FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

L'attuale approccio clinico al paziente con **Sindrome Mielodisplastica**

Napoli

IL TRAPIANTO ALLOGENICO: quando e per chi?

Angelo Michele Carella

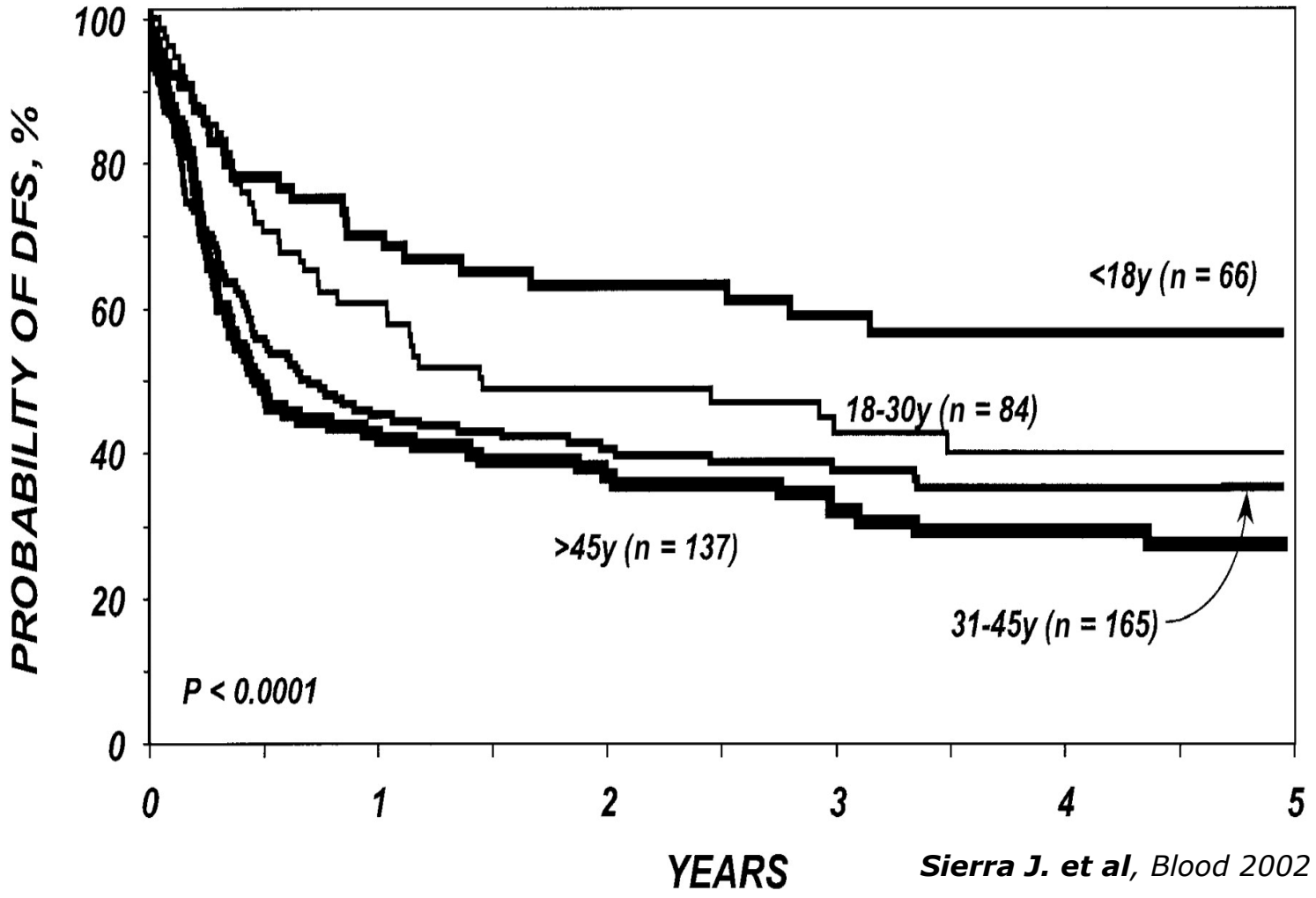
CASA SOLLIEVO DELLA SOFFERENZA • SAN GIOVANNI ROTONDO •

Allogeneic SCT for MDS

Allogeneic stem cell transplantation is a curative approach for patients with (MDS)

	5 y. DFS	TRM	Relapse
EBMT (n. casi 885)	36%	43%	36%
IBMTR (n. casi 452)	40%	37%	23%
SEATTLE (n. casi 93)	40%	44%	29%
GITMO (N casi 227)	25-65%	17-45%	26-54%

ETA' AL TRAPIANTO



Sierra J. et al, *Blood 2002*

Bone marrow transplantation for myelodisplasia

Anderson JE: *Blood Reviews* 2000
(Seattle experience in 250 patients)

TRM according to age at transplant

Age (years)	*N. of pts*	*5-year TRM*
< 21	48	23%
21-39	85	46%
40-55	96	53%

p=0.003

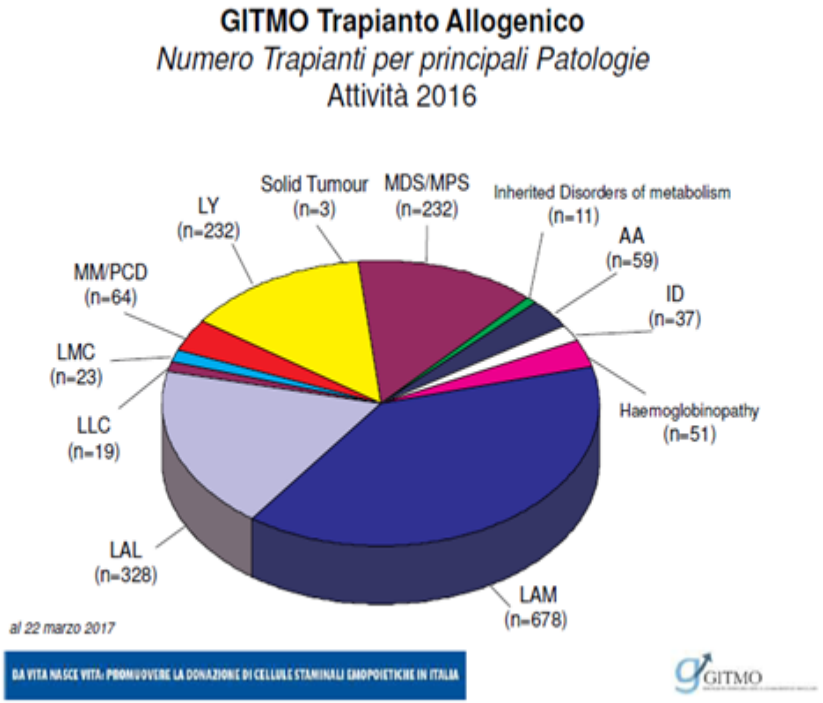
Hematopoietic Stem-Cell Transplantation for patients with MDS and sAML: a report on behalf of the CLWP of the EBMT
De Witte T et al. BJH 2000

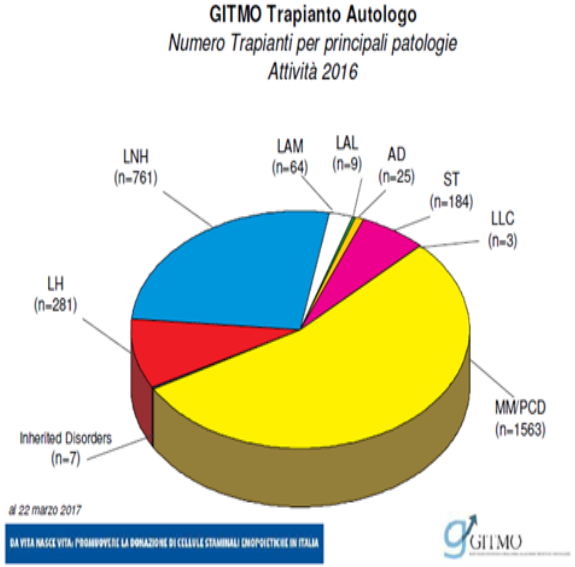
TRM according to age at transplant

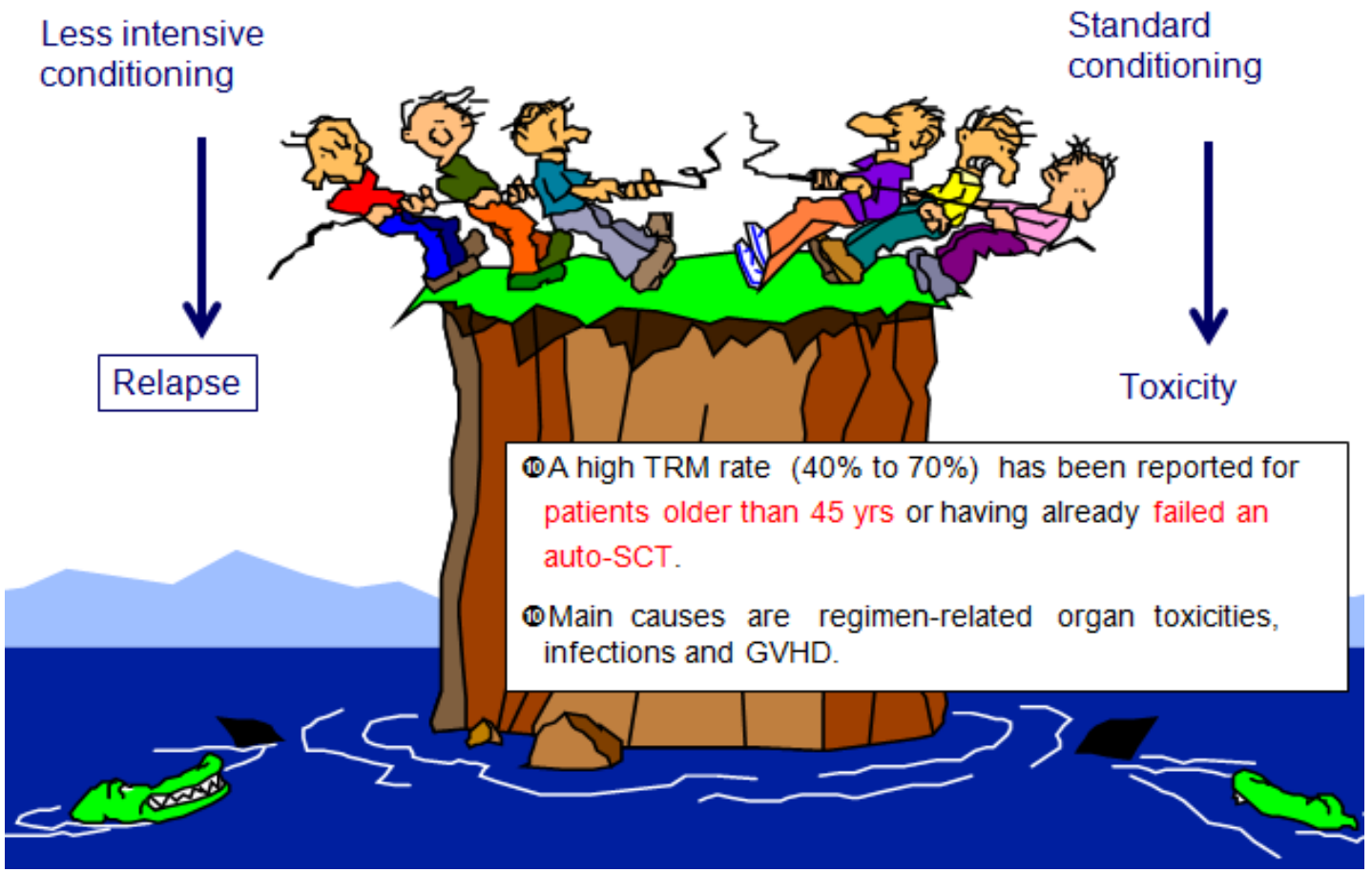
Age (years)	*N. of pts*	*3-year TRM*
< 20	163	30%
20-40	388	43%
> 40	329	50%

p<0.001

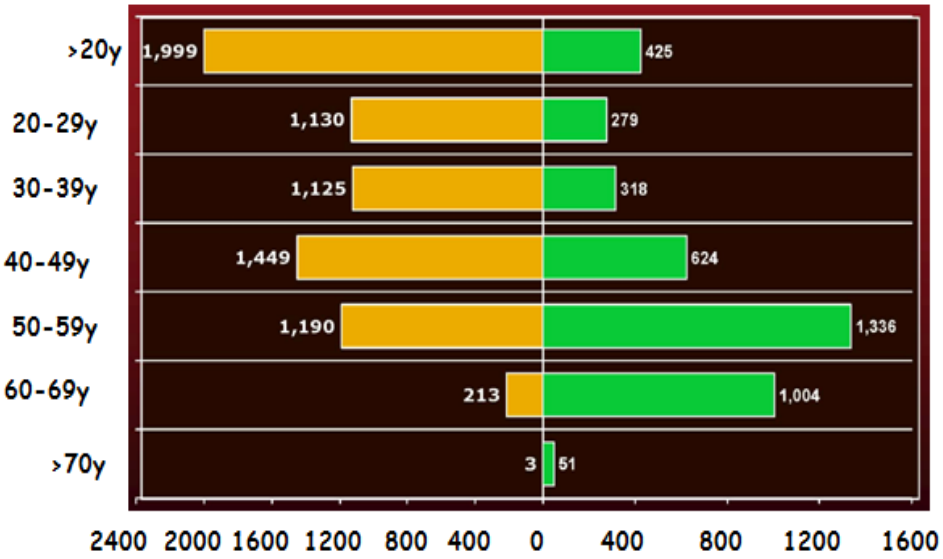
GITMO TRAPIANTO ALLOGENICO: Numero Trapianti per Princpali Patologie Attività 2016

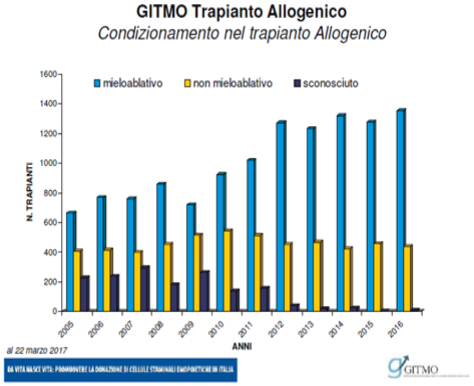


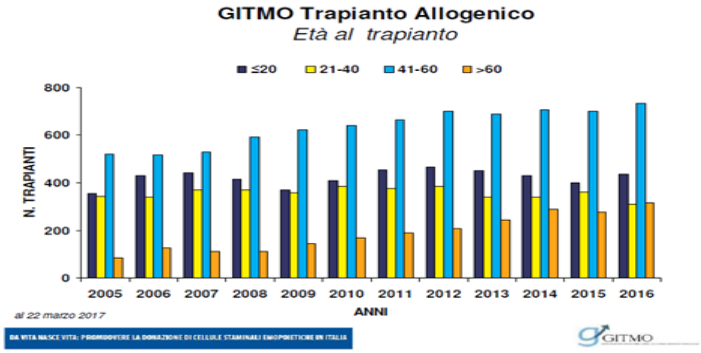



Less intensive conditioning
Standard conditioning
Relapse
Toxicity
⑩A high TRM rate (40% to 70%) has been reported for patients older than 45 yrs or having already failed an auto-SCT.
⑩Main causes are regimen-related organ toxicities, infections and GVHD.

Age distribution of Patients receveing Allogeneic transplants by Conditioning regimen intensity. 2005-2006

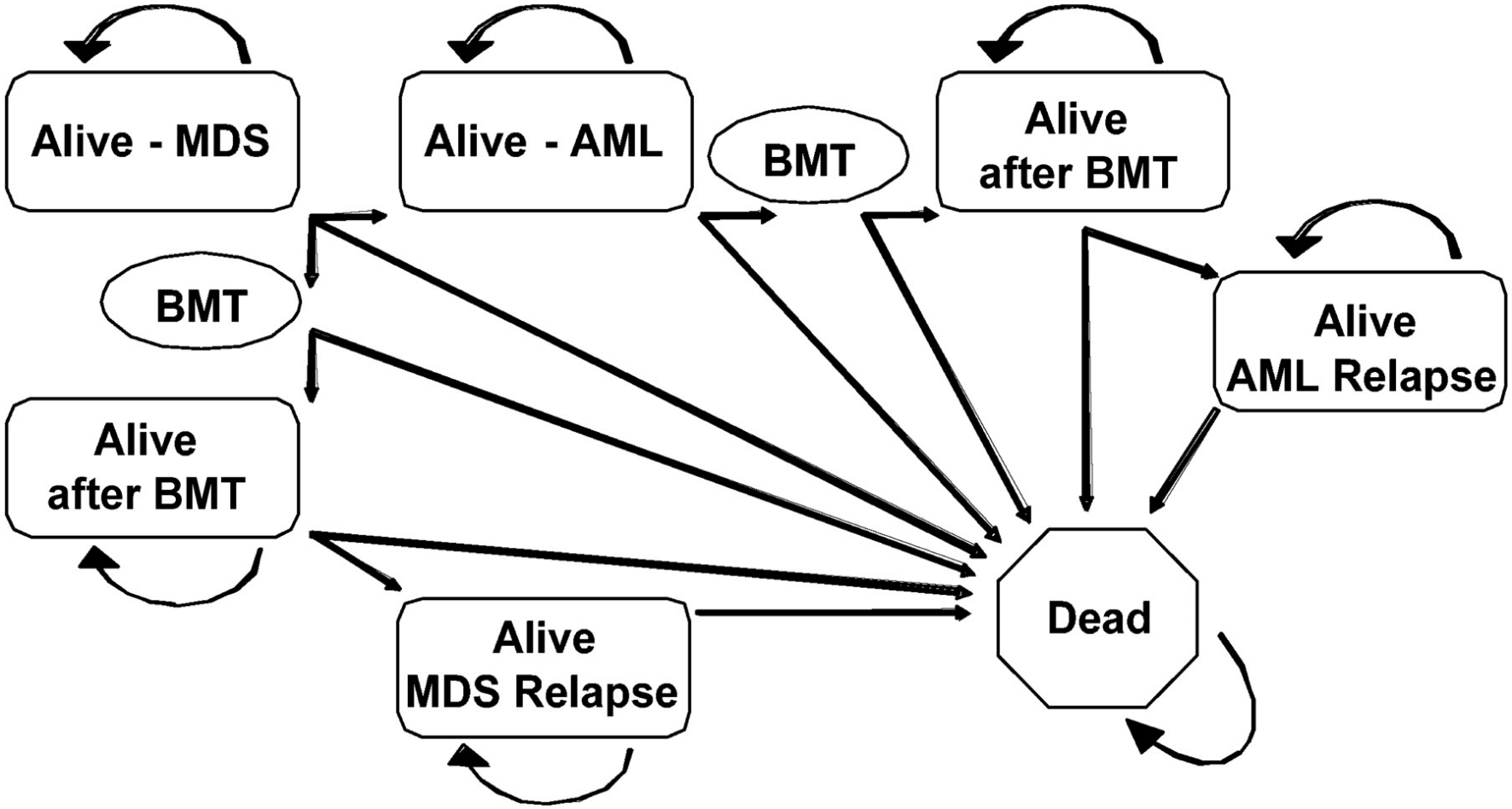






A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome

Corey S. Cutler, Stephanie J. Lee, Peter Greenberg, H. Joachim Deeg, Waleska S. Pérez, Claudio Anasetti, Brian J. Bolwell, Mitchell S. Cairo, Robert Peter Gale, John P. Klein, Hillard M. Lazarus, Jane L. Liesveld, Philip L. McCarthy, Gustavo A. Milone, J. Douglas Rizzo, Kirk R. Schultz, Michael E. Trigg, Armand Keating, Daniel J. Weisdorf, Joseph H. Antin, and Mary M. Horowitz



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HSCT IN MDS
Markov decision model

IPSS INTERMEDIO 1
IPSS basso

TRAPIANTO RITARDATO A:

COMPARSA DI NUOVE ANOMALIE CITOGENETICHE

COMPARSA DI RILEVANTE CITOPENIA

INCREMENTO PERCENTUALE DEI BLASTI MIDOLLARI

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

Table 1. Demographic and clinical characteristics of the patients with MDS or oligoblastic AML who underwent allogeneic HSCT

Parameter*	MDS	Oligoblastic AML†	Comparison between MDS and oligoblastic AML, *P*
No. of patients	374 (72%)	145 (28%)	
Age, median (range)	48 (17-67)	47 (23-72)	NS
Gender (male/female)	202/172	73/72	NS
WHO classification			
RCUD/RARS/MDS del(5q)	38	—	
RCMD	85	—	
RAEB-1	87	—	
RAEB-2	164	—	
HCT-CI§	266 (71%)	96 (66%)	
Low	168 (63%)	63 (66%)	
Intermediate	63 (24%)	18 (19%)	NS
High	35 (13%)	15 (15%)	
IPSS risk			
Low	29 (8%)	—	<.001
Intermediate-1	134 (36%)	—	
Intermediate-2	157 (42%)	20 (14%)	
High	54 (14%)	125 (86%)	
IPSS-R risk			
Low	59 (16%)	—	<.001
Intermediate	78 (21%)	11 (8%)	
High	140 (37%)	67 (46%)	
Very high	97 (26%)	67 (46%)	

31%

69%

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

A *MDS transplantation risk index (TRI) calculation*

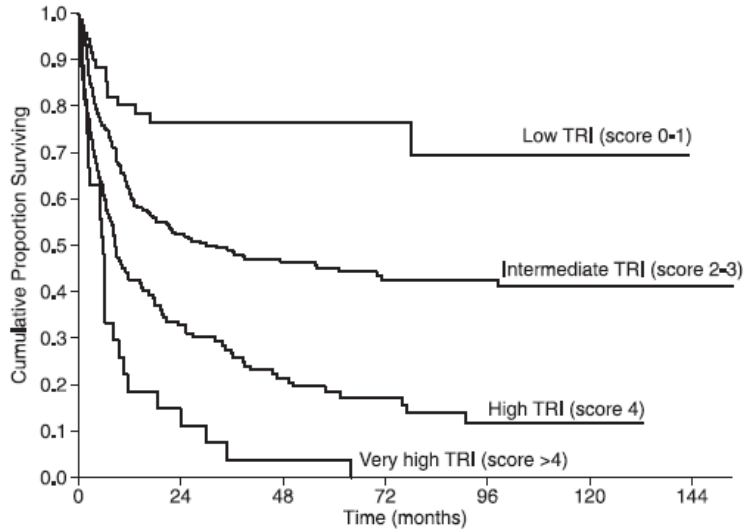
Prognostic variable	Score values			
	0	1	2	3
Age, yr	<50	≥50	-	-
IPSS-R	low	intermediate	high	very high
Monosomal karyotype	no	yes	-	-
HCT-CI	low/intermediate	high	-	-
Refractoriness to induction chemotherapy	no	yes	-	-

TRI is calculated as the sum of individual score values

TRANSPLANT INDEX RISK

Della Porta Blood 2014

B *Posttransplantation outcome according to TRI*



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)''

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%	

Should Cytoreductive Treatment Be Performed Before Transplantation in Patients With High-Risk Myelodysplastic Syndrome?

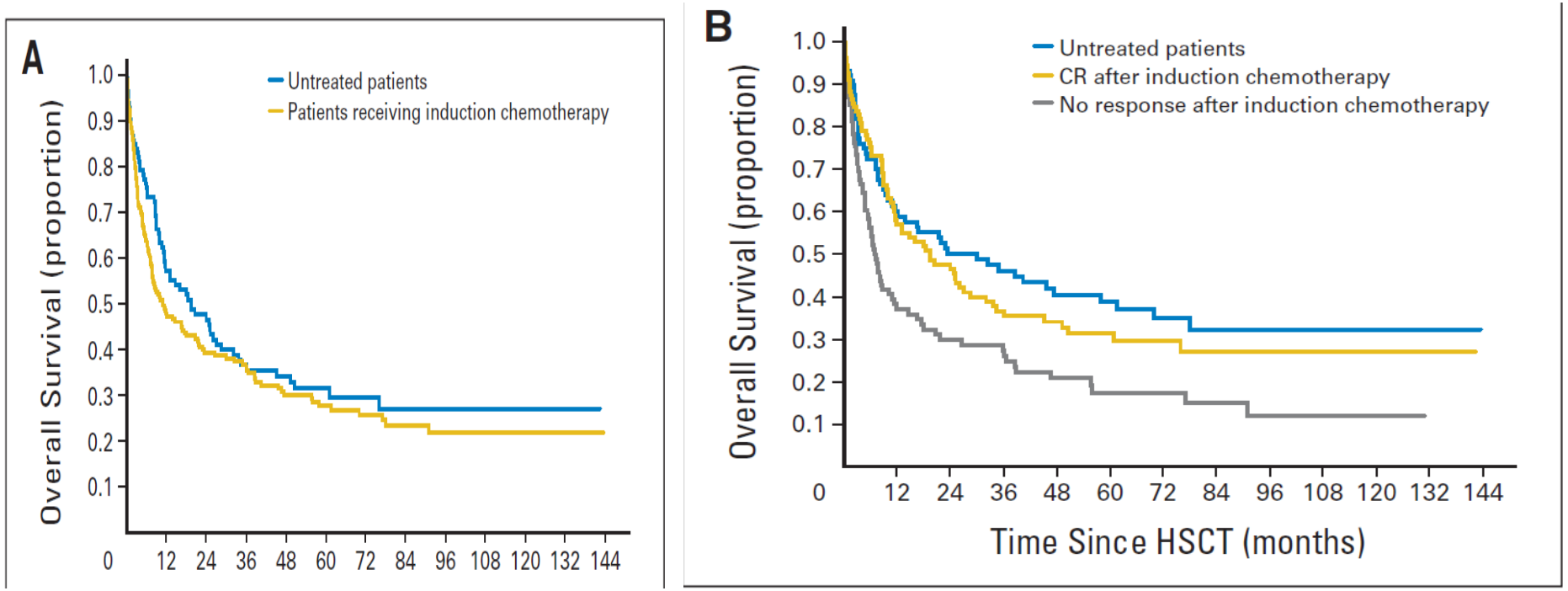


Fig 1. Post-transplantation outcome of patients with intermediate-2 and high-risk (according to the International Prognostic Scoring System) myelodysplastic syndromes stratified according to (A) whether or not induction chemotherapy was received before allogeneic hematopoietic stem-cell transplantation (HSCT), and (B) disease status at transplantation. CR, complete remission.

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

Allogeneic Hematopoietic Cell Transplantation in Patients Age 60-70 Years with De Novo High-Risk Myelodysplastic Syndrome or Secondary Acute Myelogenous Leukemia: Comparison with Patients Lacking Donors Who Received Azacitidine

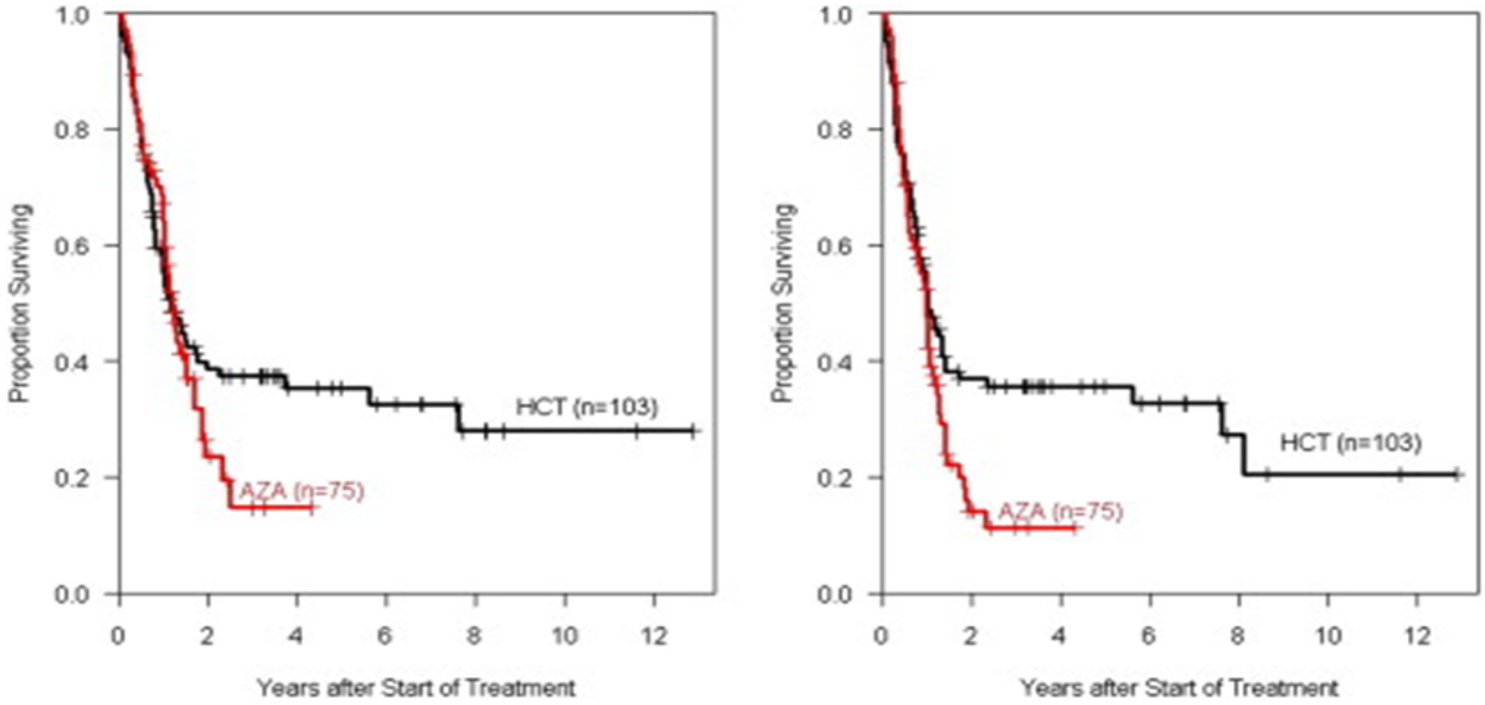
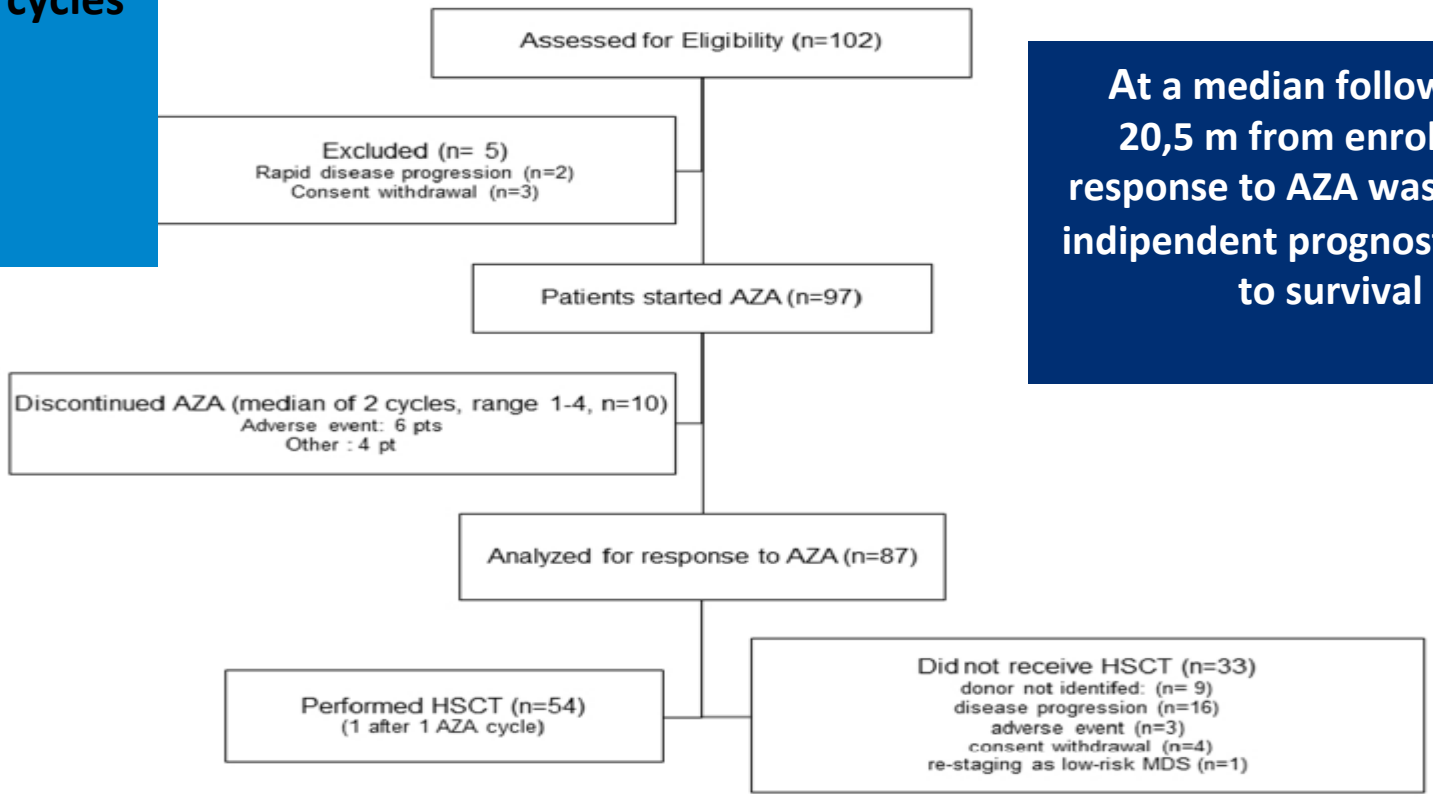


Figure 1. OS and EFS among patients with MDS followed from the start of therapy according to treatment approach.

Uwe Platzbecker, Biology of Blood and Marrow Transplantation, Volume 18, Issue 9, 2012, 1415–1421

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

After 4 AZA cycles
CR 24%
PR 14%
SD 32%
PD 22%



Voso et al, Figure 1

At a median follow-up of 20,5 m from enrolment, response to AZA was the only indipendent prognostic factor to survival

Voso MT et al. Ann Oncol 2017

Pretransplantation 5-Azacitidine in High-Risk Myelodysplastic Syndrome

Taiga Nishihori [1], Janelle Perkins [1], Asmita Mishra [1], Rami Komrokji [2], Jongphil Kim [3], Mohamed A. Kharfan-Dabaja [1], Lia Perez [1], Jeffrey Lancet [2], Hugo Fernandez [1], Alan List [2], Claudio Anasetti [1], Teresa Field [1,*]

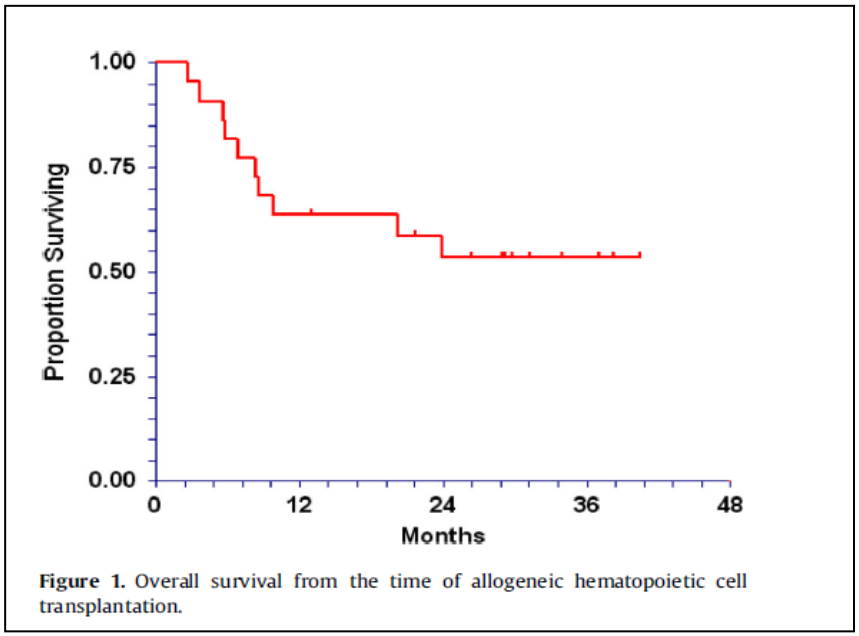


Figure 1. Overall survival from the time of allogeneic hematopoietic cell transplantation.

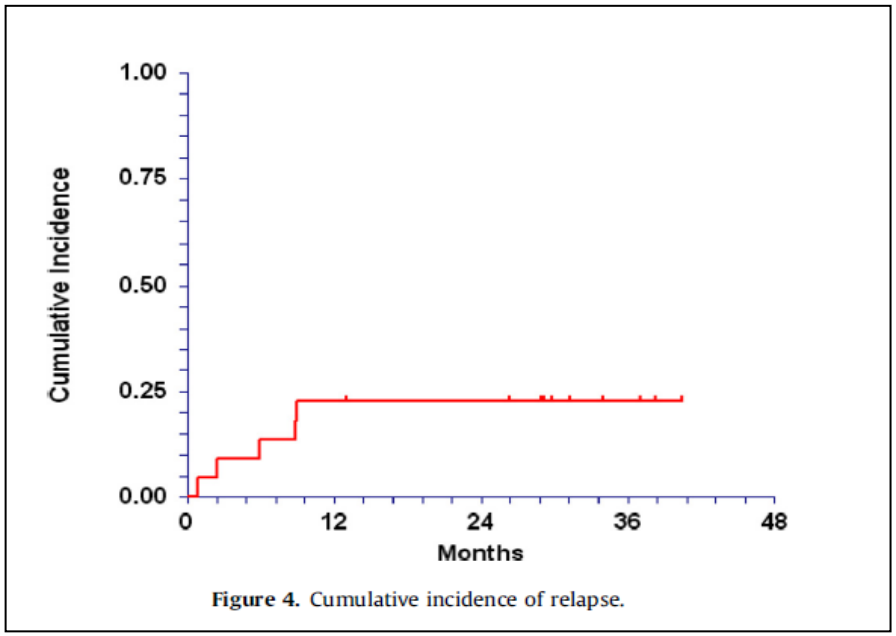
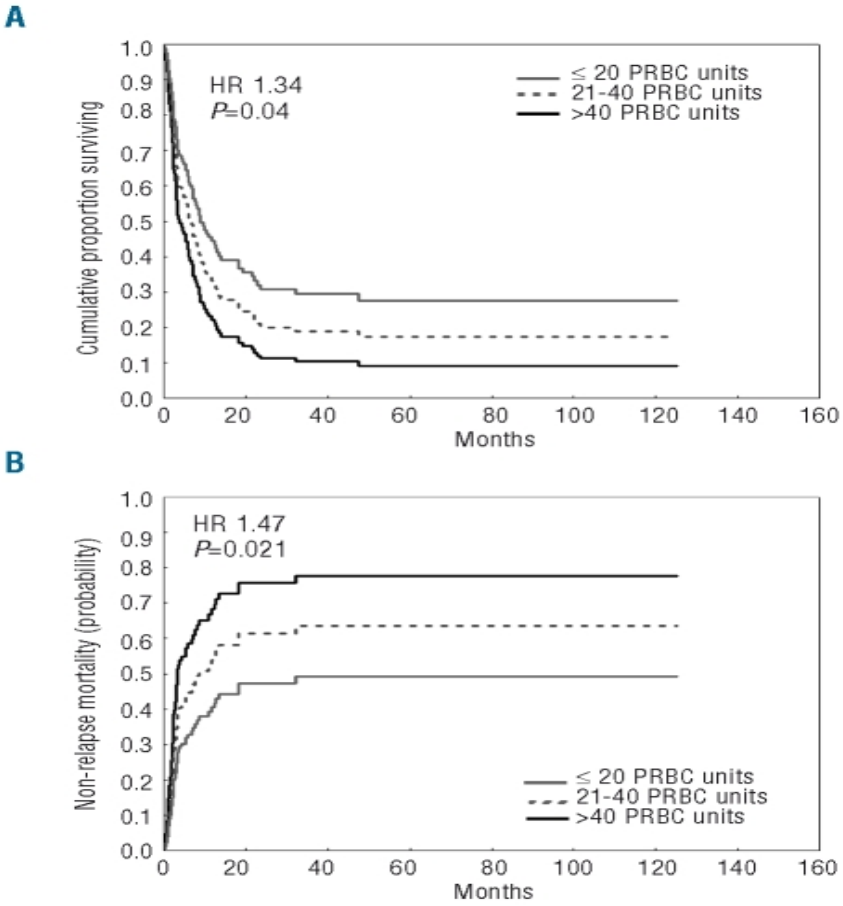


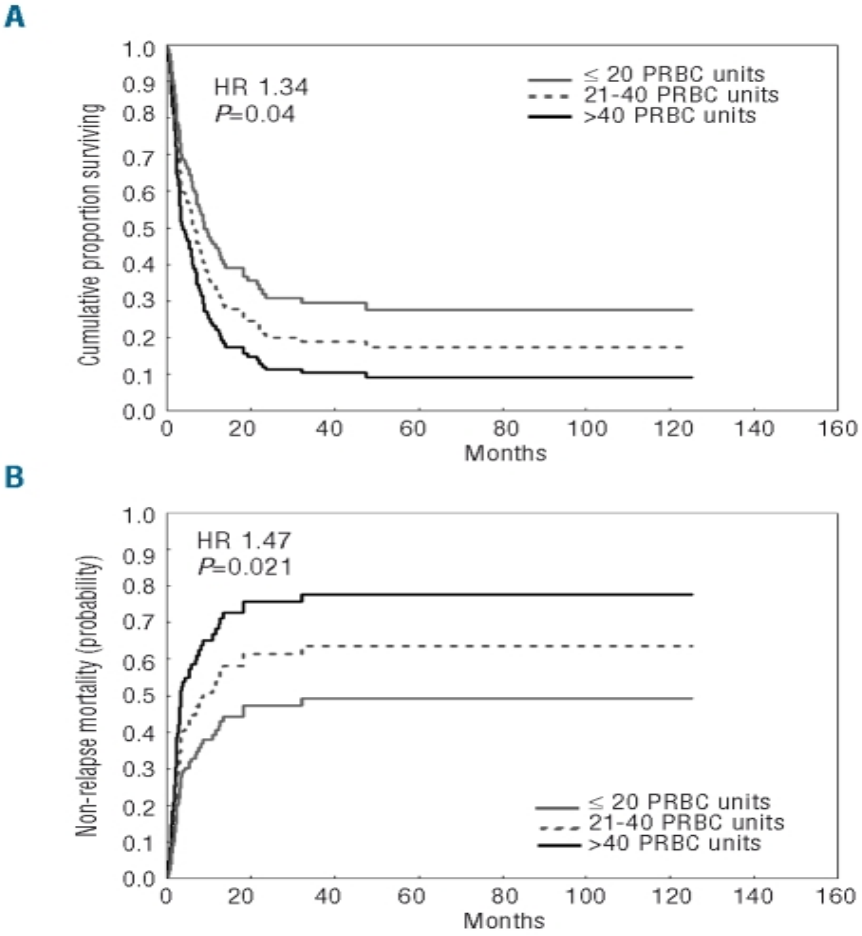
Figure 4. Cumulative incidence of relapse.

25 PAZIENTI

48% PR, 33% stable disease, and 19% progressive disease.

Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a GITMO study *EP Alessandrino et all Haematologica 2010*





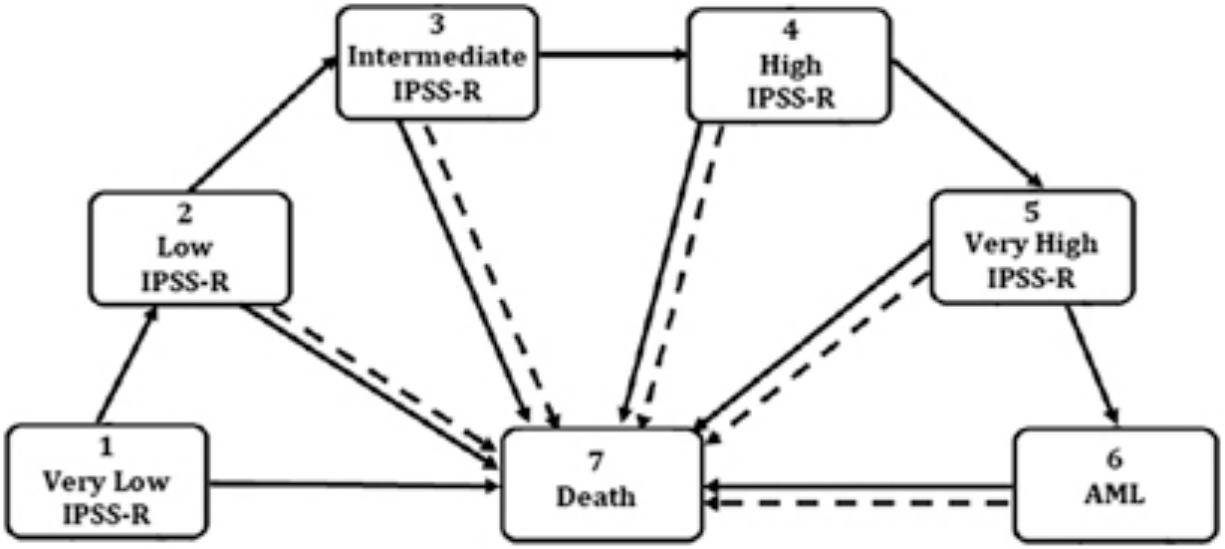
Leukemia (2017), 1–9

www.nature.com/leu

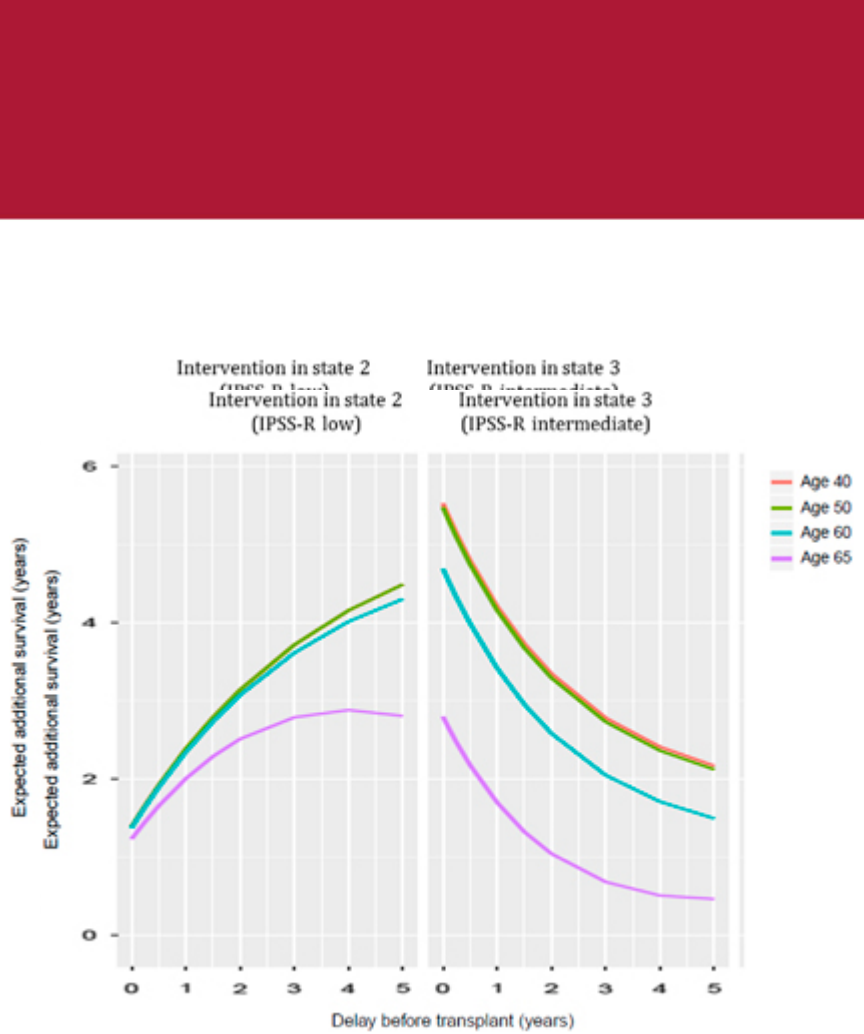
ORIGINAL ARTICLE

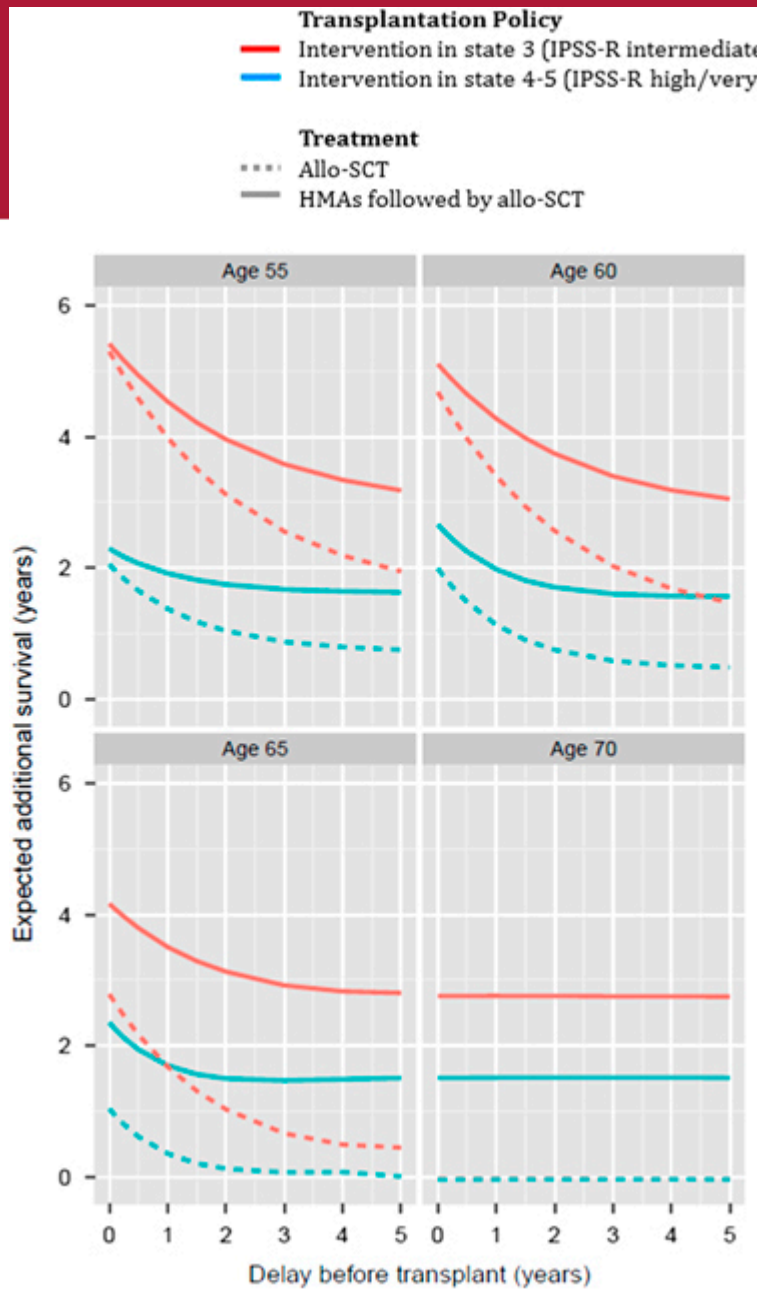
Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System

MG Della Porta[1,21], CH Jackson[2,21], EP Alessandrino[3], M Rossi[1], A Bacigalupo[4], MT van Lint[5], M Bernardi[6], B Allione[7], A Bosi[8], S Guidi[8], V Santini[8], L Malcovati[3,9], M Ubezio[3], C Milanesi[1], E Todisco[1], MT Voso[10], P Musto[11], F Onida[12], AP Iori[13], R Cerretti[14], G Grillo[15], A Molteni[15], P Pioltelli[16], L Borin[16], E Angelucci[17], E Oldani[18], S Sica[5], C Pascutto[3], V Ferretti[3], A Santoro[1], F Bonifazi[19], M Cazzola[3,9,22] and A Rambaldi[18,20,22] on behalf of the Gruppo Italiano Trapianto di Midollo Osseo (GITMO, www.gitmo.it)



Markov continuous-time multistate models of the MDS natural history. IPSS-R risk scores were adopted as time-dependent indicators of the natural course of MDS. Allo-SCT was modeled as a time-dependent covariate, and its effect on survival was estimated as an HR with respect to the 'no allo-SCT' category. Solid arrows represent transitions according to the natural course of the disease, whereas the effect of allo-SCT on mortality (that is, transition to death) in each state is represented by dot arrows.

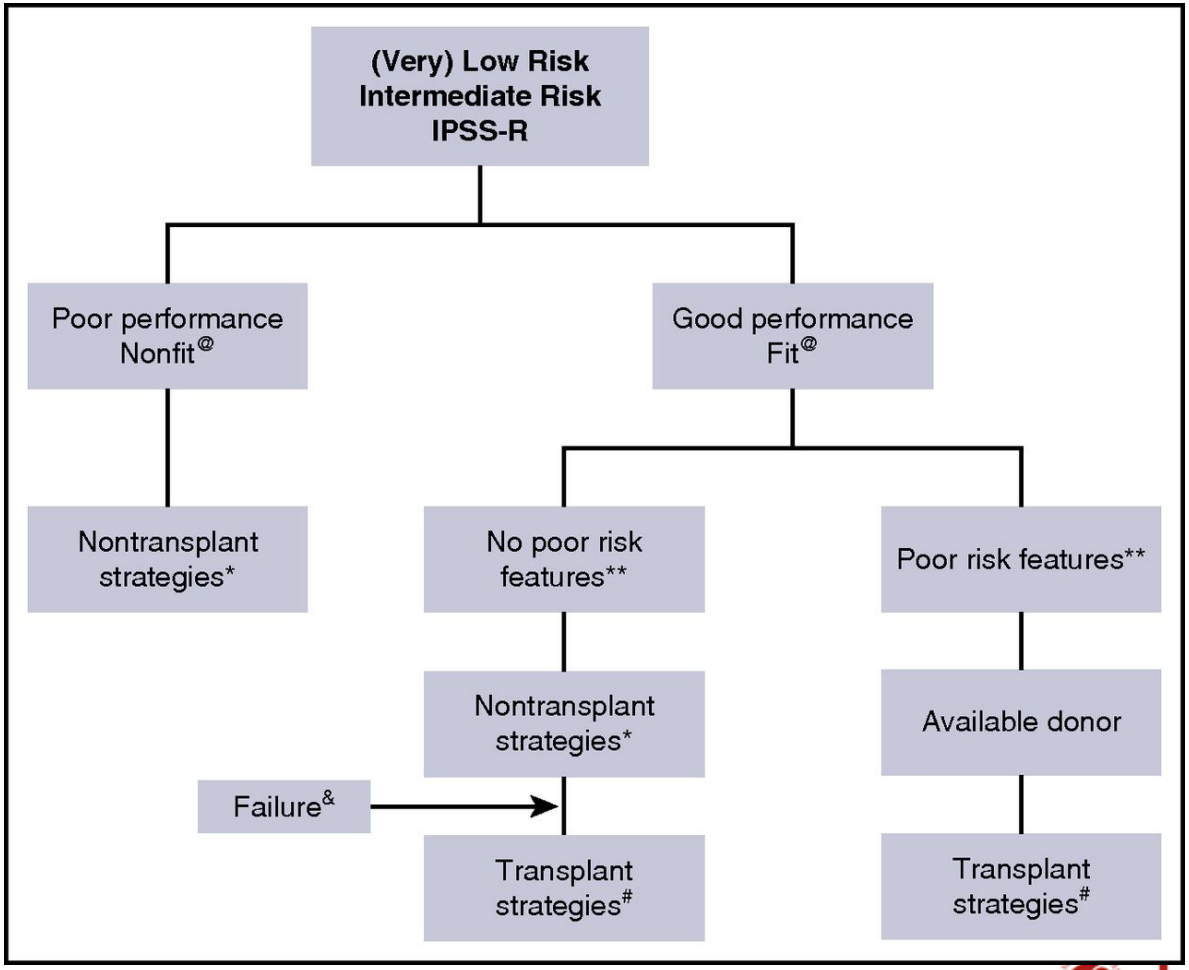




Della Porta MG Leukemia 2017

Therapeutic algorithm for adult patients with MDS and (very) low-risk or intermediate IPSS-R risk scores

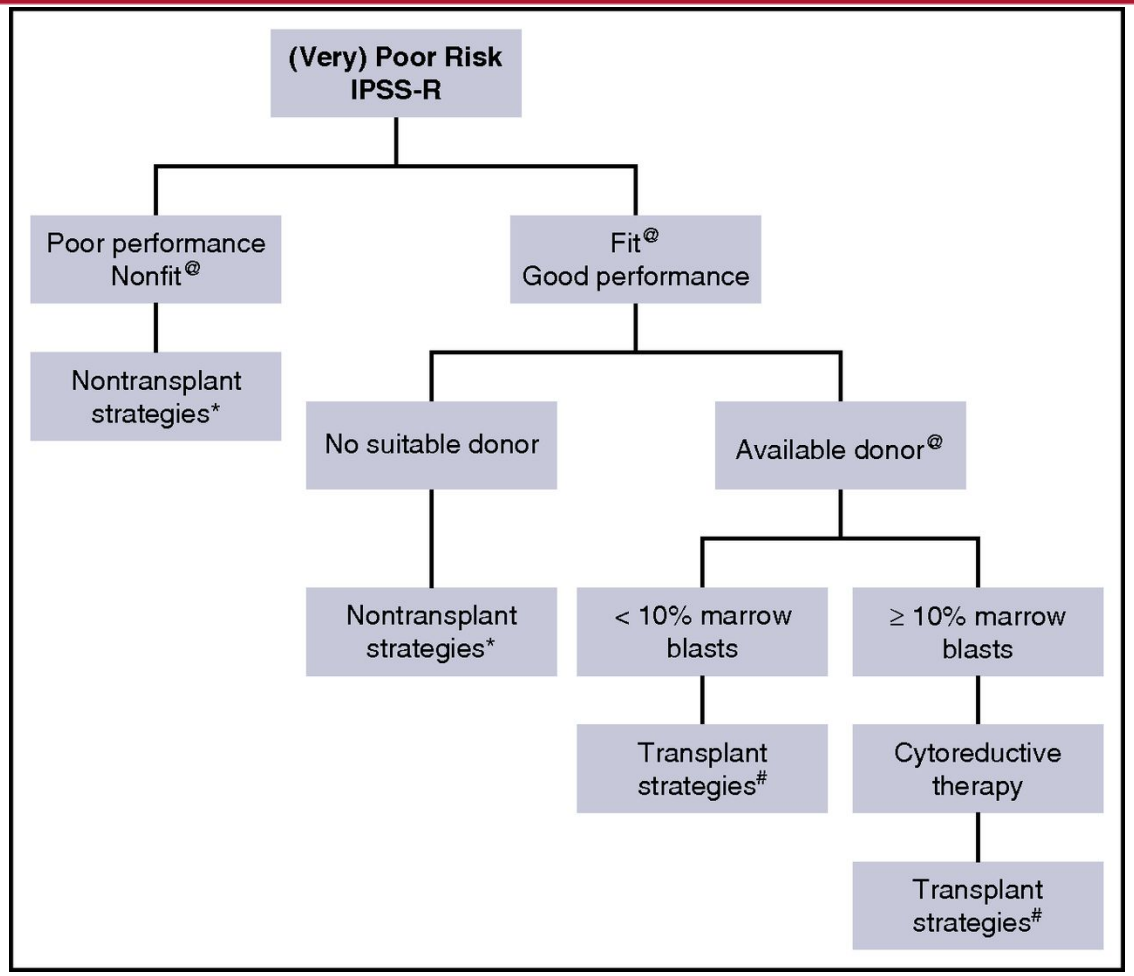
Disease risks score according to the IPSS-R and HCT-CI were recognized as relevant clinical variables for HSCT elegibility



Theo de Witte et al. Blood 2017;129:1753-1762

blood

Therapeutic algorithm for adult patients with MDS and poor IPSS-R scores.



blood

Theo de Witte et al. Blood 2017;129:1753-1762

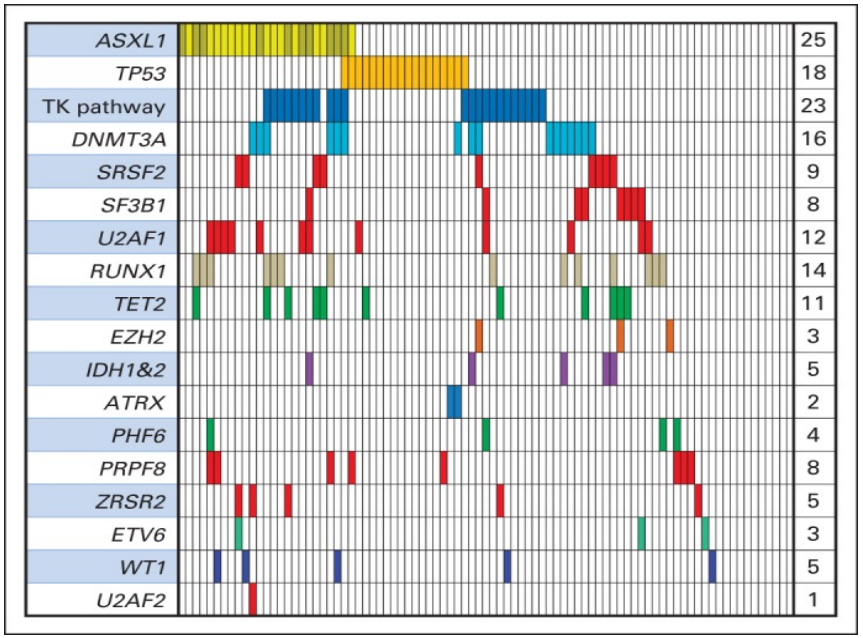
VOLUME 32 · NUMBER 25 · SEPTEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Rafael Bejar, Kristen E. Stevenson, Bennett Caughey, R. Coleman Lindsley, Brenton G. Mar, Petar Stojanov, Gad Getz, David P. Steensma, Jerome Ritz, Robert Soiffer, Joseph H. Antin, Edwin Alyea, Philippe Armand, Vincent Ho, John Koreth, Donna Neuberg, Corey S. Cutler, and Benjamin L. Ebert



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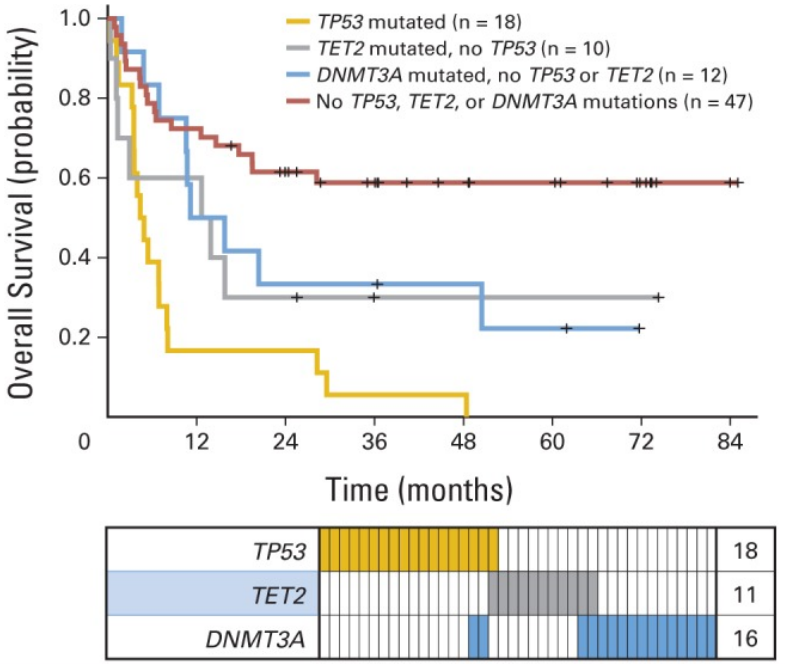
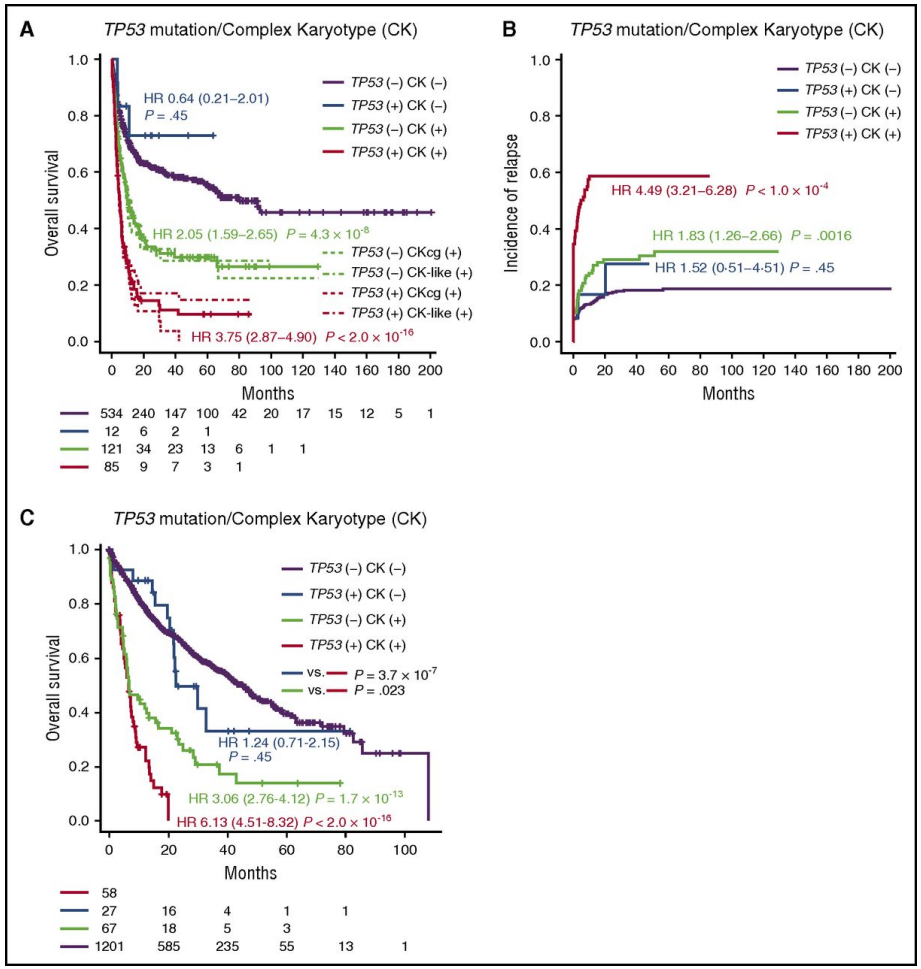


Effects of TP53 and CK on survival and relapse.



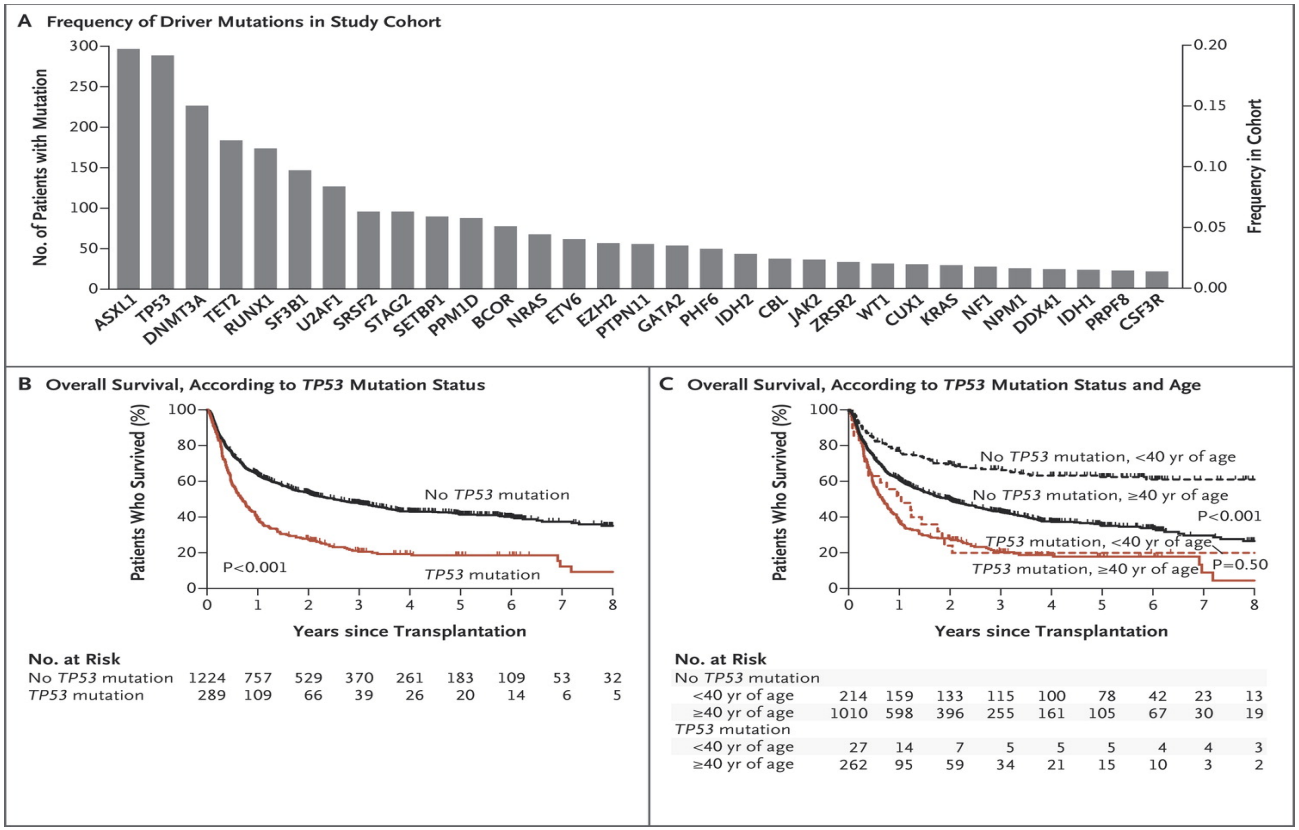
Tetsuichi Yoshizato et al. Blood 2017;129:2347-2358

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation

R.C. Lindsley, W. Saber, B.G. Mar, R. Redd, T. Wang, M.D. Haagenson, P.V. Grauman, Z.-H. Hu, S.R. Spellman, S.J. Lee, M.R. Verneris, K. Hsu, K. Fleischhauer, C. Cutler, J.H. Antin, D. Neuberg, and B.L. Ebert



Lindsley RC et al. N Engl J Med 2017;376:536-547.

Cytogenetics and comorbidity predict outcomes in older myelodysplastic syndrome patients after allogenic stem cell transplantation using reduced intensity conditioning

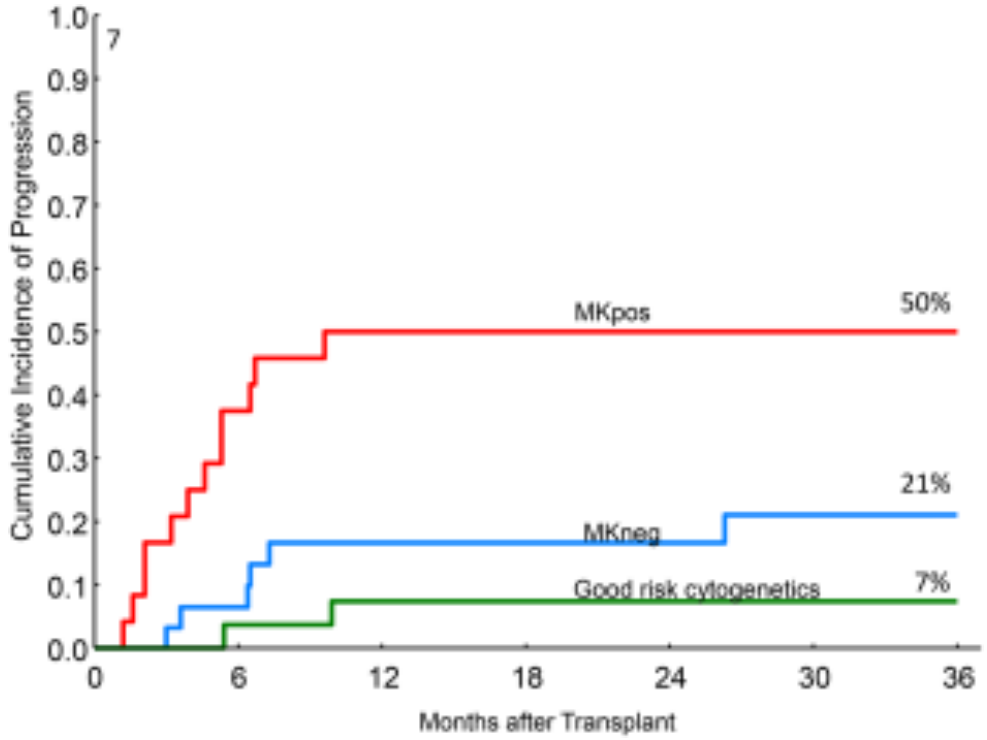
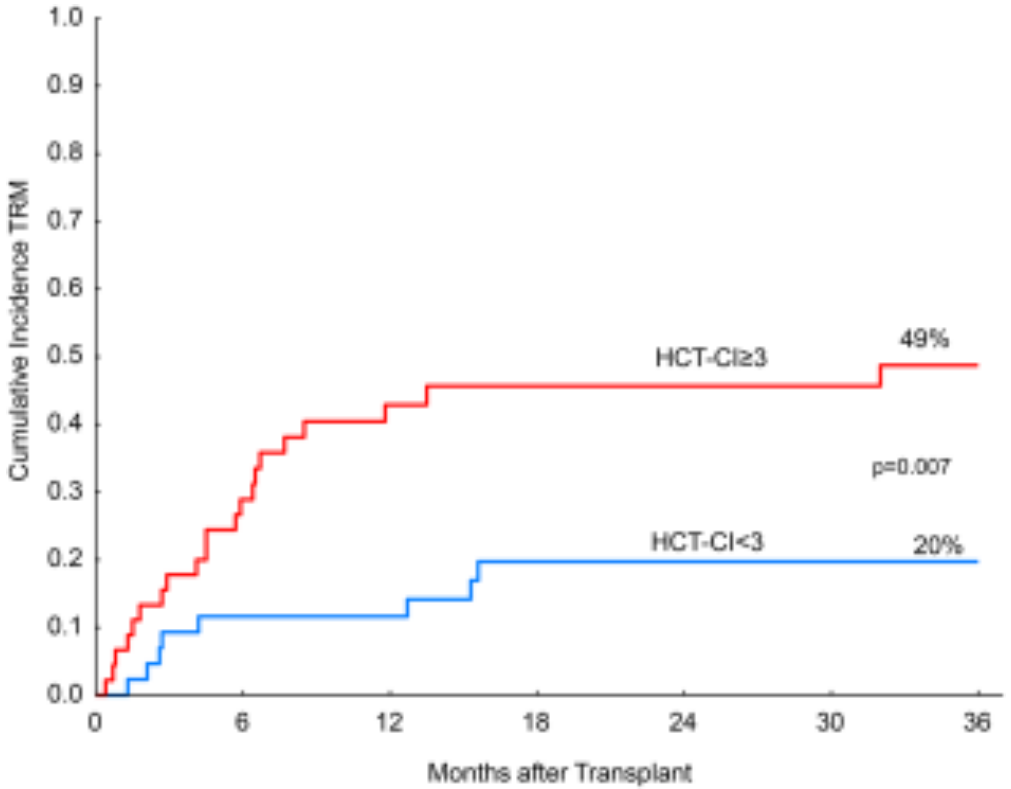


Figure 1. MKpos patients had the highest incidence of disease progression, with 50% at 3 years. MKneg and good-risk cytogenetics were associated with less relapse incidence,with 21% and 7% at 3 years, respectively.

Cancer
21 MAR 2017 DOI: 10.1002/cncr.30632
http://onlinelibrary.wiley.com/doi/10.1002/cncr.30632/full#cncr30632-fig-0001

Cytogenetics and comorbidity predict outcomes in older myelodysplastic syndrome patients after allogenic stem cell transplantation using reduced intensity conditioning



Cancer
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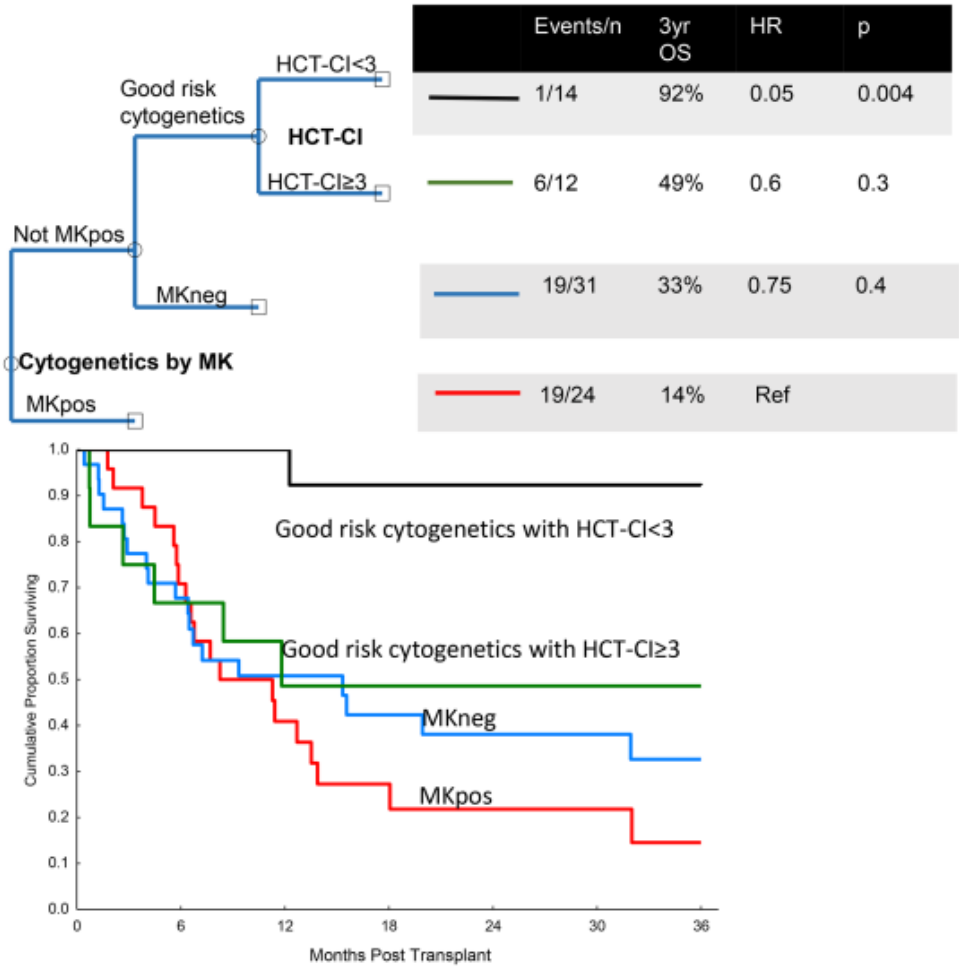
http://onlinelibrary.wiley.com/doi/10.1002/cncr.30632/full#cncr30632-fig-0002

Cytogenetics and comorbidity predict outcomes in older myelodysplastic syndrome patients after allogenic stem cell transplantation using reduced intensity conditioning

88 paz.
Età media 65 aa



Cancer
21 MAR 2017 DOI: 10.1002/cncr.30632
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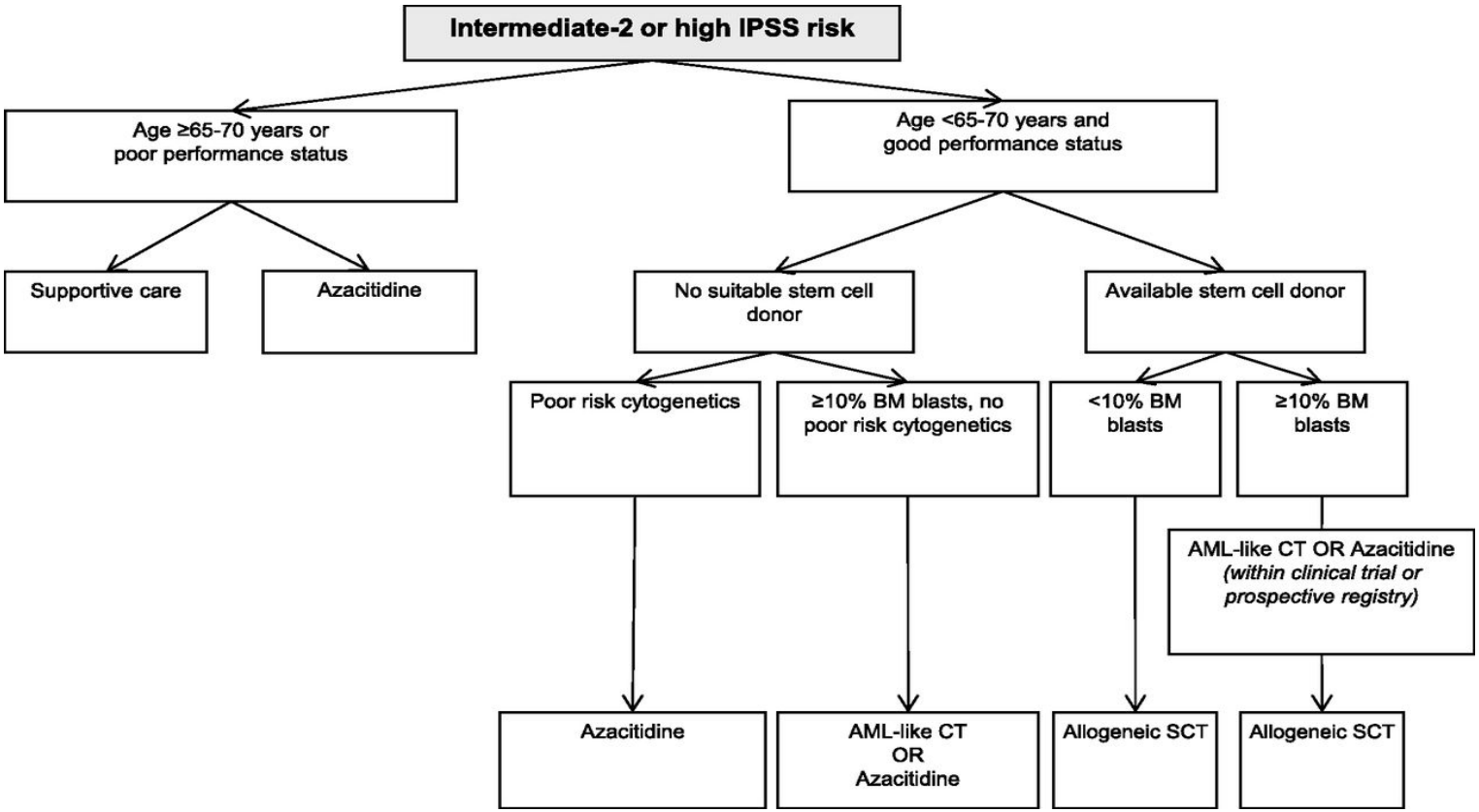
Therapeutic algorithm for adult patients with primary MDS and intermediate-2 or high IPSS score.

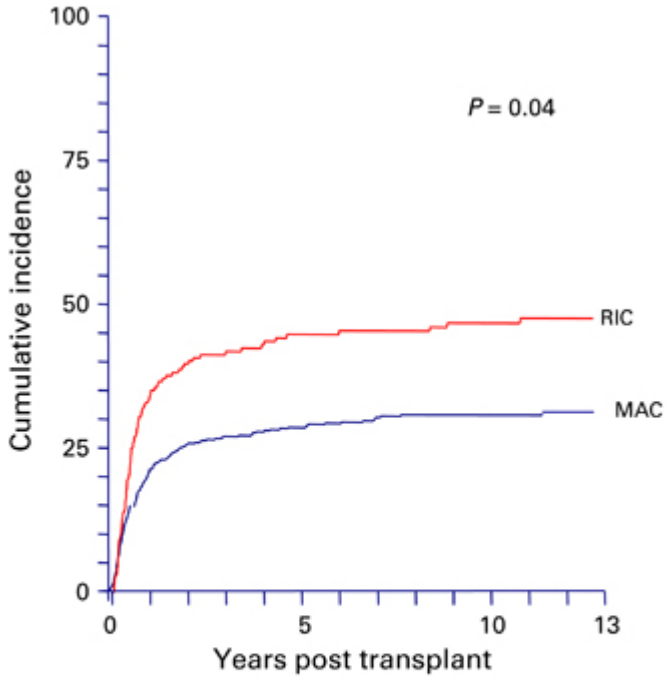


Luca Malcovati et al. Blood 2013;122:2943-2964

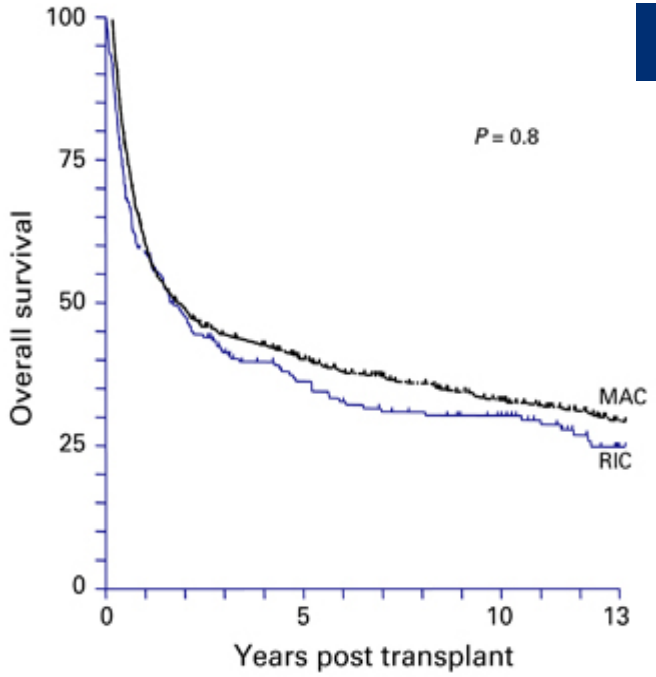
ORIGINAL ARTICLE

Long-term follow-up of a retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic transplantation from matched related donors in myelodysplastic syndromes

843 paz.



Conditioning	Number evaluable	3 yr.	6 yr.	9 yr.	13 yr.
MAC	630	239	184	150	100
RIC	213	63	46	38	19

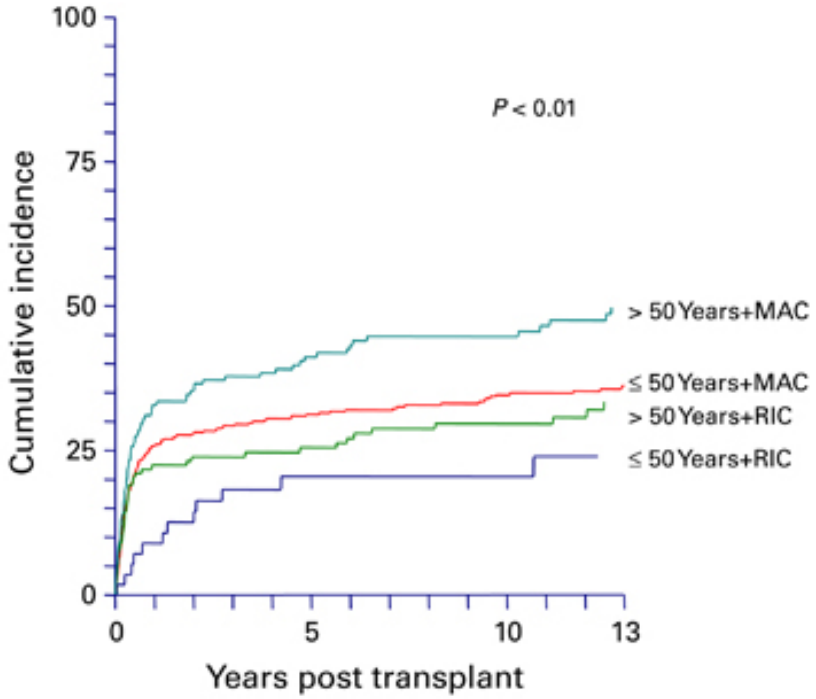


Conditioning	Number evaluable	3 yr.	6 yr.	9 yr.	13 yr.
MAC	630	264	203	164	106
RIC	213	77	55	46	24

Bone Marrow Transplantation 2017

ORIGINAL ARTICLE

Long-term follow-up of a retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic transplantation from matched related donors in myelodysplastic syndromes



Age+ Conditioning	Number evaluable				
	3 yr.	6 yr.	9 yr.	13 yr.	
Age < 50 + MAC	454	187	149	122	83
Age > 50 + RIC	153	47	34	28	14
Age > 50 + MAC	172	52	35	28	17
Age < 50 + RIC	56	16	12	10	5

Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial).

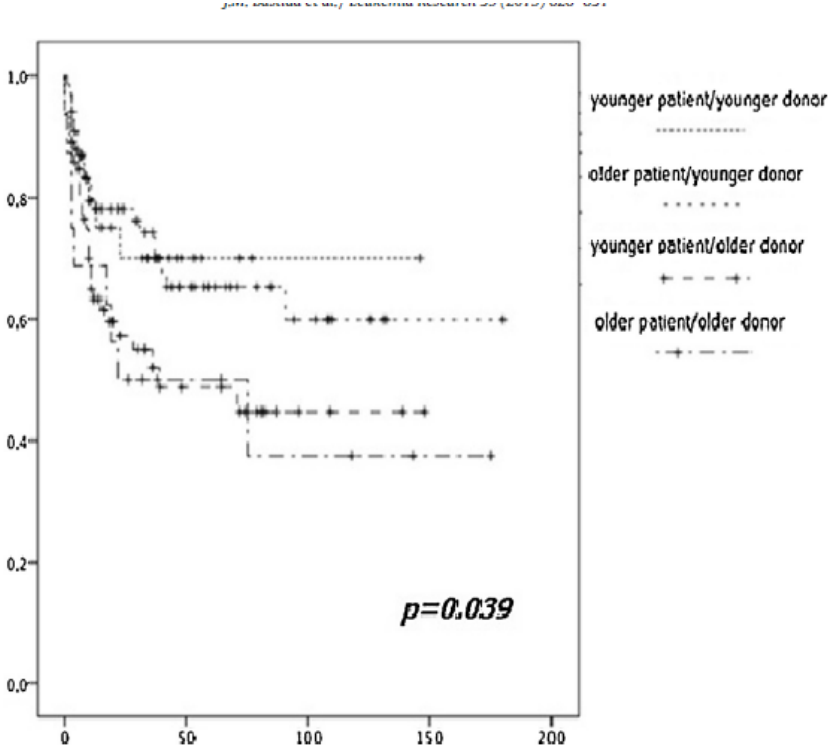
Kröger N J Clin Oncol. 2017 May

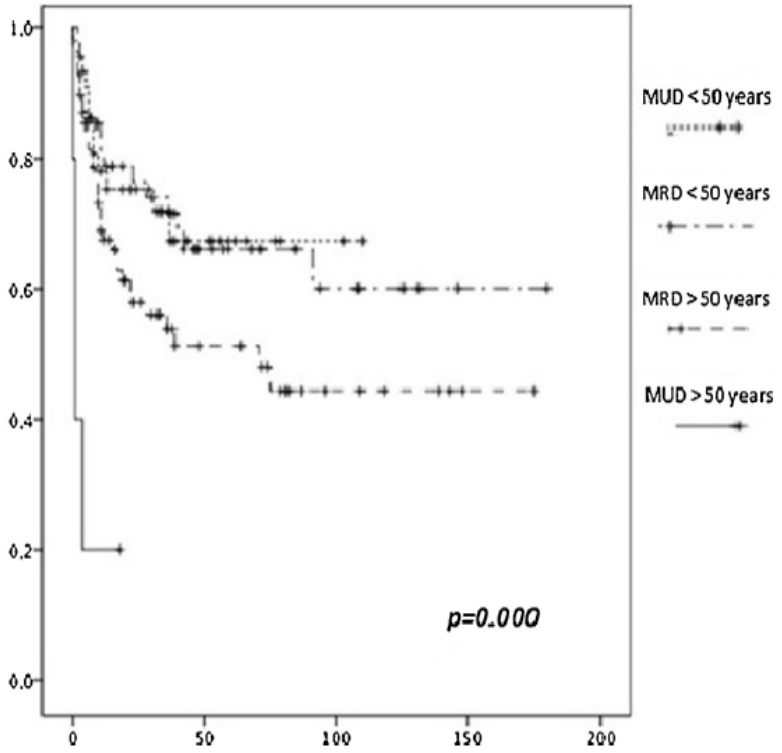
- **129 patients**
- **The CI of acute graft-versus-host disease II to IV was 32.3% after RIC and 37.5% after MAC (P = .35)**
- **The CI of chronic graft-versus-host disease was 61.6% after RIC and64.7% after MAC (P = .76)**
- **The CI of nonrelapse mortality after 1 year was 17% after RIC and 25% after MAC (P = .29)**
- **The CI of relapse at 2 years was 17% after RIC and 15% after MAC (P = .6)**
- **2-year relapse-free survival and overall survival of 62% and 76% respectively, after RIC, and 58% and 63% respectively, after MAC (P = .58 and P = .08, respectively).**

Influence of donor age in allogeneic stem cell transplant outcome in acute myeloid leukemia and myelodisplastic syndrome

J.M. Bastida*,[1], M. Cabrero[1], O. Lopez-Godino, M. Lopez-Parra, F. Sanchez-Guijo, L. Lopez-Corral, L. Vazquez, D. Caballero, C. Del Cañizo

Hematology Department; University Hospital of Salamanca, Salamanca, Spain

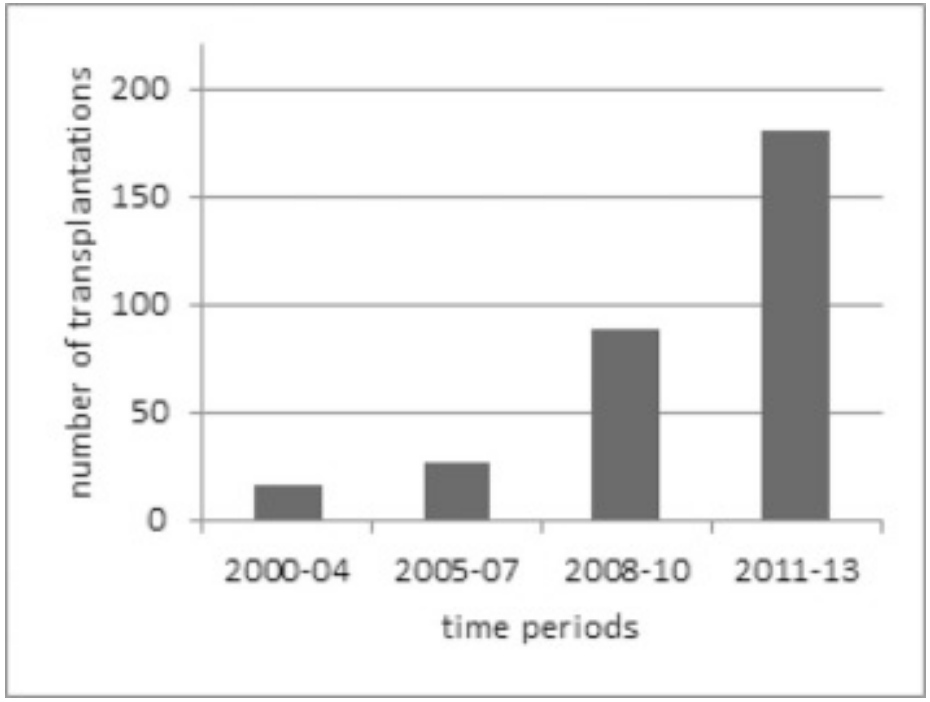


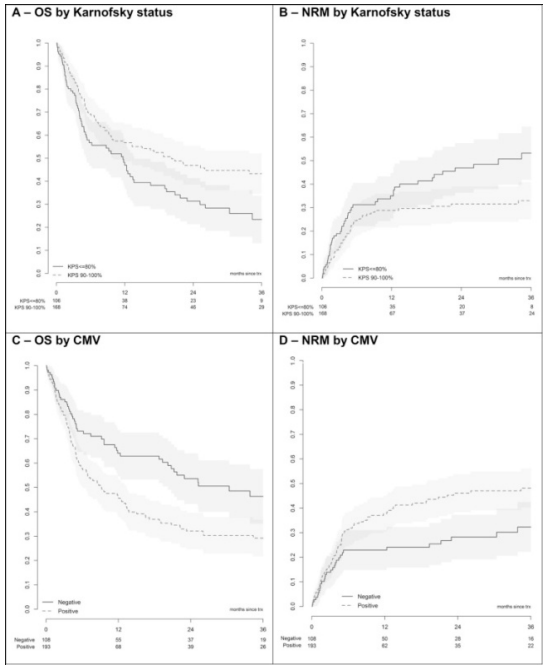


Leukemia Research2015,

Allogeneic Stem Cell Transplantation for Patients Age ≥ 70 Years with Myelodysplastic Syndrome: A Retrospective Study of the MDS Subcommittee of the Chronic Malignancies Working Party of the EBMT

Silke Heidenreich [1,*], Dimitris Ziagkos [2], Liesbeth C. de Wreede [2,3], Anja van Biezen [4], Jürgen Finke [5], Uwe Platzbecker [6], Dietger Niederwieser [7], Hermann Einsele [8], Wolfgang Bethge [9], Michael Schleuning [10], Dietrich W. Beelen [11], Johanna Tischer [12], Arnon Nagler [13], Bertram Glass [14], Johan Maertens [15], Lucrecia Yáñez [16], Yves Beguin Heinz Sill [18], Christof Scheid [19], Matthias Stelljes [20], Arnold Ganser [21], Pierre Zachée [2 Dominik Selleslag [23], Theo de Witte [24], Marie Robin [25], Nicolaus Kröger [1]





221 pt MDS
Età media 72 (70-78)

Biology of Blood and Marrow Transplantation,2017

Role of Reduced-Intensity Conditioning Allogeneic Hematopoietic Stem-Cell Transplantation in Older Patients with de Novo Myelodysplastic Syndromes: An Internetional Collaborative Decision Analysis

514 pazienti con de novo SMD con età 60-70 anni
OUTCOMES:
Life Expectancy (LE)
Quality Life
RIC versus Best Supportive Care

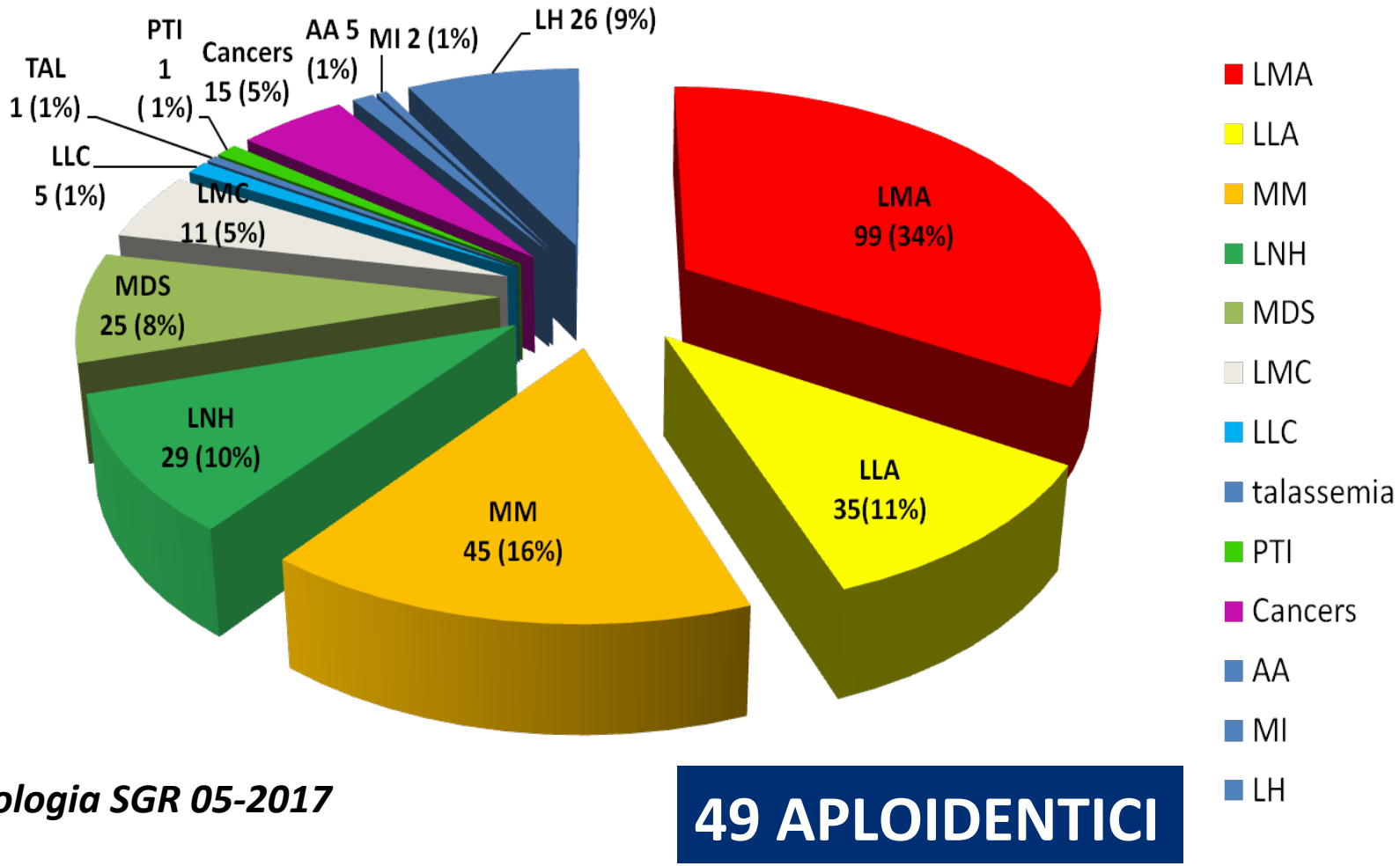
RISULTATI:
For patients with low/intermediate-1 IPSS MDS,
RIC transplantation LE was 38 m versus 77 m BSC
For intermediate-2/high IPSS MDS,
RIC transplantation LE was 36 m versus 28 m BSC

CONCLUSIONI:

For patients with de novo MDS aged 60-70 years, with low-intermediate-1 risk IPSS, nontransplantation approaches are preferred.
For intermediate-2/high IPSS, RIC transplantation offers overall and quality-adjusted survival benefit

Journal of Clinical Oncology, 2013

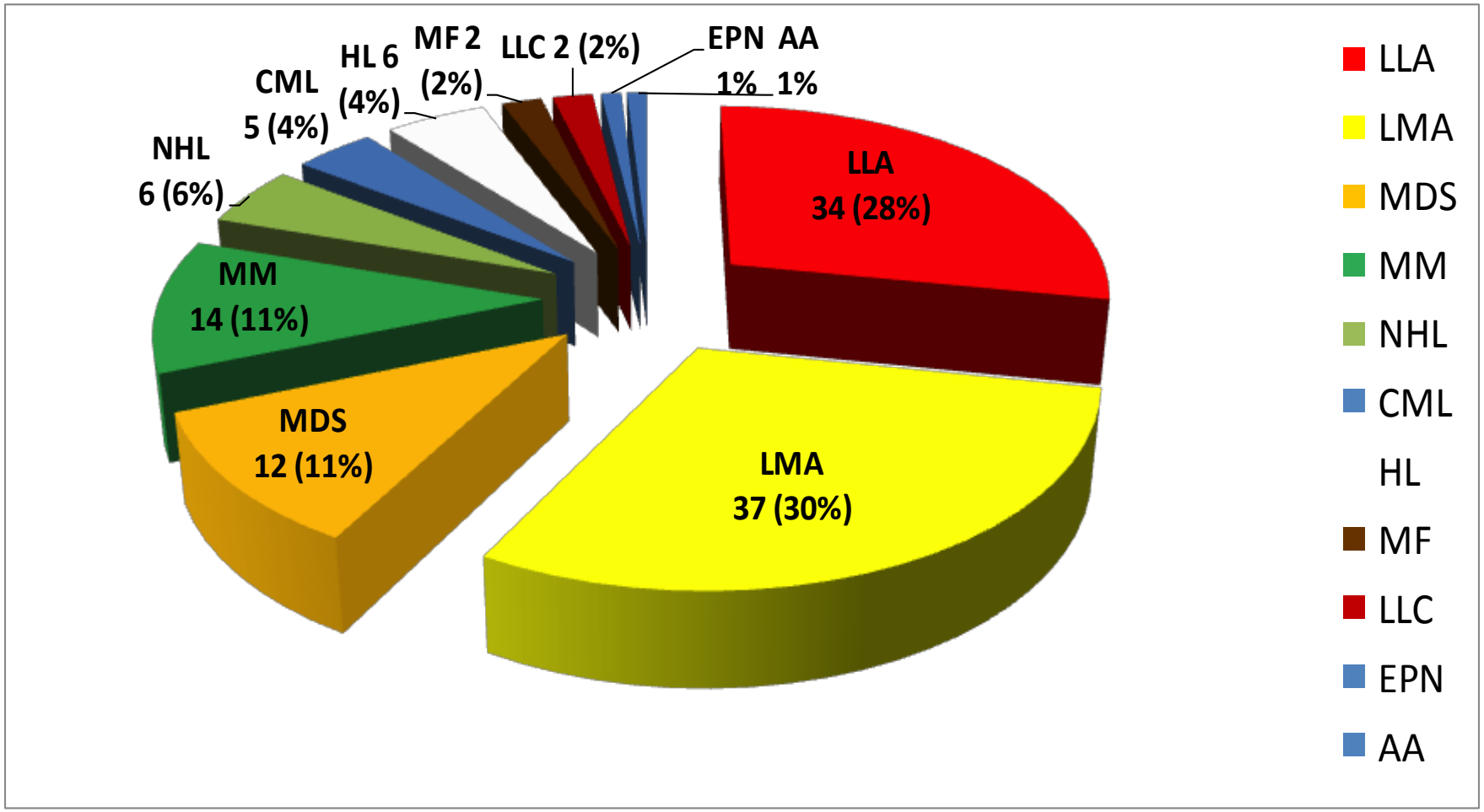
TRAPIANTO ALLOGENICO DA DONATORE FAMILIARE (n.299)



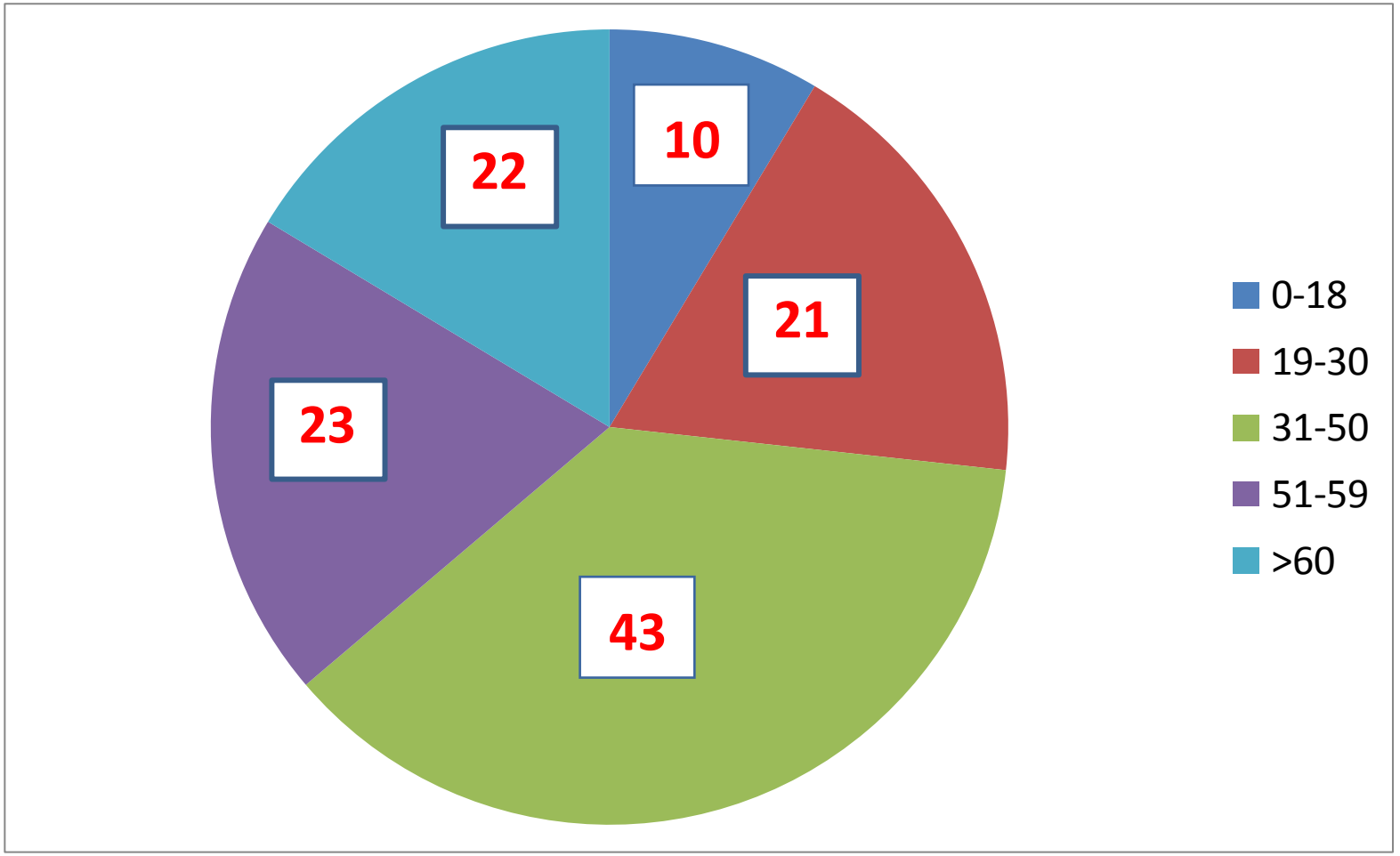
Ematologia SGR 05-2017

49 APLOIDENTICI

TRAPIANTO DA DONATORE VOLONTARIO (MUD) (n.120)

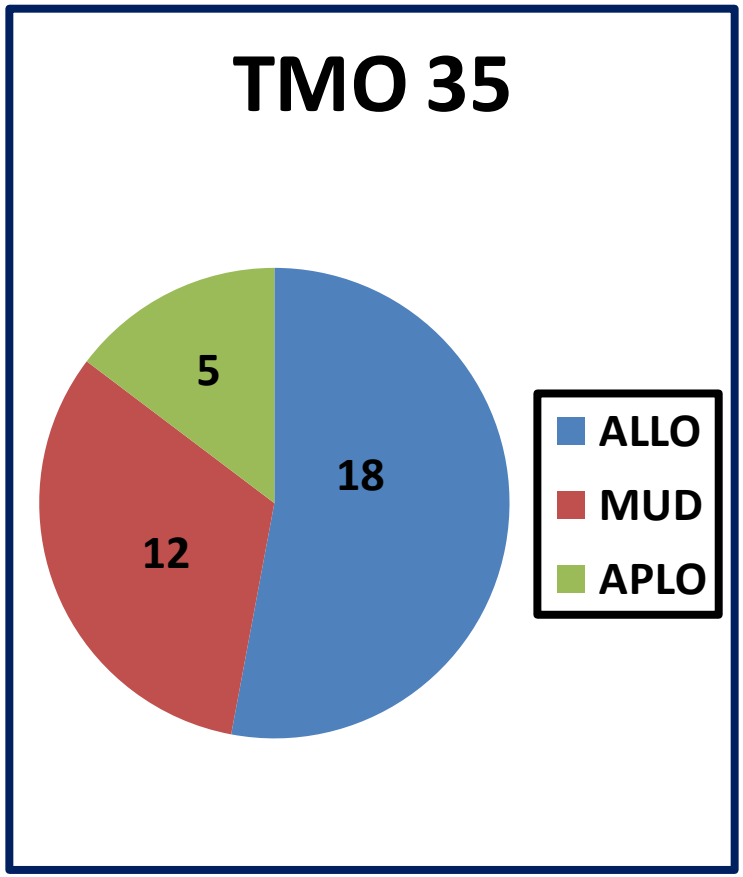


ETA' AL TMO MUD



Ematologia SGR 05-2017

SMD: TRAPIANTO esperienza San Giovanni Rotondo



PAZIENTI 35
M/F 22/13
ETA' 52 aa (17-69)
V/M 18 (51%) 17 (49%)
TRM 8 (23%)
RECIDIVE 8 (23%)
SEC. TUMORE 1 (3%)

MUD + APLO: V/M 12/17 70%