Clinical effect of somatic mutations in t-MN treated with allogeneic stem cell transplantation

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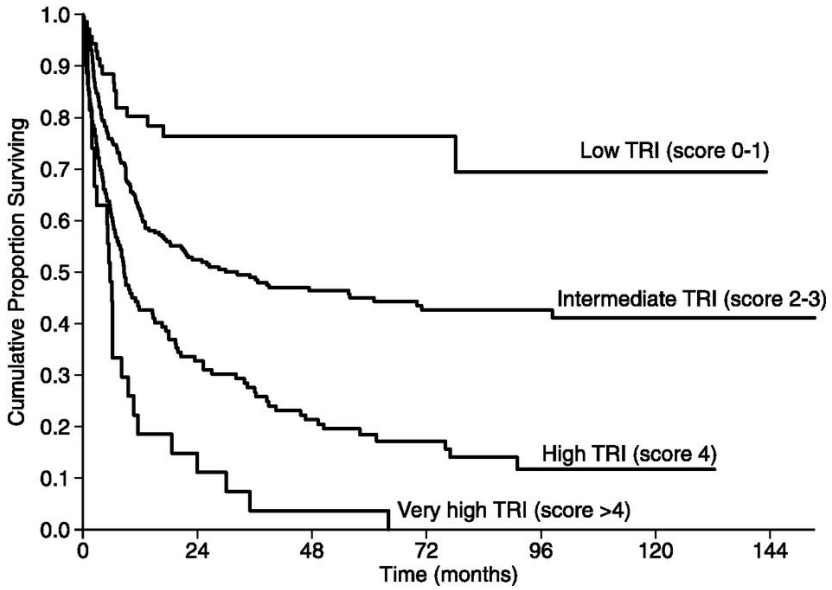
Patient-based and disease status–based risk stratification of outcome among MDS and MDS/AML receiving allo-HSCT

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

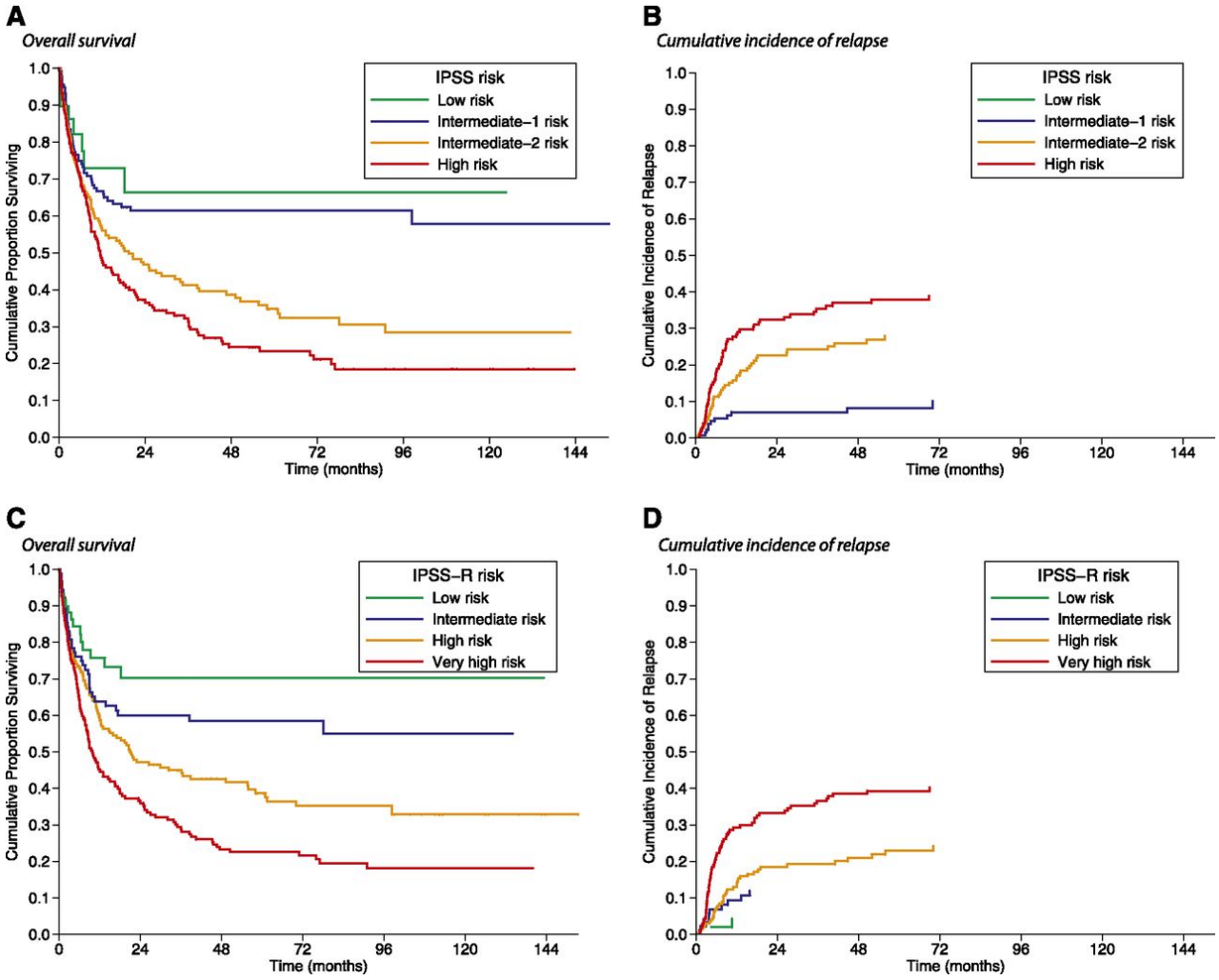
B *Posttransplantation outcome according to TRI*



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

GITMO

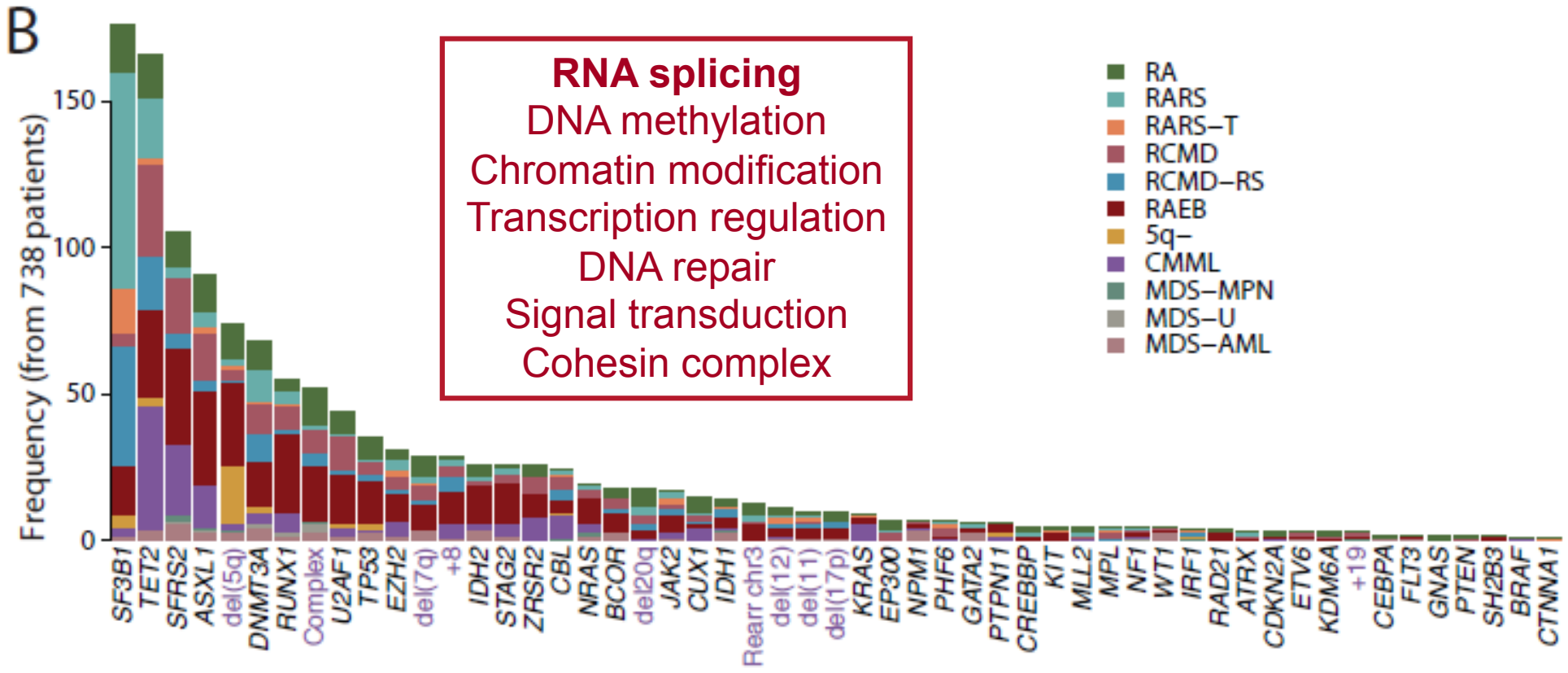
Survival and cumulative incidence of relapse following allogeneic HSCT in MDS patients stratified according to their pretransplant IPSS or IPSS-R risk.



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

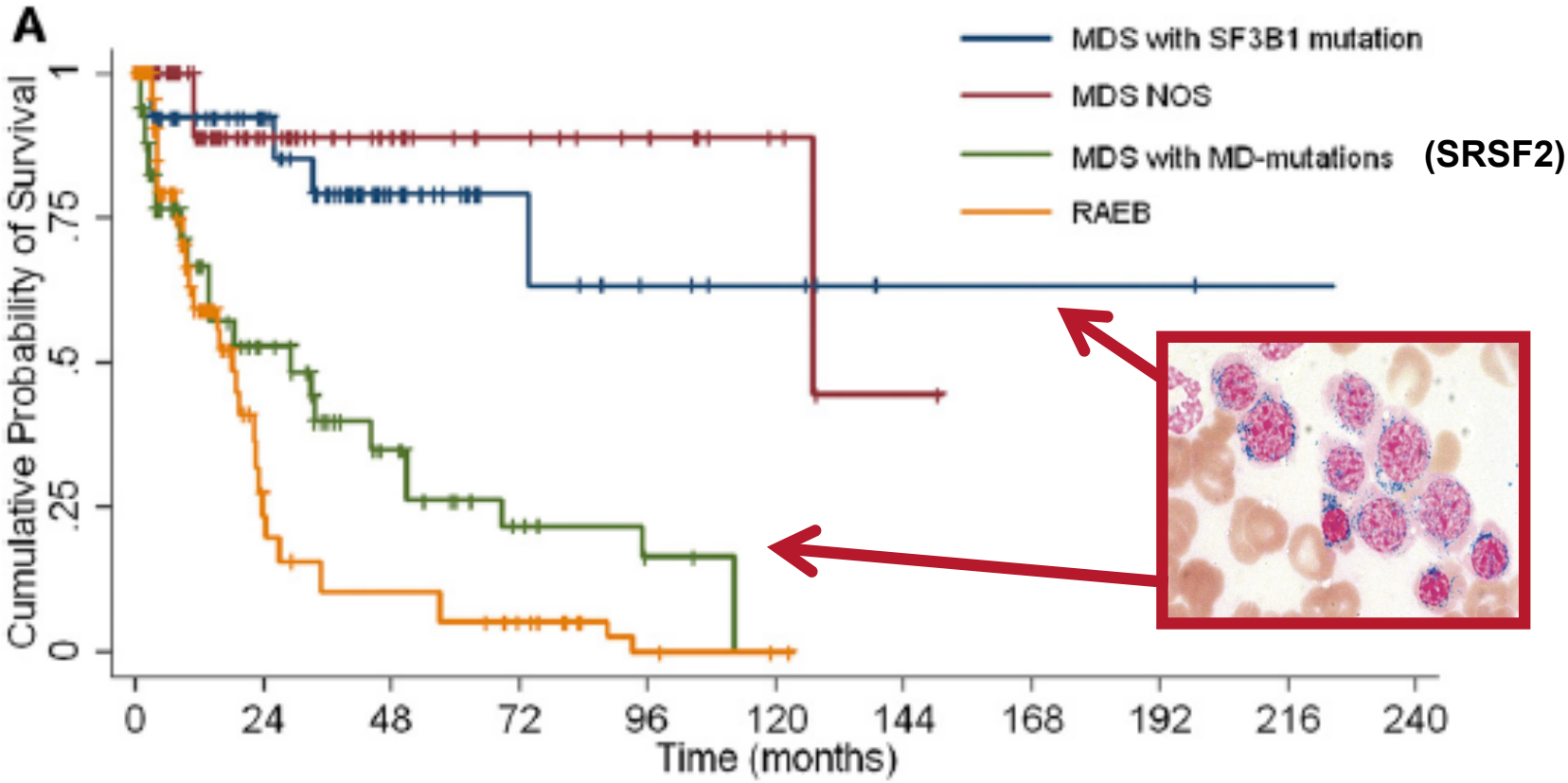
blood

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

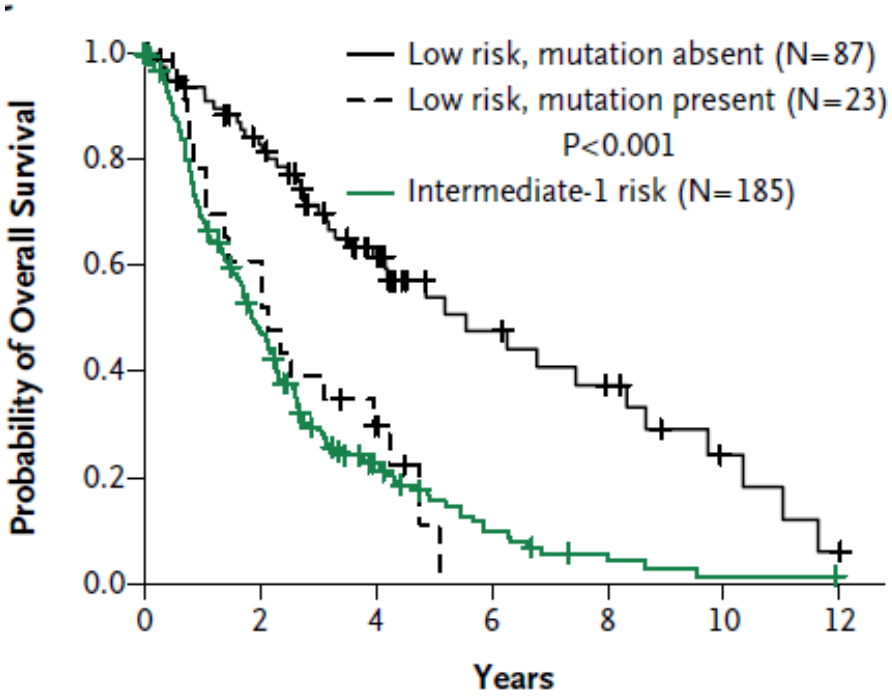


Malcovati et al. Blood 2014 Aug 28;124(9):1513-21
Della Porta MG et a. Leukemia. 2015;29(1):66-75

Clinical Effect of Point Mutations in Myelodysplastic Syndromes

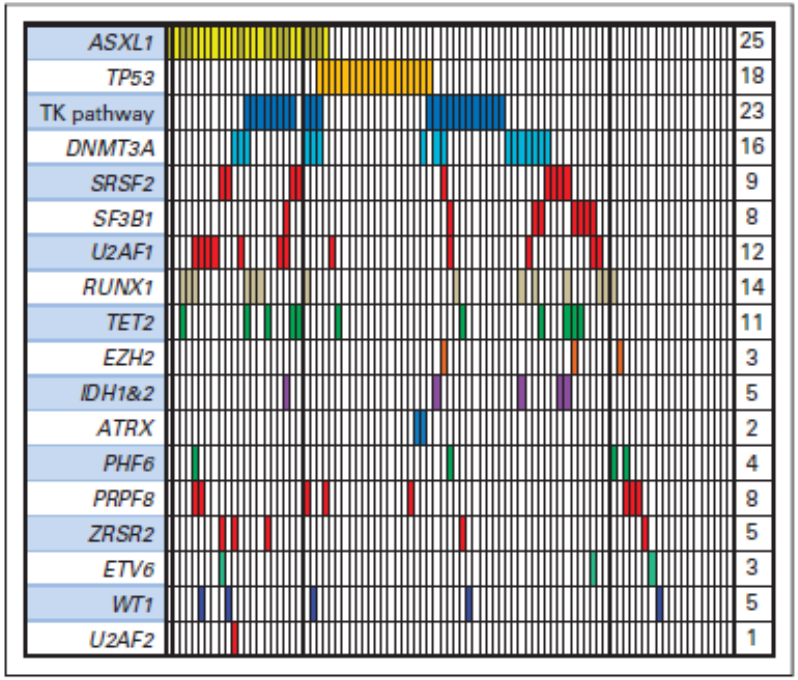
Table 2. Hazard Ratios for Death in a Multivariable Model.*

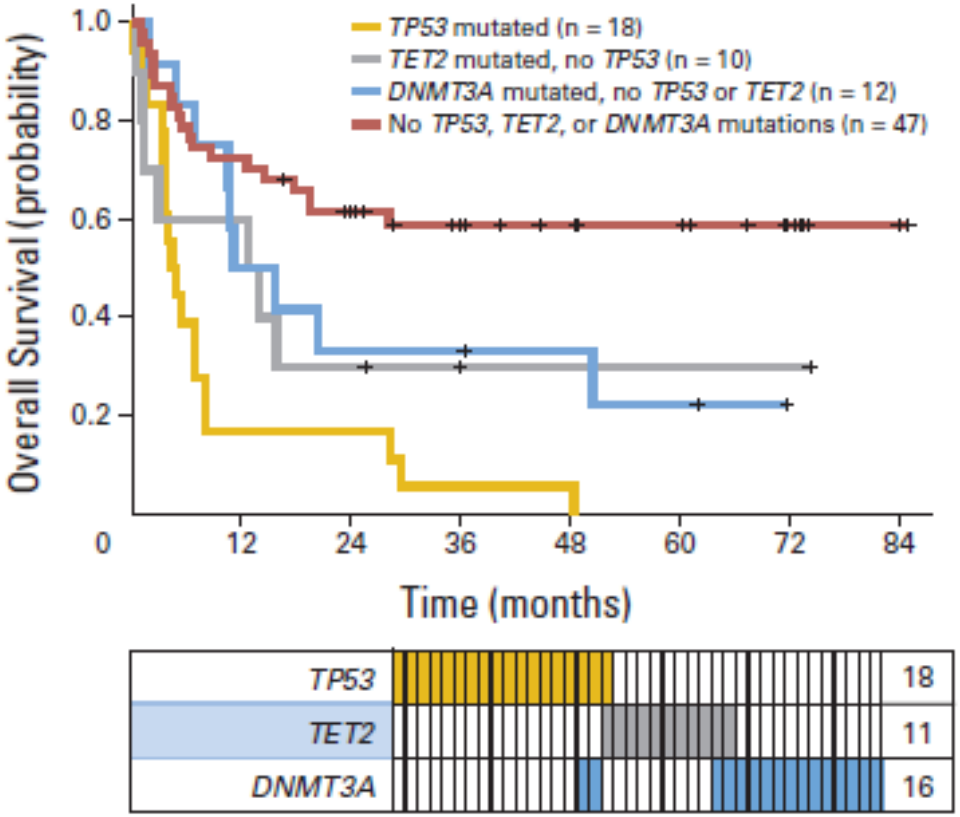
Risk Factor	Hazard Ratio (95% CI)	P Value
Age ≥55 yr vs. <55 yr	1.81 (1.20–2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69–3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42–4.91)	<0.001
High vs. low	5.85 (3.63–9.40)	<0.001
Mutational status		
TP53 mutation present vs. absent	2.48 (1.60–3.84)	<0.001
EZH2 mutation present vs. absent	2.13 (1.36–3.33)	<0.001
ETV6 mutation present vs. absent	2.04 (1.08–3.86)	0.03
RUNX1 mutation present vs. absent	1.47 (1.01–2.15)	0.047
ASXL1 mutation present vs. absent	1.38 (1.00–1.89)	0.049



Bejar R et al. N Engl J Med 2011;364:2496-506

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





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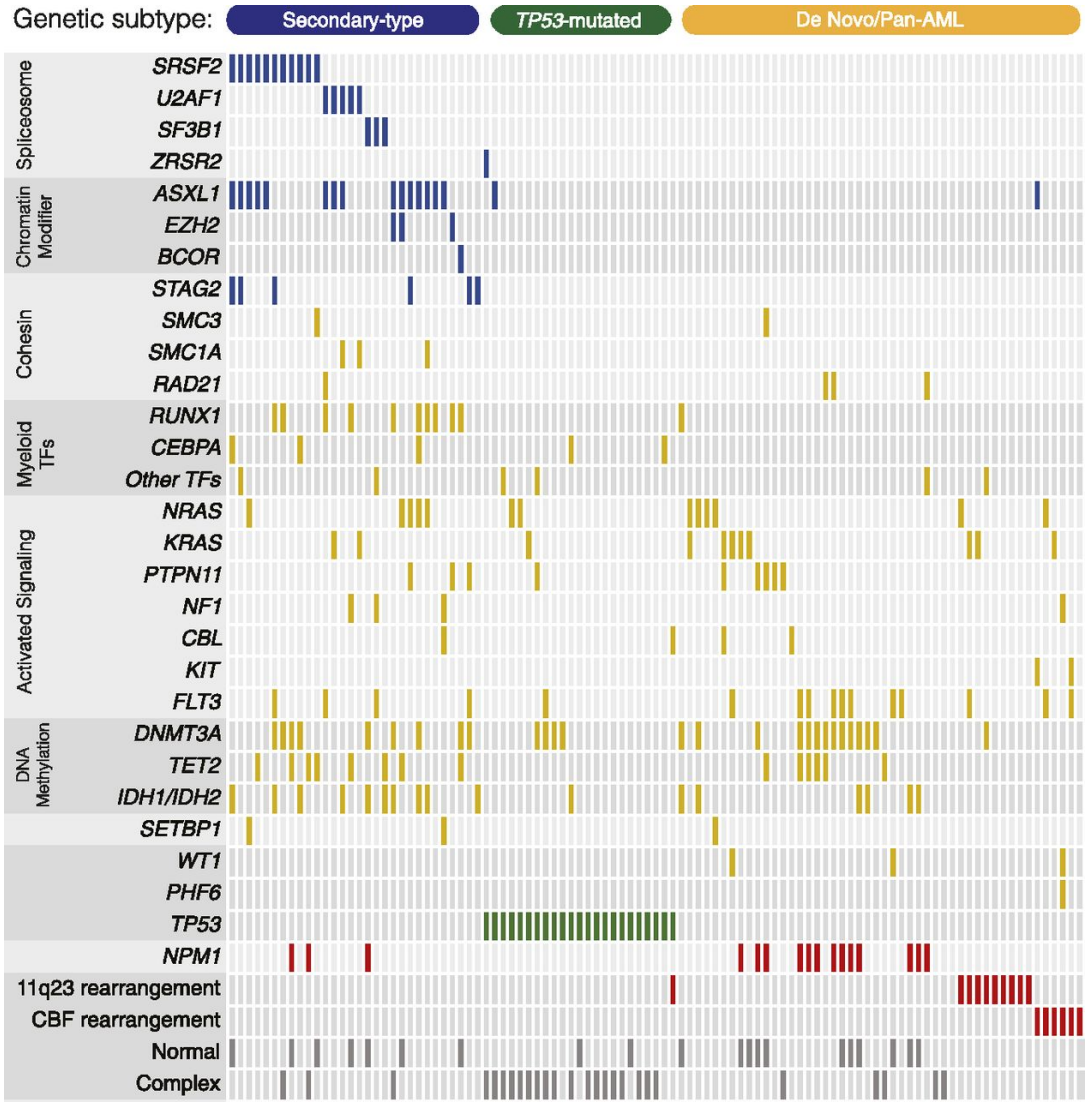
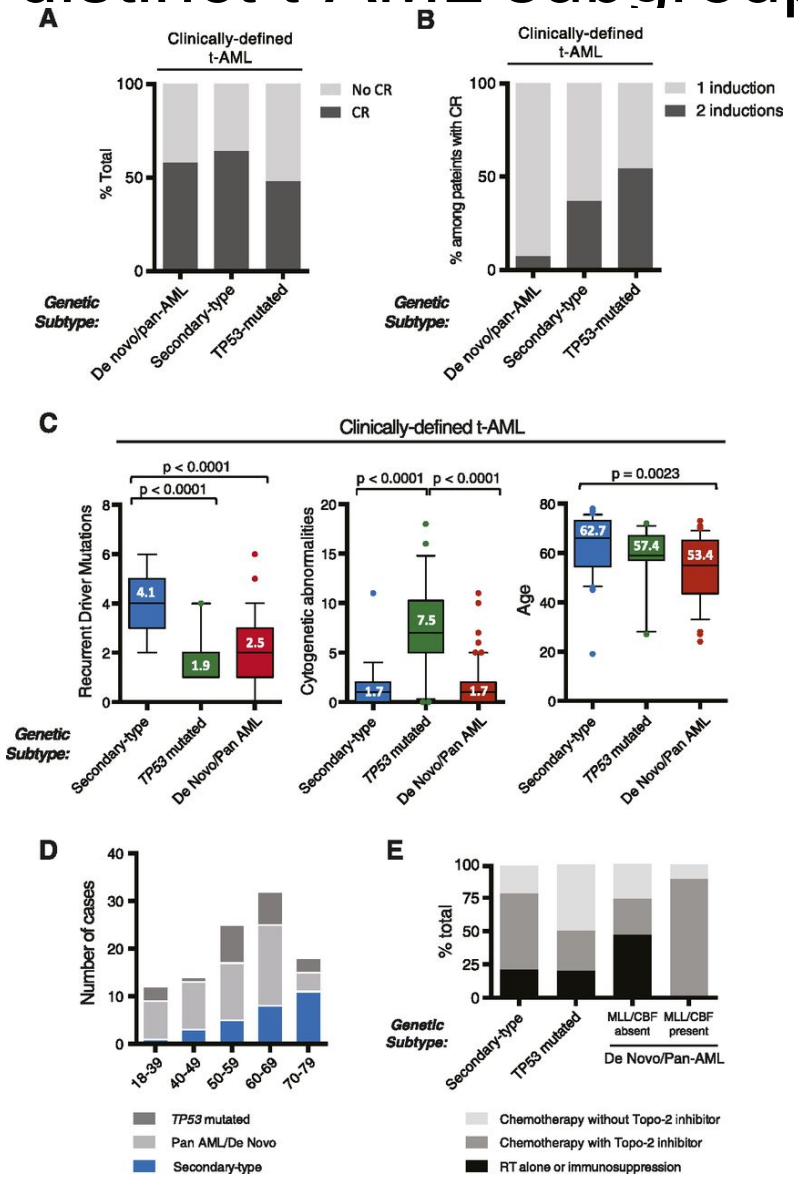
Mutations in therapy-related MN



R. Coleman Lindsley et al. Blood 2015;125:1367-1376

Ontogeny-based genetic classification defines clinically distinct t-AML subgroups.



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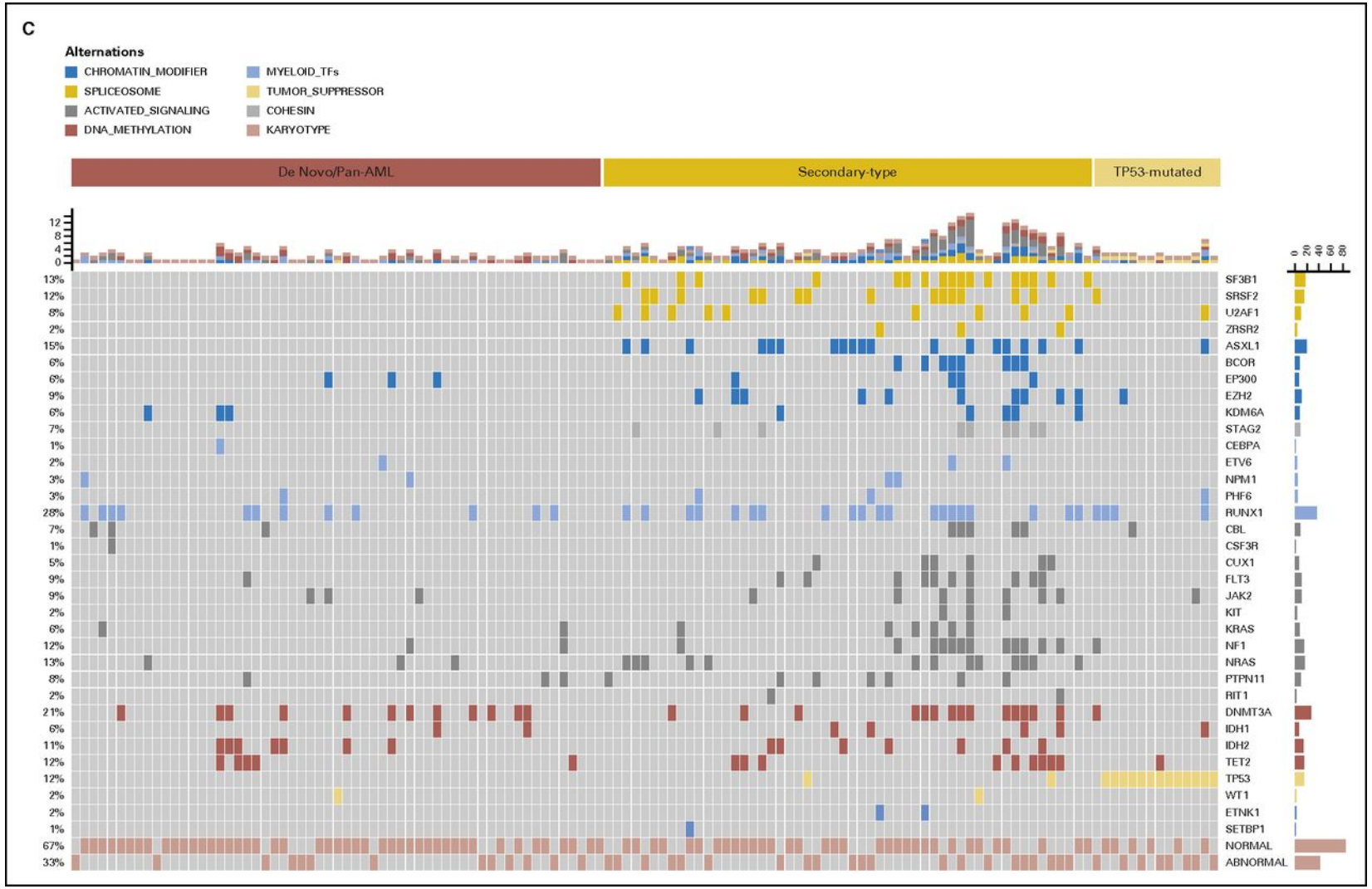
blood

Clinical Effects of Driver SomaticMutations on the Outcomes of Patients with t-MN Treated With Allogeneic Transplantation



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

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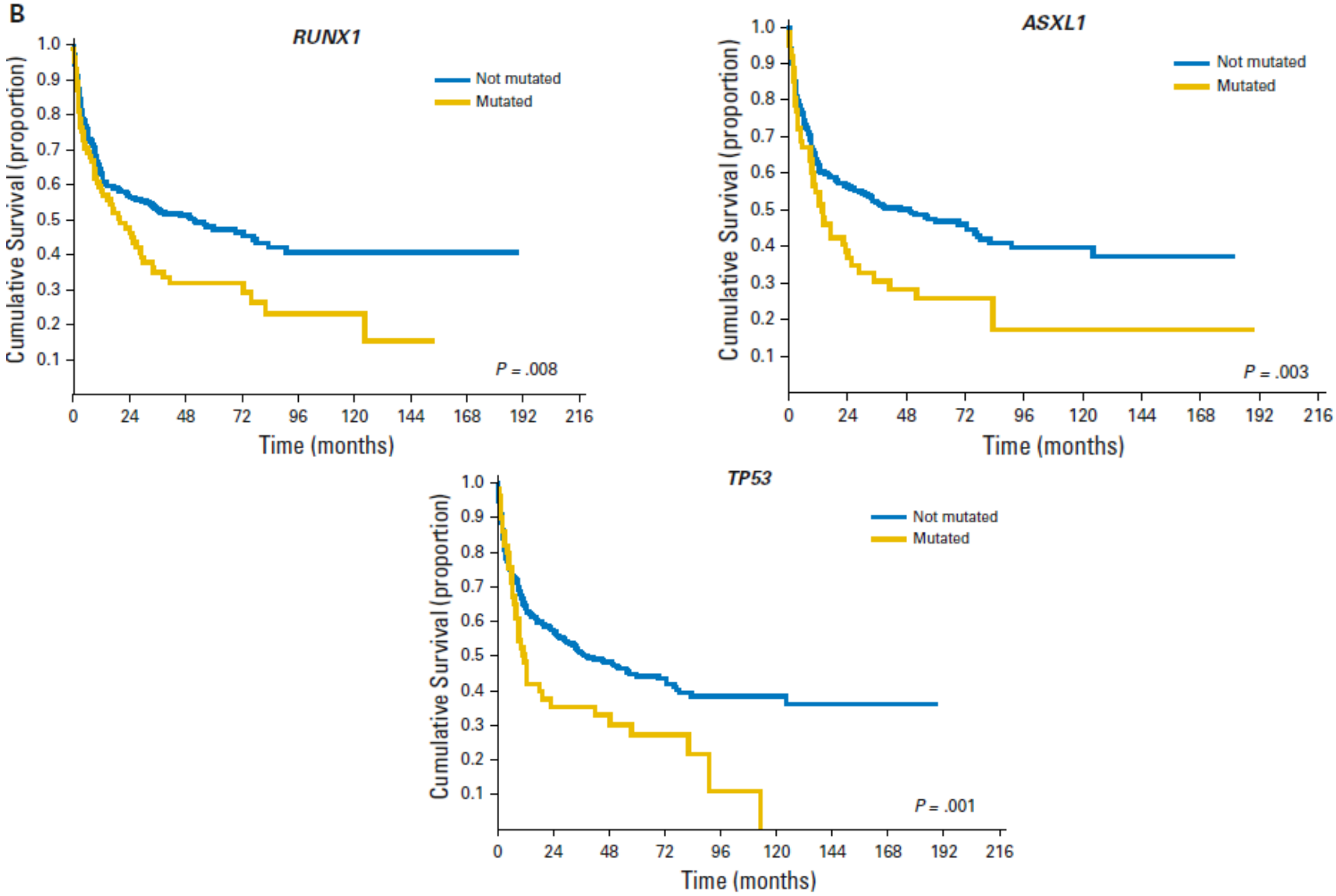

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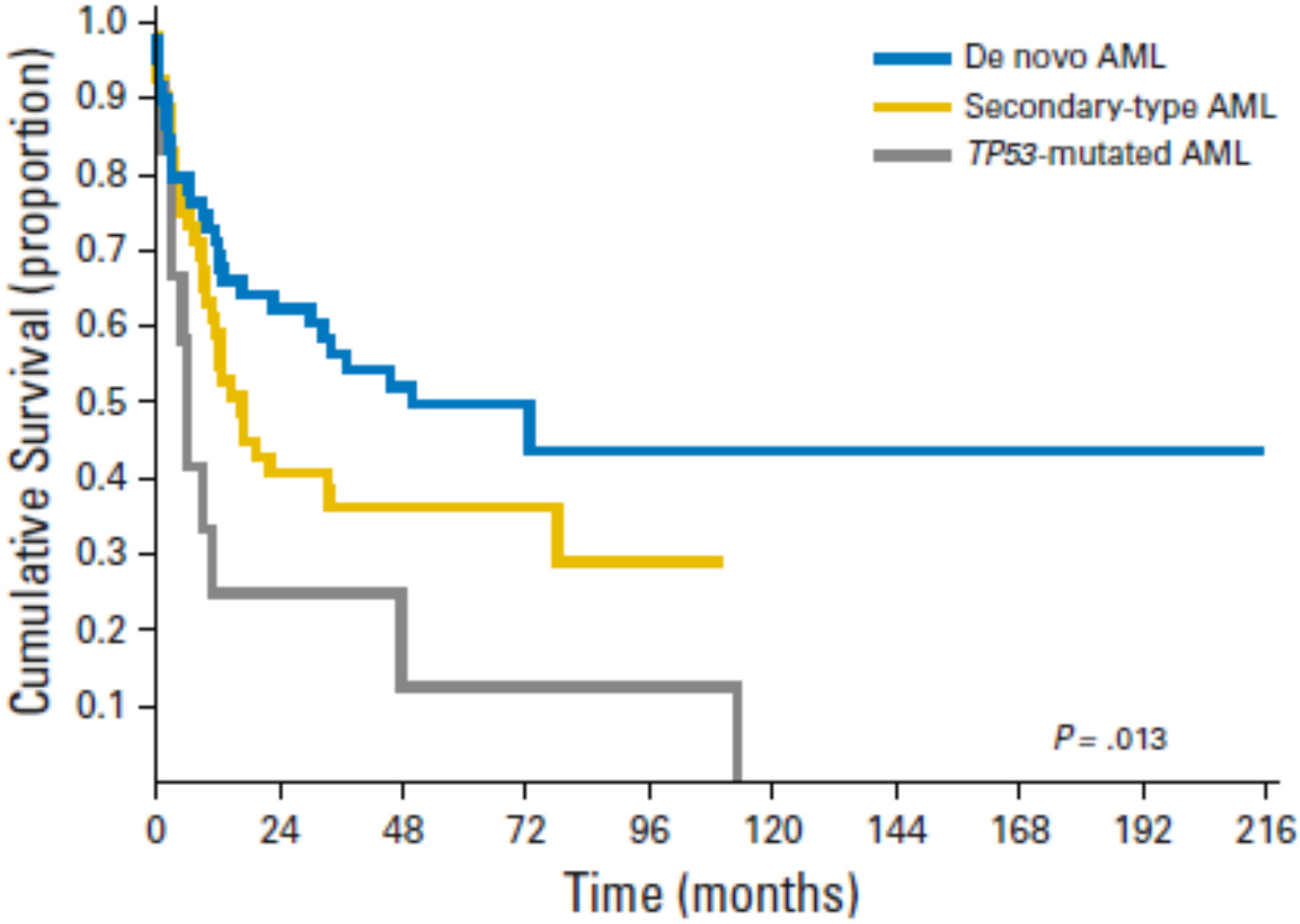

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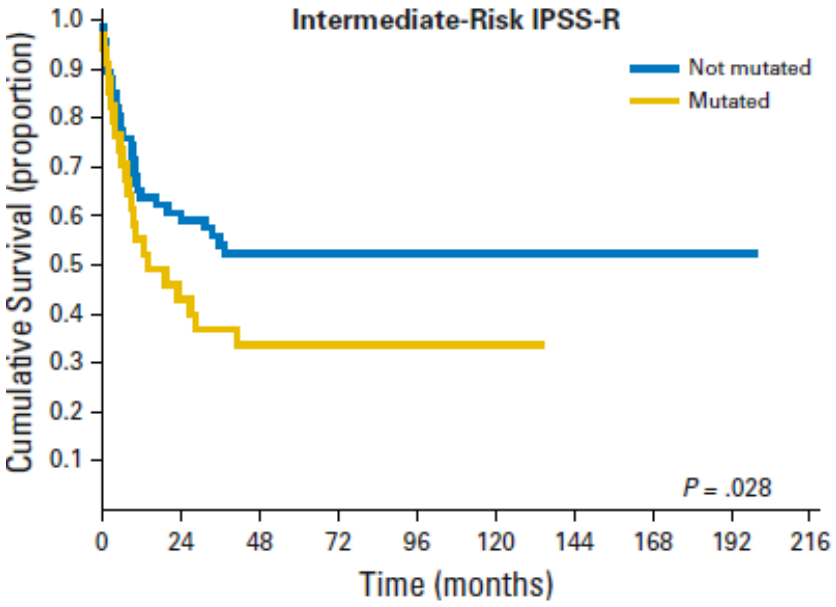
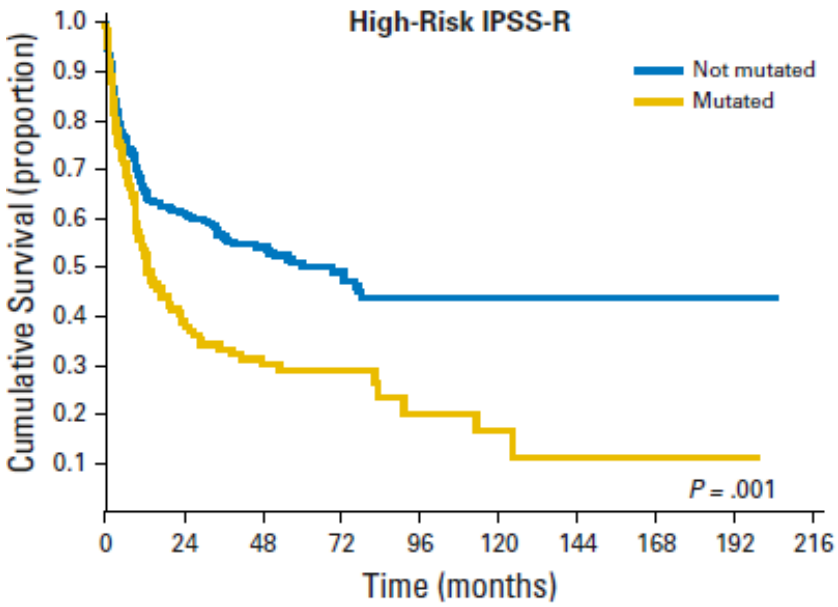
Clinical Impact of Somatic Mutations in Patients With MDS Receiving HSCT, Stratified According to IPSS-R





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

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

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Summary

- The definition of molecular basis of MDS is expected to improve diagnosis, prognostic assessment and clinical decision-making
- At least three distinct genetic subtypes may account for unique MDS/ AML clinical phenotype: secondary-type AML (including patients carrying mutations in MDS-related genes), TP53-mutated AML, and de novo AML.
- Mutation screening may affect clinical decision making in transplantation (TP53 mutations are associated with a high probability of disease relapse)
- Accounting for these genetic lesions may improve the prognostication precision in clinical practice and in designing clinical trials.

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