Treatment of Higher Risk MDS

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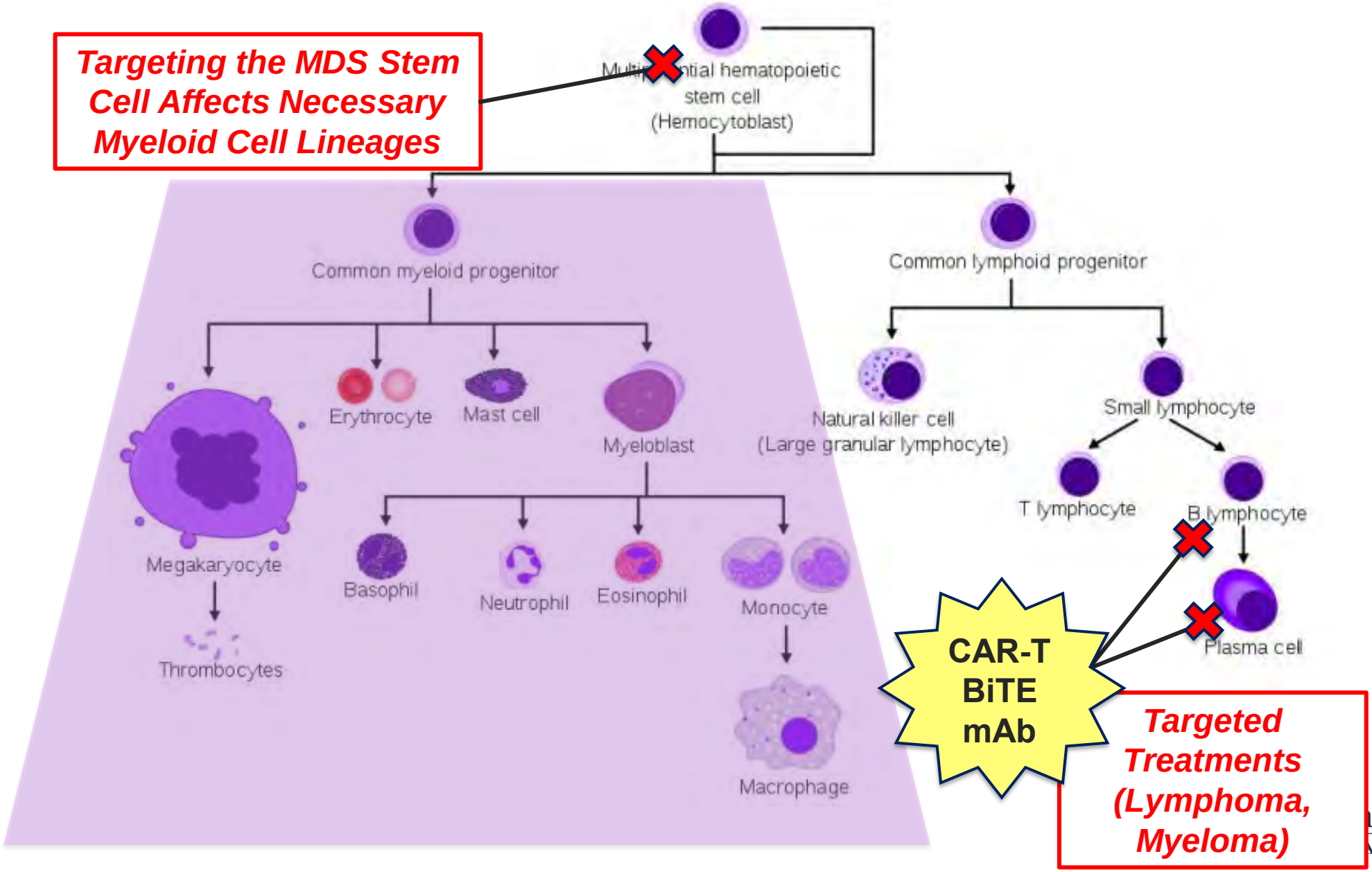
Normal Blood Cell Production



A. Rad and M. Haggstrom (StatPearls Publishing LLC)

Overview

- **Which patients have “Higher Risk MDS”?**

- **Standard MDS Therapy**
  - Hypomethylating Agents (HMAs) – Azacitidine and Decitabine
  - Allogeneic Stem Cell Transplant
  - IDH1 inhibitor – Ivosidenib

- **Investigational MDS Therapy**
  - HMA with Venetoclax
  - HMA with Tamibarotene

Standard MDS Therapy

Approved MDS Therapies

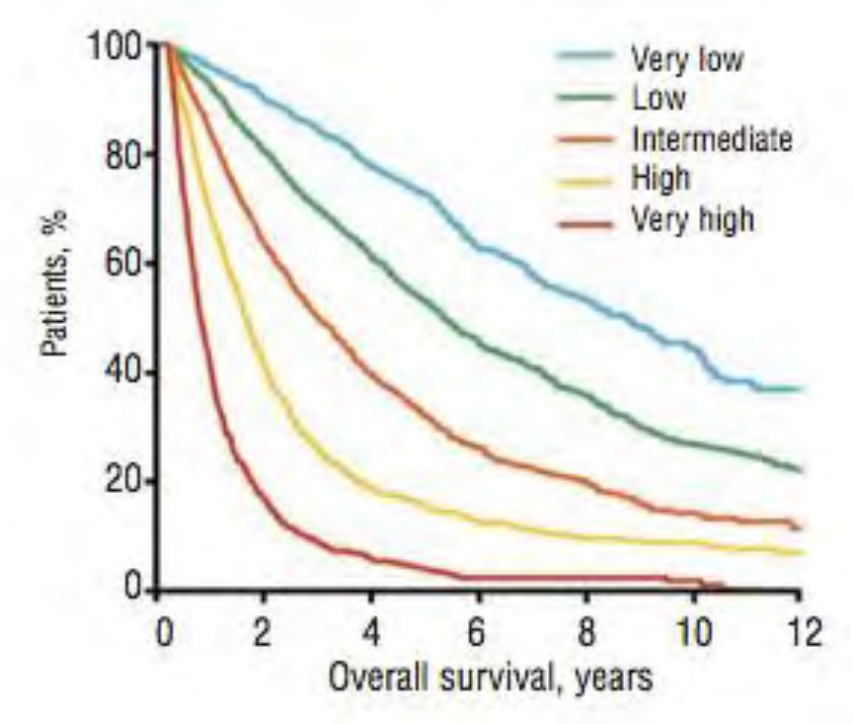
Lower Risk MDS

- Erythropoiesis Stimulating Agents (ESA)
- Lenalidomide
- Luspatercept
- Imetelstat
- Ivosidenib
- Hypoplastic MDS: Immunosuppressive Therapy (IST)*

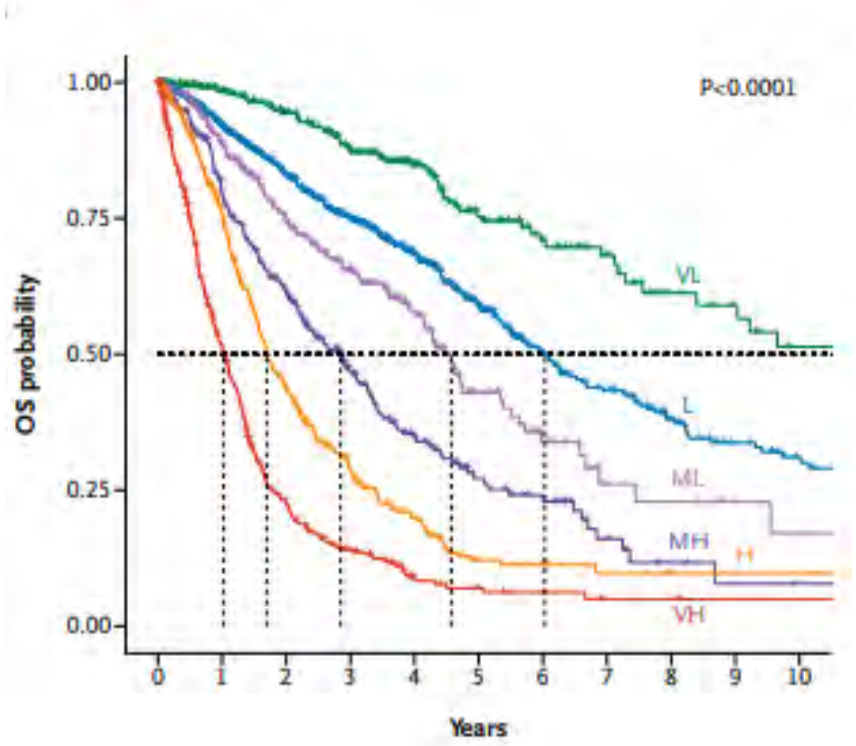
Higher Risk MDS

- Hypomethylating Agents (HMAs)
  - Azacitidine (IV or SQ)
  - Decitabine (IV) and Decitabine/Cedazuridine (pill)
- Hematopoietic Stem Cell Transplantation
- Ivosidenib

Which Patients Have Higher Risk MDS?



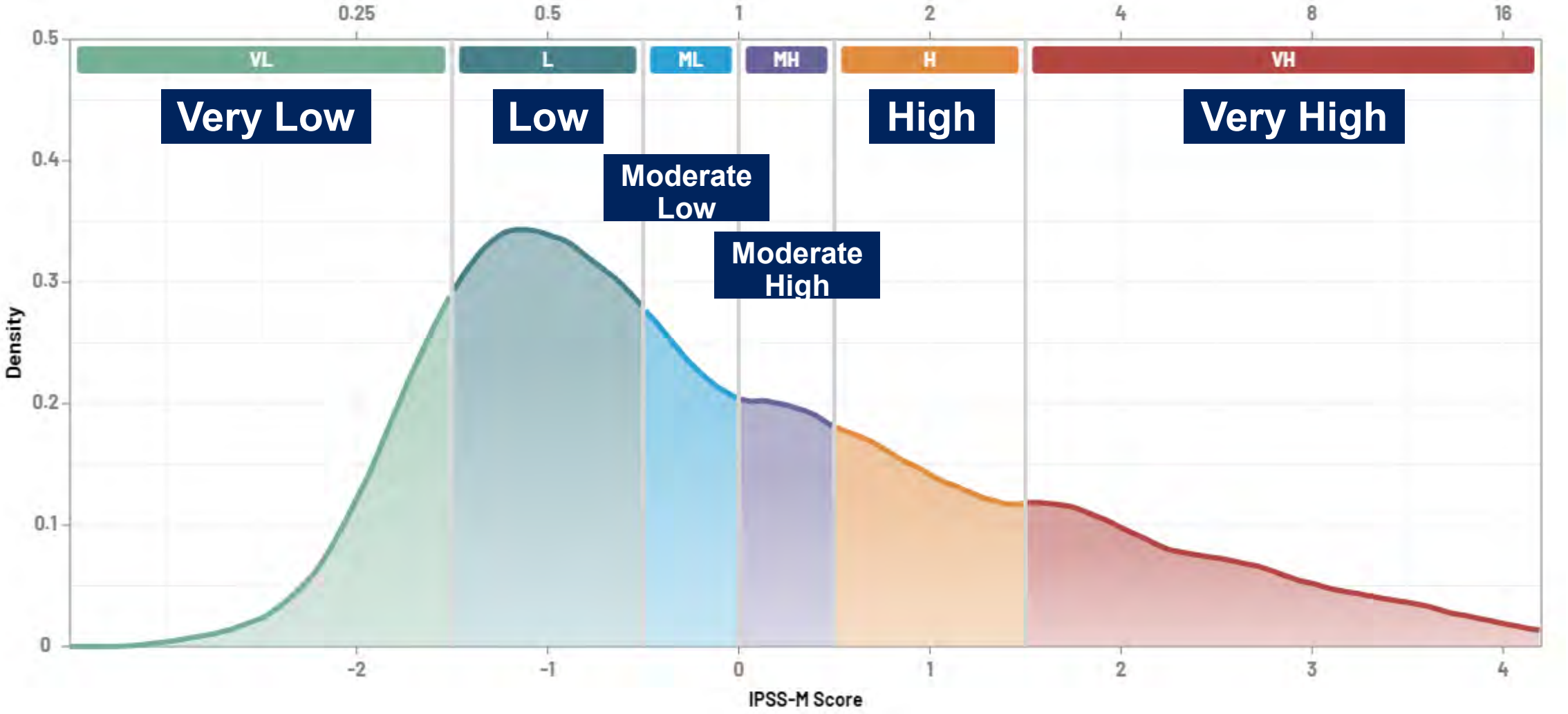
IPSS-R:
Intermediate Risk
High Risk
Very High Risk



IPSS-M:
Moderate High Risk
High Risk
Very High Risk

Greenberg *Blood* 2012, Bernard *NEJM Evidence* 2022

IPSS-M Calculator to Determine MDS Risk



mds-risk-model.com

1. Clinical

*Bone Marrow Blasts

Percentage: 7 [0-30%]

*Hemoglobin

g/dL | Change: 8.5 [4-20 g/dL]

*Platelet Count

1e9/L: 120 [0-2000 1e9/L]

OPTIONAL IPSS-R DATA

Absolute Neutrophil Count

1e9/L: 1.2 [0-15 1e9/L]

Age

Years: 50 [18-120 years]

2. Cytogenetics

*Presence of

del(5q)	**No**	Yes
-7/del(7q)	**No**	Yes
-17/del(17p)	**No**	Yes
Complex Karyoptype	**No**	Yes

*Cytogenetics Category

○ Very Good	-Y, del(11q).
● Good	Normal, del(5q), del(12p), del(20q), double including del(5q).
○ Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones.
○ Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities.
○ Very Poor	Complex: > 3 abnormalities

3. Genetics

*Number of TP53 mutations

Mutation Count	**0**	1	2+

*Loss of heterozygosity at TP53 locus (if known)

TP53 LOH	No	Yes	**N/A**

*MLL (KMT2A) and FLT3 Mutations

MLL PTD	**No**	Yes	Not Assessed
FLT3 ITD or TKD	**No**	Yes	Not Assessed

*Genes (individual weights)

ASXL1	**Non-mutated**	Mutated	Not Assessed
CBL	**Non-mutated**	Mutated	Not Assessed
DNMT3A	**Non-mutated**	Mutated	Not Assessed
ETV6	**Non-mutated**	Mutated	Not Assessed
EZH2	**Non-mutated**	Mutated	Not Assessed
IDH2	**Non-mutated**	Mutated	Not Assessed
KRAS	**Non-mutated**	Mutated	Not Assessed
NPM1	**Non-mutated**	Mutated	Not Assessed
NRAS	Non-mutated	**Mutated**	Not Assessed
RUNX1	**Non-mutated**	Mutated	Not Assessed
SF3B1	Non-mutated	**Mutated**	Not Assessed
SRSF2	**Non-mutated**	Mutated	Not Assessed
U2AF1	**Non-mutated**	Mutated	Not Assessed

*Genes (number of residual mutations)

BCOR	**Non-mutated**	Mutated	Not Assessed
BCORL1	**Non-mutated**	Mutated	Not Assessed
CEBPA	**Non-mutated**	Mutated	Not Assessed
ETNK1	**Non-mutated**	Mutated	Not Assessed
GATA2	**Non-mutated**	Mutated	Not Assessed
GNB1	**Non-mutated**	Mutated	Not Assessed
IDH1	**Non-mutated**	Mutated	Not Assessed
NF1	**Non-mutated**	Mutated	Not Assessed
PHF6	**Non-mutated**	Mutated	Not Assessed
PPM1D	**Non-mutated**	Mutated	Not Assessed
PRPF8	**Non-mutated**	Mutated	Not Assessed
PTPN11	**Non-mutated**	Mutated	Not Assessed
SETBP1	**Non-mutated**	Mutated	Not Assessed
STAG2	**Non-mutated**	Mutated	Not Assessed
WT1	**Non-mutated**	Mutated	Not Assessed

Calculate Risk

IPSS-M Results (MDS Risk, ie. Stage)

STRATIFICATION RESULTS

IPSS-M Score:
0.40 MODERATE HIGH

IPSS-R Score:
4.00 INT

IPSS-R Score (Age-adjusted):
3.40 INT

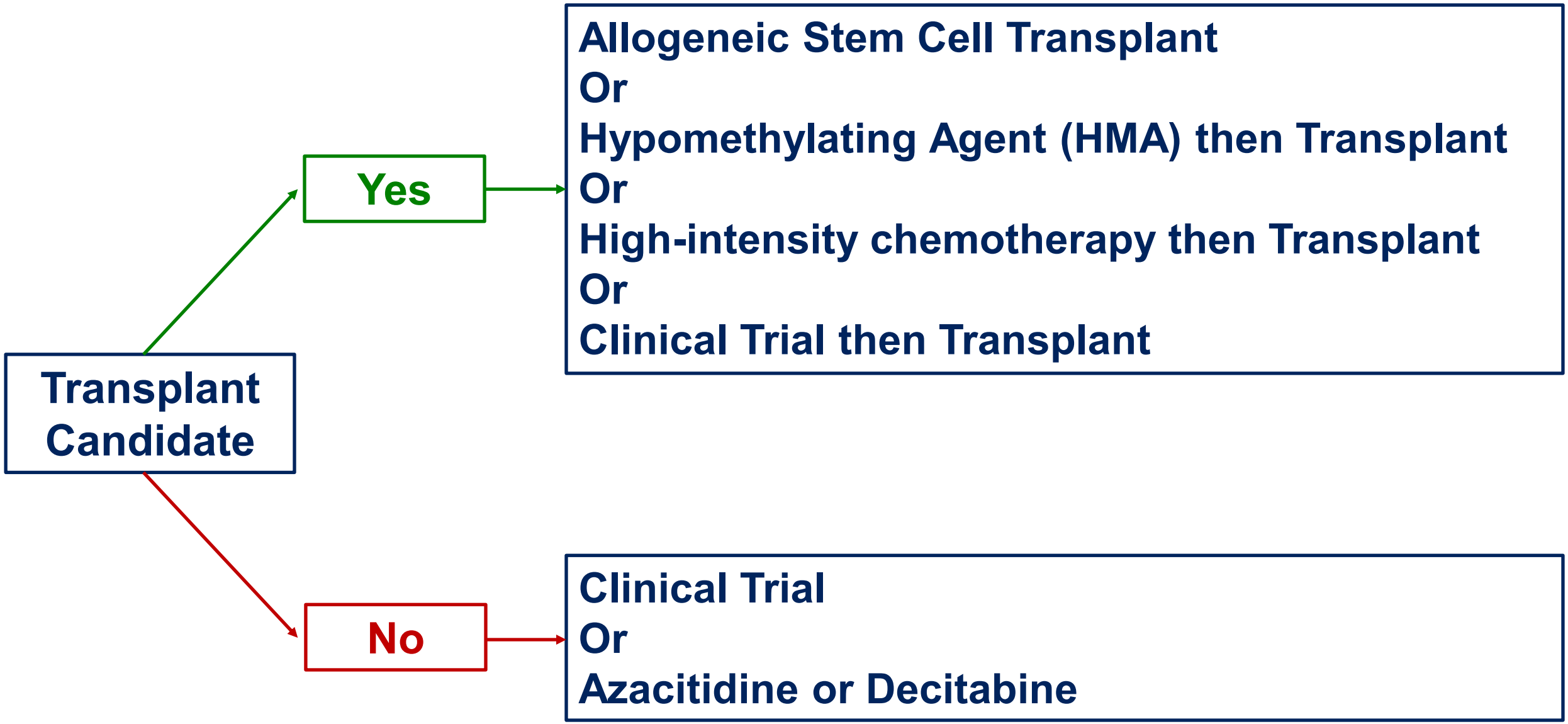
ENDPOINTS

Leukemia-Free Survival (IPSS-M):
2.3 years median
0.91-4.7 years, 25%-75% range

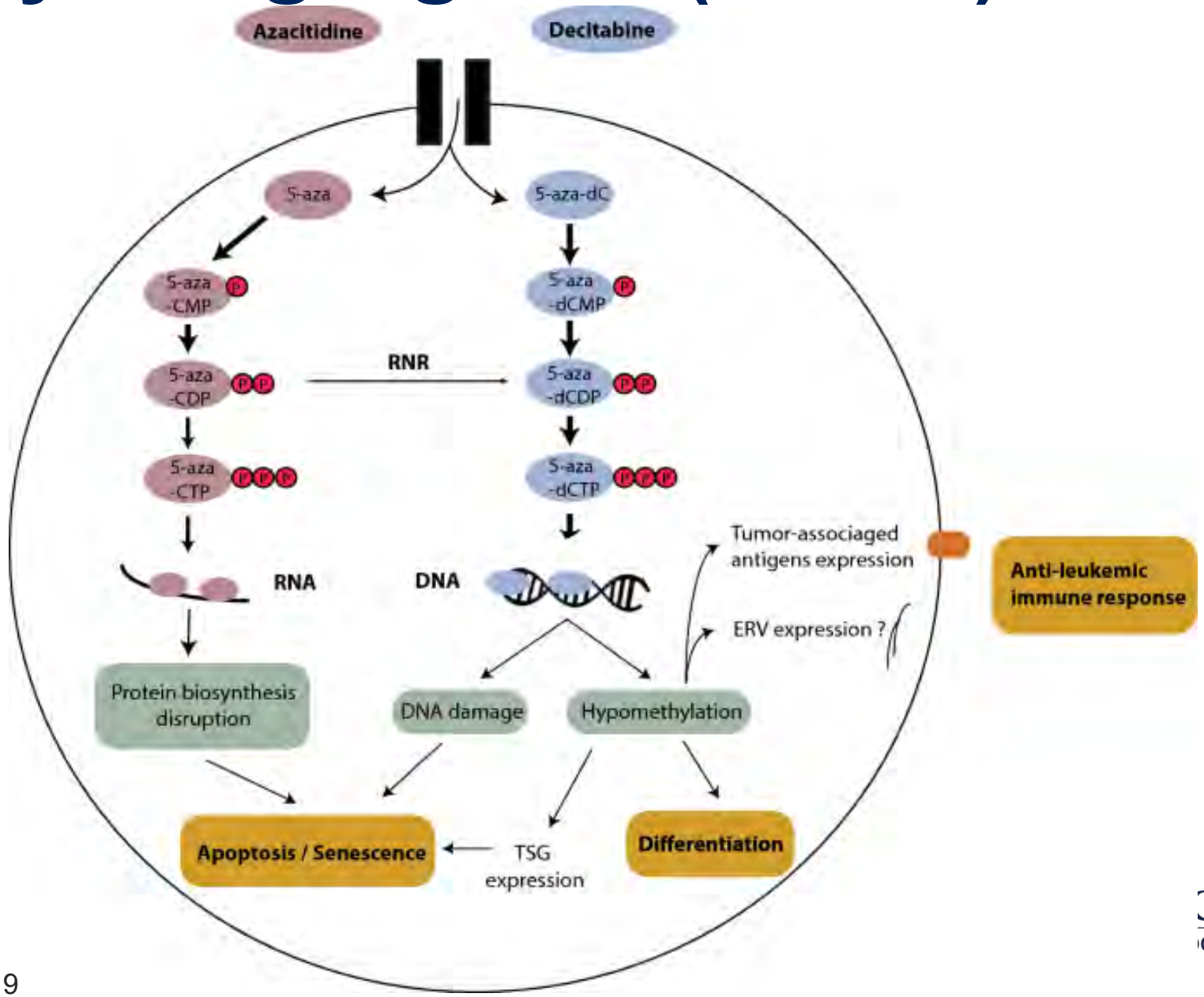
Overall Survival (IPSS-M):
2.8 years median
1.2-5.5 years, 25%-75% range

AML Transformation (IPSS-M):
9.5% by 1 year
18.9% by 4 years

Treatment of Higher Risk MDS



Hypomethylating Agents (HMAs)



Duchmann et al. *Int J Hematol* 2019

Hypomethylating Agents (HMAs)

- Azacitidine (FDA approved 2004)
  - 75 mg/m2 daily, days 1-7
  - 10-40 minute IV infusion or subcutaneous injection
  - Cycles are every 28 days

- Decitabine (FDA approved 2006)
  - 20 mg/m2 daily, days 1-5
  - One hour IV infusion
  - Cycles are every 28 days

- Decitabine/Cedazuridine (FDA approved 2020)
  - 35 mg/100 mg daily, days 1-5
  - Oral pill
  - Cycles are every 28 days

Hypomethylating Agents (HMAs)

- May improve blood count levels, reduce transfusions, improve quality of life, lengthen survival
- **Not a cure**
- 40-50% of patients benefit, slow responses in most (peak benefit after 4-6 months of treatment)
- No testing available to predict which patients will benefit
  - Cytotoxic?
  - Epigenetic?
  - Immune modulating?

How Do We Measure "Response"?

International Working Group (IWG) Criteria

Category	Response Criteria
Complete Remission (CR)	Responder (Clinical Benefit)
Partial Remission (PR)	
Hematologic Improvement (HI)	
Stable Disease	Non-Responder (No Clinical Benefit)
Disease Progression	

- **Exact IWG Response measured in clinical trials**
  - In practice, can usually gauge response by monitoring blood count trends
  - If response is unclear, then pursue bone marrow biopsy

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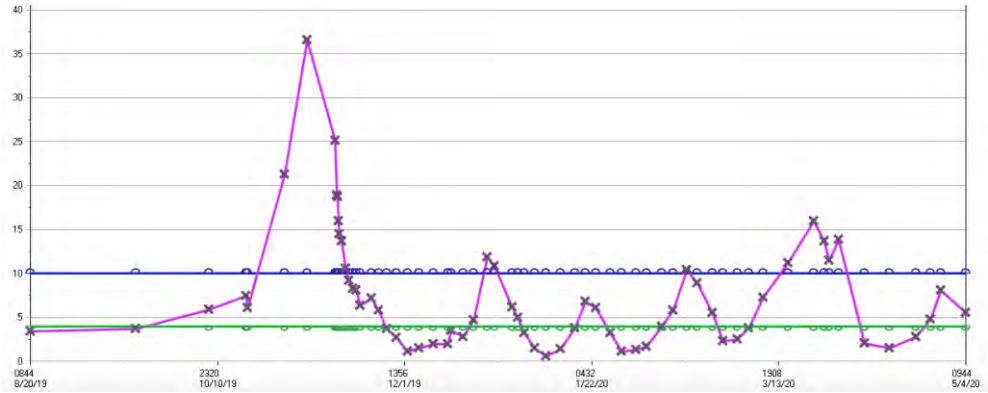
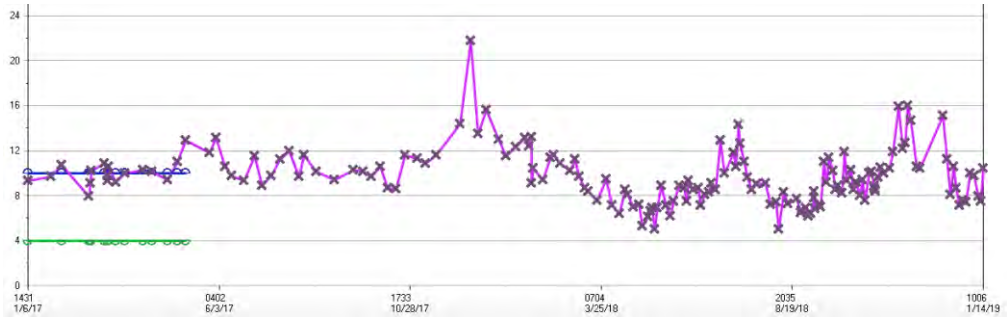
Cheson et al. *Blood* 2006

HMA Responder

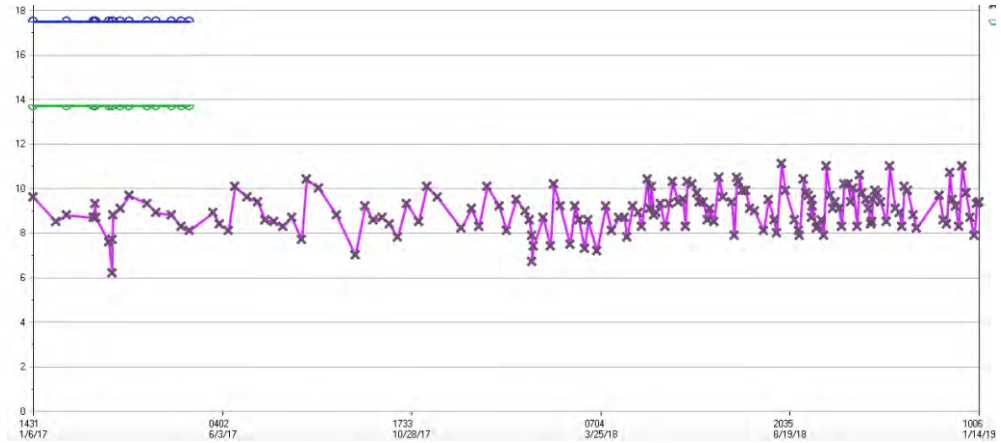
HMA Non-Responder

White Blood Cell (WBC)

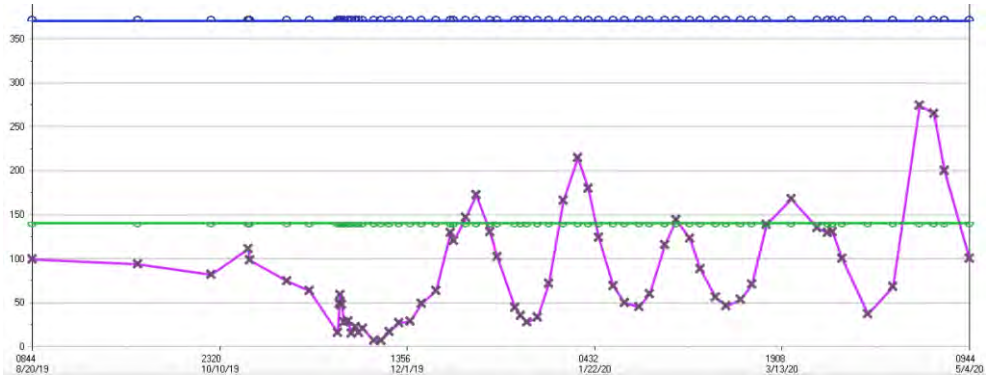




Hemoglobin (Hgb)



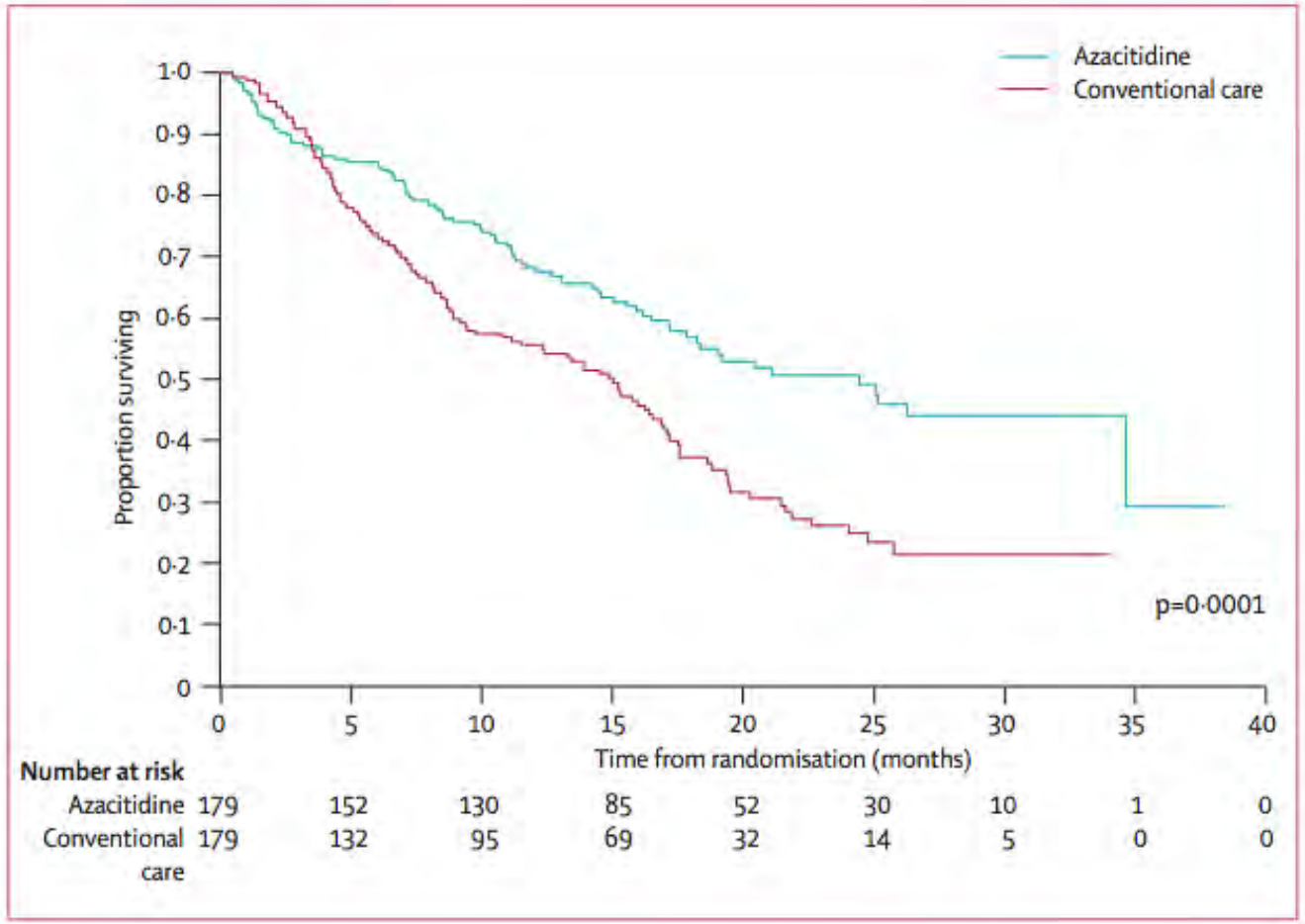
Platelet (Plt)



Azacitidine

AZA-001 Phase 3 Trial

- 358 patients with higher risk MDS
- Randomized to azacitidine vs. best conventional care
- Median overall survival
  - Azacitidine: 24.5 months
  - Conventional care: 15 months



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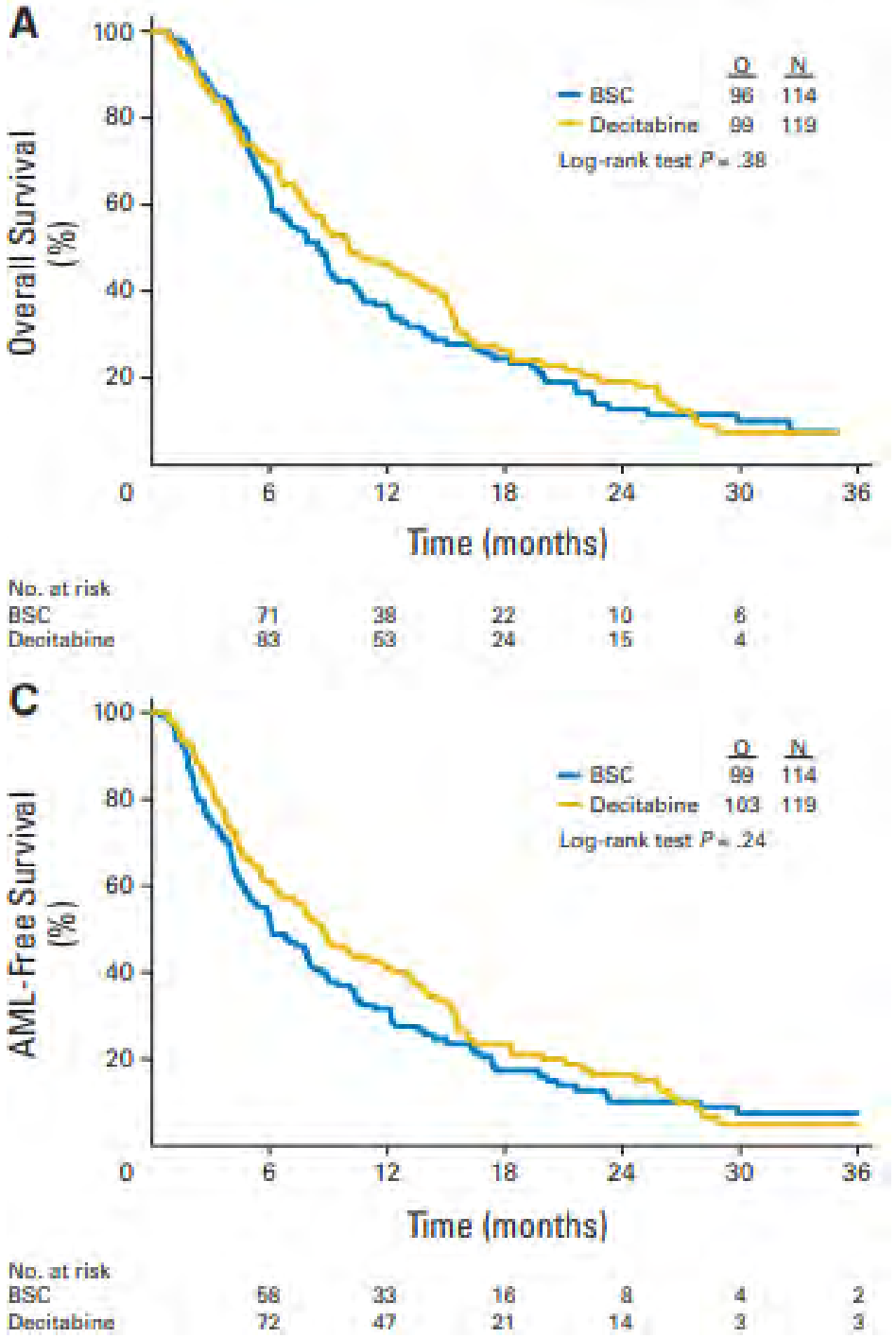
Fenaux et al. *Lancet Oncol* 2009

Decitabine

Phase 3 Trial, European Leukemia and German MDS Groups

- 270 patients with higher risk MDS
- Randomized to decitabine vs. best supportive care
- Median overall survival
  - Decitabine: 10.1 months
  - Supportive care: 8.5 months



Lubbert et al. *J Clin Oncol* 2011

Hypomethylating Agents (HMAs)

- No head-to-head comparison between azacitidine and decitabine
- Both HMAs are generally well tolerated, including in older patients
  - Common side effects (>10%): **low blood counts (bleeding, infection, fatigue, transfusion need)**, low appetite, constipation, nausea, rash, muscle or joint aches, injection site reaction/pain
  - Rare side effects: pneumonitis, hypersensitivity
- Patients who do not improve on HMAs ("refractory"):
  - 2-year survival rate 15%
  - Median survival 5.6 months

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Prebet et al. *J Clin Oncol* 2011

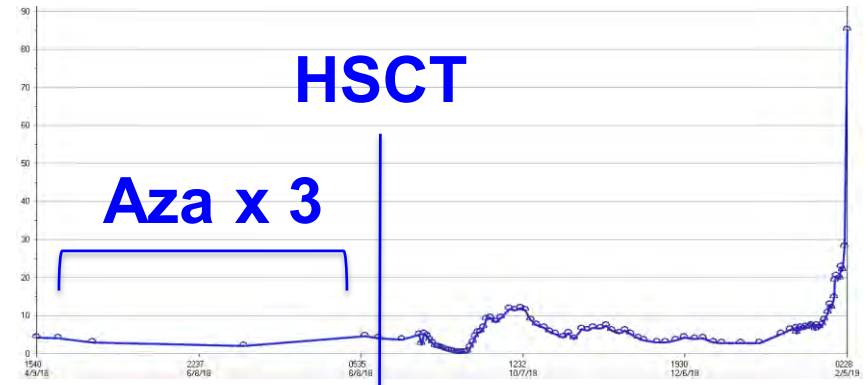
HMA Responder, but AML after transplant

AML

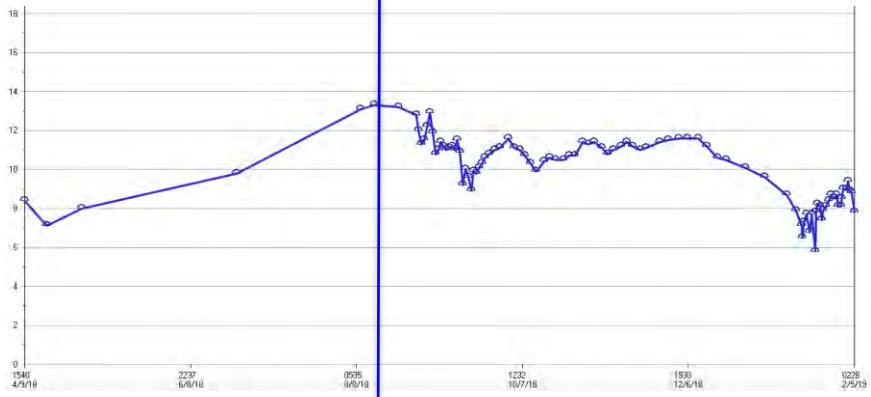
WBC

HSCT

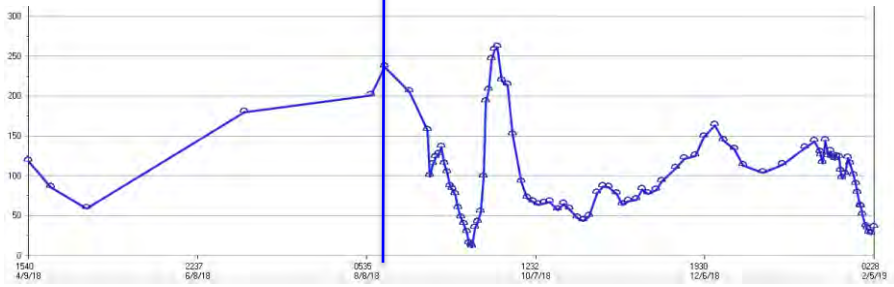
Aza x 3



Hgb



Plt



Pre-HMA

Summary of Genomic Alterations Detected:

Clinically significant variants detected:

Gene/ Transcript	Coding Variant	Protein Change	Variant Allele Fraction	Therapies approved in indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
NRAS NM_002524	c.37G>T	p.G13C	23%	None	Yes	No	Yes
SF3B1 NM_012433	c.1873C>T	p.R625C	30%	None	None	No	Yes

Post-HMA

Summary of Genomic Alterations Detected:

No clinically significant somatic variants were detected in the genomic regions interrogated.

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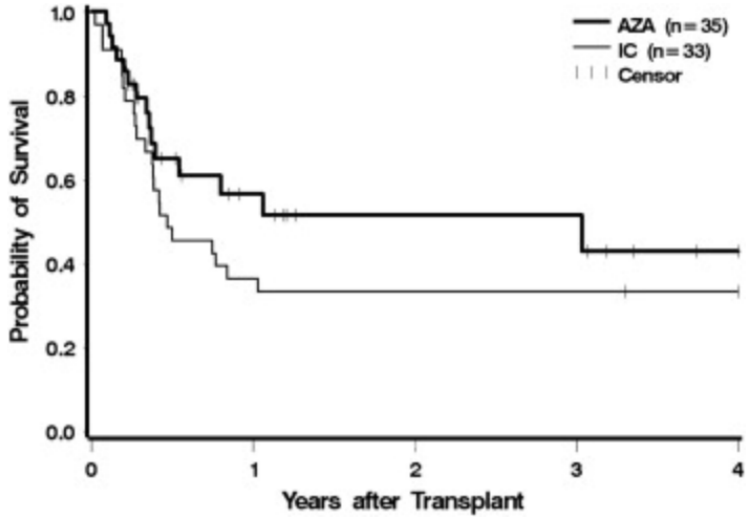
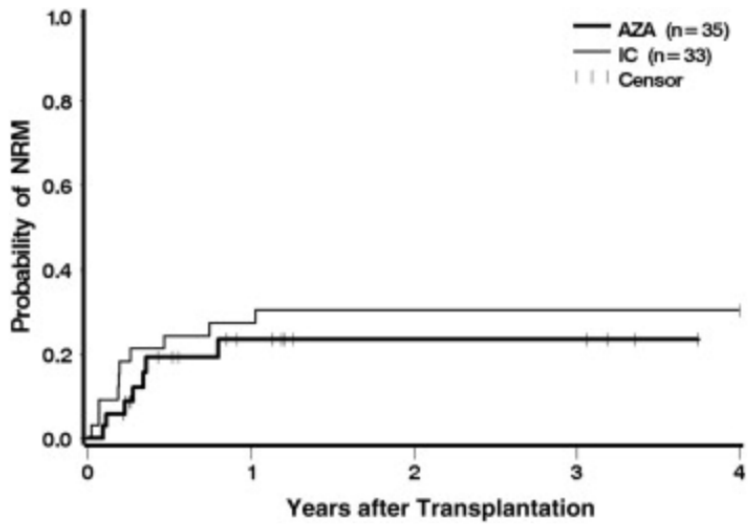
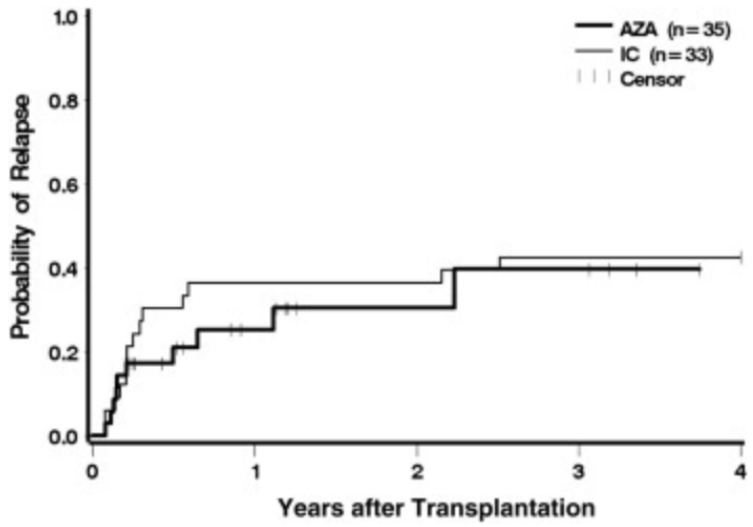
Pre-Transplant Therapy

- **Unclear benefit – data is very limited**
- Retrospective study of 68 patients with MDS/AML who underwent transplant
  - 35 patients received Azacitidine
  - 33 patients received intensive chemo
  - 1-year survival 57% in the Aza group, 36% in the chemo group
- Differences in type of transplant, conditioning chemo before transplant







Gerds et al. *Biol Blood Marrow Transplant* 2012

Allogeneic Stem Cell Transplant

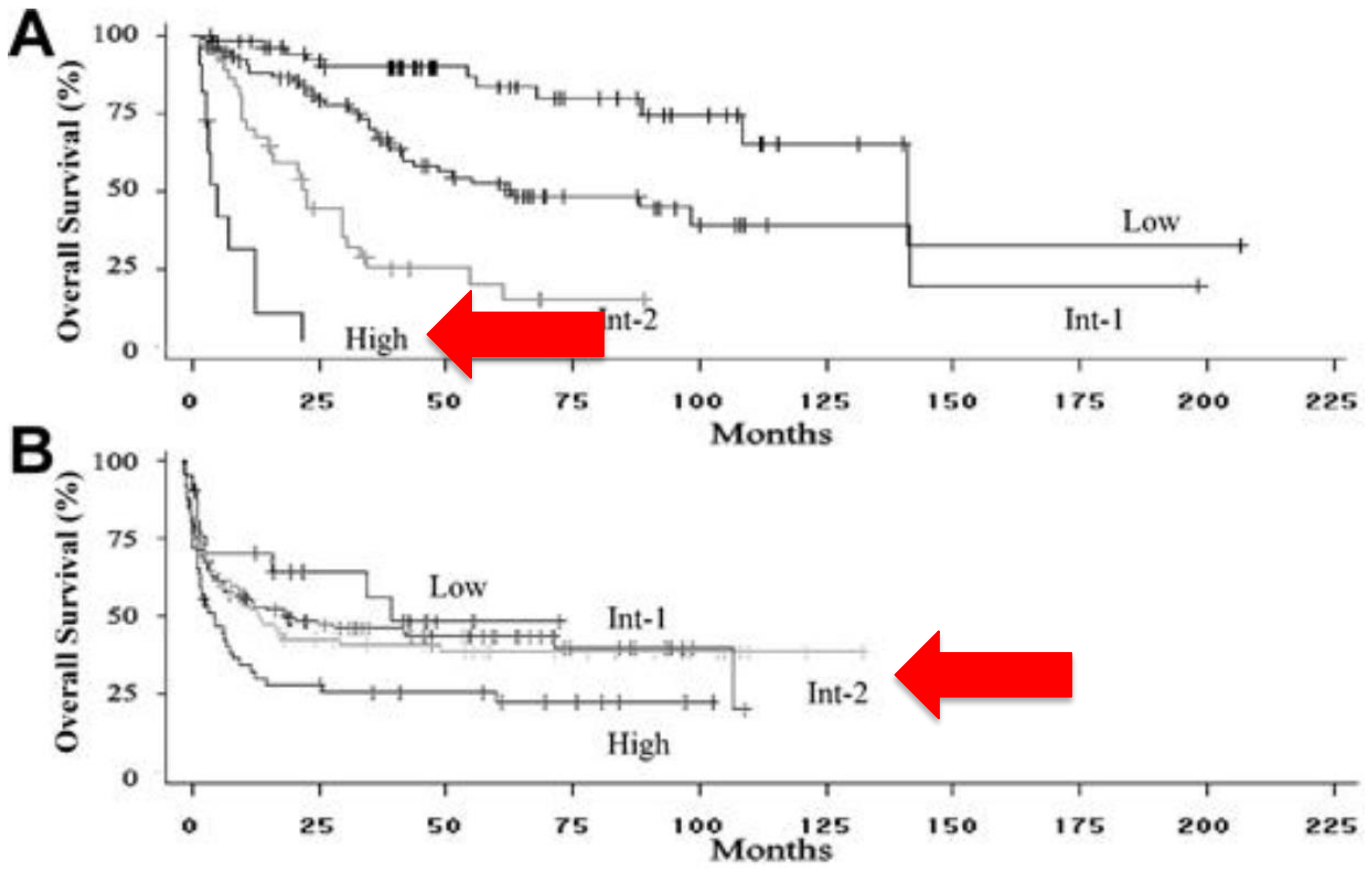
- Improved survival for higher-risk MDS – earlier is better
- Center for International Blood & Marrow Transplant Research (CIBMTR) Data

Overall survival of patients who did **not** undergo transplant

- Low: 12 years
- Int-1: 5.2 years
- Int-2: 1.9 years
- High: 0.4 year

Overall survival of patients who underwent transplant

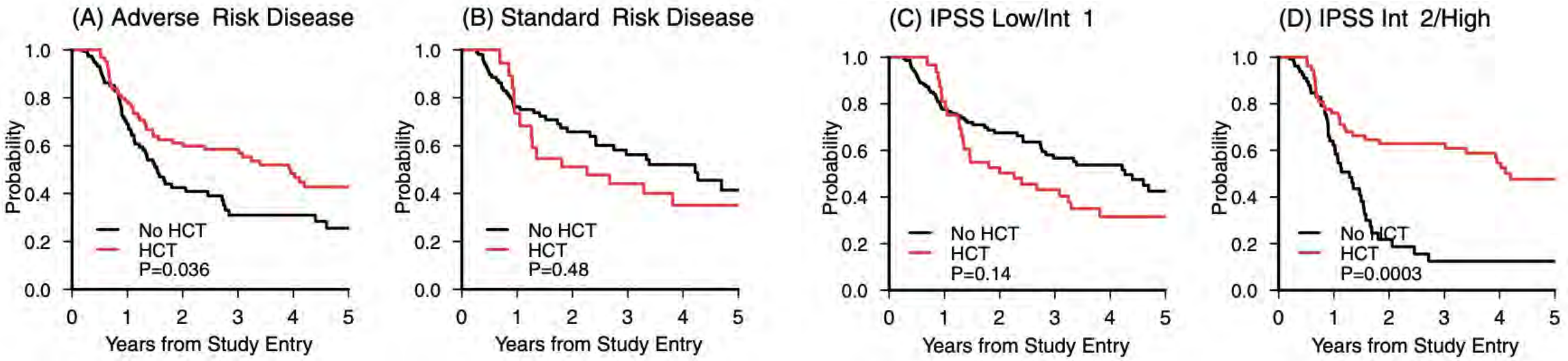
- Low: 3.3 years
- Int-1: 1.7 years
- Int-2: 1.2 years
- High: 0.5 year



Cutler et al. *Blood* 2004

Allogeneic Stem Cell Transplant

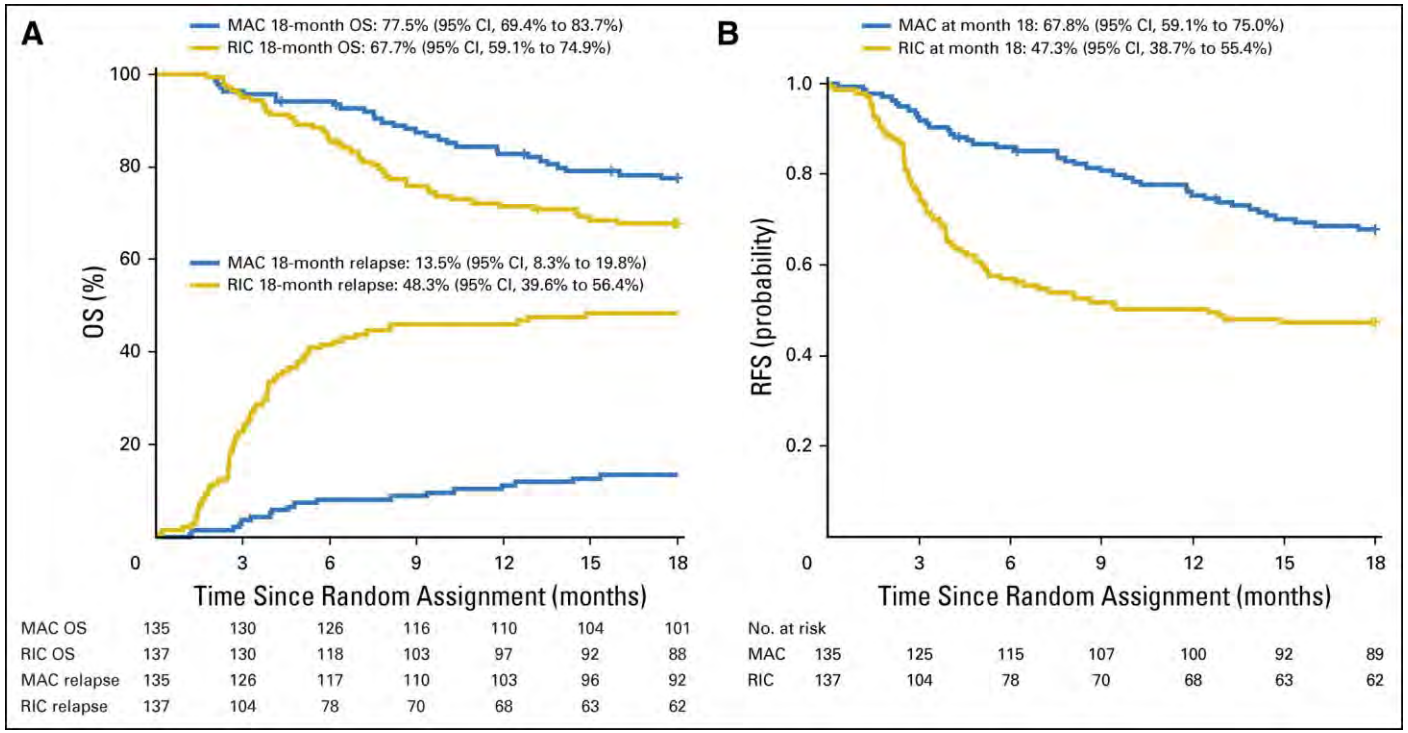
- Prospective study on 290 patients with higher risk MDS, ages 60-75
- 113 patients underwent transplant after median 5 months
- **Survival improved if transplant performed early for higher-risk MDS, but not for lower risk MDS (even if severe cytopenias present)**



Abel et al. *Leukemia* 2021

Transplant Outcomes

- Phase 3 Trial, Myeloablative (MA) vs. Reduced Intensity Conditioning (RIC)
- Patients with MDS and AML
- 18-month Overall Survival
  - MA: 77.5%
  - RIC: 67.7%
- **Transplant-Related Mortality**
  - **MA: 15.5%**
  - **RIC: 4.4%**
- Relapse Free Survival
  - MA: 67.8%
  - RIC: 47.3%



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Scott et al. *J Clin Oncol* 2017

Transplant Process

- Referral to Blood & Marrow Transplant (BMT) Physician
  - Determine likelihood of eligibility: Age ≤75 years, healthy, physically fit

- Transplant recipient process:
  - HLA typing of the patient (blood test)
  - Pre-transplant work-up of the patient
    - Echocardiogram, Pulmonary function testing, blood & urine tests
    - Social Work evaluation

- Transplant donor process:
  - HLA typing of 1st degree relatives (siblings, children, parents)
  - Matched unrelated donor (MUD) search
  - Donor selection by BMT committee
  - Donor evaluation by a separate BMT physician

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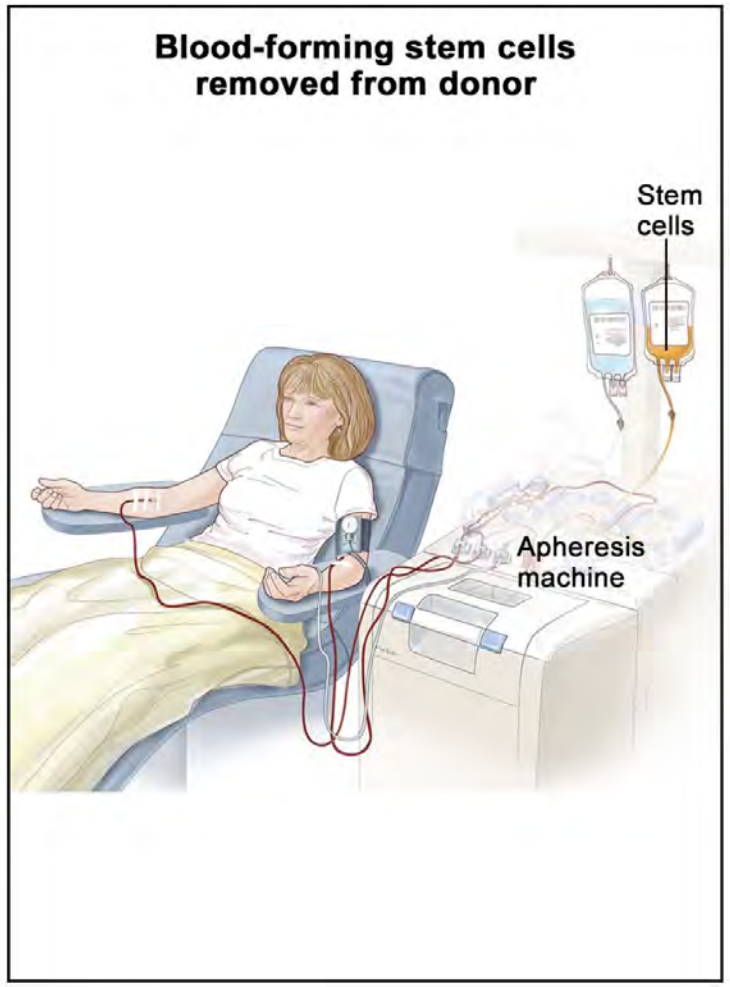
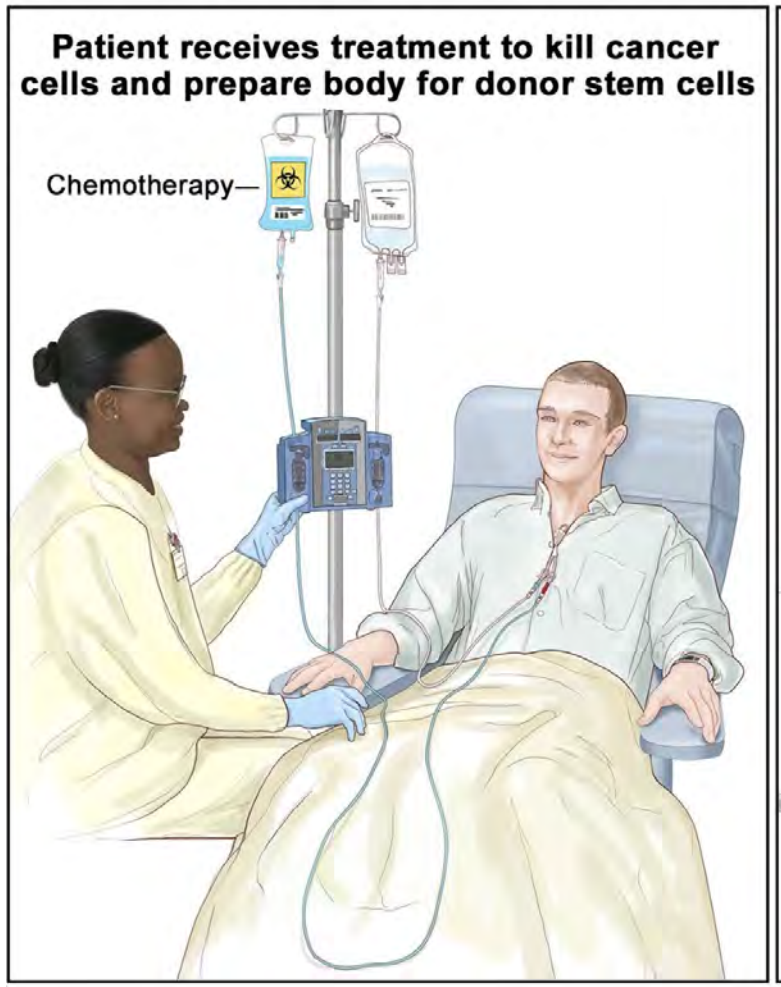
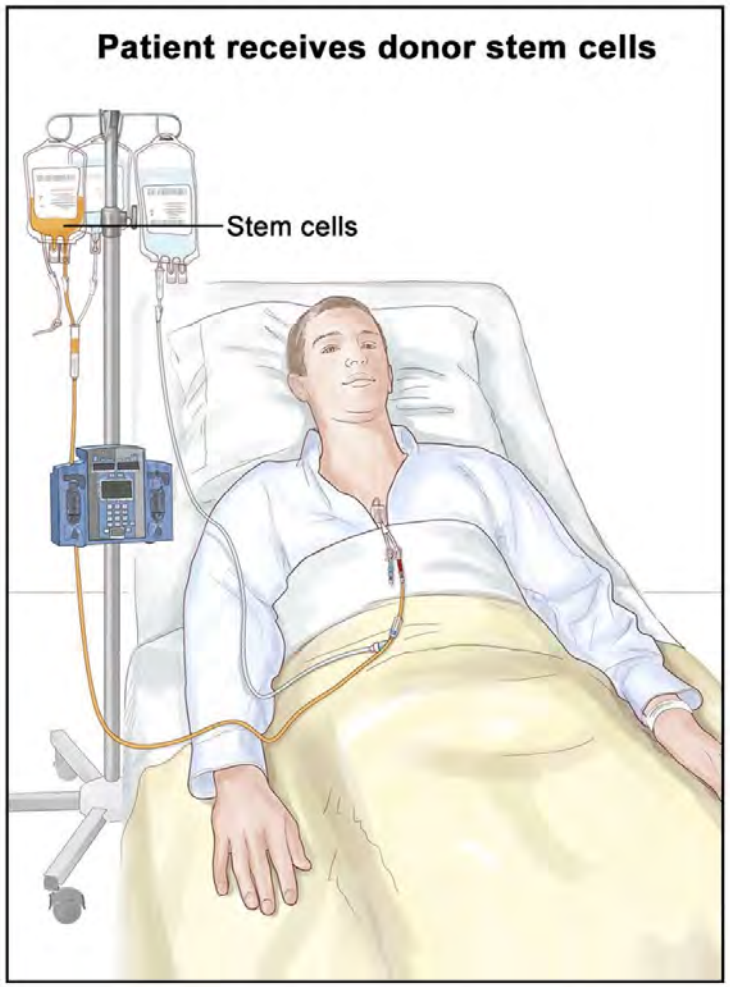
Transplant Process

DONOR



PATIENT





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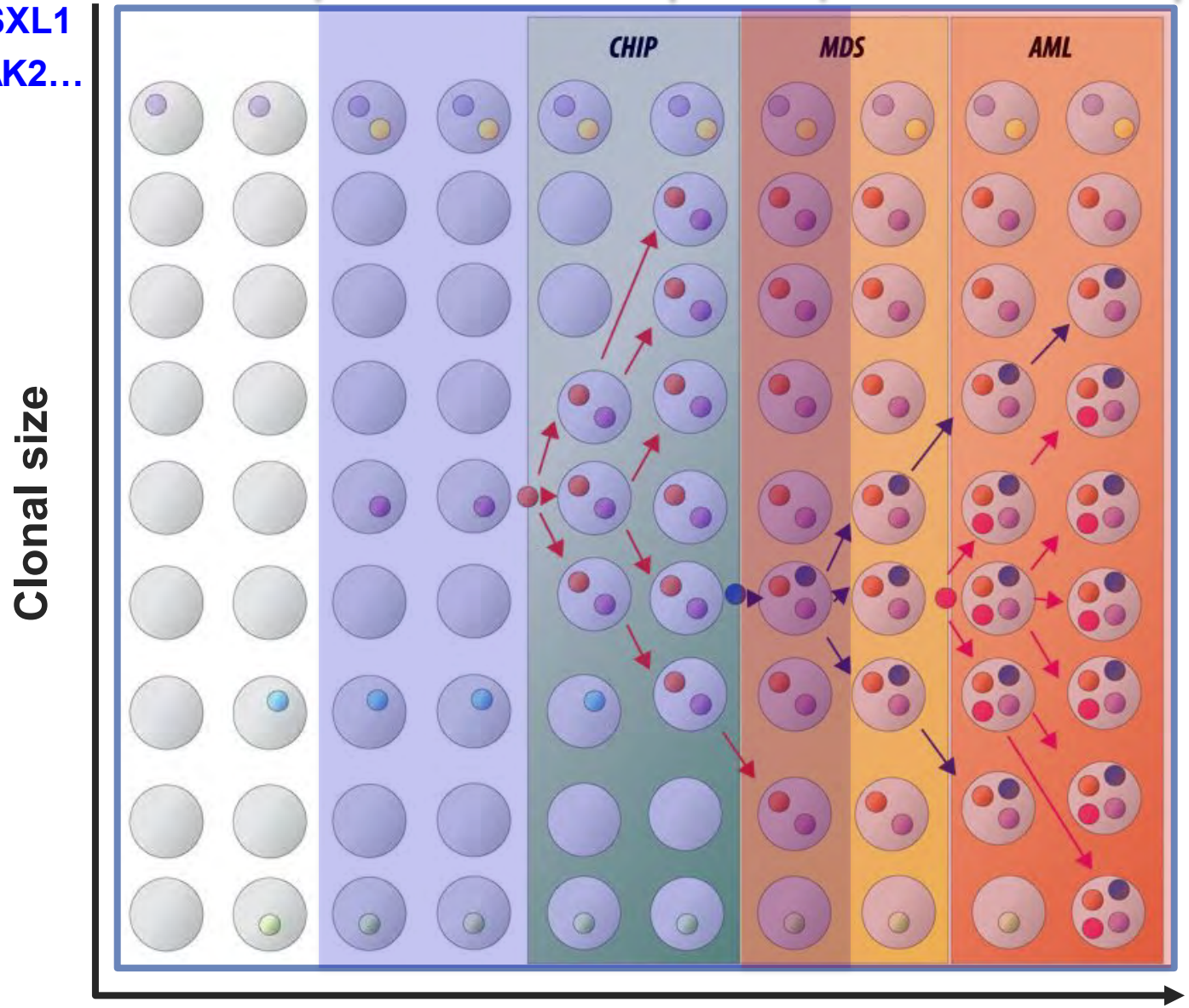
cancer.gov

TET2
DNMT3A
SF3B1
ASXL1
JAK2…

Early mutations that initiate clonal expansion

Cooperating mutations that lead to AML

IDH1, IDH2
FLT3
STAG2
RUNX1
NRAS…



Steensma *Blood* 2015

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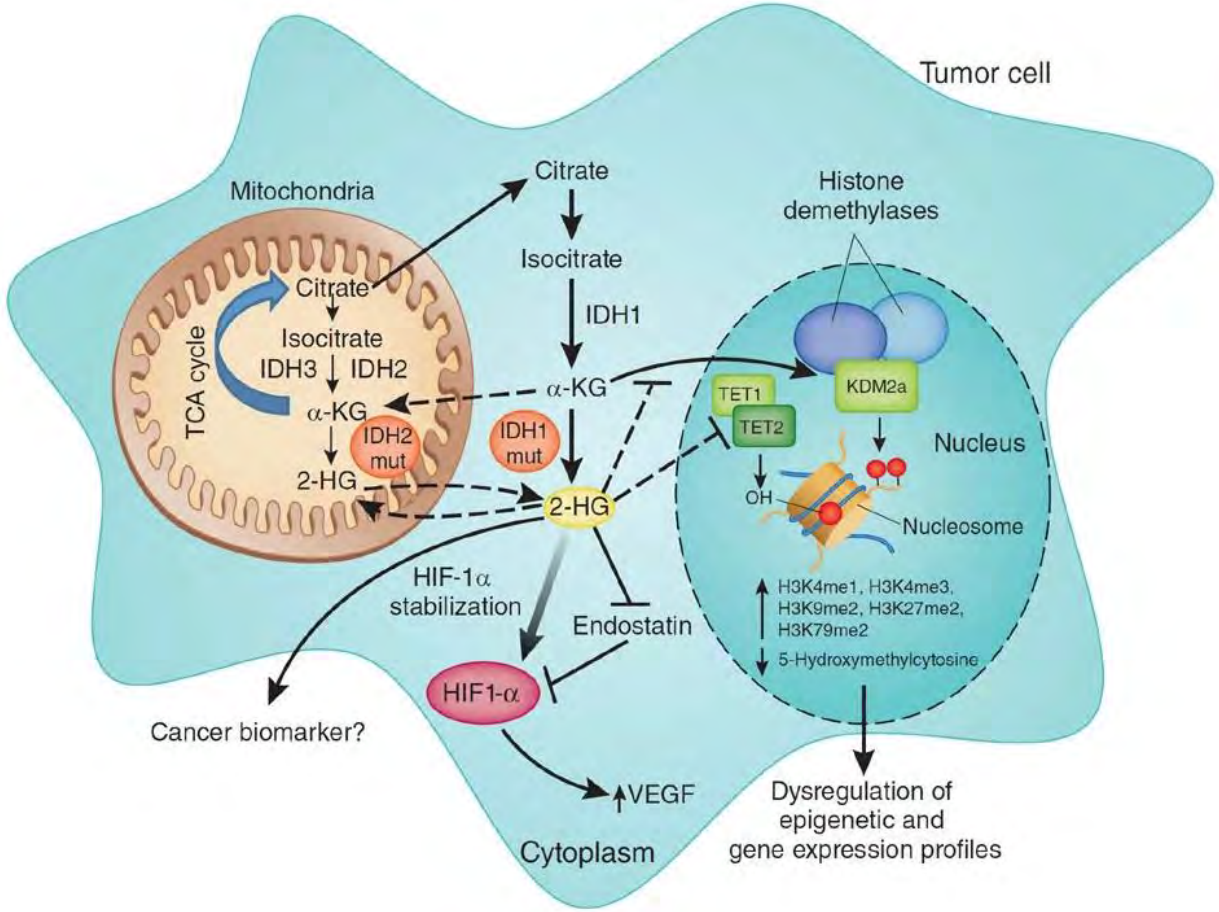
Ivosidenib

- Ivosidenib = IDH1 inhibitor, oral pill
- Approved by the FDA in 2023 for IDH1-mutated, relapsed/refractory MDS
- Phase I Trial, 18 patients
  - Overall response (benefit) rate 83%
  - Median survival 36 months
  - >70% transfusion independence
- Unique side effects
  - Differentiation syndrome
  - QTc prolongation (monitor EKG)



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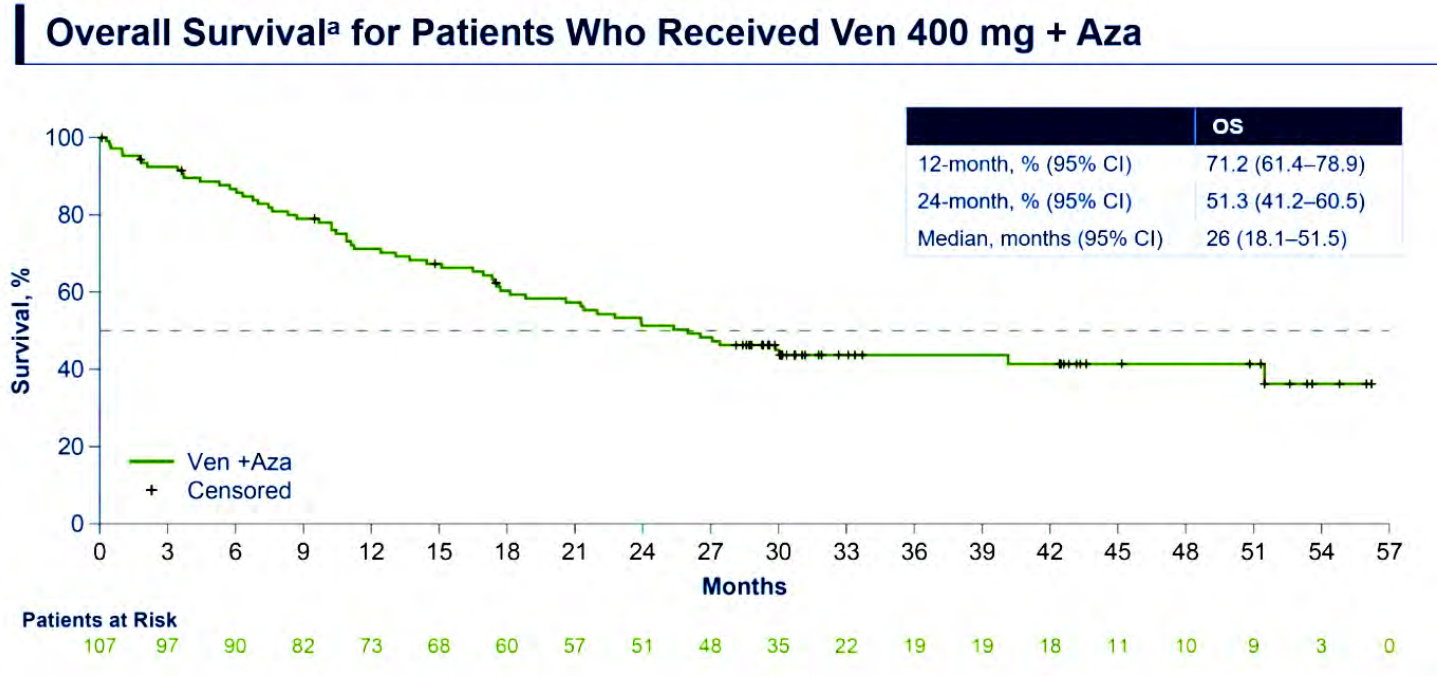
DiNardo et al. *Blood Adv* 2024

Investigational MDS Therapy

HMA + Venetoclax

- Venetoclax = BCL2 inhibitor, oral pill – effective in other blood cancers
- Phase 1b Trial, 107 newly diagnosed patients with higher-risk MDS
- Overall response (benefit) rate 80.4%, overall survival 26 months
- Median time to complete remission 2.8 months, duration 16.6 months

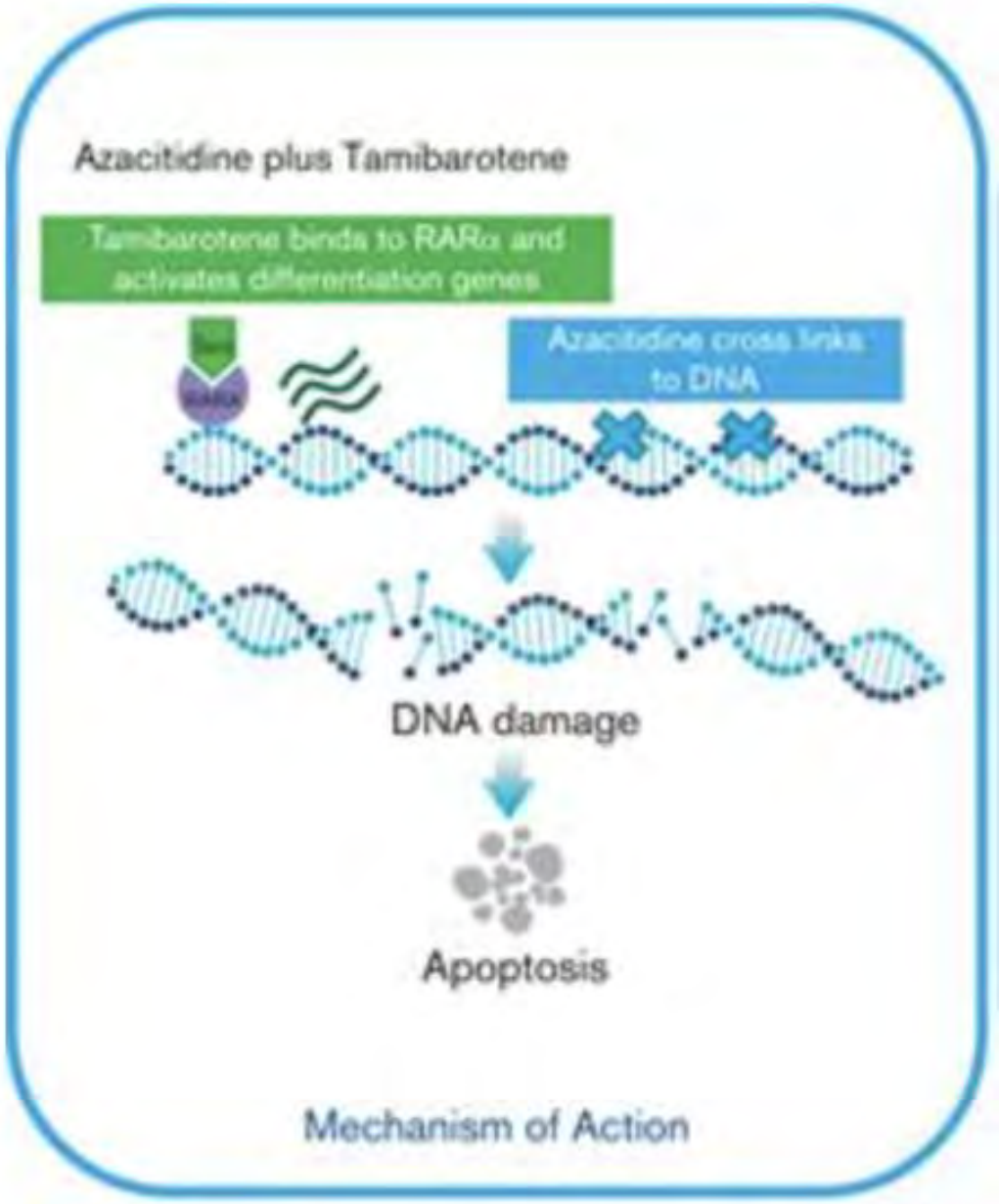
Results of the phase 3 VERONA trial (Aza/Ven vs. Aza/Placebo) *hopefully* available soon



Garcia et al. ASH 2023

Tamibarotene

- Tamibarotene = retinoid, oral pill – promotes cell differentiation
- Phase 2 Trial, 51 patients with newly diagnosed AML treated with Aza/Tami
  - CR rate 50%, time to CR 1.2 months, transfusion independence 72%
- Phase 3 SELCT MDS-1 Trial ongoing
  - Aza/Tami vs. Aza/Placebo
  - Newly diagnosed higher-risk MDS



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de Botton et al. *Blood Adv* 2023 Dezern et al *J Clin Oncol* 2022

Other Investigational Drugs

- Most experimental treatments are added to an HMA “backbone”
  - Balance increased efficacy with more toxicity
- **Phase 3 trials that did not find improved outcomes:**
  - Pevonedistat, NEDD8 inhibitor, for higher-risk MDS, CMML, AML
  - Magrolimab, CD47 antibody, higher-risk MDS and AML
  - APR-246, restores p53 function, for TP53 mutated higher-risk MDS
  - Sabatolimab, TIM3 inhibitor, higher-risk MDS

Summary

- **MDS Risk Category or Stage determines treatment**
  - IPSS-R and IPSS-M
- **Allogeneic stem cell transplant is the only cure**
- **Hypomethylating Agents (HMAs), Azacitidine & Decitabine**
  - Not curative, but can extend survival and improve quality of life
  - Relatively low side effects
- **Newer therapies are needed to improve outcomes with just HMAs**

Thank you!

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