UNIVERSITY of MARYLAND MEDICAL CENTER

MDS: Navigating Lower Risk Disease

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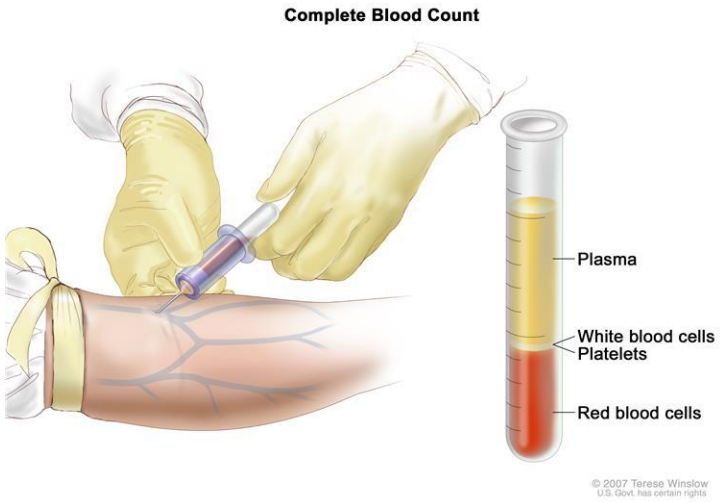
Standard Treatment Options

- Observation
- Erythropoiesis-Stimulating Agents (Growth Factors)
- Immunosuppressive Therapy
- Lenalidomide
- Hypomethylating Agents

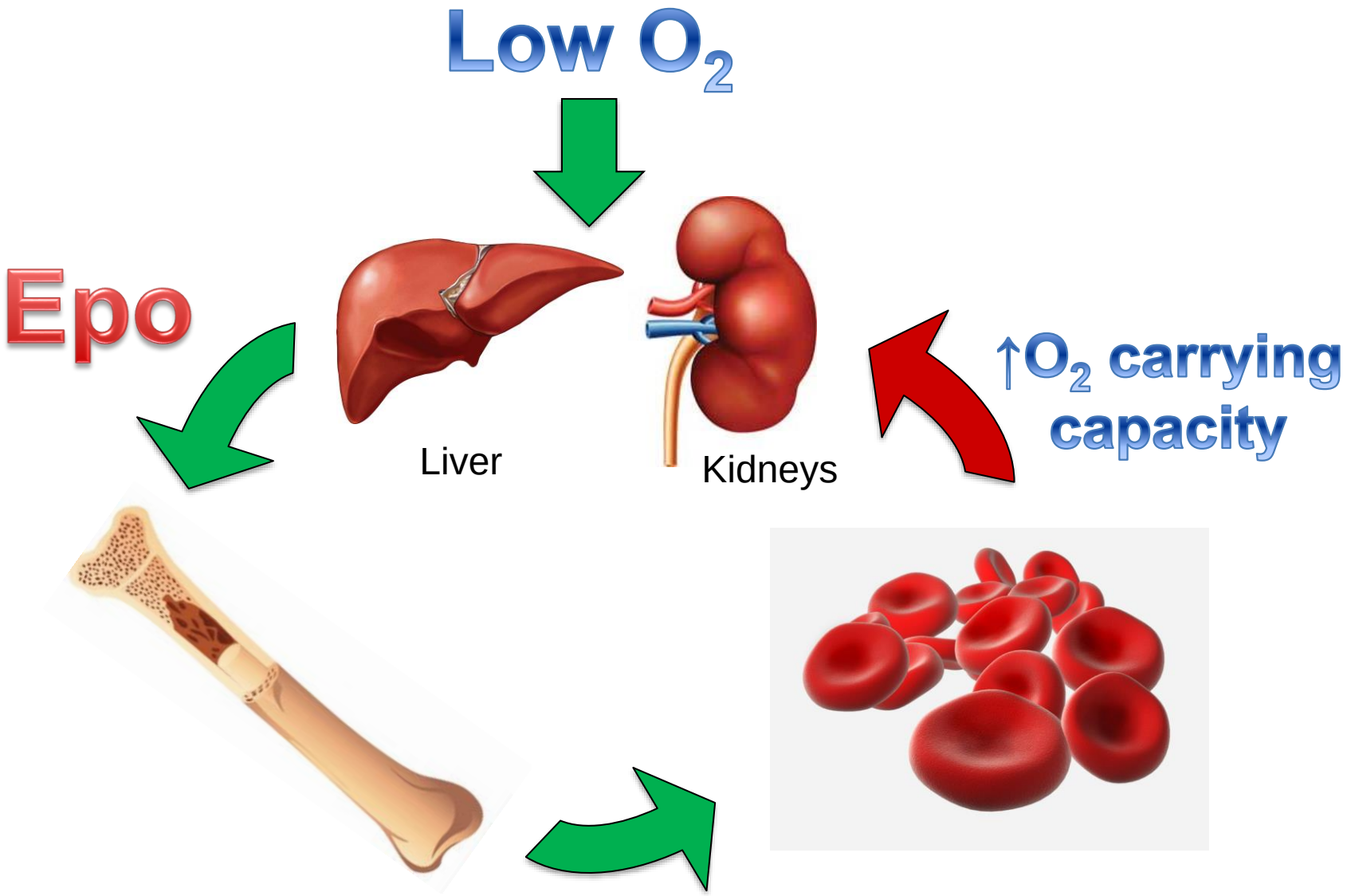
Observation

- Not all patients need active therapy for MDS
  - Mildly low blood counts
  - No need for transfusions
  - No/few symptoms
- "Watchful Waiting"

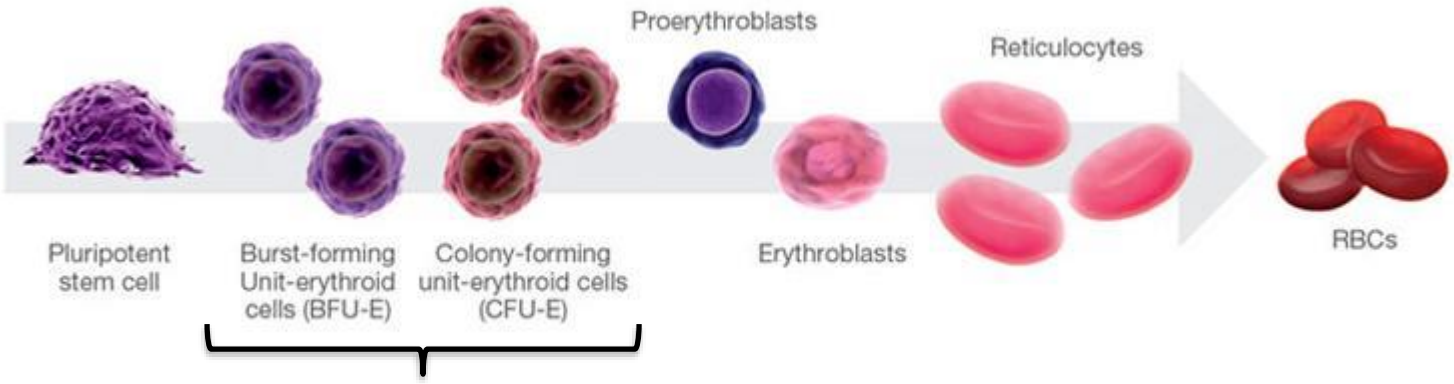


- Treating lower-risk patients early has *NOT* been shown to improve outcomes

Erythropoetin



Erythropoiesis Stimulating Agents



Erythropoiesis stimulating agents

- 30-40% response rates in patients with anemia
- Epoetin alfa (Procrit) and darbepoetin (Aranesp) are likely equally effective
- Addition of G-CSF (stimulates white blood cell production) may be helpful

Erythropoiesis Stimulating Agents

Factors associated with response:

- Low serum (endogenous) erythropoietin level
- Low transfusion dependence (<2 units/month)

	Response Rate
Neither Factor	**7%**
1 Factor	**23%**
Both Factors	**74%**

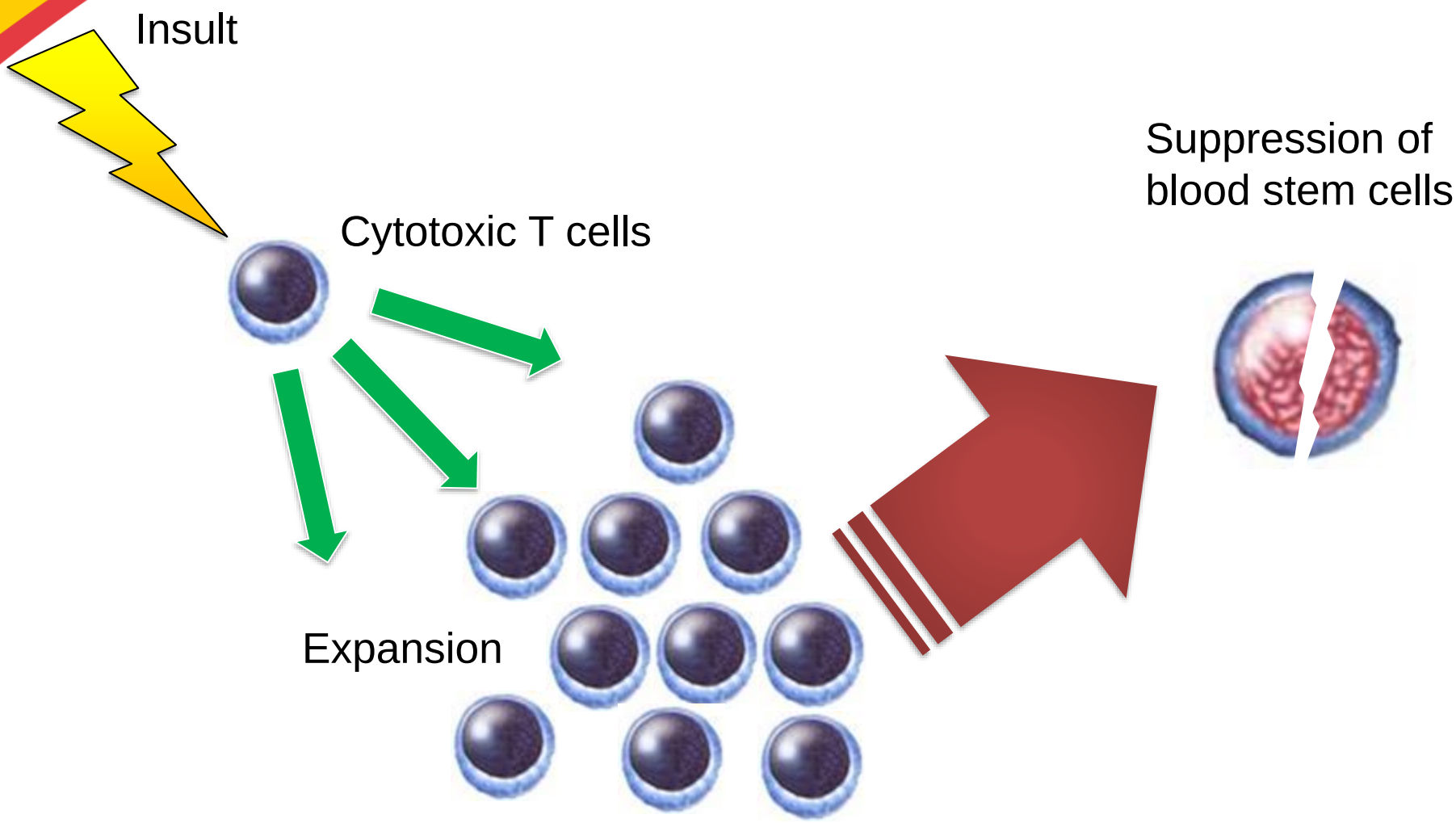
Hellstrom-Lindberg E, Br J Haematology 2003

Caution with ESAs

- Linked to increased heart attacks, stroke, blood clots, tumor growth, and death in patients with solid tumors

- This HAS NOT been shown in patients with MDS

Immune-Mediated Destruction



Anti-Thymocyte Globulin & Cyclosporine

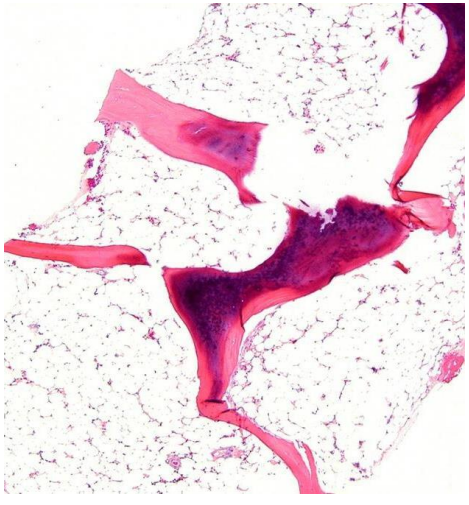
- Kill and block activity of T cells, restoring blood production
- Response rate ~30%
- Possible side effects: Allergic reactions, serum sickness, increased risk of infections, kidney dysfunction, neurologic issues

Passweg JR, JCO 2010

Anti-Thymocyte Globulin & Cyclosporine

Favorable factors for response:

- Young Age
- Immune receptor type (HLA-DR15)
- Low cellular marrow
- Ratio of T-cell subtypes (Low CD4:CD8)
- PNH clones



Lenalidomide

- Oral capsule taken daily
- Improves anemia in patients with lower-risk disease and del(5q)

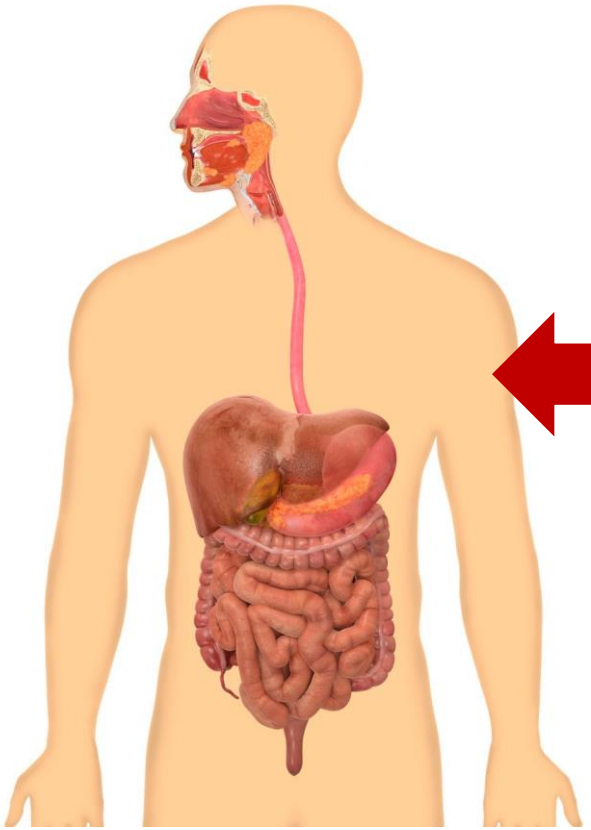
	All patients (n=148)
Red Blood Cell Response	
Transfusion Independence	**67%**
≥50% decrease in transfusions	**9%**
Total Transfusion Response	**76%**
Average Time to Response (weeks)	**4.6**

- Often causes decreased neutrophils and platelets

List AF, N Engl J Med 2006;355:1456-65

Iron Balance

Daily intake: 1-2 mg



Daily losses: 1-2 mg

~250 mg/unit

Potential long-term complications:

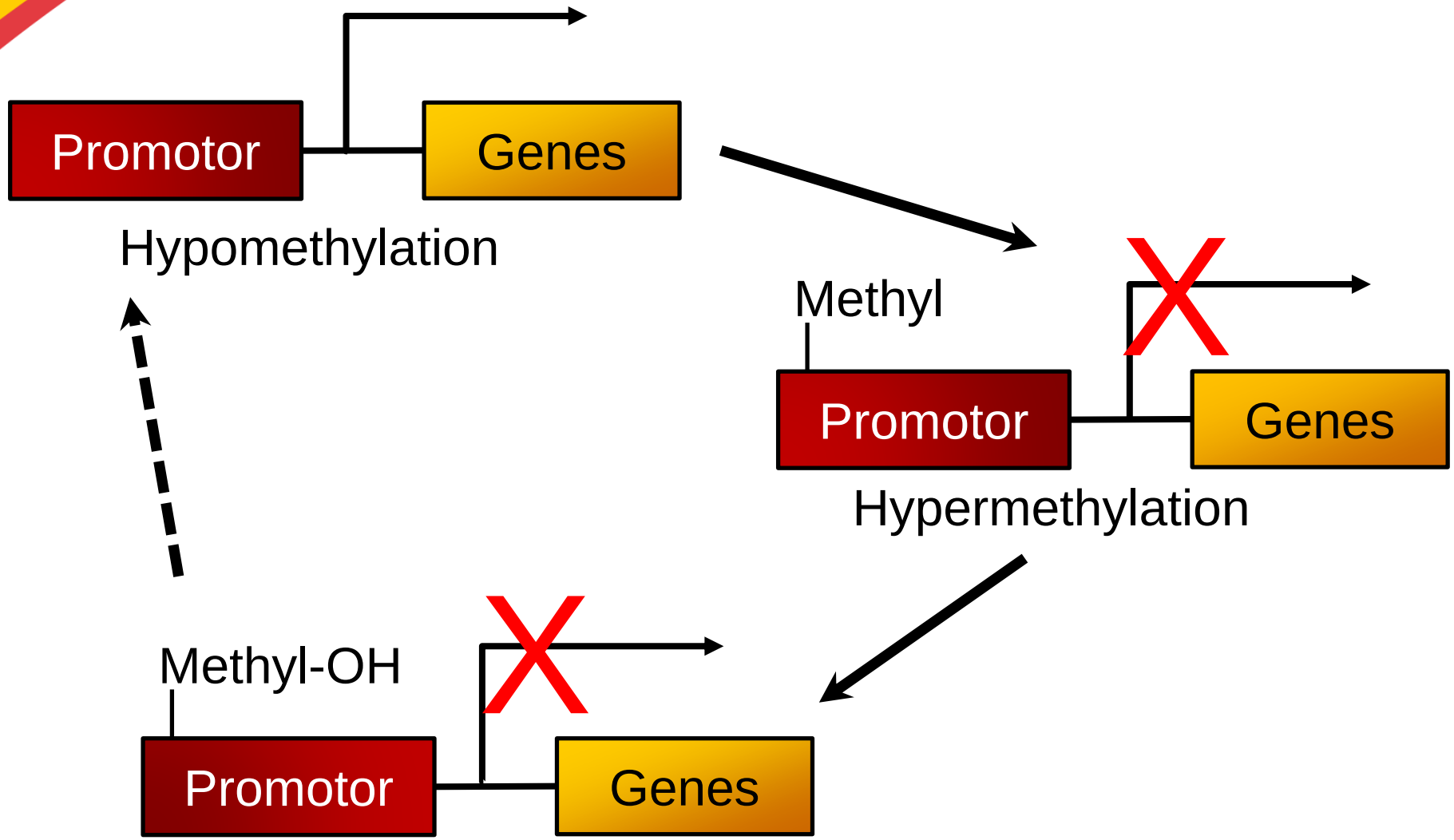
- Heart failure
- Liver disease
- Diabetes
- Skin changes
- Endocrine/hormone dysfunction

Iron Chelation Therapy

- Deferasirox decreases serum ferritin but high discontinuation rates

- Considered in patients with:
  - Lower-risk disease with long life expectancy
  - Serum ferritin (measure of iron stores) greater than 1,000-2,500 mcg/L or other evidence of iron overload

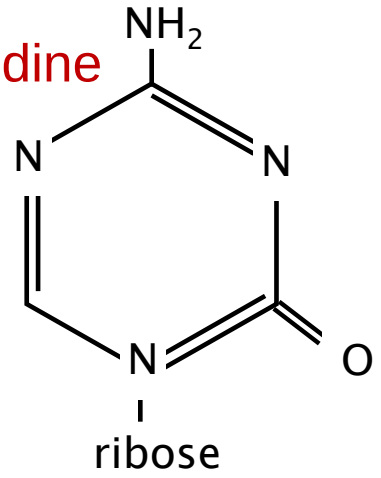
DNA Methylation



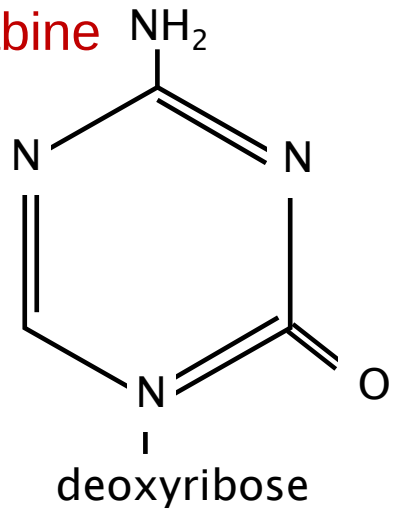
Hypomethylating Agents (HMAs)

- IV or subcutaneous administration, 5-7 days each month
- Outpatient therapy
- May take several cycles before response is seen
- Therapy should be continued indefinitely, even in patients who respond

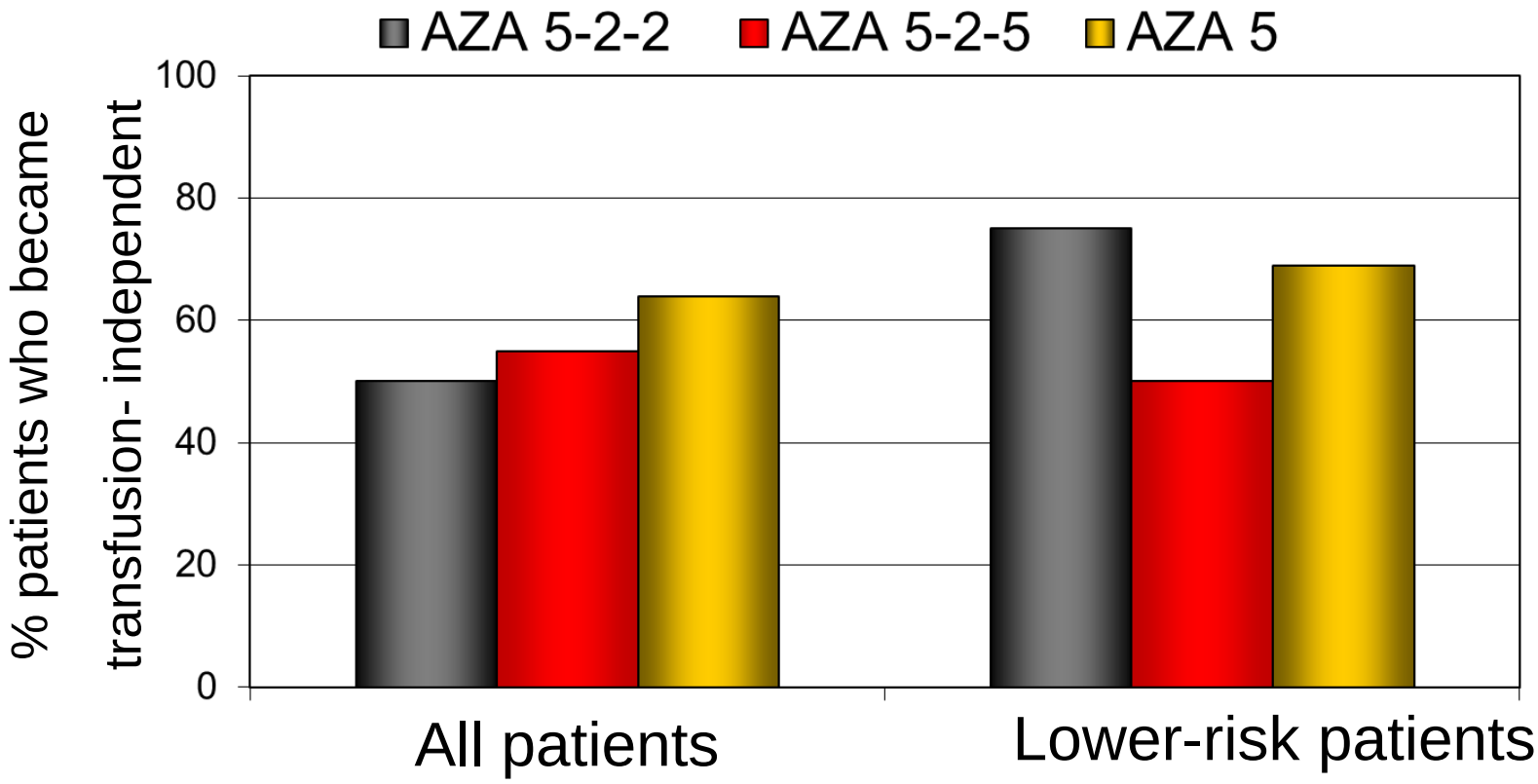
5-Azacitidine



Decitabine

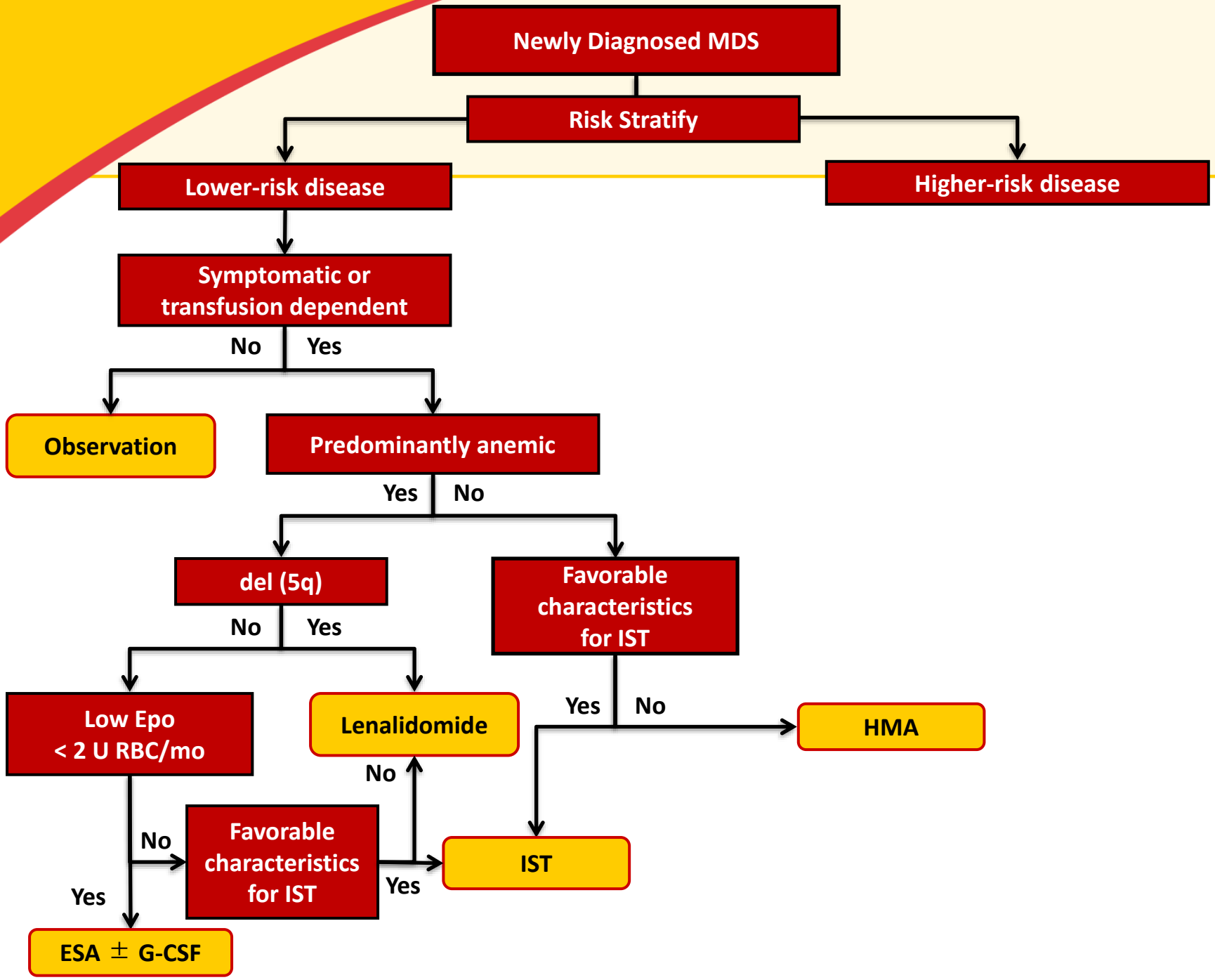


3 Alternative Dosing Schedules of Azacitidine



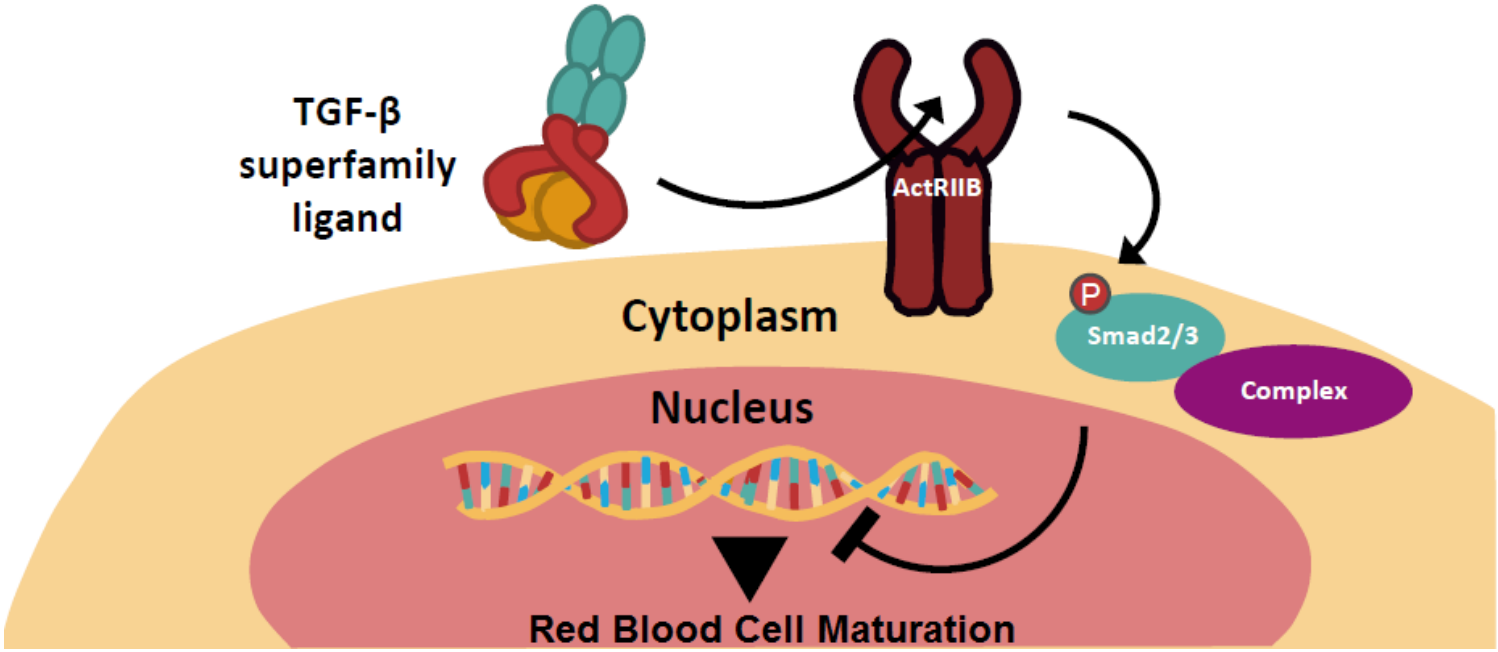
- May also improve platelets and/or neutrophils

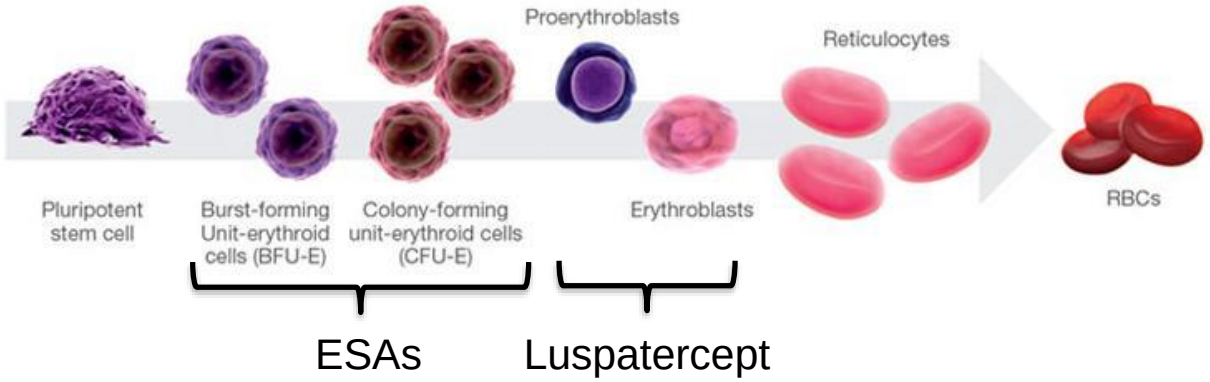
Lyons, et al., J Clin Oncol 27:1850-6, 2009


Newly Diagnosed MDS
Risk Stratify
Lower-risk disease
Higher-risk disease
Symptomatic or transfusion dependent
No
Yes
Observation
Predominantly anemic
Yes
No
del (5q)
Favorable characteristics for IST
No
Yes
Low Epo < 2 U RBC/mo
Lenalidomide
Yes
No
HMA
No
Favorable characteristics for IST
IST
Yes
Yes
ESA ± G-CSF

Recent Advancements in Lower-Risk Disease

Luspatercept





Fenaux P, et al. ASH 2018, Abstract #1

Luspatercept

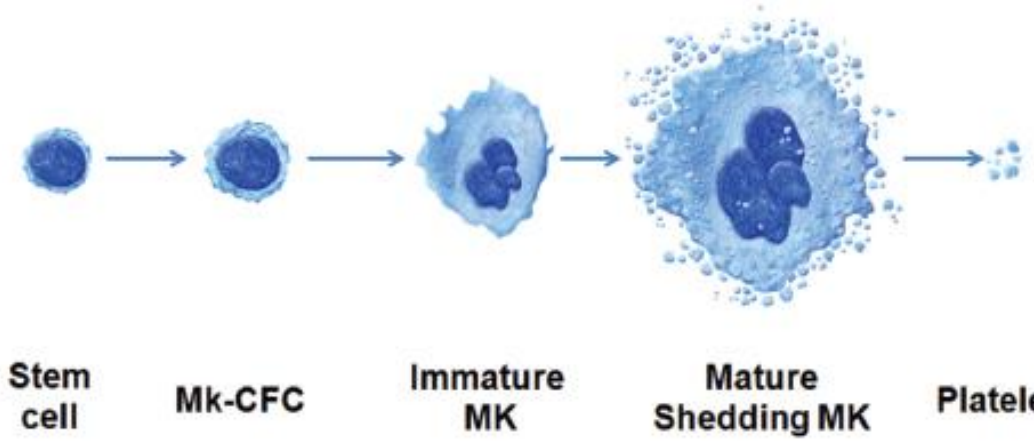
- Phase 3 study in lower-risk patients with MDS with Ring Sideroblasts, after erythropoiesis-stimulating agents

	Luspatercept	Placebo
Red Blood Cell Transfusion Independence ≥ 8 Weeks	**37.9%**	**13.2%**

- Granted priority review by the FDA
- *May* be approved as early as April 2020

Eltrombopag

- Oral drug that stimulates platelet production
- Associated with decreased blasts in preclinical models
- Currently FDA approved for immune thrombocytopenia, aplastic anemia



Eltrombopag

At 12 weeks:	Eltrombopag	Placebo
Platelet Responses	**47%**	**3%**
Disease Progression	**7%**	**3%**

- Some improvement in red blood cells and/or neutrophils was seen in a subset of patients
- *NOT* FDA approved
- Black-box Warning: May worsen disease in patients also on azacitidine

Oliva EN. Lancet Hematology 2017