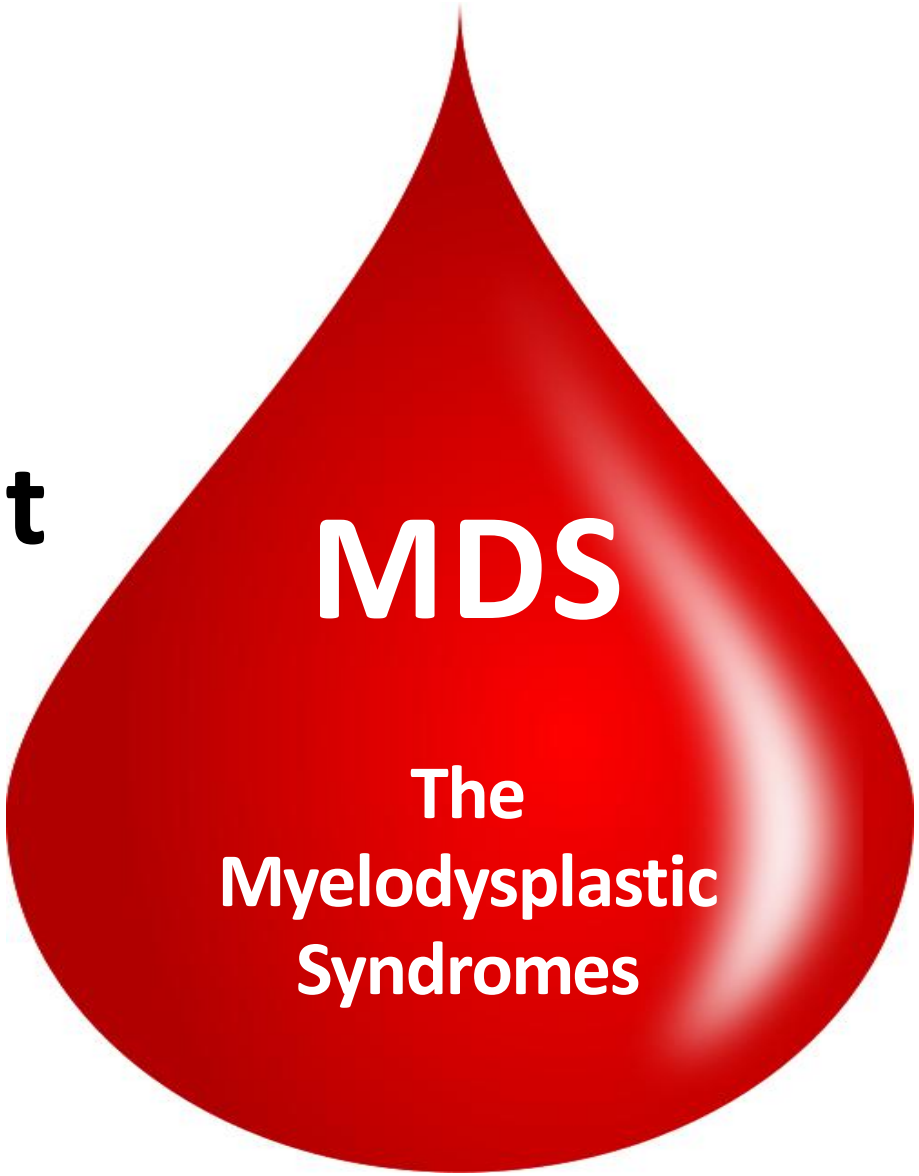
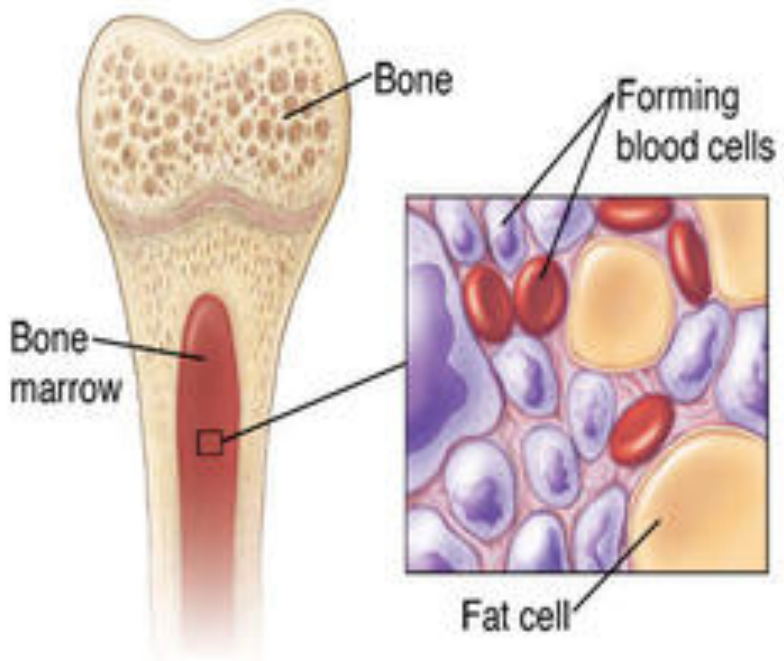
What you need to know about



Stuart Goldberg MD

The John Theurer Cancer Center
at Hackensack University Medical Center

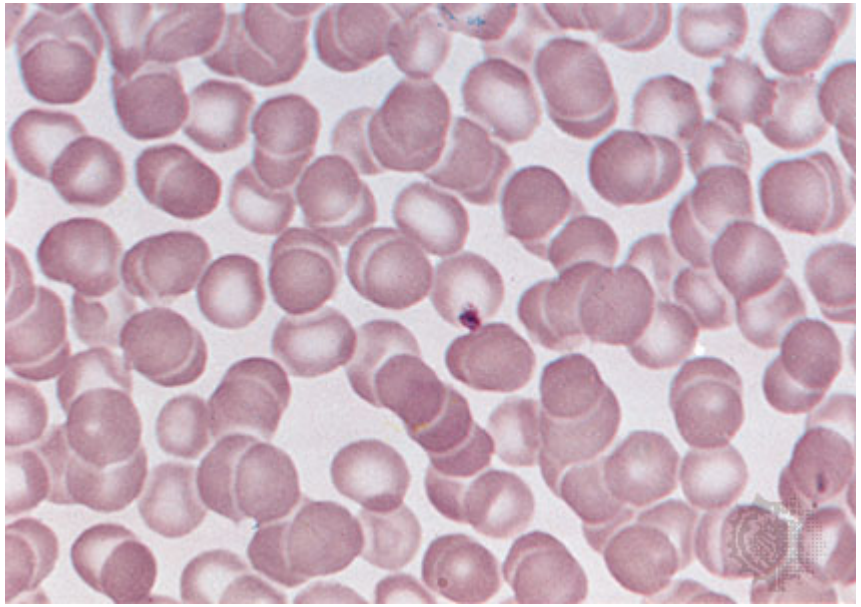
The Myelodysplastic Syndromes are a group of bone marrow failure diseases



The bone marrow is the factory that makes blood

The 4 major components of blood

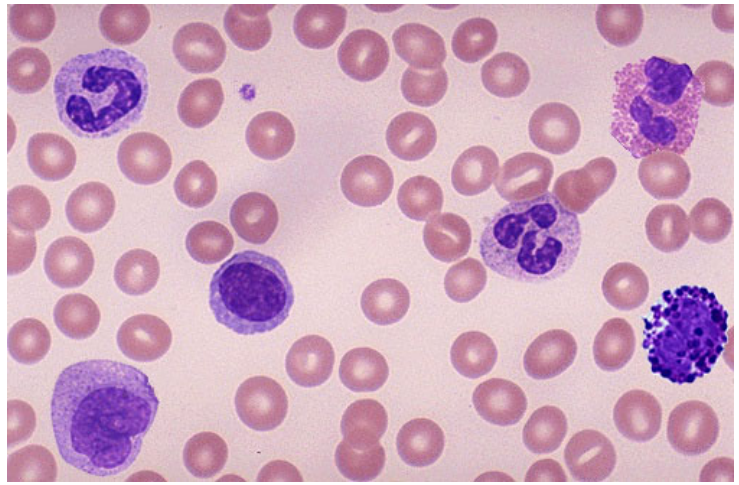
- **Red Blood Cells: Carry oxygen (energy)**
- **When low called “Anemia”**
  - **Weakness, pale, short of breath, leg swelling**
- **Usually measured as hemoglobin**
  - **Normal male 14-16 gm/dl**
  - **Normal female 12-14 gm/dl**



The 4 major components of blood

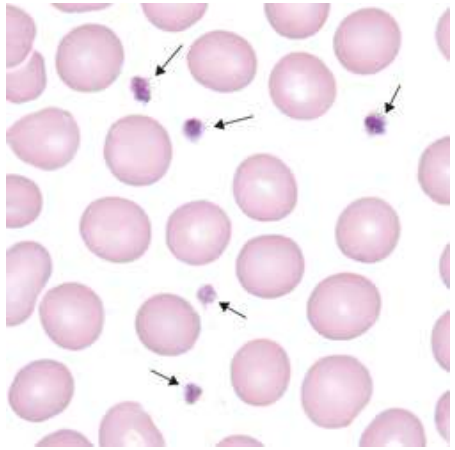
- Red Blood Cells: Carry oxygen (energy)
- **White Blood Cells: Immune system (fight infections)**
  - Neutrophils: primary bacteria fighters
  - T- lymphocytes: recognize infections
  - B- lymphocytes: make antibodies to prevent repeat infections
  - Monocytes: deep penetrating infection fighting and recognition

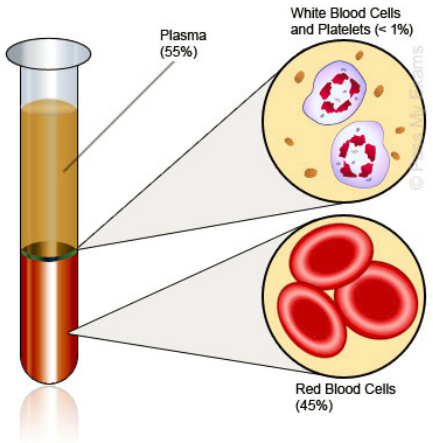
  - Normal WBC 4.5-10 X 10^9/L
  - Normal Neutrophil count 1.5-8 X 10^9/L



The 4 major components of blood

- Red Blood Cells: Carry oxygen (energy)
- White Blood Cells: Immune system (fight infections)
- **Platelets: clotting (stop bleeding)**
  - Normal platelet count 150,000 – 400,000
- **Plasma: clotting (stop bleeding)**





Too few blood cells leads to

- **Weakness**
- **Shortness of breath**
- **Pale**
- **Fevers**
- **Infections**
- **Bruising**
- **Bleeding**

In MDS

The bone marrow fails to make enough blood cells *due to a damaged bone marrow.*

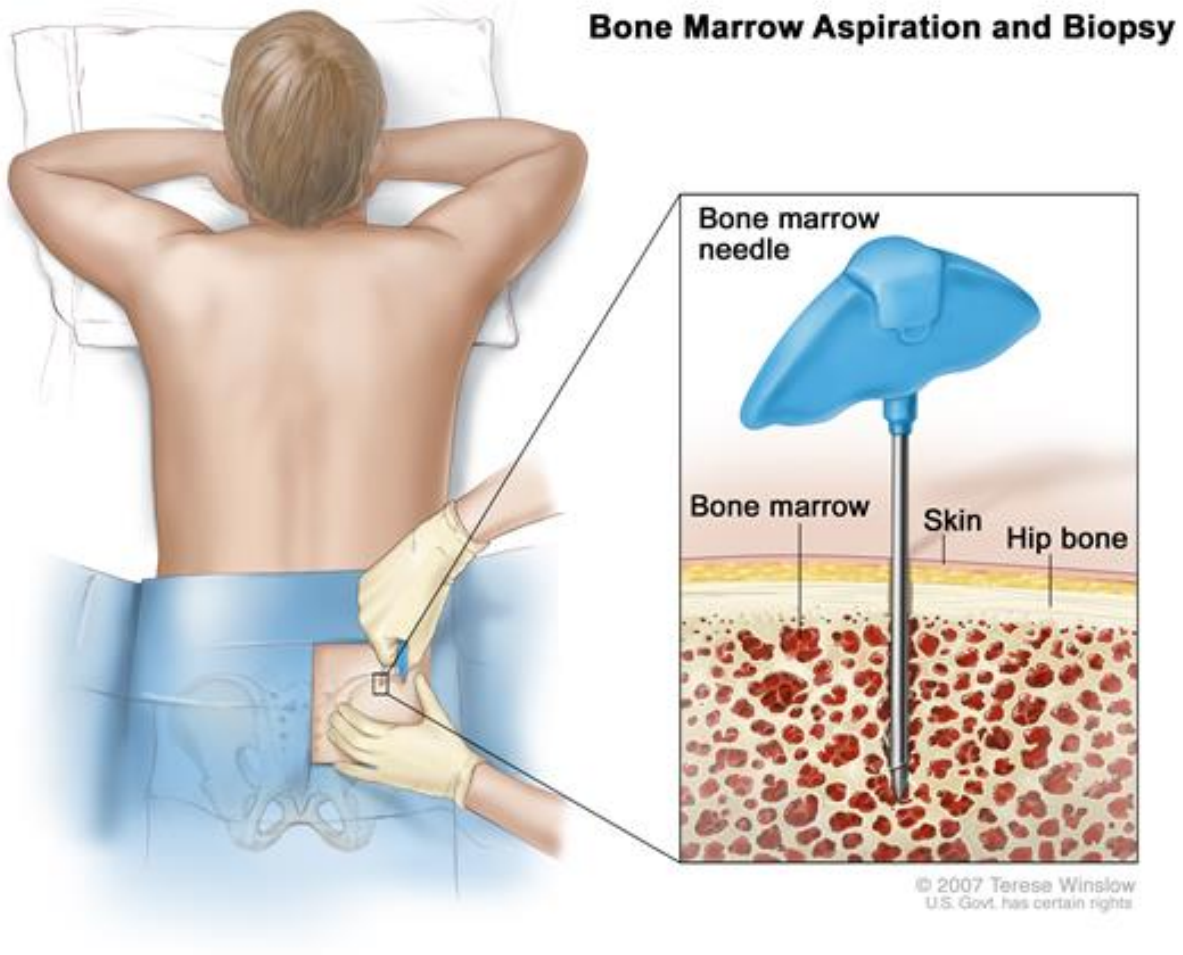
Under the microscope the bone marrow MUST show dysplasia (changes) in at least 10% of the cells of one lineage

What can cause the marrow damage?

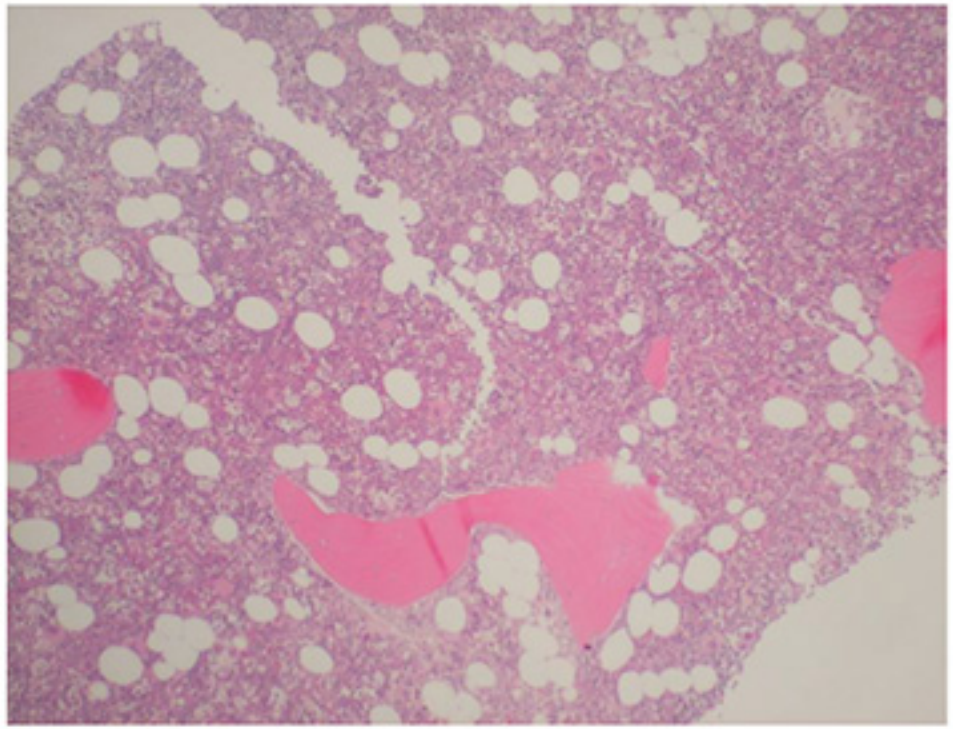
Prior treatment for a cancer with chemotherapy agent (often years ago)
Tobacco: Smoking also raises your chance of getting MDS.
Benzene: This chemical is widely used to make plastics, dyes, detergents, and other products.
Other chemicals and poisons

Inherited conditions: Some conditions include Down syndrome, Fanconi anemia, Bloom syndrome, Ataxia telangiectasia, etc.
Blood diseases: Paroxysmal nocturnal hemoglobinuria, Congenital neutropenia, etc

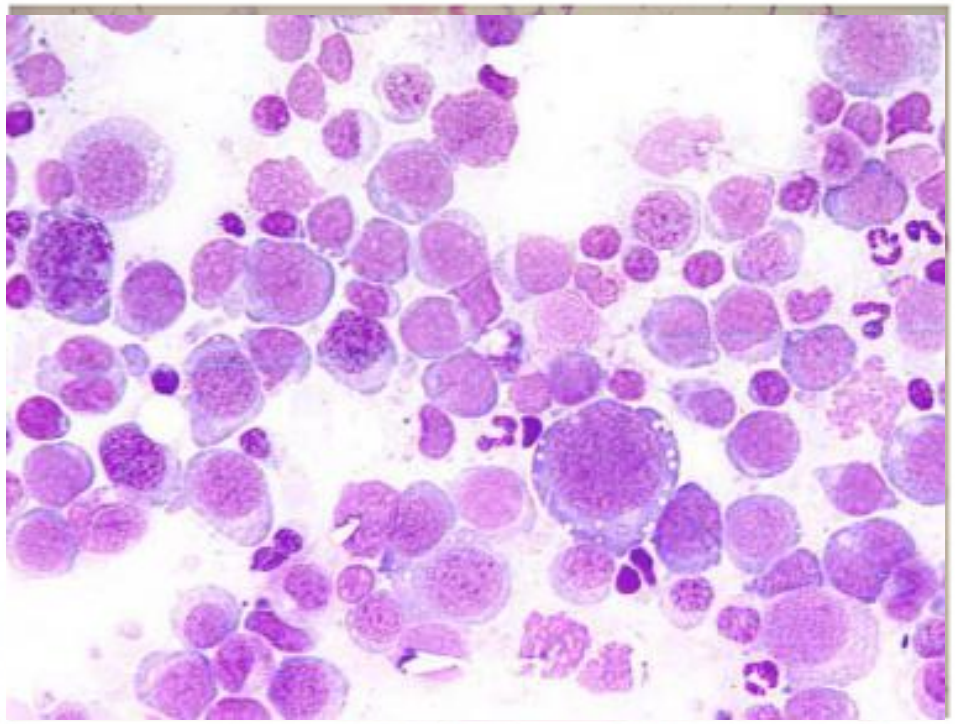
Making the Diagnosis: The Bone Marrow Biopsy



Making the Diagnosis: The Bone Marrow Biopsy



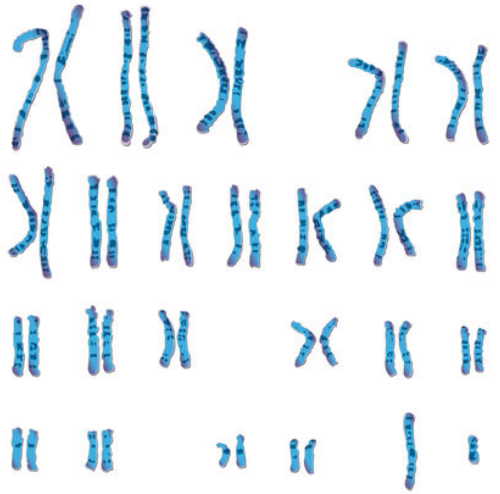
Healthy bone marrow



MDS Marrow

The “factories” are “ugly”. Thus less blood is made.

Cytogenetic Tests from the Bone Marrow



- Bone marrow cells may be examined for genetic changes
- Some chromosomal changes are more common, and may indicate more of a pre-leukemia (MDS) state with a poorer prognosis
- Genetic alterations, found by Next Generation Sequencing, are common but the implications are largely unknown (although some patterns indicate more aggressive disease)

New

“PRE”-Myelodysplastic Syndromes?

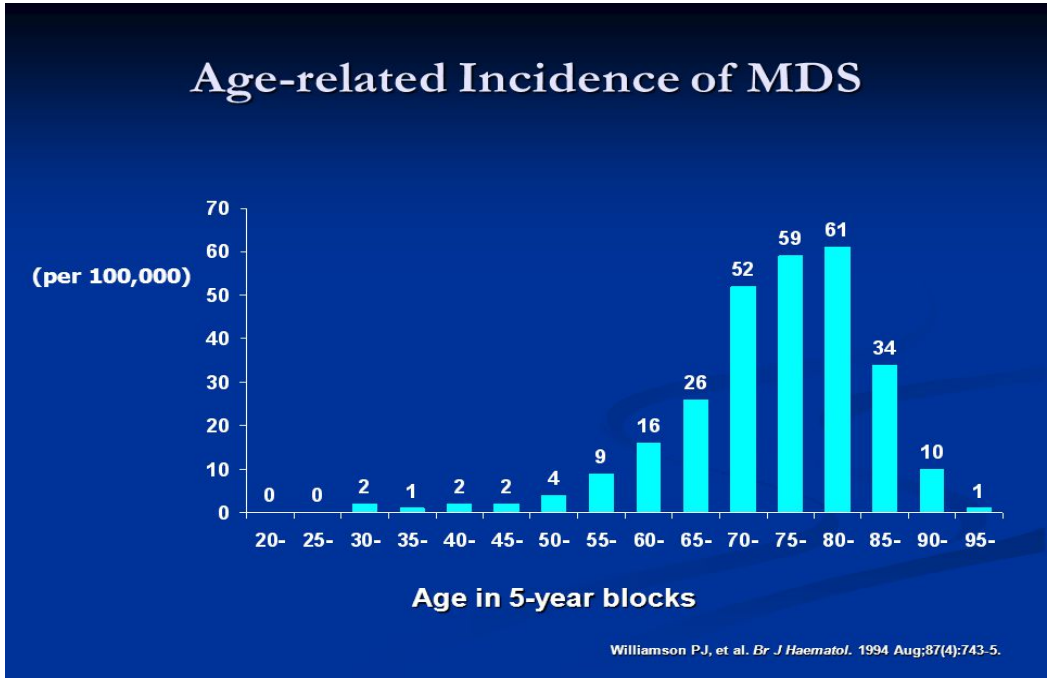
Occasionally the blood counts may be low but the marrow does not look abnormal – this might be MDS in the future, but cannot be called MDS at this time:

- **Idiopathic cytopenia of undetermined significance (ICUS)** – Single or multiple blood cytopenias that remain unexplained despite an appropriate evaluation including marrow examination.

- **Clonal hematopoiesis of indeterminant potential (CHIP)** – Identification of a clonal mutation associated with hematologic neoplasia in an individual who does not yet meet WHO criteria for diagnosis of a hematologic neoplasm.

- **Clonal cytopenia of undetermined significance (CCUS)** – Identification of a clonal mutation in a patient with one or more clinically meaningful unexplained cytopenias, yet who does not meet WHO-defined criteria for a hematologic neoplasm.

MDS is a disease of the Elderly



MDS is the MOST COMMON hematologic malignancy of the elderly

86% of MDS cases are diagnosed in individuals >60 years of age

In the USA, around 10,000 new cases per year

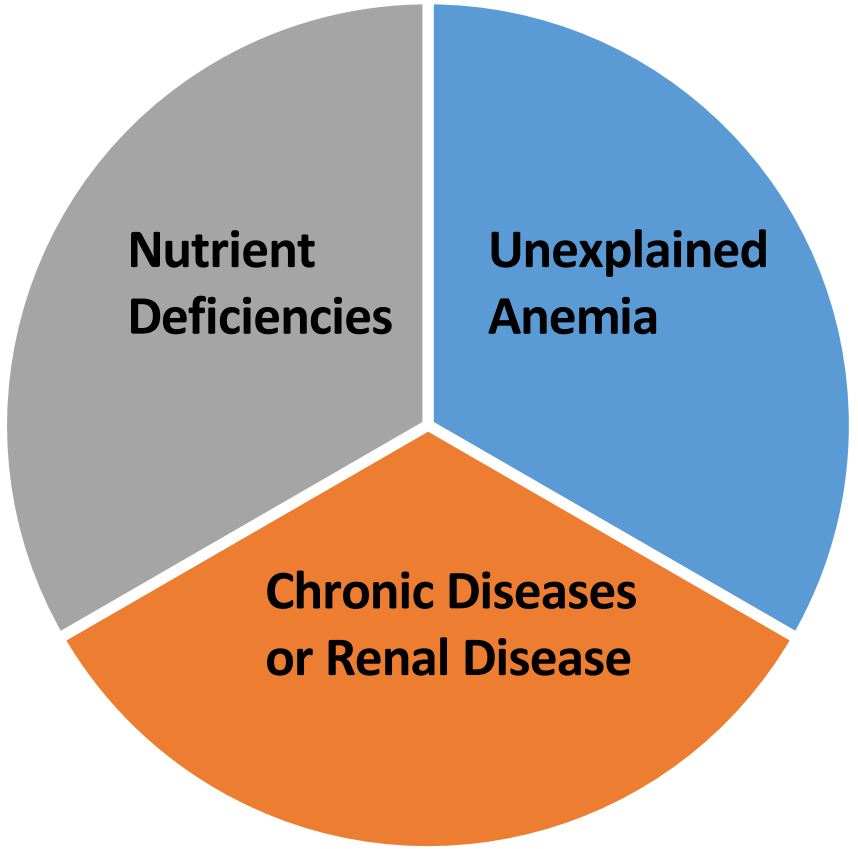
Hackensack Study suggests 40,000

Ma X, Cancer, 2007;109:1536
Rollison DE, Blood, 2008;112:45
Goldberg SL, JCO 2010: 2847

MDS may be under-diagnosed in the elderly

Anemia is common, but not normal

11% of men
10% of women
65-years or older
are anemic.

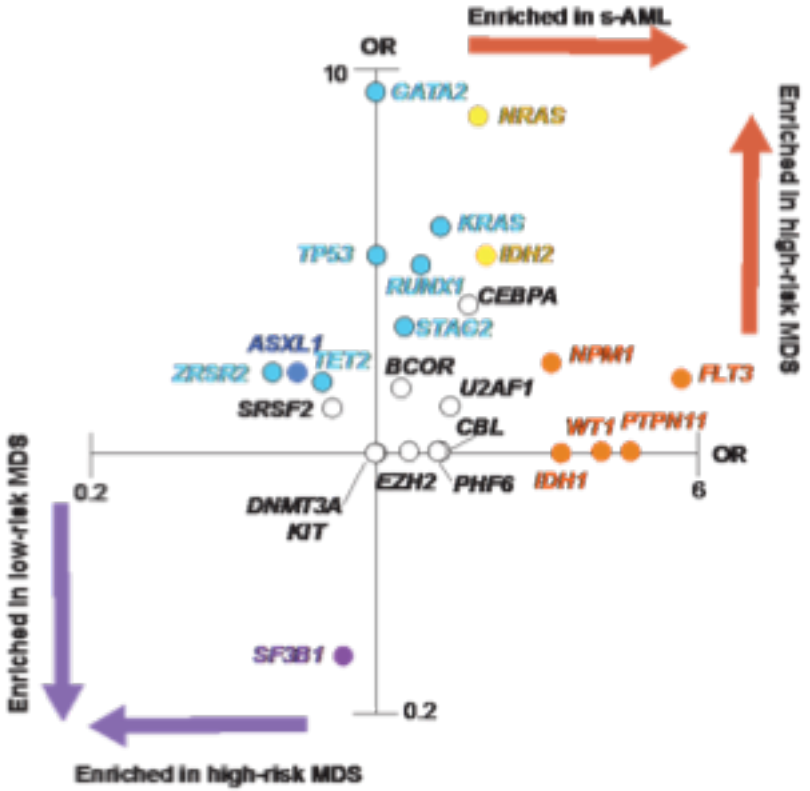


17% had macrocytosis accompanied by neutropenia or thrombocytopenia

Guralnik JM, et al: Blood. 2004;104:2263

New

Novel approaches to “diagnosis”

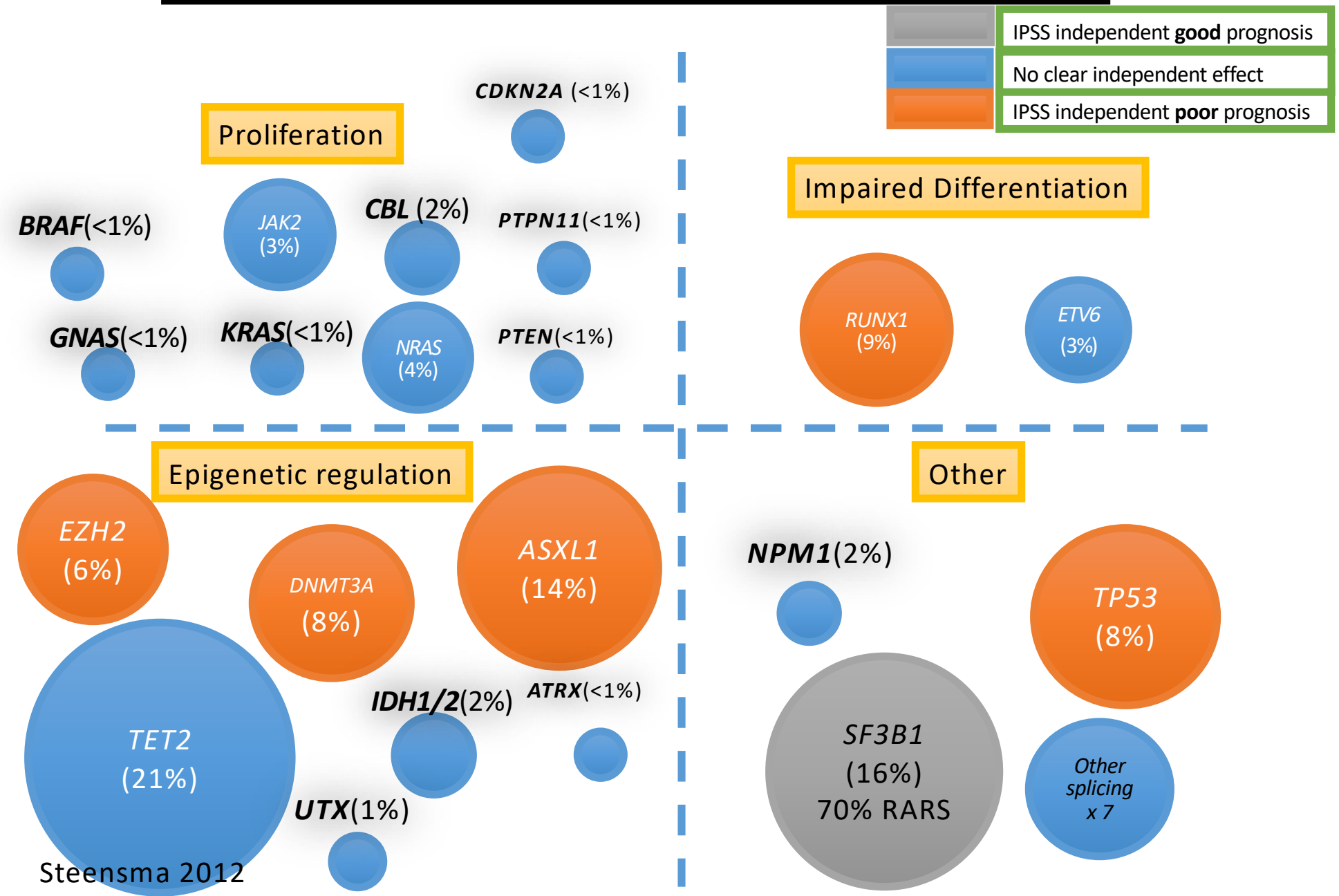


The formal diagnosis of MDS requires Bone Marrow morphologic dysplasia

Since MDS is a stem cell disorder, genomic alterations may be present in peripheral blood

“Next Generation Sequence” myeloid panels may uncover mutations *suggestive* of MDS

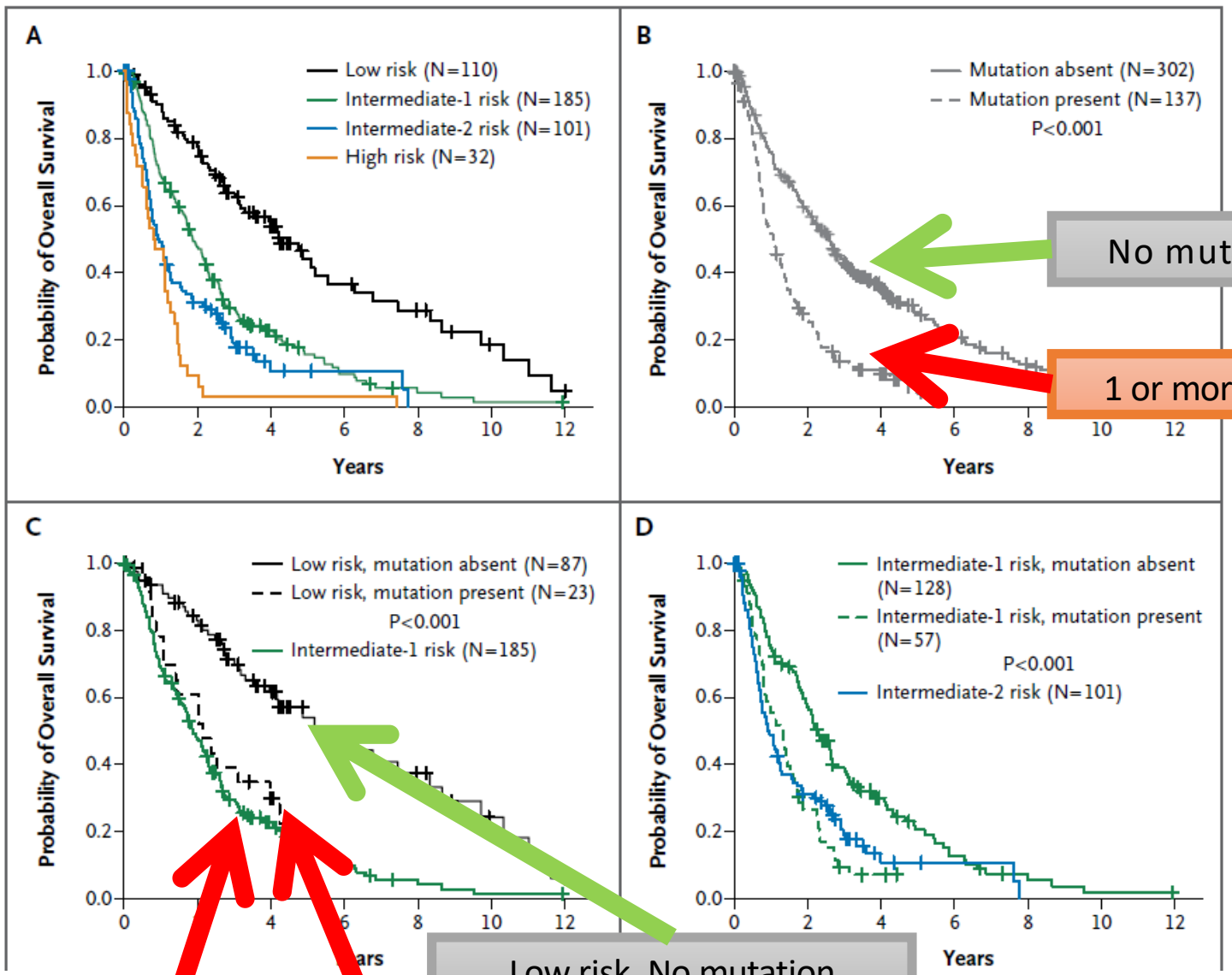
MDS mutations



Steensma 2012

New

Impact of mutations on IPSS risk



No mutation

1 or more mutations

Low risk, No mutation

Int-1

"Low" risk, 1 or more mutations

Mutations considered:

EZH2

TP53

RUNX1

ASXL1

ETV6

Bejar R et al, *N Engl J Med* 2011; 364: 2496-506.

Types of MDS

2016 WHO Classification of Myeloid Neoplasms

WHO Classification -- Subtypes of MDS

MDS with single lineage dysplasia	MDS with excess blasts in transformation
MDS with ring sideroblasts	Chronic myelomonocytic leukemia (CMML-1)
MDS with multilineage dysplasia	CMML-2
MDS with excess blasts-1	Atypical chronic myeloid leukemia, *BCRABL1* negative
MDS with excess blasts-2	Chronic neutrophilic leukemia
MDS, unclassifiable	Juvenile myelomonocytic leukemia
MDS with isolated del(5q)	MDS/MPN unclassifiable
Refractory cytopenias of childhood	MDS/MPN with ring sideroblast and thrombocytosis

Arber DA, et al. *Blood*. 2016;127:2391-2405.
NCCN Guidelines. Myelodysplastic Syndromes. V1.2017.

Low Grade (risk) vs High Grade (risk) MDS

- In low grade (risk) disease the goal of therapy is

Quality of Life Issues

- In high grade (risk) disease the goal of therapy is

Quantity of Life Issues

Prognosis in MDS

Prognostic Variable	Prognostic Score Value						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics	Very good	--	Good	--	Intermediate	Poor	Very poor
Bone marrow blast, %	≤ 2	--	> 2 to < 5	--	5-10	> 10	--
Hemoglobin, g/dL	≥ 10	--	8 to < 10	< 8	--	--	--
Platelets, x 10^9/L	≥ 100	50 to < 100	< 50	--	--	--	--
Absolute neutrophil count, x 10^9/L	≥ 0.8	< 0.8	--	--	--	--	--

The IPSS and the IPSS-R assist in defining prognosis in MDS
Based on cytopenias, blast percentages and cytogenetics
IPSS-R has an age adjustment for survival based on age

Standard Prognostic Systems Fail to Account for Many Aspects of the Elderly

- **Comorbid illnesses**
- **Secondary causes of MDS**
- **Prior therapy for MDS**
- **Other age-related health, functional, cognitive, and social problems**

Ria R et al: Clin Interv Aging 2009; 4:413
Ritchie E et al: Curr Hematol Malig Rep 2009; 4:3

Treatment of MDS

- Treatments vary depending on:
- (1) type of MDS
- (2) severity of cytopenias (how low are the blood counts)
- (3) risk of developing leukemia
- (4) prognostic models
- (5) patient factors (age, performance status, patient preference)

Standard Treatments of the MDS Patient

- **Lower Risk**
  - Transfusional Support
  - Growth Factors
  - Immunomodulatory therapy: Lenalidomide
  - Immunosuppressive medications
- **Higher Risk**
  - De-methylating agents: 5-azacytadine & decitabine
  - Allogeneic transplantation

Anemia in the elderly MDS patient

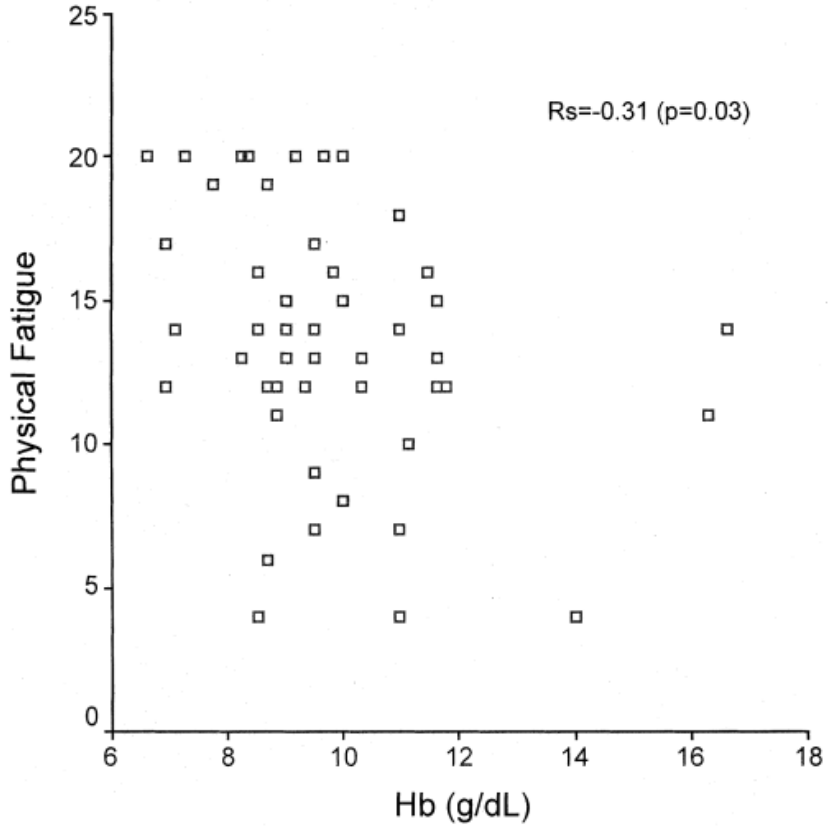
- May not be as well tolerated
- Frailty
- Cardiac effects
- Transfusion “triggers” need to be adjusted
- Not all fatigue is anemia (hypothyroidism, cor/pulm)

Chaves PH. Semin Hematol. 2008;45:255

Fried LP, et al. J Gerontol A Biol Sci Med Sci. 2001;56:M146

Zakai NA et al. Arch Intern Med. 2005;165:2214

Quality of Life measurement in transfusion-dependent MDS



Jansen A. British Journal of Haematology 2003; 121: 270

Blood Transfusions

(raise HgB about 1 gm)

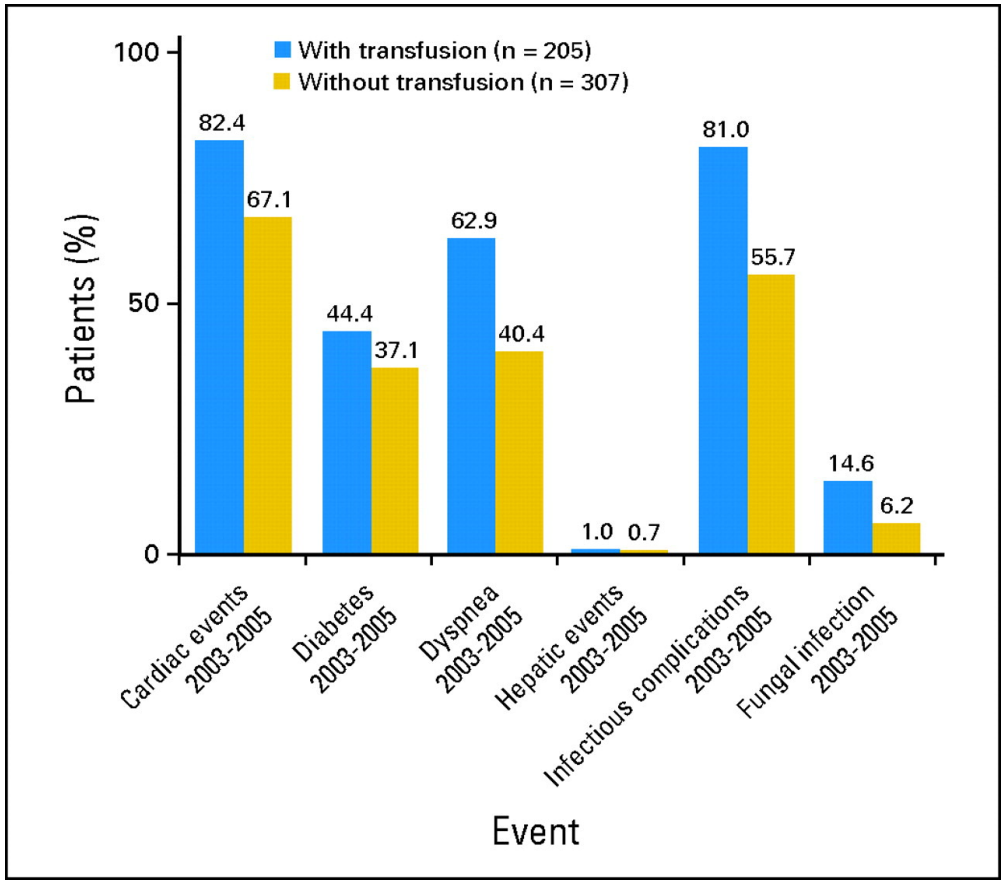
- May be necessary for symptoms of anemia or thrombocytopenia
  - Fatigue and shortness of breath with very low red blood cells
  - Bleeding with very low platelet counts
- Avoidance of family members as blood donors in BMT patients
  - Sensitization to HLA antigens which could raise risk of future transplant
- Minimize risk of CMV infection in BMT patients
  - A common infection carried in blood cells: pneumonia, diarrhea, vision issues
- Blood products typically irradiated
  - Reduce risk of graft-vs-host disease

Complications within 3 years of diagnosis among Transfused and Non-transfused MDS patients

(median age 77)

Cumulative 3-year mean Medicare costs were $49,156.

Transfused patients had greater use of hospital inpatient and outpatient services and incurred higher costs ($88,824 vs. $29,519, p < 0.001).

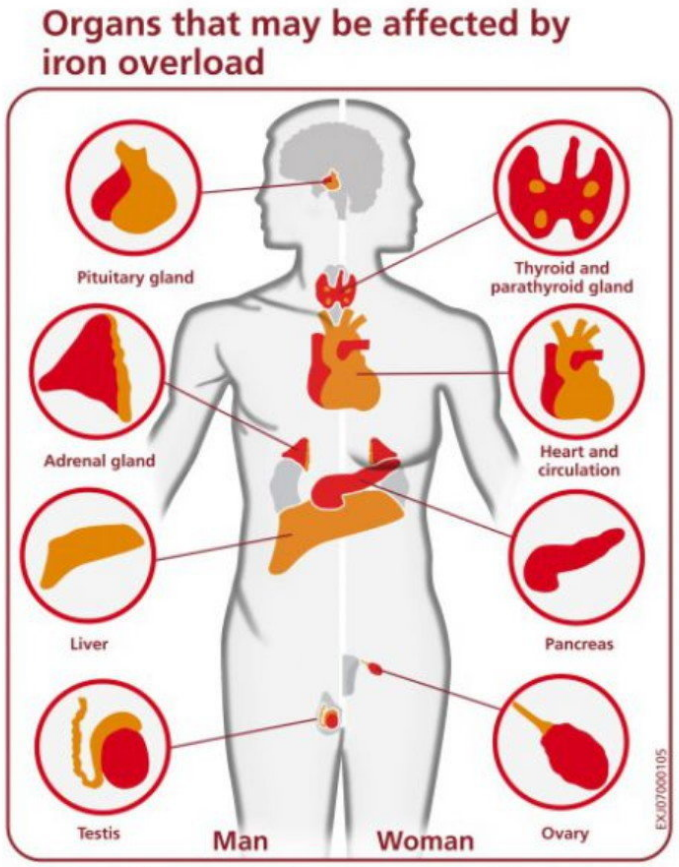


Goldberg SL et al: J Clin Oncol. 2010; 10:28:2847

Goldberg SL et al: Transfusion. 2012; 52:2131

Chelation Therapy for Transfusional Iron Overload

Repeated transfusions increase iron burden
May occur after 20 units of blood
Common triggers to consider treatment
    Ferritin >1000 in low risk patients
    Future BMT candidate
New formulation of deferasirox better tolerated



Toxic iron builds up across the body and can cause serious damage to vital organs, including the heart and liver.

Relationship Between Chelation and Clinical Outcomes in Lower-Risk MDS

- 600 pts with low risk MDS. IPSS status similar across groups.
- Chelated pts (n=271) had a greater median number of lifetime units transfused at the time of enrollment vs nonchelated pts (n=328): 38.5 vs 20.0.
-
- OS from diagnosis of MDS and time to acute myeloid leukemia (AML) were significantly greater in the chelated vs nonchelated pts (*P*<0.0001 for both).
- In pts with Cardiovascular comorbidities, median OS was also significantly greater in chelated vs nonchelated pts (67.66 vs 43.40 mo; *P*<0.0001).
- In pts with Endocrine comorbidities, median OS was also greater in chelated pts (74.98 vs 44.63 mo; *P*<0.0001).

Lyons ASH abstract 1350

Growth Factors ("fertilizers") in MDS

Can we help a dying bone marrow?

- RED CELL (energy)
- Erythropoietin (Procrit; Aranesp) is regulated by Medicare rules
- Addition of filgrastim to epo may augment effects (especially RARS)
- Analogues to epo in development (luspatercept)

Underutilized

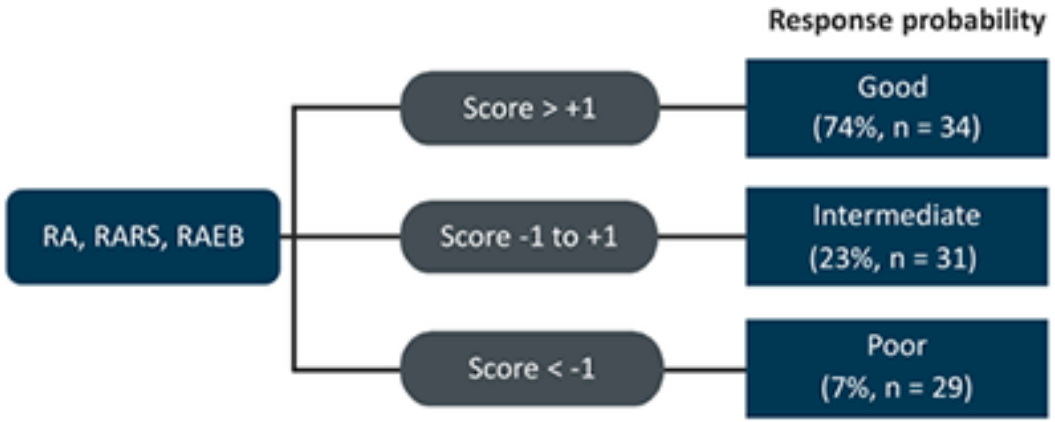
- WHITE CELL (immune system)
- Myeloid growth factors (Neupogen) typically reserved for times of infection (not chronic use)

- PLATELET (clotting)
- Platelet growth factors (Promacta; N-plate) role not standard in MDS

Erythropoietin Therapy for Low Grade MDS

Often a first treatment for Anemia

Predictive Model for Response to Treatment With EPO + G-CSF



Treatment response criteria

CR	Stable Hb > 11.5 g/dL
PR	Increase in Hb with > 1.5 g/dL or total stop in RBC transfusions

Treatment response score

S-EPO, mU/mL	< 100	+2
	100-500	+1
	> 500	-3
RBC transfusion, U/m	< 2	+2
	≥ 2	-2

Hellström-Lindberg E, et al. *Br J Hematol*. 2003;120:1037-1046.

Erythropoietin works in the Elderly

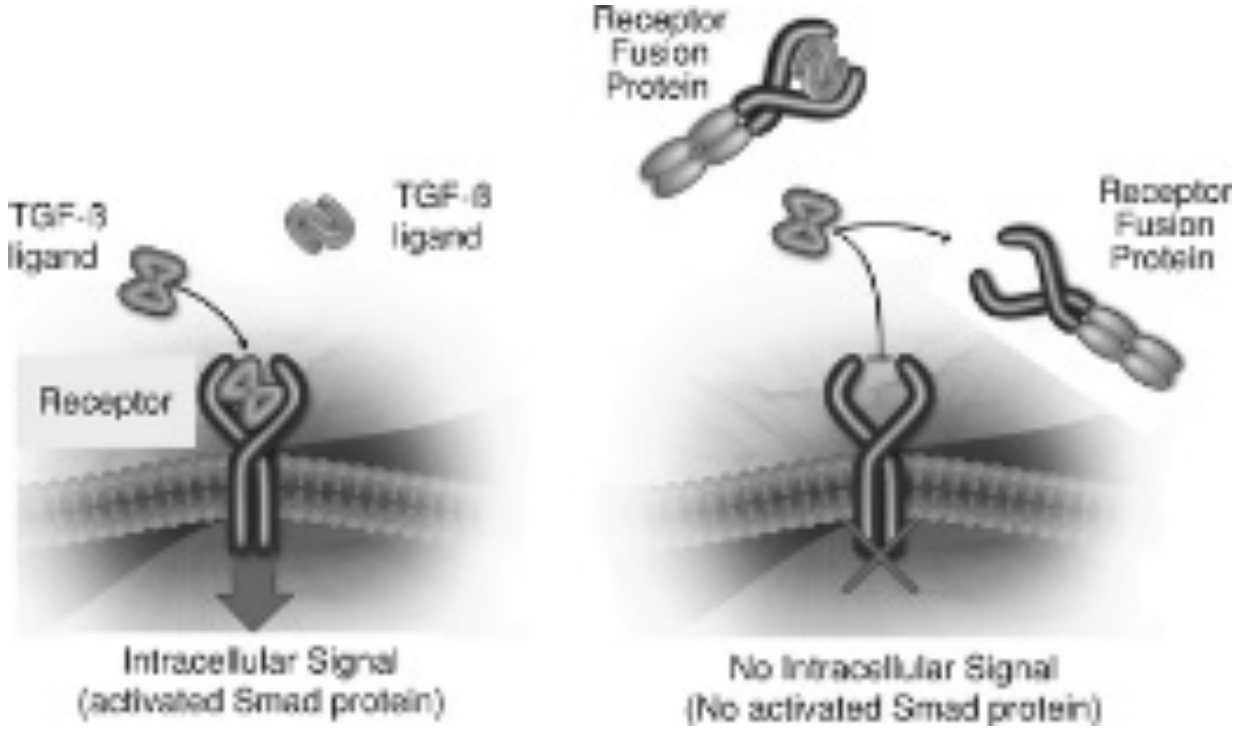
- 93 MDS patients treated with rHuEPO aged ≥80 years
- Median baseline hemoglobin (Hb) level of 9 g/dl
- The initial dose of rHuEPO was 40,000 IU/week or higher
- Erythroid response in 64%.
- No thrombotic event was reported.
- Predictive factors for response
  - low transfusion requirement before treatment
  - ferritin <200 ng/ml
  - Hb >8 g/dl
  - high-dose rHuEPO treatment

- Median OS from rHuEPO start was 49.3 months in responders versus 30.6 months in resistant patients

Tatarelli C et al: Ann Hematol. 2014; 93:1413

New

New Eythroid Growth Factors: ACE-001 (sotarercept) and ACE-536 (luspatercept)



Receptor fusion proteins act as ligand traps by binding to ligands of the TGF-β superfamily, preventing those ligands from binding to the cell surface receptors, and thereby preventing activation of Smad proteins in the target cell.

New

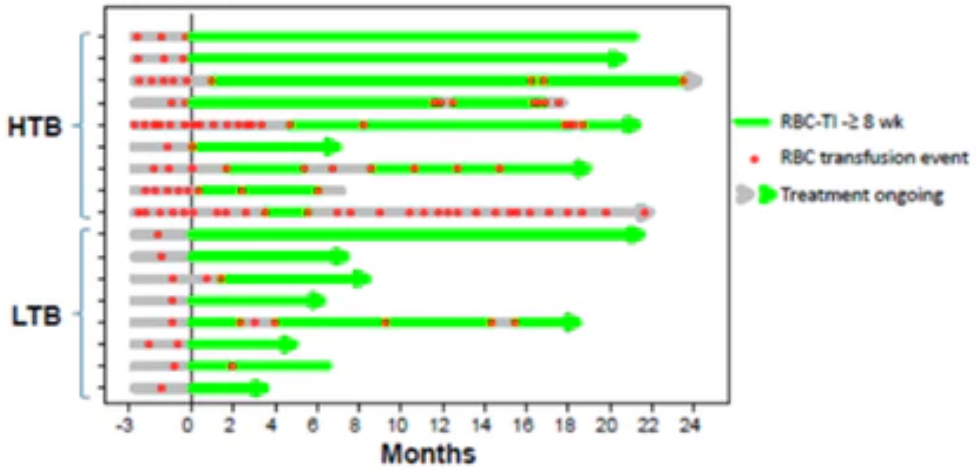
Luspatercept
Encouraging results in early studies of lower risk MDS, espectialy in RARS subtype

Platzbecker: Luspatercept Extension Trial in MDS

- Phase II, open-label, long-term extension trial
- Primary endpoints: Safety, erythroid response (IWG HI-E), RBC transfusion independence, duration of HI-E
- Luspatercept SC at starting dose of 1.0 mg/kg

17/28 (61%) achieved transfusion independence

Figure 3. Duration of Transfusion Independence in RBC-TI Responders in Extension Study



Platzbecker, U, et.al. ASH 2016. Abstract 3168

New randomized trial is currently accruing

Market Realist

Source: Celgene Investor Presentation

Lenalidomide (revlimid)

A “gentle” chemo pill for anemia in MDS

- A cousin of Thalidomide -- associated with birth defects
- **Approved for treatment of anemia in patients with a specific type of MDS having a break on chromosome 5**
  - **Up to two-thirds of patients with 5q- MDS will improve HgB in 2-3 months**
- Commonly used “off label” for anemia of other MDS types
- Associated with skin rashes, diarrhea, nausea, neuropathy, lowers plts
- Dose is lower than that used for multiple myeloma (often 5-10 mg)

Lenalidomide in Older Patients with del5q

- Lenalidomide is standard therapy for improving anemia among patients with deletion 5 q abnormalities
- Analysis of the MDS 003/004 trials demonstrated effectiveness of lenalidomide in older patients
  - equivalent rates of RBC transfusion-independence, cytogenetic response, and AML progression.
- While patients over 75 years old had a shorter duration of lenalidomide therapy, there were no differences in the reasons for discontinuation of treatment.
- From a safety perspective, lenalidomide caused a similar range of side effects
  - patients over75 years old were nearly twice as likely to require dose-reduction due to thrombocytopenia (30% vs. 17%), very few needed to stop treatment altogether for this reason (4% vs. 3%).
  - neutropenia did not appear to affect older patients selectively, although infections were somewhat more common in those over75 years old (36% vs. 20%).

Fenaux P et al: ASCO 2012

Lenalidomide for anemia in Non 5q MDS

- Recent studies have sought to define role of lenalidomide in non-deletion 5q patients
- MDS 005 study enrolled 239 patients with median age 71
- 27% of patients achieved RBC-TI ≥ 56 days
  - median duration of RBC-TI of 8.2 months;
  - 90% of pts responded within 16 weeks of treatment.
- The overall safety profile was consistent with the known safety profile

Santini V et al: JCO 2016; 34:2988

Underutilized

Immunosuppressive Therapy

- There is immune dysregulation in myelodysplastic syndromes
- The immune system may attack the bone marrow and slow down blood cell production
- Immunosuppressive therapy seeks to temporarily turn off the immune system to allow the marrow to recover

- “turn off your system and reboot”

Considered in patients <60 and <5% blasts, or hypocellular marrows, or PNH clones, or STAT mutant cytotoxic T-cells

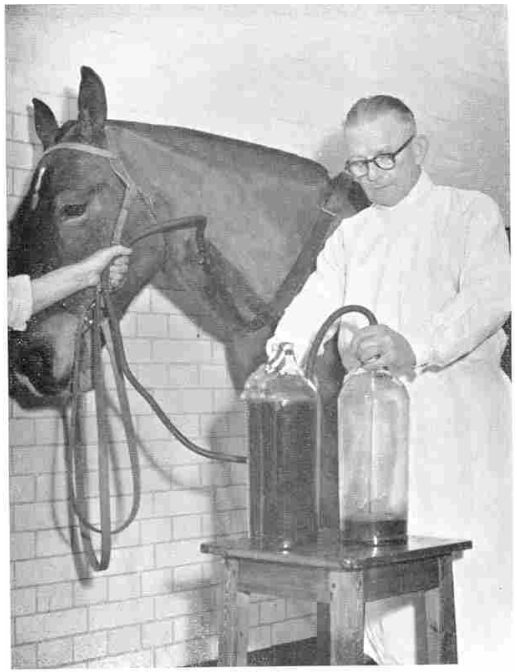


FIG. 4
The production of an antiserum bleedin amunized horse from the gular vei

Anti-thymocyte globulin (ATG)

- ***ATG: Yes, it really is horse serum***
- The T-cells in the horse's blood attack the diseased human immune system – the human immune system temporarily shuts down and cannot attack the bone marrow – then the human immune system regrows
- Given over 4-5 days in the hospital via a large intravenous line
- May cause shaking chills and low blood pressure during administration
- May cause muscle aches and rashes (serum sickness)
- Takes 10-12 weeks to see improvement in counts

Treatment of Neutropenia or Thrombocytopenia in Low Grade Patients

- Most lower risk patients have anemia with minimal other low counts
- However, some patients have low white or platelets as there only problem and thus score as low risk
- Limited easy options
  - White cells: Growth factors alone rarely used chronically
  - Platelets: Romiplostin potentially in low risk, TPA<500, few prior plt transfusions

    Eltrombopag in trials. Concern for both is accelerating leukemia
- Demethylating agents (discussed later) may be needed

  Newer studies may suggest lower dose (3 day) 15-30% success

Higher Risk MDS (intermed 2 and high IPSS)

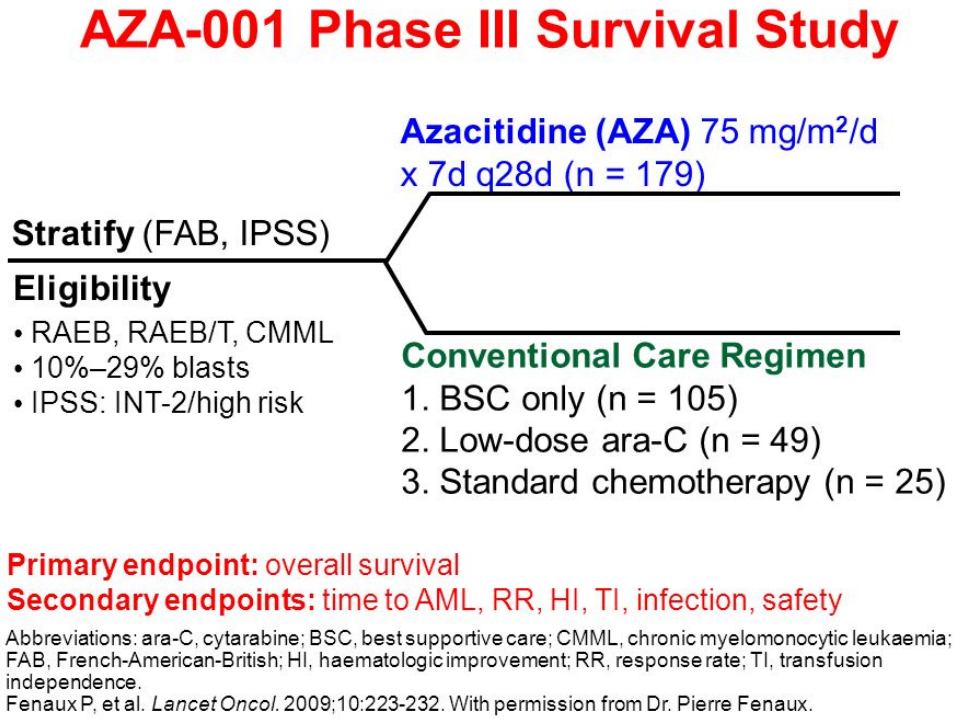
- In higher grade MDS multiple blood counts may be low
- In higher grade MDS more leukemia blasts be noted

- In addition to quality of life issues, quantity of life becomes important

- **IN YOUNGER FIT patients, consideration of BMT (transplant)**
- **IN EVERYONE ELSE strong consideration of demethylating agents**
- **Demethylating agents are a category 1 recommendation**

De-methylating Agents in MDS

- **5-Azacytadine and Decitabine are Standard of Care in higher risk MDS**
  - Improves multi-lineage hematopoiesis
  - Improves quality of life
  - Improves survival

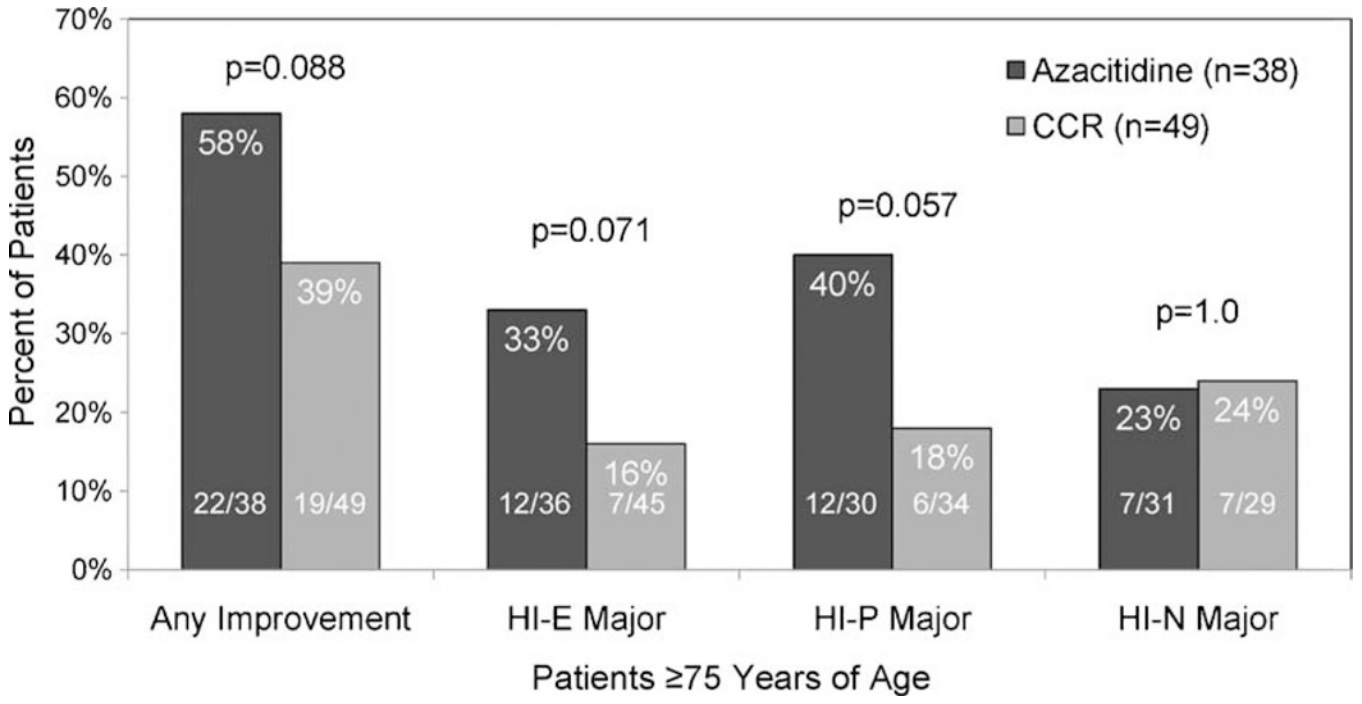


Abbreviations: ara-C, cytarabine; BSC, best supportive care; CMML, chronic myelomonocytic leukaemia; FAB, French-American-British; HI, haematologic improvement; RR, response rate; TI, transfusion independence.

Fenaux P, et al. *Lancet Oncol.* 2009;10:223-232. With permission from Dr. Pierre Fenaux.

5-AZA in MDS patients ≥75 years old

subgroup analysis AZA-001 Trial



Seymour JF et al: Crit Rev Oncol Hematol. 2010; 76: 218

**Unfortunately, despite good hopes,
to date additions to the de-methylating backbone have not resulted in improved outcomes**

National trials (S1117) with HDAC inhibitors and Lenalidomide combinations unsuccessful.

AZA alone or in combination with either lenalidomide or vorinostat (SWOG 1117)

- 276 patients ; median age 70
- IPSS: 28% int-1; 48% int-2; 22% high

- Overall response rates similar between groups
- AZA 36%; AZA+LEN 37%; AZA+VOR 22%
- Relapse free survival similar between groups
- AZA 6 mo; AZA+LEN 8 mo; AZA+VOR 11mo
- Febrile neutropenia rates similar between groups
- AZA 10%; AZA+LEN 10%; AZA+VOR 13%

Venetoclax with decitabine or azacitadine

- Venetoclax is a bcl-2 inhibitor currently approved for CLL
- Combined with DAC or AZA resulting in high responses in AML and higher risk MDS
- Recent study of 145 patients (median age 74)
- 67% complete responses
- Median survival 17.5 months

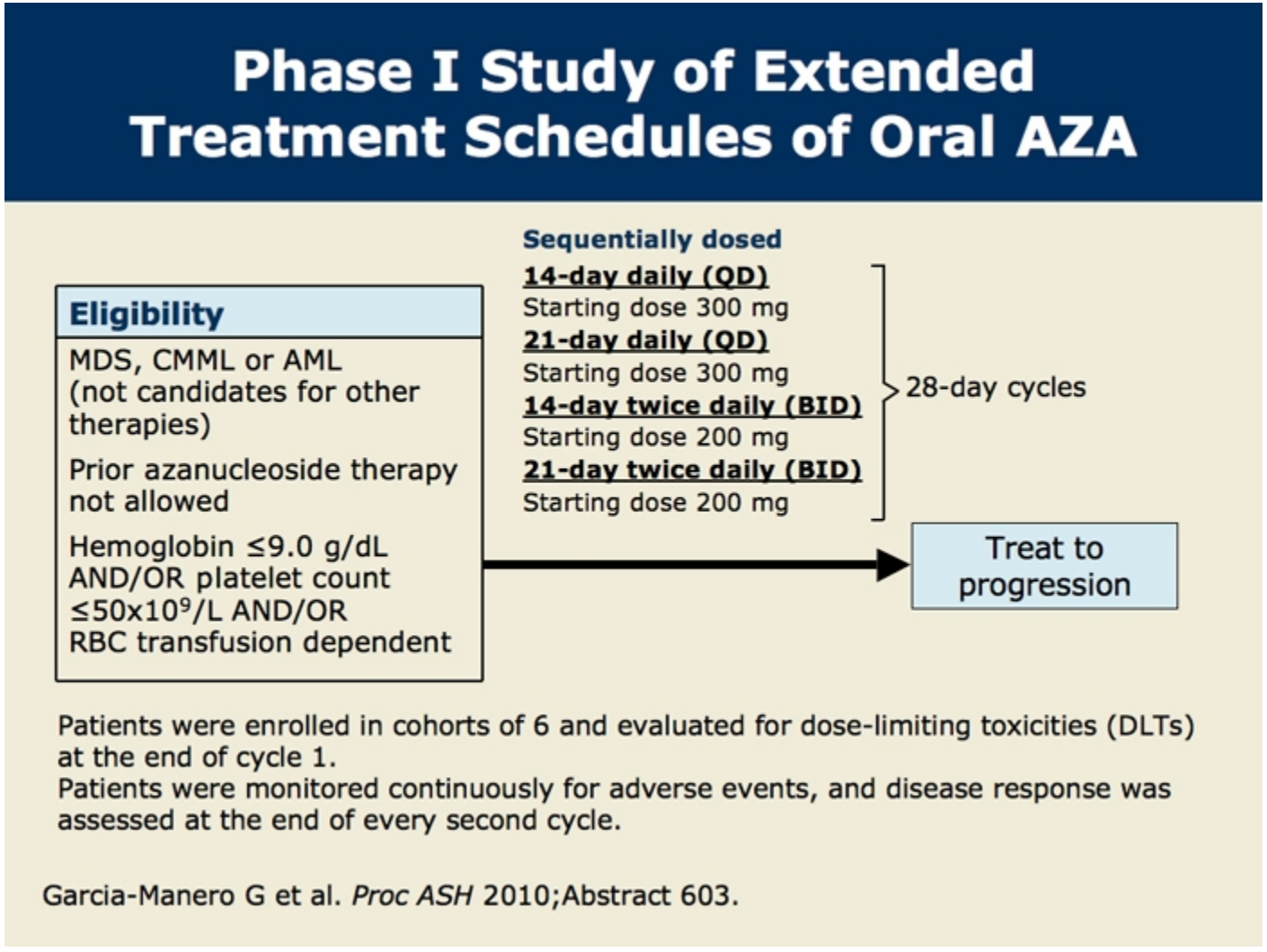
DiNardo CD, ASCO 2018

Can we make azacytadine or decitabine work better?

- Oral formulation
- Longer acting formulations
- Agents that make inhibit destruction

New

MDS-006 trial with oral form of AZA is ongoing



New

SGI-110 (Guadecitabine)
A long acting derivative of decitabine

- 110 patients with Int/High risk MDS: 53 Rel/Ref; 49 untreated
- Subcutaneous injection 5 days per month:

• 60 mg/m2	90 mg/m2
• CR+mCR 10/53 (19%)	CR+mCR 11/49 (22%)

National randomized trial is accruing for high risk patients

- Relapse/refractory 21% CR+mCR
- Treatment naïve 14% CR+mCR
- Transfusion independence 32% RBCs and 24% platelets

ASTX727:
a combination of oral decitabine with an agent that prevents decitabine breakdown

New

Abstract # 4274

A Phase 2 Dose-Confirmation Study of Oral ASTX727, a Combination of Oral Decitabine with a Cytidine Deaminase Inhibitor (CDAi) Cedazuridine (E7727), in Subjects with Myelodysplastic Syndromes (MDS)

Guillermo Garcia-Manero[1], Elizabeth A. Griffiths[2], Gail J. Roboz[3], Lambert Busque[4], Richard Wells[5], Olatoyosi Odenike[6], David P. Steensma[7], Karen W.L. Yee[8], Stefan Faderl[9], Philip Amrein[10], Laura C. Michaelis[11], Hagop Kantarjian[1], Aram Oganesian[12], James N. Lowder[12], Mohammad Azab[12], Michael R. Savona[13]

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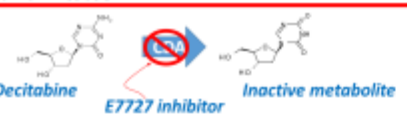
INTRODUCTION

An oral hypomethylating agent which could be administered at a dose which would emulate parenteral pharmacokinetics would be more convenient and potentially enhance adherence to treatment. Heretofore, rapid clearance by cytidine deaminase (CDA) during first pass has prevented good oral bioavailability for decitabine (DAC).[1] Cedazuridine (E7727), a novel CDAi, is orally bioavailable with a large safety margin and reproducible effectiveness in preclinical models.[2] A phase I dose finding study found that a fixed oral combination of 35 mg of decitabine and 100 mg of E7727 (ASTX727 with 35 mg decitabine/100 mg cedazuridine (ASTX727 35/100 mg) should produce similar PK to decitabine administered intravenously at 20 mg/m² as a 1-hour infusion.[3] We tested this hypothesis in a phase 2 cross-over study, and report the preliminary results here.

Figure 1. Cedazuridine Blocks First Pass Metabolism of Decitabine Permitting Oral Administration



STUDY DESIGN

Figure 2. Study Schema

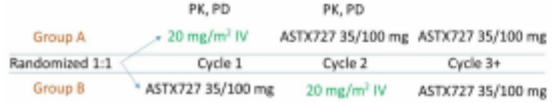


Table 1: Patient Demographics

	Group A [N=25]	Group B [N=25]	Total [N=50]
Age (y)			
Median (Range)	69 (32-87)	72 (41-86)	71.5 (32-87)
Gender			
Male	20 (80%)	21 (84%)	41 (82%)
Female	5 (20%)	4 (16%)	9 (18%)
Weight (kg)			
Median (Range)	81.8 (40-122)	87.3 (55-118)	84.75 (40-122)
BSA (m²)			
Median (Range)	2.0 (1.3-2.4)	2.1 (1.6-2.4)	2.0 (1.3-2.4)
ECOG			
0	13 (52%)	9 (36%)	22 (44%)
1	9 (36%)	15 (60%)	24 (48%)
2	3 (12%)	1 (4%)	4 (8%)
Prior HMA			
No	23 (92%)	24 (96%)	47 (94%)
IPSS Class			
Int-1	10 (40%)	10 (40%)	20 (40%)
Int-2	6 (24%)	7 (28%)	13 (26%)
High Risk	4 (16%)	4 (16%)	8 (16%)
CMML	5 (20%)	4 (16%)	9 (18%)

RESULTS

Figure 3. Pharmacokinetics of Decitabine

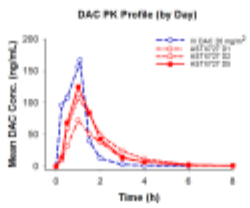


Figure 4. Decitabine individual AUC by Day

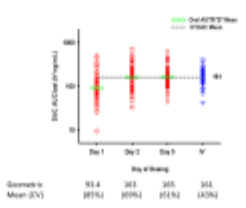


Table 2: AUC Equivalence Analysis Based on 5-day AUC Estimates

Treatment [N=43]	Adjusted Geometric Means of 5-Day AUC (ng*h/mL)	Ratio (80% CI)
ASTX727 35/100 mg	769.2	0.955 (0.80-1.13)
DAC 20 mg/m² one hour IV infusion	805.1	

Table 3: Cycles Administered

N=50	Median	Range
Cycles of Therapy	6.5	1-20

Figure 5. Cedazuridine Pharmacokinetics over 5 Days of Treatment

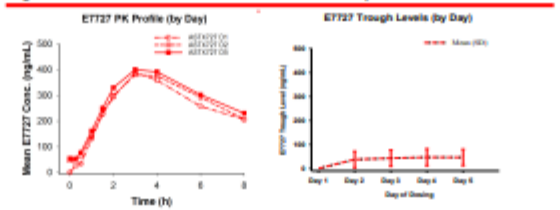
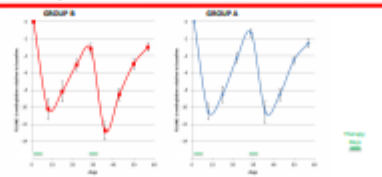


Figure 6: LINE-1 Demethylation Similar between IV-DAC and ASTX727



Maximum LINE-1 Demethylation Analysis (N=46)

SAFETY

Table 4: All Adverse Events Occurring in ≥25% of Subjects During Study

	Number (%) of Subjects [N=50 Treated]									
	IV Decitabine Cycle 1 or 2 [N=48]				Oral ASTX727 Cycle 1 or 2 [N=49]				Entire Study (n=50)	
	All Grades		≥Grade 3		All Grades		≥Grade 3		All Grades	≥Grade
Any event	46	(96)	30	(63)	45	(92)	29	(59)	50 (100)	46 (92)
Neutropenia	18	(38)	15	(31)	11	(22)	10	(20)	27 (54)	25 (50)
Thrombocytopenia	14	(29)	12	(25)	12	(25)	7	(14)	27 (54)	21 (42)
Fatigue	7	(15)	0	0	11	(22)	2	(4)	21 (42)	3 (6)
Febrile neutropenia	9	(19)	9	(19)	6	(12)	6	(12)	19 (38)	19 (38)
Diarrhoea	6	(13)	0	0	5	(10)	0	0	18 (36)	2 (4)
Constipation	6	(13)	0	0	8	(16)	0	0	16 (32)	0 0
Anemia	5	(10)	4	(8)	6	(12)	5	(10)	14 (28)	13 (26)
Nausea	5	(10)	0	0	5	(10)	0	0	14 (28)	1 (2)
Dyspnoea	1	(2)	1	(2)	7	(14)	3	(6)	13 (26)	5 (10)

CLINICAL RESULTS

Table 5: Clinical Response Data[a]

	Best Response Rate, N (%
Clinical Response	Total [N=50]
Complete Response (CR)	8 (16)
Marrow Complete Response (mCR)	14 (28)
Hematologic Improvement	9 (18)
No Response	19 (38)
RBC Transfusion Dependence at Baseline, N	22
RBC Transfusion Independence[b]	10 (45)

[a]Responses based on IWG.
[b]Proportion based on patients transfusion dependent at baseline.

CONCLUSIONS

- ASTX727 successfully emulates the AUC exposures and LINE-1 PD of 20 mg/m² IV decitabine in a 5 consecutive day regimen with a 5-day AUC ratio of 0.955.
- The 6-hour $T_{1/2}$ of cedazuridine produces steady state by Day 2 and subsequent trough levels of drug which facilitates consistent decitabine oral bioavailability on Days 2 to 5 of the cycle.
- Clinical response and safety data appear similar to that reported for 20 mg/m² IV

REFERENCES

1. Lowder JN et al. Epigenomics 7:1083-1088, 2015.
2. Oganesian A et al. Blood 122:2526 (abstract), 2013
3. Garcia-Manero G et al. ASH 114 (abstract), 2016

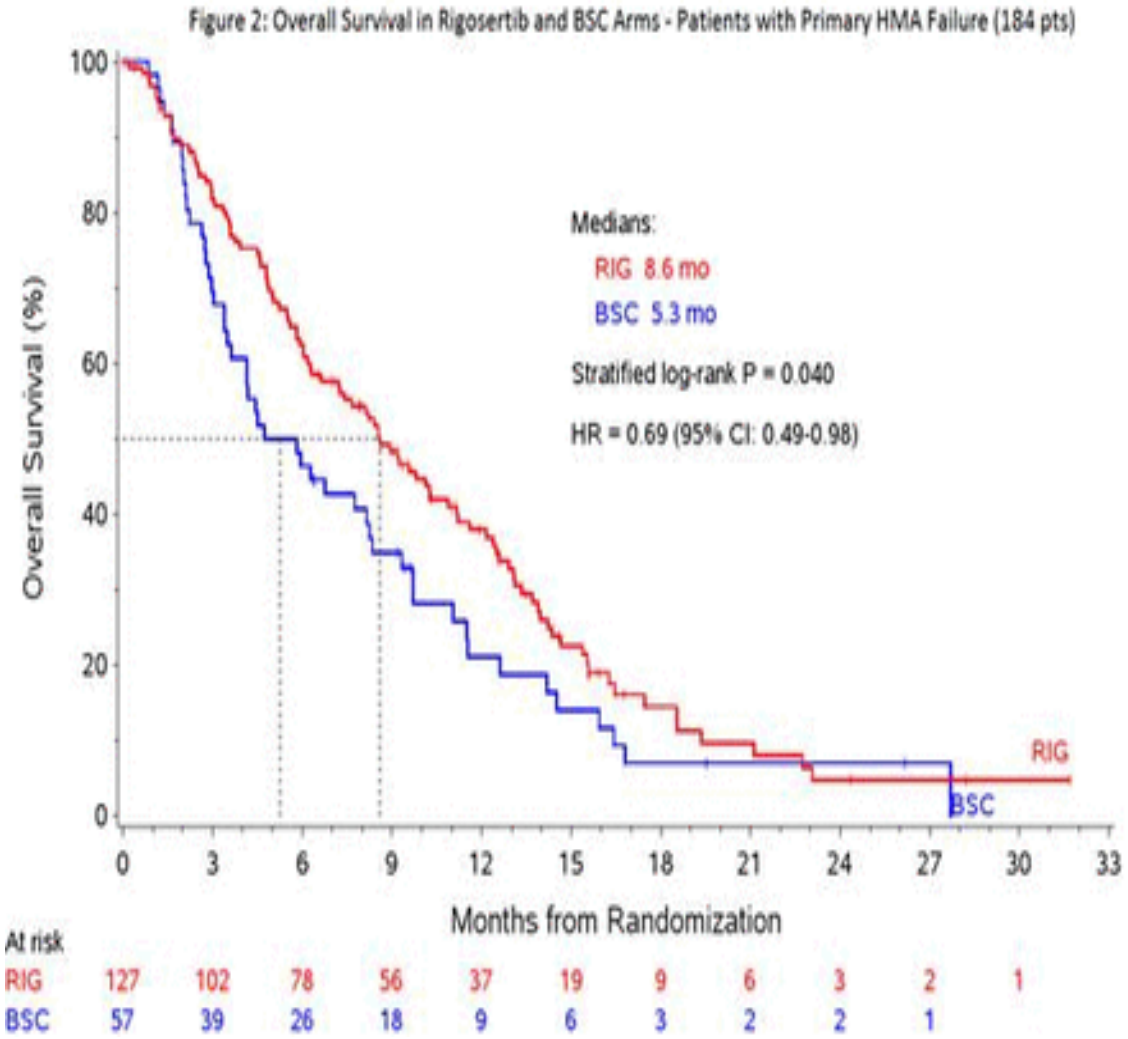
Randomized Phase III Study of Intravenous Rigosertib Versus Best Supportive Care in Higher-Risk MDS after Failure of Hypomethylating Agents

Rigosertib, a novel small molecule inhibitor of PI3-kinase and PLK pathways

Randomized investigator choice therapy in patients who had relapsed after, failed to respond to, or progressed during administration of HMA

Garcia-Manero ASH abstract 163

- 2.3-mo improvement in median OS was found in the overall (ITT) population (8.2 mo rigosertib vs. 5.9 mo BSC)
- Among the 184 patients with primary HMA failure, the median OS was 8.6 mo in the rigosertib arm (N = 127) vs. 5.3 mo in the BSC arm (N = 57), HR= 0.69, p= 0.040
- Primary endpoint for entire study not met
- Encouraging results in subgroup with primary failure to respond to HMAs and IPSS-R very high subgroups



Other hopeful new agents

- Imetelstat, a telomerase inhibitor
- Pevonedistat, an NAE inhibitor
- Selinexor, an XPO1 inhibitor
- Glasdegib, a smoothened (SMO) inhibitor

What about immunotherapy?

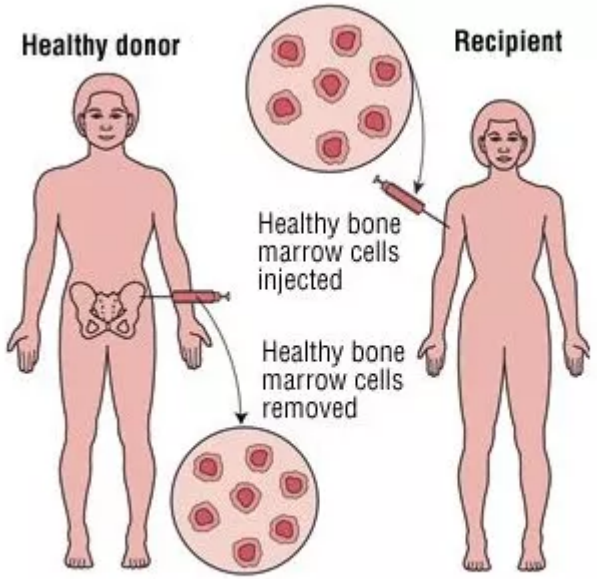
- Thus far single agent studies with immunotherapy agents have been disappointing, but …..
- Studies in combinations ongoing
- Studies following BMT ongoing

Hematopoeitic Stem Cell Transplantation

- An aggressive, but potentially curative approach
- **Age of the patient and Availability of a Donor are the major determinants of whether a BMT is performed early**

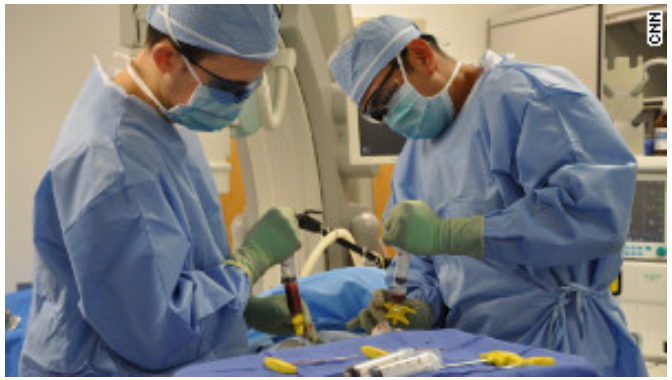
- Goal is to “Replace”

the defective bone marrow



Steps to a transplant

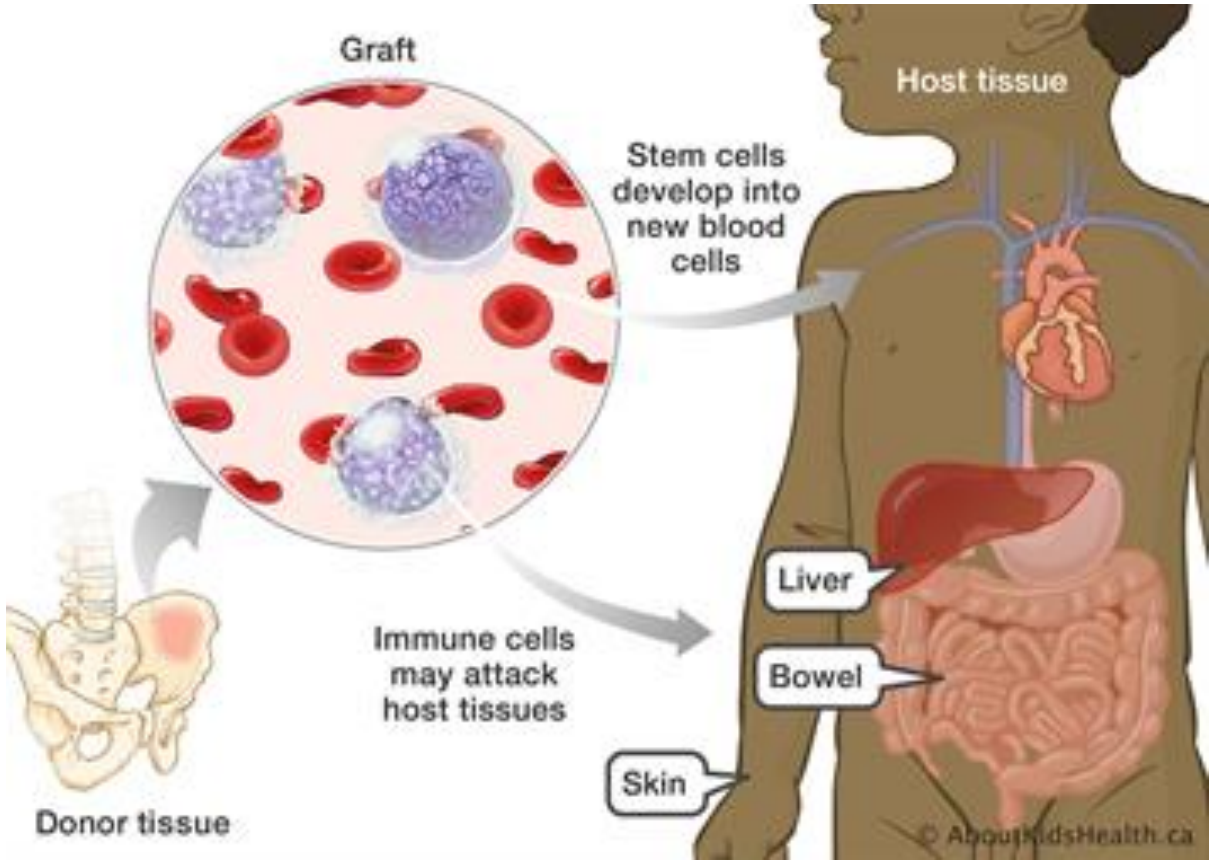
- **Find a donor**
  - **HLA typing matches white cell antigens important for rejection**
  - **Siblings match 1 in 4 times**
  - **Children and non-matched siblings may be used “haploidentical” by changing order of chemotherapy**
  - **Unrelated donors can match, but higher complications**



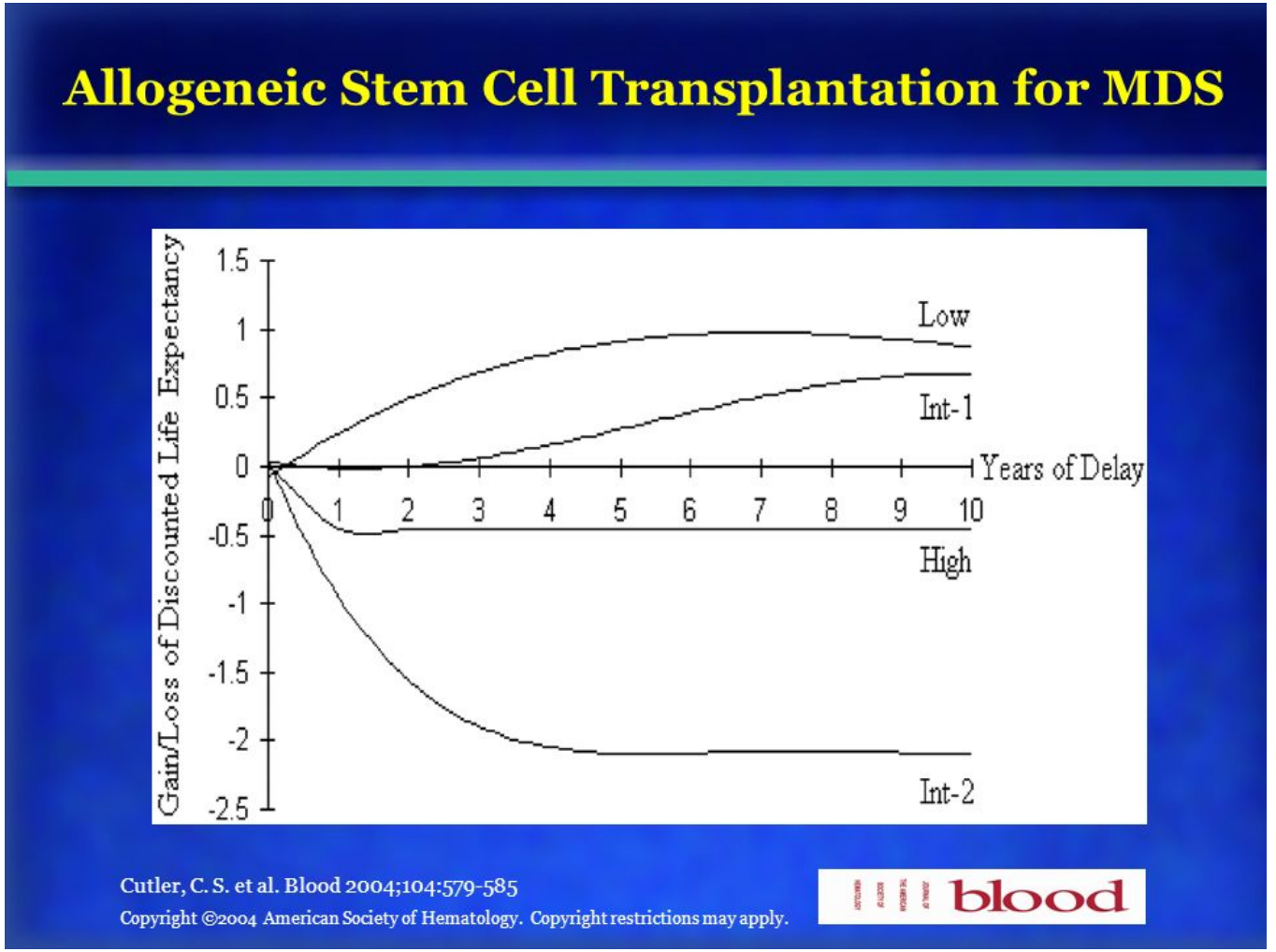
Steps of a transplant

- One month hospitalization
- Conditioning chemotherapy (several days)
  - Goal of chemotherapy is to prepare body to accept foreign graft and to kill off the damaged MDS marrow
  - Better results if leukemia blasts are lower (but delaying treatment to reduce blasts remains controversial)
- Infuse the cells
- Support during time of low blood counts
- Recover counts
- Watch for immune rejection (donor against patient and vice versa)

Graft-vs-Host Disease and MDS Relapse are the main reasons transplants do not work

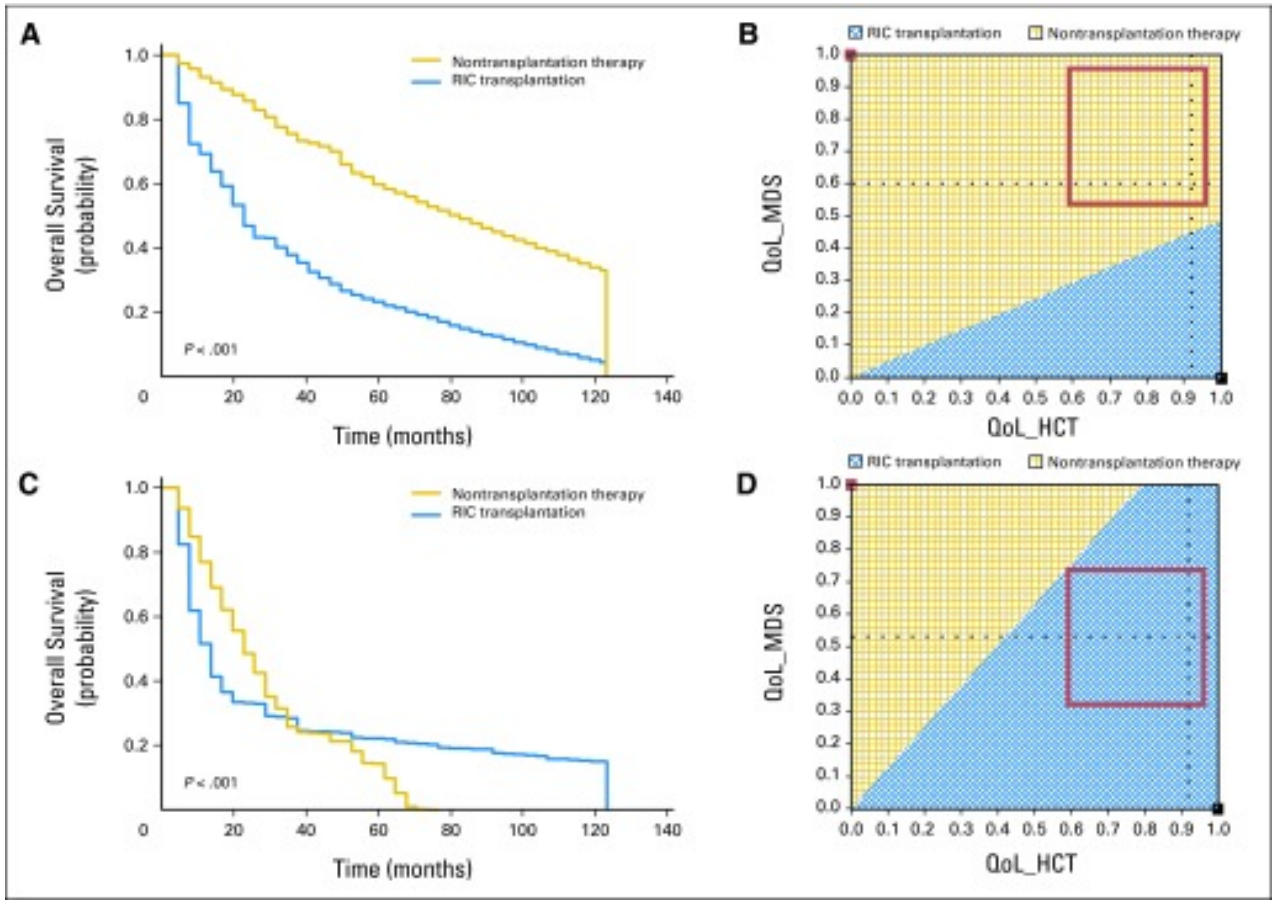


Defining the optimal timing for transplantation



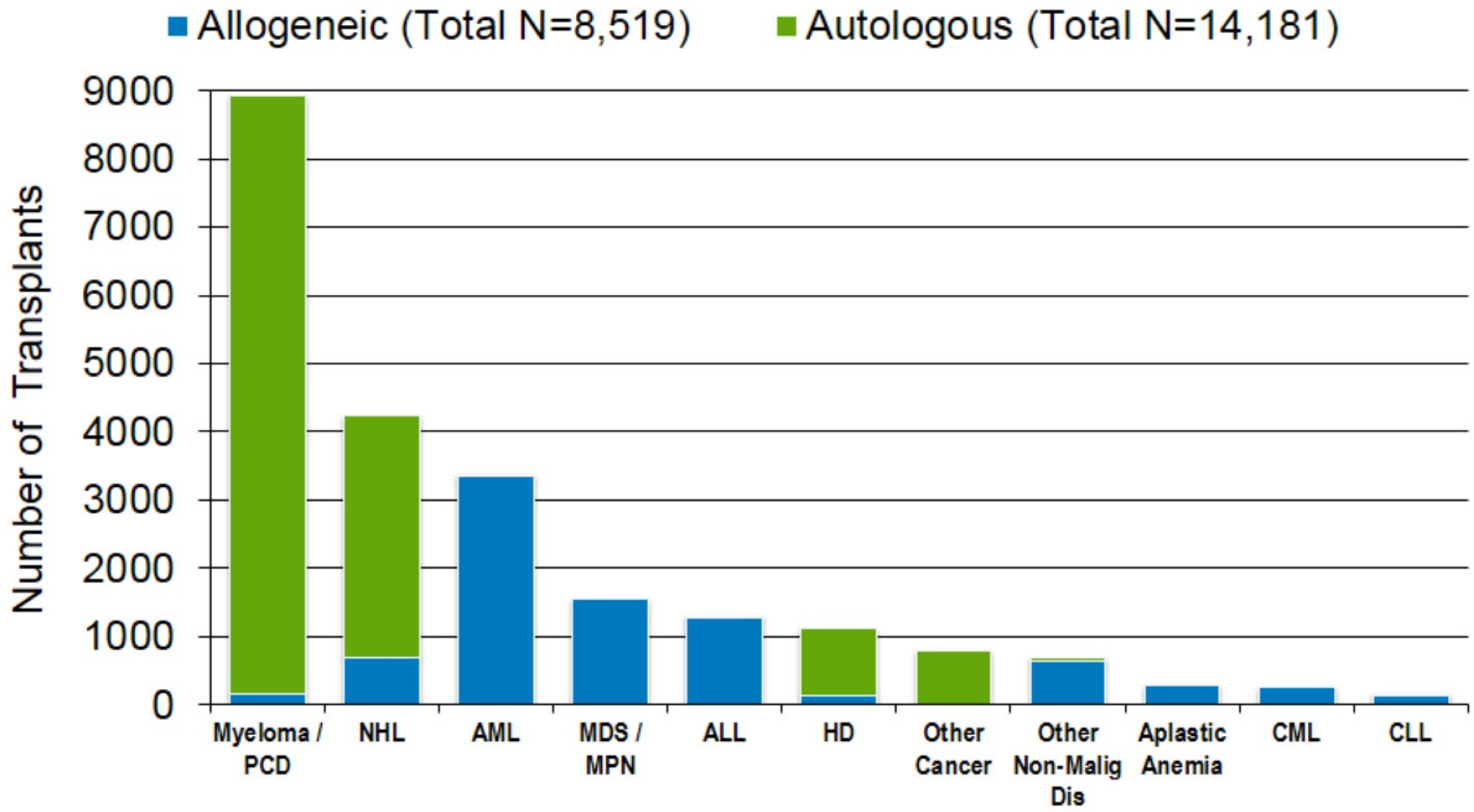
Defining the Optimal Timing for reduced intensity transplantation

Among patients 60-70 years of age, evidence suggests survival may be improved by RIC HSCT for int-2/high IPSS patients (36 versus 28 mo) but not for low/int-1 IPSS patients (38 versus 77 mo)



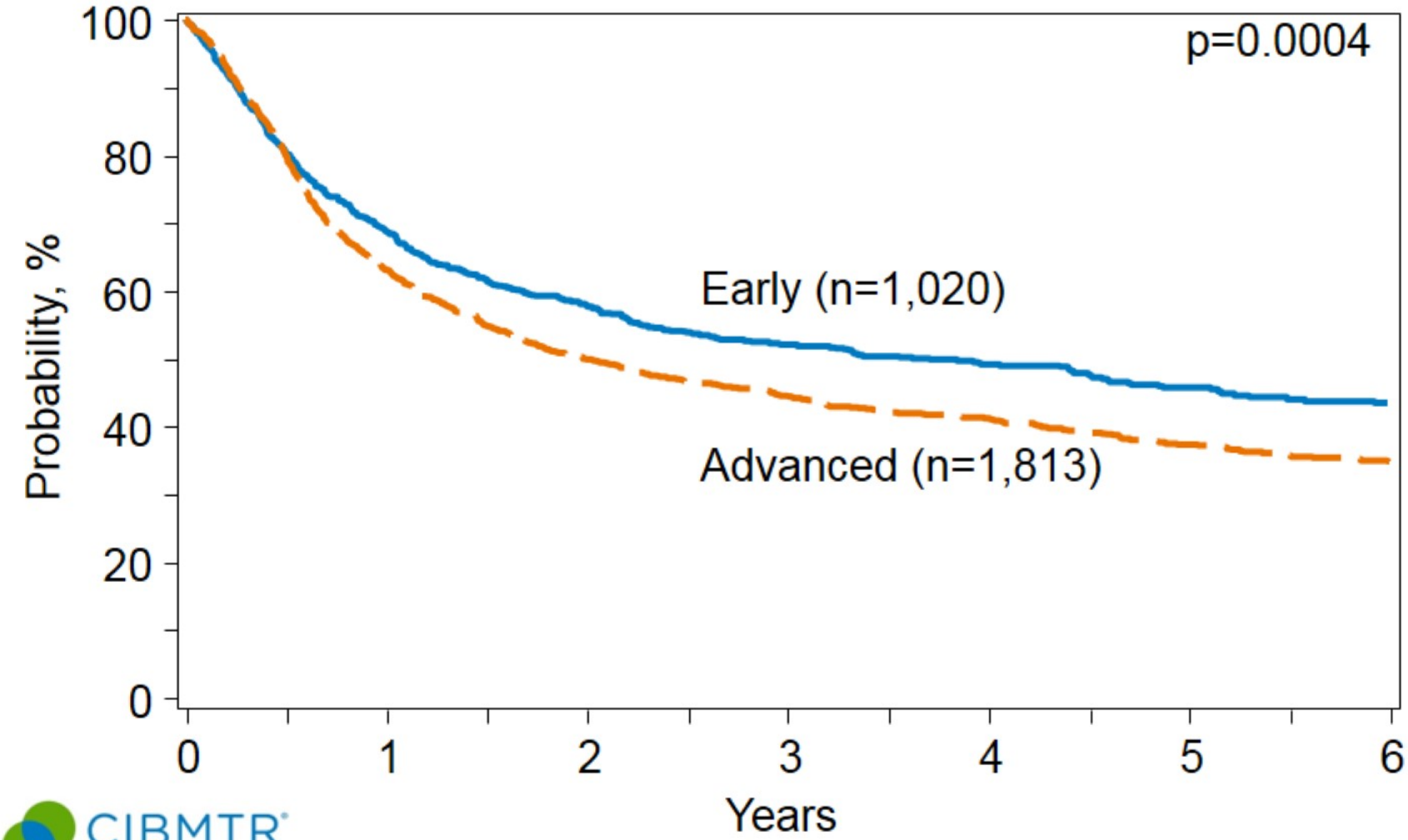
Koreth J et al: J Clin Oncol. 2013; 20; 31: 2662

Indications for Hematopoietic Cell Transplant in the US, 2016



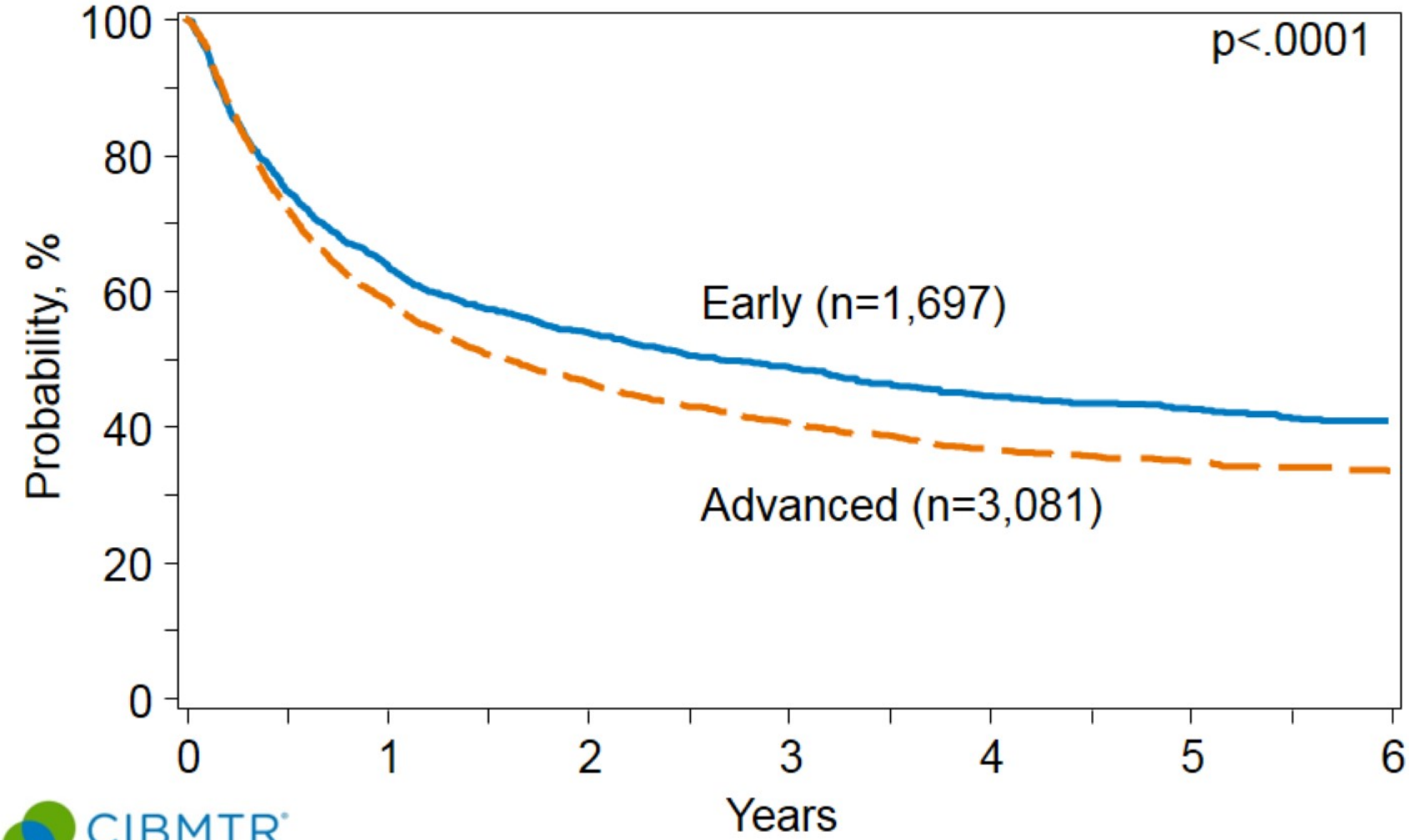
CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Survival after HLA-Matched Sibling HCT for Myelodysplastic Syndrome (MDS), 2005-2015



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Survival after Unrelated Donor HCT for Myelodysplastic Syndrome (MDS), 2005-2015



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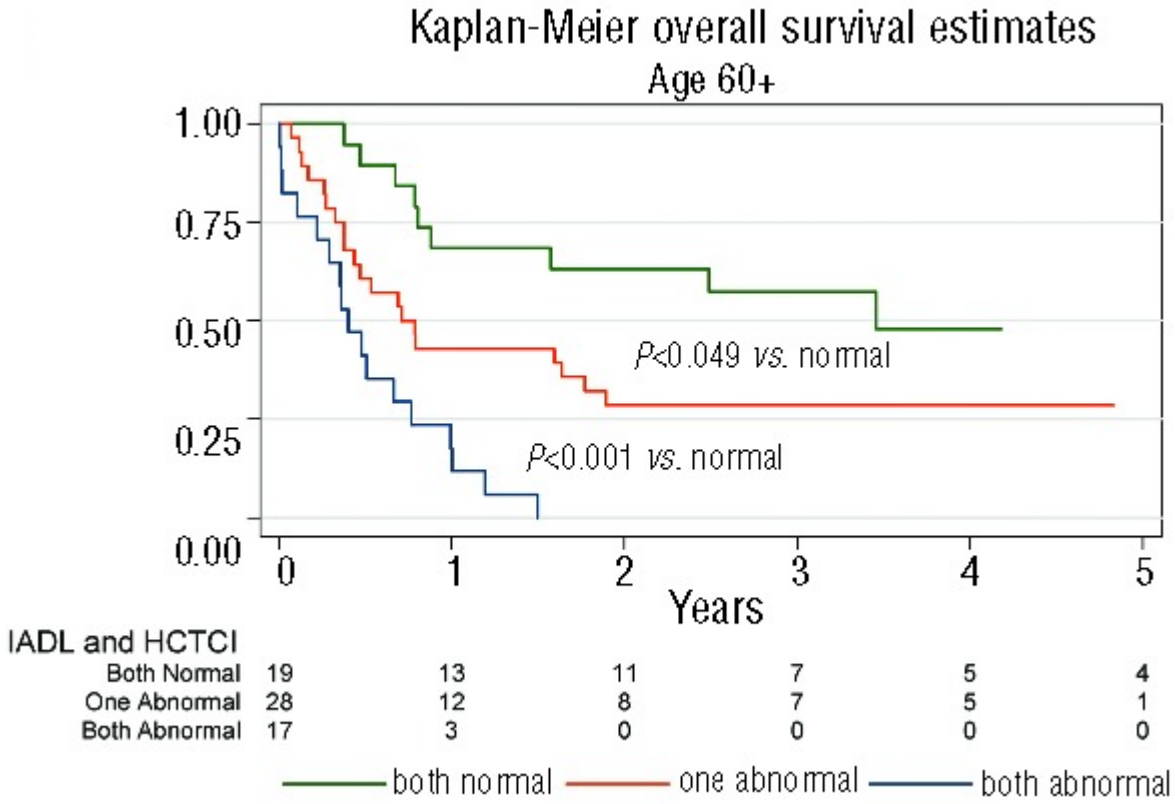
Allogeneic Transplantation in Elderly MDS

- **Represents only curative approach**
- **Contains significant risks of morbidity and mortality**
- **Even among selected patients:**
  - **1/3 cured**
  - **1/3 die of complications**
  - **1/3 die of relapse**

Kröger N. Blood 2012 119:563
Atallah E et al: Curr Hematol Malig Rep. 2014; 9: 57

Geriatric assessment to predict survival in older allogeneic HSCT recipients



Muffly LS. Haematologica 2014; 99:1373

What can you do to help yourself (or your loved one)?

- **TALK to YOUR MEDICAL TEAM**
  - Tell us how you feel
  - Tell us what you want out of the treatment
  - Tell us what support you need including finances and transportation
  - Ask us if your treatment is working
  - Ask us about what new things are coming

- Know your MDS subtype and Risk score (IPSS)
- Participate in your care – its your life and you get to make the call

Thank you.
Questions?