UPMC CancerCenter

mds foundation
the myelodysplastic syndromes foundation, inc.

Myelodysplasia:

What do we think, what do we know, what can we prove?

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UPMC MDS Center of Excellence

Myelodysplastic Syndromes: Progress!

- Cancer Treatment (Haskell, 2nd Edition/1987)…Less than 1 page
- Yearbook of Hematology (Spivak, 1996)…*Advances* = 2 pages
- Cancer, PPO (DeVita, 5th Ed., 1997)…6 pages (!) out of > 3000
- Clinical Oncology (Abeloff, 2nd Ed., 2000)…17 pages
- Hematology (Williams, 6th Ed., 2001)…17 pages, 376 references (!)
- The Myelodysplastic Syndromes (Bennett, 2002)…500+ pages

Myelodysplastic Syndromes

- First described in 1900…first defined in 1982
- Incidence in U.S.
  - 15-25,000 cases per year
- Prevalence in U.S.
  - 55,000 cases
- Types of MDS
  - 2/3 of the cases belong to the lower risk categories

Myelodysplastic Syndromes: Predisposing Factors

- Unknown in more than 80% of patients
- Older age (Median age > 60 yrs, 70% > 50 yrs)
- Secondary MDS
  - Ionizing radiation
  - Chemotherapy
  - Industrial chemicals
  - Hair dyes

Myelodysplastic Syndromes and Acute Myelogenous Leukemia Resulting from Therapy for Autoimmune Disease, a Case-Control Cohort Study of 40,011 Patients

- 86 patients had 55 MDS, 21 de novo AML, and 10 AML with antecedent of MDS
- Average age was 72 years with a slight male predominance (57%)
- Median onset of autoimmune disease to diagnosis of myeloid neoplasm was 6 years (range 1-54 years)
- A total of 57/86 cases (66.3%) received either a cytotoxic or immune-modulation
- **Azathioprine** exposure was associated with a 7 fold risk of MDS or AML (p=< 0.001)
- Trend among cytotoxic agents was exposure to cyclophosphamide (OR 3.58, NSS), followed by mitoxantrone (OR 2.73, NSS)
- Methotrexate, mercaptopurine, mycophenolate had favorable odd ratios (NSS)

Blood 2016 128:296

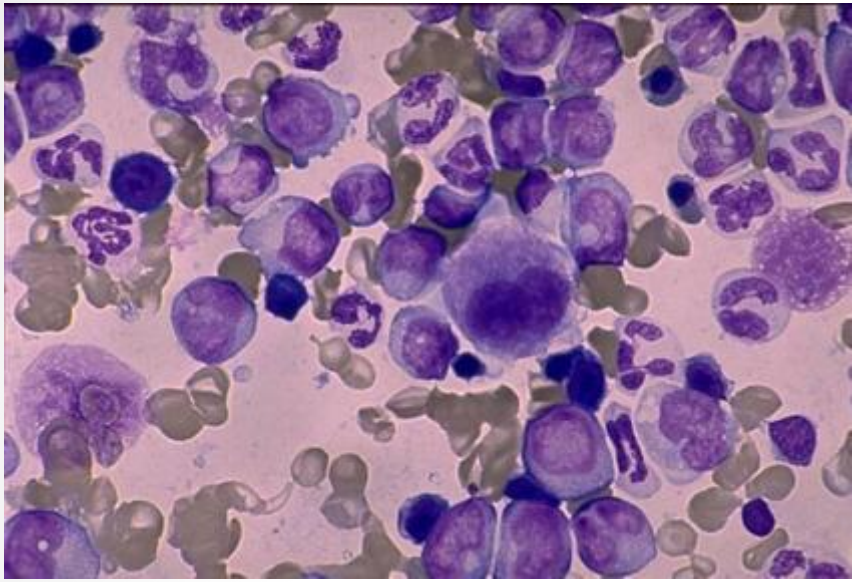
Natalie Ertz-Archambault, Gretchen Taylor, Heidi E. Kosiorek, Amylou Constance Dueck, Janna Castro, Rob Marino, Susanne Gauthier, Katalin Kelemen, Laura E. Finn, Lisa Sproat, Jeanne Palmer, Ruben Mesa, Aref Al-Kali, James M. Foran and Raoul Tibes

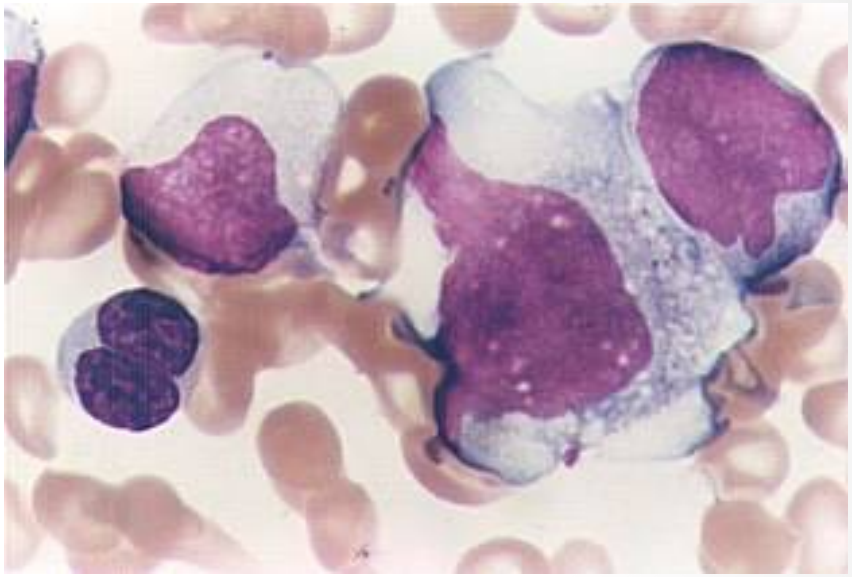
Myelodysplastic Syndromes

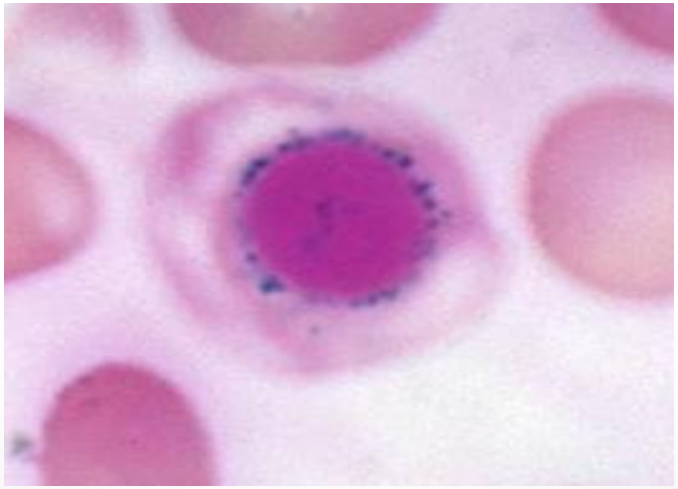
CLINICAL PARADOX OF

Variable cytopenia in a hypercellular bone marrow

MDS: Dysplastic Features







Myelodysplastic Syndromes:

Biologic Features Driving the Phenotype

- Genetic abnormalities
- Epigenetic DNA modification
- Accelerated apoptosis
- Proliferation
- Stromal dysregulation
- Medullary angiogenesis

Myelodysplastic Syndromes: Cytogenetic Abnormalities

About half of MDS patients present with a genetic abnormality

Chromosomal Abnormality	Frequency in Primary MDS
-5/del(5q)	10%–20%+
+8*	10%
–7/del(7q)	5%–10%
–Y*	10%
17p-	7%
del(20q)*	5%
t(11q23)	5%–6%
Complex karyotypes	10%–20%

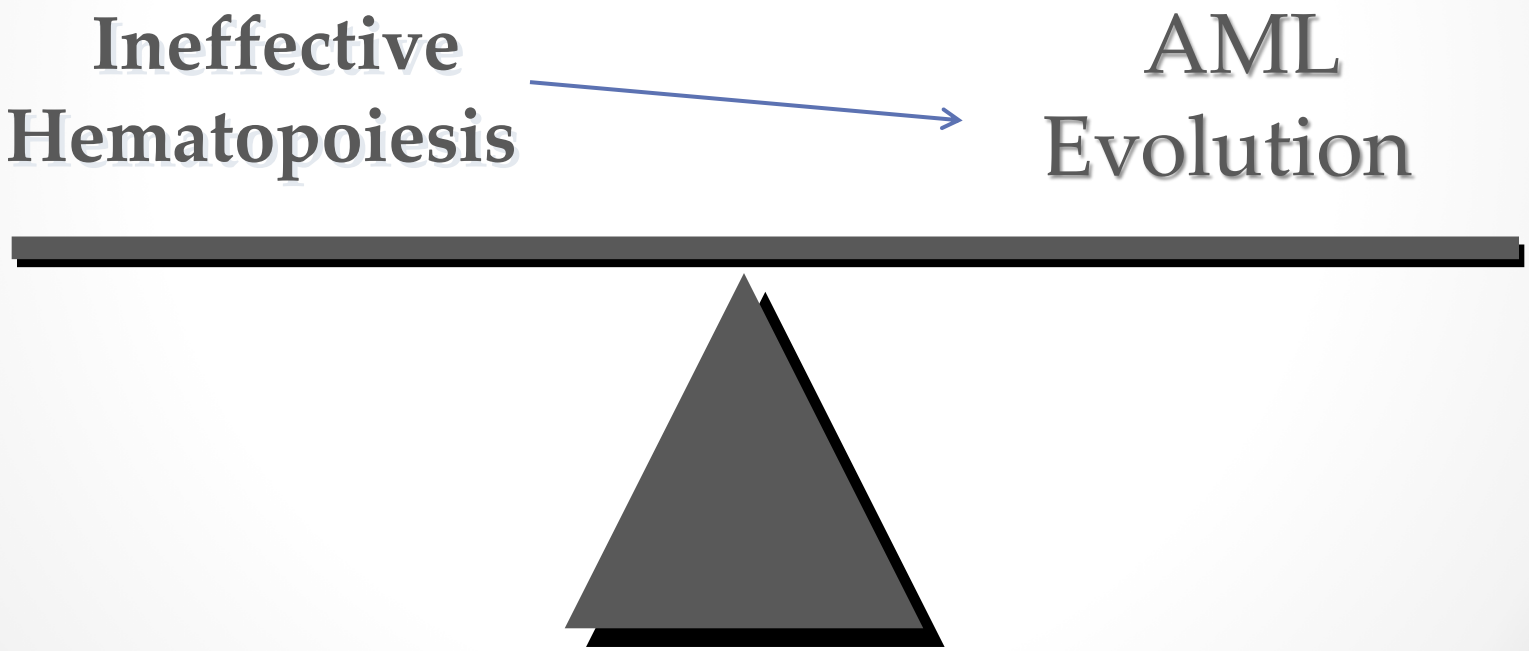
Heaney ML et al. *N Engl J Med*. 1999;340:1649
Rosenfeld C et al. *Leukemia*. 2000;14:2

*Presence as sole abnormality in cases where morphologic criteria for MDS are not met is not enough to make presumptive dx.

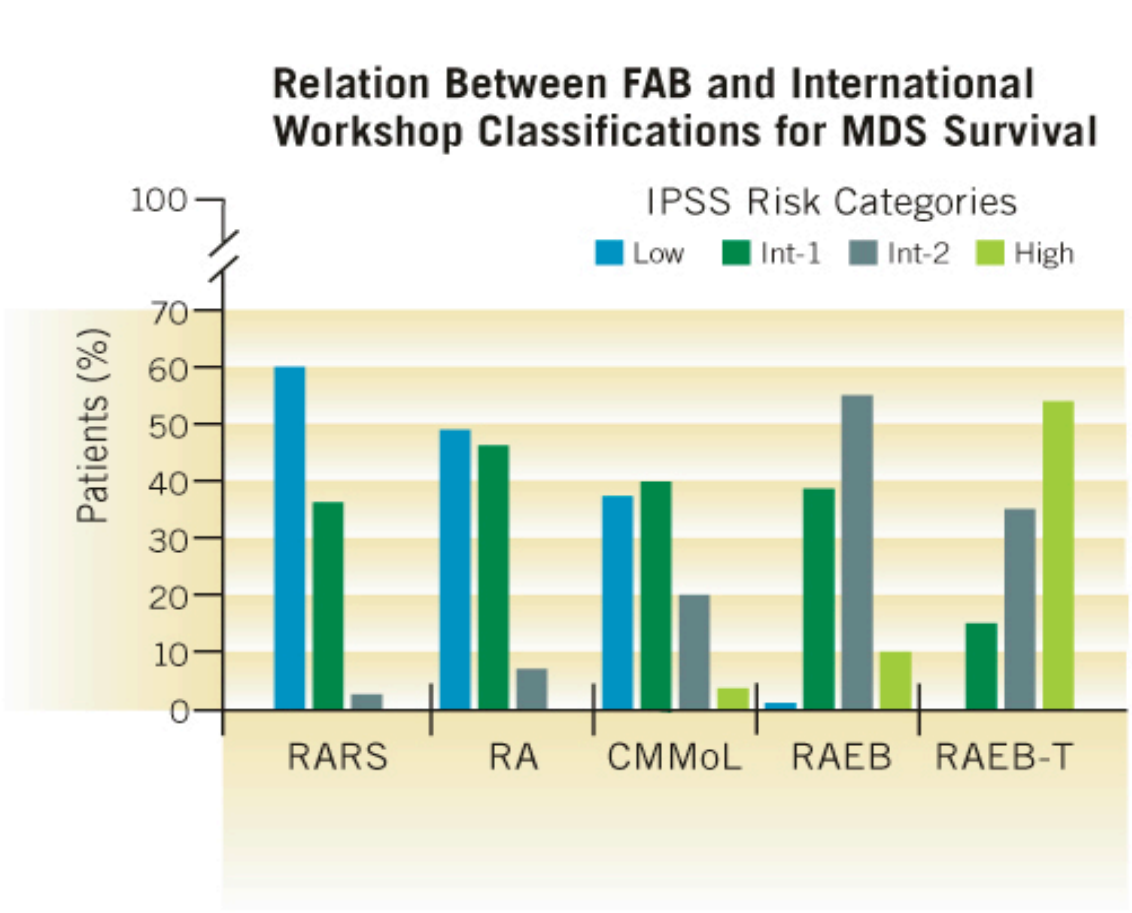
MDS - Therapeutic Challenge

Why…Who?

FAB
WHO
IPSS…



FAB versus IPSS



Cytogenetic abnormalities found in 24% of RA and 29% of RARS patients

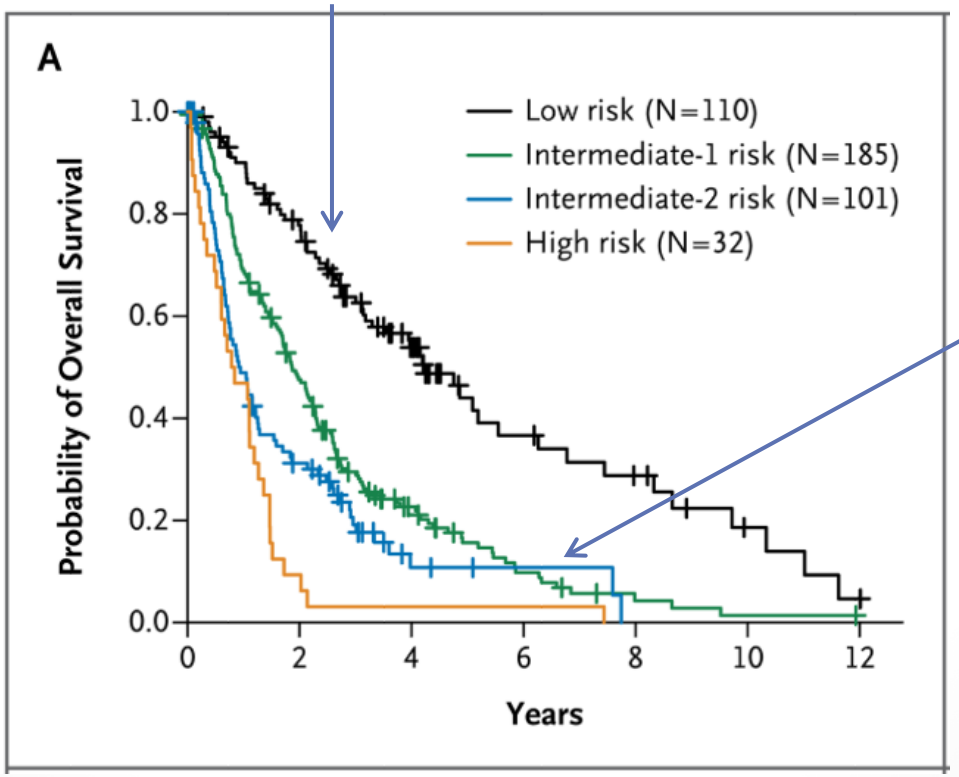
List A, Molldrem J, Sanders, J. Prognosis and treatment of myelodysplastic syndromes. Slide show presented at: Annual Meeting of the American Society of Clinical Oncology; June 5, 2004; New Orleans, La. Slide 11.

MDS - IPSS

Risk category (% IPSS population)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	$\geq$ 2.5	0.4	0.2

Heterogeneity of MDS

25% "low" risk die within 3 years



10% with Int-2 alive at 7 years without transplant

Bejar R, et al. *N Engl J Med.* 2011;364(26):2496-2506.

Cytogenetics - 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, 2 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%

IPSS-R

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

Possible range of summed scores: 0-10

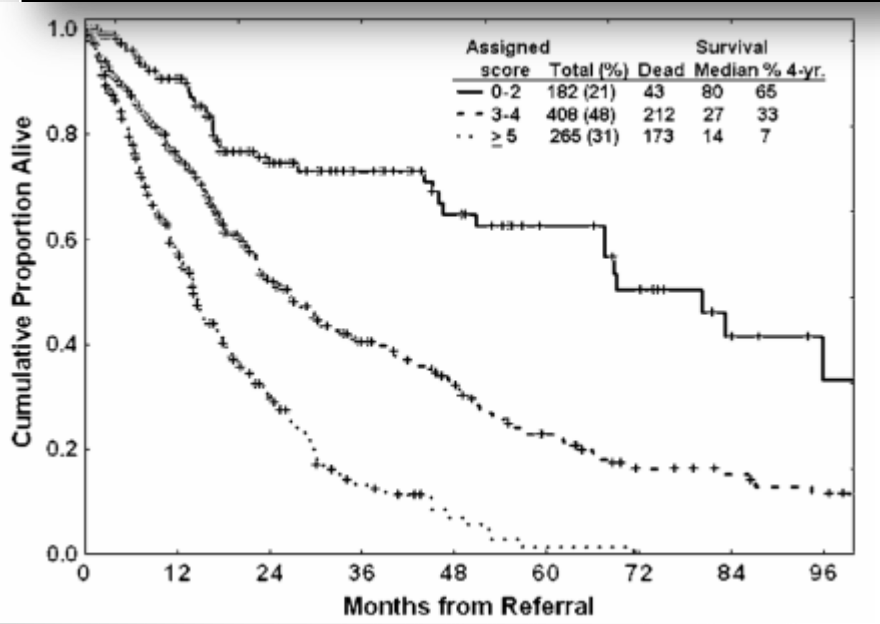
IPSS-R

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 to 3	38	5.3	10.8
Intermediate	>3 to 4.5	20	3.0	3.2
High	>4.5 to 6	13	1.6	1.4
Very High	>6	10	0.8	0.73

MD Anderson

Variable	Points
Unfavorable Cytogenetics - not normal or del(5q) alone	1
Age ≥ 60 years	2
Hemoglobin < 10 g/dl	1
Platelet Count < 50,000 per µl	2
Platelet Count 50,000-200,000 per µl	1
Bone Marrow Blasts ≥ 4 %	1

Risk Group	Total Points
Category 1	0-2
Category 2	3-4
Category 3	5-7



Garcia-Manero G, et al. *Leukemia.* 2008;22(3):538-543.

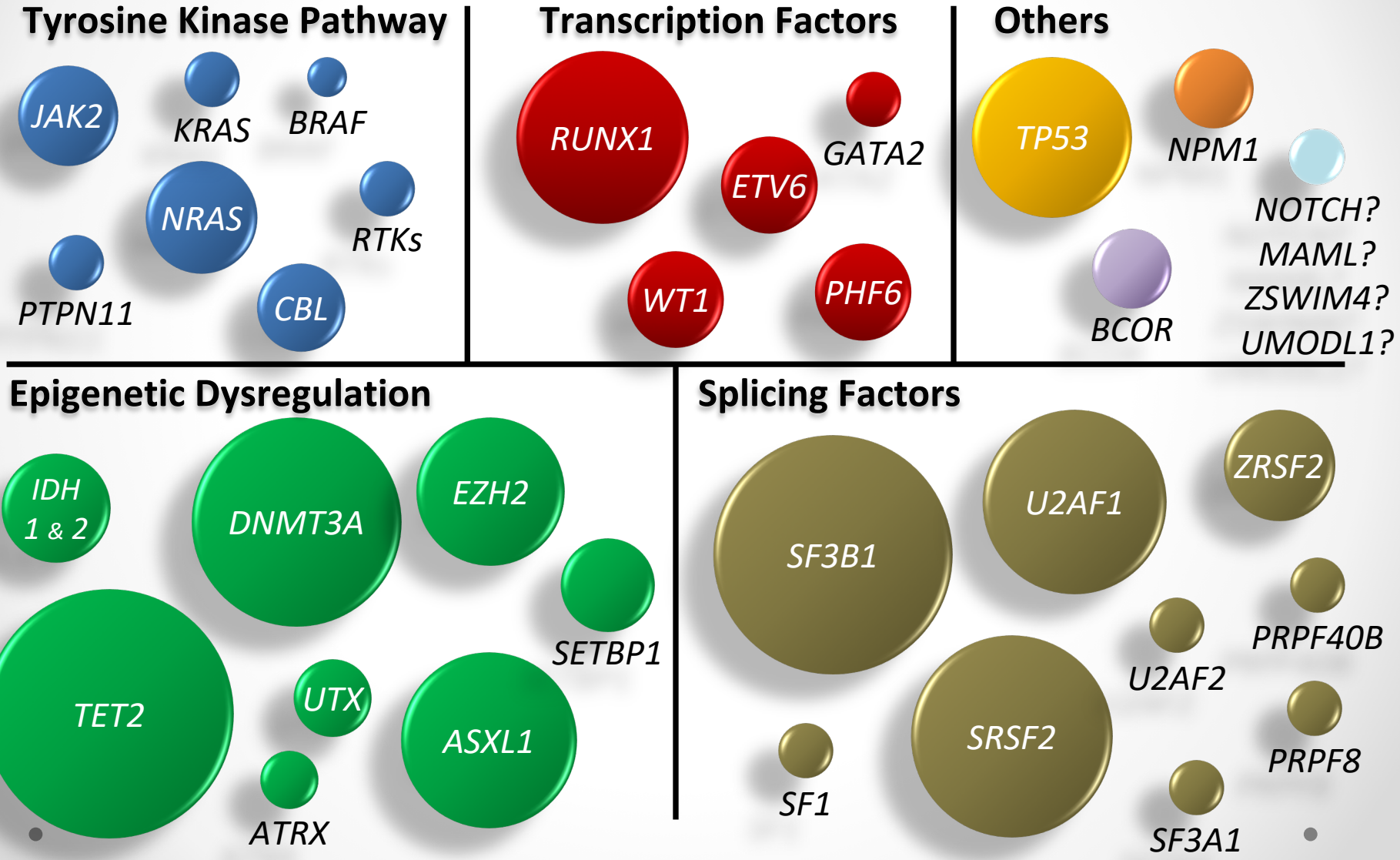
Molecular Profiling in AML

Revised Risk Stratification

Cytogenetic Classification	Mutations		Overall Risk Profile
Favorable	Any		Favorable
Normal karyotype or intermediate-risk ctyogenetic lesions	*FLT3*-ITD-negative	Mutant *NPM1* and *IDH1* or *IDH2*	
	FLT3-ITD-negative	Wild-type *ASXL1*, *MLL*-PTD, *PHF6*, and *TET2*	Intermediate
	FLT3-ITD-negative or positive	Mutant *CEBPA*	
	FLT3-ITD-positive	Wild-type *MLL*-PTD, *TET2*, and *DNMT3A* and trisomy 8–negative	
	FLT3-ITD-negative	Mutant *TET2*, *MLL*-PTD, *ASXL1*, or *PHF6*	Unfavorable
	FLT3-ITD-positive	Mutant *TET2*, *MLL*-PTD, *DNMT3A*, or trisomy 8, without mutant *CEBPA*	
Unfavorable	Any		

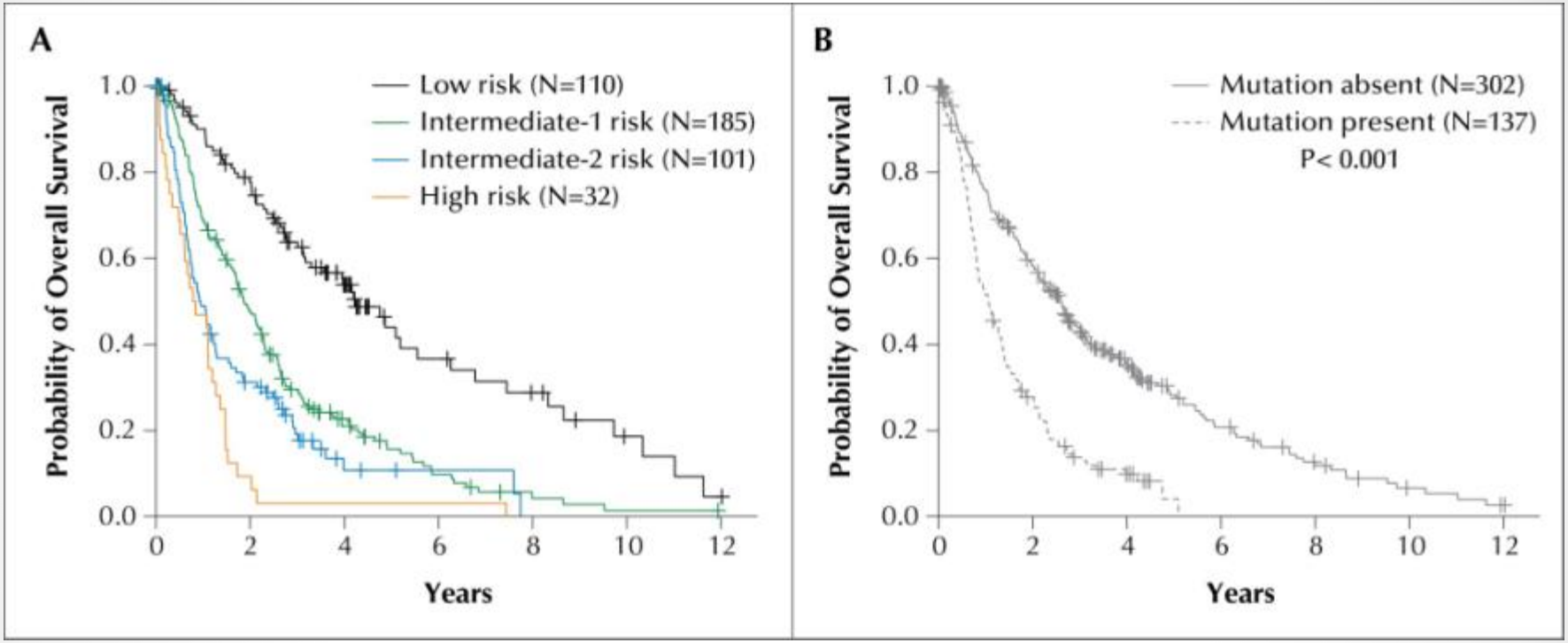
Levine, ASH education book 2012, from Patel NEJM 2012

Genes Recurrently Mutated in MDS



Bejar R.

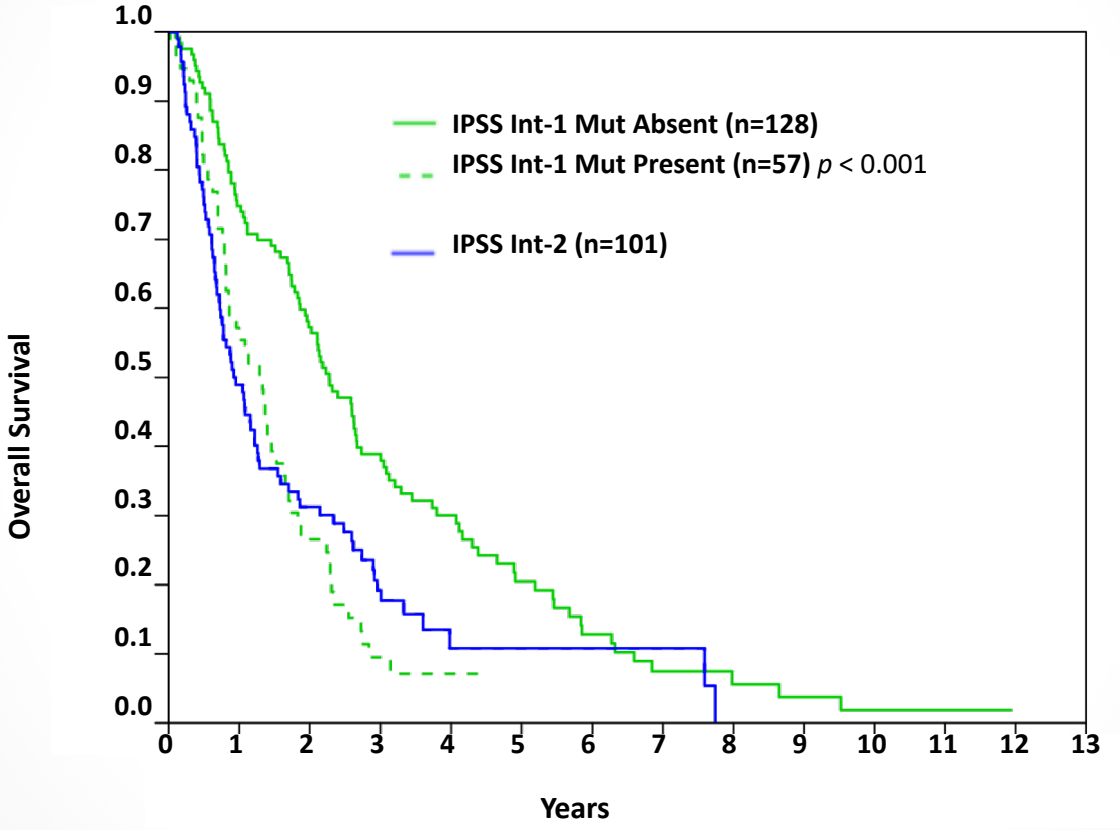
Impact of Mutation(s) on Risk Assessment



Mutations in ***TP53, EZH2, ETV6, RUNX1, and ASXL1*** were predictors of survival independent of IPSS, age, and sex

Bejar R, et al. *N Engl J Med.* 2011;364(26):2496-2506.

Impact of Reclassification



Bejar R, et al. *N Engl J Med.* 2011;364(26):2496-2506.

Incorporation of Molecular Data into the Current Prognostic Models in Treated Patients with Myelodysplastic Syndromes: Which Model Is the Best

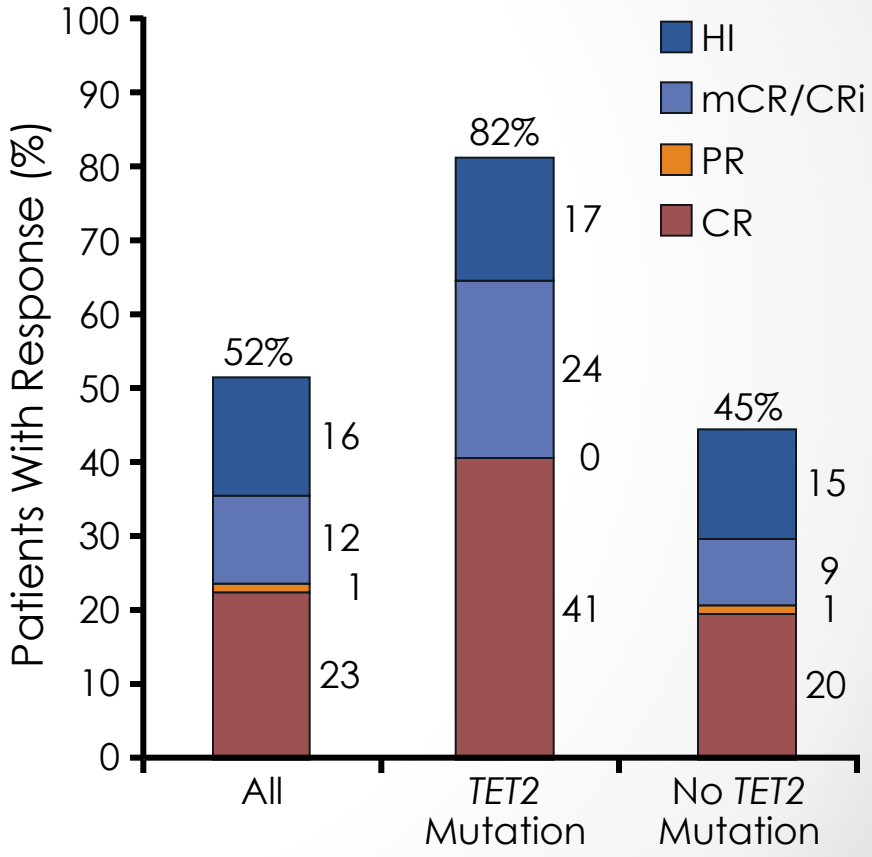
- 610 patients (two cohorts), median of 2 lines of therapy (range, 0-7), 60 gene panel
- Median OS in both cohorts assigned utilizing standard scoring systems (IPSS, WPSS, MDPSS, and IPSS-R)
- Independent prognostic factors for OS in training cohort: age, EZH2, SF3B1(+), TP53, and scoring system
- Predictive power was improved (validated in second cohort) across all scoring systems when molecular data was added
- Molecular data added to:
  - IPSS upstaged 37% of pts from lower- to higher-risk disease and downstaged 5% of intermediate-1 to low risk disease
  - WPSS upstaged 21% of pts and downstaged 24%
  - MDPSS upstaged 19% and downstaged 22% of pts from intermediate-1 to low risk
  - IPSS-R upstaged 26% to higher-risk disease and 59% of pts with intermediate risk to a higher risk category

Blood 2016 128:50

Karam Al-Issa, MD, Ahmad Zarzour, MD, Tomas Radivoyevitch, PhD, Matt Kalaycio, MD, Betty K. Hamilton, MD, Aaron T. Gerds, MD, MS5, Sudipto Mukherjee, M.D., Ph.D., M.P.H., Vera Adema, PhD, Michael J. Clemente, M.S., Bhumika Patel, MD, Cassandra M. Hirsch, BSc, Anjali S. Advani, MD, Bartlomiej P Przychodzen, MSc, Hetty E. Carraway, MD, MBA, Jaroslaw P Maciejewski, MD, PhD, FACP, Mikkael A. Sekeres, MD, MS and Aziz Nazha, MD

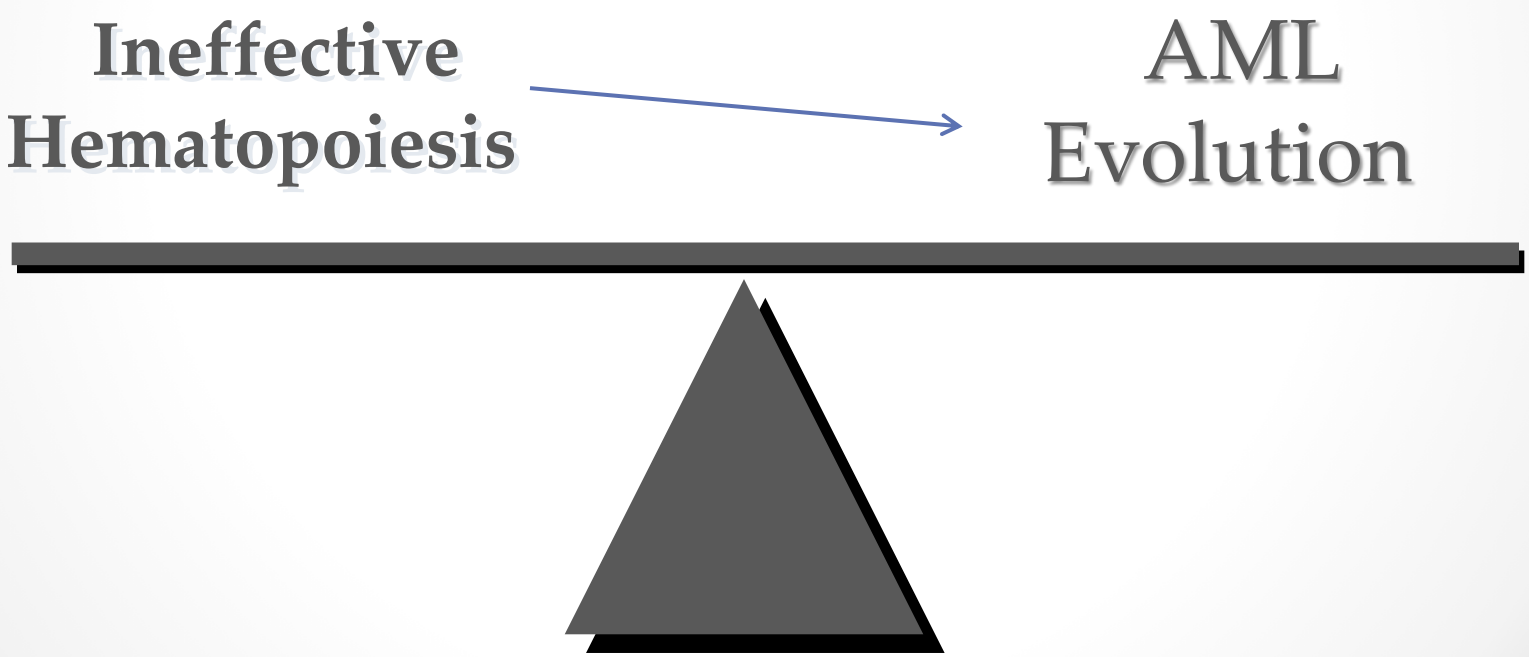
TET2 Mutation Response to Azacitidine

- 16.5% harbored *TET2* mutation
  - 21 distinct mutations identified
  - Poor cytogenetics rare in patients with *TET2* mutation: n=1 (*P* = 0.01)
- *TET2* mutation associated with significantly higher response rate to azacitidine (*P* = 0.01)
  - Independent of cytogenetic risk and number of azacitidine cycles received (*P* = 0.03)



Itzykson R, et al. ASH 2010. Abstract 439.

MDS - Therapeutic Challenge



Outcomes of Allogeneic Stem Cell Transplant

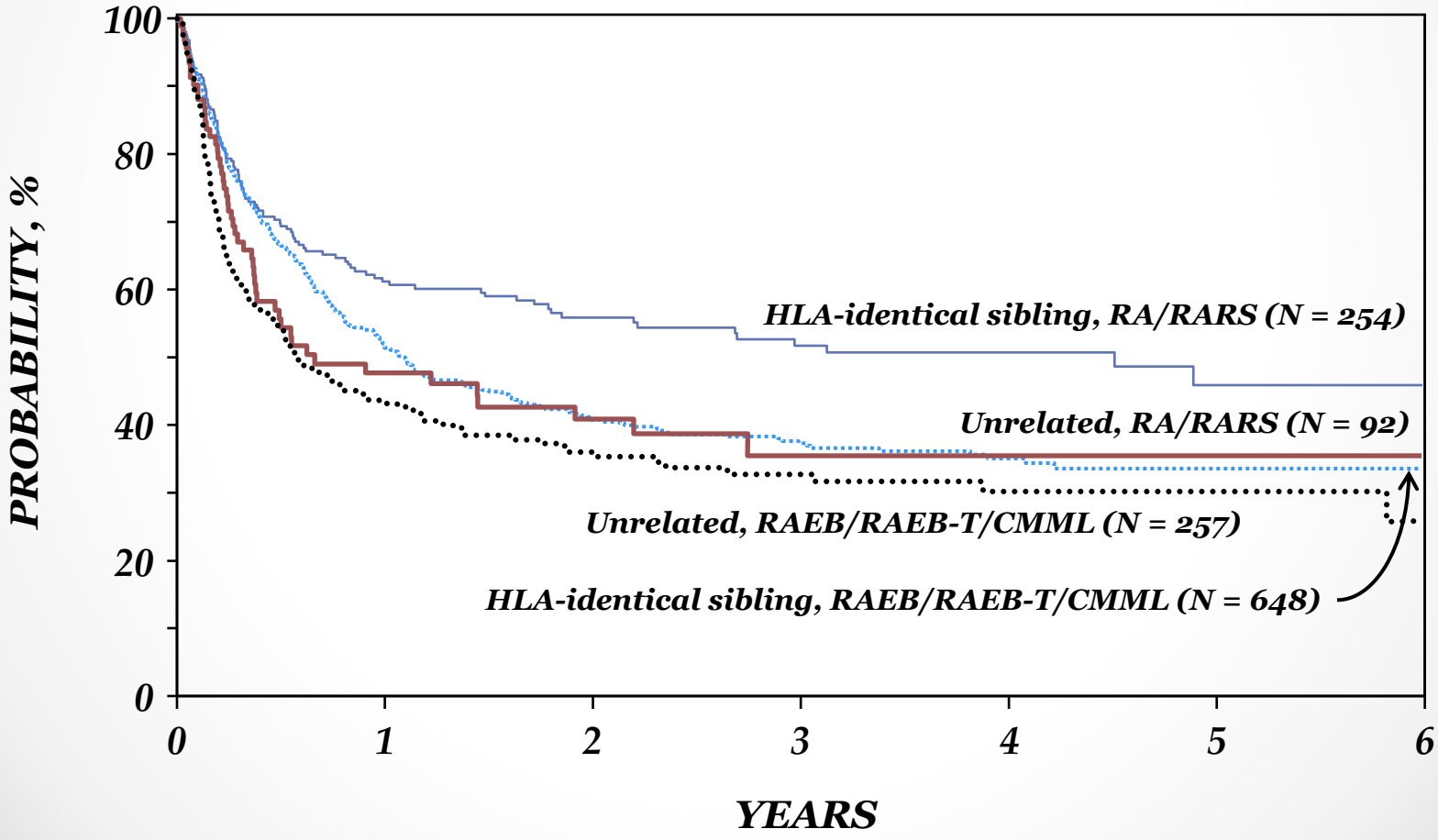
- Only curative therapy is high-dose chemotherapy (+/- TBI) with allogeneic HSCT
- Up to 50% cure rate
- Morbidity and mortality increases with age
- Allogeneic SCT appropriate for fewer than 5% of MDS patients (? now ~15%)
- Non-ablative SCT increasingly an option (?)

Allo HSCT: Approximation of Life Expectancy (Years)

	Immediate Transplant	Transplant in 2 Years	Transplant at Progression
Low	6.51	6.86	**7.21**
Int-1	4.61	4.74	**5.16**
Int-2	**4.93**	3.21	2.84
High	**3.20**	2.75	2.75

From Cutler C, et al. A Decision Analysis of Allogeneic Bone Marrow Transplantation for Myelodysplastic Syndromes: Delayed Transplantation for Low Risk Myelodysplasia is Associated with Improved Outcome. *Blood* 2004- 1st Ed Publication. Prepublished online March 23, 2004; D01.1182/Blood-2004-01-0338.

SURVIVAL, Ablative HSCT For MDS: 1996-2001, Age > 20 Years



Epigenetic Modulation: Prior or after allo-SCT

Author	n	Strategy	Remission	Outcome
Lubbert	10	Dec prior	40% CR 10% PR	33% rel/33% alive/ 33% TRM
De Padua	12	Dec prior	33% CR 50% PR	75% alive 17% relapsed
McCarty	25	Aza prior	52% ORR	EFS for aza resp not reached
Czibere	6	Relapse post-allo (aza + DLI)	CR (n=3) PR (n=2)	No GVHD (2) Relapse (3)
De Lima **included AML*	40	Aza post-allo (dose finding)	N/A	No inc GVHD Relapse (11)

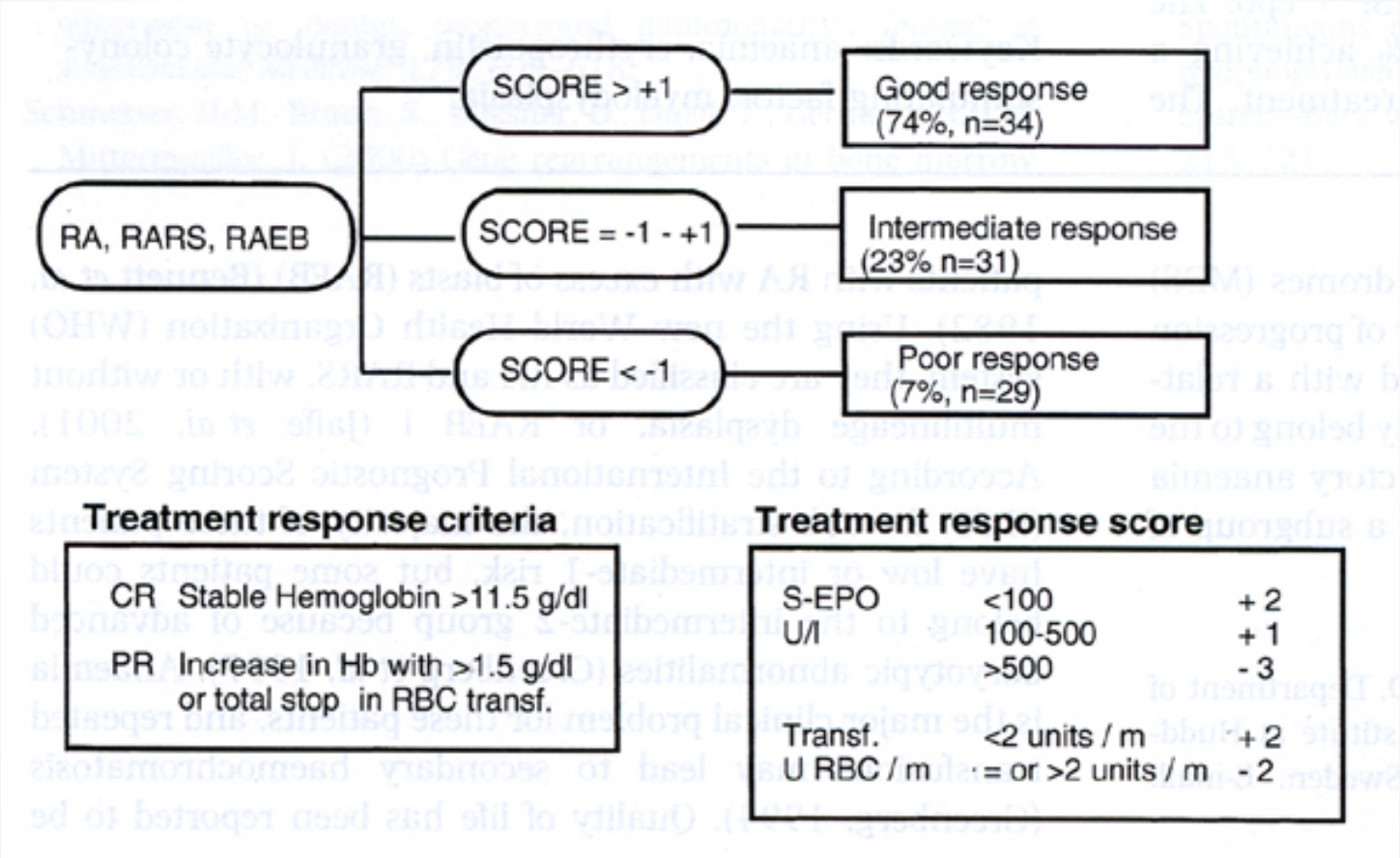
Driver Somatic Mutations and Transplantation Decision Making in Patients with Myelodysplastic Syndrome

- 401 patients undergoing allogeneic HSCT for primary MDS or MDS/AML
- Marrow blasts >10%, poor/very poor cytogenetic risk according to IPSSR, refractoriness to induction chemotherapy, and driver mutations in ASLX1/RUNX1/TP53 genes (1 point each) as predictors of relapse
- 4 risk groups: low (score=0), intermediate (score=1-2), high (score=3), and very high (score=4)
- 5-year probability of survival after allogeneic HSCT was 61%, 43%, 39% and 19%, while cumulative incidence of relapse were 9%, 19%, 24% and 35% (standard conditioning)
- Recipient age (>40 vs. ≤40 years), comorbidity risk according to HCT-CI (high vs. low/intermediate risk) type of conditioning (reduced intensity vs. standard conditioning) and HLA matching (≤7/8 vs. 8/8 match), were significant risk factors for transplant-related mortality

Blood 2016 128:53

Marianna Rossi, Matteo Giovanni Della Porta, Andrea Bacigalupo, Massimo Bernardi, Bernardino Allione, Maria Teresa van Lint, Pietro Enrico Pioltelli, Paola Marenco, Alberto Bosi, Maria Teresa Voso, Simona Sica, Maria Cuzzola, Emanuele Angelucci, Anna Gallì, Silvia Zibellini, Ettore Rizzo, Chiara Milanesi, Benedetto Bruno, Fabio Ciceri, Francesca Bonifazi, Armando Santoro, Emilio Paolo Alessandrino, Alessandro Rambaldi and Mario Cazzola

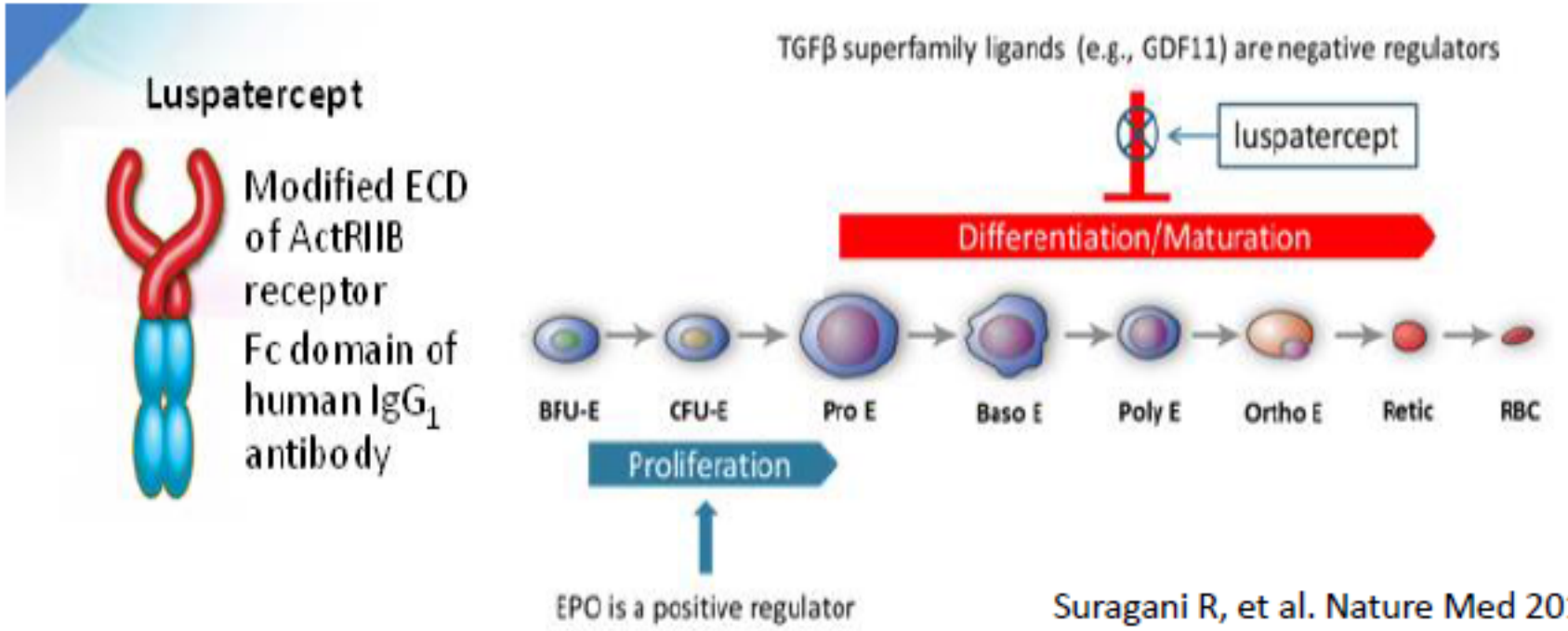
EPO +/- G: Predictive Model



British Journal of Hematology, 2003

Luspatercept in MDS: Background

- Luspatercept binds to GDF11 and other ligands of the TGF-β superfamily, and inhibits Smad2/3 signaling involved in late stages of erythropoiesis
- In contrast to EPO which acts during the early, proliferative stages of erythropoiesis.



Suragani R, et al. Nature Med 2014
Zhou L, et al., Blood 2008

COMMANDS Study Design
Randomized, Open – label Phase 3 Study

Patient population

- MDS diagnosis (WHO 2016)
- IPSS-R VL, L, INT risk
- **Include both RS(+) and RS(-) patients** (cap 40% - 60% RS+)
- **ESA naïve**
- **Endog. EPO <500**
- No prior treatment with disease modifying agents (e.g HMA)
- Not eligble for or treated with Lenalidomide (del5q)
- Requiring RBC transfusions while Hgb ≤ 9 g/dL
- **2 – 6 units of RBCs within the 8 weeks prior to randomization**

Stratification:

RBC Transfusion Burden
- 2-3 / 4-6 units

RS status:
- RS(+) / Non RS

EPO level:
- < 200 / <500

1 : 1

Luspatercept (ACE-536)
1.0 mg/kg s.c. q3W
with titration up to max 1.75 mg/kg
(n= 175)

Epoetin alfa*
450 IU/kg s.c. weekly
max. total dose 40K IU
titration up to 1050 IU/kg
max. total dose 80K IU
(n= 175)

MDS Disease Assessment after 24 wks and q6 months thereafter
Discontinue if no clinical benefit, progression to HR-MDS (high, very high) or AML

Follow-Up
subjects for ≥ 3 years post last dose for AML progression, subsequent MDS treatment and OS

- Open label
- 350 subjects (10% Dropout)
- TI 45% → 65% Power 95%

- **1° Endpoint:** RBC-Transfusion Independence for the first 24 weeks from randomization
- **Key 2° Endpoints:**
  - **HI-E per IWG (Cheson, 2006):** Proportion of subjects achieving Hematologic Improvement (HI-E) over any consecutive 56-day period in absence of transfusions
  - **Mean hemoglobin increase ≥ 1.5 g/dL:** Proportion of subjects achieving ≥ 1.5 g/dL mean increase in Hgb over a consecutive 24-week period in the absence of RBC transfusions

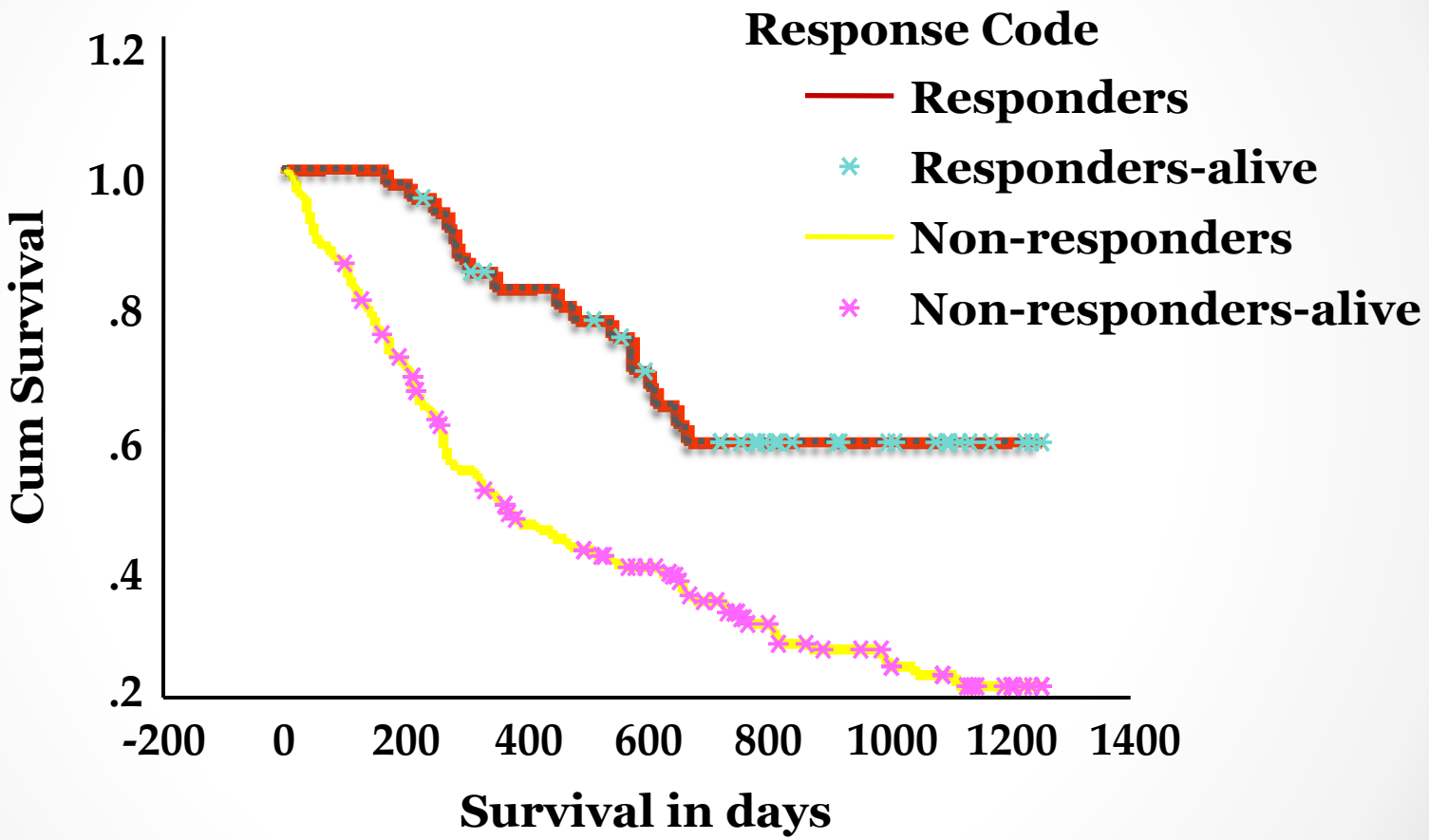
* Individual doses according to body weight will be rounded up to the next 2,000 IU dose level or up to the next 4,000 IU dose level for doses exceeding a calculated dosing of 56,000 IU according to body weight.

Immunosuppressive Therapy for MDS

ATG ± steroids ± cyclosporine:

- 40 – 70% responses in hypoplastic MDS
- Responses greatest in younger patients, shorter duration, and HLA DRB1*15
- Responses 5 years or more
- Does a PNH clone predict response?
- What is the role of IS in normo- or hyercellular MDS?

Survival Curve: Thalidomide



Median non-responders = 317 days
Median responders = none reached P =< 0.0005

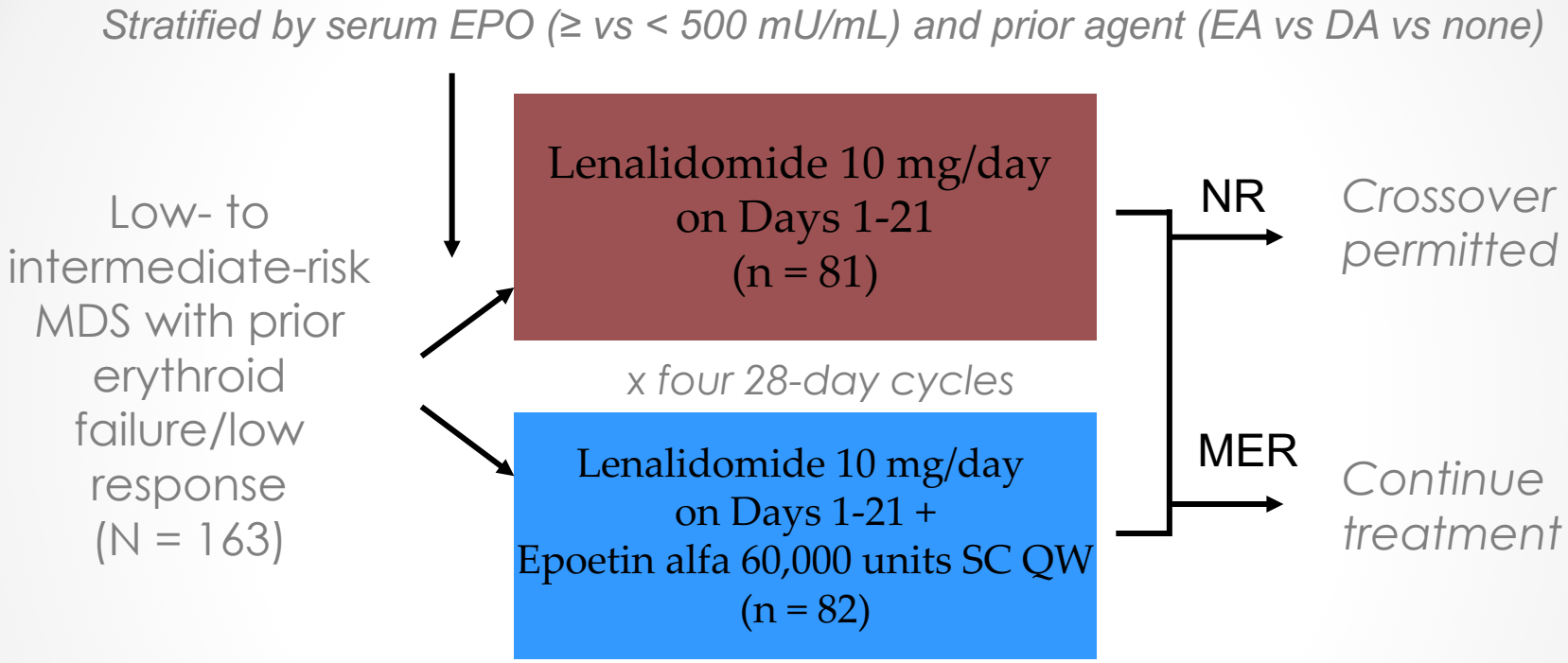
5q- Syndrome: A Subset of MDS

- Isolated chromosome 5q deletion
- Hematologic features
  - Refractory anemia
  - Mild leukopenia
  - Atypical megakaryocytes, normal to elevated platelets
  - Transfusion dependence
  - Extended survival with low frequency of AML transformation

Lenalidomide: The 5q- Experience

- Very high response rate
- 10/12 initial 5q- syndrome pts achieved CCR
- May see an early aplastic phase during treatment
- FDA approved for low-risk MDS patients with transfusion dependence and 5q- (with or without other abnormalities): Of 148 pts, 67% achieved transfusion independence with 90% doing so by month 3…median duration of 44 weeks

E2905: Study Design



- Interim analysis of pts accrued before July 2015 (fifth interim analysis)
- Primary endpoint: MER: transfusion independence for ≥ 8 consecutive wks + ≥ 1 g/dL Hg rise from baseline OR if no transfusion dependence, a ≥ 2 g/dL Hg rise from baseline for ≥ 8 wks
- Secondary endpoints: time to MER, MER duration, lenalidomide crossover MER response, response biomarkers (CD45 isoforms)

List, AF, et al. ASH 2016. Abstract 223.

E2905: Erythroid Responses

Outcome	Lenalidomide (n = 81)	Lenalidomide + EA (n = 82)	*P* Value
Intent to treat, n (%) (N = 163)			
▪ MER	9 (11.1)	21 (25.6)	.025
▪ Minor ER	15 (18.5)	13 (15.9)	.68
▪ Overall ER	24 (29.6)	34 (41.5)	.14
MER after crossover	n = 34	7 (21)	
Wk 16 evaluable, n (%) (n = 117)			
▪ MER	8 (14.3)	20 (32.8)	.029
▪ Minor ER	13 (23.1)	13 (21.3)	.83
▪ Overall ER	21 (37.5)	33 (54.1)	.09
Median duration of MER, mos	13.0	25.4	.37

List, AF, et al. ASH 2016. Abstract 223.

Myelodysplastic Syndromes: Epigenetic DNA Modification

Epigenetic Gene Silencing

- DNA hypermethylation - Promoter, global DNA hypermethylation common in MDS

Therapeutic Strategy

- DNA methyltransferase inhibitors (eg, azacitidine, decitabine) promote hypomethylation of DNA, allowing expression of previously silenced genes

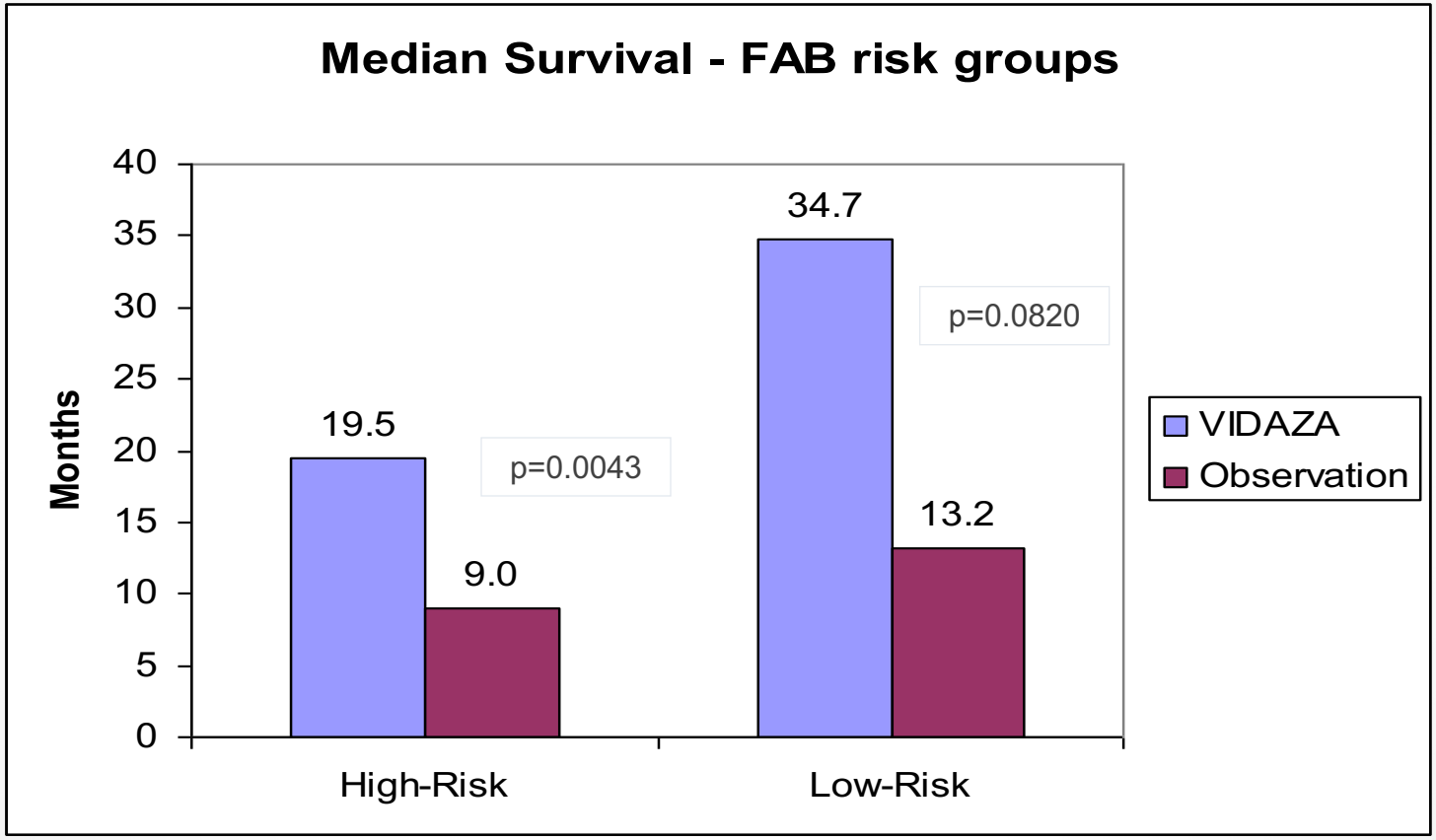
CALGB Trial of Azacitidine vs. Supportive Care

	Response	Time to leukemia or death	Transformation to AML as 1st event
Aza C (n = 99)	CR = 7% PR = 16% Improved = 37% (Overall = 60%)	21 months	15%
Supportive care (n = 92)	CR = 0% PR = 0% Improved = 5% (Overall = 5%)	13 months	38%

Quality of life significantly improved with treatment: fatigue ($P = 0.001$), dyspnea ($P = 0.0014$), physical functioning ($P = 0.0002$), positive affect ($P = 0.0077$), and psychological distress ($P = 0.015$)

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

Median Survival: FAB-based Risk Groups



Similar findings for Predicted Survival Risk Groups.

AZA-001 Trial: Baseline Clinical Characteristics*

			CCR Regimens N=179		
	VIDAZA® N=179	CCR N=179	BSC, Only N=105	LDAC N=49	7+3 Chemo N=25
Age					
Median (yrs)	69	70	70	71	65
≥65 (%)	68.1	76.0	77.1	85.7	52.0
FAB (%)					
RAEB	58.1	57.5	64.8	51.0	40.0
RAEB-T	34.1	34.6	28.6	38.8	52.0
CMMoL	3.4	2.8	3.8	2.0	0
IPSS (%)					
Int-1	2.8	7.3	8.6	4.1	8.0
Int-2	42.5	39.1	43.8	42.9	12.0
High	45.8	47.5	43.8	42.9	72.0
WHO (%)					
RAEB-1	7.8	9.5	12.4	6.1	4.0
RAEB-2	54.7	53.1	57.1	49.0	44.0
CMMoL-1	0.6	0	0	0	0
CMMoL-2	5.6	2.8	2.9	0	8.0
AML	30.7	32.4	25.7	40.8	44.0

*Numbers may not add up to 100%, some patient information unknown

Celgene Corporation, Data on File.

AZA-001 Trial: Median Overall Survival by Investigator CCR Treatment Selection

Investigator CCR Selection Pre-Randomization	Treatment Post-Randomization	OS Time (Months)	Difference in OS Time (Months)	Hazard Ratio
CCR (N=358)	**VIDAZA® (N=179) vs CCR (n=179)**	24.5 15.0	9.5	0.58
BSC (N=222)	**VIDAZA (N=117) vs BSC (n=105)**	21.1 11.5	9.6	0.56
LDAC (N=94)	**VIDAZA (n=45) vs LDAC (N=49)**	24.5 15.3	9.2	0.58
7+3 Chemo (N=42)	**VIDAZA (N=17) vs 7+3 Chemo (N=25)**	25.1 15.7	9.4	0.87

Celgene Corporation, Data on File.

Guadecitabine

- Initial Results of a Phase 2 Study of Guadecitabine, a Novel Subcutaneous Hypomethylating Agent, for Patients with Previously Untreated Intermediate-2 or High Risk Myelodysplastic Syndromes or Chronic Myelomonocytic Leukemia - Blood 2016 128:346
  - 36/40 (90%) evaluable for response at the time of analysis
  - 10 (28%) subjects met the primary endpoint by achieving CR, ORR was observed in 22 (61%) subjects, with 4 (10%) hematologic improvement (HI) and 9 (23%) CRi; Even in the presence of adverse biological features such as high frequency of complex karyotype, therapy related disease and TP53 mutations
  - Median **best** response occurred by 3 cycles
  - Median OS was 15.2 months

- Results of a Phase II Study of Guadecitabine in Higher Risk MDS, CMML or Low Blast Count AML Patients Refractory to or Relapsing after Azacitidine Treatment - Blood 2016 128:347
  - 56 pts from 13 centers were enrolled
  - Responses were seen in 4/15 (26.6%) primary refractory, and in 5/41 (12.2%) relapsing patients (p=NS)
  - Median OS from inclusion was 6.7 months

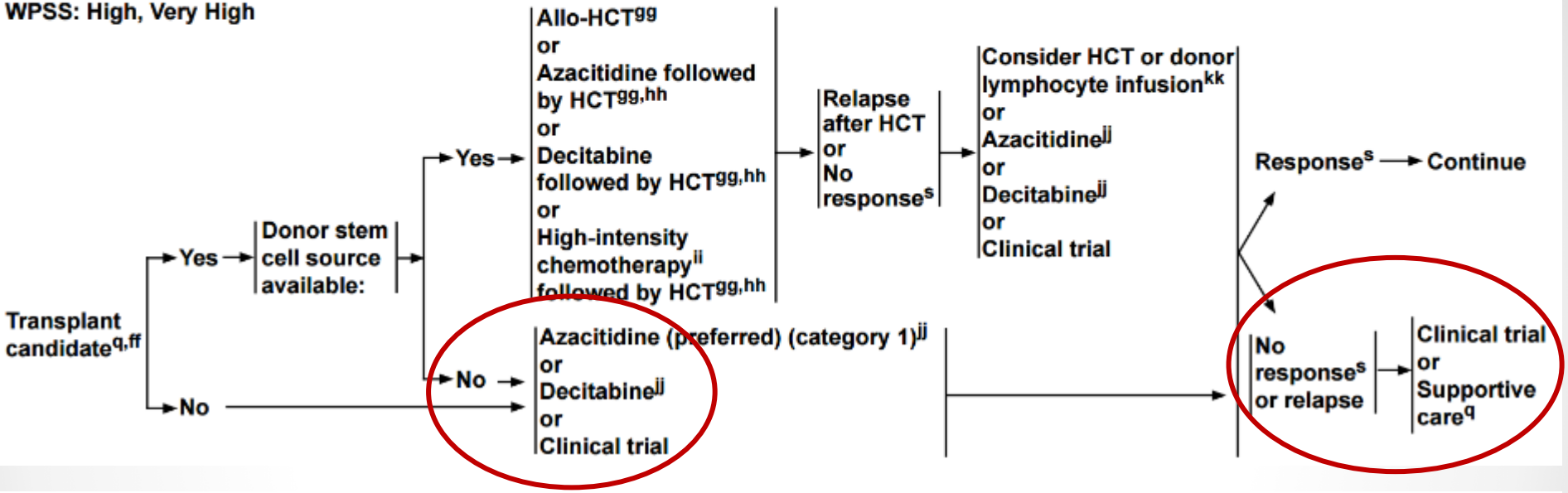
G-CSF Increases Hematological Response Among Patients with MDS Treated with Azacitidine

Treatment *(n=86)*	Overall Hematological Response	P -value
Aza Alone	51% (19/37)	
Aza + EPO	50% (6/12)	P=.09
Aza + G-CSF +/- EPO	84% (31/37)	
Aza without G-CSF	51% (25/49)	P=.003

Rossetti et al. Blood 2006;108(11):A4868.

PROGNOSTIC CATEGORY[n]
IPSS-R: Intermediate,[o] High, Very High
IPSS: Intermediate-2, High
WPSS: High, Very High

TREATMENT



[n]Presence of comorbidities should also be considered for evaluation of prognosis. (See Comorbidity Indices in the Discussion.)

[o]Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as lower risk if their score is ≤3.5 vs higher risk if score is >3.5. Pfeilstöcker M, Tuechler H, Sanz G, et al. Blood. 2016;128(7):902-910.

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

[s]Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Blood 2006;108:419-425. Failure would be considered if no response within 3–6 mo.

[ff]Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.

[gg]HCT: Allogeneic-matched sibling including standard and reduced-intensity preparative approaches or MUD.

[hh]Azacitidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability. However, these agents should not be used to delay available HCT.

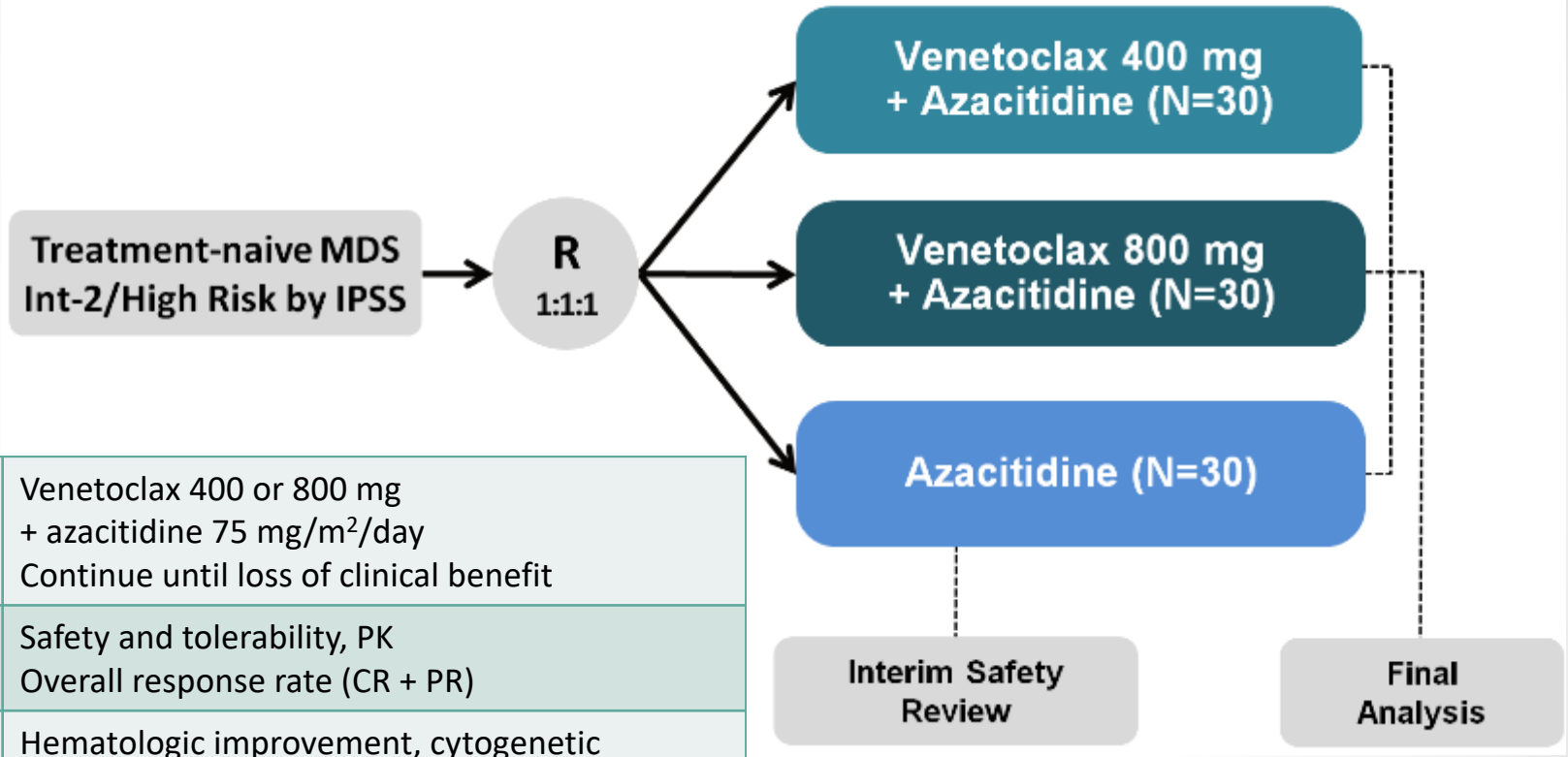
[ii]High-intensity chemotherapy:
- clinical trials with investigational therapy (preferred), or
- standard induction therapy if investigational protocol is unavailable or if it is used as a bridge to HCT.

[jj]While the response rates are similar for both drugs, survival benefit from a phase III randomized trial is reported for azacitidine and not for decitabine. Azacitidine or decitabine therapy should be continued for at least 4–6 cycles to assess response to these agents. In patients who have clinical benefit, continue treatment with the hypomethylating agent as maintenance therapy.

[kk]Consider second transplant or donor lymphocyte infusion immuno-based therapy for appropriate patients who had a prolonged remission after first transplant.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

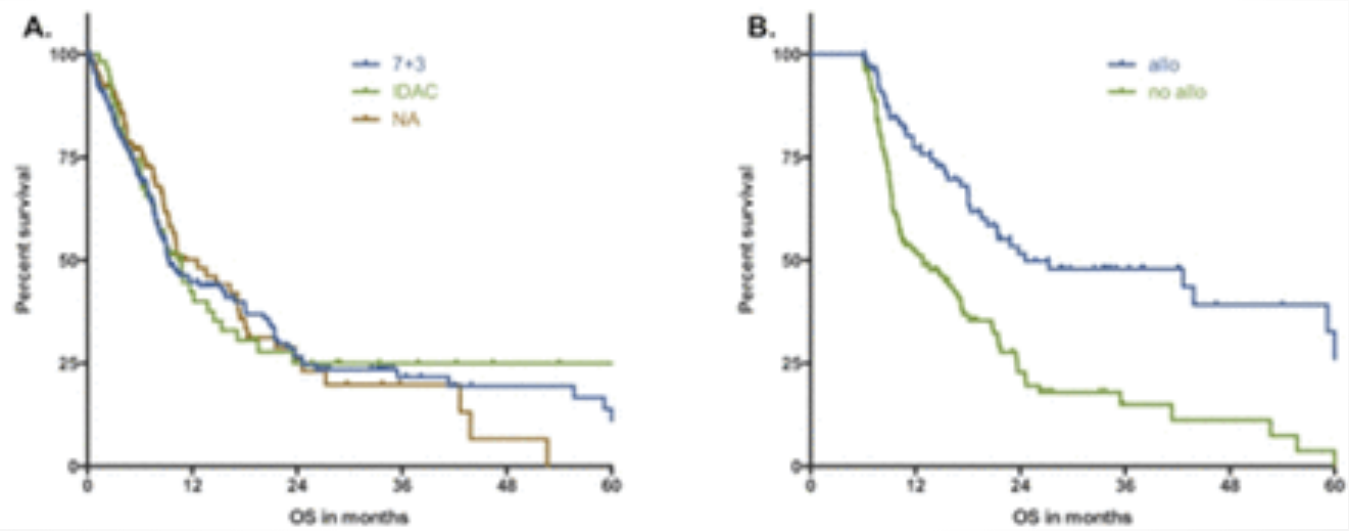
M15-531: Original Design, Randomized Dose-Ranging Study of Venetoclax + Azacitidine in 1L HR MDS



Dosing	Venetoclax 400 or 800 mg + azacitidine 75 mg/m^2/day Continue until loss of clinical benefit
Primary Endpoint	Safety and tolerability, PK Overall response rate (CR + PR)
Secondary Endpoints	Hematologic improvement, cytogenetic response, DOR, OS, EFS, PFS, DFS, time to AML progression, QoL
Exploratory Endpoints	Cytogenetics, mutation profiling, BCL-2 family expression, immune cell biology and microenvironment, methylation

Salvage Induction Chemotherapy Regimens in Higher Risk MDS and AML after Hypomethylating Agent Treatment Failure

- 366 included pts, 203 received 7+3, 56 received intermediate to high-dose Aracytine (IDAC), and 107 received a nucleoside analogue (NA)-based regimen (fludarabine, cladribine, clofarabine)
- Overall response rate to chemo was 39.6%, 8-week mortality was 7.9%, the median OS was 10m (A)
- In a landmark analysis performed at 6 months after IC, transplanted pts had improved OS vs non-transplanted pts (B. 25m vs 13m, p<0.001)



Blood 2016 128:348

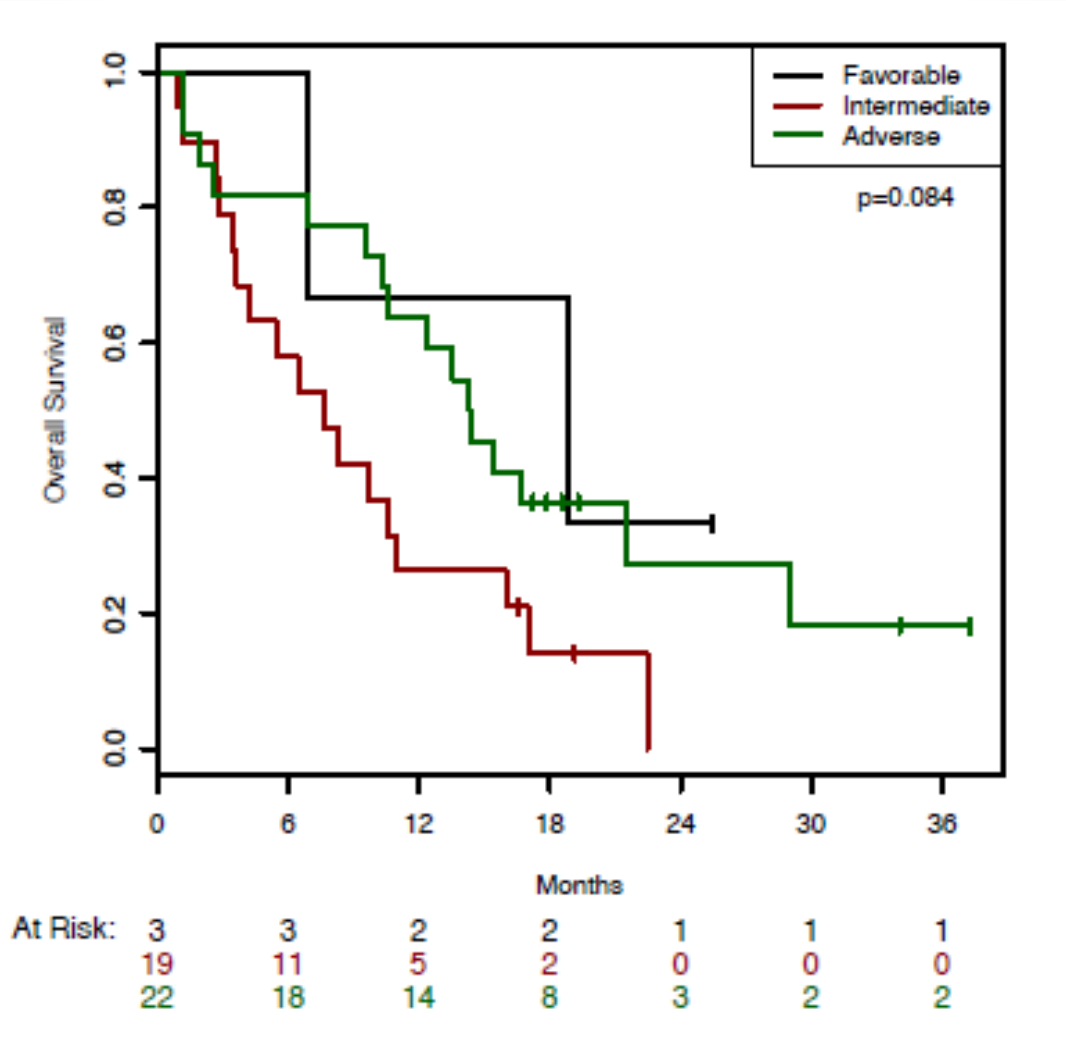
Brian Ball, Rami S. Komrokji, Lionel Ades, Mikkael A. Sekeres, Amy E. DeZern, Lisa Pleyer, Norbert Vey, Antonio Almeida, Ulrich Germing, Thomas Cluzeau, Uwe Platzbecker, Steven Gore, Pierre Fenaux and Thomas Prebet

Decitabine + Cytarabine regimen (epigenetic priming)

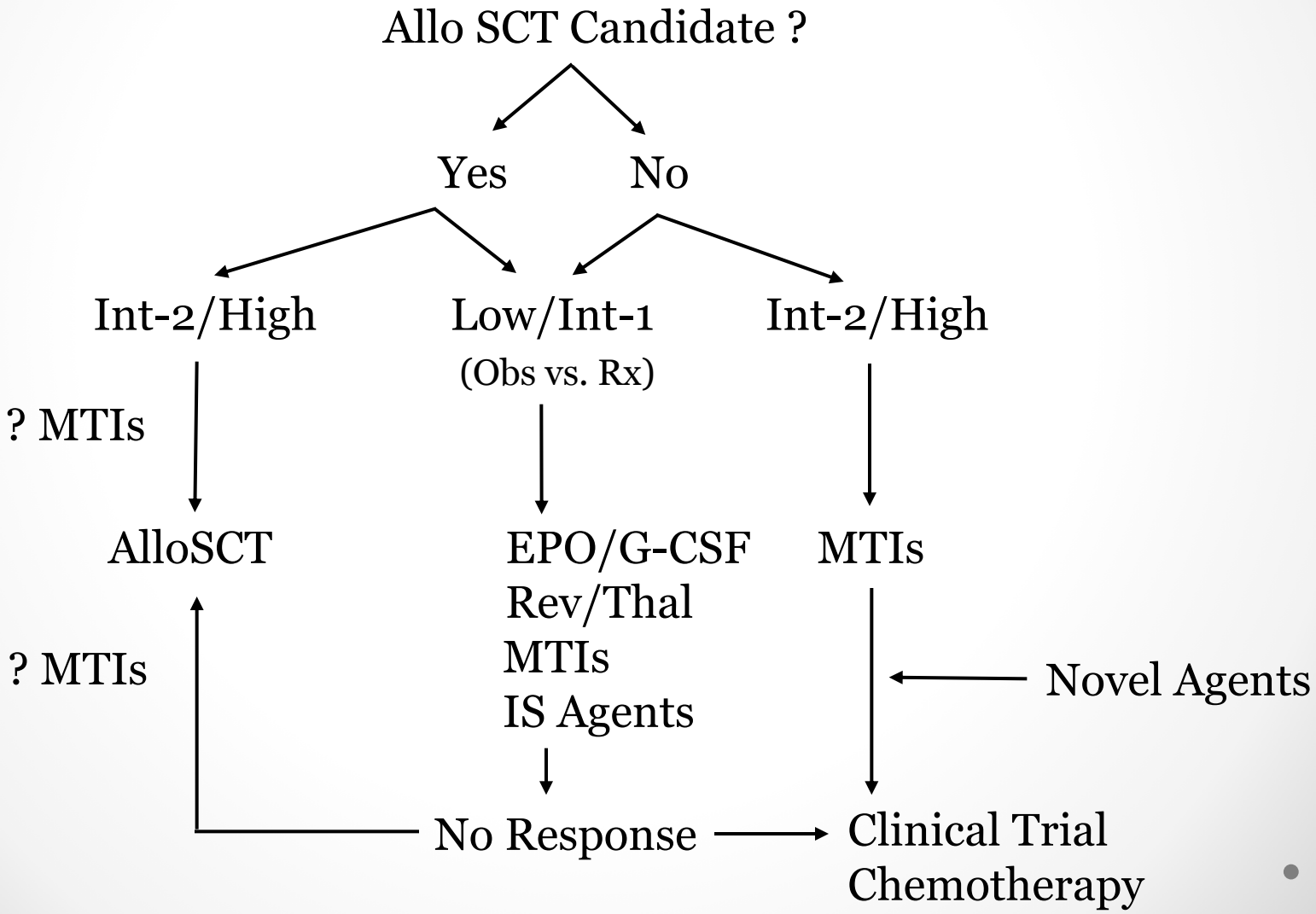
Response rates	
CR/CRi	**67% (26/39)**
PR	15% (6/39)
Refractory disease	18% (7/39)

- CR in adverse risk cytogenetics – 68% (15/22)
- 3 patients in refractory disease group went on to have CR and PR without any further treatment

Overall survival by cytogenetic risk group



MDS: Treatment Algorithm

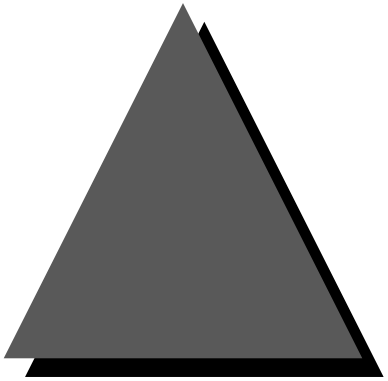


MDS - Therapeutic Challenge

Why, How, Who?

Ineffective Hematopoiesis

AML Evolution



Uniform prognostic modeling is in progress.

HI improvement is eventually lost even in low-risk patients.

High-risk patients who fail MTIs need options.

Transplant remains the only curative approach.

MDS - Therapeutic Challenge

eded

Ineffect AML

Hematop volution

Ongoi

Uniform prognost h-risk patients who
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