

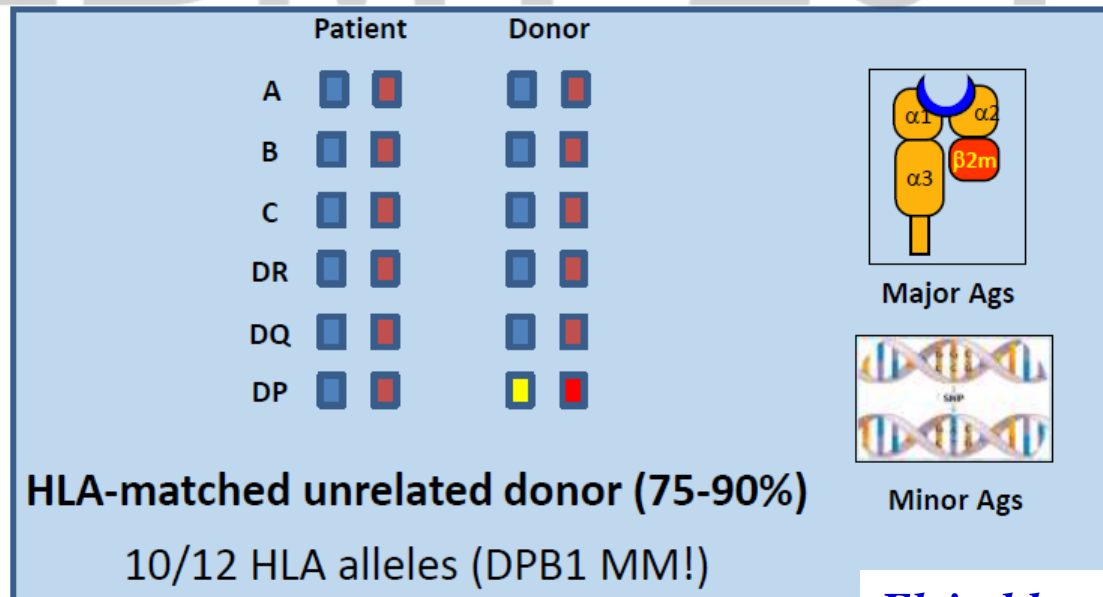
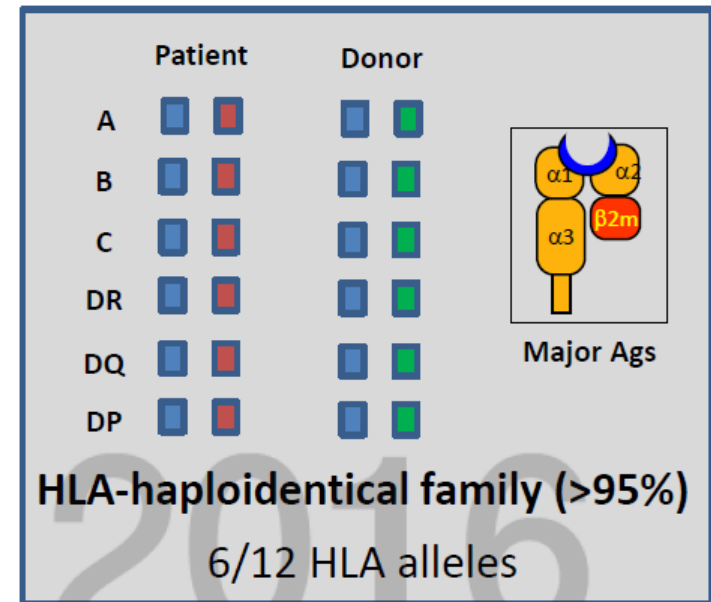
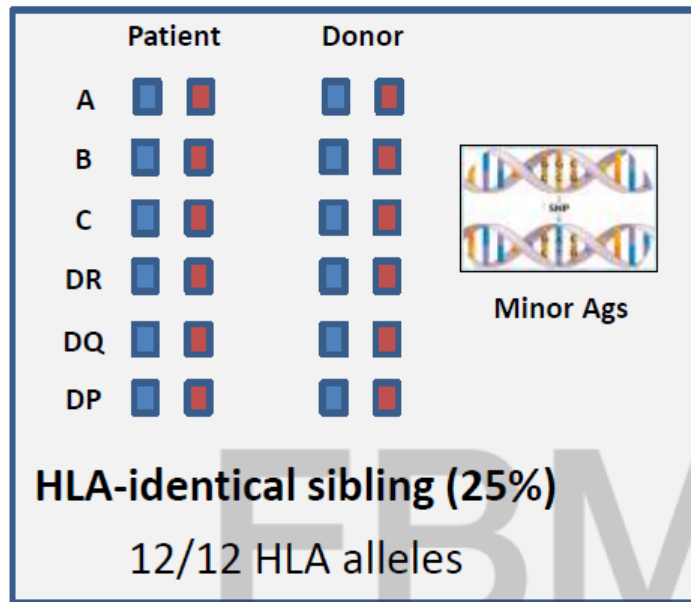
# ***XXVI Congresso Nazionale, Associazione Italiana di Immunogenetica e Biologia dei Trapianti***

***Qual è il miglior donatore di cellule staminali  
ematopoietiche nel paziente adulto?***

***Prof Paolo Bernasconi***

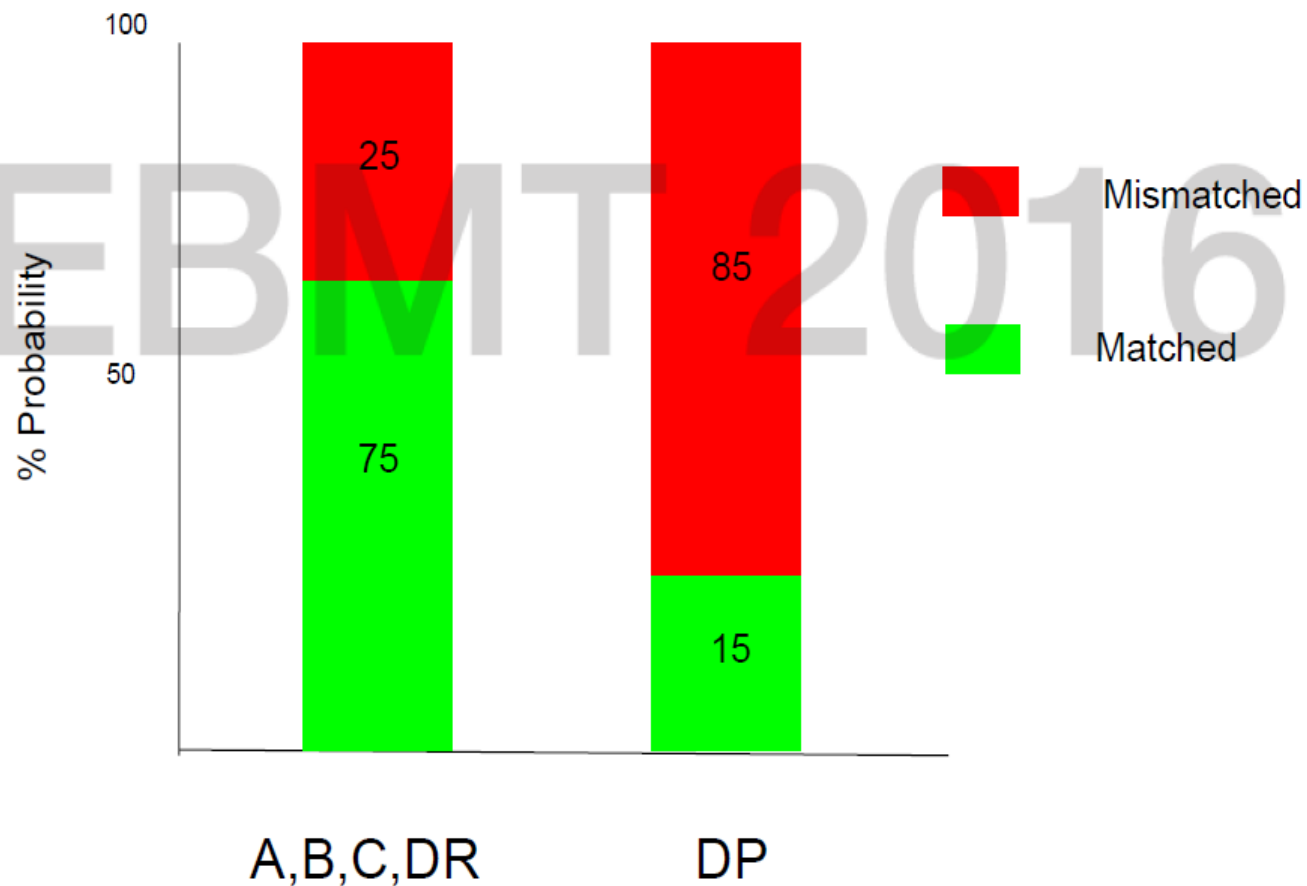
***Centro Trapianti SC Ematologia,  
Fondazione IRCCS Policlinico S. Matteo, Università di Pavia***

# Histocompatibility by Donor Source



# Unrelated Donor Availability

## HLA Mismatch Frequency



Grager, NEJM 2014

# ***Algorithm for donor selection for adult patients with hematologic malignancies***

***HLA-identical sibling donor***



***HLA-10/10 matched unrelated donor  
Beyond HLA: donor age > CMV-, sex-, ABO-matching***



***HLA-9/10 matched unrelated donor;  
HLA-mismatched related donor; Cord blood.  
Beyond HLA: donor specific antibodies, specific center exp.***

# Main Factors Affecting Patient Outcomes after Transplant from Alternative Donor **MUD, CB, Haplo**

## Patient

Diagnosis, Disease phase, Age, CMV status, Performance

## Donor /Recipient Pairs

### Matched Unrelated Donor

HLA  
Age  
Sex  
CMV status  
HLA antibodies  
Donor availability

### Cord Blood

HLA  
Cell Dose  
HLA antibodies  
Recipient CMV status  
KIR activity  
NIMA-NIPA

### Haplo Related Donor

Age  
Sex  
CMV status  
KIR activity  
NIMA- NIPA  
ABO matching

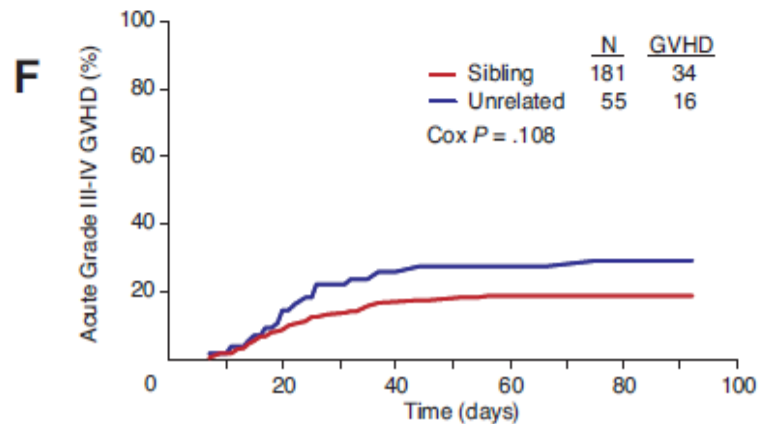
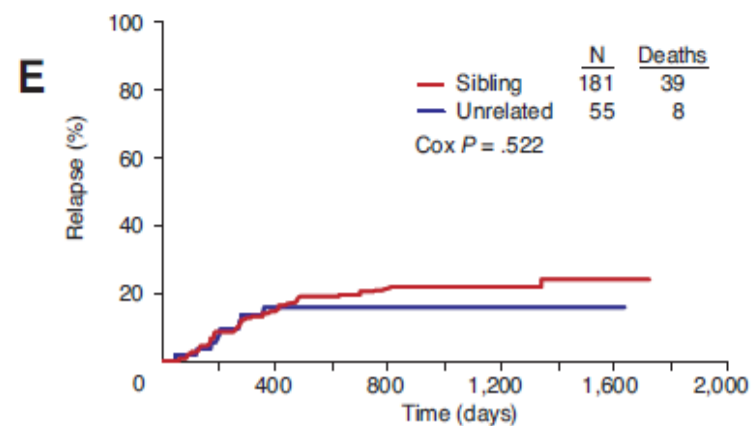
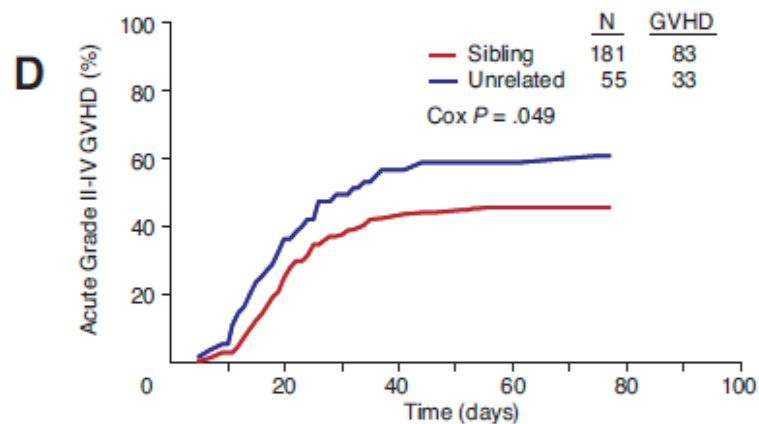
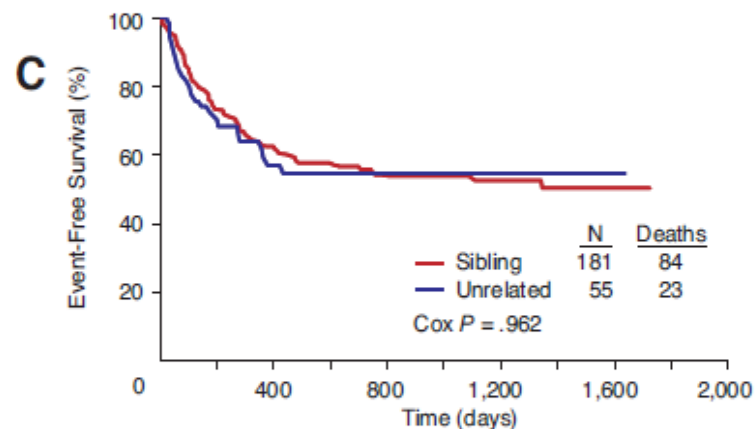
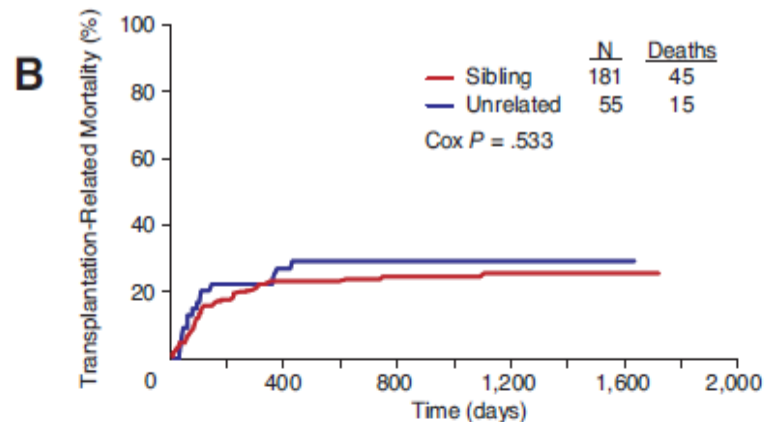
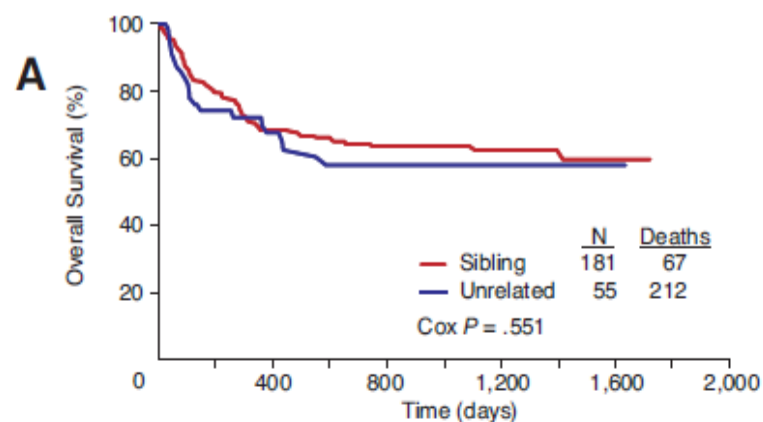
## Transplant Platform

Conditioning Regimen (MAC, RIC), GVHD Prophylaxis, T- depleted or Unmanipulated Graft

# **Development of an Unrelated Donor Selection Score Predictive of Survival after HCT: Donor Age Matters Most**

**Bronwen E. Shaw, MBChB, MRCP, PHD, FRCPATH<sup>1</sup>, Brent R. Logan, PhD<sup>1</sup>, Stephen R. Spellman, MBS<sup>2</sup>, Steven GE Marsh, BSc, PhD, ARCS<sup>3</sup>, James Robinson, BSc, MSc<sup>3</sup>, Joseph Pidala, MD, PhD<sup>4</sup>, Carolyn Hurley, PhD<sup>5</sup>, Juliet Barker, MBBS<sup>6</sup>, Martin Maiers, MS<sup>2</sup>, Jason Dehn, MPH<sup>7</sup>, Hailin Wang, MPH<sup>1</sup>, Mike Haagenson, MS<sup>2</sup>, David Porter, MD<sup>8</sup>, Effie W. Petersdorf, MD<sup>9</sup>, Ann Woolfrey, MD<sup>9</sup>, Mary M. Horowitz, MD, MS<sup>1</sup>, Michael Verneris, MD<sup>10</sup>, Katharine C. Hsu, MD, PhD<sup>6</sup>, Katharina Fleischhauer, MD<sup>11</sup>, and Stephanie J. Lee, MD, MPH<sup>1,9</sup>**

***BBMT 2018;24:1049-1056***



## TRANSPLANTATION

### The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy

Table 3. Donor characteristics associated with mortality and GVHD for transplantation period 1988 to 2006

Outcome	HR (95% CI)	P value
<b>Overall mortality*</b>		
Donor age, years		<.001
≤32	1.00	
33 to 50	1.13 (1.05-1.20)	<.001
>50	1.29 (1.14-1.46)	<.001
Donor-recipient HLA-match		<.001
8/8 HLA-match	1.00	
7/8 HLA-match	1.24 (1.15-1.34)	<.001
6/8 HLA-match	1.62 (1.47-1.79)	<.001
5/8 or lower HLA-match	1.89 (1.67-2.15)	<.001
Blood group ABO match		.001
ABO matched	1.00	
ABO minor mismatch	1.10 (1.01-1.18)	.002
ABO major mismatch	1.13 (1.05-1.21)	.001

*Kollman et al, Blood 2016;127:260-267*



## TRANSPLANTATION

### The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy

#### Nonrelapse mortality\*

Donor age, years		.03
≤32	1.00	
33 to 50	1.09 (1.01-1.19)	.03
>50	1.20 (1.03-1.40)	.02
Donor-recipient HLA-match		<.001
8/8 HLA-match	1.00	
7/8 HLA-match	1.38 (1.26-1.51)	<.001
6/8 HLA-match	1.85 (1.65-2.09)	<.001
5/8 or lower HLA-match	2.16 (1.87-2.51)	<.001
Donor sex and parity		<.001
Male	1.00	
Female, no pregnancies	1.02 (0.91-1.14)	.75
Female, 1 or more pregnancies	1.29 (1.18-1.41)	<.001

#### Relapse†

Donor age		.29
≤32 y	1.00	
33 to 50 y	1.05 (0.95-1.16)	.35
>50 y	1.17 (0.95-1.42)	.13
Donor sex and parity		.06
Male	1.00	
Female, no pregnancies	0.96 (0.84-1.10)	.57
Female, 1 or more pregnancies	0.84 (0.74-0.95)	.007

*Kollman et al, Blood  
2016;127:260-267*

## TRANSPLANTATION

### The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy

#### Grade 2 to 4 acute GVHD†

Donor age, years .01

≤32 1.00

33 to 50 1.09 (1.02-1.16) .01

>50 1.17 (1.03-1.33) .01

Donor-recipient HLA-match <.001

8/8 HLA-match 1.00

7/8 HLA-match 1.23 (1.14-1.32) <.001

6/8 HLA-match 1.26 (1.13-1.39) <.001

5/8 or lower HLA-match 1.46 (1.28-1.68) <.001

#### Chronic GVHD§

Donor sex and parity <.001

Male 1.00

Female, no pregnancies 1.01 (0.91-1.12) .88

Female, 1 or more pregnancies 1.22 (1.11-1.34) <.001

Table 5. Donor characteristics associated with survival for transplantation period 2007 to 2011

Outcome	HR (95% CI)	P value
Overall survival*		
Donor age (10-year increments)	1.055 (1.013-1.099)	.01
Donor-recipient HLA-match		
8/8 HLA-match	1.00	
7/8 HLA-match	1.37 (1.25-1.51)	<.001

*Kollman et al, Blood  
2016;127:260-267*

## Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study

Yu Wang,<sup>1</sup> Qi-Fa Liu,<sup>2</sup> Lan-Ping Xu,<sup>1</sup> Kai-Yan Liu,<sup>1</sup> Xiao-Hui Zhang,<sup>1</sup> Xiao Ma,<sup>3</sup> Zhi-Ping Fan,<sup>2</sup> De-Pei Wu,<sup>3</sup> and Xiao-Jun Huang<sup>1,4</sup>

450 LAM in prima remissione completa

A seconda della disponibilità di un donatore 231 trapianti da haplo e 219 da sib

A tre anni sopravvivenza libera da malattia 74% versus 78% ( $p=.34$ ), sopravvivenza complessiva 79% versus 82% ( $p=.36$ ), incidenza di recidiva 15% versus 15% ( $p=.98$ ) e non-relapse mortality 13% versus 8% ( $p=.13$ )

*Blood 2015;125:3956-3962*

# Comparison of Outcomes of Hematopoietic Cell Transplants from T-Replete Haploidentical Donors Using Post-Transplantation Cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 Allele-Matched Unrelated Donors and HLA-Identical Sibling Donors: A Multivariable Analysis Including Disease Risk Index



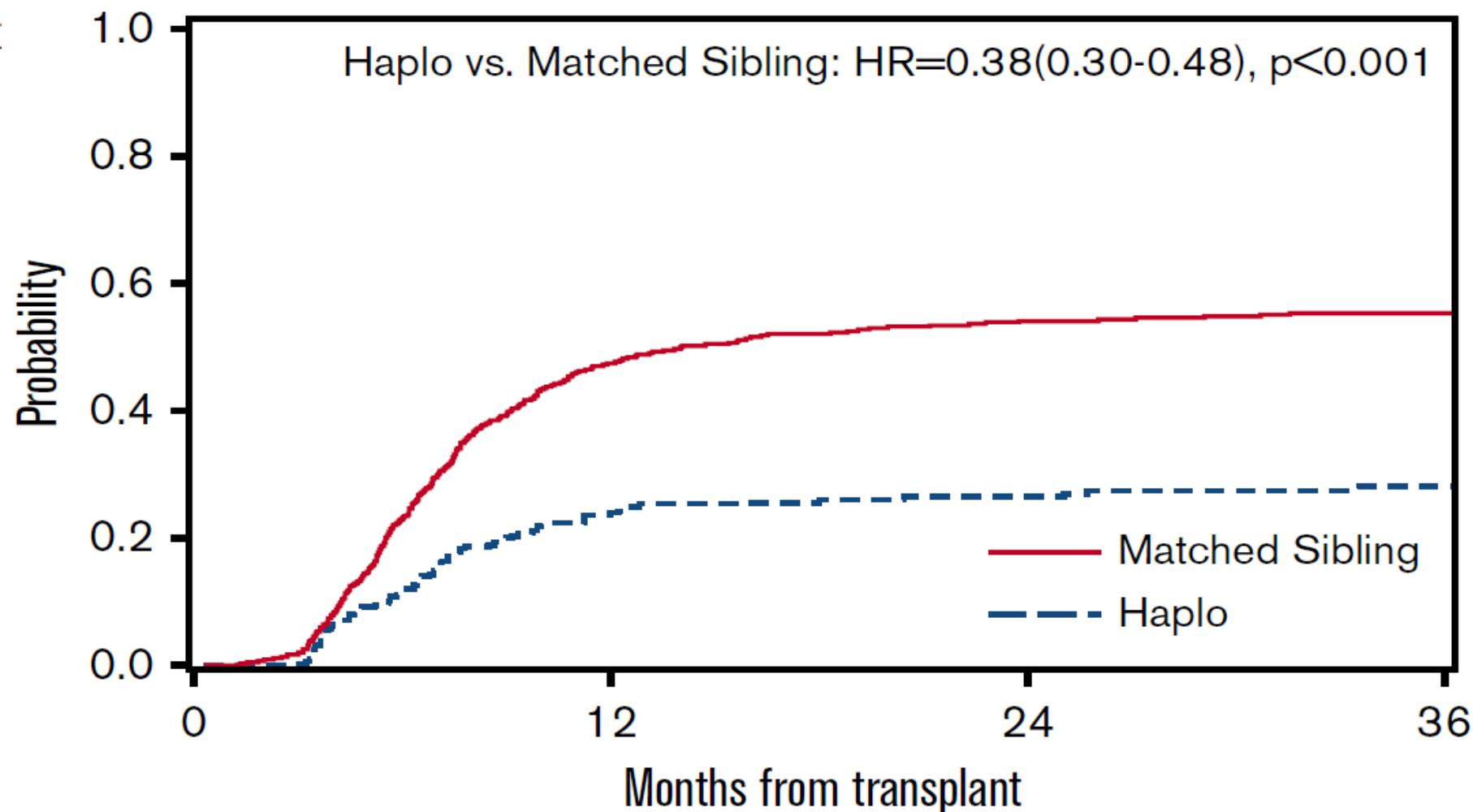
Asad Bashey<sup>1,\*</sup>, Xu Zhang<sup>2</sup>, Katelin Jackson<sup>1</sup>, Stacey Brown<sup>1</sup>, Michelle Ridgeway<sup>1</sup>, Melhem Solh<sup>1</sup>, Lawrence E. Morris<sup>1</sup>, H. Kent Holland<sup>1</sup>, Scott R. Solomon<sup>1</sup>

<sup>1</sup> Blood and Marrow Transplant Program, Northside Hospital, Atlanta, Georgia  
<sup>2</sup> Department of Mathematics and Statistics, Georgia State University, Atlanta, Georgia

A 2 anni	Sib	MUD	Haplo	p-
Sopravvivenza Complessiva	72%	59%	57%	NS
<b><i>A due anni dal trapianto GVHD moderata/severa haplo versus MUD: 25% versus 48%(p=.002)</i></b>				
Recidiva	30%	34%	29%	NS
<b><i>In multivariata sopravvivenza complessiva e sopravvivenza libera da malattia simili tra i tre tipi di trapianto ma GVHD cronica di grado moderato/severo significativamente più bassa negli haplo (p=.007)</i></b>				
Pz ancora in tp. Immuno-sopp.	35%	42%	19%	<b><i>Haplo vs MUD p=.007</i></b>

**F**

## Adjusted Curves for cGVHD



Outcomes of hematopoietic stem cell transplantation from unmanipulated haploidentical versus matched sibling donor in patients with acute myeloid leukemia in first complete remission with intermediate or high-risk cytogenetics: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation



Haematologica 2018  
Volume 103(8):1317-1328

**LAM a rischio intermedio:** 2010 (122 Haplo, 1888 Sib)

**LAM ad alto rischio:** 644 (63 Haplo, 581 Sib)

Dopo un follow-up di 30 mesi:

**Nelle LAM a rischio intermedio:** sopravvivenza complessiva, libera da malattia e libera da GVHD relativamente peggiori e GVHD/NRM più alte nel trapianto da donatore familiare HLA identici

**Nelle LAM ad alto rischio:** sopravvivenza complessiva, libera da malattia e libera da GVHD simili nei due tipi di trapianto

In conclusione, nelle categorie di LAM più alta incidenza di GVHD acuta di grado II-IV e trend verso una minor incidenza di recidiva nel trapianto da donatore haplo

**Salvatore et al 2018**

**Conclusione:** i donatori familiari HLA identici sono donatori di prima scelta per le LAM in prima remissione completa



# Comparison of matched sibling donors versus unrelated donors in allogeneic stem cell transplantation for primary refractory acute myeloid leukemia: a study on behalf of the Acute Leukemia Working Party of the EBMT

**Totale trapianti:** 1041, 660 da sib e 381 da MUD

## **Conclusioni:**

Il trapianto riesce a recuperare circa un quarto dei pazienti con LAM primariamente refrattaria

Il tipo di donatore non ha alcun impatto sul decorso del trapianto

miglior sopravvivenza libera da malattia

Condizionamento RIC associato ad una NRM significativamente più bassa



# Haploidentical versus unrelated allogeneic stem cell transplantation for relapsed/refractory acute myeloid leukemia: a report on 1578 patients from the Acute Leukemia Working Party of the EBMT

Eolia Brissot,<sup>1</sup> Myriam Labopin,<sup>1,2</sup> Gerhard Ehninger,<sup>3</sup> Matthias Stelljes,<sup>4</sup> Arne Brecht,<sup>5</sup> Arnold Ganser,<sup>6</sup> Johanna Tischer,<sup>7</sup> Nicolaus Kröger,<sup>8</sup> Boris Afanasyev,<sup>9</sup> Jürgen Finke,<sup>10</sup> Ahmet Elmaagacli,<sup>11</sup> Herman Einsele,<sup>12</sup> Mohamad Mohty<sup>1,2</sup>★ and Arnon Nagler<sup>2,13</sup>★

## ***Risultati a 2 anni di follow-up:***

Nessuna differenza significativa per quanto riguarda la sopravvivenza libera da malattia (22.8% per haplo, 28% per 10/10 e 22.8% per 9/10)

In analisi multivariata nessuna differenza tra i tre tipi di trapianto per quanto riguarda sopravvivenza libera da malattia, sopravvivenza complessiva, incidenza di recidiva, NRM, sopravvivenza libera da GVHD e da recidiva

## ***Due fattori associati ad una più alta incidenza di recidiva:***

- ***Trapianto in prima o seconda ricaduta piuttosto che in malattia primitivamente refrattaria,***
- ***Citogenetica sfavorevole***



# Who Is a Better Donor for Recipients of Allogeneic Hematopoietic Cell Transplantation: A Young HLA-Mismatched Haploidentical Relative or an Older Fully HLA-Matched Sibling or Unrelated Donor?

Eva Karam<sup>1</sup>, Justin Laporte<sup>1</sup>, Scott R. Solomon<sup>1</sup>, Lawrence E. Morris<sup>1</sup>, Xu Zhang<sup>2</sup>, H. Kent Holland<sup>1</sup>, Asad Bashey<sup>1</sup>, Melhem M. Solh<sup>1,\*</sup>

<sup>1</sup> Blood and Marrow Transplant Program at Northside Hospital, Atlanta, Georgia

<sup>2</sup> Center for Clinical and Translational Sciences, University of Texas Health Science Center, Houston, Texas

Risultati a 3 anni:

**OS:** 64% per Sib; 54% per MUD; 62% per Haplo

**DFS:** 55% per Sib, 44% per MUD e 58% per Haplo

***In analisi multivariata:***


Nessun effetto del donatore su OS, DFS, recidiva e TRM; ma i riceventi di trapianto haplo con OS simile a quello di Sib e MUD, minor incidenza di GVHD cronica e migliore sopravvivenza libera da GVHD e libera da recidiva

Sib con tasso di recidiva a tre anni significativamente inferiore rispetto ai MUD (27% versus 37%,  $p=.042$ )

Incidenza di GVHD cronica moderata/severa più bassa negli Haplo che nei Sib e MUD ( $p=.01$ )

Biol Blood Marrow Transplant 000 (2019) 1–7

# Bone Marrow Versus Mobilized Peripheral Blood Stem Cells in Haploidentical Transplants Using Posttransplantation Cyclophosphamide

Annalisa Ruggeri, MD, PhD <sup>1</sup>; Myriam Labopin, MD<sup>1,2</sup>; Andrea Bacigalupo, MD<sup>3</sup>; Zafer Gülbas, MD<sup>4</sup>; Yener Koc, MD<sup>5</sup>; Didier Blaise, MD<sup>6</sup>; Benedetto Bruno, MD<sup>7</sup>; Giuseppe Irrera, MD<sup>8</sup>; Johanna Tischer, MD<sup>9</sup>; Jose Luiz Diez-Martin, MD<sup>10</sup>; Luca Castagna, MD<sup>11</sup>; Fabio Ciceri, MD<sup>12</sup>; Mohamad Mohty, MD<sup>1,2,13</sup>; and Arnon Nagler, MD<sup>1,13,14</sup>

## ***Risultati***

Attecchimento inferiore nei pazienti che avevano ricevuto BM (92% vs 95%  
 $P < 0.001$ )

## ***Conclusioni:***

***Maggior rischio di GVHD acuta con PBSC***

A 2 anni sopravvivenza 55% vs 56% (NS) e sopravvivenza libera da malattia 49% vs 54% (NS)

## ***In analisi multivariata***

PBSC associate ad un maggior rischio di GVHD acuta di grado II-IV (hazard ratio: 2.1  $P < .001$ ) e di grado III-IV (hazard ratio: 3.8  $P < .001$ )

RIC associato ad una peggiore sopravvivenza libera da malattia ( $P < .04$ ) e maggior incidenza di recidiva ( $P < .02$ )

# CD3+ graft cell count influence on chronic GVHD in haploidentical allogeneic transplantation using post-transplant cyclophosphamide.

**Aims:** find any correlation between graft cell composition (CD34+, CD3+) and donor features on transplant outcomes in 234 patients who underwent HCT between 2010 and 2016.

## **Conclusions:**

GVHD prophylaxis should be modulated accordingly to CD3+ graft content, especially when a PBSC graft is used

- An elevated CD3+ graft content was associated with an increased incidence of all-grade chronic GVHD [HR 1.36 (95% CI = 1.06-1.74),  $p = 0.01$ ], an effect confirmed only for the PBSC graft group.
- A higher CD34+ graft content had a protective role on non-relapse mortality [HR 0.78 (95% CI = 0.62-0.96),  $p = 0.02$ ] but this was confirmed only for the bone marrow (BM)-derived graft cohort.
- Donor characteristics did not influence any outcomes.

# Demographic

<i>Patients' features</i>	<i>BM (tot. 17)</i>	<i>PB (tot. 18)</i>	<i>P value</i>
Median age, years (range)	56 (23-72)	54 (25-67)	N.S.
Sex:			
Male (%)	10 (58.8)	9 (50)	N.S.
Female (%)	7 (41.2)	9(50)	
Median graft content:			
CD34 <sup>+</sup> x10 <sup>6</sup> /kg (range)	3.62 (1.44-7.75)	6.48 (4.28-10.43)	<b>0.05</b>
CD3 <sup>+</sup> X10 <sup>8</sup> /kg (range)	0.4 (0.28-2.00)	2.73 (1.45-5.36)	<b>0.001</b>
HCT-CI score, pts (%)			
≤ 2	13 (76)	7 (40)	<b>0.05</b>
< 2	4 (24)	11 (60)	
Type of Malignancy pts			N.S.
MDS-EB1*/MDS-EB2	-/3	1/2	
AML	9	6	
ALL	2	6	
LNH/LH/MM	3/-/-	-/1/2	

# Demographic (I)

<i>Patients' features</i>	<i>BM (tot. 17)</i>	<i>PB (tot. 18)</i>	<i>P value</i>
<b>DRI score, patients (%)</b>			
<b>Low/Intermediate</b>	10 (60)	12 (67)	N.S.
<b>High/Very high</b>	7 (40)	6 (33)	
<b>CR at transplant, pts (%)</b>			
<b>Yes</b>	13 (77)	12 (67)	N.S.
<b>No</b>	4 (23)	6 (33)	
<b>Donors' age, patients (%)</b>			N.S.
<b>≤40</b>	10 (60)	12 (67)	
<b>&gt;40</b>	7 (40)	6 (33)	
<b>Donor/Recipient gender, pts (%)</b>			N.S.
<b>Female/Male</b>	4 (23)	4 (23)	
<b>Others</b>	13 (77)	14 (77)	

## ***Results: Engraftment***

Median time to neutrophil recovery ( $>500/\mu\text{l}$ ) was 22 days (range 16-39) post-transplant, 23 days (range 18-27) for BM recipients and 20 (range 16-39) for PBSC recipients ( $P=\text{N.S.}$ ). In addition, the cumulative incidence of neutrophil recovery at day +30 and day +90 was 88% (95% CI: 85-94) and 94% (95% CI: 92-98) with no difference between the two graft sources.

In all patients except one platelet recovery ( $>20.000/\mu\text{l}$ ) occurred at a median of 17 days (range 10-151) post-transplant, at a median of 20 days (11-151) post-transplant for BM recipients and at a median of 14 days (range 10-26) for PBSC recipients ( $p=0.01$ ). In addition, platelet engraftment at day +30 and +90 were 85% (95% CI: 79-91) and 94% (95% CI: 90-98) with no difference between the two graft sources.

Seven patients (two patient who received a BM graft and five patients who received a PBSC graft) never reached platelets  $>50.000/\mu\text{l}$ . A poor graft function was experienced by three patients.

# ***Overall survival and non-relapse mortality***

Mean follow-up 16.9 months (range 1.9-56.7) and median survival 20.2 months.

Non-relapse mortality at 18 months 22% (95% CI: 15-26%).

Eleven patients (31%) dead, six had received a BM graft and five a PBSC graft. In eight patients death due to transplant related complications and in three to disease relapse. Death rates for patients who received BM were similar to those for patients who received a PBSC graft: 15.4% (95% CI: 6.4-37.0) versus 32.2% (95% CI: 13.4-77.4%) (p=N.S.).

No significant differences in overall mortality by graft type [HR: 0.75 (95% CI=0.2-2.7);  $P=0.66$ ].

## *Acute and chronic GVHD*

Incidence of acute and chronic GVHD: 28.5% and 22.8%.

Patients who received BM grafts presented a rate of acute GVHD lower than that presented by patients who received a PBSC graft: 18.8% (95% CI: 7.8-45.2) versus 33.4% (95% CI: 13.9-80.2%) ( $P=NS$ )

The risk of developing acute GVHD was similar between the two groups of patients (hazard ratio [HR], 1.04;  $P = .955$ ).

Patients who received a BM graft presented a rate of chronic GVHD similar to that of patients who received a PBSC graft: 17.2% (95% CI: 6.4-45.8) versus 31.7% (95% CI: 11.7-84.4%) with a trend toward a lower risk of developing chronic GVHD for BM grafts (hazard ratio [HR], 0.7;  $P = .62$ ).



## *Relapse*

Relapse rates were 9.33 (95% CI: 3.0-28.9) for BM grafts versus 17.8 (95% CI: 5.7-55.4%) for PBSC grafts.

## ***Conclusioni***

Non vi è un miglior donatore di cellule staminali: sono lo stato della malattia al momento del trapianto e alcune caratteristiche del donatore a definire quale sia il miglior donatore per un dato paziente

***LAM in prima remissione completa:*** Donatori familiari HLA identici

***LAM a rischio intermedio:*** Donatori familiari HLA identici e donatori da Registro

***LAM ad alto rischio o refrattaria:*** Tutti i tipi di donatore

## Leukemia Before Allogeneic HSCT

