1st EDUCATIONAL MEETING ON EBMT HIGHLIGT

27 APR 2013
SATURDAY
CAPPADOCIA,KAYSERI

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- Scientific Program
- Scientific Chair
- Social Program
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- Contact

Erciyes University Faculty of Medicine
Department of Hematology
Erciyes (Cappadoccia) Transplantation Center

27 APRIL 2013,Saturday
CAPPADOCIA-KAYSERI

Welcome Address,

It gives us pleasure to invite you, for the post EBMT meeting. This will be the first annual meeting for the colleagues and physicians who are working at BMT Centers. Cappadocia is always a vibrant and popular venue . Not only will you be coming to an exciting city Kayseri but also to an exciting meeting

In 2013 we want to start to celebrate all that is good about Bone Marrow Transplantation and in addition, the meeting content particularly with respect to basic and translational science.

Wherever possible we will try to bring together basic and translational science when discussing challenging transplant topics. We will continue our focus on reporting recent developments, and education at all levels. The meeting will take place in the Genome and Stem cell Center at Erciyes University, ideally situated to allow you to concentrate on the meeting during the day and close enough to be able to enjoy Cappadocia entertainment in the evening.

There are no venues that can compete with Cappadocia for historical, cultural, and social facilities in Turkey.

Whatever your interests be assured that at post EBMT 2013 you will be able to combine work, education and pleasure of the highest quality.

See you in Cappadocia, Kayseri!

Dr. Ali Ünal

Dr. Mustafa Çetin

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Scientific Program

8.45- 9.00 - **Welcome Adress:** Fahrettin Keleştemur-Osman İlhan-Ali Ünal- Mustafa Çetin

9.00- 9.45 - **Chairs:** Osman İlhan, Ali Ünal

- ACUTE LEUKEMIA: RISK ADAPTED TRANSPLANT

- *Ahmet Elmaağaçlı*

9.45-10.30 - **Chairs:** Mehmet Ali Özcan, İsmet Aydoğdu

- MDS: STEM CELL TRANSPLANTION AND HYPOMETHYLATED AGENTS

-Mehmet Ali Özcan, Hakan Göker

10.30-10.45 - Coffee Break

10.45-11.15 - **Chairs:** Mustafa N.Yenerel, Mehmet Yılmaz

- NST - RIC :NON-MYELOABLATIVE CONDITIONING, DLI AND CELL THERAPY IN HEMATOLOGICAL MALIGNANCIESY

- *Shimon Slavin, Ali Uğur Ural*

11.15-12.30 - **Chairs:** Hakan Özdoğu, İsmail Sarı

- HAPLOIDENTICAL TRANSPLANT (T CELL SELECTION)

- *Zafer Gülbaş, Mustafa Çetin*

Haploidentical Transplantation

The often forgotten options….. From nightmare to dream

Erciyes University Faculty of Medicine
Department of Hematology
Erciyes (Cappadoccia) Transplantation Center

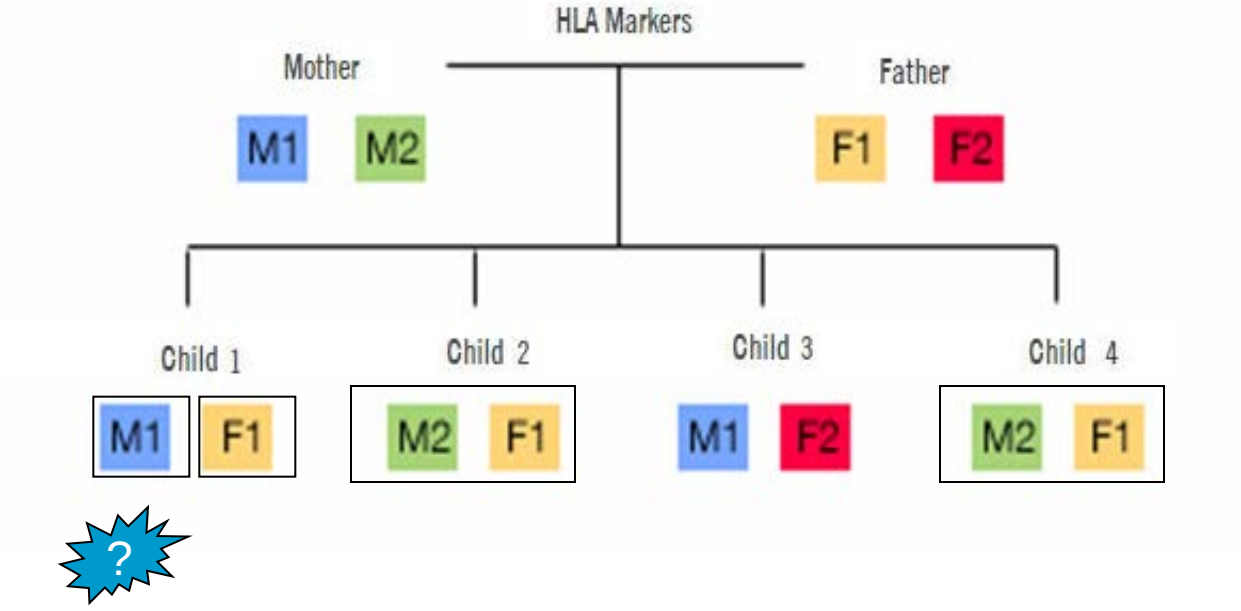
Prof. Dr. Mustafa ÇETİN

http//www.iliknakli.com.tr
http//www.hematoloji-onkoloji.com

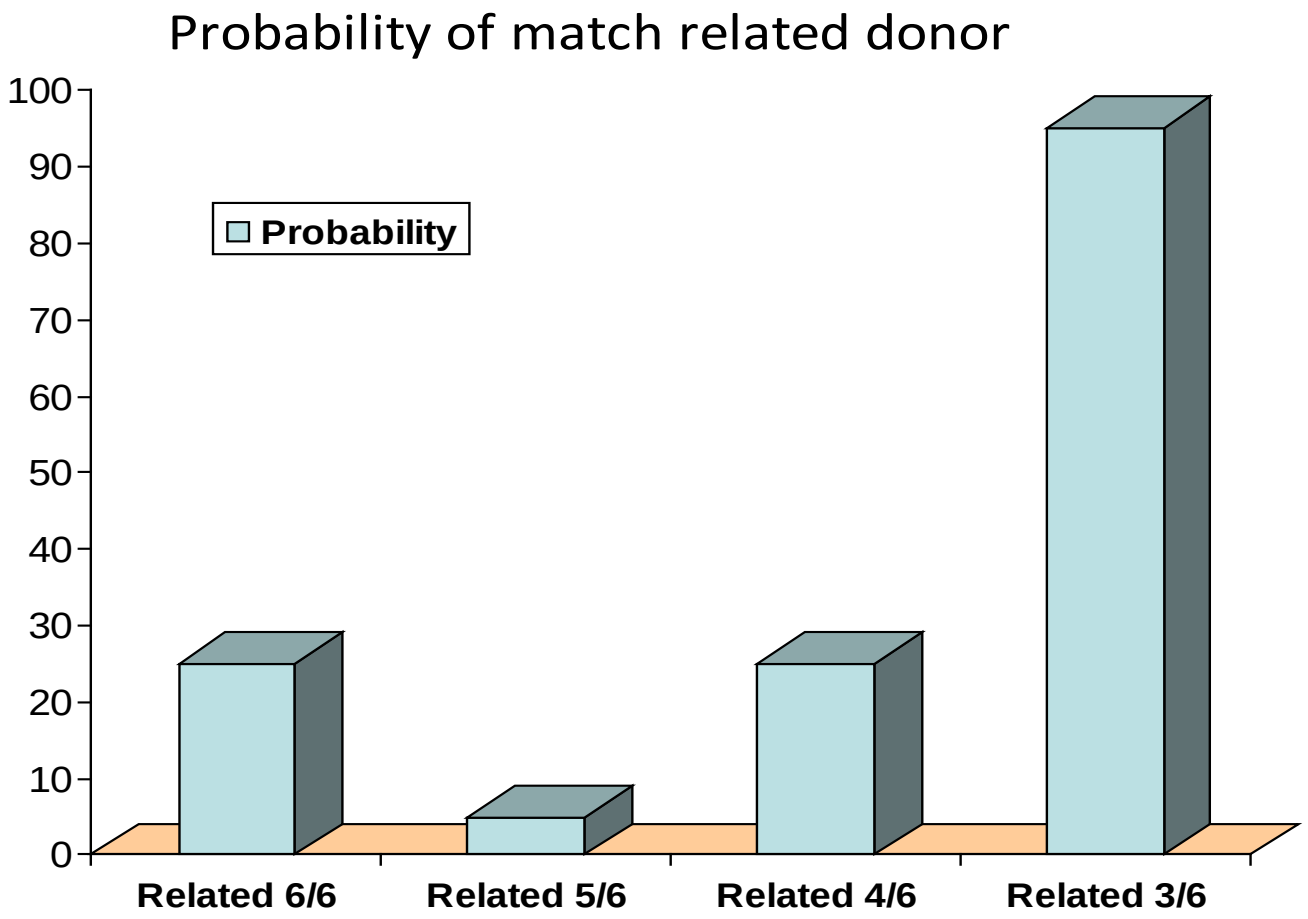
Background

- *Clinical Problem: Allogeneic Graft Availability*
- *Early studies using T- cell replete marrow grafts*
- *Earlier efforts to improve the results*
  - *More effective and selective T cell depletion*
  - *The use of GCSF-mobilized PBSC instead BM (Mega-dose concept)*
  - *NK cell alloreactivity (KIR mismatch)*
  - *Non-myeloablative regimens*
- *New Modalities to Improve Outcome*
  - *Manuplated: ''αβT cells Depletion induced tolerance '' γδT cell+ NK cell+ DC's supported & Role of the γδT cell*
  - *Unmanuplated: " drug induced tolerance" Selective Allodepletion by Post Transplantation Cyclophosphamide*
  - *Erciyes University results*

Children's possible HLA Combinations



Clinical Problem: Allogeneic Graft Availability



Clinical Problem: Allogeneic Graft Availability

What to do if no matched sibling donor available ?

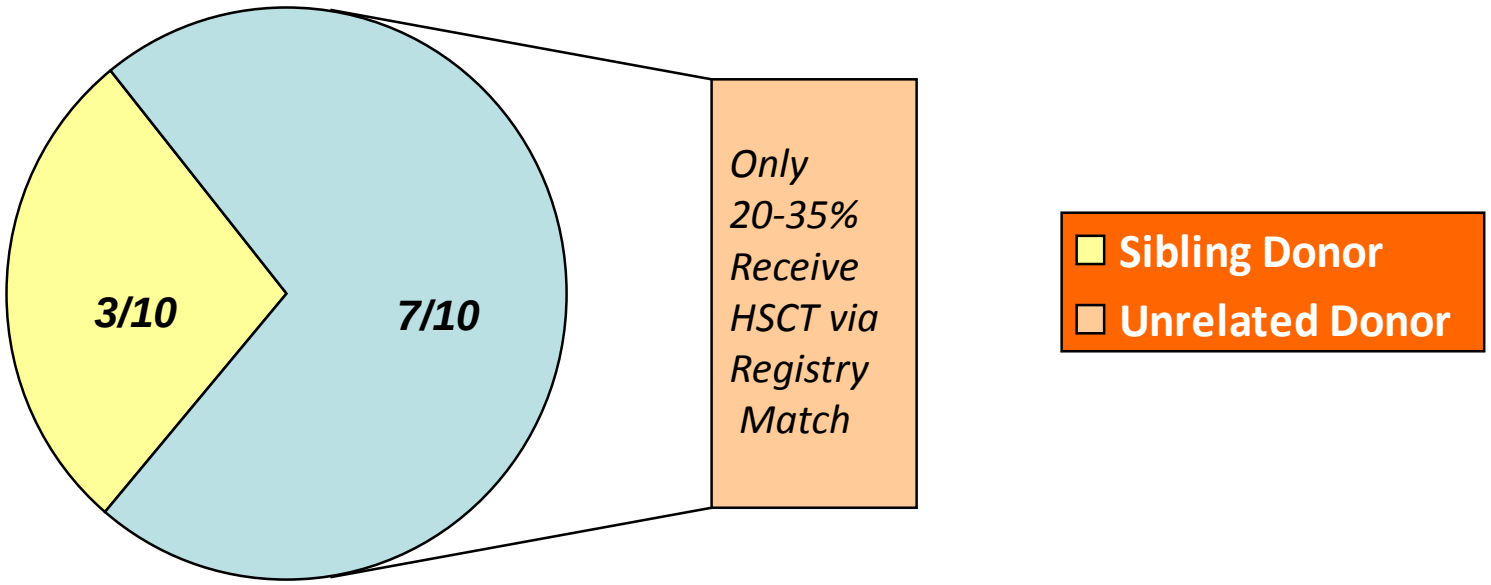
- Look for alternative donors:
  - Matched unrelated donor
  - Mismatched related donor
  - Umbilical cord blood

Choice of Donor for SCT

Choice	Family Donor	Unrelated Donor	Unrelated CB
1st	mSD or mCB		
2nd	mFD or 5/6	10/10	6/6
3rd	<4/6 (hID)	9/10	>5/6 or <4/6

Clinical Problem: Allogeneic Graft Availability

Hematology Patients Needing HSCT



Clinical Problem: Allogeneic Graft Availability

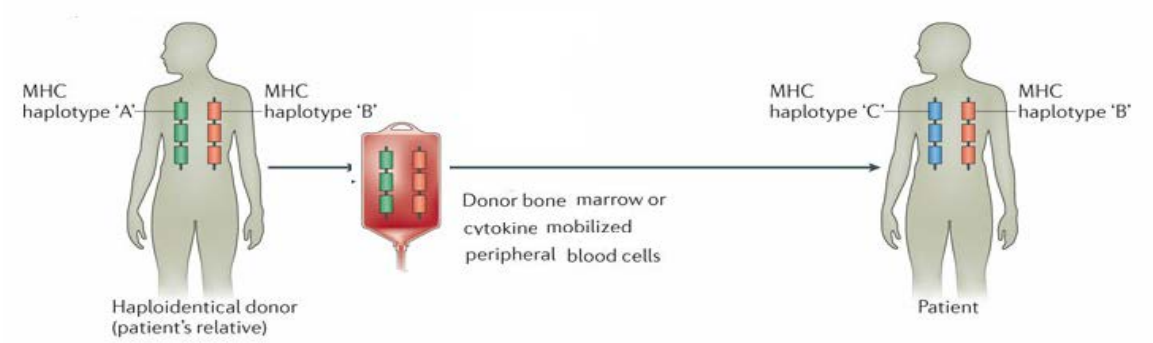
Major Obstacles for Matched Unrelated Donor Transplant

- Chance of Match: 60-70% for Caucasians
  - ≤ 10% for Ethnic Minorities
- Cumbersome searching, typing and harvesting
  - Median time 4 months.
- Many such patients do not maintain a remission or survive the long waiting period until a donation is available

Potential advantages and disadvantages of different types of stem cell donor

DONOR	AVAİLABİLİTY	ACESS (RE-ACCESS)	COST	REJECT (RİSK)	ENGRAFTMENT (SPEED)	GVHD (RİSK)	GVL	IMMUNE RECONST
SIBLING Matched	20-30 %	Fast (yes)	low	low	fast	low	T	fast
UNRELATED Matched	10/10=40% >9/10=70% Ethnic=20%	slow (possible)	high	low	moderate	moderate	T	moderate
CB Unrelated	>5/6=40% >4/6=70%	fast (no)	high	low	slow	low	T NK	moderate
HAPLO Family	>90%	Immediate (yes)	moderate	Moderate (low)	fast	low	T NK	very slow

Haploidentical Transplantation



Advantages

- Nearly all patients have a donor
- Immediate donor availability
- Financial implications:

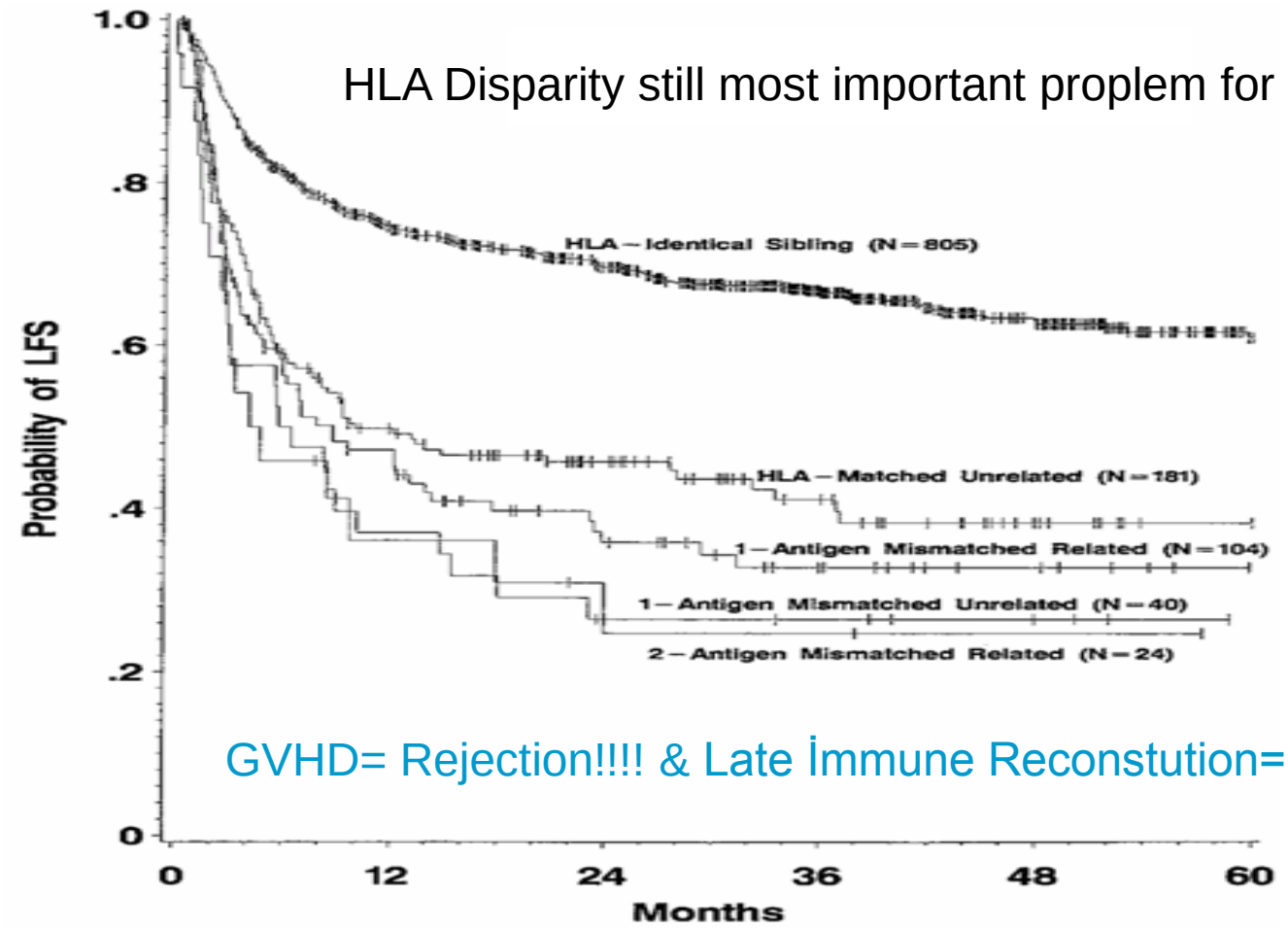
Considerable expenditure of additional typing and procurement of unrelated donor graft can be avoided.

Disadvantages

- HLA barriers:
  - Graft rejection
  - GVHD
  - Immune dysregulation

HLA Disparity and Survival

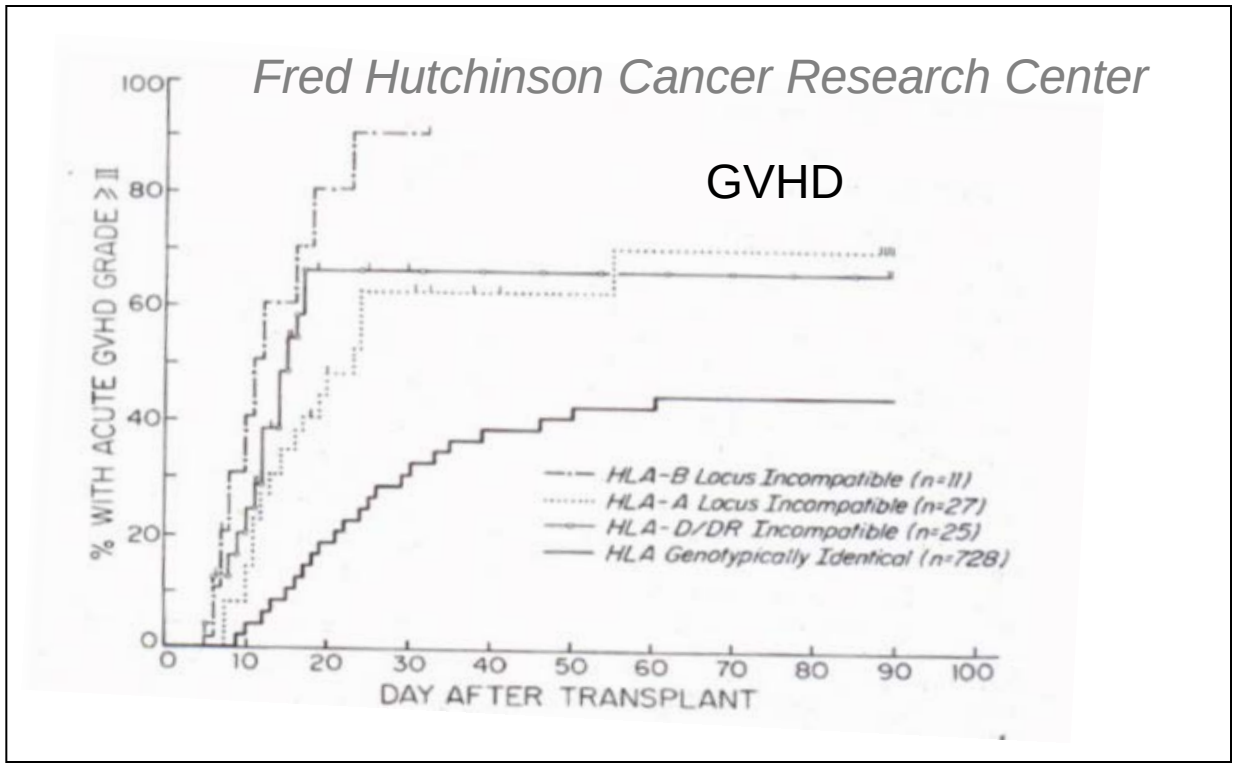
HLA Disparity still most important proplem for survival



GVHD= Rejection!!!! & Late İmmune Reconstution= TRM

Szydo et al. JCO 2010

HLA Disparity and GVHD



Haploidentical transplant using 2-3 HLA loci mismatched transplant is associated with a higher incidence of GVHD, delayed engraftment and graft failure

Beatty PG, NEJM 1985

Haploidentical Transplantation:
Early studies using T- cell replete marrow grafts

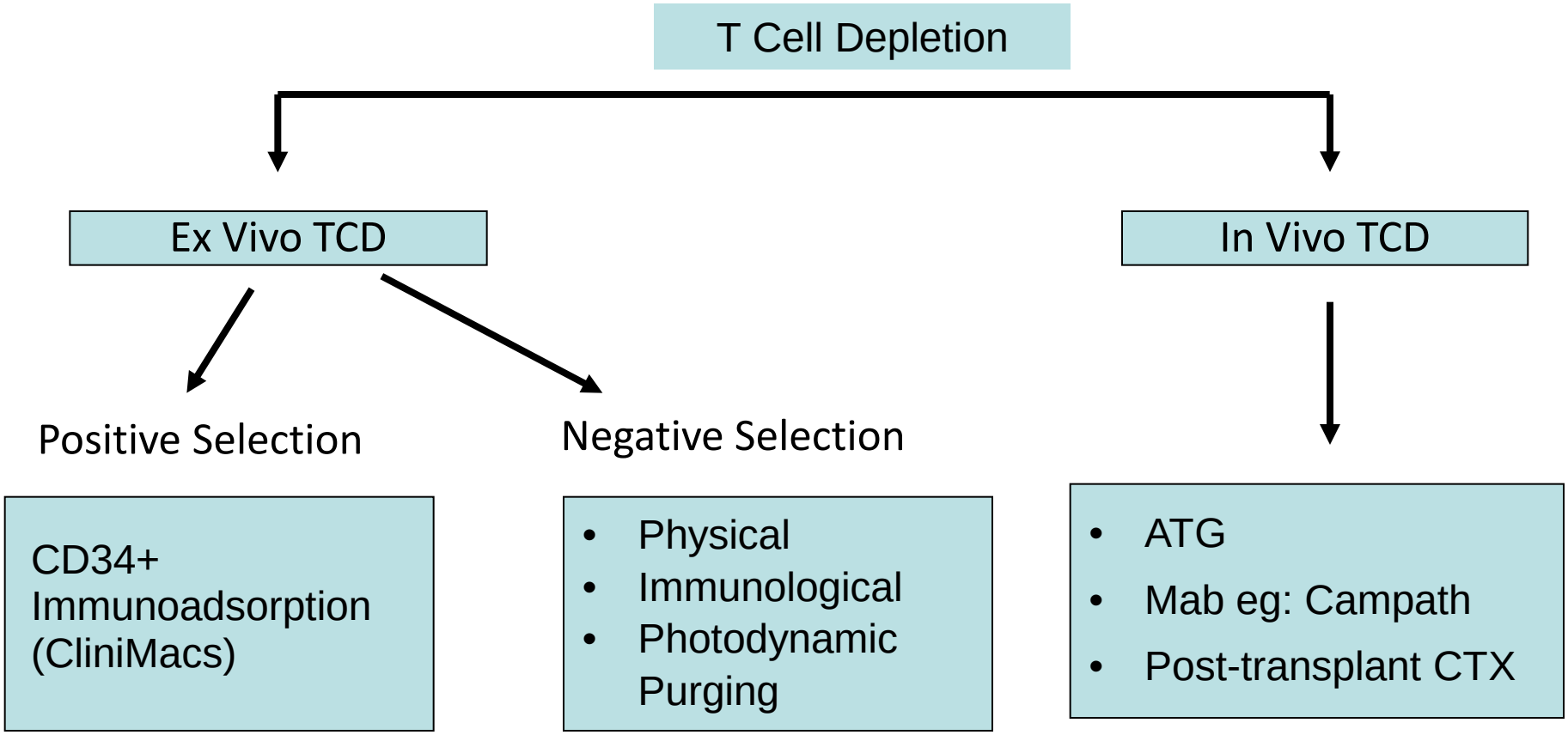
1. *Early 1990's*
2. *T–cell replete marrow graft,*
3. *Lethal conditioning,*
4. *GVHD prophylaxis with CSP +/- MTX*
5. *Largely disappointing*
6. *High incidence of non relapsed mortality (especially CMV),*
7. *Severe GVHD and Graft Rejection (up to 30%)*

Beatty PG, et al. N Engl J Med. 1985;313:765-771.
Anasetti C, et al. N Engl J Med. 1989;320:197-204.
Powles RL, et al.. Lancet. 1983;1:612-615.
Szydlo R, et al. J Clin Oncol. 1997;15:1767-1777

Earlier efforts to improve the results ; from 2000's onwards

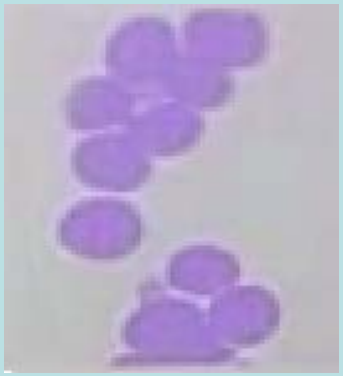
- *Substituting cyclophosphamide with fludarabine*
- *Total dose of radiation was decreased from 6 to 4 Gy.*
- *The use of GCSF to promote engraftment was eliminated from the protocol since 1999 following the observation that it impaired immune reconstitution.*
- *More effective and selective T cell depletion*
- *The use of GCSF-mobilized PBSC instead BM (Mega-dose concept)*
- *NK cell alloreactivity (KIR mismatch)*
- *Non-myeloablative regimens*

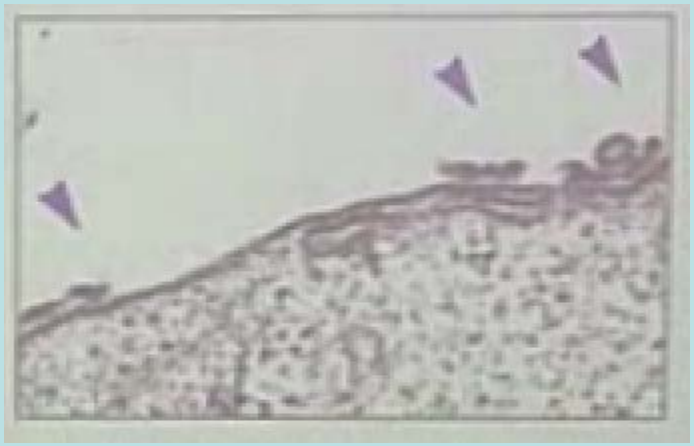
More effective and selective T cell depletion



Koh LP, Rizzieri DA. Strategies for T Cell Depletion to Prevent Graft versus Host Disease. In: Taylor CB, Ed. Immunosuppresion: New Research. Nova Science Pub Inc (May 2009)

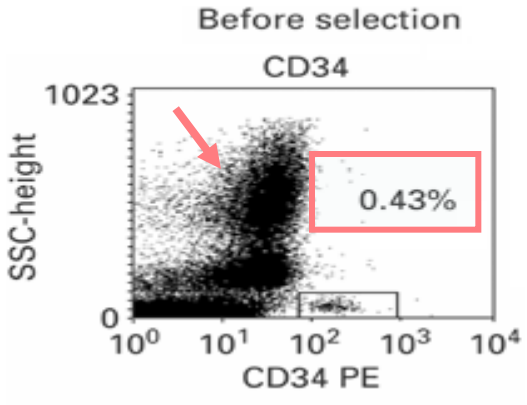
Ex vivo T cell Depletions

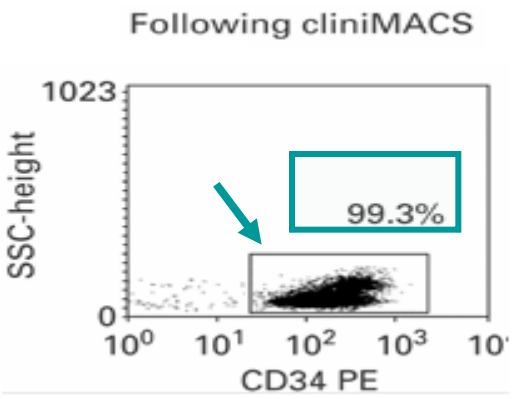




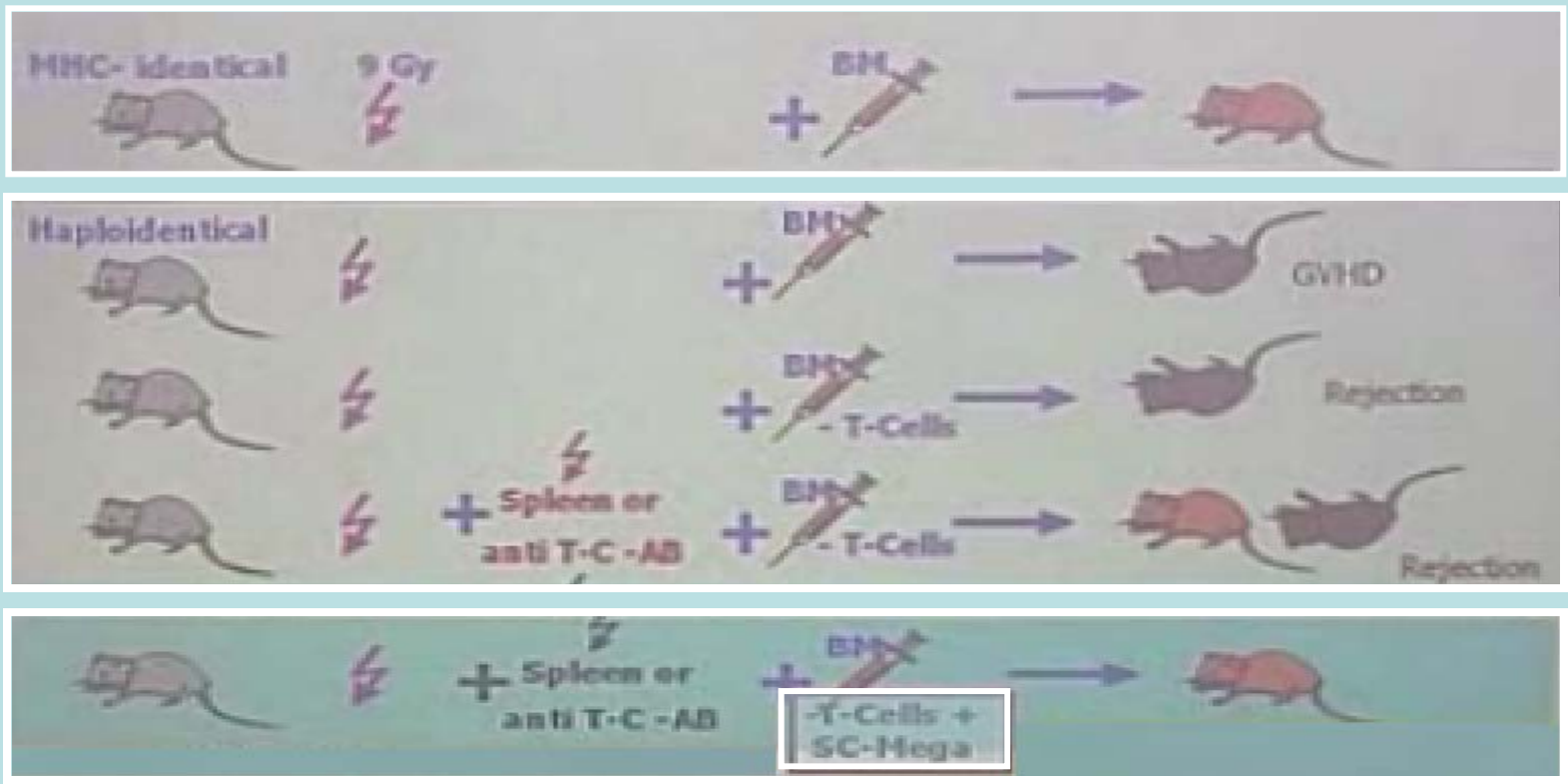
CD34+
Stem cell

Micro beads on the cell surface





Haploidentical transplantation: Mouse model" Megadose Concept"



Megadose SC & CTLp (responsible from rejection): VETO EFFECT

Yair- Reissner 1980

Milestones of Haploidentical Transplantation
İnitial successful experiences of Tcell depleted process

blood

1994: pp 3948-3955

Successful Engraftment of T-Cell–Depleted Haploidentical ''Three-Loci'' Incompatible Transplants in Leukemia Patients by Addition of Recombinant Human Granulocyte Colony-Stimulating Factor–Mobilized Peripheral Blood Progenitor Cells to Bone Marrow Inoculum

By Franco Aversa, Antonio Tabilio, Adelmo Terenzi, Andrea Velardi, Franca Falzetti, Claudia Giannoni, Roberta Iacucci, Tiziana Zei, Maria Paola Martelli, Cesare Gambelunghe, Massimo Rossetti, Pierfranco Caputo, Paolo Latini, Cynthia Aristei, Carlo Raymondi, Yair Reisner, and Massimo F. Martelli

The NEW ENGLAND JOURNAL of MEDICINE

1998; 339:1186-1193

ORİGİNAL ARTİCLE

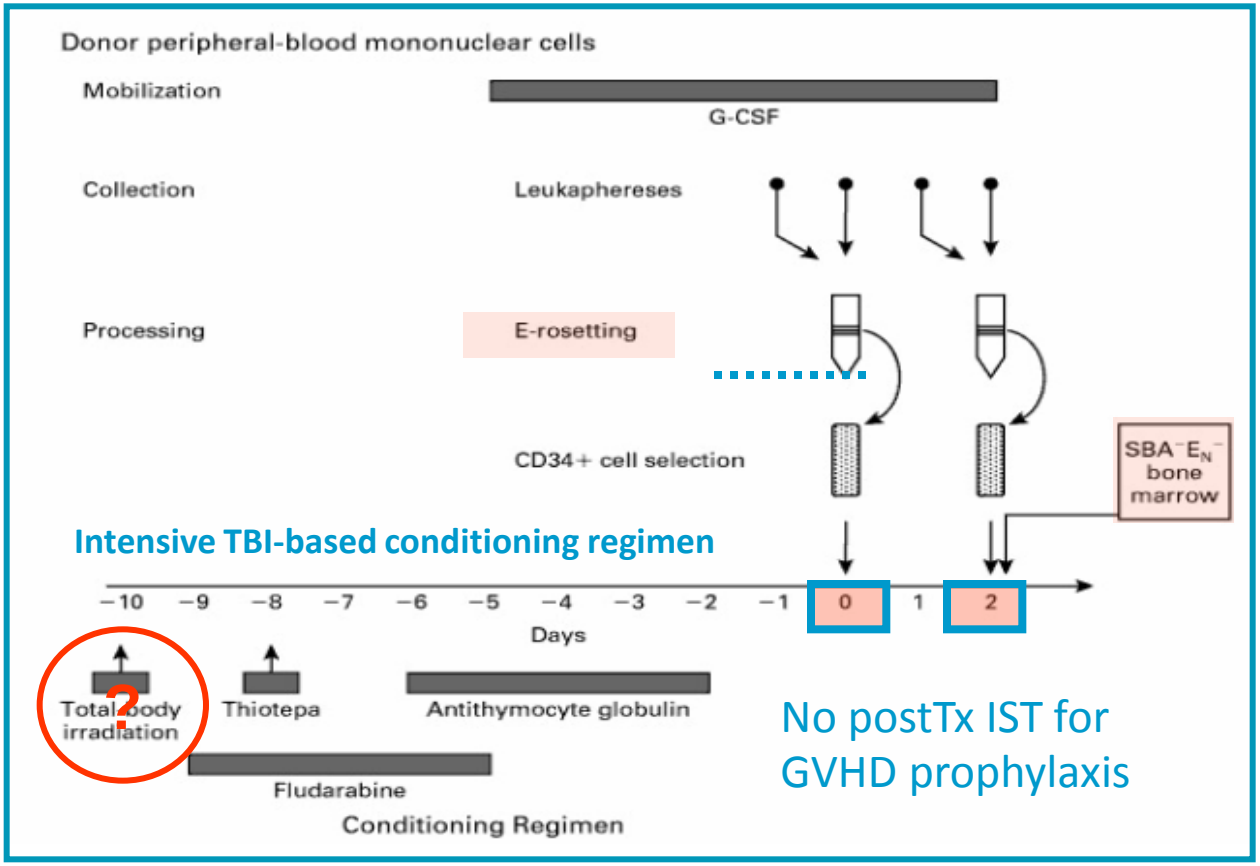
Treatment of High-Risk Acute Leukemia with T-Cell–Depleted Stem Cells from Related Donors with One Fully Mismatched HLA Haplotype

Franco Aversa, M.D., Antonio Tabilio, M.D., Andrea Velardi, M.D., Isabel Cunningham, M.D., Adelmo Terenzi, M.D., Franca Falzetti, M.D., Loredana Ruggeri, M.D., Giuliana Barbabietola, M.D., Cynthia Aristei, M.D., Paolo Latini, M.D., Yair Reisner, Ph.D., Massimo F. Martelli, M.D., Rita Felicini, M.D., Flavio Falcinelli, M.D., Alessandra Carotti, M.D., Katia Perruccio, M.D., Stelvio Ballanti, M.D., Antonella Santucci, M.D., and Cesare Gambelunghe, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

Perugia Grup: Aversa 1998

Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype.



43 patients with high risk leukemia received BM/ GCSF mobilised PBSC from family with one matched haplotype (3/6 matched)

Both ex vivo depleted of T cells by soybean agglutination and E-rosetting

Aversa F et al.: New England J. Medicine 1998;339:1186-1193.

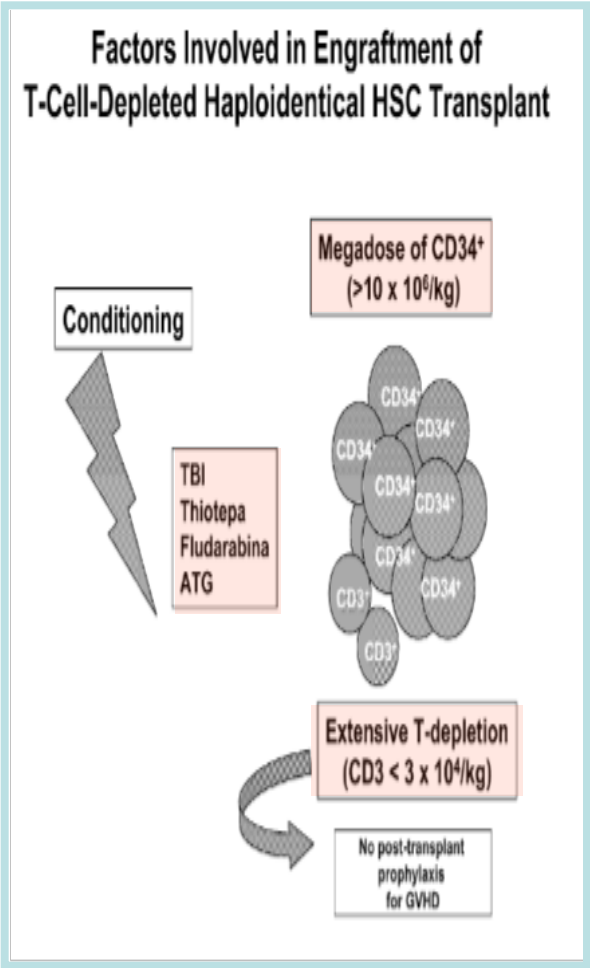
The NEW ENGLAND JOURNAL of MEDICINE

Perugia Grup: Aversa 1998

Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype.

'Mega-dose' approach to overcome MHC barrier (generating 'veto effect')

- Conditioning: TBI+ATG
- Grafts: 9±5x10^6 CD34cell/kğ megadose
- Extensively T cell-depleted : 3±2x10^4 CD3 cells /kğ
- No immunosupressive treatment after Transplantation for prophylaxis against GVHD
- 100% WBC/PLT Engraftment



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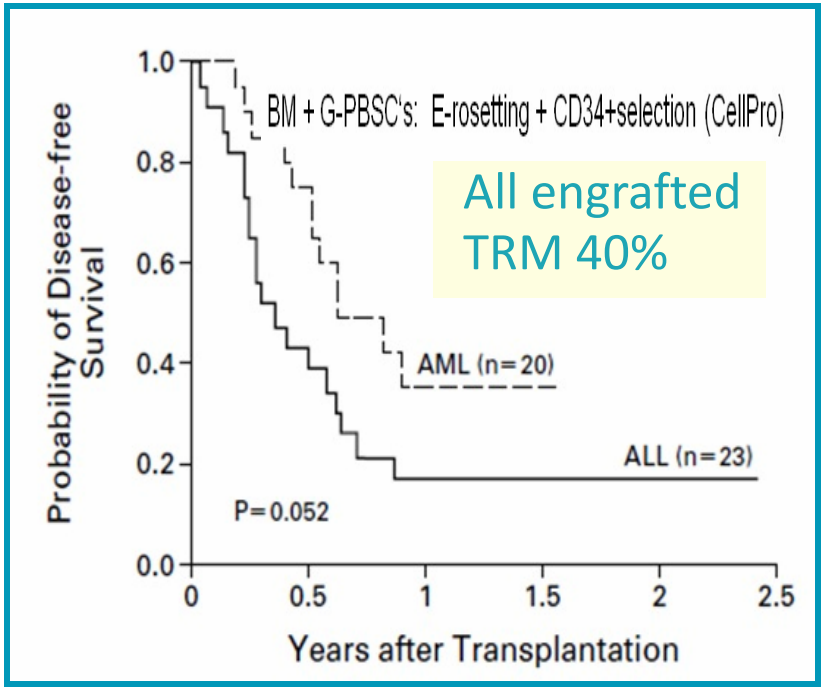


Cause of Death	No. of Patients (N=17)
Infection	11
Bacterial	5
Pseudomonas	3
Staphylococcus	2
Fungal	5
Aspergillus	3
Candida	2
Viral	1
Cytomegalovirus	1
B-cell lymphoproliferative disease	2
Other	4
Embolism	1
Renal failure	1
Acute respiratory distress syndrome	2

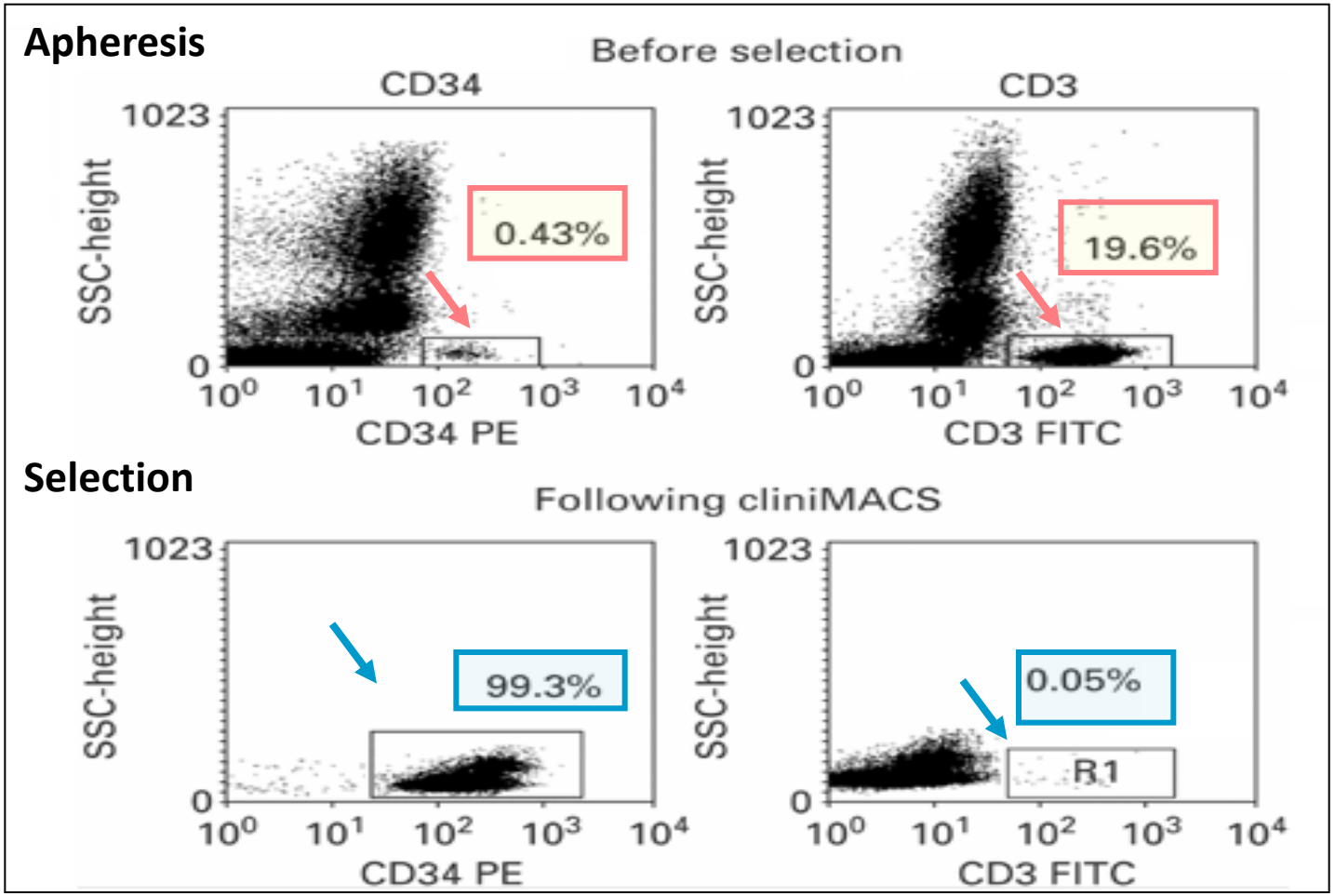
With the T cell depletion reasonable engraftment and acceptable GVHD: But still, high relapse rate and infection

Aversa F et al.: New England J. Medicine 1998;339:1186-1193.

Bone Marrow Transplantation

Tübingen Group: 2001

Megadose transplantation of purified peripheral blood CD34- Progenitor cells from HLA-mismatched parental donors in children



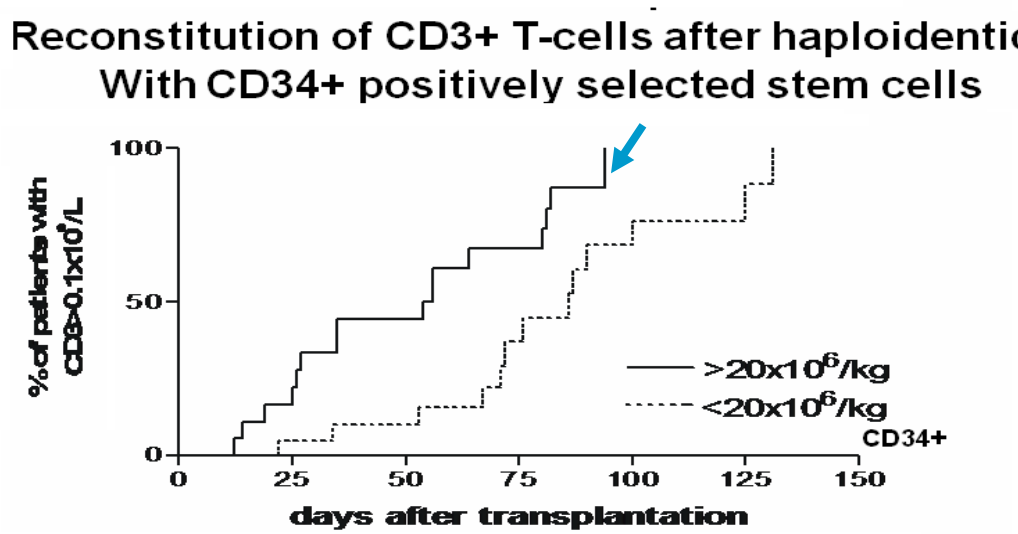
Handgretinger R. et al. ***Bone Marrow Transplant. 2001; 27: 777***

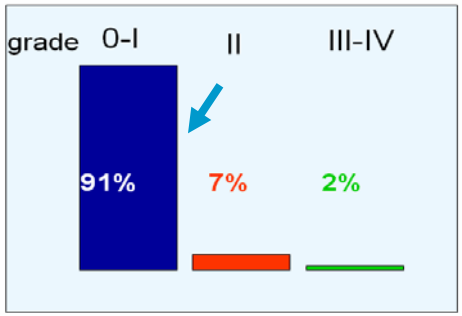
Bone Marrow Transplantation

Tübingen Group: 2001

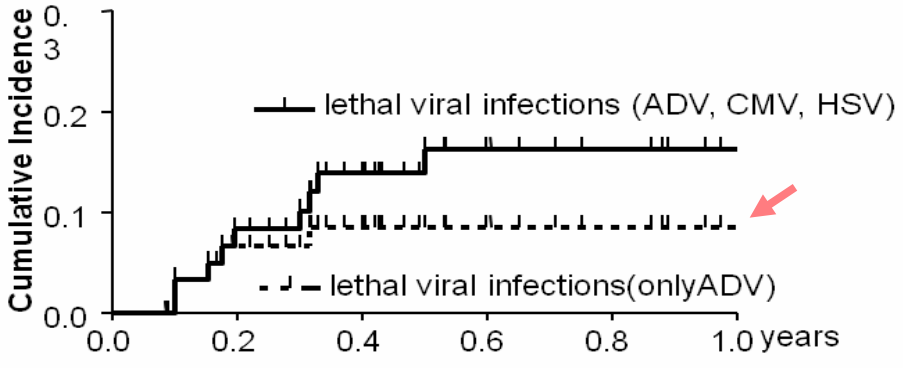
Megadose transplantation of purified peripheral blood CD34- Progenitor cells from HLA-mismatched parental donors in children

TRM: 26 %





T-cells: 10 000/kg (range 5000- 31000)



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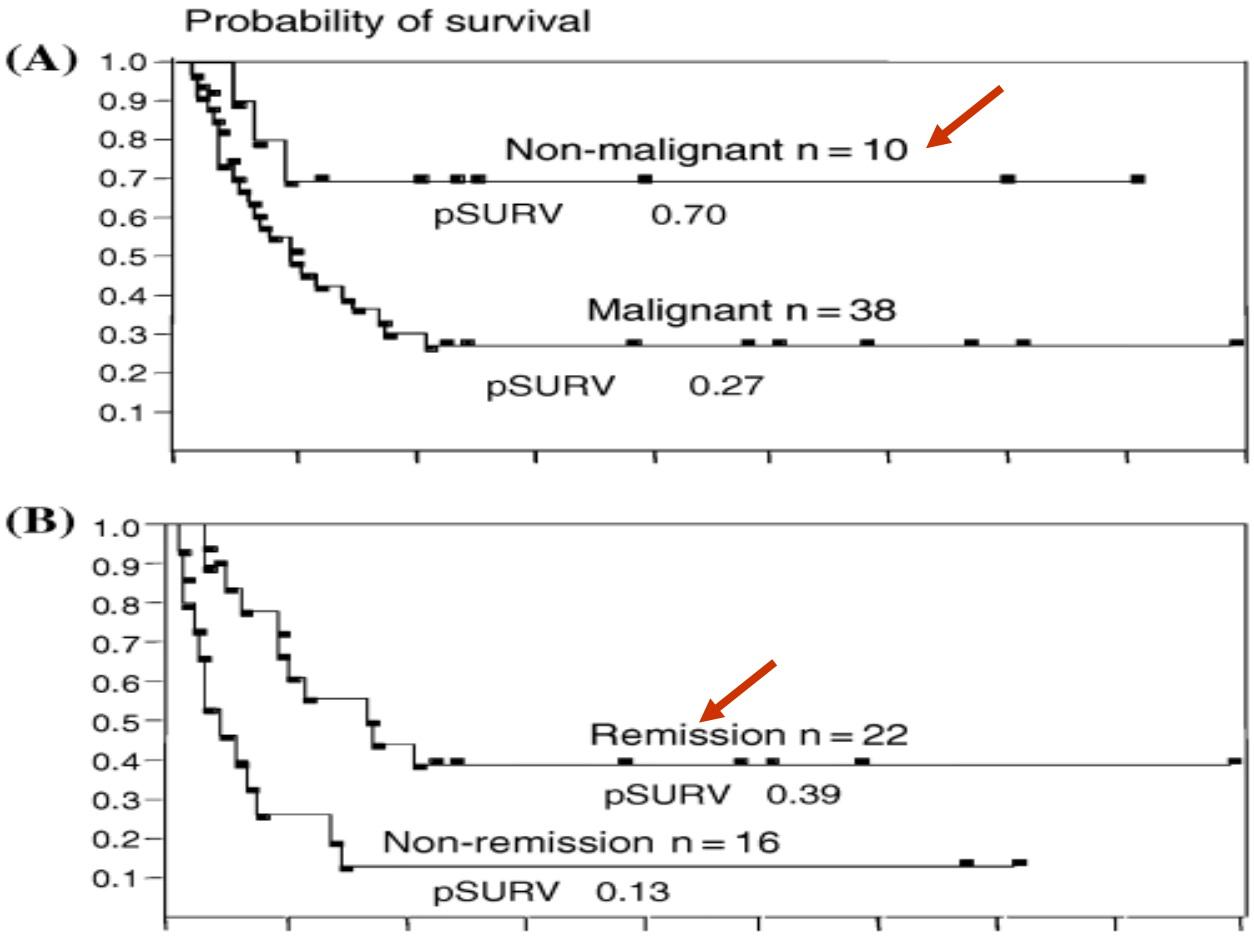

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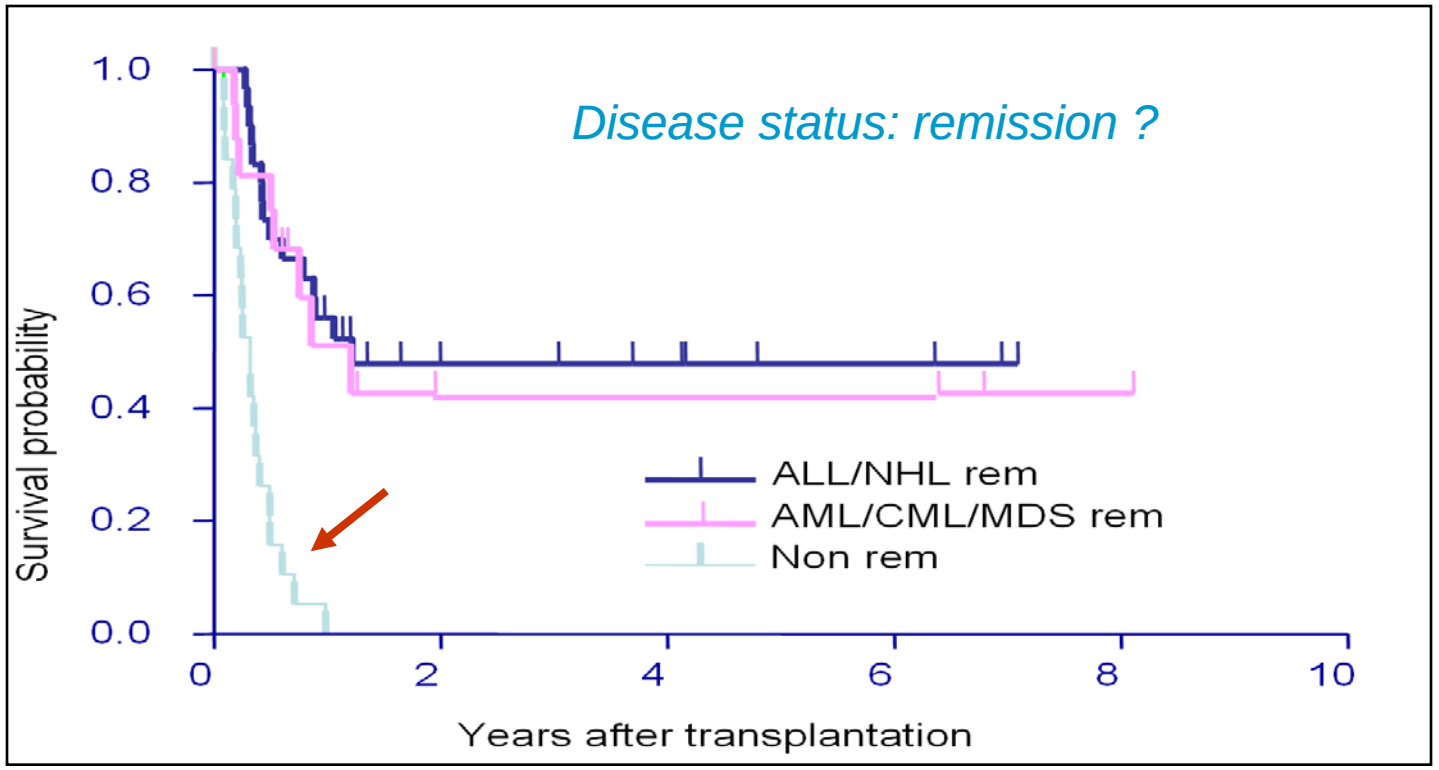


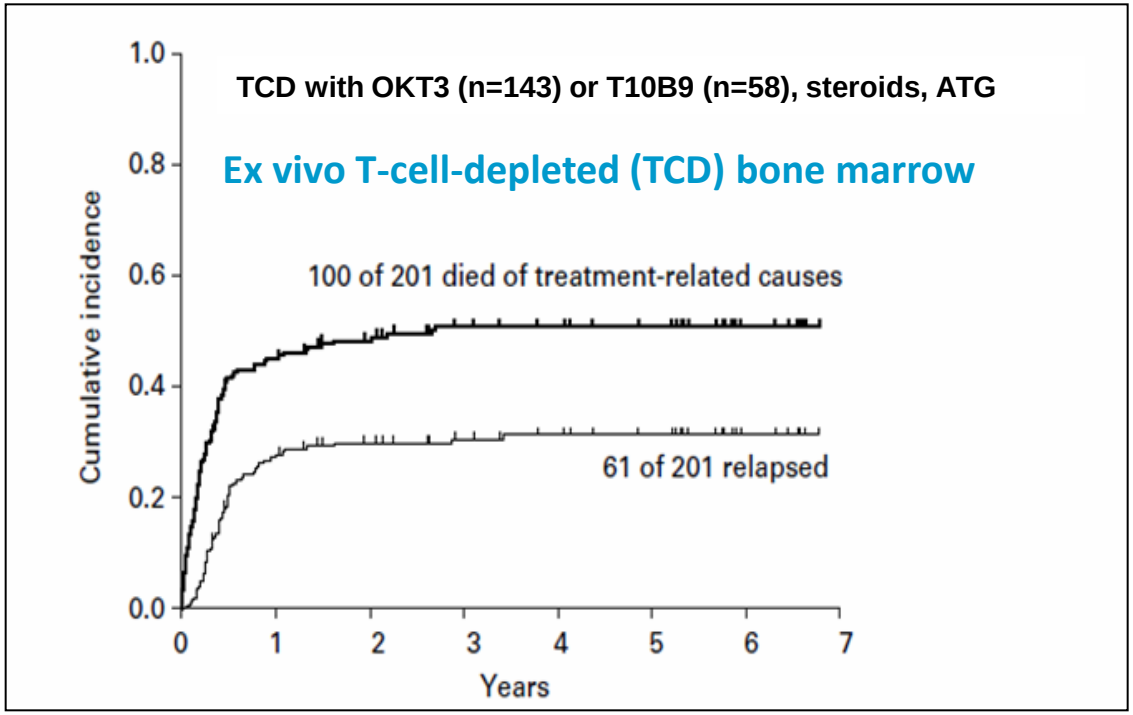
Remission most related parameter for EFS after haploidentical tx.

Handgretinger R. et al. **Bone Marrow Transplant. 2001; 27: 777**

Bone Marrow Transplantation

Mehta 2004:

Bone marrow transplantation from partially HLA-mismatched family Donors for acute leukemia: single center experience of 201 patients.



5 year OS @ PFS: 19% @ 18 %,

5 year relapse @ TRM: 31 % @ 51%,

Mehta et al. **Bone Marrow Transplantation 2004; 33: 389-396.**

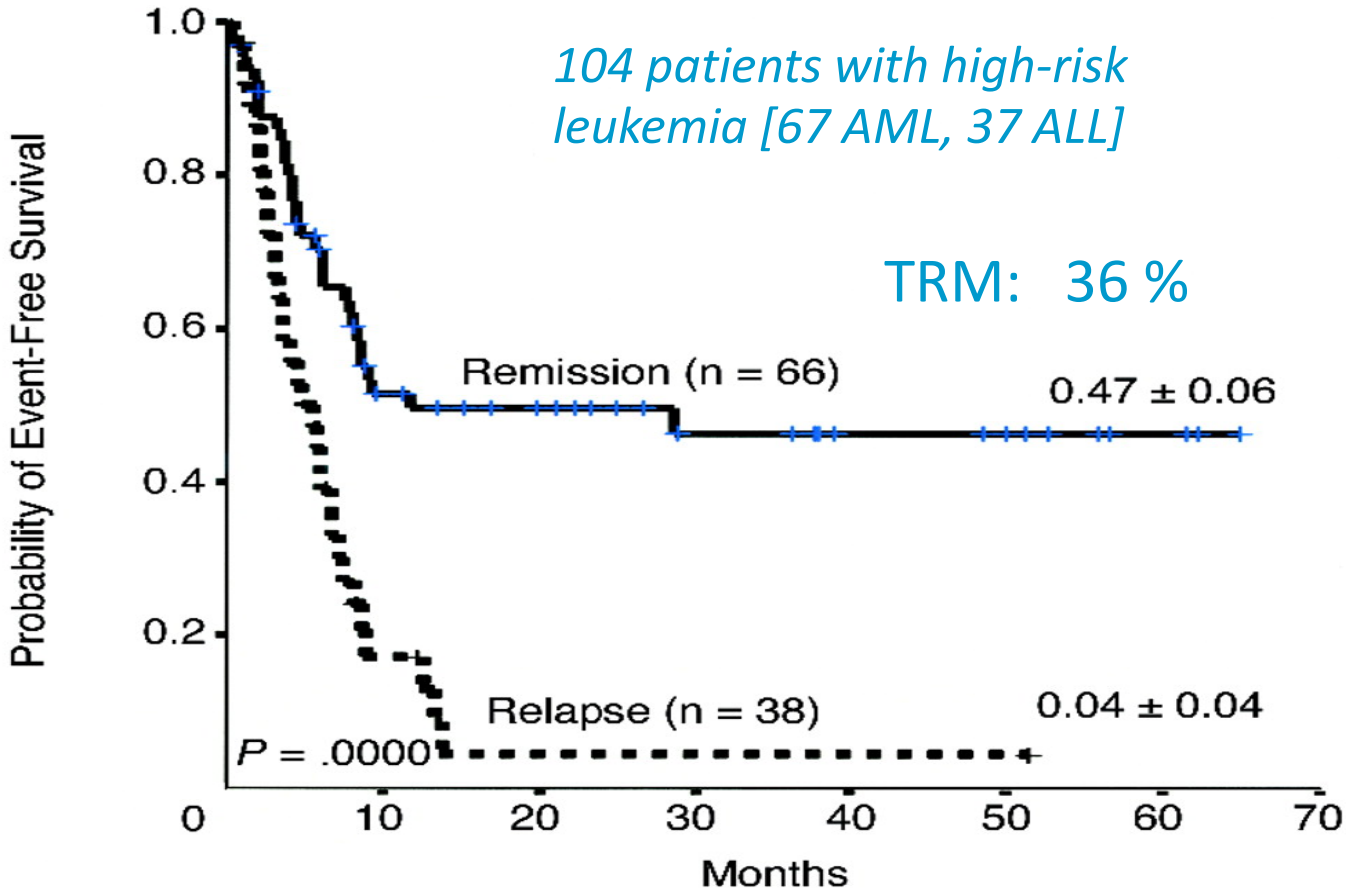
VOLUME 23 · NUMBER 15 · MAY 20 2005
JOURNAL OF CLINICAL ONCOLOGY

Perugia Group : CD34+ selection with Clinimacs

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

104 patients with high-risk leukemia [67 AML, 37 ALL]

TRM: 36 %



Aversa et al. J Clin Oncol 2005;23:3447

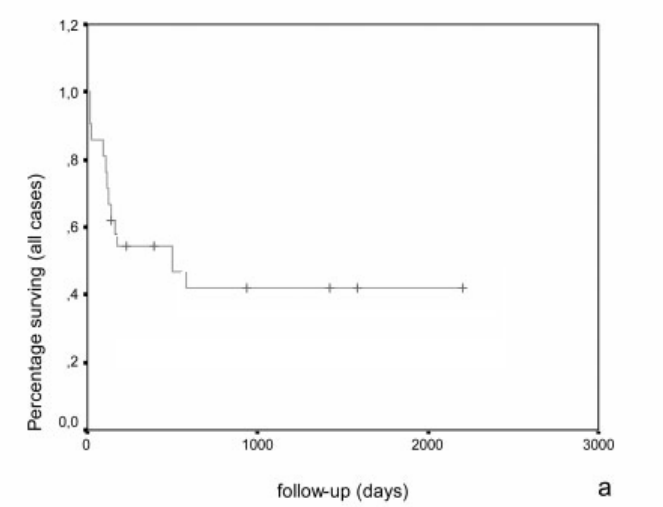
Turkish Experience :
Poor prognostic nonmalignant disorders

WILEY InterScience® DISCOVER SOMETHING GREAT

G-CSF-mobilized haploidentical peripheral blood stem cell transplantation in children with poor prognostic nonmalignant disorders

Fikret Arpacı,[1]* İlhan Tezcan,[2] Okan Kuzhan,[1] Nevin Yalman,[3] Duygu Uçkan,[4] Ahmet Emin Kürekçi,[5] Aydan İkincioğulları,[6] Ahmet Özet,[1] and Atilla Tanyeli[7]

Between 2000 and 2005, 25 children with poor prognostic nonmalignant disorders,



T-cell depletion (CliniMACS)

Severe combined immunodeficiency (n=16),

osteopetrosis (n = 2), MDS (n =1),

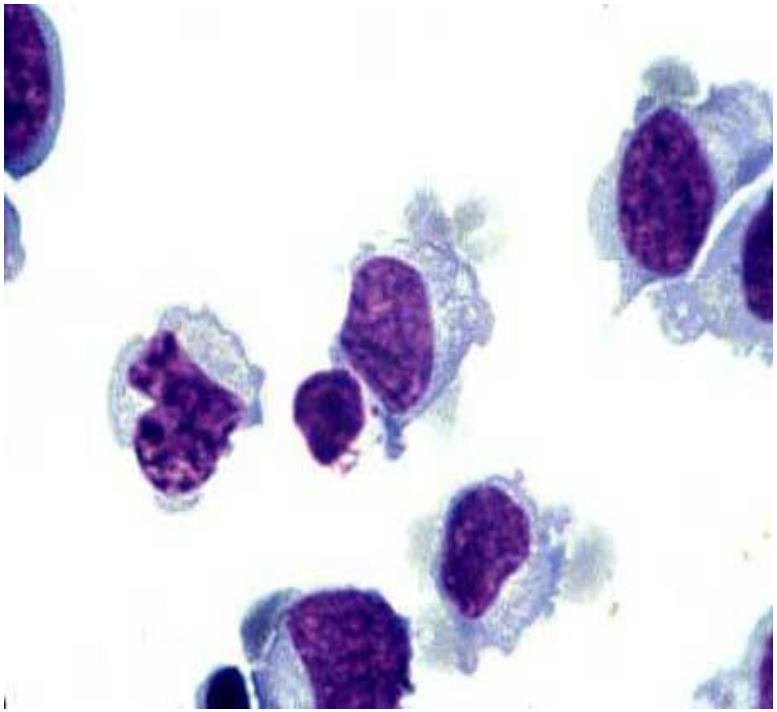
Amegakaryocytic thrombocytopenia (n= 1),

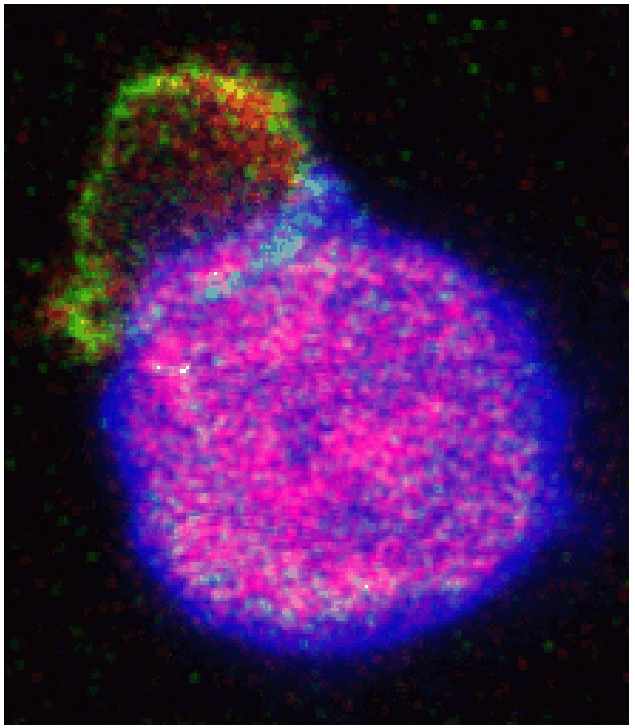
and aplastic anemia (n=5

Am. J. Hematol. 83:133–136, 2006.

blood

Role of Natural Killer cell alloreactivity in HLA-mismatched hematopoeitic stem cell transplantation.



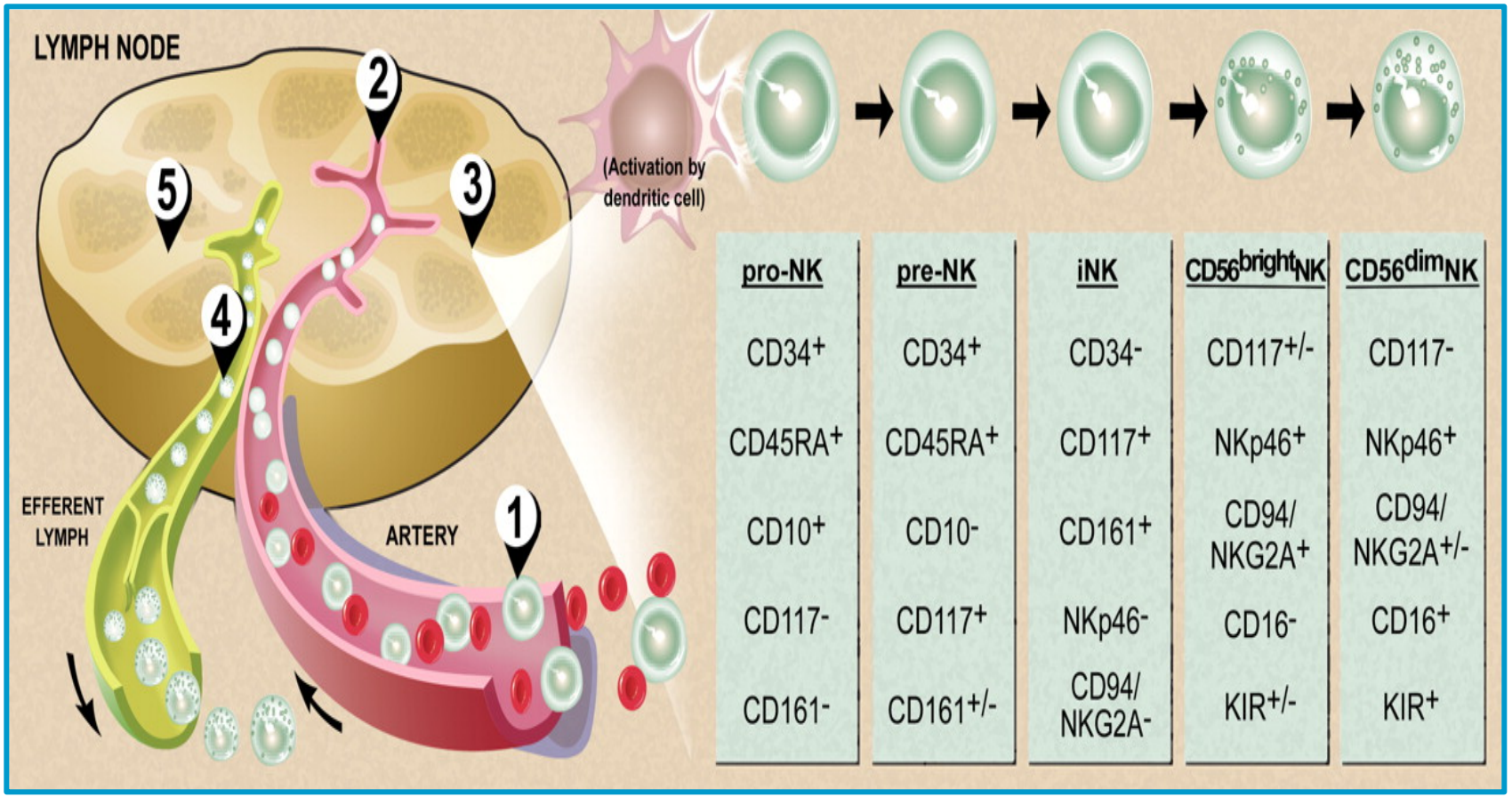


The new concept of NK alloreactivity & antitumoral effect

Ruggeri L.,…. Velardi A BLOOD 1999; 94: 333

blood

Role of Natural Killer cell alloreactivity in HLA-mismatched hematopoeitic stem cell transplantation.

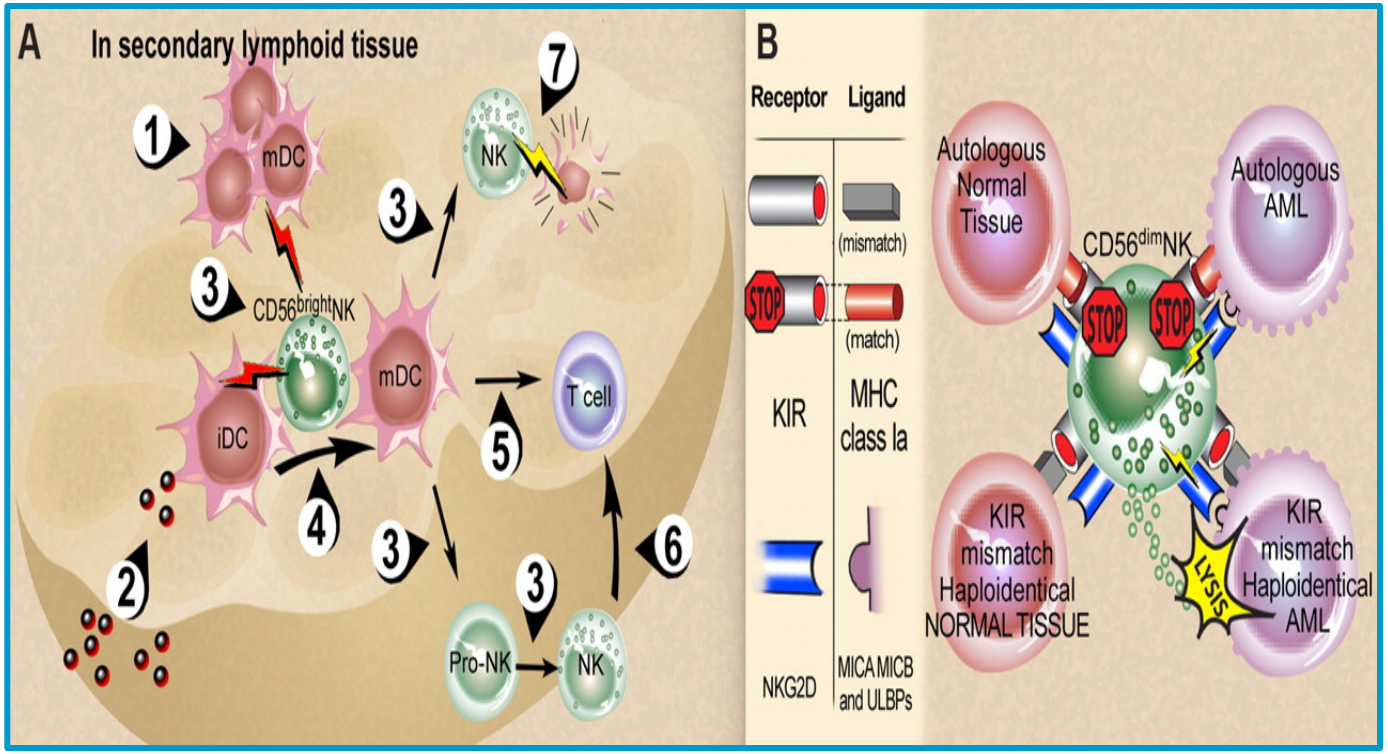


Maturing CD56dim NK cells return to the circulation via the efferent lymph, whereas some CD56bright NK cells remain within the secondary lymphoid tissue to interact with DCs.

Caligiuri M A Blood 2008;112:461-469

blood

Role of Natural Killer cell alloreactivity in HLA-mismatched hematopoeitic stem cell transplantation.

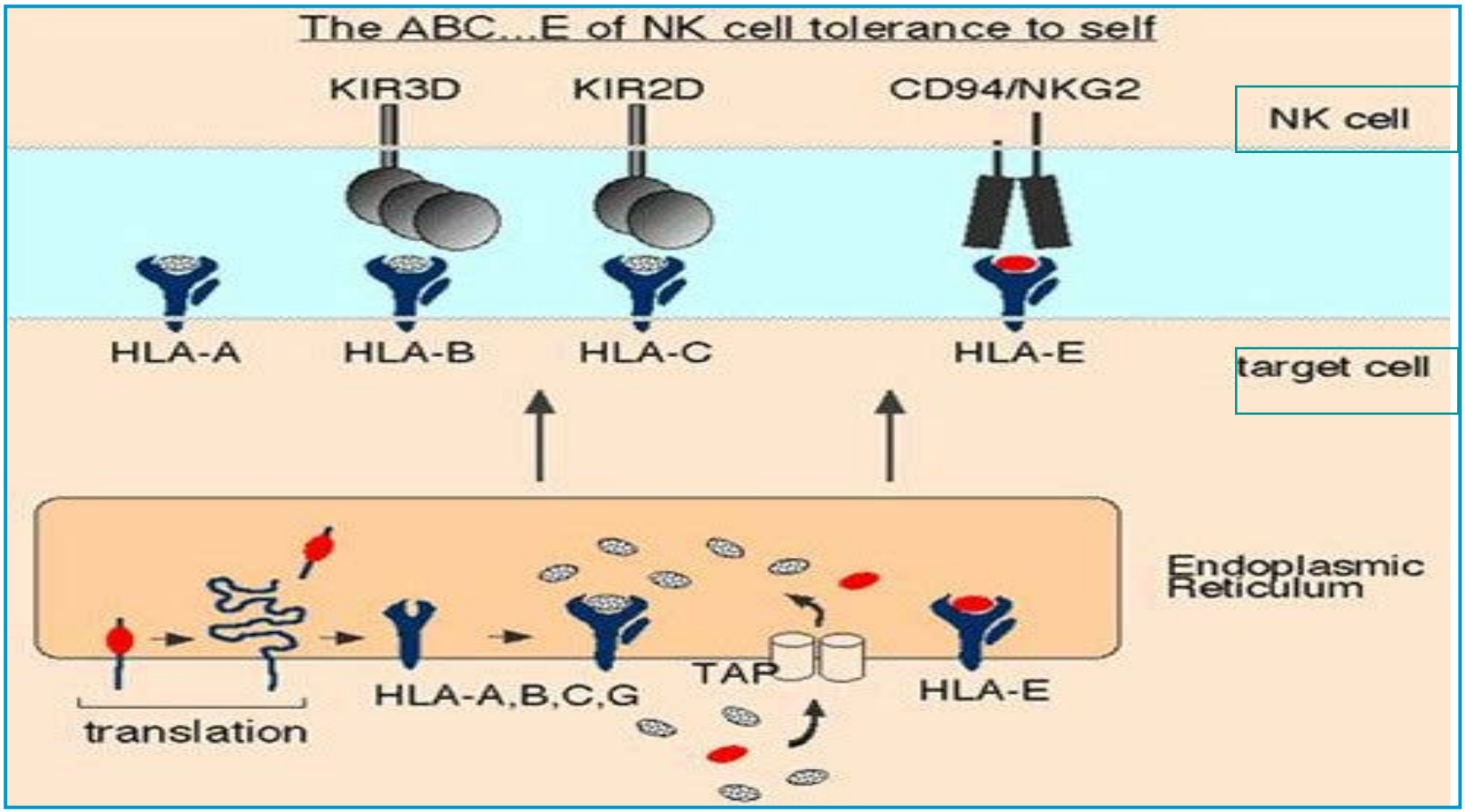


CD56bright and CD56dim NK-cell interactions.

Caligiuri M A Blood 2008;112:461-469

blood

Role of Natural Killer cell alloreactivity in HLA-mismatched hematopoeitic stem cell transplantation.



KIR mismatch in HLA direction can create an alloreactive constellation

Ruggeri L.,…. Velardi A BLOOD 1999; 94: 333

blood

Role of Natural Killer cell alloreactivity in HLA-mismatched hematopoeitic stem cell transplantation.

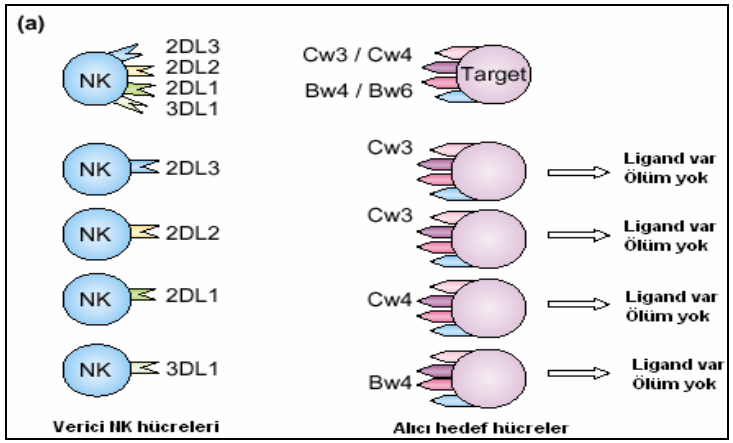
Selecting NK alloreactive donor

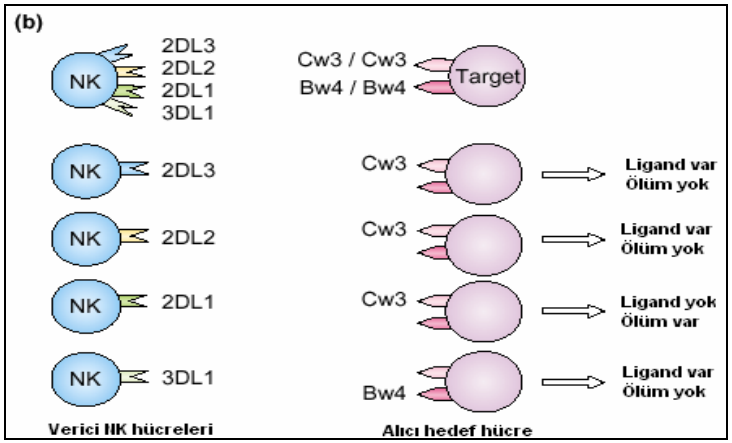
Table 2. Donor/recipient combinations predicting NK cell alloreactivity in the GvH direction.

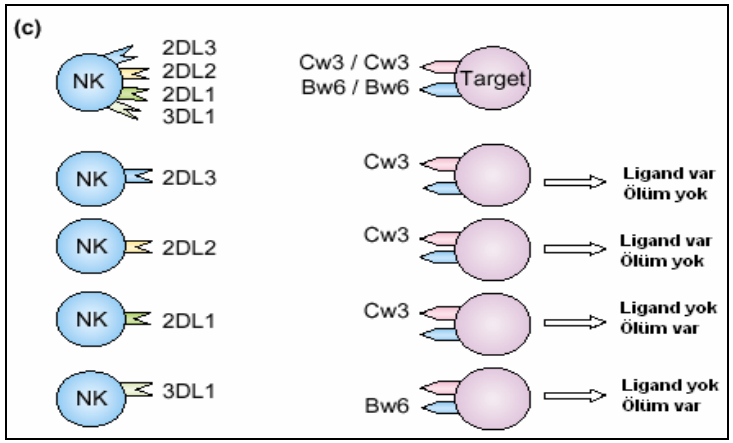
Recipient HLA type	HLA type of NK alloreactive donor*
Group 1 HLA-C, Group 2 HLA-C, HLA-Bw4	No NK alloreactive donor
Group 1 HLA-C, Group 2 HLA-C	HLA-Bw4
Group 1 HLA-C, HLA-Bw4	Group 2 HLA-C
Group 2 HLA-C, HLA-Bw4	Group 1 HLA-C
Group 1 HLA-C	Group 2 HLA-C and/or HLA-Bw4
Group 2 HLA-C	Group 1 HLA-C and/or HLA-Bw4

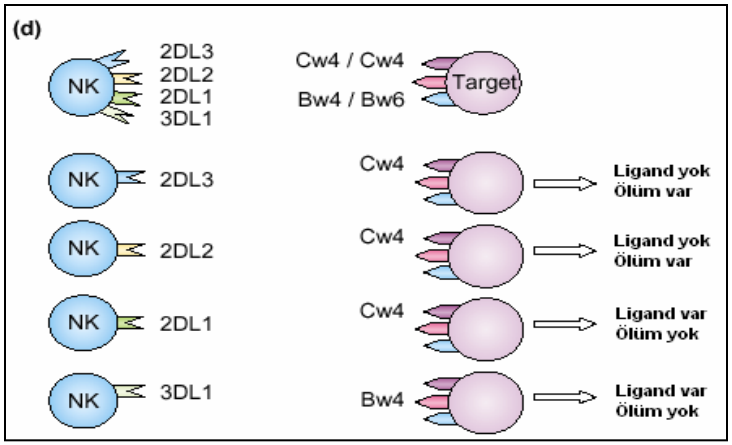
blood

Role of Natural Killer cell alloreactivity in HLA-mismatched hematopoeitic stem cell transplantation.



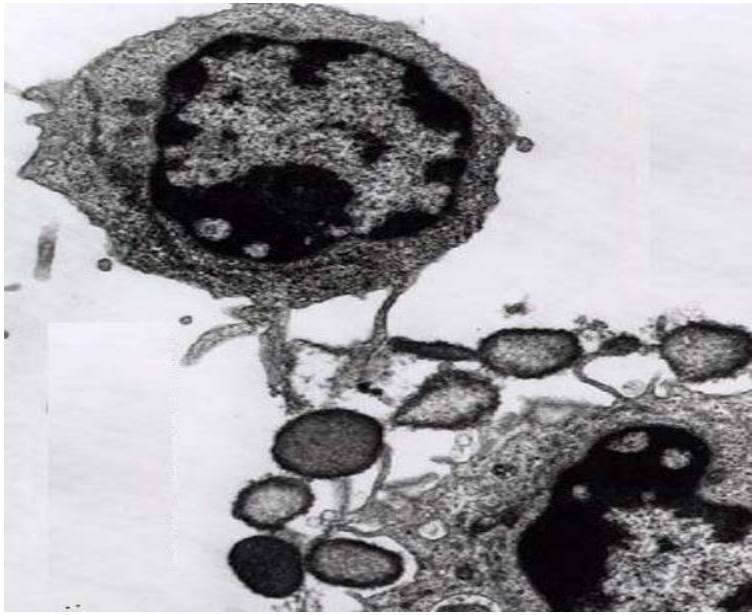


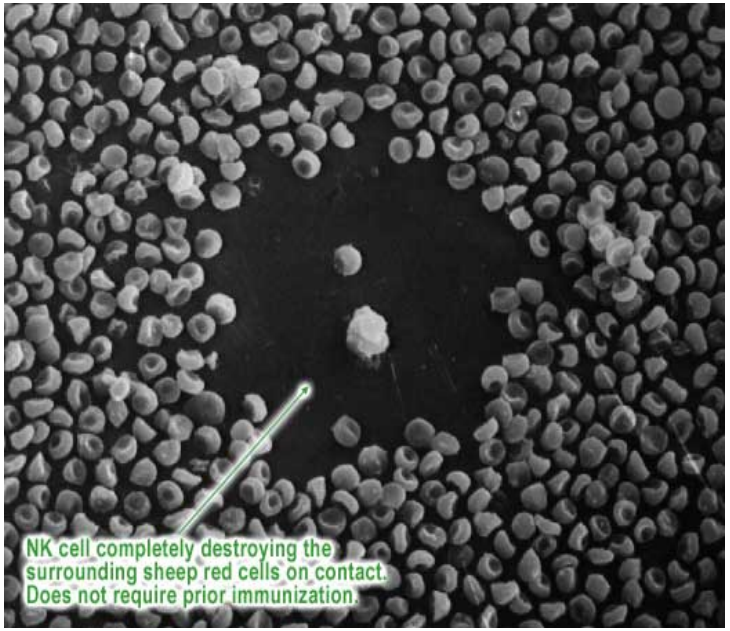




blood

Role of Natural Killer cell alloreactivity in HLA-mismatched hematopoeitic stem cell transplantation.





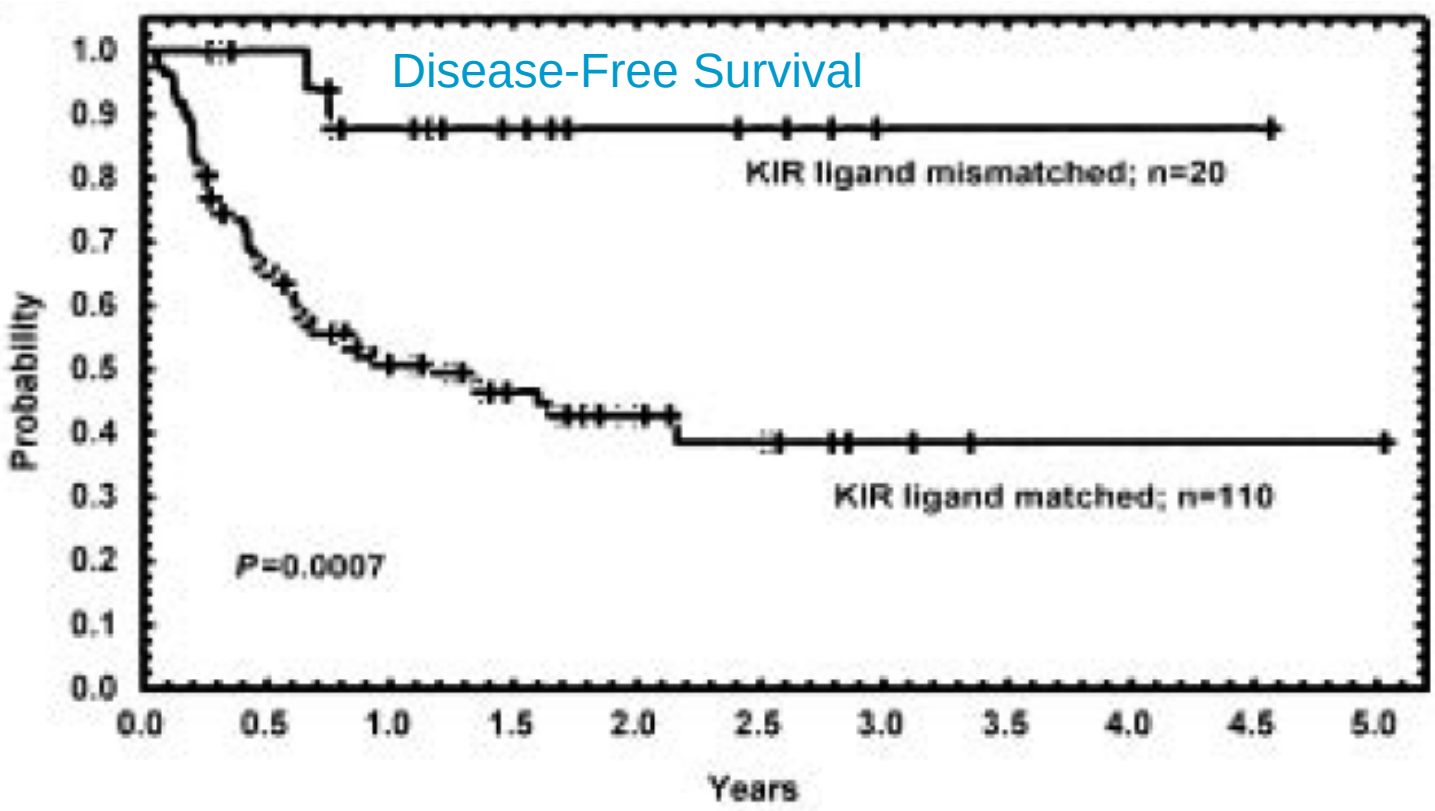
- Kendinden (otolog) olmayan epitoplarla karşılaşan NK hücreler KIR repertuarı aracılığıyla tanımladığı hücreleri Graenzim-perforin aracılığı ile öldürür veya apopitozise sevkeder.
- Bu yolla tümör hücreleri virüs ve bakteriyle karşılaşmış hücre grupları diğer koruyucu sistemlerin devreye girmesinden çok daha önce etkili bir savunma platformu oluşturur.

blood

BLOOD, 1 AUGUST 2003 •
VOLUME 102, NUMBER 3

Survival advantage with KIR ligand incompatibility in hematopoietic stem cell transplantation from unrelated donors

Sebastian Giebel, Franco Locatelli, Teresa Lamparelli, Andrea Velardi, Stella Davies, Guido Frumento, Rita Maccario, Federico Bonetti, Jerzy Wojnar, Miryam Martinetti, Francesco Frassoni, Giovanna Giorgiani, Andrea Bacigalupo, and Jerzy Holowiecki



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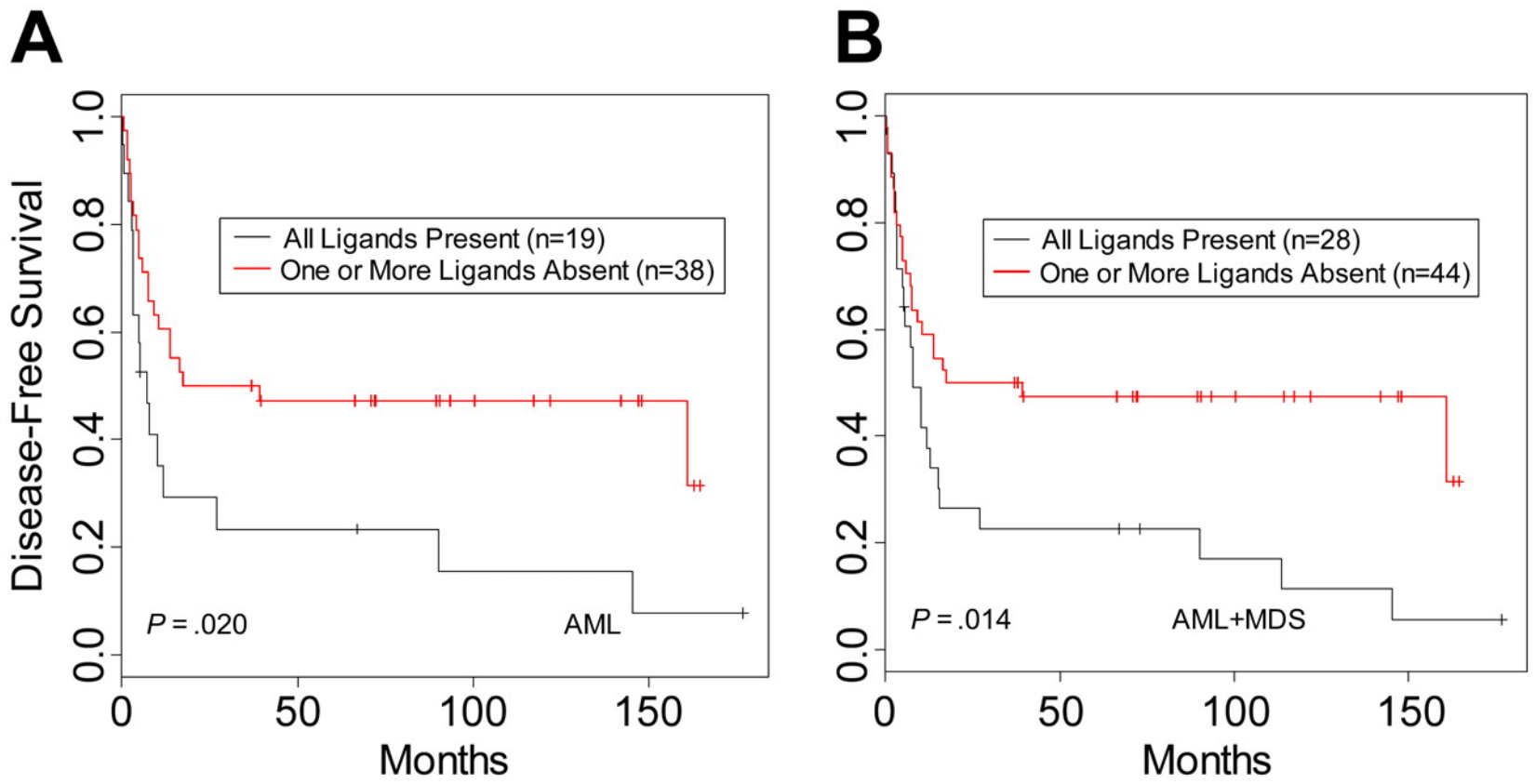
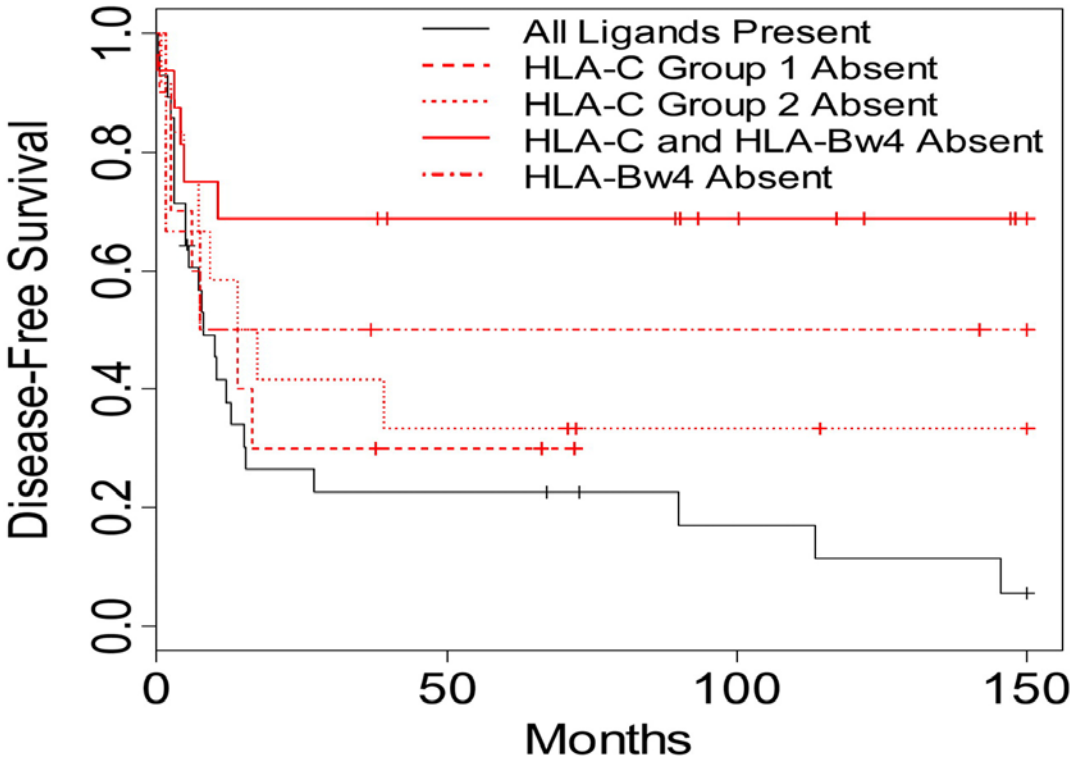
Disease-free survival of AML and MDS patients according to specific KIR ligand absence



Hsu K C et al. Blood 2005;105:4878-4884

blood

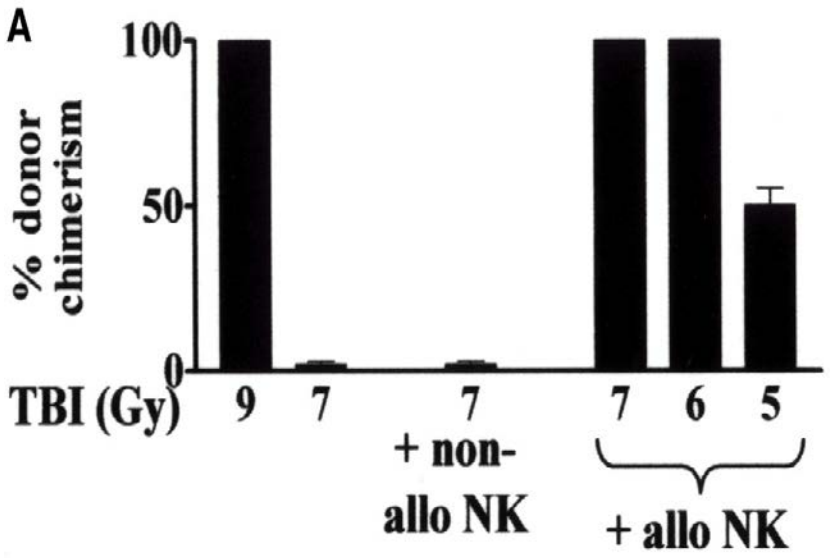
Disease-free survival of AML and MDS patients according to specific KIR ligand absence



Hsu K C et al. Blood 2005;105:4878-4884

Effectiveness of Donor Natural Killer Cell Alloreactivity in Mismatched Hematopoietic Transplants
Loredana Ruggeri *et al.* *Science* **295**, 2097 (2002);

Alloreactive NK cells facilitate engraftment in mice

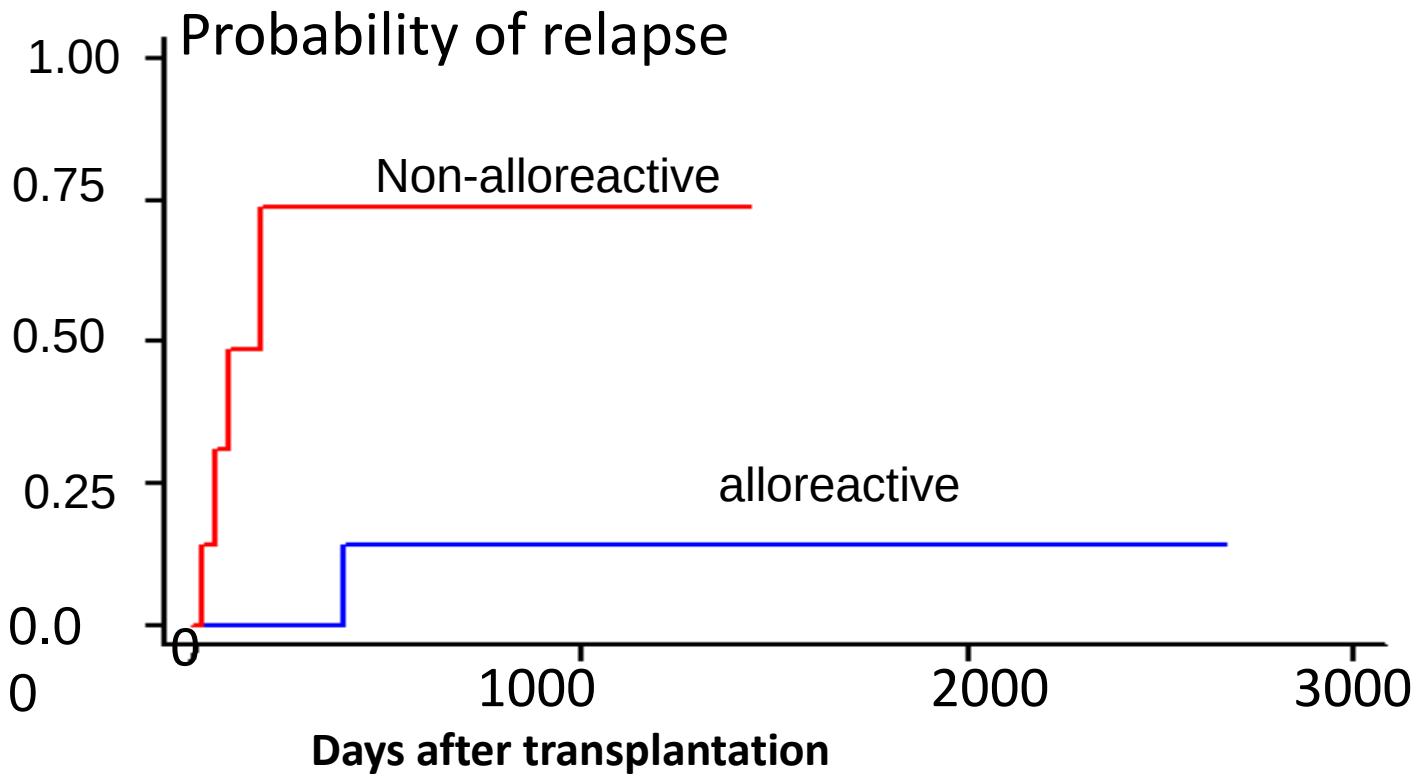


In mice, the pretransplant infusion of alloreactive NK cells obviated the need for high-intensity conditioning and reduced GVHD.

In human, donor-versus-recipient natural killer (NK)–cell alloreactivity could eliminate leukemia relapse and graft rejection and protect patients against GVHD. Journal of Immunology 172, 644-650, 2004

Risk of relapse in pediatric patients with **ALL** (n=19) after haploidentical transplantation of CD34+ stem cells from a NK alloreactive or NK nonalloreactive donor

Alloreactive NK cells support antitumor activity



Journal of Immunology 172, 644-650, 2004

Ruggeri 2007

blood

Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value

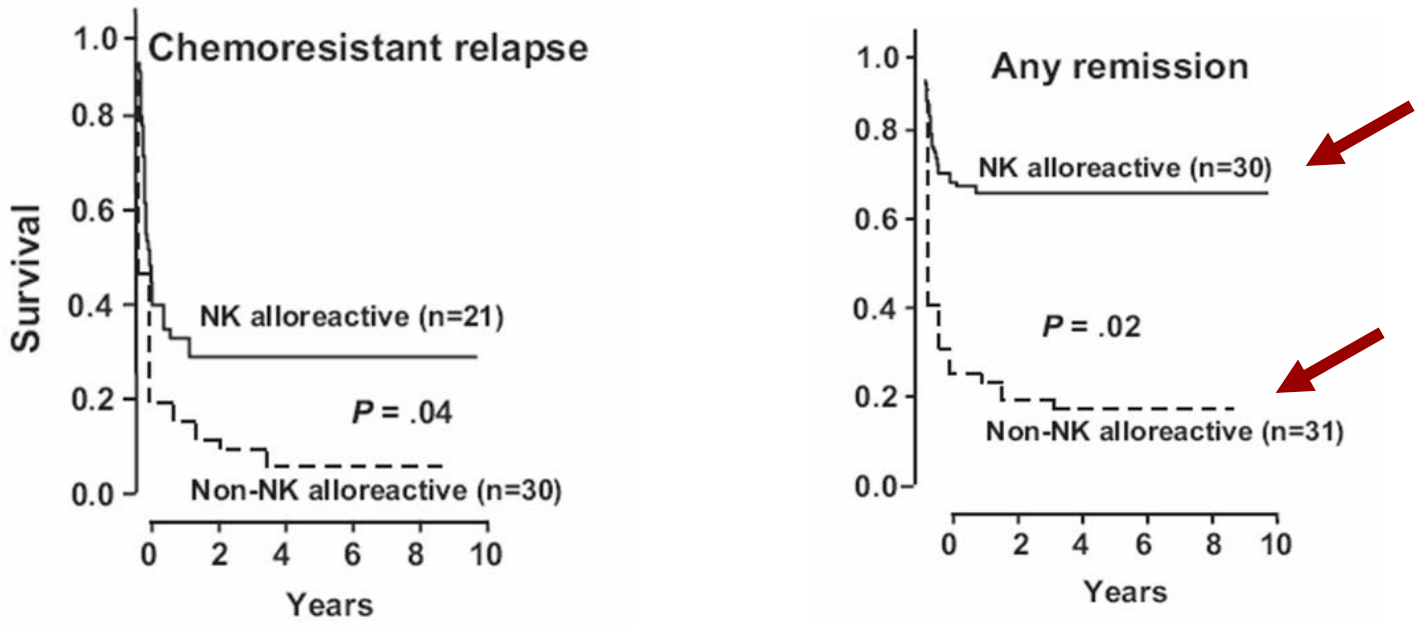


Figure 4. Transplantation from haploidentical NK alloreactive donors improves EFS. (A) EFS in patients transplanted in relapse from NK-alloreactive versus non-NK alloreactive donors. (B) EFS in patients transplanted in CR from NK alloreactive versus non-NK alloreactive donors.

Ruggeri 2007

Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value

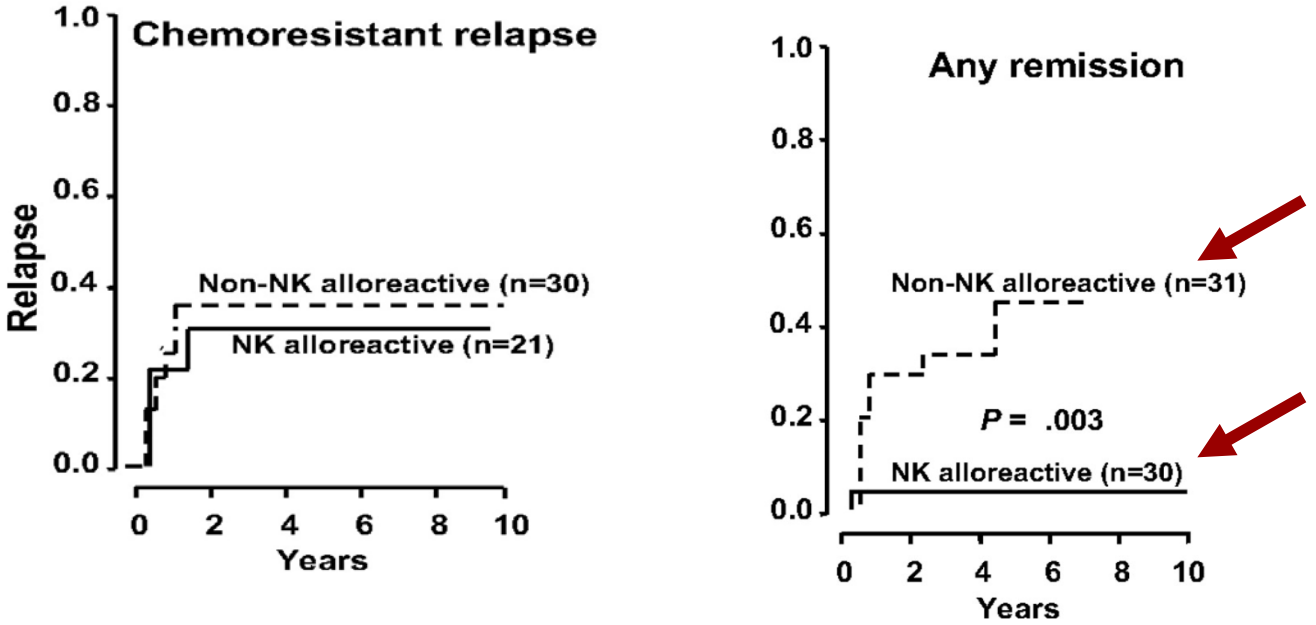


Figure 3. Transplantation from haploidentical NK alloreactive donors controls AML relapse in patients transplanted in any remission. (A) Relapse in patients transplanted in chemoresistant relapse from NK alloreactive versus non-NK alloreactive donors. (B) Relapse in patients transplanted in any remission from NK alloreactive versus non-NK alloreactive donors.

Ruggeri L et al. Blood 2007;110:433-440

Ruggeri 2007

Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value

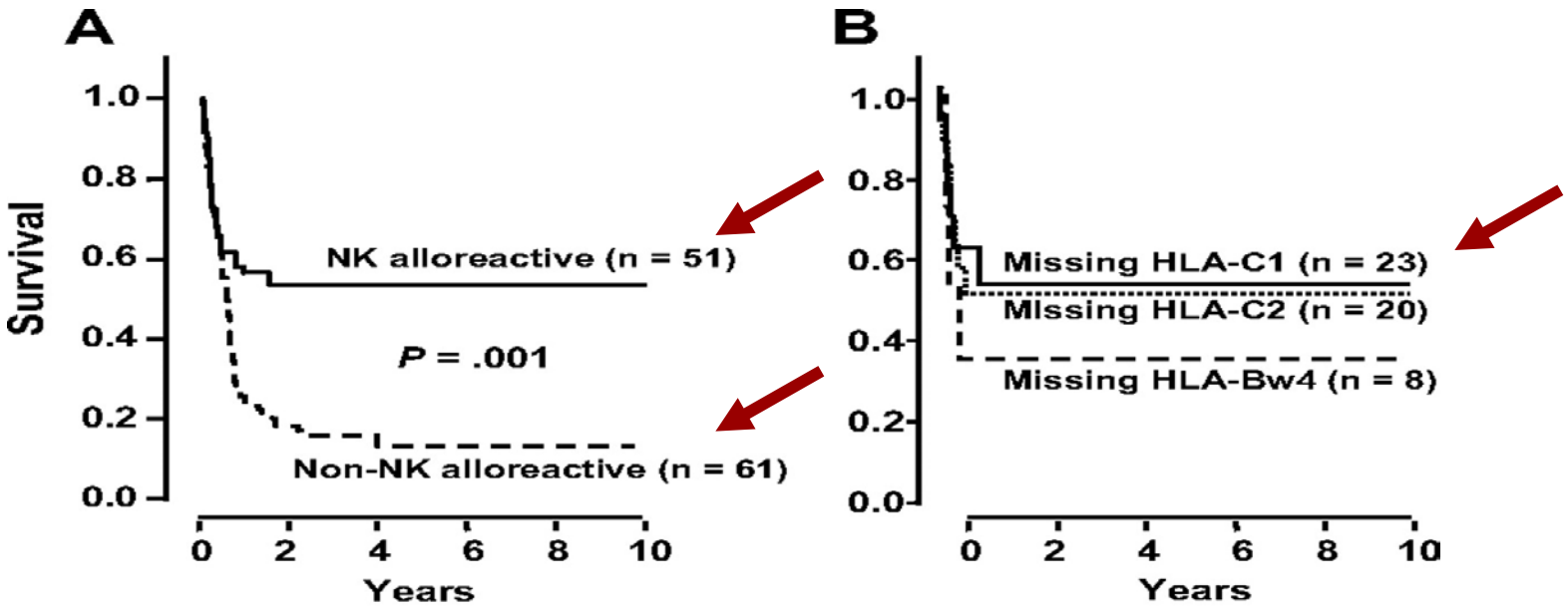


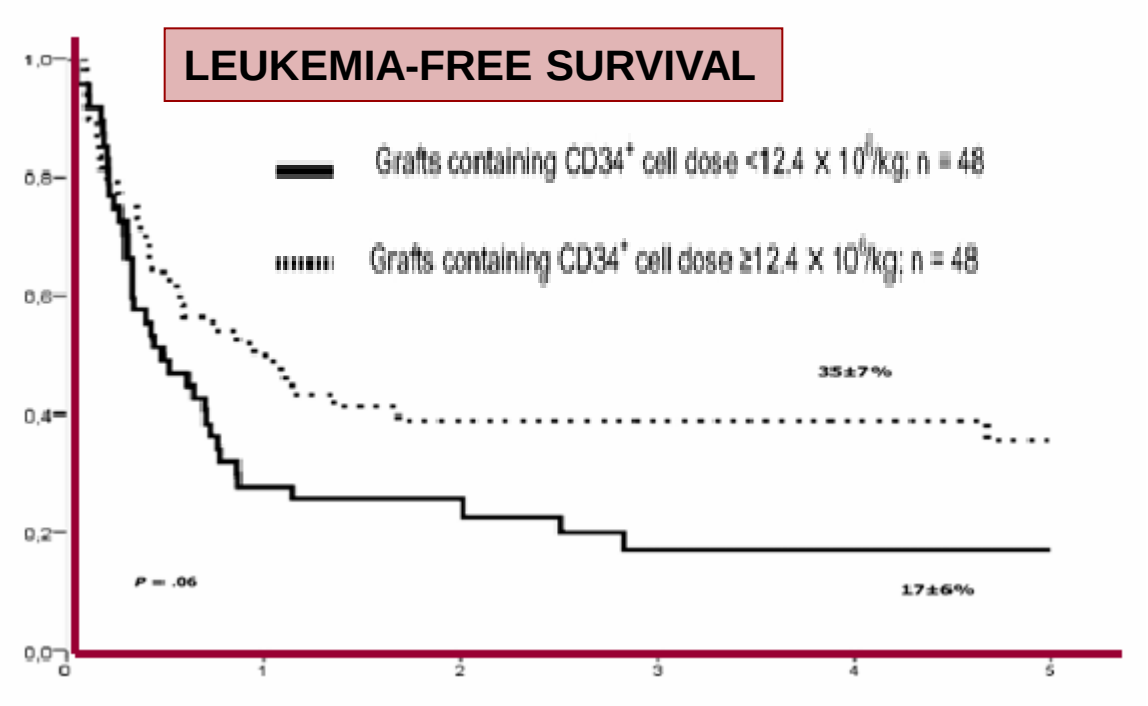
Figure 5. EFS according to NK cell alloreactivity and to specific KIR ligand mismatches. (A) EFS after transplantation from NK-alloreactive donors versus non-NK alloreactive donors in the entire series of 112 haploidentical transplant recipients. (B) EFS after transplantation from NK-alloreactive donors according to the specific donor KIR ligand that was missing in the recipient. Solid line indicates HLA-C 1; dotted line, HLA-C 2; broken line, HLA-Bw4.

Ruggeri L et al. Blood 2007;110:433-440

blood

European Blood and Marrow Transplant group

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

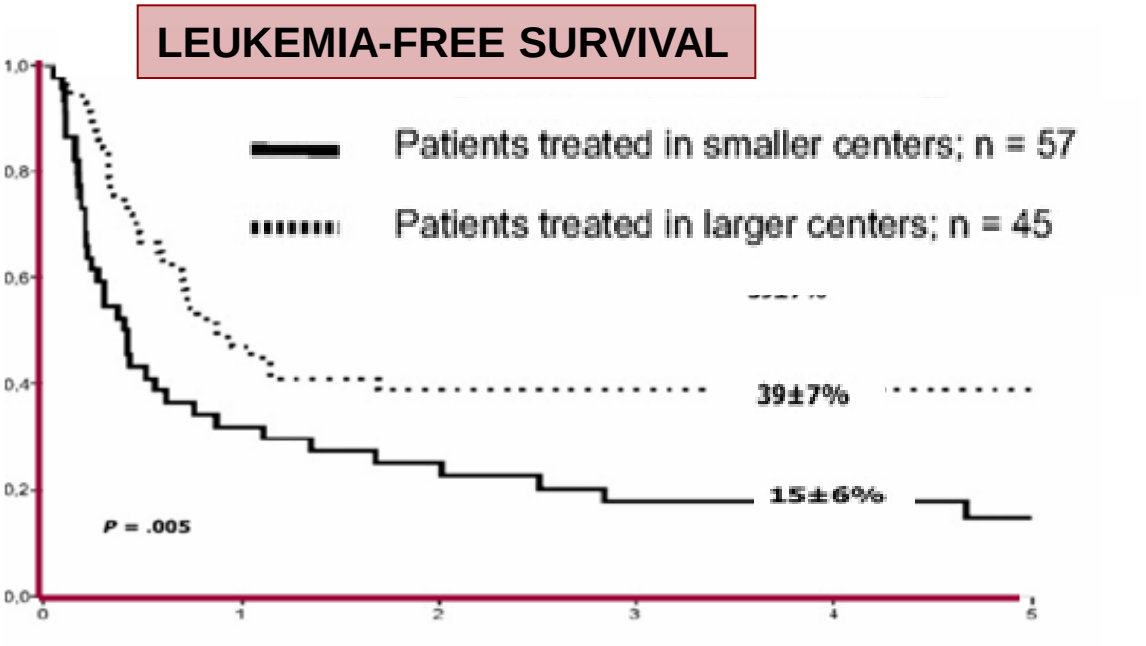


Leukemia-free survival of patients with ALL in remission according to CD34+ cell dose in the graft.

blood

European Blood and Marrow Transplant group

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

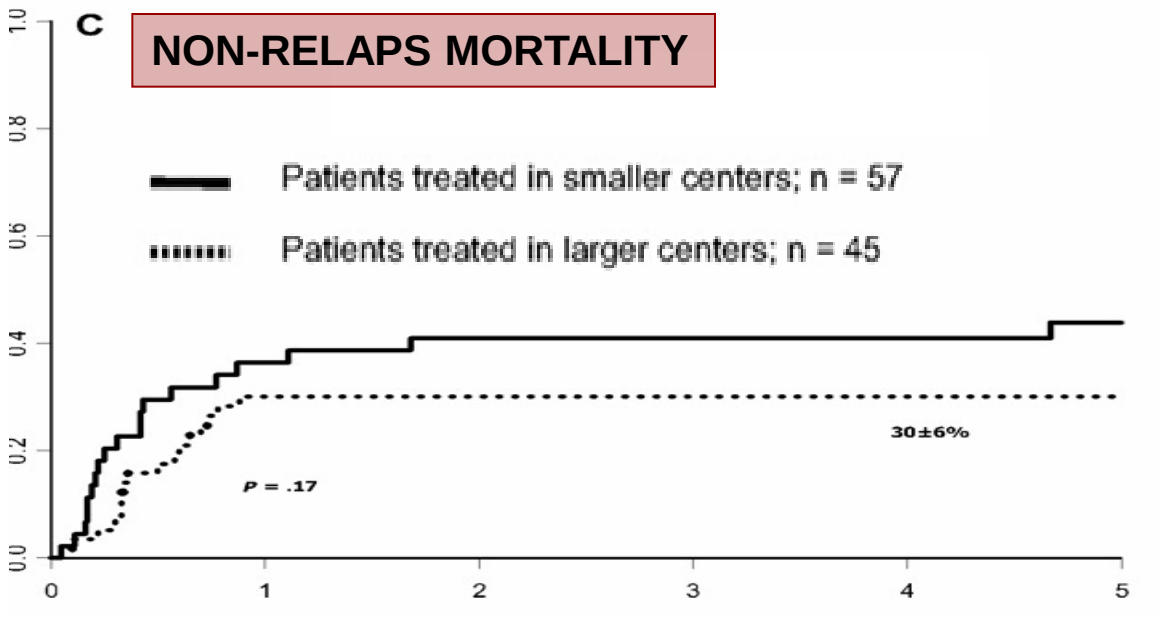


Leukemia-free survival after haploHSCT in children with ALL according to number of alloHSCTs performed in participating transplant centers

blood

European Blood and Marrow Transplant group

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



Cumulative incidence of nonrelapse mortality in patients with ALL in remission only, according to number of haploHSCTs

Limitations of the approach using "megadose" of extensively T cell-depleted GCSF mobilized PBSC cells and Myeloablative conditioning

- Many patients are too old to receive ablative conditioning.
- Concern of slow engraftment or graft failure in patients receiving a lower cell dose (delayed engraftment at CD34 doses less than 8 x 10^6/kg)
- Considerable demand on both the donors and the pheresis service for the following reasons: 1) **Long hours and multiple days of pheresis, can be exhausting with a slight increase in pheresis-related adverse effects to donors; 2)Time-consuming and labor-intensive for the pheresis and stem cell processing laboratory staff**
- Regimen related toxicity and high TRM between 25-40%.

Nonmyeloablative approach ?????

Lang P, et al. Br J Haematol. 2004;124:72-79

Koh LP, Rizzieri DA, Chao NJ. Biol Blood Marrow Transplant 2007; 13:1249-67

VOLUME 25 · NUMBER 6 · FEBRUARY 20 2007
JOURNAL OF CLINICAL ONCOLOGY

Partially Matched, Nonmyeloablative Allogeneic Transplantation: Clinical Outcomes and Immune Reconstitution

Protocol & Patient and Disease Characteristics

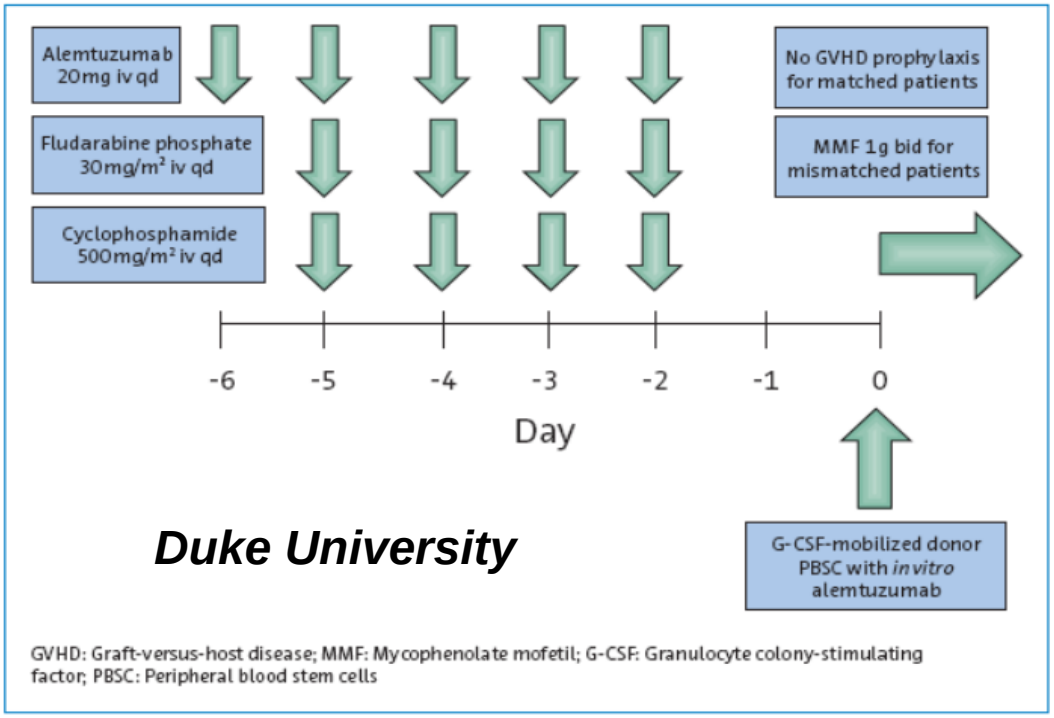


Figure 1 Treatment schema

No. of patients 49
Age 48 (range 17-65)

Diagnosis no. (%)
Lymphoma/Myeloma 15
CML 2
Leukemia/ MDS 29
MPD 3

Pre-transplant Rx no. (%)
Prior autoSCT 12 (25)
Previously untreated 2 (4)
No of prior regimen
Median 3
Range 0-8

VOLUME 25 · NUMBER 6 · FEBRUARY 20 2007
JOURNAL OF CLINICAL ONCOLOGY

Partially Matched, Nonmyeloablative Allogeneic Transplantation: Clinical Outcomes and Immune Reconstitution

- *Successful engraftment in 94% of patients*
- *Low treatment related mortality rates of 10.2% in the first 100 days.*
- *Severe GVHD (≥grade 3) of 8%.*

- *>50% not in first CR at transplantation*
- *High CR rate of 75% was achieved*

Engraftment and Response of All Patients After Partially HLA-Matched Nonmyeloablative Allogeneic Transplantation (N = 49)

Engraftment and Response	No. of Patients	%
Median donor engraftment at time after transplantation, %		
0.5 months	72	
1.5 months	87	
3 months	> 98	
6 months	> 98	
12 months	> 98	
Graft failure		
Primary	3	6
Aplasia	1	
MDS	1	
Chronic myeloid leukemia blast crisis	1	
Secondary	4	8
Cytomegalovirus/ganciclovir	3	
Respiratory syncytial virus/ribavirin	1	
Disease status at transplantation		
CR1 (MDS or high-risk AML) or untreated	7	14
First PR or CR2	12	24
PD or refractory disease	30	61
Response to transplantation		
CR	37	75
PR	5	10
SD or PD	7	14

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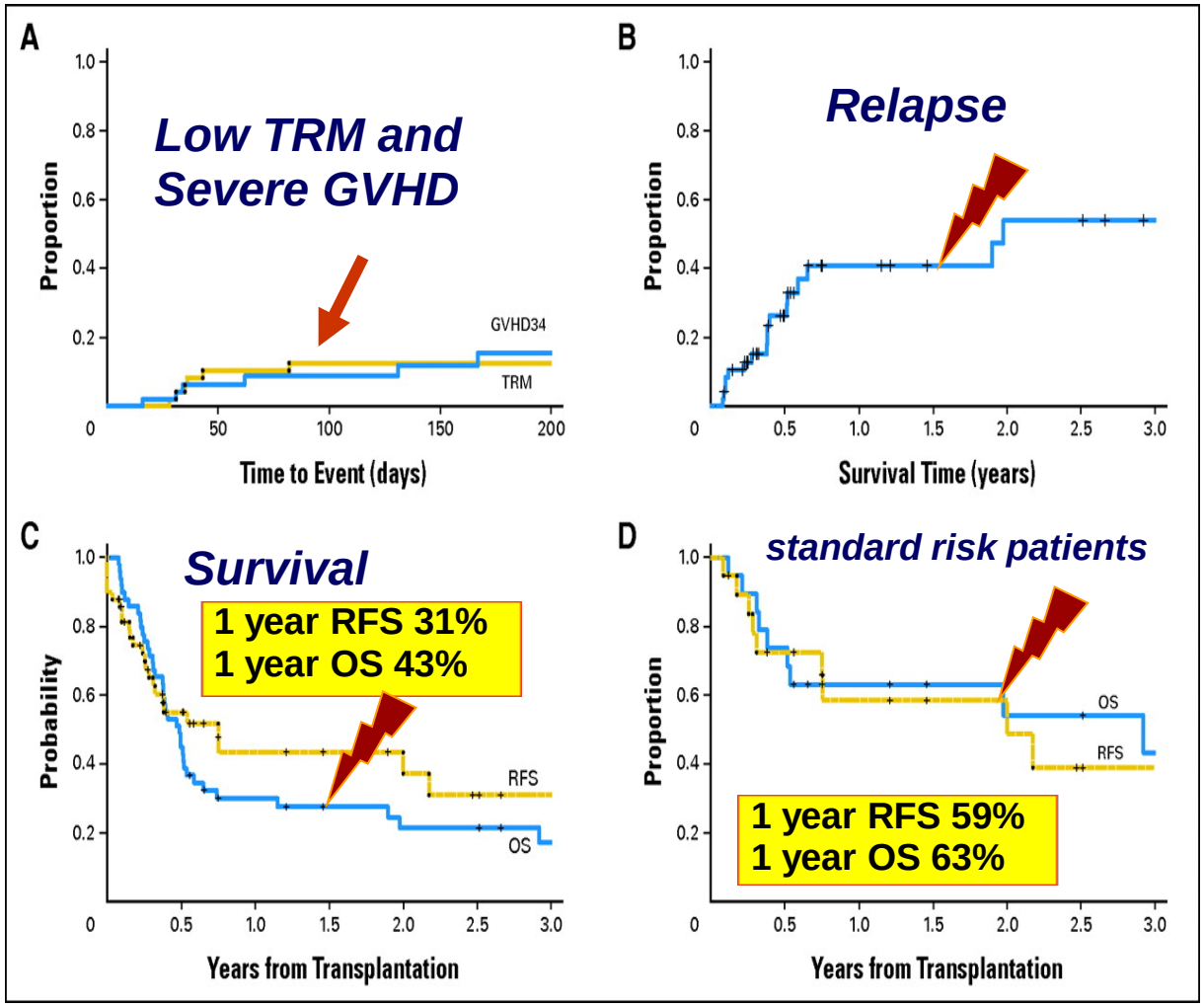
Partially Matched, Nonmyeloablative Allogeneic Transplantation: Clinical Outcomes and Immune Reconstitution



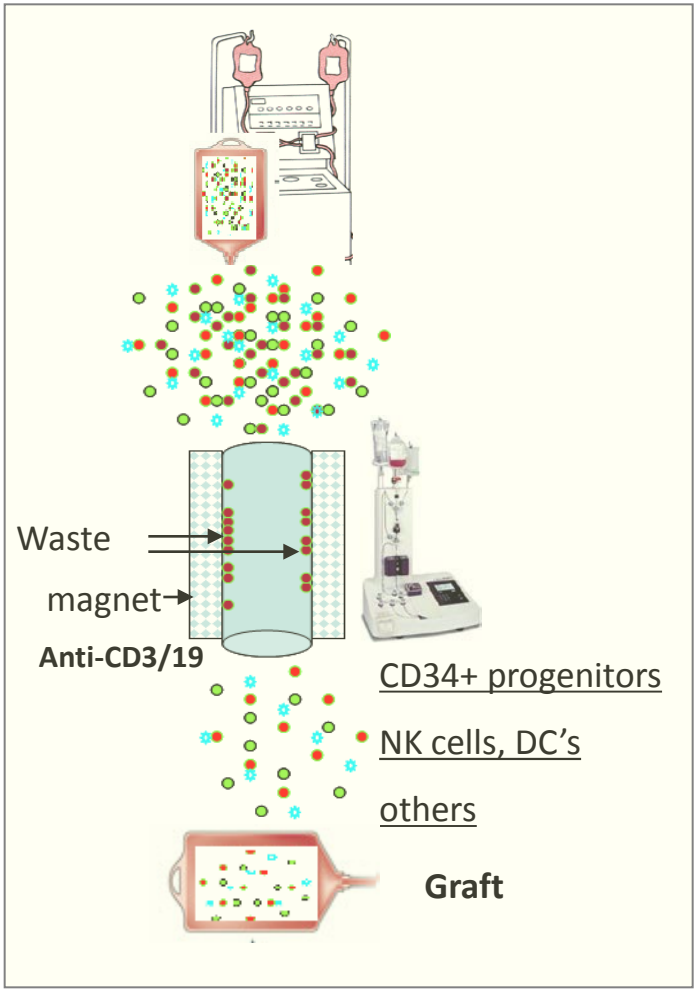
Cause of Death and Incidence of Acute GVHD

Death and GVHD	No. of Patients	%
Cause of death		
Progressive disease	24	49
Infections	11	22
PTLD	2	4
Hemolytic anemia	1	2
Neurotoxicity	1	2
Acute GVHD		
Grade 2	4	8
Grade 3	3	6
Grade 4	1	2
Grade 2-4	8	16
Grade 3-4	4	8
Chronic GVHD/failure to thrive	7	14
Limited	5	
Extensive	2	

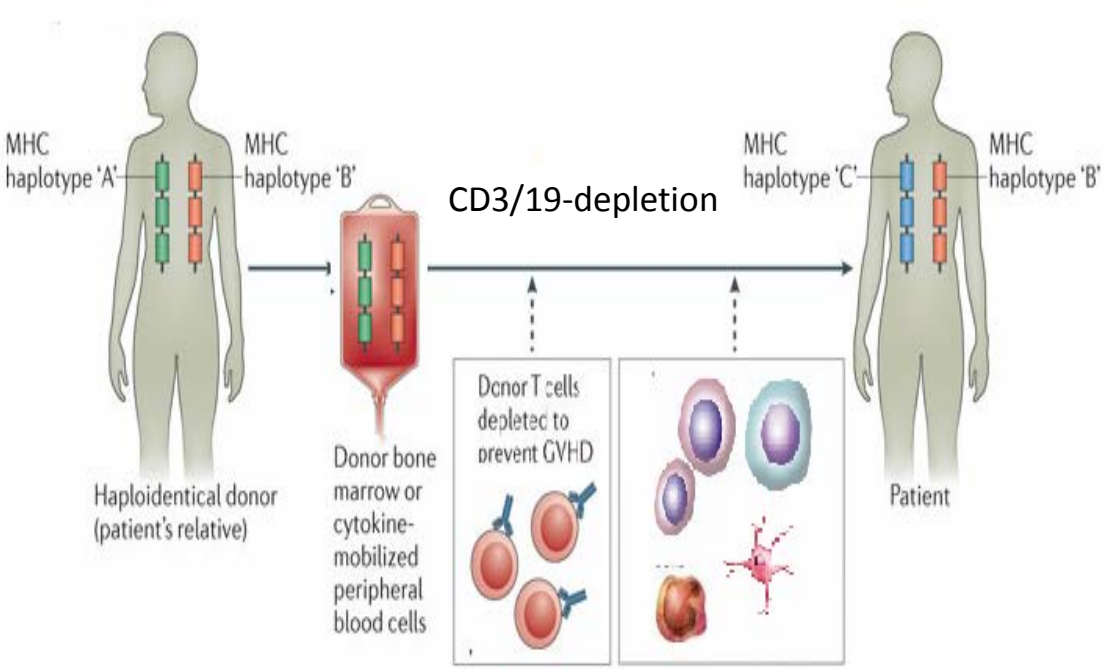
CYTOTHERAPY
The Journal of Cell Therapy

Another concept in 2000's : CD3/CD19 depletion and RIC

CD3/19-negative depletion strategy of mobilized PBSC's :



A one-step large-scale Method for T-and B-cell depletion of Mobilized PBSC for allogeneic transplantation.



Barfield R.:Cytotherapy 2004; 6:1-6.

BLOOD CELLS, MOLECULES, & DISEASES

Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced intensity conditioning: An update

Table 1. Graft composition after CD3/CD19 depletion

Cell population	CD34 selection ($n = 17$)	CD3/CD19 depletion ($n = 19$)
Total cell number pre	5.8×10^{10}	5.0×10^{10}
Total cell number post	0.03×10^{10}	1.5×10^{10}
T cells	0.11%	0.003%
T-cell depletion	4.6 log	4.4 log
CD19+ cells	not done	0.003%
Stem cell purity	97.5%	0.97%
Stem cell recovery	78%	59%
NK cells/kg BW	0.003×10^6	35×10^6
Monocytes/kg BW	0.3×10^6	130×10^6
Granulocytes/kg BW	0.3×10^6	38×10^6

Values were determined by flow cytometry pre and post each immunomagnetic selection/depletion procedure. Numbers present medians of all evaluable procedures.

Wolfgang A. Bethge

Blood Cells, Molecules, and Diseases

Volume 40, Issue 1, January–February 2008,

BLOOD CELLS, MOLECULES, & DISEASES

Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced intensity conditioning: An update

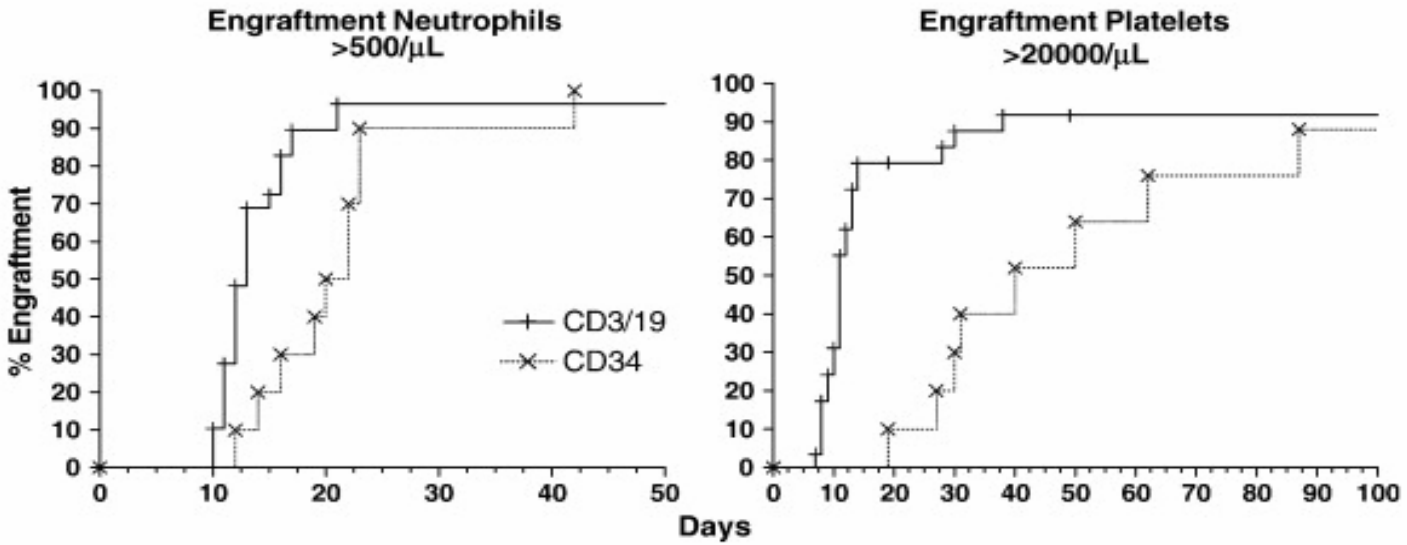


Fig. 1. Time to recovery of neutrophils and platelets. Percentage of patients engrafted by time from the day of transplantation in a cumulative curve for neutrophils > 500/µL and platelets > 20000/µL. Dotted line indicates recovery of historical patients after intensive conditioning and CD34 selection.

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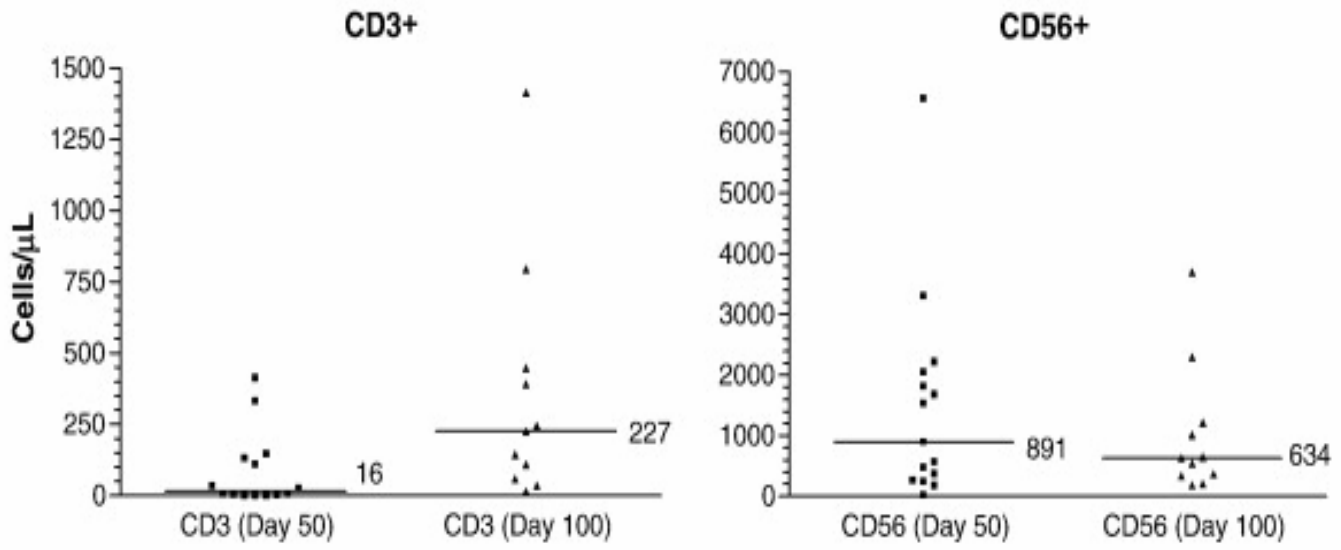

Fig. 2. Count of CD3+ T cells and CD56+ NK cells on days + 50 and + 100. Absolute CD3 and CD56+ count in 16 evaluable patients on days + 50 and + 100 (± 20 days) after HCT.

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BLOOD CELLS, MOLECULES, & DISEASES

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TRM , 100 days, 6/29 (20%)

idiopathic pneumonia syndrome (*n* = 1),

mucormycosis (*n* = 1),

pneumonia (*n* = 3)

GVHD (*n* = 1).

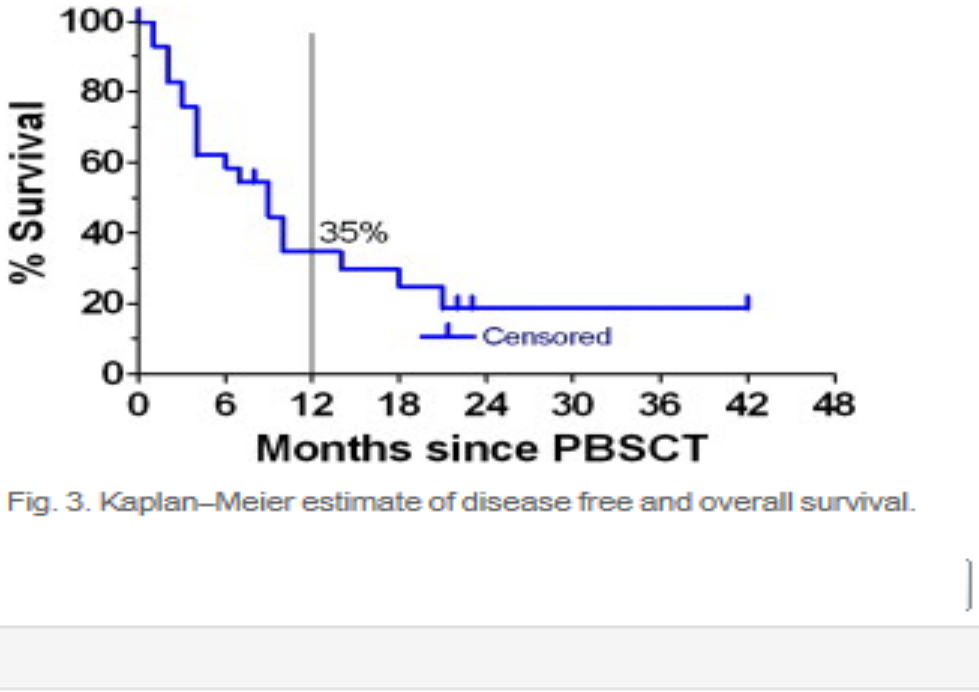
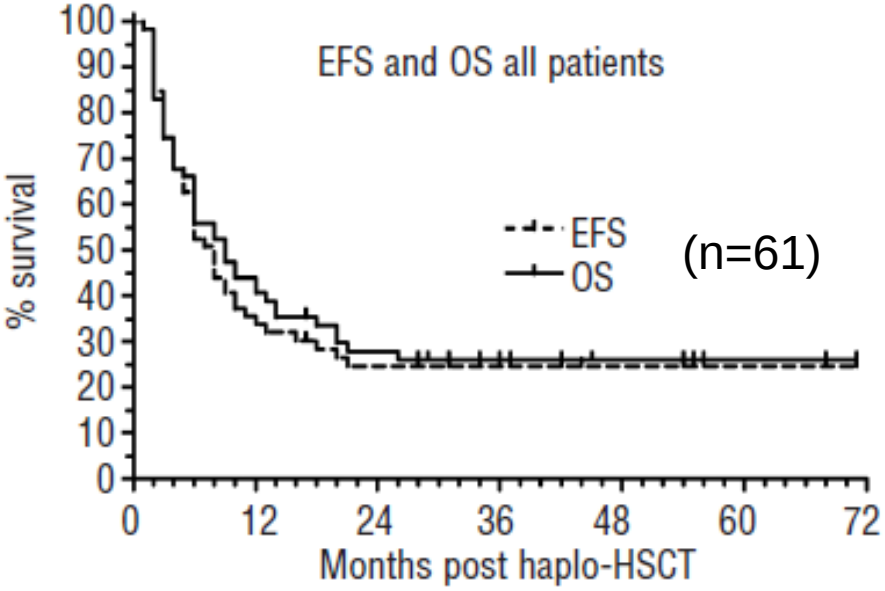


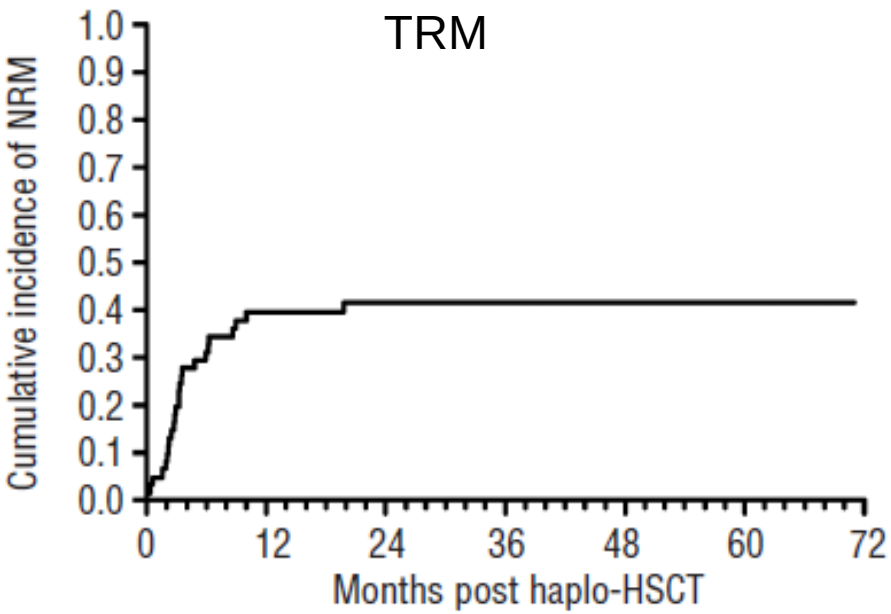
Fig. 3. Kaplan–Meier estimate of disease free and overall survival.

Overall survival is 9/29 patients (35%) with a median follow-up of 241 days

Wolfgang A. Bethge
Blood Cells, Molecules, and Diseases
Volume 40, Issue 1, January–February 2008,

Haploidentical allogeneic hematopoietic cell transplantation In adults using CD3/CD19 depeltion and reduced intensity conditioning: a phase II study.



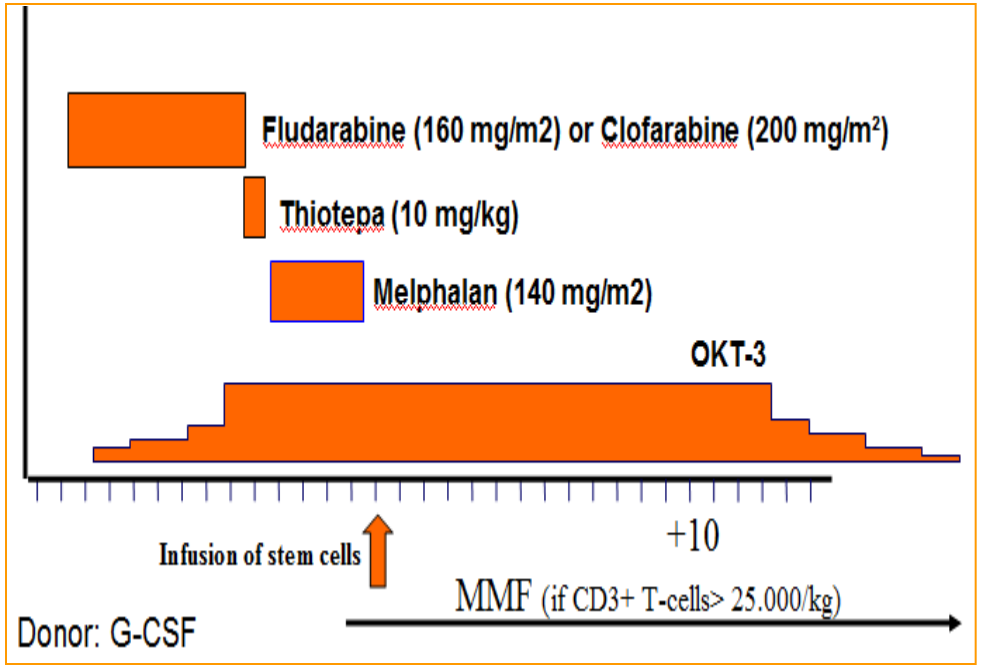


Leukemia

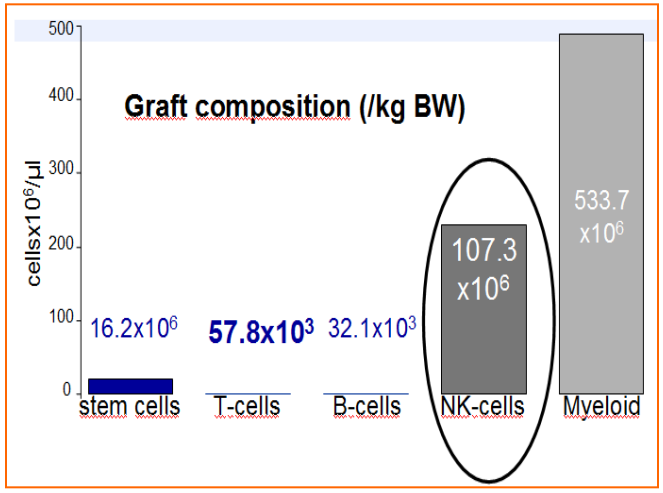
Rapid increase of NK cells, delayed T-and B-cell reconstitution

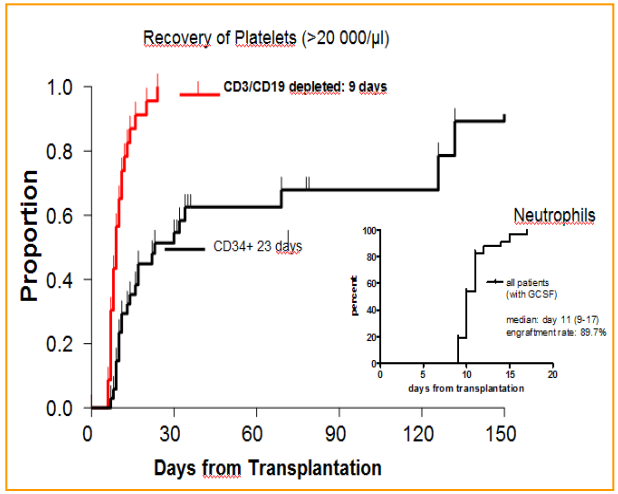
Federmann B. …Bethge W. Immune reconstitution after haploidentical hematopoietic cell transplantation: Impact of reduced intensity conditioning and CD3/CD19 depleted grafts. **Leukemia 2011; 25: 121.**

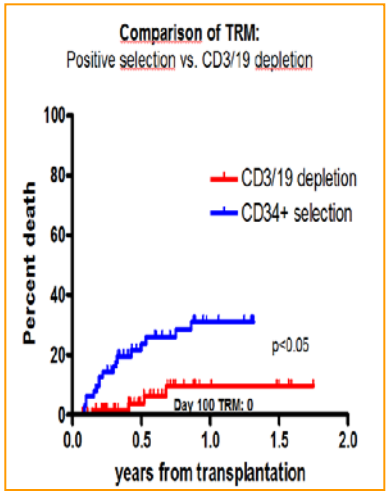
CD3/19-depleted haploidentical PBSC's using RIC regimen



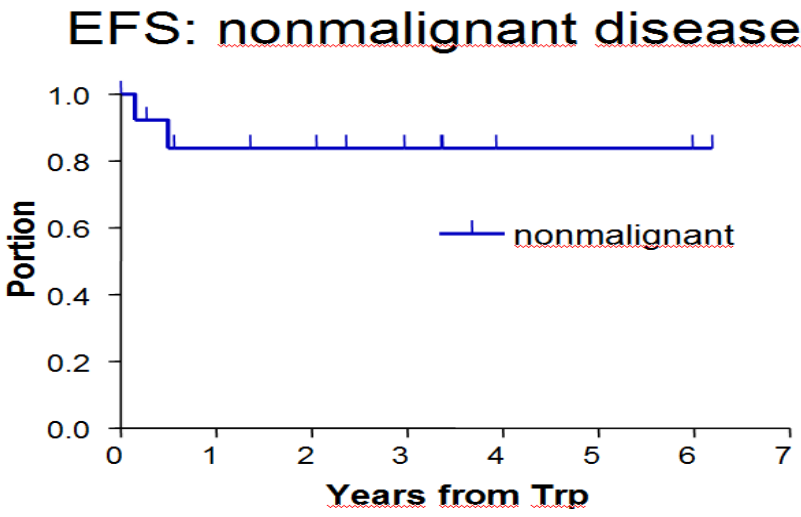
Diagnosis	n=106	Remission status	Remission status	2nd SCT
ALL	28	CR1-3=21	NR=7	11
AML	22	CR1-3=8	NR=14	4
MDS	10	RA=3	RAEB-T=7	4
Solid Tumors	**32**			
Neuroblastoma	19	CR1=7	PR/NR=11	18
Rhabdomyosarkoma	6		PR=6	1
Ewings Sarkoma	6	CR=1	PR=5	3
Synovial Sarkoma	1	CR=1		
Non-malignant	**14**			
SAA, PNH, SCID	8	INBORN ERRORS	4	

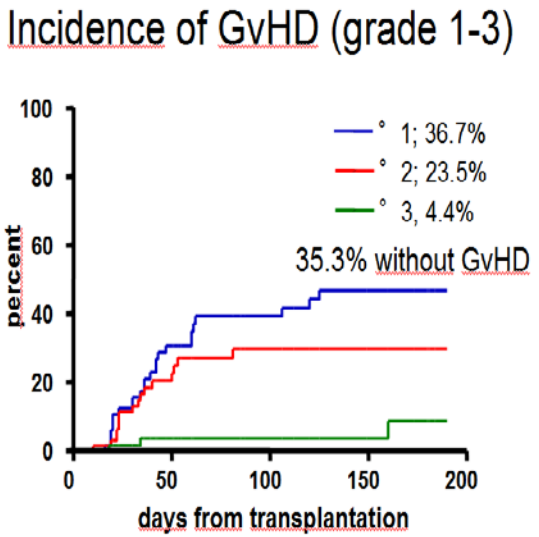


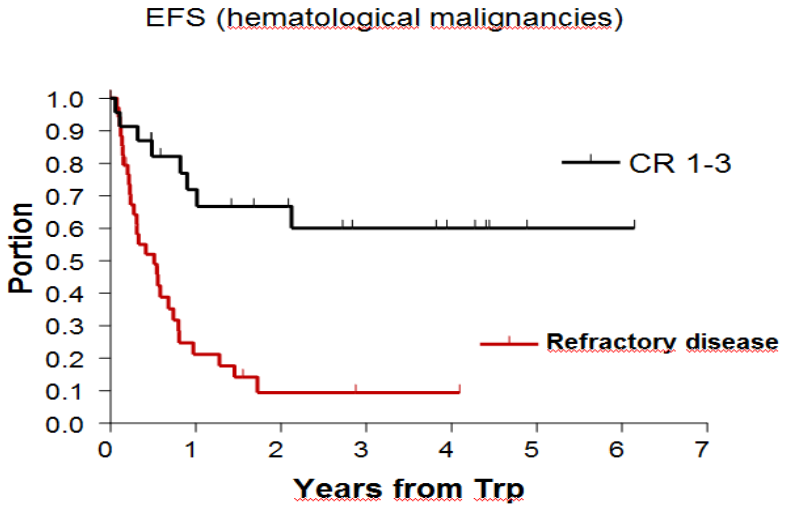


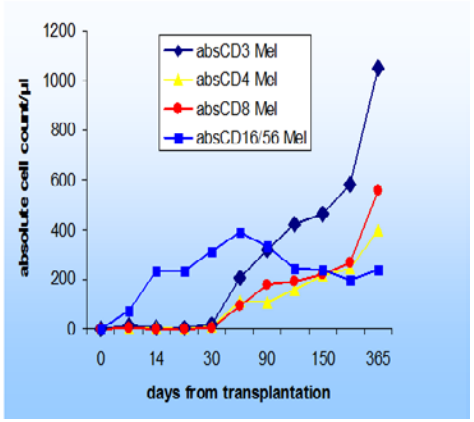


CD3/19-depleted haploidentical PBSC's using RIC regimen







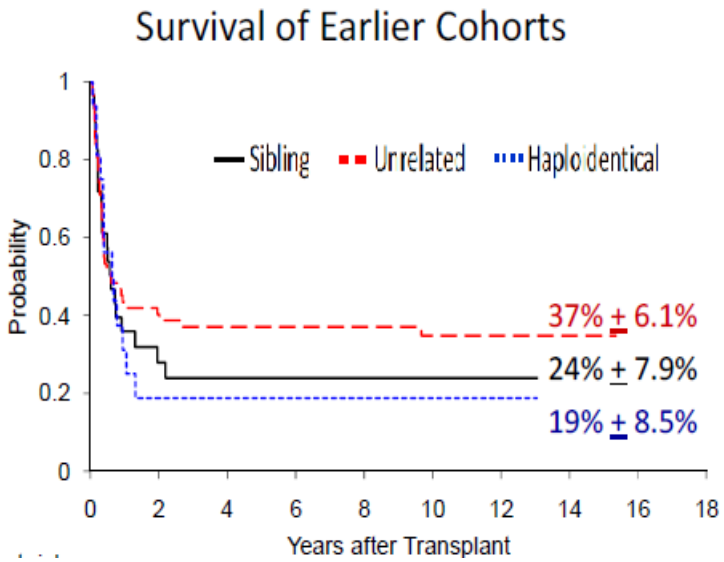


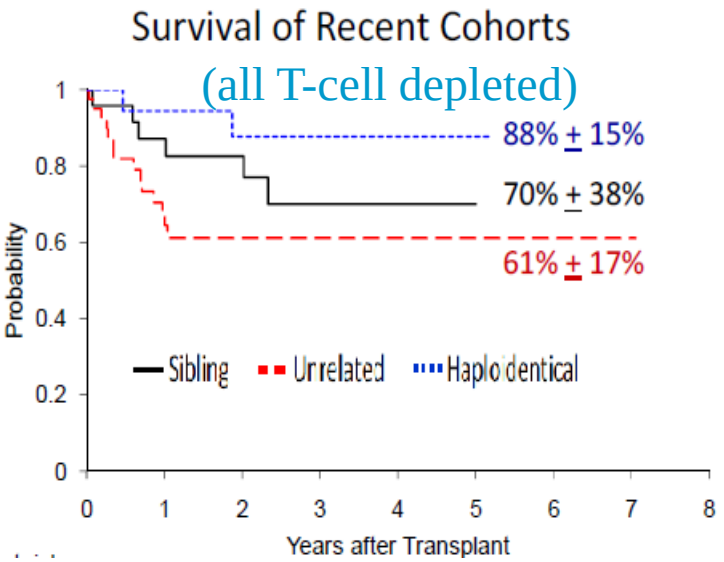
blood

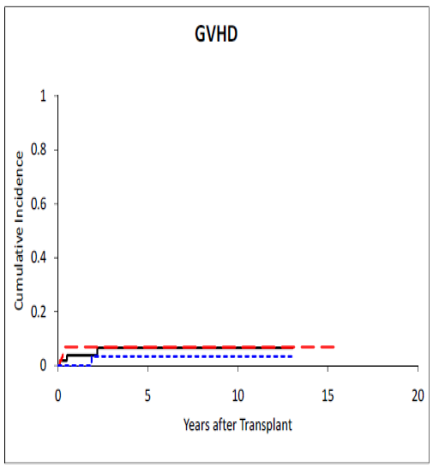
High succes of hematopoietic cell transplantation regardless of donor source in children with **very high-risk leukemia.**

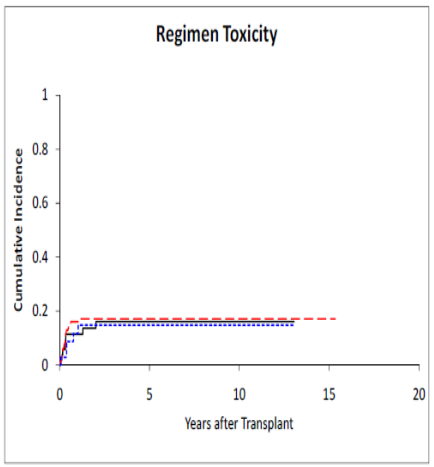
W.Leung et al., BLOOD, ahead of print May 25, 2011.

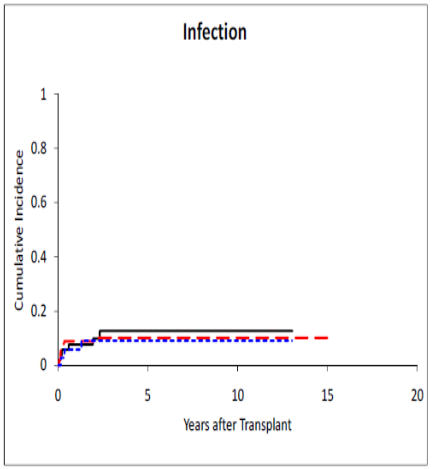
A

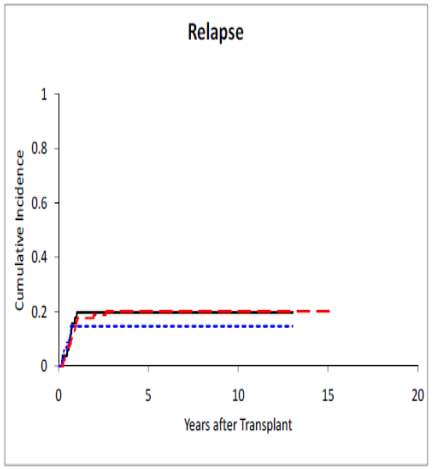












What we have learned from the older studies

- *Tcell depleted megadose HSC's may prevent rejection and support homing but dont increase GVHD*
- *NK alloreactivity induce not only antitumor effect but also stronger engraftment*
- *Center effect may be more important in haploidentical setting*
- *Non-myeablative transplant may decrease TRM but relapse rate main cause of death*

But.. Graft rejection, infection and relaps still very important proplems

New Modalities to Improve Outcome

Manuplated: **"**αβT cells Depletion induced tolerance **"**

γδT cell+ NK cell+ DC's supported & Role of the γδT cell

Unmanuplated: " drug induced tolerance"

Selective Allodepletion by Post Transplantation Cyclophosphamide

New Modalities to Improve Outcome

Manuplated: ”αβT cells Depletion induced tolerance ’’

γδT cell+ NK cell+ DC’s supported & Role of the γδT cell

Unmanuplated: “ drug induced tolerance”

Selective Allodepletion by Post Transplantation Cyclophosphamide

nature REVIEWS IMMUNOLOGY

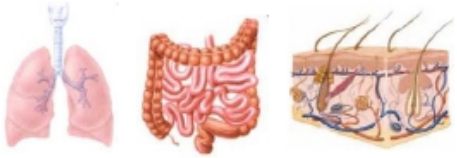
γδT cells might serve as important effectors with limited side effects after allo-SCT ?

Vδ2+ γδT cells

Best characterized

1-5% of peripheral CD3+ T cells

Vδ2- γδT cells



Up to 50% of tissue CD3+ T cells

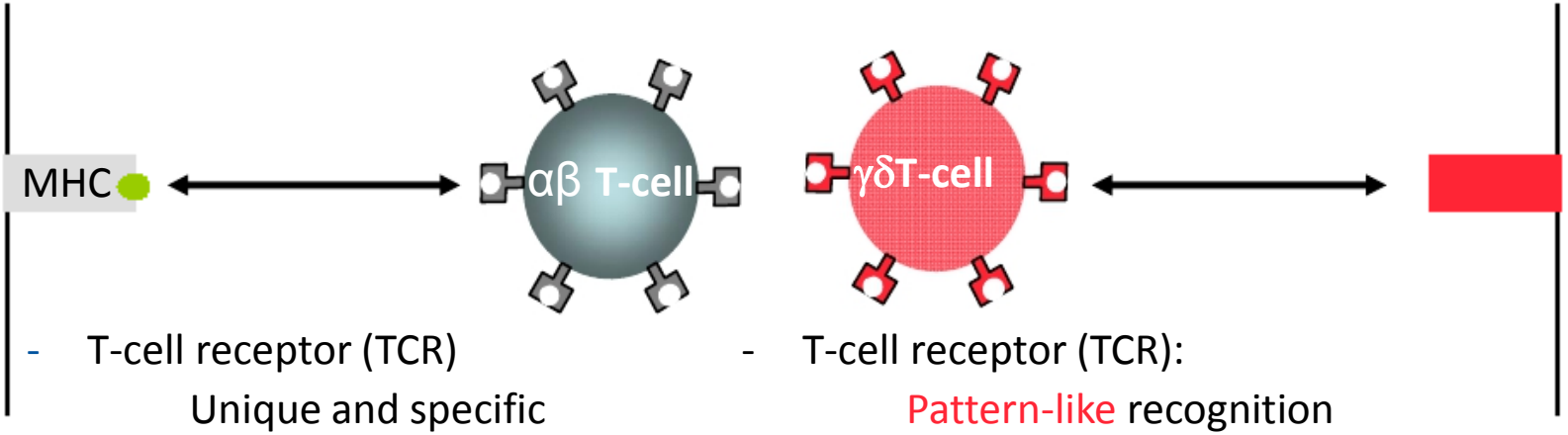
Anti-viral and anti-tumor activity!

belong to the six-of-the-best & unique contributions of γδT cells to immunology

P. *Vantourout & A. Hayday Nat Rev Immunol 2013*

nature REVIEWS IMMUNOLOGY

γδT cells might overcome major hurdles of a αβT-cell based immunotherapies



- T-cell receptor (TCR)
  Unique and specific interaction
- Applicable to a subset of patients
- Helpful and harmful
  - Recognize transformed cells
  - Recognize virally-infected cells
  - Mediate graft-versus-host-disease

- T-cell receptor (TCR):
  Pattern-like recognition of ligands
- Applicable to a broad patient population
- Interesting target specificities:
  - Recognize transformed cells
  - Recognize virally-infected cells
  - Do not mediate graft-versus-host-disease

Tackle major problems during allogeneic stem cell transplantation

e.g. Bonneville et al. Nat Rev Immunol 2010

Key observations after allo-SCT

- **Paradoxical finding after allo-SCT in the era of good anti-viral drugs:**
  - CMV infection associates with a decreased relapse rate

Behrendt et al. BBMT 2009

Elmaagacli et al. Blood 2011

Association studies investigating γδT-cells after allo-SCT

- – Increased γδT-cells are observed after CMV infection

Knight et al. Blood 2010

  - An increase in γδT-cells after allo SCT associates with an improved survival

Godder al. BMT 2007

  - Certain subsets of γδT-cells can be reactive against solid tumor cells

Halary et al. Exp Med 2005

Hypothesis

Do γδT-cells elicited after CMV-reactivation mediate anti-CMV and anti-leukemia reactivity,

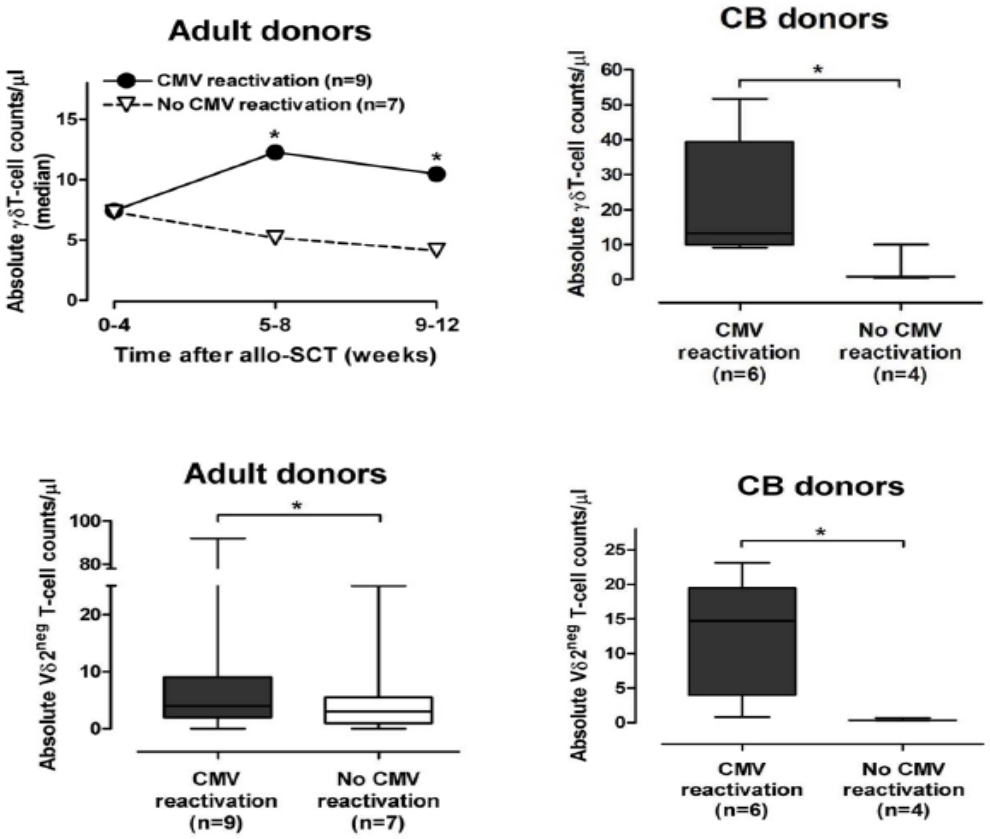
thus contribute to the observed “paradoxical” improved survival after CMV-reactivation?

- Conventional grafts (16 patients)
- Cord blood (CB) grafts (10 patients)

Scheper & van Dorp et al. Leukemia 2013

γδT-cells elicited by CMV reactivation after allo SCT cross recognize CMV and Leukemia

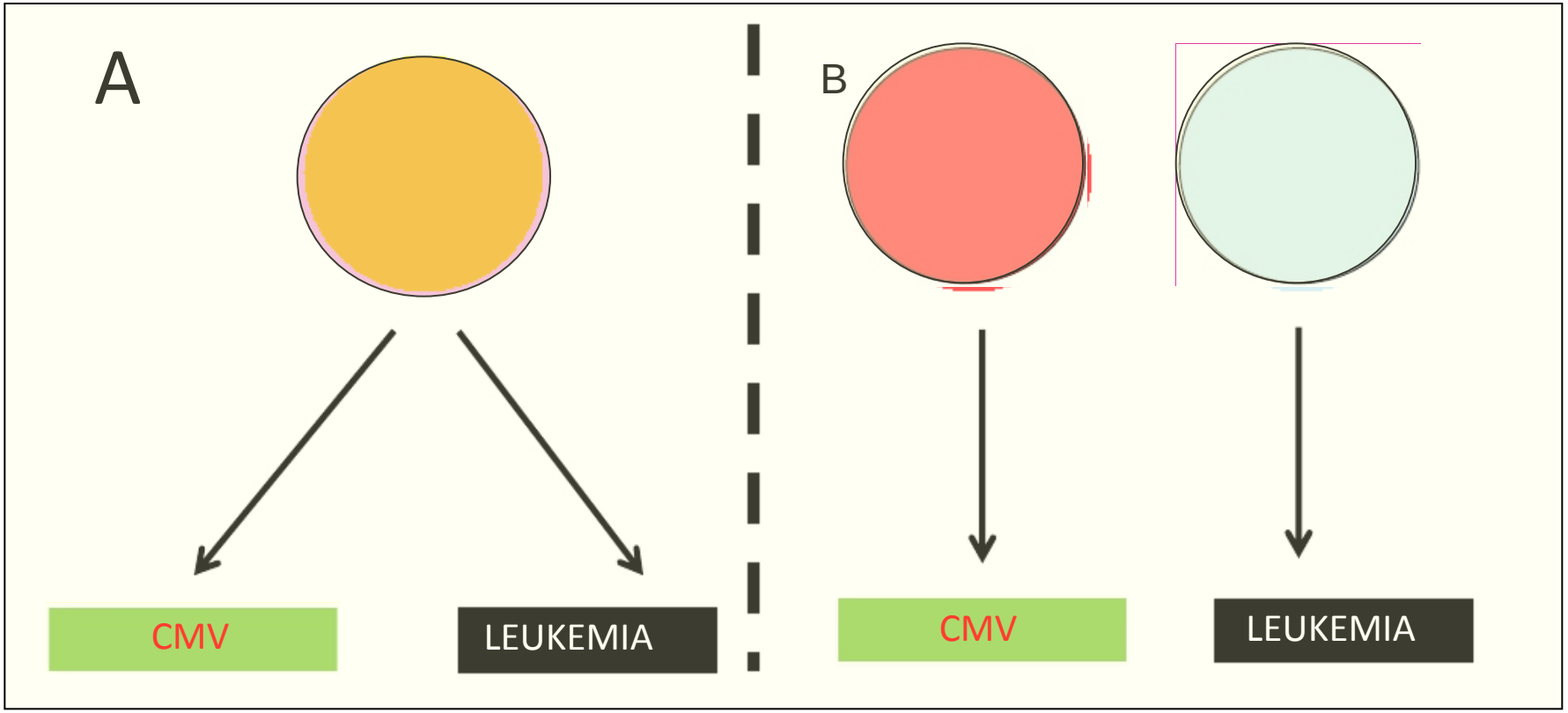
Vδ2neg γδT-cells expand during CMV- reactivation after allo-SCT



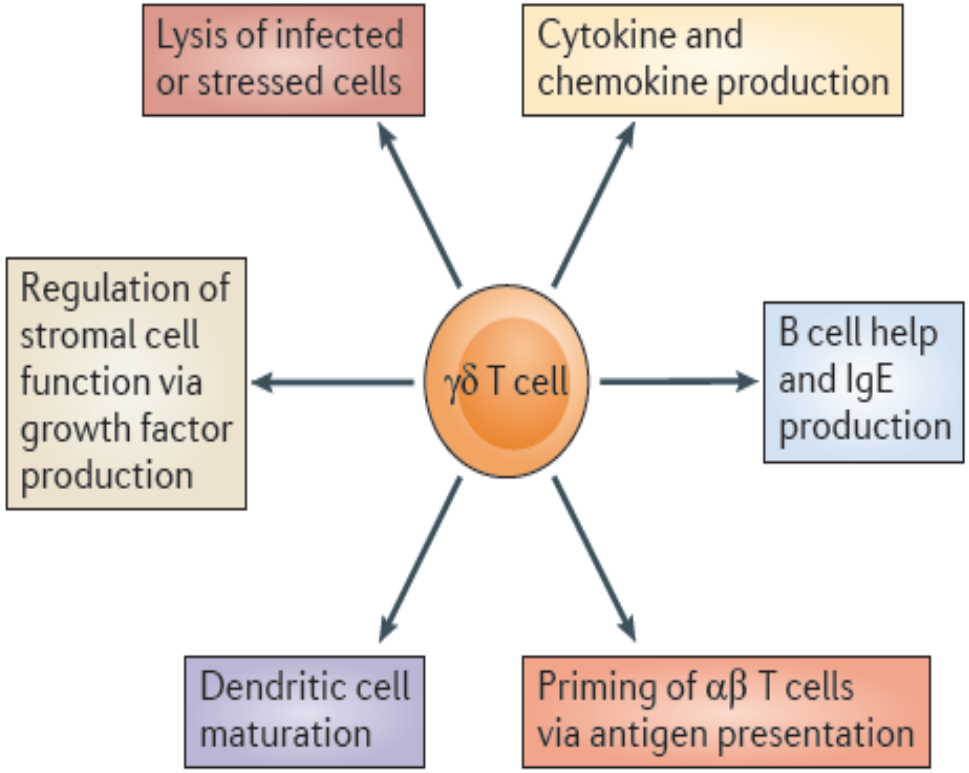
EBMT CONGRESS 2013 Scheper & van Dorp et al, oral poster # 397

γδT-cells elicited by CMV reactivation after allo SCT cross recognize CMV and Leukemia

Are CMV- and leukemia-reactivity found within the same or distinct Vδ2$_{neg}$ T cell populations?



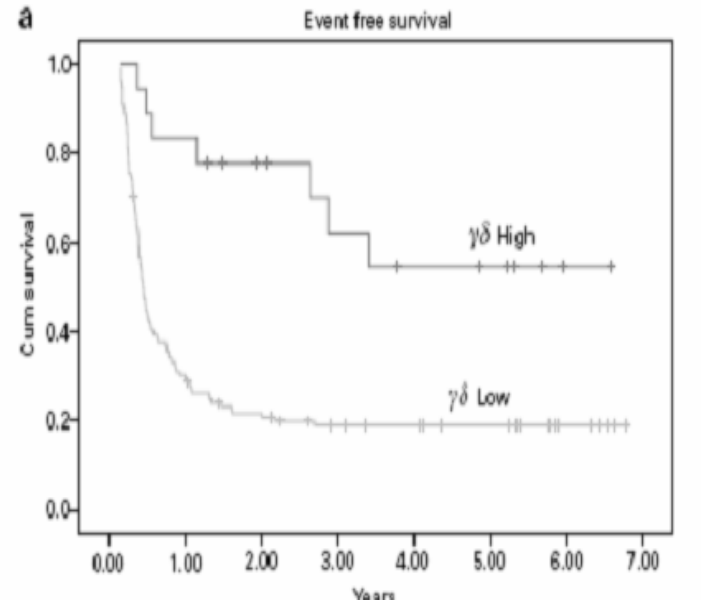
The role of gamma/delta T-cells

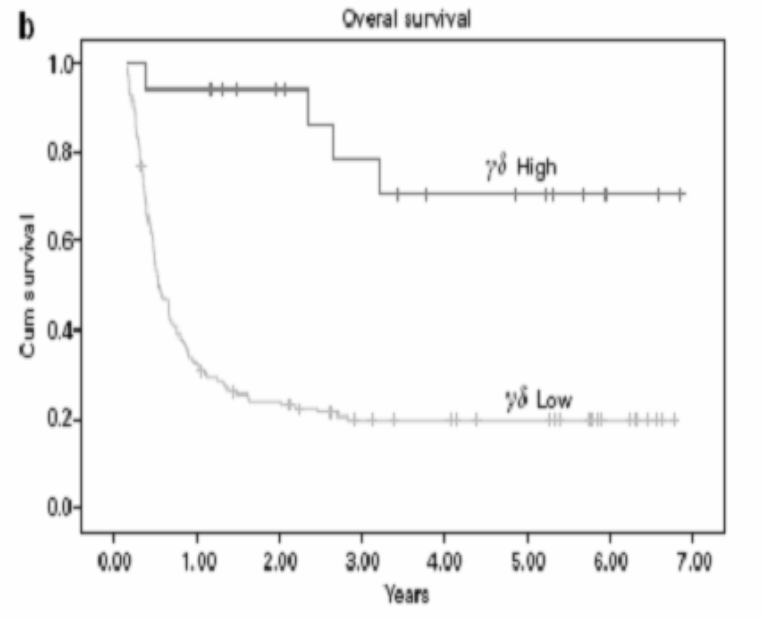


Vantourout P.
Six-of-the best: unique contributions of γδ T cells to immunology. Nat Reviews 2013; 13: 88

Otto M. .. Handgretinger R.
Human g/d T cells From G-CSF mobilized donors retain Strong tumoricidal activity and produce immunostimulatory cytokines after clinical scale isolation. J Immunotherapy 2005: 28: 73

The role of gamma/delta T-cells



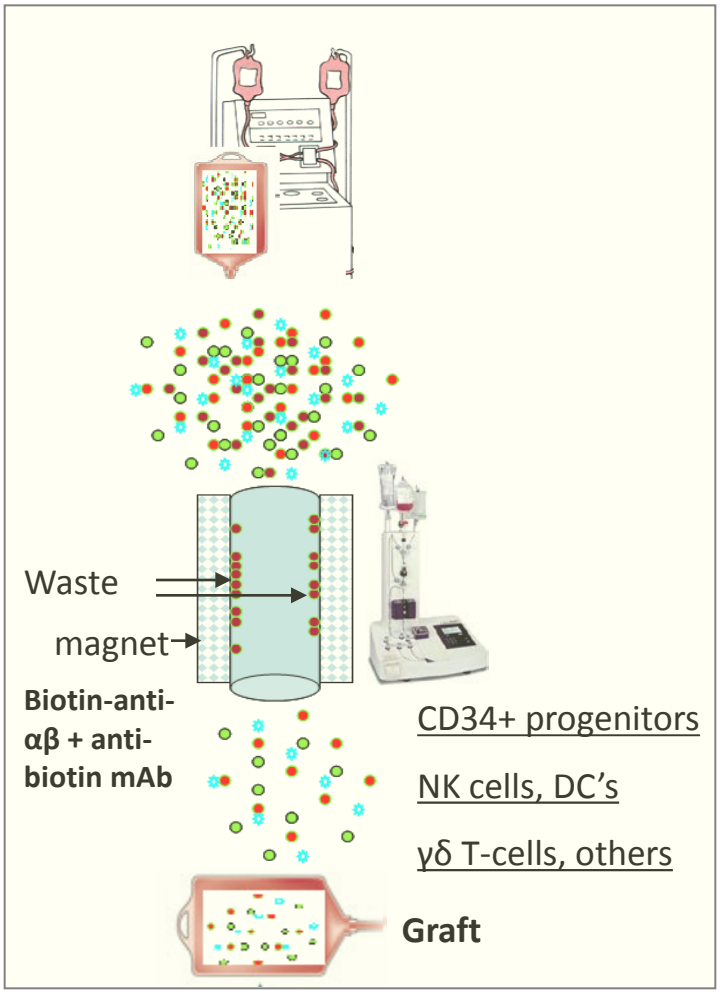


Bone Marrow Transplantation

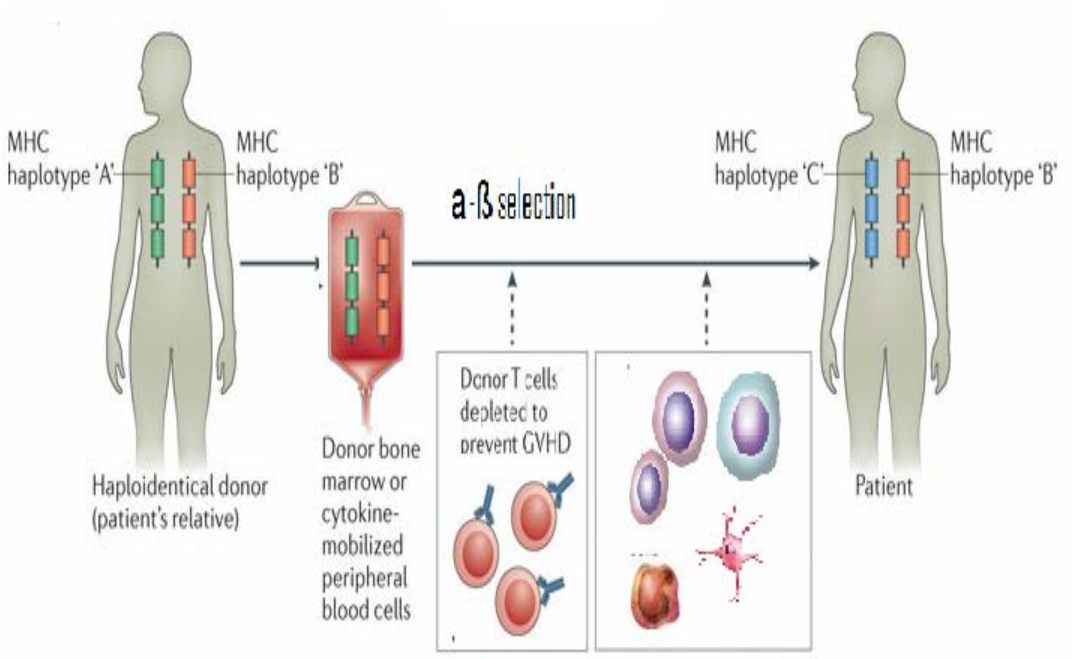
Godder et al., Long term disease-free suzrvival in acute leukemic patients Recovering with increased g/d T cells after partially mismatched related Donor bone marrow transplantation. BMT 2007; 39,751-757.

CYTOTHERAPY
The Journal of Cell Therapy

New modality for Haploidentical Tx: αβ+ T /19-negative depletion strategy of mobilized PBSC's



A large scale method for the selective Depletion of αβ+ T lymphocytes from PBSC for allogeneic Transplantation

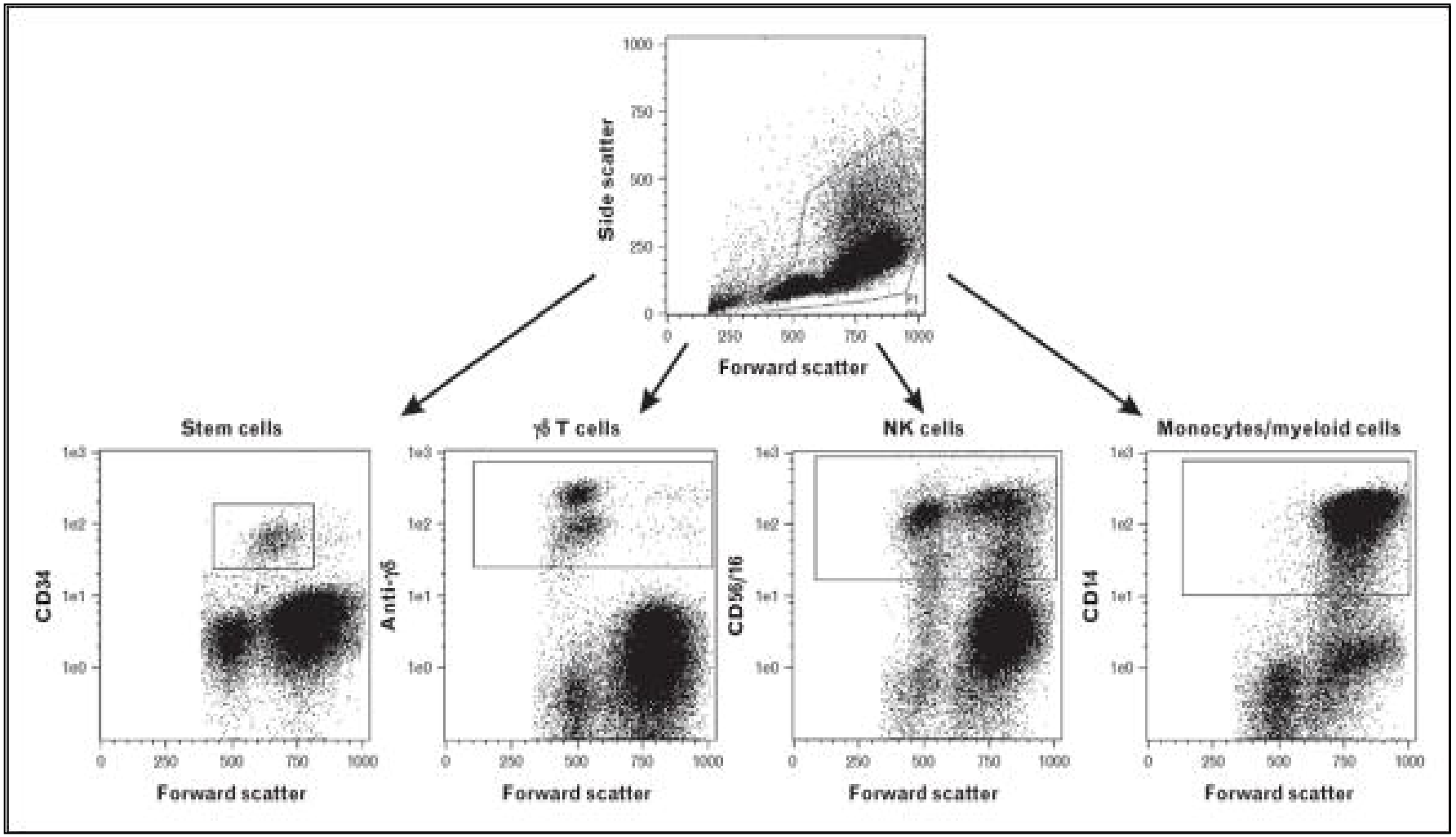


Chaleff S. et al: Cytotherapy 2007; 9: 746 -754.

Current Opinion in Hematology

Negative depletion of CD3+ and TcR[alpha][beta]+ T cells.

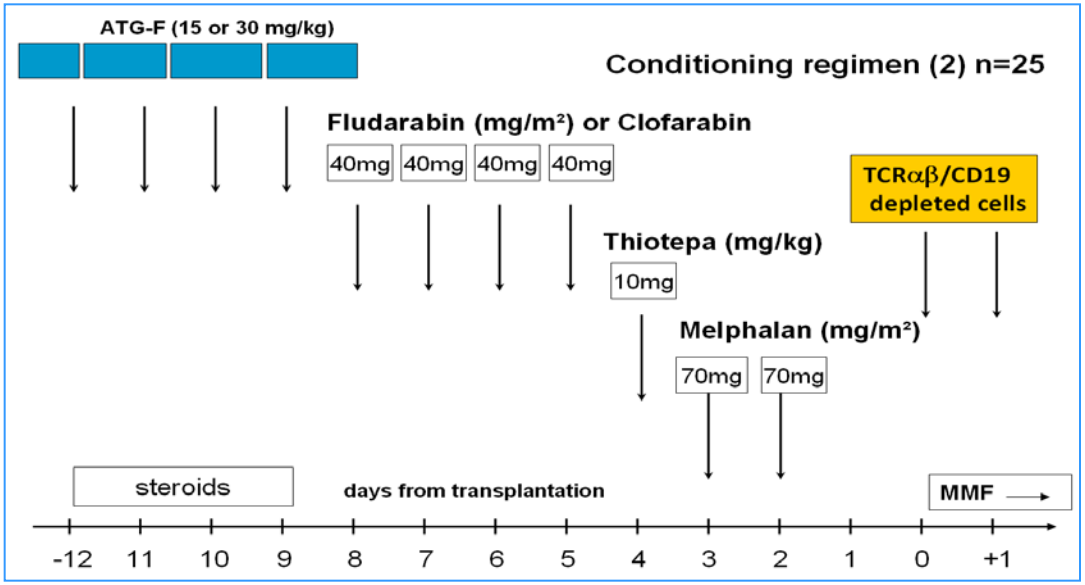
Handgretinger, Rupert



Flow cytometric analysis of a TcR[alpha][beta]/CD19-depleted graft. A forward/side scatter analysis of mobilized peripheral stem cells and the cell composition after TcR[alpha][beta]/CD19 depletion is depicted. The depleted graft is composed of CD34+ stem cells, TcR[gamma][delta]+ T cells, CD56/16+ natural killer (NK) cells and CD14+ monocytes (own unpublished data).

Current Opinion in Hematology. 19(6):434-439, November 2012.

Tubingen Experience: TcRαβ T-cell depletion

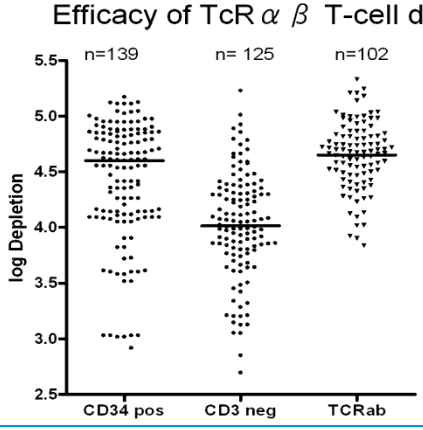


Patients (children, n=35)

Diagnosis	n=
ALL	20
AML/MDS/JMML	9
Nonmalignant	4
Solid tumors	2
Disease status	**n=**
CR2-CR6	17 (55%)
NR/active disease	11 (45%)
2nd/3rd SCT	**23 (65%)**

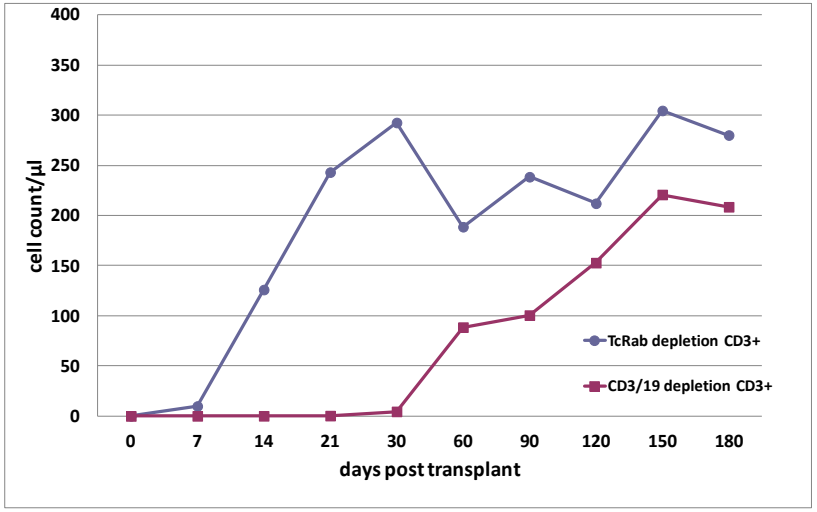
Graft composition after TCRαβ /CD19 depletion

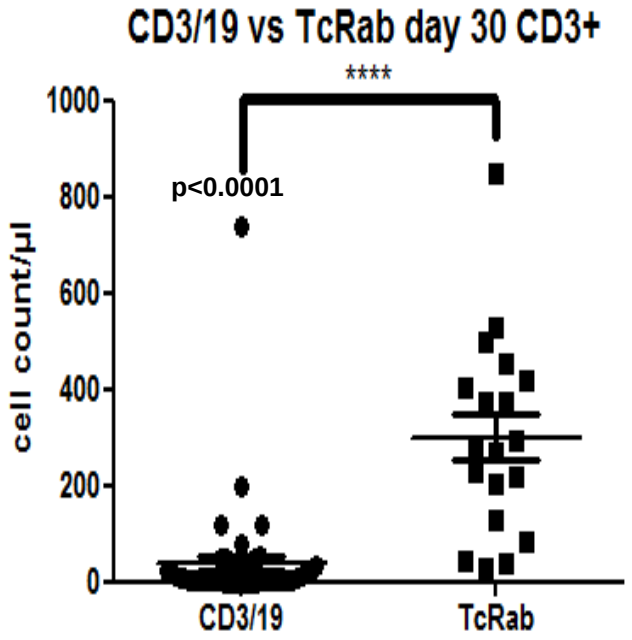
	CD34+ x10⁶/kg	CD3+ x106/kg	CD19+ x10³/kg	CD56+ x10⁶/kg	CD14+ x10⁶/kg	aßTcR+ x10³/kg	γδTcR+ x10⁶/kg
min	5	4.6	46	35	351	1.6	5
max	38	41.8	528	192.2	811	46.4	30
median	12	13.6	110	107.4	618	18.9	11

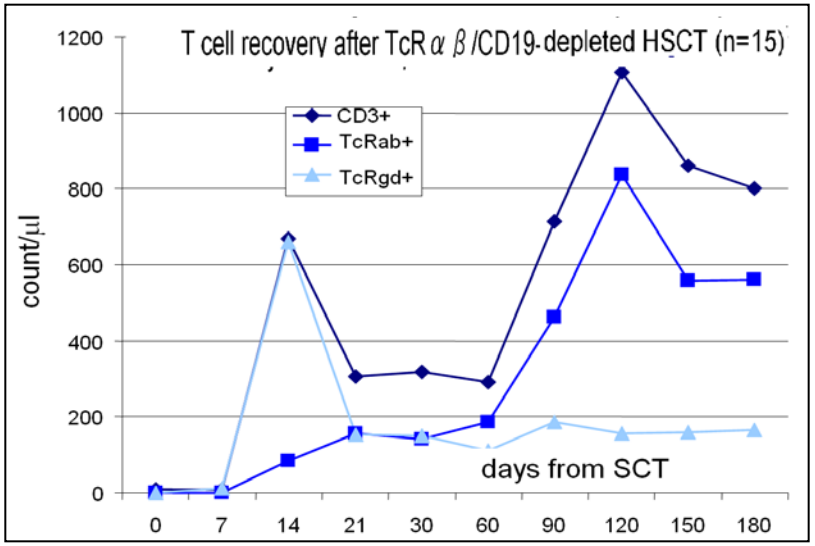


Tubingen Experience: TcRαβ T-cell depletion

Comparison of CD3+ recovery: CD3/19 vs TCRαβ/CD19 depletion

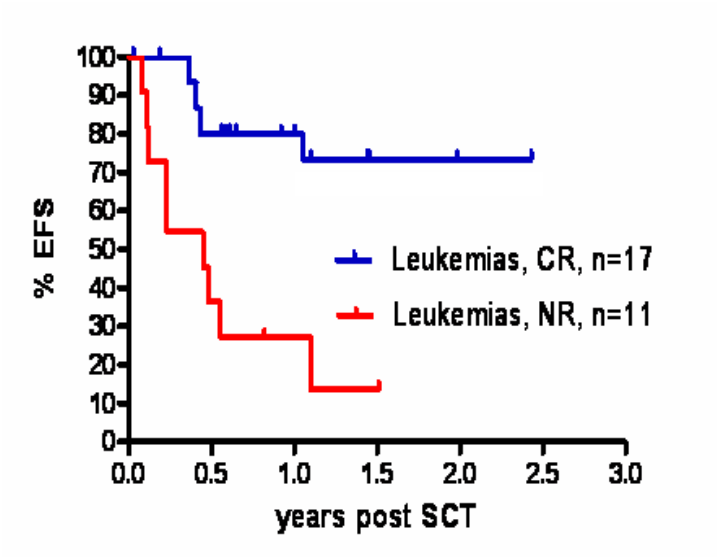


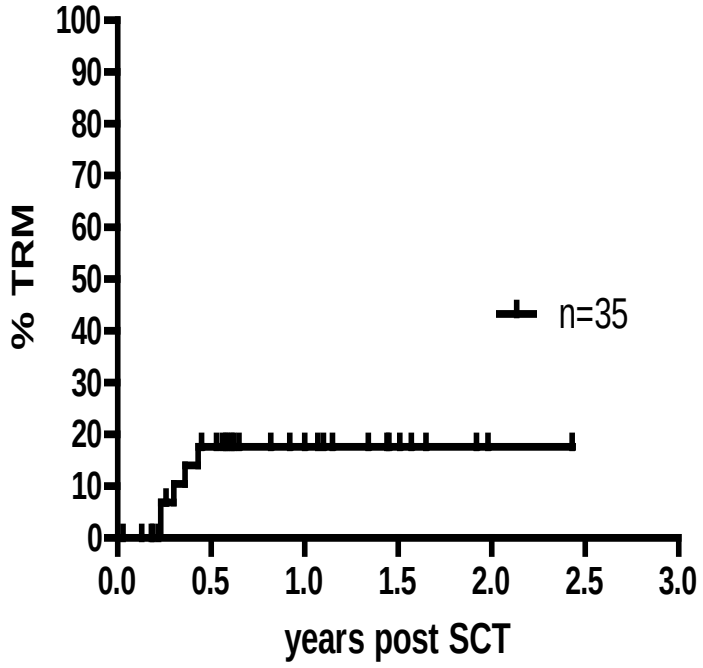




Tubingen Experience: TcRαβ T-cell depletion

EFS: according to remission status & Transplant-related mortality





4154 A New Dosing Scheme of ATG-F Prevents Rejection and Maintains Immune Recovery in Haploidentical T and B Cell Depleted Stem Cell Transplantation

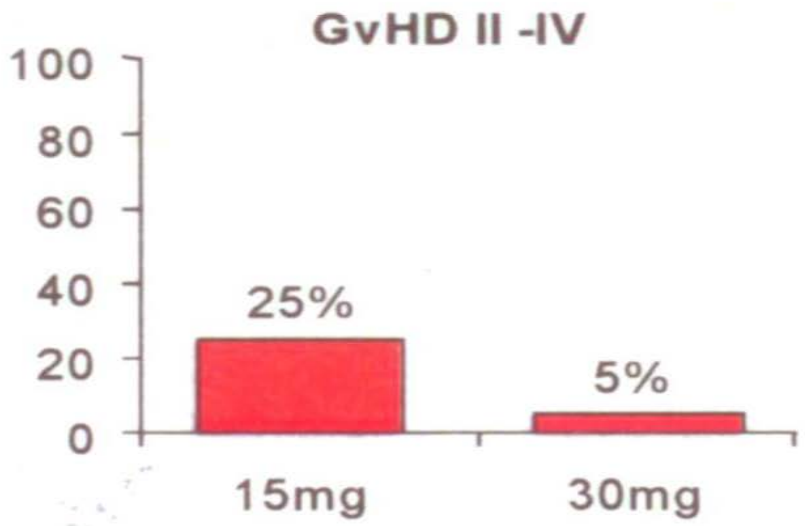
Peter Lang[1], Tobias Feuchtinger[1], Patrick Schlegel[1], Heiko-Manuel Teltschik[1], Roland Meisel[2], Friedhelm Schuster[3], Christina Kyzirakos[1], Rouwen Teltschik[1], Holger Martinius[4], Bernd Gruhn[3], Wolfgang Schwinger[4], Ansgar Schulz[5], Ulrike Pflugrad[1], Michael Schumm[1], Rupert Handgretinger[1]

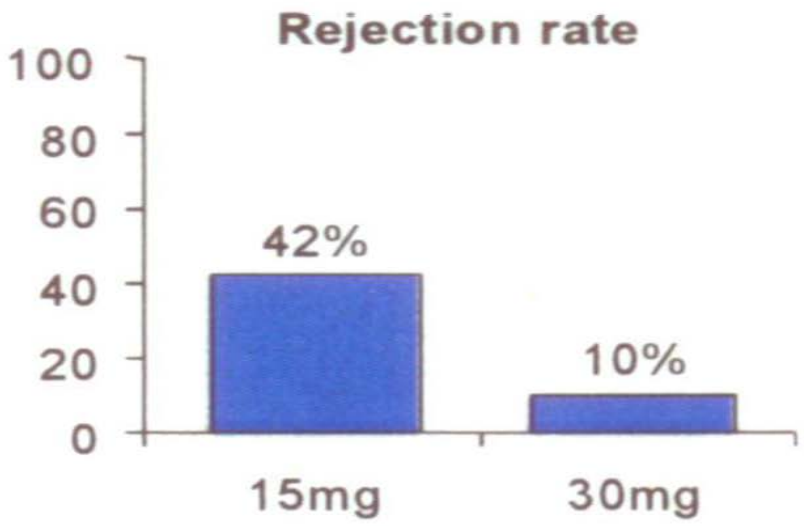
[1]University Children's Hospital Tuebingen, Germany, [2]University Children's Hospital Duesseldorf, Germany, [3]University Children's Hospital Jena, Germany, [4]University Children's Hospital Graz, Austria, [5]University Children's Hospital Ulm, Germany[6] Fresenius Biotech GmbH Muenchen, Germany

Kinderklinik Tübingen

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

	15 mg/kg ATG F	30 mg/kg ATG F
Rejection	3/7 (42%)	2/20 (10%)
Engraftment	After reconditioning: 7/7 (100%)	20/20 (100%)
ANC >500/µl (median)	9 days	9 days
GvHD II-IV in non-rejectors	1/4 (25%)	1/18 (5%)
Extended chronic GvHD	1/4	1/18





HLA Haploidentical Stem Cell Transplantation After Removal of αβ⁺ T Lymphocytes and B Lymphocytes Is an Effective Treatment for Children with Life-Threatening, Non-Malignant Disorders

Bertaine et al. ASH 2012, Poster # 2018

- HLA haploidentical hematopoietic stem cell transplantation (HSCT) is largely employed in children with life-threatening non-malignant disorders.
- Recently developed novel method of *ex vivo* T-cell depletion based on the selective elimination of αβ⁺ T cells through labeling with a biotinylated anti-TCR αβ antibody, followed by incubation with an anti-biotin antibody conjugated to paramagnetic beads (CliniMACS®, Miltenyi Biotec, Germany) has been developed
- B cells have been removed through an anti-CD19 monoclonal antibody, to prevent post-transplant EBV-associated lymphoproliferative disease (PTLD)

"All patients were transplanted from 1 parent (10 from the mother and 3 from the father), the median number of $CD34^+$ cells, αβ $CD3^+$ cells and B cells infused being $17.8x10^6$/kg, $0.64x10^5$/kg and$5.3x10^6$/kg, respectively"

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Bertaine et al. ASH 2012, Poster # 2018

Patients:

- n=13 (n=7males)
- Median age at transplantation being 3 yr and 9 mo (range 0.3-28.7)
- Primary diseases:
  - 4 patients with severe combined immune deficiency (SCID)
  - 3 Fanconi anemia (FA)
  - 2 severe aplastic anemia (SAA)
  - 1 each immune deficiency with polyendocrinopathy, enteropathy, X-linked (IPEX), congenital amegakaryocytic thrombocytopenia (CAMT), hemophagocytic lymphohistiocytosis (HLH) and thalassemia with autoimmune hemolytic anemia

Methods:

- "Conditioning regimen consisted of:
  - Treosulfan and fludarabine (FLU) in 7 children (4 SCID, 1 IPEX, 1 HLH and 1 CAMT)
  - FLU and cyclophosphamide in 5 (3 FA and 2 SAA) and busulphan, FLU and thiotepa in 1 child (thalassemia)
  - All patients were given anti-thymocyte globulin (ATG Fresenius; 3 mg/kg/day) on days -5 through -3 before allografting and, to prevent PTLD, rituximab (200 mg/m^2) on day -1
  - No patient received pharmacological prophylaxis for graft-versus-host disease (GVHD) after the allograft"

HLA Haploidentical Stem Cell Transplantation After Removal of αβ⁺ T Lymphocytes and B Lymphocytes Is an Effective Treatment for Children with Life-Threatening, Non-Malignant Disorders

Bertaine et al. ASH 2012, Poster # 2018

Results:

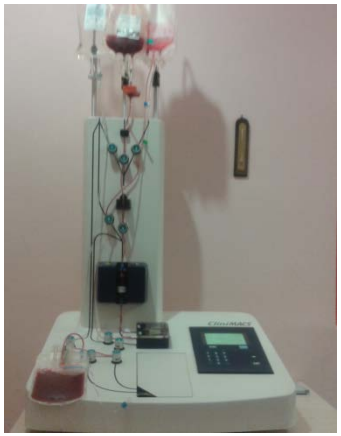
- Median time to recovery:
  - Neutrophil recovery being 13 days (range 8-19)
  - Platelet recovery :11 days (range 7-40)
- One SAA patient and one patient with thalassemia who had primary graft failure were successfully re-transplanted, the first one from the same parent and the second one from the other parent
- No patient experienced secondary graft failure
- Acute skin GVHD grade I/II occurred in 3 patients, limited skin chronic GVHD occurred in 1 of the 8 patients at risk
- No patient had visceral acute GVHD
- "The median chimerism is 100% (range 85-100). Noteworthy, all patients with primary immune disorders and FA are alive and disease-free. T-cell recovery was initially sustained by gd T cells, while, after 45 days from the allograft, αβ T cells predominated"

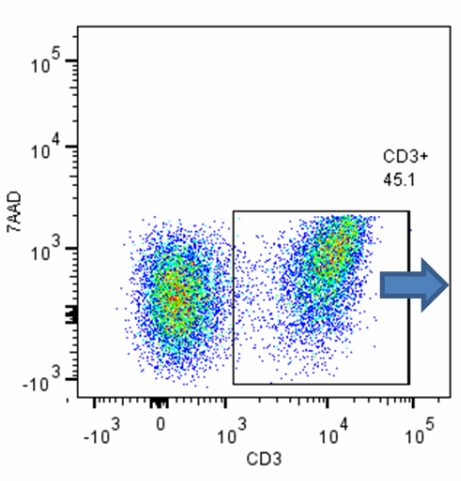
"With a median follow-up of 209 days (range 37-543), 11 out of the 13 (84%) patients are alive and disease-free, the Karnofsky/Lansky score being 100"

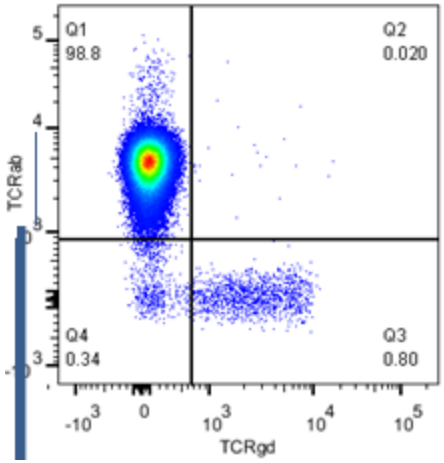
The transplantation-related mortality of 15% observed in this cohort is comparable to that observed using a HLA-matched UV

If confirmed in a larger cohort of patients and with a longer follow-up, these results suggest that this transplant option be offered to any child lacking a HLA-identical sibling"

Erciyes University Experience: TcRαβ T-cell depletion

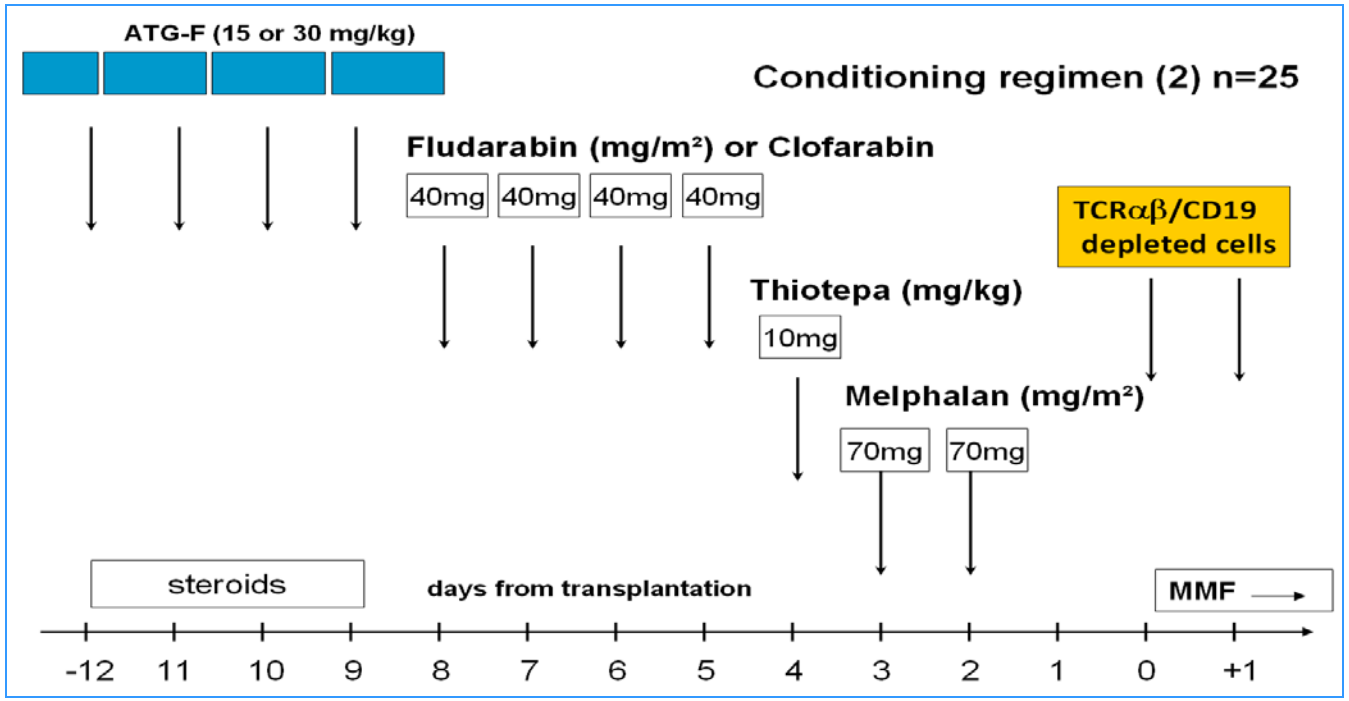






Fraktion	Vol	Conc 10e6	Total WBCs 10e9	Viability	%TCRab
Original	150	340	51	99	12,52
Target	389	114	44,35	98	0,02

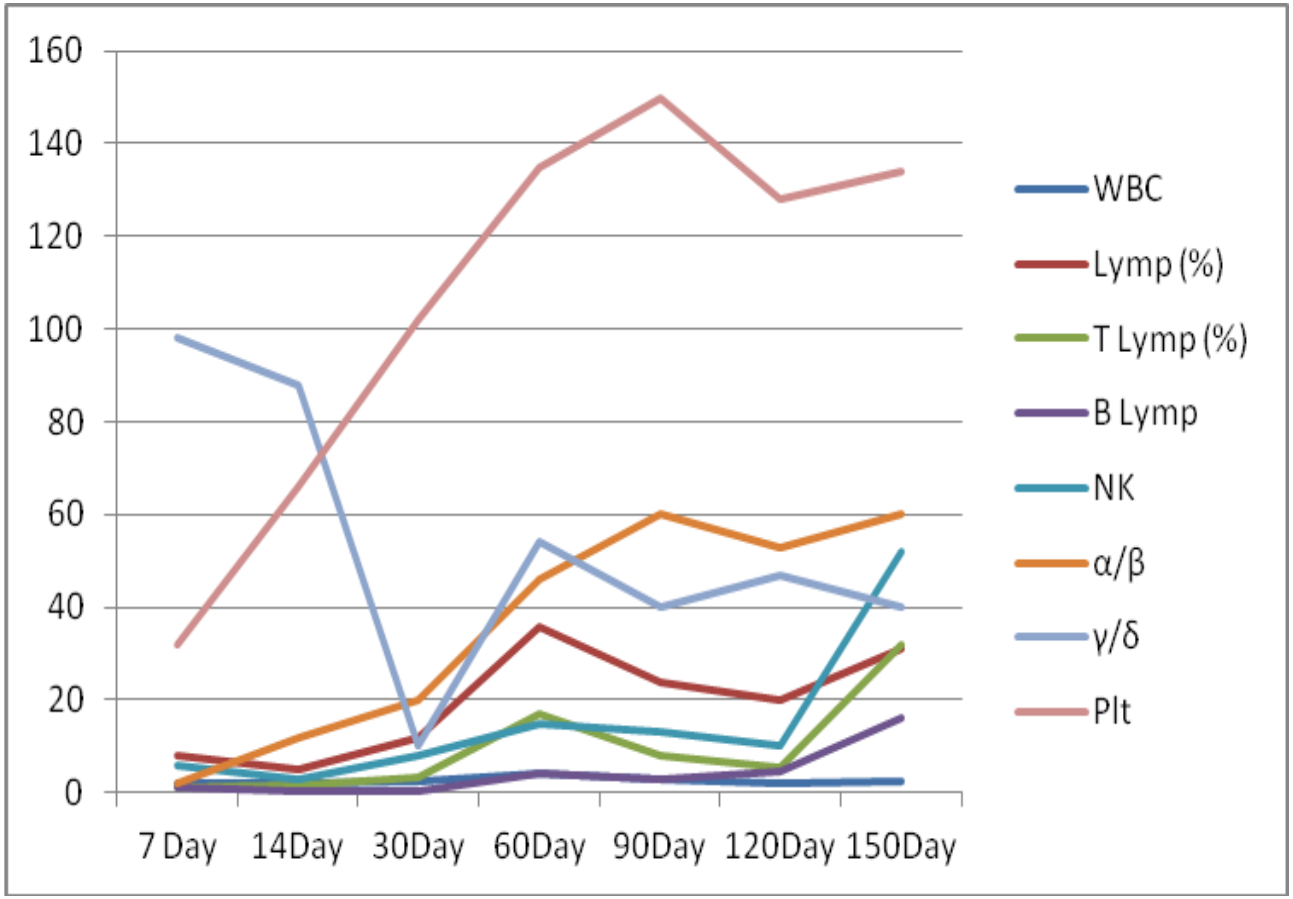
Erciyes University Experience: TcRαβ T-cell depletion



Erciyes University Experience: TcRαβ T-cell depletion

DURUM TX ÖNCESİ	NÖTROFİL ENG	TROMBOSİT ENG	GVHD	KİMERİZM SONUÇLARI	Tx SONRASI	SON DURUM
REMİSYON CR2	12	13	YOK	99	CR	SAĞ CR
REMİSYON CR1	11	12	YOK	96	CR	SAĞ CR
REMİSYON CR3	40		YOK	100	CR	SAĞ CR
REMİSYON CR1	10	12		100	CR	SAĞ CR
%15 BLAST	11	12	aGVHD	100	CR	EX
REMİSYON CR3	12	12	YOK	100	CR	NÜKS(EKSTRA MEDÜLLER)
REMİSYON CR2	13	12	YOK	97	CR	NÜKS
REMİSYON	14	12	YOK	97	CR	SAĞ CR
REMİSYON CR1	28	35	YOK	0	CR	NÜKS
CR1> BLAST	12	13	YOK		CR	EX
BLAST	12	18	YOK	100	CR	NÜKS (EKSTRA MEDÜLLER)
REMİSYON CR2	14	20	YOK		CR	SAĞ CR
REMİSYON CR3	10	14	YOK	99	CR	SAĞ CR
REMİSYON+CR2			YOK		CR	SAĞ CR
CR2> BLAST	12	12	YOK	98,5	CR	SAĞ CR
SAA	9	12	YOK	0	-	SAĞ
SAA	10	13	YOK	99,3	CR	SAĞ
CR2	9	12	YOK	99,8	CR	SAĞ
CR1 + BLAST	10	12	GRADE II	99,2	CR	SAĞ
CR2	11	13	YOK	0	-	SAĞ

Erciyes University Experience: TcRαβ T-cell depletion



New Modalities to Improve Outcome

Manuplated: ”αβT cells Depletion induced tolerance ’’

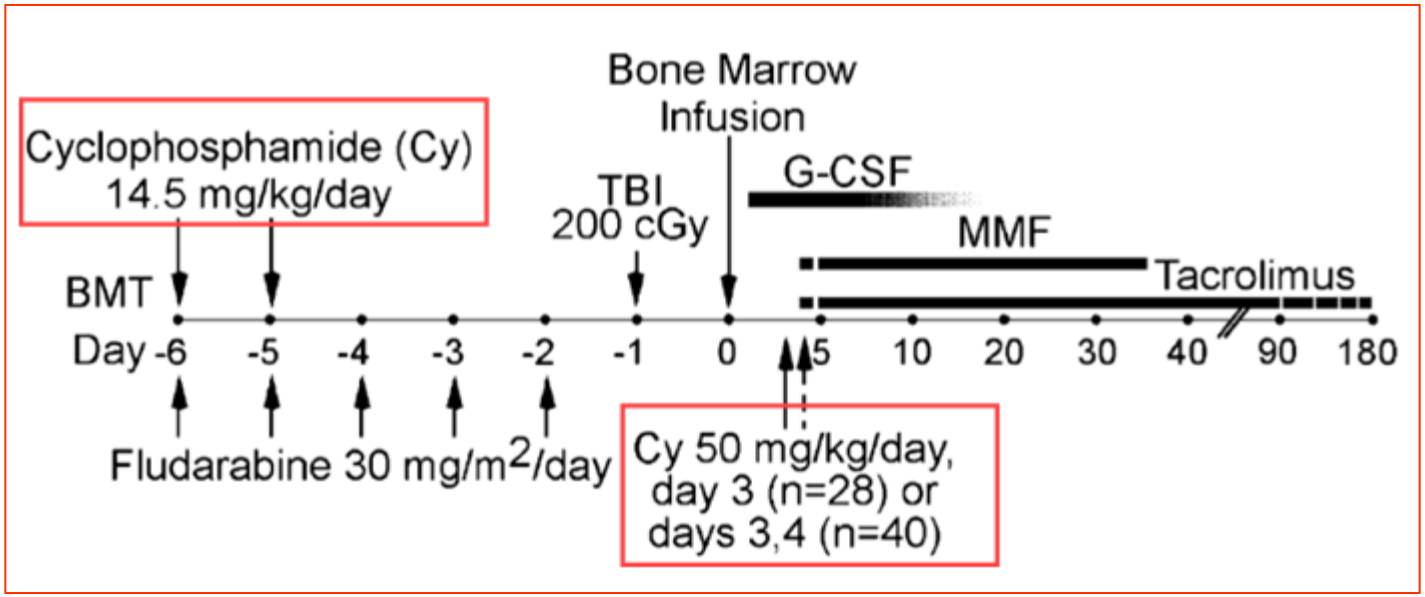
γδT cell+ NK cell+ DC’s supported & Role of the γδT cell

Unmanuplated: “ drug induced tolerance”

Selective Allodepletion by Post Transplantation Cyclophosphamide

Nonmyeloablative Haplo-SCT with High Dose Post-Transplantation Cy

The John Hopkins' / FHCRC Approach

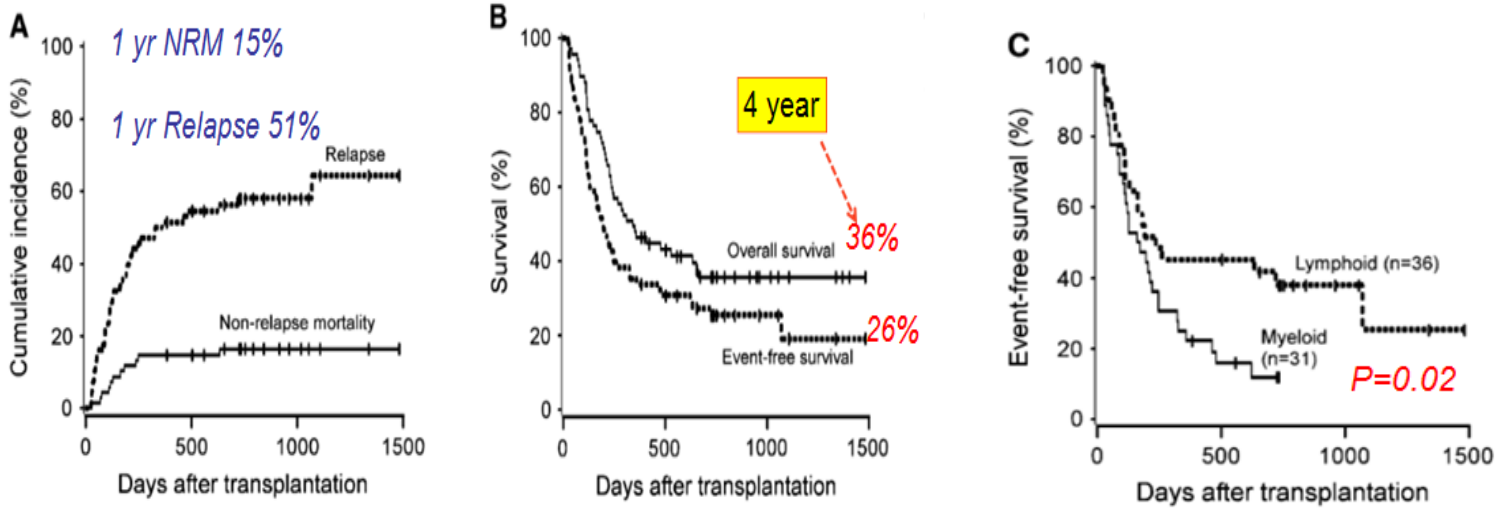


High-dose cyclophosphamide (Cy), when administered in a narrow window after transplantation, depletes alloreactive T-cells from the donor and host, and can inhibit both GVHD and graft rejection.. Takes advantage of the heightened cytotoxic sensitivity of proliferating, alloreactive T-cells over non-alloreactive, resting T-cells to being killed by a DNA damaging agent

Luznik , et al. Biol Blood Marrow Transplant 2008;14:641-651

Nonmyeloablative Haplo-SCT with High Dose Post- Transplantation Cy

The John Hopkins' / FHCRC Approach

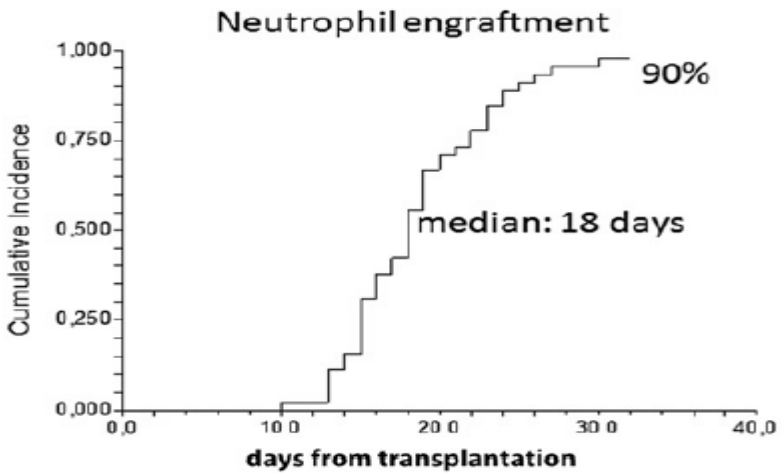


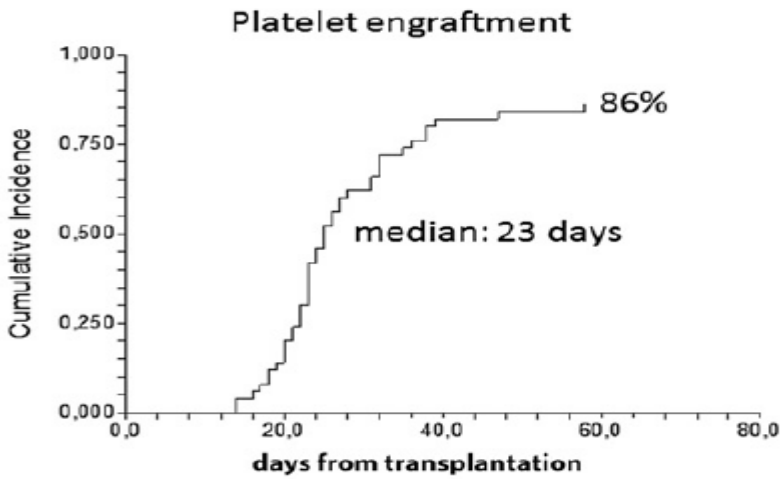
Luznik L, et al. Biol Blood Marrow Transplant 2008;14:641-651

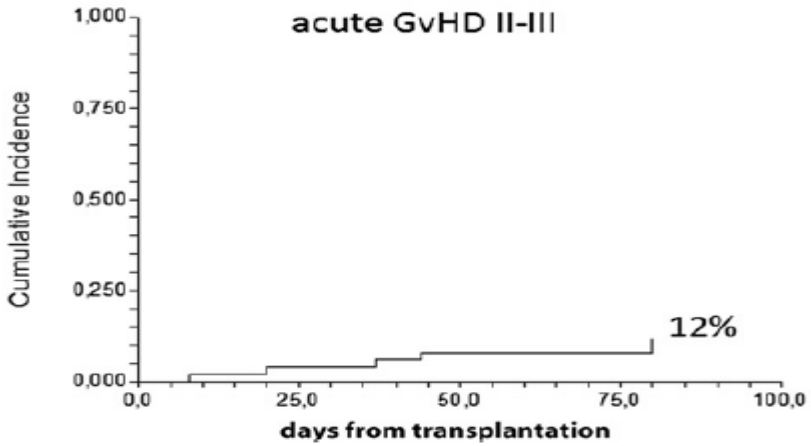
Unmanipulated Haploidentical Bone Marrow Transplantation and Posttransplantation Cyclophosphamide for Hematologic Malignancies after Myeloablative Conditioning

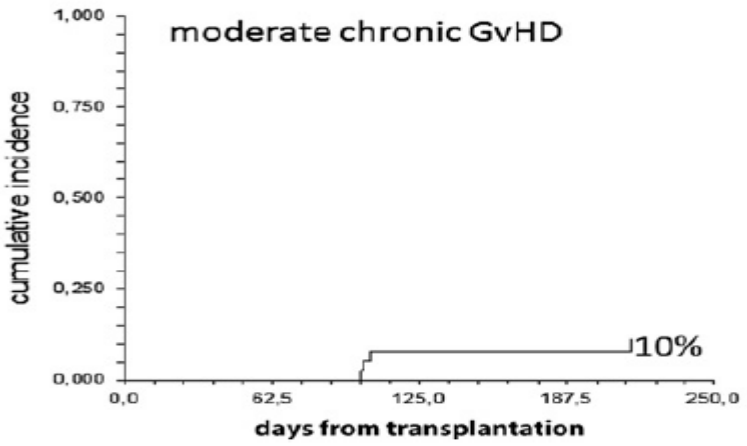
ASBMT American Society for Blood and Marrow Transplantation

Biol Blood Marrow Transplant 19 (2013) 117–122









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

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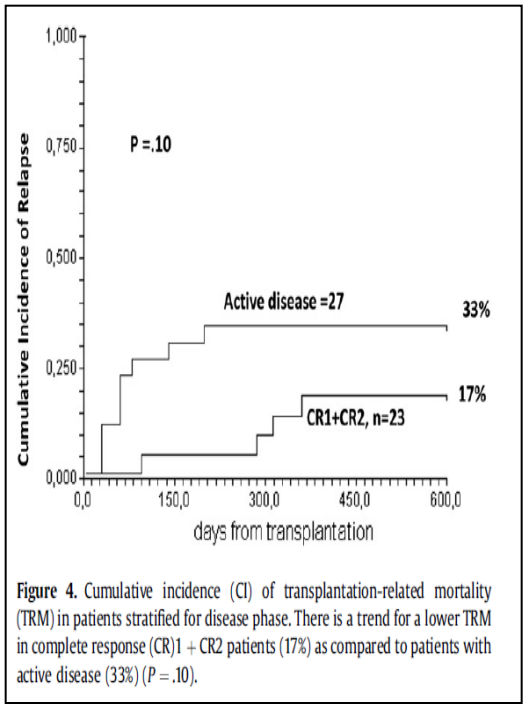

Figure 4. Cumulative incidence (CI) of transplantation-related mortality (TRM) in patients stratified for disease phase. There is a trend for a lower TRM in complete response (CR)1 + CR2 patients (17%) as compared to patients with active disease (33%) ($P = .10$).

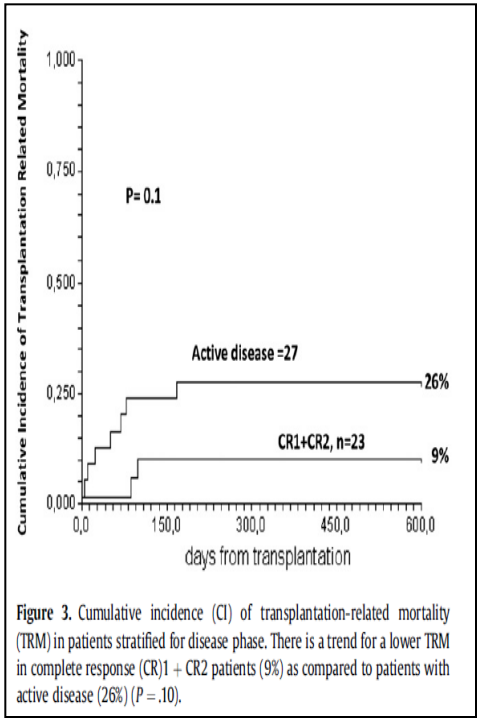

Figure 3. Cumulative incidence (CI) of transplantation-related mortality (TRM) in patients stratified for disease phase. There is a trend for a lower TRM in complete response (CR)1 + CR2 patients (9%) as compared to patients with active disease (26%) ($P = .10$).

Table 3
Clinical Outcome of Patients

Follow-up of surviving patients in days	303 (119-596)
Engraftment	
Day of neutrophil 0.5 × 10^9/L	18 (13-30)
Day of platelet 20 × 10^9/L	23 (14-58)
aGVHD	
Grade 0-I	44 (88%)
Grade II-III	6 (12%)
cGVHD	
No	18 74%
Minimal	6 16%
Moderate	4 10%
Severe	0 0%
Day +100 TRM	n = 8 (16%)
Overall TRM	n = 9 (18%)
Relapse	n = 13 (26%)
Relapse-related death	n = 7 (14%)
Surviving	n = 34 (68%)
Follow-up	333 days (149-623)

aGVHD indicates acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; TRM, transplantation-related mortality.

Strategies to Improve Outcome of Haploidentical Transplant

- Selective T cell depletion
  - CD4 or CD8 depletion
  - Insertion of suicide genes into T cells
  - Removal of alloreactive T cells
  - Memory cell depletion
- Harnessing beneficial effect of NK/KIR ligand mismatched alloreactivity (GVL without GVHD)
- Prophylatic /Pre-emptive DLI/ NK Infusion
- Cotransplantation of Mesenchymal Stem Cells
- Addition of Regulatory T cells
- Adoptive Immunotherapy and Vaccination

Conclusion (I)

1. Haploidentical SCT provides opportunity for patients to benefit from HSCT when 6/6 MSD is not available
2. Presents easier logistic and practical alternative to MUD transplant
3. Recent advances with effective TCD and RIC significantly low early TRM and GVHD, & enhance the therapeutic benefits of haploSCT

Conclusion (II)

New directions in selective allodepletion, adoptive immunotherapy (Tregs, NK, MSCs), improvement in DLI may eliminate risk of severe GVHD, while preserving anti-tumor effect and promote rapid immune reconstitution.

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