Myelodysplasia Syndromes: Therapies & Options in 2019

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Acknowledgments

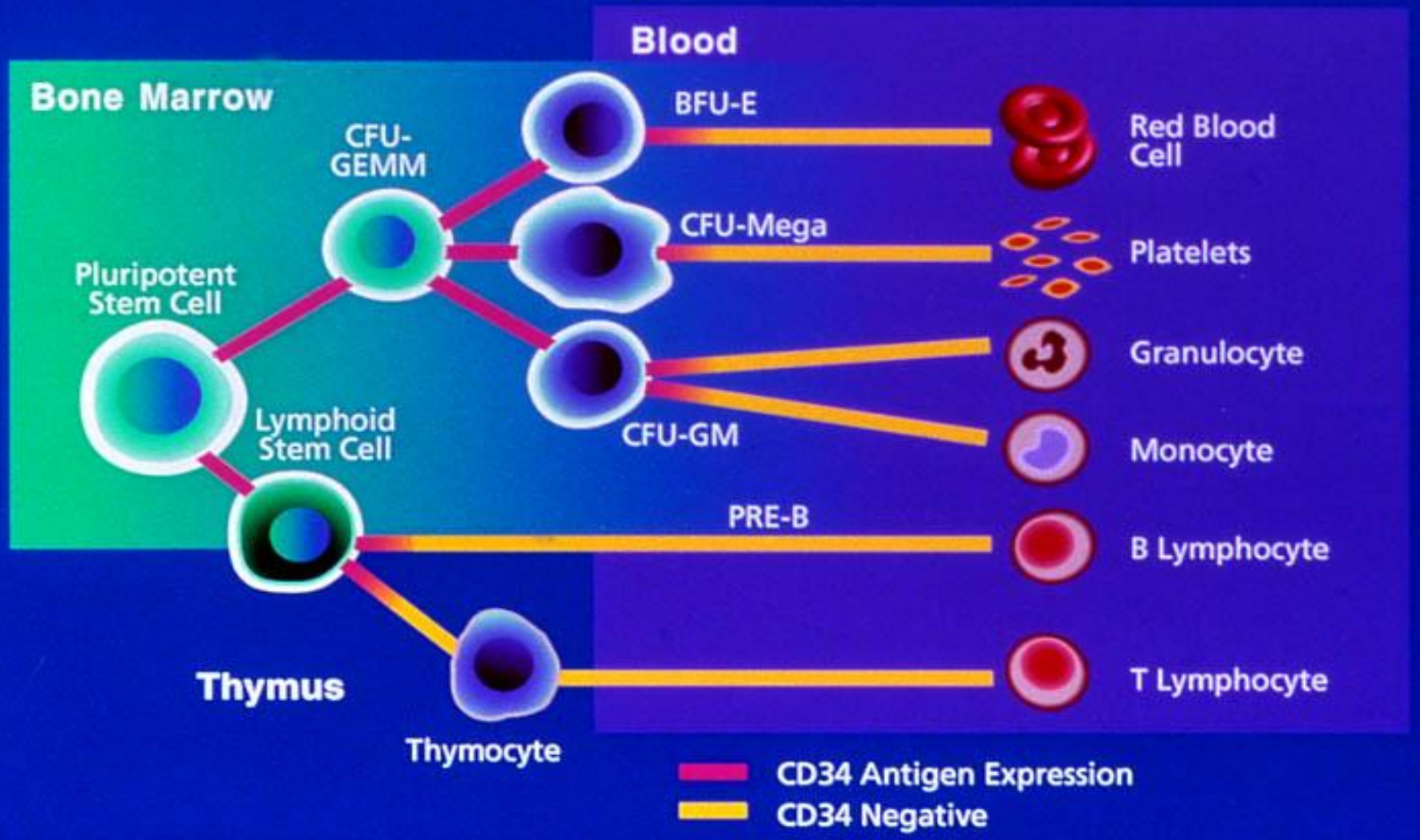
Mayo Clinic MDS Clinical Team in Florida

- Dana Raulerson, RN MSN
- Deb Fischer, PA
- Jennifer Higginbotham, RN & Virginia Lesperance, RN MSN
- Michelle Walsh MSW
- Gabriela Contreras

Physicians

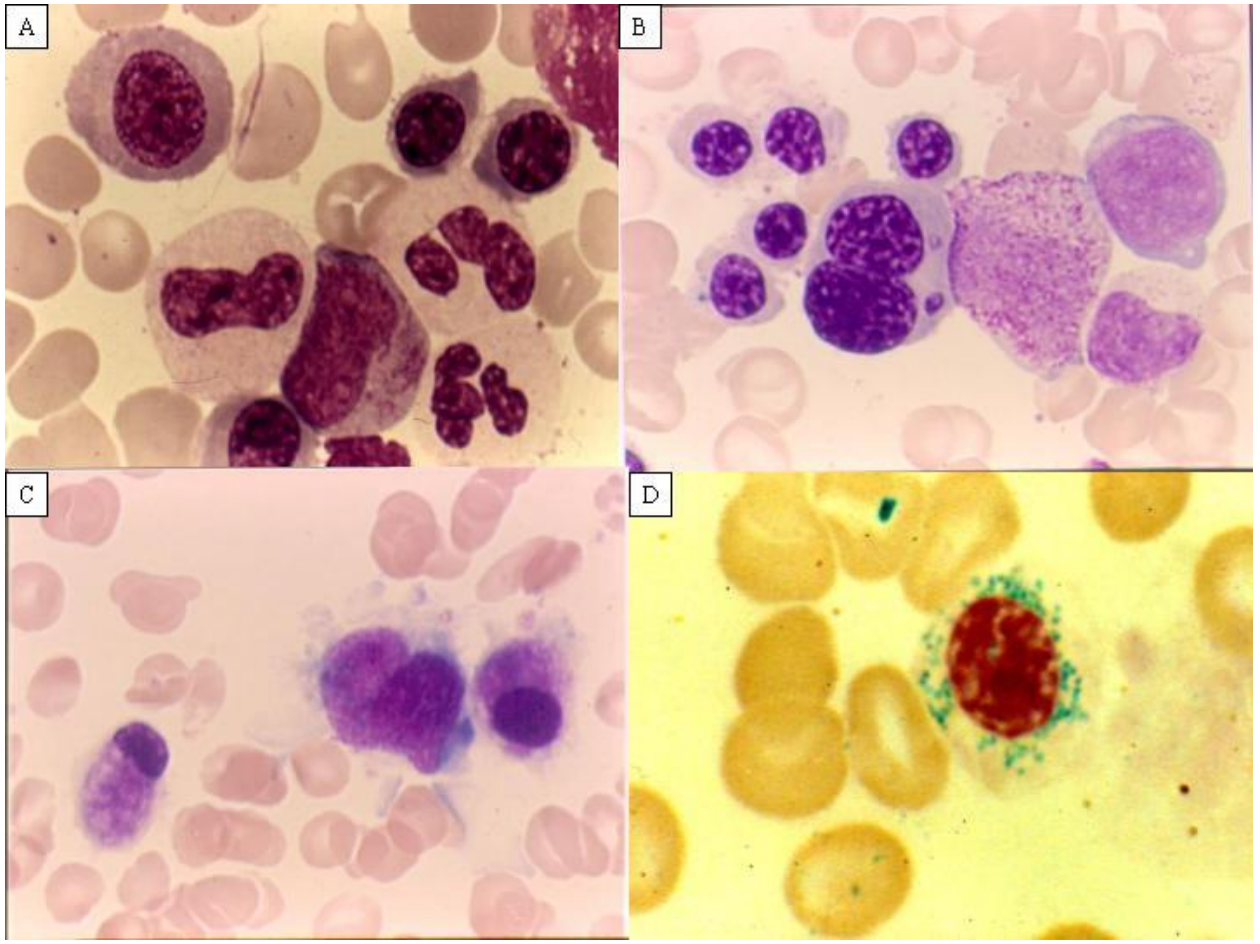
- Phoenix, AZ — Jeanne Palmer, MD, James Slack MD
- Jacksonville, FL — James Foran, MD, Candido Rivera MD
- Rochester, MN — Mark Litzow, MD, Aref Al-Kali, MD, Naseema Gangat, MD

The Hematopoietic Cascade



Definition - MDS

- Heterogeneous clonal hematopoietic disorder derived from abnormal multipotent progenitor cell
- Characterized by a *hyper*proliferative bone marrow, dysplasia of the cellular elements, and ineffective hematopoiesis
- Progressive risk of AML transformation



MDS is a Blood Cancer

Image from Bennett in Sekeres et al. Clinical Malignant Hematology. New York: McGraw-Hill 2007

MDS
Manifestations

- Nonspecific symptoms related to blood count
  - Can be ‘incidental’ and asymptomatic
- Commonly fatigue, easy bleeding, infection, shortness of breath
  - rarely can include weight loss, sweats, itching or bone/joint pains
- Low Complete Blood Count (CBC), with abnormal forms
  - RBC Anemia
  - Platelets Bruising, bleeding
  - WBC Fever or infection
- Risk of transformation to leukemia

Statistics

"You can, for example, never foretell what any one man will do, but you can say with precision what an average number will be up to. Individuals vary, but percentages remain constant.

So says the statistician."

Sherlock Holmes

1890

Why do Prognostic Factors Matter in MDS?

- Give healthcare providers & patients and their families insights into what to expect
  - Based upon what happened to those with similar MDS features before them
    - As therapies change, prognosis changes
- Relevant to determine eligibility for available treatments
  - Depends on the therapy
- Individualize prognosis, and possibly therapy whenever possible
  - Determining timing & selection for therapy
    - e.g. transfusion & red cell growth factors vs. chemotherapy or even allogeneic transplantation
  - Earlier therapy for those with “higher risk” low risk MDS, delayed for “lower risk”
  - Clinical Trial eligibility

Cytogenetic Testing

Chromosome analysis

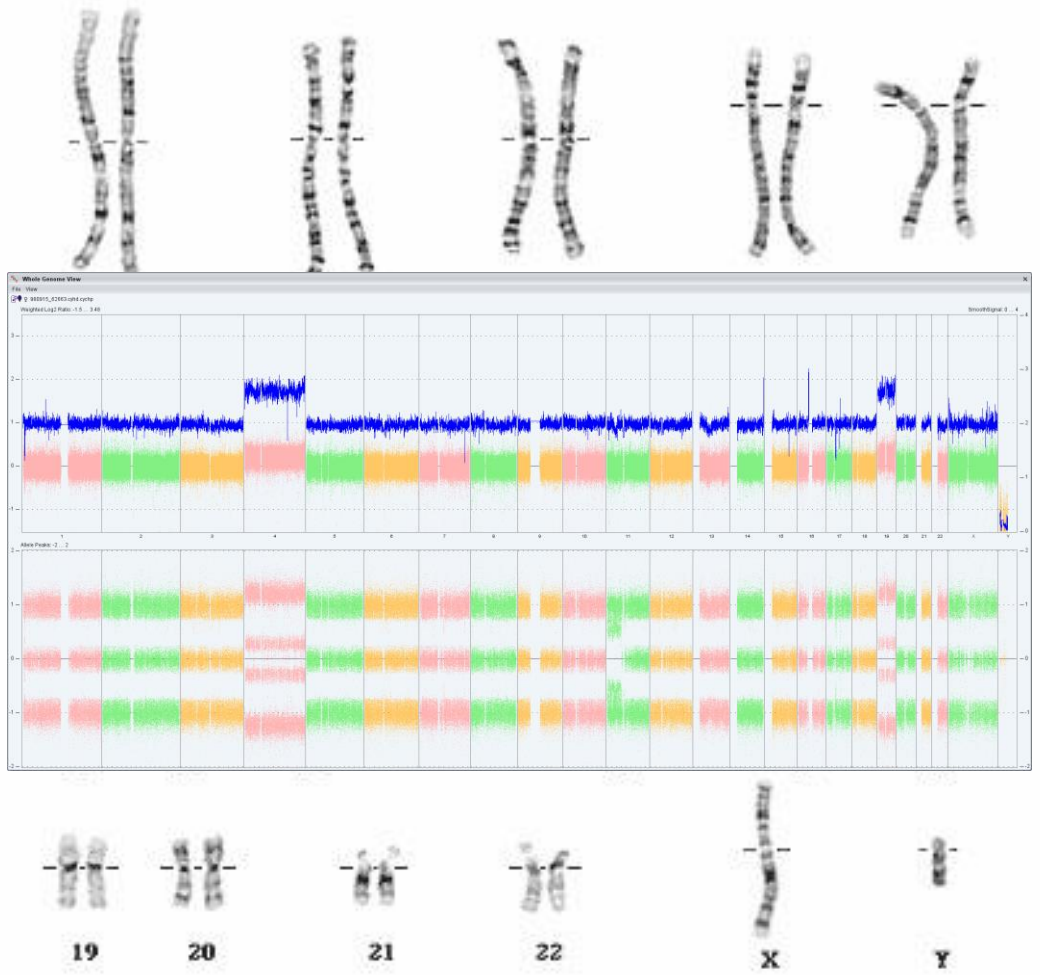
- requires dividing cells
- whole genome coverage
- low resolution (~5 Mb)

FISH analysis

- does not require dividing cells
- site-specific
- higher resolution (~100 Kb)

Microarray analysis

- does not require dividing cells
- whole genome coverage
- 2.6M copy number markers
- 750k SNPs
- high resolution (~25-50 Kb)



MDS Prognosis
In General it is Intuitive

- Better blood counts are good
- Not needing transfusions is good.
- Lower blasts are good
- Having no cytogenetic abnormalities is good
- Younger age is good
- Being able to function better is good

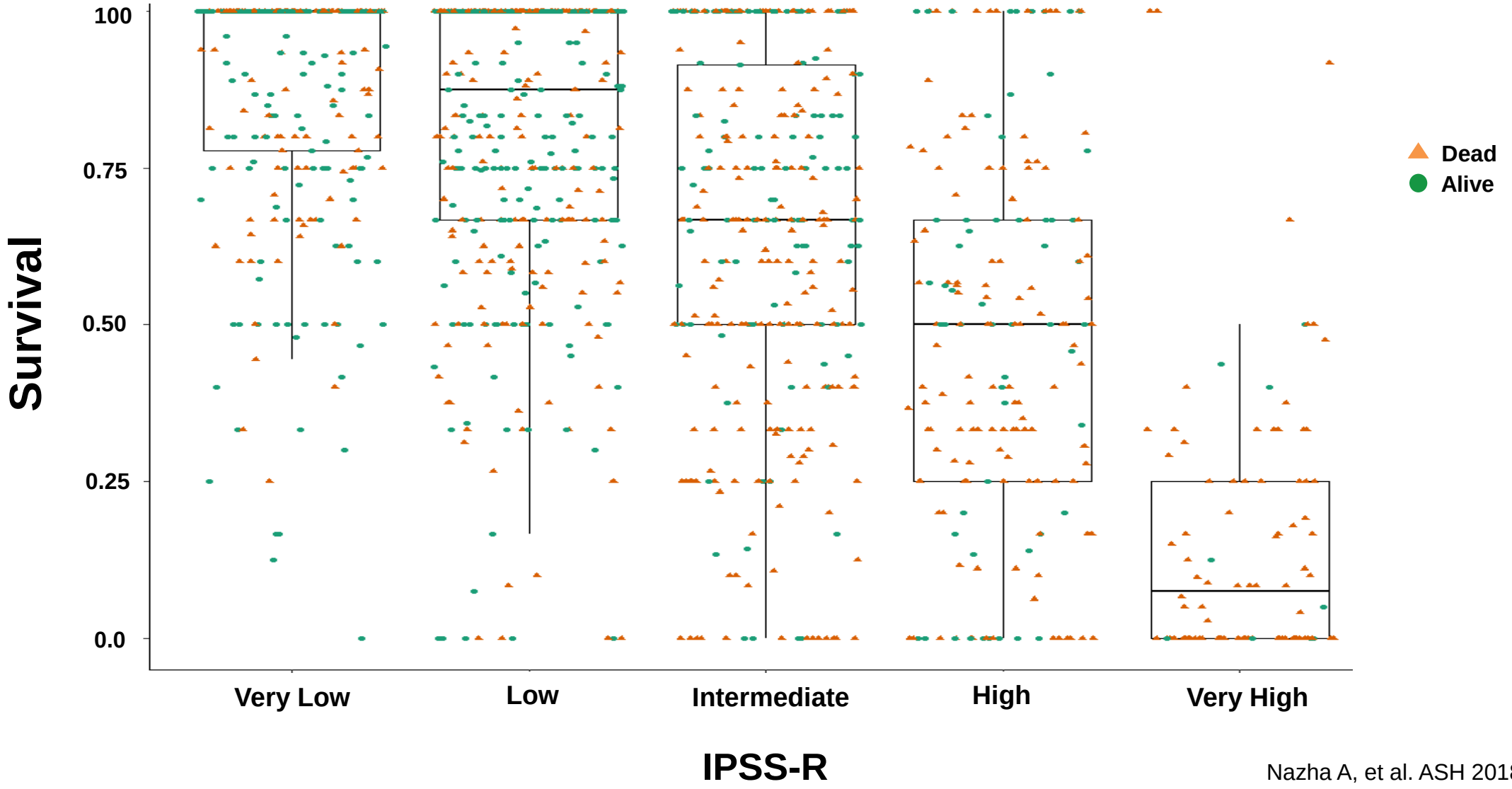
*** Lots of exceptions**

Revised International Prognostic Scoring System

	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	≥10 g/dL	8 - <10 g/dL	<8 g/dL		
	0	1	1.5		
Absolute neutrophil count	≥0.8 x 10^9/L	<0.8 x 10^9/L			
	0	0.5			
Platelet count	≥100 x 10^9/L	50 - 100 x 10^9/L	<50 x 10^9/L		
	0	0.5	1		

Risk group	Points	% patients (n=7,012 and AML data on 6,485)	Median survival, Years	Median survival Age <60 Years	Time until 25% of patients develop AML, Years
Very low	0-1.5	19%	8.8	Not reached	Not reached
Low	2.0-3.0	38%	5.3	8.8	10.8
Intermediate	3.5-4.5	20%	3.0	5.2	3.2
High	5.0-6.0	13%	1.5	2.1	1.4
Very high	>6.0	10%	0.8	0.9	0.7

Heterogeneity in Outcomes in MDS



Nazha A, et al. ASH 2018 [#793]

A Personalized Prediction Model to Risk Stratify Patients with Myelodysplastic Syndromes

Aziz Nazha, Rami Komrokji, Manja Meggendorfer, Sudipto Mukherjee, Najla Al Ali, Wencke Walter, Stephan Hutter, Eric Padron, Yazan Madanat, David Sallman, Teodora Kuzmanovic, Cassandra Hirsch, Vera Adema, David P. Steensma, Amy Dezern, Gail Roboz, Guillermo Garcia-Manero, Alan F. List, Claudia Haferlach, Jaroslaw P. Maciejewski, Torsten Haferlach, Mikkael A. Sekeres

Cleveland Clinic

@AzizNazhaMD

ASH 2018 Abstract #793

MDS
Strategy

- If possible be patient and observe if no symptoms
  - Most patients present with low grade MDS
- Low grade MDS
  - Focus on treating the low blood count (cytopenia) that is causing symptoms, prevent MDS progression
- High Grade MDS
  - Consider treatment with HMA (Azacitidine, decitabine)
  - Can sometimes use leukemia-type therapy
- BMT

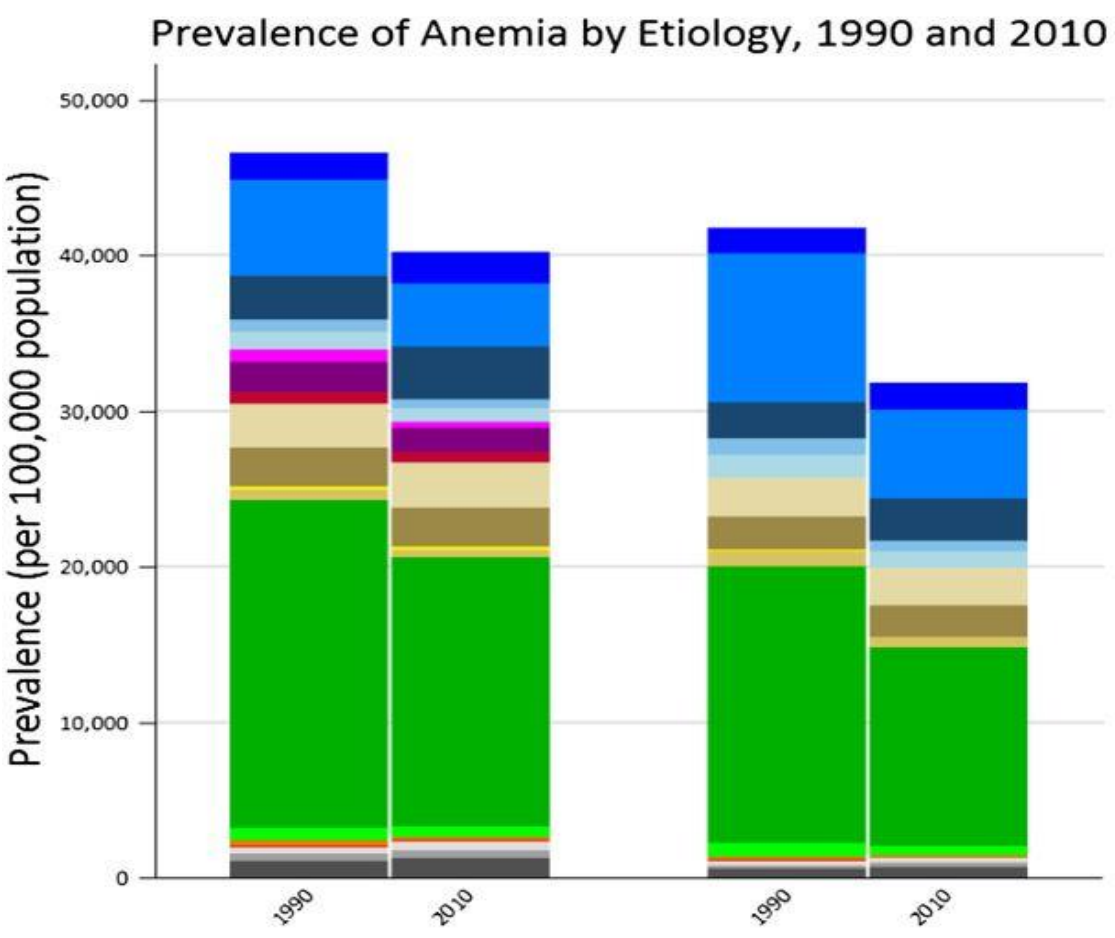
MDS: A Model for Collaborative Care

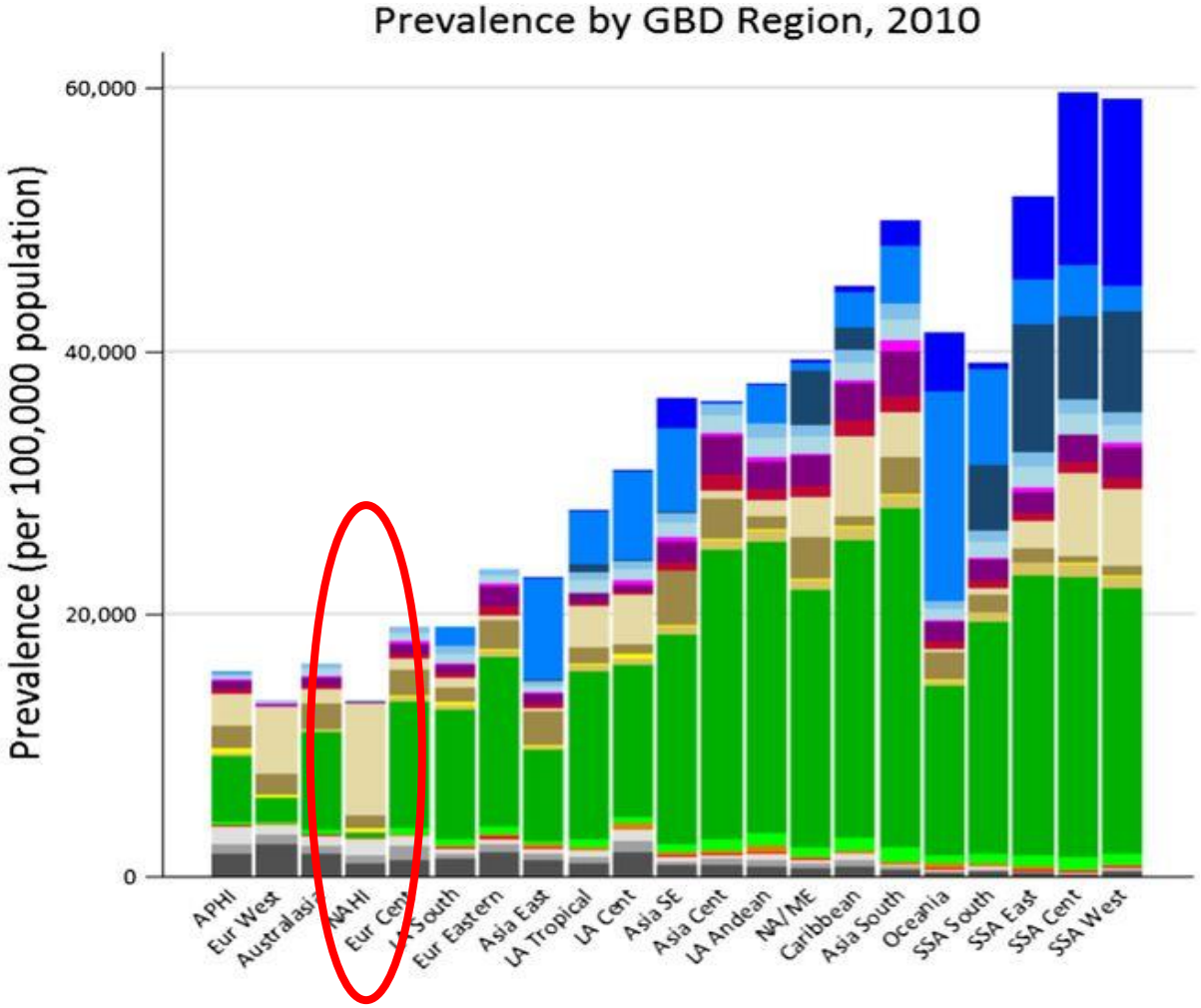
- Occurs more often in older patients with co-morbidities
  - Require more holistic medical care
- Common supportive care requirements
  - Effects of low blood counts (anemia, risk of bleeding or infection)
  - Coordination of blood product support, monitoring, antibiotics
- Treatments are prolonged
  - Effects of disease frequently worsen in early stages of therapy
    - i.e. “1 step backward before 2 steps forward”
  - Requires close coordination with MD & APP, RN, SW care team
  - Develop close relationship of patient with care team
- Balance of disease intervention while focusing on QoL

MDS
Low Grade/Lower Risk

- Rule out contributing cause
- Anemia (RBC)
  - Transfusion if very low and symptoms of fatigue, SOB
  - Erythroid Stimulating Agent (e.g. Procrit, Aranesp)
  - Lenalidomide if Del(5q)
- Thrombocytopenia (Platelets)
  - Transfusion if <10,000 or bruising/bleeding
  - Thrombopoeitic factors e.g. Promacta™ (not FDA-approved)
- Neutropenia (WBC, esp. Neutrophils)
  - Typically do not treat unless recurrent infections
  - Can use Neupogen from time-to-time
- Consider clinical trial of novel agent

Anemia Prevalence 1990 & 2010 - Global & Regional, Cause-Specific





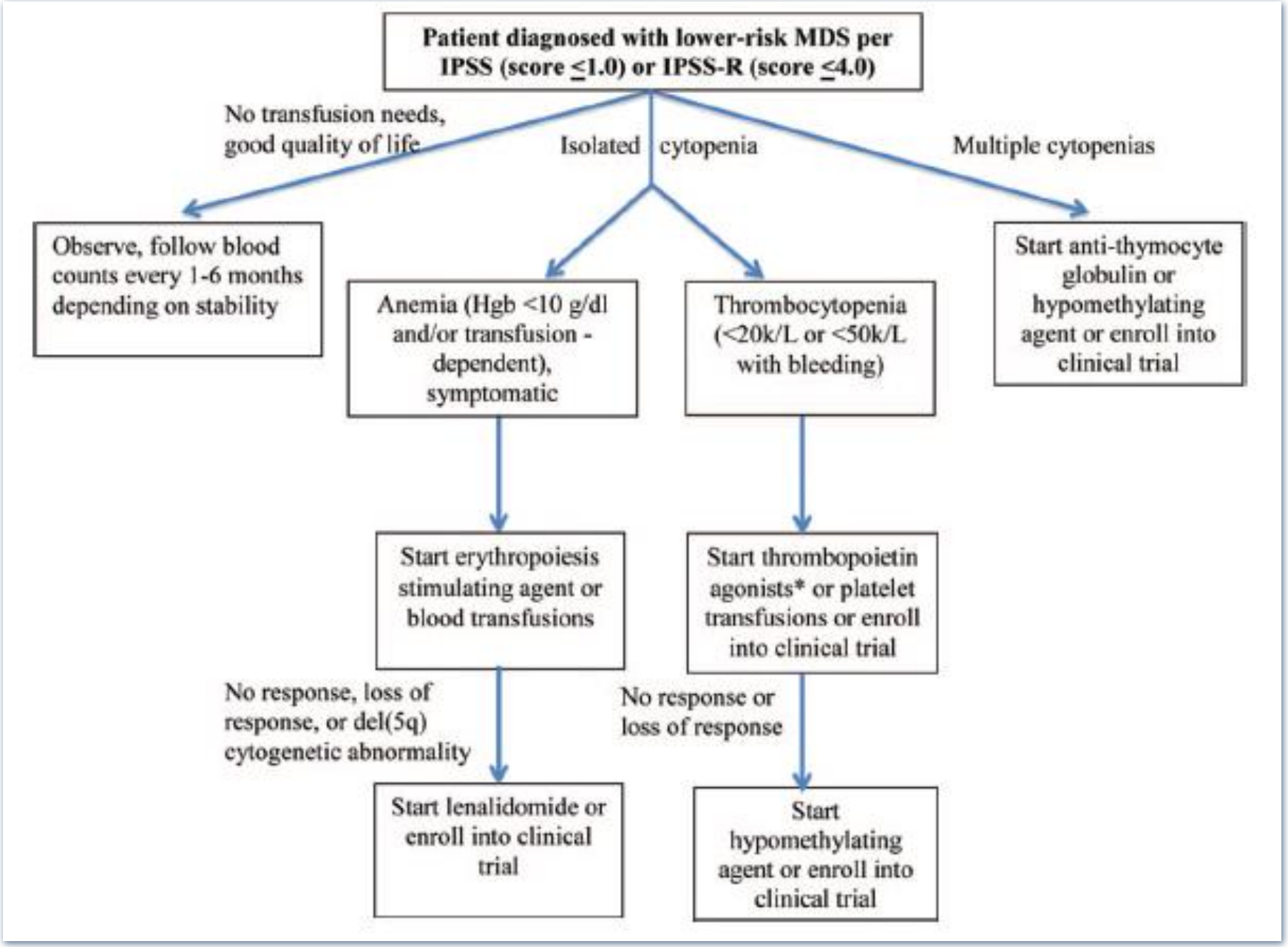
Lower prevalence anemia in North America
Different Causes:

- Less anemia from Iron deficiency, infection
- Hemoglobinopathies (e.g. SCD)
- Chronic Kidney Disease (Diabetes & HTN)
- Other (including MDS)

Sickle cell
Thalassemias
G6PD deficiency
Other hemog
Iron-deficiency anemia
Other endocrine
Gastritis & duodenitis
Peptic ulcer
Diabetic CKD
Hypertensive CKD
Other CKD

Kassebaum, Blood 123:615, 2014

MDS: Lower Risk Treatment Algorithm



Sekeres & Gerds Hematology 2014

Lower Risk Myelodysplastic Syndrome
Framing the Treatment Goals

- **Enhance quality of life during illness**
- **Eliminate, reduce, or prevent need for transfusions**
- Delay time to transformation to AML
- Cure

Anemia in MDS

- Most common cytopenia, tends to worsen over time
- Requires regular & prospective CBC monitoring
  - Need to be able to track frequency of transfusions
  - Most therapies are weekly or biweekly, with regular visits
    - ESA (Procrit™ or Aranesp™) injections, sometimes with Neupogen
  - Transfusion threshold can be individualized, as some patients need transfusion to keep HGB >7-8 g/dl
- Requires coordinated care team
  - Patient education of effects of anemia & transfusion very important
  - Patients must participate in their care

Best Supportive Care
Risks of Infection

Infection Risk is related to degree of Neutropenia

WBC counts x % neutrophils =Absolute Neutrophil Count

'Neutropenia' = ANC <1,000

Temp >101.4^0 F Antibiotics to cover likely bacteria

Prophylaxis Antibiotics (e.g. Levofloxacin, Cefdinir)

Can (occasionally) consider intermittent use of Neupogen

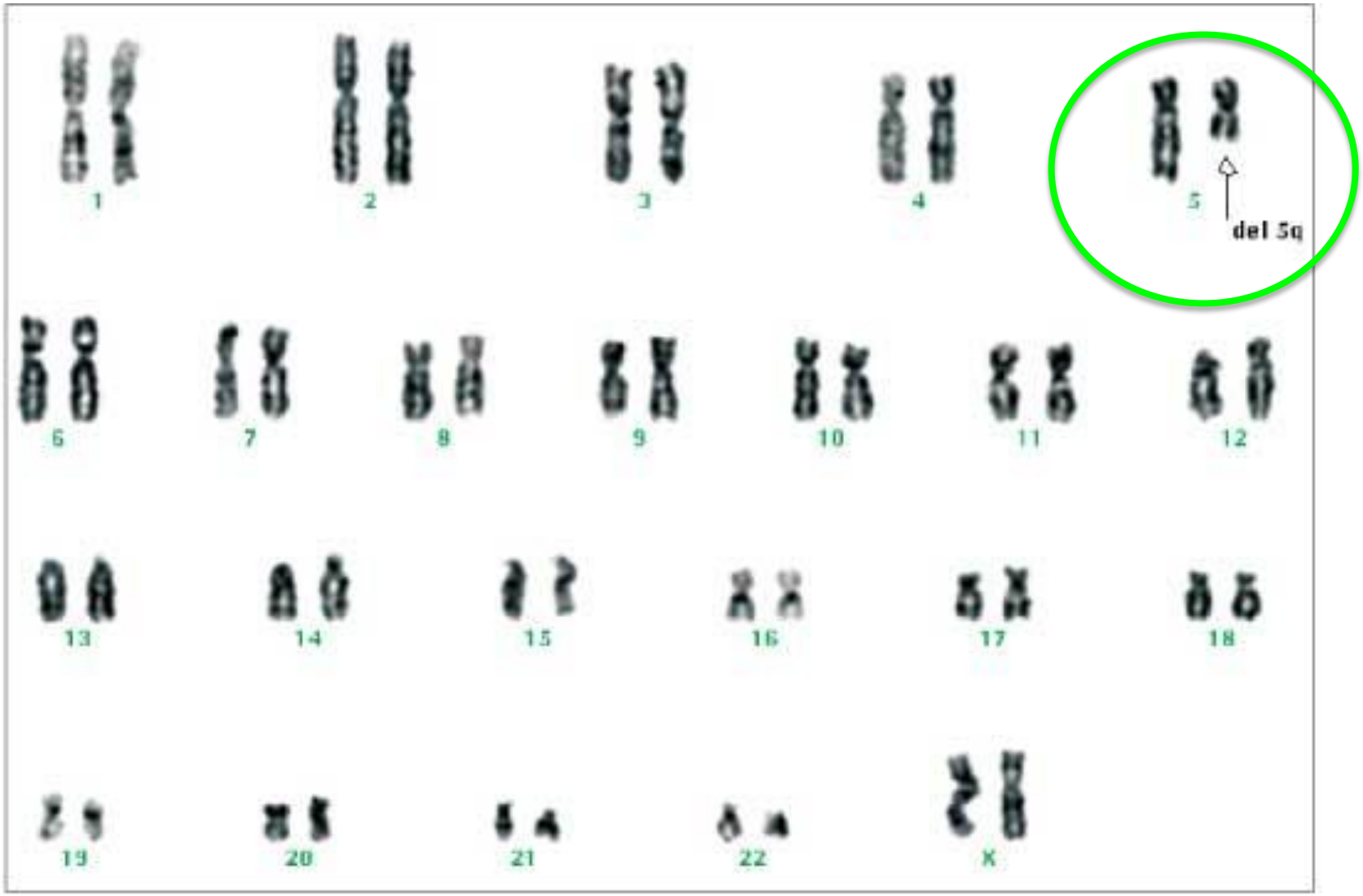


Fig. 2 *–G-banded karyotype obtained from the myelodysplastic syndrome patient at diagnosis: 46, XX, del(5)(q13;q33). The arrow shows the chromosomal abnormality*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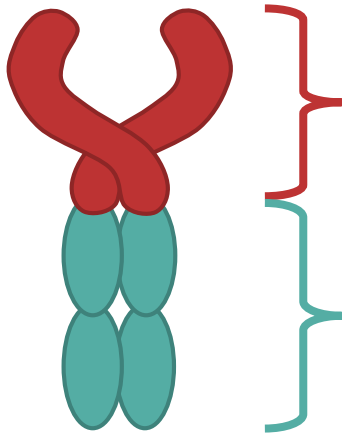
MEDALIST Trial

Luspatercept

- Luspatercept is an investigational first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase 2 study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes[2]

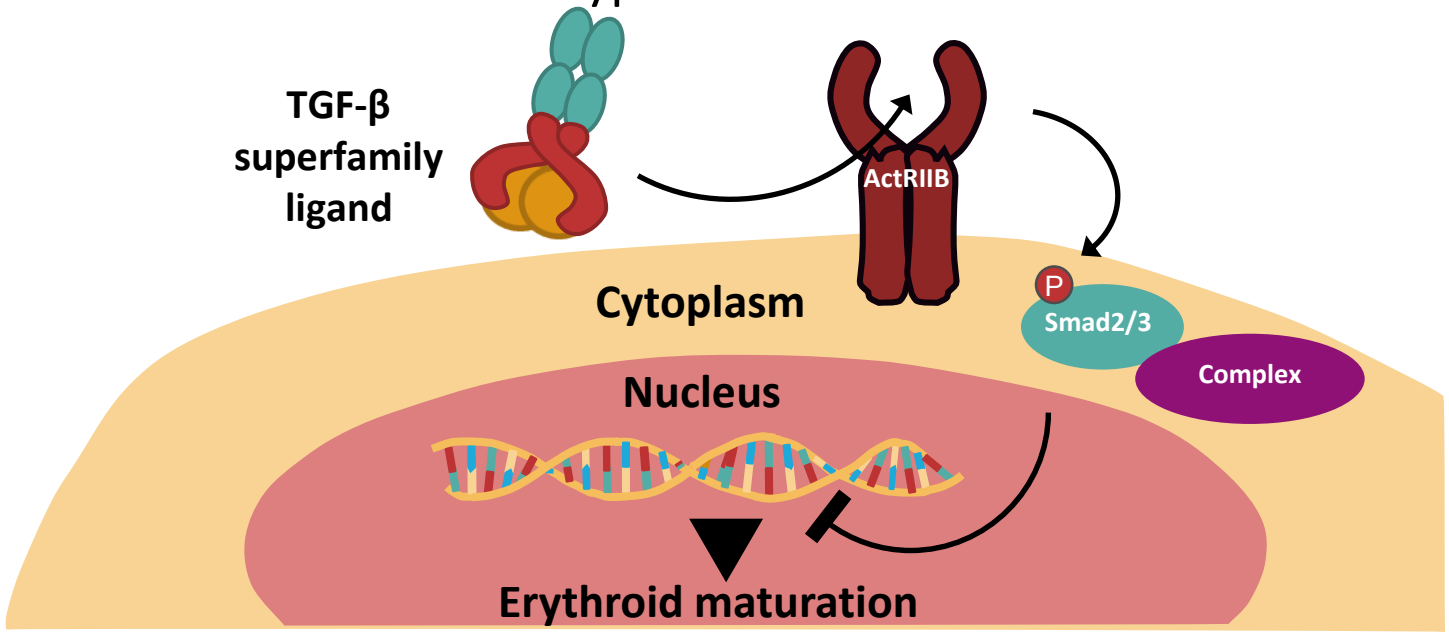
Luspatercept

ActRIIB / IgG1 Fc recombinant fusion protein



Modified extracellular domain of ActRIIB

Human IgG1 Fc domain



ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-β, transforming growth factor beta.

1. Suragani RN, et al. Nat Med. 2014;20:408-414;
2. Platzbecker U, et. A. Lancet Oncol. 2017; 18:1338.


CAUTION
THIS SIGN HAS
SHARP EDGES
DO NOT TOUCH THE EDGES OF THIS SIGN
ALSO, THE BRIDGE IS OUT AHEAD

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 Montaño 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

Iron Overload & Iron Chelation in MDS

- Anemia most frequent cytopenia in MDS, and RBC transfusion support remains important supportive care
  - Secondary iron overload (>2u PRBC q 4wks, ferritin >1000) associated with worse survival and with possible risk of cardiac events and organ toxicity

- Iron chelation - *may* improve outcomes

  * "…*should be considered for lower risk MDS patients with prolonged RBC transfusion (>1 yr) & elevated ferritin (>1000) with anticipated survival >1 year*"

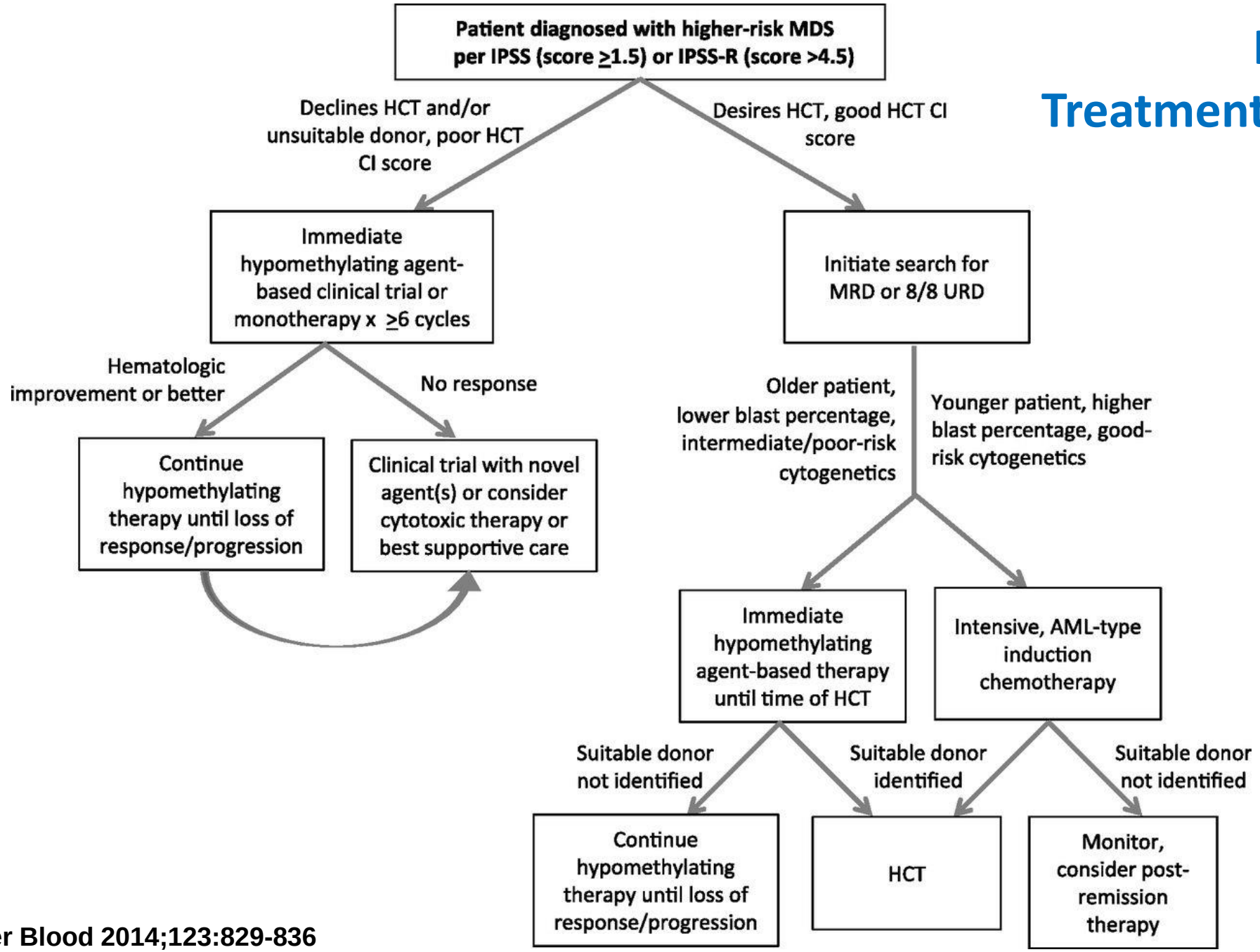
- Recent TELESTO study suggests possible advantage in adverse cardiac and clinical events
  - Balance benefits with expense, side effects

*** Bennett JM, Am J Hematol 83:858, 2008**

MDS
High Grade/Higher Risk

- More difficult, more symptomatic, or more advanced MDS
- Consider azacitidine or decitabine
  - ‘Low intensity’ chemotherapy given 5 or 7 consecutive days, every 4 weeks indefinitely
    - Do not work for everyone, or forever
  - Consider clinical trial of novel agent
- Evaluation in BMT program
- Supportive care (transfusions & antibiotics, etc.)
- Treatment of resistant MDS is very difficult

Higher Risk Treatment Algorithm



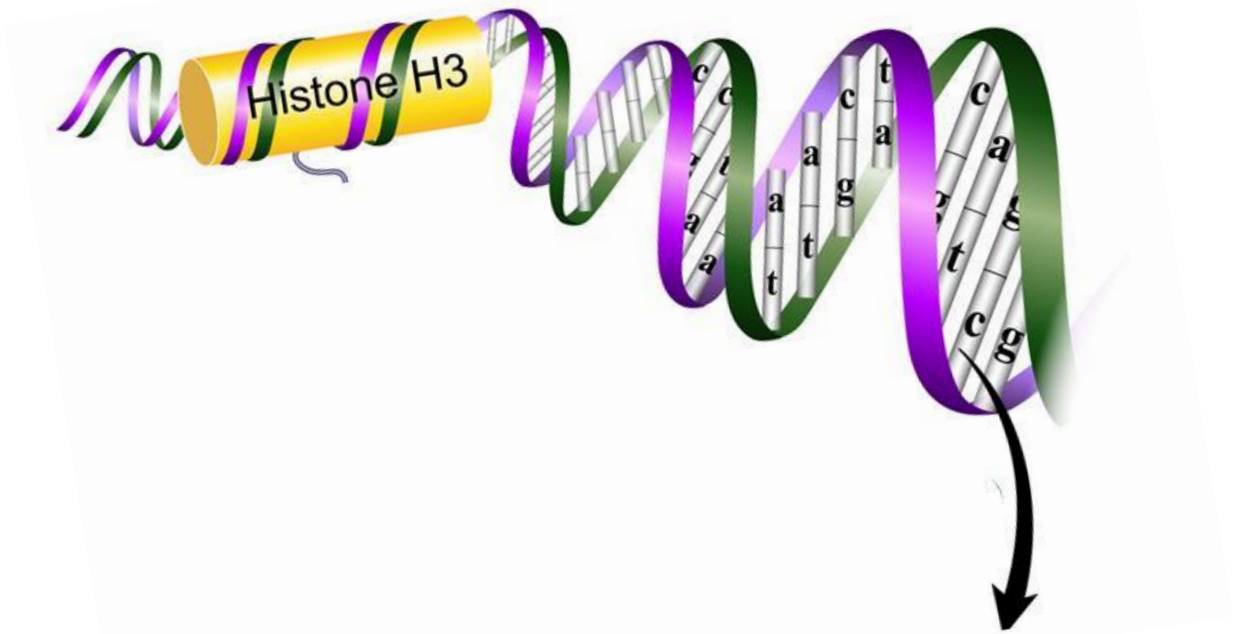
Sekeres & Cutler Blood 2014;123:829-836

blood

Treatment of MDS
What Does Success Look Like?

- Important to set expectations and goals as not all patients experience a major improvement
- Improvements in CBC
  - Decrease frequency or independence from transfusions
- Improved, or Maintained Quality of Life
  - Stronger, stamina, independent
- Continue therapy ‘long-term’ to maintain benefit & stability
- Sometimes success is ‘stability’, or not worsening of MDS
- Hard to cure – goal is often maintain control

What is a mutation?



…TTGAGTCG….

↓

…TTGAGTAG….

Mutations

- *A mutation is a change that occurs in our DNA sequence, either due to mistakes when the DNA is copied, or as the result of environmental factors such as UV light and cigarette smoke.*
- Disrupt normal gene activity and cause diseases, like cancer
- Can contribute to prognosis with standard therapies
- * Some gene mutations can be targeted

Gene Mutations in MDS
Why we should we care about them

1. Biology

   Clues about what went wrong with MDS cells

2. Diagnosis

   Already help us diagnose other bone marrow diseases

3. Prognosis

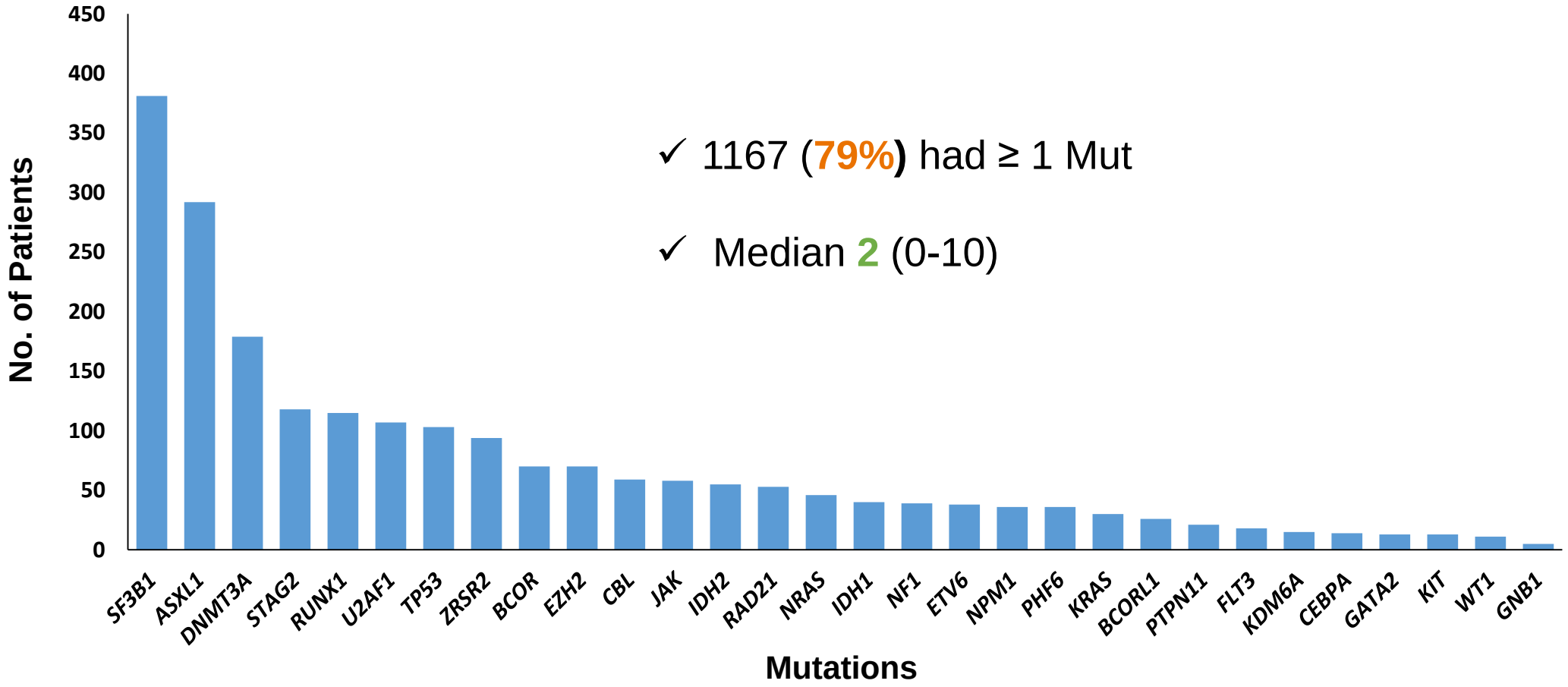
   Used to predict outcome in other bone marrow diseases

4. Therapy

   Mutations help us choose the right drugs in other bone marrow diseases

➔ *will help develop new targeted therapies in MDS, or better use the ones we have available now*

Mutation Distribution (Training)



✓ 1167 (**79%**) had ≥ 1 Mut

✓ Median **2** (0-10)

Nazha A, et al. ASH 2018 [#793]

Targeting Mutations in MDS

- Nascent field
- Some (rare) mutations could potentially be targeted
- Clinical trials
  - IDH1, IDH2 mutations
  - DNA splicing (‘Spliceosome’) mutations
    - Relatively common
      - SF3B1, SRSF2, U2AF1, ZRSR2
  - TP53 mutations
  - Potentially others

Evaluation for Allogeneic Transplantation
A Balance of Hope and Reality

- Not for everybody
  - Can be curative, but not always, and can expose to significant risks
  - Must be ‘fit’, and must have a donor and a caregiver
    - In general much harder for older patients over 65-70 years
- Provides significant reduction in risk of relapse
  - More effective if MDS under control with low blast count
    - Probably better if Iron levels well controlled, or before too high
- Improved outcomes in *Modern Era*
  - High resolution/molecular HLA typing for Unrelated Donors
  - Reduced intensity conditioning allows us to treat older adults
  - Improvements in Supportive Care
- Increased availability of donors [unrelated, and *alternative*]

Selection at BMT Center

- Patient-centered evaluation and discussion
  - Decision taken together with BMT physicians
- Balance MDS risks and prognosis with risks/benefits of Allogeneic BMT
  - Leukemia risk & remission status
  - Patient eligibility
    - Comorbid disease, psycho-social assessment, consent
  - Donor availability, caregiver support, type of healthcare insurance
- Strict national standards, recognized indications[1]
  - FACT [Foundation for Accreditation of Cellular Therapy]
    - reviewed and accredited every3 years
  - Stem Cell Therapeutic Outcomes Database *

[1]Majhail et al, BBMT 21:1863, 2015

* http://bloodcell.transplant.hrsa.gov

Patient Support & Palliative Care in MDS

- Often coordinated by the healthcare team
- Hospice and palliative care not utilized as often in MDS
  - Possibly under-utilized
  - Pain control not usually a common issue compared with other types of cancer
  - Infection & antibiotics available
  - Transfusion support difficult to administer routinely or frequently in Hospice
- Caregiver support - who cares for the caregiver?
  - Social work initiatives
  - Post-BMT support

Pearls of Wisdom

- Almost all patients benefit from therapy
  - Depends on scenario and patients needs
  - Set individual patient goals

- Current treatments still not adequate for many
  - We must work together to advance MDS treatments and outcomes
    - Clinical trials
      - Molecularly-targeted therapy

MDS
Conclusions

- Therapy for lower-risk disease remains focused on addressing specific cytopenias, particularly anemia anf thrombocytopenia
- Standard therapy for higher-risk disease is HMA (azacitidine or decitabine)
  - Many new combinations being studied, some very promising
  - Need new strategies for resistant MDS
- Allogeneic stem cell transplantation may be a consideration
  - higher risk disease, or lower risk that is either not responding or has progressed to intermediate risk disease
- The molecular landscape is becoming more complex
  - Mutations now being incorporated into diagnosis, clinical prognostic schemes, and to predict response to therapy
  - Clinical trials to target specific mutations (e.g. SF3B1, IDH1, TP53)

Acknowledgments

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"The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, a union of forces is necessary."

1910: Dr. William J. Mayo
Rush Medical College commencement address

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