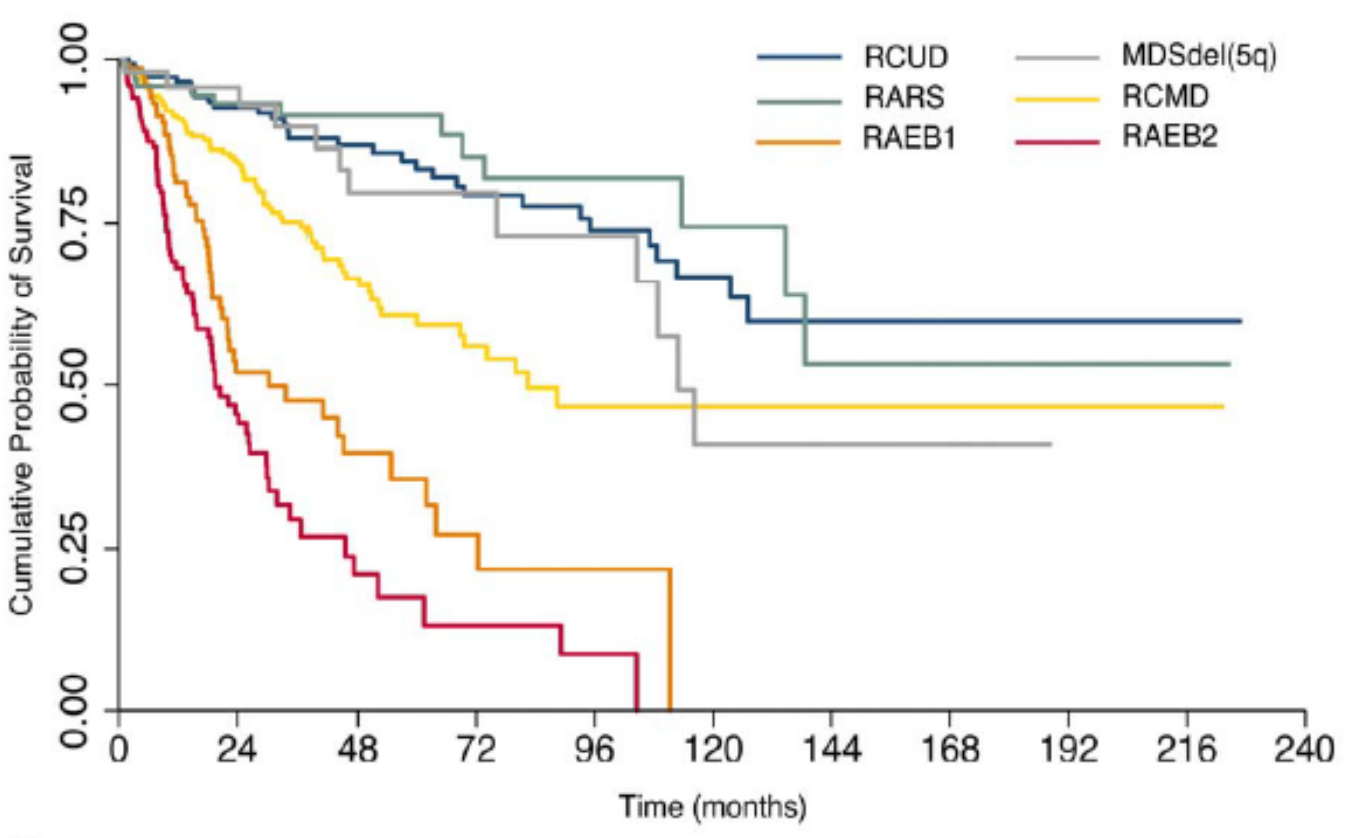
Stratificazione prognostica e scelta terapeutica individualizzata

Matteo G Della Porta

Cancer Center
IRCCS Humanitas Research Hospital
& Humanitas University
Rozzano – Milano, Italy

matteo.della_porta@hunimed.eu

MDS Pavia cohort
(1110 patients from 1990 to 2012)



Blood 2014, in press

Requirements for a prognostic score in MDS

- To stratify the natural history of the disease
- To stratify the posttherapeutical outcome
- Reproduciblity and wide implementability

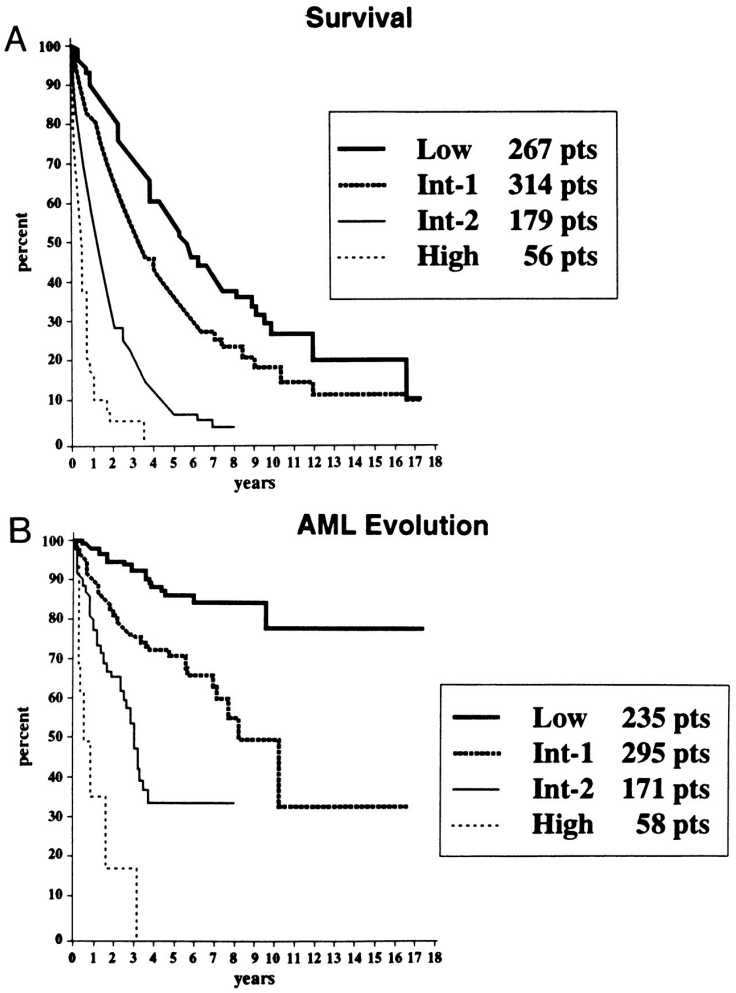
International Prognostic Scoring System for MDS

Variable	0	0.5	1	1.5	2
BM blasts %	<5	5-10	-	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias°	0/1	2/3			

**Good*: normal, -Y, del(5q), del(20q); *Poor*: complex, chromosome 7 anomalies; *Intermediate*: other abnormalities.

°Hemoglobin < 10 g/dL, absolute neutrophil count < 1,500/μL, platelet count < 100,000/μL.

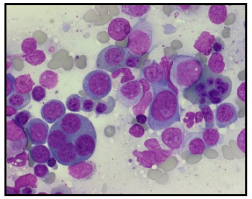
Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, 2.



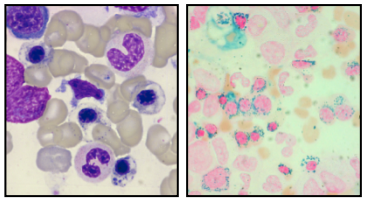
Blood 1997;89:2079-2088

WHO Classification of Myelodysplastic Syndromes

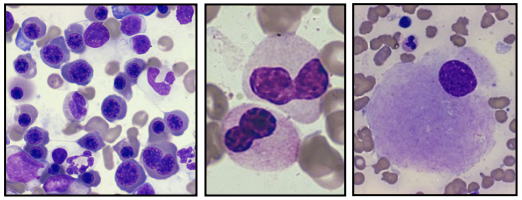
Refractory Cytopenia with Unilineage Dysplasia (RCUD)



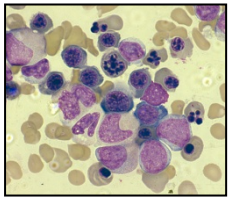
Refractory Anemia with Ring Sideroblasts (RARS)



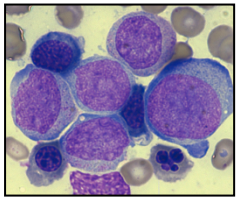
Refractory Cytopenia with Multilineage Dysplasia (RCMD)



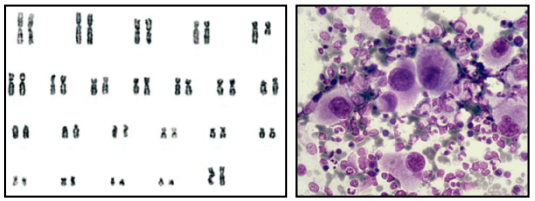
Refractory Anemia with Excess Blasts type 1 (RAEB-1)



Refractory Anemia with Excess Blasts type 2 (RAEB-2)



MDS with Isolated del(5q)



Ribosomopathies: human disorders of ribosome dysfunction

Disease	Gene Defect	Clinical Features	Cancer Risk	Diagnosis
Diamond Blackfan anemia	RPS19, RPS24, RPS17, RPL35A, RPL5, RPL11, RPS7, RPL36, RPS15, RPS27A	Macrocytic anemia Short stature Craniofacial defects Thumb abnormalities	?osteosarcoma ?MDS	RPS19/RPS24 Sequencing Elevated ADA Elevated Hgb F levels
5q-syndrome	RPS14	Macrocytic anemia Hypolobulated micromegakaryocytes	10% progression to AML	Bone marrow aspiration/biopsy with karyotype
Shwachman-Diamond syndrome	SBDS	Neutropenia/infections Pancreatic insufficiency Short stature	MDS and AML	SBDS gene testing
X-linked dyskeratosis congenita	DKC1	Cytopenias Skin hyperpigmentation Nail dystrophy Oral leukoplakia	AML Head+neck tumors	Telomere length analysis
Cartilage hair hypoplasia	RMRP	Hypoplastic anemia Short limbed dwarfism Hypoplastic hair	Non-Hodgkin lymphoma Basal cell carcinoma	RMRP sequencing
Treacher Collins syndrome	TCOF1	Craniofacial abnormalities	None reported	Physical exam (imaging if needed)

Marrow failure **Risk of AML**

Blood. 2010;115(16):3196-3205

The NEW ENGLAND JOURNAL of MEDICINE

Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

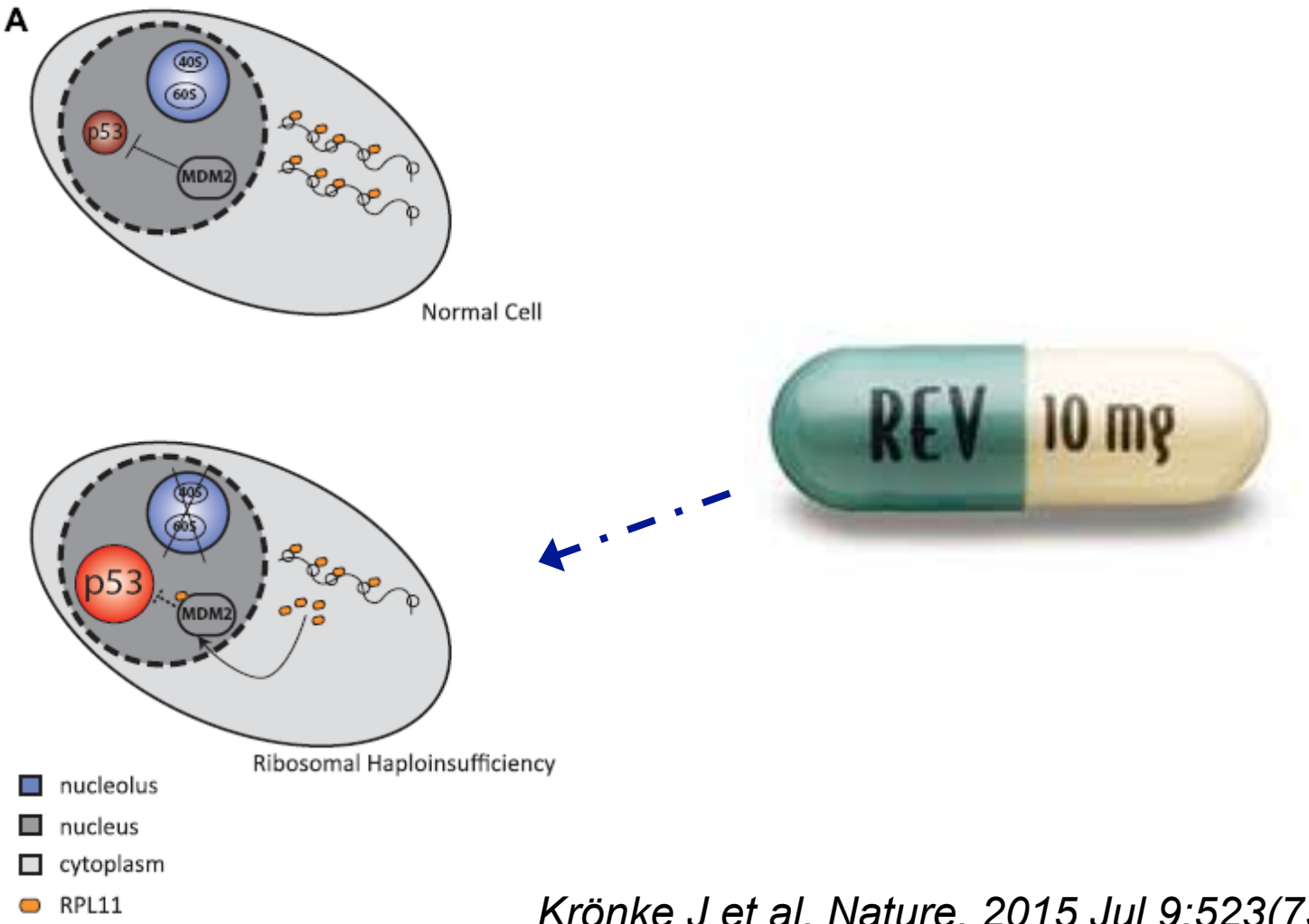
Alan List, M.D., Gordon Dewald, Ph.D., John Bennett, M.D., Aristotle Giagounidis, M.D., Azra Raza, M.D., Eric Feldman, M.D., Bayard Powell, M.D., Peter Greenberg, M.D., Deborah Thomas, M.D., Richard Stone, M.D., Craig Reeder, M.D., Kenton Wride, M.S., John Patin, M.S., Michele Schmidt, R.N., Jerome Zeldis,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

Eligibility: IPSS Low/Int-1 del(5)(q31), Transfusion dependent

Erythroid response	99/148 (67%)
Median baseline Hb	7.8 g/dL
Median Hb at response	13.4 g/dL
Complete cytogenetic remission	38/85 (45%)

N Engl J Med 2006;355:1456-65

Lenalidomide induces ubiquitination and degradation of Casein Kinase CK1α in del(5q) MDS



Krönke J et al. Nature. 2015 Jul 9;523(7559):183-8..

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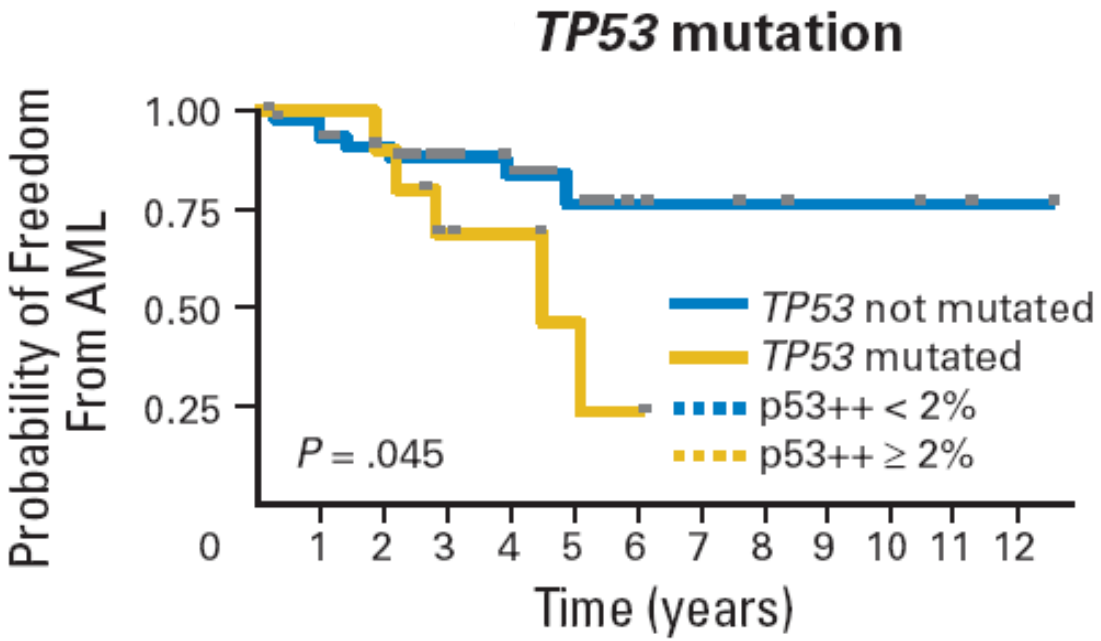
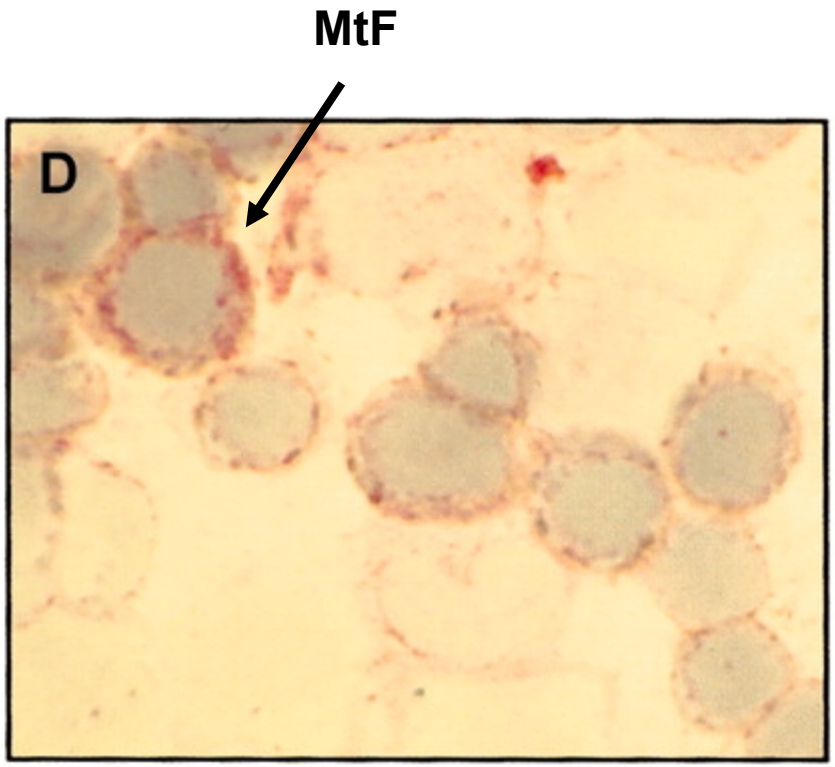
TP53 Mutations in Low-Risk Myelodysplastic Syndromes With del(5q) Predict Disease Progression



JCO 2011;29:1971-9

Refractory Anemia with Ring Sideroblasts

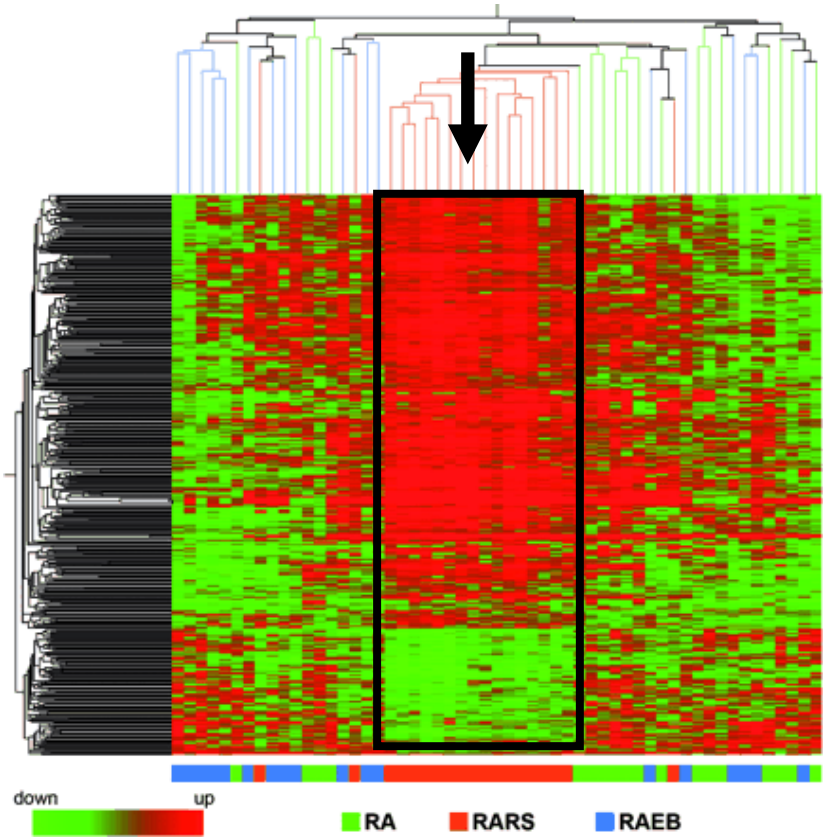
Mitochondrial Ferritin (MtF)



Iron accumulation in ringed sideroblasts is in the form of MtF

Blood. 2003;101:1996-00

Gene Expression Profile



Up-regulation of genes involved in heme synthesis (*ALAS2)*

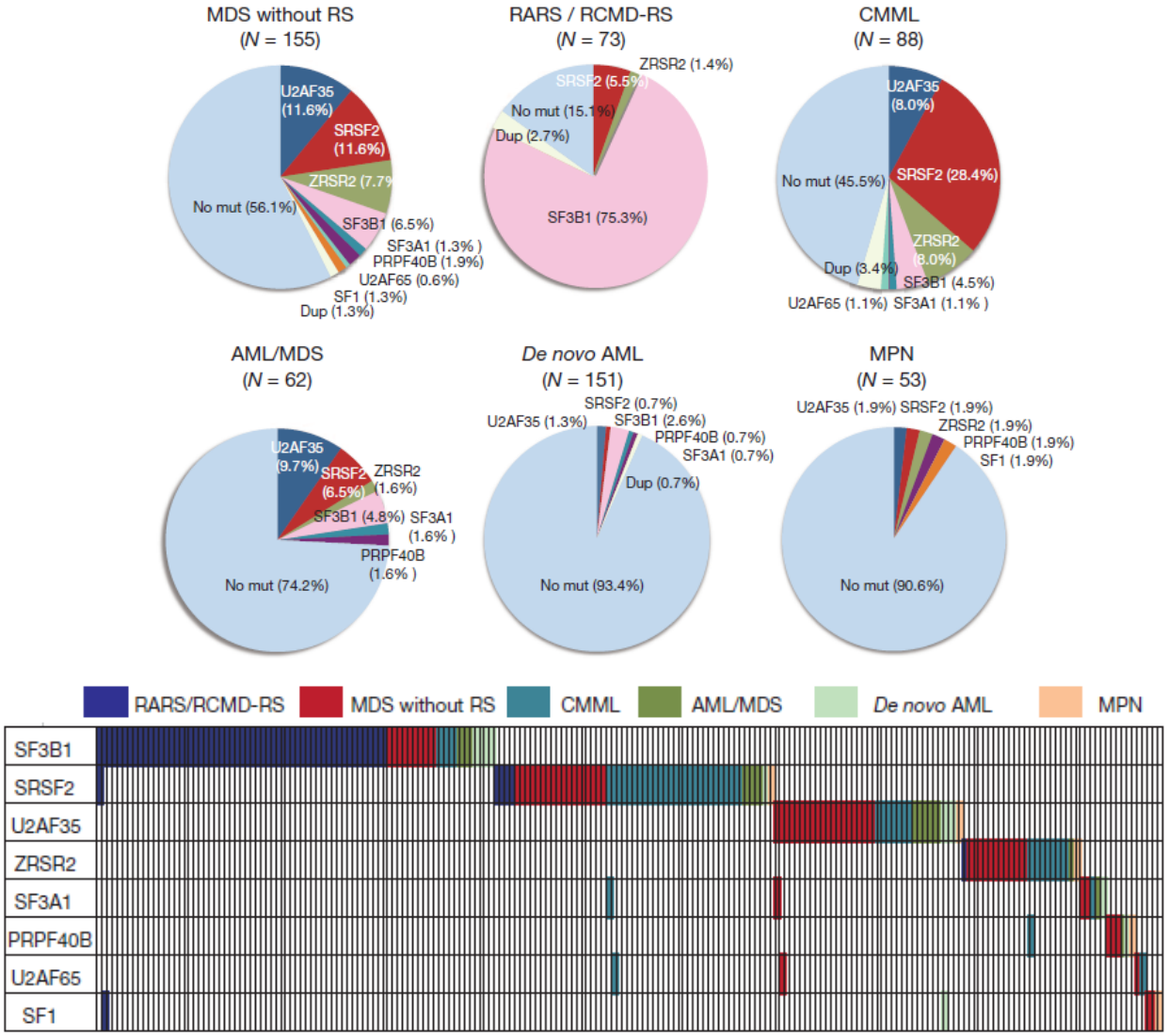
Blood. 2006;108:337-45

Somatic *SF3B1* Mutation in Myelodysplasia with Ring Sideroblasts

	Sample ID	MDS	*TET2*	*DNMT3A*	*SF3B1*
1	PD4800a	RARS	p.Q644*		
2	PD4174a	RARS			p.H662Q
3	PD4175a	RARS			p.K700E
4	PD4176a	RARS			p.H662Q
5	PD4179a	RARS			p.K700E
6	PD4180a	RARS			
7	PD4181a	RARS		p.V758fs	p.K700E
8	PD4171a	RARS		p.G510S	p.K700E

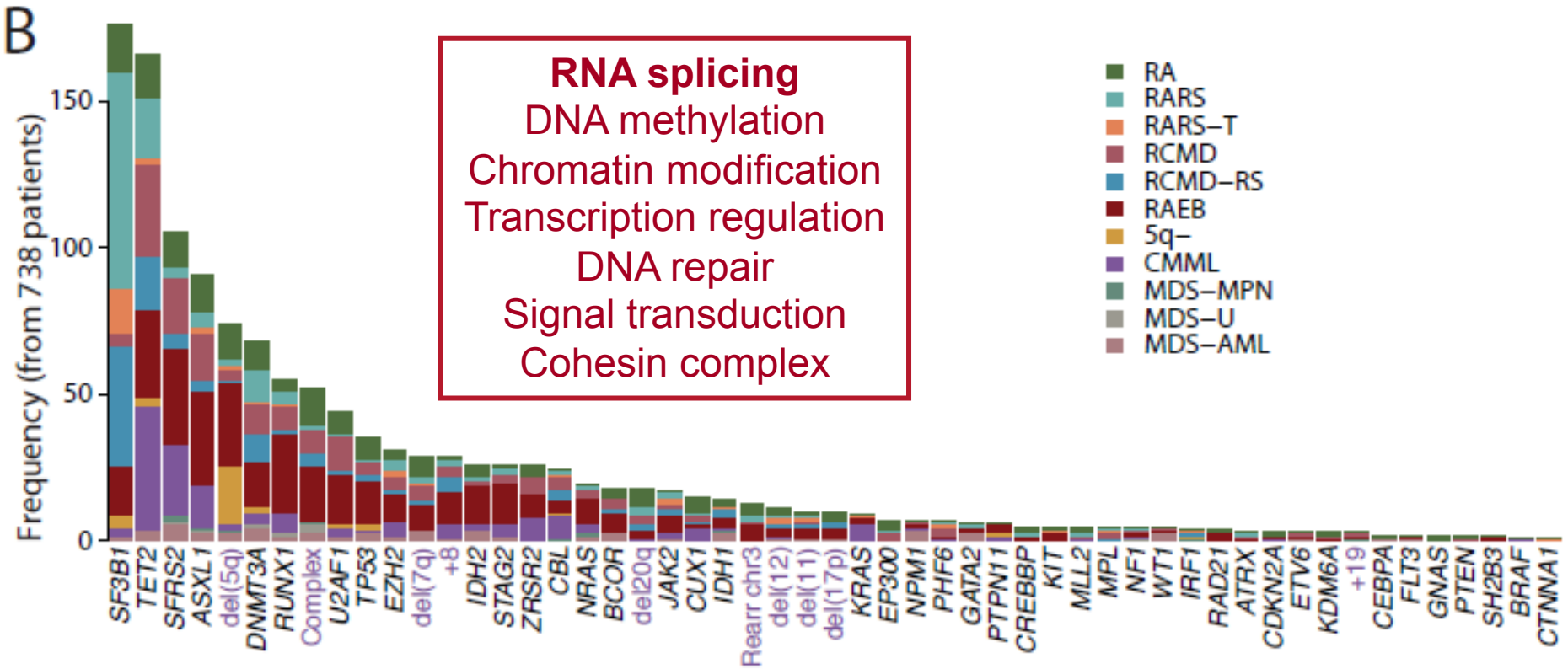
N Engl J Med 2011; 365:1384-1395

Frequent pathway mutations of splicing machinery in myelodysplasia



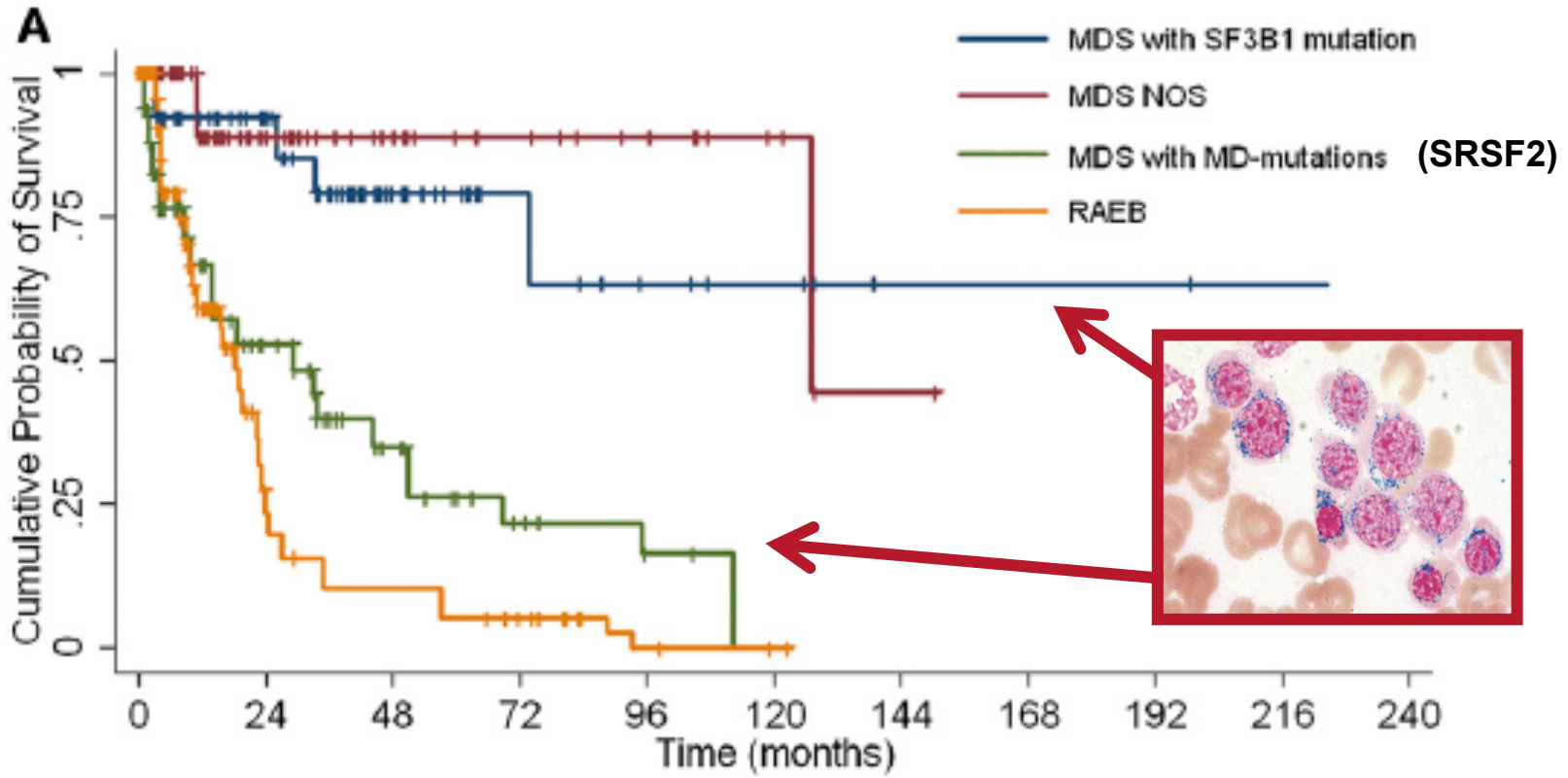
Nature. 2011 Sep 11;478(7367):64-9

Clinical Effect of Point Mutations in Myelodysplastic Syndromes



Papaemmanuil E et al. Blood. 2013;122:3616-27
Cazzola M, Della Porta MG, Malcovati L. Blood 2013;122:4021-34
Della Porta MG et al. Leukemia 2015;29:1502-13

Driver somatic mutations identify distinct disease entities within myeloid neoplasms with myelodysplasia



Malcovati et al. Blood 2014 Aug 28;124(9):1513-21
Della Porta MG et a. Leukemia. 2015;29(1):66-75

ASH 2015 - Somatic Mutations in MDS Predict Prognosis Independent of the IPSS-R (Analysis by IWG-PM)

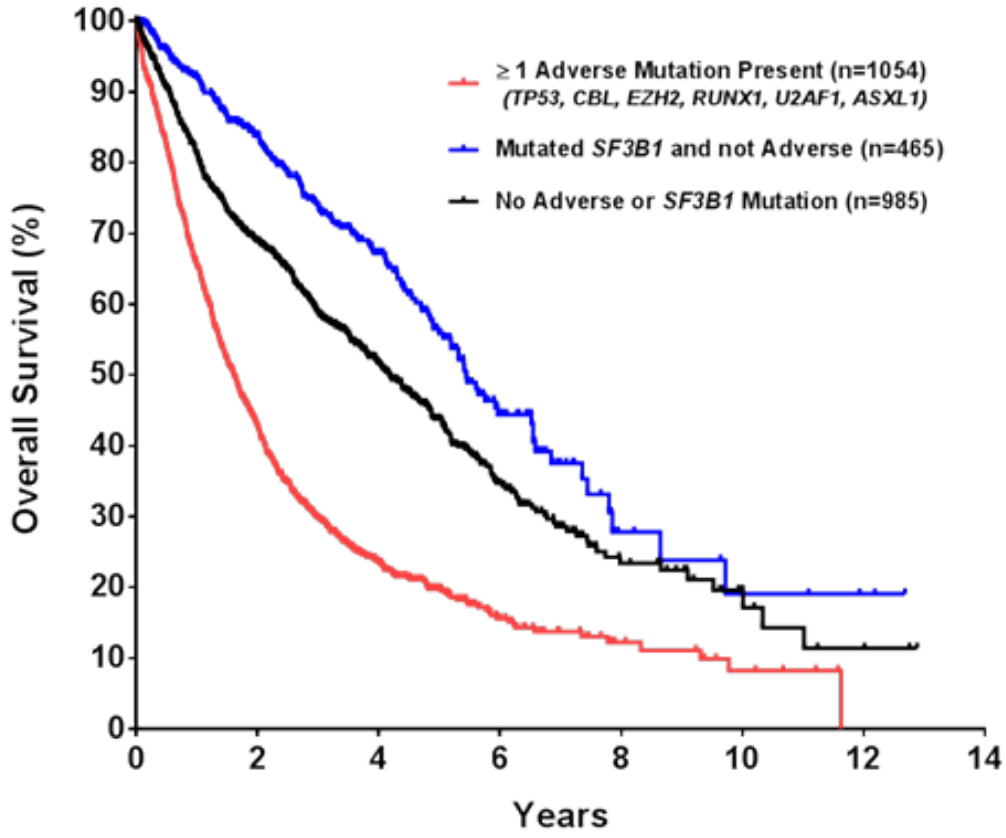


Figure 2: Kaplan-Meier curve of overall survival in years for the 2504 patients with sequence results for *SF3B1* and all six adverse genes (*TP53*, *CBL*, *EZH2*, *RUNX1*, *U2AF1*, and *ASXL1*).

Rationale for Luspatercept in Anemia

- SMAD2/3 is constitutively activated in the hematopoietic progenitors, resulting in ineffective erythropoiesis
- In preclinical murine models, luspatercept
  - Promoted maturation of late-stage erythroid precursors in vivo
  - Increased RBC, hematocrit, and Hb levels in a dose-dependent manner
- RAP-536, a murine version of luspatercept, prevented or reduced anemia in different murine anemia models, including MDS and β-thalassemia
- In a phase I clinical trial in healthy post-menopausal women
    - Luspatercept stimulated RBC production and increased Hb levels at effective dose levels

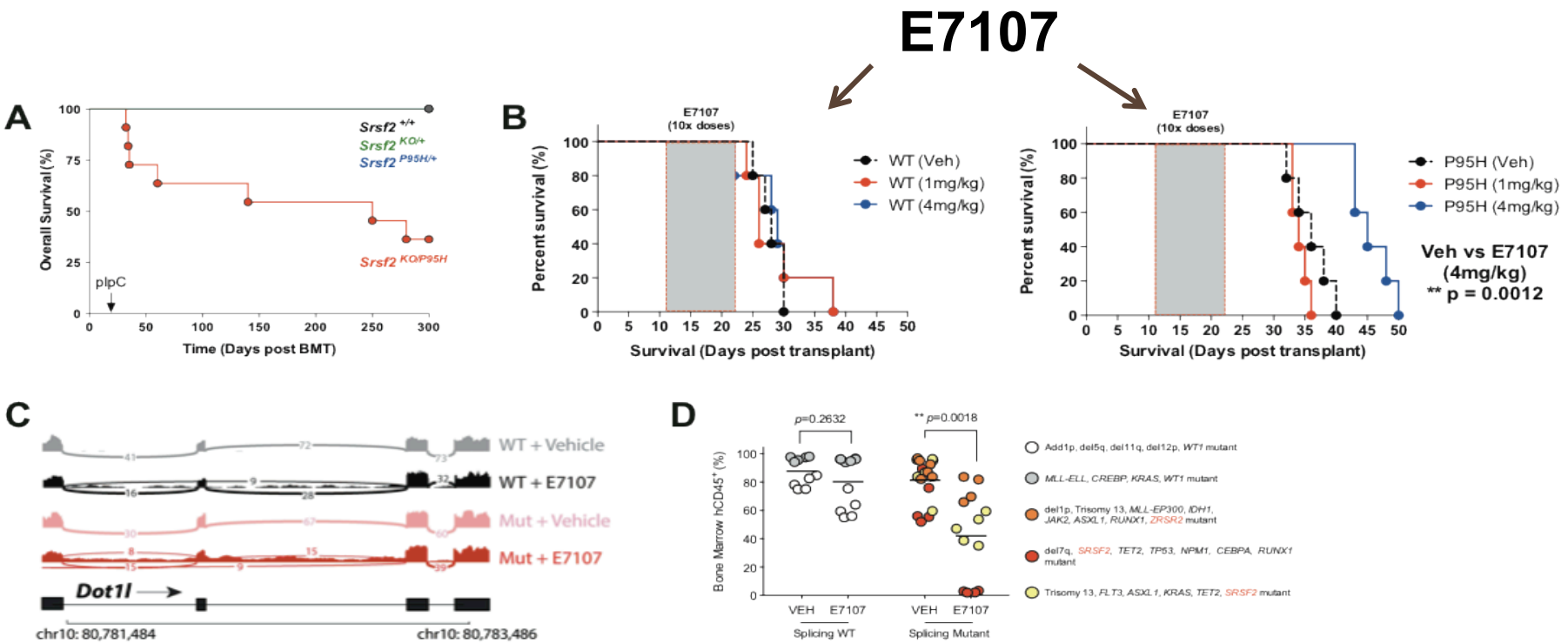
Higher response rates were observed in patients with RS, lower EPO levels, and SF mutations

Subgroup n (%)	IWG HI-E Response Rate	RBC-TI Response Rate
All	**24 of 49 (49)**	**14 of 40 (35)**
RS+	22 of 40 (55)	12 of 31(39)
RS-	2 of 7 (29)	2 of 7(29)
SF3B1 mutation	18 of 30 (60)	9 of 24 (38)
Any SF mutation	20 of 36 (58)	13 of 29 (45)
EPO < 200 U/L	16 of 25 (64)	10 of 18 (56)
EPO 200–500 U/L	4 of 11 (36)	3 of 9 (33)
EPO > 500 U/L	4 of 13 (31)	1 of 13 (8)
Prior ESA	16 of 35 (46)	10 of 29 (35)
ESA naïve	8 of 14 (57)	4 of 11 (36)

EPO, erythropoietin; ESA, erythropoietin stimulating agent ; RS, ring sideroblasts; SF, splicing factor; SF3B1, Splicing Factor 3b, Subunit 1.

Platzbecker U, et al. Biomarkers of Ineffective Erythropoiesis Predict Response to Luspatercept in Patients with Low or Intermediate-1 Risk MDS: Final Results from the Phase 2 PACE-MDS Study. *Poster presented at: Annual Meeting and Exposition of the American Society of Hematology* 2015; December 5−8; Orlando, FL. Abstract 2862.

ASH2015 - Therapeutic Targeting of Spliceosomal Mutant Myeloid Leukemias through Modulation of Splicing Catalysis



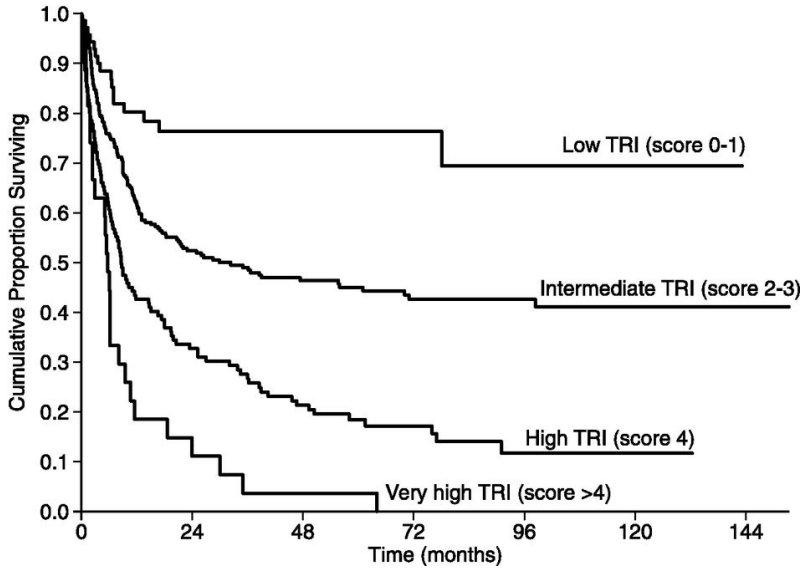
Patient-based and disease status–based risk stratification of outcome among MDS patients receiving allogeneic HSCT

A *MDS transplantation risk index (TRI) calculation*

Prognostic variable	Score values			
	0	1	2	3
Age, yr	<50	≥50	-	-
IPSS-R	low	intermediate	high	very high
Monosomal karyotype	no	yes	-	-
HCT-CI	low/intermediate	high	-	-
Refractoriness to induction chemotherapy	no	yes	-	-

TRI is calculated as the sum of individual score values

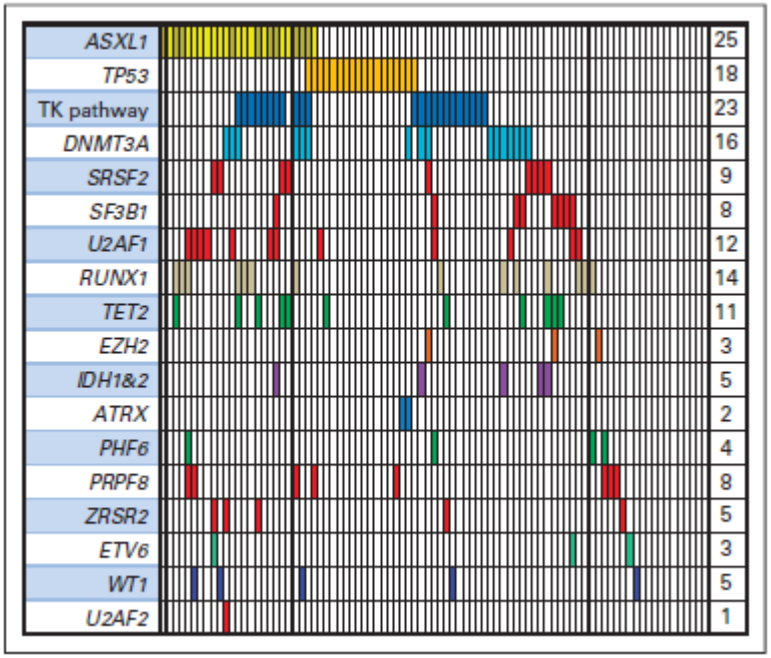
B *Posttransplantation outcome according to TRI*

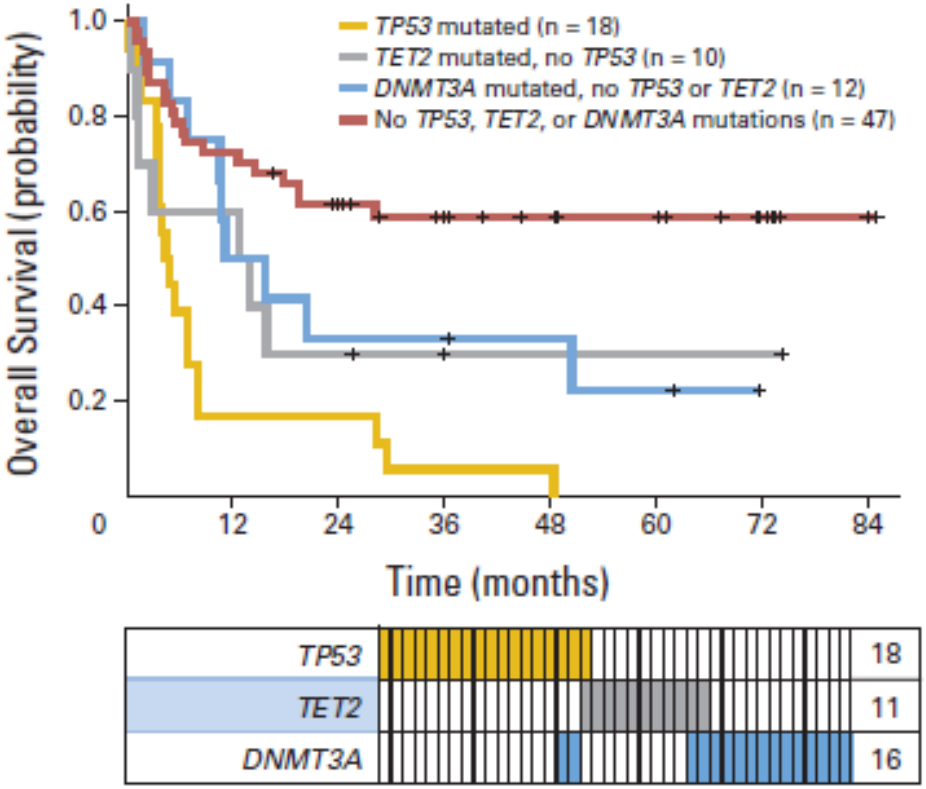


Della Porta MG et al. Blood 2014;123:2333-2342

GITMO

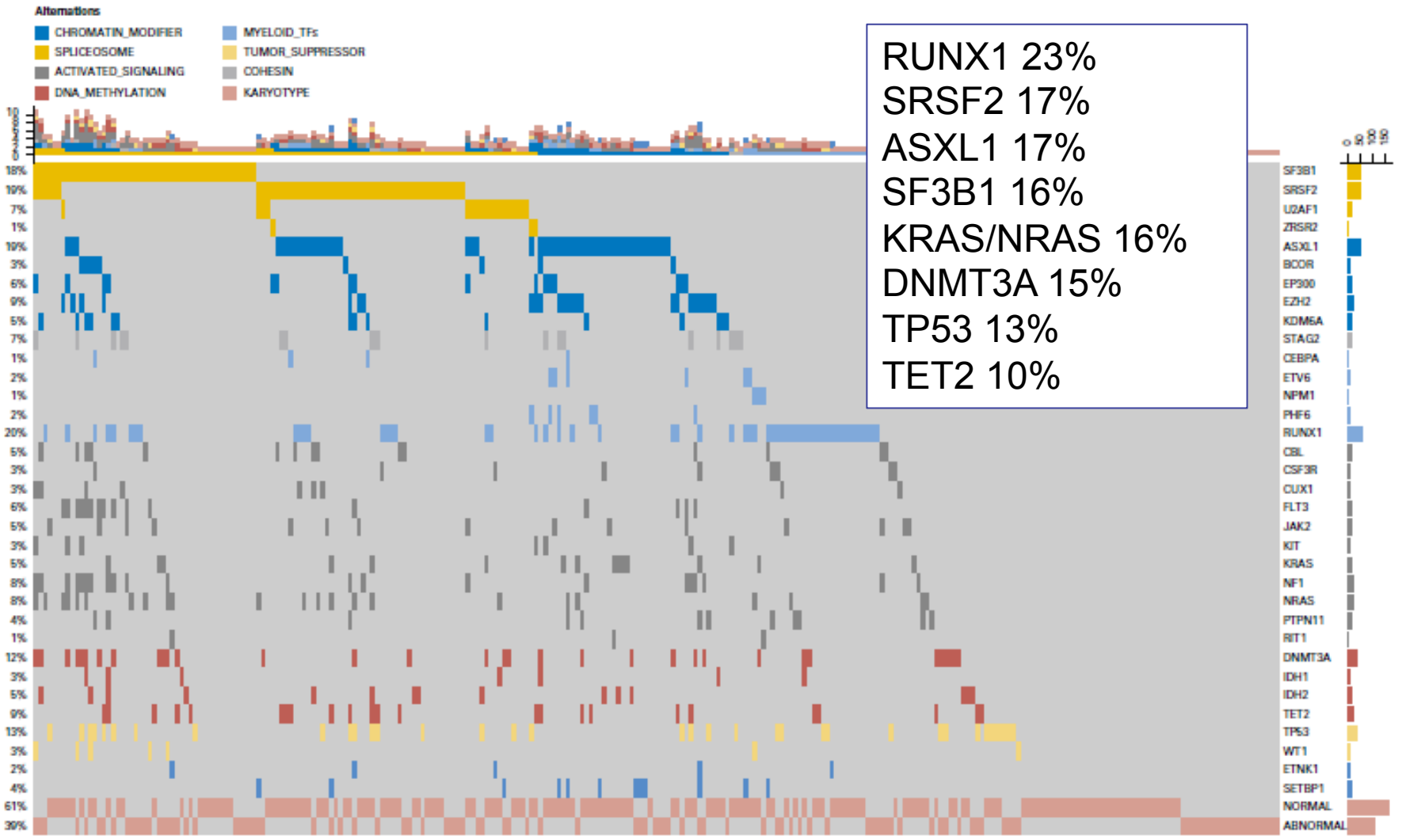
Somatic Mutations Predict Poor Outcome in Patients With MDS After Hematopoietic Stem-Cell Transplantation





Bejar R et al. J Clin Oncol 2014;32:2691-2698.

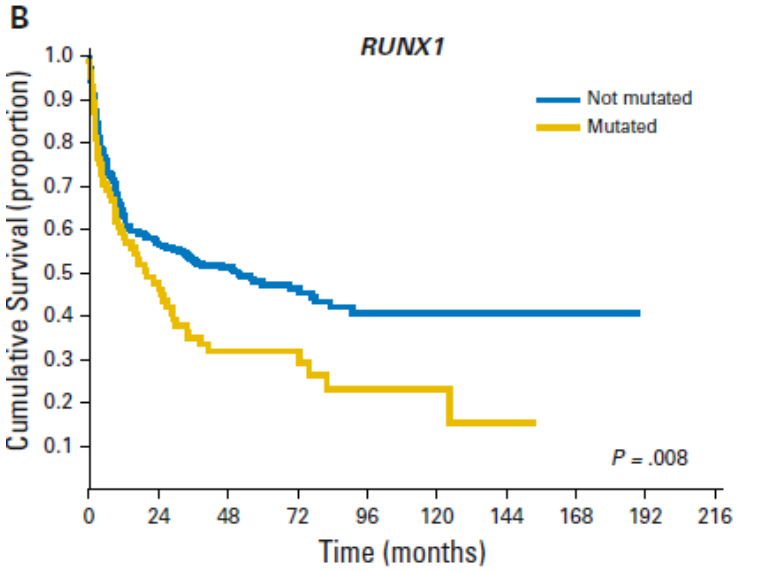
Mutation patterns observed in MDS treated with allo-HSCT

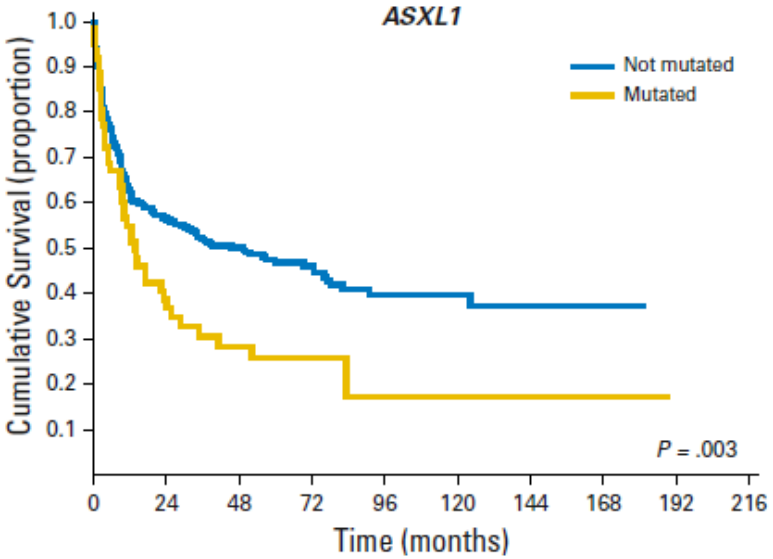


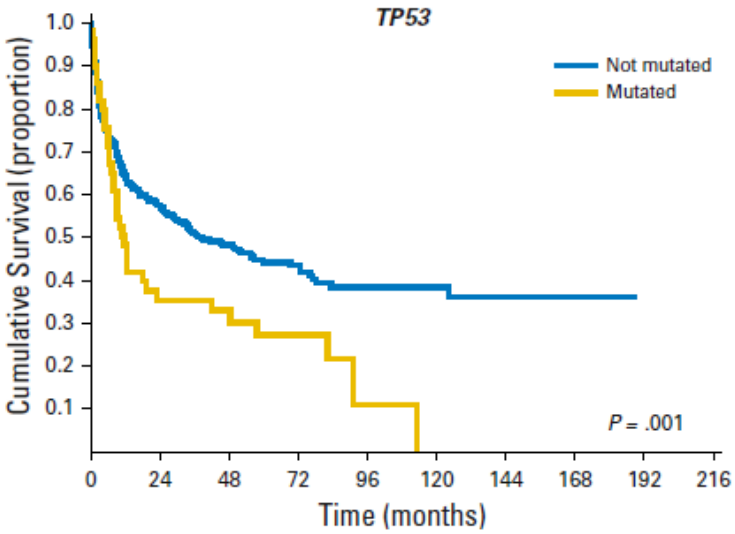
JCO doi:10.1200/JCO.2016.67.3616

GITMO

Relationship between type of oncogenic mutations and overall survival of MDS receiving allo-HSCT







Multivariable analysis				
MDS patients	**Probability of relapse**		**Overall Survival**	
Variable	HR	P	HR	P
ASXL1	1.89	.003	1.72	.008
RUNX1	1.67	.02	1.59	.035
TP53	1.90	.019	1.82	.022

Matteo G. Della Porta et al. JCO doi:10.1200/JCO.2016.67.3616

Mutation Pattern at Disease Relapse After HSCT in Patients With MDS and MDS/AML

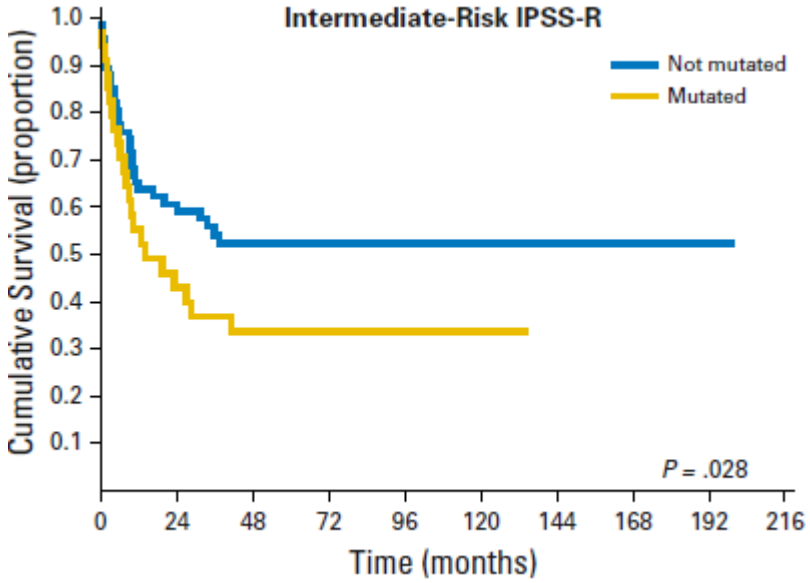
GITMO

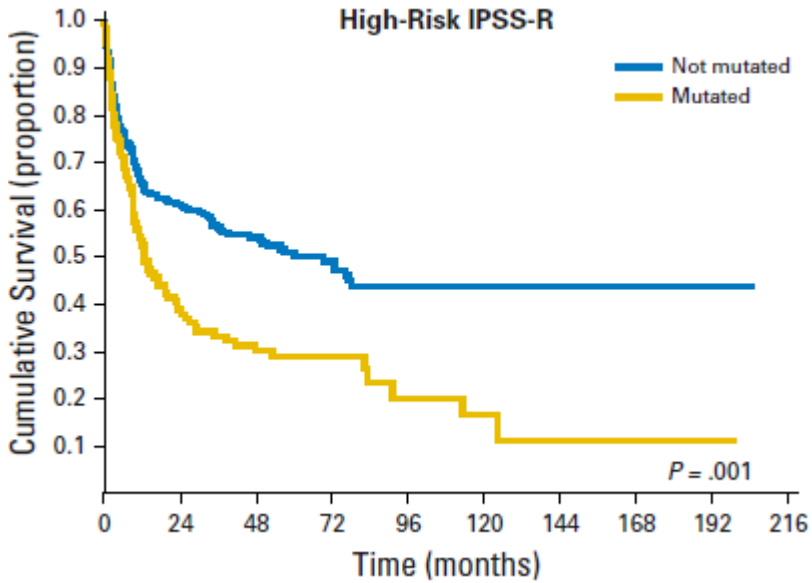
Patient	WHO Category (before HSCT)	Founding Clone (before HSCT)	Clonal Evolution (disease relapse)
GITMO 1	RAEB-2	*PTPN11*	Founder clone recurs
GITMO 2	MDS/AML	*NPM1*	Founder clone recurs
GITMO 3	RAEB-1	*RUNX1*	Founder clone recurs
GITMO 4	RAEB-2	*DNMT3A*	A subclone expands (*IDH1*)
GITMO 5	RAEB-1	*STAG2*	Founder clone recurs
GITMO 6	MDS/AML	*SRSF2*	Founder clone recurs
GITMO 7	RAEB-2	*EZH2*	A subclone expands (*RUNX1*)
GITMO 8	RCMD	*SRSF2*	Founder clone recurs
GITMO 9	RAEB-2	*SRSF2*	Founder clone recurs

Matteo G. Della Porta et al. JCO doi:10.1200/JCO.2016.67.3616

JOURNAL OF CLINICAL ONCOLOGY ASCO

Clinical Impact of Somatic Mutations in Patients With MDS Receiving HSCT, Stratified According to IPSS-R

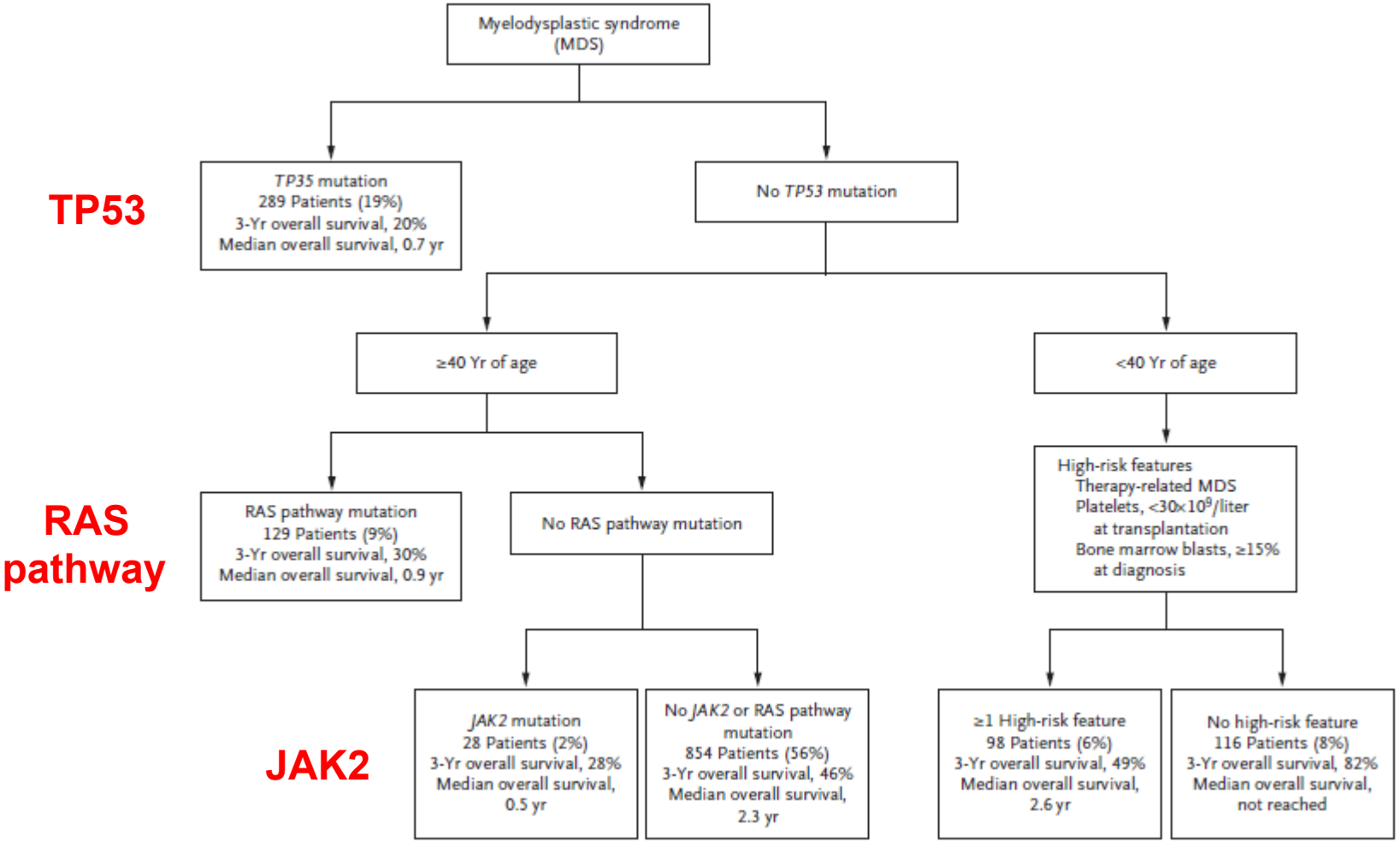




Matteo G. Della Porta et al. JCO doi:10.1200/JCO.2016.67.3616

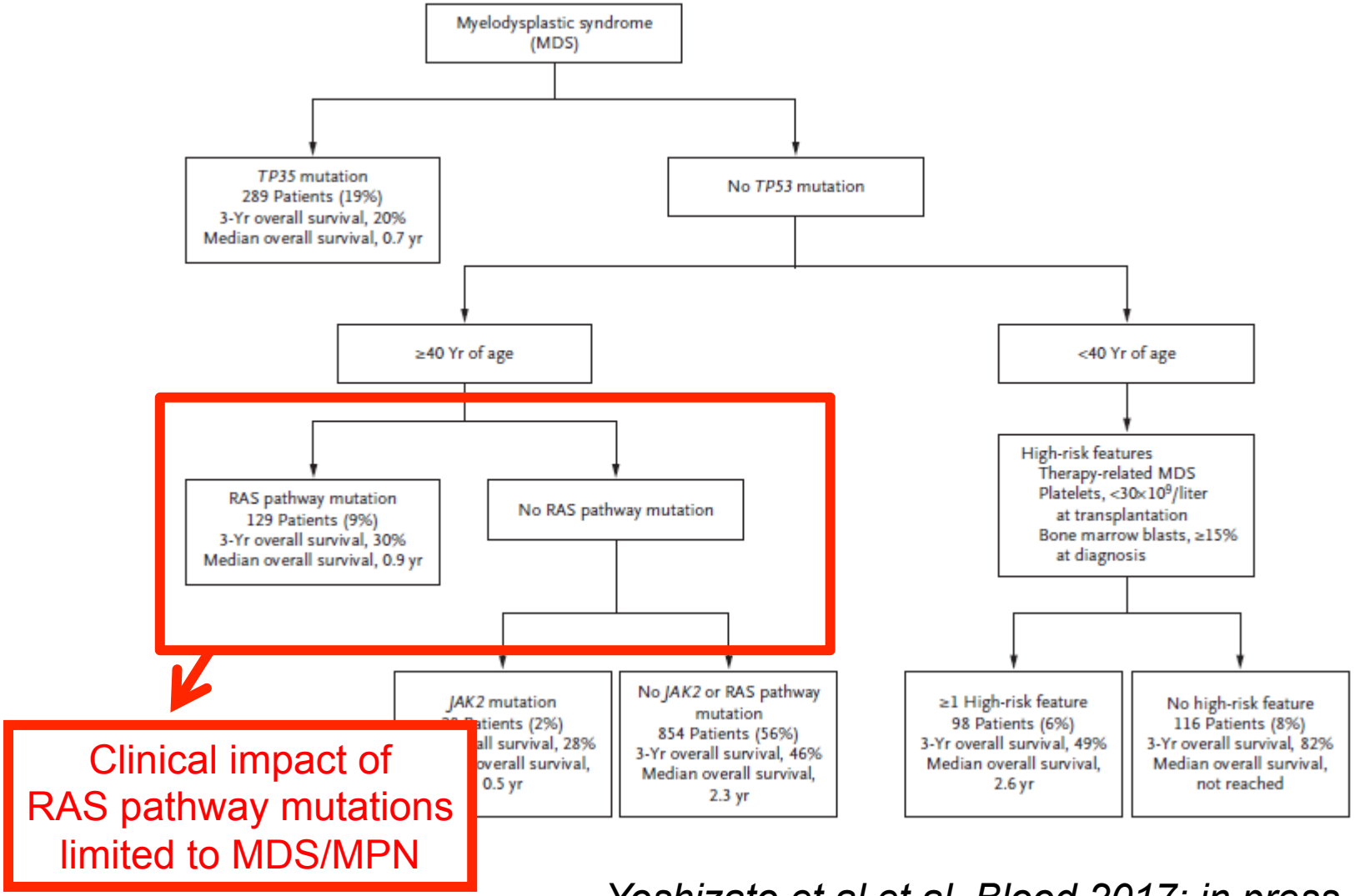
JOURNAL OF CLINICAL ONCOLOGY ASCO

Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation



Lindsley, RC et al. N Engl J Med 2017;376:536-47.

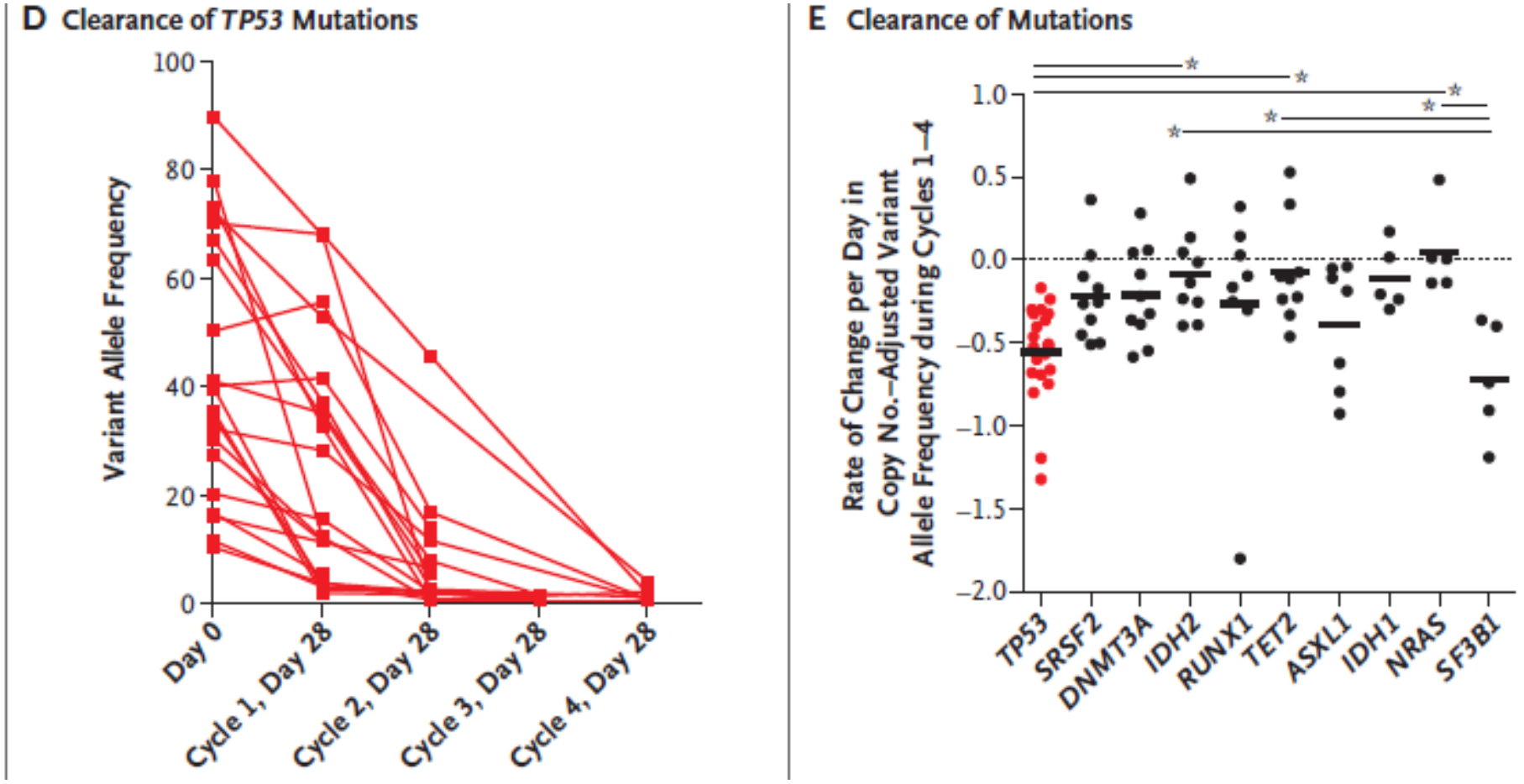
Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation



Clinical impact of RAS pathway mutations limited to MDS/MPN

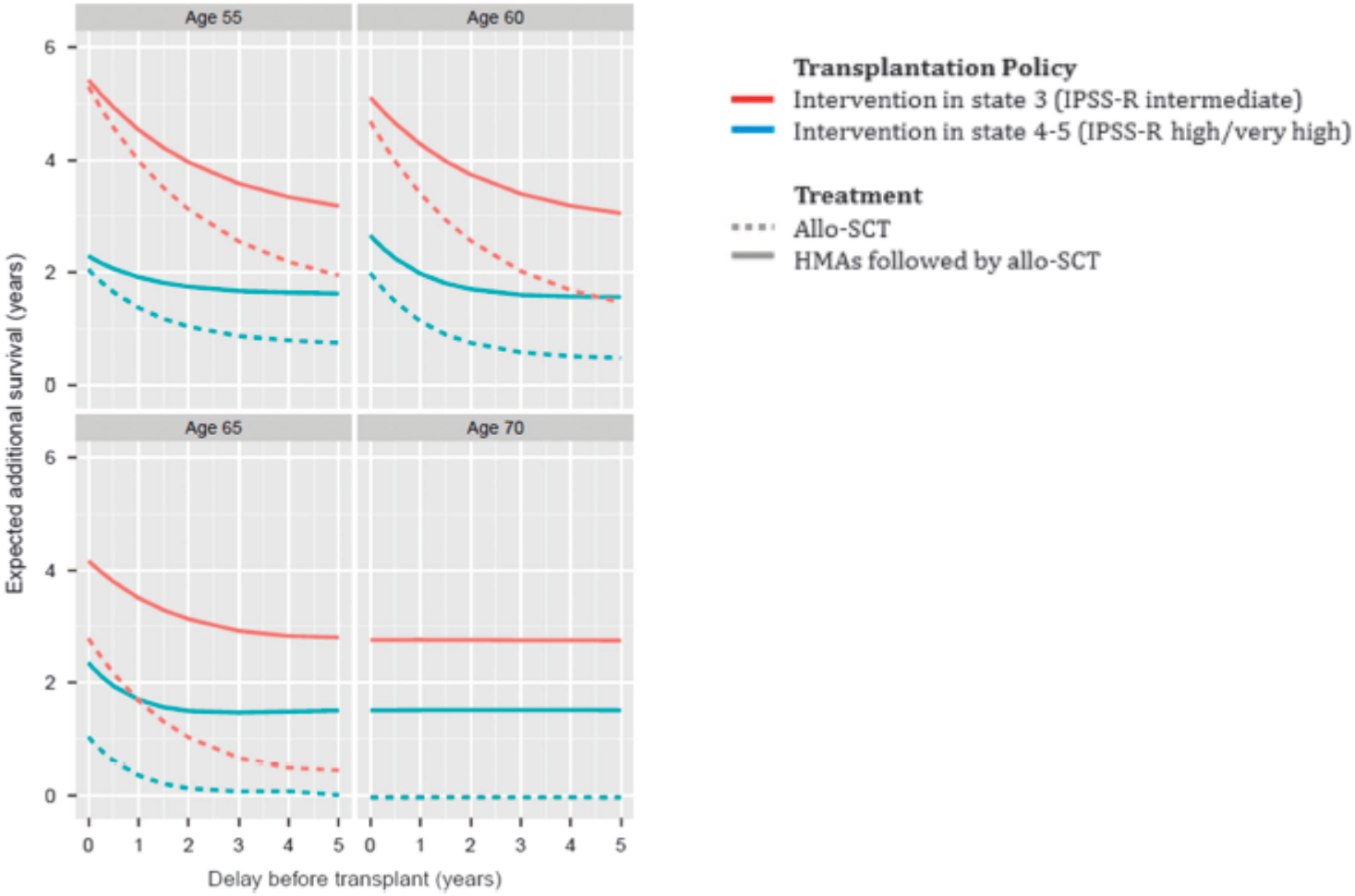
Yoshizato et al et al. Blood 2017; in press

TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes



Welch JS et al. N Engl J Med 2016;375:2023-36.

Expected gain of life expectancy in high risk MDS treated with HMAs before HSCT vs. HSCT alone



Della Porta MG et al. Leukemia 2017, in press

GITMO

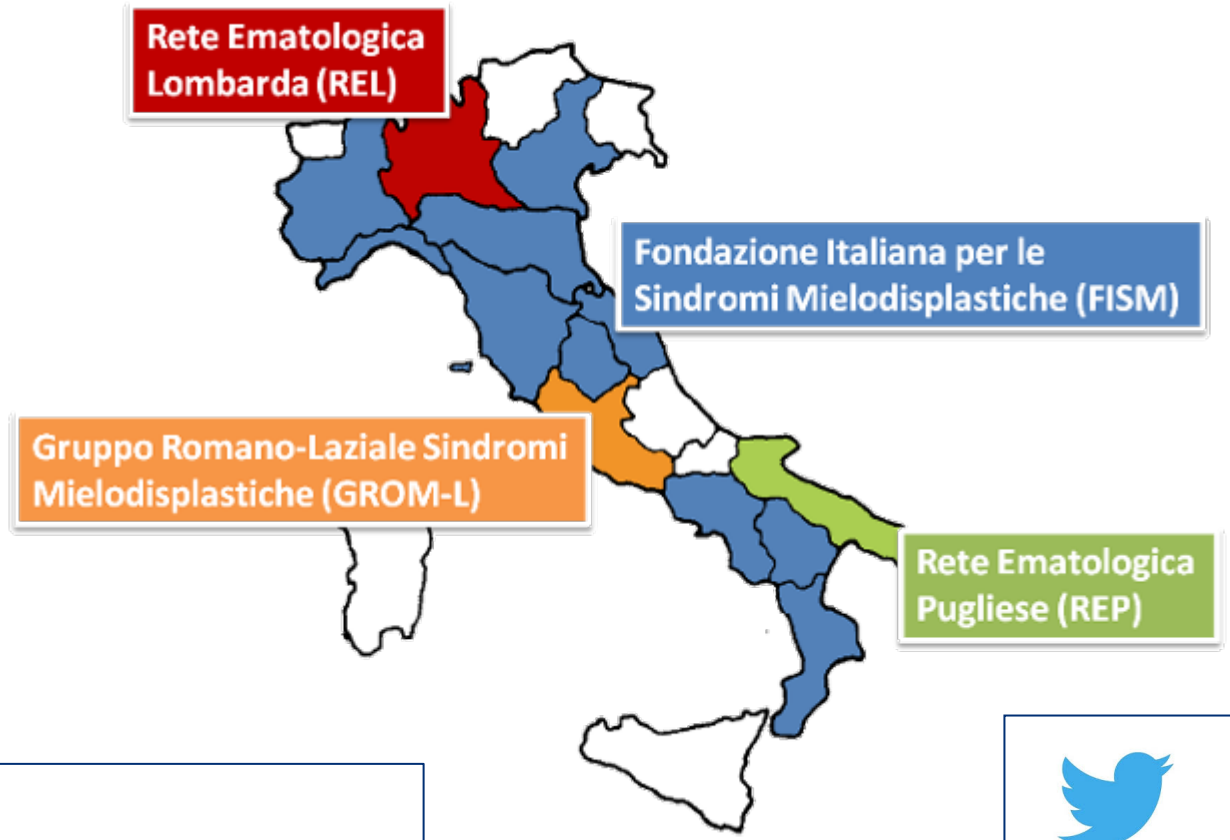
Summary

- The definition of molecular basis of MDS is expected to improve diagnosis, prognostic assessment and clinical decision-making
- Preliminary data indicate that mutation screening may affect clinical decision making in MDS and improve the capability to predict treatment response at individual patient level
- Molecular biomarkers will be a solid basis for the implementation of personalized medicine programs in hematology

Associazione Italiana Pazienti con Sindrome Mielodisplastica AIPaSiM

www.italianMDSnetwork.it

italian MDS network



Contatti:

info@italianMDSnetwork.it

@itaMDSnet

Valeria Sanitni, Maria Teresa Voso, Susanna Fenu, Esther Oliva, Emanuele Angelucci, Enrico Balleari, Giorgina Specchia, Enrica Morra, Mario Cazzola, Matteo Della Porta

www.italianMDSnetwork.it

IL NETWORK ITALIANO DELLE RETI MDS

Riunisce le Reti di patologia che operano sul territorio nazionale, con lo scopo di promuovere:

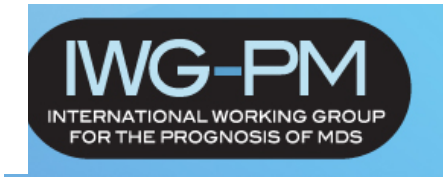
- la raccolta di dati epidemiologici su grandi popolazioni di pazienti
- la diffusione di standard di cura e assistenza sanitaria uniformi a livello nazionale
- la diffusione delle reti di patologia nelle realtà territoriali che non hanno ancora una modello organizzativo di network
- la nascita di progetti di ricerca condivisi
- lo sviluppo di studi clinici innovativi

Con il supporto di

Acknowledgments

Marianna Rossi
Elisabetta Todisco
Chiara Milanesi
Elena Saba
Marta Monari
Rosanna Asselta
Stefano Duga
Armando Santoro

Emilio Paolo Alessandrino
Andrea Bacigalupo
Alessandro Rambaldi
Francesca Bonifazi
GITMO centers



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Elli Papaemmanuil

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Enrica Morra
Commissione REL MDS

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MRC Biostatistics Unit
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