



THE UNIVERSITY OF  
**CHICAGO**

# **Myelodysplastic Syndromes Patient and Care Giver Forum 2017**

**Olatoyosi Odenike, MD**

**Associate Professor of Medicine**

**The University of Chicago**

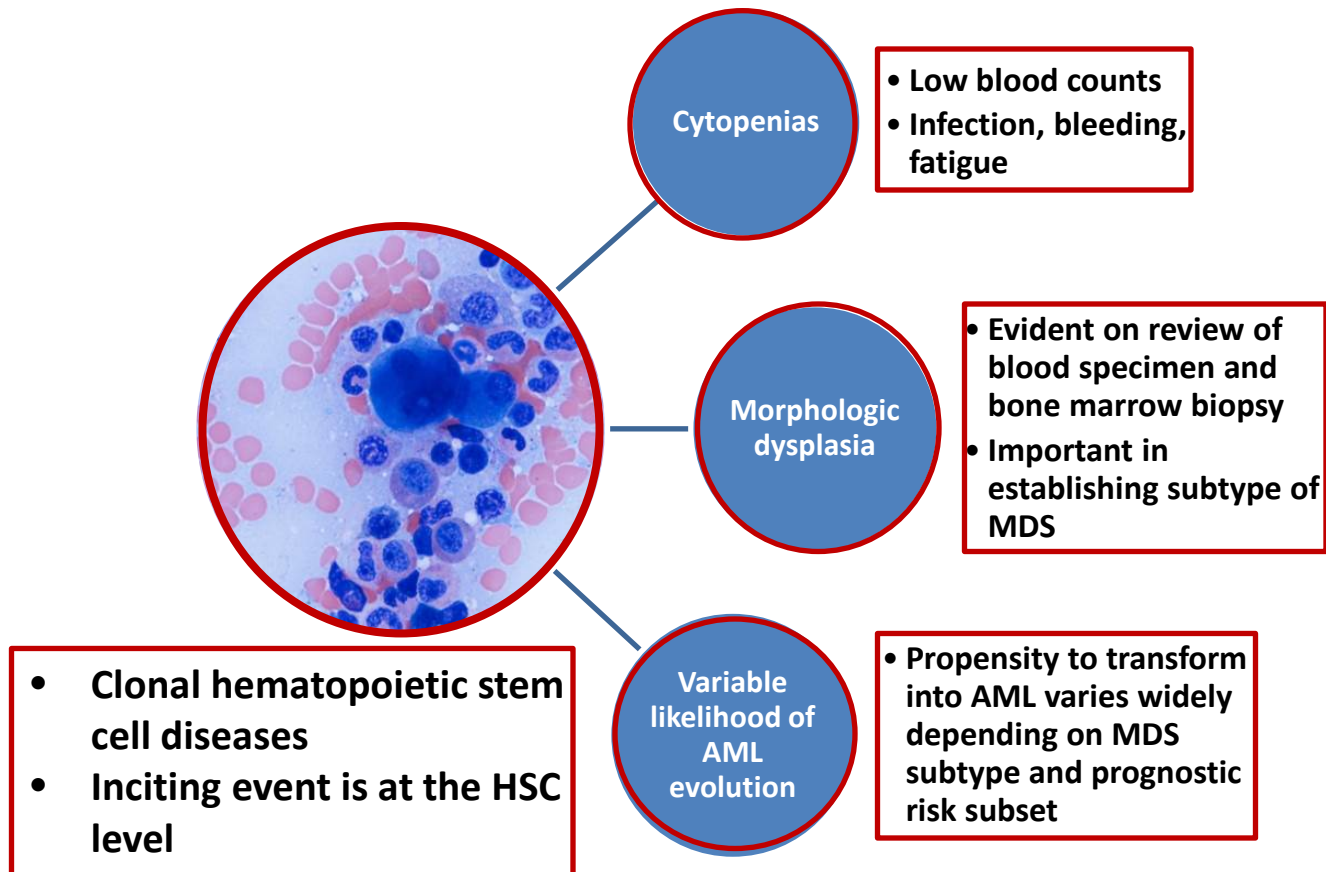
# Overview

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- **What is MDS?**
- **What are the Treatment Options?**
- **Clinical Trials for MDS**

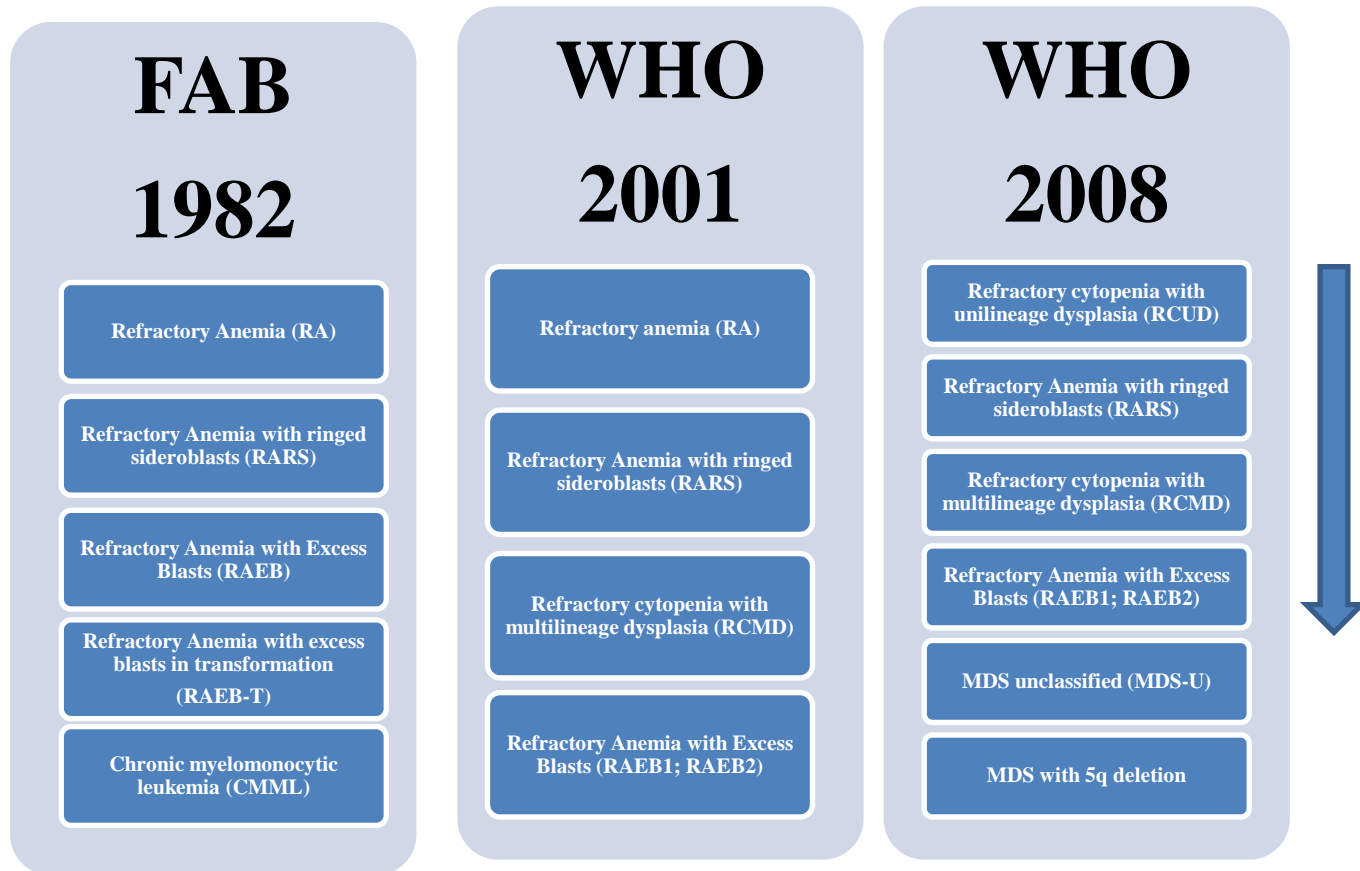
# Myelodysplastic Syndromes

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# Evolving Classification of MDS

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**FAB=French American British classification; WHO=World Health Organization classification**

# Evolving Classification of MDS

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## 2016 Revision to the WHO Classification of MDS

**MDS with single lineage dysplasia**

**MDS with ring sideroblasts (MDS-RS)**

- MDS-RS and single lineage dysplasia
- MDS-RS and multilineage dysplasia

**MDS with multilineage dysplasia**

**MDS with excess blasts**

**MDS with isolated del(5q)**

**MDS, unclassifiable**

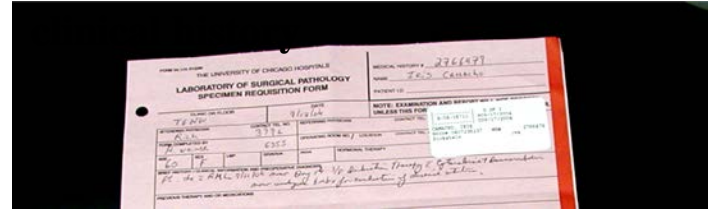
**Provisional entity: Refractory cytopenia of childhood**

**Myeloid neoplasms with germ line predisposition**

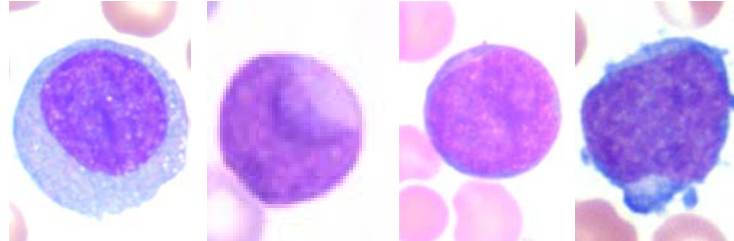
# **Approach to the Individual Patient with MDS?**

# Step 1) Establish MDS Subtype

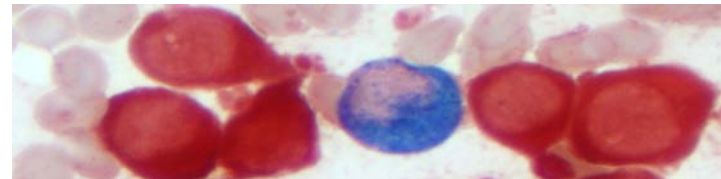
**CLINICAL**



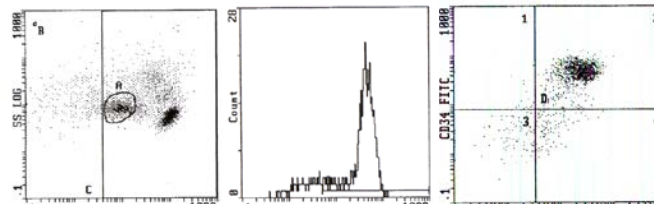
**MORPHOLOGIC**



**PHENOTYPIC**  
cytochemical



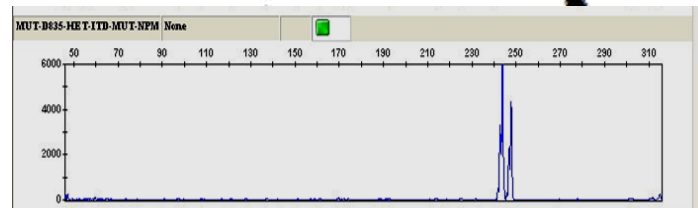
**Immunophenotypic**  
(Cell surface protein expression)



**CYTOGENETIC**  
(chromosome analysis)



**MOLECULAR GENETIC**  
(analysis of gene mutations)



## **Step 2: Risk Stratify**

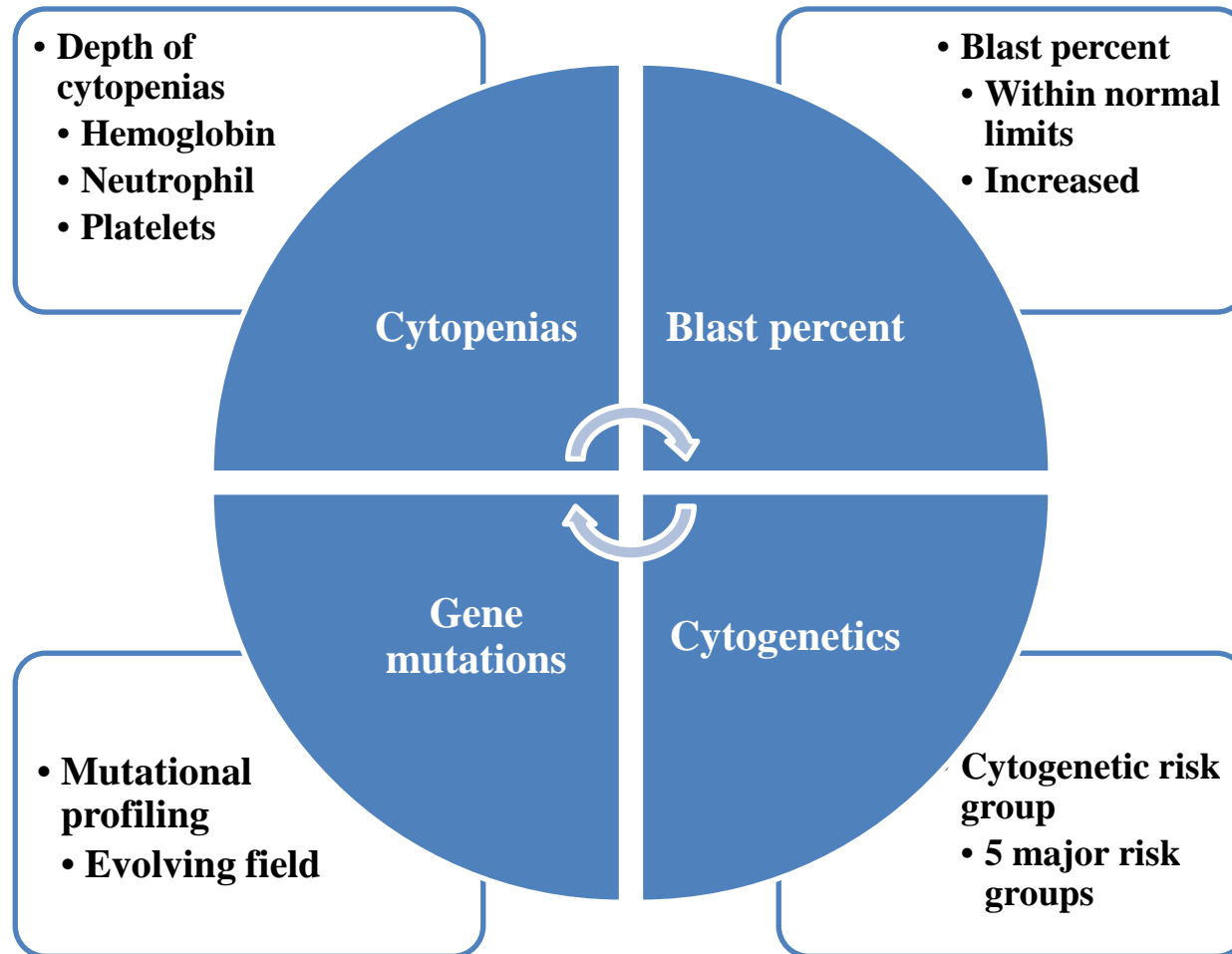
# Why Risk Stratify?

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- **Clinically and molecularly heterogeneous disease**
- **Outcomes varies substantially**
  - Even within same morphologic subtypes
- **Risk stratification facilitates tailoring of therapeutic interventions**

# Variables influencing Risk in MDS

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# Prognostic systems for MDS

Prognostic system	Age	PS	WBC or ANC	Plt	Hb	Transf	BM blast %	Cytogenetics	WHO class.	Ref
Bournemouth	X		X	X	X		X			Mufti, Br J Haem, 1985
Spanish	X			X			X			Sanz, Blood 1989
Lille				X			X	X		Morel, Leukemia 1996
IPSS			X	X	X		X	X		Greenberg, Blood 1997
WPSS						X		X	X	Malcovati, JCO 2007
MDACC	X	X	X	X		X	X	X		Kantarjian, Cancer 2008

# Revised International Prognostic Scoring System for MDS (IPSS-R)

- **Rationale:** To refine the IPSS, an important standard for assessing prognosis of primary untreated adult MDS patients (IPSS-R, N = 7,012).
- **IPSS Limitations:**
  - Validated in previously untreated patients with 1° MDS.
  - No. of cytopenias factored, but not severity, e.g., transfusion dep.
  - Limited number of cytogenetic abnormalities included, and high-risk abnormalities not accorded sufficient emphasis.

Refinements of the IPSS-R beyond the IPSS	
New marrow blast categories	≤2, >2-<5, 5, 10, >10-30%
Refined cytogenetic abnormalities and risk groups	16 (vs. 6) specific abnormalities, 5 (vs. 3) subgroups
Evaluation of the depth of cytopenias	Clinically and statistically relevant cutpoints used
Inclusion of differentiating features	Age, Performance Status, Serum Ferritin, LDH, Beta-2 microglobulin
Prognostic model with 5 (vs. 4) risk Categories	Improved predictive power

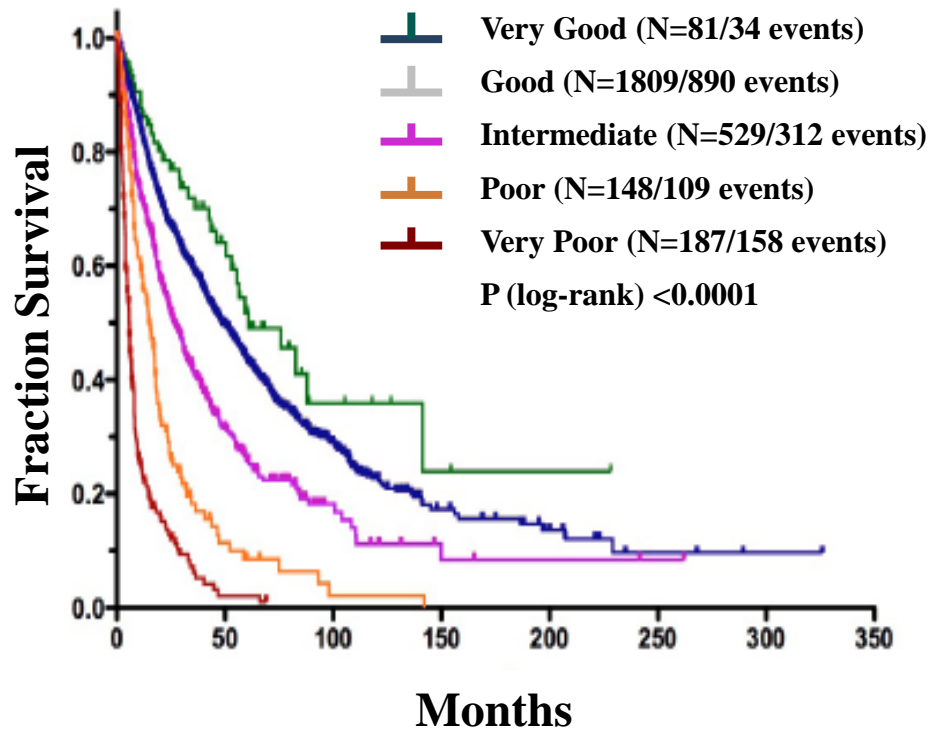
# MDS Cytogenetic Scoring System (IPSS-R)

Prognostic subgroups (% patients)	Cytogenetic abnormalities	Survival Years, median	AML evolution, 25% Years, median	Hazard ratios OS/AML	Hazard ratios OS/AML
<b>Very good (4%)</b>	-Y, del(11q)	5.4	NR	0.7/0.4	0.5/0.5
<b>Good (72%)</b>	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.5	1/1	1/1
<b>Intermediate (13%)</b>	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.6	1.5/1.8	1.6/2.2
<b>Poor (4%)</b>	-7, inv(3)/t(3q)/del(3q), double incl -7/del(7q), complex: 3 abn	1.5	1.7	2.3/2.3	2.6/3.4
<b>Very poor (7%)</b>	Complex: >3 abnormalities	0.9	0.7	3.8/3.6	4.2/4.9

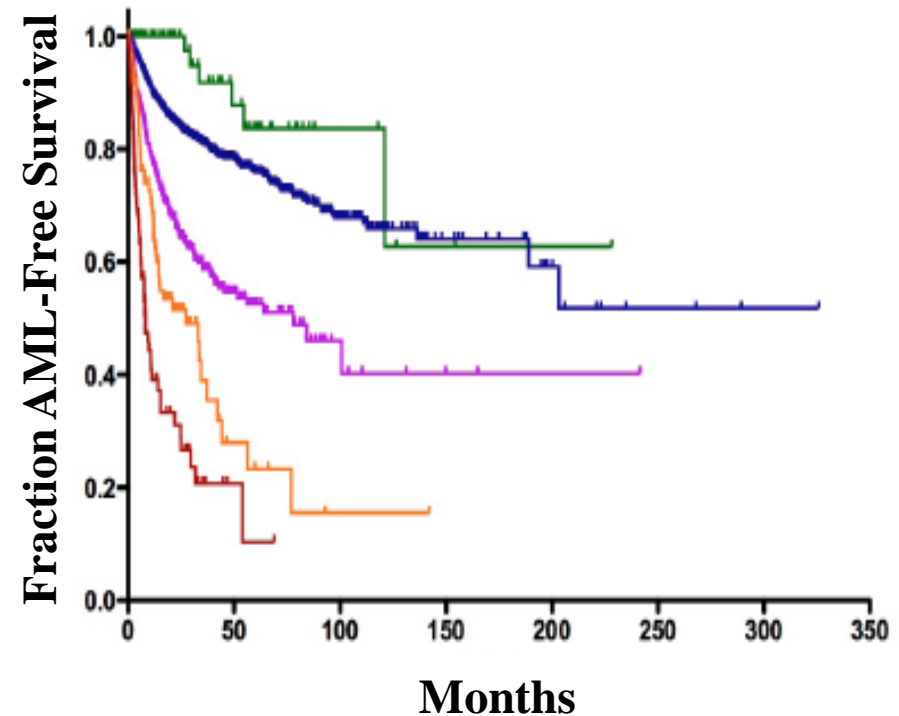
Greenberg et al., Blood, 2012

# Cytogenetic Prognostic Subgroups

## Overall Survival



## Risk of Progression to AML



# IPSS-R: Prognostic Variables and Score Values

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Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good		Good		Intermediate	Poor	Very Poor
BM blast %	$\leq 2$				5-10%	>10%	
Hemoglobin	$\geq 10$		8-<10	<8			
Platelets	$\geq 100$	50-100	<50				
ANC	$\geq 0.8$	<0.8					

BM- bone marrow; ANC-absolute neutrophil count

# Stratification based on IPSS/IPSS-R

IPSS (N=816)	Score	Risk Group	Median Survival in years
	0	Low	5.7
	0.5-1.0	Intermediate-1	3.5
	1.5-2.0	Intermediate-2	1.2
	$\geq 2.5$	High	0.4

IPSS-R (N=7,012)	Points	Risk Score	Median survival in years
	$\leq 1.5$	Very Low	8.8
	$> 1.5-3$	Low	5.3
	$>3-4.5$	Intermediate	3.0
	$>4.5-6$	High	1.6
	$>6$	Very high	0.8

# Many patients with MDS have a cytogenetically normal subtype

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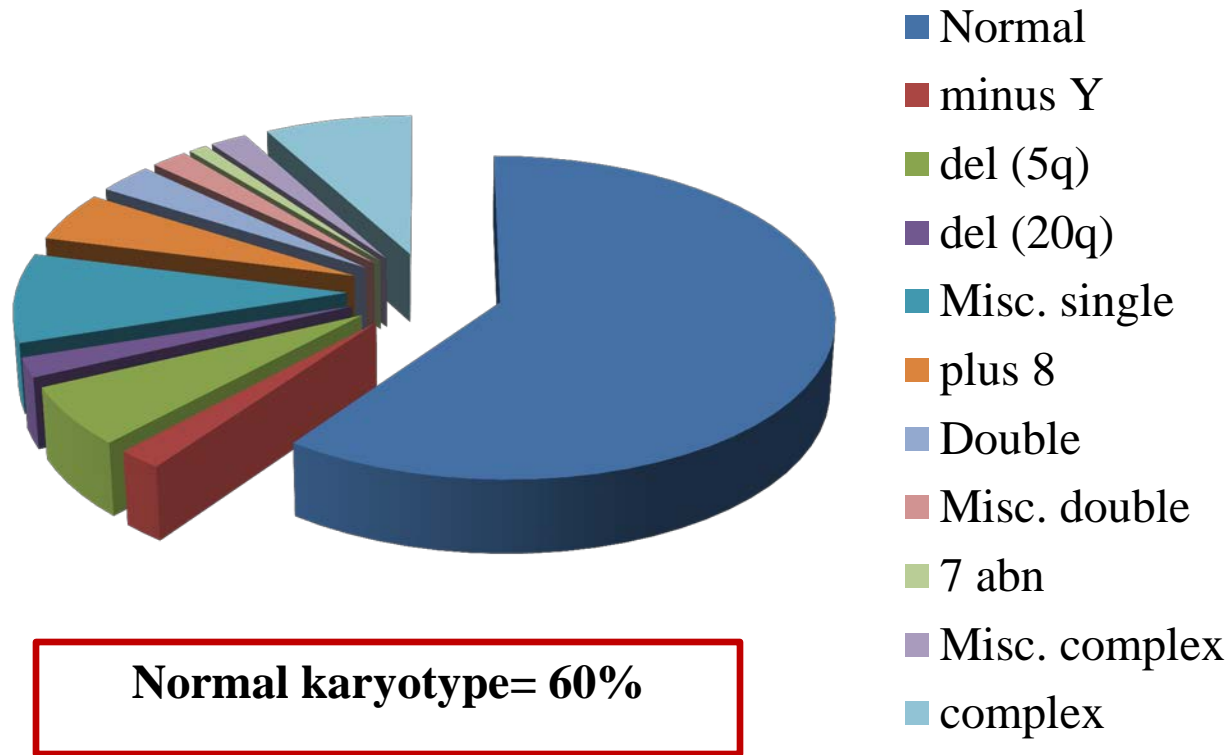
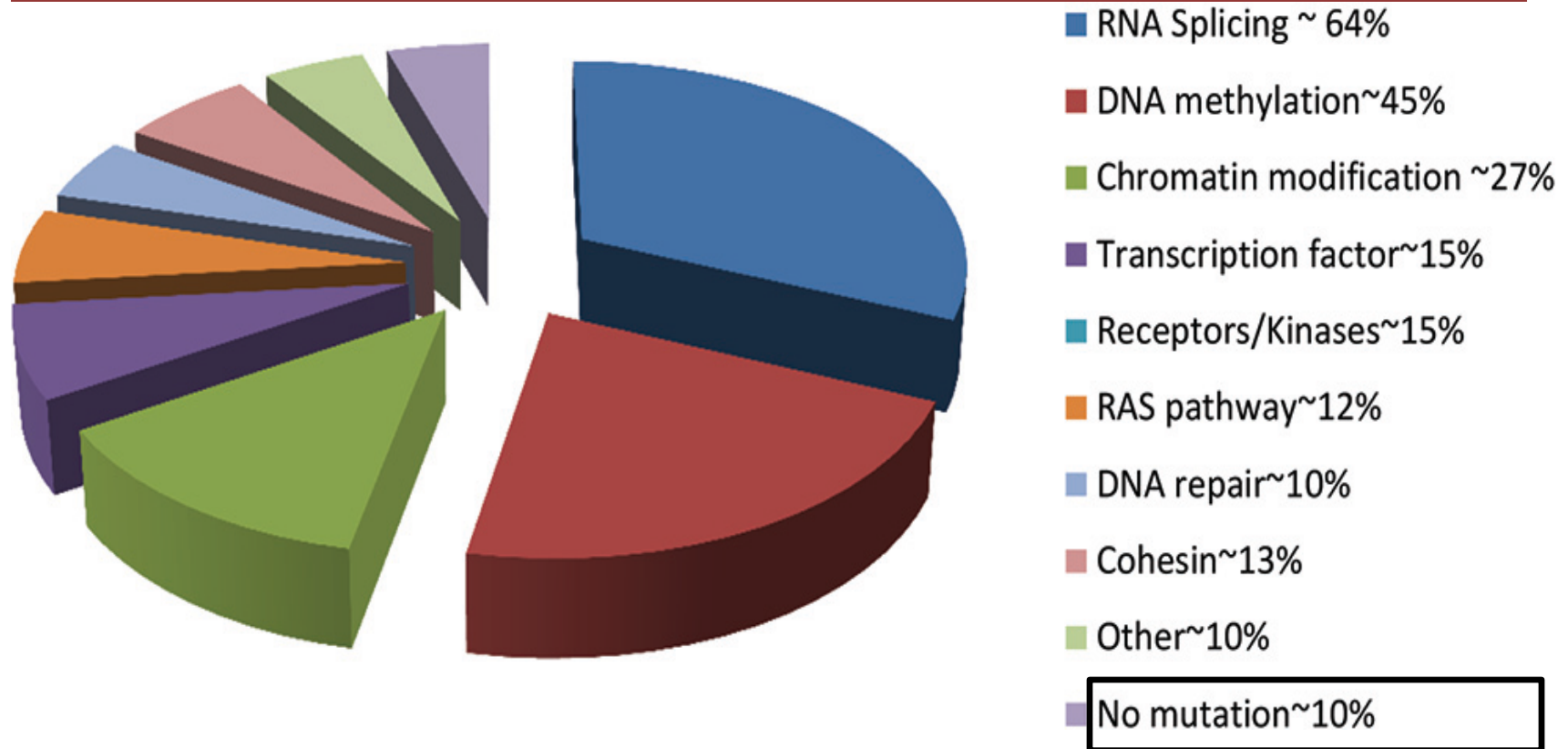


Chart derived from data published by Greenberg et al, Blood, 1997  
Recent cytogenetic data sets e.g. Schanz et al, JCO 2012 report similar percentages of patients with normal karyotype

# Mutations Occur in the Majority > 90% of Patients with MDS



**RNA splicing:** *SF3B1, SRSF2, U2AF1, U2AF2, ZRSR2*

**DNA methylation:** *TET2, DNMT3A, IDH1/2*

**Chromatin modification:** *ASXL1, EZH2*

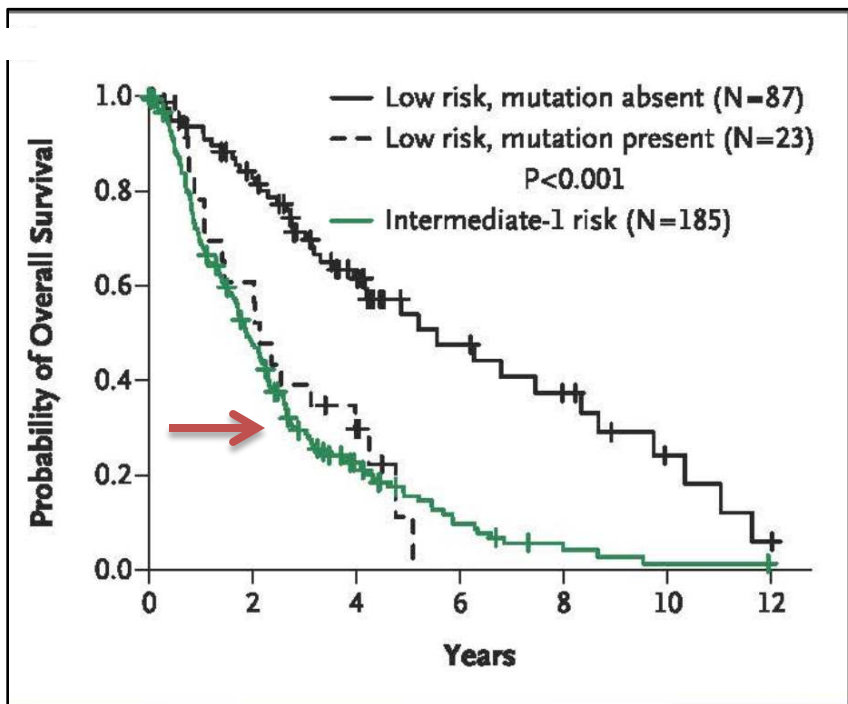
**Transcription factor:** *TP53, EVI1, RUNX1, GATA2*

**RAS/receptor kinase pathways:** *NRAS, KRAS, CBL, JAK2*

*Chart is based on data from 944 MDS patients -Haferlach et al, Leukemia 2014*

Odenike et al, ASCO  
Ed Book, 2015

# The mutational status of five genes *TP53*, *EZH2*, *ETV6*, *RUNX1*, *ASXL1* predicts poor prognosis in MDS

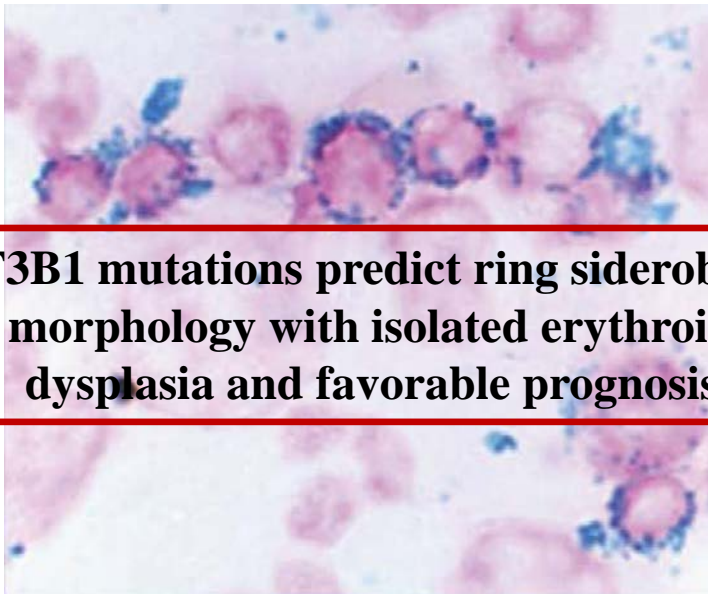


**Table 2. Hazard Ratios for Death in a Multivariable Model.\***

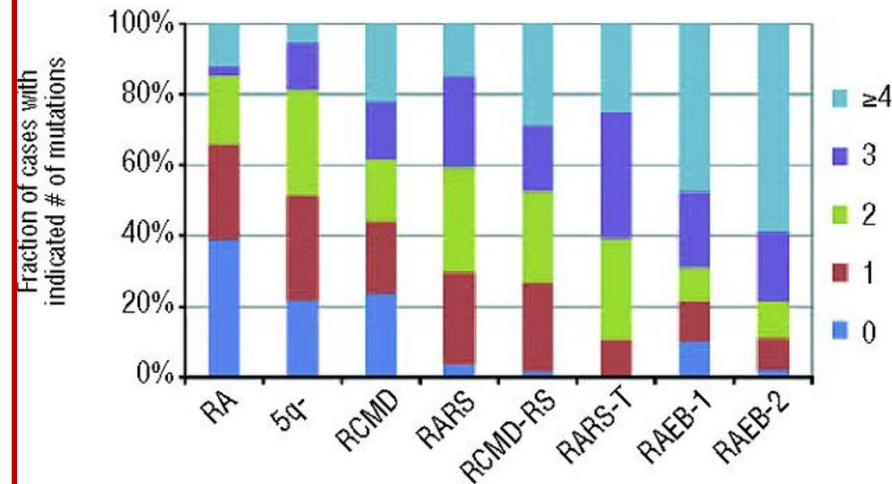
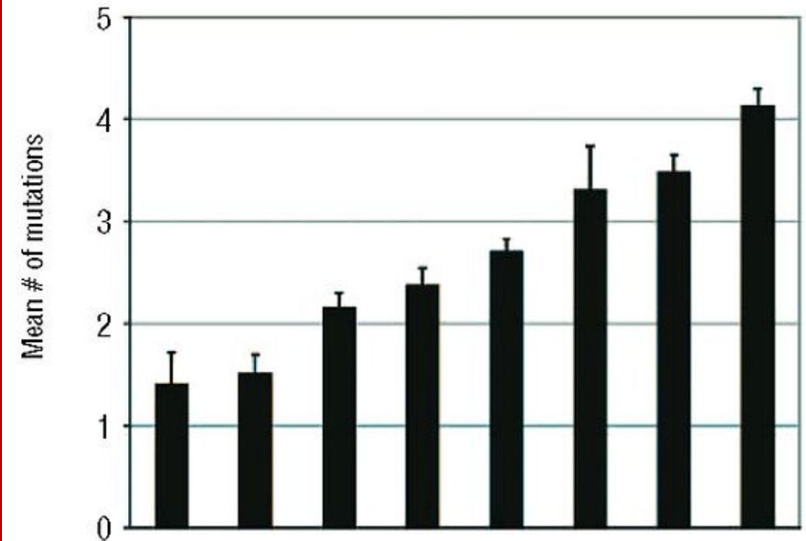
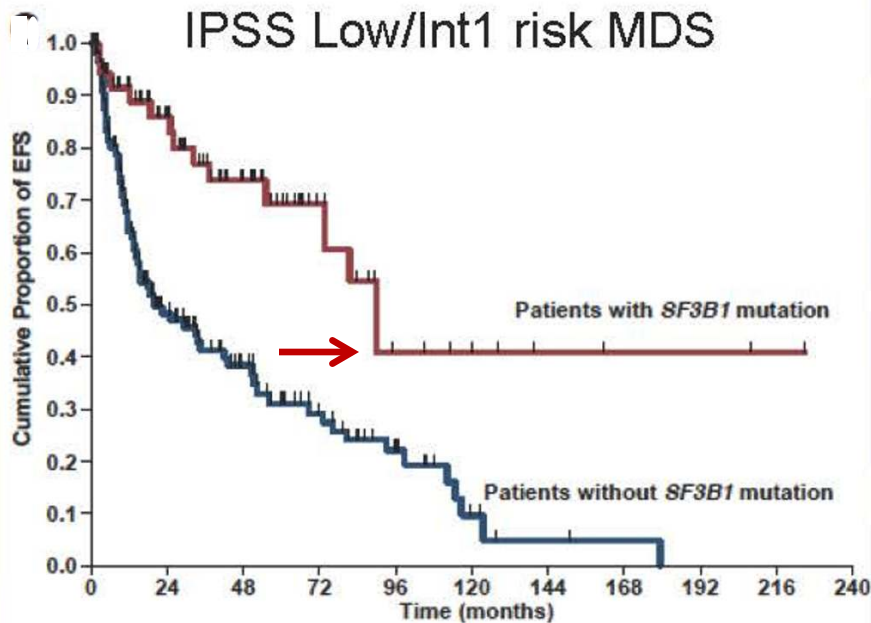
Risk Factor	Hazard Ratio (95% CI)	P Value
Age ≥55 yr vs. <55 yr	1.81 (1.20–2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69–3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42–4.91)	<0.001
High vs. low	5.85 (3.63–9.40)	<0.001
Mutational status		
<i>TP53</i> mutation present vs. absent	2.48 (1.60–3.84)	<0.001
<i>EZH2</i> mutation present vs. absent	2.13 (1.36–3.33)	<0.001
<i>ETV6</i> mutation present vs. absent	2.04 (1.08–3.86)	0.03
<i>RUNX1</i> mutation present vs. absent	1.47 (1.01–2.15)	0.047
<i>ASXL1</i> mutation present vs. absent	1.38 (1.00–1.89)	0.049

- 111 genes analyzed in 439 patients with MDS.
- Within each IPSS subgroup, the presence of one or more of these mutations resulted in a decline in overall survival approximating that of next higher risk IPSS subtype

# Clinical-Genotype Associations in MDS



**SF3B1 mutations predict ring sideroblast morphology with isolated erythroid dysplasia and favorable prognosis**



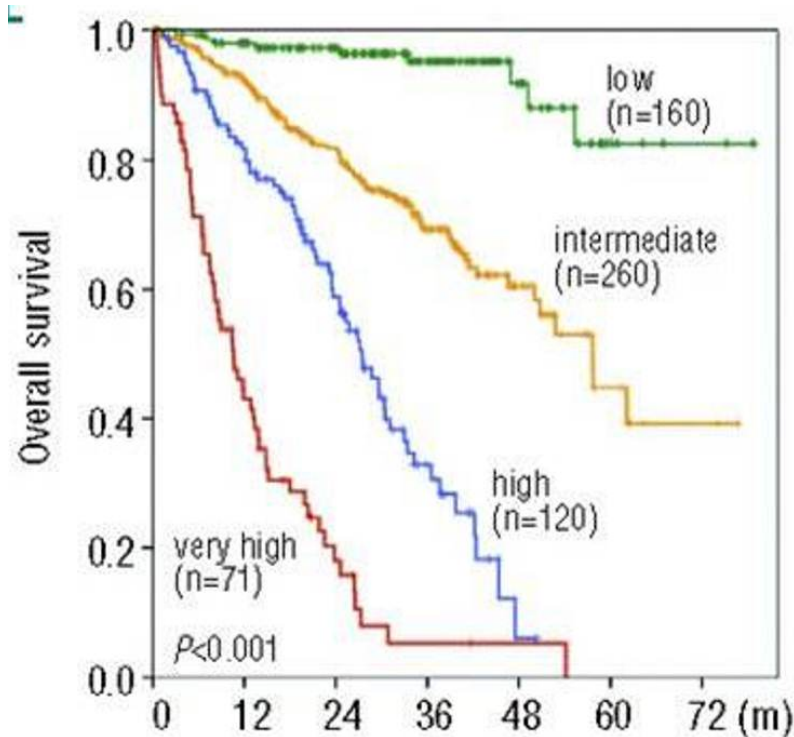
Malcovati L et al, Blood 2011; 2014; Malcovati L et al, Blood 2015; Haferlach et al, Leukemia

# Gene Mutations in MDS

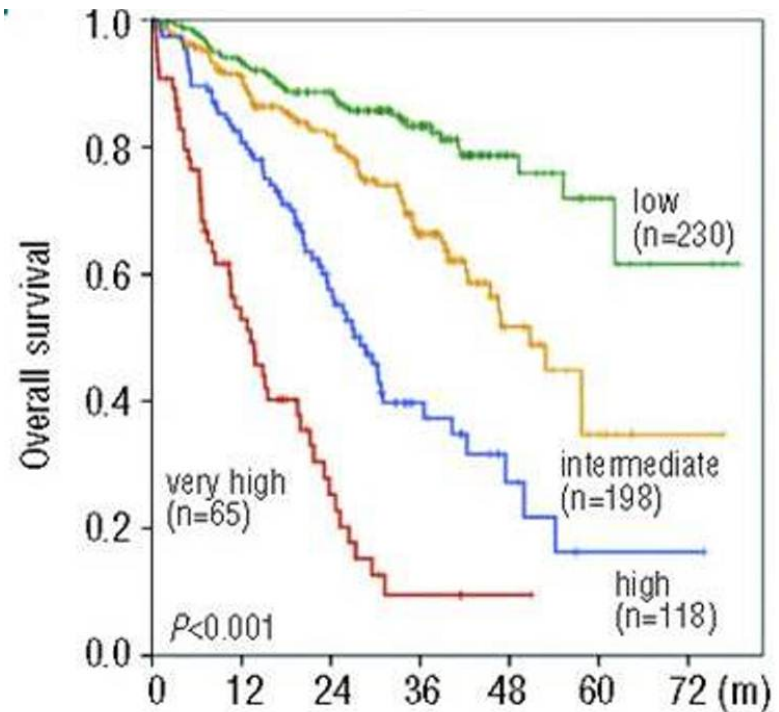
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- **Frequent**
  - Occurring in approximately 90% of patients
  - Median of 2-3 per patient (range 1-12)
  - More than 40 genes are recurrently mutated
  - Provided insights into pathogenesis of MDS
- **Specific gene mutations also associated with prognosis and/or clinical phenotype**
  - TP53, EZH2, ETV6, RUNX1, ASXL1- poor risk
  - SF3B1:ring sideroblasts- good risk

# Can molecular and clinical risk factors be integrated?



**Molecular variables only**



**Molecular+ Clinical variables**

# **STEP 3: Assess the need for therapy?**

# Indications for therapy

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- **Significant impairment in blood counts**
  - predisposes to infections, bleeding, significant fatigue or other complications of the disease
- **Higher risk disease**

# Treatment Options

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## Erythropoietin stimulating agent (ESA)

- Lower risk disease
- EPO sensitive disease
- Goal is to improve red cell count
- Includes erythropoietin (Procrit) and darbopoietin (Aranesp)

## Hypomethylating agents

- Higher risk disease
- Goals are to improve blood counts, delay transformation to acute leukemia and improve survival
- Includes azacitidine (vidaza) and decitabine (dacogen)

## Allogeneic stem cell transplantation

- Higher risk disease
- Goal is to improve survival and cure the disease
- Careful assessment of potential risks vs benefits is extraordinarily important

Treatment intensity

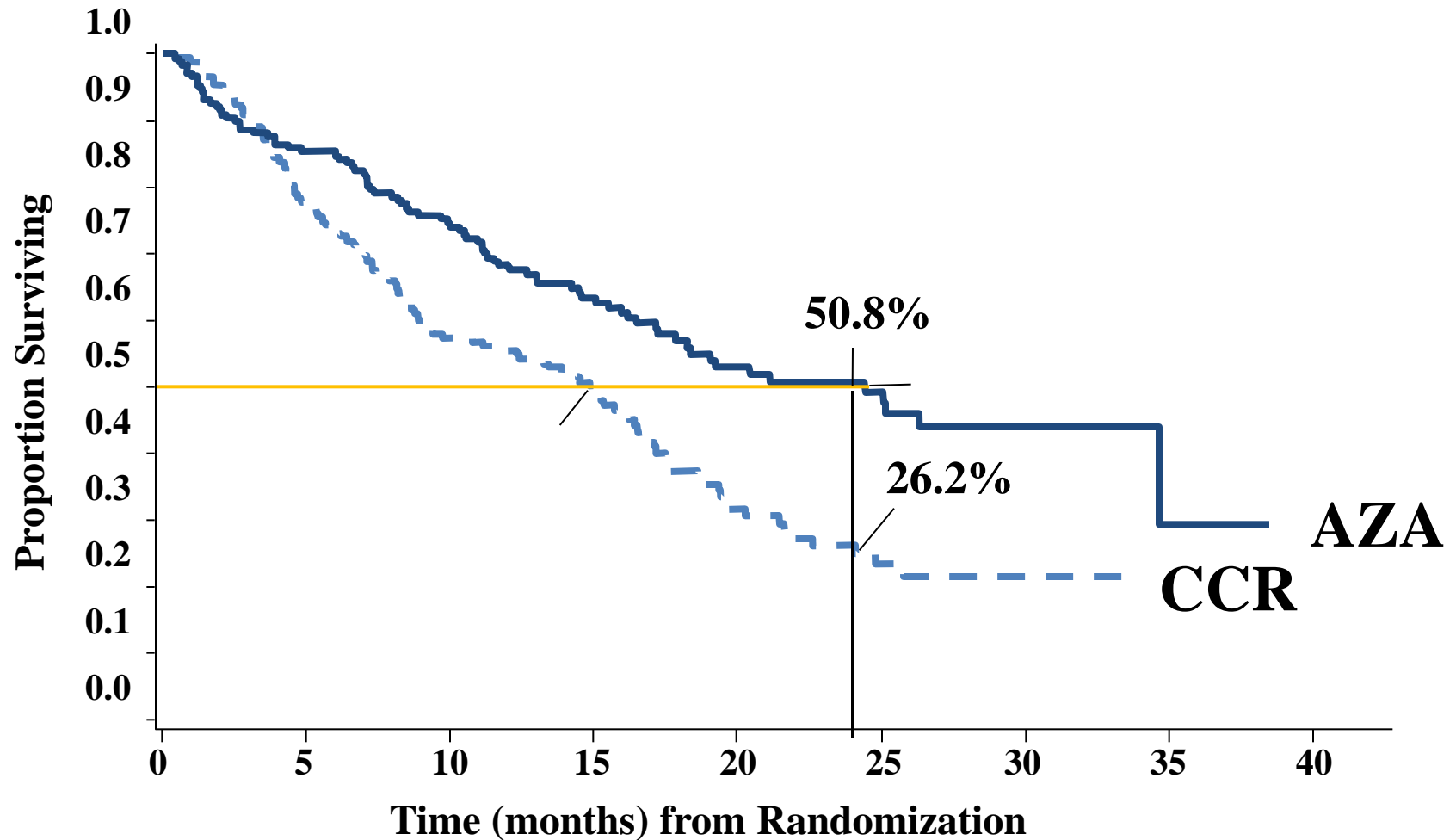


# Hypomethylating agents

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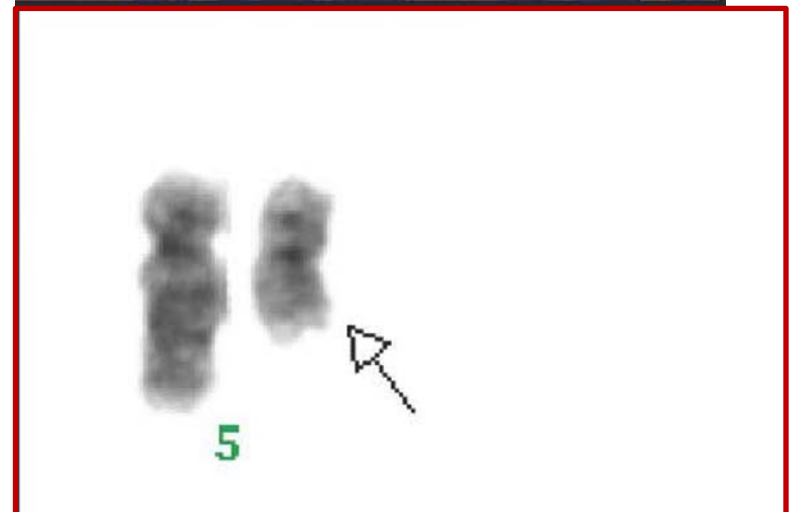
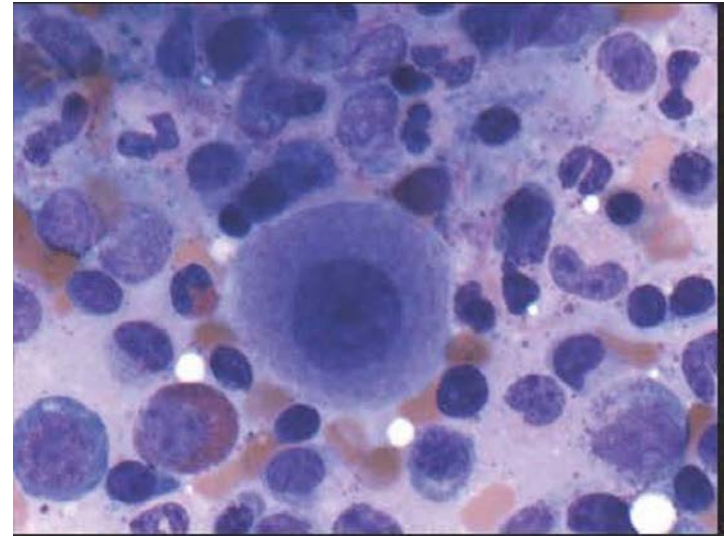
- **Azacitidine and decitabine approved in the USA**
- **Improve bone marrow function and blood counts in 40 to 50% of patients**
- **Average time to onset of response is 2 to 4 months, but responses can take up to 6 months or longer to occur**
- **Risks include significant lowering of blood counts prior to onset of response**

# Azacitidine(AZA) versus Conventional Care Regimens (CCR) in Higher Risk MDS



# Deletion 5 q MDS

- **Deletion 5 q is the only cytogenetic abnormality**
- **Dysplasia in one or more lineages**
- **Blasts are generally not increased**
- **Excellent response to lenalidomide**



# Lenalidomide in lower risk MDS

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- Immunomodulatory agent with pleiotropic effects
- Significant activity in MDS with del 5q<sup>1,2</sup>
  - Red cell transfusion independence rate of 67%
  - Sensitivity linked to haploinsufficiency of CSKN1 in commonly deleted region of 5q<sup>3</sup>
- Activity in non-del 5q is modest<sup>4</sup>
- FDA approved for use in MDS associated with del 5q

1. List A et al, NEJM 2005
2. Fenaux P et al, Blood 2011
3. Kronke J et al, Nature 2015
4. Raza A et al, Blood 2008

# Risk Stratification by IPSS/R-IPSS

**Lower risk  
+  
Need for therapy**

**Non-Del 5q**

- ESAs if EPO <500 and anemic
- Clinical trial or azanucleosides if pancytopenic and /or prior ESA exposure.
- Consider IST

**Del 5 q**

**Lenalidomide**

**Higher Risk**

- Early referral for allogeneic SCT
- Hypomethylating agent based (HMA) therapy
- Clinical trial if prior HMA exposure

# **Clinical Trials in MDS**

# **Anemia in non-del 5q MDS lower risk MDS unresponsive/refractory to ESAs**

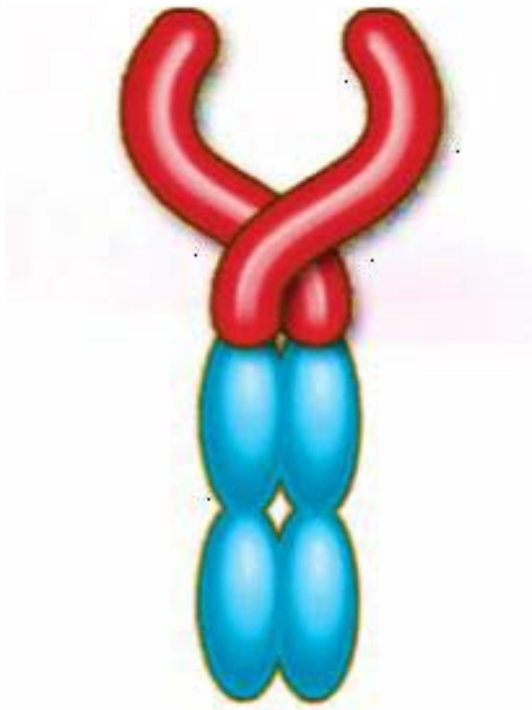
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- **Anemia remains a problematic issue in non-del 5qMDS**
  - **Combination of lenalidomide and EPO may also be beneficial <sup>1</sup>**
- **Understanding the molecular pathways mediating anemia may lead to more effective targeted therapeutic approaches given the molecular heterogeneity of this disease**

# **Novel agents for the treatment of anemia in lower risk MDS**

# Luspatercept (ACE-536)

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- **Modified activin receptor type IIB (ActRIIB) fusion protein**
  - **Binds TGF beta ligands and modulates TGF beta signaling pathway**
- **Enhances erythropoiesis**
- **Early phase clinical trials demonstrate potential for anemia improvement in MDS**
- **Larger clinical trials in lower risk MDS would be worthwhile**

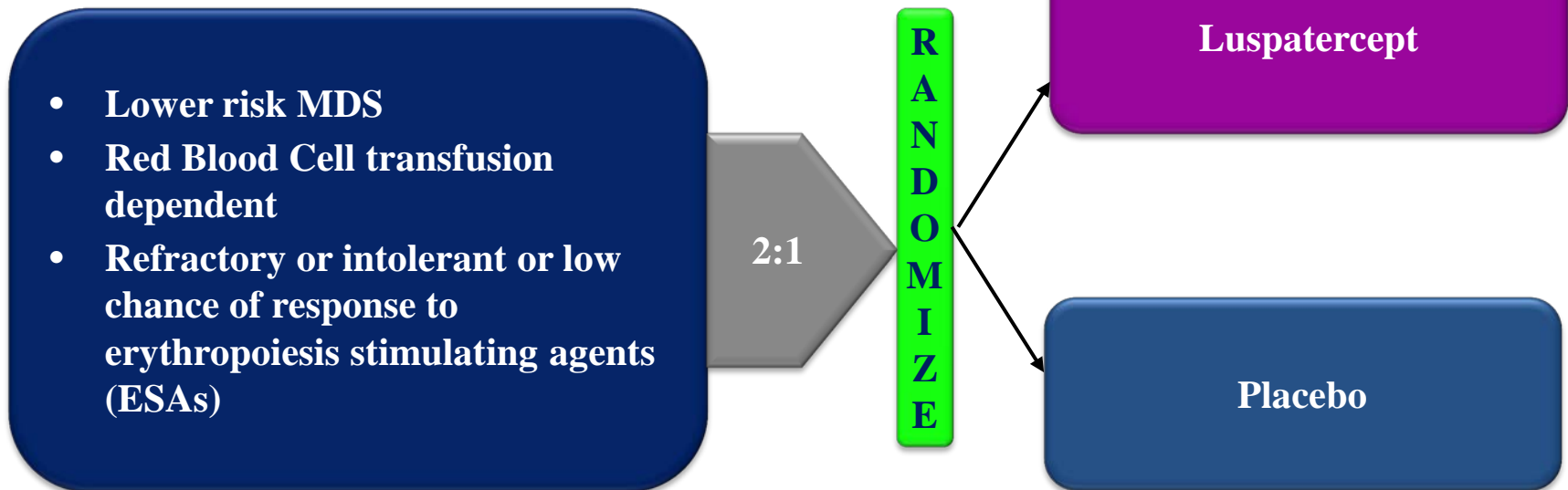
**A phase 3, randomized, double-blind study of luspatercept (ACE-536) in patients (pts) with Revised International Prognostic Scoring System (IPSS-R) very low- to intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts (RS) who require red blood cell (RBC) transfusions: The MEDALIST trial.**

**Uwe Platzbecker, Rami S. Komrokji, Pierre Fenaux, Guillermo Garcia-Manero, Ghulam J. Mufti, Mikkael A. Sekeres, Jennie Zhang, Aziz Benzohra, Abderrahmane Laadem, Bond Vo, Kenneth M. Attie, Alan F. List; Technical University Dresden, Dresden, Germany; Moffitt Cancer Center, Tampa, FL; Service d'Hématologie Séniors/Hôpital Saint-Louis, Université Paris 7, Paris, France; The University of Texas MD Anderson Cancer Center, Houston, TX; King's College Hospital, London, United Kingdom; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Celgene Corporation, Summit, NJ; Celgene Corporation, Boudry, Switzerland; Acceleron Pharma, Cambridge, MA**

# Luspatercept in lower risk MDS

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- Double blind, placebo controlled 2:1 randomization in lower risk MDS unresponsive or refractory to ESAs (n=210)
- Primary endpoint is rate of RBC transfusion independence  $\geq 8$  weeks in first 24 weeks of treatment



# Contemporary investigational approaches in MDS

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- **Novel formulations of azanucleosides**
  - SGI-110
  - Oral decitabine+cytidine deaminase inhibitor
  - Oral azacitidine
- **Immune checkpoint inhibitors**
  - Pembrolizumab
  - Nivolumab
  - MEDI4736
- **BCL2 Inhibitors**
- **Spliceosomal modulators**
- **Kinase inhibitors**
  - MEK inhibitors

# **Successful Emulation of IV Decitabine Pharmacokinetics with an Oral Fixed-Dose Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine, in Subjects with Myelodysplastic Syndromes (MDS): Final Data of Phase 1 Study**

**Guillermo Garcia-Manero, MD, Olatoyosi Odenike, MD, Philip C. Amrein, MD, David P. Steensma, MD, Amy E. DeZern, MD, MHS, Laura C. Michaelis, MD, Stefan Faderl, MD, Hagop M. Kantarjian, MD, James N. Lowder, MD, Pietro Taverna, PhD, Aram Oganessian, PhD, Xiaoping Zhang, PhD, Mohammad Azab, MD and Michael R. Savona, MD**

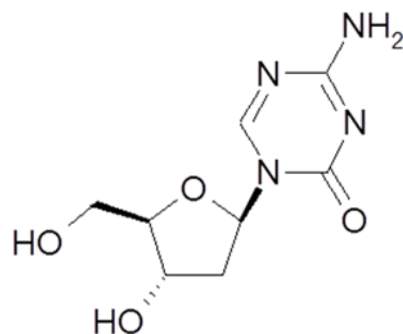
# **Oral formulations of hypomethylating agents?**

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- **Hypomethylating agents bind to DNA methyltransferase resulting in progressive loss of DNMT activity and subsequent DNA hypomethylation**
- **Orally available hypomethylating agents might permit extended administration schedules, prolonged hypomethylation, improved convenience**
- **Hypomethylating agents are rapidly cleared in the gut and liver by cytidine deaminase (CDA) therefore not orally bioavailable**

# ASTX727: Oral Decitabine plus oral cytidine deaminase inhibitor

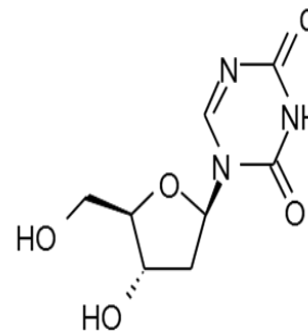
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Decitabine

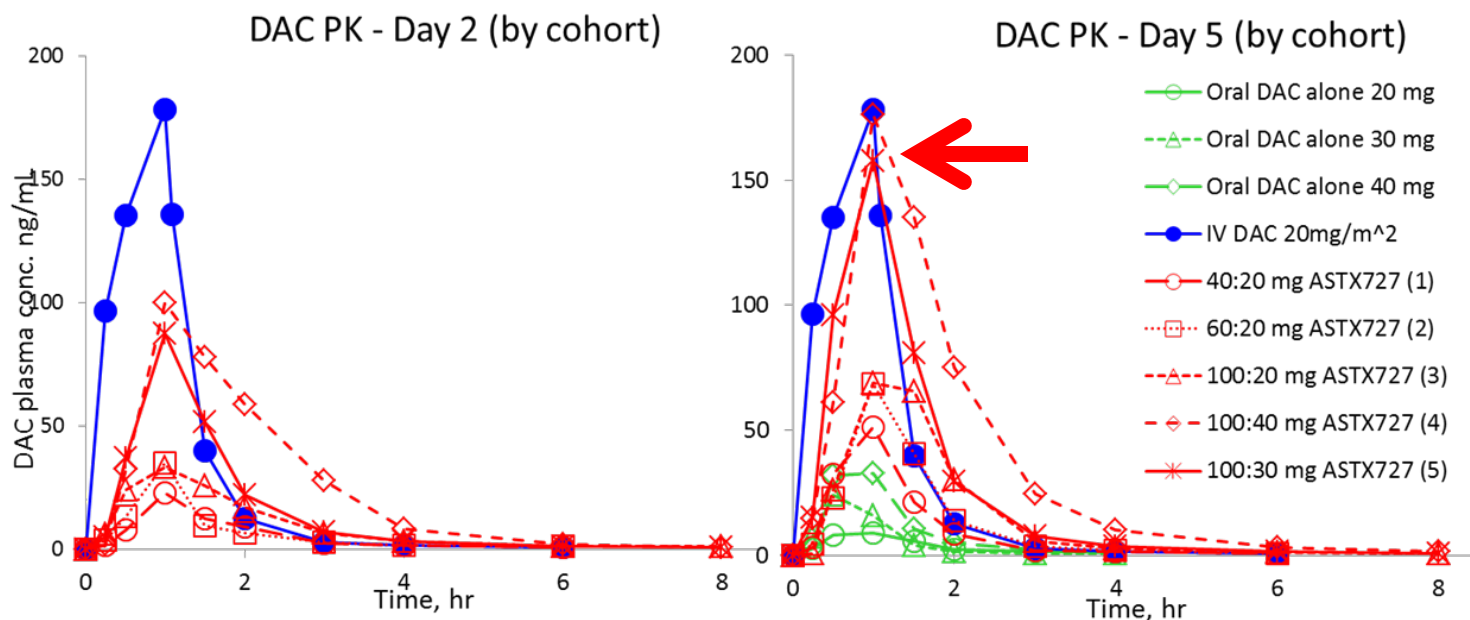


E7727 CDA inhibitor



Inactive metabolite

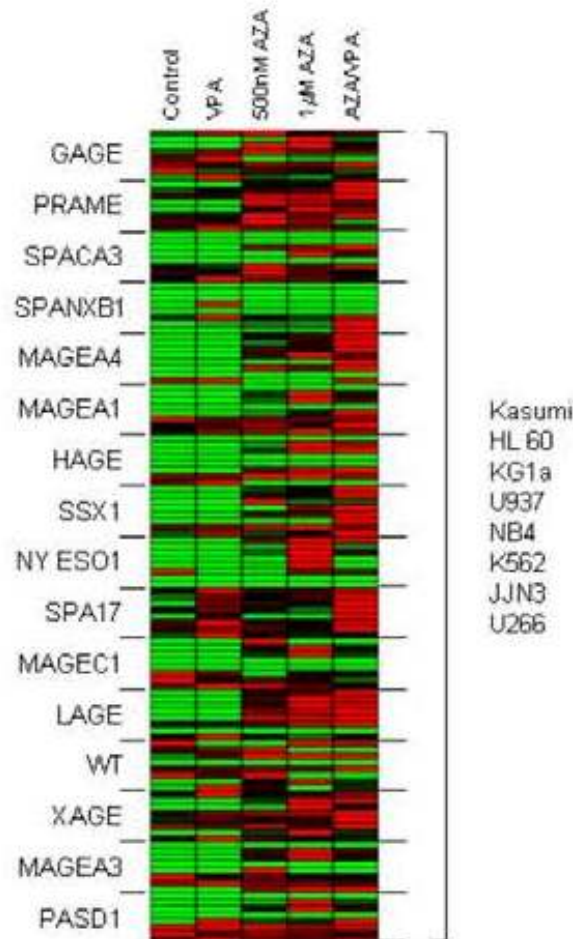
# ASTX727: Pharmacokinetics and Pharmacodynamics (n=43)



- Dose level of oral DAC 30mg plus 100mg E7727 achieves equivalent AUC as 20mg/m<sup>2</sup> IV DAC
- Similar toxicity profile
- Encouraging signs of clinical efficacy

# **Harnessing the Immune System in MDS**

# Hypomethylating agents (HMAs)



**HMAs may act as immunosensitizer and facilitate immune recognition and cytotoxic T cell killing**

# **Immune Check Point Inhibitors combined with Hypomethylating agents (HMAs)**

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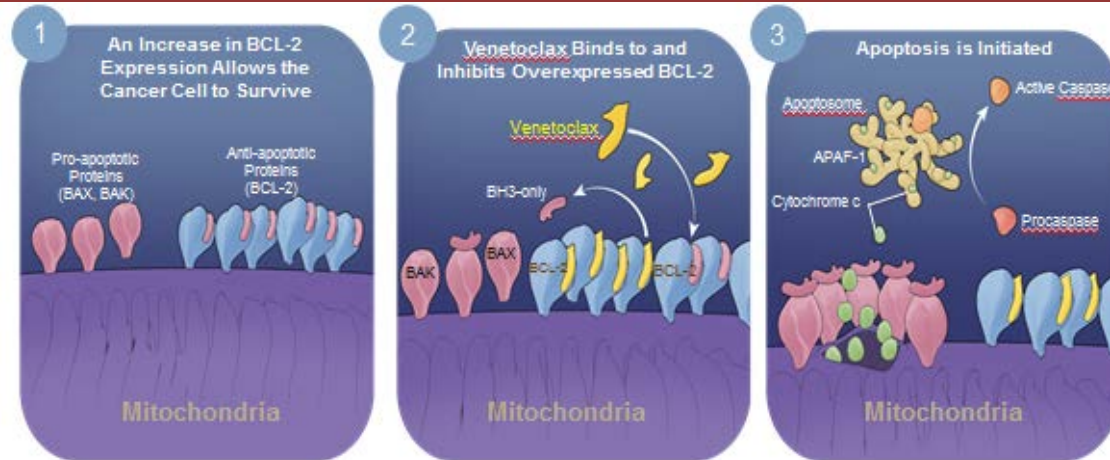
- **Anti PDL-1, anti-PD1, anti CTLA4**
  - **Block co-inhibitory molecules such as PD1/PDL1 or CTLA4, enhancing effector T cell response**
- **HMAs enhance expression of PD-1 and PDL-1 in MDS and may synergize with checkpoint inhibitors**

# Immune checkpoint inhibition in MDS: Study Design

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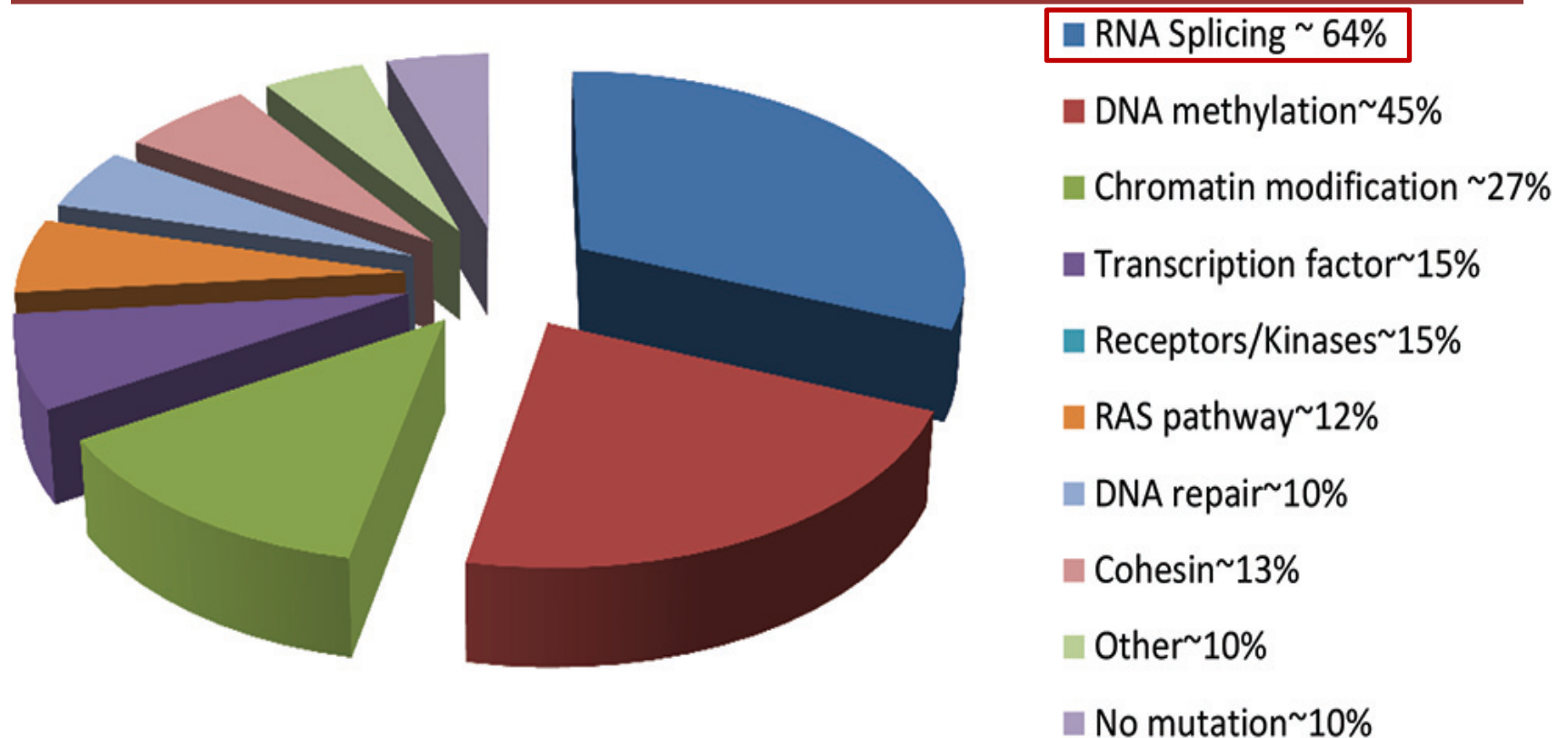
Cohort	Therapy
Cohort #1	Nivolumab 3 mg/kg IV q2 weeks
Cohort #2	Ipilimumab 3 mg/kg IV q3 weeks
Cohort #3	Nivolumab 3 mg/kg IV q2 weeks Ipilimumab 3 mg/kg IV q4 weeks
Cohort #4	Azacitidine 75 mg/m <sup>2</sup> IV x 5 days q28 Nivolumab 3 mg/kg IV on day 6 and 20
Cohort #5	Azacitidine 75 mg/m <sup>2</sup> IV x 5 days q28 Ipilimumab 3 mg/kg IV on day 6
Cohort #6	Azacitidine 75 mg/m <sup>2</sup> IV x 5 days q 28 Nivolumab 3 mg/kg IV on day 6 and 20 Ipilimumab 3 mg/kg IV on day 6

# BCL2 inhibition in myeloid neoplasia



- **BCL2 overexpression is associated with disease progression and drug resistance**
- **Venetoclax is a potent orally bioavailable inhibitor of BCL2**
- **Preclinical evidence of synergy with hypomethylating agents**
- **Ongoing clinical trials of venetoclax in combination with DEC or AZA**

# Targeting Gene mutations in MDS?



**RNA splicing (spliceosomal mutations): *SF3B1*, *SRSF2*, *U2AF1*, *U2AF2*, *ZRSR2*; occur in >60% of patients with MDS**

Chart is based on data from 944 MDS patients -*Haferlach et al, Leukemia 2014*  
Odenike et al, ASCO Ed Book, 2015

# **H3B 8800, an orally bioavailable modulator of the SF3b Complex shows efficacy in Spliceosome – mutant myeloid malignancies**

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- **Preferential inhibition of cell growth in spliceosome mutant cells compared to normal cells**
- **Activity in mouse models of spliceosome mutant myeloid malignancies**
- **Ongoing Phase I trial in relapsed refractory spliceosome mutant myeloid malignancies**

# **Ongoing trials in MDS at UCMC:**

## **Frontline trials (HMA naïve)**

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**IRB16-13:** A randomized Phase II study evaluating the safety, pharmacokinetics and efficacy of venetoclax in combination with azacitidine compared with azacitidine alone in subjects with treatment naïve higher risk MDS\*

**IRB15-17:** A Phase II, randomized, controlled, open-label, clinical study of the efficacy and safety of pevonedistat plus azacitidine versus single agent azacitidine in patients with higher risk MDS, CMML and low blast count AML

**IRB16-0375:** A randomized multicenter, open-label, phase II study evaluating the efficacy and safety of azacitidine subcut in combination with durvalumab in previously untreated subjects with higher risk MDS or in elderly AML subjects not eligible for hematopoietic stem cell transplantation

**IRB14-0702:** A Phase I/II Pharmacokinetic guided dose-escalation and dose confirmation study of ASTX727, a combination of the oral cytidine deaminase inhibitor (CDAi) E7727 with oral decitabine in subjects with MDS

**Upcoming:** Investigator initiated (IRB pending)- Phase I study of azacitidine plus the MEK inhibitor selumetinib\*

\*activation pending

# **Ongoing trials in MDS at UCMC**

## **(prior exposure to hypomethylating agents):**

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**IRB 16-1519: A Phase 1b study evaluating the safety, pharmacokinetics and efficacy of venetoclax as a single agent and in combination with azacitidine in subjects with higher risk MDS after hypomethylating agent failure\***

**IRB16-0372: A Phase II, International, multicenter, randomized, open-label, parallel group study to evaluate the efficacy and safety of CC-486 (oral azacitidine) alone and in combination with durvalumab (MEDI4736) in subjects with myelodysplastic syndromes who fail to achieve an objective response to treatment with azacitidine for injection or decitabine**

**IRB14-0702: A Phase I/II Pharmacokinetic guided dose-escalation and dose confirmation study of ASTX727, a combination of oral cytidine deaminase inhibitor E7727 with oral decitabine in subjects with myelodysplastic syndromes**

**IRB16-1525 A Phase Ib dose escalation study to assess the safety, pharmacokinetics, pharmacodynamics and preliminary efficacy of PLX51107 in subjects with advanced malignancies (this is a novel epigenetic modulator in the bromodomain inhibitor class)\***

**IRB15-1373 A Phase I/II and pharmacological study of OTS167 in patients with refractory or relapsed acute myeloid leukemia, acute lymphoblastic leukemia, advanced myelodysplastic syndromes, advanced myeloproliferative disorders or advanced CML**

**Upcoming: Investigator initiated (IRB pending)- Phase I study of azacitidine plus the MEK inhibitor selumetinib\***

**Upcoming: Phase I trial of the spliceosome inhibitor H3B 8800\***

**\*activation pending**

# Summary

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- **MDS is a clinically and molecularly heterogeneous disease**
- **Individualized treatment approach is necessary**
- **There is a significant need for new therapies in MDS and several agents are under active clinical investigation**

# Acknowledgments

**Our Patients and their Families.**

**Colleagues in the Leukemia/MDS, Transplant and Developmental Therapeutics Programs**