CORSO EDUCAZIONALE GITMO

Controversie nel Trapianto di Cellule Staminali Emopoietiche

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

Trapianto Aploidentico T Repleto

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Università "Tor Vergata", Roma
Rome Transplant Network

Bari
Villa Romanazzi Carducci
6-7 Giugno 2017

RTN
Rome Transplant Network

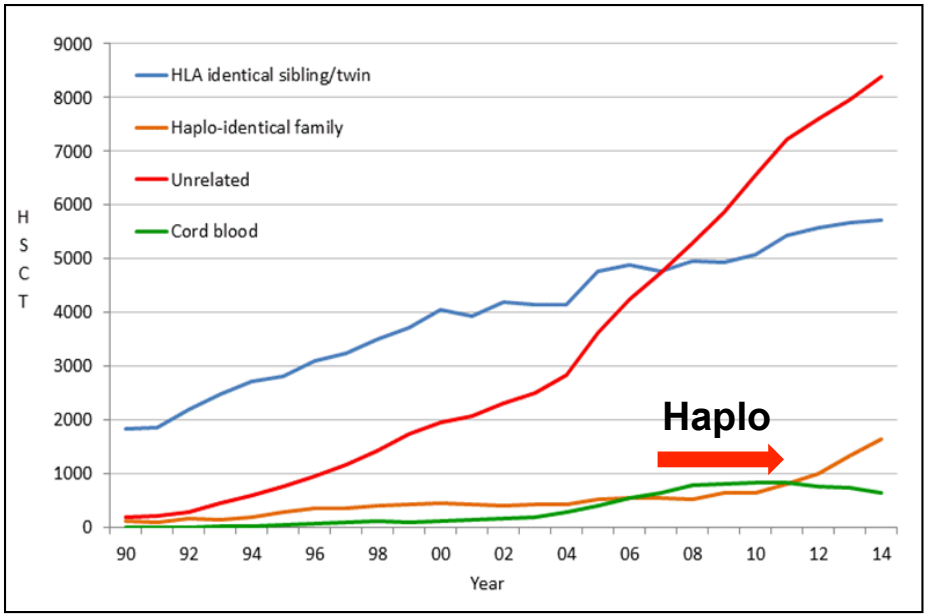
T cell Depleted or Unmanipulated Haploidentical Transplant

Similarities, Main Differences and Open Questions

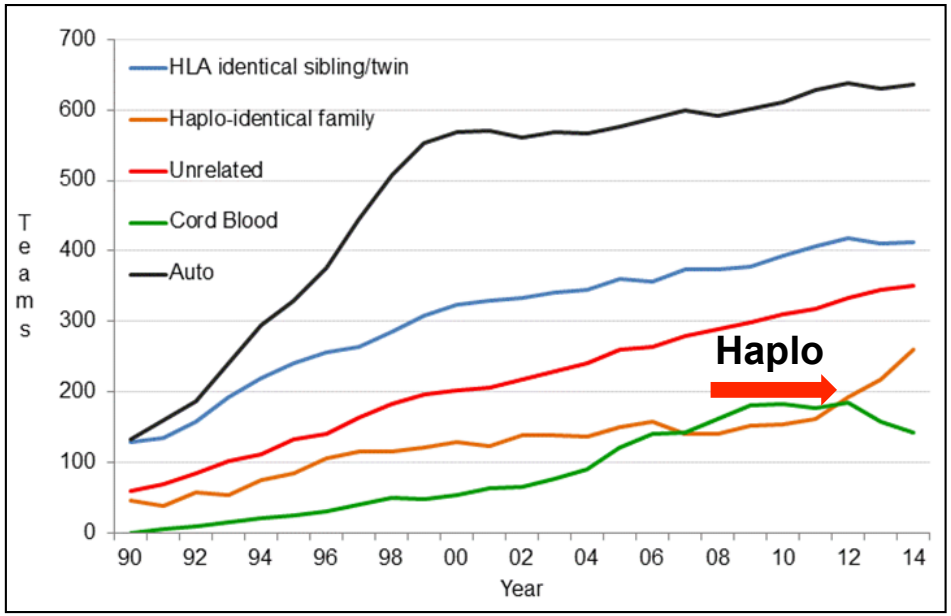
	T Cell Depleted	Unmanipulated
AML	effective	effective
ALL	effective (ped.)	undefined
Other Malignancies	undefined	undefined
Patient Follow-up	shorter	longer
NK Alloreactivity	confirmed	undefined
RIC Regimen	unproven	feasible
Lab. Facilities/Expertise	highly required	not required
Cost	high	standard
Feasibility	limited	widely

25% increase in Haplo SCT in 2014 in comparison to 2013

No. of Transplants



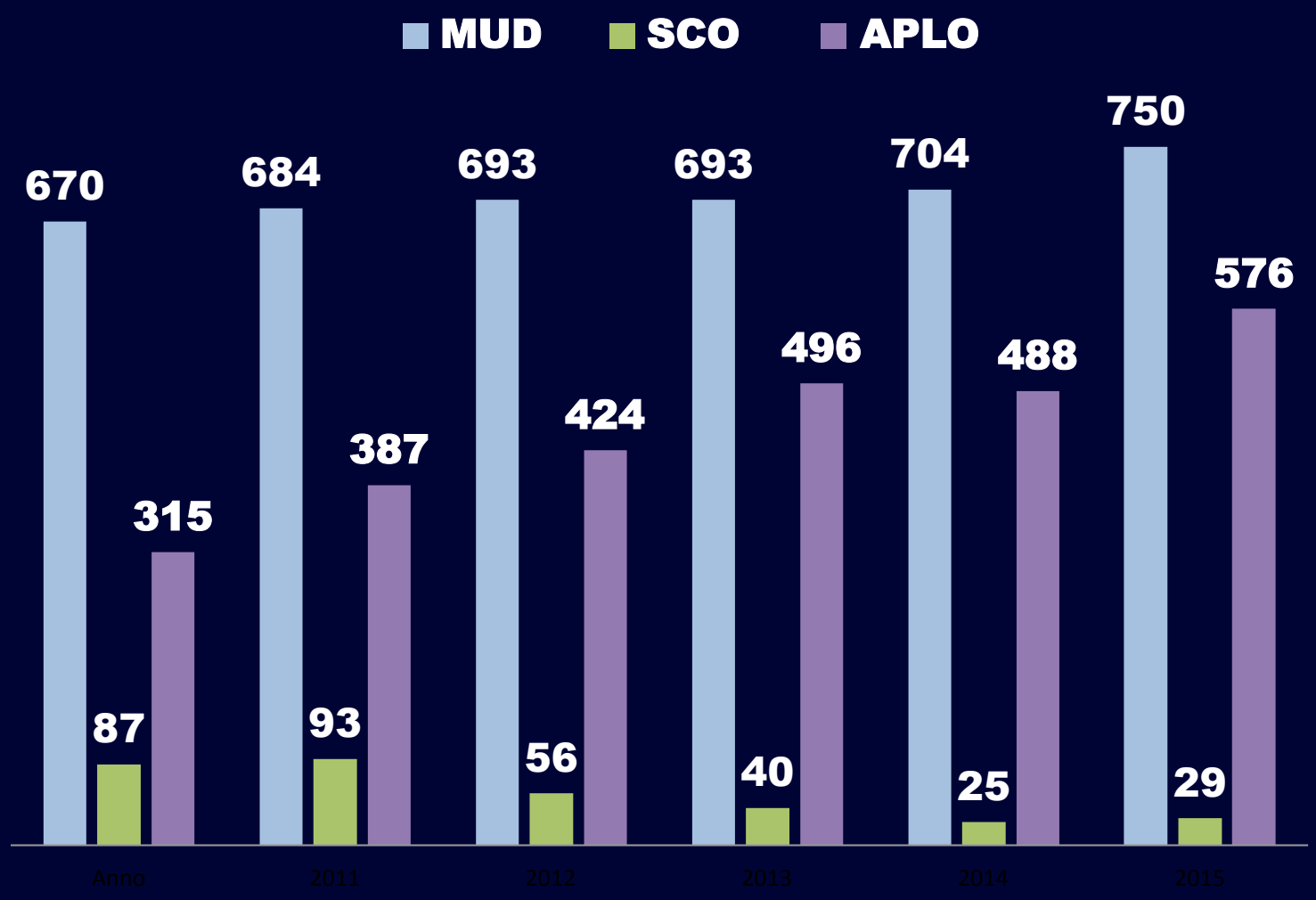
No. of Teams



- 40,829 SCT; 15,765 alloSCT (43%); 20,704 autoSCT (57%)
- Compared to 2013 – 13% increase in alloSCT for AML CR1
- Main indication for SCT is Leukemias: 11,853 (33% of total, 96% allo)

Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. *Passweg JR et al, BMT* March 2017

Numero Trapianti da Donatore Alternativo



Congresso Nazionale GITMO
Milano 4-5 Maggio 2017

Haploidentical Transplantation

T- cell depleted

Unmanipulated

Which method?

?

Which protocol?

Laboratory Potential, Expertise and Transpl. Policy of each Center significantly will affect the choice of the haploidentical transplant procedure

Unmanipulated Haploidentical Transplant

MAC and RIC Regimens

John Hopkins Hospital, **Baltimore**

San Martino Hospital, **Genova**

San Raffaele Scientific Institute, **Milano**

Chinese Transplant Group, **Benijin**

RomeTransplant Network and Pescara Hospital, **Rome-Pescara**

John Hopkins Hospital, Baltimore

	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6
CTX14.5 mg/kg	X	X											
Fludara 30 mg/m²	X	X	X	X	X								
TBI 200cGy						X							
Haplo-Bone Marrow							**X**						
CTX 50 mg/kg										X	X		
Tacrolimus 1mg/kg												X	→
MMF15mg/kg/12 H												X	→
G-CSF								X	→	→	→	→	→

San Martino Hospital, Genova

	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6
Thiotepa 5 mg/kg	X	X											
Busulfan 3.2 mg /m²			X	X	X								
Fludara 50 mg/m²			X	X	X								
Haplo-Bone Marrow							X						
CTX 50 mg/kg										X		X	
MESNA 80% of CTX										X		X	
Cyclosporine 1mg/kg							X	→	→	→	→	→	→
MMF 15mg/kg/12 H								X	→	→	→	→	→
PEG G-CSF 6mg												X	

San Raffaele Scientific Institute, Milano

	-6	-5	-4	-3	-2	-1	0	+3	+4	+5
Treosulfan 14 g/m²	X	X	X							
Thiotepa 5 mg/kg				X	X					
Fludara 30 mg/m²	X	X	X	X	X					
Haplo-PBSC							X			
Cyclophosphamide 50 mg/kg								X	X	
Rapamycin										X →
MMF										X →

Chinese Transplant Group, Benijin

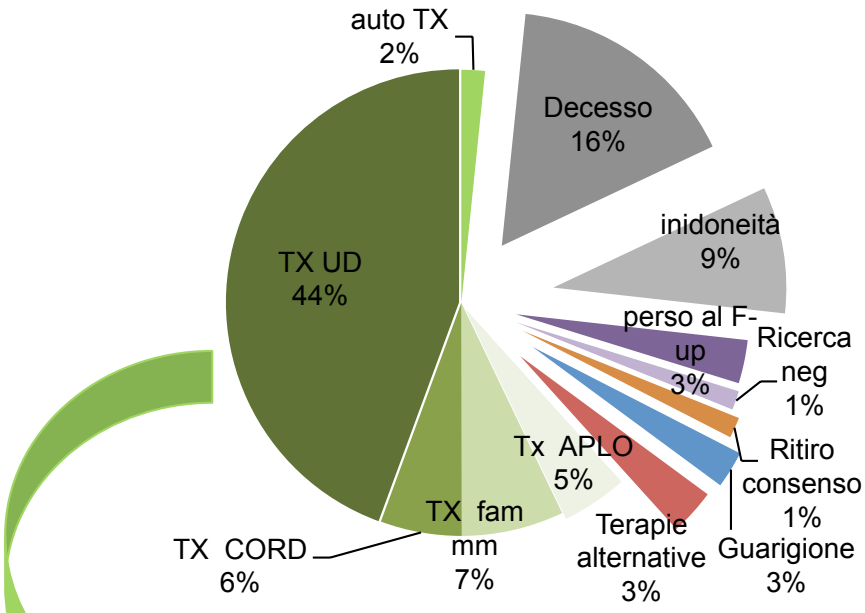
	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6
ARA-C 4 g/m²	X	X															
BU 12 mg/Kg/os			X	X	X												
CTX 1.8 gr/m²						X	X										
Me-CCNU 250 mg/ m²								X									
ATG						X	X	X	X								
Haplo G-CSF BM											X						
Haplo G-CSF PB												X	X				
MTX 15-10 mg/m²												X		X			X
CSA 2.5 mg/kg		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
MMF 0.5 gr		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
G-CSF 5 mcg/Kg					X	→	→	→	→	→	→	→	→	→	→	→	→

RTN and Pescara Hospital, Rome-Pescara

	-7	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7
Thiotepa 5 mg/kg		X	X												
Busulfan 3.2 mg/m²				X	X	X									
Fludara 50 mg/m²				X	X	X									
ATG 0 mg/Kg				X	X	X	X								
Haplo- G-CSF Primed Bone Marrow								X							
MTX 15-10 mg/m²									X		X			X	
Cyclosporine 1.5-3 mg/kg	X 1.5	→	→	→	→	→	X 3	→	→	→	→	→	→	→	→
MMF 15mg/kg/day															X
Basiliximab 20 mg								X				X			

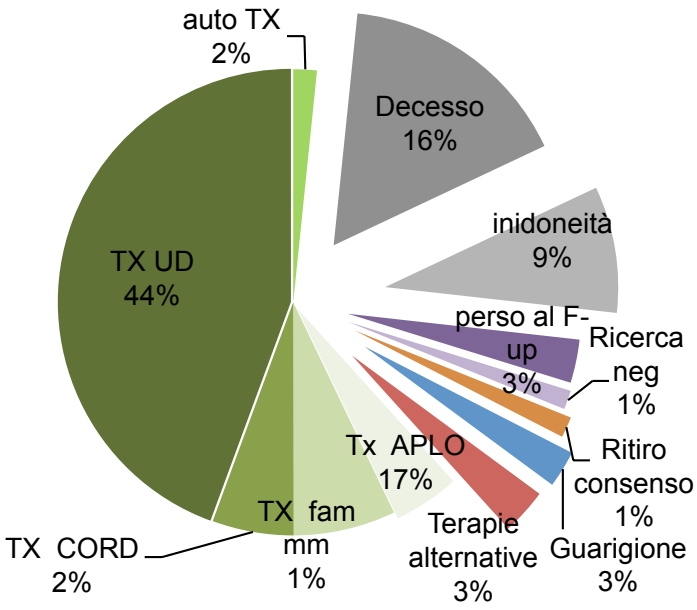
Esito delle ricerche concluse

2012



64%

2016



65%

Main Open Questions Today:

- are the results of transplant from HLA identical siblings comparable with those from alternative donors ?
- are these results specifically related to a single disease ?
- is still HLA compatibility the first criterion for the donor choice ?
- are other factors competitive with HLA in influencing the choice of the donor ?

In summary

who is the best donor for a candidate to an allogeneic transplant ?

Overview

blood advances

Related haploidentical donors are a better choice than matched unrelated donors: Point

E.J. Fuchs, 2017 1:397-400

Related haplo vs HLA-matched unrelated donors Logistical Comparison

	MUD	Haplo
Donor availability	20%-80%	>95%
Time to graft acquisition	Slower	Faster
Time between collection and infusion	Longer	Shorter
Ease of repeat donations	Harder	Easier

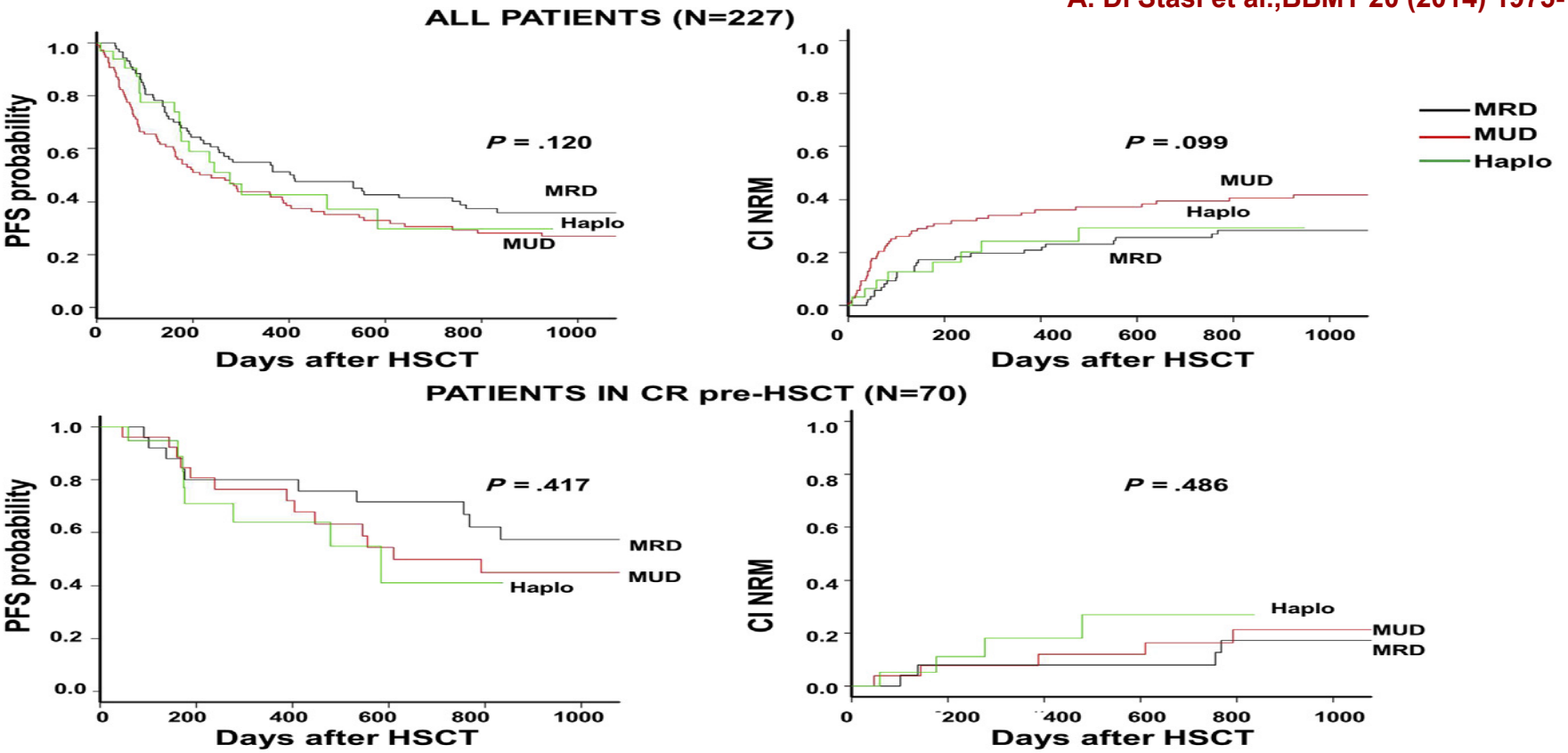
Similar Transplantation Outcomes for Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients with Haploidentical versus 10/10 Human Leukocyte Antigen-Matched Unrelated and Related Donors

MRD (n=87) vs MUD (n=108) vs Haplo (n=32)

A. Di Stasi et al.,BBMT 20 (2014) 1975-1981

Similar Transplantation Outcomes for Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients with Haploidentical versus 10/10 Human Leukocyte Antigen-Matched Unrelatedand Related Donors

A. Di Stasi et al.,BBMT 20 (2014) 1975-1981

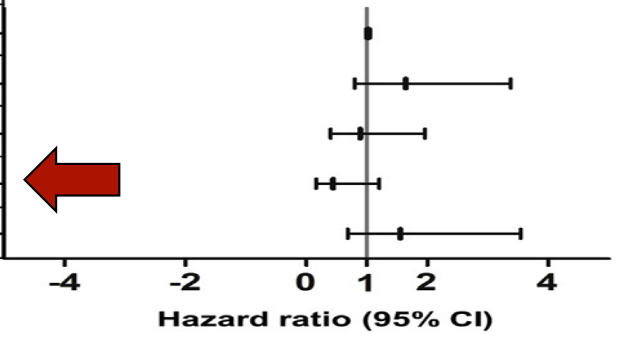


PATIENTS IN CR pre-HSCT (N=70)

Multivariable analysis for Progression free Survival

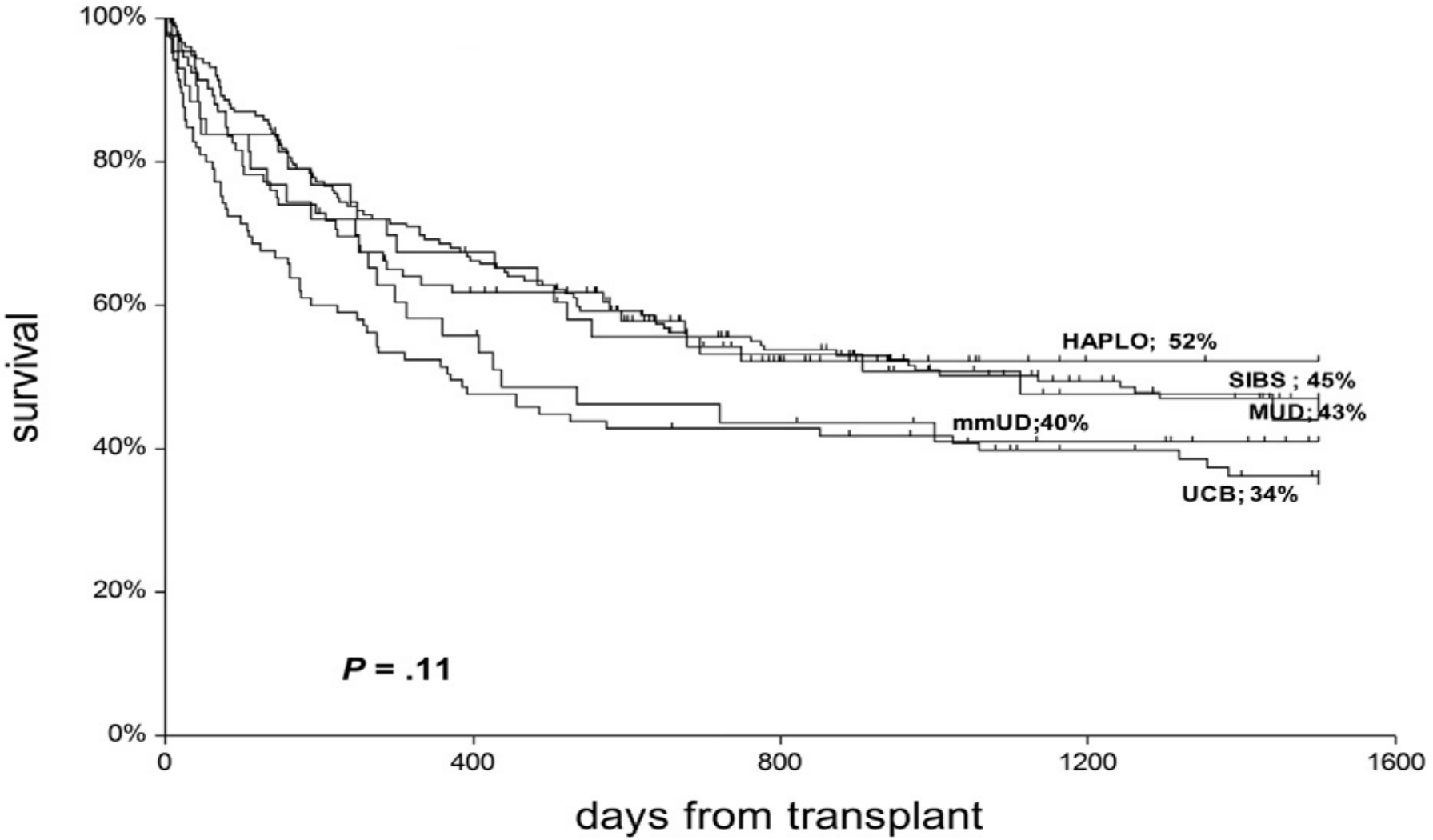
Effect	Hazard Ratio	*95% CI*	p-value
Age[a]	1.02	*0.99, 1.05*	.301
Cytogenetic (Poor vs. good+intermediate)	1.64	*0.80, 3.38*	.179
Melfalan dose (140 vs. 100)	0.89	*0.40, 1.96*	.771
Donor type (Matched vs. Haplo)	0.44	*0.16, 1.20*	.109
HCT-CI (> 3 vs. ≤ 3)	1.55	*0.68, 3.54*	.303

[a]: *age is continuous in the model*



Unmanipulated Haploidentical Transplants Compared with Other Alternative Donors and Matched Sibling Grafts

	SIB=176	MUD=43	mmUD=43	UCB=105	HAPLO=92
Acute Leukemia	85	19	19	70	39
	48%	43%	43%	66%	43%



A.M. Raiola et al., BBMT20 (2014) 1573e1579

Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia

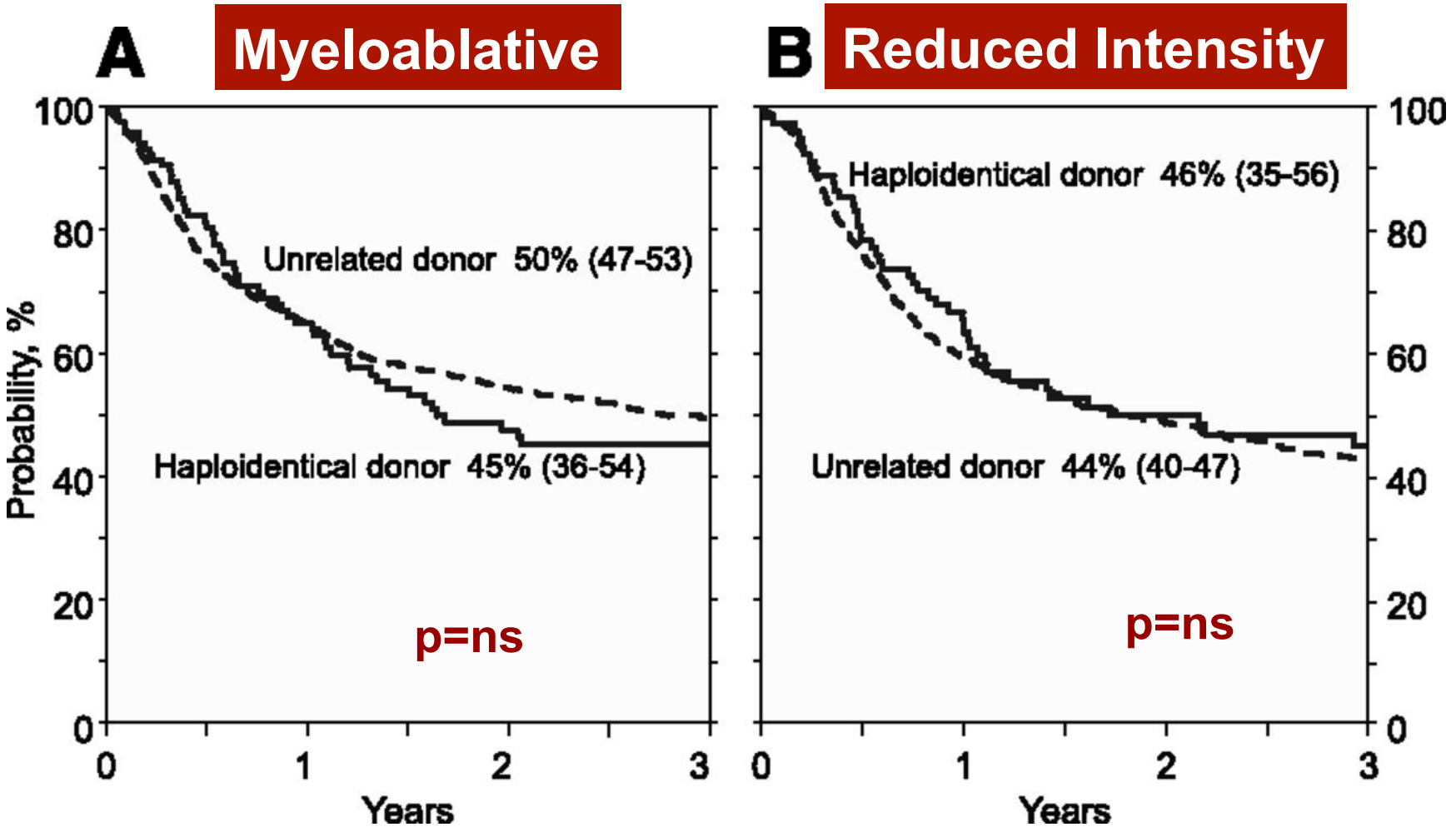
by Stefan O. Ciurea, Mei-Jie Zhang, Andrea A. Bacigalupo, Asad Bashey, Frederick R. Appelbaum, Omar S. Aljitawi, Philippe Armand, Joseph H. Antin, Junfang Chen, Steven M. Devine, Daniel H. Fowler, Leo Luznik, Ryotaro Nakamura, Paul V. O'Donnell, Miguel-Angel Perales, Sai Ravi Pingali, David L. Porter, Marcie R. Riches, Olle T. H. Ringdén, Vanderson Rocha, Ravi Vij, Daniel J. Weisdorf, Richard E. Champlin, Mary M. Horowitz, Ephraim J. Fuchs, and Mary Eapen

Conditioning	Haploidentical	MUD	Total
Myeloablative	104	1245	1349
Reduced Intensity	88	737	825
Total	192	1982	2174

Blood Volume 126(8):1033-1040, August 20, 2015

blood

Overall survival

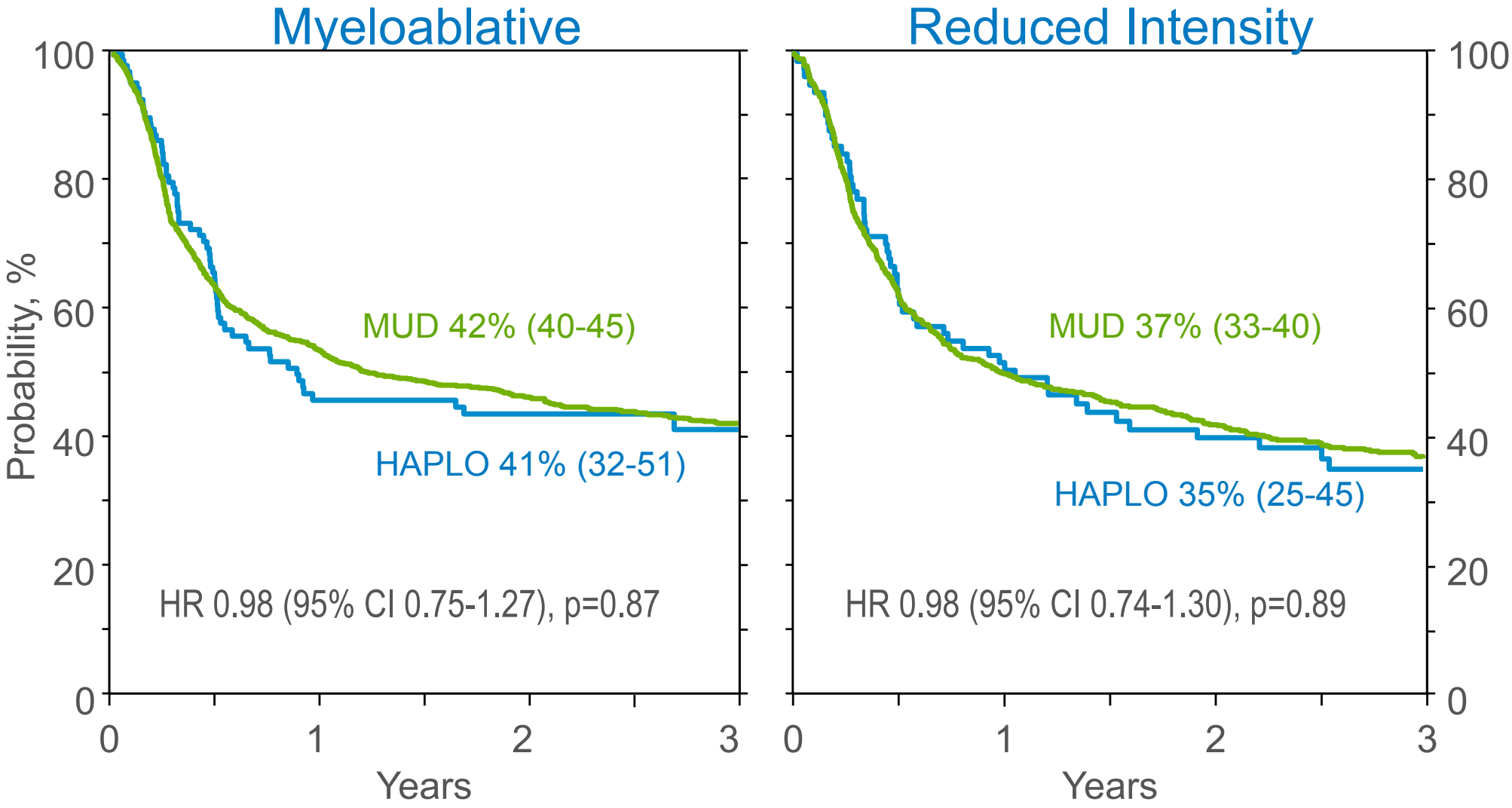


Stefan O. Ciurea et al. Blood 2015;126:1033-1040

blood

Leukemia Free Survival

Adjusted for DRI, performance score, secondary AML



Stefan O. Ciurea, Ephraim Fuchs, Mary Eapen et al Blood 2015

Haplo vs MUD, Haplo vs MMUD:
Cohort Study on the EBMT Registry

Inclusion criteria:

- Adult patients with de novo AL
- 1st allogeneic transplant (previous auto-SCT allowed)
- Mismatched Related Donor (mm >=2) or Matched Unrelated Donor(9/10 0r 10/10)
- Stem Cell Source: BM and/or PB
- Year 2007 to 2012

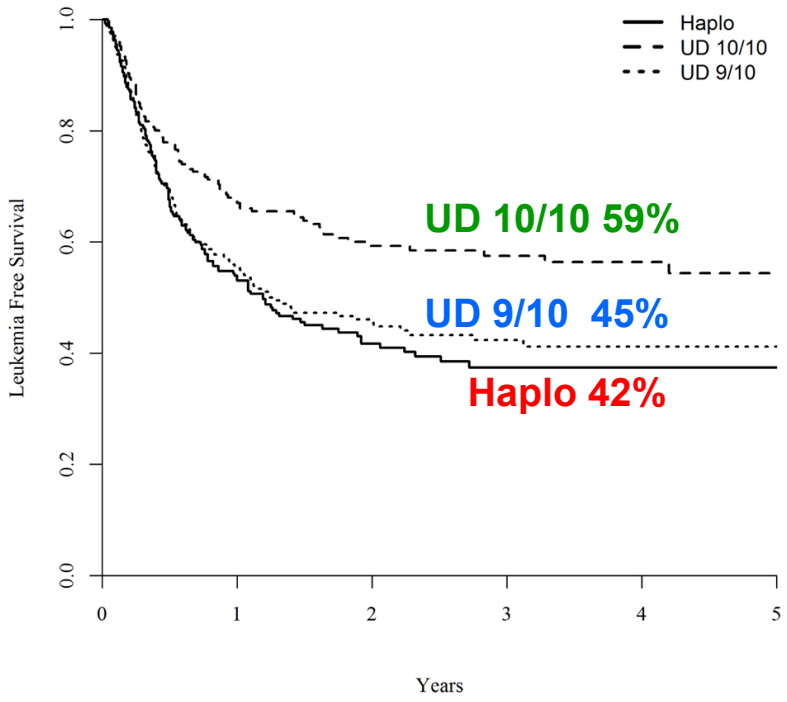
Pair-matching factors:

- Patient age +/- 5y
- AL diagnosis
- Disease Status at transplant
- Time from diagnosis to transplant +/- 1mo

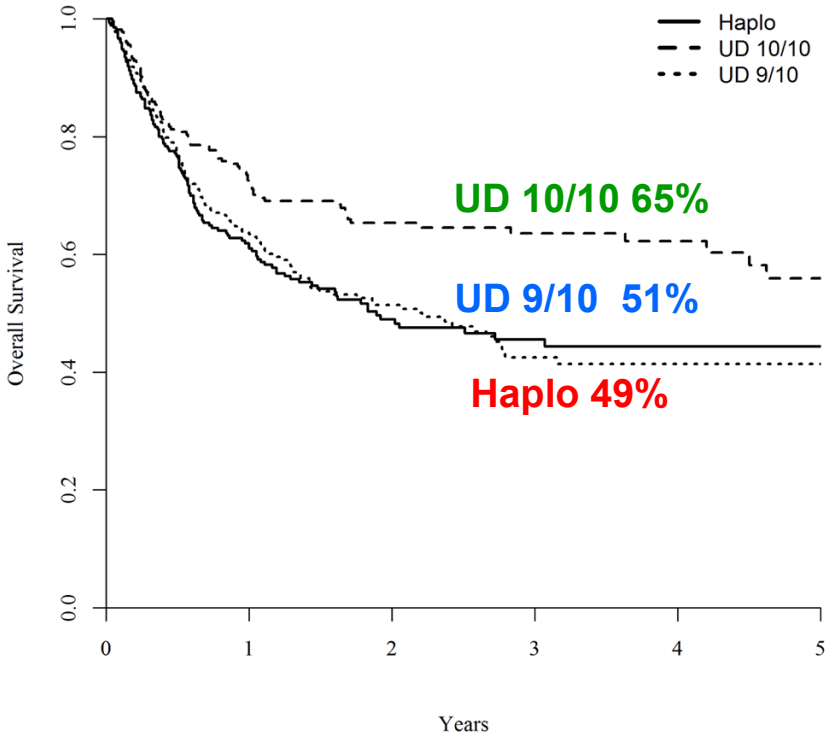
Haplo	MUD 10/10	MMUD 9/10
273	273	273

Piemontese S et al.(submitted)

Haplo vs MUD, Haplo vs MMUD:
Cox Results for LFS and OS



Mud 10/10 vs Haplo p=0,001 HR 0,61 CI: 0,45 0,81
Mud 9/10 vs Haplo p=0,45 HR 0,91 CI: 0,70 1,17



Mud 10/10 vs Haplo p=0,004 HR 0,63 CI: 0,46 0,86
Mud 9/10 vs Haplo p=0,84 HR 0,97 CI: 0,74 1,28

Piemontese S et al.(submitted)

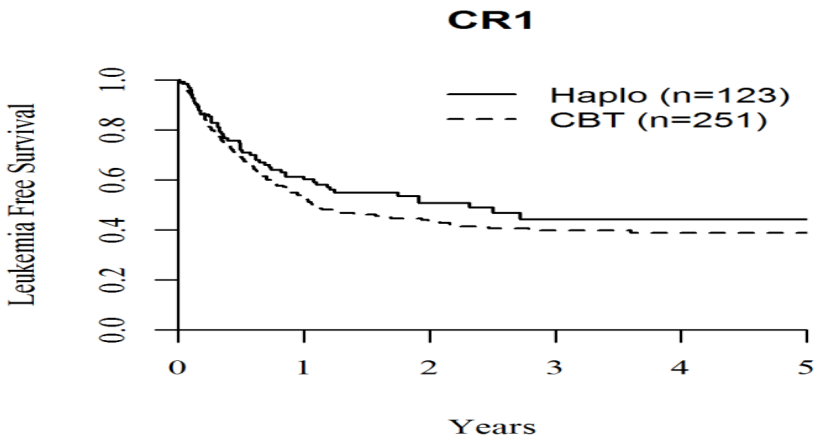
Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia

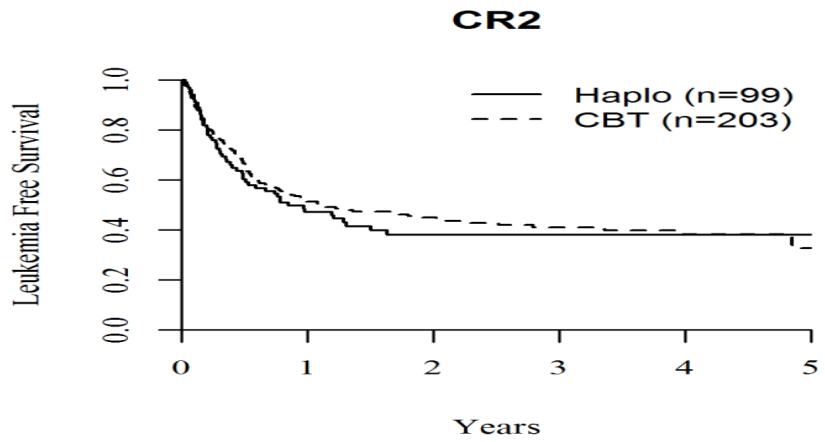
A Ruggeri, M Labopin, G Sanz, S Piemontese, W Arcese, A Bacigalupo, D Blaise, A Bosi, H Huang, D Karakasis, Y Koc, M Michallet, A Picardi, J Sanz, S Santarone, H Sengelov, J Sierra, L Vincent, F Volt, A Nagler, E Gluckman, F Ciceri, V Rocha and M Mohty on behalf of Eurocord, Cord Blood Committee of CTI-EBMT, ALWP-EBMT study

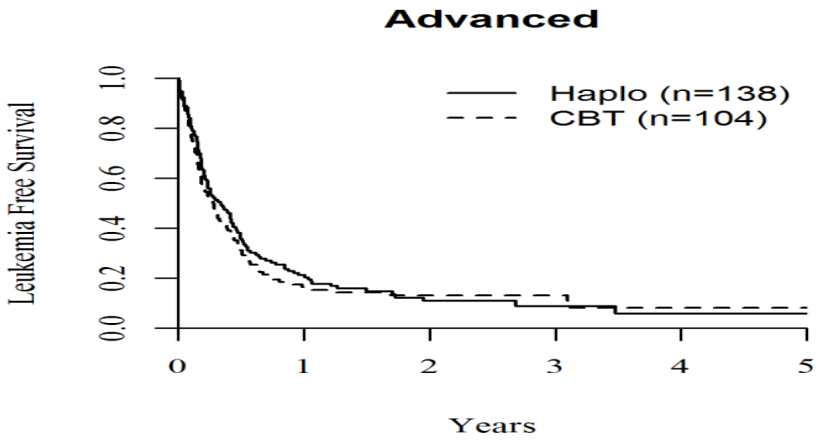
Leukemia. 2015 Sep;29(9):1891-900

Result- CBT vs Haplo for adult with AML
Leukemia Free Survival by Disease Status

AML, n=918	
Haplo; n=360	CB; n=558

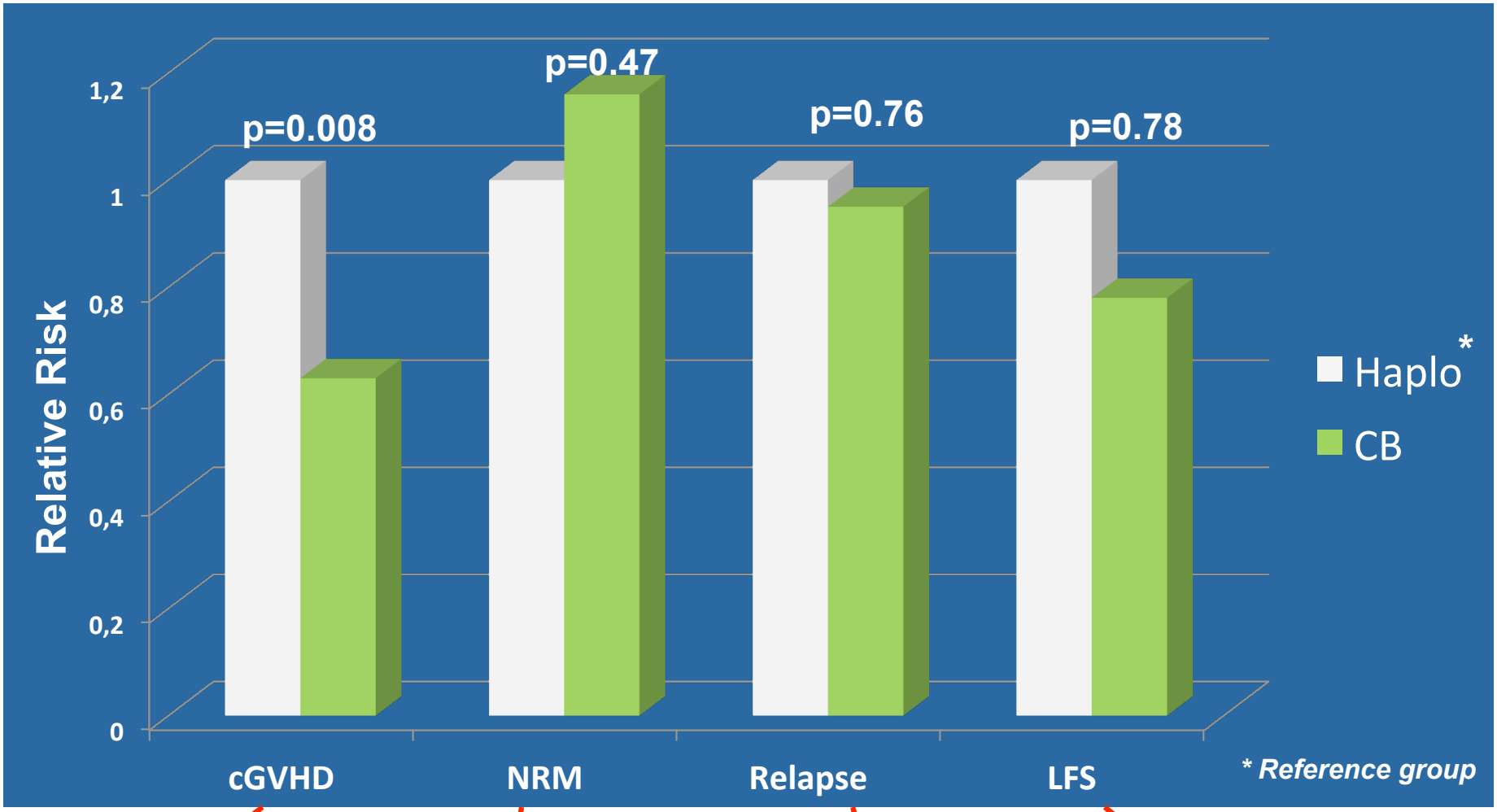






Ruggeri A. et al., Leukemia. 2015 Sep;29(9):1891-900

UCBT versus Haplo -Multivariate Analysis- AML



ATG vs.NoATG
HR=0.78 p=0.11

Adv vs. CR1→ HR=1.95 p<0.001
RIC vs. MAC→ HR=0.72 p=0.03
ATG vs. NoATG→ HR=1.64 p<0.001

Adv vs. CR1→ HR=3.74 p<0.001
RIC vs. MAC→HR=1.37 p=0.01
Interv diagn to Tx→HR=0.99 p=0.02

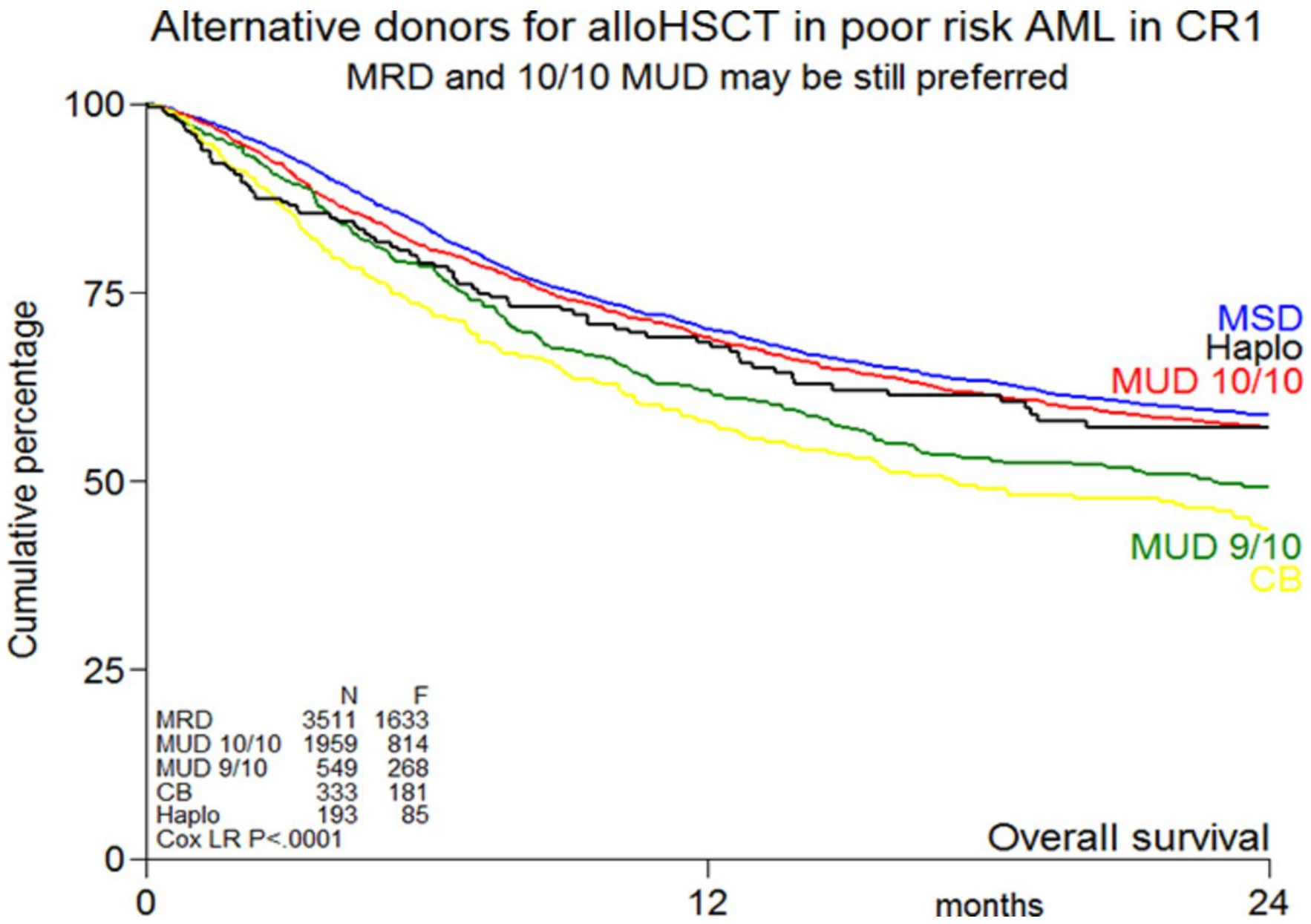
Adv vs. CR1→ HR=2.79 p<0.001
ATG vs.NoATG→ HR=1.19 p=0.04

blood advances™

Alternative donors for allogeneic hematopoietic stem cell transplantation in poor-risk AML in CR1

Jurjen Versluis, Myriam Labopin, Annalisa Ruggeri, Gerard Socie, Depei Wu, Liisa Volin, Didier Blaise, Noel Milpied, Charles Craddock, Ibrahim Yakoub Agha, Johan Maertens, Per Ljungman, Anne Huynh, Mauricette Michallet, Eric Deconinck, Patrice Chevallier, Jakob Passweg, Fabio Ciceri, Mohamad Mohty, Jan J. Cornelissenand Arnon Nagler on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT).

Blood Advances 2017 1:477-485



blood advances™

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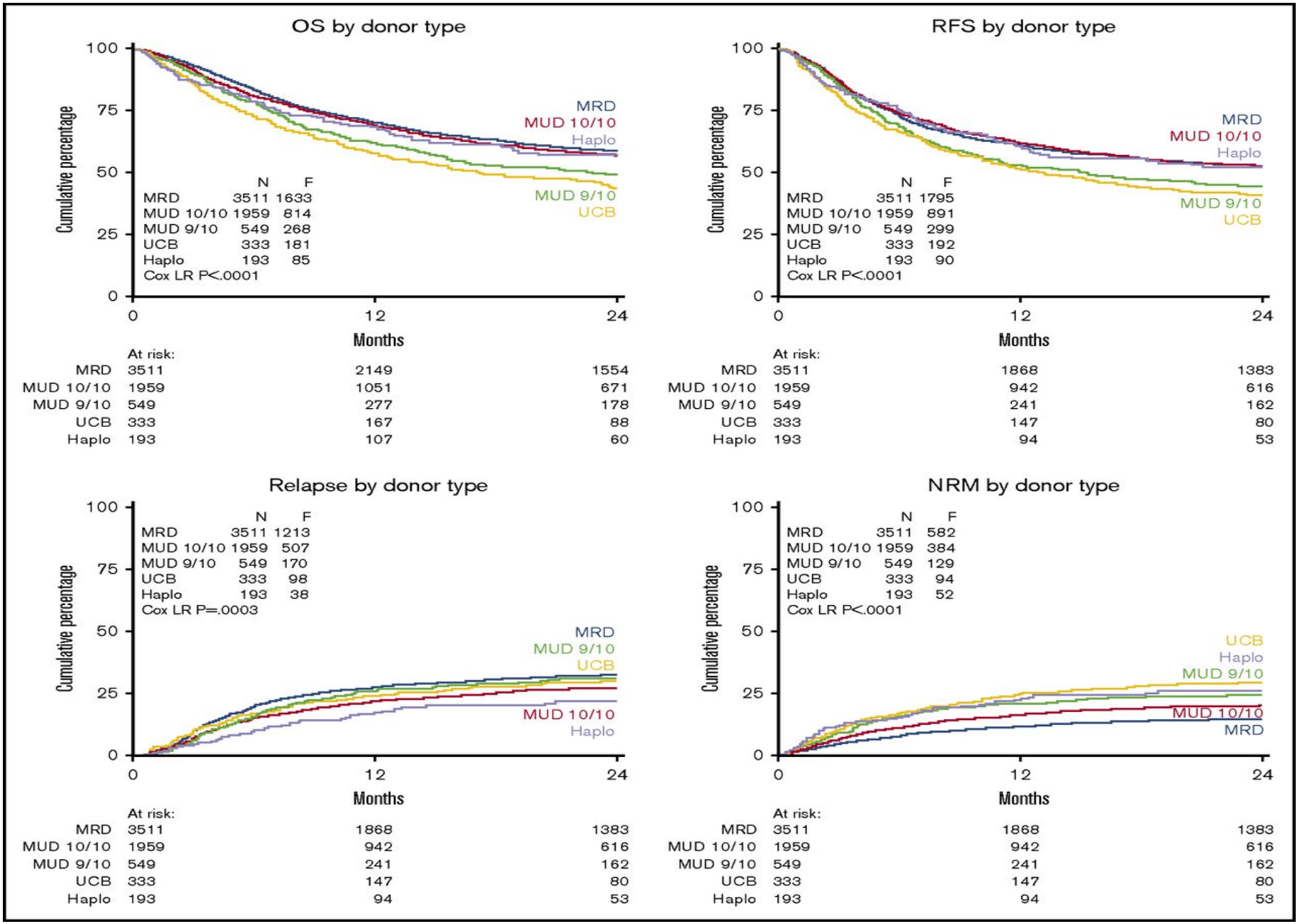
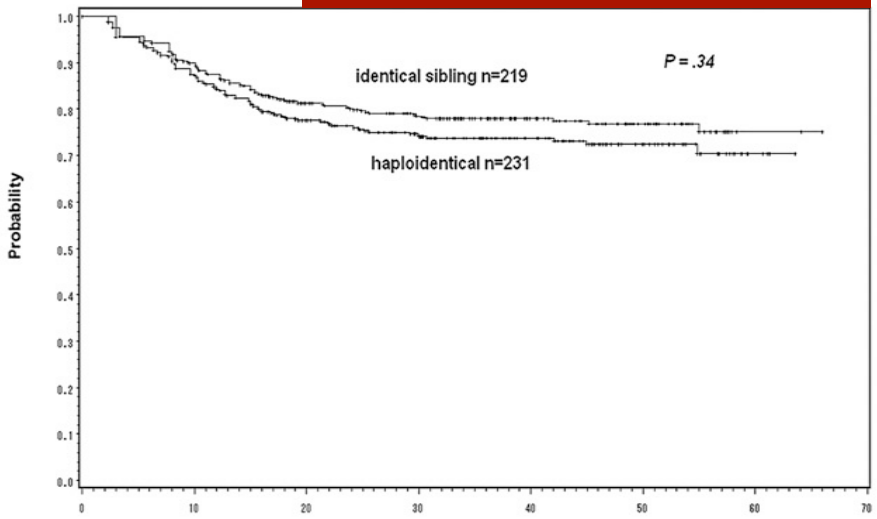


Haploidentical vs Identical-Sibling transplant for AML in remission: a multicenter, prospective study

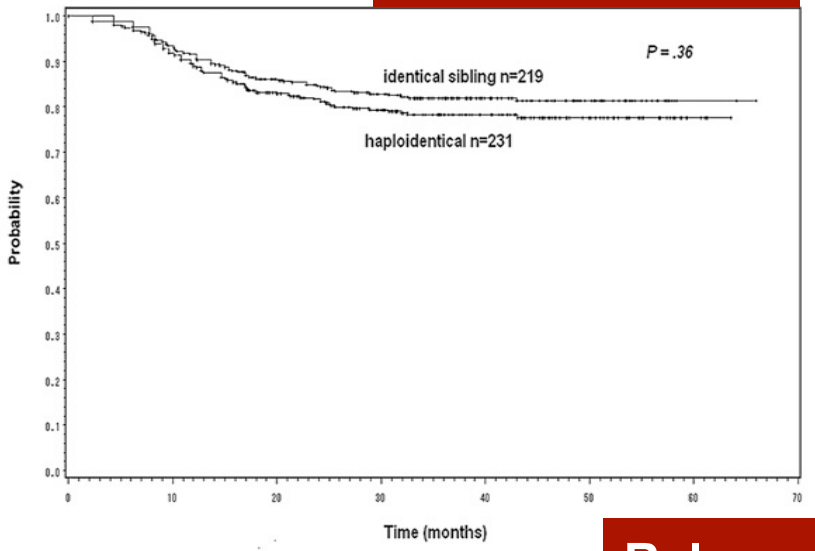
Ident.-Sib = 219
Haplo = 231

Yu Wang & Xiao-Jun Huang et al., Blood. 2015;125(25):3956-3962

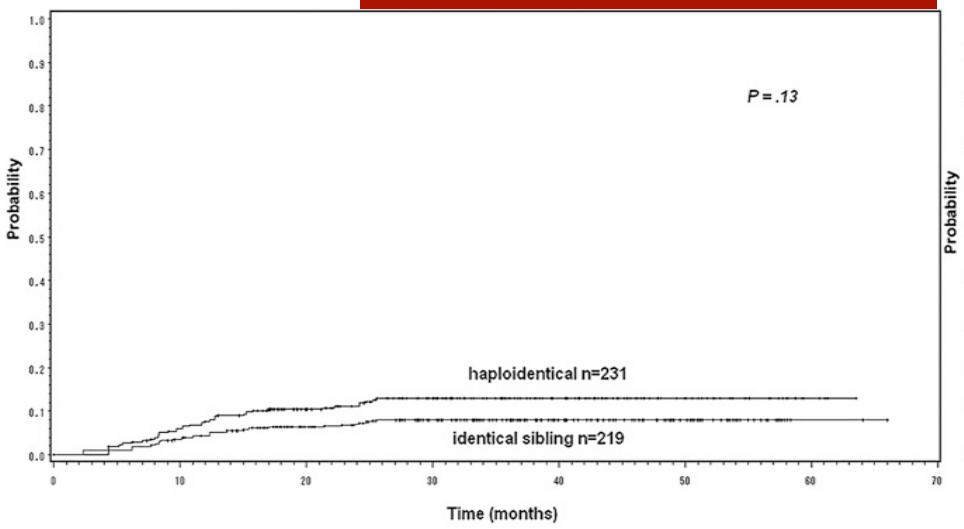
Disease Free Survival



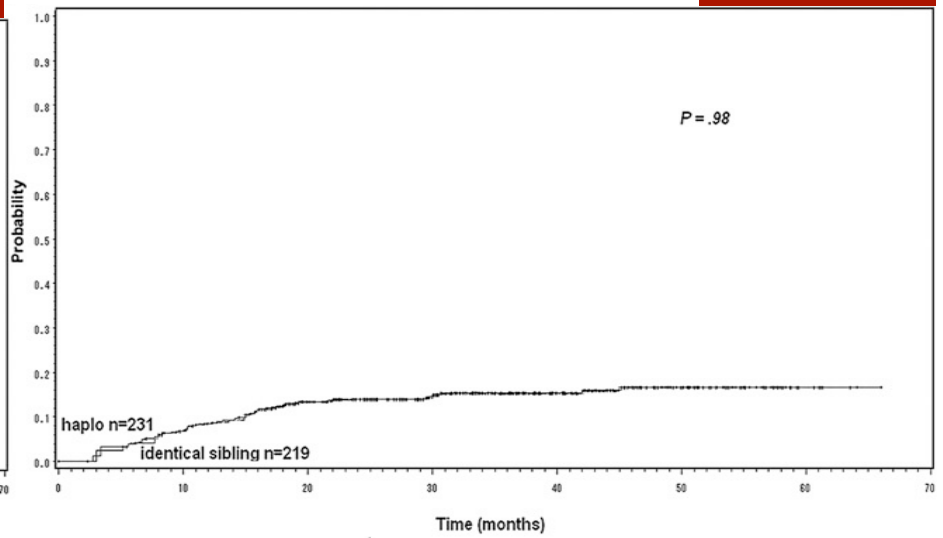
Overall Survival



Non Relapse Mortality



Relapse



Haploidentical vs Identical-Sibling transplant for AML in remission: a multicenter, prospective study

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Outcome	Hazard ratio (95% CI)	p
Non Relapse Mortality		
Identical sibling vs Haplo	0.58 (0.28-1.19)	0.14
Relapse		
Identical sibling vs Haplo	1.06 (0.58-1.92)	0.85
Disease Free Survival		
Identical sibling vs Haplo	0.83 (0.52-1.30)	0.42
Overall Survival		
Identical sibling vs Haplo	0.80 (0.47-1.37)	0.43

Rome Transplant Network

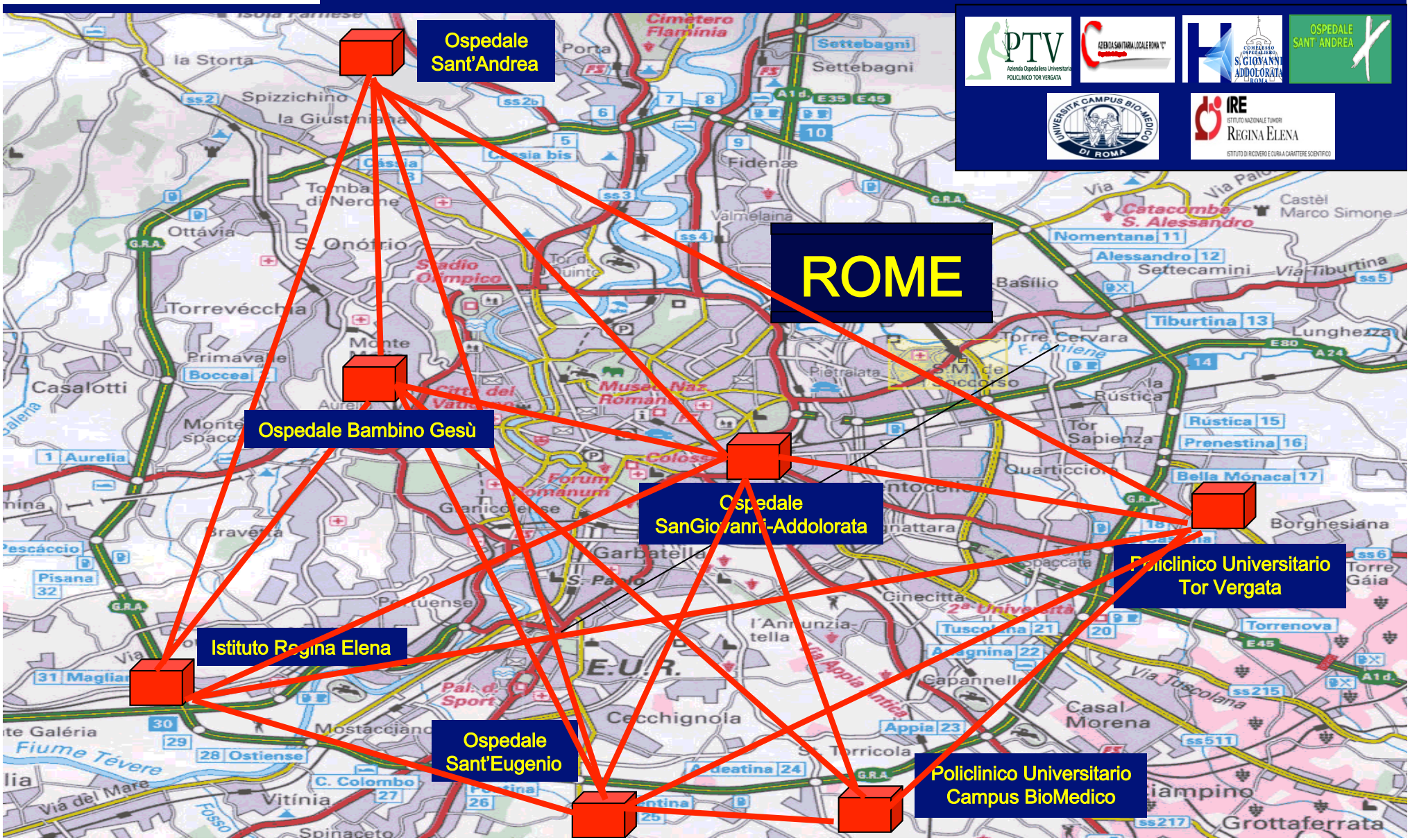
The RTN Transplant Policy

RTN
Rome Transplant Network

JACIE Metropolitan Transplant Program

RTN
Rome Transplant Network

Coordinator:
William Arcese
"Tor Vergata" University, Rome



Strategy and Policy of RTN for Allogeneic Transplantation

Summary

Patient Selection	Age ≥ 16 years < 70 years
Hierarchy of donor source	1st HLA Id. Sib. 2nd MUD 3rd CB 4th Haplo Transplant < 3 months for high-risk patients
Conditioning Regimen	TBF-MAC: ≤55 yrs and a SI ≤2 TBF-RIC : >55 yrs or ≤55 yrs with a SI >2
GVHD Prophylaxis	According to the donor source
Antinfectious Policy	Identical
Supportive Care	Identical
Transfusion Policy	Identical

RTN Rome Transplant Network

Identical Conditioning Regimen: TBF Protocol

RTN Rome Transplant Network

Myeloablative
≤55 yrs with a Sorror Index <2

MAC →

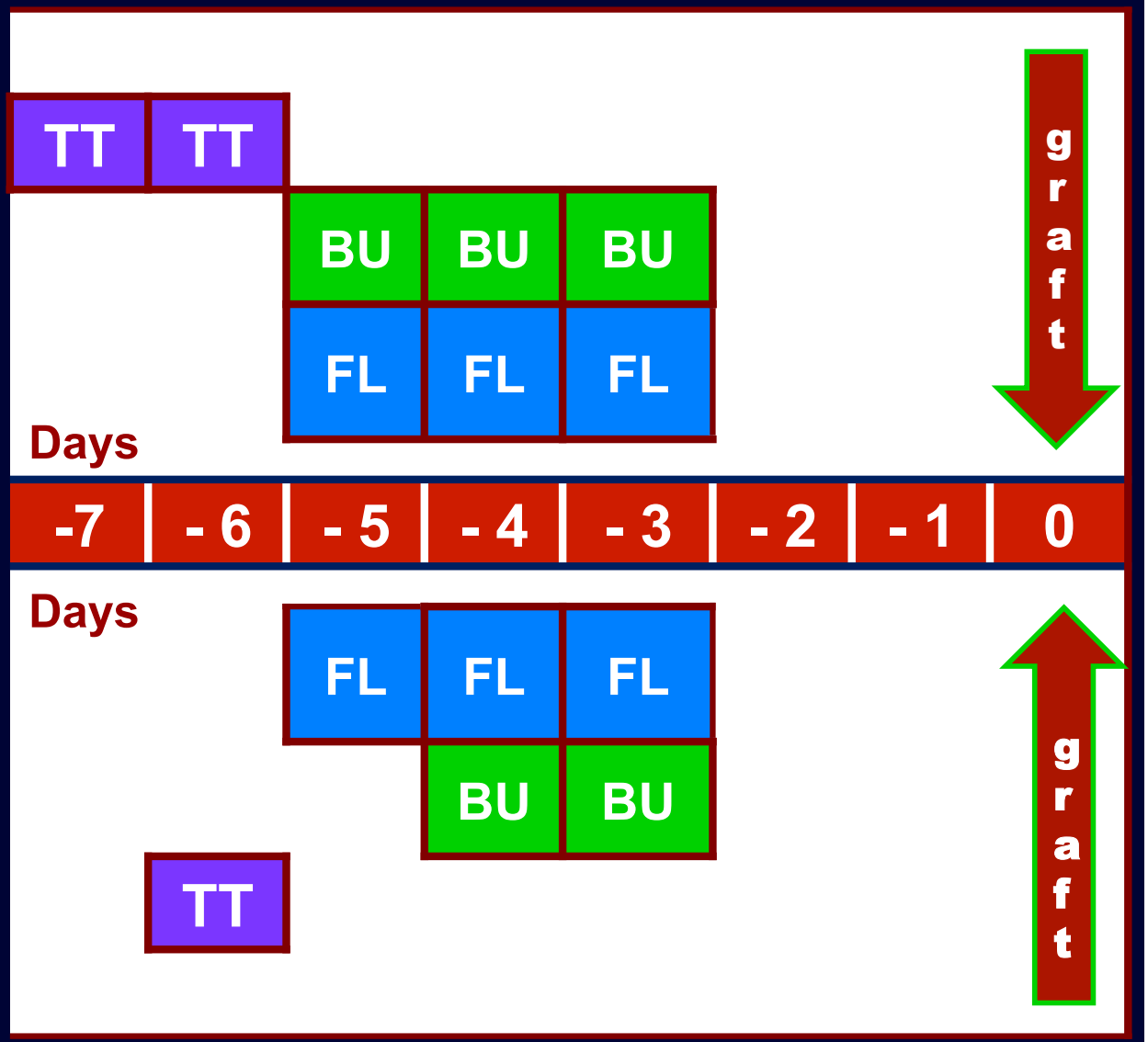
TT -Thiotepa 5 mg/kg

BU -Busilvex 3.2 mg/kg i.v.

FL -Fludarabine 50 mg/m²

RIC →

Reduced Intensity
>55 yrs or ≤ 55 yrs with a Sorror Index >2



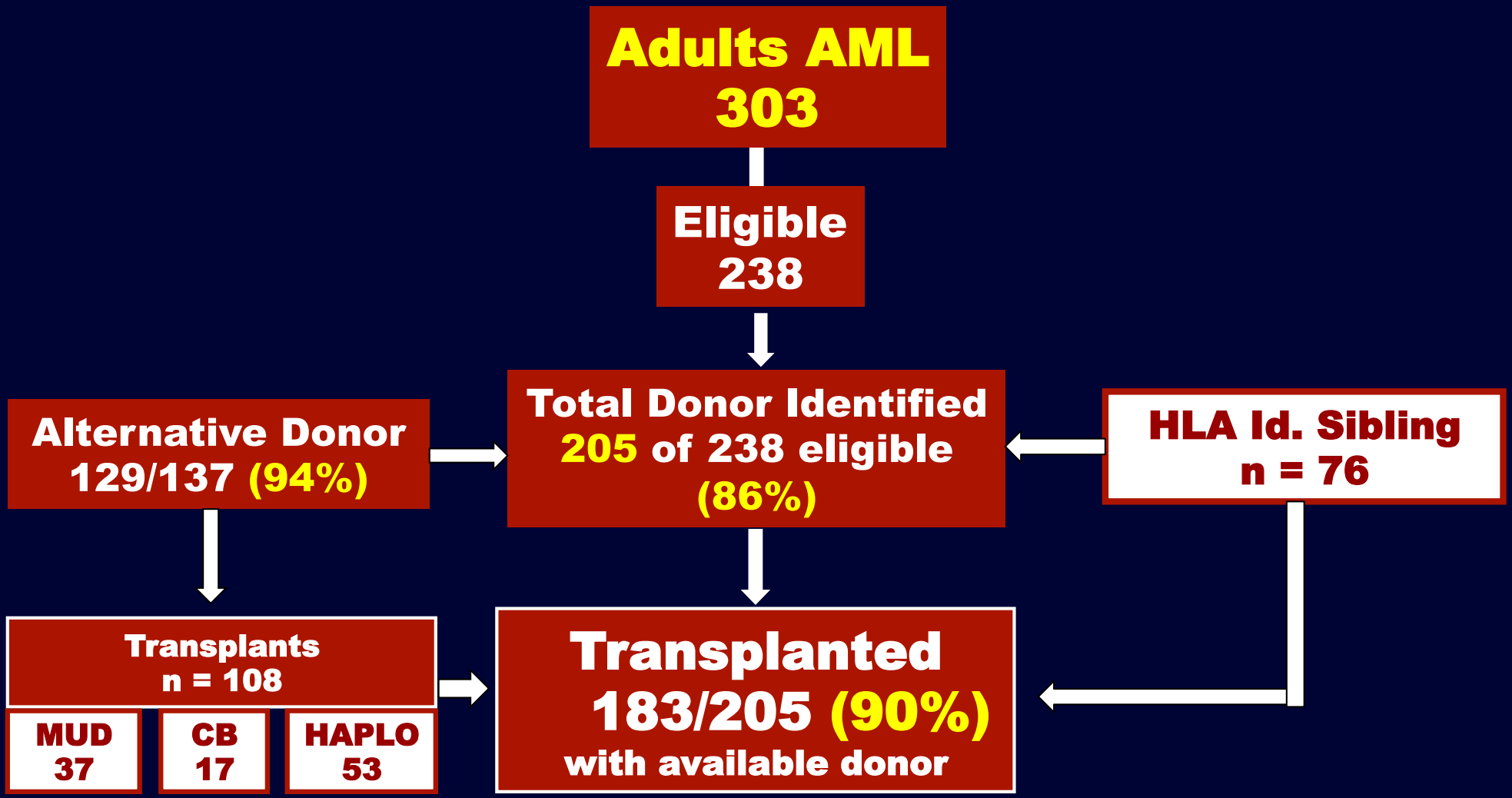
RTN
Rome Transplant Network

GVHD Prophylaxis

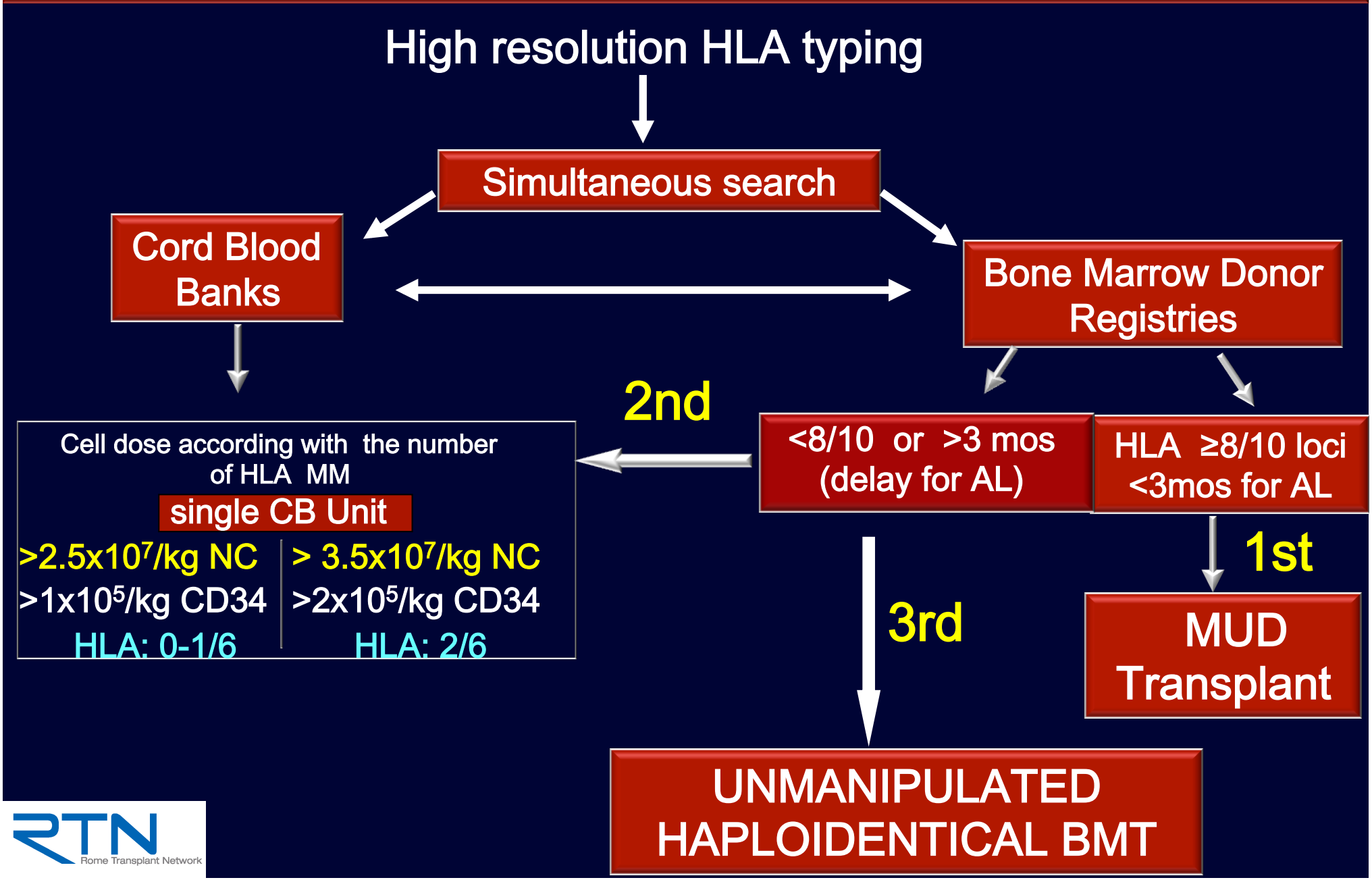
	Drugs	Dosage	days
SIBLING	Cyclosporine	1.5 mg/Kg i.v.	-7 to -2
		3 mg/Kg i.v.	-1 to +21
		6 mg/Kg os	+22 to +365
	Methotrexate	15 mg/m^2 i.v.	+1
		10 mg/m^2 i.v.	+3, +6,+11

ALGORITHM OF ALLOGENEIC TRANSPLANT IN AML

Candidates to HSCT 2006-2014
Total n=1037 - Adults n=747 – Adults AML n=303



Strategy for alternative stem cell donor search in adults with malignant disorders

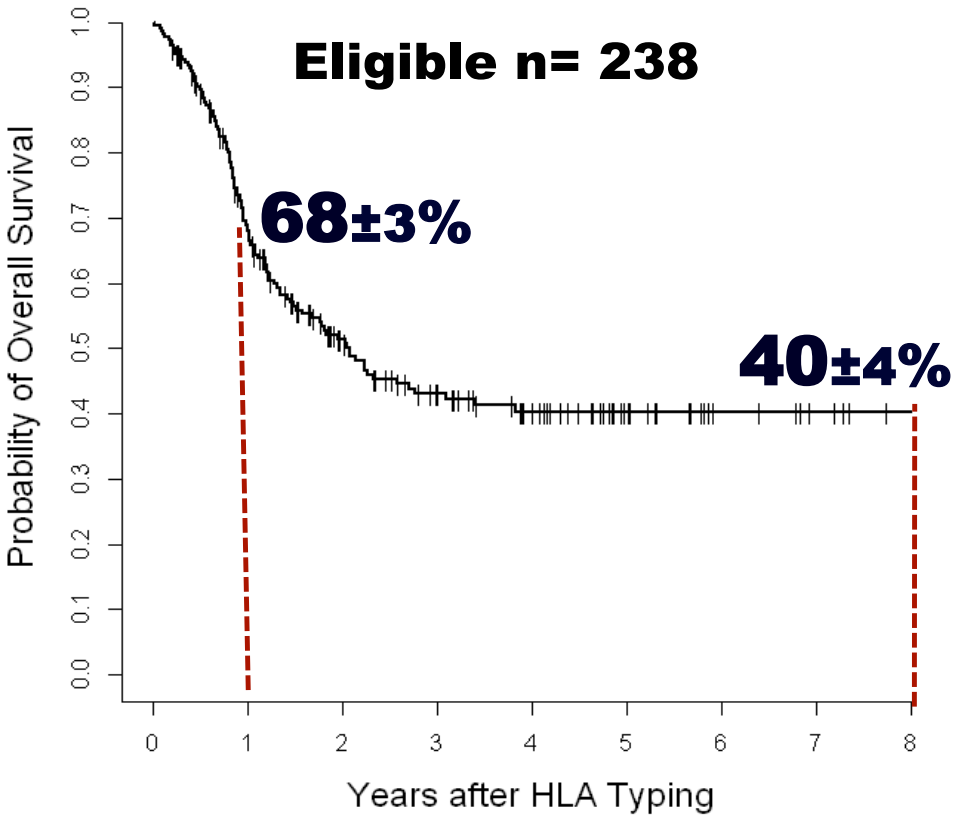


RTN Rome Transplant Network

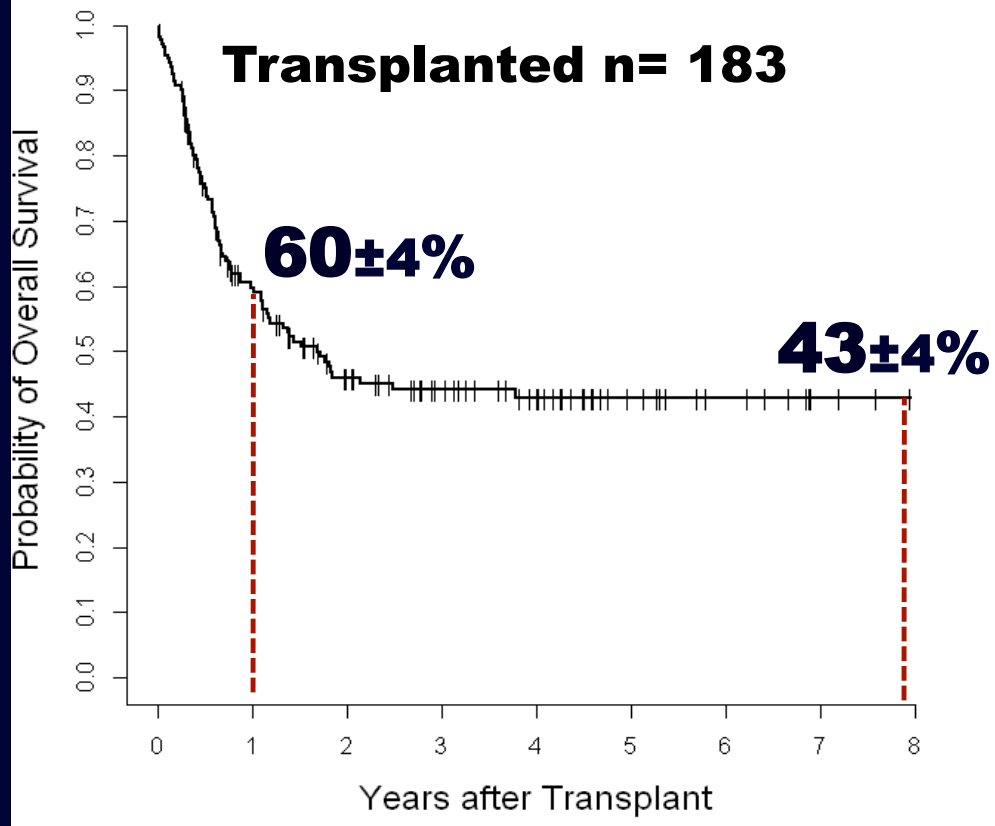
Allogeneic Transplants in Acute Myeloid Leukemia

Overall Survival
by Intention to Treat and Transplant

from HLA Typing



from Time of Transplant



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Rome Transplant Network

Allogeneic Transplants in Acute Myeloid Leukemia

Conclusions

RTN transplant policy provides donor identification for 86% of all eligible AML patients and an allogeneic transplant for 90% of all evaluable patients

Patient outcome evaluated by Intention to Treat (ITT) analysis is just alike to that of patients definitively transplanted

"Please, tell me first your general transplant policy and only afterwards give me your transplant results.

Then, I can understand ! "

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

Principali obiettivi dello studio:

1. Definizione dei criteri di selezione del donatore alternativo per ogni singola fonte di CSE.
2. Ricerca del miglior algoritmo di selezione oggi proponibile.
3. Valutazione dell'applicabilità trapiantologica all'intera popolazione di pazienti elegibili.
4. Analisi dei risultati secondo il criterio dell'intention-to-treat e per effettiva applicazione del trapianto.

La definizione di un algoritmo per la selezione del donatore è propedeutico al disegno di ogni futuro studio di comparazione tra le diverse fonti.

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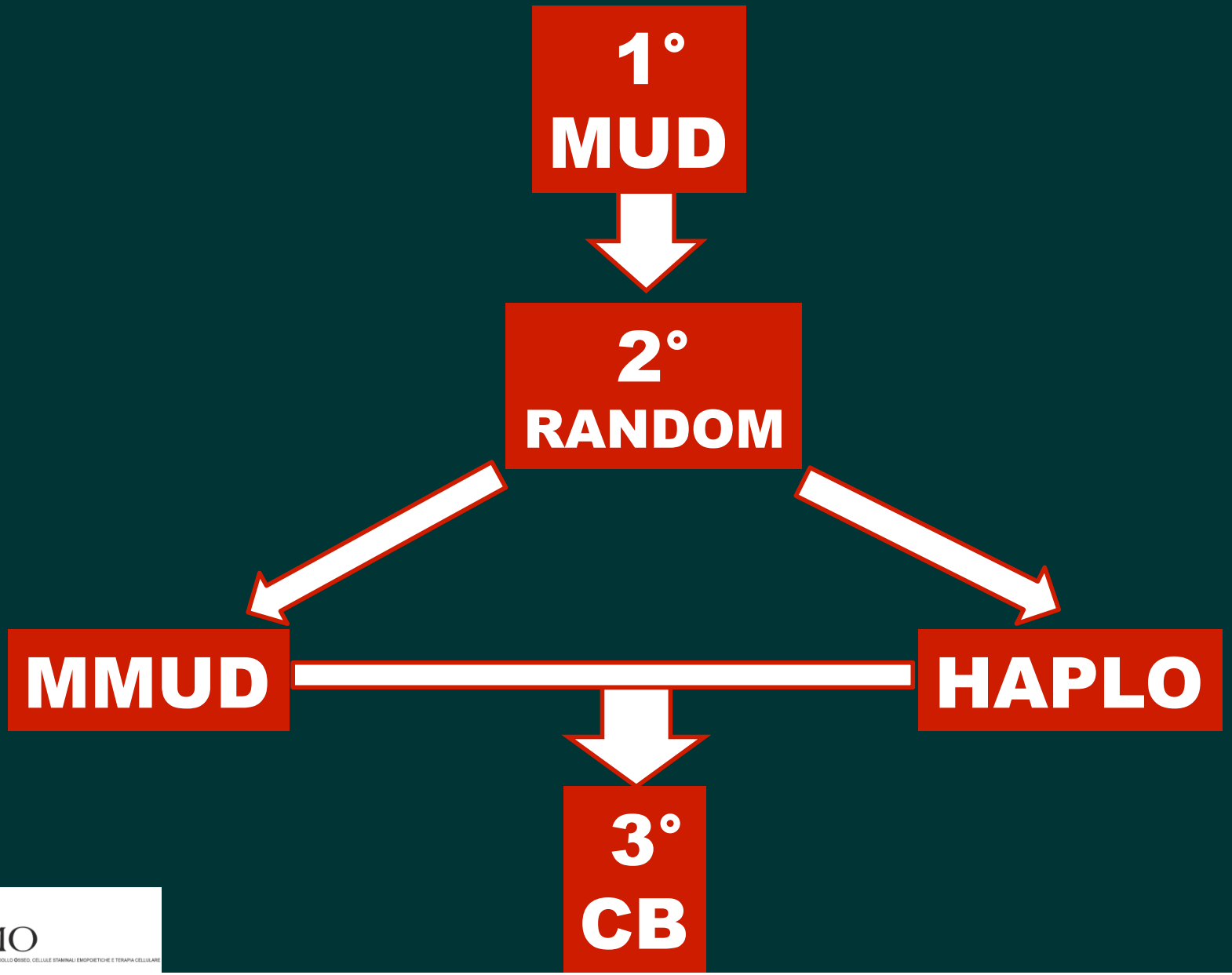
Studio prospettico per la ricerca del donatore alternativo secondo due sequenzialità algoritmiche



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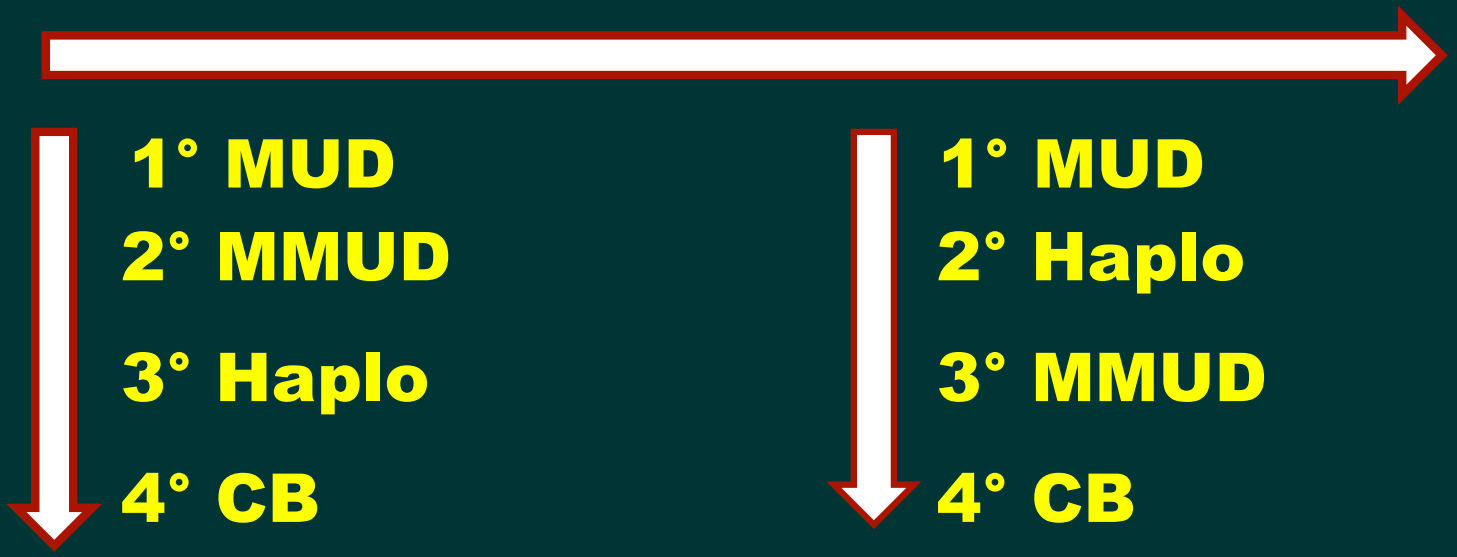
I risultati potranno essere analizzati per **intention-to-treat** e per **trapianto effettivamente eseguito**, sia in senso **verticale**, globalmente e secondo i due algoritmi di appartenenza, sia in senso **orizzontale** secondo le diverse fonti di donatore selezionato.



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