# Myelodysplastic Syndromes

Maria Amaya MD, PhD

MDS Patient Forum

9/14/24

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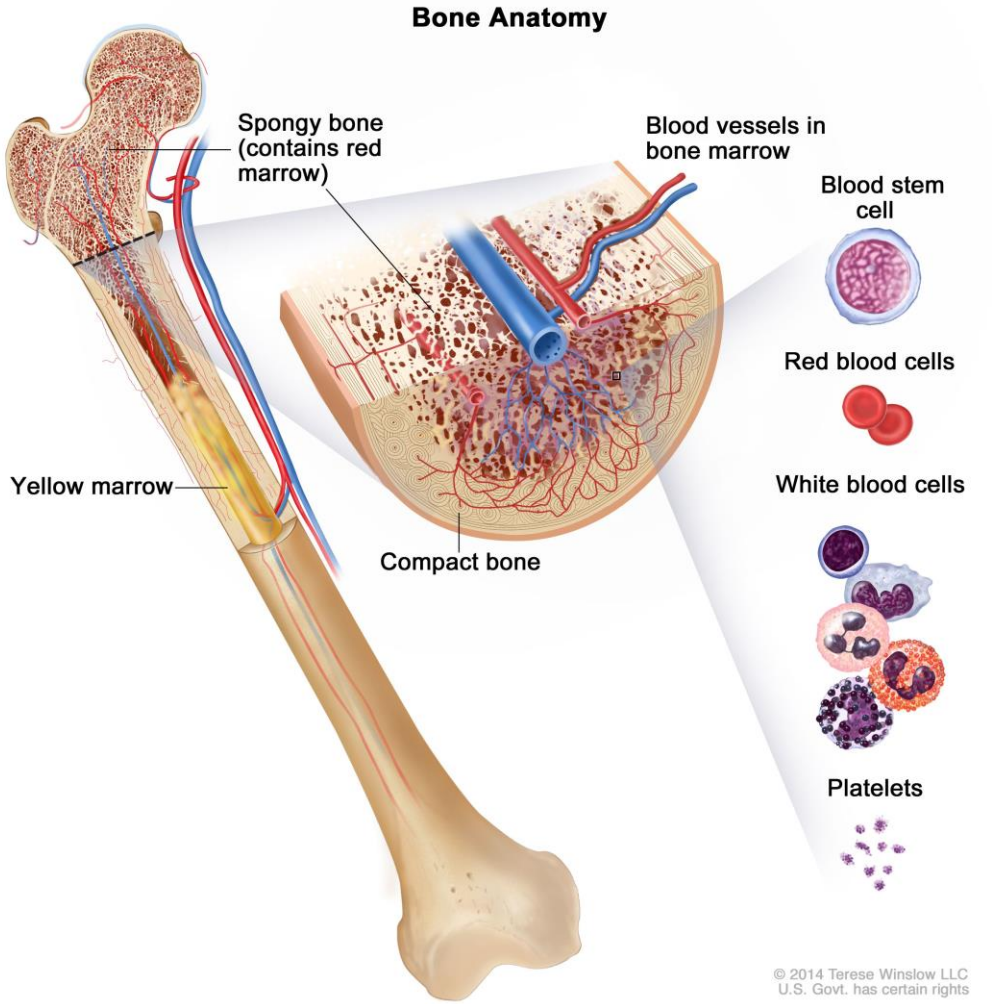
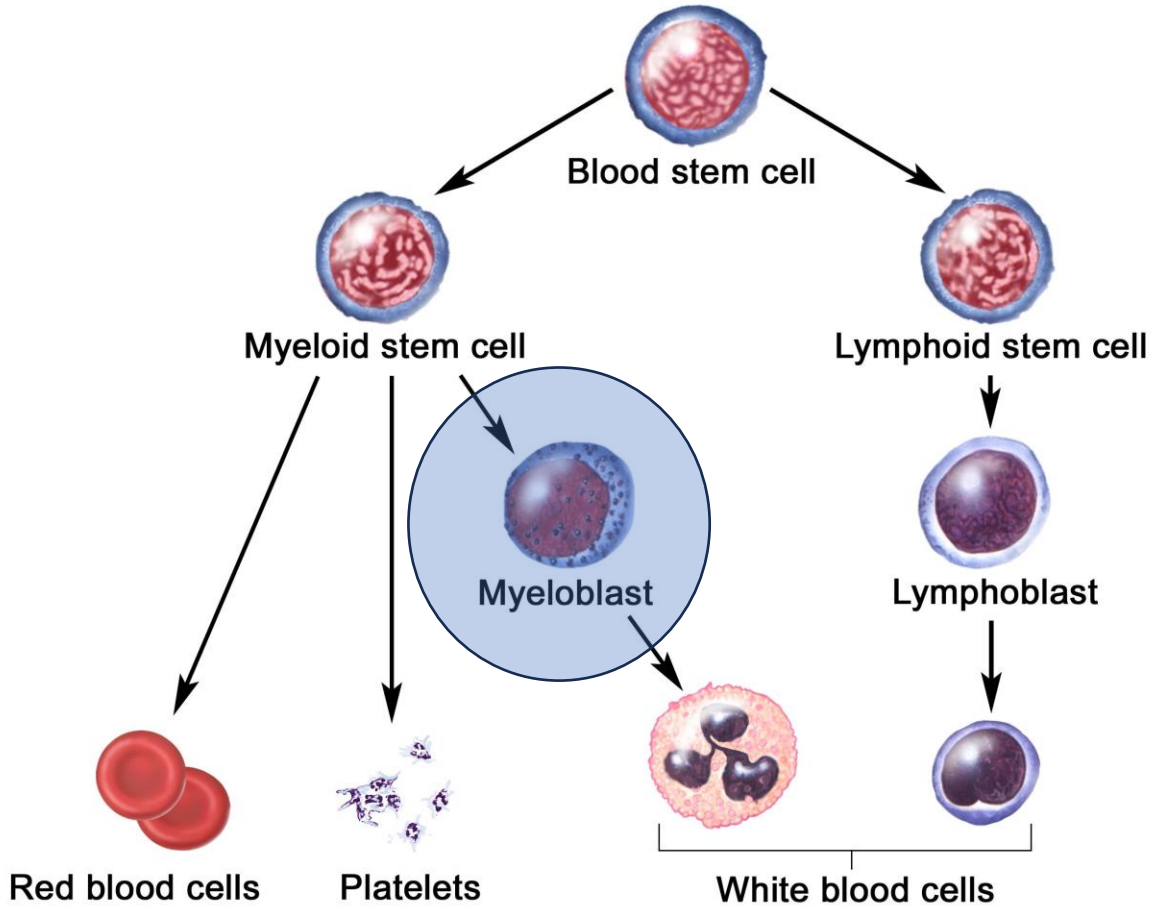
# Overview

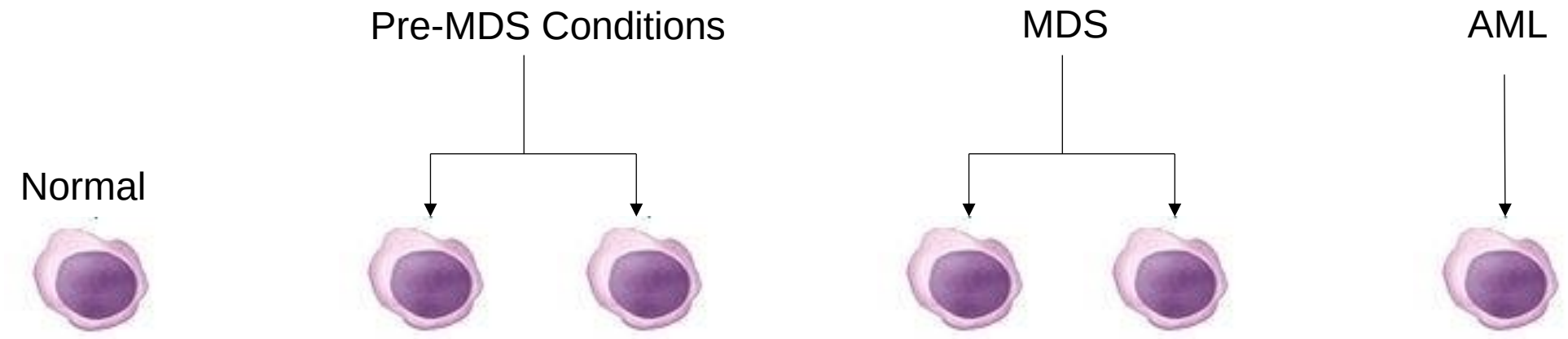
- MDS Definition and Diagnosis
- Risk Stratification
- Treatment of MDS

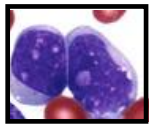
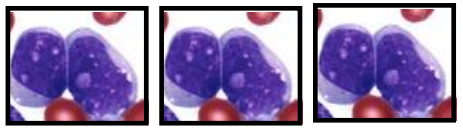
# Bone Marrow and Myeloid Cells



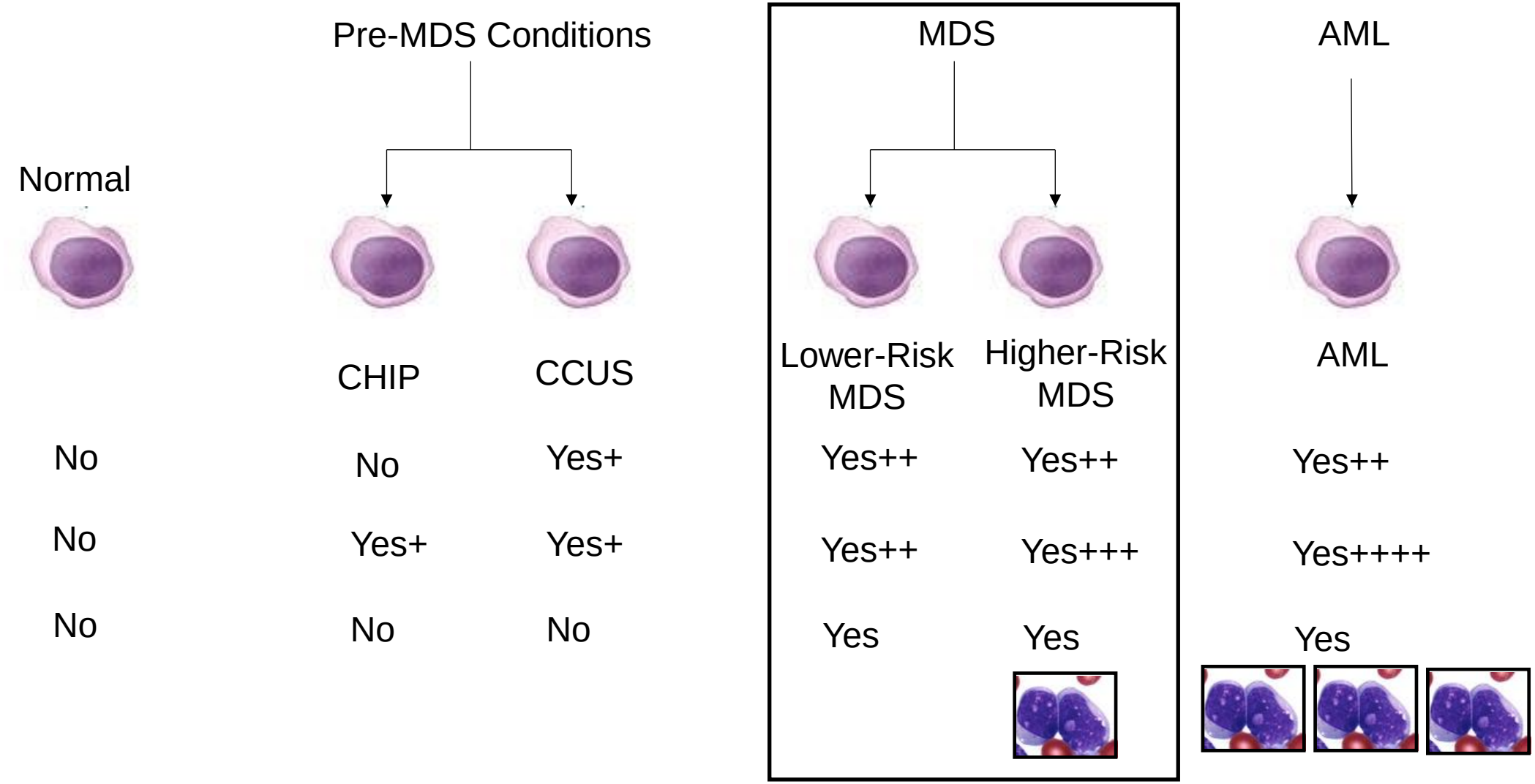
# The Myeloid Malignancy Spectrum




| | Normal | CHIP | CCUS | Lower-Risk MDS | Higher-Risk MDS | AML |
|---|---|---|---|---|---|---|
| Cytopenias | No | No | Yes+ | Yes++ | Yes++ | Yes++ |
| Mutations | No | Yes+ | Yes+ | Yes++ | Yes+++ | Yes++++ |
| Dysplasia | No | No | No | Yes | Yes | Yes |
| Blasts | | | | |  |  |

Adapted from DeZern et al. Am Soc Clin Oncol Educ Book. 2019, Garcia-Manero, SOHO 2020

# The Myeloid Malignancy Spectrum




Adapted from DeZern et al. Am Soc Clin Oncol Educ Book. 2019, Garcia-Manero, SOHO 2020

# What are Myelodysplastic Syndromes

- Clonal bone marrow neoplasm
  - Ineffective hematopoiesis
  - Bone marrow failure/cytopenias/macrocytosis
  - Morphologic evidence of dysplasia
  - Tendency to progress to a more aggressive form, acute myeloid leukemia

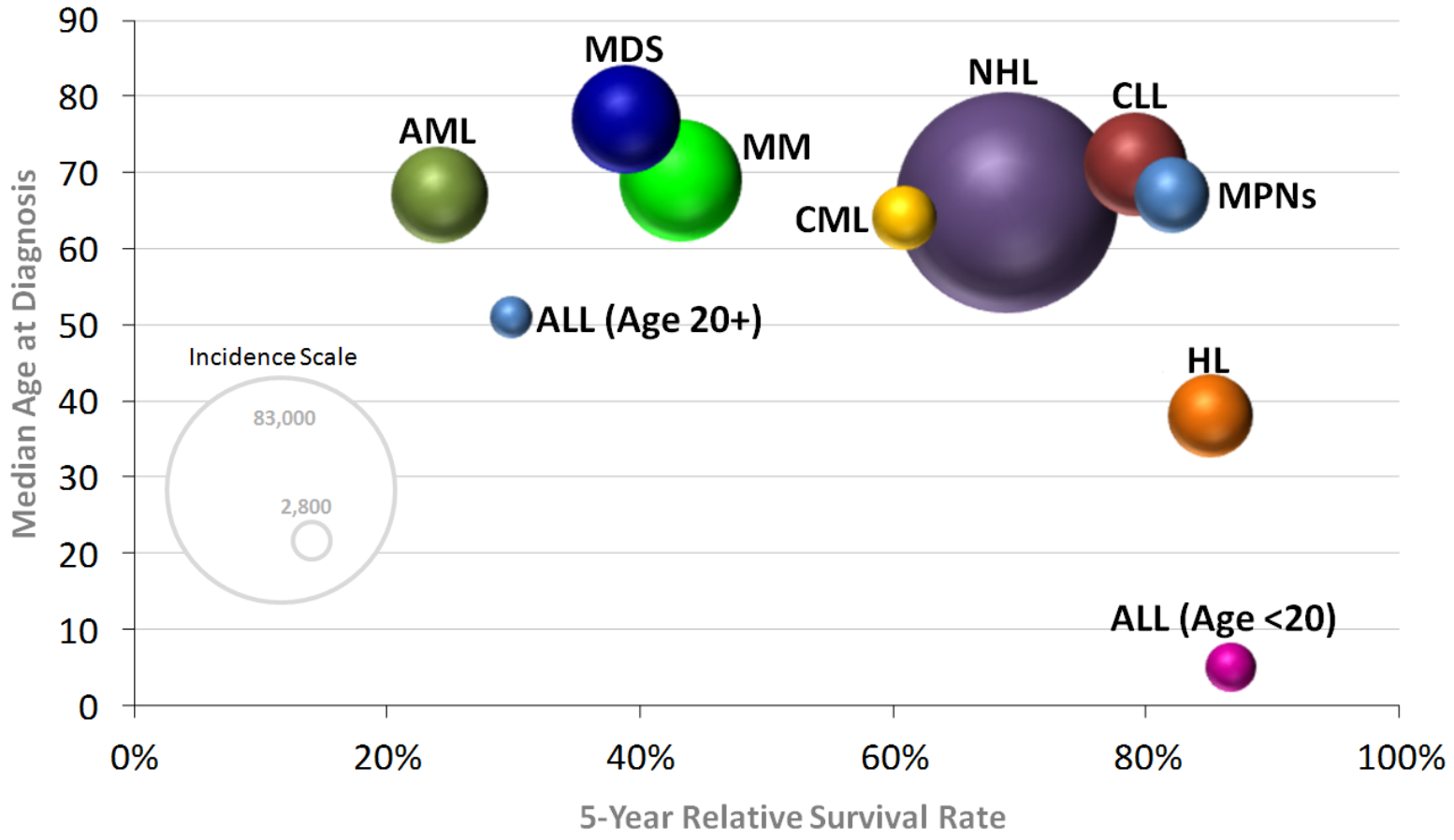
# Epidemiology

- Median age 70
- Incidence increases with age
- True incidence unknown
    - 10,000-50,000 cases/year in US
    - 5-10 cases per 100,000 persons/yr
        - Likely underestimate; many simply diagnosed with anemia or cytopenias with older age – expected ~ 75 cases per 100,000 among persons aged > 70.

# Symptoms

- Fatigue
- Shortness of breath, high heartbeat, pale skin (from low hemoglobin)
- Easy bruising or bleeding (from low platelets)

# Incidence and Prognosis of Hematologic Malignancies



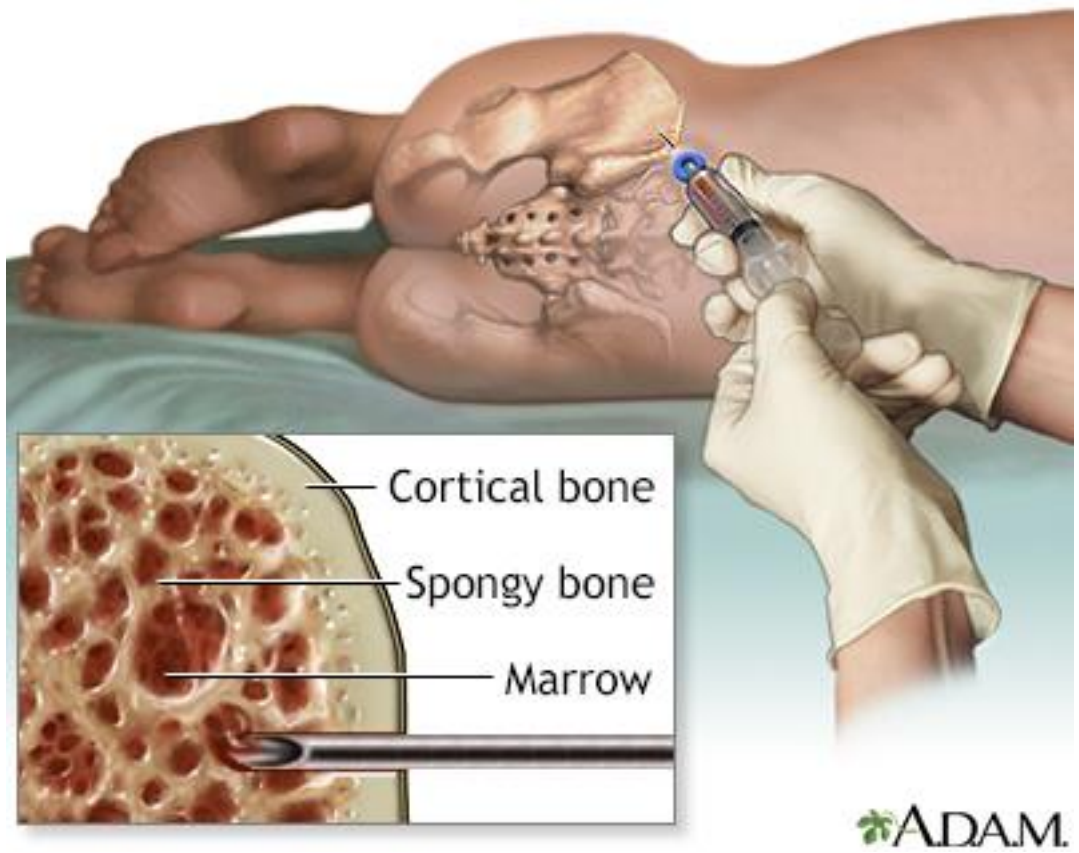

Source: SEER 18 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG). Median age and incidence counts include cases diagnosed in 2006-2010. Relative survival rates include cases diagnosed in 2003-2009.

# Diagnostic Criteria for MDS

- Constant cytopenia (low blood count) in 1 or more of the lineages
- Exclusion of all other hematopoietic or nonhematopoietic disorders as primary reason for cytopenia/dysplasia
- MDS-related (decisive) criteria (need one):
  - Dysplasia in ≥10% of all cells in 1 of the lineages in the bone marrow smear or increased ring sideroblasts (iron stain)
  - 5% to 19% blast cells in bone marrow smears

International Working Conference 2007

# How do we diagnose it?




**How do the cells look in the microscope?**
- Are there high number of myeloblasts?
- Do other cells look abnormal? (dysplasia)

**How do the genes inside the cells look like?**
- Do the chromosomes look normal?
- Are there genes that are mutated?

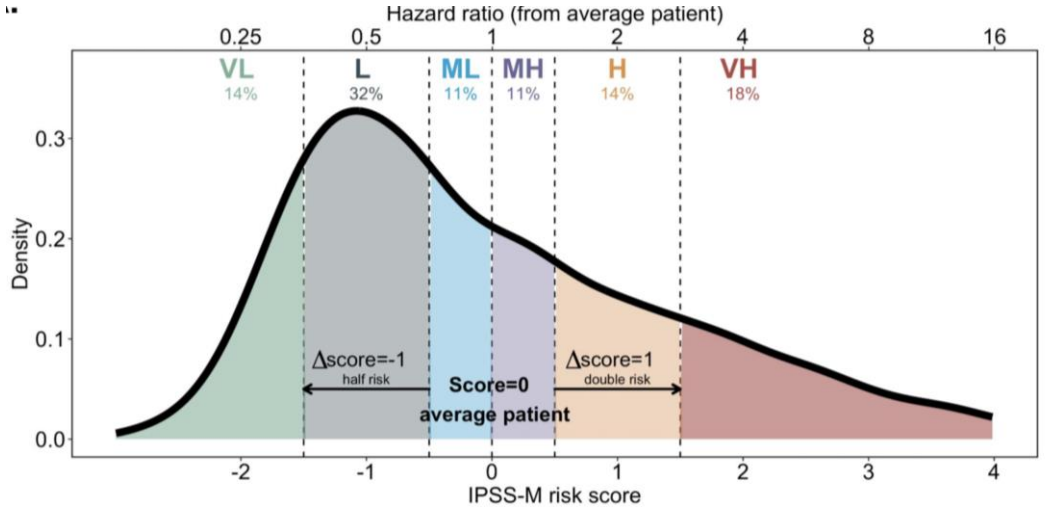
# What Are Common Mutations in MDS

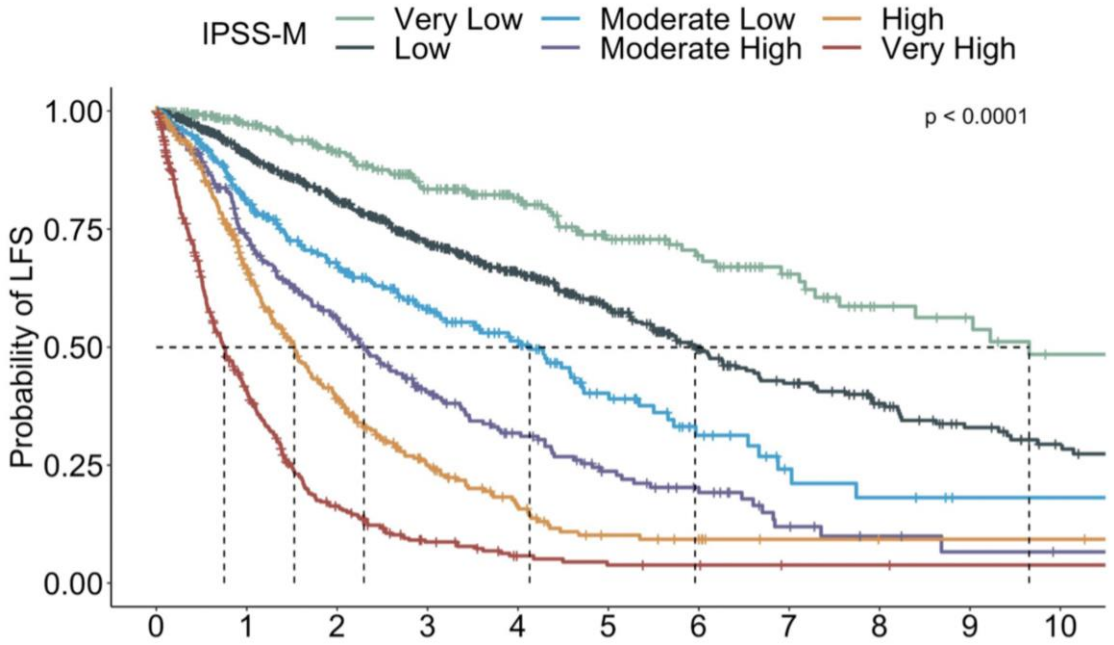
| RNA splicing | DNA repair control |
|---|---|
| ***SF3B1*** (mutated in >10% of patients) | ***TP53*** (mutated in 5-10% of patients) |
| ***SRSF2*** (mutated in >10% of patients) | ***PPM1D*** |
| ***U2AF1*** (mutated in 5-10% of patients) | ***BRCC3*** |
| ***ZRSR2*** (mutated in 5-10% of patients) | |
| ***PRPF8*** | **Signaling** |
| ***LUC7L2*** | |
| ***U2AF2*** | ***CBL*** (mutated in 5-10% of patients) |
| | ***NRAS*** (mutated in 5-10% of patients) |
| **Epigenetic regulators (DNA methylation and histone modification)** | ***KRAS*** (mutated in 2-4% of patients) |
| | ***NF1*** (mutated in 2-4% of patients) |
| ***TET2*** (mutated in >10% of patients) | ***PTPN11*** (mutated in 2-4% of patients) |
| ***ASXL1*** (mutated in >10% of patients) | ***JAK2*** (mutated in 2-4% of patients) |
| ***DNMT3A*** (mutated in >10% of patients) | ***MPL*** (mutated in 2-4% of patients) |
| ***EZH2*** (mutated in 5-10% of patients) | ***SH2B3*** |
| ***BCOR*** (mutated in 5-10% of patients) | ***KIT*** |
| ***IDH2*** (mutated in 5-10% of patients) | ***GNB1*** |
| ***IDH1*** (mutated in 2-4% of patients) | **Cohesin complex** |
| ***PHF6*** (mutated in 2-4% of patients) | |
| ***BCORL1*** | ***STAG2*** (mutated in 5-10% of patients) |
| ***ATRX*** | ***CTCF*** |
| ***EP300*** | ***RAD21*** |
| ***ZBTB33*** | ***SMC3*** |
| | ***SMC1A*** |
| **Transcription regulation** | |
| | **Miscellanea** |
| ***RUNX1*** (mutated in >10% of patients) | |
| ***CUX1*** (mutated in 2-4% of patients) | ***DDX41*** (mutated in 2-4% of patients) |
| ***ETV6*** (mutated in 2-4% of patients) | ***SETBP1*** (mutated in 2-4% of patients) |
| ***CEBPA*** (mutated in 2-4% of patients) | ***ETNK1*** (mutated in 2-4% of patients) |
| ***GATA2*** | ***NPM1*** |
| ***WT1*** | ***KMT2C*** |
| ***KDM3A*** | ***CSNK1A1*** |

Cazzola et al. NEJM. 2020

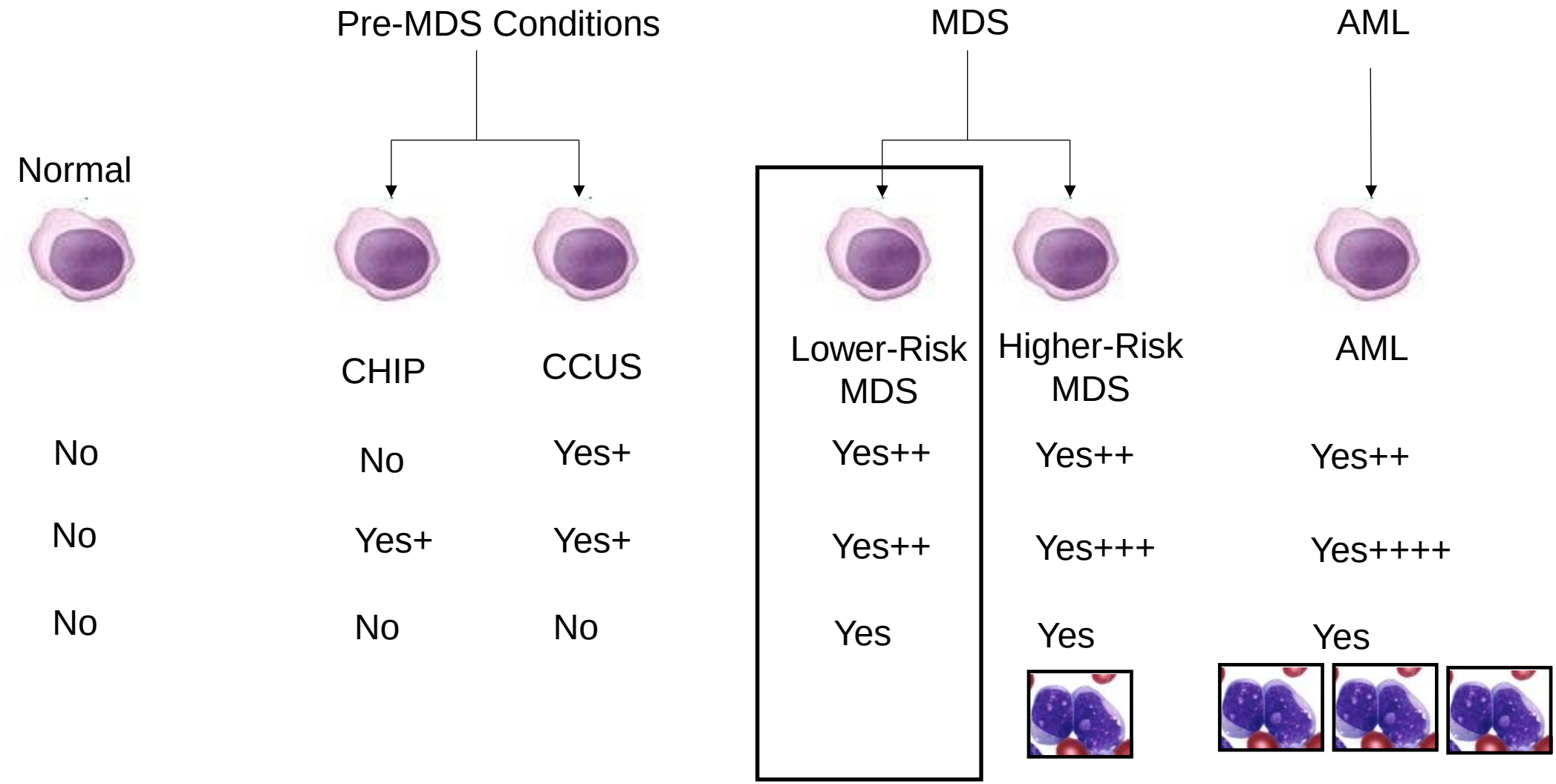
# How Do We Risk Stratify MDS Patients

- There is an international prognostic score
  - It takes into account the blood counts, number of myeloblasts and the genetics
- It helps determine who is more likely to progress to a more aggressive acute myeloid leukemia



# Management of Low Risk MDS




Adapted from DeZern et al. Am Soc Clin Oncol Educ Book. 2019, Garcia-Manero, SOHO 2020

# Management – Lower Risk MDS

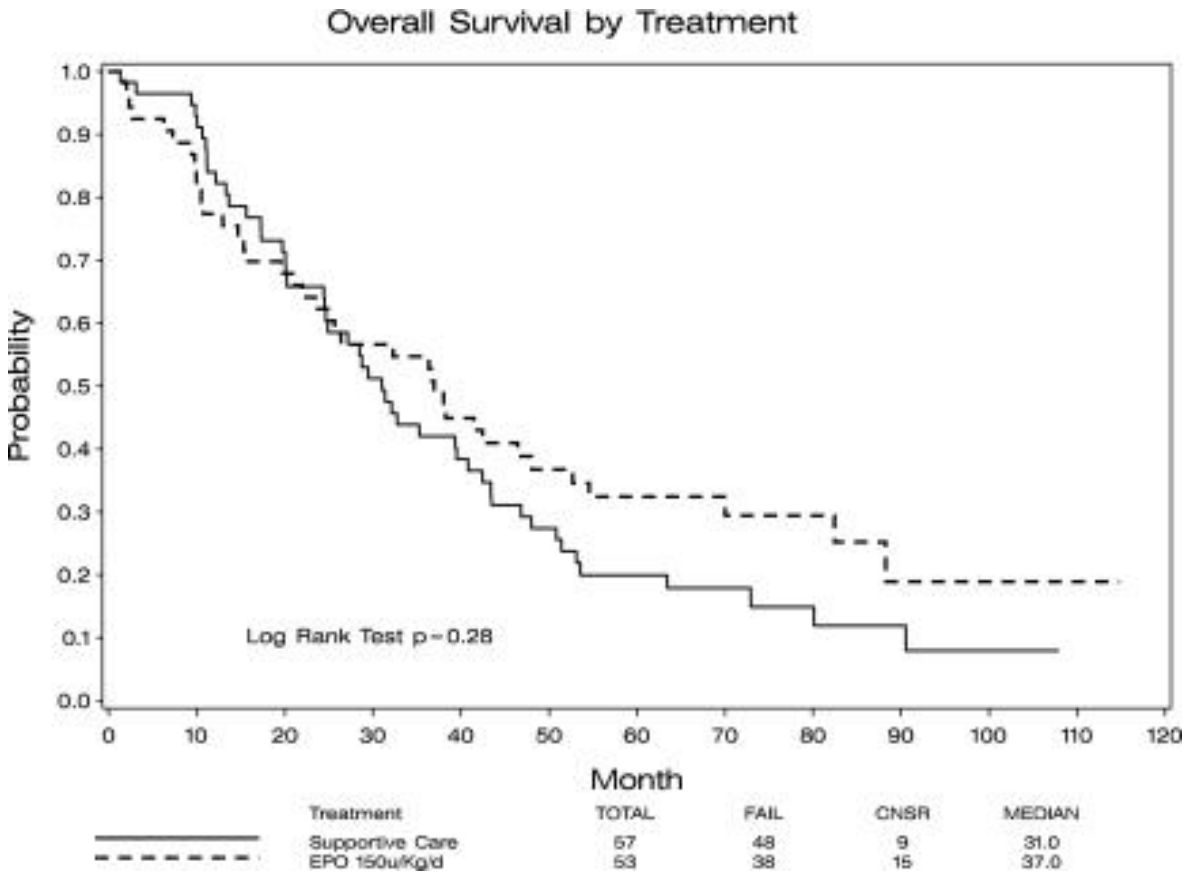
- Mostly treating symptomatic anemia
- Current therapy:
  - Transfusion support, iron chelation.
  - Growth factors (erythropoietin – helps make more red blood cells)
  - Lenalidomide (for a specific type of MDS)
  - Lusparercept
  - Imetelstat
  - Clinical trial

# Blood Transfusions

- Done at an infusion center or emergency room.
- We typically transfuse to ensure the hemoglobin is greater than 7.
- Possible risks: transfusion reaction, infections, iron overload if many blood transfusions over time.

# Erythropoietin Stimulating Agents (EPO)

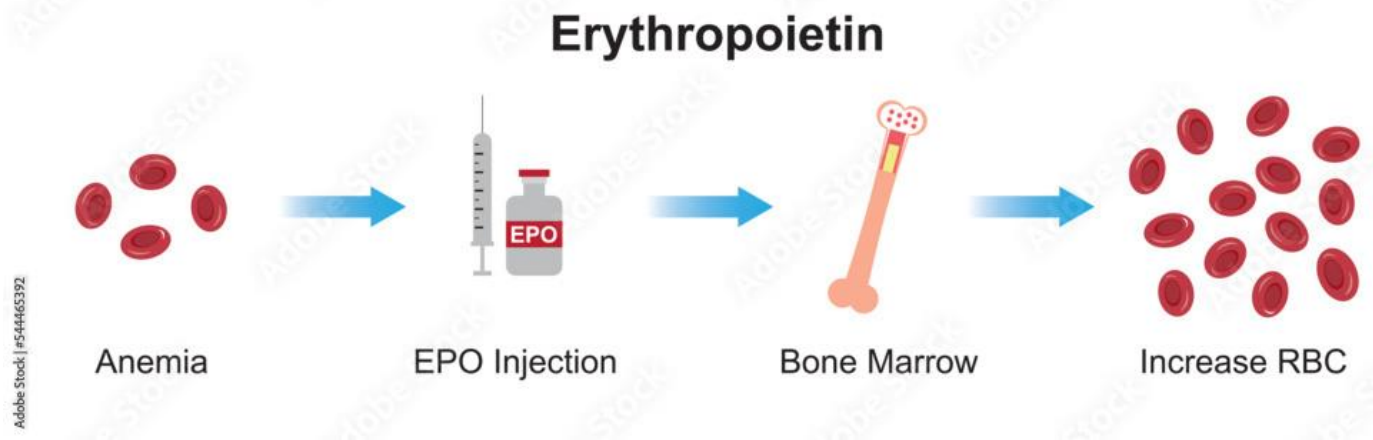
- Phase III randomized trial.
- The response rates in the EPO versus SC alone arms were **36% versus 9.6%.**
- Responses were particularly evident for patients with lower serum EPO levels and lower blast %.



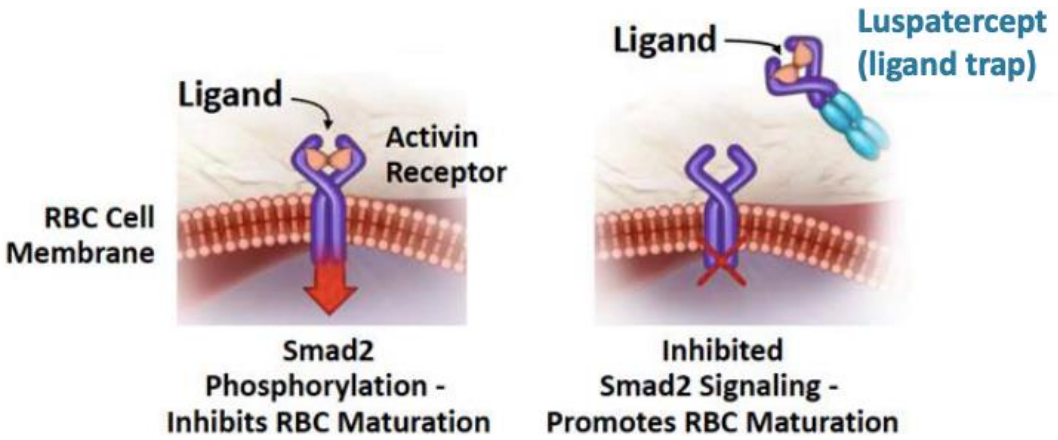

Greenberg et al. Blood. 2009

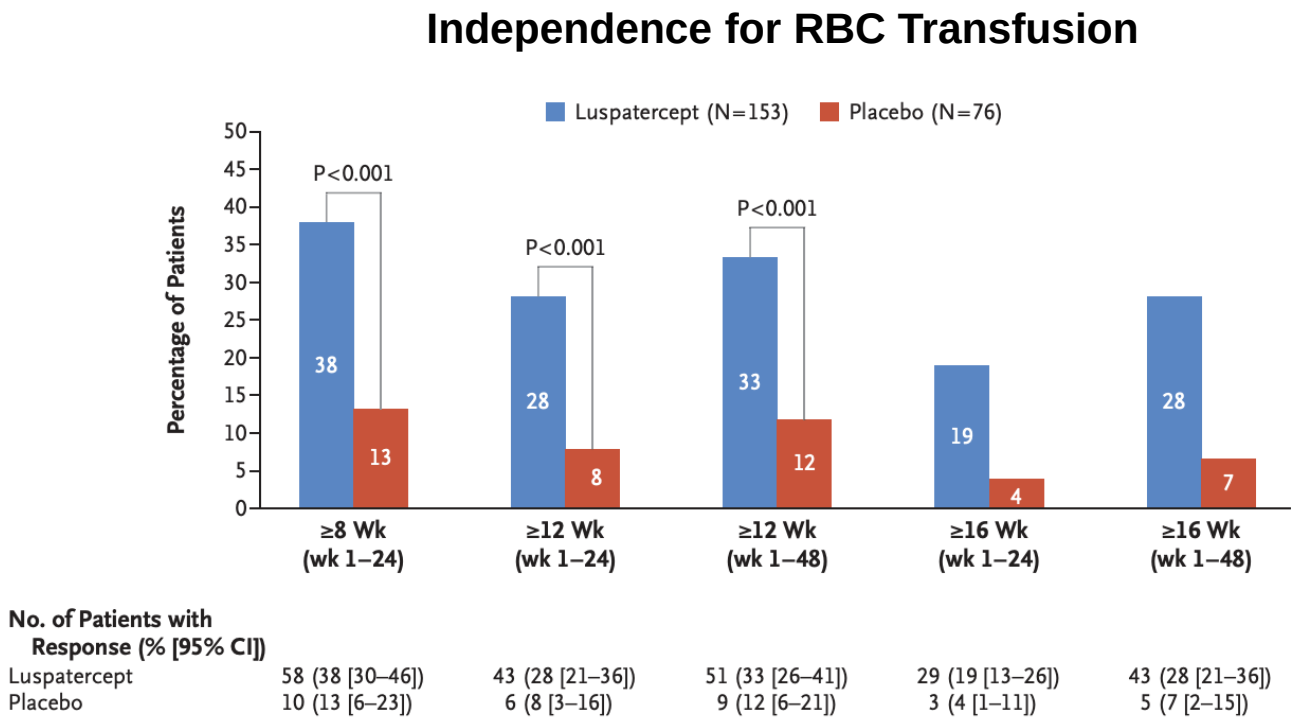
# Administration and Side Effects

- Given by injection (40-60,000 units/week)
- Mostly well tolerated (some listed side effects include HTN, headaches, nausea).
- Caution with cardiovascular disease.



# Lusparercept




| No. of Patients with Response (% [95% CI]) | ≥8 Wk (wk 1–24) | ≥12 Wk (wk 1–24) | ≥12 Wk (wk 1–48) | ≥16 Wk (wk 1–24) | ≥16 Wk (wk 1–48) |
|---|---|---|---|---|---|
| Luspatercept | 58 (38 [30–46]) | 43 (28 [21–36]) | 51 (33 [26–41]) | 29 (19 [13–26]) | 43 (28 [21–36]) |
| Placebo | 10 (13 [6–23]) | 6 (8 [3–16]) | 9 (12 [6–21]) | 3 (4 [1–11]) | 5 (7 [2–15]) |

Fenaux et al. NEJM. 2020

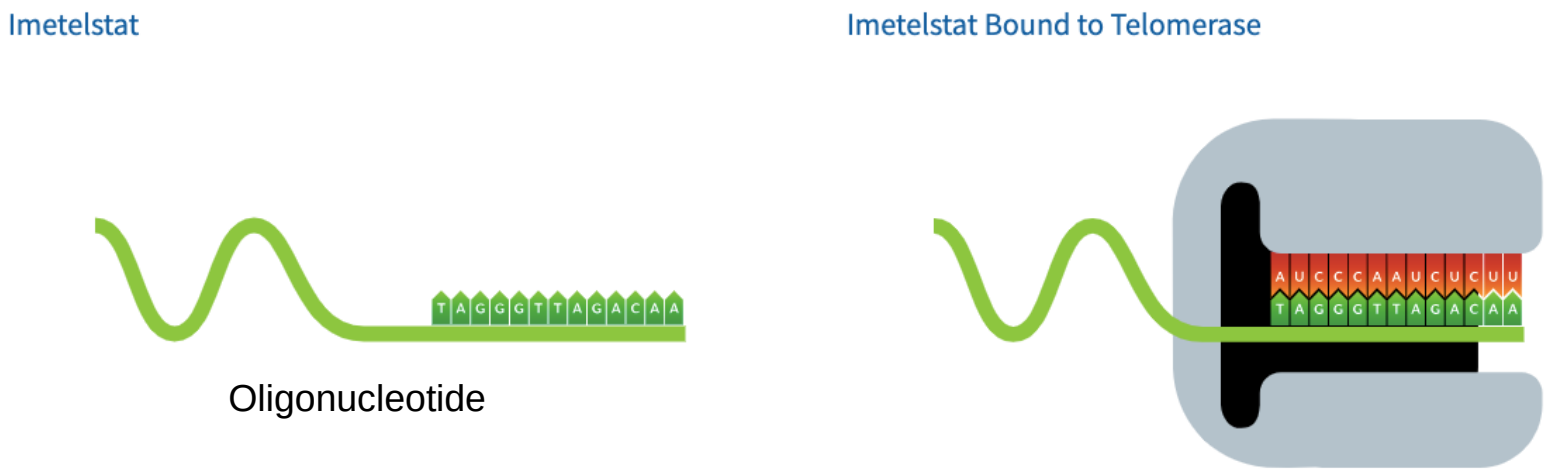
# Administration and Side Effects

- Given by Injection (1 – 1.75mg/kg) every 3 weeks

- Side effects include HTN,  fatigue, creatinine increase, dizziness.

# Imetelstat

- Imetelstat is a telomerase inhibitor that targets cells with short telomere lengths and active telomerase, characteristics observed in some MDS patients.




Steensma. ASH. 2020

# Imetelstat – Phase II Data

non-del(5q) and
HMA/lenalidomide naïve

**TABLE 2.** Summary of Efficacy Outcomes

| Parameter | Overall Population (n = 57) | Subset Population (n = 38) |
|---|---|---|
| 8-week TI[a], No. (%) | 21 (37) | 16 (42) |
| Median time to onset, weeks (range) | 8.3 (0.1-100.6) | 8.3 (0.1-40.7) |
| Median duration of TI[b], weeks (range) | 65 (17.0-140.9) | 85.9 (8.0-140.9) |
| 24-week TI[a], No. (%) | 13 (23) | 11 (29) |
| HI-E per IWG 2006, No. (%) | 37 (65) | 26 (68) |
| ≥ 1.5 g/dL increase in Hgb lasting ≥ 8 weeks | 15 (26) | 12 (32) |
| Transfusion reduction by ≥ 4 units/8 weeks | 37 (65) | 26 (68) |
| Response per IWG 2018, No. (%) | | |
| Major response: 16-week TI | 16 (28) | 14 (37) |
| Major response: 8-week TI | 21 (37) | 16 (42) |
| Minor response[c] | 28 (49) | 20 (53) |

Abbreviations: HI-E, hematologic improvement-erythroid; IWG, International Working Group; TI, transfusion independence.
[a]TI rates were assessed for all treated patients.
[b]Per Kaplan-Meier method.
[c]50% or greater RBC transfusion burden reduction/16 weeks.

Steensma et al. JCO. 2021

# Administration and Side Effects

- For patients who are refractory to erythropoietin and transfusion dependent.
- IV infusion (2 hours) every 4 weeks.

- Possible side effects: thrombocytopenia and neutropenia, HTN, bleeding.

# Treatment Algorithm for Lower Risk MDS

Symptomatic Cytopenias

↓

**Anemia**

- ESAs
- Lusparercept
- Imetelstat
- Lenalidomide

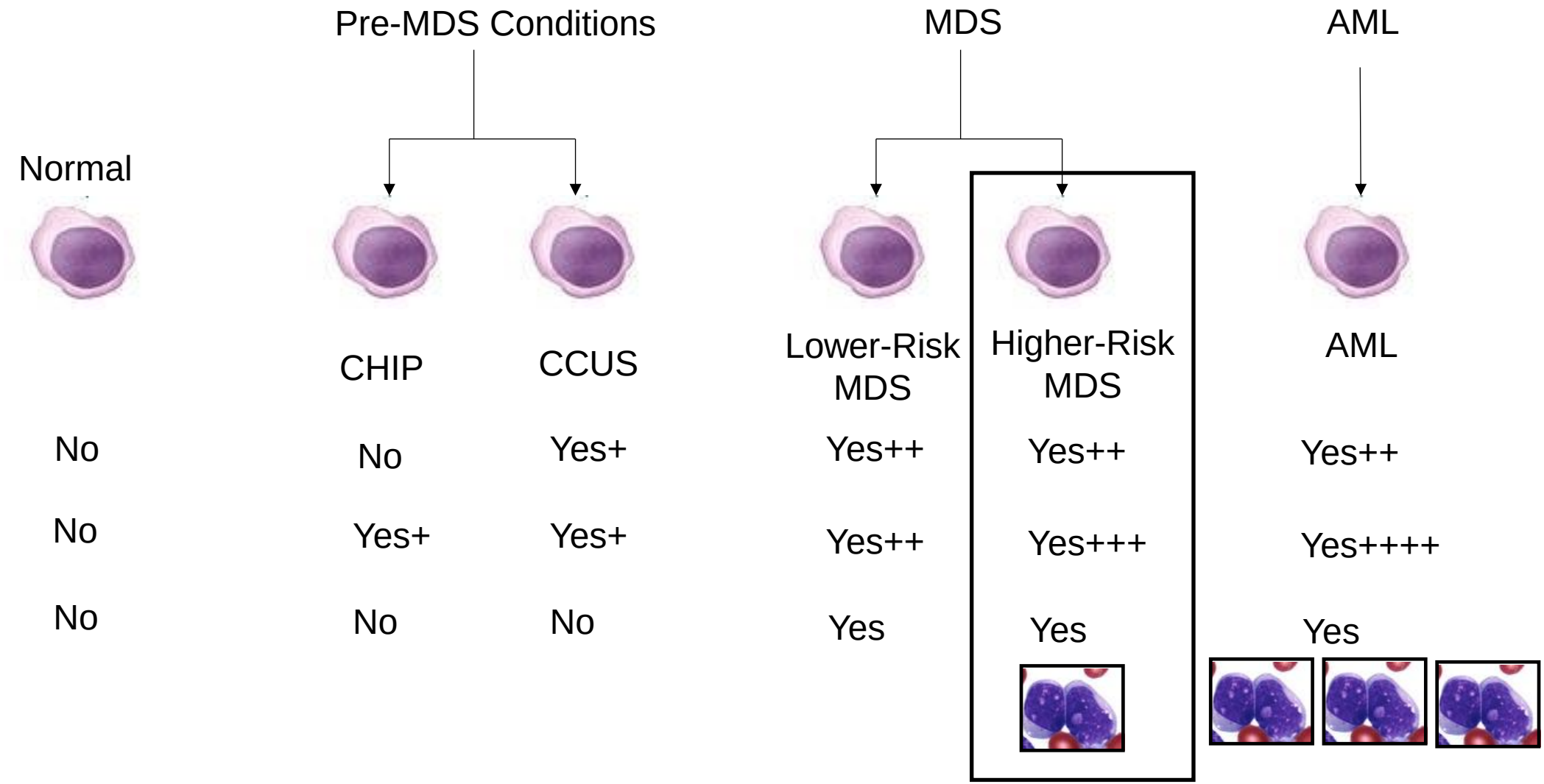
↓ No response

- HMA
- Clinical Trial

↓

Transplant

# Management of High Risk MDS



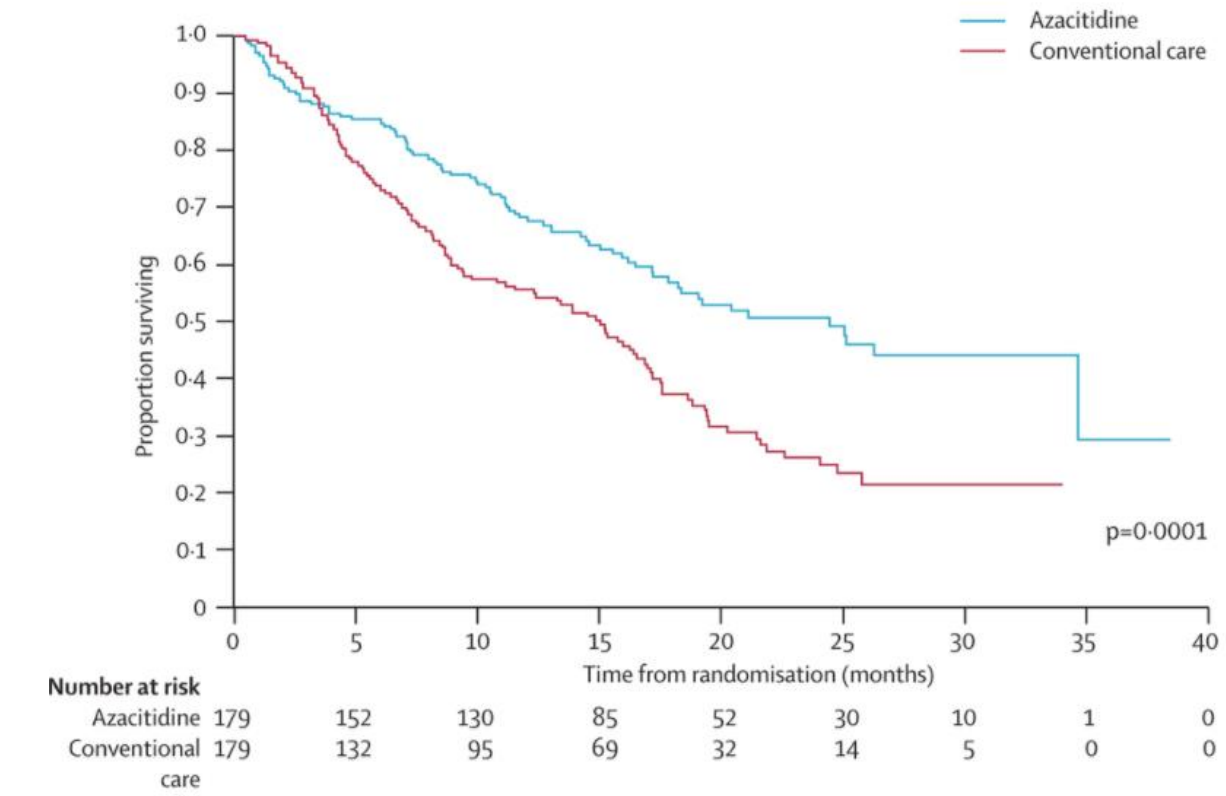

Adapted from DeZern et al. Am Soc Clin Oncol Educ Book. 2019, Garcia-Manero, SOHO 2020

# Management – Higher Risk MDS

- Current therapy – disease modifying agents
  - Hypomethylating Agents (HMAs)
  - Chemotherapy
  - Allo-SCT

# Hypomethylating Agents in MDS

- Phase III open-label trial
- High risk MDS patients
- Received azacitidine vs conventional care




Fenaux et al. Lancet Oncology. 2009.

# Administration and Side Effects

- Azacitidine (given IV) for 7 days every month
- Decitabine (given IV) for 5 days every month
- Oral Decitabine (pill form) for 5 days every month

- It takes a few months to see the response

- Potential side effects: low blood counts, nausea, infections

# Relapsed/Refractory MDS

- Regardless of HMA response, all patients eventually relapse.
- Clinical Trials are recommended

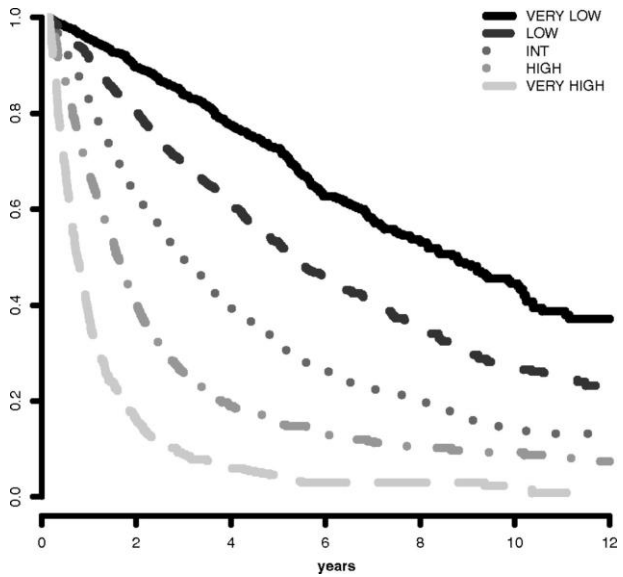

Lindsley et al. NEJM. 2017.

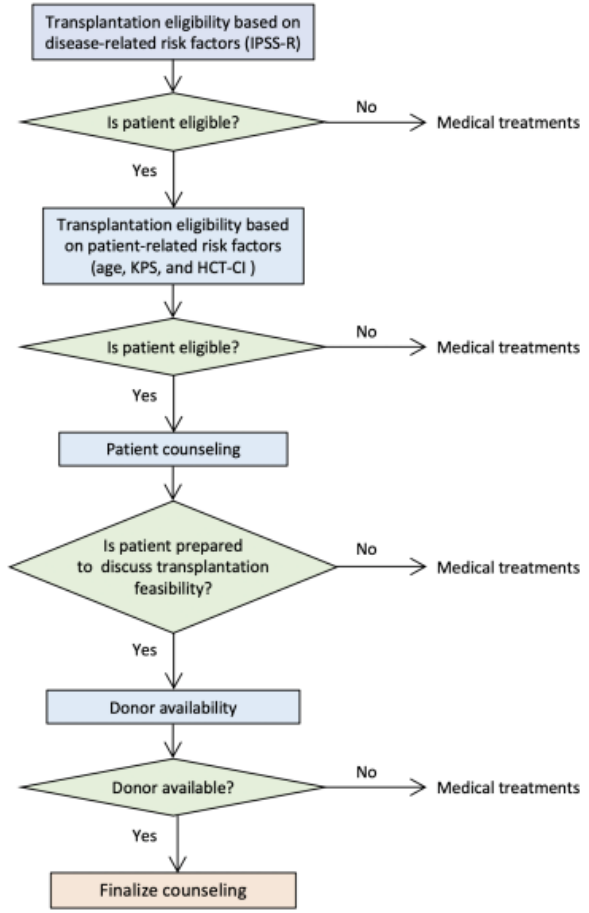
Prébet et al. 2011; Jabbour et al. 2010.

Mechanism in medicine

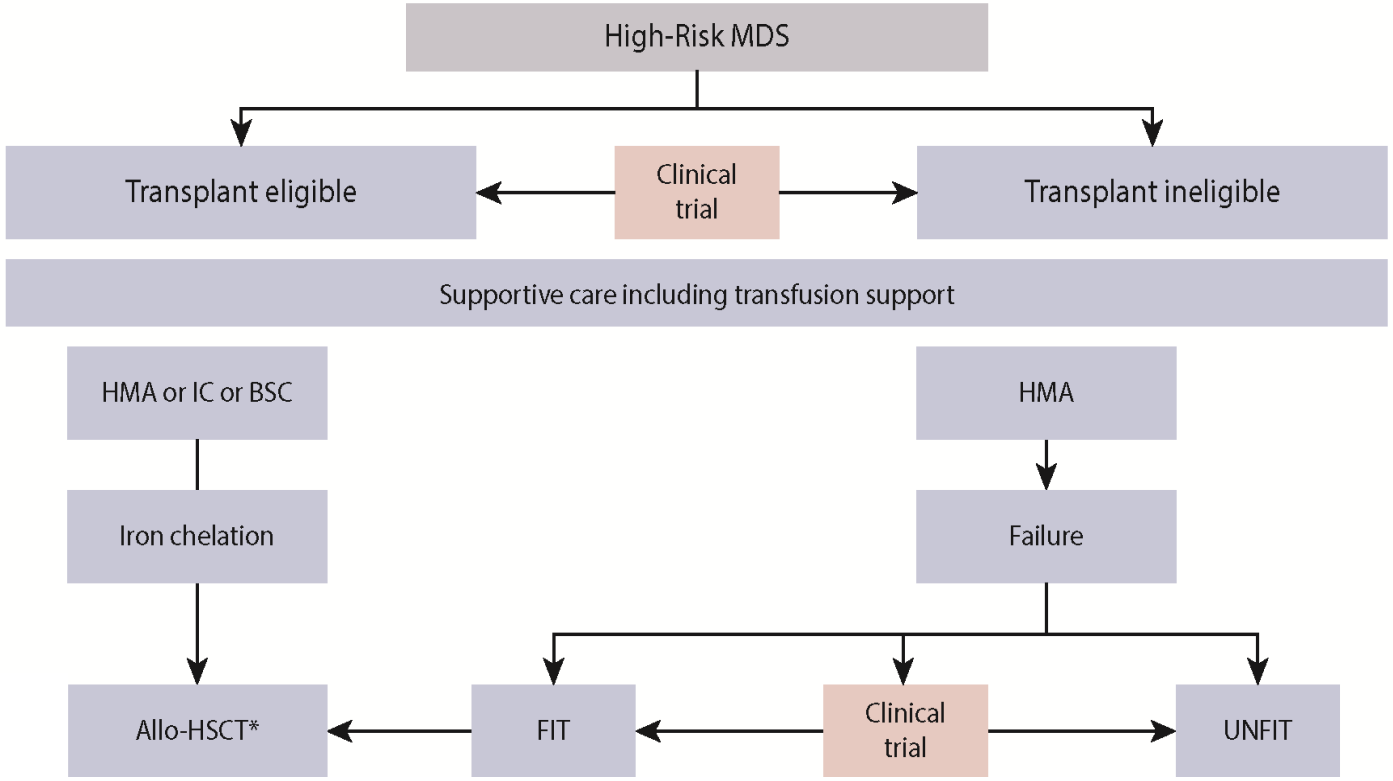
# Role of Allogeneic Stem Cell Transplant

- All patients with higher-risk MDS should be assessed for eligibility at the time of diagnosis.



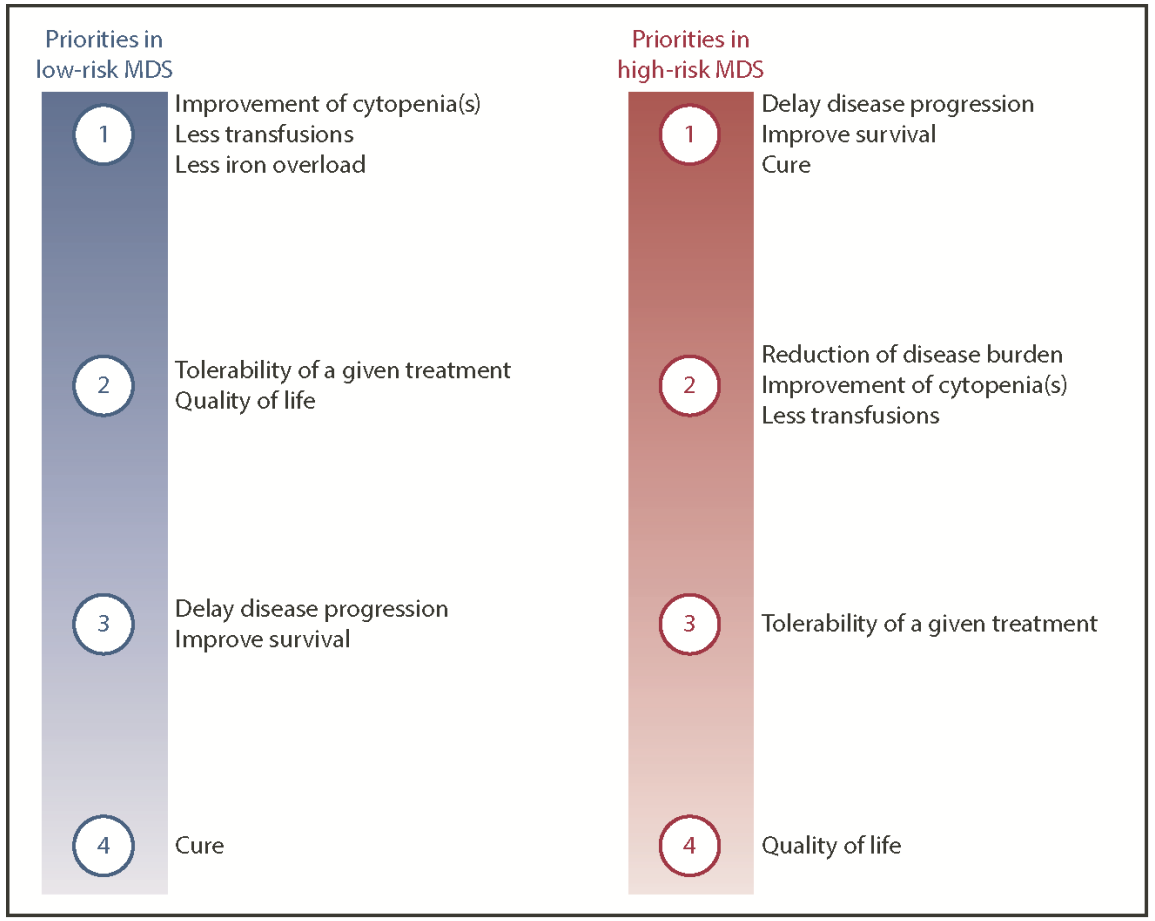



# Proposed Treatment Algorithm




Uwe Platzbecker, Treatment of MDS, Blood, 2019

# Current Goals of MDS Treatment




Uwe Platzbecker, Treatment of MDS, Blood, 2019

# Conclusions

- Myelodysplastic syndromes are a series of syndromes characterized by Ineffective hematopoiesis, and morphologic dysplasias.
- They have very different prognosis and treatment options based on their risk-stratification with IPSS-R.
- There are many treatment options for symptomatic anemia, and hypomethylating agents for higher risk MDS.