Fred Hutch Cancer Center

Myelodysplastic Syndromes

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Disclosures

- None

Objectives

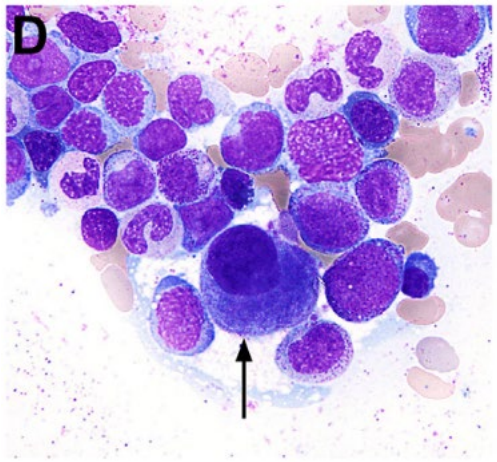
- Review Disease Mechanism and Classification
- Understand Risks and Treatment Endpoints/Goals
- Review Non-Transplant Therapies of Lower and Higher Risk disease
- Role of Transplant

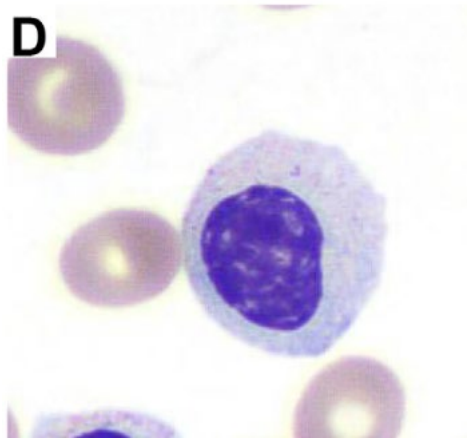
Morphologic findings in MDS

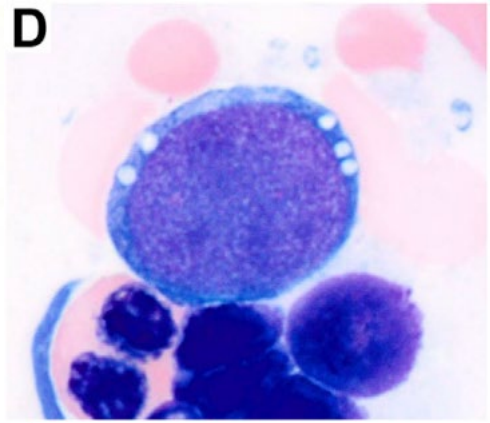
Cytopenia + 10% dysplastic cells within a given lineage are required for a morphologic MDS diagnosis.

Table 2
Features of dysplasia in hematopoietic cell lineages

	Megakaryocyte	Myeloid	Erythroid
Bone marrow biopsy and aspirate smear	Micromegakaryocytes Hypo-/monolobated nuclei Separated nuclear lobes	Hypogranular cytoplasm Pseudo Pelger-Huet (bilobed nuclei) Abnormal nuclear segmentation Clumping of chromatin Macropolycytes	Nuclear budding Internuclear bridging Cytoplasmic vacuolation Megaloblastoid change Ring sideroblasts
Peripheral blood smea	Platelet anisocytosis Giant platelets Abnormal granulation in platelets	Over 4 nuclear projections	Poikilocytosis Basophilic stippling







Definitions of MDS

- Cytopenia (*essential, secondary causes must be excluded*)*
  Persistent neutrophilia, monocytosis, erythrocytosis or thrombocytosis should prompt MDS/MPN dx (except for MDS-del5q)
  Hg < 13g/dL (male) / 12g/dL (female), ANC < 1.8, Plts < 150.
- Dysplasia (10% of cells within any lineage) *or* Genetically Defined Lesions

Myelodysplastic Neoplasm

Genetically Defined

- Del5q
  - *Del5q* alone or
  - *Del5q + 1 other abnormality other than -7/del7q*
- SF3B1 (>15% RS also okay)
- biallelic TP53 (>1 mutation or 1 mut + cnLOH or copy loss)

**AML defining genetic abnormalities excluded (KMT2A, MECOM, or NUP98 rearrangements, and NPM1, CEBPA mut)*

Morphologically Defined

- MDS w low blasts (<5% BM and <2% PB)
- MDS, hypoplastic (BM <2% cellular)
- MDS w increase blasts (MDS-IB)
  - MDS-IB1 (Blasts 5-9% BM or 2-4% PB)
  - MDS-IB2** (Blasts 10-19% BM or 5-19% PB or auer rods)
  - MDS with fibrosis (Blasts 5-19% PB or BM)
  - ** MDS-IB2 = AML/MDS (an AML equivalent)

- EPO, folate/B12, iron studies, TSH, HIV, consider nutritional status (copper) esp in pts with malabsorption, GI surgery (e.g. bypass) or on zinc supplementation.

Arber et al. *Blood* (2016) 127 (20): 2391–2405. Khoury et al. Leukemia 2022; 36: 1703–1719.

WHO and ICC Classifications

- Cytopenia (*essential, secondary causes must be excluded*)*

  Persistent neutrophilia, monocytosis, erythrocytosis or thrombocytosis should prompt MDS/MPN dx (except for MDS-del5q)

  Hg < 13g/dL (male) / 12g/dL (female), ANC < 1.8, Plts < 150.

- Dysplasia (10% of cells within any lineage) *or* Genetically Defined Lesions

WHO 2016[1]	WHO 2022[2]	ICC 2022[3]	Bone Marrow Blasts
	MDS, genetically defined		
MDS-del(5q)	MDS-5q[d]	MDS-del(5q)[d]	<5%
MDS-RS	MDS-*SF3B1*[e]	MDS-*SF3B1*[e,h]	<5%
—	MDS-bi*TP53*[f]	Myeloid neoplasms with m*TP53*[i]	<20%
	MDS, morphologically defined		
MDS-SLD, MDS-MLD	MDS-LB	MDS-NOS[j]	<5%
—	MDS-hypoplastic[g]	—	<5%
MDS-EB1	MDS-IB1	MDS-EB	5%–9%
MDS-EB2	MDS-IB2[c]	MDS/AML[c]	10%–19%
—	MDS with fibrosis	—	5%–19%
AML[c]	**AML[c]**	AML[c]	≥20%[c]

[d] Sole genetic abnormality (or allowable 1 other cytogenetic lesion other than chromosome 7 abnormality).

[e] ≥5% VAF or ≥15% RS only if molecular analysis not available; no del(5q), multiTP53, -7/del(7q), abn(3q), or complex cytogenetics.

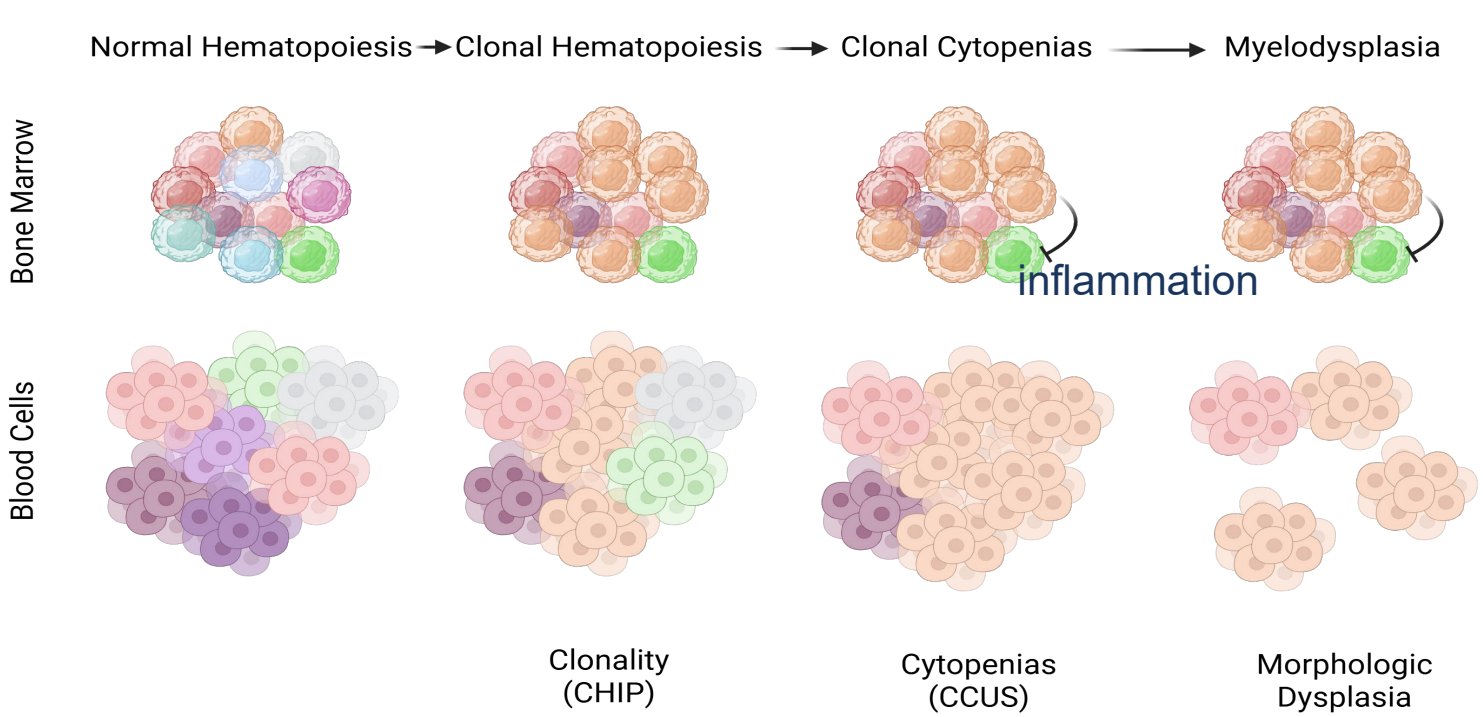
[f ,i] WHO: Biallelic mutation status determined by VAF ≥50%, >1 distinct mutations, TP53 locus deletion or cnLOH or $TP53^{mut}$ + CK.

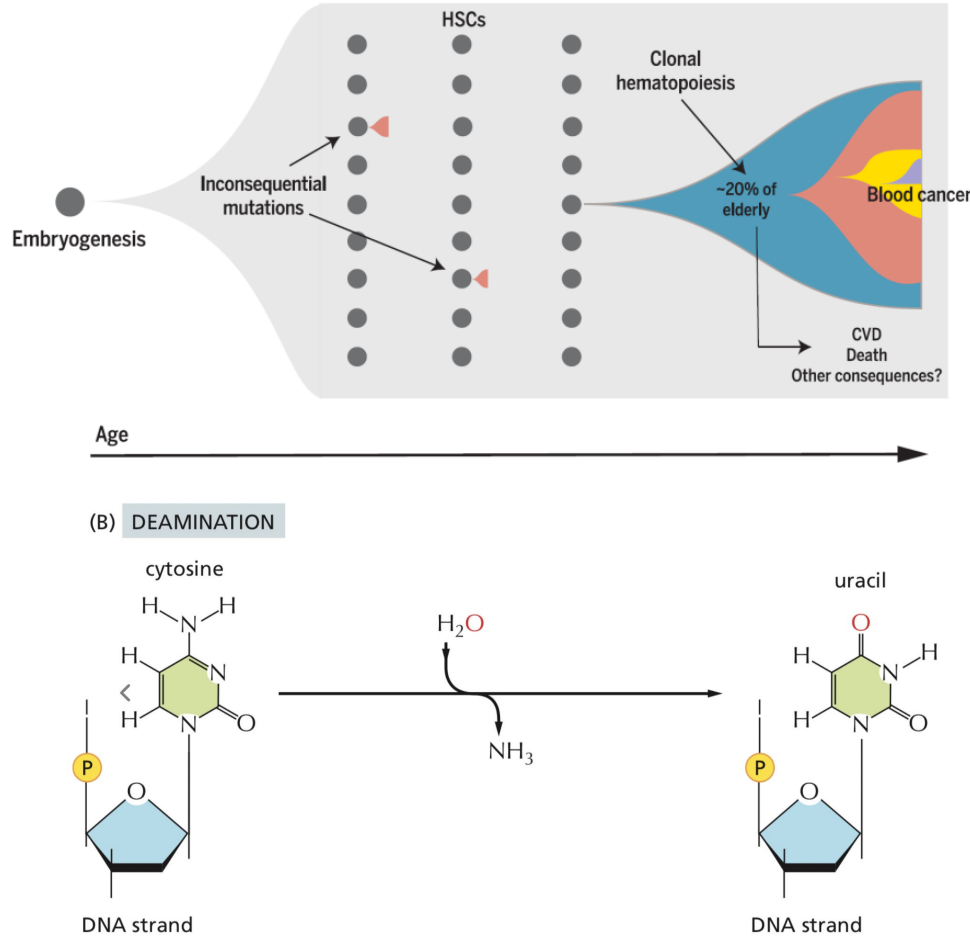
[g] ≤25% bone marrow cellularity, age-adjusted. h No RUNX1 mutation.

* EPO, folate/B12, iron studies, TSH, HIV, consider nutritional status (copper) esp in pts with malabsorption, GI surgery (e.g. bypass) or on zinc supplementation.

Arber et al. *Blood* (2016) 127 (20): 2391–2405. Khoury et al. Leukemia 2022; 36: 1703–1719.

Clonal Hematopoiesis, Cytopenias and Dysplasia



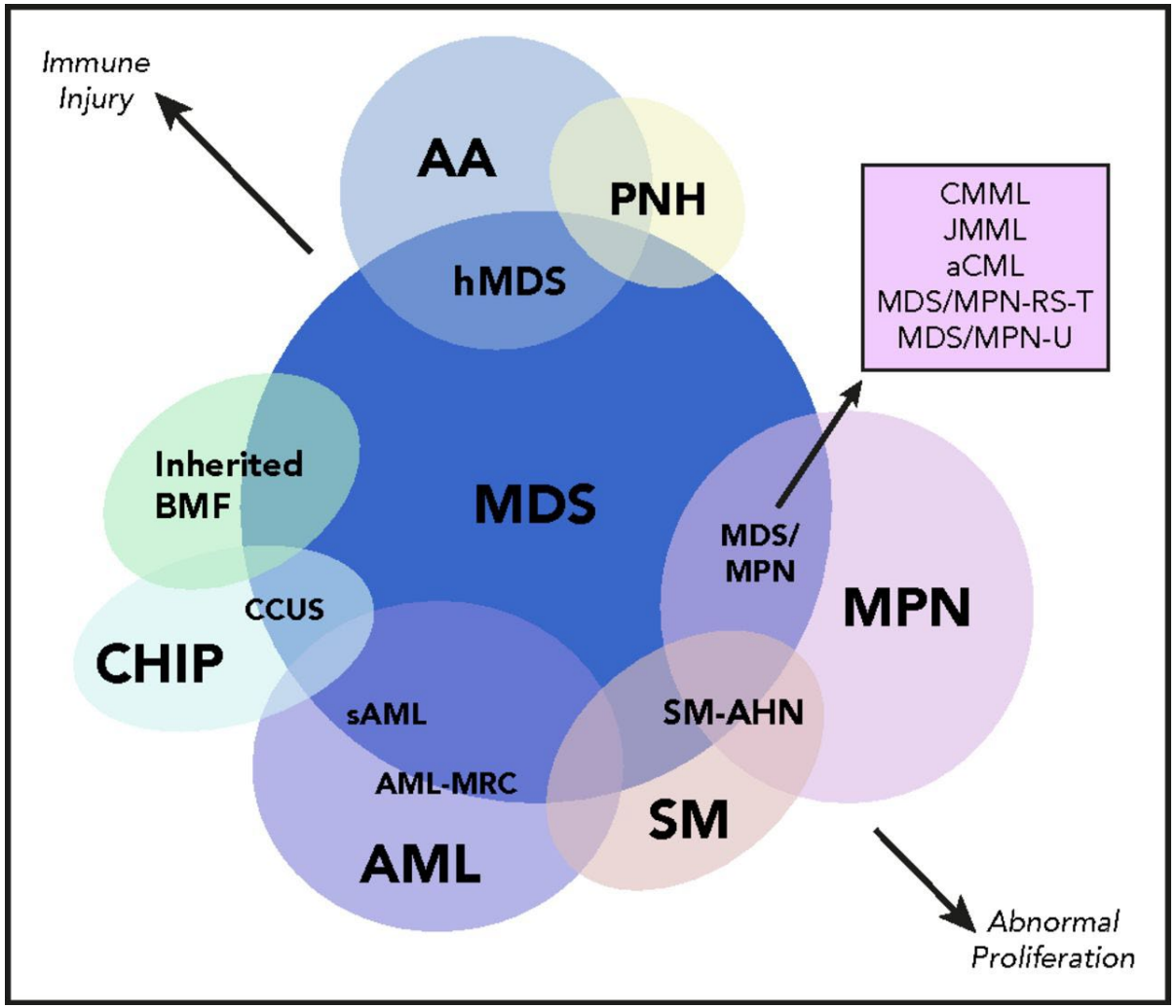


Six genes are recurrently mutated (>10%):

DNMT3a, TET2, ASXL1,
RUNX1, SRSF2, SF3B1

Age related deamination C -> U:
Turns a C/G into A/T

Myeloid disorders with clinical and genetic features shared with MDS



Tiffany N. Tanaka, and Rafael Bejar Blood 2019;133:1086-1095; slide courtesy of J Deeg

Epidemiologic Features of MDS

- Heterogenous group of clonal hematopoietic cell neoplasms characterized by ineffective hematopoiesis, manifested by morphologic dysplasia in hematopoietic cells
- Overall incidence ~5/100000, most common myeloid neoplasm
  - Median age dx 71, M>F
- Characterized by peripheral blood cytopenias and ~1/3 risk transformation AML
- Incorporates immune dysregulation
  – inflammatory symptoms (rash, fatigue, diffuse joint/muscles pain) are common and often improve with treatment
- ***Most patients will die from MDS complications, rather than transformation to AML.***

Seer Data 2008-2012

Case 0

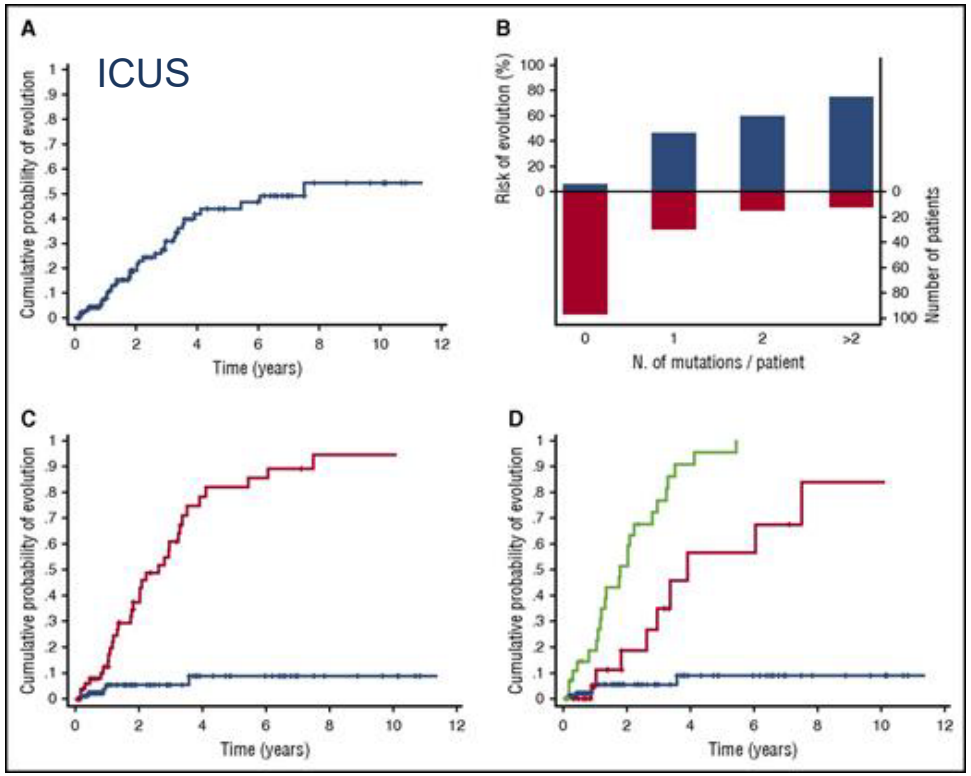
- 62 y/o F presented to her MD for annual checkup.
  A CBC found showed Hgb 10.8, MCV 94, plts 140, wbc 6.4, normal differential. Iron studies, LDH, B12 and folate are normal. Reticulocytes are low.
  BMBx showed hypercellular marrow, no dysplasia. Blasts were 0.5%. Karyotype is 46,XX [20]. MDS FISH panel is normal. NGS testing shows TET2 (VAF 27%) and DNMT3A (VAFs 18%).

- What is the next best step:
  1. Evaluation of anemia and continued monitoring
  2. Transfusion of CMV-safe pRBCs and evaluation of EPO level
  3. Luspatercept
  4. Lenalidomide
  5. Azacitidine

Identification of CCUS at very high risk of progression

- CHIP/CCUS generally has a low risk of progression (high risk ~40% at 10 yrs)

- ***HOWEVER:***
  CCUS + VAF >10% or ≥2 mutations → PPV = 0.86 - 0.88 for subsequent MN
- Spliceosome gene mutations and co-mutation patterns involving *TET2*, *DNMT3A*, or *ASXL1* had a PPV for myeloid neoplasms of 0.86-1
- **Therapy:** best supportive care, consider growth factor therapy, CV risk factor reduction



Red= 1+ mutation, blue 0 mutations

Malcovati et al. Blood (2017) 129 (25): 3371–3378

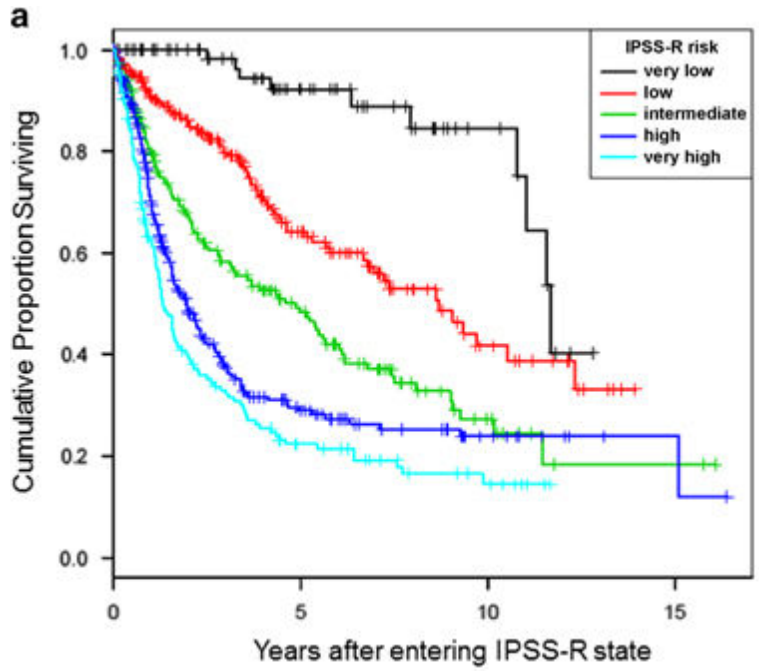
MDS Risk Stratification IPSS-R

REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R)[2]

	Score Value						
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetic[e]	Very good	—	Good	—	Intermediate	Poor	Very poor
Marrow blasts (%)	≤2	—	>2–<5	—	5–10	>10	—
Hemoglobin	≥10	—	8–<10	<8	—	—	—
Platelets	≥100	50–<100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

PROGNOSIS ACCORDING TO IPSS-R RISK SCORE[2]

IPSS-R Risk Category (% IPSS-R pop.)	Overall Score	Median Survival (y) in the Absence of Therapy	25% AML Progression (y) in the Absence of Therapy
VERY LOW (19)	≤1.5	8.8	Not reached
LOW (38)	>1.5–≤3.0	5.3	10.8
INT[3] (20)	>3.0–≤4.5	3	3.2
HIGH (13)	>4.5–≤6.0	1.6	1.4
VERY HIGH (10)	>6.0	0.8	0.7

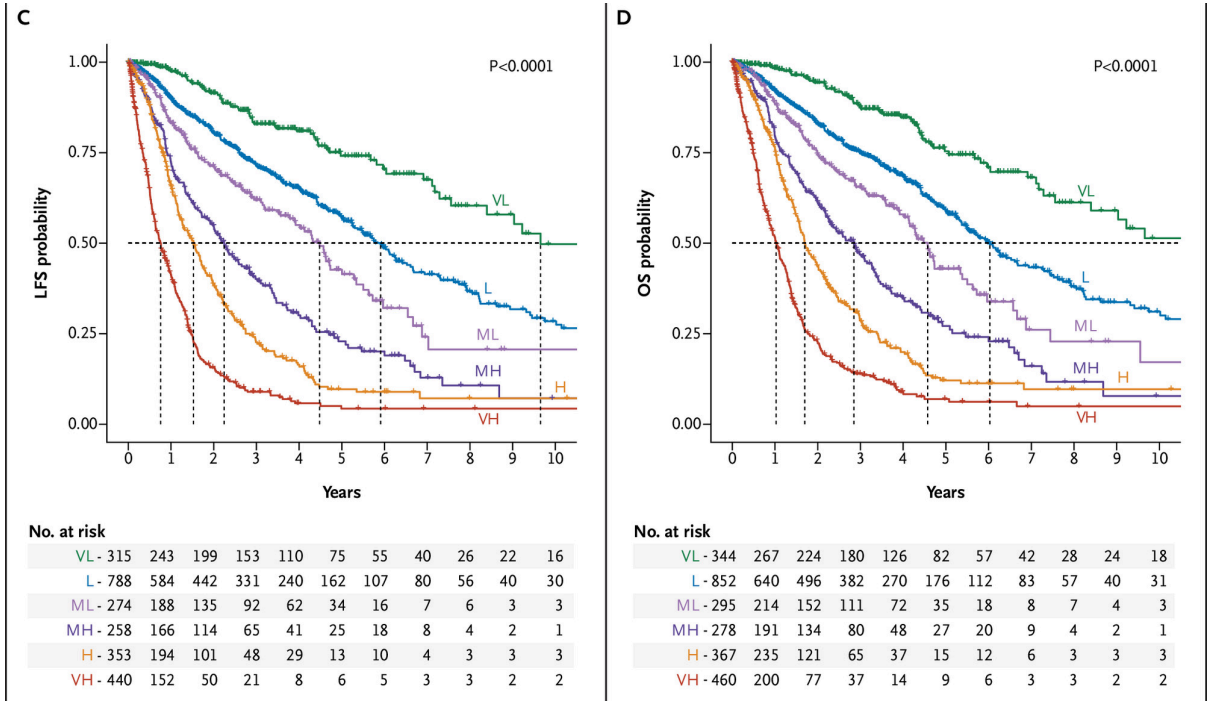


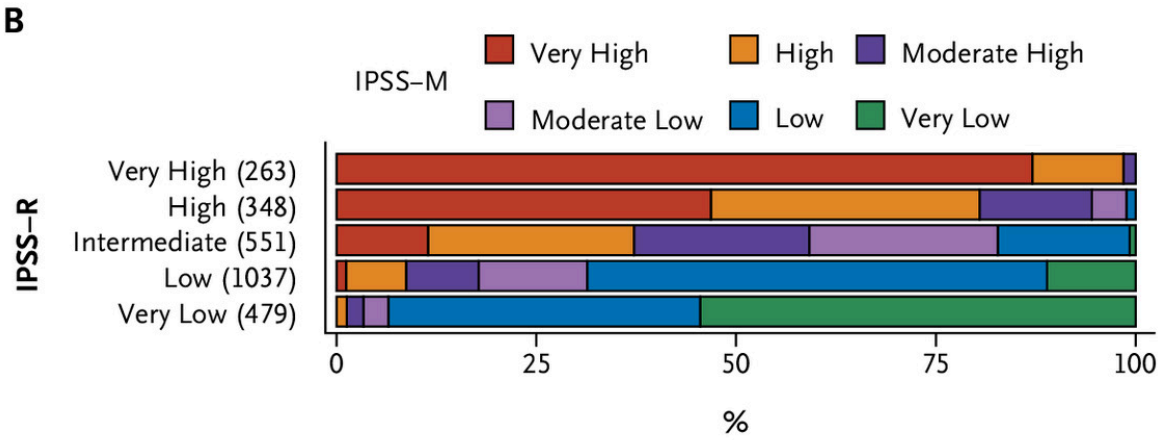
Cytogenetic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

Greenberg et al. Blood 120 (12): 454-65; Schanz J et al, J Clin Oncology 2012; 30:820-829

IPSS-M score now incorporates molecular information

- IPSS-M incorporates 31 gene mutations and TP53 allelic state
- Pts categorized into 6 categories with strong prognostication across endpoints





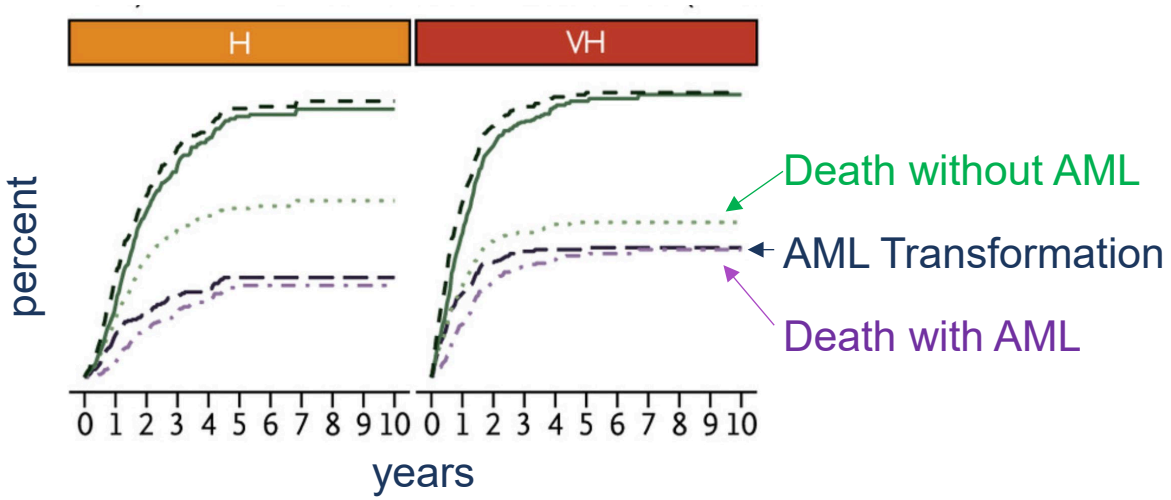
https://mds-risk-model.com/

There was a 5 pt increase in C-index from IPSS-R to IPSS-M across all endpoints

Greenberger al. Blood 2012; 120 (12): 2454-65; Bernard at al. NEJM 2022. 1 (7).

IPSS-M and Mutation Studies

- IPSS-M reassigned 46% of patients (compared to IPSS-R): 74% upstaged, 26% downstaged
- >50% patients from IPSS-R Intermediate category shifted: 18% upstaged to IPSS-M very high
- Median LFS of IPSS-R Intermediate patients re-classified as IPSS-M Very High was 0.75 years vs 6.5 years for those re-classified as IPSS-M Low.
- Works for therapy-related MDS



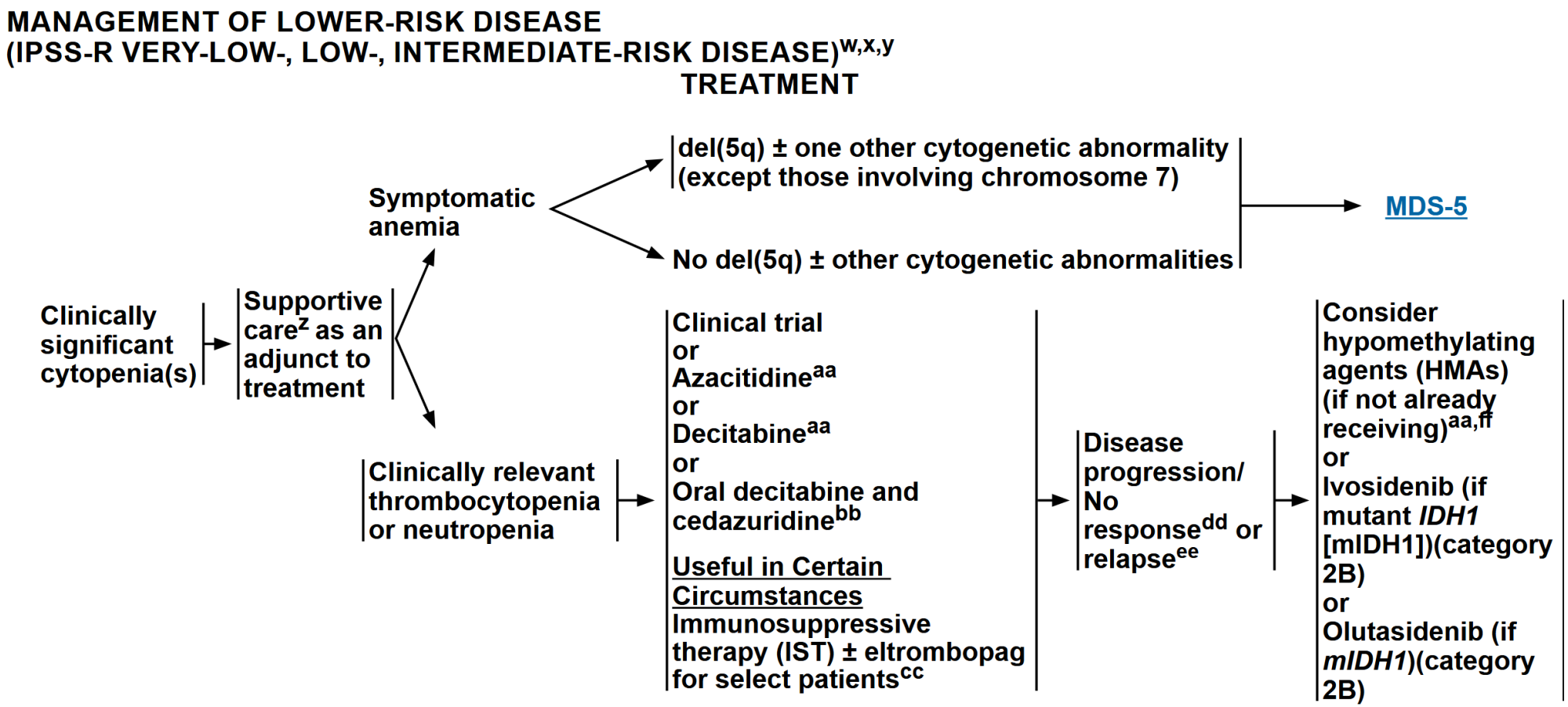
Even among the 'VERY HIGH' group, "*death without AML*" was more frequent than "*death with AML.*"

Underscores the relative risk of marrow dysfunction vs risk of AML progression.

Bernard at al. NEJM 2022. 1 (7).

MDS Therapy

Management of Lower Risk MDS



Treatment goals

- **Lower risk:**
  - Improve cytopenias– typically hemoglobin levels
  - Transfusion independence
  - Maximize QOL

- **Higher risk**
  - Improve cytopenias
  - Delay progression to AML
  - Cure disease→ allogeneic stem cell transplant

sEPO and IPSS predict rEPO response

Table 1. Baseline patient characteristics

	n = 456	Patients, %	Erythroid response (IWG 2006 criteria)	Univariate analysis *P*
EPO, mU/mL				
≤100	306	67	75	
>100	150	33	45	<.0002
≤200	393	86	75	
>200	63	13	31	<.0001

sEPO is widely available and is effective for patients without elevated sEPO levels.

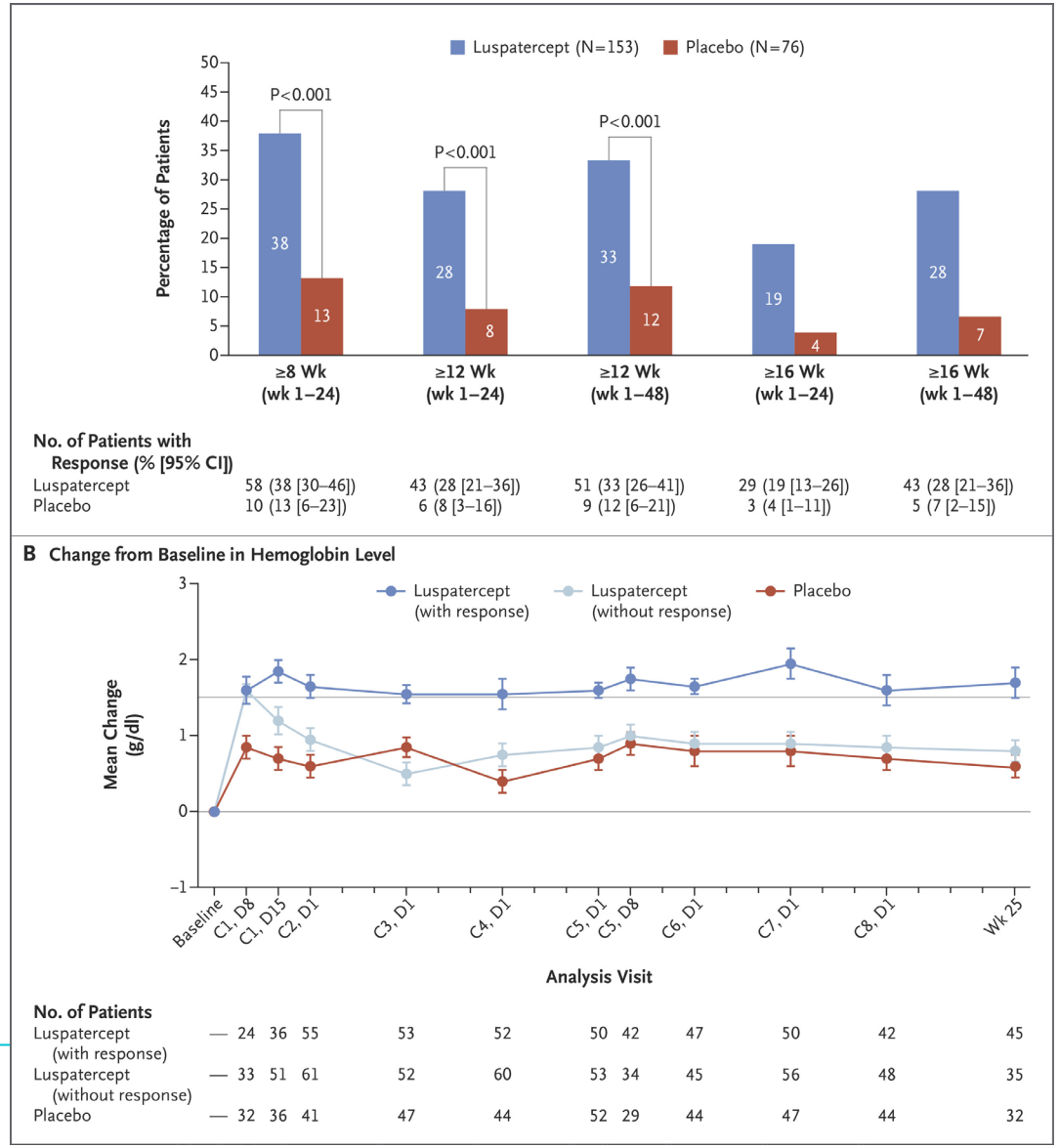
EPO is associated with higher thromboembolic risks (OR ~1.5) in the general cancer pop, but not in MDS.

NCCN classifies EPO levels using a cutoff of 500 mU/mL

1. Smith SW, Sato M, Gore SD, Baer MR, Ke X, McNally D, et al. Erythropoiesis-stimulating agents are not associated with increased risk of thrombosis in patients with myelodysplastic syndromes. Haematologica. 2012 Jan 1;97(1):15–20.

Luspatercept for LR-MDS with RS (MDS-SF3B1, *MEDALIST*)

- Adults (n = 229) w transfusion dep MDS-RS (93% SF3B1+)
  Relapsed/refractory to ESAs *OR*
  Unlikely to respond to ESA (sEPO > 200)
- Randomized Luspatercept vs Placebo (2:1)
- Endpoint: Transfusion independence 8wk, 12wk
- Median Age 71, 63% male
- IPSSR = very low (10%), Low (72%), Int (17%)
- Baseline EPO:
  - <100 = 36%
  - 100-200 = 24%
  - 200 – 500 = 25%
  - >500 = 14%
- Transfusion burden 5u/8wk



Fenaux P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. NEJM. 2020 Jan 9;382(2):140–51.

Lenalidomide for MDS w del5q (MDS-003)

- Adults (n = 148) w transfusion dep MDS-del5q
  Exclusions: ANC < 500, plts < 50k/uL
  or therapy related-MDS
- Single arm study, dose exploration
- Endpoint: Transfusion independence 8wk, 12wk
- Median Age 71, 34% male, 73% prior EPO
- IPSSR = Low (37%), Int 1 (44%), Int 2/High (5%)
- Mod Neutropenia 30%, Thrombocytopenia 19%

Table 2. Erythroid Response to Lenalidomide.

Variable	Continuous Daily Dosing (N=102)*	21-Day Dosing (N=46)*	All Patients (N=148)
Erythroid response — no. (%)			
Transfusion independence	71 (70)	28 (61)	99 (67)
95% CI			59–74
≥50% decrease in no. of transfusions	8 (8)	5 (11)	13 (9)
95% CI			5–15
Total transfusion response	79 (77)	33 (72)	112 (76)
95% CI			68–82
Time to response — wk			
Median	4.7	4.3	4.6
Range	1–34	1–49	1–49
Hemoglobin — g/dl			
Baseline†			
Median	7.7	8.0	7.8
Range	5.3–10.4	5.6–10.3	5.3–10.4
Response‡			
Median	13.4	13.5	13.4
Range	9.2–18.6	9.3–16.9	9.2–18.6
Increase			
Median	5.4	5.4	5.4
Range	2.2–11.4	1.1–9.1	1.1–11.4

* The daily dose was 10 mg.
† The baseline hemoglobin concentration was the minimum value during the baseline period.
‡ The response hemoglobin concentration was the maximum value during the transfusion-independent response period.

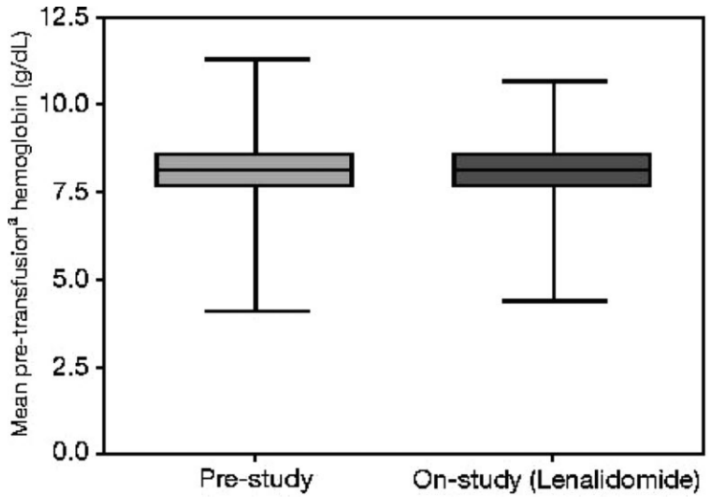
List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion. New England Journal of Medicine. 2006 Oct 5;355(14):1456–65.

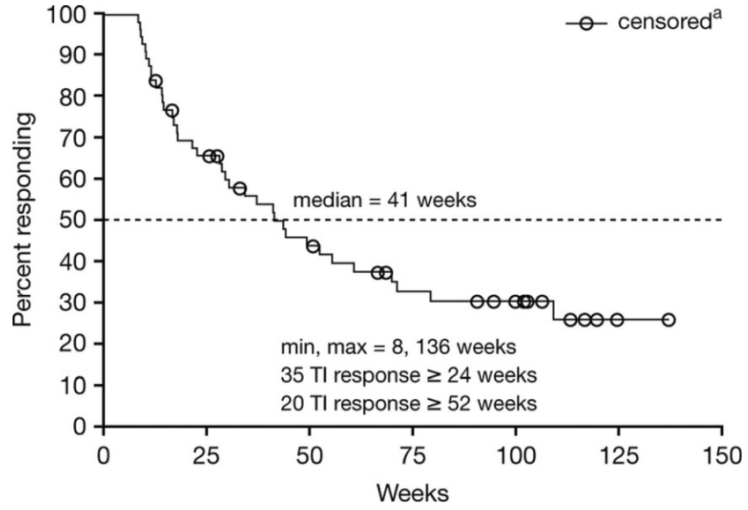
Lenalidomide for MDS w/o del5q (MDS-002; *Not Approved*)

- Adults (n = 21) w transfusion dep non-MDS-del5q
  Exclusions: del5q, ANC < 500, plts < 50k/uL
  or therapy related-MDS
- Single arm, Phase II study
- Endpoint: Transfusion independence 8wk, 12wk
- Median Age 72, 65% male
- IPSSR = Low (43%), Int 1 (36%), Int 2/High (4%)

Table 4. Modified IWG 2000 erythroid response to lenalidomide

Variable	Continuous daily dosing, n = 100*
Erythroid response, no (%) [95% CI]	
Transfusion independence and 10 g/L Hb or more increase	27 (27)
50% or greater decrease in no. of transfusions	15 (15)
Total transfusion response	42 (42)
Median time to transfusion independence, wk (range)	7.4 (1-24)
Hemoglobin, g/L	
Baseline, median (range)†	79 (62-97)
Response, median (range)‡	116 (91-168)
Increase, median (range)	33 (15-92)

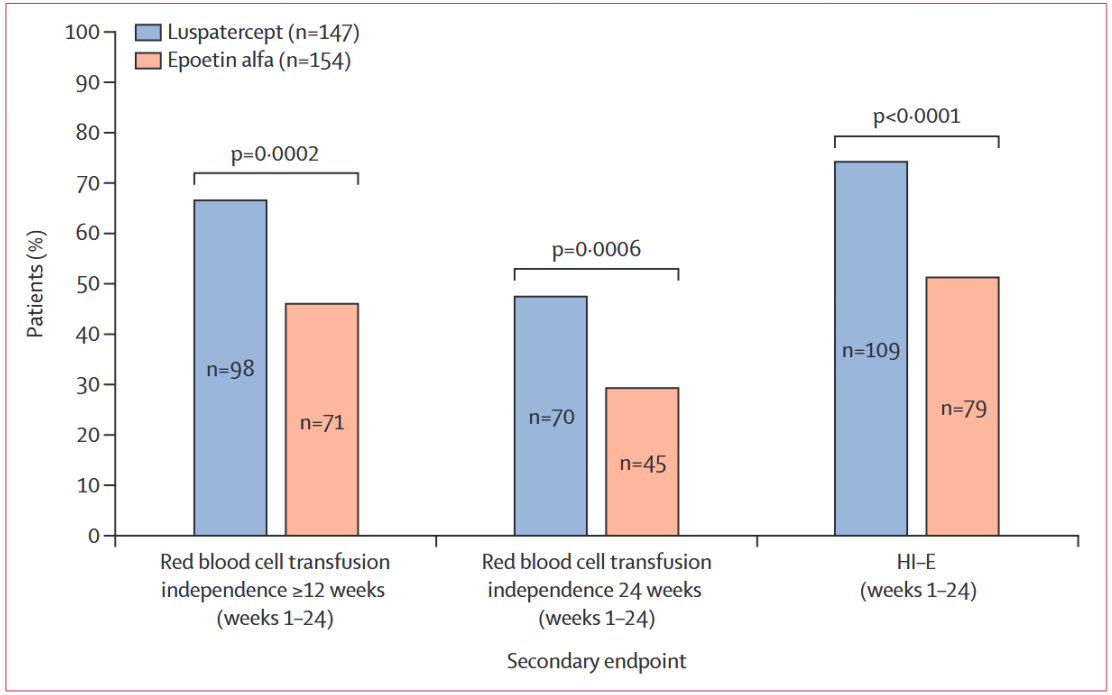




Raza A, Reeves JA, Feldman EJ, Dewald GW, Bennett JM, Deeg HJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1–risk myelodysplastic syndromes with karyotypes other than deletion 5q. Blood. 2008 Jan 1;111(1):86–93.

Luspatercept vs EPO for transfusion-dependent MDS (*COMMANDS*)

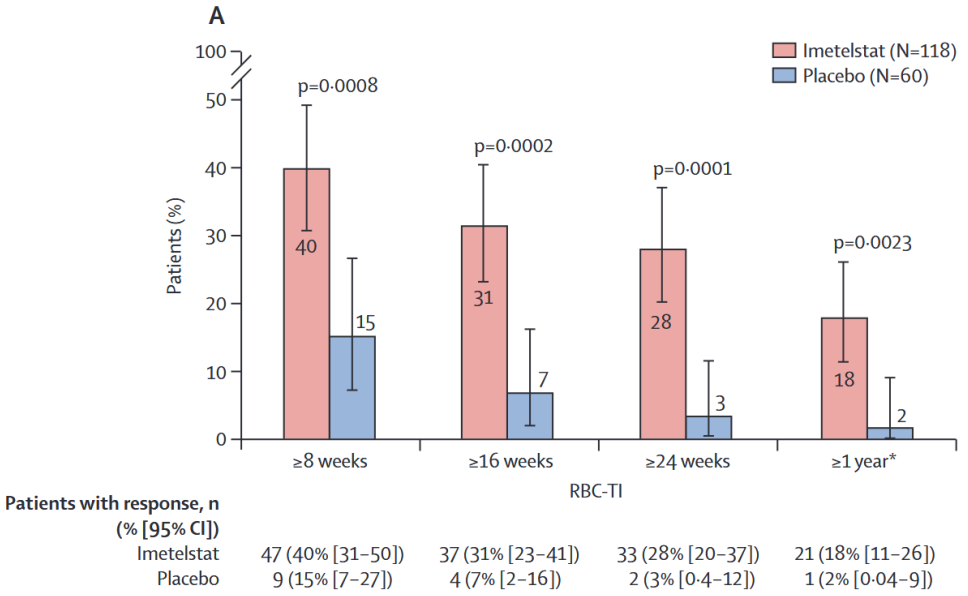
- Adults (n = 356) ESA naïve w transfusion dep MDS & EPO < 500
  Prior ESA, IMiD, HMAs, del5q excluded
- Randomized Luspatercept vs epoetin-alpha (1:1)
- Stratifications:
  Transfusion burden, epo level (200 cutoff), RS+/-
- Endpoint: transfusion independence 8wk, 12wk
- Median Age 74, 56% male
- IPSSR = very low (10%), Low (72%), Int (17%)
- Baseline EPO: median 84.5 (IQR 40.9 – 179.1)



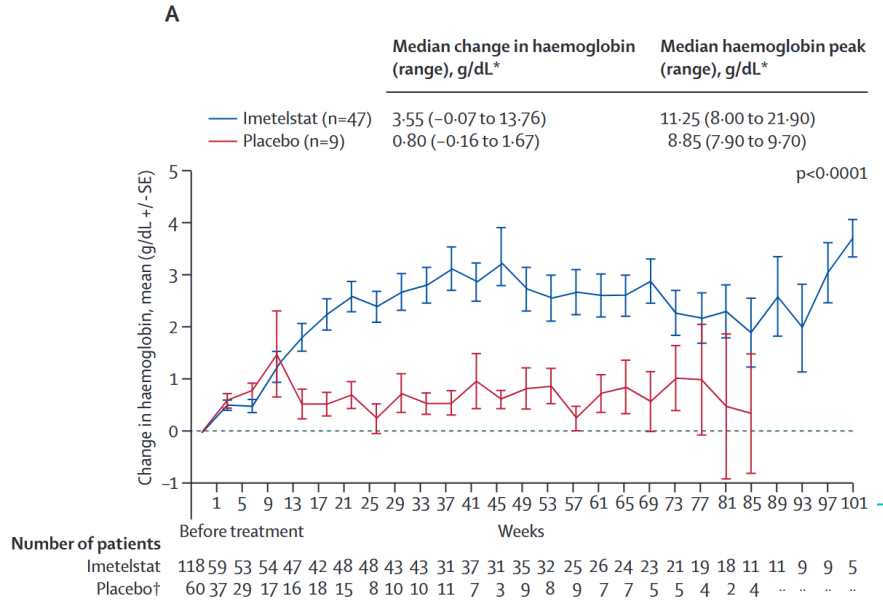
Platzbecker U, Della Porta MG, Santini V, Zeidan AM, Komrokji RS, Shortt J, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. The Lancet. 2023 July 29;402(10399):373–85.

Imetelstat for ESA failure in LR-MDS (*IMerge*)

- Adults (n = 178) LR-MDS and ESA r/r or ineligible
- Randomized Imetelstat vs placebo (2:1)
- Prior IMiD, HMA or del(5q) were excluded
- Stratifications:
  Transfusion burden, epo level (200 cutoff), RS+/-
- Endpoint: transfusion independence 8wk, 12wk
- Median Age 72, 64% male
- Ring Sideroblasts: (62%)
- IPSSR = very low (3%), Low (75%), Int (14%)
- Baseline EPO > 500: 22% (Imetelstat) vs 37% (placebo)



Patients with response, n (% [95% CI])	≥8 weeks	≥16 weeks	≥24 weeks	≥1 year*
Imetelstat	47 (40% [31–50])	37 (31% [23–41])	33 (28% [20–37])	21 (18% [11–26])
Placebo	9 (15% [7–27])	4 (7% [2–16])	2 (3% [0·4–12])	1 (2% [0·04–9])



Platzbecker U, Santini V, Fenaux P, Sekeres MA, Savona MR, Madanat YF, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2024 Jan 20;403(10423):249–60.

Low Dose HMA for LR-MDS

- Adults (n = 113) w Low or Int1 IPSS MDS or CMML
- Randomized (1:1):
  decitabine 20mg/m2 vs azacitidine 75mg/m2
  d1-3 of 28-day cycles
- Endpoint: OS, EFS, DOR (median followup 68mo)
- Prior EPO/GCSF (18%) or Len (4%) allowed.
- Baseline IPSSR:
  - V. Low (12%), Low (36%), Int (30%), High (20%)

Table 2. Response.

All Responses — no. (%)	Overall (N=113)	Decitabine (N=73)	Azacitidine (N=40)
Overall response	68 (60)	49 (67)	19 (48)
Complete response	40 (36)	26 (36)	14 (35)
Marrow complete response	10 (9)	8 (11)*	2 (5)
Hematological improvement	20 (18)	17 (23)*	3 (8)
Stable disease	39 (35)	21 (29)	18 (45)
Progressive disease	6 (5)	3 (4)	3 (8)

* Two patients were determined as having both marrow complete response and hematological improvement.

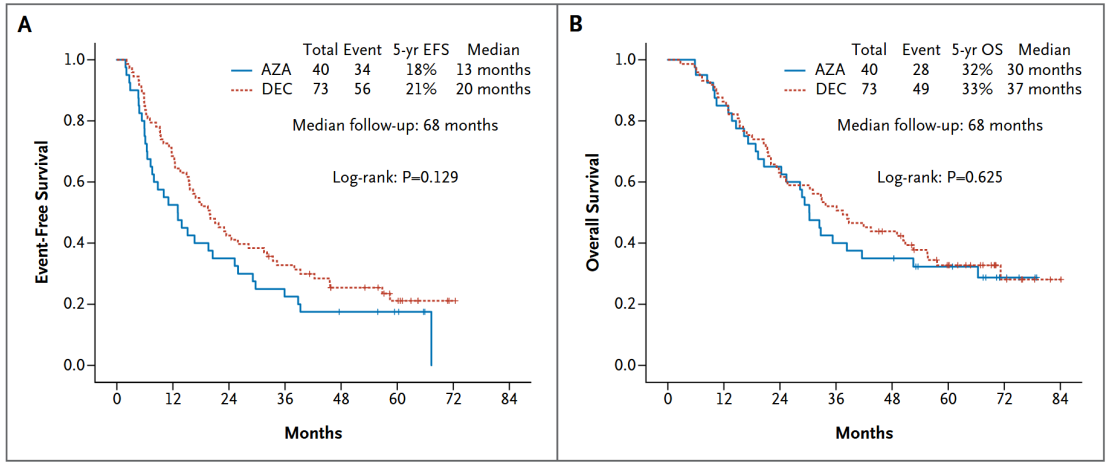
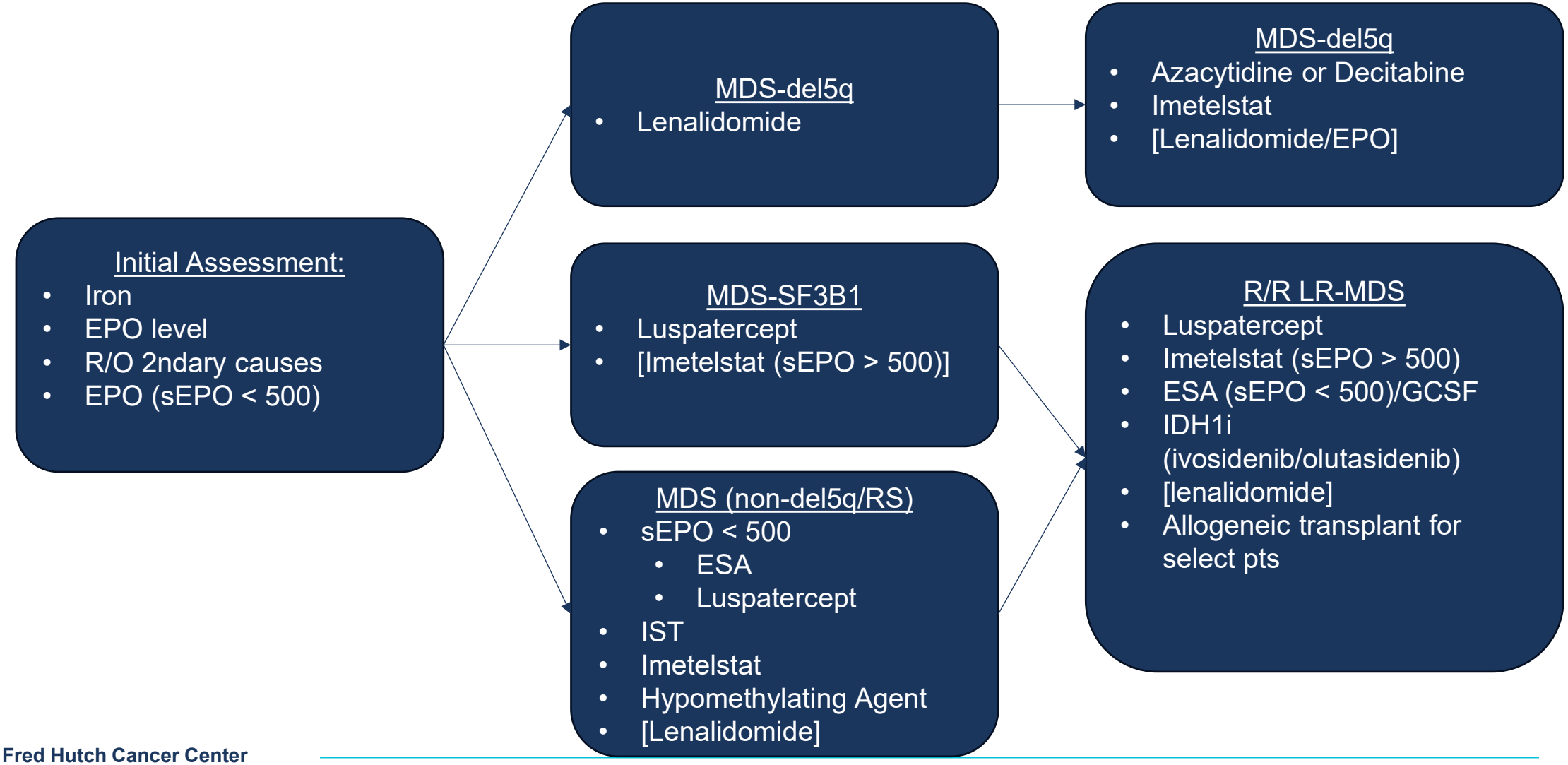


Figure 1. Survival by Therapy Event-Free Survival (Panel A) and Overall Survival (Panel B).

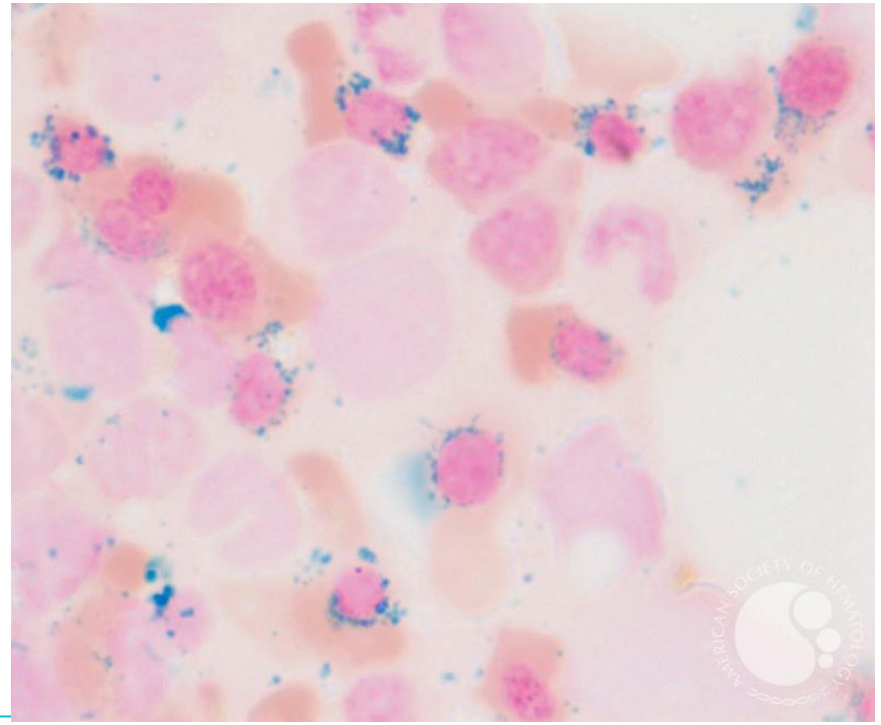
Sasaki K, Jabbour E, Montalban-Bravo G, Darbaniyan F, Do KA, Class C, et al. Low-Dose Decitabine versus Low-Dose Azacitidine in Lower-Risk MDS. NEJM Evidence. 2022 Sept 27;1(10):EVIDoa2200034.

Treatment of anemia in LR-MDS



Case 1

- A 69-year-old man presents with fatigue
- CBC notable for white blood cell count (WBC) 4.8 K/uL, hemoglobin (Hgb) 8.9 g/dL, MCV 100, platelets (plts) 156 k/μL, an absolute neutrophil counts (ANC) 2.5 K/uL, and no circulating blasts
- Studies for iron, folate, B12, copper are normal, sEPO is 120 mU/L.
- Bone marrow exam shows unilineage erythroid dysplasia without increased myeloid blasts, karyotype is 46XY[20]
- Molecular profile shows an SF3B1 mutation, iron stain is shown.



- What is the next best step:
    1. Evaluation of anemia and continued monitoring
    2. Transfusion of CMV-safe pRBCs & darbopoetin
    3. Luspatercept
    4. Lenalidomide
    5. Azacitidine

Naeim F et al. Atlas of Hematopathology. *Morphology, Immunophenotype, Cytogenetics, and Molecular Approaches*. 2013

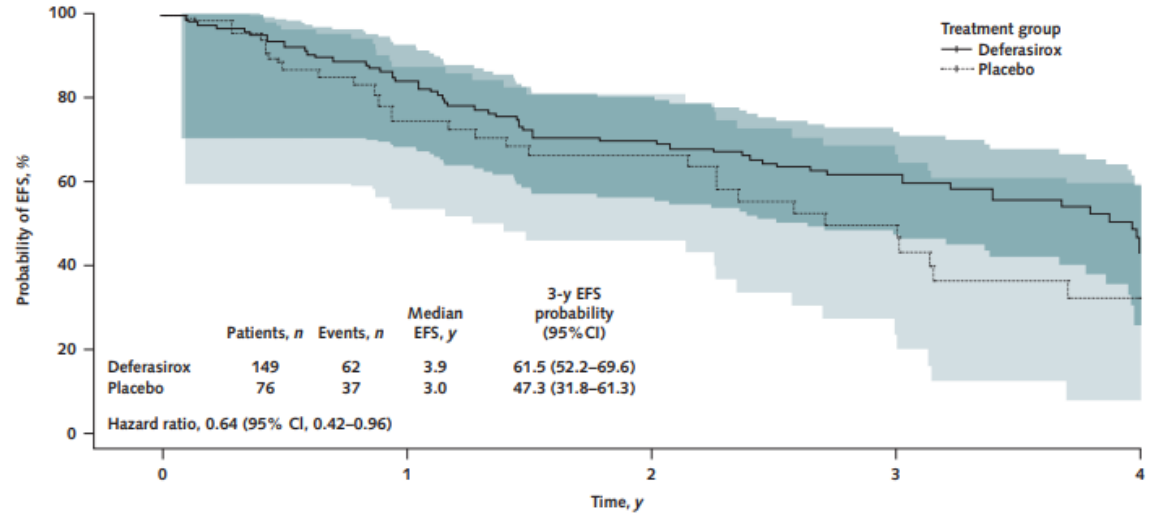
Case 2

- Patient #1 responded to darbepoetin with increase in Hgb about 2 grams
- 18 months later however his hemoglobin drifted back down and he started requiring transfusions
- ANC remains >1.5 K/uL and platelets >100 k/μL
- Next step?
- **Luspatercept-**
  - 2020 – approved for treatment of anemia in very low, low and intermediate risk MDS and MDS/MPN-RS-T for treatment **of anemia failing an ESA** and requiring ≥2 RBC units over 8 weeks
  - 2023- approved for patients **not previously failing ESA**

Iron chelation can improve outcomes in MDS

- **TELESTO study:** randomized, double-blind placebo-controlled study comparing iron chelation with deferasirox (Jadenu) to placebo in low/int-1 risk MDS patients with serum ferritin >1000
- Primary end point EFS: nonfatal event (related to cardiac or liver dysfunction and transformation to AML) or death
- Median EFS was longer with deferasirox versus placebo (3.9 years vs. 3.0 years); HR=0.64
- Some data that chelation can improve the marrow environment and therefore hematopoiesis

Figure 2. Kaplan-Meier curve of EFS, by treatment, with 95% Hall-Wellner bands.



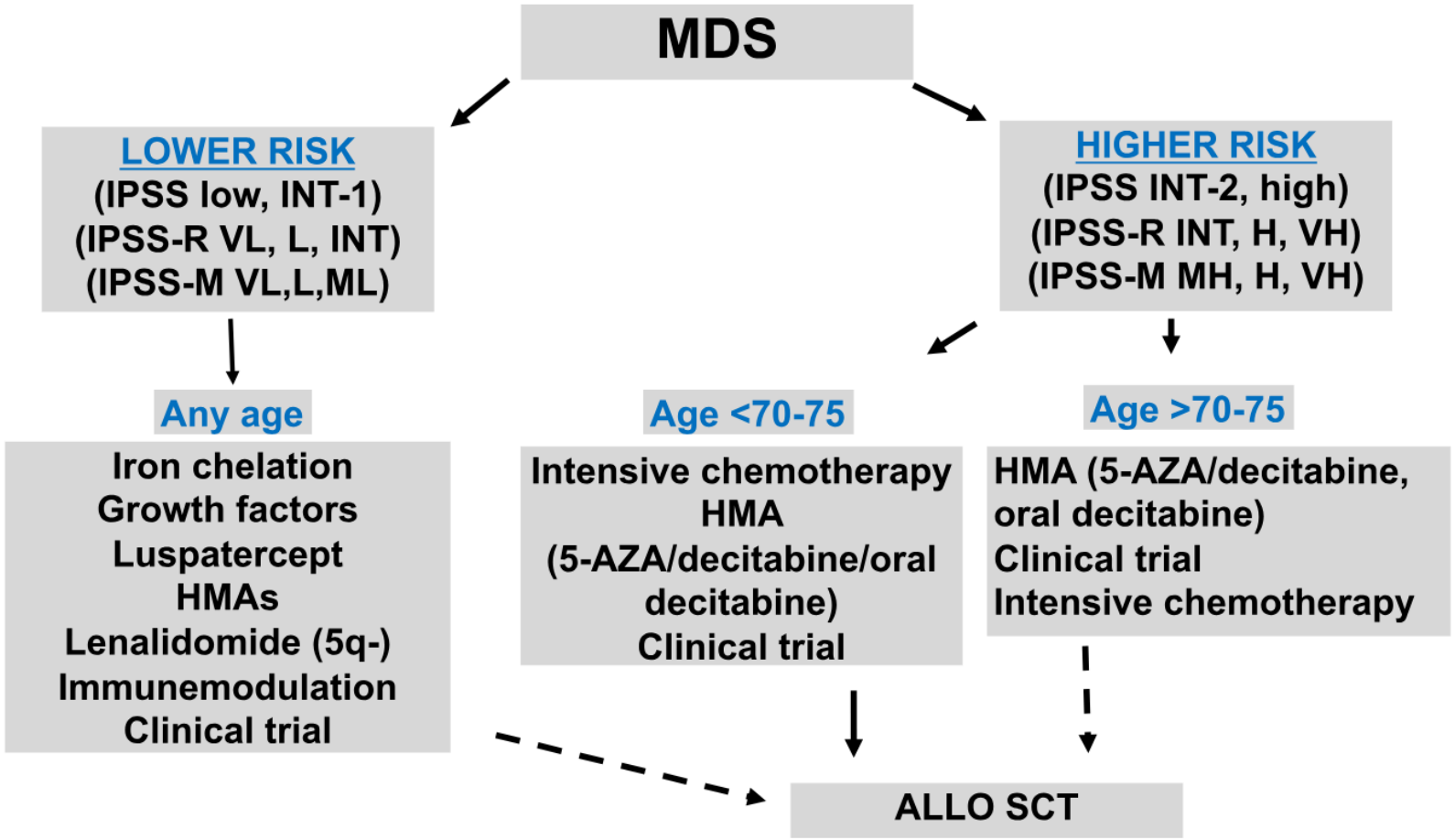
Angelucci et al. Ann Inntern Med 2020; 172 (8): 513-522

Less common scenarios in lower-risk MDS

- **Immunosuppression sometimes used (ATG +cyclosporine+/- steroids):**
  - Most often used for ”hypoplastic MDS” more likely due to immune related hematopoietic suppression
  - Features associated with increased likelihood of responding to IST: age <60 years with ≤5 percent blasts, hypocellular bone marrow, paroxysmal nocturnal hemoglobinuria (PNH)-positive clones, or *STAT3*-mutant T cell clones, HLA-DR15 positive, shorter duration RBC dependence
  - Can lead to hematologic response in ~30% but does not seem to improve survival

Fenaux et al. Blood 2011; 118: 3765; List et al. NEJM 2006; 355: 1456.
Sloand et al JCO 2008; 26: 2505. Lim et al Leukemia 2007; 21: 1436. Komrokji et al. Haematologic 2014; 99: 1176

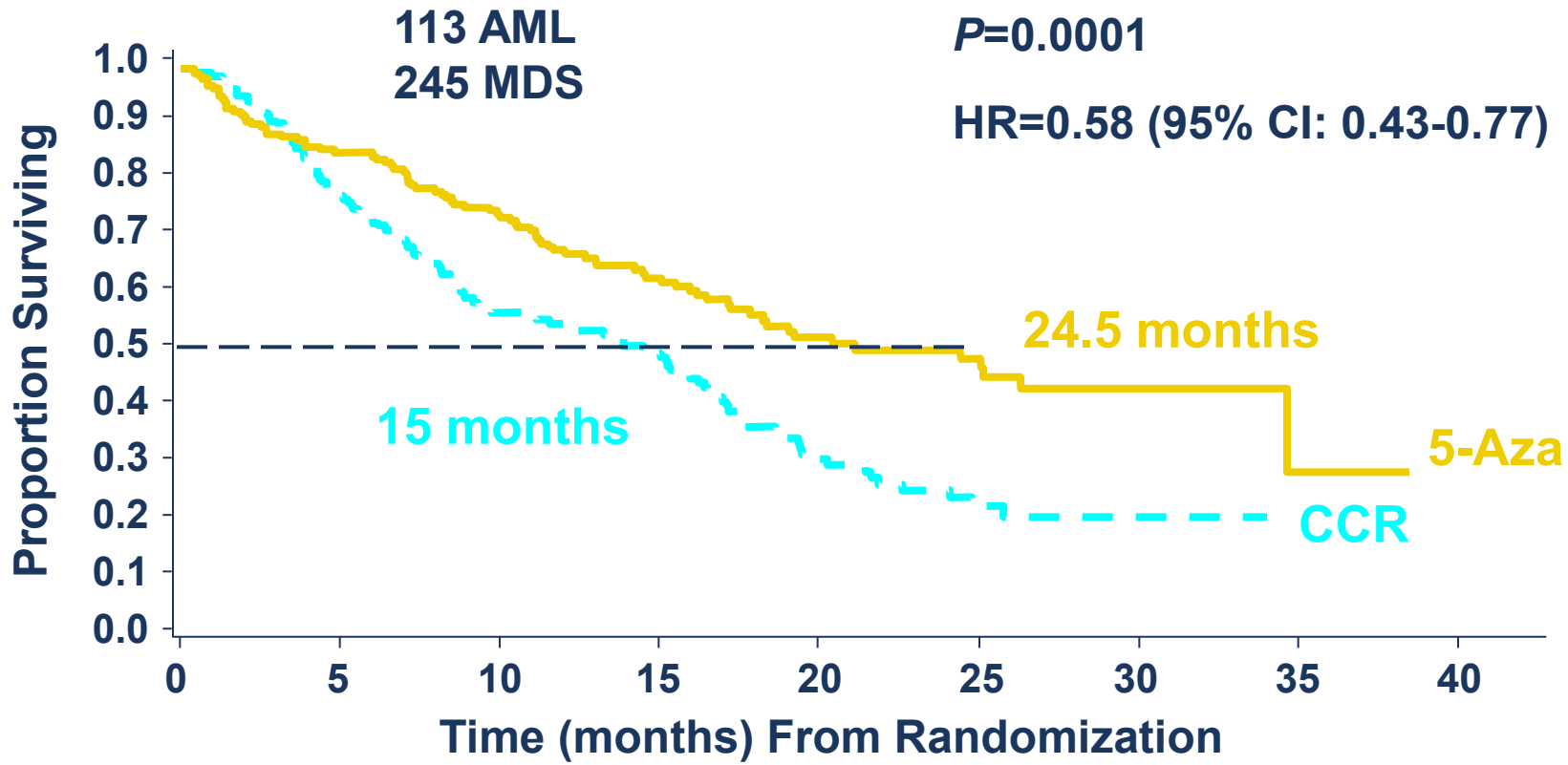
Proposed treatment algorithm for patients with MDS 2023



Garcia-Manero G. Myelodysplastic syndromes: 2023 update on diagnosis, risk-stratification, and management. American Journal of Hematology. 2023;98(8):1307–25.

Azacitidine leads to survival benefit in MDS

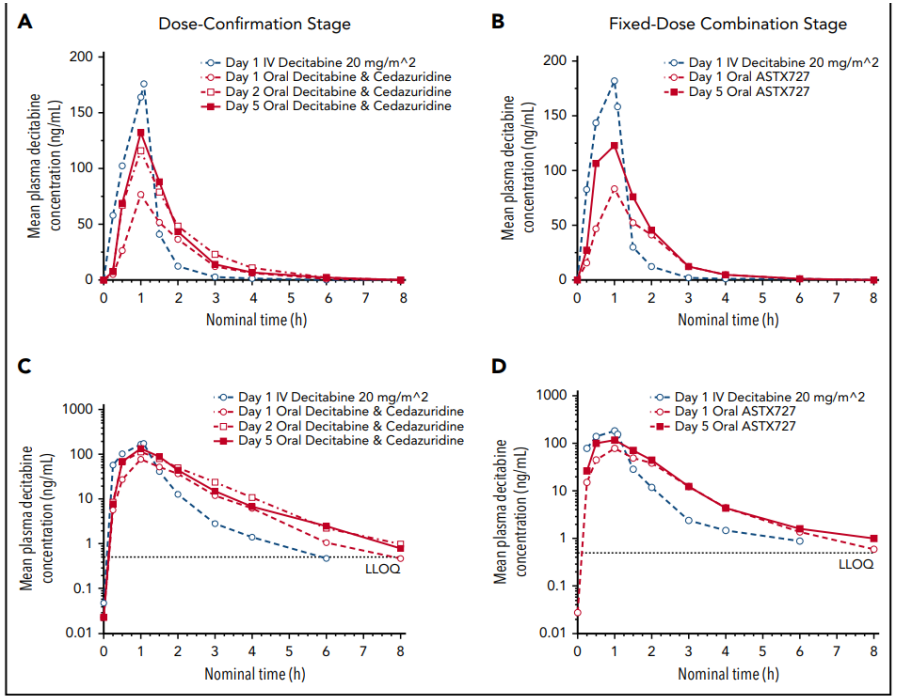
Phase 3 open label trial of Int2 or HR-MDS.
Active comparator was pre-selected for randomization vs aza: BSC (222), LDAC (94), or intensive chemo (42)



Fenaux et al. Lancet Oncology. 2009;10:223-32

Inqovi (oral decitabine and cedazuridine)

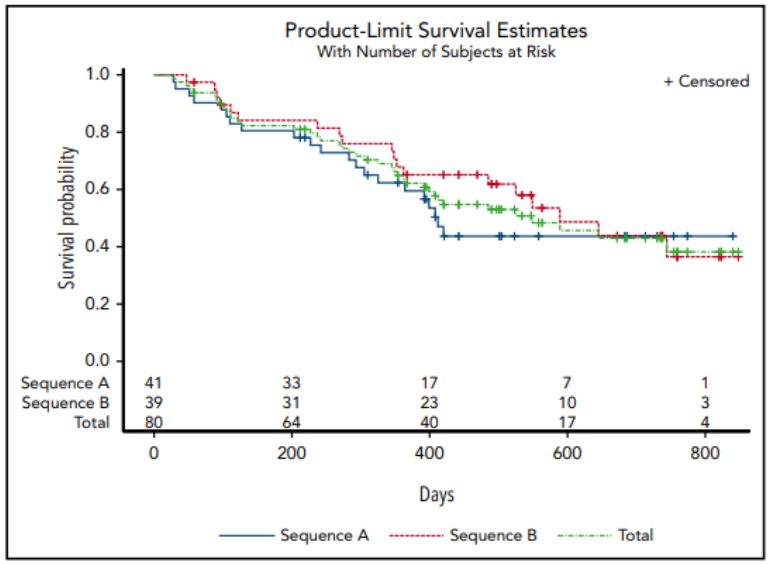
- Oral decitabine/AZA bioavailability limited by rapid inactivation by cytidine deaminase (CDA) in GI tract
- Cedazuridine is a CDA inhibitor
- 80 adults with int-1/2/high-risk MDS or CMML were randomized 1:1 to receive oral cedazuridine/decitabine or IV decitabine
- All patients received cedazuridine/decitabine cycle 3+
- Primary endpoint : mean decitabine AUC systemic exposure



gure 2. Mean decitabine plasma concentrations-time profiles following single and multiple oral doses of cedazuridine/decitabine, and following single IV infusion of citabine during dose confirmation and fixed-dose combination stages. (A-B) Linear and (C-D) semilogarithmic plots are shown. LLOQ, lower limit of quantitation.

Garcia-Manero et al. Blood 2020; 136 (6): 674-683.

Inqovi (decitabine and cedazuridine)



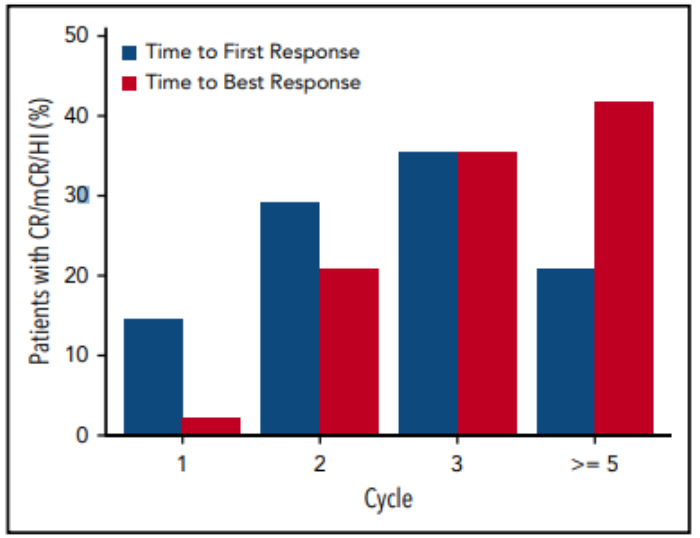


Figure 3. Time to first response and time to best response by cycle (N = 80). HI, hematologic improvement; mCR, marrow complete response.

21% of patients achieving a best response of CR with a median duration of 13.3 months. ORR 60%

FDA approval for untreated/treated MDS (IPSS int risk and higher) and CMML in 2020

Inqovi ≠ Onureg (oral azacitidine or CC-486)→ approved for AML maintenance, higher toxicity especially GI

Garcia-Manero et al. Blood 2020; 136 (6): 674-683.

Transplant

Case 4

- 57 yo otherwise healthy F presented with LUQ pain
- CBC showed pancytopenia with hemoglobin 6.6 and platelets 60, wbc 1.45 with ANC 0.39
- CT abdomen showed no abnormalities or splenomegaly
- BM bx: hypercellular 60-70% with dyspoietic erythroid hyperplasia. Flow and morph with ~ 5-10% blasts and was felt to be consistent with MDS-EB1 with erythroid predominance. Cytogenetics were very complex with multiple abnormalities including a monosomy 5, a monosomy 7, a monosomy 18
- NGS testing showed two TP53 mutations: VAF of 31%, and 34%

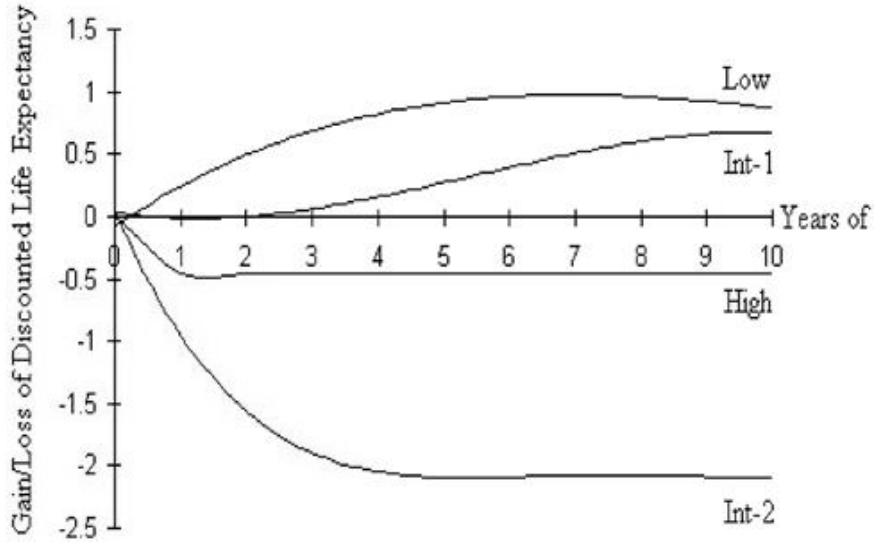
❖ MDS with bi-allelic TP inactivation

❖ IPSS-M very high risk; median survival 1-year, LFS survival 0.76 yrs

Goldilocks: when to transplant in MDS?

- Balance risks of cytopenias, iron overload, progression to AML vs. morbidity and mortality of transplant, balance QOL
- Retrospective study of ~1000 MDS patients analyzed 3 possible timings of transplant:

  1) At Diagnosis 2) At AML transformation 3) Fixed time after diagnosis

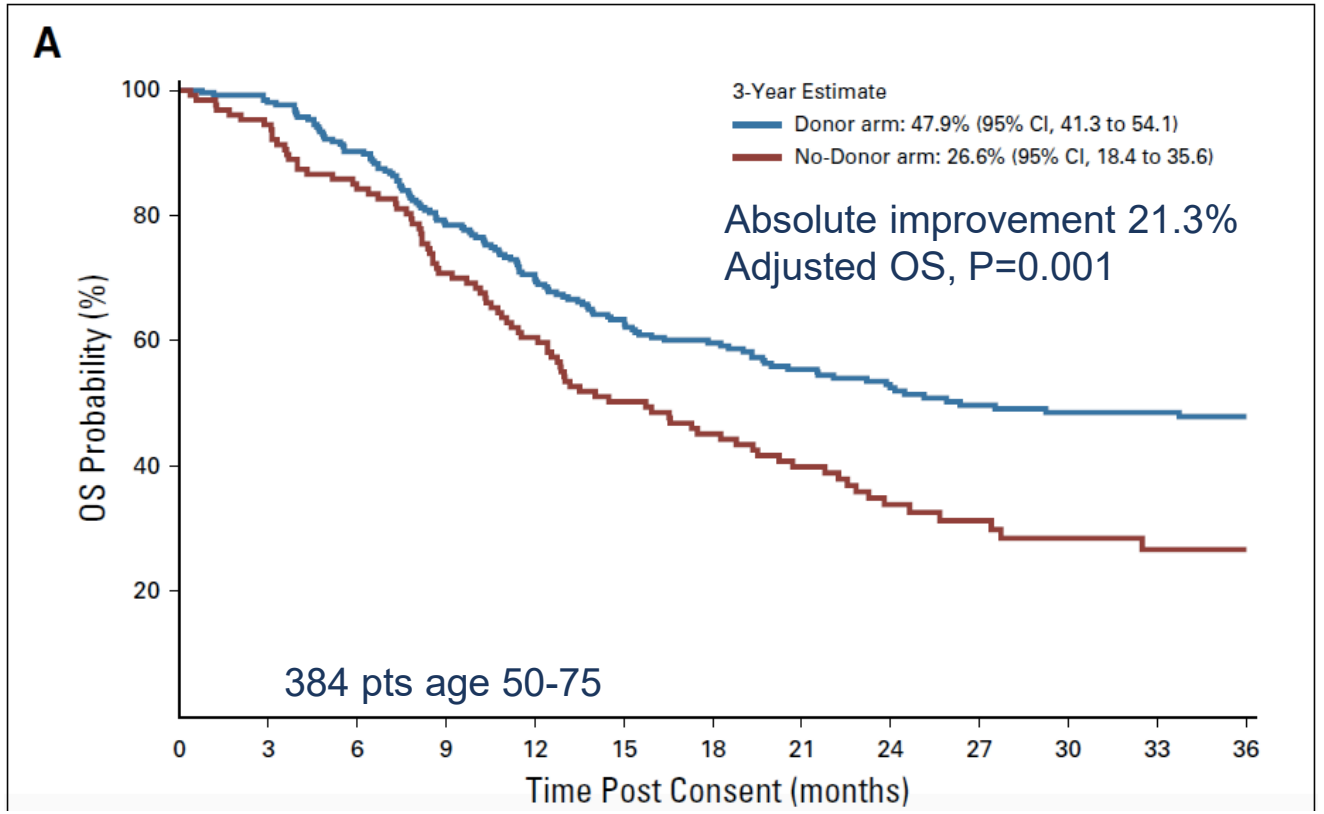


- *A net benefit for delaying transplantation for low and int-1 risk groups; delay in the time to transplantation is associated with a loss in survivorship in higher risk groups*
- Adjustment for QoL did not change the preferred treatment strategy
- Better to transplant prior to AML transformation

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

Biologic assignment trial in MDS

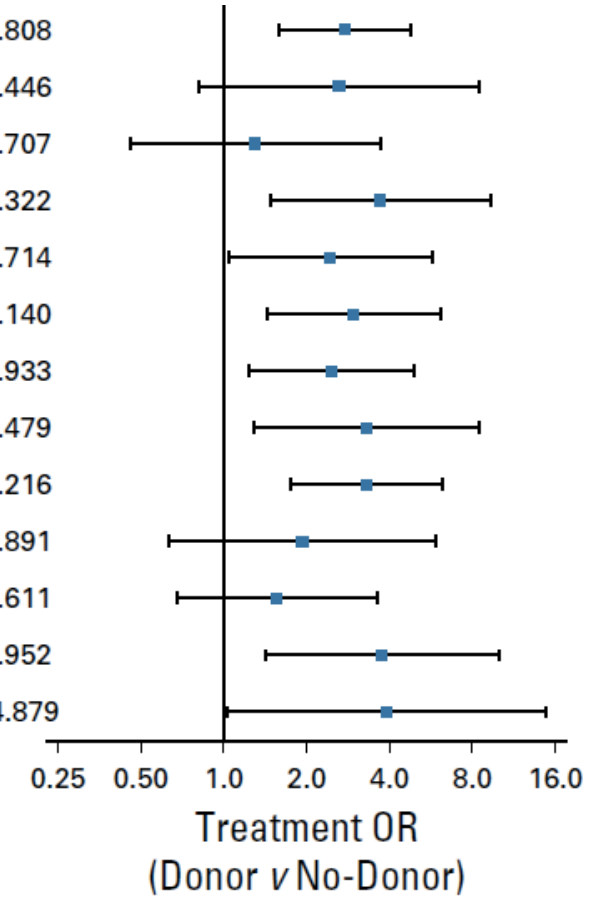
Significant survival advantage in older subjects with higher-risk MDS who have a matched donor identified and underwent RIC HCT vs AZA/BSC



Nakamura et al. J Clin Oncol 39:3328-3339.

Survival benefit of HCT was seen across subgroups

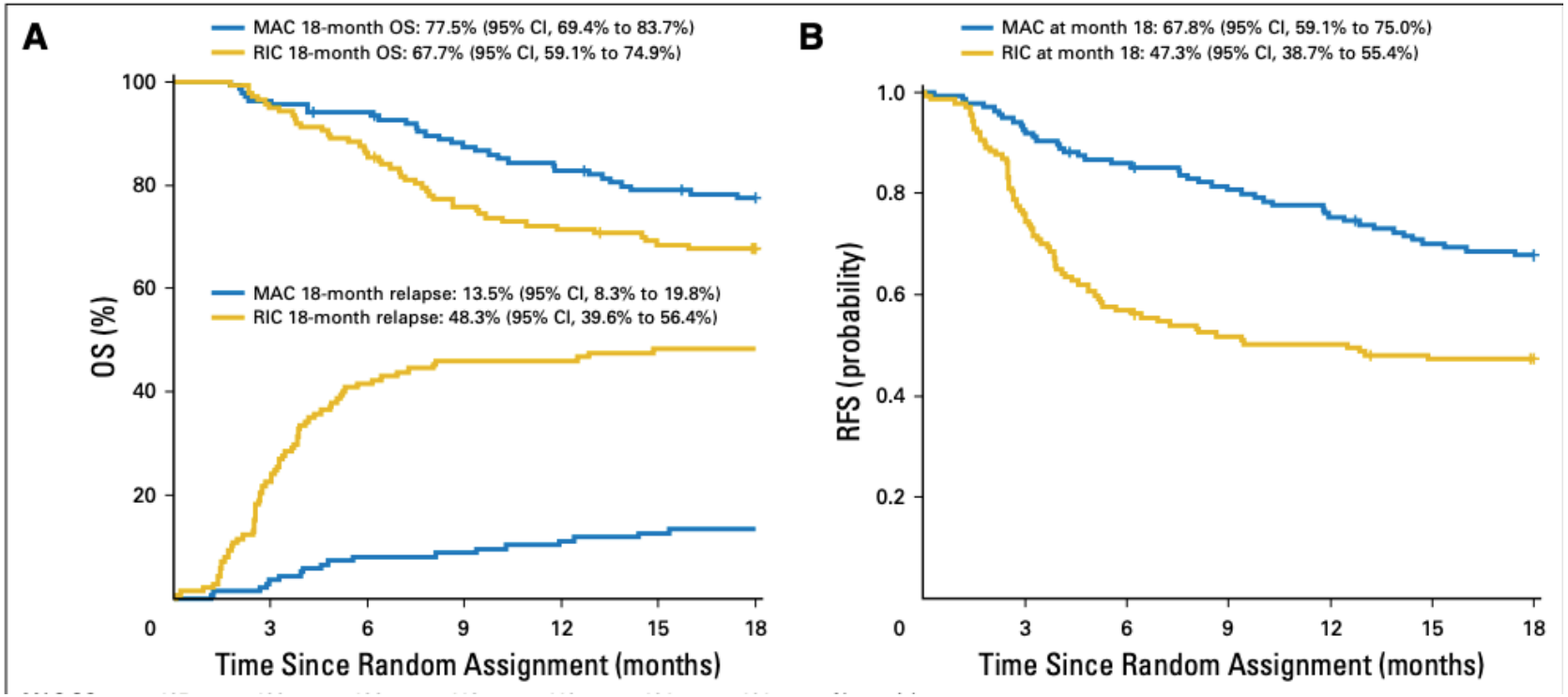
All patients	2.764	1.589 to 4.808
No response to previous hypomethylation	2.621	0.813 to 8.446
Any response to previous hypomethylation	1.301	0.457 to 3.707
No previous hypomethylation	3.708	1.475 to 9.322
≤ 65 years old	2.436	1.039 to 5.714
> 65 years old	2.962	1.429 to 6.140
MDS duration < 3 months	2.476	1.242 to 4.933
MDS duration ≥ 3 months	3.309	1.291 to 8.479
IPSS intermediate-2	3.297	1.748 to 6.216
IPSS high	1.929	0.632 to 5.891
IPSS-R very low, low, or intermediate	1.562	0.676 to 3.611
IPSS-R high	3.751	1.414 to 9.952
IPSS-R very high	3.923	1.034 to 14.879



Nakamura et al. J Clin Oncol 39:3328-3339.

MAC vs RIC in AML/MDS: higher TRM but lower relapse led to improved OS

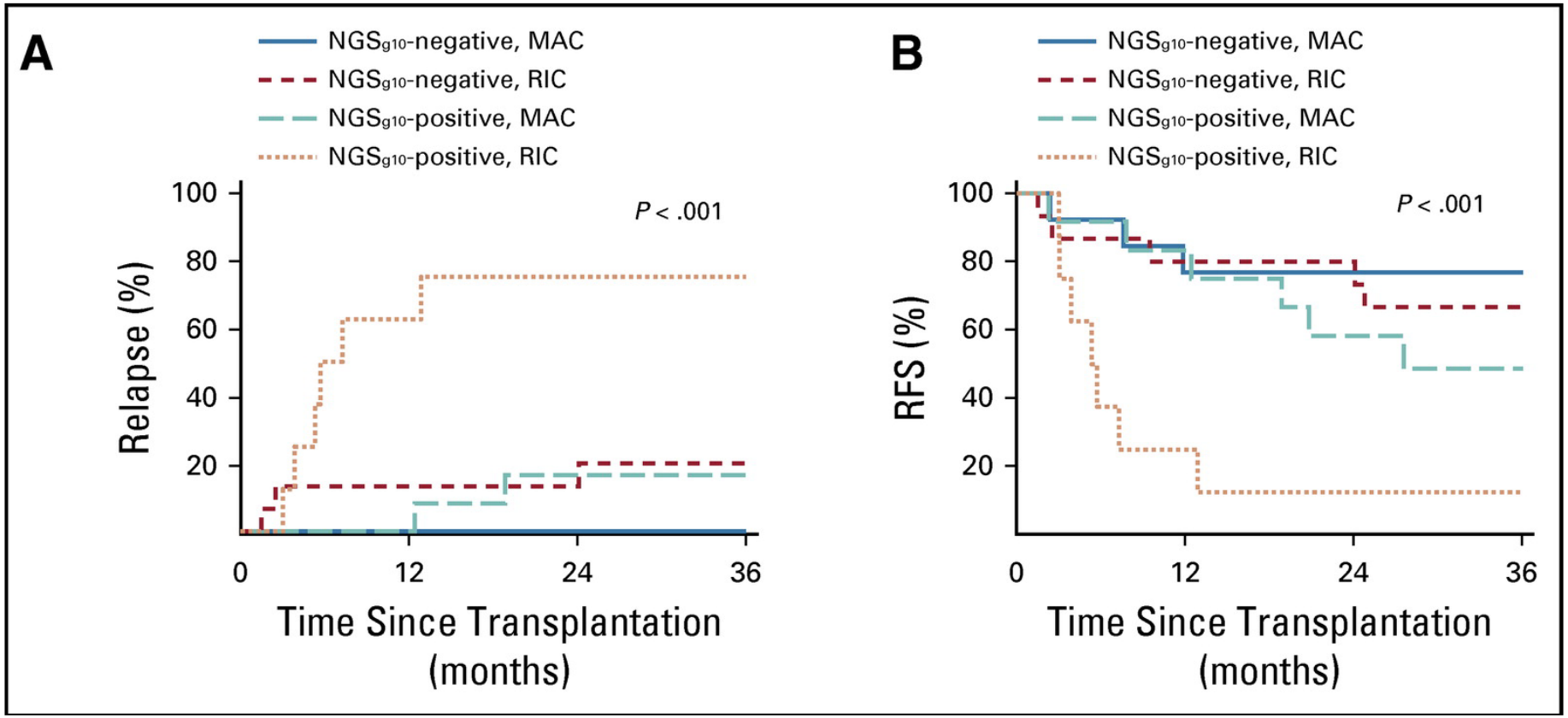
- 272 patients with AML/MDS randomized to MAC vs RIC
- TRM was significantly lower among patients in the RIC arm (4.4% v 15.8%)
- OS was inferior in patients receiving RIC; difference not stat significant



Scott et al. JCO 2017; 34: 1154.

MAC may overcome the negative affect of MRD

48 MDS patients from the prior trial with frozen whole blood prior to transplant
Ultra deep genomic testing used to predict the impact of conditioning intensity



In 58% of patients MRD neg, no difference between conditioning seen for relapse, RFS, or OS

Dillon et al JCO Precision Oncology 5:265, 2021

Conclusions

- MDS is a heterogenous disease group
  - CHIP/CCUS to MDS/AML
- Clinical factors (cytopenias), cytogenetics and mutations predict outcomes
- Given older age at presentation and wide disease spectrum, monitoring or growth factors should be considered. Comorbidities impact treatment options and success, but transplant should be considered for those with intermediate or higher risk disease who can tolerate it
  - “Age alone is not a contraindication to transplant”
- New therapies are needed for high-risk mutations (TP53) and post-HMA disease

Question 1

77yM with fatigue. CBC shows WBCs of 3k/uL, Hg 7g/dL, Plts 110/uL. He has received 4 transfusions in the prior 3 months. A marrow biopsy showed 15% erythroid dysplasia without ring sideroblasts. Blasts were not increased.

Cytogenetics showed 46XY, del(5q) in 12 of 20 metaphases. EPO level is 300 mU/mL. His brother is an HLA match.

Which of the following are appropriate initial therapies?

A. Luspatercept 1mg/kg
B. Imetelstat 7.5mg/kg IV q4 wks
C. Allogeneic transplantation
D. Azacytidine 75mg/m2
E. Lenalidomide
F. Recombinant erythropoietin stimulating agents (epoetin alfa)

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Patients with del5q were excluded from IMerge, Medalist and Commands trials evaluating imetelstat and luspatercept. Azacytidine improves hematopoiesis in some patients, but exhibits a survival advantage only in high risk patients. Allogeneic transplant should be reserved for high risk patients. Lenalidomide improved erythropoiesis and reduced transfusion burden among patients with del5q, many of whom were ESA refractory. Response rates with LEN were higher than historically observed with ESA.

Question 2

77yM with fatigue. CBC shows WBCs of 3k/uL, Hg 7g/dL, Plts 110/uL. He has received 4 transfusions in the prior 3 months. A marrow biopsy showed 15% erythroid dysplasia without ring sideroblasts. Blasts were not increased.

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G. E or F

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E. Lenalidomide

F. Recombinant erythropoietin stimulating agents (epoetin alfa)

G. E or F

Luspatercept and Imetelstat were evaluated in non-del5q patients, but imetelstat excluded patients likely to respond to EPO. The Commands trial compared luspatercept to EPO and showed superior transfusion independence rates with luspatercept.

References

- **CHIP/CCUS:**
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  - https://mds-risk-model.com/

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- **Randomized trial for AZA in MDS**:
  - Silverman et al. JCO 2002; 20: 2429-2440.
  - Fenaux P et al. Lancet Oncology 2009; 10 (3): 223-32.

- **Transplant timing MDS**: Cutler et al. Blood. 2004;104:579-585

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Thank you