Treatment of low risk MDS

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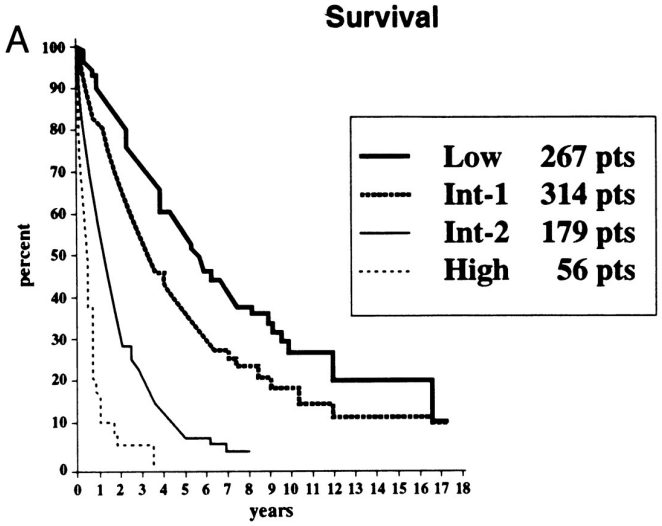
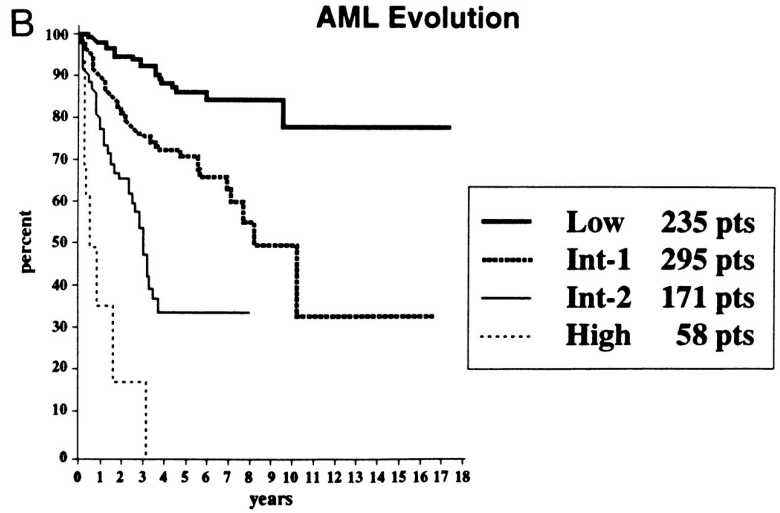
International Prognostic Scoring System for MDS

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			





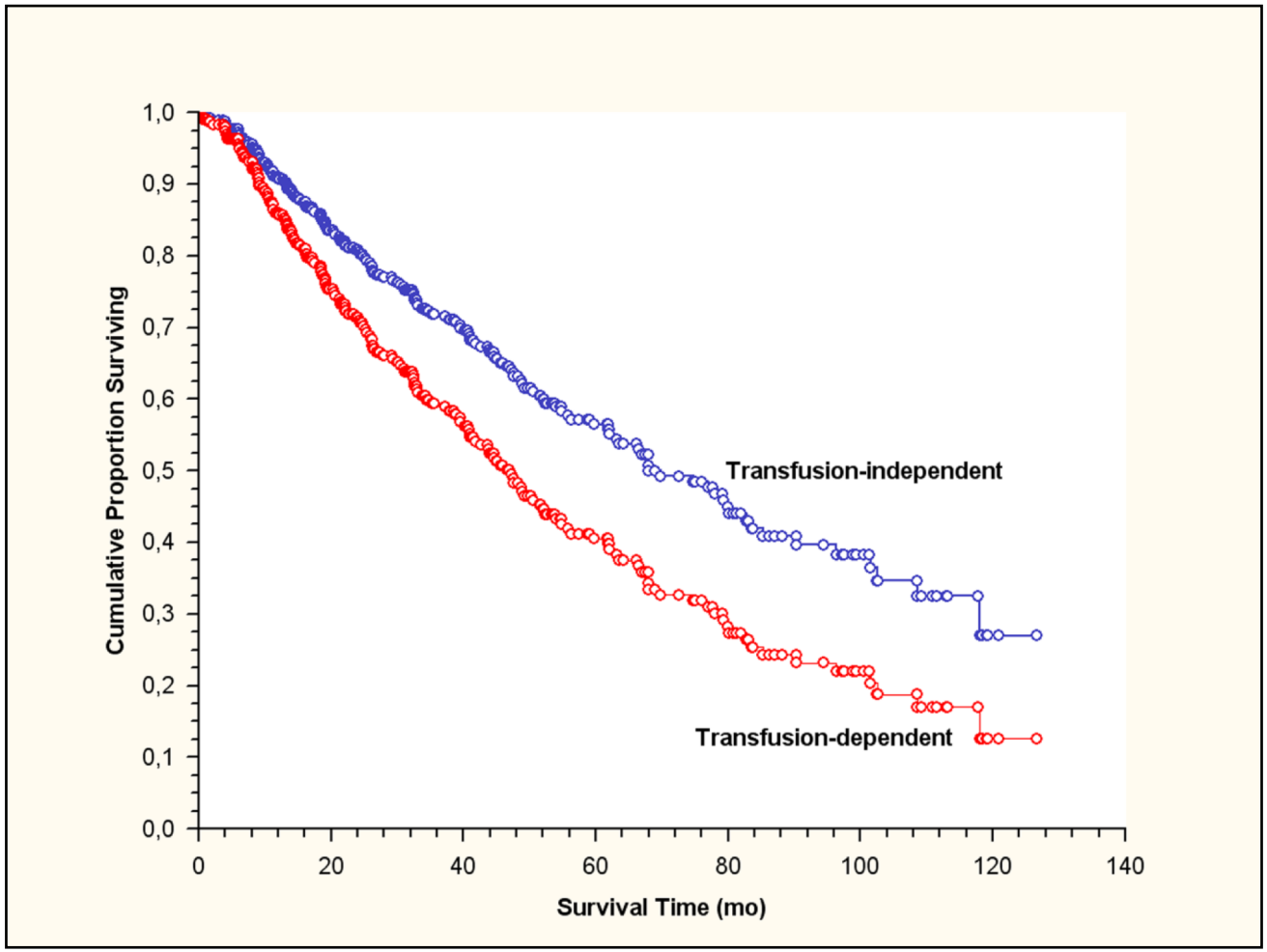
*_Good_: normal, -Y, del(5q), del(20q); _Poor_: complex, chromosome 7 anomalies; _Intermediate_: other abnormalities.

°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.

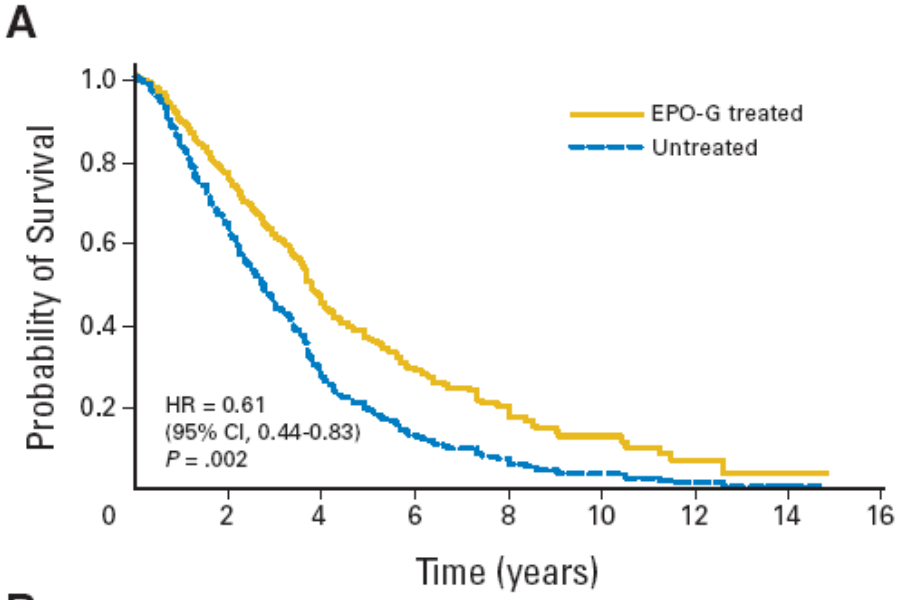
Blood 1997;89:2079-2088

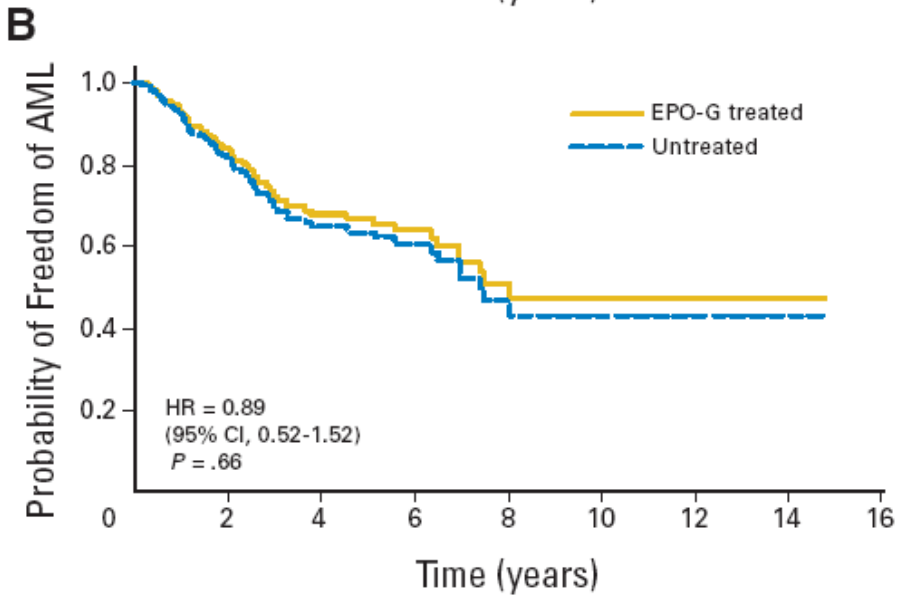
Survival of MDS patients according to transfusion-dependency

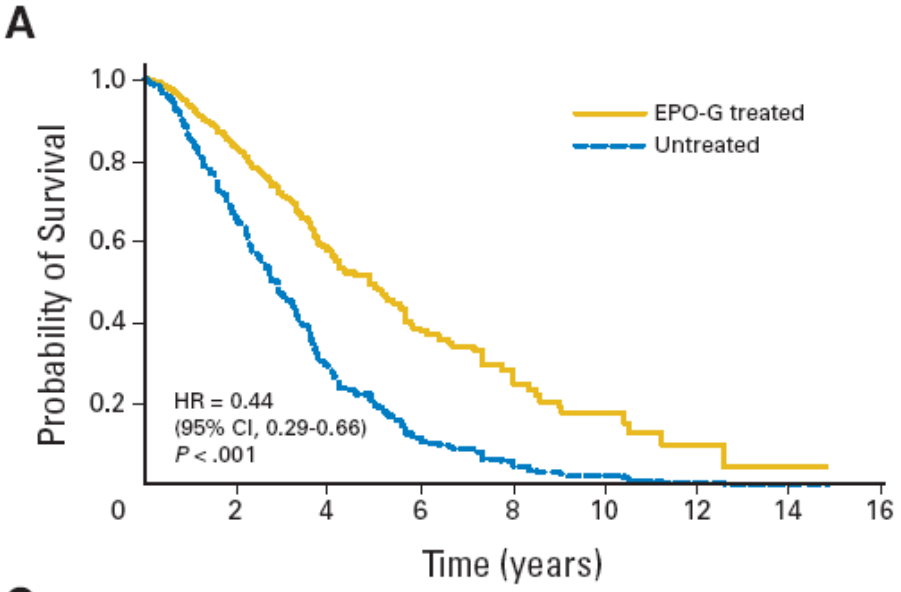


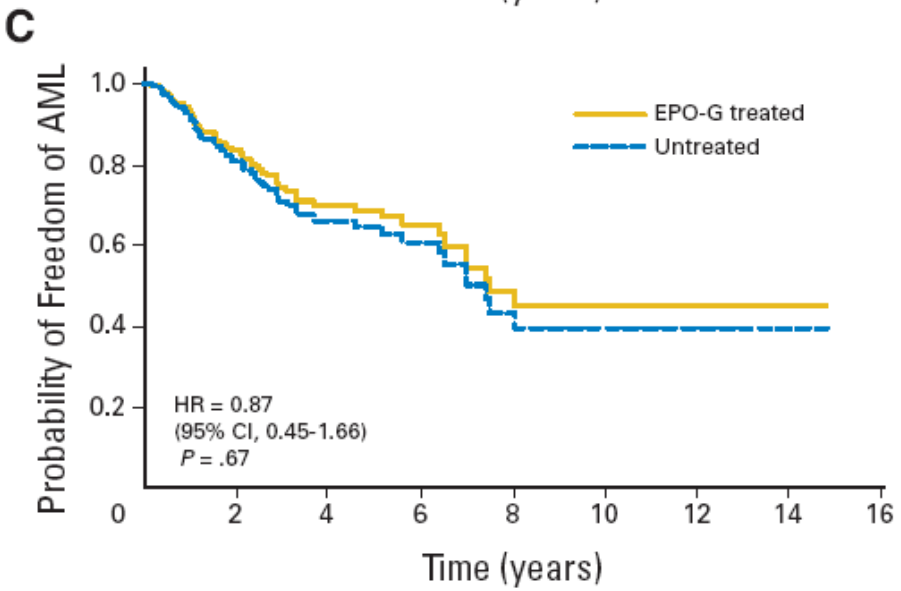
N Engl J Med 2005;352:536-8

Erythropoietin and Granulocyte-Colony Stimulating Factor Treatment Associated With Improved Survival in MDS









J Clin Oncol. 2008;26:3607-13

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

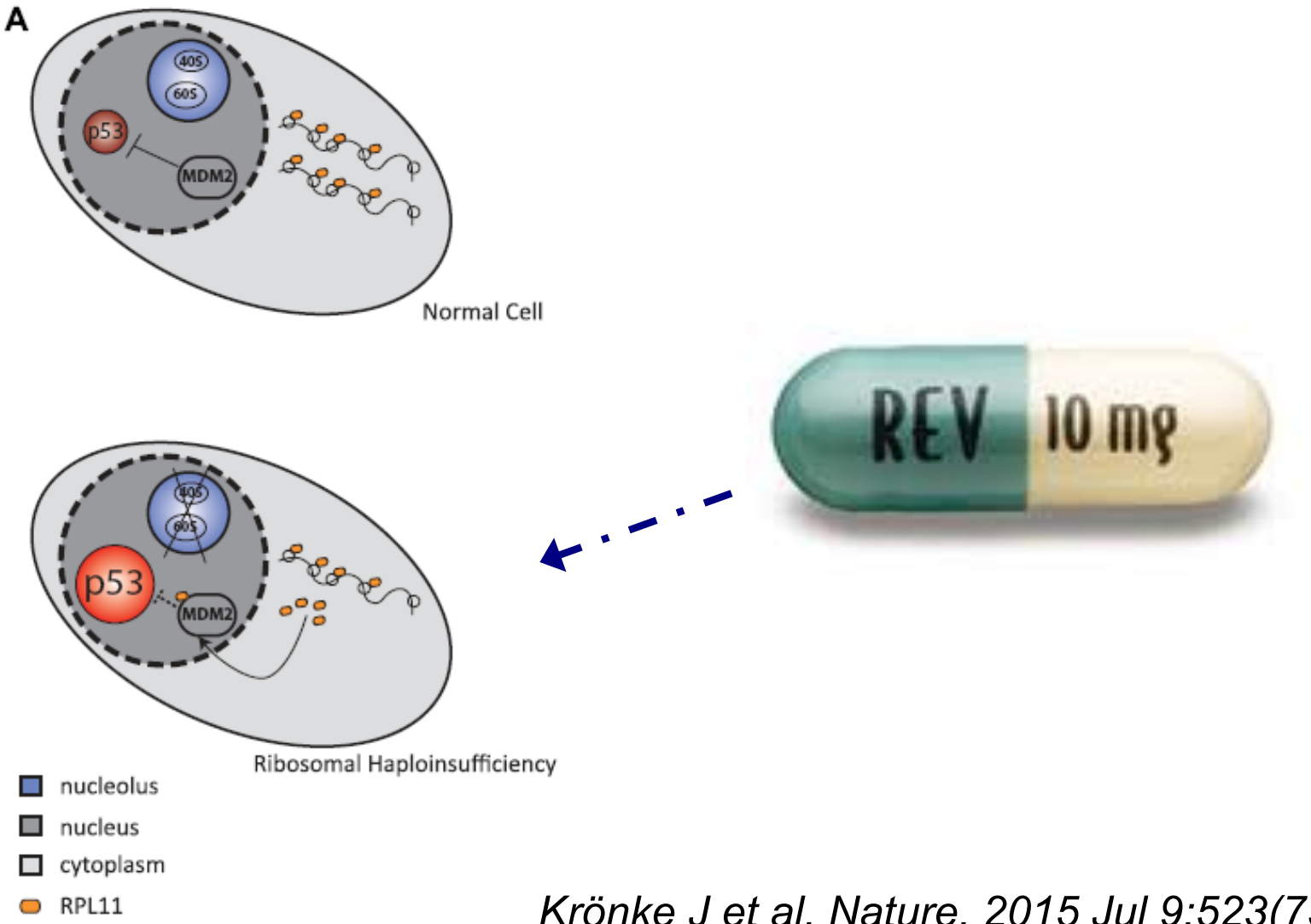
Alan List, M.D., Gordon Dewald, Ph.D., John Bennett, M.D., Aristotle Giagounidis, M.D., Azra Raza, M.D., Eric Feldman, M.D., Bayard Powell, M.D., Peter Greenberg, M.D., Deborah Thomas, M.D., Richard Stone, M.D., Craig Reeder, M.D., Kenton Wride, M.S., John Patin, M.S., Michele Schmidt, R.N., Jerome Zeldis, 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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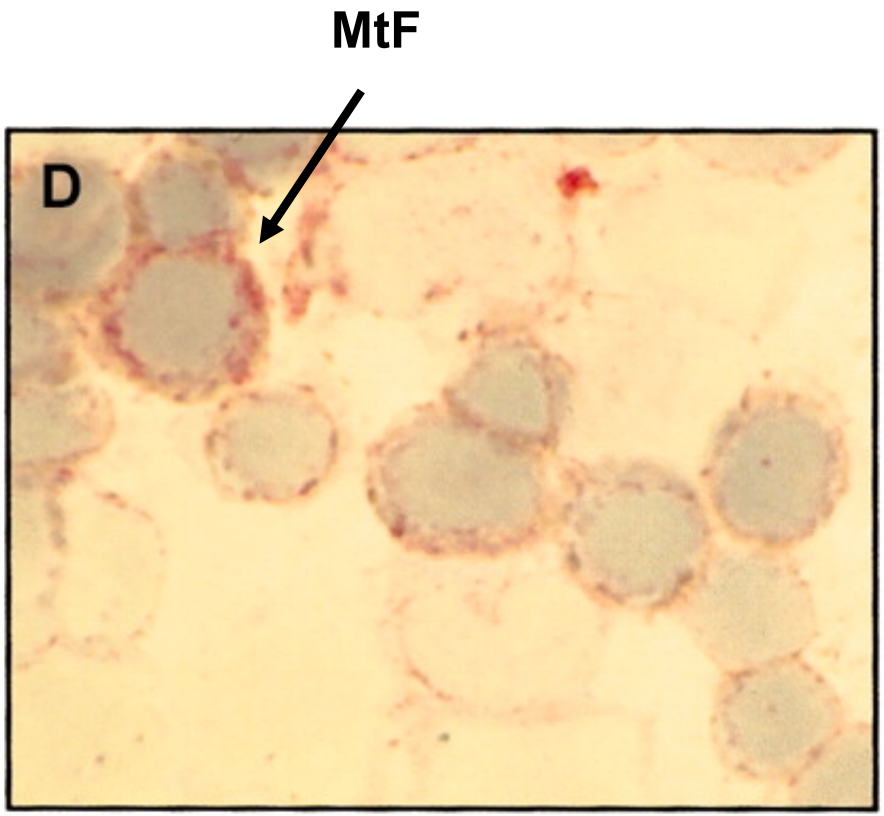
Refractory Anemia with Ring Sideroblasts

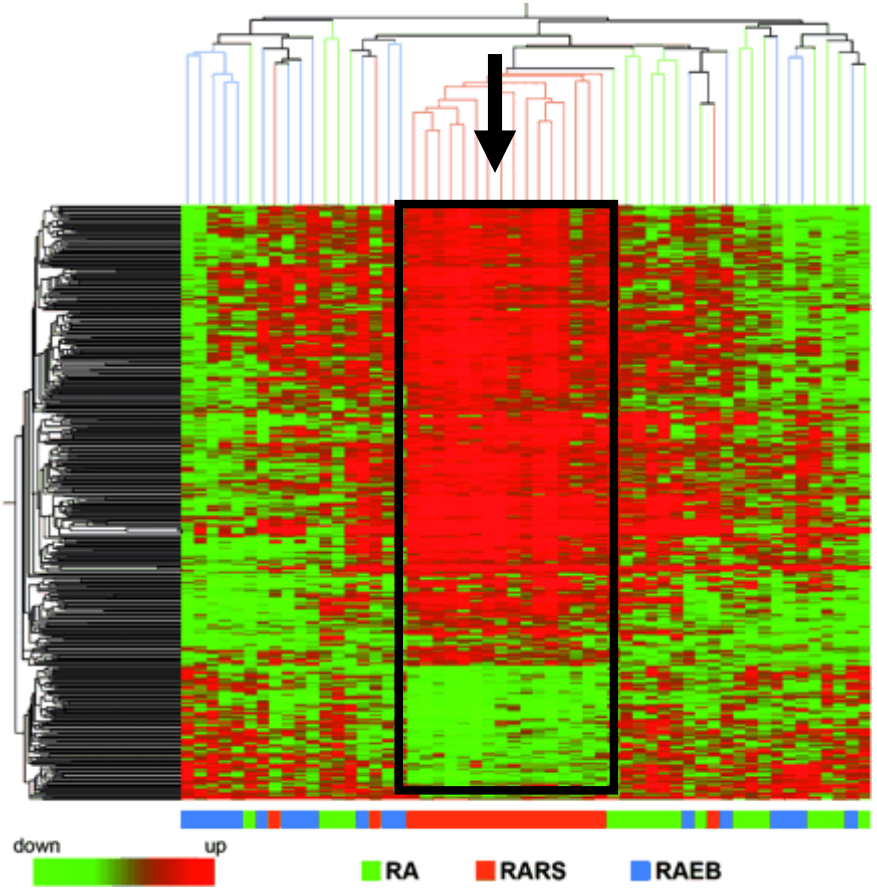
Mitochondrial Ferritin (MtF)



Iron accumulation in ringed sideroblasts is in the form of MtF

Blood. 2003;101:1996-00

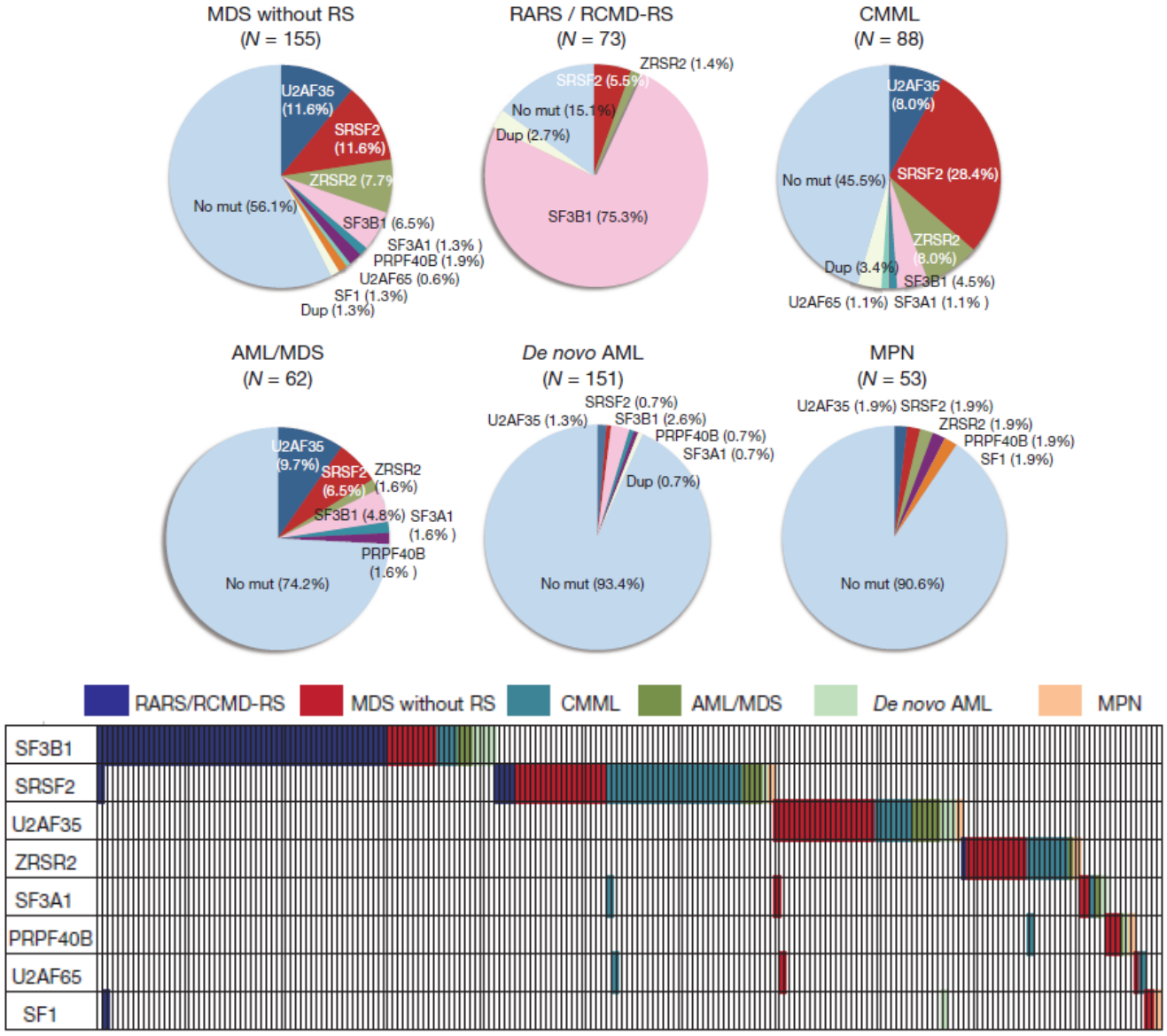
Gene Expression Profile



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

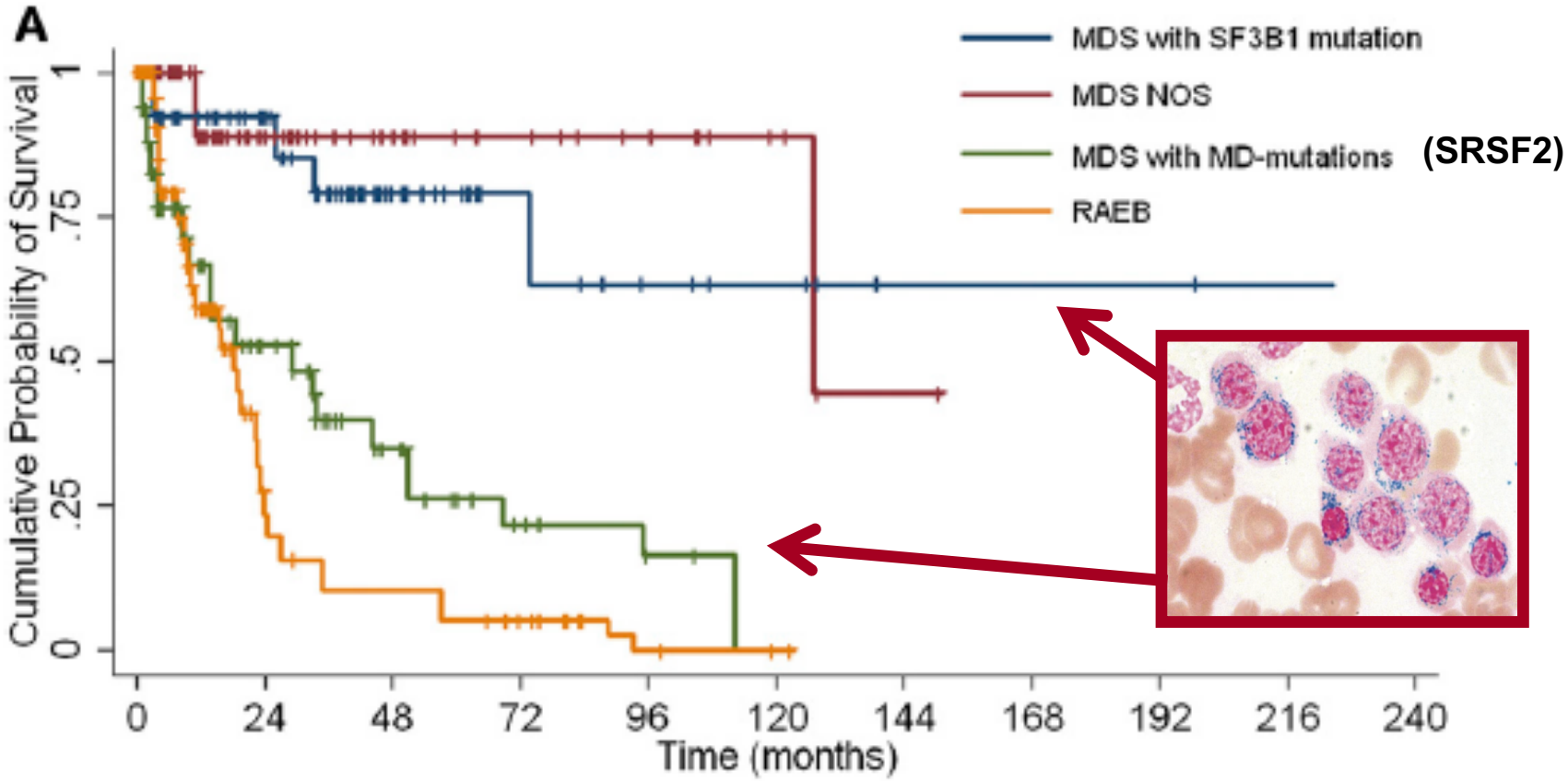
Blood. 2006;108:337-45

Frequent pathway mutations of splicing machinery in myelodysplasia



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

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

Sotatercept and Luspatercept: Novel Ligand Traps for TGF-β Superfamily Ligands

	Sotatercept[1,2]	Luspatercept[3,4]
Fusion proteinS with ligand trap activity toward the activin type 2 receptors[2,3]	 Extracellular domain of **ActRIIA**	 Modified extracellular domain of **ActRIIB**
Do not bind EPO receptors[2,3]	Fc domain of human IgG_1 antibody	Fc domain of human IgG_1 antibody
Heme effect[2,3]	+	+
Bone effect[5]	+	–

1. Komrokji R, et al. *Blood.* 2014;124(21) [poster presentation; abstract 3251]. 2. Carrancio S, et al. *Br J Haematol.* 2014;165(6):870-882. 3. Suragani R, et al. *Nat Med*. 2014;20(4):408-414. 4. Platzbecker U, et al. *Blood.* 2014;124(21) [oral presentation; abstract 411]. 5. Iancu-Rubin C, et al. *Exp Hematol*. 2013;41(12):155-166.e17.

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

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

	Base study dose concentration 0·125–0·5 mg/kg (n=9)	Base study dose concentration 0·75–1·75 mg/kg (n=49)
Age (years)	72 (27–88)	71 (30–90)
Sex		
Female	8 (89%)	16 (33%)
Male	1 (11%)	33 (67%)
Time since myelodysplastic syndromes diagnosis (years)	4·6 (1–10)	2·3 (0–14)
Transfusion burden		
Low transfusion burden (<4 red blood cell units per 8 weeks)	2 (22%)	17 (35%)
Haemoglobin concentration (g/dL)	8·7 (8·3–9·0)	8·7 (6·4–10·1)
High transfusion burden (≥4 red blood cell units per 8 weeks)	7 (79%)	32 (65%)
Red blood cell transfusion burden (units per 8 weeks)	8·0 (4·0–8·0)	6·0 (4·0–18·0)
Previous use of ESAs	3 (33%)	35 (71%)

Lancet Oncol 2017; 18: 1338–47

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

	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

Lancet Oncol 2017; 18: 1338–47

- Lower-risk MDS patients treated with luspatercept at ≥ 0.75 mg/kg achieved hematologic improvement and reduced transfusion burden / independence
- Luspatercept was generally safe and well tolerated
- Treatment for up to 1 year demonstrated sustained increases in hemoglobin and prolonged transfusion independence
- Higher response rates were observed in patients with RS and SF3B1 mutations
- Similar response rates were observed in ESA-naïve vs ESA-treated patients, and approximately 1/3 of patients with EPO 200–500 U/L responded

These results supported the initiation of Phase 3 studies of luspatercept in patients with lower-risk MDS (MEDALIST)

ASH 2017 - Somatic Mutations in MDS Predict Prognosis Independent of the IPSS-R (Analysis by IWG-PM)

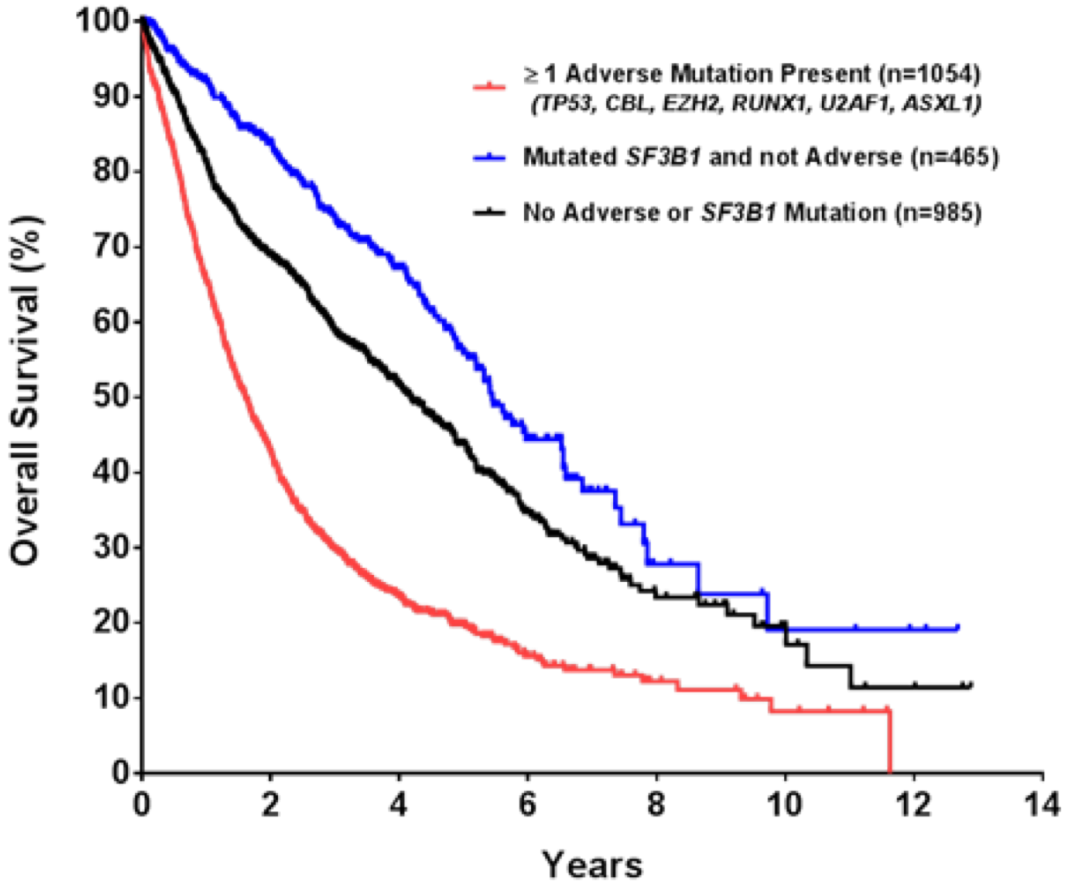
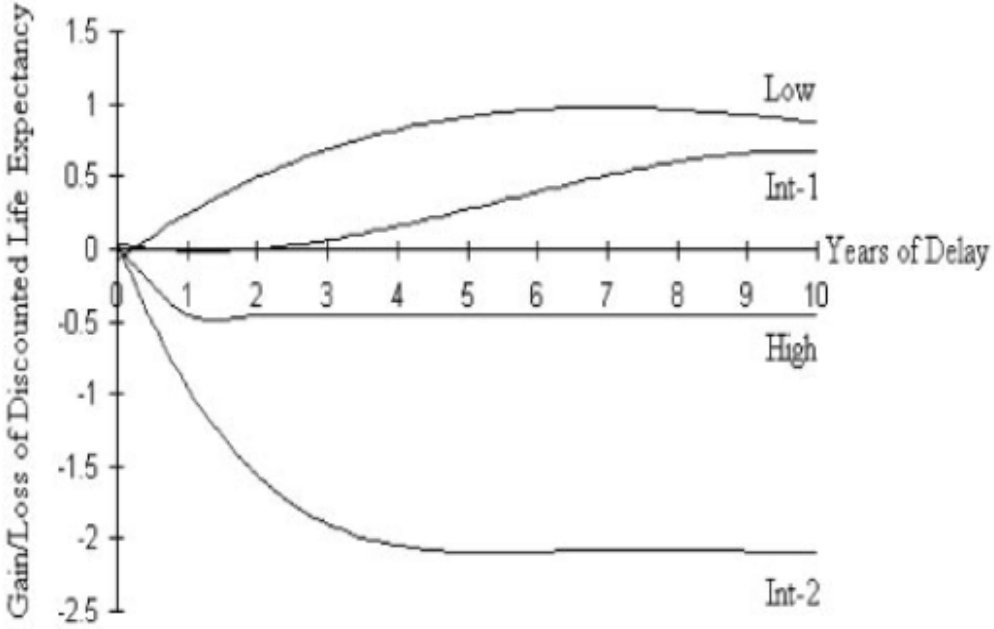


Figure 2: Kaplan-Meier curve of overall survival in years for the 2504 patients with sequence results for *SF3B1* and all six adverse genes (*TP53*, *CBL*, *EZH2*, *RUNX1*, *U2AF1*, and *ASXL1*).

Transplantation strategy according to IPSS

Discounted life expectancy, in years, for alternative transplantation strategies

Patients, by IPSS risk group	Transplantation at diagnosis	Transplantation at AML progression
All patients		
Low	6.51	7.21
Int-1	4.61	5.16
Int-2	4.93*	2.84
High	3.20*	2.75
Patients younger than 40 y		
Low	5.62	10.21*
Int-1	2.48	10.21*
Int-2	1.65*	1.53
High	—	—



Cutler CS et al. Blood 2004;104(2):579-85.

Transplantation policy according to IPSS-R

		Patient AGE		
	delay time (months)	***40***	***50-55***	***>60***
Years of life expectancy under policy 1: IPSS-R Low	***0***	16.4	16.1	15.1
	12	17.3	16.8	15.4
	24	17.9	17.3	15.6
	48	18.5	17.7	15.7
	60	18.7	17.9	15.7
Years of life expectancy under policy 2: IPSS-R intermediate	***0***	19.3	18.1	15.9
	12	17.9	17.1	14.9
	24	17.1	16.4	14.5
	48	16.3	15.7	14.2
	60	16.0	15.5	13.9

Optimal timing of alloSCT

gain of life expectancy:
- 5.3 y pts <50y
- 4.7 y pts 60 y
- 2.8 y pts 65 y

Della Porta MG et al. Leukemia. 2017 Apr 7. doi: 10.1038/leu.2017.88

GITMO

Transplantation policy according to IPSS *vs.* IPSS-R

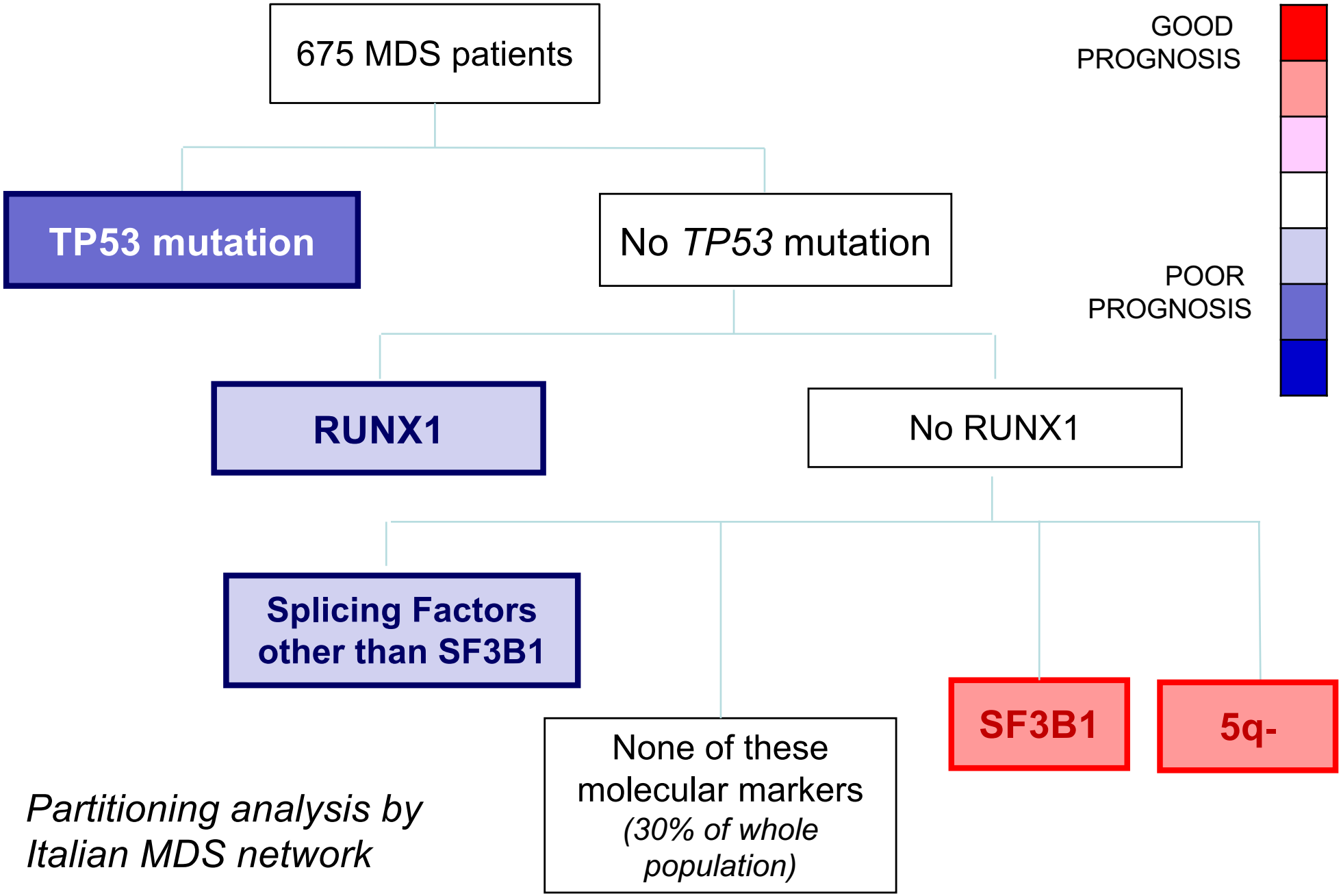
	IPSS-based policy*	***IPSS-R***	***%***	***IPSS-R based policy *****
IPSS Low	***Delayed***	**Very low**	37	***Delayed***
		Low	50	***Delayed***
		Intermediate	13	***Immediate***
		High	-	
IPSS Intermediate-1	***Delayed***	**Very low / Low**	48	***Delayed***
		Intermediate	40	***Immediate***
		High	11	***Immediate***
		Very high	1	***immediate***

** Cutler CS et al. Blood 2004;104(2):579-85.*

*** Della Porta MG et al. Leukemia. 2017 Apr 7. doi: 10.1038/leu.2017.88*

GITMO

Genotype-based transplant strategy in MDS



Partitioning analysis by Italian MDS network