MDS – Therapies and Treatment Options 2019

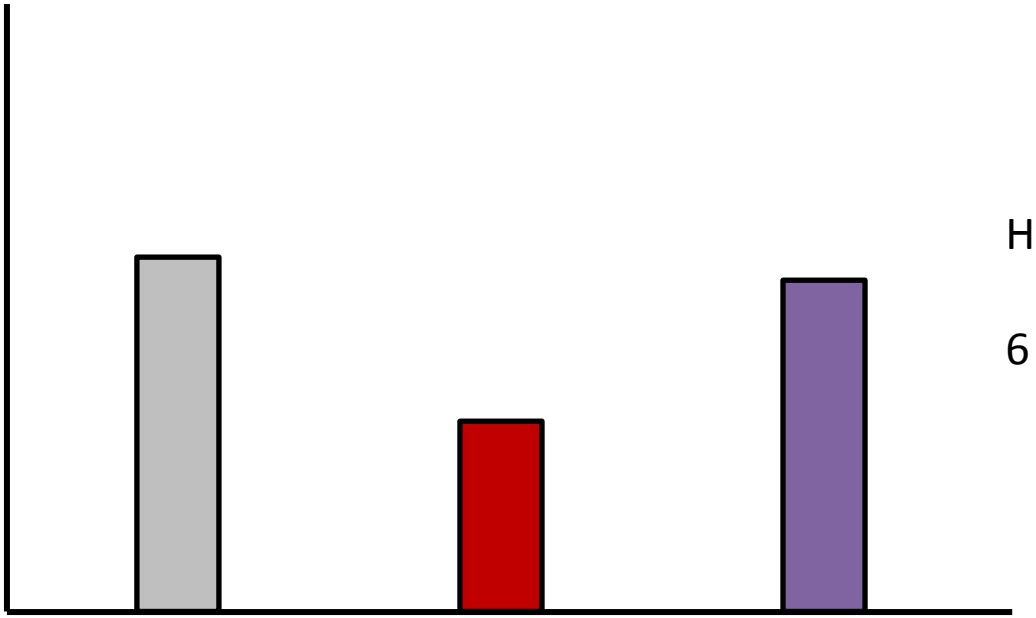
Salman Fazal, M.D
Director, Cell Transplantation,
Allegheny Health Network Cancer Institute,
Pittsburgh, PA
Assistant Professor, Temple University School of Medicine.

Objectives

- Understand the difference between low-risk and high risk MDS
- Understand the MDS classification and scoring systems and what they mean in regards to your diagnosis
- Understand your treatment options as well as the advances in MDS treatment, particularly bone marrow transplants in older MDS patients
- Understand what personalized medicine means in relationship to MDS
- Understand how to take an active role in your care

I have anemia?

72 year-old woman with worsening shortness of breath, now has blood test which showed



Hemoglobin was 11

6 months ago

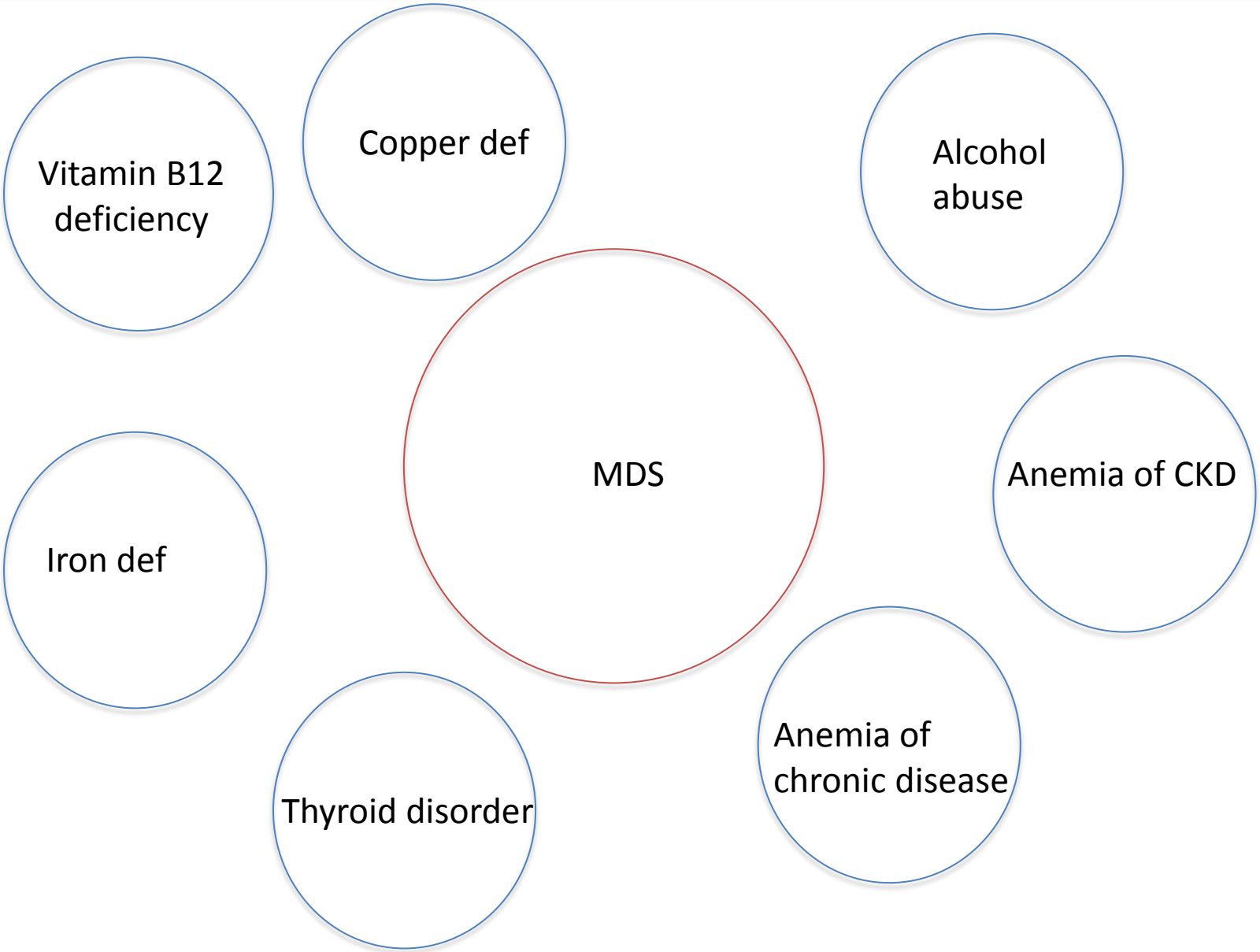
WBC	Hgb	Platelets
5,000	7	250,000

Questions

- What do I have?

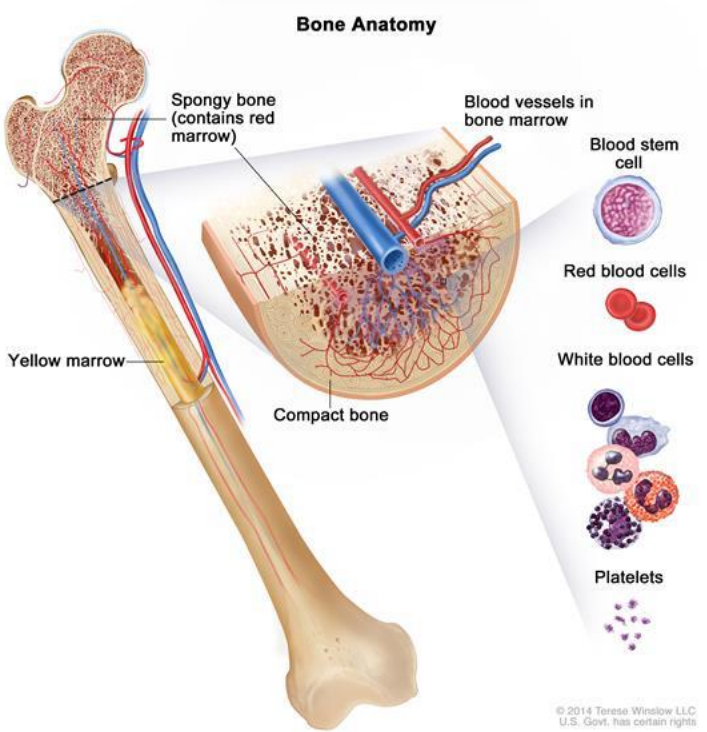
- Can I take iron or other supplements to help ?

I have anemia?

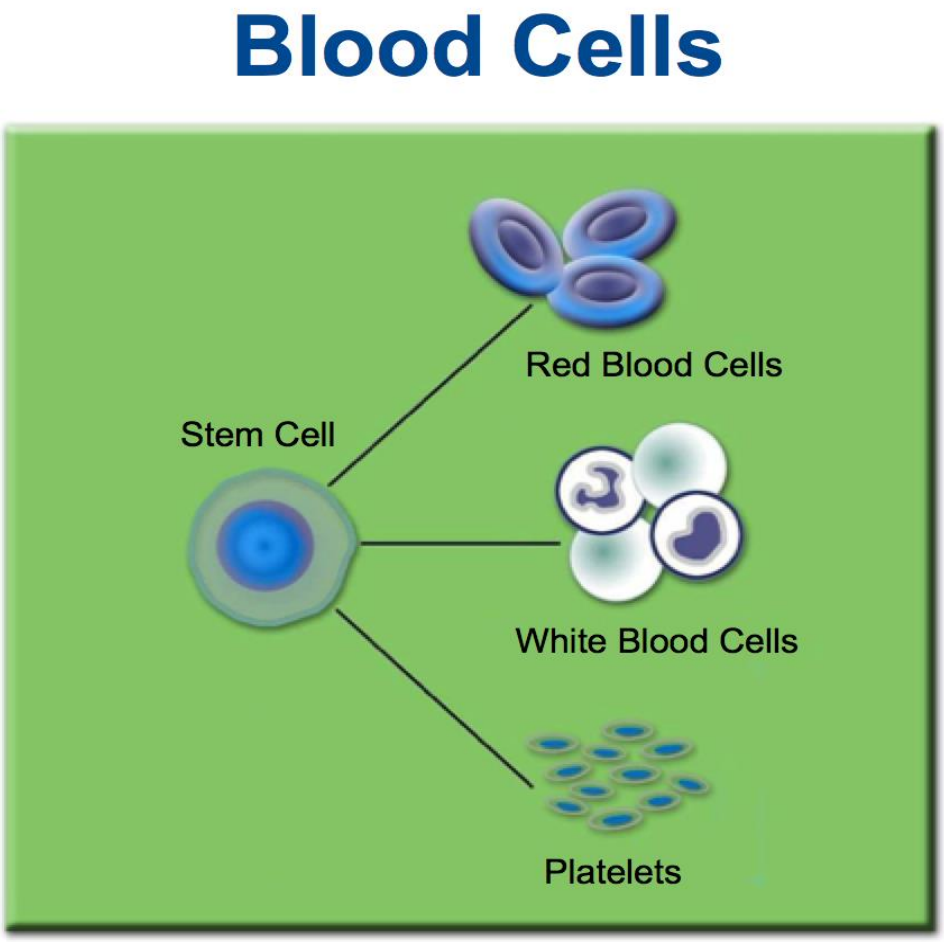


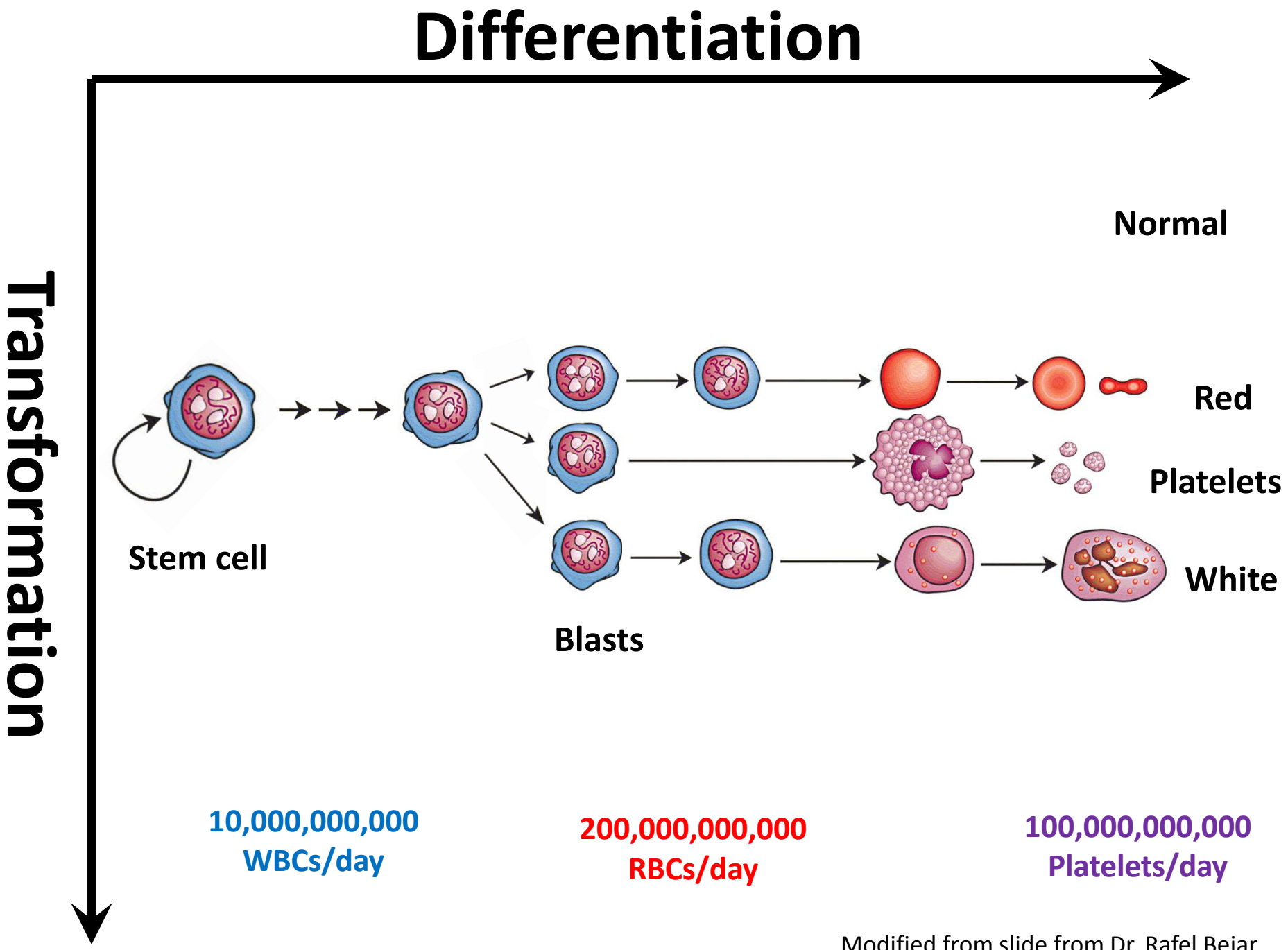
MDS – Let's build a definition

- Myelo – Bone marrow



MDS – What does bone marrow do?

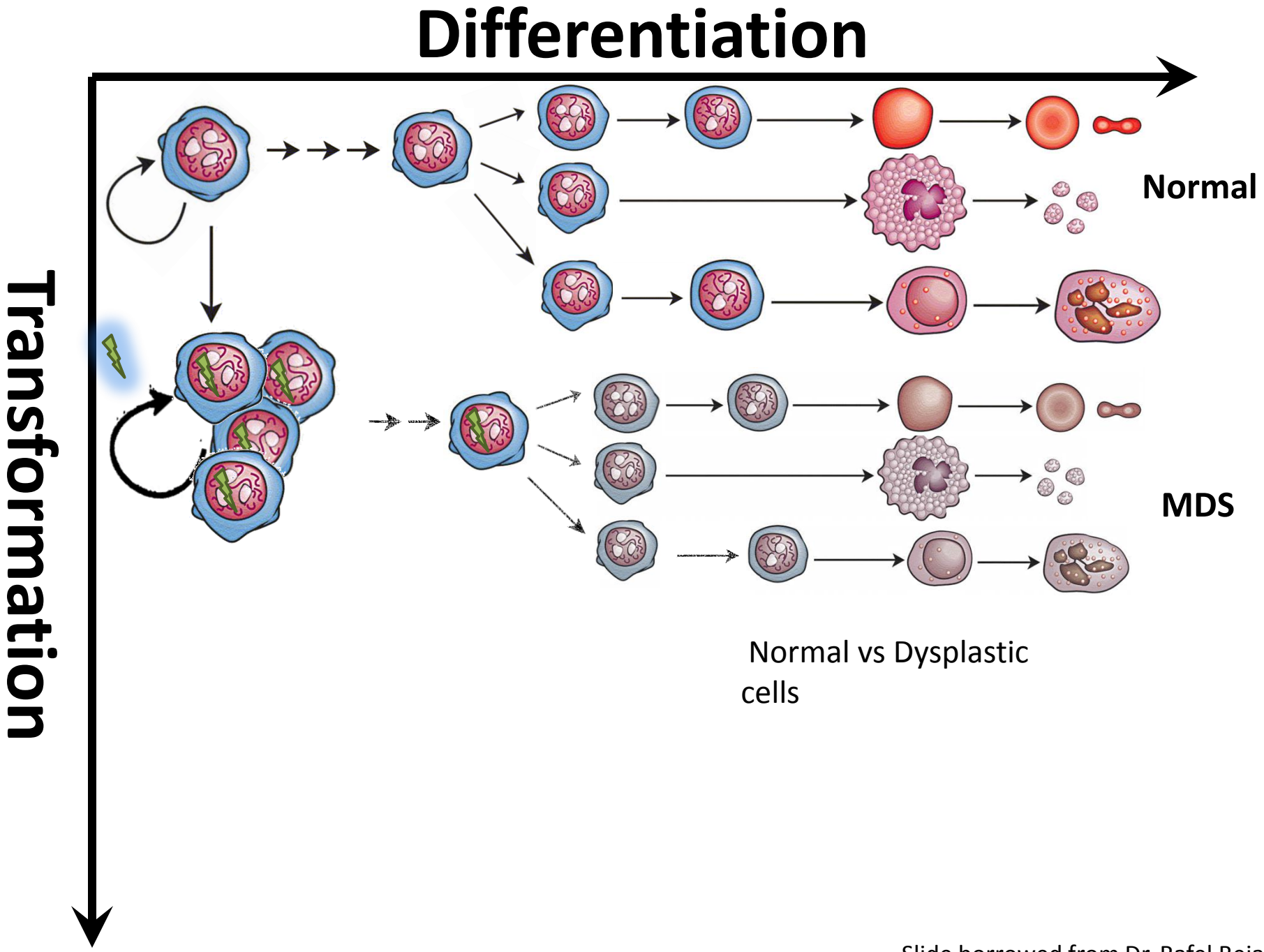




Modified from slide from Dr. Rafel Bejar

MDS – Let's build a definition

- **Dysplastic –** Funny looking
- Abnormal appearance of cells when viewed under the microscope
- Difference in shapes, sizes, granules (particles with the cell)
- Can be caused by many conditions, not only MDS



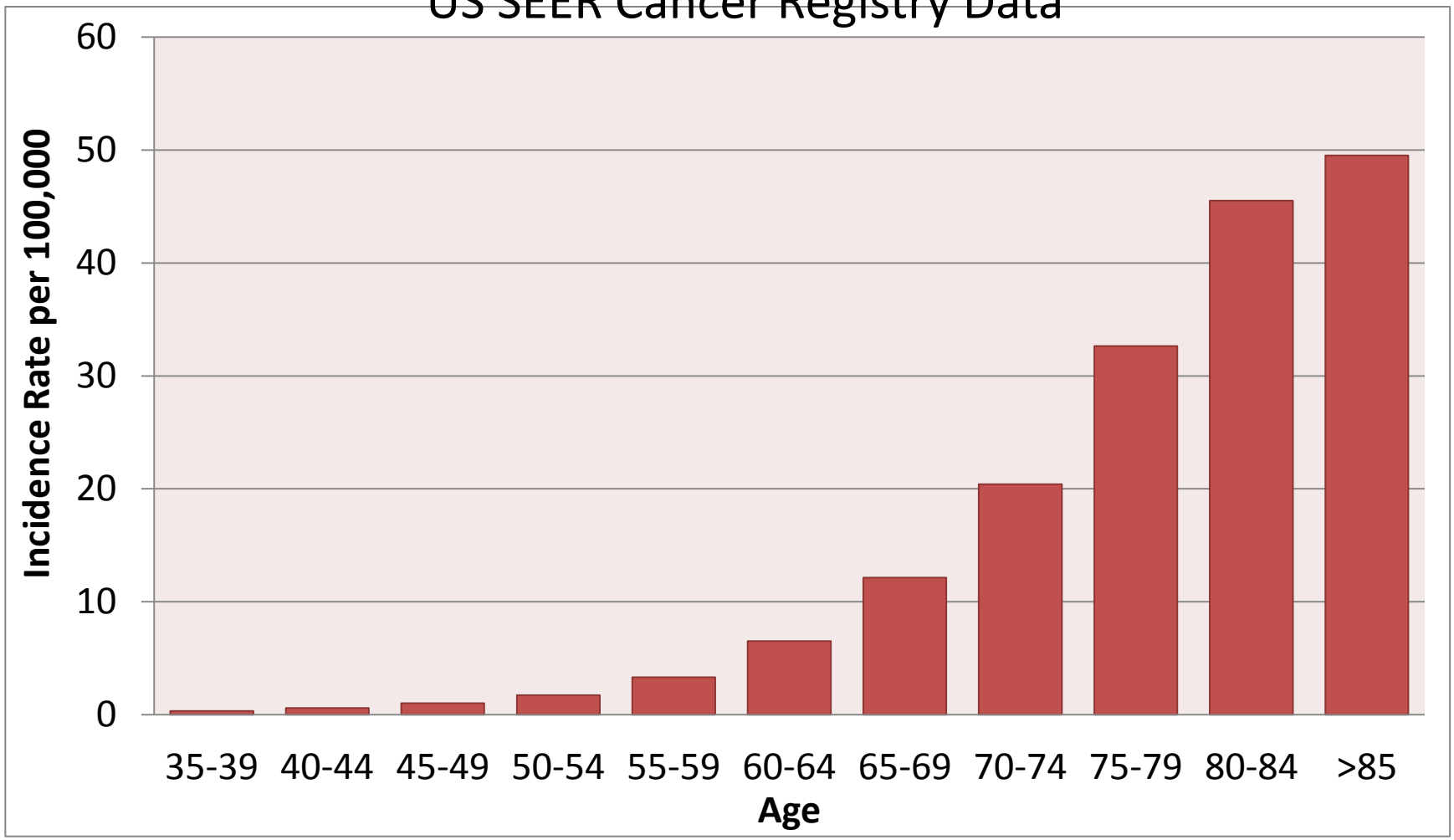
Normal vs Dysplastic cells

Slide borrowed from Dr. Rafel Bejar

MDS – Let's build a definition

- Syndrome – Collection of symptoms

MDS Incidence Rates 2000-2008



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

Etiology of MDS

85%	10-15%	<5%
"De novo" (idiopathic, primary)	**Ionizing radiation, Chemo (DNA alkylating agents)** (chlorambucil, melphalan, cyclophosphamide, etc.)	**Chemotherapy (Topoisomerase II inhibitors)** (etoposide, anthracyclines, used in Rx of Breast Ca etc.)
		
Median age ~71 years; increased risk with **aging**	Between 5-10 **years following exposure**	Peaks **1-3 years following exposure**

Slide borrowed from Dr. David Steensma

Risk factors for MDS

Environmental

AGING

Exposure to **DNA alkylating agents** *(chlorambucil, melphalan, cyclophosphamide)*

Exposure to **topoisomerase II inhibitors** *(etoposide, anthracyclines)*

Exposure to **ionizing radiation**

Environmental / occupational exposures *(hydrocarbons etc.)*

Antecedent acquired hematological disorders

Aplastic anemia (15-20%)

PNH (5-25%)

Inborn

Fanconi anemia

Familial Platelet Disorder with AML Predisposition ("FPD-AML") (**RUNX1,**

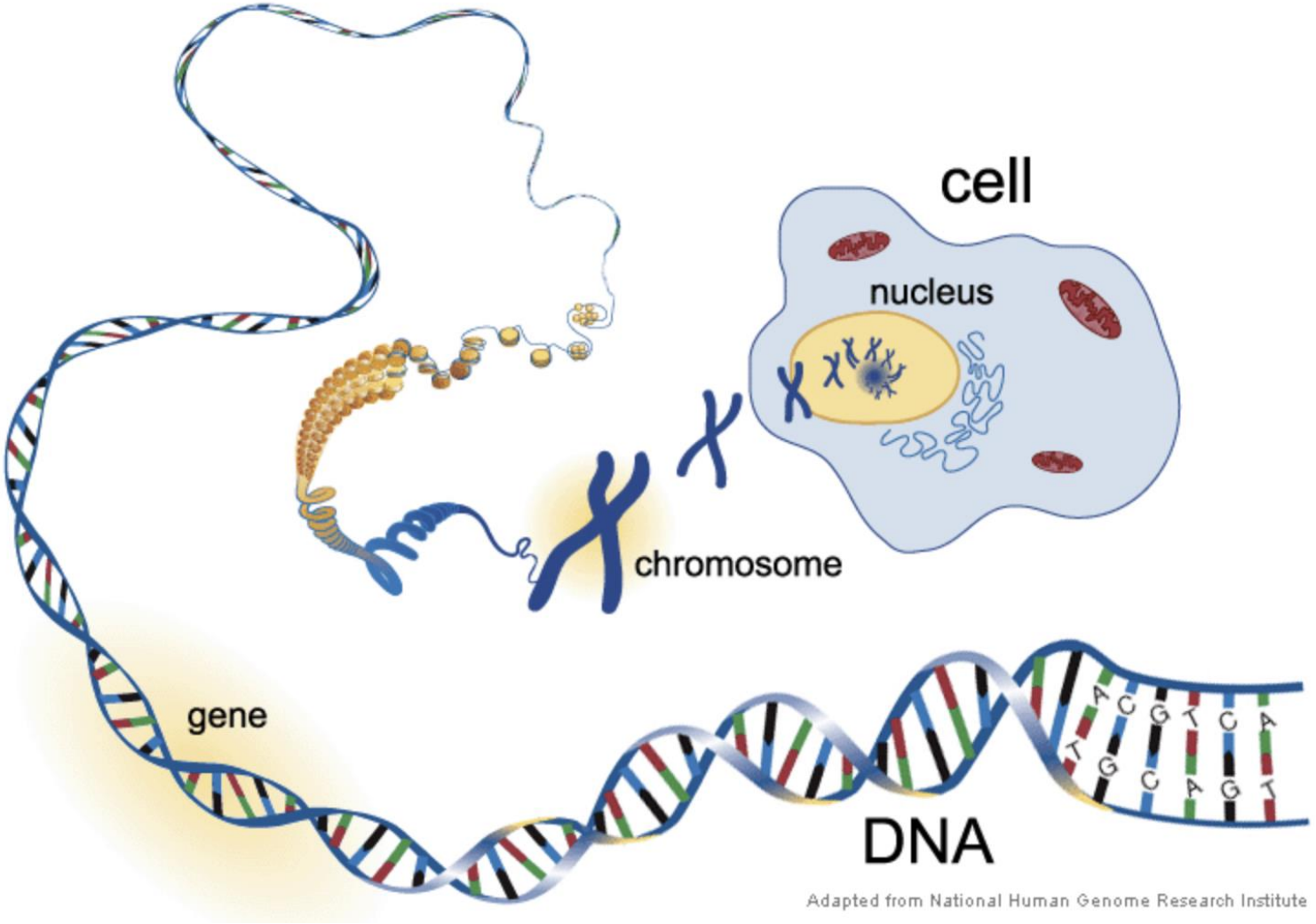
GATA2 mutant (*MonoMACsyndrome:* monocytopenia, B/NK lymphopenia, atypical mycobacteria and viral and other infections, pulmonary proteinosis, neoplasms)

Other congenital marrow failure syndromes or DNA repair defects (Bloom syndrome, ataxia-telangiectasia, etc.)

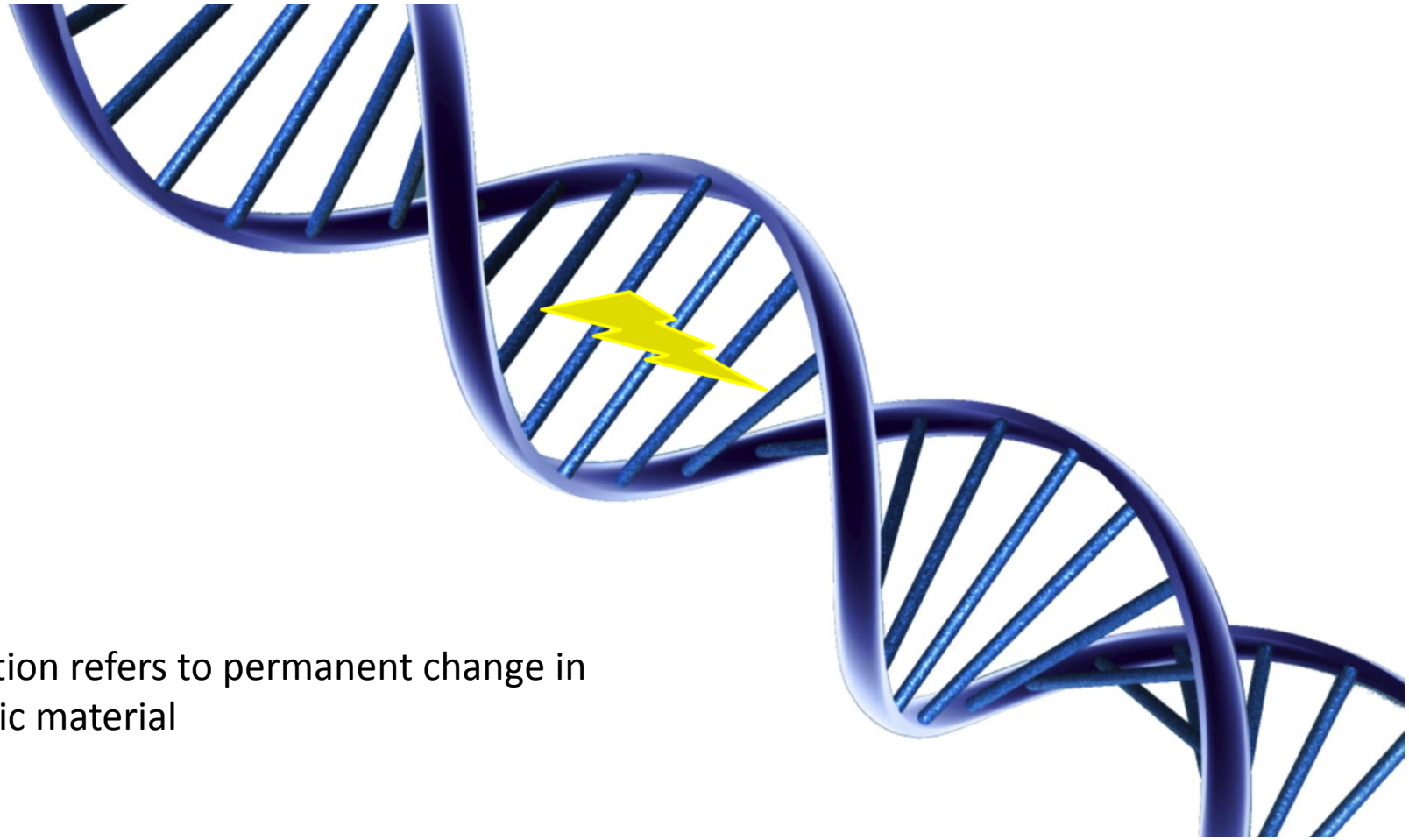
Familial syndromes of unknown origin

Slide borrowed from Dr. David Steensma

Genetics - Basics



Genetics - Mutations



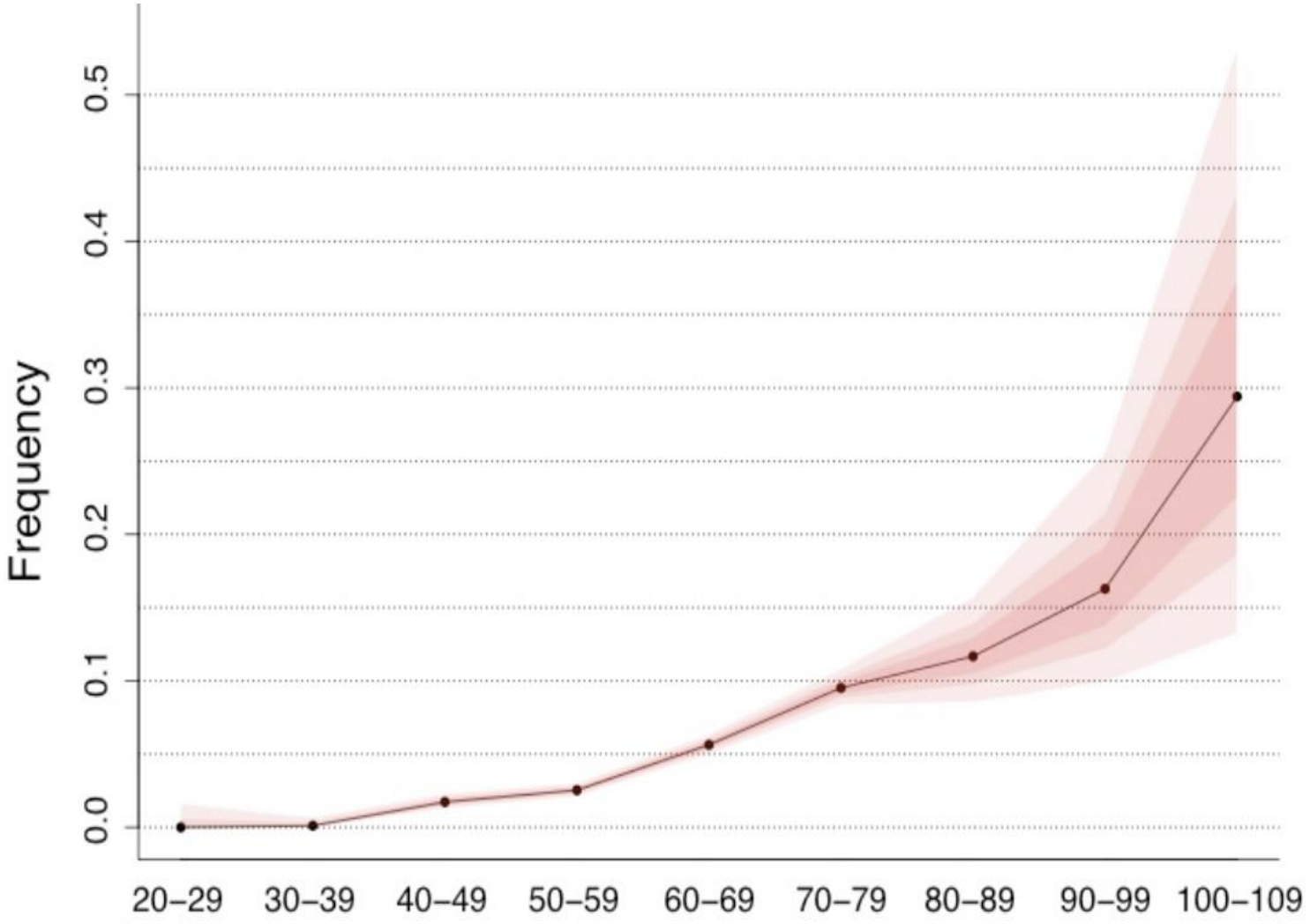
Mutation refers to permanent change in genetic material

Mutations accumulate and Get fixed When We are Young

Mutations accumulate and Get fixed (Less Well as we age)

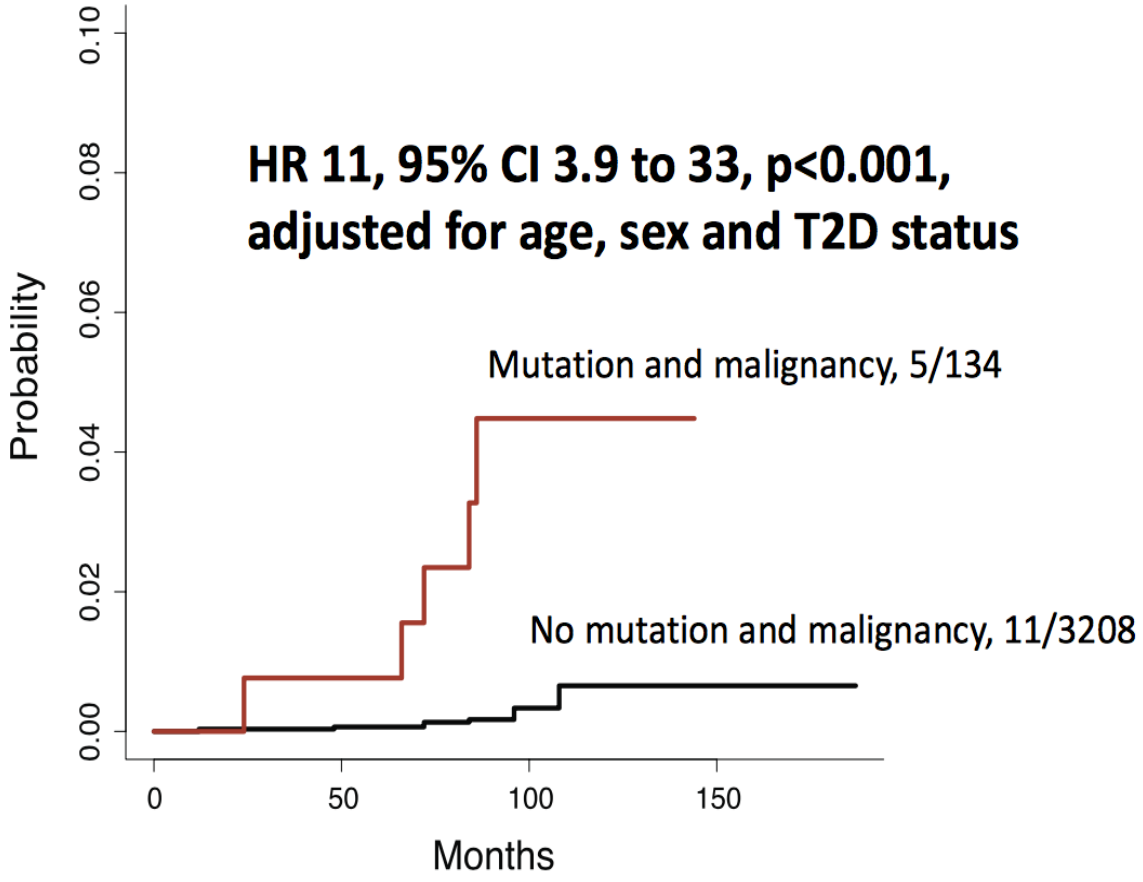
Mutations may occurs in CRITICAL areas of our genes

Age related Clonal hematopoiesis

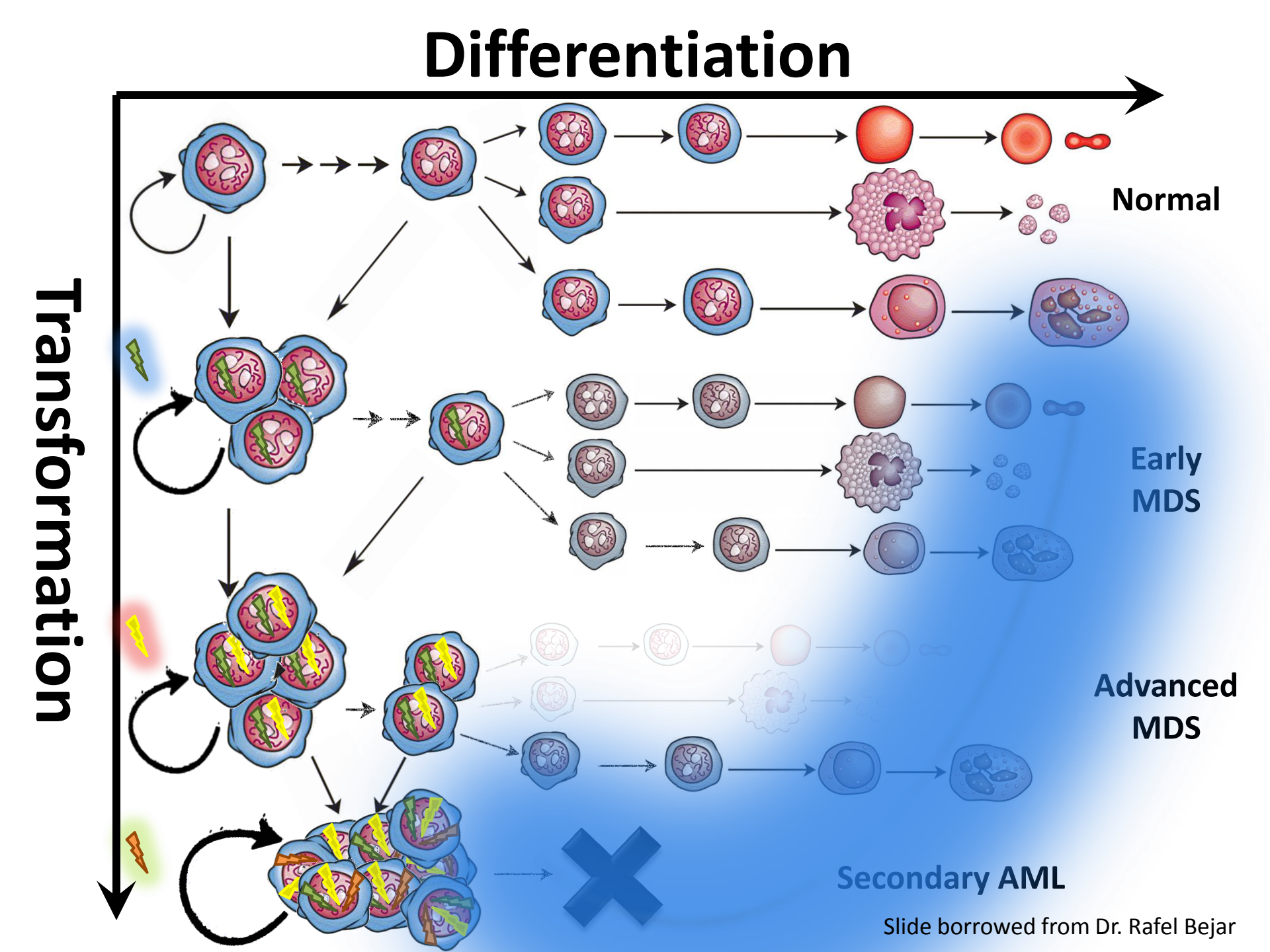


Jaiswal et al NEJM

Clonal hematopoiesis is associated with increased risk of hematologic malignancy



C.H.I.P



Slide borrowed from Dr. Rafel Bejar

Myelodysplastic Syndromes

- Ineffective Blood cell production leads to low blood counts
- Clonal expansion of abnormal cells
- **Paradox of low counts in a hypercellular bone marrow**
- Risk of transformation to Acute Myeloid leukemia
  - (Pre-leukemia?)

Signs and Symptoms

Anemia

- Fatigue
- Shortness of breath
- Chest pain (if active heart problem)
- Exacerbation of heart failure

Neutropenia

- Active infection
- At risk of infection

Thrombocytopenia

- Petechiae
- Risk of bleeding

MDS – CBC

- White Blood Cell: Important to see the differential
- Rising WBC, especially with “BLASTS” could indicate transition to more aggressive MDS or AML
- Low WBC, especially Neutrophils below 1000 can increase risk of infection,
- Hemoglobin: below 10 can cause symptoms, below 7-8 may require transfusion in symptomatic patients
- Platelets between 20,000-100,000 (20-100) generally no intervention offered but be careful of trauma as bleeding risk increases at lower levels

Making the Diagnosis

Minimal Diagnostic Criteria

Low blood counts(s):

- Hb <11 g/dL, *or*
- ANC <1500/µL, *or*
- Platelets <100 x 10^9L

MDS "decisive" criteria:

- >10% **dysplastic cells** in 1 or more cell lineages, *or*
- 5-19% **blasts**, *or*
- Abnormal **karyotype** typical for MDS, *or*
- Evidence of **clonality** (by FISH or another test)

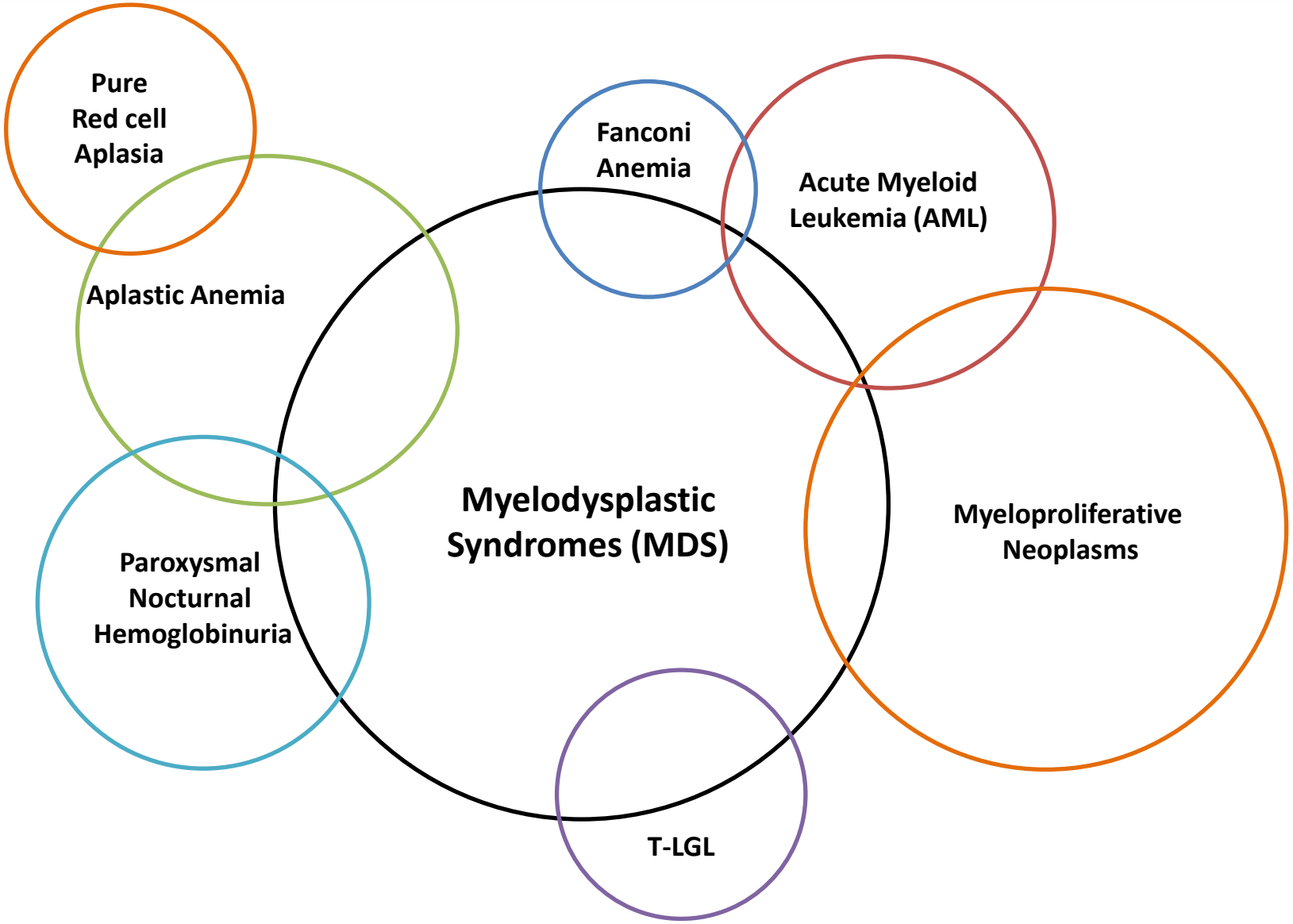
Other causes of cytopenias and morphological changes EXCLUDED:

- *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.)*

Permitted to use fromDr. David Steensma

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

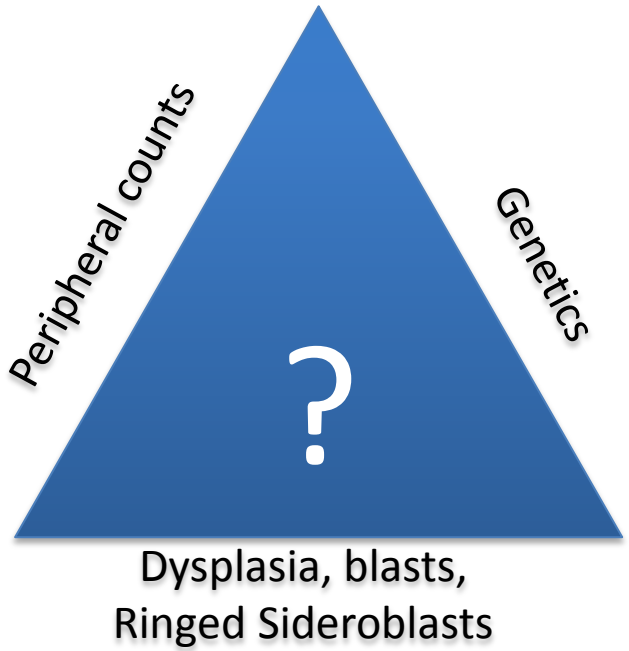
Clinical Overlap



Classification of MDS Subtypes

MDS classification 2016

- Pathologist, clinicians communicate that they are diagnosing, treating and studying the same disease



Changes in World Health Organization MDS categories (2016)

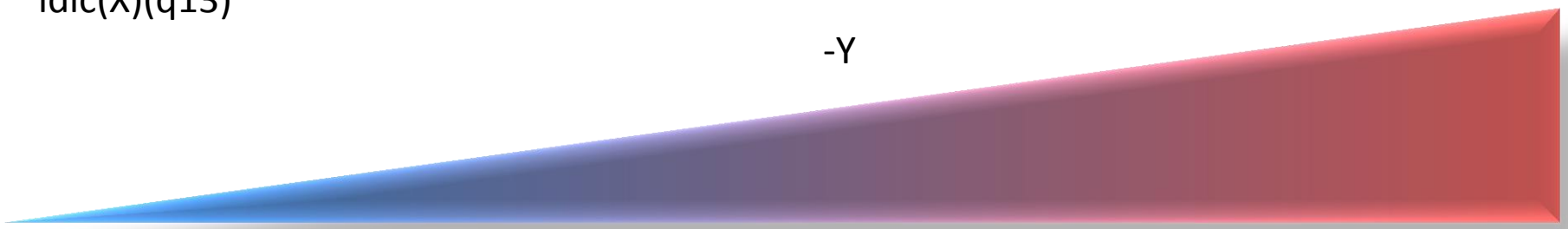
2008 Name	Abbrev	2016 Name	Abbrev
Refractory cytopenia with unilineage dysplasia	RCUD (includes RA,RN, RT)	MDS with single lineage dysplasia	MDS-SLD
Refractory anemia with ringed sideroblasts	RARS	MDS with ringed sideroblasts	MDS-RS
MDS with isolated 5q	Del (5q)	unchanged	unchanged
Refractory cytopenia with multilineage dysplasia	RCMD	MDS with multilineage dysplasia	MDS-MLD
		(with ringed sideroblasts*)	MDS-RS-MLD
Refractory anemia with excess blasts type 1	RAEB-1	MDS with excess blasts, type 1	MDS-EB-1
Refractory anemia with excess blast type 2	RAEB-2	MDS with excess blast, type 2	MDS-EB-2
MDS, unclassifiable	MDS-U	unchanged	unchanged
Refractory cytopenia(s) of childhood	RCC	unchanged	unchanged

Now includes <15% siderblasts if SF3B1 mutation is present

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition.

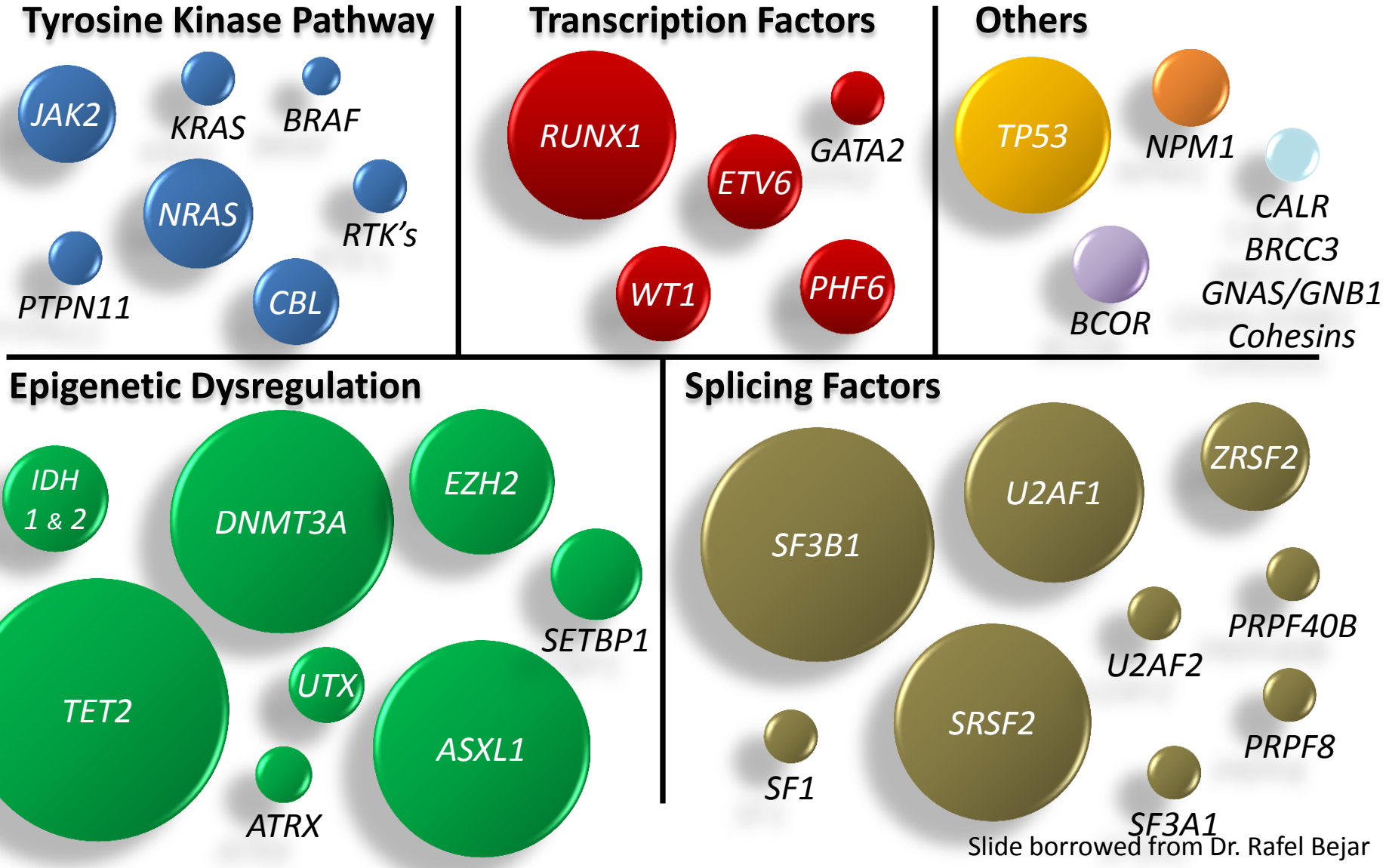
Genetic Abnormalities in MDS

Translocations / Rearrangements	Uniparental disomy / Microdeletions	Copy Number Change	Point Mutations
Rare in MDS:	Rare - often at sites of point mutations:	About 50% of cases:	Most common:
t(6;9)	4q *TET2*	del(5q)	Likely in all cases
i(17q)	7q *EZH2*	-7/del(7q)	
t(1;7)	11q *CBL*	del(20q)	~90% of cases have mutations in a known gene
t(3;?)	17p *TP53*	del(17p)	
t(11;?)		del(11q)	
inv(3)		del(12p)	
idic(X)(q13)		+8	
		-Y	



Observed Frequency in MDS

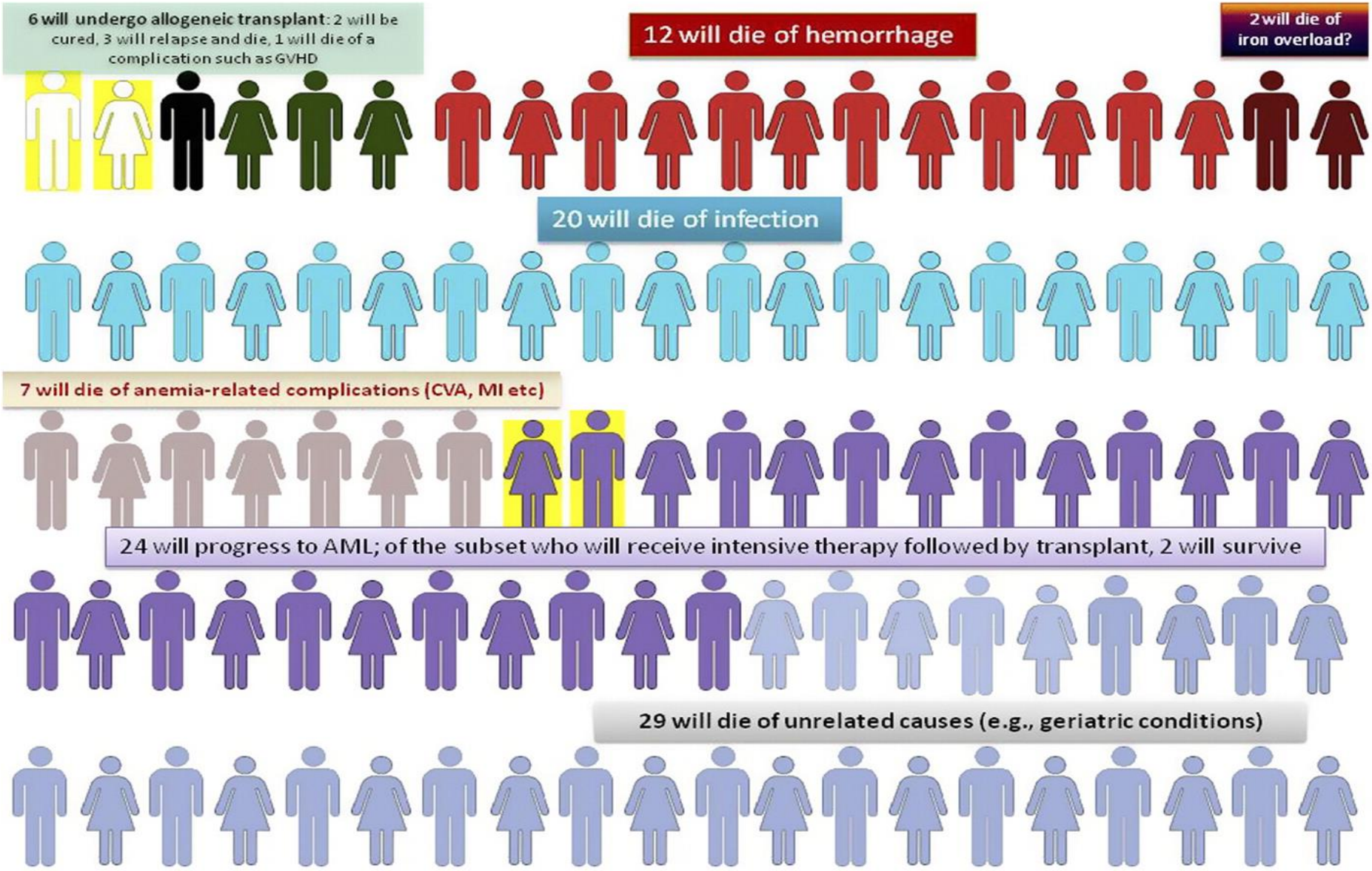
Point Mutations in MDS



Slide borrowed from Dr. Rafel Bejar

Prognostic Risk Assessment

If all of the MDS patients diagnosed in the U.S. this year were represented as 100 people…



What does this mean for me?

- Your doctor can use simple clinical information from your blood and bone marrow tests to give you SOME IDEA how long your disease is likely to remain stable

- This information is useful in helping choose therapies

IPSS-R

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% to <5%	5% to 10%	>10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥10	8 to <10	<8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥100	50 to <100	<50		
	0	0.5	1		
Absolute neutrophil count (x 10^9/L)	≥0.8	<0.8			
	0	0.5			

Possible range of summed scores: 0-10

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

Cytogenetics - 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, 2 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%

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

IPSS-R

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 to 3	38	5.3	10.8
Intermediate	>3 to 4.5	20	3.0	3.2
High	>4.5 to 6	13	1.6	1.4
Very High	>6	10	0.8	0.73

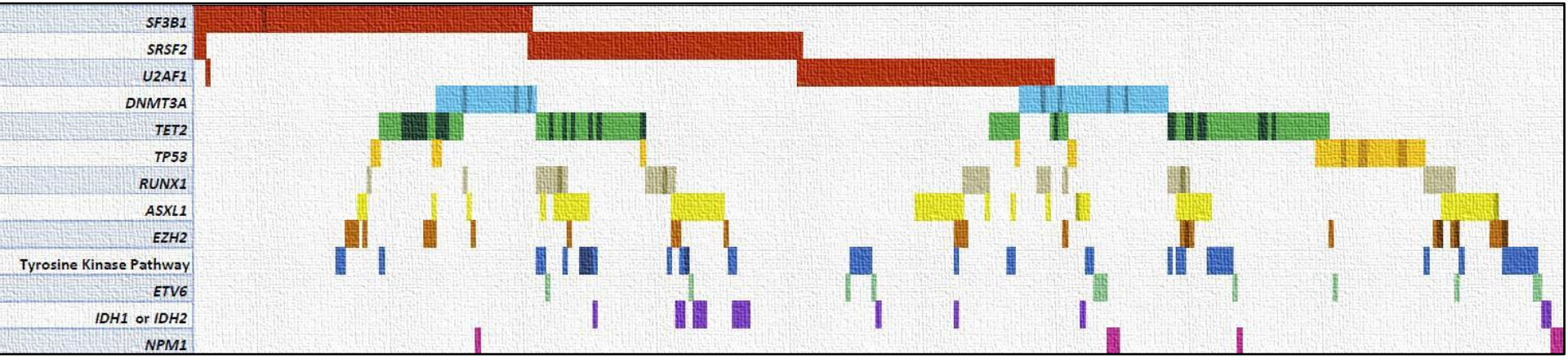
Greenberg et al. *Blood.* 2012:120:2454-65

Limitations of IPSS-R

- Roughly half of patients have relevant cytogenetic abnormalities
- Heterogeneity remains within each risk category, particularly the lower-risk categories.
- Excludes therapy-related MDS and CMML
- Is only validated at the time of initial diagnosis in untreated patients
- Cannot be applied during the course of disease

The IPSS's do not include mutational data

MDS Mutation Profile



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

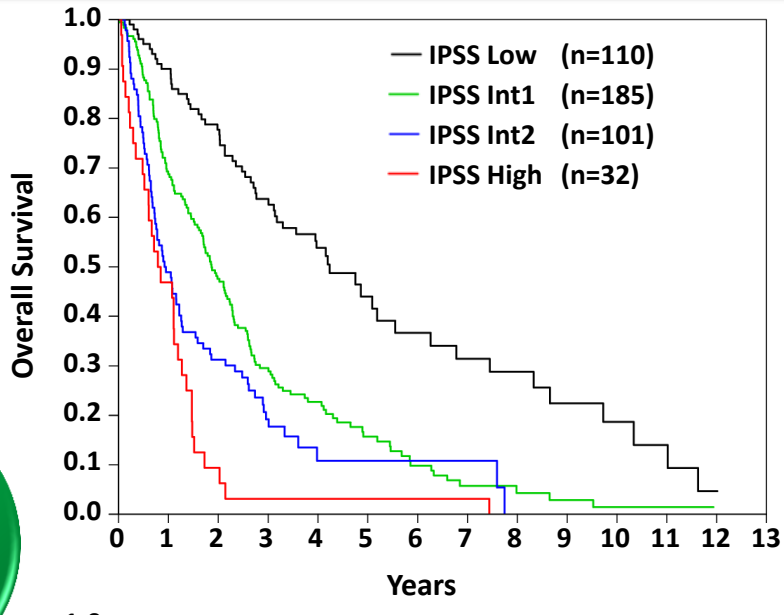
TP53

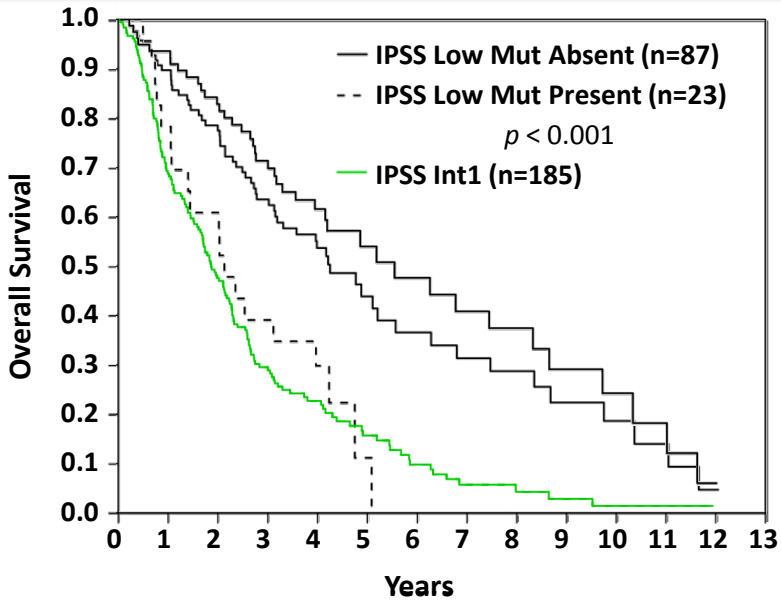
ETV6

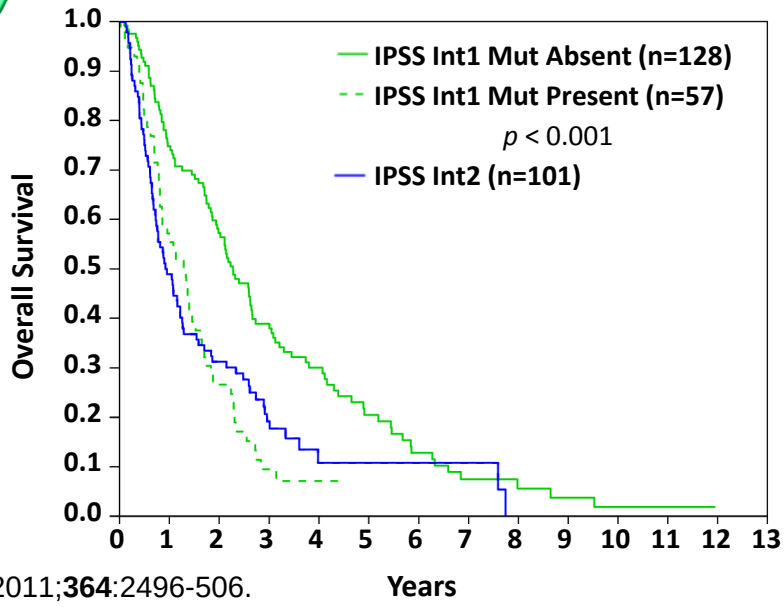
ASXL1

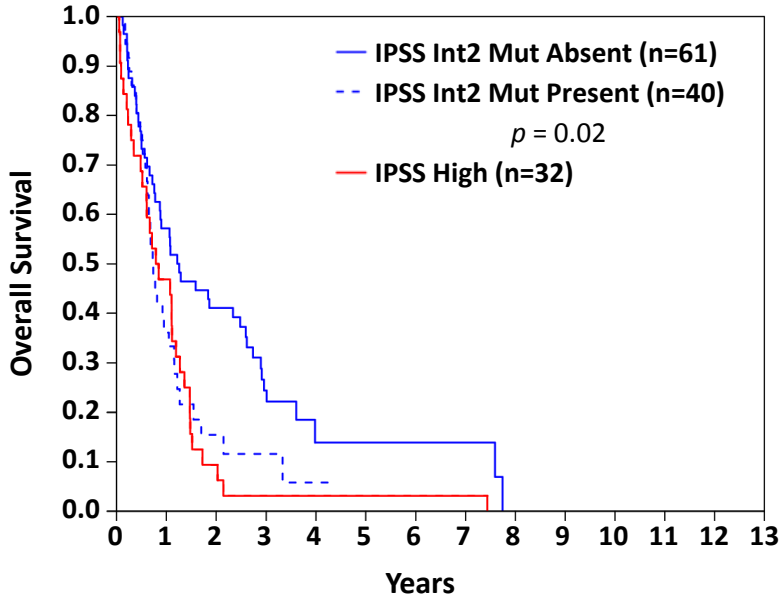
EZH2

RUNX1









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

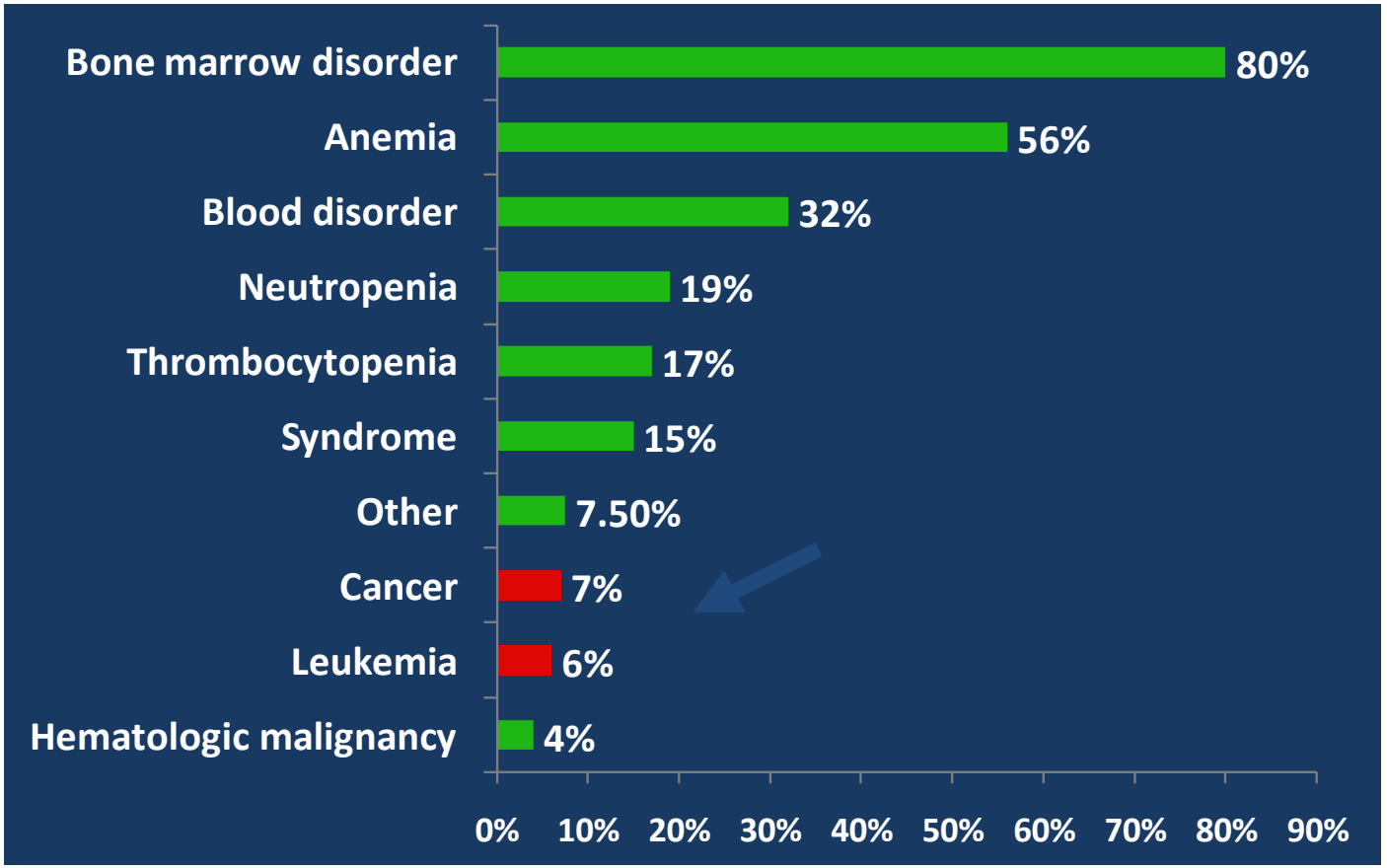
Prognostic value of self-reported fatigue on overall survival in patients with myelodysplastic syndromes: a multicentre, prospective, observational, cohort study

Fabio Efficace, Gianluca Gaidano, Massimo Breccia, Maria Teresa Voso, Francesco Cottone, Emanuele Angelucci, Giovanni Caocci, Reinhard Stauder, Dominik Selleslag, Mirjam Sprangers, Uwe Platzbecker, Alessandra Ricco, Grazia Sanpaolo, Odile Beyne-Rauzy, Francesco Buccisano, Giuseppe A Palumbo, David Bowen, Khanh Nguyen, Pasquale Niscola, Marco Vignetti, Franco Mandelli

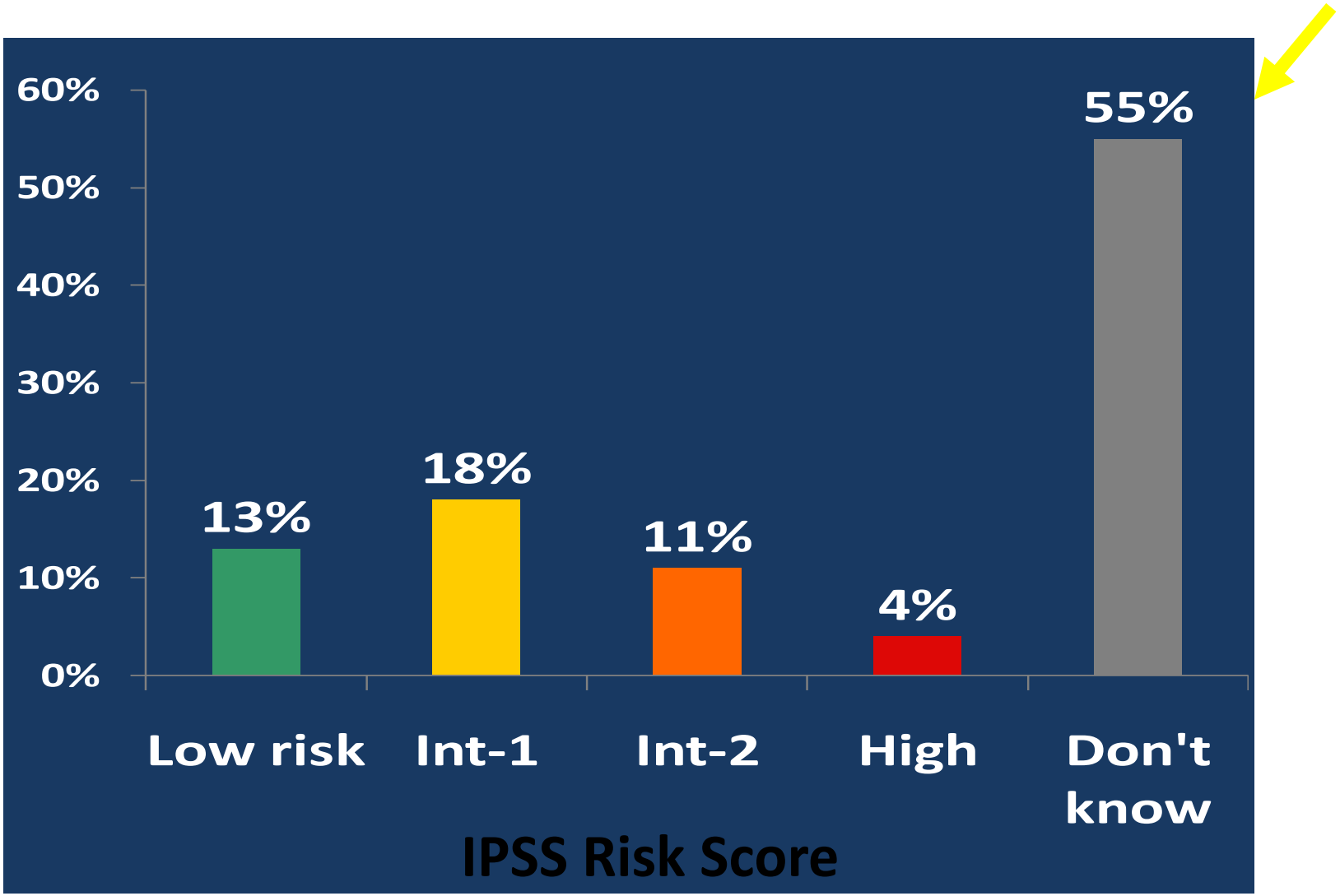
Pretreatment, patient self reported fatigue in high risk MDS provide important information about the severity of the disease

How Long Did It Take to Get an MDS Diagnosis?

How Doctors First Describe MDS



What's My Risk?



Sekeres et al. ASH 2009; abstract 1771

Risk Adapted Therapy

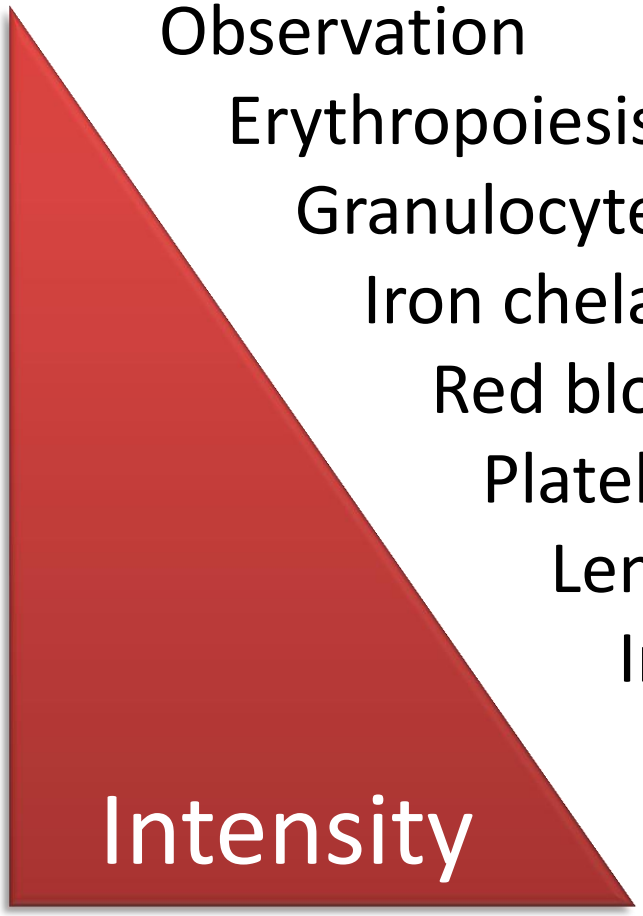
Goals of Treatment

- If possible, cure me
- If you cant cure me, atleast make me live longer and feel better
- If you cant make me live longer at least make me feel better
- If you can’t make me feel better, get me another doctor

Treatment Considerations

- Disease characteristics
  - Goals of therapy
  - Using low intensity treatment for low risk disease vs Intense therapy
- Treatment administrative characteristics
- Treatment pharmacology characteristics
  - Therapy can initially worsen patients' clinical condition
  - Avoid discontinuation of therapy before achieving benefit
- Patient characteristics
  - Age and frailty are relative but organs do have chronologic age
- Expectation management
  - Adverse events usually decrease in frequency as therapy continues
  - Treatment plans are created by mutual discussions

Treatment Options for MDS



Observation

Erythropoiesis stimulating agents

Granulocyte colony stimulating factor

Iron chelation

Red blood cell transfusion

Platelet transfusion

Lenalidomide

Immunosuppression

Hypomethylating agent

Stem cell transplantation

Clinical Trials – always the best option

Treating Lower Risk MDS

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.

Role of Transfusions

- Usually order Leukoreduced blood products.
- Can be life-saving, life-prolonging
- Platelets live about 7 days
  - 1 unit bump the platelets up by 20-30,000
  - Irradiated Platelets can have short life
- Red Blood Cells live from 7-28 days on average
  - 1 unit bumps the hemoglobin 1 point
  - Ongoing transfusion of red cells can lead to iron overload

Treating Lower Risk MDS -5q

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

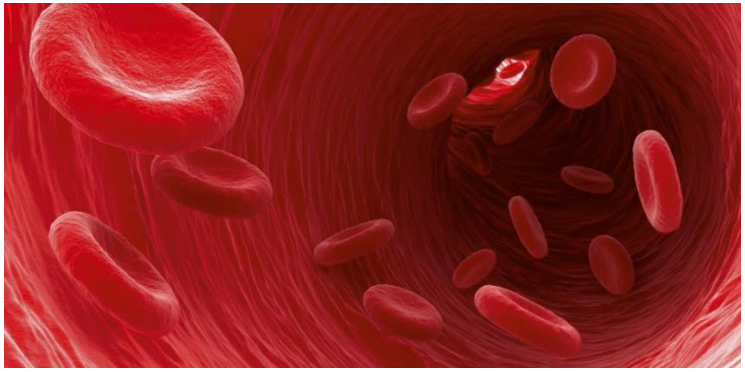
Primary Goal: to improve **QUALITY OF LIFE**

- Red blood cell growth factors
- Erythropoiesis Stimulating Agents (ESAs)

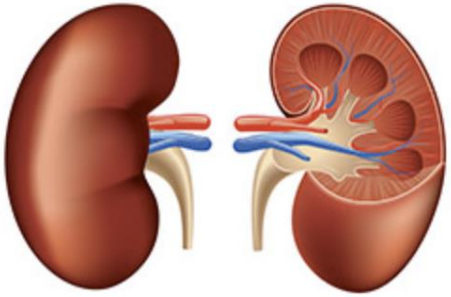
  Darbepoetin alfa (Aranesp)

  Epoetin alfa (Procrit, Epogen)

Erythropoeitin



Anemia leads to decreased oxygen to kidneys

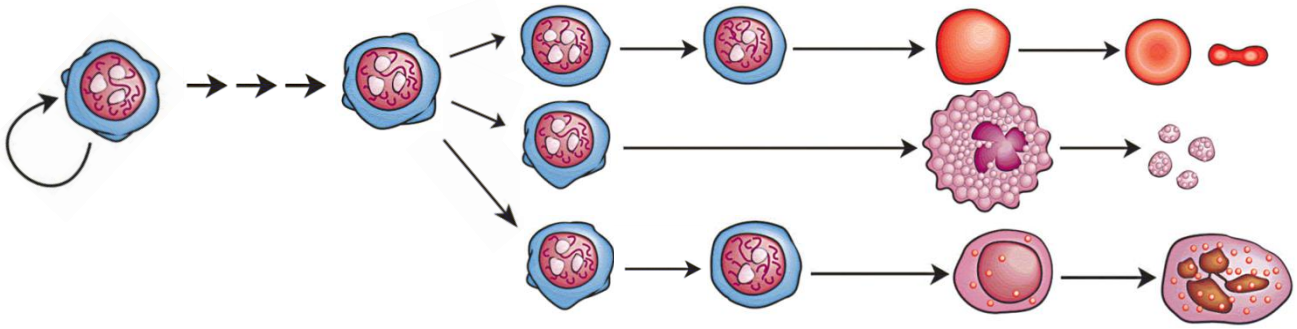


Erythropoeitin

Increased Red cell production

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

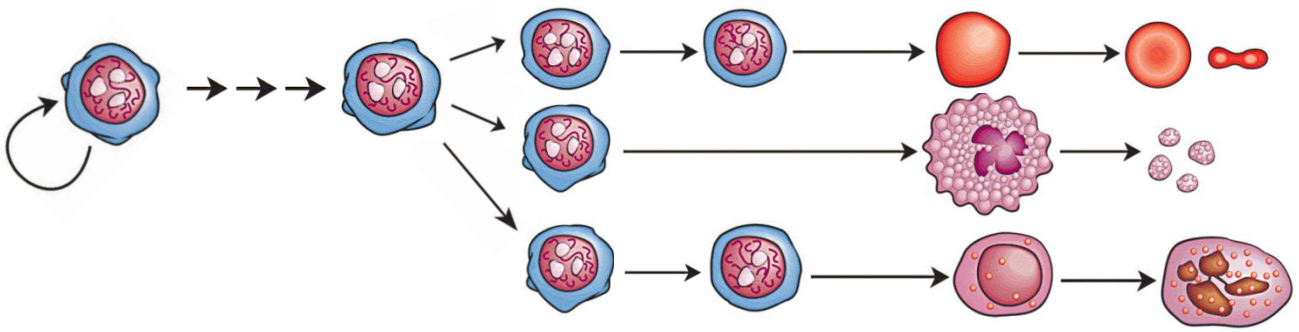
Growth factor in Low risk disease

- Majority of responses occur within 8-12 weeks
  - Trend Reticulocytes may help to see response
  - IPSS –R low and very low likely to response
  - EPO* in solid tumor patients showed increased heart attacks, stroke, heart failure, blood clots, increased tumor growth, death, especially when hgb >12
- Thrombotic events are rare provided Hgb level are controlled
- Interruption of treatment almost constantly provokes loss of response
- NOT FDA approved; major effects on insurance coverage

Park S, et al. *Blood*. 2008;111(2):574-582.; Jädersten M, et al. *J Clin Oncol*. 2008;26(21):3607-3613.; Hellström-Lindberg E, et al. *Br J Hematol*. 2003; 120:1037-1046.; Bennett CL, et al. *Semin Thromb Hemost*. 2012;38(8):783-796.; Bennett CL, et al. *JAMA*. 2008;299(8):914-924.; Bohlius J, et al. *Lancet*. 2009;373(9674):1532-1542.; Glaspy J, et al. *Br J Cancer*. 2010;102(2):301-315.; Tonelli M, et al. *CMAJ*. 2009;180(11):E62-E71.; Hershman DL, et al. *J Oncol Pract*. 2014;10(4):264-269.

Growth Factor Combinations

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



ESAs

TPO mimetics

G-CSF (neupogen)

ESAs can be combined with **G-CSF**

- response rate of **46.6%**, EPO <200 and <5% blasts predictive

ESAs can be combined with **Lenalidomide**

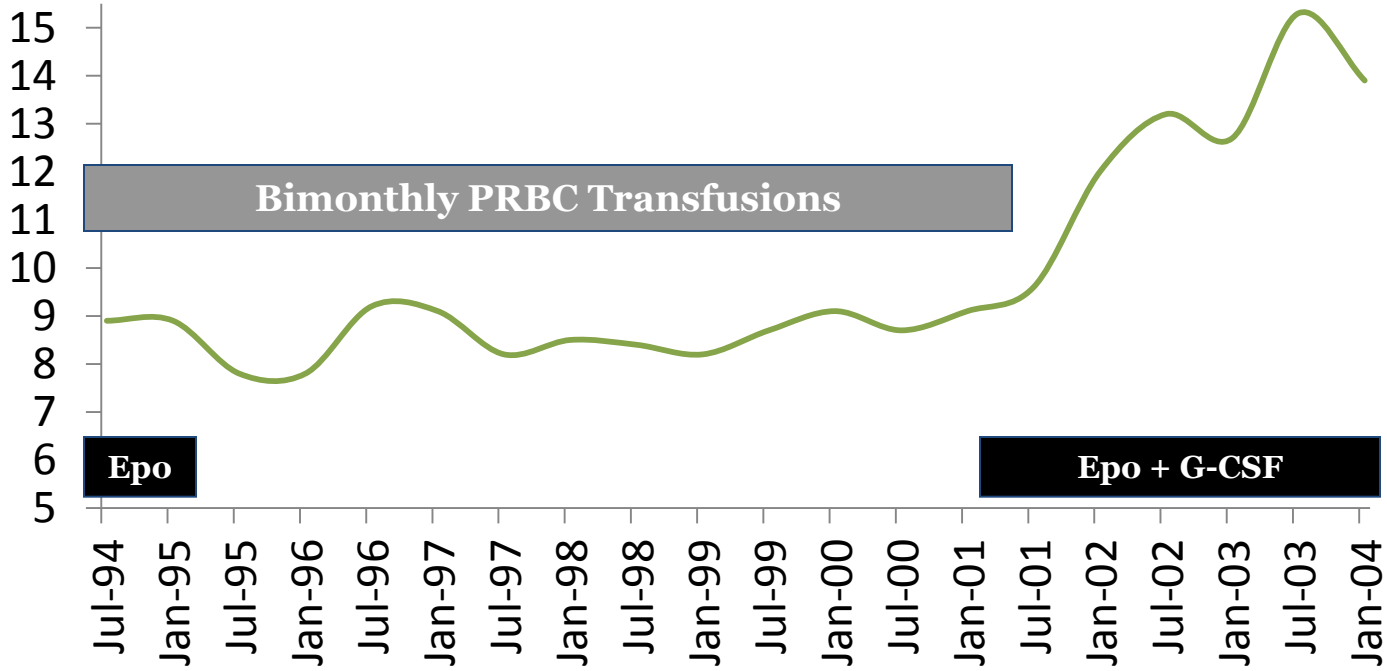
- response rate of 31% to Len, **52%** to both. TI 18.4% vs. **32.0%**!

ESAs can be combined with **Azacitidine** – not yet standard

Greenberg, P. L., Z. Sun, et al. (2009) *Blood* **114**(12): 2393-2400.
Toma A et al (*ASCO Abstract) J Clin Oncol* 31, 2013 (suppl; abstr 7002)

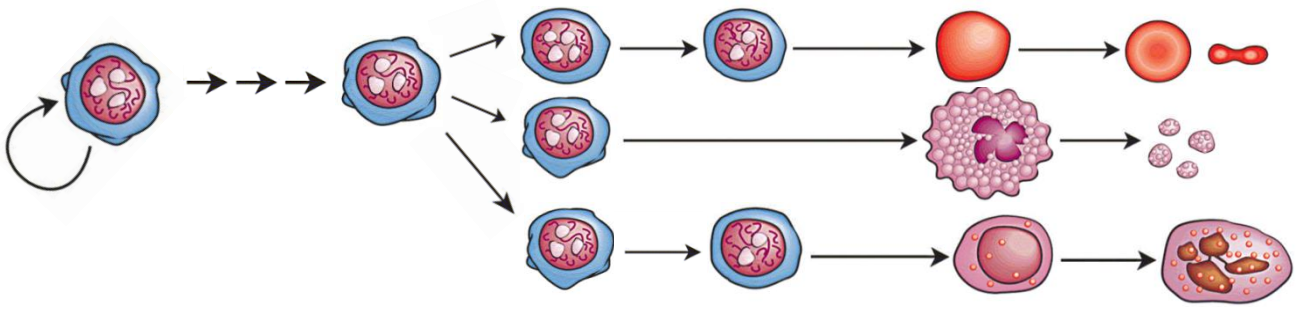
Epo + G-CSF → Synergy

81 year old female diagnosed with MDS-RARS



Thrombopoietin Mimetics

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



ESAs

TPO mimetics

G-CSF (neupogen)

Eltrombopag (Oral) & Romiplostim SC – 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

Treating Lower Risk MDS

What my next most effective therapy?

- Immunosuppression

<u>Who is likely to respond</u>

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

Immunosuppression -Underutilized

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

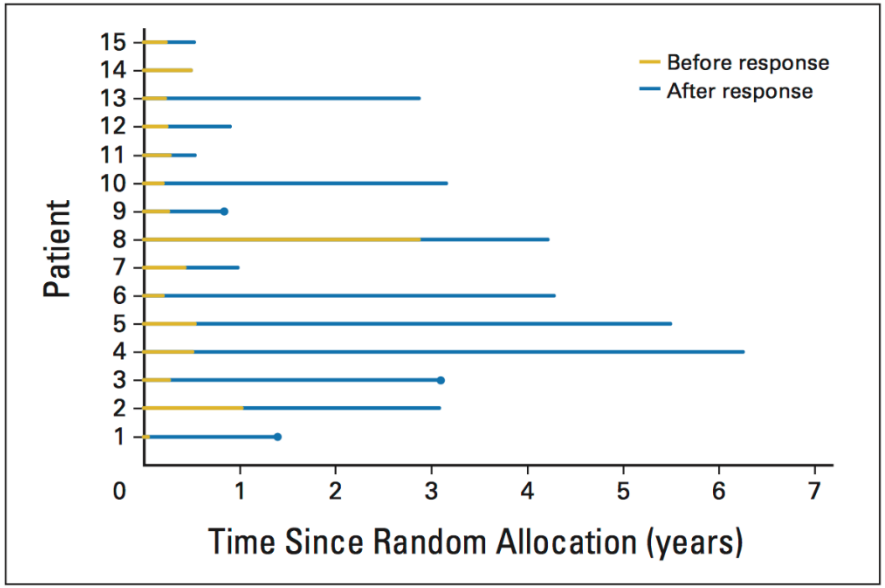
Mostly men with Lower Risk MDS

CR+PR: 29% vs. 9%

No effect on survival

Who are likely to response:

- hypocellular aspirate
- lower blast %
- younger age
- more recent diagnosis



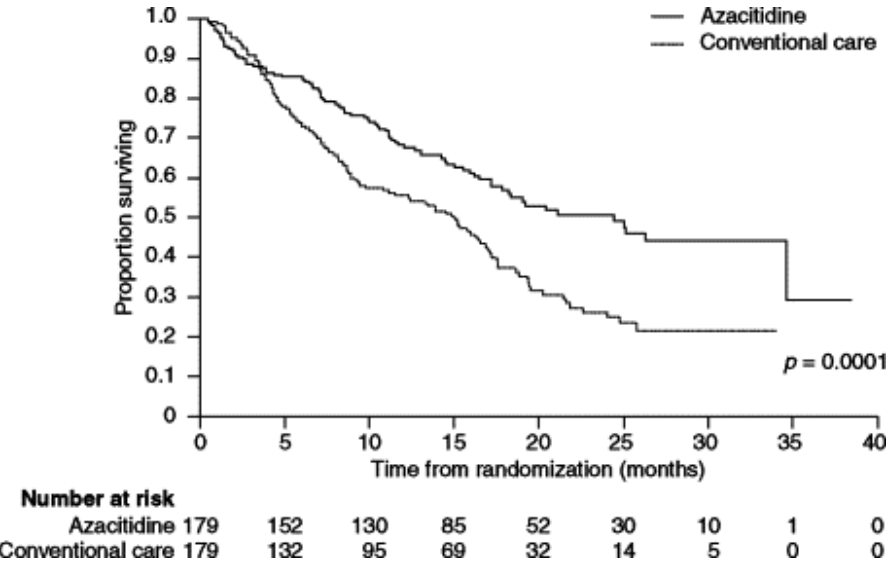
Passweg, J. R., A. A. N. Giagounidis, et al. (2011). *JCO* **29**(3): 303-309.

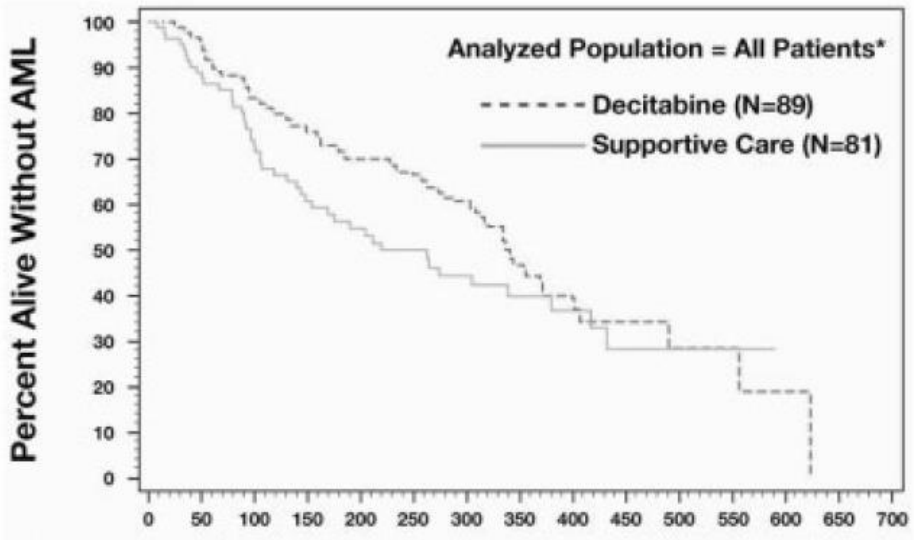
Hypomethylating Agents

Low dose Azacitdine or Decitabine

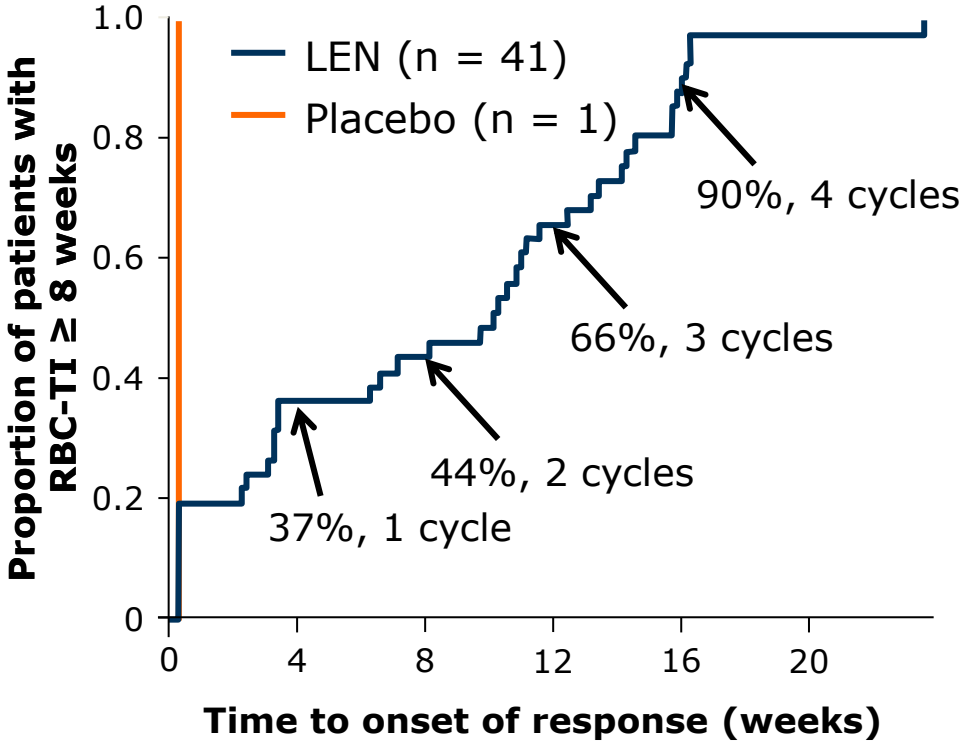
:

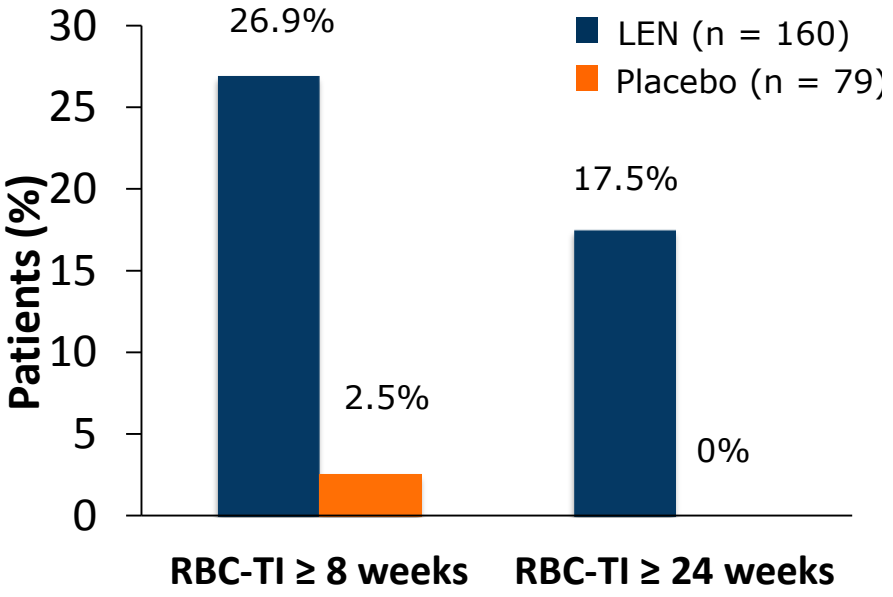
Response, n (%)	Low dose AZA or DEC
CR	36
Hematologic improvement	14
Molecular CR	9
Overall Response rate	59
SD	34
PD	7





Lenalidomide





More likely to respond after Epo failure and if Epo level is less than 500
35.1% vs 23.1 % vs 8.6% without prior Epo use

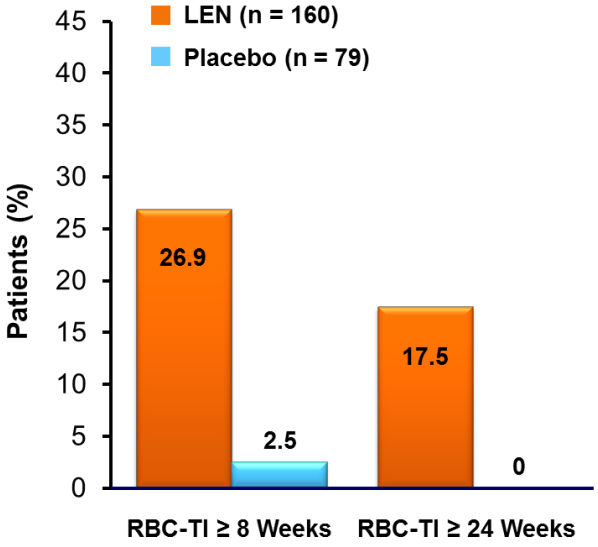
Santini V et al. *Proc ASH* 2014;Abstract 409.

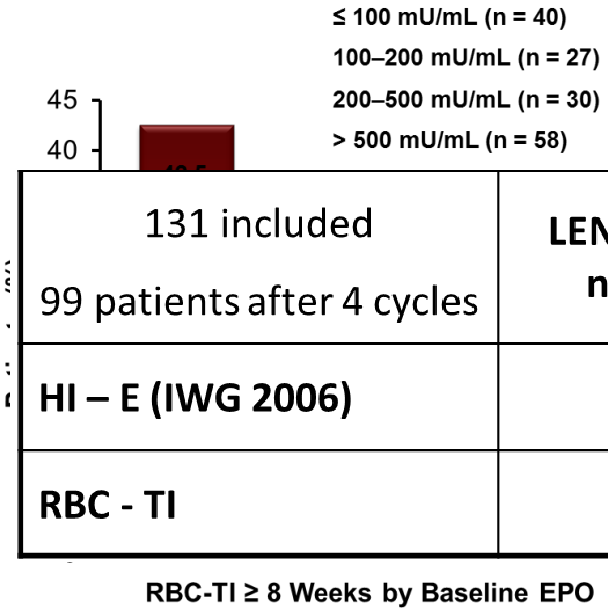
Treating Lower Risk MDS

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

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

In non-del(5q) MDS patients:



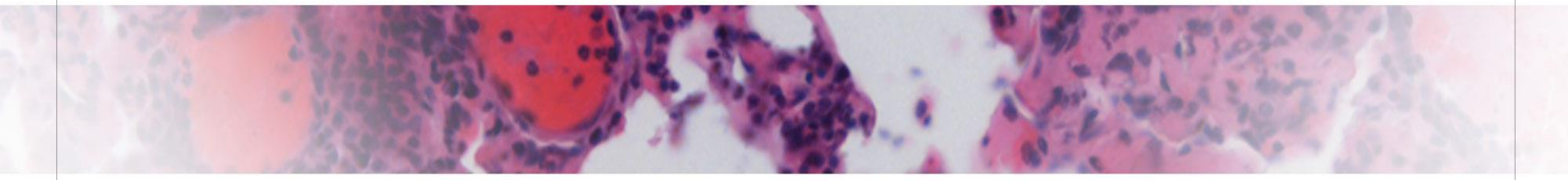


131 included 99 patients after 4 cycles	LEN + EPO n = 50	LEN n = 49	
HI – E (IWG 2006)	52%	30.6%	*P*= 0.03
RBC - TI	32%	18.4%	*P*= 0.12

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

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

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



The MEDALIST Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated Anemia With Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

Pierre Fenaux, Uwe Platzbecker, Ghulam J. Mufti, Guillermo Garcia-Manero, Rena Buckstein, Valeria Santini, María Díez-Campelo, Carlo Finelli, Mario Cazzola, Osman Ilhan, Mikkael A. Sekeres, José F. Falantes, Beatriz Arrizabalaga, Flavia Salvi, Valentina Giai, Paresh Vyas, David Bowen, Dominik Selleslag, Amy E. DeZern, Joseph G. Jurcic, Ulrich Germing, Katharina S. Götze, Bruno Quesnel, Odile Beyne-Rauzy, Thomas Cluzeau, Maria Teresa Voso, Dominiek Mazure, Edo Vellenga, Peter L. Greenberg, Eva Hellström-Lindberg, Amer M. Zeidan, Abderrahmane Laadem, Aziz Benzohra, Jennie Zhang, Anita Rampersad, Peter G. Linde, Matthew L. Sherman, Rami S. Komrokji, Alan F. List

MEDALIST Trial

Study Design – A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Patient Population

- MDS-RS (WHO): ≥ 15% RS or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks
- No prior treatment with disease-modifying agents (e.g. iMIDs, HMAs)

Randomize 2:1

Luspatercept 1.0 mg/kg (s.c.) every 21 days
n = 153

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 21 days
n = 76

Disease & Response Assessment week 24 & every 6 months Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; no crossover allowed

Subjects followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment and overall survival

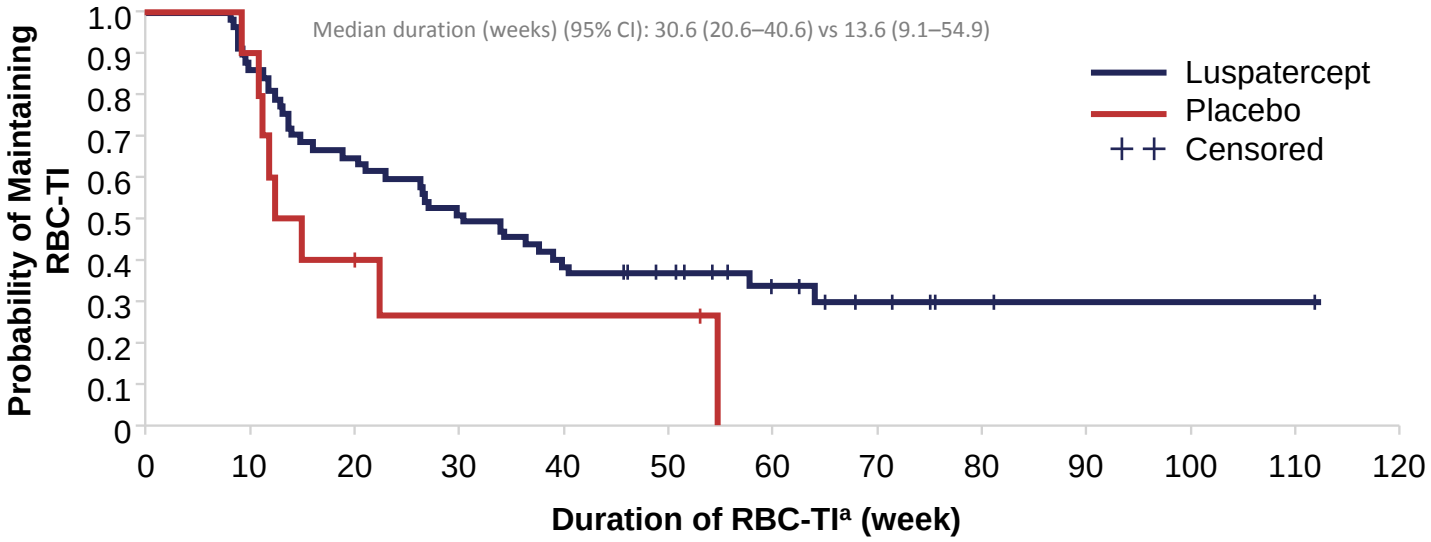
Data cutoff: May 8, 2018 Includes last subject randomized + 48 weeks.
EPO, erythropoietin; HMA, hypomethylating agent; iMID, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

- 153 Patients Luspatercept 1mg/kg SC every 21 days
  - **38%** achieved transfusion-independence at 8 weeks
  - 28% achieved transfusion-independence at 12 weeks

- 76 Patients Placebo
  - 13%achieved transfusion-independence at 8 weeks
  - 8 % achieved transfusion-independence at 8 weeks

MEDALIST Trial

Duration of RBC-TI Response in Primary Endpoint Responders



Number of patients

Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

[a] During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.

Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non-Del(5q) Lower Risk MDS Relapsed/Refractory to Erythropoiesis-Stimulating Agent Who Are Lenalidomide and HMA Naive

David P. Steensma, MD[1], Uwe Platzbecker, MD[2], Koen Van Eygen, MD[3], Azra Raza, MD[4], Valeria Santini, MD[5], Ulrich Germing, MD, PhD[6], Patricia Font, MD[7], Irina Samarina, MD[8], Maria Díez-Campelo, MD, PhD[9], Sylvain Thepot, MD[10], Edo Vellenga, MD[11], Mrinal M. Patnaik, MD, MBBS[12], Jun Ho Jang, MD, PhD[13], Jacqueline Bussolari, PhD[14], Laurie Sherman, BSN[14], Libo Sun, PhD[14], Helen Varsos, MS, RPh[14], Esther Rose, MD[14] and Pierre Fenaux, MD, PhD[15]

[1]Dana-Farber Cancer Institute (US), [2]University Hospital Carl Gustav Carus, Dresden (DE), [3]Algemeen Ziekenhuis Groeninge, Kortrijk (BE), [4]Columbia University Medical Center (US), [5]MDS Unit, AOU Careggi-University of Florence (IT), [6]Heinrich-Heine-Universität, Düsseldorf (DE), [7]Hospital General Universitario Gregorio Marañon, Madrid (ES), [8]Emergency Hospital of Dzerzhinsk, Nizhny Novgorod (RU), [9]The University Hospital of Salamanca (ES), [10]CHU Angers (FR), [11]University Medical Center Groningen (NE), [12]Mayo Clinic, Rochester (US), [13]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul (KO), [14]Janssen Research & Development, LLC (US), [15]Hôpital Saint-Louis, Université Paris (FR)

Funded by Janssen Research & Development and Geron Corporation

Abstract #463

- 38 Patients received Imetelstat 7.5 mg/kg IV every 4 weeks
  - **37%** achieved transfusion-independence at 8 weeks
  - 26% achieved transfusion-independence at 24 weeks
  - Median time to onset of transfusion Independence 8 weeks
  - Median duration of TI not reached

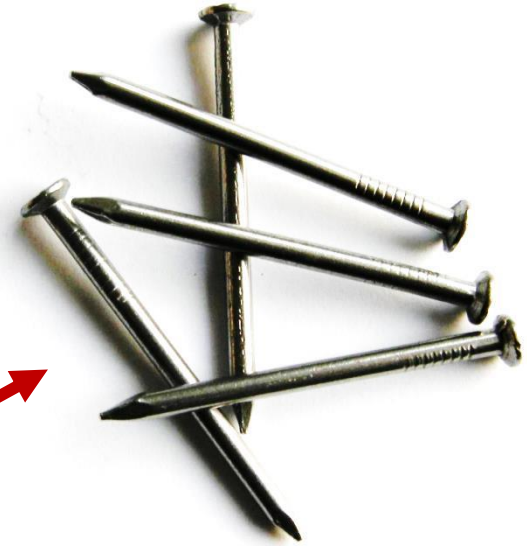
  - Neutropenia and thrombocytopenia in 20-25%

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

Permitted to use from Dr. Bejar

Iron Chelation

Three ways are FDA approved:

Deferoxamine (Desferal) – subcutaneous pump 8-12 hrs/day

Deferasirox (Exjade or Jadenu) – oral suspension or Tablet

Deferiprone (Ferriprox) – oral pill form – 3x per day

But side effects and adverse events can be significant!

At this point not commonly used in high risk disease

- Deferasirox – renal, hepatic failure and GI bleeding
- Deferiprone – agranulocytosis (no neutrophils!)

What About Iron Chelation?

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

Is high iron level has independent effect 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%).

We 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.

Safety and Efficacy, Including Event-free Survival, of Deferasirox Versus Placebo in Iron-Overloaded Patients with Low- and Int-1-Risk Myelodysplastic Syndromes (MDS): Outcomes from the Randomized, Double-Blind TELESTO Study

Emanuele Angelucci,[1] Junmin Li,[2] Peter Greenberg,[3] Depei Wu,[4] Ming Hou,[5] Efreen Horacio Montaňo Figueroa,[6] Maria Guadalupe Rodriguez,[7] Xunwei Dong,[8] Jagannath Ghosh,[8] Miguel Izquierdo,[9] and Guillermo Garcia-Manero[10]

[1]Hematology and Transplant Center, IRCCS Ospedale Policlinico San Martino, Genova, Italy; [2]Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [3]Stanford University Medical Center, Stanford, CA, USA; [4]Jiangsu Institute of Hematology, First Affiliated Hospital of Soochow University, Suzhou, China; [5]Department of Hematology, Qilu Hospital, Shandong University, Jinan, China; [6]Department of Hematology, Hospital General de México, Mexico City, Mexico; [7]Department of Hematology, Hospital de Especialidades, Centro Médico Nacional La Raza, IMSS, Mexico City, Mexico; [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [9]Novartis Pharma AG, Basel, Switzerland; [10]MD Anderson Cancer Center, University of Texas, Houston, TX, USA

Primary endpoint EFS:

All patients*	Log-rank test			Cox model
	Event/N (%)	Median time to event (95% CI), days†	*P* value‡	HR (95% CI)§
Deferasirox	62/149 (41.6)	1440 (1167, 1559)	0.015	0.636 (0.42, 0.96)
Placebo	37/76 (48.7)	1091 (820, 1348)		

*Both the log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model

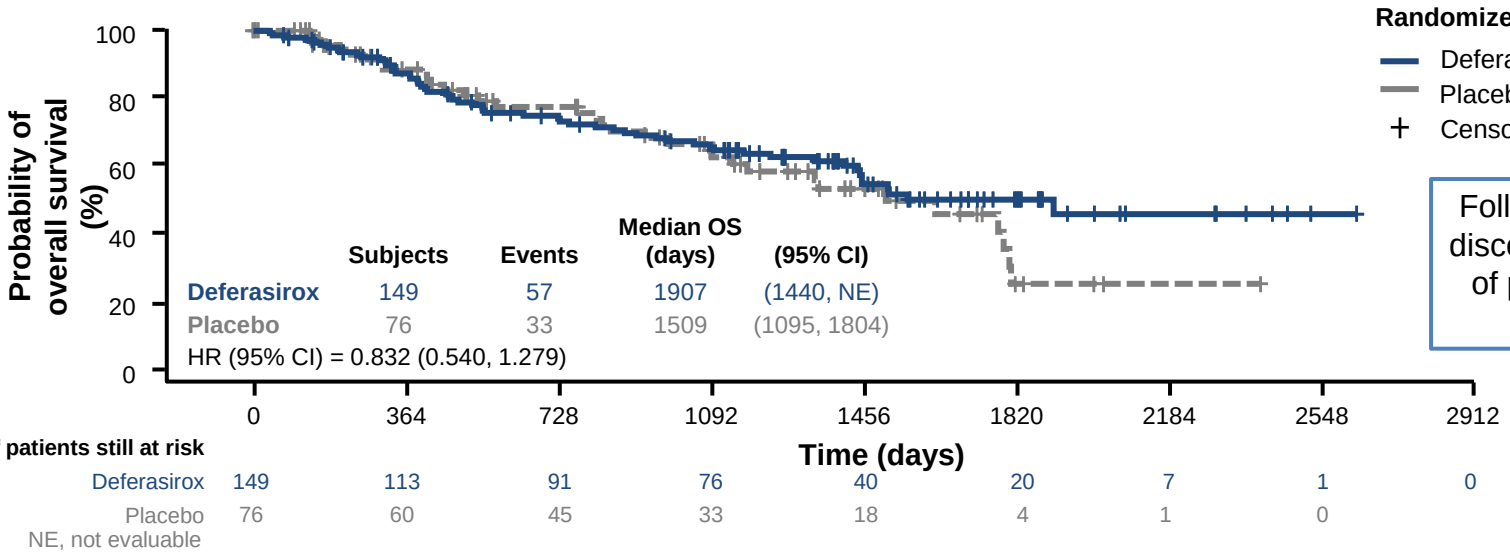
A **36.4%** risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm
(HR: 0.636; 95% CI: 0.42, 0.96; nominal *P*=0.015)

CI, confidence interval; HR, hazard ratio

Summary of overall survival

All patients*	Log-rank test			Cox model
	Event/N (%)	Median time (95% CI), days†	*P* value‡	Hazard ratio (95% CI)§
Deferasirox	57/149 (38.3)	1907 (1440, NE)	0.200	0.832 (0.54, 1.28)
Placebo	33/76 (43.4)	1509 (1095, 1804)		

*Both log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one-tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model



Following study drug discontinuation 52.1% of placebo patients started ICT

NE, not evaluable

Guidelines for Lower Risk MDS

1. Do I need to treat? - symptomatic cytopenias
2. Is LEN likely to work? - del(5q)
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, or Lenalidomide, Epo +Lena
7. ? Luspatercept ? Imetelstat
8. Consider HSCT or clinical trial!

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

Immunosuppressive Therapy

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

Overview of High Risk

- Refining Prognosis and ‘High’ Risk
- Advances in Stem Cell Transplantation

What does high risk mean

- Worsening blood counts
- Transformation to acute leukemia
- Bone marrow failure

Current Therapies

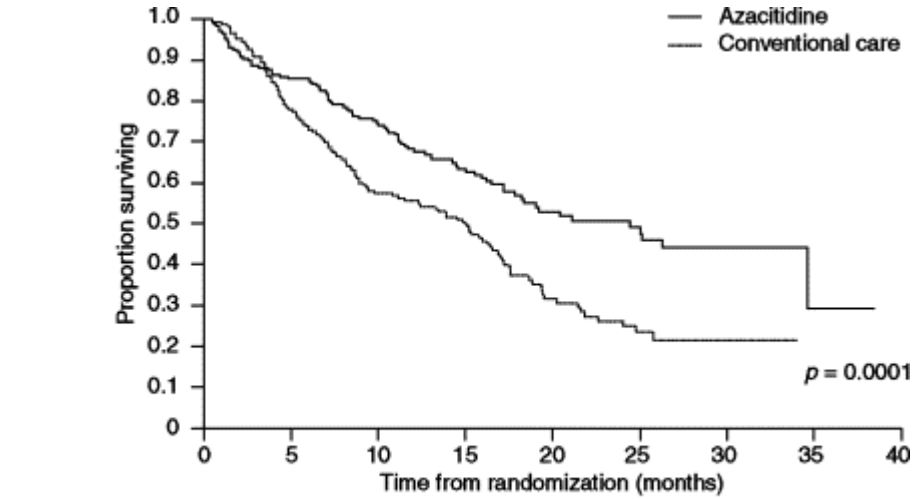
Azacitidine

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%



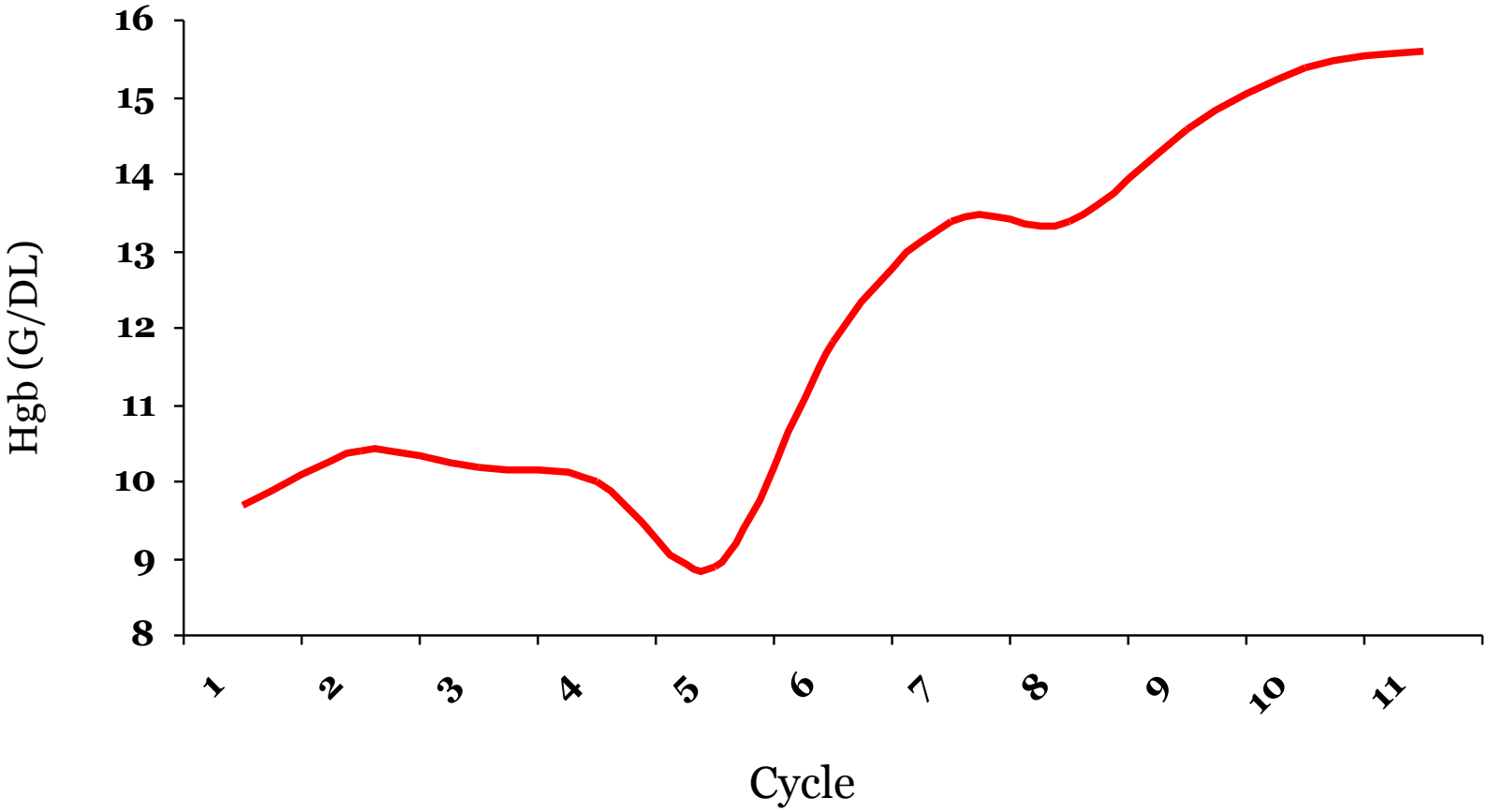
Azacitidine Response:

ORR: ~50%

CR: ~17%

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

Azacitidine response



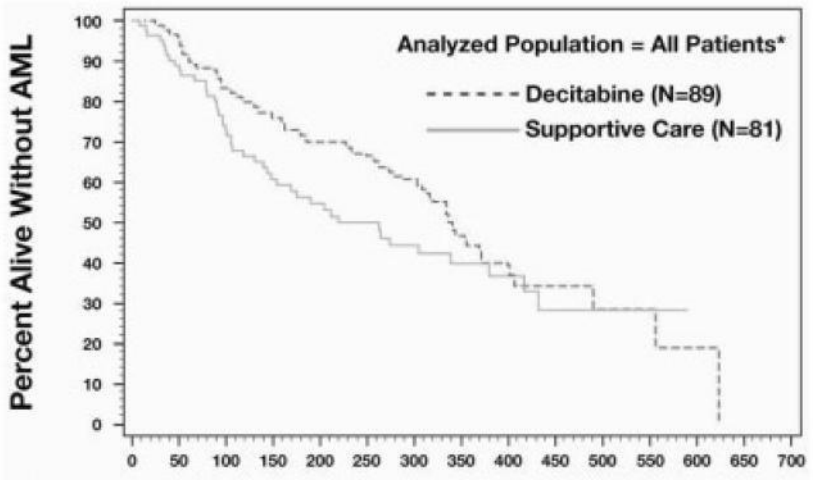
Decitabine

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% (FeverN 11%)

Thrombocytopenia: 18%

HMA Important facts!

<u>Azacitidine and Decitabine</u>

Therapy can initially worsen patients' clinical condition

Avoid discontinuation of therapy before achieving benefit, Slow Responses can take 4-6 months to appear

Continuous Treatment – 5 to 7 days every 4 weeks

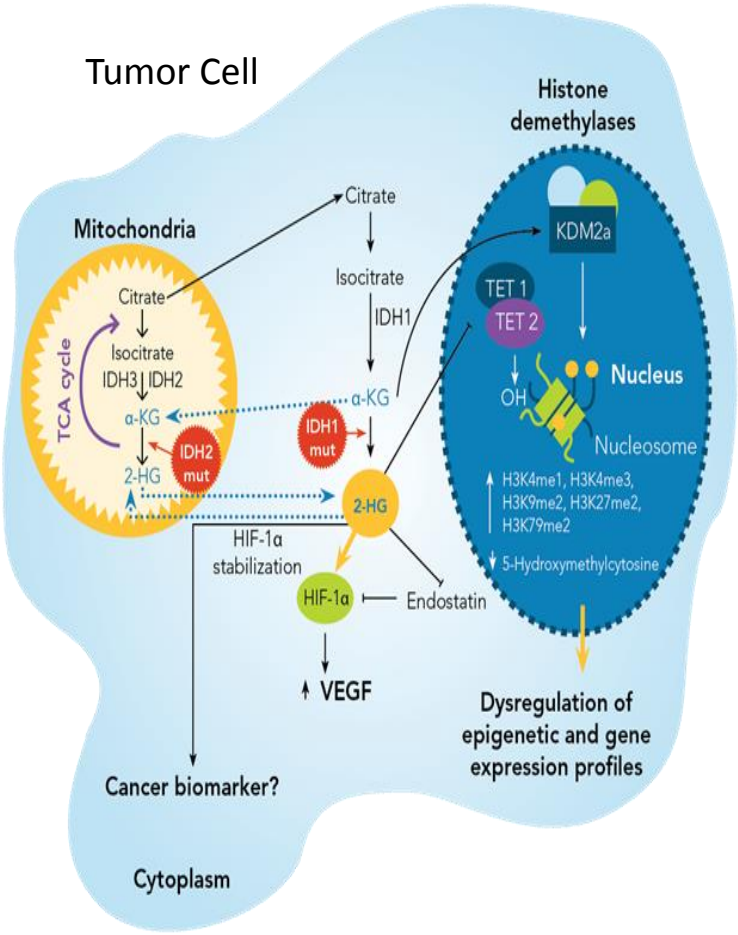
Generally well tolerated

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

Oral Decitabine

IDH Mutations as a Target in MDS

- IDH are critical enzymes of the citric acid cycle
- Mutant *IDH2* (m*IDH2*) produces 2-HG, which alters DNA methylation, blocks cellular differentiation
- m*IDH2* in ~5% of MDS
- Enasidenib (AG-221/CC-90007) - selective, oral, potent inhibitor of mIDH2 enzyme
- Objective: safety and efficacy of enasidenib in m*IDH2* MDS



1. DiNardo et al. Leukemia 2016;30(4):980-4

Stein et al. ASH 2016; abstract 343

Response and time on therapy

	MDS Patients (N=17) n (%)
Overall response rate (CR + PR + mCR + HI)	**10/17 (59)**
Best Response	
Complete remission	1/11 (9)
Partial remission	1/11 (9)
Marrow CR	3/11 (27)
Any hematologic improvement (HI)†	5/17 (29)
HI-E	3/15 (20)
HI-P	4/12 (33)
HI-N	4/10 (40)

Stein et al. ASH 2016; abstract 343

Phase 1b/2 Combination Study of APR-246 and Azacitidine (AZA) in Patients with *TP53* Mutant Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

David A Sallman[1], Amy DeZern[2], David P Steensma[3], Kendra Sweet[1], Thomas Cluzeau[4], Mikkael Sekkeres[5], Guillermo Garcia-Manero[6], Gail Roboz[7], Amy McLemore[1], Kathy McGraw[1], John Puskas[1], Ling Zhang[1], Chirag Bhagat[8], Jiqiang Yao[9], Najla H Al Ali[1], Eric Padron[1], Roger Tell[10], Jeffrey E. Lancet[1], Pierre Fenaux[11], Alan F List[1] and Rami S Komrokji[1]

[1]Malignant Hematology Department, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA.; [2]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [3]Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]Cote D'azur University, Nice Sophia Antipolis University, Hematology Department, CHU Nice, Nice, France; [5]Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; [6]Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA; [7]Weill Cornell Medical College, New York, NY, USA; [9]Cancer Informatics Core, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [10]Aprea Therapeutics, Stockholm, Sweden; [11]Hospital St Louis, Paris 7 University, Paris, France.

2018 ASH Abstract # 3091

MOFFITT CANCER CENTER

Treatment Response

Best Response at Cutoff						
	Ph1b	**Ph2**	**MDS**	**AML**	**All**	**AZA Historical**
Evaluable Patients	11	9	15	5	20	
Response Rate	100%	89%	93%	100%	95%	30-50%
CR Rate	82%	56%	67%	80%	70%	20-30%

MOFFITT CANCER CENTER

Guidelines for Higher Risk MDS

Goal:to improve **LIFE EXPECTANCY & QUALITY OF LIFE**

Special Considerations:

Refer for Transplant Early

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

Don't Ignore 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 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

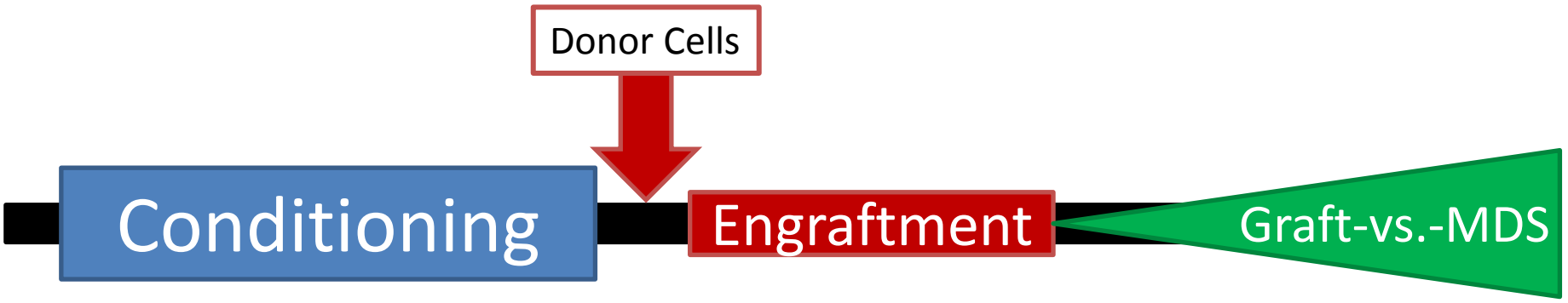
Prébet T et al, *J Clin Oncol 2011;* Aug 20;29(24):3322-7. Epub 2011 Jul 25.
Jabbour E et al, *Cancer* 2010*;* 116:3830–3834.

Stem Cell Transplantation

Goals of Transplantation

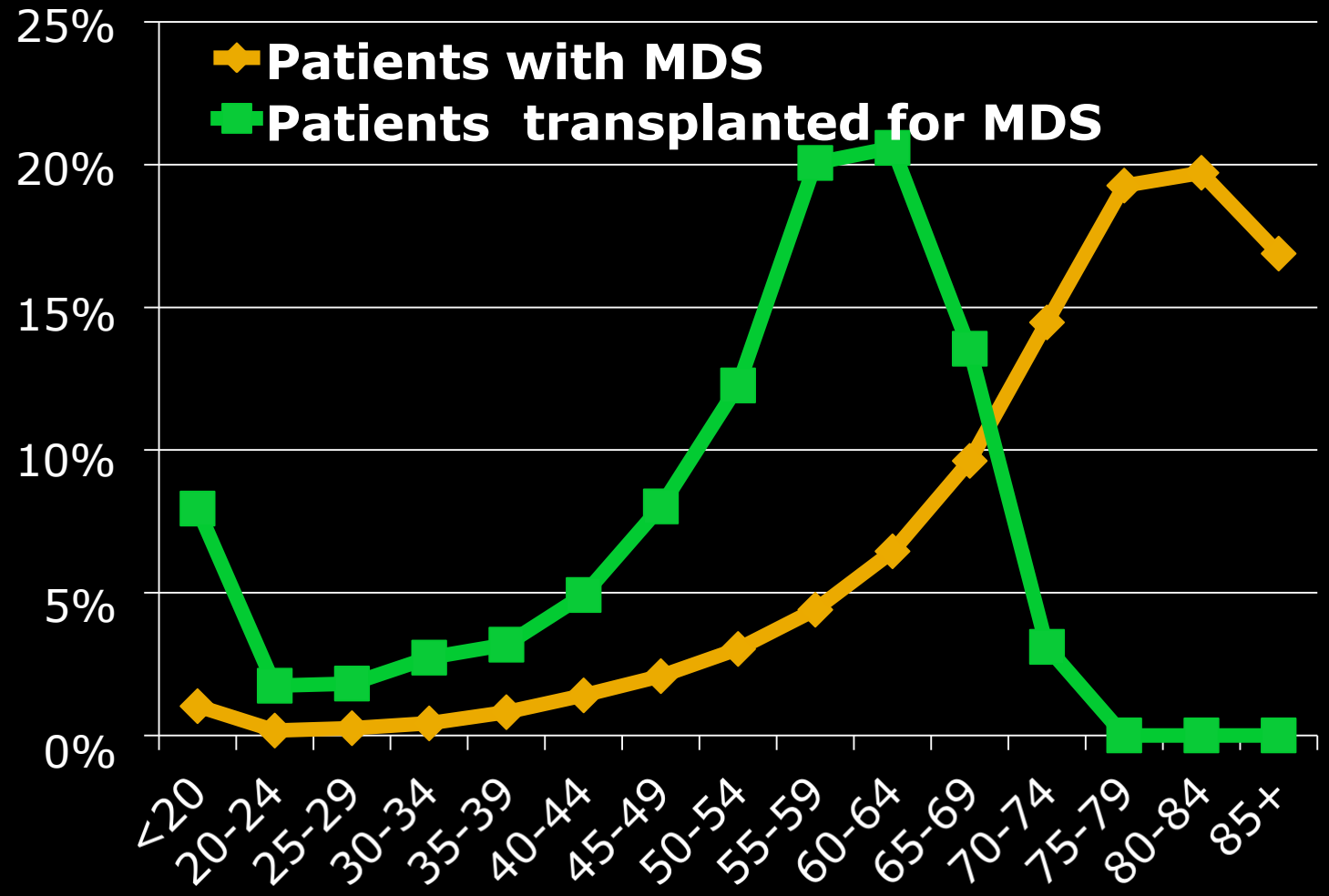
Replace a dysfunction host hematopoietic system with normal, healthy donor marrow.

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



Permitted to use from Dr. Bejar

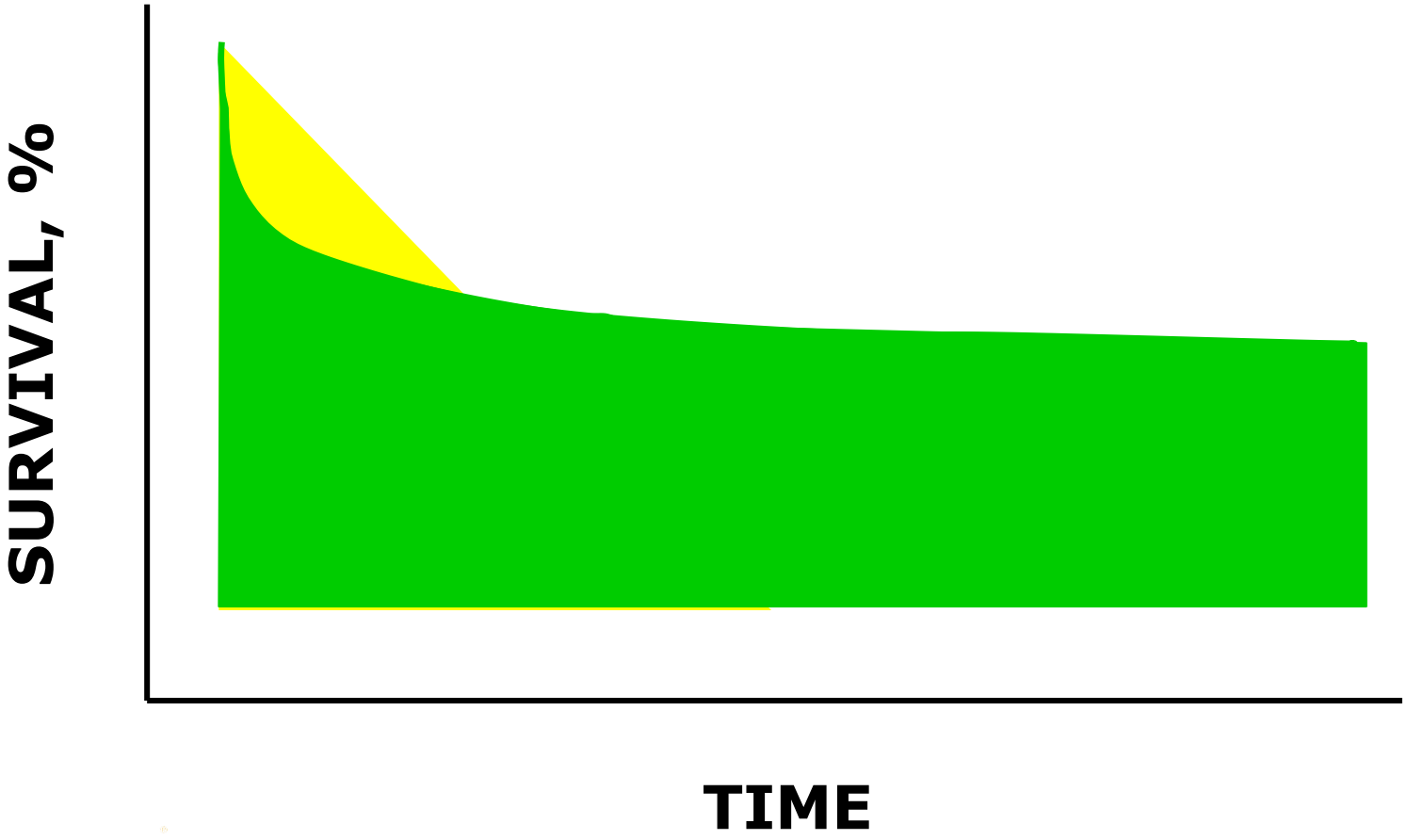
AGE DISTRIBUTION OF PATIENTS WITH MDS



CIBMTR®

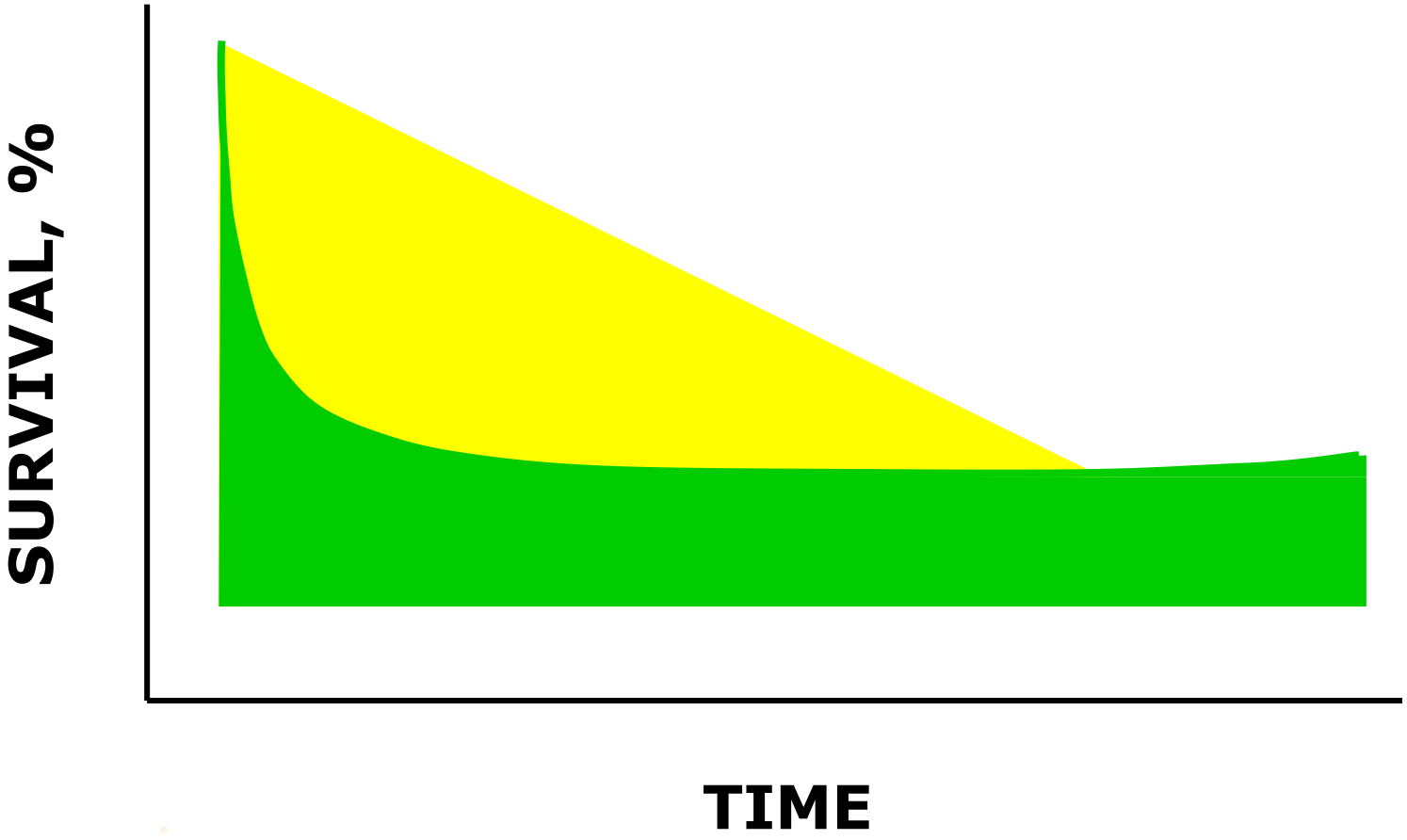
The Decision – Whether and When

HIGH RISK MDS STANDARD RISK OF TRANPLANT RELATED DEATH



The Decision – Whether and When

LOW RISK MDS **HIGH RISK OF TRANPLANT RELATED DEATH**



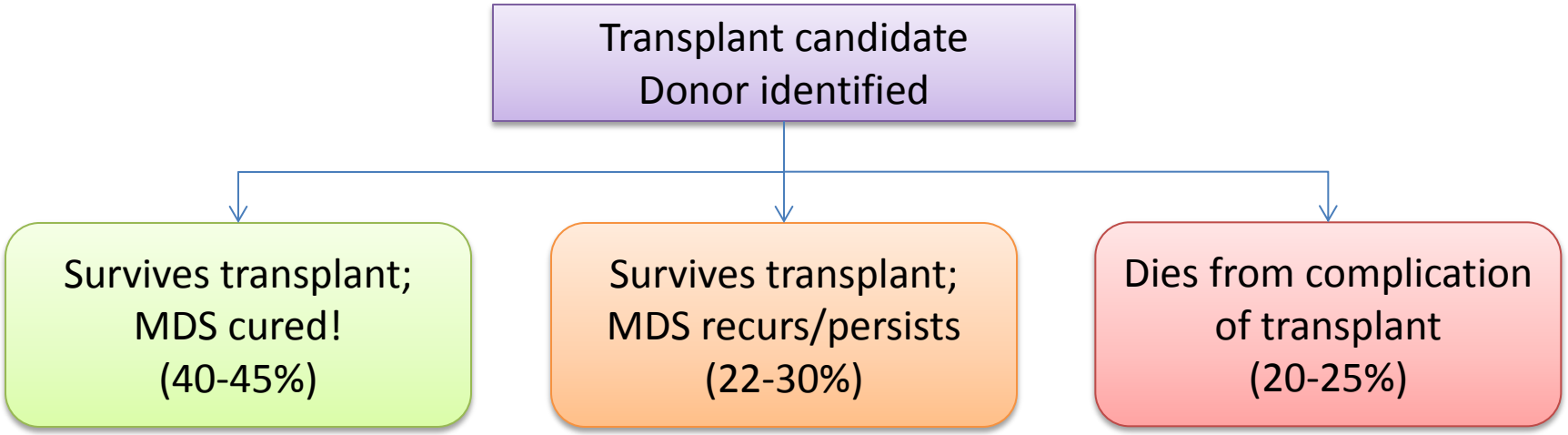
Allogeneic Stem Cell Transplantation for MDS

<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.

Allogeneic stem cell transplantation

- Transplant is curative therapy that offers survival advantage when applied at an optimal point
- In pts who are eligible for transplant there is no difference in survival for pt 55-64 compared to pts 65 yrs and older
- Age is not itself a contraindication – but comorbidities that accompany age in some people can be

Take home messages

- Ask if the diagnosis is right?
- Ask your risk category
- Risk category is important to set GOALS of therapy
- Quality of life is important goal of treatment in MDS
- Be aware about risk of infections
- Allogeneic transplantation can be curative
- Clinical Trials