# Understanding & Treating Myelodysplastic Syndrome (MDS)

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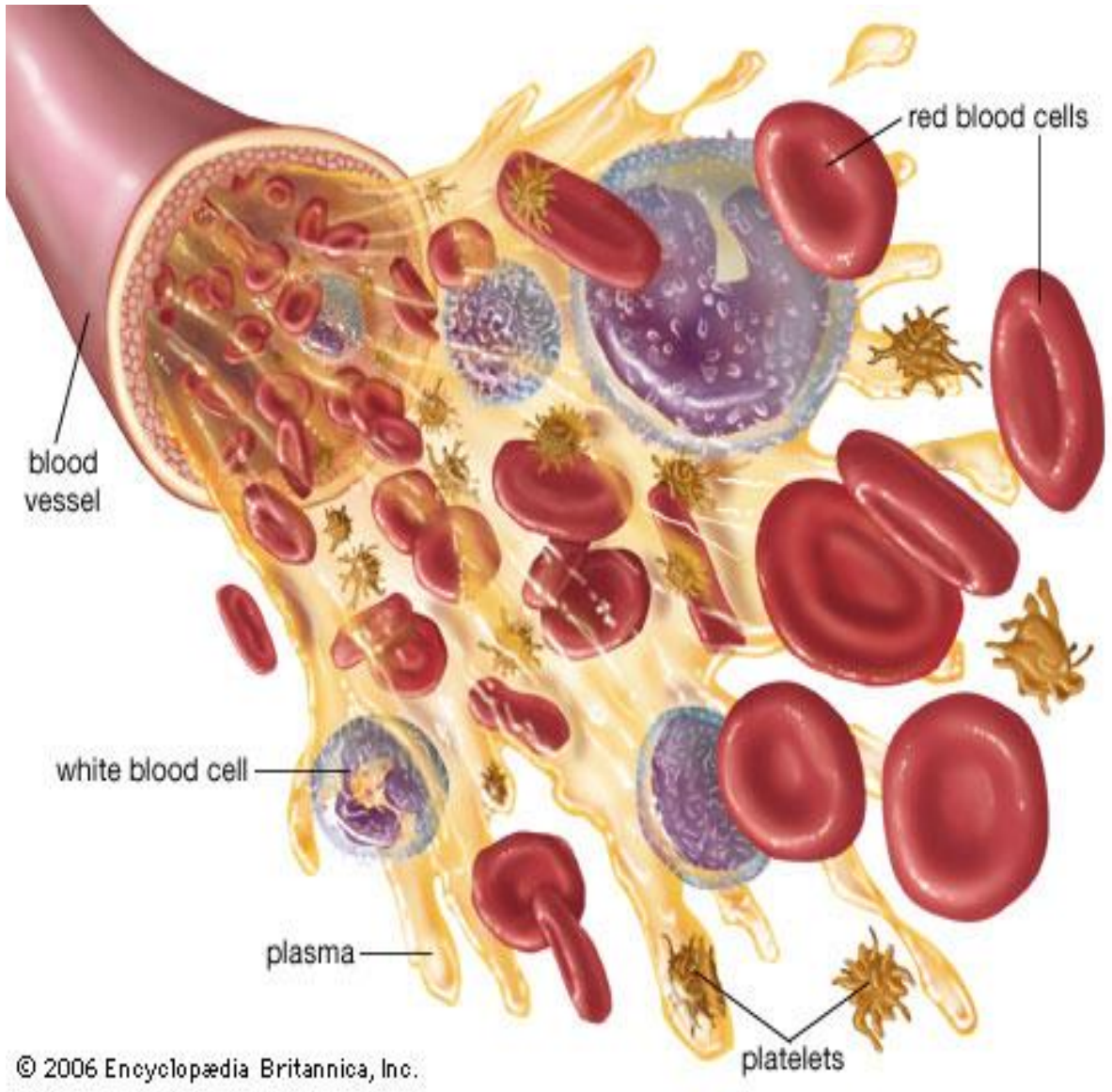
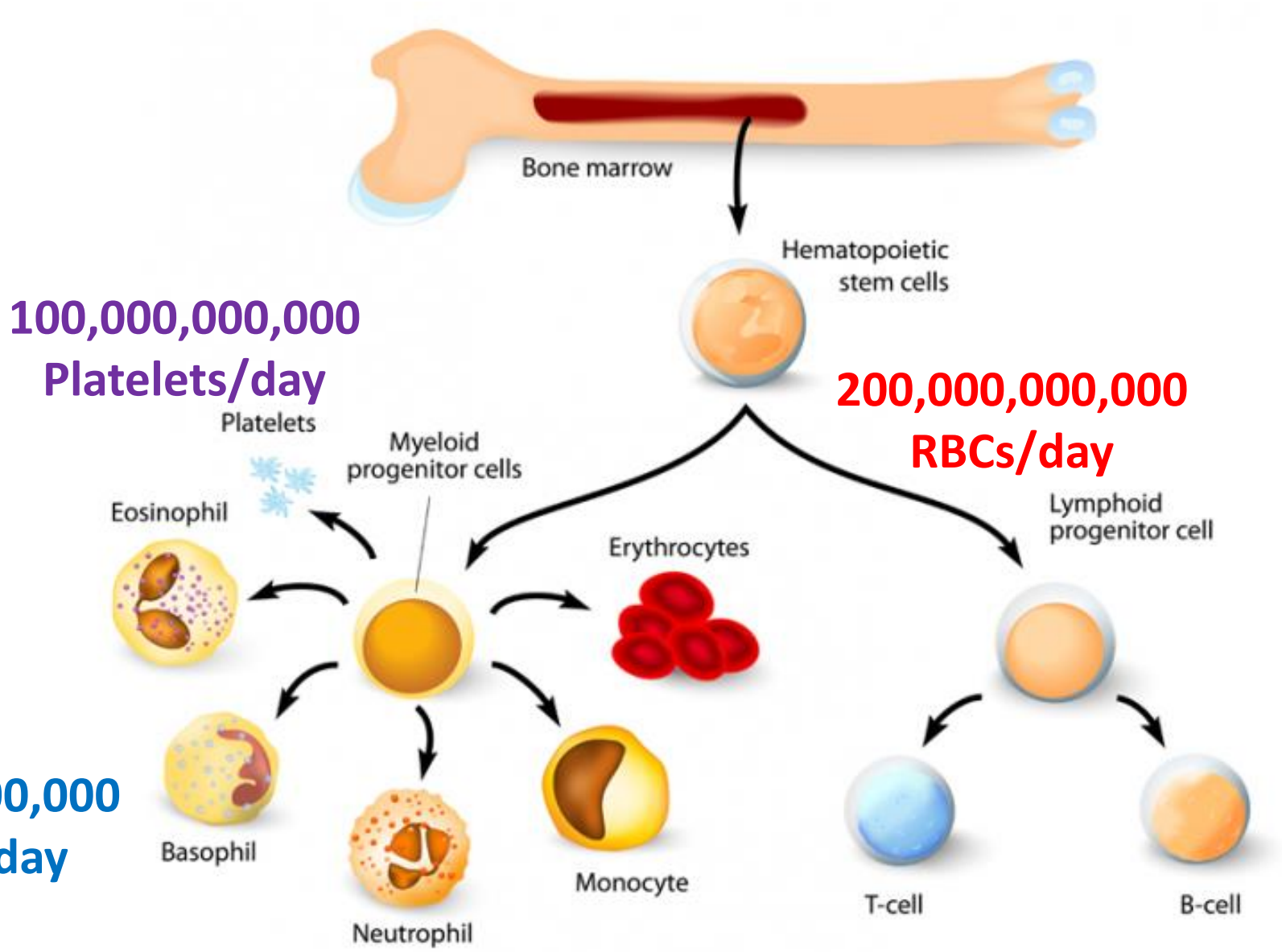
# Let’s Look at Our Blood…



# Bone Marrow: The Blood Cell Factory

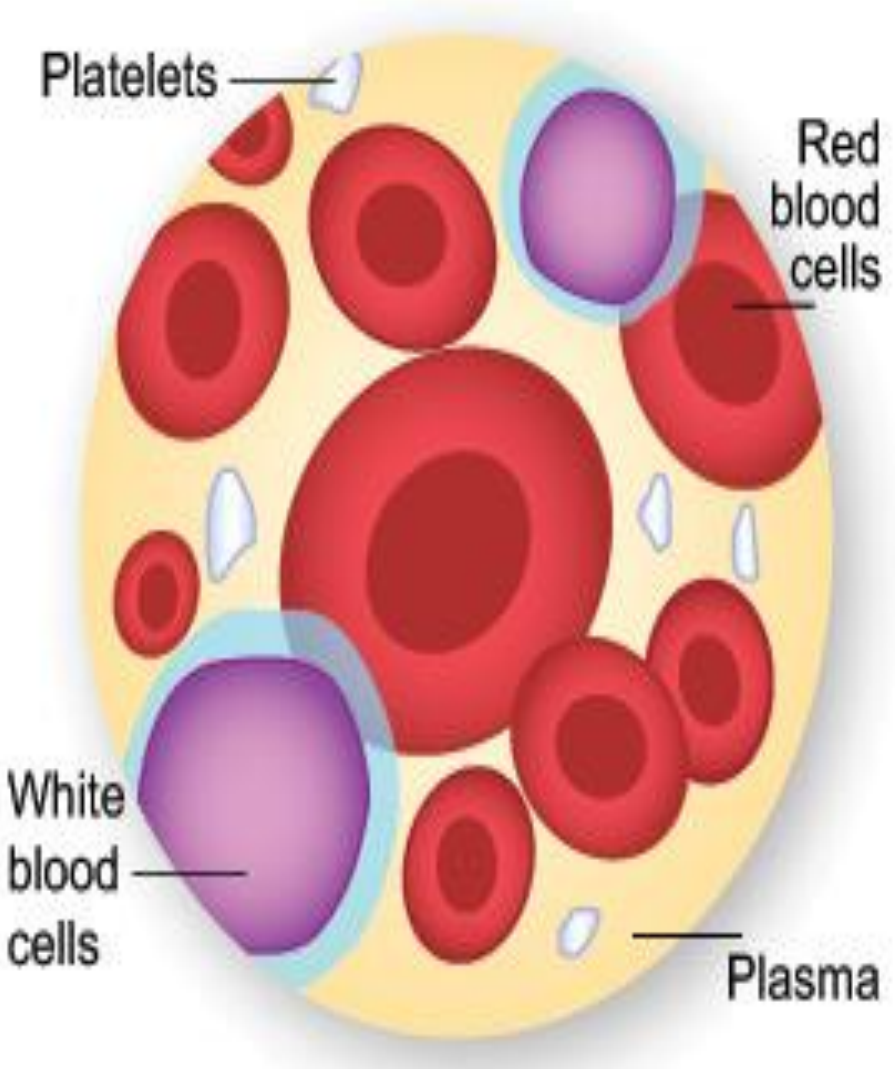



**100,000,000,000 Platelets/day**

**200,000,000,000 RBCs/day**

**10,000,000,000 WBCs/day**

# Blood: 3 Major Cell Types




RED CELLS: Carry oxygen to all the organs

PLATELETS: Help heal cuts or nicks on SKIN, MUCOSA (gums, nose, gut)

WHITE BLOOD CELLS: fight infection, help with healing

# ADDITIONAL RESOURCES

- www.keckmedicine.org/rare-blood-diseases
  - Video “How to Read Your CBC”

# CBC in MDS: What To Focus On

- WBC:  Rising WBC, especially with “BLASTS” could indicate transition to more aggressive MDS or AML (NEED THE DIFFERENTIAL)
- WBC: Low WBC, especially ANC below 1000 can increase risk of infection, may be result of treatment and can “recover” (NEED THE DIFFERENTIAL)
- HGB/HCT: below 10/30 can cause symptoms, below 7-8/21-24 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

# How Does a Factory Making 310,000,000,000 cells Daily Function for 80+ Years?????

1. **<u>Needs Ingredients</u>**: proteins, iron, oxygen, B12, Folate, copper, etc.
2. **<u>Needs Stimulus</u>**:

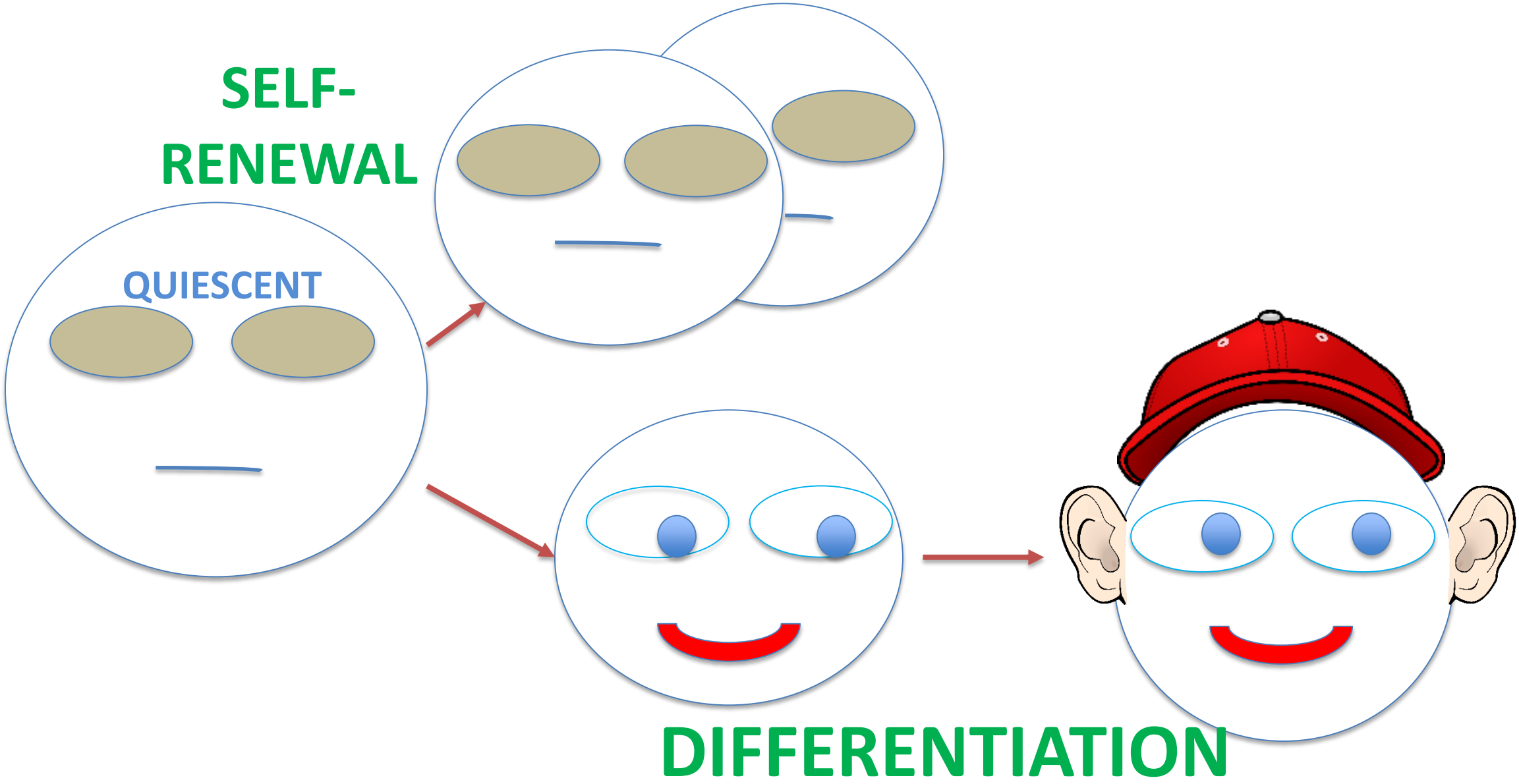
   Erythropoietin – from the kidneys stimulates Red Cell Production

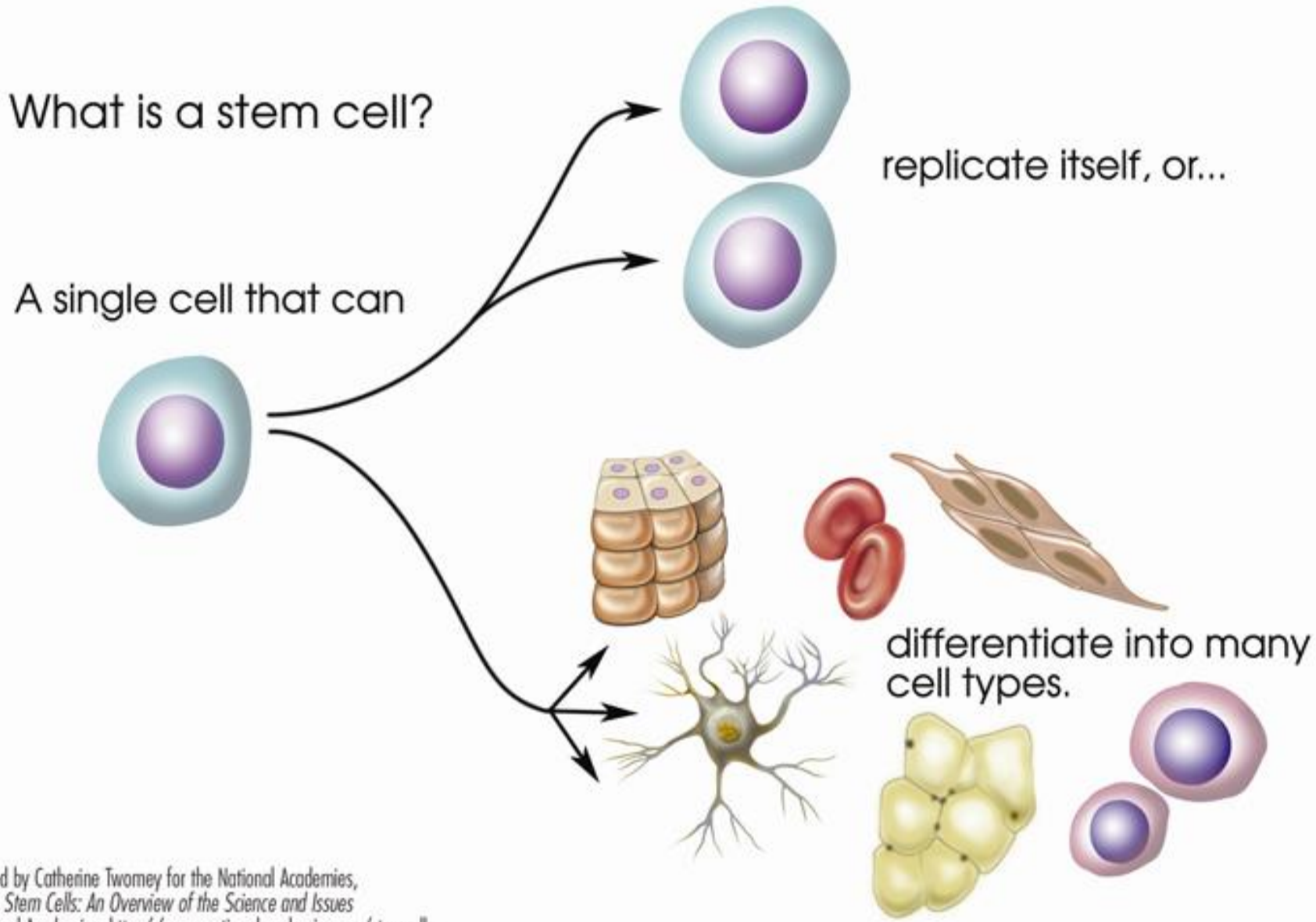
   GCSF – from blood vessel lining, immune cells stimulates WBC Production

   Thrombopoietin – from the liver stimulates Platelet Production
3. **<u>Needs Source</u>**:

   STEM CELLS

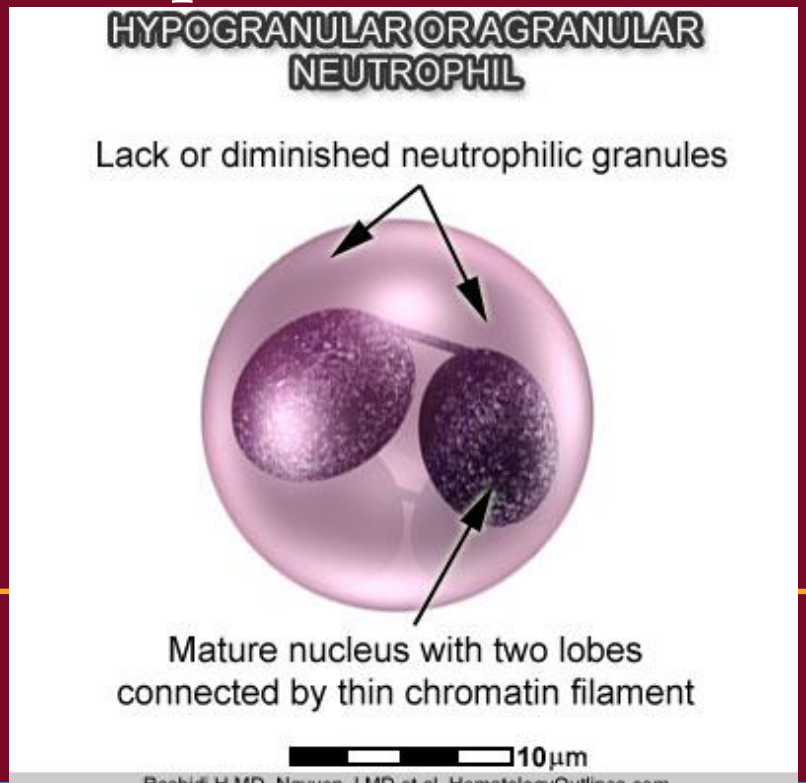
# Hematopoietic Stem Cells





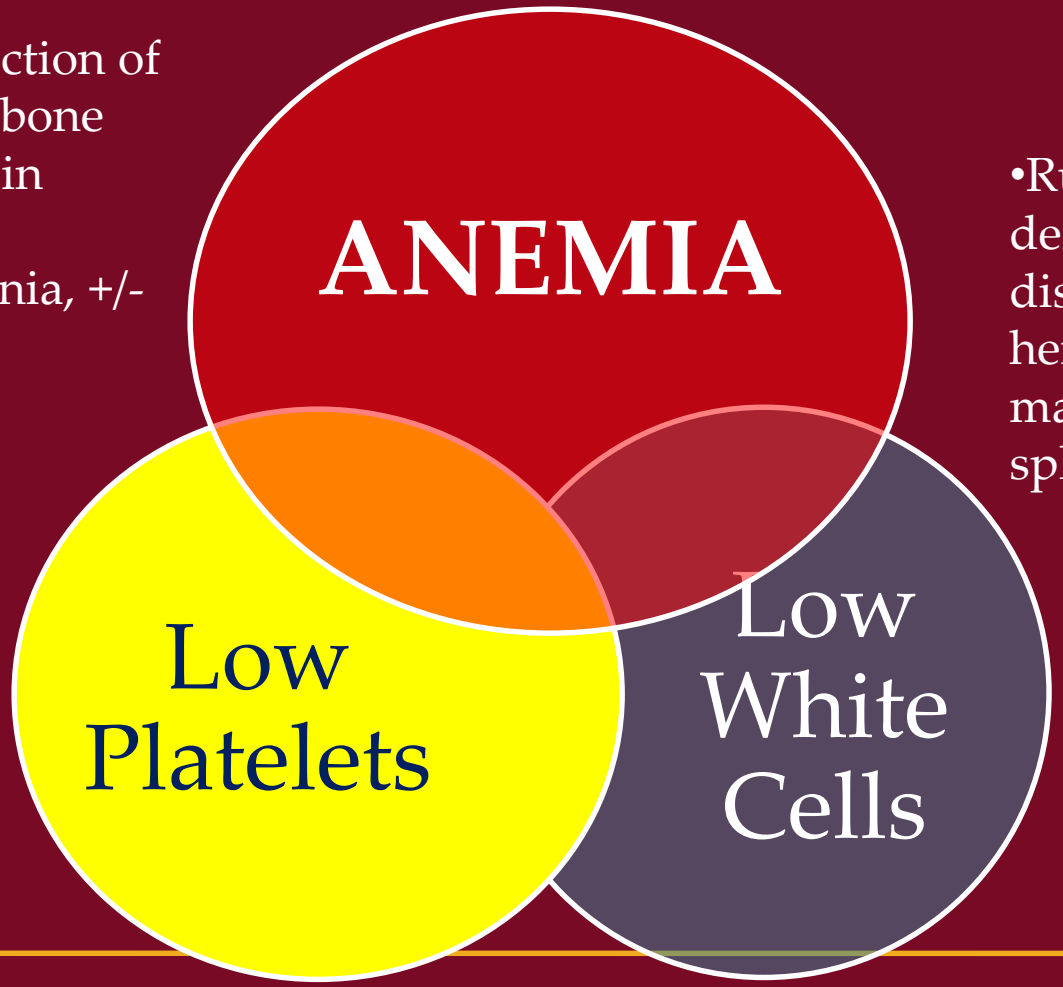
# What Is MDS?

- MYELO = Greek myelos = marrow
- DYSPLASIA= dys (ABNORMAL) + plasia (GROWTH or DEVLOPMENT)



# What Is MDS?

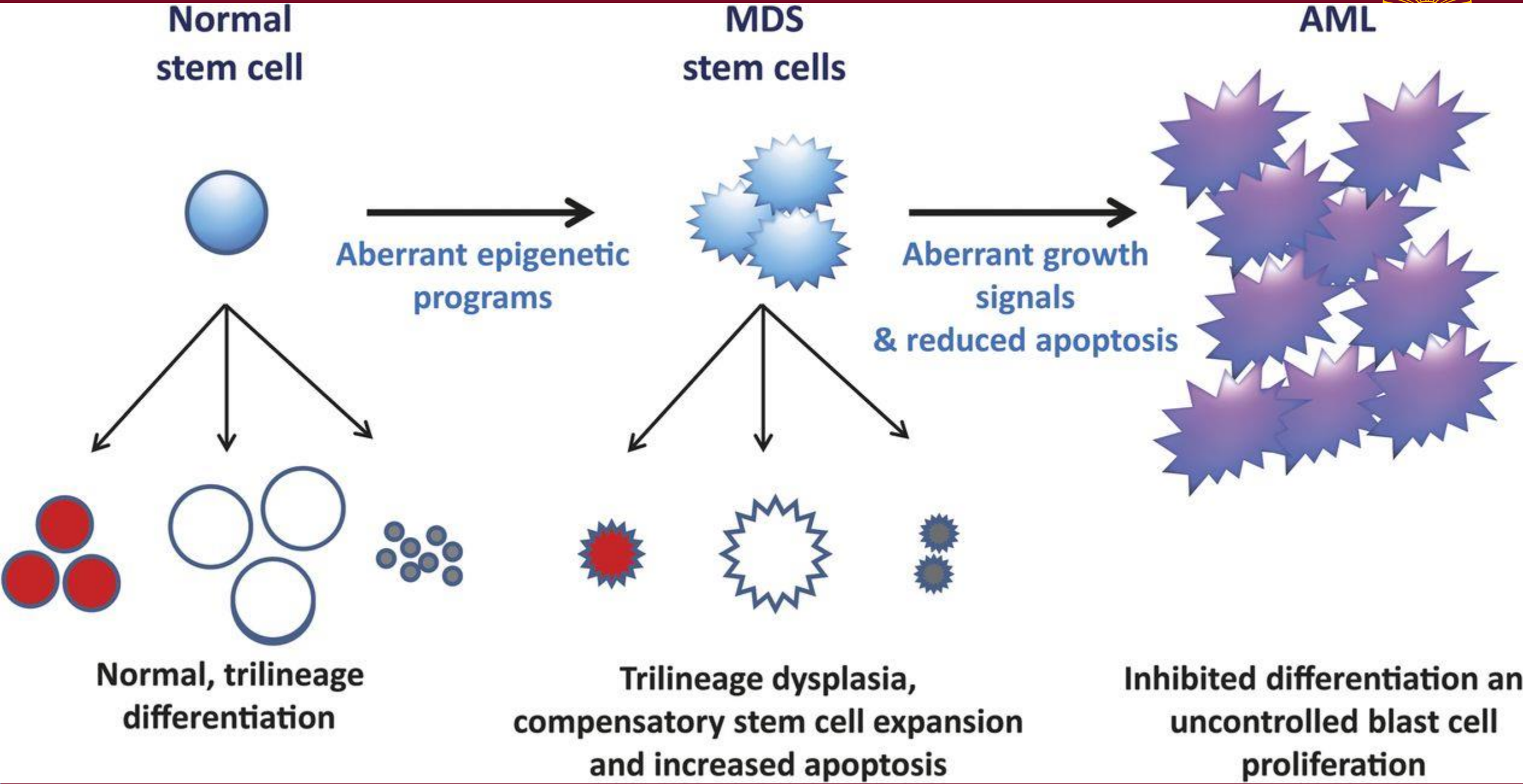
•Ineffective production of blood cells by the bone marrow resulting in anemia +/-thrombocytopenia, +/- leukopenia




•Rule out vitamin deficiencies, liver disease, other heme malignancies, splenomegaly

•Clonal hematopoietic stem cell disorder can evolve to AML

•Heterogeneous Group of disorders NOT A SINGLE DISEASE!

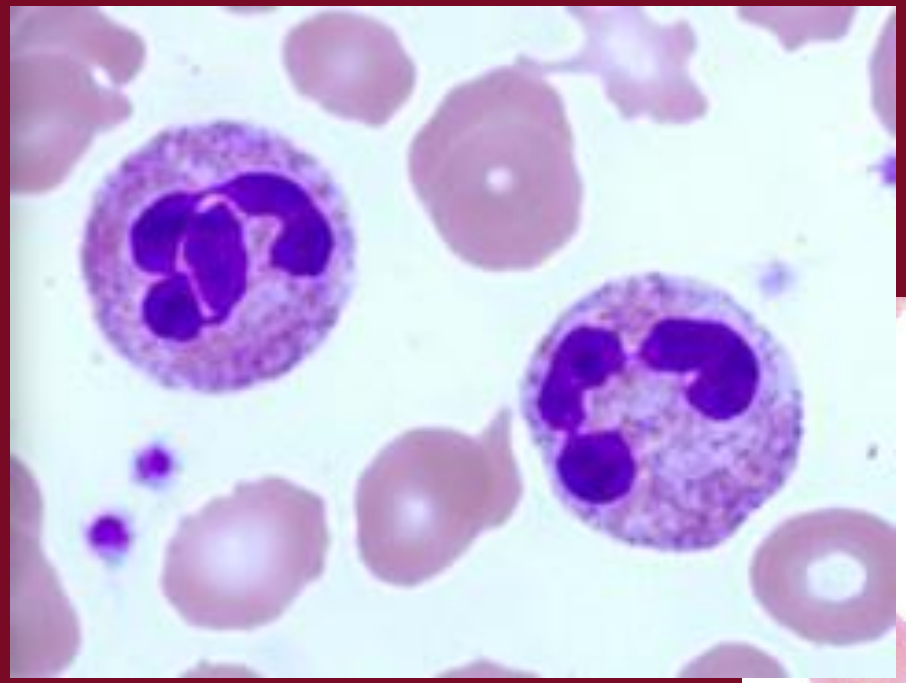

Normal
stem cell
MDS
stem cells
AML
Aberrant epigenetic
programs
Aberrant growth
signals
& reduced apoptosis
Normal, trilineage
differentiation
Trilineage dysplasia,
compensatory stem cell expansion
and increased apoptosis
Inhibited differentiation and
uncontrolled blast cell
proliferation

# What Is MDS?

## Defective HSCs lead to defective blood cell production

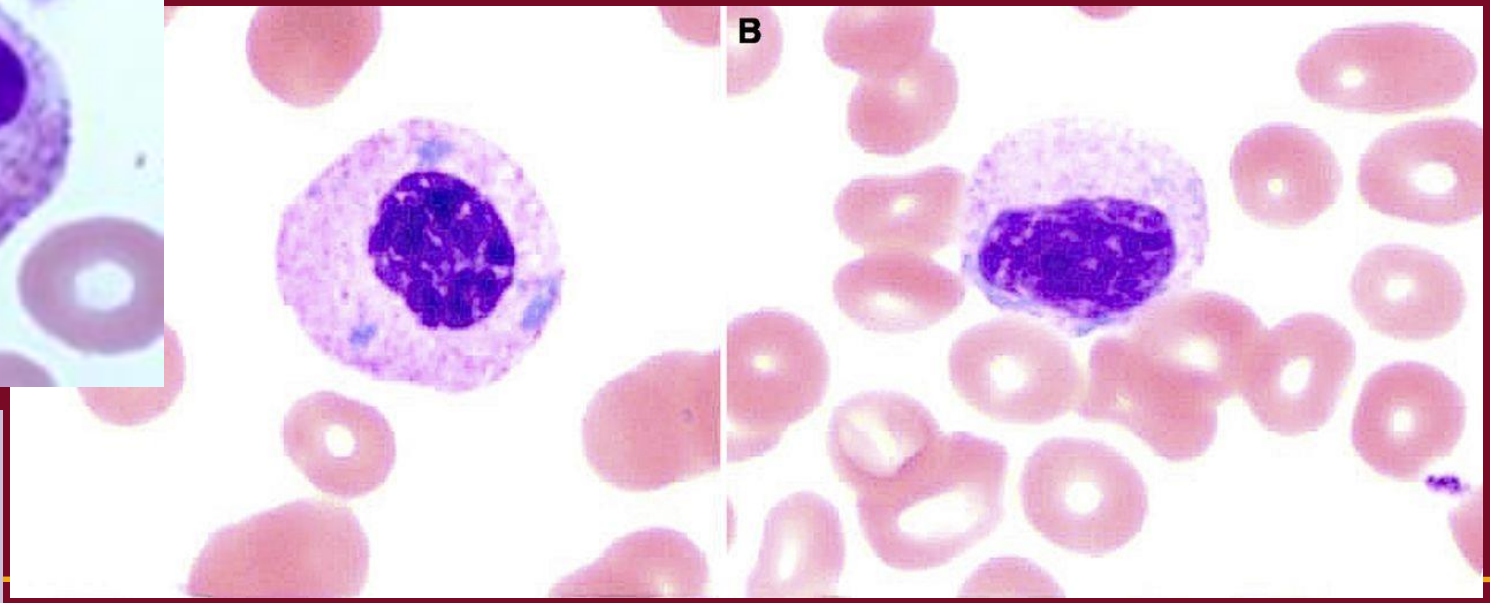
- Decreased/Defective ("Ineffective") Red Cell Production = ANEMIA
  - Fatigue, shortness of breath, weakness, fainting heart attack, stroke
- Decreased/Defective Platelet Production = Thrombocytopenia
  - Bruising, gum bleeding, nose bleeding, red dots on skin (petechiae)
- Decreased/Defective White Blood Cell Production = Neutropenia
  - Infections, fatigue, poor wound healing

# Dysplasia – easiest to see in the neutrophils



NORMAL NEUTROPHILS

DYSPLASTIC NEUTROPHILS

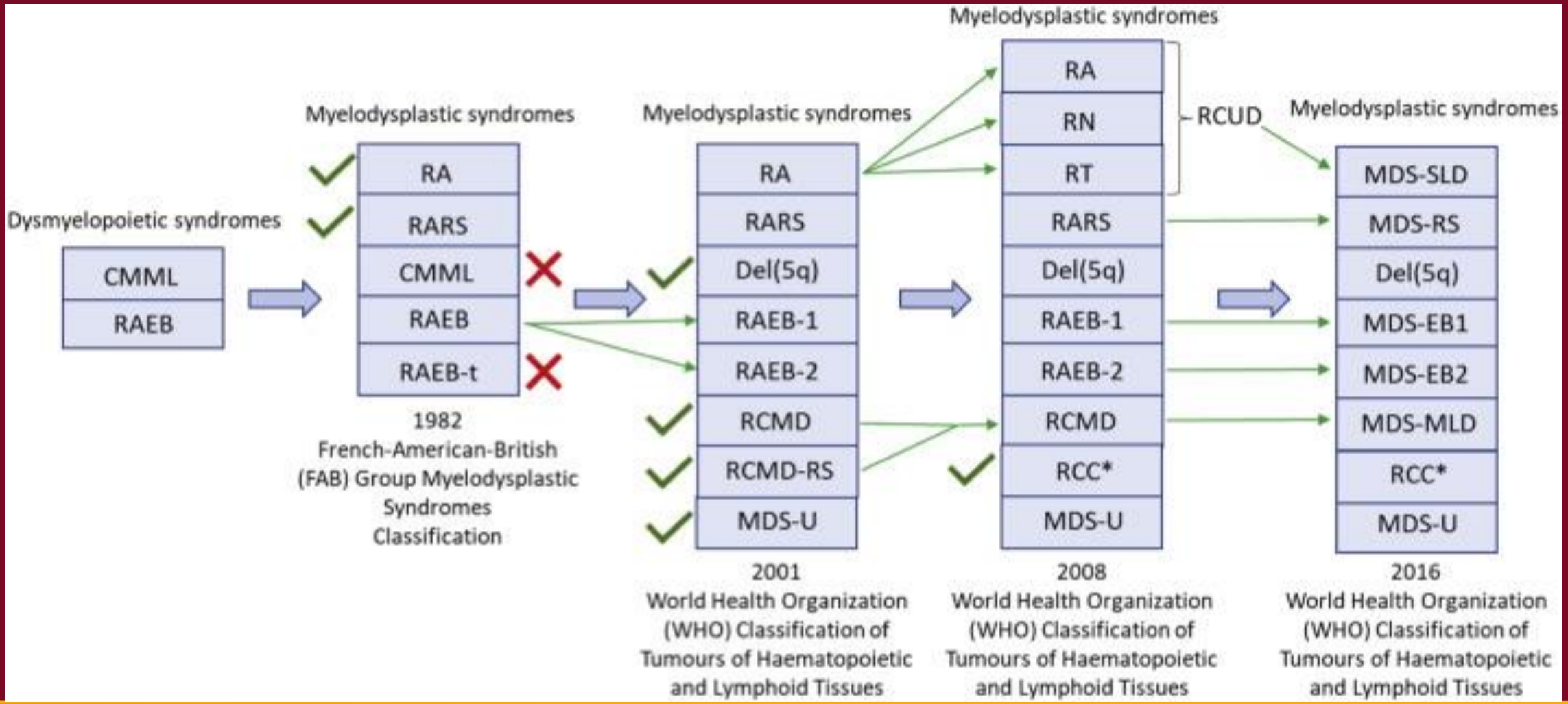


# What Causes MDS?

- Acquired DNA damage…
  - Chemotherapy
  - Benzene/chemicals
  - Radiation
  - ?Immune Dysregulation?
  - MAJORITY: IDIOPATHIC

- People are living longer after chemo….

# A DIAGNOSIS IN EVOLUTION



# MDS: NO LONGER ONE DISEASE

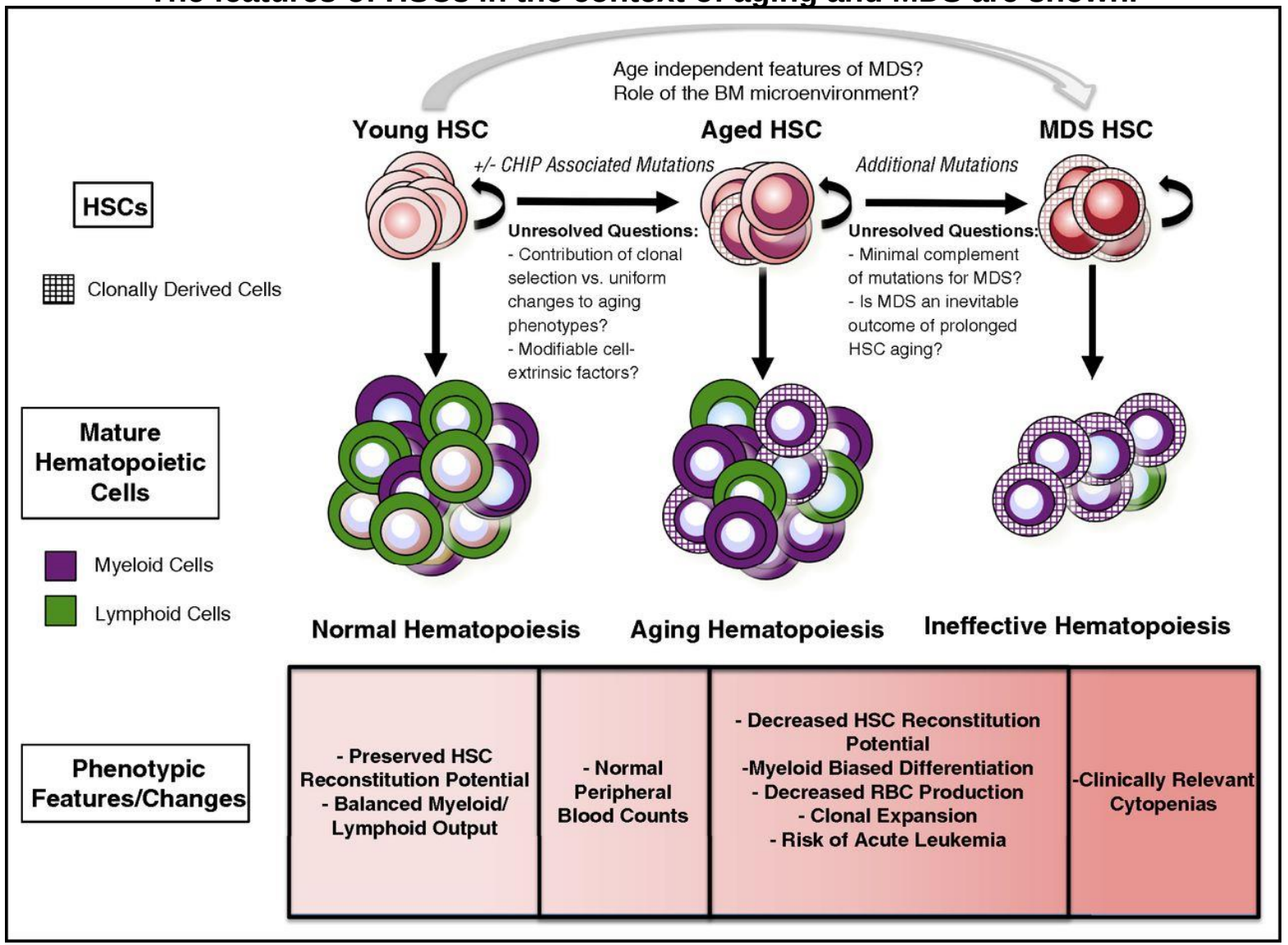
- CMML (chronic myelomonocytic leukemia) – excess production of monocytes + dysplasia + cytopenias
  - Also can evolve to AML
  - Now considered an MDS/MPN OVERLAP syndrome

- CCUS/ICUS/Early MDS

# Myeloproliferative Neoplasms: Myelofibrosis

- Stem cell defect characterized by anemia, splenomegaly, systemic symptoms
  - Can be primary
  - Can be transformed from ET/PV
- Jak-2 mutation present in 30-50%
  - Jak-2 inhibitors control symptoms
  - Only CURE is stem cell transplant
- CALR mutation present in 88% of JAK2 negative patients (NEJM, Dec 2013)
- Additional "driver" mutations similar to MDS/AML

**The features of HSCs in the context of aging and MDS are shown.**




**Stephen S. Chung, and Christopher Y. Park Blood Adv 2017;1:2572-2578**



blood advances

# EPIDEMIOLOGY OF MDS

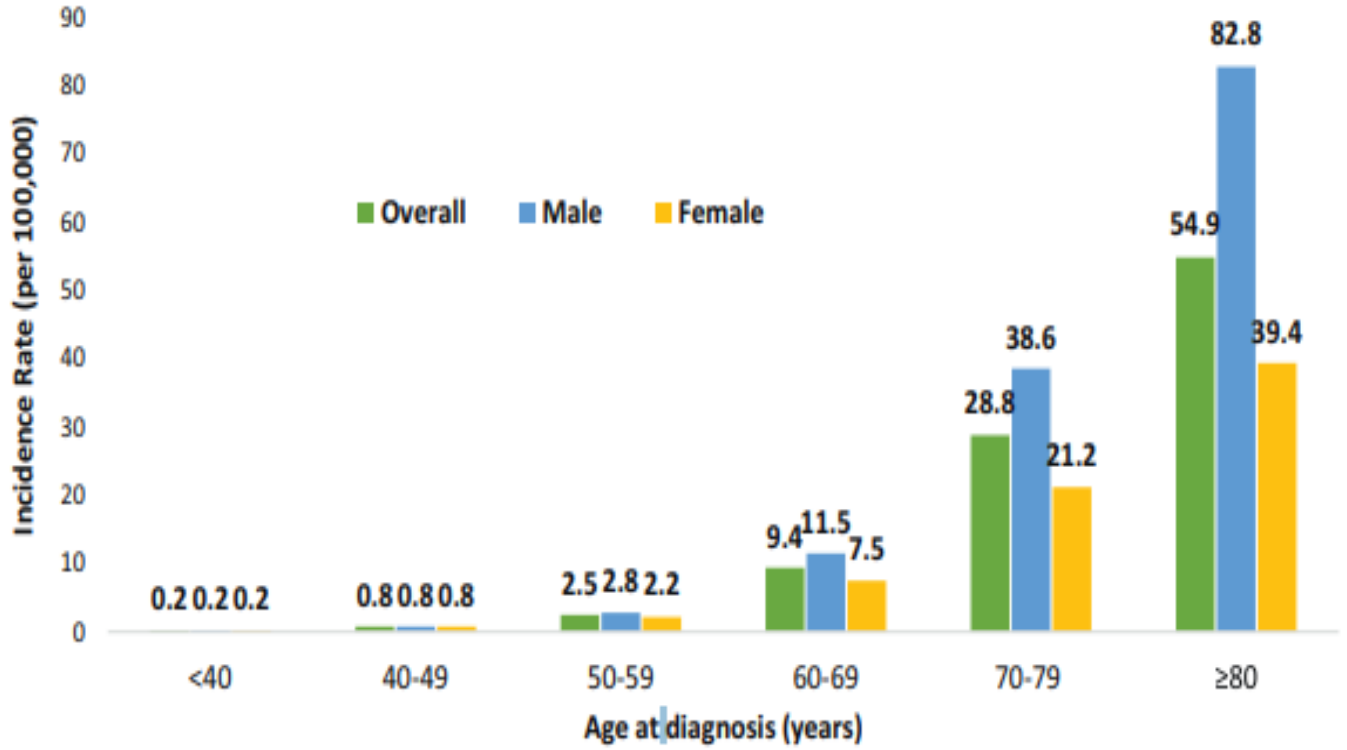



**Fig. 6.** Incidence of patients with myelodysplastic syndrome by sex and age in the United States (Surveillance, Epidemiology, and End Results data, based on the November 2017 submission).





Zeidan et al. Blood Reviews 2018 in press.

# EPIDEMIOLOGY OF MDS

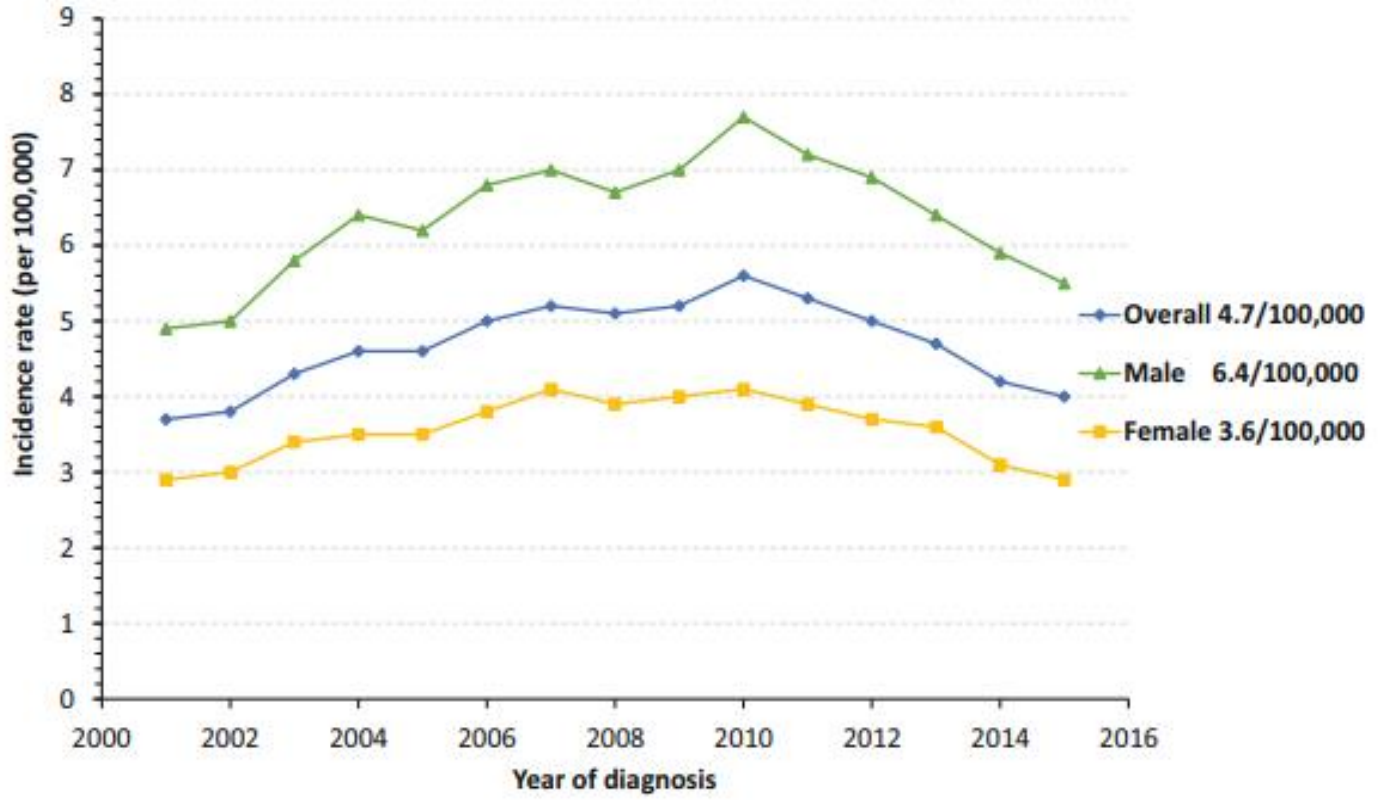



**Fig. 3.** Incidence of patients with myelodysplastic syndrome by sex in the United States (Surveillance, Epidemiology, and End Results data, based on the November 2017 submission).

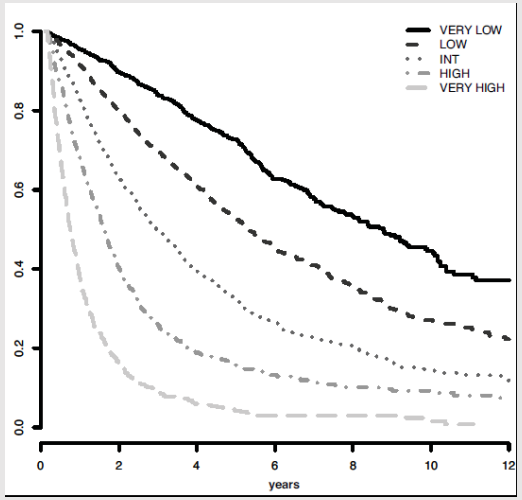
# MDS IPSS-R Components (Greenberg P et al 2012)

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

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

# IPSS-R (see: http://www.mds-foundation.org/ipss-r-calculator/)

| Risk group | Points | % patients (n=7,012; AML data on 6,485) | Median survival, years | Median survival for pts under 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 |




**Only valid for:**
***Adults***
***De novo disease***
***Treated with supportive care***
***At the time of diagnosis***

From: Greenberg P et al *Blood* 2012 Sep 20;120(12):2454-65. Epub 2012 Jun 27

# Predicting Outcomes in Myelodysplastic Syndrome

HIGH RISK:

- Blasts >10%
- >3 cytogenetic abnormalities
- Chromosome 7 or 3

LOW RISK:

- Isolated 5q-
- <2-5% blasts
- Single cytopenias

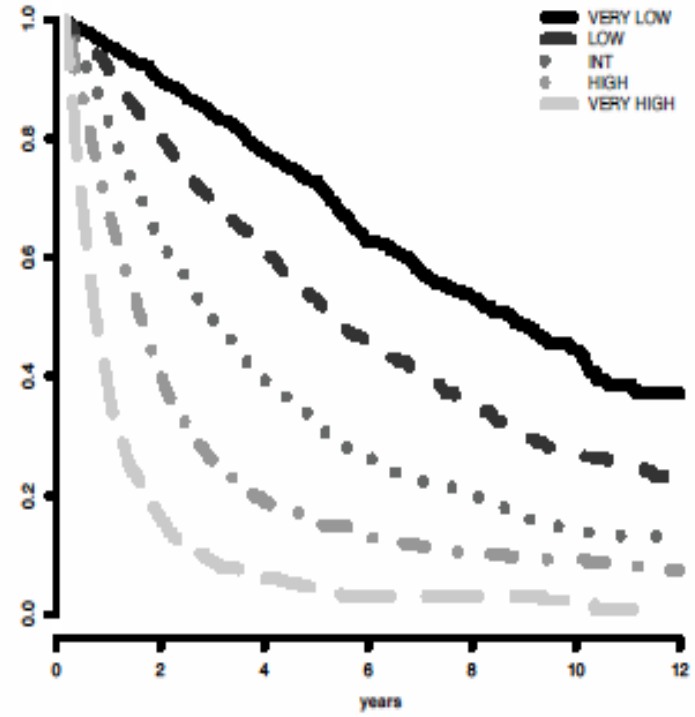



**Figure 3. Survival based on IPSS-R prognostic risk-based categories.** Survival related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 7012; Dxy 0.43, $P < .001$). The number of patients in each category and their proportional representation are shown in Table 1.

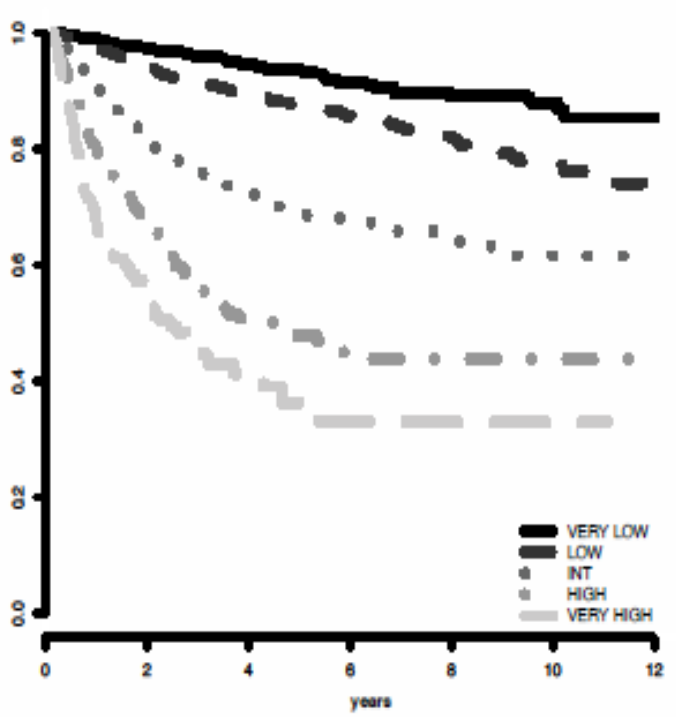
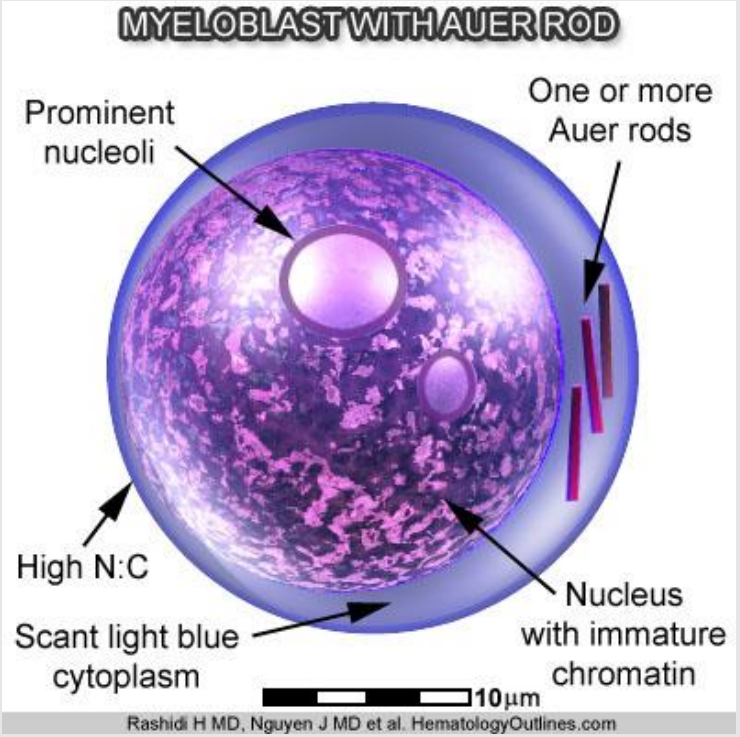
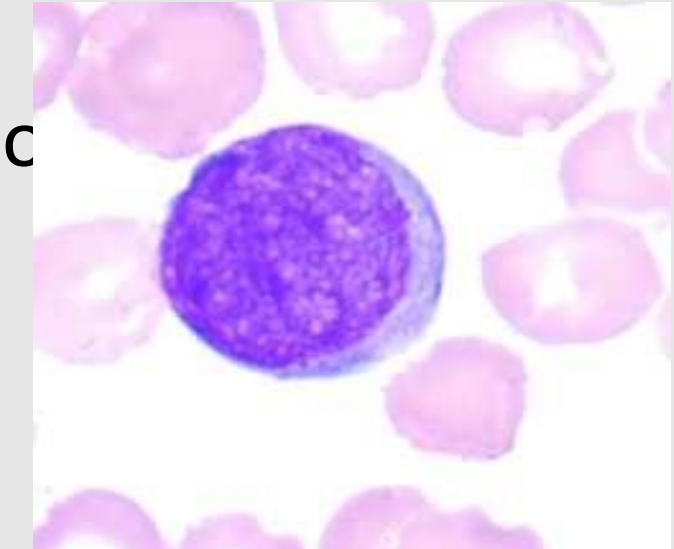



**Figure 4. AML evolution based on IPSS-R prognostic risk-based categories.** Progression to AML related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 6485; Dxy 0.52, $P < .001$). The number of patients in each category and their proportional representation are shown in Table 1.

# Acute Myeloid Leukemia Defined

- >20 “BLASTS” in blood or bone marrow
- Usually associated with worsening anemia and thrombocytopenia
- Often requires bone marrow biopsy to diagnc



# Q & A

# MDS: Current Treatment Options

# MDS Treatment: What Are We Trying to Achieve?

1. Improve Cytopenias
   - Decrease transfusion needs
   - Improve symptoms
   - Reduce risks of bleeding, infection, cardiovascular e

2. Decrease Transformation to AML
   - Reduce # Blasts
   - Time to Transformation to AML

3. Extend Life
   - Improve Median Overall Survival

**"CR" = complete remission**
**-normal CBC**
**-normal marrow**
**-normal cytogenetics**
**-not necessarily a "CURE"**

**"ORR" – overall response**
**-improvement in cbc/transfusion independence**
**-doesn't meet CR definition**

# Low Risk MDS May Respond to “Stimulants”

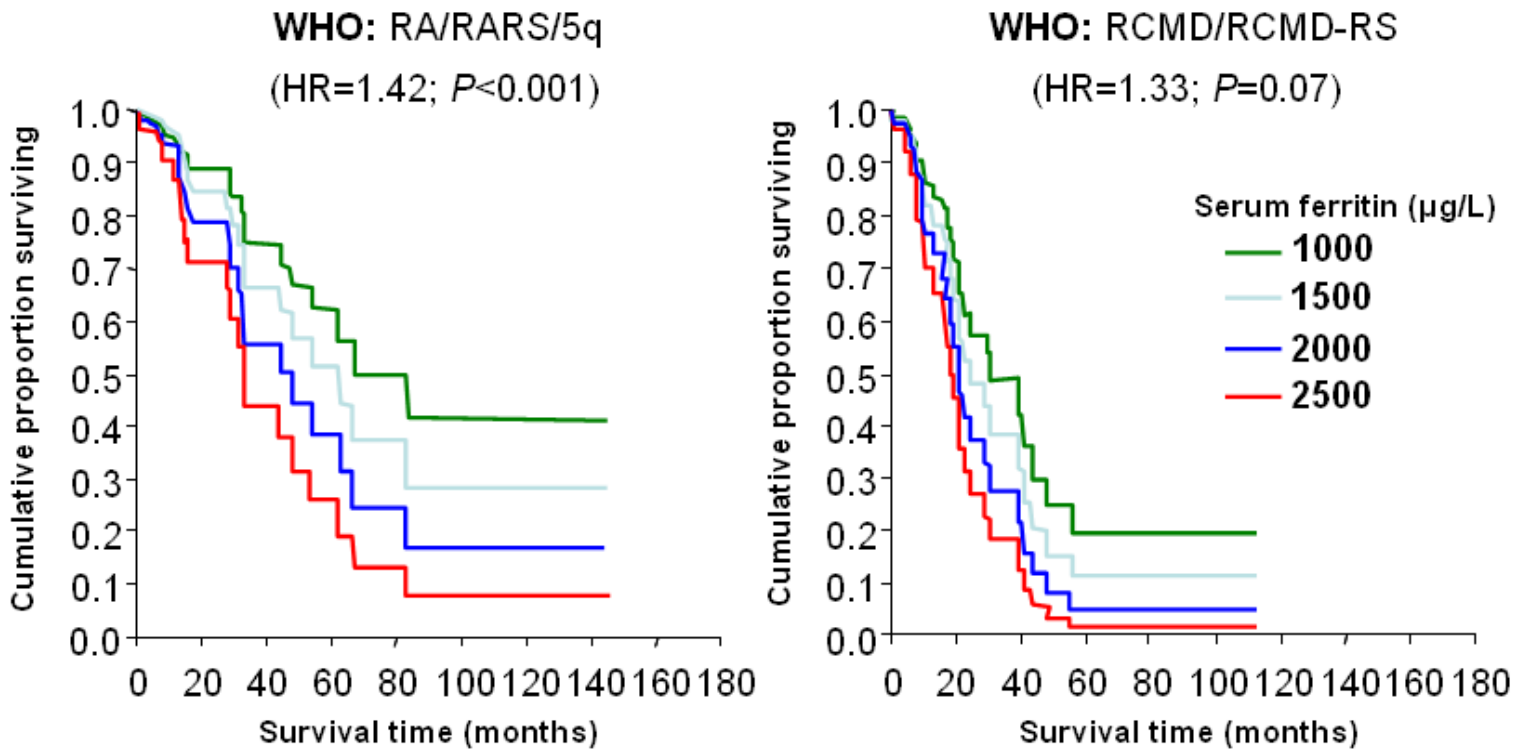
- Erythropoietin Stimulating Agents (ESAs)
  - Procrit (once weekly)
  - Epogen (once weekly)
  - Aranesp (longer lasting)

- Neutrophils Stimulating Agents (GCSF, GMCSF)
  - Neupogen
  - Neulasta (longer acting)
  - Leukine
  - Can synergize with ESA to improve HGB too

# Transfusions in MDS

- Can be life-saving, life-prolonging
- Platelets live about 7 days
  - 1 unit bump the platelets up by 45,000 (best case)
- 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 – monitor the ferritin over time, consider chelation agents

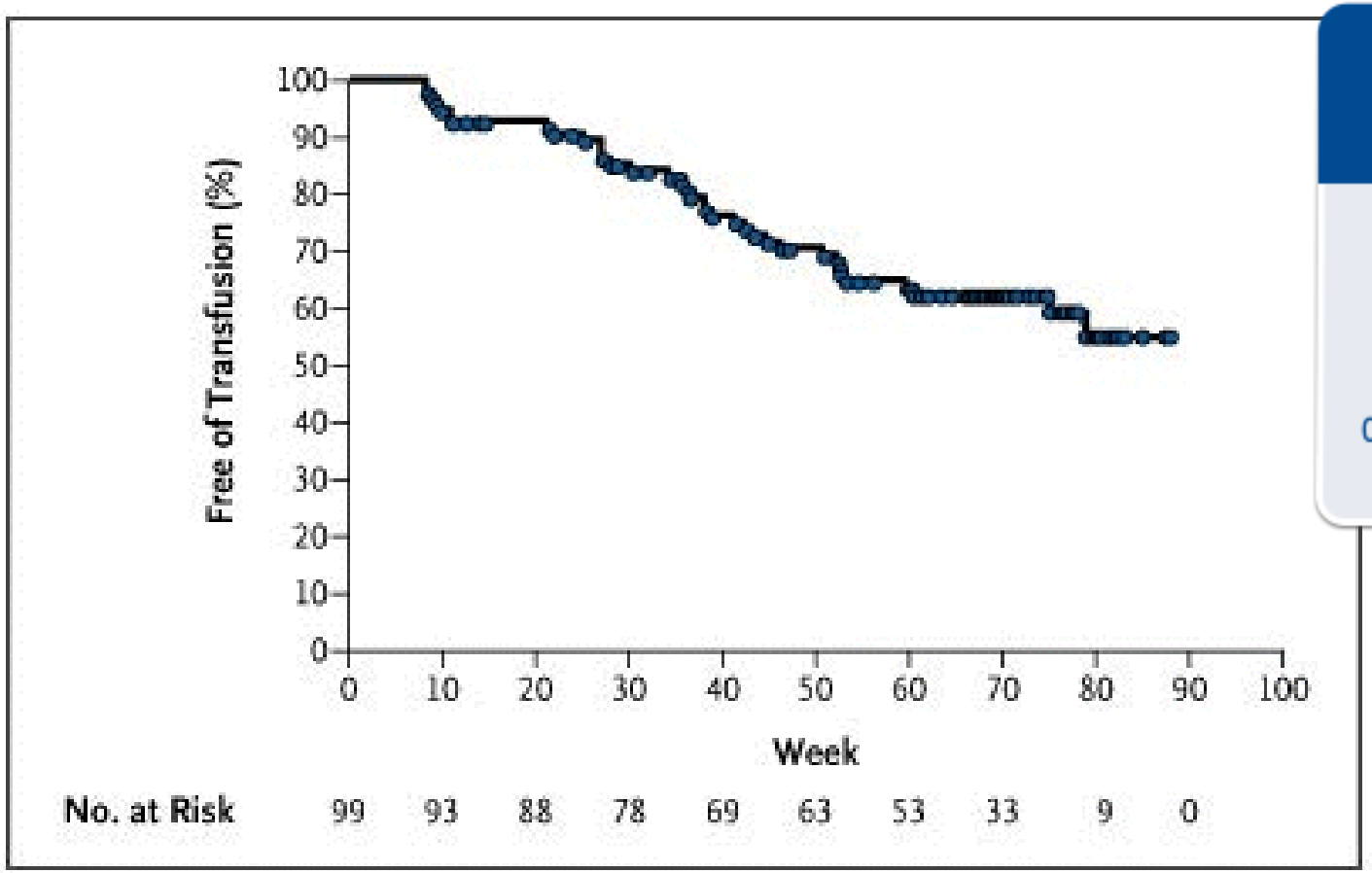
# Is serum ferritin a prognostic factor for survival in MDS?




- **Malcovati *et al.* showed that iron overload resulting from transfusion dependency had a significant impact on OS**

*Malcovati L et al. Leuk Res. 2007;31(Suppl 3):S2–S6*

# Lenalidomide (Revlimid) for Deletion 5q MDS




**Median duration of RBC transfusion independence among the 99 responders was 44 weeks (range: 0->67 weeks) at the time of the interim analysis**

# Age Does NOT Significantly Affect Outcomes in Higher Risk MDS

**Table 4. Age-Related Survival and AML Evolution of MDS Patients Within the IPSS Subgroups**

| | No. of Patients | Low | Int-1 | Int-2 | High |
|---|---|---|---|---|---|
| A. Median Survival (yr) | | | | | |
| Total no. of patients (%) | 816 | 267 (33) | 314 (38) | 176 (22) | 59 (7) |
| Median (yr) | | 5.7 | 3.5 | 1.2 | 0.4 |
| Age (yr) | | | | | |
| ≤60 | 205 (25) | 11.8 | 5.2 | 1.8 | 0.3 |
| >60 | 611 | 4.8 | 2.7 | 1.1 | 0.5 |
| ≤70 | 445 (54) | 9.0 | 4.4 | 1.3 | 0.4 |
| >70 | 371 | 3.9 | 2.4 | 1.2 | 0.4 |
| B. 25% AML Evolution (yr) | | | | | |
| Total no. of patients (%) | 759 | 235 (31) | 295 (39) | 171 (22) | 58 (8) |
| Median (yr) | | 9.4 | 3.3 | 1.1 | 0.2 |
| Age (yr) | | | | | |
| ≤60 | 187 (25) | >9.4 (NR) | 6.9 | 0.7 | 0.2 |
| >60 | 572 | 9.4 | 2.7 | 1.3 | 0.2 |
| ≤70 | 414 (55) | >9.4 (NR) | 5.5 | 1.0 | 0.2 |
| >70 | 345 | >5.8 (NR) | 2.2 | 1.4 | 0.4 |

Abbreviation: NR, not reached.

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# Methyl Groups Silence Tumor Suppressor Genes – Cancers are Highly Methylated

2 FDA-approved Hypomethylating Agents:

- **VIDAZA (5-azacytidine)**
- **DACOGEN (decitabine)**

1 Novel HMA in Clinical

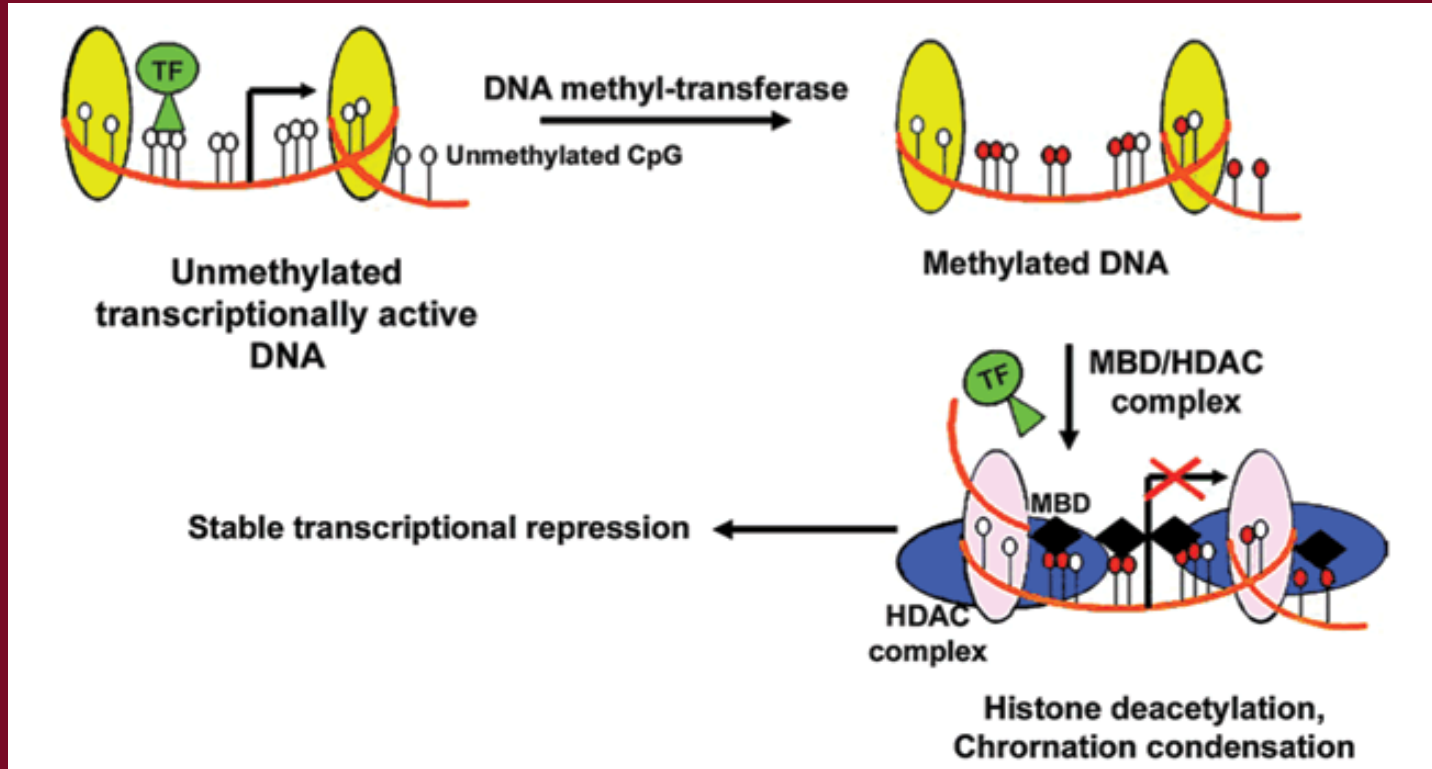


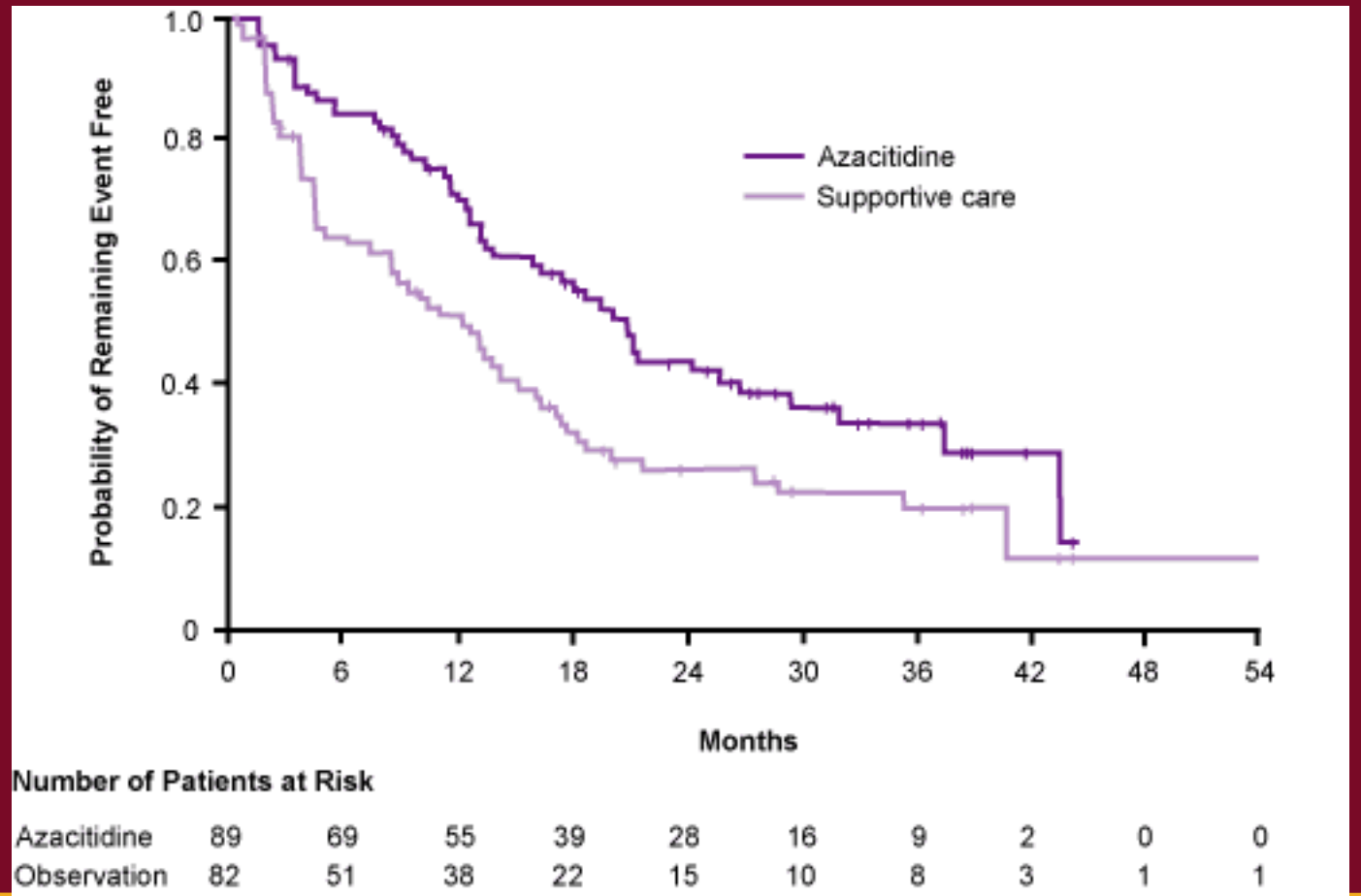

***Figure 1*** *– Epigenetic silencing of gene expression. DNA methyl-transferases carry out the methylation of CpG dinucleotides, which triggers the process of gene silencing by recruitment of methyl binding domain (MBD) and Histone deacetylases (HDAC) to bind to the methylated DNA. This results in histone deacetylation and chromatin condensation leading to loss of transcription factor binding and subsequent repression of transcription.*

# Current Treatment Options in Int/High Risk MDS

**5-AzaCytidine**

- **ORR 51%**
- **CR 16%**

**Decitabine yields similar results**

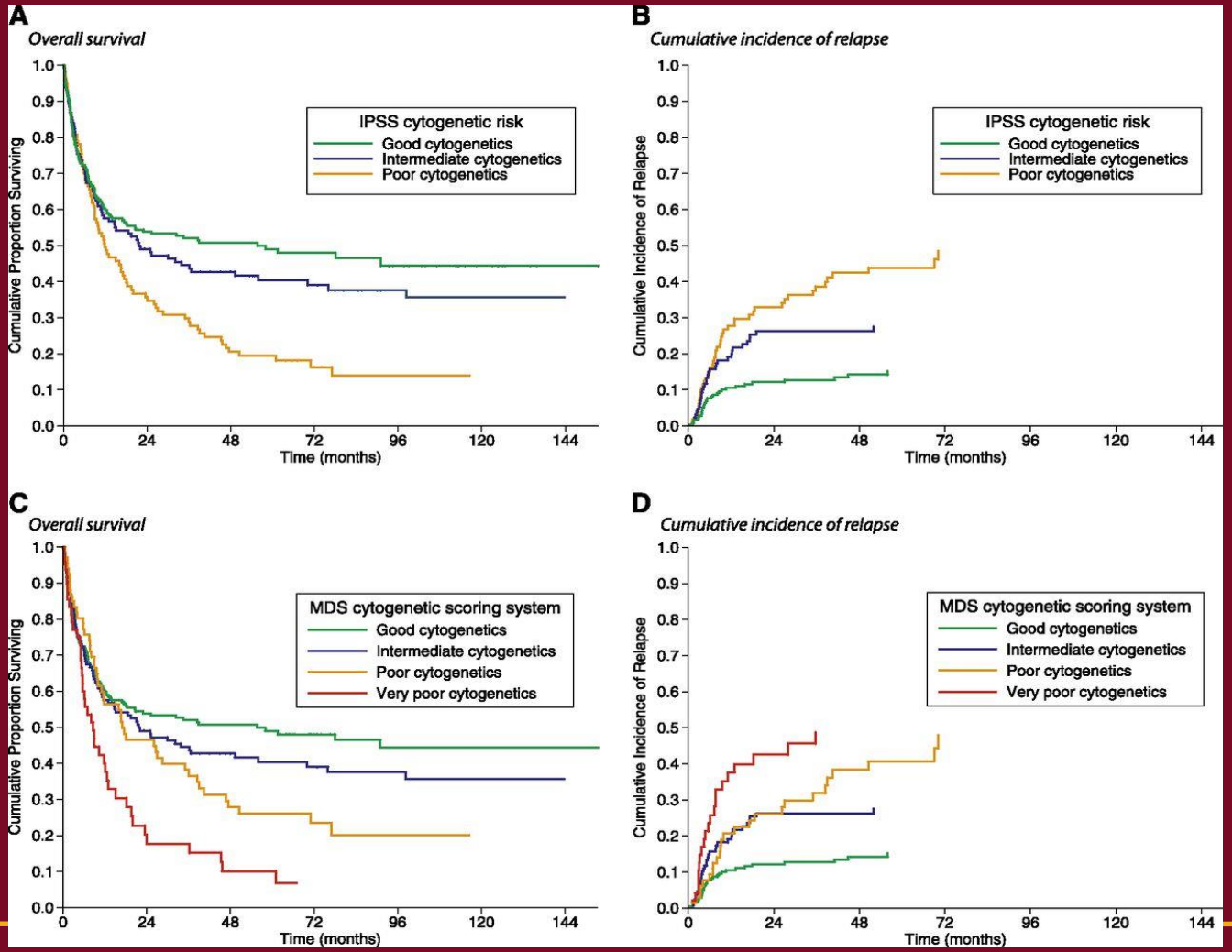



Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002;20:2429-2440. Reprinted with permission from the American Society of Clinical Oncology.

# Allogeneic Stem Cell Transplant in MDS

- Still the only option with potential for cure
- Still a high risk procedure with transplant-related mortality (TRM) approximately 15-25%
- Patient comorbidities a major risk factor for TRM
- Optimal donor younger, HLA-matched

# Kaplan-Meier analysis of survival and cumulative incidence of relapse following allogeneic HSCT in MDS patients stratified according to their pre-transplant IPSS cytogenetic risk or the new MDS cytogenetic scoring system used for the IPSS-R.

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Matteo G. Della Porta et al. Blood 2014;123:2333-2342

blood

# Q & A

# The **MEDALIST** Trial: Results of a Phase 3, RPCC Study of Luspatercept to Treat Patients with Very Low-, Low-, or Intermediate-Risk MDS Associated Anemia with Ring Sideroblasts Who Require RBC Transfusions

- 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

# Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non-Del(5q) Lower Risk MDS Relapsed/Refractory to ESA

- 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 TI 8 weeks
  - Median duration of TI not reached

  - Neutropenia and thrombocytopenia in 20-25%

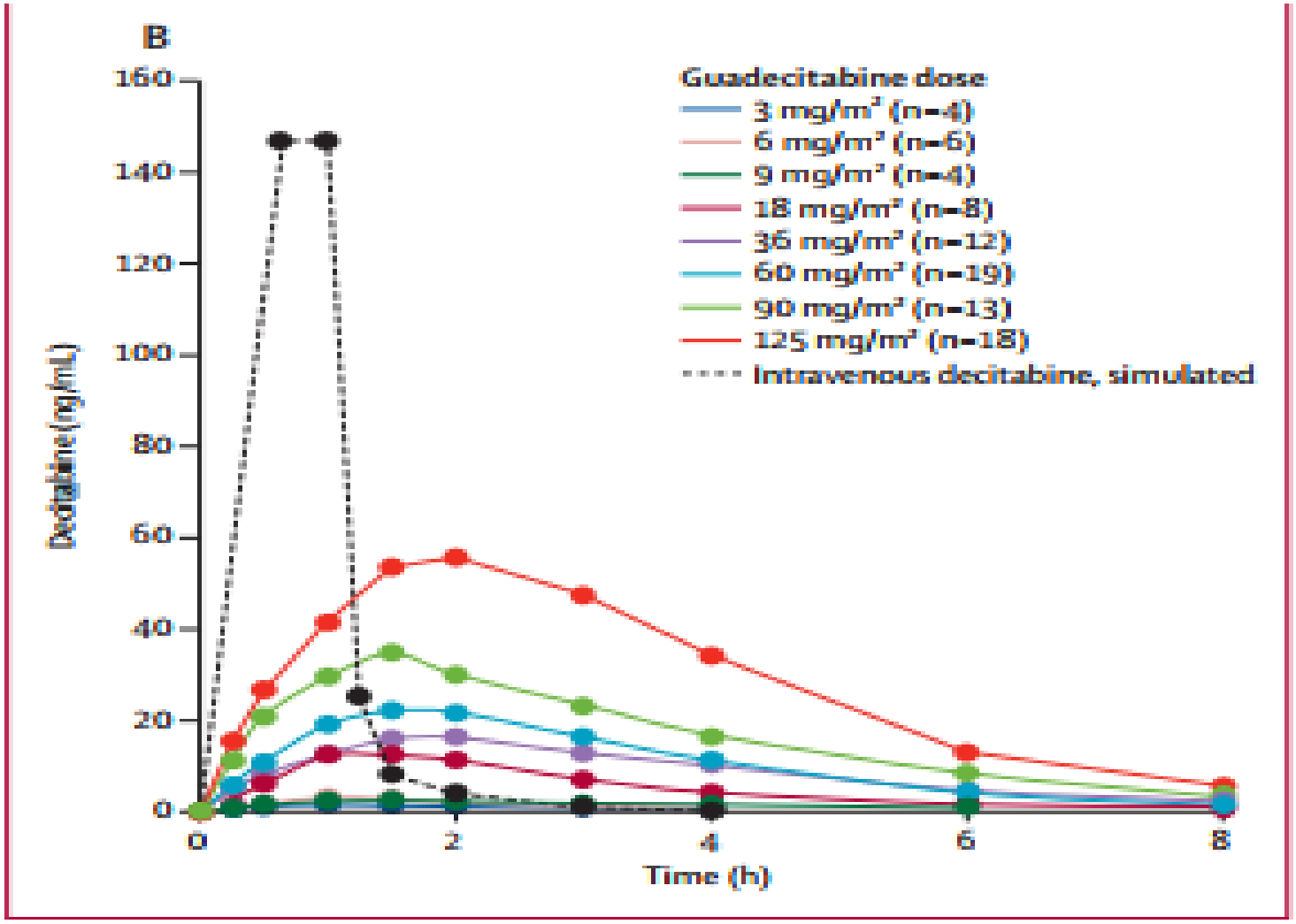
# Background: Guadecitabine (SGI110) in MDS First Evaluated by SU2C-Sponsored Dream Team

Phase I: Less rapid degradation by cytidine deaminase = longer t ½ than decitabine

Phase II: n=102, 60mg/m2 or 90mg/m2

- Previously treated patients:
  - 30% ORR
- Treatment naiive patients: 20% CR
  - 58% transfusion-independent for RBC
  - 46% transfusion-independent for platelets

# Guadecitabine PK vs Decitabine

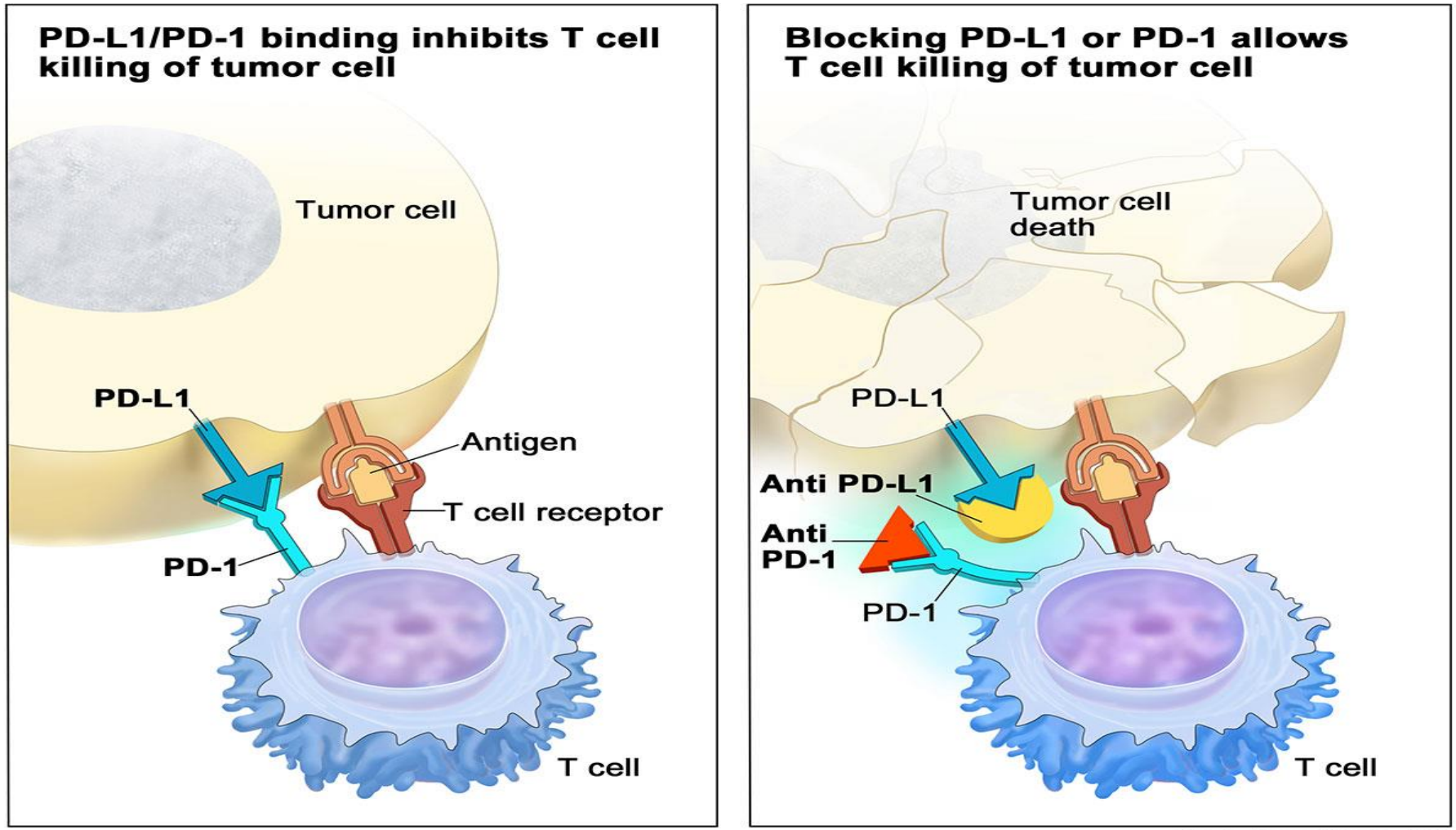



Issa et al. Lancet Oncol 2015

# MD Anderson: Guadecitabine for Int/Higher Risk MDS

- 97 patients received 60mg/m2 SC x 5 days every 28 days
- ORR 65%  (vs. 51% in the original Phase II study)
- CR 26%
- mCR + Hematologic Improvement 32%
- HI 7%

# Is Immune Exhaustion an Issue in MDS?



# Trials Using Immune Checkpoint Inhibitors?

- Phase II: Azacitidine + Nivolumab or Ipilimumab (MDA)
  - ORR 60-70% as FRONTLINE treatment
  - CR 40% with AZA + Nivolumab,  14% with AZA + IPI
  - CR 6/20 IPI alone (30%)
- Phase Ib: AZA + Atezolizumab
  - ORR 62%
  - CR 14%

# Phase I/II: Guadecitabine + Atezolizumab in HMA-Relapsed or Refractory MDS at USC, UMD, FCCC (VARI-SU2C)

- Completed Phase I for safety
- Now Enrolling Phase II
- ORR 33% as of December, 2018
- 1/9 patients from phase I in CR

# Rigosertib – No OS Difference but…

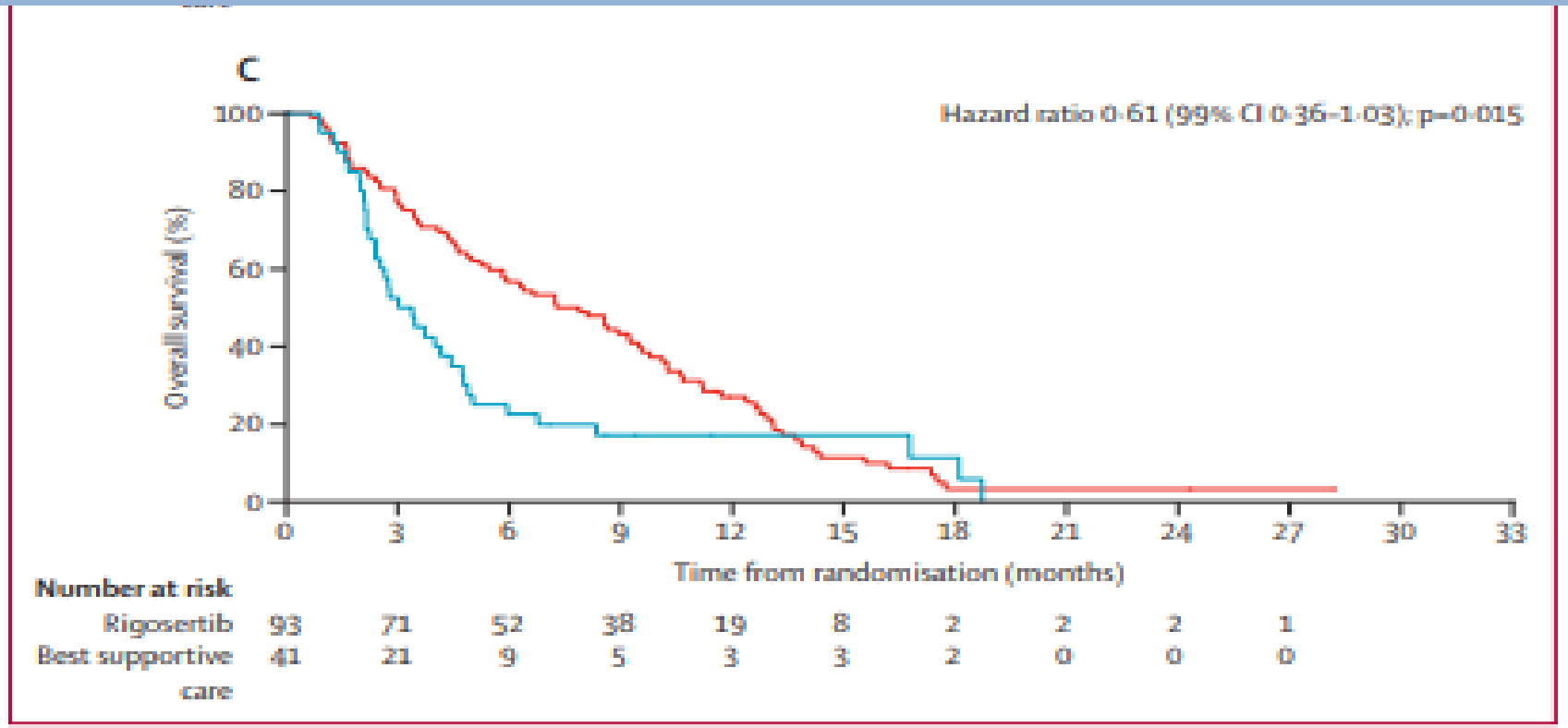



**Figure 2: Overall survival curves for the rigosertib group and best supportive care group**
(A) For the intention-to-treat population, (B) patients with primary hypomethylating drug failure, and (C) patients with IPSS-R very high risk. IPSS-R=Revised International Prognostic Scoring System.

# Rigosertib

- Interferes with RAS/RAF/MEK/PI3K pathways
- Now being combined with azacitidine in upfront treatment of MDS
  - 59% ORR in Previously Treated MDS patients
  - 79% ORR in Treatment-Naiive patients
- An oral form is now available
- GU toxicities like bleeding being addressed

# Phase 1b/2 Study of APR-246 + AZA in p53-mutated MDS and AML

- 93% ORR in MDS, 67% CR
- 100% ORR in AML, 80% CR

- GI toxicity and peripheral neuropathy

# OTHERS

- SL401R – CD123 (IL-3R) targeted therapy with some CRs in CMML, also being evaluated in HR MDS
- NEDD8 inhibitors
- IDH1/2 inhibitors
- Transplant

# Clinical Trials