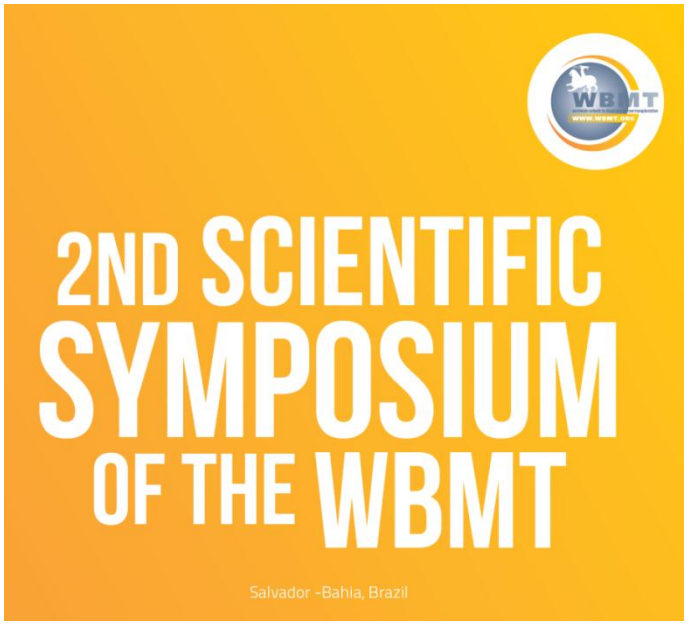
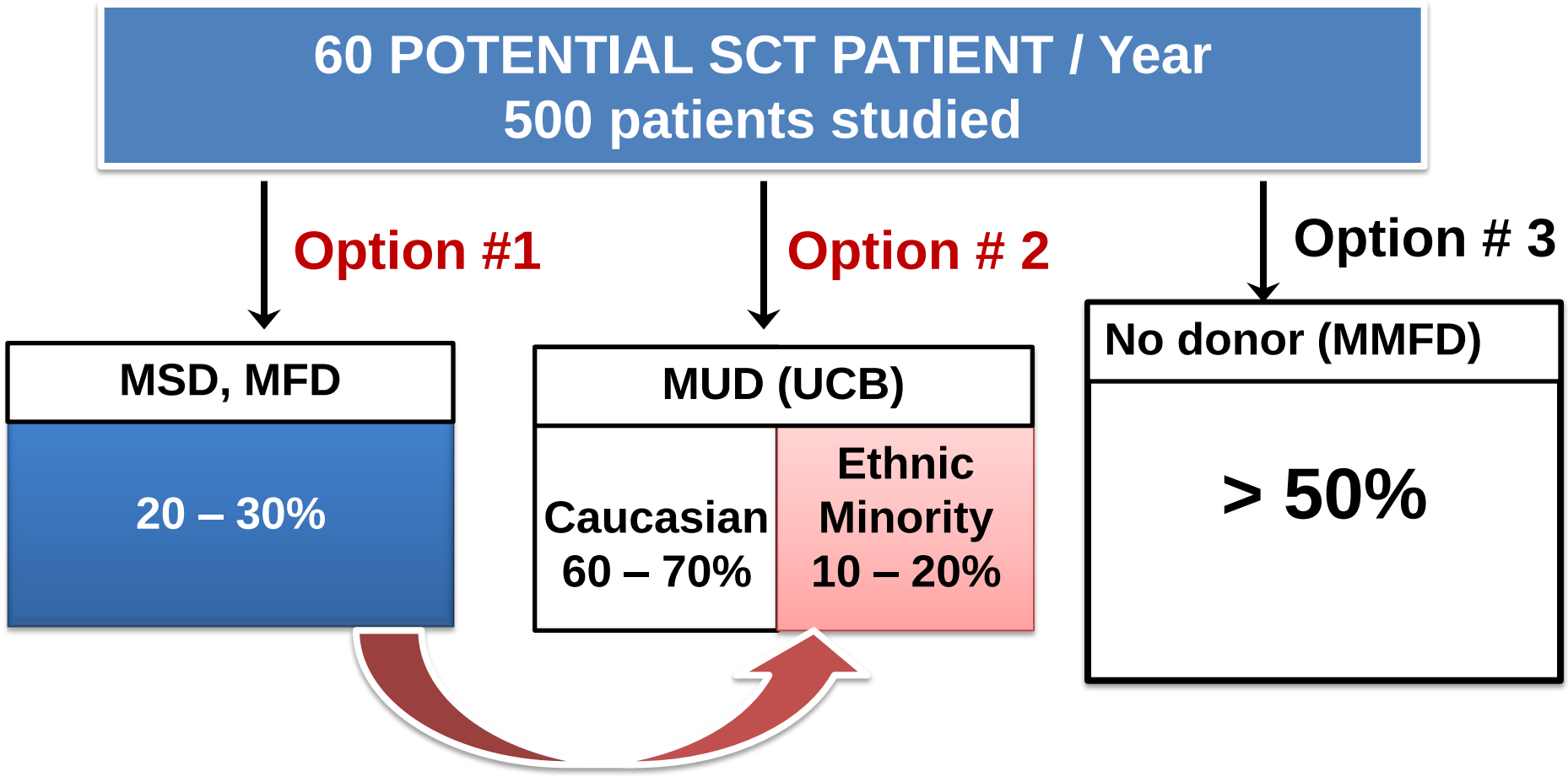


Haploidentical HSCT from Family Members (for very high-risk children with Leukemia)

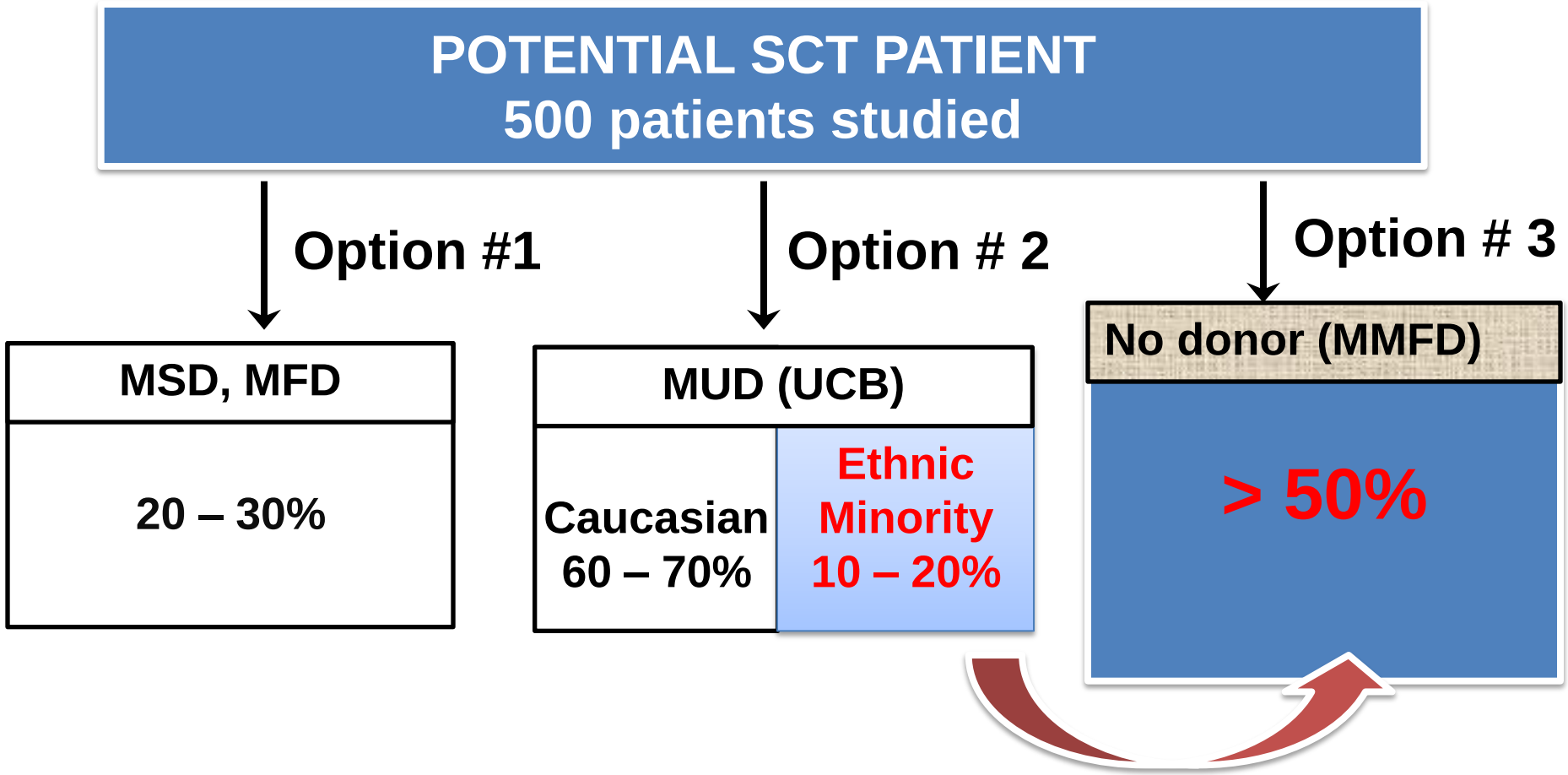
J. Palma, L. Salas, C. Sotomayor, P.Catalan, C. Paris, F. Carrion, M. Campbell

SCT Donors



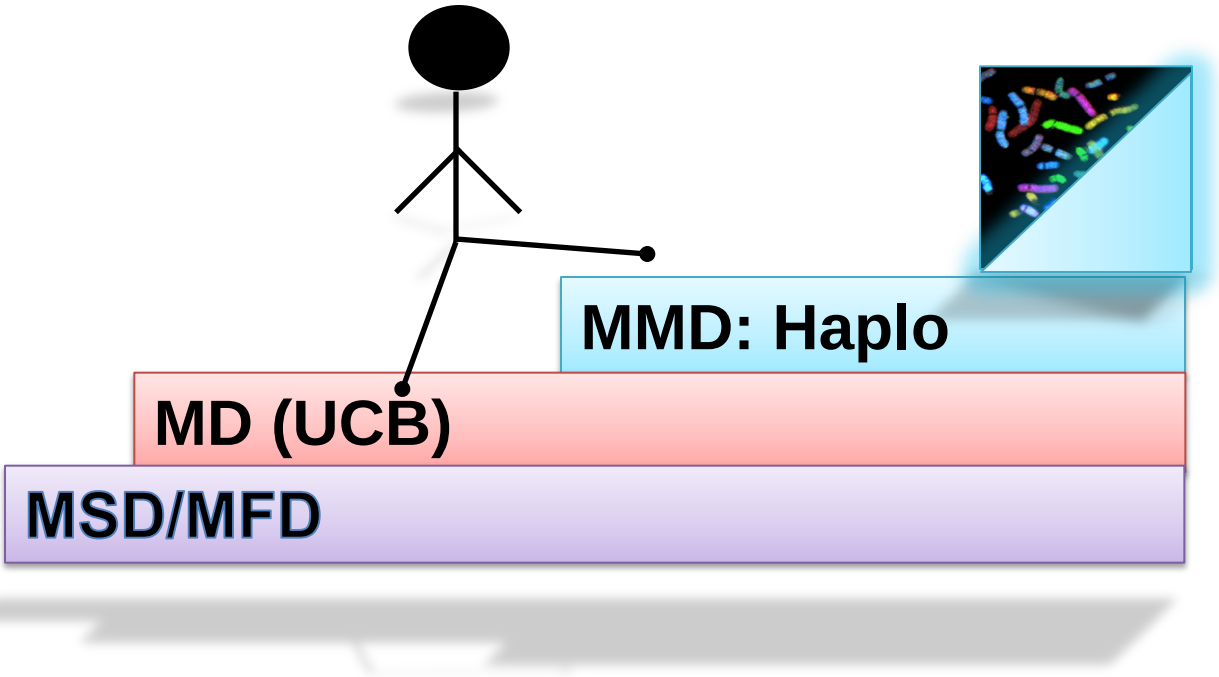
Pediatr Blood Cancer 2006, 46:803

SCT Donors


POTENTIAL SCT PATIENT
500 patients studied
Option #1
Option # 2
Option # 3
MSD, MFD
20 – 30%
MUD (UCB)
Caucasian
60 – 70%
Ethnic
Minority
10 – 20%
No donor (MMFD)
> 50%

Strategies to identify alternative donors in Chile….

Chile: “a mixed population: 64% white, 35% Amerindian, with traces of other admixture and < 4% are foreign born”



Protocol

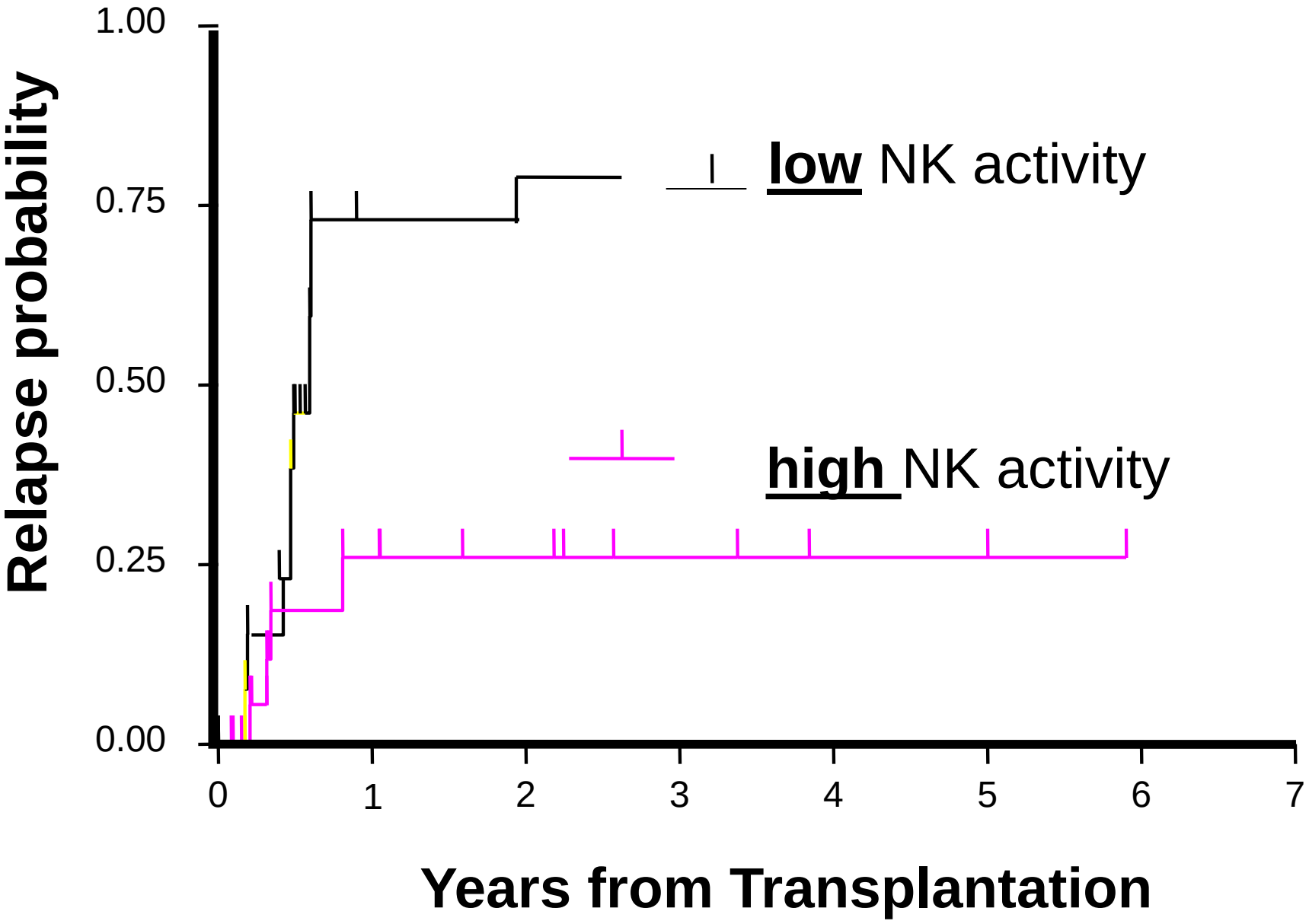
T cell Depletion

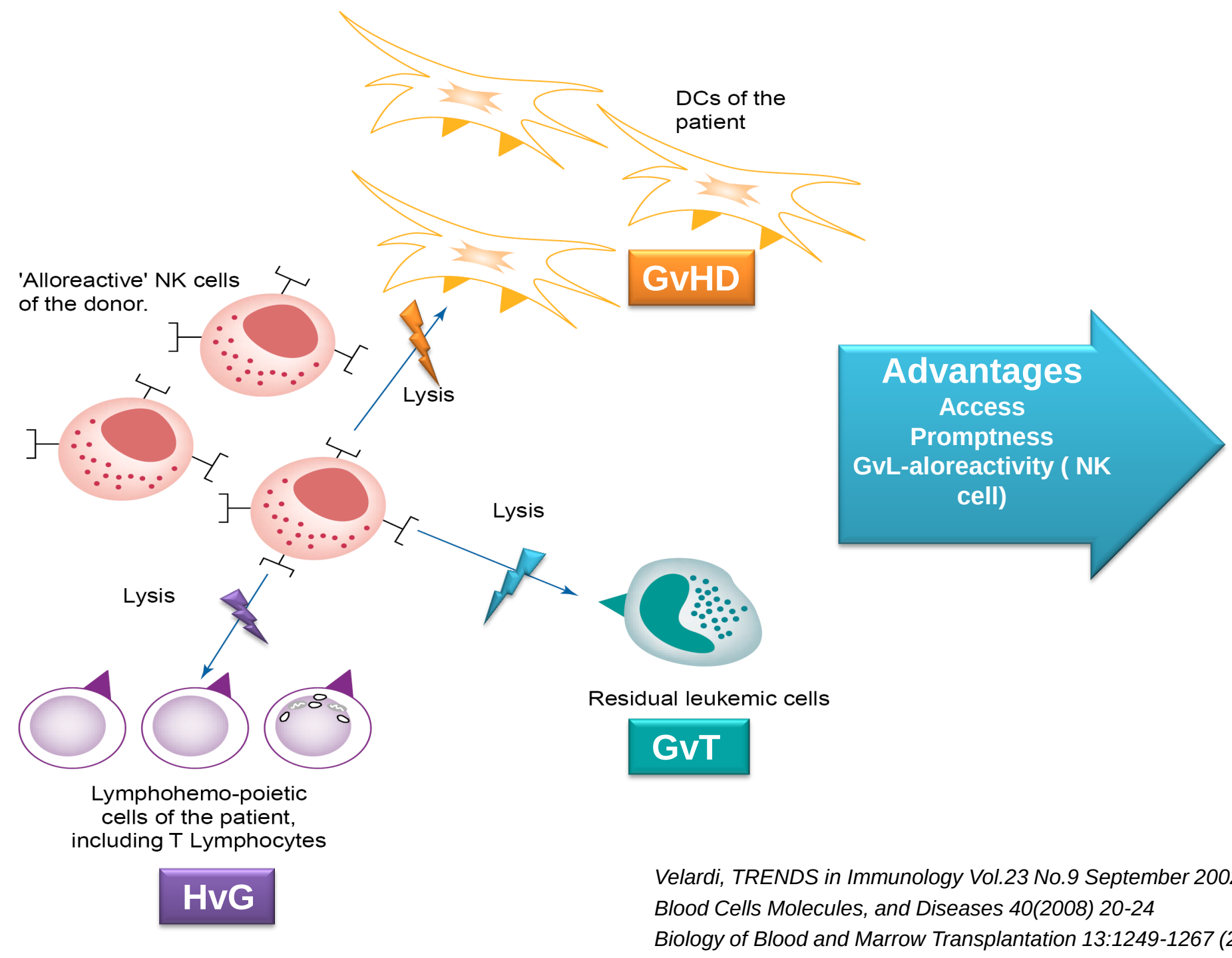
Flow

1. **Patients without MSD/MFD transplanted at St. Jude:10** √
2. **Transfer Haplo Tech to Chile 2005** √
3. **March 2006: First Haplo in Chile** √

- *Velardi and collegues: Science 295: 2097, 2002*
- *British Journal of Haematology, 2003, 123,193 - 206*
- *Schumm et al. Cytotherapy, 2006; 8: 465-472*

Relapse probability

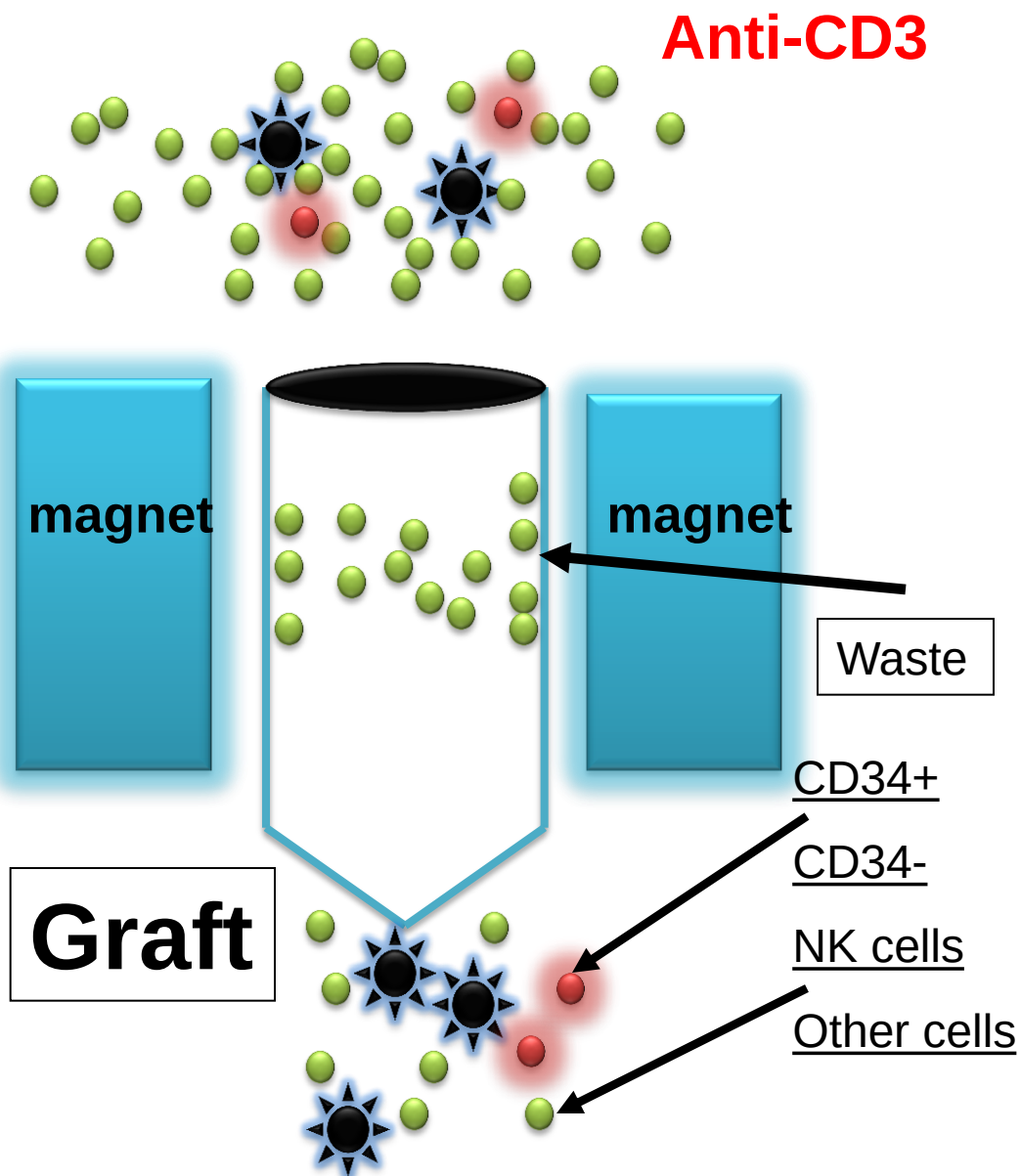




Velardi, TRENDS in Immunology Vol.23 No.9 September 2002
Blood Cells Molecules, and Diseases 40(2008) 20-24
Biology of Blood and Marrow Transplantation 13:1249-1267 (2007)

CD3+ negative depletion

Bone Marrow Transplantation 30, 69-72, 2002



Advantages

Access

Promptness

GvL-aloreactivity (NK cell)

Better IR?

Velardi, TRENDS in Immunology Vol.23 No.9 September 2002
Blood Cells Molecules, and Diseases 40(2008) 20-24
Biology of Blood and Marrow Transplantation 13:1249-1267 (2007)

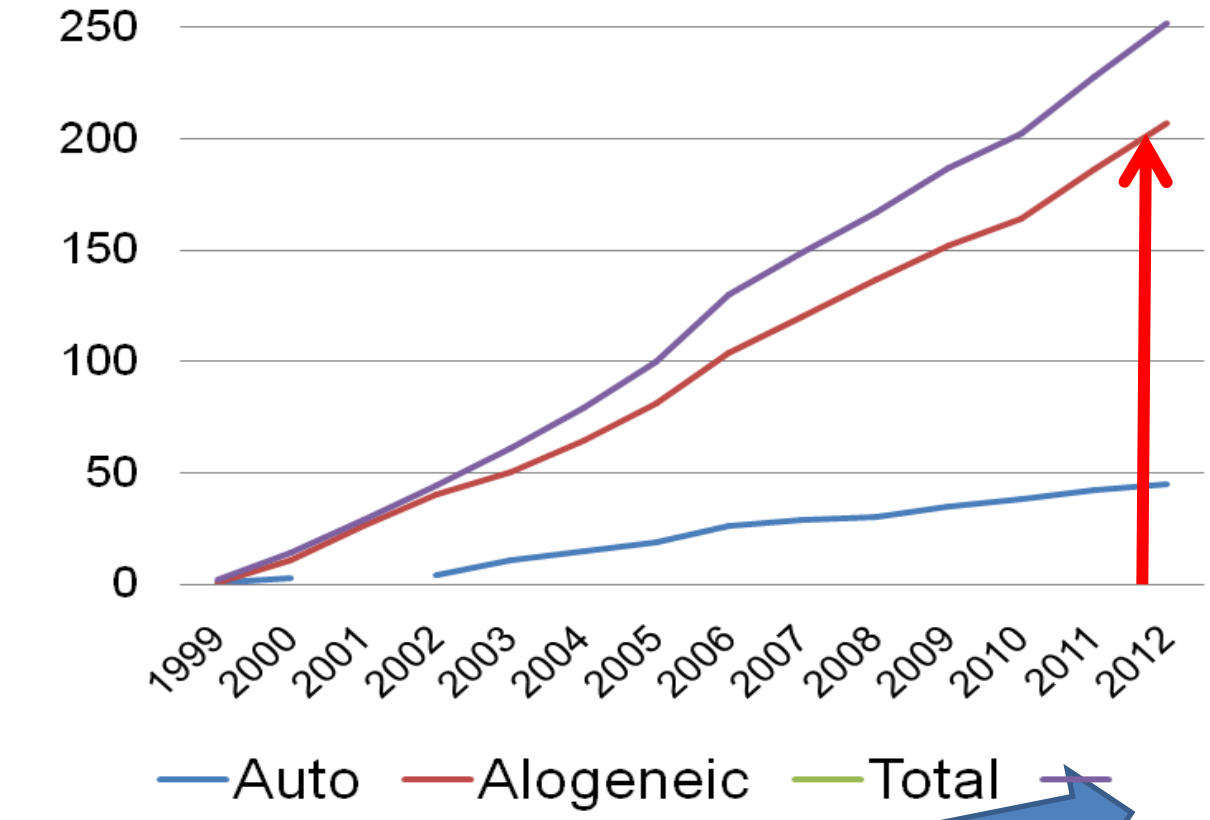
HAPLOIDENTICAL STEM CELL TRANSPLANTATION UTILIZING T-CELL DEPLETION AS THERAPY FOR PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

BMT UNIT Hospital Luis Calvo Mackenna

- ***Current status of reduced-intensity allogeneic stem cell transplantation using alternative donors,Leukemia (2008) 22, 31-41***
- ***Blood Cells, Molecules and disease 40 (2008) 33-39***

Results

HSCT Activity 1999-2012



263HSCT: >200 Allogeneic


blood 2010 115: 3437-3446
Prepublished online December 29, 2009;
doi:10.1182/blood-2009-03-207001

Results and factors influencing outcome after fully haploidentical hematopoietic stem cell transplantation in children with very high-risk acute lymphoblastic leukemia: impact of center size: an analysis on behalf of the Acute Leukemia and Pediatric Disease Working Parties of the European Blood and Marrow Transplant group

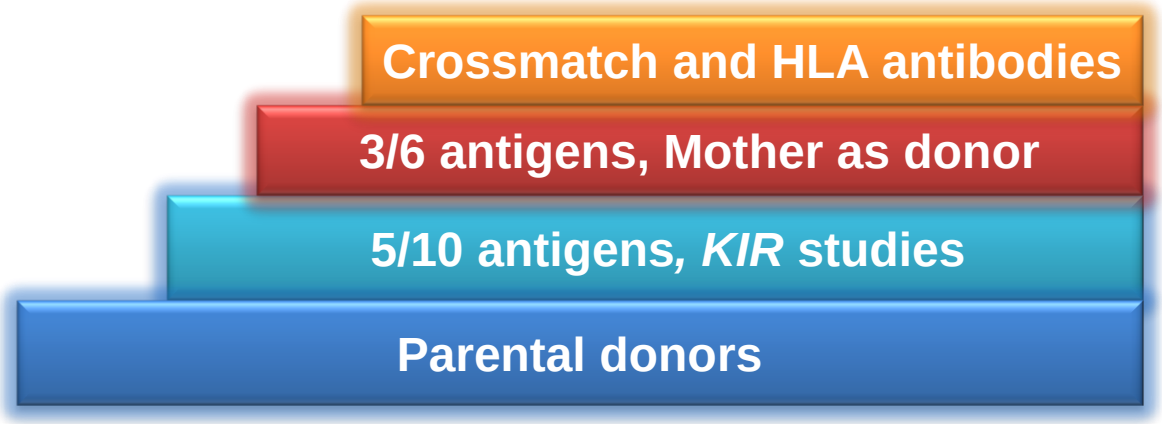
Thomas Klingebiel, Jacqueline Cornish, Myriam Labopin, Franco Locatelli, Philippe Darbyshire, Rupert Handgretinger, Adriana Balduzzi, Joanna Oniao-Lerpiech, Franca Fagioli, Reuven Or, Christina Peters, Franco Aversa, Emmanuelle Polge, Giorgio Dini and Vanderson Rocha

Patient Eligibility for Chile Haplo Protocol for refractory hematological malignancies (chemoresistant or primary induction failure) including:

Malignancy	Status	Characteristics
ALL	**CR1**	Poor prednisone responder and Ph+ Induction failure (non-responder day 33)
	CR2	Ph+, T-ALL, S3/S4
	CR>2	All patients
AML[b]	**CR1**	More than 10% blasts post-HAM More than 4 weeks of aplasia post-HAM Primary refractory disease
	CR2	Duration of CR1 < 1 year
	CR>2	All patients
CML	**CP**	Without response to Gleevec

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, CR: complete remission, S3: early relapse (< 30 months after diagnosis), S4: very early relapse (< 18 months after diagnosis), HAM: high-dose Ara-C and mitoxantrone, HSCT: hematopoietic stem cell transplantation. [a] Indications were based on the recommendations of the European Group for Blood and Marrow Transplantation.[15b] Excluding Down syndrome and promyelocytic leukemia.CML: chronic myeloid leukemia, CP: chronic phase.

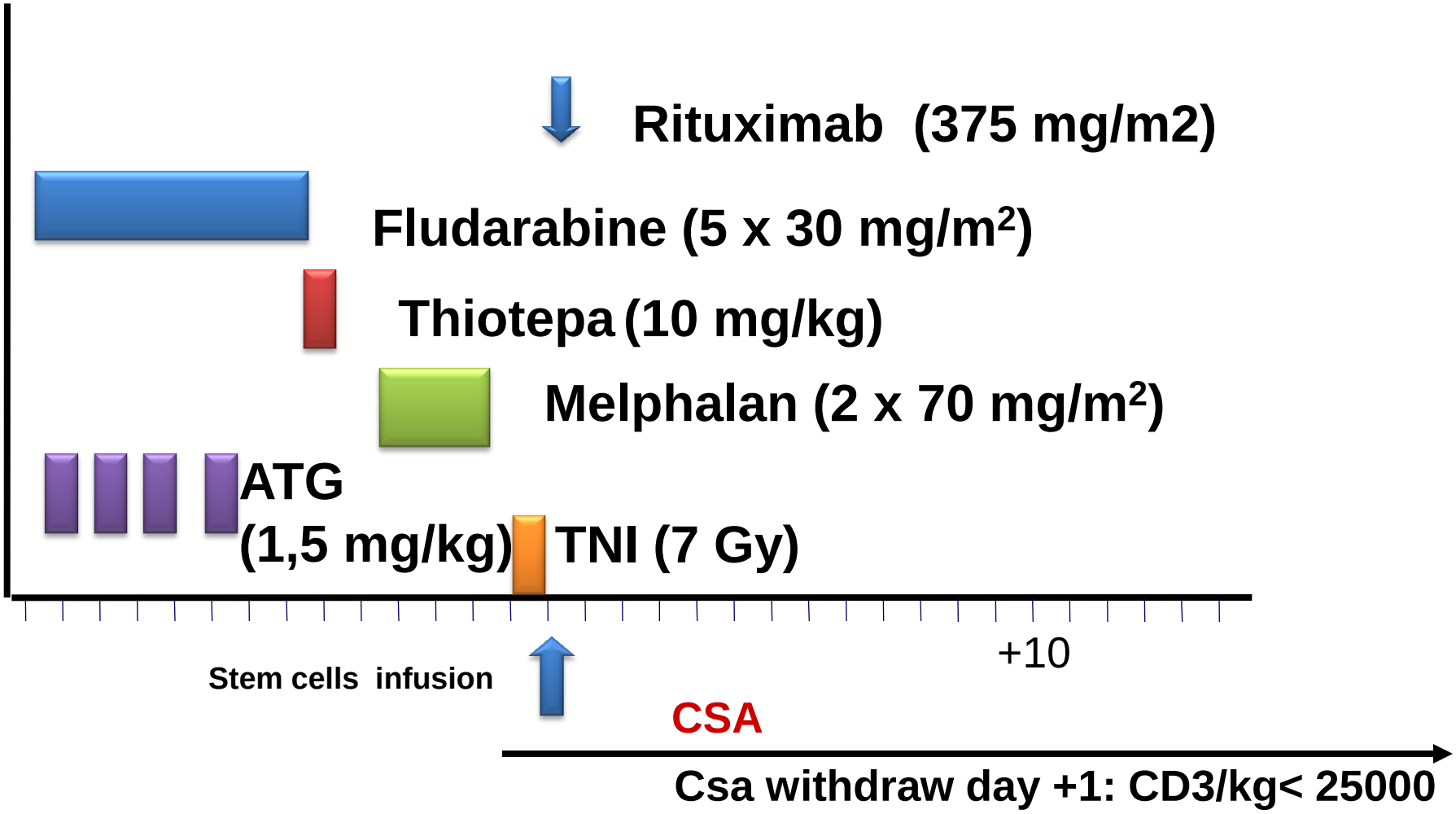
HLA typing and donor selection



Prepublished online May 20.2008;doi:10.1182/blood-2008-01-135285

Conditioning

Reduced Intensity Conditioning with <u>ATG + TNI</u>



Prophylaxis

- Aciclovir √
- Cotrimoxazole √
- Fluconazole √

Bacterial Infections √
Viral Infections: CMV, ADV, EBV “preemptive treatment”
Fungal Infections “preemptive treatment”

Results

Patients characteristics
Donor selection
Graft
Engraftment
aGvHD
crGvHD
Viral infections
Survival
TRM
Leukemia Free Survival
Influence of donor

Patient Characteristics

N: 25 patients**, 24 elegible**

- **Age** **9,1 yr (2.8-16.7)**
- **Gender** **M/F:17/7**

- **1st HSCT** **23**
  2ndHSCT **1***

***Previous autologous HSCT**

Diagnoses (n:21)
24/24 in remission

ALL	(11)	CR 1	= 1
		CR 2	= 10
		CR3	= 4
AML	(8)	CR1	= 2
		CR 2	= 5
		CR 3	= 2

Results

Patients characteristics
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Engraftment
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crGvHD
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Leukemia Free Survival
Influence of donor

HLA typing and donor selection

Parental donors: 22 Sibling:2

Mismatch:	HLA-A, B, DR
5/10	10
6/10	1
7/10	1
8/10	1
3/6	8
4/6	2
5/6	1

Results

Patients characteristics
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Graft

Peripheral stem cells mobilized by G-CSF from parental donors
Nº apheresis/patient = 1

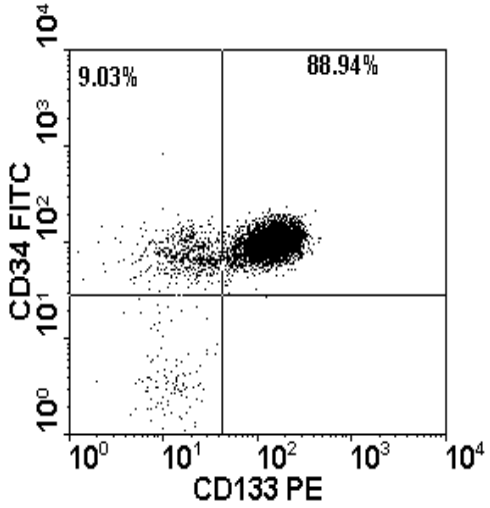
6/ 24 products required a second depletion

CD34+/kg: 10,04 x10^6/kg (2,1-20,5)

CD3+/kg: 0,54 x10^5/kg (0,01-1,5)

CD56+/kg: 79,1 x10^6/kg (7,6-131,8)

Log of depetion : 3,6 (1,69-5,05)



Results

Patients characteristics
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crGvHD
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Leukemia Free Survival
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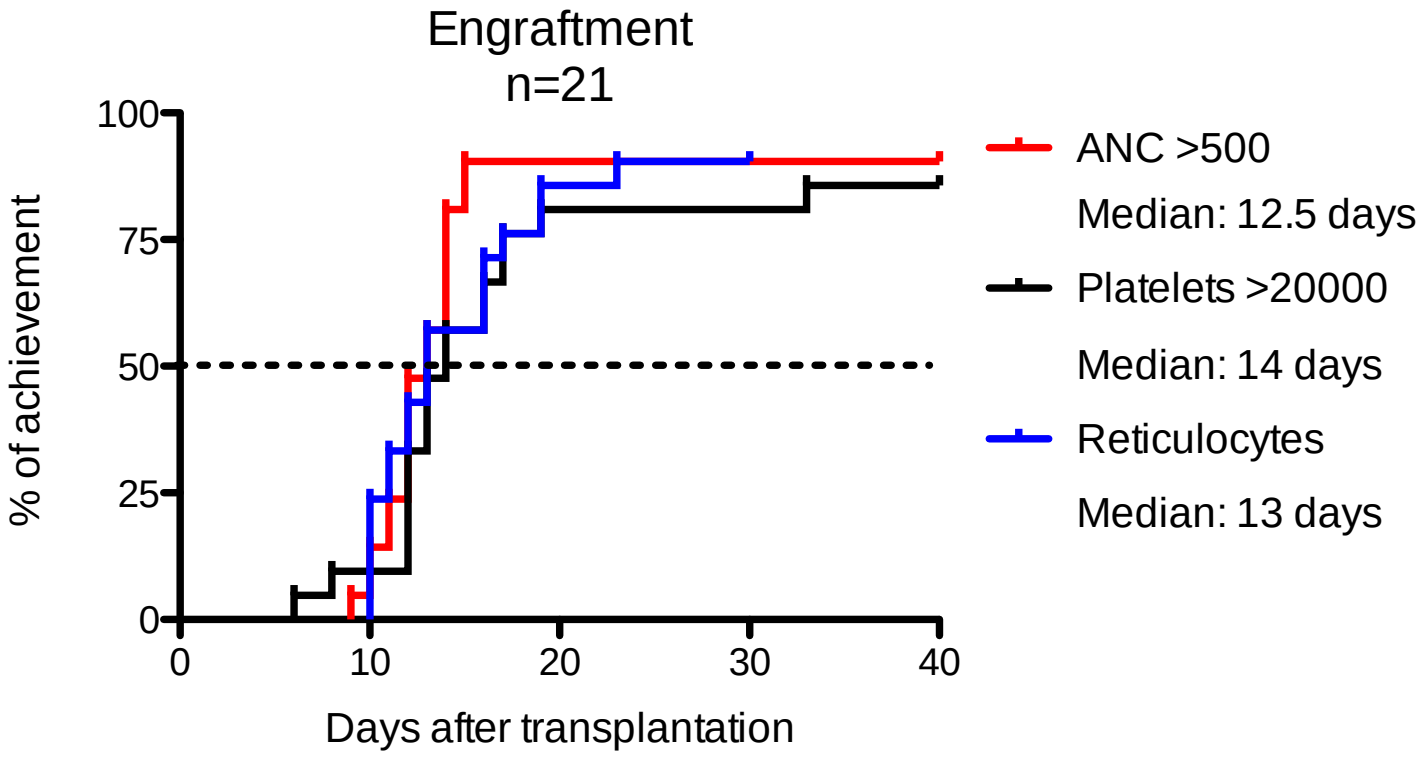
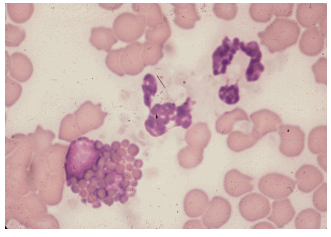
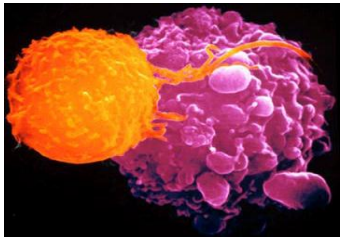
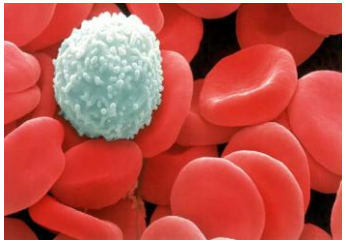
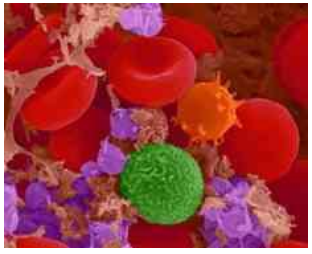
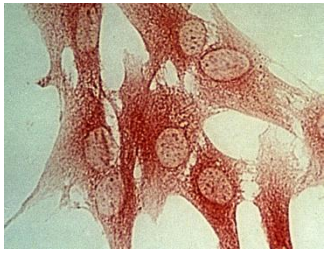
Engraftment

Primary Engraftment	22	Patients
Nonengraftment/Rejection	2	Patients
2ry Engraftment failure (33,3%)	8	Patients

Engraftment after A-Back up 10 Patients

Time to engraftment



Results

Patients characteristics
Donor selection
Graft
Engraftment
aGvHD
crGvHD
Viral infections
Survival
TRM
Leukemia Free Survival
Influence of donor

aGvHD
N:22

Grade	
0	9
I	4
II	7
III	1
IV	1
aGvHD related deaths	0

cGvHD

Grade	
Localized	3
Extense	3
cGvHD related deaths	1

Results

Patients characteristics
Donor selection
Graft
Engraftment
aGvHD
crGvHD
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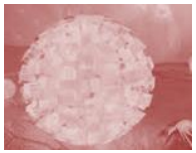
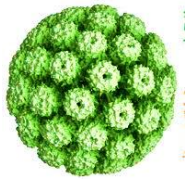
Survival
TRM
Leukemia Free Survival
Influence of donor

N=43	Nº patients	%	Letality %
CMV 			
Reactivation	**18**	**75**	**0**
Disease	**1**	**6**	**0**
ADV 	**2**	**8**	**0**
VEB 	**3**	**13**	**0**
BK 	**3**	**13**	**0**

Results

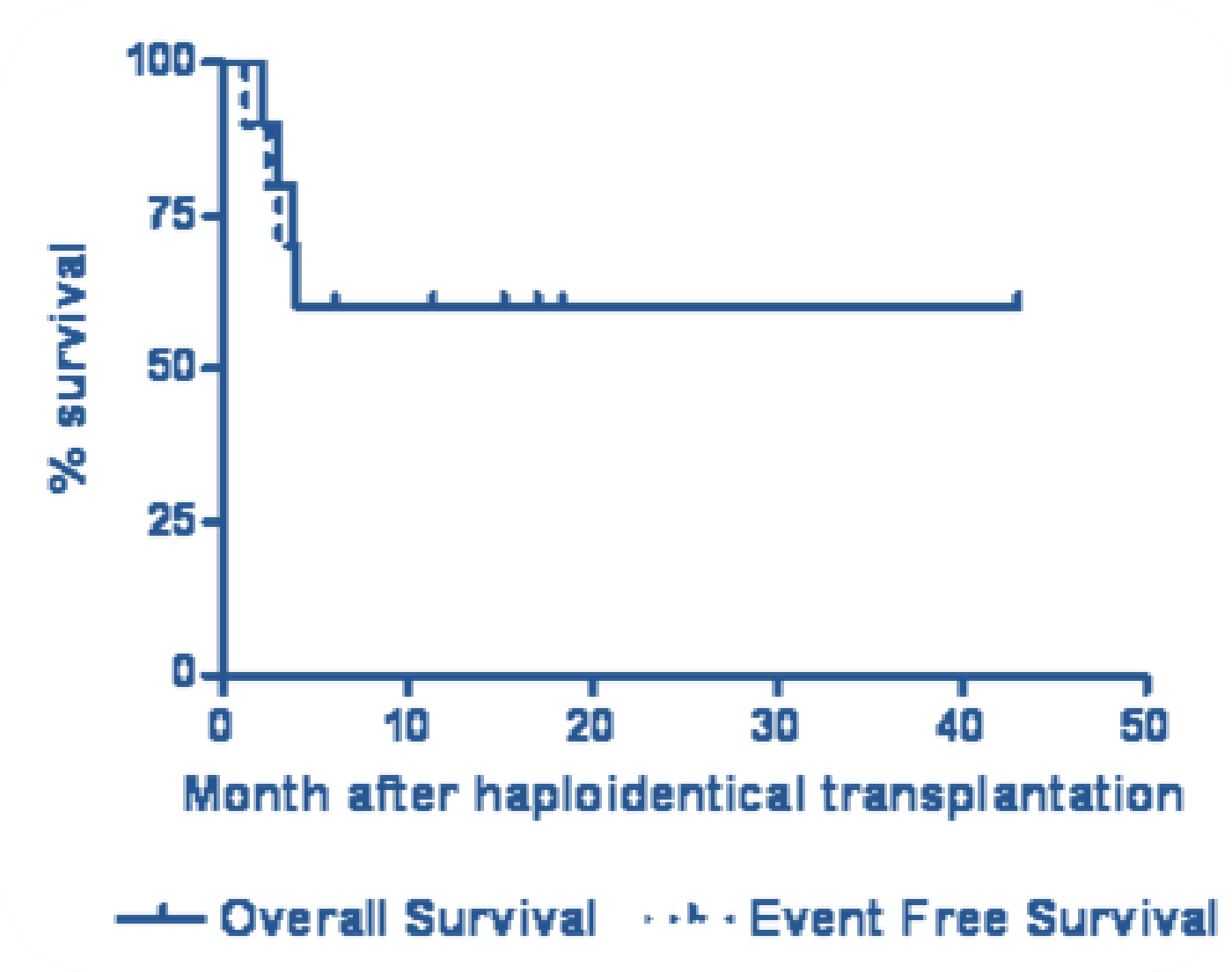
Patients characteristics
Donor selection
Graft
Engraftment
aGvHD
crGvHD
Viral infections
Survival
TRM
Leukemia Free Survival
Influence of donor

Pediatr Blood Cancer 2011;9999:1–7

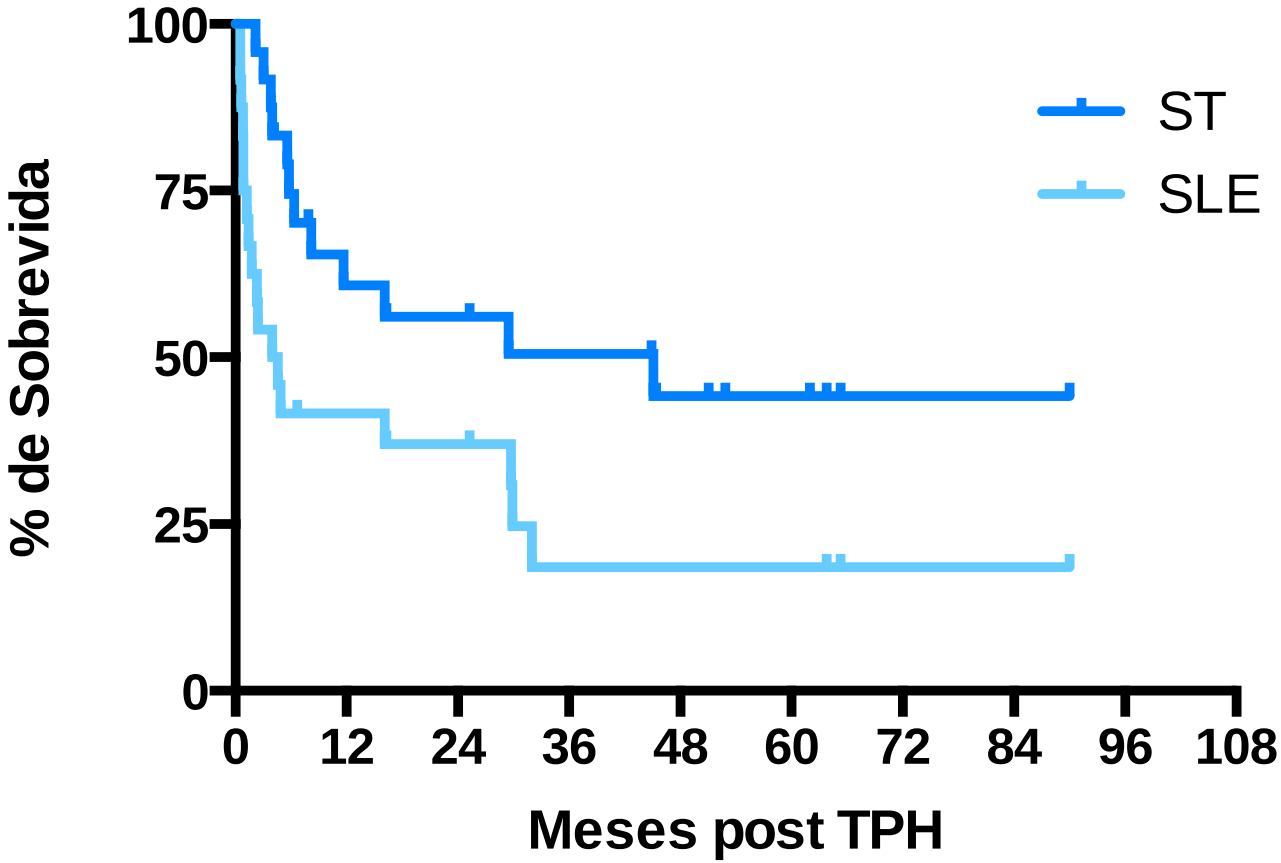
Author Proof

Haploidentical Stem Cell Transplantation for Children With High-Risk Leukemia

Julia Palma, MD,[1,2]* Lucia Salas, MT,[3] Flavio Carrión, PhD,[4] Cristián Sotomayor, MD,[1] Paula Catalán, MD,[1] Claudia Paris, MD,[1] Victoria Turner, PhD,[5] Hugo Jorquera, MT,[6] Rupert Handgretinger, MD,[7] and Gastón K Rivera, MD[5]

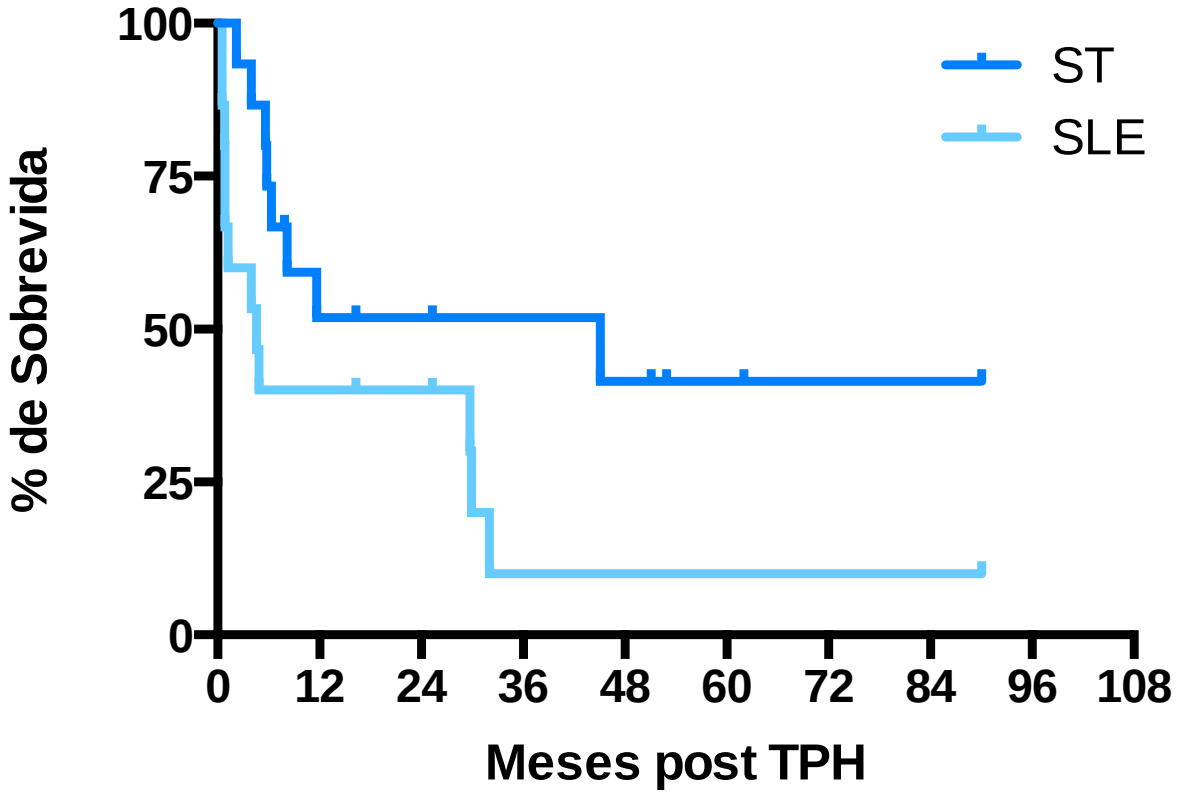


All patients Survival (n=24)
Total Survival and Event Free Survival



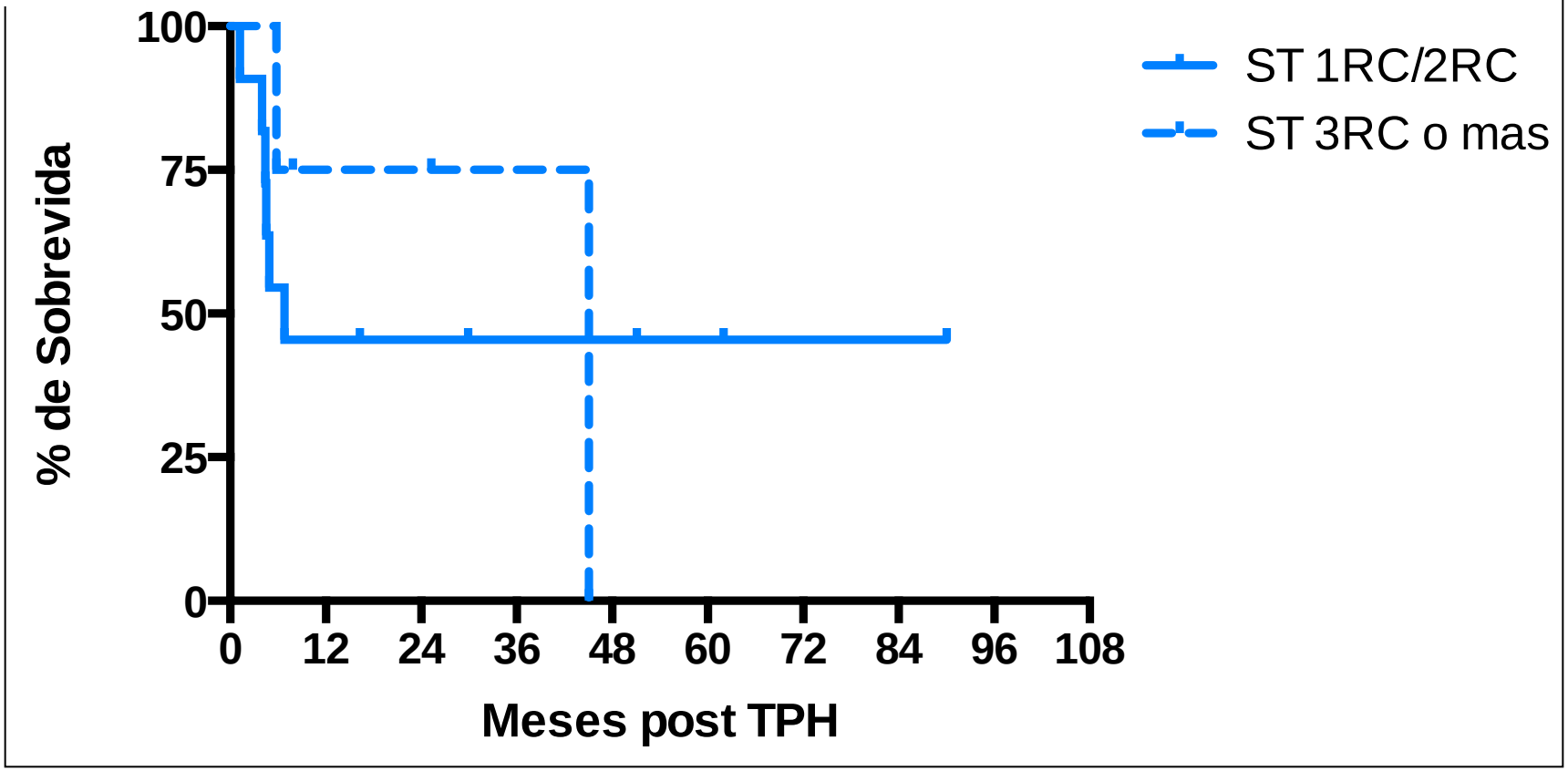
Sobrevidas	1 año	3 años	5 años
Total	60,8%	50,5%	44,2%
Libre de eventos	41,6%	18,5%	18,5%

Total Survival and Event Free Survival in ALL
N:15

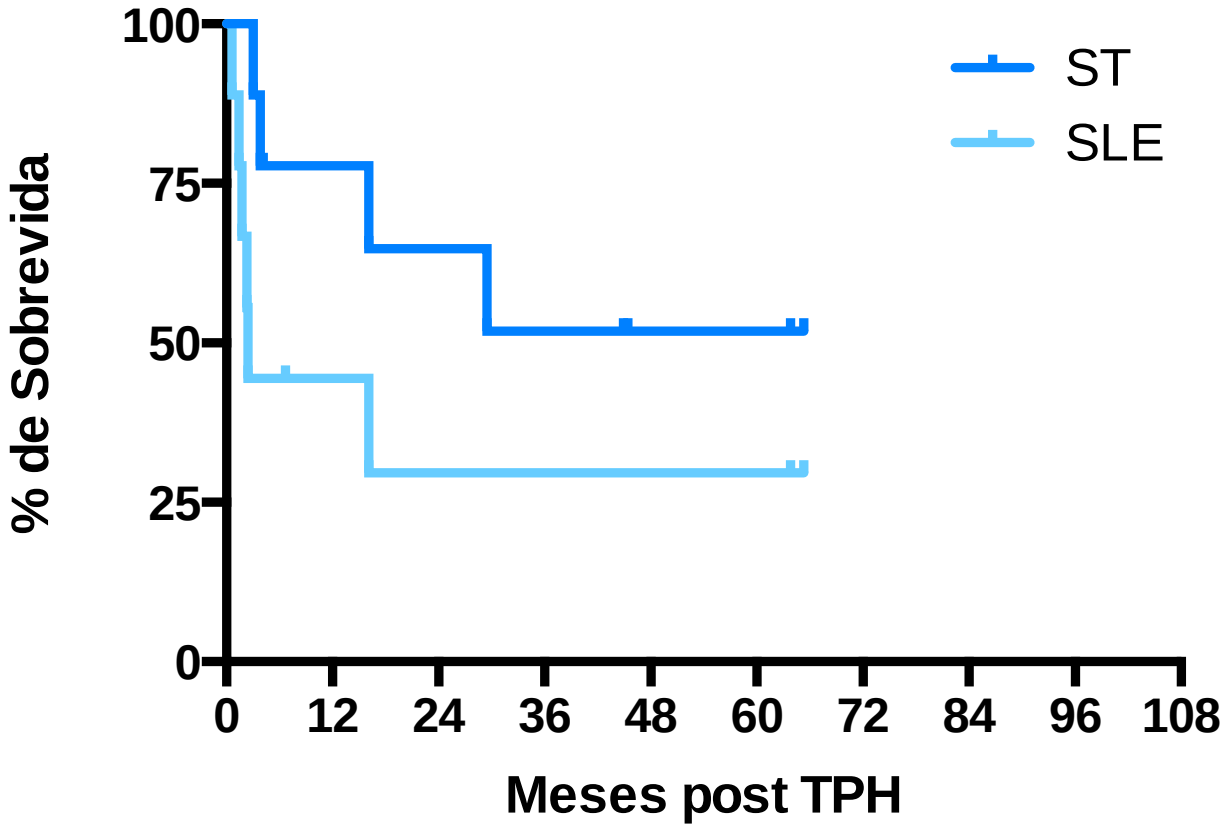


Sobrevidas	1 año	3 años	5 años
Total	51,8%	51,8%	41,4%
Libre de eventos	40,0%	10,0%	10,0%

Total Survival in ALL
1CR=1 2CR=10 3CR=4
N:15



Total Survival and Event Free Survival in AML
N:9



Sobrevidas	1 año	3 años	5 años
Total	77,7%	51,8%	51,8%
Libre de eventos	44,4%	29,6%	29,6%

ALL 1 and 2 CR
N:11

Dg	EF/B.up	Relapse	IT	2° HSCT	Status	F. Up (m)
ALL 1RC	1	10	+		F	11,7
ALL 2RC						90
ALL 2RC	4				F	4
ALL 2RC		32	+			62
ALL 2RC	1,2	1			F	2,2
ALL 2RC		23	+			52,9
ALL 2RC	1			+ (USCB)		51,1
ALL 2RC		3,3	+		F	8,2
ALL 2RC						16,3
ALL 2RC	1	4,8	+		F	5,6
ALL 2RC	1	5,4	+		F	6,3

ALL 3RC
N: 4

Dg	FEFB.up	Relapse	IT	2° HSCT	Status	F. Up (m)
ALL 3RC		15,4			F	45,1
ALL 3RC		1,2	+		F	5,8
ALL 3RC						25,3
ALL 3RC	1	7	+			7,9

AML
N: 9

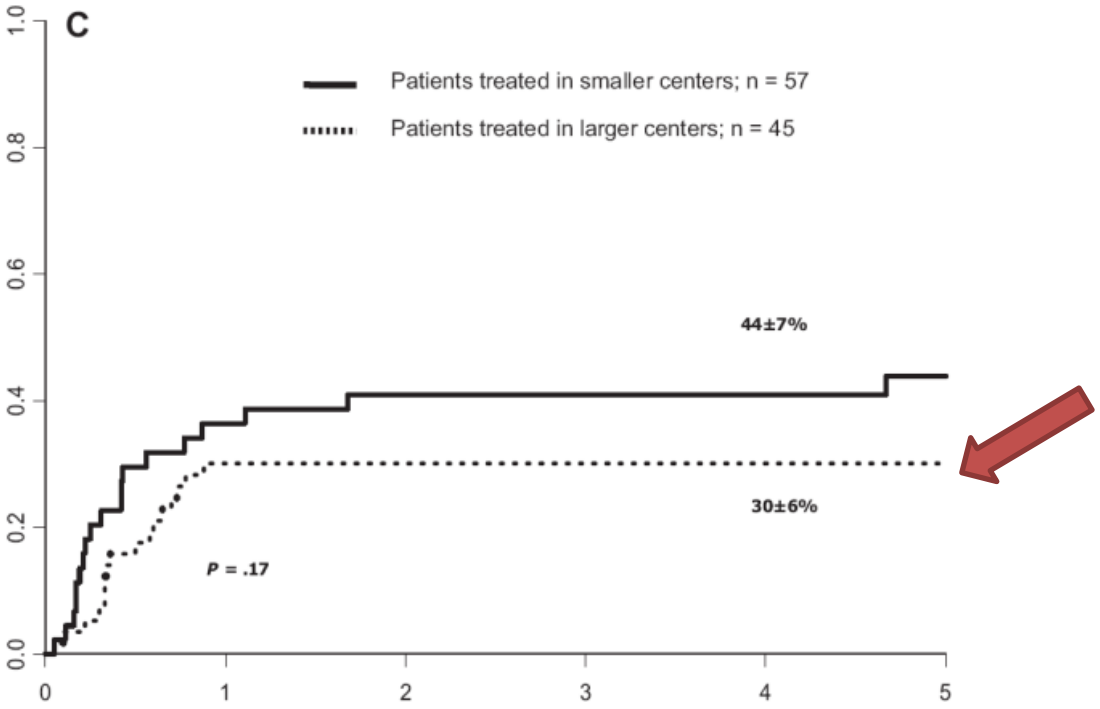
Dg	EF/B. up (m)	Relapse (m)	IT	2° HSCT	Status	F. Up(m)
AML 1CR	1	14			F	29,5
AML 1CR			+		F	16,1
AML 2CR		2,4			F	3,8
AML 2CR			+			65,3
AML 2CR						63,8
AML 2CR	1			+(USCB)		45,4
AML 2CR			+			44,9
AML 3CR	2		+			4,2
AML 3CR		1,8	+		F	3

Results

Patients characteristics
Donor selection
Graft
Engraftment
aGvHD
crGvHD
Viral infections
Survival
TRM
Leukemia Free Survival
Influence of donor

No Relapse Mortality

Total Mortality and Causes of Death



Causes of Death

Causas de Muerte	
Deaths	**12/24**
Relapse	**10**
Infecctions	**1[&]**
cGvHD	**1**
TRM **(No relapse Mortality)**	**2/24** **(8,3%)**

[&]Toxoplasmosis

Results

Patients characteristics
Donor selection
Graft
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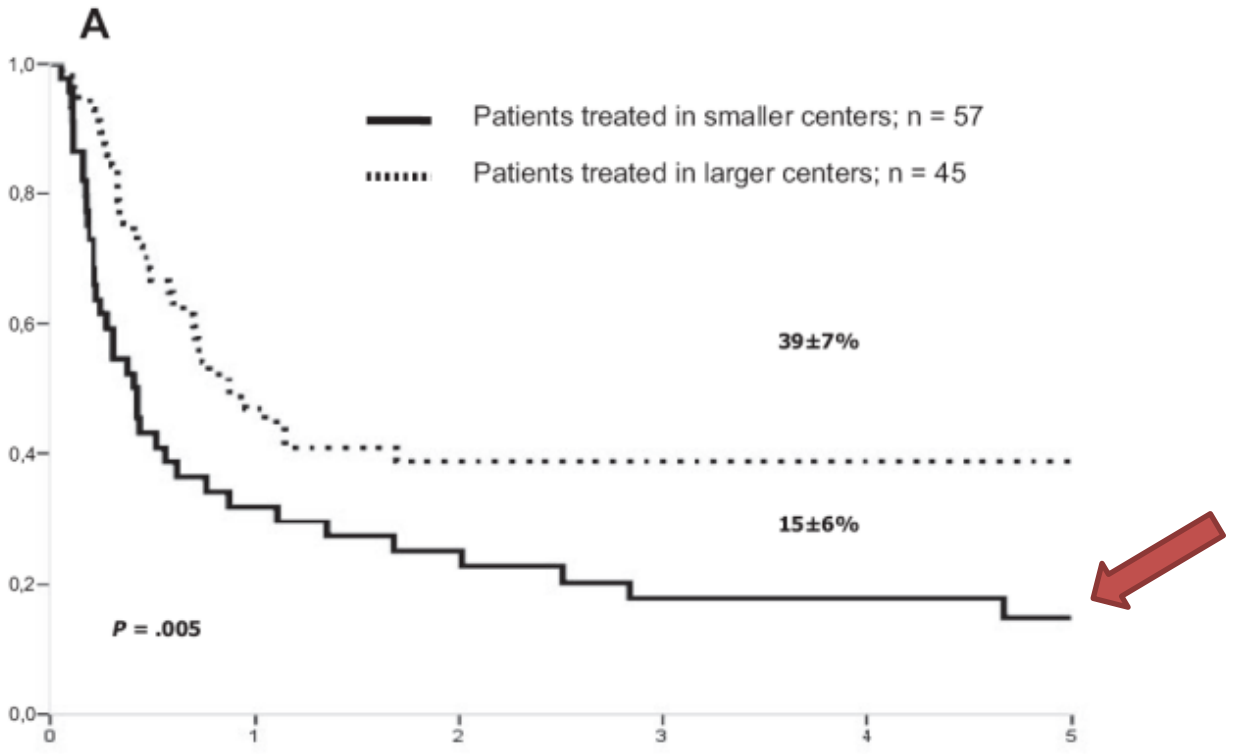
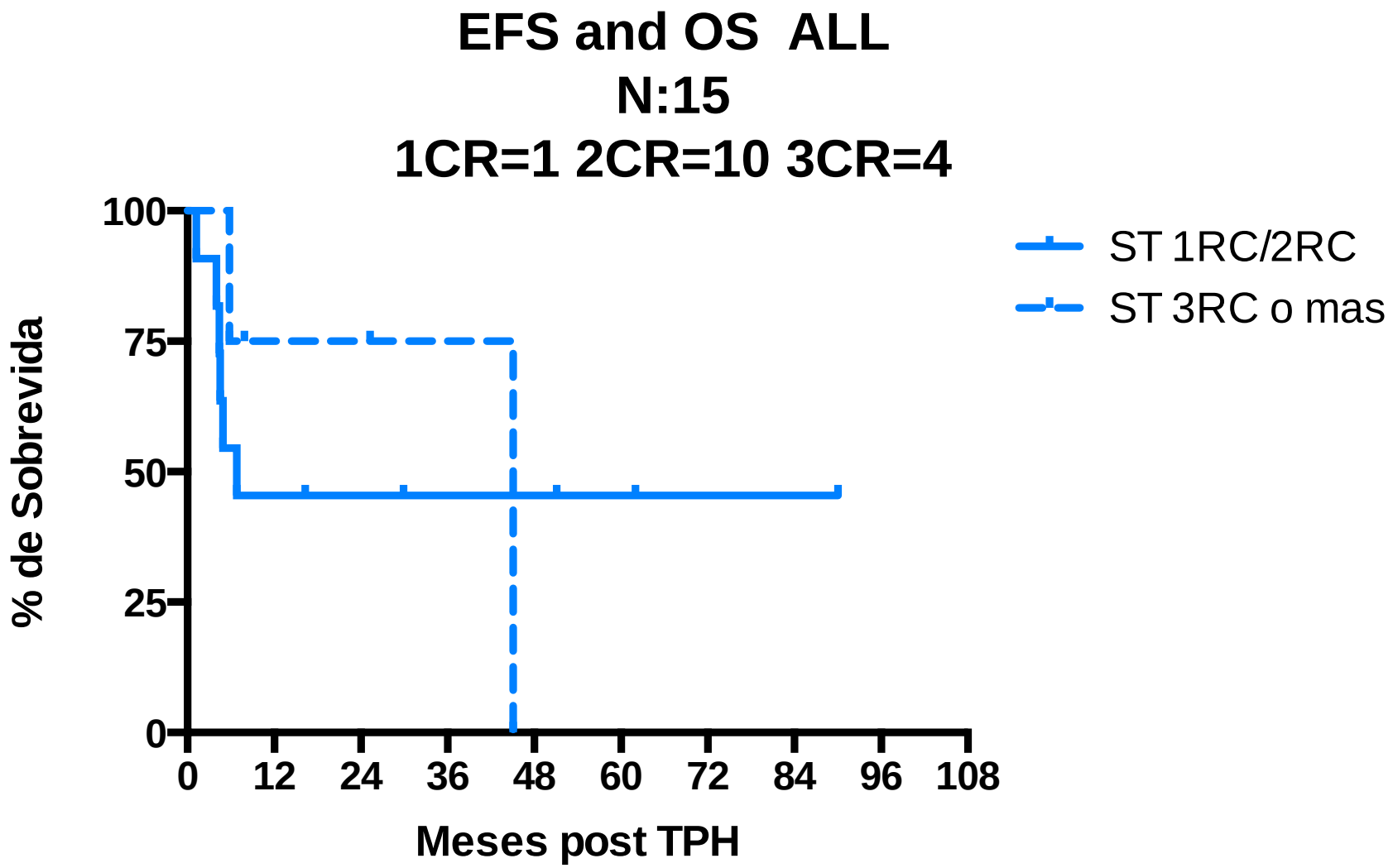
crGvHD
Viral infections
Survival
TRM
Leukemia Free Survival
Influence of donor

Leukemia-free survival after Haplo HSCT in children with ALL according to number of alloHSCTs performed

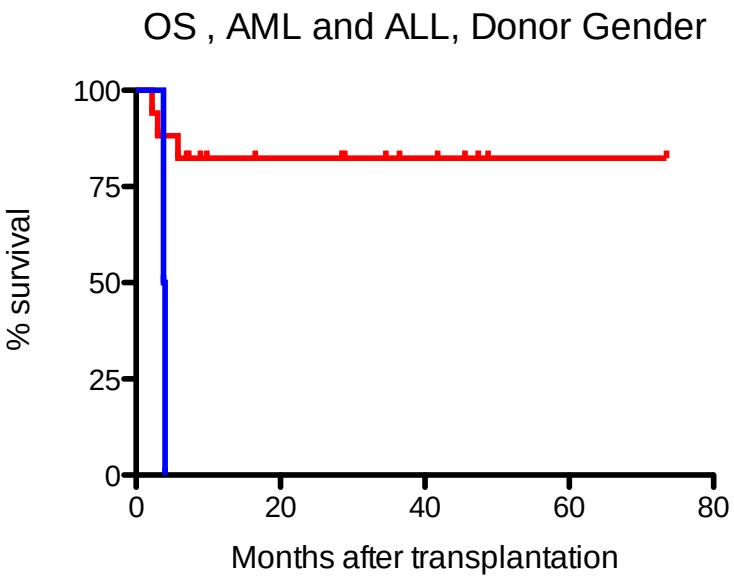


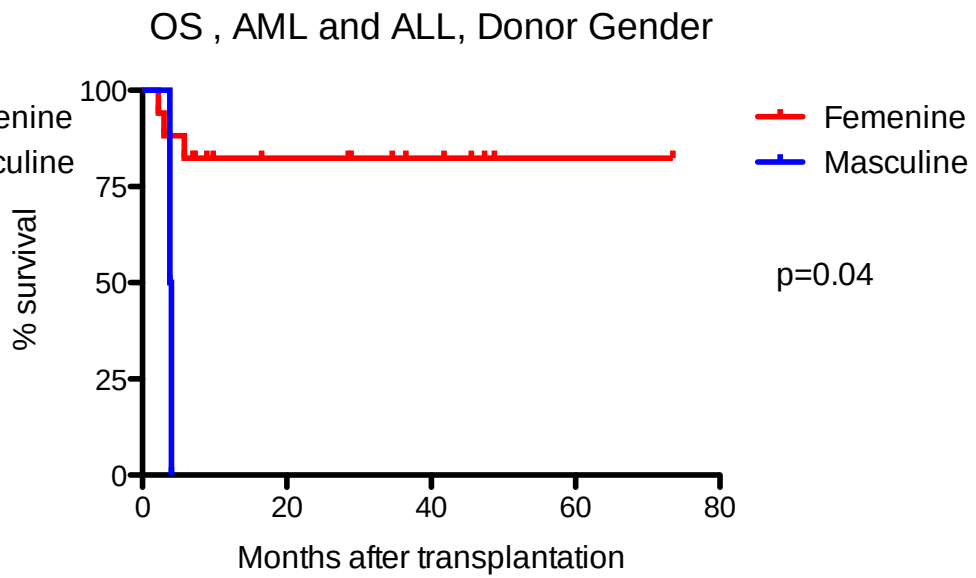

EFS and OS ALL
N:15
1CR=1 2CR=10 3CR=4
% de Sobrevida
100
75
50
25
0
0
12
24
36
48
60
72
84
96
108
Meses post TPH
ST 1RC/2RC
ST 3RC o mas

Results

Patients characteristics
Donor selection
Graft
Engraftment
aGvHD
crGvHD
Viral infections
Survival
TRM
Leukemia Free Survival
Influence of donor

EFS and OS: Influence of donor gender





Conclusions

Reduced Intensity Conditioning (ATG+TNI)

- Adequate engraftment
- Low acute and chronic GvHD
- No lethal viral infections despite preemptive approach without specific cell therapy
- Low TRM
- Encouraging survival rates, <u>not in 3CR</u>
- Adequate Leukemia-free survival
- Better results with mother as donor

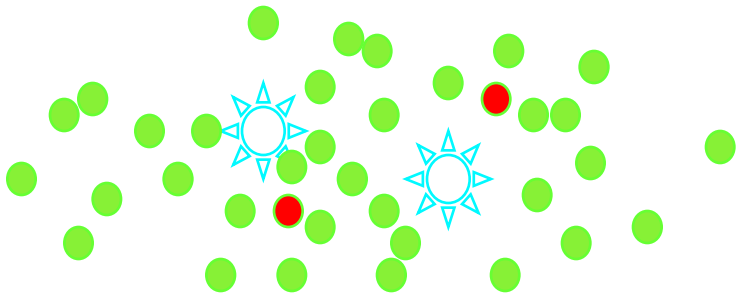
Conclusions

Reduced Intensity Conditioning (ATG+TNI)

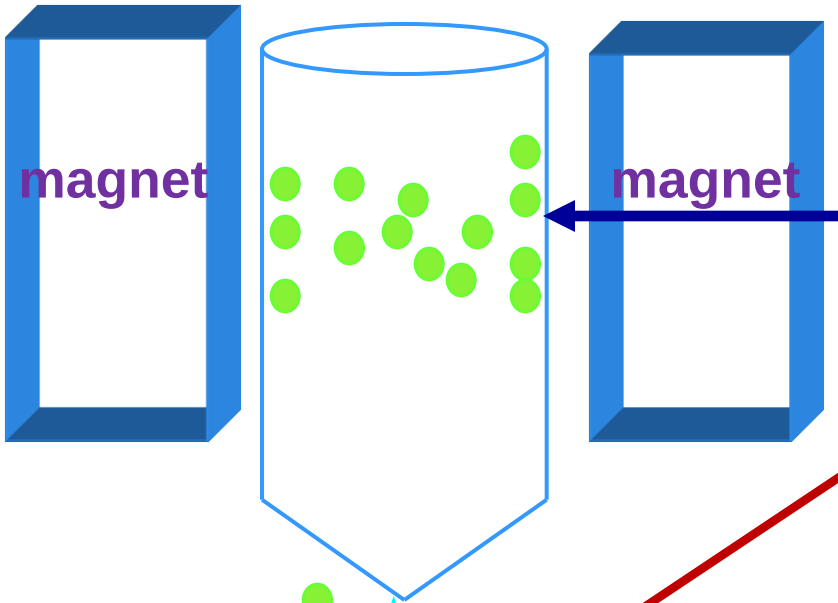
- **We have demonstrated that haploidentical transplantation is feasible in a developing country**
- **It is an option for patients without donor: specially ethnic minorities**
- **Clinical results are encouraging**

Strategy for depletion of TcRαβ+ T-cells

Chaleff S. et al.: A large scale method for the selective Depletion of α/β T-lymphocytes from PBSC for allogeneic Transplantation. Cytotherapy, 2007



1.biotin-anti-αβ mAb
2.microbeads with anti-biotin mAb



TcRαβ T cells)

CD34+ and CD34- progenitors

NK cells

Dendritic cells

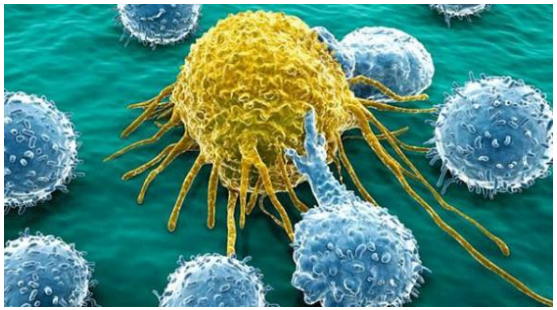
gamma/delta T-cells

Graft

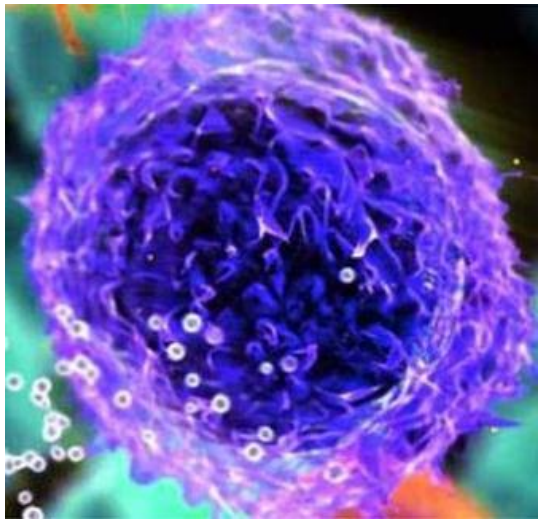
Prof.R. Handgretinger

¿Why γδ Depletion ?

- **Anti Leucemic Effect**



- **Antibacterial Activity**
- **Antiviral Activity**
- **Immune Regulation**
- **Less Graft Failure**

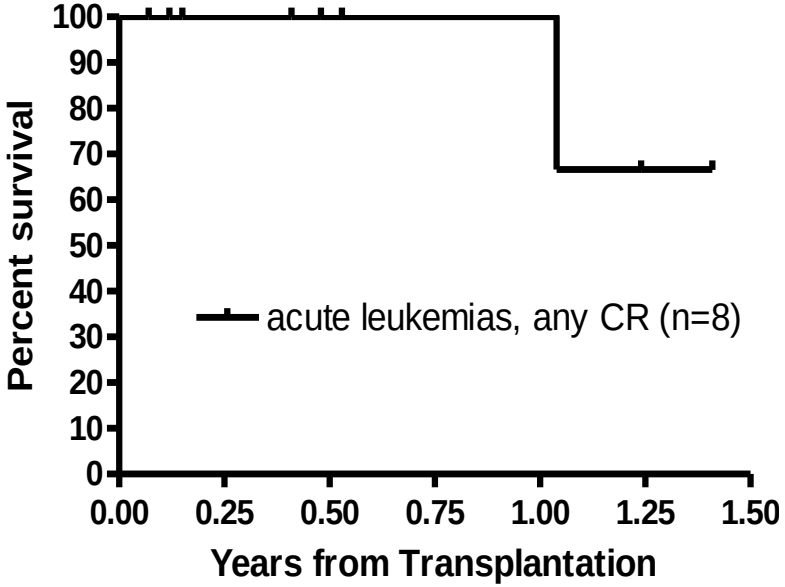


Prof. R. Handgretinger

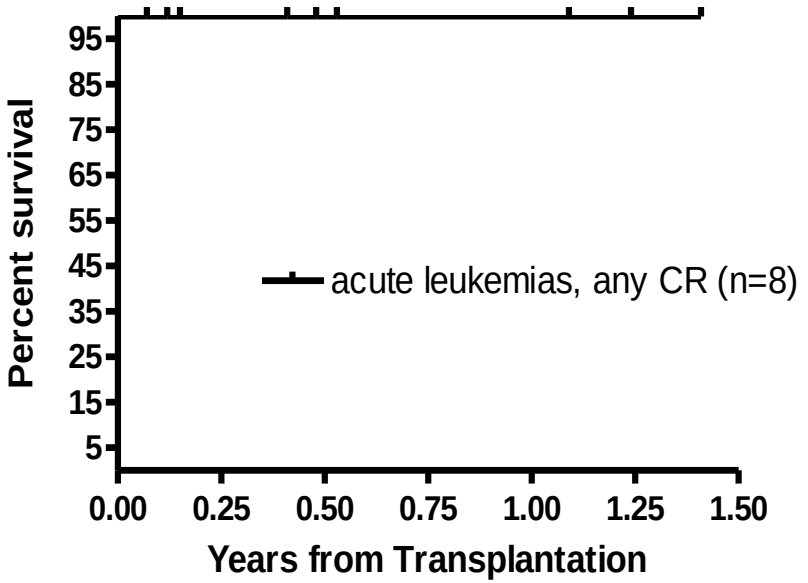
Patients in CR at time of Tx

Evernt-free survival and overall survival

EFS



OS



Prof. R. Handgretinger

Haplo with TCR αβ-Depletion

TCR αβ-Depletion results in grafts with high numbers of effector cells (γδ T cells, NK cells)

1. **Profound depletion of αβ T cells: GvHD prevention in HLA mismatched transplants**
2. **Immune recovery seems to be much faster than after other graft manipulation procedures**

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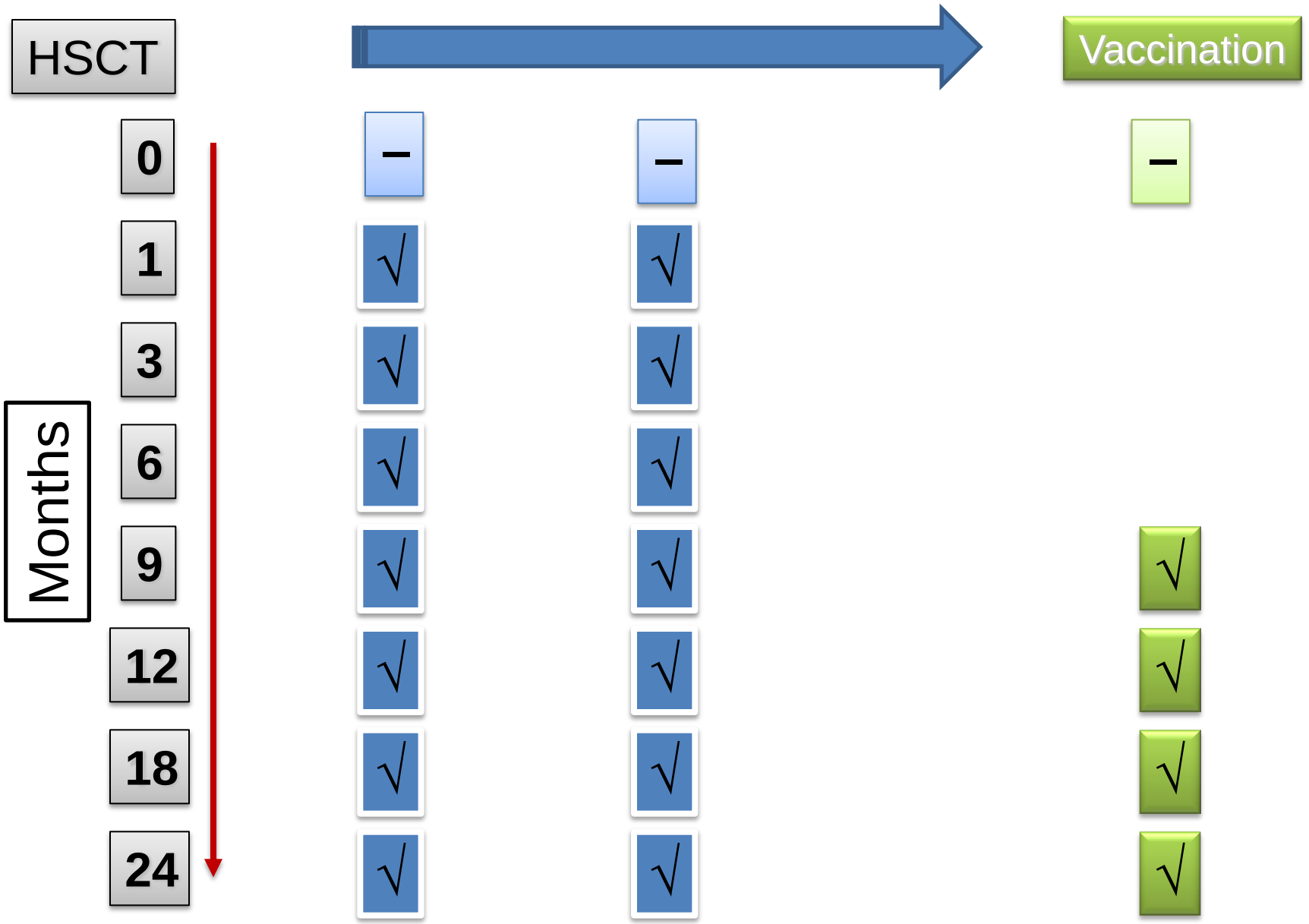
Auxiliar de servicio

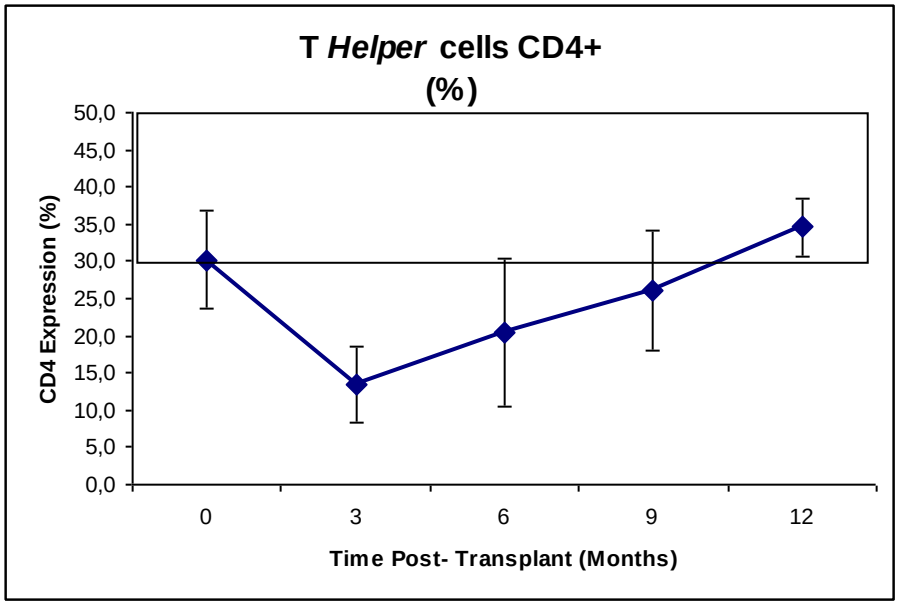
Auxiliares de aseo

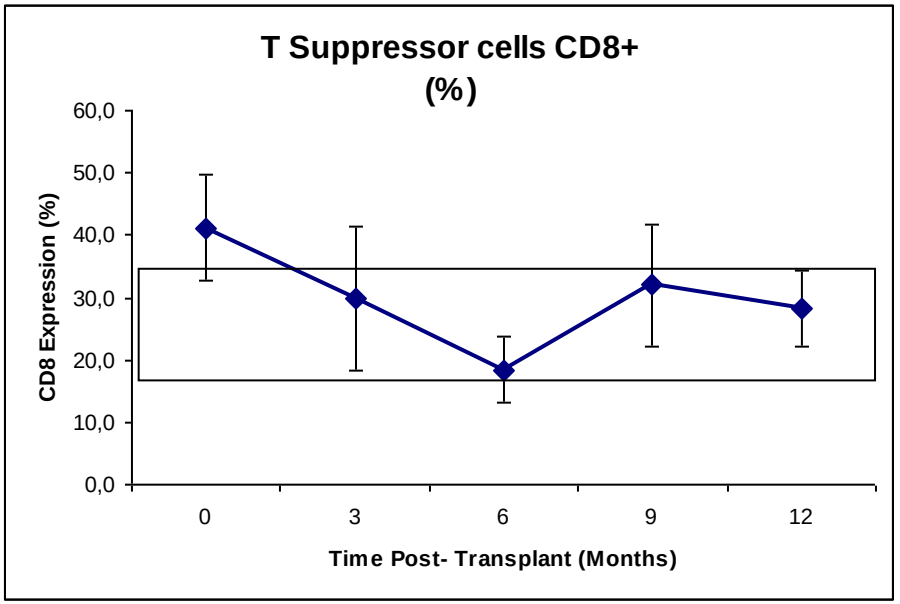
Voluntarias

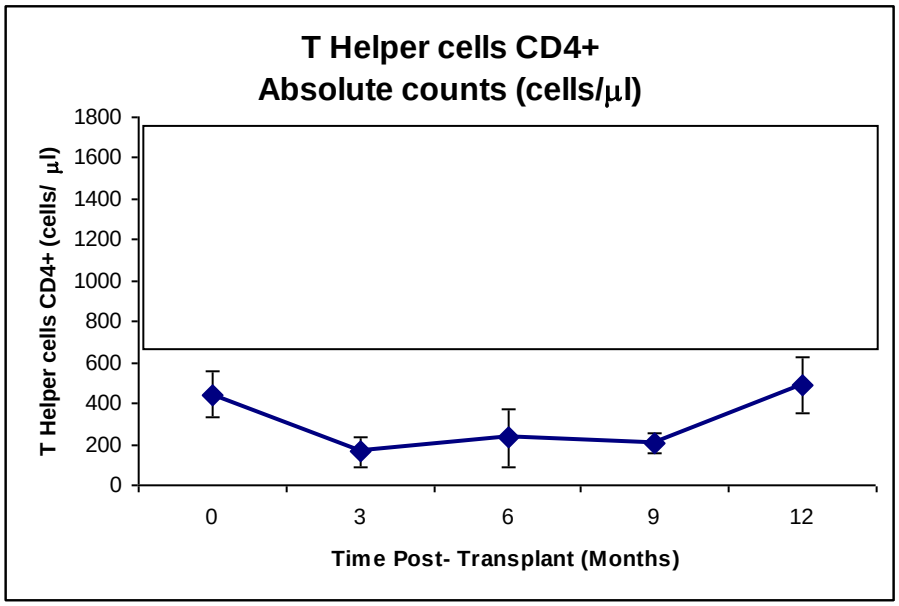
Immune reconstitution

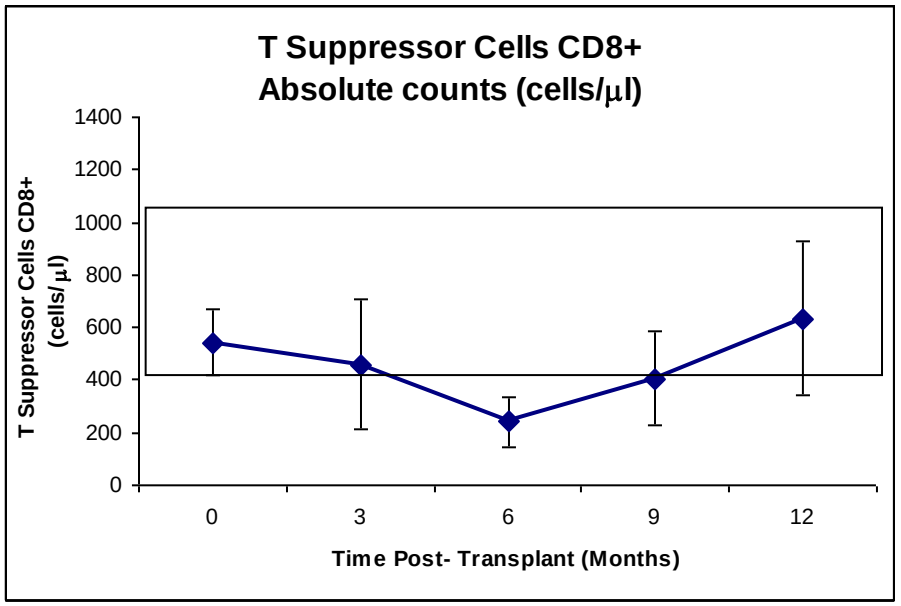


Recovery of T cells

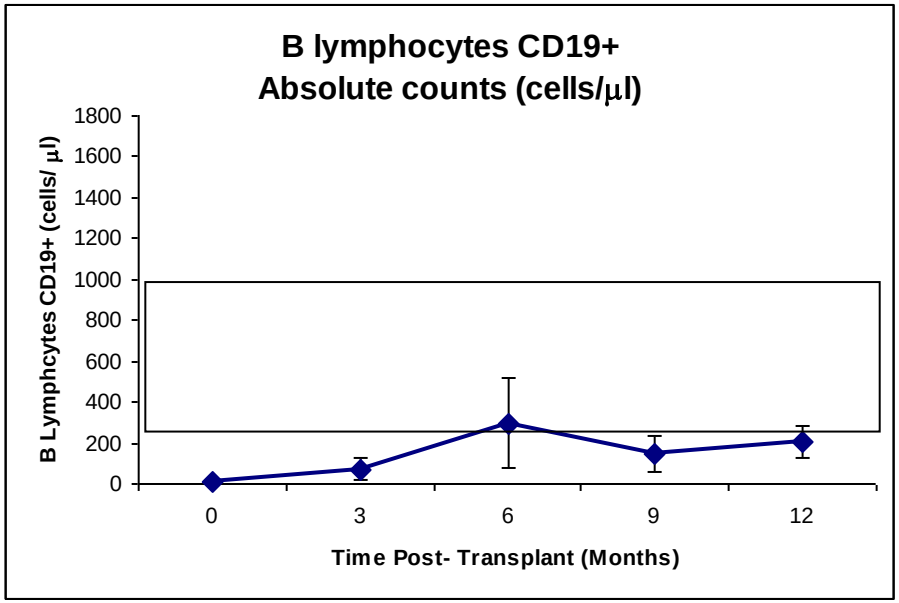


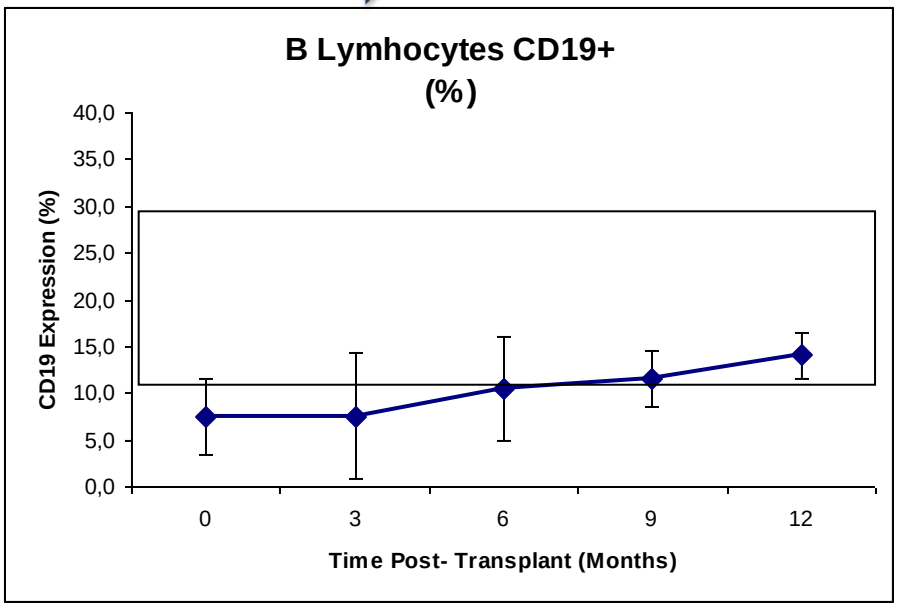


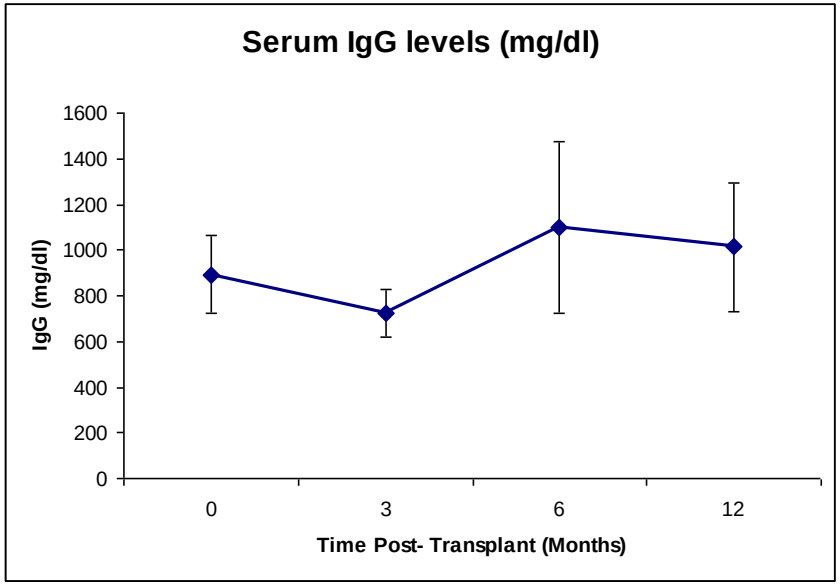




Recovery of B cells







Recovery of NK cells