MYELODYSPLASTIC SYNDROMES

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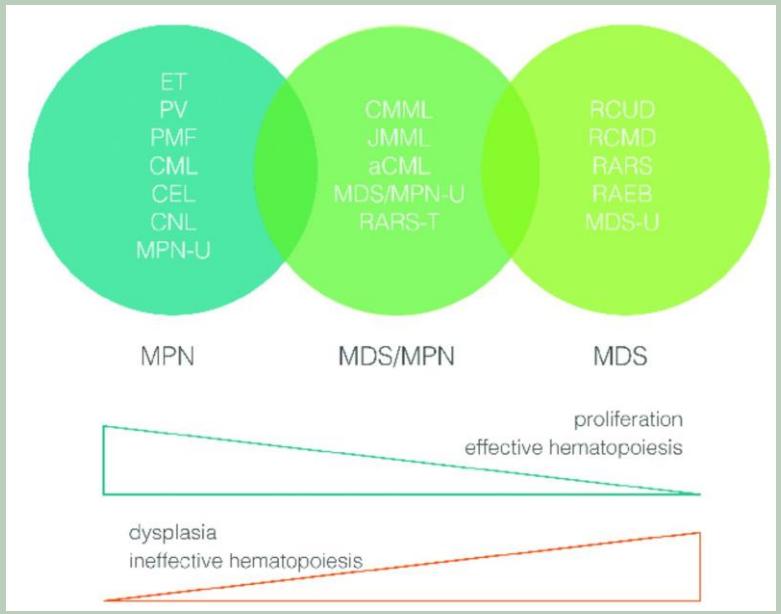
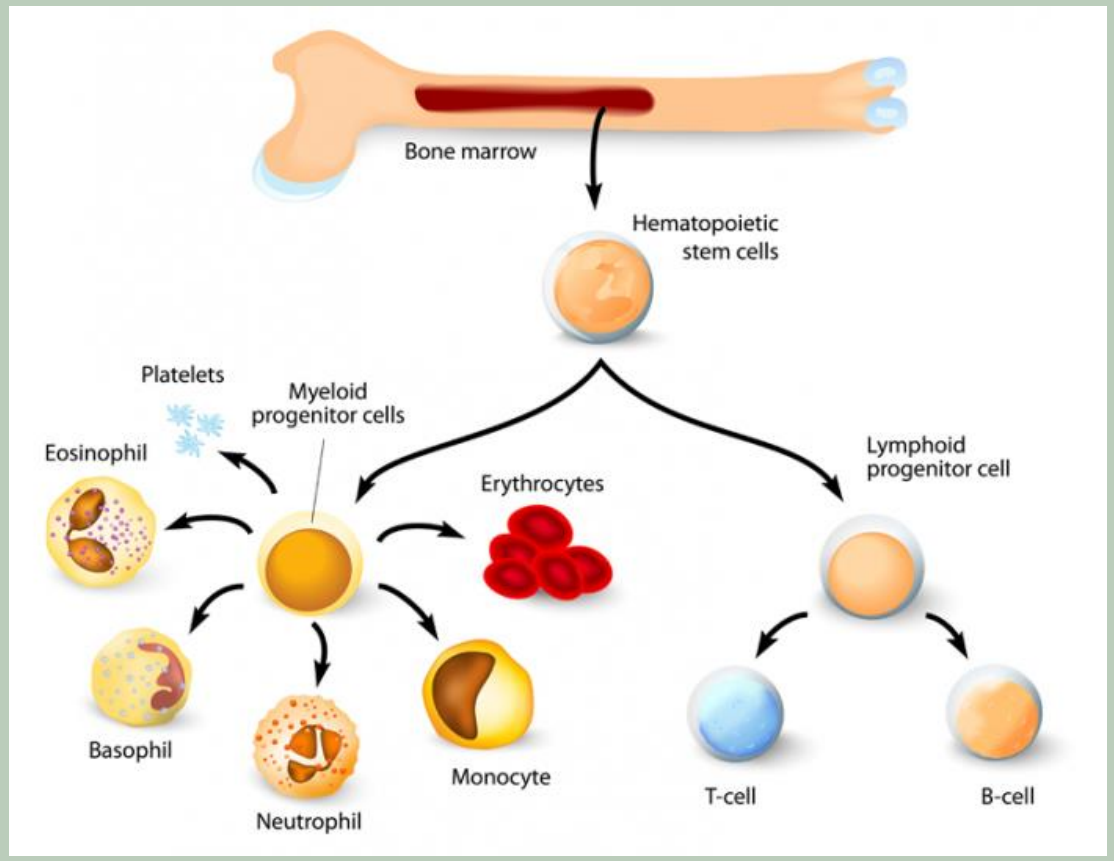
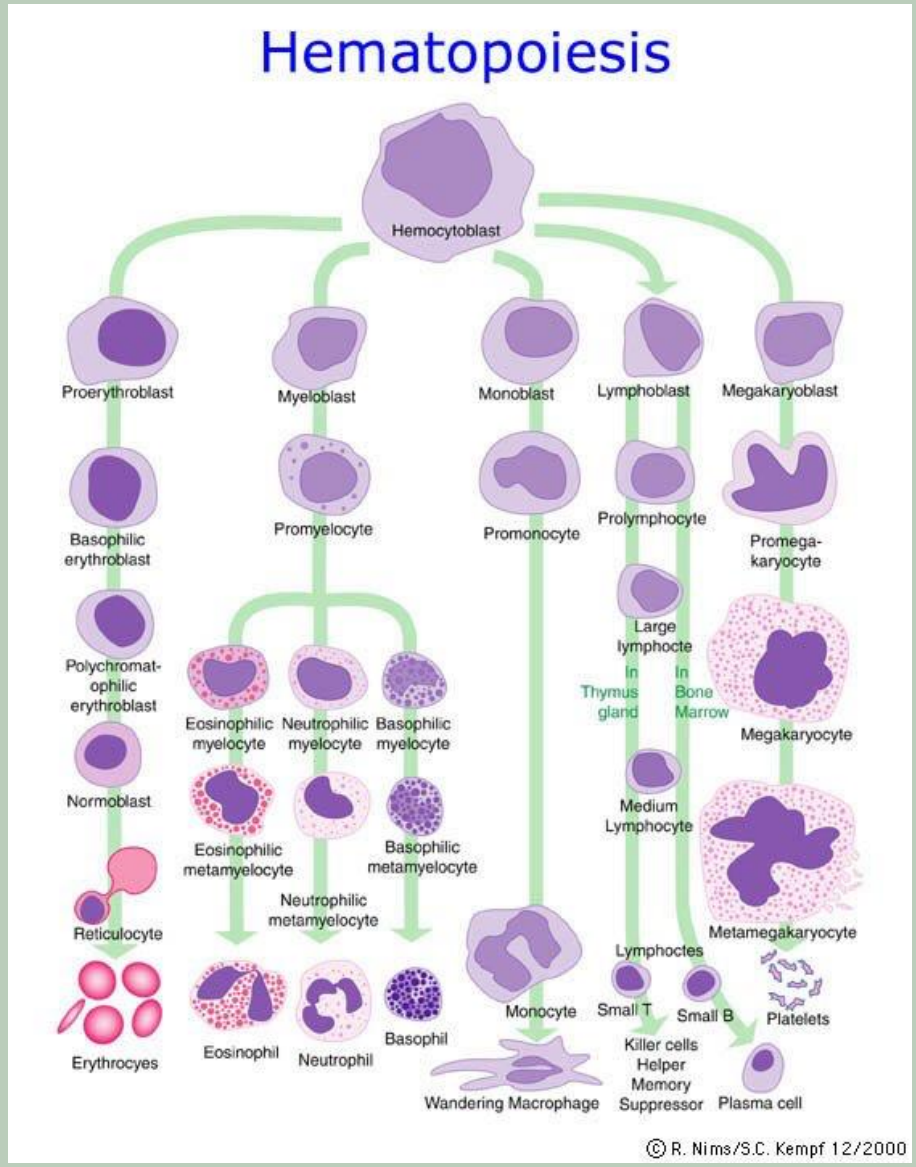
Presentation Overview

- **Myelodysplastic Syndromes (MDS)**
- **Ph-Negative Myeloproliferative Neoplasms (MPNs)**
  - *Polycythemia vera*
  - *Essential thrombocytosis*
  - *Myelofibrosis (primary MF, post-PV MF, post-ET MF)*
  - *Chronic neutrophilic leukemia*
  - *Chronic eosinophilic leukemia*
  - *MPN-unclassifiable*
- **MDS/MPN Overlap Syndromes**
  - *CMML*
  - *Atypical CMML*
  - *MDS/MPN with ring sideroblasts and thrombocytosis*
  - *Juvenile Myelomonocytic Leukemia*
  - *MDS/MPN, unclassifiable*



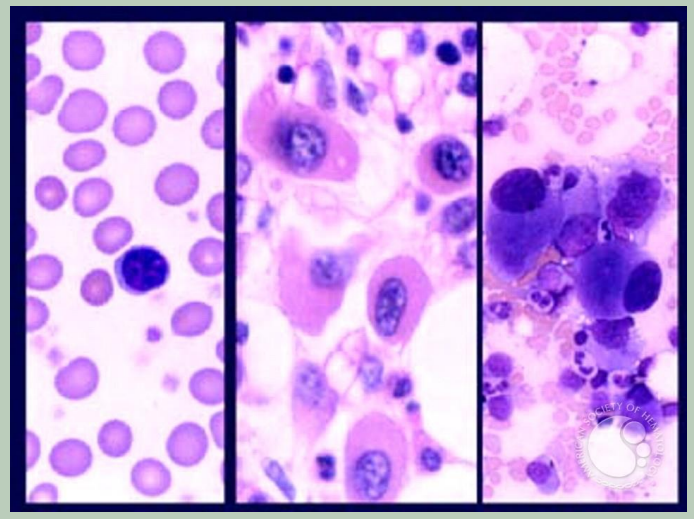
Bone Marrow: Where does it all start?





Understanding Myelodysplastic Syndromes

- Group of disorders characterized by ***ineffective hematopoiesis*** leading to ***cytopenias***, with ***increased risk of transformation to acute myelogenous leukemia (AML)***
- Accumulation of somatic mutations of HSCs => clonal hematopoiesis
- Typically incidentally found during routine blood work
- Usually asymptomatic
- May present with:
  - *Fatigue (2/2 macrocytic anemia, Hgb ~9)*
  - *Rare bleeding/bruising (2/2 thrombocytopenia)*
  - *Infections (2/2 neutropenia), exercise intolerance*



Understanding Myelodysplastic Syndromes

- ***De Novo* MDS**
  - *80-85% idiopathic*
  - *Age is most important risk factor (median age ~67 years)*
- **Secondary/Therapy-Related MDS (tMDS)**
  - *Drugs that alkylate DNA bases (Chlorambucil, Cyclophosphamide, Melphalan)*
  - *Topoisomerase II inhibitors (Etoposide, Topotecan, Anthracyclines)*
  - *Ionizing radiation*
  - *Environmental or occupational exposure to DNA toxins (hydrocarbons)*

Understanding Myelodysplastic Syndromes: Clinical workup

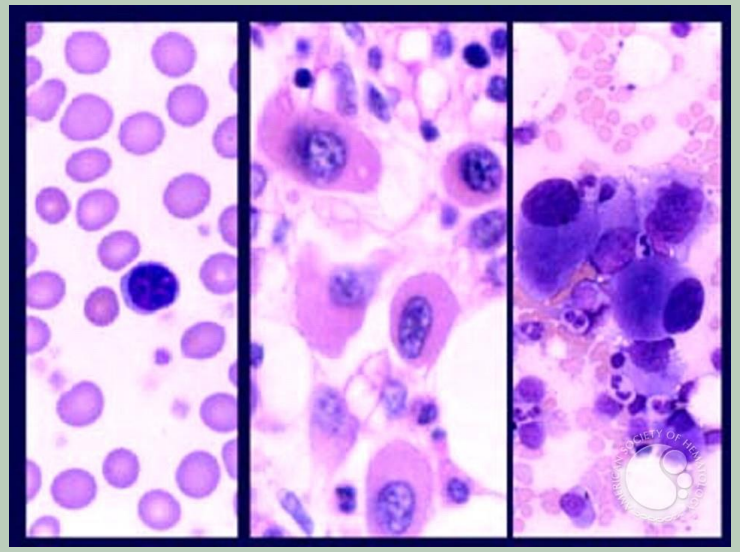
- History and Physical-
  Ask about EtOH, drug use, medications (prior/current), significant exposures, viral infections, prior cancer history including chemotherapy regimens
- **CBC with differential**
- **Reticulocyte count, Immature platelet fraction**
- **Peripheral Smear**
- EPO level
- B12, folate, iron studies, TSH, LDH
- **Bone marrow aspiration & biopsy**
- Molecular testing (Myeloid Gene Panel)
- HIV, HBV, HCV serologies
- Ceruloplasmin (copper) levels
- Consider Flow Cytometry for LGL and PNH

Understanding Myelodysplastic Syndromes: Diagnosis

- Primarily based on morphologic criteria
- Dysplastic features in peripheral blood or >10% bone marrow precursor cells in one or more lineages- erythroid, myeloid, megakaryocytic
- Less than 20% blasts
- Bone marrow is typically hypercellular, given ineffective hematopoiesis

Peripheral Smear

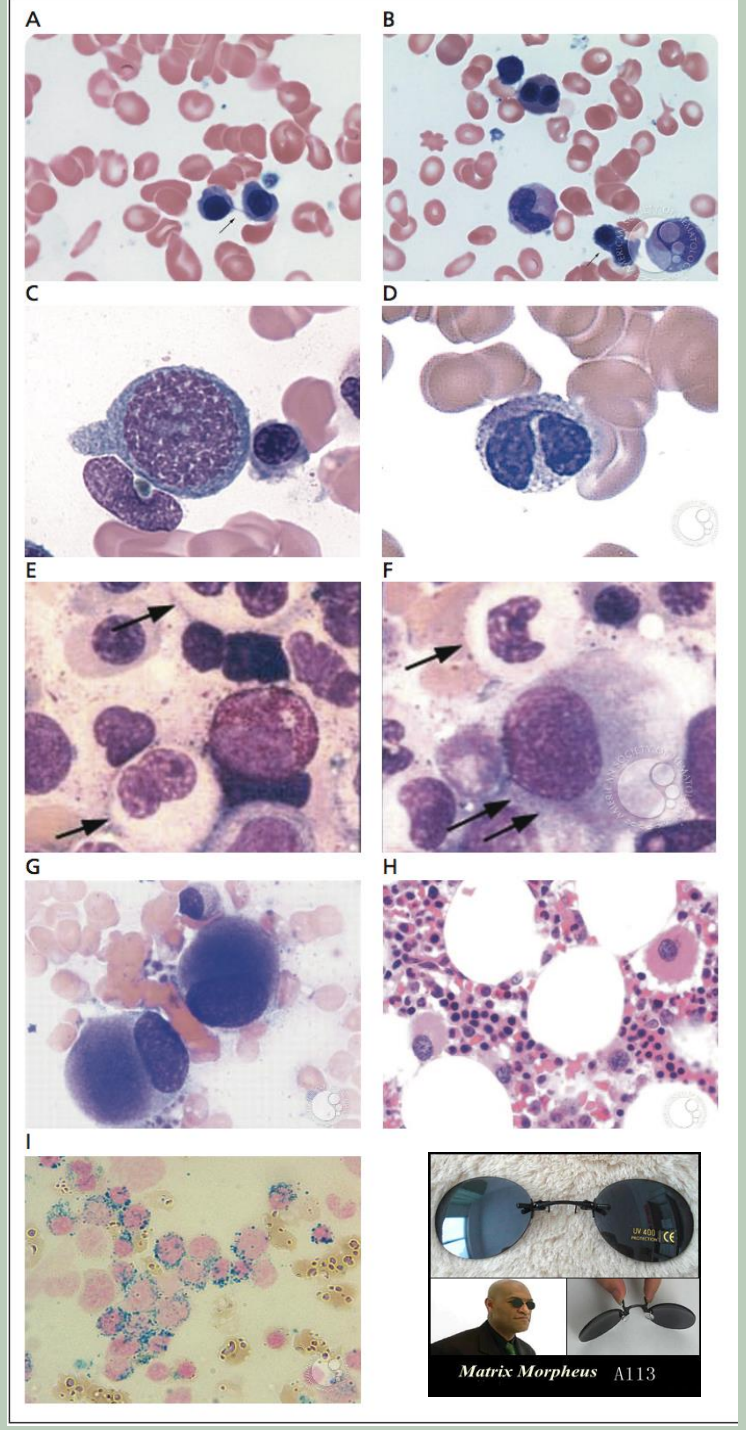
- *Oval macrocytic RBCs*
- *Hypogranular platelets*
- *Bilobated hypo-segmented neutrophils*



Diagnosis of MDS

- **BM= Usually hypercellular**
  - *with peripheral blood cytopenias, indicates ineffective hematopoeisis*
  - *10-20% of cases hypocellular (Hypoplastic MDS)*

- **Marrow Aspirate**
  - *A+B: Multinucleated erythroid precursors*
  - *C: Megaloblastoid RBC maturation (fine chromatin = immaturity; lighter cytoplasm = hemoglobinization at later stages)*
  - *D: Hypolobated neutrophils- Pseudo-Pelger Huet*
  - *E+F: hypogranular neutrophils with poor bactericidal activity; dysplastic features: nuclear and cytoplasmic blebs, misshapen nuclei*
  - *G+H: Micromegakaryocytes: eccentric, hypolobulated, or round nucleus (5q-syndrome)*
  - *Ringed sideroblasts*



Understanding Myelodysplastic Syndromes: Diagnosis

- **Cytogenetics – turn around time ~10-14 days**
  - *Risk stratification for median survival, progression to AML*
  - *½ of de novo and most t-MDS have cytogenetic abnormalities*
  - *New aberrations emerge in >25% throughout their disease (suggests genomic instability)*

- **MDS FISH – turn around time 1-7 days**
  - *Probes directed towards chromosomes frequently rearranged in MDS (5, 7, 8, 20)*
  - *Reveals specific chromosomal translocations and losses or gains of DNA*

- **Flow Cytometric Analysis**
  - *LGL and PNH clone evaluation*
  - *Enumeration of marrow blasts should not replace a manual differentiation*

- **Molecular Profiling – standard next-generation sequencing panels (40-100 genes), turn around time 2-4 weeks**
  - *Helps in ambiguous cases with bland morphology with no other explanation for cytopenias*
  - *Negative predictive value is high (> 90% of patients with MDS have a detected somatic mutation)*
  - *Caution for mutation detection in patients with normal karyotype and no morphologic dysplasia*
  - *Aids in prognostic assessment for HSCT*

Understanding Myelodysplastic Syndromes: 2016 WHO Classification

2016 WHO CLASSIFICATION OF MDS[1,2]

Subtype	Blood	Bone marrow
MDS with single lineage dysplasia (MDS-SLD)[3]	Single or bicytopenia	Dysplasia in ≥10% of one cell line, <5% blasts
MDS with ring sideroblasts (MDS-RS)	Anemia, no blasts	≥15% of erythroid precursors w/ring sideroblasts, or ≥5% ring sideroblasts if *SF3B1* mutation present
MDS with multilineage dysplasia (MDS-MLD)	Cytopenia(s), <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenia(s), ≤2%–4% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenia(s), 5%–19% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods
MDS, unclassifiable (MDS-U)	Cytopenias, ±1% blasts on at least 2 occasions	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts
Refractory cytopenia of childhood	Cytopenias, <2% blasts	Dysplasia in 1–3 lineages, <5% blasts

Replaced the 2008 WHO Classification of MDS

Understanding Myelodysplastic Syndromes: Risk Stratification – 1997 IPSS

Goal: Aid in predicting clinical outcome of untreated MDS patients, and design/analysis of clinical trials in MDS.

Table 17-5 The 1997 Revised International Prognostic Scoring System (IPSS) for myelodysplastic syndromes

	Category score (sum all three subscores for overall IPSS score)				
Prognostic factor	**0 (best)**	**0.5**	**1**	**1.5**	**2.0 (worst)**
Marrow blasts (%)	<5	5-10	–	11-20	21-30*
Karyotype	Good: normal, isolated -Y, isolated del(5q), or isolated del(20q)	Intermediate: all karyotypes not defined as good or poor	Poor: abnormal chromosome 7 or a complex karyotype (≥3 anomalies)	–	–
Peripheral blood cytopenias†	0 or 1	2 or 3	–	–	–

Table 17-6 Risk stratification of International Prognostic Scoring System (IPSS)

Risk category	Total score	Median survival (years)	Median survival (years) for patients <60 years old ($n = 205$)	Median survival (years) for patients ≥60 years old ($n = 611$)	Time until 25% of surviving patients in category developed leukemia (years)
Low risk	0	5.7	11.8	4.8	9.4
Intermediate-1 (INT-1)	0.5 or 1.0	3.5	5.2	2.7	3.3
Intermediate-2 (INT-2)	1.5 or 2.0	1.2	1.8	1.1	1.1
High	≥2.5	0.4	0.3	0.5	0.2

Greenberg et al. *Blood 1997.*

Understanding Myelodysplastic Syndromes: Risk Stratification – Revised IPSS (IPSS-R)

Updated cytogenetic classification for use in IPSS-R ($n = 7012$)

Risk group	Included karyotypes	Median survival, years	25% of patients to AML, years	Proportion of patients in this group
Very good	del(11q), -Y	5.4	N/R	4%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	4.8	9.4	72%
Intermediate	+8, del(7q), i17q, +19, any other single or double abnormality not listed, 2 or more independent clones	2.7	2.5	13%
Poor	Abnormal 3q, -7, double abnormality include -7/del(7q), complex with 3 abnormalities	1.5	1.7	4%
Very poor	Complex with >3 abnormalities	0.7	0.7	7%

	IPSS-R				
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	≥10 g/dL	8-<10 g/dL	<8 g/dL		
	0	1	1.5		
Absolute neutrophil count	$\geq 0.8 \times 10^9$/L	$<0.8 \times 10^9$/L			
	0	0.5			
Platelet count	$\geq 100 \times 10^9$/L	$50\text{-}100 \times 10^9$/L	$<50 \times 10^9$/L		
	0	0.5	1		

Overall Survival

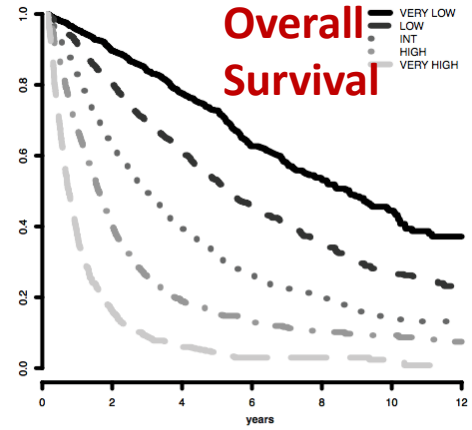


Figure 3. Survival based on IPSS-R prognostic risk-based categories. Survival related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 7012; Dxy 0.43, $P < .001$). The number of patients in each category and their proportional representation are shown in Table 1.

Progression to AML

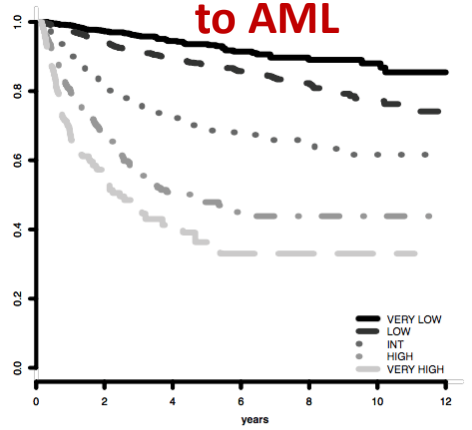
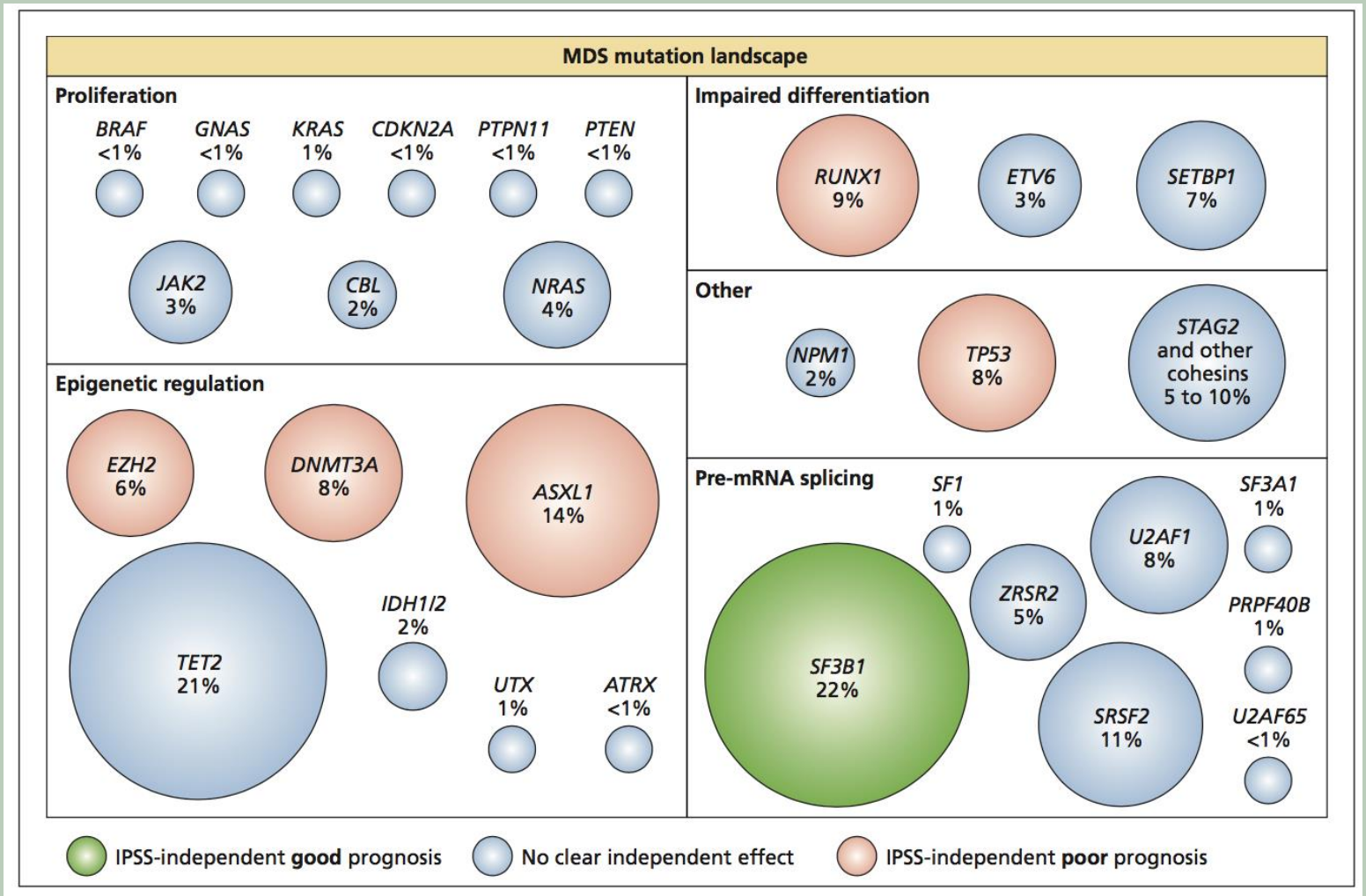


Figure 4. AML evolution based on IPSS-R prognostic risk-based categories. Progression to AML related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 6485; Dxy 0.52, $P < .001$). The number of patients in each category and their proportional representation are shown in Table 1.

Greenberg et al. *Blood 2012.*

Understanding Myelodysplastic Syndromes: Genetic Profile of MDS



IPSS-independent GOOD prognosis:

- SF3B1

IPSS-independent POOR prognosis:

- ASXL1
- RUNX1
- TP53
- DNMT3A
- EZH2

(GREATER RISK FOR TRANSFORMATION TO AML)

Steensma et al. *Mayo Clinic Proceedings* 2015.

Prognosis of Mutations in MDS

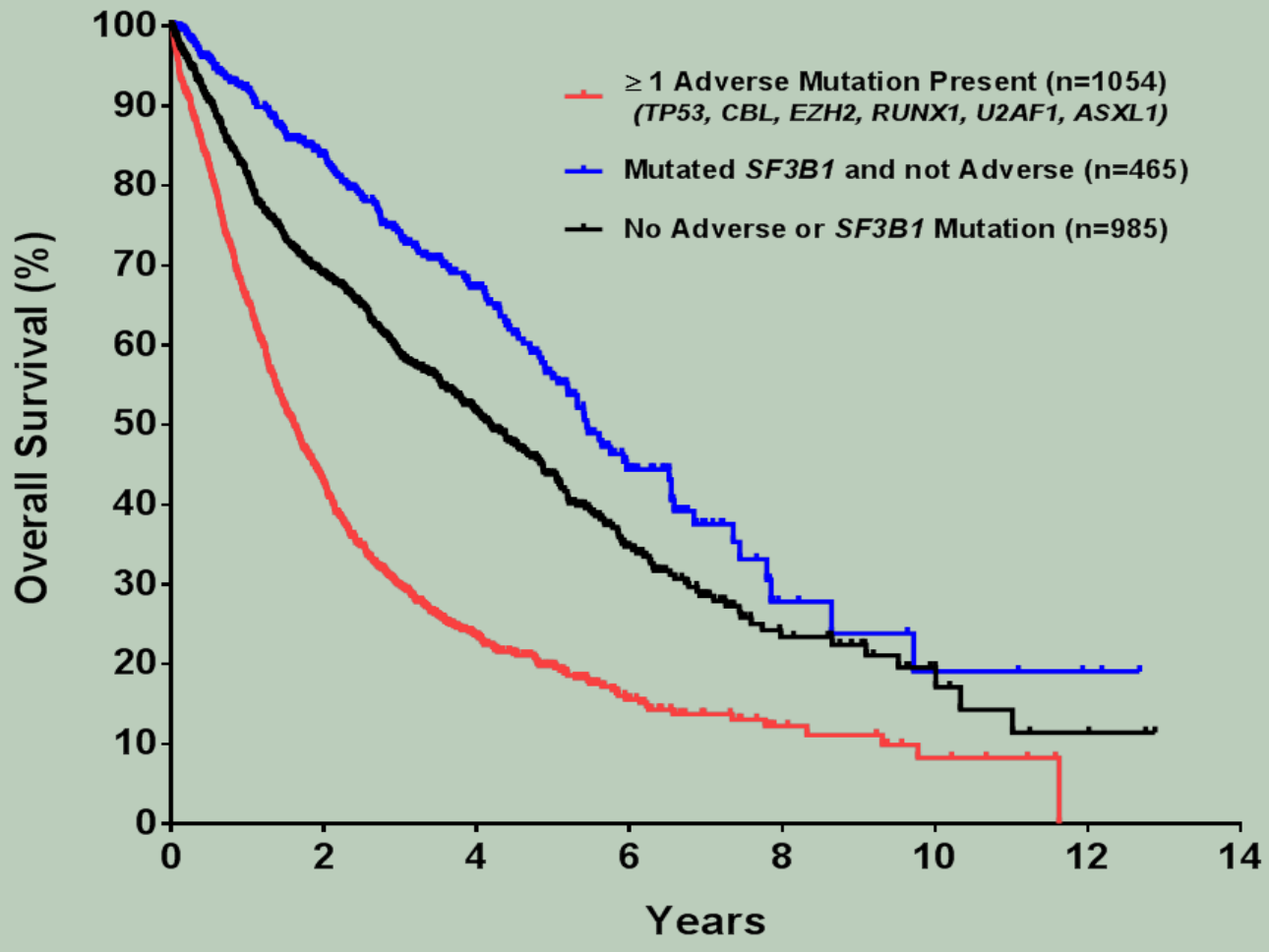


Figure 2: Kaplan-Meier curve of overall survival in years for the 2504 patients with sequence results for *SF3B1* and all six adverse genes (*TP53*, *CBL*, *EZH2*, *RUNX1*, *U2AF1*, and *ASXL1*).

Bejar et al., ASH 2015

Understanding Myelodysplastic Syndromes: Treatment of LOWER RISK MDS

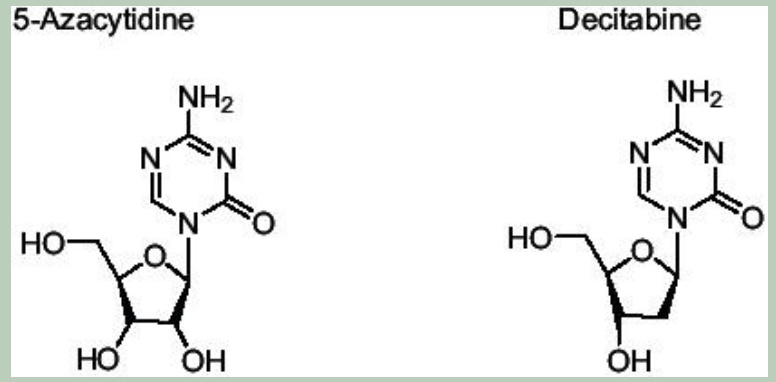
- Lower risk MDS **(IPSS-R Very Low, Low, and Intermediate)**
- Treatments:
  - *ESA's (Epoeitin, Darbopoetin):* **Anemia, NO del(5q), and EPO level < 500**
  - *Lenalidomide:* **Anemia, del(5q) +/- one additional cytogenetic abnormality except Chr 7 abnormalities** (can consider in NO del(5q), though lower response rates)
  - *Immunosuppressive therapy, IST:* **Anemia and EPO level > 500** OR clinically relevant **neutropenia/thrombocytopenia** and features predictive of response
  - *Hypomethylating agents:* Clinically significant **neutropenia/thrombocytopenia** OR increased **blasts** OR in **anemia and EPO level > 500** OR prior treatment response failure
- **Supportive care:** Blood and platelets, treat iron overload, once has received 20-30 transfusions
- **Luspatercept** (Erythroid maturation agent, FDA approved April 3, 2020)- Ring sideroblasts >15% or >5% with SF3B1 mutation; Strong concordance with SF3B1 mutation, reduces transfusion requirements for anemia.

Understanding Myelodysplastic Syndromes: Treatment of HIGHER RISK MDS

- High risk MDS includes **intermediate, high or very high risk by IPSS-R**
- **Allo-HSCT** should be considered in patients who are candidates and have available donor
  - *Only treatment with potential for cure*
  - *Limited by advanced age of most patients and donor availability*
  - *Can consider Hypomethylating agent or Intensive chemotherapy prior to transplant in high risk patients, and those with high blast percent (Various centers use different criteria, but frequently require blasts < 10% to go to transplant)*
- For patients who decline or are ineligible for transplant, **Hypomethylating agents** are standard of care.
- Clinical trial should be considered in all patients
- Supportive care as indicated in all MDS patients

Understanding Myelodysplastic Syndromes: Hypomethylating Agents

- Azacitidine (Vidaza) & Decitabine (Dacogen)
- DNA methyltransferase inhibitors (DNMTI)
- Targets epigenetic changes in MDS
- Cancer and Leukemia Group B (CALGB) Phase 3 RCT comparing 5-AZA with BSC



	Trial 8421 Phase I	Trial 8921 Phase II	Trial 9221 RCT	
	Intravenous	Subcutaneous	Supportive care	Azacytidine
Patients (No. evaluated)	43	68	92	99
CR	5 (12%)	8 (12%)	0 (0%)	7(7%)*
PR	11 (25%)	10 (15%)	0 (0%)	16 (16%)+
Improved	5 (12%)	18 (27%)	5 (5%)	37 (37%)+
Total response	21 (49%)	36 (53%)	5 (5%)	60 (60%)+

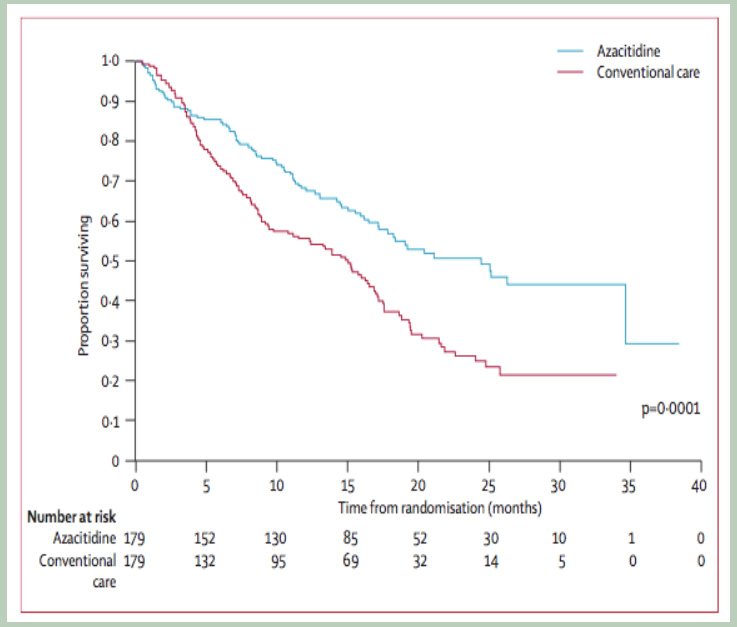
Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study

Pierre Fenaux, Ghulam J Mufti, Eva Hellstrom-Lindberg, Valeria Santini, Carlo Finelli, Aristoteles Giagounidis, Robert Schoch, Norbert Gattermann, Guillermo Sanz, Alan List, Steven D Gore, John F Seymour, John M Bennett, John Byrd, Jay Backstrom, Linda Zimmerman, David McKenzie, C L Beach, Lewis R Silverman, for the International Vidaza High-Risk MDS Survival Study Group

Design:
International, Multicenter, Control, Open Label, Phase III

Azacitidine at 75 mg/m2 x7 days in 28 day cycles for at least 6 cycles (median 9 cycles) 179 pts
VS
Conventional care (BSC w/ transfusions, ABX+G-CSF, low dose Ara-C 20 mg/m2 x14 days, 28 day cycles, or Intensive chemotx w/ 7+3 induction + consolidation, 179 pts investigators choice)

Key points:
- **Azacitidine improves OS** (compared to conventional care), OS 24 vs 15 mo.
- **Improves median time to AML transformation** (17.8 vs. 11.5 mo.)



	Total ITT (n=358)		
	Azacitidine (n=179)	CCR (n=179)	p value*
Haematological response			
Any remission	51 (29%)	21 (12%)	0·0001
Complete remission	30 (17%)	14 (8%)	0·015
Partial remission	21 (12%)	7 (4%)	0·0094
Stable disease	75 (42%)	65 (36%)	0·33
Haematological improvement†			
Any improvement	87/177 (49%)	51/178 (29%)	<0·0001
Major erythroid improvement	62/157 (40%)	17/160 (11%)	<0·0001
Major platelet improvement	46/141 (33%)	18/129 (14%)	0·0003
Major neutrophil improvement	25/131 (19%)	20/111 (18%)	0·87

Fenaux et al. *Lancet* 2009.

Design:
Phase II, Safety/PK, compare decitabine exposure/demethylation activity

ORAL Cedazuridine 100 mg/decitabine 35 mg VS standard decitabine 20 mg/m2 IV, then crossover after C2

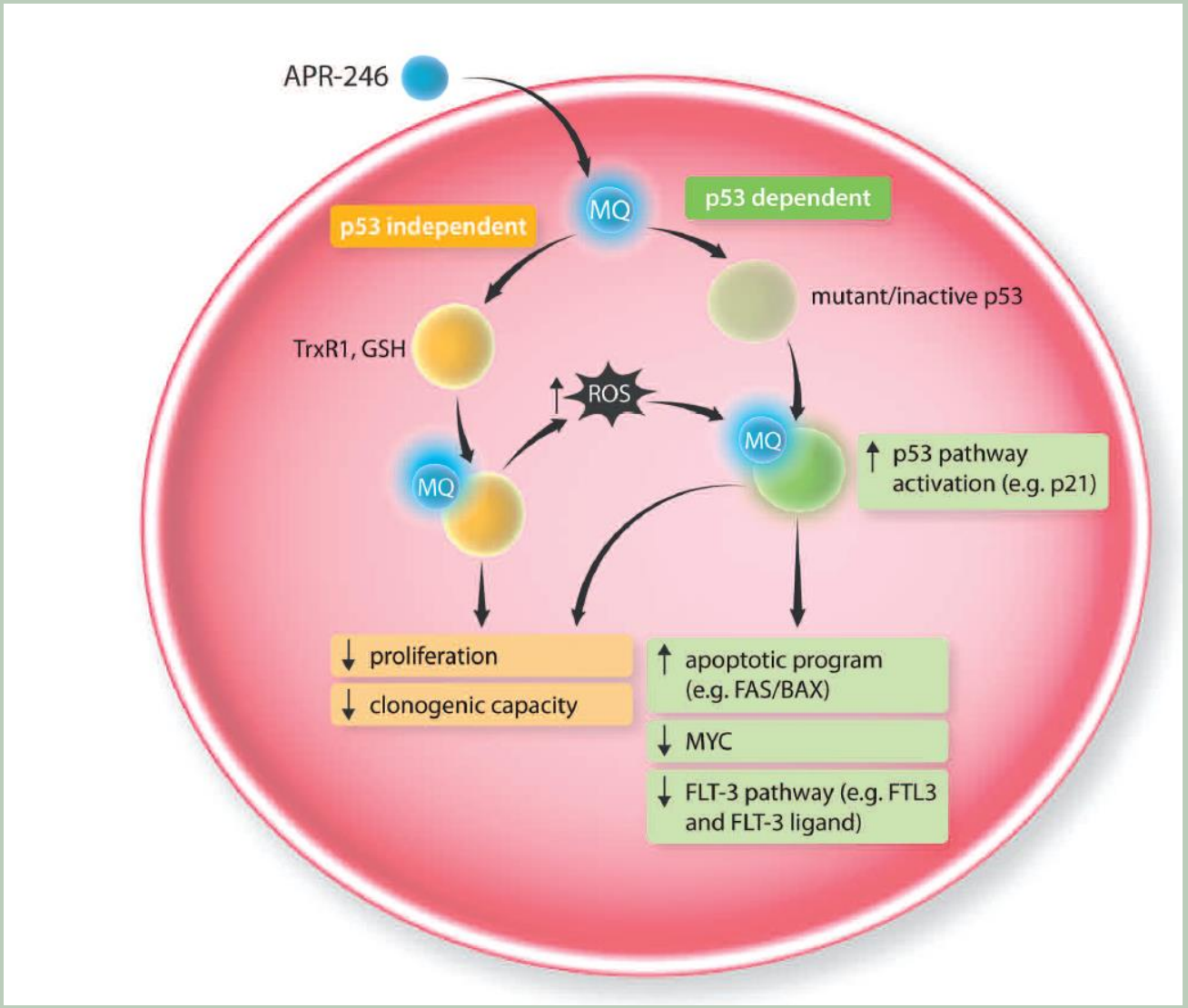
Int-1/2 or high risk MDS or CMML
1:1 randomization
Primary endpoints: Mean decitabine exposure (LSM, AUC), LINE1 DNA methylation activity, clinical response.

Key points:
- Clinical response in 60% (CR 17%), similar efficacy.
- **Grade >3 AE hematologic toxicities (29-46%).**
- **PO vs IV similar systemic exposure & DNA methylation.**

ASCERTAIN - PHASE III Cedazuridine/decitabine PO 5 day dosing for MDS and CMML met primary endpoint of equivalent decitabine exposure with fixed dose combination (ASTX727), ASTEX & Otsuka Pharmaceuticals (June 2019 data released)

Garcia-Manero et al. Blood 2020.

APR-246 Mechanism of Action



Maslah N et al., *Haematolgica* 2019; Zhang Q et al., *Cell Death Dis* 2018; Lambert JM et al., *Cancer Cell* 2009; Lehmann S et al., *J Clin Oncol* 2012

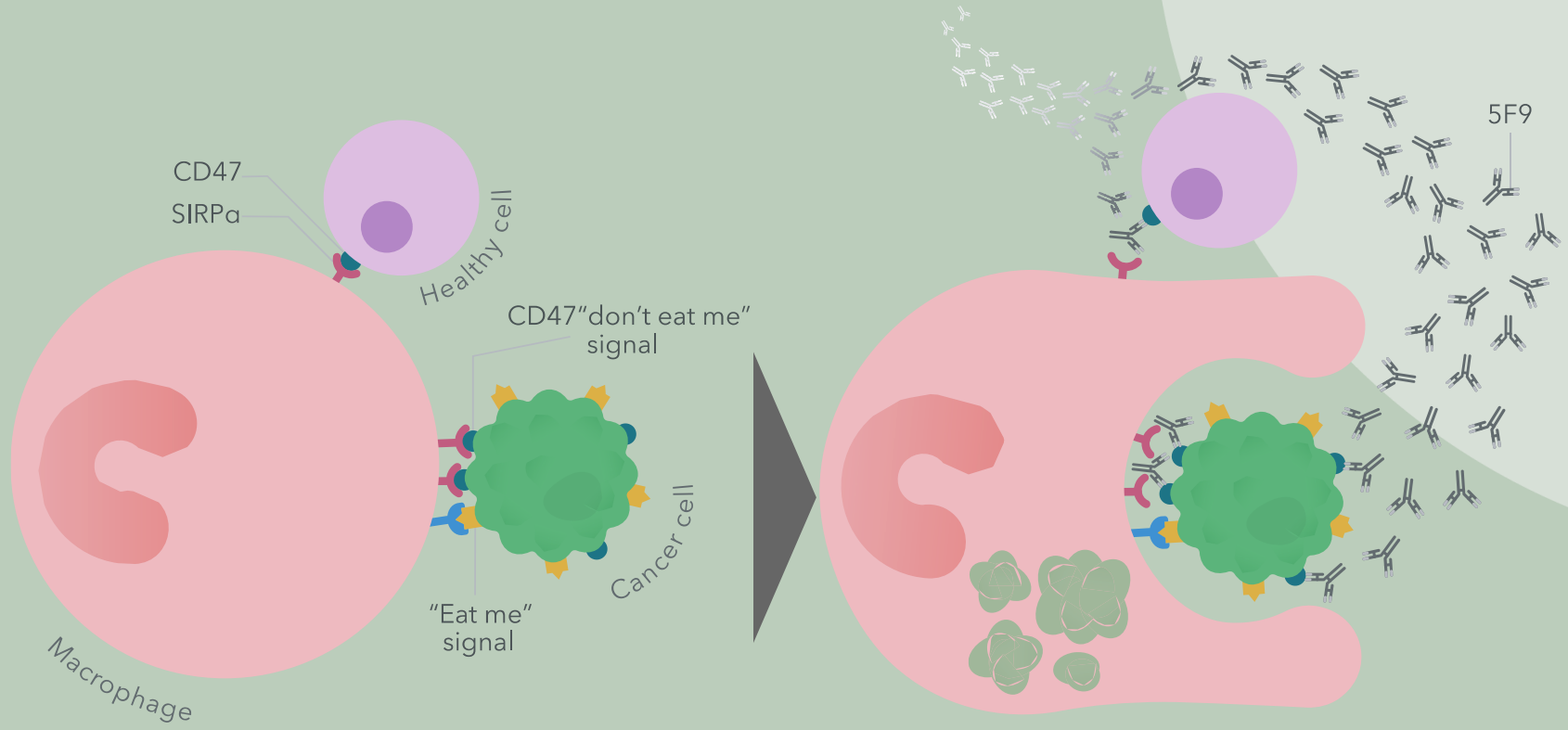
Future Directions – Treatment of *TP53* mutant MDS

APR-246

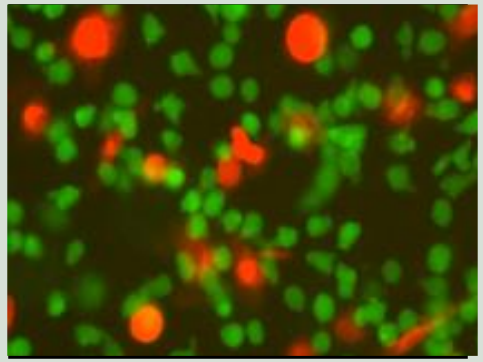
- APR-246 is a methylated small-molecule derivative PRIMA-1 analog that reactivates mutant p53 protein by restoring p53 conformation and function, thereby inducing cell cycle arrest and apoptosis in cancer cells.
- In pre-clinical trials, APR-246 demonstrated anti-tumor activity in a variety of solid and hematologic malignancies.
- In phase I/II studies, the agent's adverse event profile was acceptable to most patients, and treatment was associated with clinical responses in patients with *TP53*-mutated hematologic malignancies.
- ORR in 45 evaluable MDS patients (out of 55 total patients enrolled) was 87%, with a 53% CR rate (NCT03072043), similar findings in coinciding French trial (NCT03588078).
- APR-246 + azacytidine combination received orphan-drug and fast-track designations for MDS from the FDA, with Aprea Therapeutics.
- Ongoing Phase II trial (NCT0374571) comparing APR-246 with AZA vs AZA alone has completed accrual; As well as trials investigating role in post-SCT and novel combinations.

Sallman D et al., ASH 2019

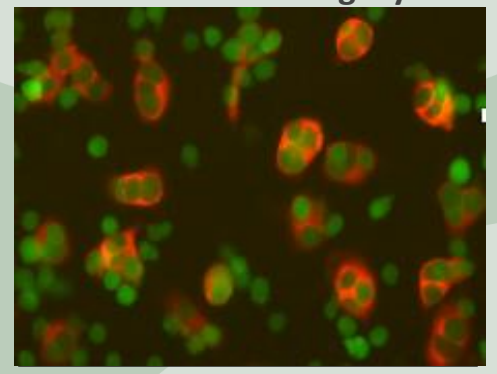
Magrolimab (Formerly 5F9) is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



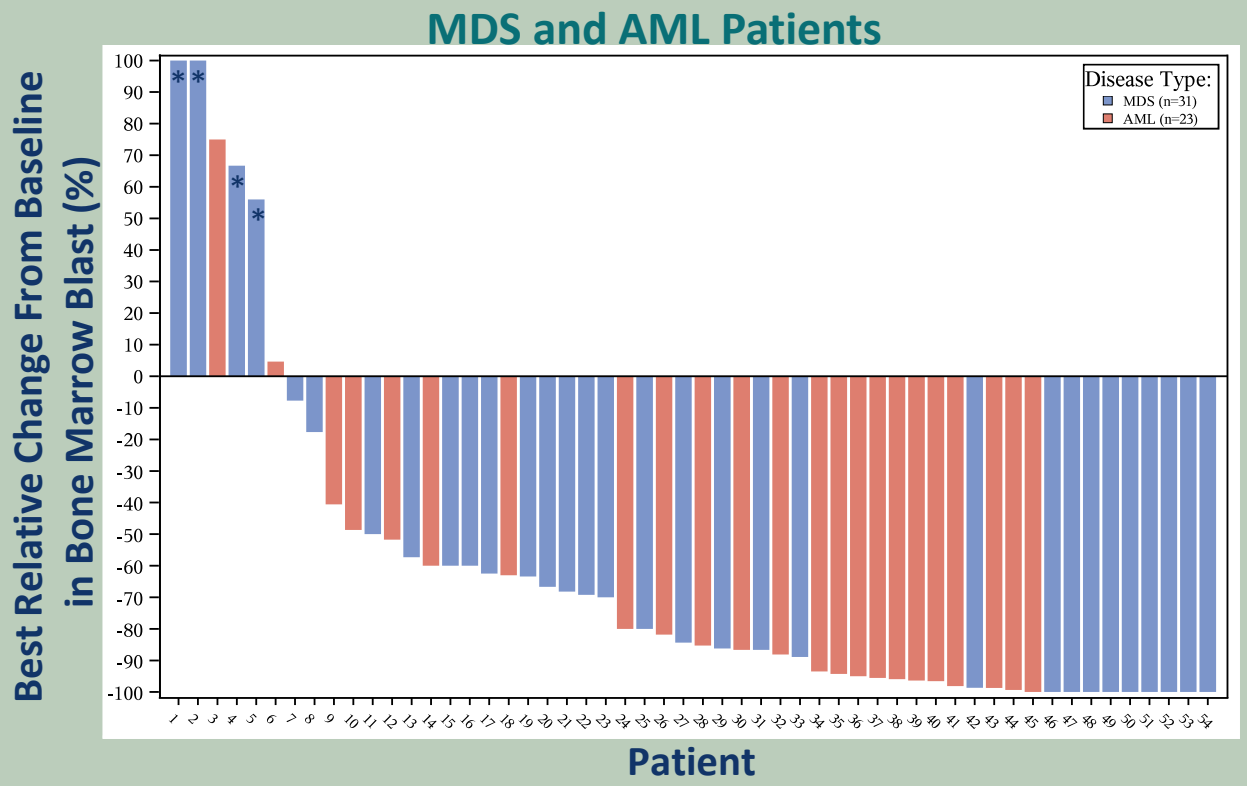
Macrophages Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody being investigated in multiple cancers
- Magrolimab was well tolerated in a UK Phase 1 trial in r/r AML with no MTD reached (Vyas et al., EHA abs 2018)

Magrolimab + AZA Induces High Response Rates in MDS and AML

Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

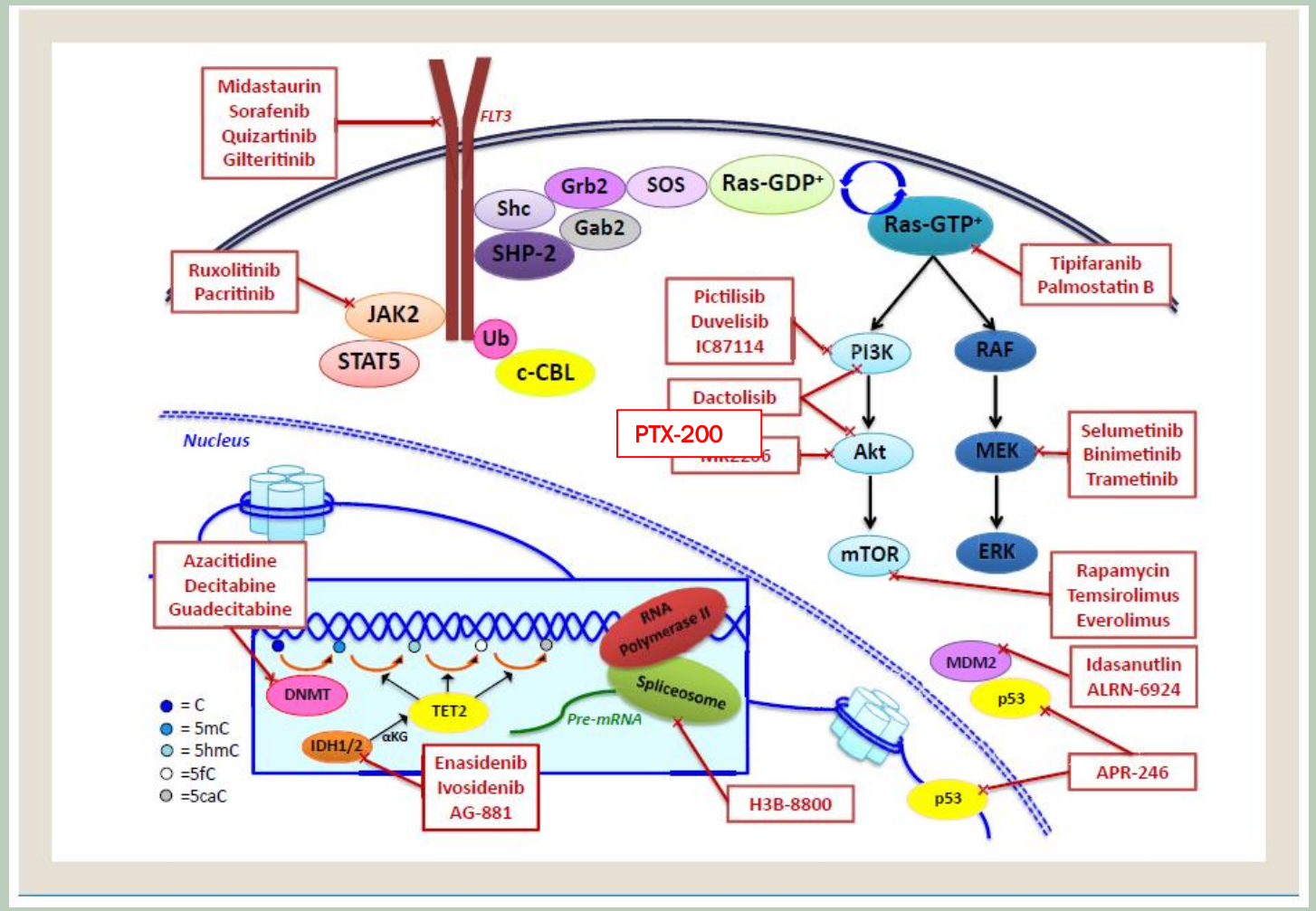
- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Additional Novel HMA Combinations

- Pevondedistat (a NEDD8 Inhibitor) + azacitidine had high CR rates (56%) and had improved event free survival but not overall survival (EHA 2020)
- MBG453 (TIM3 inhibitor) – improved overall response rates with azacitidine or decitabine (EHA 2020)
- Ventoclax (BCL-2 inhibitor) – Approved in elderly AML with azacitidine or decitabine, P3 trial ongoing in MDS
- Options or Triplet and other novel-novel strategies are planned.

Molecular Targeted Therapy in MDS/AML



Sallman et al., CLML 2017; 10:613-20

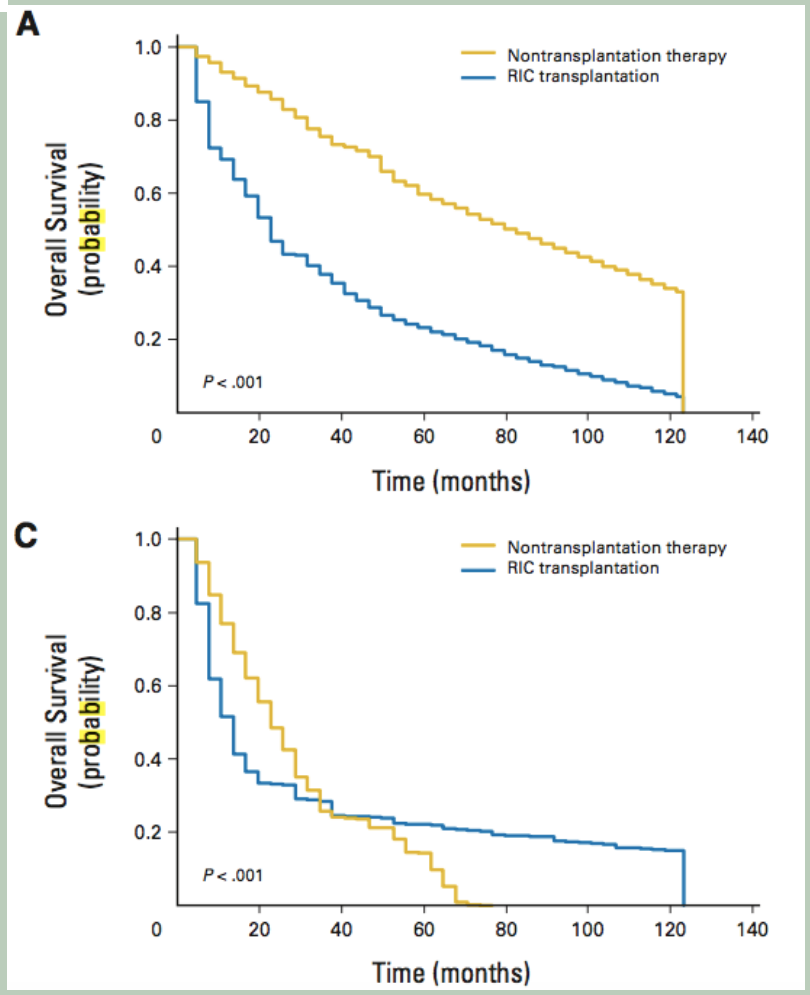
Role of Reduced-Intensity Conditioning Allogeneic Hematopoietic Stem-Cell Transplantation in Older Patients With De Novo Myelodysplastic Syndromes: An International Collaborative Decision Analysis

John Koreth, Joseph Pidala, Waleska S. Perez, H. Joachim Deeg, Guillermo Garcia-Manero, Luca Malcovati, Mario Cazzola, Sophie Park, Raphael Itzykson, Lionel Ades, Pierre Fenaux, Martin Jadersten, Eva Hellstrom-Lindberg, Robert Peter Gale, C.L. Beach, Stephanie J. Lee, Mary M. Horowitz, Peter L. Greenberg, Martin S. Tallman, John F. DiPersio, Donald Bunjes, Daniel J. Weisdorf, and Corey Cutler

Design:
Retrospective study evaluating RIC allo-HSCT in pts age 60-70 with MDS
Utilized a Markov decision model to evaluate outcomes of life expectancy (LE) and quality adjusted life expectancy

514 pts included, only MRD and MUD utilized.
RIC transplantation (n 132) stratified by IPSS risk was compared with best supportive care (n=123) and growth factors (n=94) for low/int-1 IPSS and HMAs in int-2/high risk IPSS (n= 165)

Key points:
-Life expectancy in low/int-1 risk MDS: 38 mo w/ allo-HSCT vs. 77 mo w/ conventional tx
-Life expectancy in int-2/high risk MDS: 36 mo w/ allo-HSCT vs. 28 mo w/ conventional tx



Koreth et al. *J Clin Oncol* 2013.

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ORIGINAL REPORT

Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes

Bart L. Scott, Marcelo C. Pasquini, Brent R. Logan, Juan Wu, Steven M. Devine, David L. Porter, Richard T. Maziarz, Erica D. Warlick, Hugo F. Fernandez, Edwin P. Alyea, Mehdi Hamadani, Asad Bashey, Sergio Giralt, Nancy L. Geller, Eric Leifer, Jennifer Le-Rademacher, Adam M. Mendizabal, Mary M. Horowitz, H. Joachim Deeg, and Mitchell E. Horwitz

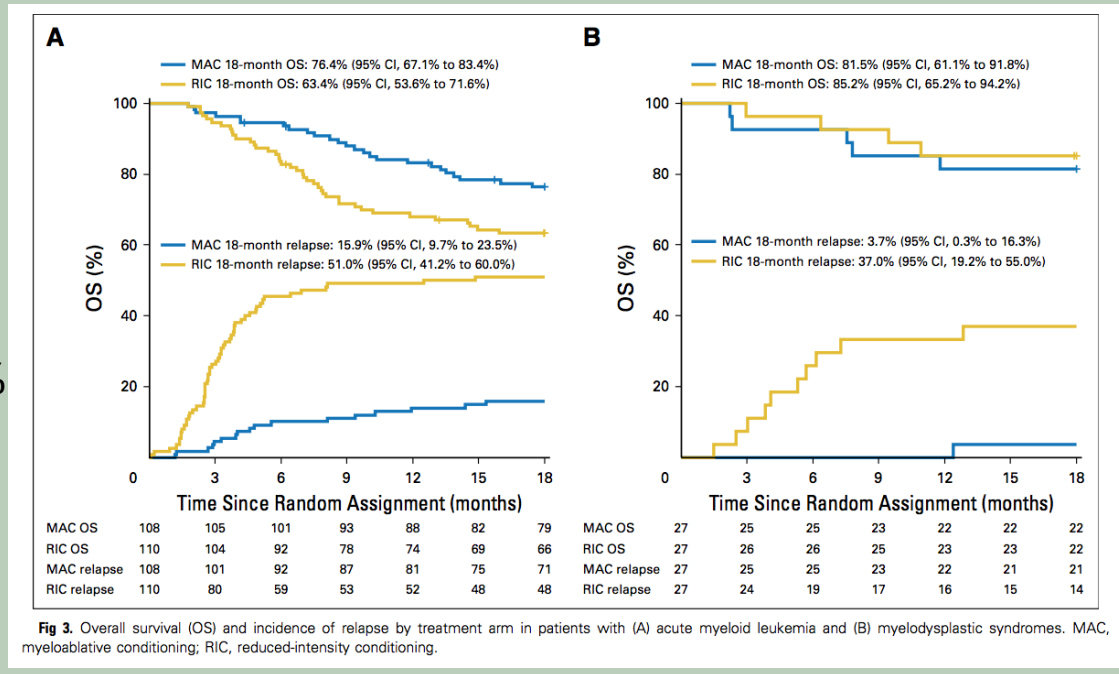


Fig 3. Overall survival (OS) and incidence of relapse by treatment arm in patients with (A) acute myeloid leukemia and (B) myelodysplastic syndromes. MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

Design:

272 patients age 18-65 with HCT comorbidity index ≤ 4 and <5% marrow blasts (majority had AML, however) randomly assigned to MAC (135) or RIC (137) followed by HSCT from MRD or MUD

Primary endpoint = OS 18 months based on intent-to-treat analysis

Secondary endpoints = relapse free survival and treatment-related mortality

Key points:

-After 18 months, OS for RIC arm 67.7% vs. MAC arm 77.5% (p = 0.07)

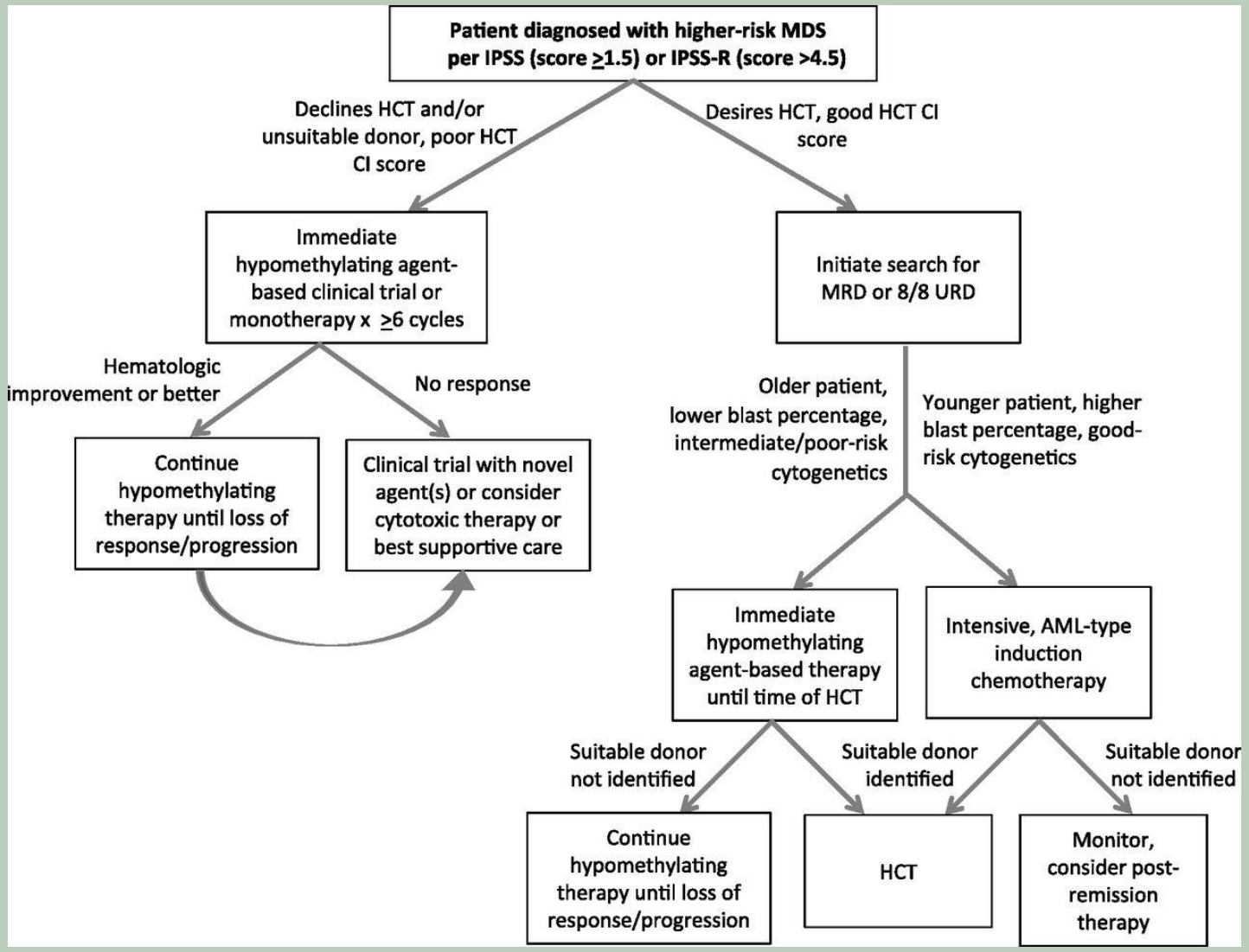
-TRM with RIC 4.4% (95% CI, 1.8% to 8.9%) vs. 15.8% (95% CI, 10.2% to 22.5%) with MAC (P = .002).

-RFS with RIC 47.3% vs. 67.8% MAC (P < .01).

-OS was higher in MAC but not statistically significant.

-RIC had lower TRM but higher relapse rates, with a statistically significant advantage in RFS with MAC

Understanding Myelodysplastic Syndromes: Transplant or Not to Transplant?



QUESTIONS?