EUROPEAN HEMATOLOGY ASSOCIATION

MADRID 22ND CONGRESS JUNE 22-25 | 2017 European Hematology Association

Novità nelle MDS

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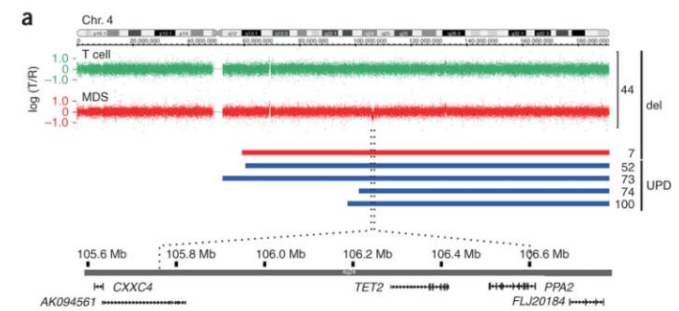
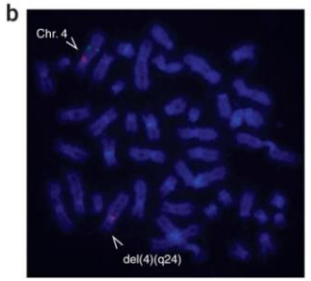
HUMANITAS UNIVERSITY

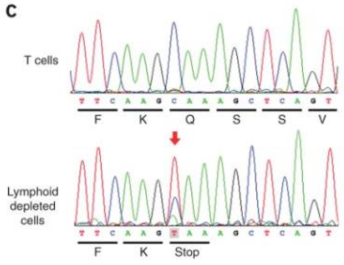
Outline

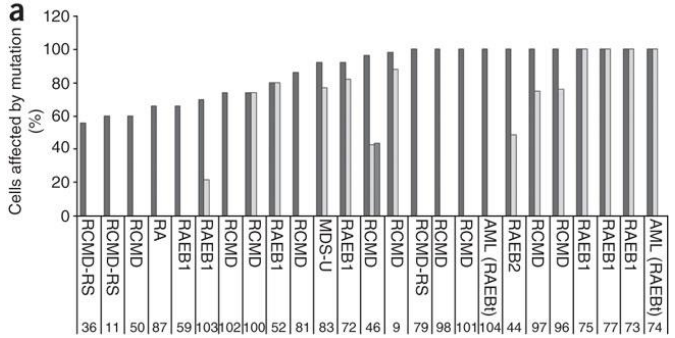
- ARCH
- Predictive value of somatic mutations
- Treatment of anemia

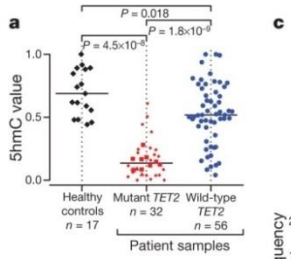
Acquired mutations in *TET2* in myeloid neoplasms

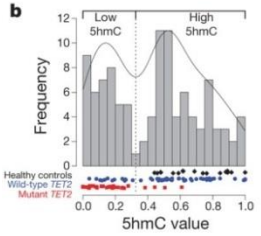


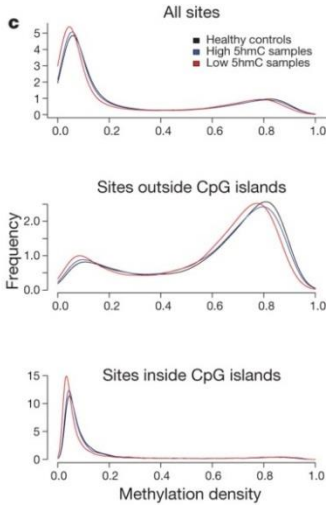


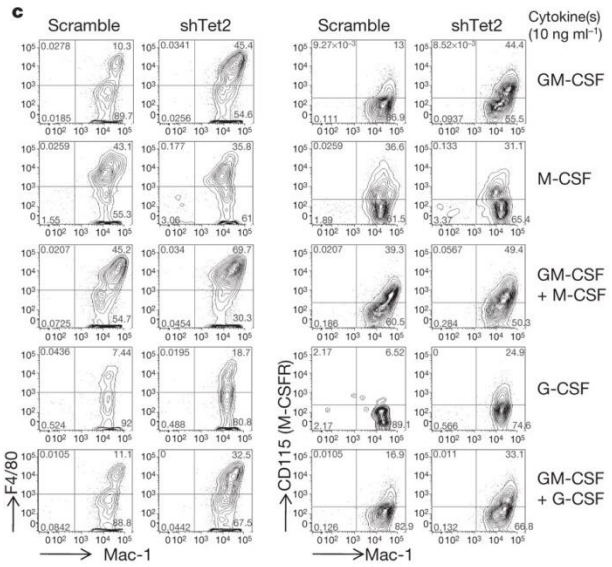












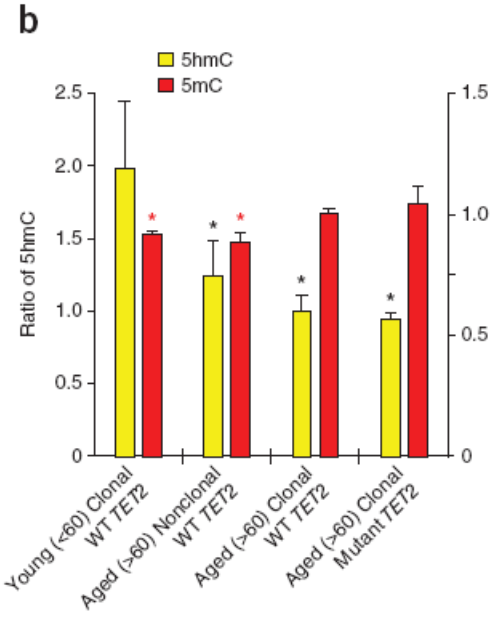
N Engl J Med 2009;360:2289-301; Nature Genetics 2009;41:838-842; Nature 2010;468:839-43

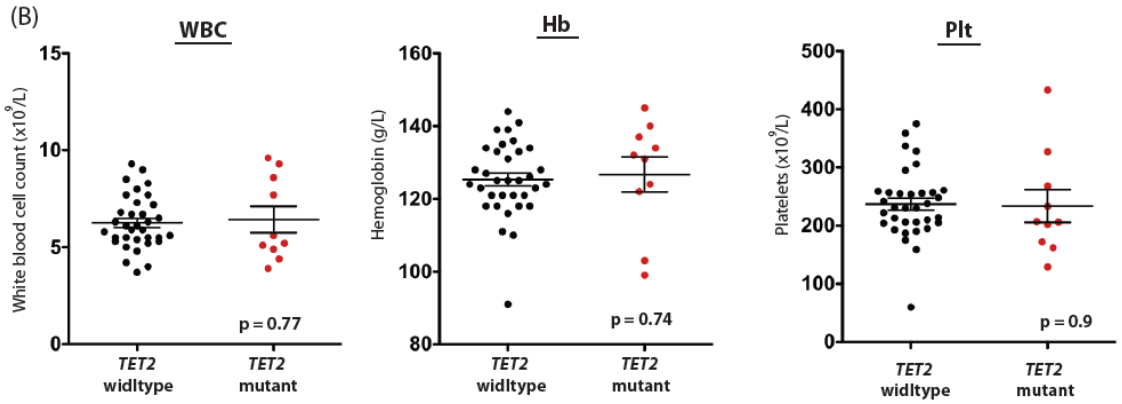
Recurrent somatic *TET2* mutations in normal elderly individuals with clonal hematopoiesis

Table 1 ***TET2*** **somatic mutations found in normal elderly individuals (*n* = 10)**

Nucleotide substitution[a]	Amino-acid substitution	Chromosome	Position
c.286_298delCGCAC AGTTAGTG	p.Arg96Asnfs*12	4	106155385
c.1330delA	p.Thr444Hisfs*6	4	106156429
c.1348delA	p.Lys450Lysfs*2	4	106156447
c.1547delC	p.Pro516Hisfs*16	4	106156646
c.1630C>T	p.Arg544*	4	106156729
c.3311_3312insAT	p.Phe1104Leufs*3	4	106158411
c.3991A>C	p.Thr1331Pro	4	106182952
c.5200delA	p.Met1734Leufs*11	4	106196867
c.5575insT	p.Ile1859tyrfs*16	4	106197239
c.5725G>T	p.Glu1909*	4	106197392

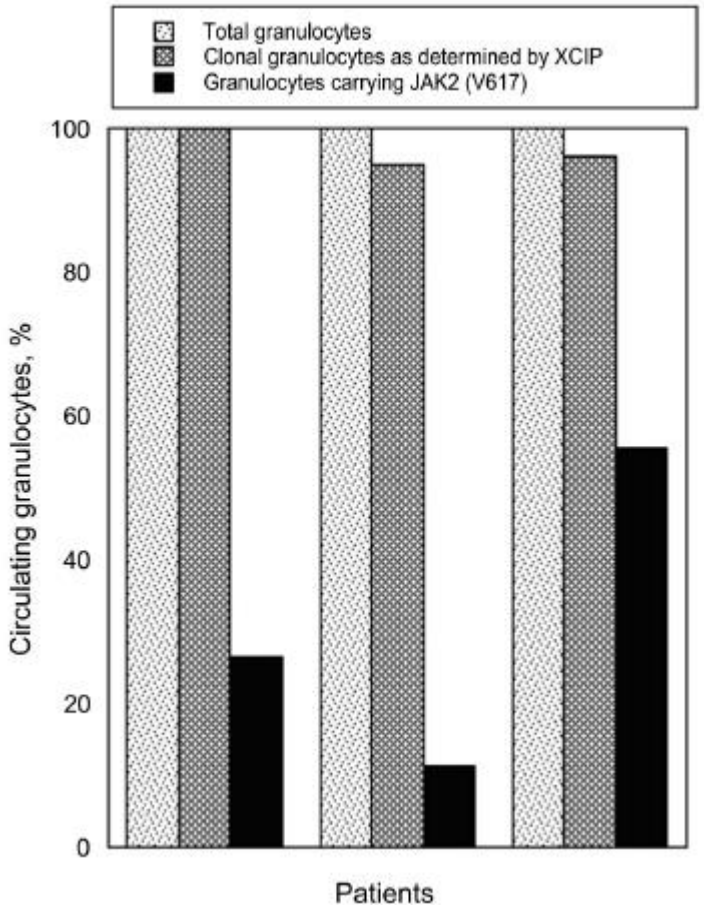
[a]The reference sequence used to annotate *TET2* mutations was NM_001127208.

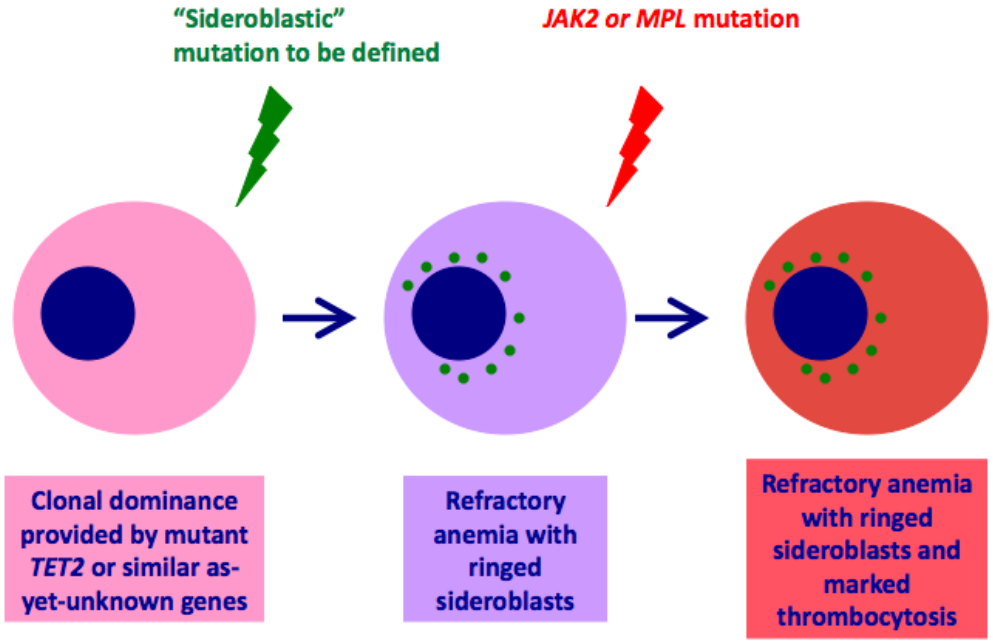




Nat Genet. 2012 Sep 23. [Epub ahead of print]

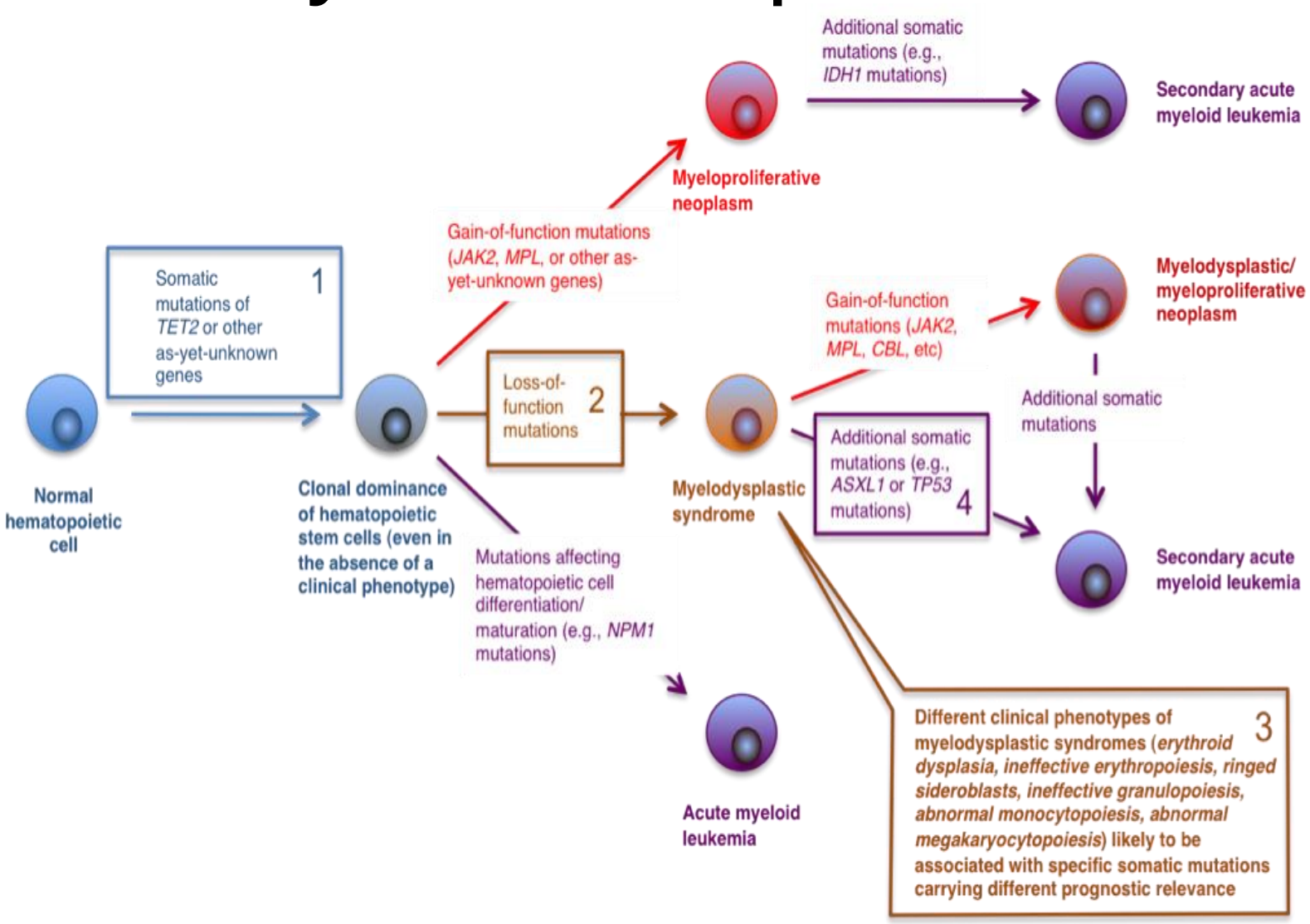
Molecular and clinical features of refractory anemia with ringed sideroblasts associated with marked thrombocytosis



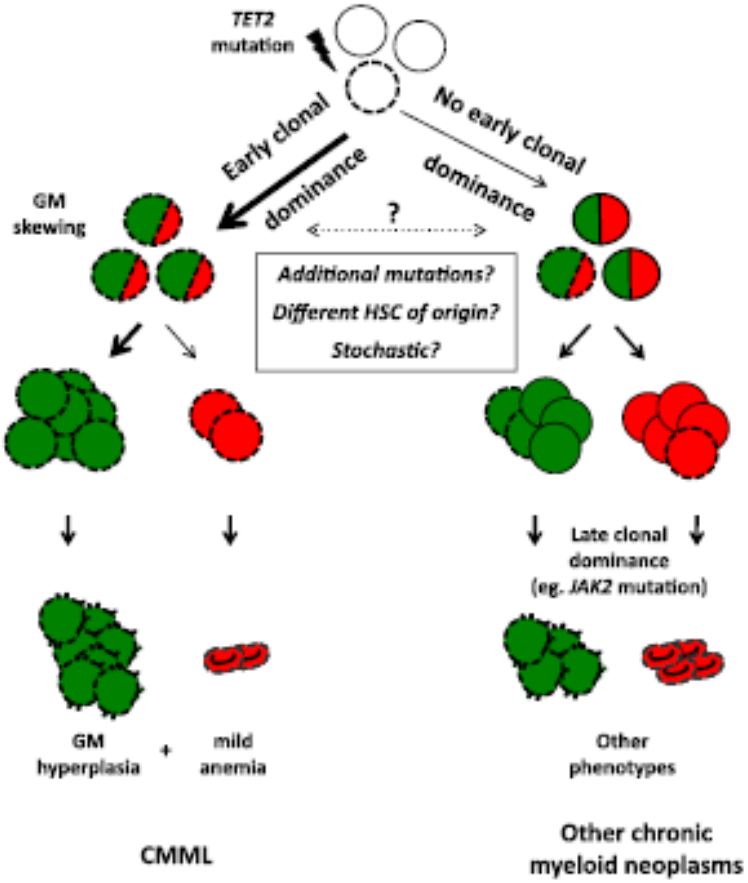


Blood. 2009;114:3538-3545

Molecular pathogenesis of Myeloid Neoplasms



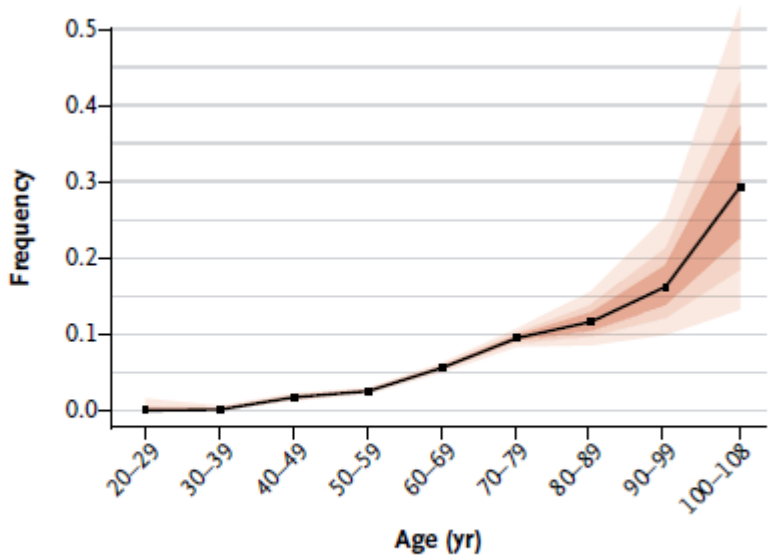
Clonal architecture of chronic myelomonocytic leukemias



Blood. 2013;121(12):2186-2198)

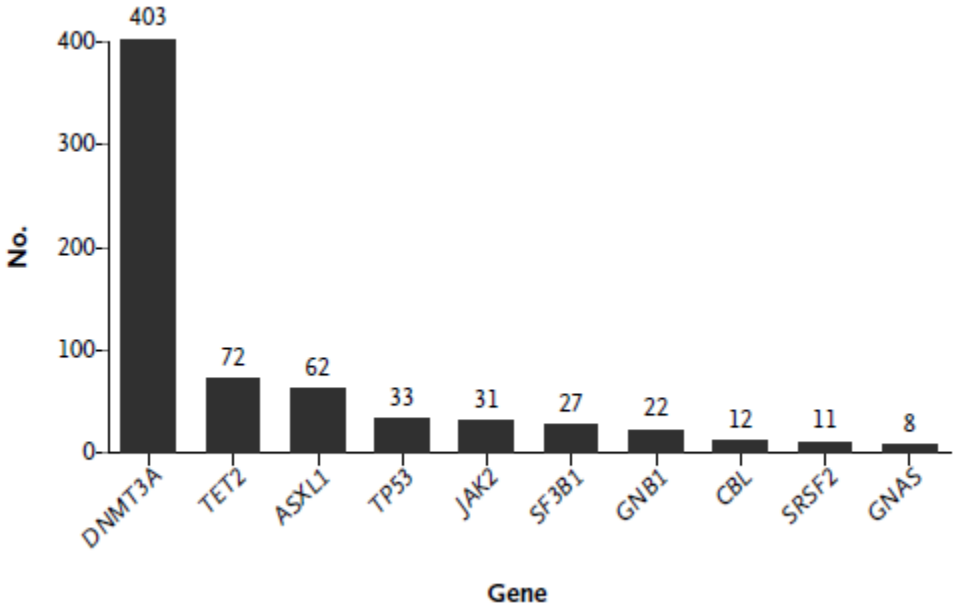
Age-Related Clonal Hematopoiesis

Prevalence of Somatic Mutations, According to Age.



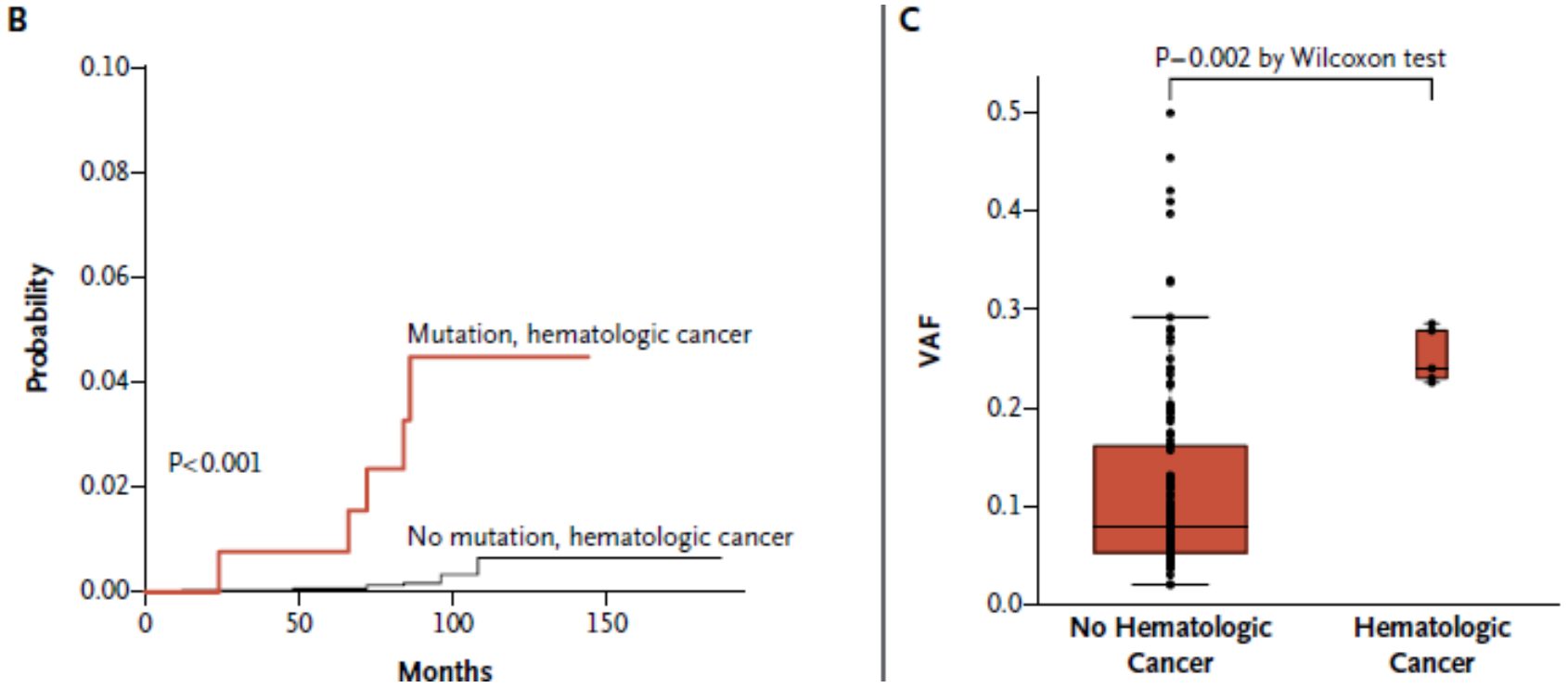
No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

Characteristics of Candidate Somatic Variants.



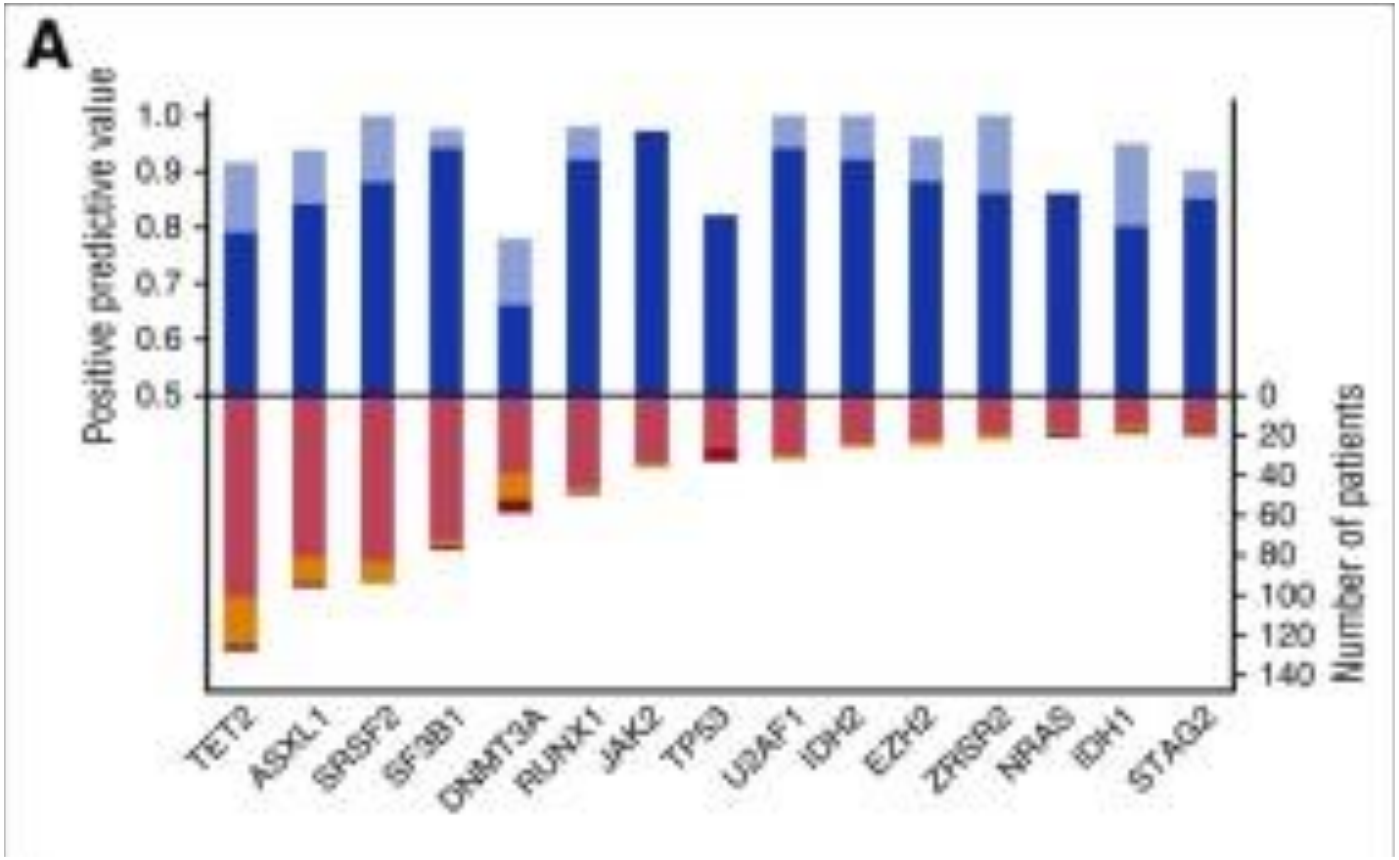
Jaiswal S et al. N Engl J Med 2014;371:2488-98.

ARCH is associated with an increase in the risk of hematologic cancer (HR 11.1)



Jaiswal S et al. N Engl J Med 2014;371:2488-98.

Clinical significance of somatic mutation in unexplained blood cytopenia



Blood. 2017 Jun 22;129(25):3371-3378

Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease.

- Case control analysis (8000 subjects)
- Carriers of CHIP had a risk of coronary heart disease and infarction that were 1.9 and 4.0 times as great as in non-carriers
- Hypercholesterolemia-prone mice engrafted with BM from homozygous or heterozygous Tet2 knockout mice had larger atherosclerotic lesions
- Macrophages from Tet2 knockout mice showed elevated expression of several chemokine and cytokine genes that contribute to atherosclerosis

N Engl J Med 2017 Jul 13;377(2):111-121

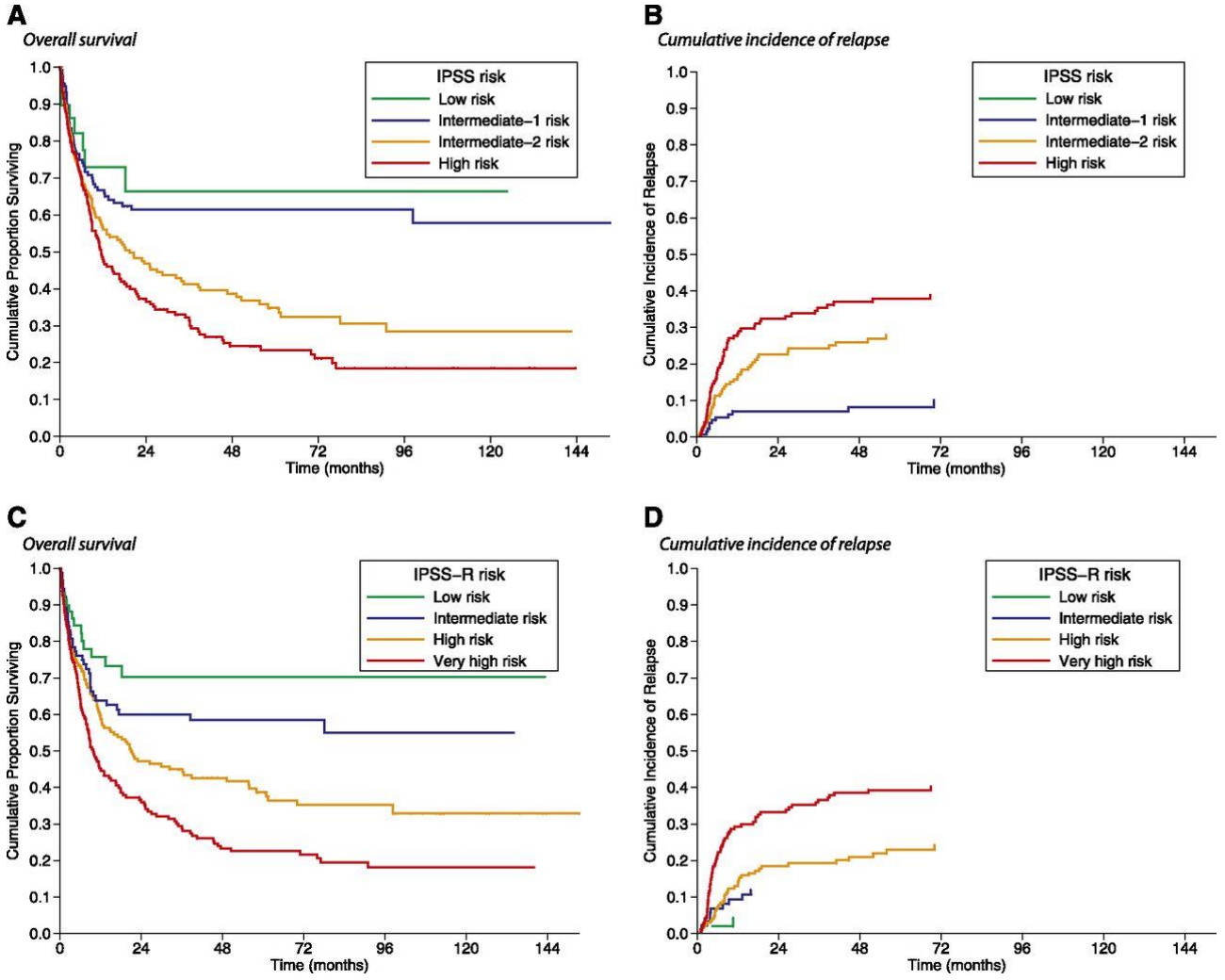
ARCH - summary

- ARCH is associated with increased risk of hematological malignancies
- In ARCH carriers, type of mutation, VAF, co-mutations are major determinant of the individual risk of developing myeloid cancers
- ARCH is associated with cardiovascular risk (by inducing inflammation)

Outline

- ARCH
- Predictive value of somatic mutations
- Treatment of anemia

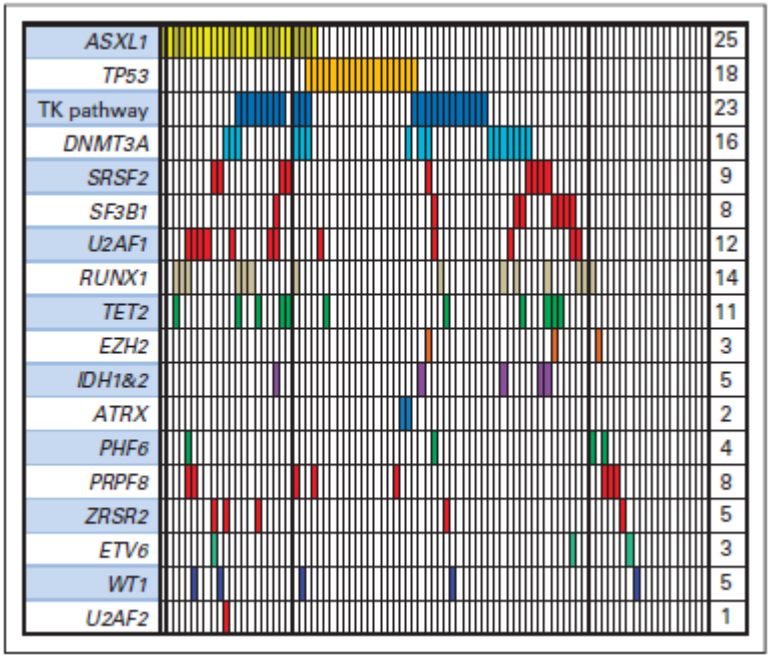
Kaplan-Meier analysis of survival and cumulative incidence of relapse following allogeneic HSCT in MDS patients stratified according to IPSS or IPSS-R risk.

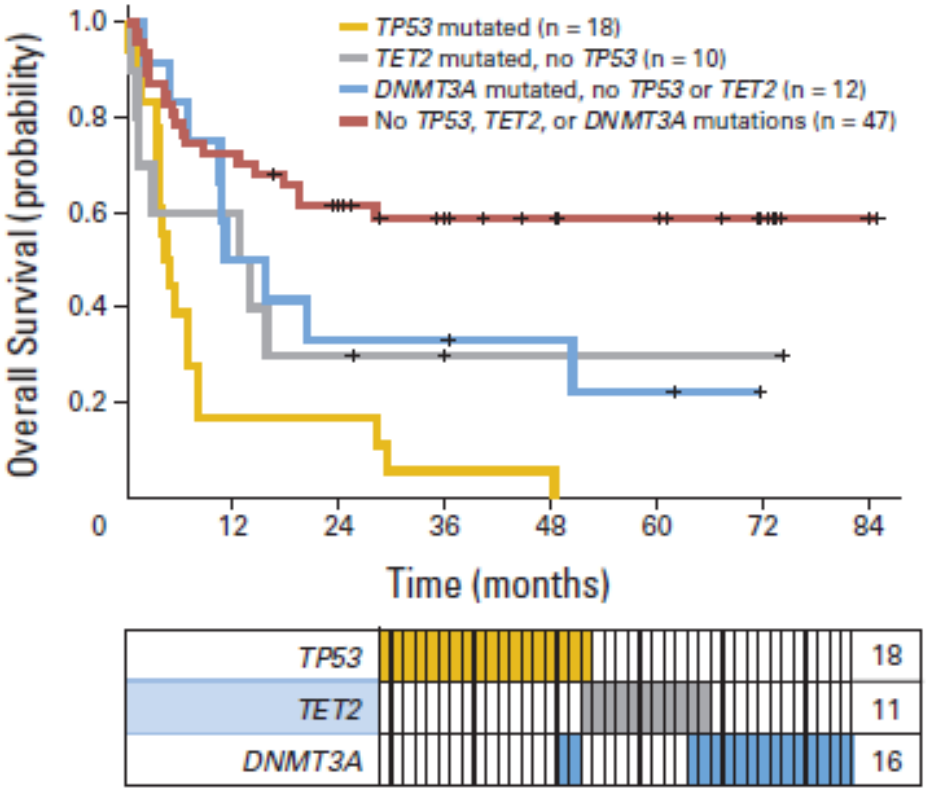


Della Porta MG et al. Blood 2014;123:2333-2342
Della Porta MG et al. Leukemia. 2015 ;29:1502-13.

blood

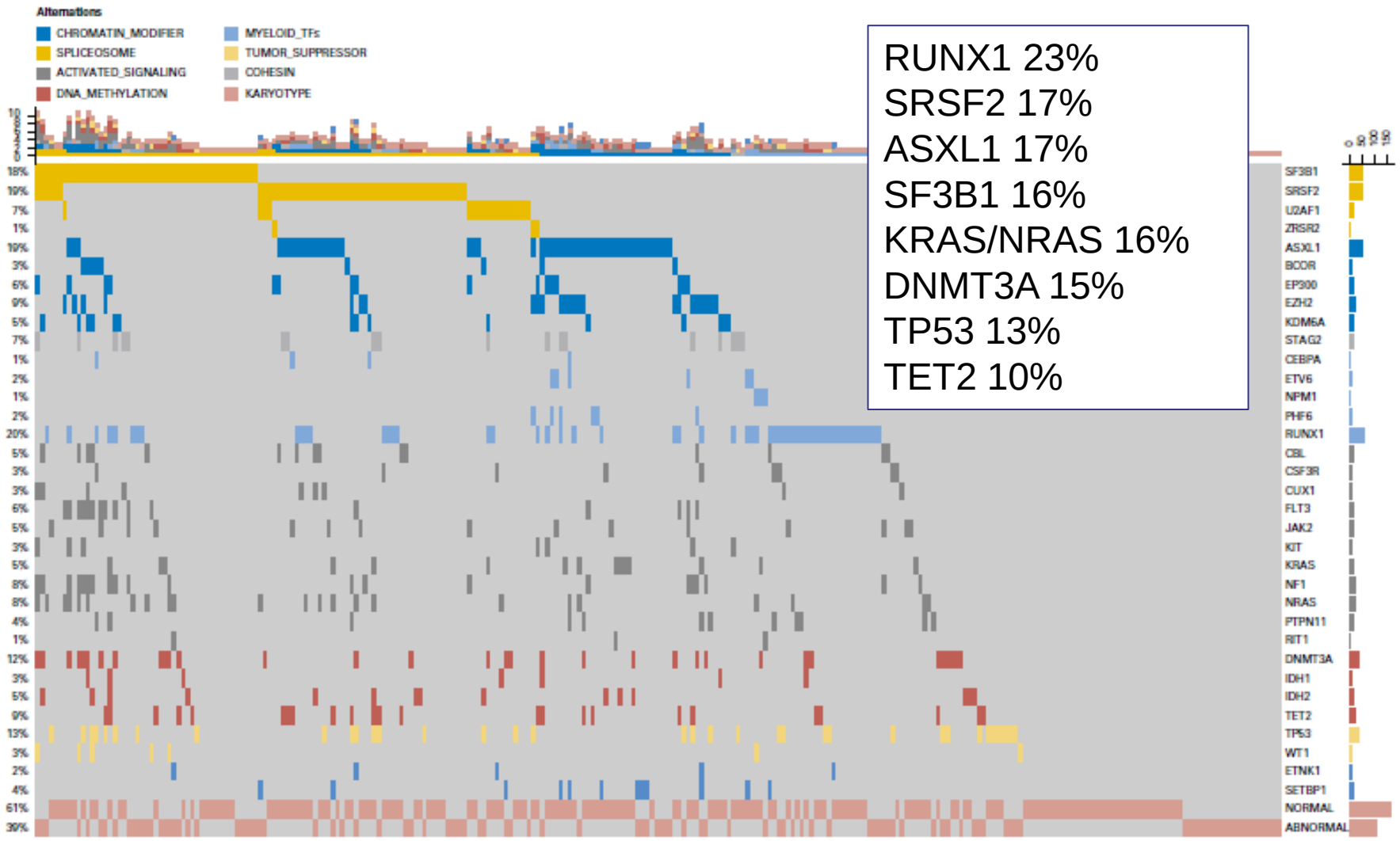
Somatic Mutations Predict Poor Outcome in Patients With MDS After Hematopoietic Stem-Cell Transplantation





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

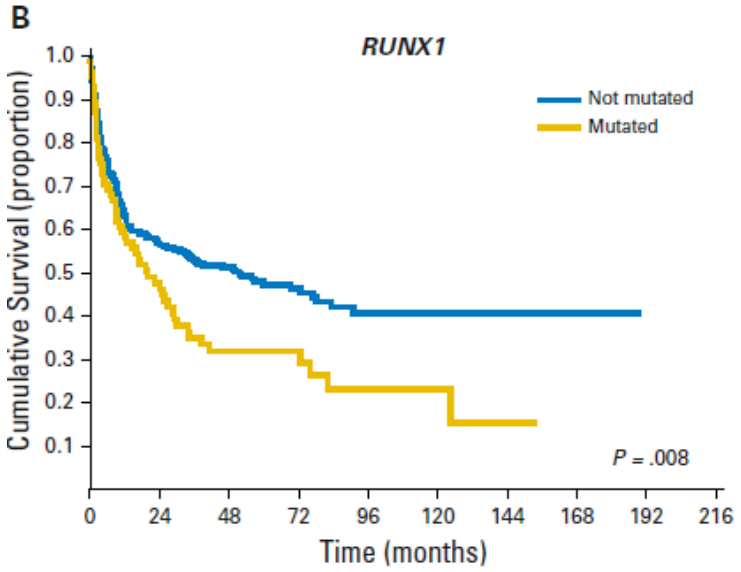
Mutation patterns observed in MDS treated with allo-HSCT

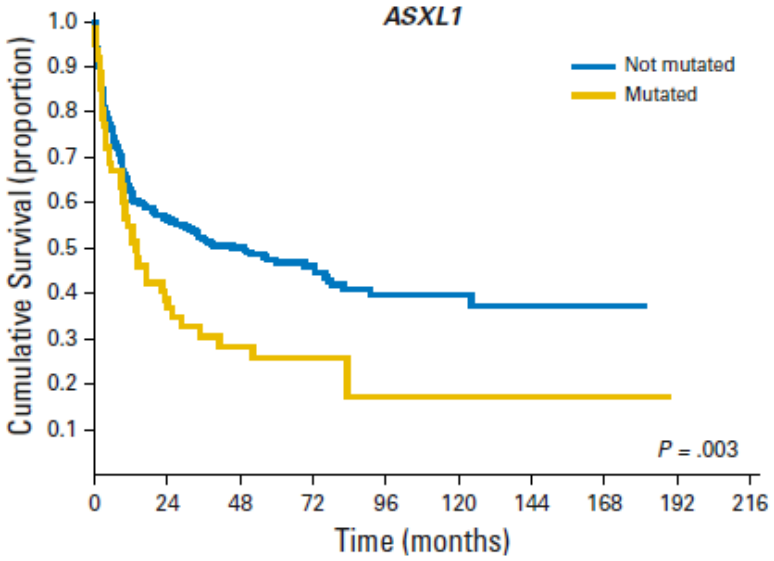


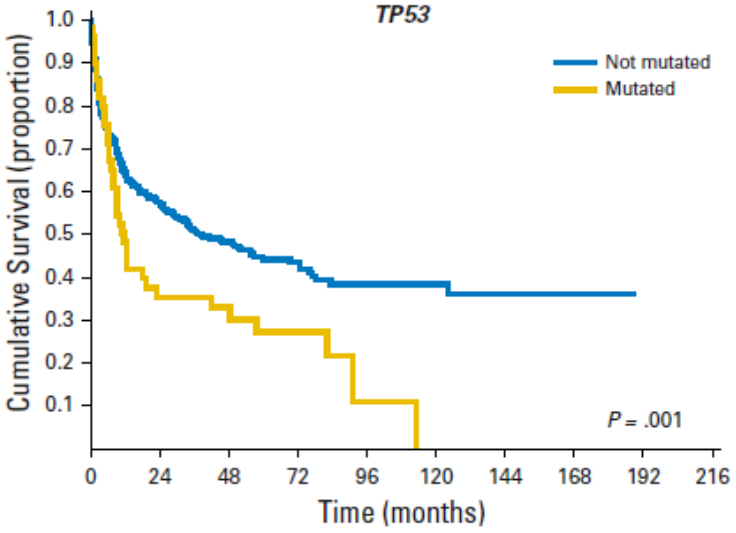
Matteo G. Della Porta et al. JCO doi:10.1200/JCO.2016.67.3616

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

GITMO

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

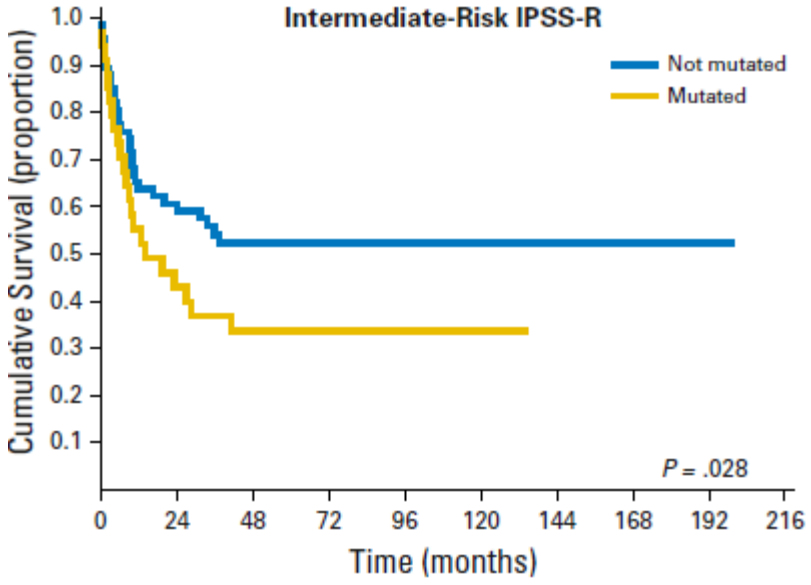
GITMO

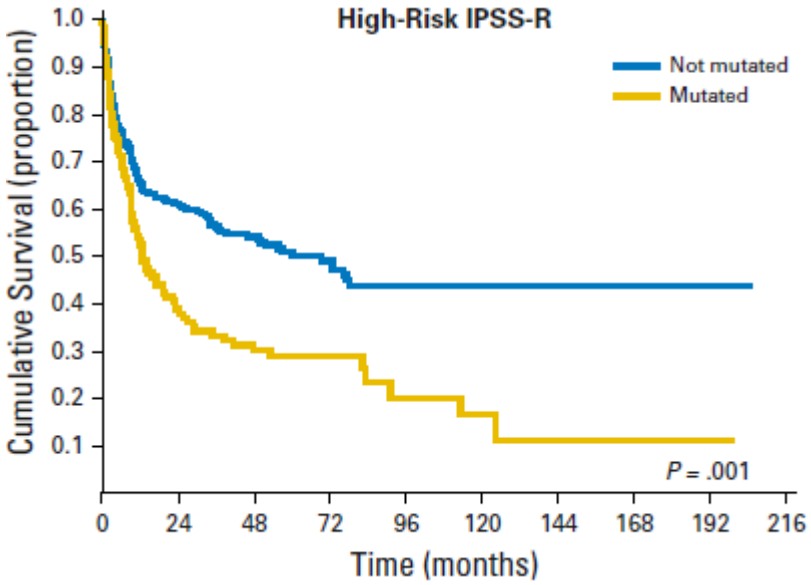
Patient	WHO Category (before HSCT)	Founding Clone (before HSCT)	Clonal Evolution (disease relapse)
GITMO 1	RAEB-2	*PTPN11*	Founder clone recurs
GITMO 2	MDS/AML	*NPM1*	Founder clone recurs
GITMO 3	RAEB-1	*RUNX1*	Founder clone recurs
GITMO 4	RAEB-2	*DNMT3A*	A subclone expands (*IDH1*)
GITMO 5	RAEB-1	*STAG2*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

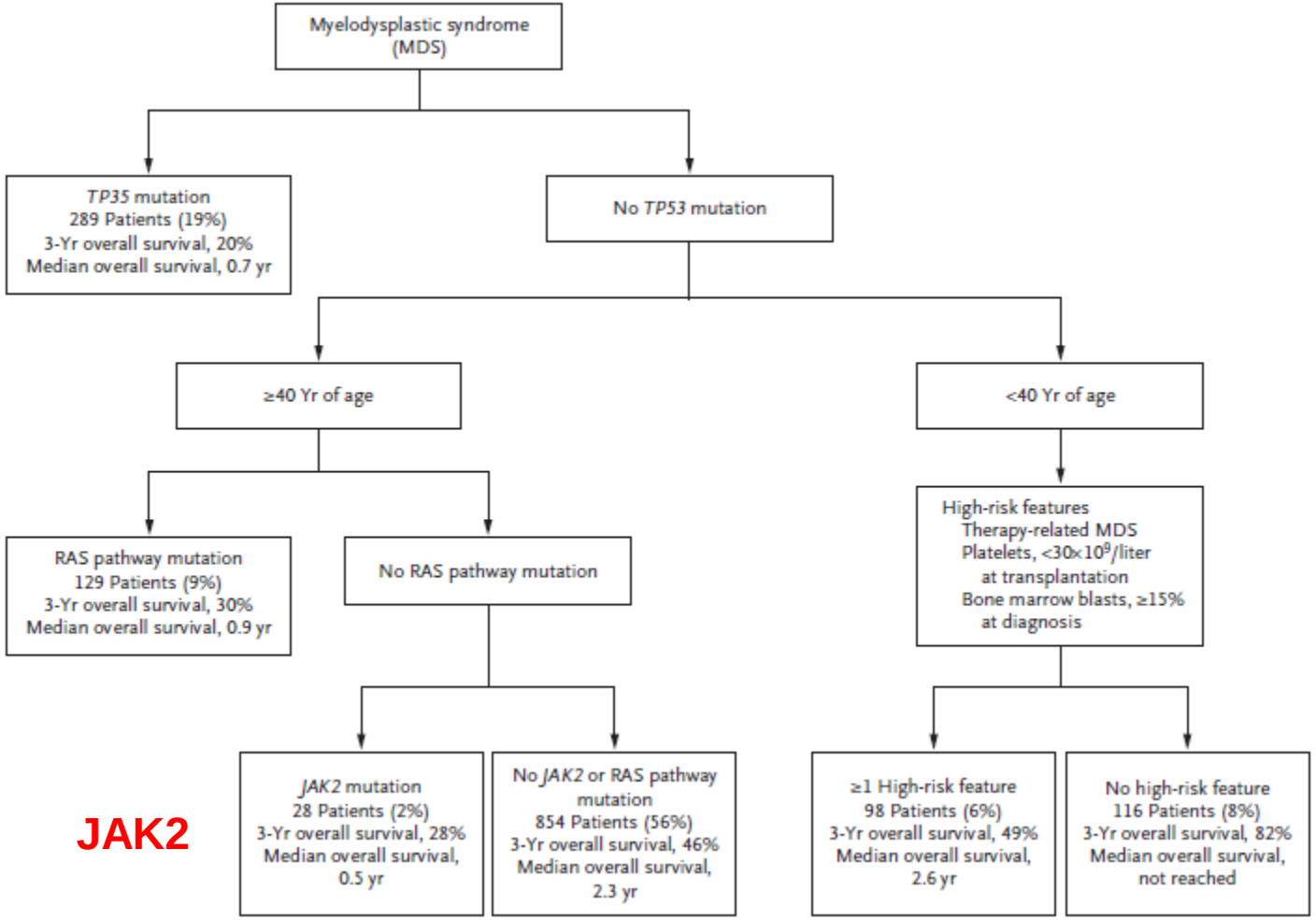




Matteo G. Della Porta et al. JCO doi:10.1200/JCO.2016.67.3616

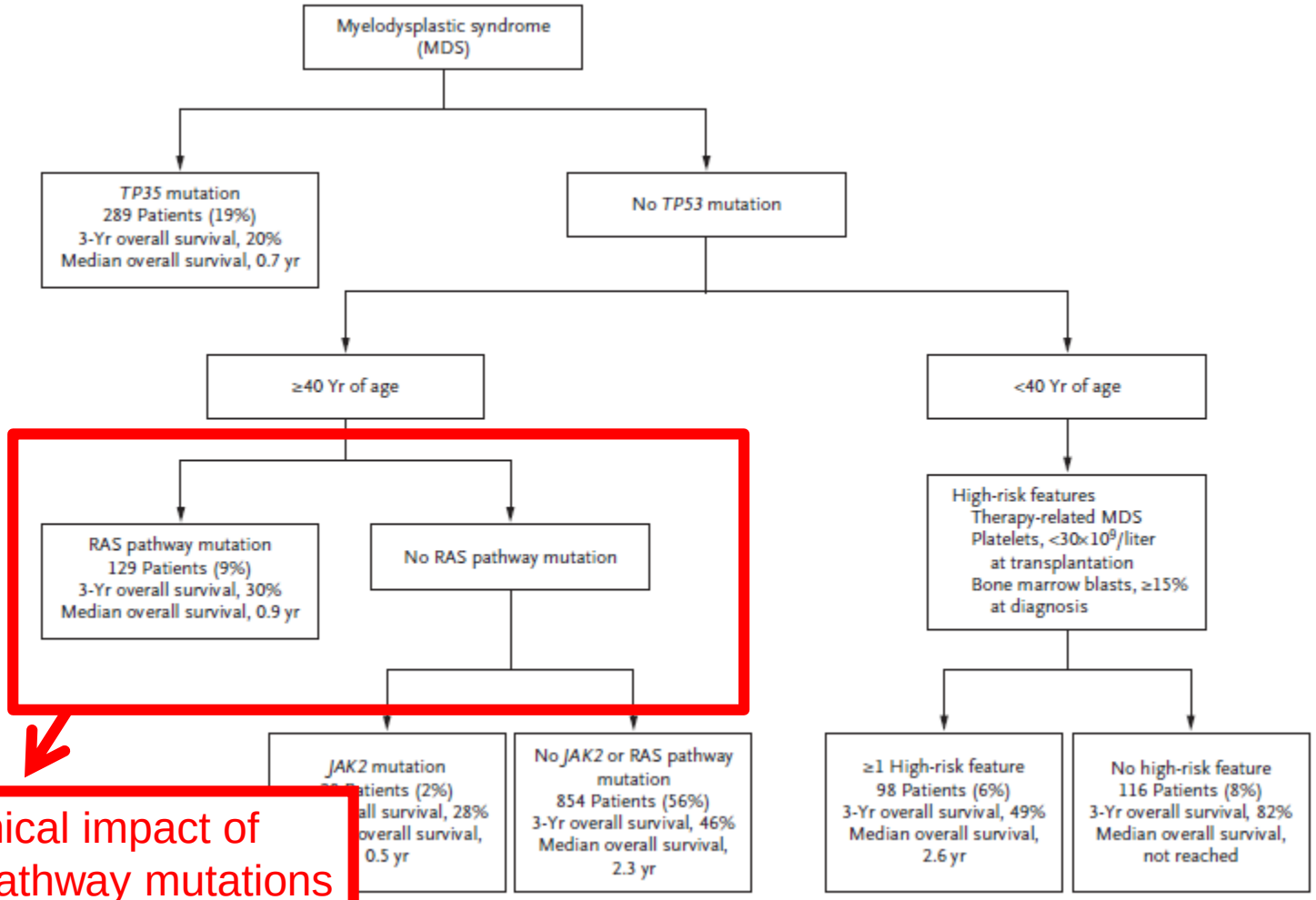
JOURNAL OF CLINICAL ONCOLOGY ASCO

Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation



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

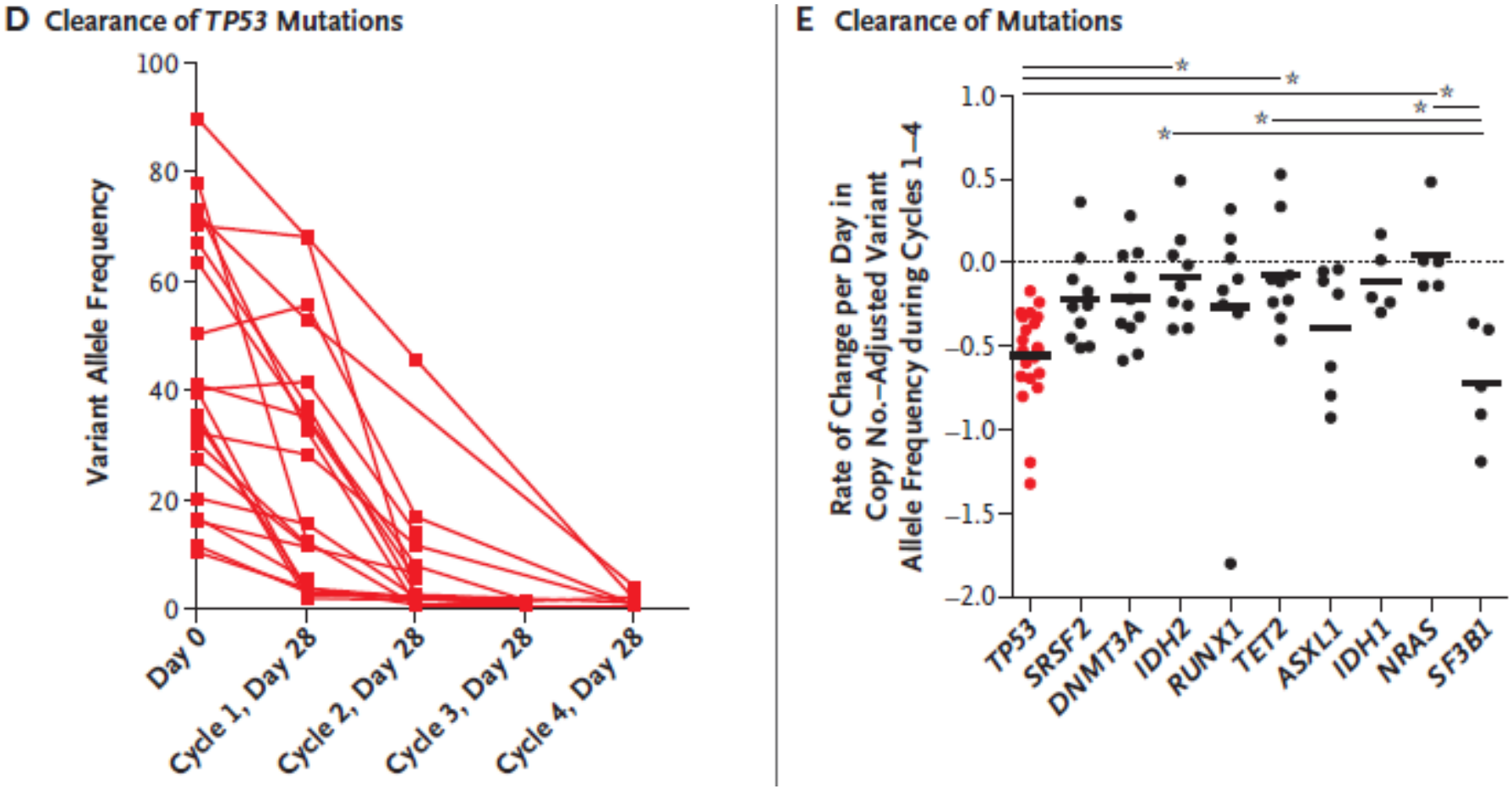
Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation



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.

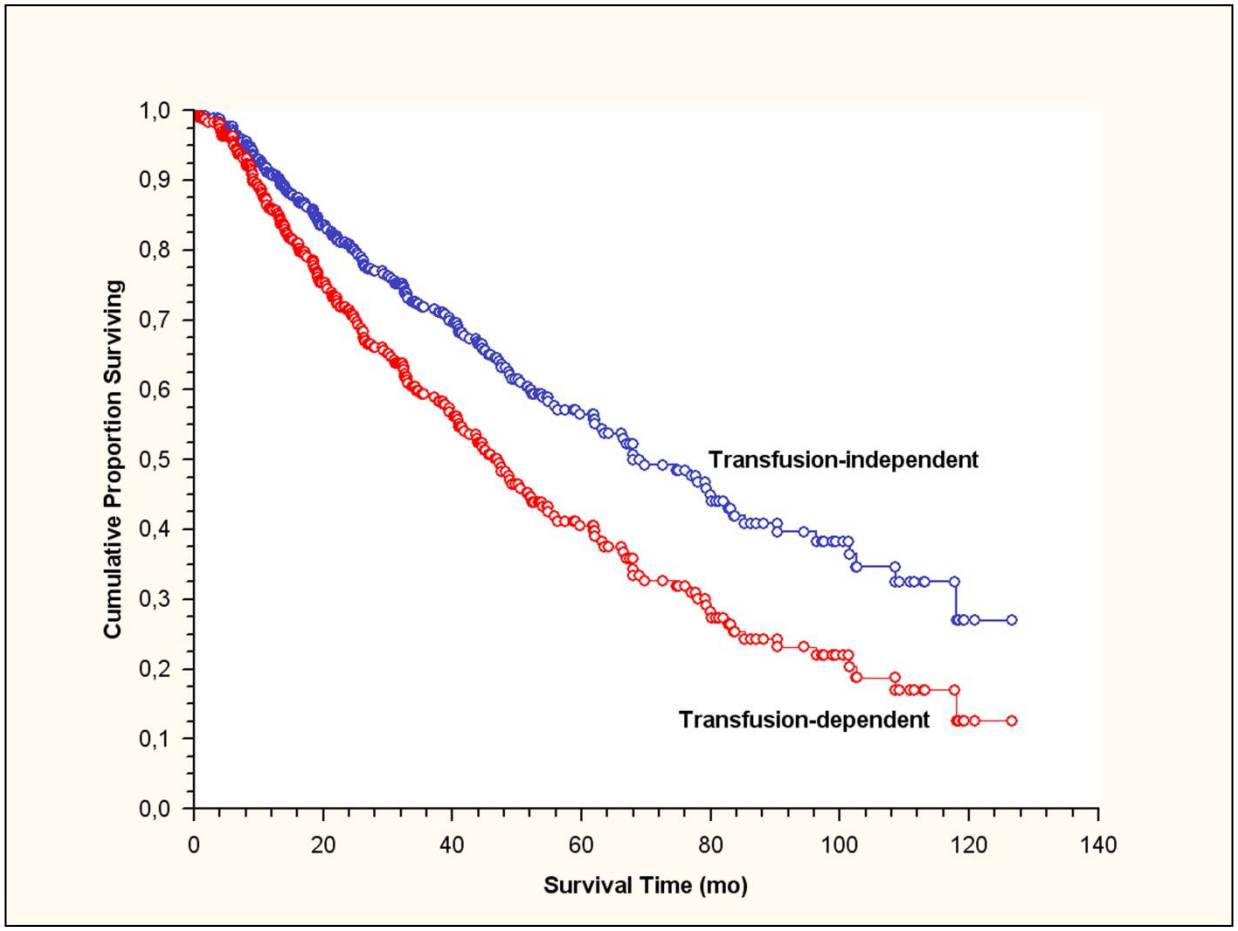
Predictive value of somatic mutations - Summary

- The definition of molecular basis of MDS is expected to improve diagnosis, prognostic assessment and clinical decision-making
- Mutation screening may affect clinical decision making in transplantation (TP53 mutations are associated to a high probability of disease relapse)
- Molecular biomarkers will be a solid basis for the implementation of personalized medicine programs in hematology

Outline

- ARCH
- Predictive value of somatic mutations
- Treatment of anemia

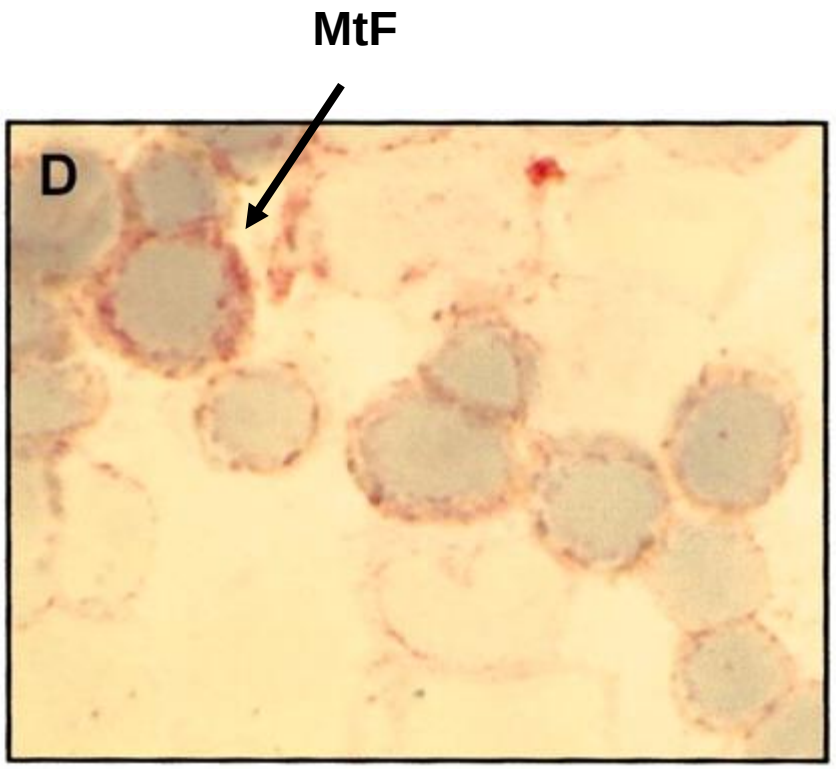
Survival of MDS patients according to transfusion-dependency



N Engl J Med 2005;352:536-8

Refractory Anemia with Ring Sideroblasts

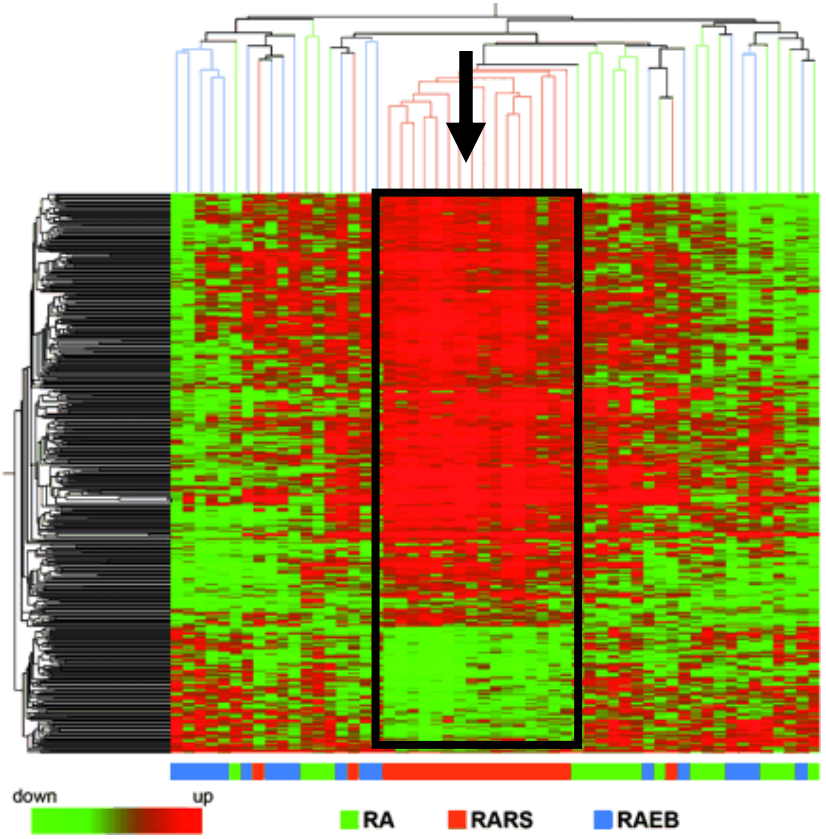
Mitochondrial Ferritin (MtF)



Iron accumulation in ringed sideroblasts is in the form of MtF

Blood. 2003;101:1996-00

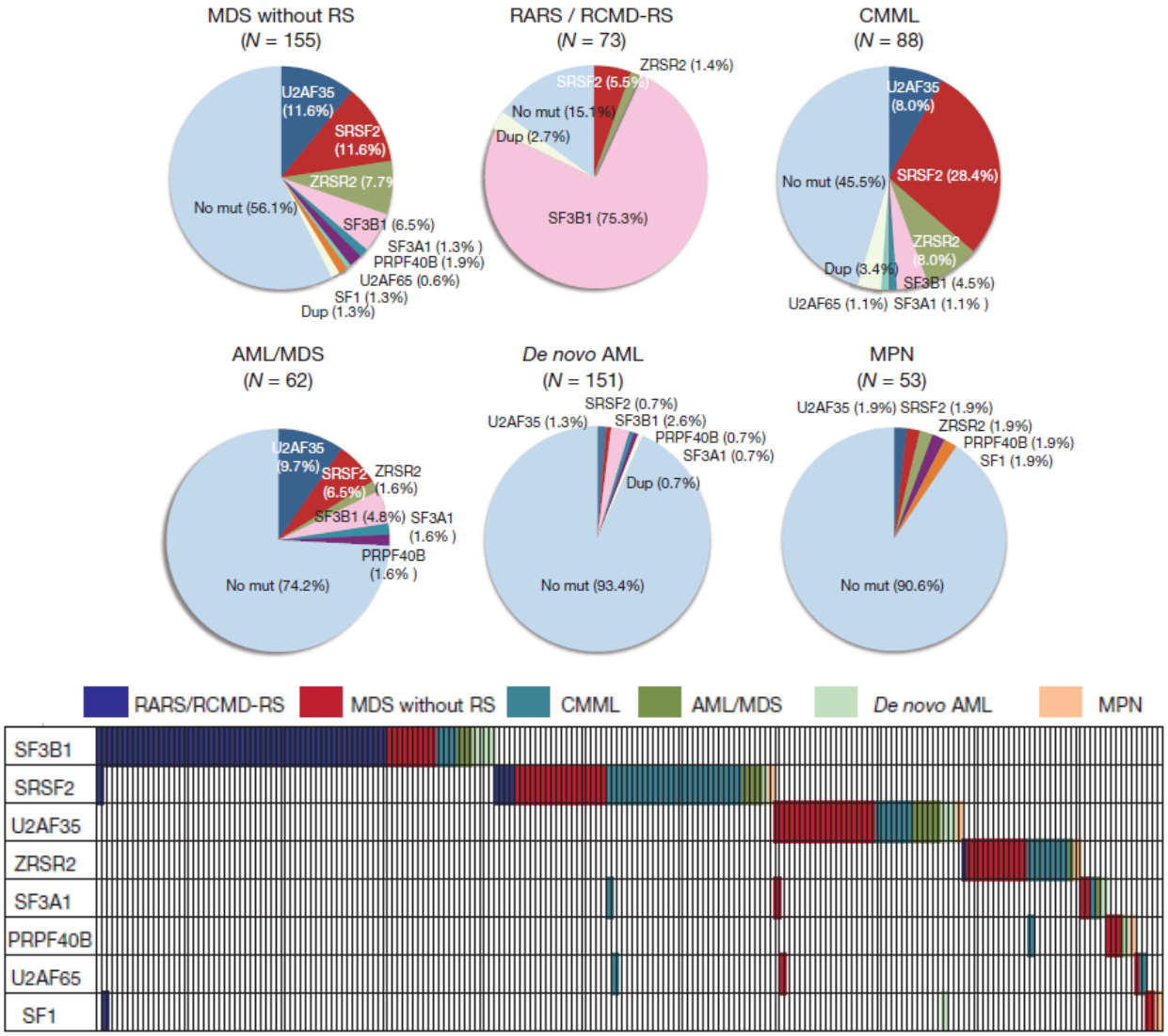
Gene Expression Profile



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

Blood. 2006;108:337-45

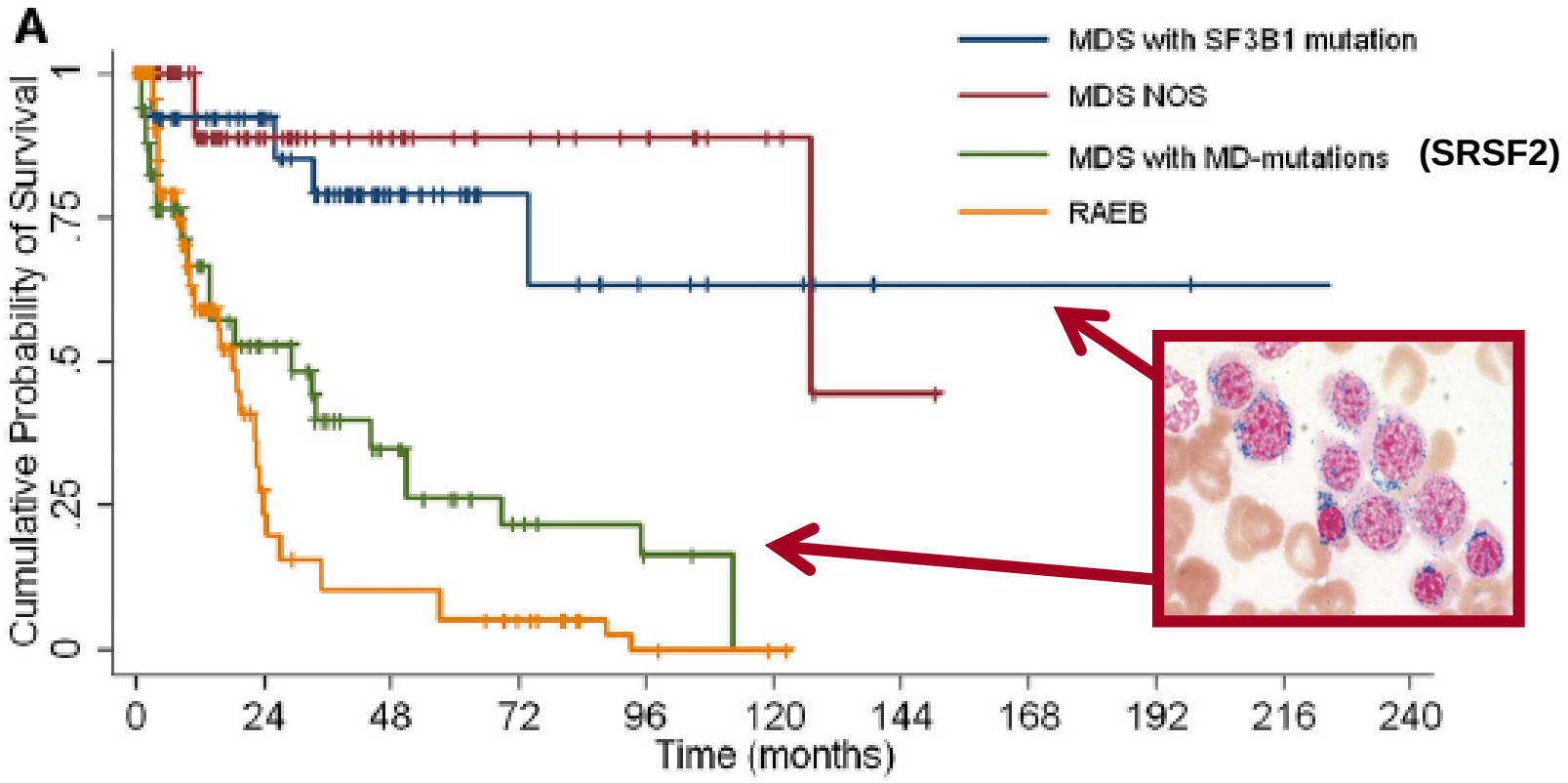
Frequent pathway mutations of splicing machinery in myelodysplasia



N Engl J Med 2011; 365:1384-1395

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

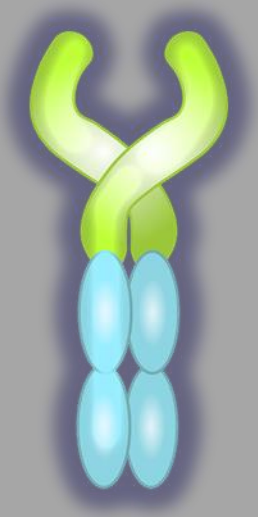
Driver somatic mutations identify distinct disease entities within myeloid neoplasms with myelodysplasia

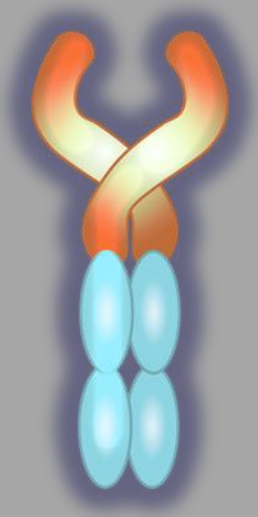


Malcovati et al. Blood 2014 Aug 28;124(9):1513-21
Della Porta MG et a. Leukemia. 2015;29(1):66-75

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

Lancet Oncol. 2017 Sep 1. pii: S1470-2045(17)30615-0

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.

Lancet Oncol. 2017 Sep 1. pii: S1470-2045(17)30615-0

Treatment of anemia - Summary

- The definition of molecular basis of MDS is expected to improve diagnosis, prognostic assessment and clinical decision-making
- Luspatercept is an effective treatment options for patients with anemia due to ineffective erythropoiesis, especially in those with SF3B1 mutation
- Molecular biomarkers will be a solid basis for the implementation of personalized medicine programs in hematology

Spunti discussione

- Early detection: Implicazioni cliniche
- Implementazione clinica dell'uso delle mutazioni somatiche per la diagnosi, il prognostic assessment e la decisione terapeutica a livello individuale
- Sviluppo di programmi di medicina personalizzata nelle MDS