CONTROVERSIE NEL TRAPIANTO DI CELLULE STAMINALI EMOPOIETICHE

RUOLO DEL SECONDO TRAPIANTO NELLA LEUCEMIA ACUTA MIELOIDE IN RECIDIVA

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CORSO EDUCAZIONALE GITMO
BARI, 6 – 7 Giugno 2017

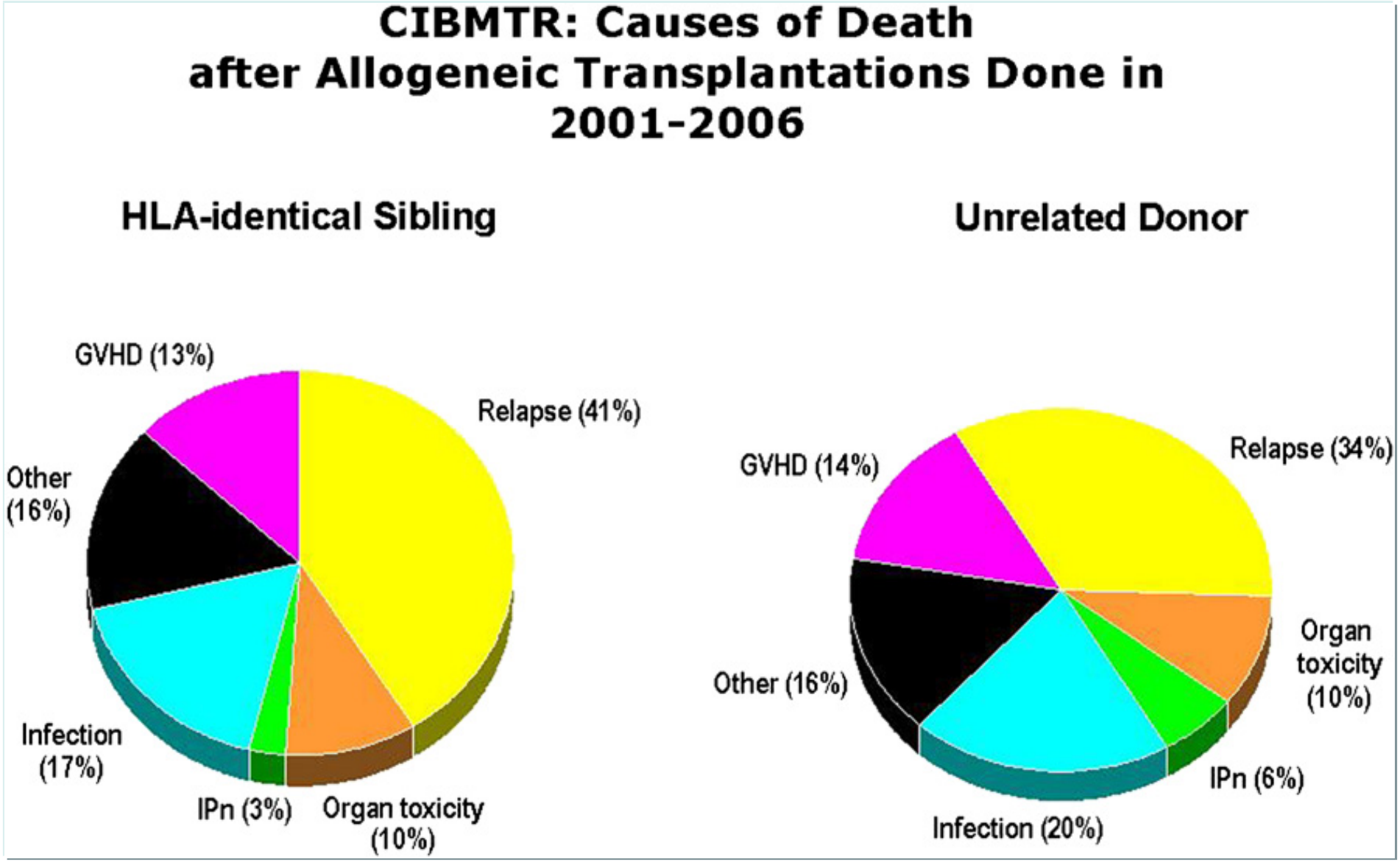
GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

- Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for patients with acute leukemia.

- During the last 15 years transplant related mortality (TRM) has been significantly reduced due to better supportive care, improving in HLA-typing, prophylaxis and treatment of infections and the introduction of reduced intensity conditioning regimens.

- On the contrary relapse related death (RRD) has remained unchanged over the past 3 decades.

Van den Brink, BBMT, 2010



Van den Brink, BBMT, 2010

- Treatment options for relapsed patients after allogeneic HSCT included:

- **DLI**
- **Chemotherapy with/without DLI**
- **Novel drugs with/without DLI**

- **Second allogeneic transplantation**

SECOND ALLOGENEIC STEM CELL TRANSPLANTATION FOR ACUTE AND CHRONIC LEUKEMIA

- A Prognostic Factor Analysis -

Eapen et al. Bone *Marrow Transplant* 2004;34:721-727

International Bone Marrow Transplant Registry

IBMTR

ABMTR

Autologous Blood and Marrow Transplant Registry

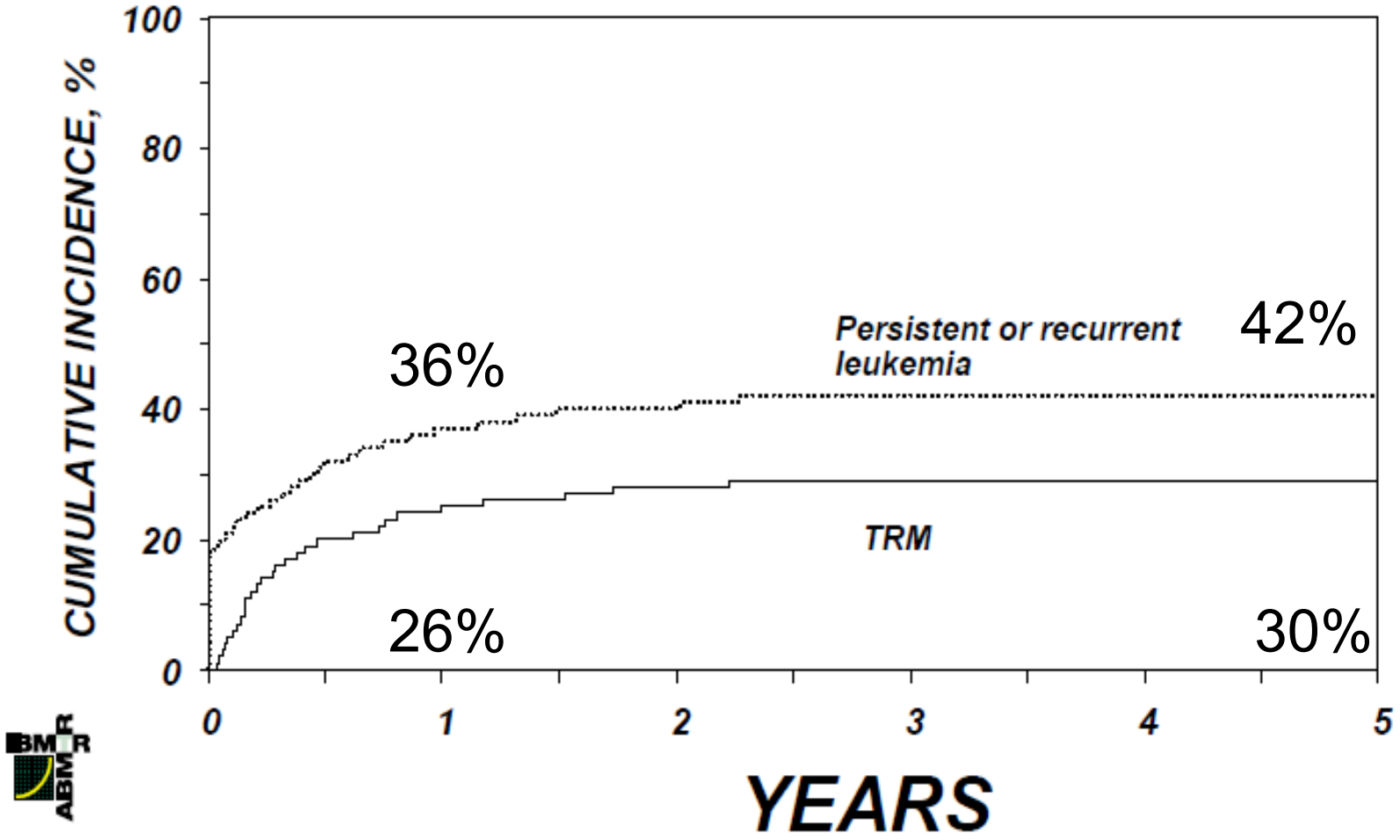
N=279 pts

INCLUSION AND EXCLUSION CRITERIA

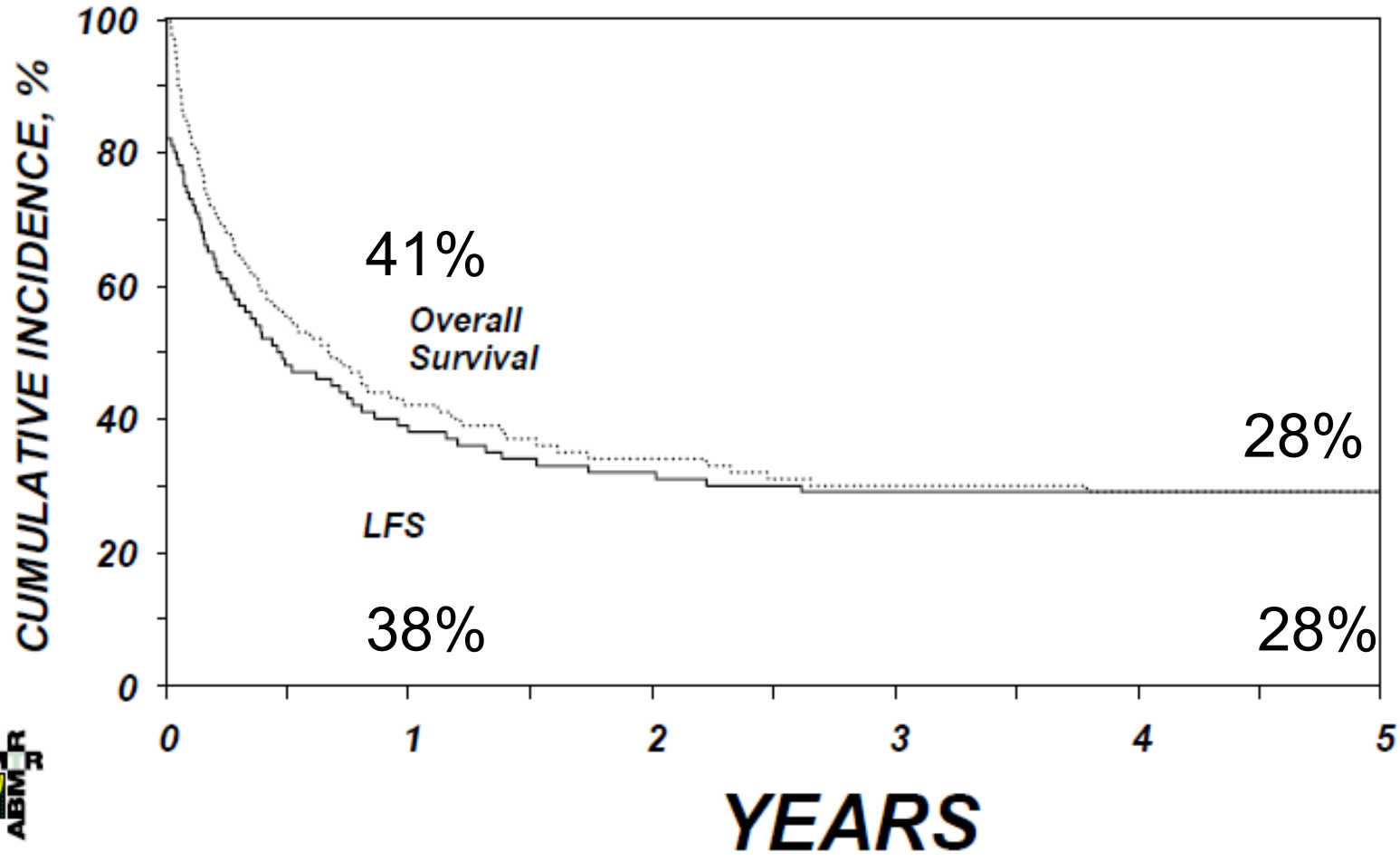
- *Inclusion criteria*
  ALL, AML and CML
  HLA-identical sibling donor for 1st and 2nd SCT
  2nd SCT between 1990-2000

- *Exclusion criteria*
  Recipients of alternative donor 2nd SCT
  Recipients of donor leukocyte infusion
  Recipients of non-myeloablative SCT

CUMULATIVE INCIDENCE OF TRM AND RELAPSE AFTER 2ND TRANSPLANTATION



PROBABILITY OF LFS AND OVERALL SURVIVAL AFTER 2ND TRANSPLANTATION



IBMTR: OS ACCORDING TO RISK FACTORS

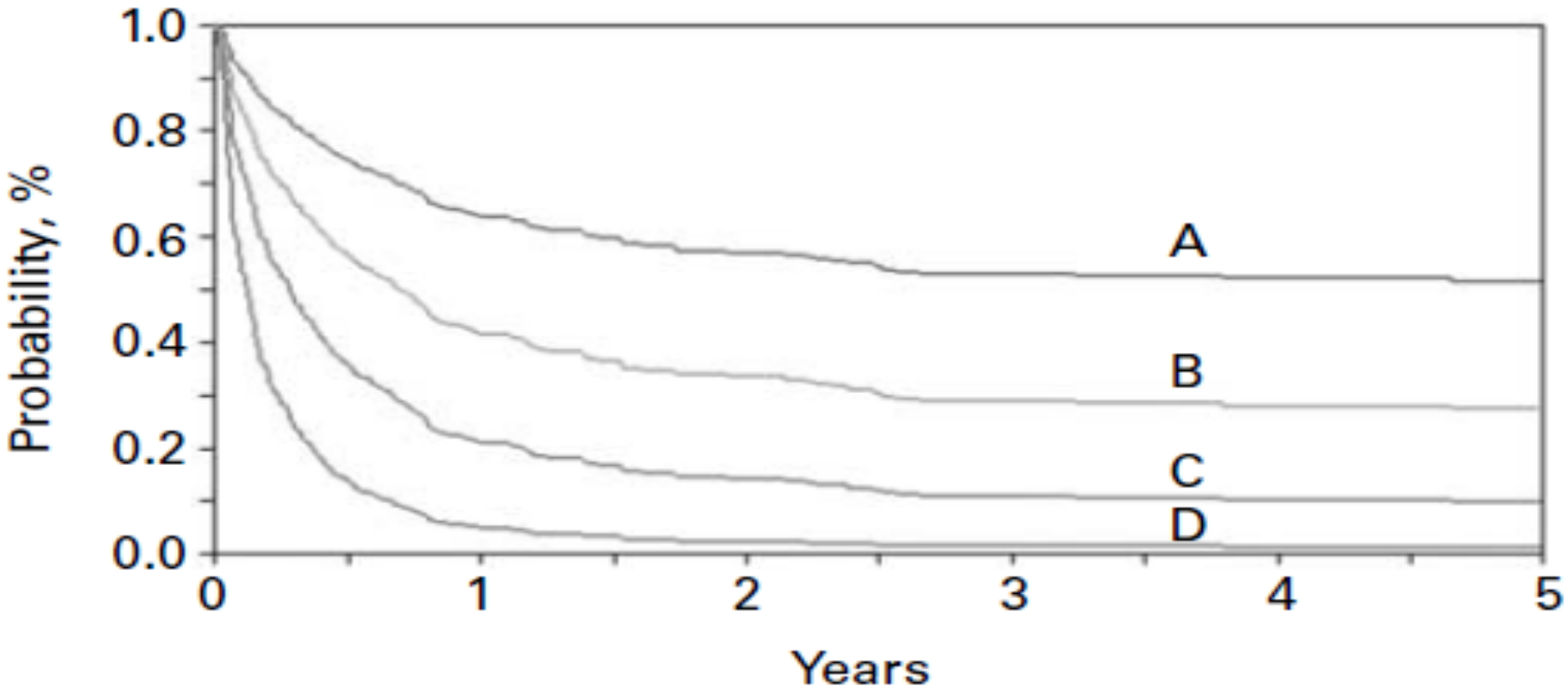


Figure 3 Probability of overall survival after second transplantation. (A) Age ⩽20 years, duration of remission >6 months; (B) age >20 years, duration of remission >6 months; (C) age ⩽20 years, duration of remission ⩽6 months; and (D) age >20 years, duration of remission ⩽6 months.

EBMT Risk Score Predicts Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Patients Who Have Failed a Previous Transplantation Procedure

Katayoun Rezvani, Edward J Kanfer, David Marin, Ian Gabriel, Amin Rahemtulla, Alexandra Taylor, Donald MacDonald, Francesco Dazzi, Dragana Milojkovic, Letizia Foroni, Jiri Pavlu, Jeremy Sargent, Rifca Le Dieu, John M Goldman, Jane Apperley, Richard Szydlo

Biol Blood Marrow Transplant ■: 1-6 (2011)

124 consecutive patients received a second transplant from October 1985 to July 2010, **after prior allogeneic (n=60)** or autologous (n=64) HSCT

Table 2. EBMT Risk Score at Second SCT (A)

Table (A)

	N (%)	Score
Age (years)		
<20	4 (3.2)	0
20-40	62 (50.0)	1
>40	58 (46.8)	2
Disease stage		
Early	9 (7.3%)	0
Intermediate	53 (42.3%)	1
Advanced	62 (50.0)	2
Duration of disease		
Pre-second SCT (months)		
<12	9 (7.3)	0
>12	115 (92.7)	1
Donor match		
HLA-id.sib.	75 (60.5)	0
Other	49 (39.5)	1
Patient/donor gender		
M/F	22 (17.7)	1
Other	100 (82.3)	0

SCORE: 0 - - - - >7

Rezvani, BBMT 2011

NRM and OS according to the EBMT RISK SCORE at SECOND TRANSPLANT

EBMT Score at Second SCT	N (%)	Probability of NRM at 1 Year (95% CI)	*P* Value	Probability of Survival at 5 Years (95% CI)	*P* Value
EBMT score			.0003		.0003
0-3	25 (20.2)	28.0 (15-53)		51.7 (33-70)	
4	40 (32.3)	33.2 (21-52)		29.3 (17-46)	
>4	57 (46.0)	58.8 (47-73)		10.4 (4-24)	

SCT indicates stem cell transplantation; CI, confidence interval; EBMT, European blood and marrow transplant; NRM, nonrelapse mortality.

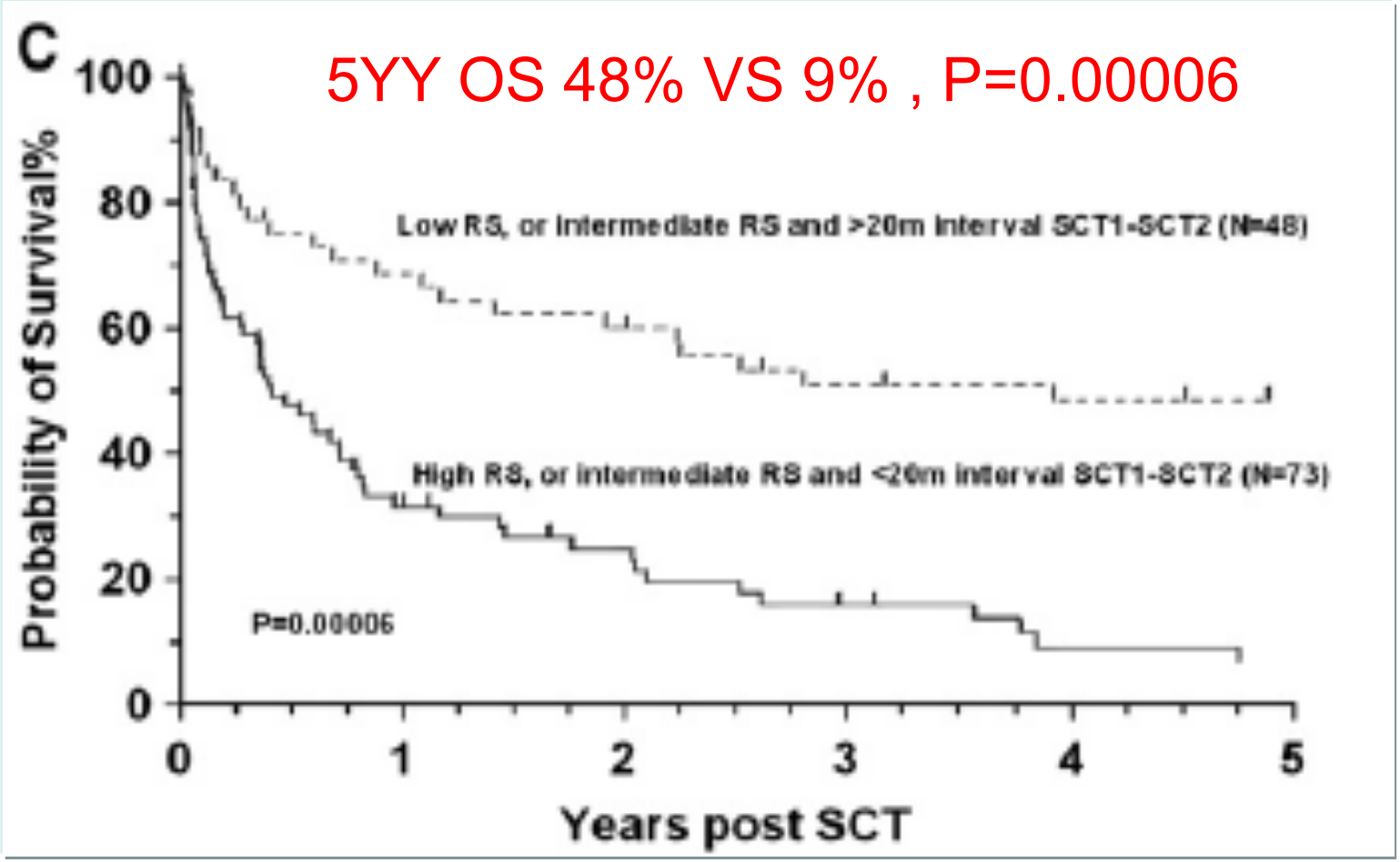
Rezvani, BBMT 2011

PREDICTING FACTORS OF SURVIVAL IN MULTIVARIATE ANALYSIS

	RR	P
HIGH SCORE	2.83	0.001
INT SCORE	1.75	0.09
INT 1ST TX -> 2ND TX (< 20 months)	1.59	0.03

Rezvani, BBMT 2011

OS according to RISK SCORE and INTERVAL TRANSPLANT



Rezvani, BBMT 2011

Bone Marrow Transplantation (2015) **50,** 1508–1512

www.nature.com/bmt

ORIGINAL ARTICLE

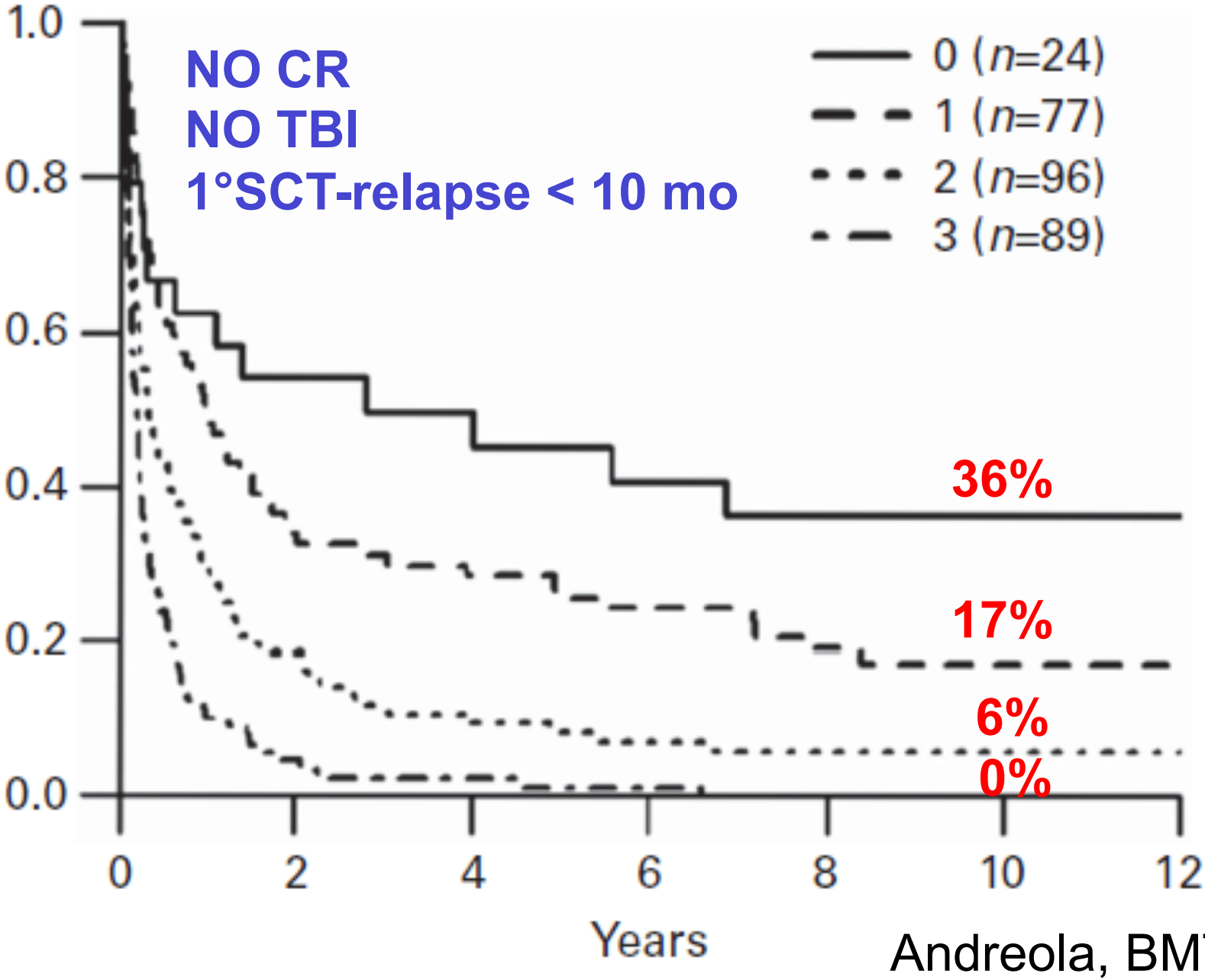
Long-term outcome and prognostic factors of second allogeneic hematopoietic stem cell transplant for acute leukemia in patients with a median follow-up of ⩾10 years

G Andreola[1], M Labopin[2], D Beelen[3], P Chevallier[4], R Tabrizi[5], A Bosi[6], M Michallet[7], S Santarone[8], G Ehninger[9], E Polge[2], D Laszlo[1], C Schmid[10,12], A Nagler[11] and M Mohty[2,12]

n= 286 AML = 166 ALL = 120
MAC
YY of TX 1985 – 2000
Median FUP 11.3 yy

EBMT registry

10 yy OS according to RISK SCORE



Andreola, BMT 2015

- Studio retrospettivo all'interno del GITMO
- Promotore FA-R.I.T.M.O nel 2012
- 40 centri (adulti e pediatrici)
- YY TX 2006-2011
- 208 pazienti
- AML (n=138) e ALL (70)
- OS obiettivo primario

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CIC		ADESIONE	INVIATO I DATI
141	BRESCIA	SI	SI
217	GENOVA	SI	SI
232	ROMA	SI	SI
240	BOLOGNA	SI	SI
248	PESCARA	SI	SI
274	GENOVA	SI	SI
286	PAVIA	SI	
304	FIRENZE	SI	SI
307	ROMA	SI	SI
526	SG ROTONDO	SI	
606	CUNEO	SI	SI
658	BERGAMO	SI	SI
788	ANCONA	SI	SI
790	BOLOGNA	SI	SI
792	CATANIA	SI	SI
813	MILANO	SI	
299	BOLZANO	SI	SI
649	BARI	SI	SI
766	NAPOLI	SI	SI
231	TORINO	SI	
285	PADOVA	SI	
557	PAVIA	SI	
692	PALERMO	SI	
756	ROMA	SI	
791	CAGLIARI	SI	
705	UDINE	SI	SI

ADESIONI
26 CENTRI

INVIO DATI
16 CENTRI

GITMO

Emendamento al protocollo nel 2013

Includere pazienti fino al 31.12.2012

Informazioni aggiuntive:
DLI e/o CHT+DLI pre e post II TX
GVHD a/c grado massimo/timing
Stesso donatore o diverso
Condizionamento RIC/MAC
Stop IS post II TX
DLI profilattiche post II TX

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Criteri di inclusione/esclusione

Diagnosi AML
ALL

Recidiva di malattia dopo I trapianto di midollo osseo allogenico

Rigetto

Poor graft function

Chimerismo misto

Assenza di recidiva di malattia

Diagnosi diversa da AML e ALL

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GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

PATIENTS CHARACTERISTICS (n=208)

		n	%
DISEASE			
	AML	138	66
	ALL	70	34
DISEASE PHASE			
	CR	59	28
	No CR	149	72
Sex mism			
	F→M	45	24
	other	159	76

Age 40 (4-66) yy

Year of tx 2006-2012

Int 1°-2°tx 377 (35-4719) dd
Int 1°Tx - REL 236 (15-4553) dd
Int 1°REL -2°tx 103 (16-2167) dd

Median FUP 250 (4-3794) dd

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TRANSPLANT CHARACTERISTICS (1) (n=208)

		n	(%)
DONOR TYPE			
	SIB+FAM MISM	78	37
	ALT(MUD/MISM/HAPLO)	130	63
CONDITIONING			
	RIC	100	48
	MA	108	51
SC SOURCE			
	BM	54	26
	PB	132	63
	CB	22	11
<> DONOR AT 2°TX			
	YES	118	57
	NO	90	43
GvHD PROPH			
	YES	190	91
	NO	18	8

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TRANSPLANT CHARACTERISTICS (2) (n=208)

		n	(%)
aGVHD	**I-II**	66	31
	III	7	7
	IV	9	4
cGVHD	**LIM**	24	11
	EXT	40	19
STOP IS	**<= d100**	39	12
	101-180	33	19
	>180	21	10
	NO	26	12
PROPH DLI	YES	7	3
w/o REL	NO	192	93
DLI	YES	11	5
post REL	NO	109	52
Alive/Dead		**36/172**	
Dead for RELAPSE		**110**	
Dead for NRM		**62**	

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FACTORS PREDICTING OVERALL SURVIVAL IN UNIVARIATE ANALYSIS (1)

	5yyOS	p
Disease phase		***0,03***
CR	28%	
No CR	9%	
Donor type		***0,03***
Sib	22%	
Alt	6%	
Recipient Age		**0,01**
<30yy	24%	
>30yy	21%	
Int. 1°-2°tx		**0,002**
<365dd	10%	
>365dd	16%	
Int. REL-2°tx		**0,005**
<100dd	10%	
>100dd	15%	

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FACTORS PREDICTING OVERALL SURVIVAL IN UNIVARIATE ANALYSIS (2)

		5yyOS	p
SC source			**0,004**
	BM	20%	
	PB	15%	
	CB	0%	
Sex mism			**0,91**
	F vs M	15%	
	other	12%	
Conditioning			**0,66**
	RIC	14%	
	MA	14%	
Donor 2°tx			**0,56**
	=	18%	
	<>	11%	

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NEGATIVE PREDICTORS OF OVERALL SURVIVAL IN MULTIVARIATE ANALYSIS

			RR	P
Donor type:		alternative	1,67	0,002
Recipient Age:		>=30yy	1,52	0,01
Int. 1°-2° TX:	<365dd	1,81	0,0001	
Disease phase 2ndTx:		no CR	1,20	0,07

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NEGATIVE PREDICTORS OF RELAPSE AND NRM IN MULTIVARIATE ANALYSIS

Cox on relapse			**RR**	**P**
Recipient Age:	>=30yy		1,44	0,07
Int. 1°-2° TX:	<365dd	2.29	0,0001	

Cox on NRM		**RR**	**P**
Source	CB	3.79	0,003
	PB	1.3	0,4

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RISK SCORE FOR OS AT SECOND TX

Donor type:	sibling	0
	alternative	1
Recipient Age:	<30yy	0
	>=30yy	1
Int. 1°-2° TX	<365dd	1
	>=365dd	0
Disease phase:	CR	0
	no CR	1

SCORE: 0 - - - - >4

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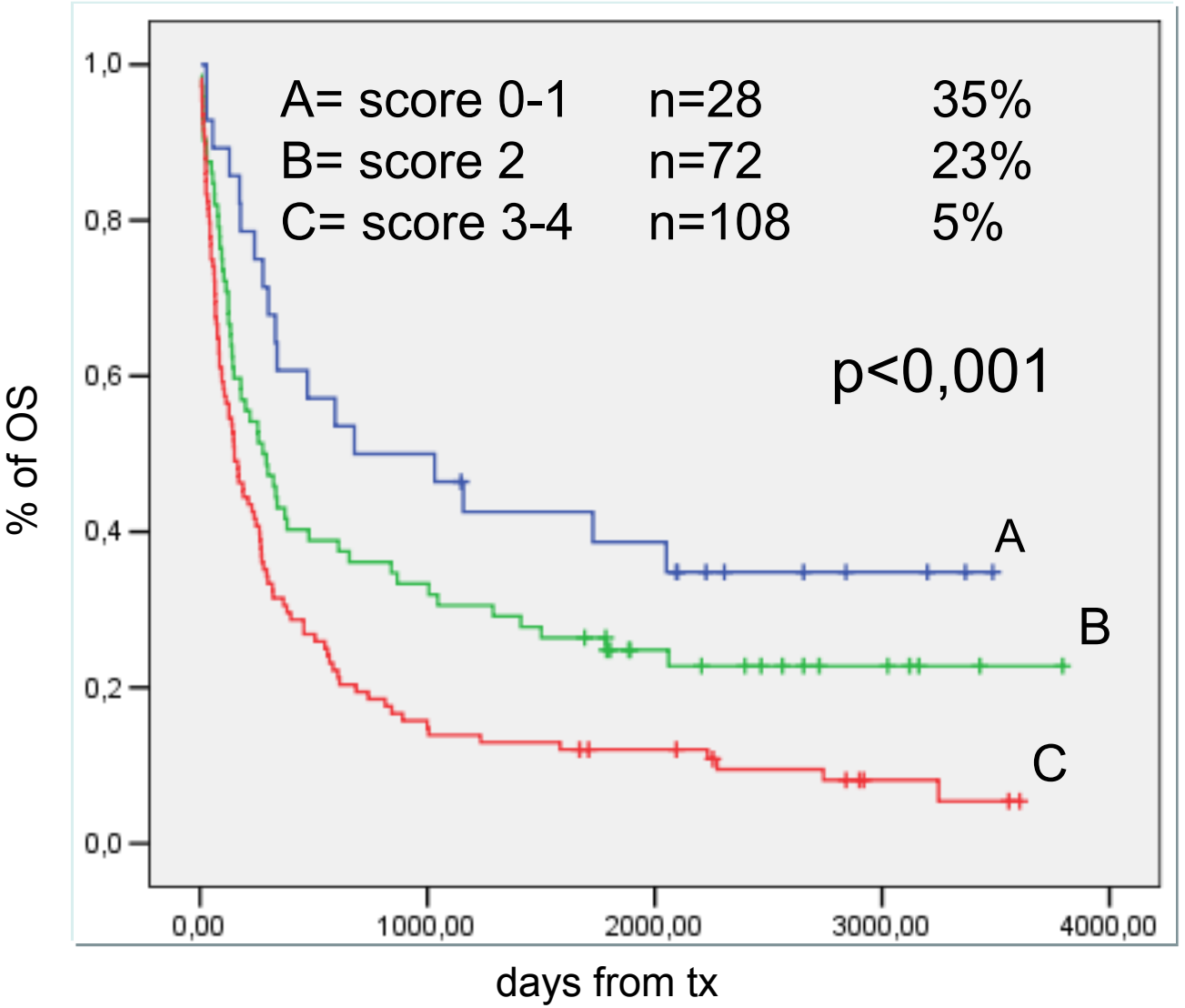
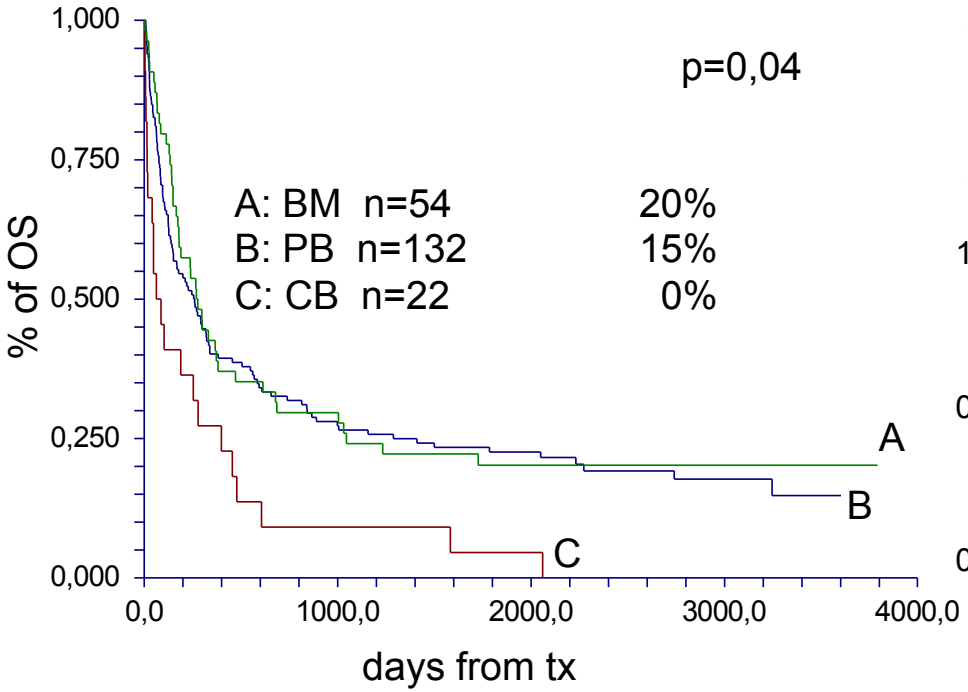
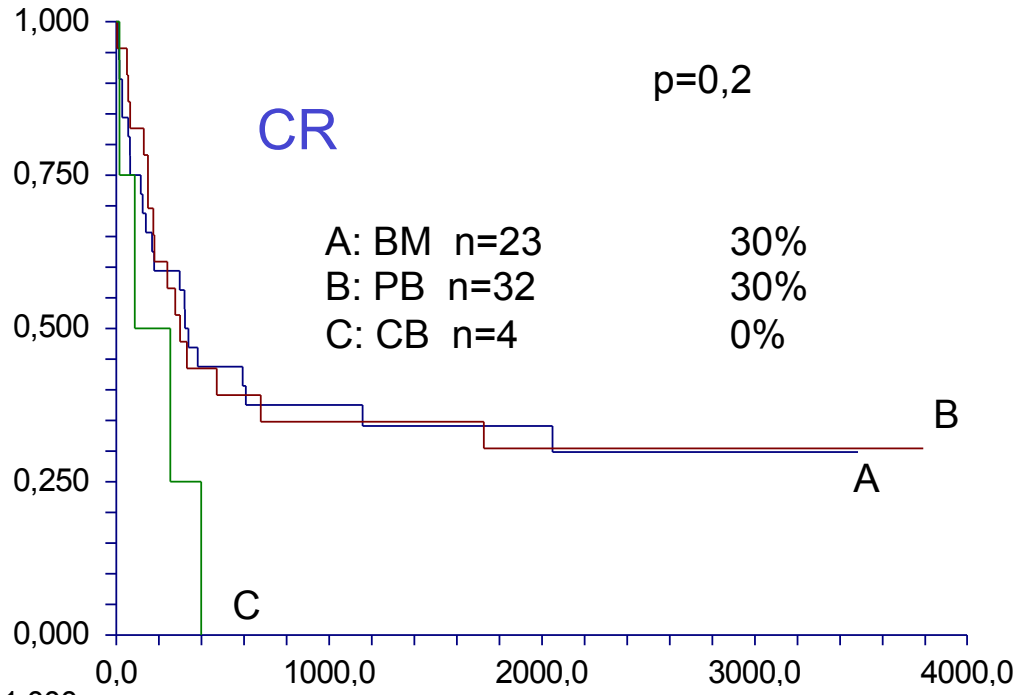
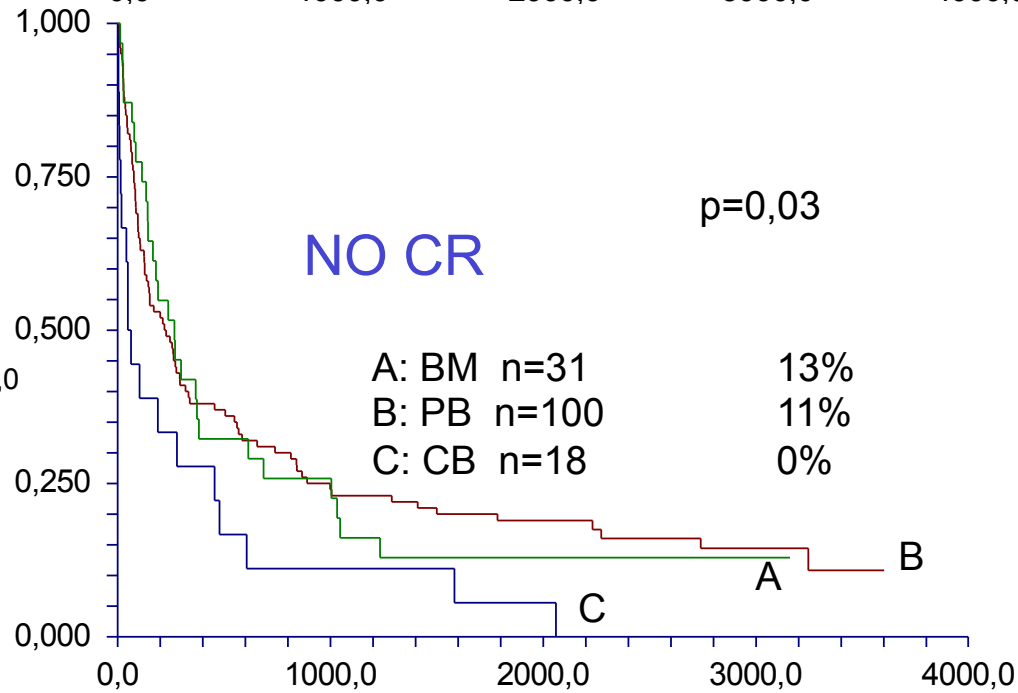
GITMO data :5 yy OS according to risk score



NEGATIVE IMPACT OF CB AS STEM CELL SOURCE







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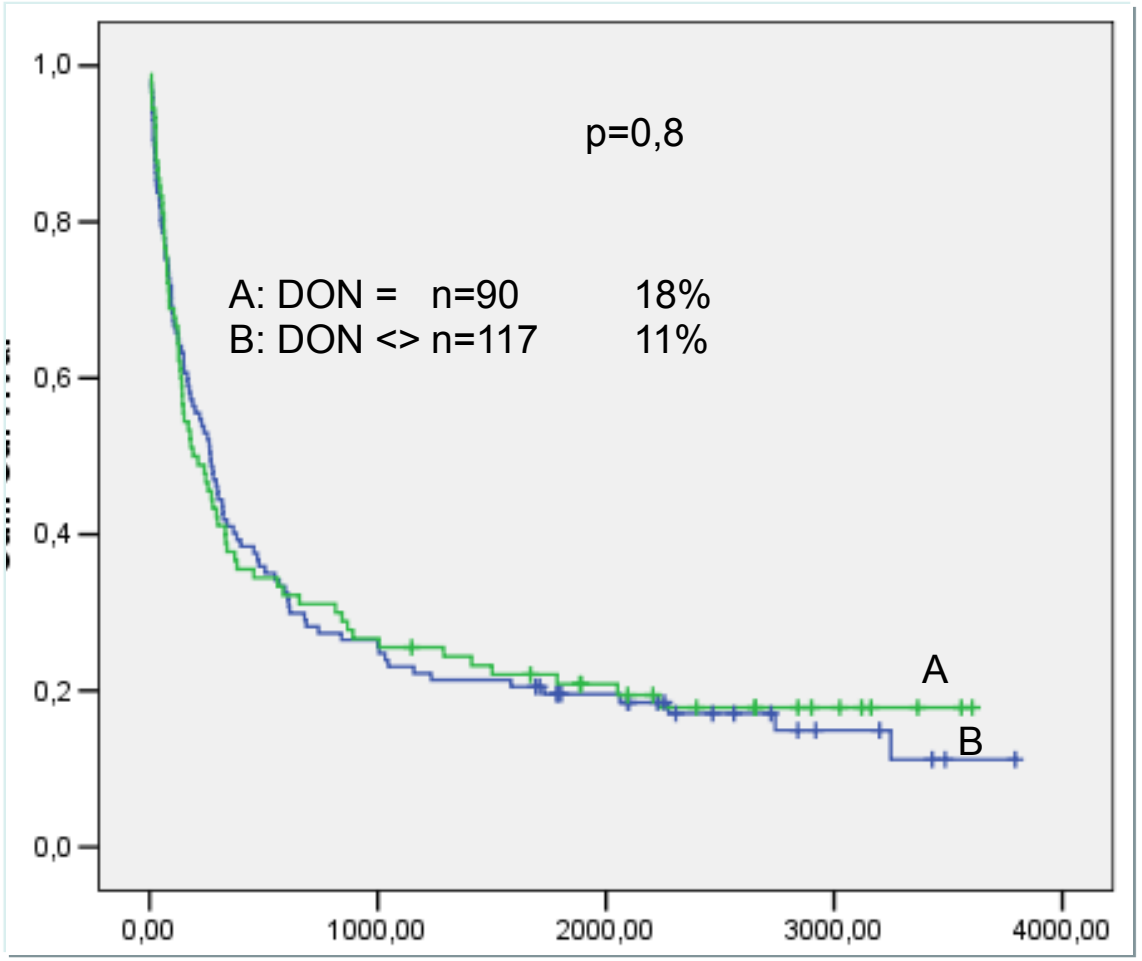
CHANGING DONOR AT 2°TX DOES NOT INFLUENCE THE OUTCOME



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CONCLUSIONS (1)

Patients with acute leukemia relapsed after allogeneic HSCT have a very poor prognosis

A second allogeneic HSCT is a treatment option, but risk assessment shoul be evaluated

Younger age (< =30 yy), interval time 1°2°Tx > 1 yy, hla-identical sibling, CR at the time of 2°Tx are the best preditors of outcome

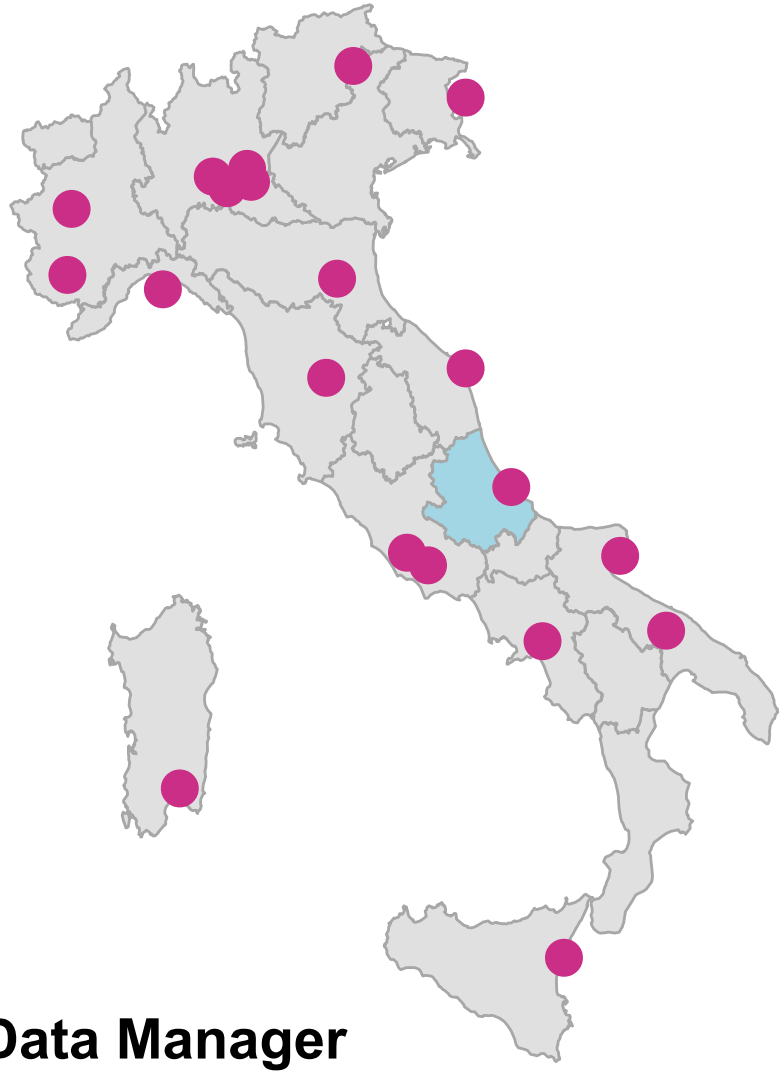
CONCLUSIONS(2)

Short interval time between 1° and 2 ° Tx is the most important negative predictor of outcome in multivariate analysis

MA conditioning should be used for patients in remission at 2°TX to improve survival

Changing donor at 2° Tx had no impact on the outcome

Centers
Milano San Raffaele
Genova - Ospedale San Martino
Torino Ospedale San Giovanni Battista
Pescara Ospedale Civile
Firenze AO Careggi
Ancona Ospedali Riuniti
Bologna Policlinico Sant'Orsola
Bologna pediatrico
Bergamo Ospedali Riuniti
Genova Gaslini
Bari-Policlinico
Bolzano Osped Reg Generale
Roma Policlinico Gemelli
Roma Univerita' La Sapienza
Brescia Ospedali Civili
Cuneo S. Croce
Napoli Federico II
Cagliari Businco
Monza Osp San Gerardo
Catania Ferrarotto
Udine Policlinico Universitario



Data Manager
Barbara Bruno
Elena Oldani

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GRUPPO ITALIANO TRAPIANTO MIDOLLO OSSEO

NEGATIVE PREDICTORS OF SURVIVAL IN MULTIVARIATE ANALYSIS (first analysis)

			HR	P
Donor type:	alternative		1,53	0,005
Disease phase 2ndTx:	no CR		1,50	0,014
Int. 1°-2° TX:	<365dd	1,46	0,011	
Recipient Age:	>=30yy		1,40	0,025

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RISK SCORE FOR OS AT SECOND TX

Recipient Age:	<30yy	0
	>=30yy	1
Disease phase:	CR	0
	no CR	1
Int. 1°-2° TX	<365dd	1
	>=365dd	0
Donor type:	sibling	0
	alternative	1

SCORE: 0 - - - - >4

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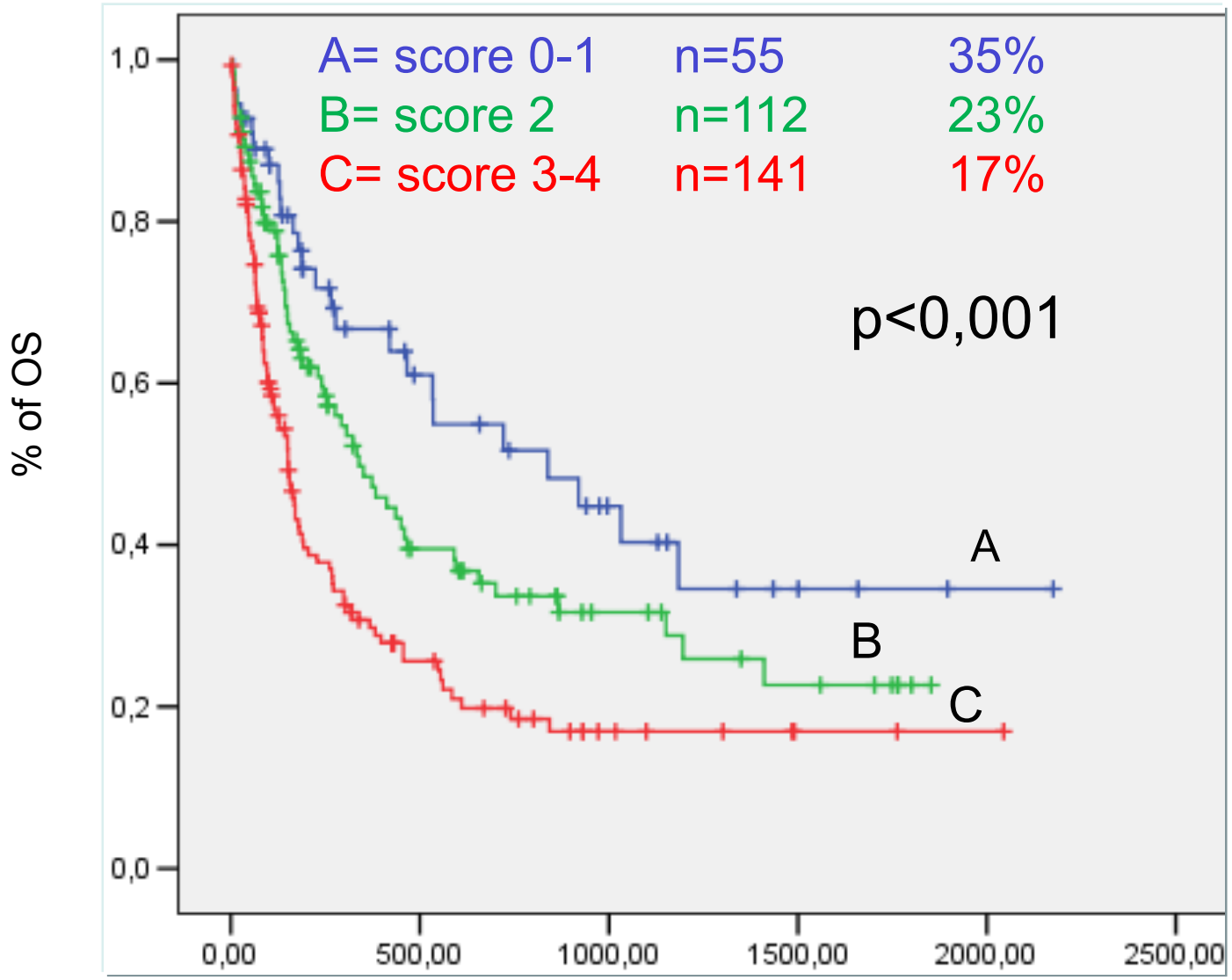
GITMO data : 5 yy OS according to risk score



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