Overview of the Myelodysplastic Syndromes (MDS)

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February 4, 2017

UCDAVIS
COMPREHENSIVE
CANCER CENTER

What do these individuals have in common?

1) Astronomers
2) Newscasters
3) Politicians
4) MDS

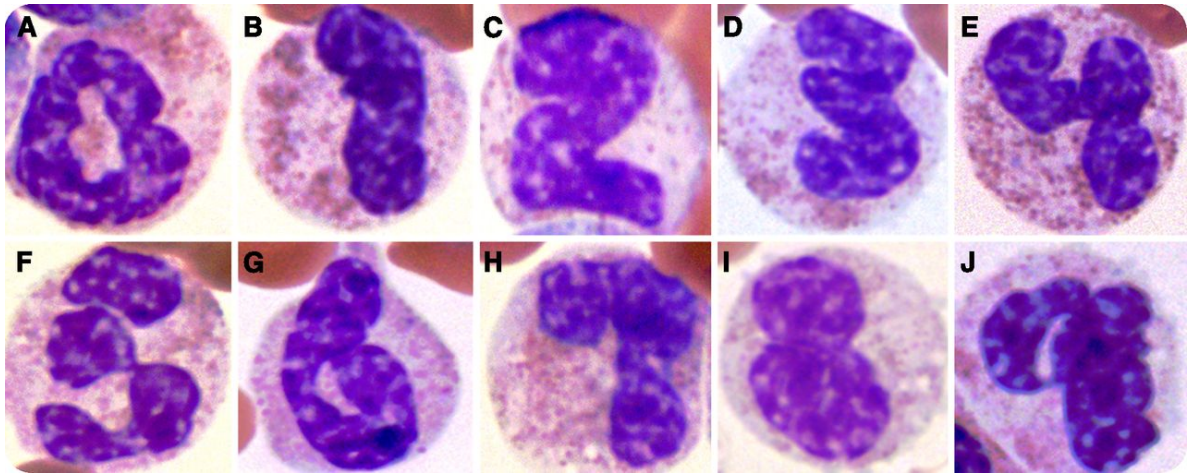
MDS Questions to be Answered

- What is MDS?
- Why did I get MDS?
- What does it mean for my life?
- Is there treatment for it?
- How should I be treated?
  - When?
  - Why?
- What are some of the new advances in MDS?

Essentials for the Informed Pt with MDS

- Know your IPSS-R risk group
- Know your treatment options
  - Including transplant, clinical trials
- Know what your treatment goals are
- Know the potential side effects of your treatments
- Know available MDS resources
- Have a caregiver available/involved

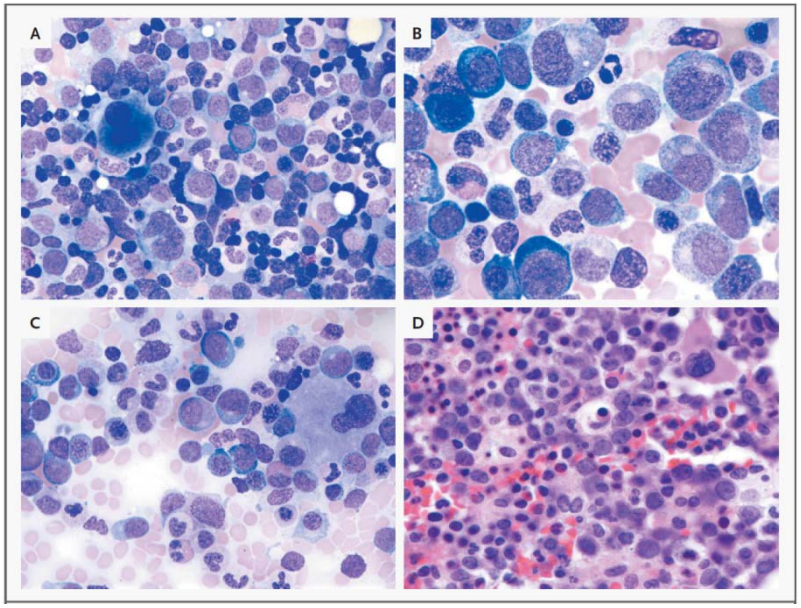
The Myelodysplastic Syndromes

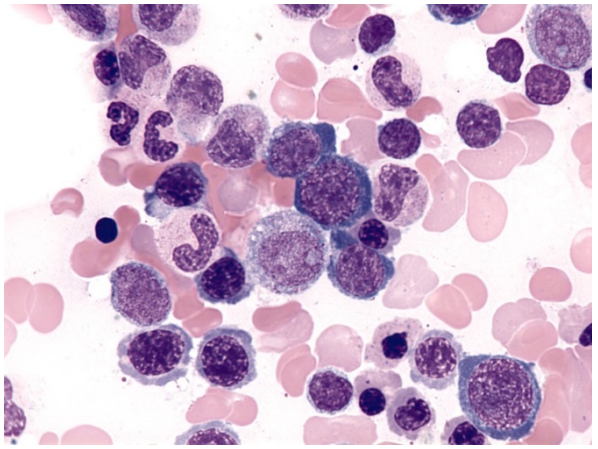


Blood, 2014.

The Myelodysplastic Syndromes (MDS)

- Heterogeneous group of clonal bone marrow failure syndromes
- 10-30,000 cases per year in US
- Median age 76, > in males
- Ineffective hematopoiesis
  - Bleeding, infections, anemia
- Transformation to AML
- Variable clinical course
  - Need for accurate prognostication

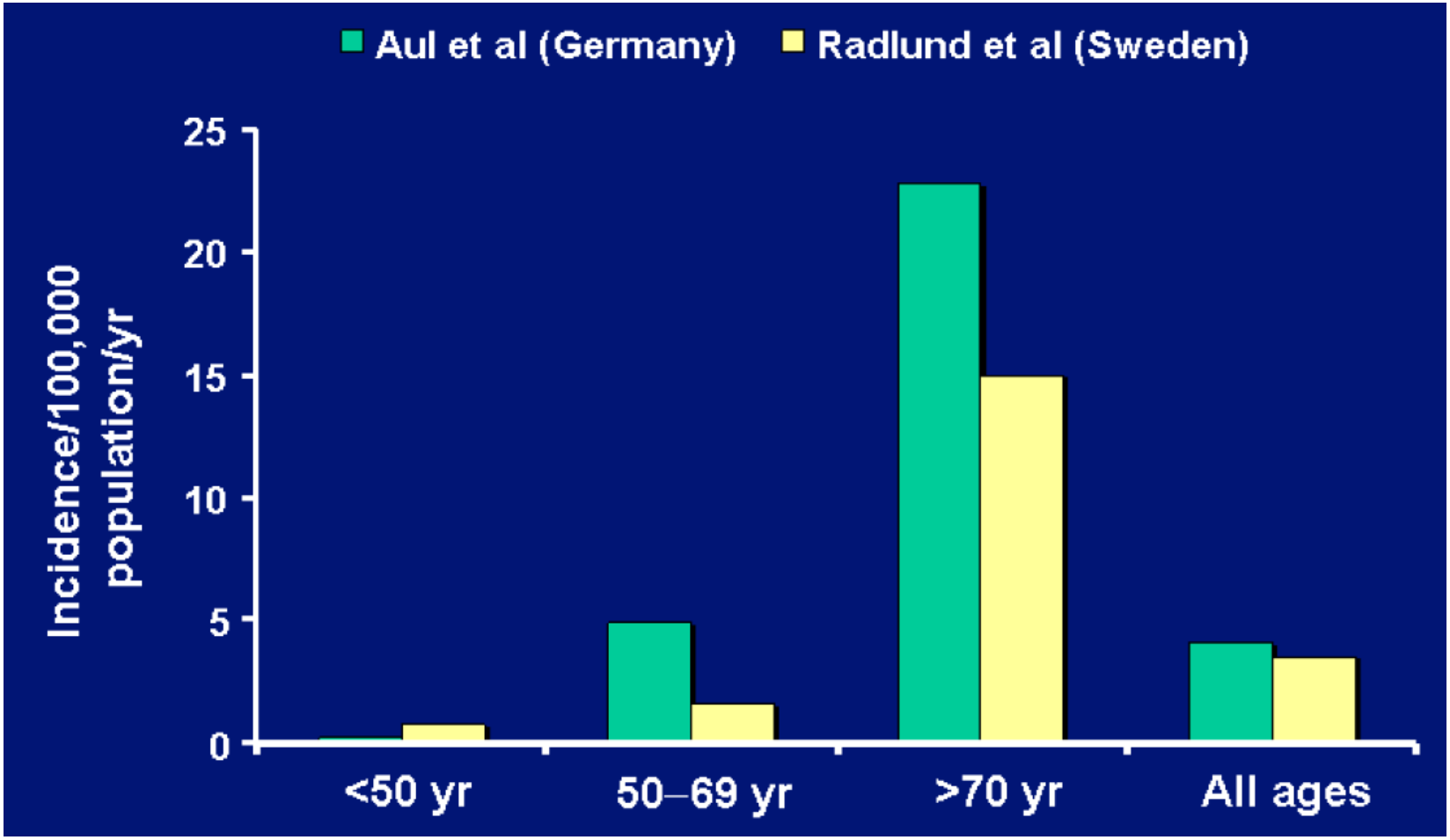




List et al. NEJM 2005.
Ma et al. Cancer 2007.

Epidemiology of MDS

MDS Incidence Increases With Age



Aul et al. Leuk Res 1998.
Radlund et al. Eur J Haematol 1995.

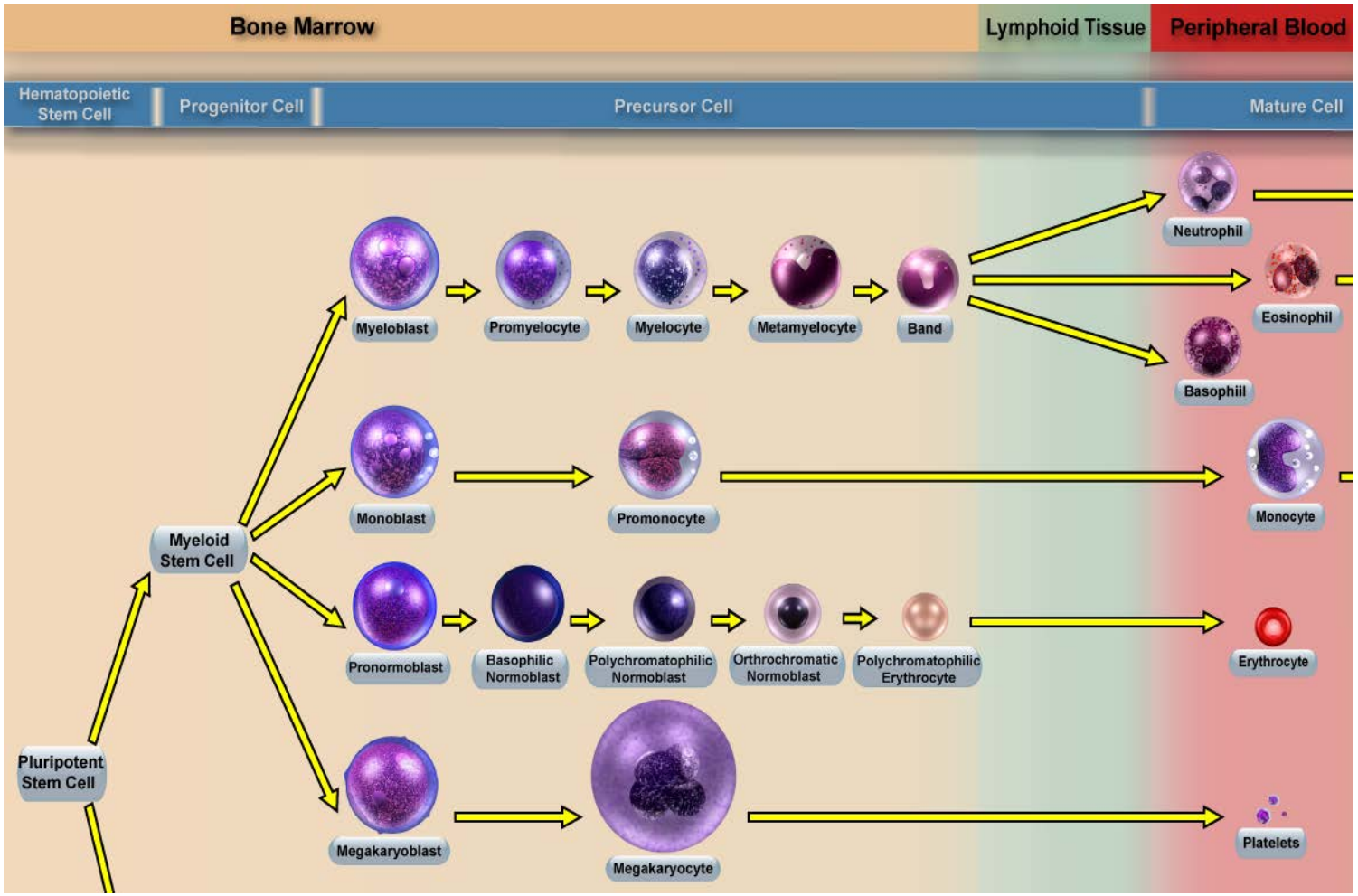
Predispositions and Risk Factors for MDS

- Acquired Risk Factors (**common**)
  - Age
  - Mutagen exposure (chemotherapy, radiation, benzenes, tobacco)
  - Other hematologic disorders (e.g. AA, PNH)
- Heritable Predisposition (**rare**)

Pathogenesis of MDS

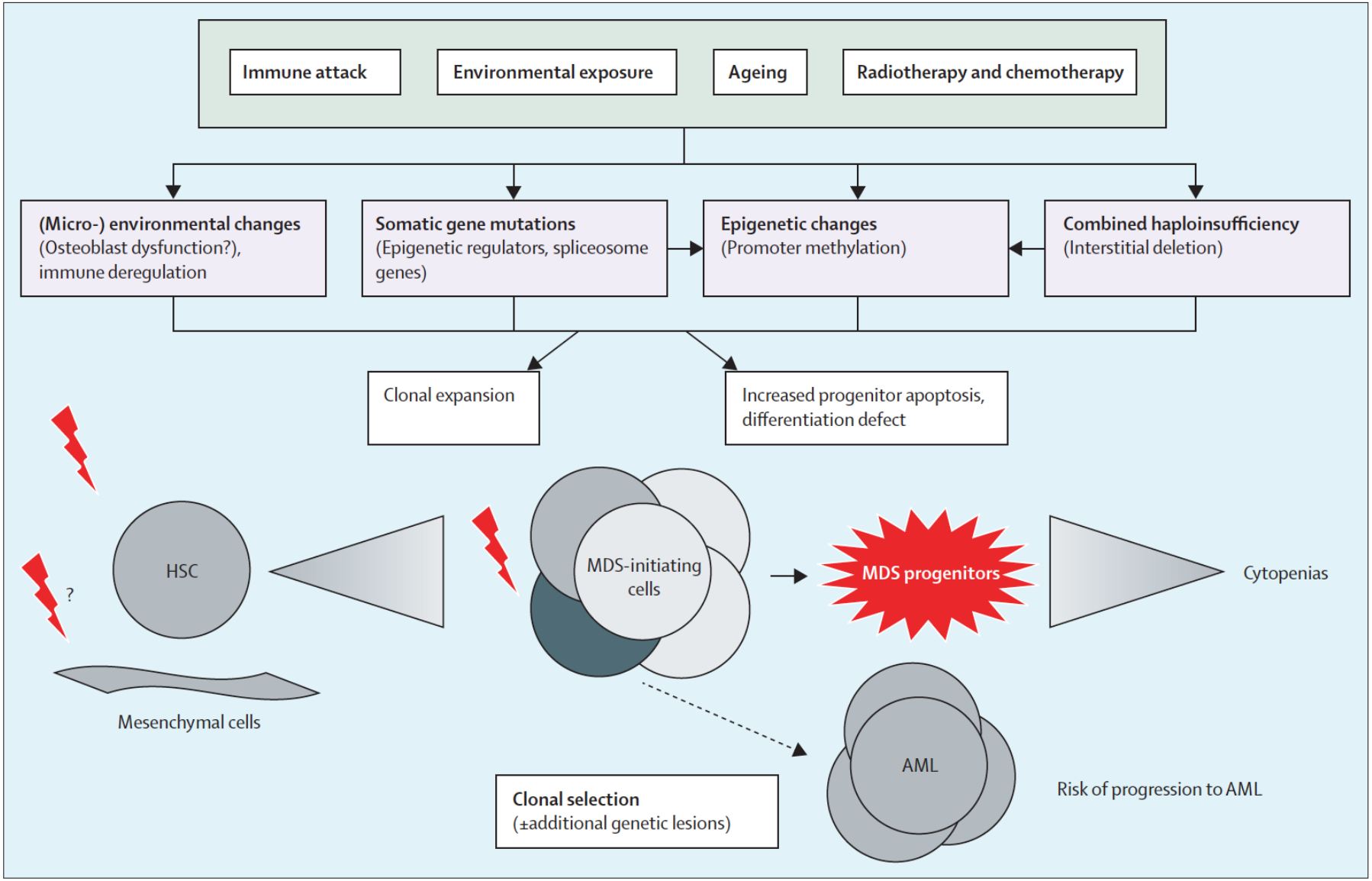
MDS is Like a Broken Down Assembly Line

Normal and Dysplastic Hematopoiesis



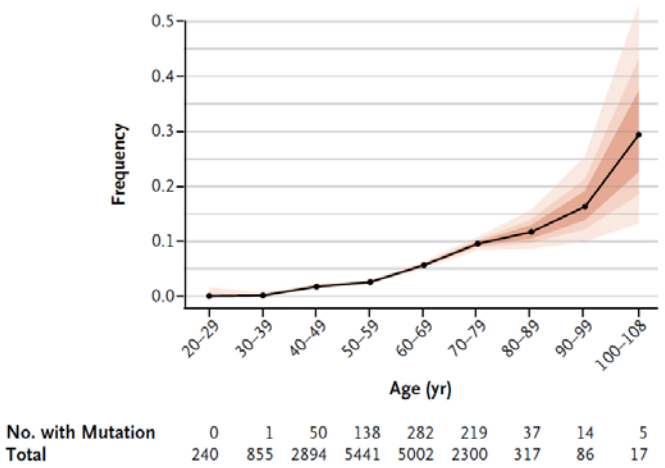
Dysfunctional progression along the maturation pathway

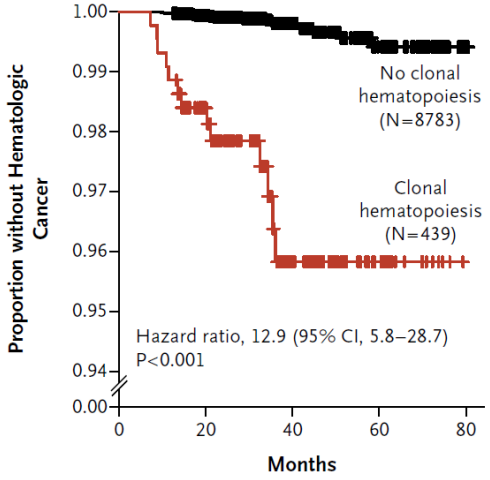
Pathogenesis of MDS

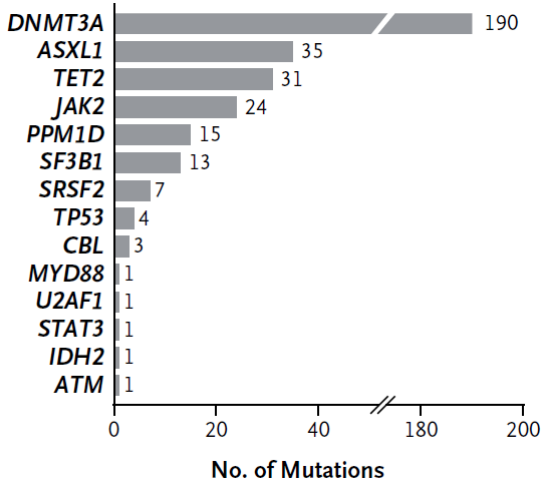


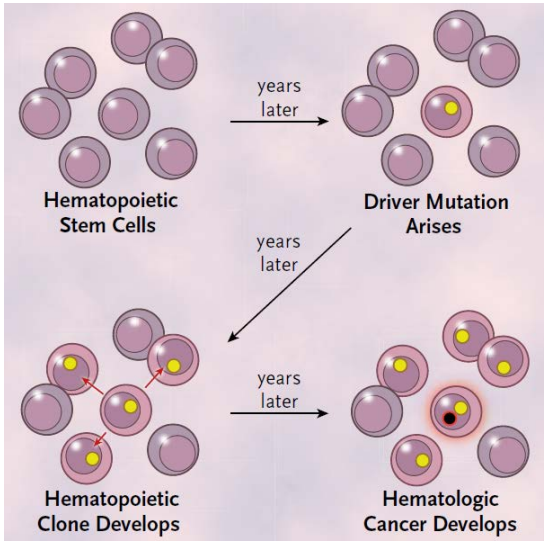
Ades et al. Lancet 2014.

Aging is Associated with Clonal Hematopoiesis with Driver Mutations



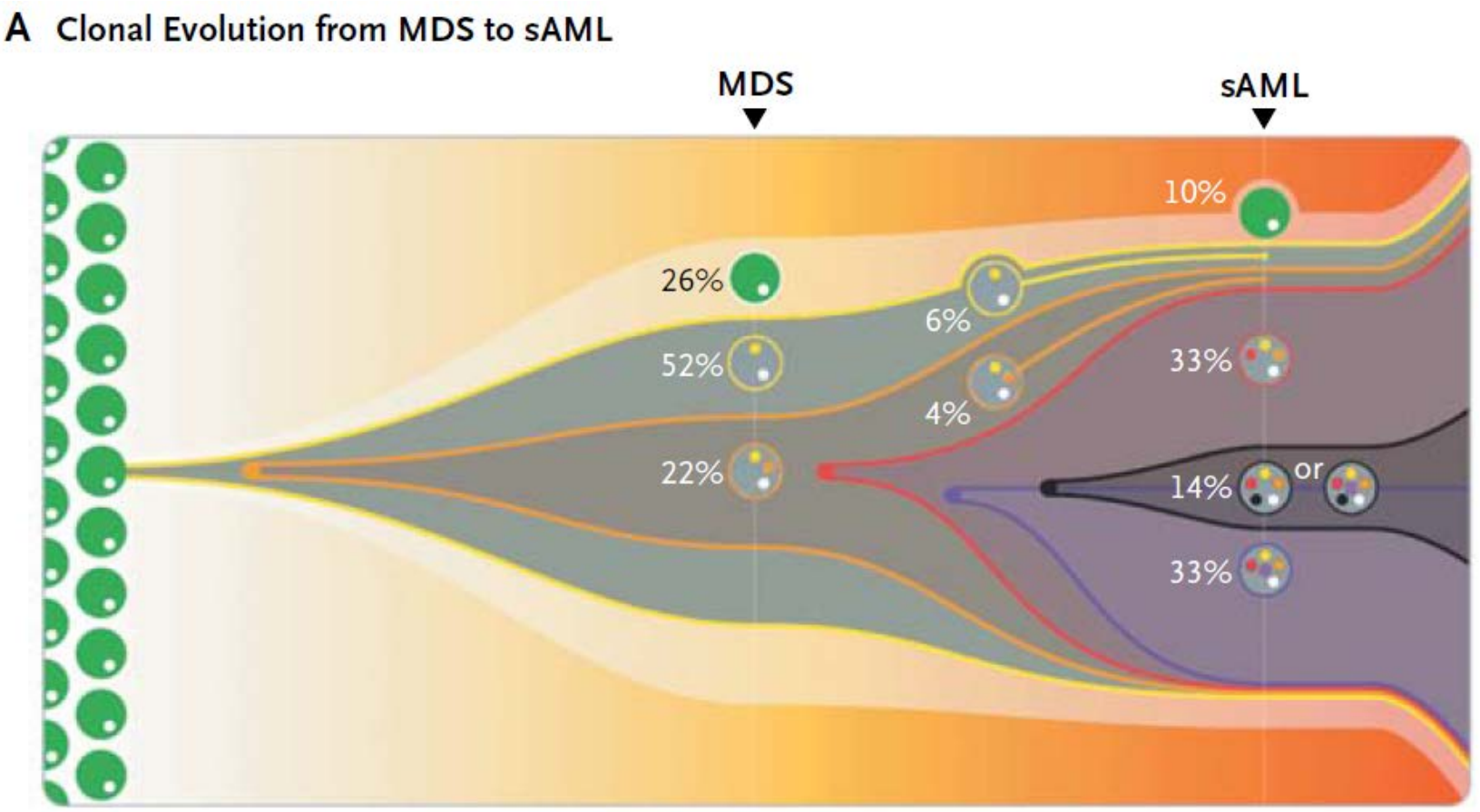






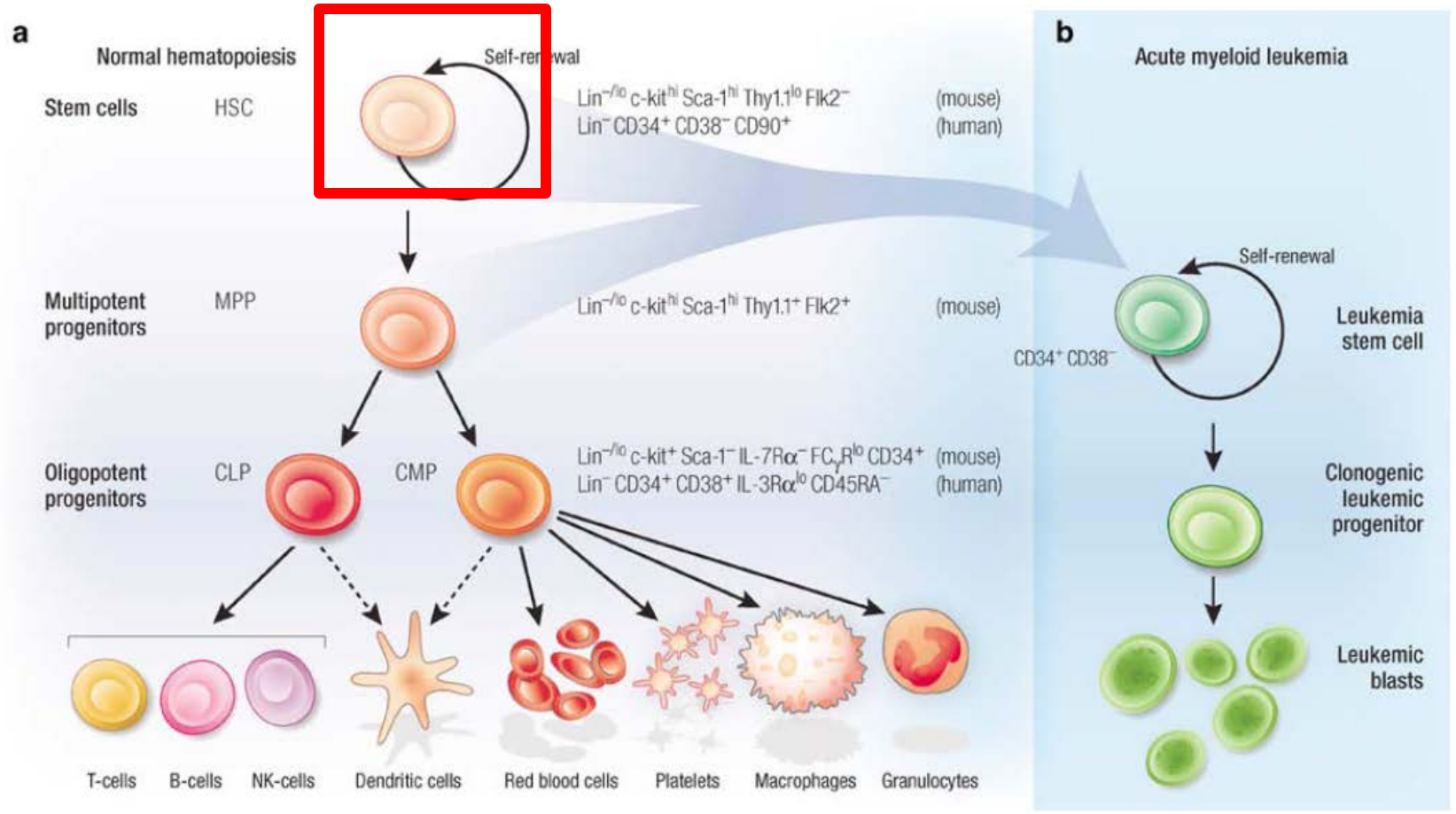
Jaiswal et al, NEJM, 2014.
Genovese et al, NEJM, 2014.

MDS is a Cancer



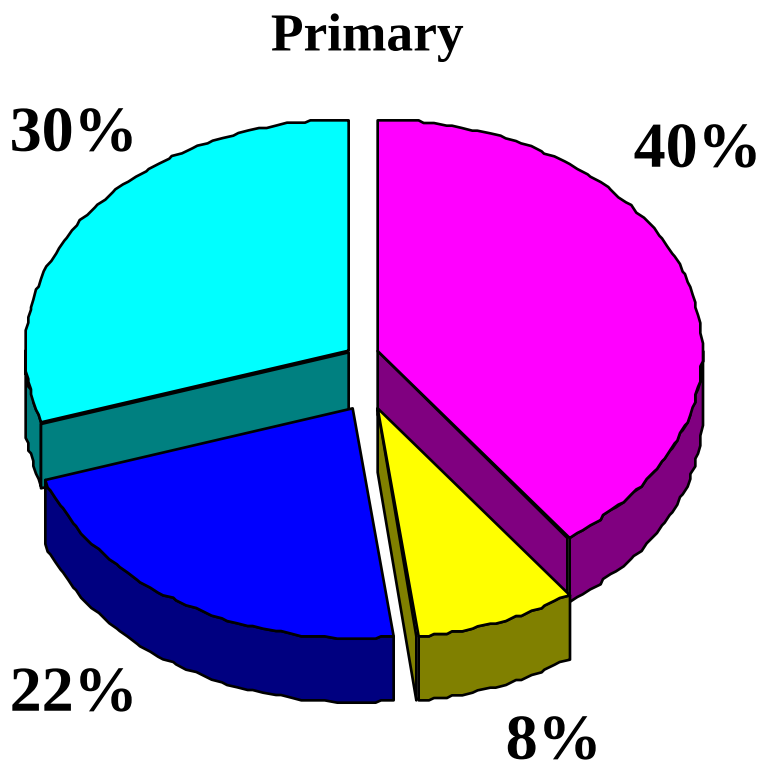
Walter et al. NEJM 2012.

The MDS "Stem Cell" is the primitive Hematopoietic Stem Cell



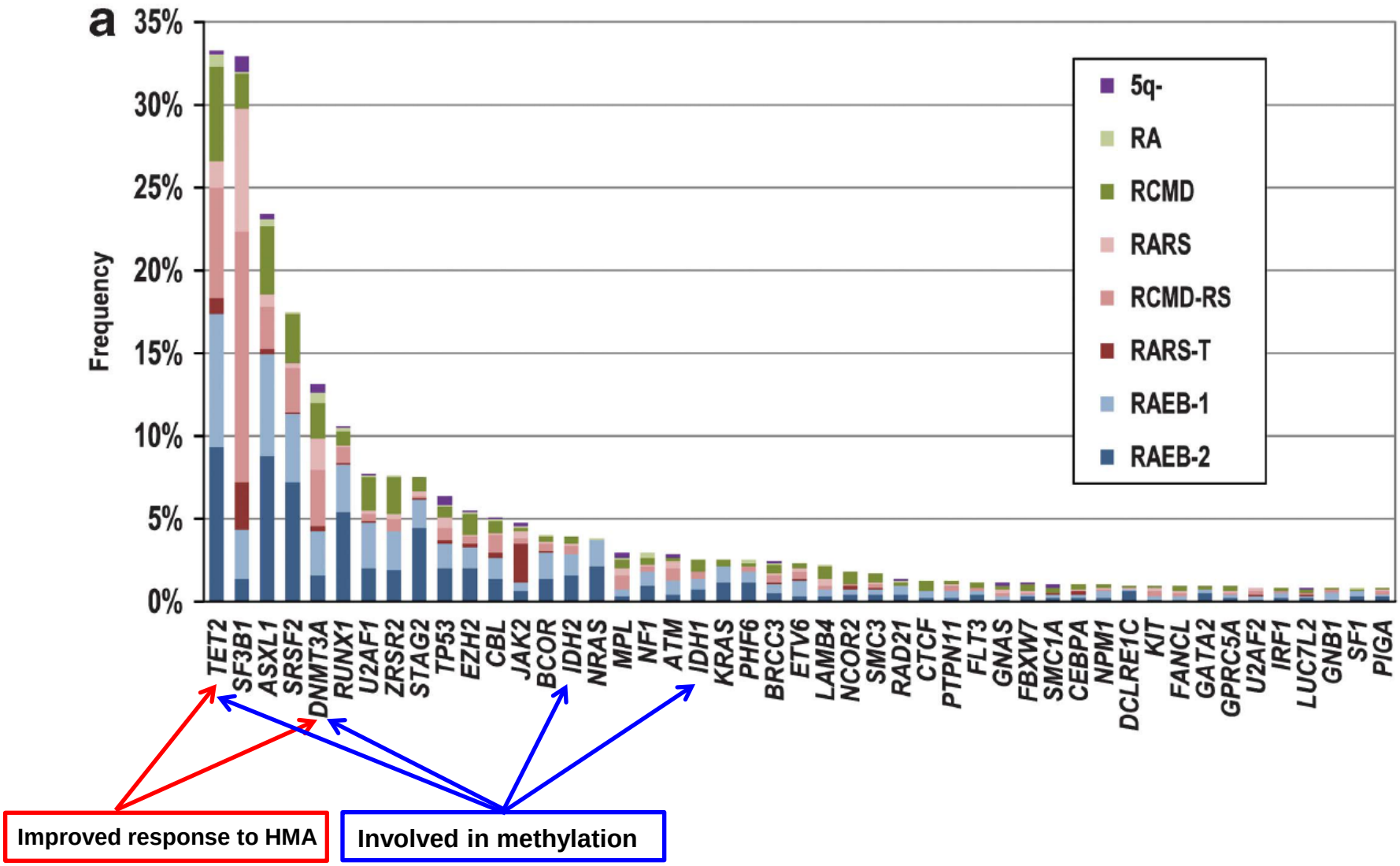
Nilsson et al. Blood 2007.
Tehranchi et al. NEJM 2010.
Pang et al. PNAS 2013.

MDS is Associated with Chromosome Abnormalities…



Olney et al. Leuk Res 2006.

Recurrent Mutations in MDS



Haferlach et al. Leukemia 2014; Bejar et al. Blood 2014.

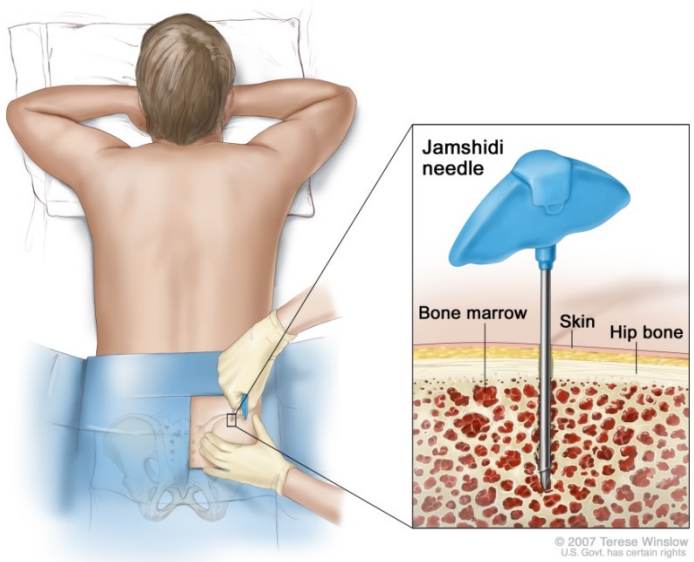
Presentation and Diagnosis of MDS

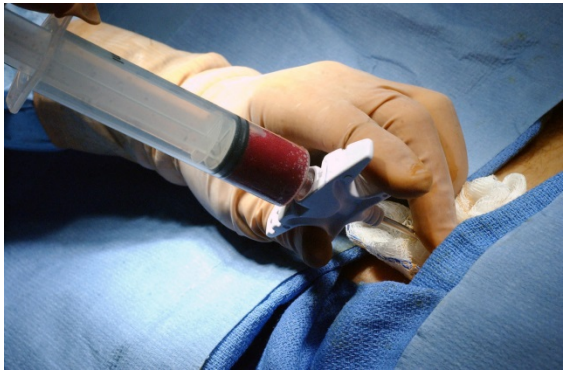
MDS Presentation

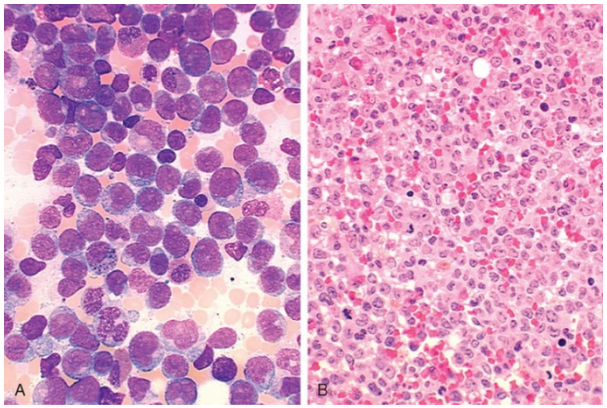
- Symptoms
  - Some are asymptomatic
  - Fatigue
  - Weakness
  - Bruising
  - Infections
- Signs
  - Pallor
  - Ecchymoses
- CBC
  - Anemia (most common)
    - Macrocytic
  - Neutropenia
    - Pelger-Huet cells
  - Thrombocytopenia

Diagnosis of MDS

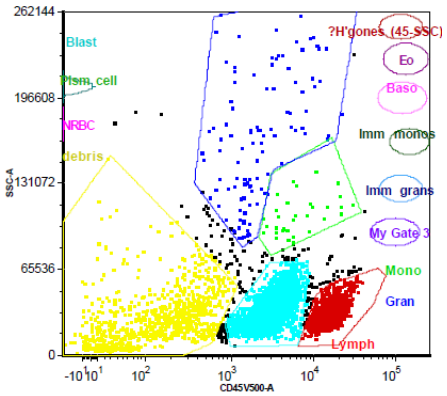
Bone Marrow Biopsy and Aspirate



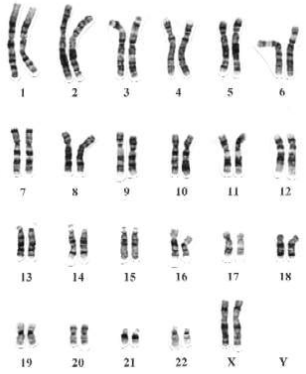




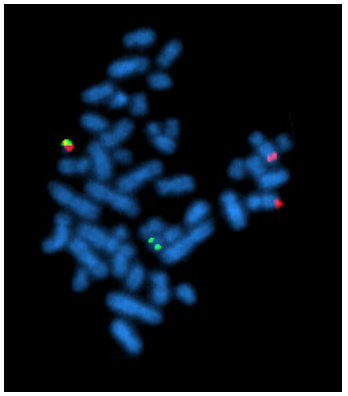
Morphology



Flow Cytometry



Cytogenetics



FISH/Molecular

Differential Diagnosis of MDS

Spectrum of Indolent Myeloid Hematopoietic Disorders[2,3]					
Feature	**ICUS**	**IDUS**	**CHIP**	**CCUS**	**MDS**
Somatic mutation	-	-	+/-[1]	+/-[1]	+/-
Clonal karyotypic abnomality	-	-	+/-[1]	+/-[1]	+/-
Marrow dysplasia	-	+	-	-	+
Cytopenia	+	-	-	+	+

ICUS, idiopathic cytopenia of unknown significance;
IDUS, idiopathic dysplasia of unknown significance;
CHIP, clonal hematopoiesis of indeterminate potential;
CCUS, clonal cytopenia of unknown significance;
MDS, myelodysplastic syndromes

- Acute myeloid leukemia
- Other MPNs
- Aplastic anemia
- Nutritional deficiencies
- Medications

Prognostication of MDS

Prognostic Features in MDS

- Clinical
  - CBC, marrow blasts, cytogenetics
  - Age, PS, ferritin, LDH, β2M, marrow fibrosis
  - Treatment/Response
- Molecular
  - Specific mutations
  - Number of mutations

FAB and 2008 WHO Classification of MDS

French-American-British (FAB)	2008 World Health Organization (WHO)
Refractory Anemia (RA)	Refractory Cytopenia with Unilineage Dysplasia (RCUD)
“	RC with Multilineage Dysplasia (RCMD)
“	MDS associated with isolated del(5q)
RA with Ringed Sideroblasts (RARS)	RARS with unilineage dysplasia
	RCMD with ringed sideroblasts
RA with Excess Blasts (RAEB)	RAEB-1 (5-9% blasts)
“	RAEB-2 (10-19% blasts)
RAEB in Transformation (RAEB-T)	Acute Myeloid Leukemia (20+% blasts)
Chronic Myelomonocytic Leukemia (CMML)	MDS/MPN Overlap
N/A	MDS Unclassified (MDS-U)

Vardiman et al. Blood 2002.
Vardiman et al. Blood 2009.

2016 WHO Classification of MDS

Subtype	Blood	Bone marrow
MDS with single lineage dysplasia (MDS-SLD)[3]	Single or bicytopenia	Dysplasia in ≥10% of one cell line, <5% blasts
MDS with ring sideroblasts (MDS-RS)	Anemia, no blasts	≥15% of erythroid precursors w/ring sideroblasts, or ≥5% ring sideroblasts if SF3B1 mutation present
MDS with multilineage dysplasia (MDS-MLD)	Cytopenia(s), <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenia(s), ≤2%–4% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenia(s), 5%–19% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods
MDS, unclassifiable (MDS-U)	Cytopenias, ±1% blasts on at least 2 occassions	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts
Refractory cytopenia of childhood	Cytopenias, <2% blasts	Dysplasia in 1–3 lineages, <5% blasts
MDS with excess blasts in transformation (MDS-EB-T)[2]	Cytopenias, 5%–19% blasts	Multilineage dysplasia, 20%–29% blasts, ± Auer rods

NCCN Guidelines, MDS v1.2017.

International Prognostic Scoring System for MDS (IPSS)

International Prognostic Scoring System (IPSS)[s,t]

Survival and AML evolution					
	Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)[u]	<5	5-10	---	11-20	21-30
Karyotype[v]	Good	Intermediate	Poor		
Cytopenia[w]	0/1	2/3			

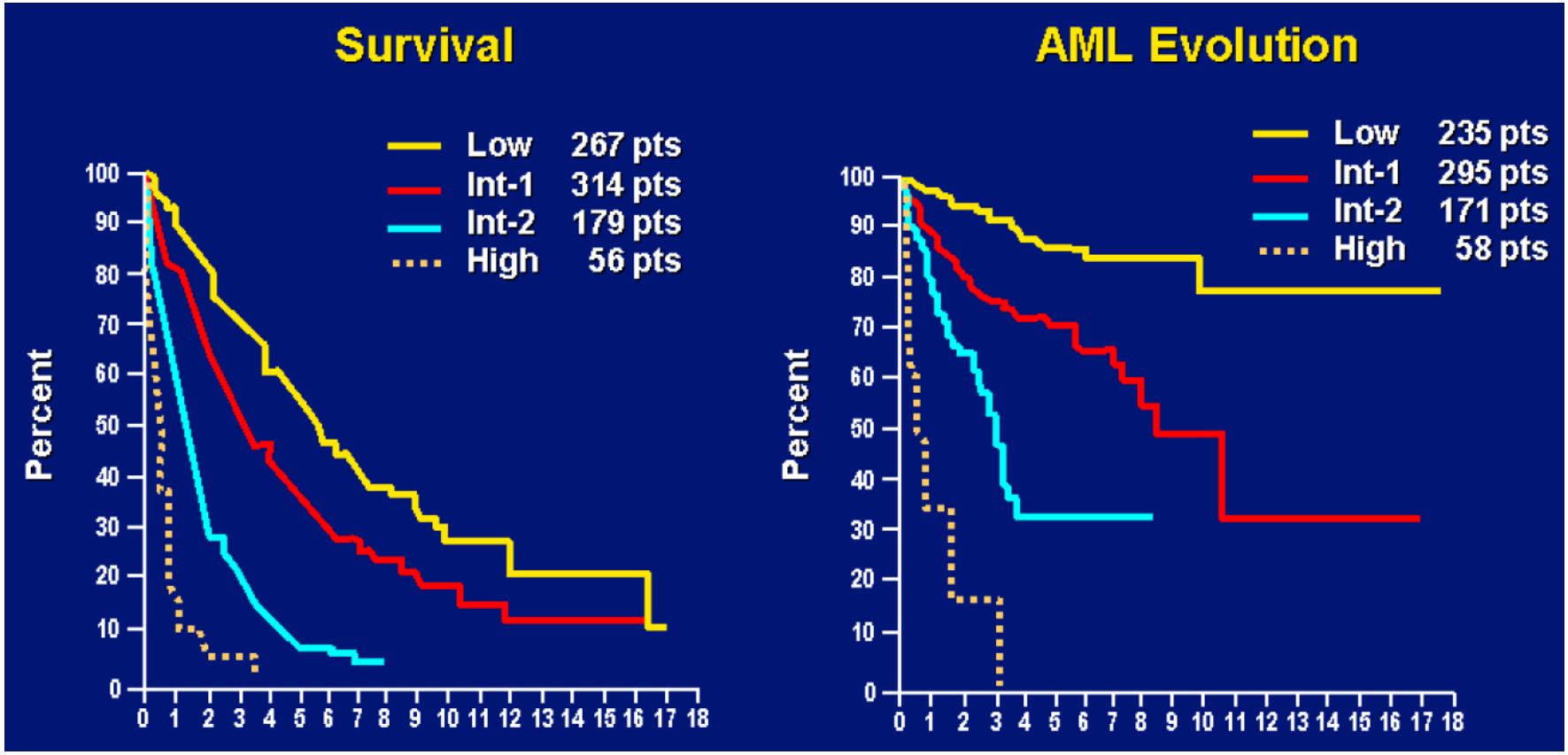
IPSS Risk category (% IPSS pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	≥2.5	0.4	0.2

Cytopenias:
Hgb < 10
ANC < 1800
Plt < 100,000

Cytogenetics:
Good – normal, -Y only, del(5q) only, del(20q) only
Intermediate – +8, single misc, double abnormalities
Poor – complex (≥3), abnormality of chromosome 7

Greenberg et al. Blood 1997.

IPSS



Greenberg et al. Blood 1997.

Revised International Prognostic Scoring System

- IPSS-R built upon prior IPSS
- Multinational IWG-PM project
- **7,012** patients with median age 71
- MDS classified by FAB and WHO
- New MDS cytogenetic classification
- Considered depth of cytopenias, age, LDH, ferritin, b2M, fibrosis, and PS

Greenberg et al, Blood 2012.
Schanz et al, JCO 2012.

IPSS-R: Determining the Score

IPSS-R Score Values

Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	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					

Cytogenetic Risk	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
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex = 3
Very Poor	Complex >3

Greenberg et al, Blood 2012.

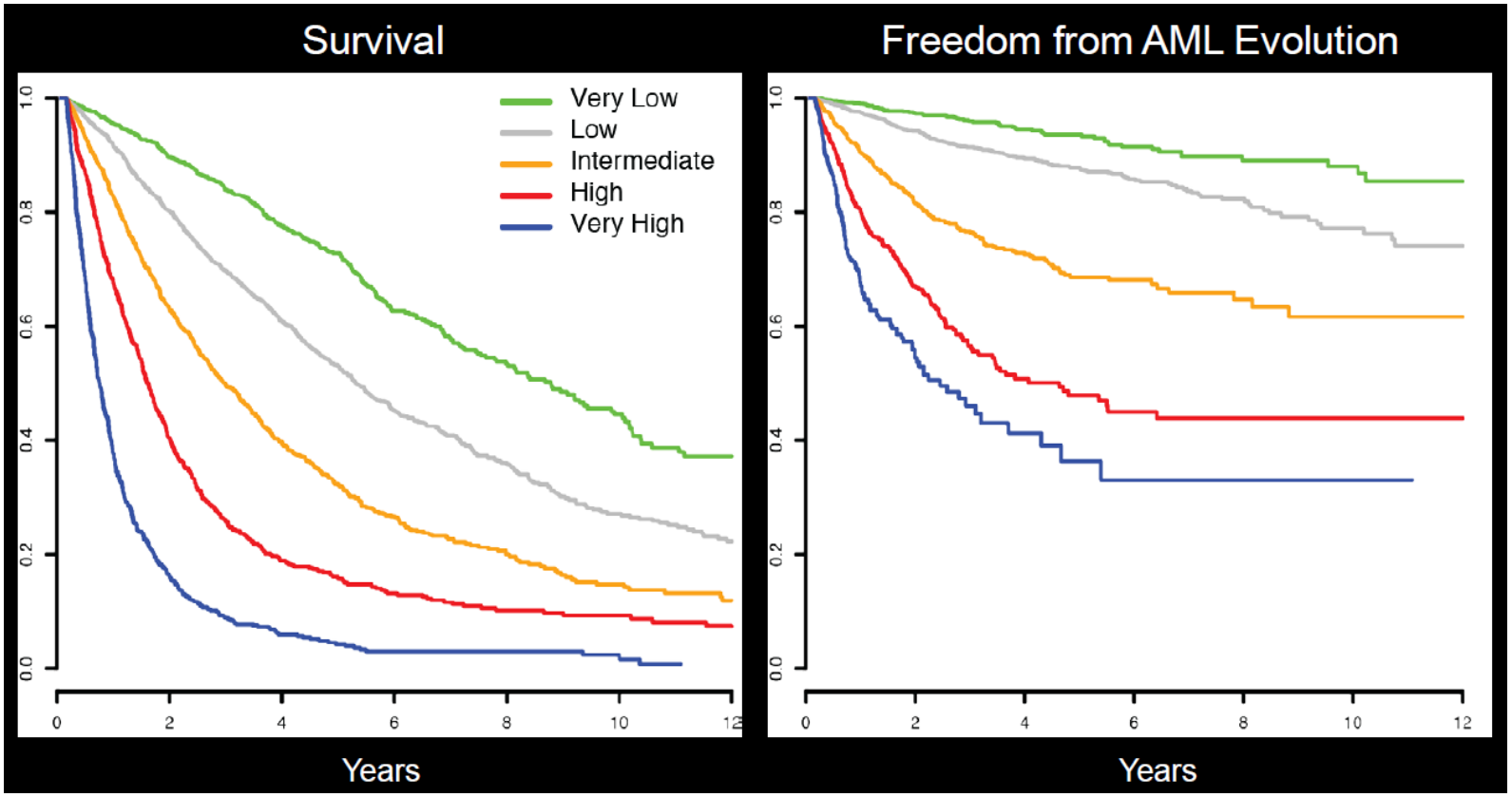
IPSS-R: Calculating the Score

IPPS-R Risk	IPSS-R Score	Median OS (yr)	25% AML Progression (yr)
Very Low	≤1.5	8.8	NR
Low	>1.5-3	5.3	10.8
Intermediate	>3-4.5	3	3.2
High	>4.5-6	1.6	1.4
Very High	>6	0.8	0.7

Greenberg et al, Blood 2012.

IPSS-R: Survival and AML Progression

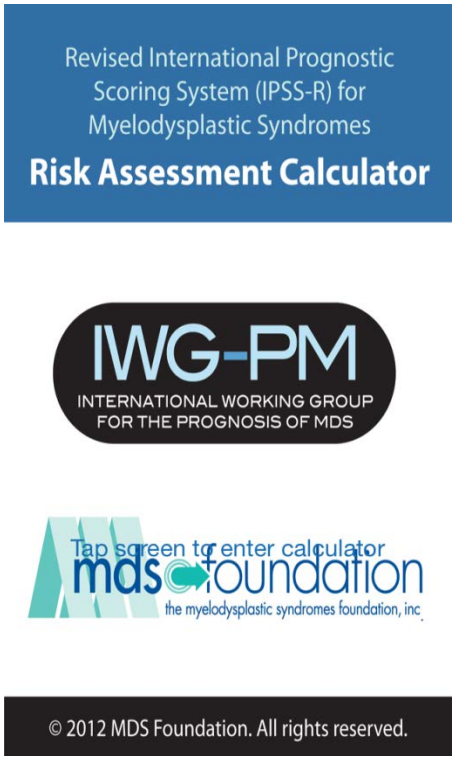
- CBC values, bone marrow blasts, cytogenetics

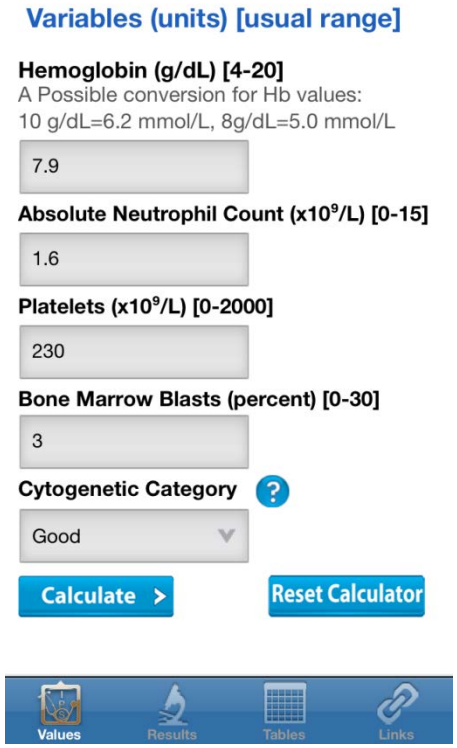


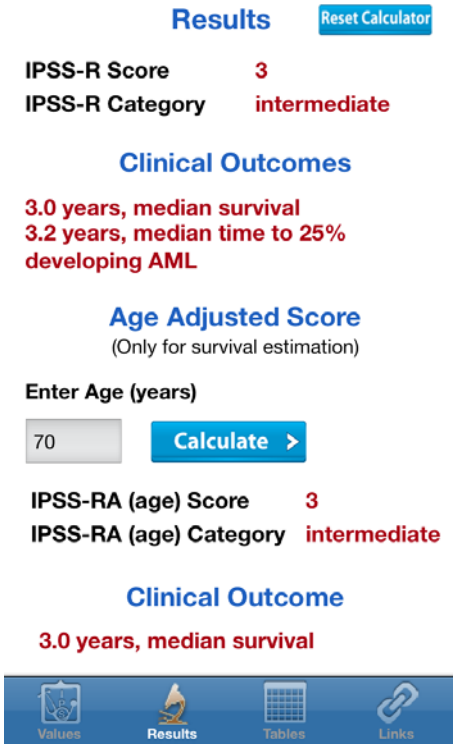
Greenberg et al, Blood 2012.
Schanz et al, JCO 2012.

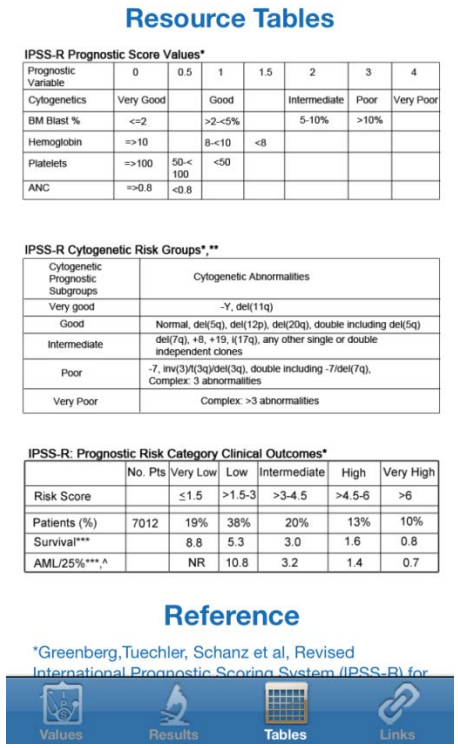
IPSS-R Calculator from the MDS Foundation

Online tool and smartphone app available for free from the MDS Foundation:
http://www.mds-foundation.org/interactive-tools/





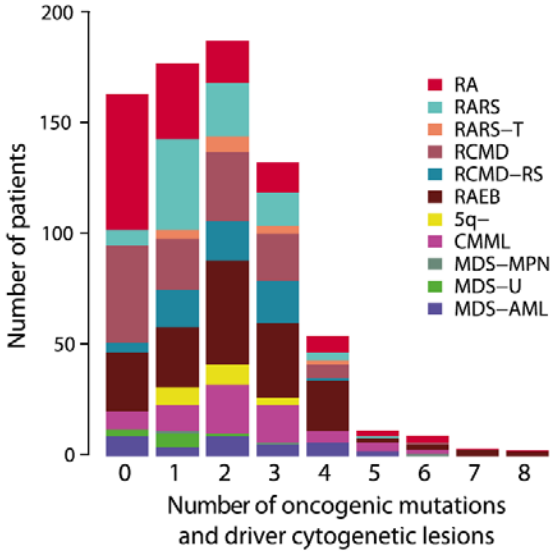


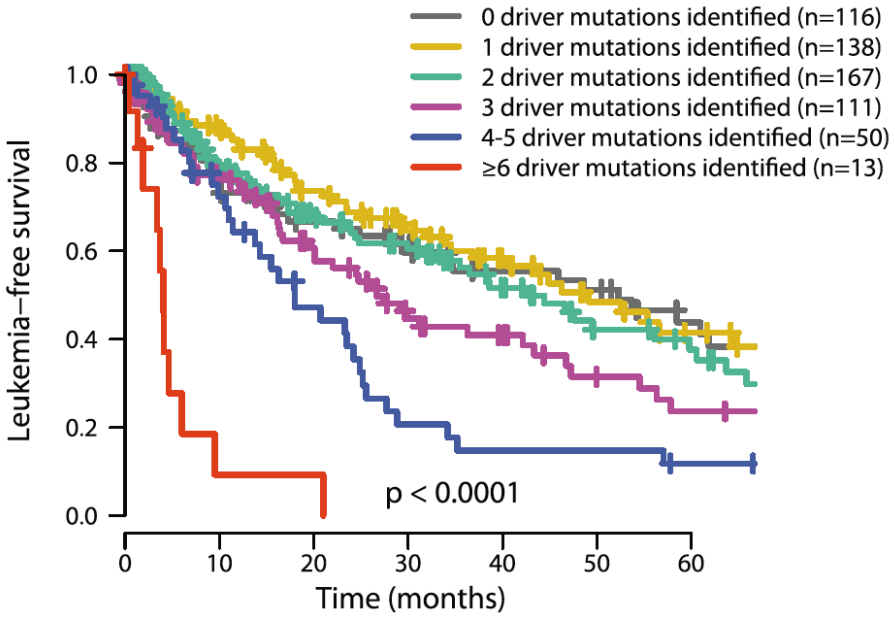


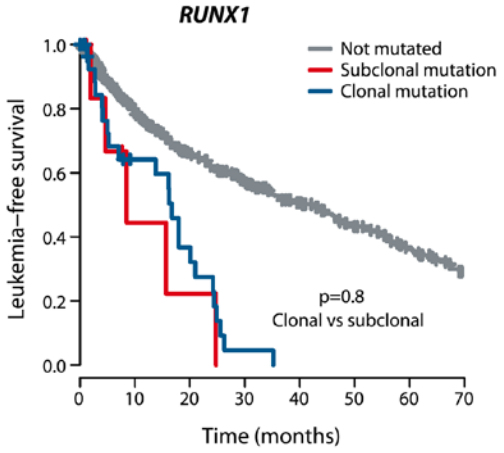
Improving MDS Prognostication

- Rapid advances in understanding MDS pathogenesis
- Improvements in diagnostic and analytic tools
- Future PSS likely to include:
  - Flow cytometry
  - Gene mutations
  - Comorbidity assessments

Number of Driver Mutations Affects Prognosis







From Papaemmanuil et al, Blood 2013.

Recurrent and Prognostic Gene Mutations

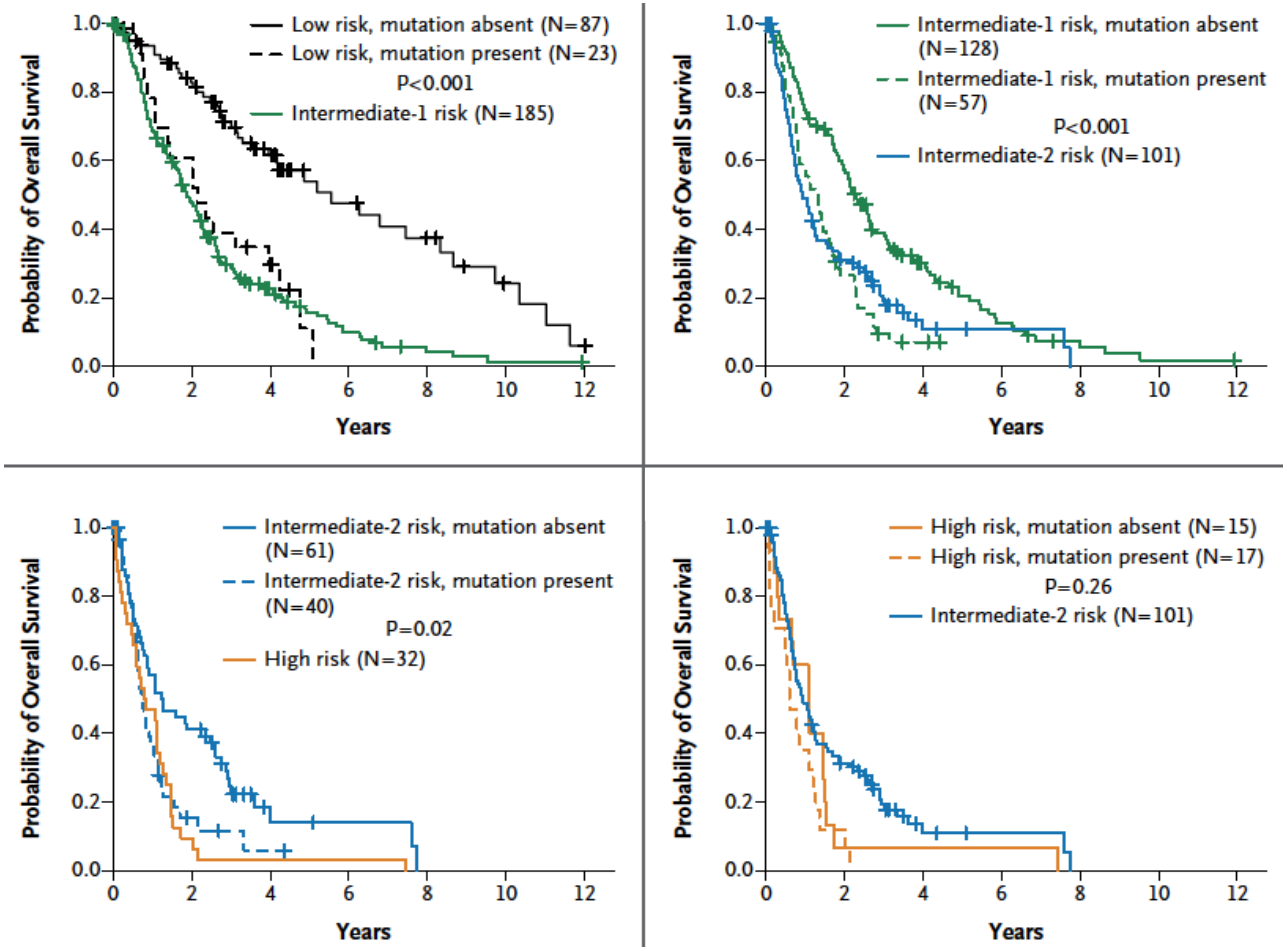
Function	Gene
Epigenetic/Chromatin Modifiers	**TET2**, **DNMT3A#, ASXL1, EZH2**
Splicing	**SF3B1**, **SRSF2, U2AF1#, ZRSR2**
Differentiation	**RUNX1**
DNA Damage Response/Apoptosis	**TP53*, BCOR**
Cohesin Complex	**STAG2**
Signaling	**CBL**

Recurrent in >5% of MDS patients across multiple studies
Favorable prognostic impact
Negative prognostic impact
Neutral prognostic impact
*Strong negative prognostic impact in therapy-related MDS
#Strong negative prognostic impact in CMML

Table adapted from: Haferlach et al, Leukemia 2014; Bejar et al, NEJM 2011; Papaemmanuil et al, Blood 2013; Walter et al, Leukemia 2013; and Thol et al; Blood 2012.

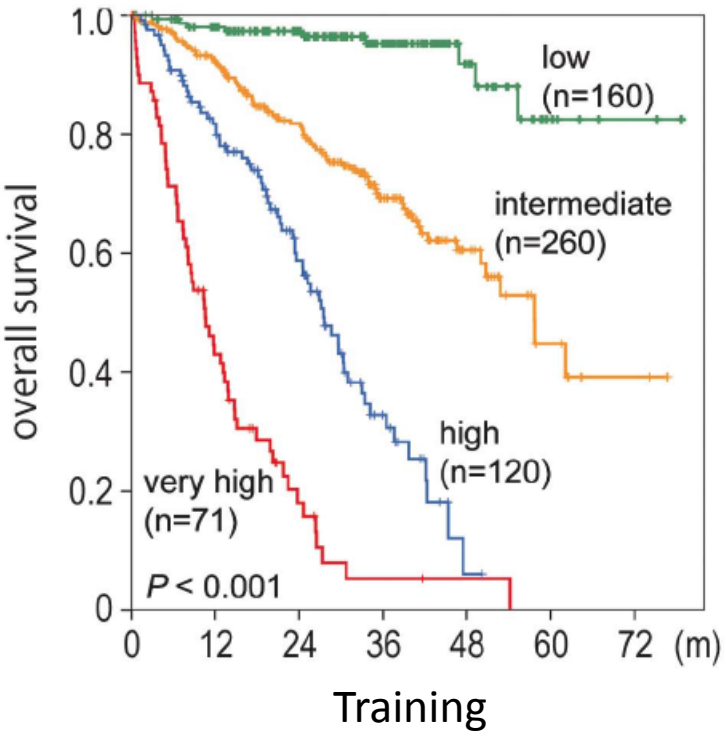
Combining Mutations with IPSS Can Improve Prognostication

IPSS and TP53, EZH2, ETV6, RUNX1 and ASXL1 mutations

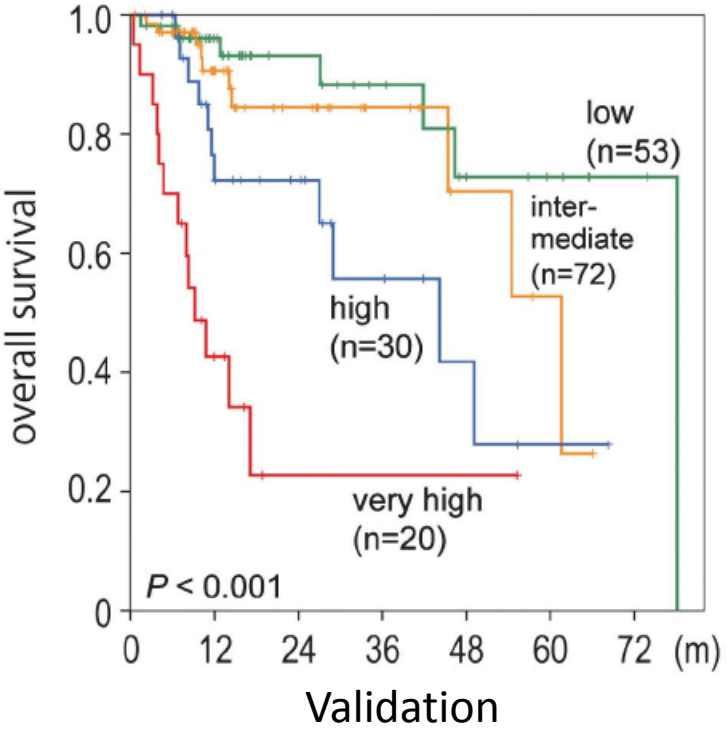


From Bejar et al, NEJM 2011.

Revised IPSS-R: Incorporation of Mutations



Training



Validation

Model:

Gender, Age, IPSS-R Variables

Mutations in: **ASXL1, CBL, ETV6, EZH2, KRAS, LAMB4, NCOR2, NF1, NPM1, NRAS, PRPF8, RUNX1, TET2 and TP53**

Haferlach et al, Leukemia 2014.

Treatment of MDS

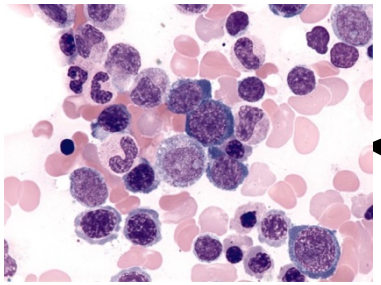
Considerations for MDS Therapy

- Age, comorbidity, quality of life, and psychosocial assessments
- Treatment goals based on risk and mode of disease-related mortality
- All patients get “best supportive care”
  - Transfusions for anemia, thrombocytopenia
  - Antibiotics -/+ G-CSF for infections
- Iron chelation therapy may be required

FDA Drug Approvals

- Epo 1993; Darbepoetin 2002
  - for chemotherapy-induced anemias
- GCSF 1996; Peg-GCSF 2002
  - for infection (‘93 w/ Epo SUH)
- Azacitidine 2004
- Lenalidomide 2005 for (del)5q MDS
- Decitabine 2006
  - 2010: 5 day outpt regimen
- Deferasirox 2005; Deferiprone 2011
  - for iron chelation

Treatment Approaches in MDS



Diagnosis of MDS

***Higher Risk*:**
IPSS-R Int*, HR, VHR

***Lower Risk*:**
IPSS-R VLR, LR, Int*

Treatment Goal	**Treatment Options**
Alter disease natural history	• Hypomethylating agents (HMA) • High-intensity chemotherapy (IC) • Allogeneic HCT • Clinical Trial
Hematologic improvement	• Growth factors • Lenalidomide • Immune suppressive therapy (IST) • HMA • Watch and Wait • Clinical Trial

* Differentiating features: age, performance status, ferritin, LDH

Treatment Options for Lower Risk MDS

- Supportive care (transfusions, antibiotics)
- Anemia (EPO<500): Erythroid Stimulating Agents (ESAs)
  - Erythropoietin (*Procrit/Epogen*)
  - Darbepoetin (*Aranesp*) +/- G-CSF (*Neupogen*)
- 5q-: Lenalidomide (*Revlimid*)
- non-5q-: Lenalidomide (*Revlimid*) +/- Erythropoietin (*Procrit/Epogen*)
- Int-1/'young': ATG, cyclosporin
- RBC transfusions >20-30u: Iron chelation
  - Deferasirox (*Exjade* oral) or Deferoxamine (*Desferal* sc)
  - If ferritin >2500, goal is <1000
- Thrombocytopenia:
  - [Eltrombopag (*Promacta*), Romiplostim (*Nplate*)]
- Neutropenia: G-CSF (*Neupogen/Neulasta*)
- Clinical trials

Therapeutically Targeted Subtypes of MDS

- RARS
- 5q-
- Hypoplastic/<60yo HLA-DR15+
- CMML w/ t(5q31-33)/ PDGFRβ gene rearrang't
- GCSF + Epo
- Lenalidomide
- Immunosuppression (ATG, CSA)
- Imatinib

Lenalidomide is Effective for MDS with del(5q)

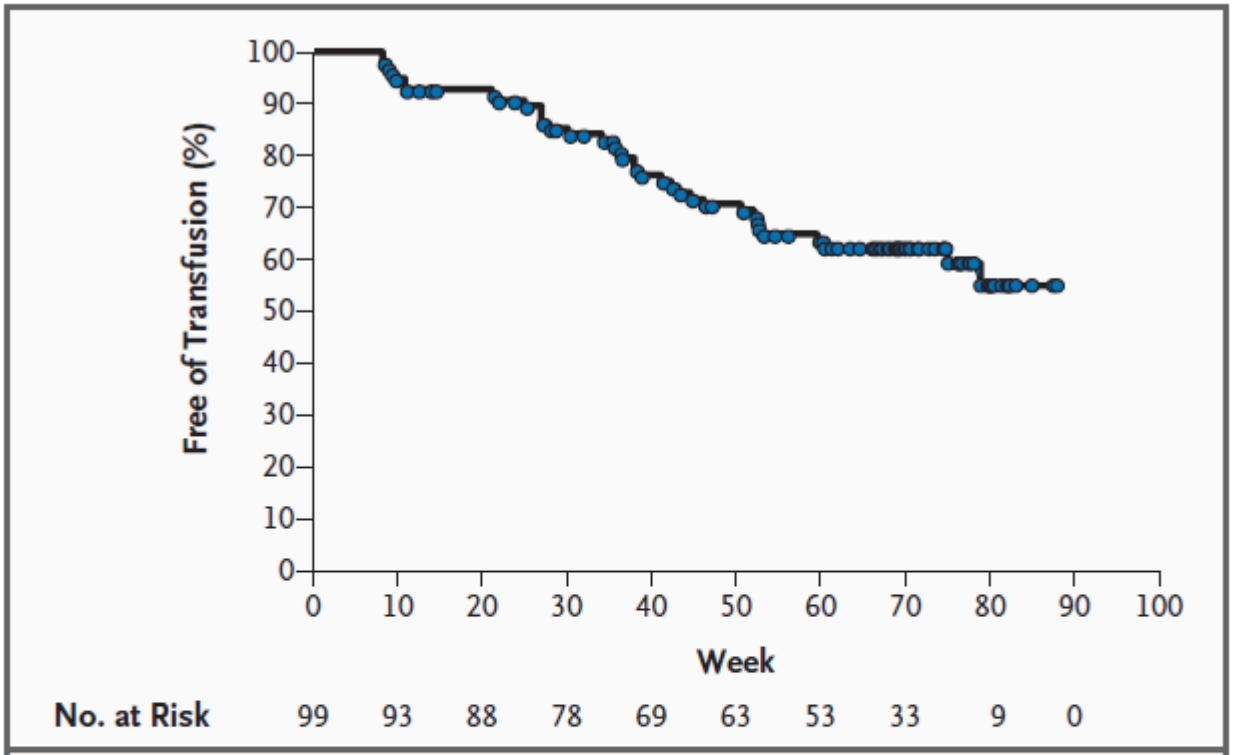


Figure 1. Kaplan–Meier Estimate of the Duration of Independence from Red-Cell Transfusion.

Circles represent censored data from patients who remained transfusion-free at the time of data cutoff (July 15, 2005) or at the time of study discontinuation. On the x axis, 0 indicates the day after the patient's last transfusion preceding a response to treatment. After a median follow-up of 104 weeks, the median duration of transfusion independence could not be estimated.

List et al. NEJM 2006.

Lenalidomide is Effective for MDS with del(5q)

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 et al. NEJM 2006.

Lenalidomide is Also Effective for non-del(5q)

Phase II Study of Lenalidomide in Low and Int-1 Risk MDS with Normal or Abnormal Karyotypes Other than del(5q) [a,1] (n=214)			
	Lenalidomide 10 mg q day (n=100)	**Lenalidomide 10 mg q day X 21 days every 28 days (n=114)**	**All Patients**
Erythroid Response: Transfusion-independence[b,c]	27%	25%	26%
Median Time to response (weeks)	7.4	4.1	4.8
Baseline Hb (gm/dL)	7.9	8.1	8.0
Median Hb at Response (gm/dL)	11.6	11.0	11.6
Median Increase in Hb (gm/dL)	3.3	3.1	3.2

[a] IPSS: 79% low and int-1, 4% int-2, 18% indeterminate; 83% IPSS cytogenetic group good, 13% intermediate, 1% poor, 3% missing

[b] 19% patients had cytogenetic response with 8% patients with complete cytogenetic remission

[c] Median duration of transfusion-independence was 41 weeks for median follow-up of 76 weeks

Toxicities (all patients):

Neutropenia, grade 3-4	25%
Thrombocytopenia, grade 3-4	20%
Rash, grade 3-4	4%
Autoimmune hemolytic anemia	3%

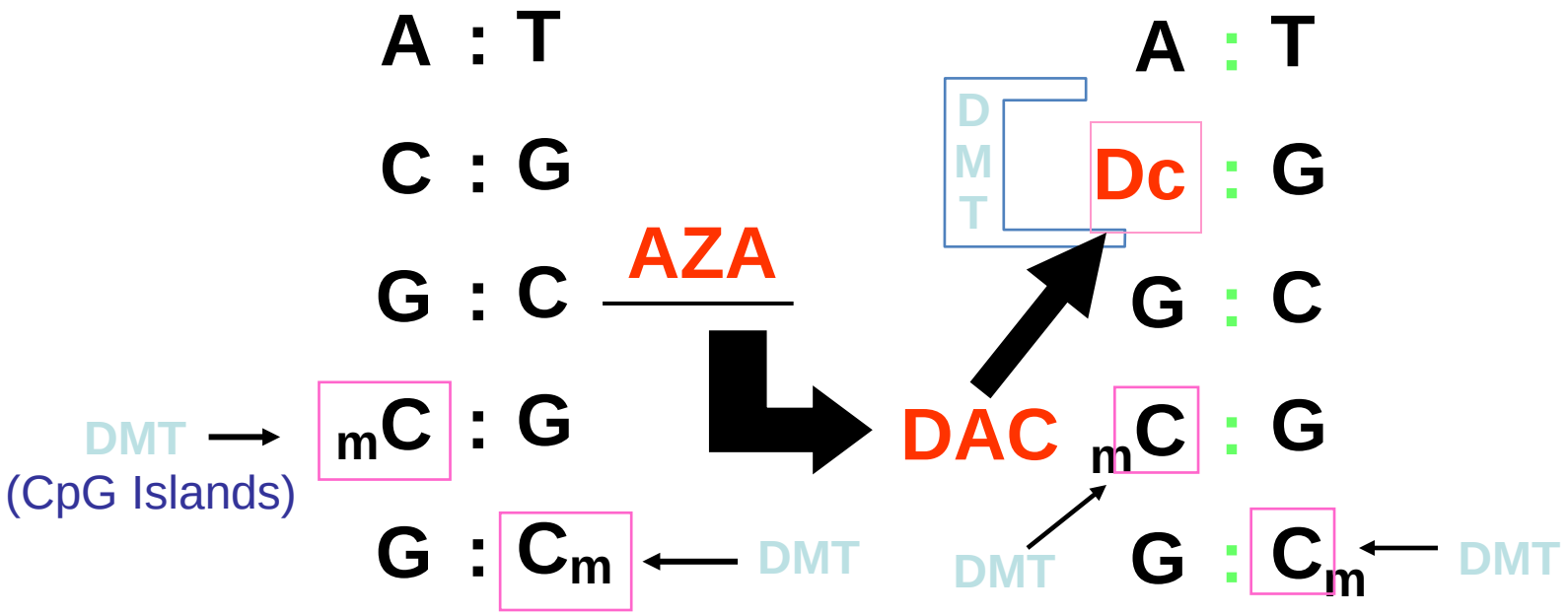
Raza et al. Blood 2008.

Treatment Options for Higher Risk MDS

- Supportive care (transfusions, antibiotics)
- Low intensity therapy
  - Azacitidine (*Vidaza*)
  - Decitabine (*Dacogen*)
  - Clinical trial
- High intensity therapy
  - Intensive chemotherapy (standard or clinical trial)
  - Stem Cell Transplant (standard or reduced intensity)

    --donor available, performance status, age

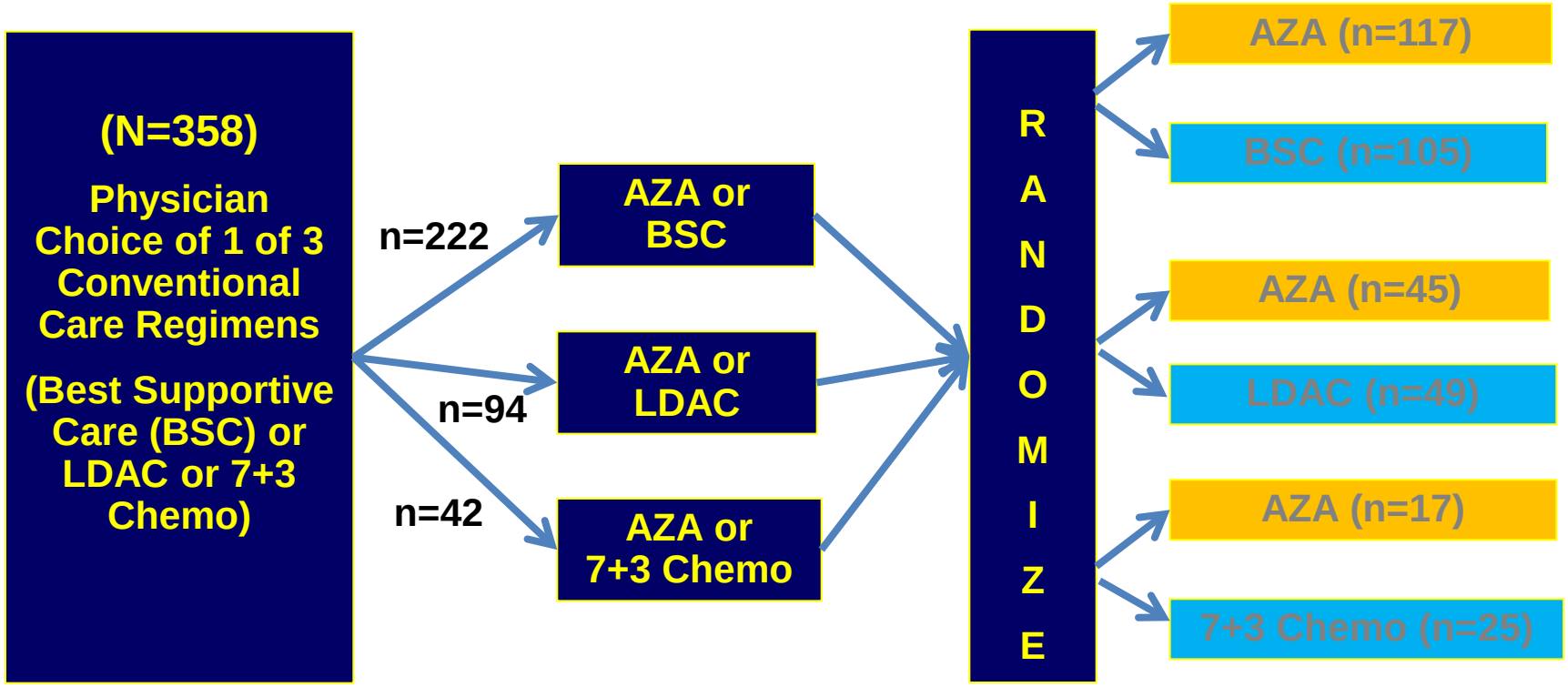
HMA inhibit DNA methyltransferases and induce DNA Hypomethylation and Gene Activation



- **Hypomethylating agents: 5-Azacitidine (AZA) and 5-aza-2'-deoxycytidine (Decitabine/DAC)**
- **Pyrimidine nucleoside analogs**
- **AZA/DAC are incorporated into DNA *in lieu* of cytosine residue**
- **Leads to inactivation of DMT**
- **Leads to formation of newly synthesized DNA with unmethylated cytosine residues**
- **Results in hypomethylation and transcription of previously quiescent genes**

Silverman L. *The Oncologist.* 2001;6(S5):8-14.

AZA-001 – AZA vs Conventional Care in Higher Risk MDS

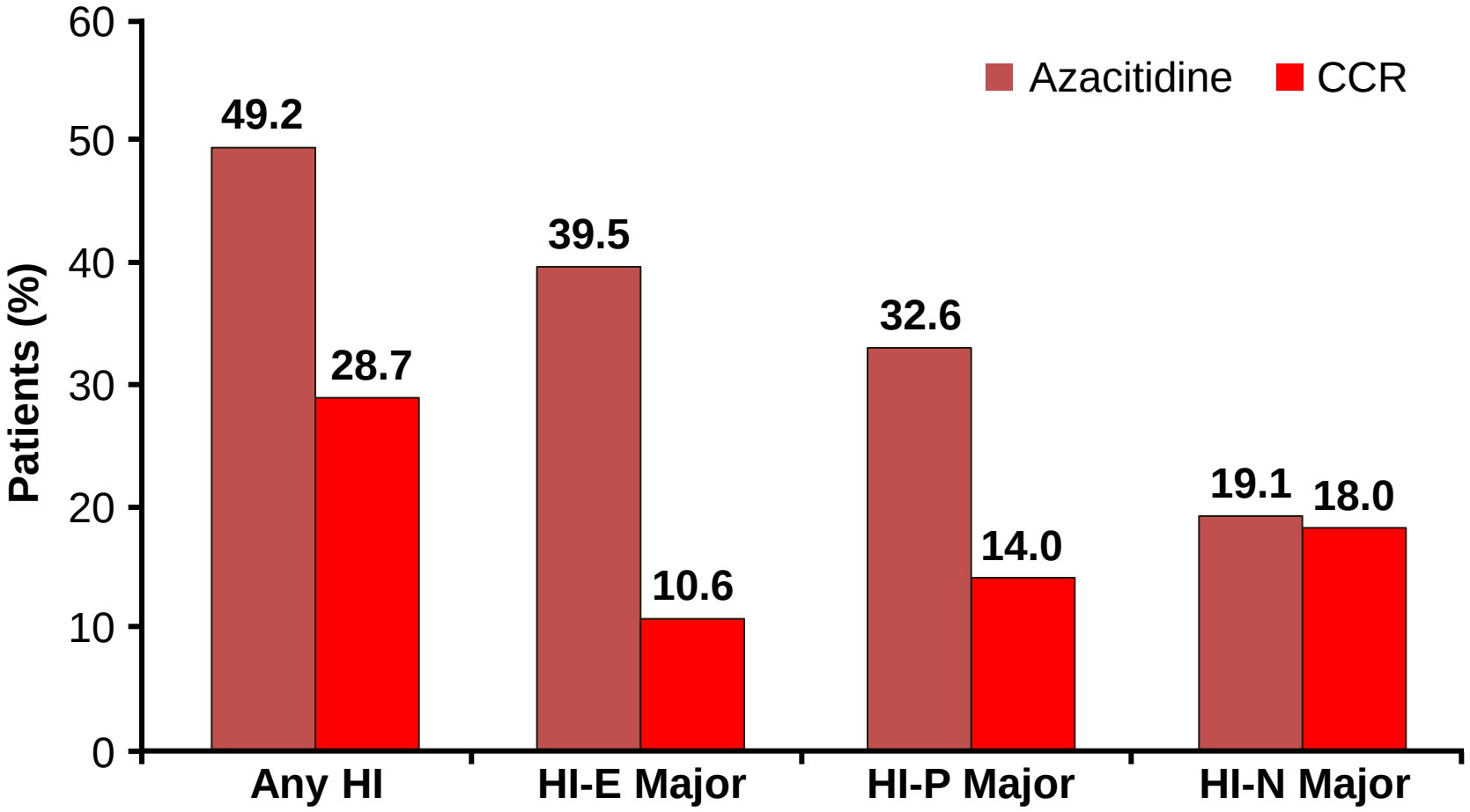


Higher Risk MDS
(IPSS Int-2 or HR)
FAB-defined
P3, international, multicenter, randomized

AZA: 75mg/m2 SC days 1-7 every 28 days (at least 6 cycles)
BSC: transfusions, G-CSF (for febrile neutropenia)
LDAC: 20mg/m2 SC days 1-14 every 28 days (at least 4 cycles)
IC (7+3 chemo): Cytarabine 100-200mg/m2/day CIV x7d
Anthracycline IV daily x3d

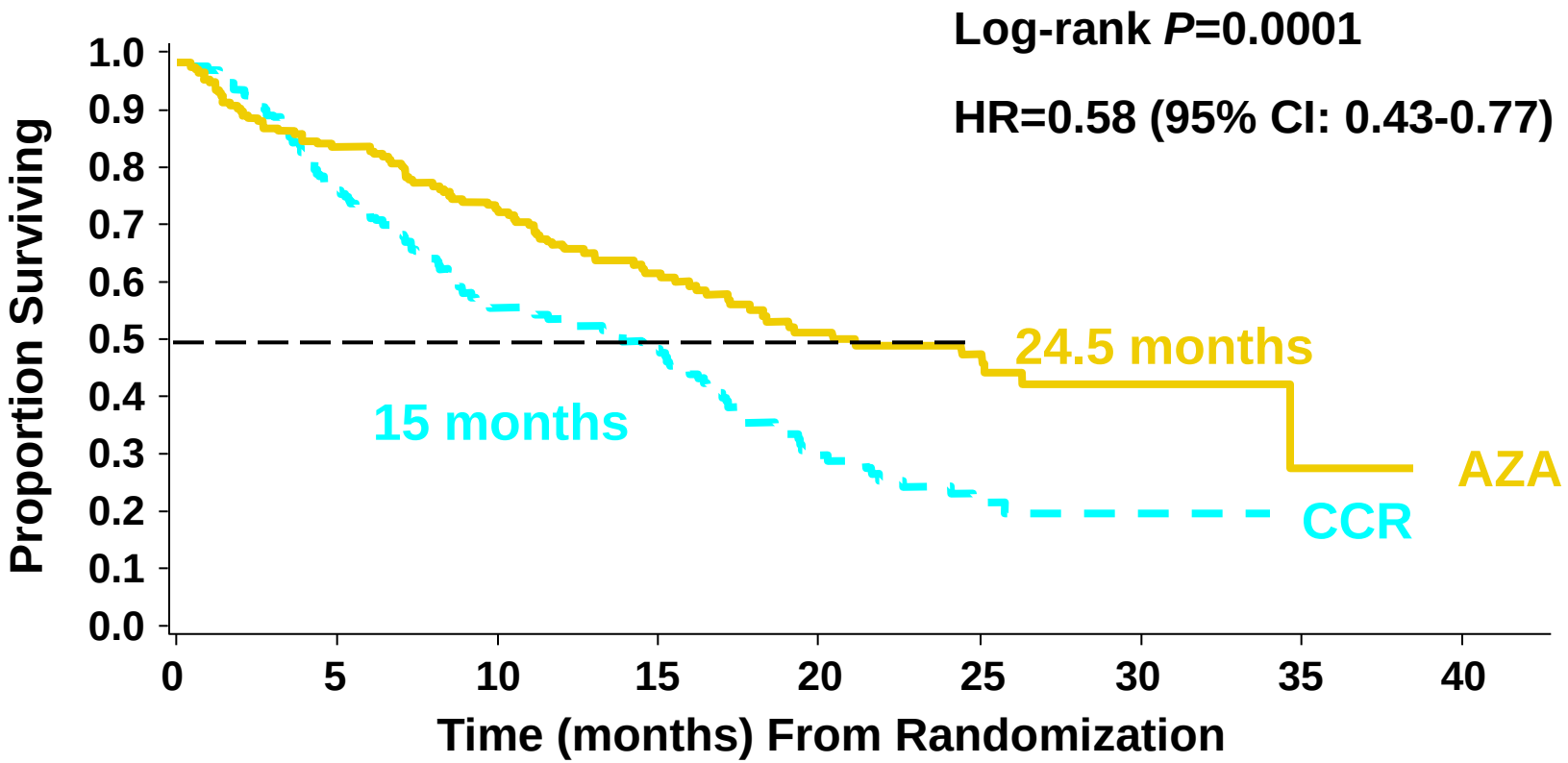
Fenaux et al. Lancet Oncology 2009.

AZA-001: Hematologic Improvement (2000 IWG)



Fenaux et al. Lancet Oncology 2009.

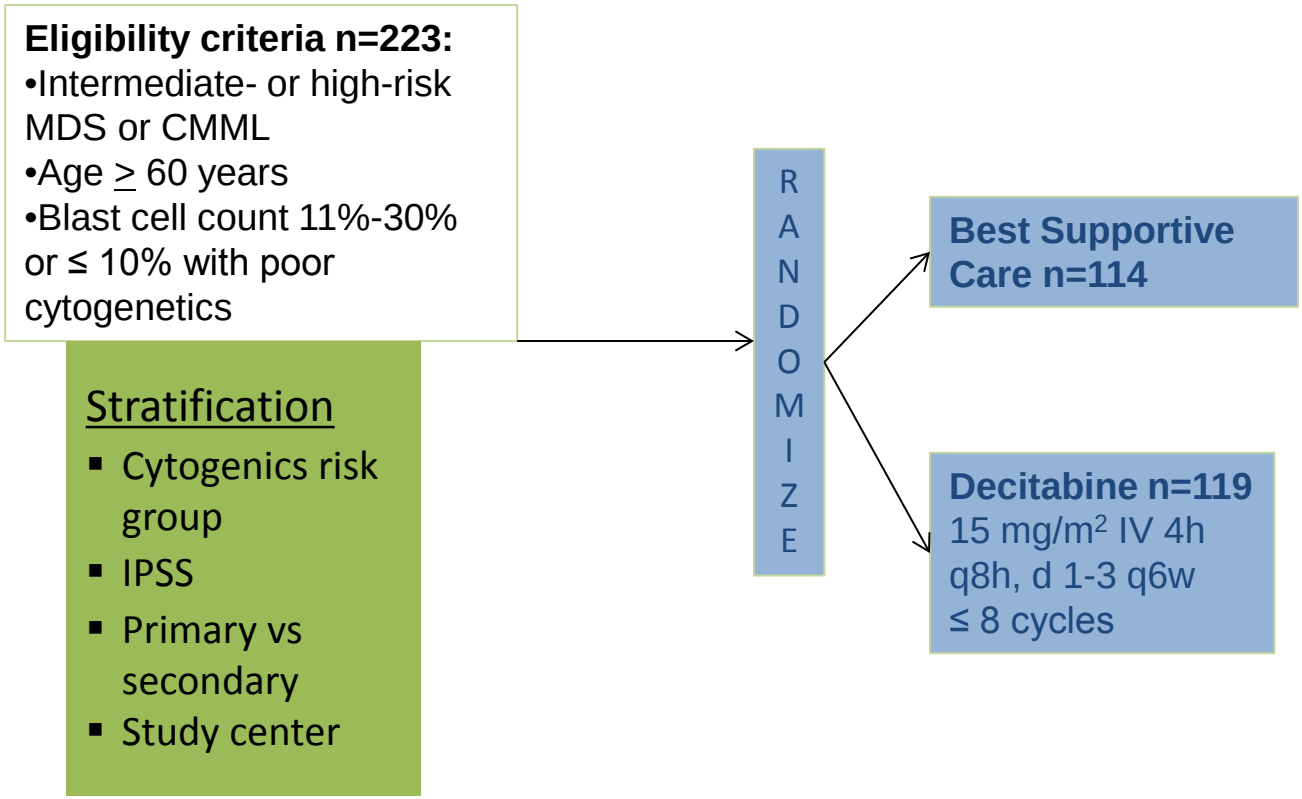
Azacitidine (HMA) Significantly Improves Survival in Higher Risk MDS



CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat.

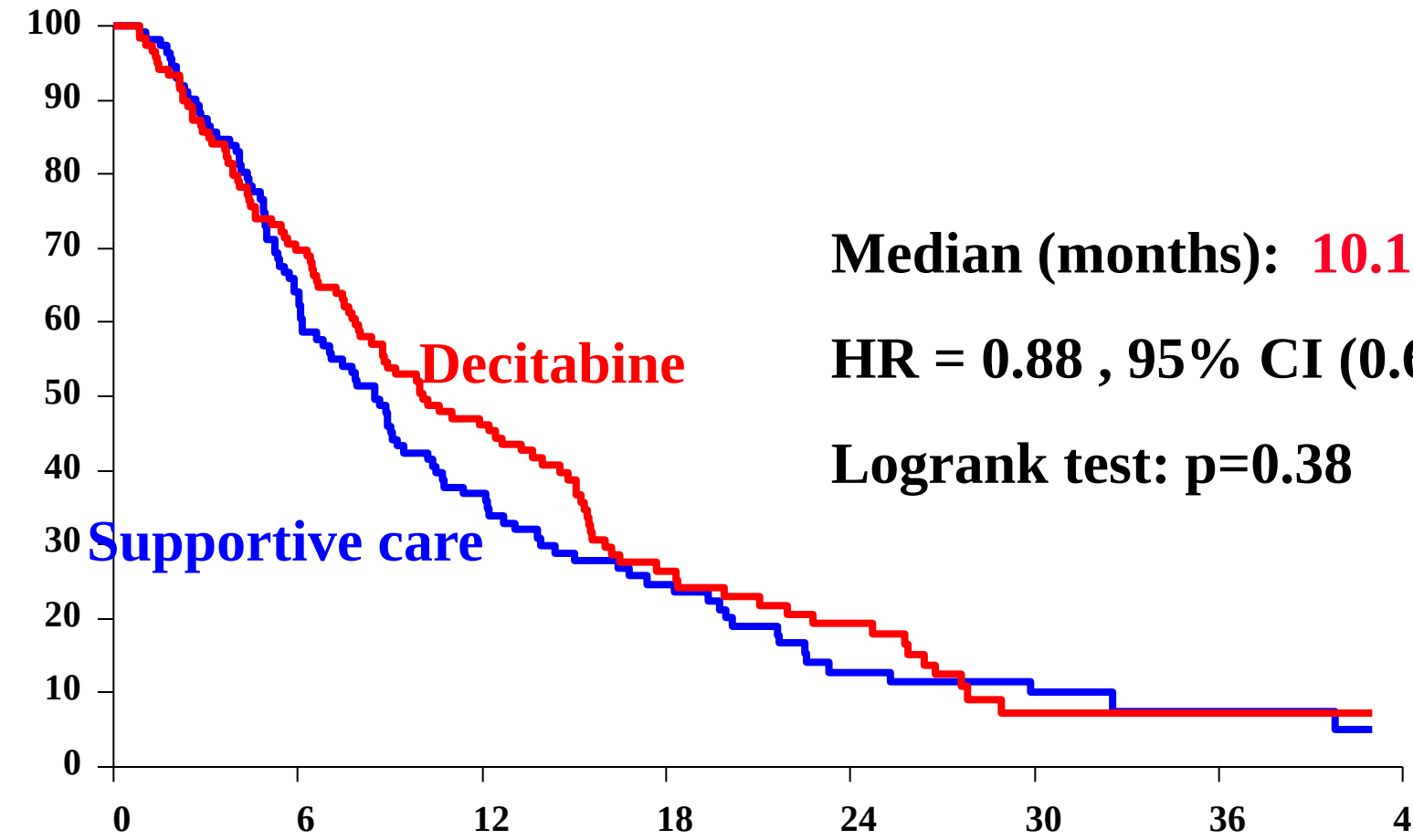
Fenaux et al. Lancet Oncology 2009.

EORTC-06011: Randomized Phase 3 Study of Low-Dose Decitabine vs BSC for Higher-Risk MDS



Lubbert et al, JCO 2011.

EORTC-06011: Overall Survival



Median (months): 10.1 vs 8.5

HR = 0.88 , 95% CI (0.66, 1.17)

Logrank test: p=0.38

O	N	Number of patients at risk :					
96	114	71	38	22	10	6	3
99	119	83	53	24	15	4	4

Supportive care

Decitabine

Lubbert et al, JCO 2011.

EORTC-06011: Response and Toxicity

Response	BSC	Decitabine
CR	0%	13%
PR	0%	6%
HI	2%	15%
SD	22%	14%
PD	68%	29%
Hypoplasia	0%	14%
Inevaluable	8%	8%

Decitabine arm:

26% went off protocol for treatment completion

16% for toxicity

Why no survival advantage?

Limited courses?

More poor risk cytogenetics, older, lower PS?

Dosing/schedule?

Aza is better?

Table 3. Adverse Events

Adverse Event	BSC (n = 114) No. of Patients	BSC (n = 114) %	Decitabine (n = 114)* No. of Patients	Decitabine (n = 114)* %
Febrile neutropenia				
Grade 3	6	5.3	25	21.9
Grade 4	2	1.8	4	3.5
Infection with grade 3/4 neutropenia				
Grade 3	33	28.9	35	30.7
Grade 4	7	6.1	19	16.7
Infection				
Grade 3	45	39.5	44	38.6
Grade 4	12	10.5	22	19.3
Hemorrhage				
Grade 3	14	12.3	15	13.2
Grade 4	4	3.5	5	4.4
Fatigue				
Grade 3	12	10.5	5	4.4
Grade 4	4	3.5	5	4.4
Nausea				
Grade 1	9	7.9	25	21.9
Grade 2	8	7.0	8	7.0
Grade 3	1	0.9	2	1.8
Vomiting				
Grade 1	3	2.6	13	11.4
Grade 2	7	6.1	5	4.4
Grade 3	1	0.9	1	0.9
Diarrhea				
Grade 1	9	7.9	12	10.5
Grade 2	9	7.9	17	14.9
Grade 3	5	4.4	4	3.5

Abbreviation: BSC, best supportive care.
*Patients randomly assigned in the decitabine arm who received at least one decitabine infusion were included in this analysis.

Lubbert et al, JCO 2011.

ADOPT Trial: Confirmation of 5-day Decitabine Dosing

Initial decitabine study dosing is 15mg/m2 IV over 3h q8h x3d every 6 weeks
Authors studied a convenient schedule for outpatients: 20mg/m2 IV over 1h days 1-5 every 4 weeks and confirmed Kantarjian et al. Blood 2007.

Table 2. Responses to Decitabine Treatment

Response by 2006 IWG Criteria	ITT (N = 99) No. of Patients	%
Overall complete response rate, CR + mCR	32	32
Overall response rate, CR + mCR + PR	32	32
Overall improvement rate, CR + mCR + PR + HI	50	51
Rate of stable disease or better, CR + mCR + PR + HI + SD	74	75
CR	17	17
mCR	15	15
PR	0	0
HI	18	18
SD	24	24
PD	10	10
Not assessable*	15	15

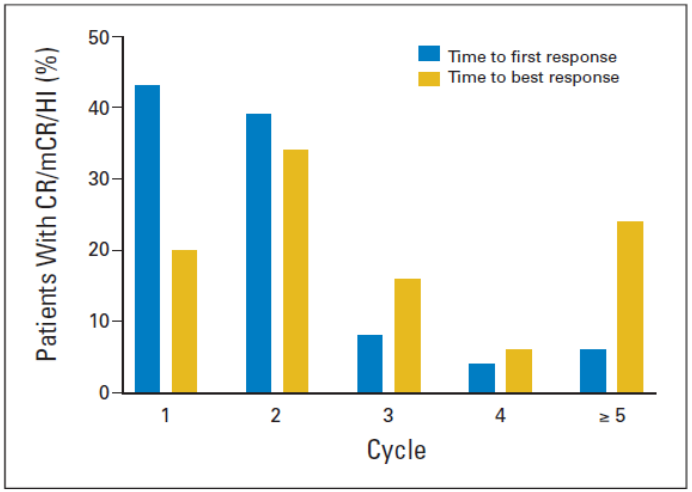


Fig 1. Time to first response and best response by cycle (n = 50). CR, complete response; mCR, marrow CR; PR, partial response; HI, hematologic improvement.

Median time to best response 1.7months

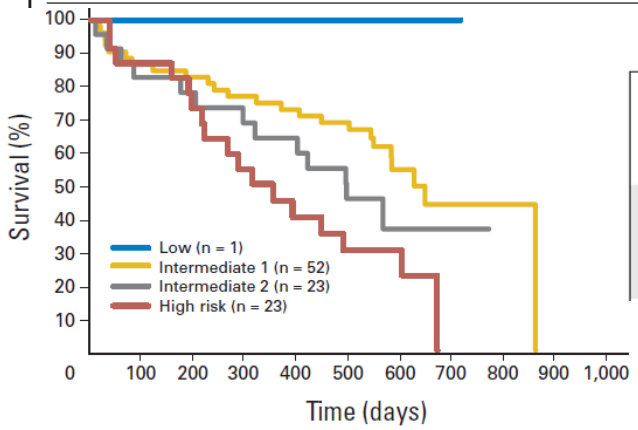


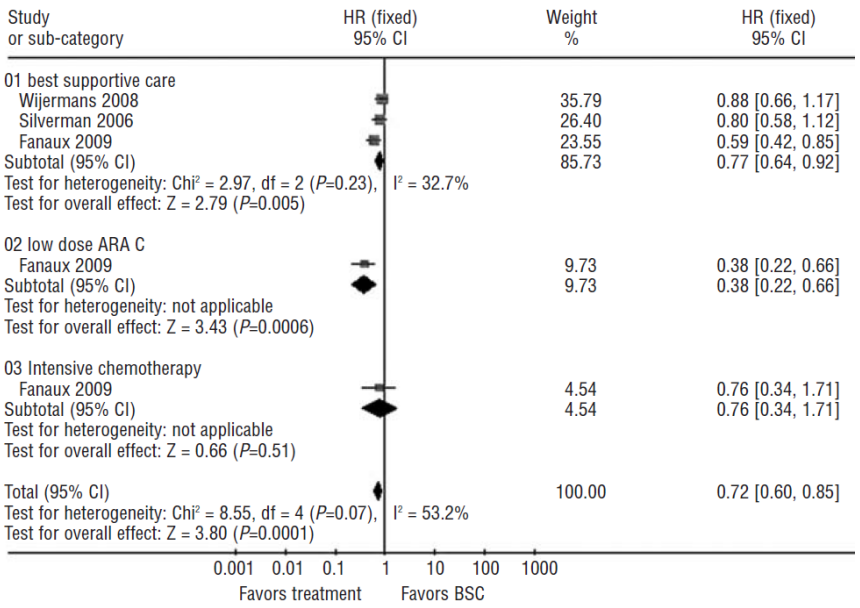
Table 4. Summary of Adverse Events Occurring in ≥ 10% of Patients

Event	% of Patients Grade 1-2	Grade ≥ 3
Hematologic		
Neutropenia	1	31
Thrombocytopenia	2	18
Febrile neutropenia	3*	14
Anemia	5	12
Nonhematologic		
Fatigue	26	5
Nausea	26	1
Pyrexia	17	0
Diarrhea	12	0
Anorexia	12	0
Constipation	11	0
Pneumonia	1	11
Vomiting	10	1
Chills	10	0

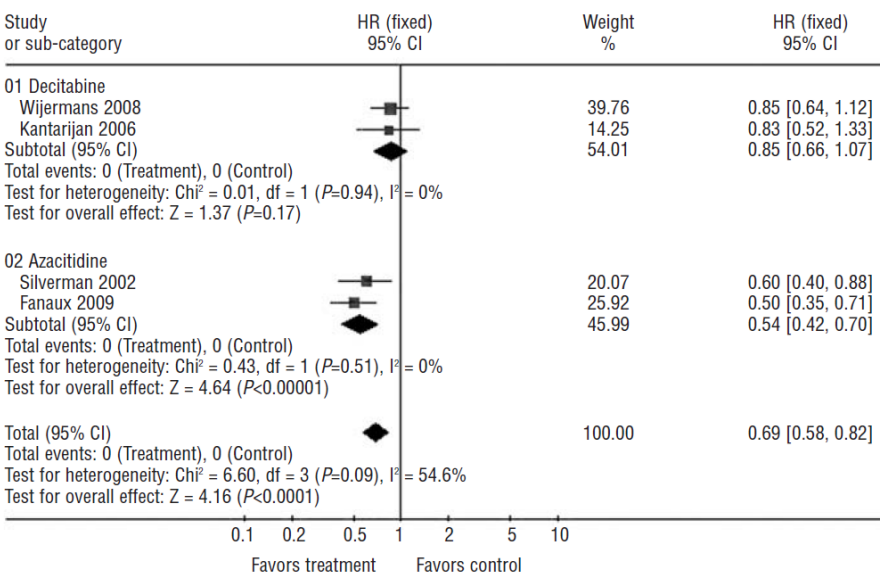
Steensma et al. JCO 2009.

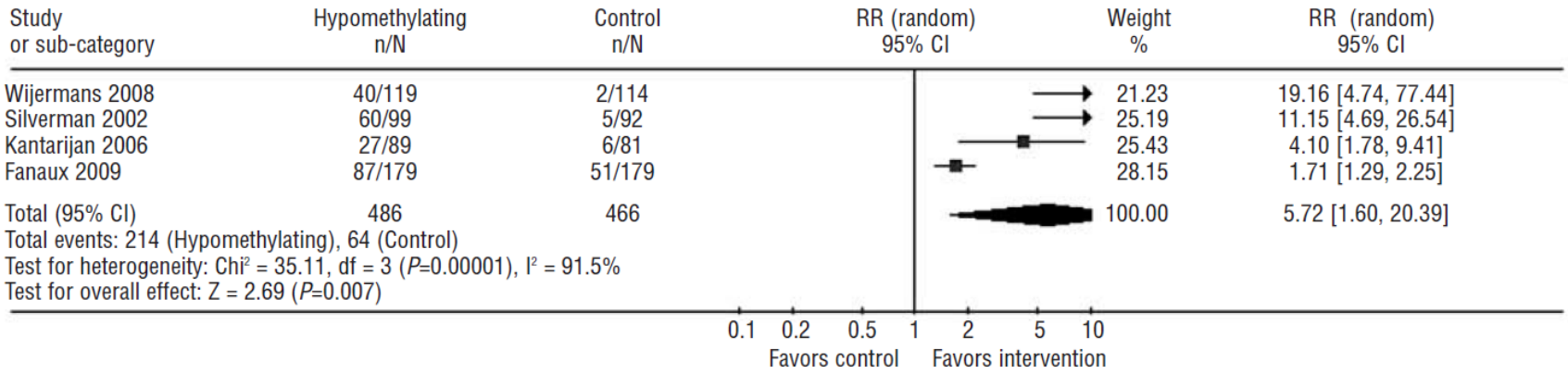
Meta-Analysis of HMA vs Conventional Care

Overall Survival



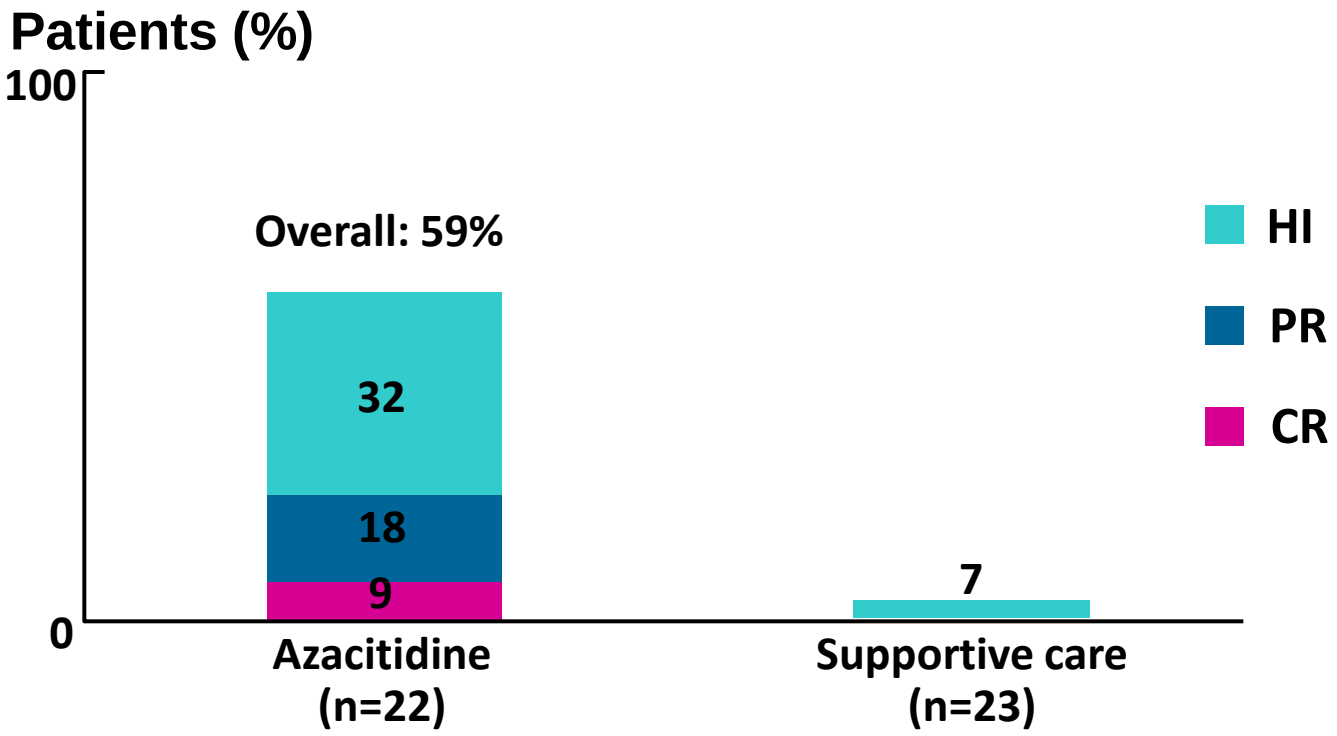
Time to AML or Death





Gurion et al. Haematologica 2010.

CALGB 9221: Responses in Lower-Risk MDS



Median time to response: 2 mos
Median duration of response: 15 mos (all pts)

HI: 50% improvement in 1 or 2 peripheral blood counts or 50% decrease in transfusion requirements
PR: 50% improvement in 3 peripheral blood counts and transfusion independent and ≤50% initial marrow blasts
CR: Normalization of peripheral blood counts and ≤5% marrow blasts

Silverman et al. JCO 2002

Decitabine after AZA Failure can salvage some patients

Table II. Response summary.

	Number (percent)	Median (range)
Responses		
CR	3 (21)	
Marrow CR with HI	1 (7)	
Stable disease	5 (36)	
Progressive disease/death	4/1 (29/7)	
Number of DAC courses to response		3 (1–5)
Median survival (months)		6 (1–14.8)

CR, complete remission; HI, hematological improvement; DAC, decitabine.

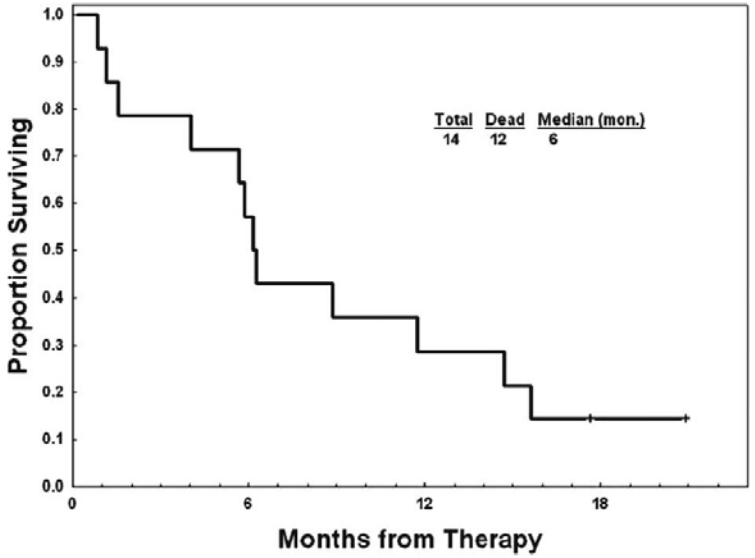


Figure 1. Overall survival of all the 14 patients.

Table III. Characteristics of responders.

	Number of prior Aza courses	Best response to Aza	Reason off Aza/weeks off Aza	Weeks from prior Aza before DAC	Best response to DAC/courses to response	Response duration (months)	Percent marrow blasts pre/at response	Platelets pre/at response	ANC pre/at response
1	8	Marrow CR	PD	3	CR/3	9.7	15/1	24/336	1.1/3.2
2	4	SD	NR	11	Marrow CR/3	8.2	8/4	65/95	1.8/5.1
3	4	SD	NR	9	CR/5	11.3+	12/3	80/234	0.6–1.4
4	1	N/A	Toxicity	5	CR/1	10.2	13/4	24/110	0.38/2.8

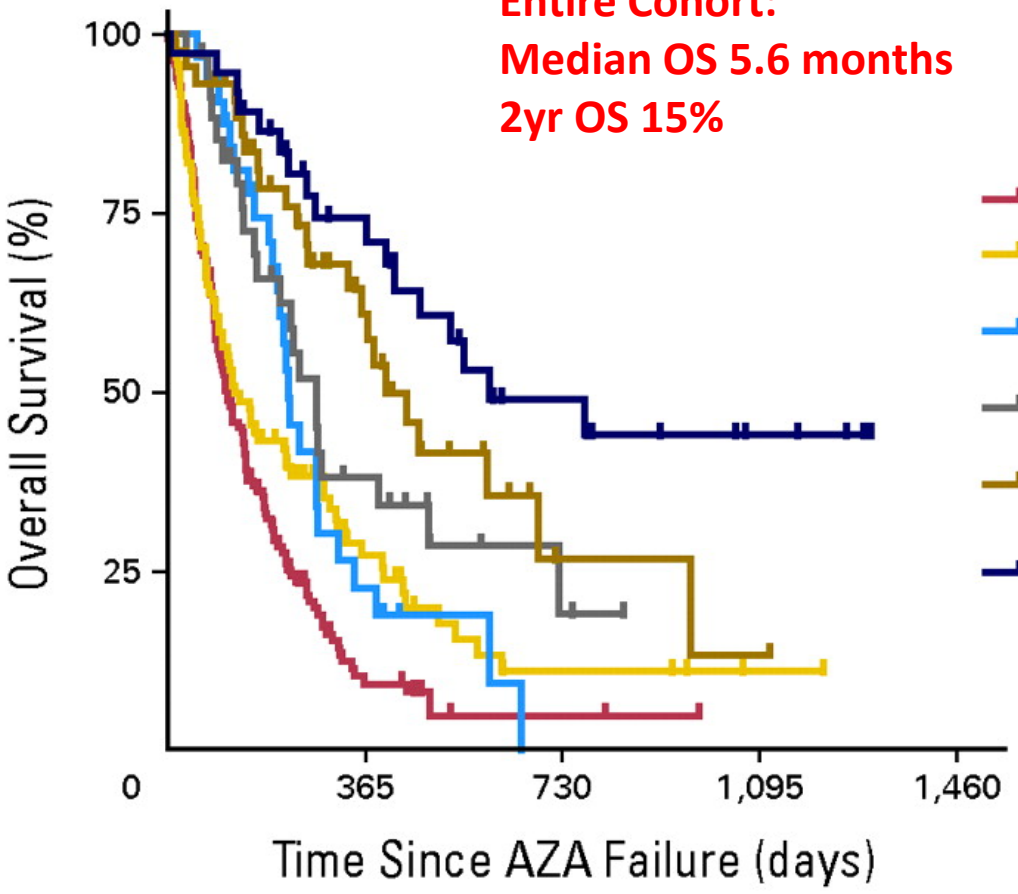
CR, complete remission; Aza, azacitidine; DAC, decitabine; SD, stable disease; PD, progressive disease; NR, no response; ANC, absolute neutrophil count.

Decitabine 20mg/m2 IV days 1-5 on a 28-day cycle

Borthakur et al. Leuk Lymph 2008.

HR MDS Post HMA Failure OS by Salvage Rx

Entire Cohort:
Median OS 5.6 months
2yr OS 15%

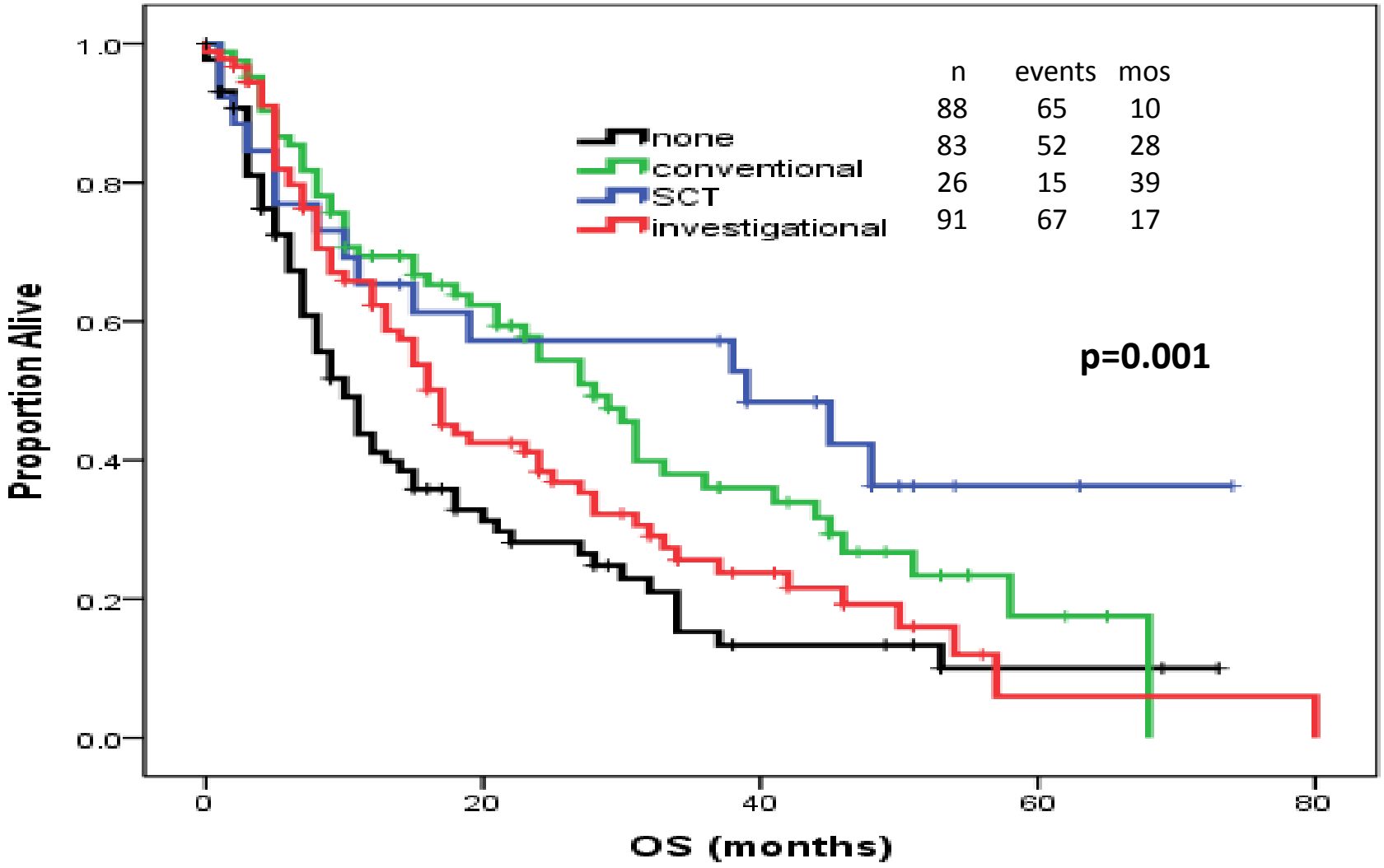


Type of salvage	N	ORR	Median OS (months)
	435		
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

2014 ASH Abstracts:
3275 (Nazha et al.): IPSS-R best predicts outcomes
3273 (Nazha et al.): SD after 6mo unlikely to improve -> clinical trials

Prébet et al. JCO 2011.

LR MDS Post HMA Failure OS by Salvage Rx



Jabbour et al. ASH 2013 abstract 388

Induction Chemotherapy for MDS

Retrospective, MD Anderson Experience
n=394 (no 5q- patients included)

	Induction Regimen [a]					
	IA	FA	FAI	TA	CAT	Total
Number of patients	67	76	118	74	59	394
Median age, years	58	63	62	64	63	
FAB: RAEB	21%	33%	33%	47%	31%	
RAEB-T	79%	69%	67%	53%	69%	
IPSS: Int-1	17%	18%	7%	21%	17%	
Int-2	40%	33%	37%	38%	42%	
High	42%	48%	56%	41%	42%	
Early death (first 6 weeks)	15%	18%	21%	5%	15%	
Overall CR rate	**72%**	**61%**	**48%**	**59%**	**58%**	**58%**
IPSS: Int-1						64%
Int-2						60%
High						56%
Median survival[b], weeks	**88**	**33**	**30**	**45**	(c)	
IPSS: Int-1						**85**
Int-2						**45**
High						**38**
Median survival[b] for patients achieving CR (n=229), weeks	**91**	**30**	**36**	**41**	(c)	
IPSS: Int-1						**77**
Int-2						**54**
High						**31**

[b] After achieving CR, most patients proceeded to consolidation chemotherapy, and some patients (0–11% across the five regimens) proceeded to HSCT

CR 40-60%, median duration CR <1yr
Early mortality 17%, 5yr OS 8%

Consider in:

Younger fit patients <65-70
High blast percentage (>10%)
Non-adverse cytogenetics
Transplant candidate with donor
Post-remission chemotherapy should be given

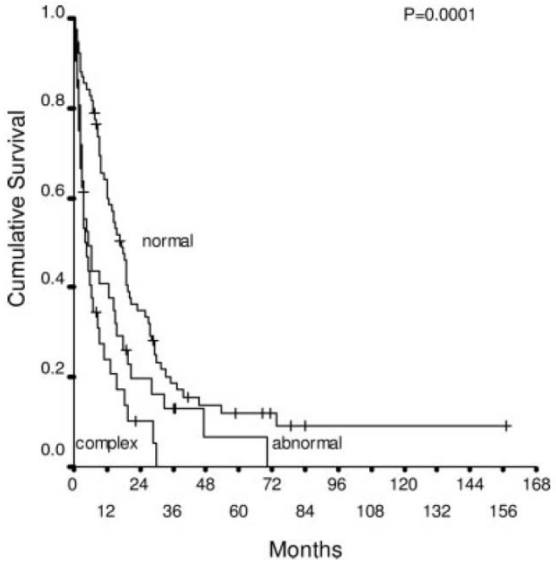


FIGURE 3. Survival of patients with normal versus abnormal versus high-risk karyotypes.

Beran et al. Cancer 2001.
Kantarjian et al. Cancer 2006.
Knipp et al. Cancer 2007.
Malcovati et al, Blood, 2013.

HMA vs Induction chemotherapy in MDS with 10-30% blasts

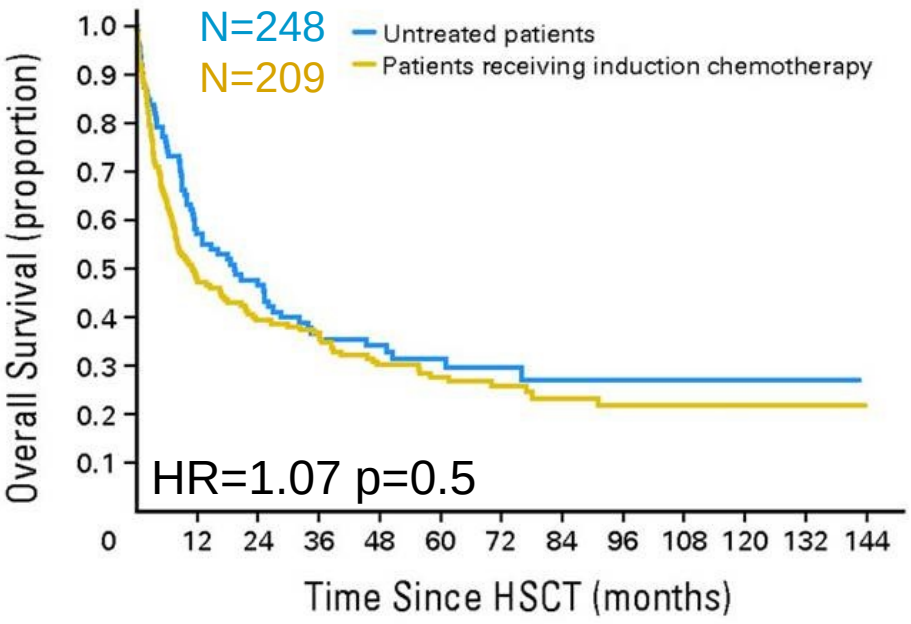
- 330 pts: 93 (28%) Rx with HMA and 237 (72%) with chemo Rx

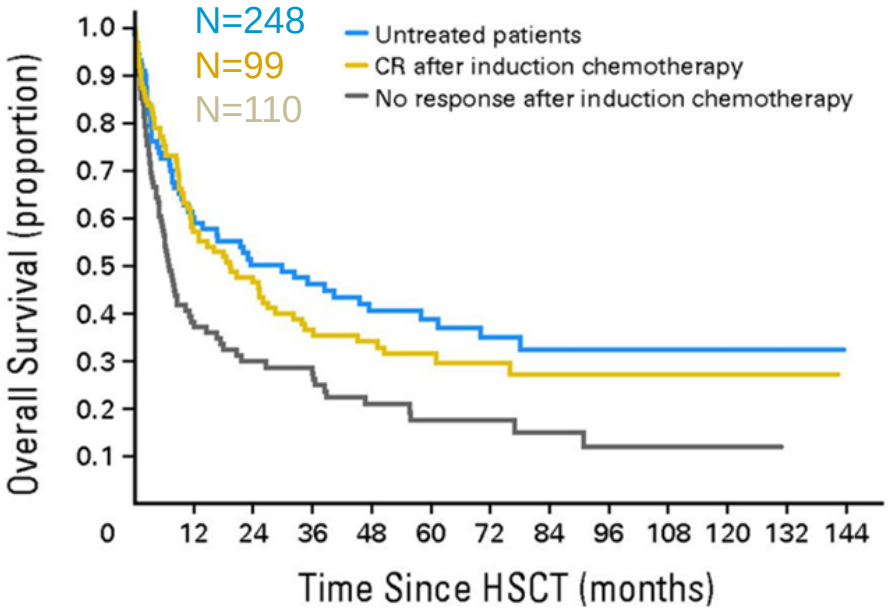
Parameter	HMA	Intensive Chemo Rx	p value
-% CR + CRp	42	60	.01
-Median Rem. dur. (mos)	14.7	14.7	
-%8-wk mortality	10	13	
-median OS (mos)	18.8	14.6	.32

- Multivariate analysis: worse OS with chemo Rx

Nazha et al. Blood 2013: Abstract 2788.

Allogeneic Transplant Can Cure MDS





Retrospective analysis GITMO
Adjusted for age, IPSS, donor type and conditioning intensity

Alessandrino et al. JCO 2013.

Timing of Allogeneic Transplant in MDS

Retrospective analysis of MDS patients <60 with MA MRD allo-HCT or 60-70yo with RIC MRD allo-HCT using a Markov decision model.

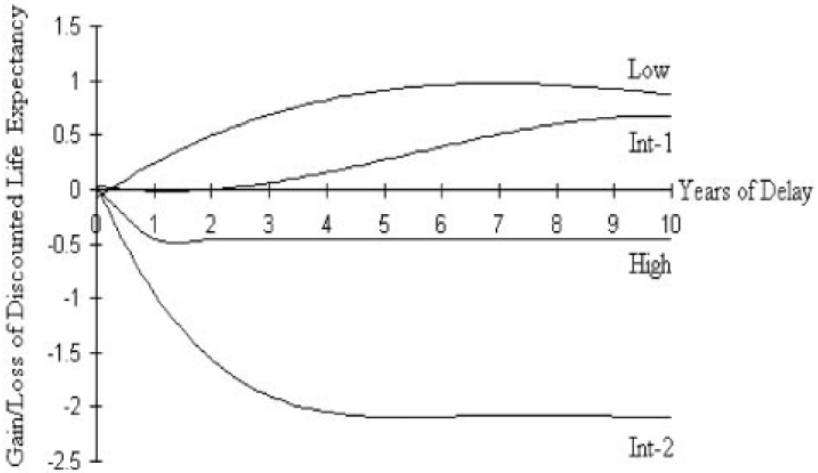
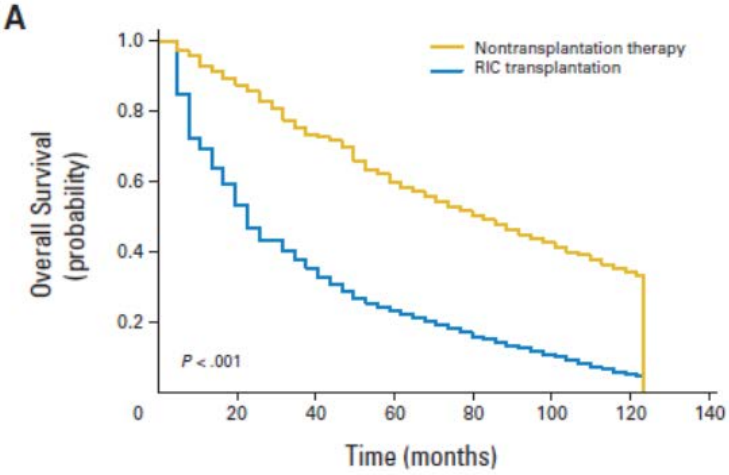


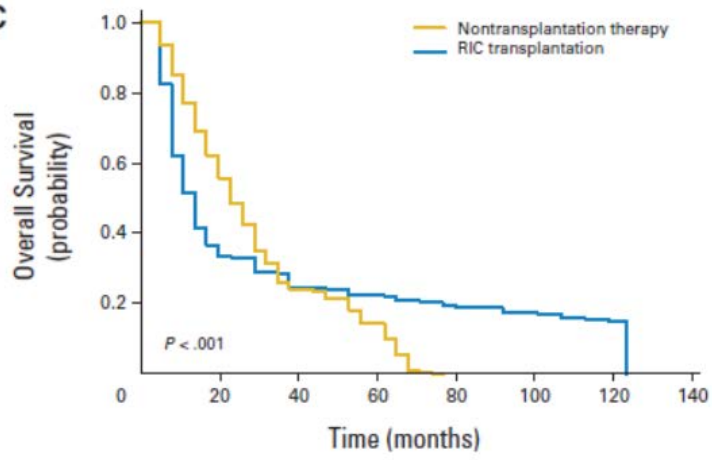
Figure 3. Net benefit or loss of overall discounted life expectancy for the 4 IPSS risk groups are shown above and below the x-axis. A net benefit for delaying transplantation is noted for low and int-1 risk groups, whereas any delay in the time to transplantation is associated with a loss in survivorship in the higher risk groups.

<60yo: Cutler et al. Blood 2004.

Low
Int-1



Int-2
High



Della Porta et al, ASH 2014 Abstract#531:
IPSS-R Int should be considered for Allo-HCT

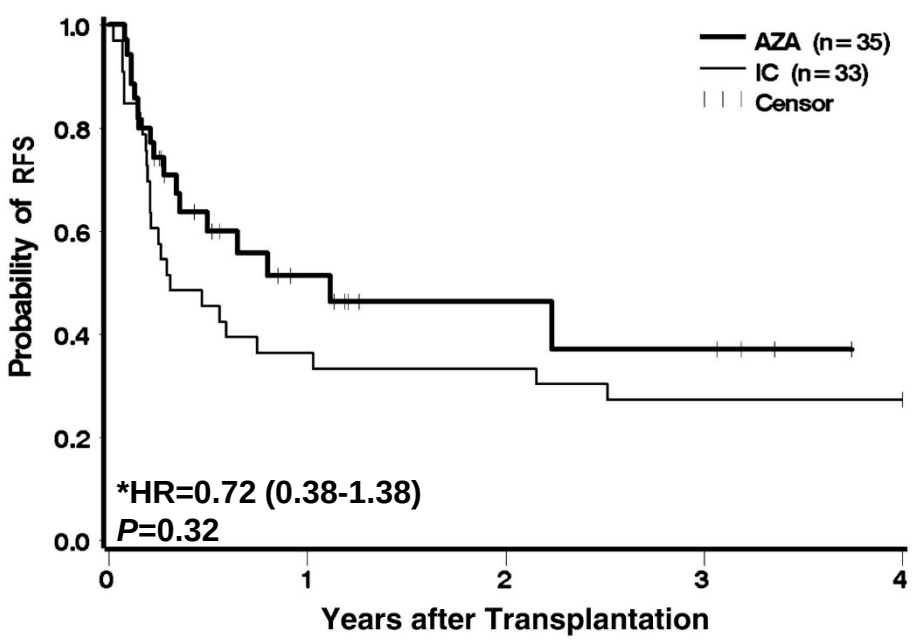
60-70yo: Koreth et al. JCO 2013.

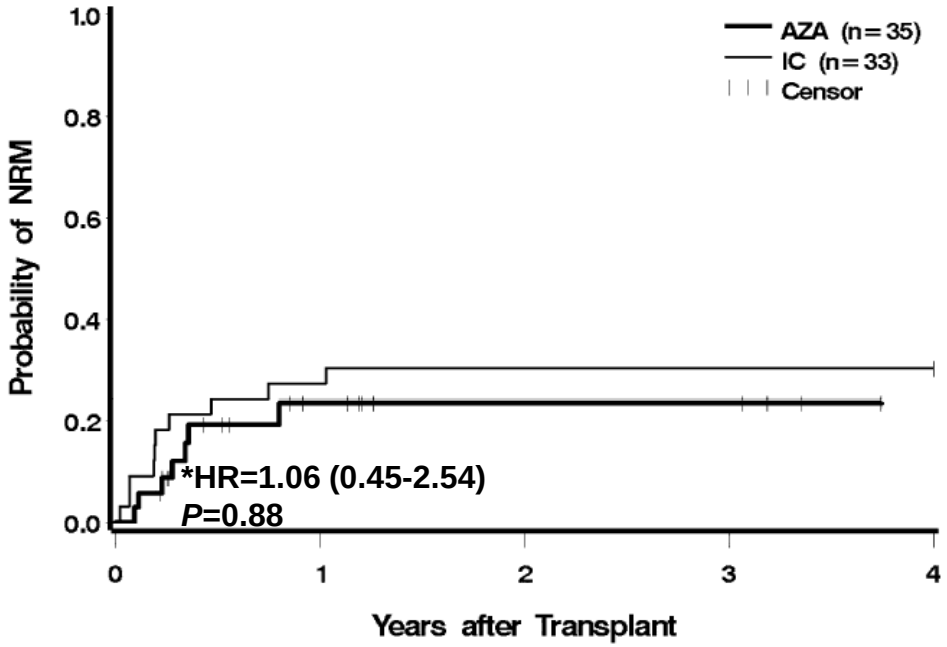
Pre-Transplant Therapy in MDS

- Pretransplant blasts >5% and failure to achieve CR correlate with relapse with RIC HCT
- Retrospective analyses of IC before HCT show no convincing evidence
- No significant differences in outcomes between HMA and IC pre-transplant
- No significant benefit of HCT after HMA/IC compared to upfront HCT
- <u>High-risk MDS patients should proceed directly to transplant without delay if possible</u>
  - Fit younger patients may benefit from “rescue” IC
  - Older patients and those with poor-risk cytogenetics may benefit from “bridging therapy” with HMA

Reviewed in: Mukherjee et al. BBMT 2014.

AZA vs IC Pre-Transplant





*Adjusted for Cyto Risk, IPSS, Donor Source

Med age: aza 60; IC 47
High intensity: aza 40%; 100% IC
RAEB-T: aza 6%; 33% IC
Aza 2004-2010; IC 1992-2002

Gerds et al. BBMT 2012.

Iron Chelation Therapy

- RBC transfusions: ≥20-30
- Symptomatic anemia/Further RBC txn need

  -- mainly Low, Intermediate-1 IPSS subtypes
- Evidence/pre-history of organ dysfunction

  -- cardiac, hepatic, endocrine
- Serum ferritin >2500→1000; ↑ Liver iron content
- Rx: Deferrioxamine (*Desferal*) SQ or
- oral iron chelator Deferasirox (*Exjade*)

New Advances in MDS

Novel Agents/Combinations in MDS

- Lower Risk MDS:
  - Oral Azacitidine (CC-486)
  - Eltrombopag
  - Luspatercept
  - Sotatercept
- Higher Risk MDS:
  - Rigosertib
  - Azacitidine combinations
    - Vorinostat
    - Rigosertib
    - Eltrombopag
    - Birinapant
    - Lenalidomide
    - Entinostat
    - Pracinostat
- Other novel agents/combinations
  - Guadecitabine (SGI-110)
  - Sapacitabine (CYC682)
  - Clofarabine plus LDAC
  - Vosaroxin plus Decitabine
  - Ibrutinib
  - Bcl-2 inhibitors
  - PD-1 pathway inhibitors
  - IDH1/2 inhibitors
  - WT1 peptide vaccine
  - Targeted agent for splice factor mutations

UC Davis Comprehensive Cancer Center MDS Trials

• Lower risk (IPSS-R VL/L/I)	• None
• Higher risk (IPSS-R I/H/VH)	• P1b Azacitidine + Ibrutinib • P1 Lenalidomide + Ibrutinib

www.ucdmc.ucdavis.edu/CANCER/clinical_trials/

UCDAVIS COMPREHENSIVE CANCER CENTER

Stanford MDS Center: Biologically Focused Clinical Trials

- **Lower risk:**
  (*IPSS-R VL, Low, Int)*
  - Luspatercept,III
    (TGFβ inhibitor for ring sideroblastic MDS)
  - Spliceosome inhibitor, I/II
    (H3B-8800)

- **Higher risk:**
  (*IPSS-R High, Very High)*
  - Spliceosome inhibitor,I/II
    (H3B-8800)
  - AzaC & PD-L1 inhibitor,I/II
    (atezolizumab)
  - RIC HSCT vs HMA,III

1/2017

UCSF MDS Trials

- Lower risk

  (IPSS-R VL/L/I)

  - None

- Higher risk

  (IPSS-R I/H/VH)

  - MDM2 inhibitor
  - IDH1 inhibitor (AG-120)

Summary and Concluding Thoughts

MDS Summary

- MDS is a heterogeneous group of BM failure syndromes
- Variable clinical presentation and course
- Choice of therapy is primarily based on IPSS-R score, symptoms, age and comorbidities
- Understanding of pathogenesis, prognostication and treatment is evolving
- Novel biospecific therapies are being evaluated

MDS Resources

- Leukemia and Lymphoma Society
- MDS Foundation
- Aplastic Anemia and MDS Foundation
- National Comprehensive Cancer Network (NCCN)
- UCD, UCSF and Stanford Cancer Centers
  - Brian Jonas (UCD)
  - Peter Greenberg (Stanford)
  - Rebecca Olin (UCSF)

MDS Questions to be Answered

- What is MDS?
- Why did I get MDS?
- What does it mean for my life?
- Is there treatment for it?
- How should I be treated?
  - When?
  - Why?
- What are some of the new advances in MDS?

Essentials for the Informed Pt with MDS

- Know your IPSS-R risk group
- Know your treatment options
  - Including transplant, clinical trials
- Know what your treatment goals are
- Know the potential side effects of your treatments
- Know available MDS resources
- Have a caregiver available/involved

Questions?

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