MDS con mutazione di *SF3B1*: nuove acquisizioni clinico-molecolari

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CONFLICT OF INTEREST DISCLOSURE
Luca Malcovati, MD

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
NA	NA	NA	NA	NA	NA	NA	NA

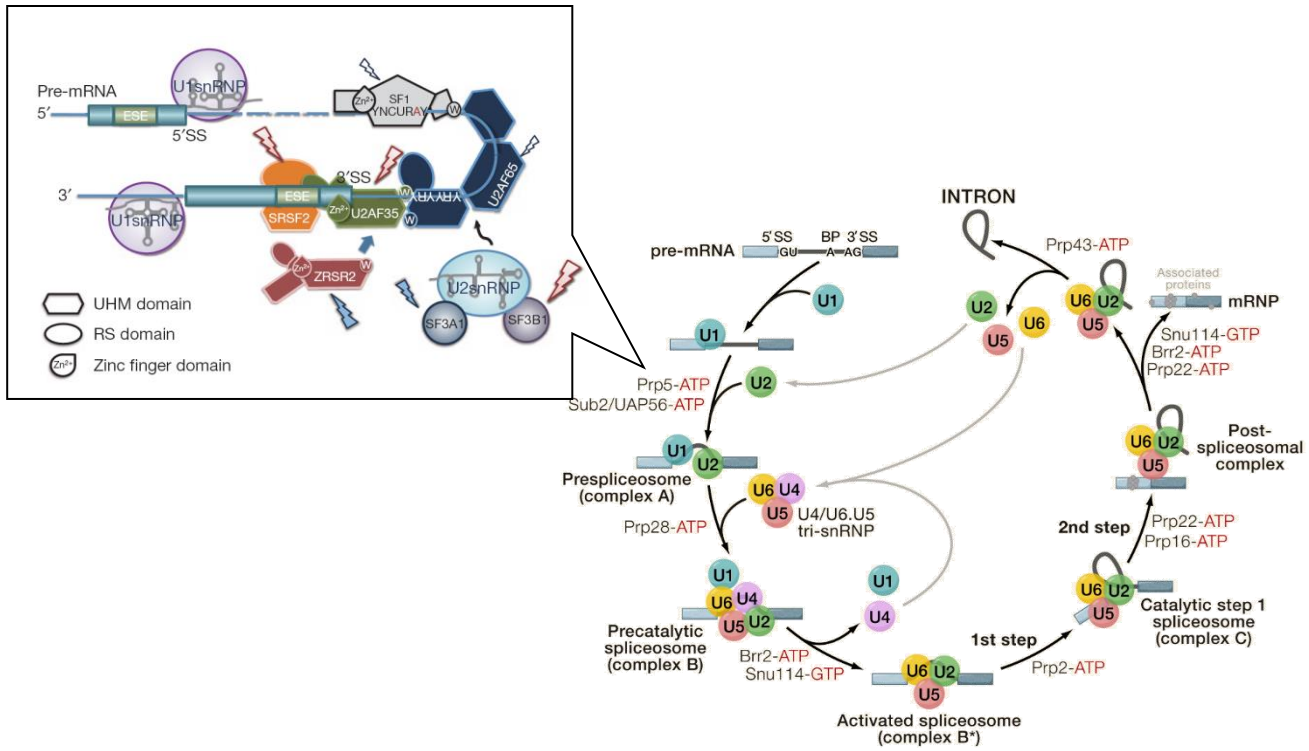
Outline

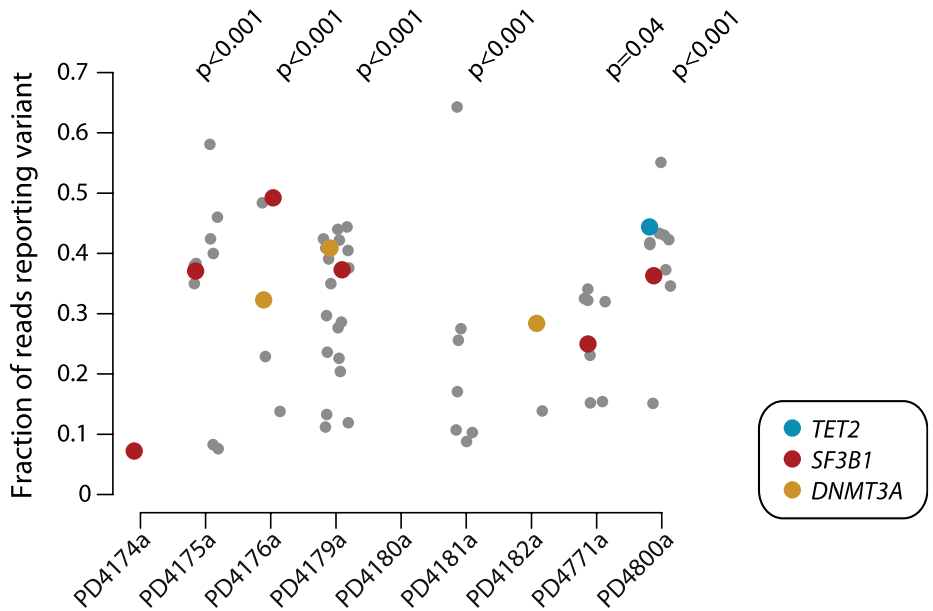
- *SF3B1* mutation in the pathophysiology of MDS with ring sideroblasts
- Clinical correlates of *SF3B1* mutation and classification of MDS-*SF3B1*
- Evolutionary trajectories of *SF3B1*-mutant clones
- Therapeutic targeting of spliceosome mutations and its functional consequences
- *SF3B1*-mutated clones and precursor states: CHIP, CCUS & early MDS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Adapted from Cell 2009;136:701-18 and Nature 2011;478:64-9

Papaemmanuil et al. N Engl J Med. 2011;365:1384-95

SF3B1 mutations in patients with myeloid neoplasms and other cancers

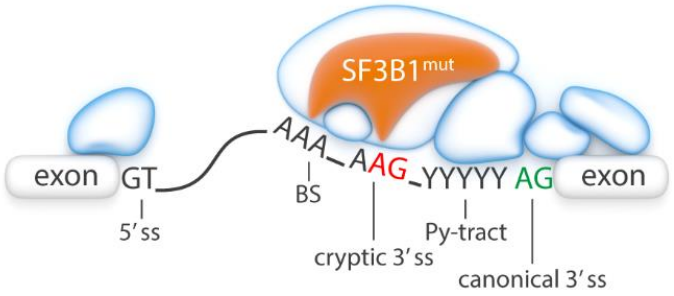
Subtype	N. pts	*SF3B1* mutation
MDS	**533**	**150 (28.1%)**
MDS/MPN	**83**	**16 (19.2%)**
AML-MDS	**38**	**2 (5.3%)**
MPN	**473**	**12 (2.5%)**
Other tumors	**1047**	**15 (1%)**

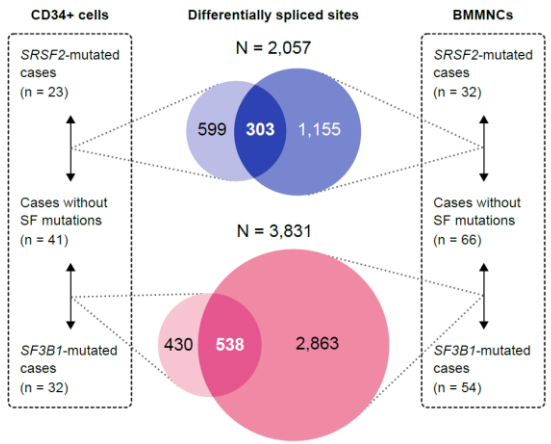
Subtype	N. pts	*SF3B1* mutation
MDS		
RA	122	14 (11.5%)
RARS	105	83 (79.0%)
RCMD	96	6 (6.3%)
RCMD-RS	52	30 (57.7%)
RAEB-1	83	7 (8.4%)
RAEB-2	53	6 (11.3%)
MDS del(5q)	22	4 (18.2%)
MDS/MPN		
CMML	62	4 (6.5%)
RARS-T	18	12 (66.7%)
MDS/MPN-U	3	0

Papaemmanuil et al. N Engl J Med. 2011;365:1384-95; Malcovati et al., Blood 2011;118:6239-46

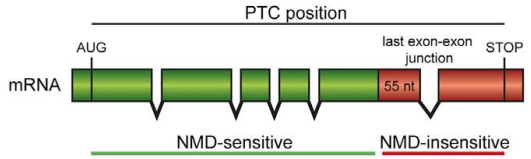
SF3B1 mutations induce cryptic 3' splice site selection contribute to MDS through a non-classical path to haploinsufficiency

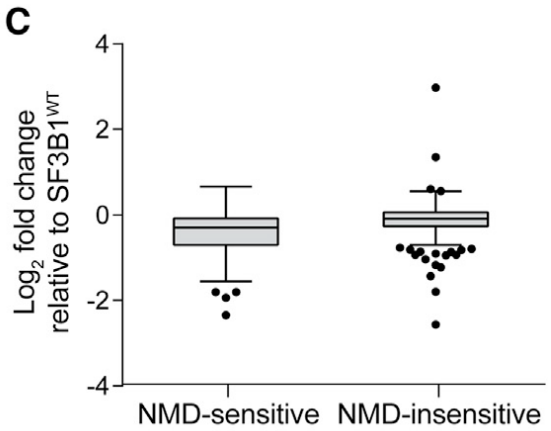
SF3B1 Hotspot Mutations



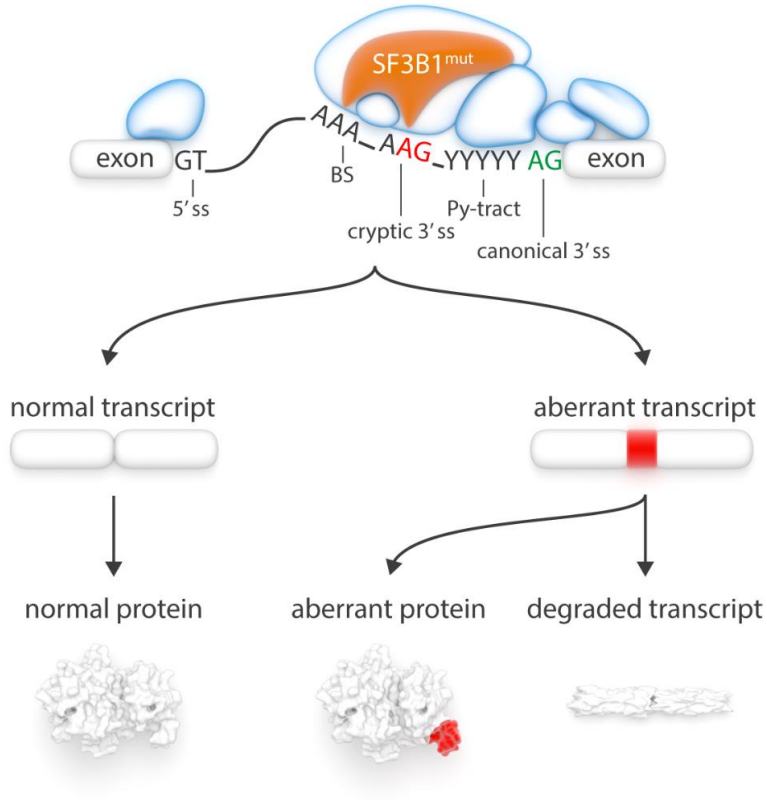


Nonsense-mediated decay



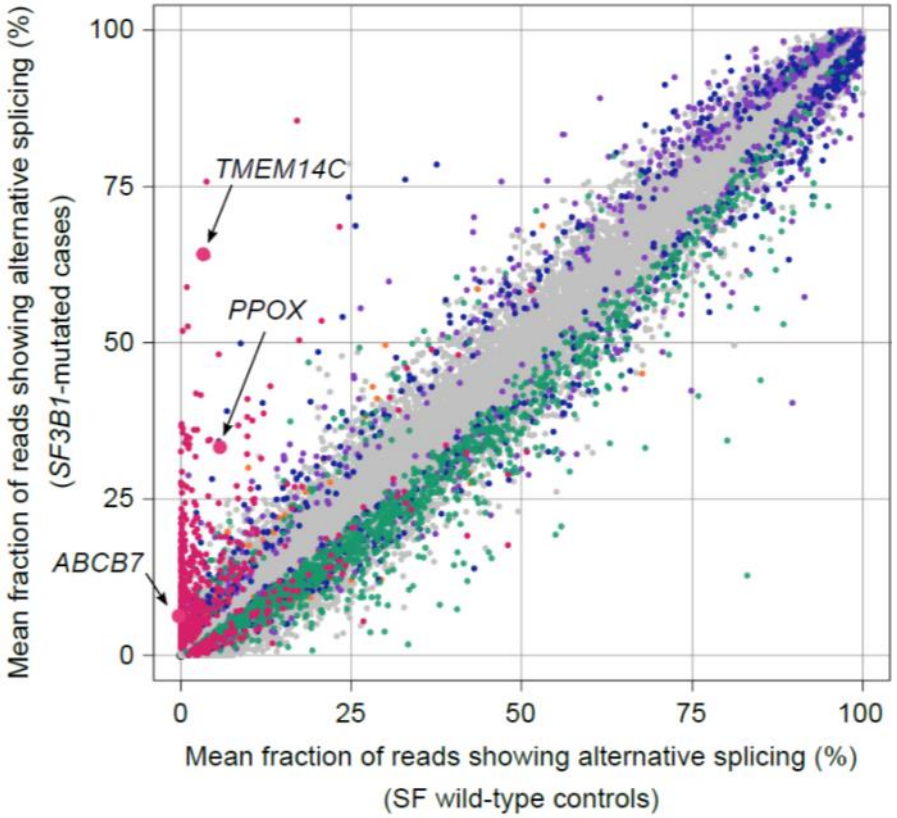


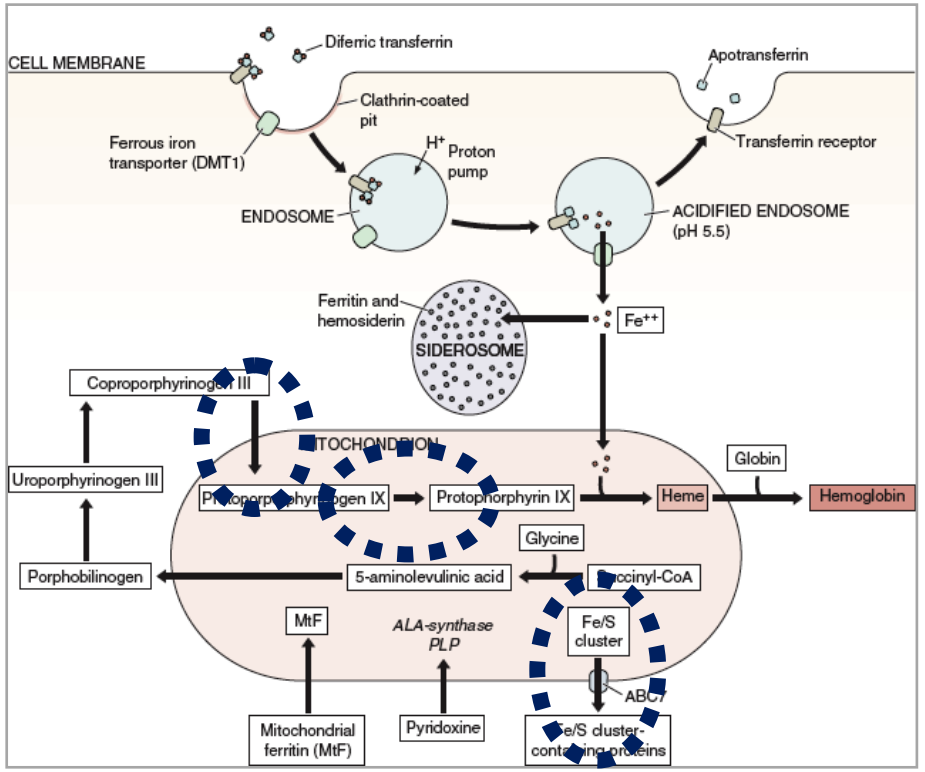
Haploinsufficiency



Darman et al. Cell Rep. 2015;13:1033-45; Malcovati L. BJH 2016;174:847-58; Shiozawa et al. Blood 2015 126:139

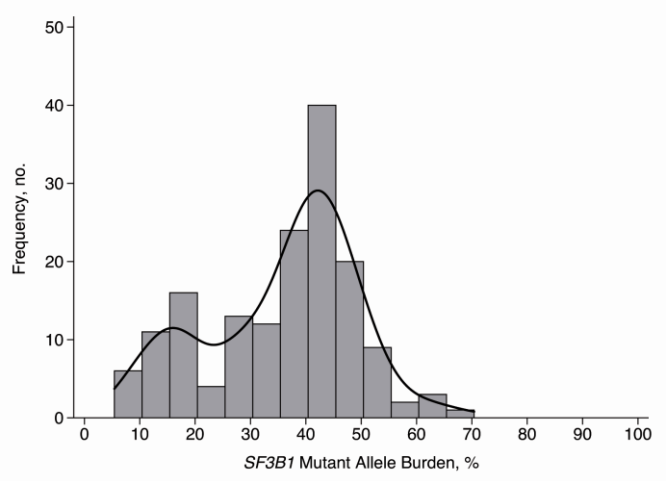
Alternative Splicing Events Associated with *SF3B1* Mutation

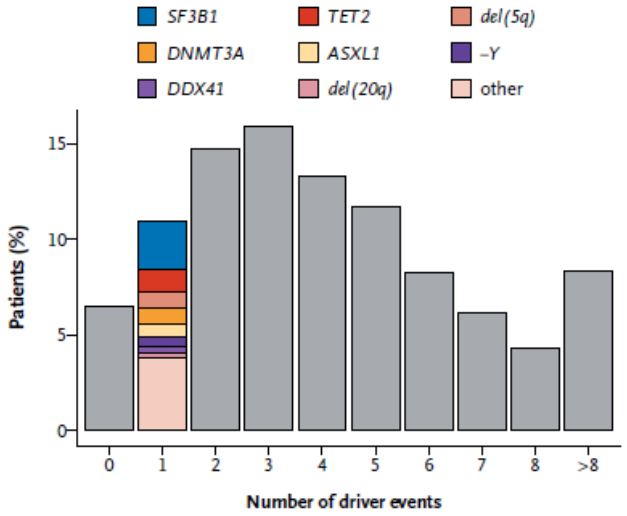


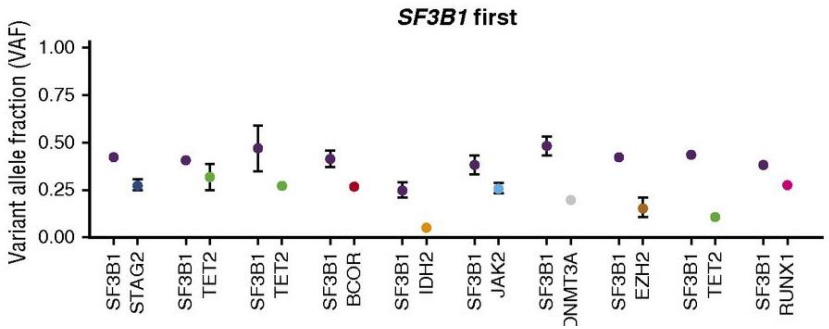


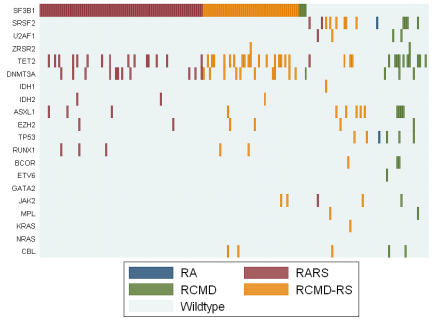
Shiozawa et al. Blood 2015 126:139

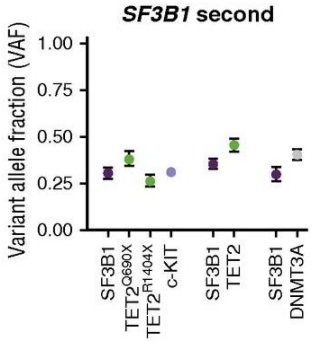
SF3B1 mutation is a founding driver mutation in MDS

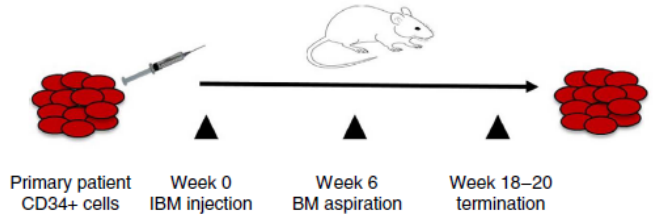












Blood 2011;118:6239-46; Blood 2013;122:3616-27; Nat Commun. 2015;6:10004; Blood 2017;130:881-890: NEJM Evid 2022

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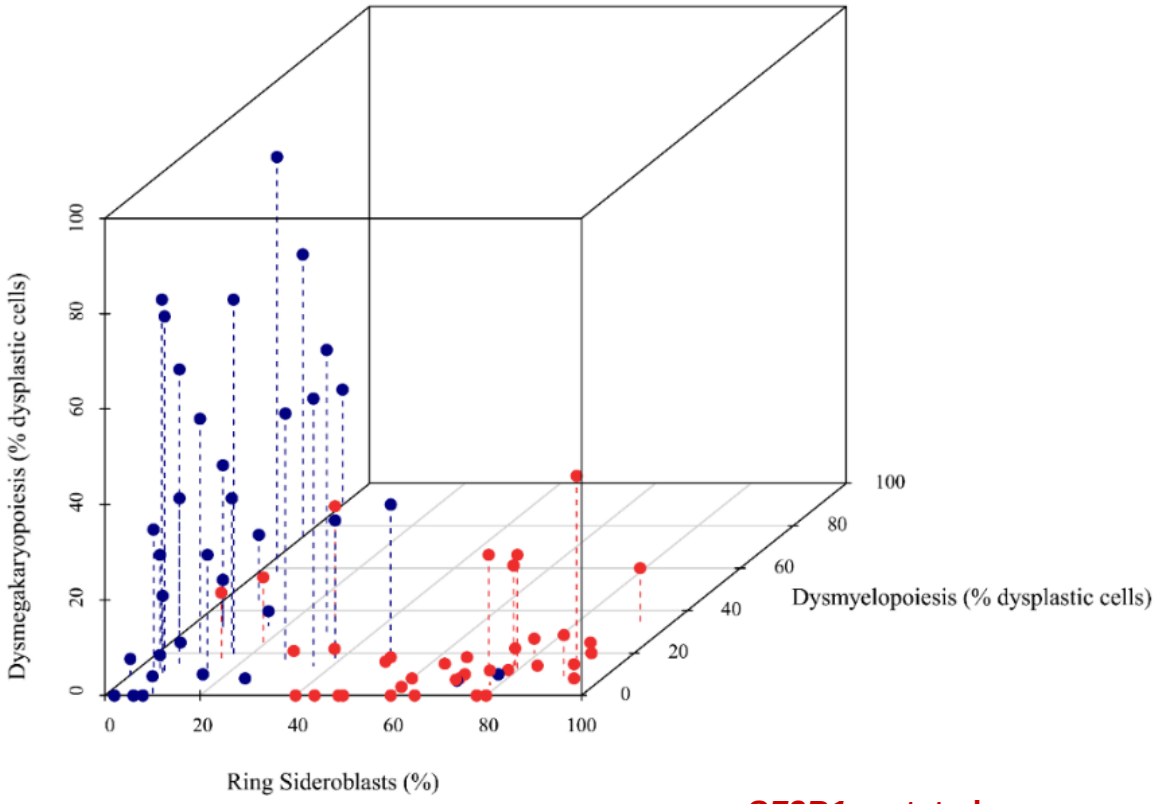
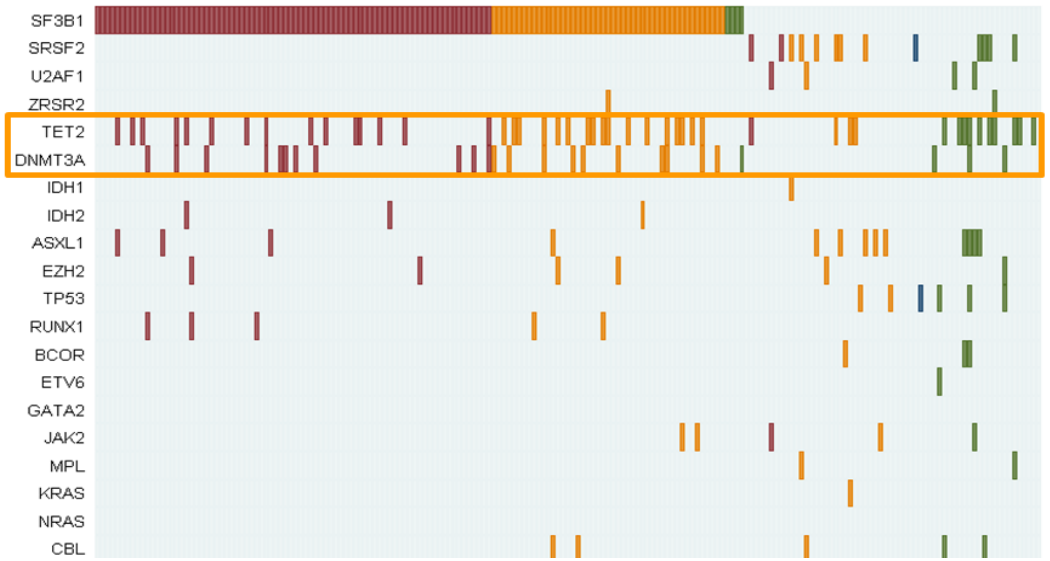
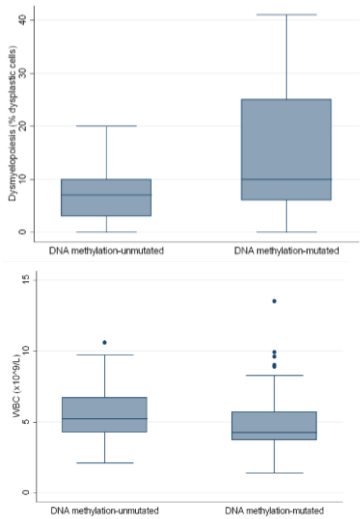
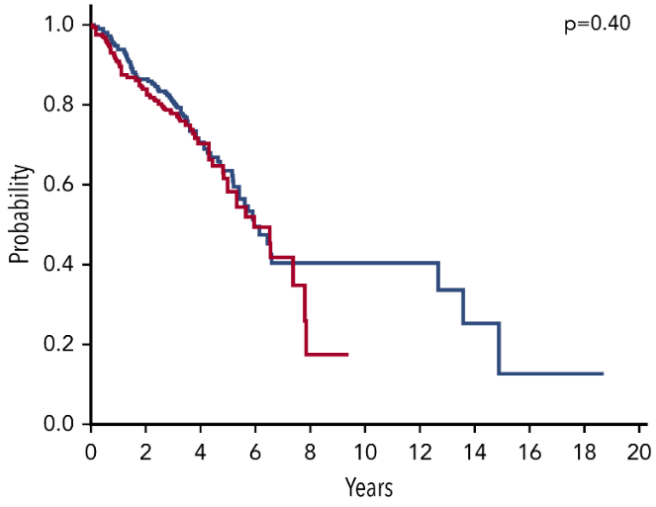
SF3B1 mutation identifies a distinct subset of MDS with ring sideroblasts



- ***SF3B1*-mutated**
- ***SF3B1*-unmutated**

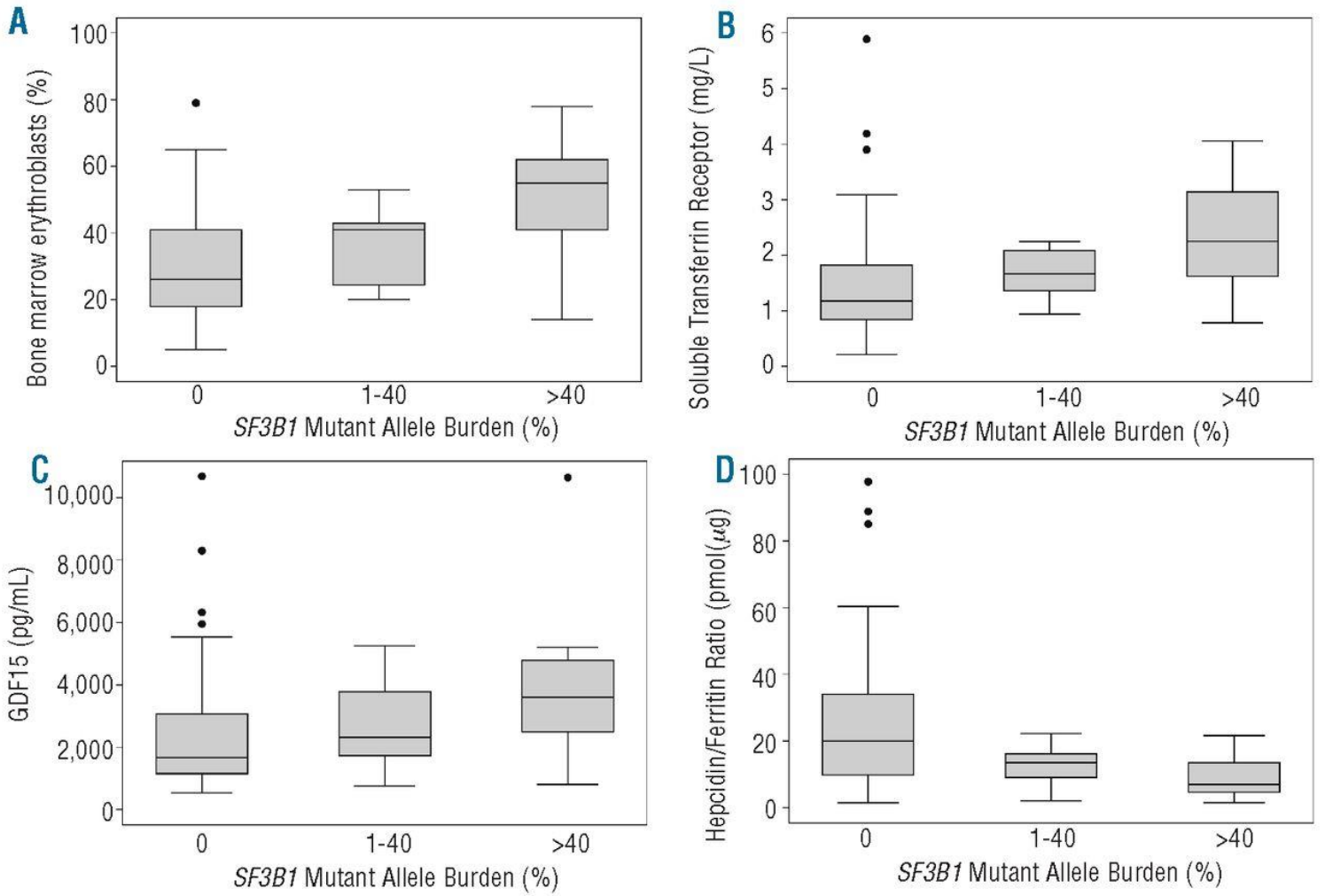






Malcovati et al. Blood 2014;124:1513-1521; Blood 2015;126:233-41

Relationship between *SF3B1* mutation, erythroid marrow activity and ineffective erythropoiesis



Ambaglio I et al. Haematologica 2013;98:420-423

MDS with *SF3B1* mutation (MDS-SF3B1)

	WHO Classification	IC Classification
Cytopenia	Any, ≥1	Any, ≥1
Blasts	<5% BM and <2% PB	<5% BM and <2% PB
Genetics	Absence of del(5q), -7, or complex karyotype	Any, except del(5q), -7/del(7q), abn3q26.2, or complex
Mutations	*SF3B1*,* without multi-hit *TP53*	*SF3B1* (≥10% VAF),* without multi-hit *TP53*, or ***RUNX1***
	**Detection of ≥15% ring sideroblasts may substitute for SF3B1 mutation*	**SF3B1-unmutated MDS-RS are classified as MDS, NOS, irrespective of the number of RS.*

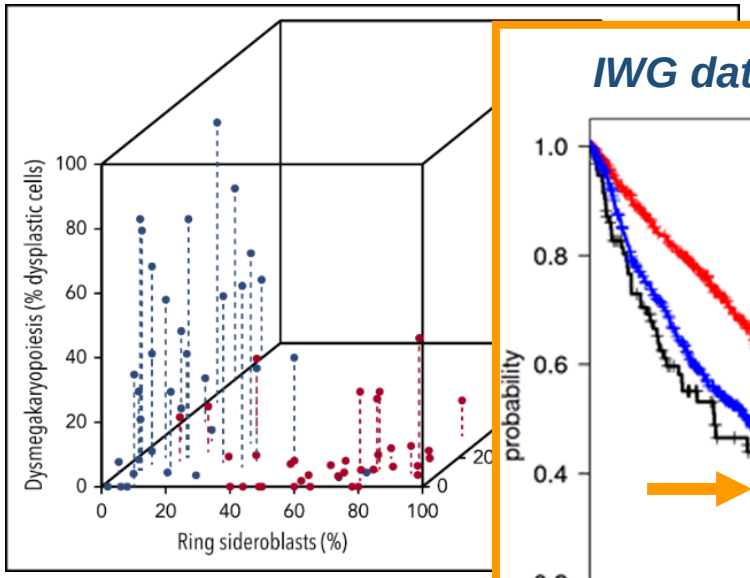
Khoury et al. Leukemia 2022

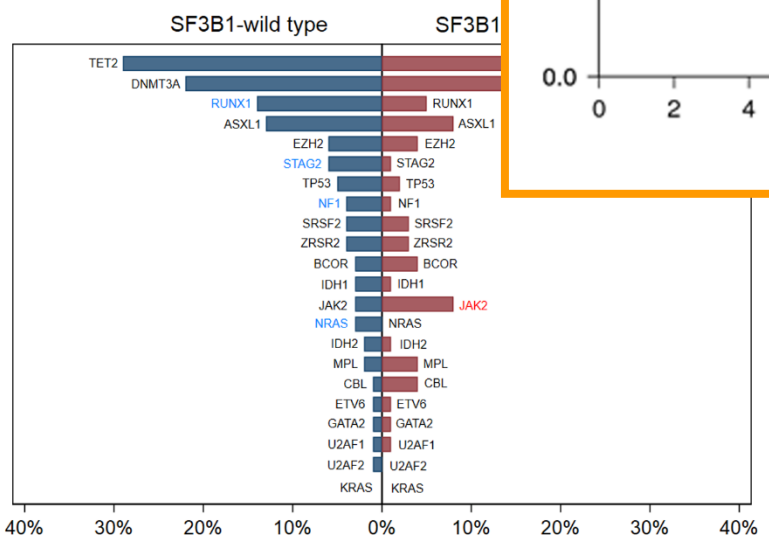
Arber et al. Blood 2022

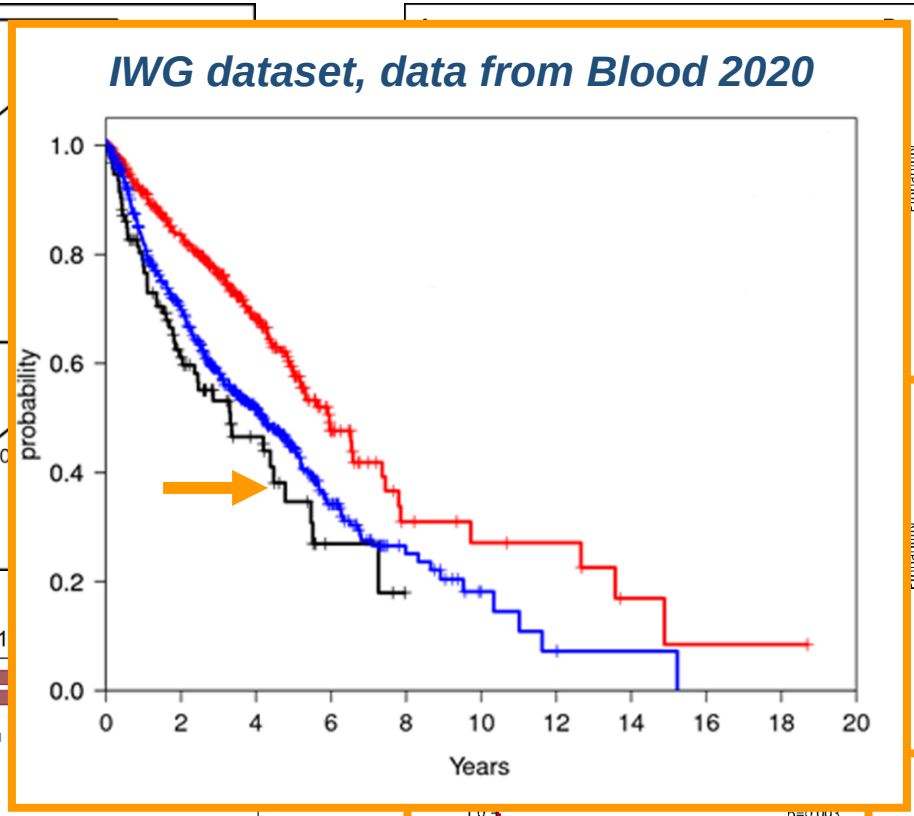
MDS with ring sideroblasts without *SF3B1* mutation

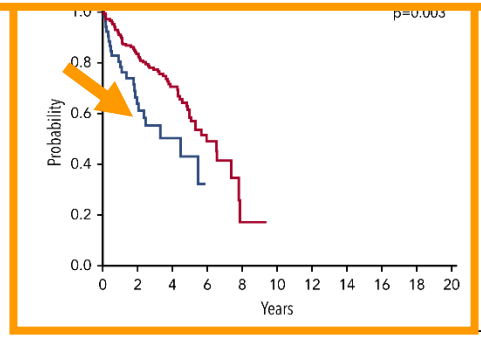
Variable	*SF3B1* WT	*SF3B1* mutated	P
Number of patients	2684	795	
Sex			
Female	978 (36)		
Male	1706 (64)		
WHO 2008			
Del(5q)			
RARS	60 (2)	273 (34)	
RA/RCUD	238 (9)	21 (3)	
RCMD	520 (19)	18 (2)	
RCMD-RS	56 (2)	171 (22)	
RAEB-1	412 (15)	49 (6)	
RAEB-2	426 (16)	28 (4)	
Unknown	735 (27)	206 (26)	
FAB			
RA	611 (23)	61 (8)	
RARS	103 (4)	352 (44)	
RAEB	763 (28)	86 (11)	
RAEB-T	48 (2)	5 (1)	
CMML	61 (2)	4 (1)	
Unknown	1098 (41)	287 (36)	
11-20	486 (18)	33 (4)	
21-30	23 (1)	2 (<1)	
Unknown	179 (7)	31 (4)	
Hemoglobin (g/dL), median (IQR)	9.9 (8.7, 11.3)	9.5 (8.6, 10.5)	<.001
<8.0	307 (11)	102 (13)	0.001
8.0-9.99	1000 (37)	353 (44)	
10.0-11.99	774 (29)	249 (31)	
≥12.0	447 (17)	34 (4)	
Unknown	156 (6)	57 (7)	
ANC (×10⁹/L), median (IQR)	1.6 (0.8, 3.3)	2.73 (1.7, 4.24)	<.001
<0.5	262 (10)	20 (3)	<.001
0-5 to 0.99	393 (15)	43 (5)	
1.0-1.8	415 (15)	96 (12)	
≥1.8	940 (35)	410 (52)	
Unknown	674 (25)	226 (28)	
Platelets (×10⁹/L), median (IQR)	93 (48, 171)	261 (150, 378)	<.001
<50	639 (24)	41 (5)	<.001
50-100	668 (25)	60 (8)	
100- 149	410 (15)	76 (10)	
150-449	662 (25)	422 (53)	
≥450	74 (3)	118 (15)	
Unknown	231 (9)	78 (10)	

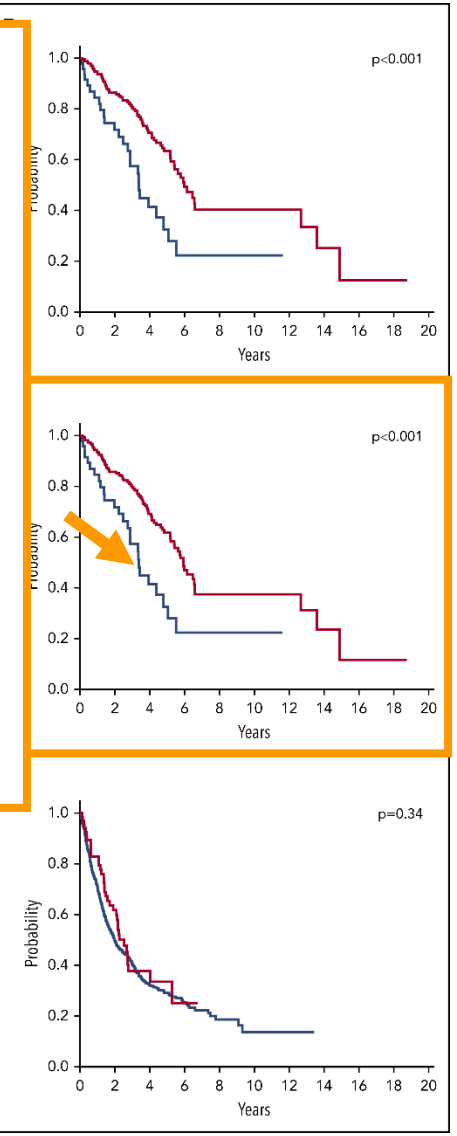
WHO 2017
19% of MDS-RS











Malcovati et al. Blood 2020; 136:157-170

Relationship between del(5q) and *SF3B1* mutation

Variable	*SF3B1* WT	*SF3B1* mutated	P
Number of patients	2684	795	
Sex			
Female	978 (36)	349 (44)	<.001
Male	1706 (64)	446 (56)	
Age (y) at sample, median (range)	69 (18-99)	72 (34-94)	<.001
WHO 2008			
Del(5q)	91 (3)	20 (3)	<.001
RARS	60 (2)	273 (34)	
RA/RCUD	238 (9)	21 (3)	
RCMD	520 (19)	18 (2)	
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≥450	74 (3)	118 (15)	
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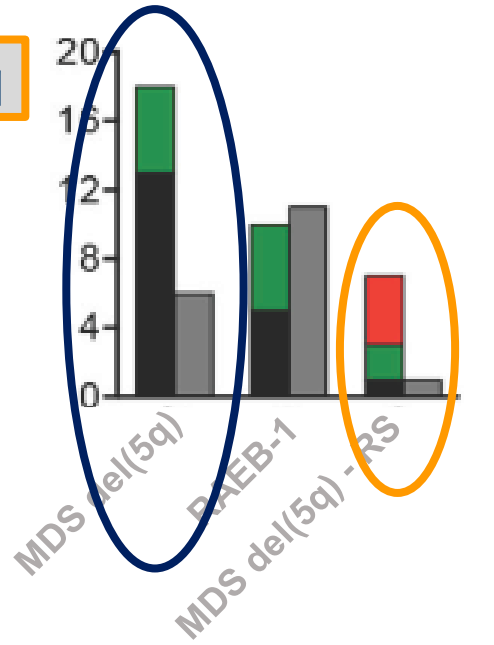
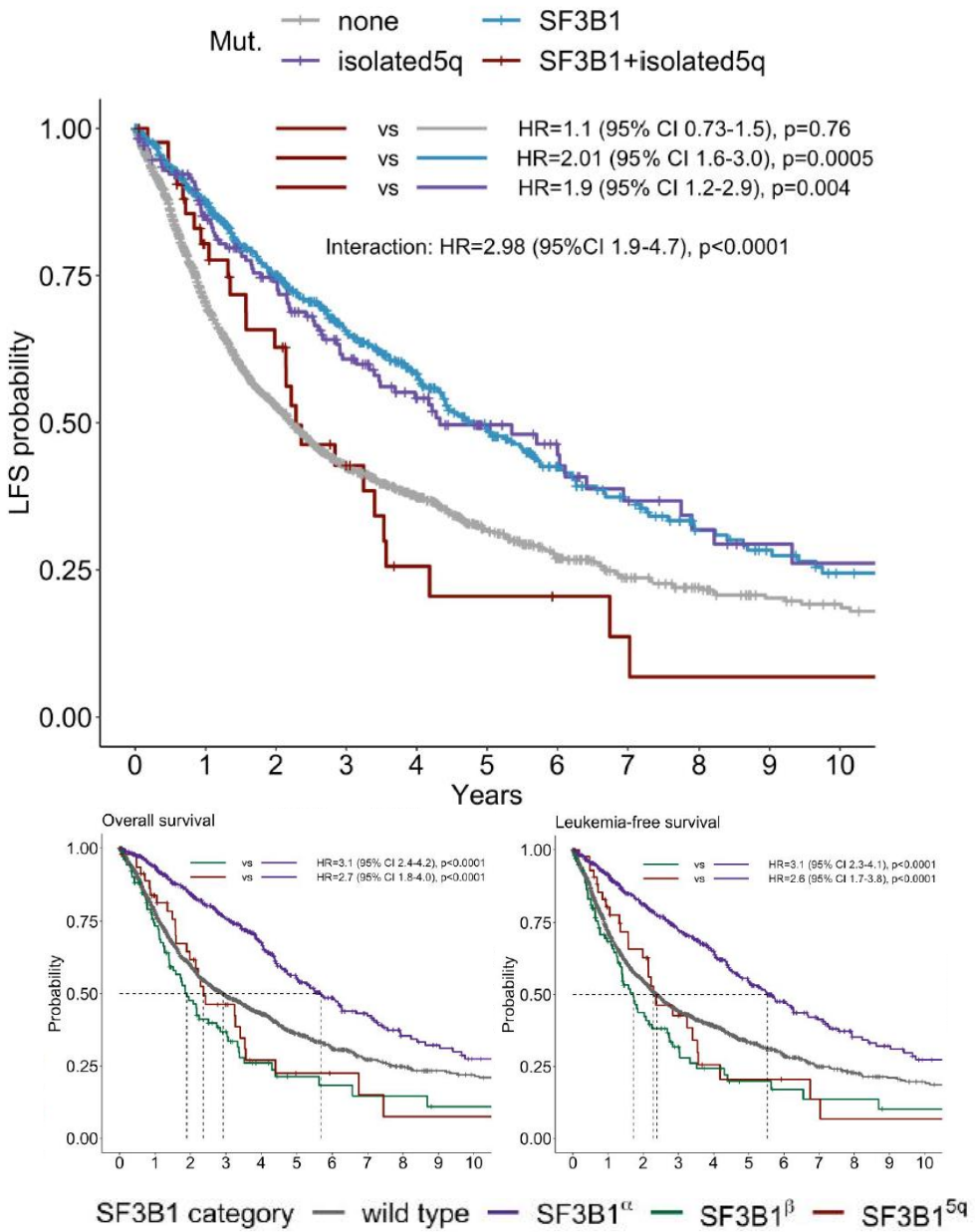
18% of MDS-5q





Cancer Cell. 2014;25:794-808; Blood 2020; 136:157-170; NEJM Evidence 2022

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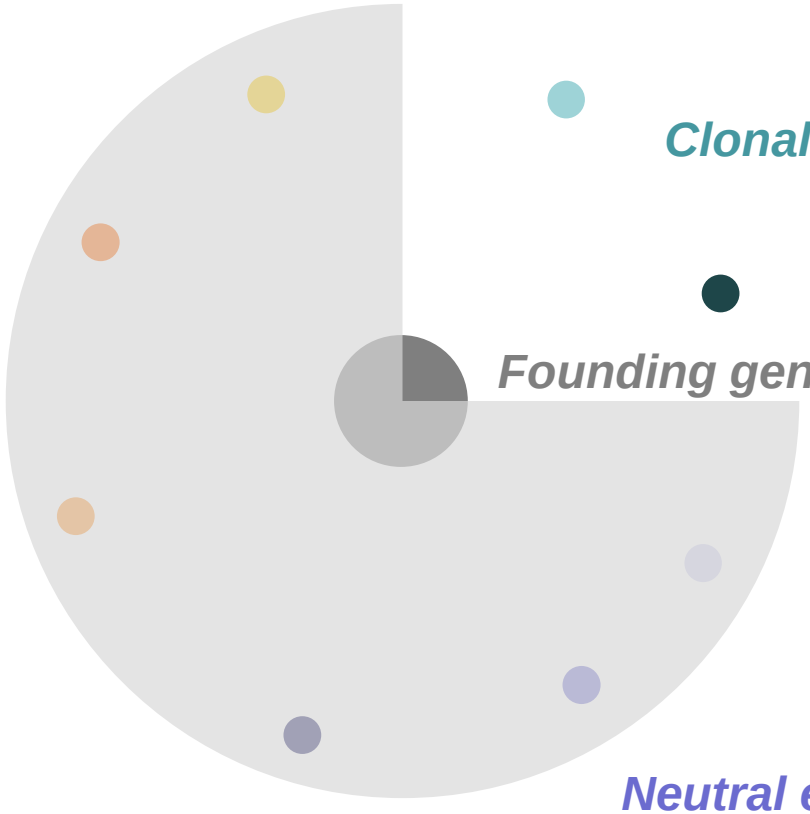
Genetic canalization (predestination) dictated by founding mutation

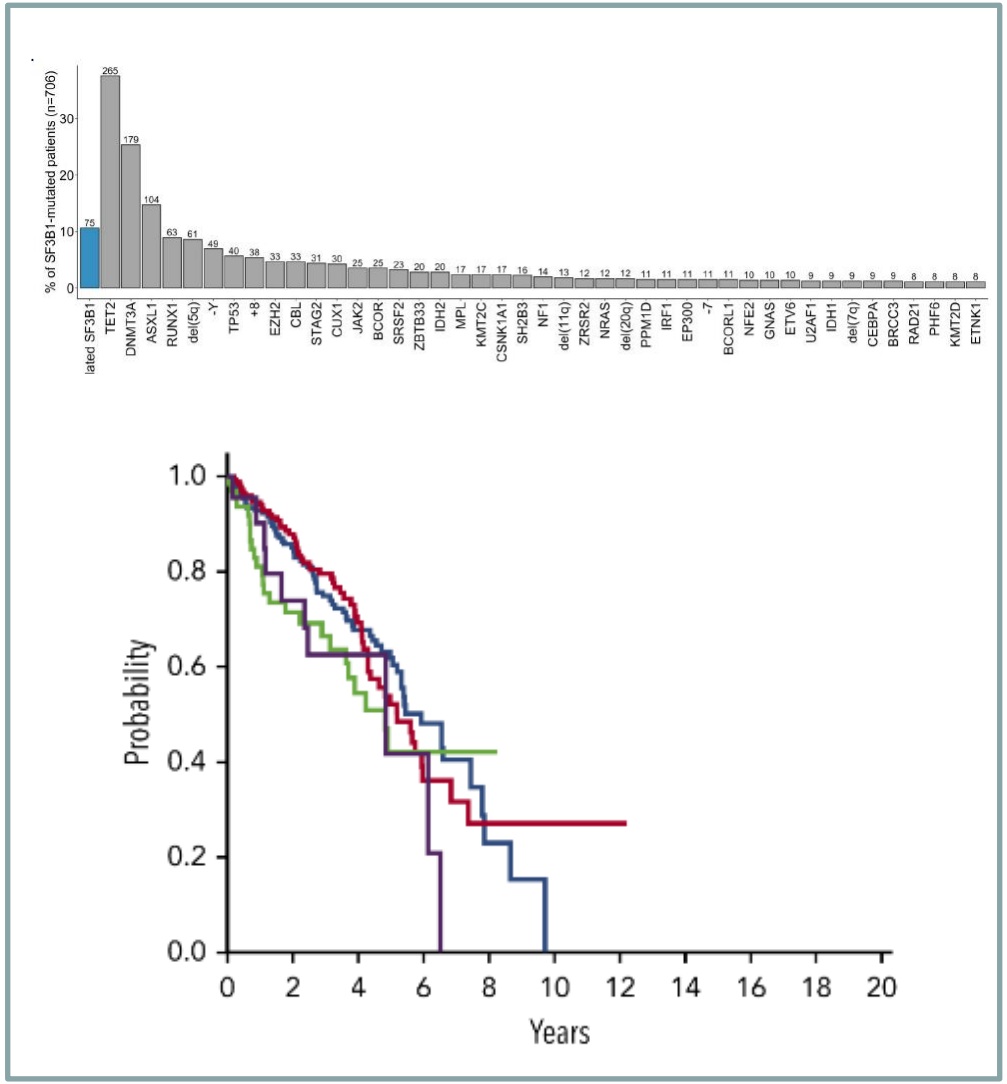


Cell death

Clonal progression

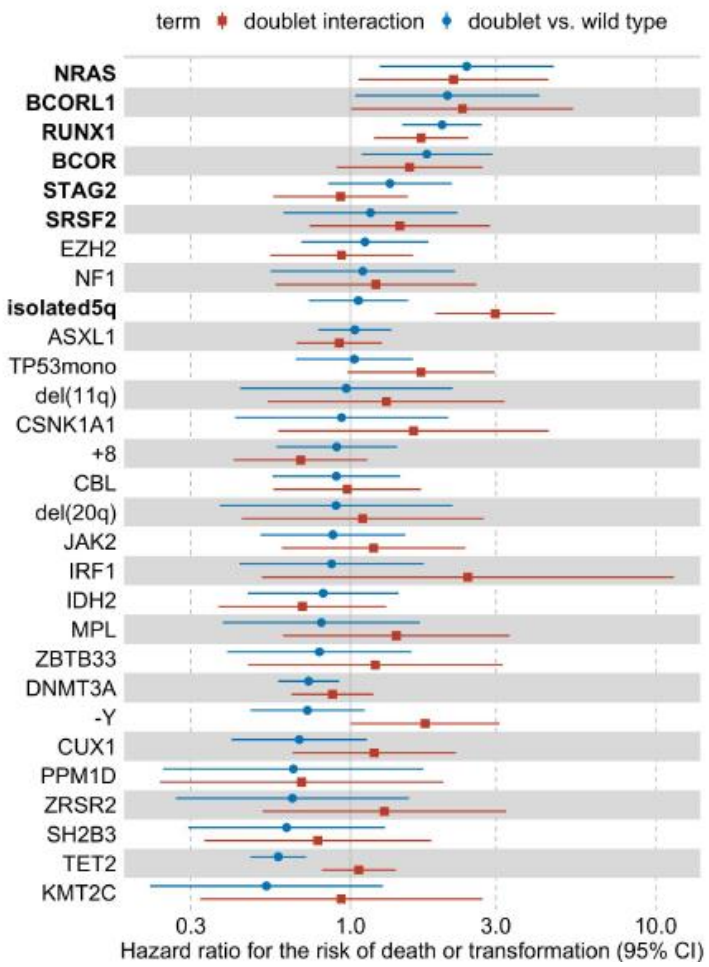
Founding genetic lesion

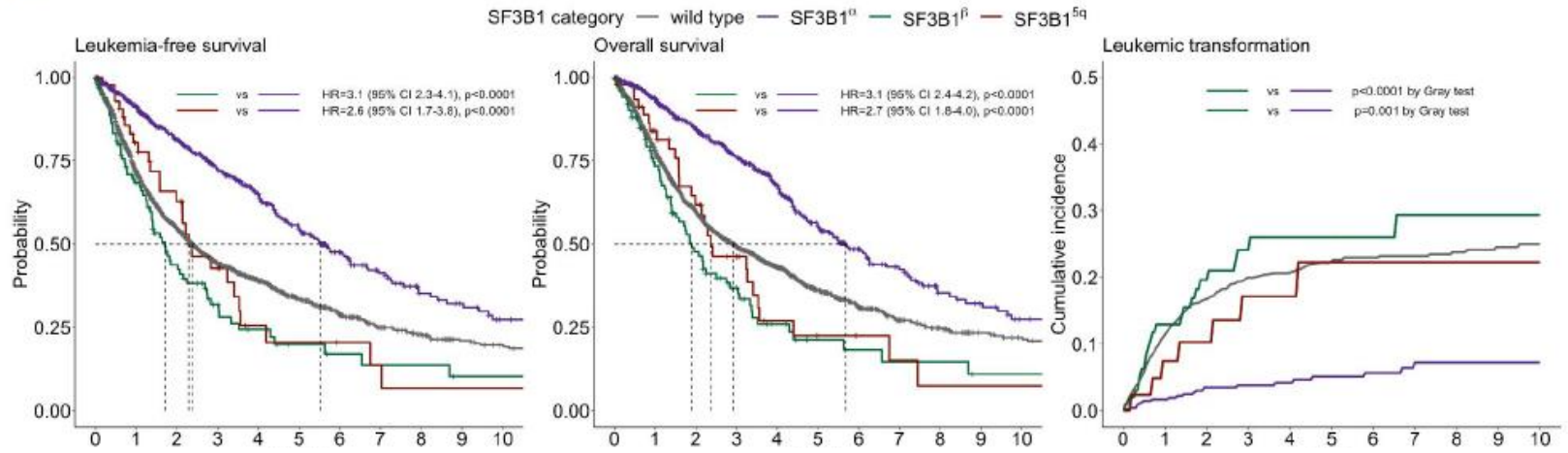
Neutral effect

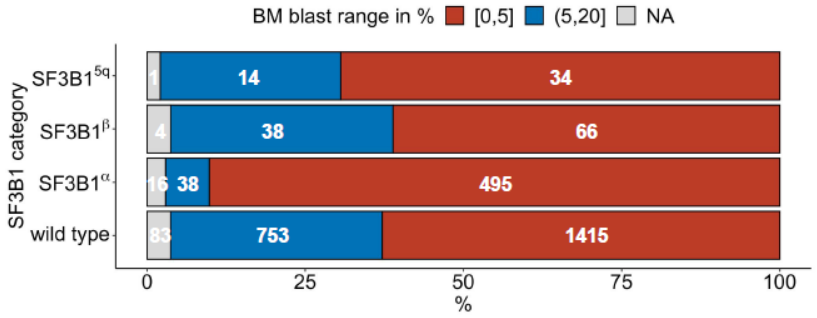


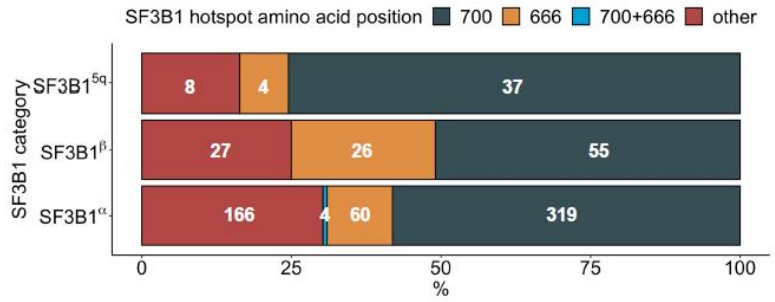
Malcovati et al. Blood 2020; Bernard et al. NEJM Evidence 2022

SF3B1 co-mutations and effect on outcomes







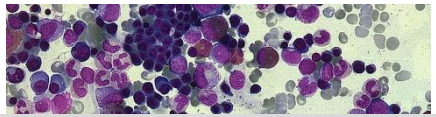


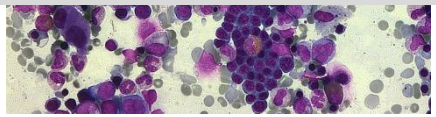
Bernard et al. NEJM Evidence 2022

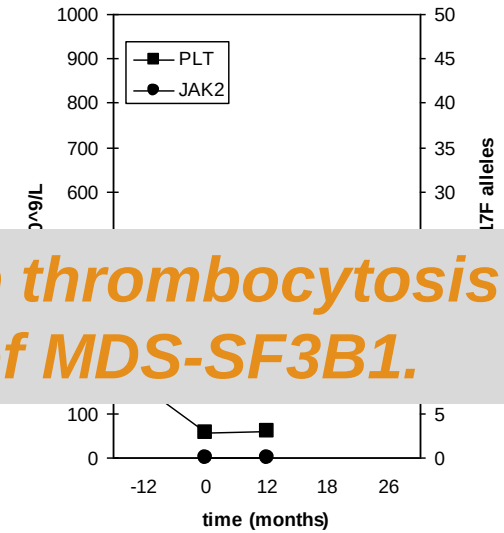
MDS/MPN with thrombocytosis and *SF3B1* mutation

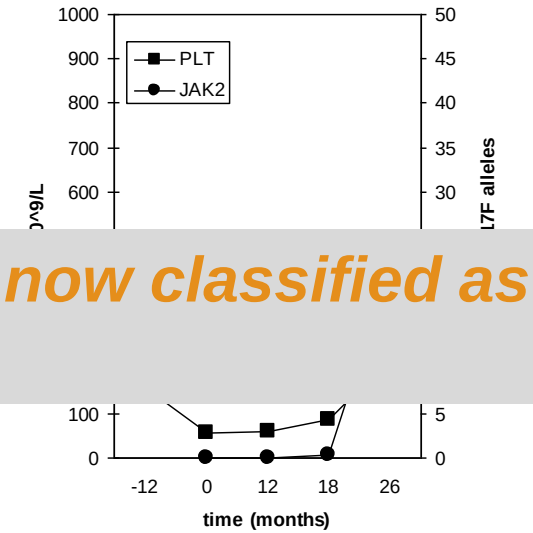
***SF3B1* muta**

***JAK2, MPL or CALR* mutation**









MDS-SF3B1 that later develop thrombocytosis are now classified as thrombocytotic progression of MDS-SF3B1.

Malcovati et al. Blood. 2009;114:3538-45; Blood. 2011;118:6239-46; Blood 2015;126:233-41

Outline

- *SF3B1* mutation in the pathophysiology of MDS with ring sideroblasts
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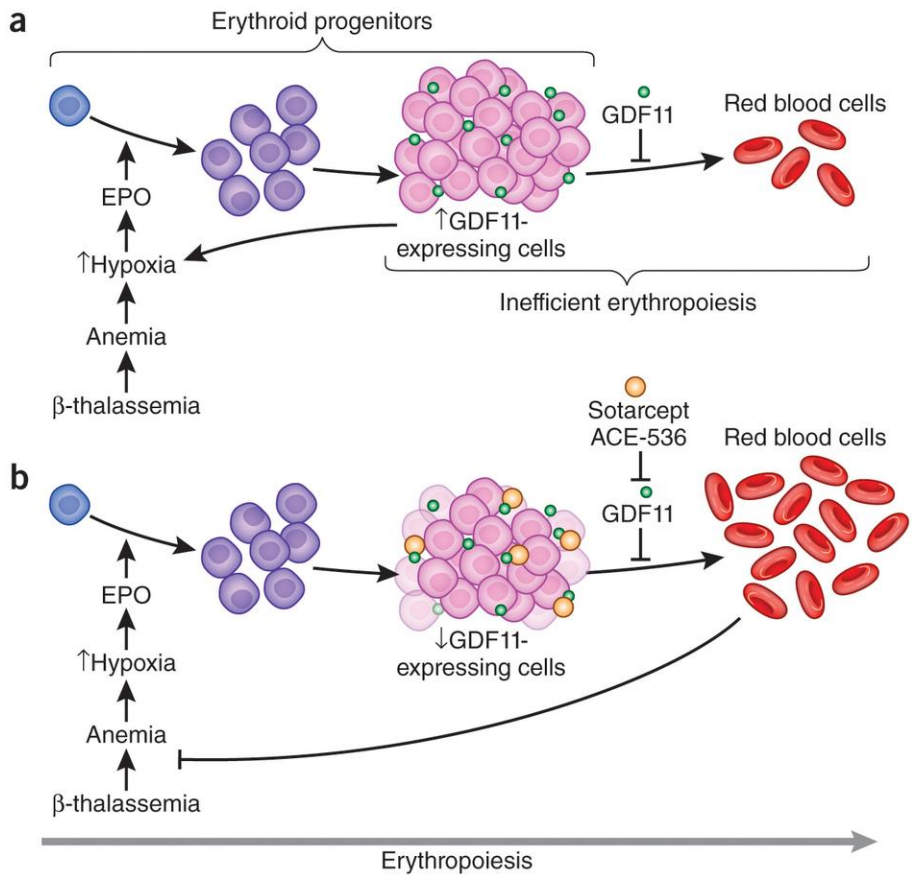
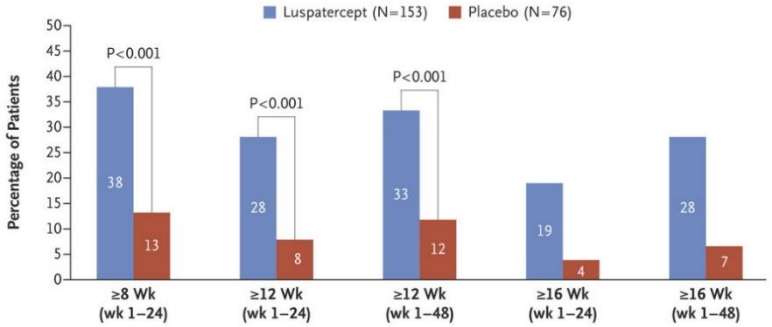
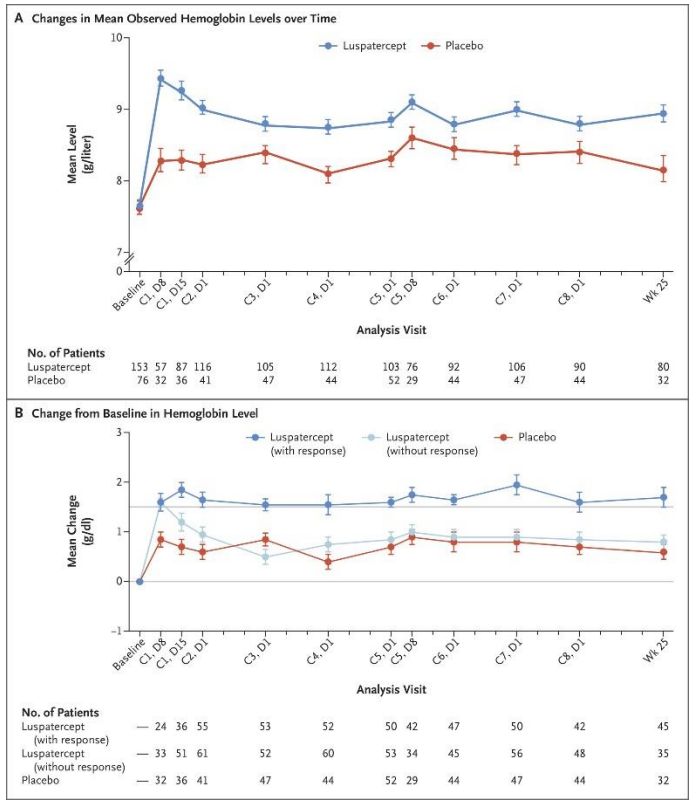
- *SF3B1*-mutated clones and precursor states: CHIP, CCUS & early MDS

Inhibition of GDF11 in anemia with ineffective erythropoiesis



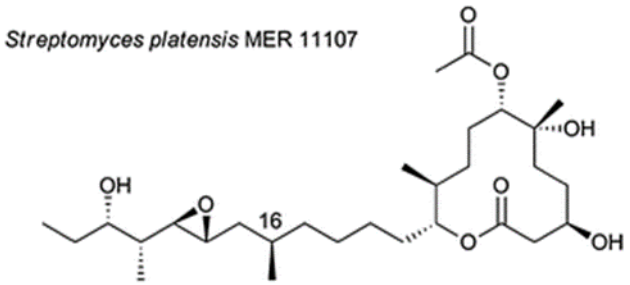


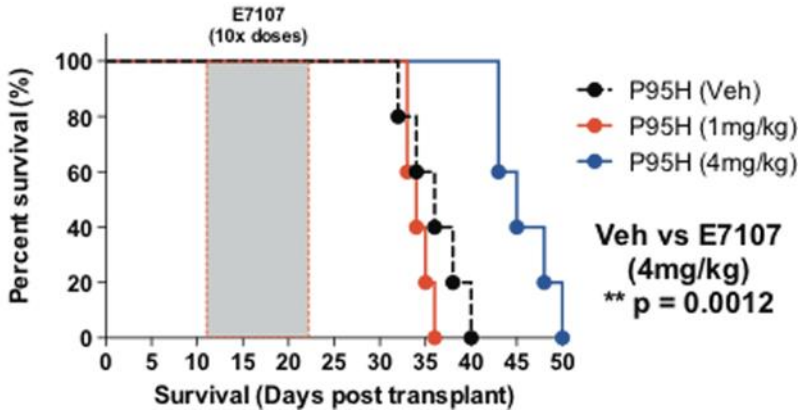


Nat Med. 2014; Lancet Oncol. 2017; N Engl J Med 2020

Therapeutic targeting of RNA splicing in MDS

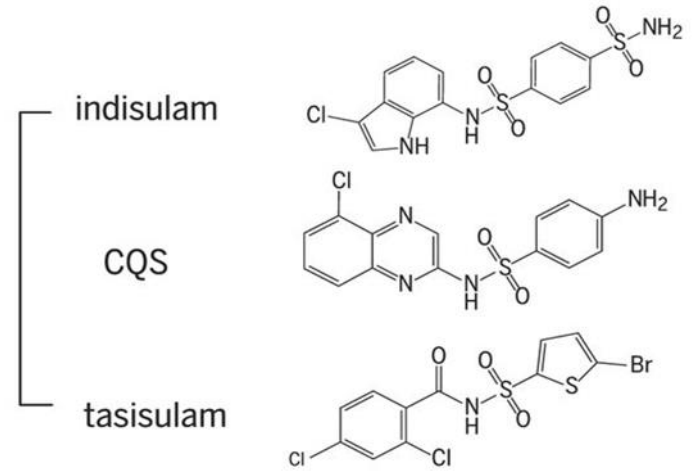
Pladienolides

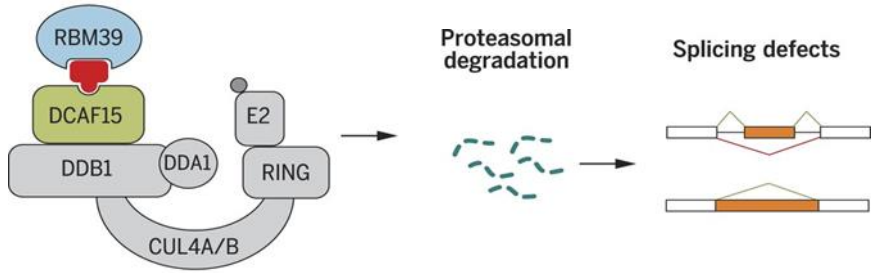




Lee et al. Blood 2015 126:4

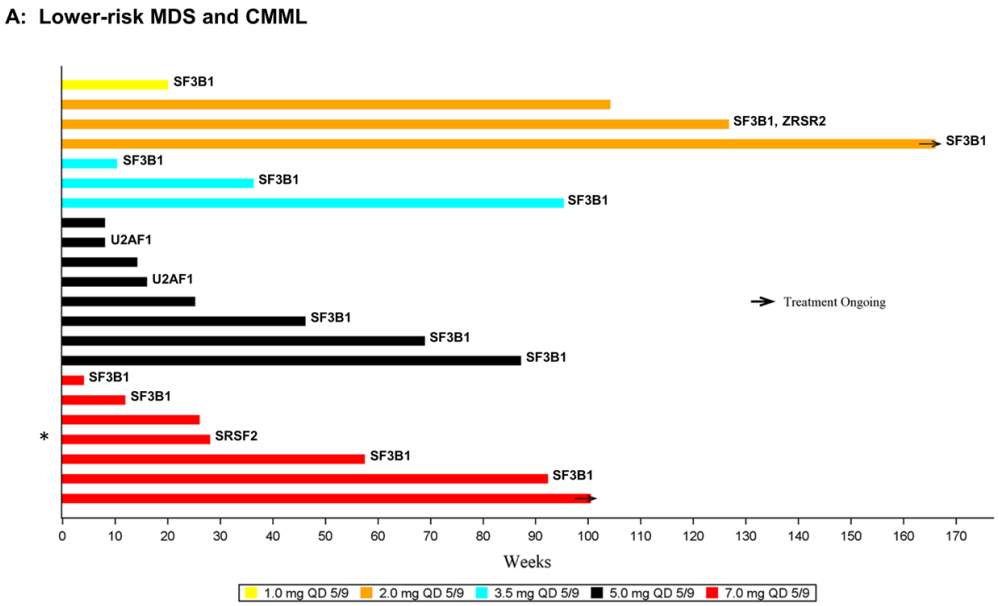
Sulfonamides

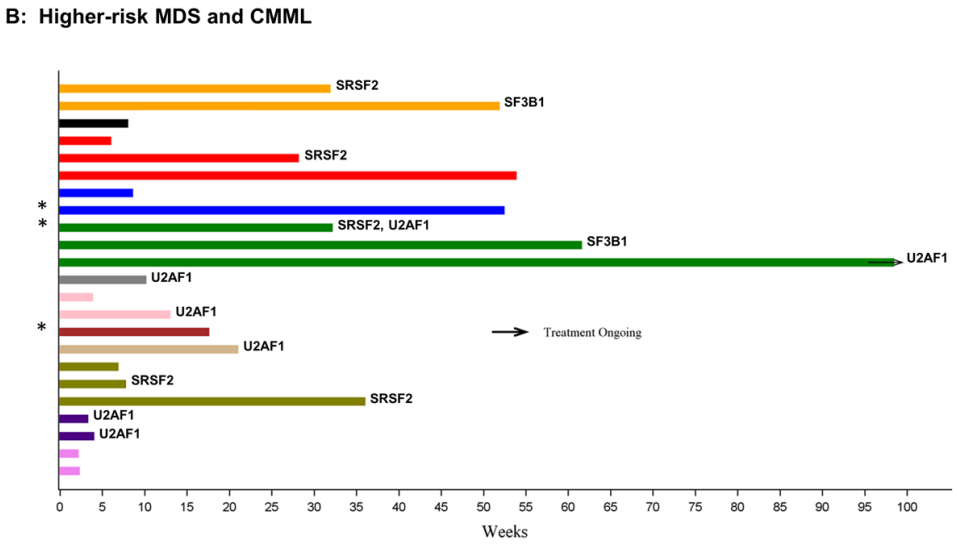


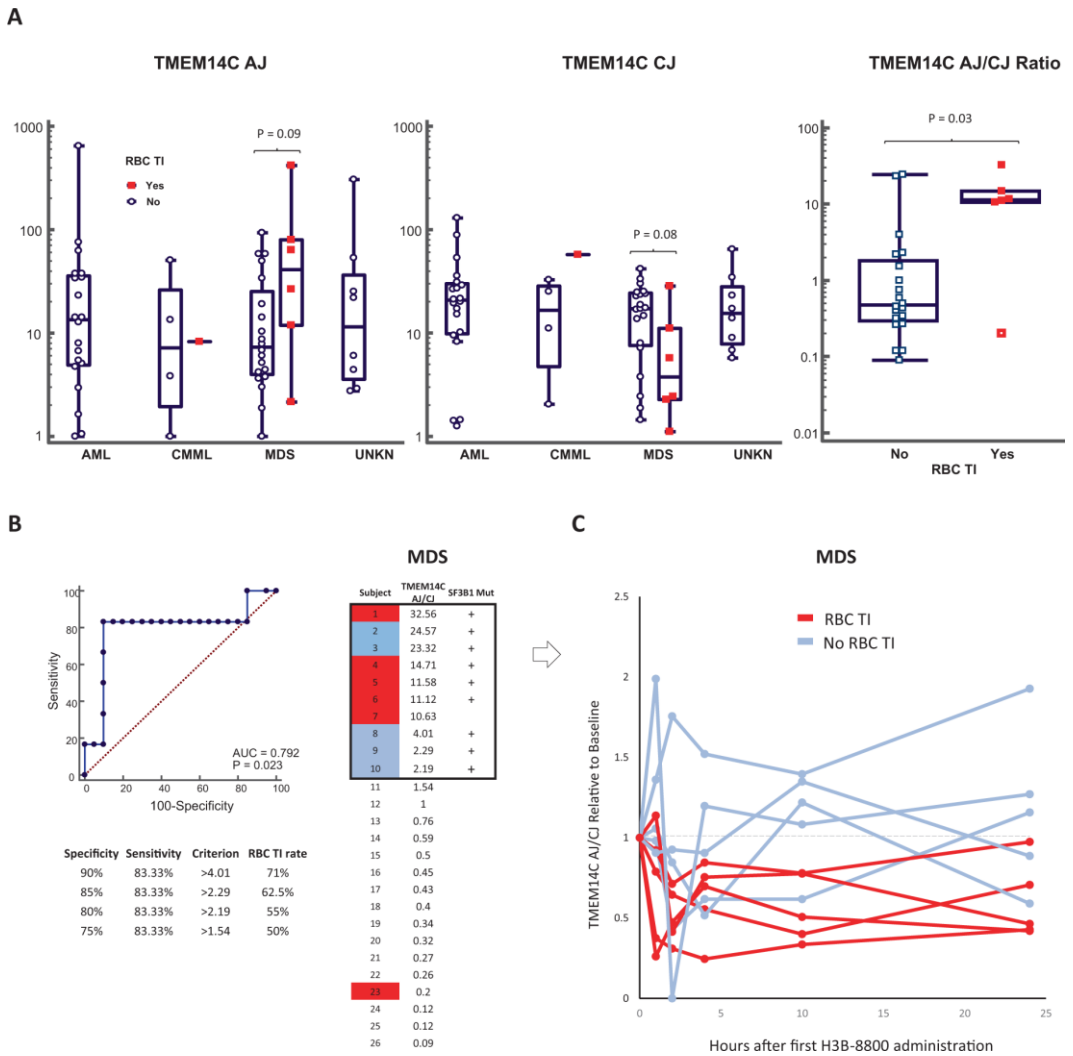


Han et al. Science 2017;356:eaal3755

Phase I First-in-Human Study of the oral SF3B1 modulator H3B-8800 in myeloid neoplasms







Leukemia. 2021;35:3542-3550

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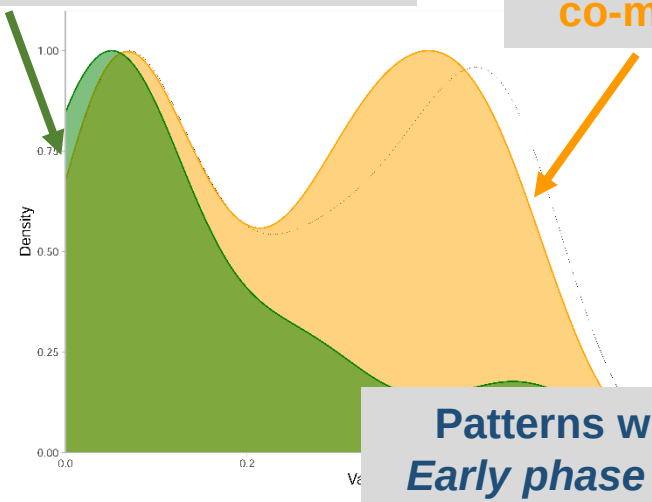
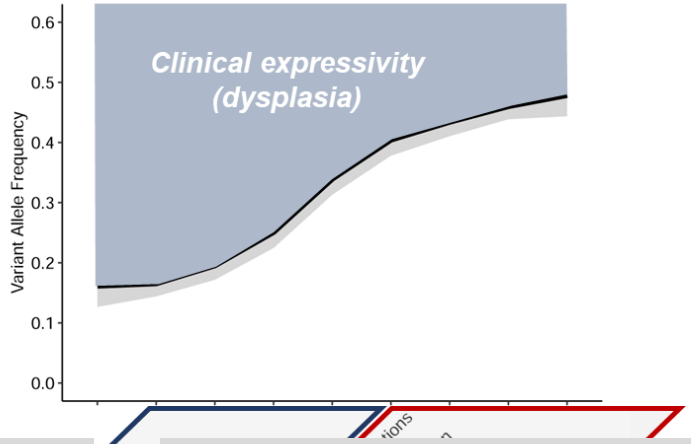
Segregation of CCUS into pre-malignant and early-malignant states

Isolated *DNMT3A* mutation

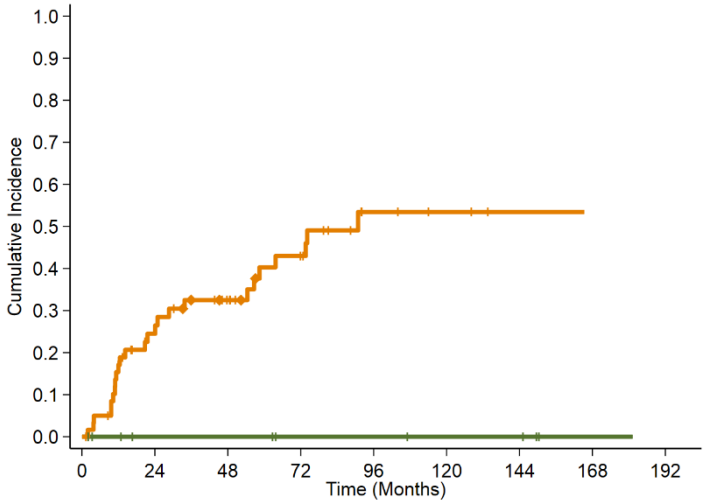
TET2, _ASXL1_, SF co-mutation patterns

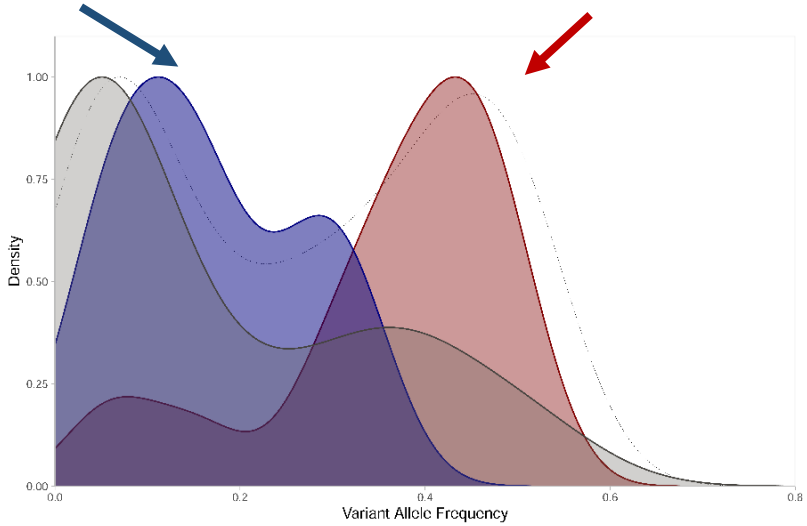




Patterns with strong clinical expressivity
Early phase of malignant clones that do not have yet reached full clinical expressivity

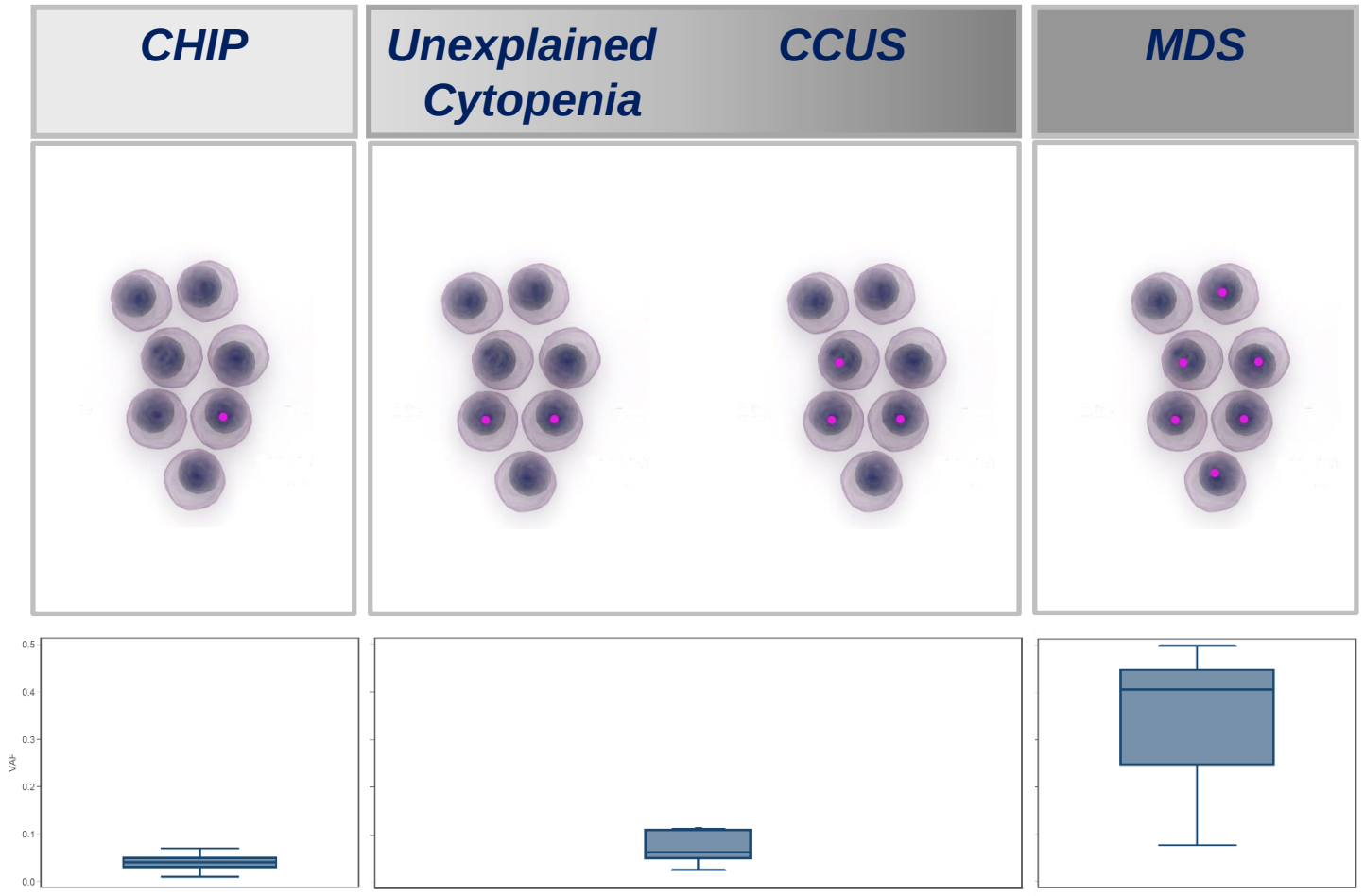
Patterns with mild clinical expressivity
Dominant clones with clone metrics not different from overt MDS





Gallì A et al. Blood 2021.

Relationship between *SF3B1* clone size and hematologic phenotype



Malcovati et al. Blood 2011;118:6239-46; Blood. 2017;129:3371-3378

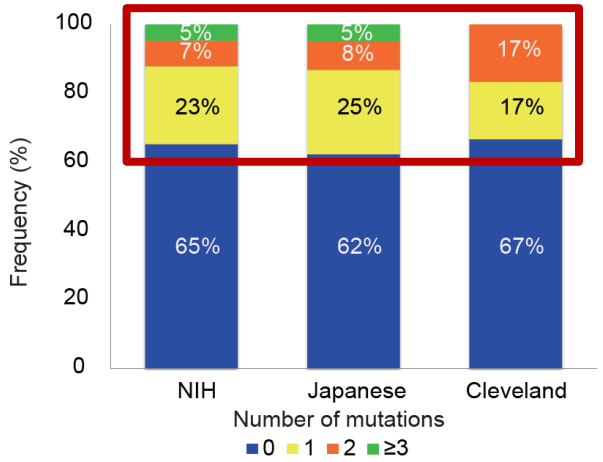
MDS with *SF3B1* mutation (MDS-SF3B1)

Cytopenia	Any, ≥1
Blasts	<5% BM and <2% PB
Genetics	Any, except del(5q), -7/del(7q), abn3q26.2, or complex
Mutations	*SF3B1* (≥10% VAF), without multi-hit *TP53*, or ***RUNX1***

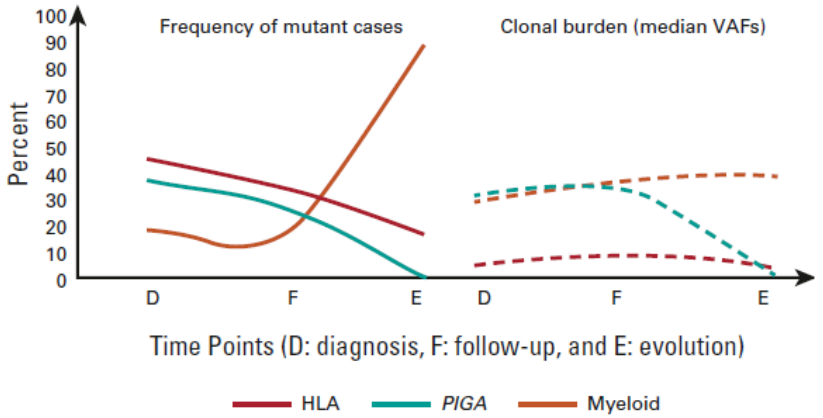
Although dysplasia is typically present, it is not required.

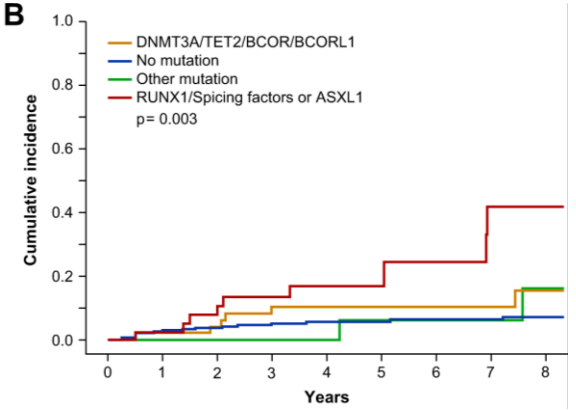
Arber et al. Blood 2022

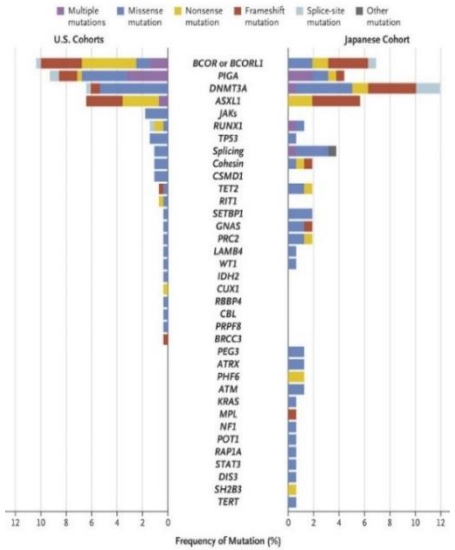
Somatic mutations and clonal hematopoiesis in aplastic anemia

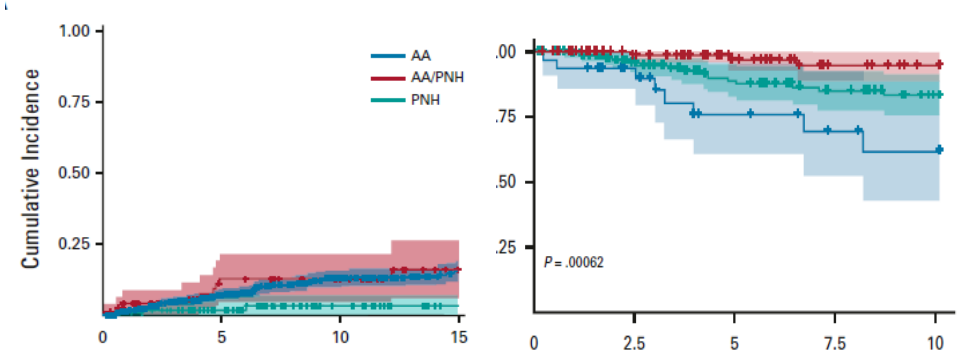


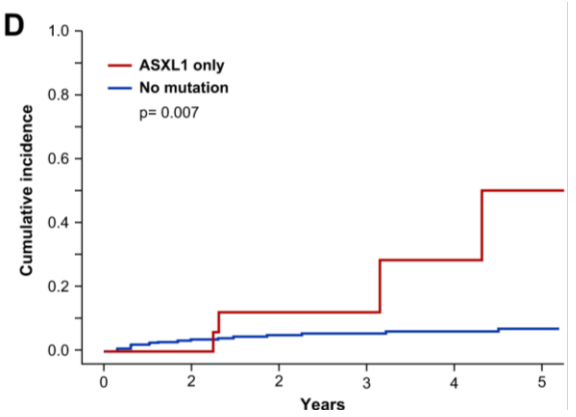
36%











N Engl J Med. 2015; Blood. 2014; Blood 2016; Blood 2017; J Clin Oncol 2022; Leukemia 2022

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