High-risk MDS and clinical trials

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MDS risk stratification and prognostic factors

- Give healthcare providers & patients and their families insights into what to expect
  - Based upon what happened to those with similar MDS features before them
  - As therapies change, prognosis changes
- Relevant to determine eligibility for available treatments
  - Depends on the therapy
- Individualize prognosis, and possibly therapy whenever possible
  - Determining timing & selection for therapy
    - e.g. transfusion & red cell growth factors vs. chemotherapy or even allogeneic transplantation
  - Clinical Trial eligibility

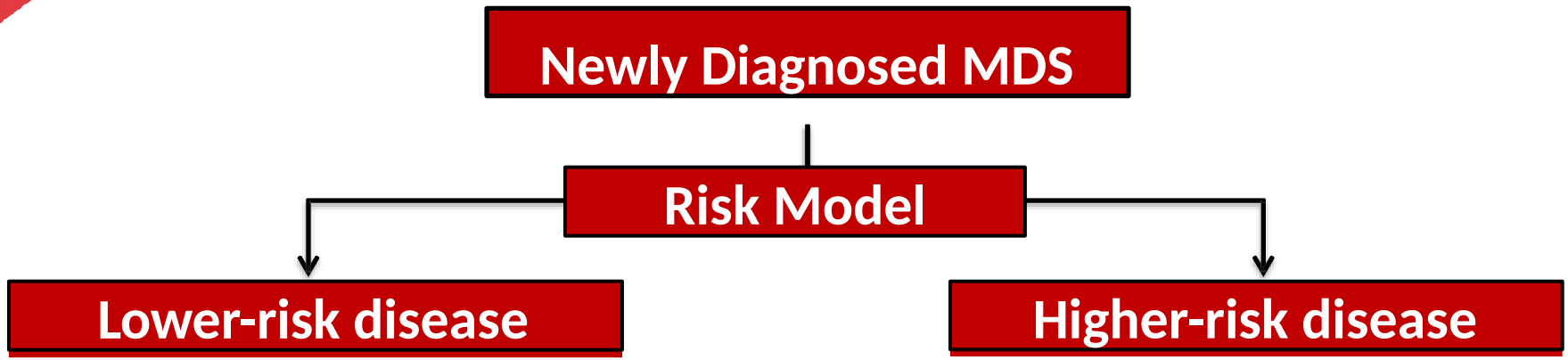
MDS prognostic factors

- Better blood counts are good
- Not needing transfusions is good
- Lower blasts are good
- Having no cytogenetic abnormalities is good
- Younger age is good
- Being able to function better is good

Other prognostic factors

- Therapy-related: prior chemotherapy or radiation therapy
- Albumin
- Ferritin (iron stores)
- Presence of blood blasts
- Age, general health, performance status
- Bone marrow fibrosis
- Many others

Risk Assessment



- Decrease transfusion burden
- Decrease symptoms
- Improve quality of life

- Alter natural history of disease
- Prevent progression to acute myeloid leukemia
- Improve overall survival

International Prognostic Scoring System

	0	0.5	1.0	1.5	2
BM blasts (%)	**<5**	**5-10**	**--**	**11-20**	**21-30**
Chromosomes*	**Good**	**Intermediate**	**Poor**		
Low blood counts	**0/1**	**2/3**			

*Good: nl, -y, del(5q), del(20q) Int: all others Poor: complex or chromosome 7 abn

Low: 0	**Lower Risk**
Intermediate-1: 0.5-1	
Intermediate-2: 1.5-2	**Higher Risk**
High: ≥ 2.5	

Greenberg P et al, Blood 1997; 89:2079-88

Revised IPSS

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

Prognostic variable	0	0.5	1	1.5	2	3	4
Chromosomes	Very good	--	Good	--	Int	Poor	Very Poor
BM blast, %	≤ 2	--	>2 - <5	--	5 - 10	>10	--
Hemoglobin, g/dL	≥ 10	--	8 - <10	< 8	--	--	--
Platelets, K/µL	≥ 100	50 - <100	< 50	--	--	--	--
ANC, K/µL	≥ 0.8	< 0.8	--	--	--	--	--

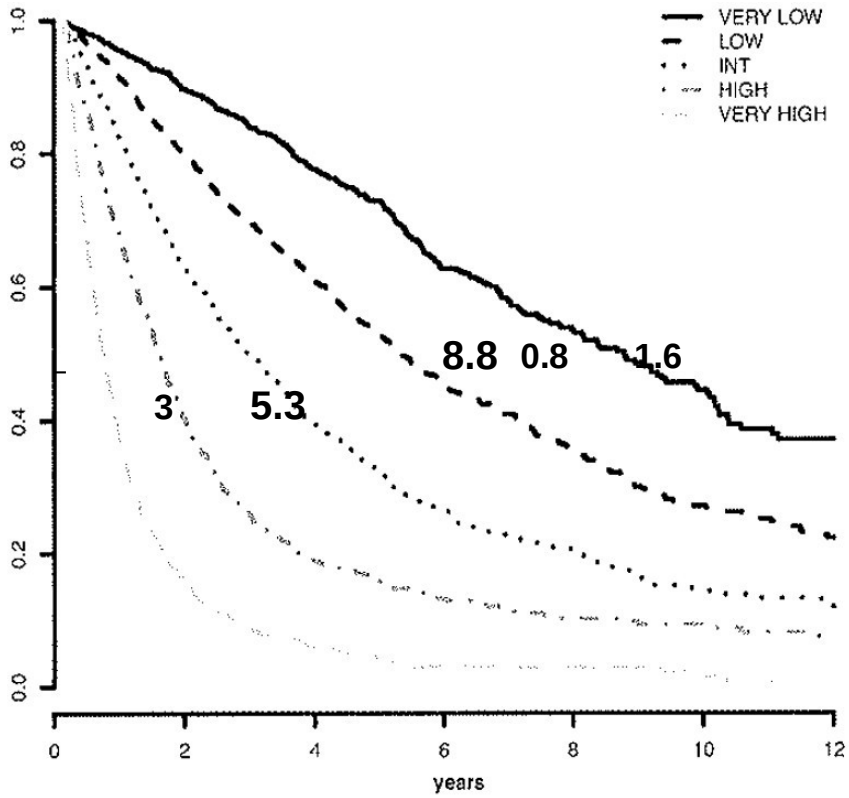
Greenberg P. Blood 2012;120: 2454-2465

Revised IPSS

Category	Score
Very Low	≤ 1.5
Low	> 1.5 – 3
Intermediate	> 3 – 4.5
High	> 4.5 – 6
Very High	> 6

Lower

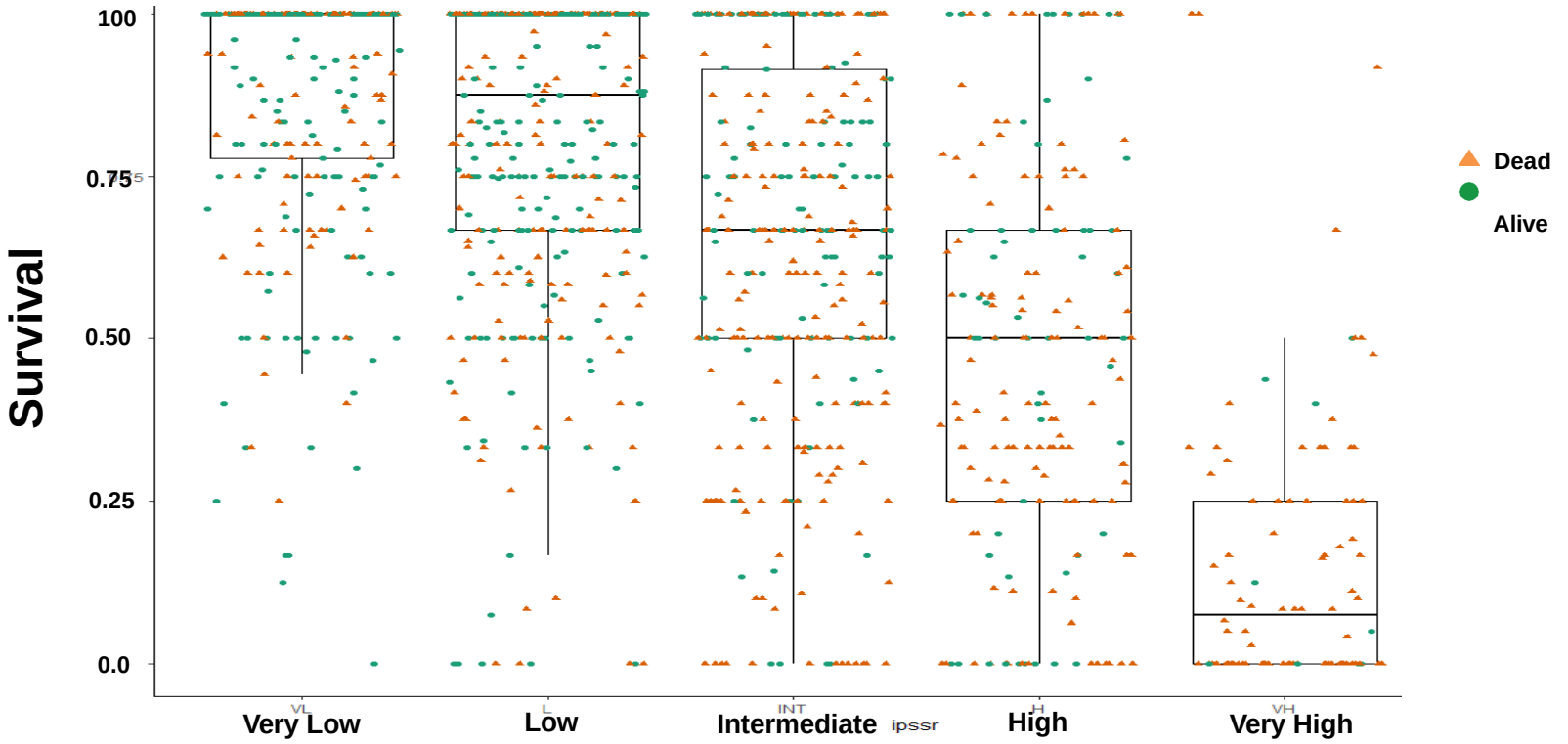
Higher



Greenberg P. Blood 2012;120: 2454-2465

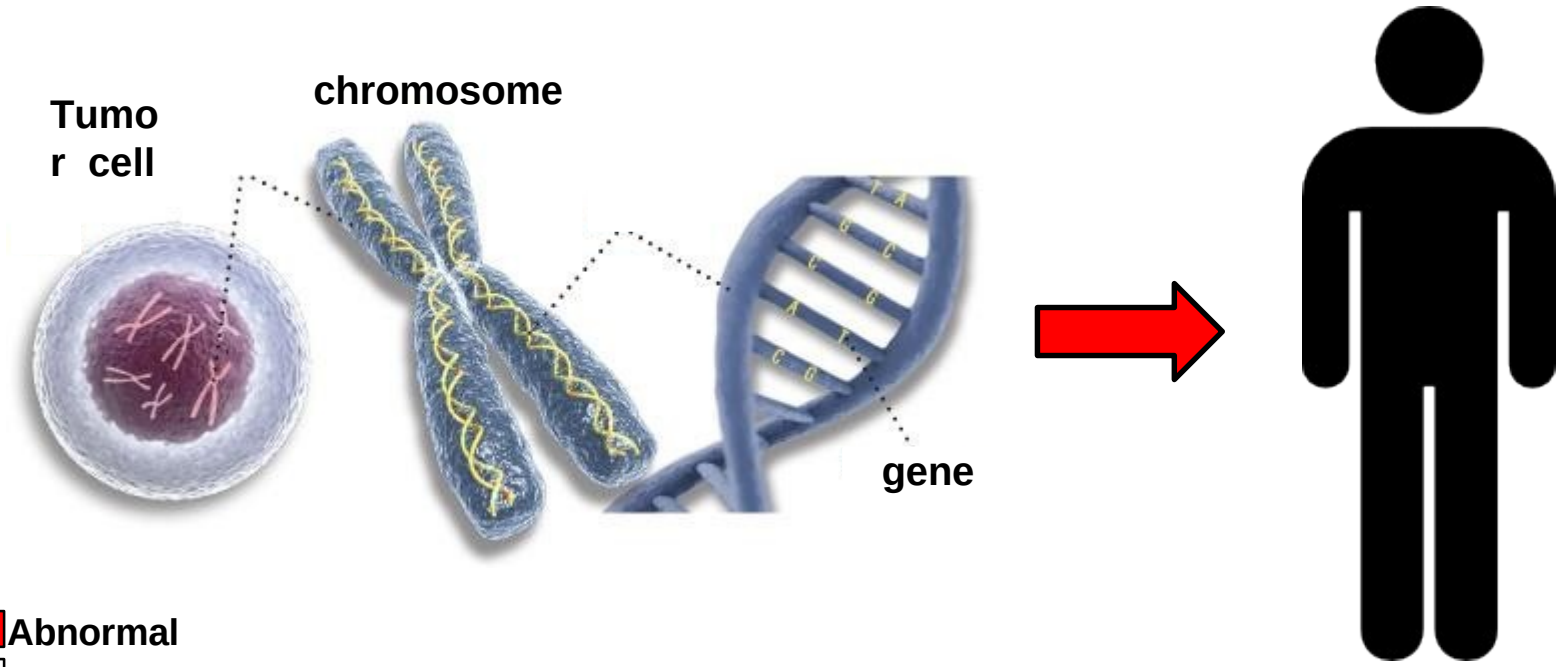
You can, for example, never foretell what any one man will do, but you can say with precision what an average number will be up to. Individuals vary, but percentages remain constant. So says the statistician.” - Sherlock Holmes 1890 [Sir Arthur Conan Doyle: The Sign of Four, Chapter 10, p.137]

Heterogeneity in Outcomes in MDS



Nazha A, et al. ASH 2018

Cancer Genomics



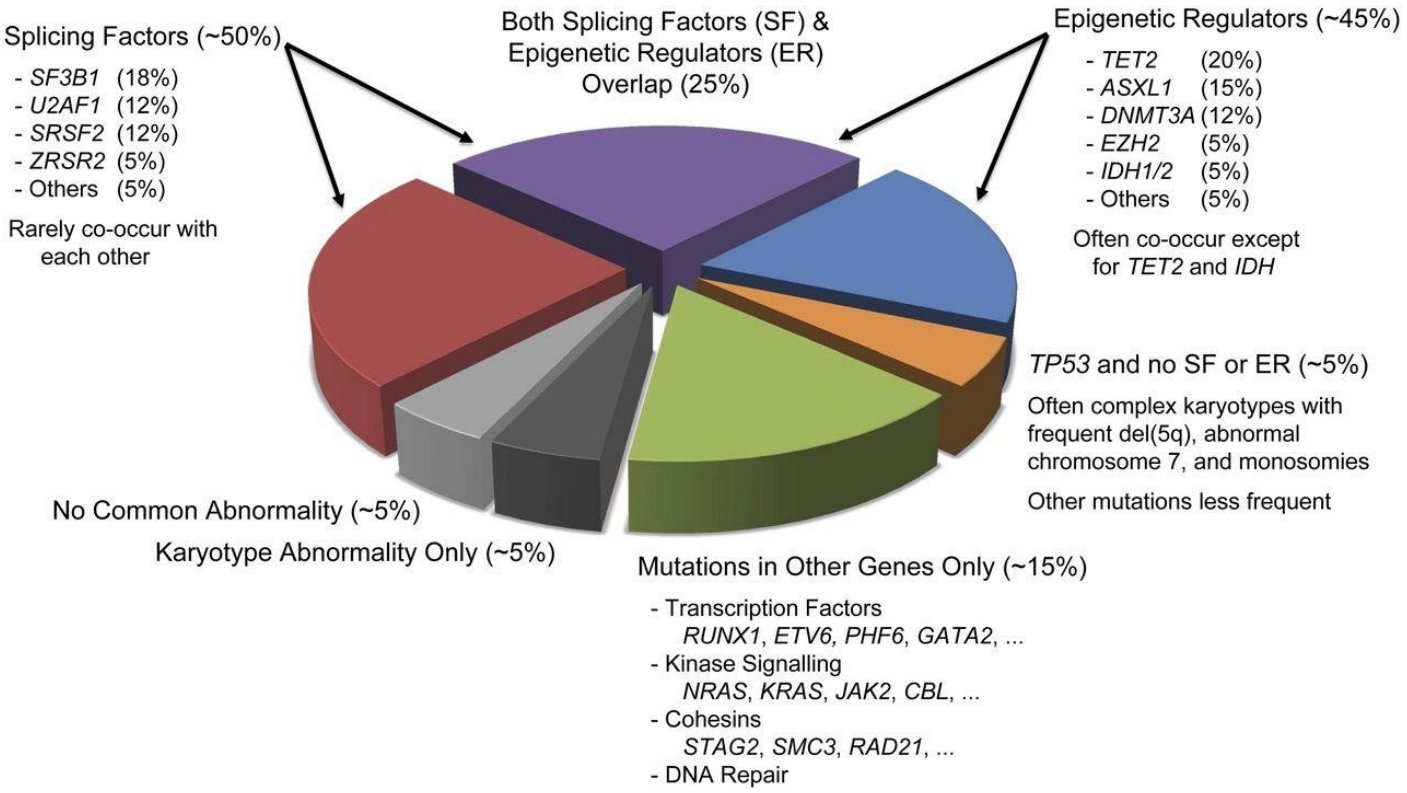
Mutation discovery /Clonality Patient care

- Cytogenetics
- Candidate gene sequencing
- Whole Genome Sequencing (unbiased comprehensive platform)

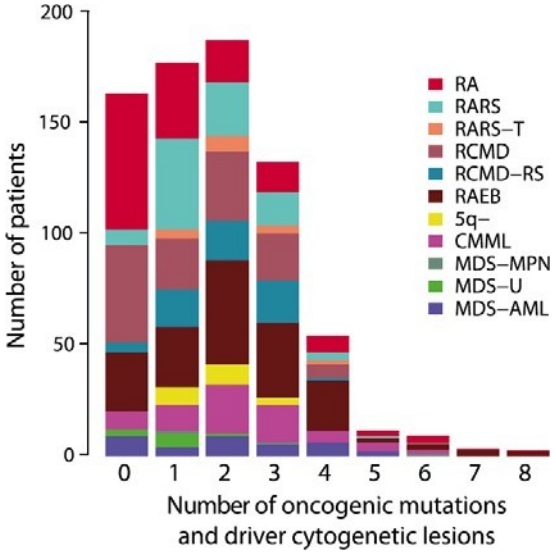
- diagnosis
- risk stratification
- therapy

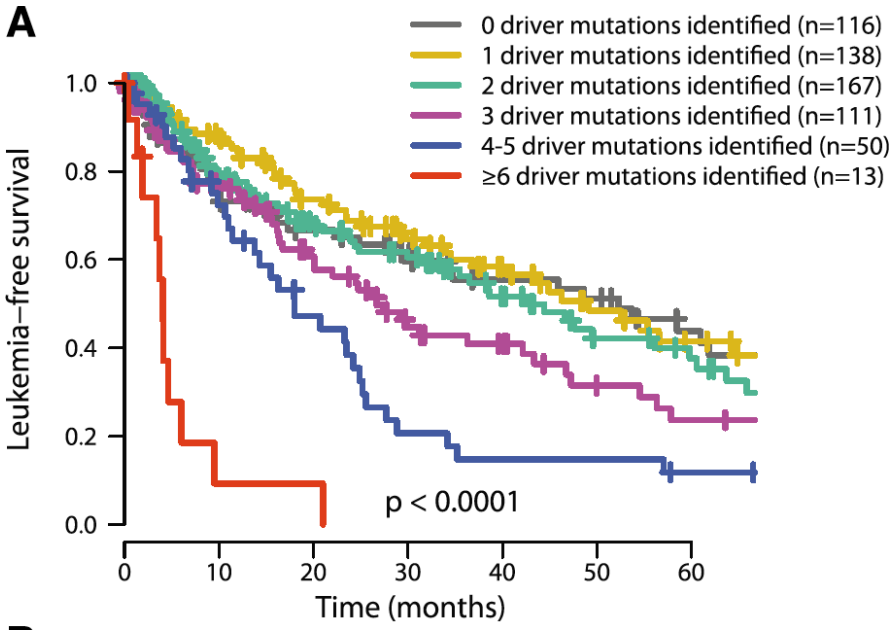
Molecular Mutations in MDS

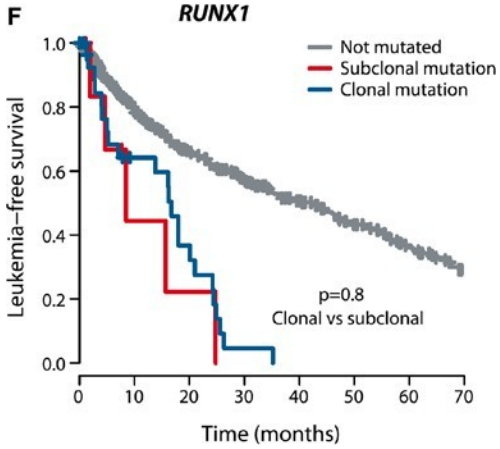
- >90% of patients with MDS have at least 1 mutation



Bejar R and Steensma D, Blood 2014

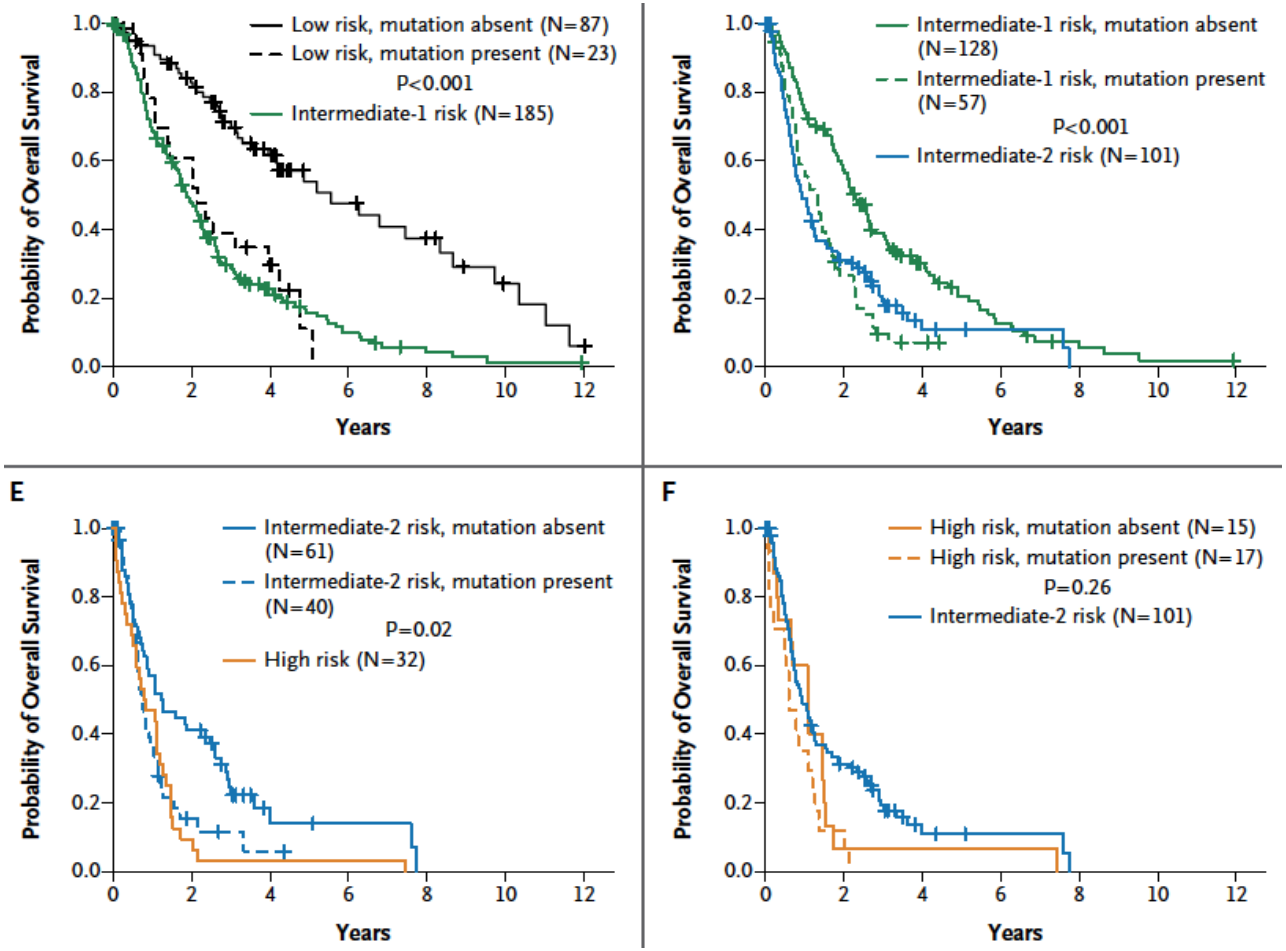






From Papaemmanuil et al, Blood 2013.

IPSS and TP53, EZH2, ETV6, RUNX1 and ASXL1 mutations

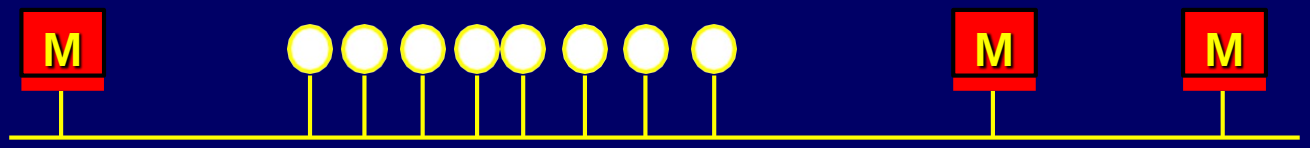


From Bejar et al, NEJM 2011.

Treatments for high-risk MDS

- Decitabine
- Azacitidine
- Intensive Chemotherapy
- Stem-cell transplant
- Clinical trials

Gene hypermethylation in MDS

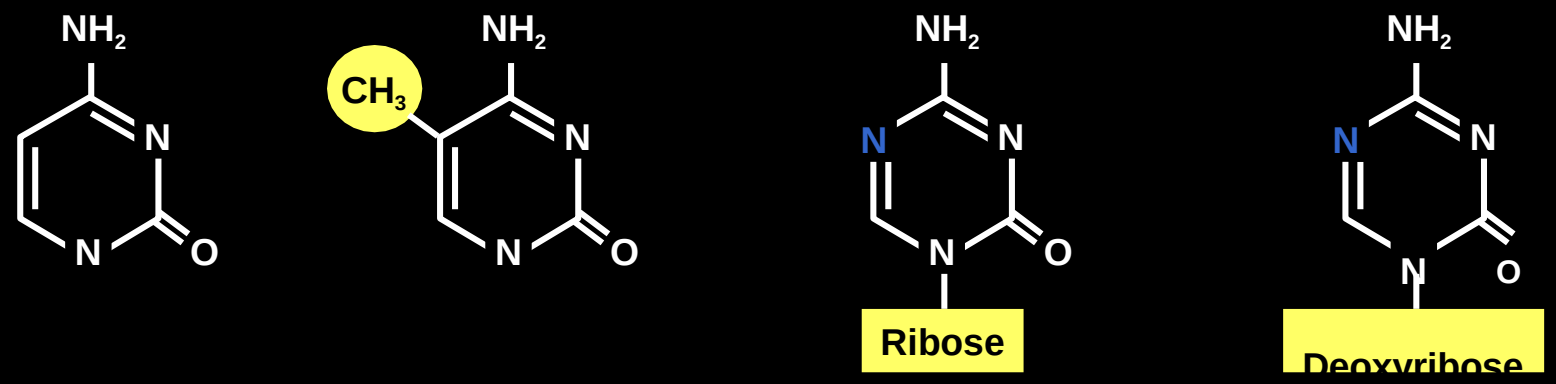


Expressed (or ready for expression)

Silenced

Adapted from of Issa, JP

Hypomethylating cytosine analogs



Cytosine | 5-methyl-cytosine | Azacytidine | Decitabine

Santini V, Kantarjian, HM, Issa, JP. Ann Intern Med 2001, Apr 3;134(7):573-86.

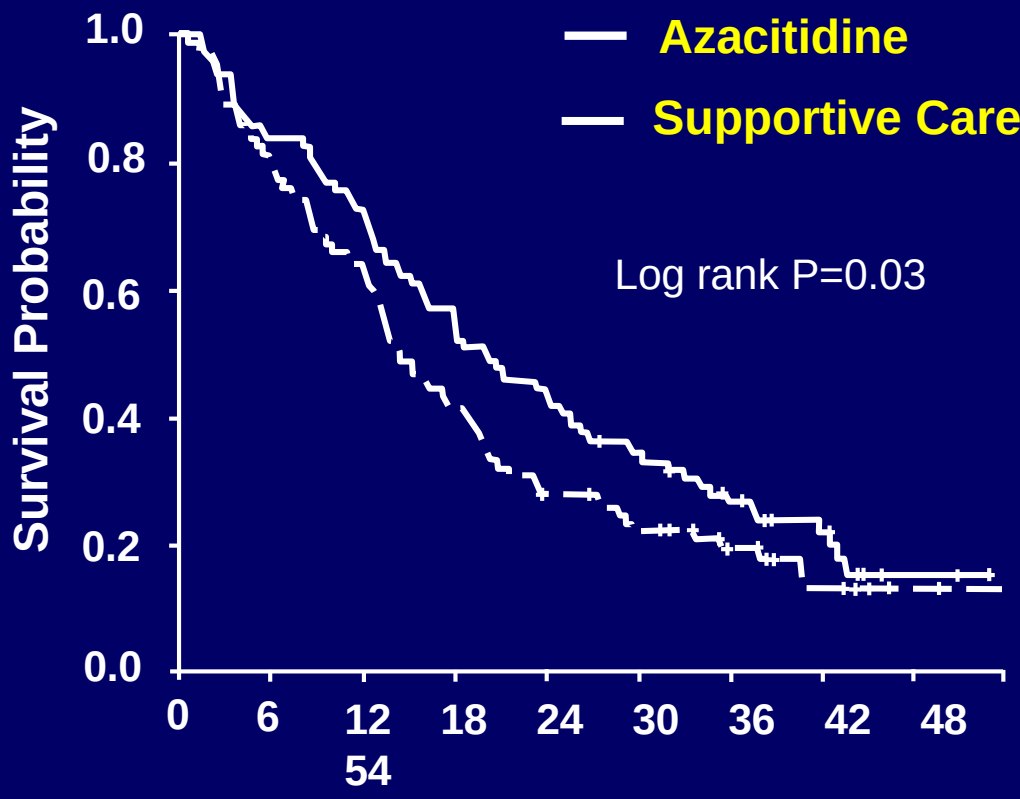
First randomized study of azacitidine in patients with MDS

75 mg/m^2/d SC x 7 days every 4 weeks

Responses (after 4 cycles)

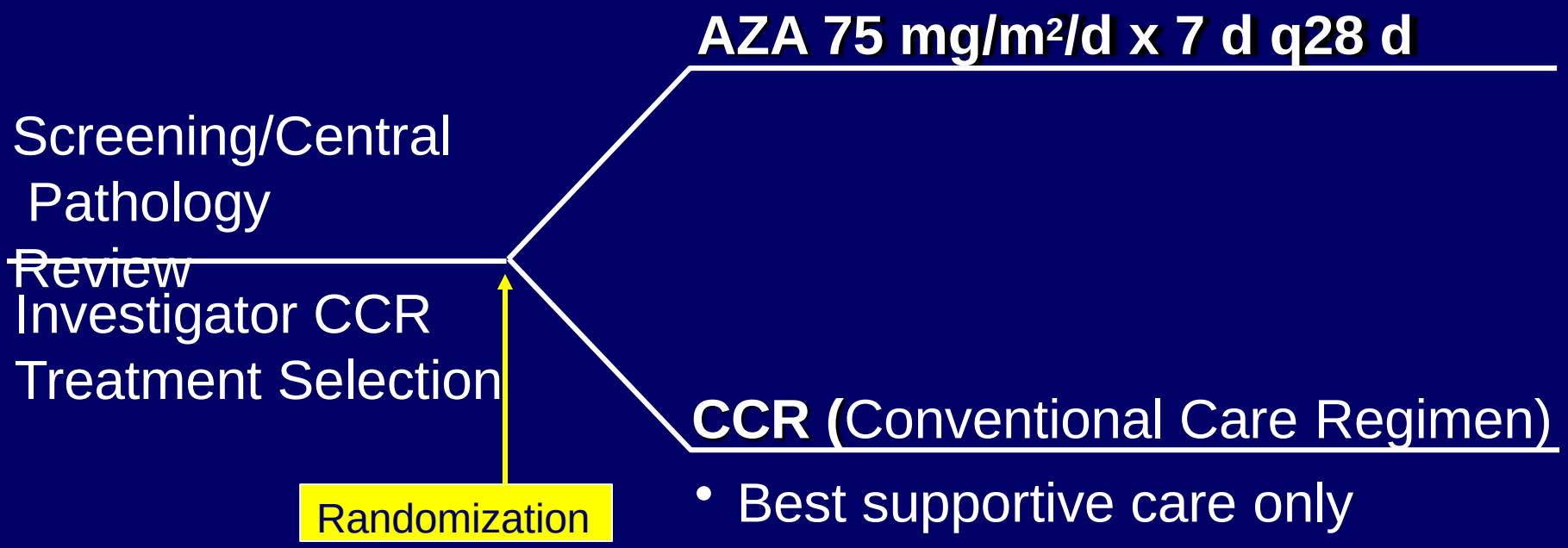
Complete remission - 7%
Partial remission - 16%
Improved - 37%

Total - 60%



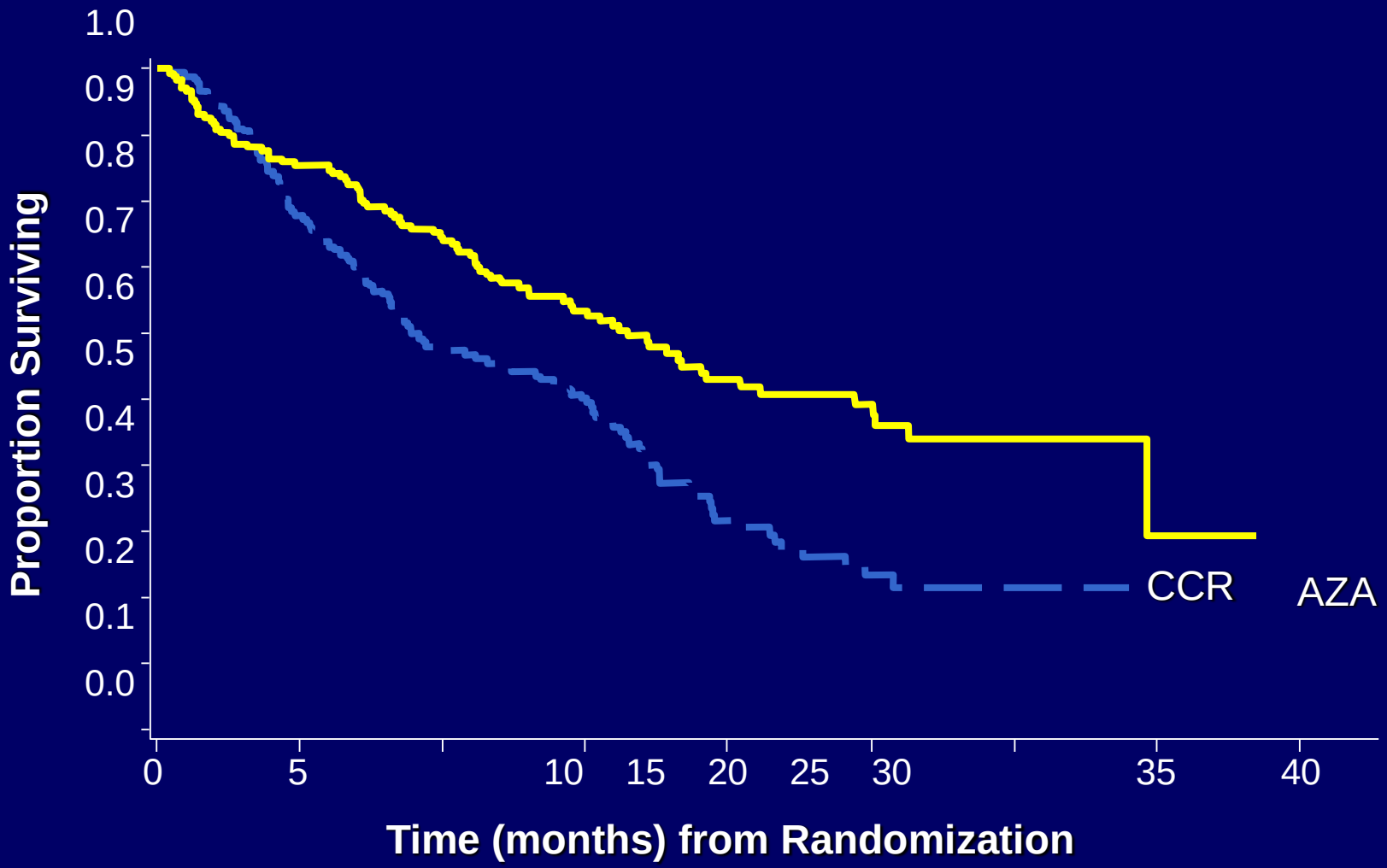
Silverman et al. *J Clin Oncol*. 2002;20:2429

Azacitidine survival study in higher-risk MDS



Fenaux P, et al. Lancet Onc 2009;10:223

Overall Survival in higher-risk: Azacitidine vs CCR



Fenaux P, et al. Lancet Onc 2009;10:223

Azacitidine treatment

- Subcutaneous or intravenous injections daily for 7 [or 5(+2)] days every 28 days
- Median cycles to first response: 2-3
- Response may require 4-6 cycles
- Do NOT need a complete response for benefit
- Responders need to continue treatment to sustain response.

Decitabine- ADOPT study

- Decitabine 20 mg/m2 IV daily x for 5 days; 28-day cycles
- Overall response rate 32% (17% complete remission and 15% marrow complete remission)
- Overall improvement rate 51%, including 18% improvement in blood counts.
- Similar response rates in all risk categories.
- 82% of patients who improved showed responses by the end of cycle two.
- Survival advantage not yet demonstarted for decitabine, likely due to inferior study designs.

Steensma et al. J Clin Oncol 27:3842-8, 2009

Decitabine after Azacitidine may help some patients

Table II. Response summary.

	Number (percent)	Median (range)
Responses		
CR	3 (21)	
Marrow CR with HI	1 (7)	
Stable disease	5 (36)	
Progressive disease/death	4/1 (29/7)	
Number of DAC courses to response		3 (1–5)
Median survival (months)		6 (1–14.8)

CR, complete remission; HI, hematological improvement; DAC, decitabine.

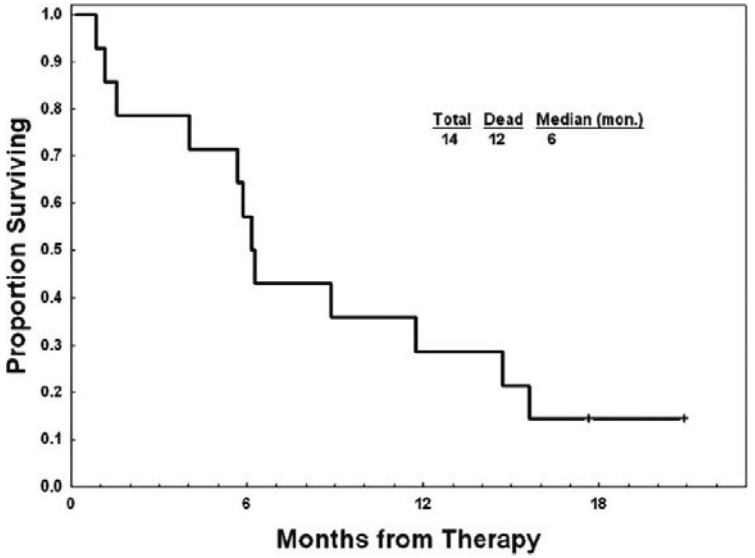


Figure 1. Overall survival of all the 14 patients.

Table III. Characteristics of responders.

	Number of prior Aza courses	Best response to Aza	Reason off Aza/weeks off Aza	Weeks from prior Aza before DAC	Best response to DAC/courses to response	Response duration (months)	Percent marrow blasts pre/at response	Platelets pre/at response	ANC pre/at response
1	8	Marrow CR	PD	3	CR/3	9.7	15/1	24/336	1.1/3.2
2	4	SD	NR	11	Marrow CR/3	8.2	8/4	65/95	1.8/5.1
3	4	SD	NR	9	CR/5	11.3+	12/3	80/234	0.6–1.4
4	1	N/A	Toxicity	5	CR/1	10.2	13/4	24/110	0.38/2.8

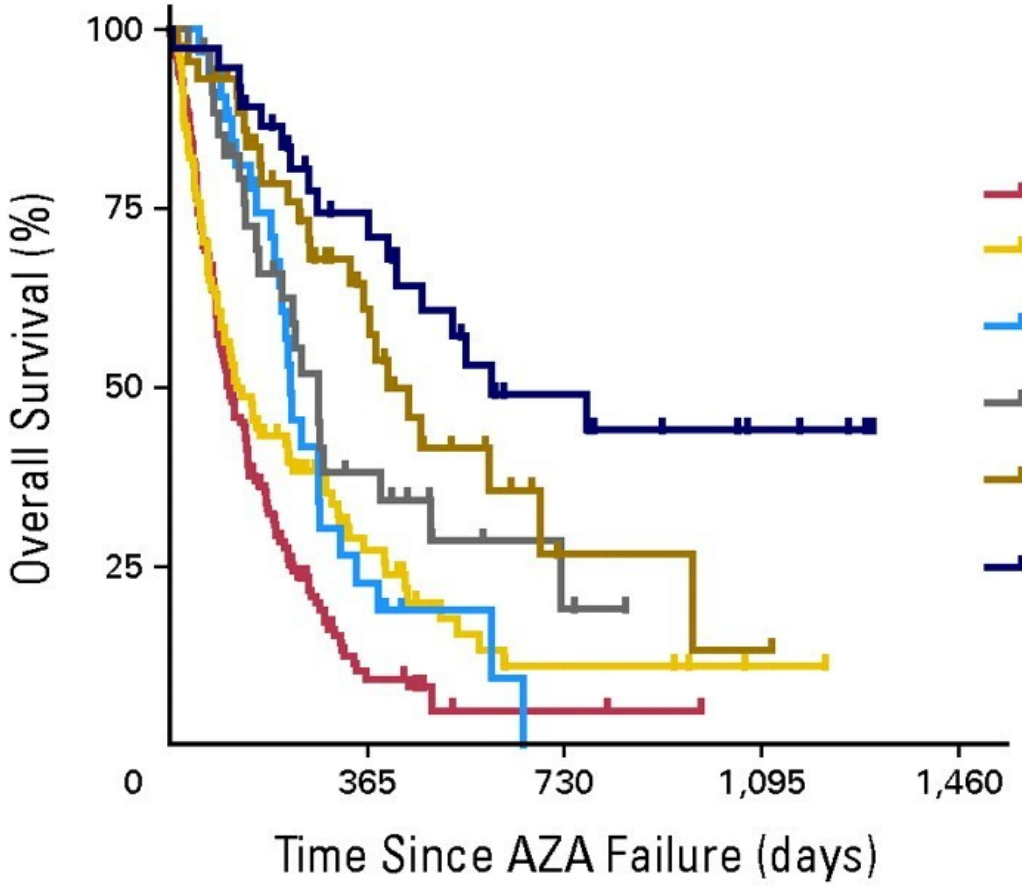
CR, complete remission; Aza, azacitidine; DAC, decitabine; SD, stable disease; PD, progressive disease; NR, no response; ANC, absolute neutrophil count.

Decitabine 20mg/m2 IV days 1-5 on a 28-day cycle

Borthakur et al. Leuk Lymph 2008.

Azacitidine vs. Decitabine

Outcomes after failure of treatment



Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

Prébet et al. JCO 2011.

2014 ASH Abstracts:

3275 (Nazha et al.): IPSS-R best predicts outcomes

3273 (Nazha et al.): SD after 6mo unlikely to improve -> clinical trials

Intensive chemotherapy

Retrospective, MD Anderson Experience
n=394 (no 5q- patients included)

	Induction Regimen [a]					
	IA	FA	FAI	TA	CAT	Total
Number of patients	67	76	118	74	59	394
Median age, years	58	63	62	64	63	
FAB: RAEB	21%	33%	33%	47%	31%	
RAEB-T	79%	69%	67%	53%	69%	
IPSS: Int-1	17%	18%	7%	21%	17%	
Int-2	40%	33%	37%	38%	42%	
High	42%	48%	56%	41%	42%	
Early death (first 6 weeks)	15%	18%	21%	5%	15%	
Overall CR rate	**72%**	**61%**	**48%**	**59%**	**58%**	**58%**
IPSS: Int-1						64%
Int-2						60%
High						56%
Median survival[b], weeks	**88**	**33**	**30**	**45**	(c)	
IPSS: Int-1						**85**
Int-2						**45**
High						**38**
Median survival[b] for patients achieving CR (n=229), weeks	**91**	**30**	**36**	**41**	(c)	
IPSS: Int-1						**77**
Int-2						**54**
High						**31**

Consider in:

Younger fit patients <65-70

High blast percentage (>10%)

Non-adverse cytogenetics

Transplant candidate with donor

Post-

chen

giver

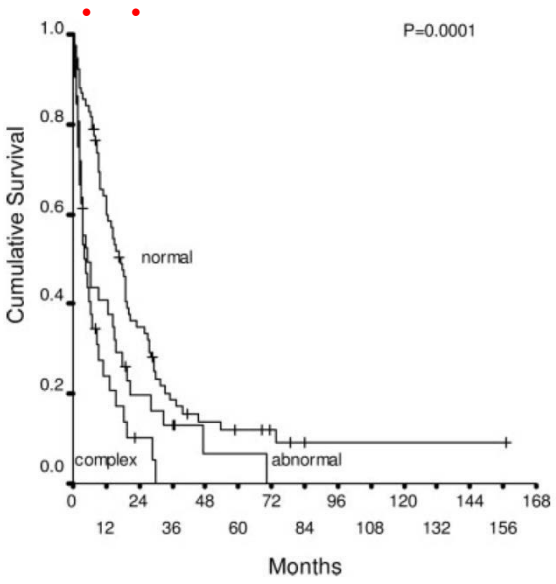


FIGURE 3. Survival of patients with normal versus abnormal versus high-risk karyotypes.

CR 40-60%, median duration CR <1yr

Early mortality 17%, 5yr OS 8%

Beran et al. Cancer 2001.
Kantarjian et al. Cancer 2006.
Knipp et al. Cancer 2007.
Malcovati et al, Blood, 2013.

Pearls - 1

- Occurs more often in older patients with co-morbidities
  - Require more holistic medical care
- Common supportive care requirements
  - Effects of low blood counts (anemia, risk of bleeding or infection)
  - Coordination of blood product support, monitoring, antibiotics
- Treatments are prolonged
  - Effects of disease frequently worsen in early stages of therapy
    - i.e. “1 step backward before 2 steps forward”
  - Requires close coordination with MD, APP, RN, SW care team
- Balance of disease intervention while focusing on QoL

Pearls - 2

- More difficult, more symptomatic, or more advanced MDS
- Consider azacitidine or decitabine
  - ‘Low intensity’ chemotherapy given 5 or 7 consecutive days, every 4 weeks indefinitely
    - Do not work for everyone, or forever
  - Consider clinical trial of novel agent
- Evaluation in BMT program
- Supportive care (transfusions & antibiotics, etc.)
- Treatment of resistant MDS is very difficult

Pearls - 3

- Important to set expectations and goals as not all patients experience a major improvement
- Improvements in CBC
  - Decrease frequency or independence from transfusions
- Improved, or Maintained Quality of Life
  - Stronger, stamina, independent
- Continue therapy ‘long-term’ to maintain benefit & stability
- Sometimes success is ‘stability’, or not worsening of MDS
- Hard to cure – goal is often maintain control

Pearls - 4

- Almost all patients benefit from therapy
  - Depends on scenario and patients needs
  - Set individual patient goals

- Current treatments still not adequate for many
  - We must work together to advance MDS treatments and outcomes
    - Clinical trials
      - Molecularly-targeted therapy

Essentials for MDS patients

- Know your IPSS-R risk group
- Know your treatment options
  - Including transplant, clinical trials
- Know what your treatment goals are
- Know the potential side effects of your treatments
- Know available MDS resources
- Have a caregiver available/involved

- Knowledge = Power
- Take ownership of your care
- Do you have a framework for approaching a new cancer diagnosis?

- Disease specifics (micro-level)
  - exact subtype of leukemia / MDS
  - genetic information of MDS

- Disease specifics (macro-level)
  - Risk-stratification

- Prognosis
  - is it curable?
  - chance of remission
  - overall survival

- Treatment
  - Primary treatment
    - Chemotherapy, stem-cell transplant
  - Phases of treatment
    - Continuous treatment?
    - Induction, consolidation, maintenance?
  - Supportive care

For personalized disease, treatment or support information, please contact one of our Information Specialists:

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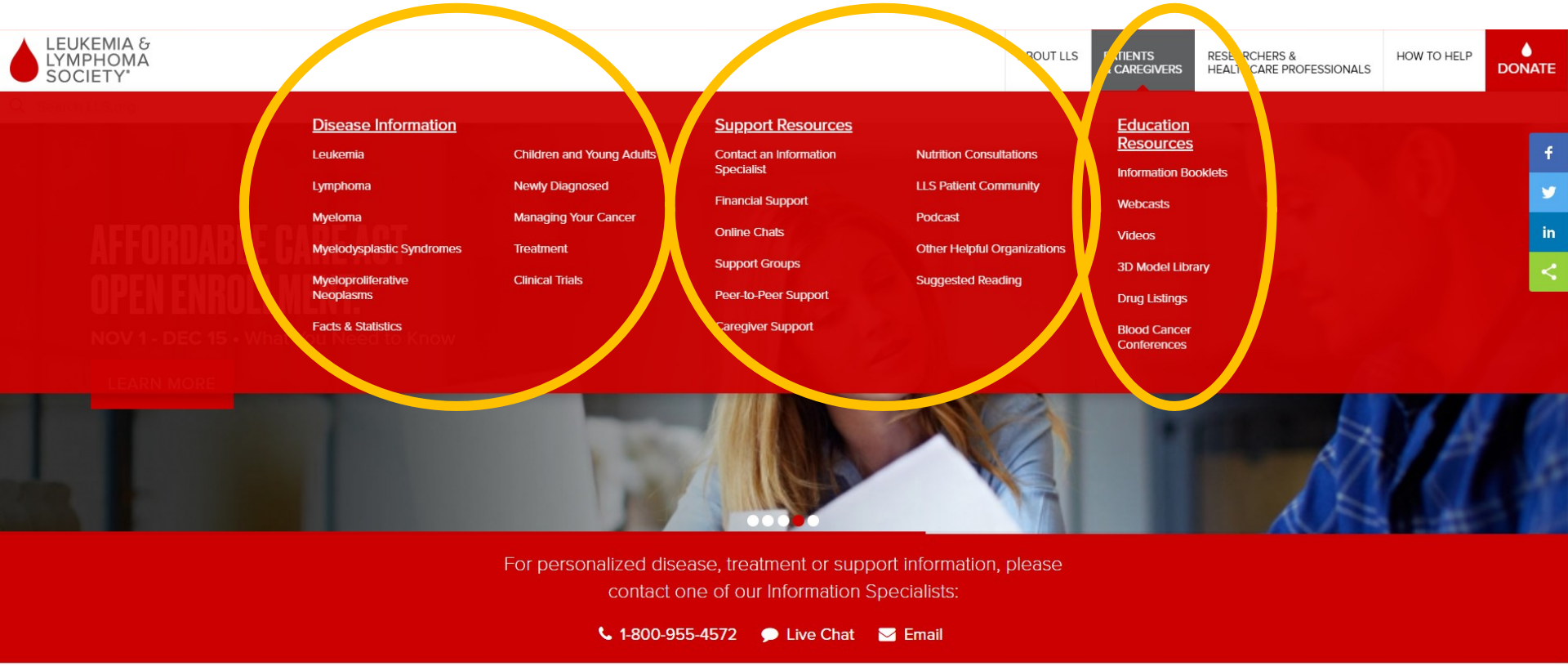
NEWS AND UPDATES



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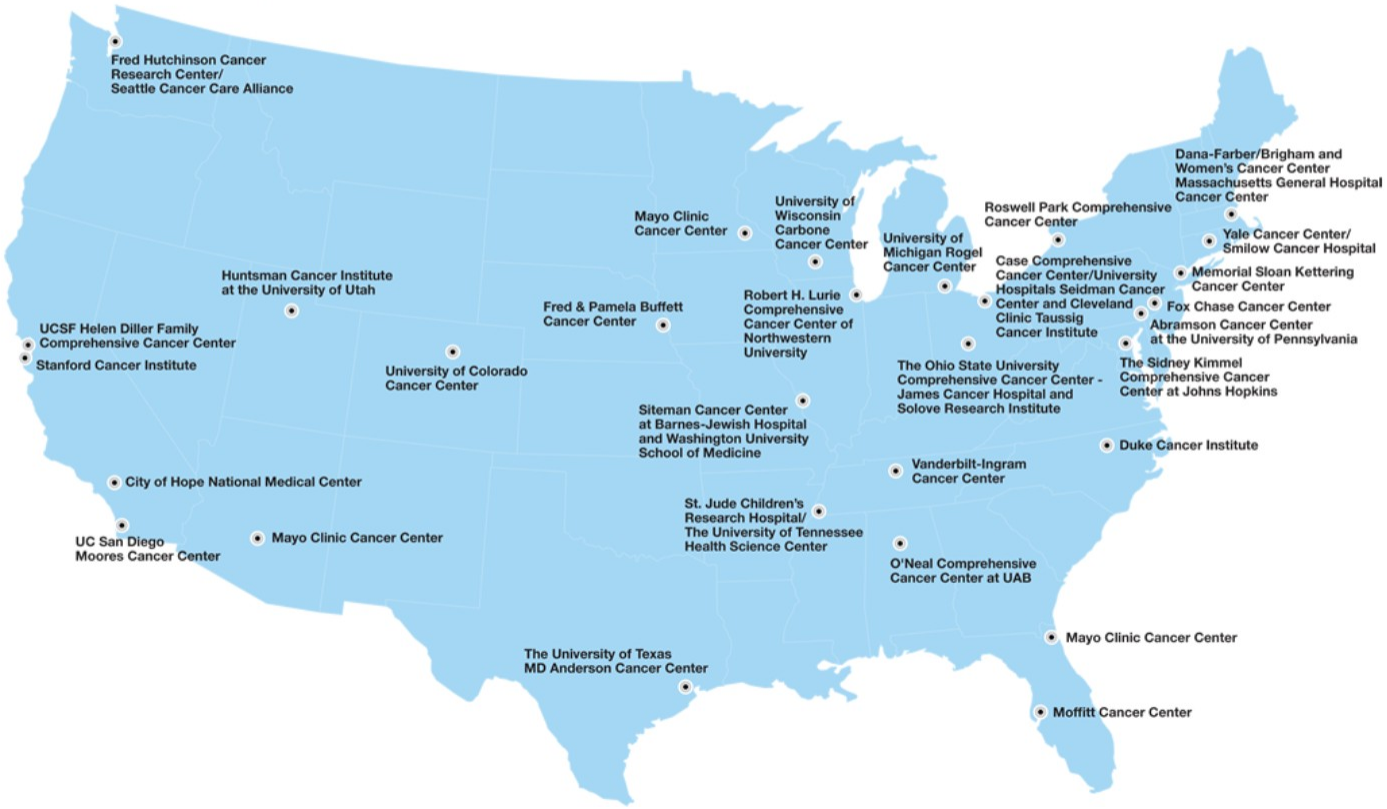

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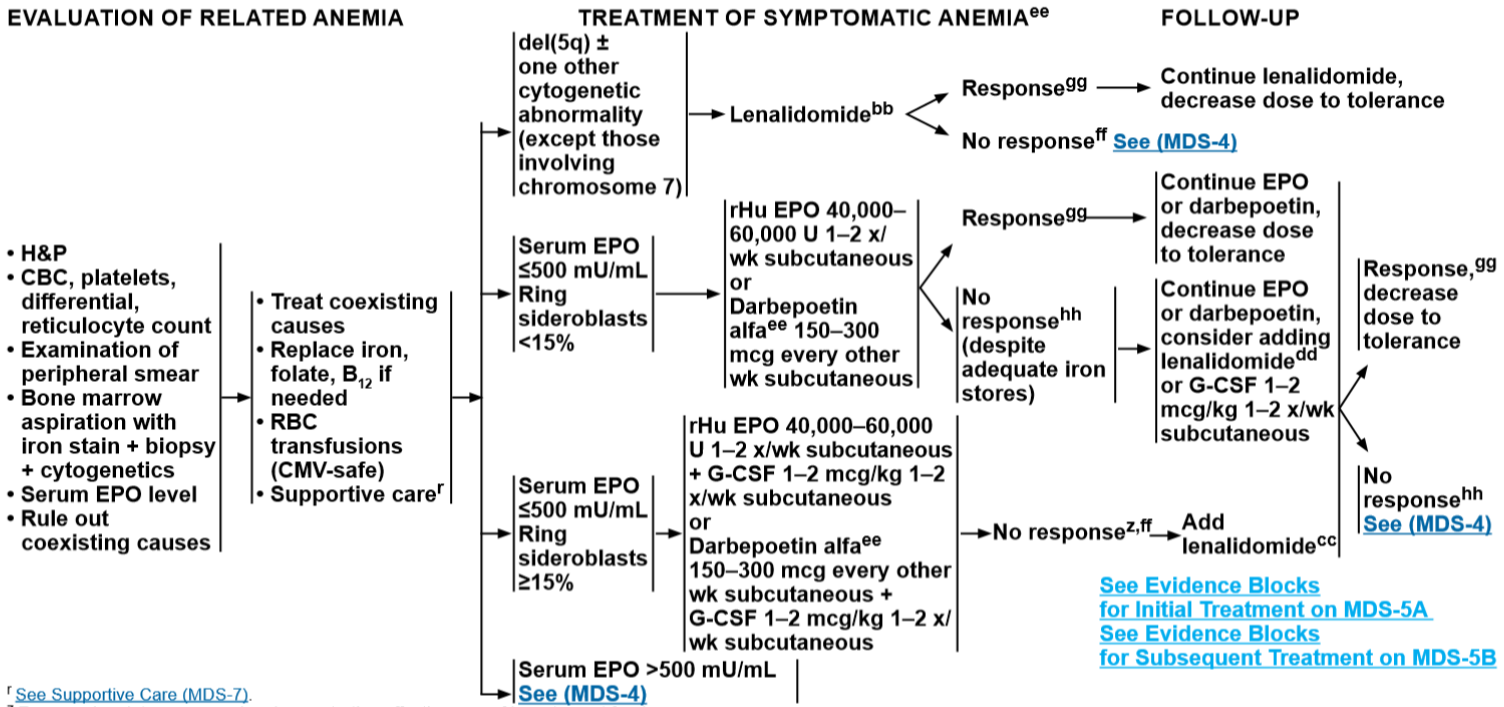

[r] See Supportive Care (MDS-7).

[z] Encouraging data are emerging demonstrating effectiveness of luspatercept for ring sideroblastic lower-risk MDS patients (Fenaux P, Platzbecker U, Mufti G, et al. The MEDALIST Trial: Luspatercept to Treat Anemia in Patients with Lower risk MDS with Ring

[cc] Lenalidomide 10 mg daily if ANC >0.5, platelets >50,000; Toma A, Kosmider O, Chevret S, et al. Leukemia 2016;30(4):897-905

https://www.mds-foundation.org/

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Clinical trials

- Frontline
- Relapsed / Refractory setting

The **MEDALIST** Trial: Results of a Phase 3, RPCC Study of Luspatercept to Treat Patients with Very Low-, Low-, or Intermediate-Risk MDS Associated Anemia with Ring Sideroblasts Who Require RBC Transfusions

- 153 Patients Luspatercept 1mg/kg SC every 21 days
  - **38%** achieved transfusion-independence at 8 weeks
  - 28% achieved transfusion-independence at 12 weeks

- 76 Patients Placebo
  - 13%achieved transfusion-independence at 8 weeks
  - 8 % achieved transfusion-independence at 8 weeks

Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non- Del(5q) Lower Risk MDS Relapsed/Refractory to ESA

- 38 Patients received Imetelstat 7.5 mg/kg IV every 4 weeks
  - **37%** achieved transfusion-independence at 8 weeks
  - 26% achieved transfusion-independence at 24 weeks
  - Median time to onset of TI 8 weeks
  - Median duration of TI not reached
  - Neutropenia and thrombocytopenia in 20-25%

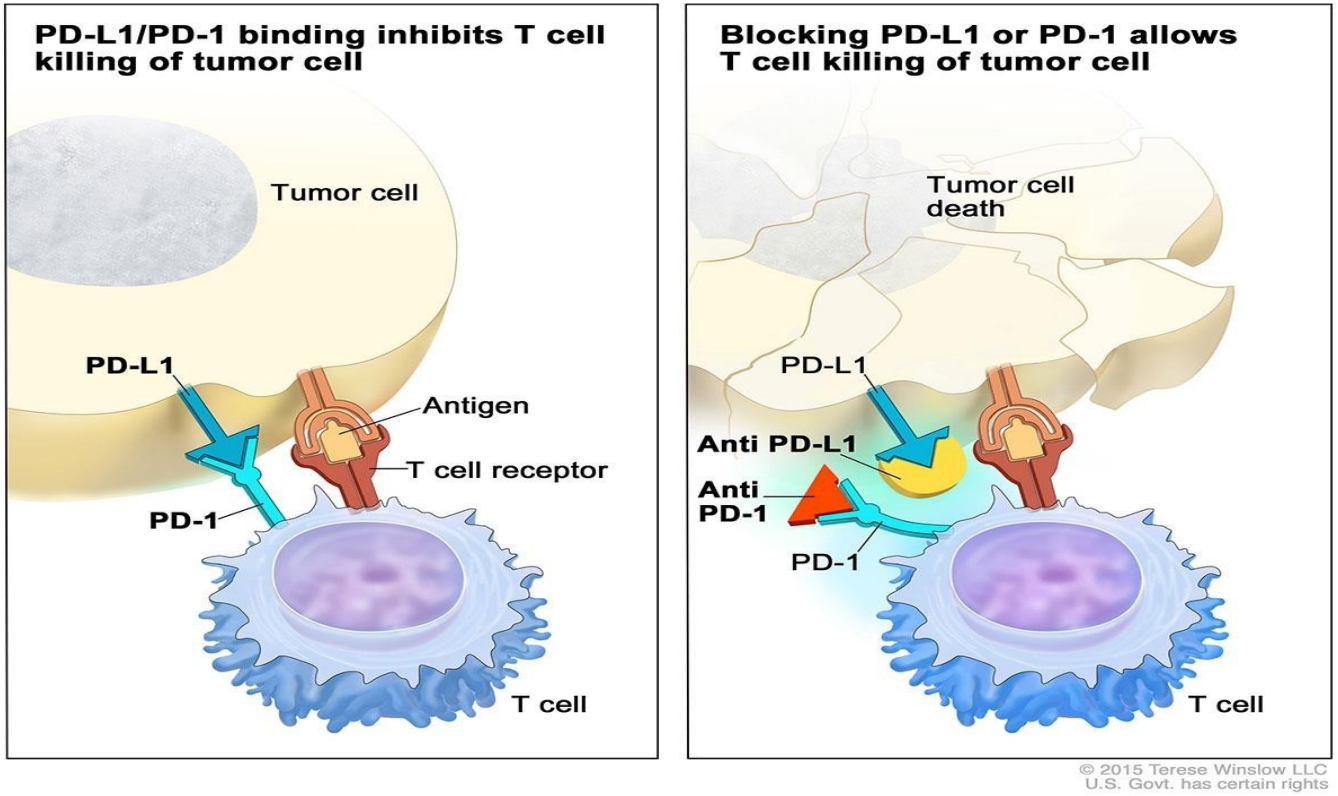
Guadecitabine (SGI110)
in MDS

Phase I: Less rapid degradation by cytidine deaminase = longer half life than decitabine

Phase II: n=102, 60mg/m2 or 90mg/m2

- Previously treated patients:
  - 30% ORR
- Treatment naiive patients: 20% CR
  - 58% transfusion-independent for RBC
  - 46% transfusion-independent for platelets

Is Immune Exhaustion an Issue in MDS?

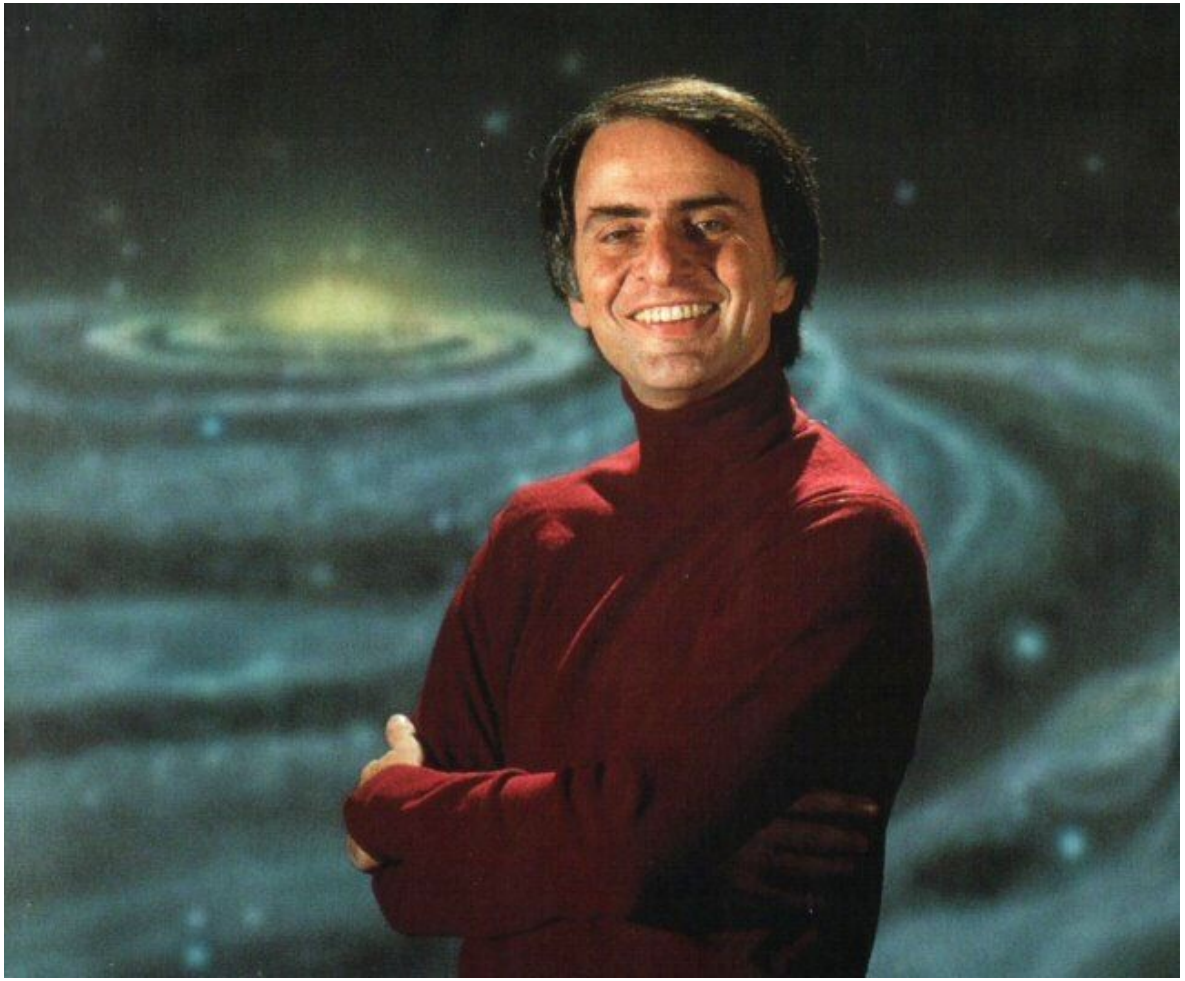


Trials Using Immune Checkpoint Inhibitors?

- Phase II: Azacitidine + Nivolumab or Ipilimumab (MDA)
  - ORR 60-70% as FRONTLINE treatment
  - CR 40% with AZA + Nivolumab, 14% with AZA + IPI
  - CR 6/20 IPI alone (30%)
- Phase Ib: AZA + Atezolizumab
  - ORR 62%
  - CR 14%

New drugs and targets

- NTX-301
- ASTX-727 LD
- GSK3326595
- SEA-CD70
- APR-246
- Anti-CD47 Antibody Magrolimab (5F9)
- Pevonidistat
- Rigosertib

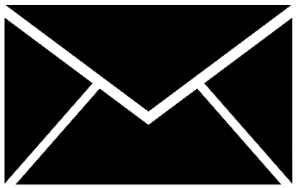


The nitrogen in our DNA, the calcium in our teeth, the iron in our blood, the carbon in our apple pies were made in the interiors of collapsing stars. We are made of star stuff.
– Carl Sagan

It is something that is called MDS. It is a rare blood disorder that affects the bone marrow. I'm going to beat this. My doctors say it and my faith says it.

-Robin Roberts

Pankit Vachhani, MD



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