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Until every cancer is cured

What is MDS?

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Sidney Kimmel Cancer Center
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Philadelphia, PA

Disclosures

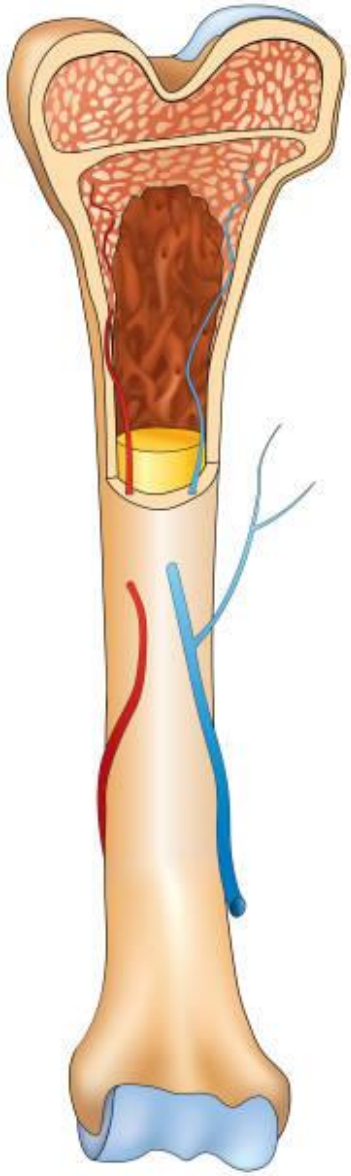
- Research funding from Gilead and Protagonist

Goals

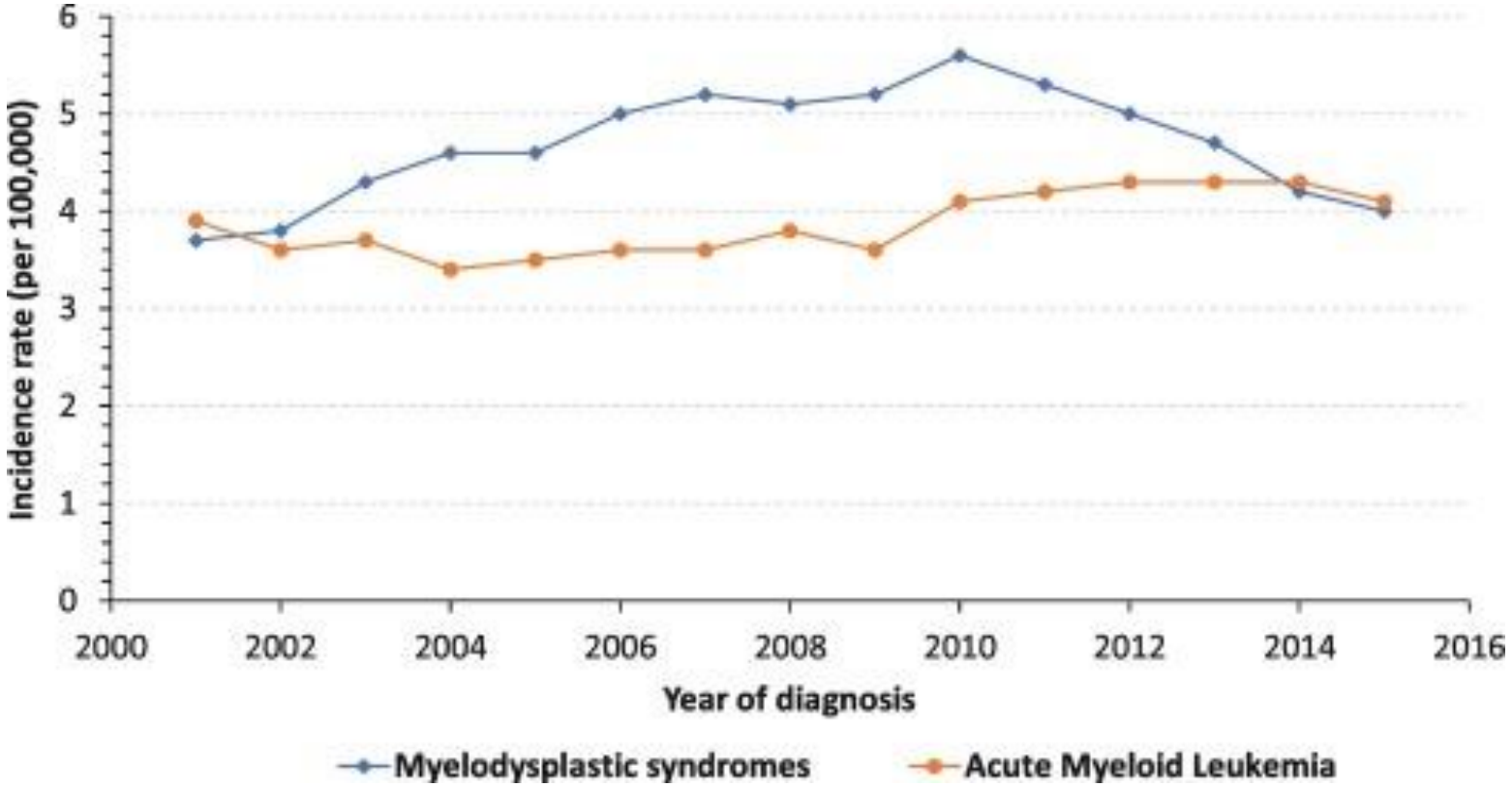
- Review the incidence of MDS
- Understand how the bone marrow works
- Describe how MDS changes bone marrow function

What is MDS?

- MDS is a heterogeneous group of blood cancers that are characterized by low blood counts
- In MDS, the bone marrow fails to make normal, healthy blood cells
- ~35-40% of patients with MDS will progress to having acute myeloid leukemia (AML)



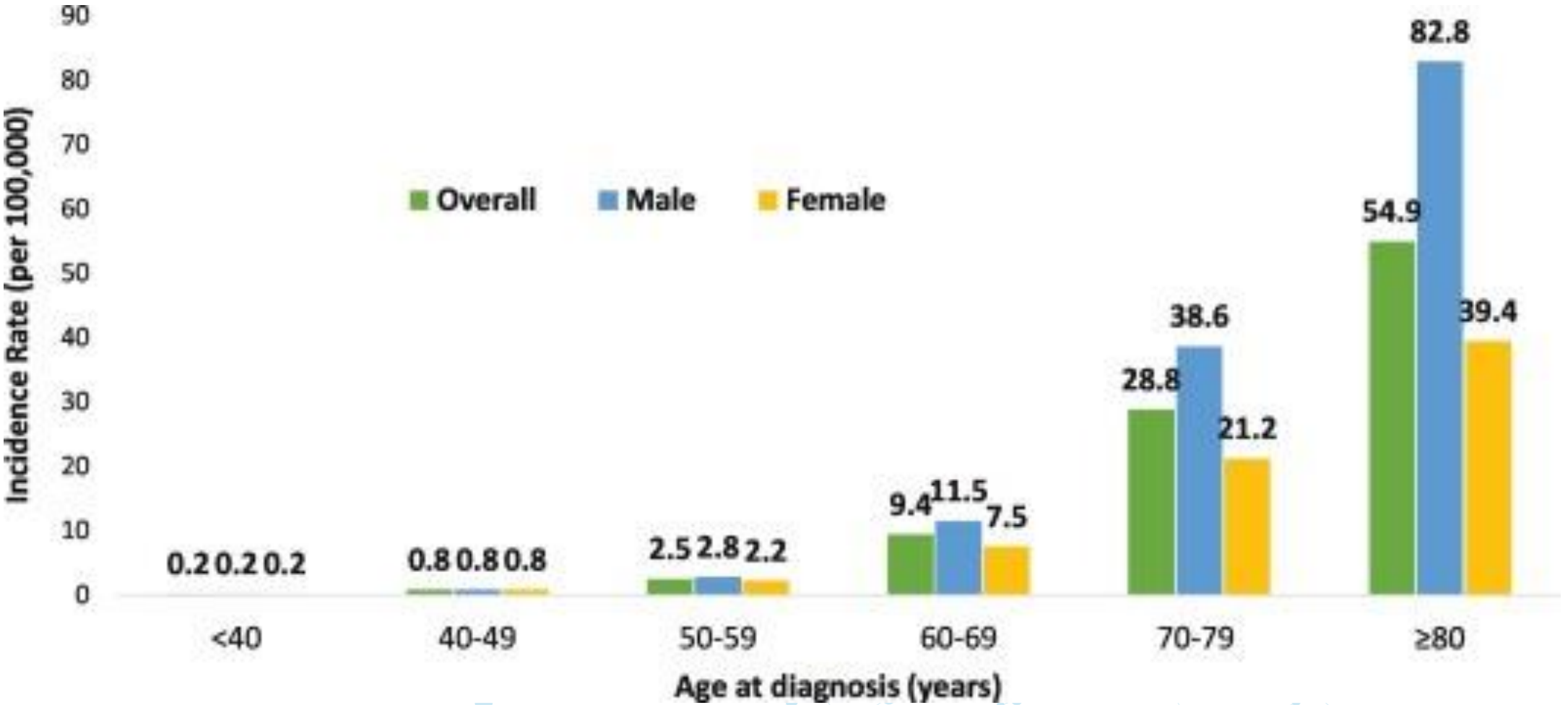
How Common is MDS?



~4.7/100,000

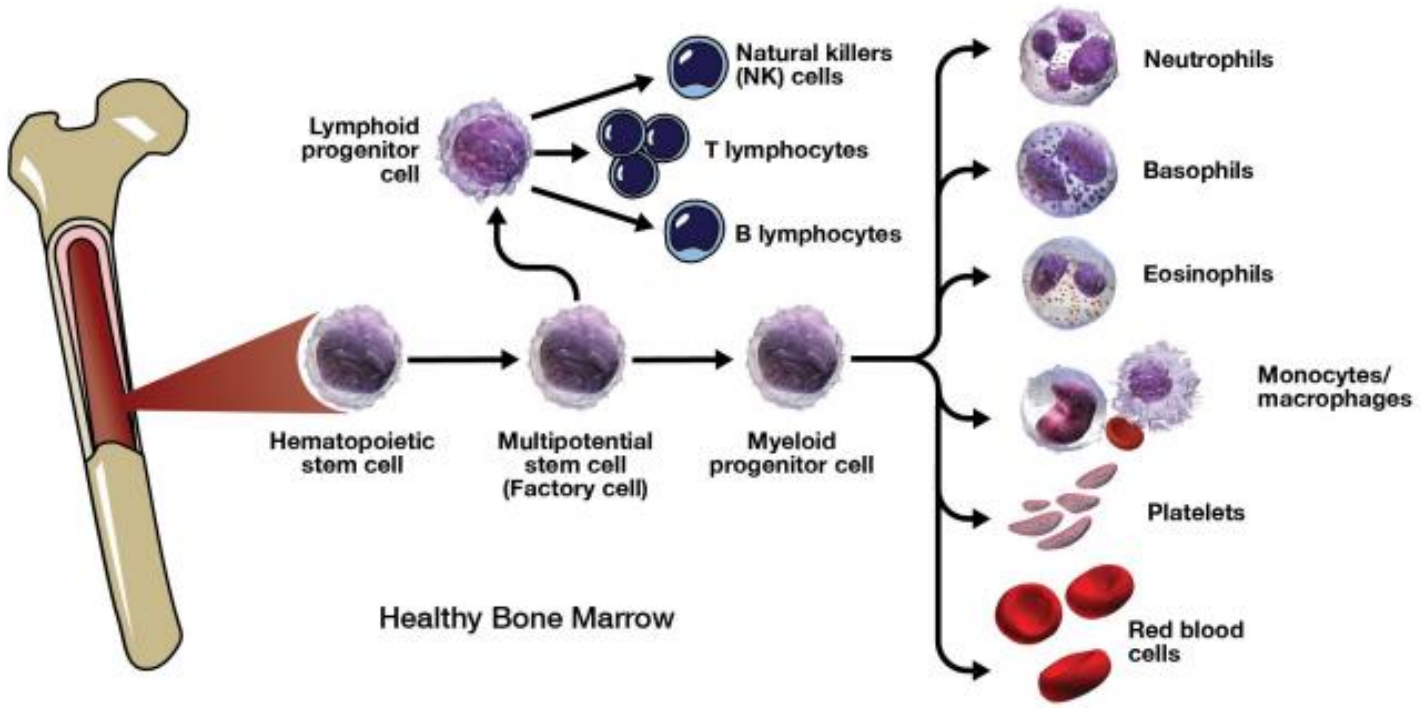
Zeidan, Amer M., et al. "Epidemiology of myelodysplastic syndromes: why characterizing the beast is a prerequisite to taming it." *Blood reviews* 34 (2019): 1-15.

Does MDS Become More Common as We Age?



Zeidan, Amer M., et al. "Epidemiology of myelodysplastic syndromes: why characterizing the beast is a prerequisite to taming it." *Blood reviews* 34 (2019): 1-15.

What is the Bone Marrow?

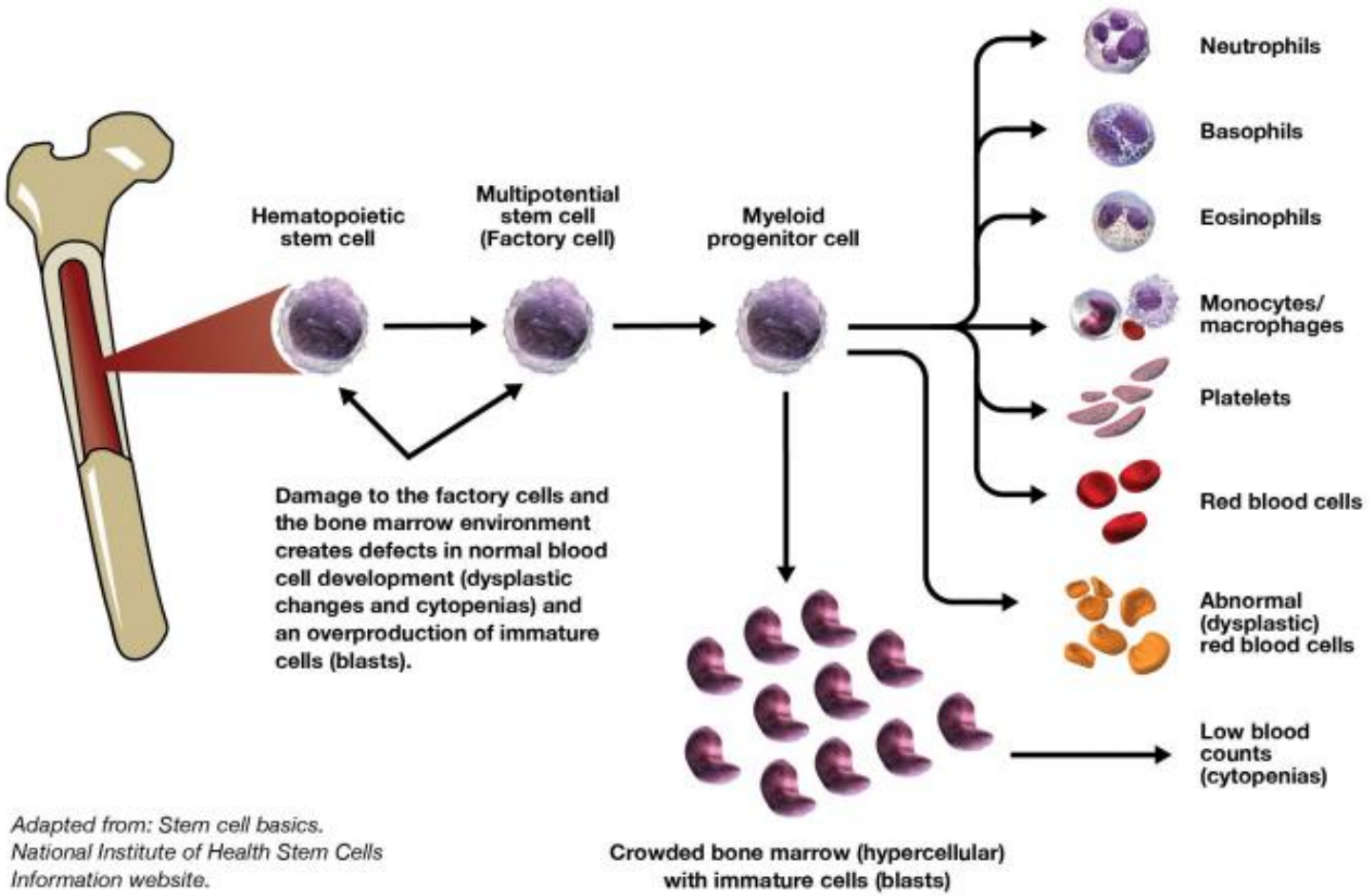


Red Blood Cells- Carry oxygen

White Blood Cells- Prevent/fight infection

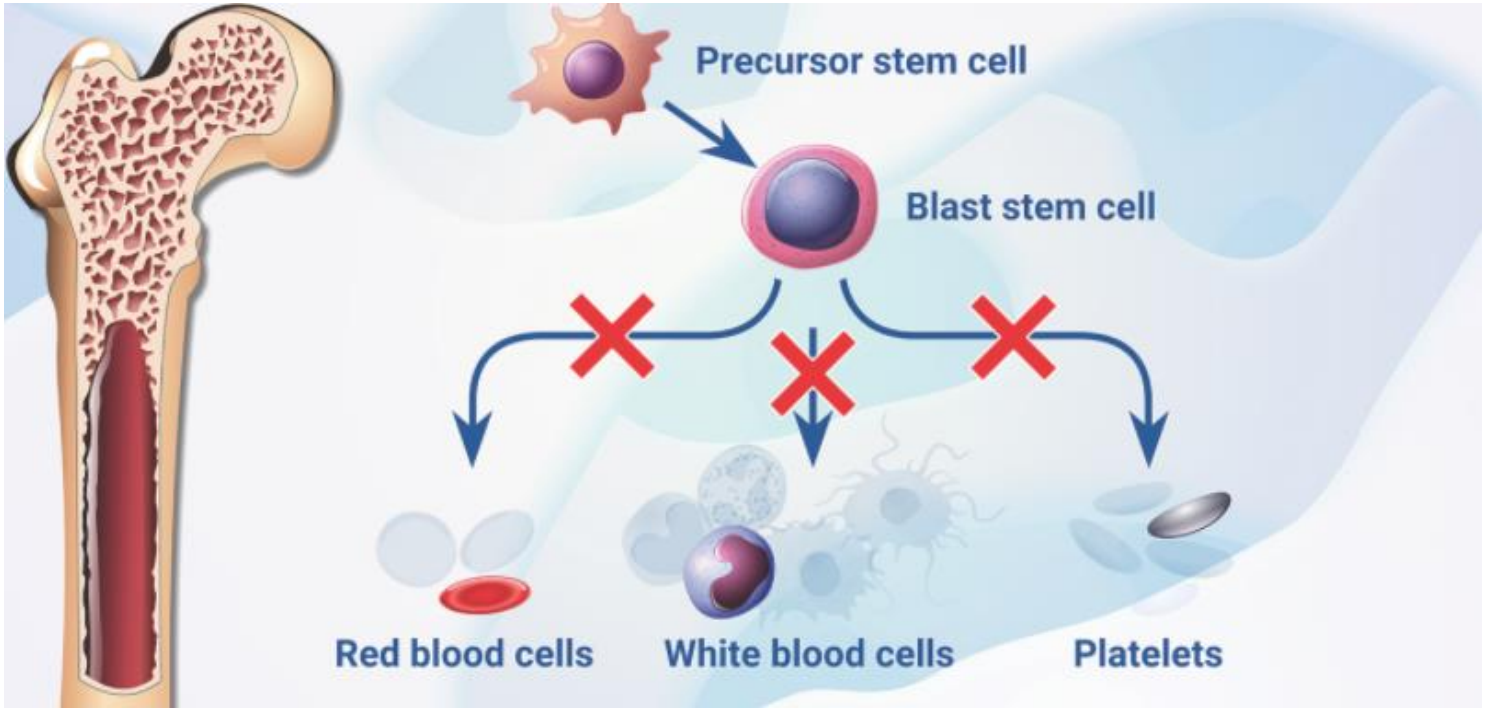
Platelets- Clot blood and prevent bleeding

What Happens to the Bone Marrow in MDS?



Adapted from: Stem cell basics. National Institute of Health Stem Cells Information website.

What Happens When Blood Counts are Low?



Anemia (Low hemoglobin)
-Fatigue
-Shortness of breath
- Pale eyes or skin
- Abnormal heartbeat

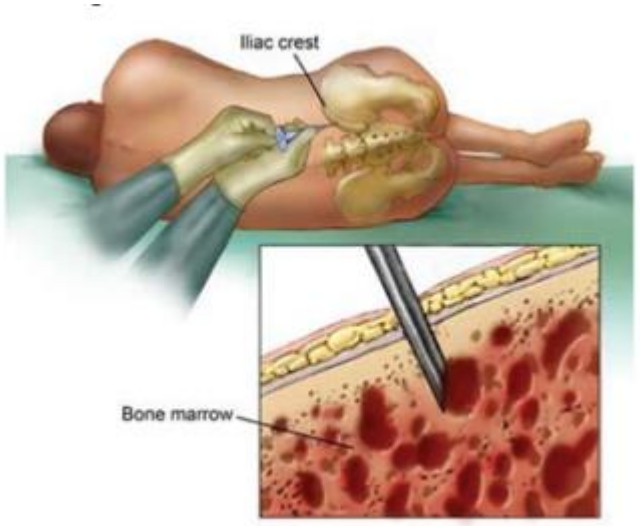
Leukopenia/ neutropenia (Low white blood cells)
- Fever
- Infections

Thrombocytopenia (Low platelets)
- Bleeding
- Bruising
- Rash

How Is MDS Diagnosed?

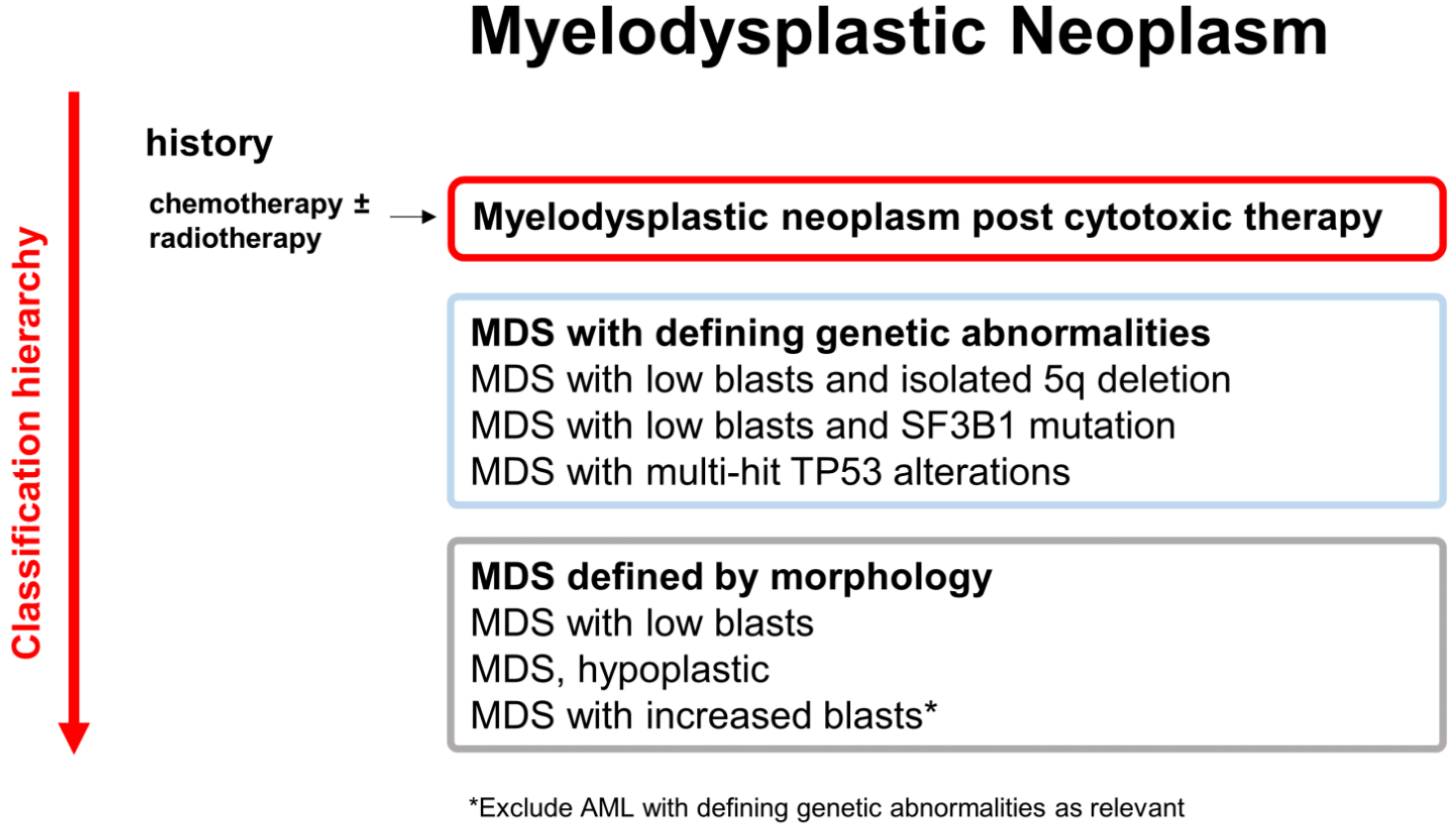
- Complete blood count (CBC)

- Bone marrow aspirate and biopsy



How is MDS Classified?

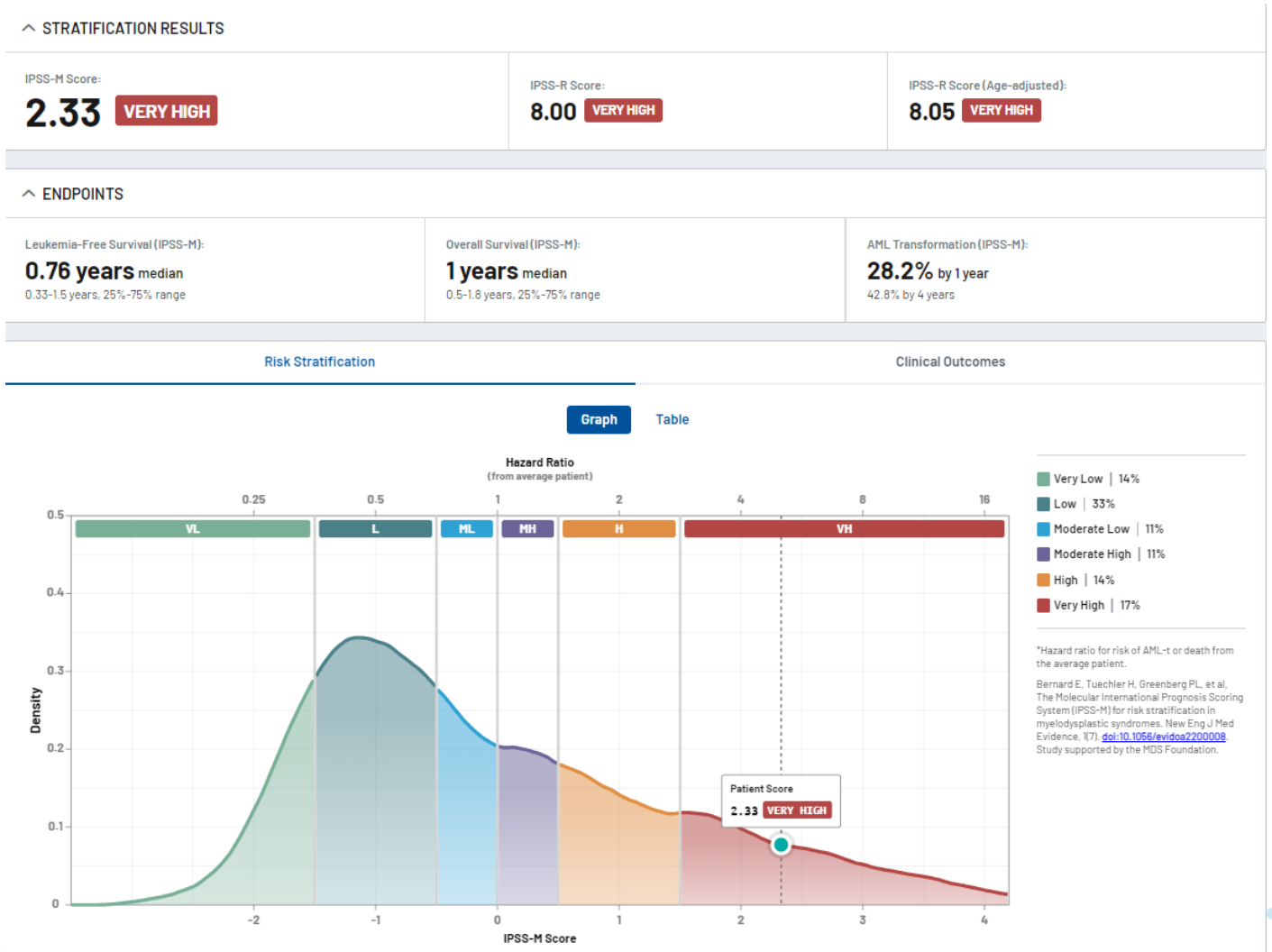
2022 WHO Classification



Khoury, J.D., Solary, E., Abla, O. *et al.* The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia* **36**, 1703–1719 (2022). https://doi.org/10.1038/s41375-022-01613-1

How Do We Determine the Prognosis for MDS?

How Do We Determine the Prognosis for MDS?



Thank you!


mds foundation
the myelodysplastic syndromes foundation, inc.

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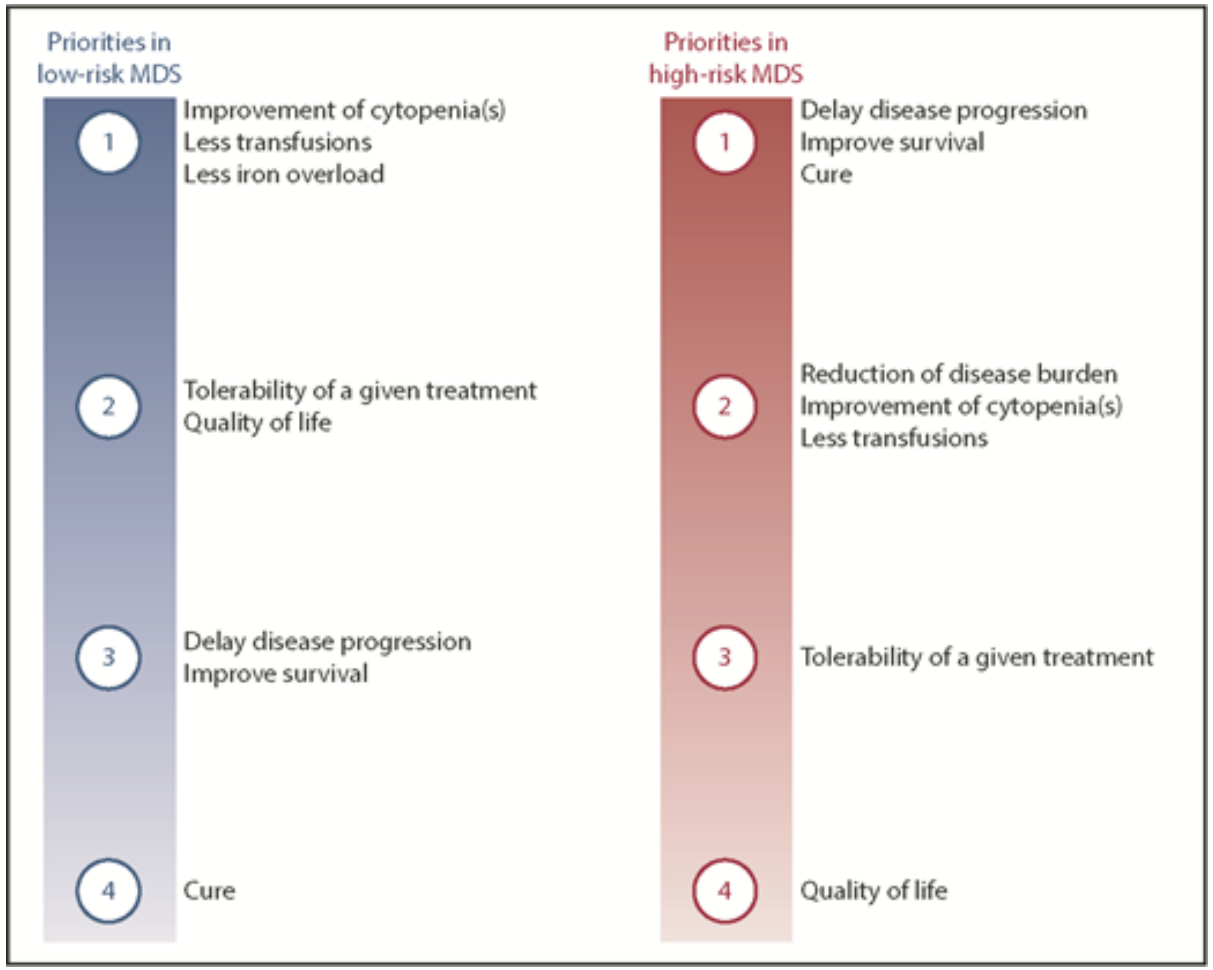
How do we treat MDS?

Margie Kasner, MD MSCE
Professor of Medical Oncology
Director, Leukemia Program
Medical Director, Cancer Clinical Research Operations
Sidney Kimmel Cancer Center
Thomas Jefferson University Hospital
Philadelphia, PA

Treatment Paradigm

- Define the risk
- Defining the treatment goals
- The only curative treatment for MDS is allogeneic stem cell transplant

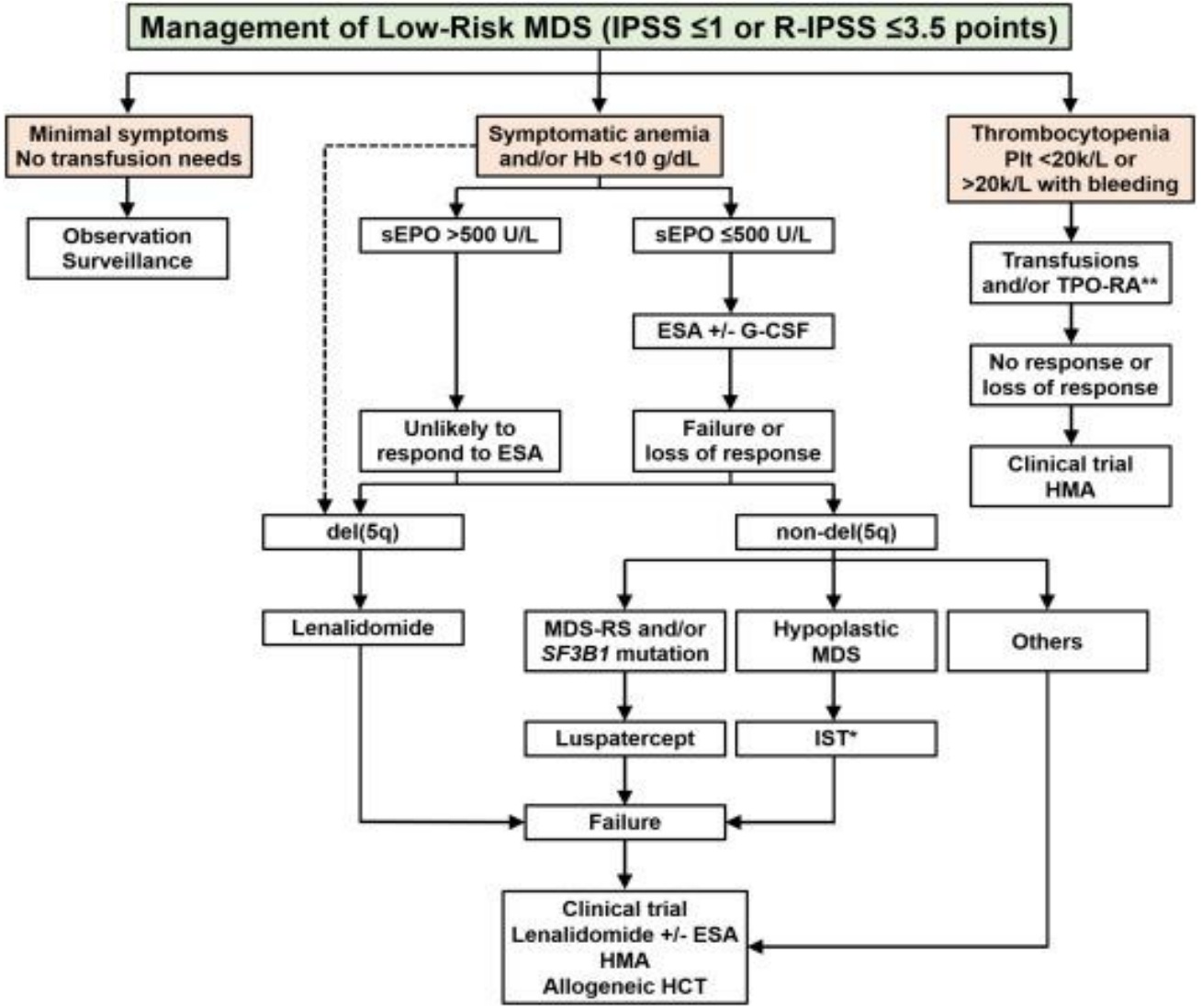


Platzbecker, U. Treatment of MDS. Blood, 2019.

Management of Lower- MDS

Treatment Goals:

- Improving cytopenias
- Decreasing transfusion burden
- Improving QOL



Saygin C, Carraway HE. Current and emerging strategies for management of myelodysplastic syndromes. Blood Reviews, 2021.

Lower-Risk without Ring Sideroblasts and no SF3B1: First Line

Epo < 500

- Luspatercept
- ESA/Epo (red cell growth factor)
- If no response can increase dose or add white cell growth factor

Epo > 500

- Luspatercept ????
- Hypomethylating agents (azacitadine,decitabine,oral decitabine)

If platelets are the problem

Oral or subcutaneous platelet growth factors (eltrombopag, romiplostim)

Lower-Risk without Ring Sideroblasts and no SF3B1: Second Line and beyond

Epo < 500

- ESA (red cell growth factor)
- If no response can increase dose or add white cell growth factor
- Luspatercept

Epo > 500

- Received hypomethylating agents:
  - Clinical trial
  - Transplant
  - Supportive care
- Haven’t received hypomethylating agents:
  - Hypomethylating agent
  - Lenalidomide

Lower-Risk WITH Ring Sideroblasts and/or SF3B1: First Line

Epo < 500

- Luspatercept
- ESA (red cell growth factor)
- If no response can increase dose or add white cell growth factor

Epo > 500

- Luspatercept

If platelets are the problem

Oral or subcutaneous platelet growth factors (eltrombopag, romiplostim)

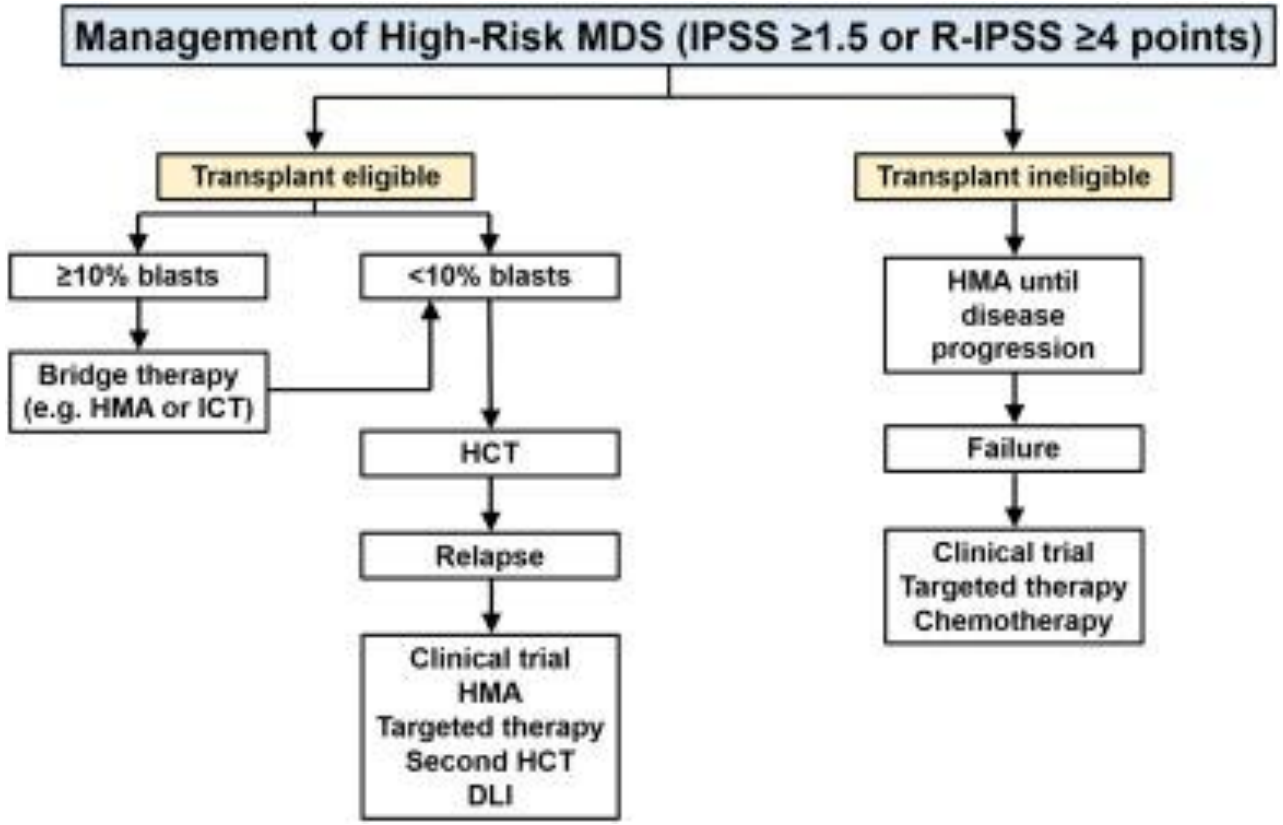
Lower-Risk WITH Ring Sideroblasts and/or SF3B1: Second Line and beyond

- Luspatercept (if the first line was growth factors)
- Growth factors if the first line was luspatercept
- Lenalidomide
- Hypomethylating agent
  - Clinical trial
  - Transplant
  - Supportive care

Lower-Risk – Deletion (5q-) syndrome

- Isolated cytogenetic abnormality
- Less than 5% blasts
- Anemia
- Elevated platelets

- First line: Lenalidomide
- Second line and beyond:
  - Growth factor if eligible
  - Hypomethylating agents
  - Clinical Trials
  - Supportive Care



Saygin C, Carraway HE. Current and emerging strategies for management of myelodysplastic syndromes. Blood Reviews, 2021.

Higher-Risk: First Line

Transplant candidate (or not)

- Hypomethylating agents (azacitadine, decitabine, oral decitabine)
  - 40-50% respond
  - Median duration of response is about 1 year
- Leukemia-like therapy including chemotherapy if blast count is higher than 10%

Higher-Risk: Second Line and beyond

Transplant candidate (or not)

- Clinical trial
- Leukemia-type therapy including chemotherapy
- Targeted therapy
- Supportive care
- Palliative care

Thank you!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MDS Research

Gina Keiffer, MD
Assistant Professor of Medical Oncology
Sidney Kimmel Cancer Center
Thomas Jefferson University Hospital
Philadelphia, PA

Why do we need research in MDS?

- MDS is a complex spectrum of disease with variable cytopenias and risk of progression to AML and treatment must be individualized.
- Lower-risk patients may struggle with transfusion burden and debilitating symptoms for which treatment options are limited.
- Higher-risk patients may progress quickly to AML or may not be candidates for stem cell transplant.
  - Median survival with standard of care azacytidine is only 12 months.
- Outcomes are poor after failure of initial treatment.

Why is MDS so complicated to treat?

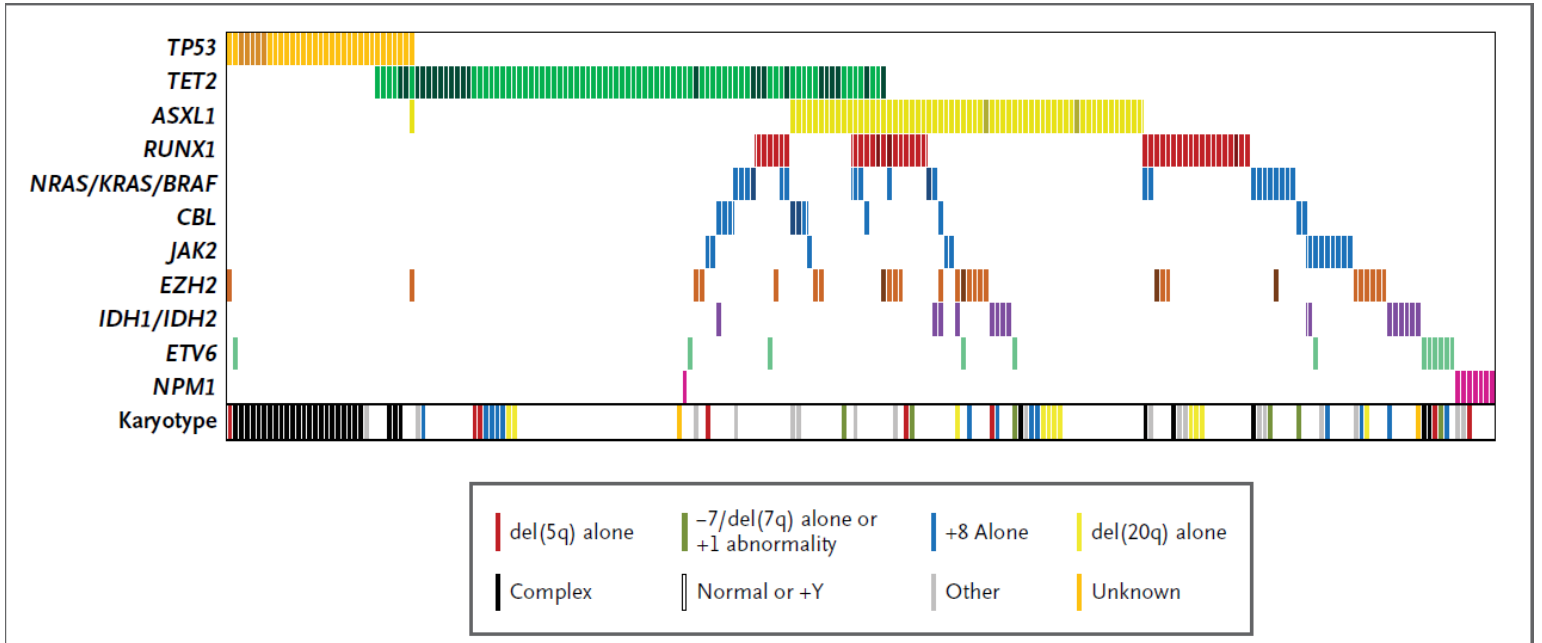
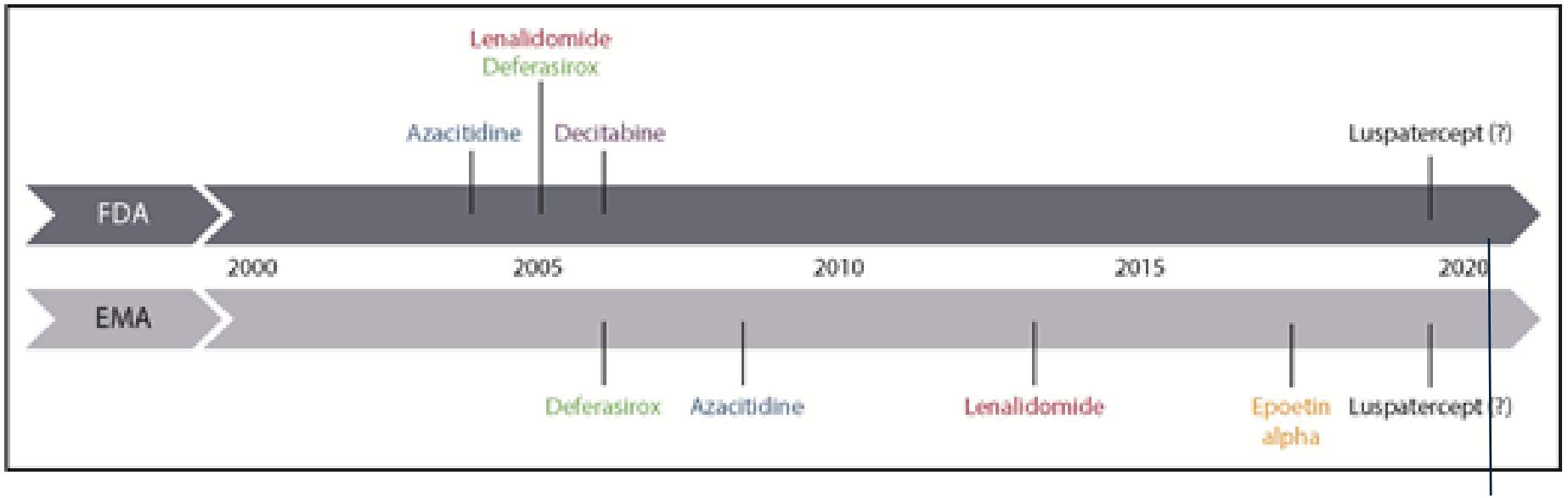


Figure 1. Mutations and Cytogenetic Abnormalities in 223 Samples with at Least One Mutation.

Mutations in the 11 most frequently mutated gene groups are shown by colored bars. Each column represents 1 of the 223 samples with a mutation in one or more of the genes listed. Darker bars indicate samples with two or more distinct mutations in that gene group. The karyotype of each of the 223 samples is also shown.

Bejar R, Stevenson, K, Abdel-Wahab O, et al. Clinical Effect of Point Mutations in MDS. NEJM, 2011.

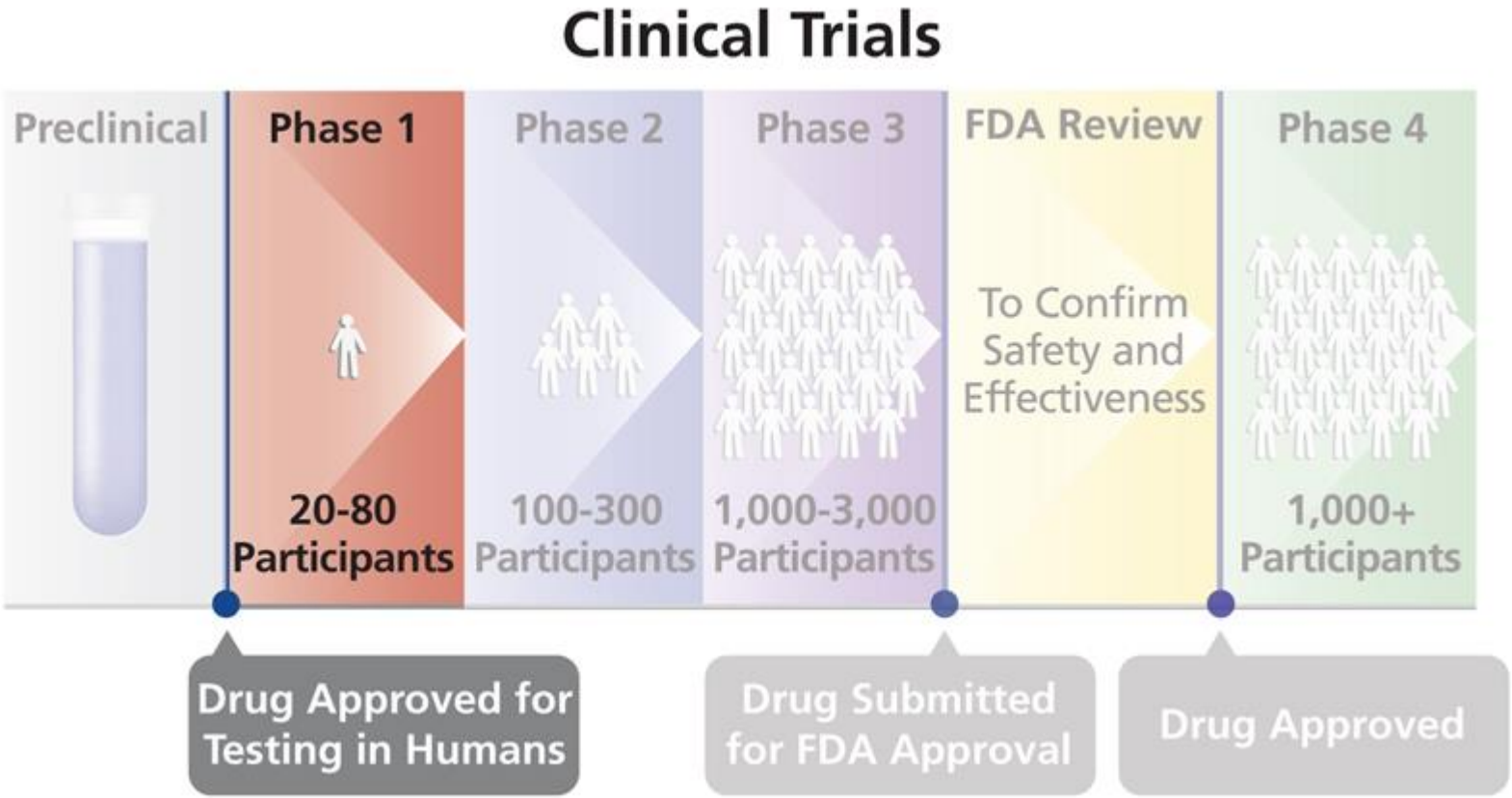
Drug approvals in MDS



Decitabine/Cedazuridine

Platzbecker, U. Treatment of MDS. Blood, 2019.

Research Process



Ongoing Research in MDS

(Some) Research Questions in MDS

- How do we decrease burden of cytopenias in lower-risk MDS?
- Does starting treatment before transfusion-dependence develops lessen, delay or prevent transfusion burden?
- How should available therapies be combined in the treatment of higher-risk MDS?
  - Who benefits from combination treatment?
  - What is the optimal dosing regimen?
- What is the optimal all-oral treatment?

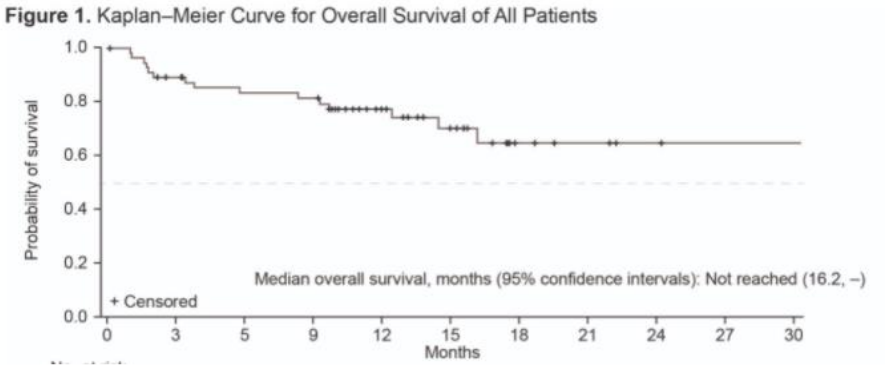
Studies with Venetoclax in HR-MDS

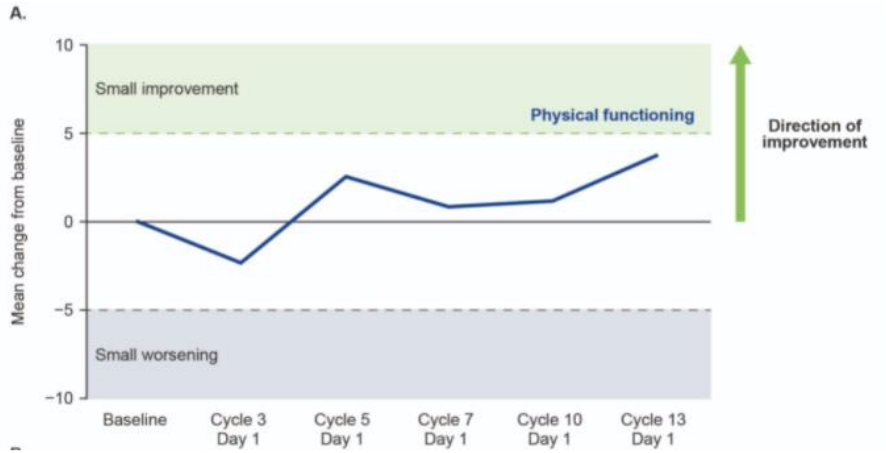
Authors	Treatment	Population	Median PFS	Median OS (Median Follow UP)	ORR	CR	Patients Enrolled	Study Phase
Garcia JS et al.	Venetoclax + AZA	Rx-naïve HR-MDS	-	27.5	77%	42%	78	Ib
Ball et al.	Venetoclax + HMAs	Rx-naive and R/R MDS	15.4 months	19.5 (7.6)	59%	14%	44	Ib
Zeidan AM et al.	Venetoclax + AZA	R/R MDS	8.6 months	12.2 (21.2)	39%	7%	37	Ib

Adapted from: El-Cheikh J, et al. AJH, 2023.

Azacitidine + Venetoclax

- Phase Ib/II single-arm with Aza + Venetoclax for treatment-naive high-risk MDS
  - Aza 75 mg/m2 days 1-7 every 28 days
  - Ven 100-400 mg days 1-14 every 28 days
- Primary endpoint: Safety and recommended phase II dose
- Median OS: NR (16.1 mos – NR)
- Median PFS: 17.5 mos





Garcia JS, Wei AH, Borate U, et al. Safety, Efficacy and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk MDS: a phase 1bstudy. ASH Annual Meeting, 2020.

Select Enrolling Studies in Lower-Risk MDS

Agent(s)	NCT#	Population	Phase
Oral AZA + BSC vs placebo	05469737	Lower-risk MDS	III
Luspatercept	05949684	Non-transfusion dependent	III
Eltrombopag	04797000	Platelet-transfusion dependent	II
Canakinumab (anti-IL-1b) + darbopoietin	04798339	RBC-transfusion dependent who failed ESA	Ib/II
Hetrombopag	05392647	With thrombocytopenia	II
Luspatercept + lenalidomide	04539236	Non-5q- MDS	I/II

Clinicaltrials.gov

Select Enrolling Studies in Higher-Risk MDS

Agent(s)	NCT#	Population	Phase
Lemzoparlimab (anti-CD47) + AZA vs AZA	05709093	Treatment-naïve	III
Oral AZA vs placebo	04173533	Maintenance tx post-alloSCT	III
AZA + cedazuridine	04256317	MDS, AML, CMML	III
Orca-T (engineered T cells)	05316701	AlloSCT recipients with hematologic malignancies	III
Oral AZA + venetoclax	**05782127**	Treatment-naïve	I/II

Clinicaltrials.gov

Sometimes research comes with disappointments…

Press Releases

July 21, 2023

Gilead To Discontinue Phase 3 ENHANCE Study of Magrolimab Plus Azacitidine in Higher-Risk MDS

FOSTER CITY, Calif.--(BUSINESS WIRE)-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced that the Phase 3 ENHANCE study in higher-risk myelodysplastic syndromes (MDS) has been discontinued due to futility based on a planned analysis. The safety data seen in this study is consistent with the known magrolimab profile and adverse events that are typical in this patient population. Gilead recommends discontinuing treatment with magrolimab in patients with MDS. Magrolimab is a potential first-in-class, anti-CD47 immunotherapy with a clinical development program spanning ten potential indications including ongoing trials in solid tumors and two pivotal trials: ENHANCE-2 study in acute myeloid leukemia (AML) with TP53 mutations and ENHANCE-3 in first-line, unfit AML.

Gilead.com

Interested in Participating in MDS Research?
MDS Research Resources

- Jefferson Resources:
  - Visit: research.jefferson.edu
  - Email: JCRI@Jefferson.edu, askphase1@Jefferson.edu

- MDS Foundation:
  - Search clinical trials: mds-foundation.org/clinical-trials

- Leukemia and Lymphoma Society Clinical Trial Support Center: lls.org
  - One-on-One assistance with LLS Clinical Trial Nurse Navigator

- National Clinical Trials Database: clinicaltrials.gov

Thank you!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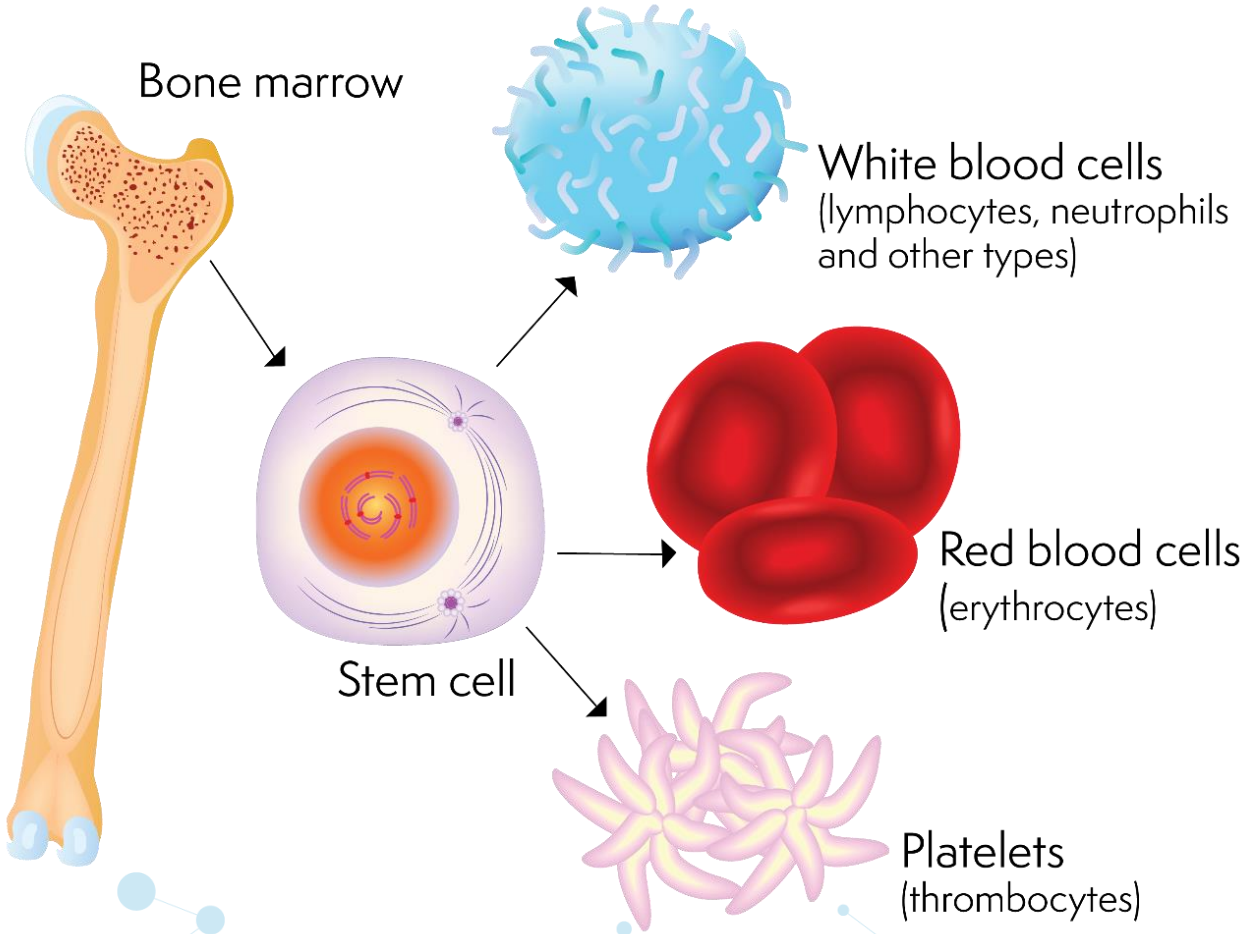
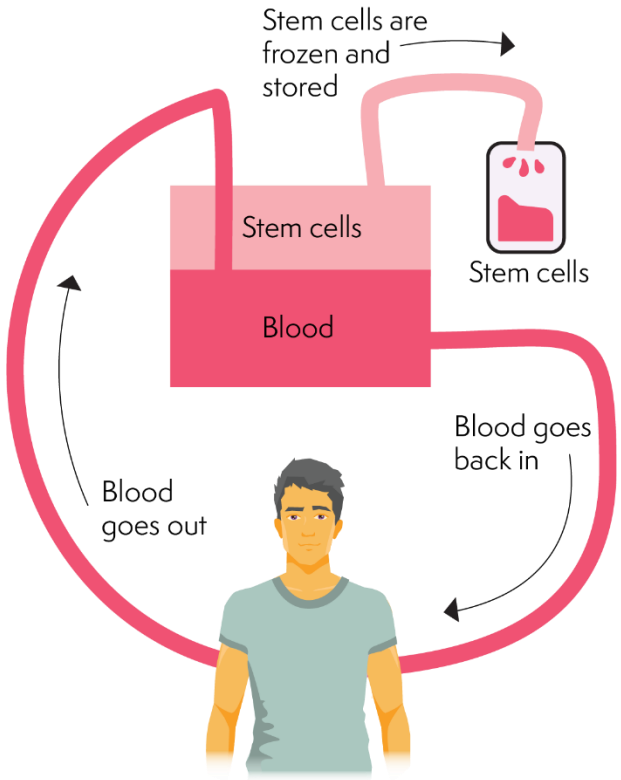
Overview of Stem Cell Transplant

Xia Bi, MD
Assistant Professor
Department of Medical Oncology
Division of Hematologic Malignancy and Stem Cell Transplantation
Sidney Kimmel Cancer Center, Thomas Jefferson University

What are Stem Cells?



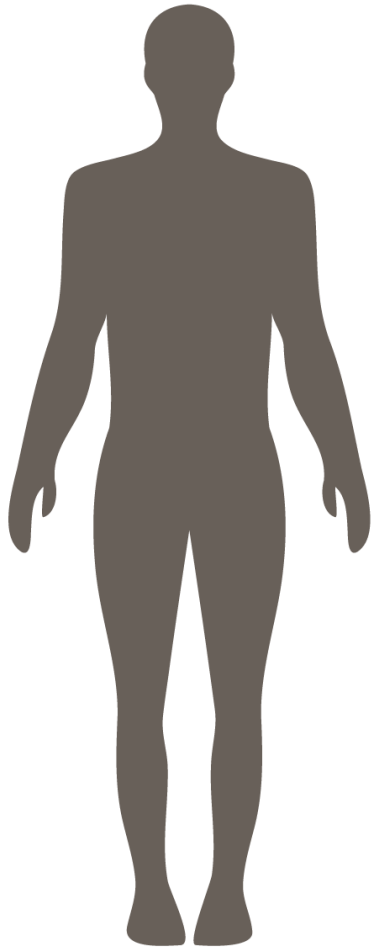


How aHSCT Works

STEP 1
Pre-treatment releases blood stem cells from bone marrow into the bloodstream

STEP 2
Blood stem cells are collected from the bloodstream

STEP 3
Blood stem cells are frozen in the laboratory



STEP 4
Undergo chemotherapy to suppress or partially suppress the immune system

STEP 5
Blood stem cells are thawed and infused back into the body through the vein

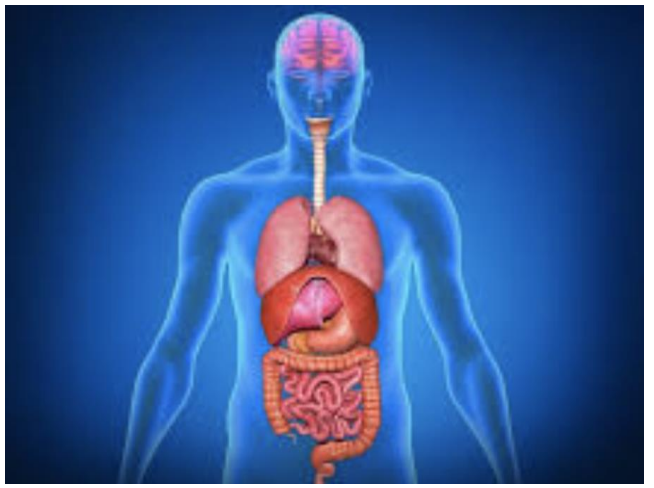
STEP 6
Continue medical treatment as the immune system rebuilds

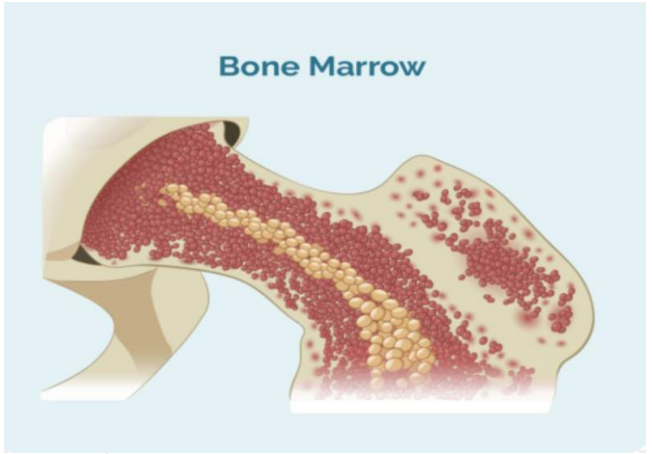
Image originally created by MS Australia: msaustralia.org.au

Types of stem cell transplants

- Autologous Transplant
  - Utilizes the patient's own stem cells
- Allogeneic Transplant
  - Utilizes someone else's stem cells donated by:
    - Family members – siblings, parents, children
    - Unrelated donors from the National or International Marrow Donor Program (NMDP)
    - Umbilical cord donations
- Syngeneic Transplant
  - Utilizes an identical twin

Criteria for stem cell transplant





Age is NOT a barrier!

Donor evaluation

- Related donors – he/she will work with a specialized doctor and coordinator to ensure safe and individualized care
- Unrelated donors – institution will work with the National Marrow Donor Program (Be The Match)

Hospital stay

- Allogeneic ~ 4-5 weeks depending on the conditioning regimen and recovery process
- Closed BMT unit
- Physicians, midlevel practitioners, BMT pharmacist, RNs, etc

Supportive care

- Blood transfusions
- Antibiotics, antivirals, antifungals – many of these will continue outpatient for some time
- Fluid & electrolyte replacement
- Additional side effect management

Discharge & beyond

- Criteria for discharge
  - 1. Blood counts
  - 2. Nutrition
  - 3. Mobility
- Medications
- Caretaker
- Follow up

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