Haploidentical Stem cell Transplantation

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MDPB-R Educational Course
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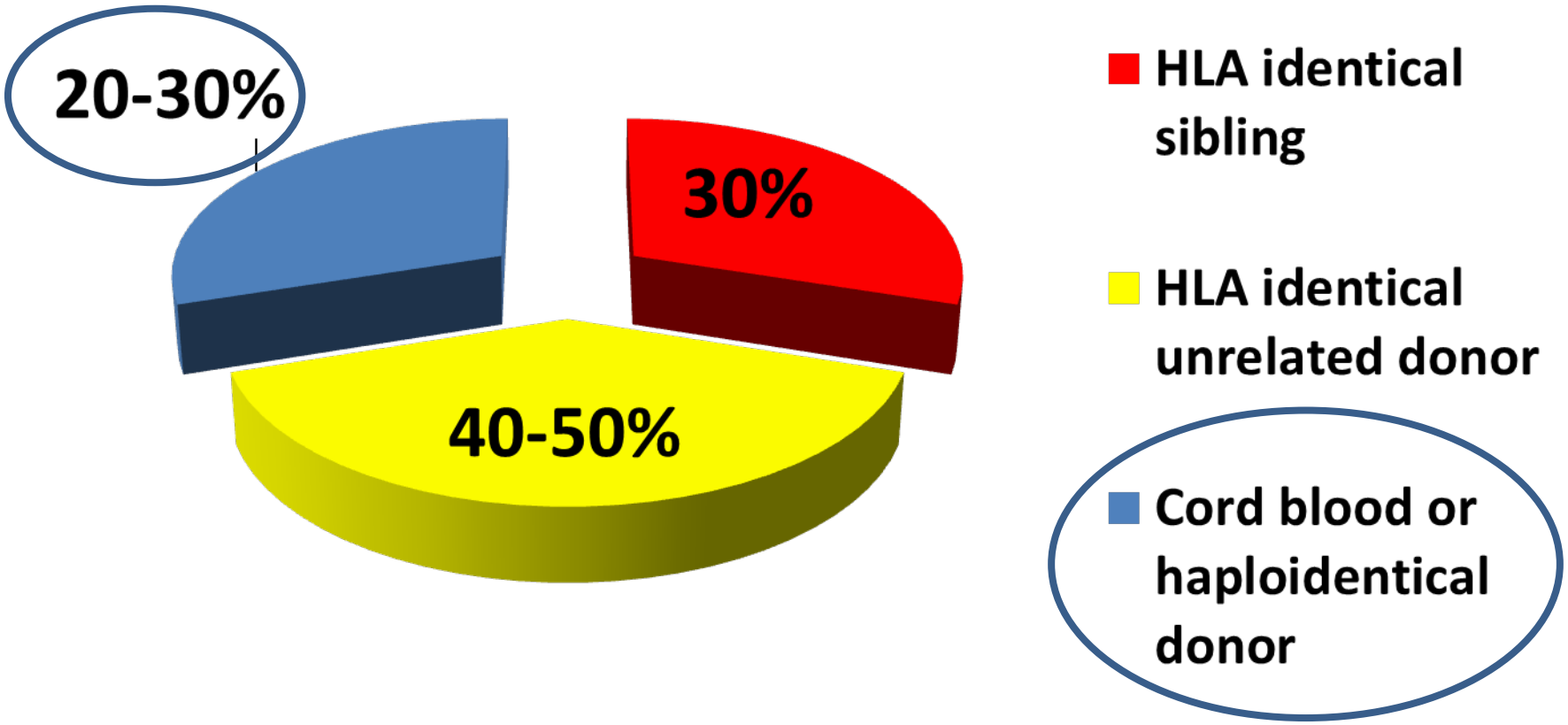
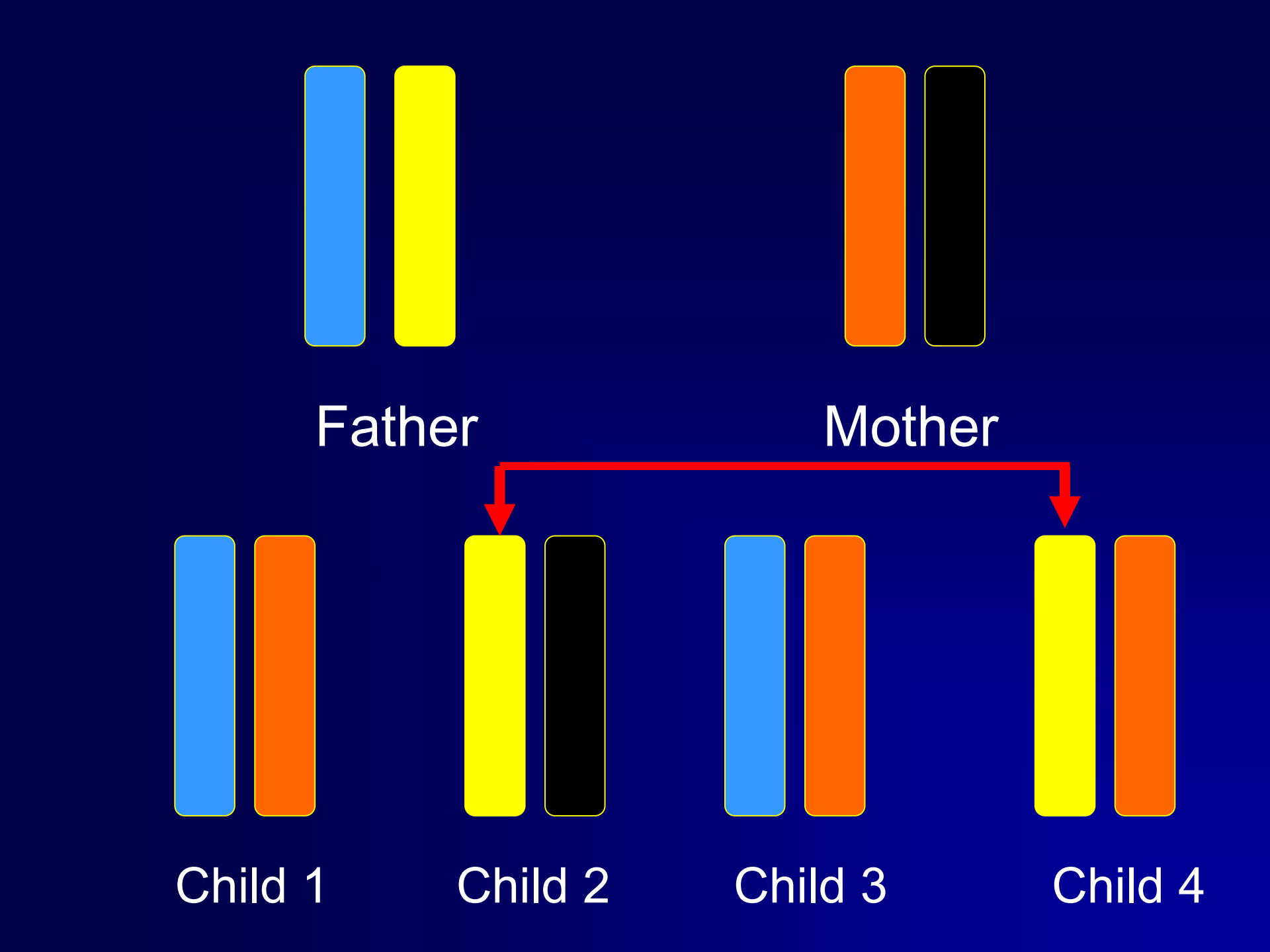
Background

- Allogeneic SCT is the only curative option for
  - High risk AML, ALL
  - Resistant acute leukemia
  - AML, AML in second or later CR
- Ideal donor is a HLA identical sibling
- Only 30 % of patients have a HLA identical sibling

Alternative donors




Father
Mother
Child 1
Child 2
Child 3
Child 4

Haploidentical stem cell transplant

- **Advantage**
  - Nearly all patients have haploidentical donor
  - Immediate donor availability
  - Choice between multiple donors
  - Control of graft composition
  - Cellular therapy (DLI) or second transplant possible
- **Disadvantages (T cell depleted haplo)**
  - Very slow recovery of T cell immunity
  - High risk of opportunistic infections

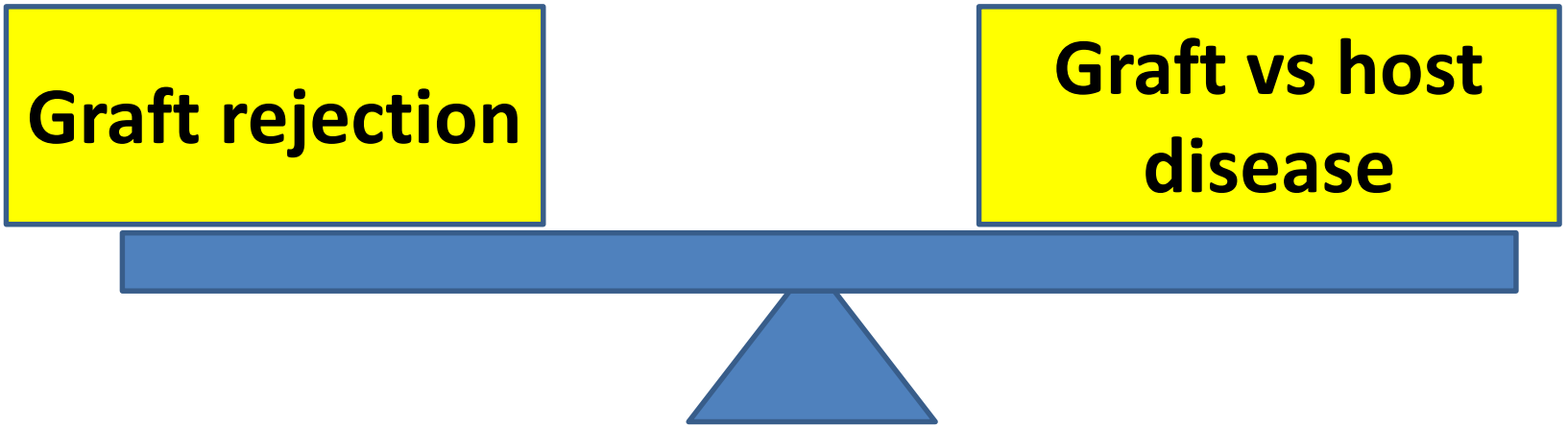
Pioneers of haploidentical SCT

Prof Franco Aversa

Prof Massimo Martelli

Principles of haplotransplantation

Experience of Perugia

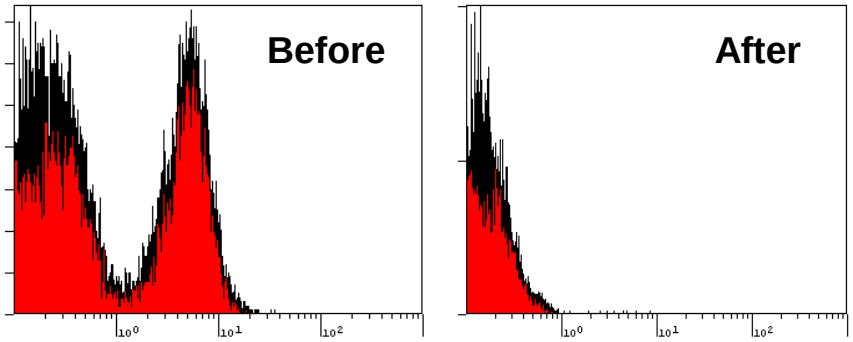


- Megadosis CD34 cells
- Conditioning with ATG/fludarabine/TBI
- T celdepletion log 4.5 by Clinimacs
- No posttransplant immune suppression

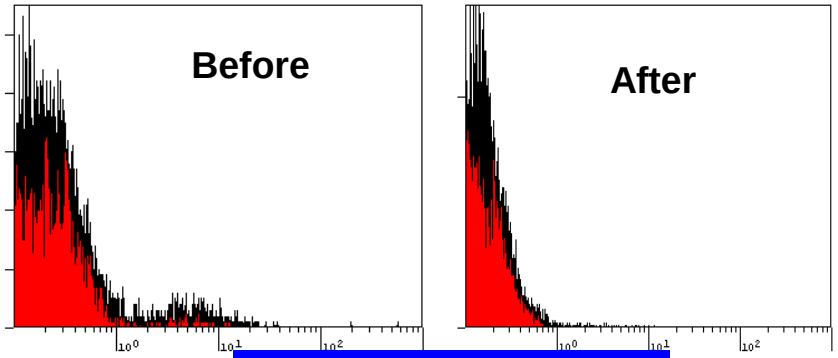
ONE-STEP GRAFT PROCESSING (January 1999 →)

Fully automated
One step procedure
3 hours to finish
Closed system

T and B cell depletion

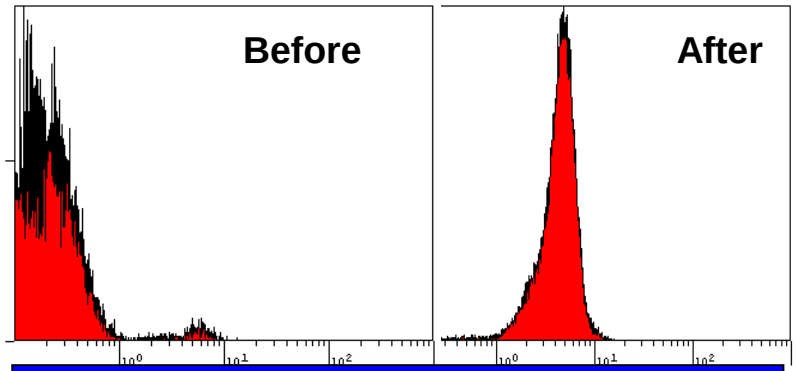


CD3 log depletion 4.5*



CD20 log depletion 3.2*

CD34⁺ cell purity and recovery



Purity	95%
Recovery	78% (range 45-146)

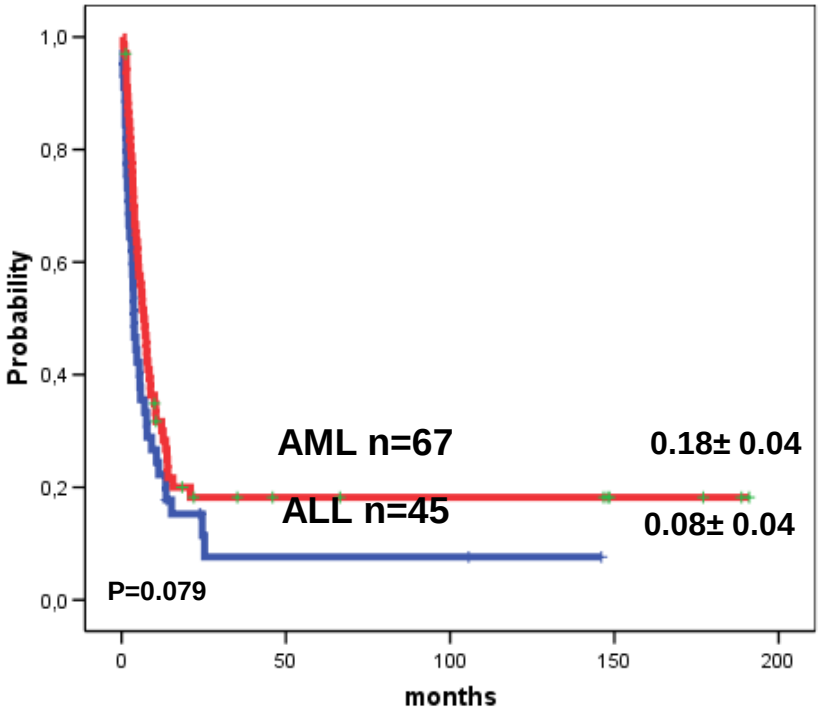
Median infused cell doses/Kg recipient b.w.

CD34⁺	12.8 x 10^6 (range 3.4 - 37)
CD3⁺	1.0 x 10^4 (range 0.1 - 3.0)
CD20⁺	4.1 x 10^4 (range 2.8 – 7.8)

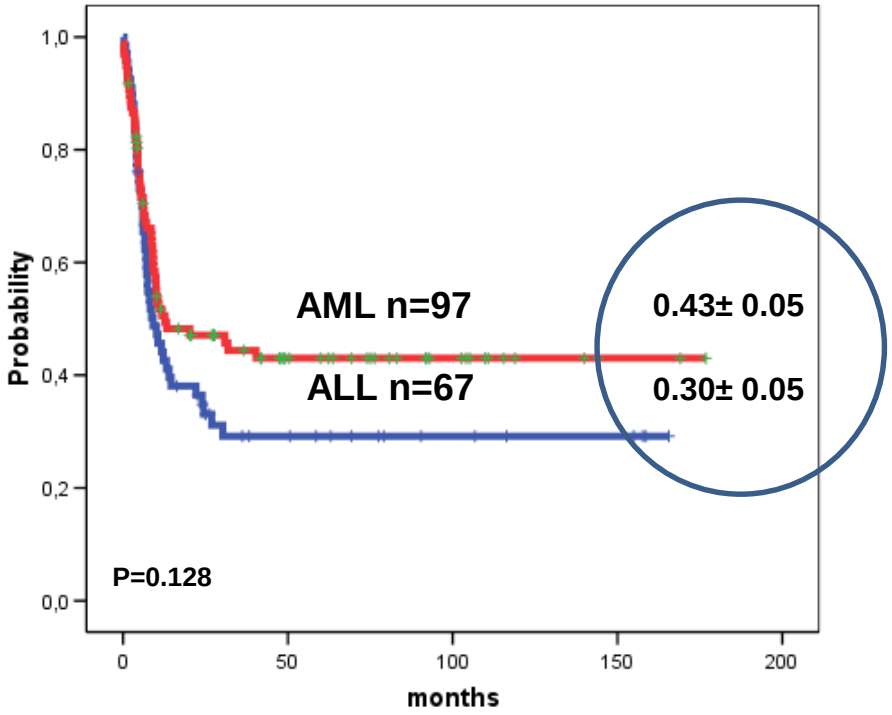
* (median of > 700 procedures in 196 pts)

Perugia: Event-free Survival

All Relapses (n=112)



All CR (n=164)

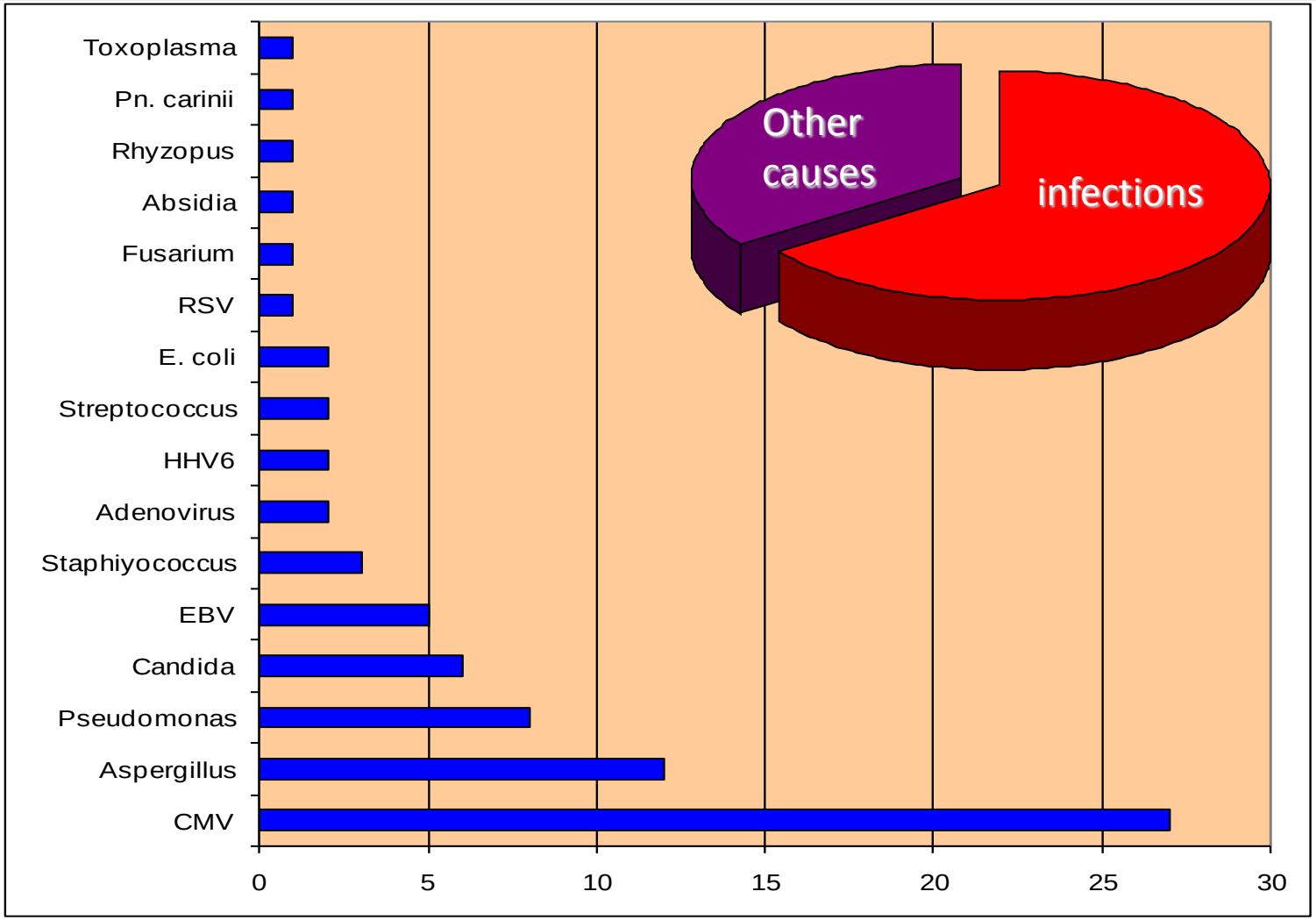


Median age < 35 jr

Non relapse mortality 42 %

Non-Relapse Mortality

118/276 (42.7%)



CMV Serology

D/R

N/P= 12

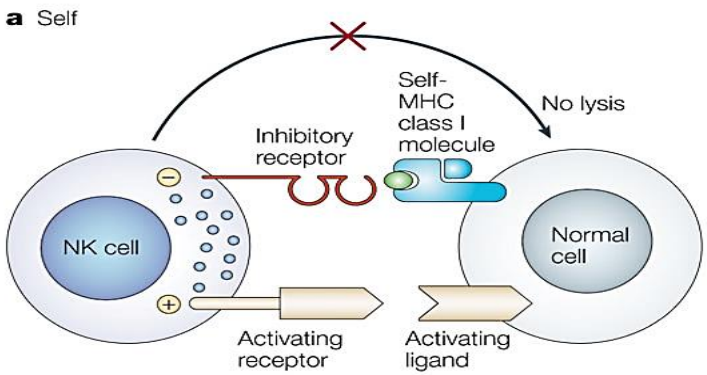
P/P= 219

P/N= 17

N/N= 18

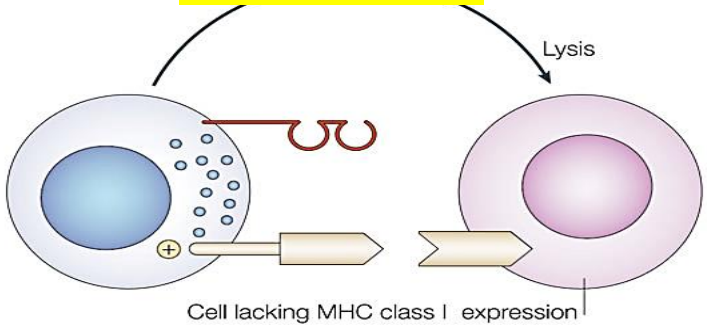
NK cells are important players in the outcome of haploidentical stem cell transplantation especially if T cell depletion techniques are used

NK cell biology



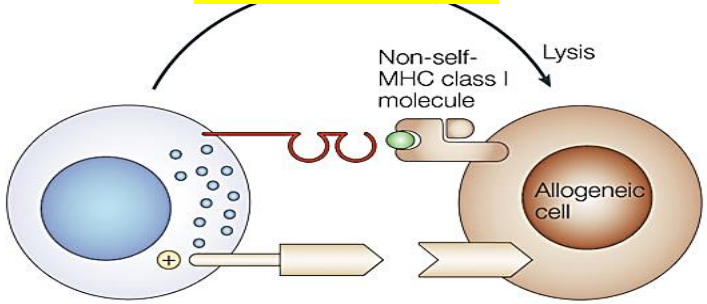
b Missing self

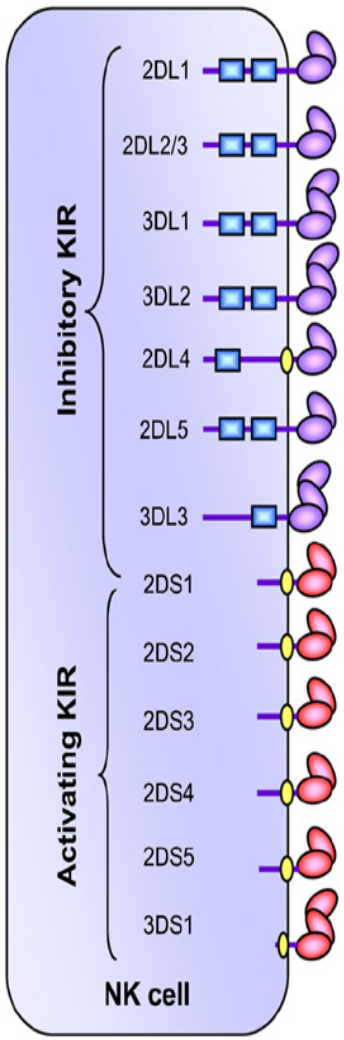
Licence to kill



c Non-self

Licence to kill

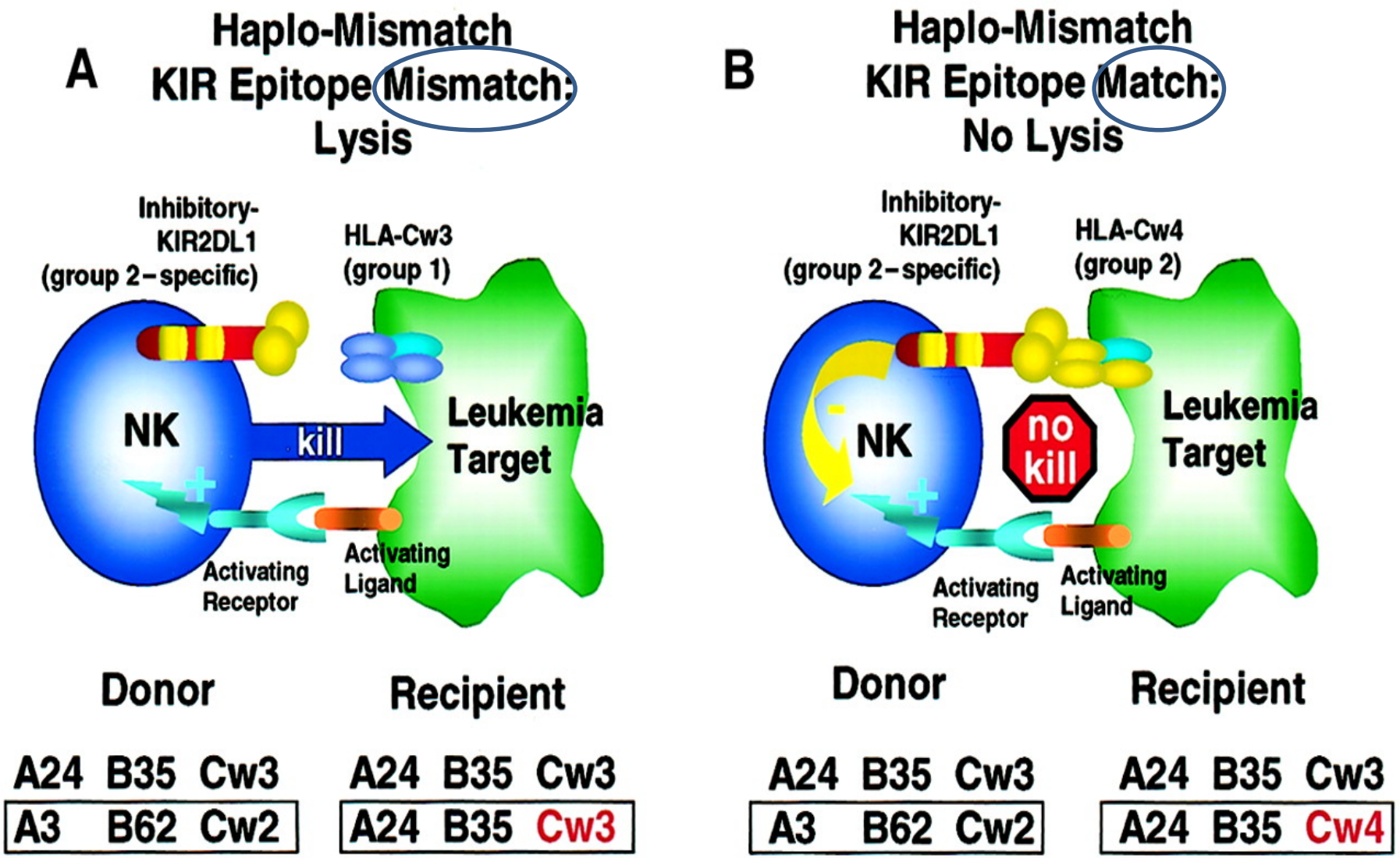




Number of protein variants	HLA class I ligand
24	HLA-C group-2
11/17	HLA-C group-1, B46, B73, some HLA-C group-2
58	HLA-Bw4
61	HLA-A3, A11 (peptide dependent)
22	HLA-G
17	Not known
55	Not known
7	HLA-C group-2
8	Not known
5	Not known
13	HLA-A11 and subsets of HLA-C
11	Not known
12	Not known

Nature Reviews | Immunology

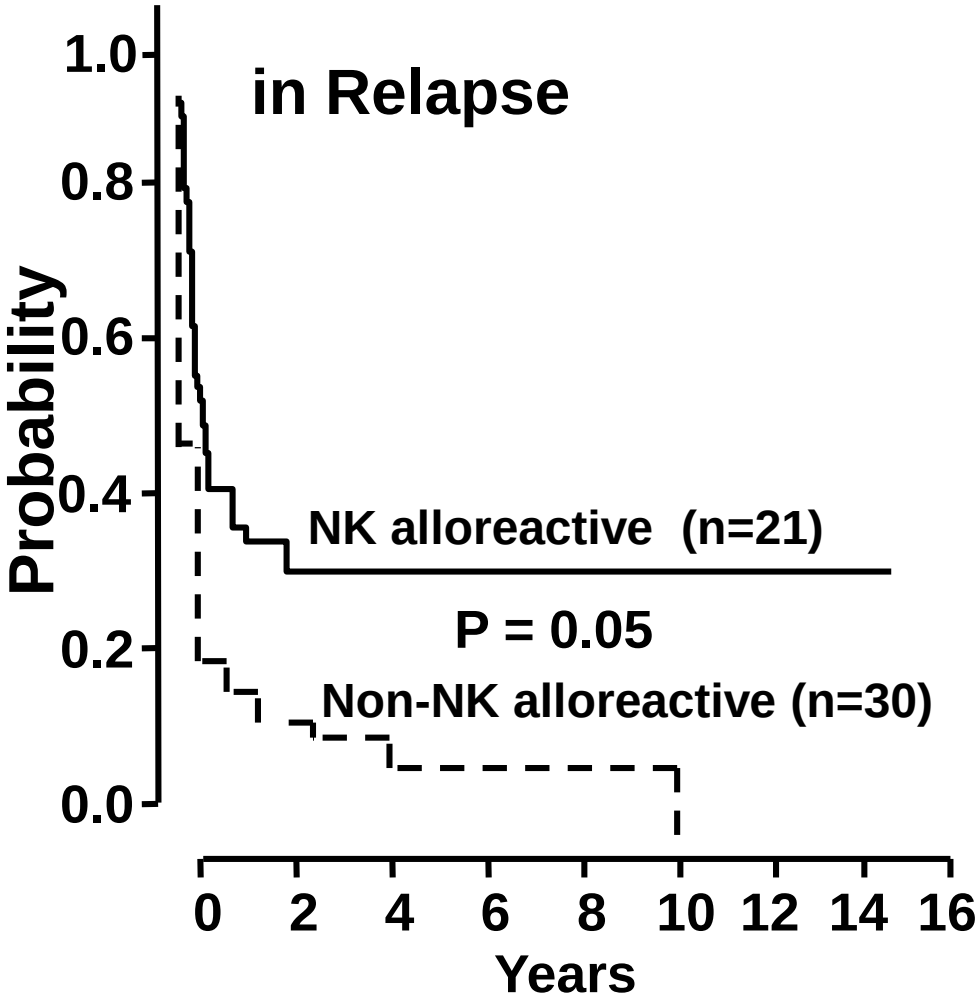
Group 1 HLA-C Alleles (Ser77, Asn80)	Group 2 HLA-C Alleles (Asn77, Lys80)	HLA-Bw4 Alleles
Cw1 (all)	Cw2 (all)	B5 (all)
Cw3 (all except C*0307, C*0310, C*0315)	C*0307	B13 (all)
Cw7 (all except C*0707, C*0709)	C*0315	B17 (all)
Cw8 (all)	Cw4 (all)	B27 (all)
Cw12 (all except C*1205, C*12041, C*12042)	Cw5 (all)	B37 (all)
Cw13 (all)	Cw6 (all)	B38 (all)
Cw14 (all except C*1404)	C*0707	B44 (all)
C*1507	C*0709	B47 (all)
Cw16 (all except C*1602)	C*1205	B49 (all)
	C*12041	B51 (all)
	C*12042	B52 (all)
	Cw15 (all except C*1507)	B53 (all)
	C*1602	B57 (all)
	Cw17 (all)	B58 (all)
	Cw18 (all)	B59 (all)
		B63 (all)
		B77 (all)
		B*1513
		B*1516
		B*1517
		B*1523
		B*1524

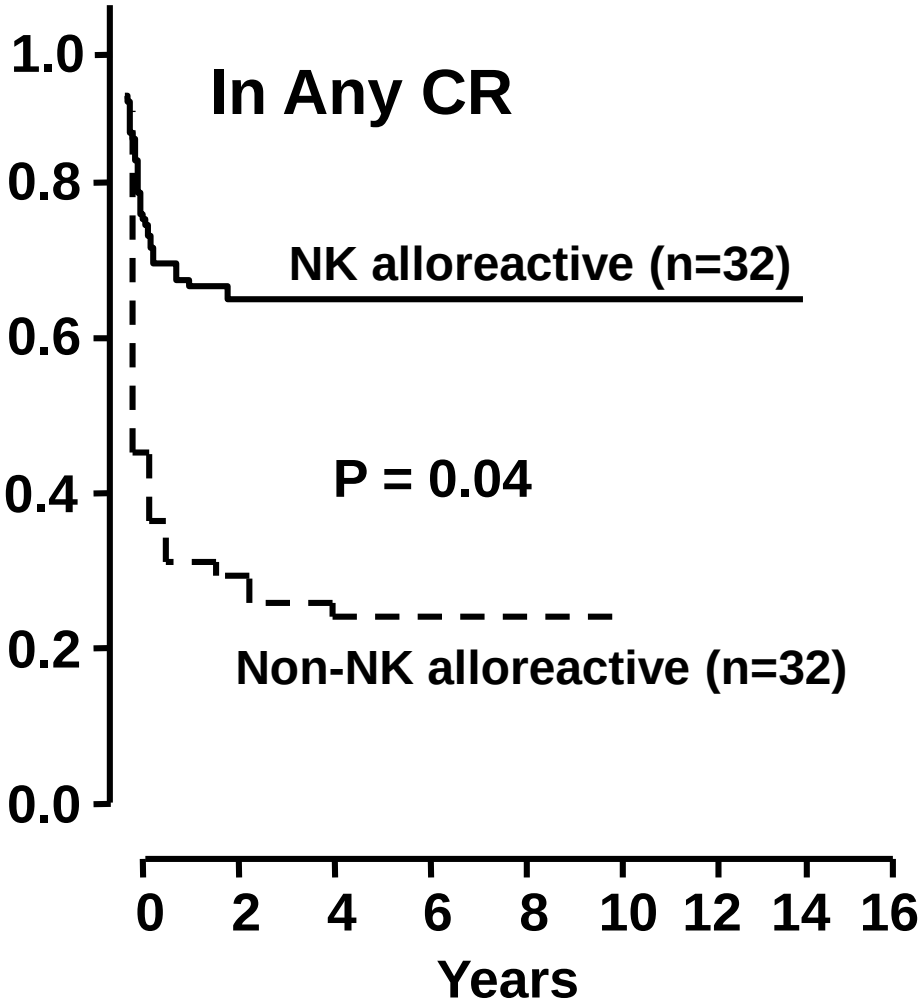


KIR = Killer Immunoglobulin like Receptor

EFS by NK alloreactivity and disease status

115 AML (from 1993 through 2008)





Ruggeri et al., Science 2002; Blood 2007; Stern et al., Blood 2008

Organisation of KIR locus on chrom 19q

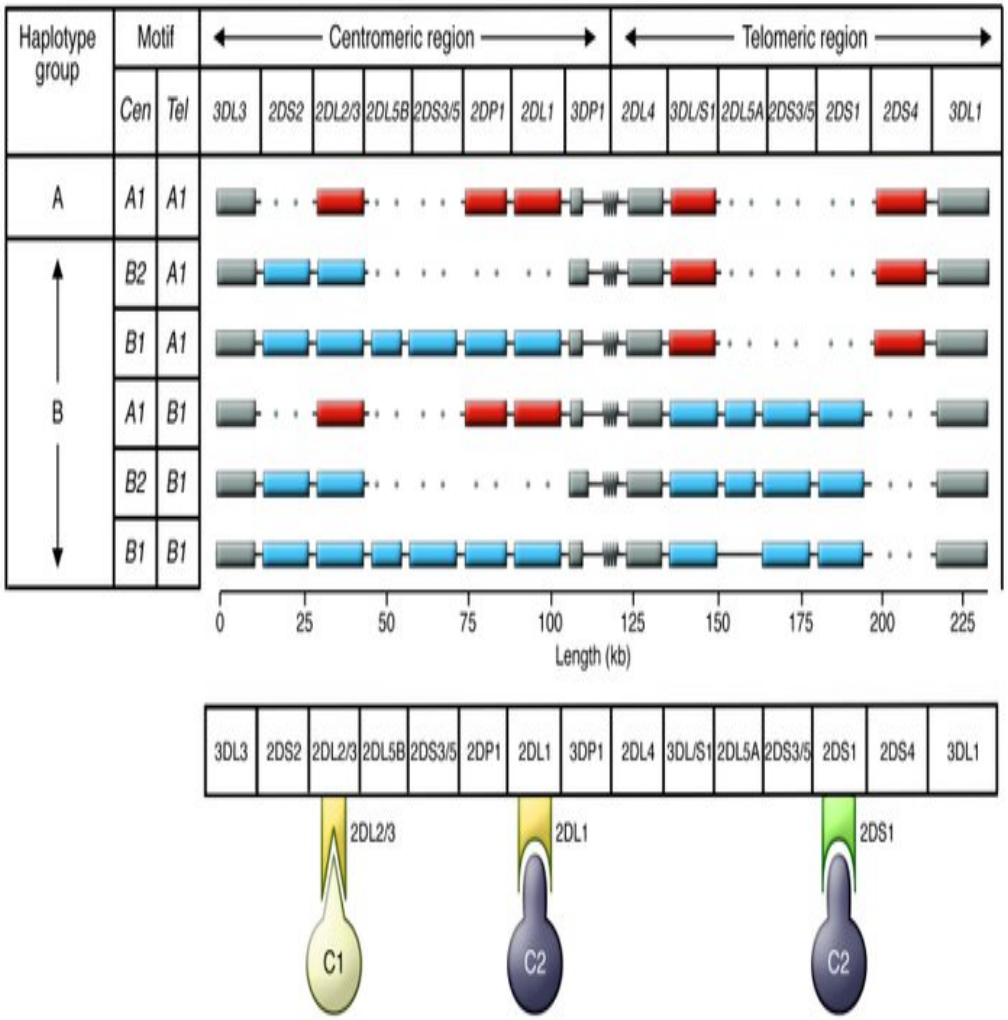


Table 1. Inhibitory and activating genes of KIR A and KIR B haplotypes

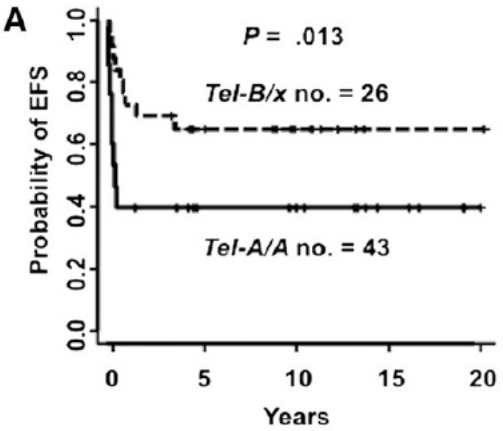
KIR	Inhibitory genes	Activating genes	Inhibitory / activating genes
A Haplotype	KIR3DL3 KIR2DL3 KIR2DL1 KIR3DL1 KIR3DL2	KIR2DS4	KIR2DL4
B Haplotype	KIR2DL2 KIR2DL5	KIR2DS2 KIR2DS3 KIR2DS5 KIR2DS1 KIR3DS1	-

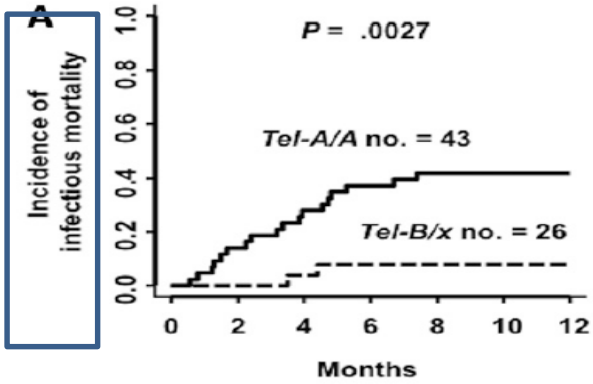
Red = inhibitory KIR
Blue = activating KIR

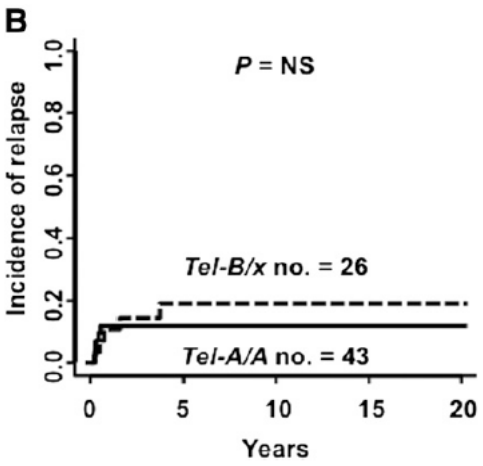
Haploidentical hematopoietic transplantation from KIR ligand–mismatched donors with activating KIRs reduces nonrelapse mortality

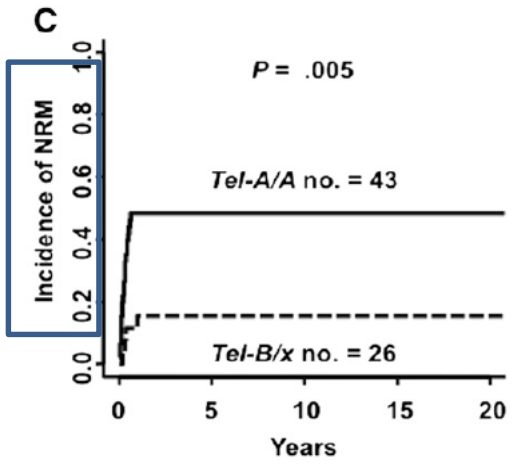
Blood 2015

Antonella Mancusi,[1] Loredana Ruggeri,[1] Elena Urbani,[1] Antonio Pierini,[1] Maria Speranza Massei,[1] Alessandra Carotti,[1] Adelmo Terenzi,[1] Franca Falzetti,[1] Antonella Tosti,[1] Fabiana Topini,[1] Silvia Bozza,[2] Luigina Romani,[2] Rita Tognellini,[3] Martin Stern,[4] Franco Aversa,[5] Massimo F. Martelli,[1] and Andrea Velardi[1]

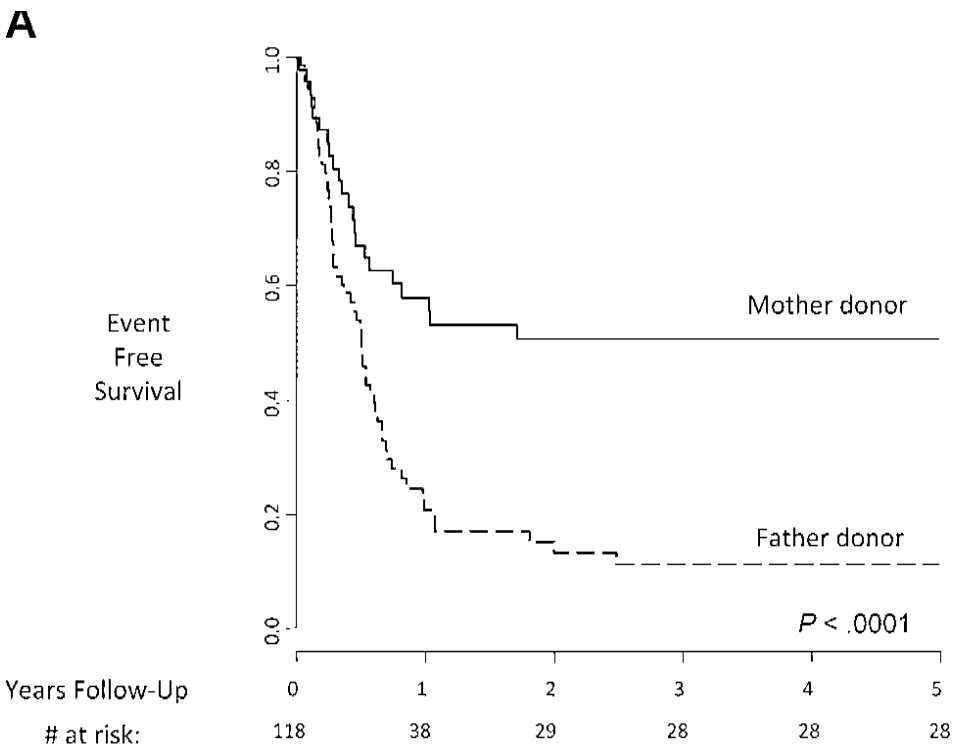








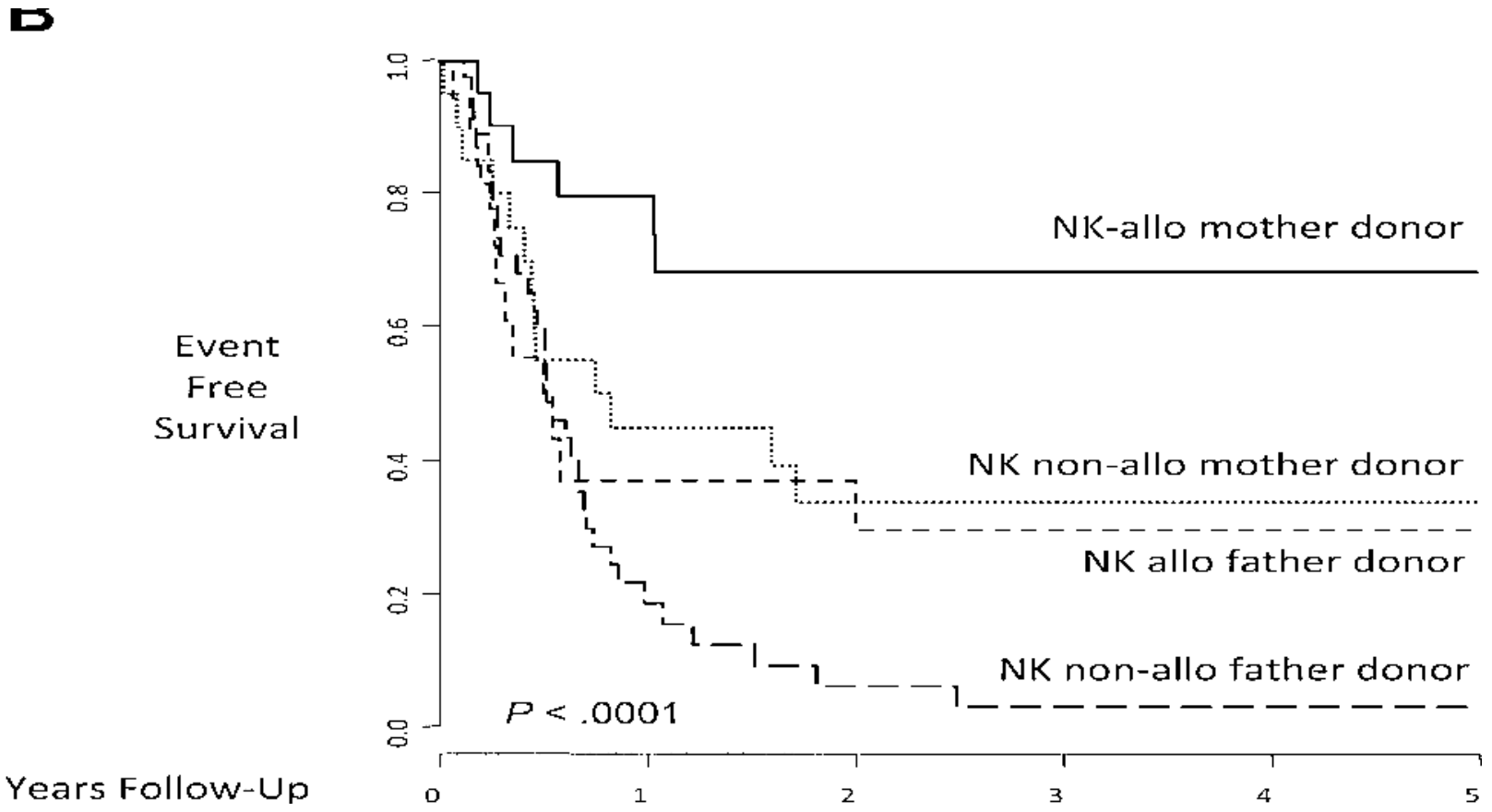
Event-free survival of patients receiving parental donor haploidentical HSCT for acute leukemia.



Less relapse due to immunisation of mother against paternal HLA-antigens on the fetal cells

Stern M et al. Blood 2008;112:2990-2995

Event-free survival of patients receiving parental donor haploidentical HSCT for acute leukemia.



Stern M et al. Blood 2008;112:2990-2995

Donor selection for T cell depleted haplotransplant (Perugia experience)

- CMV negative donor/receptor
- CMV positive donor/receptor
- NK alloreactive donors: KIR/KIR-ligand mismatch
- Haplotype B donors
- Mother > father

Experience AZ Sint-Jan Brugge

- 4/2004- 9/2011
- 51 transplants in 45 patients
  - 4 patients received 2 or 3 transplants for graft rejection or relapse
- Perugia approach
- Single centre (AZ Sint-Jan Brugge)

WAT BATEN KAARS EN BRIL

Management in spreekwoorden
Wat je op school niet leert

HUGO VANDAMME

Roularta Books

WAT BATEN KAARS EN BRIL HUGO VANDAMME


Cheque
€ 10.000
Tienduizend euro
GESCHONKEN AAN:
Wetenschappelijk Fonds Hematologie

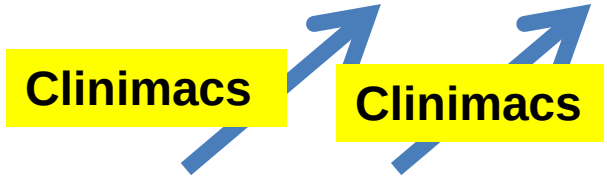
Patient selection criteria

- Any type of haematological malignancy
- Likely to benefit from allotransplantation
- No HLA matched sibling donor
- No 10/10 or 9/10 matched unrelated donor available within 2-3 months
- No search for cord blood performed

Conditioning regimen I

Day-11	Day-7	Day-6	Day-5	Day -4	Day-3	Day-2	Day-1	Day 0	Day+1
TBI 8 Gy	Thiotepa 2 x 5 mg/kg		Fludarabine 40 mg/m2 x 4 ATG-Fresenius 5 mg/kg x 4					SCT 1	SCT 2

Lung shielding 4 Gy

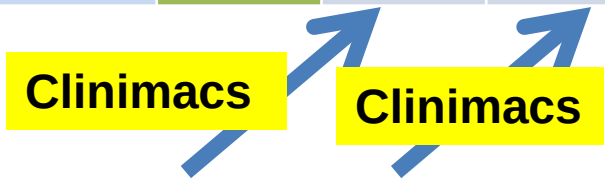


Day 1	Day 2	Day 3	Day 4	Day 5
G SCF 5 mcg/kg bid			Apheresis 1 GCSF 10mcg/kg	Apheresis2

No Cyclosporine or GCSF posttransplant

Conditioning regimen II

Day -9	Day -8	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1
Thiotepa 2 x 5 mg/kg		Fludarabine 40 mg/m2 x 5 ATG-Fresenius 5 mg/kg x 5					Melphalan 100 - 140 mg/m2		SCT 1	SCT 2



Day 1	Day 2	Day 3	Day 4	Day 5
G SCF 5 mcg/kg bid			Apheresis 1 GCSF 10mcg/kg	Apheresis 2

No Cyclosporine or GCSF posttransplant

Posttransplant prophylaxis

- *Cotrimoxazole*
  - 3 tablets per week for 1 year
- *Fluconazole*
  - 2 x 200 mg per day for 3 months
- *Acyclovir*
  - 800 mg per day for 1 year
- Monitoring CMV-PCR, EBV-PCR, Galactomannan :
  - 1-2 x per week for 1 year , no Toxo PCR

Patients

- Age (yrs) median 55 (16-71)
- Sex F/M 19/26
- Donor type

father	3	mother	7
brother	8	sister	3
son	**11**	**daughter**	**10**
cousin	3		

- KIR/KIR-L MM D/R 37/40 transplants
- Conditioning

TBI	8 Gy	15
Mel	100-140	30

Patients: diagnosis

- Previous autoTx: 8/45 (HD 2, DLBCL 1, MCL 1, MM 2, AML 2)
- Diagnosis:
  - Lymphoma/CLL 8 (HD 2, DLBCL 1, MCL 1, NKT 1, CLL 3)
  - Myeloma 2
  - MDS, AML postMDS 12
  - CML 2 (CML, 2nd CP after LB)
  - AML prim refractory 8
  - AML high risk 2 (EVI1 +, MLL +)
  - AML relapse 9
  - ALL relapse 2

33 myeloid malign

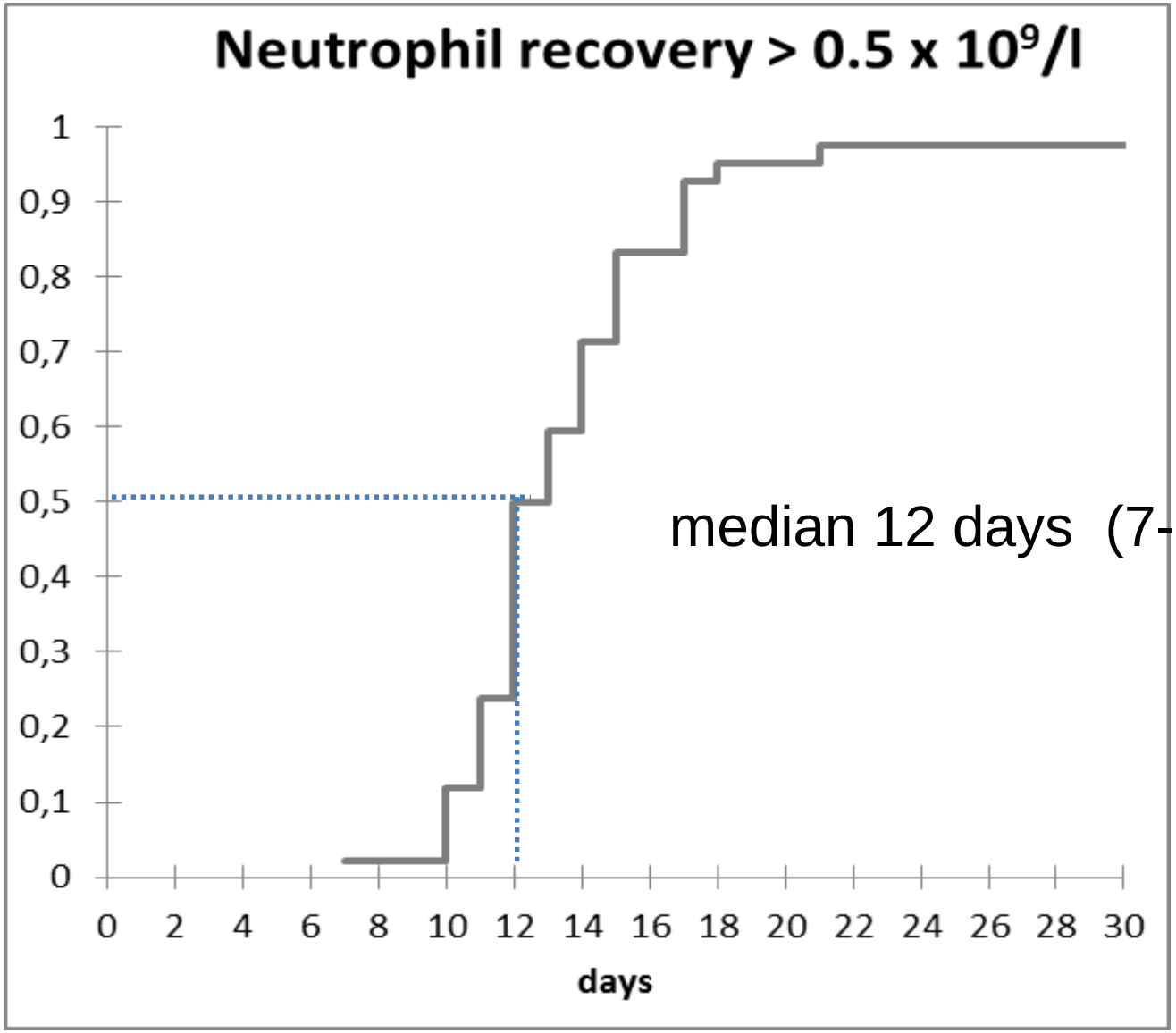
Haploidentical SCT on 2-4-2004 at age of 69 years
Died in complete remission on 16-11-2015

Graft characteristics

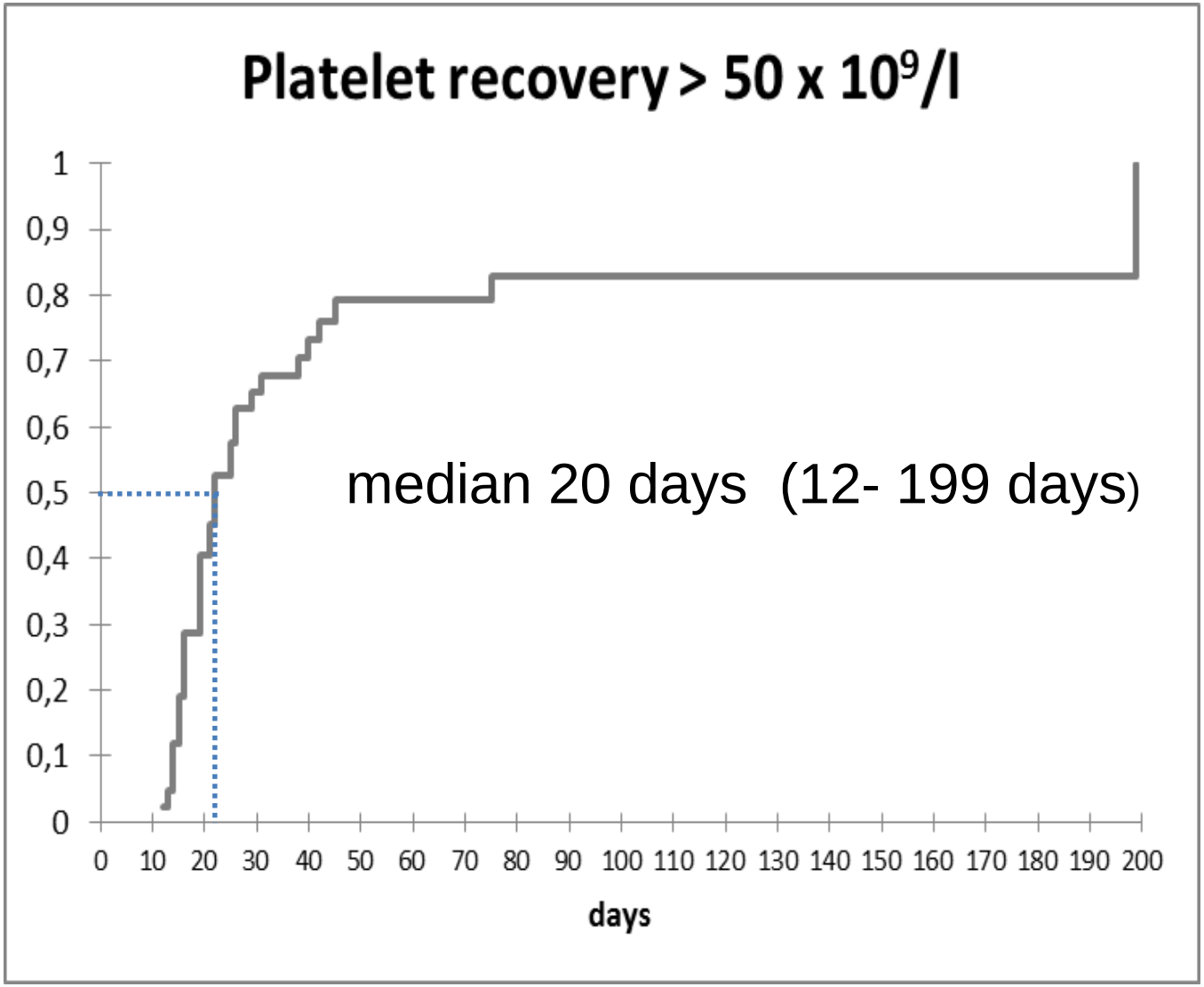
- CD34 infused *(target > 8 x 10^6/kg)*
  - median 9,09 (2,63-16,66)
  - 31/51 transplants > target
- CD3 infused *(target < 5 x 10^4/kg)*
  - median 1,05 (0,15-3,15)
  - 51/51 transplants < target

Engraftment

- *Engraftment :* in 100 %
- *Secondary* graft rejection after 1st Tx
  - **6 / 45 (13 %)**
  - 5/6 had received non TBI regimen,
  - 1/6 HHV6 infection
  - No correlation with number of CD34 infused

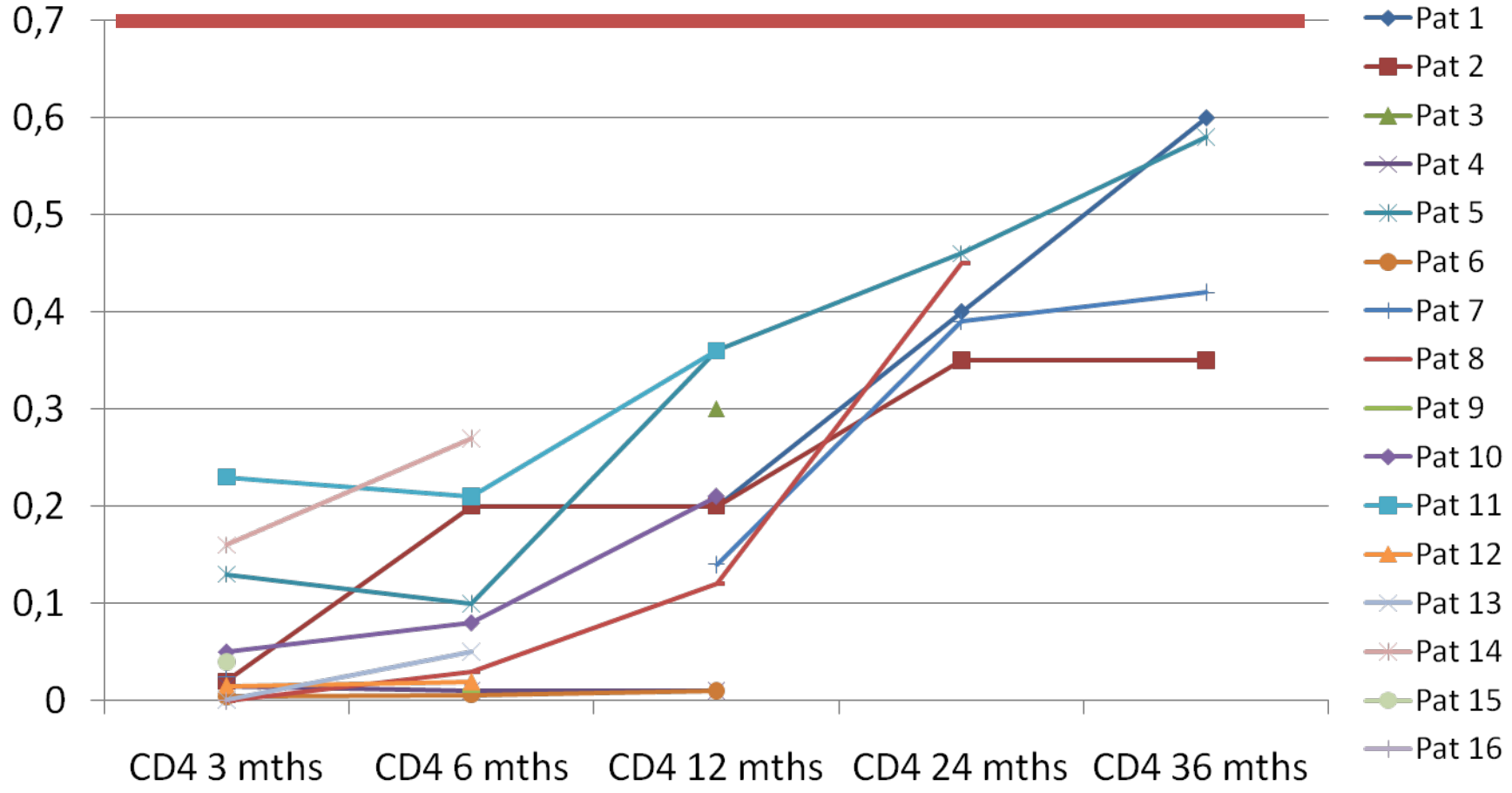


median 12 days (7-21 days)


Platelet recovery > 50 x 10⁹/l
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
days
median 20 days (12- 199 days)

Immune recovery

CD4 cells (in 10^9/l) (normal 0.7-1.4)



Graft versus host disease

- Acute GVHD
  - Before DLI:
    - grade I 5/45
    - **grade II-IV 12/45 = 26 %**
  - After DLI 3/9 (3 grade III-IV)

- Chronic GVHD
  - Limited 0
  - Extensive 3 (1 BOOP after DLI)

Infectious complications

- **Viral**
  - CMV
    - 18 (D) or (R) CMV + , 4 died early > 14 at risk
    - CMV reactivation : **13/14**
    - CMV disease : 4 (despite pre-emptive therapy)
      - 1 CMV retinitis,
      - 3 CMV encephalitis,
      - 1 CMV colitis
    - Resistant CMV :
      - 4 (foscavir 1, ganciclovir 3)
    - 1 death due to CMV encephalitis

Infectious complications

- **Viral**
  - HSV 8/45
    - 5 ACV resistant HSV,
    - 1 HSV pneumonia
  - VZV 8 /45 (after stopping acyclovir)
    - 1 death from VZV encephalitis at d 883
  - EBV 4/45 (3 with LPD),
    - all responded to RTX, 2 to RTX + DLI
  - RSV 1/45 pneumonia
  - Hepatitis E 1/45
  - Adenovirus 2/45 fulminant hepatitis
  - HHV6 1/45 encephalitis

Infectious complications

- **Fungal infections**
  - Aspergillosis **25/45** (15 probable/proven)
    (pulmonary, CNS, disseminated)
  - Penicillium lungs 1
- Disseminated Toxoplasmosis 2/45 (1 on profylaxis)
- Pneumocystis 2/45 (> 2 yrs after SCT)
- Cryptosporidium 1/45
- Clostridium colitis 2/45
- Listeria sepsis/meningitis 1/45
- Mycoplasma 1/45

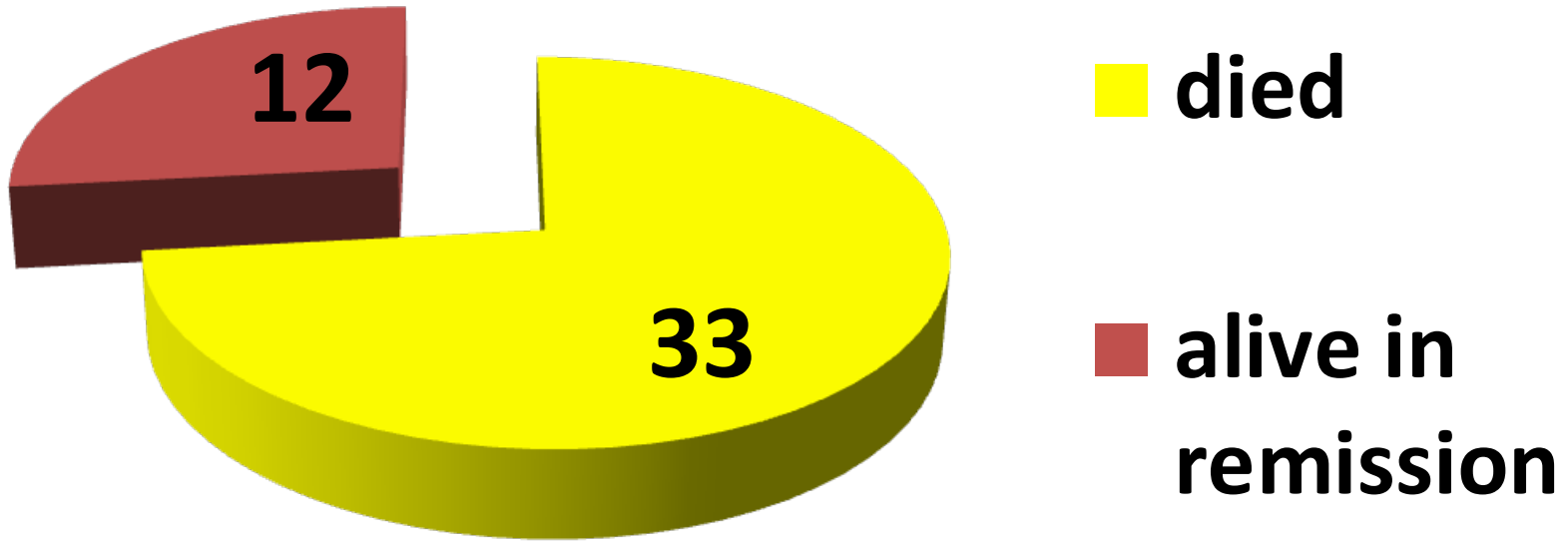
Infectious complications

- **Bacterial**
  - Gram positive
    - Staph aureus pneumonia 2/45 (after > 1 year)
    - CNS spondylodiscitis 1/45
  - Gram negative sepsis/pneumonia 14/45
    - Salmonella 1
    - Enterobacter 2
    - Klebsiella 2
    - E coli 4
    - Pseudomonas 3
    - Stenotrophomonas 2

Non infectious complications

- VOD/TTP 2
- Acute renal failure (dialysis) 5
- Chronic renal failure 2 (1 dialysis)
- **Autoimmune hypothyroidism 3**
- **Pure red cell aplasia 1**
- **Autoimmune trombocytopenia 1**
- **Autoimmune hemolytic anemia 2**
- Epithelioma tongue + CNS mets 1

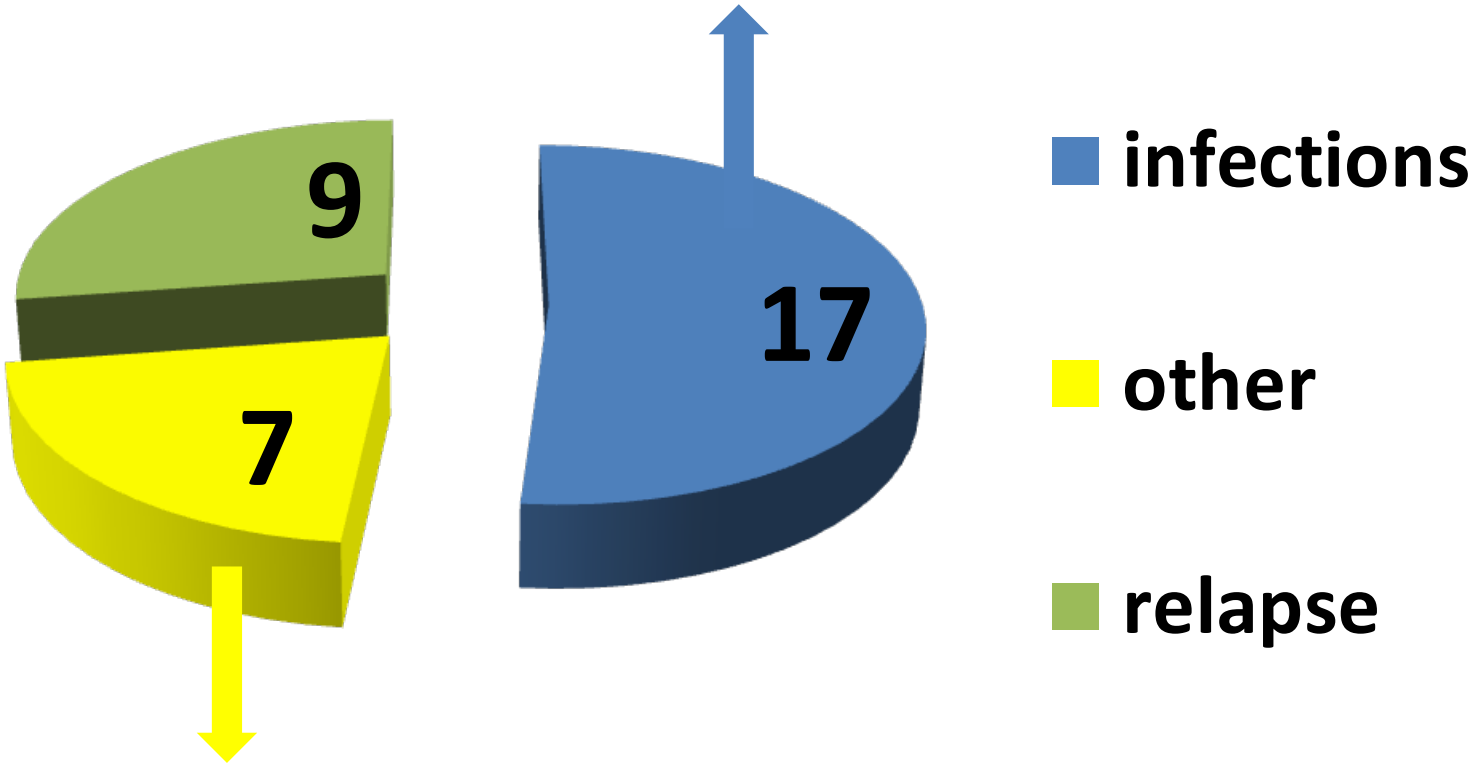
Survival (n = 45)



Median follow up of survivors: 1088 (165-2711) days

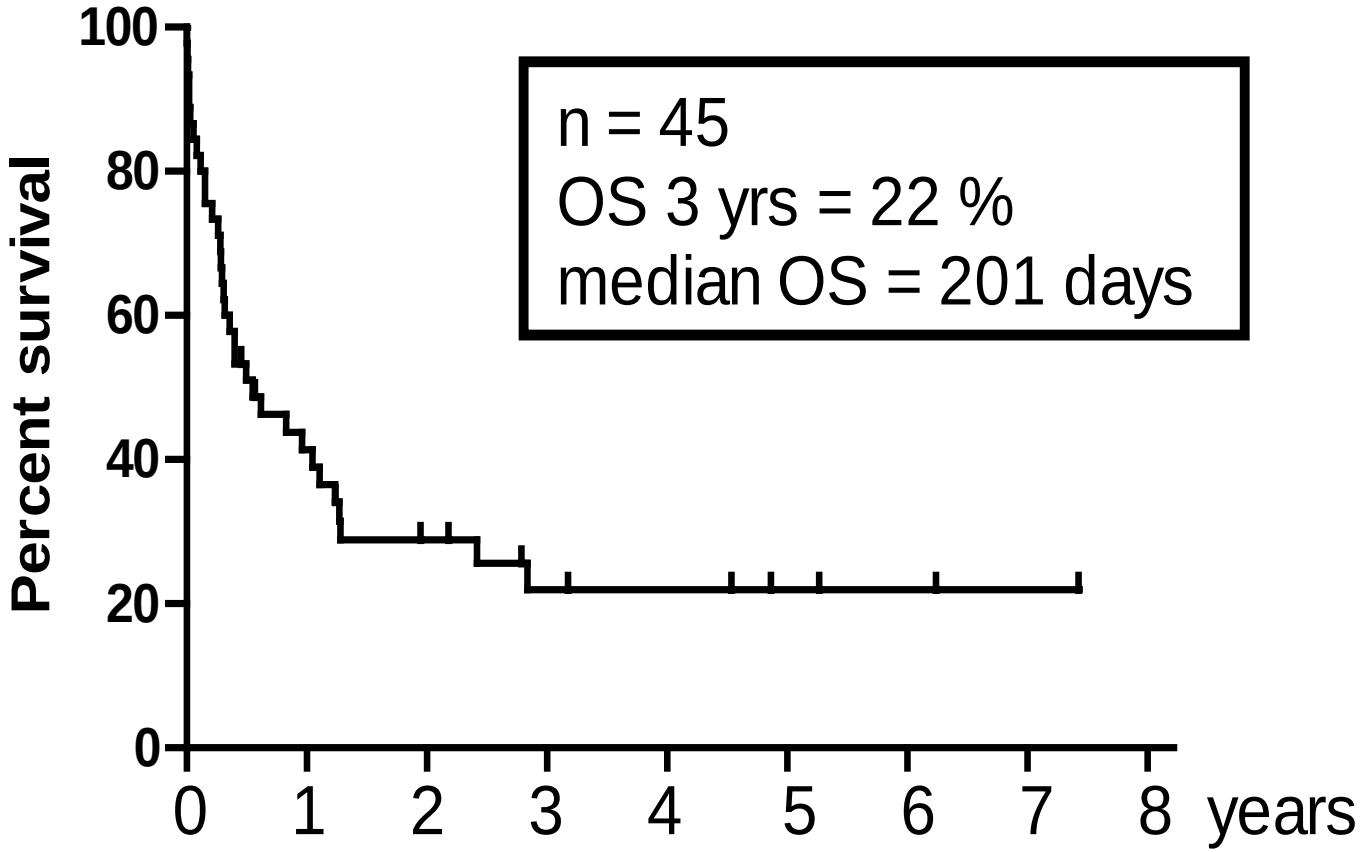
Cause of death (n = 33)

11 aspergillosis (6 < 100 d, 5 > 100 d)
2 pseudomonas pneumonia

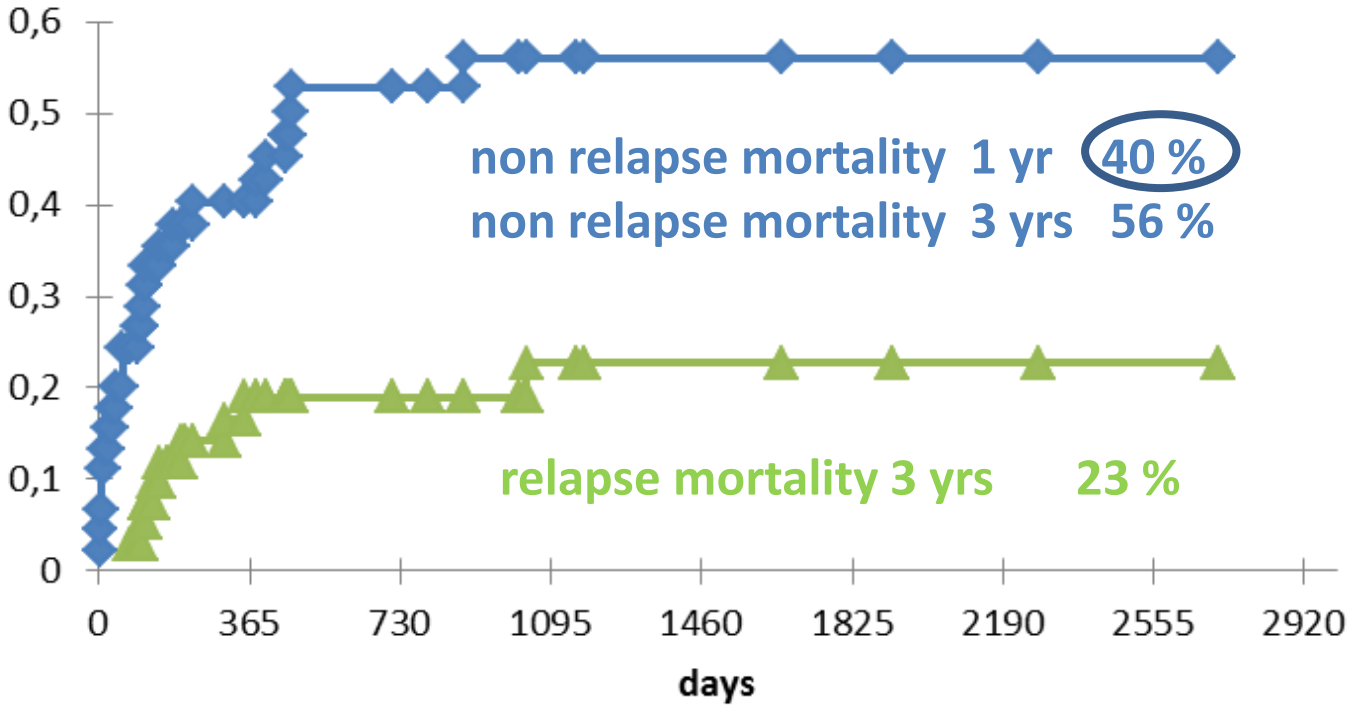


2 VOD/TTP, 1 ARDS, 2 CNS bleeding, 1 pericarditis, 1 BOOP

Survival after haplotransplantation



Cumulative Incidence of relapse and non relapse mortality after haploidentical transplantation



Conclusion (1)

- Haploidentical SCT with Perugia approach is feasible even in a group of elderly patients *for whom there is no alternative therapy*
- Cure rate in this population is 22 %
- Non relapse mortality is very high (40 % at 1yr)
- Engraftment is prompt
- Recovery of T cell immunity is very slow

Conclusions (2)

- High risk of severe GVHD (25%) despite CD34 selection (age effect ?)
- High risk of autoimmune complications
- 70% of non relapse mortality is caused by infections, most commonly aspergillosis
- *Aspergillosis* occurred in 50 % of pts
- *CMV infection* occurred in nearly 100 % of pts at risk (donor or receptor CMV +) and may be very difficult to eradicate
- *Late* opportunistic infections are common and are a source of late mortality

New strategies for haploidentical transplantation

Focus on strategies *that improve immune reconstitution without causing GVHD*

1. T cell depleted haplo
   - New techniques of T cell depletion

     Ex: negative CD3/CD19 selection
   - CD34 selection + T cell add back

     Ex: Treg, HSV-TK gene modified T cells, photodepleted T cells
2. T cell replete haplo
   - Posttransplant cyclophosphamide
   - Posttransplant rapamycin
   - PB + GSCF primed BM

New techniques of T cell depletion

- **Negative CD3/C19 depletion by CliniMacs**
  - NK cells and graft facilitating cells remain in graft
  - T cells 10-fold higher than with CD34 selection
  - Federmann, Haematologica 2012
    - 61 adults, Flu-Mel-TT-OKT3
    - **Ac GVHD higher** than CD34 selected, **still delayed IR**
- **Negative depletion of CD19/Tαβ by Clinimacs**
  - T cell depletion comparable to CD34 selection (log 4.5)
  - Enrichment of **NK/ T γδ cells** (innate T cells that protect against infection / relapse and do not cause GVHD)
  - Handgretinger pioneered in pediatric pts
    - Low GVHD, **very rapid IR**
  - Aversa: unpublished results in adults:
    - Same experience

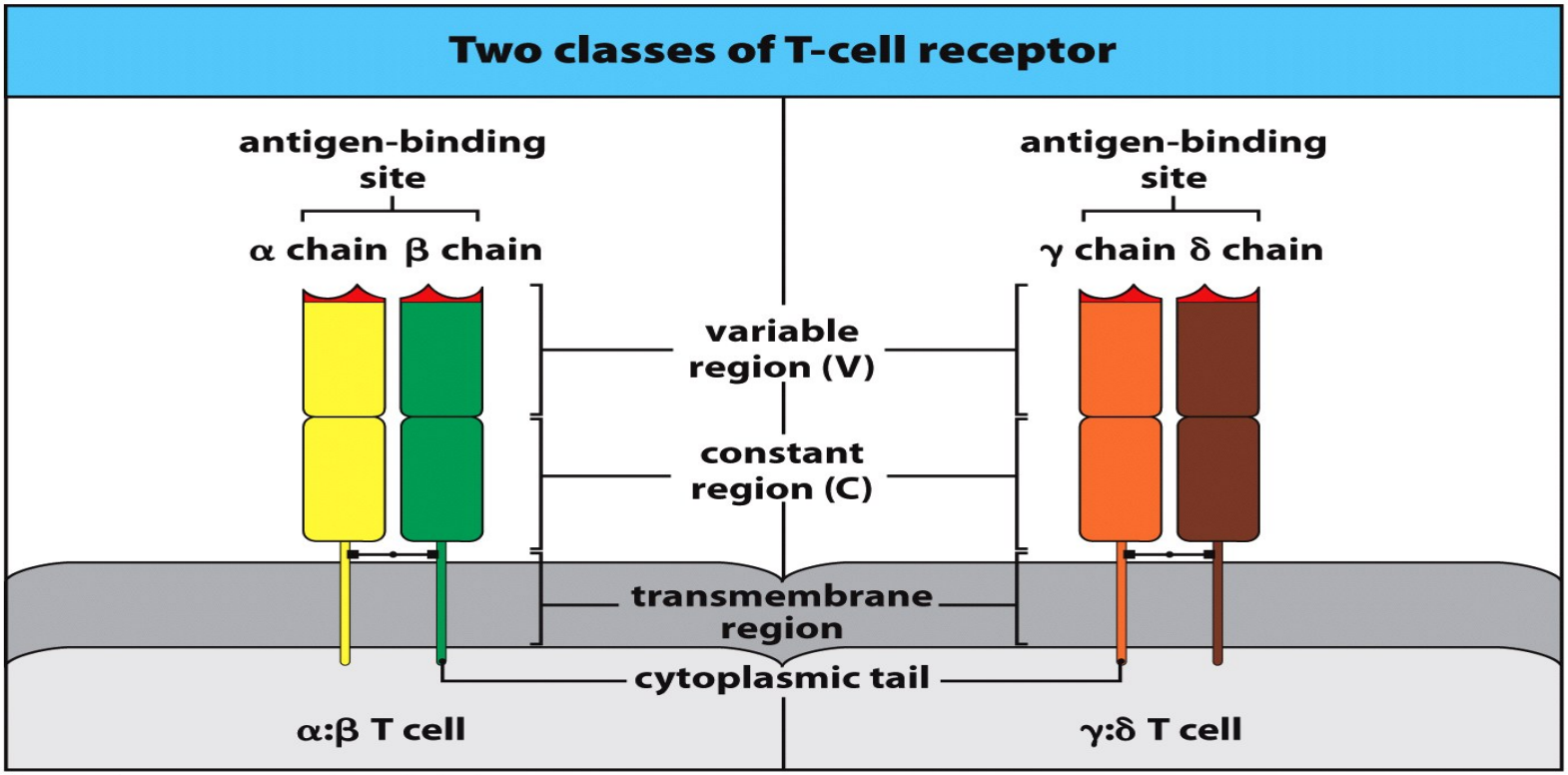


Figure 5.7 The Immune System, 3ed. (© Garland Science 2009)

γδ T cells:

small subset of T cells (< 10%)

more prevalent in gut mucosa

not MHC restricted , recognize proteins without MHC molecules

role in innate immunity (first line defense)

role in protection against certain viral and bacterial infections

protective against relapse

CD34 selection and T cell add back

- **Infusion of regulatory + conventional T cells**
  - Perugia (Di Ianni)
- **Infusion of allodepleted T cells**
  - CD25 selection
  - Photodepletion (Kiadis)
- **Infusion of TK gene modified T cells** (Milan)

What are regulatory T lymphocytes ?

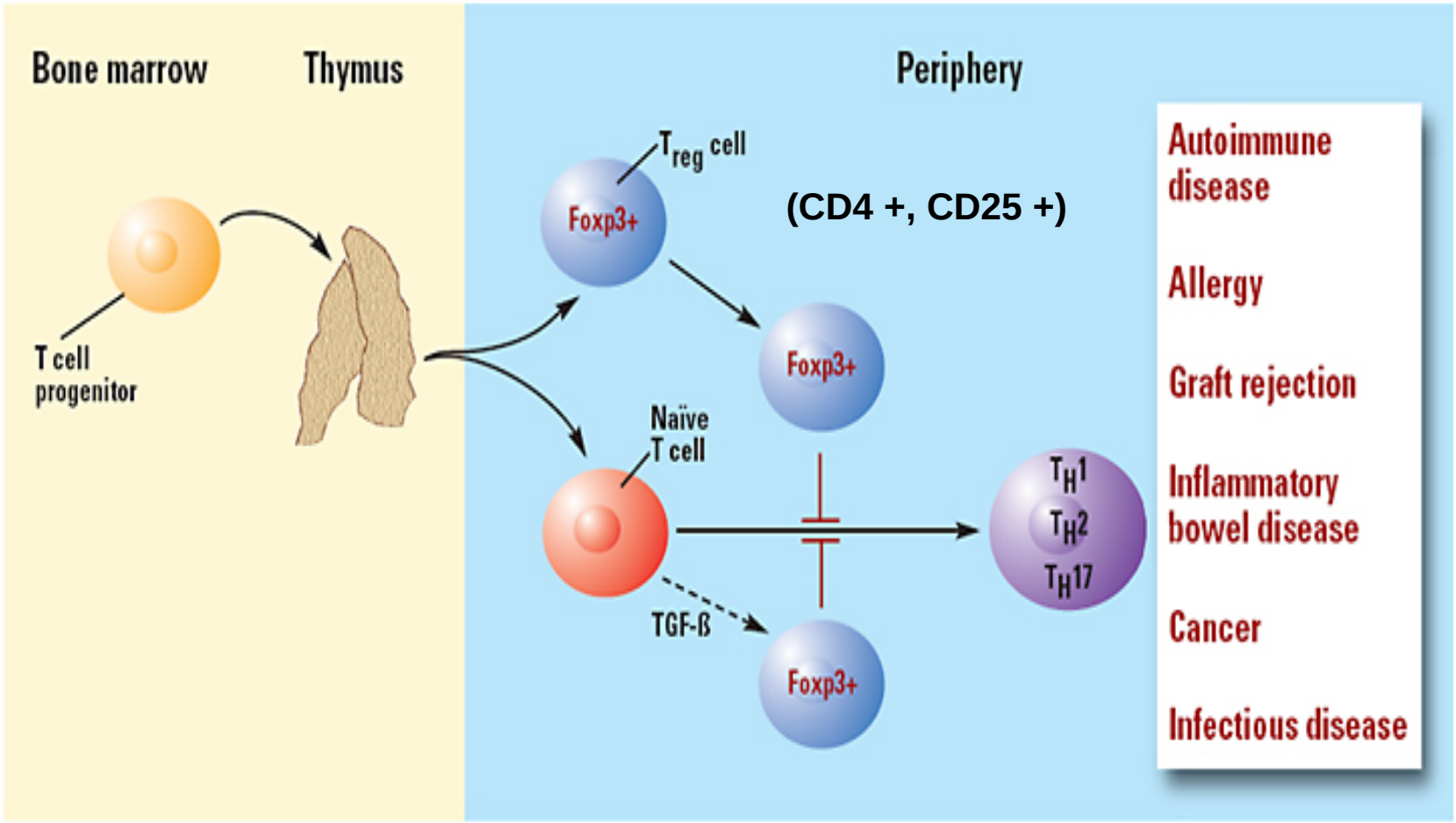
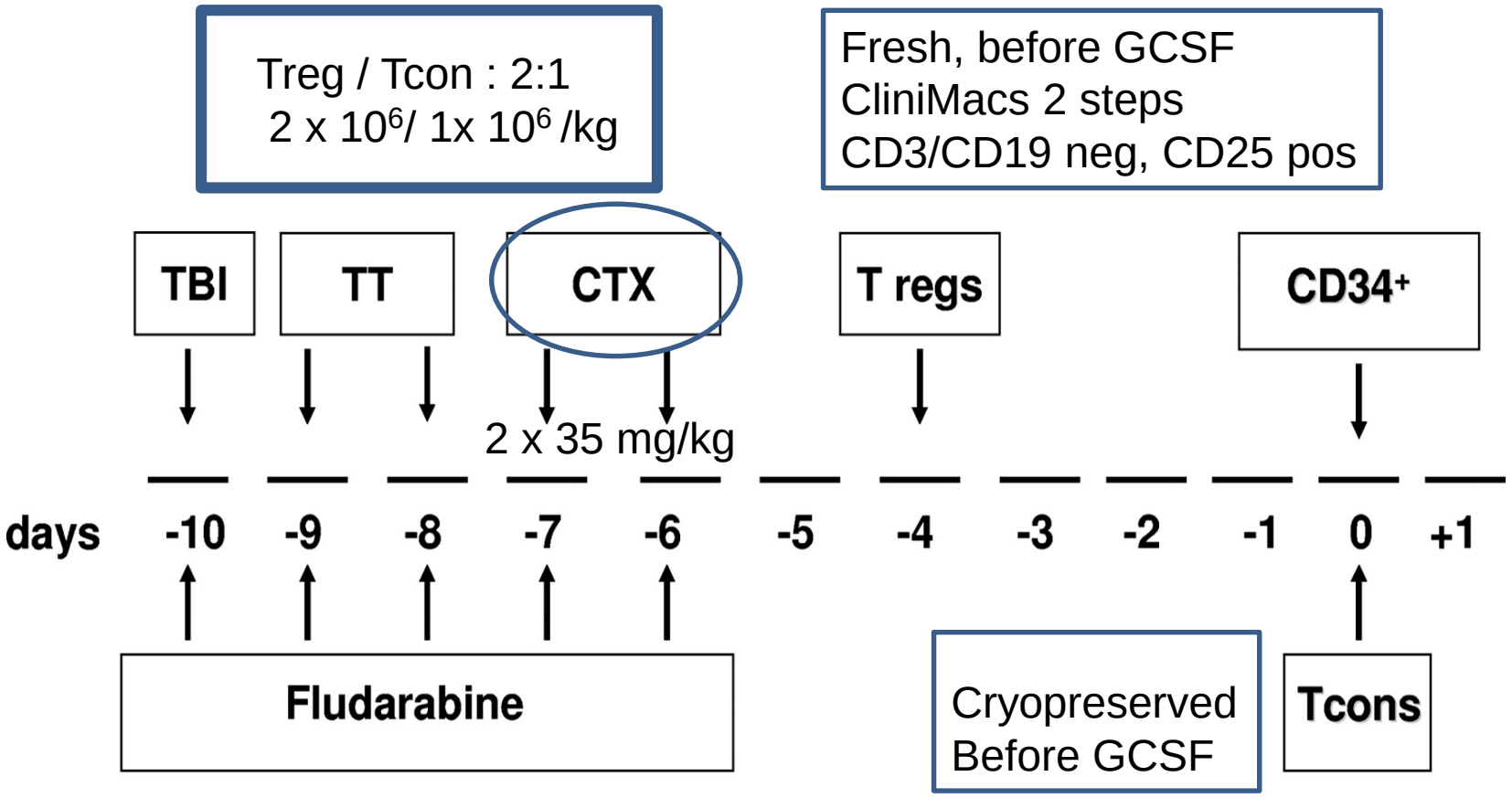


Figure 3. Generation and function of regulatory T cells. *Foxp3⁺ Treg cells are produced by the thymus. They suppress the activation and expansion of naïve T cells and their differentiation to effector T cells, including the T helper cell types T_H1, T_H2, and T_H17, which mediate a variety of pathological and physiological immune responses. Foxp3⁺ Treg cells can also differentiate from naïve T cells in the periphery, although the physiological significance of this Treg-generative pathway remains to be determined.*

Infusion of regulatory T cells (Di Ianni, Blood, 2011)

- Murine MHC mismatched transplants :
  - Treg + Tcon suppress lethal GVHD and improve IR
  - T con prevent relapse

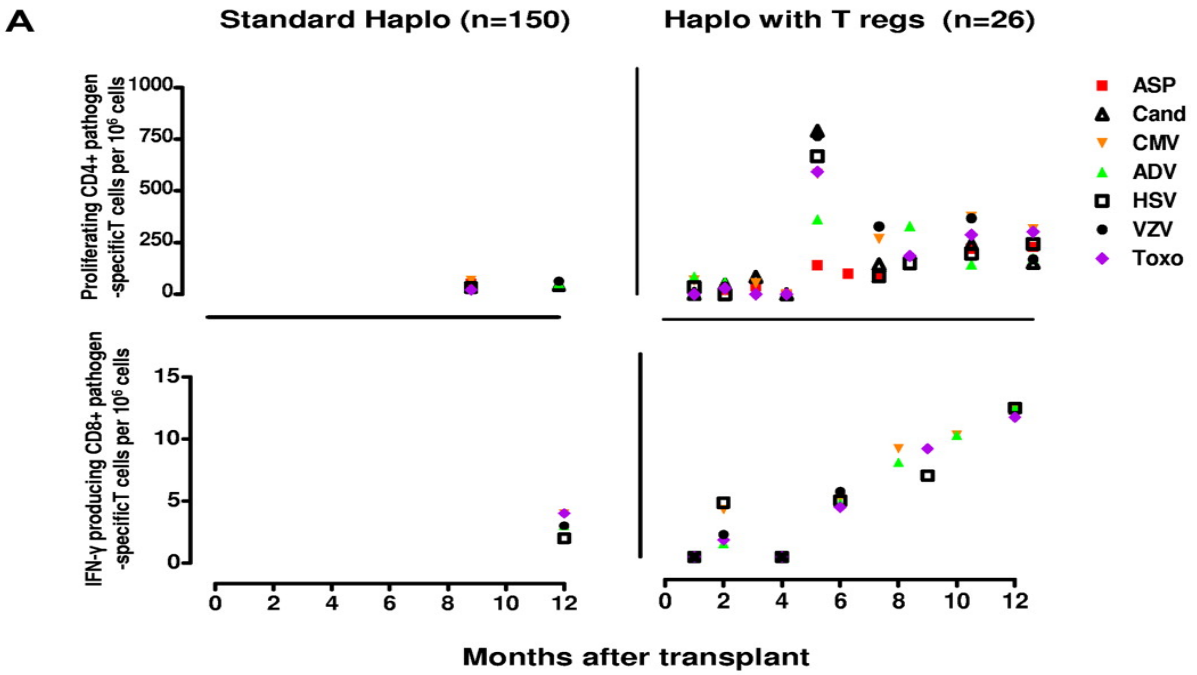


Infusion of regulatory T cells (Di Ianni, Blood, 2011)

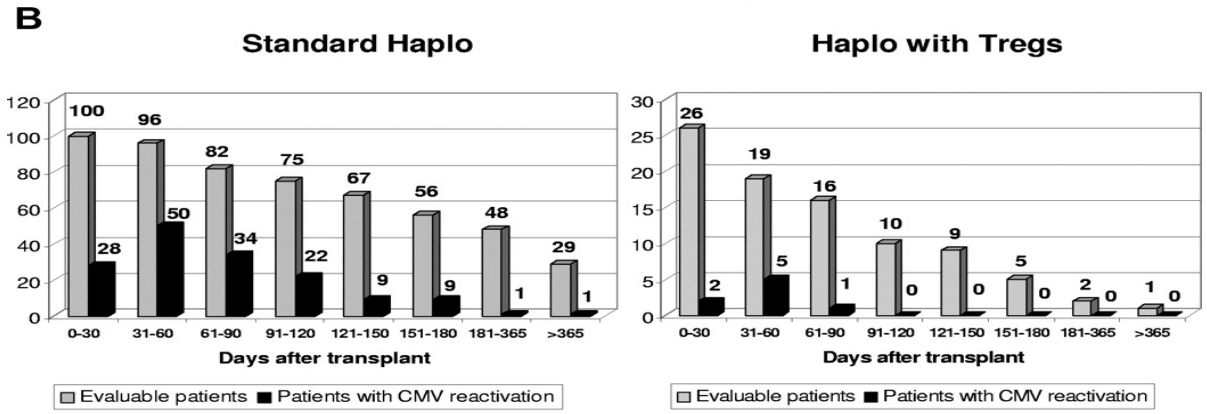
- Results: N = 28
  - Engraftment 26/28
  - **Acute GVHD >= 2 2/26**
  - Chronic GVHD 0/26
  - **Rapid and sustained IR**
  - **TRM 13/26 = 50 %**
    - VOD,MOF, infections (< 2 months)
    - Next study: Cyclophosphamide > Alemtuzumab
  - **Relapse 1/26**
    - No suppression of GVL by Treg
  - 1 yr DFS 12/26 = 46 %

Immune reconstitution after Treg based transplantation

Level of pathogen specific T cells

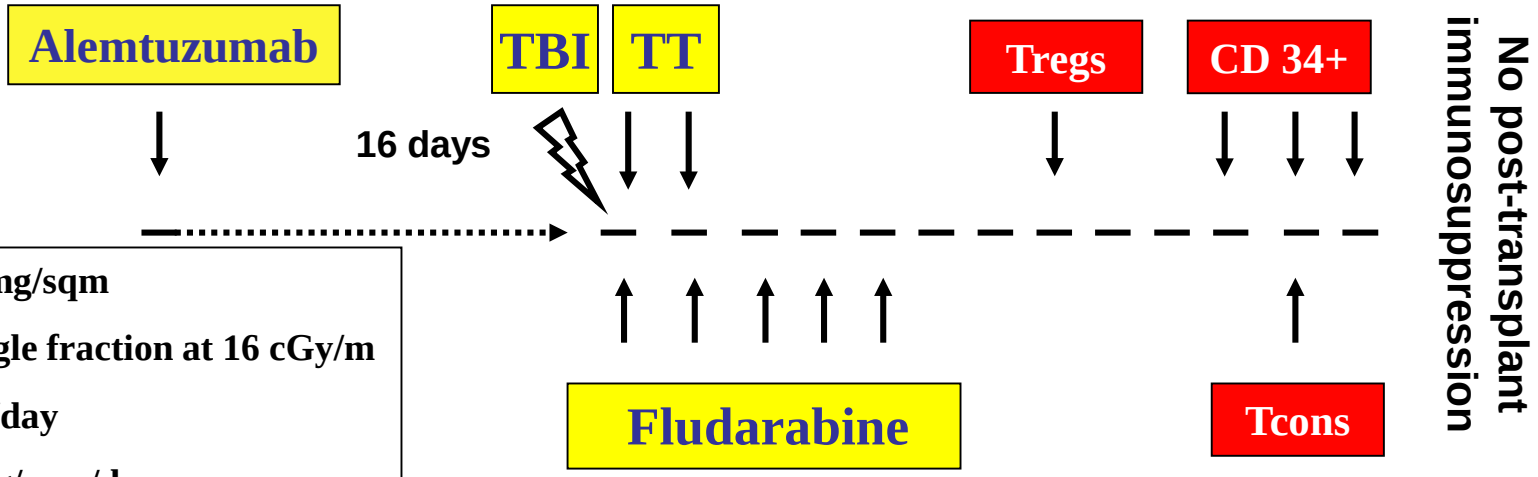


Proportion of pts with CMV reactivation



Tregs in HLA-haploidentical transplantation

Less regimen related toxicity



Alemtuzumab 20mg/sqm

8 Gy TBI in a single fraction at 16 cGy/m

Thiotepa 4 mg/kg/day

Fludarabine 40 mg/sqm/day

Improvement in Treg purification

FoxP3+ cell yield from 70% to 90%

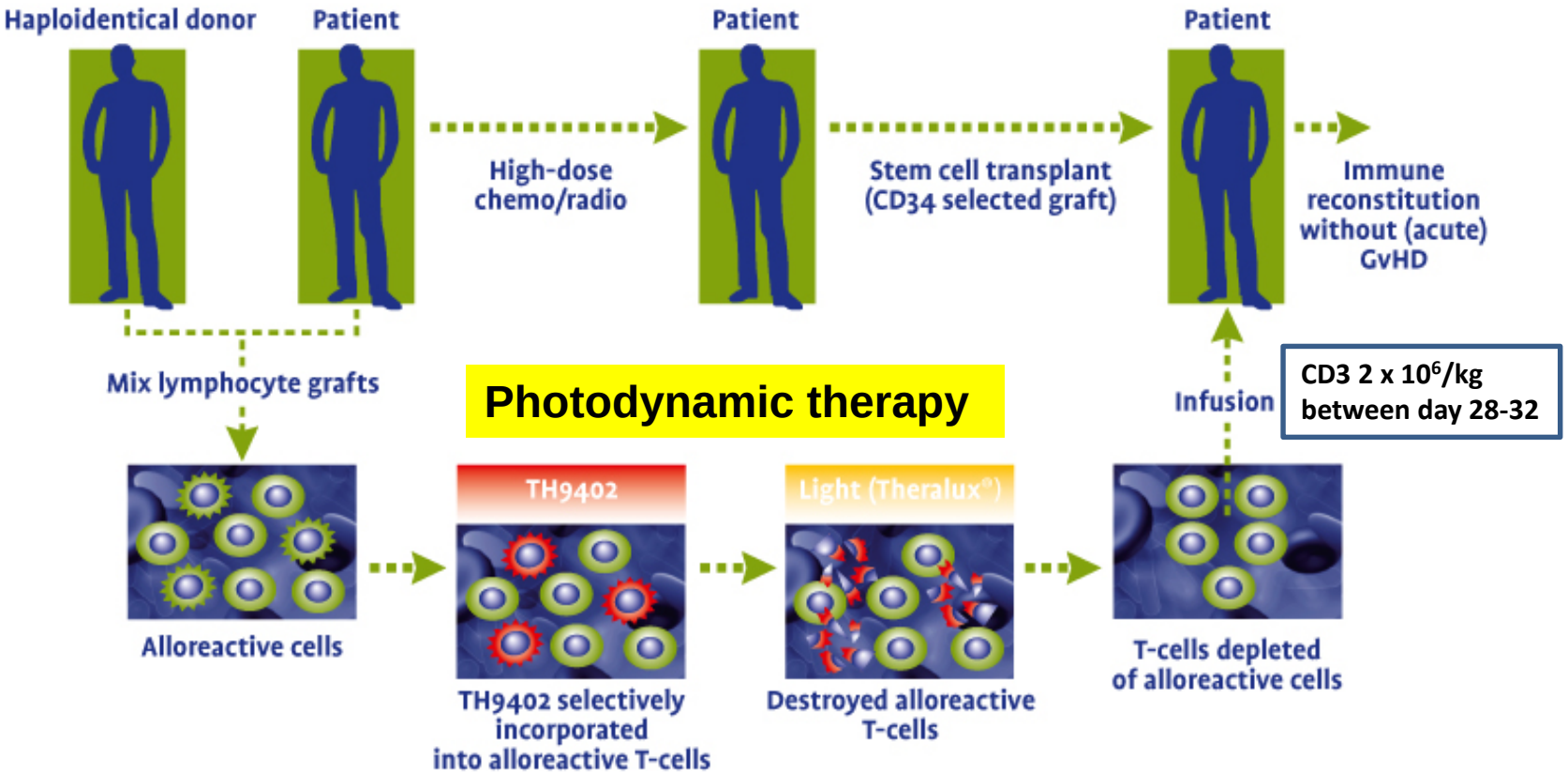
Doses (Kg/bw) of CD34$^+$,Tregs and Tcons infused into the recipient

CD34$^+$ (x10^6)	8.9 (8.1-10.5)
Tregs (x10^6)	2.9 (1.6-4.8)
Tcons (x10^6)	0.9 (0.5-3)

Results confirmed by follow up study Martelli et al, Blood, 2014

- N = 43
- ALL, AML, high risk
- Engraftment 95 %
- **NRM** 40 %
  (**21%** with ATG/alemtuzumab)
- **Ac GVHD >= 2** **15%** (vs 11% naked)
- **relapse** **5%** (vs 21% naked)
- DFS 18 mths 56 %
- Rapid immune recovery

ATIR = Add back of T cells for Immune Reconstitution

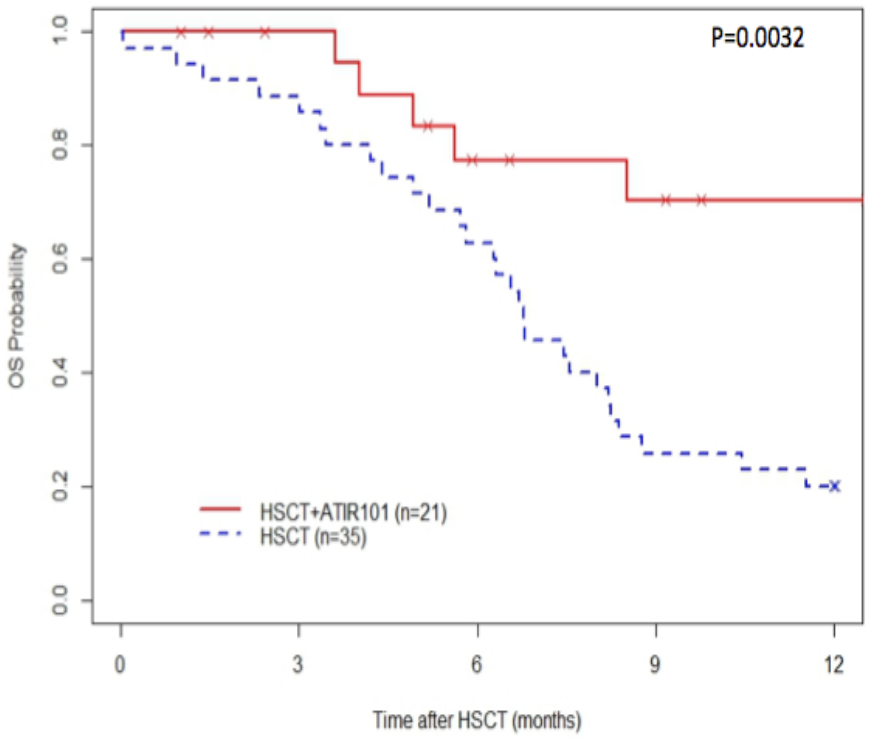


TH9402 = photosensitizer 4,5-dibromo-rhodamine 123

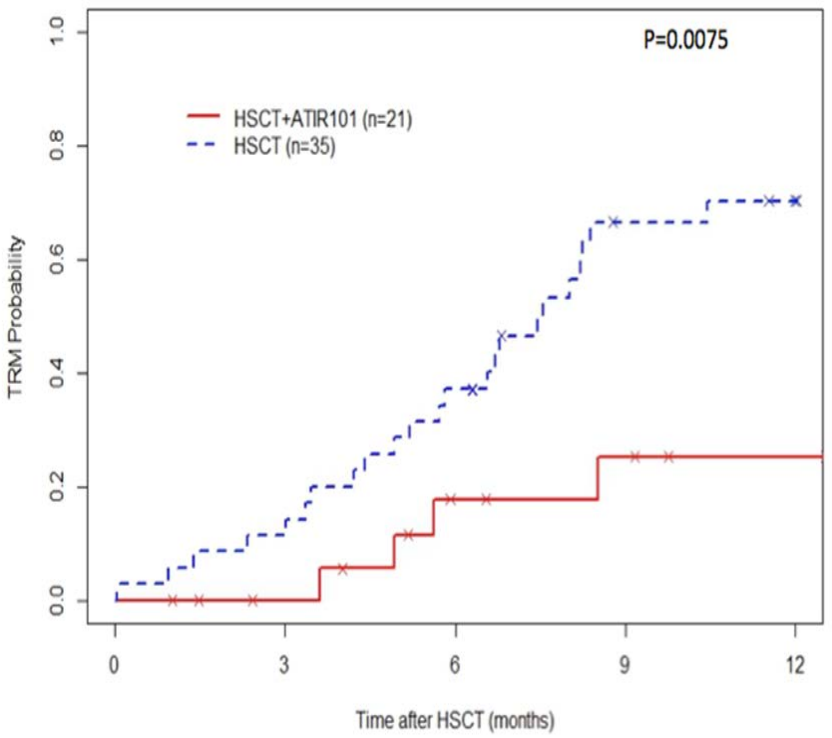
Donor lymphocytes depleted of alloreactive T-cells (ATIR101) reduce transplant related mortality and improve overall survival in haploidentical HSCT for patients with AML and ALL, using an immunosuppressant-free transplant regimen.

Denis-Claude Roy, Silvy Lachance, Jean Roy, Irwin Walker, Ronan Foley, Johan Maertens, Philippe Lewalle, Eduardo Olavarria, Dominik Selleslag, Manfred Rüdiger, Jurjen Velthuis, Karen Reitsma, Jeroen Rovers, Halvard Bönig and Stephan Mielke.

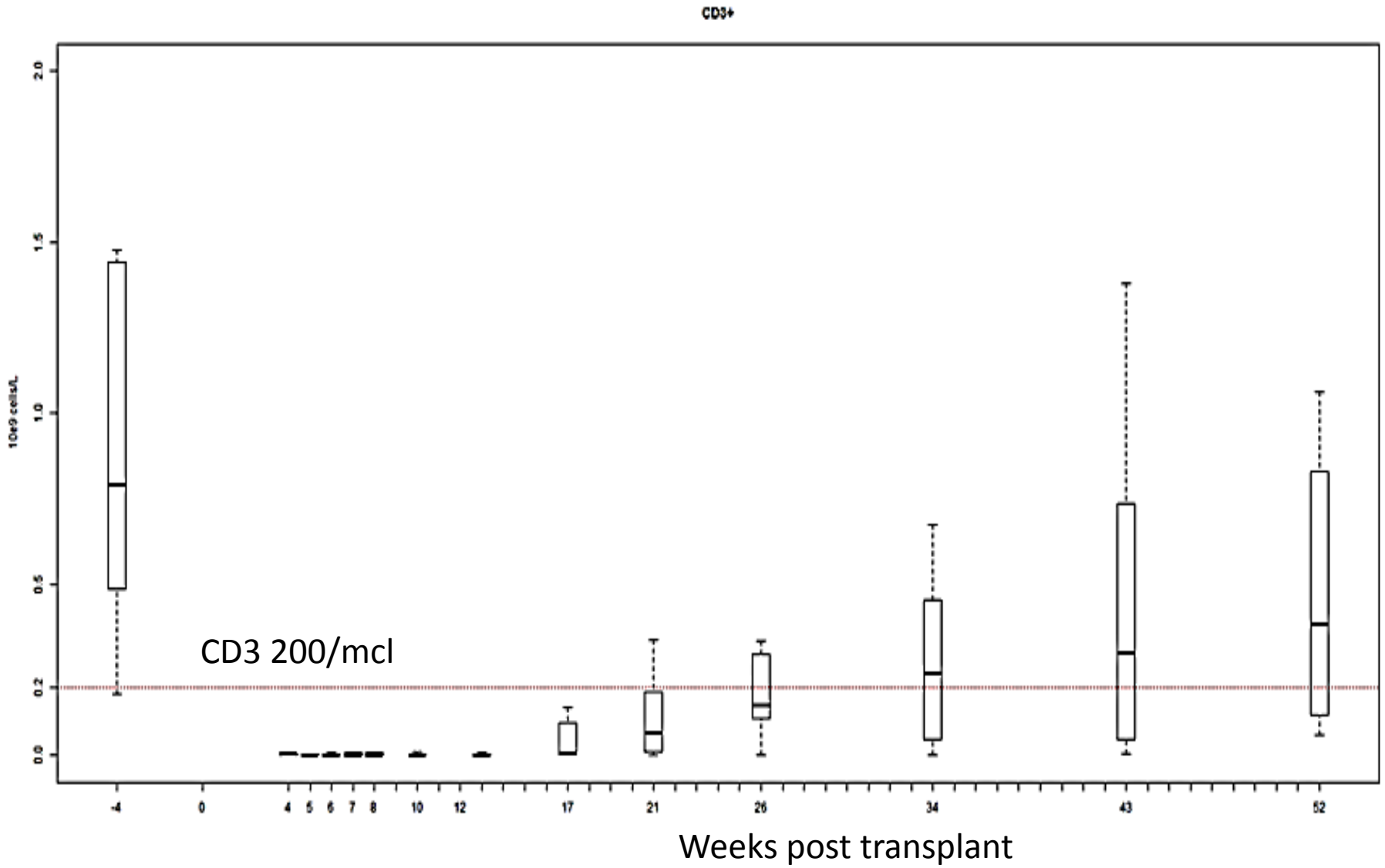
Overall survival



Transplant related mortality

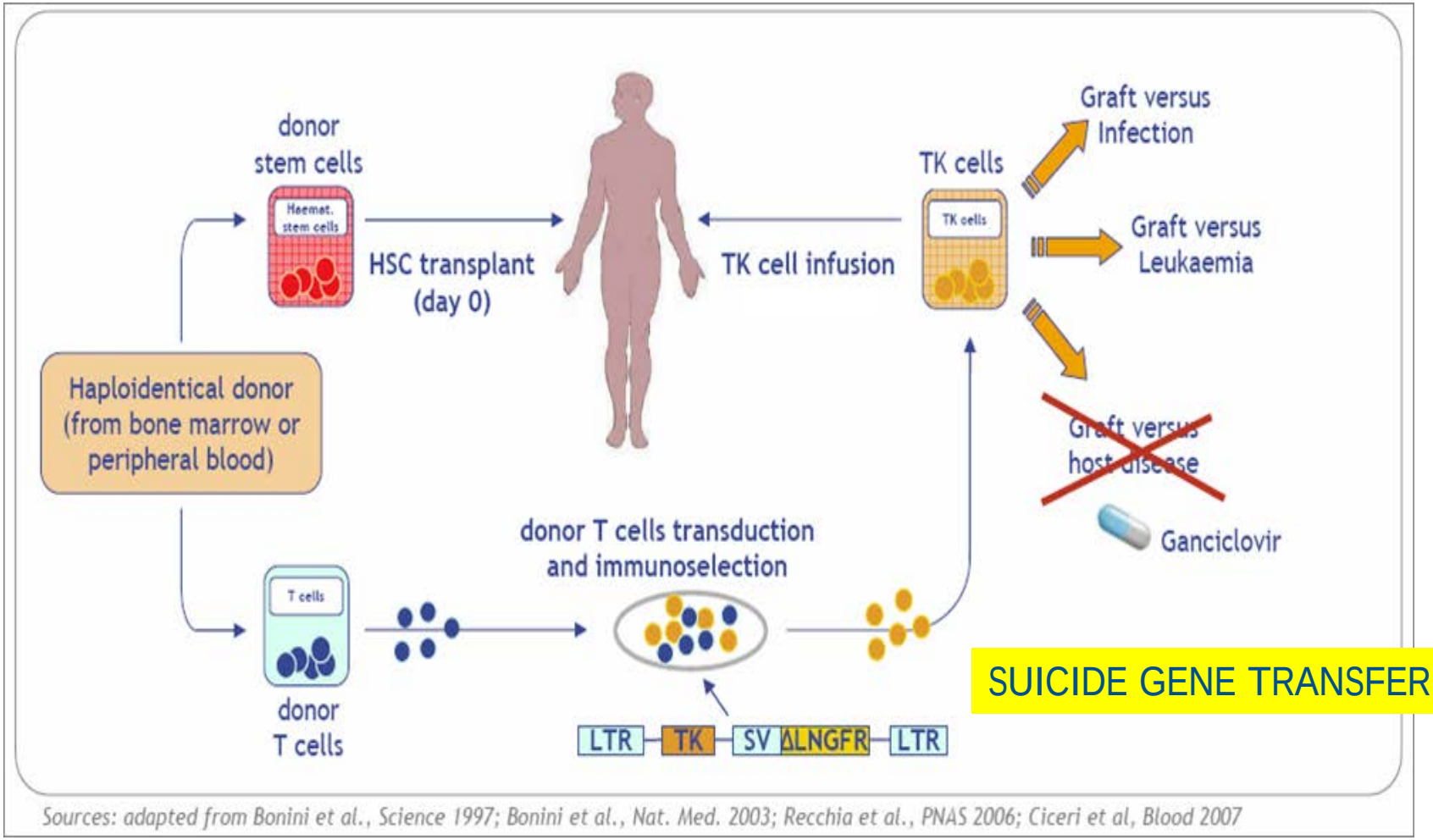


T cell (CD3) immune reconstitution after ATIR infusion



HSV-TK approach: engineering of donor T cells (1)

Overview of the TK therapy procedure:

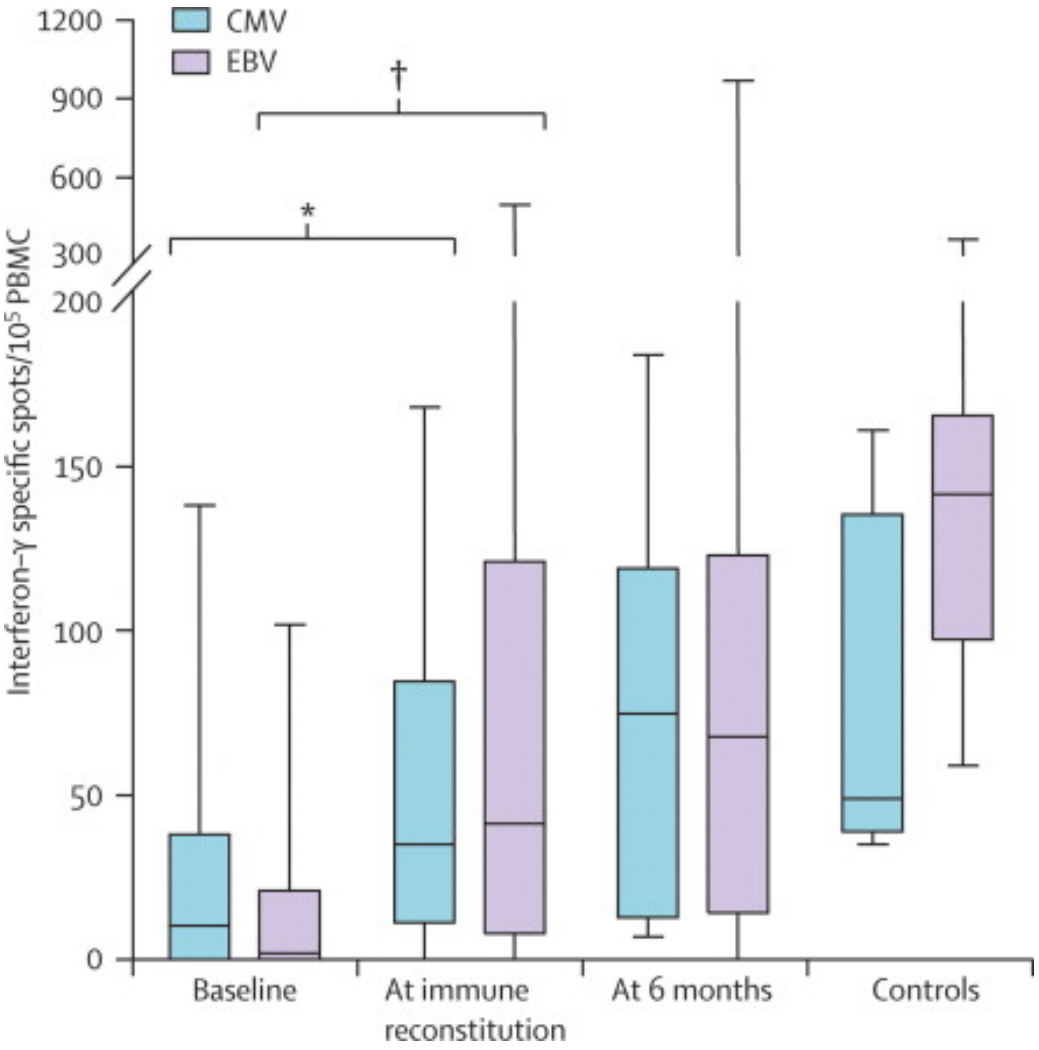


Phase I/II-TK007(2)

- **Schedule of HSV-TK cells add-backs**:

- up to 4 infusions of HSV-TK cells following Haplo-HCT **depending on level of immune reconstitution and absence of GvHD**
- with the following **schedule**:
  - Day +21-+49 1st infusion: dose $1x10^7$ c/kg
  - 30 days after the 1st infusion: $1x10^7$ c/kg
  - 30 days after the 2nd infusion: $1x10^6$ c/kg+IL2(6.000.000 IU/m^2 sc x 5 days)
  - 30 days after the 3rd infusion: $1x10^7$ c/kg+IL2(6.000.000 IU/m^2 sc x 5 days)

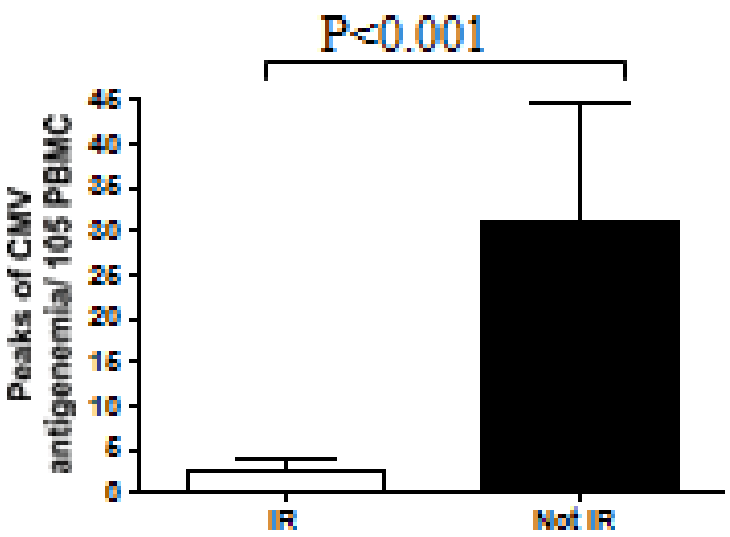
TK cells add-back induce a rapid recovery of immune responses to EBV and CMV



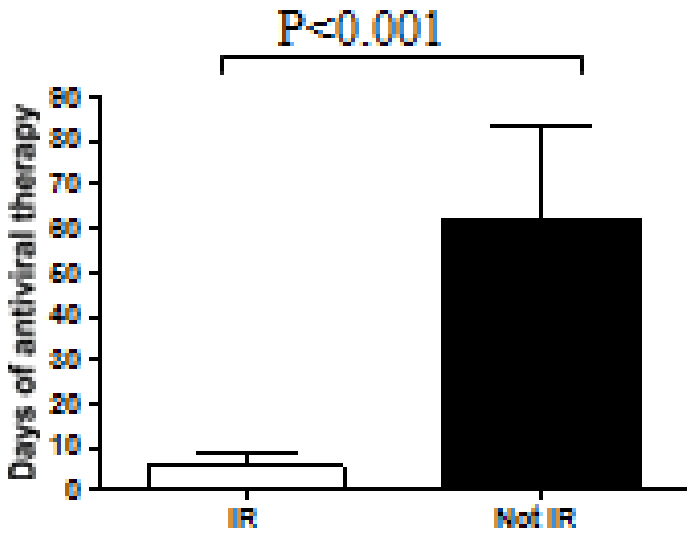
MOLMED

Immune reconstitution obtained with TK cells add-back is protective against CMV

Peaks of CMV antigenemia



Days of antiviral therapy



MOLMED

Acute and chronic GvHD

- **Acute GvHD considered related to the HSV-TK cells occurred in 10 patients out of 30 treated**
- One patient developed a chronic GvHD
- The clinical treatment patients experiencing GvHD was as follow:
  - 1 patient grade 1 (skin), no treatment;
  - 7 patients grade 2 (skin), 3 treated with GCV and 4 with valGCV;
  - 1 patient grade 3 (skin), treated with valGCV;
  - 1 patient grade 4 (gut and liver), treated with GCV;
  - 1 patient chronic GvHD (skin, mouth and eyes), treated with valGCV, mycophenolate mofetil and dexamethasone

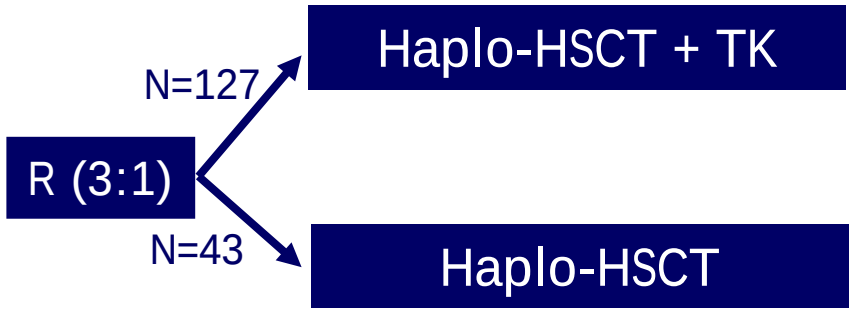
GvHD was controlled by Ganciclovir/Val Ganciclovir

TK008: Randomized **phase III trial** of haploidentical HCT with or without an add back strategy of HSV-TK donor lymphocytes in patients with high risk acute leukemia"(IPR/21.A)

EudraCT number: 2009-012973-37

TK 008: FDA recommendation

- Key inclusion criteria:
  - AML-ALL at high-risk in first CR
  - AML-ALL in ≥ second CR
  - secondary AML in CR
  - absence of HLA-matched family or unrelated donor
- Primary endpoint:
  - Leukemia-free survival
- Secondary aims:
  - NRM, overall survival, immune-reconstitution, engraftment, aGvHD, cGvHD, relapse, disease-free survival, infectious, safety, quality of fife, pharmacoeconomics

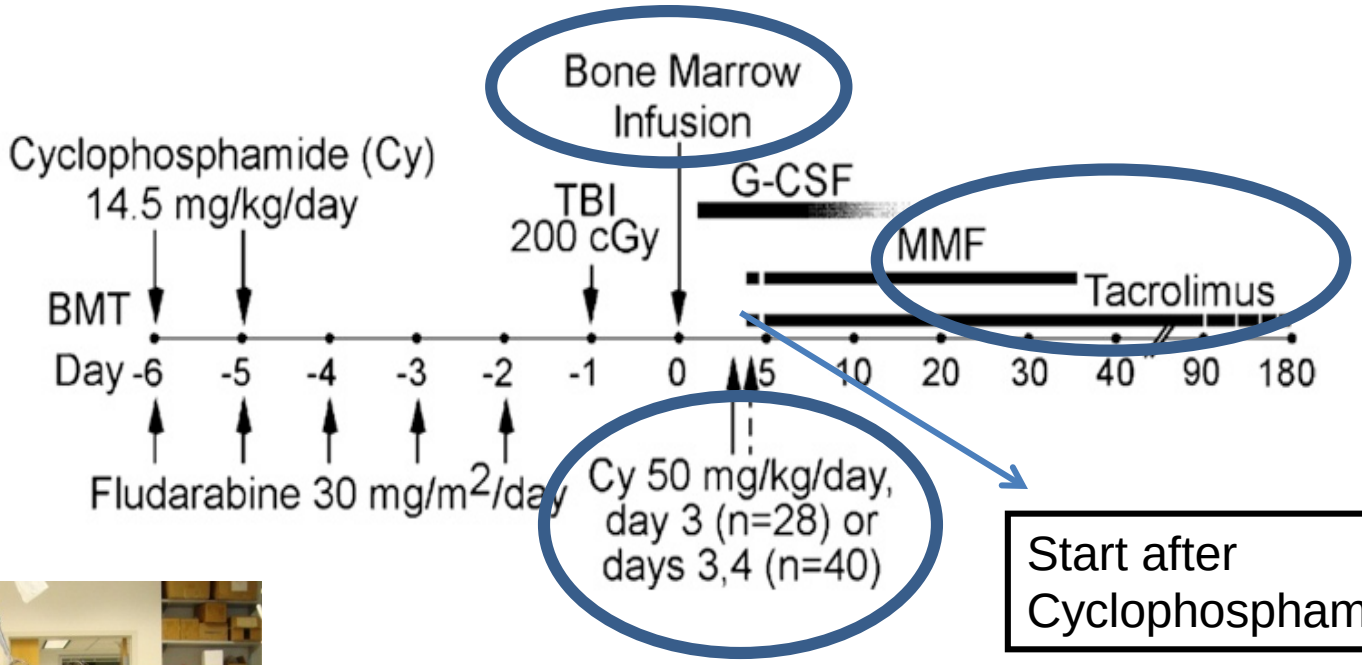


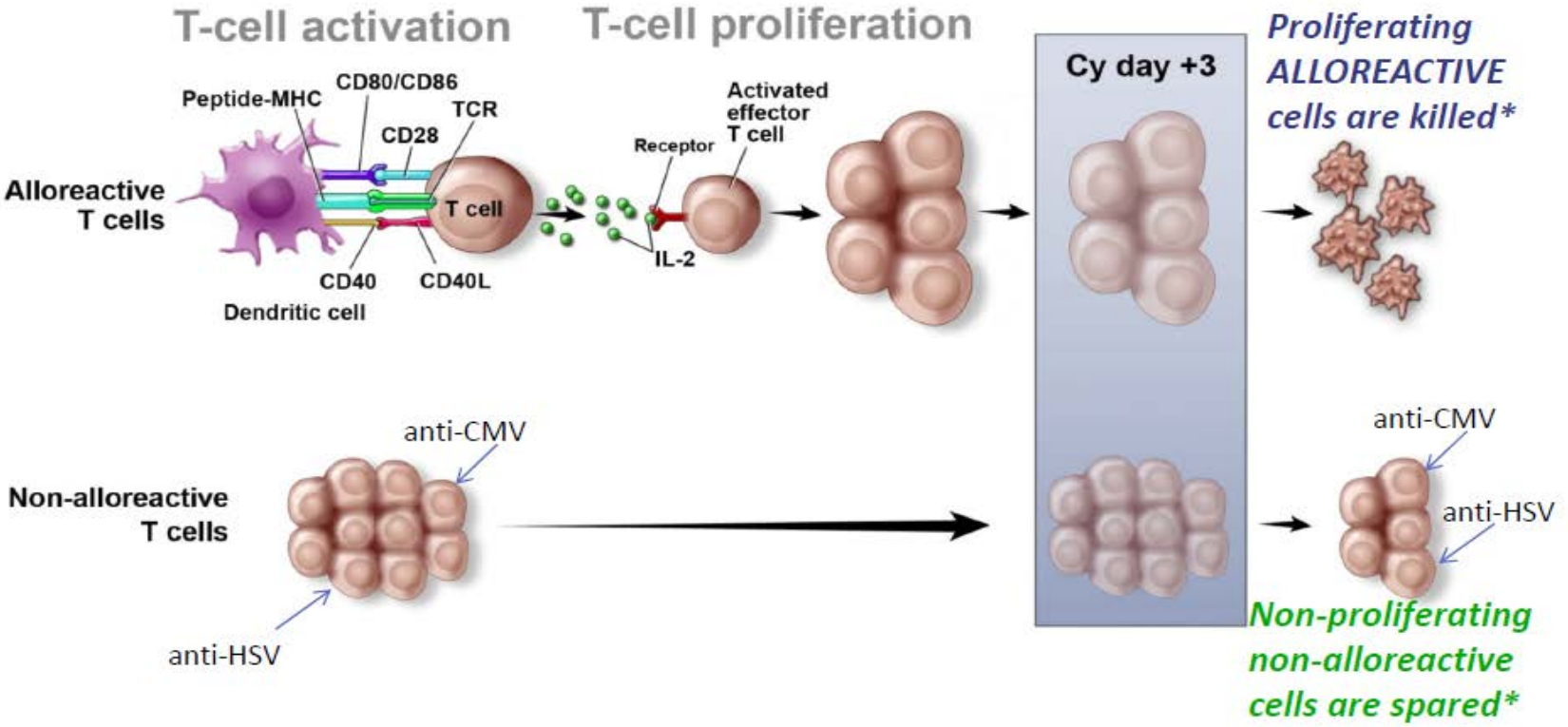
- 1-year NRM standard haplo:60%
- 1-year NRM ph II study TK: 37%
- Relapse rate standard haplo 25%
- Relapse rate ph II study TK 18%
- **Power = 80%; HR= 0.55**
- LFS 30% in standard haplo
- LFS 52% expected in TK008 exp arm
- 91 events (death + leukemia relapse)
- N=170 patients

T cell replete haplotransplant

- Posttransplant cyclophosphamide *(Hopkins)*
- Posttransplant rapamycin *(Milan)*
- PB + GSCF primed BM *(Peking)*

T cell replete haplo with posttransplant cyclophosphamide (L.Luznik, BBMT 2008)





Rationale:

High-dose Cy, when administered in a narrow window **after** transplantation, depletes alloreactiveT cells from the donor and the host, and can inhibit both GvHD and graft rejection

- Proliferating T cells express low levels of ALDH and are sensitive to Cy
- Resting T cells and stem cells express higher levels of ALDH and are resistant to Cy.

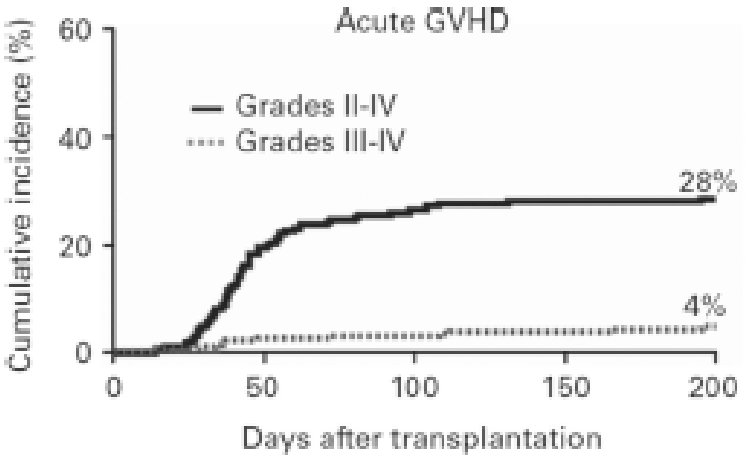
T cell replete haplo with posttransplant cyclophosphamide (L.Luznik, BBMT 2008)

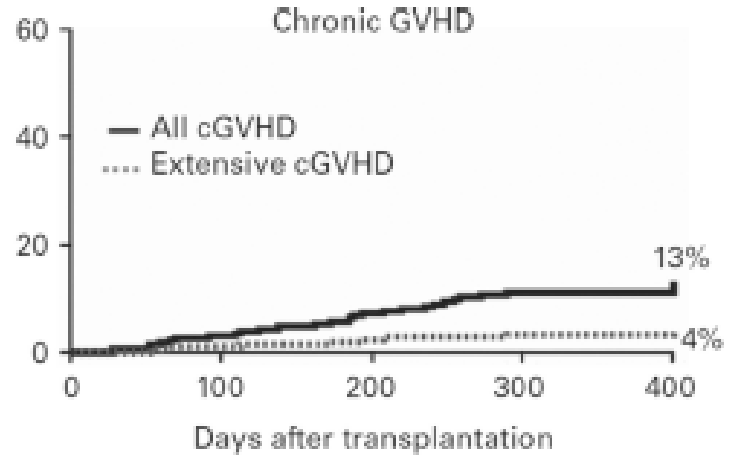
- Results: N = 68 (Hopkins + Seattle)
  - Advanced haematological malignancies
  - **Graft failure** **13 %**
  - ANC > 0.5 15 days
  - Platelets > 20 24 days
  - **Ac GVHD gr III-IV** **6 %**
  - Less extensive c GVHD with 2 doses of Cyclophosphamide
  - **NRM at 1 yr** **15 % (6 % due to infections)**
  - **Relapse at 1 yr** **51 %**
  - OS at 2 yrs 36 %

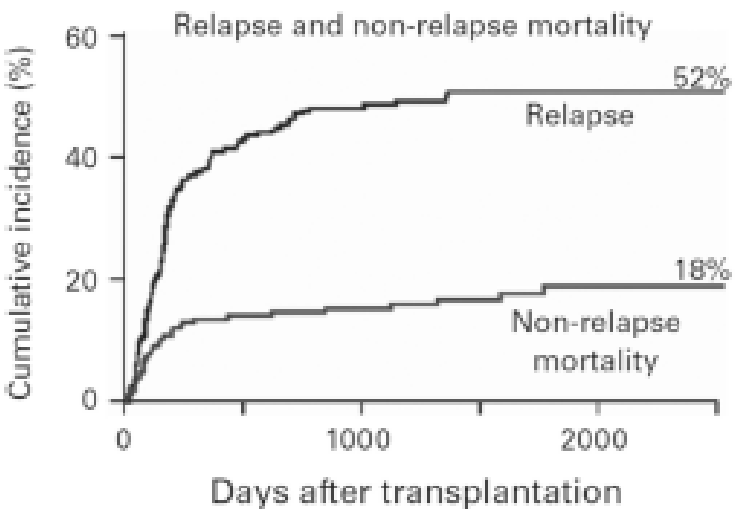
Outcome of non-myeloablative haploidentical BMT with PTCy in 372 patients with haematological malignancies at John Hopkins, Baltimore

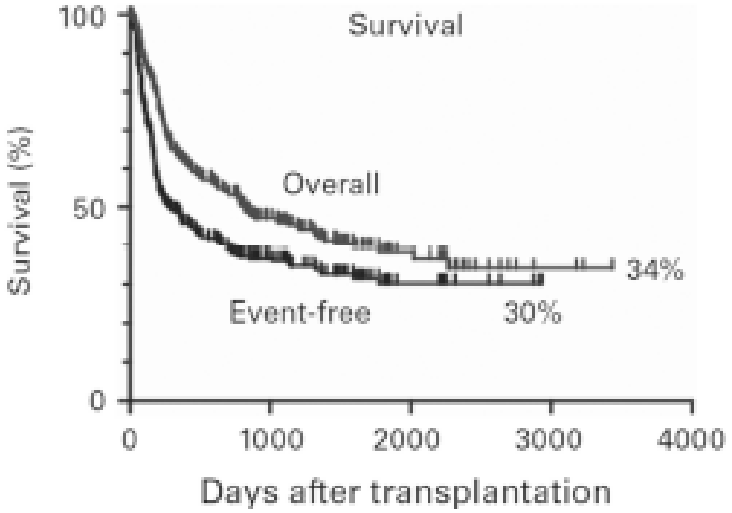
Mc Curdy S et al, Blood 2015

Fuchs E, BMT 2015



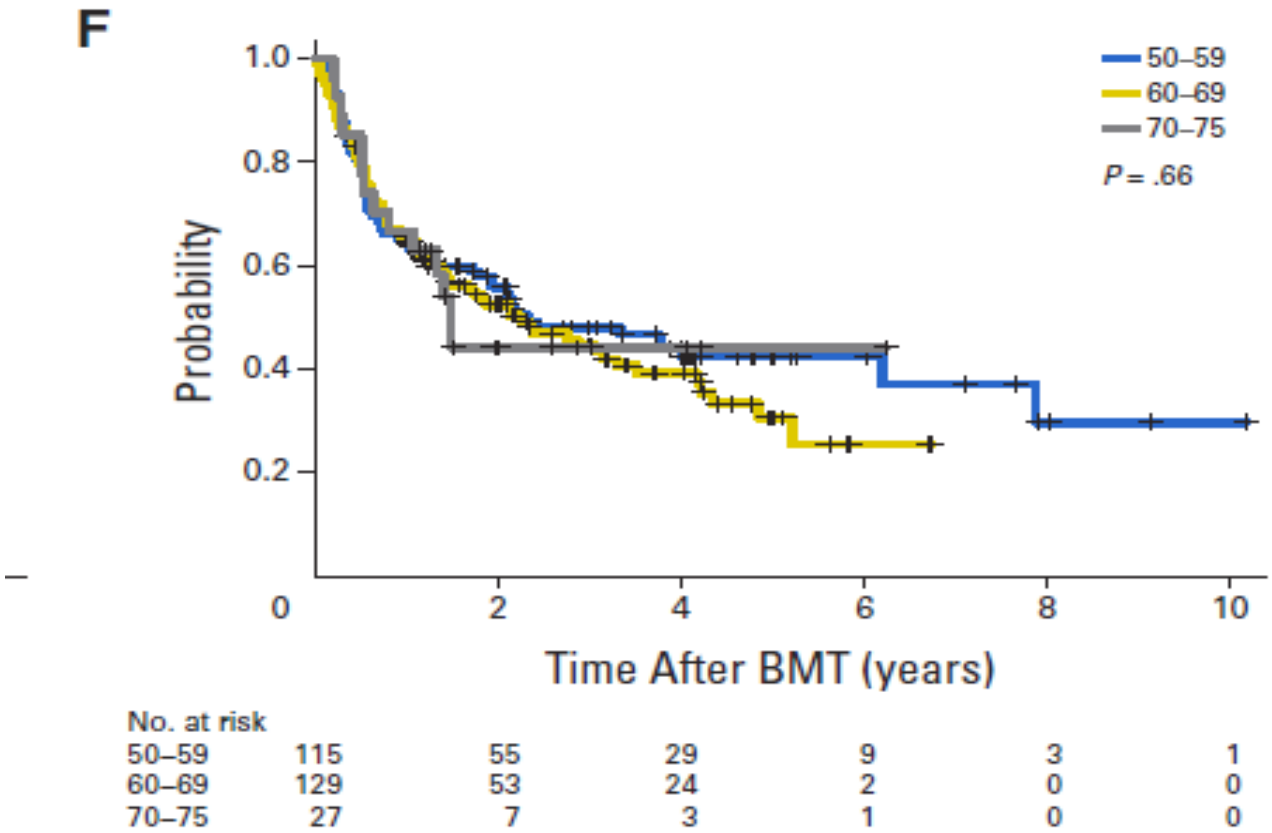






Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults

Kasamon Y et al, JCO, 2015



Comparison of Outcomes of HLA-Matched Related, Unrelated, or HLA-Haploidentical Related Hematopoietic Cell Transplantation following Nonmyeloablative Conditioning for Relapsed or Refractory Hodgkin Lymphoma

Lauri M. Burroughs,[1] Paul V. O'Donnell,[1] Brenda M. Sandmaier,[1] Barry E. Storer,[1] Leo Luznik,[2] Heather J. Symons,[2] Richard J. Jones,[2] Richard F. Ambinder,[2] Michael B. Maris,[3] Karl G. Blume,[4] Dietger W. Niederwieser,[5] Benedetto Bruno,[6] Richard T. Maziarz,[7] Michael A. Pulsipher,[8] Finn B. Petersen,[9] Rainer Storb,[1] Ephraim J. Fuchs,[2] David G. Maloney[1]

BBMT, 2008

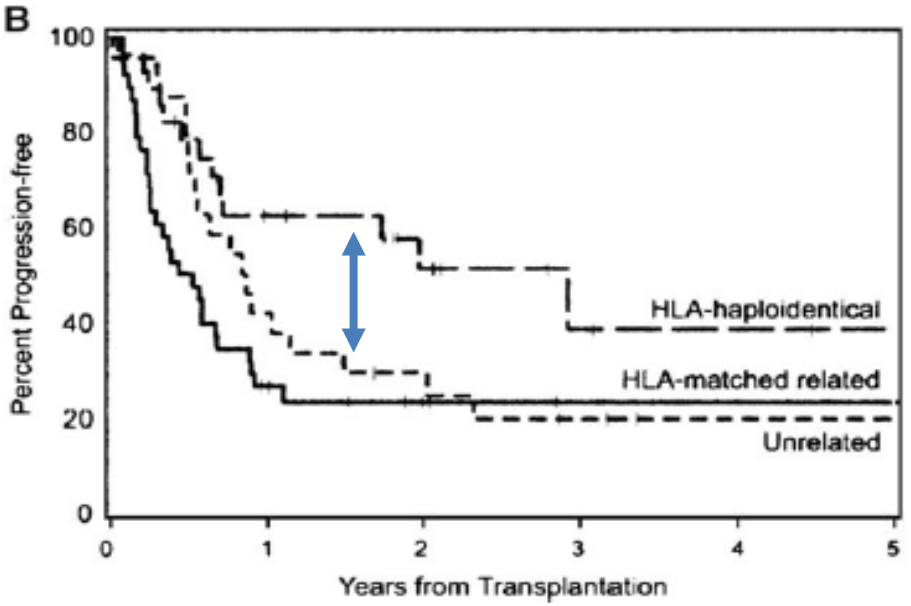


Figure 3. Incidences of (A) OS, and (B) PFS according to donor type.

Can bone marrow be replaced by peripheral blood stem cells ?

Bone Marrow Compared with Peripheral Blood Stem Cells for Haploidentical Transplantation with a Nonmyeloablative Conditioning Regimen and Post-transplantation Cyclophosphamide

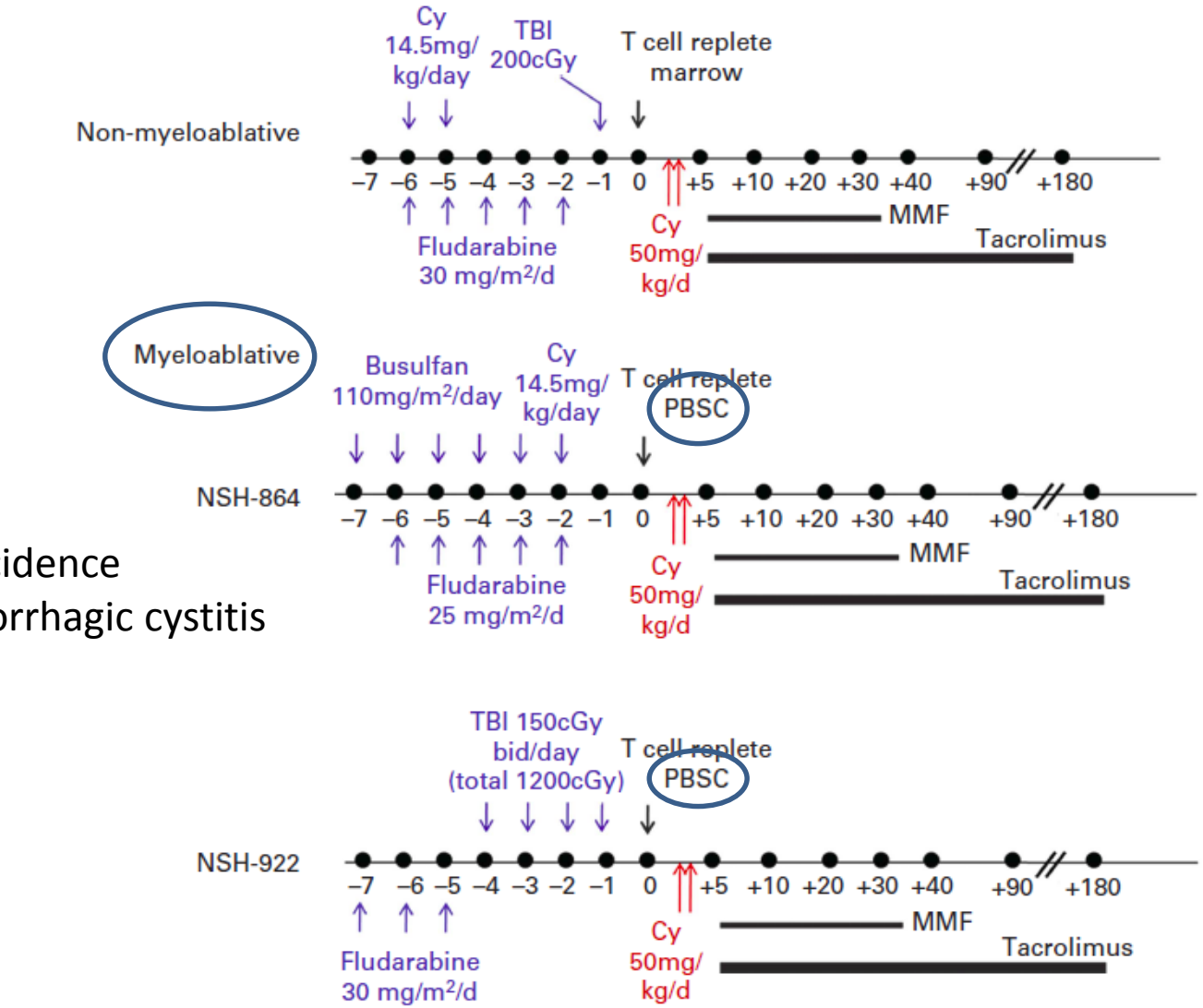
BBMT 2014

Luca Castagna [1,*], Roberto Crocchiolo [1], Sabine Furst [2], Stefania Bramanti [1], Jean El Cheikh [2], Barbara Sarina [1], Angela Granata [2], Elisa Mauro [1], Catherine Faucher [2], Bilal Mohty [2], Samia Harbi [2], Christian Chabannon [3,4,5], Carmelo Carlo-Stella [1], Armando Santoro [1], Didier Blaise [2,4,5]

	BM	PBSC
ANC > 0.5	21 days	20 days
Plat > 20	29 days	27 days
NRM	22%	12%
GVHD acute II-IV	25%	33%
cGVHD	13%	13%
survival	No difference	

Retrospective comparison, no significant differences

Haploidentical myeloablative conditioning with PTCy (Atlanta)



High incidence
of hemorrhagic cystitis

Improved Early Outcomes Using a T Cell Replete Graft Compared with T Cell Depleted Haploidentical Hematopoietic Stem Cell Transplantation

BBMT 2012

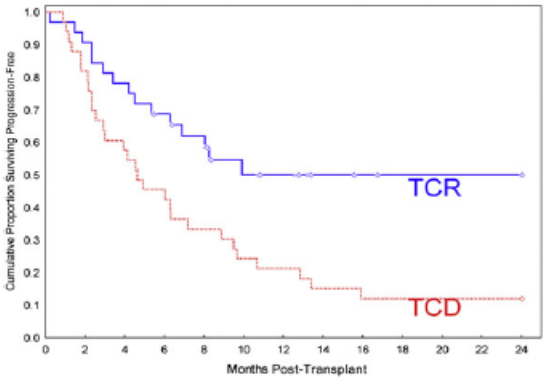
Stefan O. Ciurea,[1] Victor Mulanovich,[2] Rima M. Saliba,[1] Ulas D. Bayraktar,[1]

- Single centre study (MDACC)
- Retrospective comparison
  - TCD: n = 33
    - FluMelThiotepa + ATG +CD34 selected PB (Perrugia)
    - Tacrolimus MMF
  - TCR : n = 32
    - FluMelTiotepa + BM + PTCy
    - Tacrolimus MMF

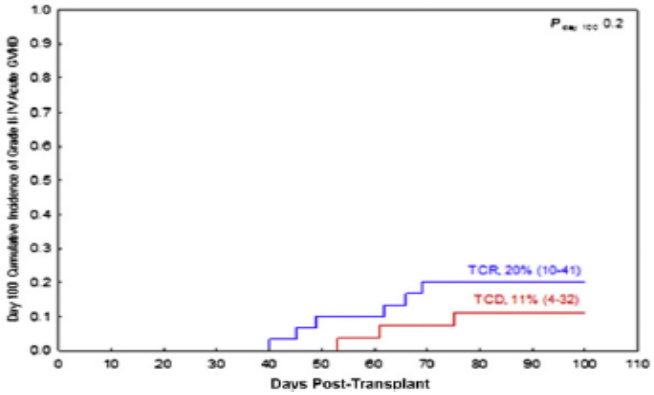
Improved Early Outcomes Using a T Cell Replete Graft Compared with T Cell Depleted Haploidentical Hematopoietic Stem Cell Transplantation

Stefan O. Ciurea,[1] Victor Mulanovich,[2] Rima M. Saliba,[1] Ulas D. Bayraktar,[1]

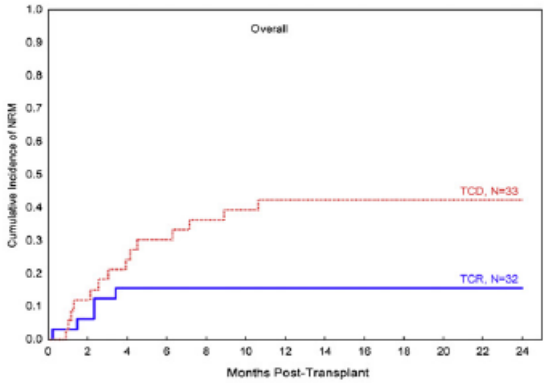
A Progression-free survival for all patients.



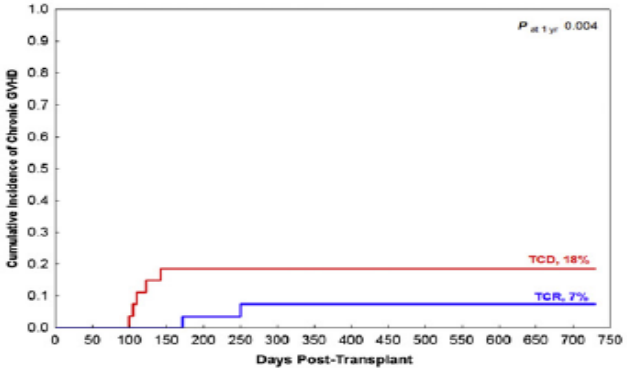
Cumulative incidence of gr II-IV aGVHD.



C Non-relapse mortality for all patients.



E Cumulative incidence of cGVHD.

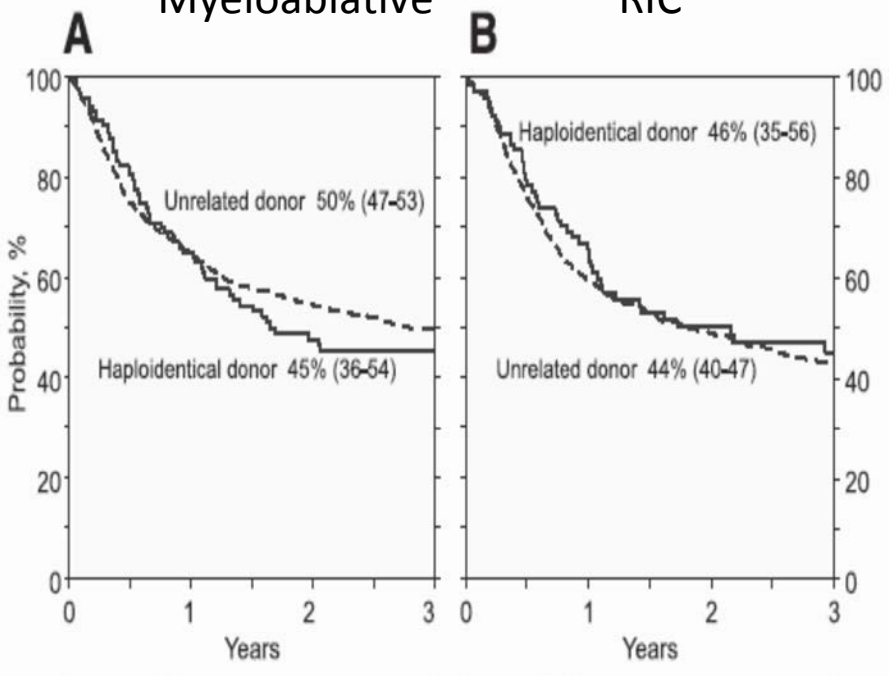


Less cGVHD with PTCy

Haplo vs MUD

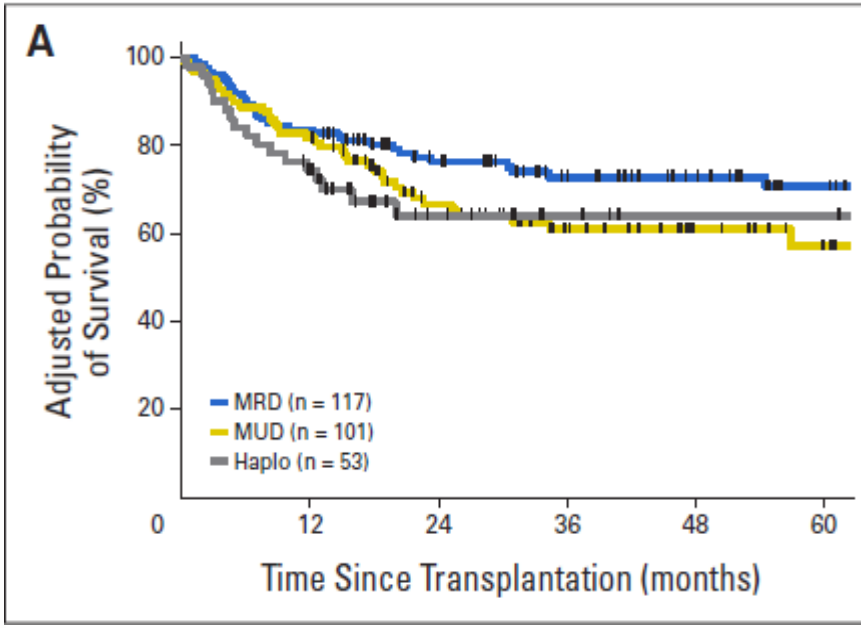
Overall survival

Myeloablative



RIC

Myeloablative+ RIC



Ciurea et al, CIBMTR,Blood 2015

AML, CR or relapse

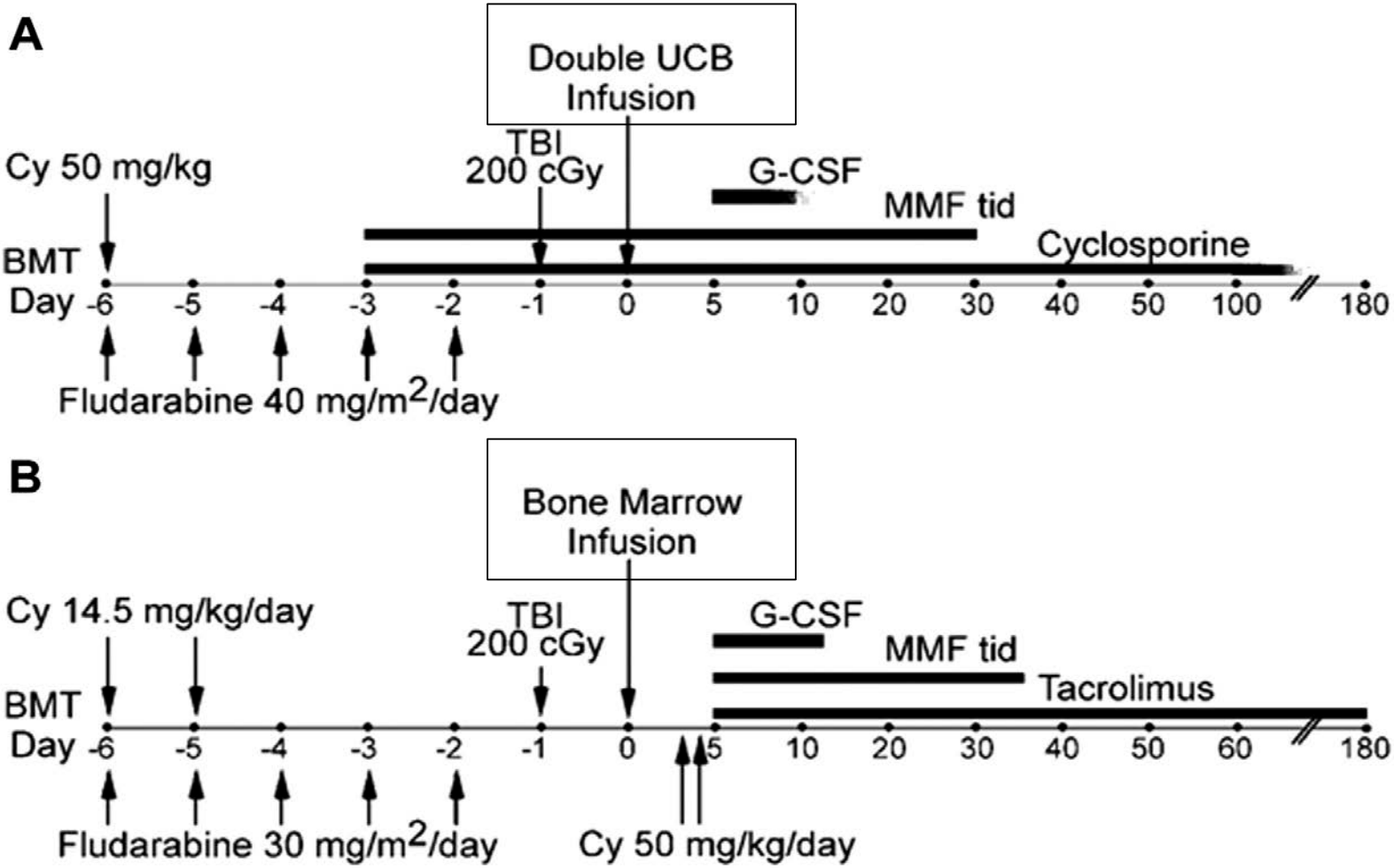
Less Acute and chronic GVHD with haplo

Bashey A et al, JCO 2013/BBMT 2015

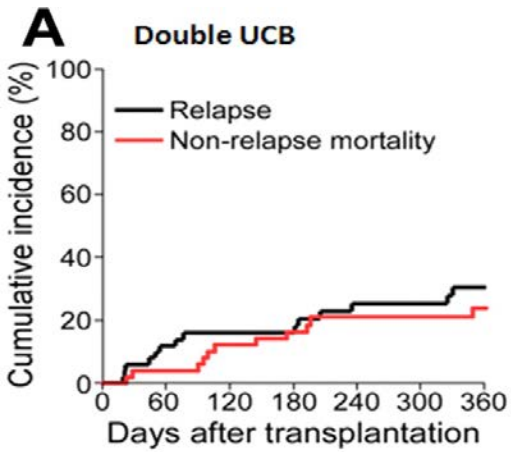
Haem malignancies

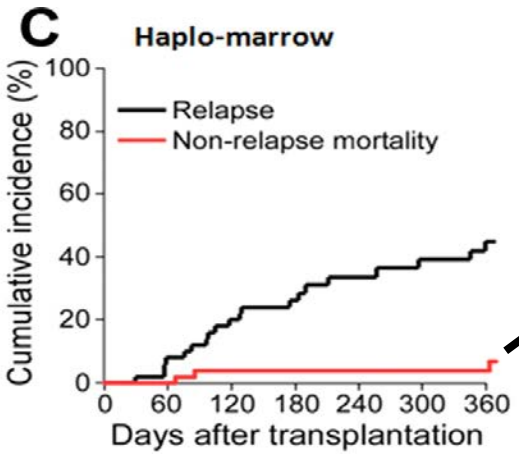
Less severe chronic GVHD with haplo

Comparison between two parallel multicentric phase II trials of Clinical Trials Network
(C. Brunstein , Blood 2011)

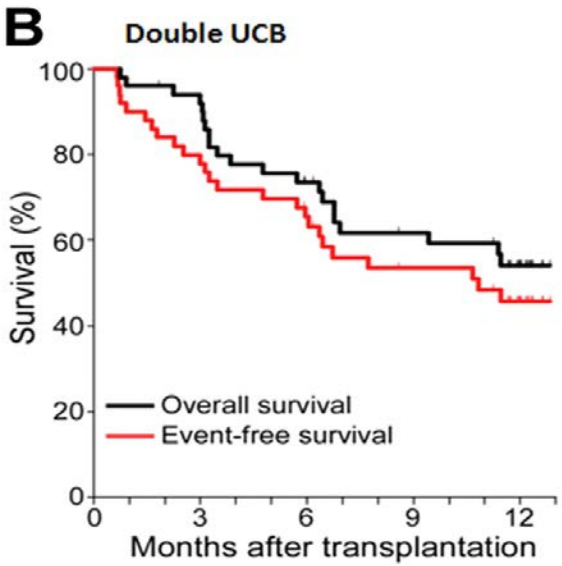


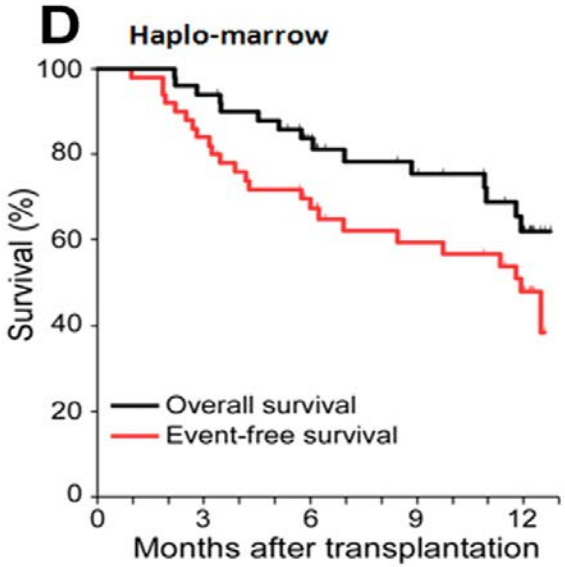
Long-term outcomes





NRM 1 yr	**7 %**
Ac GVHD III-IV	**0 %**





Phase III ongoing

Brunstein C G et al. Blood 2011;118:282-288

Table 5. Comparison of practical considerations between matched unrelated donor (MUD), double umbilical cord blood (DUCB) units and T-replete haploidentical donor using post-transplant CY (Haplo-post-HCT-CY) as graft sources

	Matched unrelated donor	*DUCB*	*Haplo-post-HCT-CY*
Donor availability	Limited for ethnic minorities and mixed race	Greater availability for ethnic minorities but limited for large/ obese recipients	Almost universal donor availability with greater than two donors available for average recipient
Expense	Significant built-in cost of graft acquisition significant	Greater graft acquisition cost than matched unrelated donor in most cases	Costs significantly lower-limited to collection of graft by marrow harvest or leukapheresis
Time from search initiation to transplant	Initiation of search to transplant can take up to 6 months or beyond in some cases	More rapid progression from search initiation to transplant	Most rapid progress from search initiation to transplant–most control over access to donor
DLI for relapse of malignancy	Usually available but may be delayed depending on donor availability	Not available–major limitation in relapsing patients	Available-concerns for severe GVHD but safety increasingly being demonstrated
Use in donors sensitized to HLA antigens	Use of 10 of 10 or 12 of 12 matched donor feasible even in highly sensitized patients	Grafts usually have multiple HLA mismatches with recipient, so use usually not possible in HLA-sensitized recipients	Use not recommended in recipients sensitized to mismatched antigens. Desensitization may be feasible
Immune reconstitution	Depends upon degree of match and conditioning regimen	Slowest immune reconstitution of three options in adults	Rapid immune reconstitution-at least equivalent to matched unrelated donor and may be more rapid

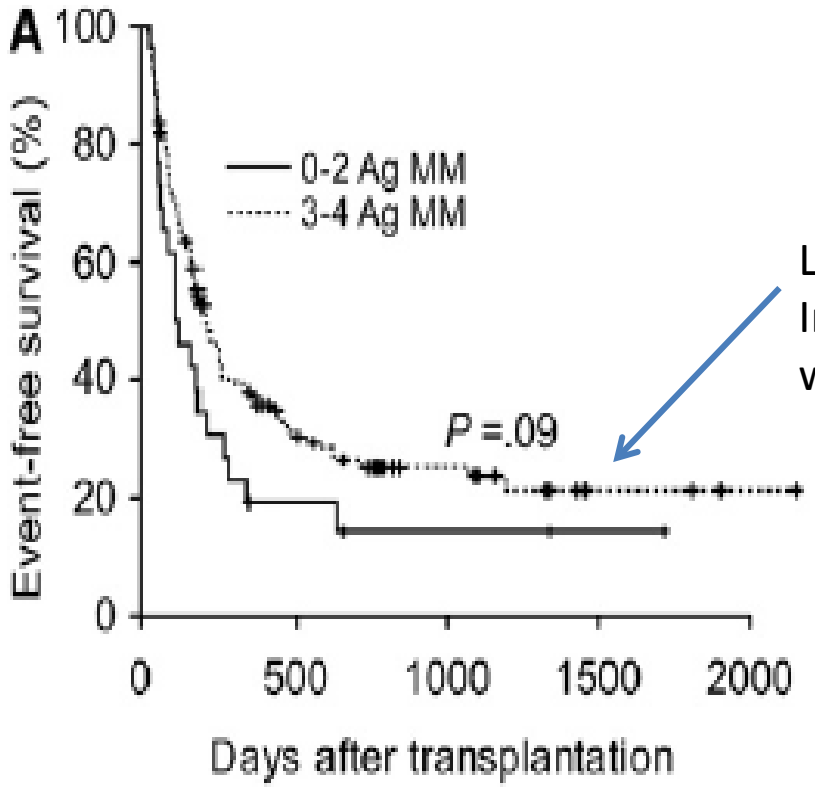
Donor selection for haplo with PTCy

- Screen recipient for *donor specific anti-HLA antibodies* and select donors with negative DSA and cross match
- Choose donor with *greatest number of HLA mismatches* on non shared haplotype
- Choose a *donor with inhibitory KIR mismatches and/or KIR group B haplotype*
  - More studies required
- Avoid parental donors, *also mother*
- Prefer haploidentical sibling donors with *NIMA* (versus NIPA) *mismatch* in non shared haplotype
- Prefer young male donors
- Prefer ABO compatibility

Nonmyeloablative HLA-Haploidentical Bone Marrow Transplantation with High-Dose Posttransplantation Cyclophosphamide: Effect of HLA Disparity on Outcome

BBMT 2010

Yvette L. Kasamon,[1] Leo Luznik,[1] Mary S. Leffell,[1] Jeanne Kowalski,[1] Hua-Ling Tsai,[1]

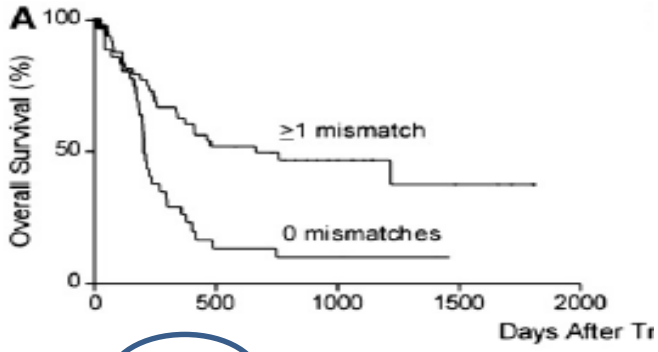


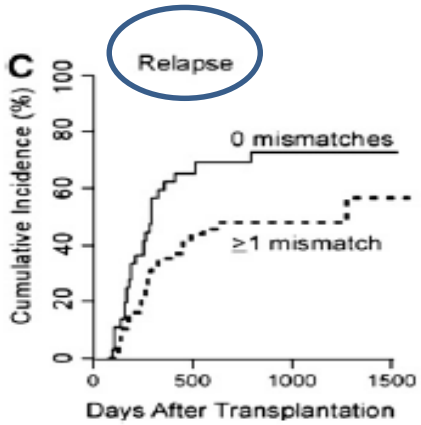
Lower relapse rate
In multivariate analyse
without increased NRM or GVHD

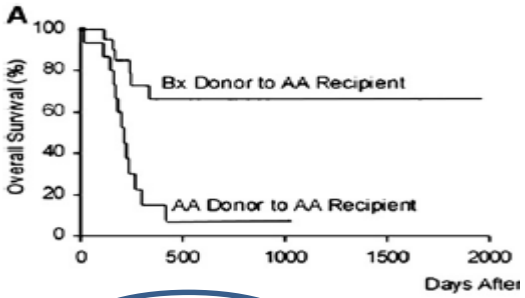
Improved Survival with Inhibitory Killer Immunoglobulin Receptor (KIR) Gene Mismatches and KIR Haplotype B Donors after Nonmyeloablative, HLA-Haploidentical Bone Marrow Transplantation

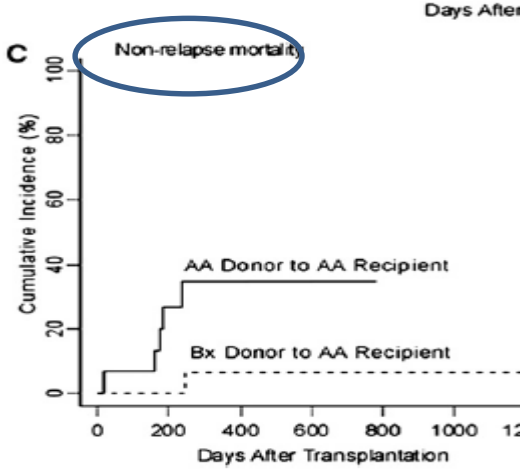
BBMT 2010

Heather J. Symons,[1] M. Sue Leffell,[2] Nancy D. Rossiter,[2] Marianna Zahurak,[1] Richard J. Jones,[1] Ephraim J. Fuchs[1]



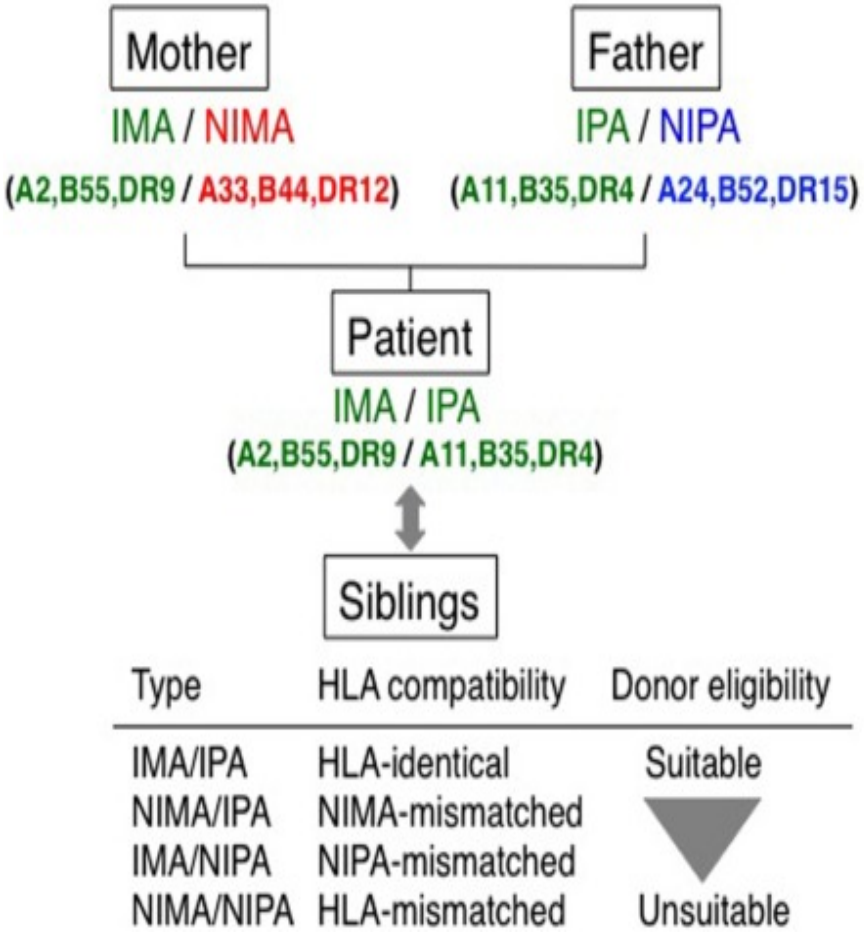


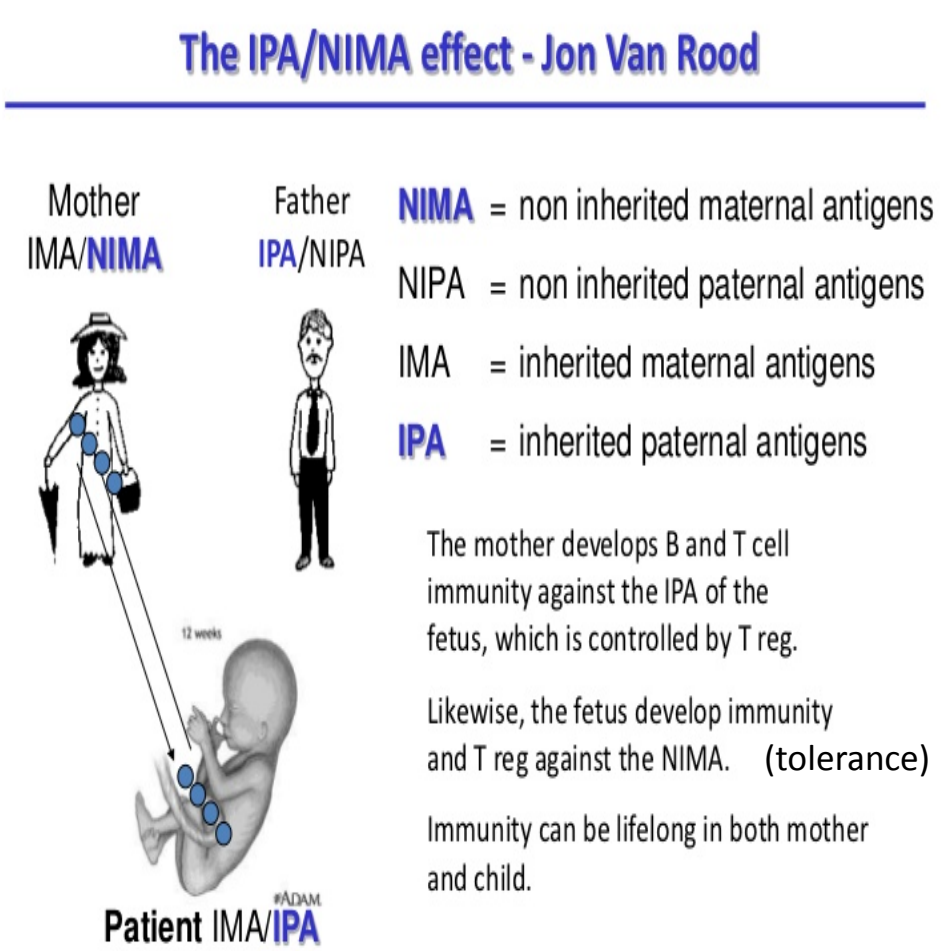




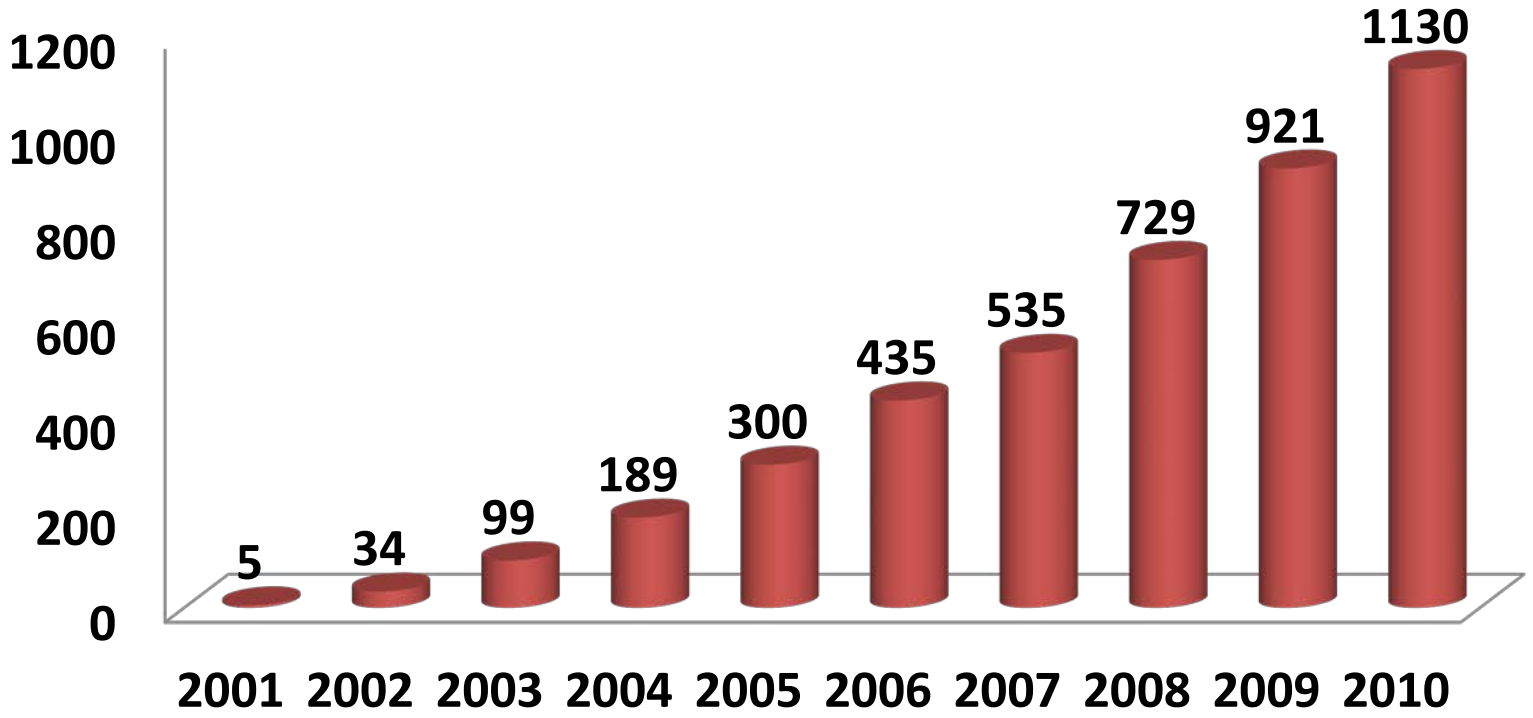
Improved outcome with iKIR gene mismatching and KIR group B haplotype donors
= Tcell depleted technique

NIMA mismatched haploidentical sibling donors are associated with less acute GVHD (Jon Van Rood, 2002)



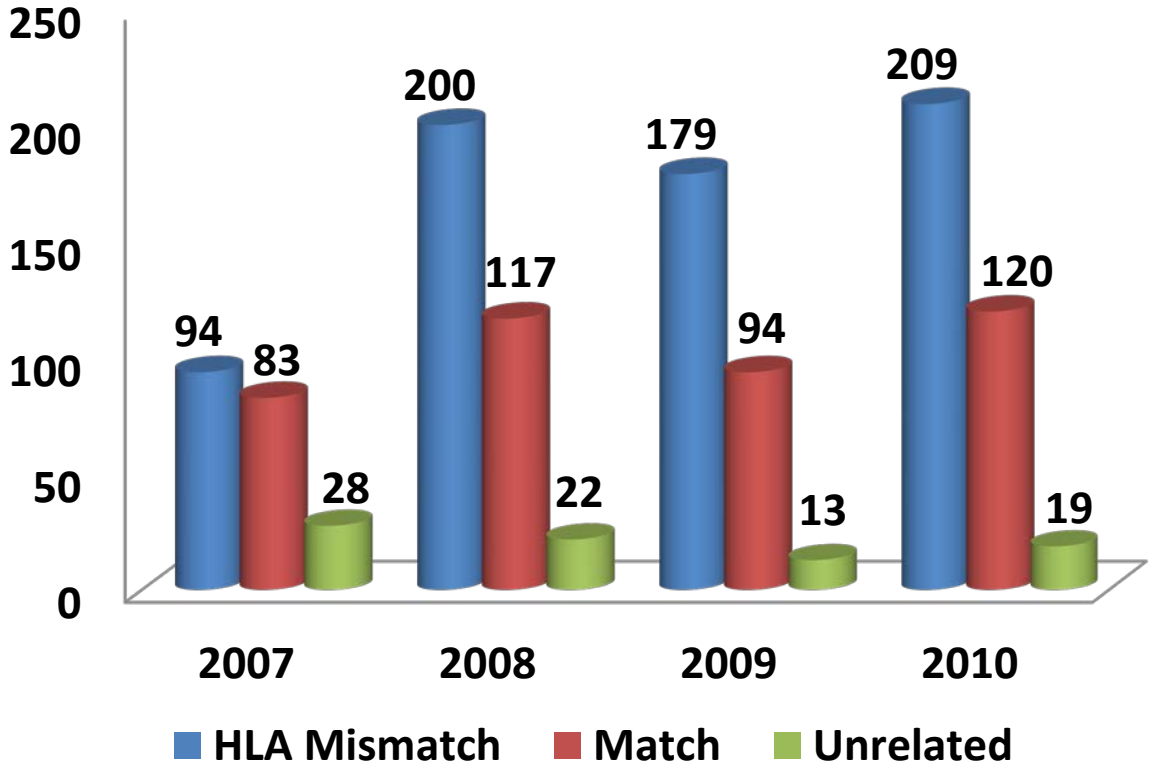


No. of Haploidentical HSCT accumulated in PUIH



Peking University Institute of Haematology

The changing of Composition of Haploidentical allo-HSCT in PUIH from 2007 to 2009



%	Haplo-identical
2007	45.9
2008	59.0
2009	62.6
2010	60.1

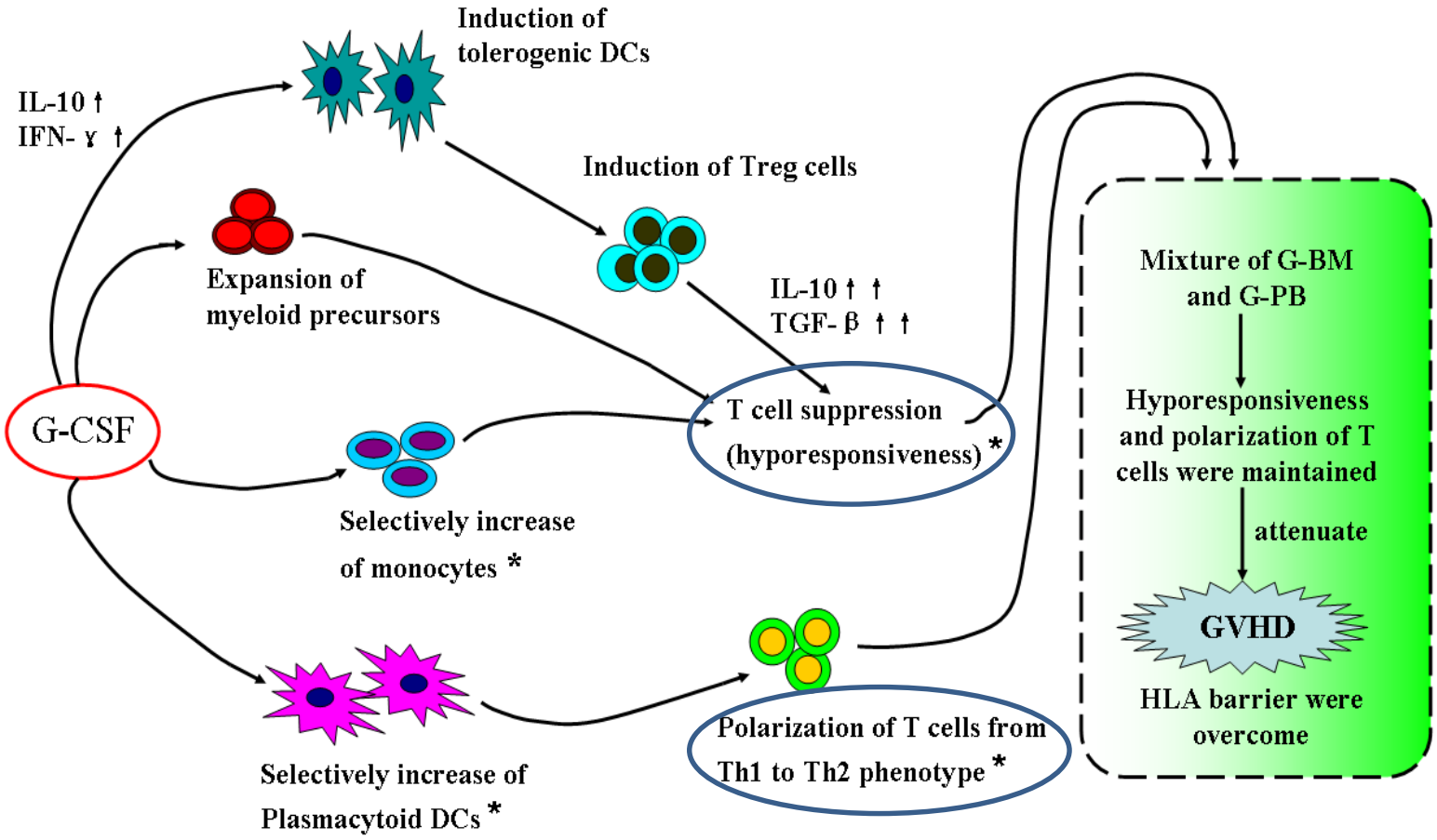
PUIH data

GIAC protocol

- G: donor treatment with rhG-CSF
- I: intensified immunological suppression
- A: anti-human thymocyte immunoglobulin (ATG) for the prevention of GVHD
- C: combination of G-PB and G-BM

Huang XJ, et al. Blood, 2006, 107(8):3065-3073
Huang XJ, et al. Annals of Medicine, 2008, 40,444-455
Huang XJ, et al. Clin Cancer Res. 2009;15:4777-4783
Huang XJ, et al. BBMT. 2011 Jun;17(6):821-30.

Immunoregulatroy Effects after G-CSF Administration to Healthy Donors



Huang XJ, et al. Biol Blood Marrow Transplant.2011;17(2):197-204

GCSF primed BM + PB
Huang XJ, BBMT 2009

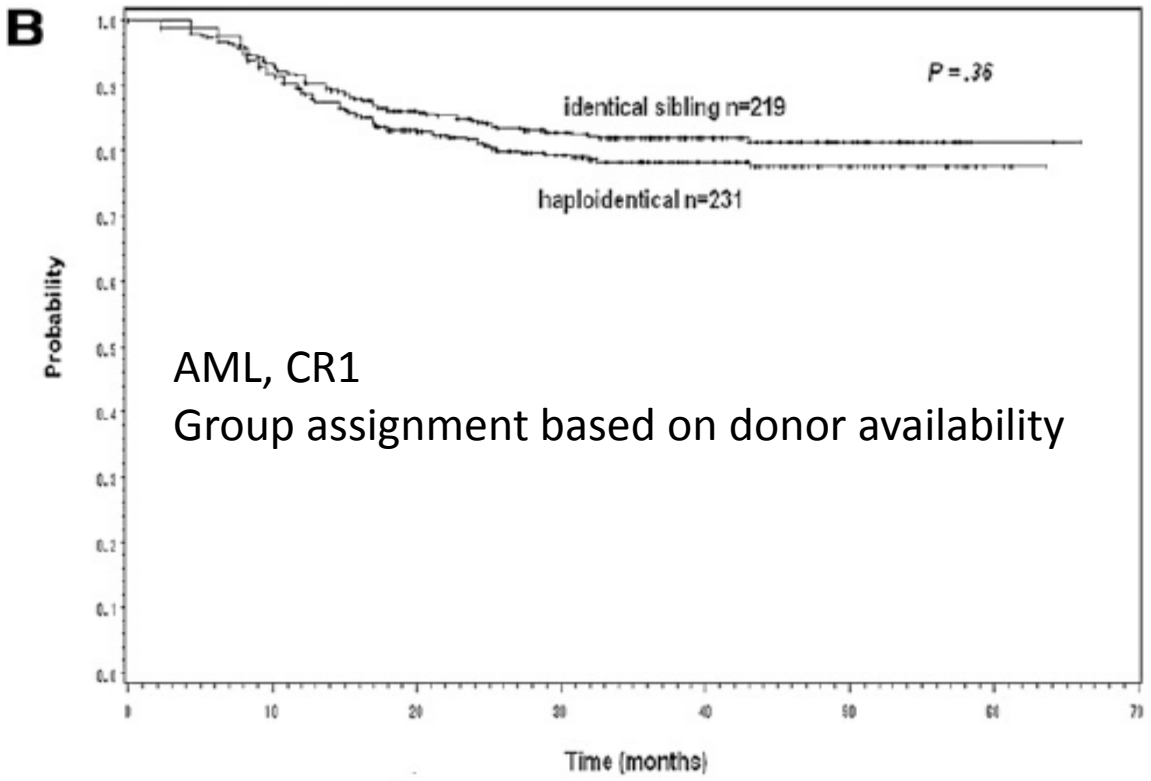
- **Rationale:** GCSF: Th1 > Th2
- Conditioning: BuCy + AraC + CCNU + rATG
- GVHD prophylaxis: CsA + short MTX + MMF (D60)
- Graft: G-CSF primed BM + PB
- Results: n = 250, AML/ALL, SR + HR
  - Engraftment 100 %
  - Acute GVHD III-IV 13 %
  - **cGVHD extensive 22 %**
  - **TRM D100 7 %**
  - **Relapse SR 15 %**
  - LFS SR AML 3 yr 70 %

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

Blood, 2015

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

Overall survival



AML, CR1

Group assignment based on donor availability

TRANSPLANTATION

Blood 2013

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]

- n = 80
- Conditioning: Thiotepa, Fludarabine, busulfan
- GVHD prophylaxis: CsA, MTX, MMF , ATG, basiliximab
- Low incidence of acute and chronic GVHD
- Chinese results reproducible
- Comparable to MUD and Cord blood transplants

Conclusion

- T cell replete haploSCT with PTCy
  - has superior outcome in comparison to T cell depleted haploSCT
  - Is easier to perform
- HaploSCT has several advantages over Cord blood and MUD transplants (donor access, immune reconstitution …)
- Retrospective comparison show similar outcomes
- Randomized studies are required to compare outcome with different stem cell sources
- If outcomes appear equivalent haploSCT with PTCy may become first choice and standard of care
- In the future haploSCT may offer universal access to donor also for ethnic minorities

SPECIAL REPORT

Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants

BMT 2015

JR Passweg[1], H Baldomero[1], P Bader[2], C Bonini[3], S Cesaro[4], P Dreger[5], RF Duarte[6], C Dufour[7], JHF Falkenburg[8], D Farge-Bancel[9], A Gennery[10], N Kröger[11], F Lanza[12], A Nagler[13], A Sureda[6] and M Mohty[14] for the European Society for Blood and Marrow Transplantation (EBMT)