



CONVEGNO FISiM

Firenze, CSF Montedomini

“Il Fuligno”

24-25 ottobre 2024

HSCT: where do we stand ?
IRCCS Ospedale Policlinico San Martino



OSPEDALE POLICLINICO SAN MARTINO

Sistema Sanitario Regione Liguria

Istituto di Ricovero e Cura a Carattere Scientifico

Disclosures

- DMC member for Vertex, BMS and Vifor
- Advisory board for Novartis and Menarini
- Contract for Menarini



Statement

- Allogeneic HCT is the only available possibility to cure MDS
 - No curative alternatives
 - Survival vs disease free survival
- Who are the patients for whom a curative intent is reasonable.
- How to maximize curative possibility.



Where do we stand ? Agenda

- Patients selection
 - Disease and patient
- Road to transplant
- Conditioning
- Post transplant care



- Who is the patient for whom a curative intent is reasonable.
 - Age
 - Clinical condition, organ damage (HCT-CI)
 - wiliness
 - Disease

AGE

Effect of Age on Outcome of Reduced-Intensity Hematopoietic Cell Transplantation for Older Patients With Acute Myeloid Leukemia in First Complete Remission or With Myelodysplastic Syndrome

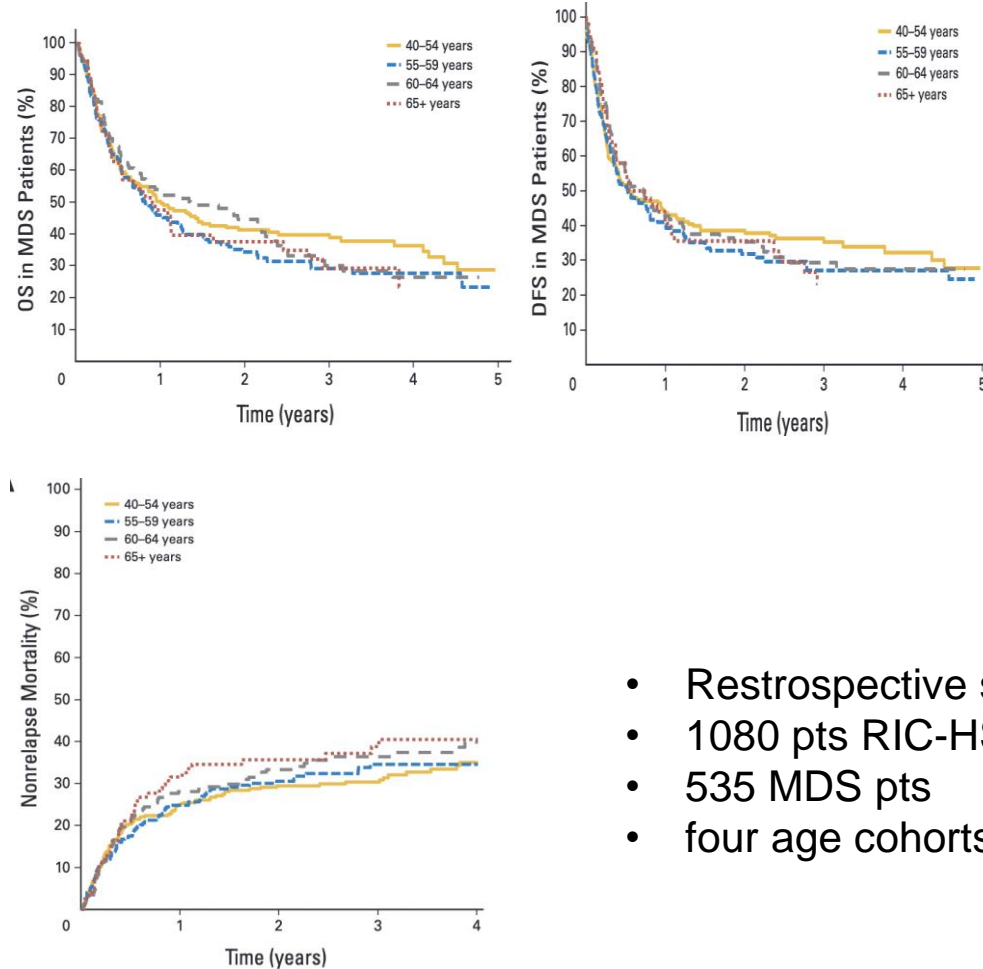
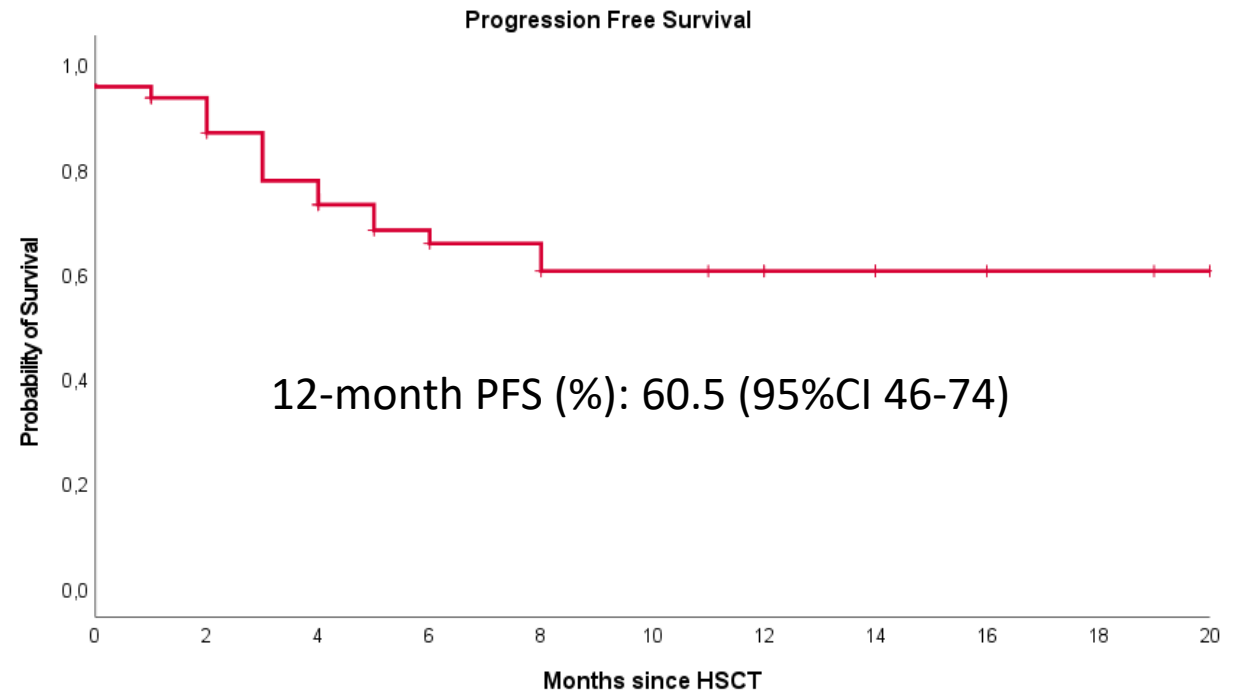
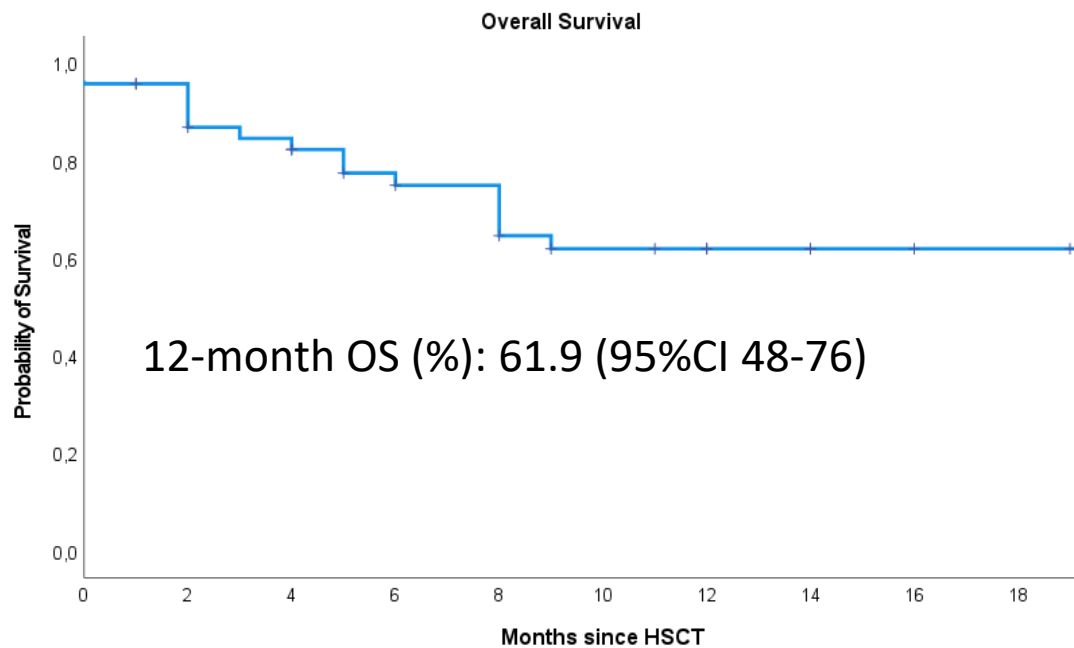


Table 5. Multivariate Analysis of 2-Year Disease-Free Survival and Overall Survival After Allogeneic HCT for Patients With AML in First Complete Remission and MDS

Variable	No. of Patients	Disease-Free Survival			Overall Survival			
		OR	95% CI	P	No. of Patients	OR	95% CI	P
Age, years								
40-54	399	1.00*		.81†‡	401	1.00*		.74†‡
55-59	289	1.03	0.82 to 1.29	.81	291	1.02	0.82 to 1.27	.85
60-64	255	1.12	0.89 to 1.42	.33	255	1.09	0.86 to 1.37	.48
≥ 65	116	1.07	0.79 to 1.45	.68	116	1.16	0.86 to 1.57	.32
Significant covariates								
KPS								
≥ 80	878	1.00*		.003†§	882	1.00*		.003†§
< 80	107	1.06	0.74 to 1.51	.75	107	1.63	1.21 to 2.20	.001
Unknown	74	1.58	1.01 to 2.45	.04	74	0.87	0.61 to 1.25	.46
Donor/recipient match								
HLA-identical sibling	457	1.00*		.003†	460	1.00*		.05†
Well matched	365	1.48	1.12 to 1.95	.01	366	1.20	0.98 to 1.47	.08
Partially matched	151	1.46	1.06 to 2.02	.02	151	1.21	0.92 to 1.57	.17
Mismatched	54	2.53	1.54 to 4.15	< .001	54	1.85	1.21 to 2.85	.005
Unknown	32	1.37	0.81 to 2.31	.24	33	1.15	0.69 to 1.90	.60
Donor age (continuous)								
	1066	1.01	1.00 to 1.02	.02	1066	—	—	—
Cytogenetic risk group								
AML, favorable/intermediate	390	1.00*		.006†¶	390	1.00*		.006†¶
AML, unfavorable	83	2.13	1.44 to 3.14	< .001	83	2.01	1.39 to 2.91	< .001
AML, unknown	63	1.01	0.68 to 1.49	.97	63	0.89	0.60 to 1.32	.57
MDS, good/intermediate	204	1.12	0.88 to 1.42	.37	206	1.04	0.81 to 1.33	.75
MDS, poor	228	1.27	1.01 to 1.61	.05	229	1.22	0.96 to 1.54	.10
MDS, unknown	91	1.15	0.82 to 1.61	.42	92	1.09	0.78 to 1.51	.62

- Restrospective study CIBMTR
- 1080 pts RIC-HSCT (age 40 to 78 yrs)
- 535 MDS pts
- four age cohorts (40-54, 55-59, 60-64, >65 years)

Genova Experience. AML and MDS 70-75 years old patients (#47)



FU, median duration: 12 months 95% CI: 6-33)

COMORBIDITIES

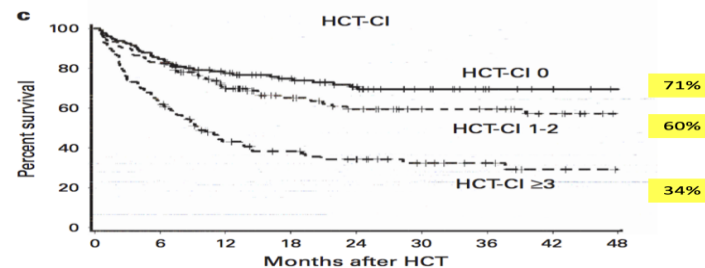
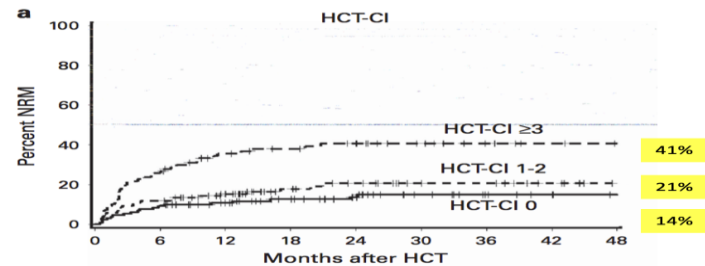
Hematopoietic cell transplantation (HCT)- specific comorbidity index

Blood 2005;106:2912-9

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac‡	Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild‡	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	1
Obesity†	Patients with a body mass index > 35 kg/m ²	1
Infection†	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal‡	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary‡	DLco and/or FEV ₁ 66%-80% or dyspnea on slight activity	2
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary‡	DLco and/or FEV ₁ ≤ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	3

<http://www.hctci.org/Home/Calculator>

Sorrer, Blood 2013





- Who is the patient for whom a curative intent is reasonable.
 - Age
 - Clinical condition, organ damage (HCT-CI)
 - wiliness
 - Disease



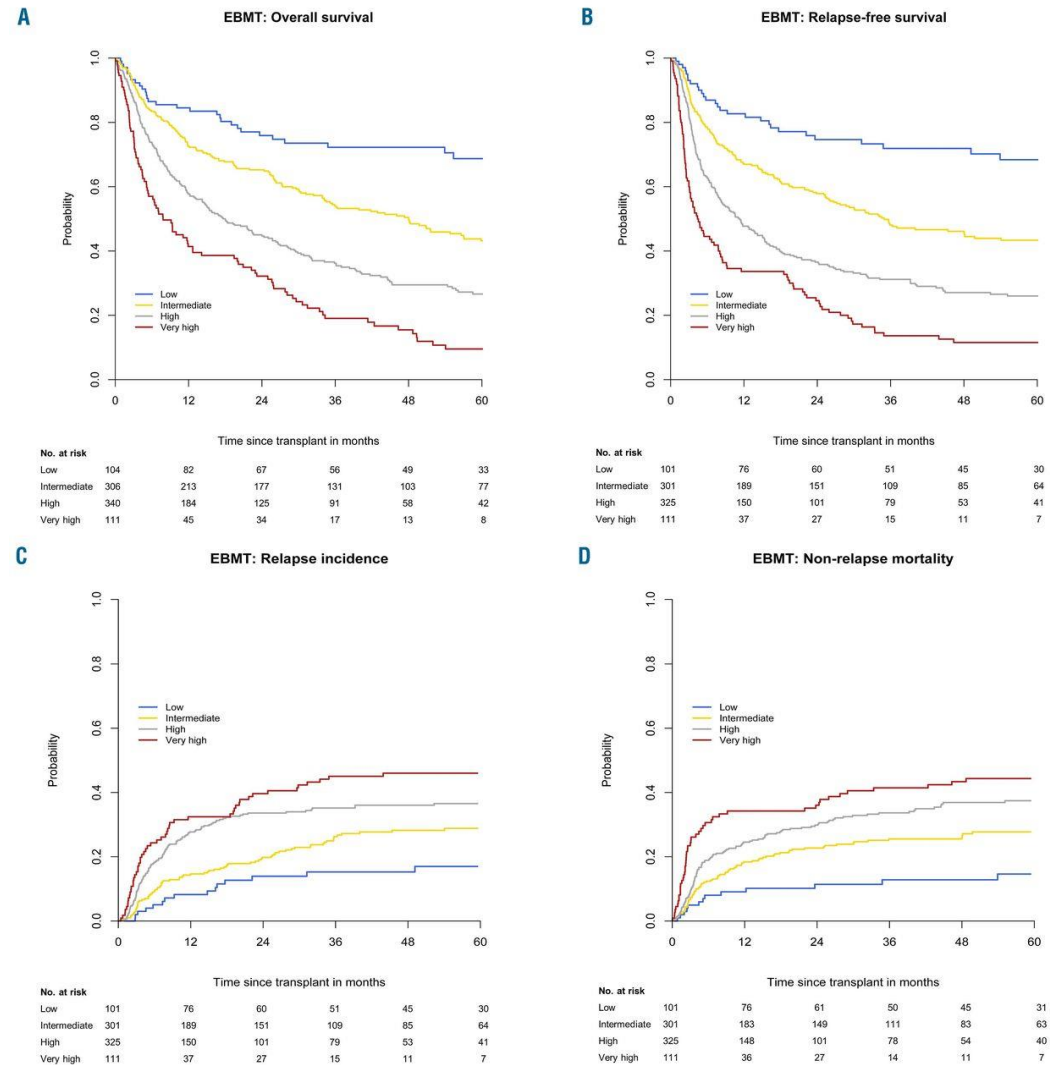
Variables (units) [usual range]	Value
Hemoglobin (g/dL) [4-20] A possible conversion for Hb values: 10 g/dL= 6.2 mmol/L, 8 g/dL= 5.0 mmol/L	<input type="text"/>
Absolute Neutrophil Count (x10⁹/L) [0-15]	<input type="text"/>
Platelets (x10⁹/L) [0-2000]	<input type="text"/>
Bone Marrow Blasts (percent) [0-30]	<input type="text"/>
Cytogenetic Category	
<input type="radio"/> Very Good <input type="radio"/> Good <input type="radio"/> Intermediate <input type="radio"/> Poor <input type="radio"/> Very Poor	

IPSS-R SCORE	IPSS-R CATEGORY
-	-

RISK CATEGORY	RISK SCORE
Very Low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

HCT

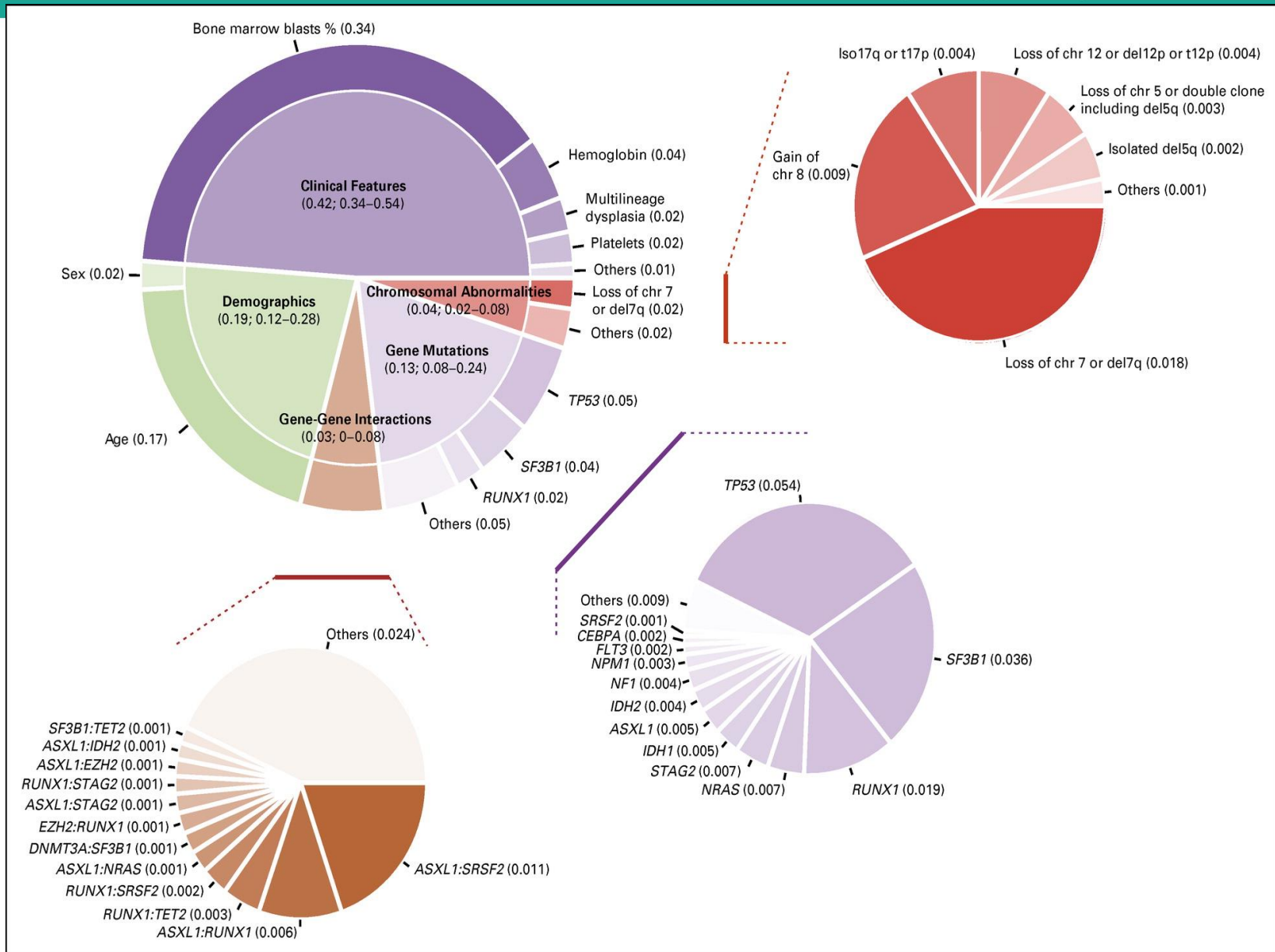
Kaplan-Meier analysis of survival following allogeneic stem cell transplantation in patients with myelodysplastic syndrome stratified according to each risk group of the EBMT transplant-specific risk score.



Nico Gagelmann et al. *Haematologica* 2019;104:929-936



Bersanelli M et al. JCO 2021 Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes



Fraction of explained variation that was attributable to different prognostic factors for overall survival

PROGNOSTIC SCORES

IPSS-Molecular

- 2957 MDS samples from 24 centers
- 9254 oncogenic mutations across 121 genes in 90% of pts
- 3186 cytogenetic alterations in 41% of pts



Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.²

Category and Variable	Adjusted Hazard Ratio (95% CI) [†]	Model Weight [‡]
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10 ⁹ /l	0.998 (0.997–0.999)	-0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	-0.171
Cytogenetic		
IPSS-R cytogenetic category [§]	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)[¶]		
<i>TP53</i> ^{multihit}	3.27 (2.38–4.48)	1.18
<i>MLL</i> ^{PTD}	2.22 (1.49–3.32)	0.798
<i>FLT3</i> ^{ITD+TKD}	2.22 (1.11–4.45)	0.798
<i>SF3B1</i> ^{S⁹}	1.66 (1.03–2.66)	0.504
<i>NPM1</i>	1.54 (0.78–3.02)	0.430
<i>RUNX1</i>	1.53 (1.23–1.89)	0.423
<i>NRAS</i>	1.52 (1.05–2.20)	0.417
<i>ETV6</i>	1.48 (0.98–2.23)	0.391
<i>IDH2</i>	1.46 (1.05–2.02)	0.379
<i>CBL</i>	1.34 (0.99–1.82)	0.295
<i>EZH2</i>	1.31 (0.98–1.75)	0.270
<i>U2AF1</i>	1.28 (1.01–1.61)	0.247
<i>SRSF2</i>	1.27 (1.03–1.56)	0.239
<i>DNMT3A</i>	1.25 (1.02–1.53)	0.221
<i>ASXL1</i>	1.24 (1.02–1.51)	0.213
<i>KRAS</i>	1.22 (0.84–1.77)	0.202
<i>SF3B1</i> [*]	0.92 (0.74–1.16)	-0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)		
min(Nres,2)	1.26 (1.12–1.42)	0.231

IPSS-M Risk Calculator for Myelodysplastic Syndromes (MDS)

Input Patient Data

1 Clinical Data 2 Cytogenetics 3 Molecular Data

*Bone Marrow Blasts [0–30%]
3

*Hemoglobin [4–20 g/dl]
9.7

*Platelet Count [0–2000 1e9/l]
130

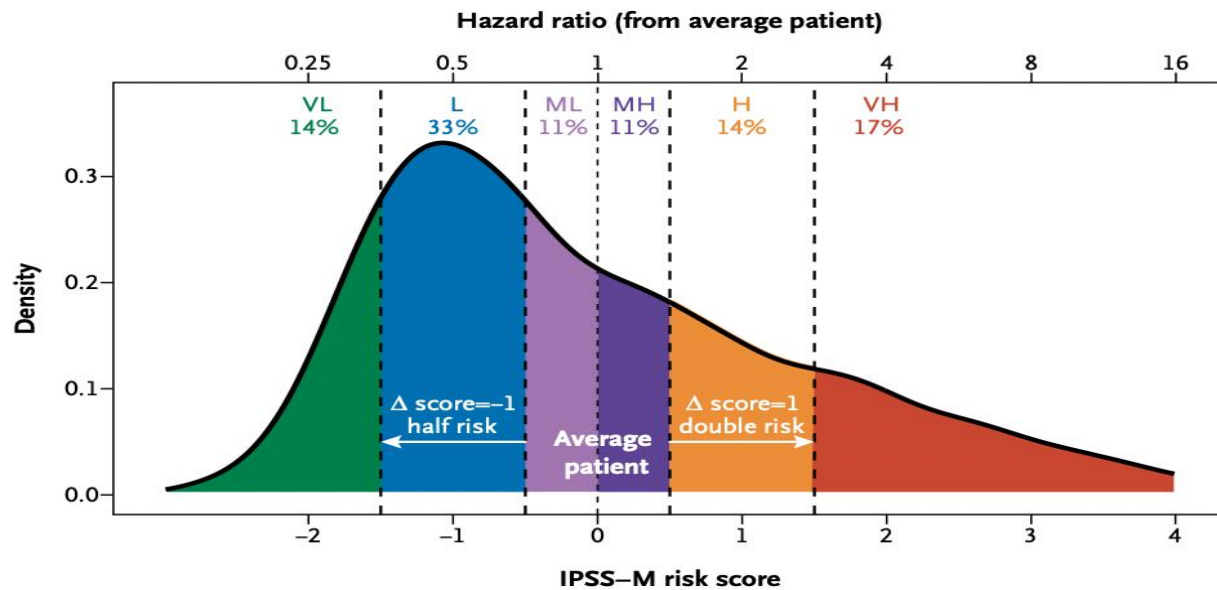
Absolute Neutrophil Count [0–15 1e9/l]
1.9

Skip Variable. Only needed to calculate IPSS-R

Age [18–120 years]
72

PROGNOSTIC SCORES

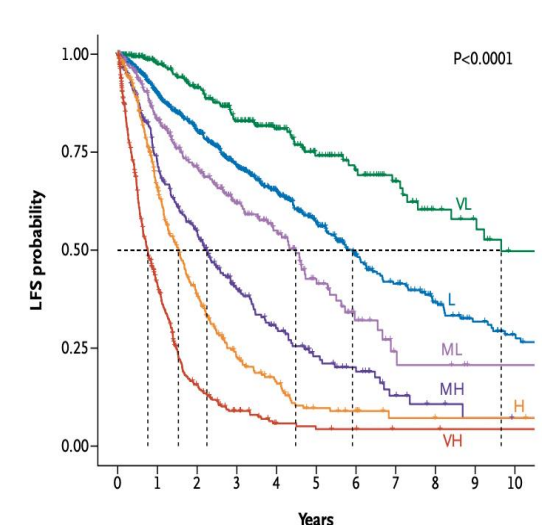
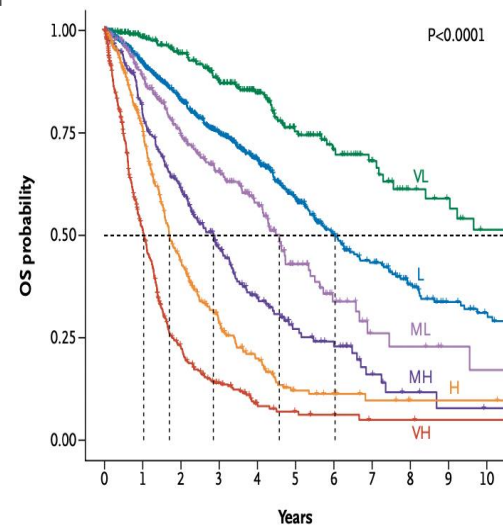
IPSS-Molecular



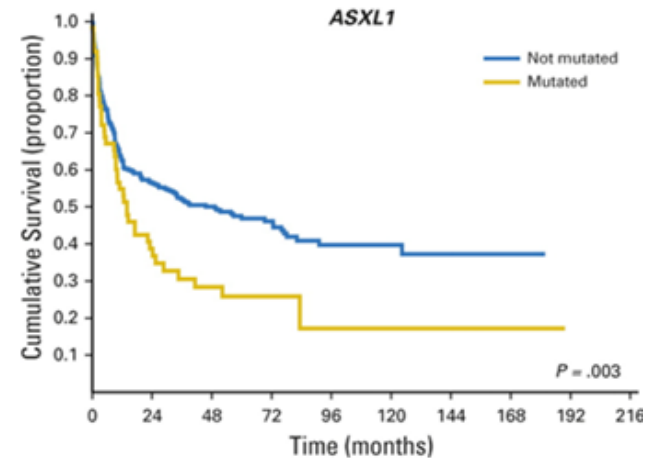
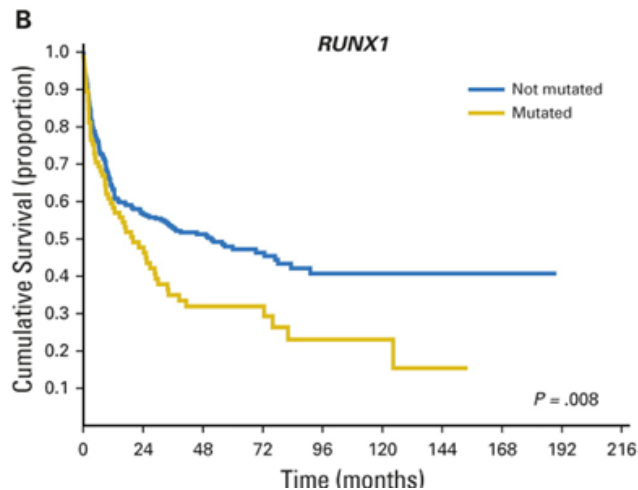
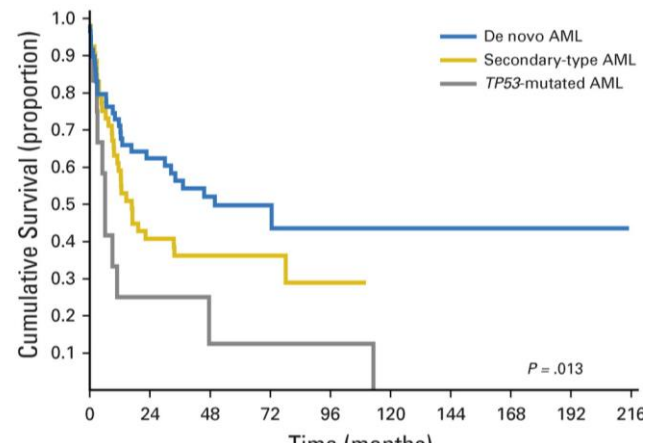
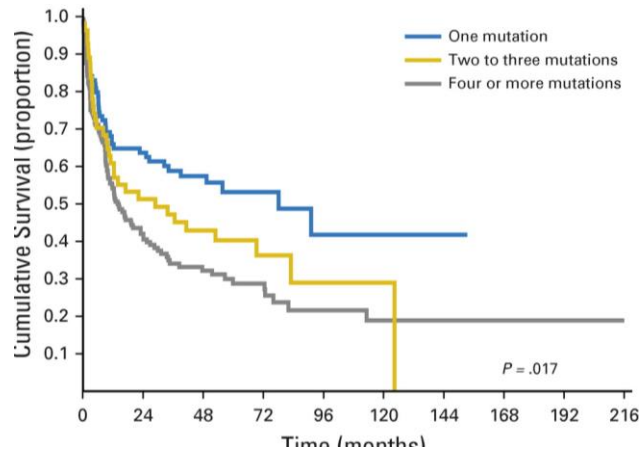
IPSS-M Categories:

- Very Low
- Low
- Moderate Low
- Moderate High
- High
- Very High

- Restratification of pts from IPSS-R to IPSS-M: 46% of pts change risk group
- 50% of int-risk shift to high risk



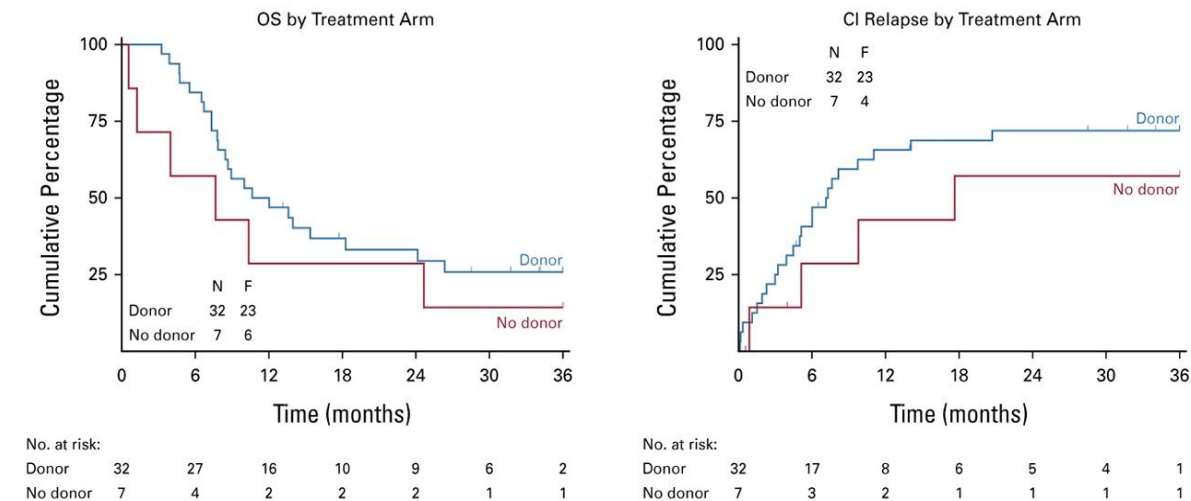
MDS TREATED WITH HSCT: IMPACT OF DRIVER SOMATIC MUTATIONS ON SURVIVAL OUTCOMES



- **ASXL1 // RUNX1 // TP53**: independent predictors of OS and relapse after HSCT in MDS and AML post-MDS
- The **number of somatic mutations** is associated with survival outcome
- **Gene ontology** is an independent predictor of post-HSCT outcome

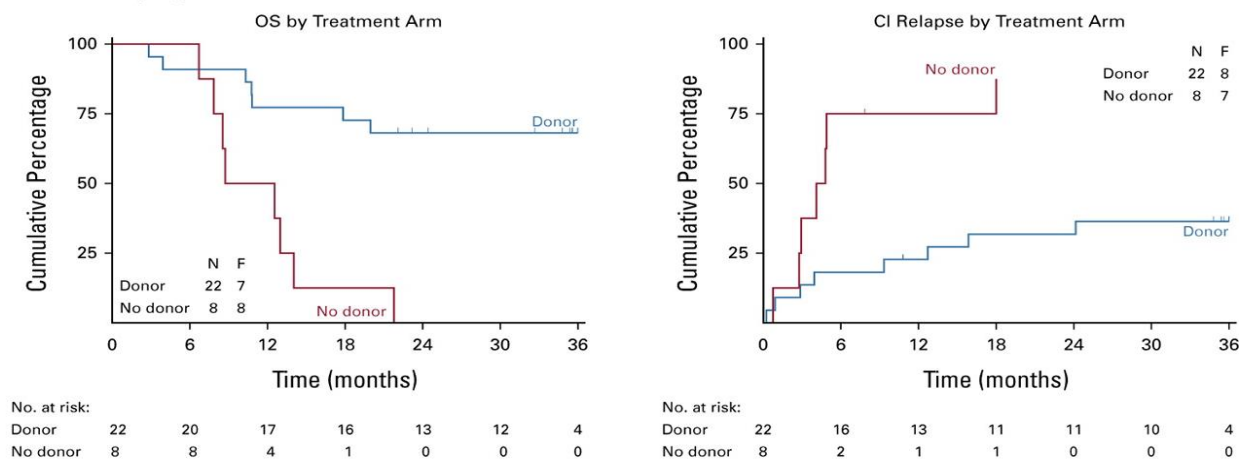
GENETIC ANALYSIS OF THE BMT CTN 1102 STUDY PROSPECTIVE COHORT – POST HOC GENETIC ANALYSES

C IPSS-M Very High Risk—TP53 Mutation Present



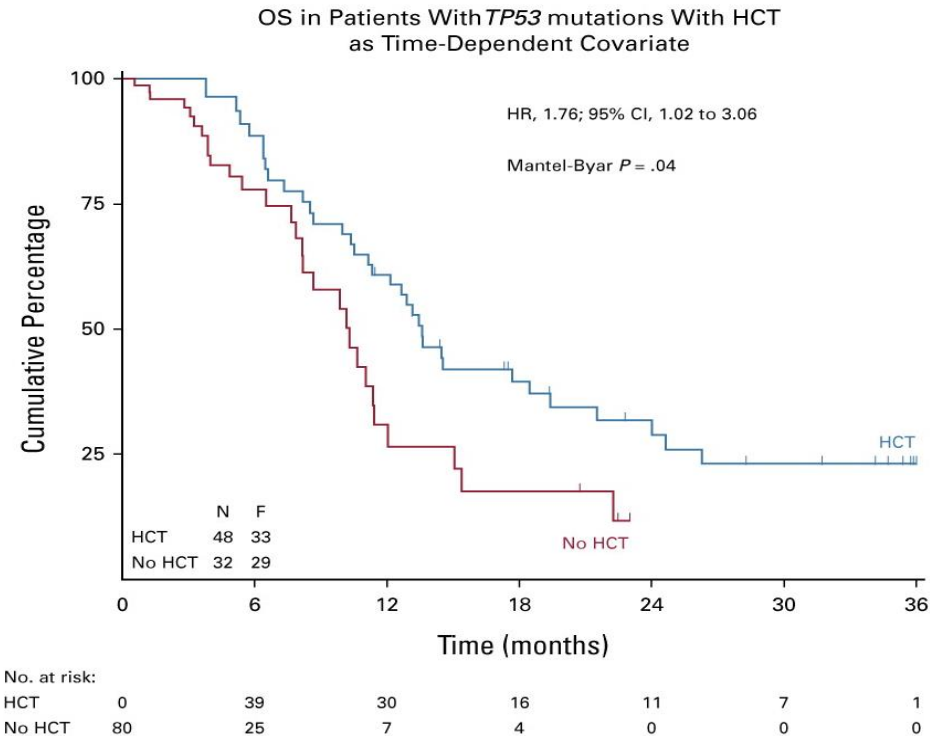
OS among patients with molecular IPSS (IPSS-M) very high risk without a TP53 mutation was significantly improved if they had a donor ($68\% \pm 10\%$ v $0\% \pm 12\%$ at 3 years; $P = .001$).

D IPSS-M Very High Risk—TP53 Mutation Absent



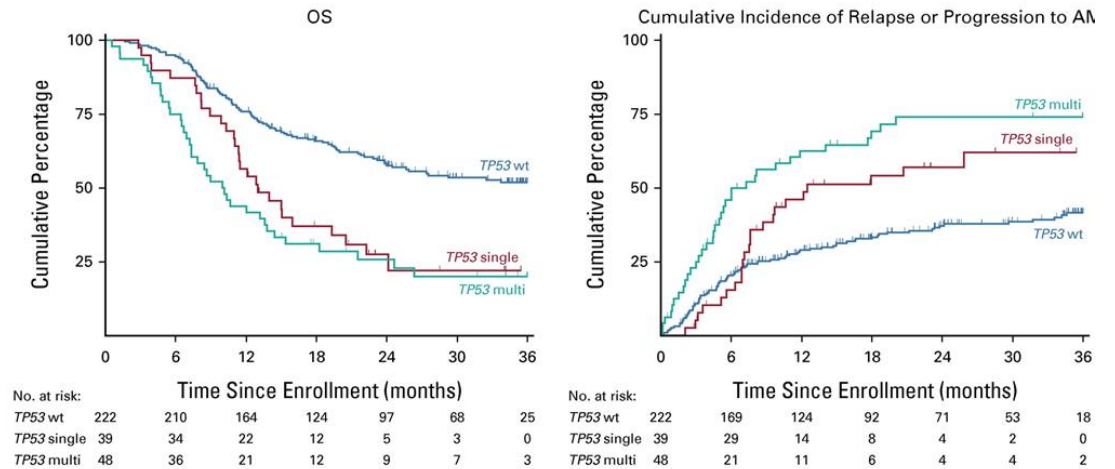
GENETIC ANALYSIS OF THE BMT CTN 1102 STUDY PROSPECTIVE COHORT – POST HOC GENETIC ANALYSES

B



OS in *TP53* mut patients was worse compared with *TP53* wt patients ($21\% \pm 5\%$ [SE] v $52\% \pm 4\%$ at 3 years; $P < .001$).

No significant OS difference between *TP53*single versus *TP53*multihit ($22\% \pm 8\%$ v $20\% \pm 6\%$ at 3 years; $P = .31$).

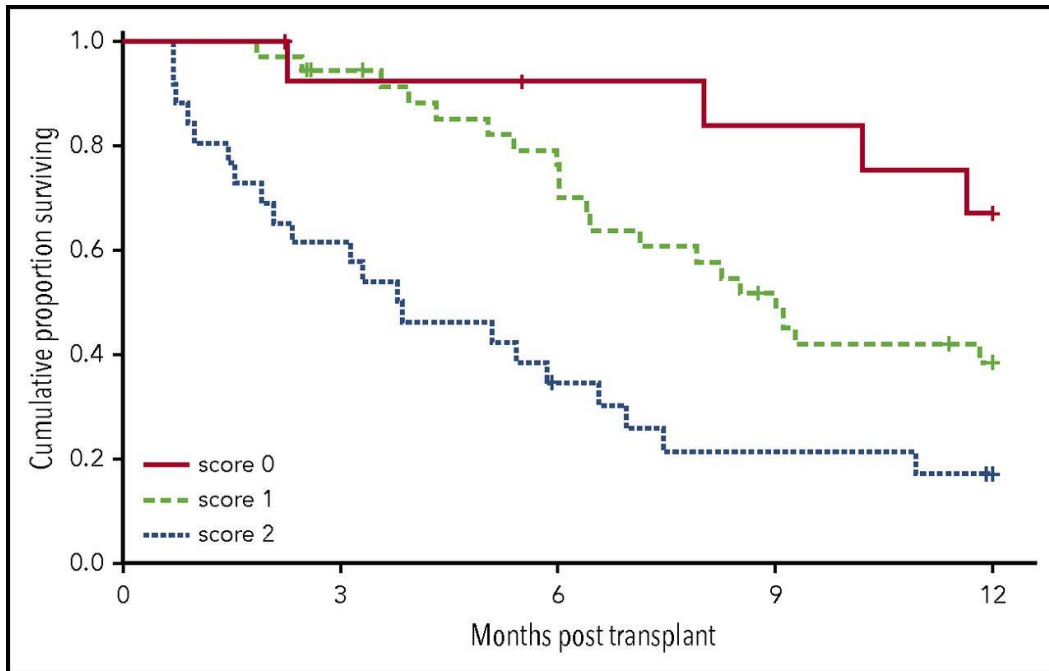


TP53 mut patients undergoing HCT had **improved OS** compared with non-HCT treatment (OS at 3 years: $23\% \pm 7\%$ v $11\% \pm 7\%$; $P = .04$)
HR of 3.89; 95% CI, 1.87 to 8.12; $P < .001$

TRANSPLANT FOR TP53-MUTATED MDS

RETROSPECTIVE STUDY

(84 PATIENTS, 55 HCT)



Retrospective series of 84 TP53 mut patients

3 independent factors associated with worse OS: HCT-CI > 4 // KPS ≤ 80% // disease not in CR1/2

1 year OS according to risk score (0, 1 and ≥ 2). 67% - 39% - 17%



Who are the patients for whom a curative intent is reasonable ?

- Disease: Intermediate/ high/ very high R-IPSS
- Lower risk with well defined clinical and/or molecular risk
- Age <70-75 years
- Clinical condition, organ damage (HCT-CI)
- wiliness

How to maximize curative possibility.

- Selecting the right patient at the right moment
- Selecting conditioning intensity on relapse risk (M-IPSS)
- Selecting the right donor (DSA)
- Road to transplant

CONDITIONING REGIMENS

Overview of transplant preparatory regimens

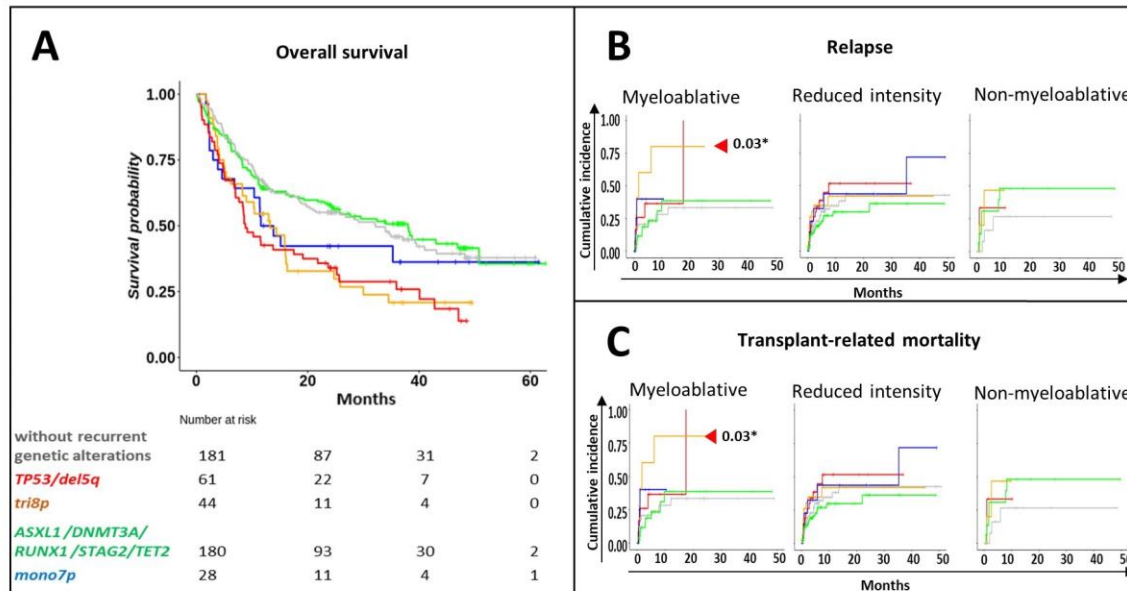
Type of regimen	Description
Conventional myeloablative (high) intensity (MA) regimen	Standard dose total body irradiation (TBI) (>500 cGy, single dose or >800 cGy fractionated dose) with or without standard dose cyclophosphamide (Cy) or fludarabine (Flu); busulphan (Bu) and Cy/Flu in standard doses (Bu: ≥ 9 mg/kg orally or equivalent intravenous dose); ²⁰ melphalan >150 mg/m ² \pm other agents. new regimens, including treosulfan (42 g/m ²) and fludarabine (Flu: 150 mg/m ²) ²³
Intermediate, reduced intensity conditioning (RIC)	Reduced TBI dose >200 cGy and <500 cGY single dose or fractionated TBI dose <800 cGY \pm other reduced Cy/Flu; reduced dose of Bu ≤ 8 mg/kg oral dose or equivalent intravenous dose combined with reduced dose of Cy/Flu; melphalan: ≤ 150 mg/m ² total dose combined with reduced dose Cy/Flu ¹⁹
Non myeloablative (low) intensity (NMA) regimen	2Gy TBI \pm Flu or Cy + Flu ¹⁹

- Higher risk patients with good performance status and no comorbidities are candidates for MA regimens, whereas less fit patients with comorbidities should be considered for RIC schedules (recommendation level C- de Witte et al. Blood 2017)



ASH 2021. #3678 Genomic Subgroups Impact Post-Transplant Survival in Patients with Myelodysplastic Syndrome: A CIBMTR Analysis. Tao Zhang, PhD^{1*}, 494 patients

Figure.1 The characteristics of molecular signatures and survival outcomes in MDS patient genomic subgroups. A. Survival curve of post-transplant overall survival outcome in different MDS patient subgroups. B. Cumulative risk curve of relapse in different MDS patient subgroups. C. Cumulative risk curve of transplant-related mortality in different MDS patient subgroups.

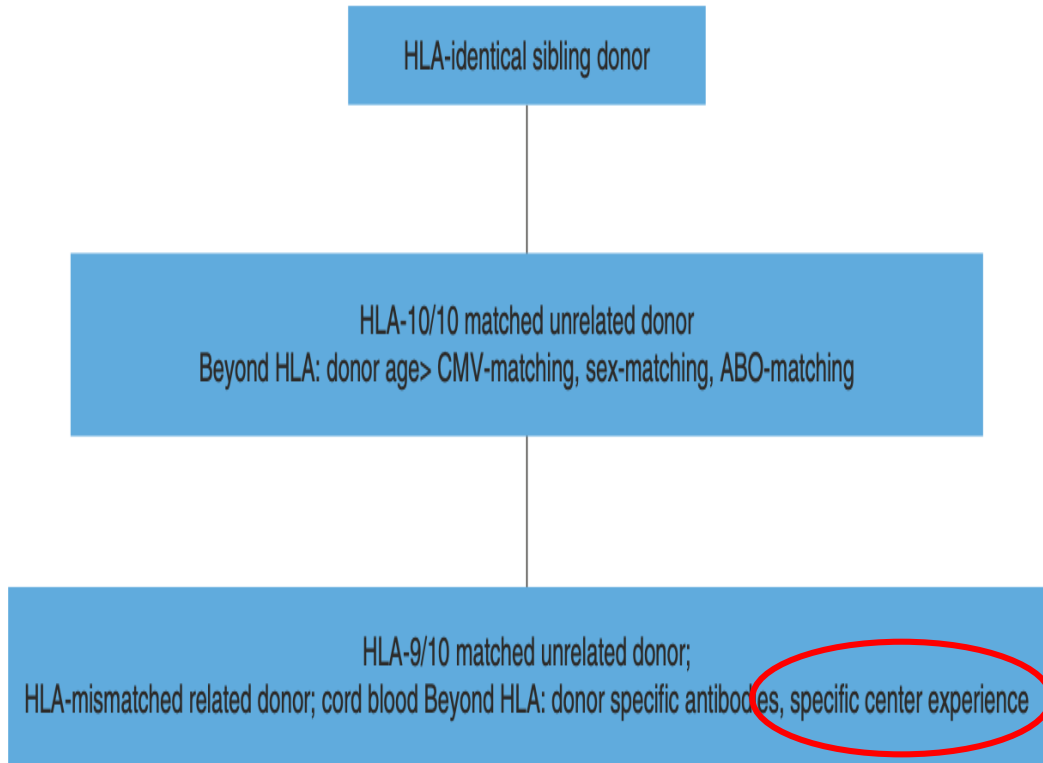


Conclusion

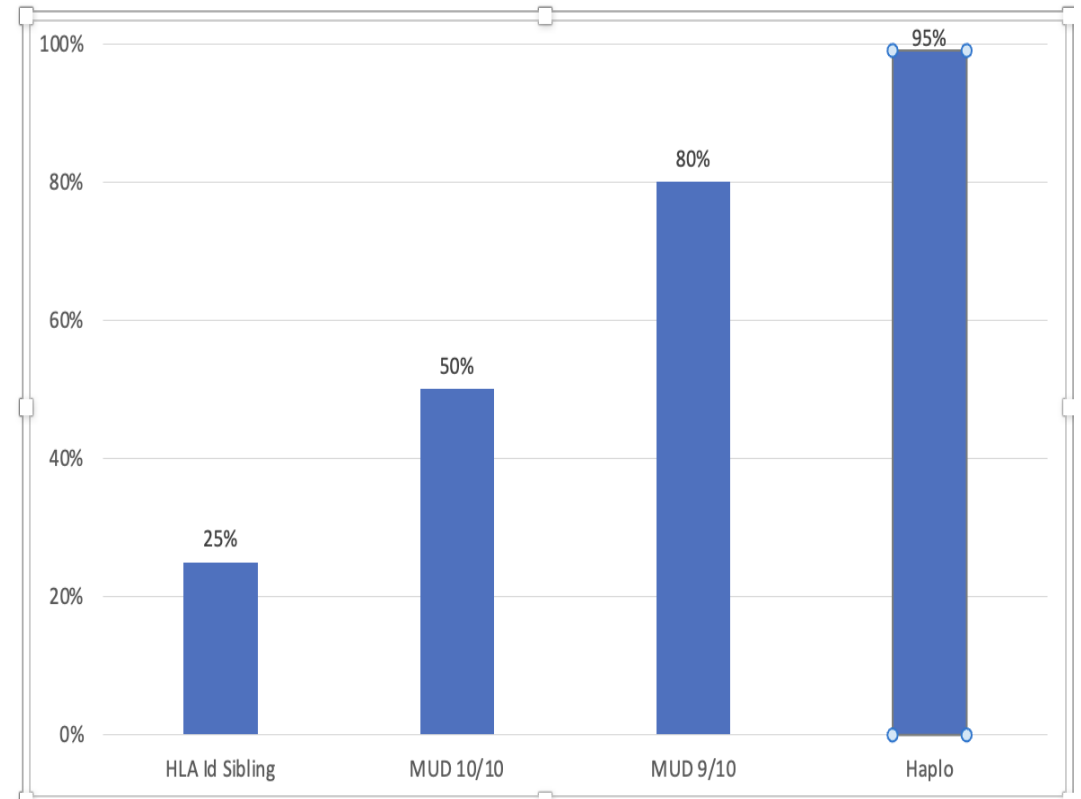
- Molecular signatures from MDS patient genomes at HCT may provide an independent prognosis of post-transplant survival.
- The choice of regimen intensity could be informed by knowledge of the individual genomic signature of a given MDS patient.

DONOR

Algorithm for donor selection for adult patients with hematological malignancies



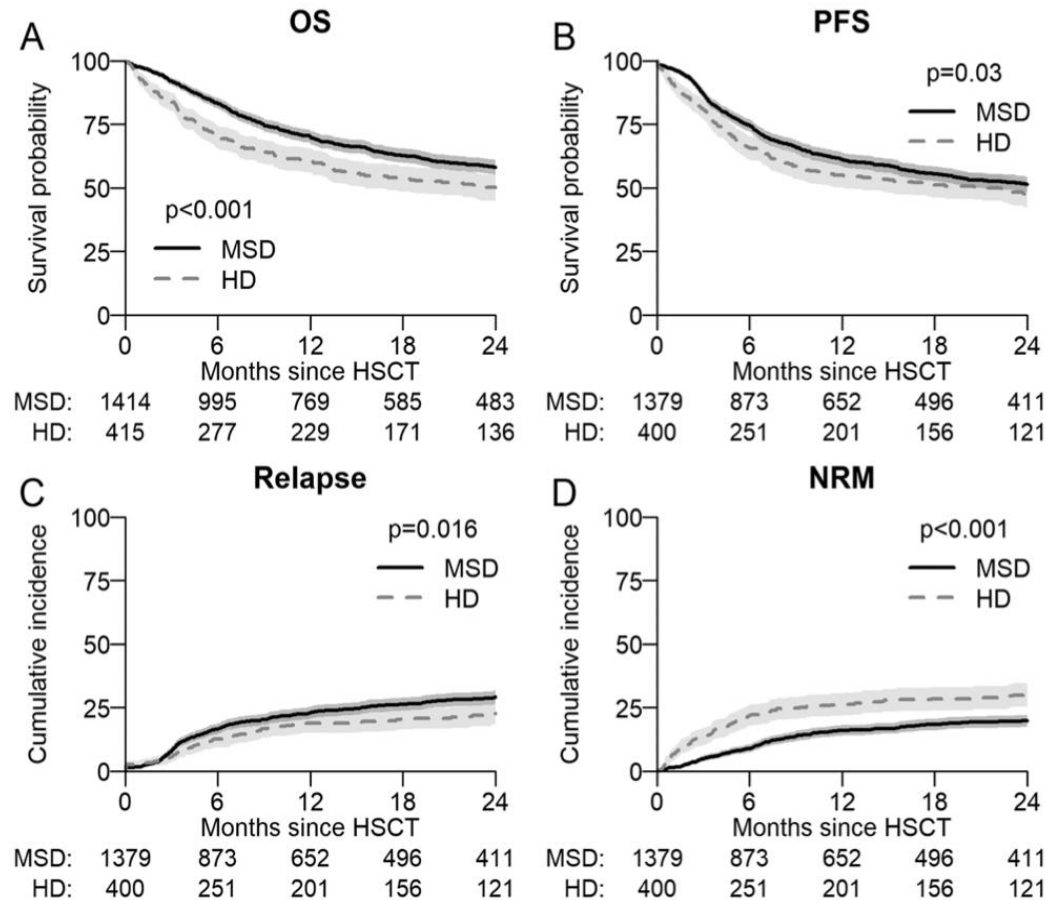
Probability to Find a Donor



Role of anti HLA ab

DONOR

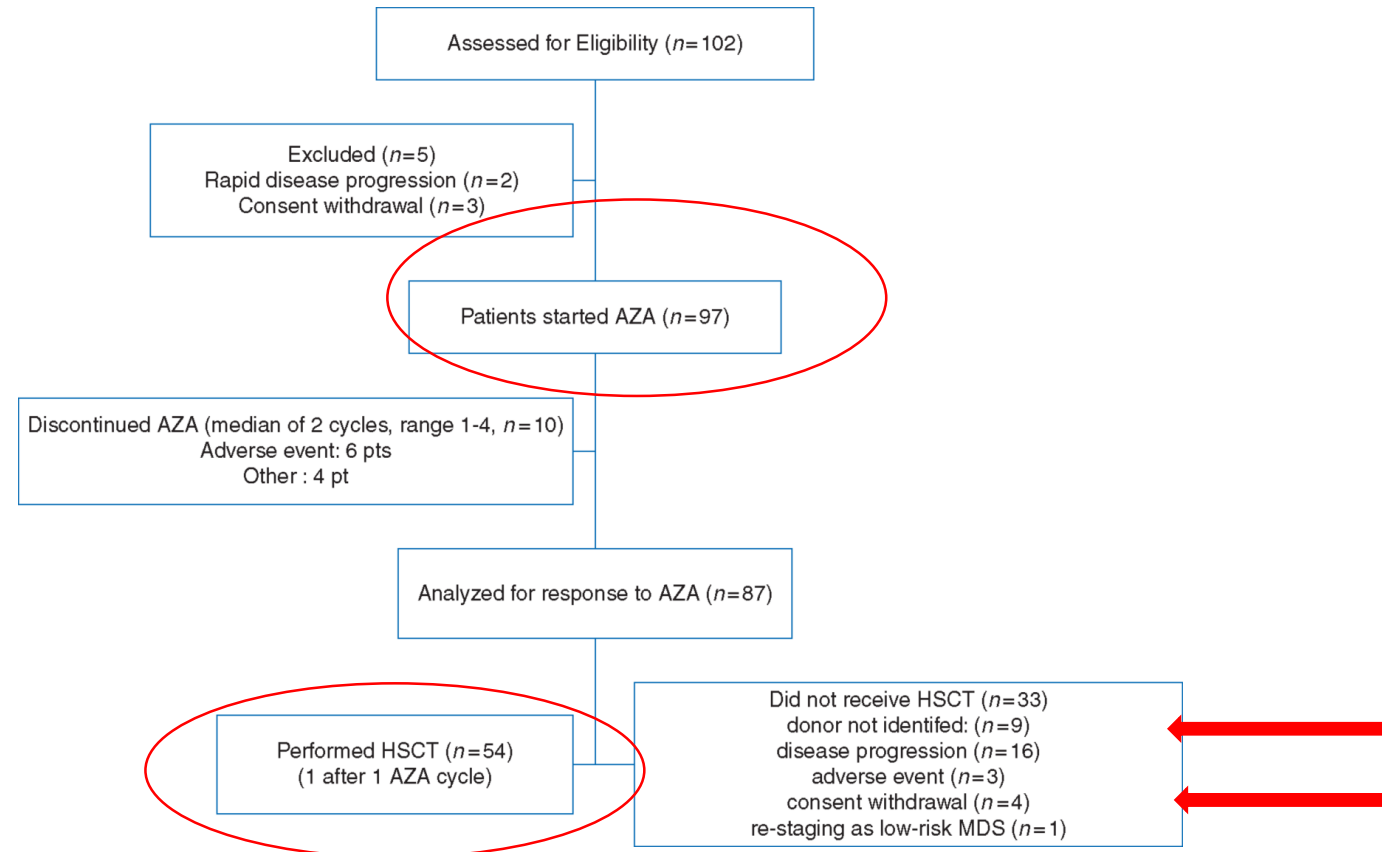
Comparison of outcomes for HLA-matched sibling and haplo- identical donors in Myelodysplastic syndromes: report from the chronic malignancies working party of EBMT



- Restrospective study
- 1414 MSD pts median age 58 yrs
- 415 HD-PTCY pts median age 61 yrs
- MSD better OS,PFS,NRM vs haplo donor



Feasibility of allogeneic stem-cell transplantation after azacitidine bridge in higher-risk myelodysplastic syndromes and low blast count acute myeloid leukemia: results of the BMT-AZA prospective study



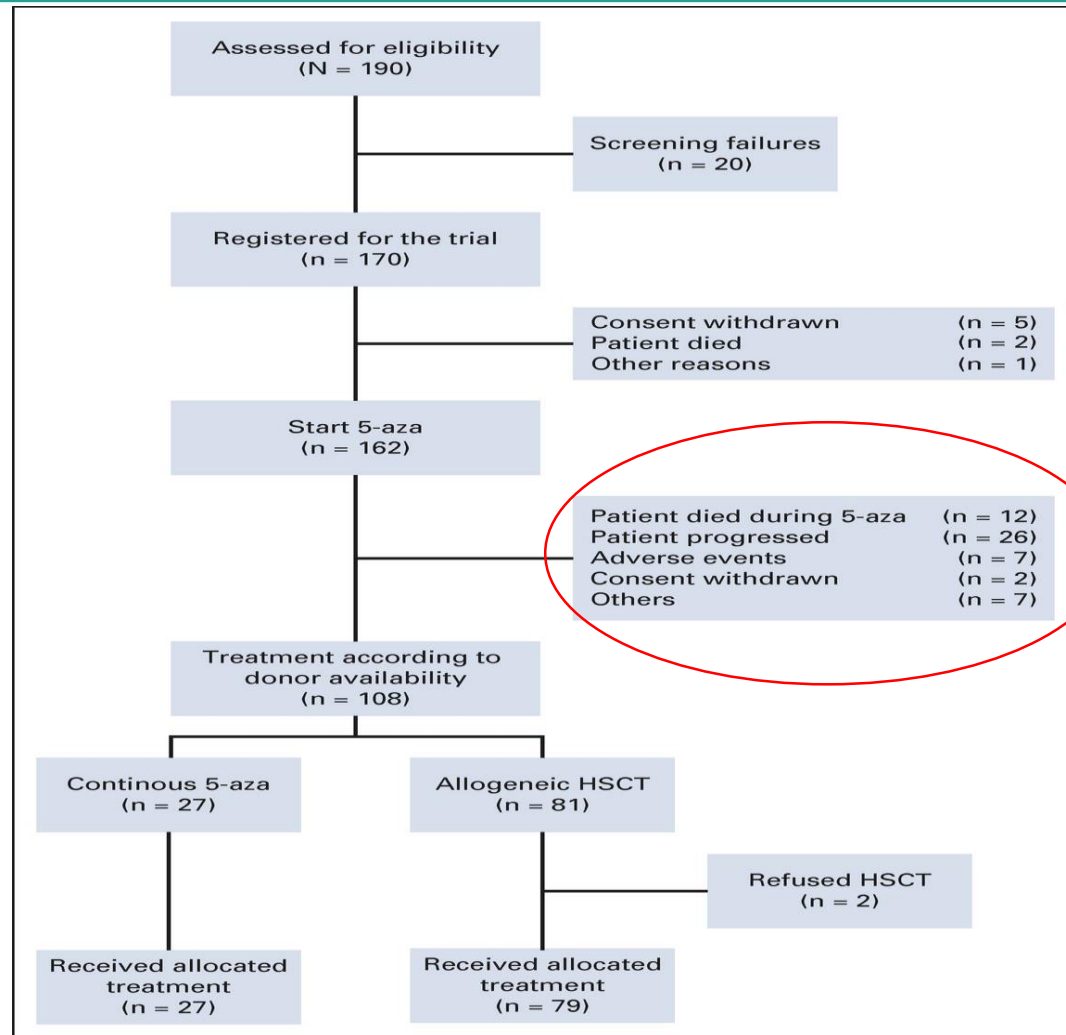


FIG 1. Flow diagram. 5-aza, 5-azacytidine; HSCT, allogeneic stem-cell transplantation.

German MDS Study Group and the German Cooperative Transplant Study Group

Prospective multicenter phase 3 study comparing 5-azacytidine (5-Aza) induction followed by SCT vs continuous 5-Aza according to donor availability in elderly MDS pts (55-70 years) (VidazaAllo Study)



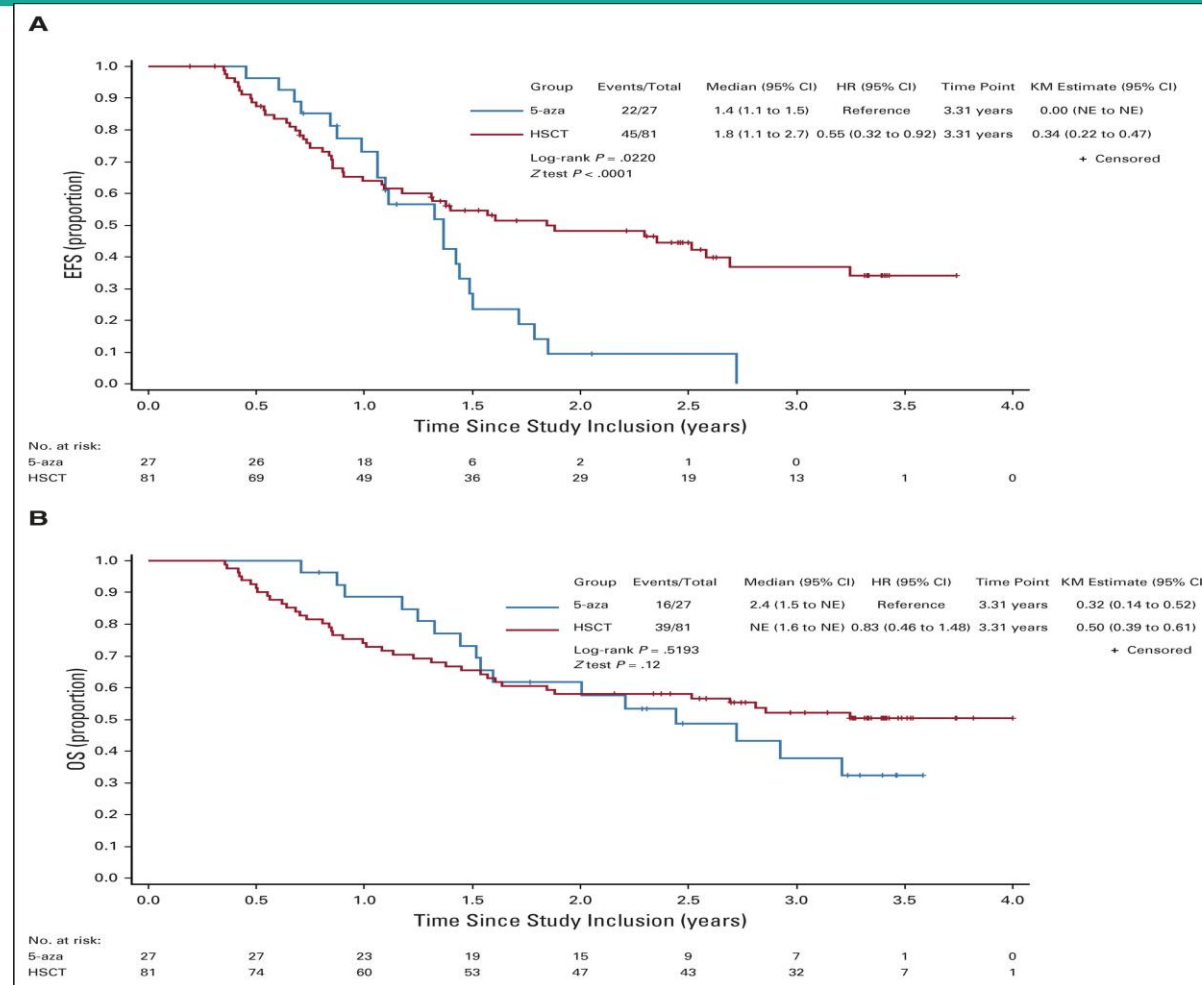
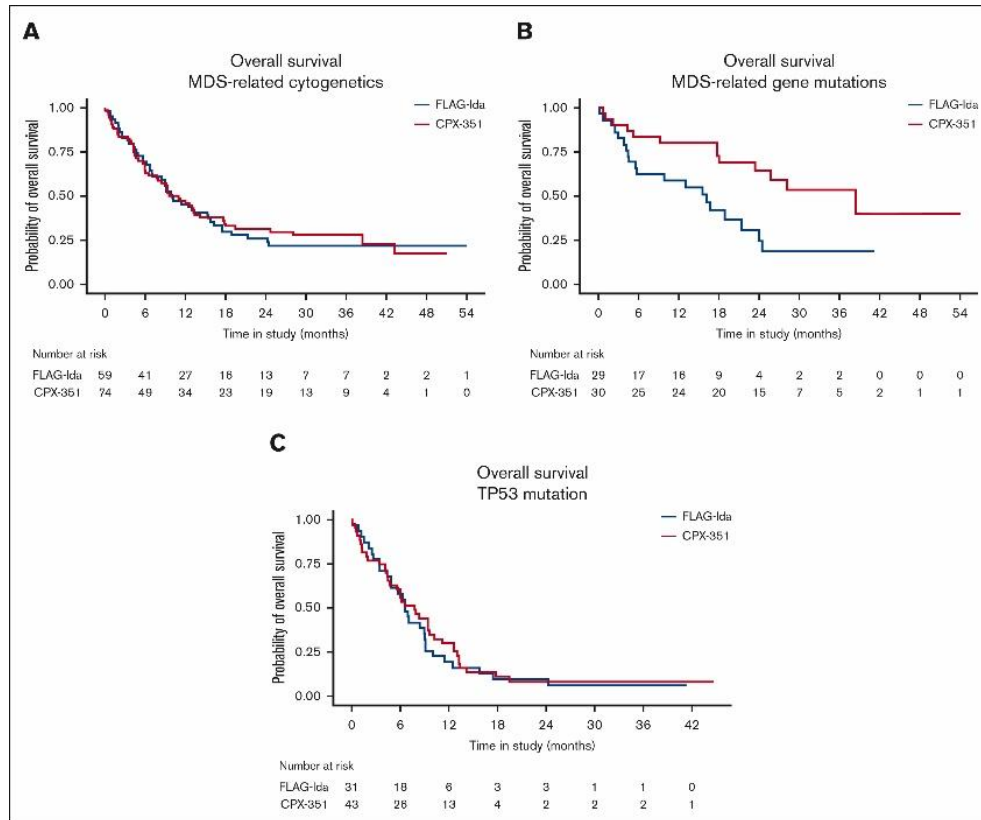


FIG 2. Kaplan-Meier estimates of (A) EFS and (B) OS after allocation to 5-aza or HSCT. 5-aza, 5-azacytidine; EFS, event-free survival; FAS, full analysis data set; HR, hazard ratio; HSCT, allogeneic stem-cell transplantation; KM, Kaplan-Meier; NE, not evaluable; OS, not evaluable, overall survival.

A RANDOMIZED COMPARISON OF CPX-351 AND FLAG-IDA IN ADVERSE KARYOTYPE AML AND HIGH-RISK MDS: THE UK NCRI AML19 TRIAL



- ✓ 189 patients: 30% high-risk MDS.
- ✓ No difference in OS (13.3 months vs 11.4 months) or EFS in multivariable analysis.
- ✓ In high-risk AML and MDS, CPX-351 did not improve response or survival compared with **FLAG-Ida but produced better relapse-free survival.**
- ✓ In the exploratory subgroup of patients defined by the presence of mutations in MDS-related genes, CPX-351 improved OS.

AZACITIDINE PLUS VENETOCLAX IN PATIENTS WITH HIGH-RISK MDS: PHASE 1-2 STUDY

Phase I/II study

23 patients enrolled in phase I (74% HMAs naïve, 26% post-HMAs failure)

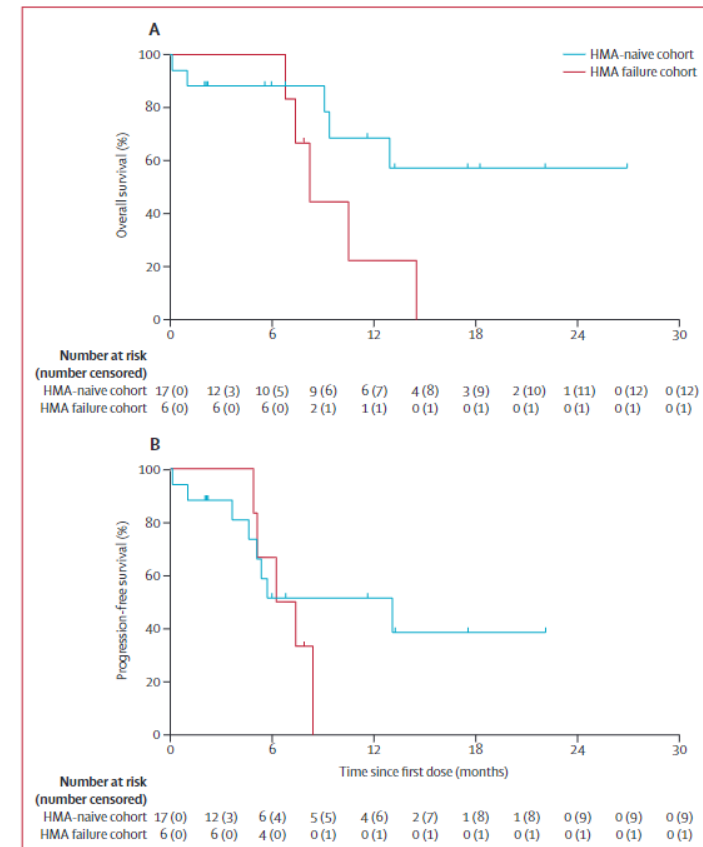
Median FU 13.2 months

Dose/duration reduction in azacytidine and venetoclax administration

ORR 87%; median TTR 1 cycle

Median OS not reached in HMAs-naïve cohort vs 8.3 months in HMAs failure

Median PFS 13.1 mo vs 6.2 mo



POST-HSCT MAINTENANCE NEW PERSPECTIVES

Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial

Uwe Platzbecker*, Jan Moritz Middeke*, Katja Sockel*, Regina Herbst*, Dominik Wolf*, Claudia D Baldus*, Uta Oelschlägel*, Anke Mütterig*, Lars Fransecky*, Richard Noppeney*, Gesine Bug*, Katharina S Götzte, Alwin Krämer*, Tilmann Bochtler*, Matthias Stelljes*, Christoph Groth*, Antje Schubert*, Marika Mende*, Friedrich Stölzel*, Christin Borkmann*, Anne Sophie Kubasch*, Malte von Bonin*, Hubert Serve*, Mathias Hänel*, Ulrich Dührsen*, Johannes Schetelig*, Christoph Röllig*, Michael Kramer*, Gerhard Ehninger*, Martin Bornhäuser*, Christian Thiede*

original reports

Eprenetapopt Plus Azacitidine After Allogeneic Hematopoietic Stem-Cell Transplantation for TP53-Mutant Acute Myeloid Leukemia and Myelodysplastic Syndromes

Asmita Mishra, MD¹; Roni Tamari, MD²; Amy E. DeZern, MD³; Michael T. Byrne, DO⁴; Mahasweta Gooptu, MD⁵; Yi-Bin Chen, MD⁶; H. Joachim Deeg, MD⁷; David Sallman, MD⁸; Phillip Gallacher, BSc⁹; Anders Wennborg, MD, PhD⁹; Denice K. Hickman, BSN, RN⁵; Eyal C. Attar, MD⁹; and Hugo F. Fernandez, MD¹⁰

REGULAR ARTICLE

 blood advances

Enasidenib as maintenance following allogeneic hematopoietic cell transplantation for IDH2-mutated myeloid malignancies

Amir T. Fathi,¹ Haesook T. Kim,² Robert J. Soiffer,³ Mark J. Levis,⁴ Shuli Li,² Annette S. Kim,⁵ Alice S. Mims,⁶ Zachariah DeFilipp,¹ Areej El-Jawahri,¹ Steven L. McAfee,¹ Andrew M. Brunner,¹ Rupa Narayan,¹ Laura W. Knight,¹ Devon Kelley,¹ AJ S. Bottoms,¹ Lindsey H. Perry,¹ Jonathan L. Wahl,³ Jennifer Brock,³ Elayne Breton,⁴ Vincent T. Ho,³ and Yi-Bin Chen¹

¹Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; ²Department of Data Science, Dana-Farber Cancer Institute, Harvard School of Public Health, Boston, MA; ³Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; ⁴Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; ⁵Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and ⁶The Ohio State University Comprehensive Cancer Center, Columbus, OH

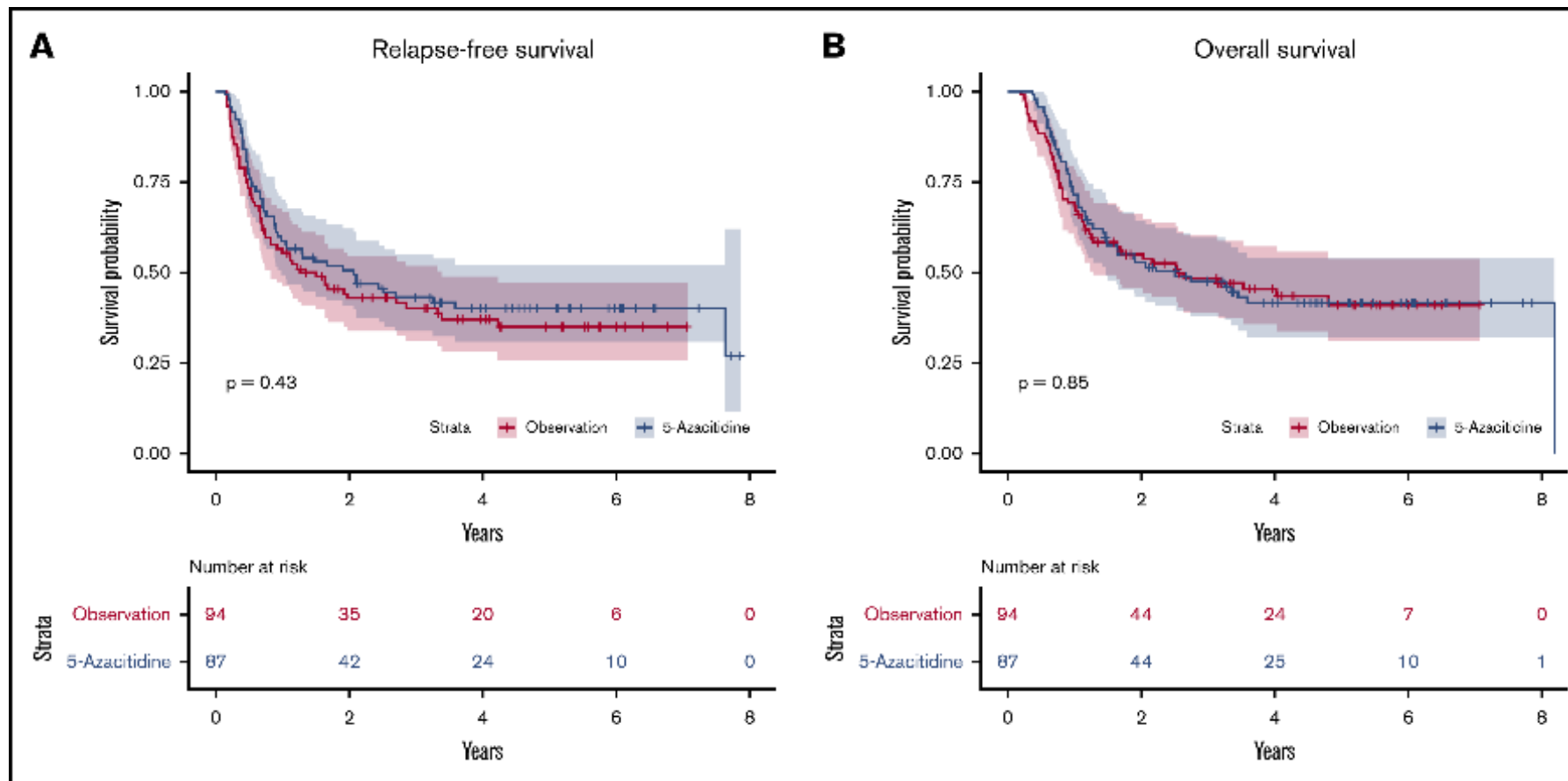
1. Eprenetapopt plus azacitidine after allogeneic hematopoietic stem-cell transplantation for TP53-mutant acute myeloid leukemia and myelodysplastic syndromes, *J Clin Oncol* (2022);40:3985-3993

2. AT Fathi, HT Kim, RJ Soiffer, et al. Enasidenib as maintenance following allogeneic hematopoietic cell transplantation for IDH2-mutated myeloid malignancies *Blood Adv*, 6 (2022), pp. 5857-5865

3. U Platzbecker, JM Middeke, K Sockel, et al. Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an

open-label, multicentre, phase 2 trial *Lancet Oncol*, 19 (2018), pp. 1668-1679

POST-HSCT MAINTENANCE NEW PERSPECTIVES



The use of subcutaneous 5-azacitidine as posttransplant maintenance strategy was not associated with improved RFS (A) and OS (B) compared with observation arm.

Betül Oran, Marcos de Lima, Guillermo Garcia-Manero, Peter F. Thall, Ruitao Lin, Uday Popat, Amin M. Alousi, Chitra Hosing, Sergio Giralt, Gabriela Rondon, Glenda Woodworth, Richard E. Champlin, A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients, Blood Adv, 2020, Figure 2.

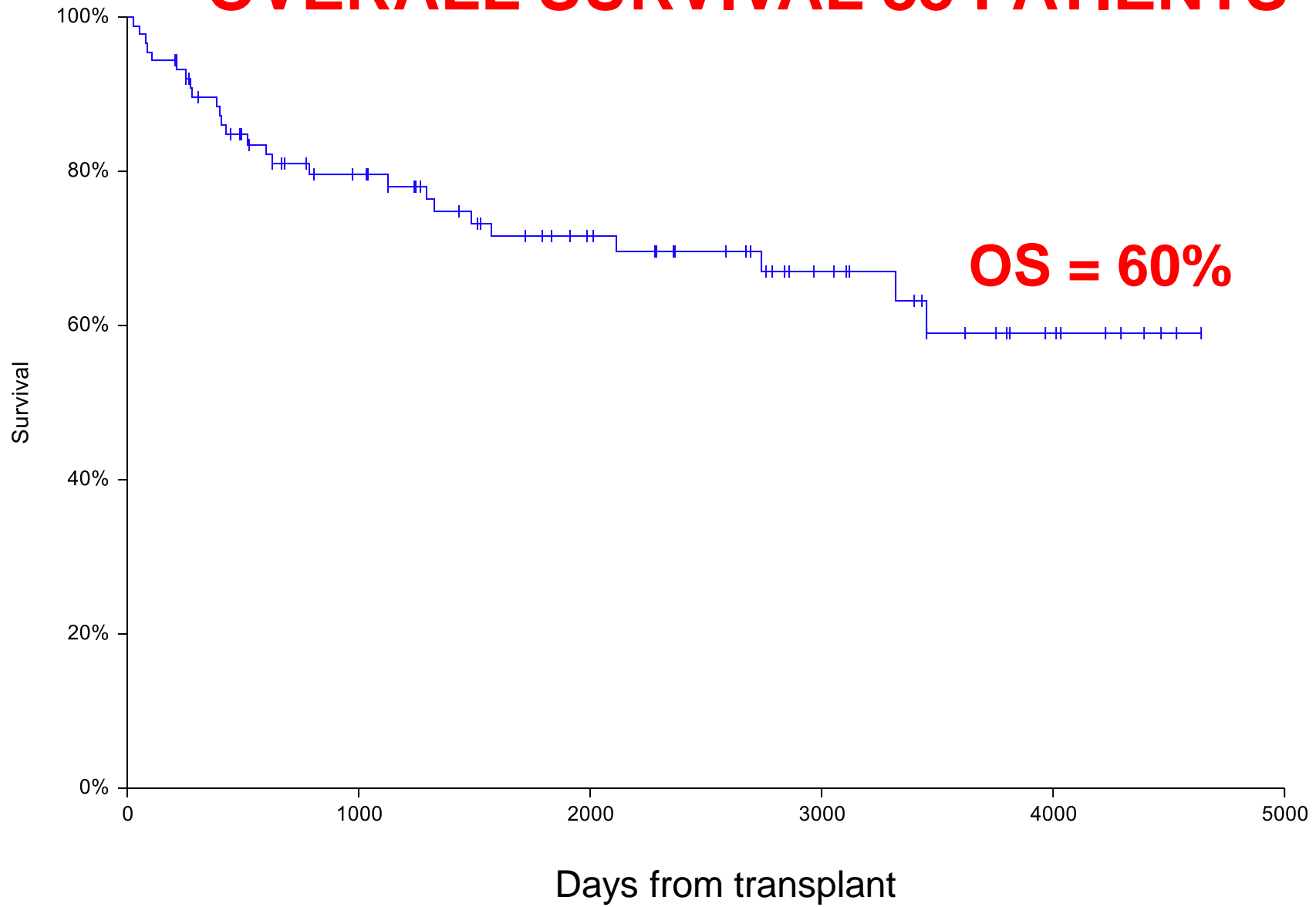
Post transplant immunologic treatment

- To increase the immunological effect (GvL) without improving GvHD
- Prophylactic DLI
- Preventive DLI
- Increase activity of T cells and NK cells

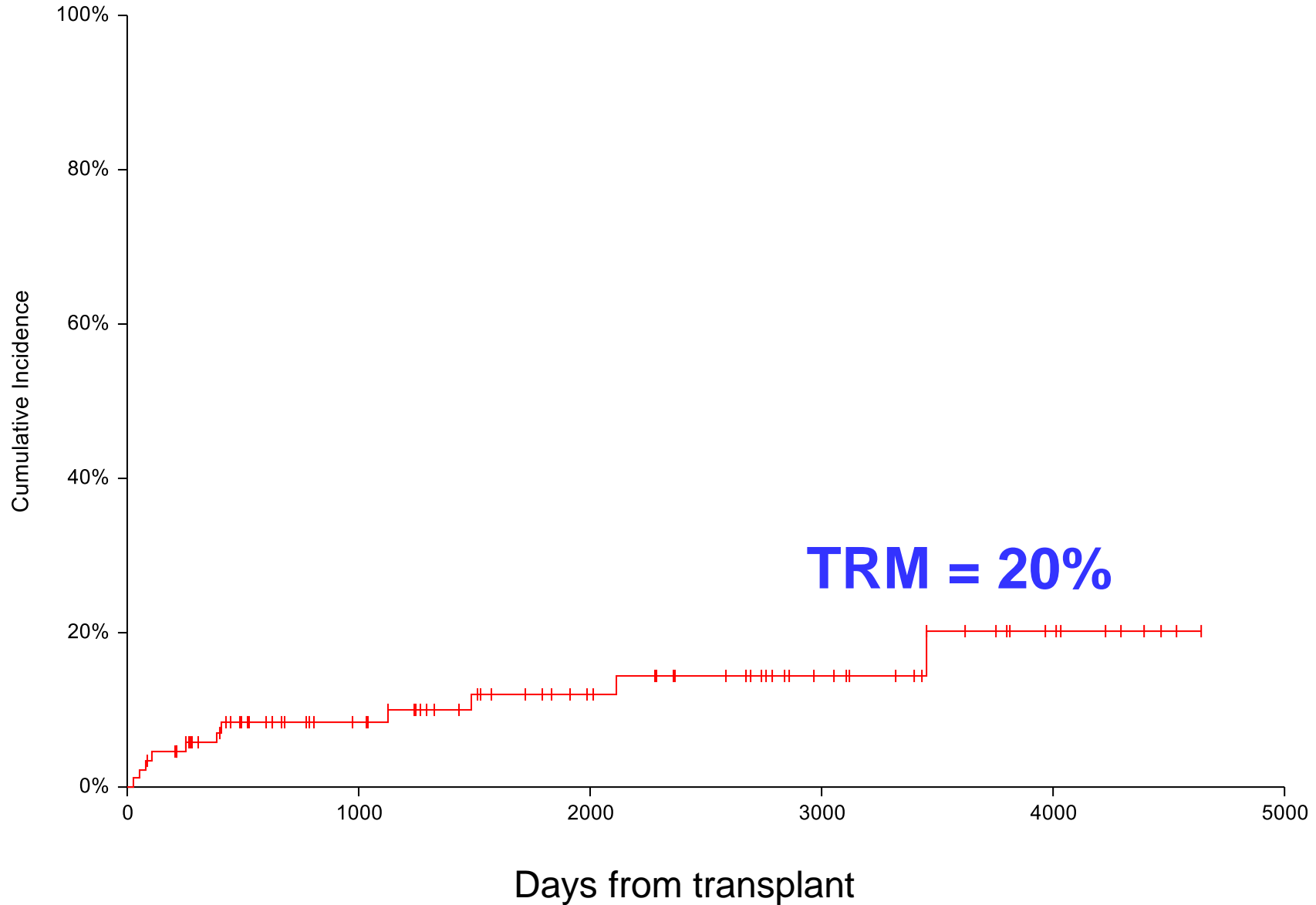
HSCT in MDS
San Martino experience Jan 2012 – Mar 2024

	MDS
Patients	88
R-IPSS Low / Intermediate / high / very high	13 / 27 / 28 / 20
Pre HSCT therapy no /yes	39 / 49
Source (BM / PB)	61/ 27
Donor MSD ID-SIB/ MUD / HAPLO / MMUD	13 / 20 / 54 / 1
AGE	60 (18-73)
Median duration follow up (dd)	2280 (206-4643)

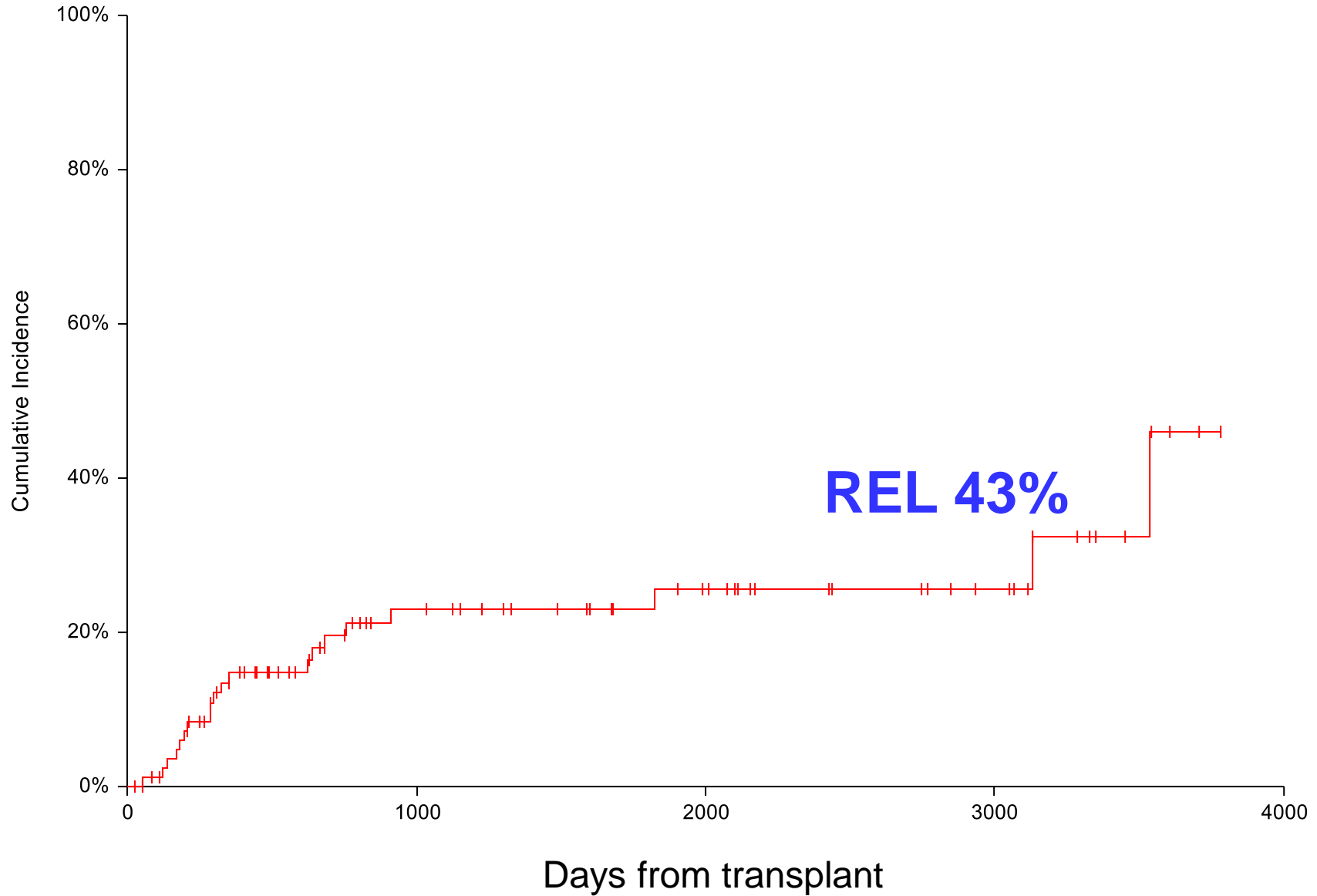
OVERALL SURVIVAL 88 PATIENTS



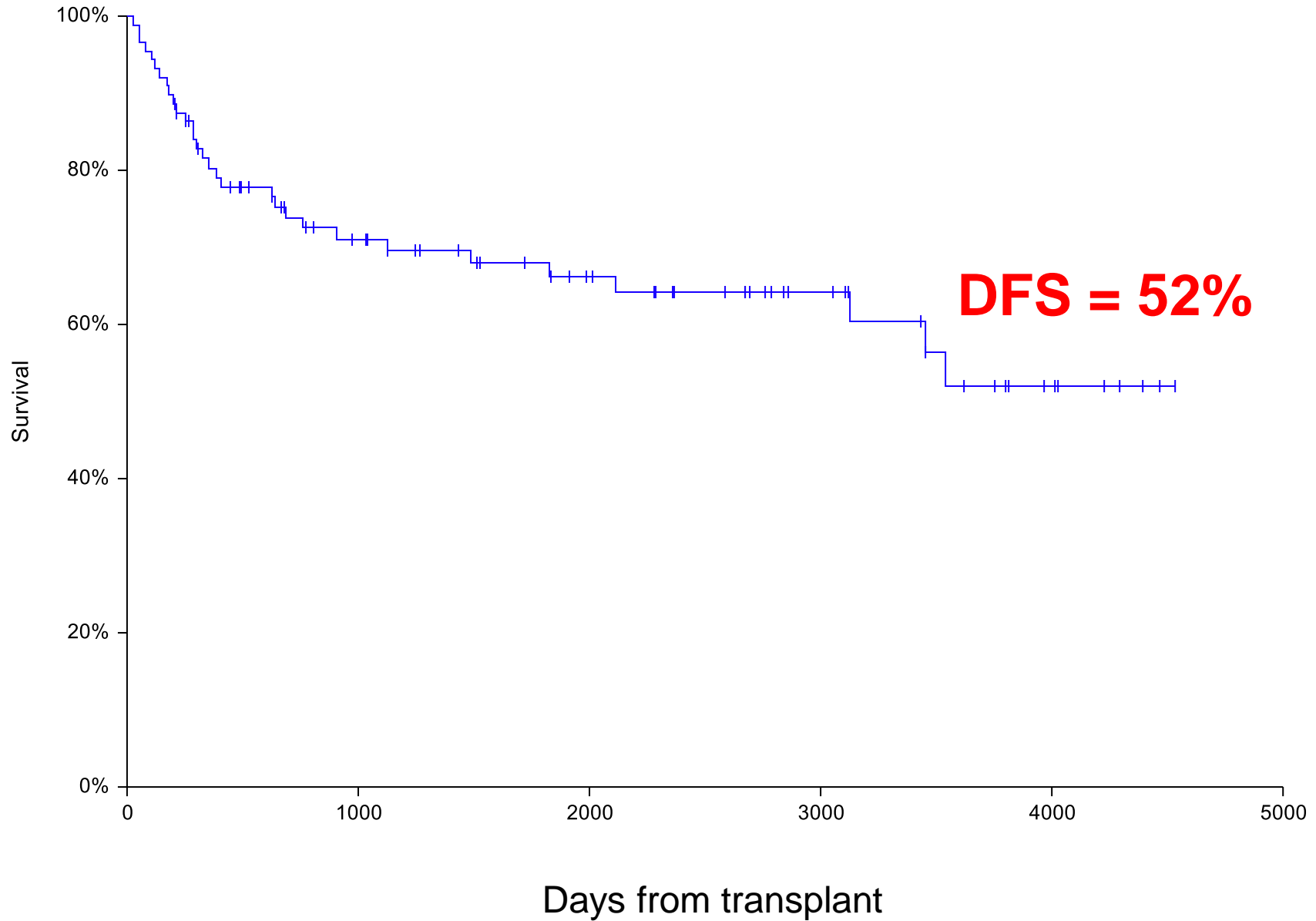
NON RELAPSE MORTALITY 88 PATIENTS



OVERALL INCIDENCE OF RELAPSE



OVERALL DFS 88 PATIENTS





- How to maximize curative possibility.
 - Transplant consultation ASAP
 - Work together with transplanters (since the beginning)

*MEDICINES CAN CURE DISEASES BUT ONLY
DOCTORS CAN CURE PATIENTS.*

C.G. Jung -



Thank you for your kind attention



OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico