AIBT

WINTER SCHOOL, Ravascletto (UD) 3-5 dicembre 2015

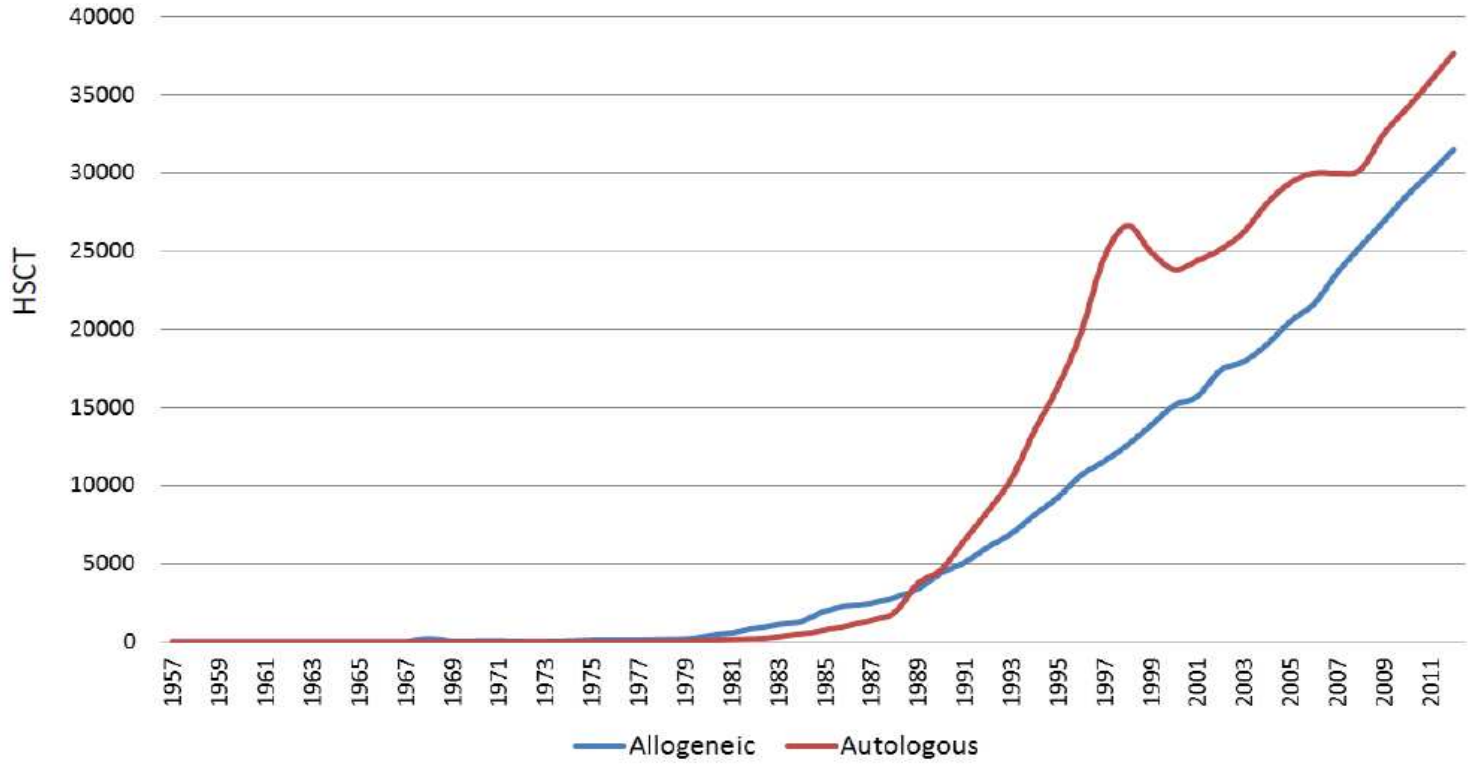
Il trapianto aploidentico e la sfida alla immunogenetica

Stefano Guidi
TMO
AOU Careggi - Firenze

>1.000.000 HSCT December 2012

Global Transplant Numbers:

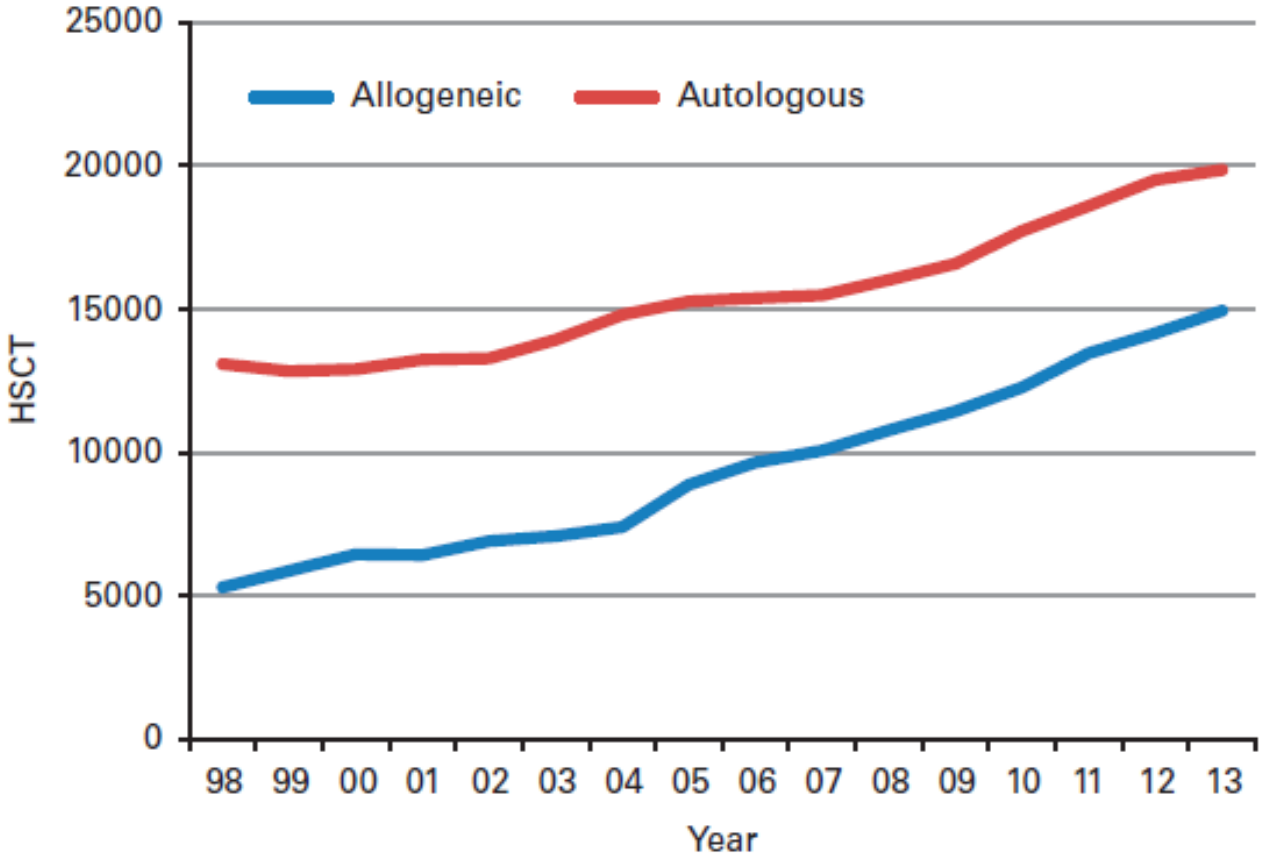
Allogeneic and autologous



preliminary data

Worldwide Network for Blood and Marrow Transplantation
NGO in official relations with World Health Organization

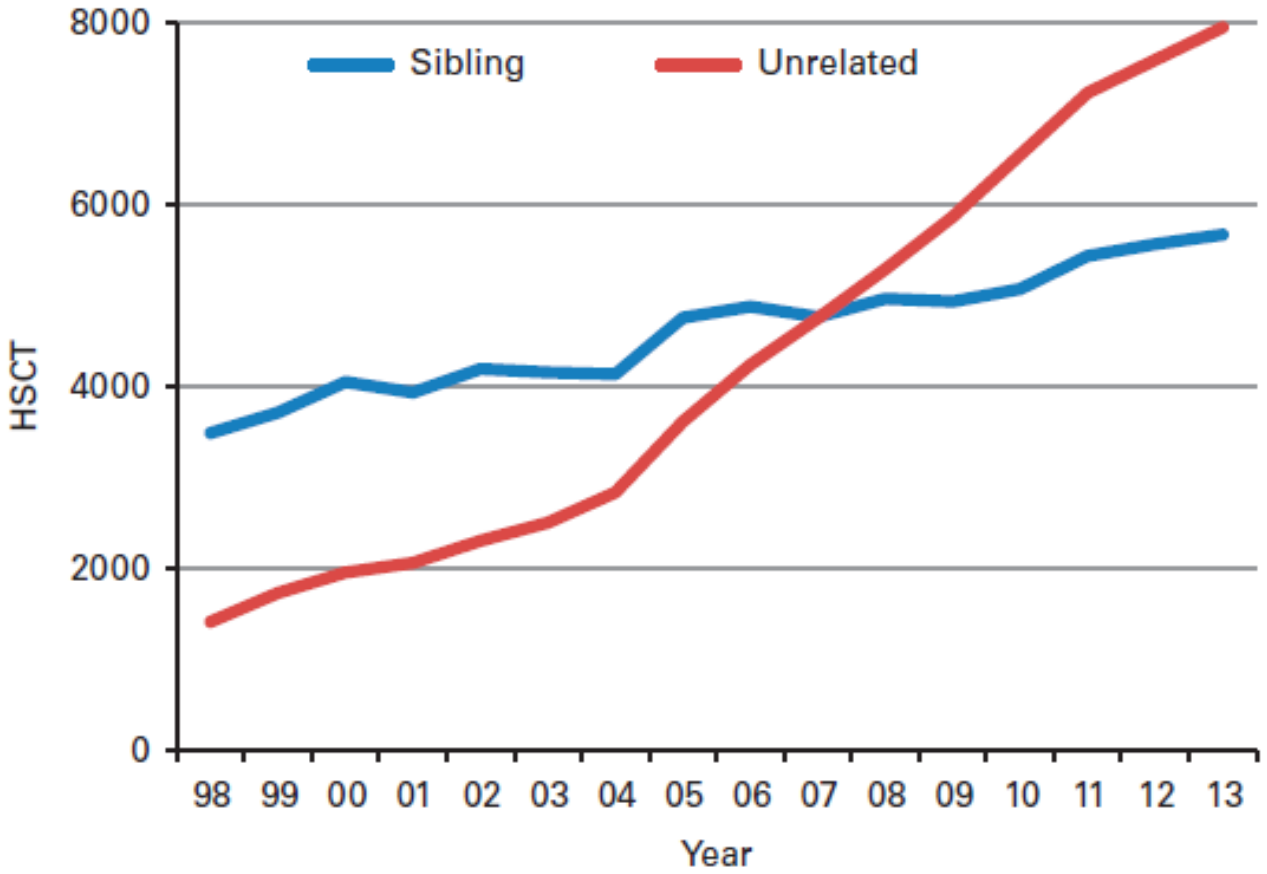
Auto 20.000 Allo 15.000



EBMT activity survey 2013

JR Passweg *et al* Bone Marrow Transplantation (2015) **50,** 476–482

MUD vs id Sibling



EBMT activity survey 2013

JR Passweg *et al* Bone Marrow Transplantation (2015) **50,** 476–482

19 Settembre 2015

Giornata Mondiale per la donazione di cellule staminali emopoietiche

IBMDR

Potenziali donatori adulti in **Italia:359.122**

Unita' di sangue cordonale disponibili per la ricerca in Italia: **33.424**

WMDA

Potenziali donatori adulti nel mondo: **26.626.115**

Unita' di sangue cordonale disponibili per la ricerca nel mondo: **682.273**

al 30-11-2015

HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry

Loren Gragert, B.S., B.A., Mary Eapen, M.B., B.S., Eric Williams, Ph.D., John Freeman, B.S., Stephen Spellman, M.B.S., Robert Baitty, M.P.P., Robert Hartzman, M.D., J. Douglas Rizzo, M.D., Mary Horowitz, M.D., Dennis Confer, M.D., and Martin Maiers, B.A.

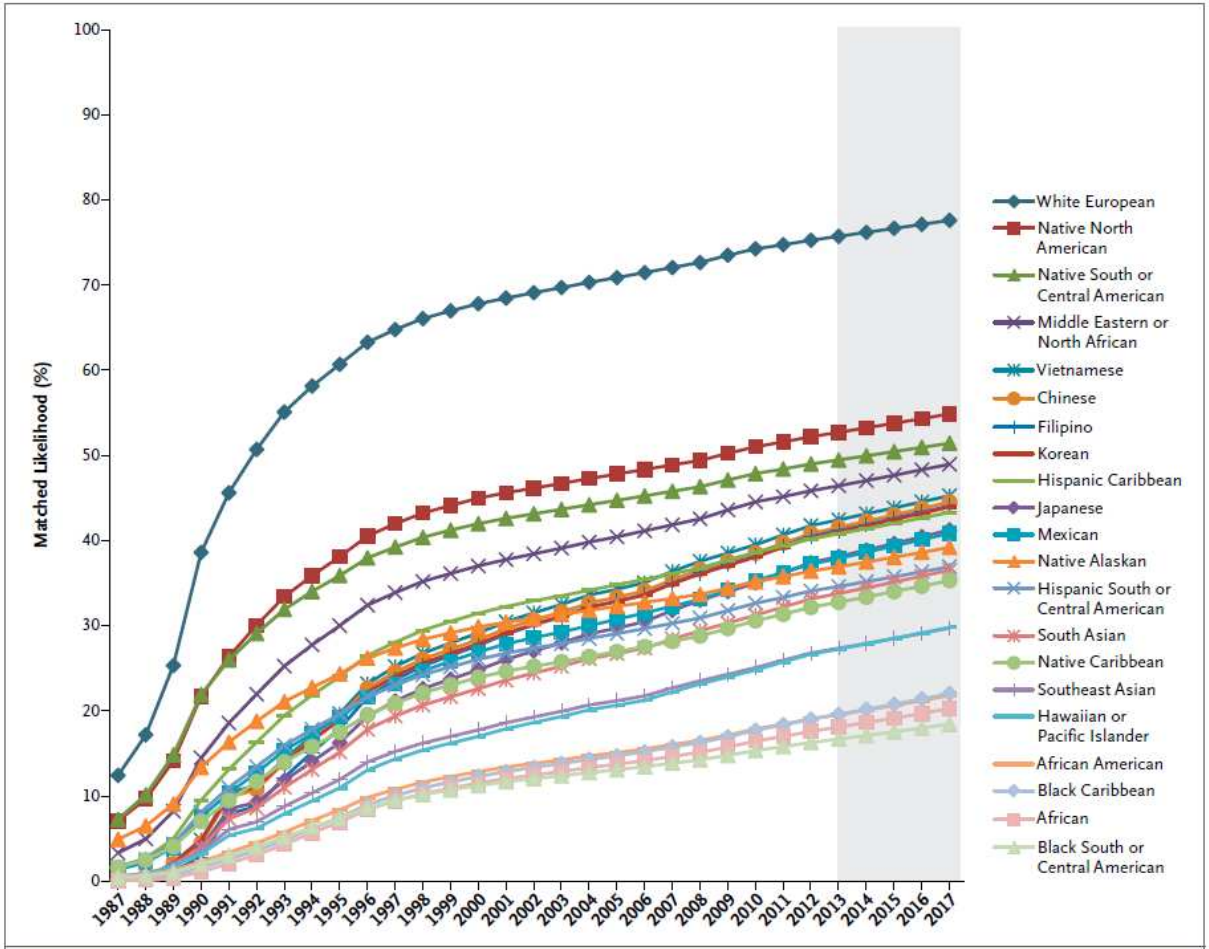


Figure 2. Likelihood of Finding an 8/8 HLA Match by Year End, Based on Current Donor Availability and with Recruitment Trends Extended to 2017.

Projected match likelihoods for 2013 through 2017 (shaded area) were calculated on the basis of anticipated recruitment growth of 9% cumulatively each year.

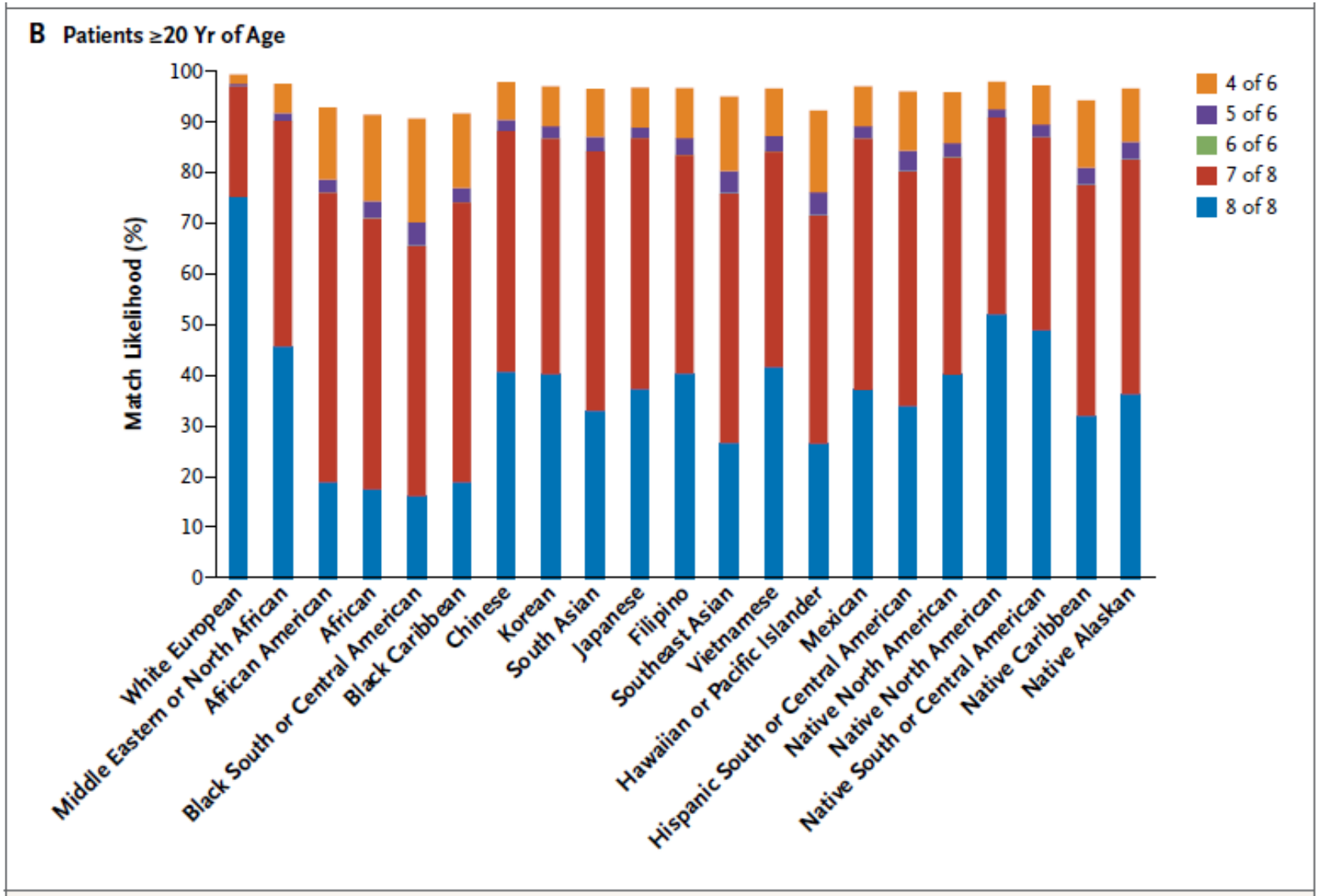


Figure 1. Match Likelihoods According to Racial and Ethnic Group and Age.

The likelihood of finding a match with the use of a search strategy in which an 8/8 HLA-matched donor is sought first, then a 7/8 HLA-matched donor, and thereafter a cord-blood unit with an adequate cell dose is shown.

Table 2. Adult-Donor Availability in 2010, According to Broad Racial and Ethnic Category.

Racial and Ethnic Category*	Confirmatory Typing Available†	Typing Not Discrepant‡	Workup Available§	Available Overall
	percentage of donors			
White	62	98	83	51
Black	36	95	69	23
Asian or Pacific Islander	42	97	73	29
Hispanic	44	96	68	29
Native American	45	98	63	28

CBT

Costi

Attecchimento tardivo

Impossibili DLI

Alta mortalità trapiantologica

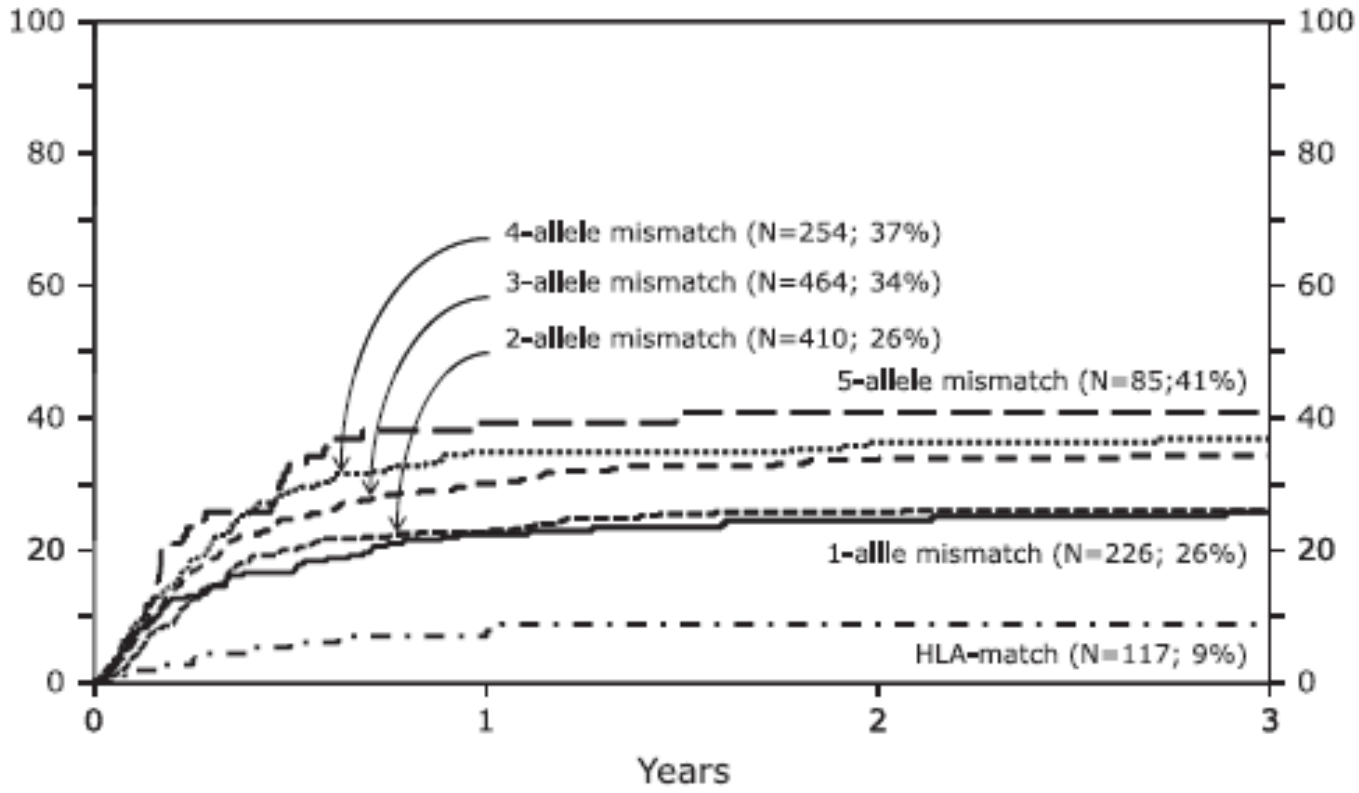
Cellularità > 3 x 10^7/kg

Il matching allelico gioca un ruolo centrale nell‘ outcome del CBT

Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy

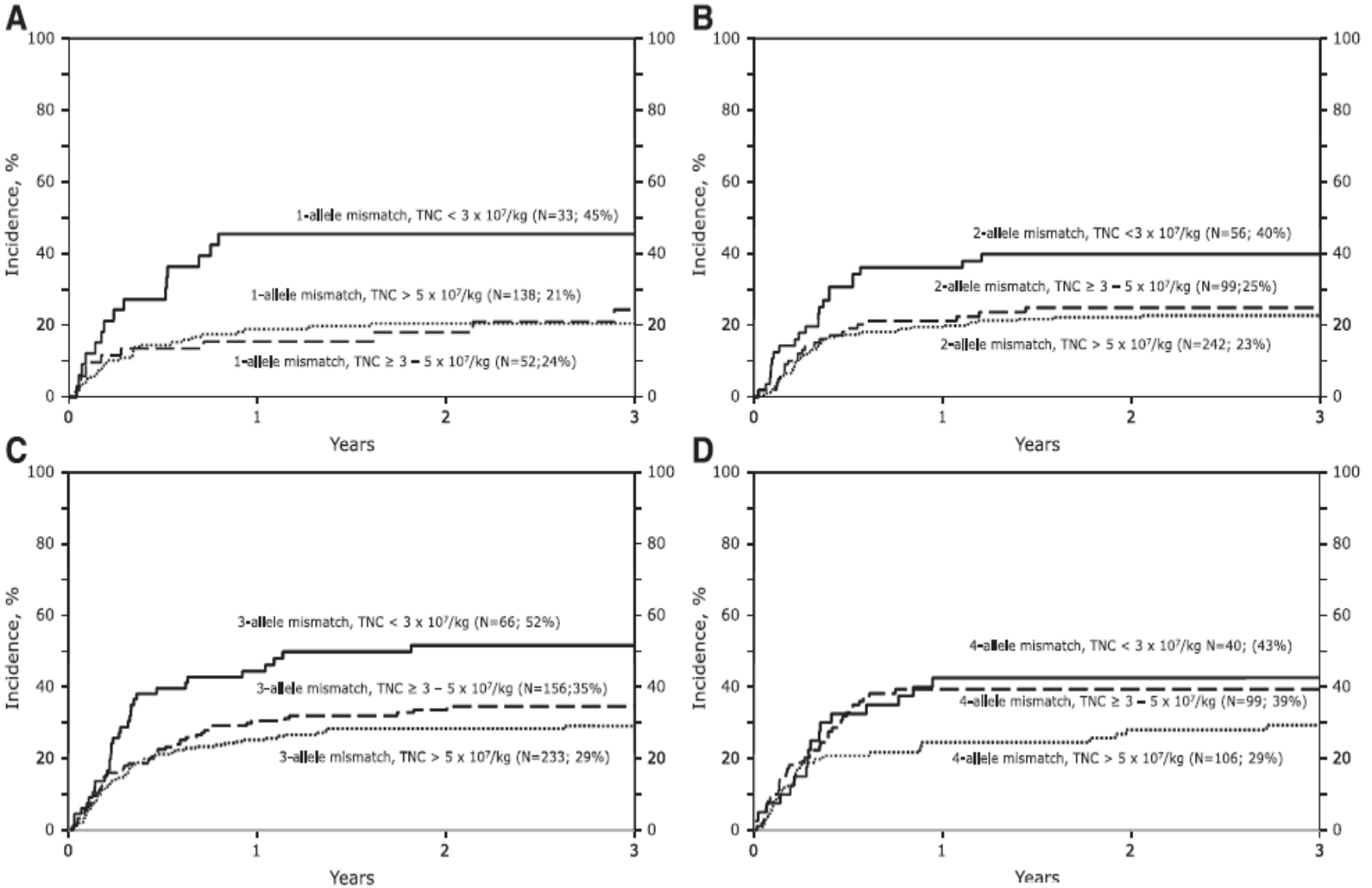
Mary Eapen,[1,2] John P. Klein,[1,3] Annalisa Ruggeri,[4] Stephen Spellman,[5] Stephanie J. Lee,[6] Claudio Anasetti,[7] William Arcese,[8] Juliet N. Barker,[9] Lee Ann Baxter-Lowe,[10] Maria Brown,[5] Marcelo A. Fernandez-Vina,[11] John Freeman,[12] Wensheng He,[1,2] Anna Paola Iori,[13] Mary M. Horowitz,[1,2] Franco Locatelli,[14,15] Susana Marino,[16] Martin Maiers,[12] Gerard Michel,[17] Guillermo F. Sanz,[18] Eliane Gluckman,[4] and Vanderson Rocha,[19] for the Center for International Blood and Marrow Transplant Research, Netcord, Eurocord, and the European Group for Blood and Marrow Transplantation

NRM



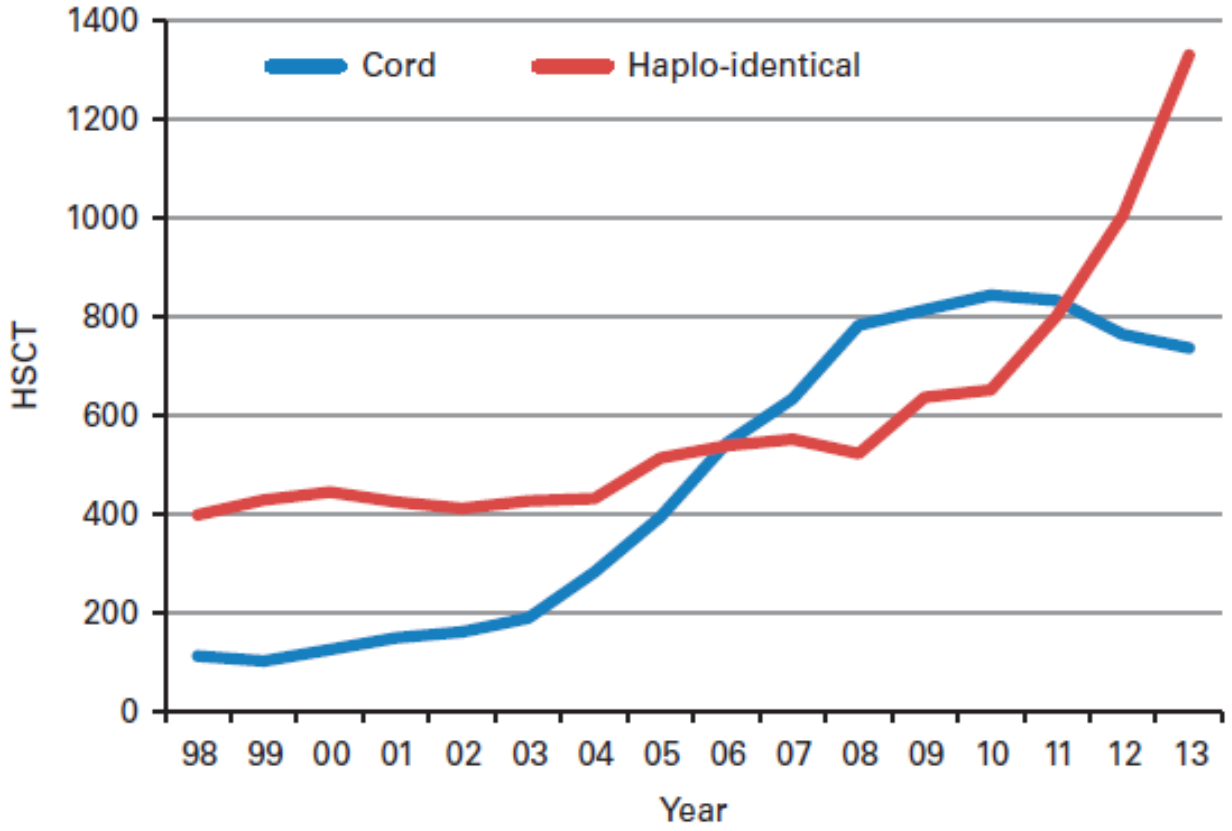
BLOOD, 2 JANUARY 2014 • VOLUME 123, NUMBER 1

La cellularità influenza la mortalità del CBT più dell' HLA



BLOOD, 2 JANUARY 2014 • VOLUME 123, NUMBER 1

Haplo vs CBT: il sorpasso



EBMT activity survey 2013

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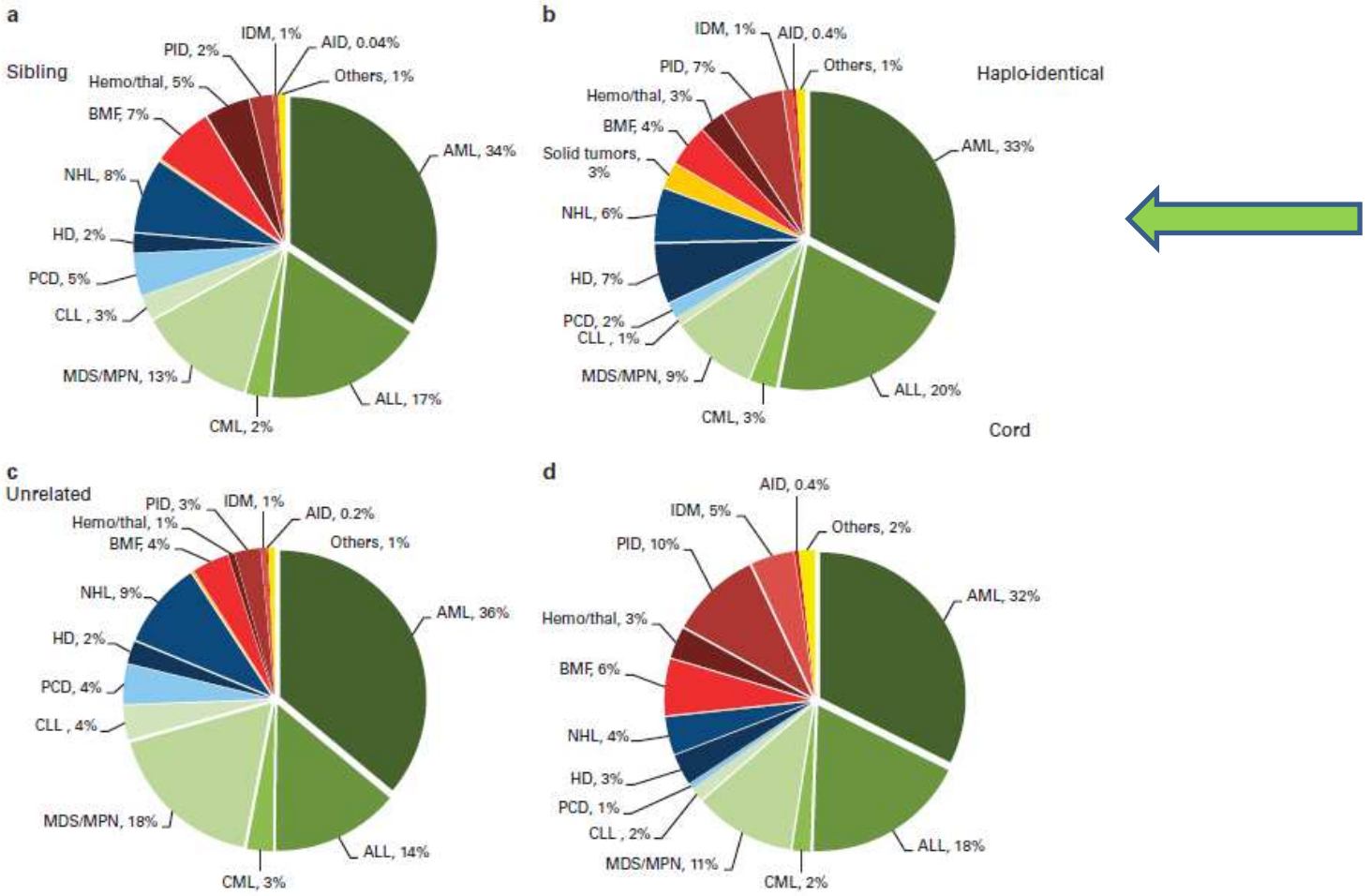
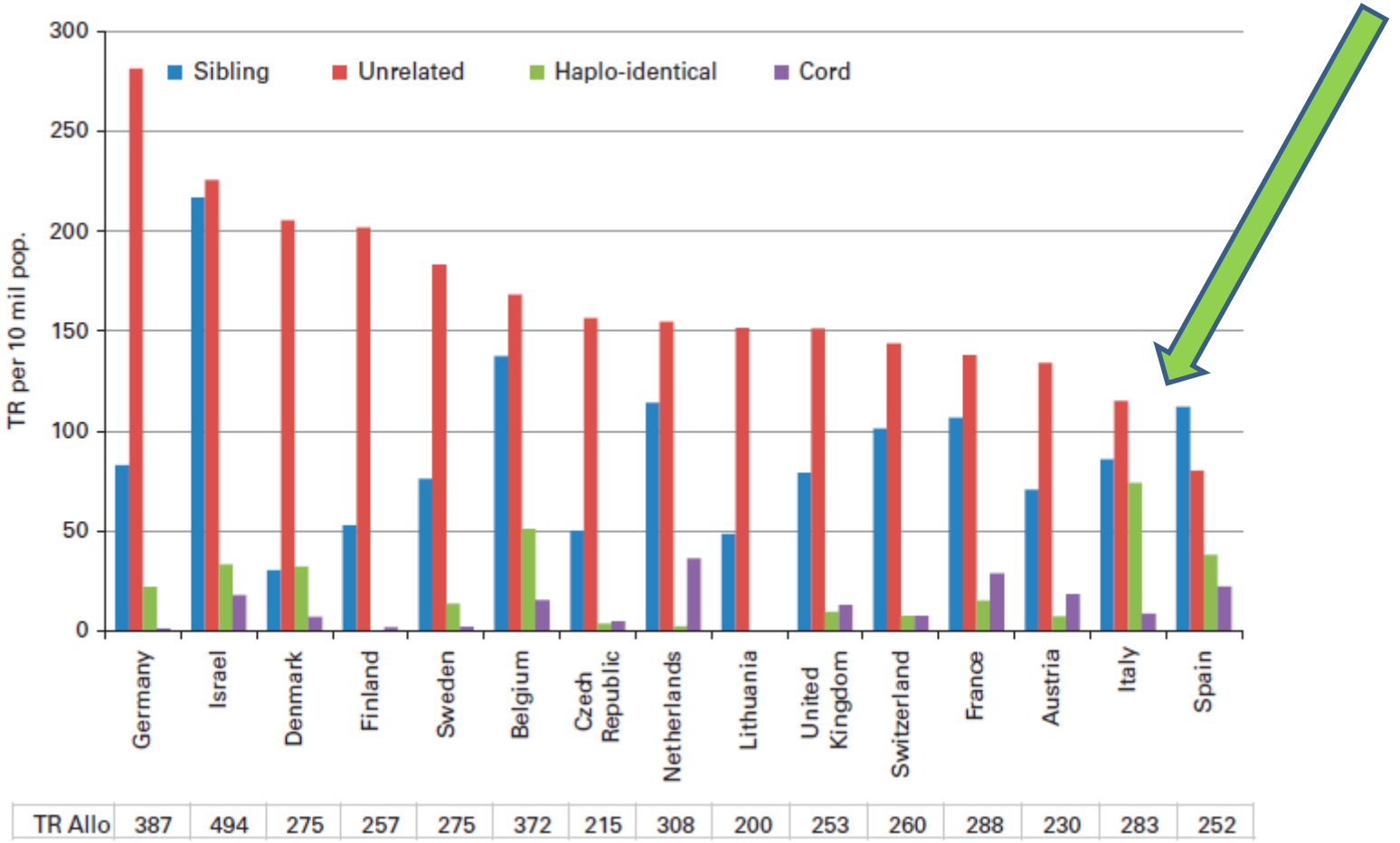
Indicazioni per tipo di donatore



EBMT activity survey 2013

JR Passweg *et al* Bone Marrow Transplantation (2015) **50,** 476–482

W l' Italia ???

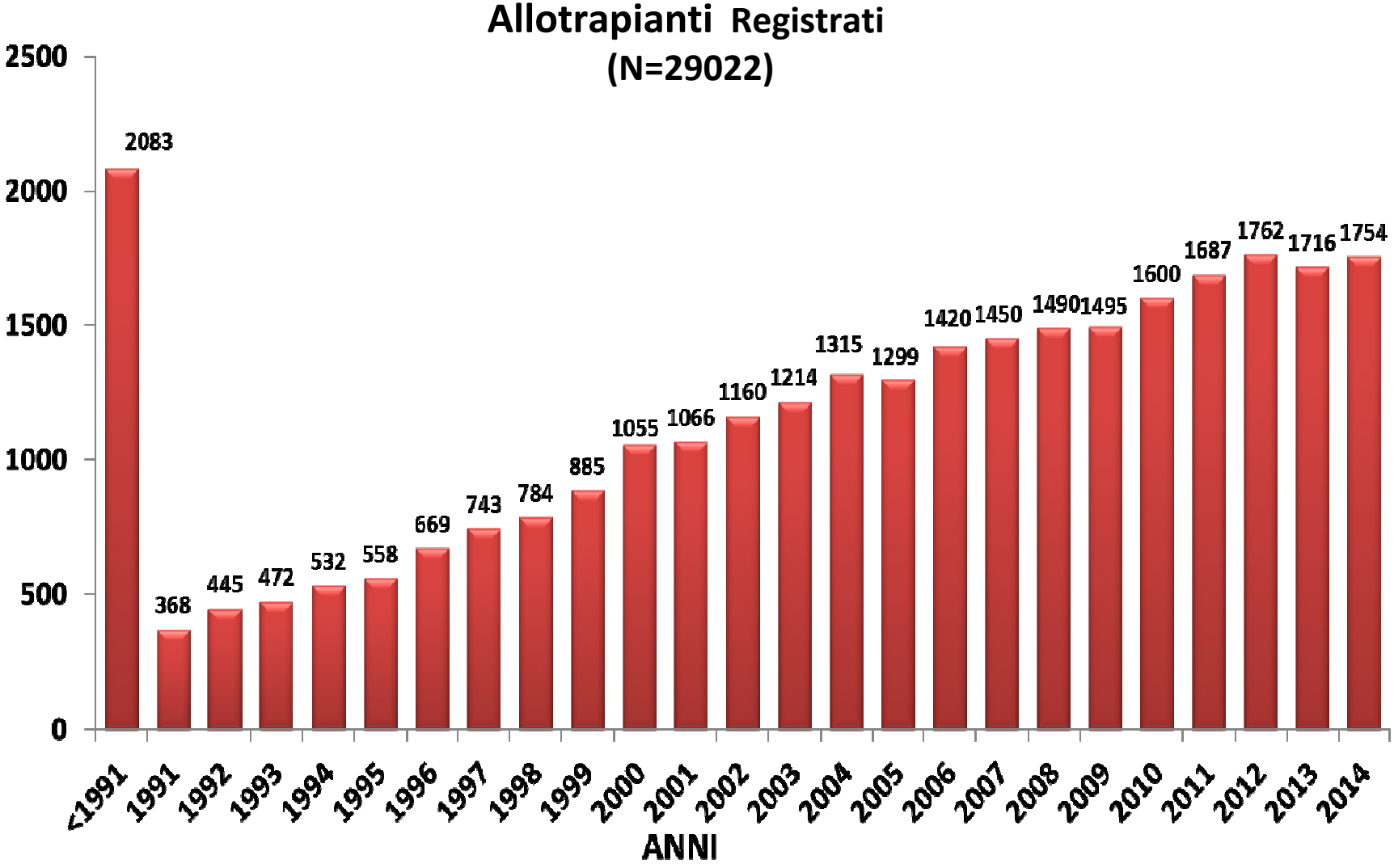


TR Allo	387	494	275	257	275	372	215	308	200	253	260	288	230	283	252

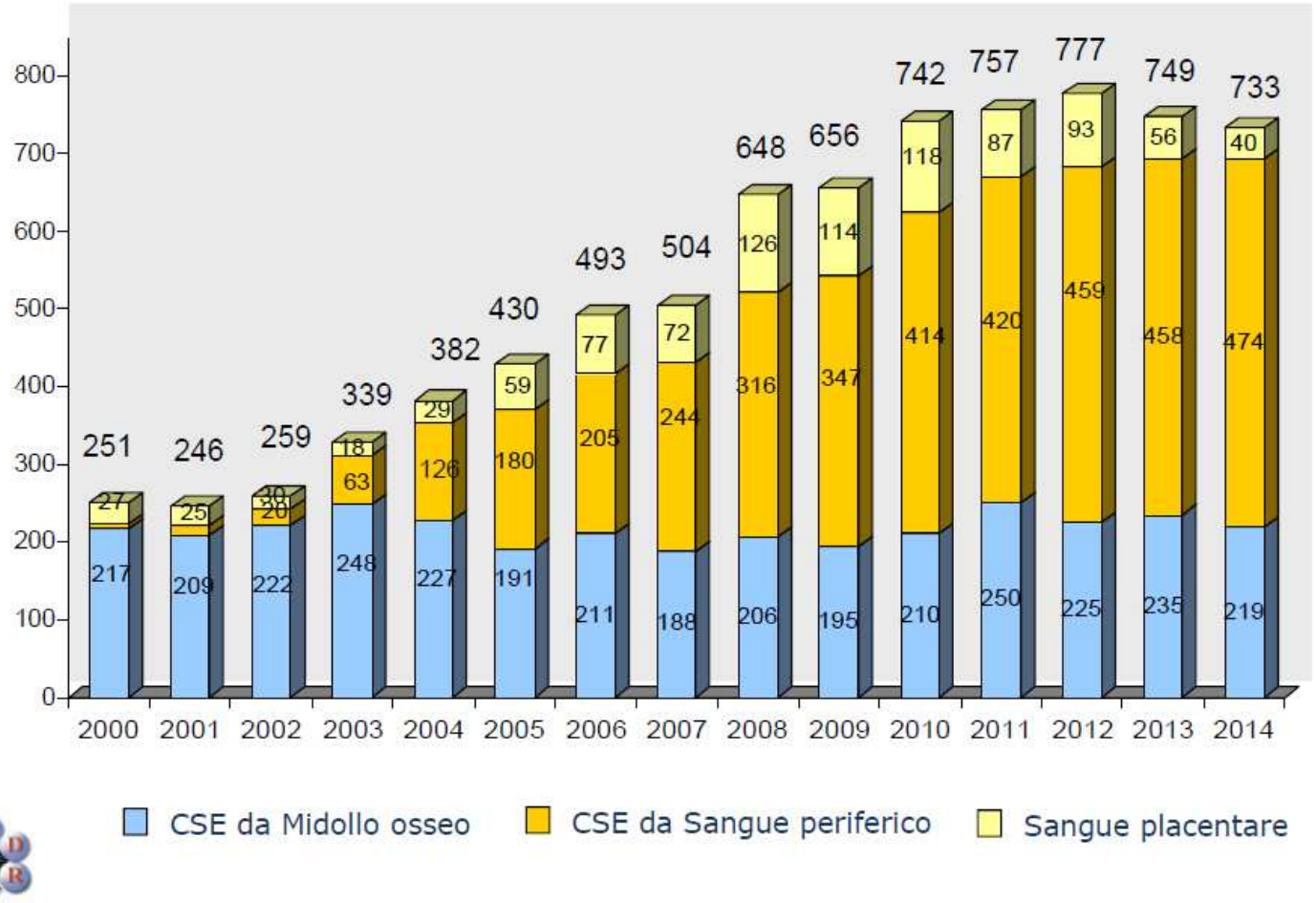
EBMT activity survey 2013

JR Passweg *et al* Bone Marrow Transplantation (2015) **50,** 476–482

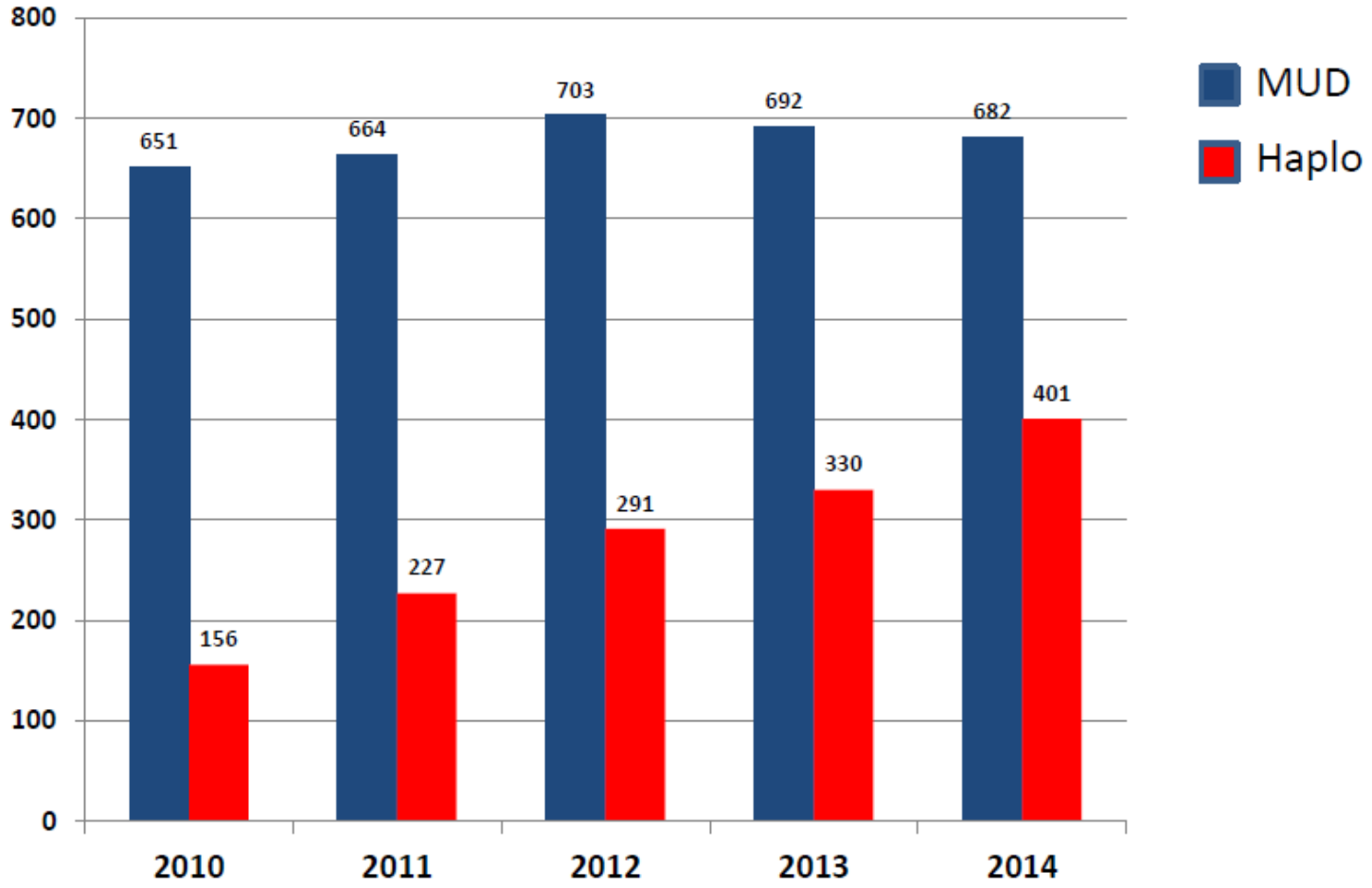
TRAPIANTO ALLOGENICO



Trapianti di CSE da non consanguineo in Italia

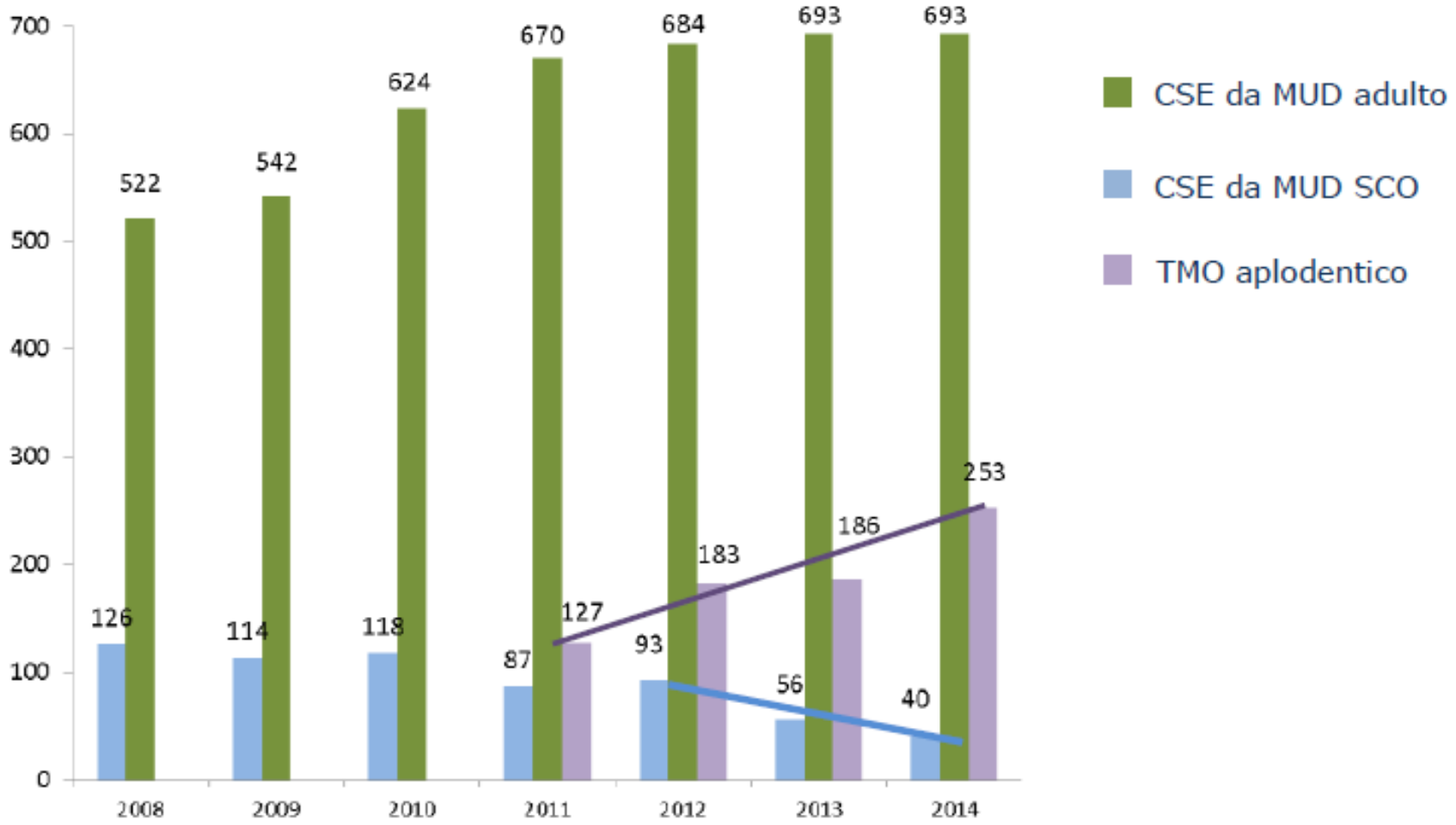


Pazienti, qualsiasi età sottoposti ad 1 solo trapianto (APLO o MUD) nel periodo 2010-2014

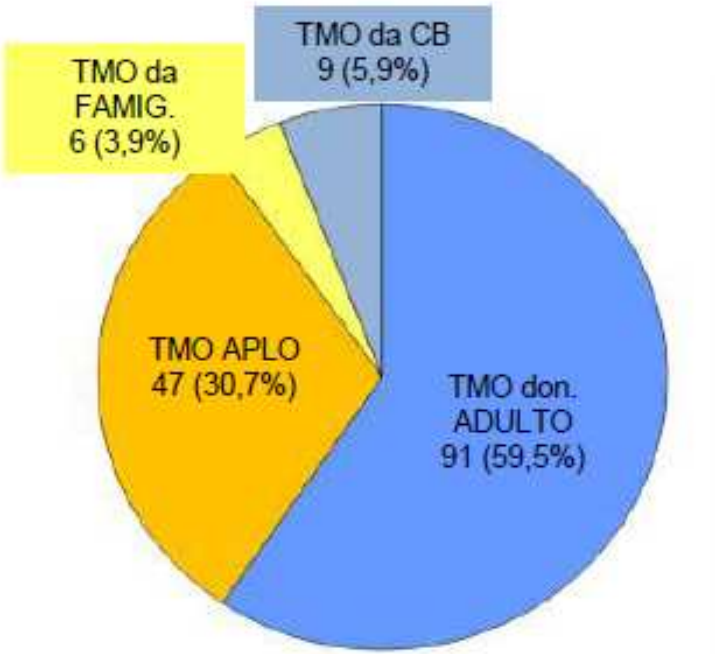


GITMO

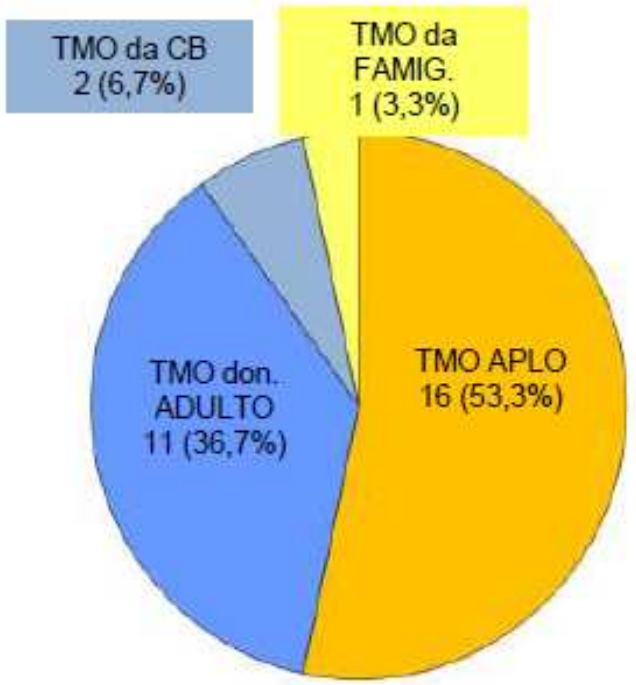
Numero trapianti– impatto aplo



Un fenomeno esplosivo



Ultimo trimestre 2014



Primo trimestre 2015

La storia I

THE LANCET

MISMATCHED FAMILY DONORS FOR BONE-MARROW TRANSPLANTATION AS TREATMENT FOR ACUTE LEUKAEMIA

R.L. Powles, H.E.M. Kay, H.M. Clink, A. Barrett, M.H. Depledge, J. Sloane, H. Lumley, S.D. Lawler, G.R. Morgenstern, T.J. Mcelwain, P.J. Dady, B. Jameson, J.G. Watson, M. Leigh, D. Hedley, J. Filshie, B. Robinson

35 patients, 10 (29%) experienced graft failure.
GVHD was a contributing cause of death in six patients (17%)
12 (34%) died of an inflammatory syndrome suggestive of hyperacute GVHD
None of the 12 patients over 30 years of age survived.

Lancet Volume 321, 8325, 1983, 612–615

La storia II

Marrow Transplantation from Related Donors Other Than HLA-Identical Siblings

Patrick G. Beatty, M.D., Ph.D., Reginald A. Clift, F.I.M.L.S., Eric M. Mickelson, Brenda B. Nisperos, Nancy Flournoy, Ph.D., Paul J. Martin, M.D., Jean E. Sanders, M.D., Patricia Stewart, M.D., C. Dean Buckner, M.D., Rainer Storb, M.D., E. Donnall Thomas, M.D., and John A. Hansen, M.D.

FHCRC Seattle 1985-1990
Tipizzazione sierologica

105 Haplo vs 728 id sib
12 phenotypically but not genotypically id
63 one locus mm
24 two loci mm
6 three loci mm

graft failure /delayed (24% vs 14%; *P* <0.005)
grade II–IV a GVHD (70% vs 42%; *P* <0.001)

Risultati confermati in altri 2 studi :

•*Anasetti C et al.* Effect of HLA compatibility on engraftment of bone marrow transplants in patients with leukemia or lymphoma. *N. Engl. J. Med.* 320, 197–204 (1989).
•Anasetti, C. *et al.* Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. *Hum. Immunol.* 29, 79–91 (1990).

N Engl J Med 1985; 313:765-771S eptember 26, 1985

La storia III

Results of allogeneic bone marrow transplants for leukemia using donors other than HLA-identical siblings.

R Szydlo, J M Goldman, J P Klein, R P Gale, R C Ash, F H Bach, B A Bradley, J T Casper, N Flomenberg, J L Gajewski, E Gluckman, P J Henslee-Downey, J M Hows, N Jacobsen, H J Kolb, B Lowenberg, T Masaoka, P A Rowlings, P M Sondel, D W van Bekkum, J J van Rood, M R Vowels, M J Zhang and M M Horowitz

Studio IBMTR 2055 pt 1985-1991
Tipizzazione sierologica
1224 id sib
Alternativi :
238 haplo 1 mm
102 haplo 2 mm
383 MUD 6/6
108 MUD 1 mm

Early pts
TRM 21% id sib vs 50% alternative
Relative risks treatment failure
2.43 (P < .0001) with 1-HLA-mm
3.79 (P < .0001) with 2-HLA-mm,
2.11 (P < .0001) with HLA-MUD 6/6,
3.33 (P < .0001) with 1-HLA-mm UD.

J Clin Oncol. 1997 May;15(5):1767-77

La storia IV

In conclusione

Il trapianto da donatore aploidentico era caratterizzato da intensa alloreattività

HVG ⟷ GVH

Incidenza inaccettabilmente alta di Rigetto, GvHD e quindi di Mortalità

STRADA NON PERCORRIBILE

ma ….. l' Idea: T Deplezione

T cells are considered key mediators of GVHD and graft rejection, with the T-cell content of the graft having a clear association with the risk of GVHD

Remove T cells from the allograft before infusion

Memorial Sloan Kettering Cancer Center

Clinical haplo BMT using this approach resulted in sustained engraftment in three of four patients without any detectable GVHD

Graft failure remained a persistent problem, affecting more than 20% of patients receiving TCD–alloBMT from donors other than HLA-matched siblings.

Reisner, Y., Ravid, A. & Sharon, N. Use of soybean agglutinin for the separation of mouse B and T lymphocytes. *Biochem. Biophys Res. Commun.* 72, 1585–1591 (1976).
Reisner, Y., Itzicovitch, L., Meshorer, A. & Sharon, N. Haemopoietic stem cell transplantation using mouse bone marrow and spleen cells fractionated by lectins. *Proc. Natl Acad. Sci. USA* 75, 2933–2936 (1978).
Reisner, Y., Kapoor, N., O'Reilly, R. J. & Good, R. A. Allogeneic bone marrow transplantation using stem cells fractionated by lectins: VI, *in vitro* analysis of human and monkey bone marrow cells fractionated by sheep red blood cells and soybean agglutinin. *Lancet* 2, 1320–1324 (1980).
Reisner, Y. et al. Transplantation for acute leukaemia with HLA-A and B nonidentical parental marrow cells fractionated with soybean agglutinin and sheep red blood cells. Lancet 2, 327–331 (1981).
Reisner, Y. et al. Transplantation for severe combined immunodeficiency with HLA-A, B, D, DR incompatible parental marrow cells fractionated by soybean agglutinin and sheep red blood cells. Blood 61, 341–348 (1983).

l' idea/2 : Megadose di cellule

graft failure is direct adverse effect of TCD,

graft failure is associated with conditioning-resistant, anti-donor T cells in the host

mouse studies showed that full donor engraftment without GVHD could be achieved by infusion of 'megadoses' of TCD bone marrow.

…..competition for the stem-cell niche in the marrow,

but also a 'veto effect' in which CD34+ cells directly inhibited T-cell alloreactivity.

Lapidot, T. *et al.* Enhancement of bone marrow allografts from nude mice into mismatched recipients by T cells void of graft-versus-host activity. *Proc. Natl Acad. Sci. USA* 87, 4595–4599 (1990).

Bachar-Lustig, E., Rachamim, N., Li, H. W., Lan, F. & Reisner, Y. Megadose of T cell-depleted bone marrow overcomes MHC barriers in sublethally irradiated mice. *Nat. Med.* 1, 1268–1273 (1995).

Rachamim, N. *et al.* Tolerance induction by "megadose" haematopoietic transplants: donor-type human CD34 stem cells induce potent specific reduction of host anti-donor cytotoxic T lymphocyte precursors in mixed lymphocyte culture. *Transplantation* 65, 1386–1393 (1998).

Reisner, Y., Gur, H., Reich-Zeliger, S., Martelli, M. F. & Bachar-Lustig, E. Haematopoietic stem cell transplantation across major genetic barriers: tolerance induction by megadose CD34 cells and other veto cells. *Ann. N. Y. Acad. Sci.* 996, 72–79 (2003).

Il sogno: un trapianto per tutti

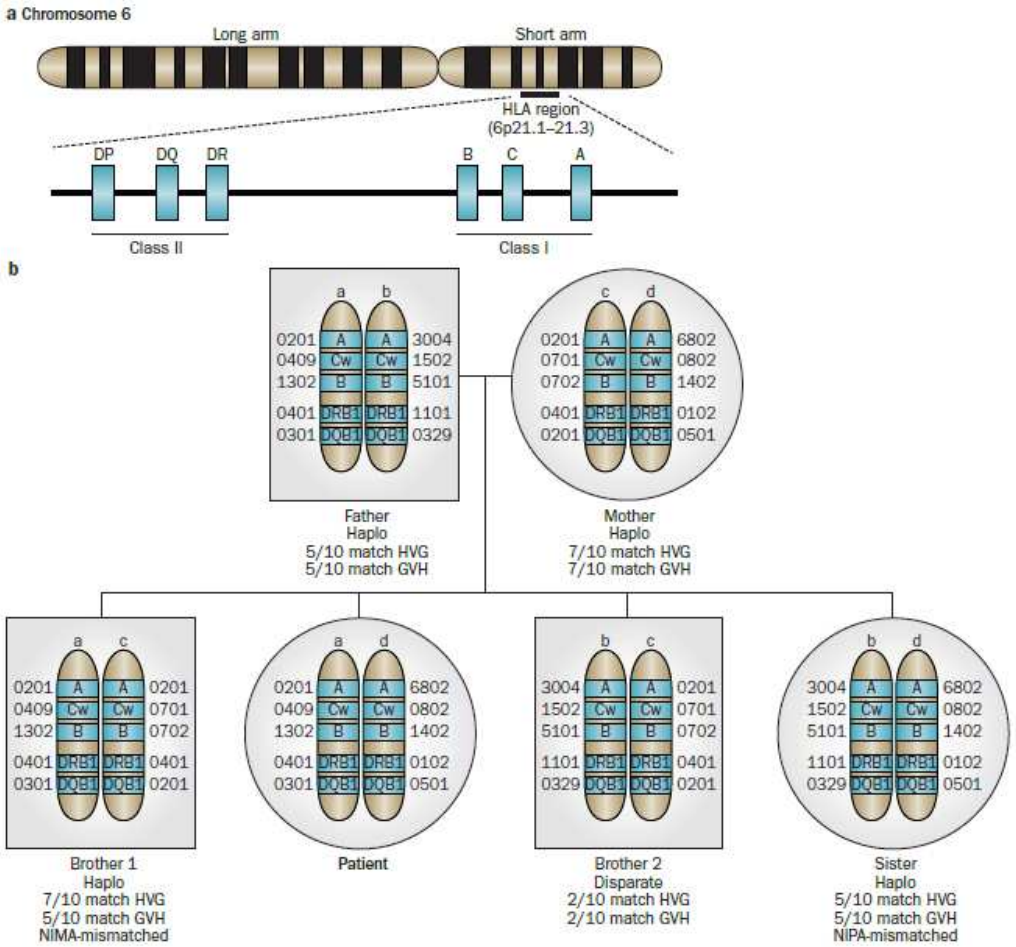
Trapianto Aploidentico

Oltre il 90 % dei pazienti ha un donatore aploidentico

Donatori prontamente disponibili

Costi competitivi con MUD e CB se non manipolati

Haplo donor e anche meglio

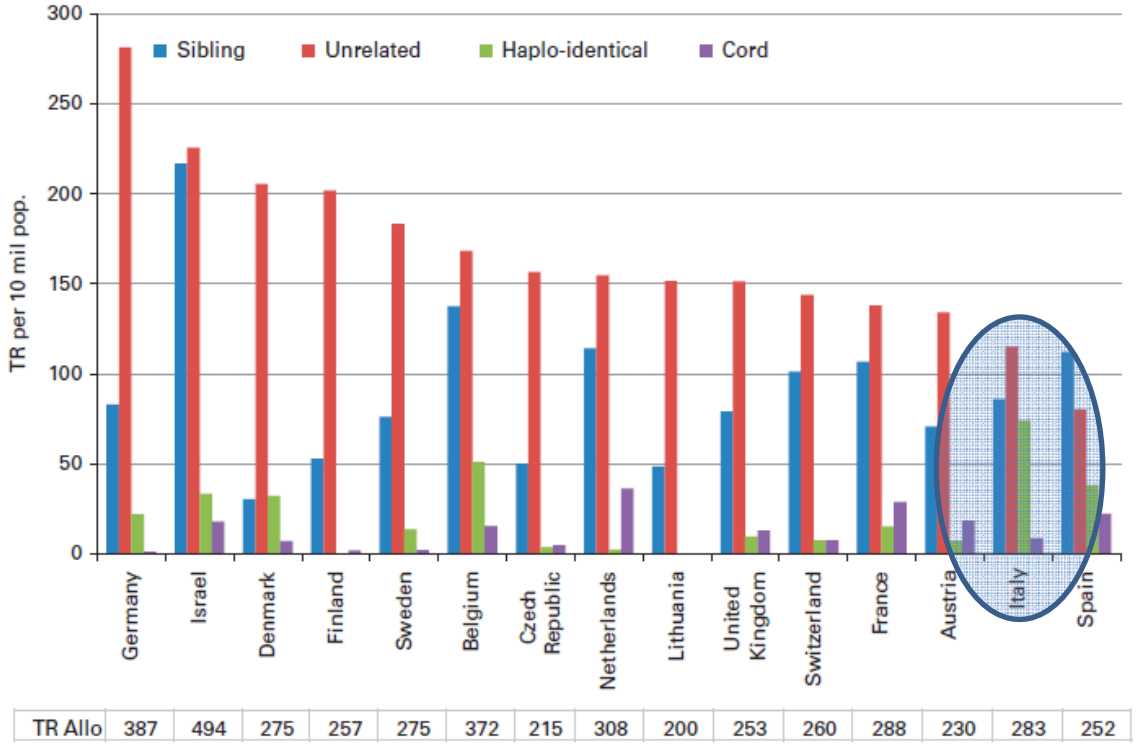


Kanakry, C. G. *et al. Nat. Rev. Clin. Oncol.* advance online publication 25 August 2015

Oggi più piattaforme

1. T-Depletion
   - Ex vivo T-Depletion
   - MAC Intensified Conditioning
   - Megadose CD 34+
2. GIAC:
   - G-CSF primed BM
   - Intensified Immunosuppression CYA+MTX+MMF
   - ATG
   - Combined BM + (PBSC)
3. Post Transplantation HD Cyclophosphamide
4. TrRaMM study: Sirolimus

Perché tanto successo in Italia ?



TR Allo	387	494	275	257	275	372	215	308	200	253	260	288	230	283	252

Perugia T deplezione

Regime di condizionamento intensificato:

Thiotepa +cyclophosphamide + TBI + ATG.

donor bone marrow + GCSF-mobilized peripheral-blood stem cells (PBSCs)

stem-cell dose megadoses, (7/10-fold than in bone-marrow allografts)

allografts were T depleted(soybean agglutination + erythrocyte rosetting).

No post-grafting immunosuppression was given.

This study showed that the historical barriers to haploBMT of graft failure and GVHD both could be overcome by intensive myeloablative and immunosuppressive conditioning followed by TCD 'megadose' allografts, without any need for additional GVHD prophylaxis.

Successful engraftment of……. *Aversa F et al Blood* 84, 3948–3955 (1994)

Perugia II

Full Haplotype-Mismatched Hematopoietic Stem-Cell Transplantation: A Phase II Study in Patients With Acute Leukemia at High Risk of Relapse

Franco Aversa, Adelmo Terenzi, Antonio Tabilio, Franca Falzetti, Alessandra Carotti, Stelvio Ballanti, Rita Felicini, Flavio Falcinelli, Andrea Velardi, Loredana Ruggeri, Teresa Aloisi, Jean Pierre Saab, Antonella Santucci, Katia Perruccio, Maria Paola Martelli, Cristina Mecucci, Yair Reisner, and Massimo F. Martelli

They substitute cyclophosphamide with Fludarabine

G-CSF-mobilized peripheral-blood stem cells (PBSCs)

T depletion: immunomagnetic selection

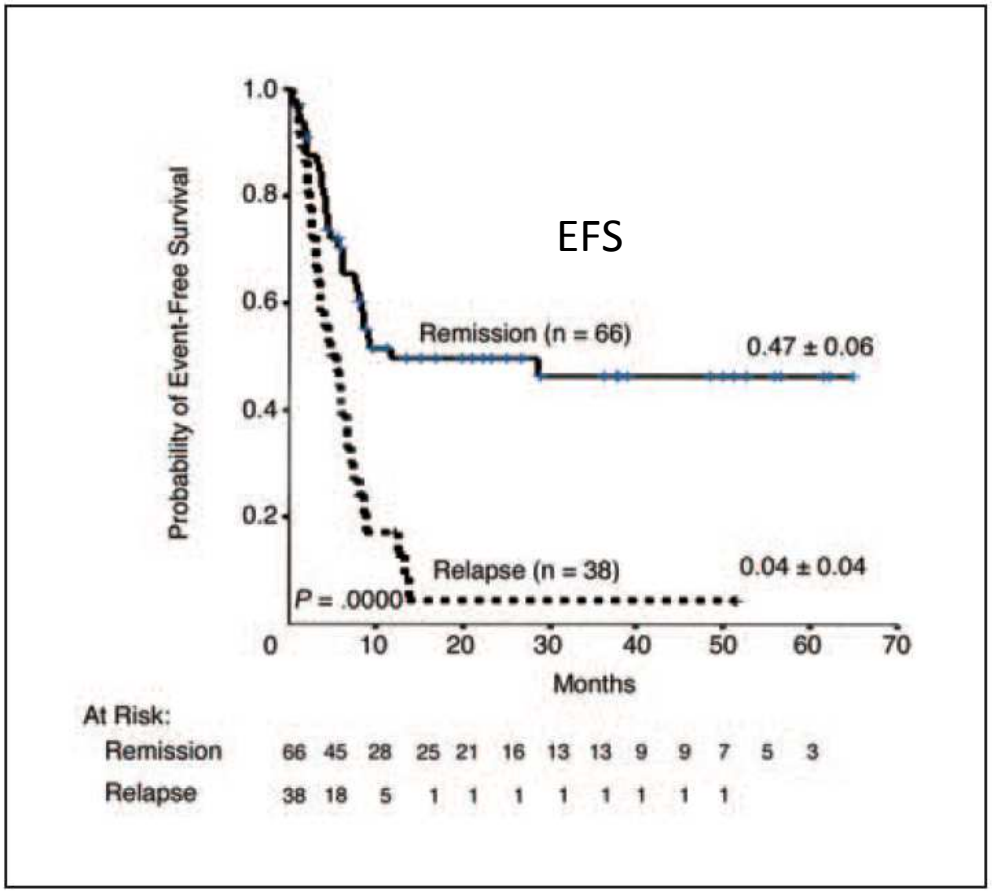
No post-grafting immunosuppression

Graft failure 5-7%

GvHD < 10%

J Clin Oncol 23:3447-3454. © 2005

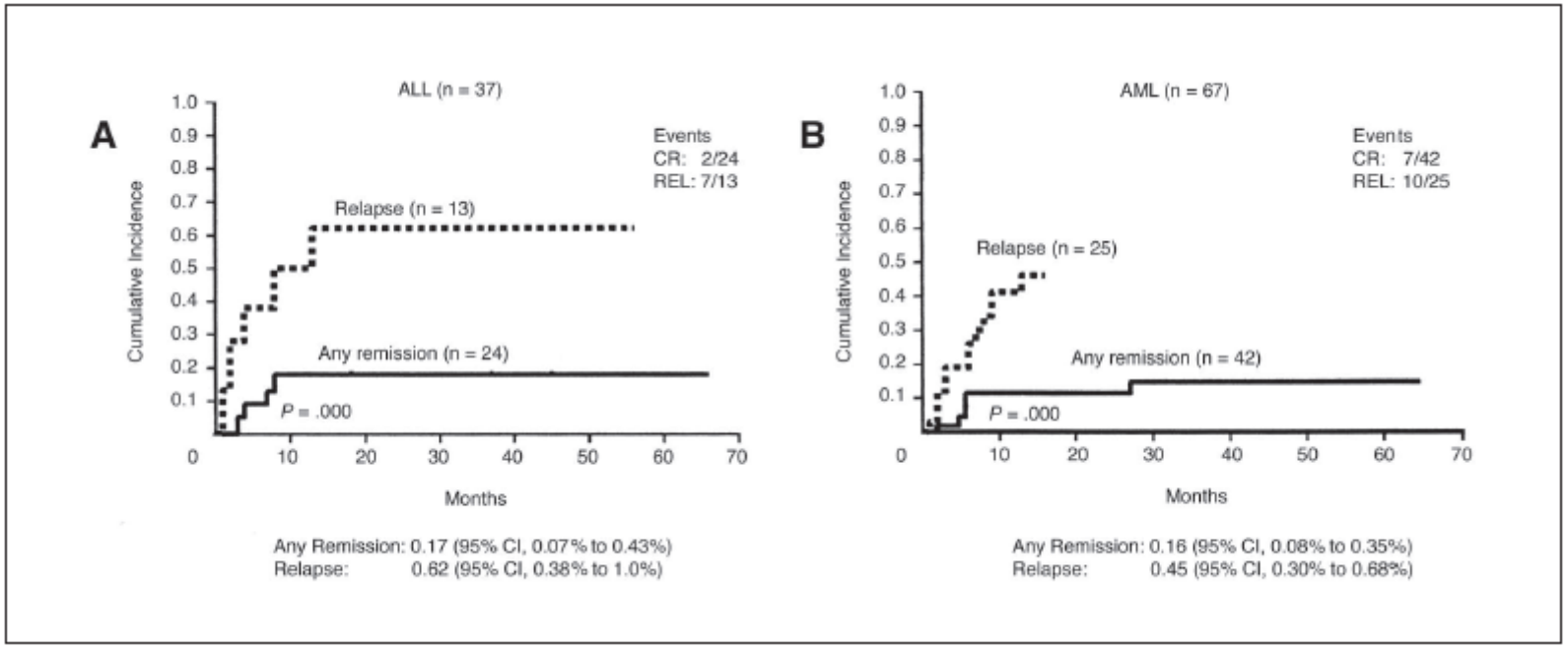
Perugia III



J Clin Oncol 23:3447-3454. © 2005

Perugia IV

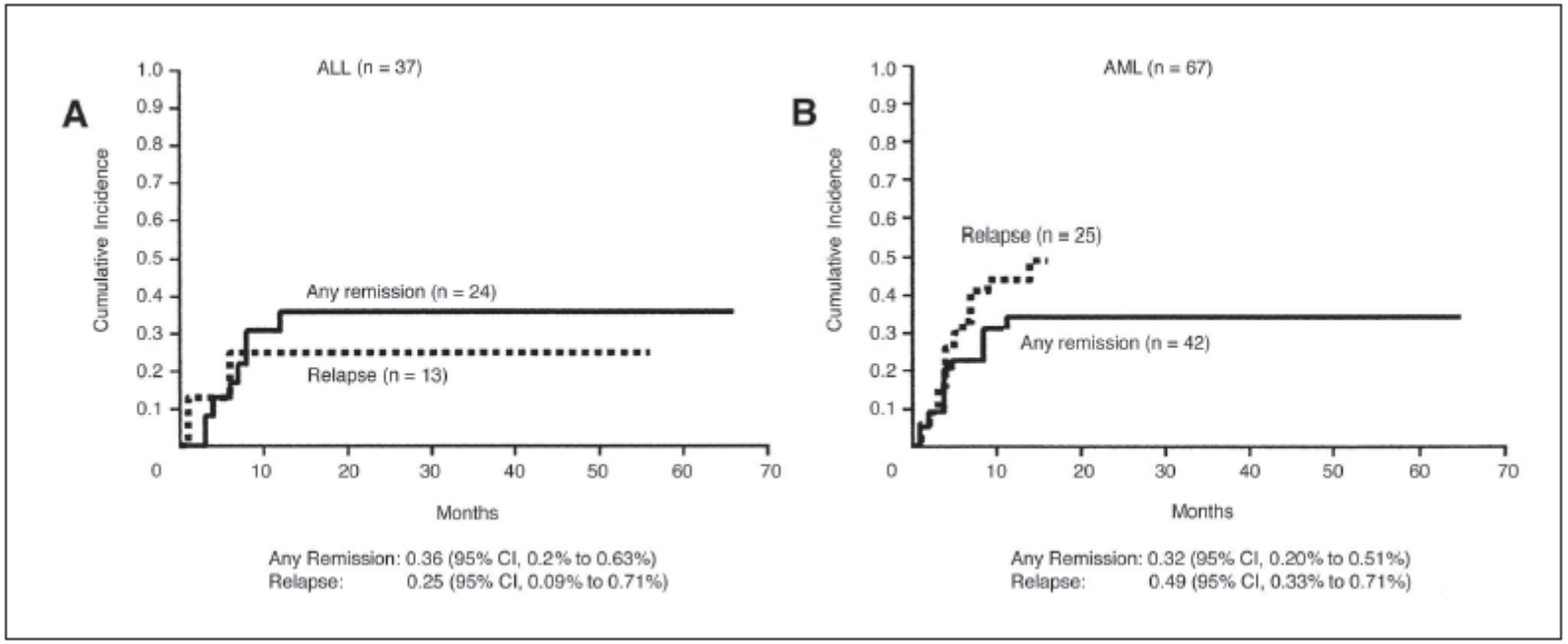
Relapse



J Clin Oncol 23:3447-3454. © 2005

Perugia V

TRM



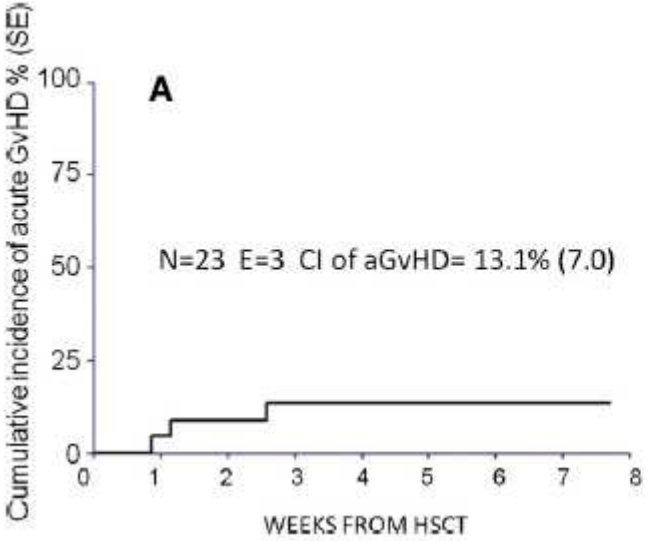
J Clin Oncol 23:3447-3454. © 2005

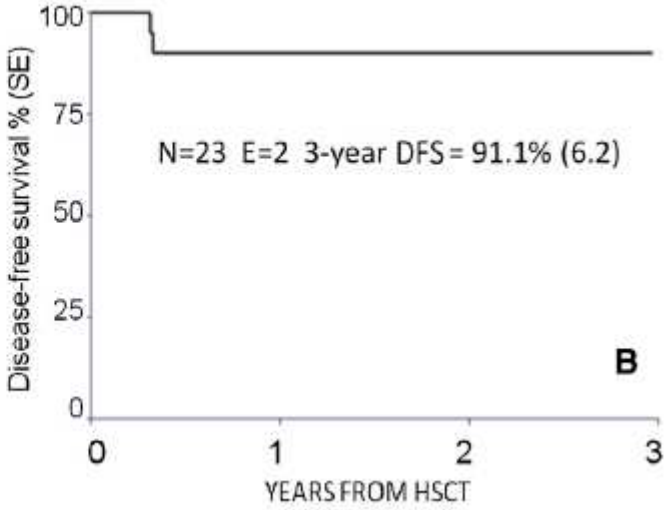
Oggi AlfaBeta-T e B deplezione

HLA-haploidentical stem cell transplantation after removal of $\alpha\beta^+$ T and B cells in children with nonmalignant disorders

Alice Bertaina, Pietro Merli, Sergio Rutella, Daria Pagliara, Maria Ester Bernardo, Riccardo Masetti, Daniela Pende, Michela Falco, Rupert Handgretinger, Francesca Moretta, Barbarella Lucarelli, Letizia P. Brescia, Giuseppina Li Pira, Manuela Testi, Caterina Cancrini, Nabil Kabbara, Rita Carsetti, Andrea Finocchi, Alessandro Moretta, Lorenzo Moretta and Franco Locatelli

Condizionamento + ATG + PBSC + selezione $\alpha\beta$ e B no immunosuppression post





BLOOD, 31 JULY 2014 • VOLUME 124, NUMBER 5

Basi Biologiche GIAC

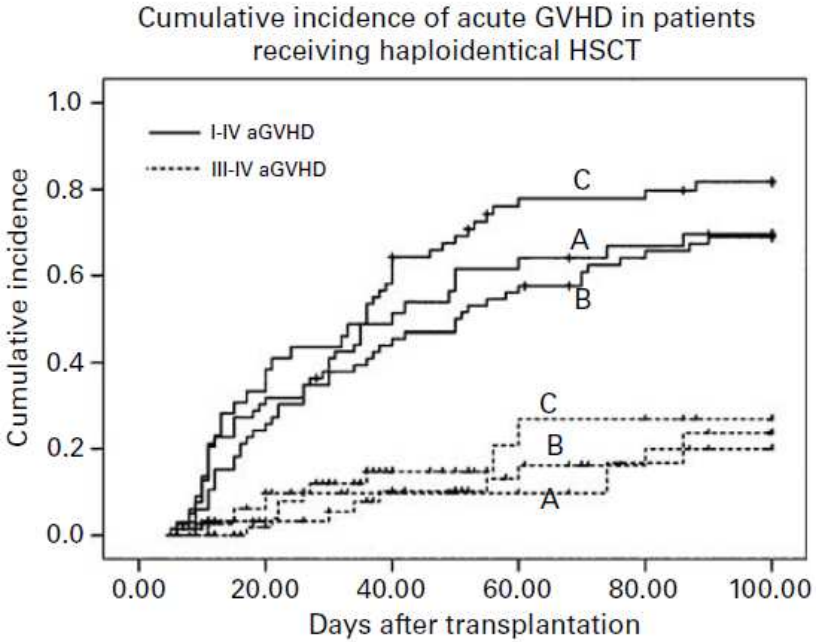
- G-CSF primed BM
- Intensified Immunosuppression CYA+MMF+MTX
- ATG
- Combined BM + (PBSC)

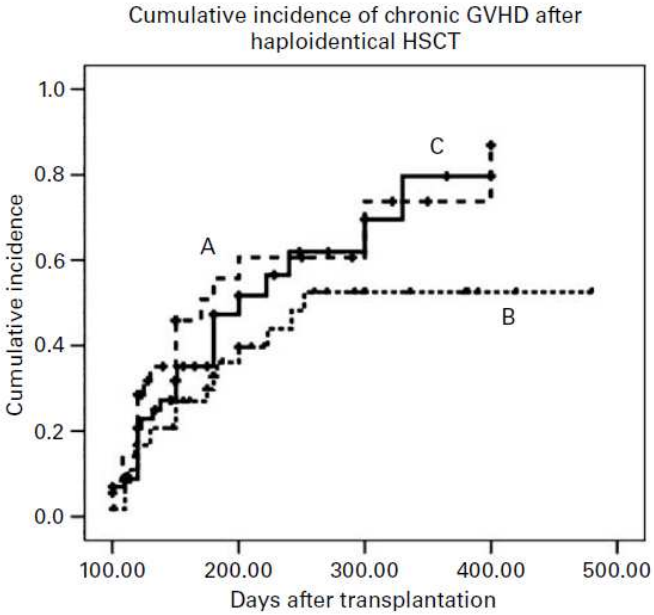
- T-helper type 1 (TH1) cell differentiation promote GVHD
- T-helper type 2 (TH2) cell differentiation protects from GvHD
- T cells mobilized from the bone marrow into the blood under the influence of GCSF are less proliferative, have reduced production of TH1 cytokines, and have increased production of the TH2 cytokine IL-4.
- GCSF also resulted in mobilization of dendritic cells, promoting skewing of T cells towards a TH2 phenotype.
- Such immunological effects could be maintained when mixing GCSF-stimulated PBSC and bone-marrow allografts.
- Administration of GCSF post-transplantation, potentiated skewing towards a TH2 phenotype at the cost of delayed recovery of normal TH1 responses to pathogens.

Pechino: famiglie monofiglio

Haploidentical hematopoietic stem cell transplantation without *in vitro* T-cell depletion for the treatment of hematological malignancies

X-J Huang, D-H Liu, K-Y Liu, L-P Xu, H Chen, W Han, Y-H Chen, J-Z Wang, Z-Y Gao, Y-C Zhang, Q Jiang, H-X Shi and D-P Lu



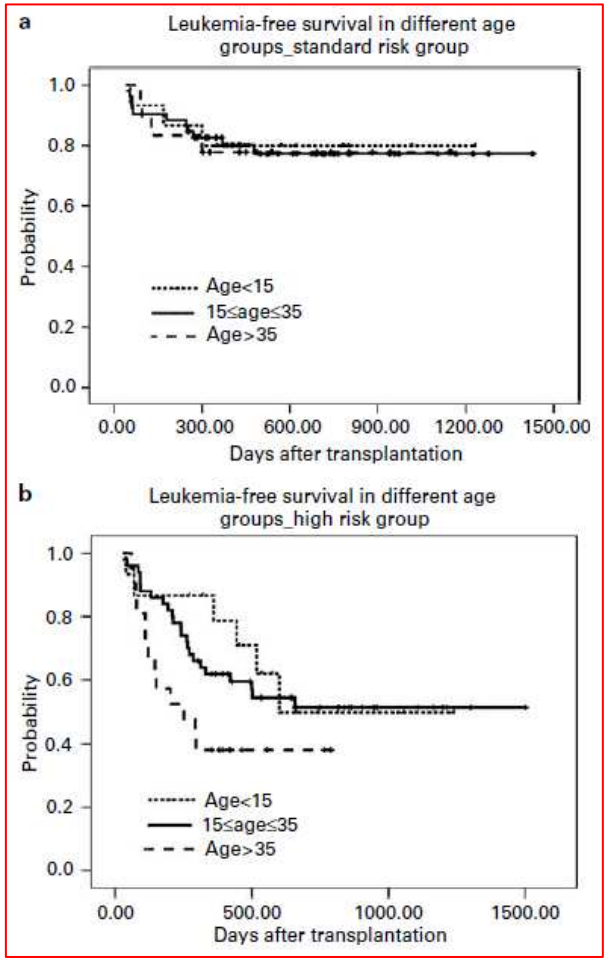


Condizionamento ARA-C +BU+ Cy+CCNU MAC o RIC
Profilassi GvHD ATG, CSA, MTX, MMF,
Donazione di midollo stimolato con G-CSF + PBSC

A,B,C= 1, 2 o 3 mm

Bone Marrow Transplantation (2006) 38, 291–297

Leukemia free survival



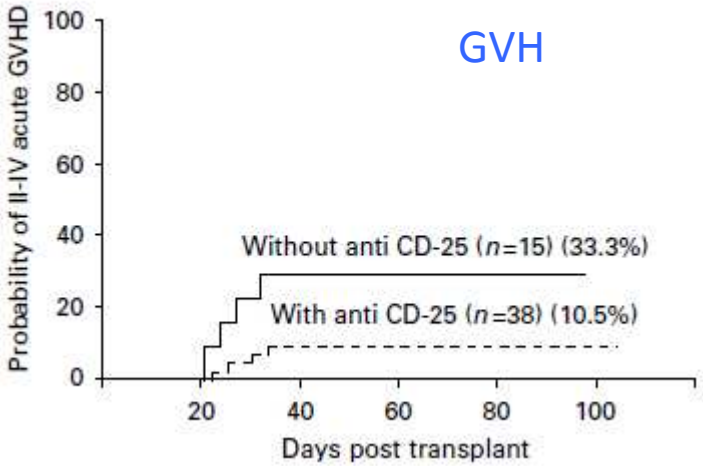
A,B,C= 1, 2 o 3 mm

Bone Marrow Transplantation (2006) 38, 291–297

Basiliximab

Anti-CD25 monoclonal antibody (basiliximab) for prevention of graft-versus-host disease after haploidentical bone marrow transplantation for hematological malignancies

S-Q Ji[1], H-R Chen[1], H-M Yan[1], H-X Wang[1], J Liu[1], P-y Zhu[1], M-h Xiao[1] and C-Q Xun[2]



GVH

Profilassi GVH

ATG

CSA

MTX

MMF

con o senza Anti CD 25

Condizionamento ARA-C +TBI+ Cy MAC

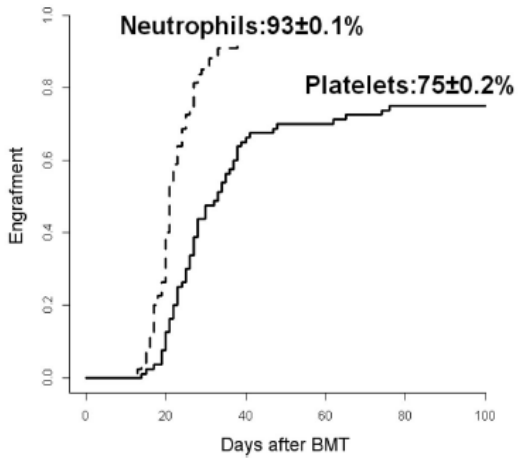
Donazione di midollo stimolato con G-CSF

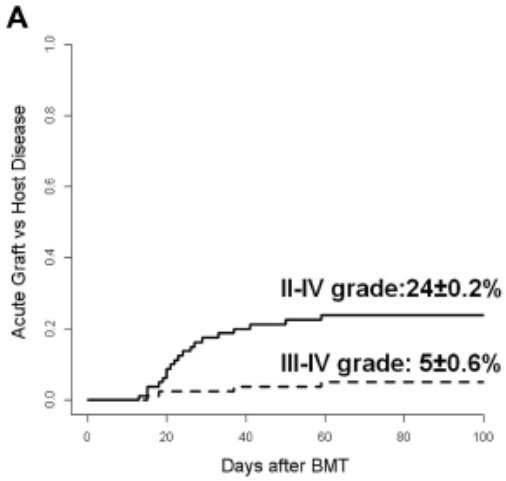
Bone Marrow Transplantation (2005) 36, 349–354

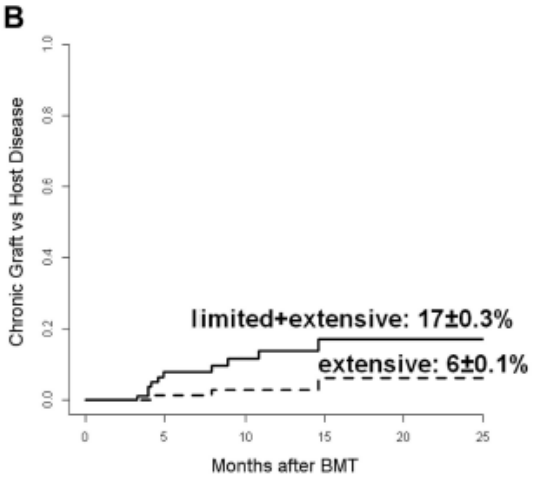
Esperienza Pesaro - Roma

Haploidentical, unmanipulated, G-CSF–primed bone marrow transplantation for patients with high-risk hematologic malignancies

Paolo Di Bartolomeo,[1] Stella Santarone,[1] Gottardo De Angelis,[2] Alessandra Picardi,[2] Laura Cudillo,[2] Raffaella Cerretti,[2] Gaspare Adorno,[3] Stefano Angelini,[2] Marco Andreani,[4] Lidia De Felice,[5] Maria Cristina Rapanotti,[2] Loredana Sarmati,[6] Pasqua Bavaro,[1] Gabriele Papalinetti,[1] Marta Di Nicola,[7] Franco Papola,[8] Mauro Montanari,[9] Arnon Nagler,[10] and William Arcese[2]







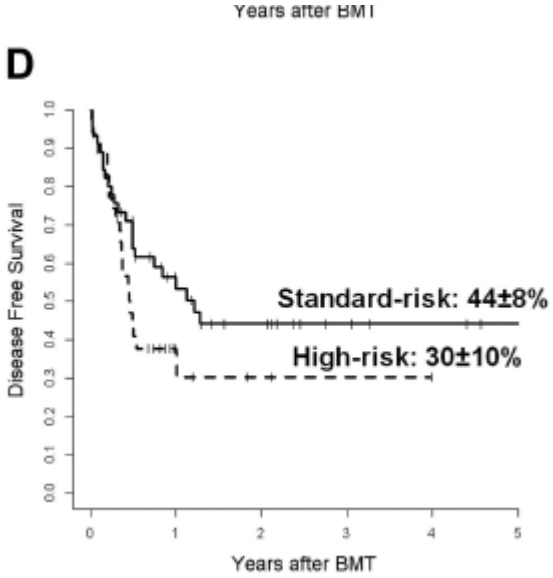
Condizionamento TBF MAC o RIC

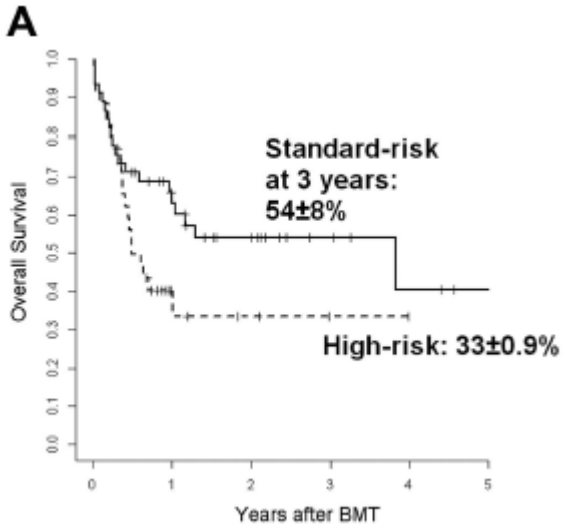
Profilassi GvHD ATG, CSA, MTX, MMF, Anti CD 25

Donazione di midollo stimolato con G-CSF non manipolato

BLOOD, 31 JANUARY 2013 • VOLUME 121, NUMBER 5

Survival


Years after BMT
D
Disease Free Survival
Standard-risk: 44±8%
High-risk: 30±10%
Years after BMT


A
Overall Survival
Standard-risk
at 3 years:
54±8%
High-risk: 33±0.9%
Years after BMT

Ciclofosfamide postrapianto

Tolleranza in senso bidirezionale GVH e HVG

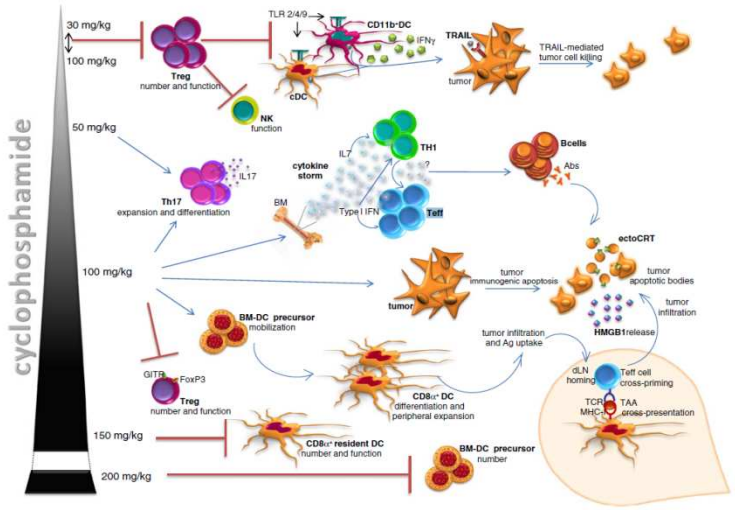


Fig. 1 Example of a chemotherapy exhibiting potent immunomodulatory effects

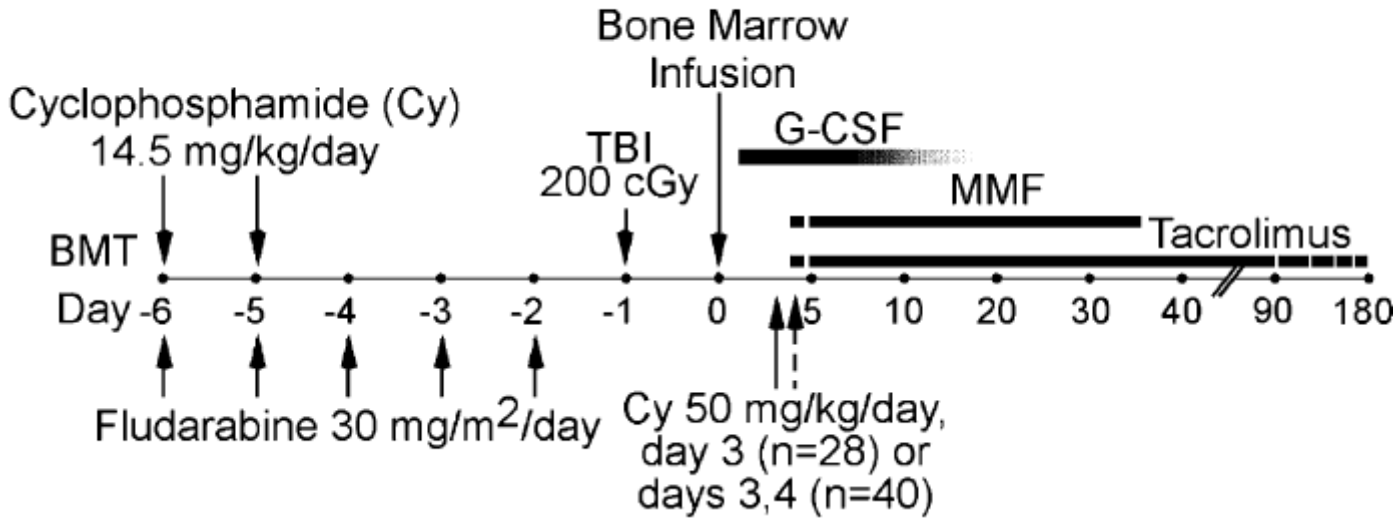
- **distruzione selettiva delle cellule T alloreattive in vivo**
  - è una fase immediatamente post trapianto con distruzione delle T anti donatore e anti ricevente
- **delezione clonale intratimica delle cellule T del donatore anti ricevente**
  - fenomeno più tardivo ma persistente ed indispensabile per la tolleranza a lungo termine
- **sviluppo di tolleranza periferica**
  - per espansione delle Tregs non ostante la linfopenia persistente
- **Induce tolleranza solo ad alte dosi**
- **Non è tossica per le CSE perché ricche di aldeide deidrogenasi**

Sistigu et al Semin Immunopathol. 2011;

Ciclofosfamide post RIC

HLA-Haploidentical Bone Marrow Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and High-Dose, Posttransplantation Cyclophosphamide

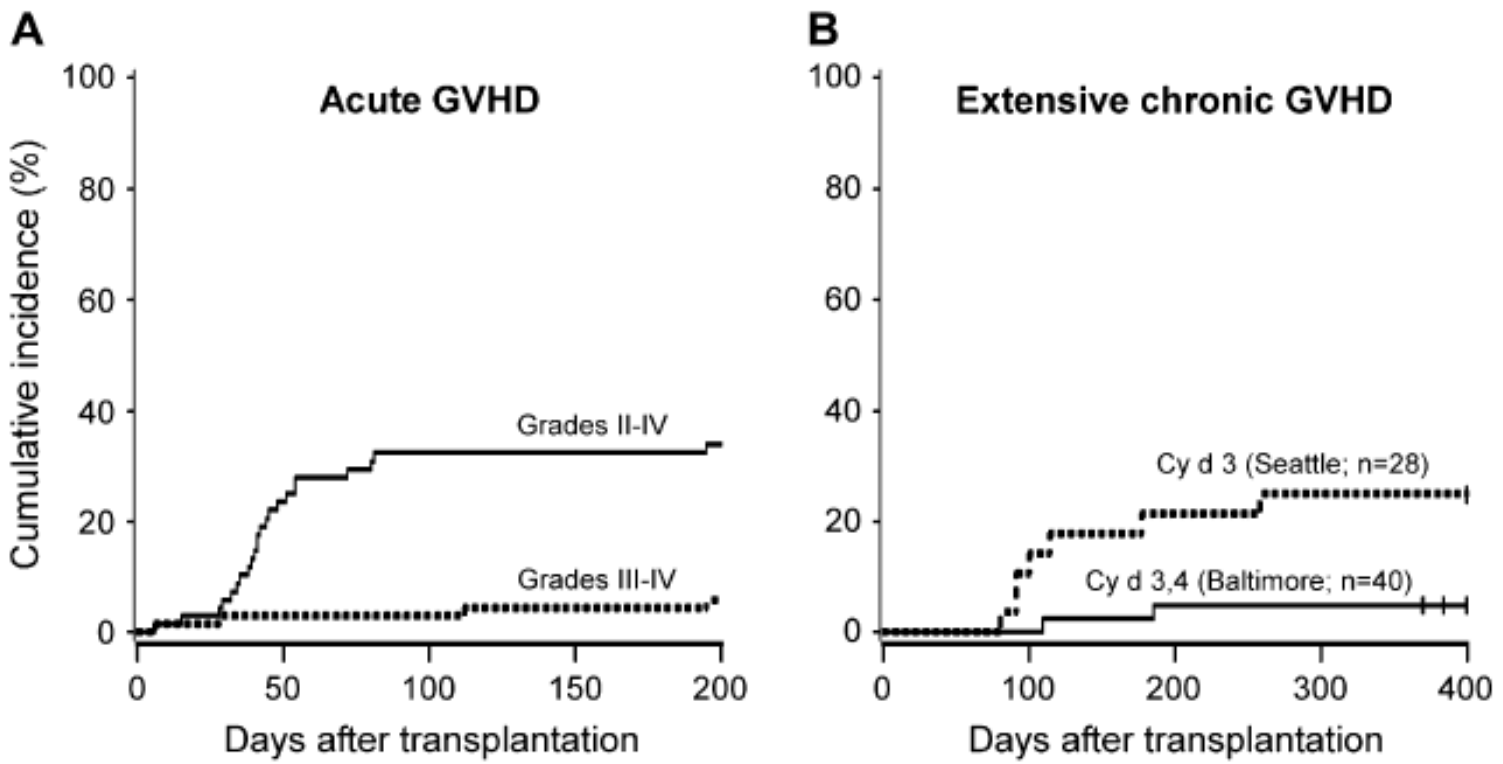
Leo Luznik,[1] Paul V. O'Donnell,[2,3]* Heather J. Symons,[1] Allen R. Chen,[1] M. Susan Leffell,[1] Marianna Zahurak,[1] Ted A. Gooley,[2,3] Steve Piantadosi,[1] Michele Kaup,[1] Richard F. Ambinder,[1] Carol Ann Huff,[1] William Matsui,[1] Javier Bolaños-Meade,[1] Ivan Borrello,[1] Jonathan D. Powell,[1] Elizabeth Harrington,[2] Sandy Warnock,[2] Mary Flowers,[2,3] Robert A. Brodsky,[1] Brenda M. Sandmaier,[2,3] Rainer F. Storb,[2,3] Richard J. Jones,[1] Ephraim J. Fuchs[1]*



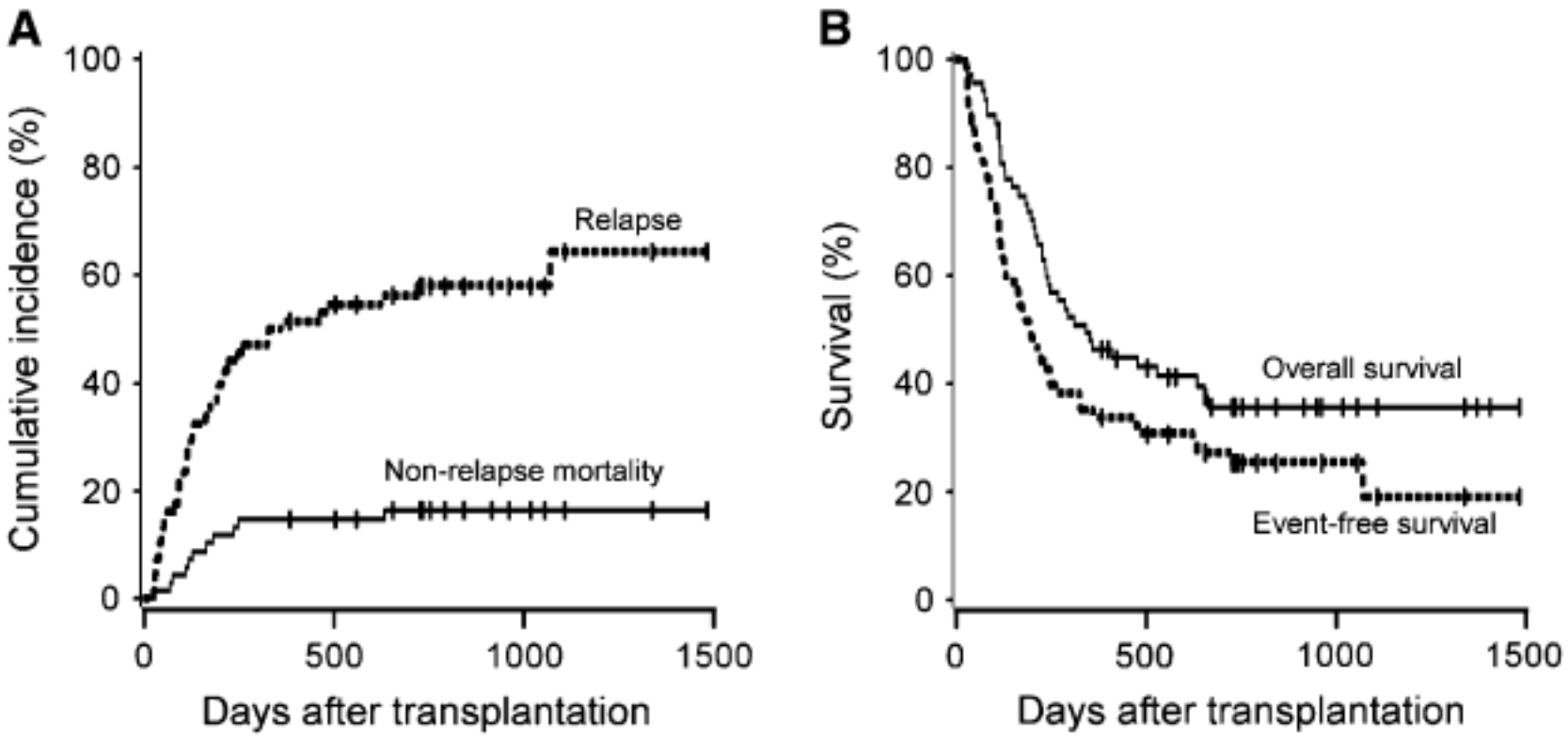
Biology of Blood and Marrow Transplantation 14:641-650 (2008)

……. death w/o engraftment

Biology of Blood and Marrow Transplantation 14:641-650 (2008)



Biology of Blood and Marrow Transplantation 14:641-650 (2008)



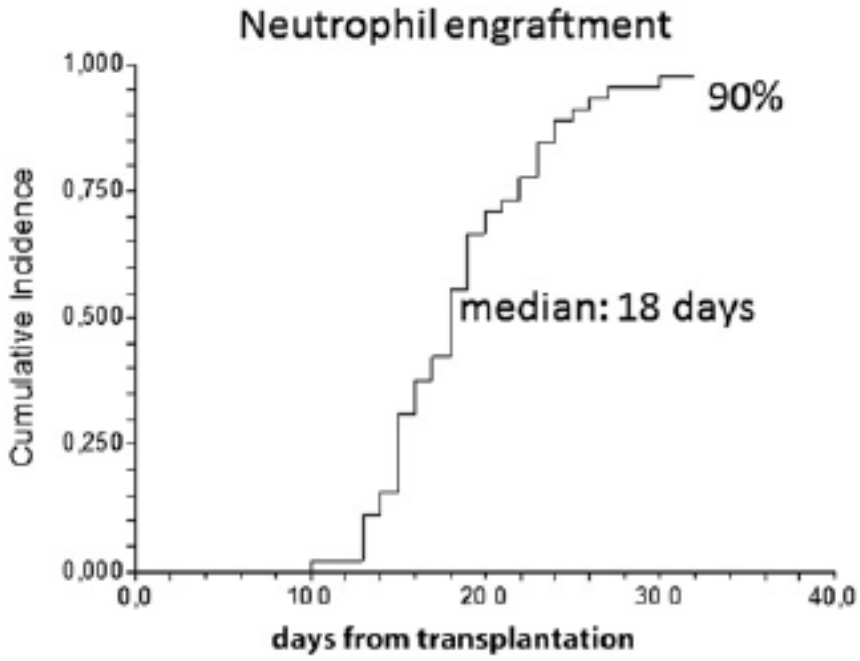
Biology of Blood and Marrow Transplantation 14:641-650 (2008)

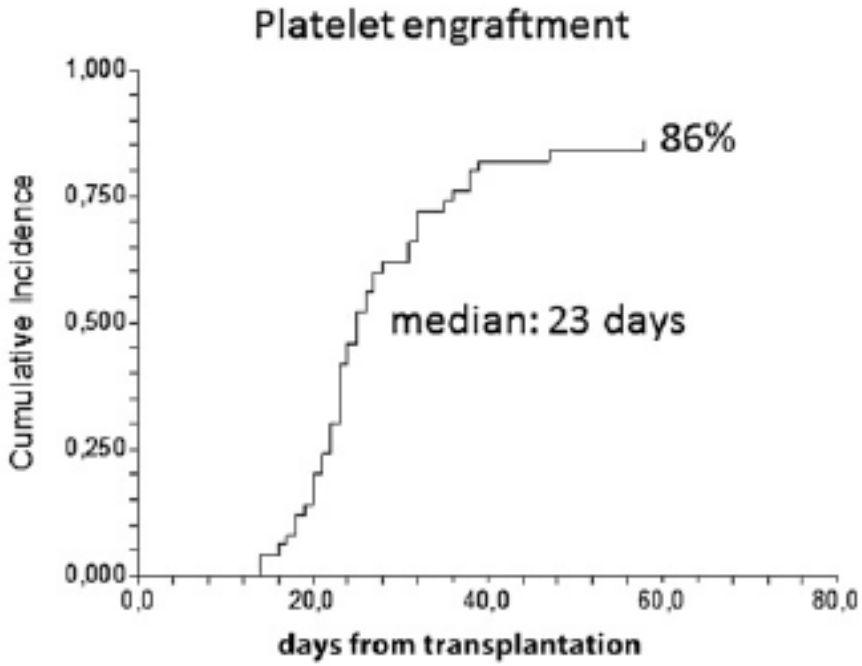
Ciclofosfamide post MAC Genova

Unmanipulated Haploidentical Bone Marrow Transplantation and Posttransplantation Cyclophosphamide for Hematologic Malignancies after Myeloablative Conditioning

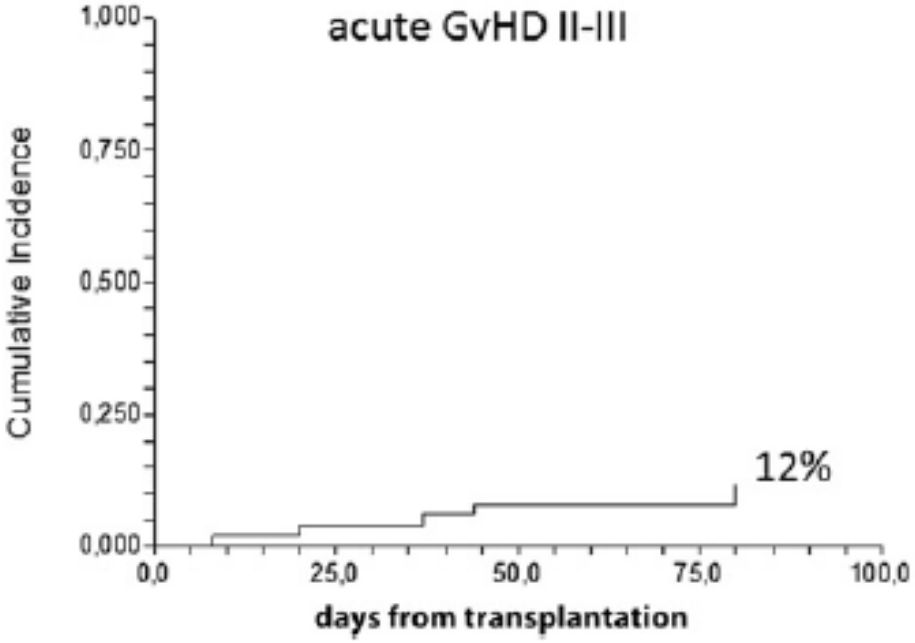
Anna Maria Raiola, Alida Dominietto, Anna Ghiso, Carmen Di Grazia, Teresa Lamparelli, Francesca Gualandi, Stefania Bregante, Maria Teresa Van Lint, Simona Geroldi, Silvia Luchetti, Filippo Ballerini, Maurizio Miglino, Riccardo Varaldo, Andrea Bacigalupo*

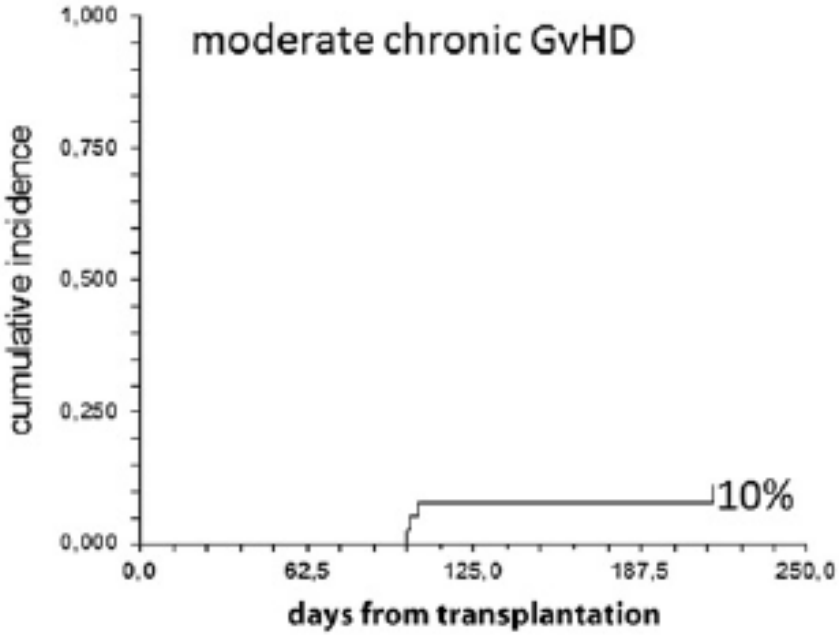
MAC TBF o TBI + Fluda
CSA da 0 ATG MMF
Cy +3 e +5
BM



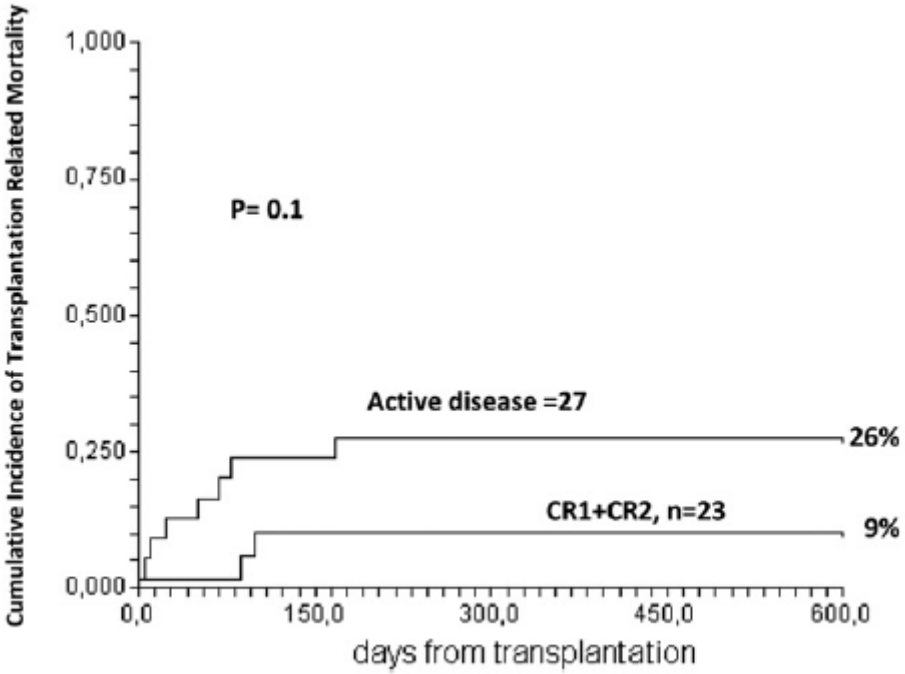


Biol Blood Marrow Transplant 19 (2013) 117–122

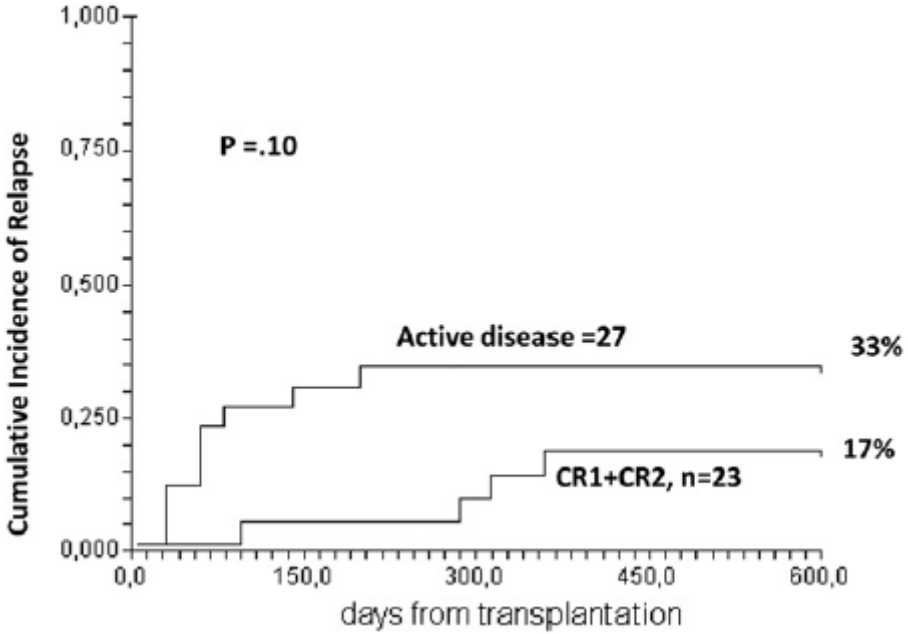

acute GvHD II-III
Cumulative Incidence
1,000
0,750
0,500
0,250
0,000
0,0
25,0
50,0
75,0
100,0
12%
days from transplantation


moderate chronic GvHD
cumulative incidence
1,000
0,750
0,500
0,250
0,000
0,0
62,5
125,0
187,5
250,0
10%
days from transplantation

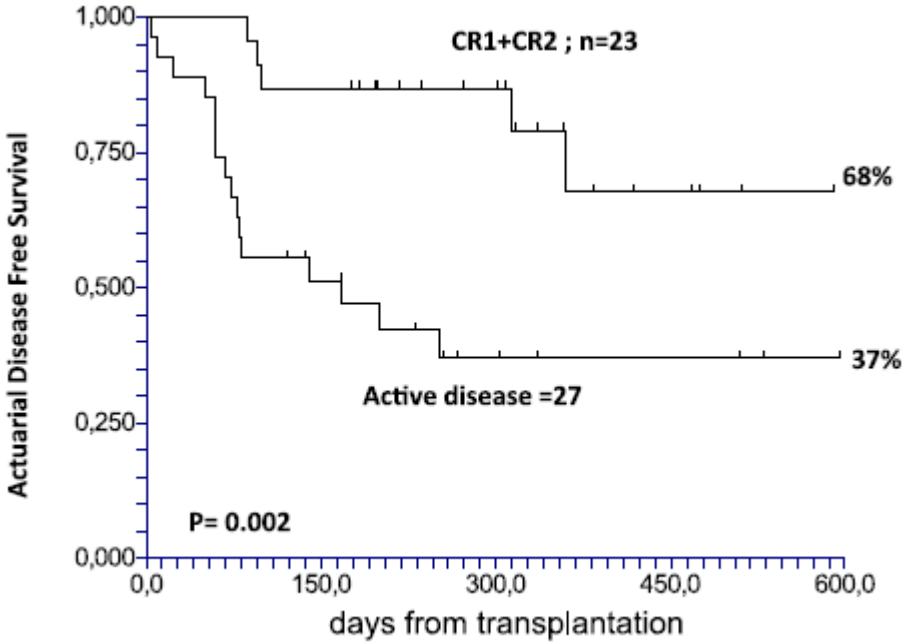
TRM



Relapse



Biol Blood Marrow Transplant 19 (2013) 117–122

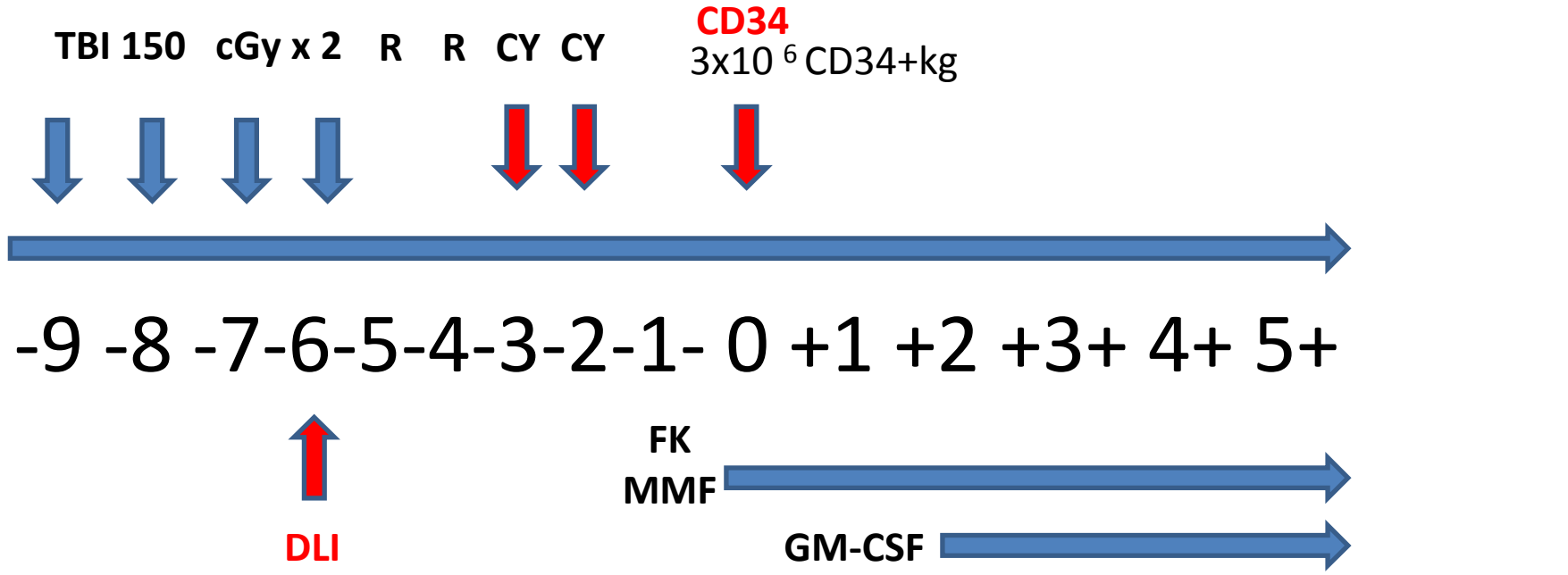

1,000
0,750
0,500
0,250
0,000
Actuarial Disease Free Survival
CR1+CR2 ; n=23
68%
37%
Active disease =27
P= 0.002
0,0
150,0
300,0
450,0
600,0
days from transplantation

Trapianto in due fasi

A 2-step approach to myeloablative haploidentical stem cell transplantation: a phase 1/2 trial performed with optimized T-cell dosing

Dolores Grosso,[1] Matthew Carabasi,[1] Joanne Filicko-O'Hara,[1] Margaret Kasner,[1] John L. Wagner,[1] Beth Colombe,[2] Patricia Cornett Farley,[3] William O'Hara,[4] Phyllis Flomenberg,[5] Maria Werner-Wasik,[6] Janet Brunner,[7] Bijoyesh Mookerjee,[1] Terry Hyslop,[1] Mark Weiss,[1] and Neal Flomenberg[1]

2-step myeloablative approach to haploidentical HSCT for which the primary goal was to provide a fixed—and ideally maximized—dose of T cells in the context of CY tolerization



BLOOD, 27 OCTOBER 2011 • VOLUME 118, NUMBER 17

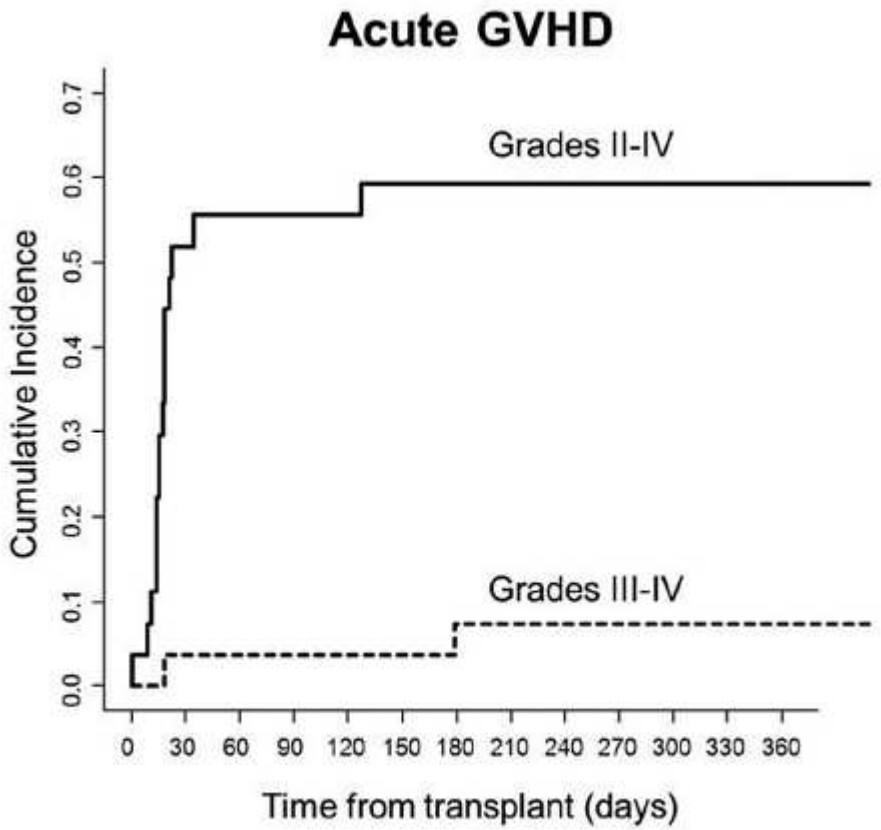


Figure 4. Acute GVHD. Cumulative incidences of grades II-IV and III-IV GVHD were 59.2% and 7.4%, respectively.

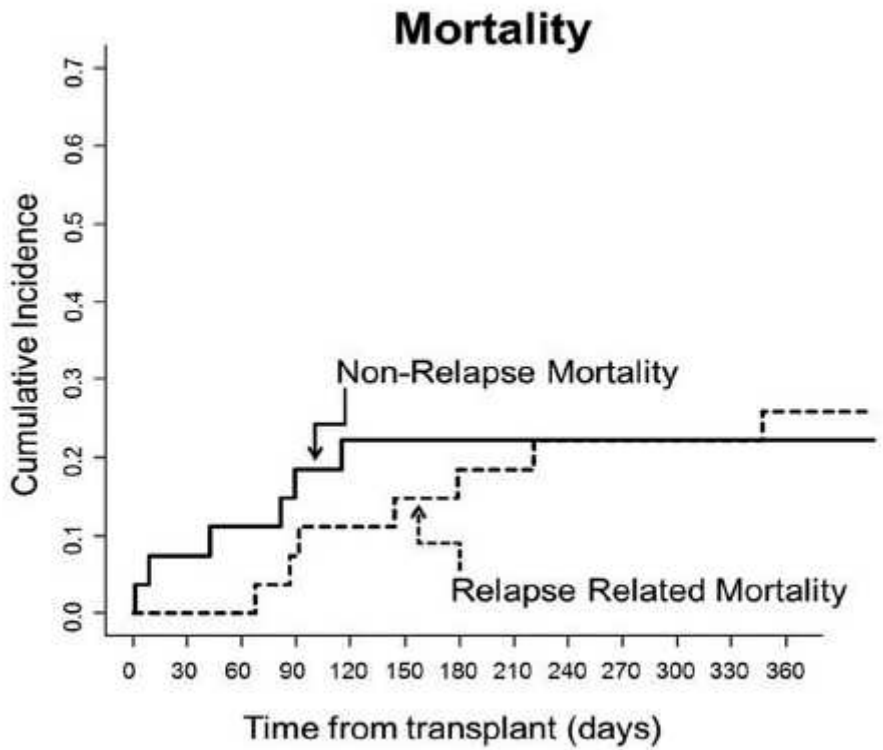


Figure 5. Relapse-related mortality and NRM. Cumulative incidences of relapse-related mortality and NRM were 29.6% and 22.2%, respectively.

TRM

Relapse

PTCy complicazioni

- Febbre “citochinica da alloreattività” +1 e +2 più frequente se PBSC
- Cistite emorragica da BKV
- Rigetto/ No take legato a DSA (Donor HLA Specific Antibodies)
- Desensibilizzazione Anti CD20 +plasma exchange
- Assenza di EBV related lymphoproliferative disease o altre malignità

Sirolimus

Rapamycin Promotes Expansion of Functional CD4$^+$CD25$^+$FOXP3$^+$ Regulatory T Cells of Both Healthy Subjects and Type 1 Diabetic Patients[1]

Manuela Battaglia,[2*†] Angela Stabilini,[*] Barbara Migliavacca,[*] Jutta Horejs-Hoeck,[‡] Thomas Kaupper,[§] and Maria-Grazia Roncarolo[2*¶]

……..activation of human CD4 T cells from healthy subjects in the presence of rapamycin leads to growth of CD4+CD25+FOXP3+ Tregs and to selective depletion of CD4+CD25- T effector cells, which are highly sensitive to the antiproliferative effect of the compound. The rapamycin-expanded Tregs suppress proliferation of both syngeneic and allogeneic CD4 and CD8 T cells.

J Immunol 2006; 177:8338-8347;

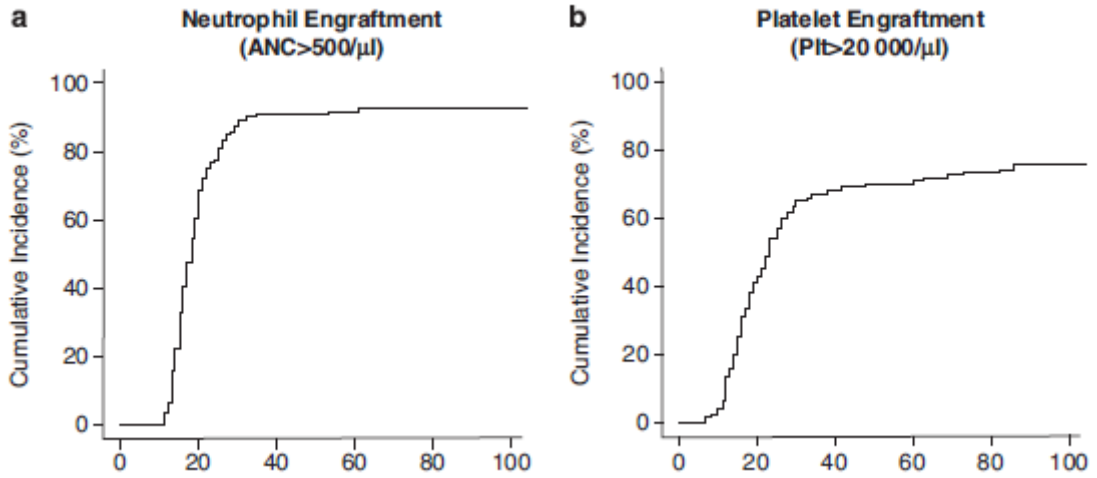
MILANO TrRaMM Study

ORIGINAL ARTICLE

Sirolimus-based graft-versus-host disease prophylaxis promotes the *in vivo* expansion of regulatory T cells and permits peripheral blood stem cell transplantation from haploidentical donors

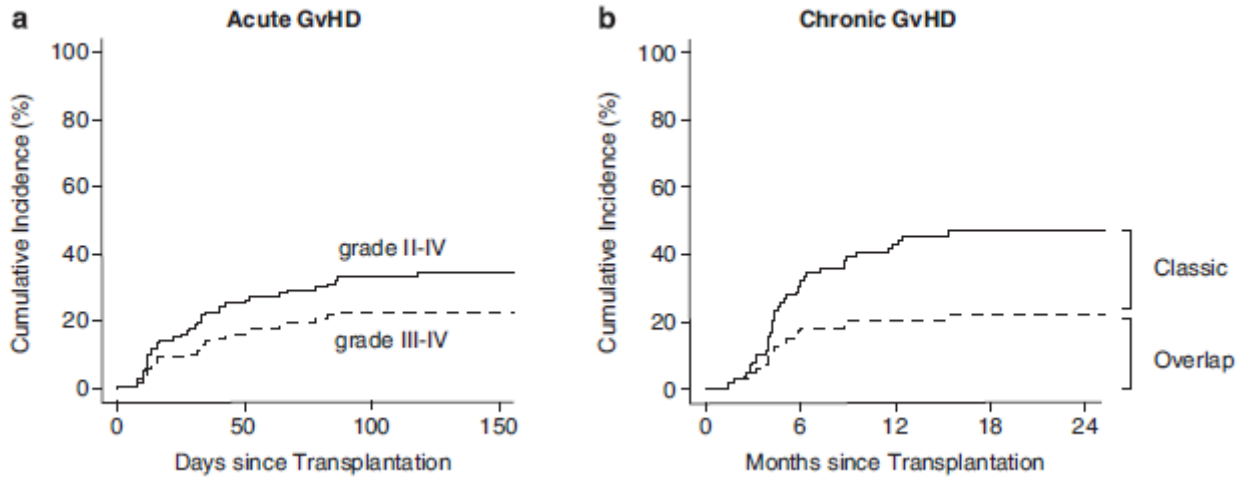
J Peccatori[1], A Forcina[1,2], D Clerici[1], R Crocchiolo[1,3], L Vago[1,4], MTL Stanghellini[1], M Noviello[2], C Messina[1], A Crotta[1], A Assanelli[1], S Marktel[1], S Olek[5], S Mastaglio[1], F Giglio[1], L Crucitti[1], A Lorusso[1], E Guggiari[1], F Lunghi[1], M Carrabba[1], M Tassara[1], M Battaglia[6], A Ferraro[6], MR Carbone[2], G Oliveira[2], MG Roncarolo[7,8,9], S Rossini[10], M Bernardi[1], C Corti[1], M Marcatti[1], F Patriarca[11], M Zecca[12], F Locatelli[13], C Bordignon[9,14], K Fleischhauer[4], A Bondanza[1,15], C Bonini[2] and F Ciceri[1]

Conditioning regimen: treosulfan and fludarabine
PBSC non manipolate
GvHD prophylaxis : ATG-F, rituximab, sirolimus and mycophenolate



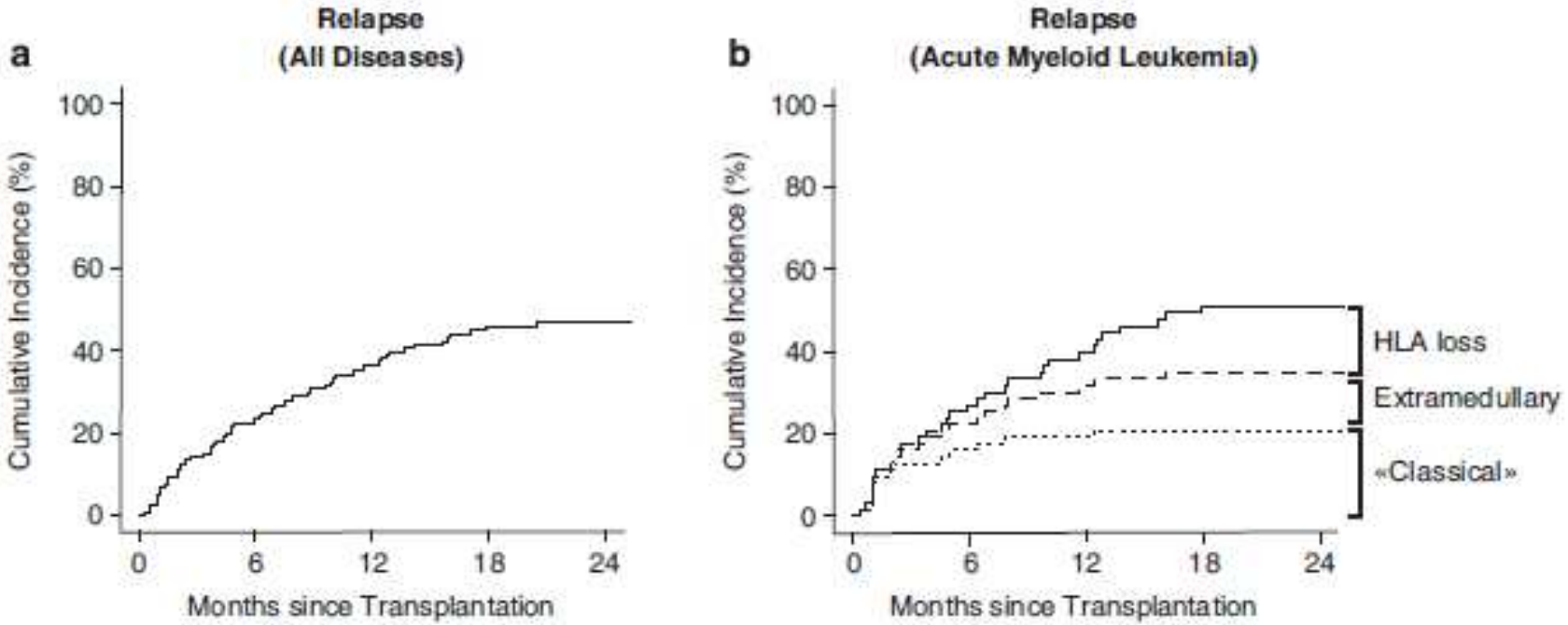
Leukemia (2015) 396 – 405

GvHD



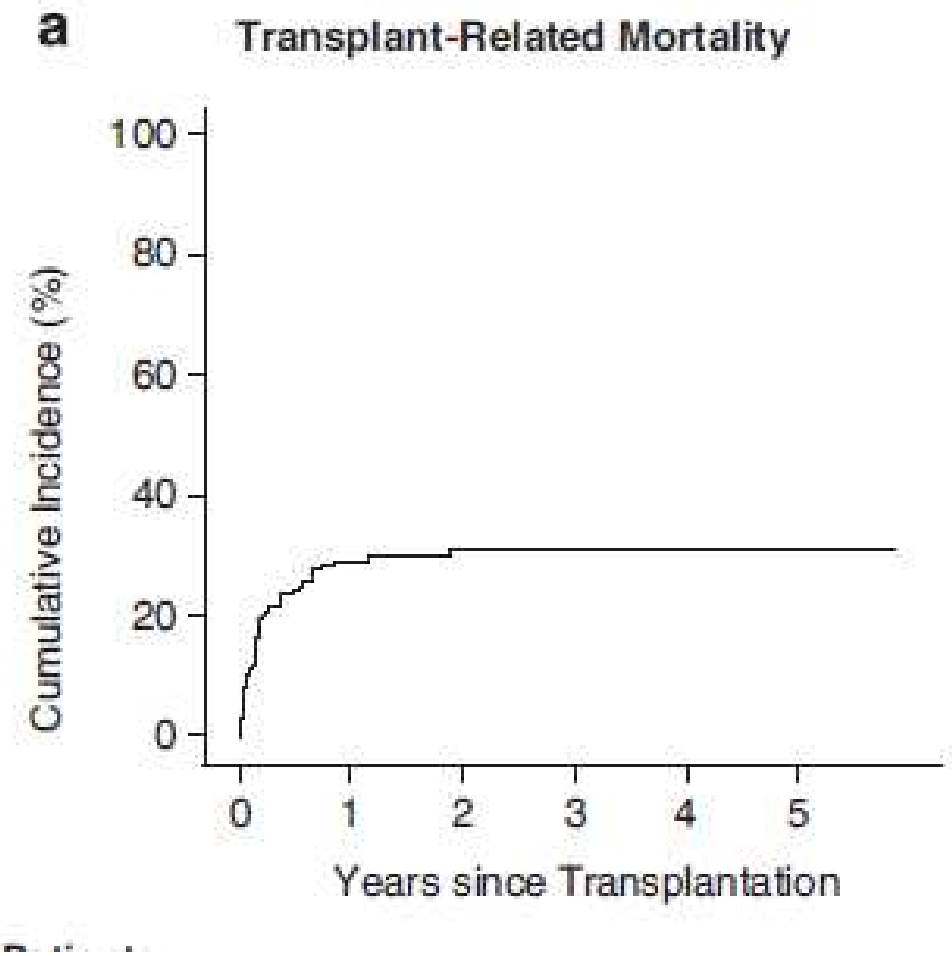
Leukemia (2015) 396 – 405

Relapse



Leukemia (2015) 396 – 405

TRM



Leukemia (2015) 396 – 405

Trapianti da donatori alternativi: come comportarsi in assenza di studi randomizzati

Hematopoietic stem cell transplantation donor sources in the 21st century: choosing the ideal donor when a perfect match does not exist

Natasha Kekre and Joseph H. Antin

BLOOD, 17 JULY 2014 • VOLUME 124, NUMBER 3

Are Alternative Donors Really Still "Alternative?"

Christopher G. Kanakry, Leo Luznik* *Biol Blood Marrow Transplant 20 (2014) 1461–1464*

Non abbiamo studi randomizzati ma abbiamo alcuni dati su cui ragionare

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

Anna Maria Raiola [1], Alida Dominietto [1], Carmen di Grazia [1], Teresa Lamparelli [1], Francesca Gualandi [1], Adalberto Ibatici [1], Stefania Bregante [1], Maria Teresa Van Lint [1], Riccardo Varaldo [1], Anna Ghiso [1], Marco Gobbi [2], Angelo Michele Carella [3], Alessio Signori [4], Federica Galaverna [1], Andrea Bacigalupo [1,*]

MONOCENTRO

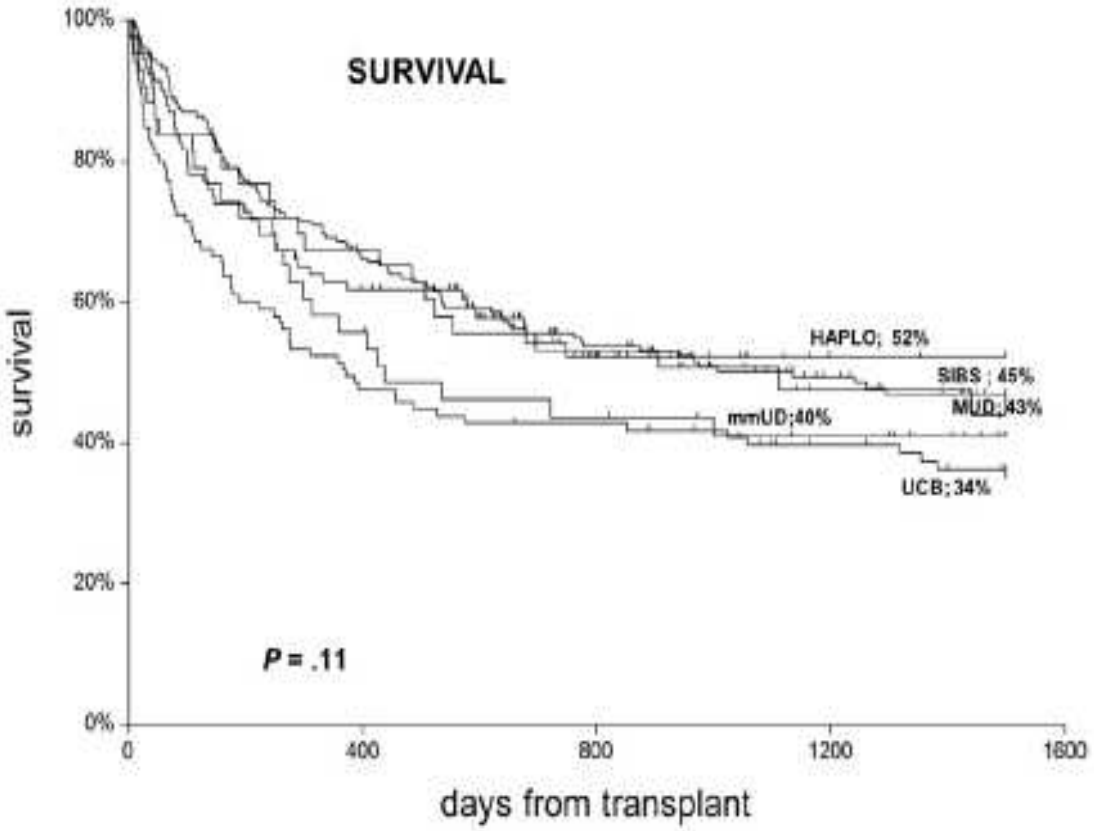
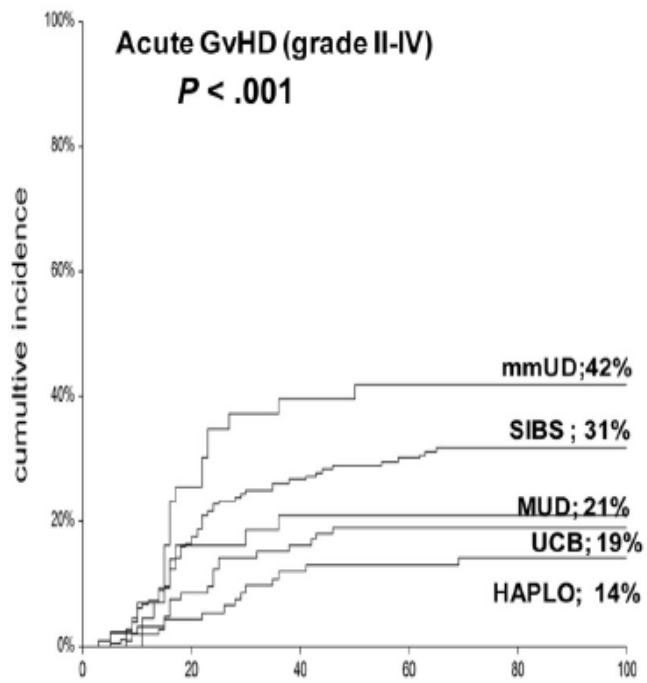
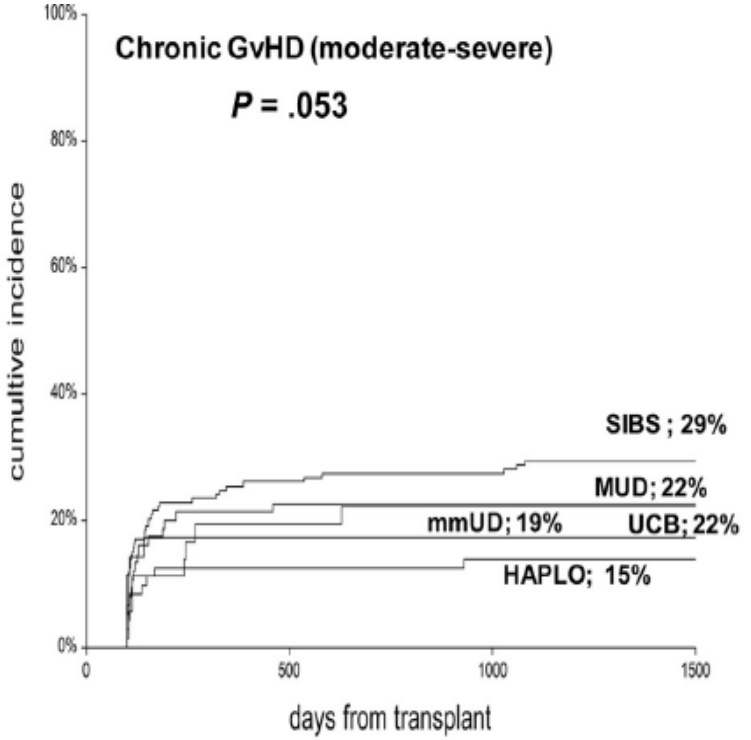


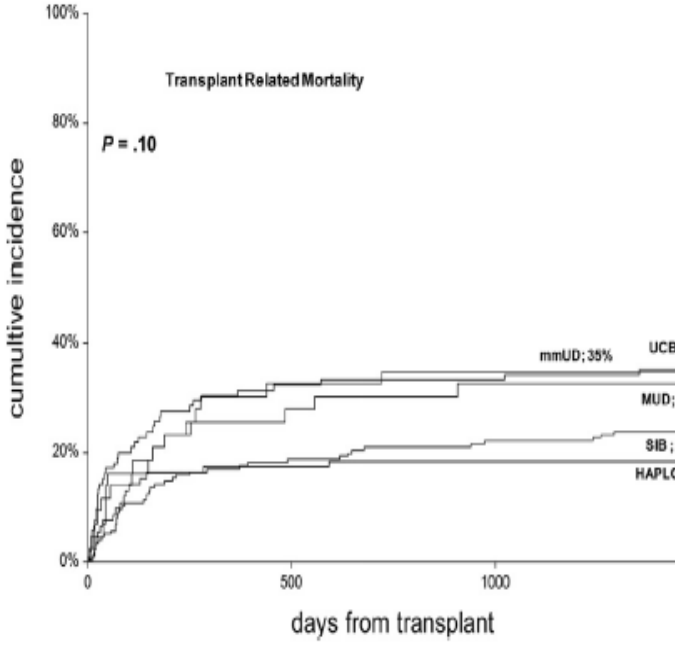
Figure 4. Actuarial survival of patients stratified for donor type. Overall there is no statistically significant difference in survival.

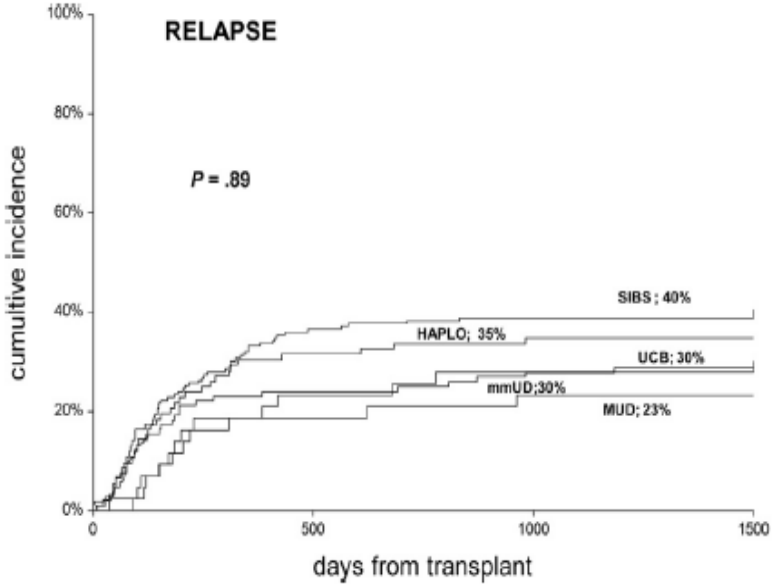
Multivariate Cox Analysis of Survival

Variable	Baseline	Comparison	HR	95% CI	*P* Value
Disease phase	CR1+CR2	Advanced	2.44	1.8-3.2	<.0001
Diagnosis	Chronic disease	Acute leukemia	1.84	1.3-2.5	.0001
Patient age	≤44 yr	>44 yr	1.21	0.9-1.5	.13
Donor type	SIB	MUD	1.01	0.6-1.6	.96
	SIB	mmUD	1.21	0.7-1.8	.40
	SIB	UCB	1.40	1.0-1.9	.03
	SIB	HAPLO	0.95	0.6-1.3	.80
Donor/recipient sex	Other	Female/male	1.14	0.8-1.5	.36


Acute GvHD (grade II-IV)
P < .001
cumultive incidence
100%
80%
60%
40%
20%
0%
0
20
40
60
80
100
mmUD;42%
SIBS ; 31%
MUD; 21%
UCB; 19%
HAPLO; 14%


Chronic GvHD (moderate-severe)
P = .053
cumultive incidence
100%
80%
60%
40%
20%
0%
0
500
1000
1500
days from transplant
SIBS ; 29%
MUD; 22%
mmUD; 19%
UCB; 22%
HAPLO; 15%


Transplant Related Mortality
P = .10
cumultive incidence
100%
80%
60%
40%
20%
0%
0
500
1000
days from transplant
mmUD; 35%
UCB
MUD;
SIB ;
HAPLO


RELAPSE
P = .89
cumultive incidence
100%
80%
60%
40%
20%
0%
0
500
1000
1500
days from transplant
SIBS ; 40%
HAPLO; 35%
UCB; 30%
mmUD;30%
MUD; 23%

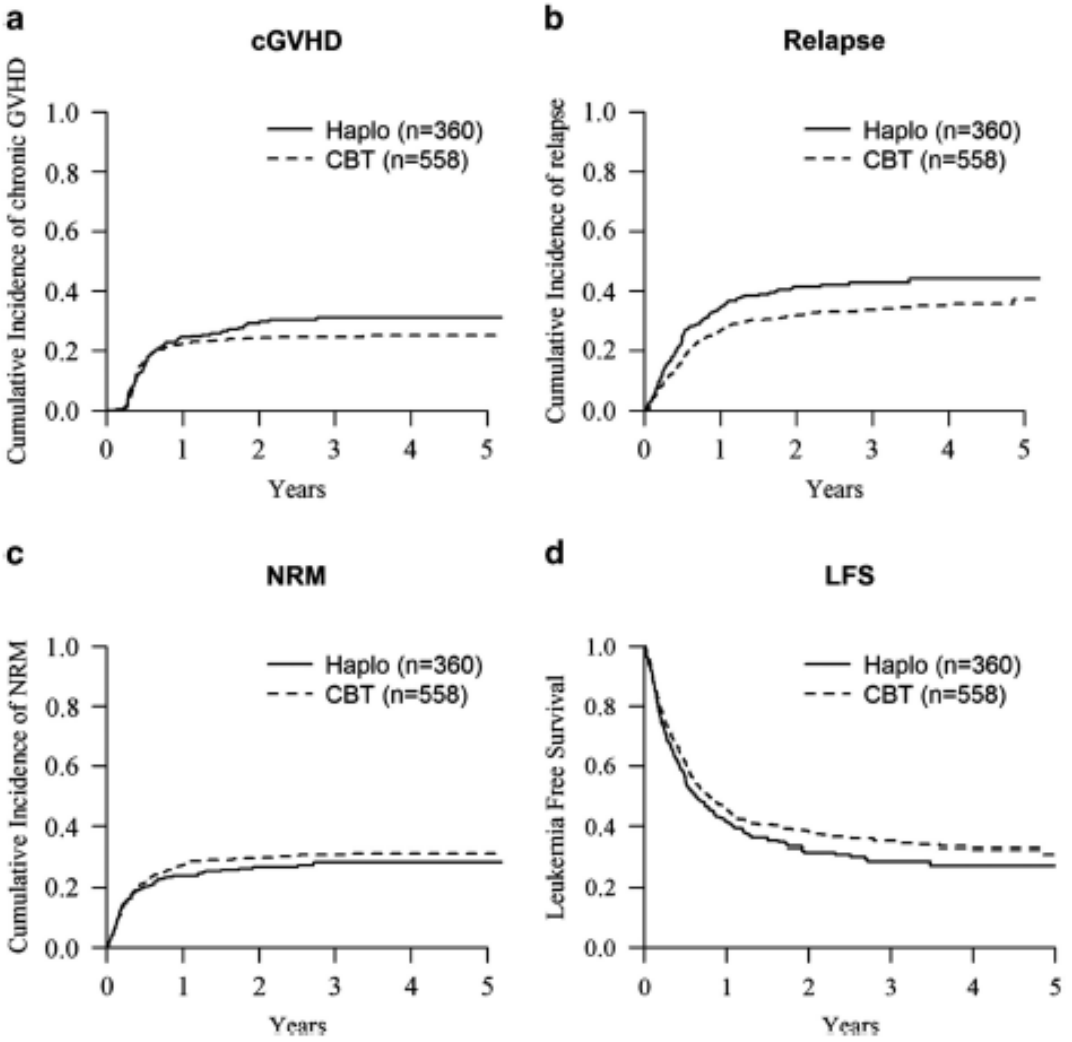
Studi di confronto

Trapianti da donatore aploidentico vs

- CBT 2015
- MUD 8/8 2015
- MUD 10/10 e identical sibling 2015
- Identical sibling (PTCY 2 step) 2015

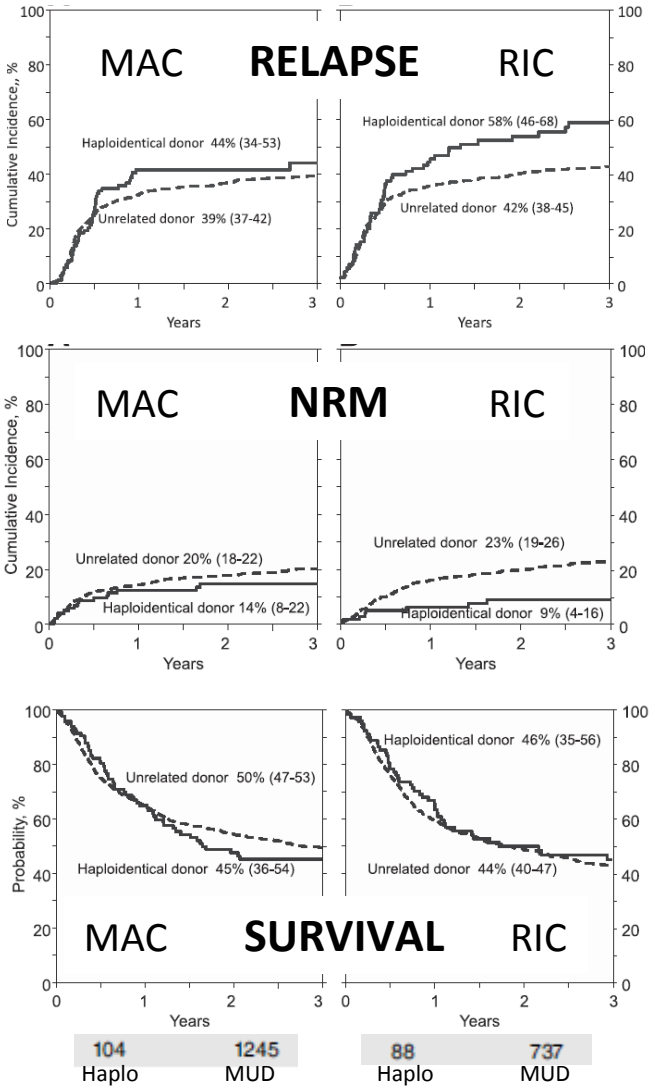
Non confronto fra piattaforme diverse

CBT vs Haplo



Comparison of UCBT and unmanipulated Haplo for acute leukemia A Ruggeri *et al* Leukemia (2015) 1891 – 1900

MUD 8/8 vs Haplo PTCy



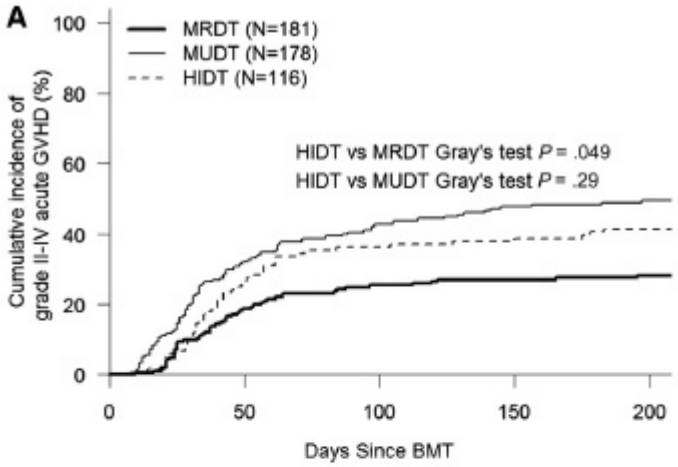
No T depleted

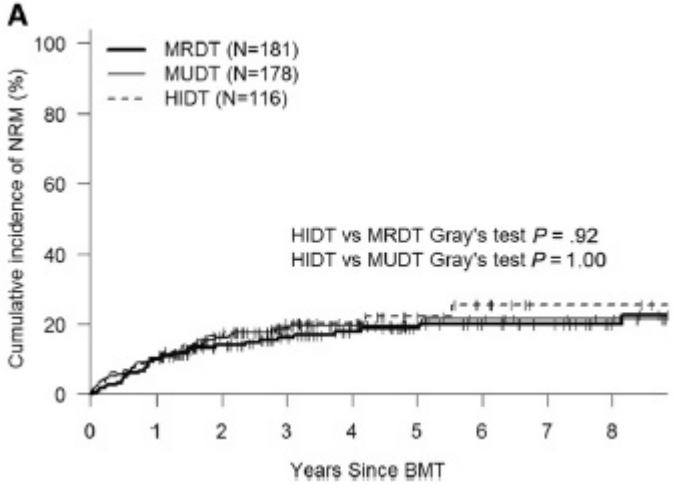
Table 5. Multivariate analysis (subset): risks of acute and chronic GVHD, nonrelapse mortality, relapse, and OS by donor type

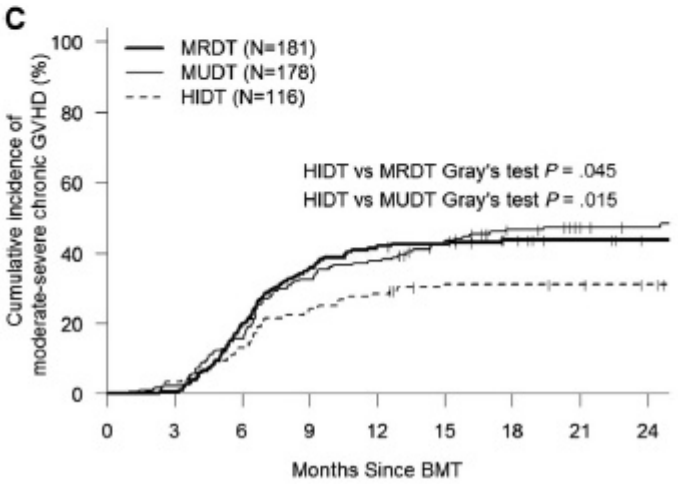
Outcome	Transplant conditioning regimen intensity: Myeloablative* Hazard ratio (95% CI)	Transplant conditioning regimen intensity: Reduced intensity† Hazard ratio (95% CI)
Grade 2-4 acute GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.37 (0.23-0.61) *P* = .0001	0.71 (0.44-1.15) *P* = .16
Grade 3-4 acute GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.33 (0.14-0.81) *P* = .02	0.21 (0.05-0.86) *P* = .03
Chronic GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.44 (0.29-0.66) *P* = .0001	0.45 (0.28-0.71) *P* = .0006
Nonrelapse mortality		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.93 (0.54-1.61) *P* = .83	0.59 (0.27-1.29) *P* = .19
Relapse		
Matched unrelated donor	1.00	1.00
Haploidentical donor	1.28 (0.911.81) *P* = .16	1.53 (1.08-2.22) *P* = .02
Overall mortality		
Matched unrelated donor	1.00	1.00
Haploidentical donor	1.19 (0.87-1.61) *P* = .28	1.06 (0.76-1.51) *P* = .70

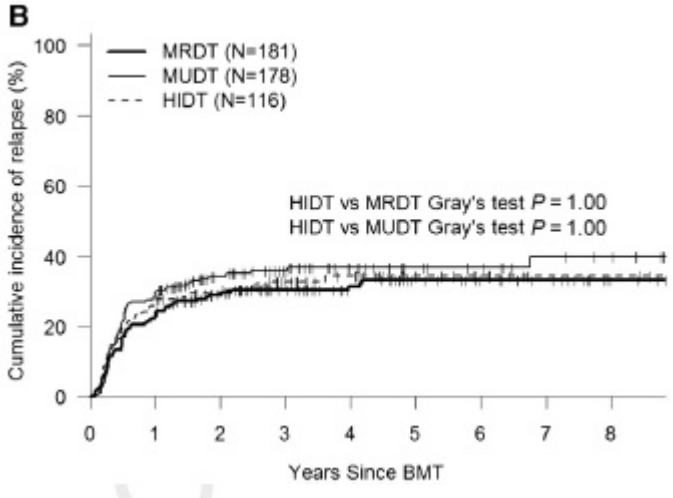
HAPLOIDENTICAL VS UNRELATED DONOR TRANSPLANT CIUREA et alBLOOD, 20 AUGUST 2015 • VOLUME 126, NUMBER 8

MUD 10/10 vs id sib vs Haplo PTCy



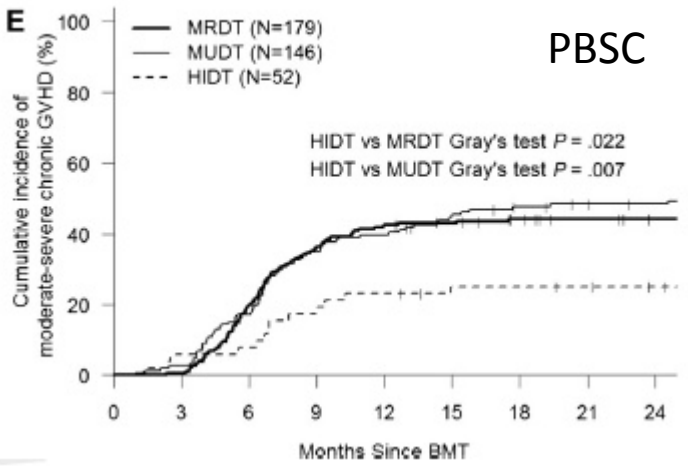




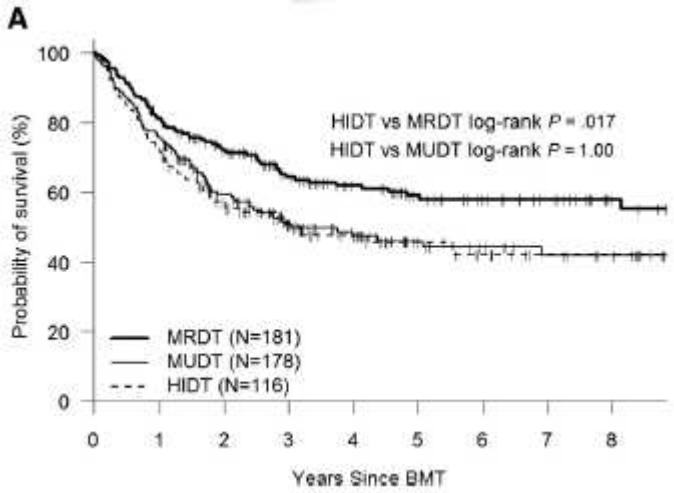


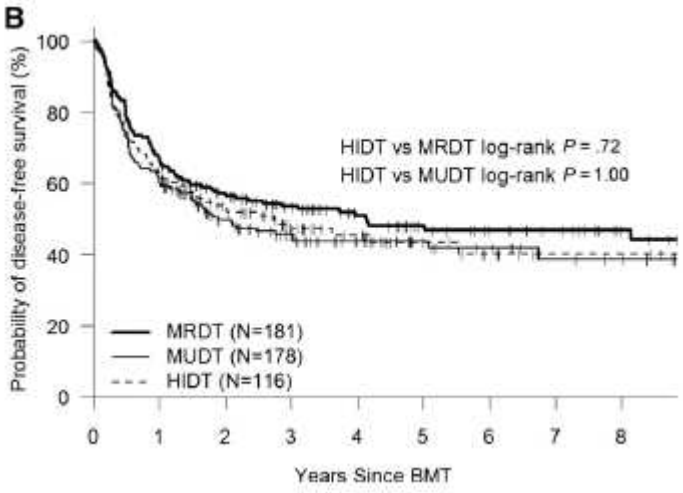
T-replete HLA-haploidentical donors and post-transplantation cyclophosphamide *A. Bashey et al. / Biol Blood Marrow Transplant xxx (2015)*

MUD 10/10 vs id sib vs Haplo PTCy



PBSC





T-replete HLA-haploidentical donors and post-transplantation cyclophosphamide *A. Bashey et al. / Biol Blood Marrow Transplant xxx (2015)*

Due fasi Haplo vs MRD

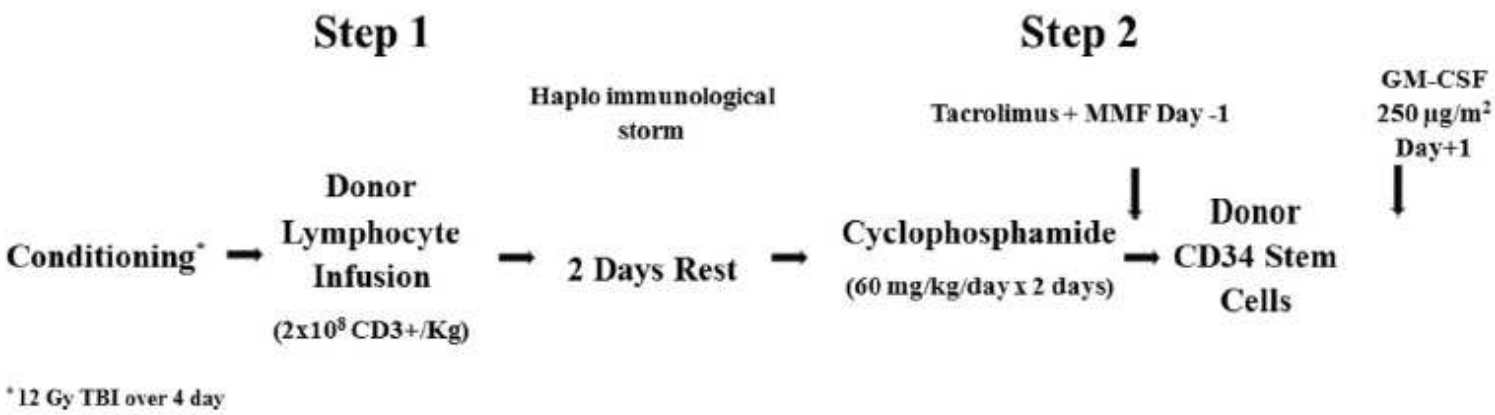
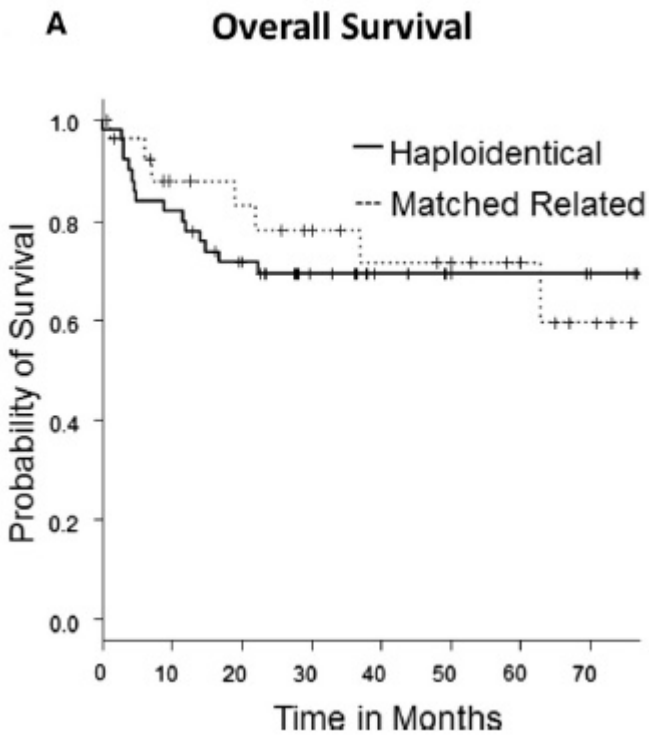
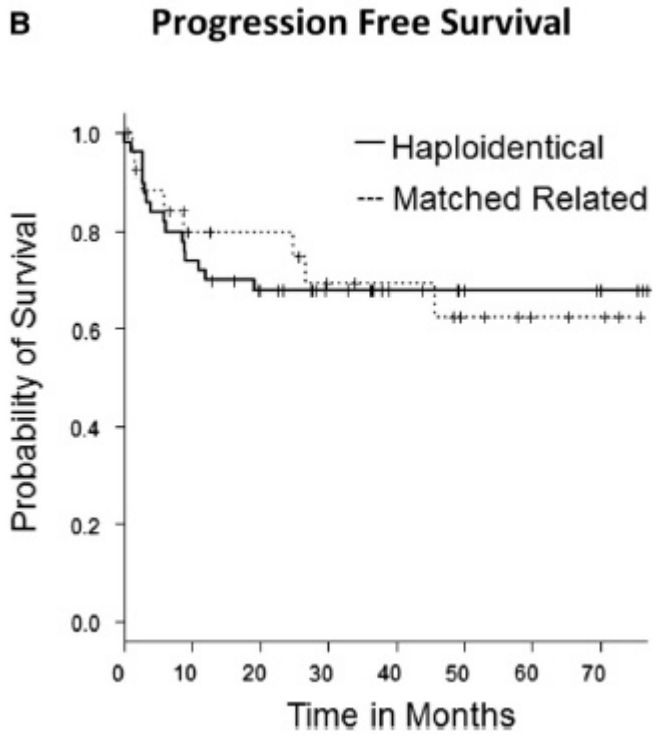


Figure 1. Outline of the 2-step approach. After total body irradiation conditioning, patients receive a donor lymphocyte infusion product containing 2×10^8 $CD3^+$ cells/kg. This is followed by 2 days of rest and then 2 doses of high-dose cyclophosphamide. A CD34-selected stem cell product is then infused.

A Two-Step Haploidentical Versus Matched Related Allogeneic *S. Gaballa et al. / Biol Blood Marrow Transplant xxx (2015)*

Un trapianto in due fasi: survival

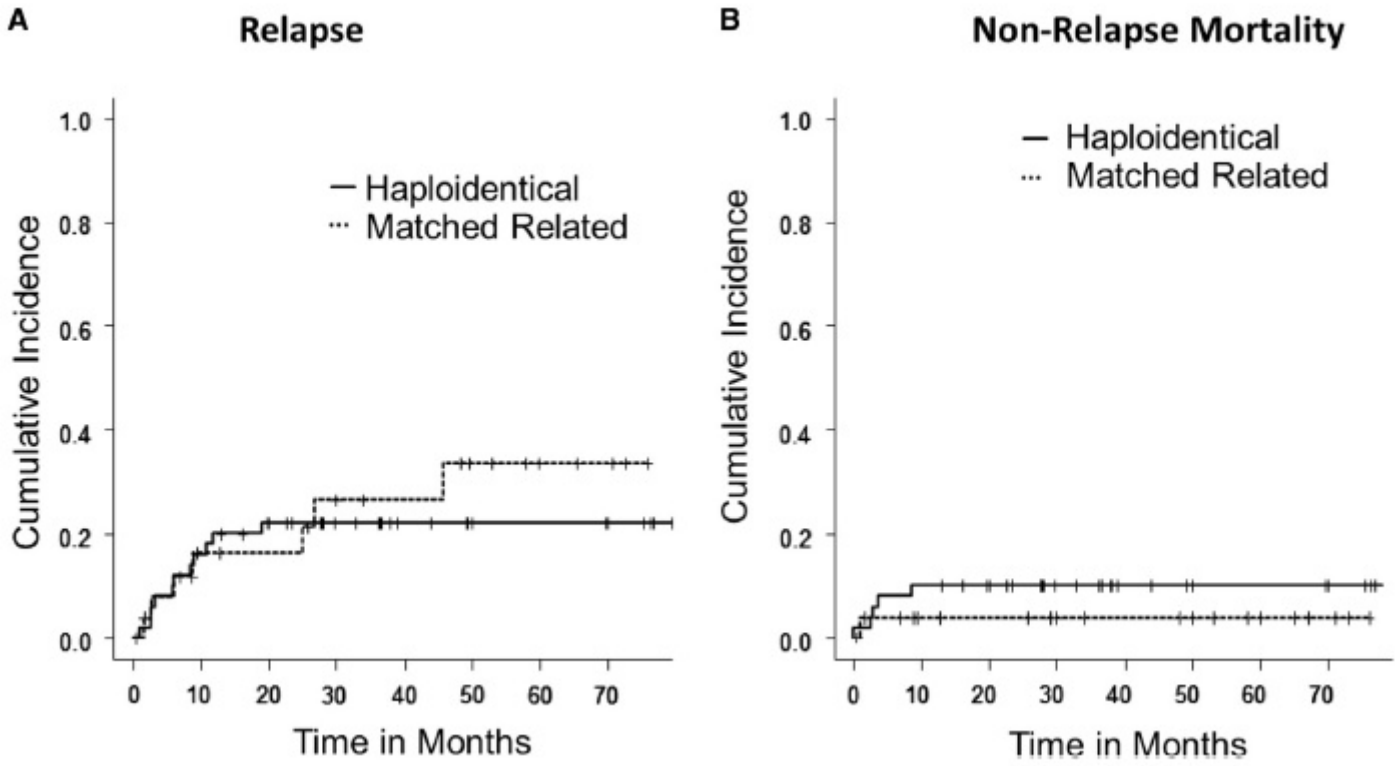




A Two-Step Haploidentical Versus Matched Related Allogeneic

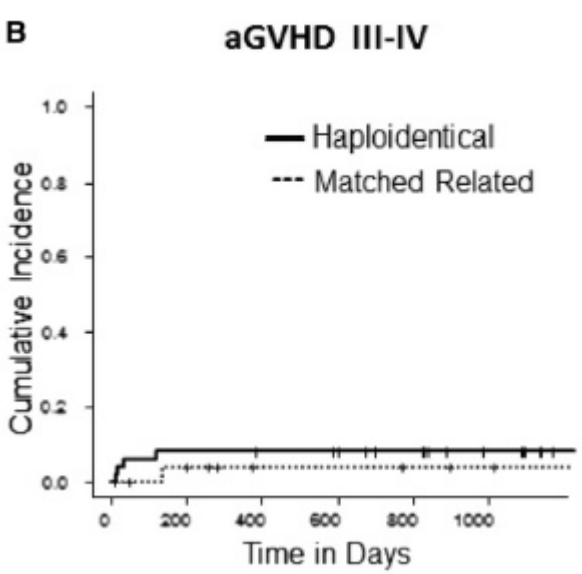
S. Gaballa et al. / Biol Blood Marrow Transplant xxx (2015)

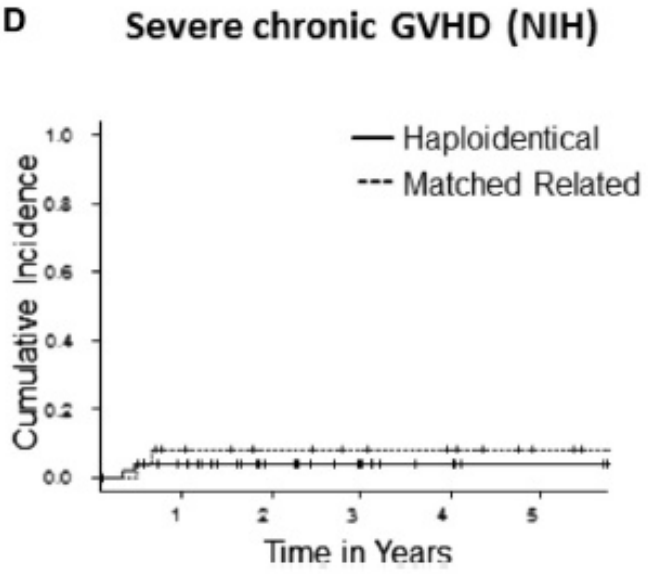
Un trapianto in due fasi: Rel NRM



A Two-Step Haploidentical Versus Matched Related Allogeneic

Un trapianto in due fasi: GvHD





A Two-Step Haploidentical Versus Matched Related Allogeneic

S. Gaballa et al. / Biol Blood Marrow Transplant xxx (2015)

Conclusioni I

- Ogni paziente ha “diritto” ad un trapianto indipendentemente dalla sorgente: id sib, MUD, CBT, Aplo . L’ Aplo ha aperto questa possibilità.

- Non esiste uno standard of care

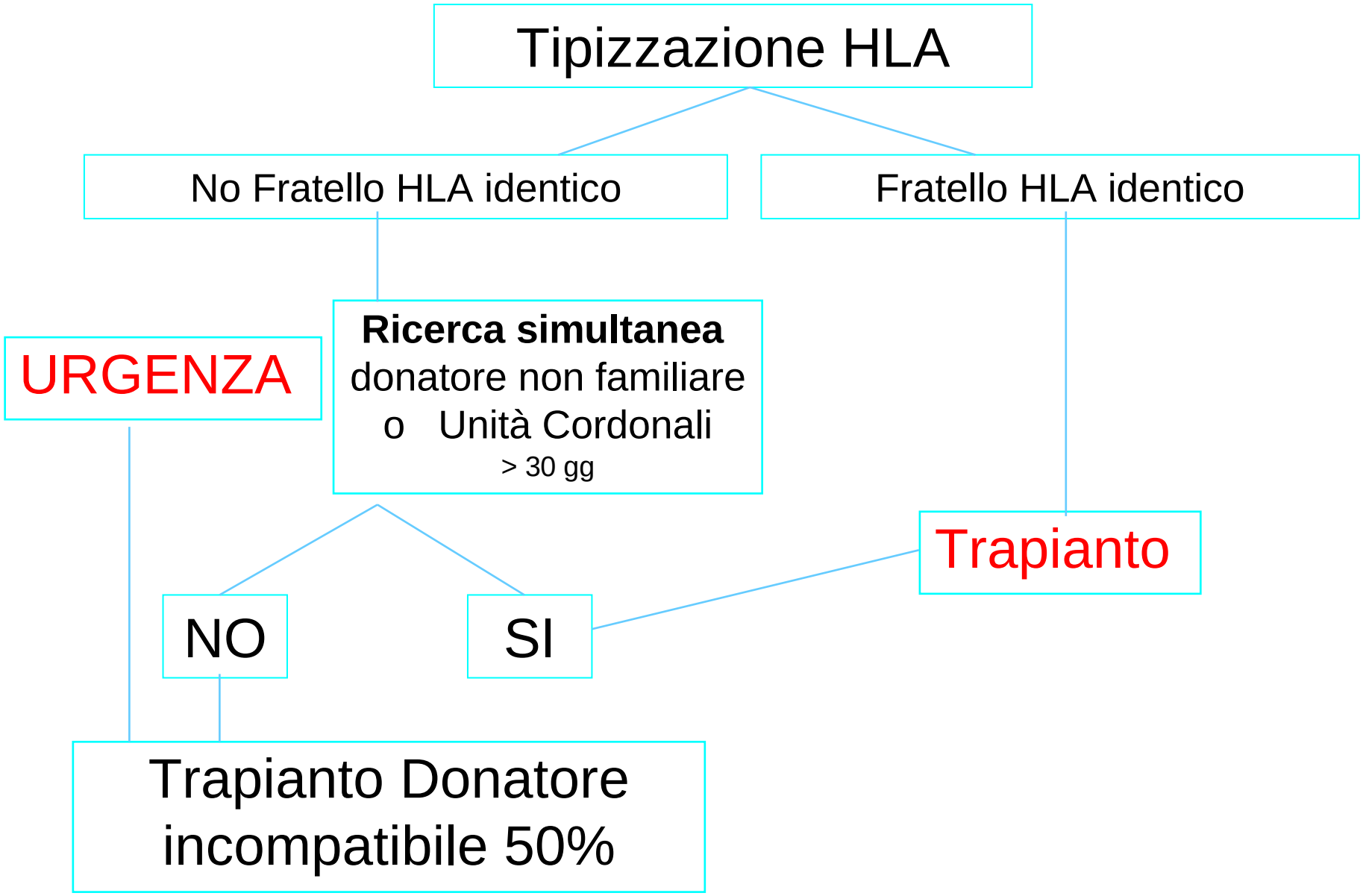
- Risultati sono comparabili fra Aplo ed altre tipologie, ma non ci sono studi randomizzati Aplo vs CBT vs MUD 8/8 vs 7/8 vs id sibling

- Assenza di studi randomizzati di confronto fra piattaforme Aplo diverse.

Conclusioni II

- Trapianti T Depletati da effettuare in CT esperti di manipolazione di CSE che dispongano di una strategia di immunoterapia adottiva post TMO
- Il mondo trapiantologico guarda all' Italia come "laboratorio" per l' aploidentico
- Registrazione GITMO/IBMDR per raccogliere dati
- Ogni Centro TMO deve avere la sua Strategia e deve condividerla con la Immunogenetica di riferimento e con IBMDR

ALGORITMO SELEZIONE DONATORI



Strategia Ricerca Donatore Alternativo
TMO FIRENZE 2015

RICERCA SIMULTANEA
minimo 30 gg

~~HLA~~
~~Id sib~~

MUD
8/8-7/8
HR

- 8/8 permissività DPB1
- 7/8 indifferente antigene/allele
- DQB1, DRB 3,4,5

Anticorpi DSA (donor secific antibodies)

CBT
Singolo CB
>3 TNC/kg
≥4/8
CT HR CBB

CBT
Doppio CB
Ognuno
>2 TNC/kg≥4/8

APLO+CBT
CB >1 TNC/kg ≥4/8
+
Aplo PBSC CD34

APLO
Cyclo post

EMERGENZA


GRAZIE
Un grazie speciale alla
Immunogenetica AOU CAREGGI