Myelodysplastic Syndrome

A Family-Oriented Approach on Diagnosis and Treatment Options

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MDS Patient & Family/Caregiver Forum
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mds foundation
the myelodysplastic syndromes foundation, inc.

University of New Mexico Comprehensive Cancer Center


F-GJJE
105

Quote of the Day

"There are two primary choices in life: to accept conditions as they exist, or accept the responsibility of changing them"

- Dennis Waitley

Overview

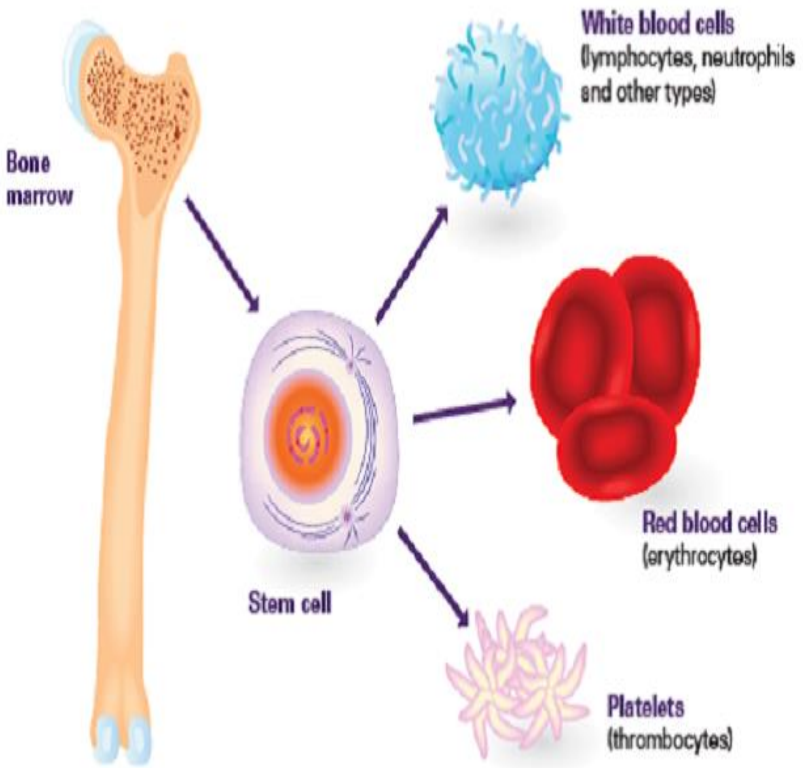
- Introduction to MDS
- Pathophysiology
- Diagnosis and Risk Stratification
- Treatment Options
- Future Directions/Challenges

What is MDS? (~~What Dr. Google says?~~)

- MDS are a group of blood cancers in which the bone marrow does not produce healthy blood cells.

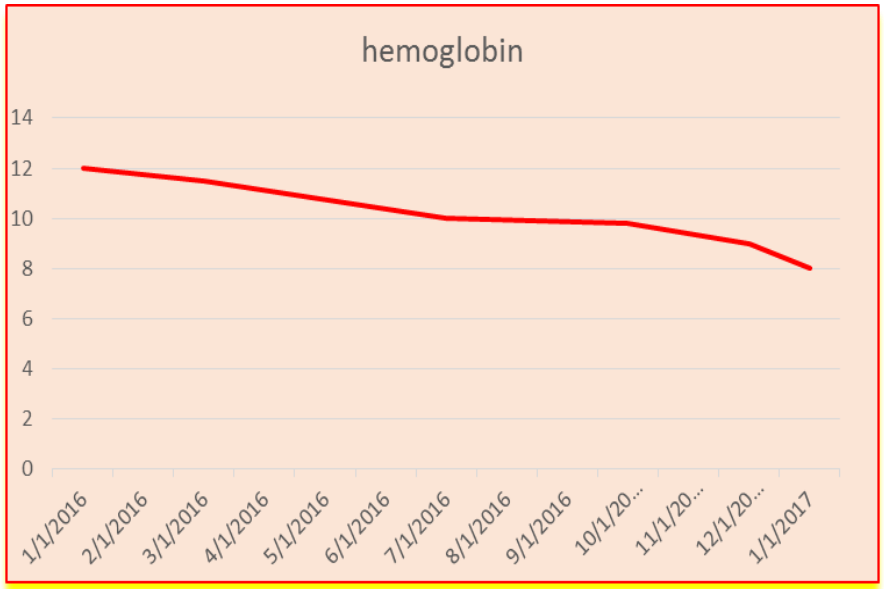
- Is considered a “bone marrow failure disorder”.

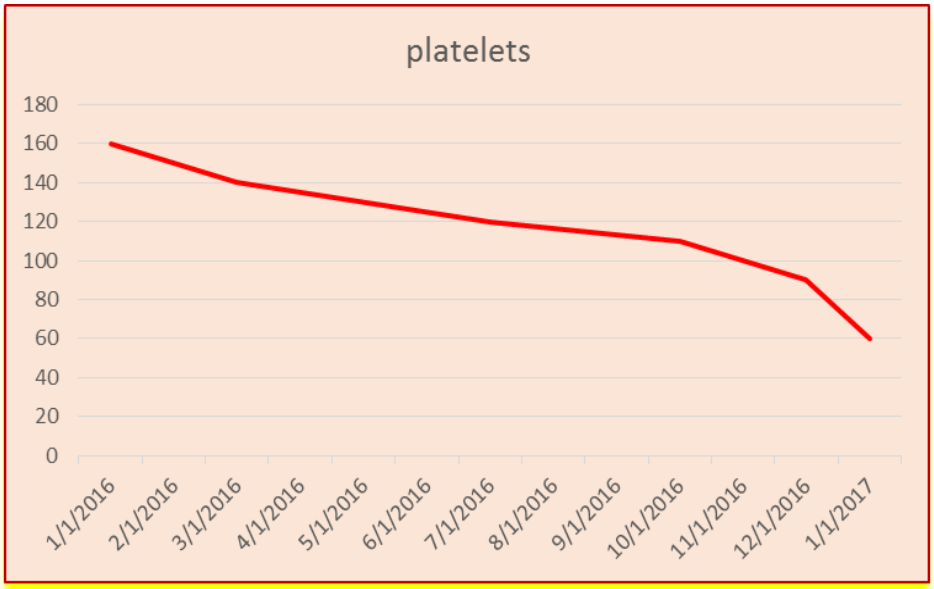
- Risk of transformation to acute leukemia.



MDS Case : Low blood counts

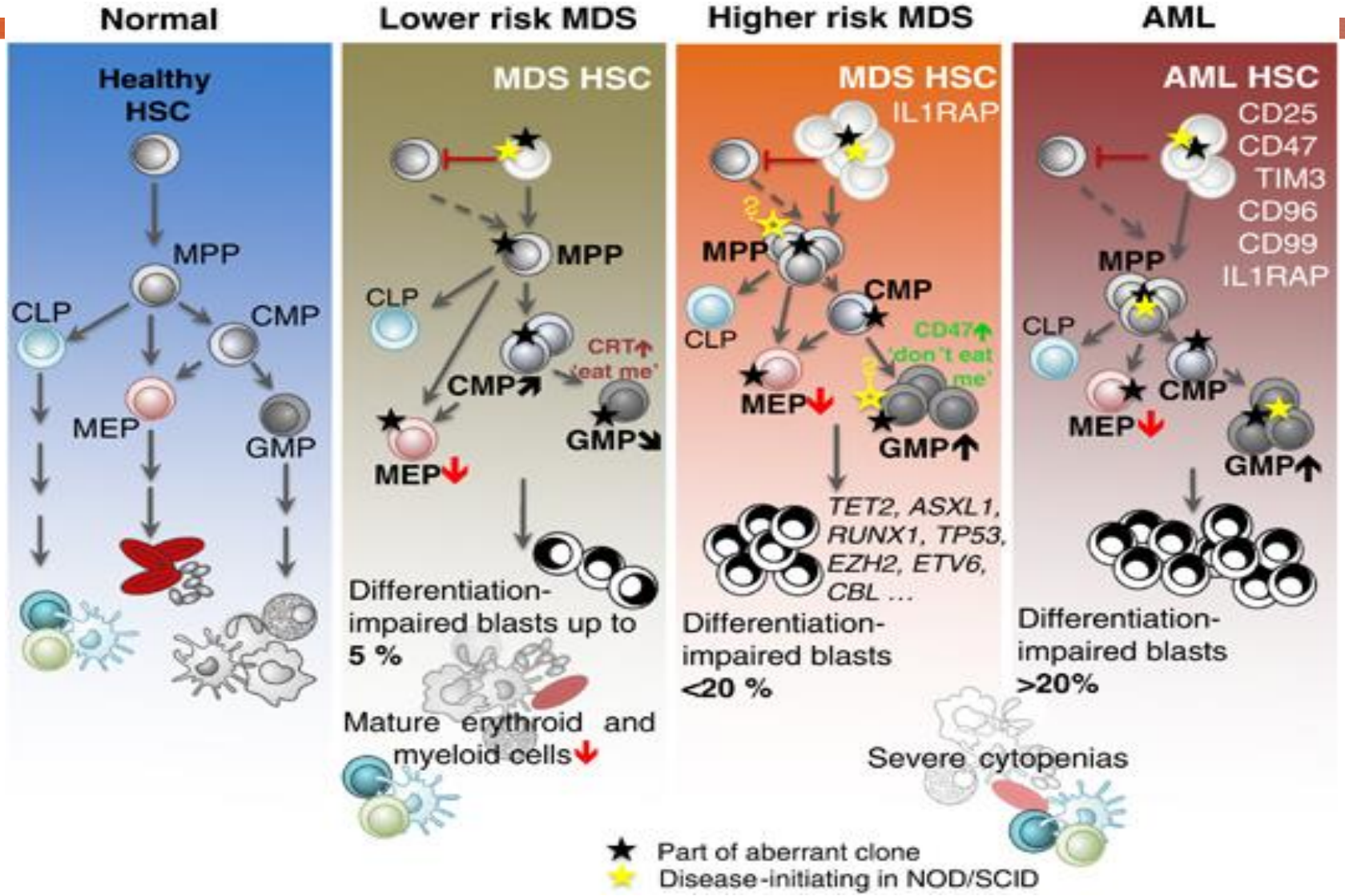
- Mr. T is a 70 year-old male with worsening anemia and thrombocytopenia over the past 2 years.





- Patient words: “I am exhausted”; “I feel dizzy”; “I have bruises in my arms”

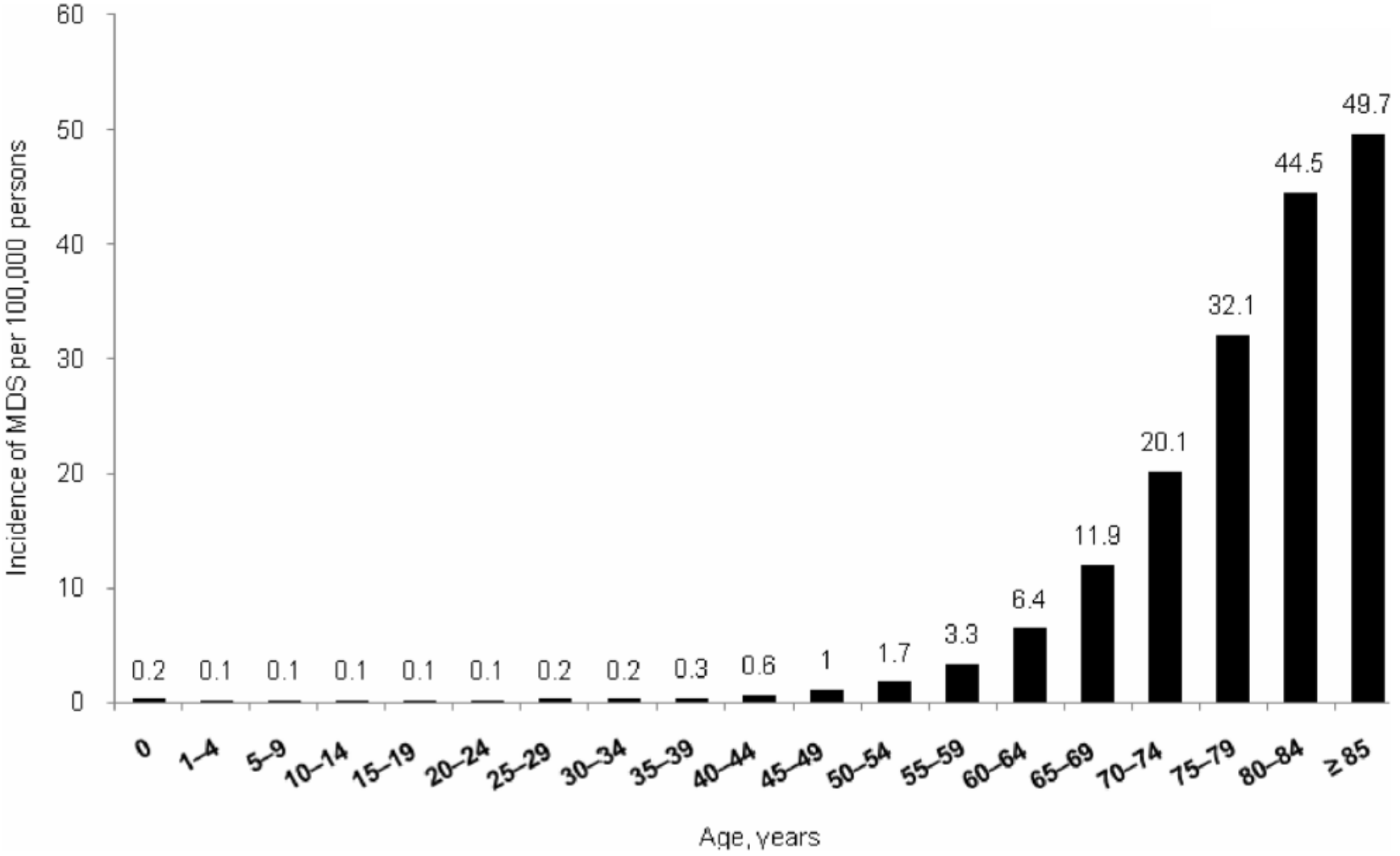
Aberrant hematopoiesis



Elias HK, et al Oncogene 2013, 1-12

MDS Features

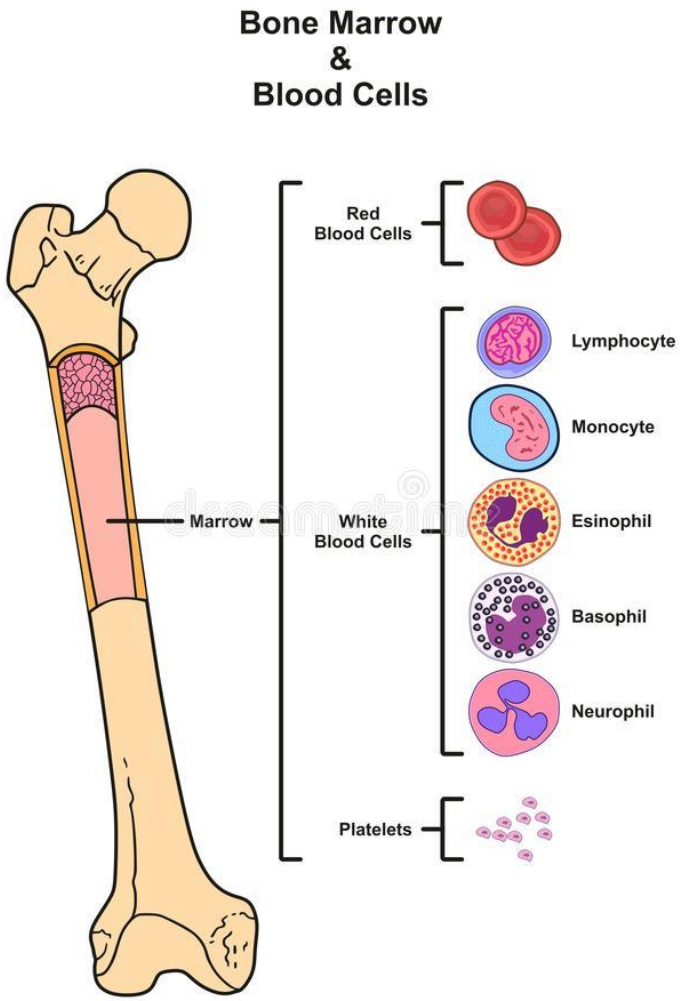
- Estimated 15,351 new cases from 2009 to 2013.
- Incidence: 4.9 per 100,000.
- Median age 71 M>F
- Clonal disorder: Multi-lineage hematopoietic progenitor.
- Ineffective hematopoiesis with cytopenias
- Symptoms: Fatigue, infection or bleeding

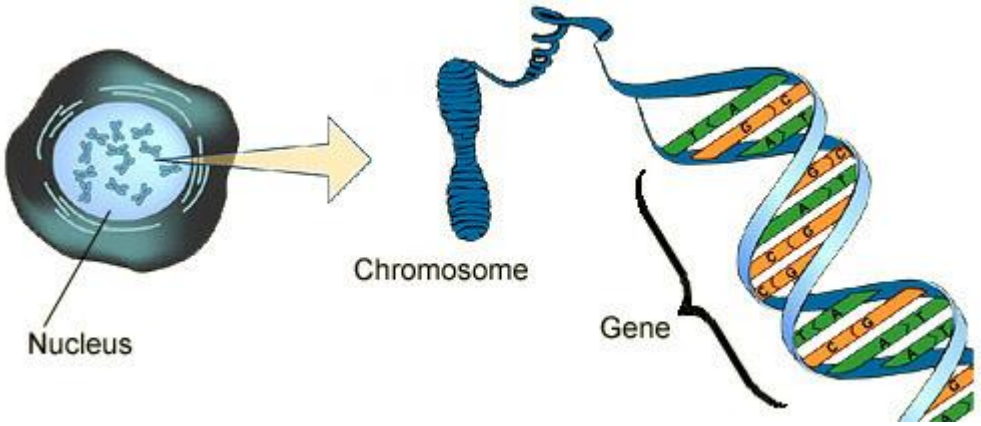


Ma X. Am J Med 2012;125 (7 Suppl):S2-S5

Pathophysiology of MDS

MDS Basic Concepts



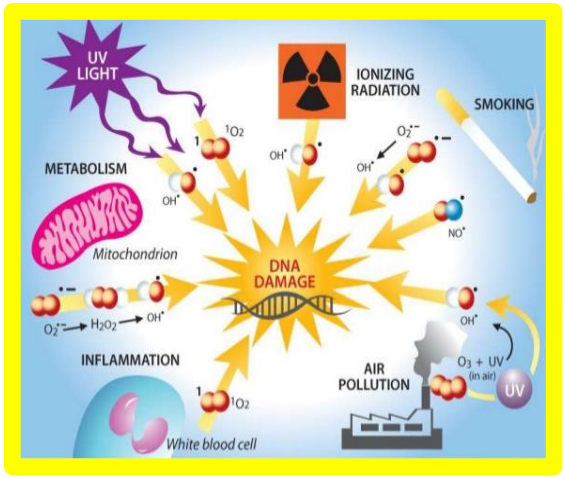


MDS Pathogenesis

- Incompletely understood
- Stepwise acquisition of genetic mutations or after exposure to agents.

De novo (80%)

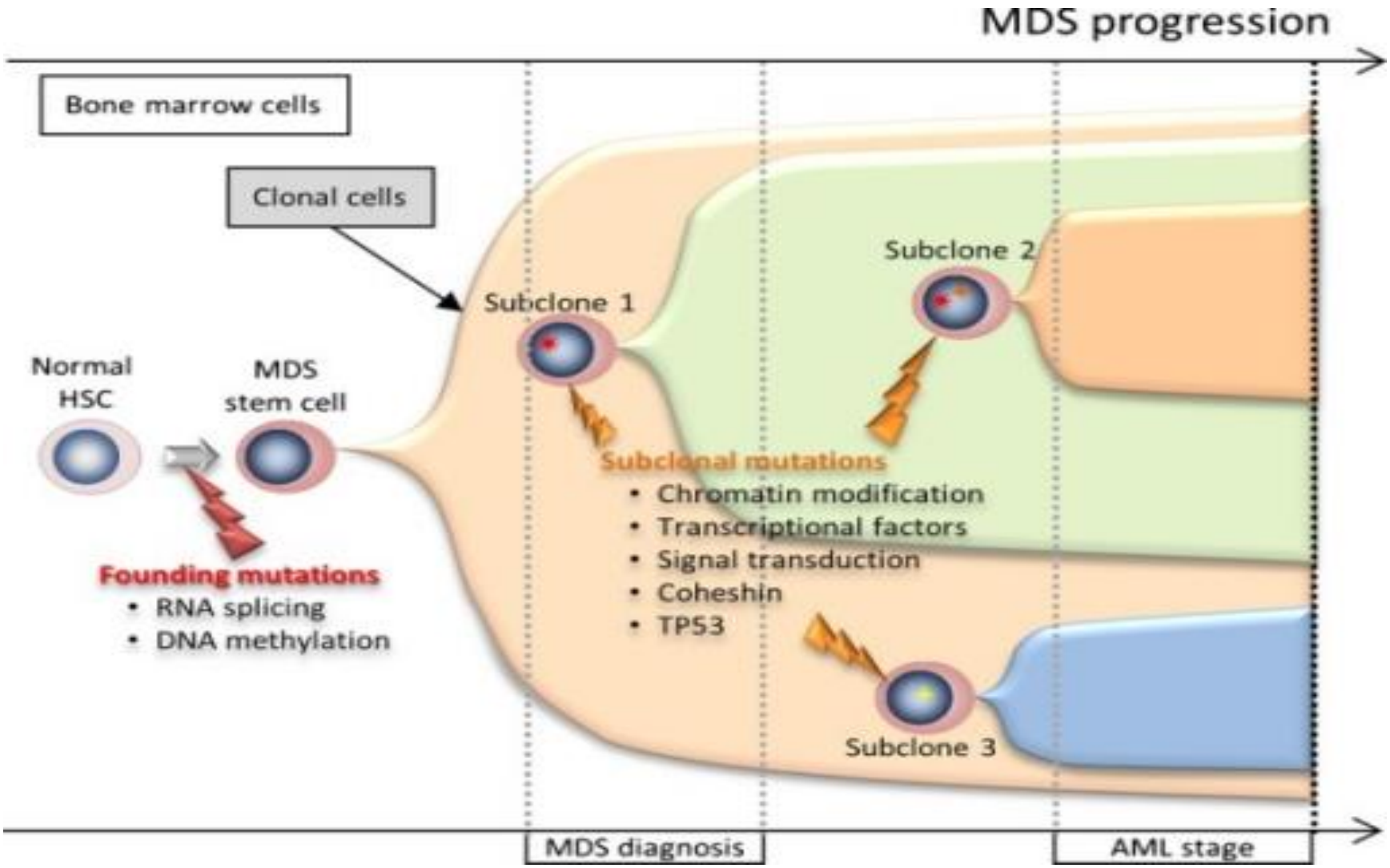
- Primary
- No history of previous cancer/radiation
  Increased risk with aging



Secondary MDS (20%)

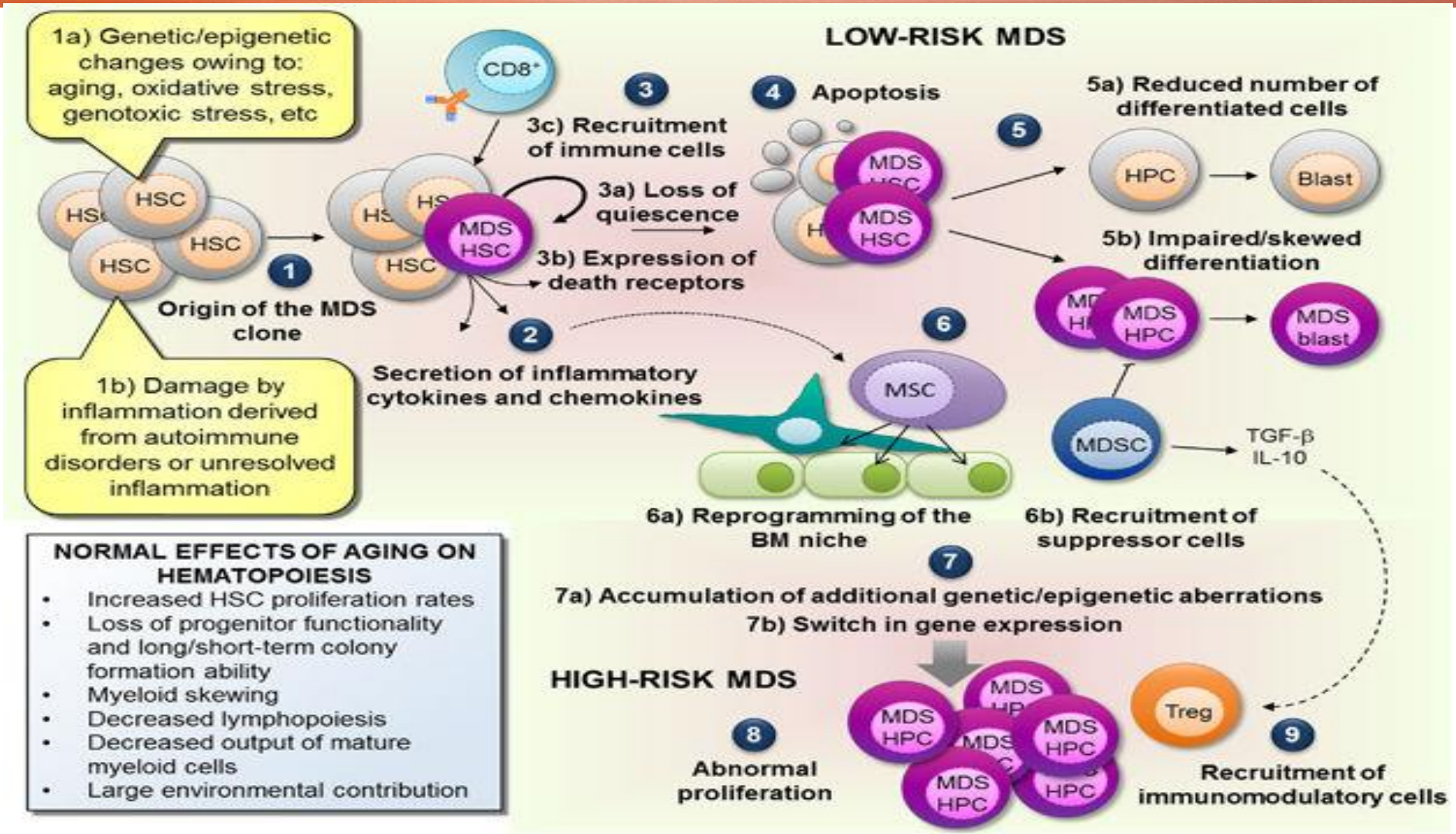
- Previous chemo/radiation
- DNA alkylating agents peaks 5-7 years
- Topoisomerase inhibitors peaks 1-3 years
- Prognosis is usually poor

Molecular Pathogenesis: The Clone Wars



Harada et al Cancer Sci 2015

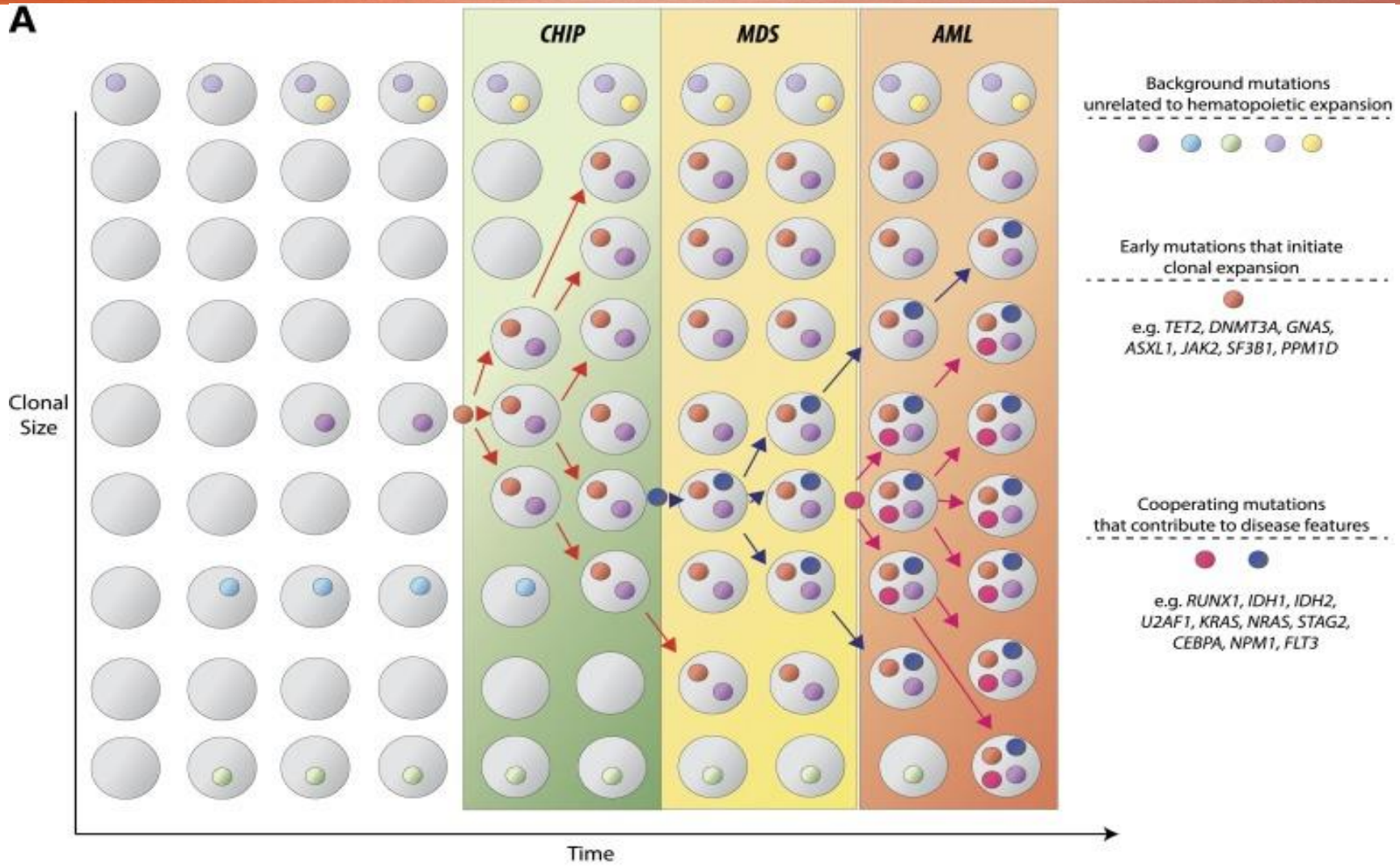
Bone marrow niche, Immune response and MDS



Ganan-Gomez et al Leukemia 2015 29,1458-1469

CHIP: PRECURSOR TO HEME NEOPLASMS

Clonal **H**ematopoiesis of **I**ndetermined **P**otential



Steensma et al. Blood 2015 126(1):9-16

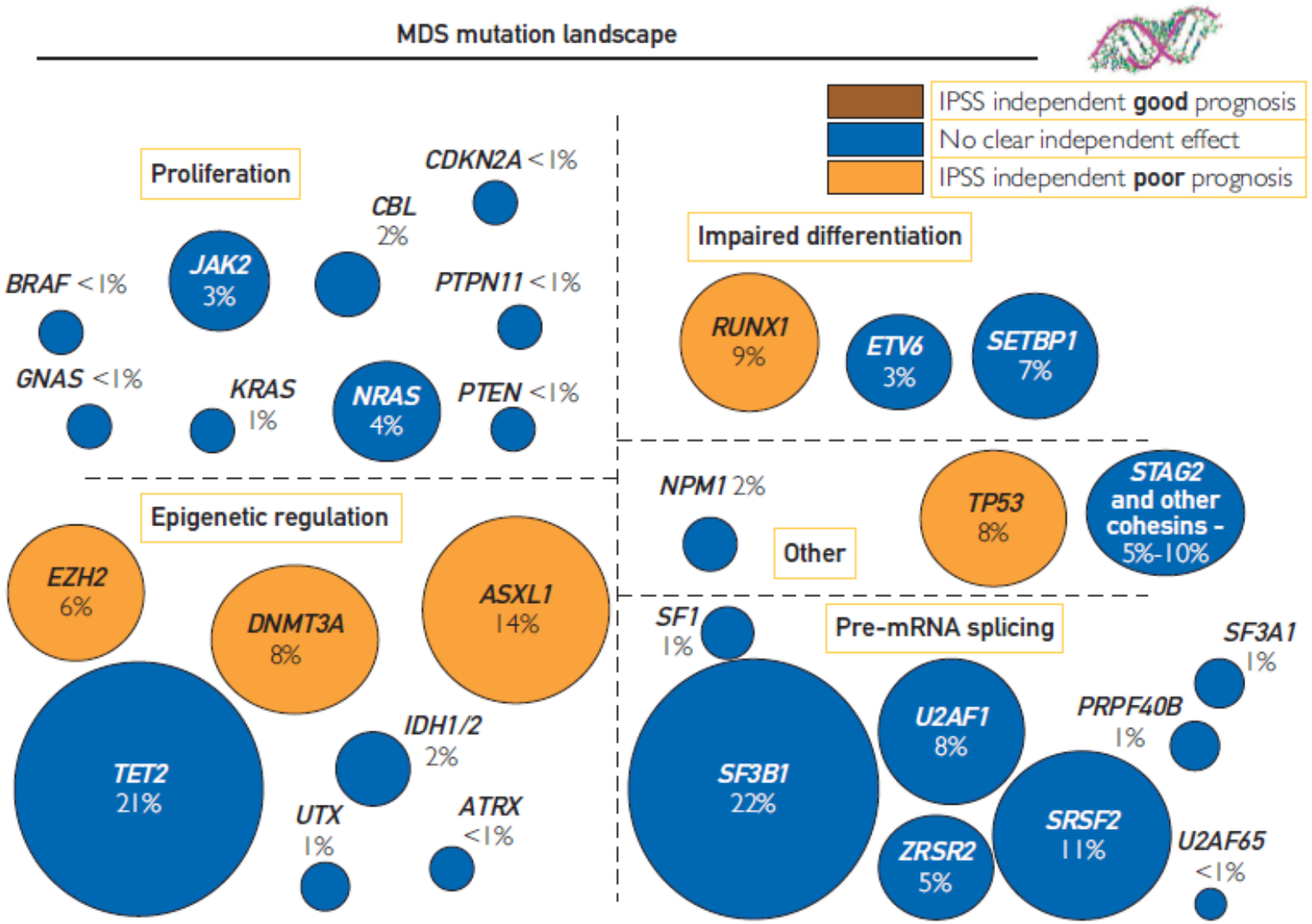
Spectrum of Hematopoietic Disorders

FEATURE	ICUS	IDUS	CHIP	CCUS	MDS
Somatic mutation	-	-	+/-	+/-	+/-
Clonal karyotypic abnormality	-	-	+/-	+/-	+/-
Marrow dysplasia	-	+	-	-	+
Cytopenia	+	-	-	+	+

ICUS: Idiopathic Cytopenia of Unknown Significance
IDUS: Idiopathic Dysplasia of Unknown Significance
CHIP: Clonal Hematopoiesis of Indeterminat Potential
CCUS: Clonal Cytopenia of Unknown Significance

NCCN MDS Version 2.2018

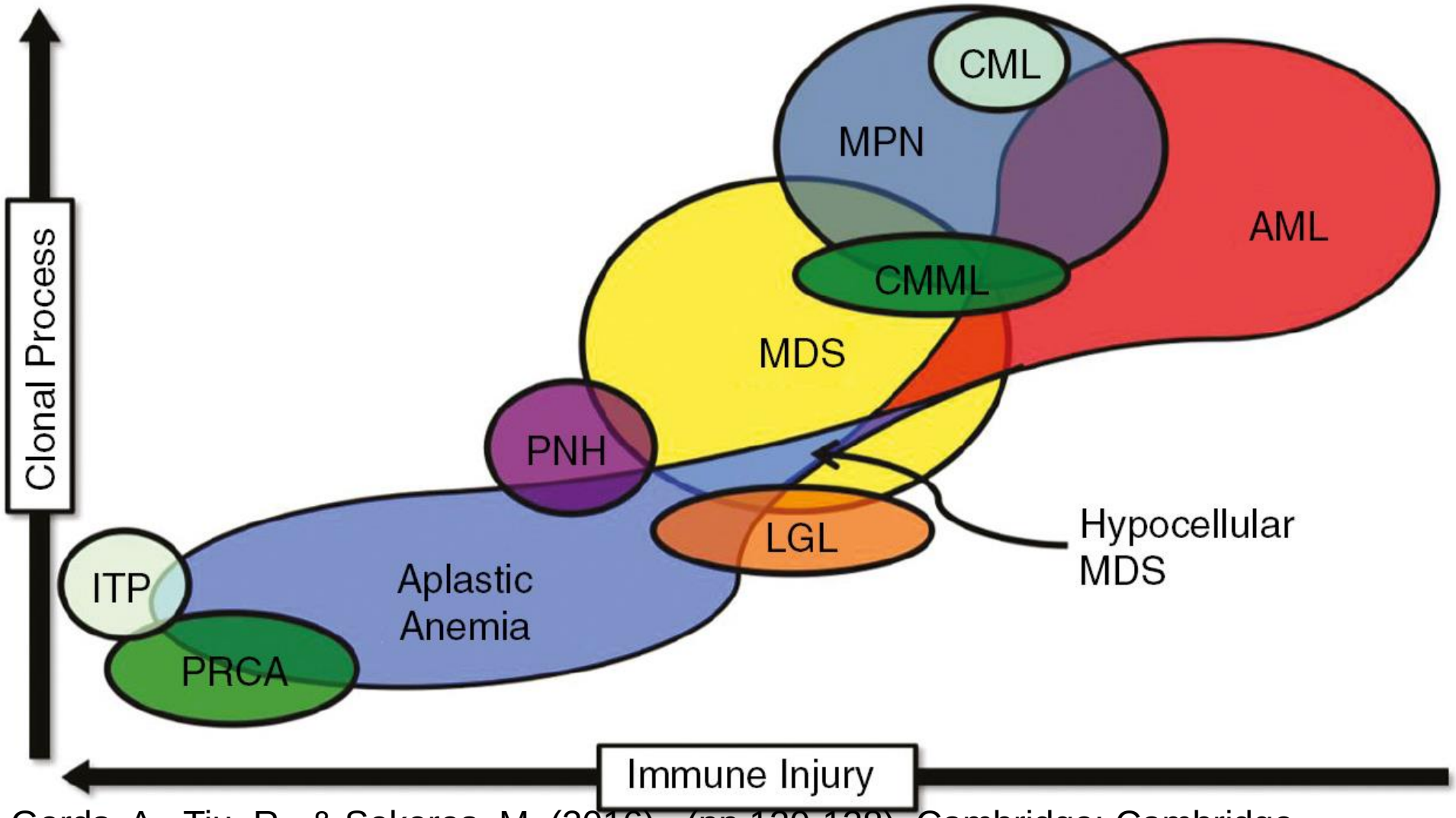
Genes involved in MDS



Steensma et al Mayo Clin Proc 2015 90(7):969-983

Diagnosis

Overlap Syndromes



Gerds, A., Tiu, R., & Sekeres, M. (2016). (pp.120-128). Cambridge: Cambridge University Press. doi:10.1017/CBO9781316017852.015

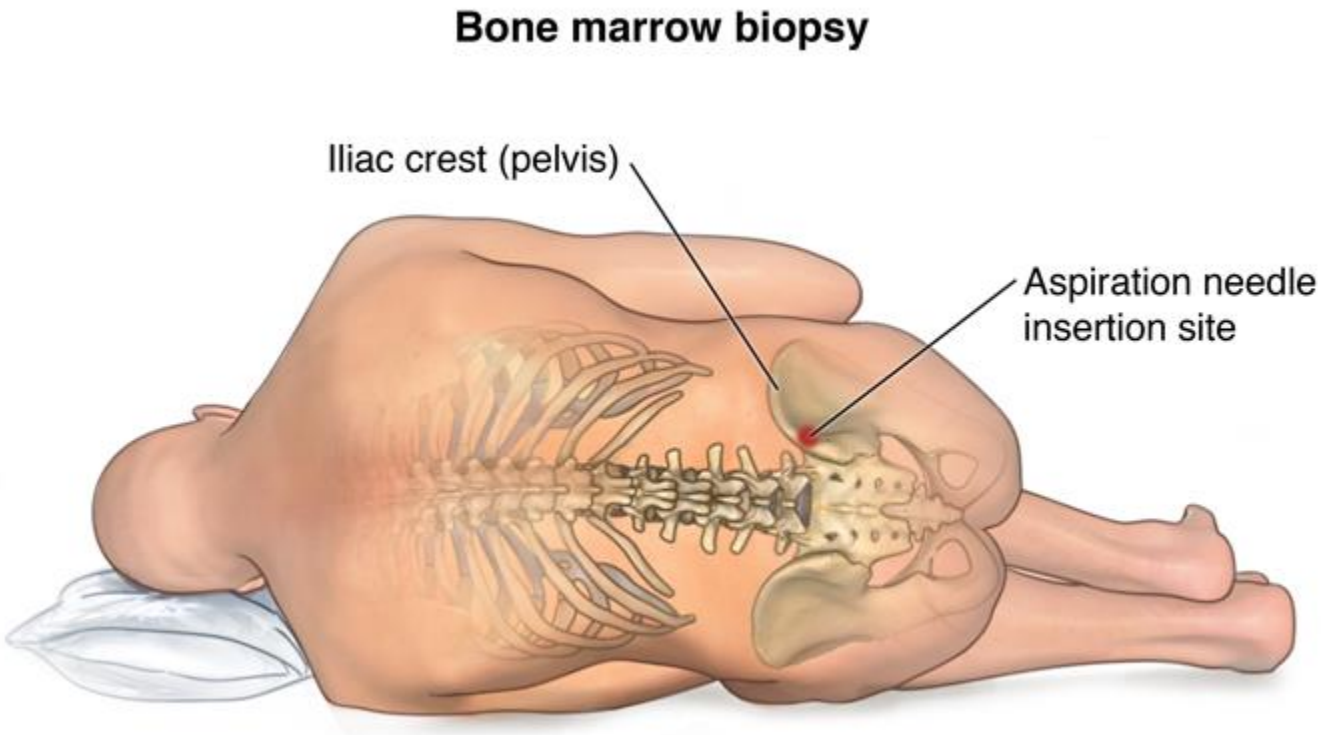
How do we make the diagnosis?

- Signs and symptoms are unspecific:
    a. Fatigue (Anemia)
    b. Infections (Neutropenia)
    c. Bleeding (Thrombocytopenia)
- Laboratory studies showing isolated cytopenia/bycytopenia/pancytopenia.
- Gold standard: Bone marrow biopsy.

Diagnostic Evaluation

Needed for most patients	Needed for some patients
Medical history and physical exam	Copper level
CBC with differential	HIV
LDH	HLA typing
Reticulocyte counts	Flow cytometry
Blood smear	FISH
Serum EPO	Molecular testing
Iron, ferritin, folate and vitamin B12	Check for congenital medical conditions
Thyroid function	
Bone marrow biopsy and aspiration	
Cytogenetic testing	

Bone marrow examination



Diagnostic Confirmation

- Signs and symptoms
- Laboratory studies
- Pathology confirmation:

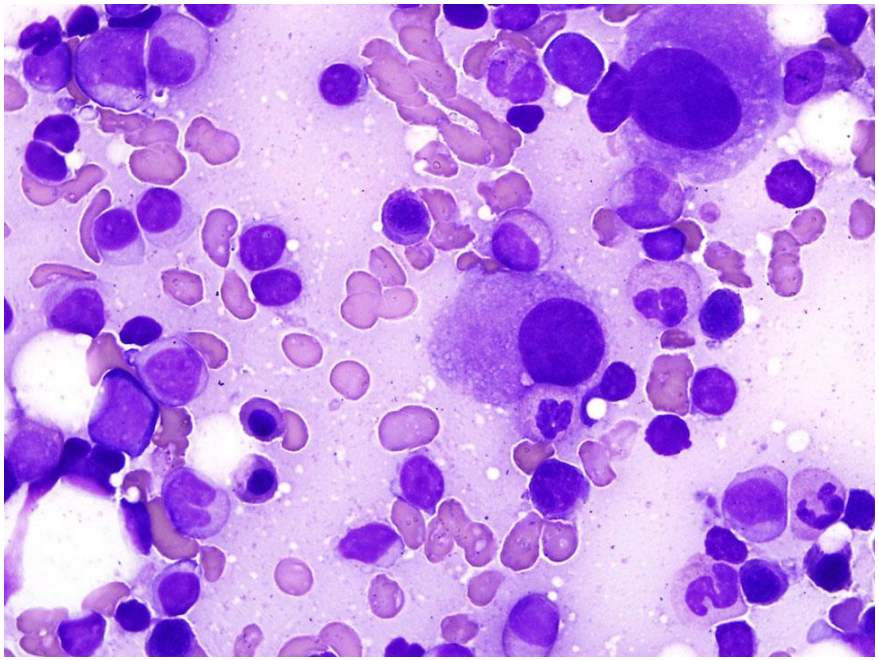
    - Dysplasia in red cells/white cells and/or platelet precursors

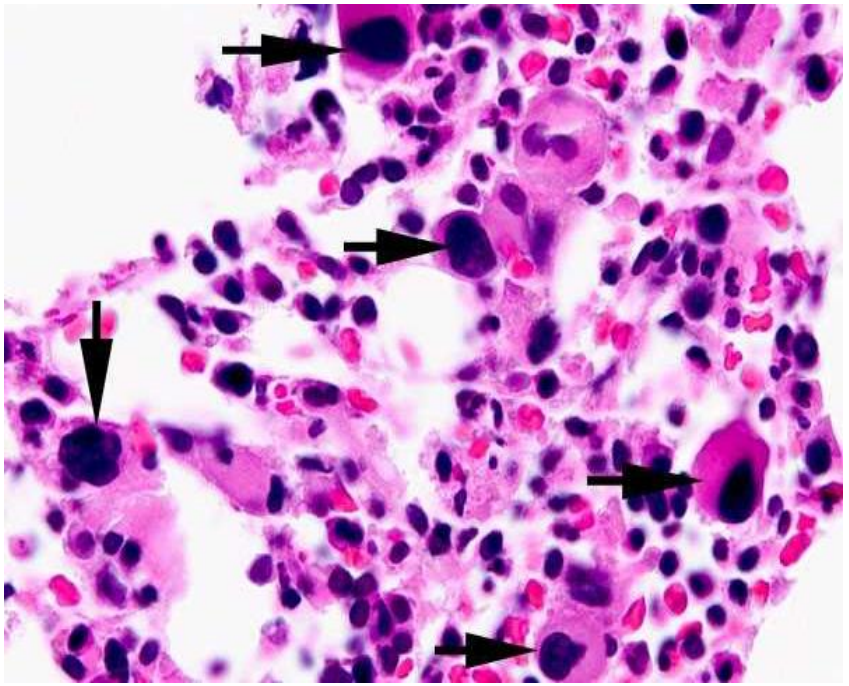
    - Blasts < 20%

    - Clonality demonstrated in chromosomes, FISH or molecular studies.

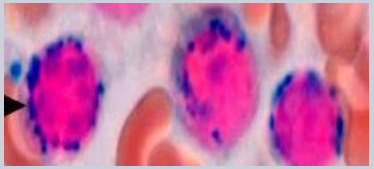
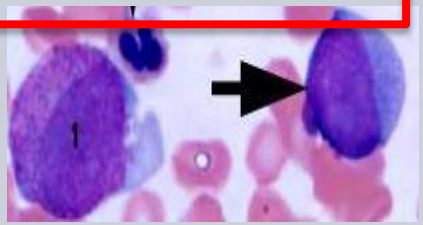
MDS Case

- Mr. T had the following labs: WBC: 5000, Hb:8. Plts: 30,000
- Bone marrow biopsy: MDS, Cytogenetics: 5q- blasts 3%





WHO 2016 MDS CLASSIFICATION

Disease	Blood findings	Bone marrow findings
MDS with single lineage dysplasia (MDS-SLD)	Single cytopenia or bicytopenia. No blast	Unilineage dysplasia <5% blasts <15% ringed sideroblasts
MDS-SLD with ring sideroblasts	Anemia No blasts	Erythorid dysplasia only. >15% ringed sideroblasts <5% blasts
MDS with multilineage dysplasia -MDS-MLD with ring sideroblasts	Cytopenias <5% blasts No Auer rods <1 x 10 9 monocytes	Unilineage or multilineage dysplasia 
MDS with isolated del 5q	Anemia No or rare blasts	Increased megakaryocytes with hypolobulated nuclei <5% blasts
MDS with excess blasts -MDS-EB1 -MDS-EB2	Cytopenias 1: <5% blasts 2: 5-19% blasts	 1: 5-9% blasts 2: 10-19% blasts
MDS unclassifiable (MDS-U)	Cytopenias	Dysplasia in <10% of cells plus CG abnormality, <5% blasts

What is the prognosis of MDS?

(including Mr. T)

The importance of MDS Scoring Systems

- Prediction of outcomes: Survival, acute leukemia transformation risk.
- Treatment decisions. (To treat or not to treat)
- Key factors:
    - MDS subtype
    - Percent of blast cells
    - Chromosome changes

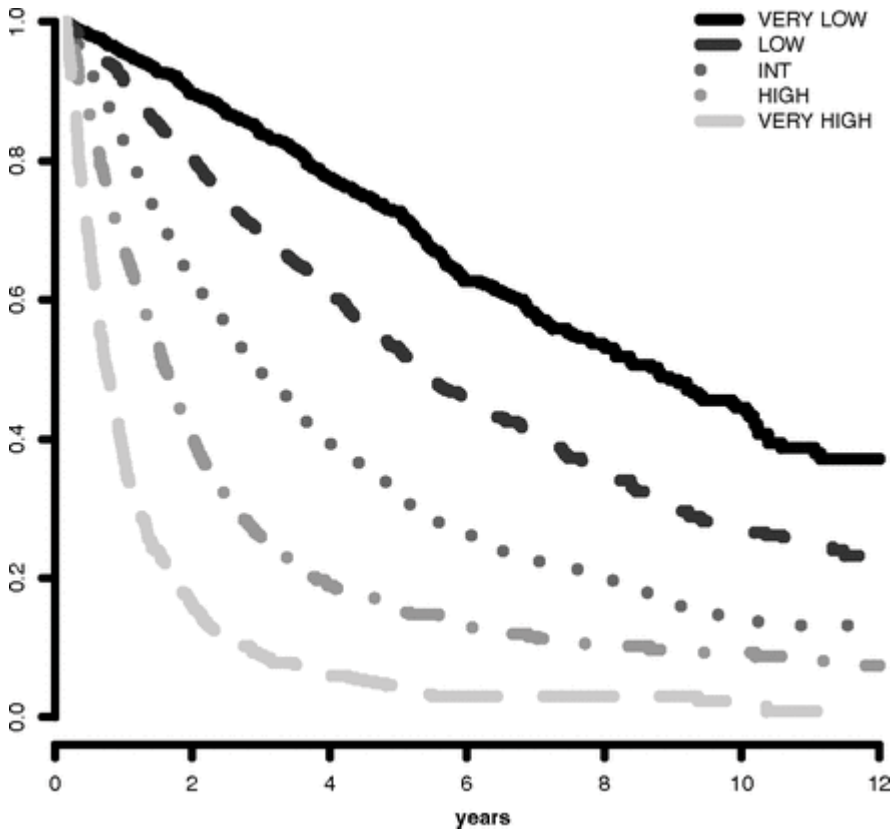
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
Blasts (%)	<2%		>2-<5%		5-10%	>10%	
Hemoglobin	>10		8-10	<8			
Platelets	>100,000	50-100,000					
ANC	>0.8	<0.8					

IPSS-R

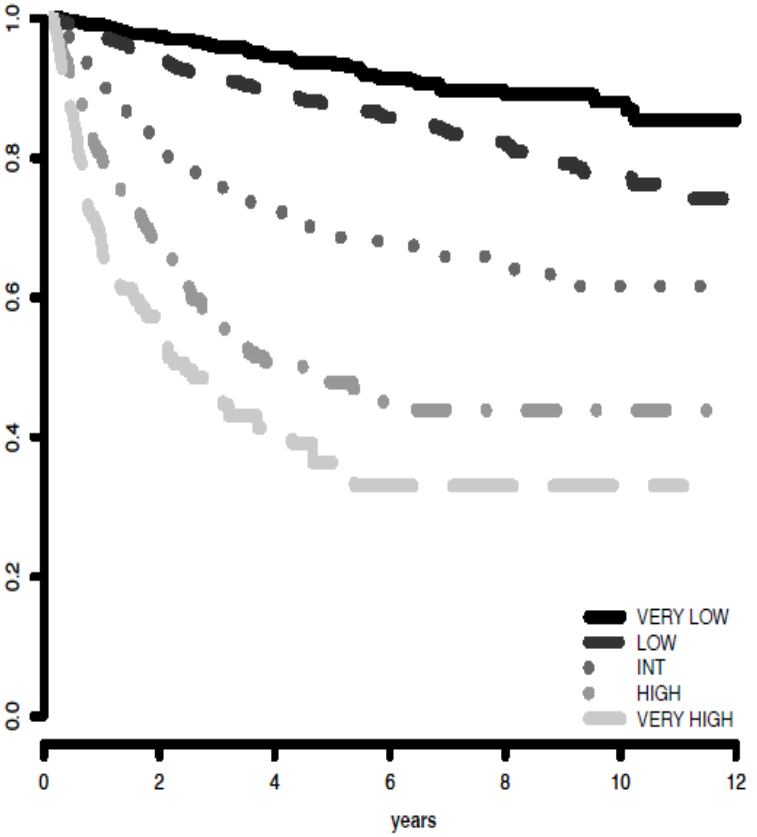
SCORING SYSTEM

Cytogenetics Risk Grouping	Cytogenetic Types	Survival
Very Good	Del 11q, -Y	5.4 y
Good	Normal, del 5q, del 12p, del 20, del 5	4.8
Intermediate	Del 7q,+8, +19, i17q, any other single or double independent clones	2.7
Poor	-7, inv(3), t3q, del 3q, double including -7/del 7q, complex: 3 abnormalities	1.5
Very Poor	Complex> 3 abnormalities	0.7

Score	<1.5 Very Low	>1.5-3 Low	>3-4.5 Intermediate	>4.5-6 High	>6 Very High
Survival	8.8	5.3 years	3	1.6	0.8
Risk of AML in 25% of patients	NR	10.8 years	3.2	1.4	0.73



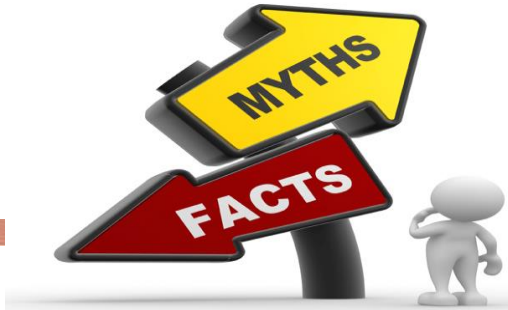
Survival according to IPSS-r category



AML evolution per IPSS-R category

TREATMENT

MDS Treatment Myths and Facts



- ~~"One size fits all"~~: Risk-oriented treatment
- ~~"All you need is chemotherapy"~~: Chemo is only one option among many
- ~~"I am too old to get treatment"~~: QOL and survival are treatment goals
- ~~"Transplant is not an option"~~: It is for some patients

Treatment Goals

Very low
Low Risk MDS

Int-2
High Risk MDS

GOALS OF CARE

Improve quality of life
Improve transfusion independence
Improve marrow function
Cure!

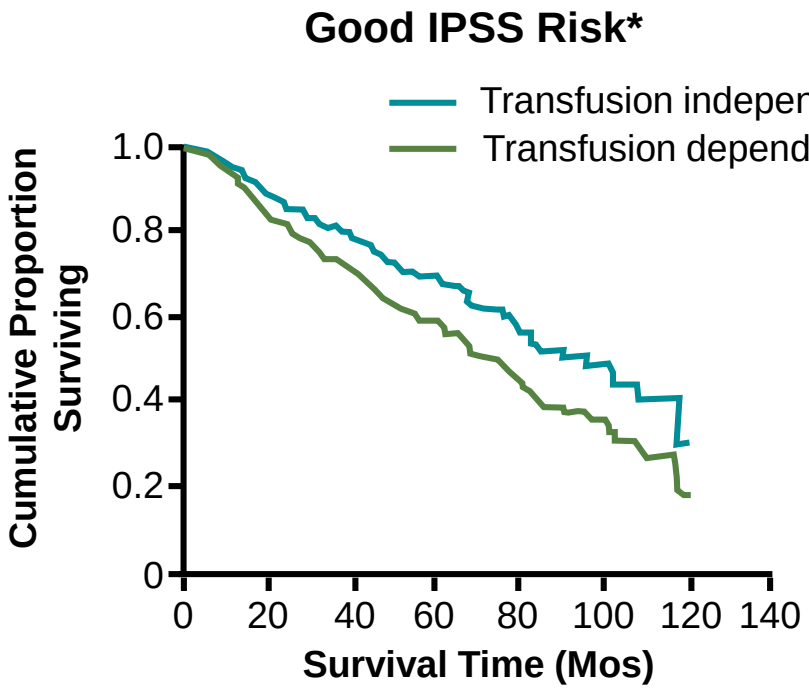
Decrease risk of leukemic transformation
Improve survival
Improve quality of life
Cure!

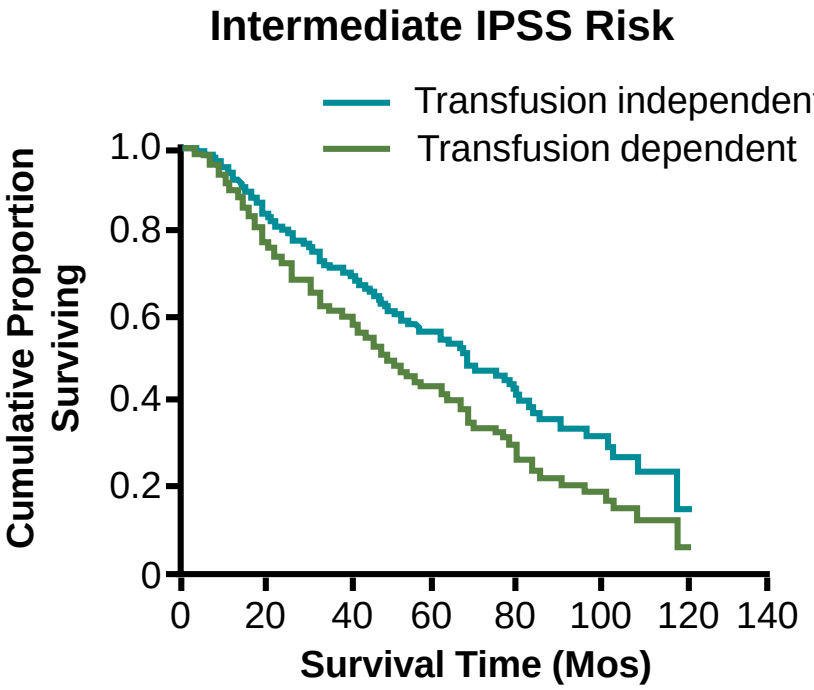
Low Risk MDS Treatment

- Observation
- Transfusions
- Iron chelation
- Hematopoietic growth factors
- Immunosuppresive therapy
- Immunomodulatory drugs (Lenalidomide)

This is my favorite one !

Transfusion Independency: Key Goal on MDS





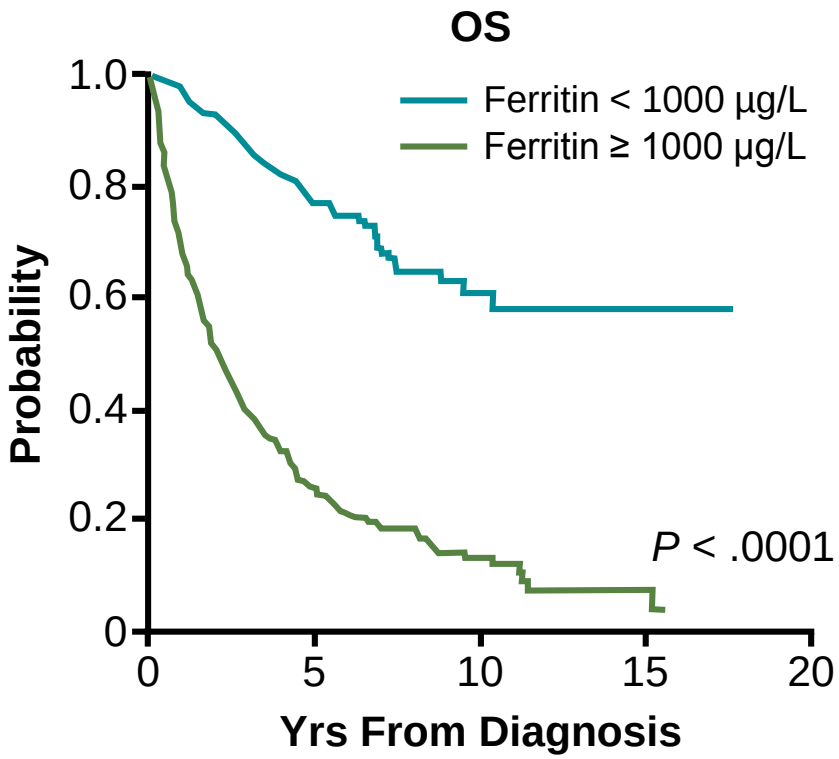
*Excludes isolated del(5q)

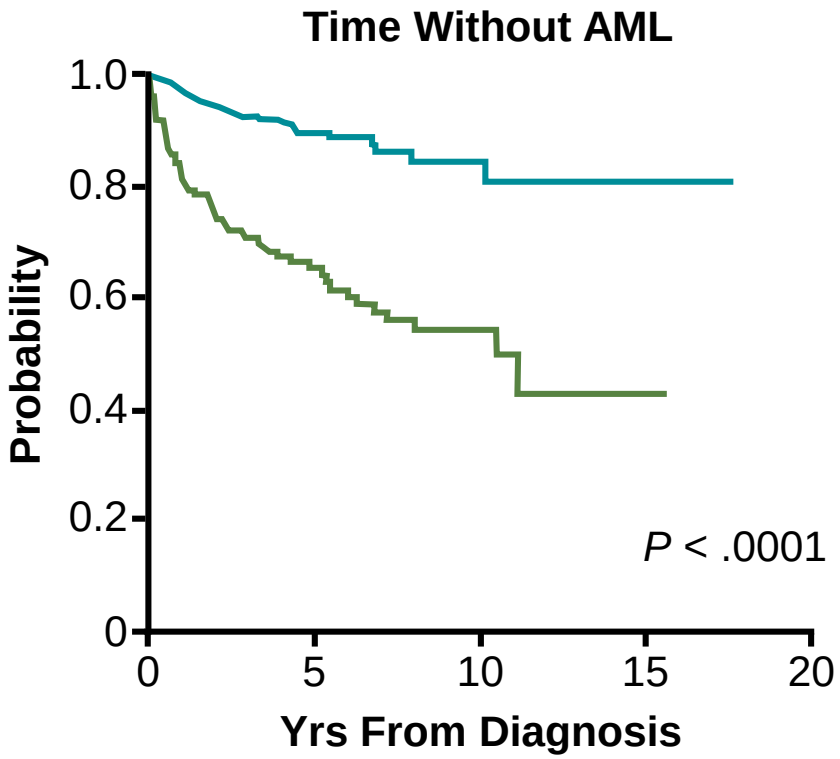
- Transfusion-dependent patients had worse OS than transfusion-independent patients (HR: 2.16; $P < .001$)

Malcovati L, et. al. J Clin Oncol. 2005;23:7594-7603.

Serum Ferritin is Predictive of Survival and Risk of AML in MDS

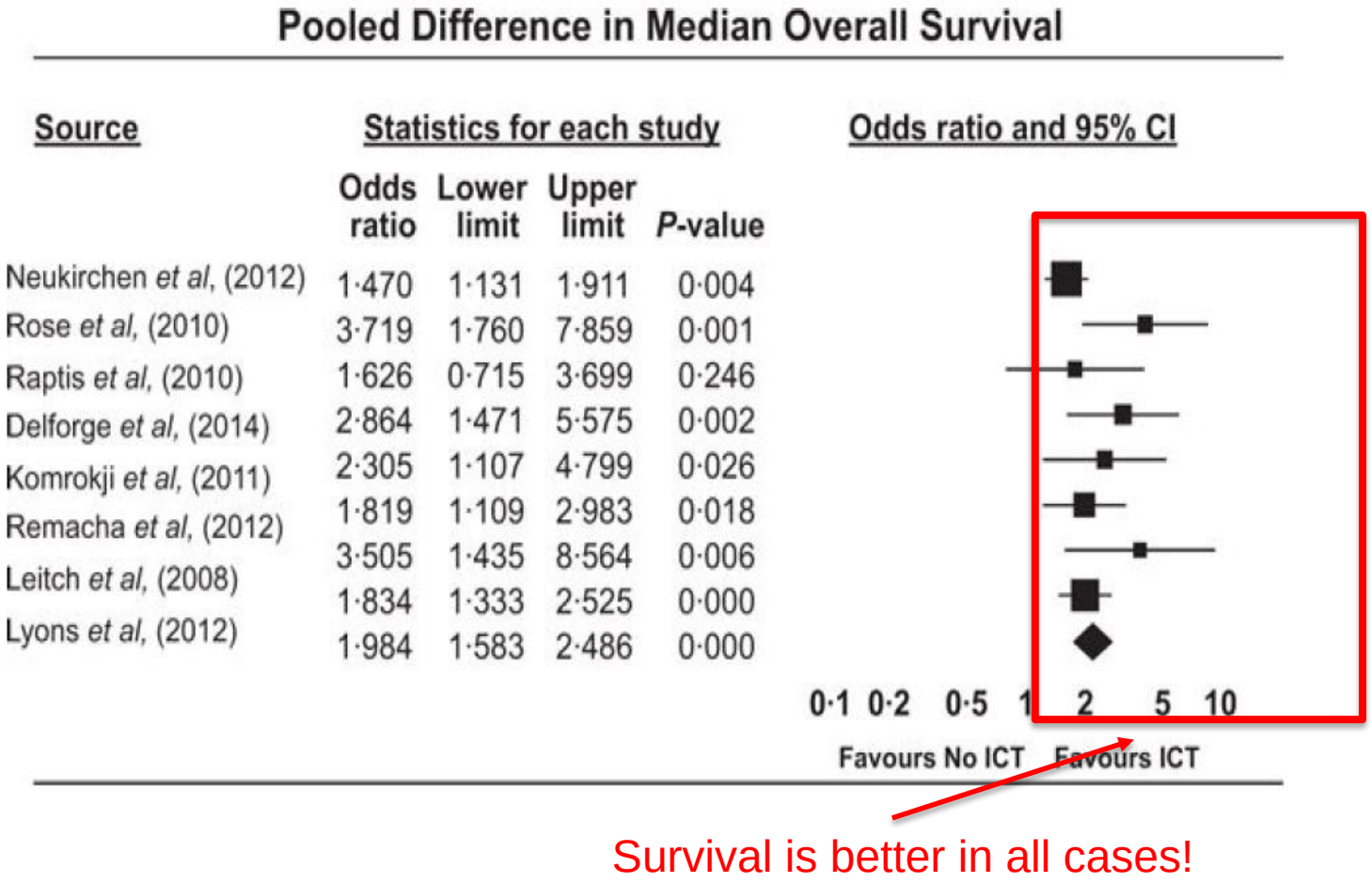
- Iron overload is a prognostic factor for OS and transformation to AML





Sanz G, et al. 2008 ASH. Abstract 640.

Iron Chelation and Survival



Survival is better in all cases!

Mainous III A, et al. BJH 2014 Dec;167(5):720-23

Hematopoietic Growth Factors

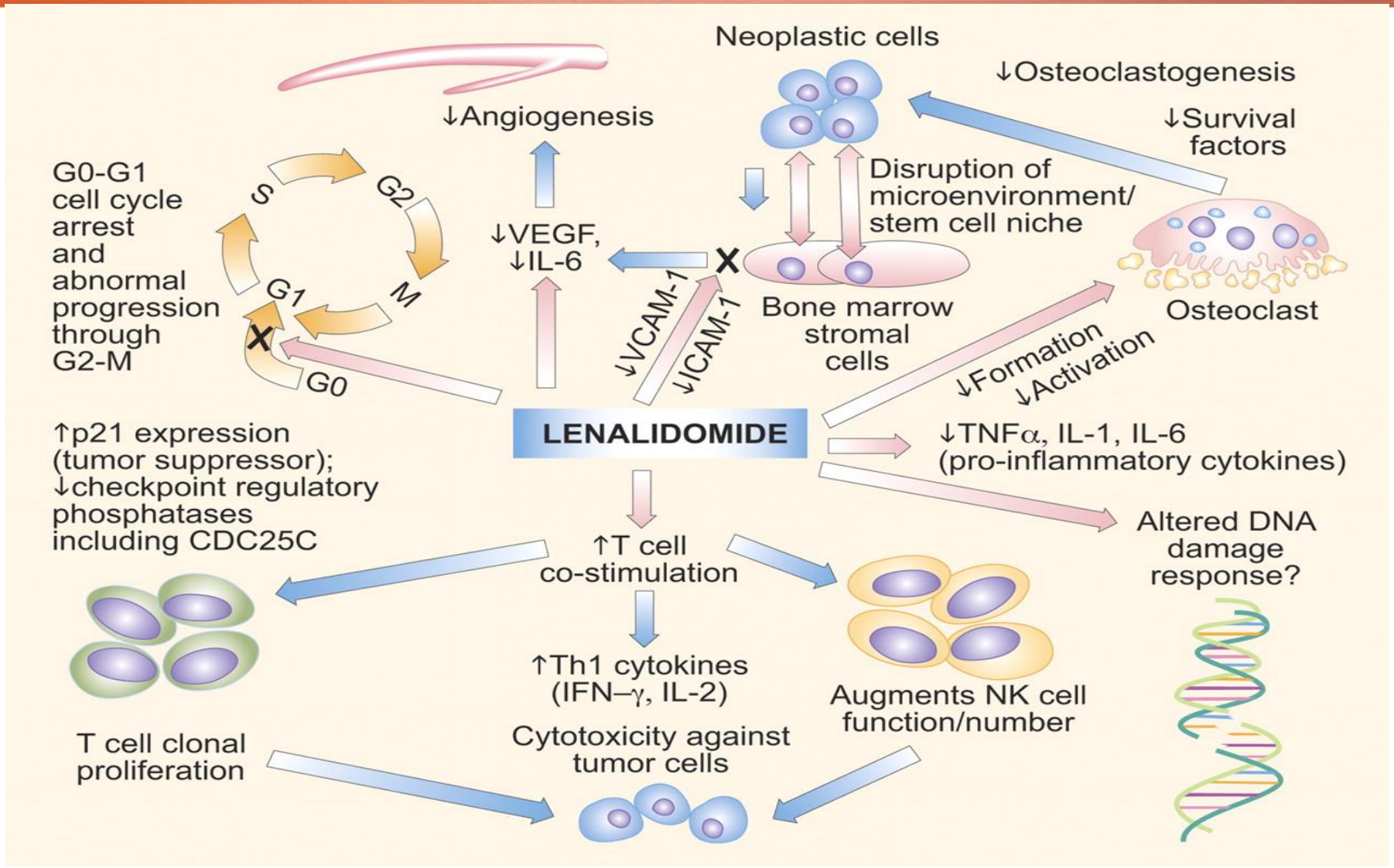
	Generic Names	Brand Names	Mechanism of Action	Responses
ESA	Epoetin alfa Darbopoietin	Epogen, Procrit Aranesp	Increase red cell counts	40% Epo levels below 500
GCSF	Filgrastim	Neupogen, Zarxio	Increase Neutrophil counts	38% OS: NR
1. Thrombopoietin*	Eltrombopag	Promacta	Increase platelets	47% *

* Not FDA approved yet

ESA and GSCF can be used in combination

1. Oliva EN et al. Lancet Haematol 2017 Mar 4(3):e127-e136

Lenalidomide



Steensma D et al. Blood 2011 118:481-82

MDS-002/003: Lenalidomide in MDS

- Phase II studies of lenalidomide efficacy and safety
- Shared eligibility requirements include: IPSS low/int-1 MDS; ≥ 2 U RBC/8 Wks; PLT > 50,000/µL; ANC > 500/µL
- Lenalidomide dosing: 10 mg/day QD or for 21 Days/28 Day cycle
- Response assessment after 24 Wks of treatment

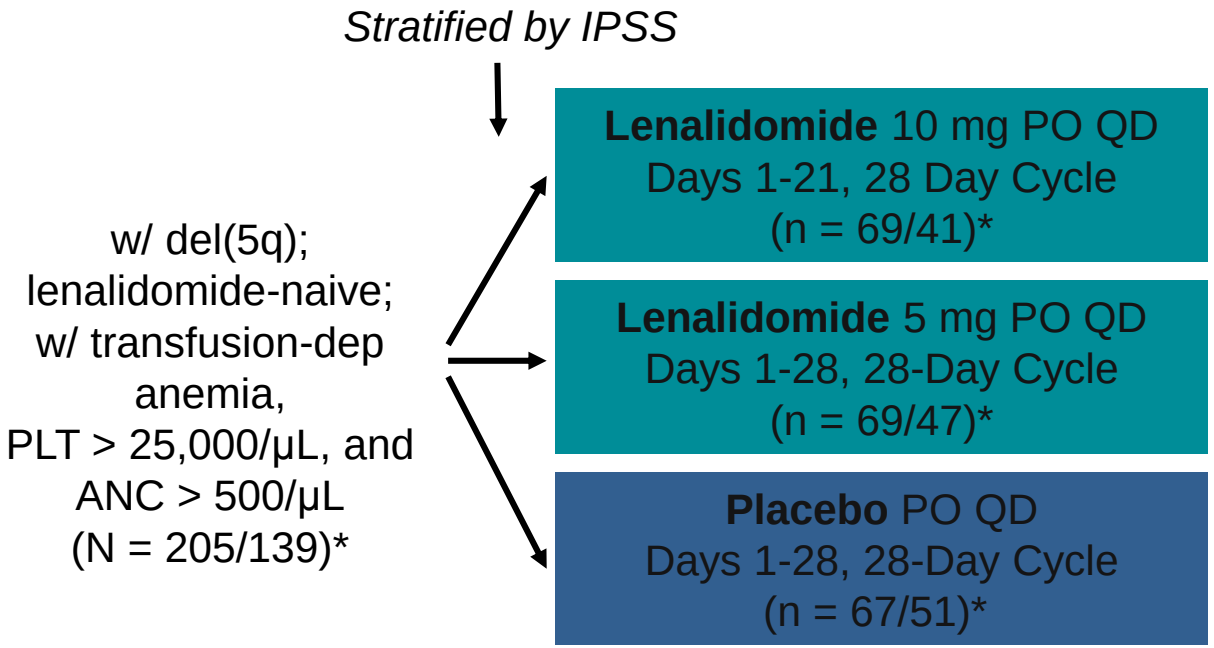
Parameter	MDS-002[1] Non-del(5q)	MDS-003[2] del(5q)
Pts, N	214	148
Erythroid Response, % ▪ TI ▪ TI + minor*	 26 **43**	 **67** **76**
Cytogenetic Response, % ▪ CCR ▪ CCR + PR	 9 19	 45 73
Median Hb increase, g/dL	3.2	5.4
Time to response, Wks	4.8	4.6
Median treatment duration, Wks	41	> 104

*TI + minor: overall hematologic improvement, including TI and pts with ≥ 50% reduction in transfusions.

1. Raza A, et al. Blood. 2008;111:86-93.
2. List A, et al. N Engl J Med. 2006;355:1456-1465.

MDS-004: Lenalidomide in MDS With del(5q)

- Randomized, double-blind, placebo-controlled, phase III trial



	RBC-TI ≥ 8 weeks†	RBC-TI ≥ 26 weeks
Lenalidomide 10 mg	61.0%	56.1%
Lenalidomide 5 mg	51.1%	42.6%
Placebo	7.8%	5.9%

- Median duration: not reached; median follow-up: 1.55 yrs
- Overall safety consistent with known lenalidomide safety profile

Fenaux P, et al. Blood. 2011;118:3765-3776.

In Summary

- Observation: Isolated cytopenia, no symptoms.

- Low risk MDS with symptoms:
  - Consider growth factors
  - Transfusions/iron chelation
  - Lenalidomide in 5q MDS
  - Clinical Trial

Going back to Mr. T Case…

- He started treatment with lenalidomide.
- No need for transfusions or growth factors.
- Blood counts started to improve.

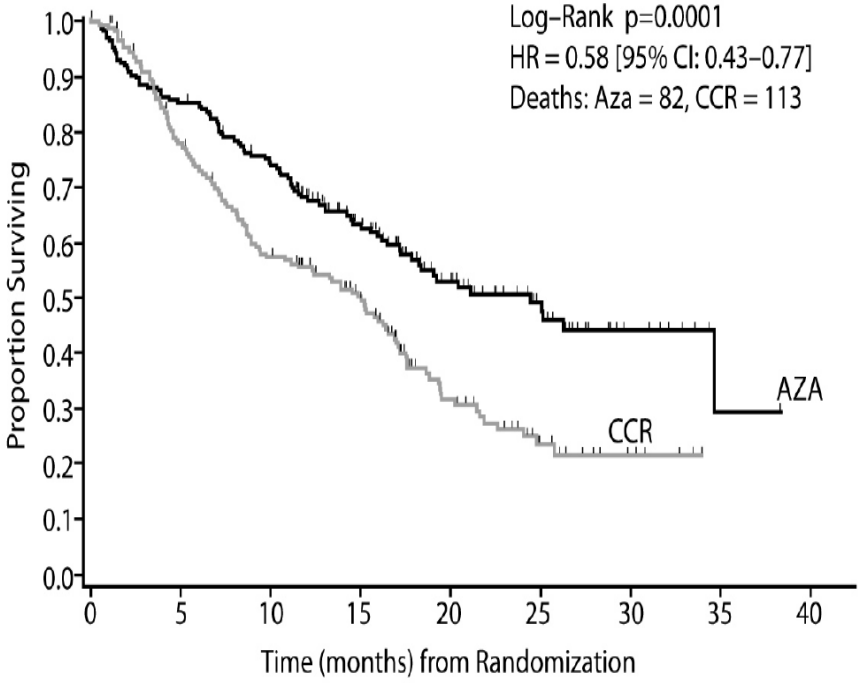
High Risk MDS Treatment (What comes first?)

- Hypomethylating Agents: Azacytidine, Decitabine.
- Intense chemotherapy.
- Clinical Trials.
- Stem cell transplant.

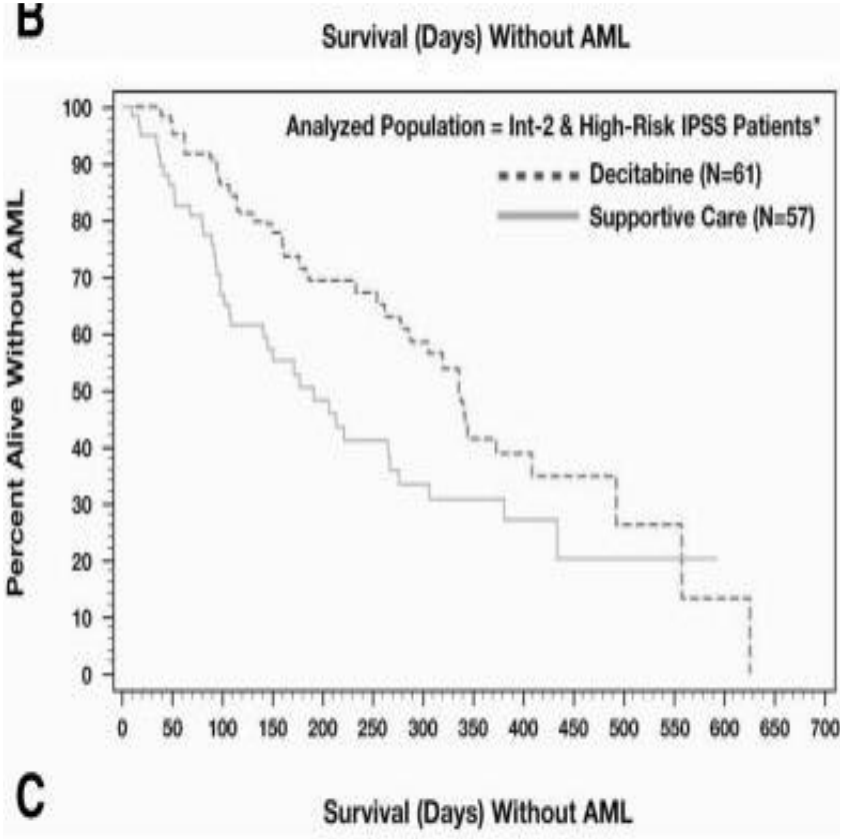
Assessment before treatment	Treatment options
Allogeneic HCT is a good option for you, and a well-matched donor is available	Allogeneic HCT Azacitidine or decitabine followed by HSCT High intensity chemo followed by HSCT
Allogeneic HCT may be a good option for you, but a well-matched donor is not avaliable	Azacitidine Decitabine **Clinical trial**
Allogeneic HCT is not a good option for you, or a well-matched donor is not available	Azacitidine (preferred) Decitabine **Clinical trial**

NCCN Guidelines for Patients, 2018

Hypomethylating Agents

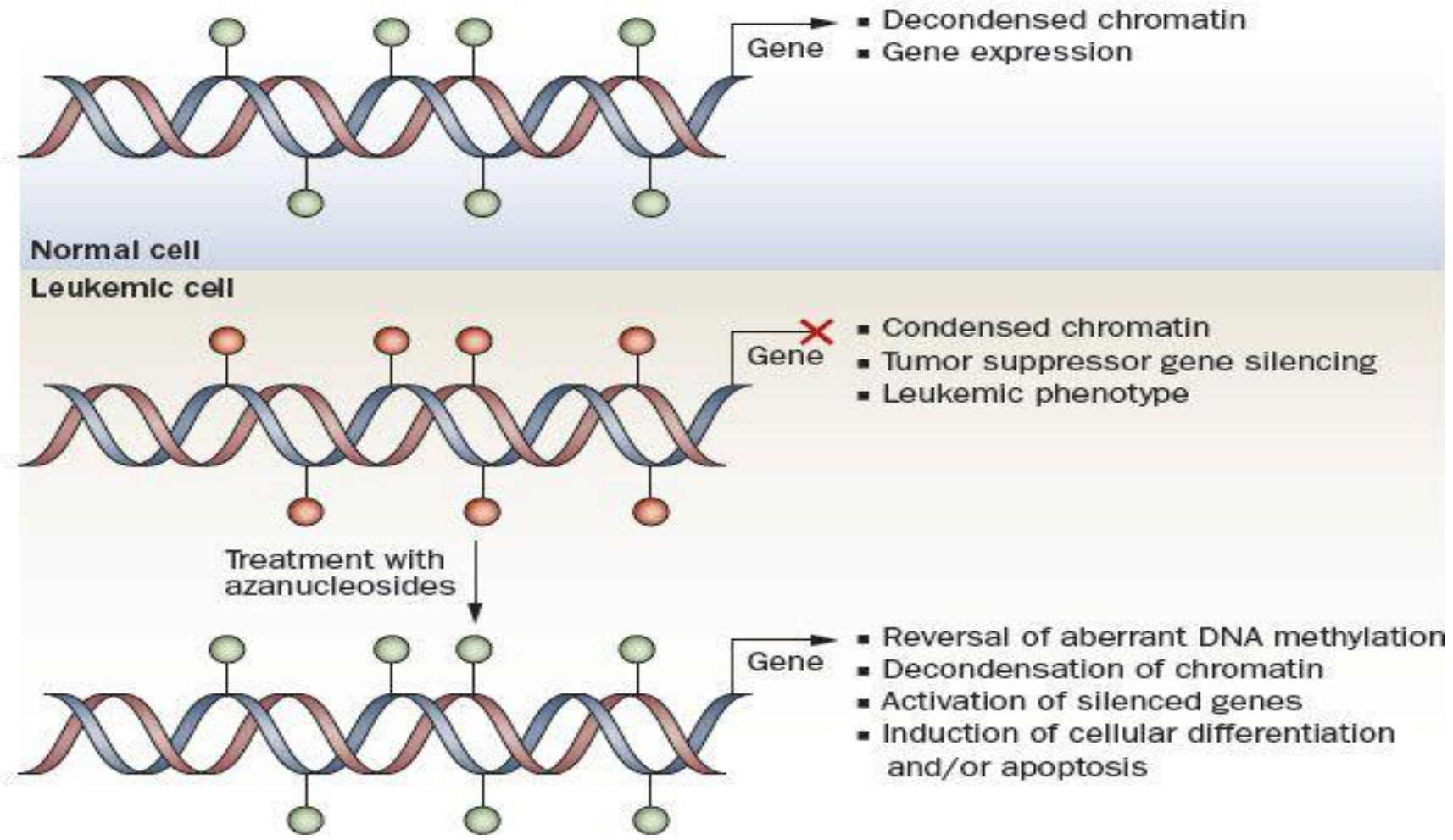


# at risk									
AZA	179	152	130	85	52	30	10	1	0
CCR	179	132	95	69	32	14	5	0	0



1. Fenaux, et al. Lancet Oncology 2009;10223-232
2. Kantarjian et al Cancer 2006, Vol 106, issue 8

HMA Mechanism of Action

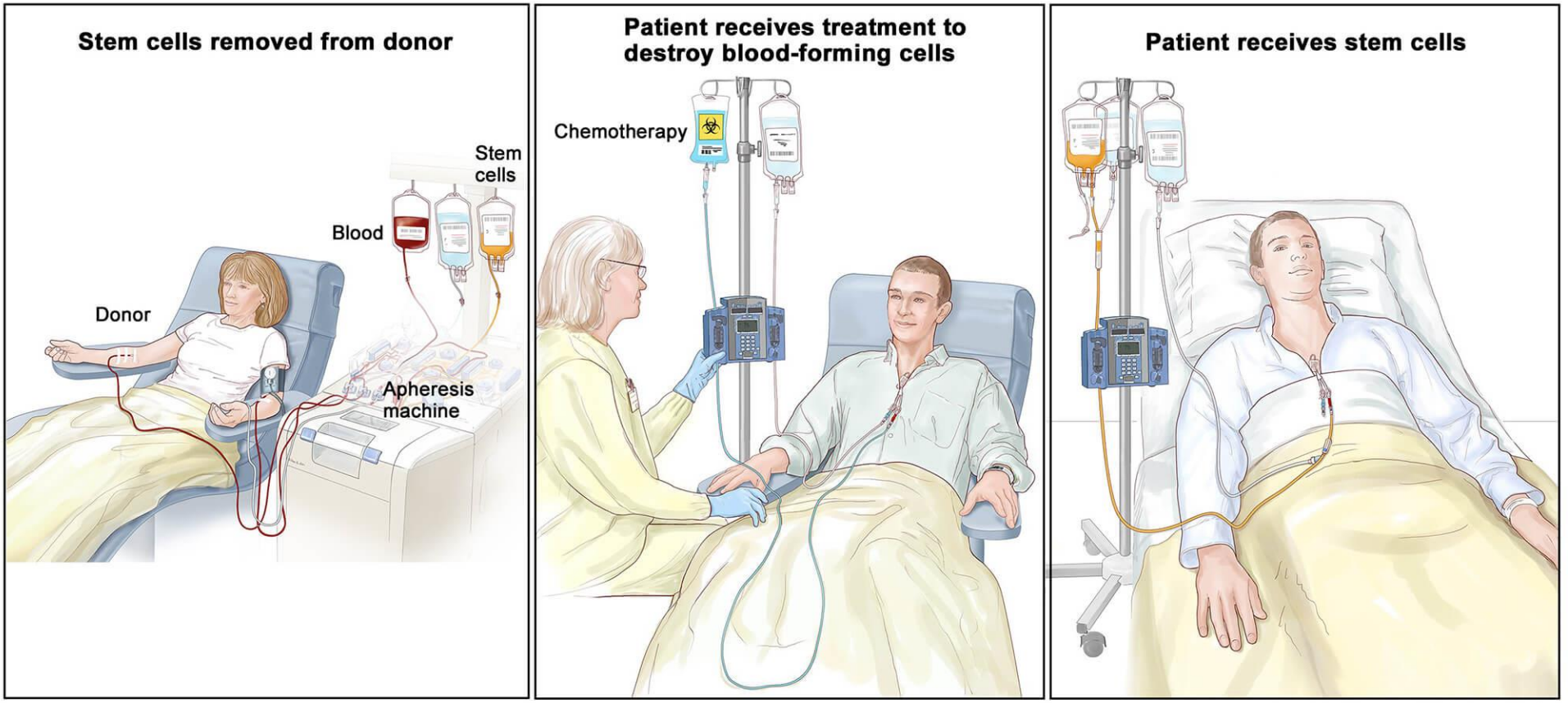


Nat Rev Clin Onc 2010

Azacitidine/Decitabine

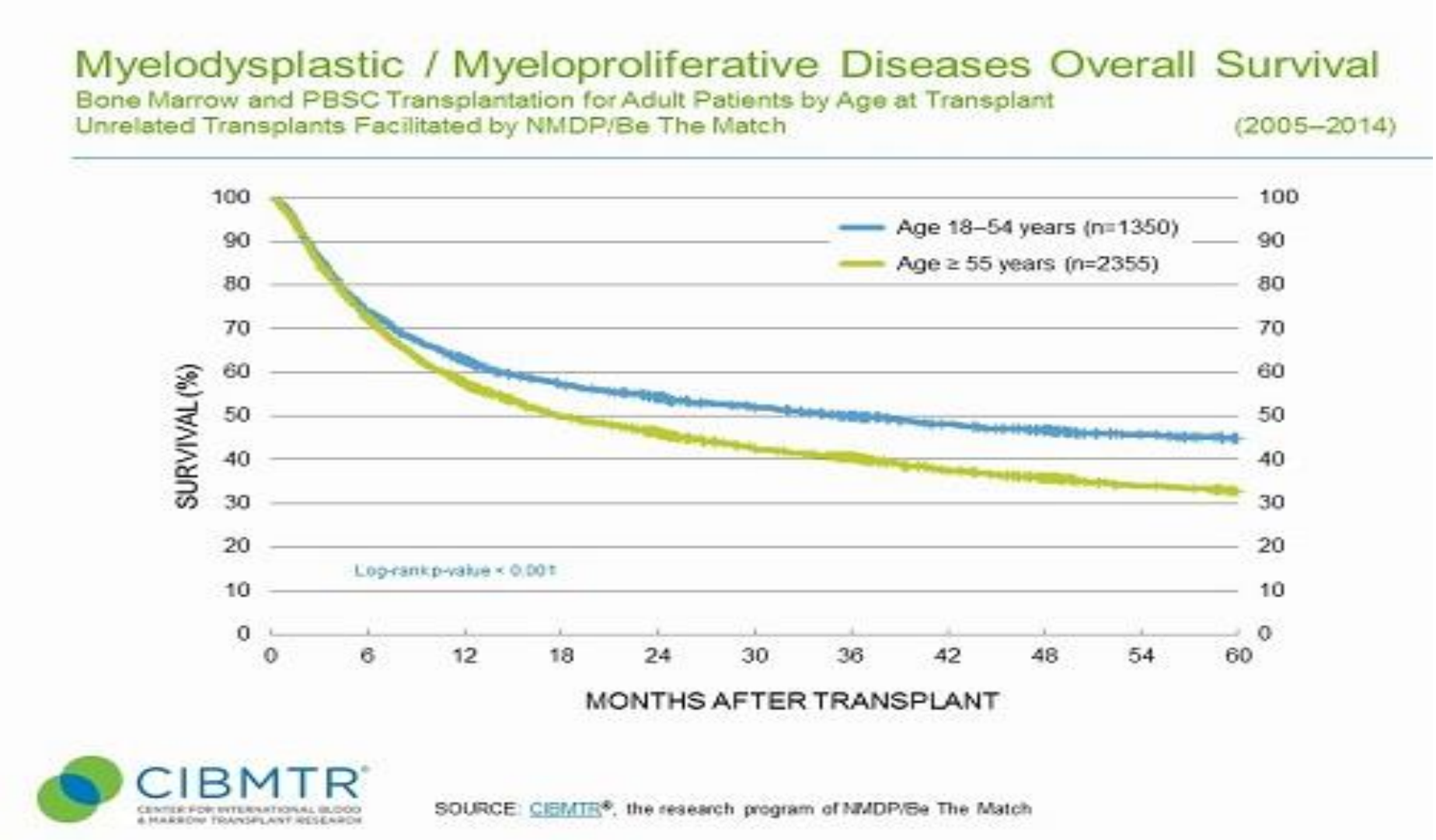
- Administer every 28 days
- At least 4 to 6 cycles
- Side effects: Nausea/vomiting, decreased counts, infections

Allogeneic Stem Cell Transplant



NCI 2017

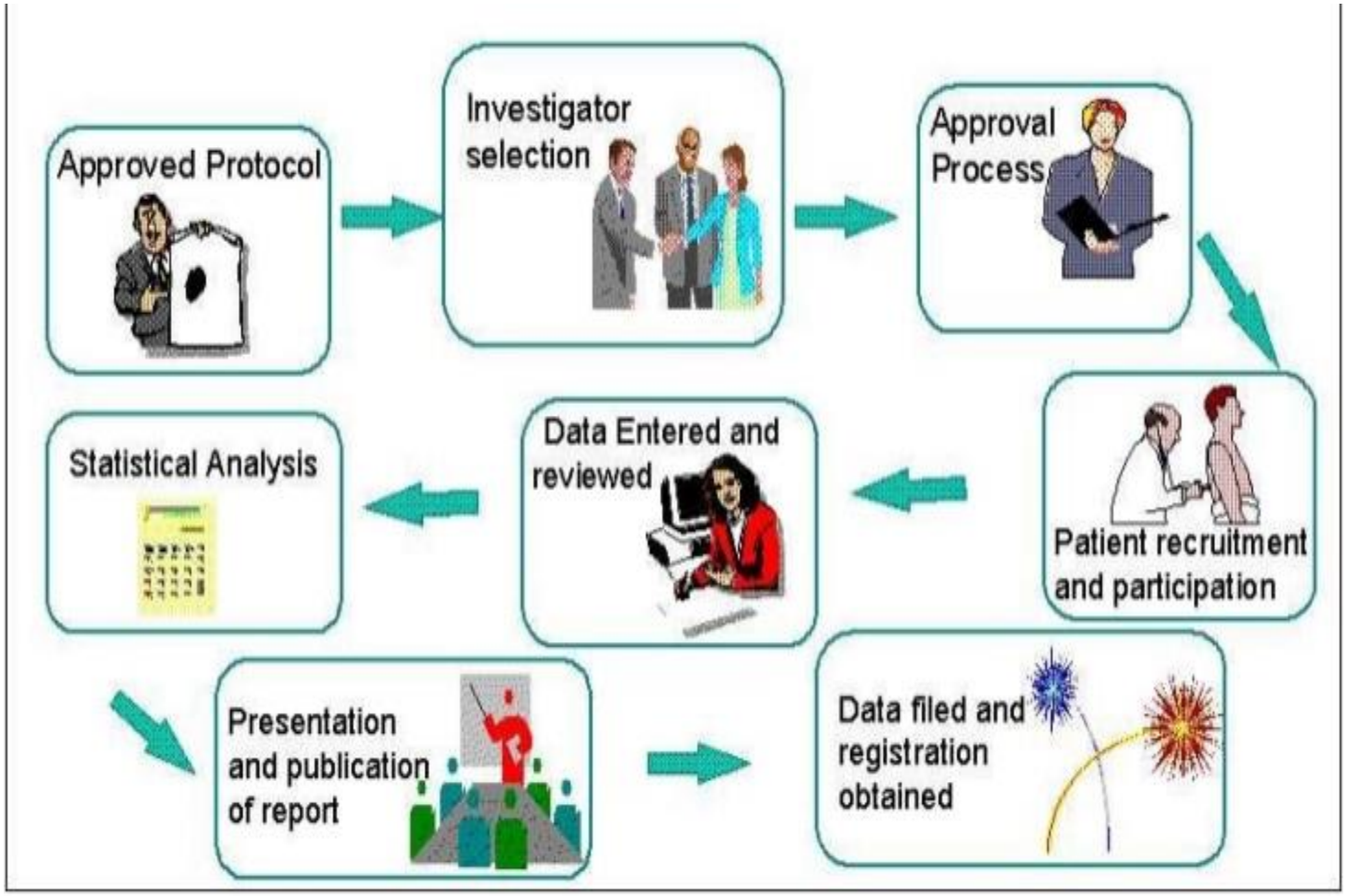
Survival after HSCT by age



HSCT Challenges

- Donor selection:
  Related/Unrelated/Alternative donors.
- Patient AND FAMILY selection: Fit for transplant/family support.
- Insurance coverage: This is a big deal!
- Risks versus benefits

CLINICAL TRIALS IN MDS: WHY ARE SO IMPORTANT?



CLINICAL TRIALS IN MDS

- Patient always comes first
- The goal is research
- Provides “evidence-based” patient care
- Improves quality of care
- Better than standard of care

MDS trials are available in Albuquerque

Trial	Title	Who can participate?	Status
ECOG-ACRIN NHLBI-MDS	A prospective, multi-center cohort supporting research studies in MDS natural history	MDS diagnosis within 6 months. Other cytopenias MDS/MPN	Open active
MEI-011	A safety and efficacy study of pracinostat and azacitidine in patients with high risk MDS	High risk MDS	Open active
SWOG 1612	Azacitidine With or Without Nivolumab or Midostaurin, or Decitabine and Cytarabine Alone in Treating Older Patients With Newly Diagnosed Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome	High risk MDS	In review
ORIEN	Oncology Research Information Exchange Network	Low and high risk MDS	Open active
INST 1512	INST 1512: A new drug discovery platform using High throughput Flow Cytometry and a PDX tissue repository in AML and MDS	MDS and AML	Open active

Conclusions

- Treatments for MDS are effective
- Risk stratification is important: Low vs. High
- Low risk treatments are different than high risk MDS treatments.
- Quality of life is always a goal.
- More clinical trials are needed to continue improving outcomes.

THANK YOU

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To all patients and their caregivers