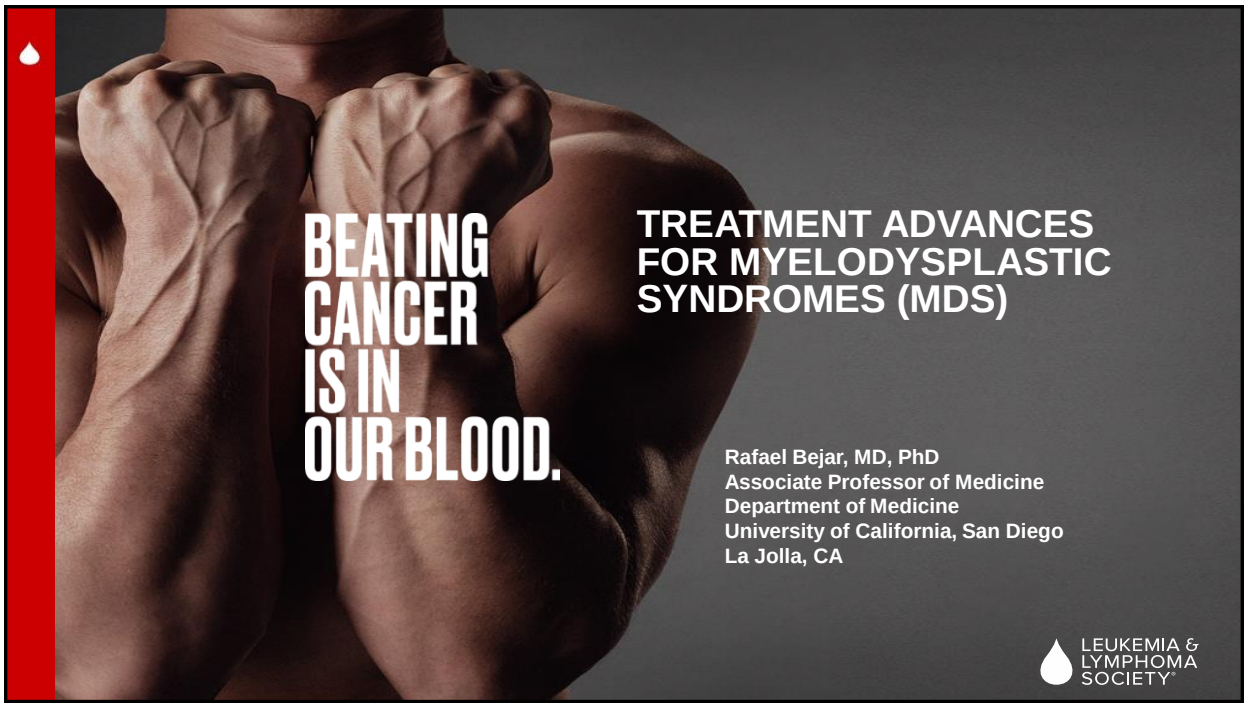

TREATMENT ADVANCES FOR MYELODYSPLASTIC SYNDROMES (MDS)

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University of California, San Diego
La Jolla, CA

LEUKEMIA & LYMPHOMA SOCIETY®

1

DISCLOSURE

Treatment Advances for Myelodysplastic Syndromes (MDS)

Rafael Bejar, MD, PhD has affiliations with: AbbVie, Astex, Celgene, Daiichi-Sankyo, Forty Seven, Inc, NeoGenomics, Takeda, and Xian-Janssen.

Treatment Advances for Myelodysplastic Syndromes (MDS)

Rafael Bejar MD, PhD

The Leukemia and Lymphoma Society

National Patient Webcast

December 17, 2019

UC San Diego Moores Cancer Center

LEUKEMIA & LYMPHOMA SOCIETY®

3

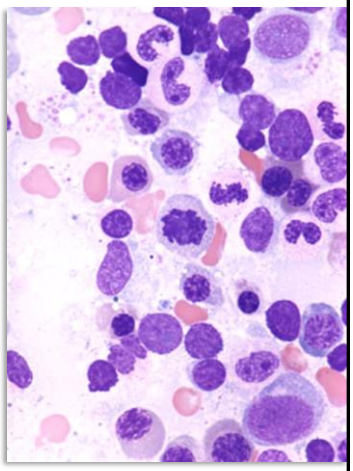
Overview

- Introduction to MDS
- Diagnosis, Classification, and Risk stratification
- Treatment of Lower Risk MDS
- Treatment of Higher Risk MDS
- Novel and Emerging Therapies
- Questions and Answers

4

Myelodysplastic Syndromes

- Shared features:
  - Low blood counts
  - Clonal overgrowth of bone marrow cells
  - Risk of transformation to acute leukemia
- Afflicts 15,000 – 45,000 people annually
- Incidence rises with age (mean age 71)



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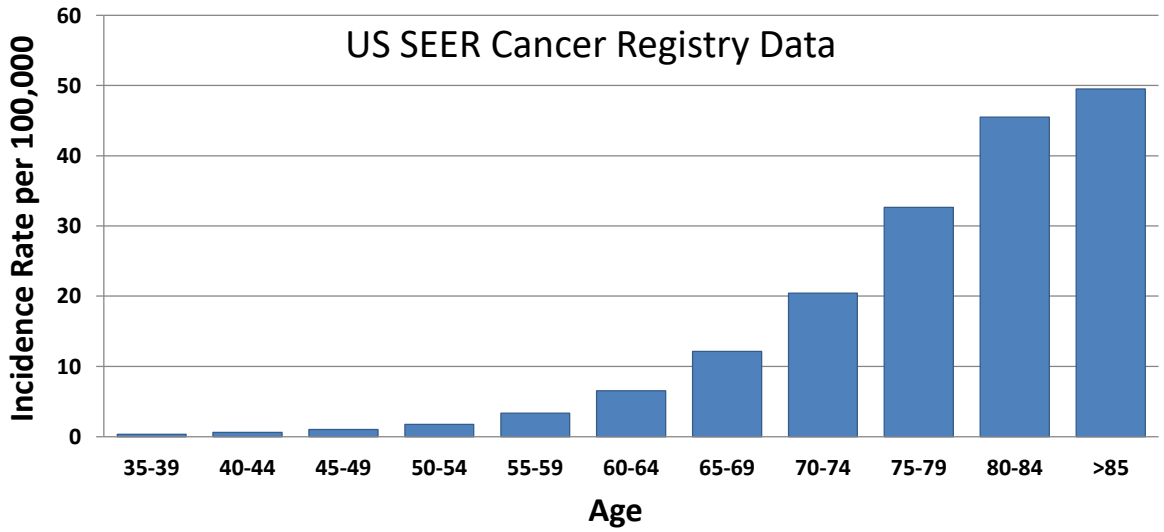
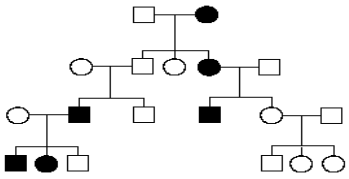
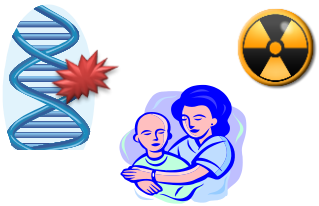
MDS Incidence Rates 2000-2008



http://seer.cancer.gov, Accessed May 1, 2013.

6

Etiology of MDS

<10%	10-15%	80%
Familial or Congenital	**Topoisomerase II inhibitors** **Ionizing radiation** **DNA alkylating agents**	**"De novo"** (idiopathic, primary)
		
Often early onset and part of a larger syndrome	**Peaks 1-3 or 5-7 years following exposure**	Median age ~71 years; increased risk with **aging**

Slide adapted from Dr. David Steensma

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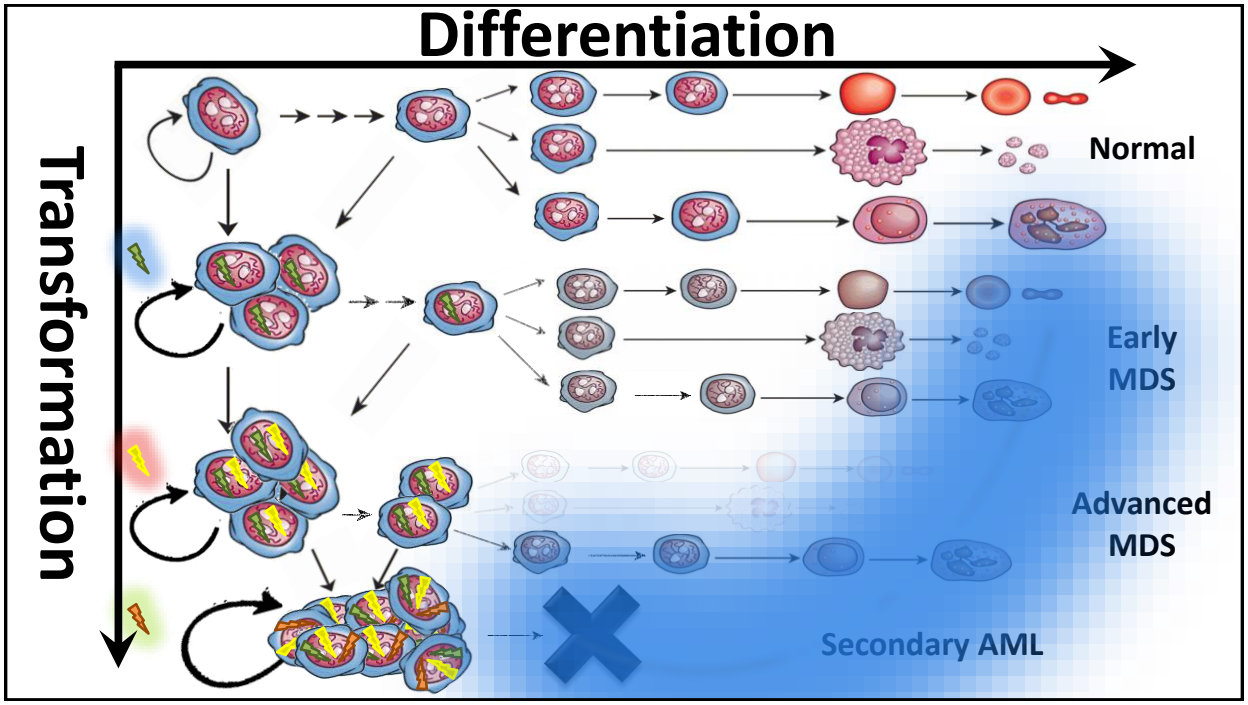

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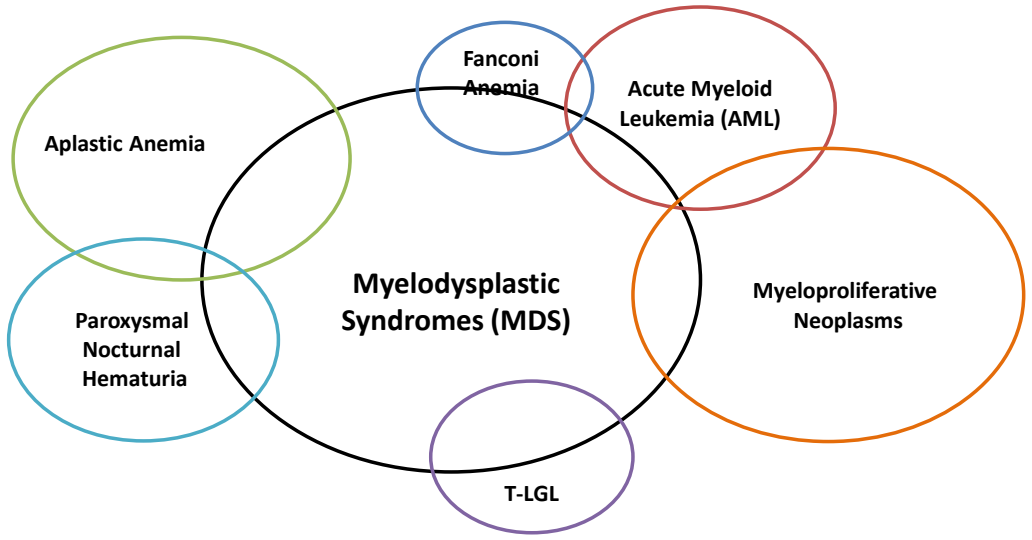
Making the Diagnosis

9

Diagnostic Overlap



10

Minimal Diagnostic Criteria

Cytopenia(s):

- Low hemoglobin, *or*
- Low neutrophil count, *or*
- Low platelet count

MDS "decisive" criteria:

- >10% **dysplastic cells** in 1 or more lineages, *or*
- 5-19% **blasts**, *or*
- Abnormal **karyotype** typical for MDS, *or*
- Specific **mutation** typical of MDS

Other causes of cytopenias and morphological changes EXCLUDED:

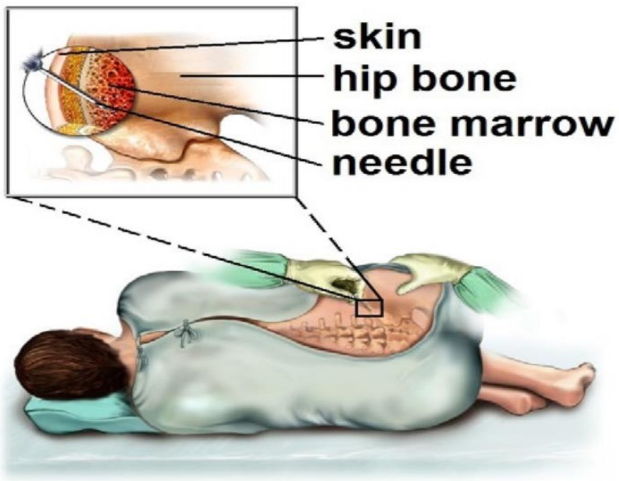
- *Vitamin B12/folate deficiency*
- *HIV or other viral infection*
- *Copper deficiency*
- *Alcohol abuse*
- *Medications (esp. methotrexate, azathioprine, recent chemotherapy)*
- *Autoimmune conditions (ITP, Felty syndrome, SLE etc.)*
- *Congenital syndromes (Fanconi anemia etc.)*
- *Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)*

Slide borrowed from Dr. David Steensma

Valent P et al *Leuk Res* 2007;31:727-736.

11

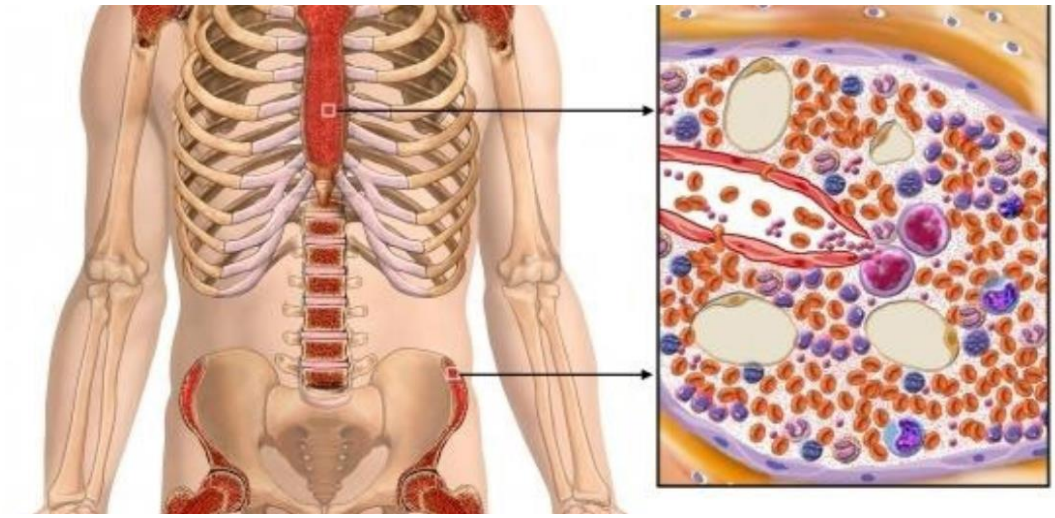
Bone Marrow Biopsy



From: NCCN Guidelines for Patients: MDS

12

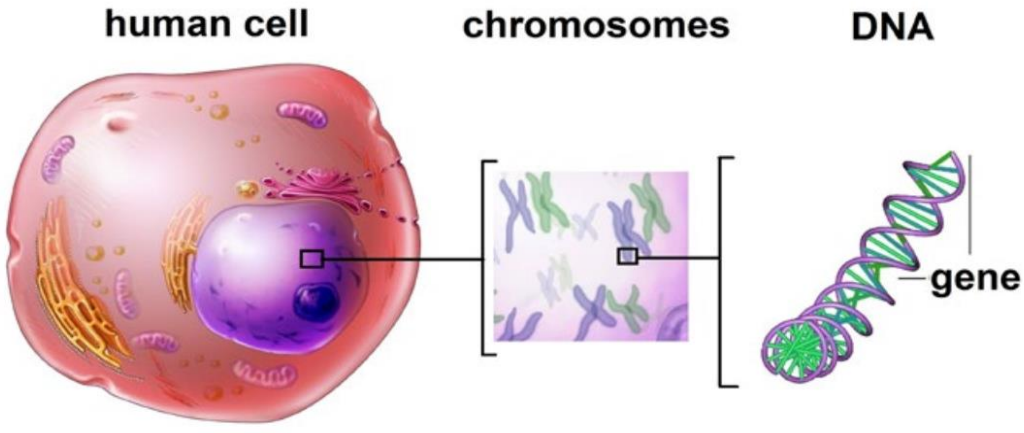
The Bone Marrow



From: NCCN Guidelines for Patients: MDS

13

Chromosomes and Mutation Testing



14

Classification of MDS Subtypes

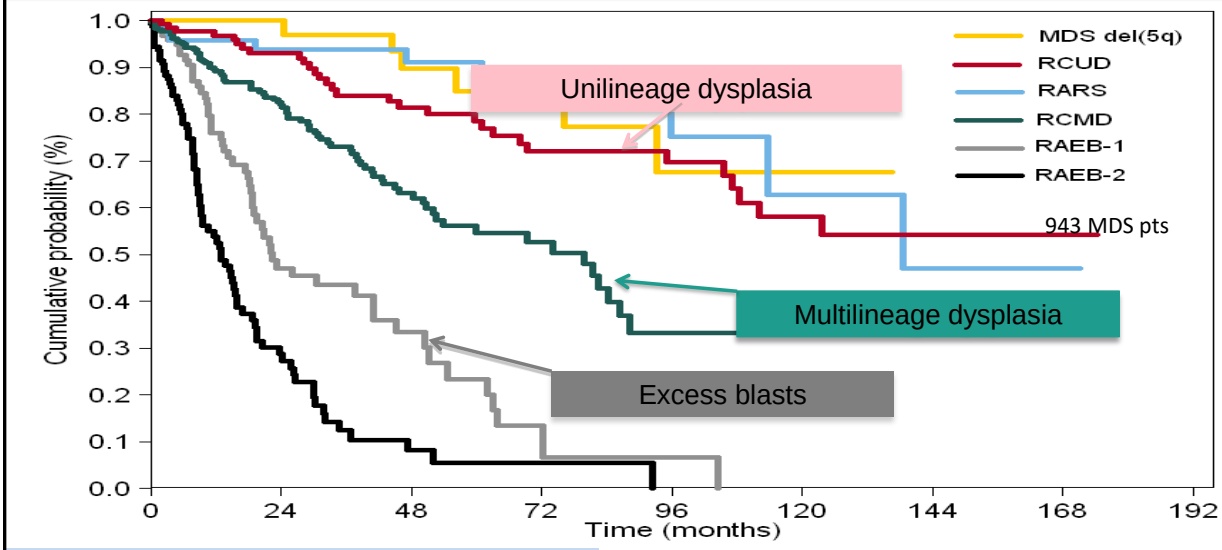
15

World Health Organization MDS categories (2016)

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 occassions	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
MDS with excess blasts in transformation (MDS-EB-T)[2]	Cytopenias, 5%–19% blasts	Multilineage dysplasia, 20%–29% blasts, ± Auer rods

16

World Health Organization MDS categories (2016)



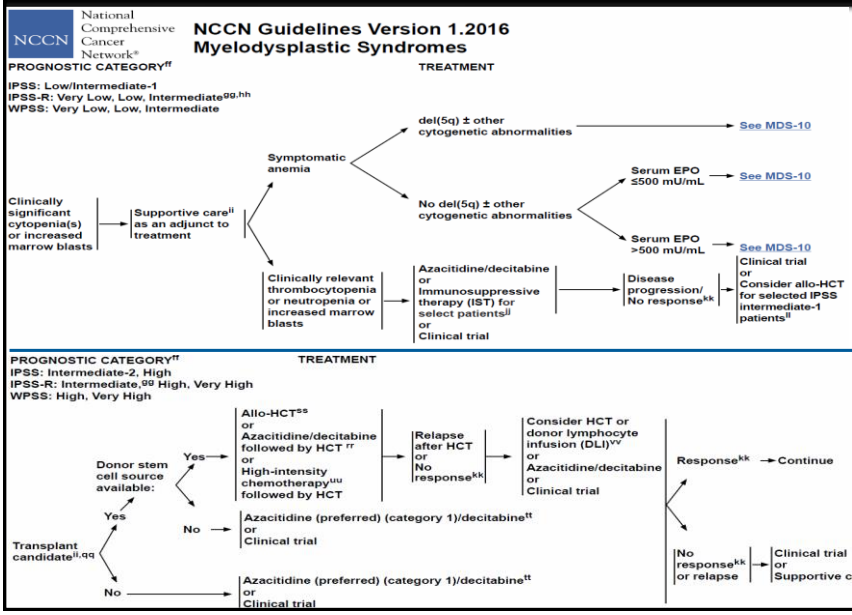
Cazzola. Haematologica. 2011 Mar;96(3):349-52.

17

Prognosis & Risk Assessment

18

MDS Treatment is Highly Risk Stratified



Lower Risk

- Observation
- EPO
- Lenalidomide
- Immune suppression
- Iron Chelation

Higher Risk

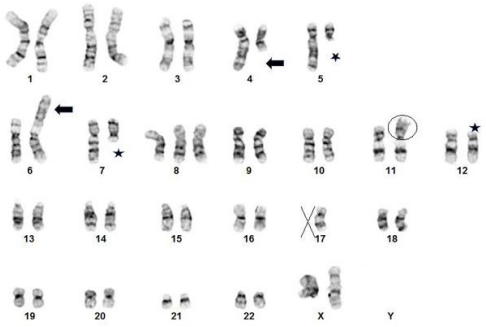
- Azacitidine
- Decitabine
- Allo-HSCT
- Clinical Trials

19

IPSS-Revised (IPSS-R)

Cytogenetic Risk Group	IPSS-R Karyotype Abnormalities (19 categories)
Very good	del(11q), -Y
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities
Very Poor	Complex with > 3 abnormalities

IPSS-R Parameter	Categories and Associated Scores				
Cytogenetic Risk Group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Bone Marrow Blast %	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet Count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Absolute Neutrophil Count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			



IPSS-R Risk Group	Points	% of Patients	Median survival, years	Time to 25% with AML, years
Very low	≤ 1.5	19%	8.8	Not reached
Low	> 1.5 - 3	38%	5.3	10.8
Intermediate	> 3 - 4.5	20%	3	3.2
High	> 4.5 - 6	13%	1.6	1.4
Very High	> 6	10%	0.8	0.73

Greenberg et al. *Blood.* 2012:120:2454-65.

20

Limitations of the IPSS-R

Risk group	Included karyotypes (19 categories)	Median survival, months	Proportion of patients in this group
Very good	del(11q), -Y	60.8	2.9%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	48.6	65.7%
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones	26.1	19.2%
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities	15.8	5.4%
Very poor	Complex with > 3 abnormalities	5.9	6.8%

Parameter	Categories and Associated Scores				
	Very good	Good	Intermediate	Poor	Very Poor
Cytogenetic risk group	0	1	2	3	4
Marrow blast proportion	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Abs. neutrophil count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤ 1.5	19 %	8.8	Not reached
Low	> 1.5 – 3	38 %	5.3	10.8
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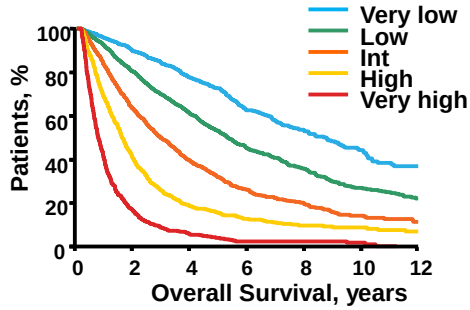
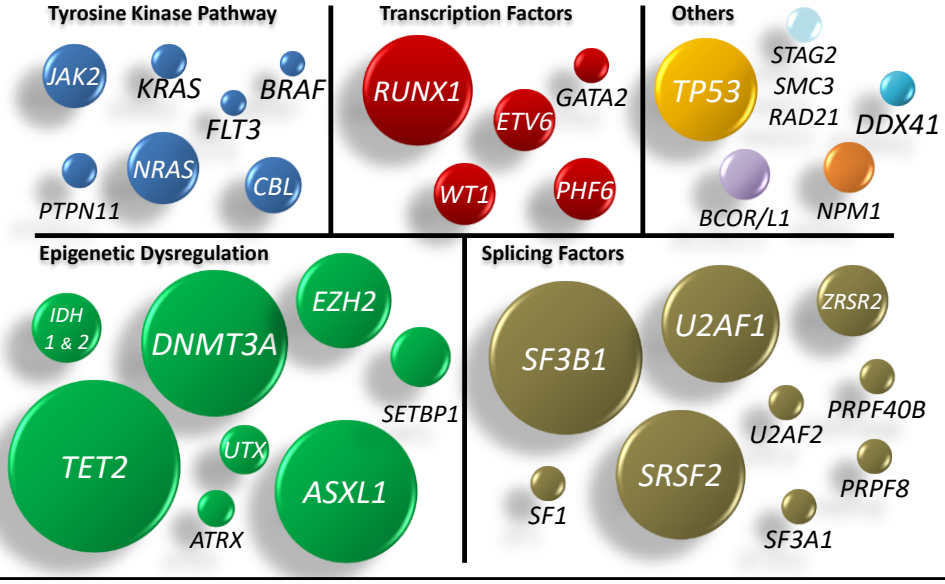
Very High	> 6	10 %	0.8	0.73



- Considers only UNTREATED patients
- IPSS-R does not consider somatic mutations
- Somatic mutations are common in MDS
- Several mutated genes have prognostic significance independent of the IPSS-R

21

Most Frequently Mutated Genes

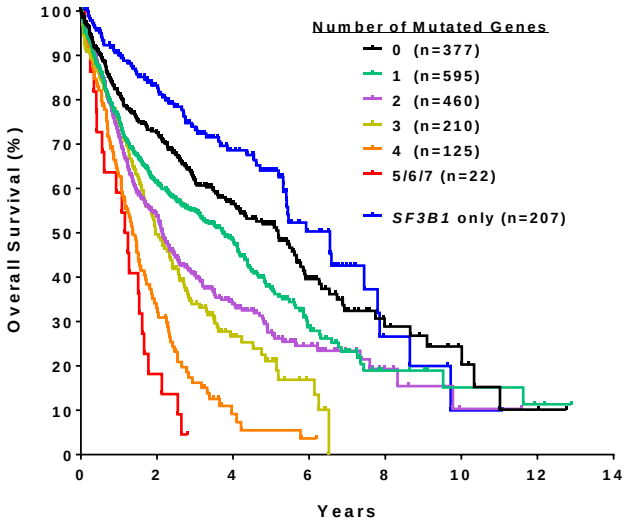


22

Overall Survival by Mutation Number

17 genes sequenced in
1996 patients with OS data

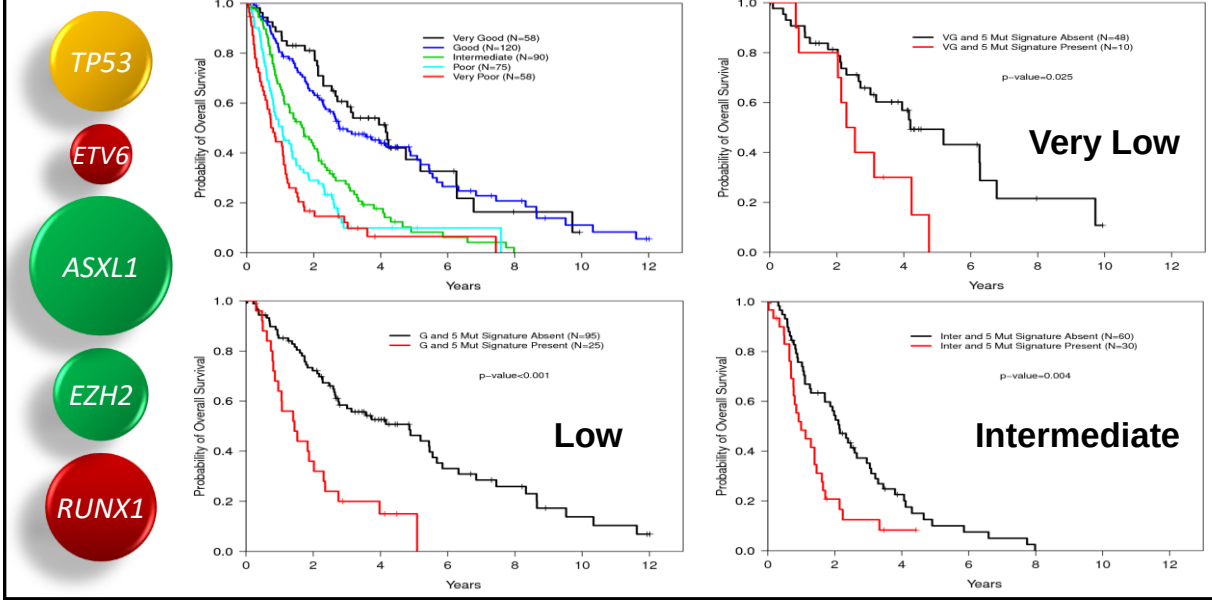
ASXL1	*NPM1*
CBL	*NRAS*
DNMT3A	*RUNX1*
ETV6	*SRSF2*
EZH2	*TET2*
IDH1	*TP53*
IDH2	*U2AF1*
JAK2	
KRAS	***SF3B1***



From the IWG-PM Collaborative Meta-analysis

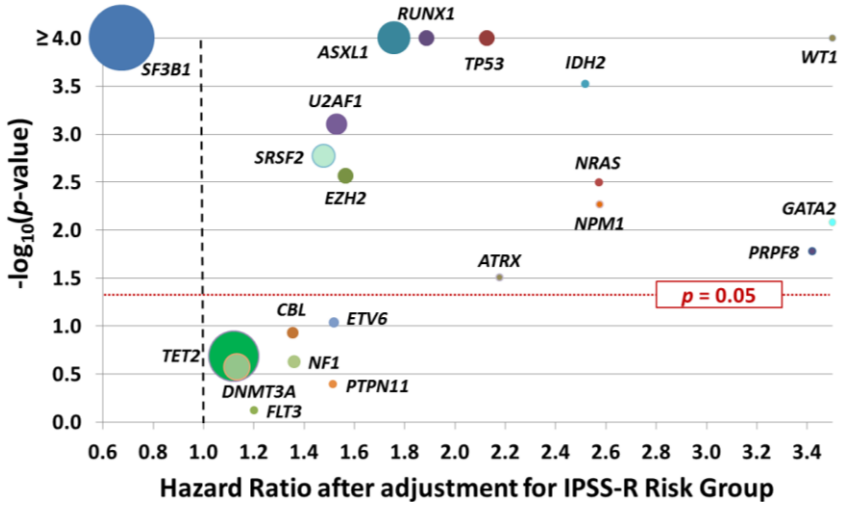
23

Impact of Mutations by IPSS-R Group



24

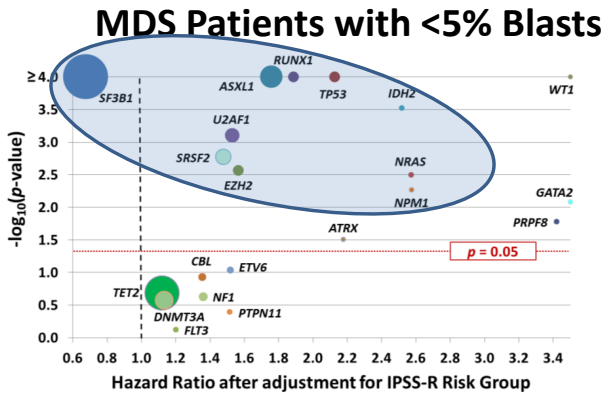
Prognostic Mutations by Blast % (<5%)

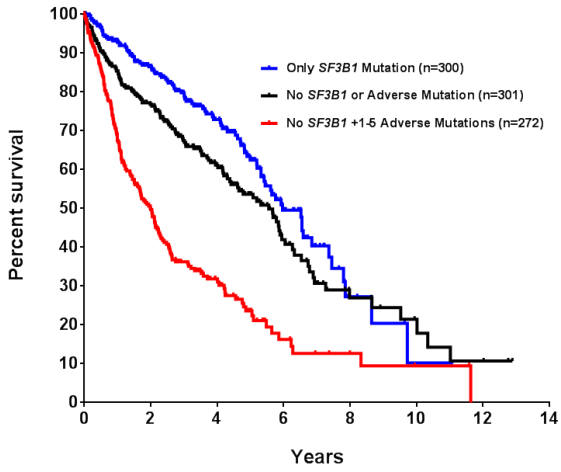


35%

25

Prognostically Adverse Mutations in MDS

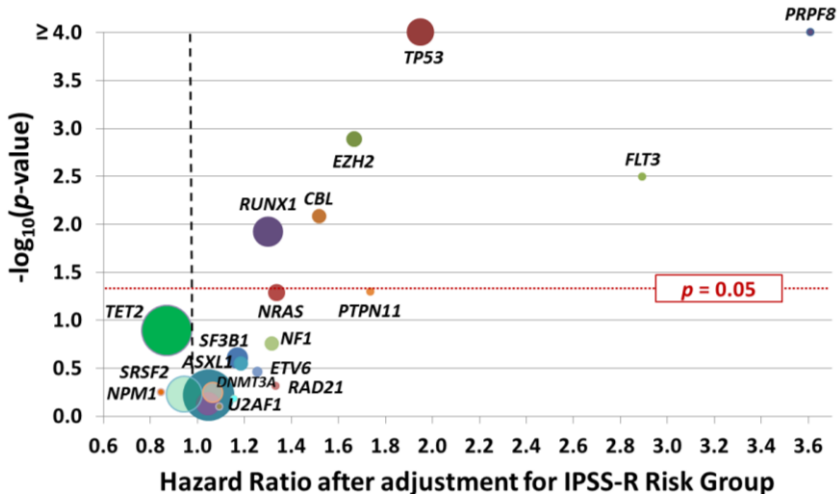




From the IWG-PM Collaborative Meta-analysis

26

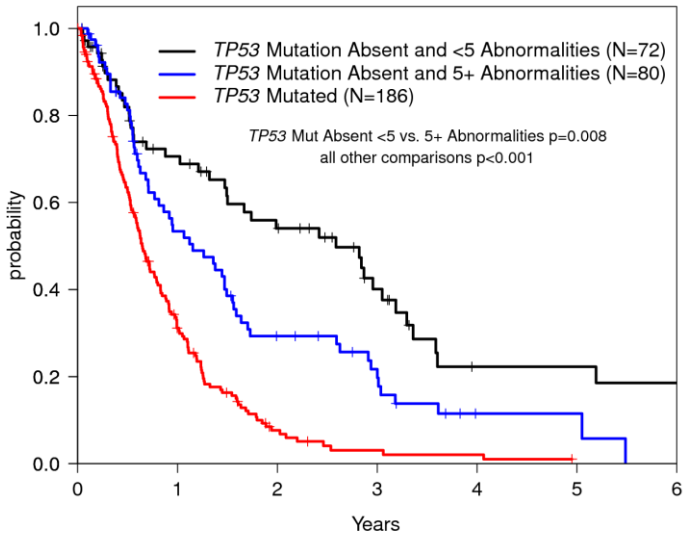
Prognostic Mutations by Blast % (5-30%)



34%

27

Karyotype Features and *TP53* and Survival



Median Overall Survival:

7.2 months

14.4 months

31.2 months

Haase et al. *Leukemia*. 2019 Jul;33(7):1747-58.

28

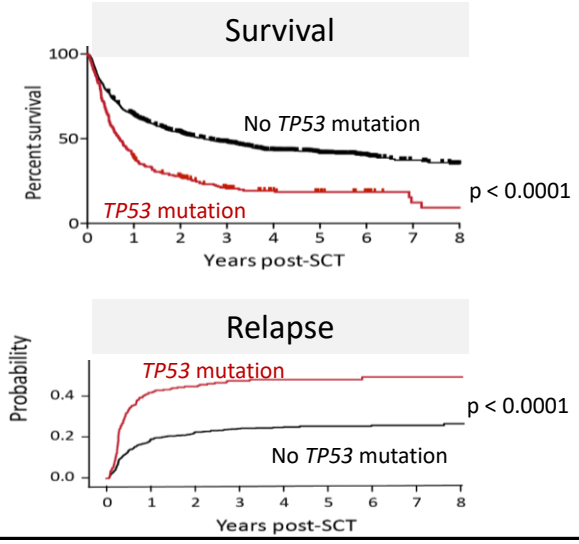
TP53 mutated MDS

Poor prognosis due to early relapse

MDS

***TP53* mutation**
Median OS = 8 months

No
TP53 mutation



29

Risk Adapted Patient Specific Therapy

30

Treatment Options for MDS

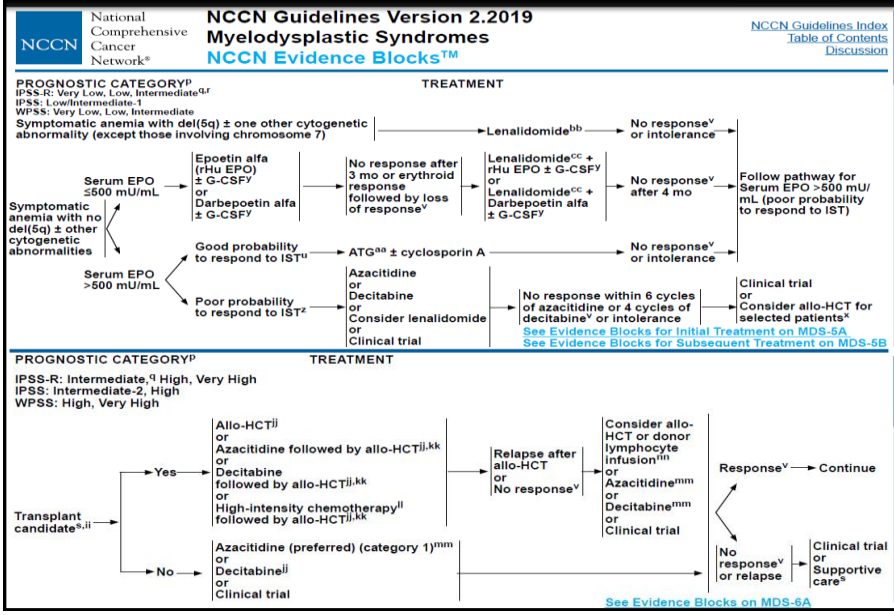
Options

- Observation
- Erythropoiesis stimulating agents
- Granulocyte colony stimulating factor
- Iron chelation
- Red blood cell transfusion
- Platelet transfusion
- Lenalidomide
- Immune Suppression
- Hypomethylating agent
- Stem cell transplantation

Clinical Trials – often the best option

31

MDS Treatment is Highly Risk Stratified



Lower Risk

- Observation
- ESAs
- Lenalidomide
- Immune suppression
- Iron Chelation

Higher Risk

- Azacitidine
- Decitabine
- Allo-HSCT
- Clinical Trials

32

Treating Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

1. Do I need to treat at all?
   - No advantage to early aggressive treatment
   - Observation is often the best approach

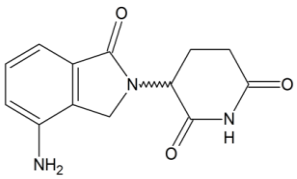
2. Are transfusions treatment?
   - No! They are a sign that treatment is needed.

33

Treating Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

What if treatment is needed?

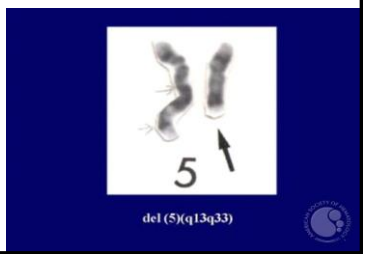


1. Is my most effective therapy likely to work?
   - Lenalidomide (Revlimid)

In del(5q) – response rates are high

50%-70% respond to treatment

Median 2-years transfusion free!



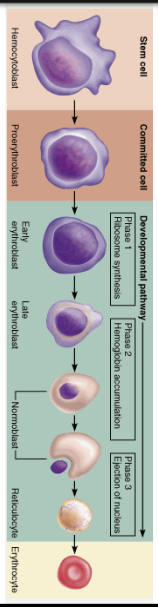
34

Treating Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

Is my second most effective therapy likely to work?

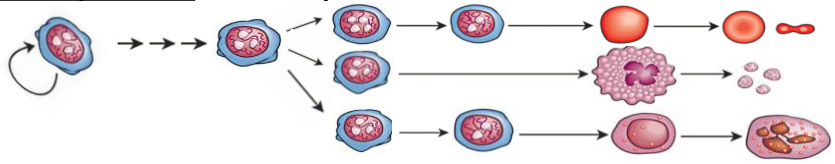
- Red blood cell growth factors
- Erythropoiesis Stimulating Agents (ESAs)
- Darbepoetin alfa (Aranesp)
- Epoetin alfa (Procrit, Epogen)
- Lance Armstrong Juice → **EPO**



35

Erythropoiesis Stimulating Agents

Primary Goal: to improve **QUALITY OF LIFE**



ESAs
TPO mimetics
G-CSF (neupogen)

ESAs – act like our own erythropoietin

Serum EPO level (U/L)	RBC transfusion requirement
<100 = *+2 pts*	<2 Units / month = *+2 pts*
100-500 = *+1 pt*	≥2 Units / month = *-2 pts*
>500 = *-3 pts*	

Total Score	Response Rate
High likelihood of response: > +1	**74%** (n=34)
Intermediate likelihood: -1 to +1	**23%** (n=31)
Low likelihood of response: < -1	**7%** (n=39)

Hellstrom-Lindberg E et al *Br J Haem* 2003; 120:1037

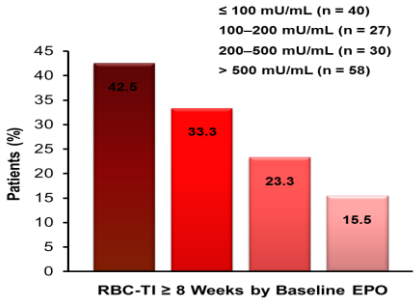
36

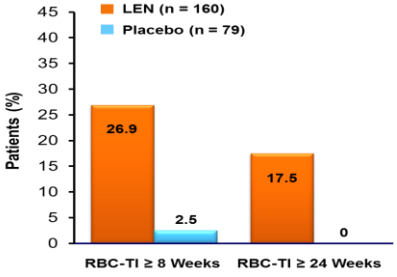
Treating Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

Is a LEN +/- ESA likely to work?

In non-del(5q) MDS patients:





131 included 99 patients after 4 cycles	LEN + EPO n = 50	LEN n = 49	
HI – E (IWG 2006)	52%	30.6%	*P*= 0.03
RBC - TI	32%	18.4%	*P*= 0.12

Santini V, et al. J Clin Oncol. 2016;34:2988-2996.

Toma et al, Leukemia. 2016 Apr;30(4):897-905

37

Treating Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

What my next most effective therapy?

- Immunosuppression

Some MDS patients have features of aplastic anemia

- Hypoplastic bone marrow (too few cells)
- PNH clones
- Certain immune receptor types (HLA-DR15)

38

Immune Suppression for MDS

Primary Goal: to improve **QUALITY OF LIFE**

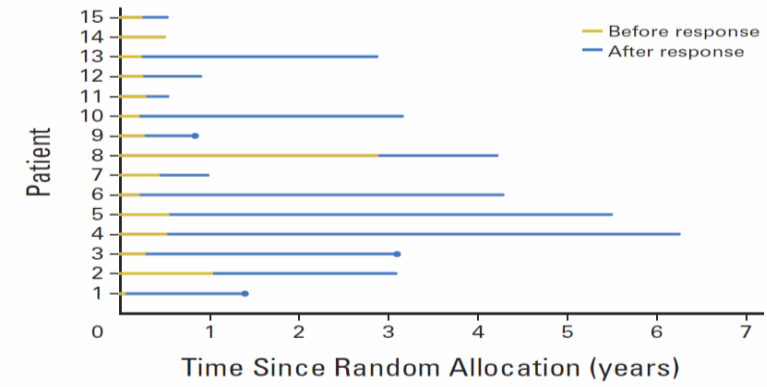
Swiss/German Phase III RCT of ATG + Cyclosporin (88 patients)

Mostly men with Lower Risk MDS

CR+PR: 29% vs. 9%

No effect on survival

Predictors of Response:
- hypocellular aspirate
- lower aspirate blast %
- younger age
- more recent diagnosis



Passweg, J. R., A. A. N. Giagounidis, et al. (2011). *JCO* **29**(3): 303-309.

39

Guidelines for Lower Risk MDS

Primary Goal: to improve **QUALITY OF LIFE**

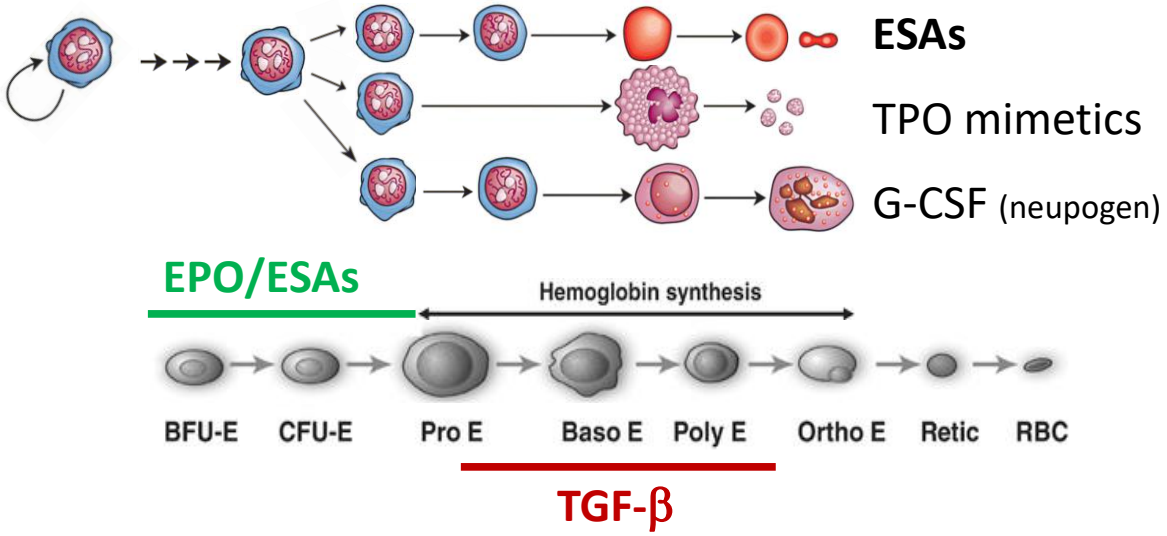
1. Do I need to treat? - symptomatic cytopenias
2. Is LEN likely to work? - del(5q) or after ESA
3. Are ESA likely to work? - Serum EPO < 500
4. Is IST likely to work? - hypocellular, DR15, PNH
5. Think about iron! - 20 or more transfusions
6. Consider AZA/DEC
7. Consider HSCT or clinical trial!

40

Novel Treatments for Lower Risk MDS

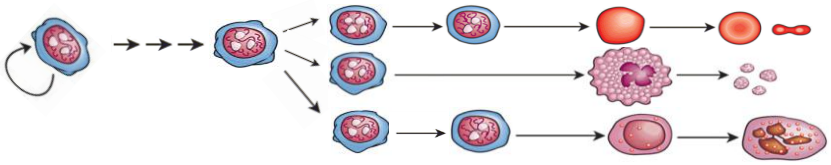
41

Luspatercept

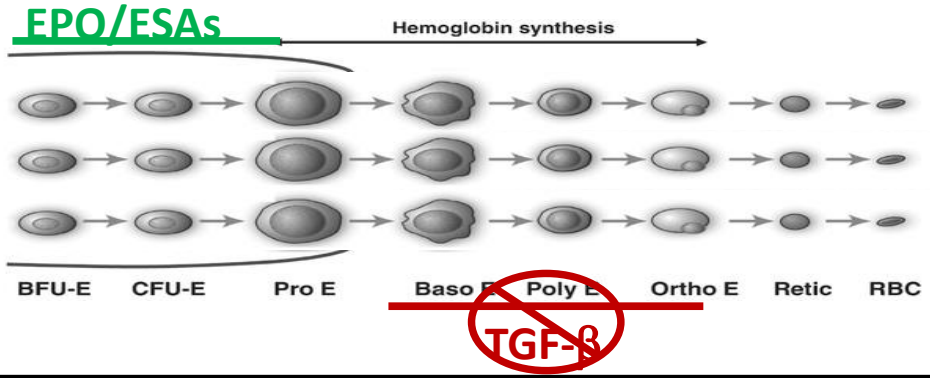


42

Luspatercept



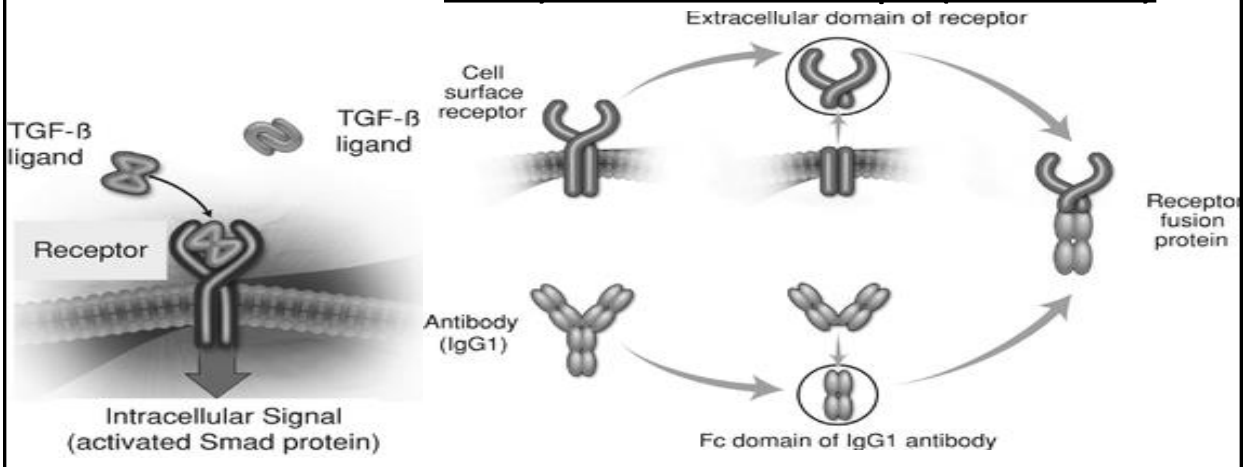
ESAs
TPO mimetics
G-CSF (neupogen)



43

Promoting Red Cell Production

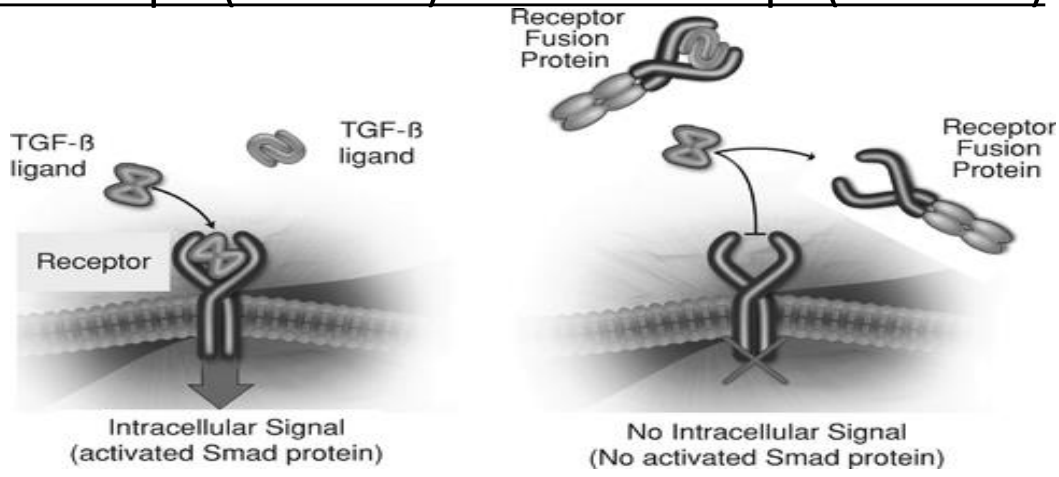
Luspatercept (ACE-536) and Sotatercept (ACE-011)



44

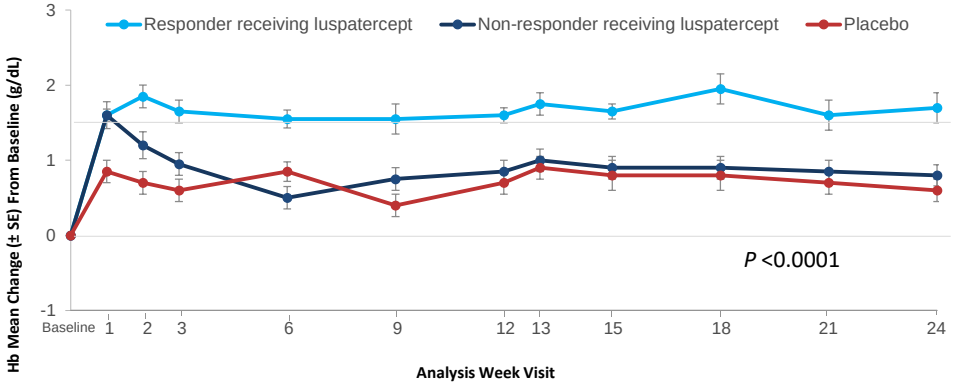
Promoting Red Cell Production

Luspatercept (ACE-536) and Sotatercept (ACE-011)



45

MEDALIST Trial - Change in Hemoglobin Concentration



- Median peak hemoglobin increase in luspatercept responders: 2.55 g/dL (1–4.1 g/dL)

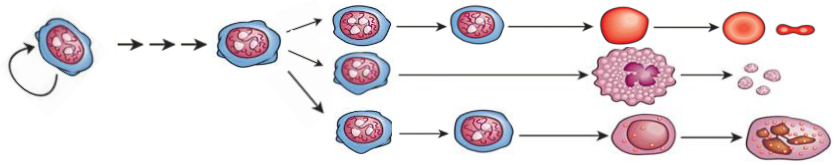
Number of patients												
Responder[a]	153	24	36	55	53	52	50	42	47	50	42	45
Non-responder		33	51	61	52	60	53	34	45	56	48	35
Placebo	76	32	36	41	47	44	52	29	44	47	44	32

[a] LS mean difference (95% CI) for luspatercept responders versus placebo: 1.08 (0.84, 1.31), $P < 0.0001$.
Only patients with RBC-TI ≥ 8 weeks during weeks 1–24 are included. Hb measurement was excluded within 14 days after a RBC transfusion unless within 3 days prior to another RBC transfusion. Mean and SE were not calculated if the number of patients was < 8 in the luspatercept non-responder group or < 4 in the placebo group. SE, standard error.

46

Platelet Growth Factors

Eltrombopag or Romiplostim - TPO mimetics



ESAs
TPO mimetics
G-CSF (neupogen)

Eltrombopag and Romiplostim - approved, but not yet in MDS

Initial concern about increasing blasts and risk of AML

Follow-up suggests both drugs are safe in lower risk patients

Mittleman M et al *ASH Abstracts*, 2013. Abstract #3822 Olivia et al. *Lancet Haematol*. 2017 Mar;4(3):e127-e136.

47

Hypomethylating Agents in LR-MDS

Randomized study of **Azacitidine 75 mg/m2 x 3 days** vs.
Decitabine 20 mg/m2 x 3 days on a 28-day cycle in lower-risk MDS.

Conclusion – 3-day Decitabine is a viable regimen for LR MDS

Table 2. Response

Parameter	Overall, n (%)	Decitabine, n (%)	Azacitidine, n (%)
Morphologic response, N	109	70	39
CR	40 (37)	26 (37)	14 (36)
mCR	8 (7)	6 (9)	2 (5)
HI	20 (18)	17 (24)	3 (8)
Overall	68 (62)	49 (70)	19 (49)
Transfusion response, N	57	38	19
RBC	11/46 (24)	8/29 (28)	3/17 (18)
Platelets	3/5 (60)	3/4 (75)	0/1
RBC + Platelets	1/6 (17)	1/5 (20)	0/1
Overall	15 (26)	12 (32)	3 (16)

Jabbour et al. *Blood* 2017.

48

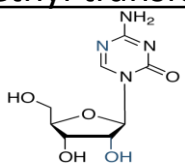
Treatment of Higher Risk MDS

49

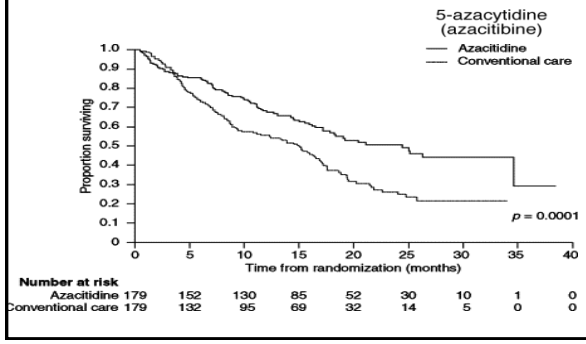
Hypomethylating Agents

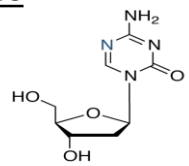
Inhibitors of DNA methyl transferases:

Azacitidine
VIDAZA



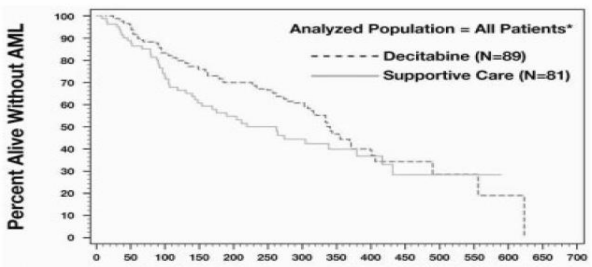
5-azacytidine
(azacitibine)





5-aza-2'-deoxycytidine
(decitabine)

Decitabine
DACOGEN



50

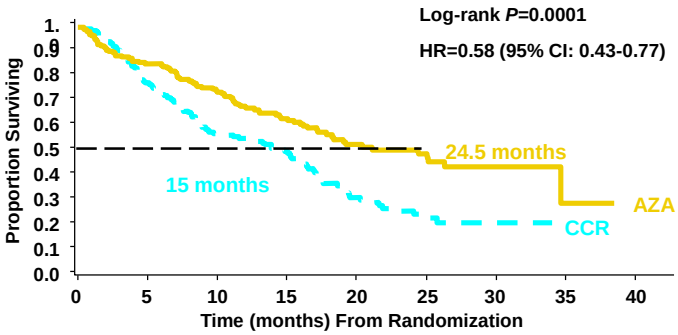
Azacitidine vs Decitabine

AZA-001 Phase III: AZA vs. ld-ARA-C vs. supportive care

OS benefit: + 9.5 mos

Time to AML: 17.8 vs. 11.5 mos

TI: 45% vs. 11%



Azacitidine Response:

ORR: ~50%

CR: ~17%

Median time to response: 3 cycles (81% by cycle 6)

Fenaux et al. *Lancet Oncology* 2009.

51

Novel Treatments for Higher Risk MDS

52

Guidelines for Higher Risk MDS

Goal: to improve **DURATION OF LIFE**

Special Considerations:

Refer for Transplant Early
- Even patients in their 70's can benefit from RIC transplant

AZA > DEC (for now)
- AZA has been shown to have a survival advantage, DEC has not (yet)

Don't forget Quality of Life
- Consider treatment palliative and weigh against patient needs

Look for Clinical Trials
- Few option after AZA are available and none are approved

53

Outcomes After Azacitidine

- Data available on 435 pts
  - *from AZA001, J9950, J0443, French compassionate program*
- **Overall median survival after azacitidine failure: 5.6 months**

Subsequent therapy	Number of patients (%)	Median survival
Allogeneic transplant	37 (9%)	19.5 months
Investigational therapy (e.g. IMiD, HDACi, other)	44 (10%)	13.2 months
Intensive cytotoxic therapy (e.g., 3&7)	35 (8%)	8.9 months
Low-dose chemotherapy (e.g. LDAC, 6-MP)	32 (7%)	7.3 months
Palliative / supportive care	122 (28%)	4.1 months
Subsequent therapy unknown	165 (38%)	3.6 months

Slide borrowed from Dr. David Steensma

Prébet T et al *J Clin Oncol* 2011; 29:3322-7
Jabbour E et al *Cancer* 2010;116(16):3830-4

54

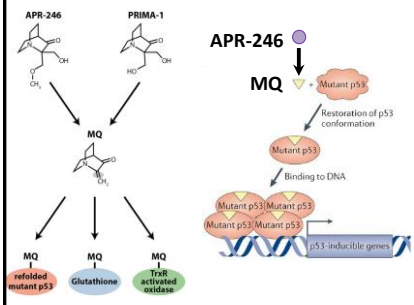
Treatment of Higher Risk MDS

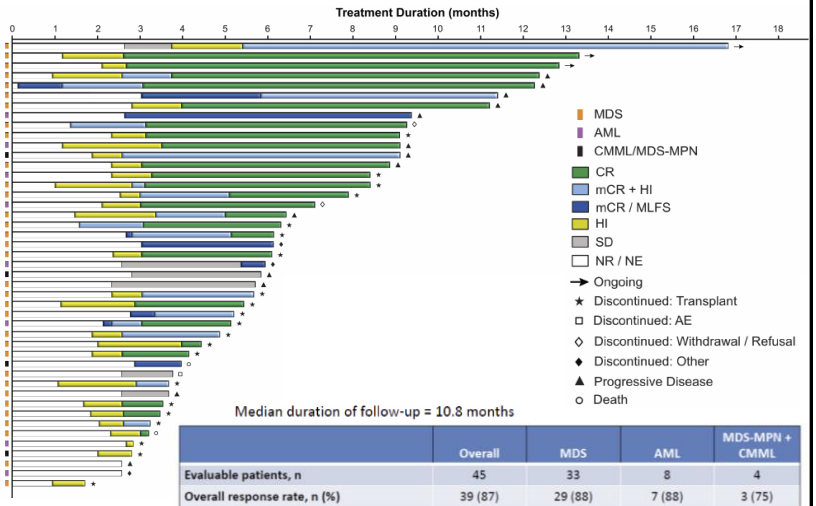
We need **BETTER** therapies!

We need **MORE** therapies!

55

Targeting Mutant *TP53* with APR-246





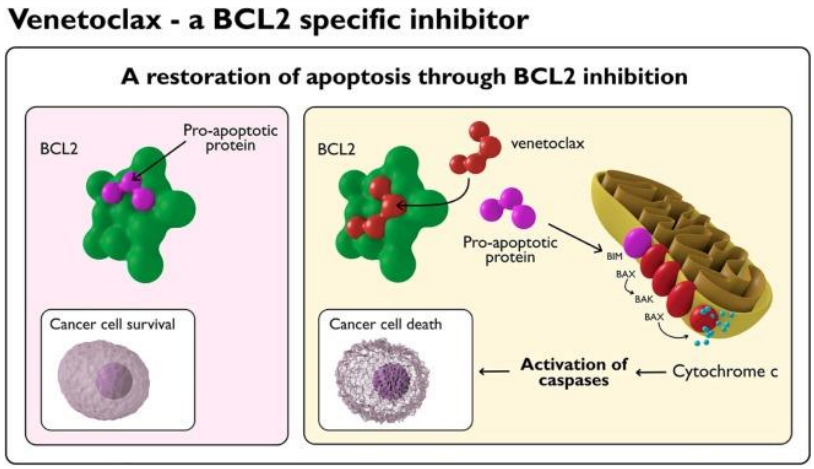
Median duration of follow-up = 10.8 months

	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)

Sallman D et al ASH 2019

56

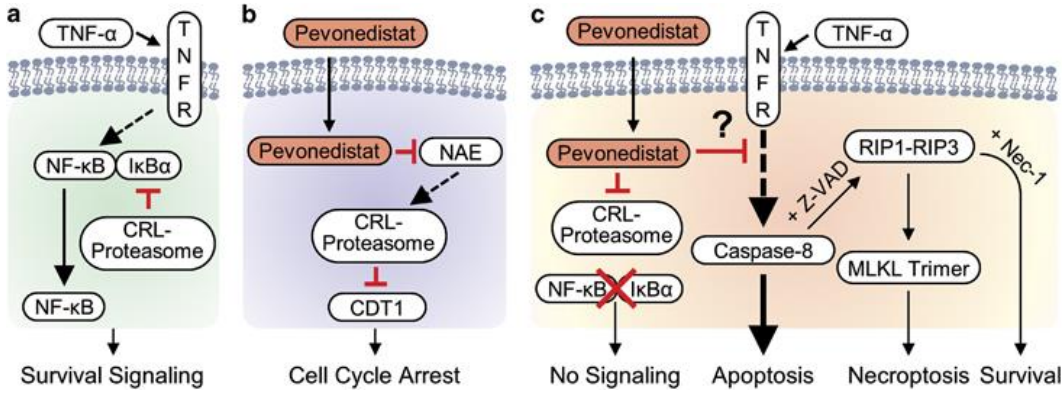
Targeting Cell Death with Venetoclax



Approved for CLL and for AML in combination with an HMA
In trials for MDS in combination with HMA

57

Pevonedistat

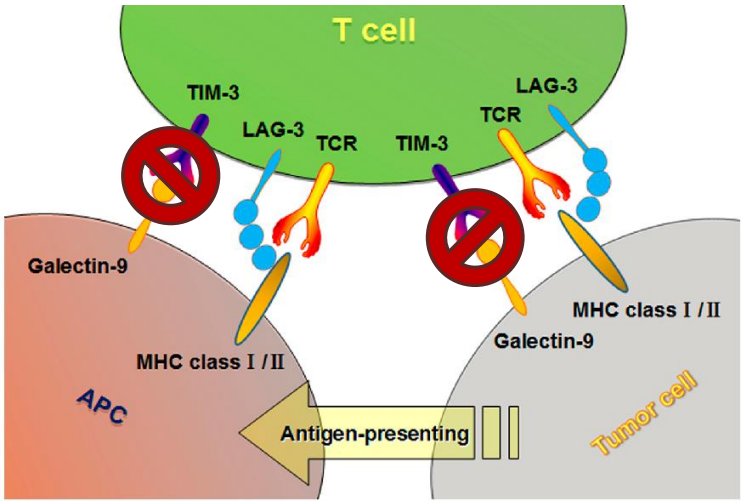


In Phase III study in combination with Azacitidine
for higher risk MDS/CMML/AML

58

Harnessing the Immune System

Anti-TIM-3 Antibody MBG453



Higher Risk MDS and AML

Treated in combination with **decitabine**

Early phase studies appear safe

Has evidence of activity

Represents a new paradigm in MDS treatment

59

Harnessing the Immune System

Magrolimab (5F9) – Anti-CD47

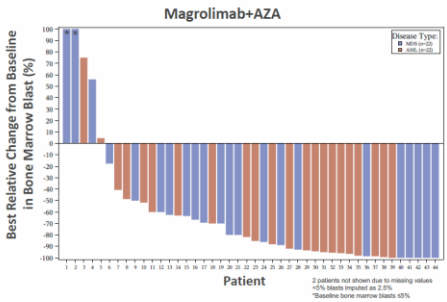
Anti-Leukemic Activity is Observed with Magrolimab + AZA in MDS and AML

Parameter	1L MDS N=24	1L AML N=22
RBC transfusion independence[1]	4/9 (44%)	8/11 (73%)
Complete cytogenetic response in responders[2]	5/19 (26%)	6/10 (60%)
MRD negativity in responders	5/22 (23%)	8/14 (57%)
Median duration of response (months)	Not reached (0.03+ – 9.76+)	Not reached (0.03+ – 15.1+)
Median follow-up [range] (months)	6.4 [2.0 – 14.4]	8.8 [1.9 – 16.9]

Minimal residual disease (MRD) was evaluated by multiparameter flow cytometry
Cytogenetic response defined per 2003 and 2006 IWG criteria;
[1]Patients shown for those who were RBC transfusion dependent at baseline and achieved RBC transfusion independence at any time on study
[2]Responses shown for all responding patients with abnormal cytogenetics at baseline

Best Overall Response	1L MDS N=24	1L AML N=22
ORR	22 (92%)	14 (64%)
CR	12 (50%)	9 (41%)
CRi	-	3 (14%)
PR	0	1 (5%)
MLFS/ marrow CR	8 (33%) 4 with marrow CR + HI	1 (5%)
Hematologic improvement (HI)	2 (8%)	-
SD	2 (8%)	7 (32%)
PD	0	1 (5%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria; Patients with at least one 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 (1 AE, 2 early withdrawal)
"-" not applicable



- Magrolimab + AZA induces a 92% ORR (50% CR) in MDS and 64% ORR (55% CR/CRi) in AML
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy

Sallman D et al ASCO 2019

60

Acknowledgements

MDS Center of Excellence at UC San Diego

Marla McArdle	Soo Park	- Bejar Clinic
Jennifer Galvan	Olivia Reynolds	
Elizabeth Broome	Huanyou Wang	- Hematopathology
Edward Ball	Peter Curtin	- BMT Group
Matthew Wieduwilt	Divya Koura	
Carolyn Mulroney	Caitlin Costello	
Januario Castro	Dimitrios Tzachanis	
Aaron Goodman	Dan Kauffman	
Sandy Shattil	John Adamson	- Hematology Group
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Erin Reid	Tom Kipps	
Natalie Galanina	Annette Von Drygalski	
Srila Gopal	Tiffany Tanaka	
Ben Heyman		

Bejar Lab

Tim Luger	Soo Park
Tiffany Tanaka	Brian Reilly
Armon Azizi	Raluca Ciochina
Laura Williams	

UC San Diego Moores Cancer Center

All of our PATIENTS and INFUSION CENTER nurses and staff!

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61

Questions?

62

Q&A SESSION

Treatment Advances for Myelodysplastic Syndromes (MDS)

- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
  - Click “Ask a question”
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

BEATING CANCER IS IN OUR BLOOD.

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63

LLS EDUCATION & SUPPORT RESOURCES

- **Information Specialists**

  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - **EMAIL:** infocenter@LLS.org
  - **TOLL-FREE PHONE:** 1-800-955-4572
- **Caregiver support:** www.LLS.org/caregiver
- **Free education booklets:** www.LLS.org/booklets
- **Free telephone/web programs:** www.LLS.org/programs
- **Live, weekly online chats:** www.LLS.org/chat
- **LLS Community:** www.LLS.org/community
- **Information about leukemia:** www.LLS.org/leukemia

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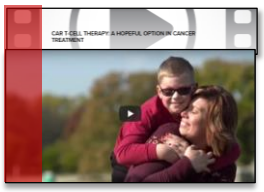
64

LLS EDUCATION & SUPPORT RESOURCES

- **LLS Patient Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: **www.thebloodline.org**



- **Education Videos**

  Free education videos about survivorship, treatment, disease updates, and other topics: **www.LLS.org/educationvideos**

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: **www.LLS.org/firstconnection**

65

LLS EDUCATION & SUPPORT RESOURCES

- **Free Nutrition Consults**

  Telephone and e-mail consultations with a registered dietitian: **www.LLS.org/nutrition**

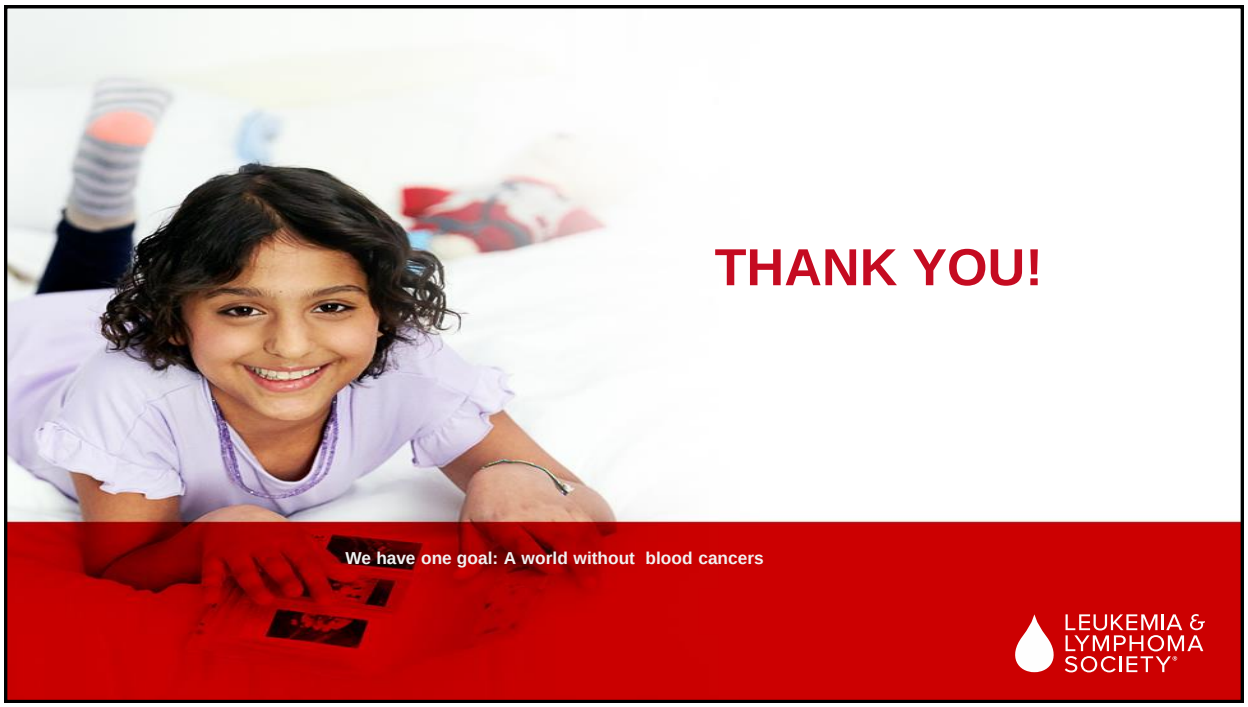
- **What to Ask**

  Questions to ask your treatment team: **www.LLS.org/whattoask**

- **Other Support Resources**

  LLS community, blogs, support groups, financial assistance, and more: **www.LLS.org/support**

66

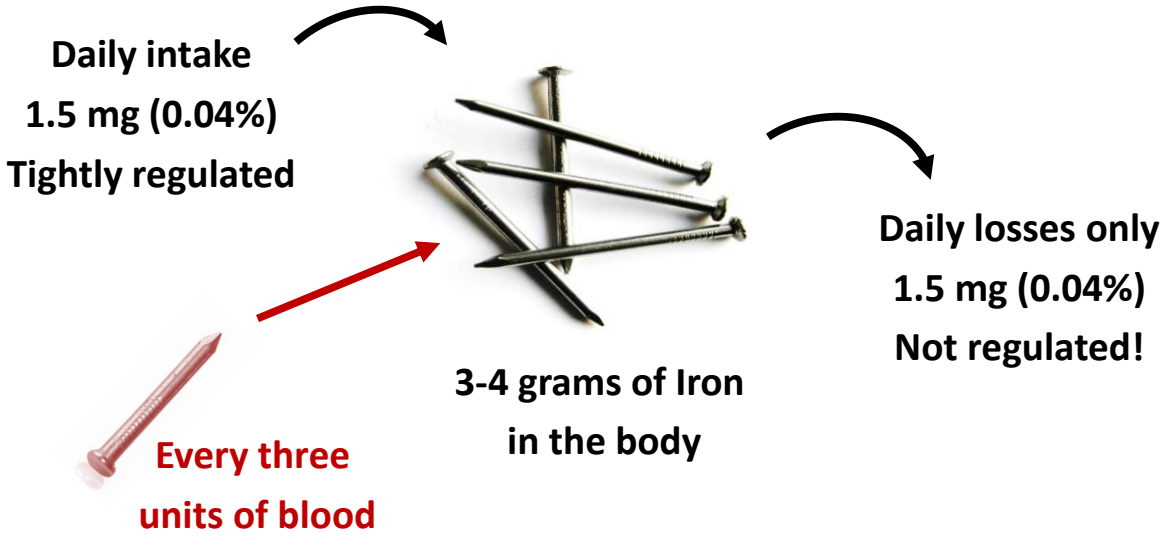


67

Additional Information

68

Iron Balance and Transfusions



69

What About Iron Chelation?

More transfusions and elevated ferritin levels are associated with poor outcomes in MDS patients.

Are these drivers of prognosis or just reflective of disease?

Retrospective studies suggest survival advantage!

small prospective and large population based Medicare studies show survival benefit, INCLUDING hematologic responses (11-19%).

I consider treatment in lower risk, transfusion dependent patients with long life expectancy after 20+ transfusions.

Zeidan et al. ASH Meeting. 2012. Abstract #426.

Nolte et al. Ann Hematol. 2013. 92(2):191-8.

70

TELESTO
Deferasirox in LR/Int-1 MDS With Transfusional Iron Overload

Multicenter, randomized (2:1), double-blind, placebo-controlled, phase 2 trial

Low- or Int-1-risk MDS per IPSS, serum ferritin > 1000 µg/L and < 2500 µg/L (planned N = 630)

Deferasirox
10 mg/kg/d (d 1-14)
20 mg/kg/d (wk 2-12)
Up to 40 mg/kg/d (> 12 wk)
(n = 420)

Placebo
10 mg/kg/d (d 1-14)
20 mg/kg/d (wk 2-12)
Up to 40 mg/kg/d (> 12 wk)
(n = 210)

Continue treatment ≤ 5 y; interim analysis at 50% of primary composite events (~3 y) and 75% of primary composite events (~4 y)

- Primary endpoint: EFS (includes death and nonfatal cardiac and liver function events)
- Secondary endpoints: hematologic improvement, OS, disease progression, endocrine and metabolic function, safety, serum ferritin > 2 × BL

Figure 2. Serum ferritin levels over time by treatment group

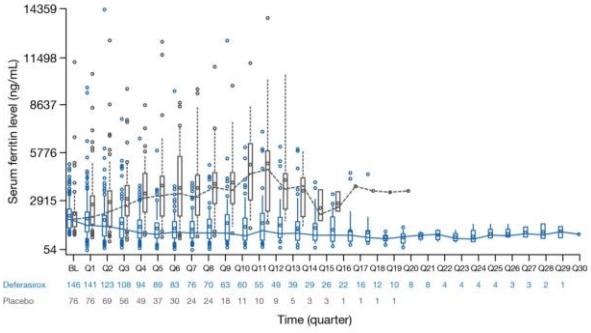
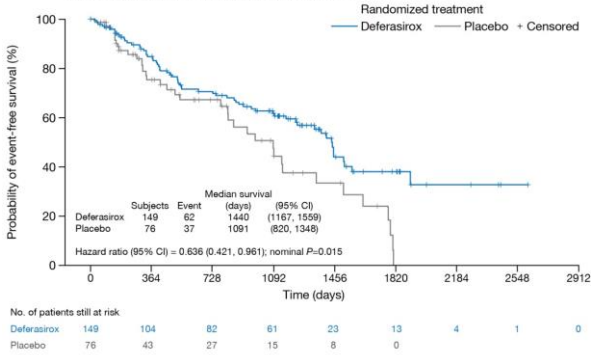


Figure 1. Kaplan-Meier curve of event-free survival



71

How to Chelate Iron

<u>Three ways are FDA approved</u>:

- Deferoxamine (Desferal) – subcutaneous pump 8-12 hrs/day
- Deferasirox (Exjade/Jadenu) – powder/pill – once per day
- Deferiprone (Ferriprox) – oral pill form – 3x per day

But side effects and adverse events can be significant!

Deferasirox – renal, hepatic failure and GI bleeding

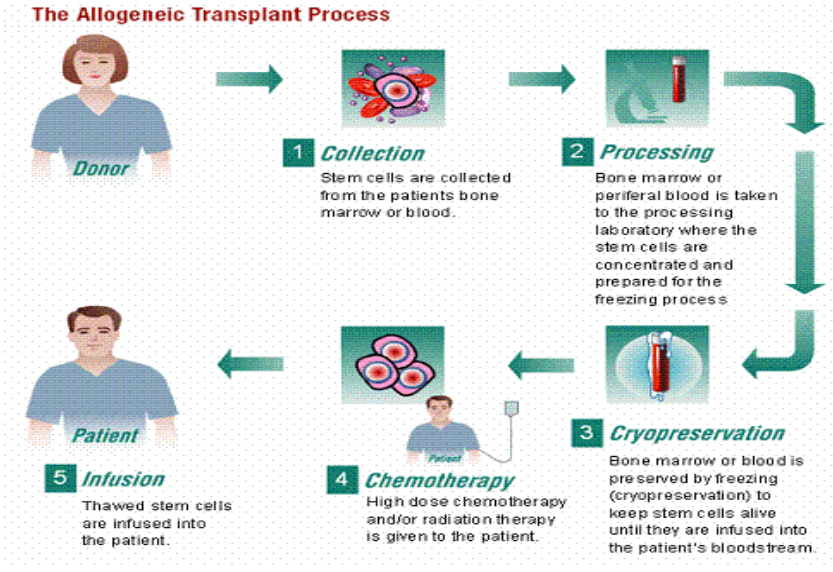
Deferiprone – agranulocytosis (no neutrophils!)

72

Stem Cell Transplantation

73

Stem Cell Transplantation



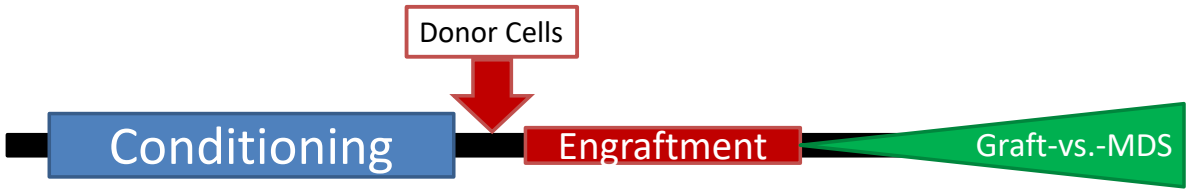
74

Trends in Transplantation

Goal of Hematopoietic Stem Cell Transplantation:

#1) Replace a dysfunction host hematopoietic system with normal, healthy donor marrow.

#2) Allow the donor immune system to destroy the abnormal, diseased host cells (MDS).



75

Allogeneic Stem Cell Transplantation for MDS

<5% of patients with MDS currently undergo allogeneic SCT

"Only curative therapy"

Patients who go in to RIC allo SCT with <10% blasts appear to have lower relapse

Optimal timing, pre-transplant therapy, conditioning unclear;
usually reserved for IPSS Int-2/High (IBMTR Markov analysis)

Transplant candidate
Donor identified

- Survives transplant; MDS cured! (35-40%)
- Survives transplant; MDS recurs/persists (30-40%)
- Dies from complication of transplant (20-25%)

Slide borrowed from Dr. David Steensma

Cutler C et al *Blood* 2004; 104(2):579-85
Sekeres M et al *JNCI* 2008;100(21):1542-51.

76

Obstacles to Transplantation

Graft Rejection
- need to suppress the host immune system

Toxicity
- infection
- organ damage
- graft versus host disease

Finding a Donor
- siblings match only 25% of the time
- and are often too old or ill to donate

77

Overcoming Obstacles

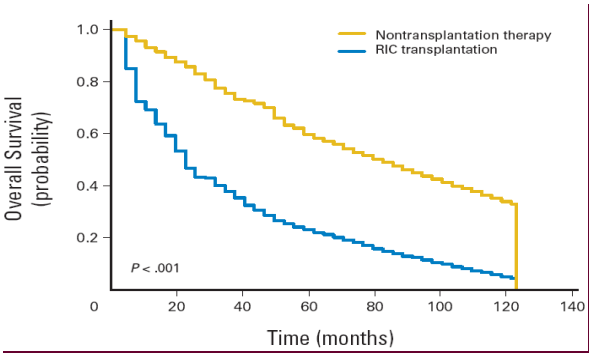
Avoiding Graft Rejection
- better approaches to immune suppression

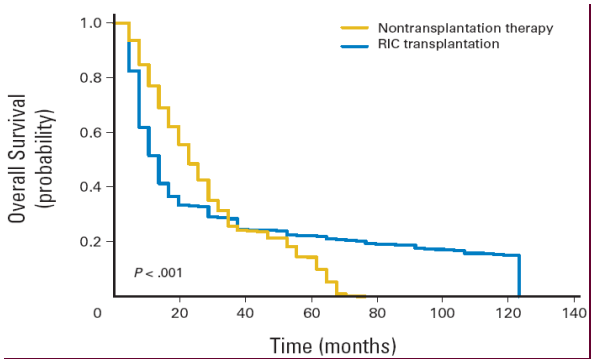
Less Toxicity
- better supportive care
- better antigen matching
- **reduced intensity conditioning**

Alternative Sources for Stem Cells
- haploidentical – "half" match
- umbilical cord blood stem cells

78

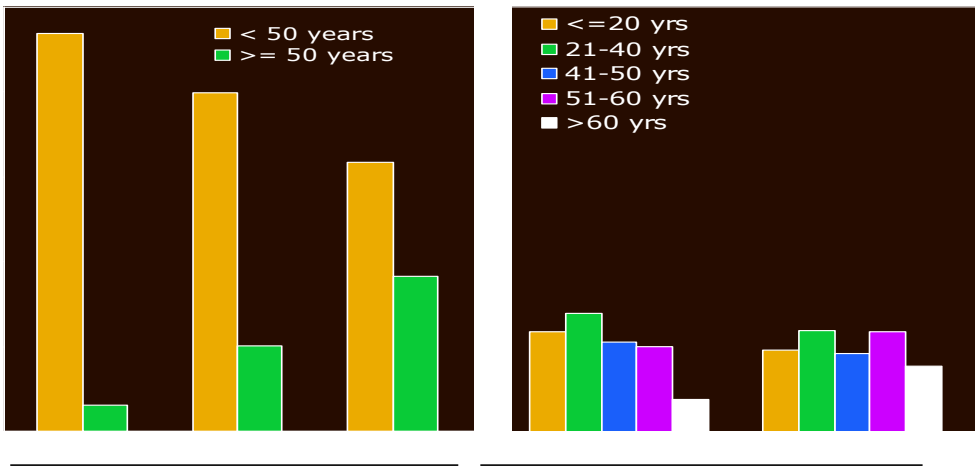
Reduce intensity conditioning transplantation in Older Patients with *De Novo* MDS





79

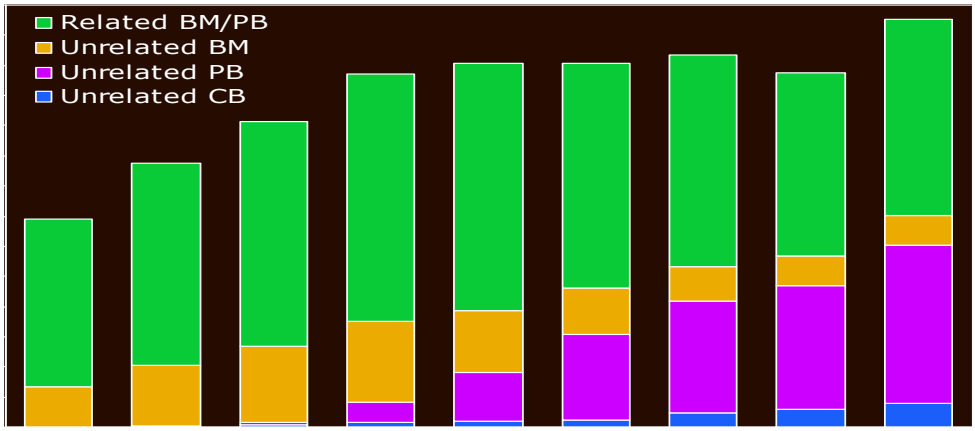
Trends in Allogeneic Transplants by Transplant Type and Recipient Age* 1990-2010



80

Allogeneic Transplants for Age > 20yrs, Registered with the CIBMTR, 1993-2010

- by Donor Type and Graft Source -



81