MDS ad alto rischio: terapia ipometilante e trapianto o trapianto up-front?

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Clinical characteristics of the patients with MDS or oligoblastic AML who received allo HSCT (GITMO registry 2000-2013)

Parameter*	MDS	MDS/AML
No. of patients	374	145
Age, median (range)	48 (17-67)	47 (23-72)
Sex (male/female)	202 /172	73/72
WHO classification:		
RCUD/RARS/del(5q)	38	-
RCMD	85	-
RAEB-1	87	-
RAEB-2	164	-
IPSS risk:		
Low	29 (8%)	-
Intermediate-1	134 (36%)	-
Intermediate-2	157 (42%)	20 (14%)
High	54 (14%)	125 (86%)

31%

69%

Della Porta MG et al. Blood. 2014;123:2333-42.

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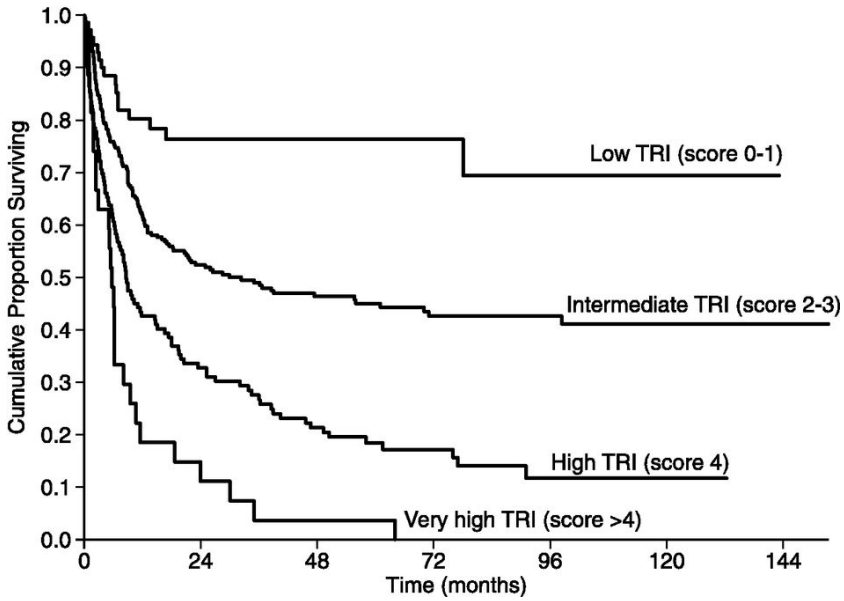
Patient-based and disease status–based risk stratification of outcome among MDS patients receiving allogeneic HSCT

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

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Diagnosis and treatment of primary MDS in adults: recommendations from the European LeukemiaNet

Remission induction therapy before allogeneic SCT

" …. On the basis of the available evidence, intensive chemotherapy should be administered to those patients with 10% or more bone marrow blasts who are candidates for allogeneic SCT (recommendation level D)"

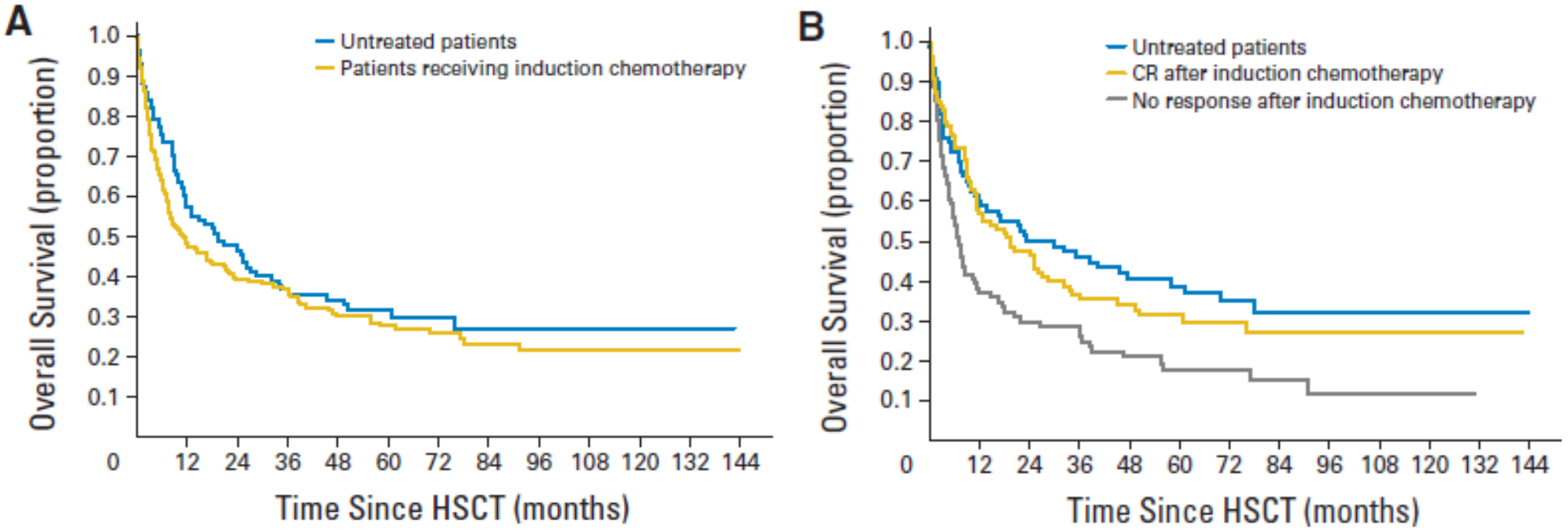
Malcovati L et al. Blood. 2013;122(17):2943-2964

ELN European LeukemiaNet

AML-like chemotherapy before allogeneic HSCT in high risk MDS patients and MDS/AML

Study	Patients	%CR	Findings
De Witte T et al, *Br J Haematol 2000*	MDS AML from MDS	41%	OS was not different between patients receiving vs. not receiving chemotherapy before HSCT
Nakai K et al, *Leukemia 2005*	MDS AML from MDS	43%	
Alessandrino EP et al, *Blood 2008*	MDS AML from MDS	54%	

Post-transplantation outcome of patients with intermediate-2 and high IPSS risk stratified according to (A) whether or not induction chemotherapy was received before allo-HSCT, and (B) disease status at transplantation.



Alessandrino EP, Della Porta MG et al J Clin Oncol. 2013;31:2761-2

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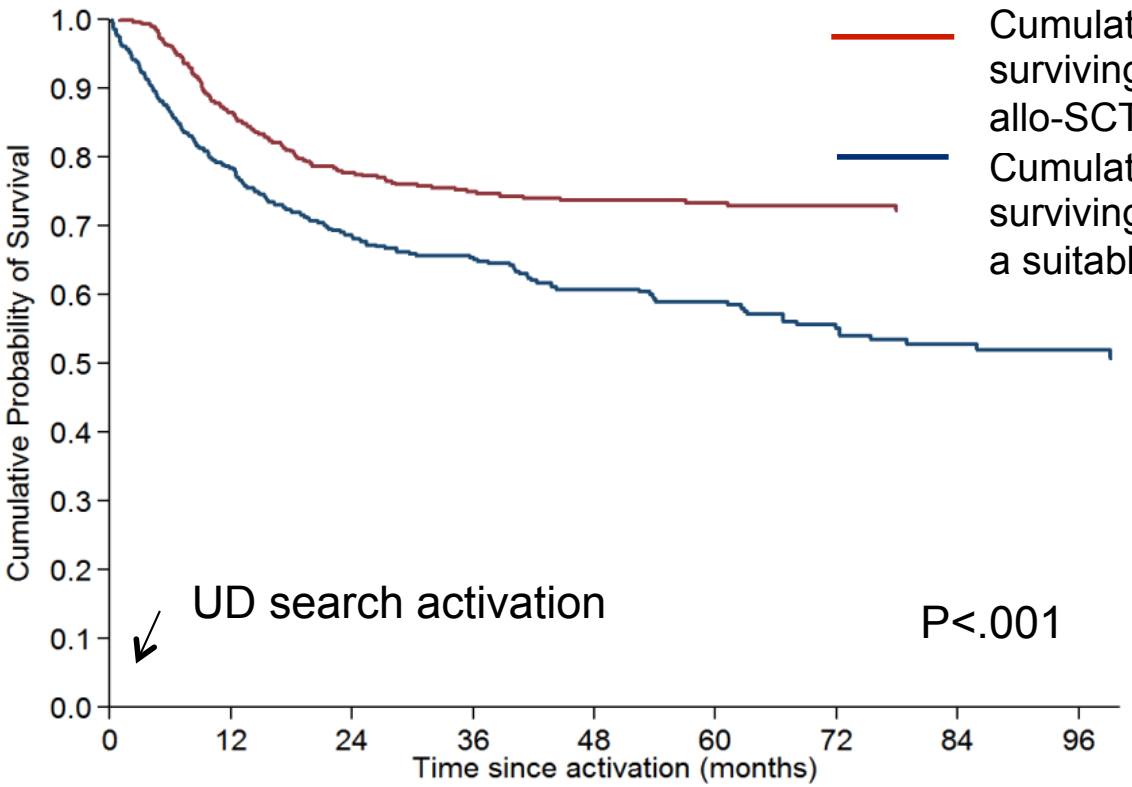
Impact of time spent waiting for a suitable unrelated donor (UD) on the outcome of 529 MDS patients candidate to allogeneic HSCT



Cumulative probability to receive allo-HSCT	25%	38%	42%	45%
CI leukemic evolution	14%	18%	22%	27%
CI death before HSCT	11%	15%	18%	20%

Della Porta MG et al. manuscript in preparation

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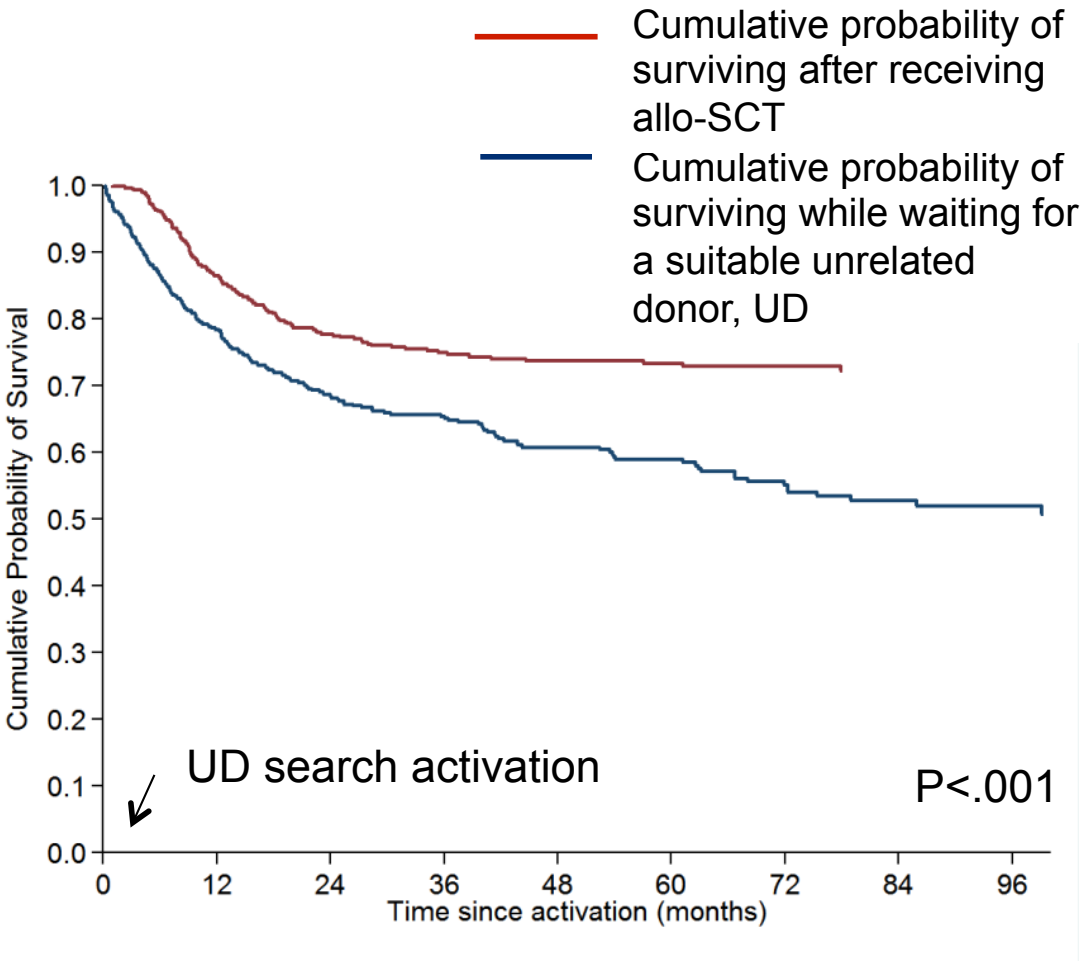
Patient drop-out (patients who received induction chemotherapy but never received allo-HSCT because of death or toxicity)



MDS patients activating UD search

529

MDS patients with suitable donor

298 (56%)

Drop out for disease progression, failure/toxicity induction chemotherapy or death

57 (19%)

Della Porta MG et al. manuscript in preparation

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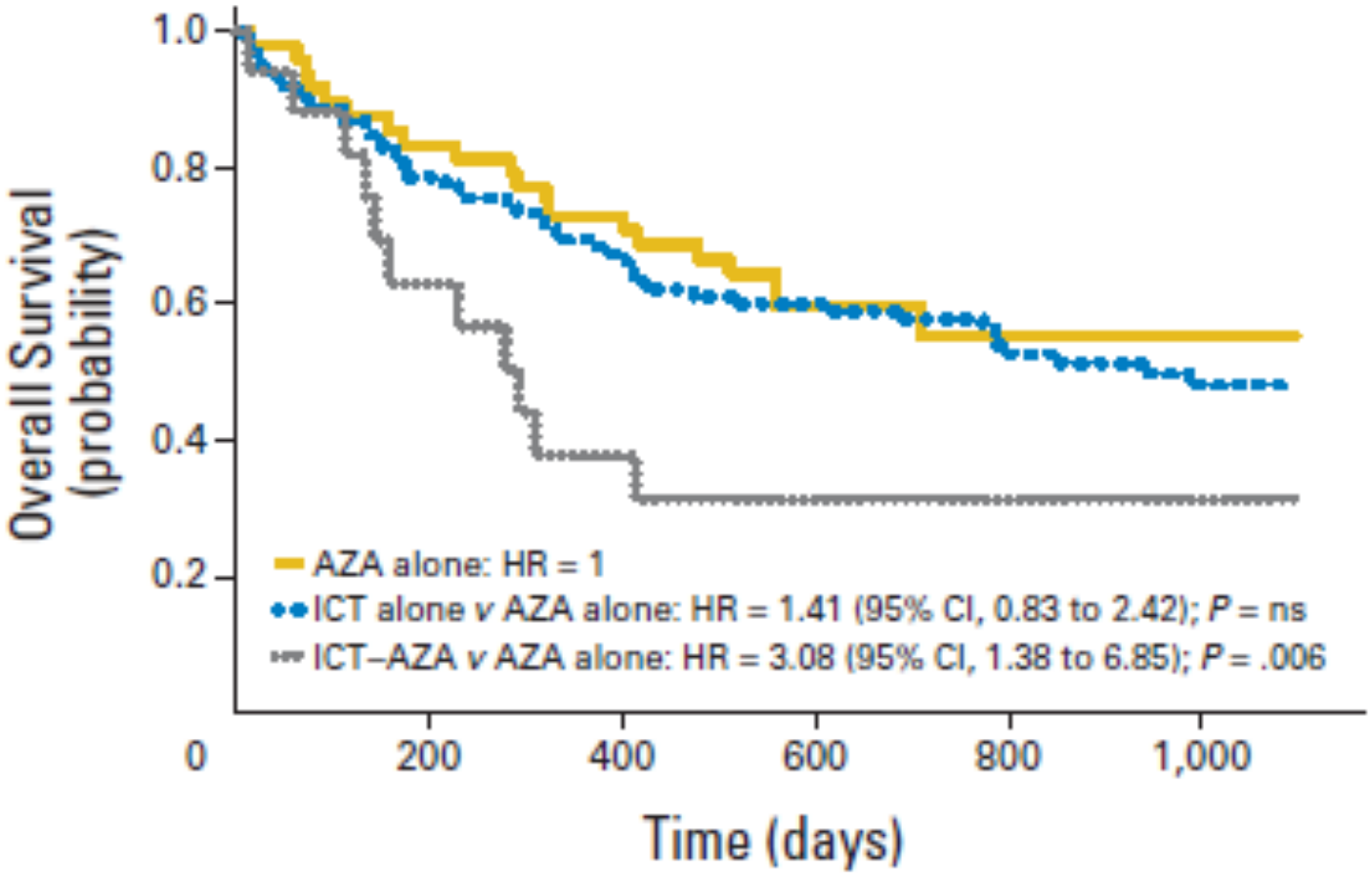
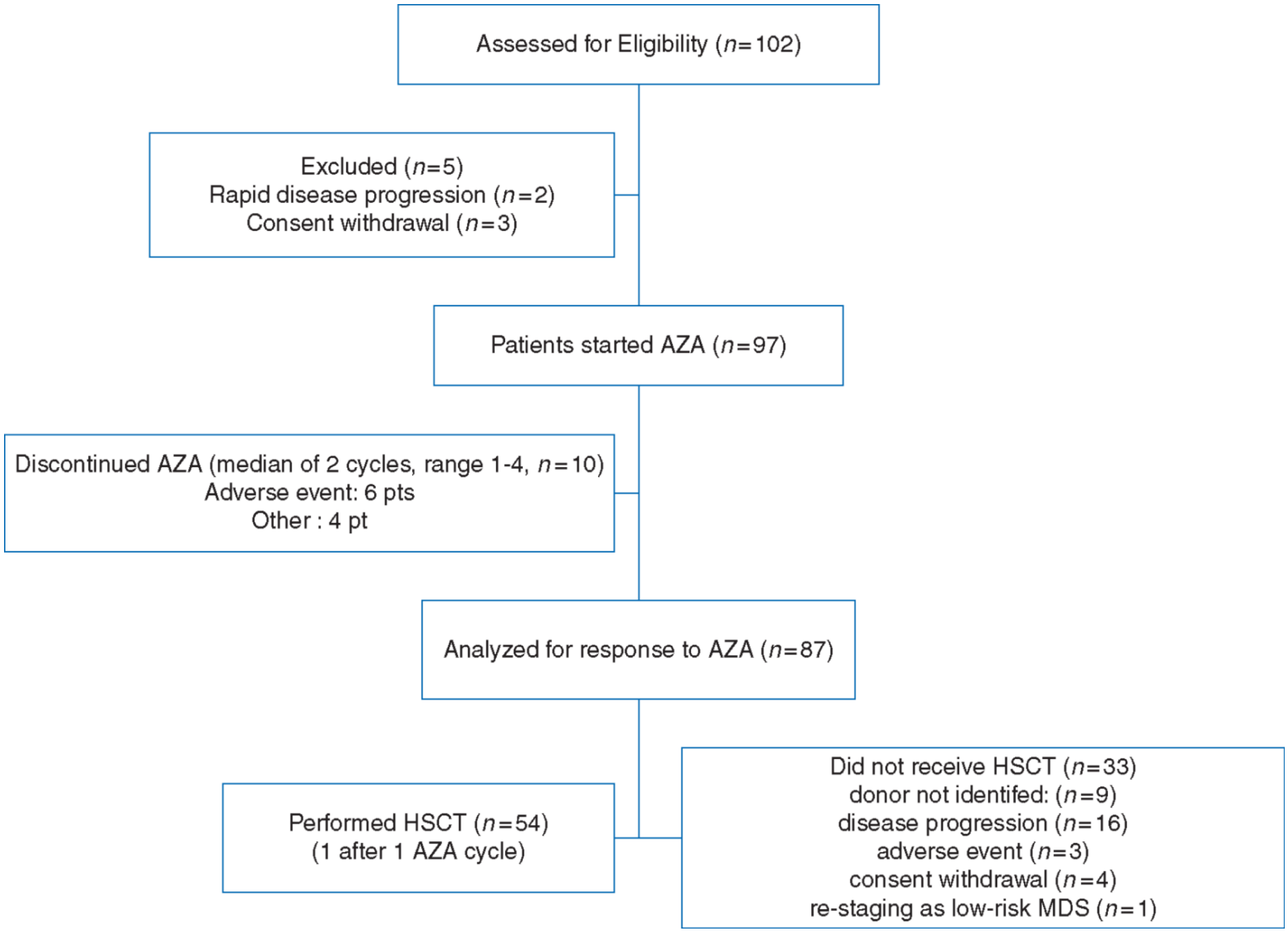
Impact of Azacitidine before allo-HSCT for myelodysplastic syndromes



Damaj G et at. J Clin Oncol 2012;30:4533-4540

Feasibility of allogeneic stem-cell transplantation after azacitidine bridge in higher-risk MDS and low blast count AML: results of the BMT-AZA prospective study



Voso MT et al. Ann Oncol 2017 in press

Cytoreduction before allo-HSCT in high risk MDS patients

Treatment	**Which patients**
Chemotherapy	Selected medically fit patients with immediate availability of a suitable donor
Hypomethylating agents	Mainly for older patients which are at risk of losing eligibility for a transplantation procedure as a result of death or treatment-related toxicity and as a bridging strategy to HSCT in those where no donor has yet been identified Hypomethylating agents may be active in patients with complex karyotype

Della Porta MG, Alessandrino EP. Biol Blood Marrow Transplant. 2014 ;20:1260-1

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, in press

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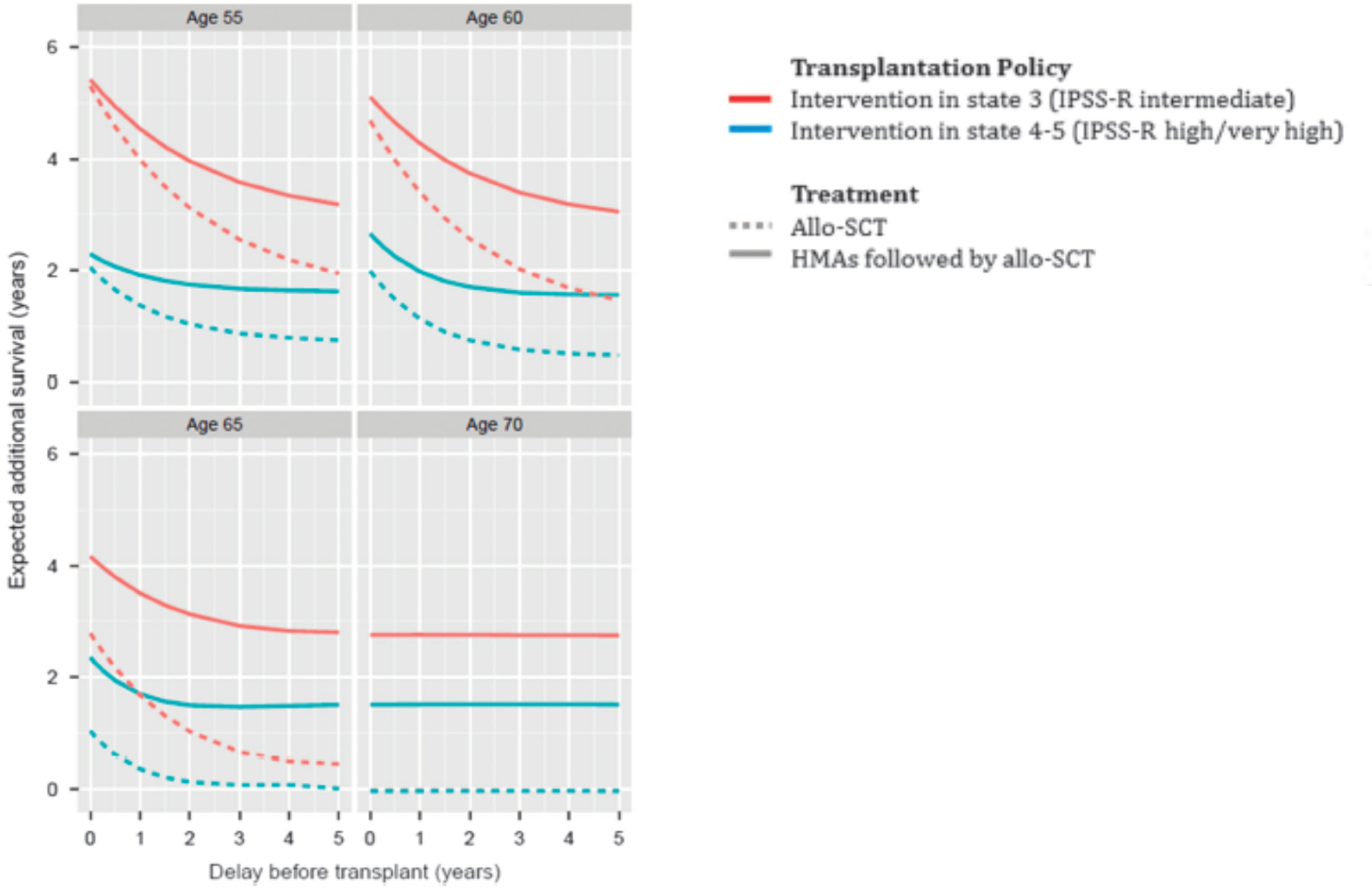
Expected gain of life expectancy in high risk MDS treated with HMAs before HSCT vs. HSCT alone



Della Porta MG et al. Leukemia 2017, in press

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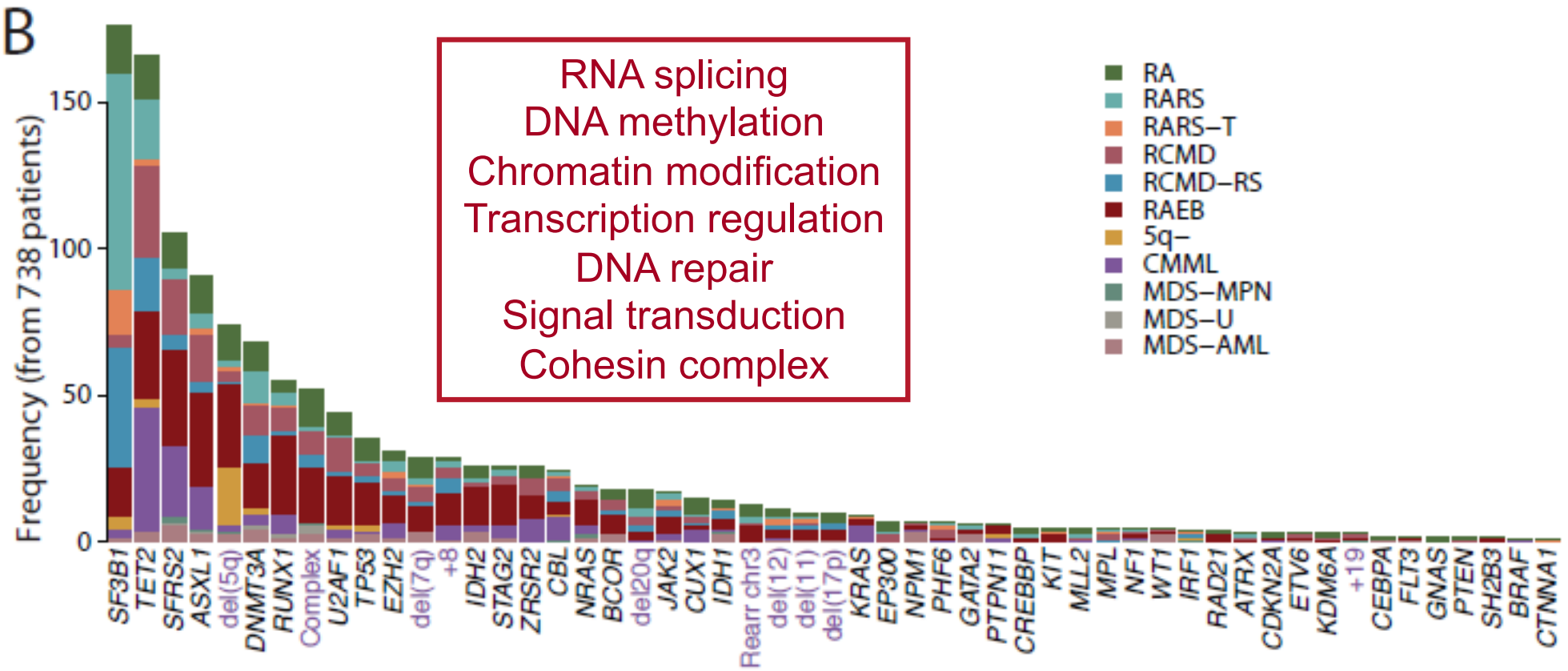
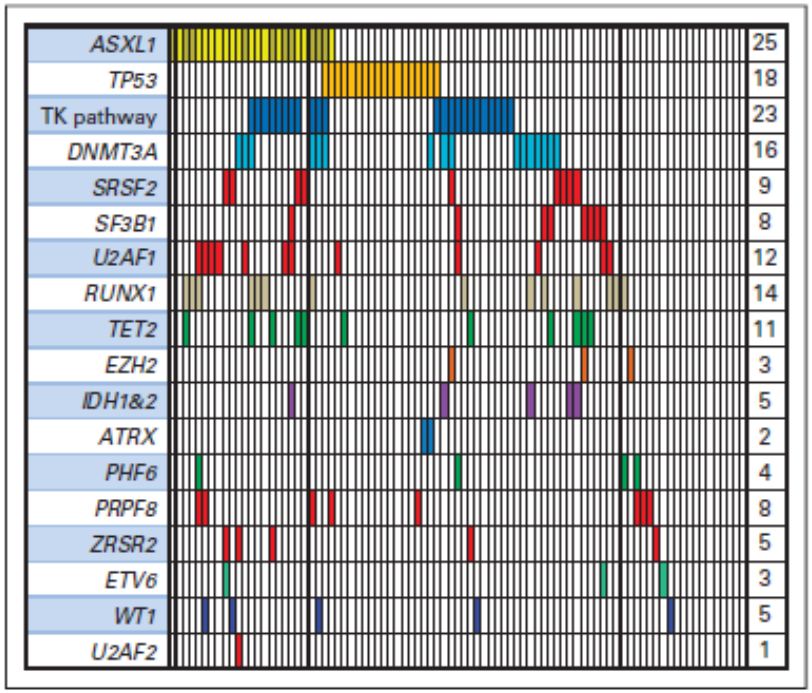
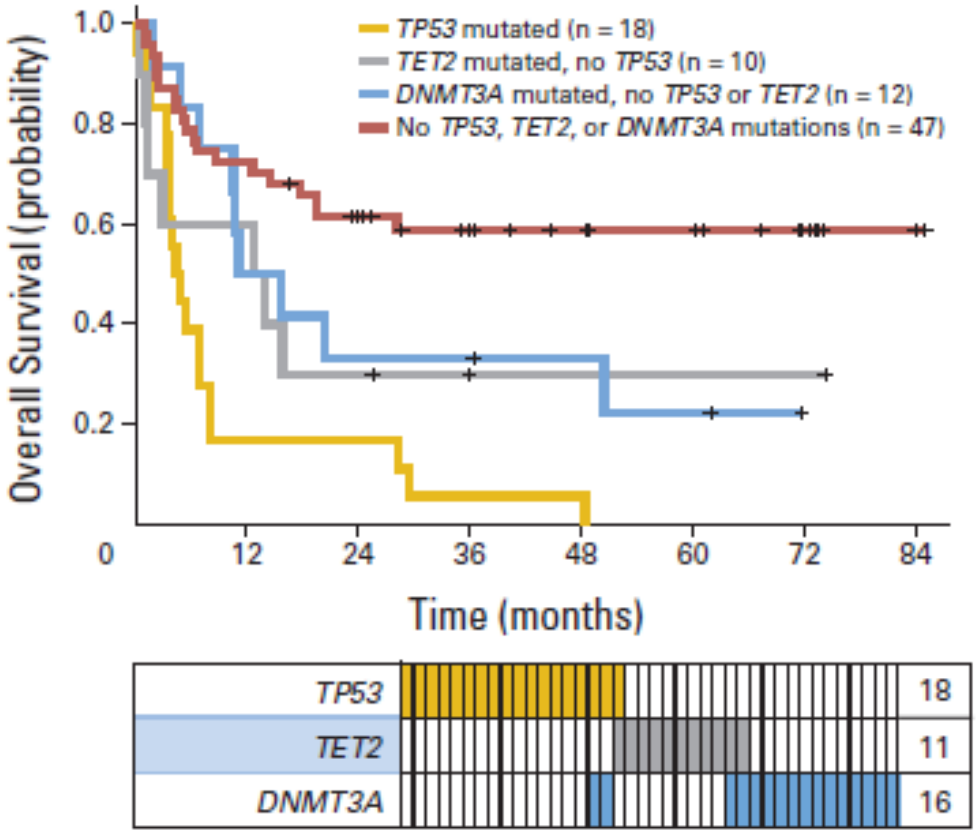
Clinical Effect of Point Mutations in Myelodysplastic Syndromes



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

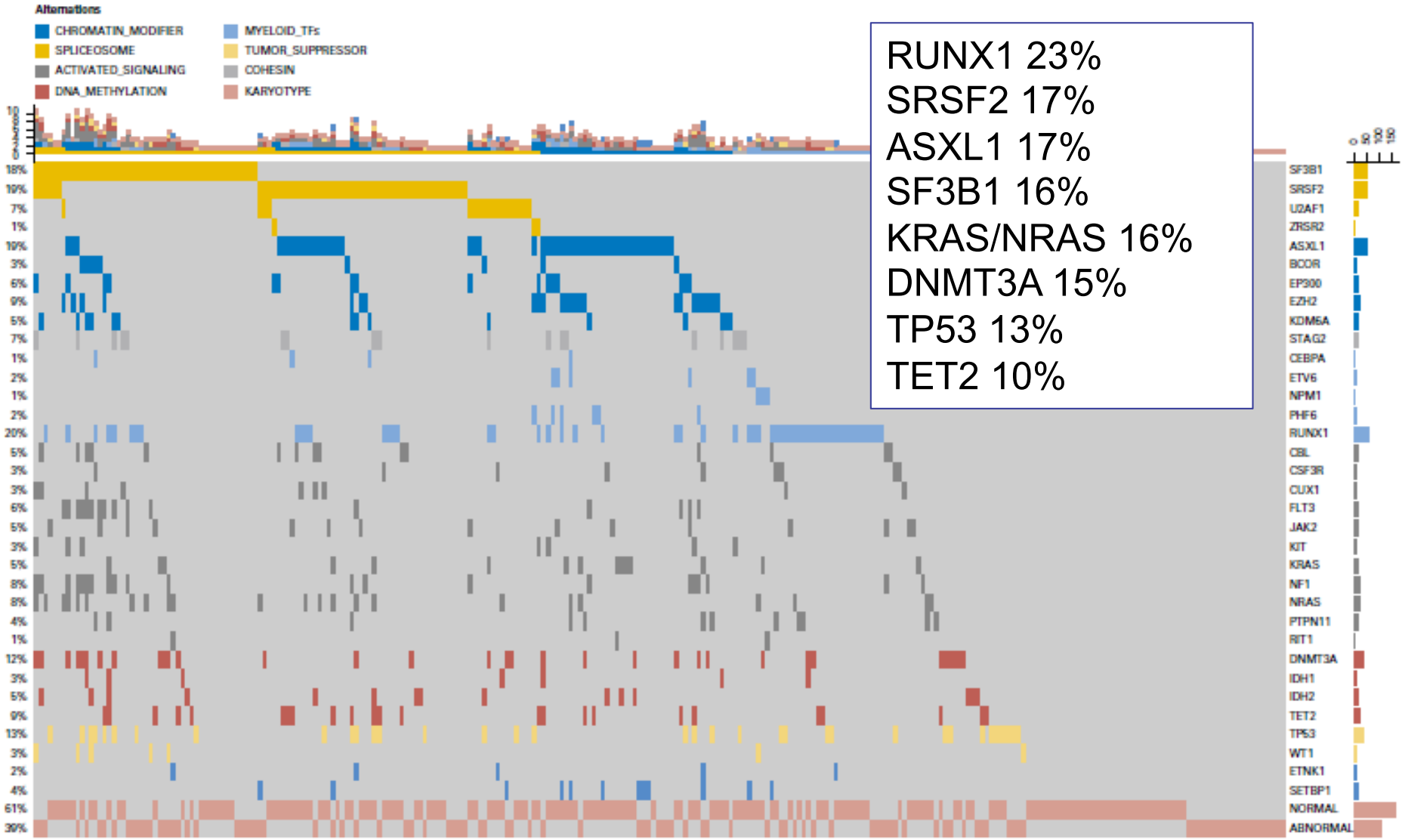
Somatic Mutations Predict Poor Outcome in Patients With MDS After Hematopoietic Stem-Cell Transplantation





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

Mutation patterns observed in MDS treated with allo-HSCT



RUNX1 23%
SRSF2 17%
ASXL1 17%
SF3B1 16%
KRAS/NRAS 16%
DNMT3A 15%
TP53 13%
TET2 10%

JCO doi:10.1200/JCO.2016.67.3616

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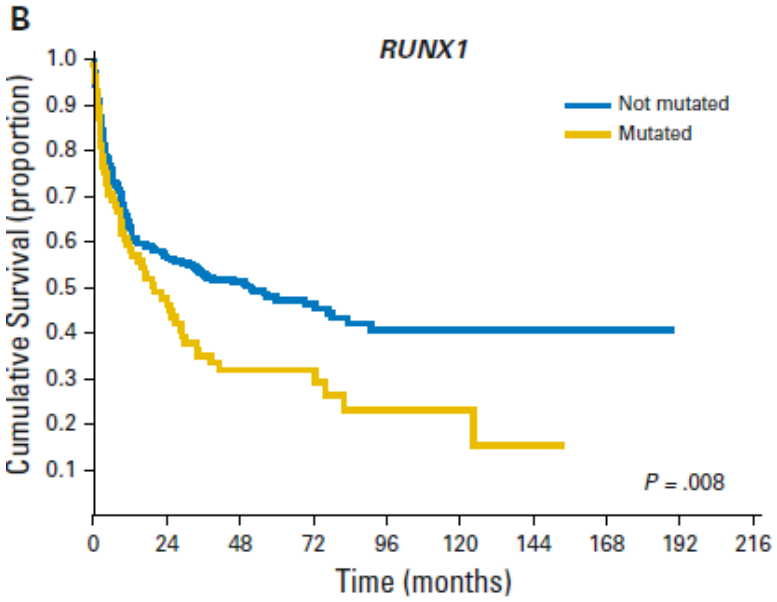
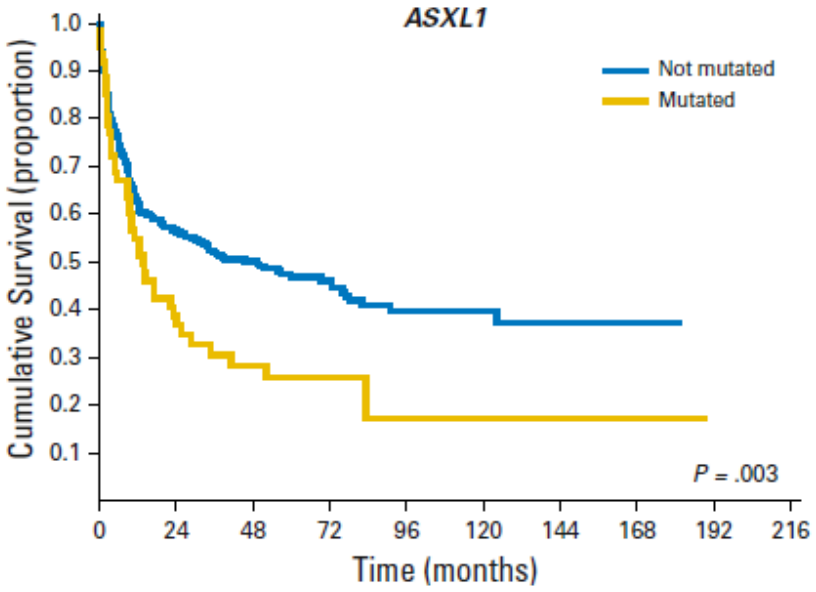
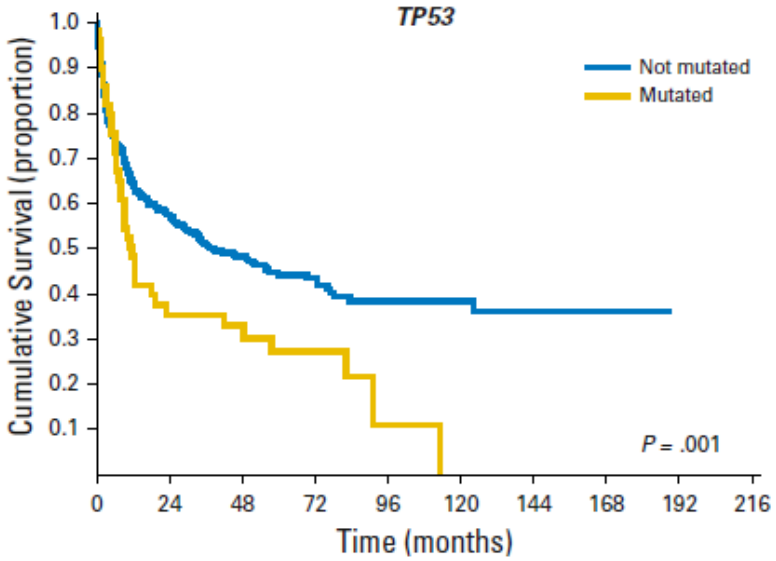
Relationship between type of oncogenic mutations and overall survival of MDS receiving allo-HSCT







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

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

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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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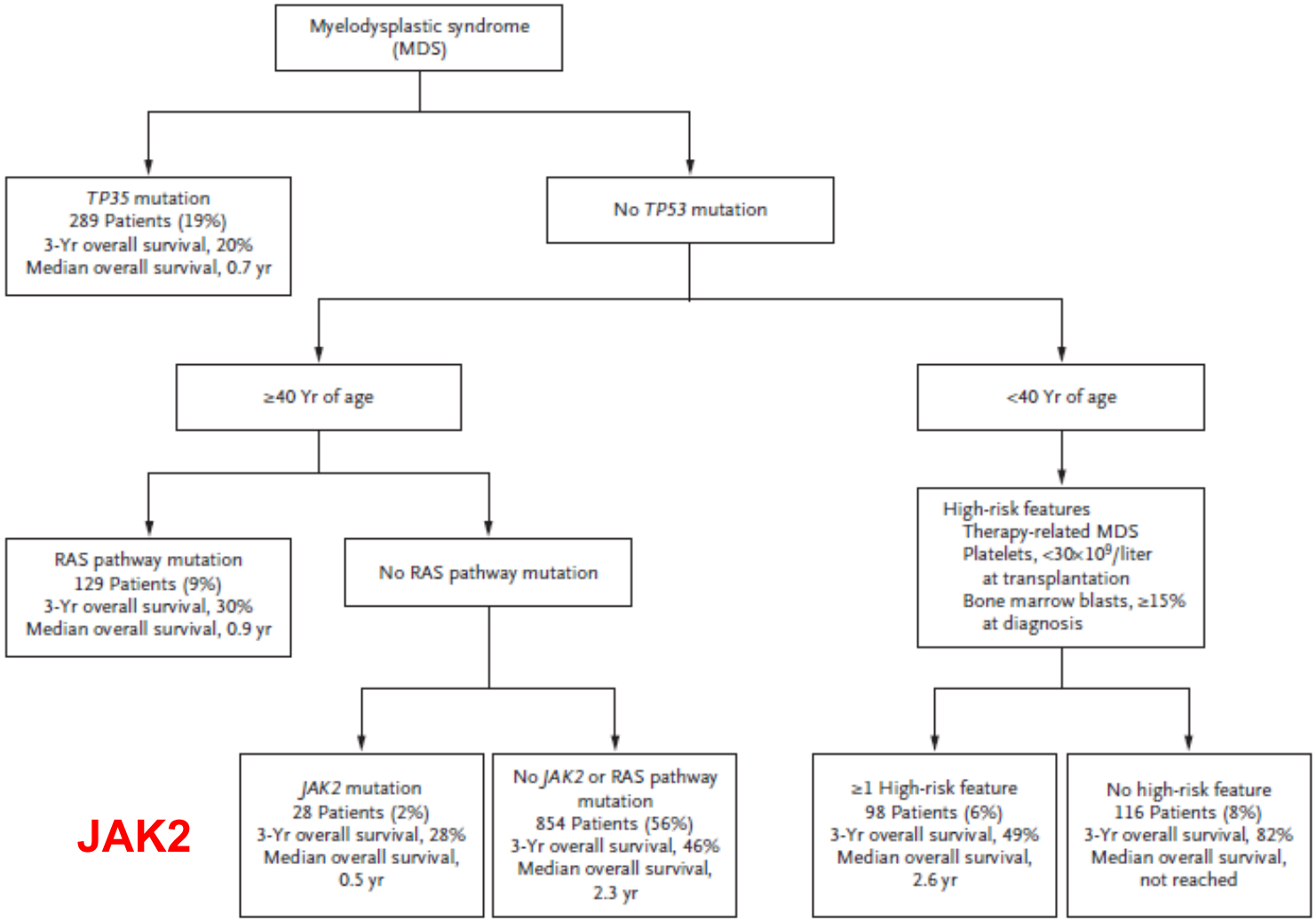
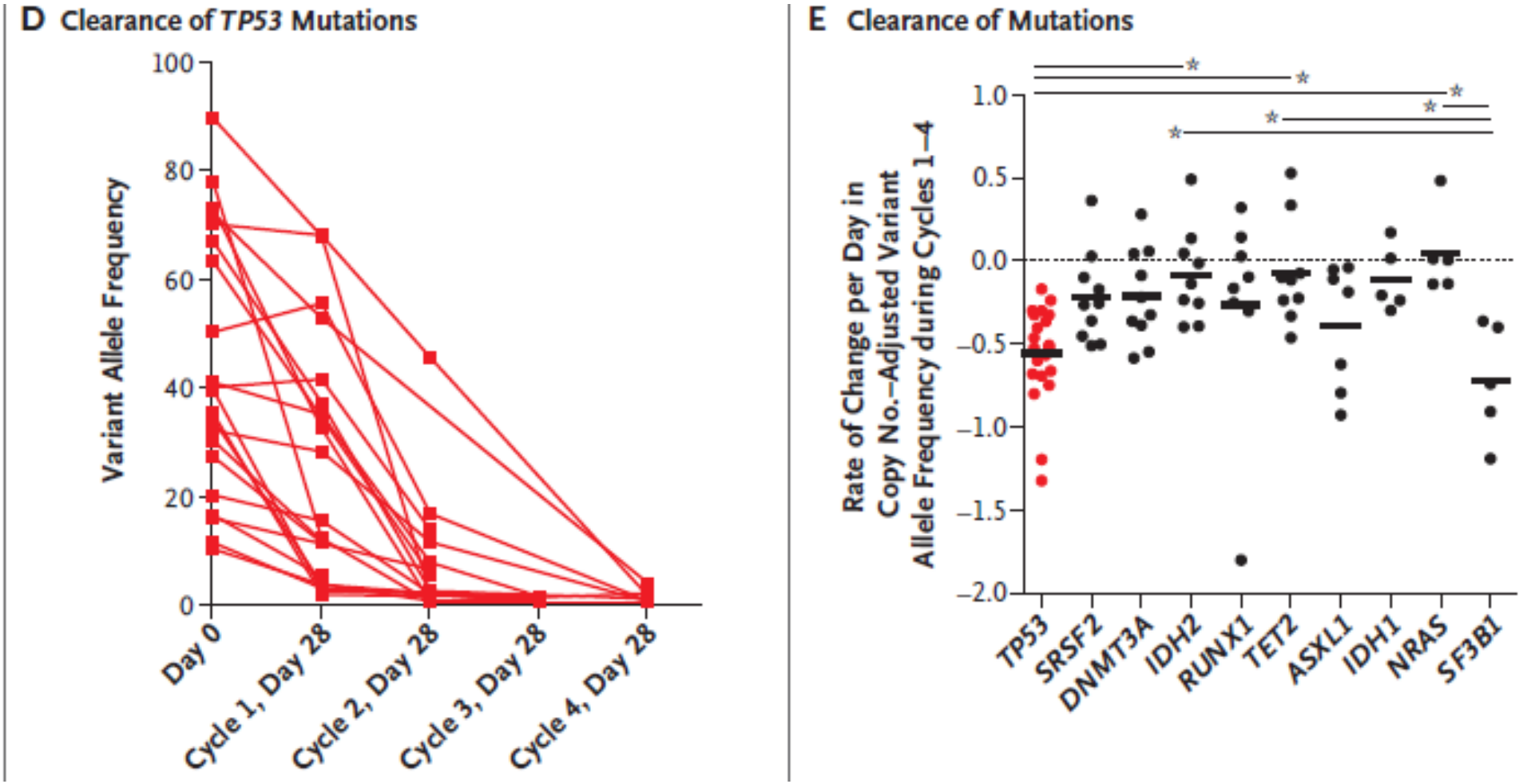
Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation



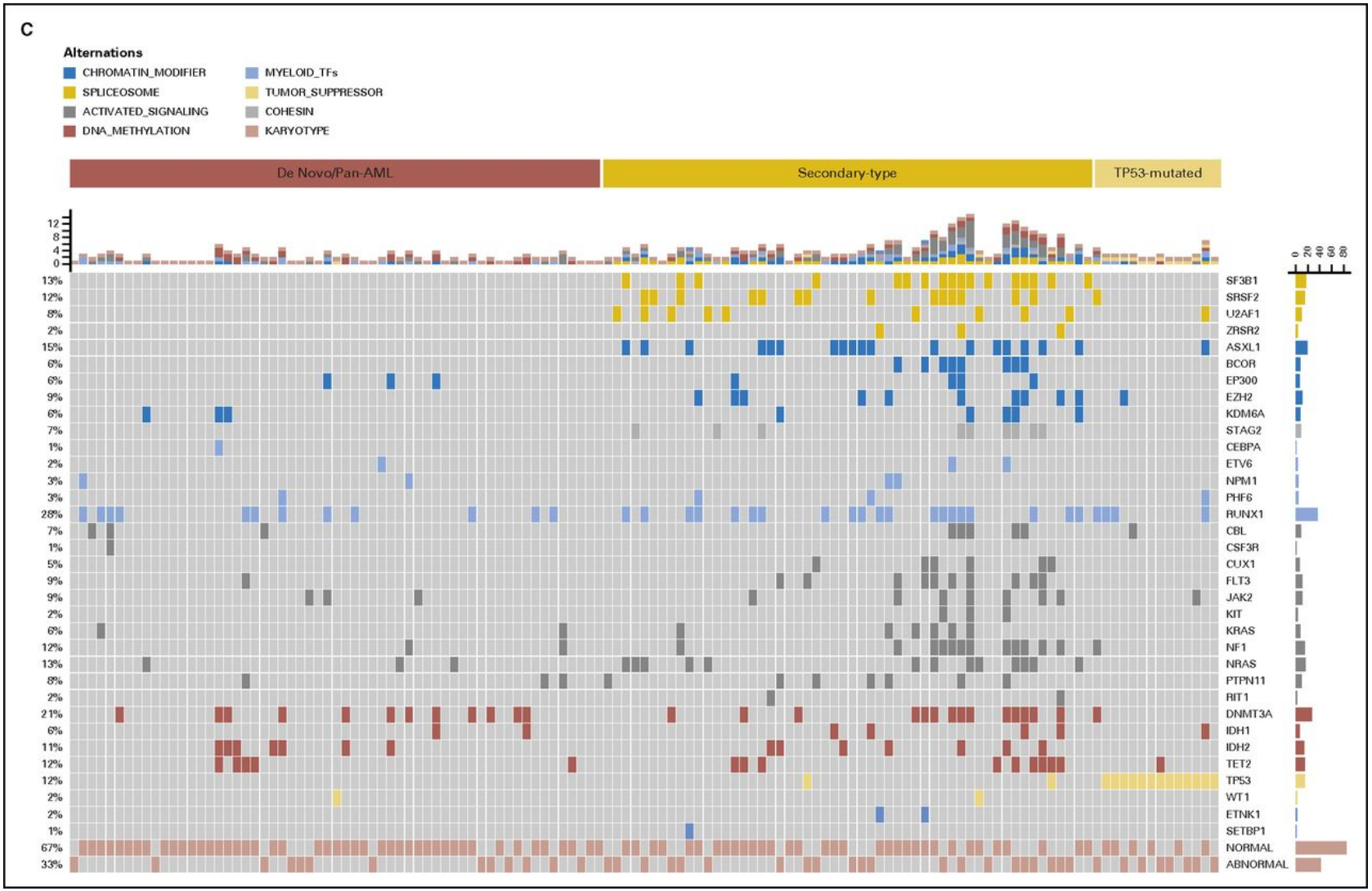
Lindsley, RC et al. N Engl J Med 2017;376:536-47.

TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes



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

Mutation patterns observed in MDS/AML treated with allo-HSCT



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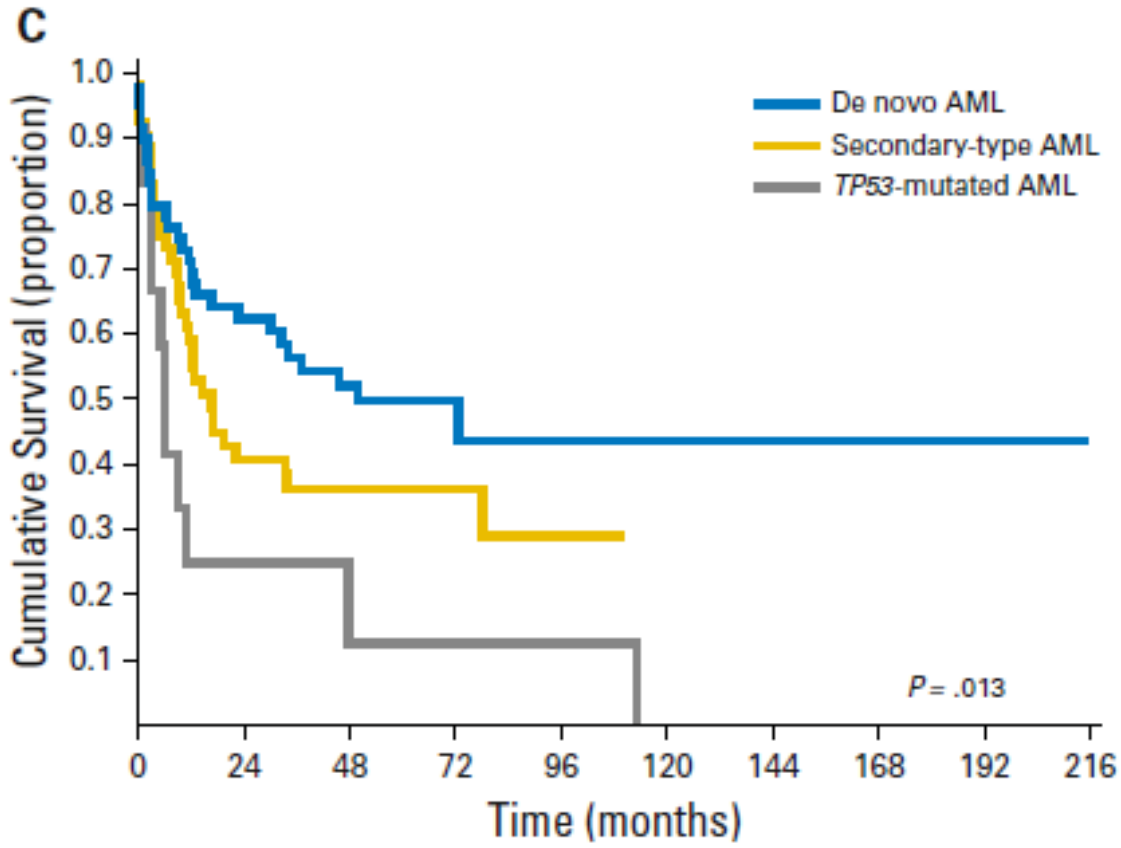
Posttransplantation overall survival among patients with acute myeloid leukemia (AML) evolving from MDS according to genetic ontogeny group.



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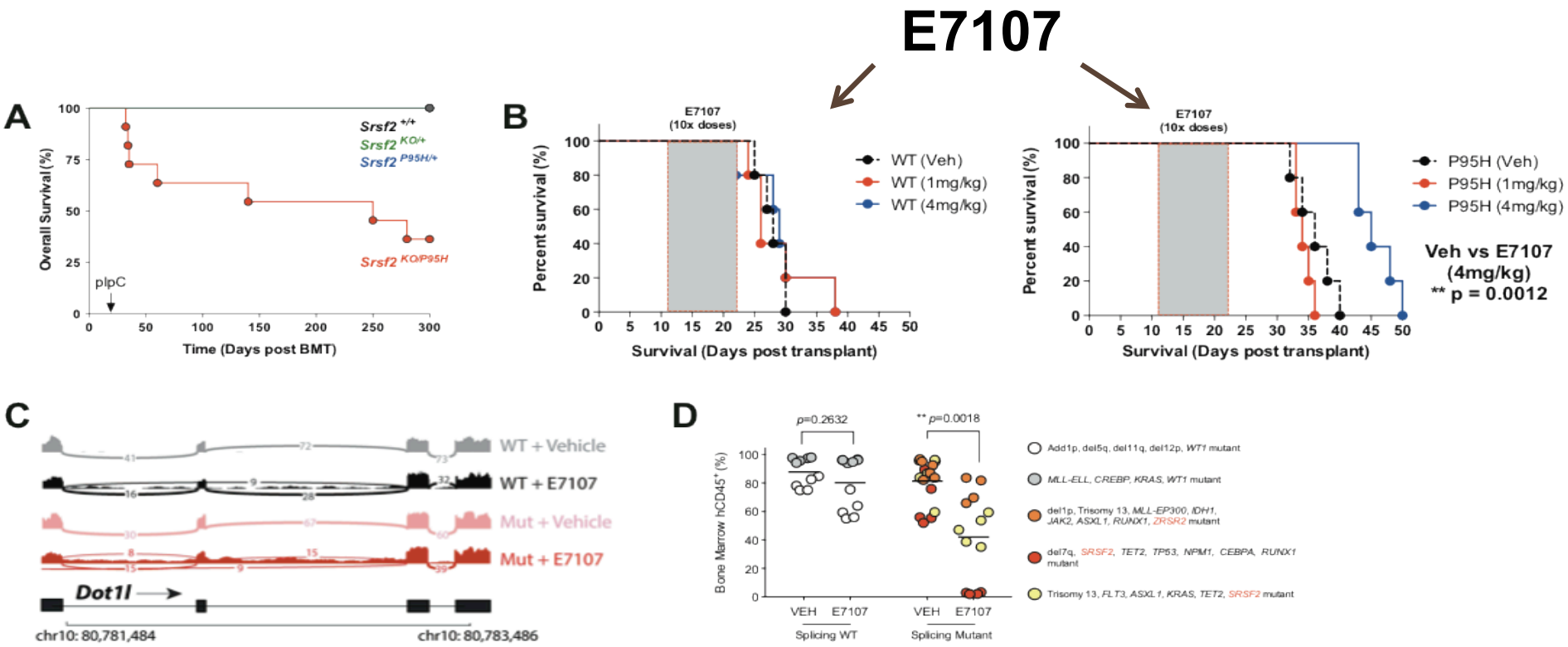
ASH2015 - Therapeutic Targeting of Spliceosomal Mutant Myeloid Leukemias through Modulation of Splicing Catalysis



Summary

- Disease burden significantly affect posttransplantation outcome in MDS receiving allo-HSCT.
- Cytoreduction should be considered in patients with 10% or more bone marrow blasts who are candidates for transplantation, but the decision should be made on an individual basis, accounting for clinical considerations with respect to each specific patient.
- AML-like chemotherapy may be the best option in medically fit patients (with immediate availability of a donor and without complex karyotype)
- Hypomethylating agents could be considered mainly for older patients and as a bridging strategy to HSCT in those where no donor has yet been identified.
- Hypomethylating agents are active in patients with complex karyotype, for whom conventional chemotherapy invariably fails.
- Somatic mutations are expected to improve clinical decision making process in transplatation

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