Fred Hutch Cancer Center

Myelodysplastic Syndromes

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Disclosures

- None

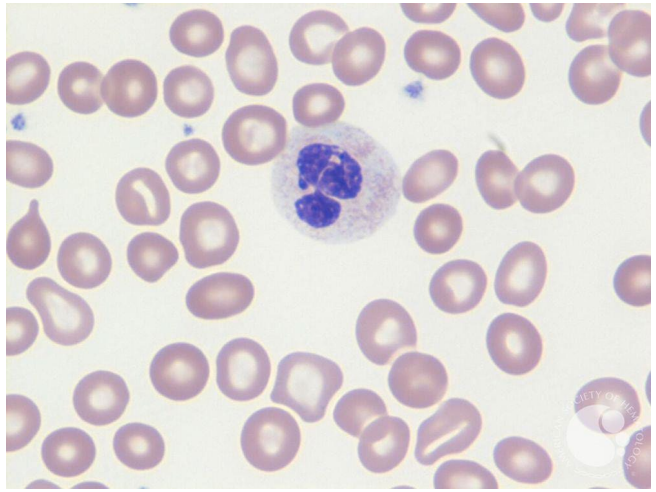
Objectives

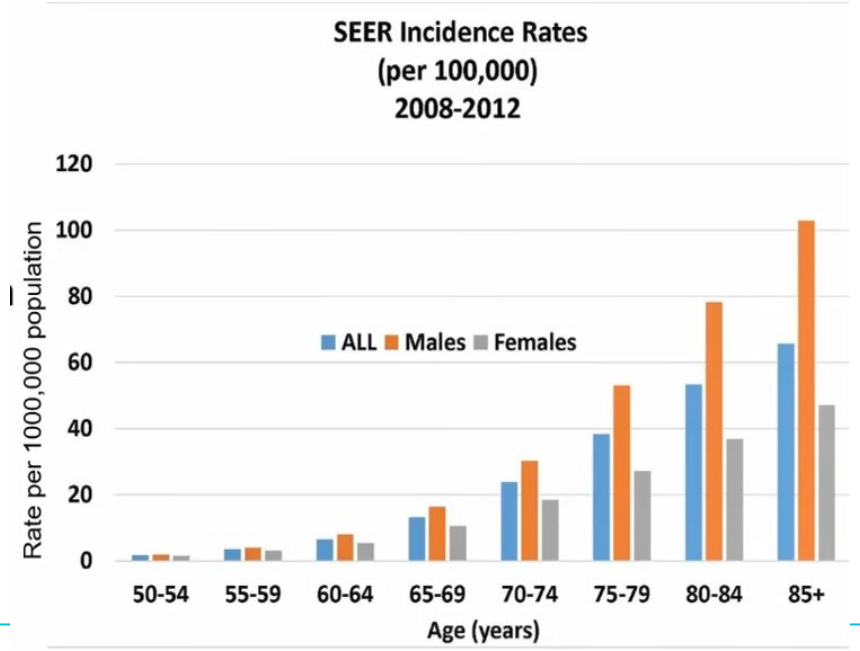
- Diagnosis and Disease classification
- Mechanisms of Disease
- Risk Stratification
- Non-Transplant Therapies of lower and higher risk disease
- Role of Transplant
- CMML
- Upcoming Therapies

Presentation and Mechanisms of Disease

What is 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





Seer Data 2008-2012

Diagnosis of MDS: WHO 2016--> 2022 Criteria

Table 15. PB and BM findings and cytogenetics of MDS

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.

Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 × 10^9/L; and absolute neutrophil count, <1.8 × 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 × 10^9/L

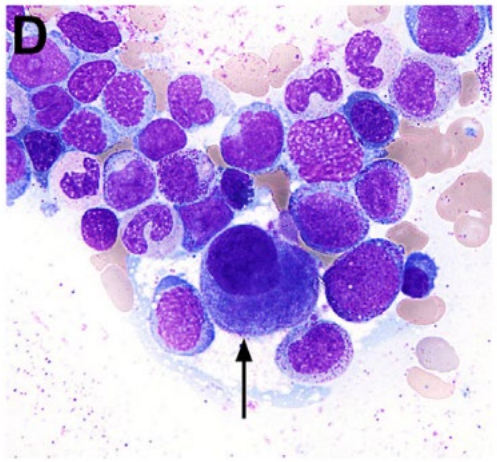
Arber et al. *Blood* (2016) 127 (20): 2391–2405. Khoury et al. Leukemia 2022; 36: 1703–1719.

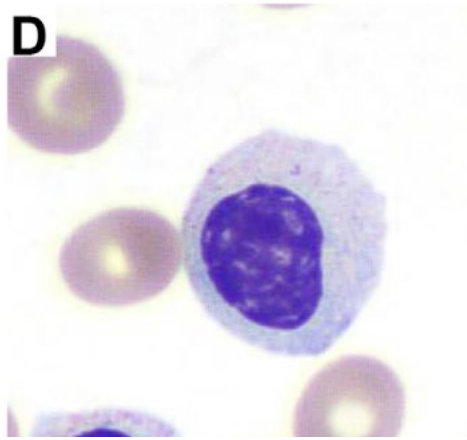
Morphologic findings in MDS

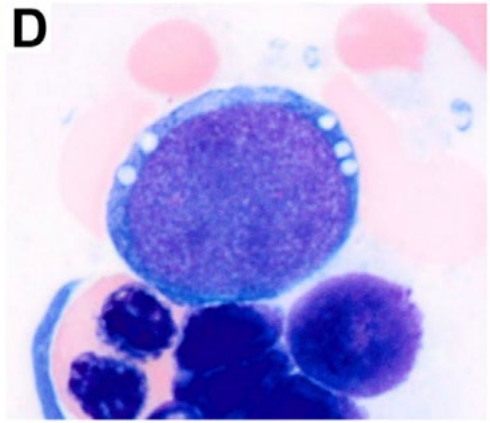
10% dysplastic cells within a given lineage are required for a dysplasia classification.

Table 2
Features of dysplasia in hematopoietic cell lineages

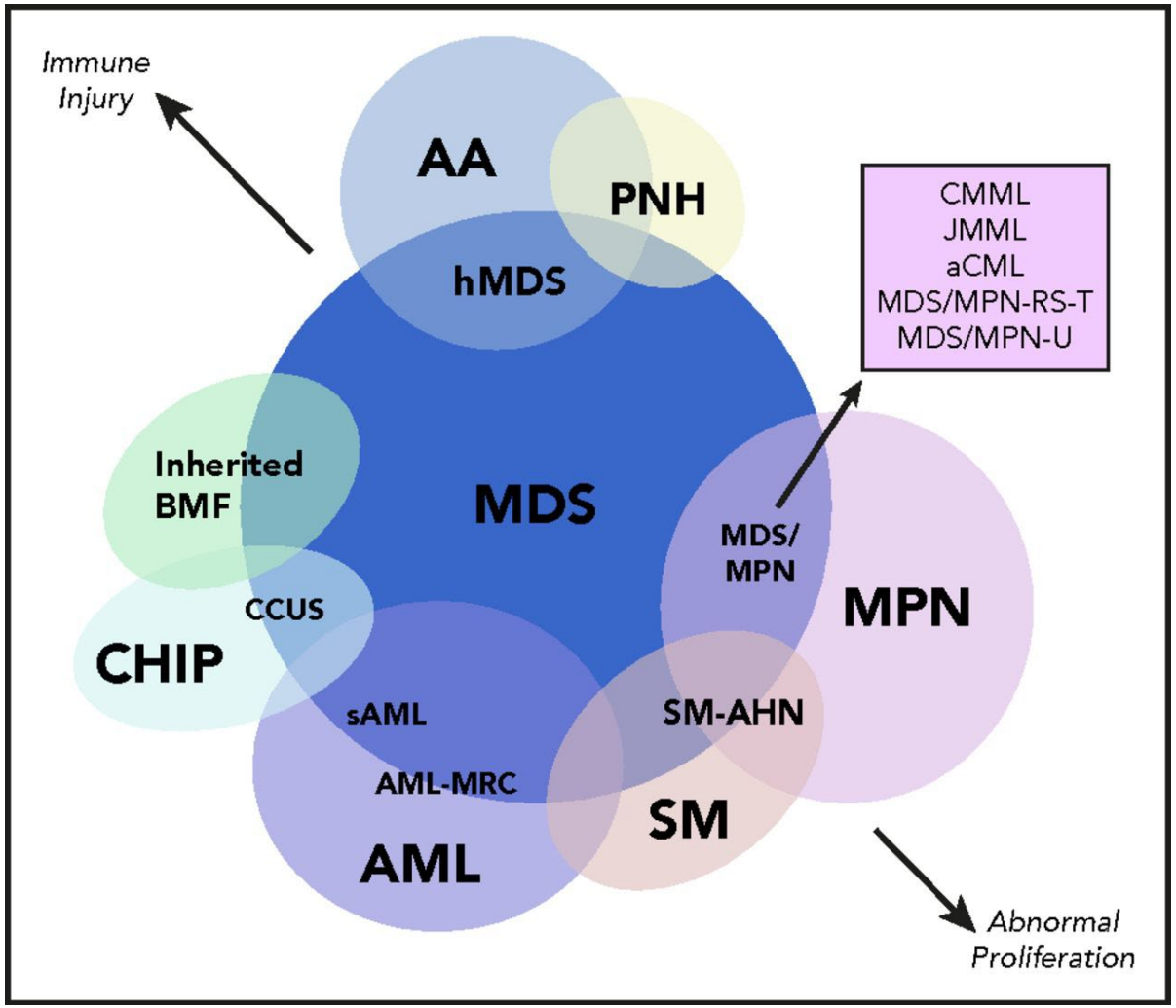
	Megakaryocyte	Myeloid	Erythroid
Bone marrow biopsy and aspirate smear	Micromegakaryocytes Hypo-/monolobated nuclei Separated nuclear lobes	Hypogranular cytoplasm Pseudo Pelger-Huet (bilobed nuclei) Abnormal nuclear segmentation Clumping of chromatin Macropolycytes	Nuclear budding Internuclear bridging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







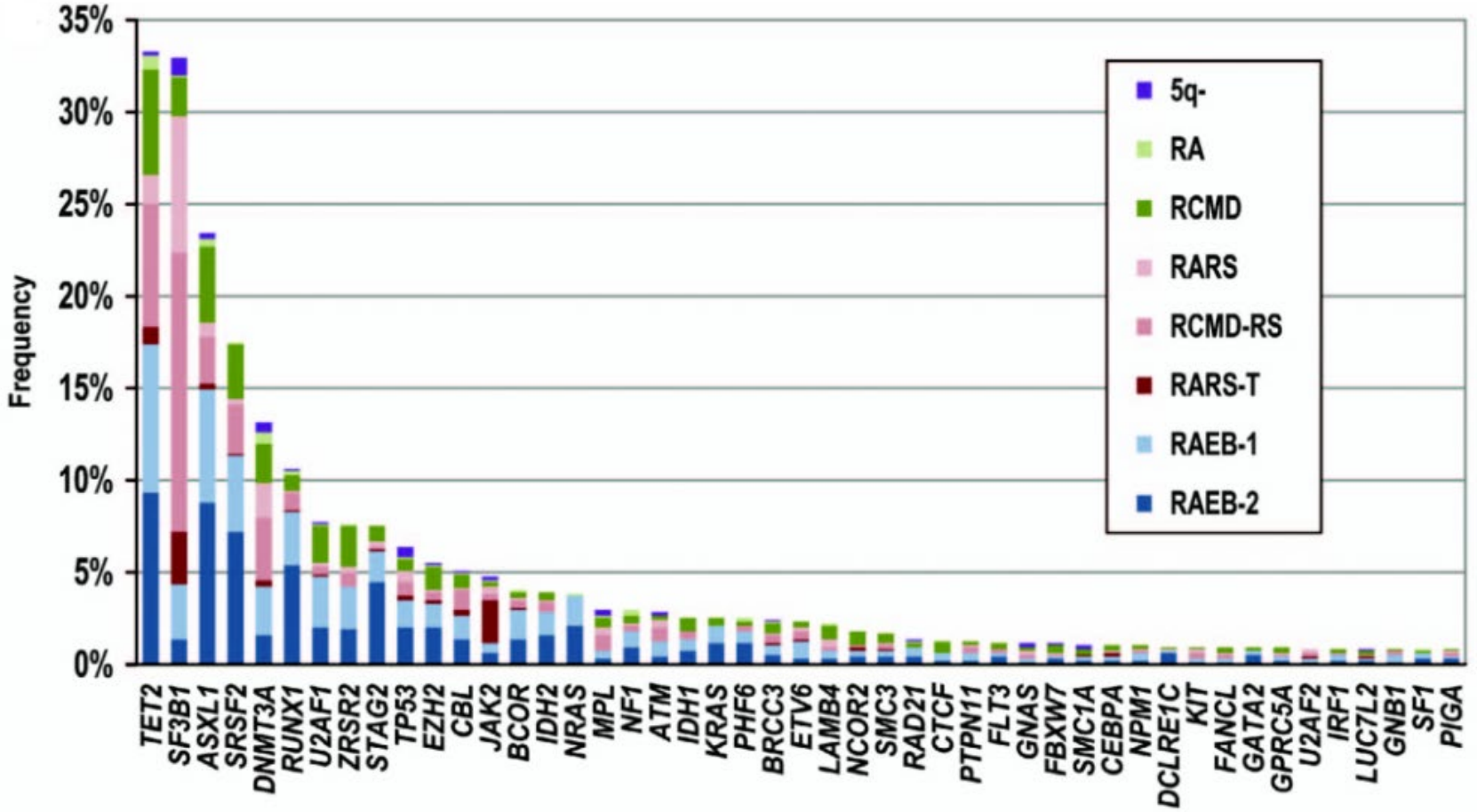
Myeloid disorders with clinical and genetic features shared with MDS



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

Recurrent Genetic Mutations in MDS

~89% of patients had a mutation by NGS



WHO 2016

MDS isol. 5q

MDS-SLD

MDS-MLD

MDS-RS-SLD

MDS-RS-MLD

(MDS/MPN)

MDS-EB-1

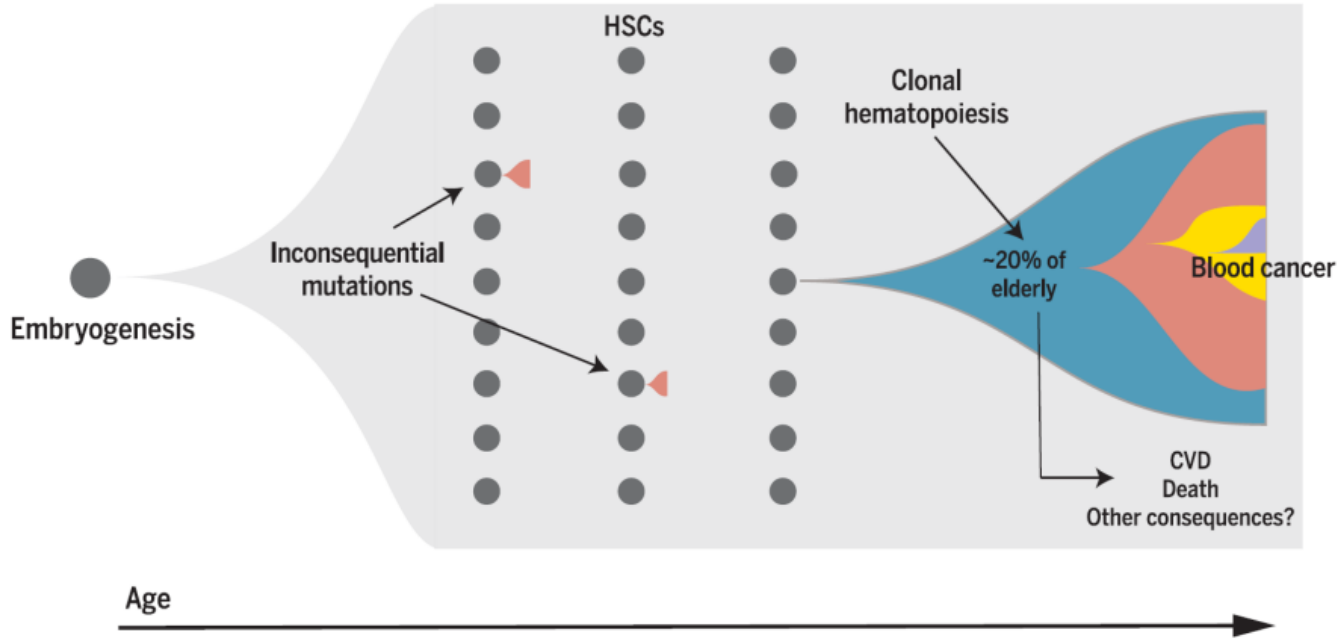
MDS-EB-2

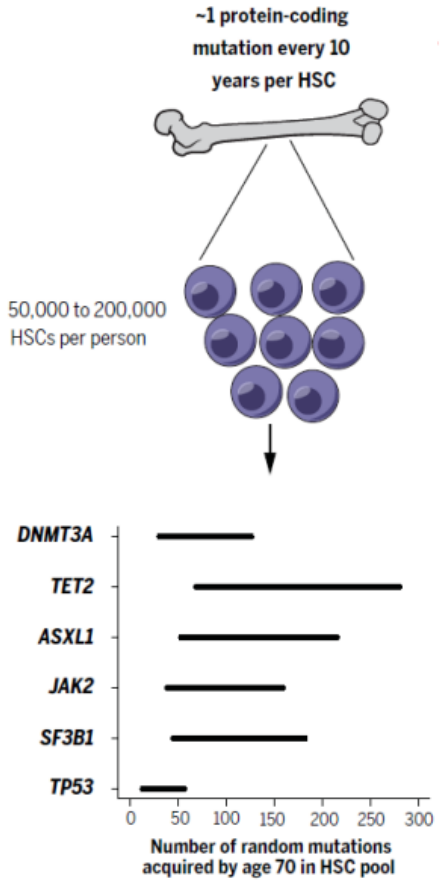
TET2 is an epigenetic modifier, is the most common mutation, tumor suppressor function lost on mutation

DNMT3A involved in DNA methylation, U2AF1 is a spliceosome mutation

Haferlach et al., *Leukemia* (2014) 28, 241–247; doi:10.1038/leu.2013.336. Slide courtesy of j Deeg

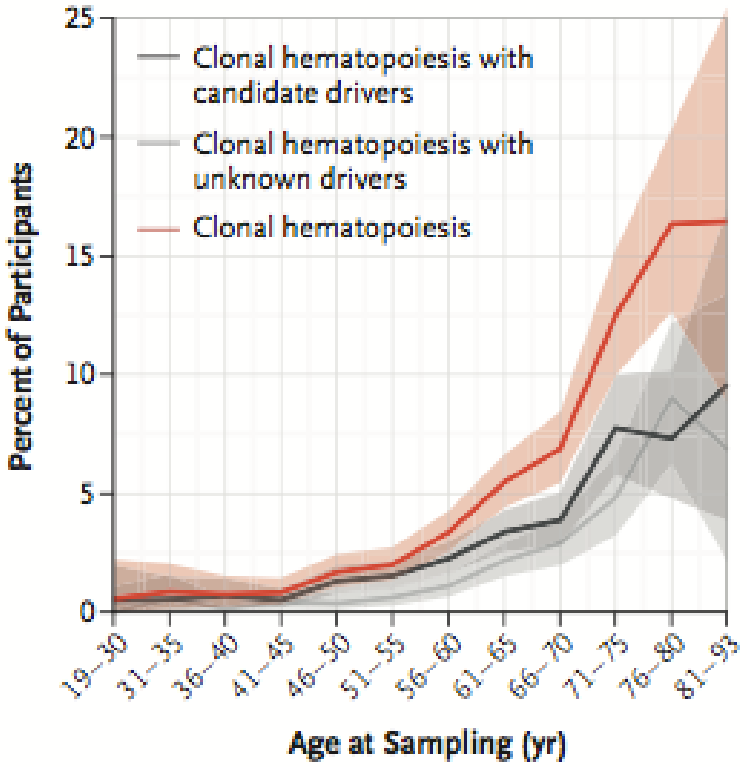
Acquisition of Somatic Mutations during Ageing





Jaiswal S, et al. Science. 2019; 366. Slide courtesy of Gregor Hormann, MLL Münchner Leukämie Labor.

Somatically-derived clones increase with age



Genovese et al NEJM, 2014

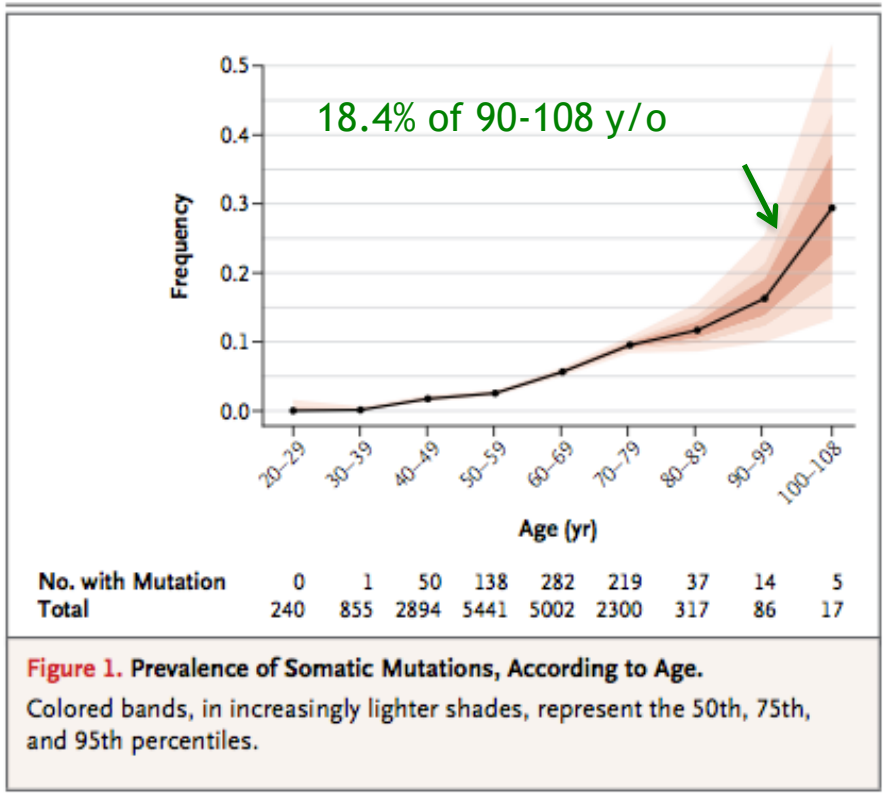
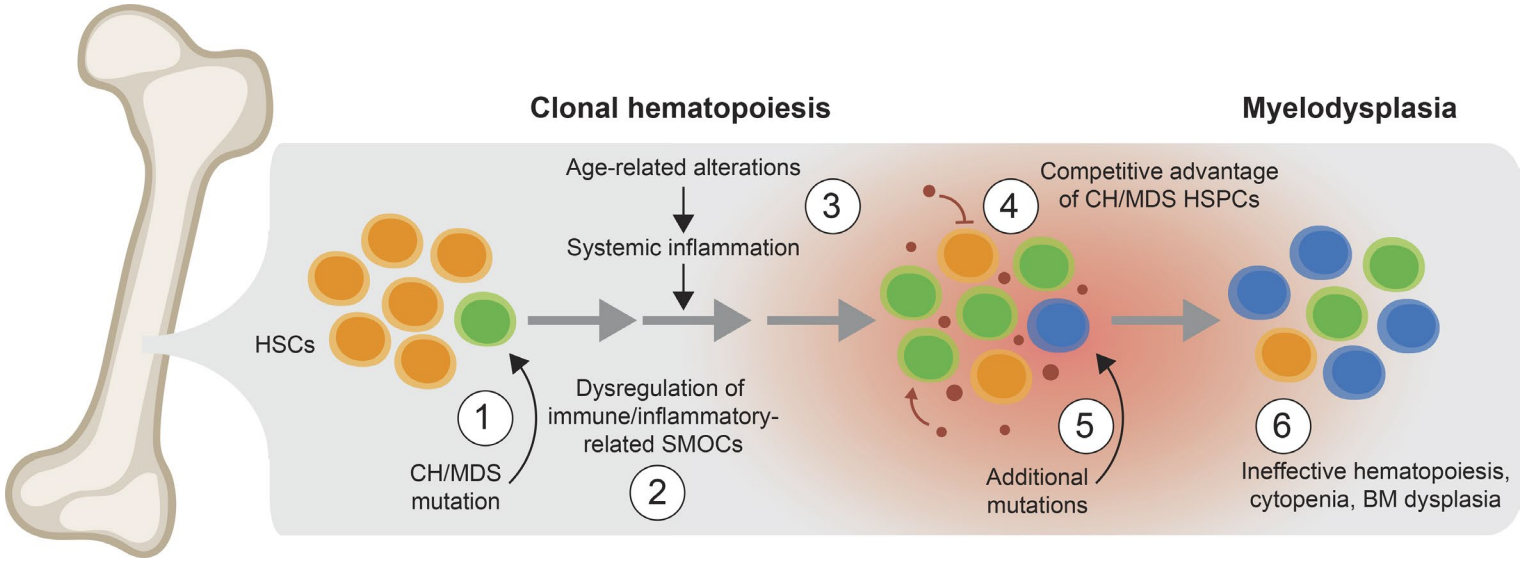
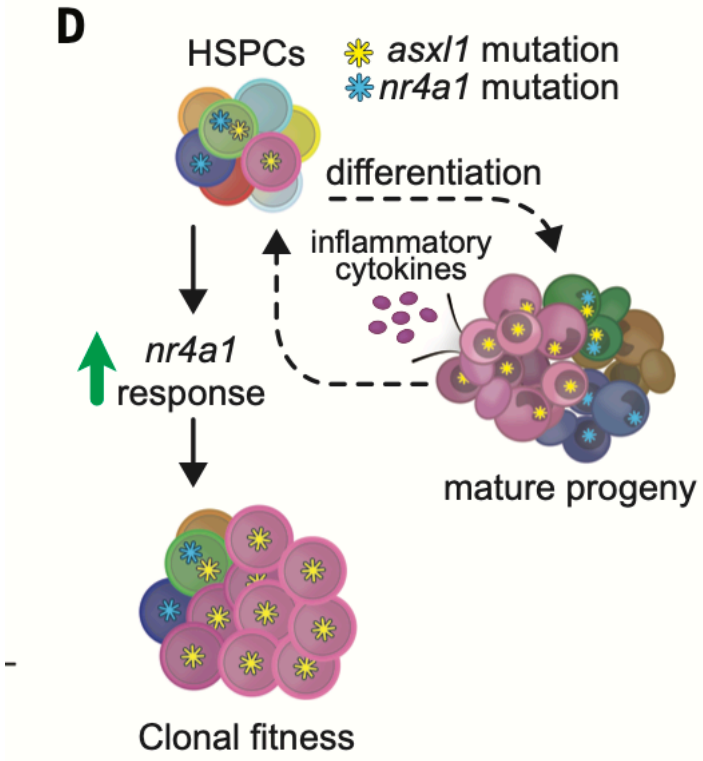


Figure 1. Prevalence of Somatic Mutations, According to Age.
Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

Jaiswal et al, NEJM, 2014

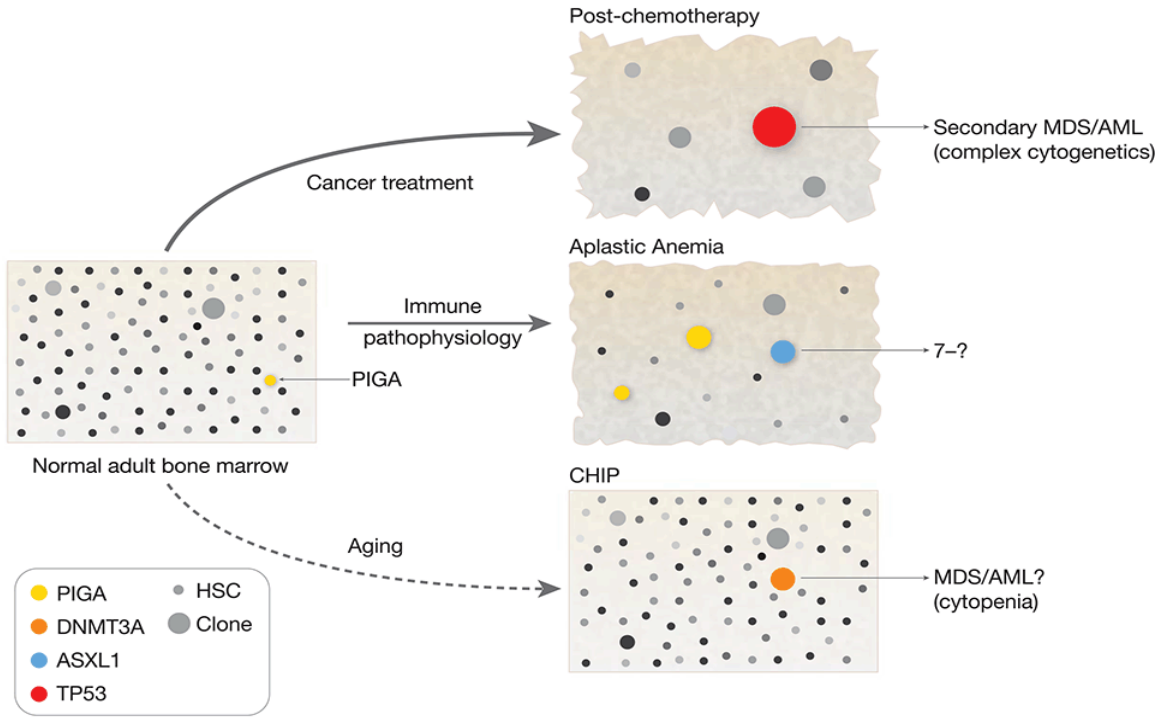
Inflammation:
Driver of marrow suppression and clonal expansion





Mechanisms of Disease: Intersection of Immunity and Inflammation

- Inflammation
- Clonal evolution
- Myeloid derived suppressor cell
- T cells (auto-immunity) and LGLs
- Altered gene expression in the bone marrow stroma



Cooper & Young, Blood 130: 2363, 2017. Slide courtesy of J Deeg

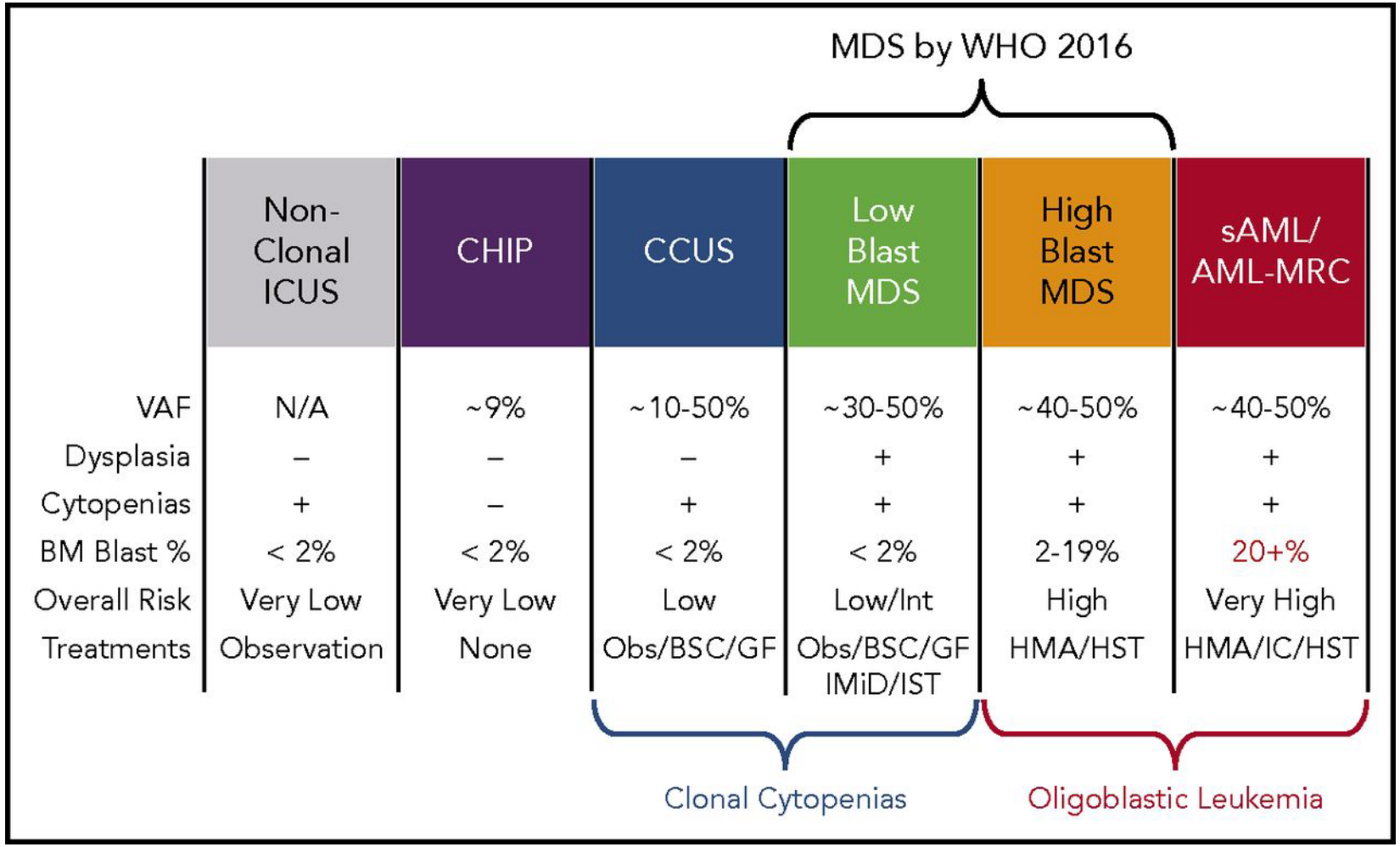
Case 0

- 66 yo F presented with fatigue and found to have Hgb 10.2, MCV 94, plts 140, wbc 6.4, normal differential
  - Workup show normal stores of iron, B12, folate, copper, no inflammatory conditions
- Bone marrow biopsy was normocellular with normal trilineage hematopoiesis and no dysplasia or increased blasts
- Cytogenetics were 46,XX[20], normal MDS FISH panel
- NGS testing shows: TET2 and DNMT3A with VAFs of 27% and 18% respectively

→ Diagnosis of CCUS (clonal cytopenias of uncertain significance)

“MDS” Disease Spectrum

Comparison of features between cytopenic and clonal hematopoietic states that border MDS

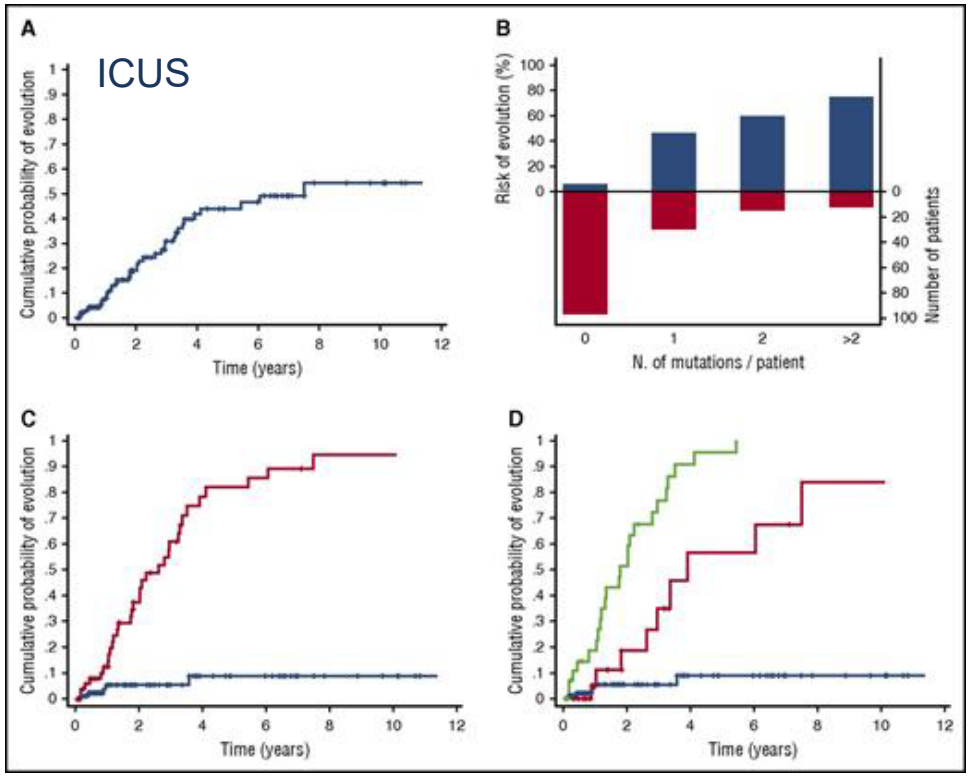


ICUS = Idiopathic clonal hematopoiesis of undetermined significance

Bejar Blood 2019;133:1086-1095. Steensma DP et al. Blood 2015; 126 (1): 9-16

Prediction of ICUS and CCUS Progression

- Patients with CCUS with mutations with VAF >10% or ≥2 mutations in recurrently mutations genes in myeloid disorders have a PPV for an eventual diagnosis of myeloid neoplasm of 0.86 and 0.88
- 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

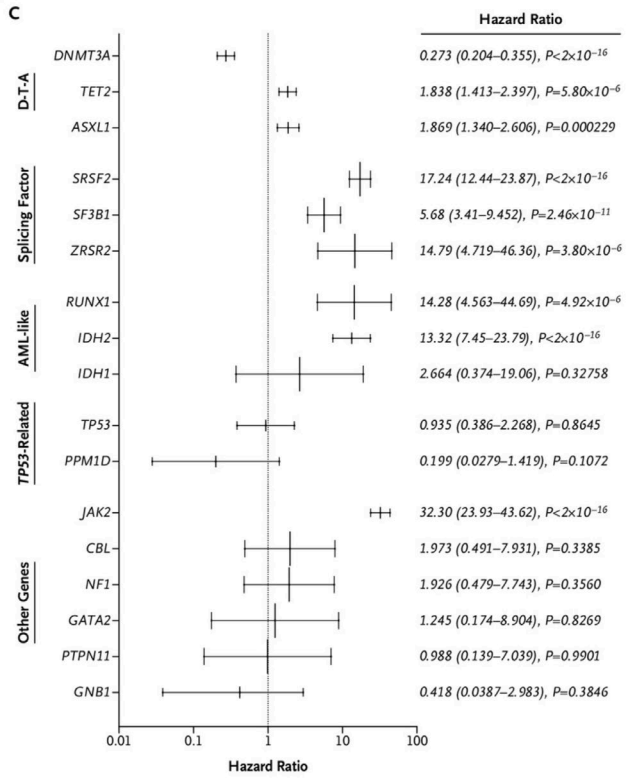


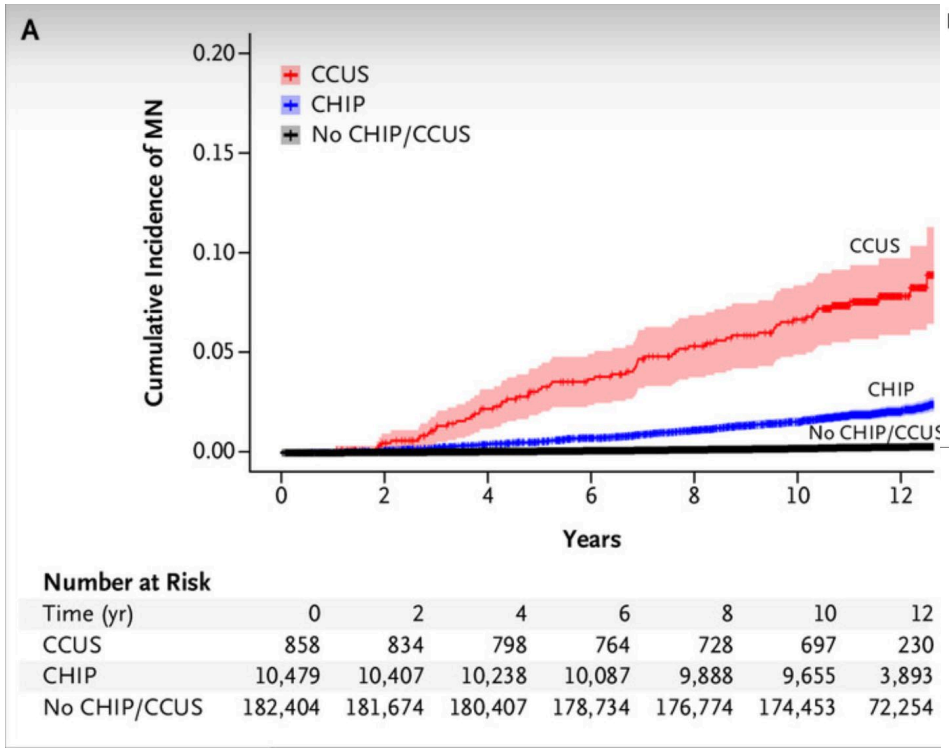
Red= 1+ mutation, blue 0 mutations

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

Prediction of ICUS and CCUS Progression

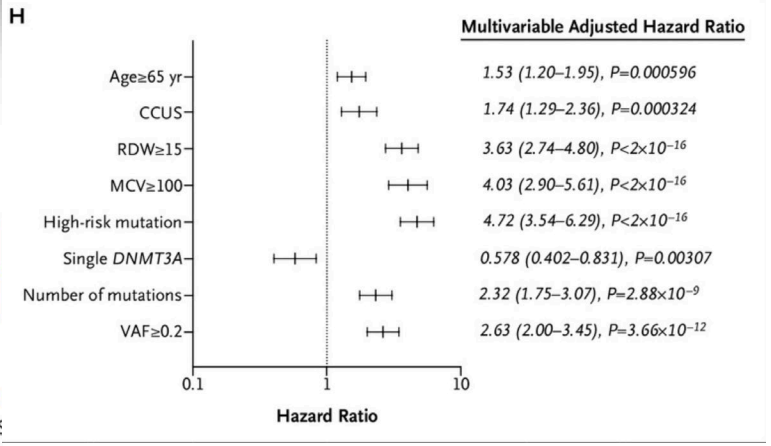
- Some patients with ICUS/CCUS/CHIP progress to MDS or AML.
- http://www.chrsapp.com/





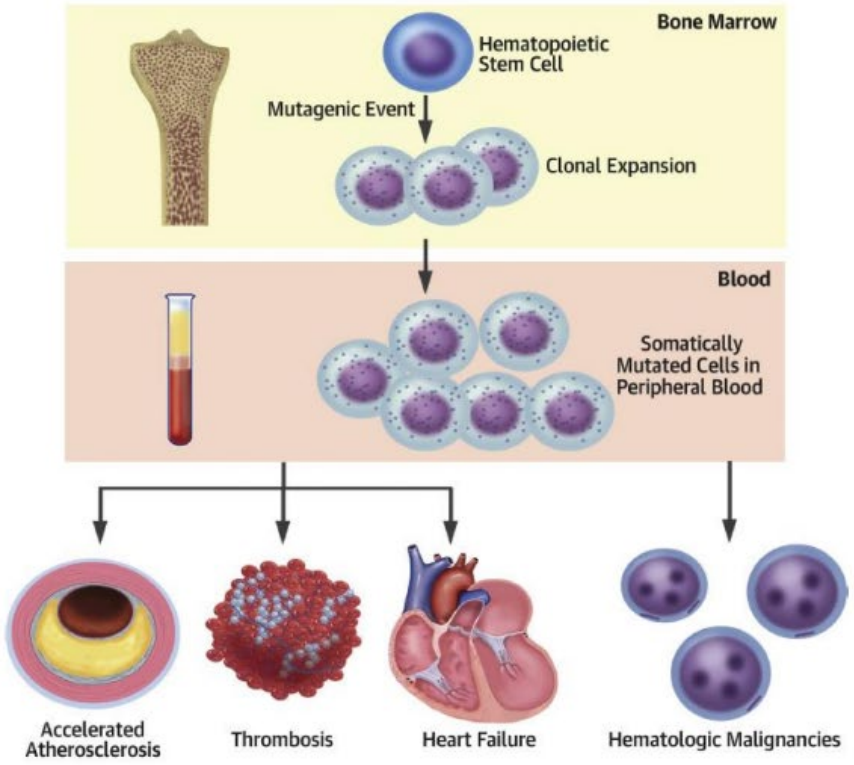
Number at Risk

Time (yr)	0	2	4	6	8	10	12
CCUS	858	834	798	764	728	697	230
CHIP	10,479	10,407	10,238	10,087	9,888	9,655	3,893
No CHIP/CCUS	182,404	181,674	180,407	178,734	176,774	174,453	72,254



Weeks LD et al. NEJM Evidence (2023) 2 (5): EVIDoa2200310.
Malcovati et al. Blood (2017) 129 (25): 3371–3378

CHIP and Cardiovascular Disease



Hazard ratio for CVD based on Framingham risk factors and CHIP

B

	HR (95% CI)
Age 50-59	**2.2** (1.3-3.7)
Age 60-69	**2.4** (1.4-4.0)
Age ≥70	**6.3** (3.8-10.4)
Female	**0.7** (0.5-0.9)
Has T2D	**2.2** (1.6-3.0)
Former or current smoker	**1.4** (1.0-1.9)
Hypertension stage II-IV	**1.4** (1.0-1.9)
TC >200 mg/dL	**1.4** (1.0-1.9)
HDL<35 mg/dL	**1.4** (1.0-2.2)
HDL>60 mg/dL	**0.8** (0.5-1.1)
CHIP present	**1.8** (1.1-2.9)

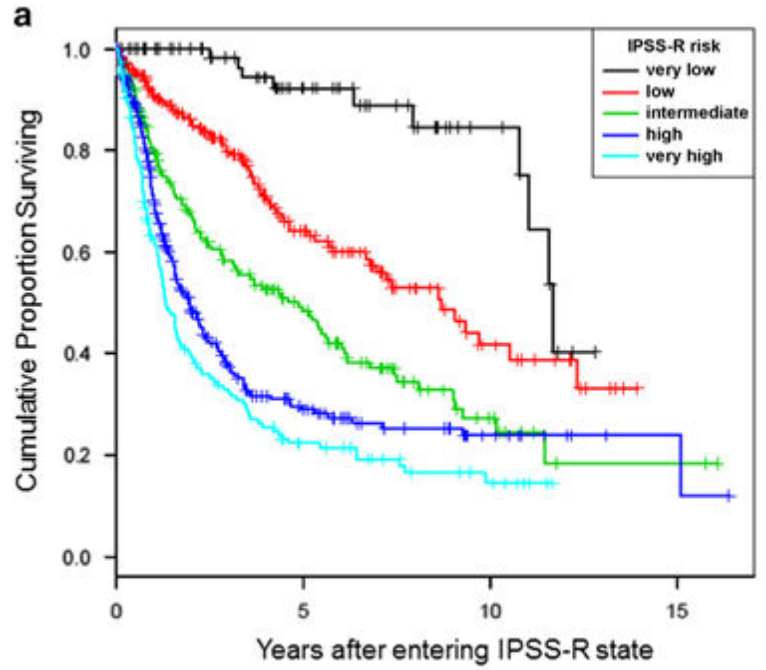
Libby P, et al. J Am Coll Cardiol. 2019;74(4):567-577. | Jaiswal S, et al. Science. 2019;366(6465).
Jaiswal S, et al. N Engl J Med. 2017;377(2):111-121. | Fuster JJ, et al. Science. 2017;355(6327):842-847

Prognostic Models

MDS Risk Stratification IPSS-R

Parameter	Categories and Associated Scores (Scores in italics)				
Cytogenetic risk group[a]	Very good	Good	Intermediate	Poor	Very Poor
	0	*1*	*2*	*3*	*4*
Marrow blast proportion	≤2.0%	>2.0–<5.0%	5.0–<10.0%	≥10.0%	
	0	*1*	*2*	*3*	
Hemoglobin	≥10 g/dL	8–<10 g/dL	<8 g/dL		
	0	*1*	*1.5*		
Absolute neutrophil count	≥0.8 × 10^9/L	<0.8 × 10^9/L			
	0	*0.5*			
Platelet count	≥100 × 10^9/L	50–100 × 10^9/L	<50 × 10^9/L		
	0	*0.5*	*1*		

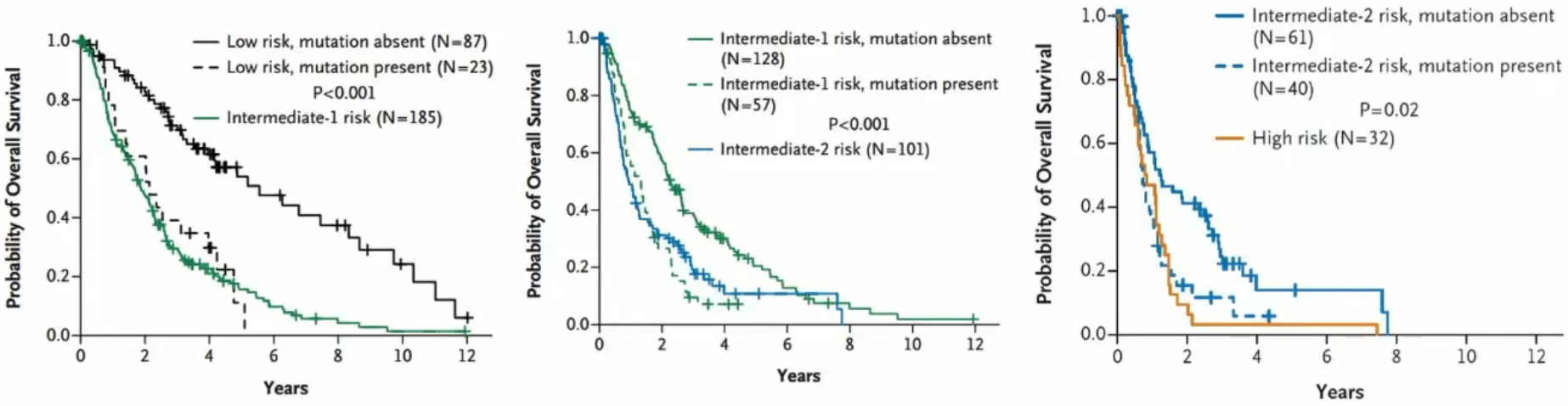
Risk group	Total score[b]	Proportion of patients in category (%)	Median survival (survival data based on *n* = 7012) (years)	Time until AML progression (AML data available based on *n* = 6485) (years)
Very low	0–1.0	19	8.8	Not reached
Low	1.5–3.0	38	5.3	10.8
Intermediate	3.5–4.5	20	3.0	3.2
High	5.0–6.0	13	1.5	1.4
Very high	>6.0	10	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

Prognostic Value of Single Somatic Gene Mutations by IPSS Group (*TP53, ETV6, EZH2. RUNX1, ASXL1*)

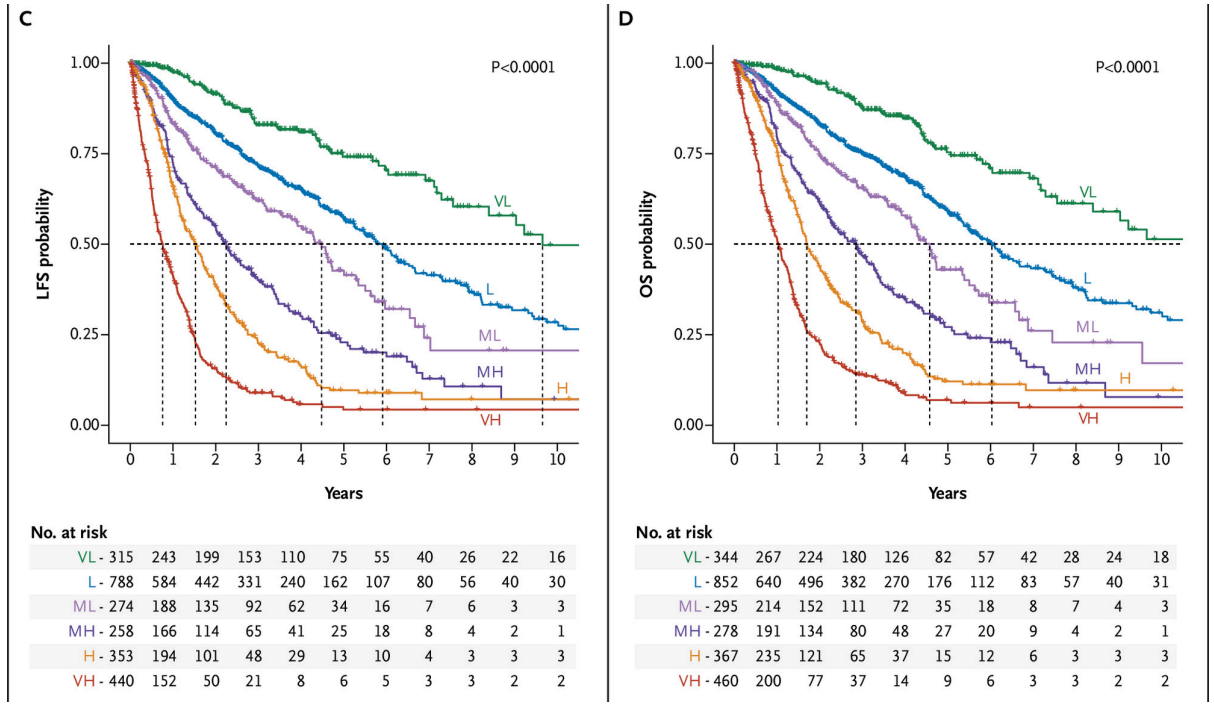


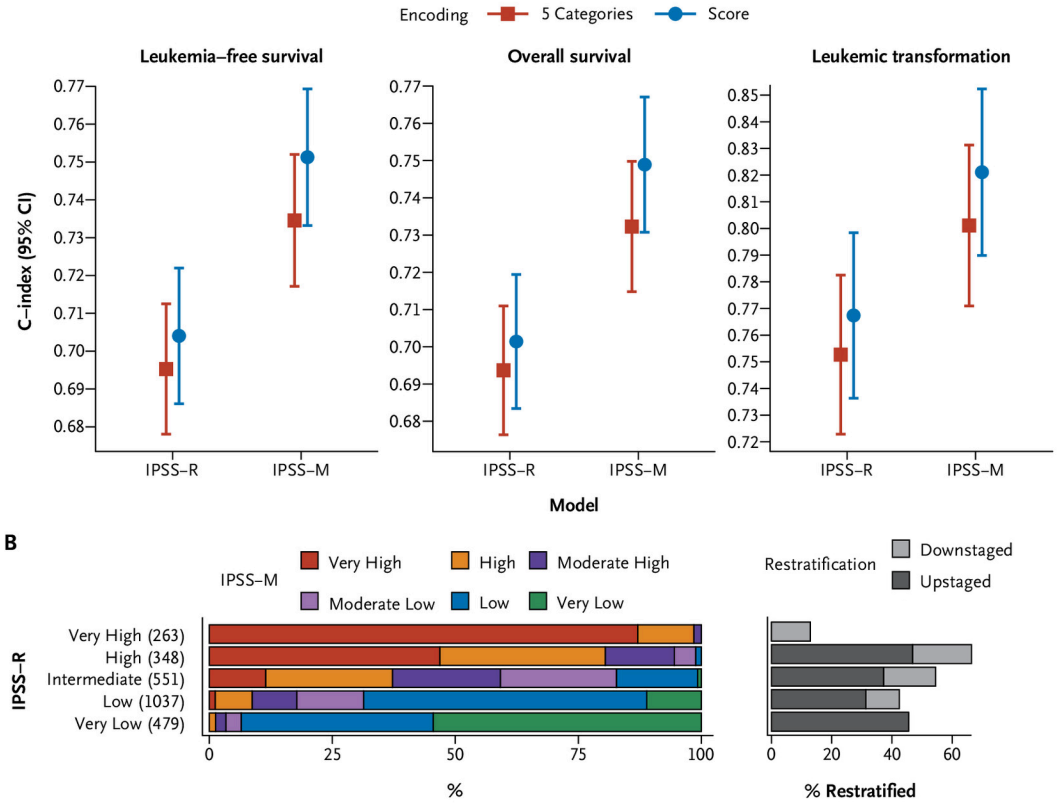
- Mutation in 1 of 5 genes is independently associated with a decreased overall survival.
- Low risk MDS pts having mutated EZH2 or ASXL1 are at higher risk than predicted by IPSS
- TP53 mutations are strongly associated with shorter OS after adjustment for IPSS

Bejar et al. 2011 NEJM 364: 26.

IPSS-M score now incorporates molecular information

- Major criticism of IPSS-R does not take into account molecular data
- IPSS-M now developed, incorporates 31 gene mutations and TP53 allelic state
- Pts categorized into 6 categories with strong prognostication across endpoints



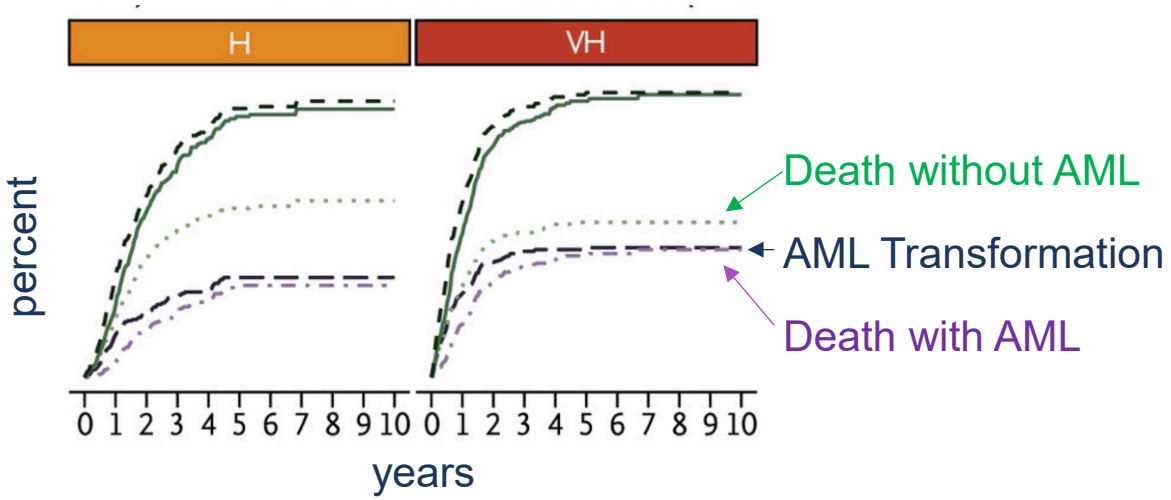


There was a 5 pt increase in C-index from IPSS-R to IPSS-M across all endpoints

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



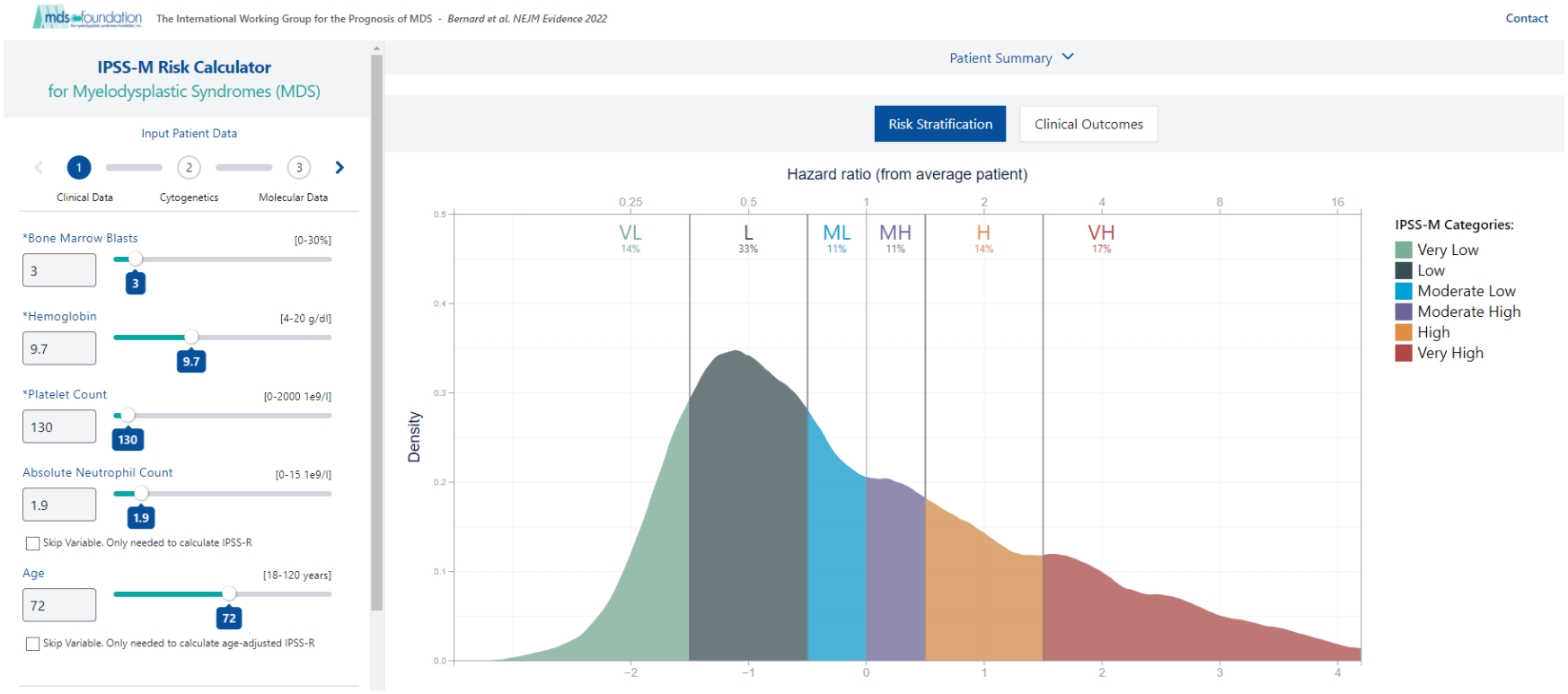
Even among the 'VERY HIGH' group, "*death without AML*" was more frequent than "*death with AML.*"

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

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

IPSS-M: Current prognostic model of choice

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



MDS Therapy

Treatment goals

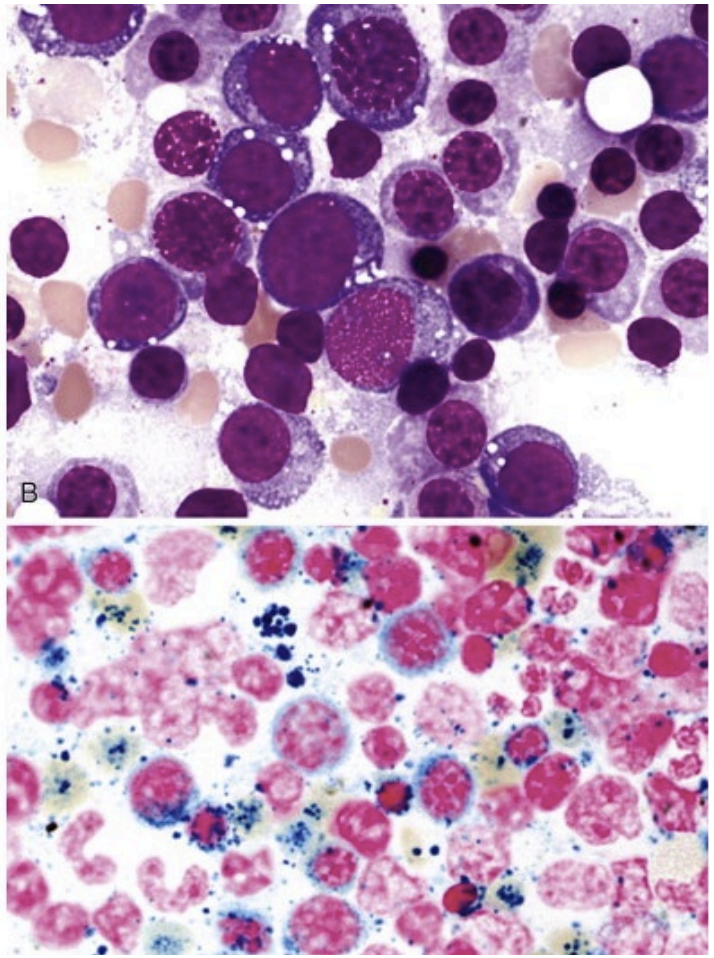
- **Lower risk:**
  - Improve cytopenias– typically hemoglobin levels
  - Transfusion independence
  - Maximize QOL

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

Non-Transplant therapy

- Erythropoietin-stimulating agents (ESA): e.g. Darbopoietin, Procrit
- Luspatercept
- Lenalidomide
- Imetelstat
- Iron chelation
- Immune suppression (ATG)+cyclosporine
- Eltrombopag
- Azacitidine (Vidaza)
- Decitabine/Inqovi
- Ivosidenib (IDH1 mutated)
- Induction-type chemotherapy

Case 1



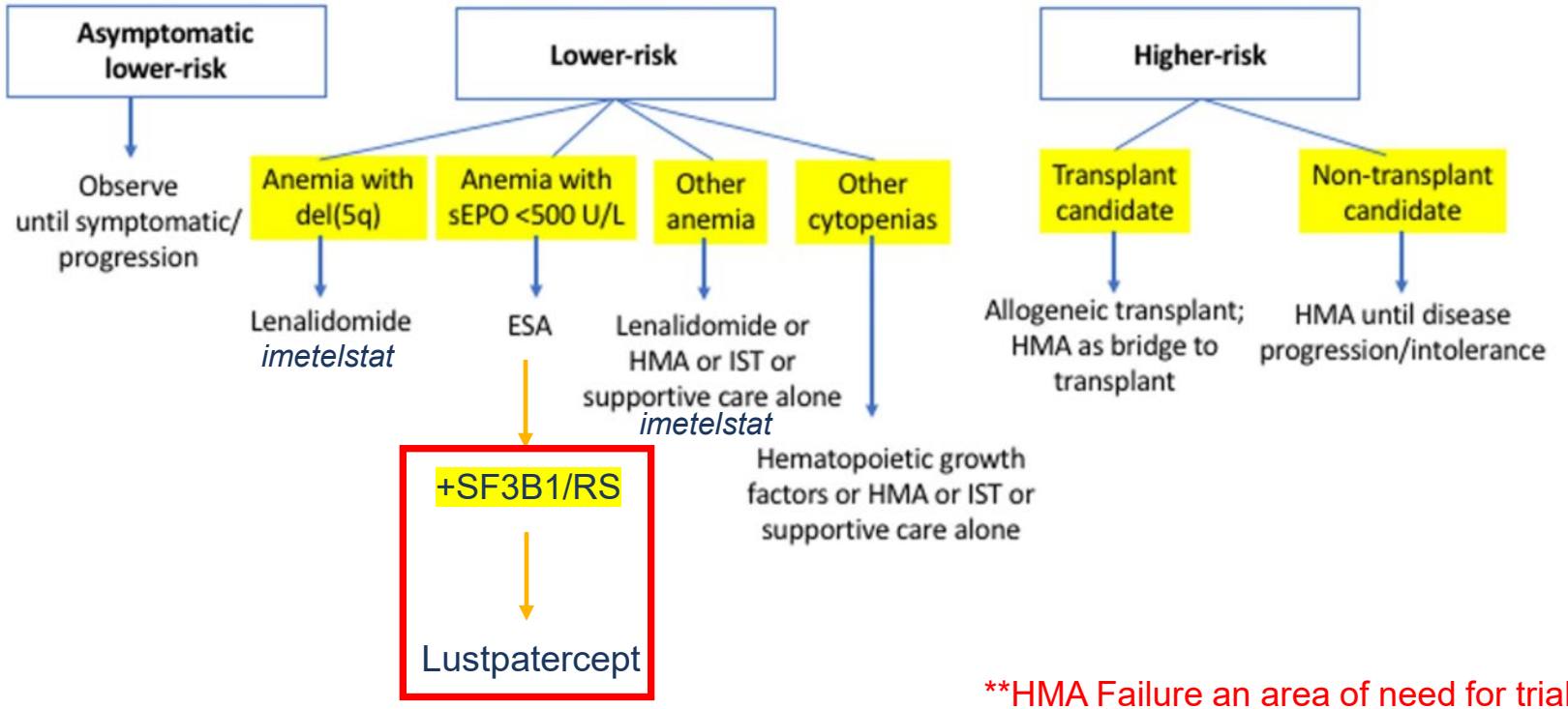
- A 69-year-old man presents with fatigue
- CBC notable for white blood cell count (WBC) 4.8 K/uL, hemoglobin (Hgb) 8.9 g/dL, MCV 100, platelets (plts) 156 k/μL, an absolute neutrophil counts (ANC) 2.5 K/uL, and no circulating blasts
- Studies for iron, folate, B12, copper are normal
- Bone marrow exam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

→ Diagnosis is MDS with low blasts and SF3B1 mutation per WHO 2022

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

Current Treatment Algorithm in Myelodysplastic Syndromes

Consider clinical trial enrollment for all patients
Supportive care (e.g., transfusions and antimicrobials as needed) for all patients
Risk stratification using IPSS-R supplemented by molecular testing



**HMA Failure an area of need for trials

ESA= erythropoietin stimulating agent;
HMA= hypomethylating agent

Adapted from Steensma 2018. Blood Cancer Journal 8:47.

Prediction of response to ESAs

- Anemia is the most common presenting feature of LR-MDS
- Associated with worse QOL
- Transfusion associated with iron overload and long-term morbidity/mortality
- Treatment with ESA therapy can improve Hgb and reduce transfusion need in 40-60% of patients
- Typical duration of response is 18-24 months; most responses occur in first 12 weeks

Factor	Points
Serum Epo level, U/l	
<100	+2
100-500	+1
>500	-3
Transfusion units RBC/month	
<2 units/month	+2
≥ 2 units/month	-2

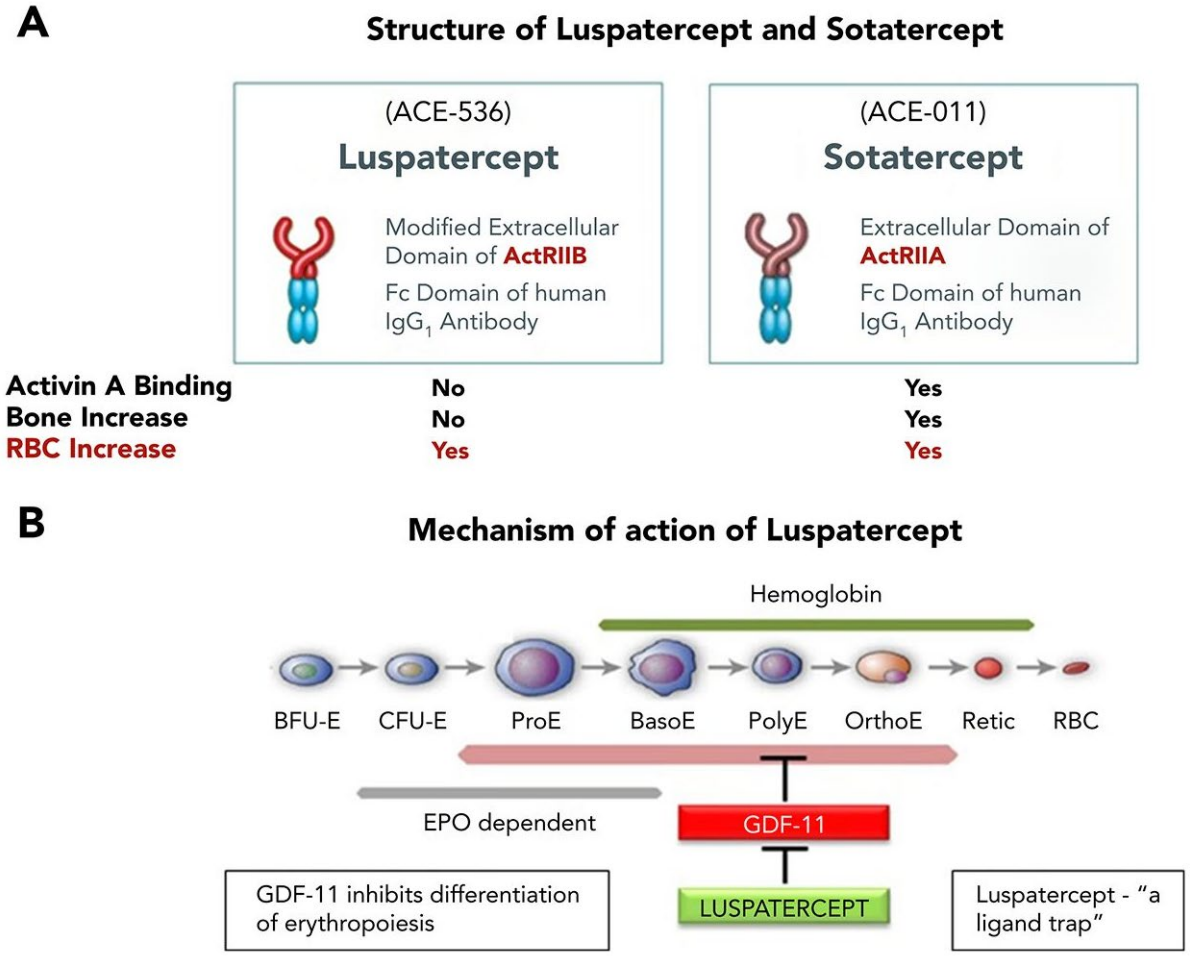
Score	% Responders
≥1	74%
-1 to +1	23%
<-1	7%

Adapted from Hellstrom-Lindber et al. British Journal of Haematology, 1997 Volume: 120, Issue: 6, Pages: 1037-1046; *British Journal of Haematology 1997, 99 (2): 344-51*

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**

Luspatercept: works on late-stage erythropoiesis



Novel fusion protein that blocks transforming growth factor-ß superfamily inhibitors: reduces aberrant Smad 2/3 signaling and enhance late stage erythropoiesis

Fenaux et al. *Blood 2019.* 133(8): 790-794.

Medalist Trial → approval Luspatercept ESA RR MDS

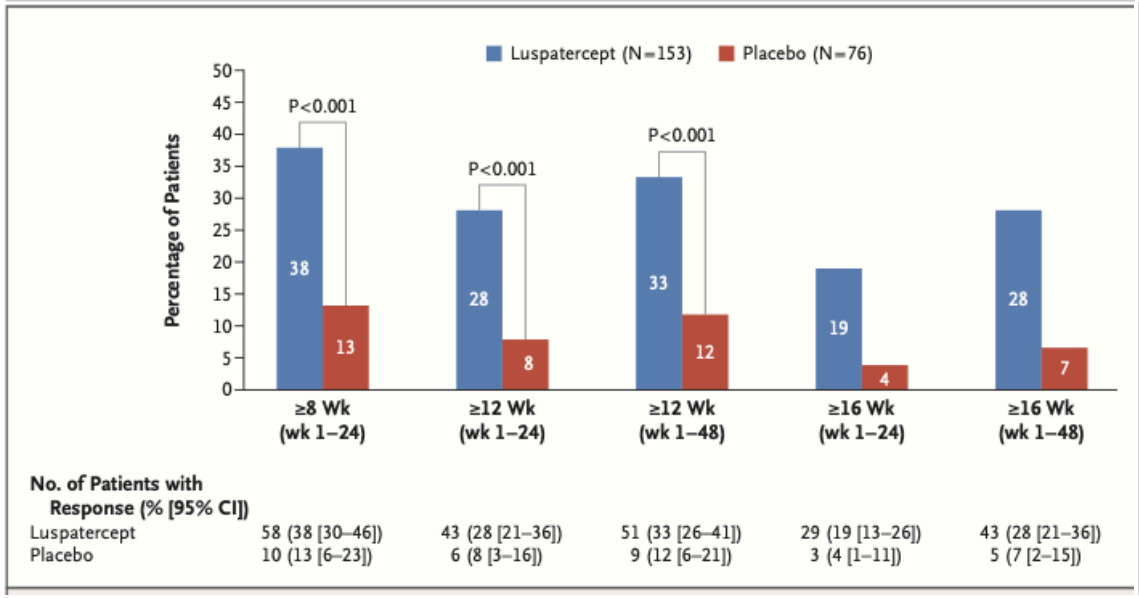
Population: v/low and intermediate MDS with RS: either ≥15% RS or ≥5% RS +*SF3B1 mutation*

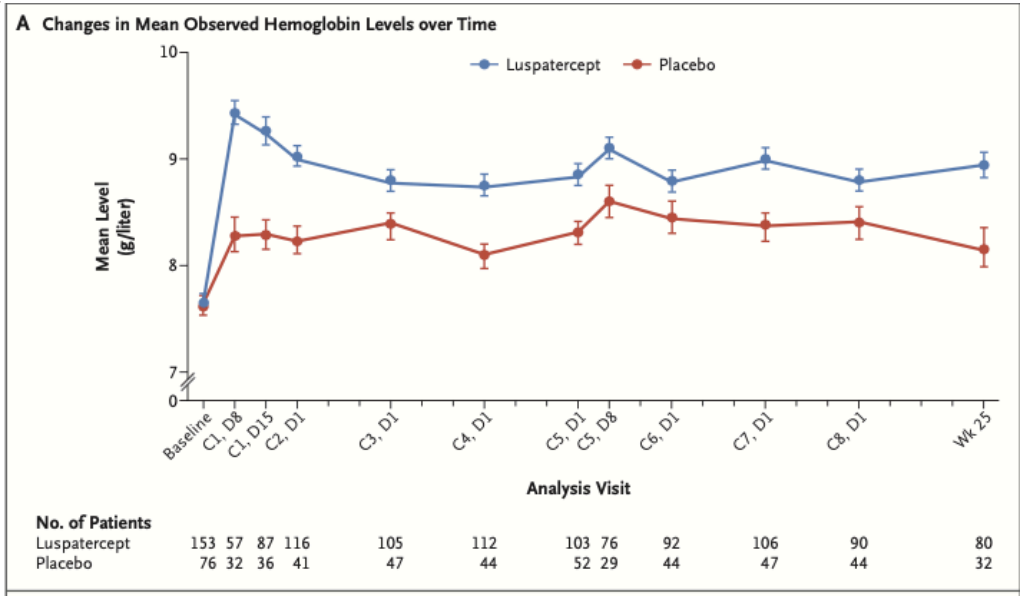
- Transfusion dependent before randomization
- Refractory to or was unlikely to respond to ESA (endogenous erythropoietin level of >200 U/L)

Primary endpoint: transfusion independence for ≥8 weeks during weeks 1-24

229 patients, ~90% with SF3B1 mutation and almost all ESA-refractory

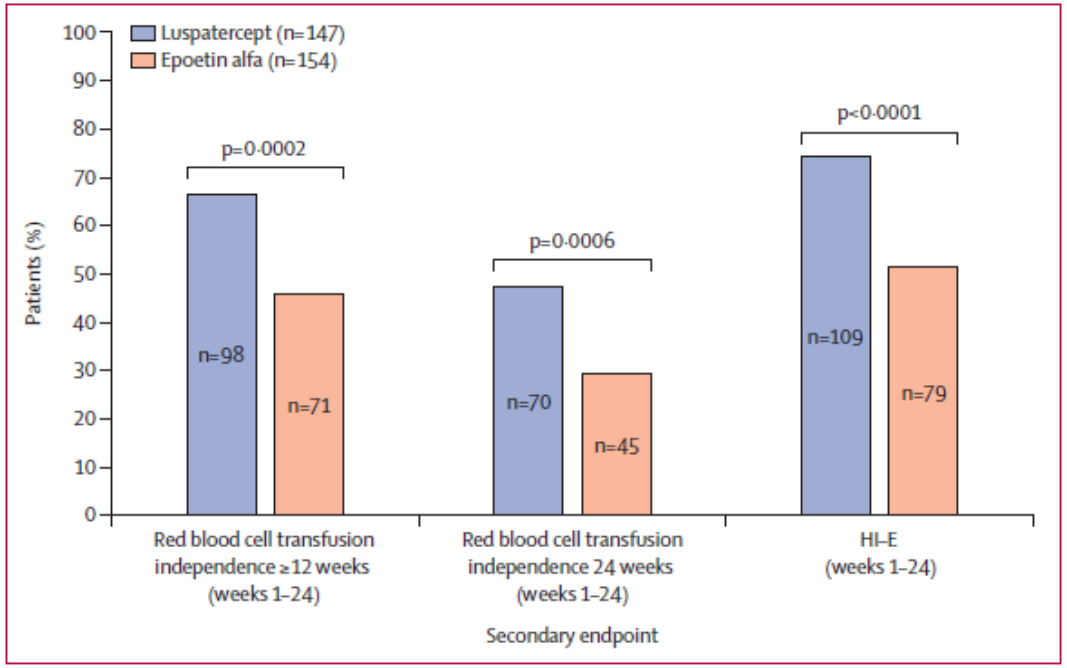
Transfusion Independence





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

COMMANDS TRIAL → approval Luspatercept upfront MDS



- Phase 3 open label trial
- 301 patients with low/int risk MDS
- ESA naïve
- Requiring PRBC transfusion
- Randomized to Luspatercept or Epo
- Primary endpoint: 12-wk transfusion independence + Hgb increase >1.5

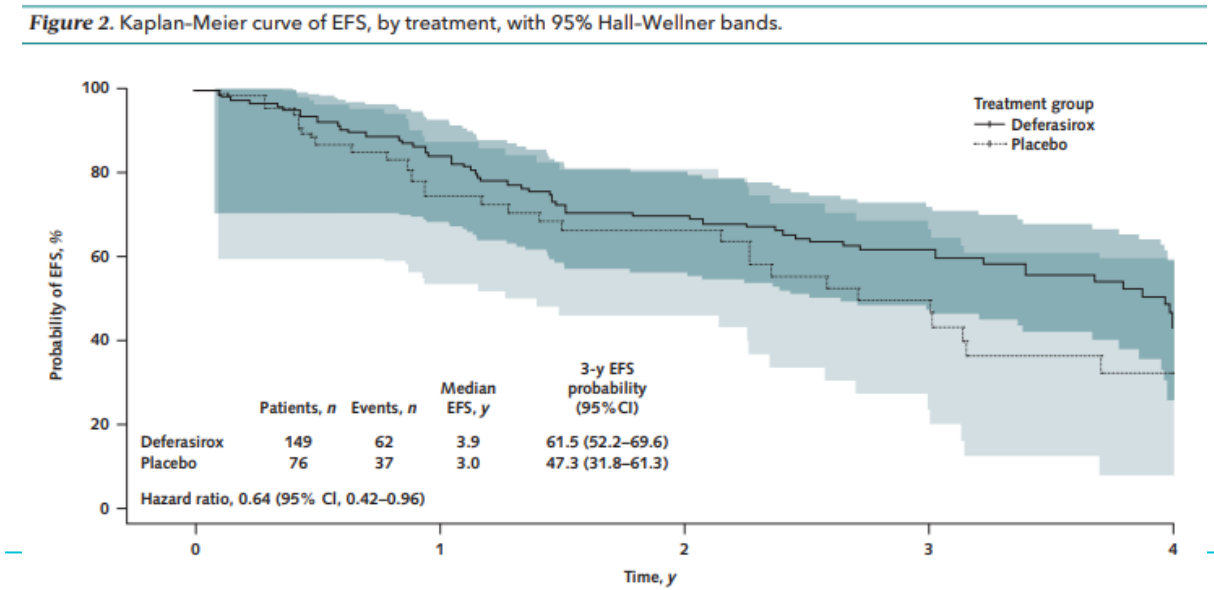
	Luspatercept (n=178)		Epoetin alfa (n=176)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
General disorder or administration site conditions				
Fatigue	26 (15%)	1 (1%)	12 (7%)	1 (1%)
Peripheral oedema	23 (13%)	0	12 (7%)	0
Asthenia	22 (12%)	0	25 (14%)	1 (1%)
Infections and infestations				
COVID-19	19 (11%)	6 (3%)	17 (10%)	2 (1%)
Gastrointestinal disorders				
Diarrhoea	26 (15%)	2 (1%)	20 (11%)	1 (1%)
Nausea	21 (12%)	0	13 (7%)	0
Respiratory, thoracic, or mediastinal disorders				
Dyspnoea	21 (12%)	7 (4%)	13 (7%)	2 (1%)
Vascular disorders				
Hypertension	23 (13%)	15 (8%)	12 (7%)	8 (5%)
Blood and lymphatic system disorders				
Anaemia	17 (10%)	13 (7%)	17 (10%)	12 (7%)

- **59% Luspatercept vs. 31% Epo met primary endpoint**
- Responses in all molecular/subgroup categories favor Luspatercept except non-ringed sideroblasts (41% Luspatercept vs 46% Epo)

Platzbecker U et al. Lancet 2023; 402: 373-85.

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



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

Less common scenarios in lower-risk MDS

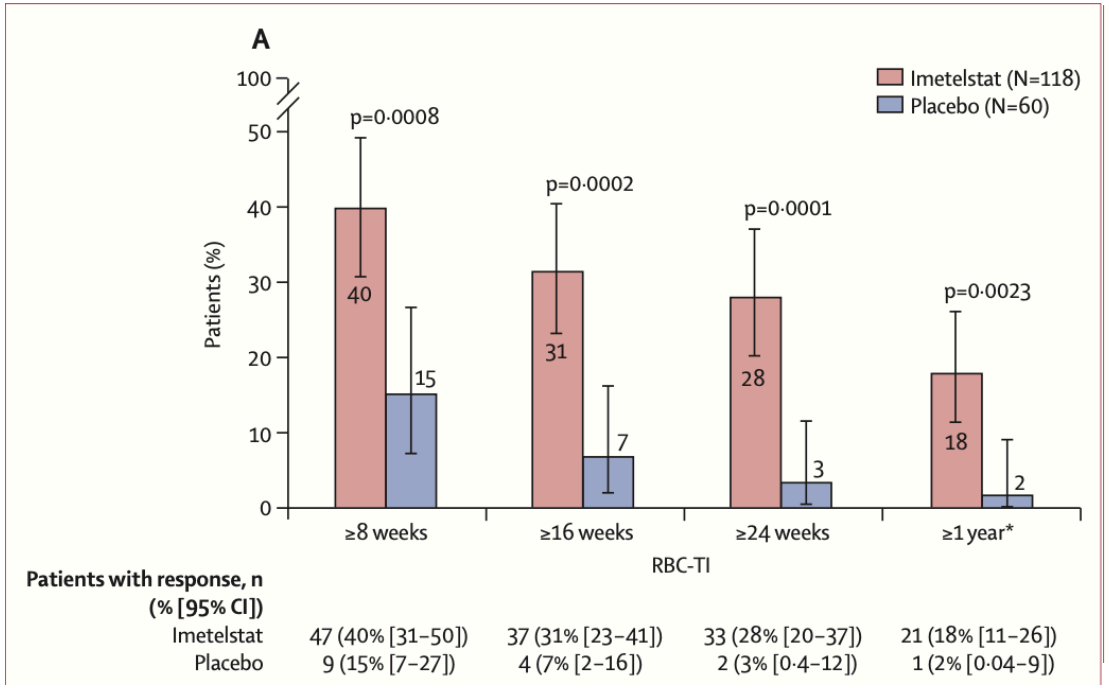
- **Del5q MDS: 5% of MDS patients**
  - Lenalidomide is an immunomodulatory agent selectively suppresses the del(5q) clone
  - Lenalidomide reduces transfusion needs in 2/3 of patients with del(5q) but does not delay progression to AML; median response 2 years
  - Follow for TP53 closely- clone can expand
  - Lenalidomide also can reduce transfusion needs for ~1/4 of patients without del(5q)

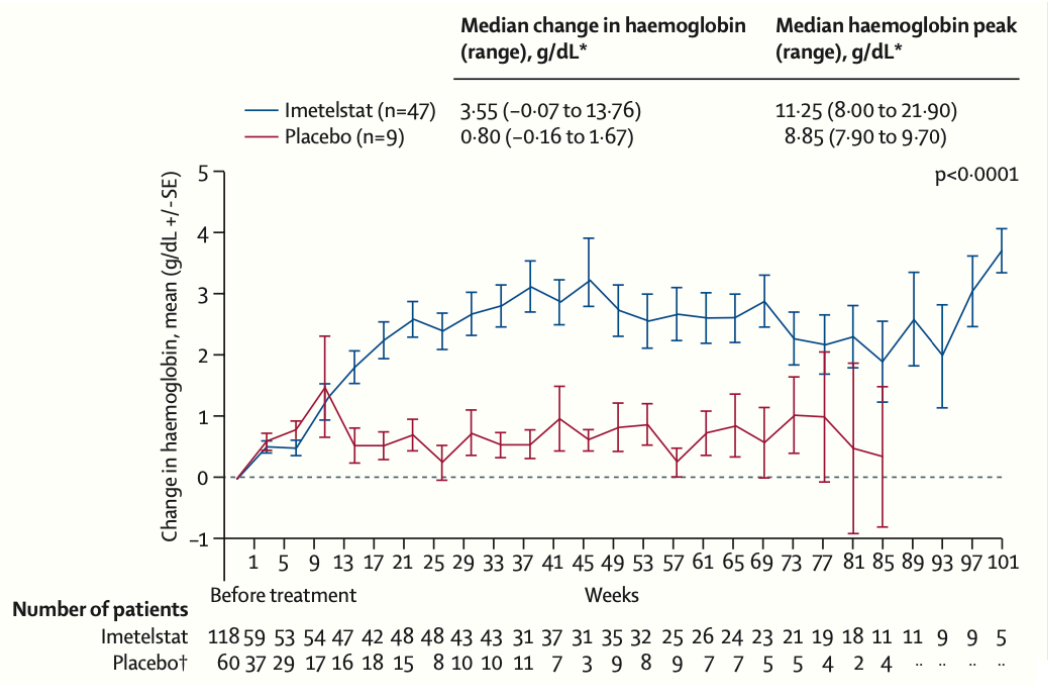
- **Immunosuppression sometimes used (ATG +cyclosporine+/- steroids):**
  - Most often used for ”hypoplastic MDS” more likely due to immune related hematopoietic suppression
  - Features associated with increased likelihood of responding to IST: age <60 years with ≤5 percent blasts, hypocellular bone 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

IMerge TRIAL → approval imetelstat LR-MDS with anemia

- Phase 3 open label trial (randomization 2:1 imetelstat vs placebo)
- 178 patients with low risk transfusion dependent MDS (not del5q)
- ESA refractory or ineligible
- Requiring PRBC transfusion (>4U / 8wks)
- Primary endpoint: 8-wk transfusion independence (PFS, OS, AML incidence not mature)



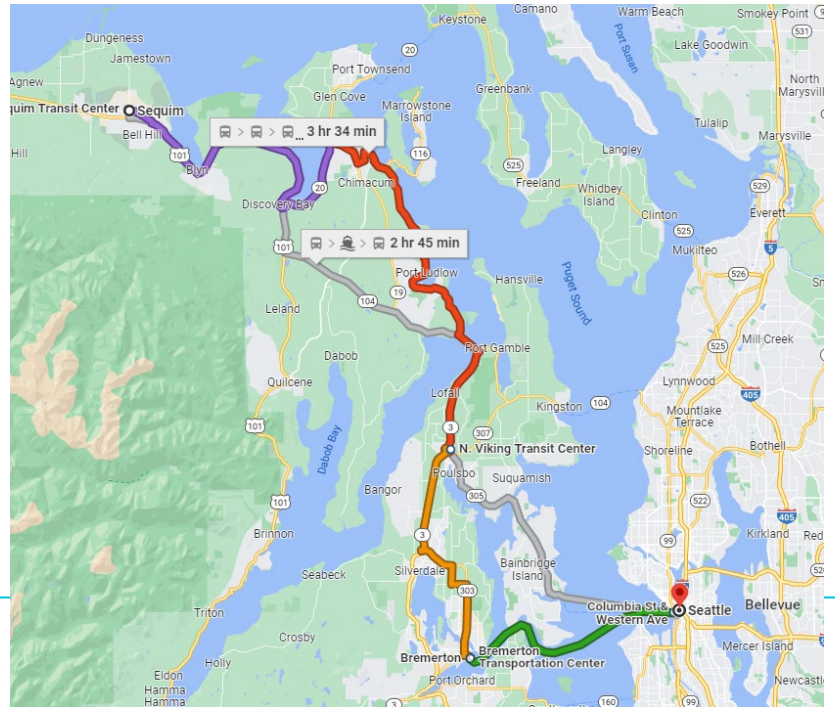


Platzbecker U et al. Lancet 2024; 402: 373-85.

Case 3

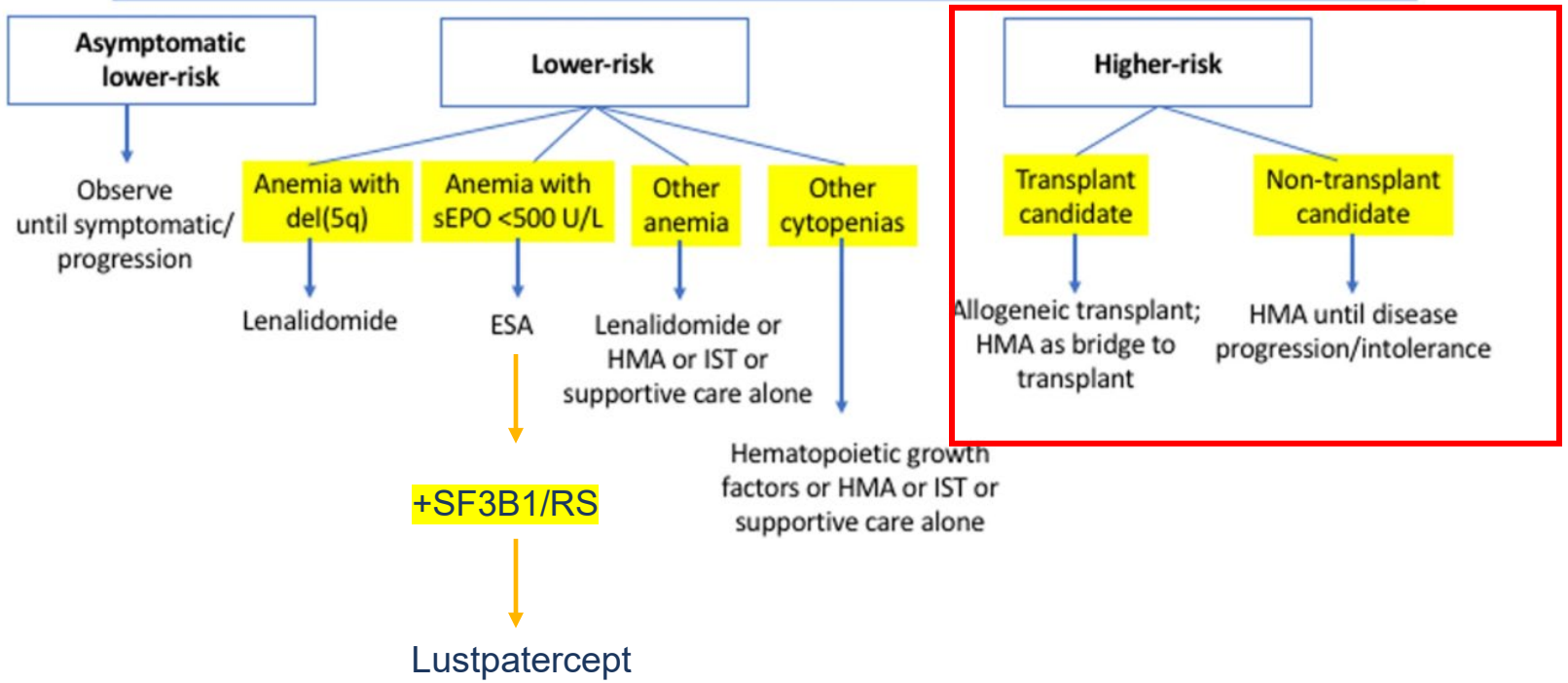
- 76 yo M has a 5-year history of lower grade MDS, on just ESAs, now with progressive pancytopenia
  - WBC 1.5 with ANC 0.6, Hgb 8 and Plts 24
- Bone marrow biopsy shows a hypercellular marrow with 4% blasts on morphology, +8[16] on cytogenetics and NGS Myeloid Gene Panel demonstrating EZH2 and SRSF2
- IPSS-R and IPSS-M score is high, median 1.7 year OS
- Comorbidities: COPD and BPH
  - Not a transplant candidate
- Lives in Sequim → clinical trials difficult
- Is a candidate for HMA, oral choices

may be good for him



Current Treatment Algorithm in Myelodysplastic Syndromes

Consider clinical trial enrollment for all patients
Supportive care (e.g., transfusions and antimicrobials as needed) for all patients
Risk stratification using IPSS-R supplemented by molecular testing



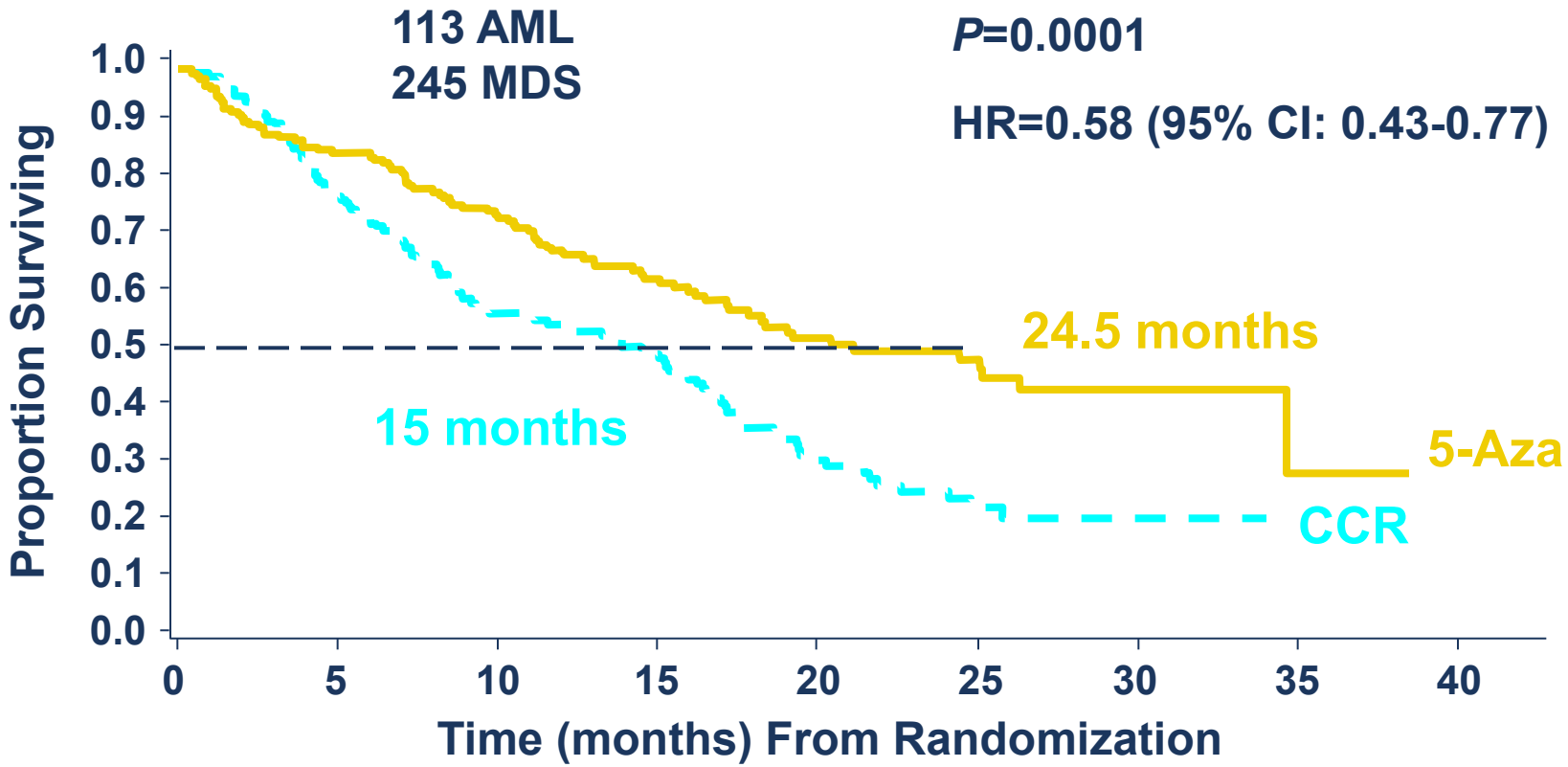
ESA= erythropoietin stimulating agent;
HMA= hypomethylating agent

**HMA Failure an area of need for trials

Adapted from Steensma 2018. Blood Cancer Journal 8:47.

Azacitidine leads to survival benefit in MDS

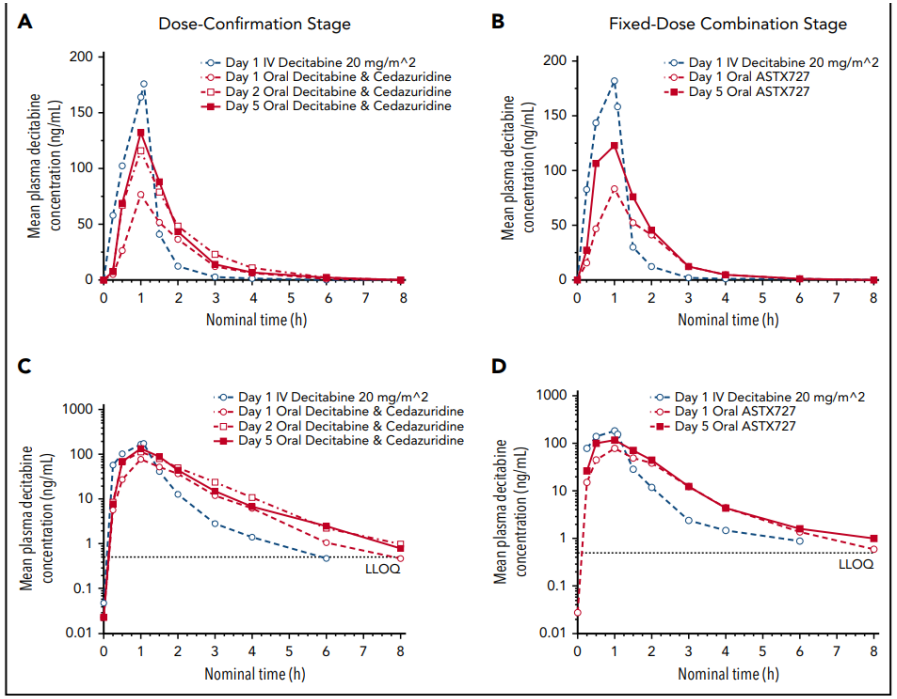
Phase 3 open label trial, aza vs CC: BSC (222), LDAC (94), or intensive chemo (42)



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

Inqovi (oral decitabine and cedazuridine)

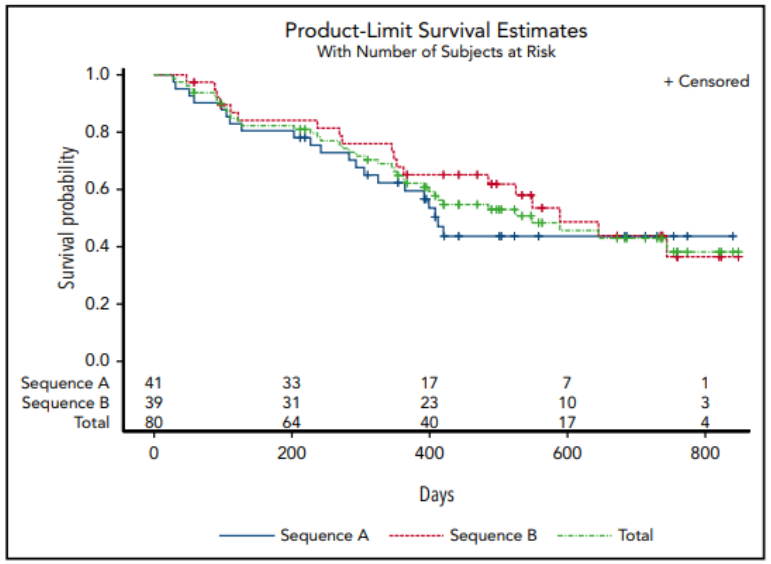
- Oral decitabine/AZA bioavailability limited by rapid inactivation by cytidine deaminase (CDA) in GI tract
- Cedazuridine is a CDA inhibitor
- 80 adults with int-1/2/high-risk MDS or CMML were randomized 1:1 to receive oral cedazuridine/decitabine or IV decitabine
- All patients received cedazuridine/decitabine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



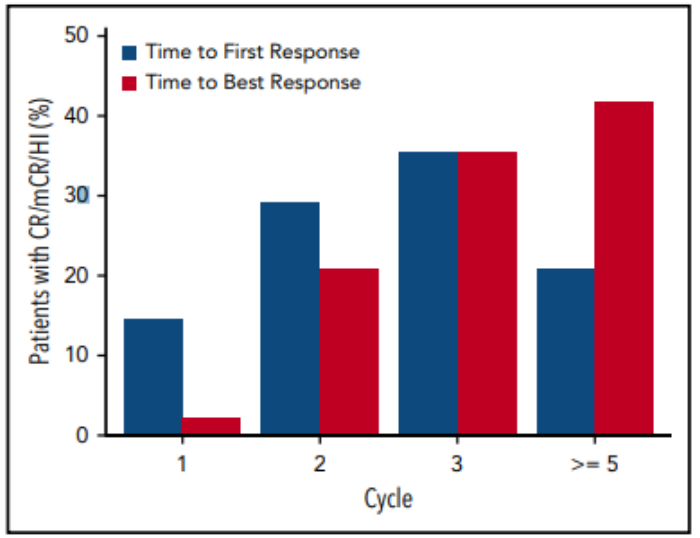


Figure 3. Time to first response and time to best response by cycle (N = 80). HI, hematologic improvement; mCR, marrow complete response.

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%

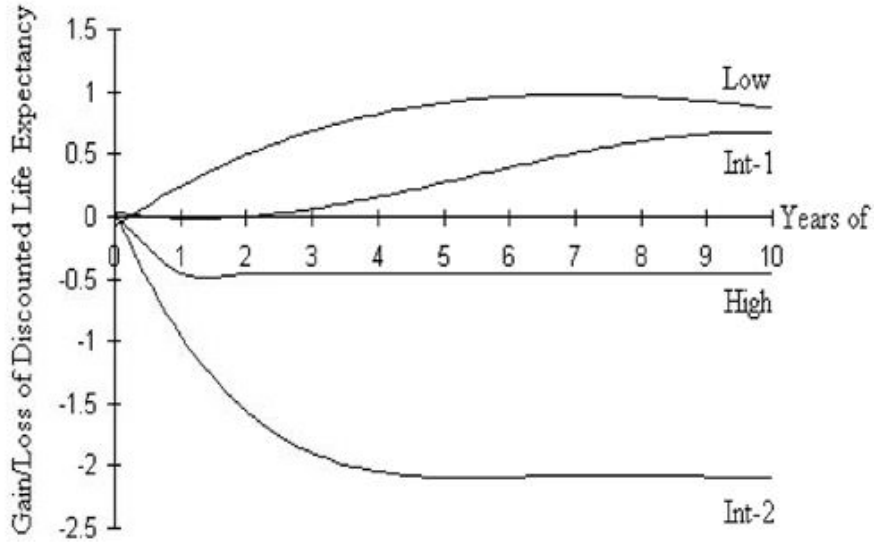
❖ MDS with bi-allelic TP inactivation

❖ 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

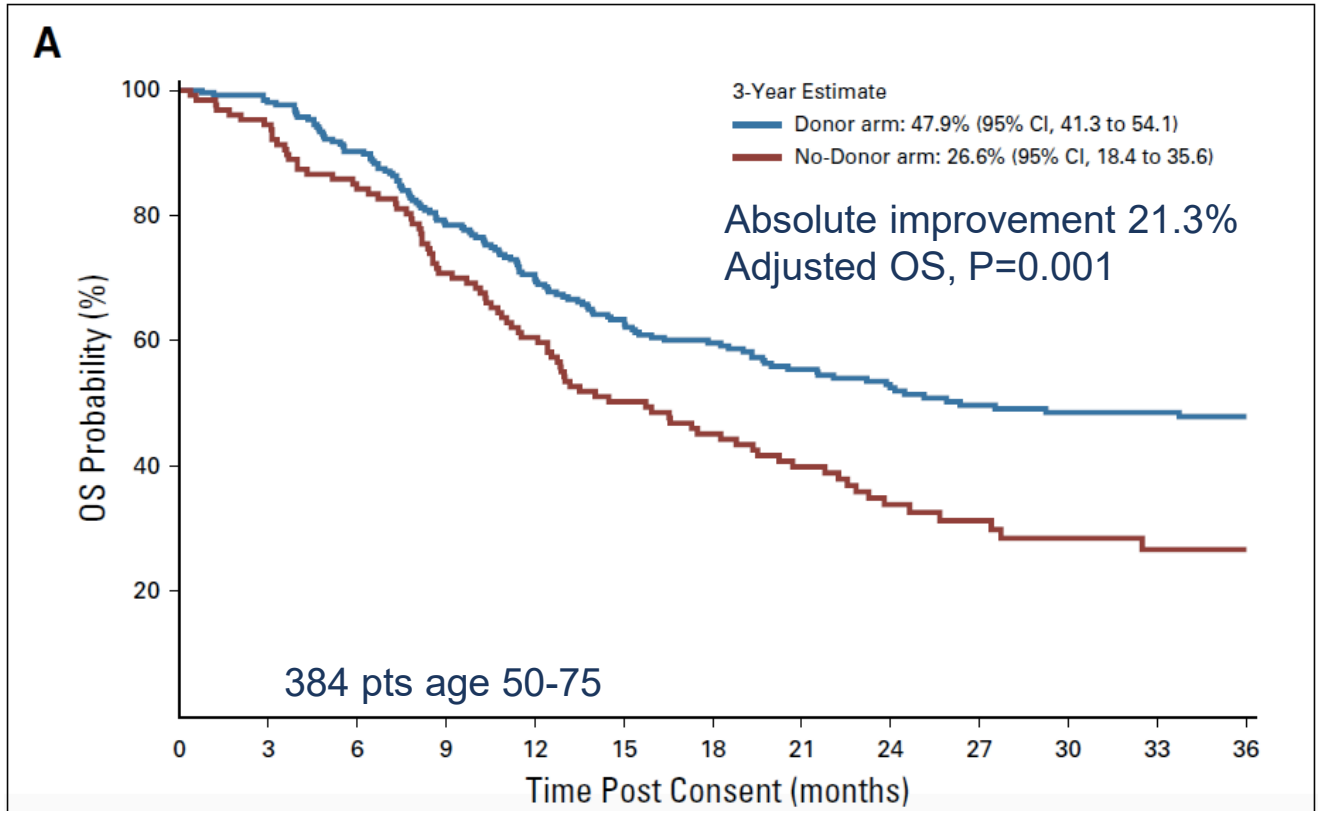


- *A net benefit for delaying transplantation for low and int-1 risk groups; delay in the time to transplantation is associated with a loss in survivorship in higher risk groups*
- Adjustment for QoL did not change the preferred treatment strategy
- Better to transplant prior to AML transformation

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

Biologic assignment trial in MDS

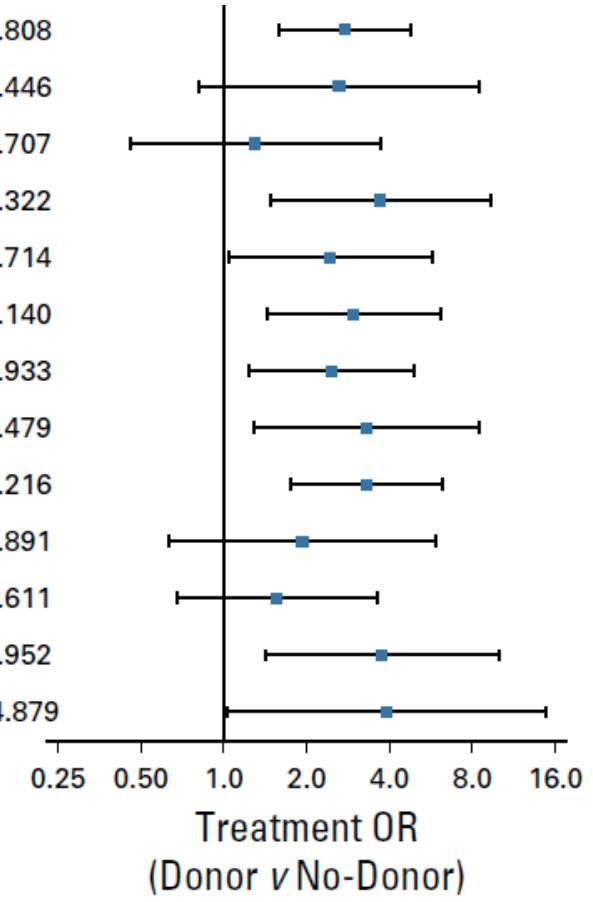
Significant survival advantage in older subjects with higher-risk MDS who have a matched donor identified and underwent RIC HCT vs AZA/BSC



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

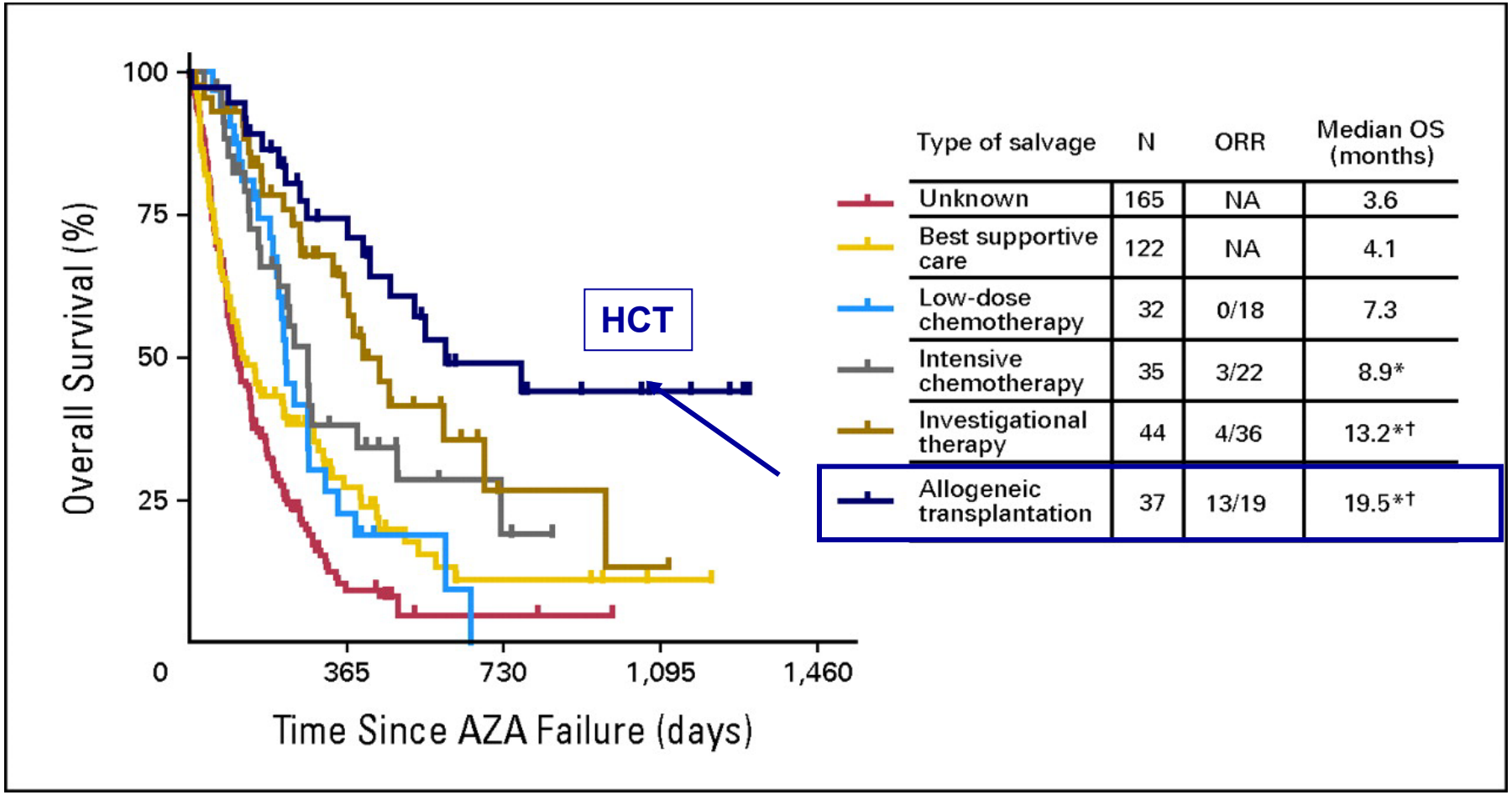
Survival benefit of HCT was seen across subgroups

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.

HR MDS post AZA failure OS by Salvage Therapy



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*†

Median OS is 5.6 months

Prébet et al. *J Clin Oncol* 2011;29:3322-3327

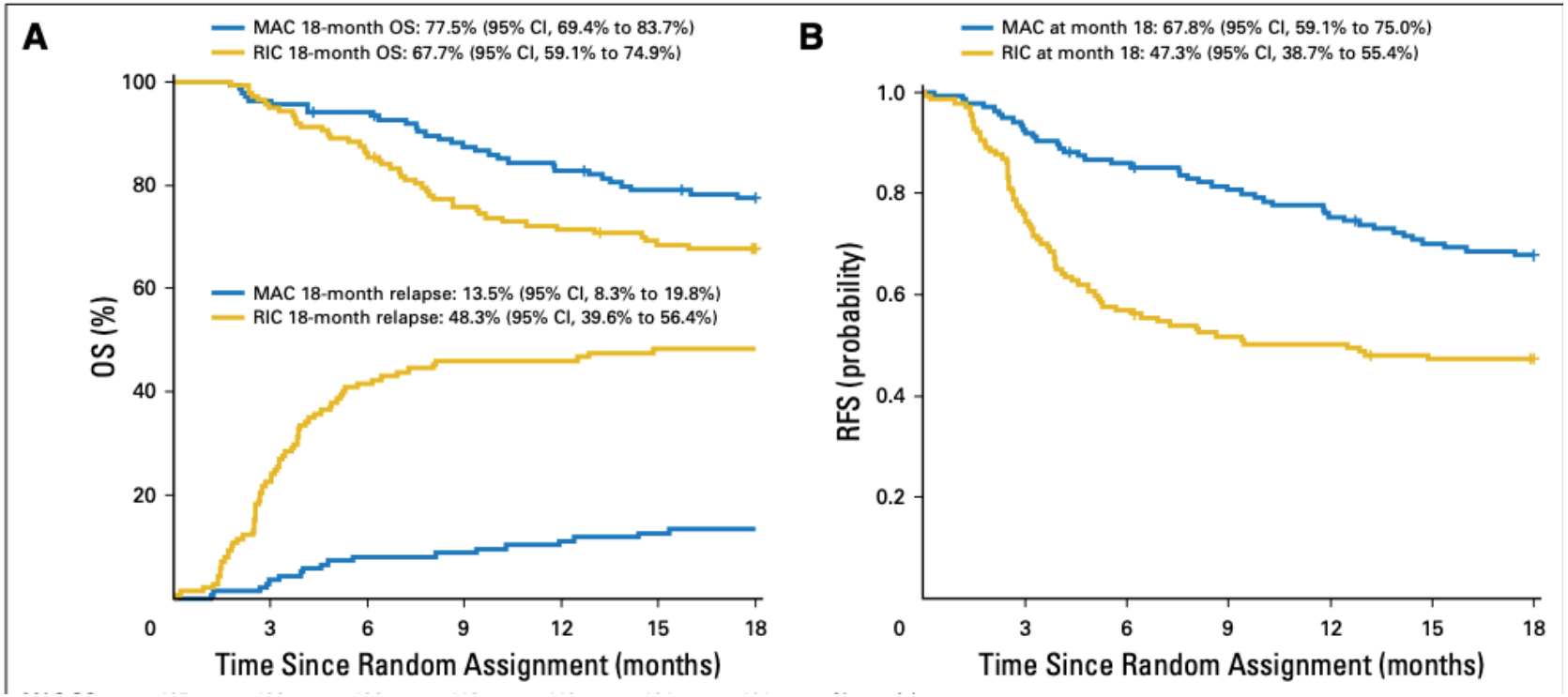
Is cytoreductive therapy needed prior to HCT?

- No definitive evidence of a survival benefit for patients who receive cytoreductive therapy prior to HCT
- Only randomized trial stopped early due to slow accrual; most retrospective single institution studies inconclusive or did not account for selection bias
- A higher burden of disease at the time of transplantation associated with inferior outcomes,
  - Unclear if cytoreductive treatment can alter outcomes or if a higher blast count reflects the biology of the MDS.
- No one cytoreductive bridging therapy has been shown to achieve superior outcomes following transplantation.
  - A retrospective study of bridging therapy showed that AZA vs intensive therapy achieved a comparable rate of post-transplant relapse, but caused less toxicity
  - Another study: similar outcomes between AZA vs intensive therapy
  - Other studies reported that survival after HCT was comparable without any therapy or intensive therapy before transplant
- Here our approach depends on age/comorbidities, cyto/mutations, time to transplant, conditioning intensity MAC vs RIC

De Witte et al. Br J Haematol 2000; 110 (3): 620. Alessandrino et al. Bloo 2008; 112: 895. Nakai et al. Leukemia 205; 19: 396. Della Porta et al. Blood 2014' 123: 2333.
Gerds et al. Biol blood Marrow Transplant 2012; 18: 1211. Damaj et al. JCO 2012; 30: 453. Scott et a. biol Blood Marrow Transplant 2005; 11: 65. Scott et al. JCO 2017; 34: 1154.

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

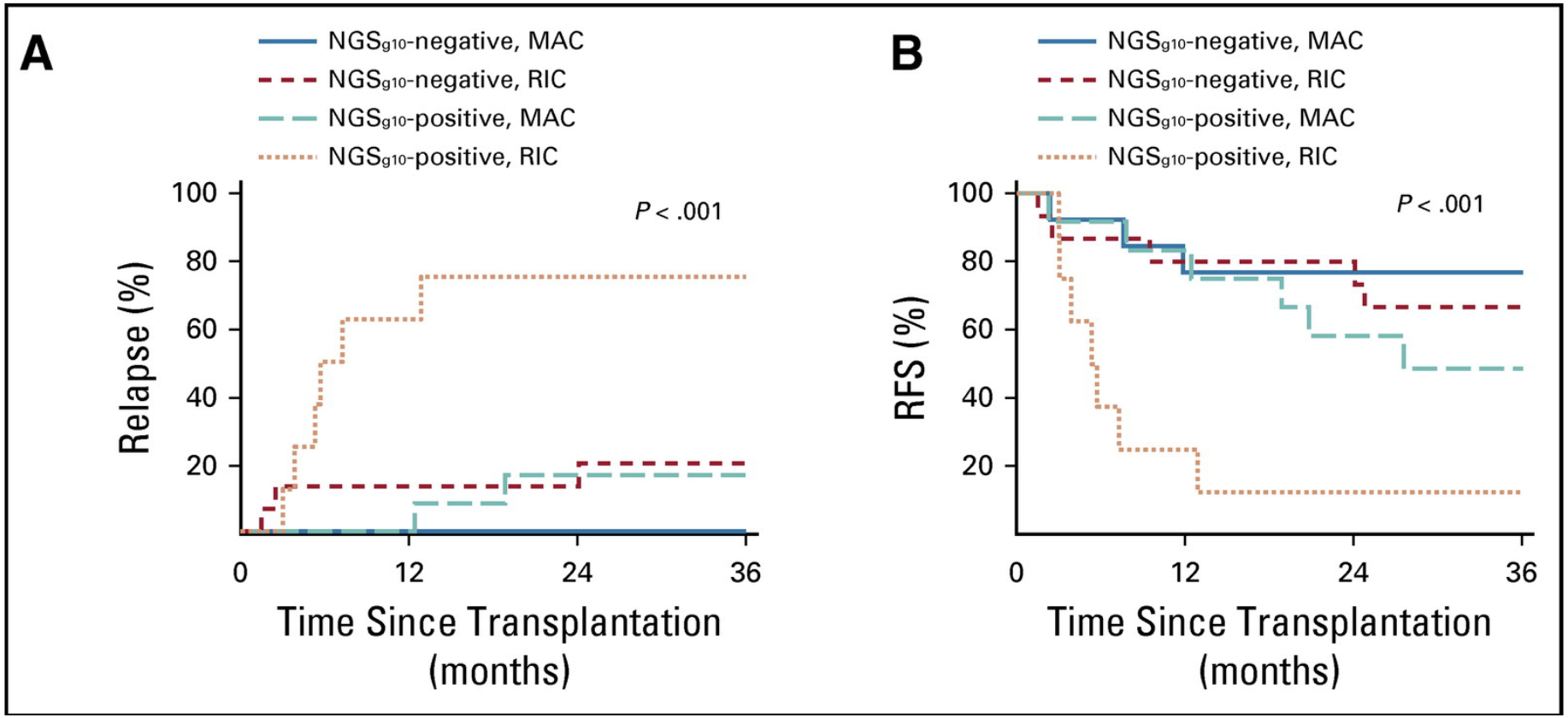
- 272 patients with AML/MDS randomized to MAC vs RIC
- TRM was significantly lower among patients in the RIC arm (4.4% v 15.8%)
- OS was inferior in patients receiving RIC; difference not stat significant



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
- Cytogenetics and mutations drive prognosis and risk
- Given older age at presentation and wide disease spectrum, patients can often be monitored or supported with growth factor without chemotherapy
- 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)
G. E or F

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G. E or F

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. E or F are appropriate.

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

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

References

- **CHIP/CCUS:**
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- **Randomized trial for AZA in MDS**:
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- **Transplant timing MDS**: Cutler et al. Blood. 2004;104:579-585

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Cancer Center

Thank you