Best Practices and Emerging Therapies for Myelodysplastic Syndromes

Erica Warlick, MD
Associate Professor of Medicine
University of Minnesota
October 17, 2018

Overview

- **General Review of MDS**
  - Biology
  - Current Classification Systems

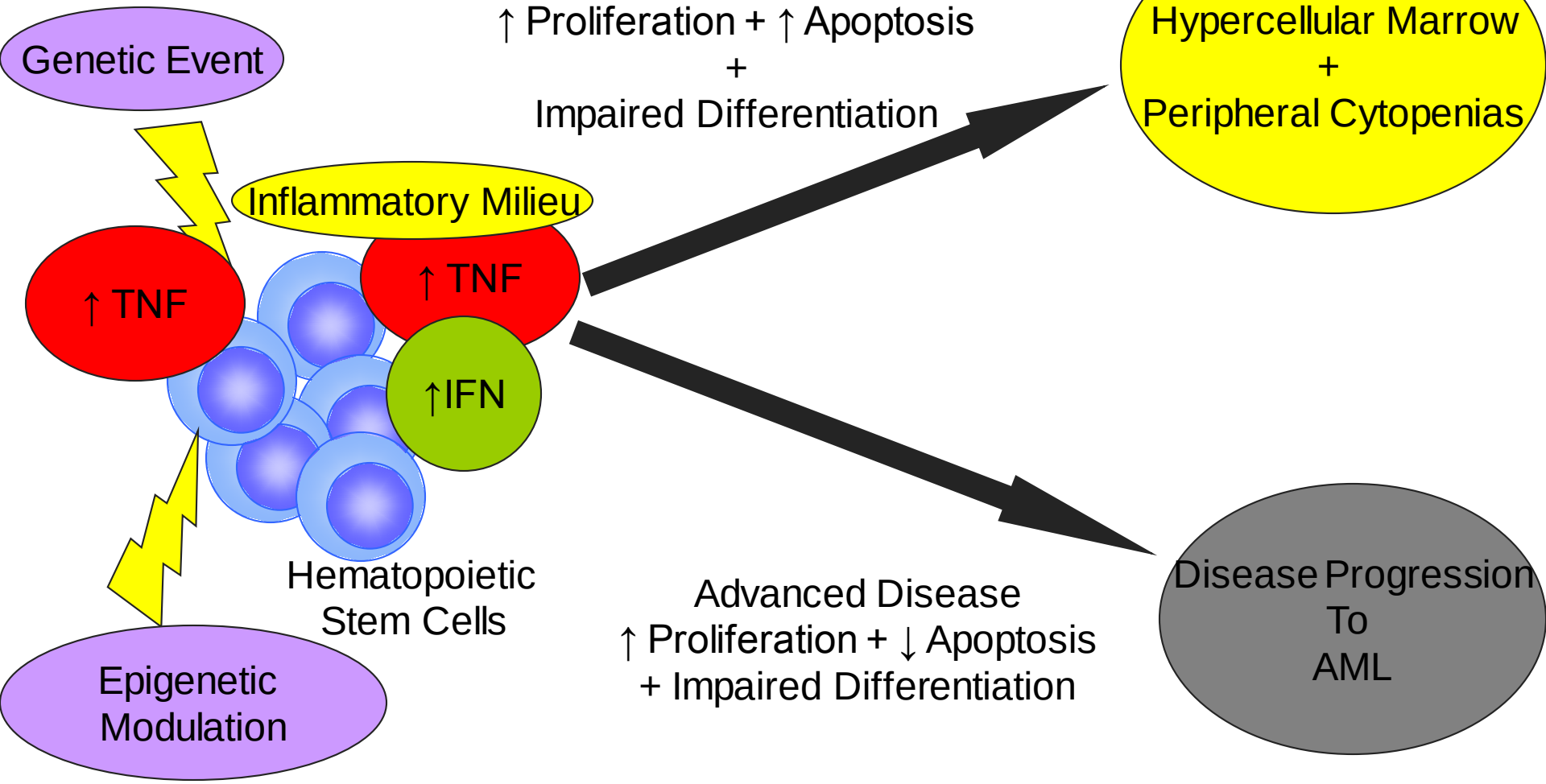
- **Best Practices: Treatment**
  - Treatment Decision-Making:
    - Non-transplant Therapy:
    - Stem Cell Transplant
    - Emerging Therapies

Overview of MDS

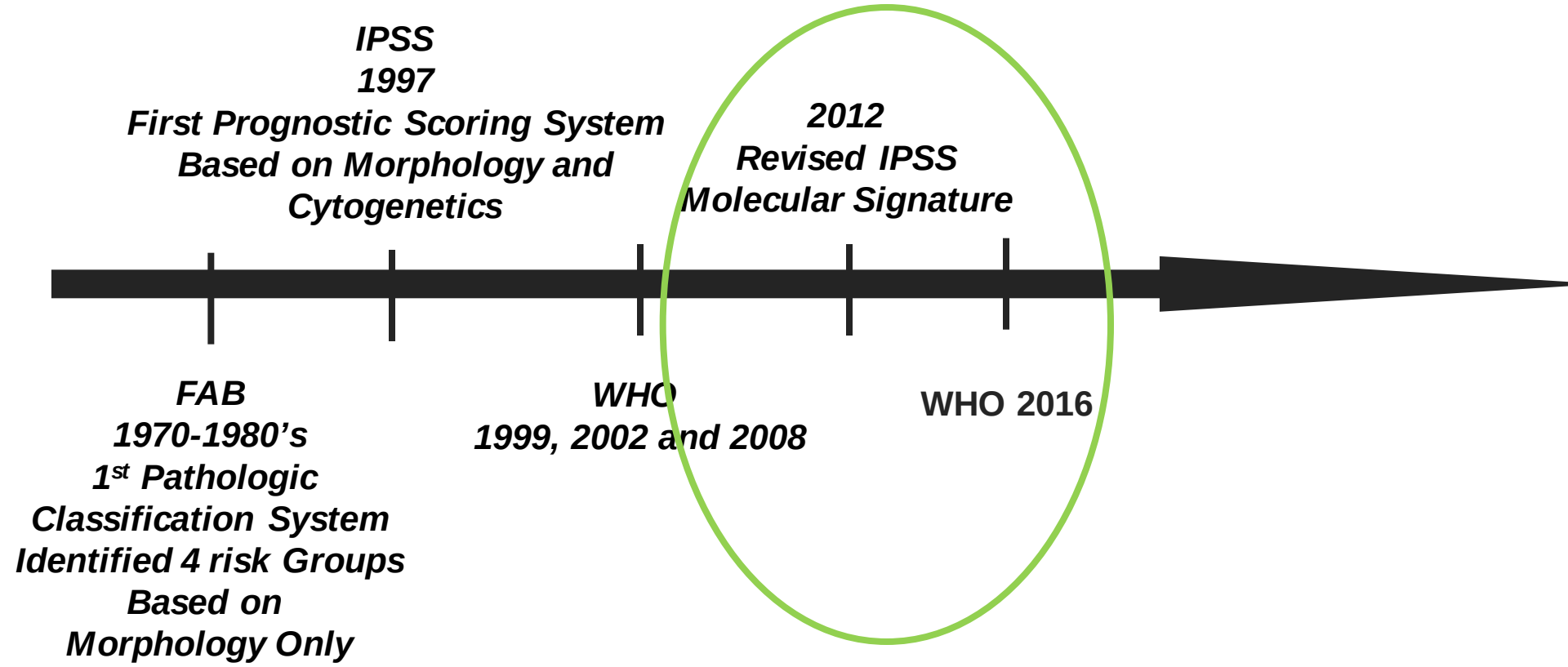
"MDS: What is it?"

- Heterogeneous and complex group of clonal hematopoietic stem cell disorders with wide range of clinical severity characterized by:
  - Ineffective Hematopoiesis (in the absence of nutritional deficiencies)
  - Dysplasia
  - Peripheral cytopenias
  - Increased risk of infection
  - Varying degree of risk for transformation to acute leukemia (AML)

MDS Pathogenesis



"How Do We Classify It? The Evolution of MDS Classification"



Revised IPSS

Revised International Prognostic Scoring System for Myelodysplastic Syndromes

Peter L. Greenberg,[1] Heinz Tuechler,[2] Julie Schanz,[3] Guillermo Sanz,[4] Guillermo Garcia-Manero,[5] Francesc Solé,[6] John M. Bennett,[7] David Bowen,[8] Pierre Fenaux,[9] Francois Dreyfus,[10] Hagop Kantarjian,[5] Andrea Kuendgen,[11] Alessandro Levis,[12] Luca Malcovati,[13] Mario Cazzola,[13] Jaroslav Cermak,[14] Christa Fonatsch,[15] Michelle M. Le Beau,[16] Marilyn L. Slovak,[17] Otto Krieger,[18] Michael Luebbert,[19] Jaroslaw Maciejewski,[20] Silvia M. M. Magalhaes,[21] Yasushi Miyazaki,[22] Michael Pfeilstöcker,[2] Mikkael Sekeres,[20] Wolfgang R. Sperr,[15] Reinhard Stauder,[23] Sudhir Tauro,[24] Peter Valent,[15] Teresa Vallespi,[25] Arjan A. van de Loosdrecht,[26] Ulrich Germing,[11] and Detlef Haase[3]

BLOOD, 20 SEPTEMBER 2012 • VOLUME 120, NUMBER 12

Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

Refinements in Cytogenetic Categorization

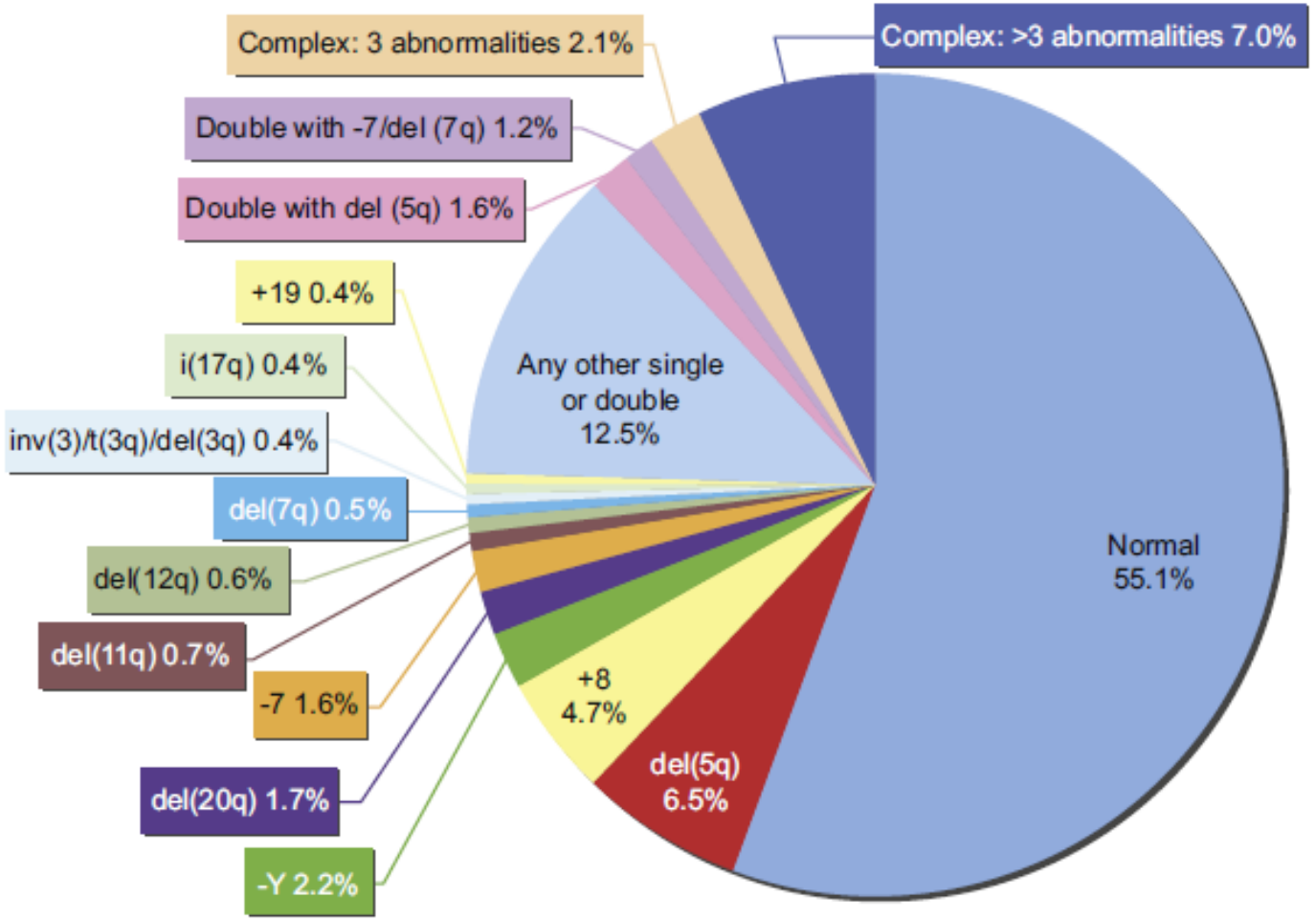
- IPSS-R: 5 Category System (improved from prior 3 category system)

Table 2. MDS Cytogenetic Scoring System

Prognostic subgroups, % of patients	Cytogenetic abnormalities	Median survival,* y	Median AML evolution, 25%,* y	Hazard ratios OS/AML*	Hazard ratios OS/AML†
Very good (4%*/3%†)	−Y, del(11q)	5.4	NR	0.7/0.4	0.5/0.5
Good (72%*/66%†)	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4	1/1	1/1
Intermediate (13%*/19%†)	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5	1.5/1.8	1.6/2.2
Poor (4%*/5%†)	−7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities	1.5	1.7	2.3/2.3	2.6/3.4
Very poor (7%*/7%†)	Complex: > 3 abnormalities	0.7	0.7	3.8/3.6	4.2/4.9

Cytogenetic Distribution

Nybakken and Bagg



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IPSS-R Categories Impact on Survival

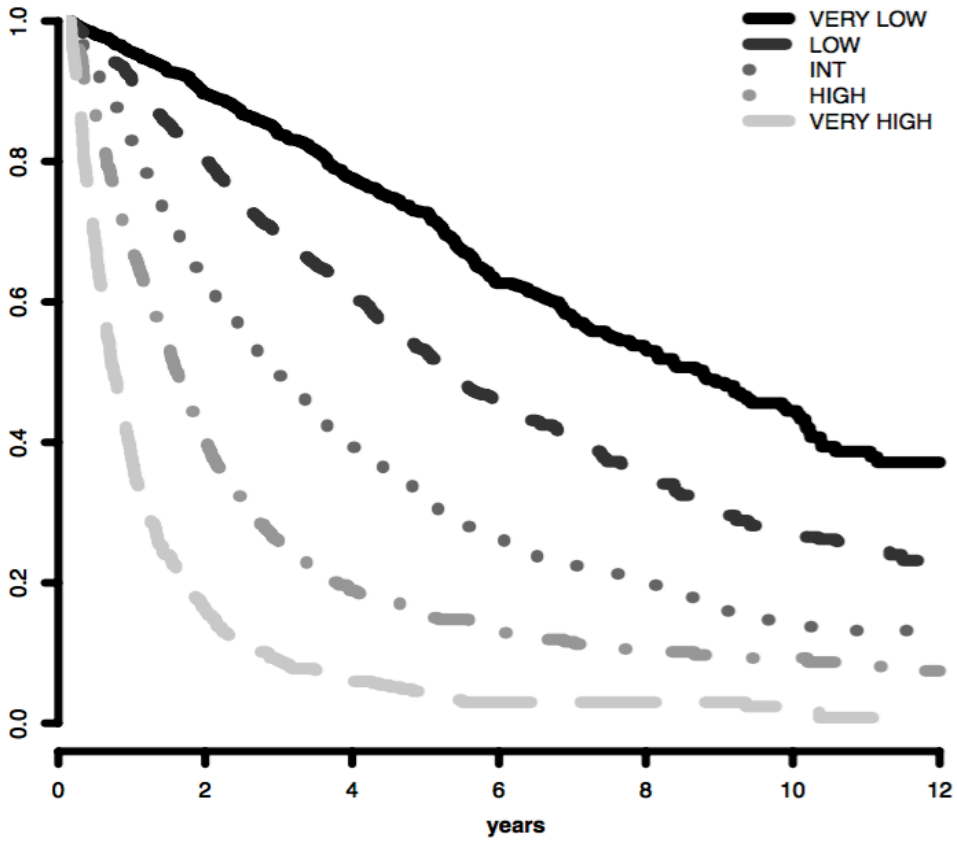


Figure 3. Survival based on IPSS-R prognostic risk-based categories. Survival related to MDS patients' prognostic risk categories (Kaplan-Meier curves, n = 7012; Dxy 0.43, $P < .001$). The number of patients in each category and their proportional representation are shown in Table 1.

Significant Survival Differences: IPSS-R Categories Based On Age

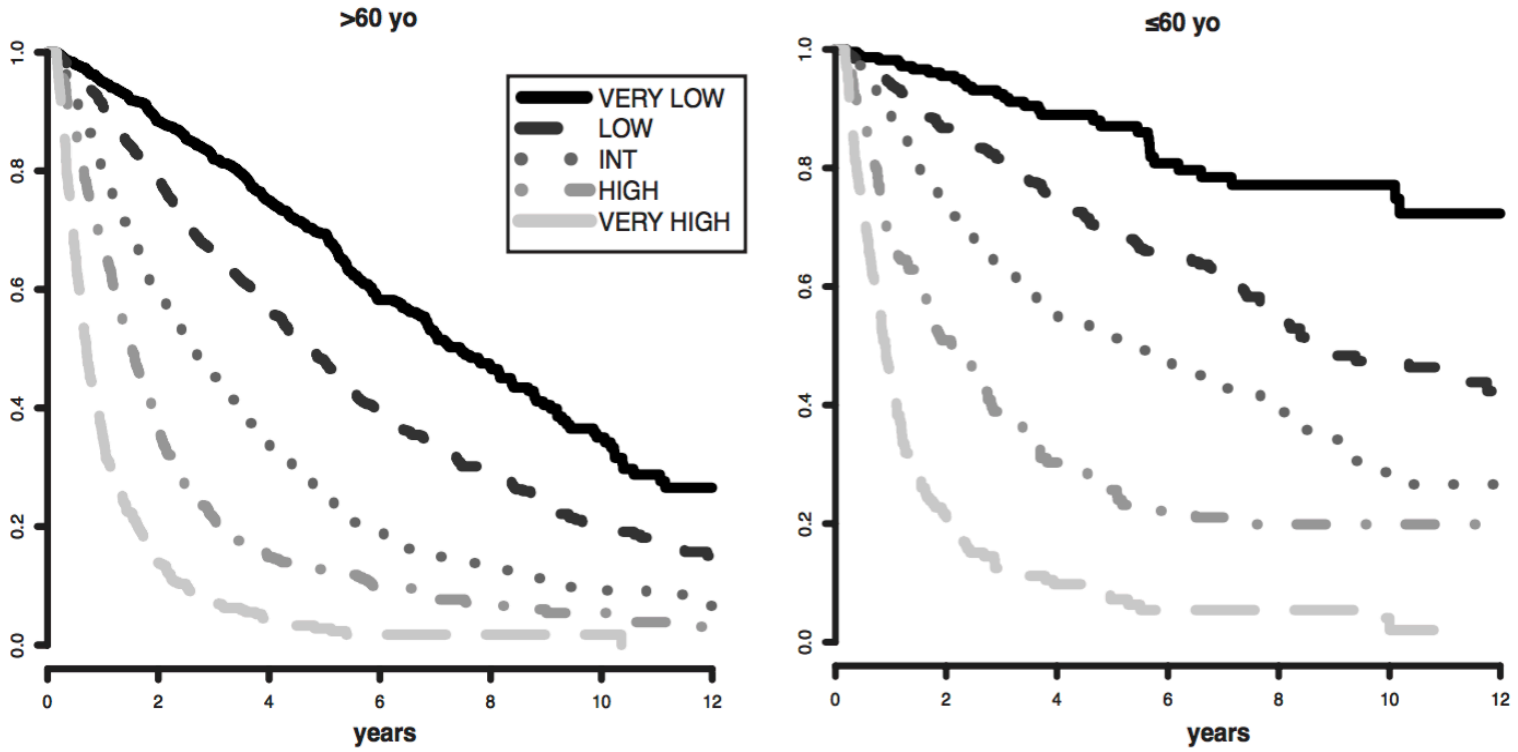


Figure 5. Survival based on patient ages > 60 years vs ≤ 60 years related to their IPSS-R prognostic risk-based categories (Kaplan-Meier curves). Age-related differential survivals are shown for patients in all groups, particularly for those in lower risk categories.

Updated WHO

Pathologic Classification

2016

WHO 2016

Table 15. PB and BM findings and cytogenetics of MDS

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

New Methods of Classification

Molecular Analysis

2011 and Beyond…..

Refinements in Risk Prediction based on Molecular Signatures

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Effect of Point Mutations in Myelodysplastic Syndromes

Rafael Bejar, M.D., Ph.D., Kristen Stevenson, M.S., Omar Abdel-Wahab, M.D., Naomi Galili, Ph.D., Björn Nilsson, M.D., Ph.D., Guillermo Garcia-Manero, M.D., Hagop Kantarjian, M.D., Azra Raza, M.D., Ross L. Levine, M.D., Donna Neuberg, Sc.D., and Benjamin L. Ebert, M.D., Ph.D.

N ENGL J MED 364;26 NEJM.ORG JUNE 30, 2011

MDS Molecular Signature

Table 1. Frequency of Mutation and Association with Median Survival.*

Mutated Gene	No. of Samples (%)	Median Survival (95% CI)	P Value
		yr	
All samples	439 (100)	1.86 (1.60–2.14)	
TET2	90 (20.5)	1.88 (1.26–2.55)	0.48
ASXL1	63 (14.4)	1.33 (0.96–1.88)	0.003
RUNX1	38 (8.7)	1.16 (0.77–1.53)	<0.001
TP53	33 (7.5)	0.65 (0.44–1.10)	<0.001
EZH2	28 (6.4)	0.79 (0.67–1.40)	<0.001
NRAS	16 (3.6)	1.03 (0.44–1.98)	0.006
JAK2	13 (3.0)	2.14 (1.02–3.12)	0.96
ETV6	12 (2.7)	0.83 (0.62–2.29)	0.04
CBL	10 (2.3)	1.52 (0.14–1.71)	0.02
IDH2	9 (2.1)	1.58 (0.50–2.14)	0.03
NPM1	8 (1.8)	2.18 (0.59–2.74)	0.43
IDH1	6 (1.4)	3.30 (0.35–9.52)	0.52
KRAS	4 (0.9)	0.89 (0.36–7.44)	0.54
GNAS	3 (0.7)		
PTPN11	3 (0.7)		
BRAF	2 (0.5)		
PTEN	1 (0.2)		
CDKN2A	1 (0.2)		

* Median survival is listed for specific mutations present in at least 4 of the 439 samples (1%). A patient could have multiple mutations. The P values are for median survival in the group of patients with a mutated gene versus the group of patients without a mutation in that gene. CI denotes confidence interval

MDS Molecular Signature

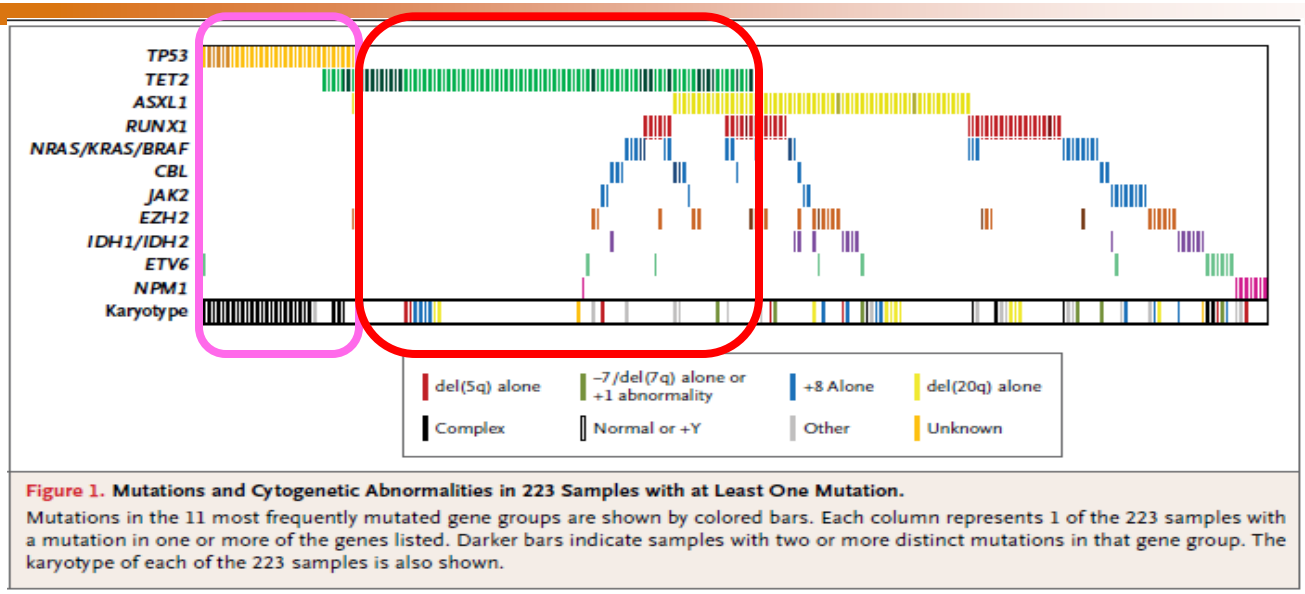
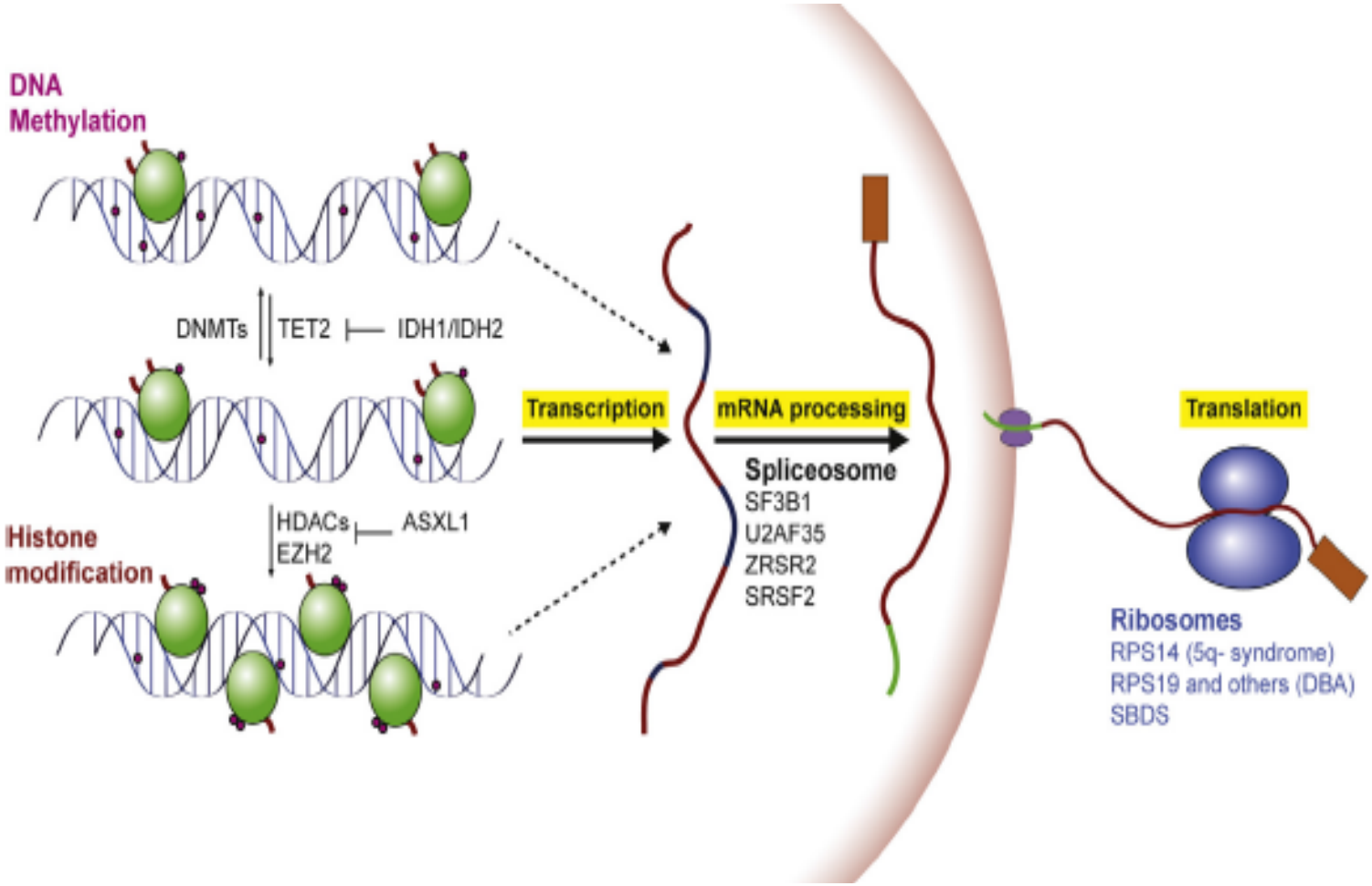


Figure 1. Mutations and Cytogenetic Abnormalities in 223 Samples with at Least One Mutation.
Mutations in the 11 most frequently mutated gene groups are shown by colored bars. Each column represents 1 of the 223 samples with a mutation in one or more of the genes listed. Darker bars indicate samples with two or more distinct mutations in that gene group. The karyotype of each of the 223 samples is also shown.

Cytogenetic/Clinical Associations:

- **TP53 mutations** found in highest frequency with **complex cytogenetics**
- **TET2 mutations** found in highest frequency with **normal cytogenetics**
- RUNX1, TP53, NRAS mutations associated with severe thrombocytopenia and increased blast %
- Mutations in ASXL1, RUNX1, TP53, EZH2, ETV6 had biggest impact on survival

Categories of Molecular Mutations



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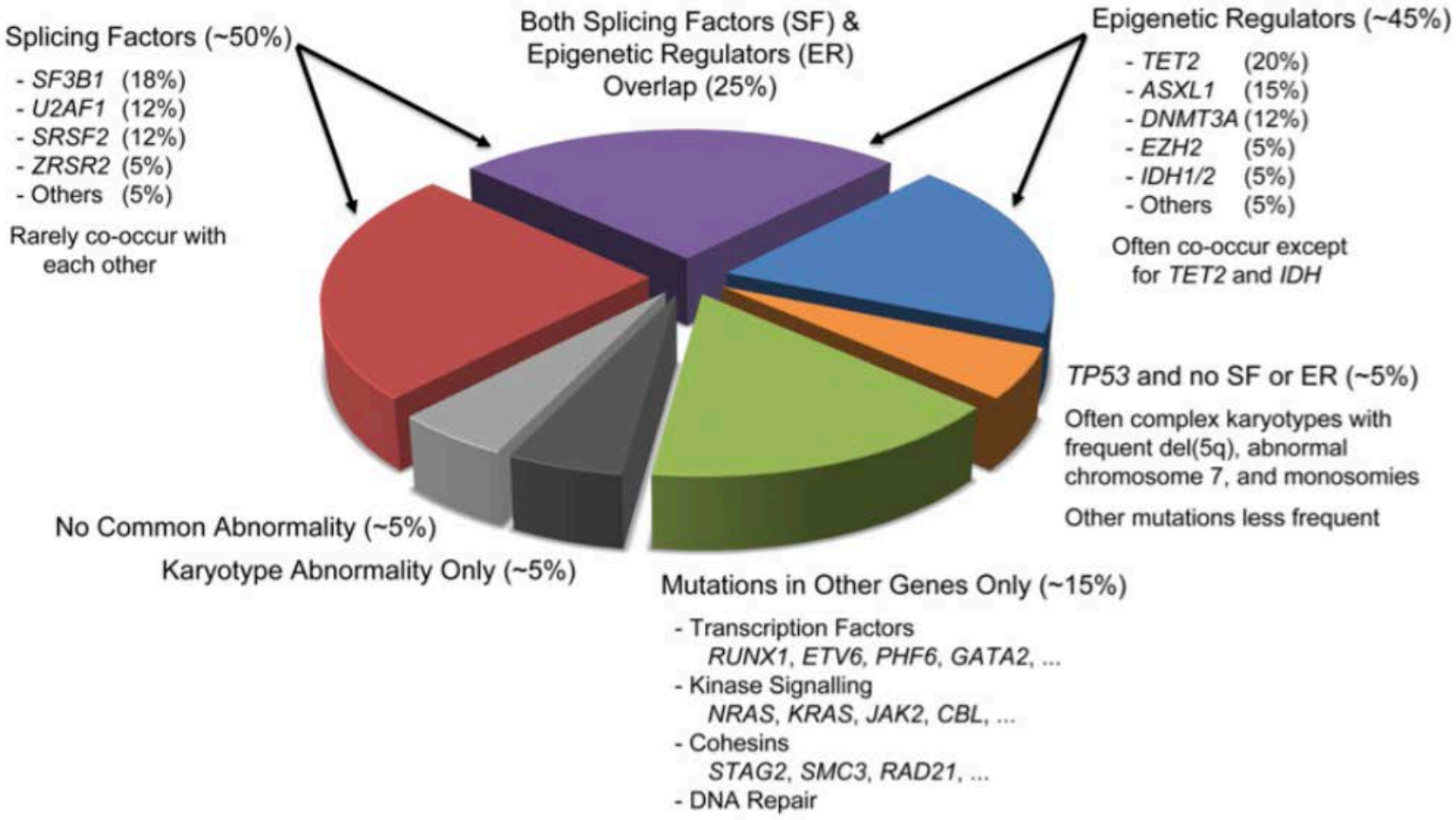
Molecular Distribution



Driver Mutation Concept

- Defined as a “statistically significant excess of somatic mutations in a given cancer gene”
- Expected Pattern of the Mutation:
  - Inactivation of tumor suppressor protein
  - Hot spot mutation in an oncogene

Clinical and biological implications of driver mutations in myelodysplastic syndromes

Elli Papaemmanuil,[1] Moritz Gerstung,[1] Luca Malcovati,[2] Sudhir Tauro,[3] Gunes Gundem,[1] Peter Van Loo,[1,4,5] Chris J. Yoon,[1] Peter Ellis,[1] David C. Wedge,[1] Andrea Pellagatti,[6] Adam Shlien,[1] Michael John Groves,[3] Simon A. Forbes,[1] Keiran Raine,[1] Jon Hinton,[1] Laura J. Mudie,[1] Stuart McLaren,[1] Claire Hardy,[1] Calli Latimer,[1] Matteo G. Della Porta,[2] Sarah O'Meara,[1] Ilaria Ambaglio,[2] Anna Galli,[2] Adam P. Butler,[1] Gunilla Walldin,[7] Jon W. Teague,[1] Lynn Quek,[8] Alex Sternberg,[8,9] Carlo Gambacorti-Passerini,[10] Nicholas C. P. Cross,[11] Anthony R. Green,[12,13] Jacqueline Boultwood,[6] Paresh Vyas,[7] Eva Hellstrom-Lindberg,[7] David Bowen,[14] Mario Cazzola,[2] Michael R. Stratton,[1] and Peter J. Campbell[1,12,13] on behalf of the Chronic Myeloid Disorders working group of the International Cancer Genome Consortium

Table 1. Baseline characteristics of patients in the study

Variable	Baseline distribution in cohort	
Sample		
Sample size for sequencing	738	
Sample size with outcome data	595	
Median (range) follow-up	12 (0-155) months	
Demographics		
Sex		
Male	415 (56%)	
Female	323 (44%)	
Age, mean ± SD	68 ± 13 years	
MDS classification	**Total**	**With outcome data**
RA	139 (19%)	109
RARS	92 (12%)	75
RARS-T	17 (2%)	17
RCMD	126 (17%)	99
RCMD-RS	59 (8%)	58
RAEB	167 (23%)	138
5q-	20 (3%)	16
CMML	70 (9%)	61
MDS-MPN	3 (0.4%)	1
MDS-U	10 (1%)	1
MDS-AML	35 (5%)	20

Sequenced 738 MDS patients
Looking at 111 known cancer genes

Categorized the mutations as:
- Driver Mutations
- Oncogenic Variants
- Mutations of unknown significance

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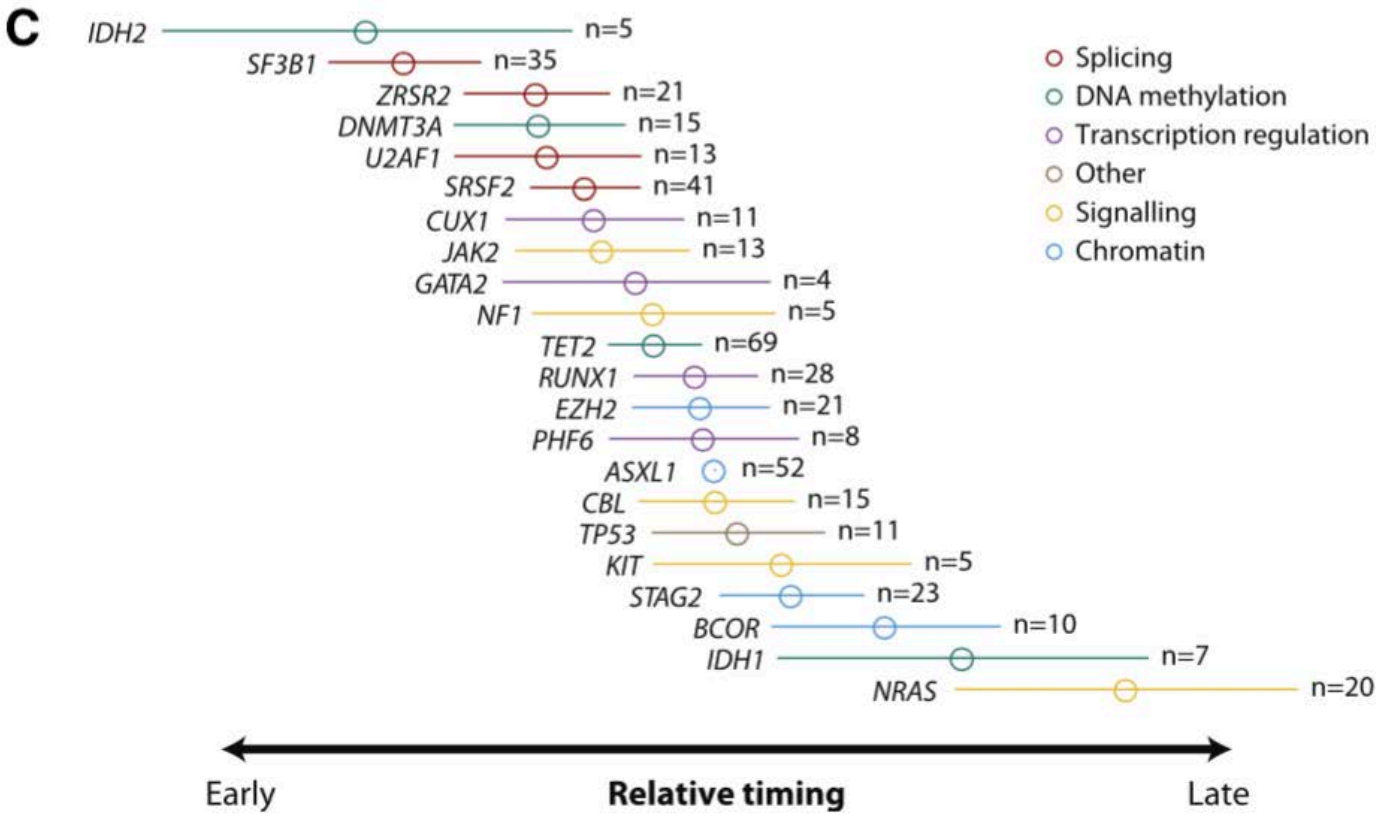
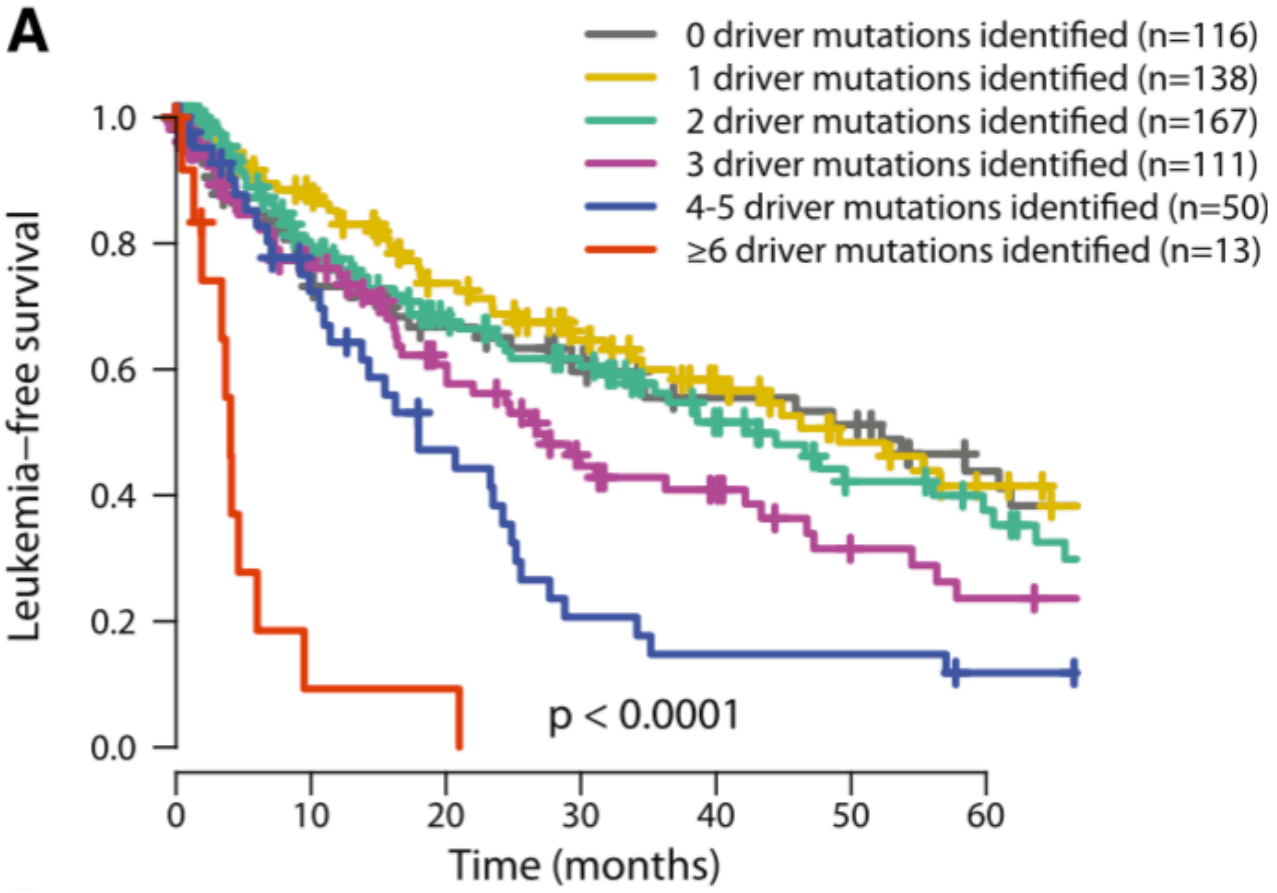
Timing of Mutations in MDS Course



Outcomes worsen with increasing number of mutations



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Why is all this classification and molecular assessment necessary?

- MDS is a heterogeneous disease with diverse natural history
  - Indolent disease → explosive disease progressing to AML
- Curative treatment (transplant) → high morbidity and mortality
  - Timing of transplant when benefits > risks is crucial and risk stratifying informs this decision
- IPSS/IPSS-R helps to predict survival without intervention and helps to stratify who needs observation only, who needs non-transplant therapy, and in whom transplant should be considered up front
- Molecular Data will further refine treatment timing decision-making

Mutations Up-Stage IPSS-R

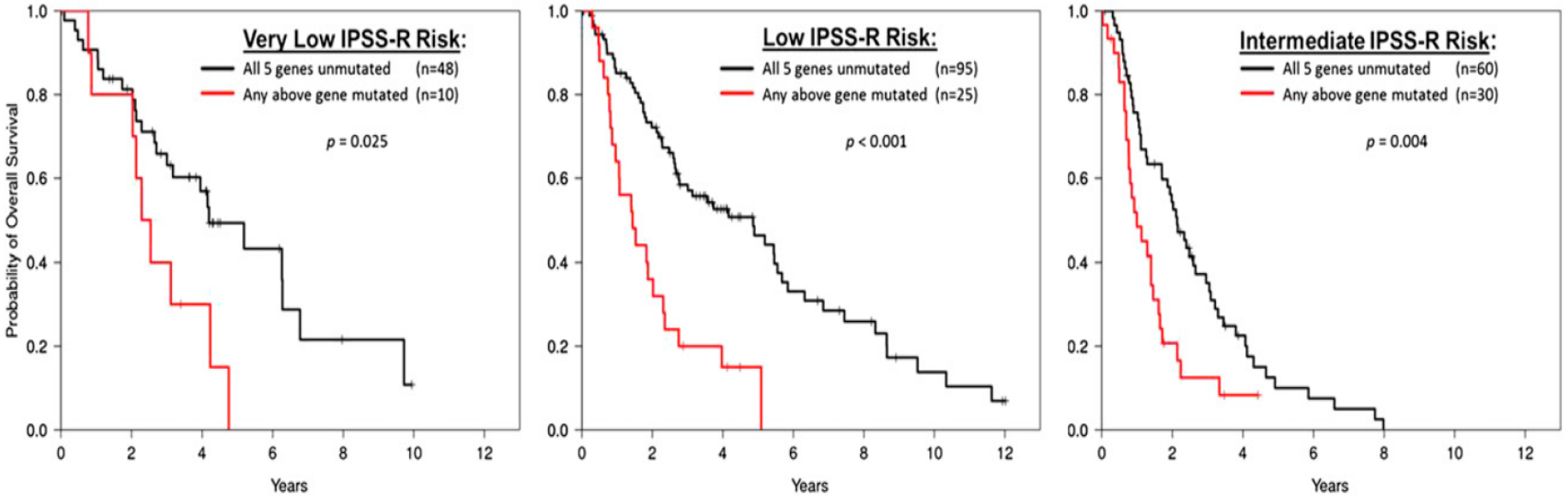
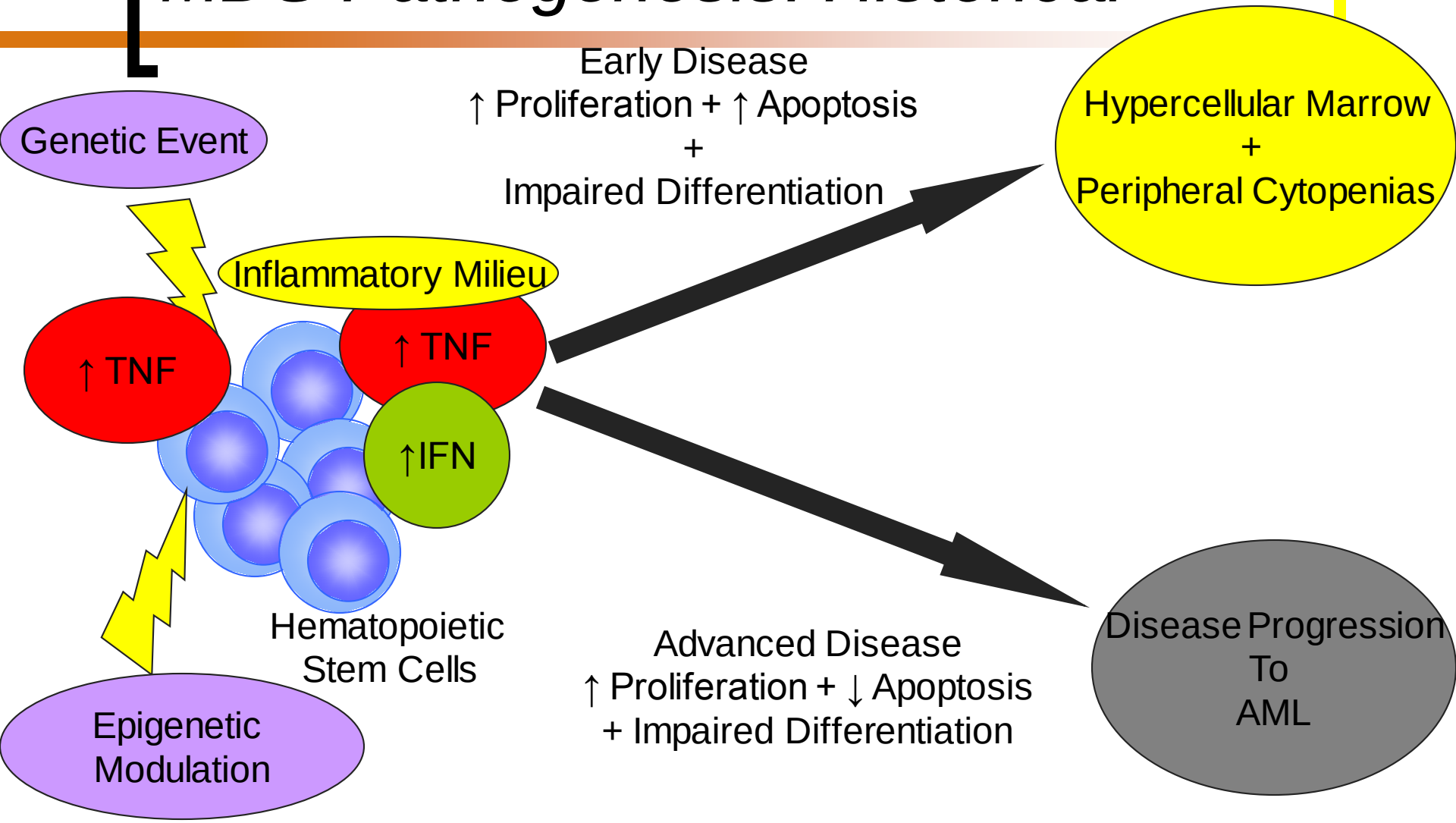


Figure 3. Somatic mutation in any of the 5 genes (*TP53*, *EZH2*, *RUNX1*, *ASLX1*, or *ETV6)* shown in Bejar et al[48] to have prognostic significance independent of the International Prognostic Scoring System (IPSS) identifies patients from that same cohort with shorter overall survival than predicted by Revised IPSS (IPSS-R) for the 3 lowest IPSS-R risk groups. One-third of patients in the IPSS-R Intermediate risk group have shorter than predicted overall survival and may better categorized using mutation analysis as having higher risk disease. Modified from Bejar[127] and used with permission.

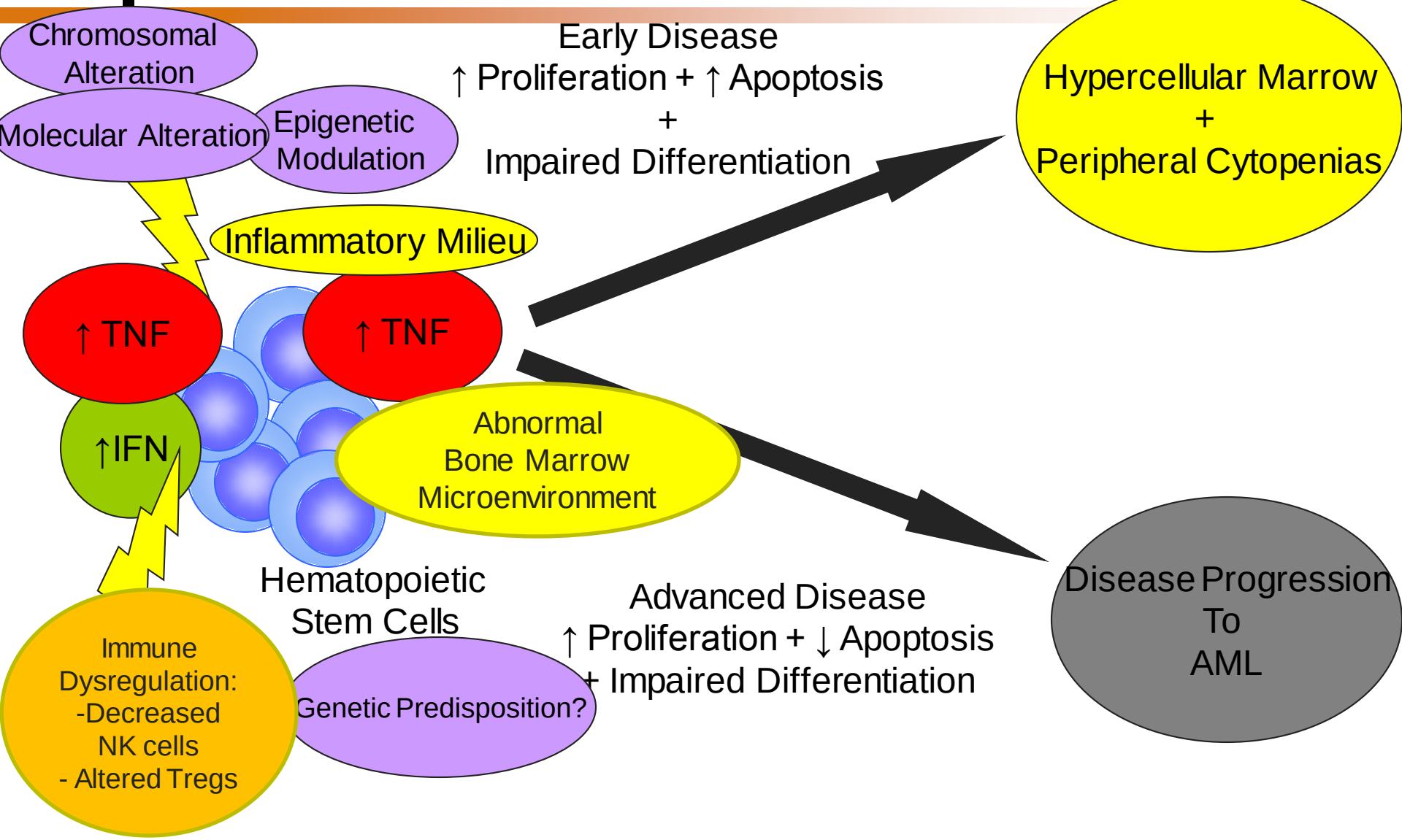
How can we further utilize the molecular data in the setting of MDS?

- Possible new therapeutic targets
- Possible improved disease monitoring in future
  - Identifying major clones and sub-clones at diagnosis and identifying sub-clonal progression prior to morphologic progression
- Highlights further challenges:
  - Clinical heterogeneity
  - Molecular pathway heterogeneity
    - Presents treatment challenges

MDS Pathogenesis: Historical



MDS Pathogenesis: Current Paradigm



Treatment Decision-Making

Treatment Goals

- Supportive care only:
  - Transfusions, growth factors, minimal medical interventions
- "Disease Modifying" Treatments:
  - Treatments that may change the natural history of the MDS and improve survival but don't "cure"
    - Examples: Azacitidine, decitabine, lenalidomide
- "Curative" Therapy:
  - Stem Cell Transplant

Treatment Selection

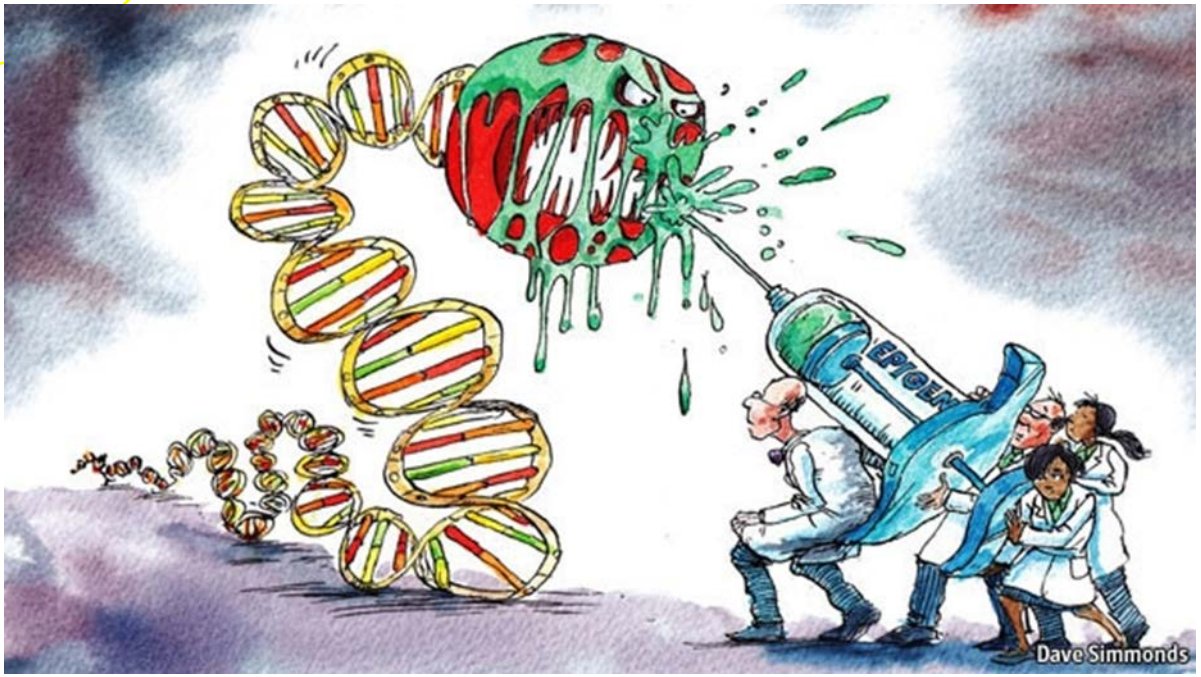
- Once treatment goals established then a treatment strategy is developed with decisions based on:
  - Current MDS Status:
    - IPSS-R Risk Scoring
    - Current MDS impact on quality of life
  - Patient Goals:
    - If potentially curative therapy desired:
      - Timing of Transplant: Early or delayed
      - If pre-transplant therapy is needed
    - If disease modifying treatment desired:
      - Timing of treatment start

MDS "Disease Modifying" Treatment Options

Non-Transplant Therapies

- Azacitidine : FDA Approved May 2004
- Lenalidomide: FDA Approved in December 2005 for Low/INT-1 risk with 5q- phenotype
- Decitabine: FDA Approved May 2006
- What has happened since 2006????

Azacitidine
“Epigenetic” therapy



Azacitidine

- First “disease modifying” non-transplant therapy to gain approval for therapy for MDS patients

- Categorized as “Hypomethylating agent”
  - Hypermethylation of key tumor supressor proteins and cell cycle machinery noted in MDS.
  - Hypomethylating agents act to reverse the hypermethylation of DNA sequences attempting to restore normal cellular function
  - Interestingly, documented “hypomethylation” not required for a response so likely other mechanisms of action not yet described

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

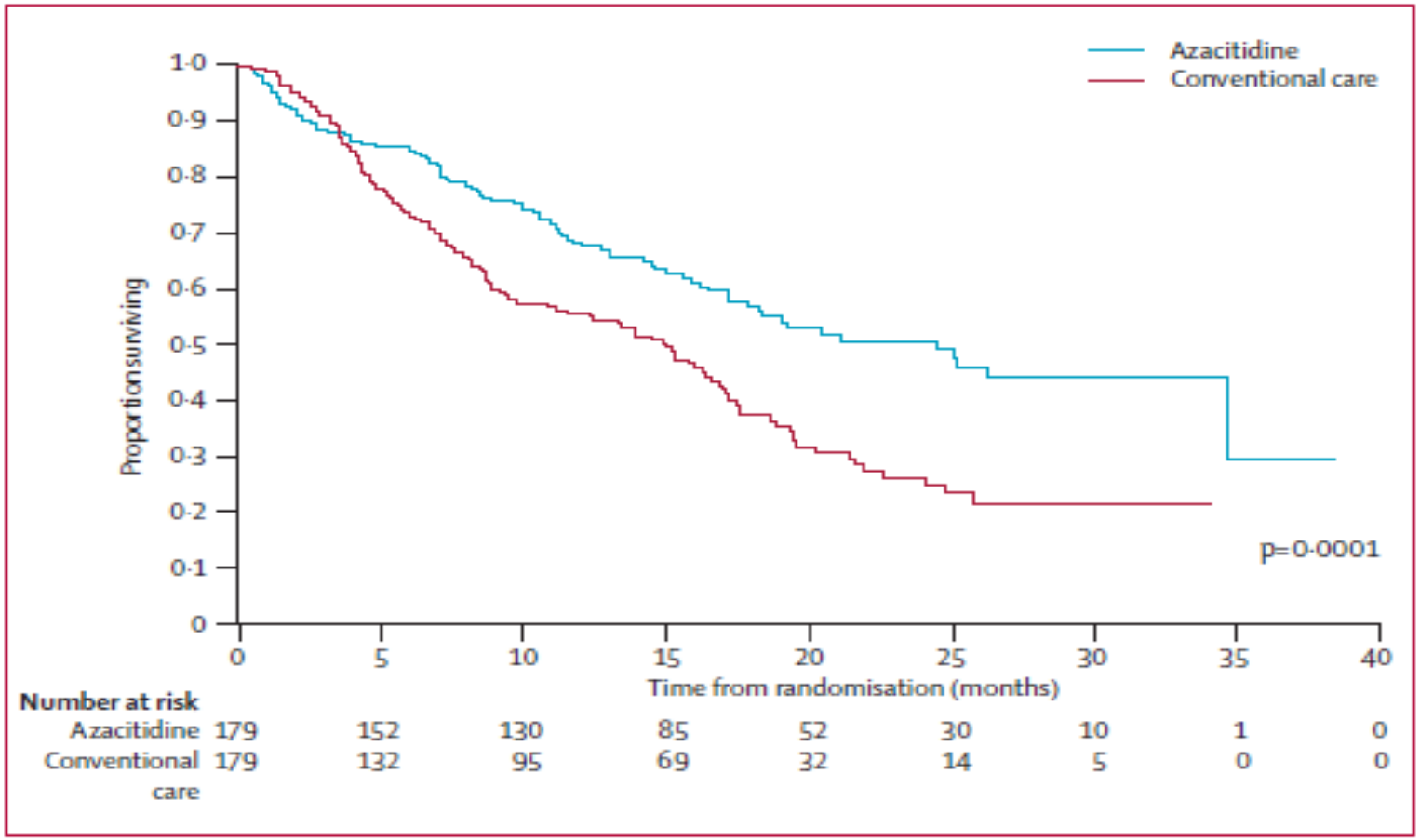
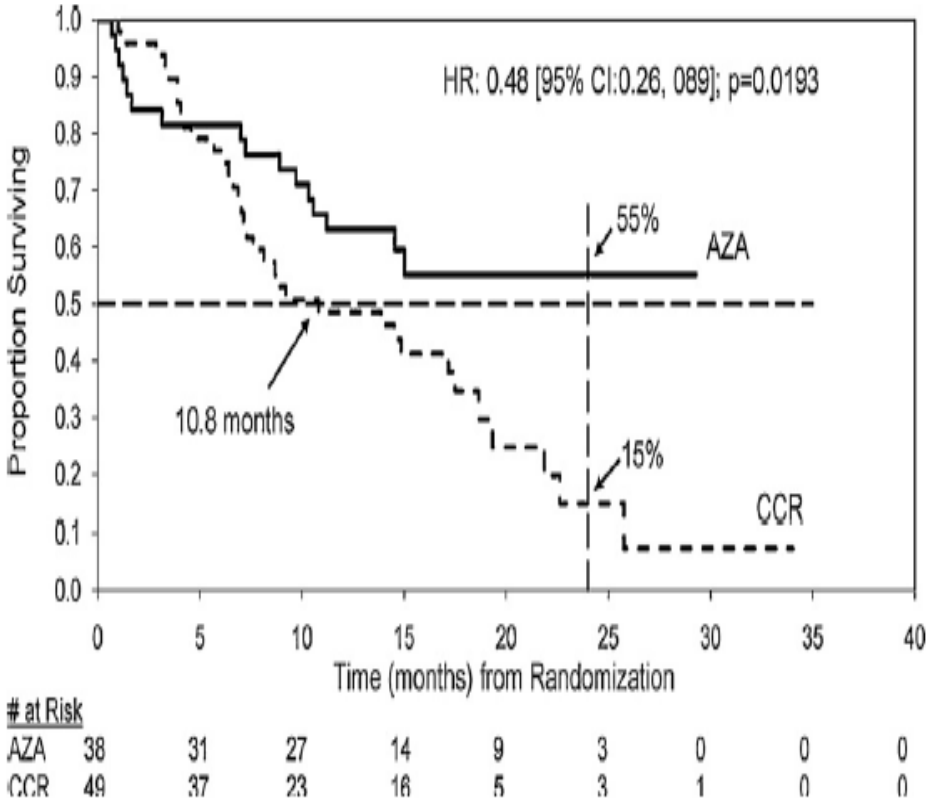
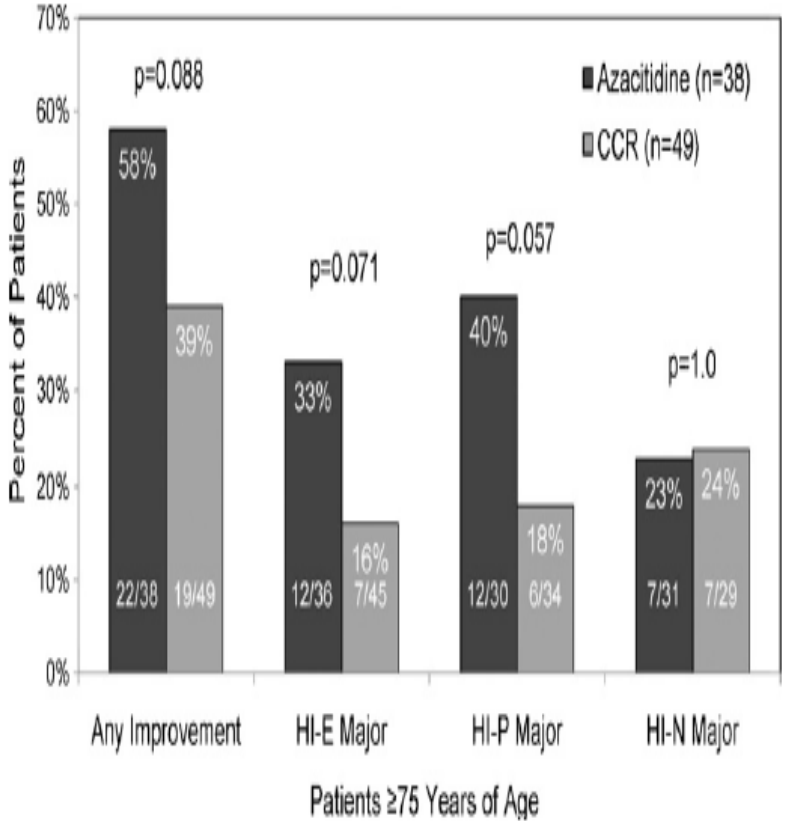


***Figure 3:* Overall survival**

Effects of azacitidine compared with conventional care regimens in elderly (≥75 years) patients with higher-risk myelodysplastic syndromes☆

John F. Seymour[a,*], Pierre Fenaux[b], Lewis R. Silverman[c], Ghulam J. Mufti[d], Eva Hellström-Lindberg[e], Valeria Santini[f], Alan F. List[g], Steven D. Gore[h], Jay Backstrom[i], David McKenzie[i], C.L. Beach[i]





How Do We Know Who Will Respond?

Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine

*Raphael Itzykson,[1] *Sylvain Thépot,[1,2] Bruno Quesnel,[3] Francois Dreyfus,[4] Odile Beyne-Rauzy,[5] Pascal Turlure,[6] Norbert Vey,[7] Christian Recher,[8] Caroline Dartigeas,[9] Laurence Legros,[10] Jacques Delaunay,[11] Célia Salanoubat,[12] Sorin Visanica,[13] Aspasia Stamatoullas,[14] Francoise Isnard,[15] Anne Marfaing-Koka,[16] Stephane de Botton,[17] Youcef Chelghoum,[18] Anne-Laure Taksin,[19] Isabelle Plantier,[20] Shanti Ame,[21] Simone Boehrer,[1,2] Claude Gardin,[1] C. L. Beach,[22] Lionel Adès,[1,2] and Pierre Fenaux,[1,2] on behalf of the Groupe Francophone des Myelodysplasies (GFM)

[1]Service d'Hématogie, Clinique Hôpital Avicenne, Assistance Publique–Hôpitaux de Paris (AP-HP), and Paris 13 University, Paris, France; [2]Inserm U848, Villejuif, Villejuif, France; [3]Service des Maladies du Sang, Centre Hospitalier Universitaire (CHU) Lille, France; [4]Service d'Hématologie Clinique, Hôpital Cochin, AP-HP and Paris 5 University, Paris, France; [5]Service de Médecine Interne, CHU Toulouse, Toulouse, France; [6]Service d'Hématologie Clinique, CHU Limoges, Limoges, France; [7]Département d'Hématologie, Institut Paoli Calmettes, Marseille, France; [8]Service d'Hématologie Clinique, CHU Toulouse, Toulouse, France; [9]Service d'Oncologie et Maladies du Sang, CHU Tours, Tours, France; [10]Service d'Hématologie, CHU Nice, Nice, France; [11]Service d'Hématologie, CHU Nantes, Nantes, France; [12]Service d'Hématologie, Centre Hospitalier du Sud Francilien, Corbeil, Corbeil, France; [13]Service d'Hématologie Clinique, CHR Metz-Thionville, Thionville, France; [14]Service d'Hématologie, Centre Henri Becquerel, Rouen, France; [15]Service d'Hématologie, Hôpital Saint-Antoine, AP-HP and Paris 6 University, Paris, France; [16]Service d'Hématologie, Hôpital Antoine Béclère, Clamart, France; [17]Service d'Hématologie, Institut Gustave Roussy, Villejuif, Villejuif, France; [18]Service d'Hématologie, Hôpital Edouard Herriot, Lyon, France; [19]Service d'Hémato-Oncologie, Hôpital André Mignot, Versailles, Versailles, France; [20]Service d'Hématologie Clinique, CH Roubaix, Roubaix, France; [21]Service d'Hémato-Oncologie, CHU Strasbourg, Strasbourg, France; and [22]Clinical R&D, Celgene Corporation, Overland Park, KS

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Study showed estimates of response and duration of response based on all Characteristics Of the MDS (Path subtype, Cytogenetics, Age of patient, performance status, etc)

Table 4. Prognostic factors of overall survival

	Univariate analysis		Multivariate analysis	
	Median OS	*P*	HR (95% CI)	*P*
Age		.38		
> 70 y	12.7			
≤ 70 y	15.0			
ECOG PS		< .0001		< .0001
0-1	15.7		1	
≥ 2	7.1		2.0 [1.4-2.9]	
MDS type		.002		
Secondary	9.2			
De novo	15.3			
WHO diagnosis		.32		
RA/RARS/RCMD	11.0			
RAEB1	13.1			
RAEB2	15.2			
AML (RAEB-t)	9.7			
Interval from diagnosis		.05		
> 6 mo	15.8			
≤ 6 mo	10.3			
Prior LD AraC		.75		
Yes	14.9			
No	13.1			
Prior ESA		.73		
Yes	13.4			
No	13.3			
Cytogenetic risk		< .0001		< .0001
Favorable	22.4		1	
Intermediate	15.0		1.4 [0.8-2.3]	.23
Unfavorable	8.8		3.0 [2.0-4.3]	< .0001
IPSS risk		.004		
Intermediate-2	16.1			
High	9.1			
Transfusion dependence		< .0001		< .0001
≥ 4 RBC units/8 weeks	10.3		1.9 [1.4-2.6]	
0-3 RBC units/8 weeks	19.2		1	
ANC		.10		
≥ 1.0 G/L	12.0			
< 1.0 G/L	15.1			
Platelets		.02		
≥ 100 G/L	19.6			
< 100 G/L	12.3			
PB blasts		< .0001		< .0001
Present	9.4		2.0 [1.5-2.7]	
Absent	19.8		1	
Bone marrow blasts		.11		
> 15%	10.9			
≤ 15%	15.4			

Azacitidine Summary

- Benefits:
  - Well tolerated (even in PS 2+ patients and elderly patients)
  - Outpatient
  - Improves survival, delays transformation to acute leukemia, improves quality of life
  - Response extend to most high risk cytogenetic groups (monosomy 7)
  - Extended therapy can improve responses

- Drawbacks:
  - Chronic therapy: continue monthly therapy as long as benefit and minimal toxicity
  - Not curative: eventually patients will progress
  - Large scale studies to date have excluded those patients with treatment related MDS so less clear if similar benefits will be seen in that patient population

Hypomethylating Agents: A good start: Far from perfect

- How can we use these drug more strategically in MDS?
  - Who derives the most benefit? *Still sorting this out*
  - Utilize for patients medical unfit for more aggressive therapy as a chronic therapy (current approach)- *I typically use azacitidine here for the survival and prolonged time to AML*
  - Bridge to curative therapies: Stem Cell transplant
    - Becoming a more common strategy- *Decitabine may be best as opposed to induction chemo in the therapy related MDS with TP53 mutations based on recent NEJM paper*
    - Comparison between hypomethylating agents and induction chemotherapy pre-transplant unknown – *Comments as above*
  - Can we use post-transplant maintenance to reduce relapse risk? – *Would seem reasonable in those high risk patients*
  - In combinations with other drugs – *Combination with HDAC inhibitors hasn't panned out as we had hoped.*

VOLUME 29 · NUMBER 24 · AUGUST 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcome of High-Risk Myelodysplastic Syndrome After Azacitidine Treatment Failure

Thomas Prébet, Steven D. Gore, Benjamin Esterni, Claude Gardin, Raphael Itzykson, Sylvain Thepot, François Dreyfus, Odile Beyne Rauzy, Christian Recher, Lionel Adès, Bruno Quesnel, C.L. Beach, Pierre Fenaux, and Norbert Vey

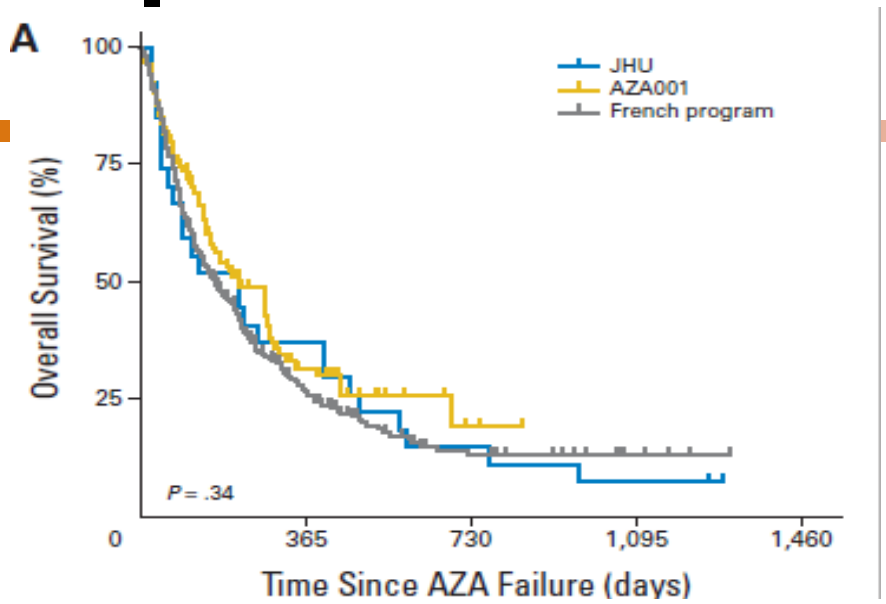
Patients and Methods

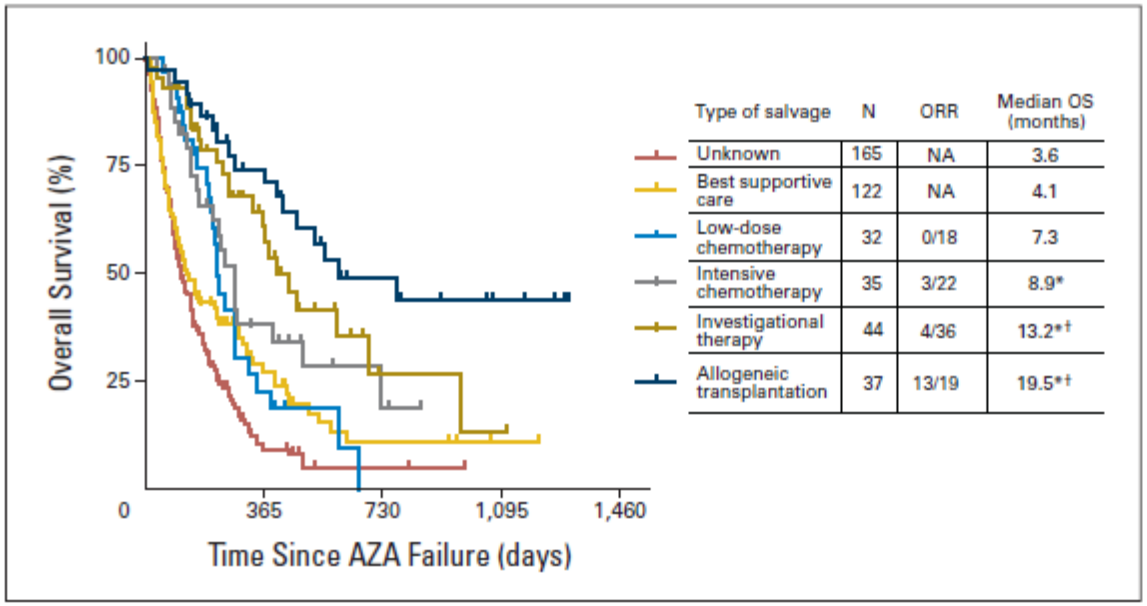
Overall, 435 patients with high-risk MDS and former refractory anemia with excess blasts in transformation (RAEB-T) were evaluated for outcome after AZA failure. The cohort of patients included four data sets (ie, AZA001, J9950, and J0443 trials and the French compassionate use program).

Table 2. Distribution of Patients According to the Type of Failure

Disease Status	Patients	
	No.	%
Primary failure*	229	55
Stable disease	91	24
Progressive disease	138	31
Secondary failure†	164	36
Failure after CR	32	7
Failure after PR	12	2
Failure after HI	120	27
AZA intolerance	42	9
Without ongoing response	29	6
During response to AZA	13	3

Outcomes Post Azacitidine Failure





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*†

Fig 2. Survival analysis according to the salvage treatment regimens. Overall response rate for each treatment group is presented with the number of patients evaluable for response in each cohort. (*) Univariate analysis (log-rank test) showed significant differences between palliative care and intensive chemotherapy (CT; $P = .04$), investigational therapy (IT; $P < .001$), or allogeneic stem-cell transplantation (ASCT; $P < .001$). (†)There was also a significant difference between intensive CT and IT ($P = .05$) and intensive CT and ASCT ($P = .008$). The difference between IT and ASCT reached borderline significance ($P = .09$). AZA, azacitidine; NA, not applicable; ORR, overall response rate; OS, overall survival.

Take Home Points

- Numerous studies support these findings that outcomes are poor post azacitidine/HMA failure
- Clinical trials should be considered for this group utilizing novel treatment approaches

Lenalidomide

First Karyotype Specific MDS Therapy

5q minus Syndrome

- Syndrome of refractory macrocytic anemia with normal to elevated platelet count and retained neutrophil count
- Typically occurs in middle age/older women
- Bone marrow with micromegakaryocytes, < 5% blasts, and cytogenetics showing isolated 5q deletion
- Clinical Course: Relatively benign clinical course over years with varying need for PRBC transfusions

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

Alan List, M.D., Gordon Dewald, Ph.D., John Bennett, M.D., Aristotle Giagounidis, M.D., Azra Raza, M.D., Eric Feldman, M.D., Bayard Powell, M.D., Peter Greenberg, M.D., Deborah Thomas, M.D., Richard Stone, M.D., Craig Reeder, M.D., Kenton Wride, M.S., John Patin, M.S., Michele Schmidt, R.N., Jerome Zeldis, M.D., and Robert Knight, M.D., for the Myelodysplastic Syndrome-003 Study Investigators*

Table 1. Clinical and Hematologic Characteristics of the 148 Patients.

Characteristic	Value
Age — yr	
Median	71
Range	37–95
Sex — no. (%)	
Male	51 (34)
Female	97 (66)
Duration of the myelodysplastic syndrome — yr	
Median	2.5
Range	0.1–20.7
Red cells transfused in previous 8 wk — units	
Median	6
Range	0–18
≥2 Units of red cells transfused/mo — no. (%)	105 (71)
IPSS risk category — no. (%)	
Low	55 (37)
Intermediate 1	65 (44)
Intermediate 2 or high	8 (5)
Unclassified	20 (14)
FAB type — no. (%)	
Refractory anemia	77 (52)
Refractory anemia with ringed sideroblasts	18 (12)
Refractory anemia with excess blasts	30 (20)
Chronic myelomonocytic leukemia	3 (2)
Acute myeloid leukemia	1 (1)
Atypical chronic myeloid leukemia	3 (2)
Inadequate specimen	16 (11)
Neutropenia — no. (%)*	44 (30)
Thrombocytopenia — no. (%)†	28 (19)

Lenalidomide in del 5q31: *Transfusion Independence*

Table 2. Erythroid Response to Lenalidomide.

Variable	Continuous Daily Dosing (N=102)*	21-Day Dosing (N=46)*	All Patients (N=148)
Erythroid response — no. (%)			
Transfusion independence	71 (70)	28 (61)	99 (67)
95% CI			59–74
≥50% decrease in no. of transfusions	8 (8)	5 (11)	13 (9)
95% CI			5–15
Total transfusion response	79 (77)	33 (72)	112 (76)
95% CI			68–82
Time to response — wk			
Median	4.7	4.3	4.6
Range	1–34	1–49	1–49
Hemoglobin — g/dl			
Baseline†			
Median	7.7	8.0	7.8
Range	5.3–10.4	5.6–10.3	5.3–10.4
Response‡			
Median	13.4	13.5	13.4
Range	9.2–18.6	9.3–16.9	9.2–18.6
Increase			
Median	5.4	5.4	5.4
Range	2.2–11.4	1.1–9.1	1.1–11.4

* The daily dose was 10 mg.
† The baseline hemoglobin concentration was the minimum value during the baseline period.
‡ The response hemoglobin concentration was the maximum value during the transfusion-independent response period.

Long Term Follow-Up in 5q MDS: MDS-003

OPEN

Leukemia (2014) **28,** 1033–1040

www.nature.com/leu

ORIGINAL ARTICLE

Extended survival and reduced risk of AML progression in erythroid-responsive lenalidomide-treated patients with lower-risk del(5q) MDS

AF List[1], JM Bennett[2], MA Sekeres[3], B Skikne[4], T Fu[4], JM Shammo[5], SD Nimer[6], RD Knight[4] and A Giagounidis[7] on behalf of the MDS-003 Study Investigators[8]

Lenalidomide is the approved treatment for patients with red blood cell (RBC) transfusion-dependent lower-risk myelodysplastic syndromes (MDS) and chromosome 5q deletion (del(5q)). We report the long-term outcomes (median follow-up 3.2 years) in patients treated with lenalidomide in the MDS-003 trial. RBC transfusion independence (TI) ⩾8 weeks was achieved in 97 of 148 treated patients (65.5%), with a median response duration of 2.2 years. Partial or complete cytogenetic response was achieved by 63 of 88 evaluable patients (71.6%). Median overall survival (OS) was longer in patients achieving RBC-TI ⩾8 weeks (4.3 vs 2.0 years in non-responders; $P<0.0001$) or cytogenetic response (4.9 vs 3.1 years in non-responders; $P=0.010$). Time to acute myeloid leukemia (AML) progression was longer in patients achieving RBC-TI ⩾8 weeks or any cytogenetic response versus non-responders ($P=0.001$ and $P=0.0002$, respectively). In a landmark multivariate analysis, RBC-TI ⩾8 weeks was associated with prolonged OS ($P<0.001$) and a trend toward reduced relative risk of AML progression ($P=0.080$). Among these lower-risk MDS patients with del(5q), lenalidomide was associated with prolonged RBC-TI and cytogenetic responses, which were linked to improved OS and reduced risk of AML progression.

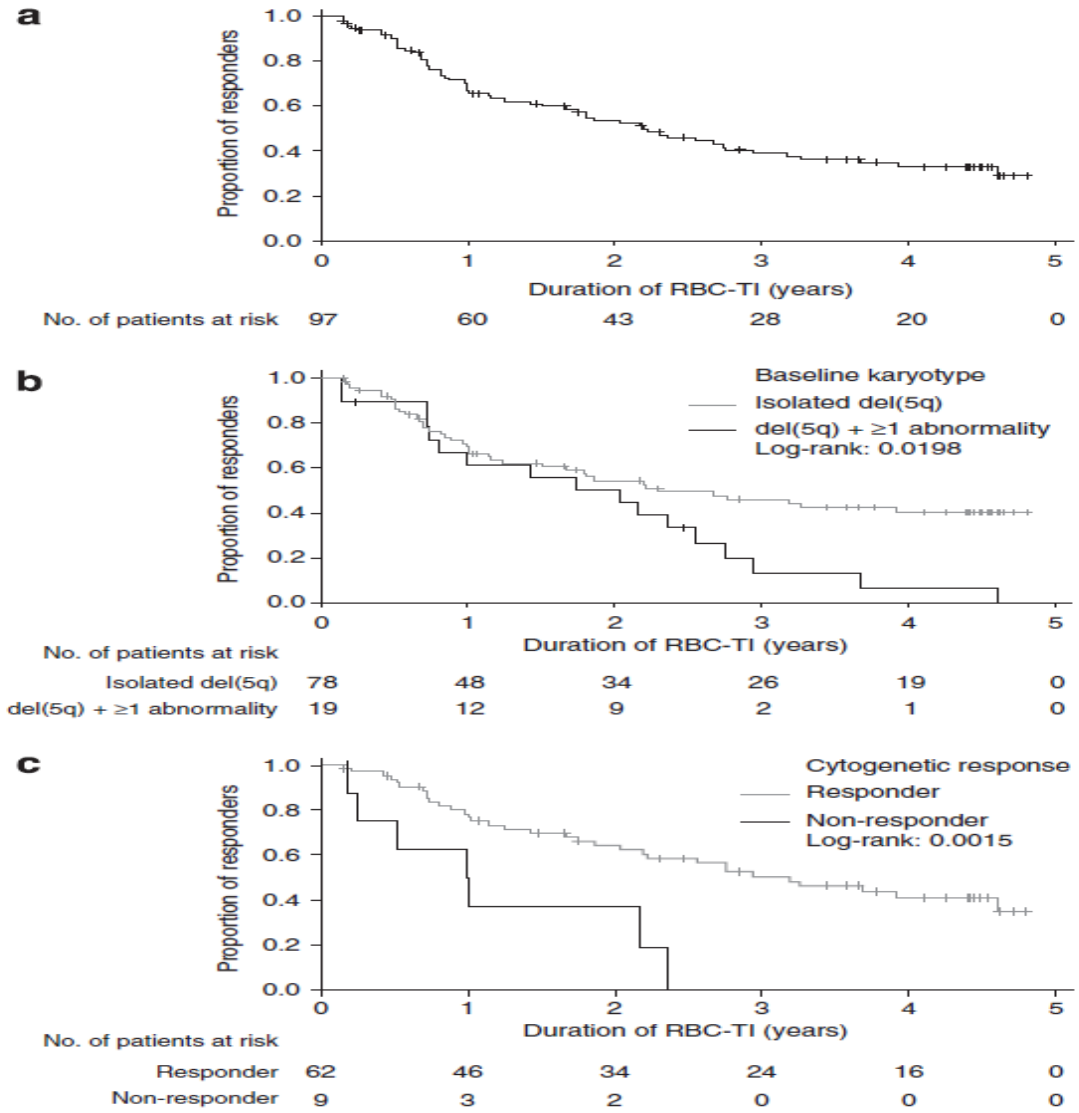


Figure 1. Duration of red blood cell-transfusion independence (RBC-TI) ⩾8 weeks response to lenalidomide in: (**a**) the overall population; (**b**) by baseline karyotype and (**c**) by cytogenetic response. Symbols indicate censored patients who remain transfusion independent at the time of data cutoff or at the time of study discontinuation. Abbreviation: del(5q), chromosome 5q deletion.

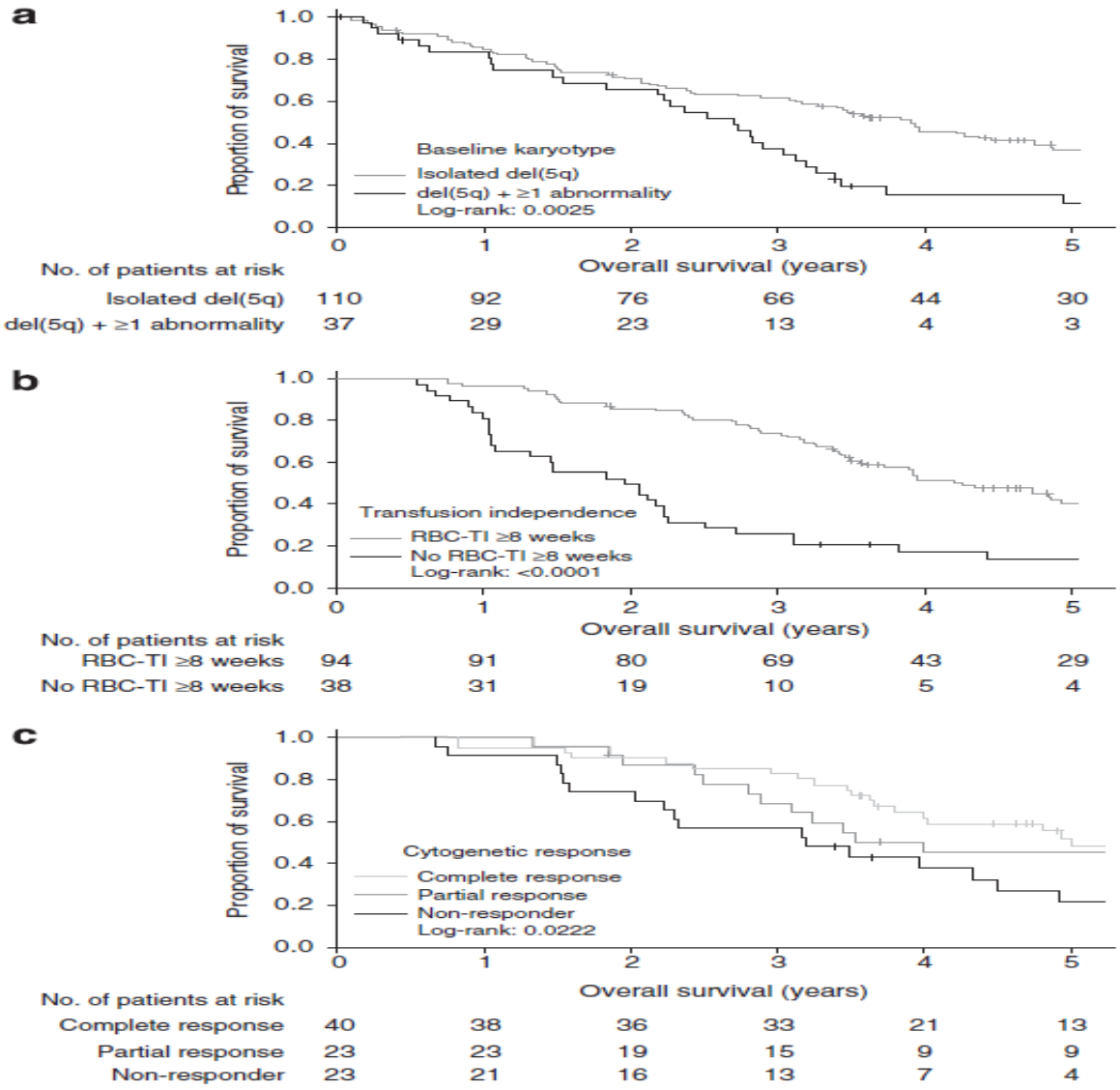


Figure 2. Kaplan–Meier estimates of overall survival according to: (**a**) baseline karyotype (1 patient had no baseline karyotype available and was excluded from the analysis); (**b**) red blood cell-transfusion independence (RBC-TI) ⩾8 weeks response (by the 6-month landmark analysis) and (**c**) partial or complete cytogenetic response (by the 6-month landmark analysis). Abbreviation: del(5q), chromosome 5q deletion.

Lenalidomide Summary

- Benefits:
  - High response rate of transfusion independence in **Low/INT-1** pts with **isolated 5q minus**
  - Relatively quick time to response
    - Cytopenias appear to predict who will respond
  - Oral/outpatient regimen

- Drawbacks:
  - Potential for significant neutropenia/thrombocytopenia
  - Chronic therapy until progression or intolerance
  - Not curative

Potentially Curative Therapy

Hematopoietic Stem Cell Transplant

Hematopoietic Stem Cell Transplantation

- Allogeneic Bone marrow transplant only definitive/curative treatment available with 2-3 year disease free survival ranging from 30-70%

- Patient eligibility limited by:
  - Age
  - Performance status
  - End organ function
  - Availability of donor

- Numerous Disease and Transplant Variables Impact Outcome
  - Timing: Early versus Delayed
  - Pre-transplant therapy
  - Disease Variables: IPSS-R, cytogenetics, molecular signature
  - Conditioning Intensity
  - Donor Source (not discussing today)

Timing of Transplant

Impact of Pre-transplant HMA

MA Decision Analysis Model:

Net benefit or loss of life expectancy by IPSS

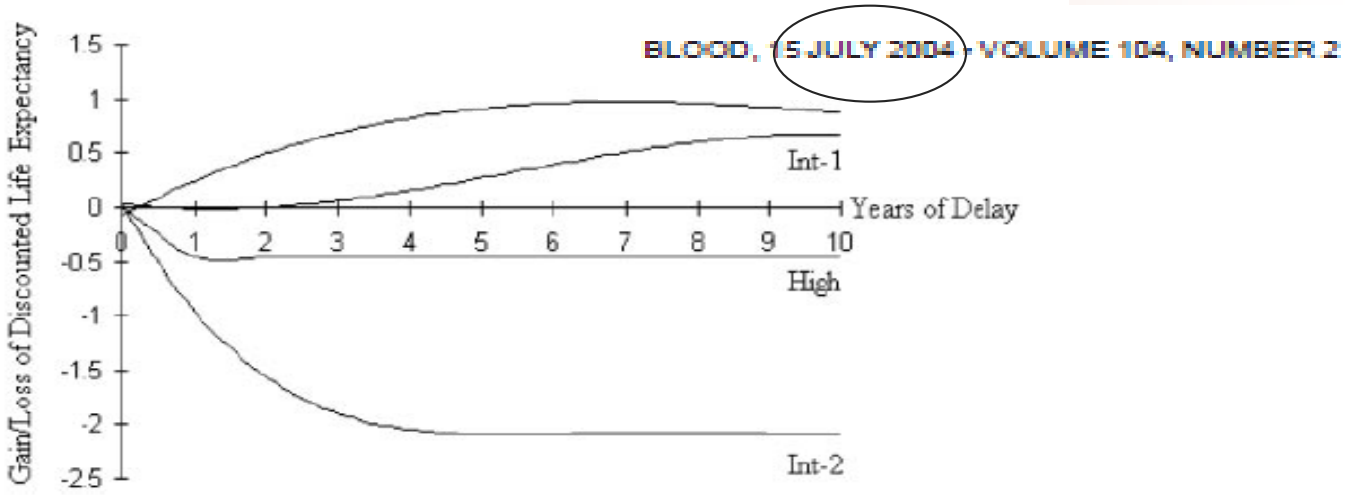
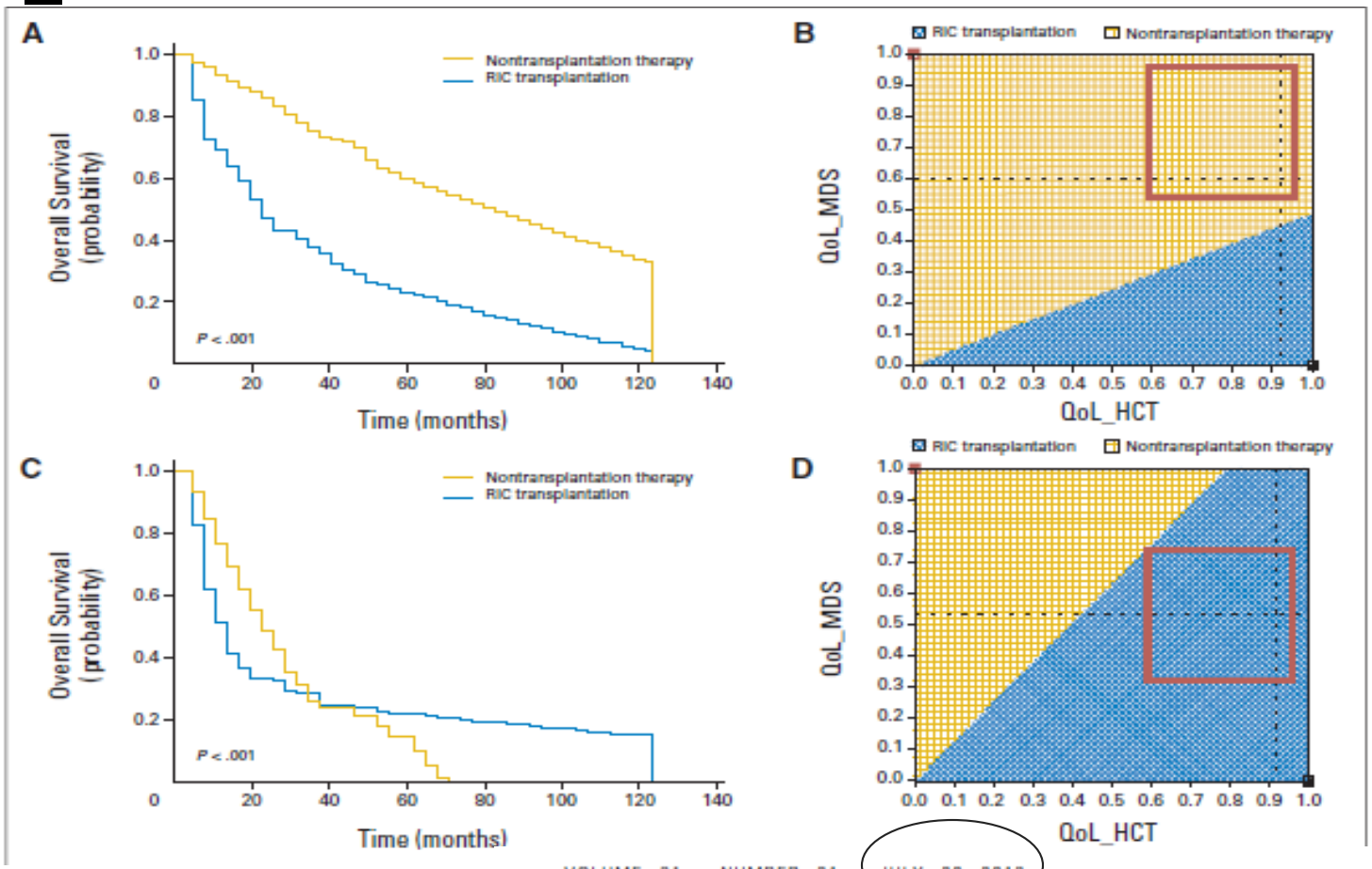


Figure 3. Net benefit or loss of overall discounted life expectancy for the 4 IPSS risk groups are shown above and below the x-axis. A net benefit for delaying transplantation is noted for low and int-1 risk groups, whereas any delay in the time to transplantation is associated with a loss in survivorship in the higher risk groups.

- Take Home Points:(Note: median age of non-HCT-50 and HCT-40's)
  - For Low/INT-1: transplantation at leukemic progression or at fixed interval after diagnosis prior to AML development associated with higher life expectancy
  - For INT-2/High Risk: Transplantation at DX associated with higher life expectancy
    - Important to note that this analysis was based on all MA sib transplants so may or may not be applicable to pts eligible for NMA transplants

RIC HCT Decision Analysis



Low/INT-1 IPSS

INT-2/High IPSS

VOLUME 31 · NUMBER 21 · JULY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

HCT Decision Analysis Based on Dynamic R-IPSS and HMA Prior to HCT

Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System (IPSS-R)

Della Porta et al.

Leukemia. 2017 November ; 31(11): 2449–2457.

Abstract

Allogeneic hematopoietic stem cell transplantation (allo-SCT) represents the only curative treatment for patients with myelodysplastic syndrome (MDS), but involves non-negligible morbidity and mortality. Crucial questions in clinical decision making include the definition of optimal timing of the procedure and the benefit of cytoreduction before transplant in high risk patients. We carried out a decision analysis on 1728 MDS who received supportive care, transplantation or hypomethylating agents (HMAs). Risk assessment was based on the revised International Prognostic Scoring System (IPSS-R). We used a continuous-time multistate Markov model to describe the natural history of disease and evaluate the effect of different treatment policies on survival. Life expectancy increased when transplantation was delayed from the initial stages to intermediate IPSS-R risk (gain of life expectancy 5.3, 4.7 and 2.8 years for patients aged ≤55, 60 and 65 years, respectively), and then decreased for higher risks. Modelling decision analysis on IPSS-R vs. original IPSS changed transplantation policy in 29% of patients, resulting in a 2-year gain in life expectancy. In advanced stages, HMAs given before transplant is associated with a 2-year gain of life expectancy, especially in older patients. These results provide a preliminary evidence to maximize the effectiveness of allo-SCT in MDS.

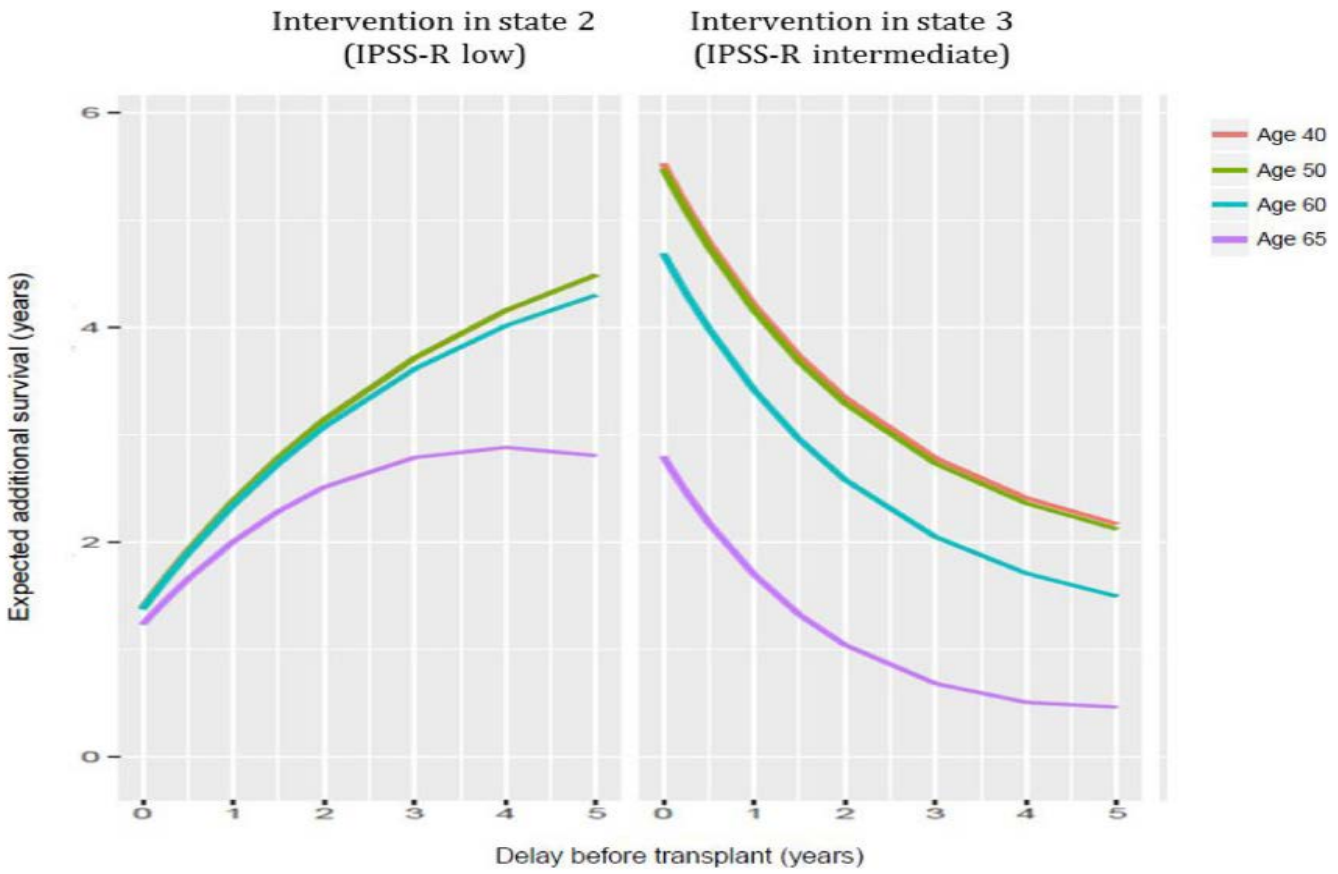


Figure 3.
Gain in expected survival under different transplant policies with respect to a nontransplantation policy. We assumed that the MDS patient was classified as very low IPSS-R risk at the time of diagnosis. Each policy was then evaluated for a set of different ages at diagnosis (as shown in the box) and for different waiting times t (between 0 and 5 years since entering any disease state).

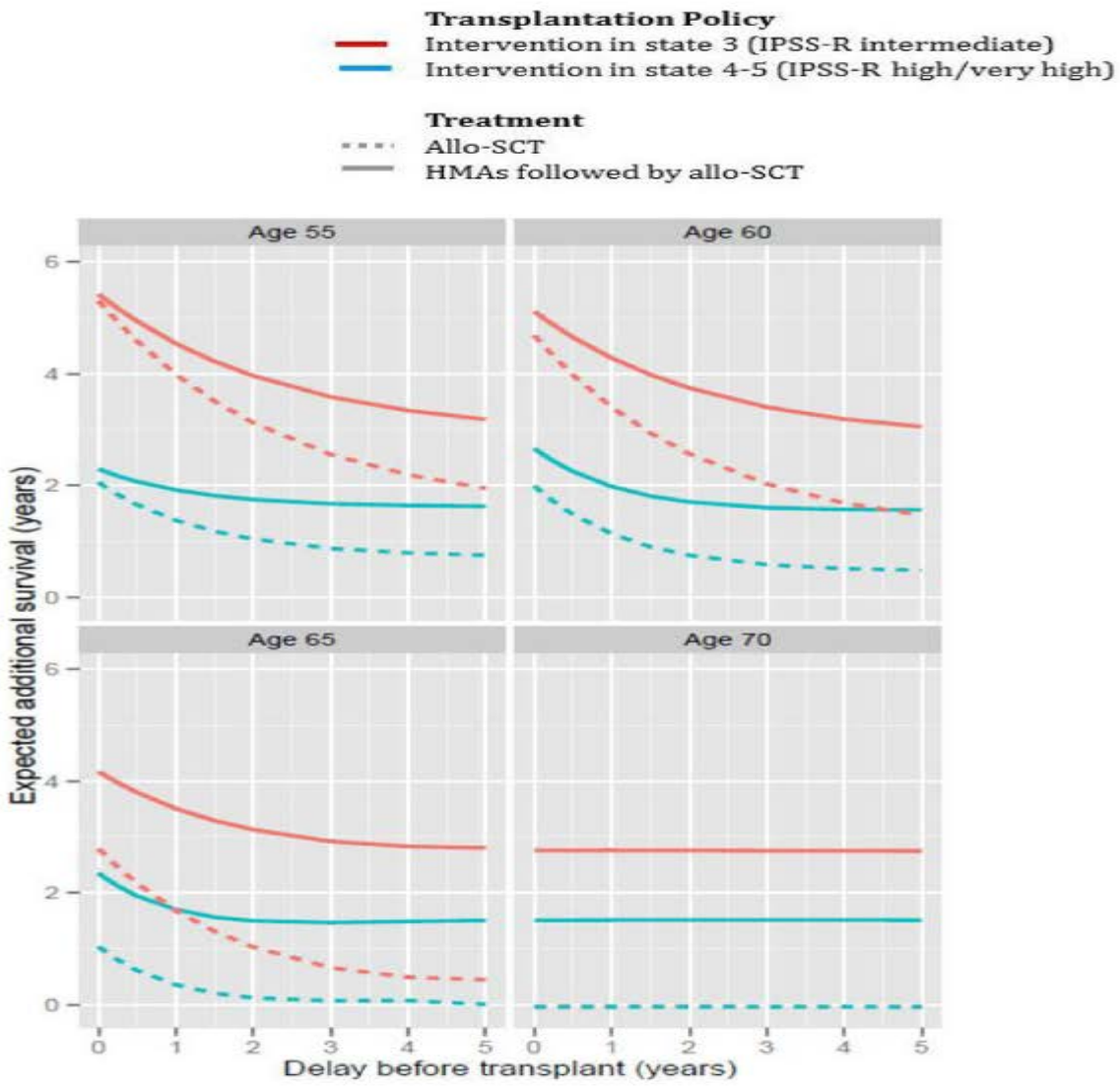


Figure 4.
Expected additional survival (compared to no-intervention), by transplant policy, age and treatment with HMA.

Take Home Points: Transplant based on IPSS-R

- Delay Transplant for Very low and low risk IPSS-R patients
- Offer immediate transplant to IPSS-R intermediate and above
  - HMA administration prior to transplant may improve survival outcomes

Factors that impact transplant outcomes

Patient Variables:

HCT-CI

Disease Variables:

IPSS-R, Cytogenetics, Disease Burden, Molecular Profile

Transplant Variables:

Conditioning Intensity, Donor Source

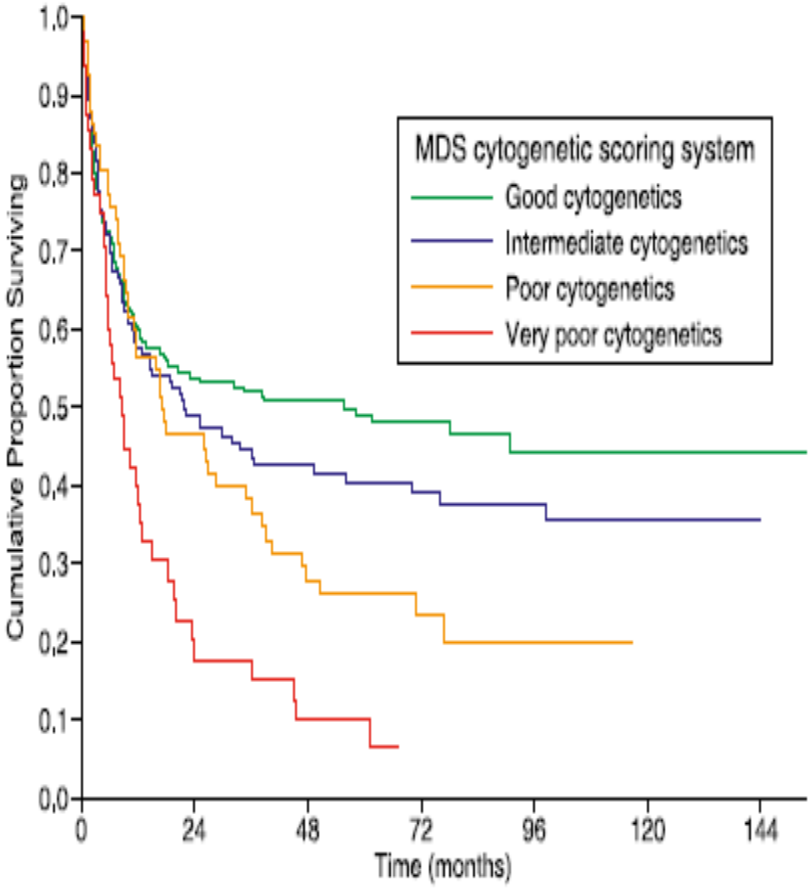
Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R

Matteo G. Della Porta,[1,2] Emilio Paolo Alessandrino,[1] Andrea Bacigalupo,[3] Maria Teresa van Lint,[3] Luca Malcovati,[1,4] Cristiana Pascutto,[1] Michele Falda,[5] Massimo Bernardi,[6] Francesco Onida,[7] Stefano Guidi,[8] Anna Paola Iori,[9] Raffaella Cerretti,[10] Paola Marenco,[11] Pietro Pioltelli,[12] Emanuele Angelucci,[13] Rosi Oneto,[3] Francesco Ripamonti,[1] Paolo Bernasconi,[1,4] Alberto Bosi,[8] Mario Cazzola,[1,4] and Alessandro Rambaldi,[14] on behalf of Gruppo Italiano Trapianto di Midollo Osseo

BLOOD, 10 APRIL 2014 • VOLUME 123, NUMBER 15

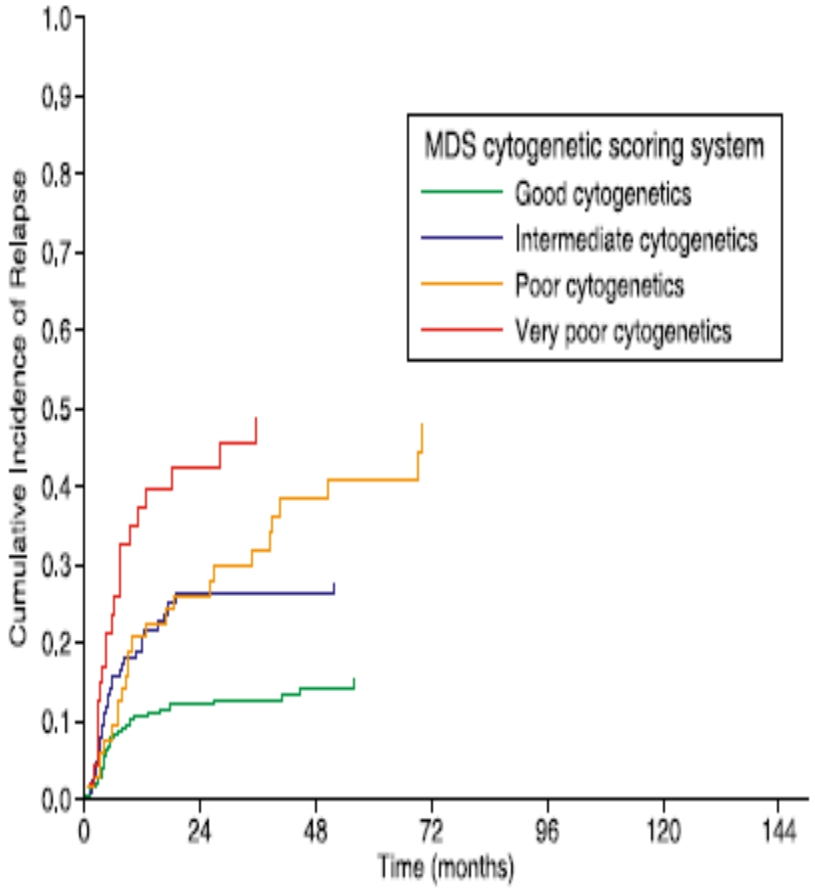
C

Overall survival

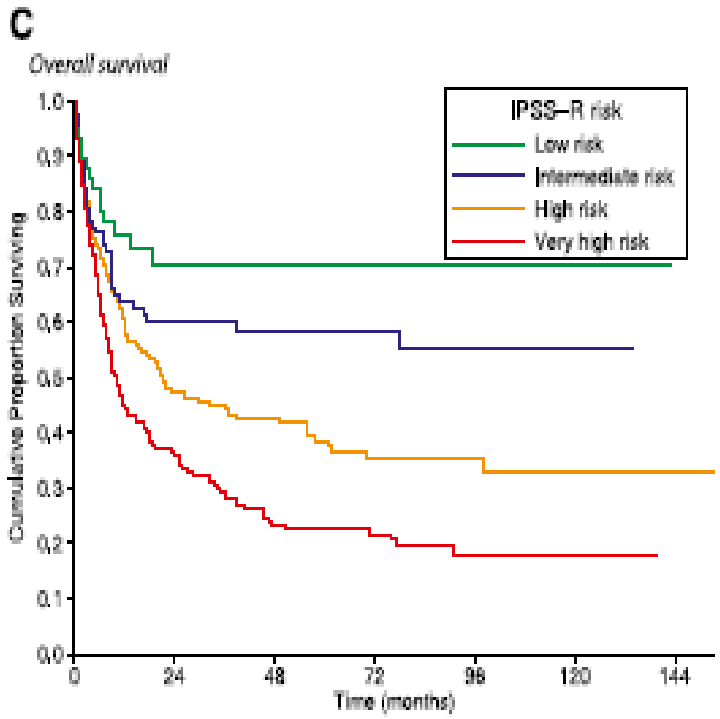


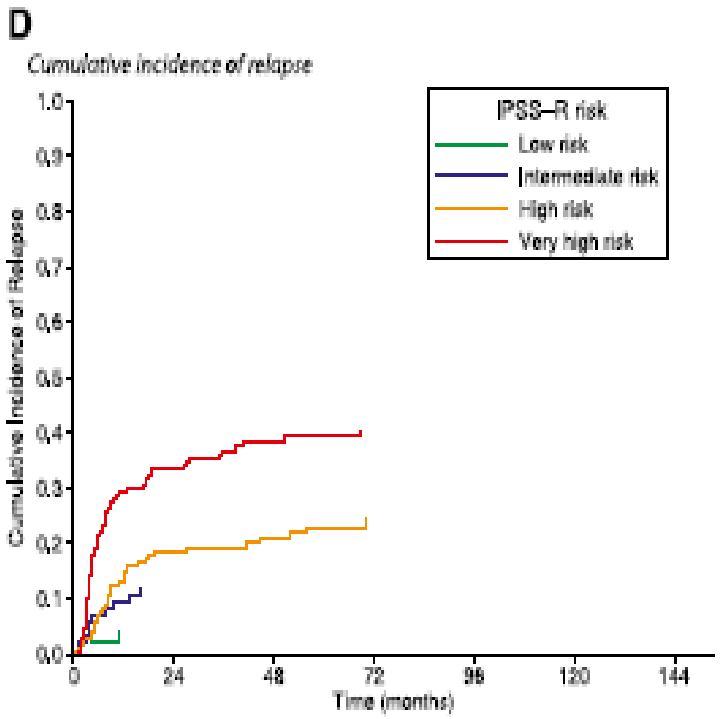
D

Cumulative incidence of relapse



Impact of IPSS-R on HCT Outcomes





They also found that > 10% blasts had negative outcome on survival and relapse

Molecular Signature

JOURNAL OF CLINICAL ONCOLOGY

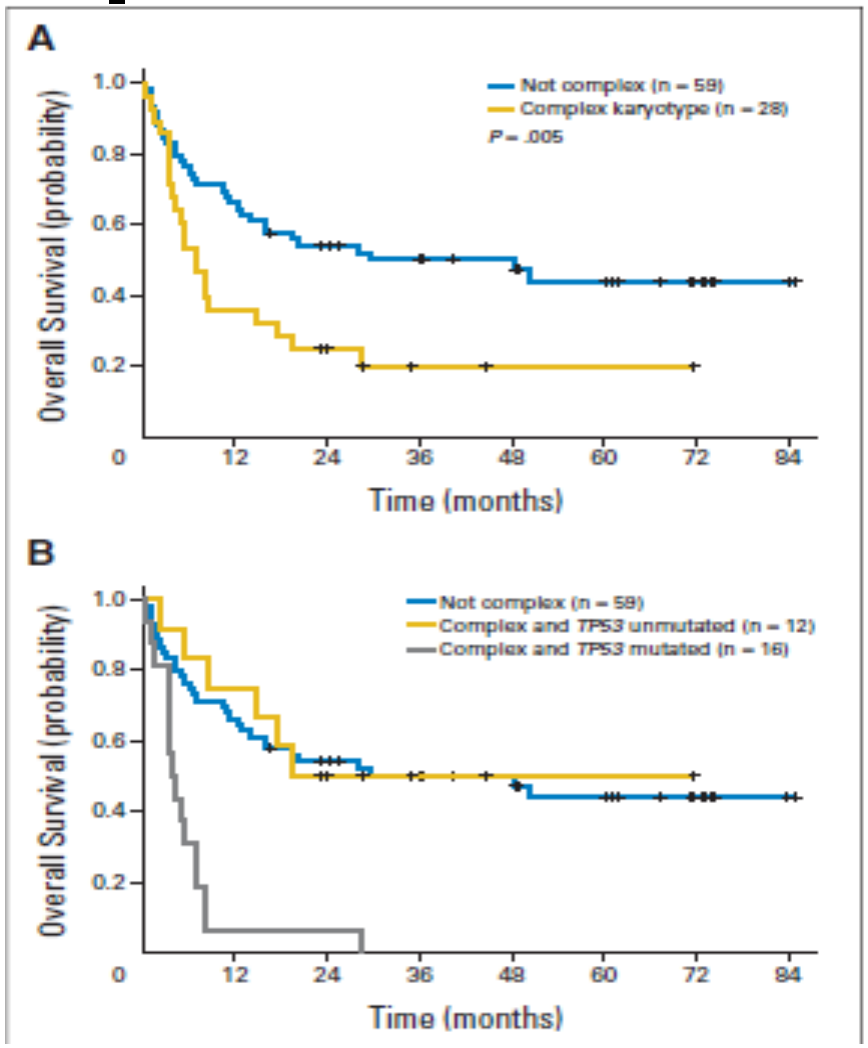
ORIGINAL REPORT

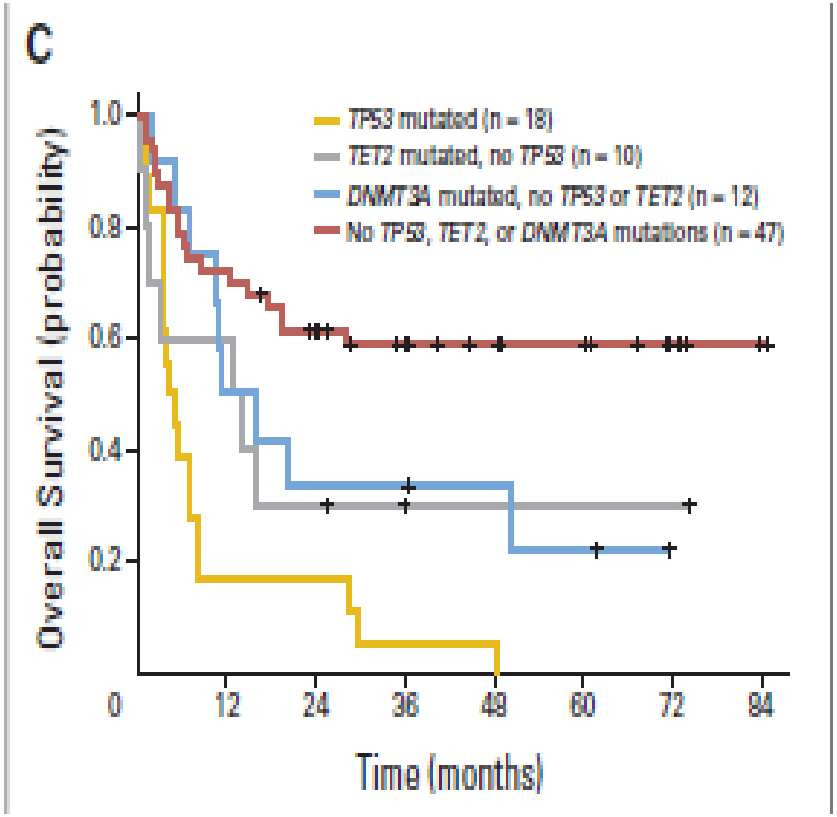
Somatic Mutations Predict Poor Outcome in Patients With Myelodysplastic Syndrome After Hematopoietic Stem-Cell Transplantation

Rafael Bejar, Kristen E. Stevenson, Bennett Caughey, R. Coleman Lindsley, Brenton G. Mar, Petar Stojanov, Gad Getz, David P. Steensma, Jerome Ritz, Robert Soiffer, Joseph H. Antin, Edwin Alyea, Philippe Armand, Vincent Ho, John Koreth, Donna Neuberg, Corey S. Cutler, and Benjamin L. Ebert

VOLUME 32 · NUMBER 25 · SEPTEMBER 1 2014

Impact of Molecular Data On HCT Outcomes in MDS





VOLUME 32 · NUMBER 25 · SEPTEMBER 1 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation

R.C. Lindsley, W. Saber, B.G. Mar, R. Redd, T. Wang, M.D. Haagenson, P.V. Grauman, Z.-H. Hu, S.R. Spellman, S.J. Lee, M.R. Verneris, K. Hsu, K. Fleischhauer, C. Cutler, J.H. Antin, D. Neuberg, and B.L. Ebert

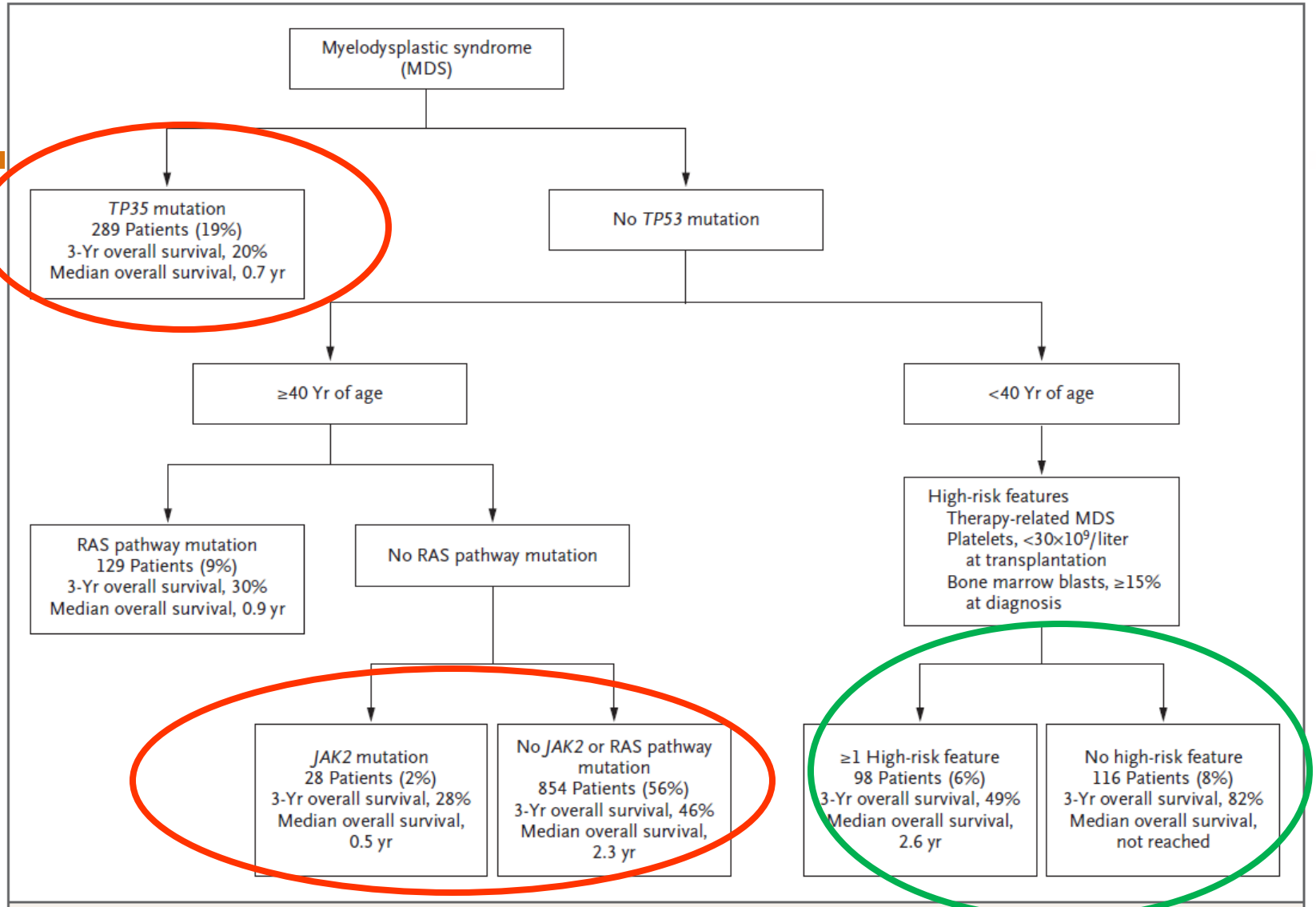


Figure 4. Models for Overall Survival, Including Clinical and Genetic Variables and Effect of Conditioning Intensity.
Shown is a hierarchical prognostic model for overall survival that was based on recursive partitioning analysis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mutation Clearance after Transplantation for Myelodysplastic Syndrome

E.J. Duncavage, M.A. Jacoby, G.S. Chang, C.A. Miller, N. Edwin, J. Shao, K. Elliott, J. Robinson, H. Abel, R.S. Fulton, C.C. Fronick, M. O'Laughlin, S.E. Heath, K. Brendel, R. Saba, L.D. Wartman, M.J. Christopher, I. Pusic, J.S. Welch, G.L. Uy, D.C. Link, J.F. DiPersio, P. Westervelt, T.J. Ley, K. Trinkaus, T.A. Graubert, and M.J. Walter

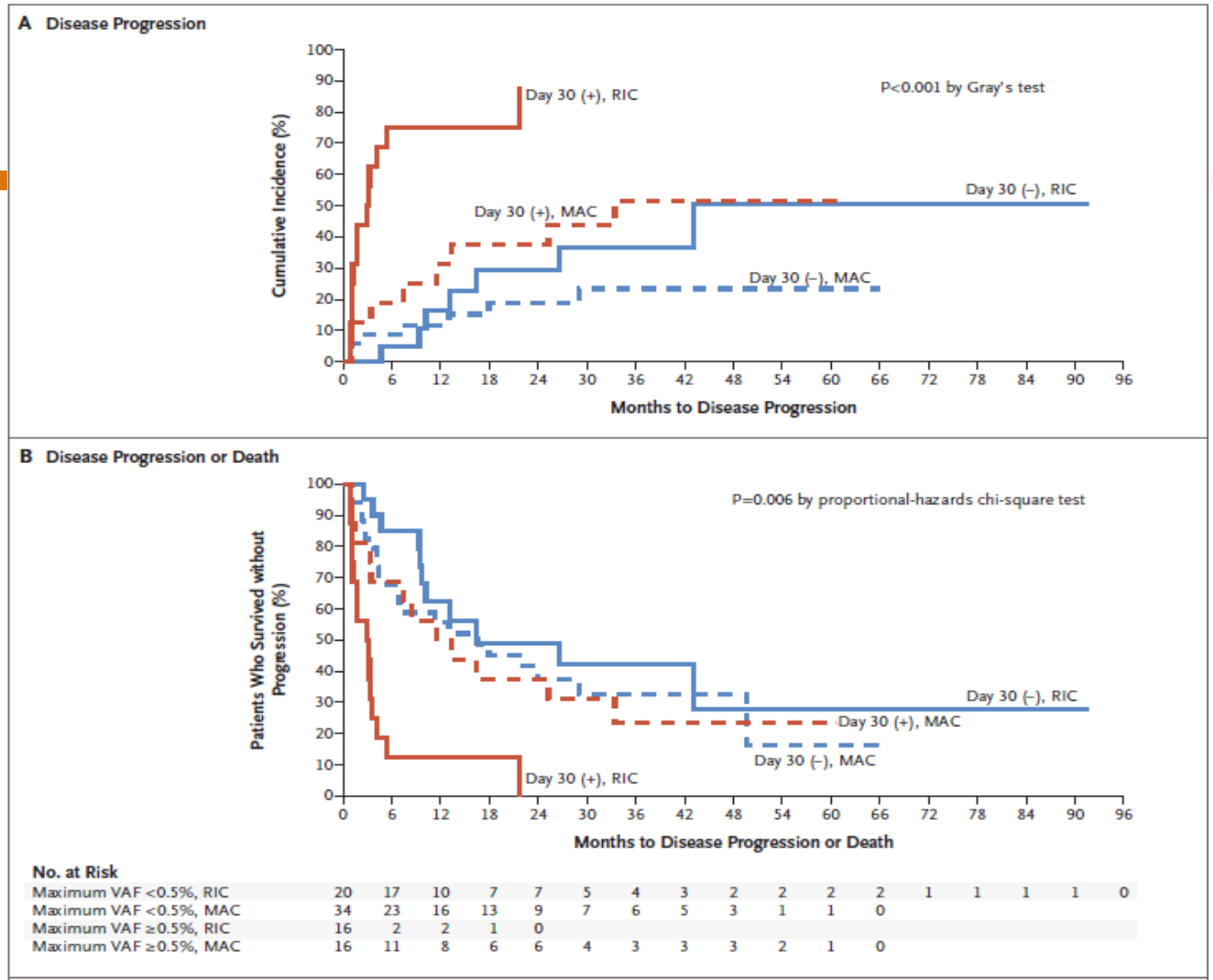


Figure 3. Association of Mutation Clearance with Outcomes.

The VAF on day 30 after transplantation was determined with the use of error-corrected sequencing interrogating single-nucleotide variant mutations identified by enhanced exome sequencing of samples before transplantation. Patients are grouped according to the presence of positive (+) or negative (–) results for at least one mutation VAF of at least 0.5% (red lines) or all VAFs less than 0.5% (blue lines) and according to whether the patient received a reduced-intensity conditioning regimen (RIC, solid lines) or myeloablative conditioning (MAC, dashed lines). The rates of disease progression (Panel A) and disease progression or death (Panel B) are shown.

Conditioning Intensity

MA versus RIC

Is one better than the other?

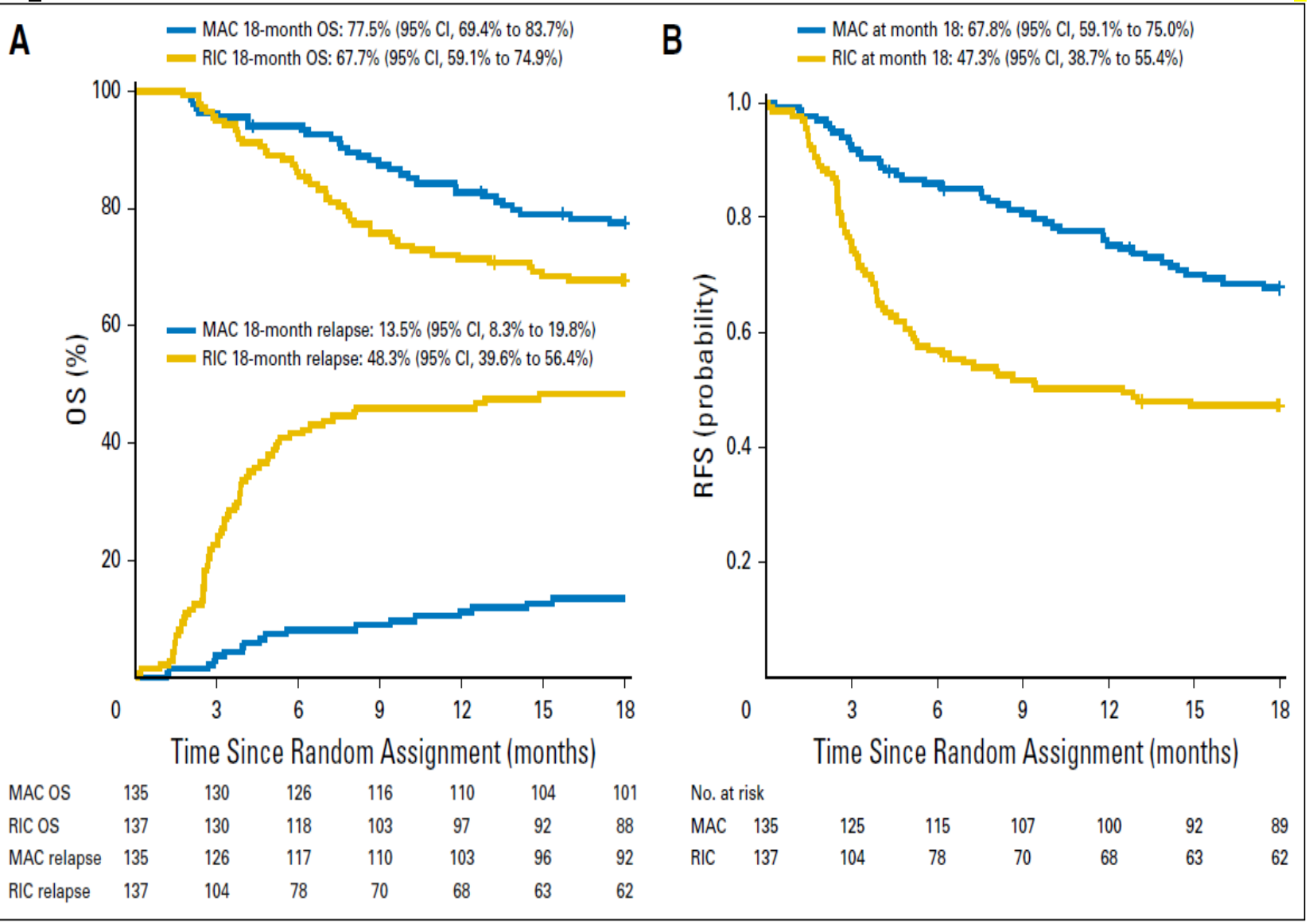
VOLUME 35 · NUMBER 11 · APRIL 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

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


A
MAC 18-month OS: 77.5% (95% CI, 69.4% to 83.7%)
RIC 18-month OS: 67.7% (95% CI, 59.1% to 74.9%)
MAC 18-month relapse: 13.5% (95% CI, 8.3% to 19.8%)
RIC 18-month relapse: 48.3% (95% CI, 39.6% to 56.4%)
OS (%)
100
80
60
40
20
0
3
6
9
12
15
18
Time Since Random Assignment (months)
MAC OS 135 130 126 116 110 104 101
RIC OS 137 130 118 103 97 92 88
MAC relapse 135 126 117 110 103 96 92
RIC relapse 137 104 78 70 68 63 62
B
MAC at month 18: 67.8% (95% CI, 59.1% to 75.0%)
RIC at month 18: 47.3% (95% CI, 38.7% to 55.4%)
RFS (probability)
1.0
0.8
0.6
0.4
0.2
0
3
6
9
12
15
18
Time Since Random Assignment (months)
No. at risk
MAC 135 125 115 107 100 92 89
RIC 137 104 78 70 68 63 62

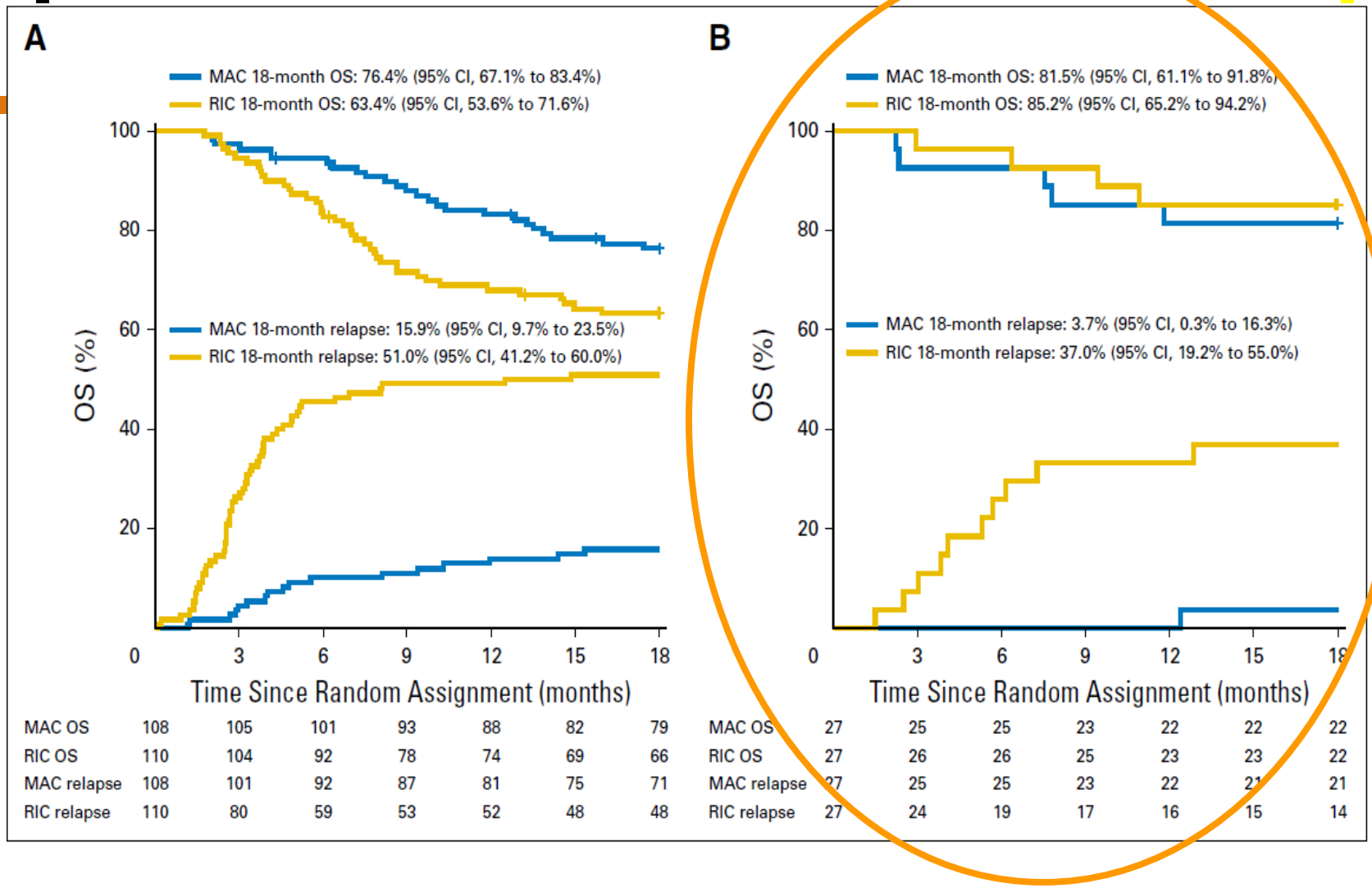


Fig 3. Overall survival (OS) and incidence of relapse by treatment arm in patients with (A) acute myeloid leukemia and (B) myelodysplastic syndromes. MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

Summary: Predictors of Transplant Outcomes

MDS Characteristics

- Disease Characteristics at Diagnosis:
  - IPSS-R
  - Cytogenetics
  - Molecular Signature
- Treatment Responsiveness:
  - Resistant Disease predicts worse outcome
- Disease Burden at Transplant:
  - < 5% blasts (possibly <10% for MA)
- Current studies implicate persistent molecular mutations post transpslant as poor risk feature

Transplant Characteristics

- Donor Source:
  - 1st Choice: MRD
  - 2nd Choice: URD versus UCB
- Conditioning Intensity:
  - MA ? better due to decreased relapse
  - Survival seems similar though in the MDS cohort

Emerging Therapies in MDS

MDS Therapies in Development

Table 1. Agents in development for MDS in clinical trials that are actively recruiting patients

Agent (synonyms)	Putative mechanism
Kinase inhibitors	
INCB047986	Janus-associated kinase (JAK) inhibitor
KB004	Antibody against ephrin A3 (EphA3) receptor tyrosine kinase
LGH447	Pim kinase inhibitor
MEK 162	Inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2)
Midostaurin (PKC412)	Protein kinase C (PKC) inhibitor
PD-616 (12-*O*-tetradecanoylphorbol-13-acetate)	Protein kinase C (PKC) inhibitor
Quizartinib (AC220)	Fms-like tyrosine kinase 3 (FLT3) inhibitor
Rigosertib (SyB C-1101, SyB L-1101, ON 01910.Na)	Phosphoinositide-3 (PI3) kinase inhibitor, Polo-like kinase pathway inhibitor
Ruxolitinib (INCB18424)	Janus-associated kinase (JAK) inhibitor
Sorafenib	Inhibition of Raf, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Fms-like tyrosine kinase 3 (FLT3) and other kinases
Volasertib (BI 6727)	Polo-like kinase 1 (PLK1) inhibitor
ziv-Aflibercept	Vascular endothelial growth factor (VEGF) inhibitor

MDS Therapies in Development

Deacetylase inhibitors and DNA methyltransferase inhibitors	
Oral azacitidine (CC-486)	DNA methyltransferase inhibitor
Oral decitabine and E7727 (ASTX727)	DNA methyltransferase inhibitor combined with cytidine deaminase inhibitor
SGI-110	Nucleoside analog with DNA methyltransferase inhibitory activity
Mocetinostat (MGCD0103)	Deacetylase inhibitor
Panobinostat (LBH-589)	Deacetylase inhibitor
Pracinostat (SB939)	Deacetylase inhibitor
Vorinostat (suberanilohydroxamic acid, SAHA)	Deacetylase inhibitor
Altered cell metabolism	
AG-120, AG-221	Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) inhibitors
Coenzyme Q10 and L-carnitine	Alteration of intracellular metabolism and electron transport chain
CPI613	Inhibition of pyruvate dehydrogenase and ketoglutarate dehydrogenase
INCB024360	Indoleamine 2,3-dioxygenase (IDO1) inhibitor

MDS Therapies in Development

Cytotoxic agents/cell cycle inhibitors	
Cladribine (2-CDA)	Nucleoside analog
Clofarabine	Nucleoside analog; resists deamination and phosphorolysis
CPX-351	Liposomal daunorubicin and cytarabine in a fixed 1:5 ratio
Lurbinectidin (PM01183)	Synthetic tetrahydroisoquinoline alkaloid DNA minor groove covalent binder
Vosaroxin (SNS-595)	Quinolone derivative; replication-dependent DNA damage agent
Immunomodulatory and immunosuppressive agents	
ALT-803	Interleukin (IL)-15 superagonist mutant and a dimeric IL-15 receptor αSu/Fc fusion protein
DEC-205/NY-ESO-1 fusion protein CDX-1401	Immunostimulator (DEC=endocytic dendritic cell receptor; NY-ESO-1 is a tumor associated antigen)
[illegible]	[illegible]
Ipilimumab (MDX-101)	Cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor
MK-3475	Anti-programmed death 1 (PD1) antibody
Pomalidomide (CC4047)	Immunomodulatory agent with diverse activities; modulation of cereblon E3 ubiquitin ligase activity
Sirolimus	Mammalian target of rapamycin (mTOR) inhibitor
Temsirolimus	Mammalian target of rapamycin (mTOR) inhibitor
Apoptosis modulation	
ACE-536	Transforming growth factor β (TGFβ) superfamily ligand trap
APG101	CD95 Fc fusion protein (inhibits Fas signaling)
Birinapant (TL32711)	Peptidomimetic of second mitochondrial-derived activator of caspases (SMAC) and inhibitor of inhibitor of apoptosis protein (IAP) family proteins
LY2157299	Transforming growth factor β (TGFβ) receptor I (TβRI) inhibitor
Sotatercept (ACE-011)	Soluble fusion protein: extracellular domain of activin receptor type IIA (ActRIIA) linked to the Fc protein of human IgG1; transforming growth factor β (TGFβ) pathway inhibitor

Low Risk MDS: Luspatercept

Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study

Uwe Platzbecker*, Ulrich Germing*, Katharina S Götze*, Philipp Kiewe*, Karin Mayer*, Jörg Chromik*, Markus Radsak*, Thomas Wolff*, Xiaosha Zhang, Abderrahmane Laadem, Matthew L Sherman, Kenneth M Attie, Aristoteles Giagounidis*

Lancet Oncol 2017; 18: 1338–47

- Scientic Background: Elevated TGF beta ligands in bone marrow are linked to ineffective erythropoiesis in MDS
- Luspatercept = novel fusion protein that binds to TGF beta superfamily ligands to restore late stage erythropoiesis
- Phase II Open Label study in Low/INT-1 IPSS patients with anemia +/- transfusion dependence

	IWG HI-E*	RBC-TI†
All patients	32/51 (63%)	16/42 (38%)
Transfusion burden		
Low transfusion burden (<4 red blood cell units per 8 weeks)	11/17 (65%)	6/8 (75%)
High transfusion burden (≥4 red blood cell units per 8 weeks)	21/34 (62%)	10/34 (29%)
Previous use of ESAs		
Yes	21/34 (62%)	11/29 (38%)
No	11/17 (65%)	5/13 (39%)
Previous use of lenalidomide		
Yes	5/8 (63%)	1/8 (13%)
No	27/43 (63%)	15/34 (44%)
Serum erythropoietin concentration		
<200 IU/L	19/25 (76%)	10/19 (53%)
≥200 IU/L to ≤500 IU/L	7/12 (58%)	4/9 (44%)
>500 IU/L	6/14 (43%)	2/14 (14%)
Ring sideroblast status		
Positive (≥15% ring sideroblasts)	29/42 (69%)	14/33 (42%)
Negative (<15% ring sideroblasts)	3/7 (43%)	2/7 (29%)
Unknown	0/2	0/2
SF3B1 mutation status		
Positive	24/31 (77%)	11/25 (44%)
Negative	6/15 (40%)	5/13 (39%)
Unknown	2/5 (40%)	0/4
Any splicing factor‡		
Positive	27/37 (73%)	15/30 (50%)
Negative	5/14 (36%)	1/12 (8%)

Luspatercept

- Based on this Phase II data a Phase III trial is in the works:
  - COMMANDS Study: Luspatercept versus Epo for VL, Low, Intermediate IPSS-R MDS with transfusion needs
  - NCT03682536
  - Trial Not Yet Recruiting

Next Generation HMA = SGI-110

- SGI-110 = Guadecitabine
  - Guadecitabine (SGI-110) is a novel hypomethylating dinucleotide of decitabine and deoxyguanosine resistant to degradation by cytidine deaminase.
- Phase II Studies: 2 recently completed and 2 ongoing for either treatment naïve or HMA refractory MDS/low volume AML…data not yet available
- Look for Phase III trials to come pending Phase II results

PI3K Inhibitor: Rigosertib

Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial

*Guillermo Garcia-Manero, Pierre Fenaux, Aref Al-Kali, Maria R Baer, Mikkael A Sekeres, Gail J Roboz, Gianluca Gaidano, Bart L Scott, Peter Greenberg, Uwe Platzbecker, David P Steensma, Suman Kambhampati, Karl-Anton Kreuzer, Lucy A Godley, Ehab Atallah, Robert Collins Jr, Hagop Kantarjian, Elias Jabbour, Francois E Wilhelm, Nozar Azarnia, Lewis R Silverman, for the ONTIME study investigators**

www.thelancet.com/oncology **Vol 17 April 2016**

High Risk MDS Patients progressed on HMA were eligible
Rigosertib Arm: n= 199; Best Supportive Care Arm: n=100

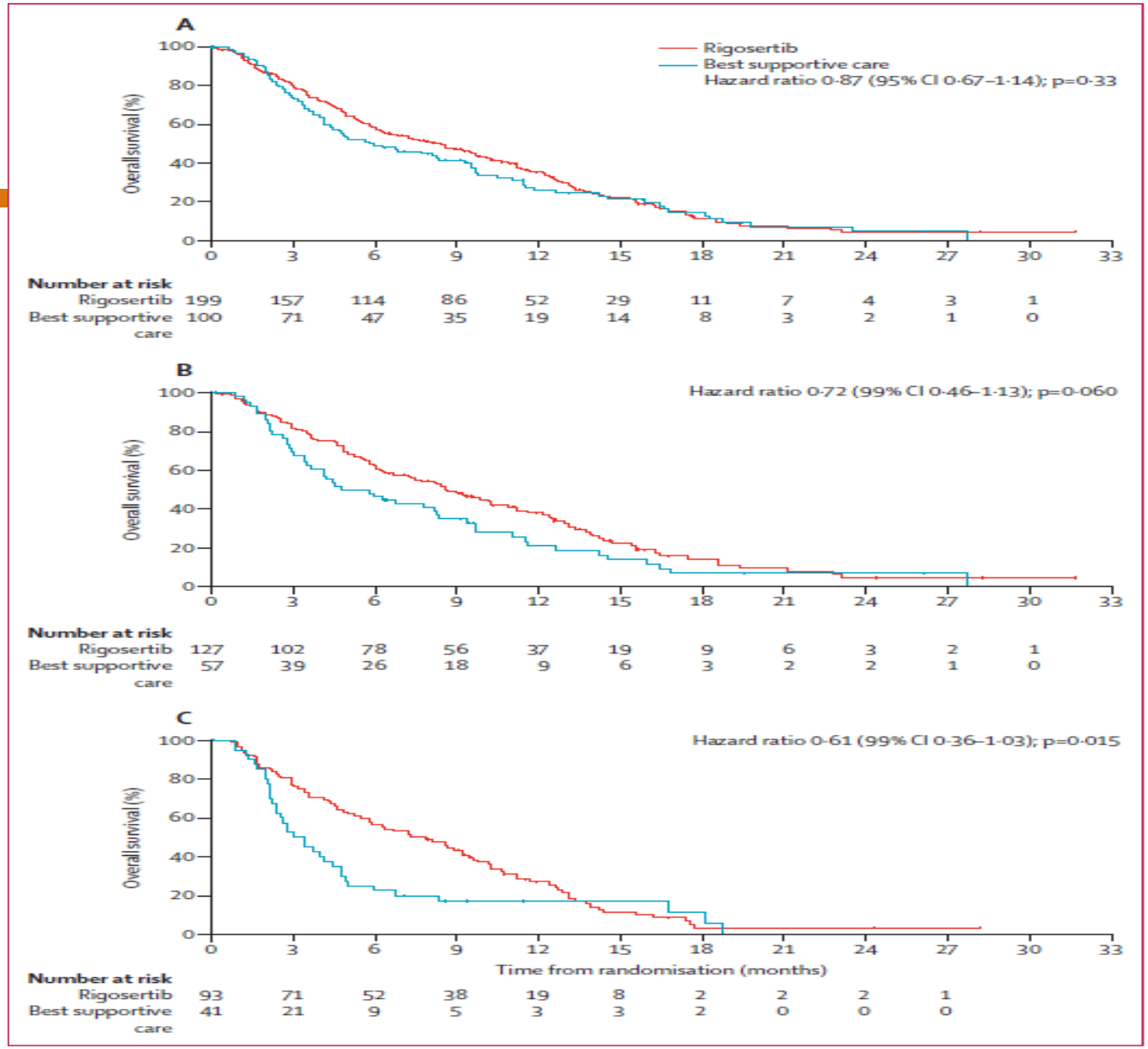
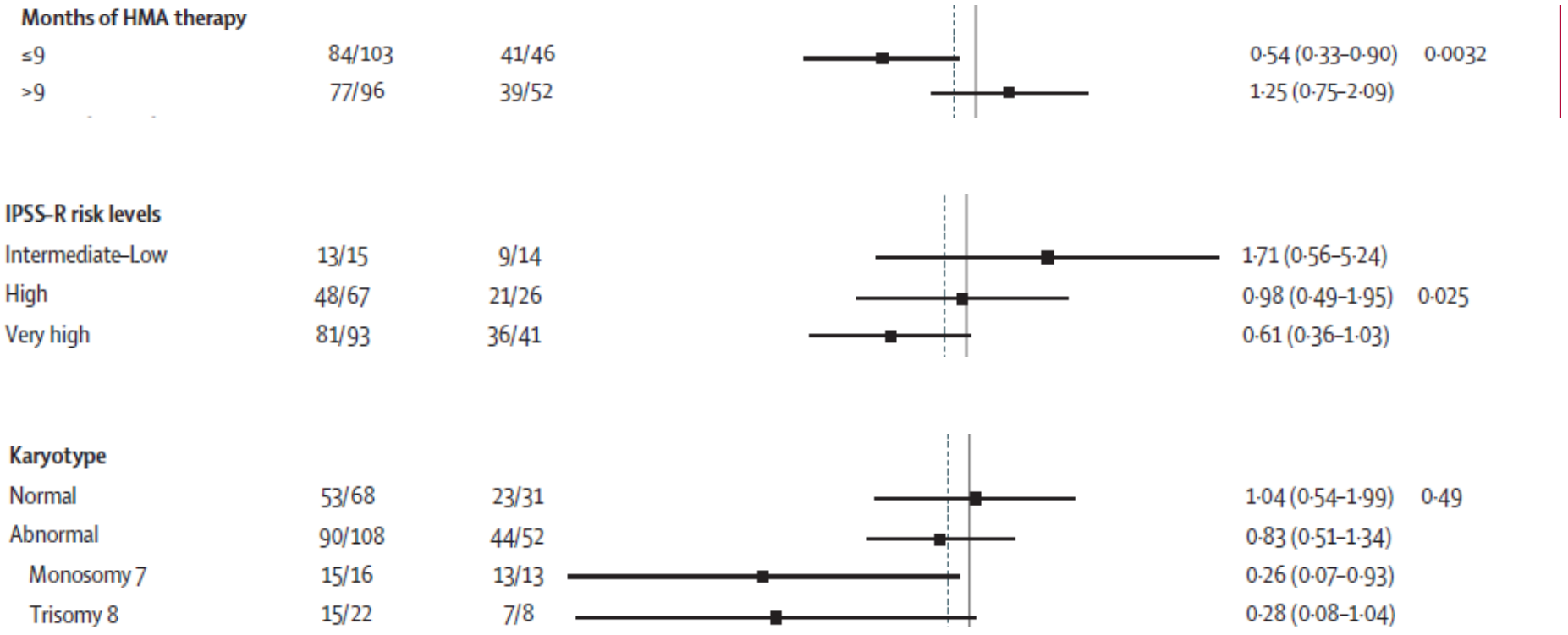


Figure 2: **Overall survival curves for the rigosertib group and best supportive care group**
(A) For the intention-to-treat population, (B) patients with primary hypomethylating drug failure, and (C) patients with IPSS-R very high risk. IPSS-R=Revised International Prognostic Scoring System.

Did Anyone Benefit?



Based on these findings, updated Randomized Phase III Trial Underway for:
High/Very-High Risk MDS with 9 months or less of azacitidine

Immunotherapy

New Area of Investigation in MDS

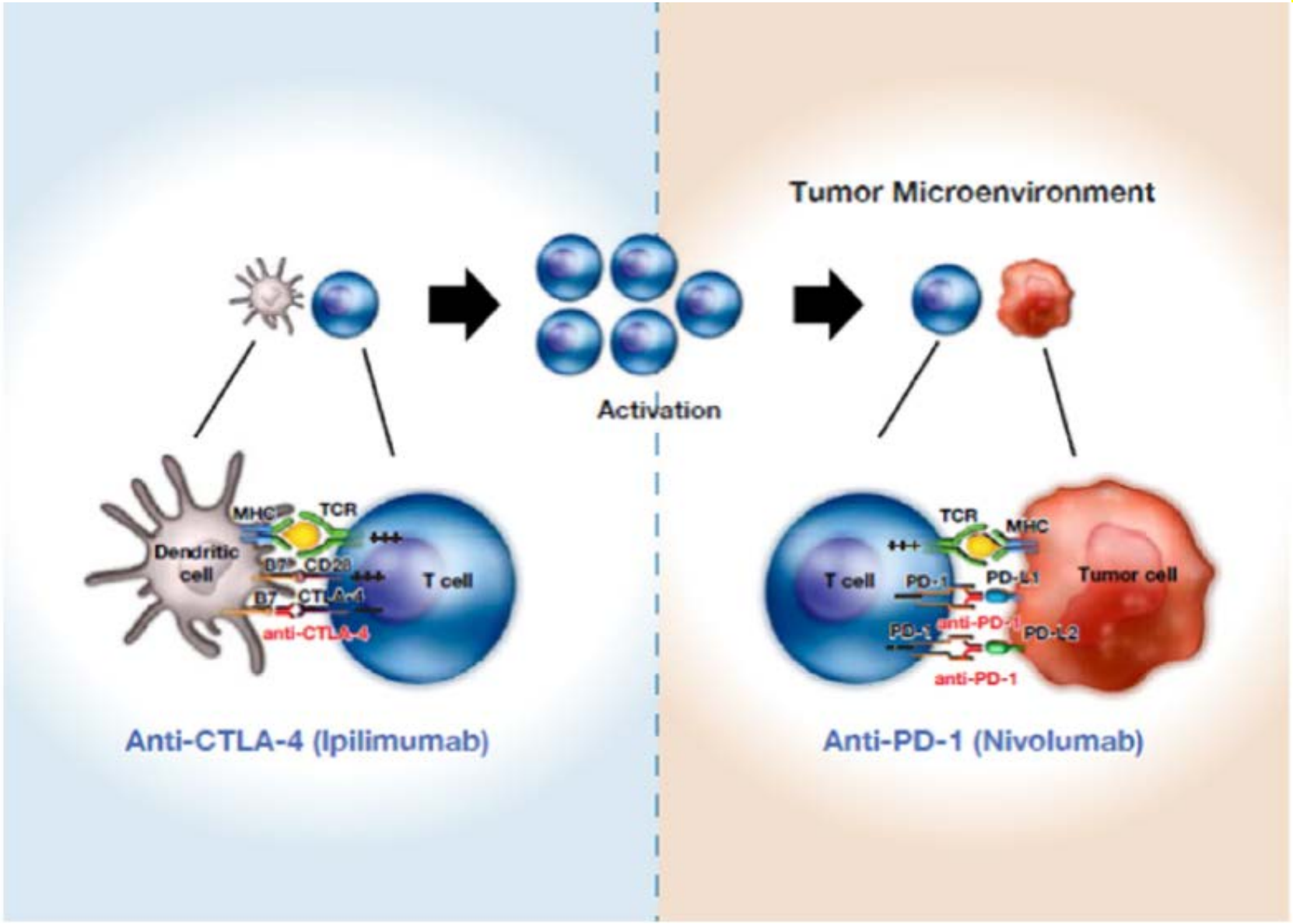
Tumor Immunity Review

- T Cells are Potent Cancer Fighting Immune Cells
  - PD-1 is a surface protein on activated T cells
  - Cancer Cells sometimes express a cell surface protein called Programmed Cell Death Ligand 1 or 2 (PDL1 or PDL2)
  - If PDL1/2 binds PD-1 → The T Cell Becomes inactive and no longer able to kill the cancer cell
- Cancer Cells Express Antigens that can be presented to Cytotoxic T cells via dendritic cells leading to T cell killing of cancer cells
  - Dendritic cells have inhibitory functions too and if they bind to CTLA4 on the T cell → The T cell is turned off

Immune Modulators

- Nivolumab = PD-1 Blocker allowing the T cell to remain activated and target the cancer cell

- Ipilimumab = CTLA-4 blocker, blocking the inhibitory signal, allowing T cell proliferation



Pharmacology & Therapeutics 148 (2015) 132–153

Immunomodulatory Trials in MDS

- Numerous trials registered in Clinical Trials.Gov investigating nivolumab, ipilimumab in combinations
- This approach stimulates the bodies own immune cells to fight off the cancer instead of chemotherapy to kill the cancer cell

Targeted Inhibitors

- IDH1 Inhibitor
  - Ivosidenib (August 2018 FDA Approval for AML)
- IDH2 Inhibitor:
  - Enasidenib (Summer 2017 FDA Approval for AML)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

C.D. DiNardo, E.M. Stein, S. de Botton, G.J. Roboz, J.K. Altman, A.S. Mims, R. Swords, R.H. Collins, G.N. Mannis, D.A. Pollyea, W. Donnellan, A.T. Fathi, A. Pigneux, H.P. Erba, G.T. Prince, A.S. Stein, G.L. Uy, J.M. Foran, E. Traer, R.K. Stuart, M.L. Arellano, J.L. Slack, M.A. Sekeres, C. Willekens, S. Choe, H. Wang, V. Zhang, K.E. Yen, S.M. Kapsalis, H. Yang, D. Dai, B. Fan, M. Goldwasser, H. Liu, S. Agresta, B. Wu, E.C. Attar, M.S. Tallman, R.M. Stone, and H.M. Kantariian

N ENGL J MED 378;25 NEJM.ORG JUNE 21, 2018

CLINICAL TRIALS AND OBSERVATIONS

Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia

Eytan M. Stein,[1,2,*] Courtney D. DiNardo,[3,*] Daniel A. Pollyea,[4] Amir T. Fathi,[5,6] Gail J. Roboz,[2,7] Jessica K. Altman,[8] Richard M. Stone,[9] Daniel J. DeAngelo,[9] Ross L. Levine,[1] Ian W. Flinn,[10] Hagop M. Kantarjian,[3] Robert Collins,[11] Manish R. Patel,[12] Arthur E. Frankel,[11] Anthony Stein,[13] Mikkael A. Sekeres,[14] Ronan T. Swords,[15] Bruno C. Medeiros,[16] Christophe Willekens,[17,18] Paresh Vyas,[19,20] Alessandra Tosolini,[21] Qiang Xu,[21] Robert D. Knight,[21] Katharine E. Yen,[22] Sam Agresta,[22] Stephane de Botton,[17,18,†] and Martin S. Tallman[1,2,†]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Weill Cornell Medical College, New York, NY; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Division of Hematology, University of Colorado School of Medicine, Aurora, CO; [5]Massachusetts General Hospital Cancer Center, Boston, MA; [6]Department of Medicine, Harvard Medical School, Boston, MA; [7]New York Presbyterian Hospital, New York, NY; [8]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; [9]Dana-Farber Cancer Institute, Boston, MA; [10]Sarah Cannon Research Institute, Nashville, TN; [11]University of Texas Southwestern Medical Center, Dallas, TX; [12]Florida Cancer Specialists and Sarah Cannon Research Institute, Sarasota, FL; [13]City of Hope Comprehensive Cancer Center, Duarte, CA; [14]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [15]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; [16]Stanford Comprehensive Cancer Center, Stanford University, Stanford, CA; [17]Département d'Hématologie et Département d'Innovation Thérapeutique, Gustave Roussy, Villejuif, France; [18]University Paris Sud and Université Paris-Saclay, Le Kremlin-Bicêtre, France; [19]Medical Research Council Molecular Haematology Unit, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom; [20]National Institute for Health Research Oxford Biomedical Research Center, Oxford University Hospital, Oxford, United Kingdom; [21]Celgene Corporation, Summit, NJ; and [22]Agios Pharmaceuticals, Inc., Cambridge, MA

BLOOD, 10 AUGUST 2017 • VOLUME 130, NUMBER 6

IDH1 and IDH2 Inhibitors in MDS

- IDH1 and IDH2 mutations are found in MDS as well
- Numerous trials open at Clinical trials.gov utilizing these inhibitors in MDS

Summary:

- MDS is complicated!
- Wide spectrum of disease severity
- Numerous MDS disease characteristics impact outcome
  - IPSS-R
  - Cytogenetics
  - Molecular mutations
- Treatment options include
  - Supportive Care
  - Disease modifying
  - Curating Therapy
- Treatment choice and timing of treatment dependent on:
  - MDS impact on life
  - Patient Goals
  - Risk stratification

Summary:

- Transplant Outcomes Impacted By:
  - Timing of transplant
  - Disease status at transplant
  - Baseline cytogenetics, IPSS-R, molecular profile
  - Patient factors (performance status)
  - Donor source

- Numerous Novel therapeutic approaches in development
  - Hopefully leading to new agents FDA approved for MDS treatment soon
  - Most exciting areas: Immune therapies, targeting therapies, small molecular inhibitors

Questions