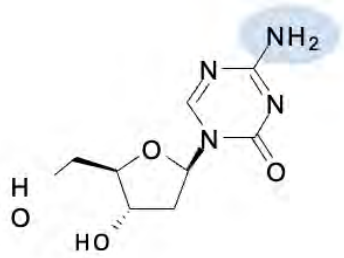
Figure 3: Overall survival

- **Azacitidine and decitabine**
  - "Workhorse" chemo for (high-risk) MDS.
  - Azacitidine and decitabine - interchangeable.
- **Low dose regimens** for low-risk disease.
- **Oral formulations** now developed.
- **Additions (doublet and triplet therapy)** ***in development***
  - Venetoclax
  - IDH inhibitors
  - Checkpoint blockade
  - More

Fenaux et al. *Lancet Oncol* 2009;10:223-32; Lubbert et al. *J Clin Oncol* 2011;29:1987-96;
Jabbour et al. *Blood* 2017;130:1514-22; Garcia-Manero et al. *Blood* 2020; 136:674-83; Sasaki et al. *NEJM Evi* 2022

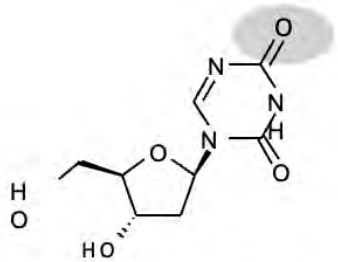
Oral Decitabine-Cedazuradine (Inquovi)

- Oral administration of HMAs limited by degradation by cytidine deaminase (CDA) in GI tract (liver/gut).
- Cedazuridine is a CDA inhibitor.
- Ascertain established bioequivalence of oral decitabine-cedazuridine and IV decitabine

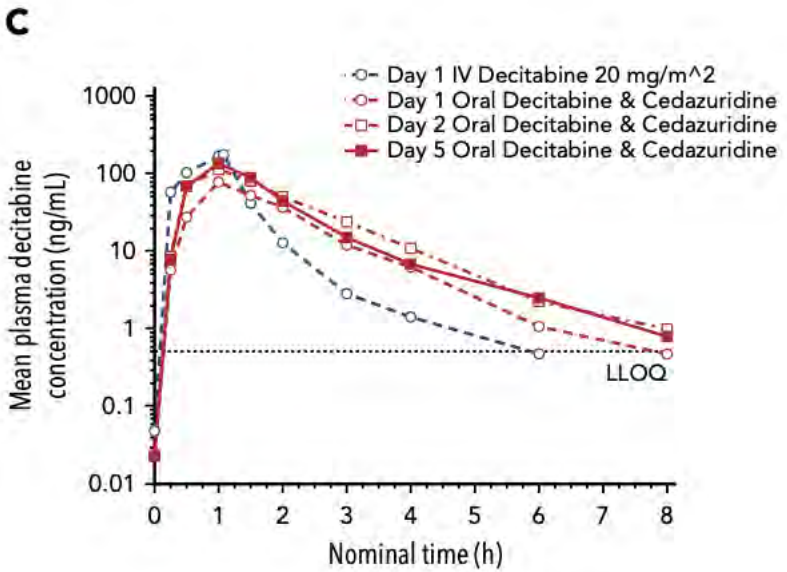


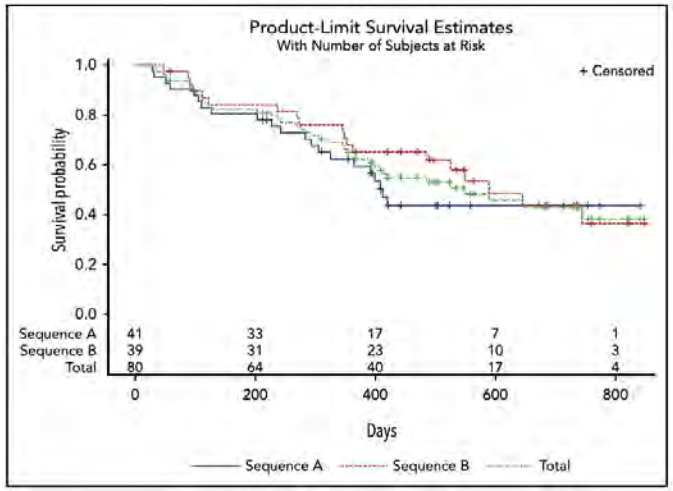
Decitabine

CDA Inhibitor



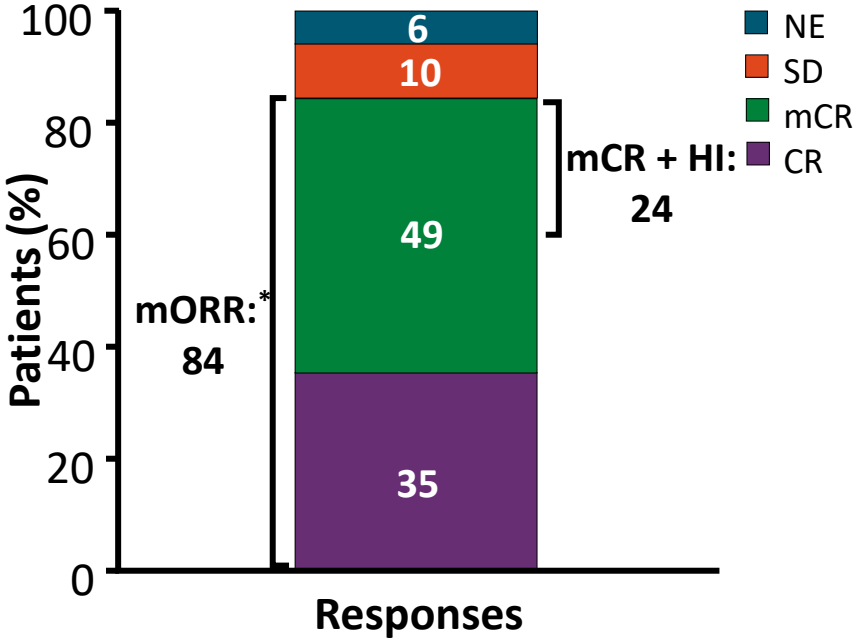
Inactive Metabolite

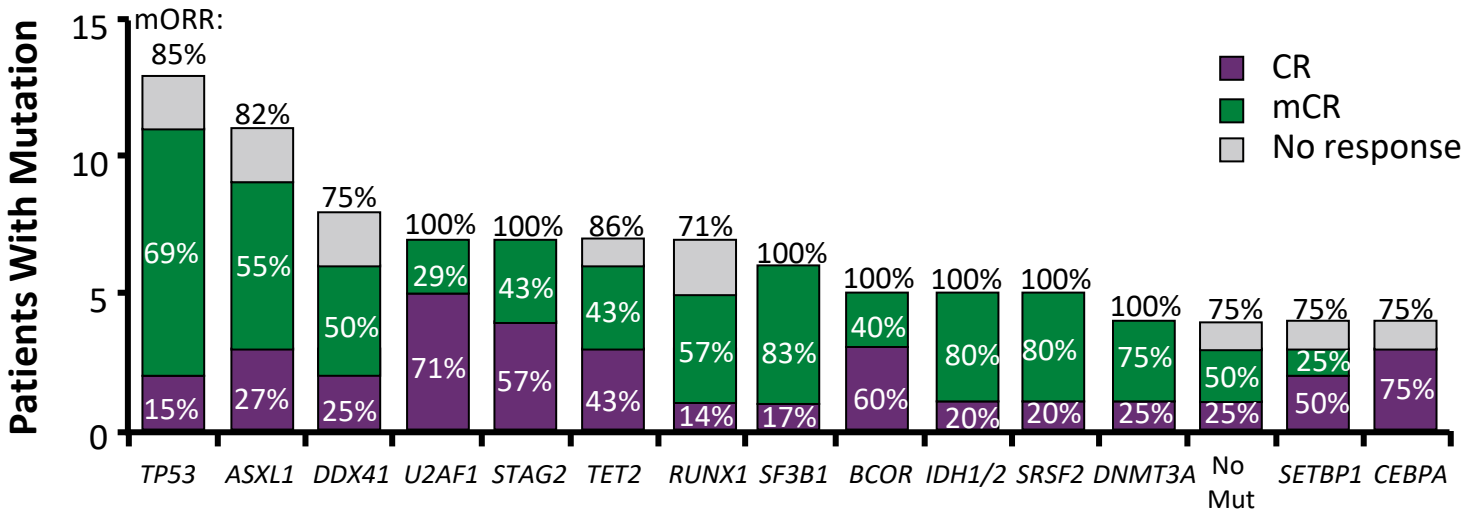




Garcia-Manero et al. *Blood* 2020; 136:674-83

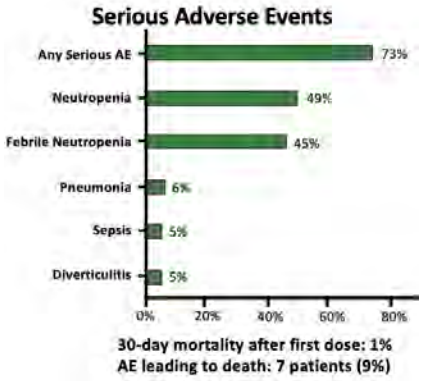
Azacitidine plus venetoclax (Phase Ib)





51 patients received the **RP2D Ven 400 mg D1-14**
Median follow-up: 23 mo (range 0.1-44.2)
ORR: 84% at RP2D
Median TTR: 0.9 mo (95% CI: 0.7-5.8)
Median DoR: 12.4 mo (95% CI: 9.9-NR)

VERONA Trial: Venetoclax vs Placebo plus Azacitidine in Treatment-Naïve Patients with HR MDS



Garcia et al. *Blood* 2021; Abstract 241

Hypomethylating Agents: Summary (1)

Goals:

- Improvement in OS and delayed progression to AML in high risk patients.
- Improve cytopenias when other drugs failed.

- Traditional given IV, but oral formulations now here.
- Time to response can be slow (4-6 cycles, or more).
- Azacitidine and decitabine likely equivalent benefit (registry and retrospective comparisons), only azacitidine demonstrated to have a survival benefit.

Modest responses:

- Few complete remissions (<20%) but ~50% have some hematologic improvement.
- Median OS ~1 year if excess blasts.
- Real world outcomes likely inferior to trial data.
- Switching from azacitidine to decitabine likely ineffective.

Fenaux et al. *Lancet Oncol* 2009;10:223-32; Lubbert et al. *J Clin Oncol* 2011;29:1987-96; Zeiden et al. *Leukemia* 2016;30:649-57; Prebet et al. *J Clin Oncol* 2011;29:3322-7; Zeidan Br J Haematol 2016;175:829-40; Zeiden et al. *Blood* 2018;131:1818-821; Harel et al. *Leuk Res* 2015;39:501-4; Duong et al. *Leuk Lymph* 2015;56:1718-22

Hypomethylating Agents: Summary (2)

Modest responses:

- Few complete remissions (<20%) but ~50% have some hematologic improvement.
- Median OS ~1 year if excess blasts.
- Real world outcomes likely inferior to trial data.
- Switching from azacitidine to decitabine likely ineffective.

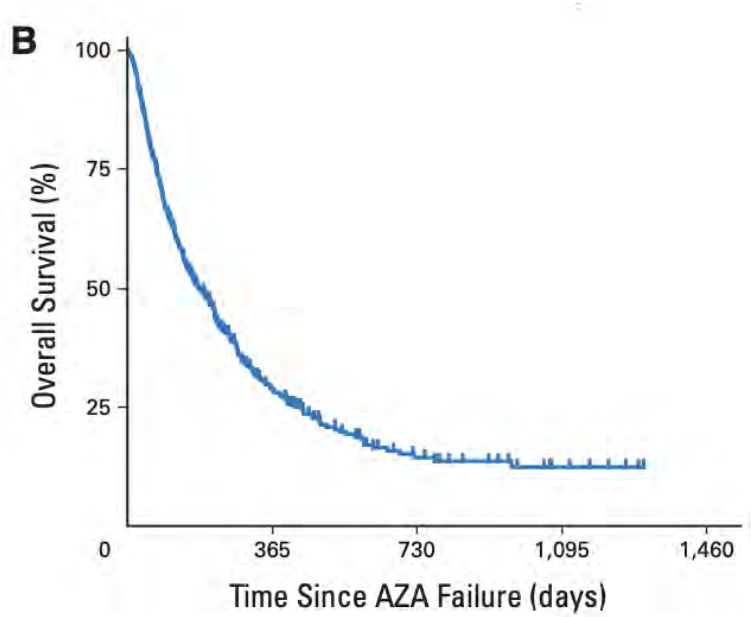
Challenging Disease to Target!

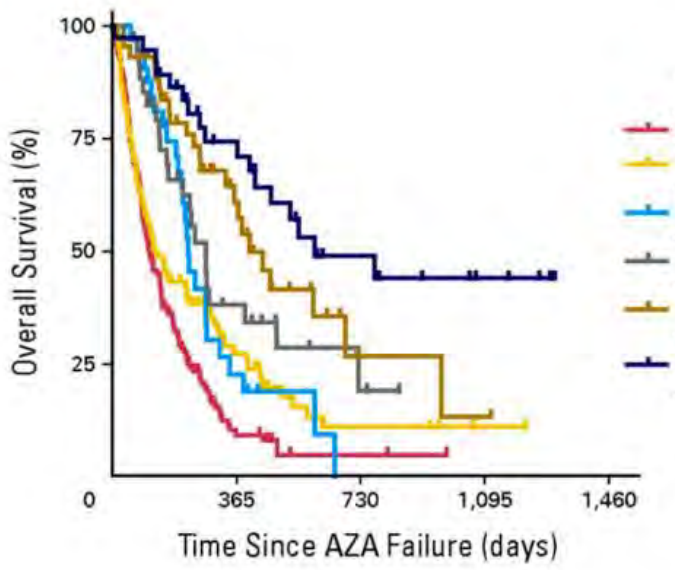
- Patients typically older and comorbidities → difficult clinical trial population.
- Requires complex supportive care.
- Heterogeneous disease.
- HMA failure particularly challenging.

Fenaux et al. *Lancet Oncol* 2009;10:223-32; Lubbert et al. *J Clin Oncol* 2011;29:1987-96; Zeiden et al. *Leukemia* 2016;30:649-57; Prebet et al. *J Clin Oncol* 2011;29:3322-7; Zeidan Br J Haematol 2016;175:829-40; Zeiden et al. *Blood* 2018;131:1818-821;

After hypomethylating agent failure

- Outcomes after failure of HMAs (and transplant) are very poor.
- Transplant represents best chance for durable remission (few eligible).



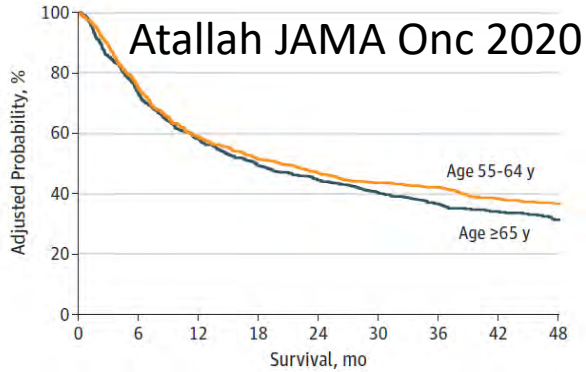


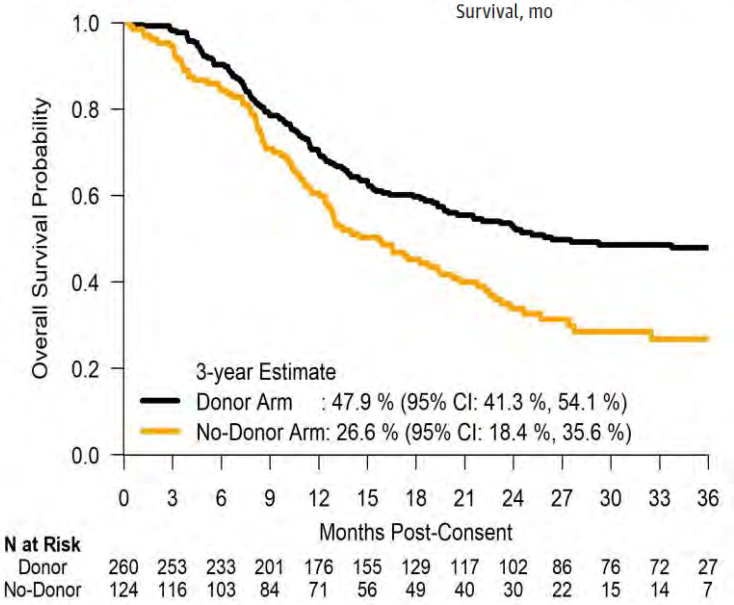
Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

Prebet et al. *J Clin Oncol* 2011;29:3322-7; Guieze et al. *Biol Blood Marrow Transplant* 2016;22:240-7

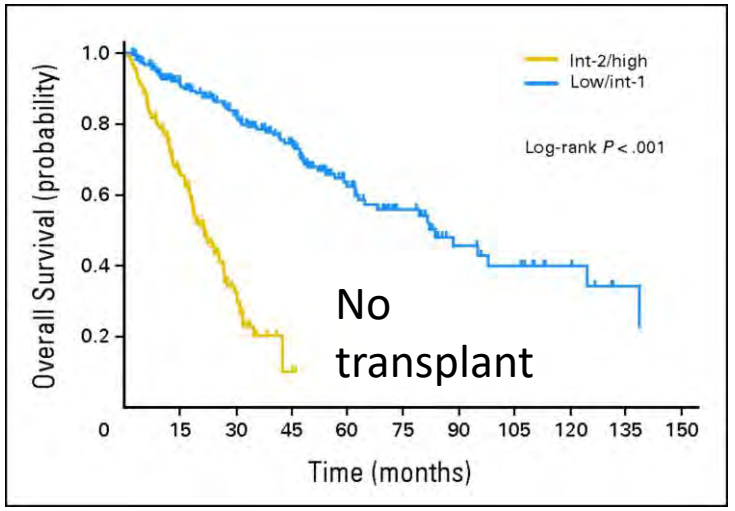
Transplant for MDS: A Word

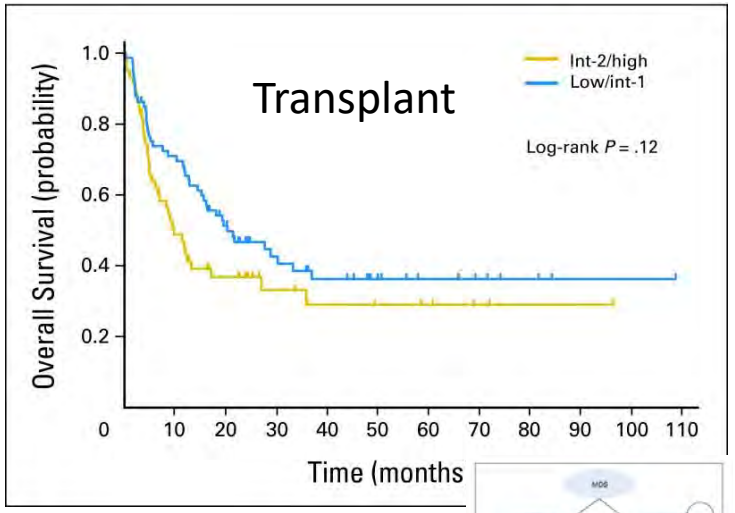
- Only curative therapy.
- Indicated for **IPSS Int-2/High**
  - Retrospectively (Markov models) – Cutler, Koreth
- *If fit,* age is not an exclusion and benefit. Older patients do as well as younger patients.
  - Retrospective – Atallah
  - Prospective observational – Abel
  - Prospective donor randomization – Cutler (aged 50-75 years, IPSS Int-2 or High)



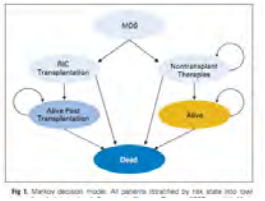


Cutler ASH 2020





Koreth J Clin Oncol 2013



Cutler et al. *Blood* 2004;15:579-85; Koreth et al. *J Clin Oncol* 2013;31:2662-70; Abel et al. *Leukemia* 2020; Atallah et al. *JAMA Onc* 2020;6:486-93; Nakamura *J Clin Oncol* 2021;39:3328-39

Allogeneic Stem Cell Transplant

- Increasingly clearly that age itself should not be barrier HCST as it has not been correlated with outcomes.
- Recommend that all fit patients up to mid-70s with higher-risk MDS be referred for formal allogeneic HSCT consultation.
- HSCT increasingly being used for treatment of older adults with MDS.

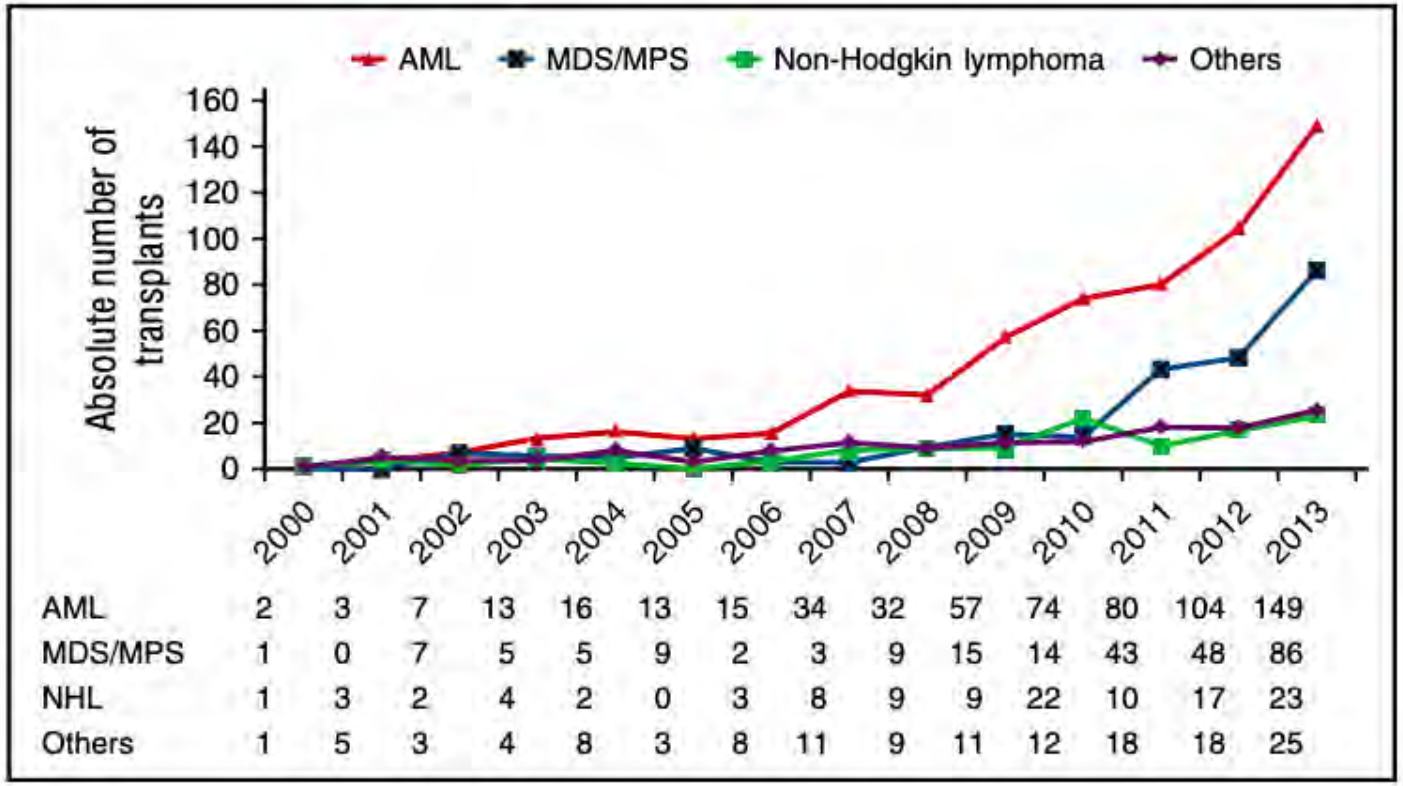
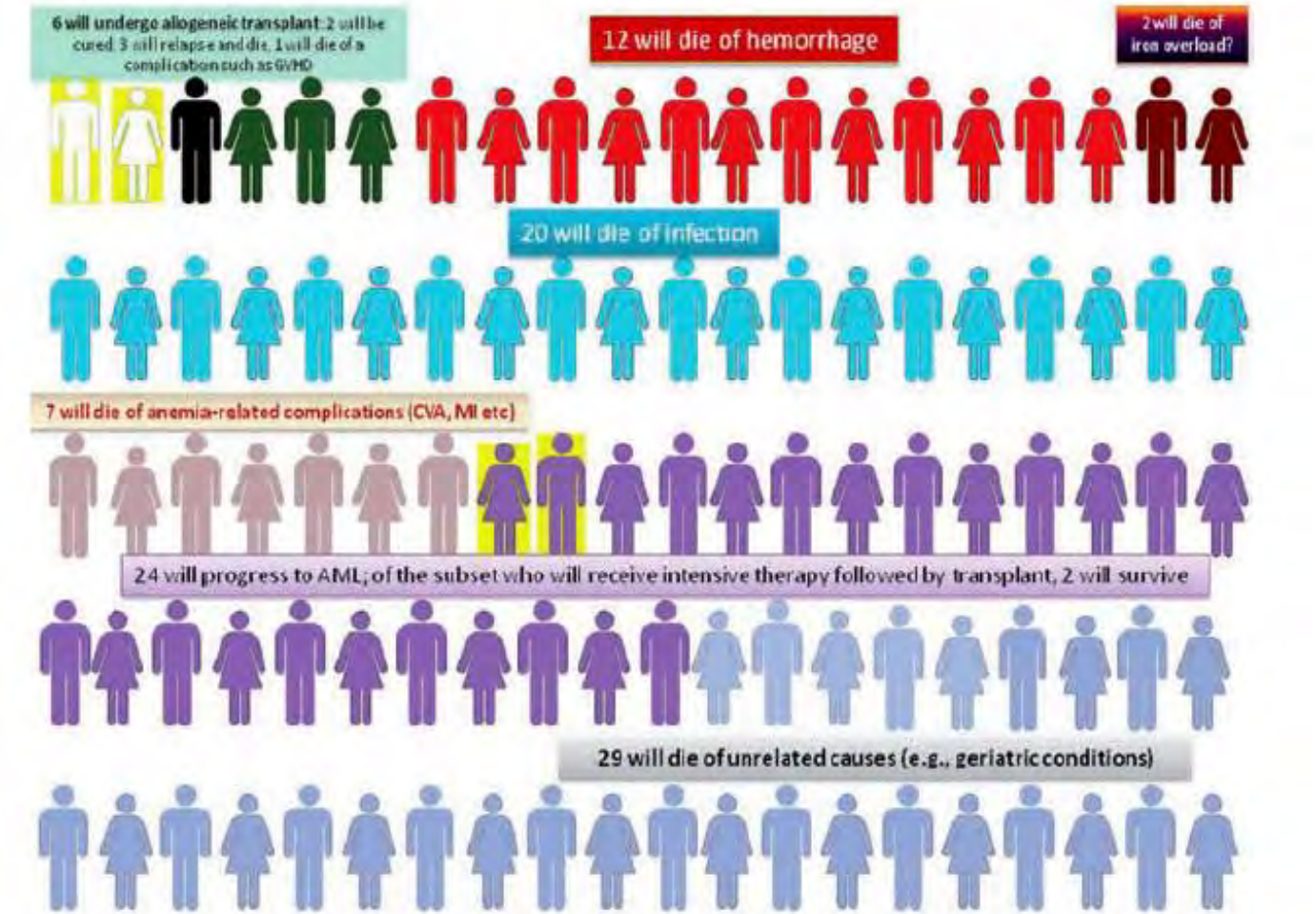


Figure 1. Annual number of HCTs in patients 70 years and older by indication. MPS, myeloproliferative syndrome.

Muffly et al. *Blood* 2017;130:1156-64

Death from MDS



Steensma DP *Leuk Lymph* 2016;57:17-20

My Approach to MDS (and outline of this talk…)

- **Make a diagnosis:** *From cytopenias to MDS.*
  - *Bone marrow biopsy*
  - *Cytogenetics and molecular analysis*
  - *?germline/inherited predisposition*

- **Risk stratification:** *IPSS and beyond.*
  - *IPSS-R and IPSS-M*
  - *Age, comorbidity, fitness*

- **Treatment decisions:** *Define goals and individualize management.*
  - *Define goals*
  - *Supportive versus disease modifying.*
  - *Curative versus non-curative intent*

Thank You: DFCI Adult Leukemia Team

- Richard M. Stone MD
- Daniel J. DeAngelo MD, PhD
- Martha Wadleigh MD
- Jacqueline S. Garcia MD
- Eric S. Winer MD
- Rahul Vedula MD
- Maximilian Stahl MD
- Gregory Abel MD
- Lachelle Weeks MD
- Christopher Reilly MD
- Evan Chen MD
- Andrew Lane MD PhD
- R. Coleman Lindsley MD PhD
- Zuzana Tothova MD PhD
- Mark Murakami MD
- Anthony Letai MD PhD

- Ilene Galinsky NP
- Mary Gerard PA-C
- Theresa Nguyen NP
- Kelly Ling PA-C
- Patrice Osullivan NP

- **DF/HCC Fellows**
- **BWH Housestaff**
- **DFCI BWH Inpatient Oncology PA Team**

Find a specialty you love, a patient population you love caring for, and a team you love being a part of!