Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

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How I treat high-risk MDS

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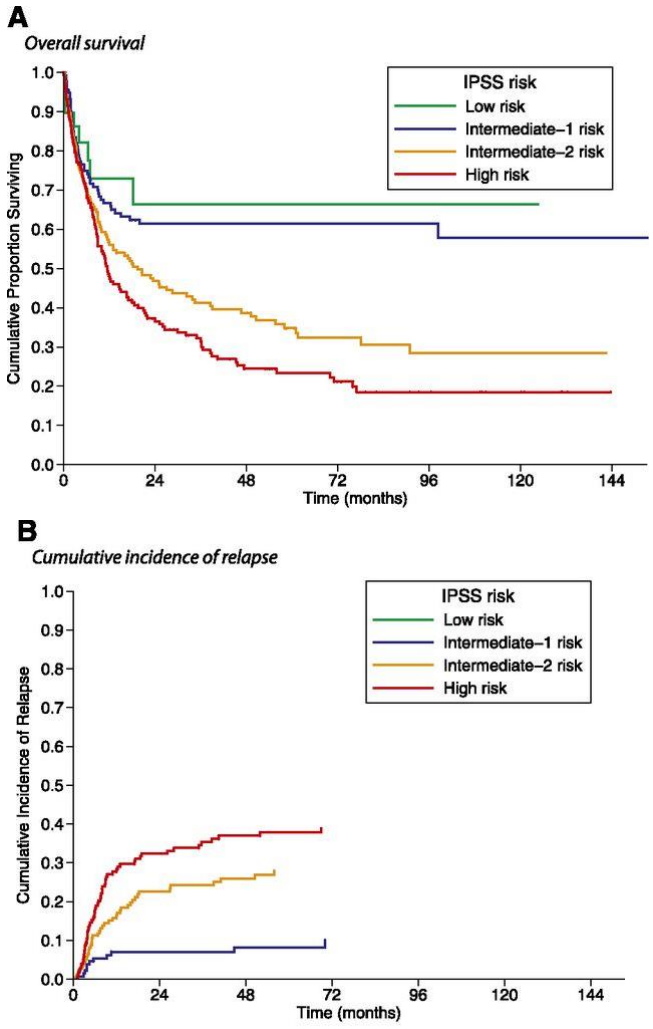
Clinical decision making in MDS - Critical issues

- How we can define HIGH-RISK MDS?

International Prognostic Scoring System (IPSS) 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.

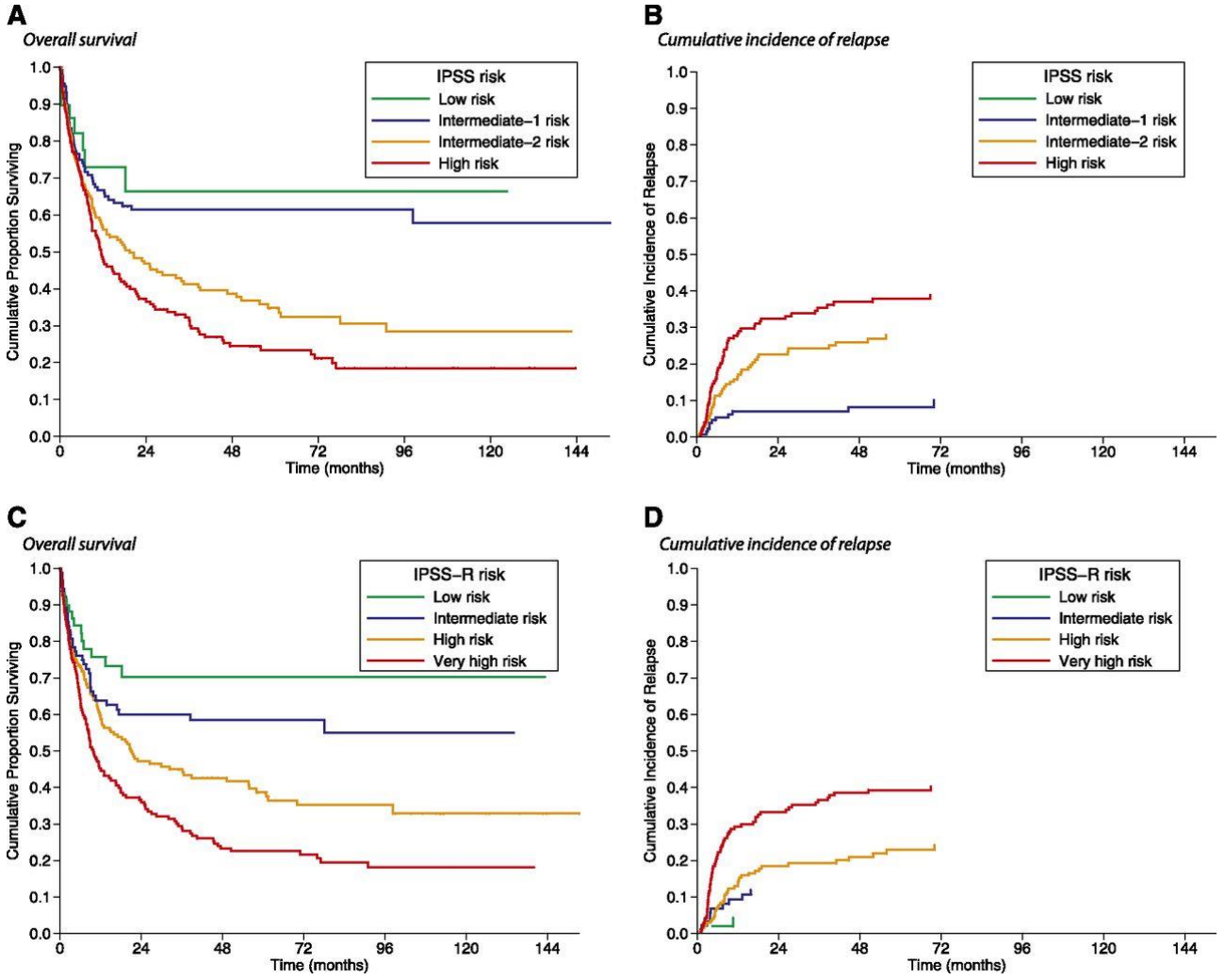
°Hemoglobin < 10 g/dL, absolute neutrophil count < 1,500/µL, platelet count < 100,000/µL.

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

Greenberg P et al. Blood 1997;89:2079-2088

Alessandrino P et al. Blood 2008;112:895-902

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

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

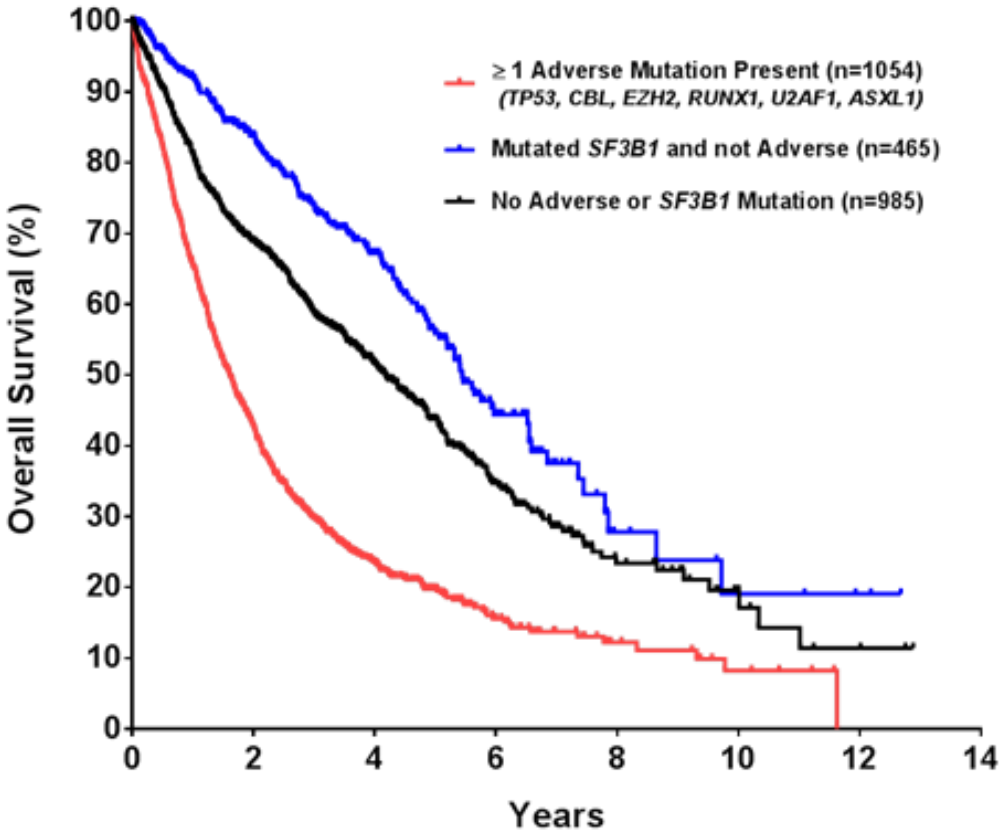


Figure 2: Kaplan-Meier curve of overall survival in years for the 2504 patients with sequence results for *SF3B1* and all six adverse genes (*TP53*, *CBL*, *EZH2*, *RUNX1*, *U2AF1*, and *ASXL1*).

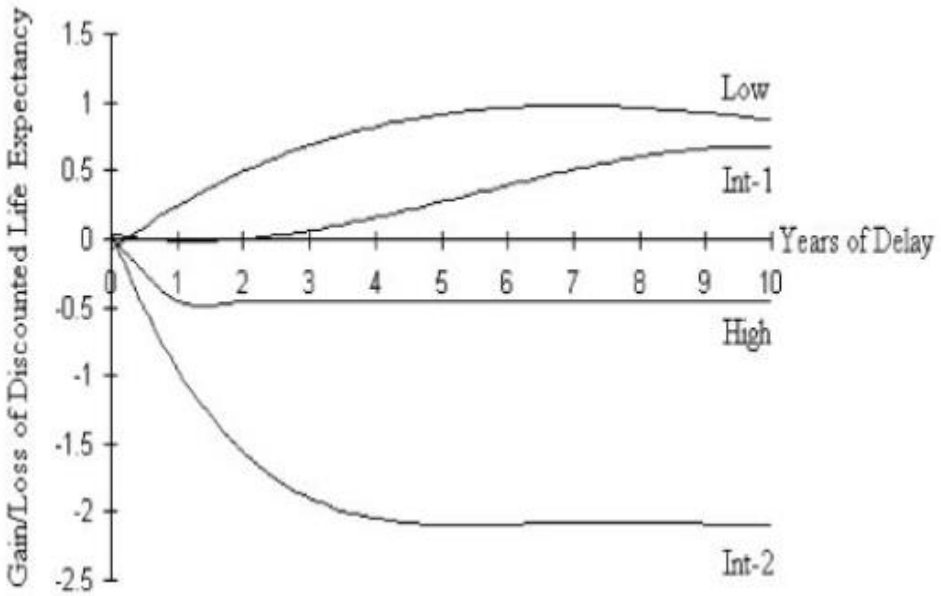
Transplantation decision making in MDS - Critical issues

- Which tools are available for transplant decision making?
- How we can define optimal timing of transplantation in individual patient?
- What is the clinical relevance of somatic mutations in transplantation decision making in MDS?

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*

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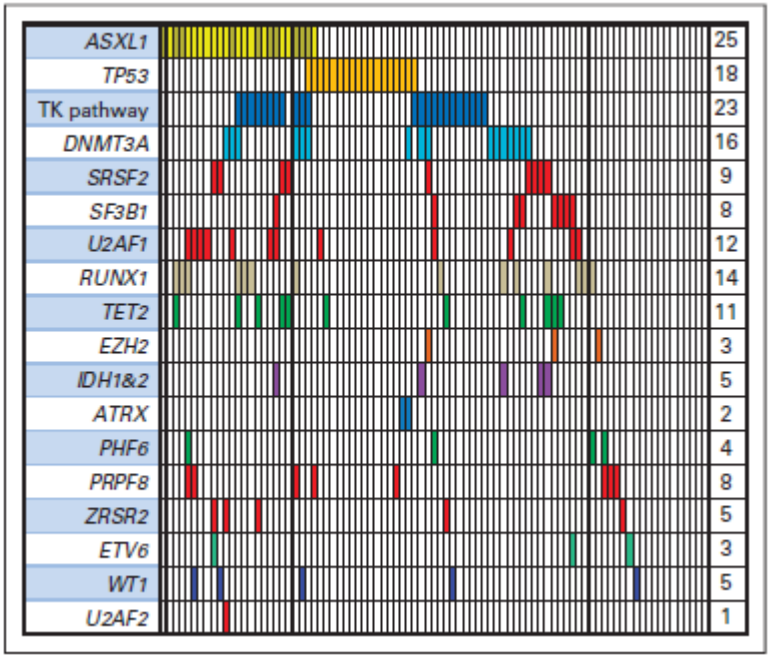
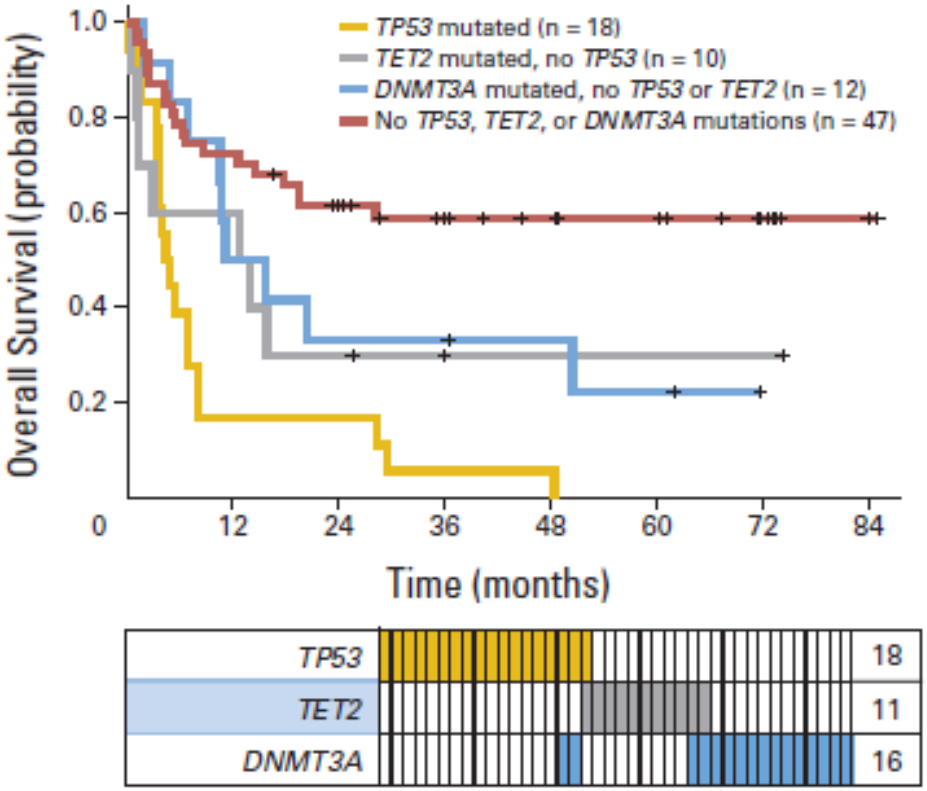
Transplantation decision making in MDS - Critical issues

- What is the clinical relevance of somatic mutations in transplantation decision making in MDS?

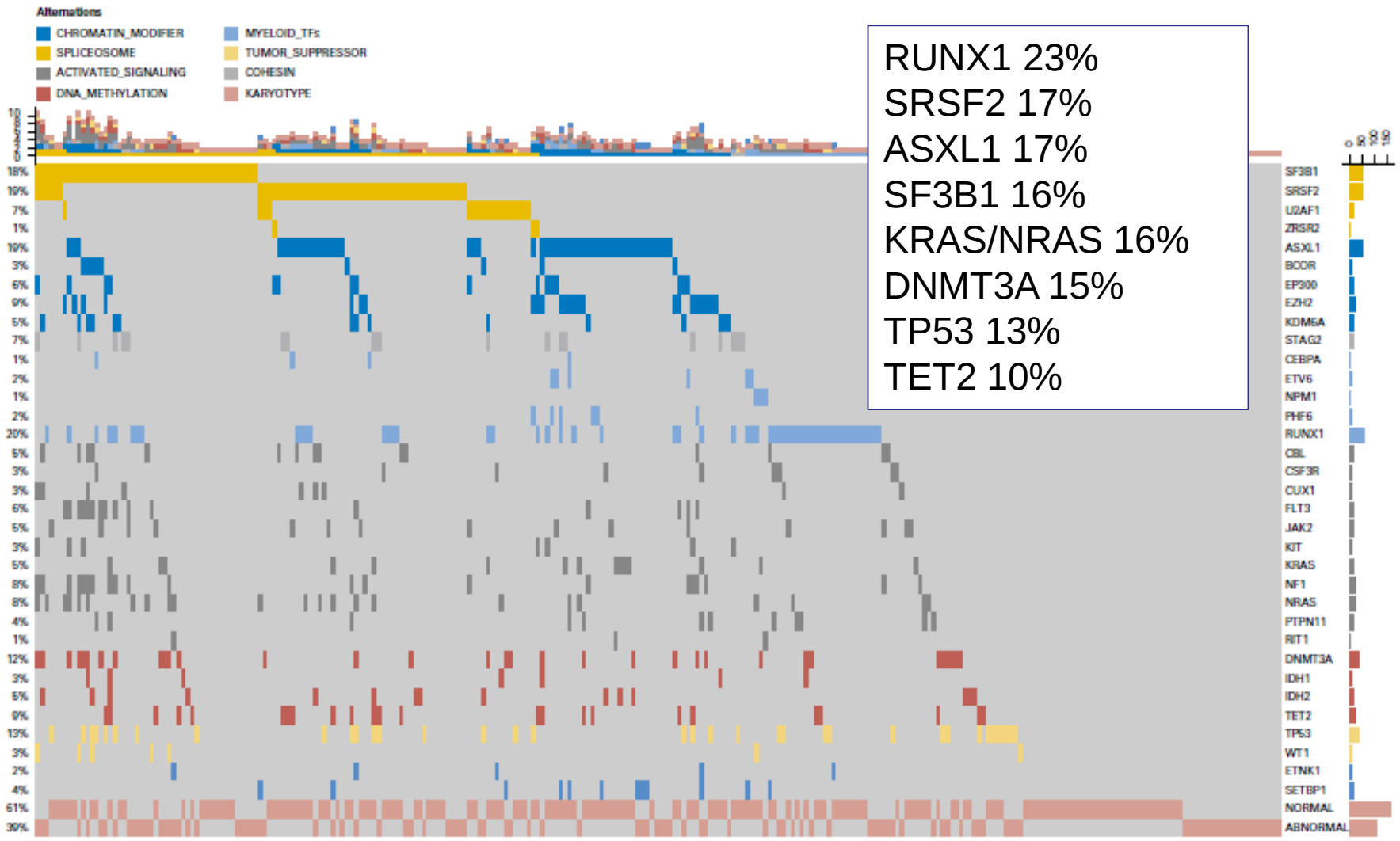
Somatic Mutations Predict Poor Outcome in Patients With MDS After Hematopoietic Stem-Cell Transplantation





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

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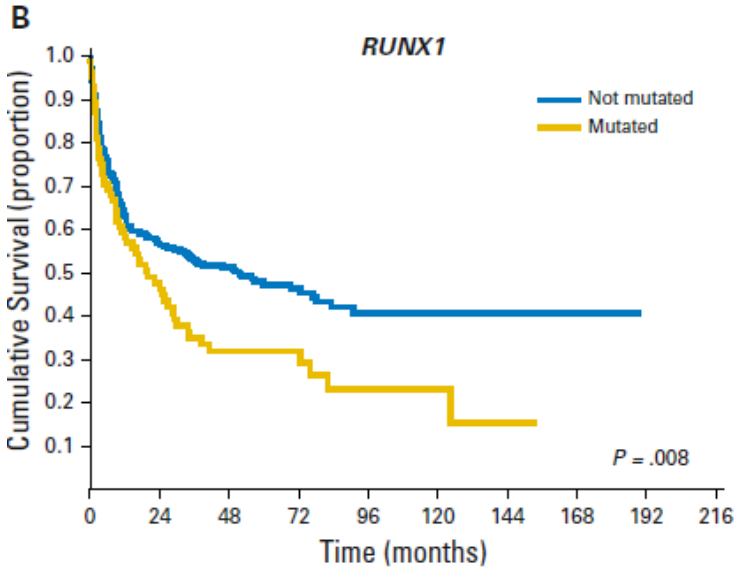
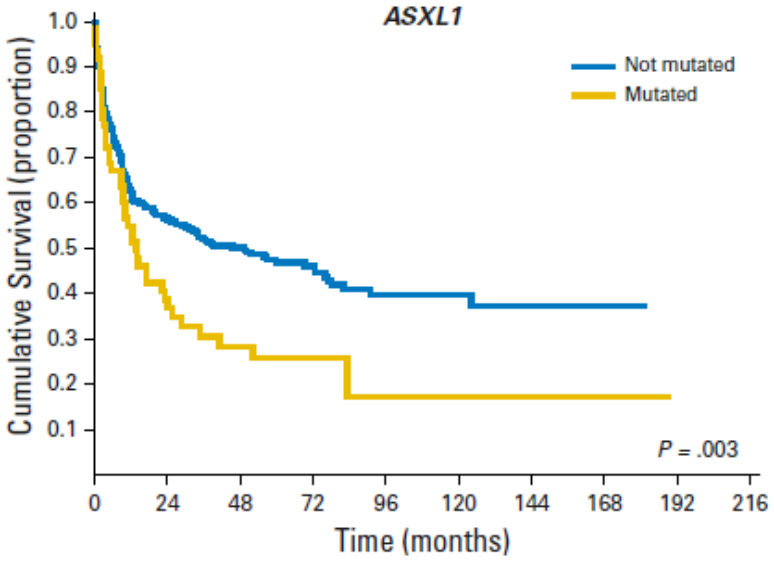
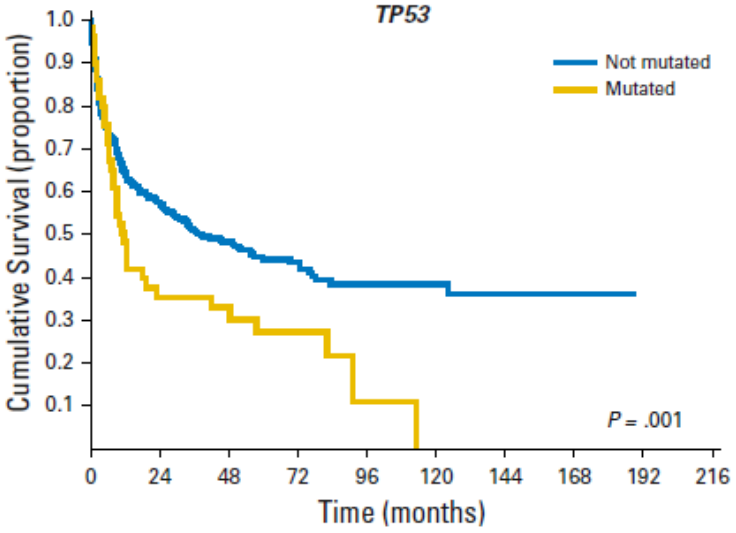
Relationship between type of oncogenic mutations and overall survival of MDS receiving allo-HSCT







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

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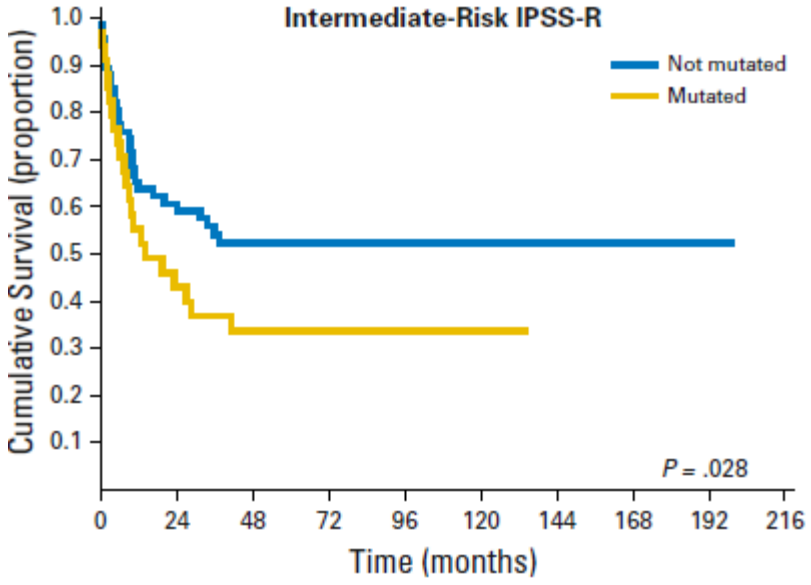
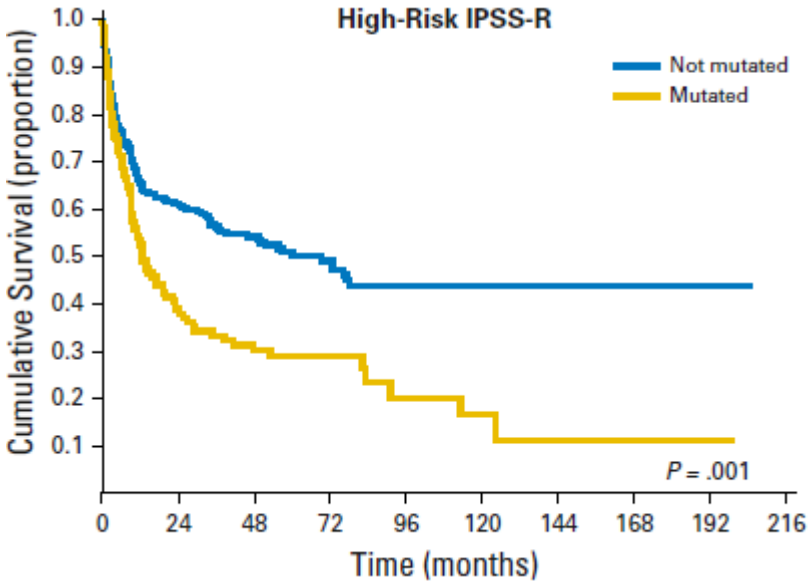
Clinical Impact of Somatic Mutations in Patients With MDS Receiving HSCT, Stratified According to IPSS-R





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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

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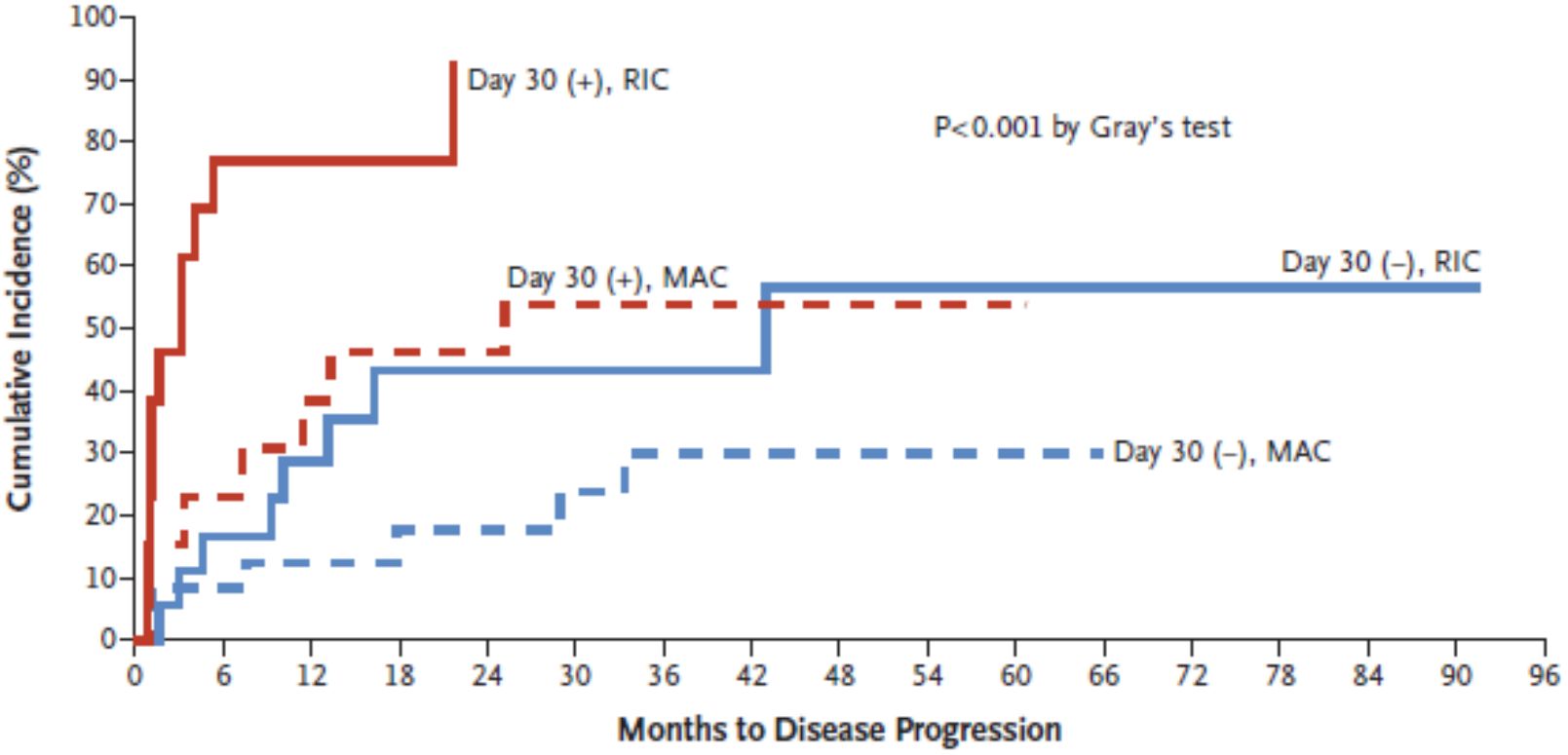
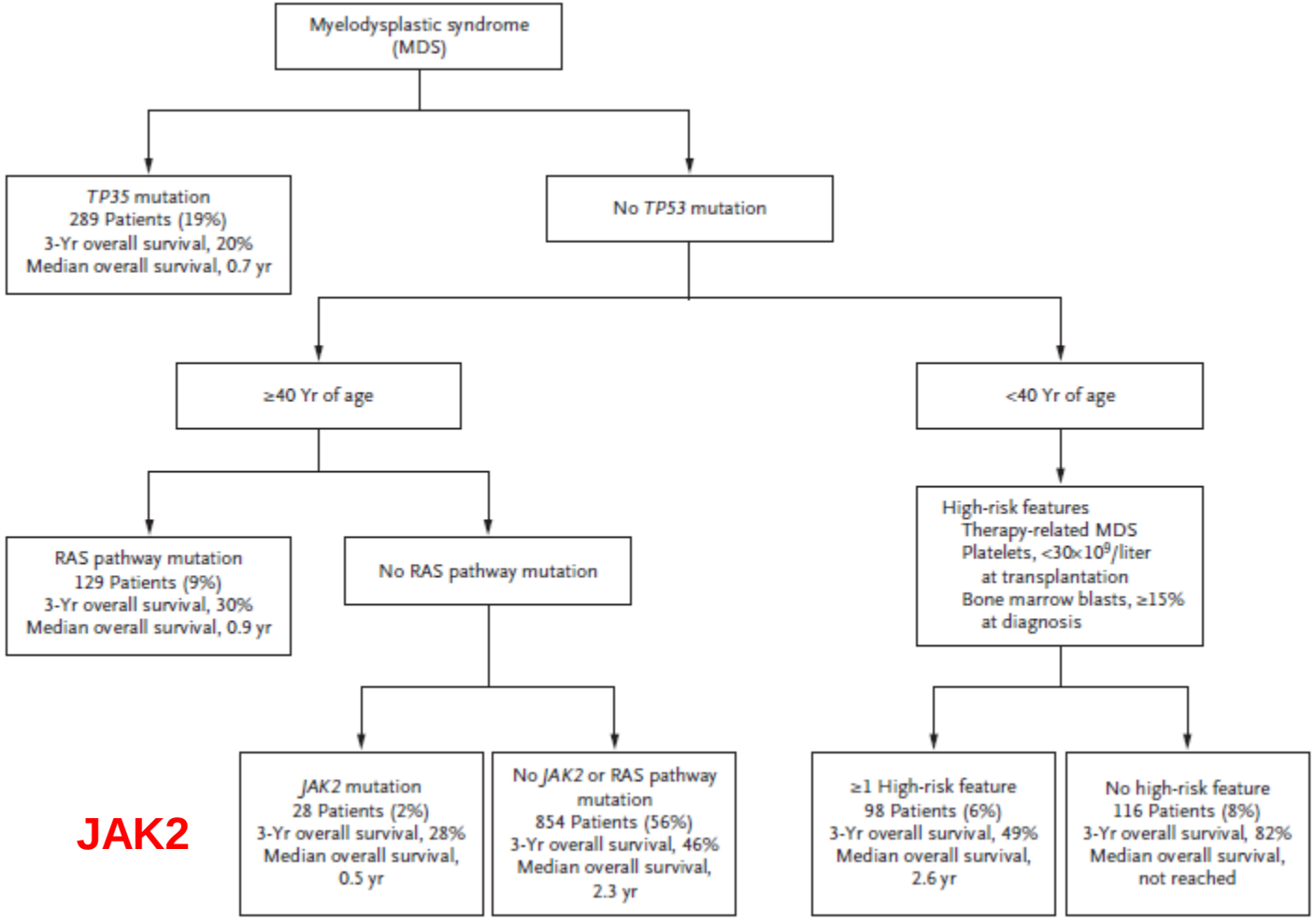
Mutation Clearance after Transplantation for Myelodysplastic Syndrome



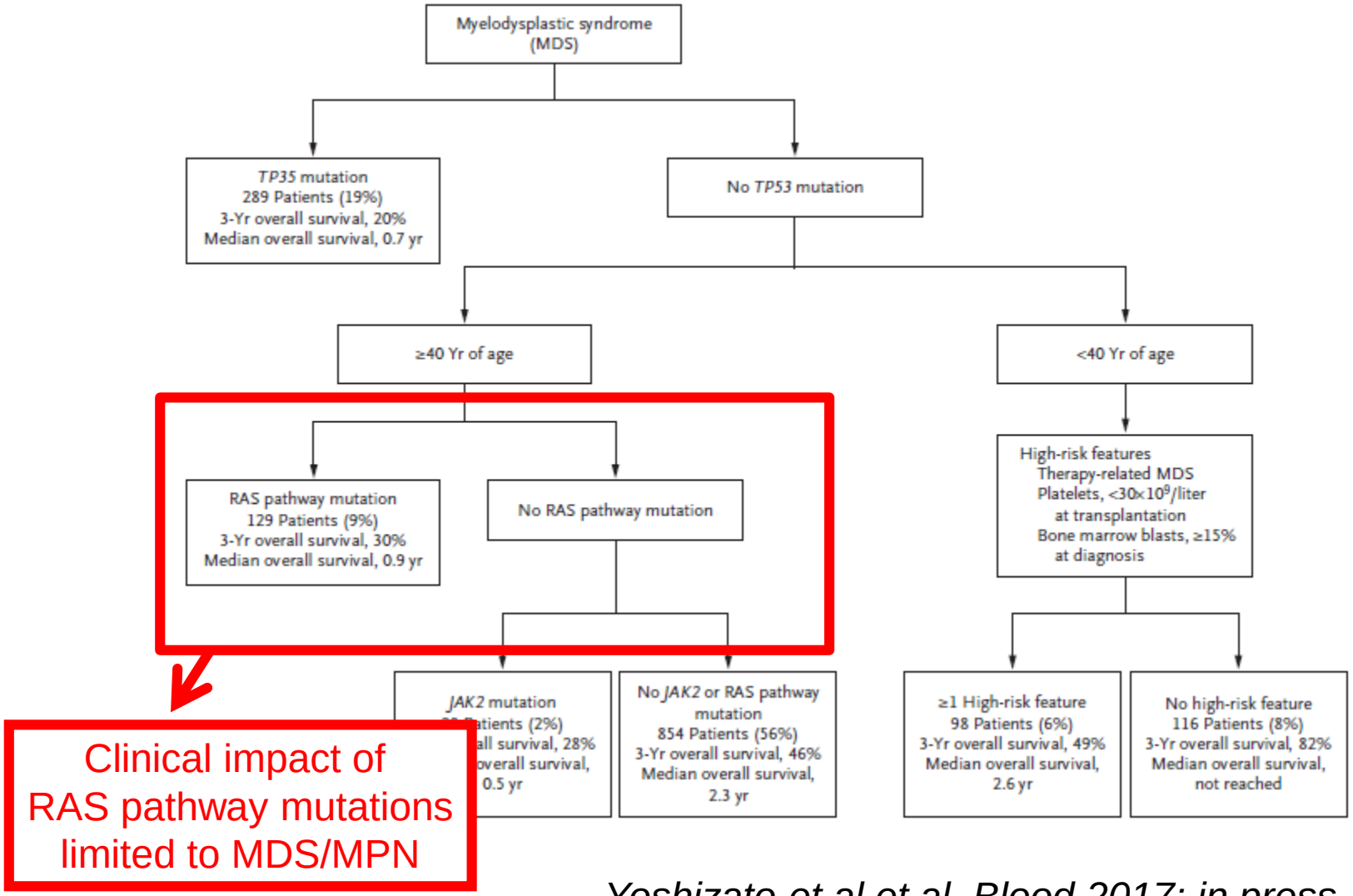
N Engl J Med 2018;379:1028-41.

Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation



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

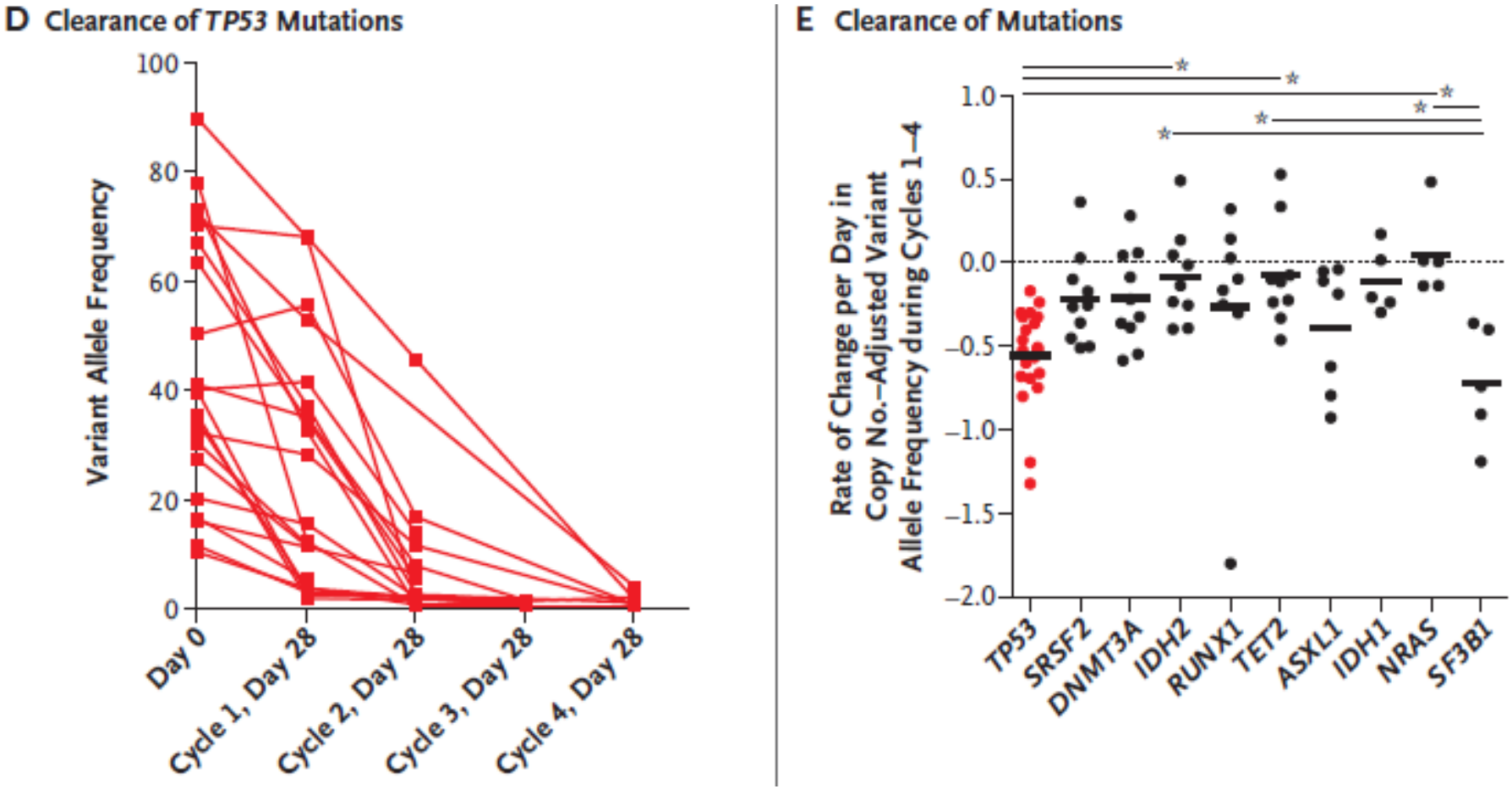
Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation



Clinical impact of RAS pathway mutations limited to MDS/MPN

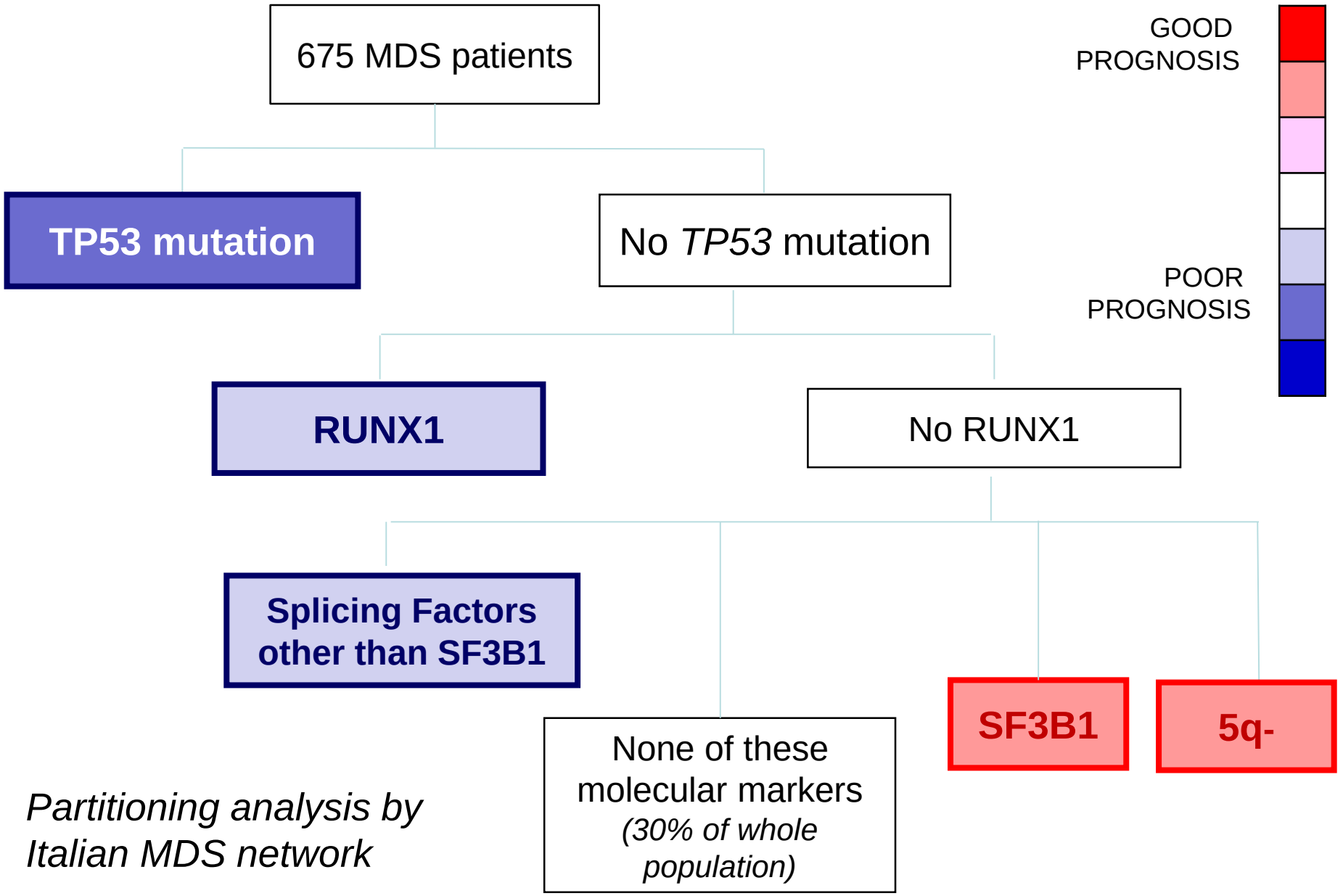
Yoshizato et al et al. Blood 2017; in press

TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes



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

Genotype-based transplant strategy in MDS



Partitioning analysis by Italian MDS network

SUMMARY

- The implementation of IPSS-R is expected to result in a more effective prognostic assessment among patients with early disease stage
- Mutation screening provides relevant prognostic information at individual patient level
- According to a IPSSR-based transplantation strategy, maximal life expectancy was obtained when delaying allo-HSCT after progression to the intermediate risk score.
- Mutation screening may affect clinical decision making in transplantation (TP53 mutations are associated to a high probability of disease relapse)

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