High Risk MDS to AML

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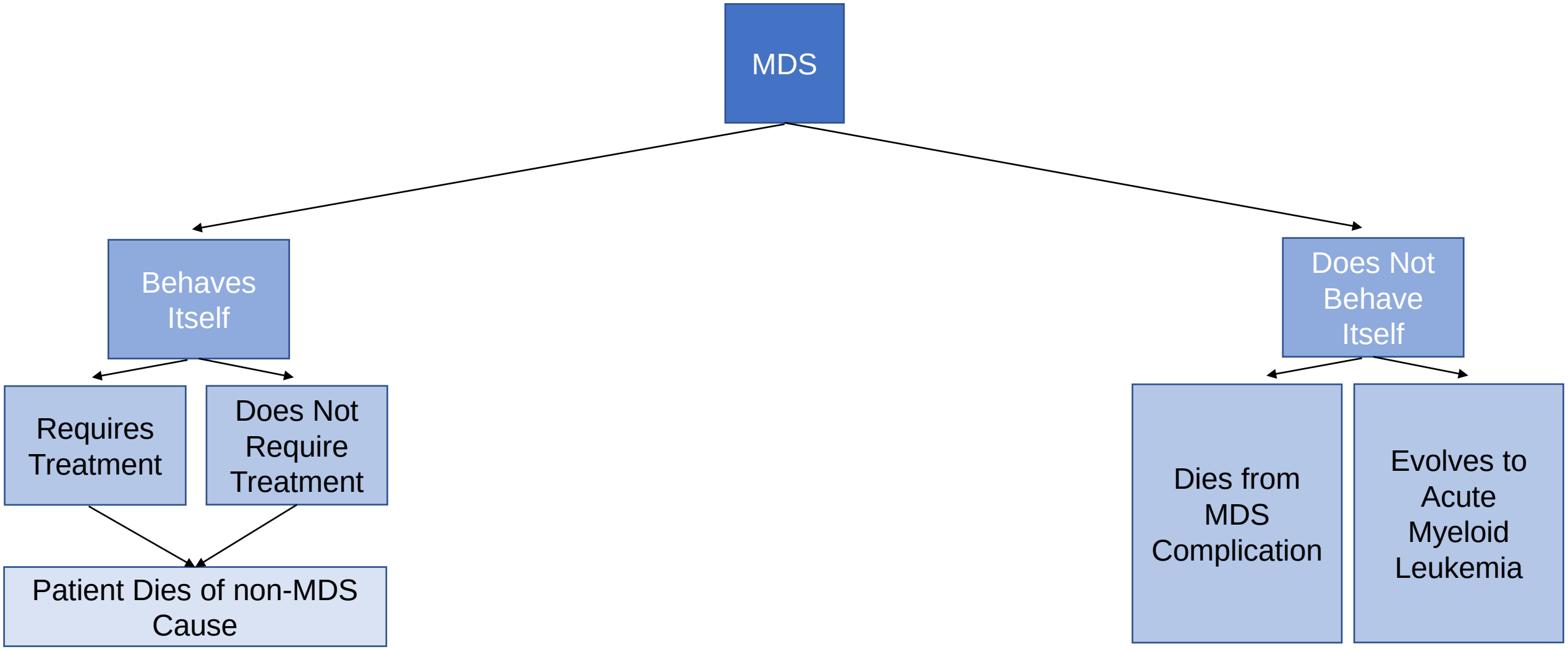
Agenda

- What is the difference between AML and MDS?
- How does MDS evolve to AML and can this be prevented?
- How does one know when MDS progresses to AML?
- Prognosis
- Treatment

Possible Outcomes for MDS Patients



How to Distinguish AML from MDS

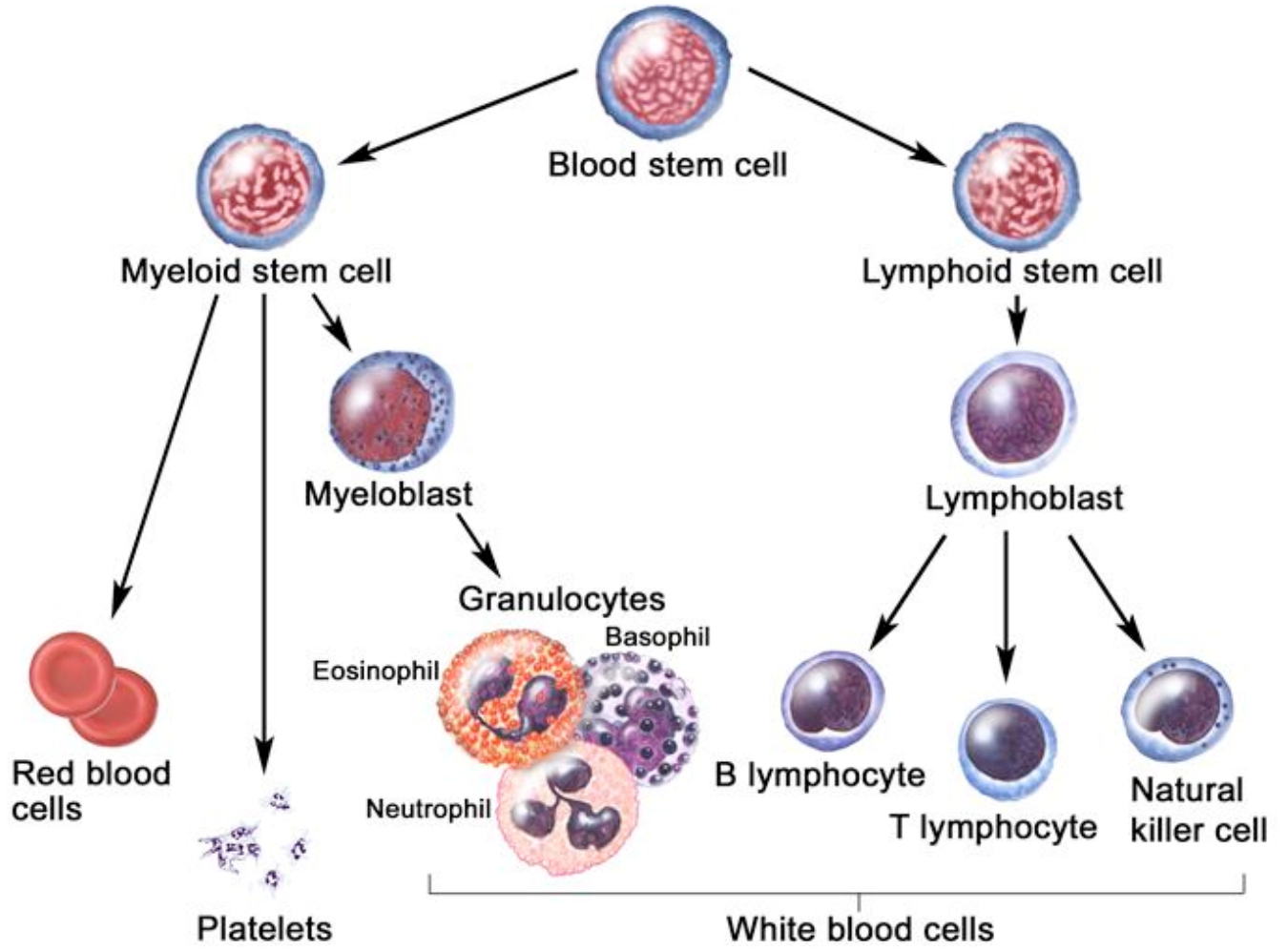
MDS

- Myeloid cancer
- Affects the bone marrow
- Causes abnormal blood counts
- Less than 20% of the bone marrow (or peripheral blood) are **blasts**

AML

- Myeloid cancer
- Affects the bone marrow
- Causes abnormal blood counts
- Greater than 20% of the bone marrow (or peripheral blood) are **blasts**

What are Blasts?



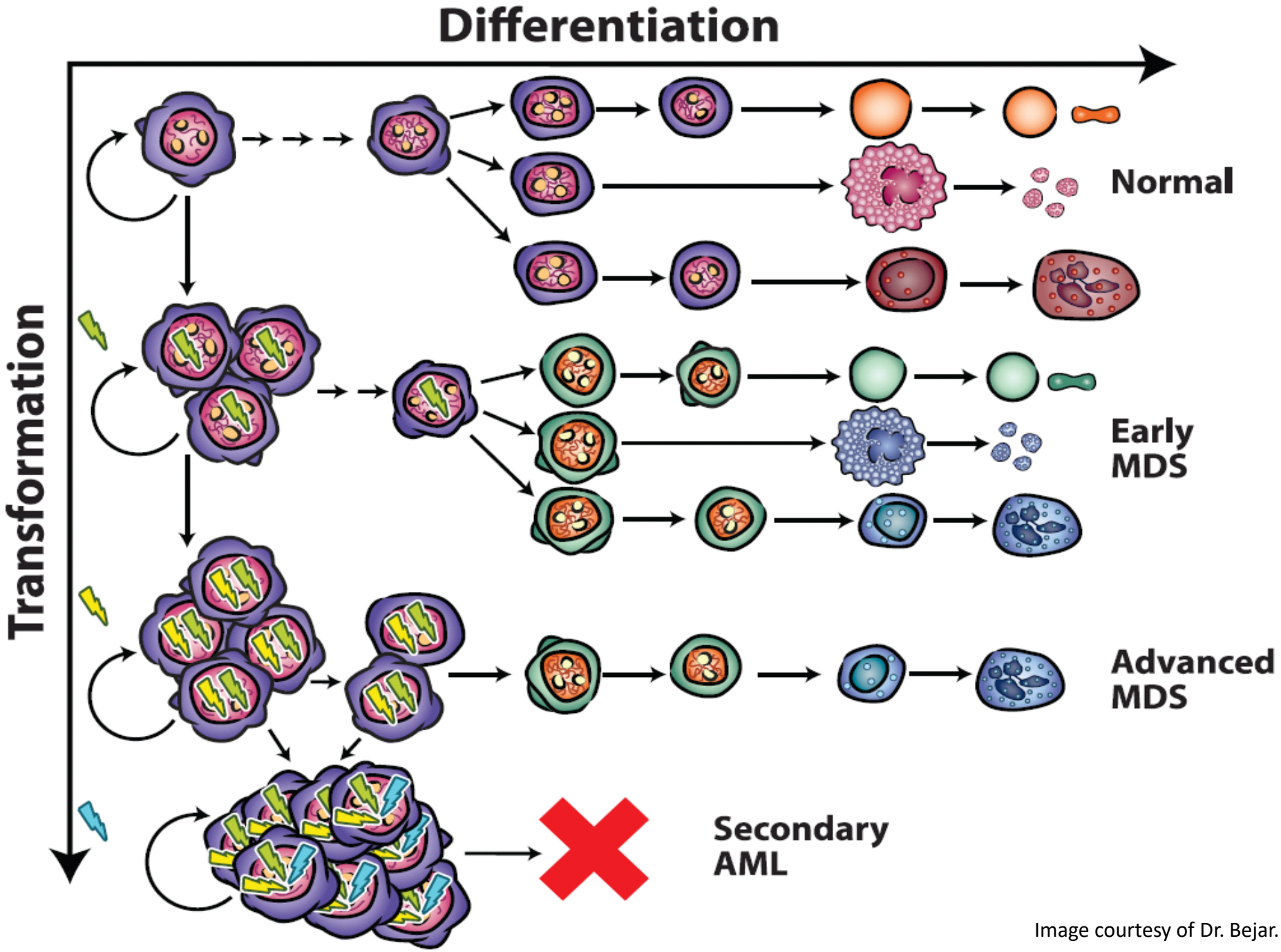


Image courtesy of Dr. Bejar.

Can Progression of MDS to AML be Prevented?

- For patients who require treatment for MDS, thin evidence to support the use of a hypomethylating agent (azacitidine or decitabine) can prevent progression

- For patients who do not require treatment for MDS, no evidence that treating them can prevent progression

- No lifestyle or environmental factors implicated in the progression of MDS to AML

Silverman et al, Cancer 2011

How Can You Know When MDS Progresses?

- Bone marrow biopsy is the gold standard
  - Occasionally will see >20% blasts in the peripheral blood, or an increase in peripheral blood blasts or the appearance of peripheral blood blasts
- Changing blood counts
  - Worsened anemia, decreased platelets and/or white blood cells
  - Increasing white blood cell count
- Symptoms
  - Worsened fatigue, bruising, bleeding or infections
  - None

How Likely is MDS to Progress to AML? IPSS-R

Parameter	Categories and Associated Scores				
Cytogenetic ris	Very good	Good	Intermediate	Poor	Very Poor
Mar pr					
Her					
Plat (x					
Abs. neutrophil count (x 10^9/L)	≥0.8	<0.8			
	0	0.5			

IPSS-R: Prognostic Risk Category Clinical Outcomes*

	No. pts	Very Low	Low	Intermediate	High	Very High
Patients (%)	7012	19%	38%	20%	13%	10%
Survival***		8.8	5.3	3.0	1.6	0.8
AML/25%***,^		NR	10.8	3.2	1.4	0.7

https://www.mds-foundation.org/ipss-r-calculator/

“Secondary AML” is AML from MDS

- ~25-30% of all AML patients
- More likely to be older
- More likely to resist treatment or relapse after a response
- Historically, prognosis has been poor
- Worse outcomes compared to “de novo” AML

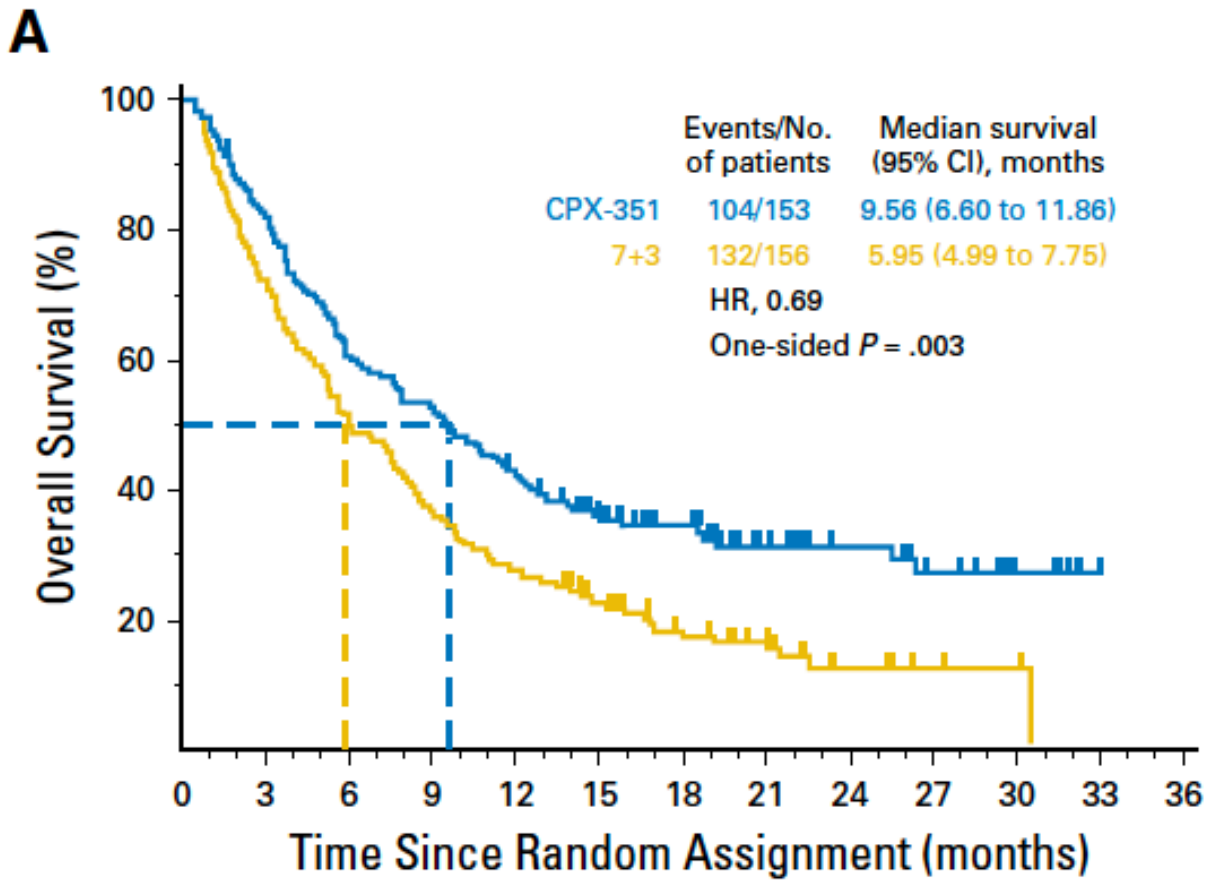
Oliai et al, BJH 2020

Treatment Options

- Intensive approaches
  - Induction chemotherapy
  - CPX-351
- Less-intensive approaches
  - Hypomethylating agents
  - Genomically-targeted therapies
  - Non-genomically targeted therapies
- Allogeneic stem cell transplantation

Intensive Chemotherapy

- "7+3" and similar regimens
  - Only for candidates likely to tolerate this therapy
  - More likely to be refractory or to relapse after treatment
- Liposomal daunorubicin-cytarabine (CPX-351)
  - Better outcomes than 7+3
  - Survival ~9 months



Lancet et al, JCO 2018

Hypomethylating Agents

- Azacitidine or decitabine*
  - Remission rate 18-28%
  - Remission duration ~10 months
  - Takes 4-6 months to know if effective
  - Well tolerated
  - Overall survival 8-10 months

Dombret et al, Blood 2015
Kantarjian et al, JCO 2012

*For all AML, not just secondary, so assume outcomes for secondary AML are worse than shown here

Genomically-Targeted Therapies

FLT3

- No approved FLT3 inhibitors for newly diagnosed AML patients who are not getting intensive induction chemotherapy
- Use midostaurin with induction chemotherapy if FLT3+ and suitable for induction
- FLT3 incidence is low in secondary AML

Stone et al, NEJM 2017

IDH

- IDH1 inhibitor ivosidenib approved as a single agent for IDH1+ newly diagnosed AML patients
- IDH2 inhibitor enasidenib not approved but has equivalent efficacy
- 20% incidence in AML in general; much lower in secondary AML

Roboz et al, Blood 2020
Pollyea et al, Leukemia 2019

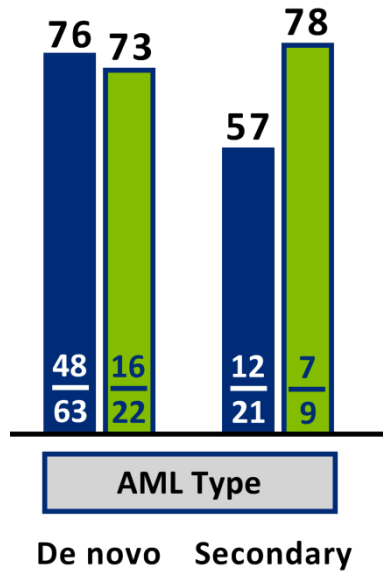
Non-Genomically Targeted Therapy #1: Glasdegib

- Inhibitor of the Hedgehog signaling pathway
- Oral, combine with low-dose cytarabine
- In newly diagnosed AML patients deemed poor candidates for intensive induction chemotherapy, overall survival was about 8 months
- Responses not broken down according to secondary vs de novo AML

Cortes et al, Leukemia 2018

Non-Genomically Targeted Therapy #2: Venetoclax

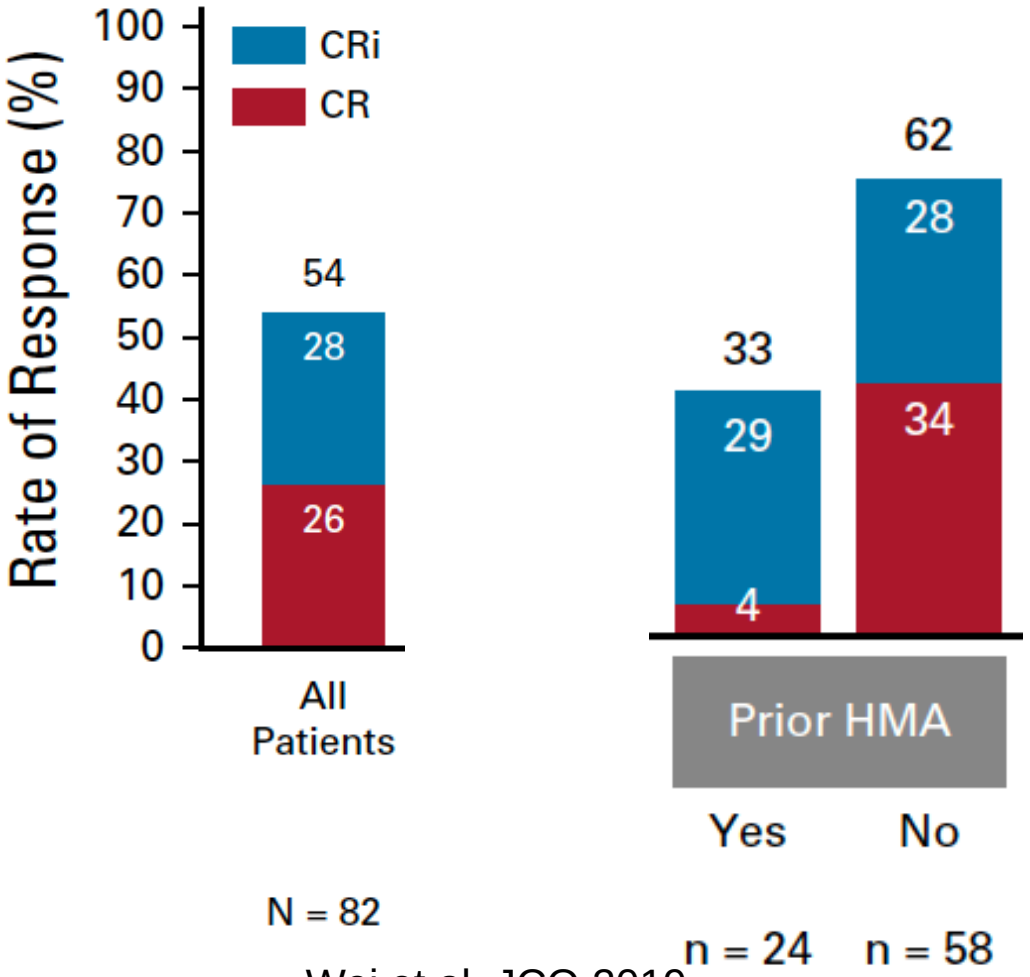
- Inhibitor of the protein BCL-2
- High response rates (~70%) when combined with azactidine/decitabine in newly diagnosed AML
- Overall survival ~16 months



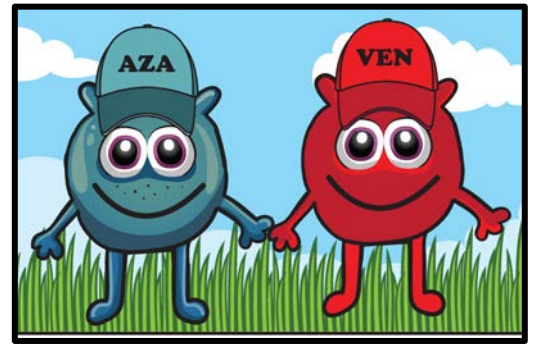
DiNardo et al, Blood 2019

Pollyea et al, ASH 2018

Accounting for the Impact of a Prior Therapy for MDS on Venetoclax Response



Wei et al, JCO 2019



Prior hypomethylating agent associated with worse response rates

Winters et al, Blood Advances, 2019

Allogeneic Stem Cell Transplantation

- The only potentially curative option
- Improves outcomes compared to those who do not get a transplant (but complicated by bias)
- However, ~30% likely die from a transplant related complication

Oliai et al, BJH 2020

Conclusions

- MDS can evolve to AML
  - This outcome is not within the control of any individual
  - Requires a bone marrow biopsy to confirm
- Predictive scores can help assess risk of this occurring
- Historical outcomes have been poor
  - Now more therapeutic options
  - Lots of optimism for improvement


Thank You!