Myelodysplastic Syndromes:

Disease Overview, New Therapies, and Treatment Options

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MDS Foundation

Patients & Caregivers LIVING with MDS Forums

February 3, 2018

UC San Diego
Moores Cancer Center

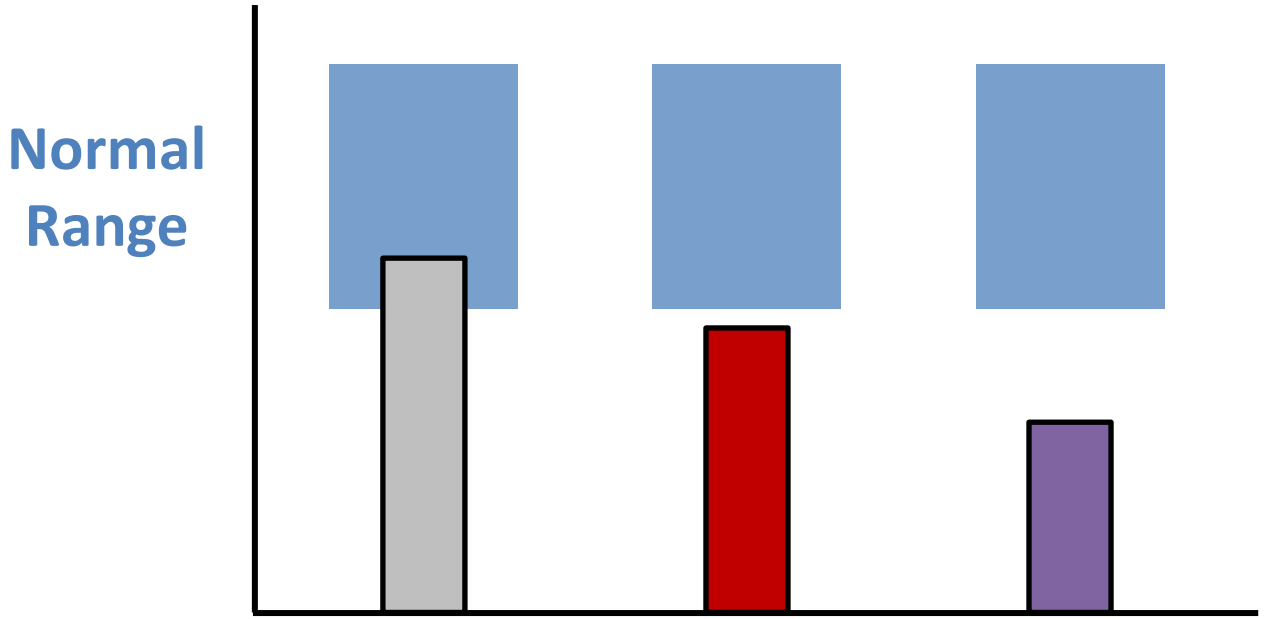
mds foundation
the myelodysplastic syndromes foundation, inc.

Overview

- Introduction to MDS
- Clinical Practice
  - Making the diagnosis
  - Classification
  - Risk stratification
- Treatment Goals and Options
- Novel Therapies
- Questions and Answers

Low Blood Counts

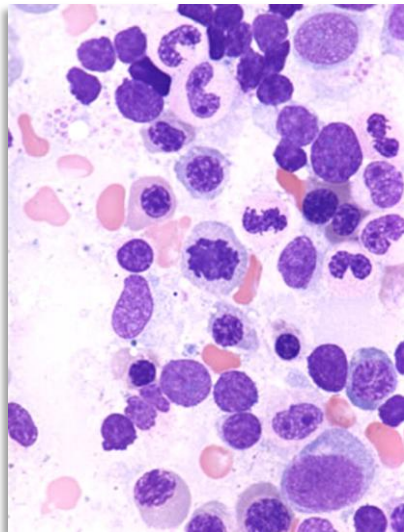
65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.



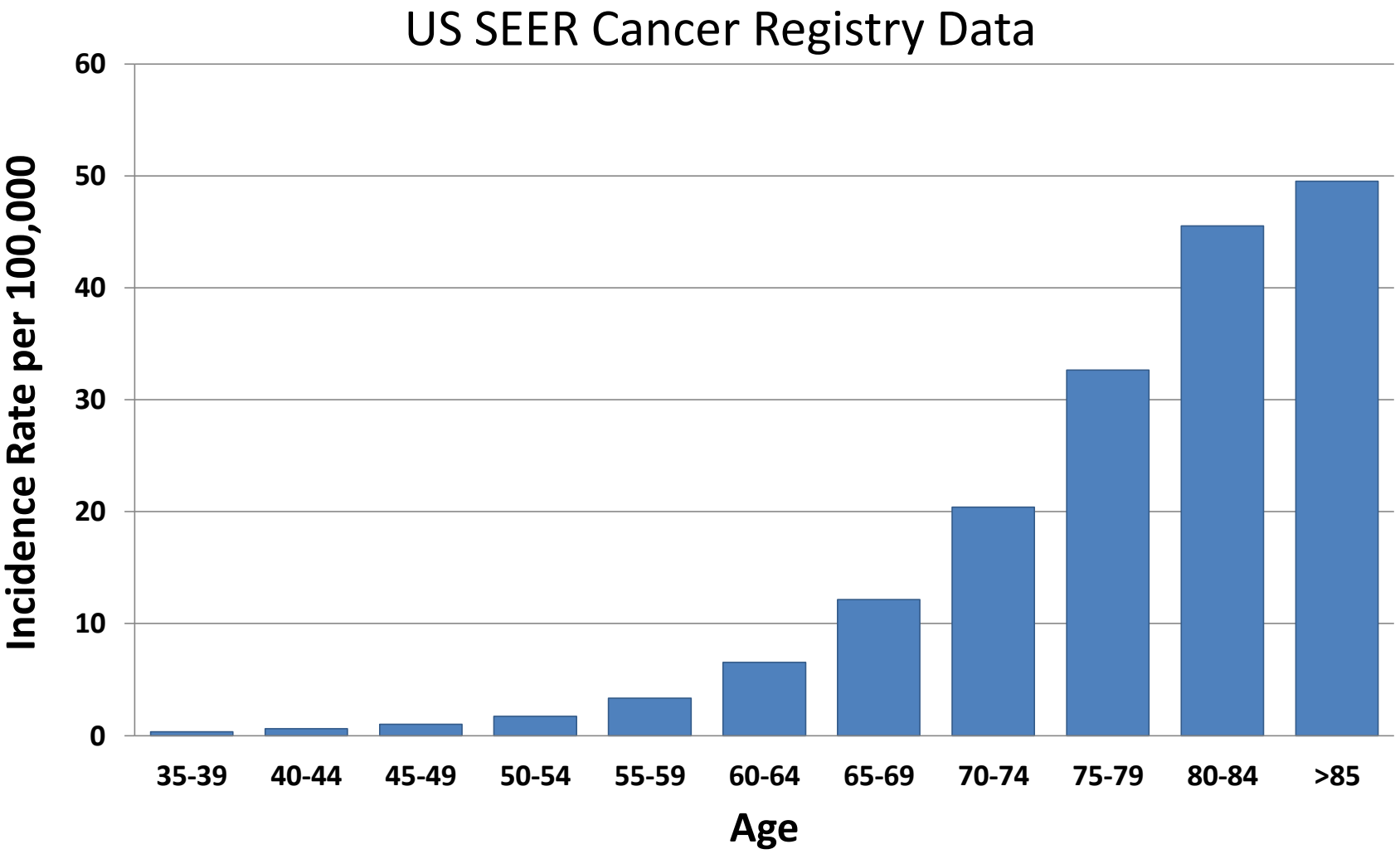
Myelodysplastic Syndromes

- Shared features:
  - Low blood counts
  - Clonal overgrowth of bone marrow cells
  - Risk of transformation to acute leukemia
- Afflicts 15,000 – 45,000 people annually
- Incidence rises with age (mean age 71)

ASH Image Bank



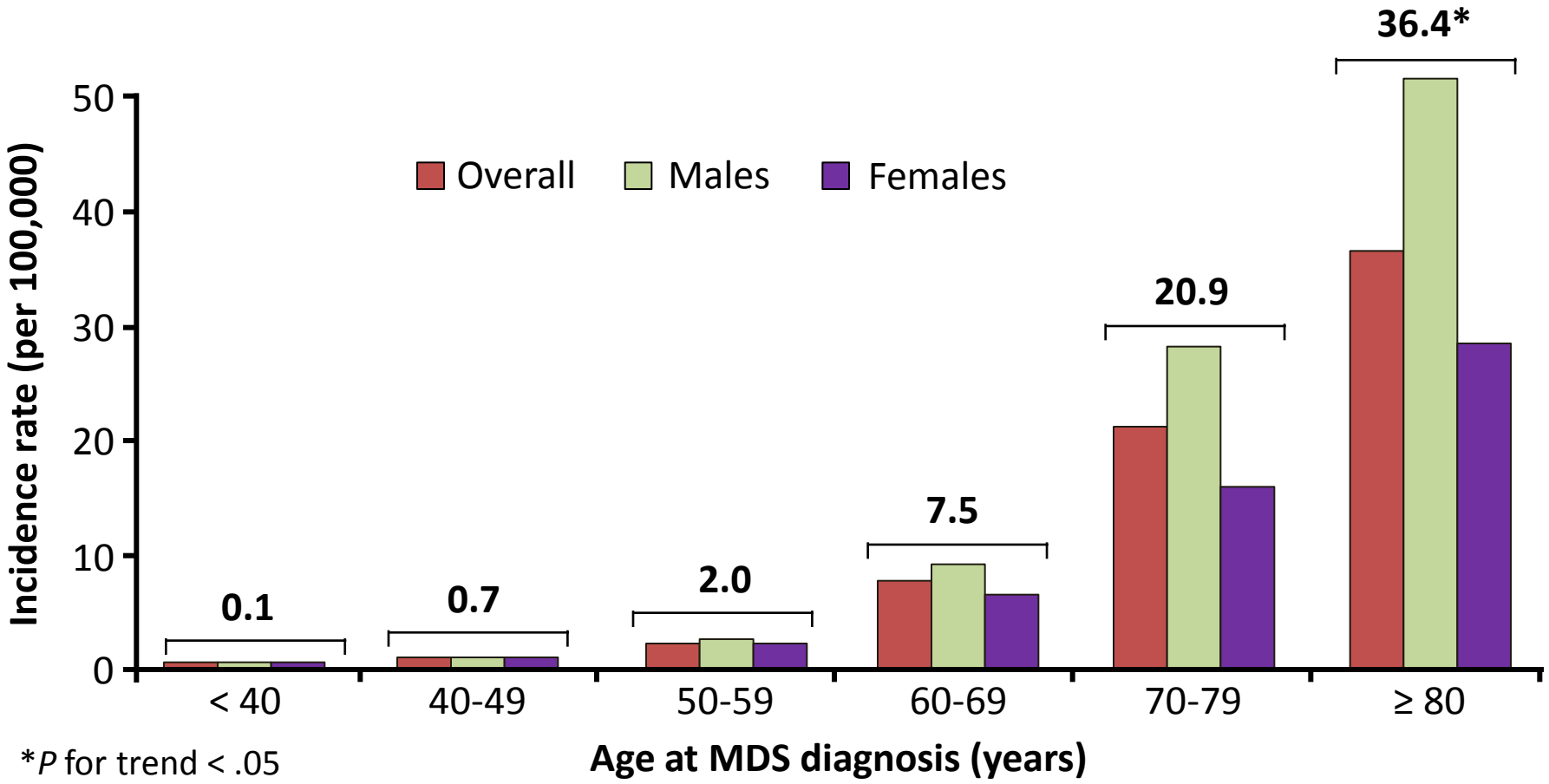
MDS Incidence Rates 2000-2008



http://seer.cancer.gov. Accessed May 1, 2013.

Age and Sex in MDS

- *Overall incidence in this analysis: 3.4 per 100,000*

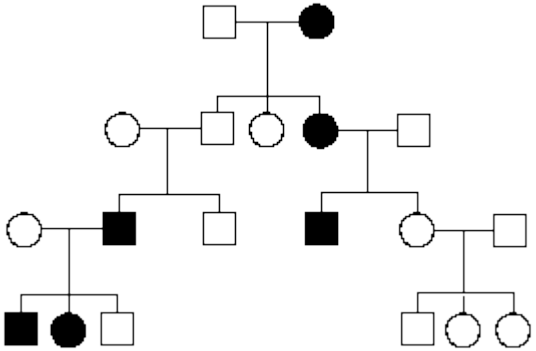
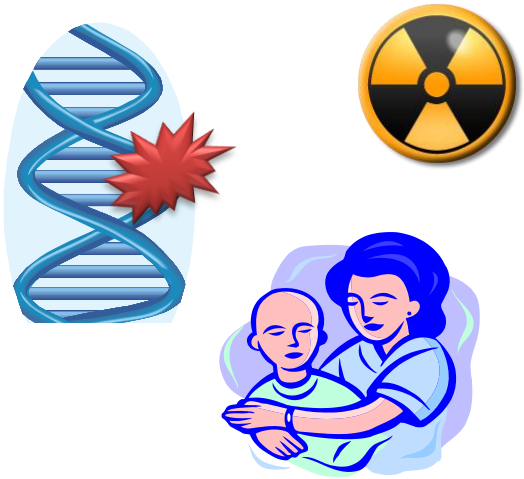


**P* for trend < .05

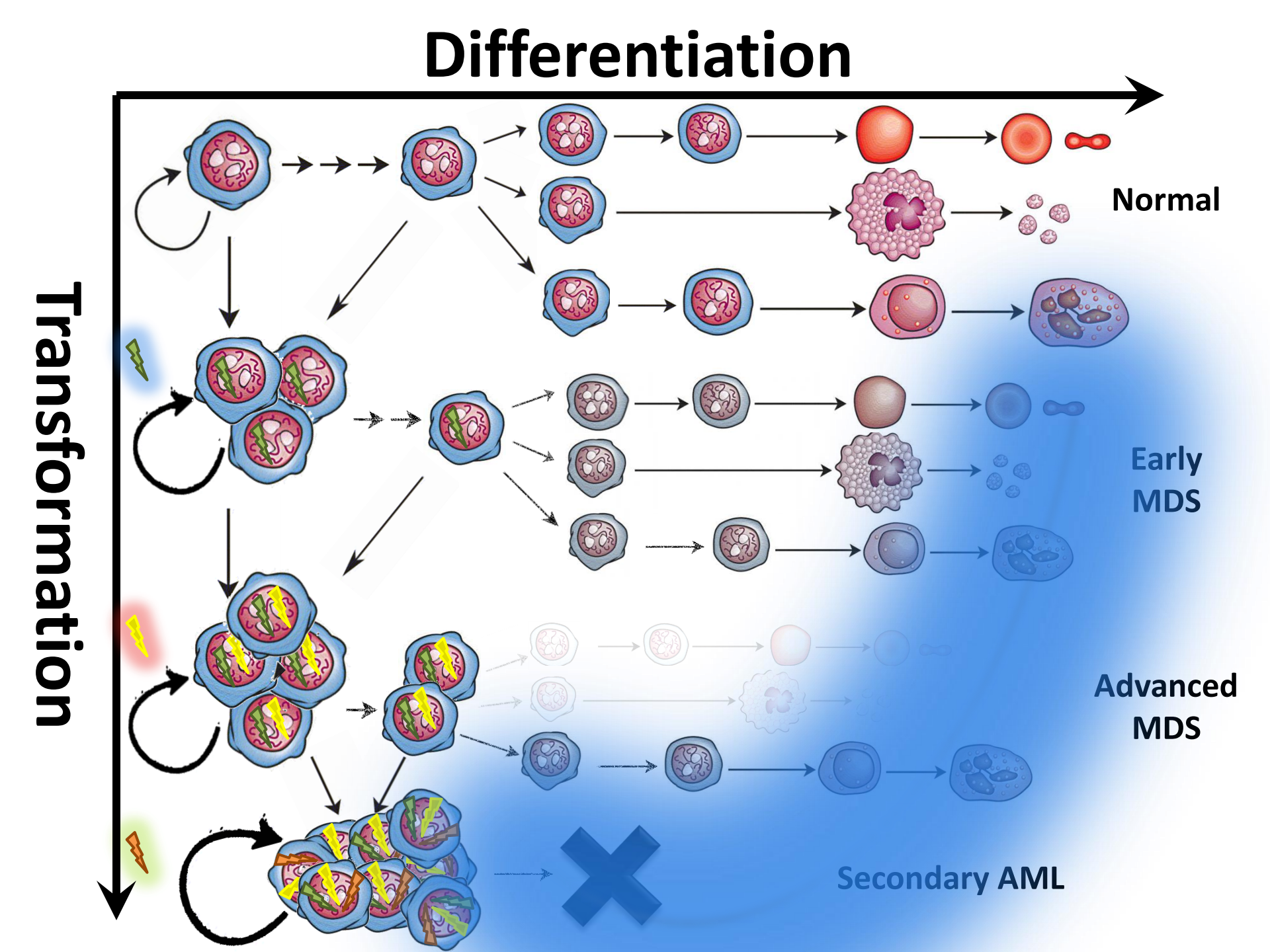
Slide borrowed from Dr. David Steensma

Rollison DE et al Blood 2008;112:45-52.

Etiology of MDS

<5%	10-15%	**85%**
Familial or Congenital	**Topoisomerase II inhibitors** **Ionizing radiation** **DNA alkylating agents**	**"De novo"** (idiopathic, primary)
		
Often early onset and part of a larger syndrome	**Peaks 1-3 or 5-7 years following exposure**	Median age ~71 years; increased risk with **aging**

Slide adapted from Dr. David Steensma


Differentiation
Transformation
Normal
Early MDS
Advanced MDS
Secondary AML

Making the Diagnosis

Minimal Diagnostic Criteria

Cytopenia(s):

- Low hemoglobin, *or*
- Low neutrophil count, *or*
- Low platelet count

MDS "decisive" criteria:

- >10% **dysplastic cells** in 1 or more lineages, *or*
- 5-19% **blasts**, *or*
- Abnormal **karyotype** typical for MDS, *or*
- Specific **mutation** typical of MDS

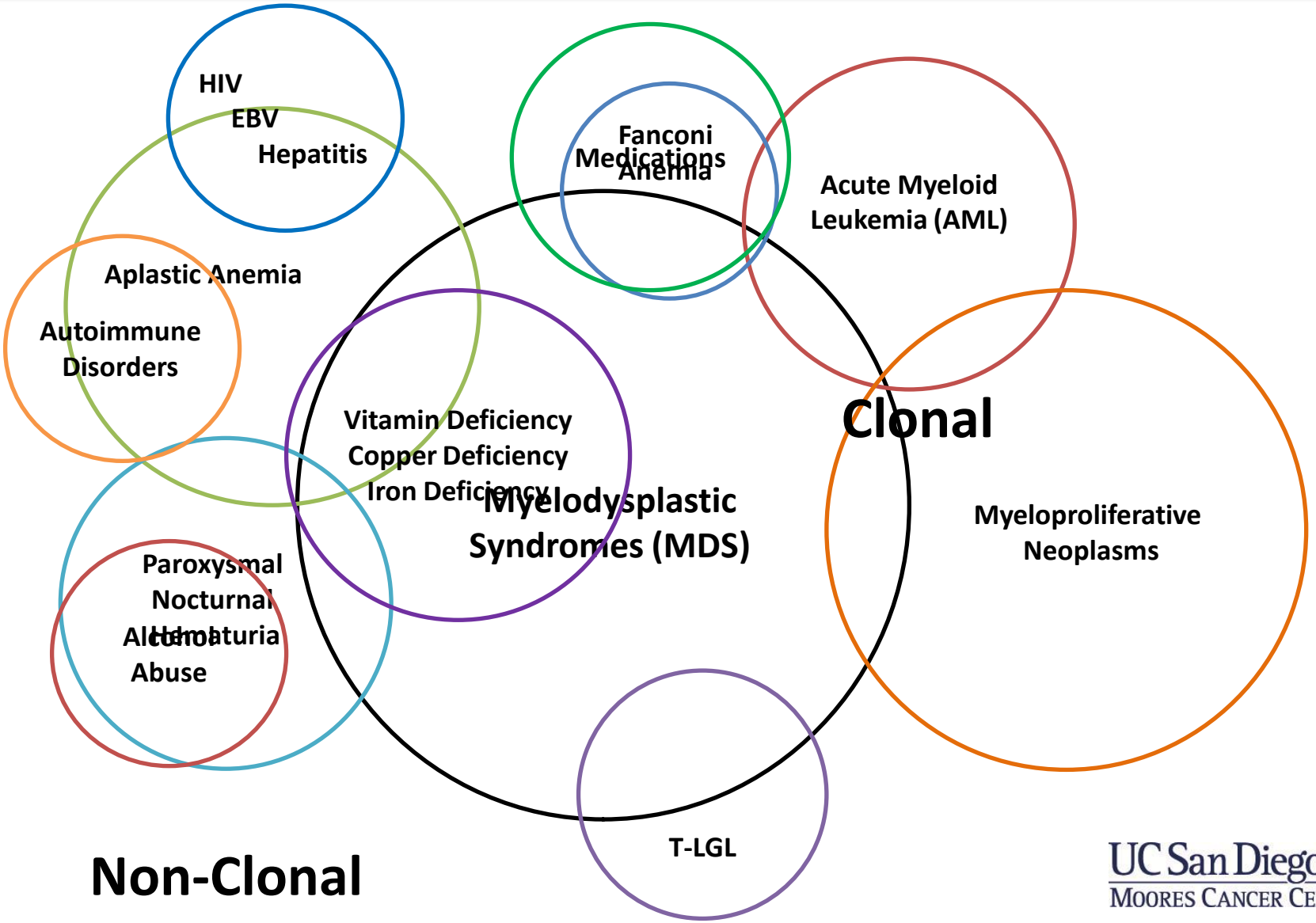
Other causes of cytopenias and morphological changes EXCLUDED:

- *Vitamin B12/folate deficiency*
- *HIV or other viral infection*
- *Copper deficiency*
- *Alcohol abuse*
- *Medications (esp. methotrexate, azathioprine, recent chemotherapy)*
- *Autoimmune conditions (ITP, Felty syndrome, SLE etc.)*
- *Congenital syndromes (Fanconi anemia etc.)*
- *Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)*

Slide borrowed from Dr. David Steensma

Valent P et al *Leuk Res* 2007;31:727-736.

Diagnostic Overlap



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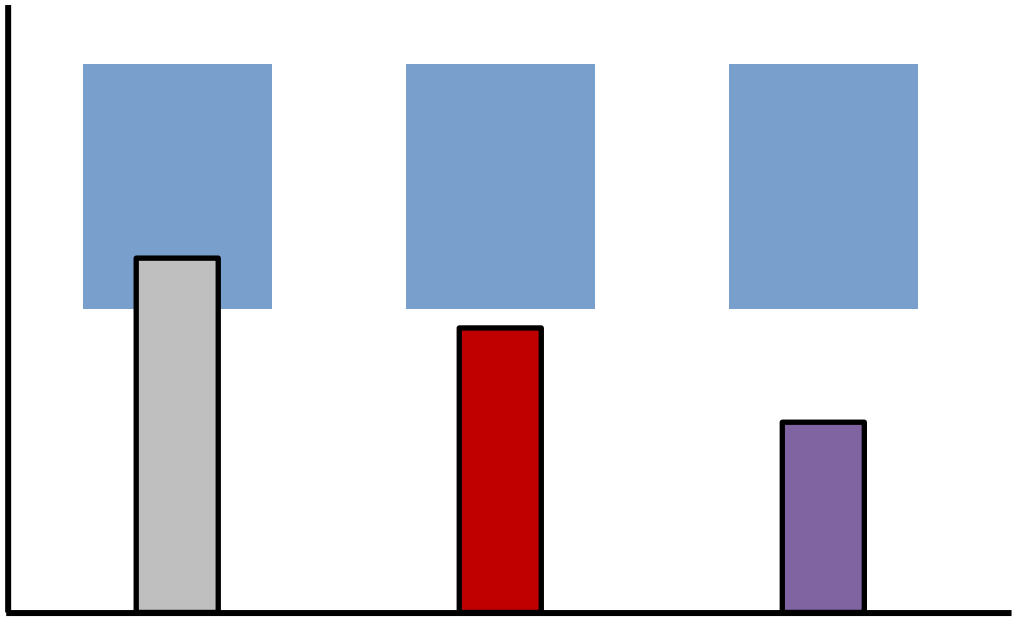
Looking for Answers

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

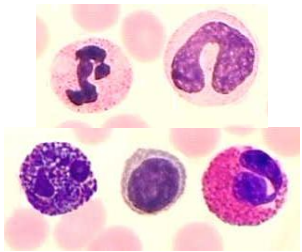


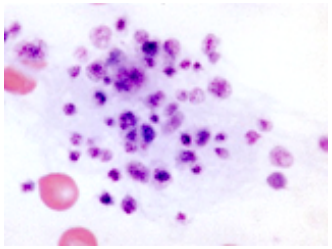
B12 level - Normal
Folate - Normal
Thyroid - Normal

No toxic medications

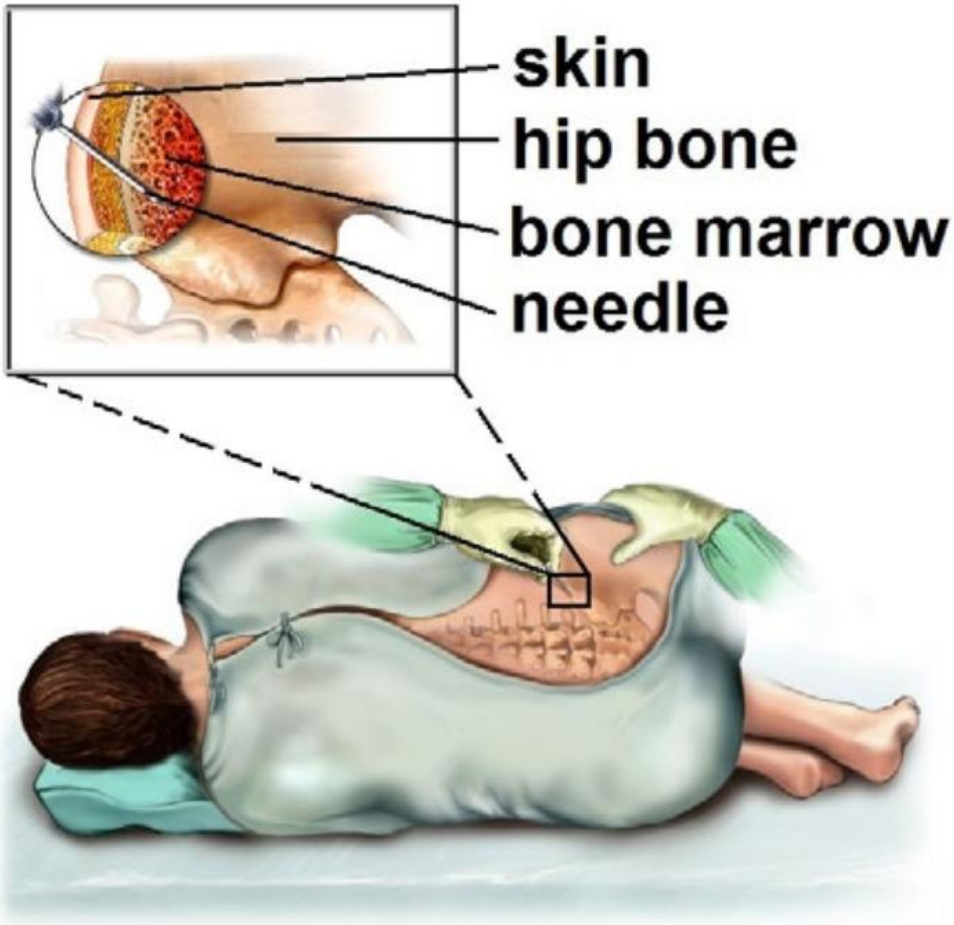
No alcohol use

No chronic illness



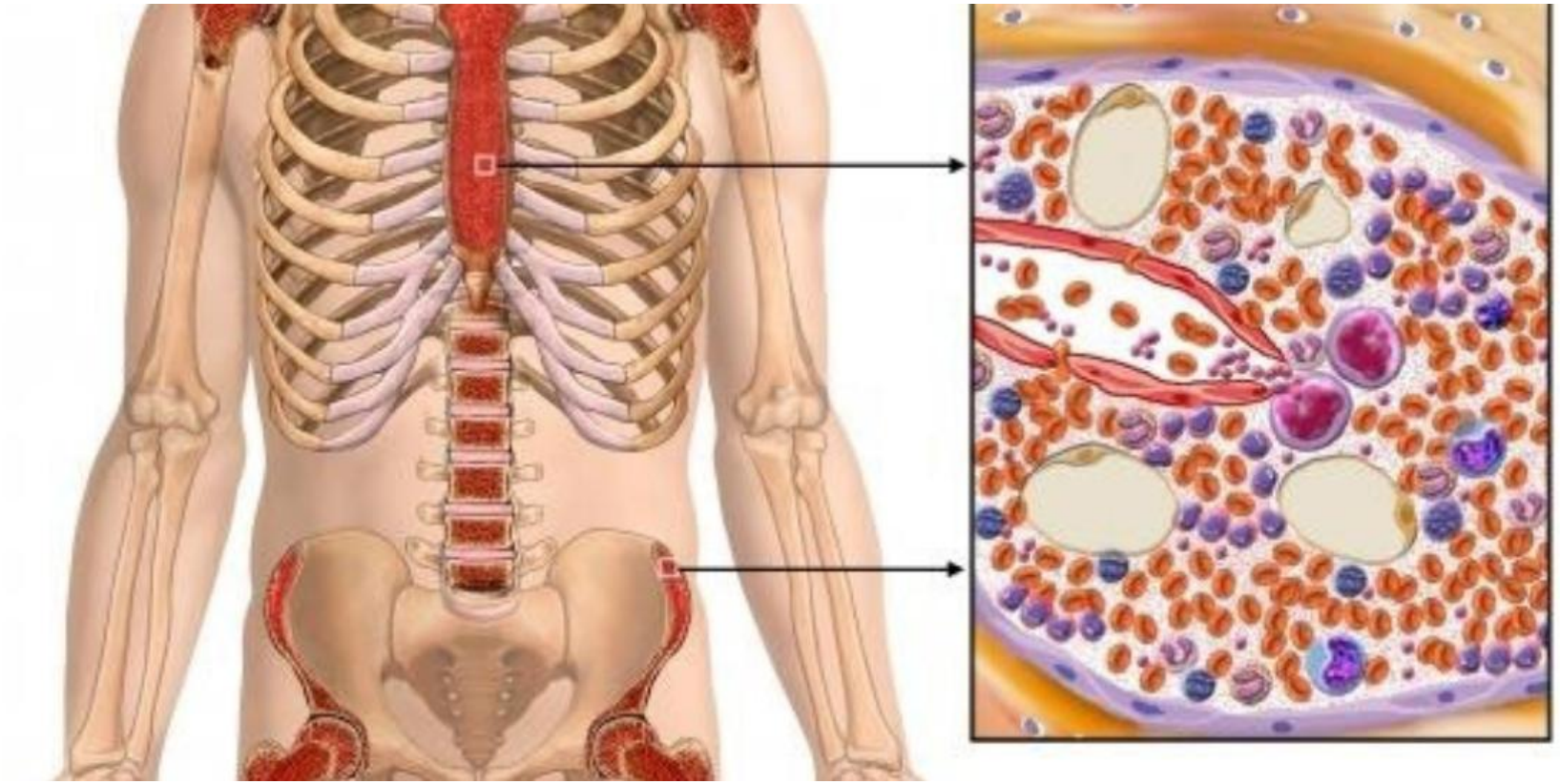


Bone Marrow Biopsy



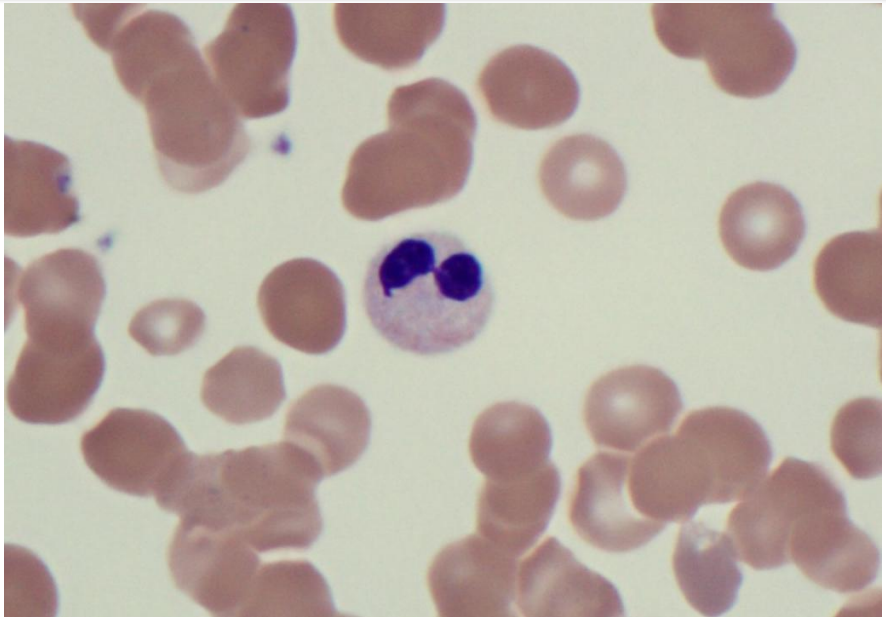
From: NCCN Guidelines for Patients: MDS

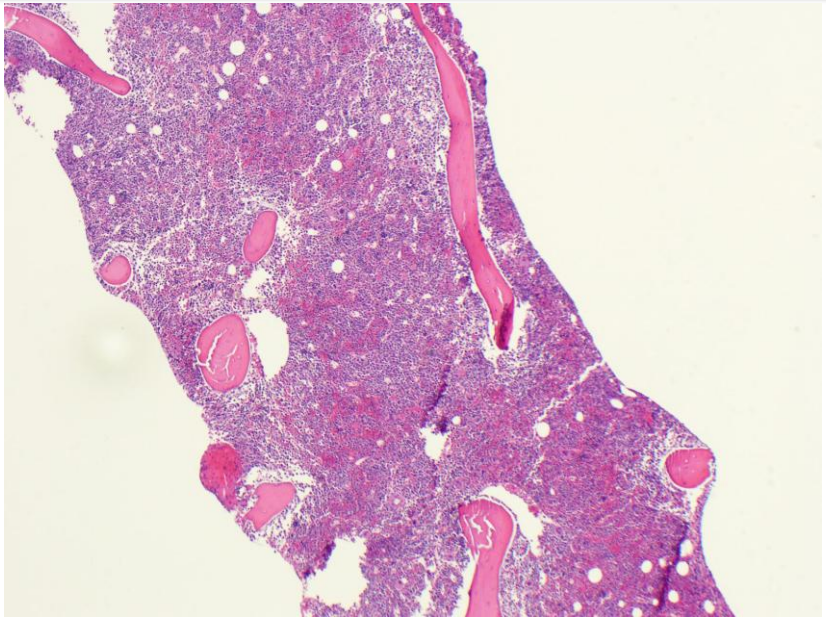
The Bone Marrow

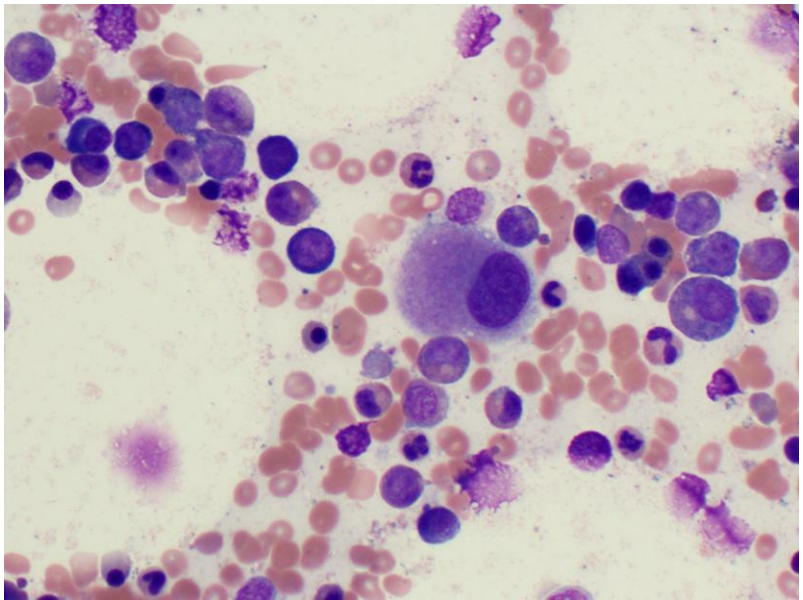


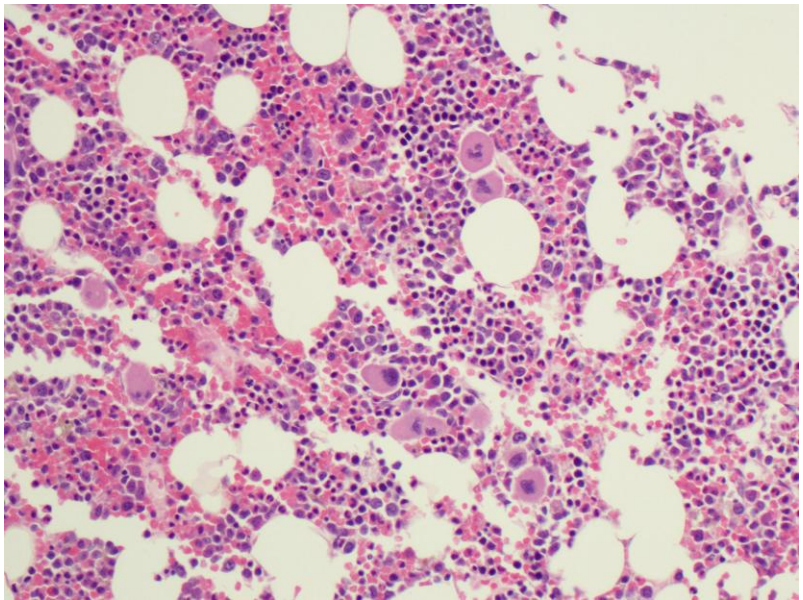
From: NCCN Guidelines for Patients: MDS

Bone Marrow Dysplasia

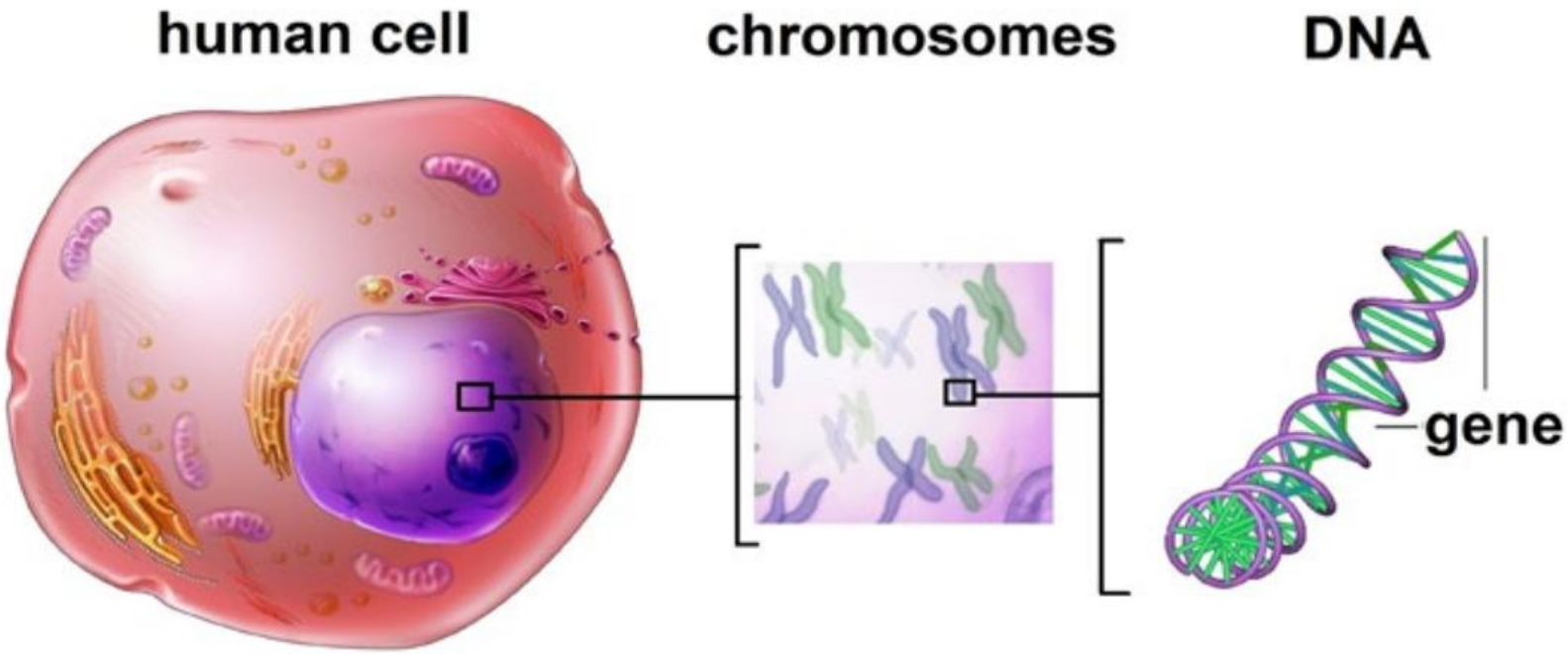








Chromosomes and Mutation Testing



Bone Marrow Biopsy

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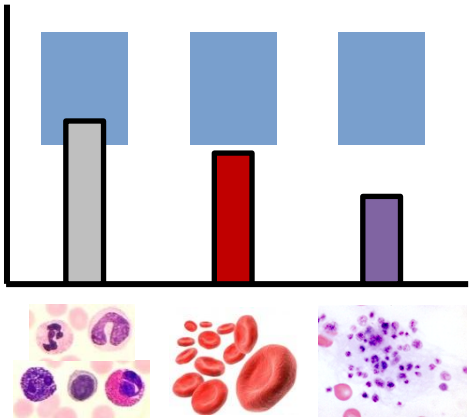
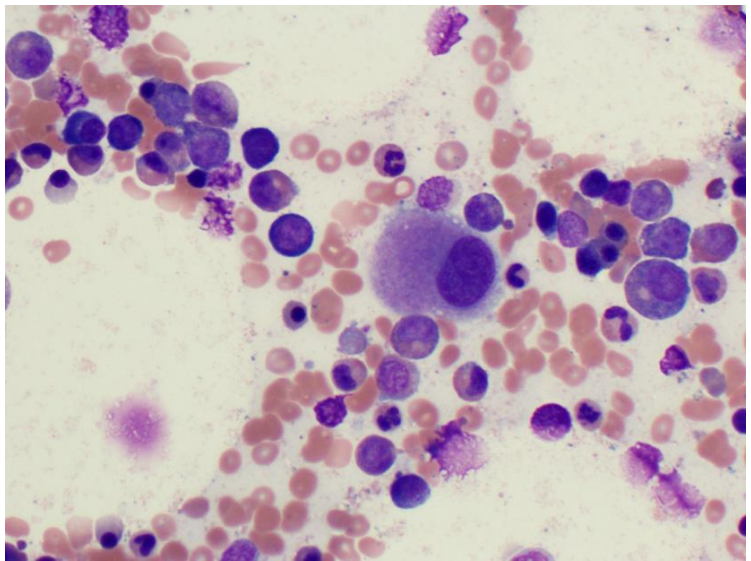


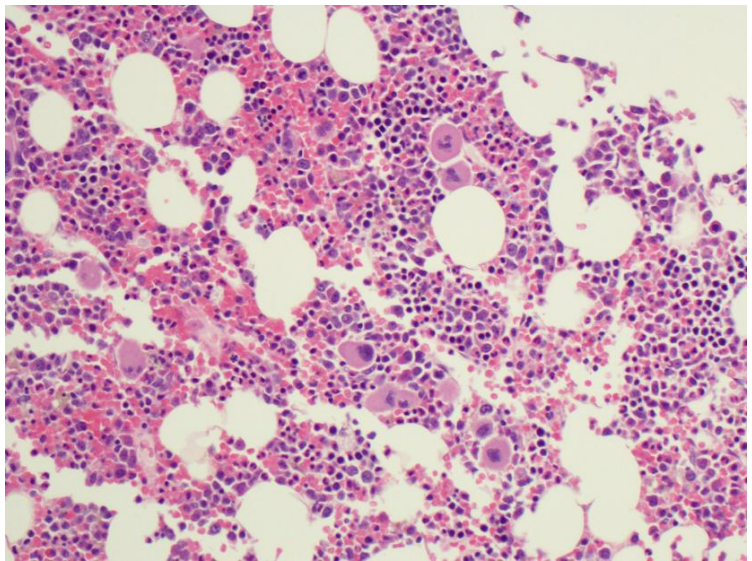
Too many cells in the bone marrow

Developing cells are dysplastic (abnormal)

No extra ‘blasts’ seen

Chromosomes are NORMAL





Classification of MDS Subtypes

World Health Organization MDS categories (2008)

Name	Abbreviation	Blood findings	Bone Marrow findings
Refractory cytopenia with unilineage dysplasia (RCUD)	**Refractory anemia (RA)** **Refractory neutropenia (RN)** **Refractory thrombocytopenia (RT)**	• Unicytopenia; occasionally bicytopenia • No or rare blasts (<1%)	• **Unilineage dysplasia (≥10% of cells in one myeloid lineage)** • <5% blasts • <15% of erythroid precursors are ring sideroblasts
Refractory anemia with ring sideroblasts	**RARS**	• Anemia • No blasts	• **≥15% of erythroid precursors are ring sideroblasts** • Erythroid dysplasia only • <5% blasts
MDS associated with isolated del(5q)	**Del(5q)**	• Anemia • Usually normal or increased platelet count • No or rare blasts (<1%)	• **Isolated 5q31 deletion** • **Normal to increased megakaryocytes with hypolobated nuclei** • <5% blasts • No Auer rods
Refractory cytopenia with multilineage dysplasia	**RCMD**	• Cytopenia(s) • No or rare blasts (<1%) • No Auer rods • <1 x 10^9/L monocytes	• **≥10% of cells in ≥2 myeloid lineages dysplastic** • <5% blasts • No Auer rods • ±15% ring sideroblasts
Refractory anemia with excess blasts, type 1	**RAEB-1**	• Cytopenia(s) • <5% blasts • No Auer rods • <1 x 10^9/L monocytes	• Unilineage or multilineage dysplasia • **5-9% blasts** • No Auer rods
Refractory anemia with excess blasts, type 2	**RAEB-2**	• Cytopenia(s) • 5-19% blasts • ±Auer rods • <1 x 10^9/L monocytes	• Unilineage or multilineage dysplasia • **10-19% blasts** • **±Auer rods**
MDS - unclassified	**MDS-U**	• Cytopenia(s) • ≤1% blasts	• Minimal dysplasia but clonal cytogenetic abnormality considered presumptive evidence of MDS • <5% blasts

Swerdlow SH, Campo E, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th edition. Lyon: IARC Press, 2008, page 89 (Section: Brunning RD et al, "Myelodysplastic syndromes/neoplasms, overview)".

World Health Organization MDS/MPN categories (2008)

Name	Abbreviation	Blood findings	Bone Marrow findings
Refractory anemia with ring sideroblasts and thrombocytosis	**RARS-T**	• Anemia • No blasts • ≥450 x 10^9/L platelets	• **≥15% of erythroid precursors are ring sideroblasts** • Erythroid dysplasia only • <5% blasts • proliferation of large megakaryocytes
Chronic myelomonocytic leukemia, type 1	**CMML-1**	• >1 x 10^9/L monocytes • **<5% blasts**	• Unilineage or multilineage dysplasia • **<10% blasts**
Chronic myelomonocytic leukemia, type 2	**CMML-2**	• >1 x 10^9/L monocytes • **5%-19% blasts or Auer rods**	• Unilineage or multilineage dysplasia • **10%-19% blasts or Auer rods**
Atypical chronic myeloid leukemia	**aCML**	• WBC > 13 x 10^9/L • Neutrophil precursors >10% • <20% blasts	• Hypercellular • <20% blasts • *BCR-ABL1* negative
Juvenile myelomonocytic leukemia	**JMML**	• >1 x 10^9/L monocytes • <20% blasts	• Unilineage or multilineage dysplasia • <20% blasts • *BCR-ABL1* negative
MDS/MPN – unclassified ('Overlap Syndrome')	**MDS/MPN-U**	• Dysplasia with myeloproliferative features • No prior MDS or MPN	• Dysplasia with myeloproliferative features

Swerdlow SH, Campo E, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th edition. Lyon: IARC Press, 2008, page 89 (Section: Brunning RD et al, "Myelodysplastic syndromes/neoplasms, overview)".

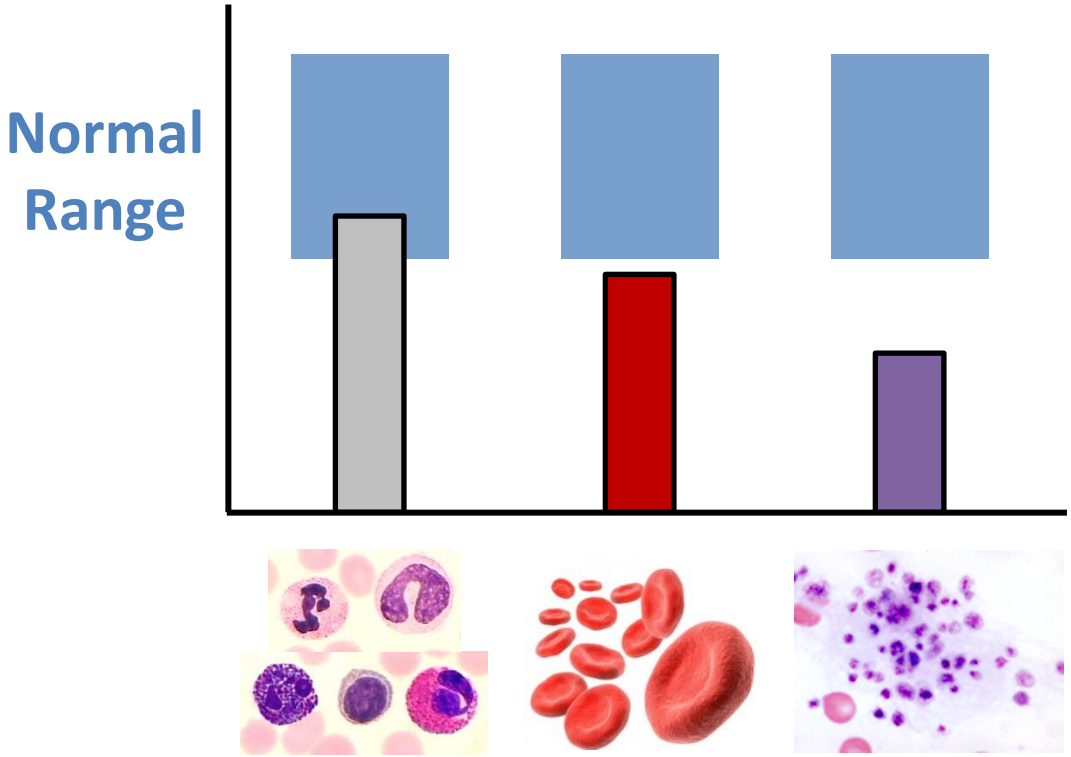
World Health Organization MDS categories (2016)

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

Prognosis & Risk Assessment

MDS Risk Assessment

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.



<u>Diagnosis</u>:

MDS with single lineage dysplasia - **MDS-SLD**

International Prognostic Scoring System

Cytogenetic Risk Group	IPSS Karyotype Abnormalities (7 categories)
Good	Normal, -Y, del(5q), del(20q)
Intermediate	+8, any other single or double abnormality
Poor	Complex with ≥ 3 abnormalities, anomaly of chromosome 7

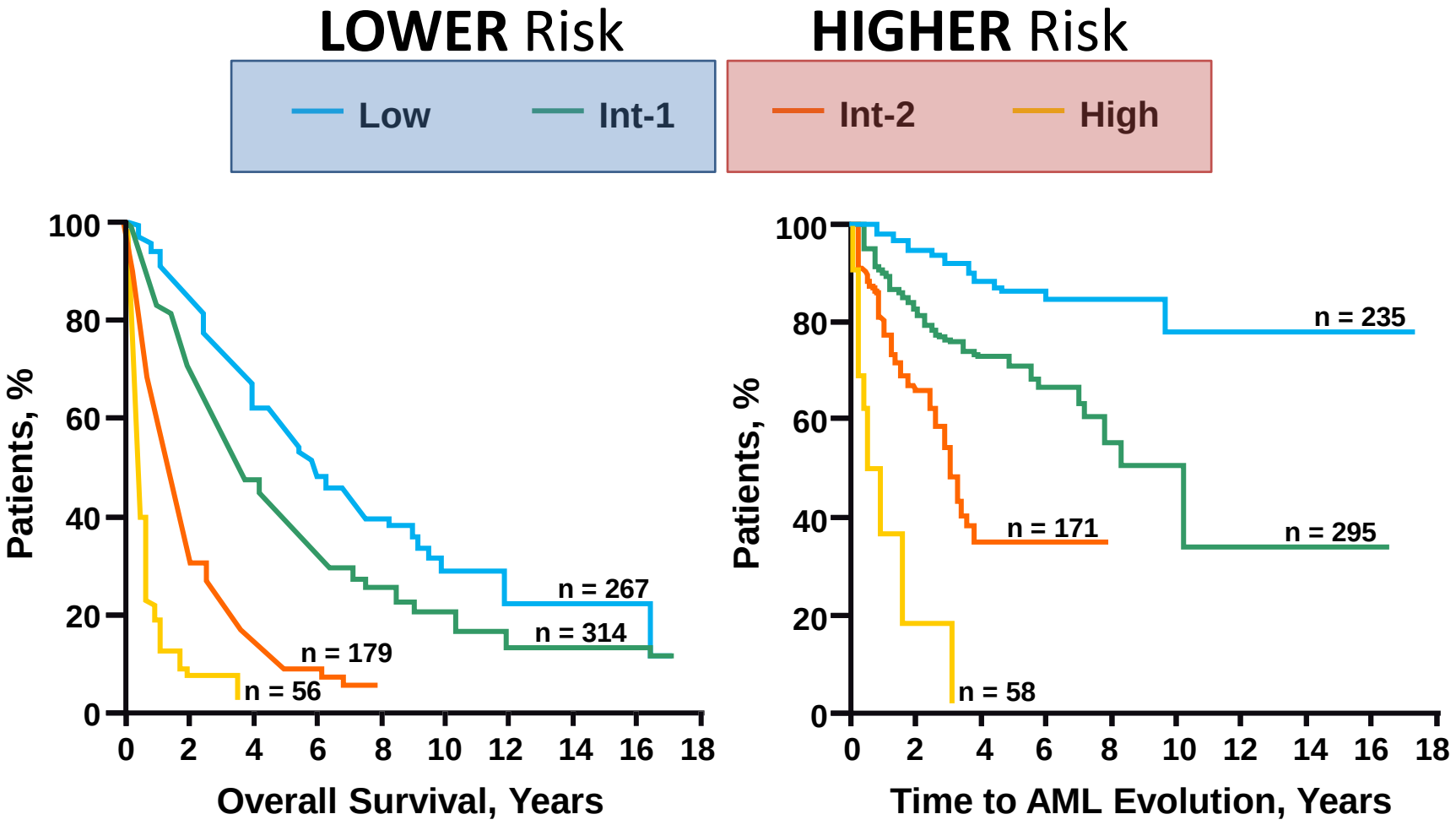
IPSS Parameter	Categories and Associated Scores				
Cytogenetic Risk Group	Good	Intermediate	Poor		
	0	0.5	1		
Bone Marrow Blast %	≤ 5%	5%-10%		11% - 20%	21% - 30%
	0	0.5		1.5	2
Number of Cytopenias	0 or 1	2 or 3			
	0	0.5			

Definition of Cytopenias
Hemoglobin < 10 g/dL
Neutrophil Count < 1.80 x 10^9/L
Platelet Count < 100 x 10^9/L

IPSS Risk Group	Points	% of Patients	Median survival, years	Time to 25% with AML, years
Low	0	33%	5.7	9.4
Intermediate-1	0.5 - 1	38%	3.5	3.3
Intermediate-2	1.5 - 2	22%	1.1	1.1
High	≥ 2.5	7%	0.4	0.2

Greenberg et al. *Blood*. 1997;89:2079-88.

International Prognostic Scoring System



IPSS-Revised (IPSS-R)

Cytogenetic Risk Group	IPSS-R Karyotype Abnormalities (19 categories)
Very good	del(11q), -Y
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities
Very Poor	Complex with > 3 abnormalities

IPSS-R Parameter	Categories and Associated Scores				
Cytogenetic Risk Group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Bone Marrow Blast %	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet Count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Absolute Neutrophil Count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

ipss-r.com

IPSS-R Risk Group	Points	% of Patients	Median survival, years	Time to 25% with AML, years
Very low	≤ 1.5	19%	8.8	Not reached
Low	> 1.5 - 3	38%	5.3	10.8
Intermediate	> 3 - 4.5	20%	3	3.2
High	> 4.5 - 6	13%	1.6	1.4
Very High	> 6	10%	0.8	0.73

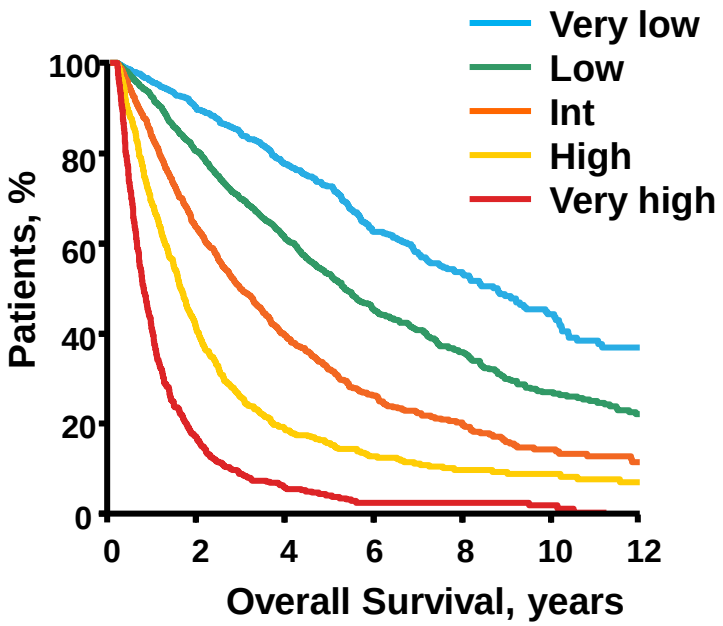
Greenberg et al. *Blood.* 2012:120:2454-65.

Limitations of the IPSS-R

Risk group	Included karyotypes (19 categories)	Median survival, months	Proportion of patients in this group
Very good	del(11q), -Y	60.8	2.9%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	48.6	65.7%
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones	26.1	19.2%
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities	15.8	5.4%
Very poor	Complex with > 3 abnormalities	5.9	6.8%

Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Abs. neutrophil count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤ 1.5	19 %	8.8	Not reached
Low	> 1.5 – 3	38 %	5.3	10.8
Intermediate	> 3 – 4.5	20 %	3.0	3.2
High	> 4.5 – 6	13 %	1.6	1.4
Very High	> 6	10 %	0.8	0.73



- Considers only UNTREATED patients
- IPSS-R does not consider somatic mutations
- Somatic mutations are common in MDS
- Several mutated genes have prognostic significance independent of the IPSS-R

MDS Risk Assessment

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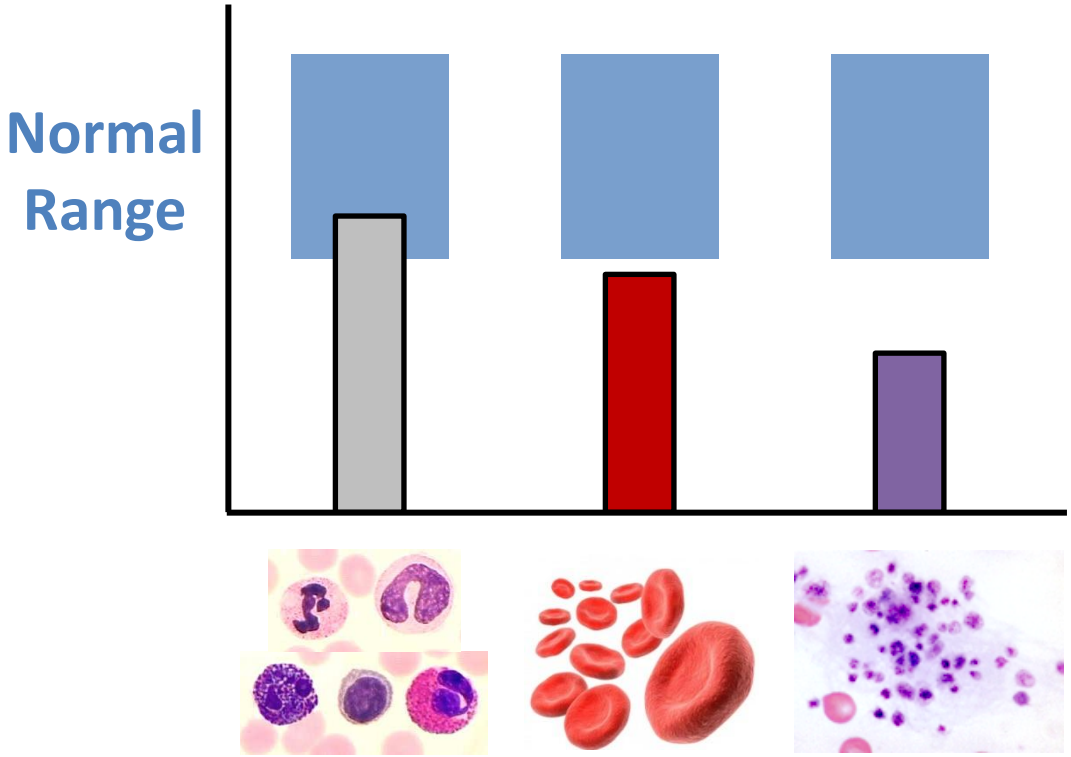


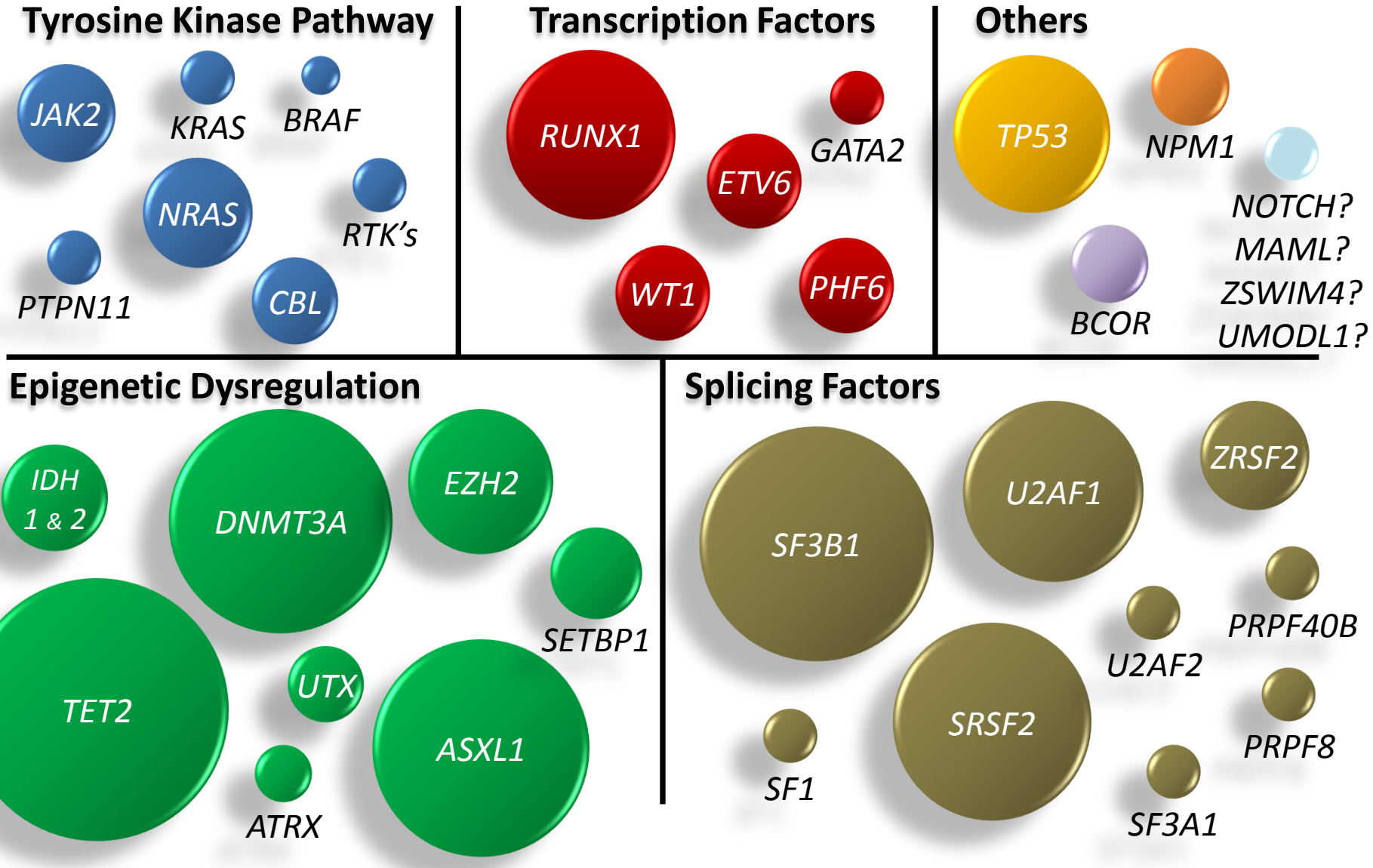
<u>Diagnosis</u>:

MDS with single lineage dysplasia - **MDS-SLD**

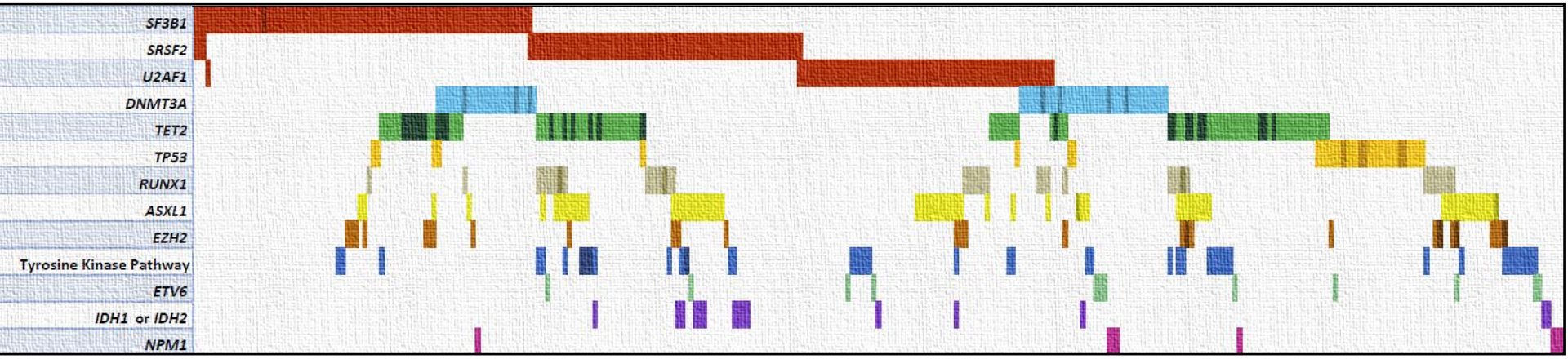
WPSS - Very Low Risk
IPSS - Low Risk
IPSS-R- Very Low Risk

Mutations?

Gene Mutations in MDS



MDS Mutation Profiles



30% of MDS patients have a mutation in one of these genes

These mutations indicate more severe disease!

Bejar et al. *NEJM*. 2011;**364**:2496-506.

Bejar et al. *JCO*. 2012;**30**:3376-82.

Impact of Mutations by IPSS Group

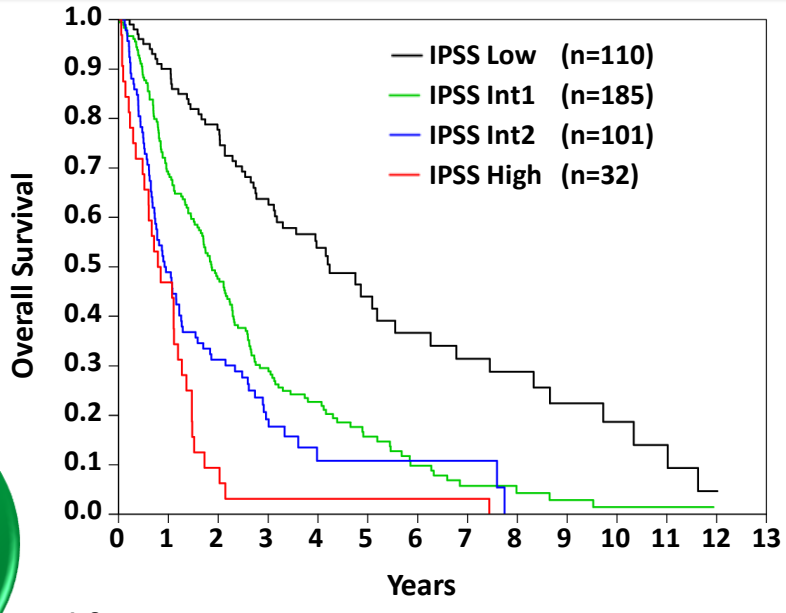
TP53

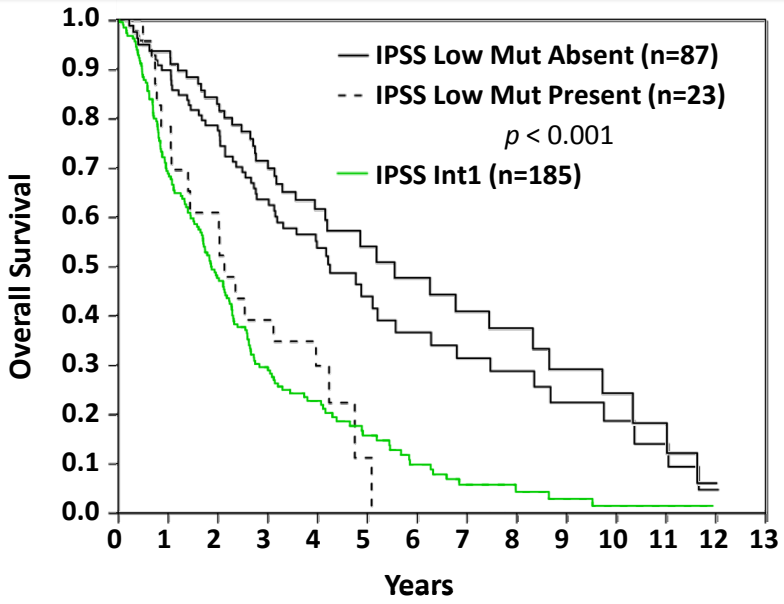
ETV6

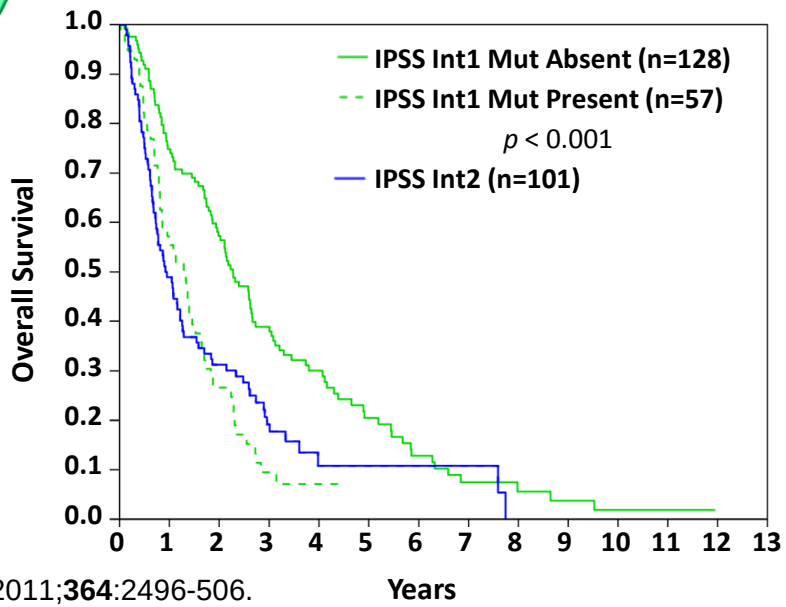
ASXL1

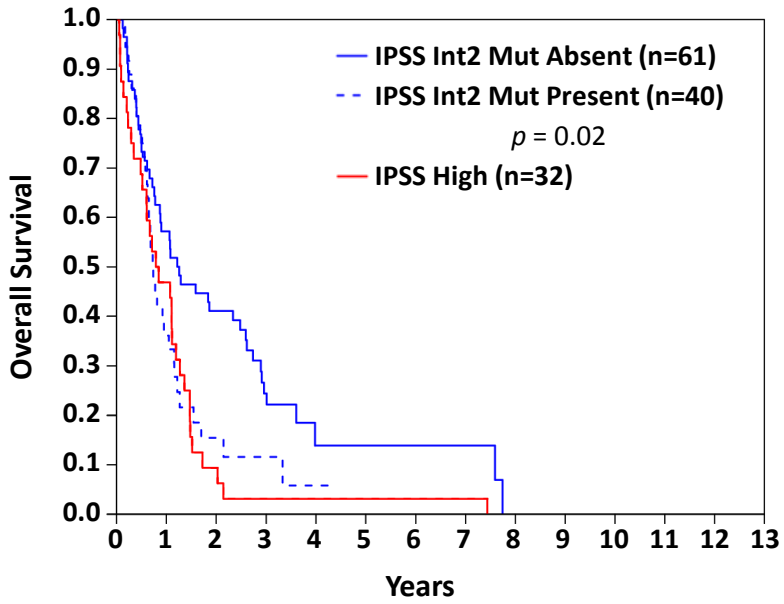
EZH2

RUNX1









Bejar et al. *NEJM*. 2011;**364**:2496-506.

Impact of Mutations by IPSS-R Group

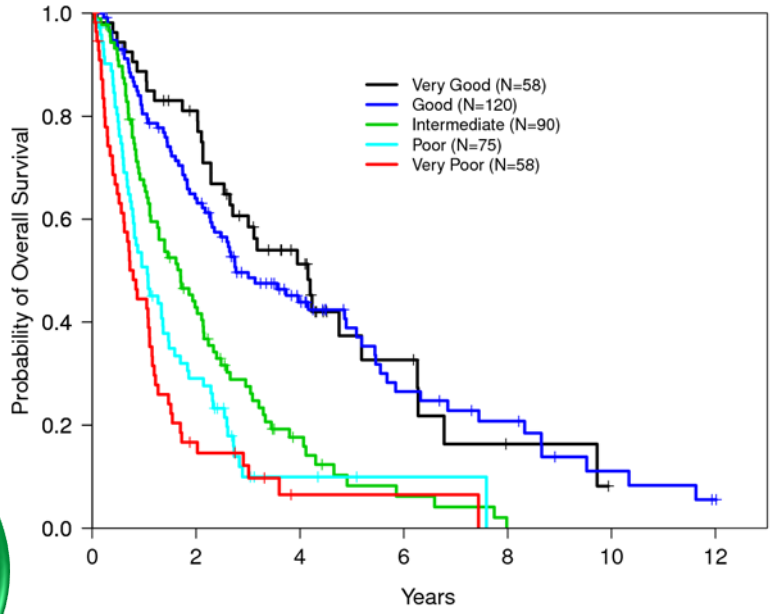
TP53

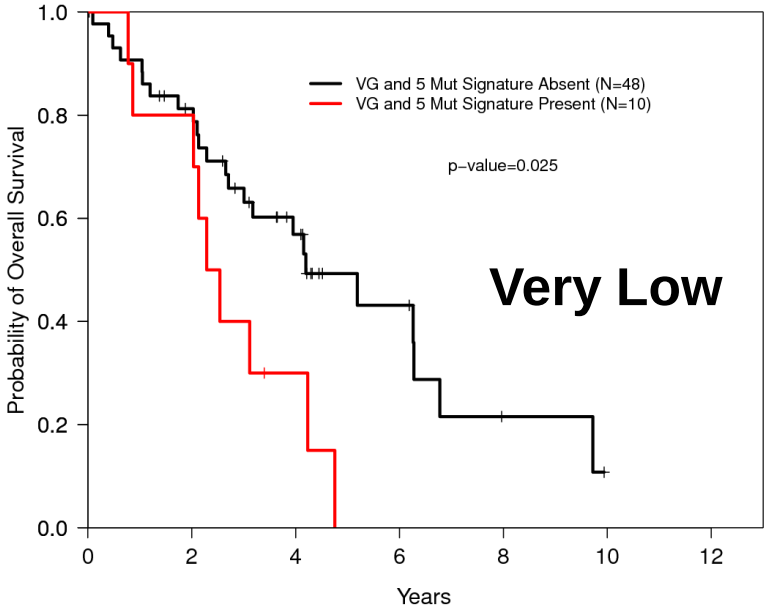
ETV6

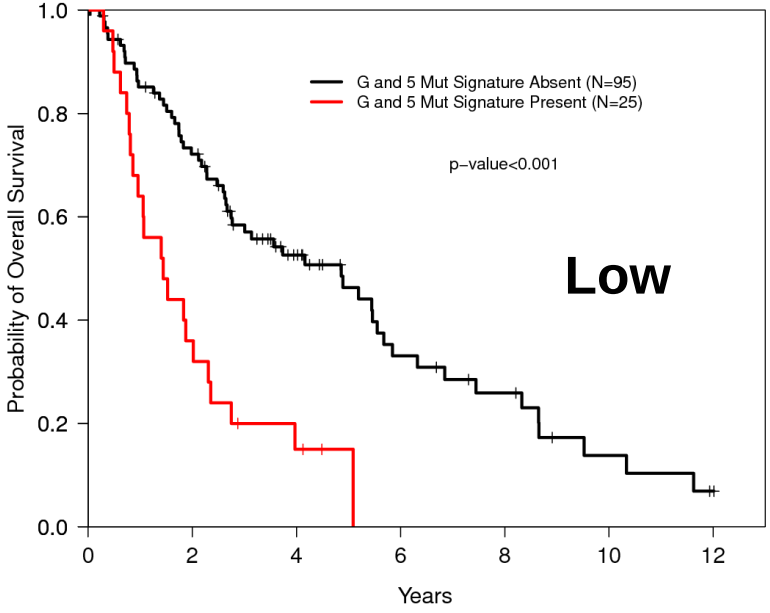
ASXL1

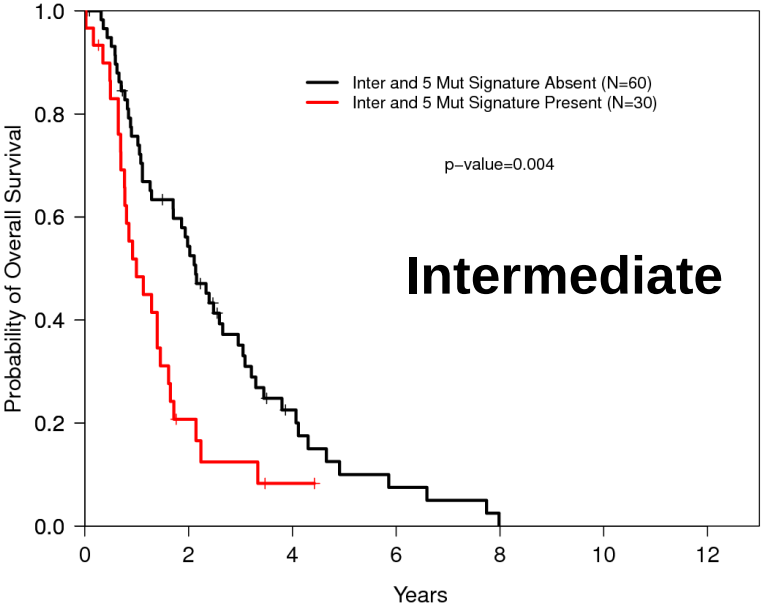
EZH2

RUNX1

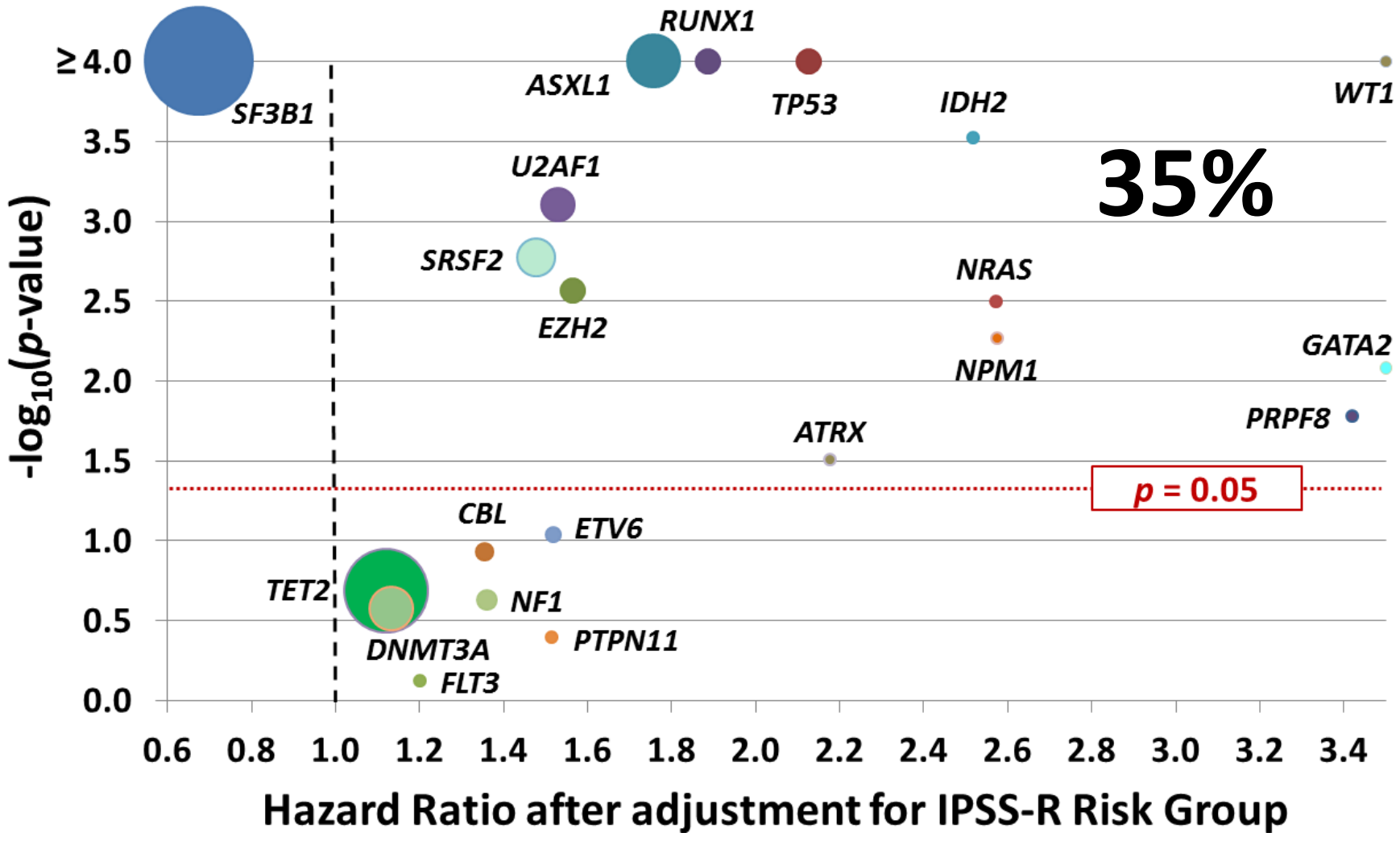




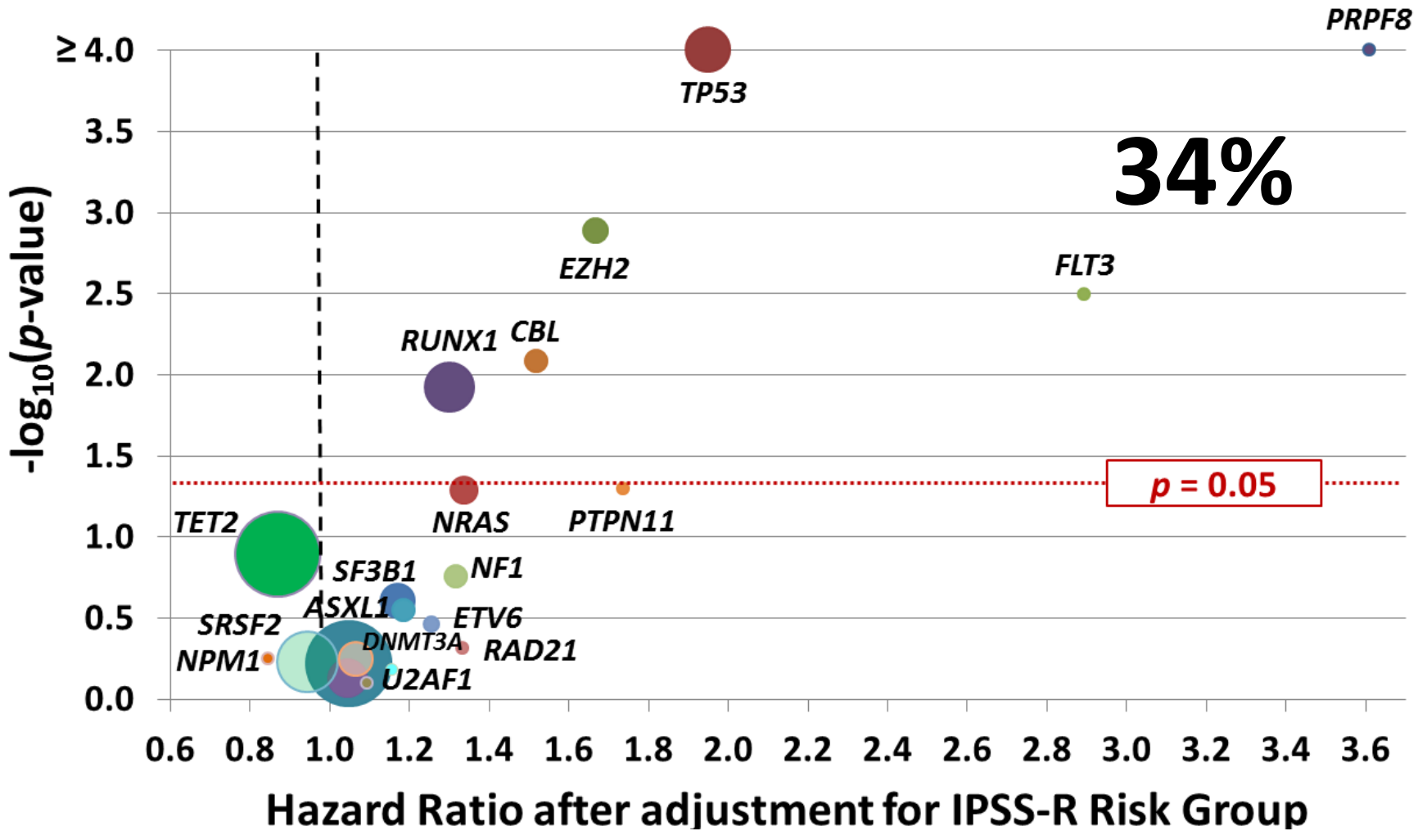




Prognostic Mutations by Blast % (<5%)



Prognostic Mutations by Blast % (5-30%)



Clinical Sequencing and Banking

Targeted Massively Parallel Sequencing

Epigenetic Regulator	Splicing Factor	Transcription Factor	Kinase Signalling	Other
ASXL1	*LUC7L2*	*CEBPA*	***BRAF***	*CDH11*
ATRX	*PRPF40B*	*ETV6*	***CBL***	*CUL1*
BAP1	*PRPF8*	*GATA2*	***CBLB***	*CUX1*
BCOR	*SF1*	***MLL***	***FLT3***	*FMN2*
BCORL1	*SF3A1*	*PHF6*	***JAK2***	***GNAS***
DNMT3A	***SF3B1***	*RUNX1*	***KIT***	*MYBL2*
EED	***SRSF2***	*TP53*	***KRAS***	***NPM1***
EZH2	***U2AF1***	*WT1*	***MPL***	*RAD21*
IDH1	*U2AF2*		*NF1*	*UMODL1*
IDH2	*ZRSR2*		***NRAS***	*ZSWIM4*
JARID2			*PTEN*	
SETBP1			*PTPN11*	
SUZ12			*SH2B3*	
TET2				

Clinical Information

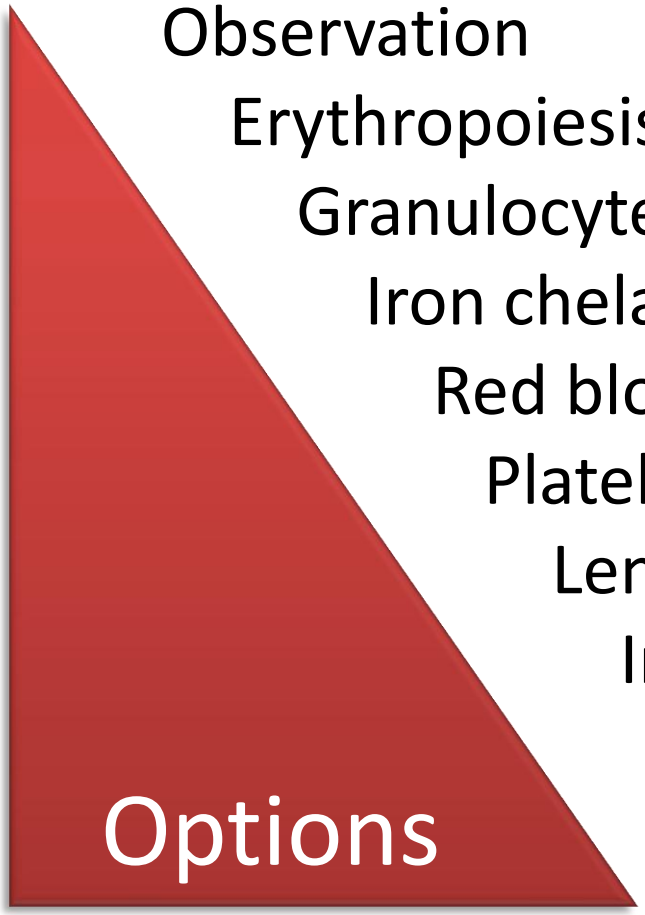
Viable Cells
Tumor DNA/RNA
Germline DNA

Biorepository

Extensive
Genotypic
Annotation

Risk Adapted Patient Specific Therapy

Treatment Options for MDS



Observation

Erythropoiesis stimulating agents

Granulocyte colony stimulating factor

Iron chelation

Red blood cell transfusion

Platelet transfusion

Lenalidomide

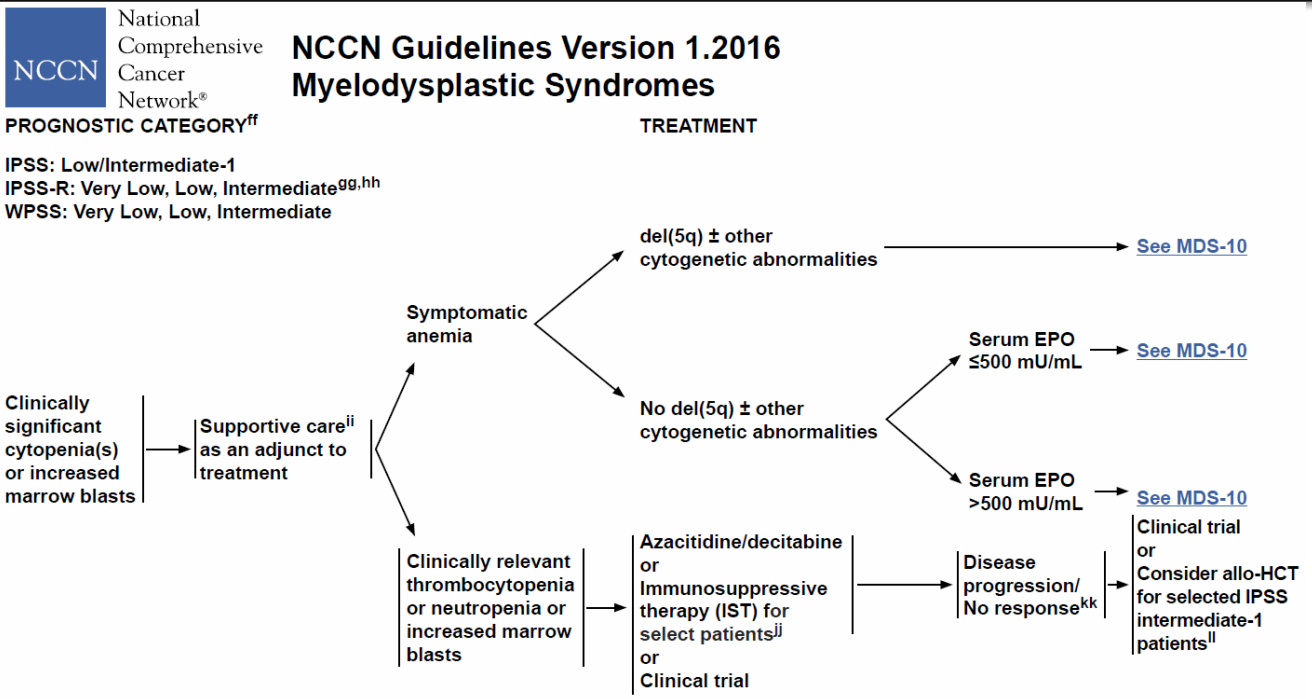
Immune Suppression

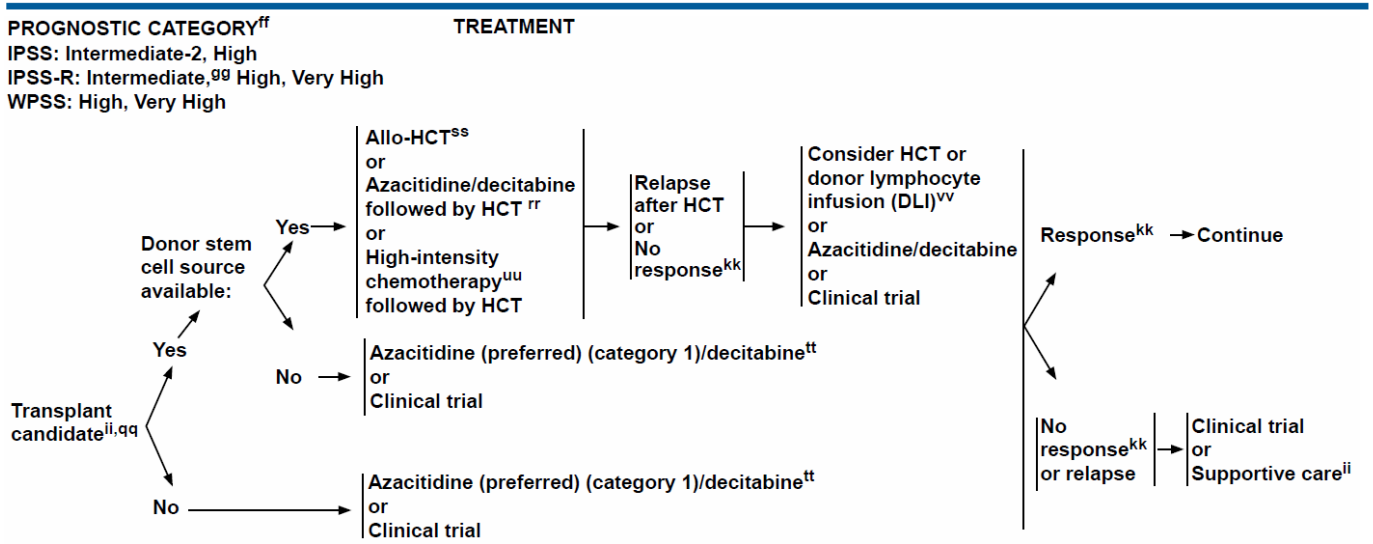
Hypomethylating agent

Stem cell transplantation

Clinical Trials – always the best option

MDS Treatment is Highly Risk Stratified





Lower Risk

- Observation
- EPO
- Lenalidomide
- Immune suppression
- Iron Chelation

Higher Risk

- Azacitidine
- Decitabine
- Allo-HSCT
- Clinical Trials

Treating Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

1. Do I need to treat at all?

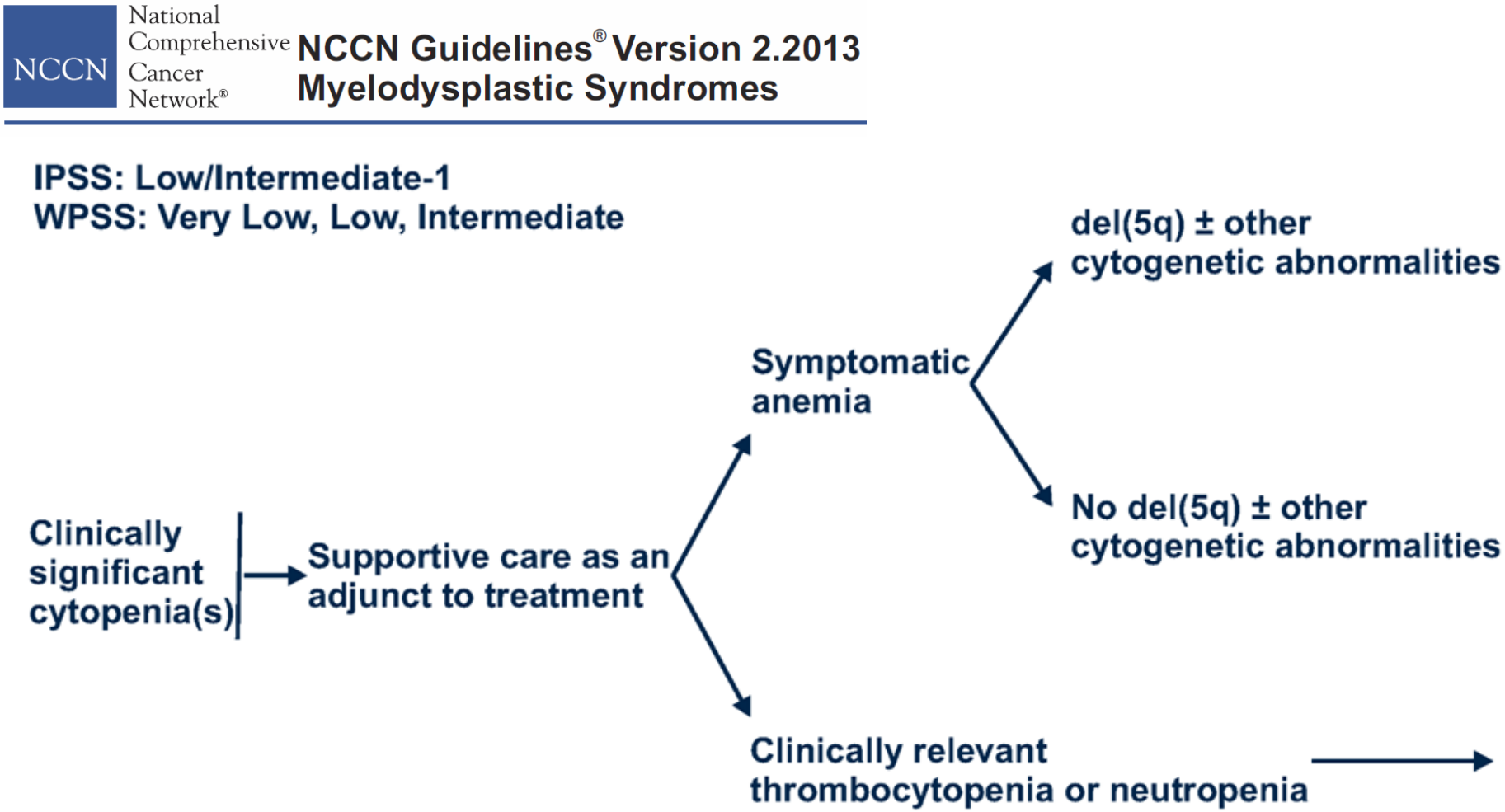
    - No advantage to early aggressive treatment
    - Observation is often the best approach

2. Are transfusions treatment?

    - No! They are a sign that treatment is needed.

Guidelines for Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**



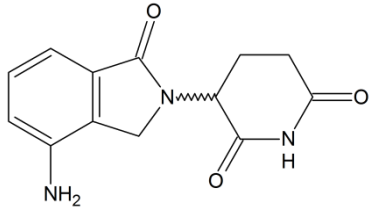
Treating Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

What if treatment is needed?

1. Is my most effective therapy likely to work?

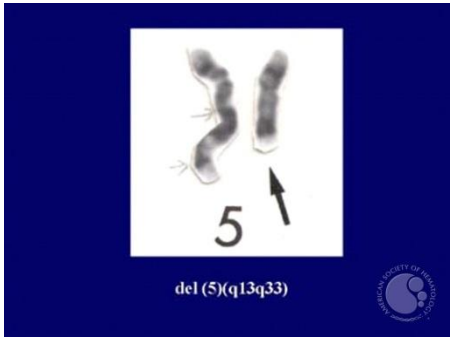
   - Lenalidomide (Revlimid)



In del(5q) – response rates are high

50%-70% respond to treatment

Median 2-years transfusion free!



Treating Lower Risk MDS

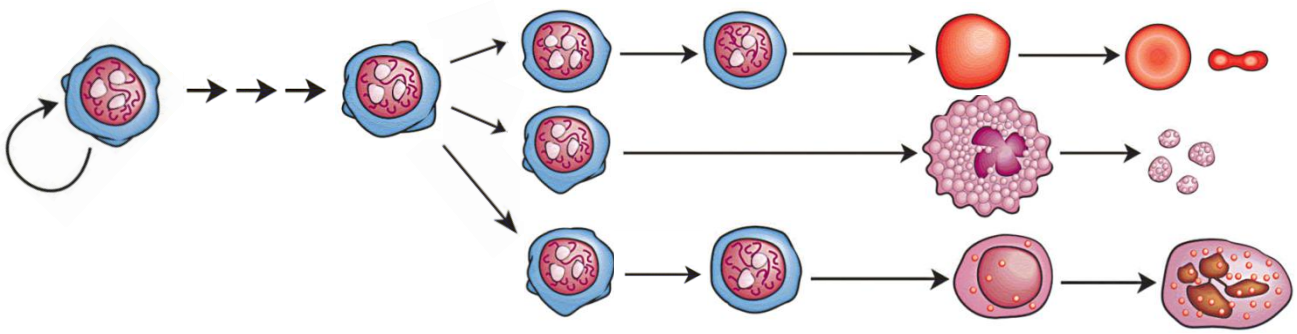
Primary Goal: to improve **QUALITY OF LIFE**

Is my second most effective therapy likely to work?

- Red blood cell growth factors
- Erythropoiesis Stimulating Agents (ESAs)
- Darbepoetin alfa (Aranesp)
- Epoetin alfa (Procrit, Epogen)
- Lance Armstrong Juice → **EPO**

Erythropoiesis Stimulating Agents

Primary Goal: to improve **QUALITY OF LIFE**



ESAs

TPO mimetics

G-CSF (neupogen)

ESAs – act like our own erythropoietin

Serum EPO level (U/L)	RBC transfusion requirement
<100 = *+2 pts*	<2 Units / month = *+2 pts*
100-500 = *+1 pt*	≥2 Units / month = *-2 pts*
>500 = *-3 pts*	

Total Score	Response Rate
High likelihood of response: > +1	**74%** (n=34)
Intermediate likelihood: -1 to +1	**23%** (n=31)
Low likelihood of response: < -1	**7%** (n=39)

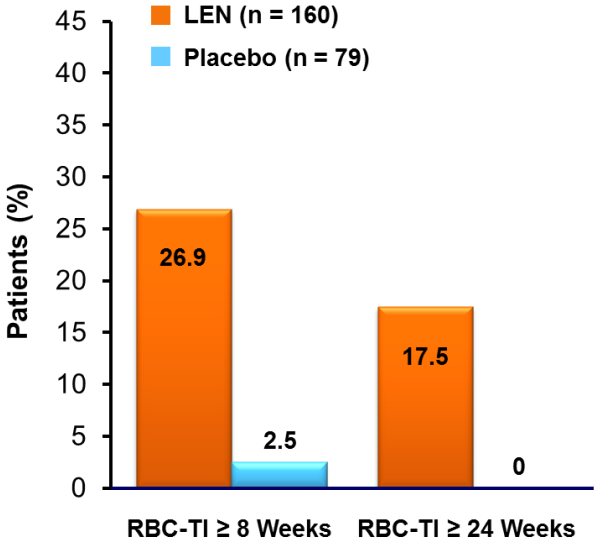
Hellstrom-Lindberg E et al *Br J Haem* 2003; 120:1037

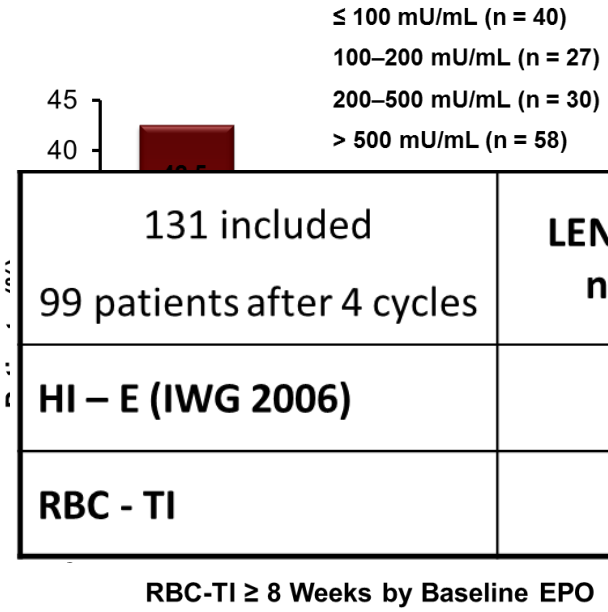
Treating Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

Is a combination of LEN +/- ESA likely to work?

In non-del(5q) MDS patients:





131 included 99 patients after 4 cycles	LEN + EPO n = 50	LEN n = 49	
HI – E (IWG 2006)	52%	30.6%	*P*= 0.03
RBC - TI	32%	18.4%	*P*= 0.12

Santini V, et al. J Clin Oncol. 2016;34:2988-2996.

Toma et al, Leukemia. 2016 Apr;30(4):897-905

Treating Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

What my next most effective therapy?

- Immunosuppression

Some MDS patients have features of aplastic anemia

- Hypoplastic bone marrow (too few cells)
- PNH clones
- Certain immune receptor types (HLA-DR15)

Immune Suppression for MDS

Primary Goal: to improve **QUALITY OF LIFE**

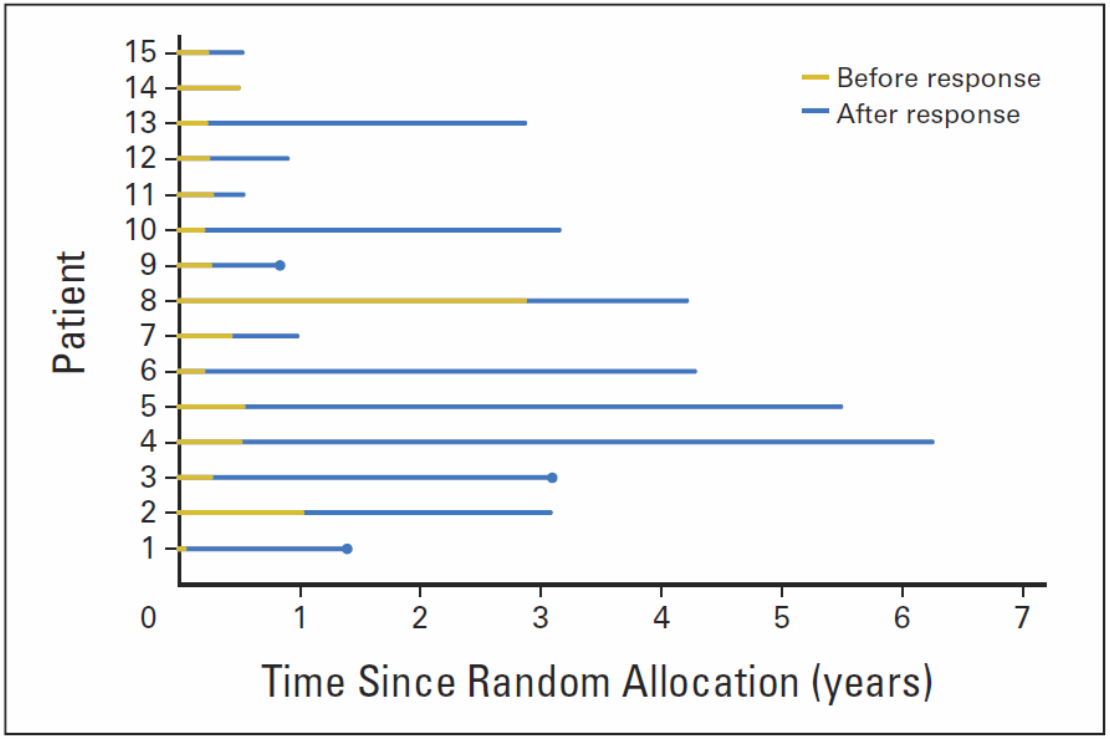
Swiss/German Phase III RCT of ATG + Cyclosporin (88 patients)

Mostly men with Lower Risk MDS

CR+PR: 29% vs. 9%

No effect on survival

Predictors of Response:
- hypocellular aspirate
- lower aspirate blast %
- younger age
- more recent diagnosis



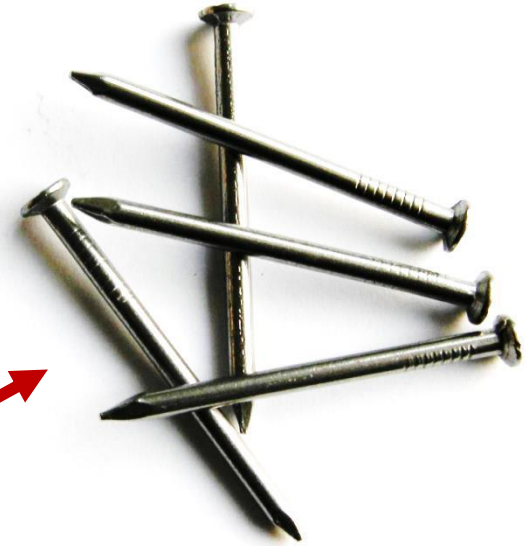
Passweg, J. R., A. A. N. Giagounidis, et al. (2011). *JCO* **29**(3): 303-309.

Iron Balance and Transfusions

Daily intake

1.5 mg (0.04%)

Tightly regulated



3-4 grams of Iron in the body

Daily losses only

1.5 mg (0.04%)

Not regulated!

Every three units of blood

What About Iron Chelation?

More transfusions and elevated ferritin levels are associated with poor outcomes in MDS patients.

Are these drivers of prognosis or just reflective of disease?

Retrospective studies suggest survival advantage!

small prospective and large population based Medicare studies show survival benefit, INCLUDING hematologic responses (11-19%).

I consider treatment in lower risk, transfusion dependent patients with long life expectancy after 20+ transfusions.

Zeidan et al. ASH Meeting. 2012. Abstract #426.

Nolte et al. Ann Hematol. 2013. 92(2):191-8.

How to Chelate Iron

Three ways are FDA approved:

- Deferoxamine (Desferal) – subcutaneous pump 8-12 hrs/day
- Deferasirox (Exjade/Jadenu) – powder/pill – once per day
- Deferiprone (Ferriprox) – oral pill form – 3x per day

But side effects and adverse events can be significant!

Deferasirox – renal, hepatic failure and GI bleeding

Deferiprone – agranulocytosis (no neutrophils!)

Guidelines for Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

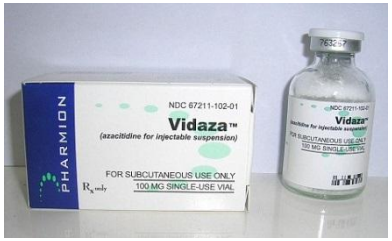
1. Do I need to treat? - symptomatic cytopenias
2. Is LEN likely to work? - del(5q) or after ESA
3. Are ESA likely to work? - Serum EPO < 500
4. Is IST likely to work? - hypocellular, DR15, PNH
5. Think about iron! - 20 or more transfusions
6. Consider AZA/DEC
7. Consider HSCT or clinical trial!

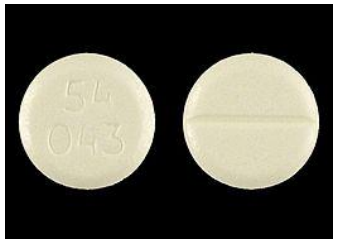
Novel Treatments for Lower Risk MDS

Oral Azacitidine

Oral Azacitidine – in Phase III clinical trials

- more convenient
- similar response rates
- more GI side effects



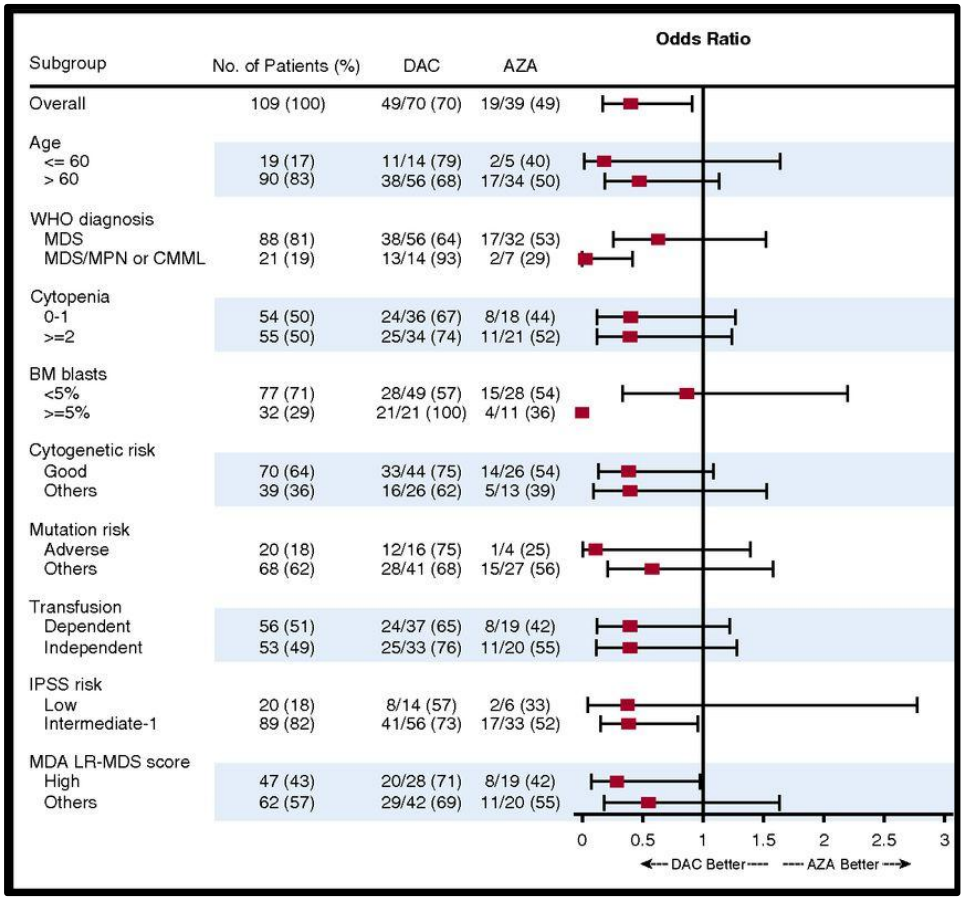


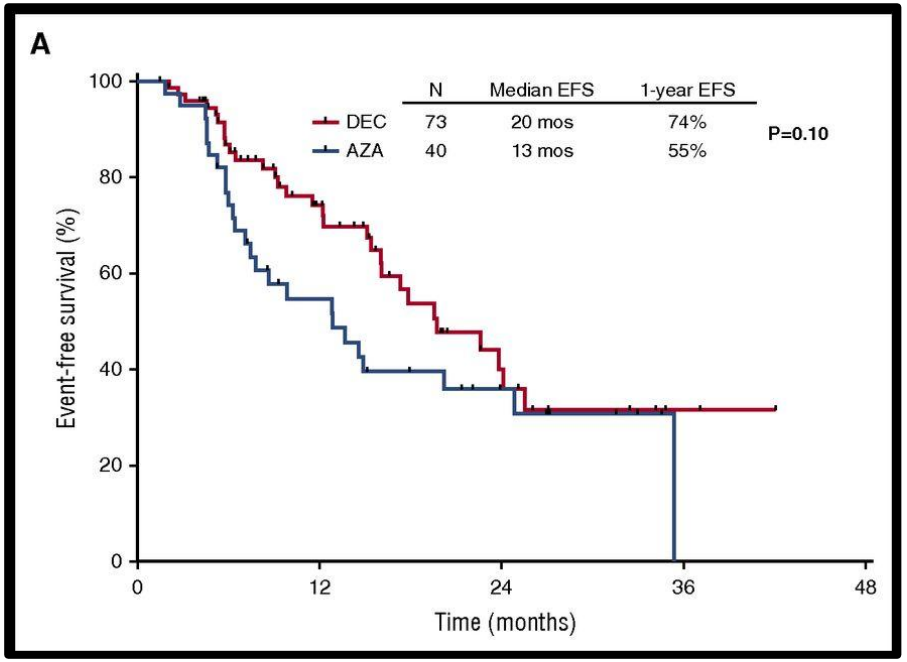
May be more effective as it can be taken longer

Low Dose Azacitidine/Decitabine

Decitabine 20 mg/m2 intravenously daily for 3 days - 60% dose - 70% ORR

Azacitidine 75 mg/m2 intravenously daily for 3 days - 43% dose - 49% ORR

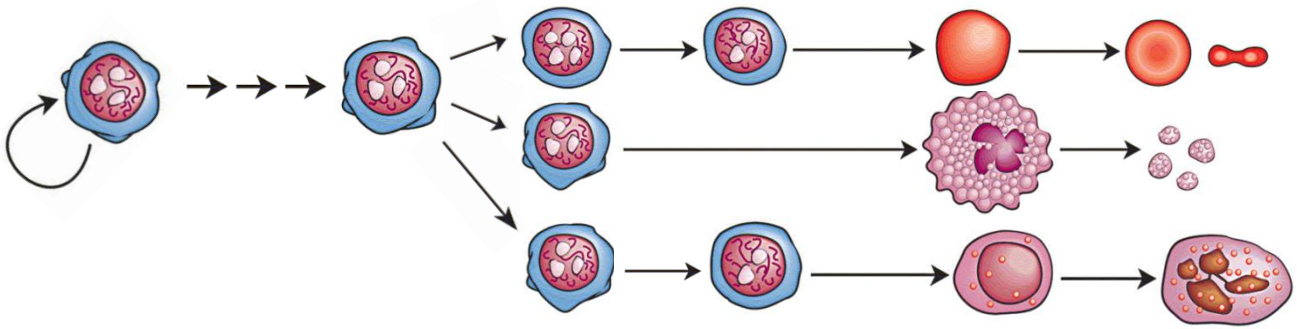




Jabbour et al., *Blood* 2017 130:1514-1522.

Platelet Growth Factors

Eltrombopag or Romiplostim - TPO mimetics



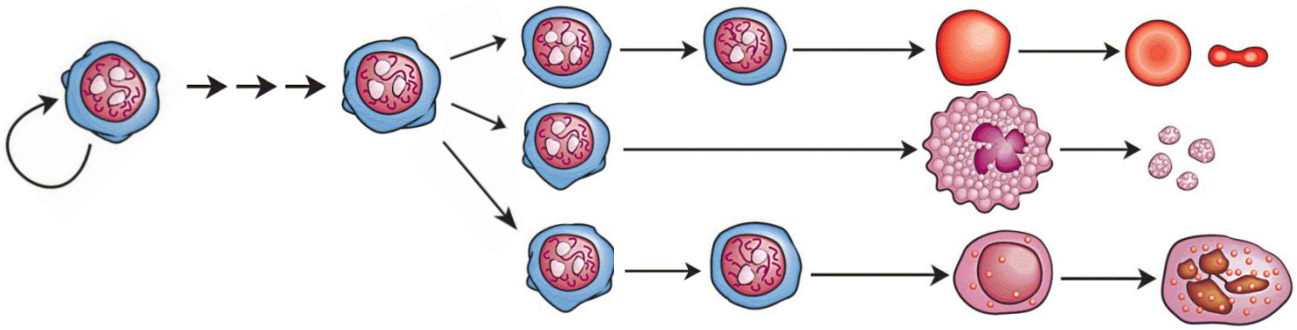
Eltrombopag and Romiplostim - approved, but not in MDS

Initial concern about increasing blasts and risk of AML

Follow-up suggests Romiplostim safe in lower risk patients

Mittleman M et al *ASH Abstracts*, 2013. Abstract #3822 Kantarjian H et al *ASH Abstracts*, 2013. Abstract #421

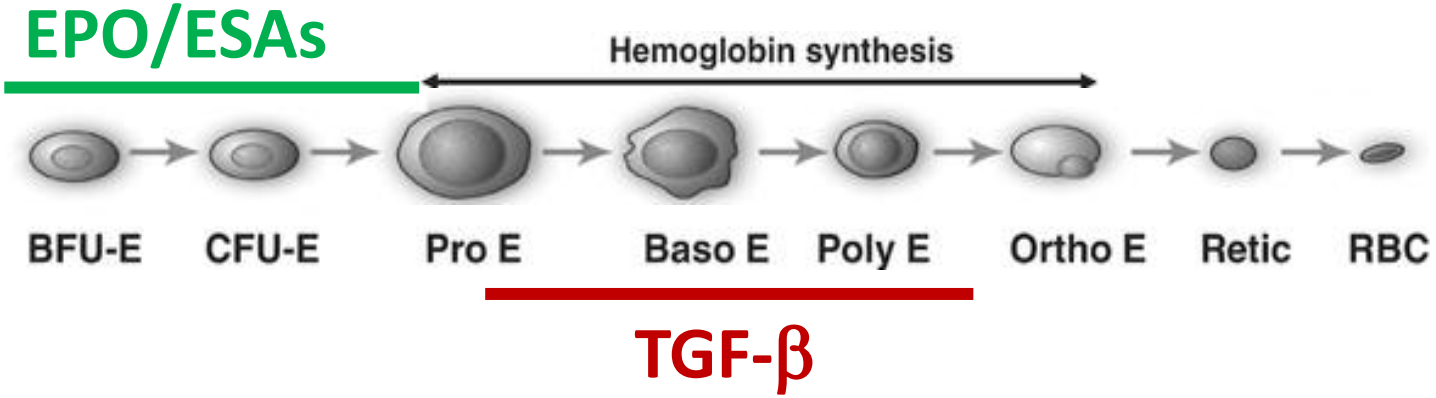
Luspatercept



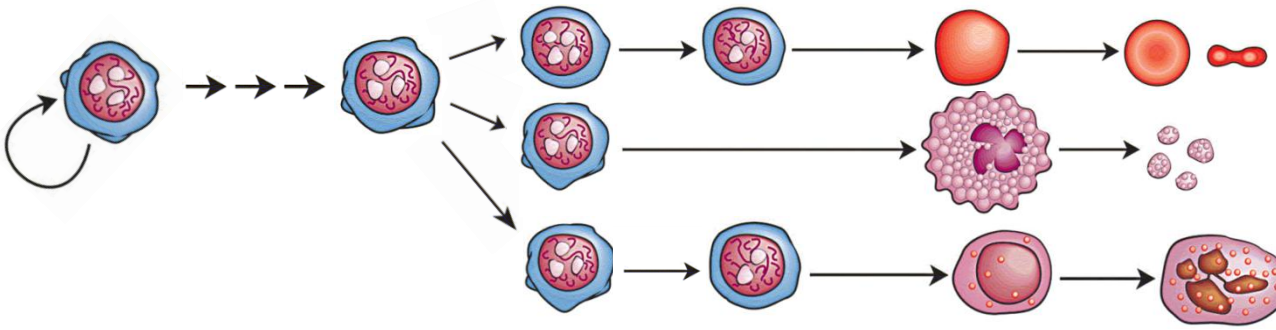
ESAs

TPO mimetics

G-CSF (neupogen)



Luspatercept



ESAs

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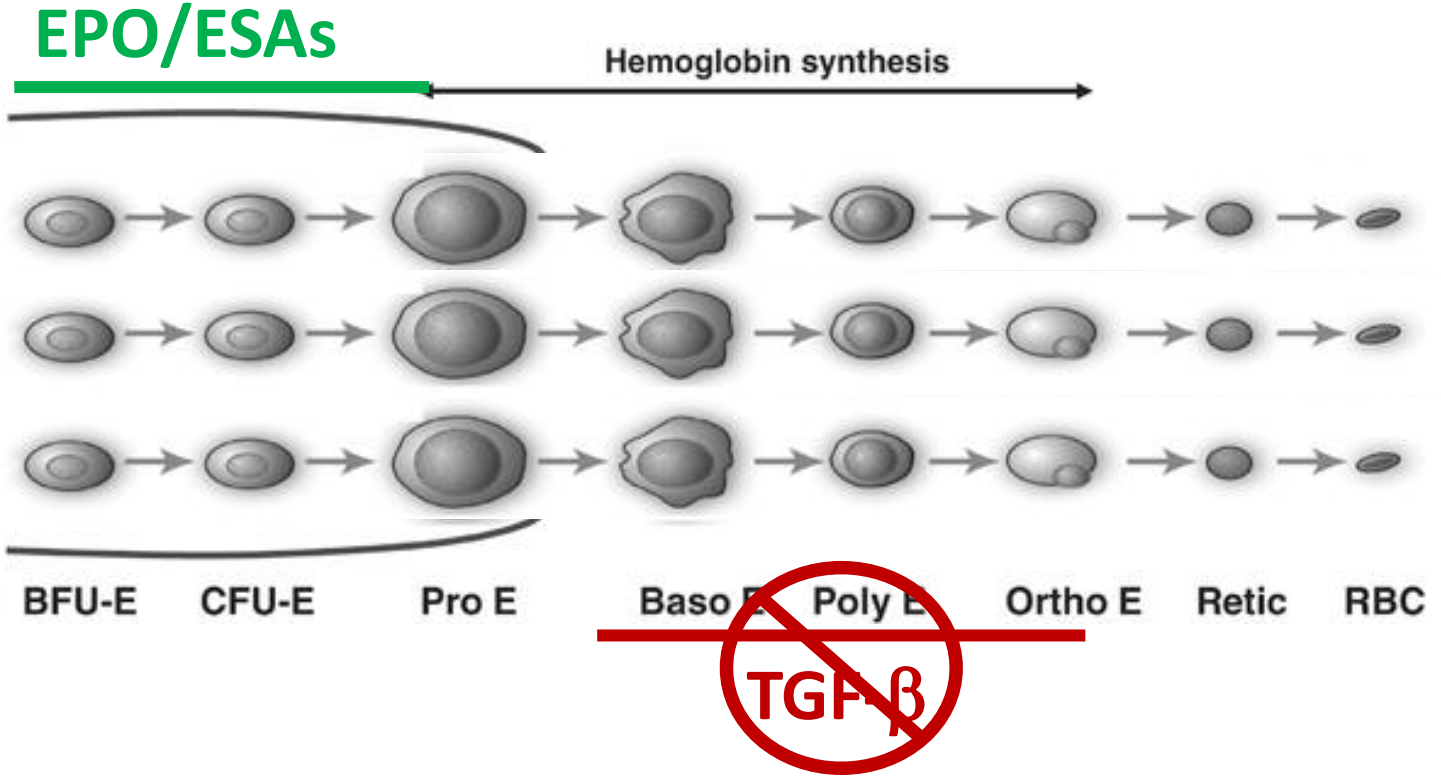
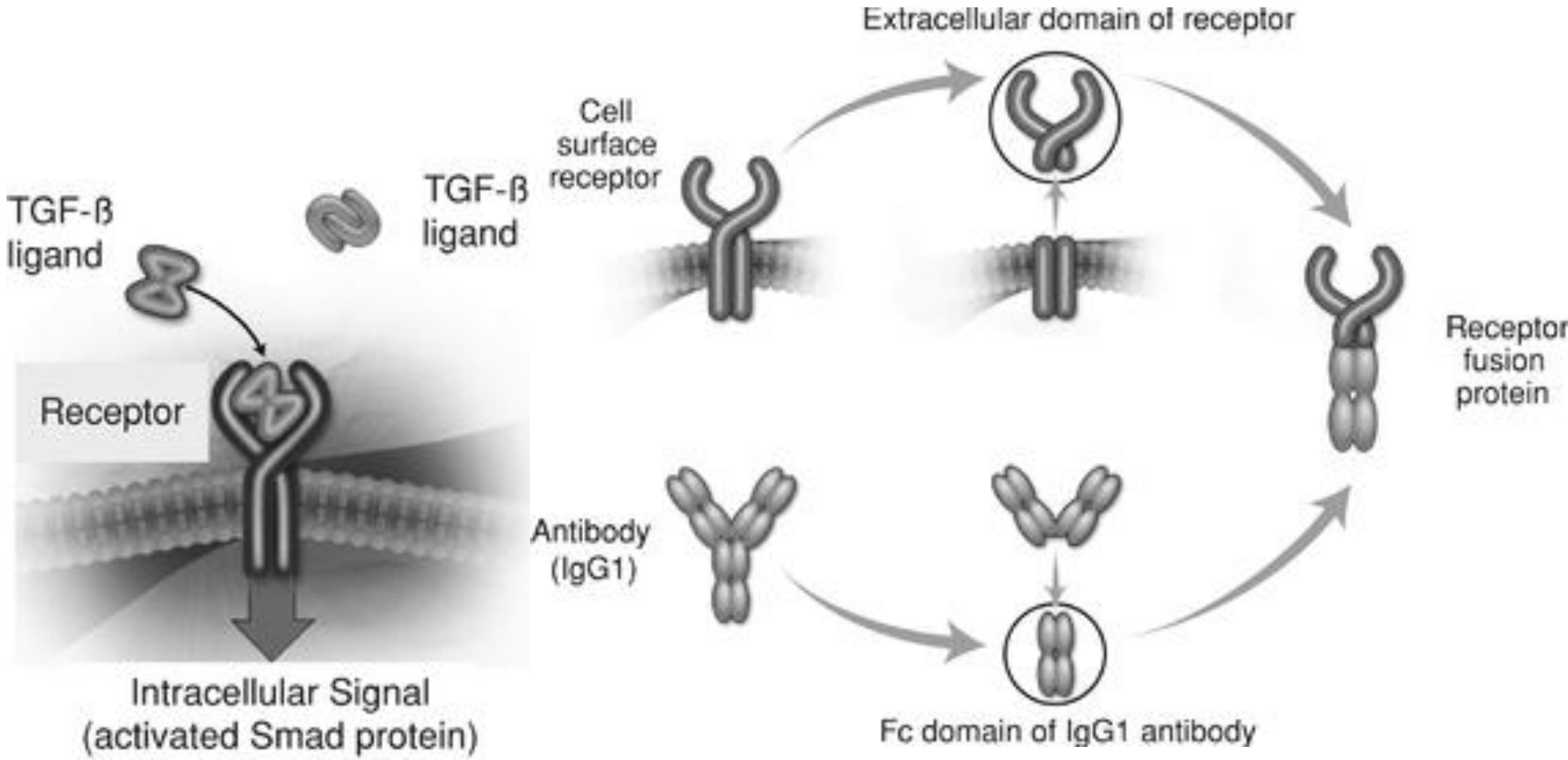


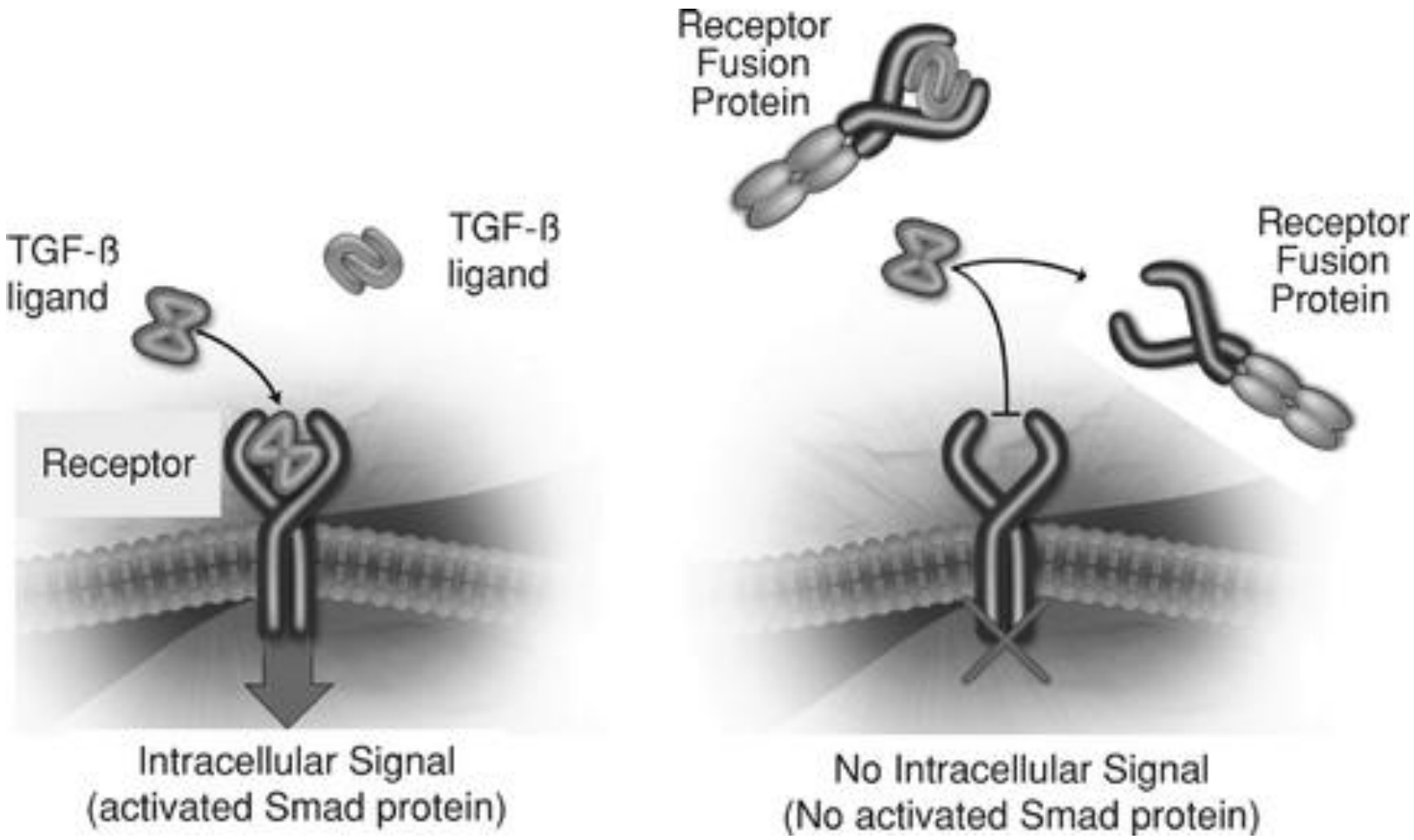
Promoting Red Cell Production

Luspatercept (ACE-536) and Sotatercept (ACE-011)

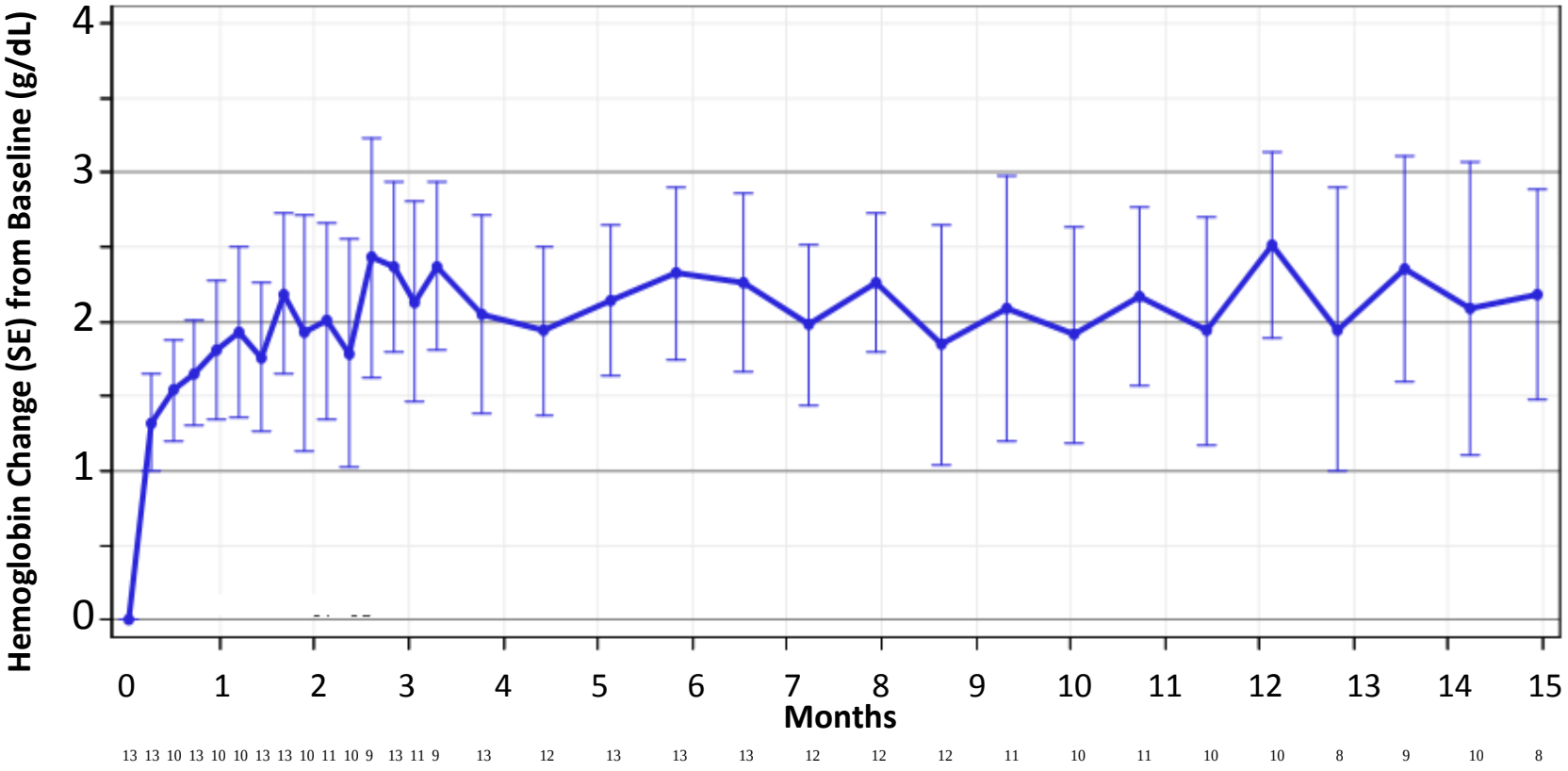


Promoting Red Cell Production

Luspatercept (ACE-536) and Sotatercept (ACE-011)



Increase in Mean Hemoglobin in LTB Patients with > 3 Months of Treatment (Extension Study)



- 11/13 (85%) HI-E responders; median time to response: 6 weeks

LTB: Low transfusion burden patients (< 4 Units/8 wk, Hb <10 g/dL)

Data as of 04 Mar 2016

Guidelines for Lower Risk MDS

Special Considerations:

Transfusion Dependence

- Indication for treatment – even with AZA/DEC, consider chelation

Del(5q)

- High response rate to LEN even if other abnormalities

Serum EPO level

- Used to predict EPO response, > 500 → unlikely to work

Indication for G-CSF

- used to boost EPO, not for primary neutropenia

Immunosuppresive Therapy

- ≤ 60y, hypocellular marrow, HLA-DR15+, PNH clone

Acknowledgements

MDS Center of Excellence at UC San Diego

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- Hematology Group

Bejar Lab

Tim Luger
Tiffany Tanaka
Emily Wheeler
Robyn Raban
Soo Park
Brian Reilly
Armon Azizi

UC San Diego
Moores Cancer Center

To all of our AMAZING PATIENTS and our INFUSION CENTER nurses and staff!

mds foundation
the myelodysplastic syndromes foundation, inc.

High Risk MDS and Novel Therapies: What's on the Horizon?

Rafael Bejar MD, PhD

MDS Foundation

Patients & Caregivers LIVING with MDS Forums

February 3, 2018

UC San Diego
Moores Cancer Center

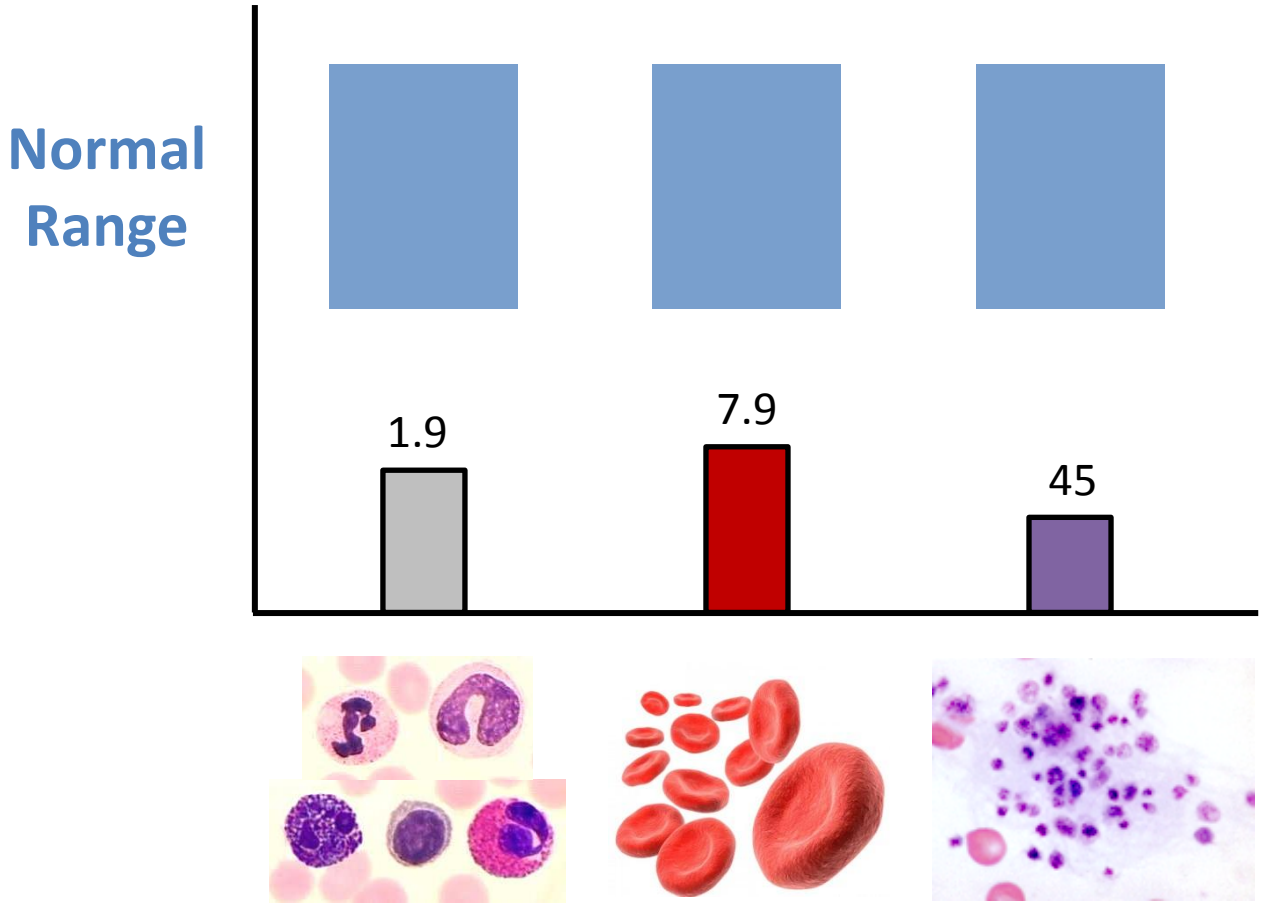
mds foundation
the myelodysplastic syndromes foundation, inc.

Overview

- Treatment of Higher Risk MDS
- Stem Cell Transplanation
- Novel Drug Therapies
- Immune Therapies

Low Blood Counts

71 year-old man with big red cells and low blood counts that developed over the past 6 months.



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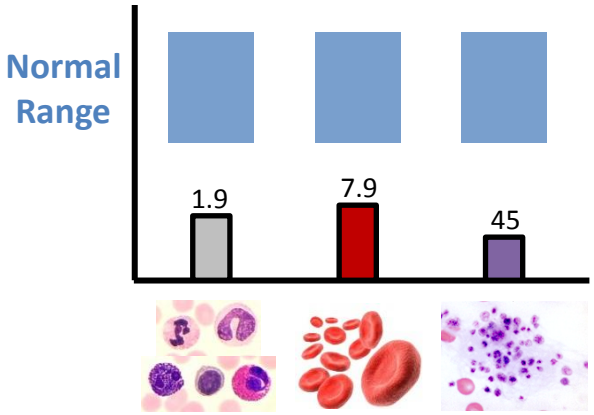
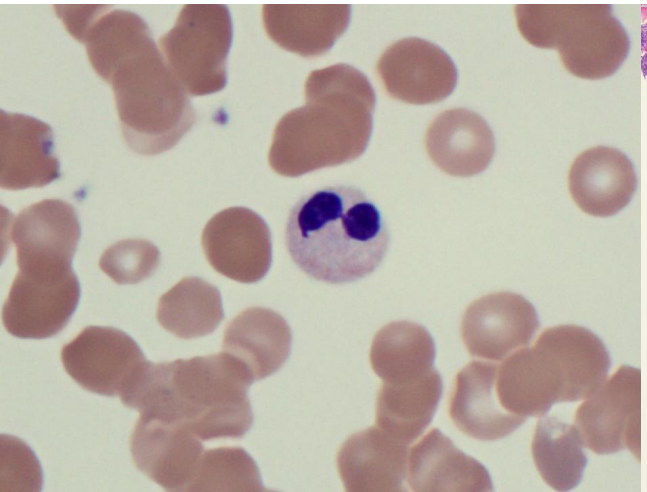
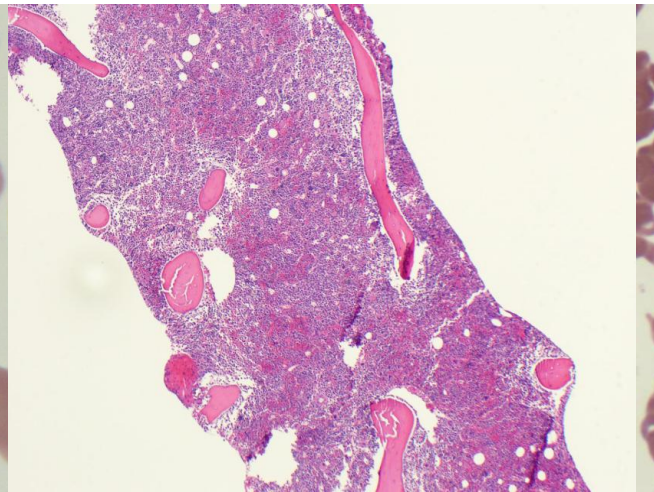


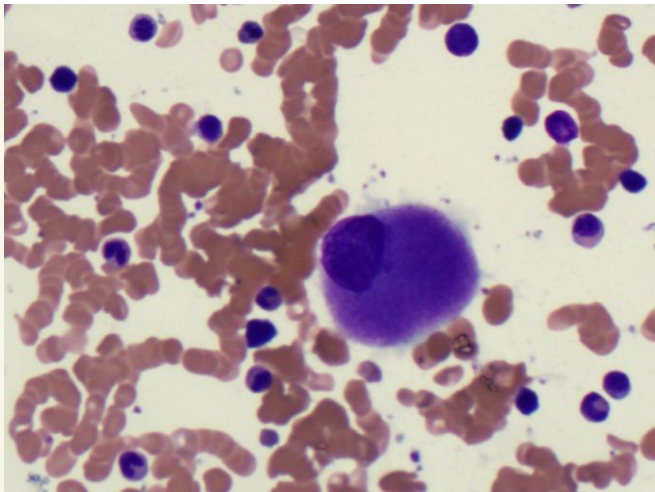
Way too many cells in the bone marrow
4% blasts in aspirate

Dysplasia in all three cell types

Normal Karyotype (chromosomes ok)







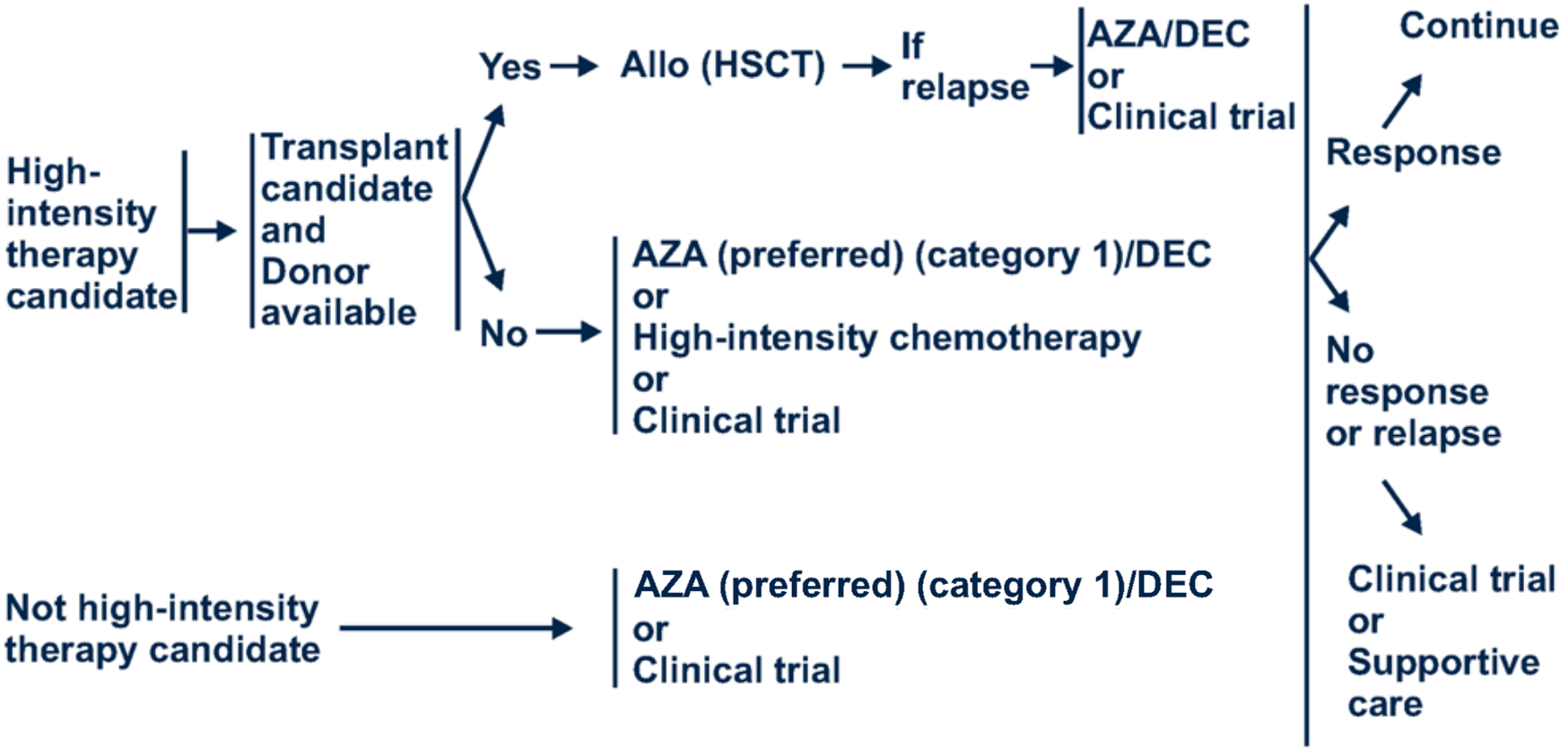
Treatment of Higher Risk MDS

Guidelines for Higher Risk MDS

Goal: to improve **DURATION OF LIFE**

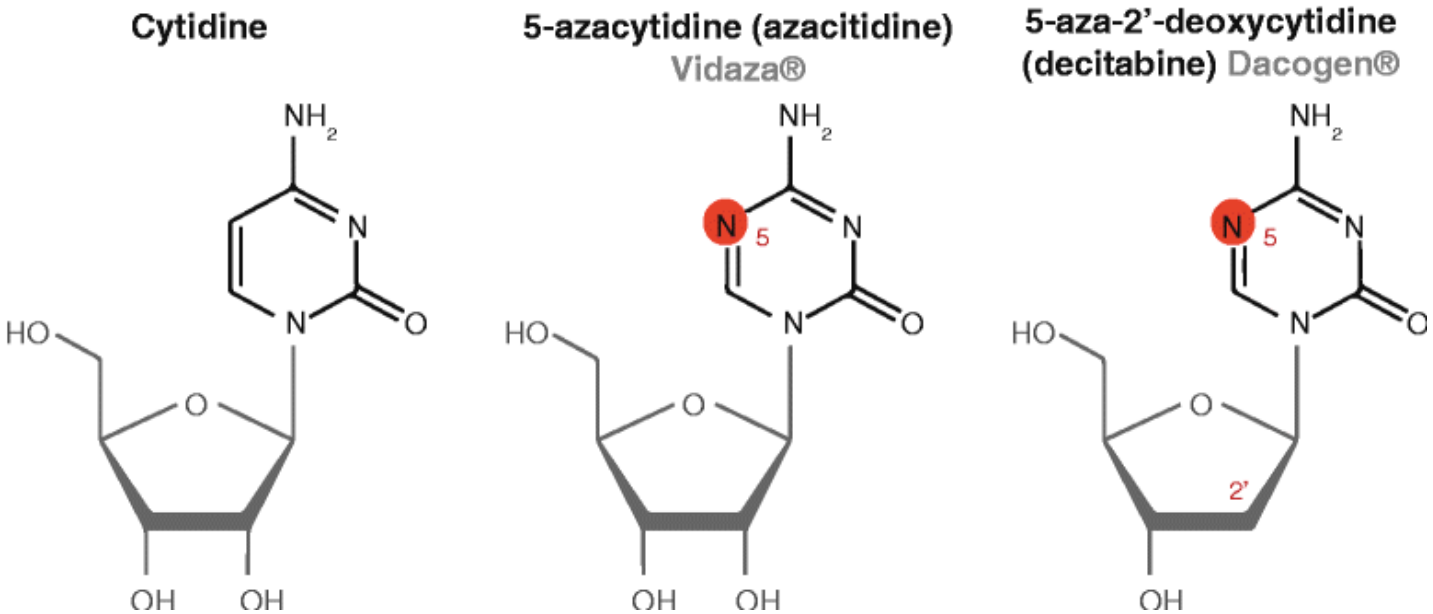
National Comprehensive Cancer Network®

NCCN Guidelines® Version 2.2013
Myelodysplastic Syndromes



Hypomethylating Agents

Inhibitors of DNA methyl transferases:



Both incorporate into DNA and cause hypomethylation (DEC > AZA)

AZA preferentially causes DNA damage and induces apoptosis

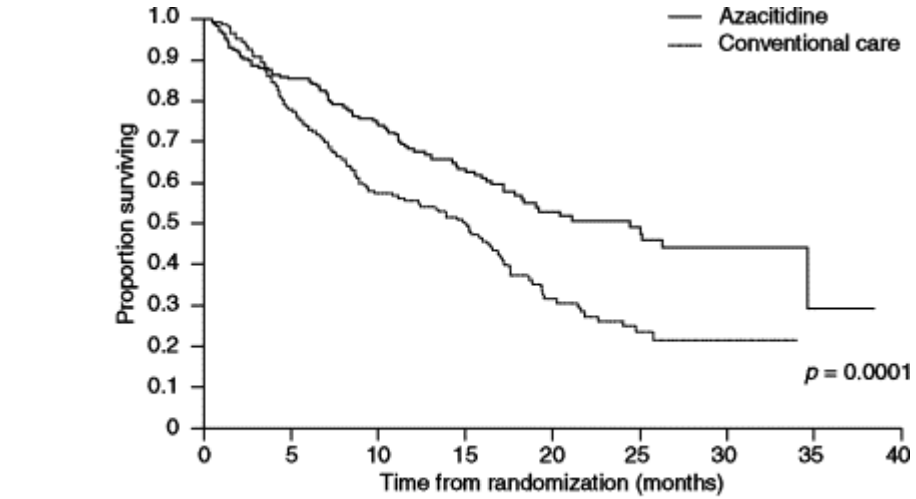
Azacitidine

AZA-001 Phase III: AZA vs. ld-ARA-C vs. supportive care

OS benefit: + 9.5 mos

Time to AML: 17.8 vs. 11.5 mos

TI: 45% vs. 11%



Azacitidine Response:

ORR: ~50%

CR: ~17%

Median time to response: 3 cycles (81% by cycle 6)

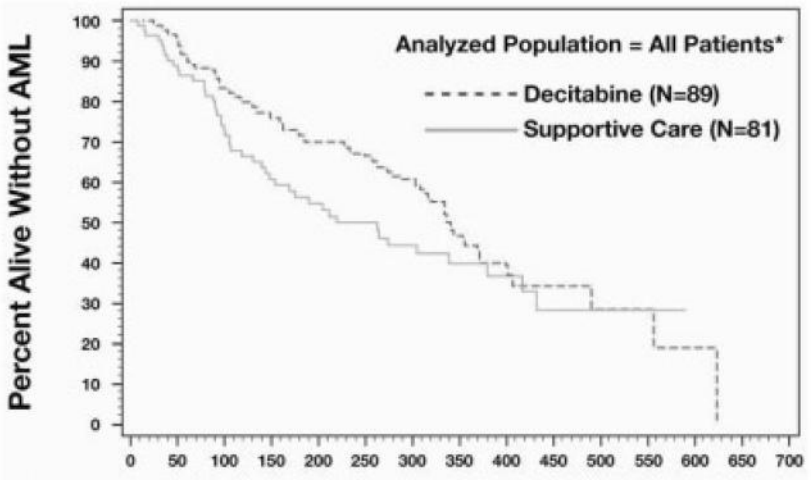
Decitabine

Decitabine Phase III Trial

Dosed q8h x 3 days per 28 days

CR: 17%

CR+PR: 30%



ADOPT Trial and 3-Schedule Trial

Dosed q24h x 5 days per 28 days

CR: 17%

CR+PR: 32%

ORR: 52% (+ heme response)

Best response: 50% at 2 cycles

Major Toxicity:

Neutropenia: 31% (FN 11%)

Thrombocytopenia: 18%

HMA Clinical Pearls

Azacitidine and Decitabine are imperfect drugs:

- Treatment is intensive – 5 to 7 days evey 4 weeks
- Overall response rate is only 45% and CR rate is ~15%.
- Responses can take 4-6 months to appear!
- Counts get worse for EVERYONE initially – expected
  - Risks include neutropenic fever, bleeding, new transfusion requirements

But, they're not all bad:

- HMAs are generally well tolerated
  - No hair loss or mucositis
  - Little to no nausea or vomiting
  - Common side effects are fatigue and constipation (Zofran ?)

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Special Considerations:

Refer for Transplant Early

- Even patients in their 70's can benefit from RIC transplant

AZA > DEC (for now)

- AZA has been shown to have a survival advantage, DEC has not (yet)

Don't forget Quality of Life

- Consider treatment palliative and weigh against patient needs

Look for Clinical Trials

- Few option after AZA are available and none are approved

Outcomes After Azacitidine

Reasons for "failure" in azacitidine failure study

9% didn't tolerate AZA (69% were not responding, 31% had an initial response)
55% primary failure (progression in 60% , stable disease without response in 40%)
36% secondary failure after initial response (best response: CR 20% , PR 7%, HI 73%)

Outcomes after failure

Median overall survival for whole cohort post-AZA: **5.6 months**
2 year survival: **15%**
Favorable factors: **female, younger (<60), better risk karyotype, <10% blasts, some response to azacitidine**

Comparison to decitabine failures @ MDACC: **median survival 4.3 months**, n=87

Slide borrowed from Dr. David Steensma

Prébet T et al, *J Clin Oncol 2011;* Aug 20;29(24):3322-7. Epub 2011 Jul 25.
Jabbour E et al, *Cancer* 2010*;* 116:3830–3834.

Outcomes After Azacitidine

- Data available on 435 pts
  - *from AZA001, J9950, J0443, French compassionate program*
- **Overall median survival after azacitidine failure: 5.6 months**

Subsequent therapy	Number of patients (%)	Median survival
Allogeneic transplant	37 (9%)	19.5 months
Investigational therapy (e.g. IMiD, HDACi, other)	44 (10%)	13.2 months
Intensive cytotoxic therapy (e.g., 3&7)	35 (8%)	8.9 months
Low-dose chemotherapy (e.g. LDAC, 6-MP)	32 (7%)	7.3 months
Palliative / supportive care	122 (28%)	4.1 months
Subsequent therapy unknown	165 (38%)	3.6 months

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Prébet T et al *J Clin Oncol* 2011; 29:3322-7
Jabbour E et al *Cancer* 2010;116(16):3830-4

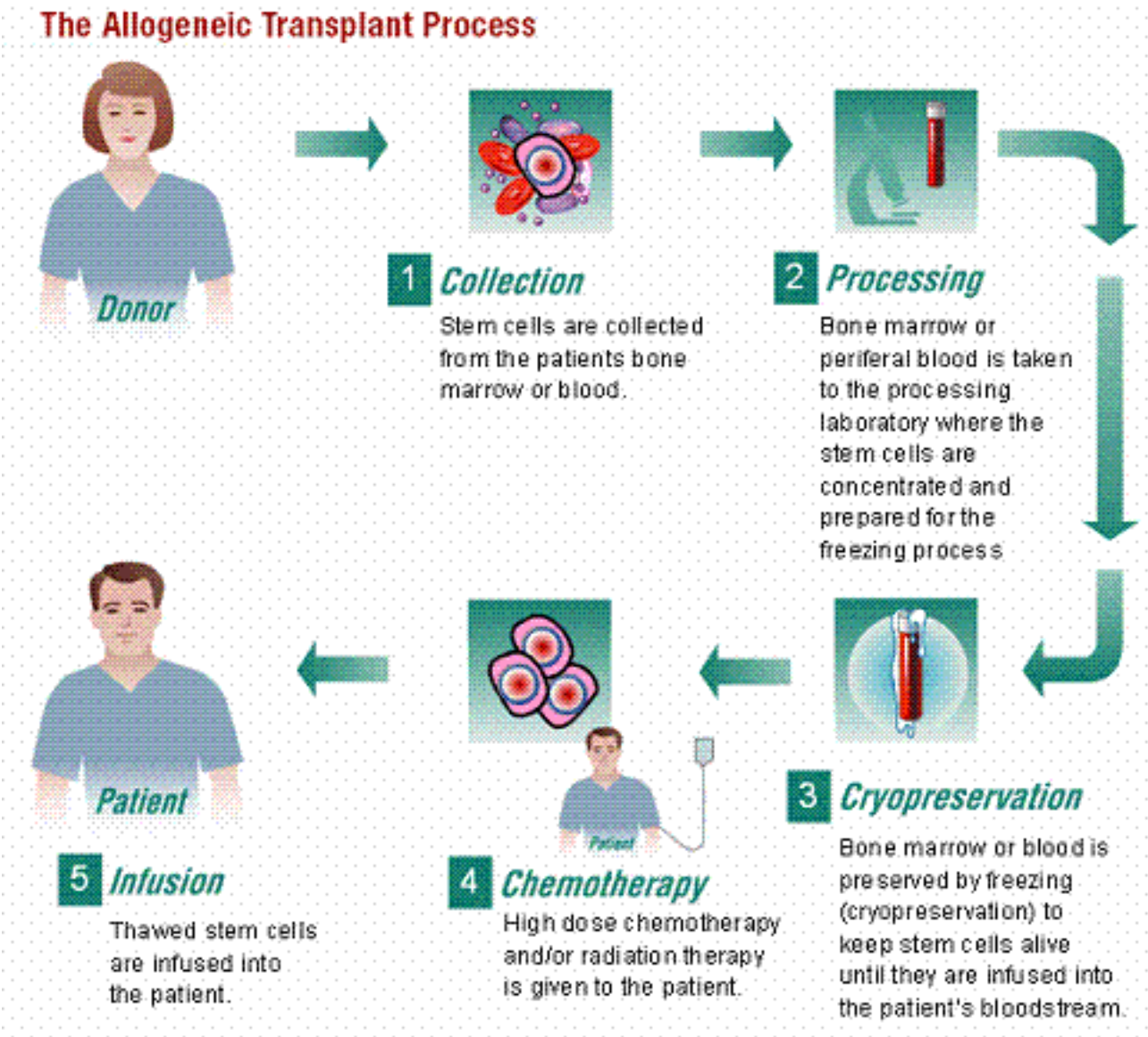
Treatment of Higher Risk MDS

We need **BETTER** therapies!

We need **MORE** therapies!

Stem Cell Transplantation

Stem Cell Transplantation

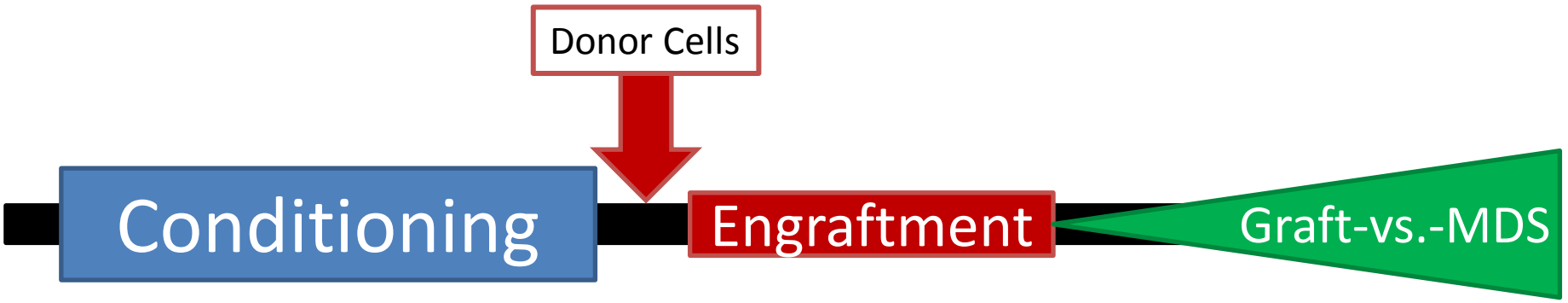


Trends in Transplantation

Goal of Hematopoietic Stem Cell Transplantation:

#1) Replace a dysfunction host hematopoietic system with normal, healthy donor marrow.

#2) Allow the donor immune system to destroy the abnormal, diseased host cells (MDS).



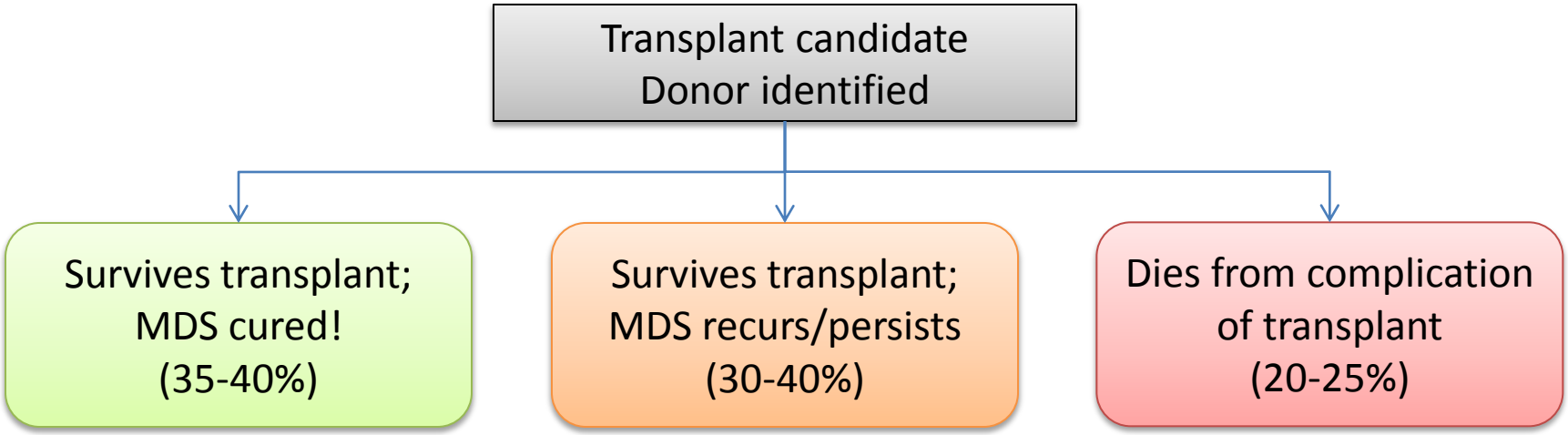
Allogeneic Stem Cell Transplantation for MDS

<5% of patients with MDS currently undergo allogeneic SCT

"Only curative therapy"

Patients who go in to RIC allo SCT with <10% blasts appear to have lower relapse

Optimal timing, pre-transplant therapy, conditioning unclear;
usually reserved for IPSS Int-2/High (IBMTR Markov analysis)



Slide borrowed from Dr. David Steensma

Cutler C et al *Blood* 2004; 104(2):579-85
Sekeres M et al *JNCI* 2008;100(21):1542-51.

Obstacles to Transplantation

Graft Rejection

- need to suppress the host immune system

Toxicity

- infection
- organ damage
- graft versus host disease

Finding a Donor

- siblings match only 25% of the time
- and are often too old or ill to donate

Overcoming Obstacles

Avoiding Graft Rejection

- better approaches to immune suppression

Less Toxicity

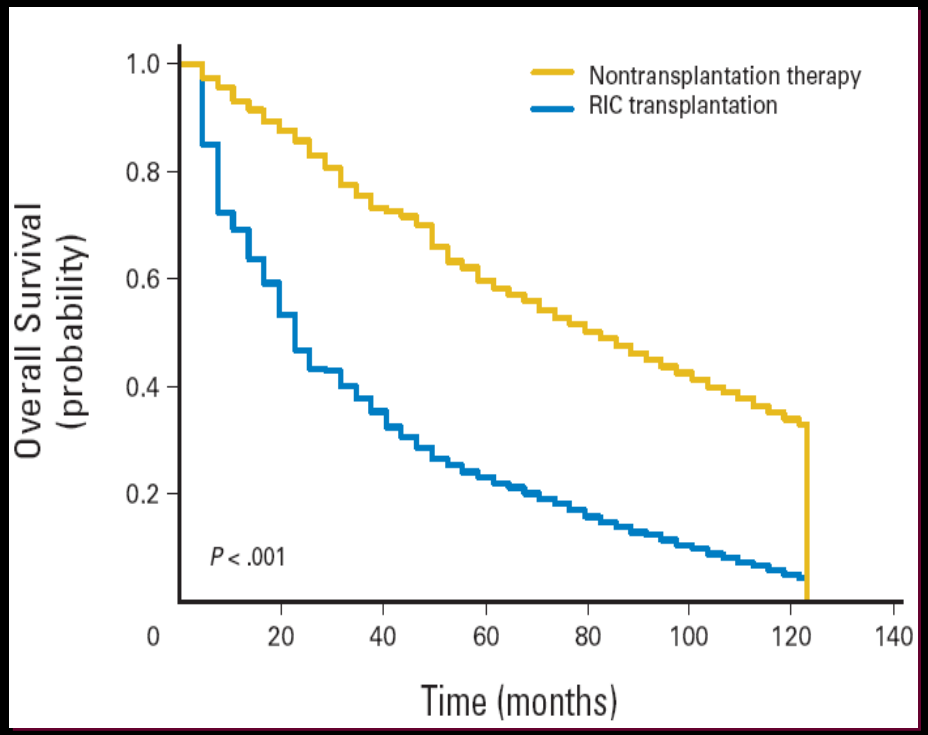
- better supportive care
- better antigen matching
- **reduced intensity conditioning**

Alternative Sources for Stem Cells

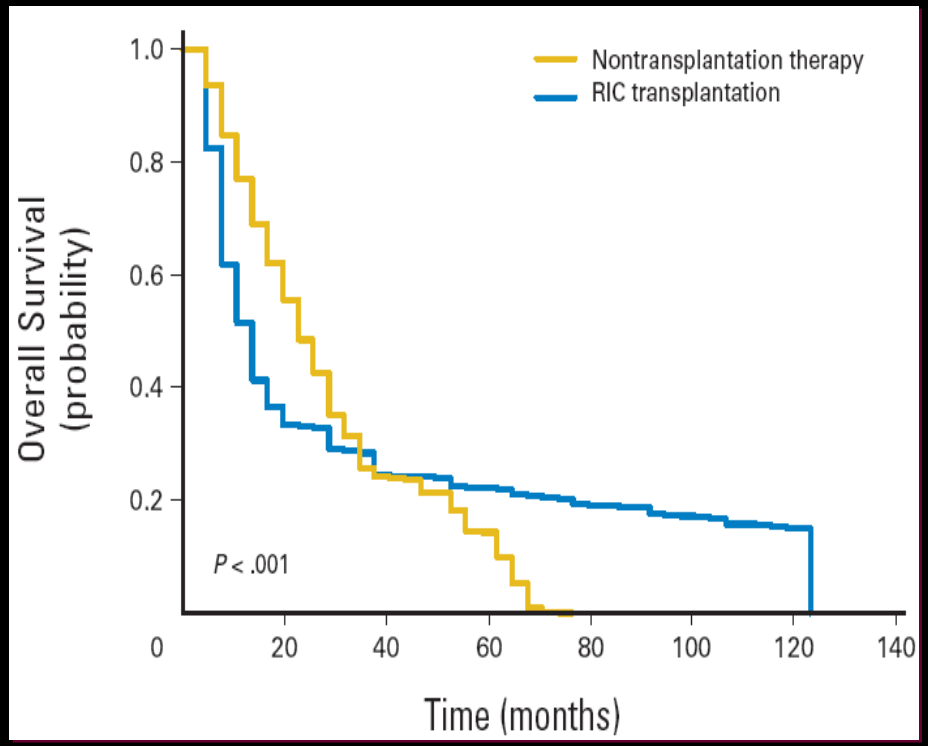
- haploidentical – “half” match
- umbilical cord blood stem cells

Reduce intensity conditioning transplantation in Older Patients with *De Novo* MDS

IPSS Low/Int1

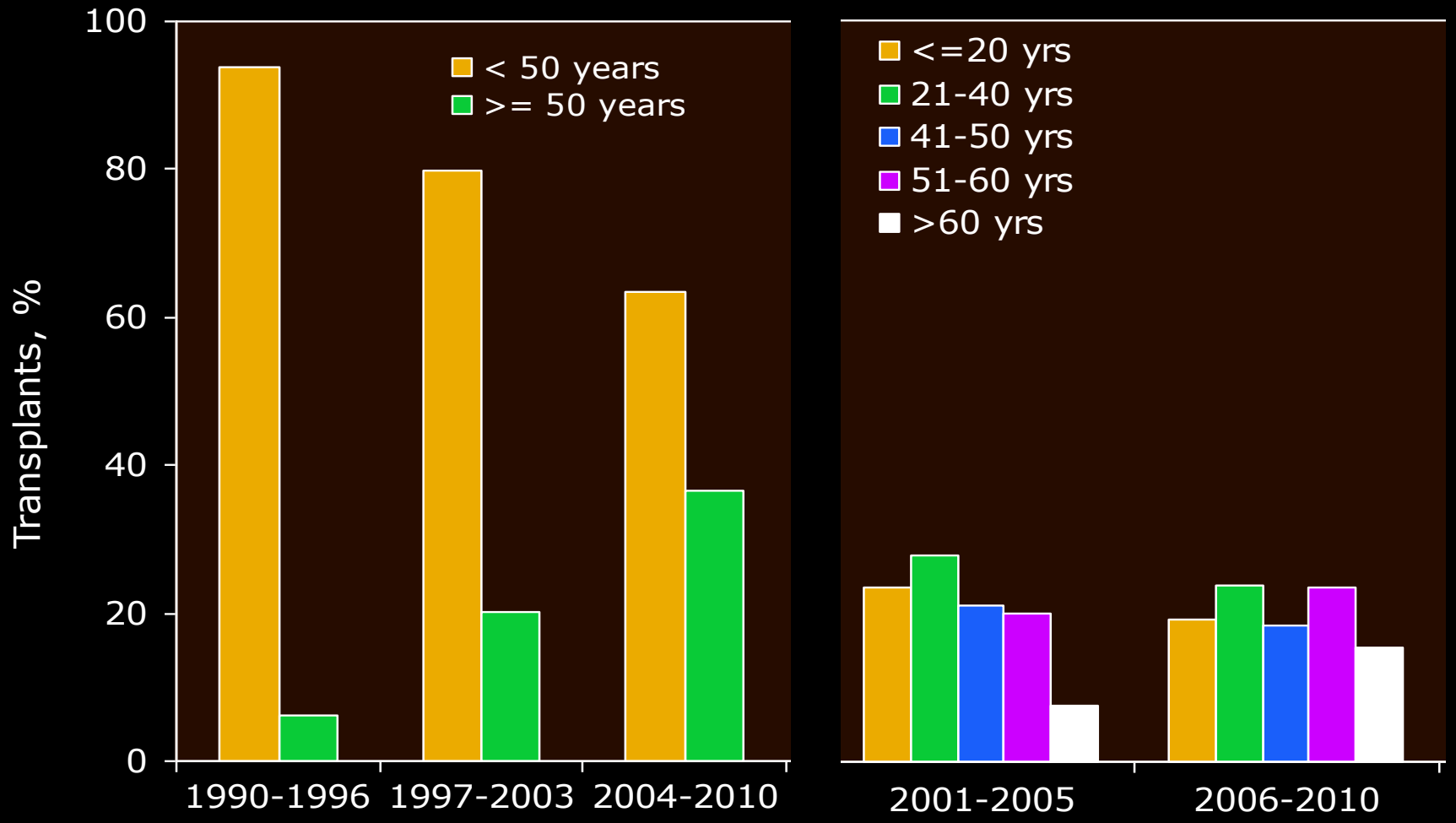


IPSS Int2/High



Koreth J, et al. J Clin Oncol. 2013.

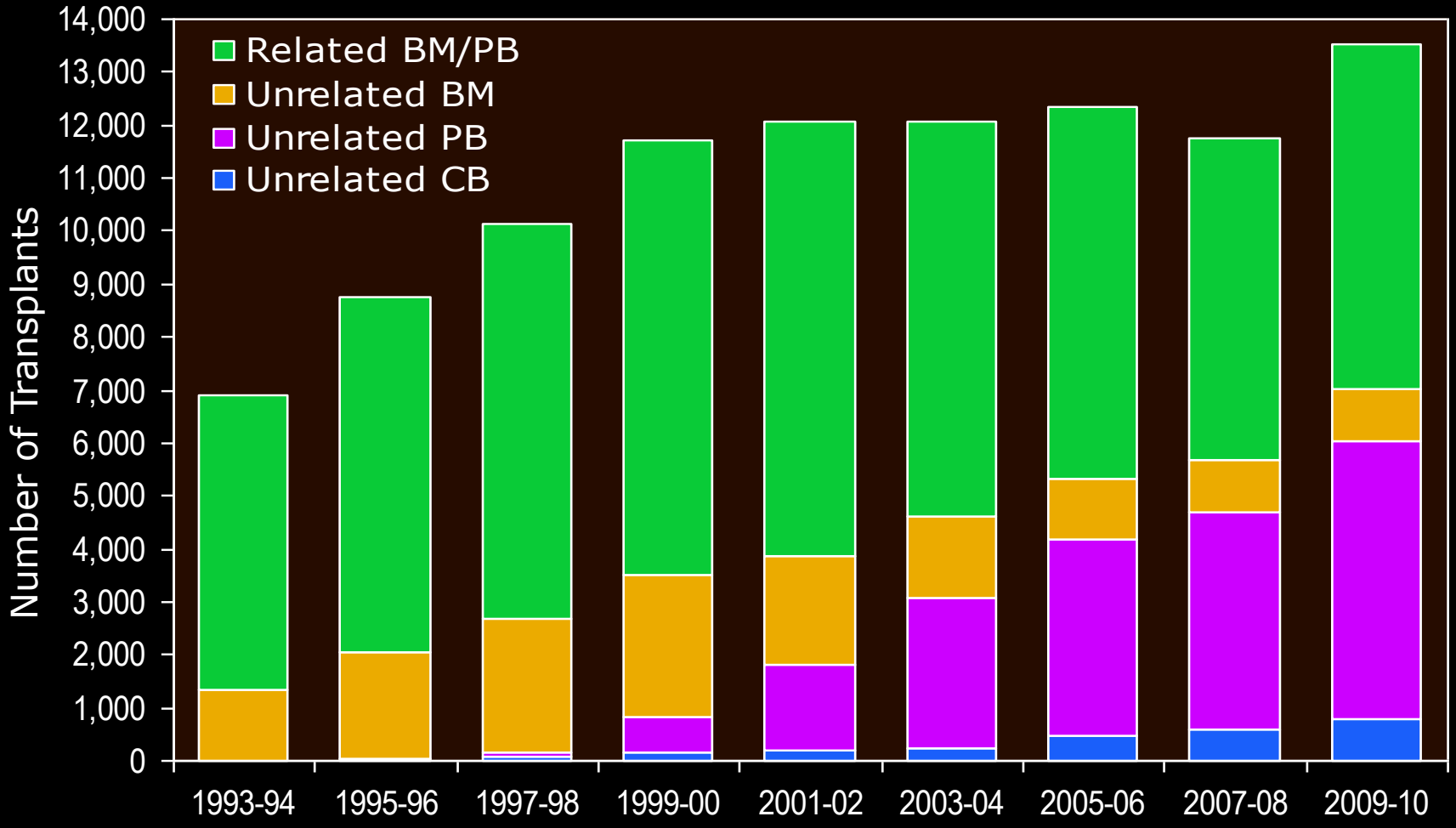
Trends in Allogeneic Transplants by Transplant Type and Recipient Age* 1990-2010



* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

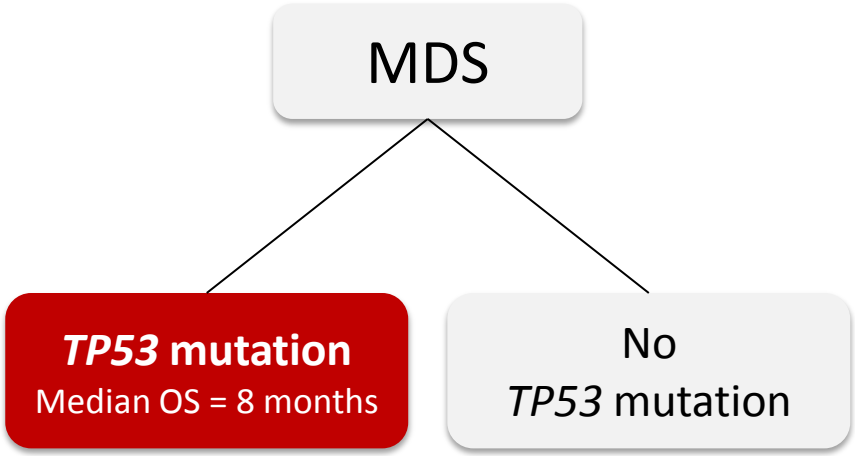
Allogeneic Transplants for Age > 20yrs, Registered with the CIBMTR, 1993-2010

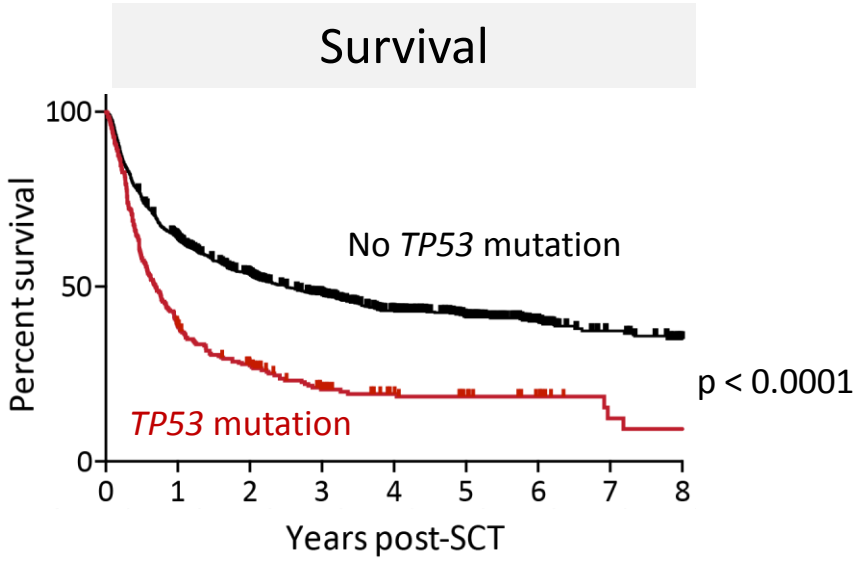
- by Donor Type and Graft Source -

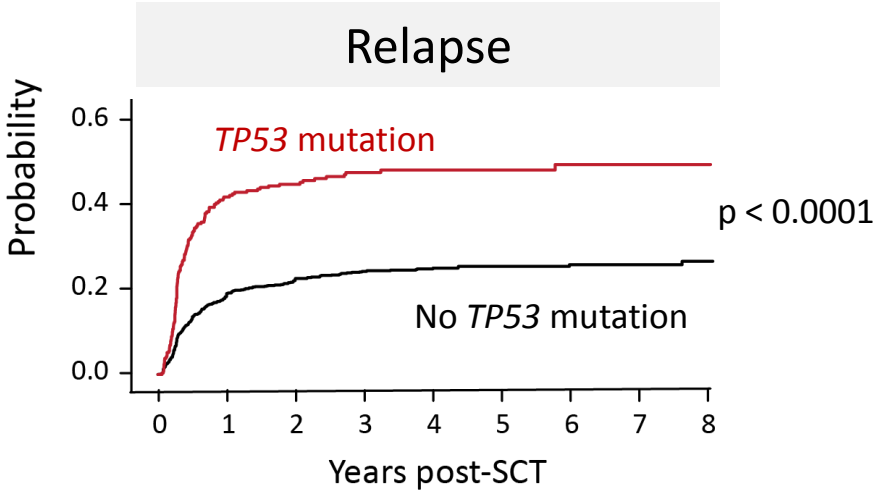


TP53 mutated MDS

Poor prognosis due to early relapse







Novel Treatments for Higher Risk MDS

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Look for Clinical Trials

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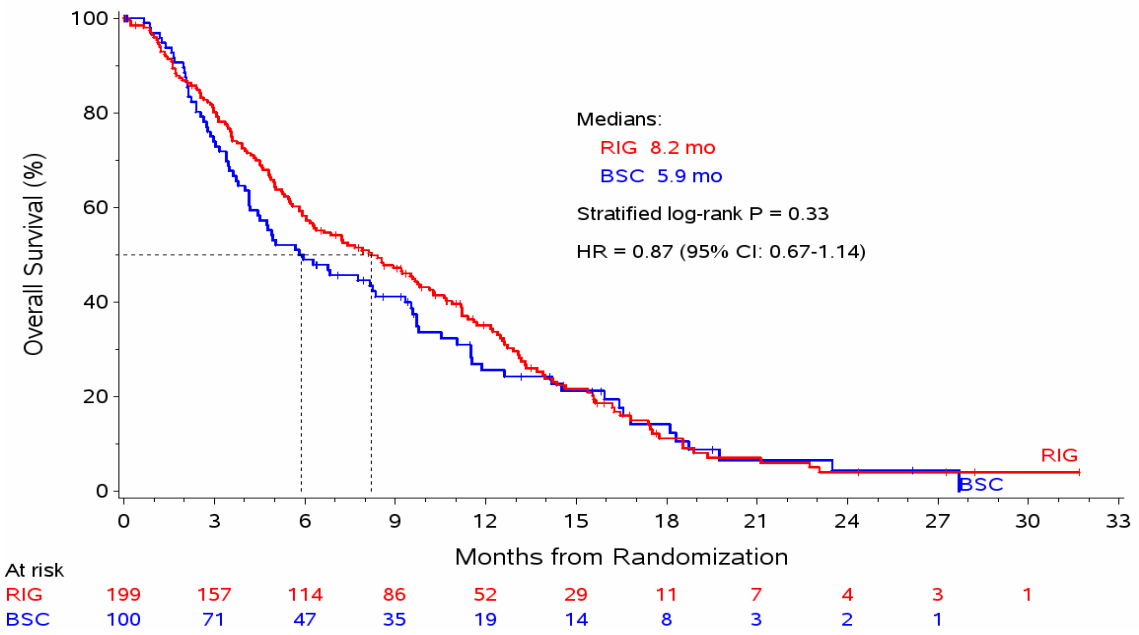
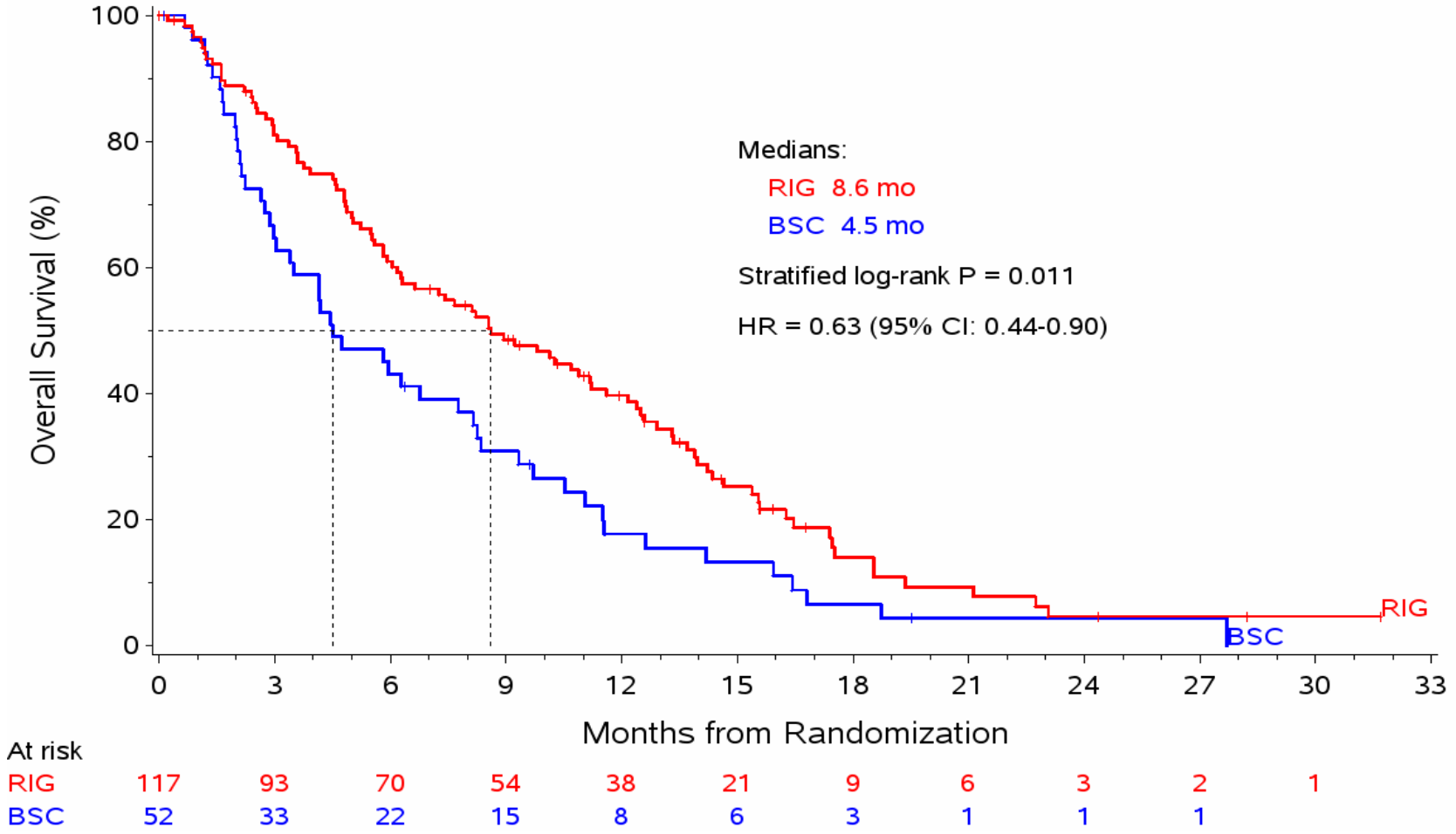
Rigosertib Phase III Result

	Rigosertib N = 199	BSC N = 100
Number (%) of deaths	161 (81%)	81 (81%)
Median follow-up (months)	17.6	19.5
Median survival (months)	8.2	5.9
95% CI	6.0 - 10.1	4.1 - 9.3
Stratified HR (rigosertib/BSC)	0.87	
95% CI	0.67 - 1.14	
Stratified log-rank p-value	0.33	



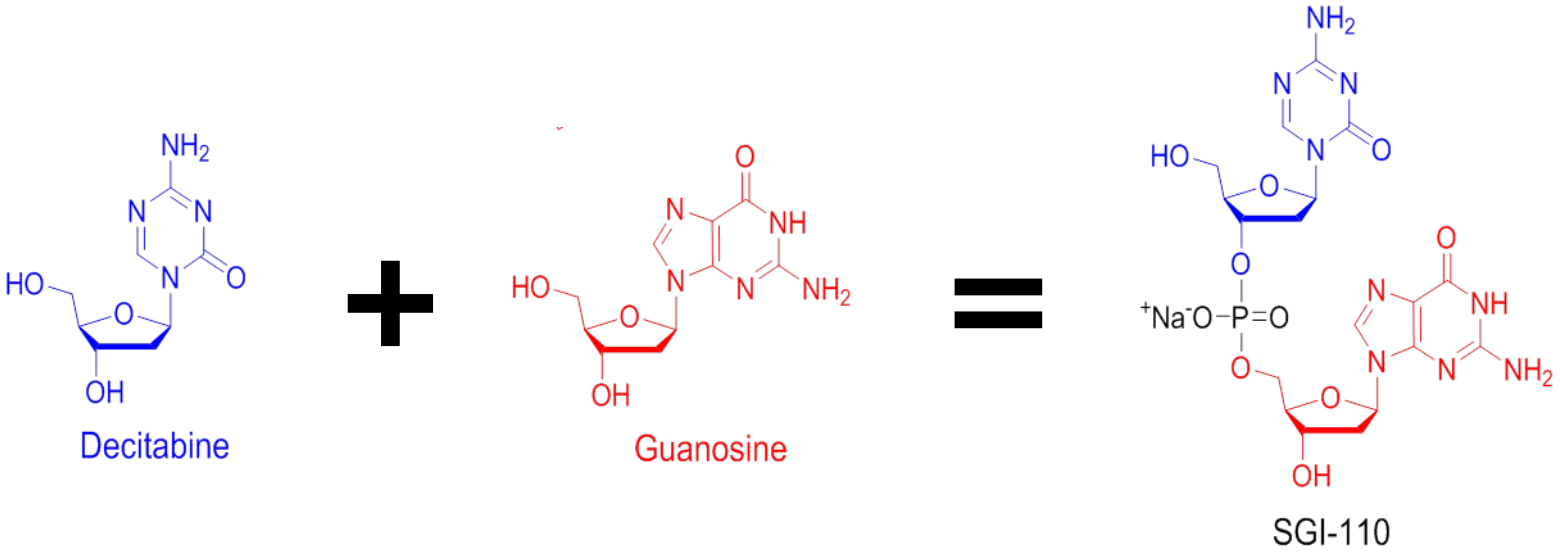
All Patients

ONTIME Trial: Median Overall Survival for Pts with Primary HMA Failure - Blinded, Centralized Assessment



Per Prebet 2011, "Primary HMA Failure" was defined as either no response to or progression during HMA therapy

SGI-110 Phase II Results

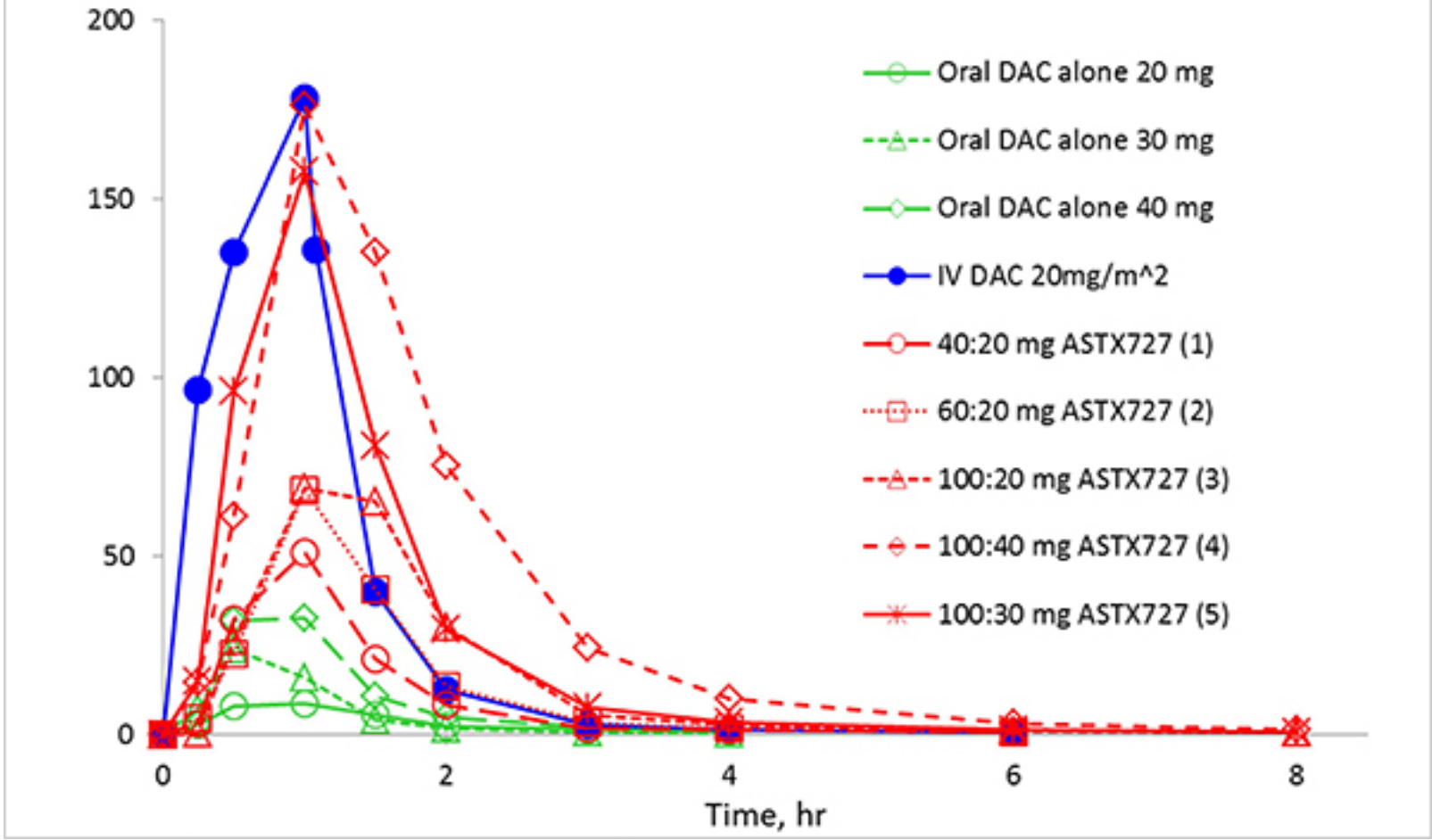


	60 mg/m2 (n=53)	90 mg/m2 (n=49)
8-week **RBCs Transfusion Independent** n (%)	7/27 (26%)	5/24 (21%)
8-week **Platelet Transfusion Independent** n (%)	4/13 (31%)	5/15 (33%)

Oral Decitabine + CDAi

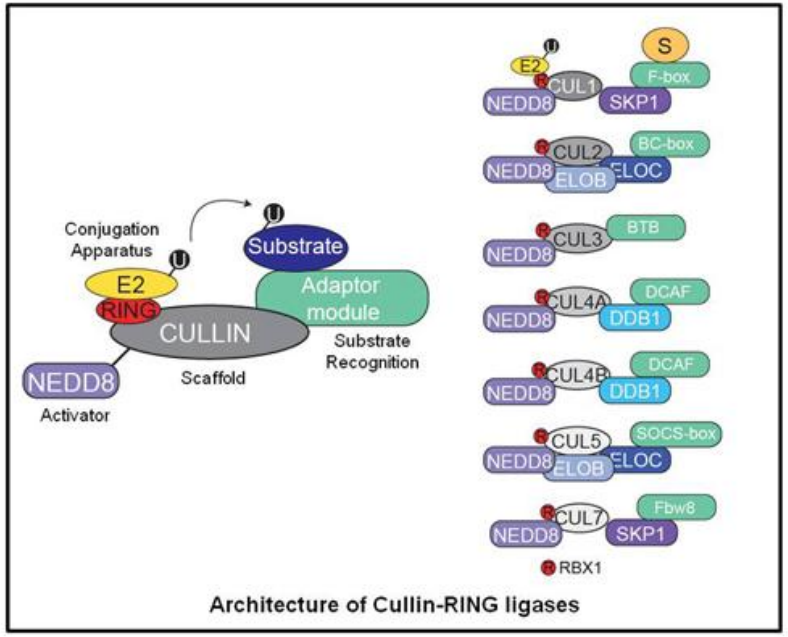
Pharmacokinetics

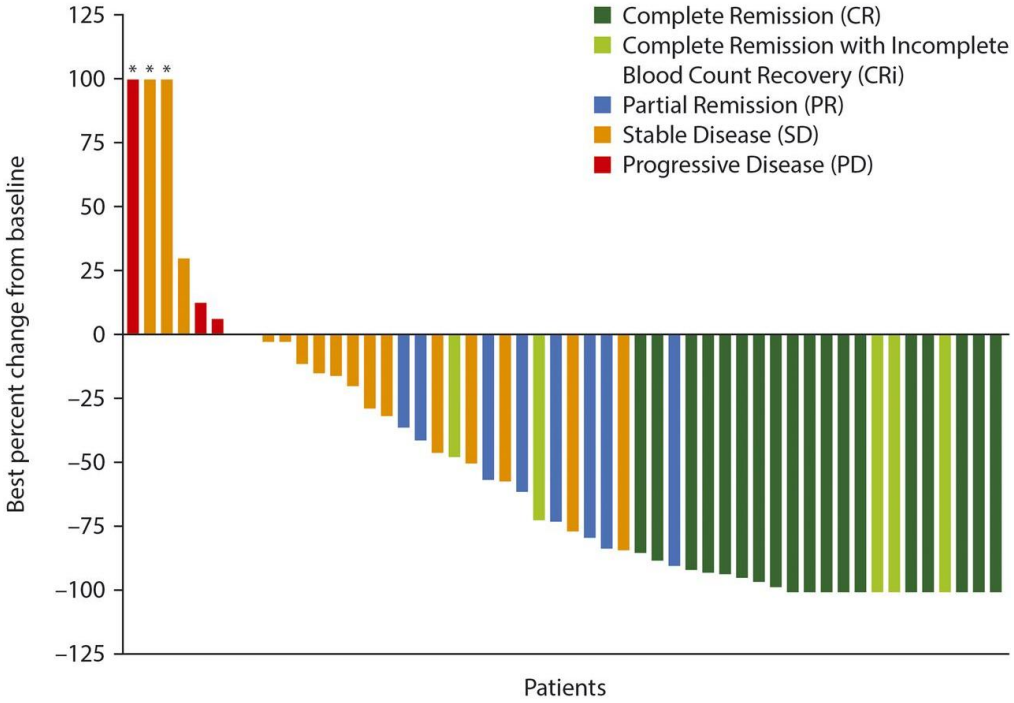
Decitabine PK profile, IV vs oral, without/with CDAi



Pevonedistat

Has activity in AML when combined with azacitidine

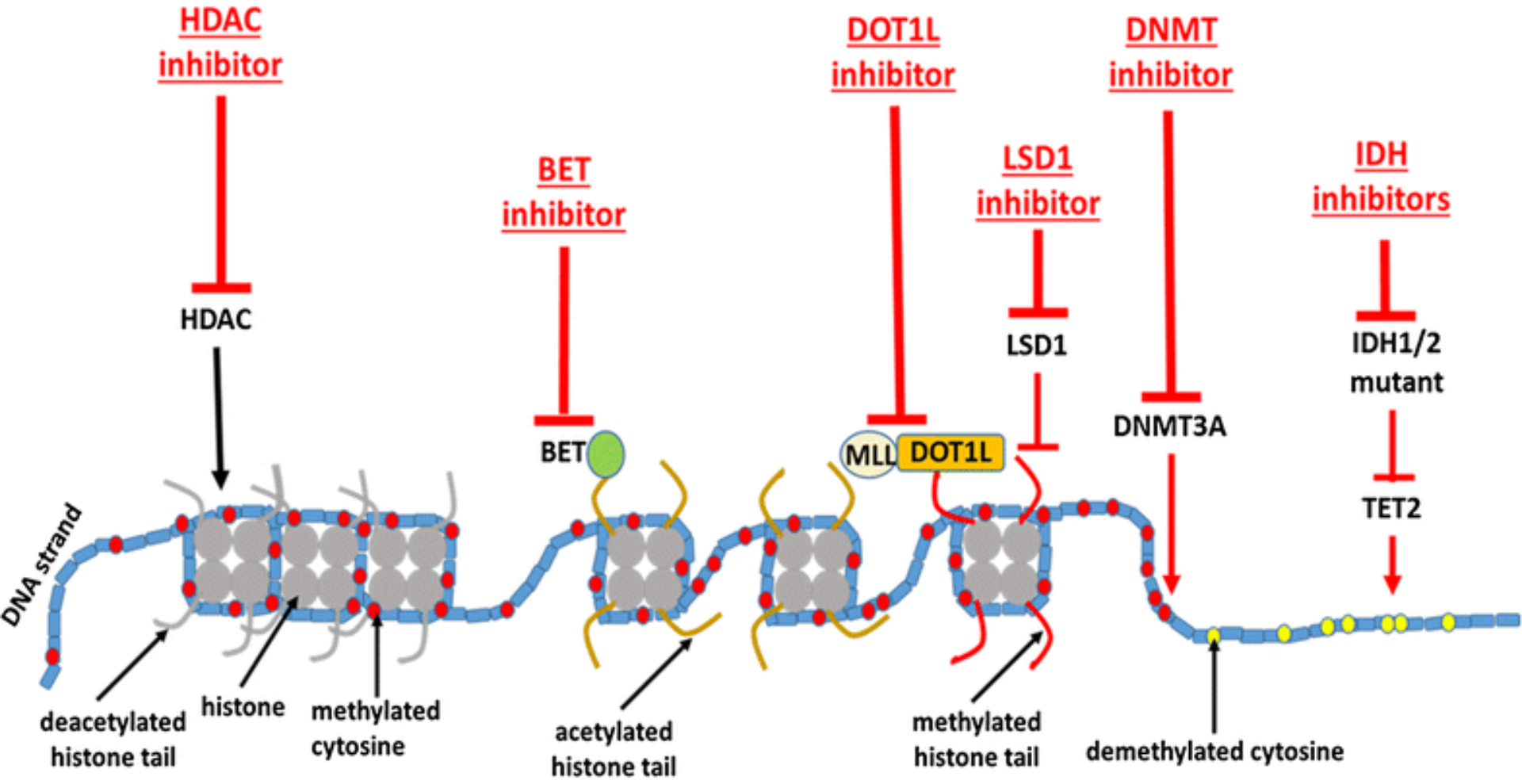




*Best percent change from baseline >100%.
SD represents those evaluations which did not qualify for response or PD.

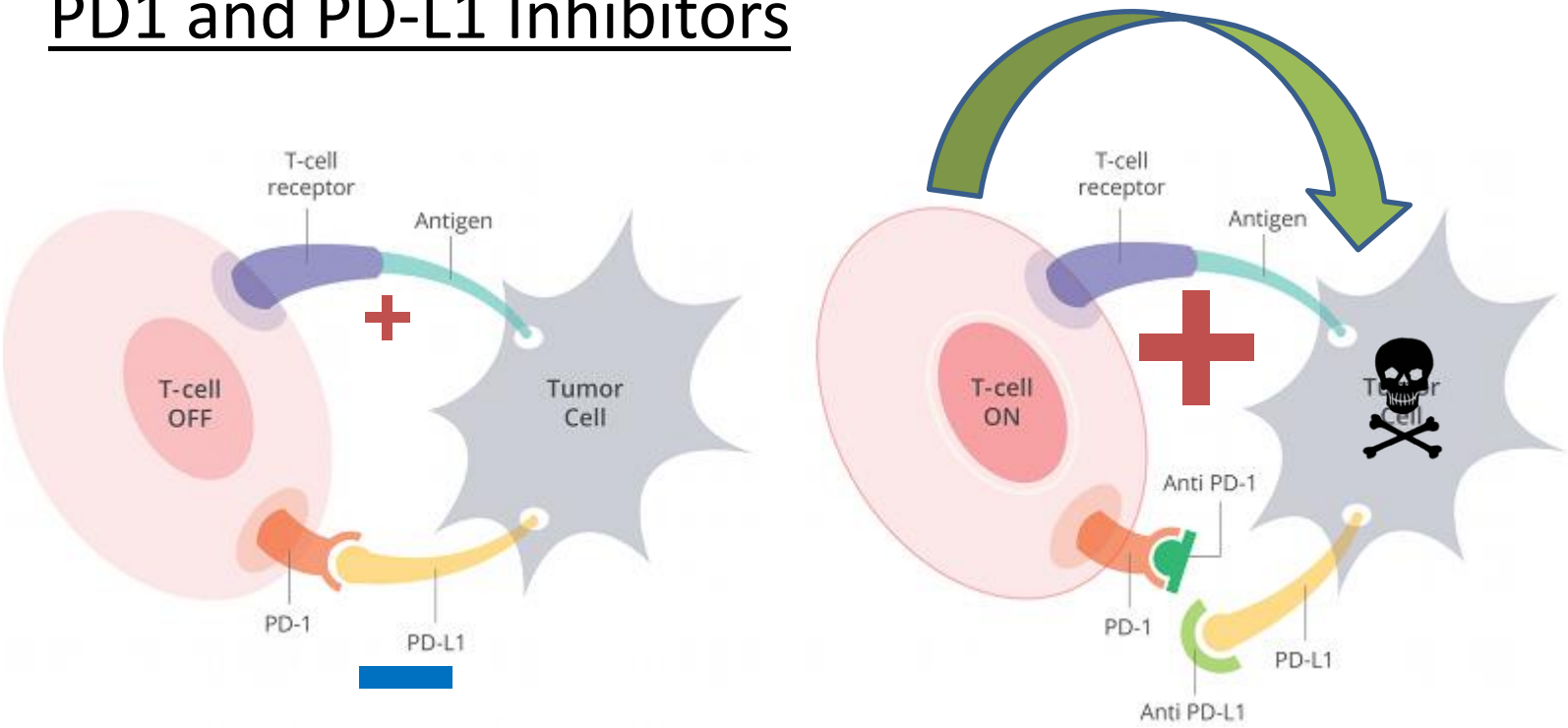
Now in a phase III clinical trial in MDS/CMML/sAML

Other Epigenetic Drugs



Immune Regulation

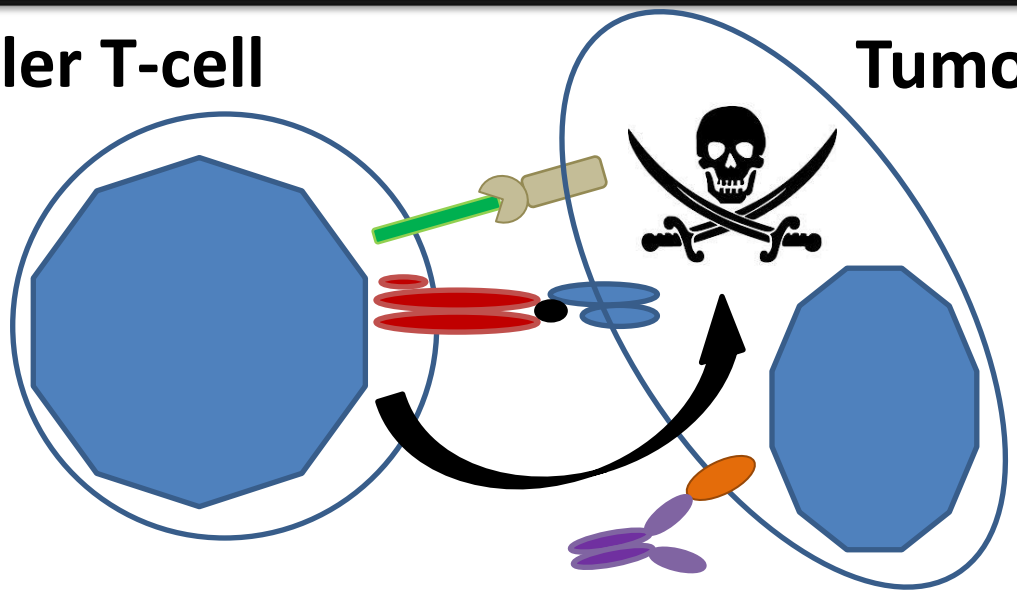
PD1 and PD-L1 Inhibitors



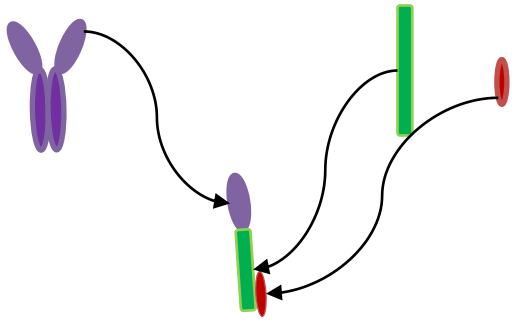
Phase I/II Trial will be opening here at UCSD

Immunologic Therapy

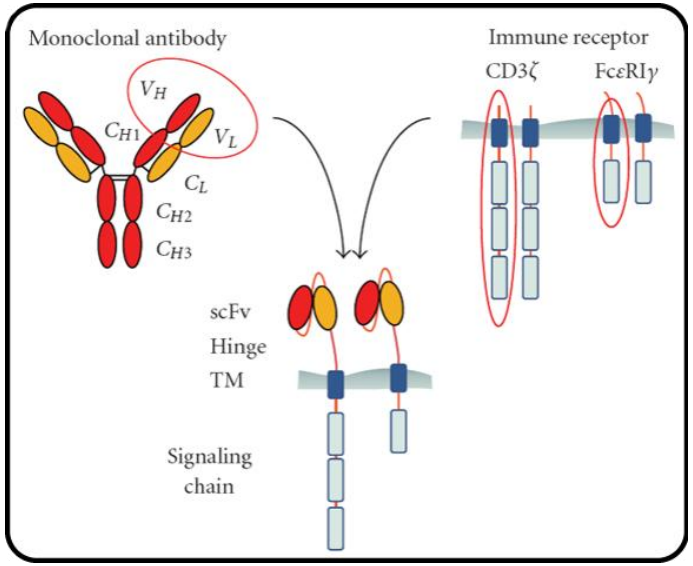
Killer T-cell

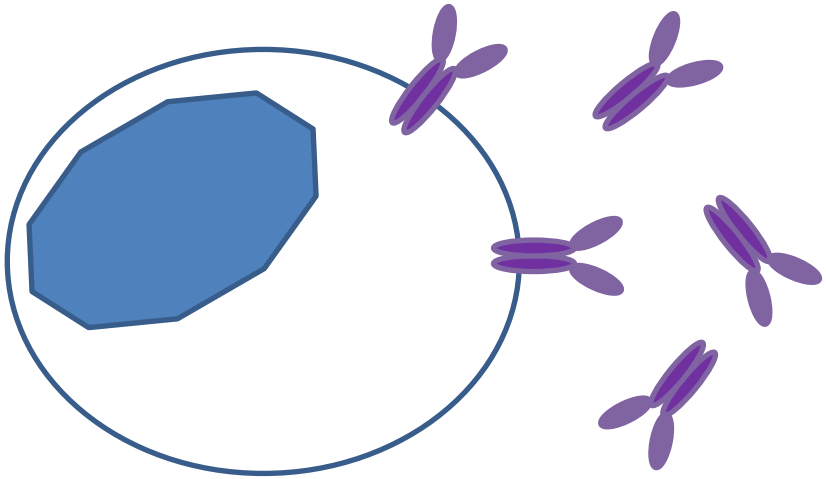


Tumor Cell



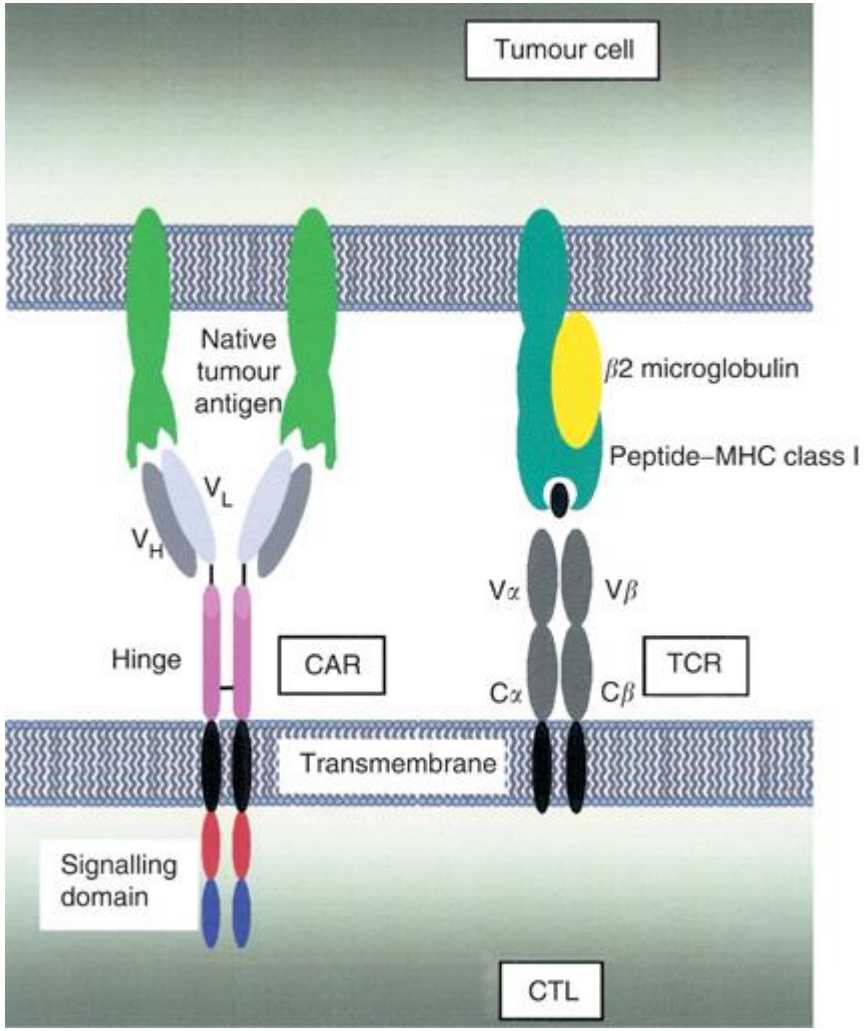
Chimeric Antigen Receptor



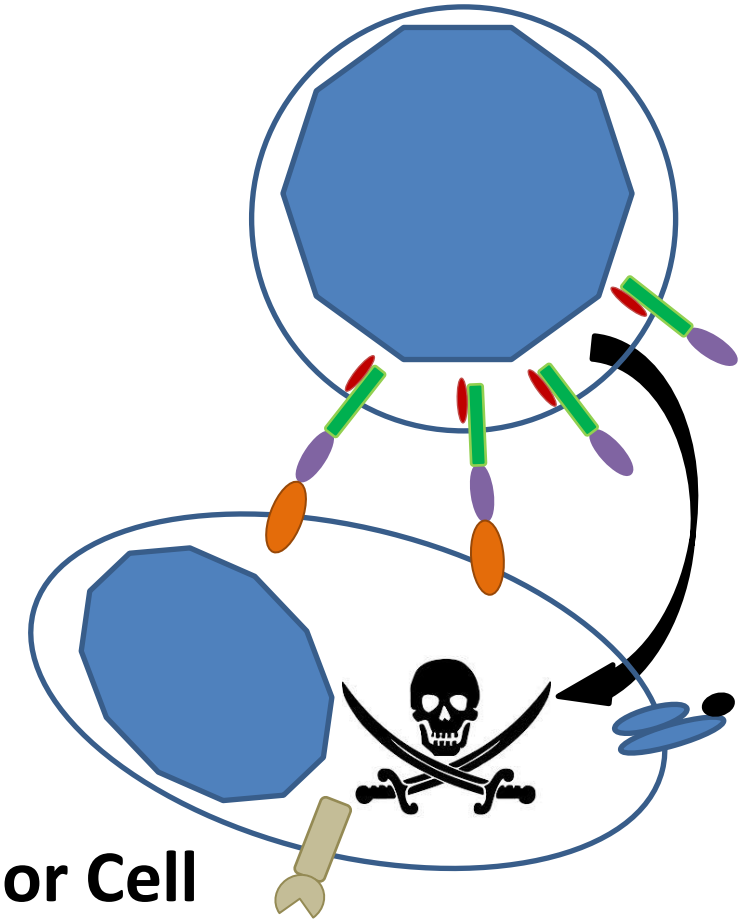


Plasma B-cell

Immunologic Therapy



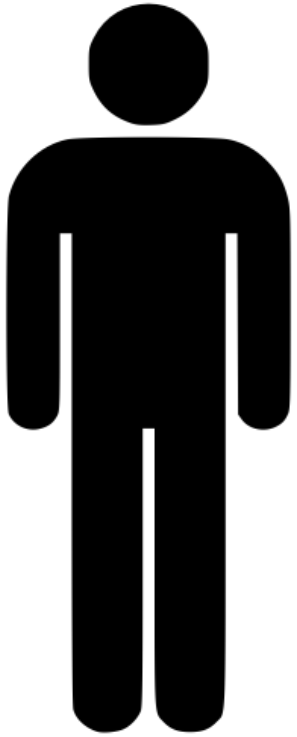
Chimeric Antigen Receptor Modified T-cell



Tumor Cell

UC San Diego
Moores Cancer Center

From Genetic Biomarkers to Disease Targets



Skin Biopsy

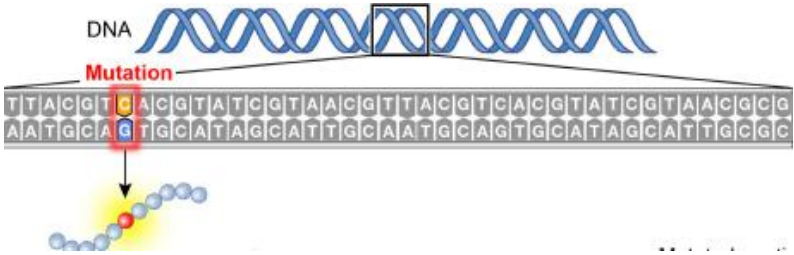
Bone Marrow Aspirate

Blood Apheresis

Whole Exome and Whole Transcriptome Sequencing
$CD34^+$ and monocytes

Isolation of Autologous Killer T-Cells and
Antigen Presenting B-Cells

Somatic Mutations Expressed by MDS Cells



PersImmune

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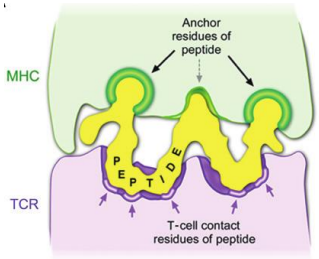
Genetically Targeted Immunotherapy

Isolation of Autologous Killer T-Cells

Somatic Mutations Expressed by MDS Cells

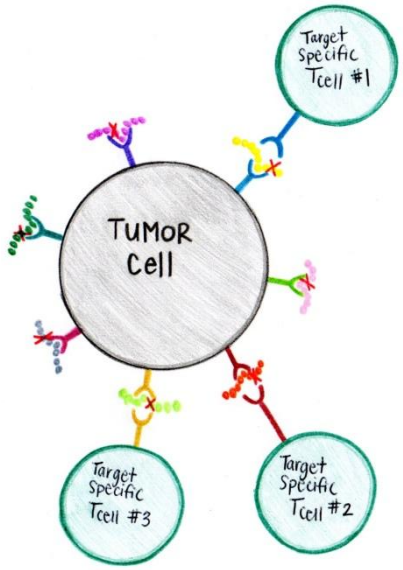


Incubation of Antigen Presenting Cells And Killer T-Cells

Antigen Presenting Cells + Synthetic HLA-Compatible Mutated Peptide Fragments

***Ex-vivo* Selection and Expansion of Antigen Reactive T-Cells**

Patient Infusion!



PersImmune

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Bejar Lab

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Tiffany Tanaka
Emily Wheeler
Robyn Raban
Soo Park
Brian Reilly
Armon Azizi

UC San Diego
Moores Cancer Center

To all of our AMAZING PATIENTS and our INFUSION CENTER nurses and staff!

mds foundation
the myelodysplastic syndromes foundation, inc.