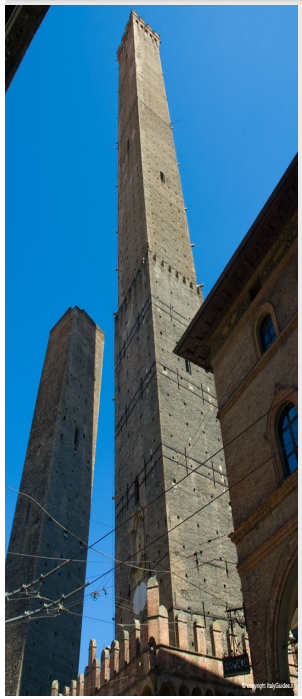
Novità in Ematologia: la comunicazione, le terapie innovative e di supporto, la sostenibilità

MODENA

18-19 MAGGIO

2017

NOVITÀ IN TEMA DI TRAPIANTO ALLOGENICO



FRANCESCA BONIFAZI

Hematology Seragnoli

University Hospital S. Orsola-Malpighi, Bologna

GVHD PROPHYLAXIS

GVHD TREATMENT

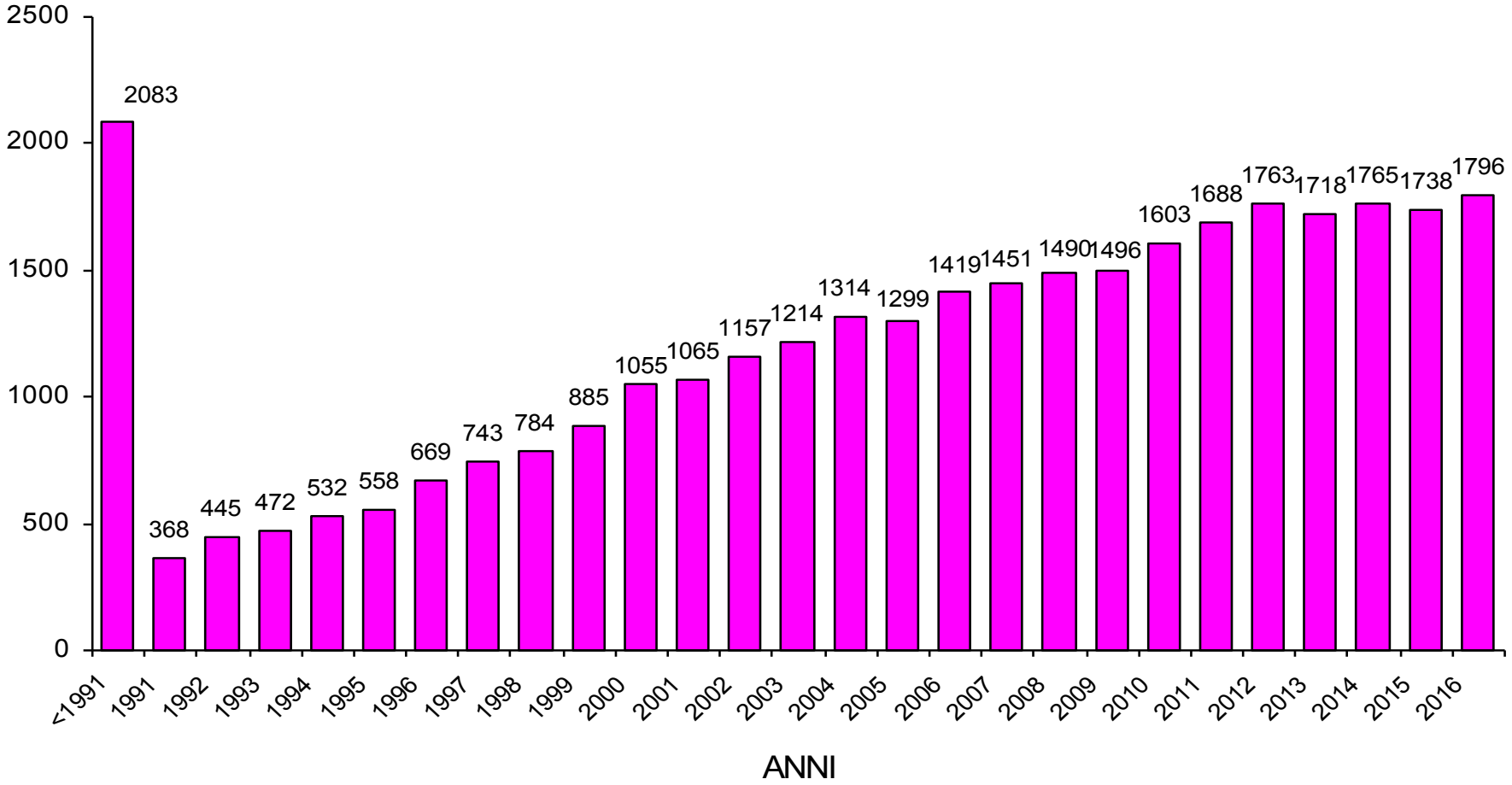
ALGORITHM OF DONOR CHOICE

ITALIAN ACTIVITY OF

ALLOGENEIC STEM CELL TRANSPLANT

GITMO Trapianto Allogenico

Allotrapianti registrati
(N=32570)



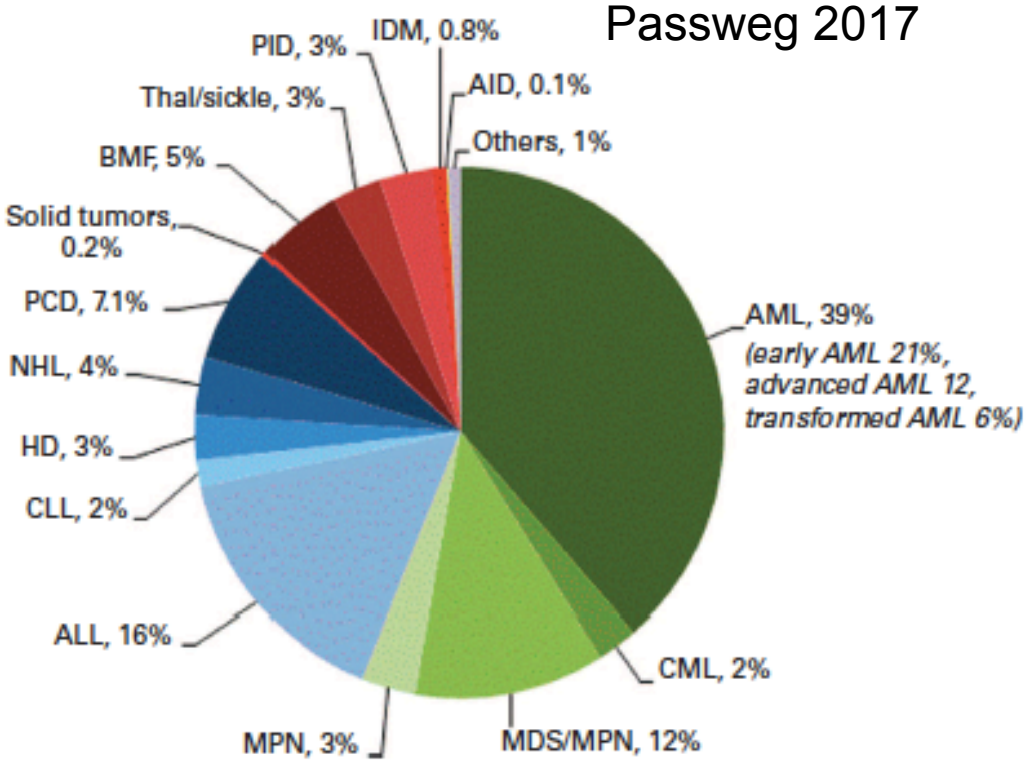
al 22 marzo 2017

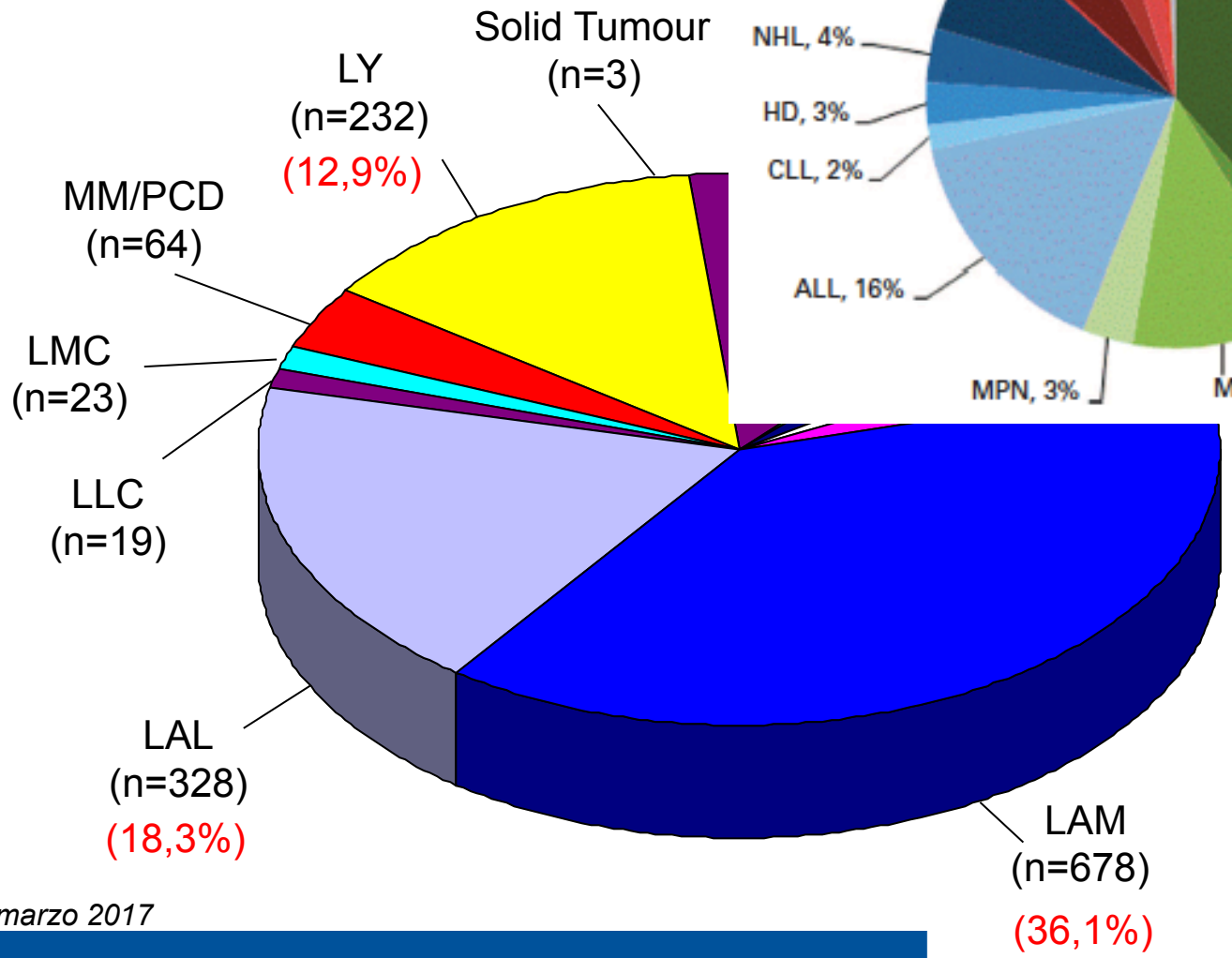
GITMO

GITMO Trap

Numero Trapianti

Atti





al 22 marzo 2017

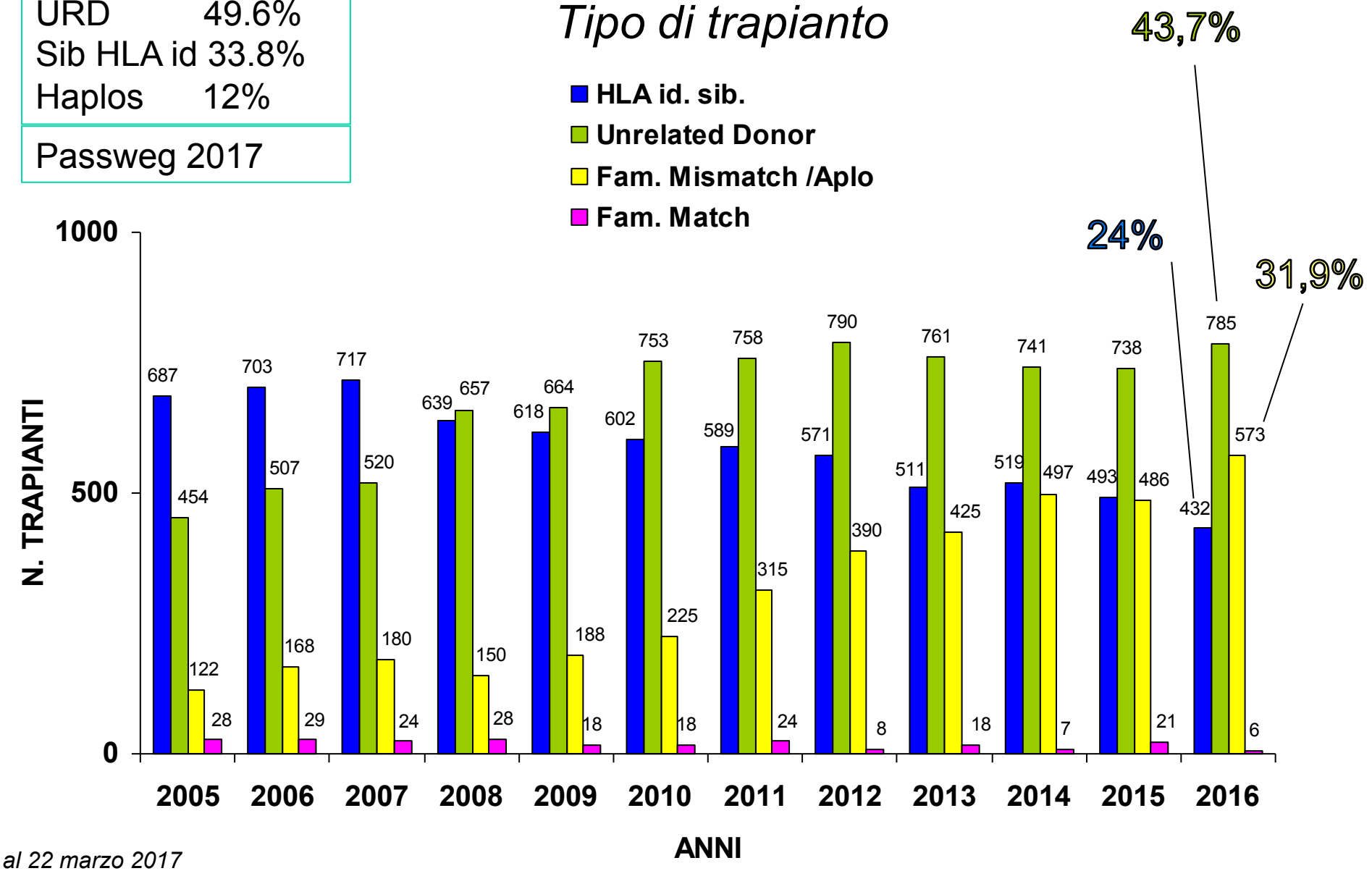
GITMO

GITMO Trapianto Allogenico

Tipo di trapianto

URD	49.6%
Sib HLA id	33.8%
Haplos	12%

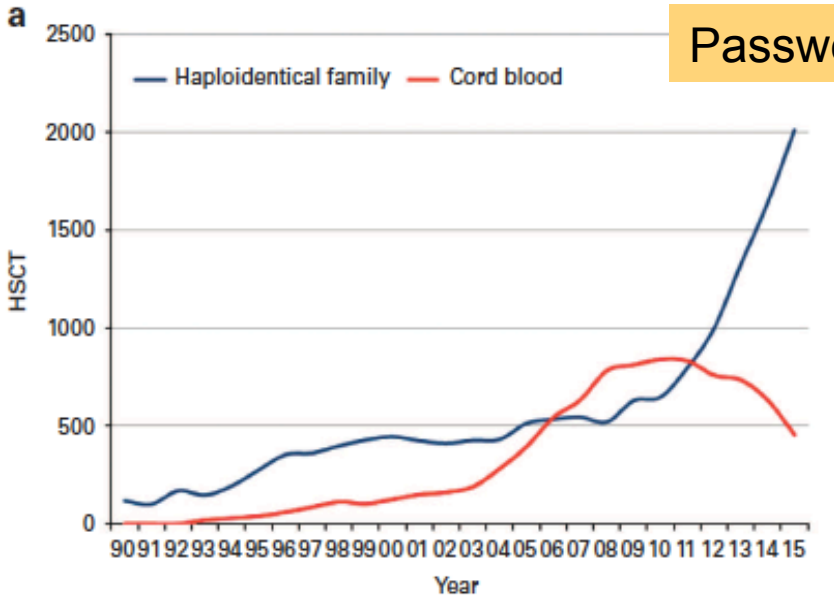
Passweg 2017

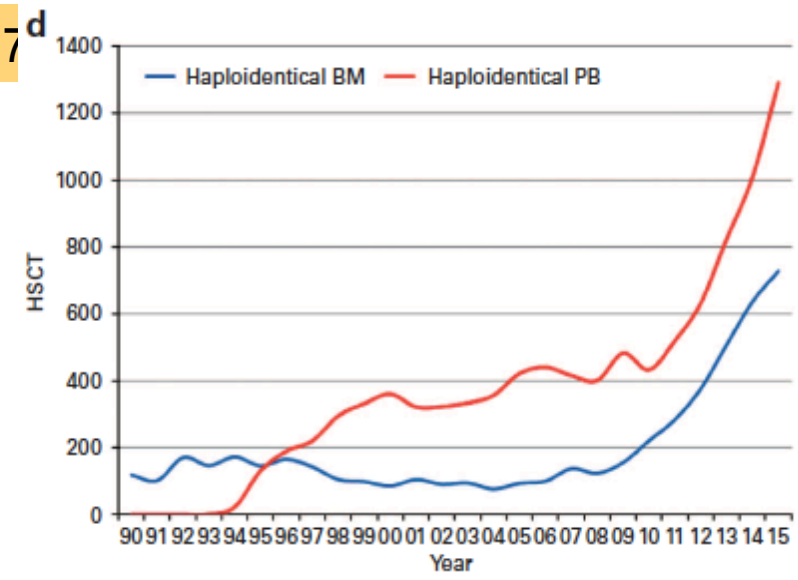


al 22 marzo 2017

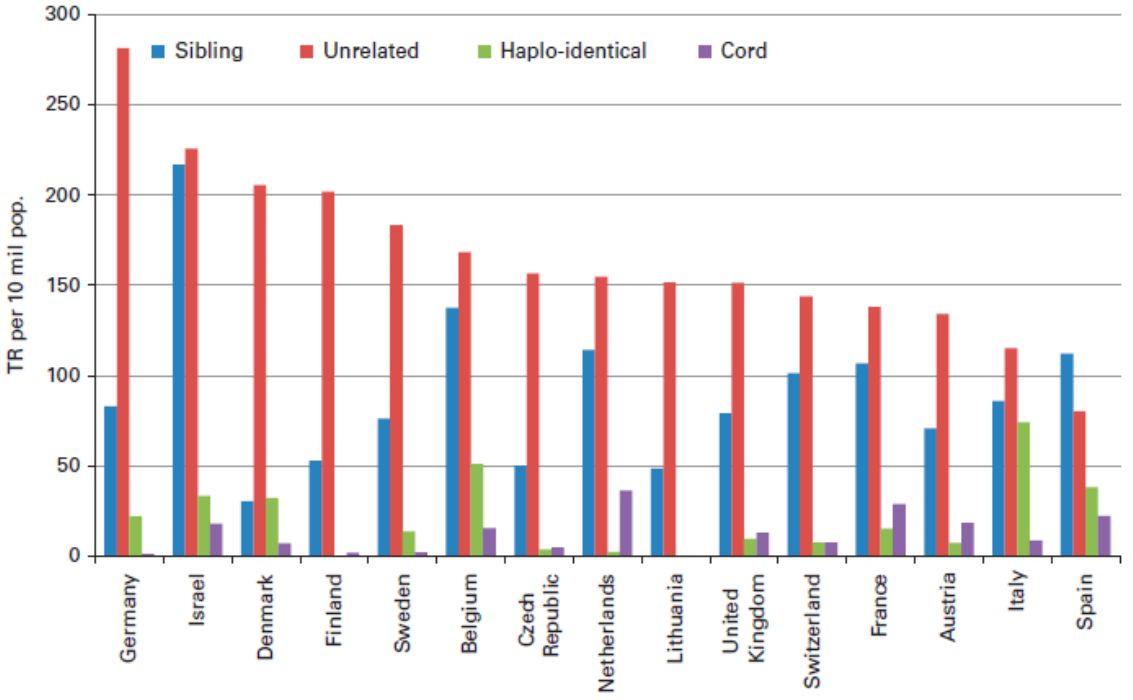
GITMO

Passweg 2017





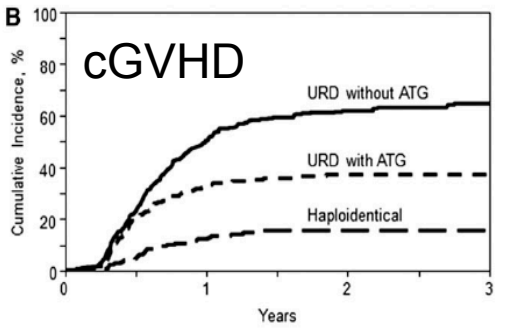
Passweg BMT 2015

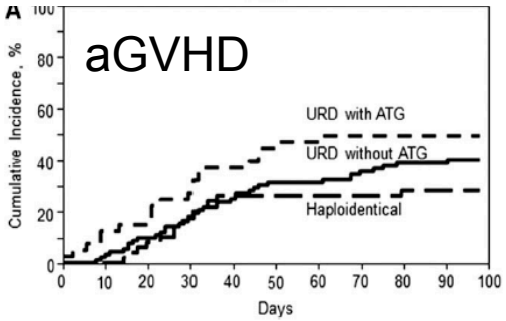


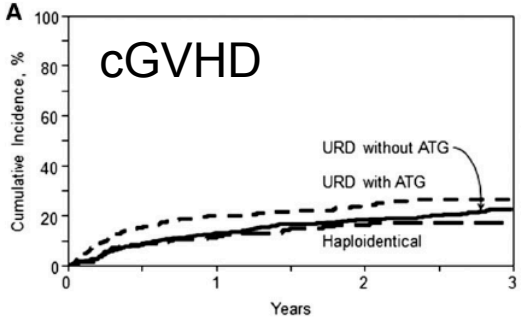
TR Allo	387	494	275	257	275	372	215	308	200	253	260	288	230	283	252

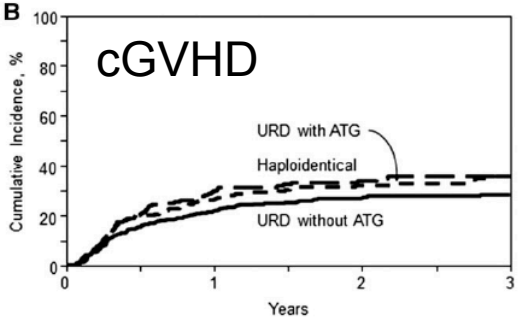
PT-CY and Haplos

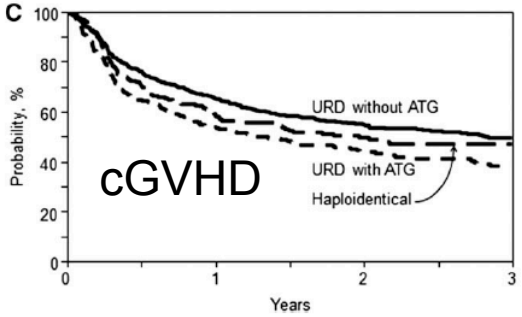
Kanate, Mussetti, Blood 2016

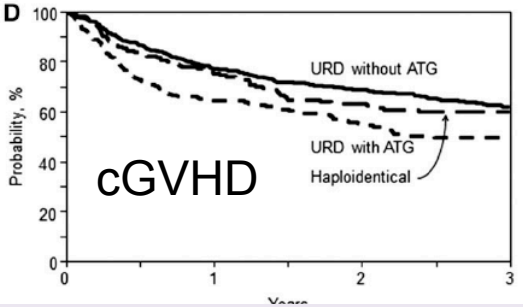












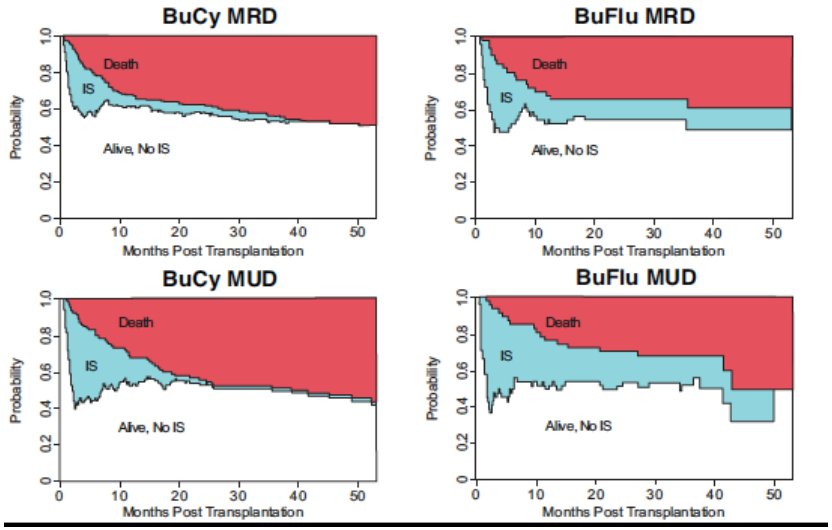
Ciurea et al Blood 2015

Outcome	Donor type: Haploidentical	Donor type: Unrelated	*P*
Myeloablative transplants			
Grade 2-4 acute GVHD at day 90	16% (10-24)	33% (30-35)	<.0001
Grade 3-4 acute GVHD at day 90	7% (3-13)	13% (11-15)	.02
Chronic GVHD			
At 12 mo	28% (20-37)	45% (42-47)	.0005
At 36 mo	30% (21-39)	53% (50-56)	<.0001
Nonrelapse mortality			
At 12 mo	12% (7-19)	14% (12-16)	.56
At 36 mo	14% (8-22)	20% (18-22)	.14
Relapse			
At 12 mo	41% (33-50)	32% (30-35)	.04
At 36 mo	44% (34-53)	39% (37-42)	.37
OS			
At 12 mo	65% (56-73)	65% (63-68)	.98
At 36 mo	45% (36-54)	50% (47-53)	.38

Reduced intensity transplants			
Grade 2-4 acute GVHD at day 90	19% (12-28)	28% (25-31)	.05
Grade 3-4 acute GVHD at day 90	2% (0-7)	11% (8-13)	<.0001
Chronic GVHD			
At 12 mo	27% (19-37)	43% (40-47)	.001
At 36 mo	34% (24-44)	52% (48-55)	.002
Nonrelapse mortality			
At 12 mo	6% (2-12)	16% (13-18)	.0001
At 36 mo	9% (4-16)	23% (19-26)	.0001
Relapse			
At 12 mo	43% (32-53)	34% (31-38)	.12
At 36 mo	58% (46-68)	42% (38-45)	.006
OS			
At 12 mo	64% (53-73)	60% (56-63)	.46
At 36 mo	46% (35-56)	44% (40-47)	.71

Low immunosuppressive burden after HLA-matched related or unrelated BMT using PT-Cy

	BuCy MRD	BuFlu MRD	BuCy MUD	BuFlu MUD
GVHD				
Cumulative incidences of acute GVHD at 1 year, % (95% CI)				
Grade II-IV	40% (32-47%)	42% (28-56%)	54% (43-63%)	60% (44-72%)
Grade III-IV	12% (8-18%)	13% (5-25%)	15% (9-23%)	19% (9-32%)
Cumulative incidences of chronic GVHD at 2 years	6.5% (3-11%)	6.7% (2-17%)	9.7% (5-17%)	21% (11-34%)
IMMUNOSUPPRESSION				
Cumulative incidences of initiation by 3 years, % (95% CI)				
Corticosteroid	46% (38-54%)	51% (36-65%)	65% (54-73%)	68% (53-80%)
Any non-steroidal immunosuppressant	40% (32-48%)	40% (26-54%)	58% (47-67%)	64% (47-77%)
Calcineurin inhibitor	36% (28-44%)	40% (26-54%)	50% (39-59%)	51% (36-65%)
Never required IS beyond PTCy:				
All patients	51%	47%	31%	26%
Patients alive at last follow-up	49%	50%	24%	30%
Duration of IS in those requiring IS beyond PTCy				
Corticosteroid, median (IQR) # of days	57 (40-99)	74 (41-206)	63 (46-133)	147 (49-481)
Any non-steroidal IS, median (IQR) # of days	141 (55-218)	151 (53-354)	162 (64-254)	232 (87-561)
Pharmacologic	142 (77-190)	147 (78-231)	158 (70-281)	149 (69-264)
Calcineurin inhibitor	135 (79-175)	147 (78-231)	156 (67-281)	145 (62-278)
Phototherapeutic	45 (28-109)	225 (146-262)	113 (64-148)	612 (281-738)
Probability of being alive and off IS at:				
1 year	61%	53%	53%	51%
3 years	53%	48%	49%	56%



Kanakry, Blood 2017

HAPLO ≠ PT-CY

T- repleted HAPLO platforms:

- PT-CY
- ATG-CSA-MMF-MTX-BASI
- SIROLIMUS based approach

T- depleted HAPLO platforms

- T-conv/reg
- αβ-depletion

+ suicide genes (IC9, Zalmoxis)

BP-004 Clinical Trial Sites

- OPBG Lead Clinical Site – 3 additional sites in EU
- Multiple sites in US

United States active sites:

- Texas Children's Hospital
- Children's Hospital Los Angeles
- Children's Healthcare of Atlanta at Egleston
- Boston Children's Dana Farber
- Children's National Medical Center, Washington DC
- Seattle Children's Hospital/UW/FHRCC
- Children's Hospital – OHSU, Portland
- Children's Hospital UTSW, Dallas
- The Children's Hospital at Montefiore, New York

Europe active sites:

- Ospedale Pediatrico Bambino Gesù, Rome
- Great Ormond Street Hospital, London
- Great North Children's Hospital Research Unit, Newcastle

BP-004 Evaluation-Non-Malignant & Malignant (EU and US)

With ≥ 100 days F/U *(as of 1/20/17)* **N=91**

Selected Non-Malignant Subset evaluation (EU and US)

PID (≥ 100d F/U) *(as of 1/20/17)* **N=25**

Thalassemia $\beta_0\beta_0$ (≥ 100d F/U) *(as of 1/20/17)* **N=9**

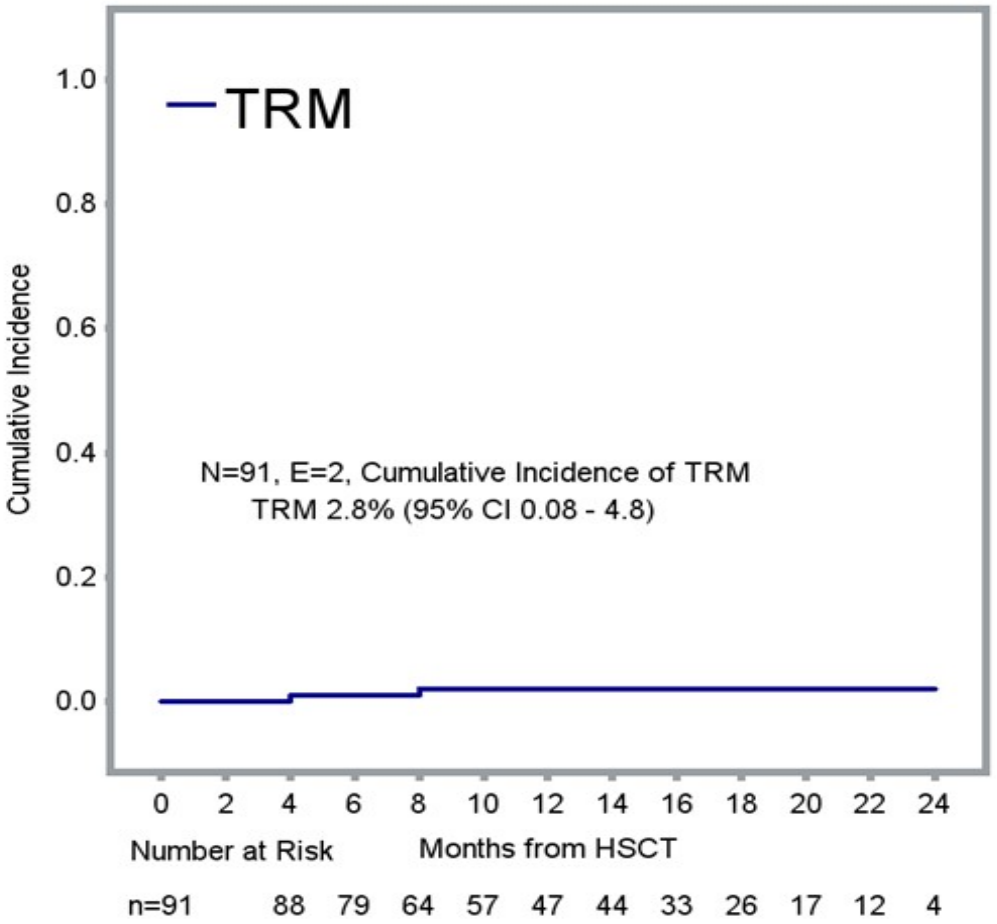
Fanconi anemia (≥ 60d F/U) *(as of 3/20/17)* **N=9**

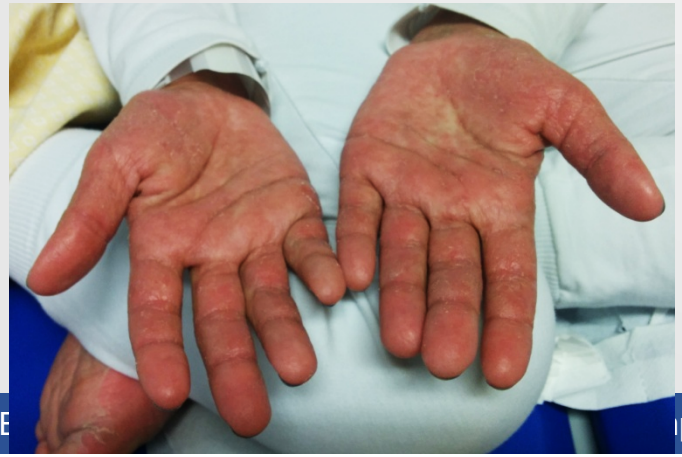
Selected Malignant Subset evaluation (EU-OPBG only)

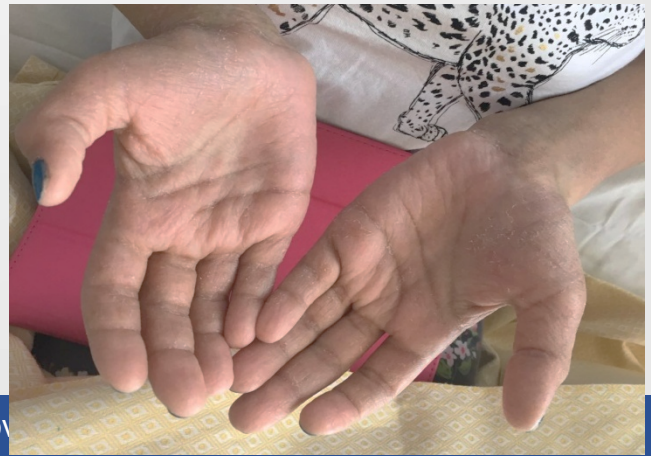
Acute Leukemia (≥ 60d F/U) *(as of 3/20/17)* **N=43**

ALL & AML (CR1, CR2)

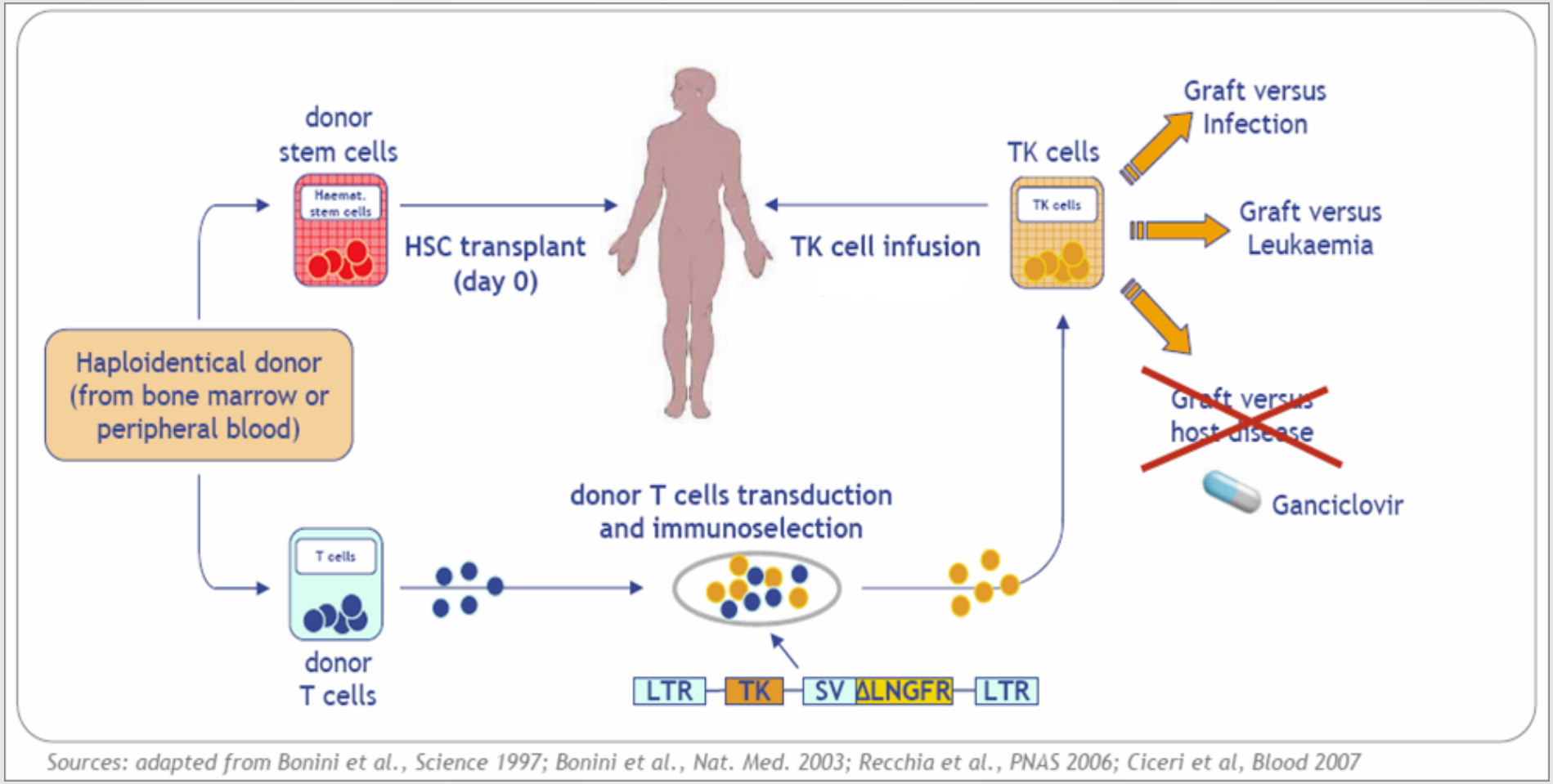
BP-004 Trial Outcomes: TRM/NRM (N=91 patients with ≥100d F/U; EU and US)







HSV-TK cells (Zalmoxis) approach



Sources: adapted from Bonini et al., Science 1997; Bonini et al., Nat. Med. 2003; Recchia et al., PNAS 2006; Ciceri et al, Blood 2007

13

TK cells clinical trials

Phase I-II TK007

NCT00914628

Ciceri, Bonini et al, Lancet Oncol 2009

Haplo-HSCT* plus TK cells

*T-depleted (T cells, $1x10^4$/Kg)

Dose of TK cells ($1-x10^7$/Kg - $1x10^7$/Kg)
Up to 4 monthly doses up to IR (CD3+ cell count >/= 100/mcl)
Starting 21 to 49 days after HSCT in absence of IR and/or GvHD

Phase III TK008

MOLMED
NCT00914628

R (3:1)

- **Haplo-HSCT* plus TK cells**
- **Haplo-HSCT****

*T-depleted (T cells, $1x10^4$/Kg)

**T-depleted (T cells, $1x10^4$/Kg)
or
** unmanipulated BMT/PB + HD CTX

Dose of TK cells ($1x10^7$/Kg)
Up to 4 monthly doses up to IR (CD3+ cell count >/= 100/mcl)
Starting 21 to 49 days after HSCT in absence of IR and/or GvHD

✓**Italian activity shows a peculiar clinamen in the attitutude to haplo transplants**

✓**Italy is the cradle of new innovative approaches to T-depleted haplo platforms**

✓**The extraordinary success of PT-Cy in haplo transplants will extend this option also to standard transplants hopefully on the basis of prospective randomised trials.**

✓**The potential success of new GVHD platforms could modify the current algorithm of donor choice: this should be done only in an evidence –based approach.**

GVHD TREATMENT

- ✧GVHD IS DIFFICULT TO CURE:
  - ✧approximately 50% of patients will not achieve a sustained CR after first-line therapy with steroids and <50% of CR are maintained.

- ✧GVHD (SR or severe) NEGATIVELY IMPACTS OUTCOME

  OS in steroid-resistant (SR) aGVHD: 15% at 2 years (median 6 months).

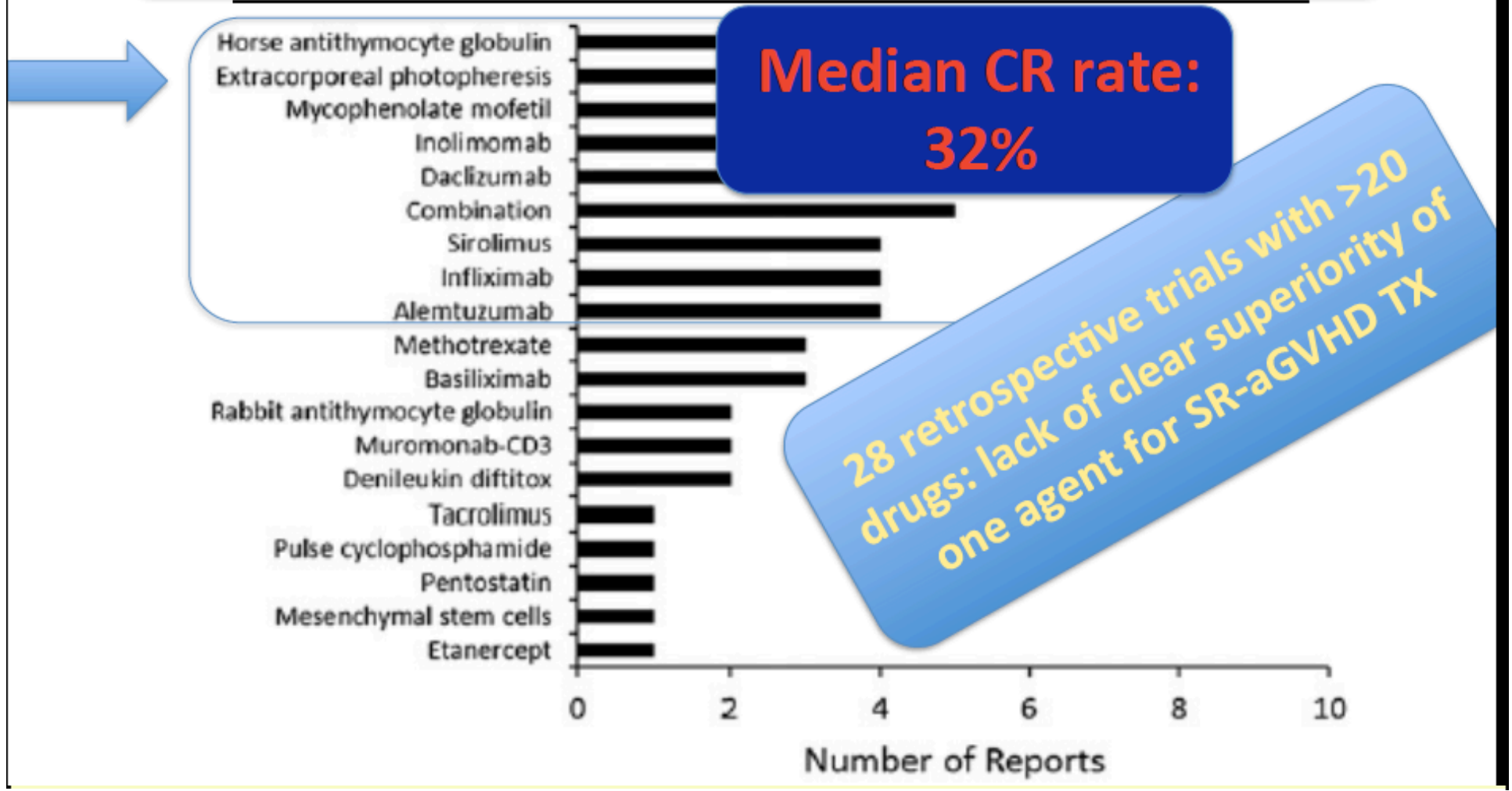
- ✧GOLDEN STANDARD FOR SECOND-LINE THERAPY STILL MISSING

American Society for Blood and Marrow Transplantation

REVIEW

Secondary Treatment of Acute Graft-versus-Host Disease: A Critical Review

Paul J. Martin,[1,2] Yoshihiro Inamoto,[1,2] Mary E. D. Flowers,[1,2] Paul A. Carpenter[1,3]



GVHD TREATMENT

THERAPIES

- NEW DRUGS FOR SR GVHD ARE GOING TO BE TESTED

BEGELOMAB

RUXOLITINIB

IBRUTINIBINIB

VEDOLIZUMAB

α1ANTITRYPSIN

MESENCHIIMAL CELLS

GVHD PROPHYLAXIS

PROPHYLAXIS of acute or/and chronic GVHD?

Table 4. Impact of aGVHD prophylactic strategies on cGVHD.

Strategy	Results on GVHD	Reference
Current strategies		
Calcineurin inhibitor ± methotrexate (MTX)	Little/no impact	[9]
Calcineurin inhibitor + mycophenolate mofetil (MMF)	Little/no impact	[9]
Anti-T cell globulin (ATG)	Decreased incidence	[63,64]
Alemtuzumab	Decreased incidence	[67]
Ex vivo $CD34^+$ cell selection	Decreased incidence	[74]
Novel strategies		
Pentostatin	Unknown	–
Suicide gene therapy in T cells	Decreased incidence[a]	[77]
Post-transplant cyclophosphamide (Cy)	Decreased incidence	[79]
Ex vivo photodepletion of anti-host reactive donor T cells (TH9402, Kiadis)	Unknown	–
Ex vivo depletion of $TCR\alpha\beta^+$ donor T cells	Decreased incidence[a]	[81]
Ex vivo depletion of $CD45RA^+$ naive T cells	Decreased incidence[a]	[82]
Proteasome inhibitors (bortezomib)	Decreased incidence[a]	[90]
CTLA-4 immunoglobulin	Unknown	–
mTOR inhibitors (sirolimus)	Little/no impact	[92]
JAKs inhibitors	Unknown	–
Demethylating agents (5-azacytidine)	Decreased incidence[a]	[94]
Histone deacetylase inhibitors	Unknown	–
Anti-IL-6 receptor antibody (tocilizumab)	Unknown	–
CCR5 inhibitor (maraviroc)	Unknown	–
Recombinant urate-oxidase (rasburicase)	Unknown	–
Anti-CD20 antibody (rituximab)	Decreased incidence	[9]
Treg infusion	Unknown	–
Low dose IL-2	Unknown	–
MSC coinfusion	Unknown	–

[a]These results have to be validated in further studies.

Servais. Exp Opin on invest Drugs 2016;25: 957-972

FOCUSING THE SETTING

BM
PBSC
CB

SIBL
URD
HAPLO

9
combinations…….

BM
PBSC
CB

SIBL
URD
HAPLO

MA
RIC
NMA

Malign
Non malign

54
combinations…….

…on the standard transplant

GVHD PROPHYLAXIS: THE EVIDENCES

Table 1. T-cell depleting approaches.

Drug or pathway	Main mechanism of action	Level of clinical evidence	Ongoing clinical studies for novel therapies (ClinicalTrials.gov)
Anti-T-cell globulin (ATG)	Donor T-cell depletion	Phase III [63,64]	Standard approach in the PBSC setting
Alemtuzumab	Depletion of CD52$^+$ cells (including donor T cells)	Phase I–II [71]	–
Ex vivo CD34$^+$ cell selection	*Ex vivo* depletion of graft's immune cells	Phase II [74]	–
Anti-CD2 monoclonal antibody (siplizumab)	Donor T-cell depletion	–	Phase II: #NCT00113646
Pentostatin	Apoptosis of donor T cells through inhibition of adenosine deaminase	Phase I–II [76]	Phase I: #NCT00096161
Suicide gene therapies: transducing T cells with herpes simplex 1 virus thymidine kinase (HSV-TK), CD20, EGF-R, inducible caspase (iCasp)	Donor T-cell depletion with specific molecules, i.e. ganciclovir, anti-CD20 antibodies, anti-EGFR antibodies, AP1903.	HSV-TK: Phase I–II [77] iCasp: phase I [78]	iCasp: phase I–II: #NCT01744223, #NCT02065869
Post-transplant cyclophosphamide (Cy)	Depletion of early proliferating alloreactive donor T cells after graft infusion	Phase II [79]	Cy combined with standard prophylaxis: phase II: #NCT01349101, #NCT01374841, #NCT02065154 Single-agent postransplant Cy: phase III: #NCT02345850
Ex vivo photodepletion of anti-host reactive donor T cells (TH9402, Kiadis)	Depletion of anti-host alloreactive donor T cells	Phase II [80]	Phase II: #NCT01794299
Ex vivo depletion of TCR$\alpha\beta^+$ donor T cells	Depletion of mature TCR$\alpha\beta^+$ donor T cells (preservation of donor-derived NK cells and TCR$\gamma\delta^+$ T cells)	TCR$\alpha\beta^+$/CD19$^+$ depletion: phase I–II [81]	TCR$\alpha\beta^+$/CD19$^+$ depletion: phase II–III: #NCT02323867, #NCT02600208 TCR$\alpha\beta^+$ depletion: phase I–III: #NCT02327351, #NCT02193880
Ex vivo depletion of CD45RA$^+$ naive T cells	Depletion of naive donor T cells, based on the postulate that they are the main T-cell subset mediating GVHD	Phase II [82]	Phase II: #NCT 00914940, #NCT02220985

Servais. Exp Opin on Invest Drugs 2016;25: 957-972

Table 2. Other (non T-cell depleting) pharmacological approaches.

	Drug or pathway	Main mechanism of action	Level of clinical evidence	Ongoing clinical studies for novel therapies (ClinicalTrials.gov)
Standard approaches	Methotrexate (MTX)	Inhibition of T-cell proliferation by acting as folate antagonist	Phase II–III, in combination with a calcineurin inhibitor (reviewed in [52])	–
	Cyclosporin A	Inhibition of TCR-induced T-cell activation by blocking calcineurin	Phase II–III, in combination with MTX or MMF (reviewed in [52])	–
	Tacrolimus	Inhibition of TCR-induced T-cell activation by blocking calcineurin	Phase II–III, in combination with MTX or MMF (reviewed in [52])	–
	Mycophenolate mofetil	Inhibition of T-cell proliferation by blocking *de novo* synthesis of guanosine nucleotides	Phase II–III, in combination with a calcineurin inhibitor (reviewed in [52])	–
Novel approaches	*Functional inhibition of donor T-cell activation*			
	Proteasome inhibitors (bortezomib)	Inhibition of T-cell activation downstream TCR stimulation through inhibition of NFkB (additional effects on cytokine secretion, chemotactism, APC functions and Treg differentiation)	Early administration after alloHSCT: phase II [90]	Bortezomib: phase II: #NCT02208037 Carfilzomib: phase I: #NCT01991301
	CTLA-4 Ig (abatacept, belatacept)	Blockade of T-cell CD28 positive costimulatory signal	Phase II [91]	Phase II: #NCT01012492, #NCT01743131
	mTOR inhibitors (sirolimus)	Inhibition of cell-cycle progression in response to IL-2 in T cells	Phase III [92]	Phase II: #NCT01428973, #NCT01251575
	JAKs inhibitors (JAK1/2 inhibitor ruxolitinib, JAK3 inhibitor tofacitinib)	Blockade of cytokine-induced signal transduction in T cells	Retrospective study [93]	Ruxolitinib: phase I: #NCT02528877
	Epigenetic modulation in immune cells			
	Demethylating agents (5-aza-cytidine, decitabine)	Inhibition of activation and proliferation of alloreactive donor T cells, induction of Treg	Phase I–II [94]	5-Azacitdine: phase I–II: #NCT01747499, #NCT02204020, #NCT02458235, #NCT01541280, #NCT01835587, #NCT02017457 Decitabine: phase I–II: #NCT01758367
	Histone deacetylase inhibitors (vorinostat, givinostat)	Decreased secretion of inflammatory cytokines, increased expression of IDO by dendritic cells, suppression of innate and allo-stimulating functions of APCs, increase in Treg numbers	Phase I–II [95]	Vorinostat: phase II: #NCT01789255, NCT01790568
	Inhibition of signals mediated by extracellular mediators			
	Anti-IL-6 receptor antibody (tocilizumab)	Inhibition of IL-6-mediated effects	Phase I–II [96]	Phase II: #NCT02206035
	CCR5 inhibitor (maraviroc)	Inhibition of T-cell trafficking towards target organs	Phase I–II [97]	Phase II: #NCT01785810, #NCT02208037
	Recombinant urate-oxidase (rasburicase)	Oxidation of the uric acid (that acts as a DAMP) into an inactive soluble metabolite	Phase I [98]	–
	B-cell depletion			
	Anti-CD20 antibody (rituximab)	B-cell depletion	–	Phase II: #NCT01044745, #NCT01810926

Table 3. Cellular approaches.

Drug or pathway	Main mechanism of action	Level of clinical evidence	Ongoing clinical studies (ClinicalTrials.gov)
Regulatory T cells (Tregs)			
Treg infusion	Promotion of immune tolerance	Phase I–II [75,124]	Phase I: #NCT01795573, #NCT01937468 Phase II: #NCT02118311
Low dose IL-2	Promotion of Treg expansion and immune tolerance	Phase I [115]	Phase I: #NCT01937468 Phase II: #NCT01927120
Mesenchymal stem cells (MSCs)			
MSC coinfusion	Promotion of Tregs	Phase I-II [125,126]	Phase II: #NCT01045382
Invariant natural killer T (iNKT) cells			
iNKT cell content in the graft	Promotion of immune tolerance	Retrospective study [127]	Phase 0: # NCT02194868
Conditioning regimen involving total lymphoid irradiation and ATG	Sparing of iNKT cells	Phase II [128,129]	Phase II: # NCT01566656, #NCT00896493
Myeloid-derived suppressor cells (MDSCs)			
MDSC infusion	Promotion of immune tolerance	Animal models [47,48]	–

Servais. Exp Opin on invest Drugs 2016;25: 957-972

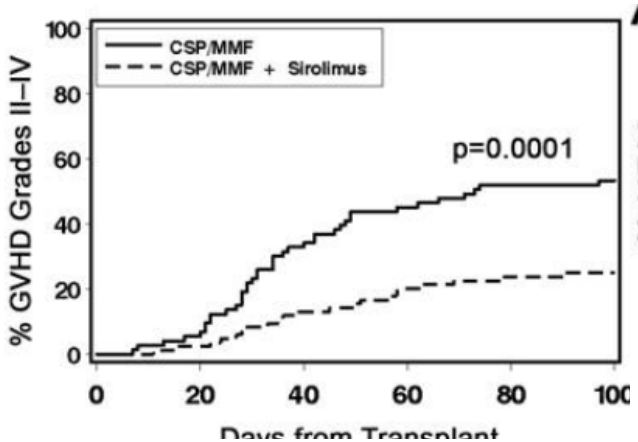
506 Sirolimus Combined with Mycophenolate Mofetil (MMF) and Cyclosporine (CSP) Significantly Improves Prevention of Acute Graft-Versus-Host-Disease (GVHD) after Unrelated Hematopoietic Cell Transplantation (HCT): Results from a Phase III Randomized Multi-Center Trial

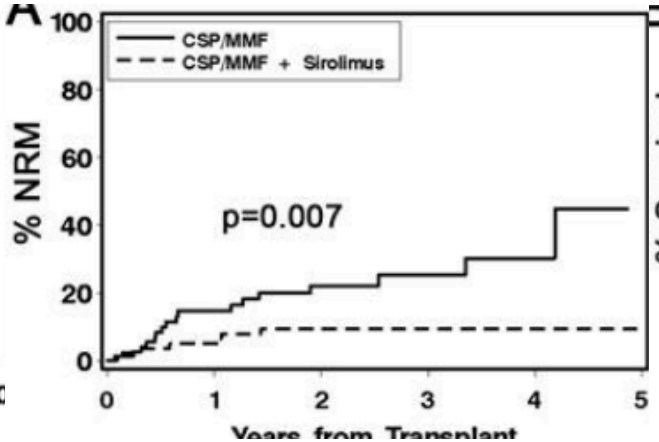
Clinical Allogeneic Transplantation: Acute and Chronic GVHD, Immune Reconstitution
Program: Oral and Poster Abstracts
Type: Oral
Session: 722. Clinical Allogeneic Transplantation: Acute and Chronic GVHD, Immune Reconstitution: Phase II-III Trials and Predictive Biomarkers

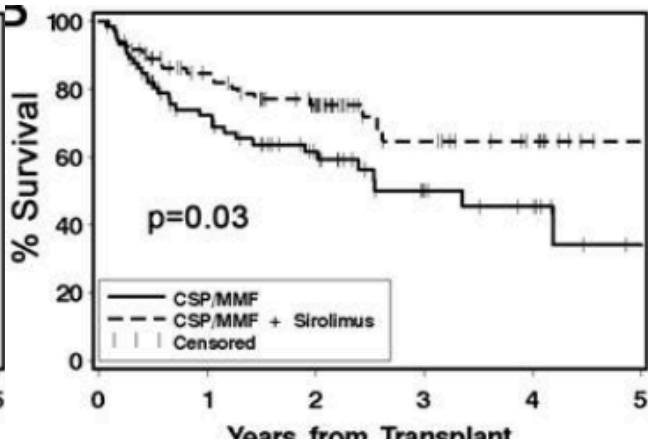
Sunday, December 4, 2016: 4:45 PM
Grand Hall C (Manchester Grand Hyatt San Diego)

Brenda M Sandmaier, MD[1,2], *David G Maloney, MD, PhD*[1,2], *Barry E. Storer, PhD*[3*], *Gitte Olesen, MD*[4*], *Michael B. Maris, MD*[5], *Jonathan A Gutman, MD*[6], *Soren Lykke Petersen, MD, DMSC*[7*], *Amelia Langston, MD*[8], *Thomas Chauncey*[1,2,9*], *Wolfgang Bethge, MD*[10*], *Michael A Pulsipher, MD*[11], *Brian Thomas Kornblit, MD, PhD*[7*], *Ann E Woolfrey, MD*[1,12], *Marco Mielcarek, MD*[1,2], *Paul J. Martin, MD*[1,2,13], *Mary E.D. Flowers, MD*[1,2] *and Rainer F. Storb, MD*[1,2]

	Arm 1	Arm 2	HR[1] (95% CI)	P
Acute II-IV GVHD, day 100	53%	25%	0.38 (0.2-0.6)	0.0001
Acute III-IV GVHD, day 100	8%	2%	0.23 (0.0-1.1)	0.04
Chronic GVHD, 1 year	49%	48%	0.98 (0.6-1.5)	0.94
Non-relapse mortality, 1 year	15%	5%	0.32 (0.1-0.8)	0.007
Relapse/progression, 1 year	21%	19%	0.95 (0.5-1.7)	0.86
Overall survival, 1 year	72%	85%	0.54 (0.3-0.9)	0.03
Progression-free survival, 1 year	65%	77%	0.65 (0.4-1.1)	0.08







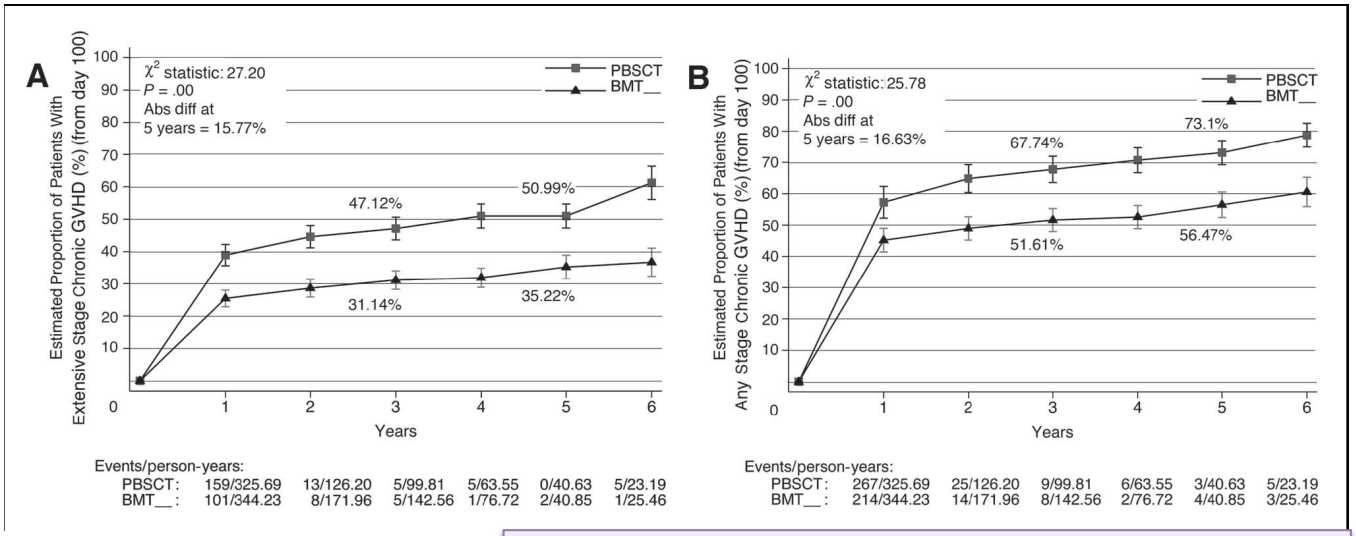
HLA IDENTICAL SIBLING TRANSPLANT:

A STANDARD INDICATION

A STANDARD GVHD PROPHYLAXIS

Which is the "true" incidence of cGVHD after a sibling HLA identical PBSCT?

extensive cGVHD **any grade cGVHD**



Stem Cell Trialists Collaborative Group JCO 2005.

@ 1 yr 40%

@ 3 yrs 47%

@ 1 yr 59%

@ 3 yrs 68%

These data apply to myeloablative transplants!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

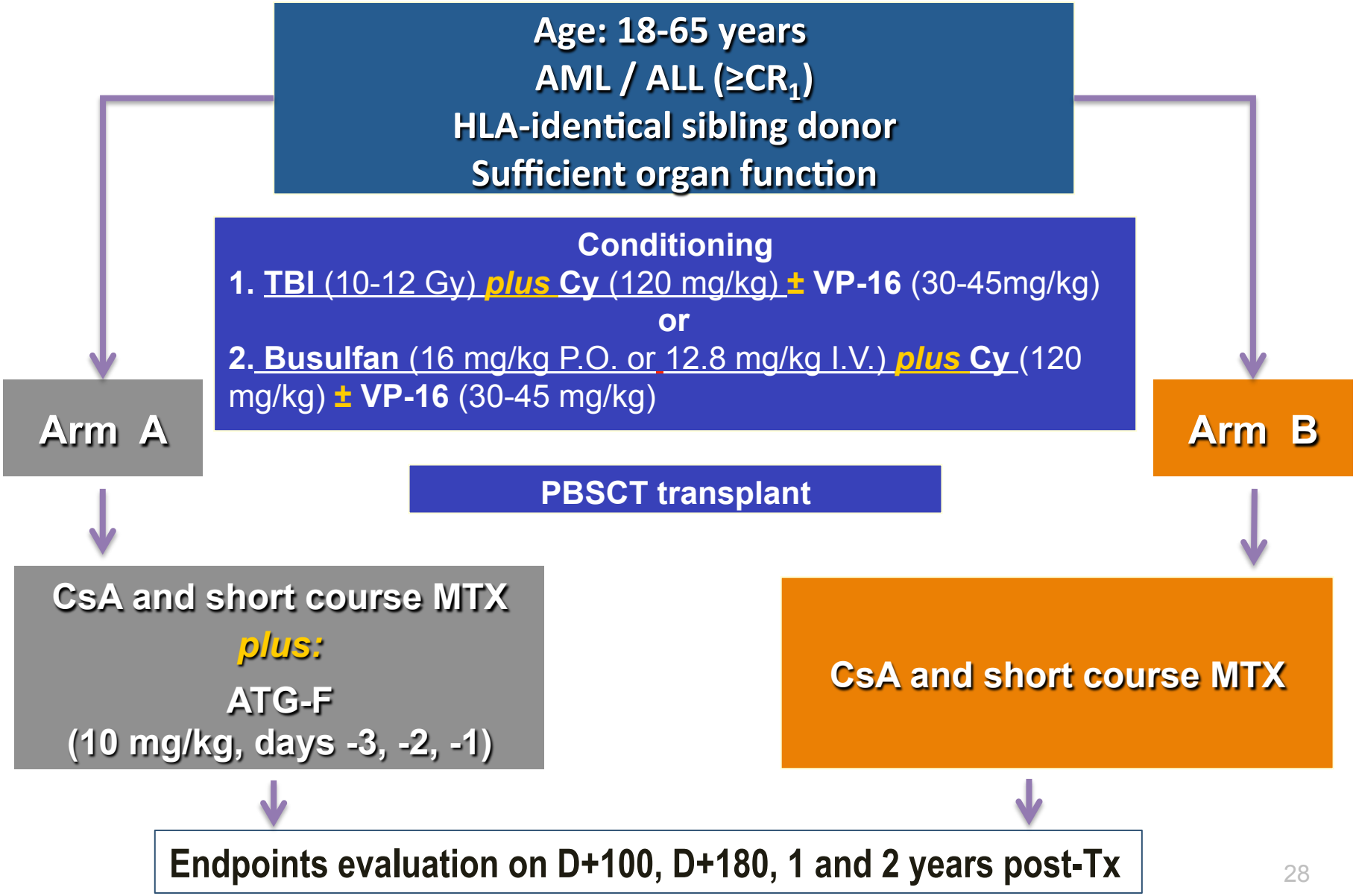
Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease

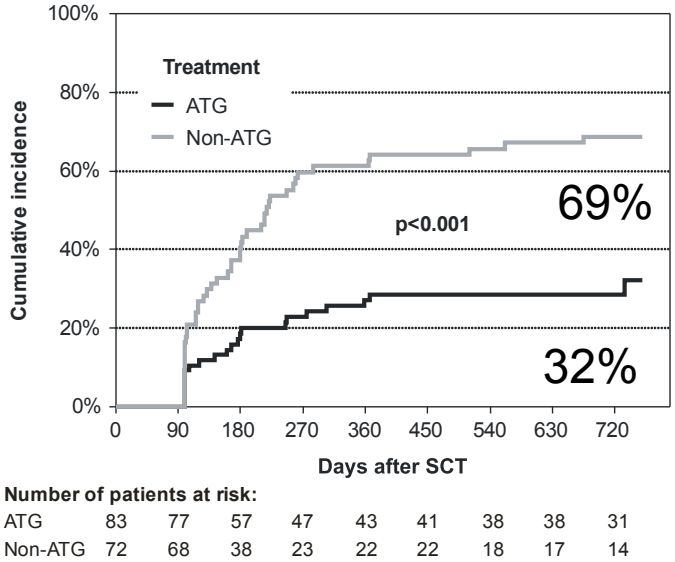
Nicolaus Kröger, M.D., Carlos Solano, M.D., Christine Wolschke, M.D., Giuseppe Bandini, M.D., Francesca Patriarca, M.D., Massimo Pini, M.D., Arnon Nagler, M.D., Carmine Selleri, M.D., Antonio Risitano, M.D., Ph.D., Giuseppe Messina, M.D., Wolfgang Bethge, M.D., Jaime Pérez de Oteiza, M.D., Rafael Duarte, M.D., Angelo Michele Carella, M.D., Michele Cimminiello, M.D., Stefano Guidi, M.D., Jürgen Finke, M.D., Nicola Mordini, M.D., Christelle Ferra, M.D., Jorge Sierra, M.D., Ph.D., Domenico Russo, M.D., Mario Petrini, M.D., Giuseppe Milone, M.D., Fabio Benedetti, M.D., Marion Heinzelmann, Domenico Pastore, M.D., Manuel Jurado, M.D., Elisabetta Terruzzi, M.D., Franco Narni, M.D., Andreas Völp, Ph.D., Francis Ayuk, M.D., Tapani Ruutu, M.D., and Francesca Bonifazi, M.D.

ATGfamilystudy (NCT 00612875)

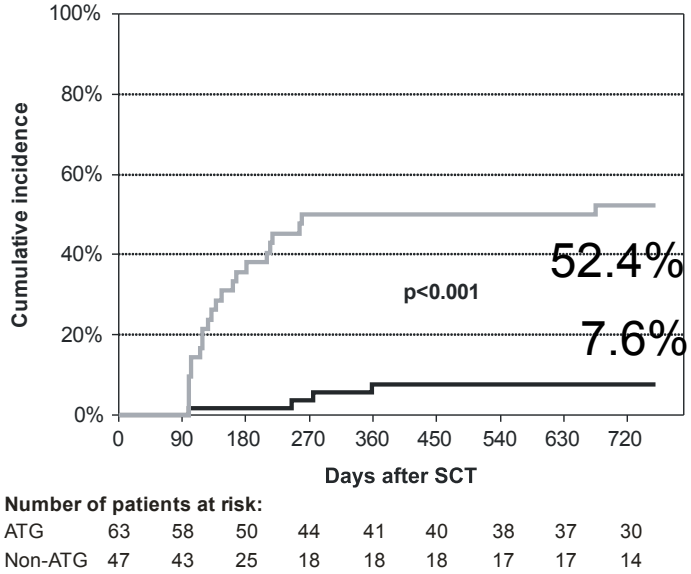
Sponsor	University of Hamburg	Germany
Principal Investigator	Nicolaus Kröger	Hamburg, Germany
National Coordinators	Nicolaus Kröger	Hamburg, Germany
	Francesca Bonifazi	Bologna, Italy
	Carlos Solano	Valencia, Spain
	Arnon Nagler	Tel Hashomer, Israel

Treatment plan





cGVHD



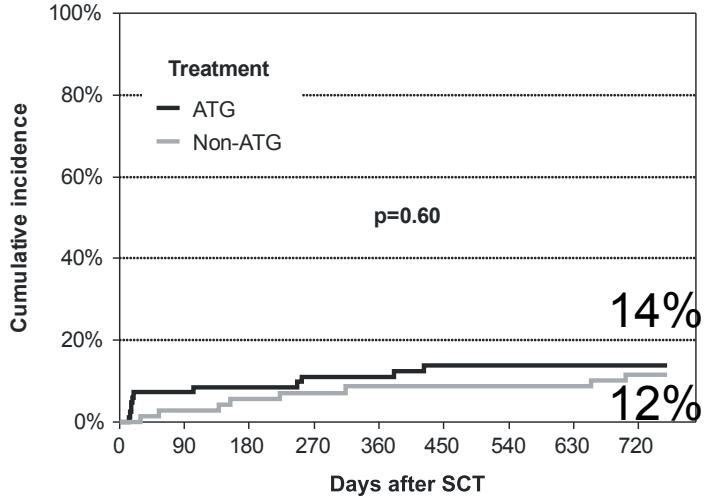
cGVHD-ext

maximum organ involvement according to NIH criteria (NIH score ≥ 2)

Organ	ATG-arm	non ATG arm	risk difference and 95% CI
Skin	**0 (0.0%)**	**14 (19.4%)**	**-19.4% [-30%; -10.7%]**
Oral mucosa	**1 (1.2%)**	**7 (9.7%)**	**-8.5% [-17.6%; -1.3%]**
Eyes	**0 (0.0%)**	**12 (16.7%)**	**-16.7% [-26.9%; -8.5%]**
Liver	5 (6.0%)	11 (15.3%)	-9.3% [-19.9%; +0.5%]
GI tract	1 (1.2%)	2 (2.8%)	-1.8% [-8.4%; +4.1%]
Pulmonary	1 (1.2%)	4 (5.6%)	-4.4% [-12.3%; +1.9%]
Genitals	1 (1.2%)	0 (0.0%)	+1.2% [-4.0%; +6.5%]
Joint and fascia	0 (0.0%)	3 (4.2%)	-4.2% [-11.5%; +1.0%]

Kroger et al N Engl J Med 2016

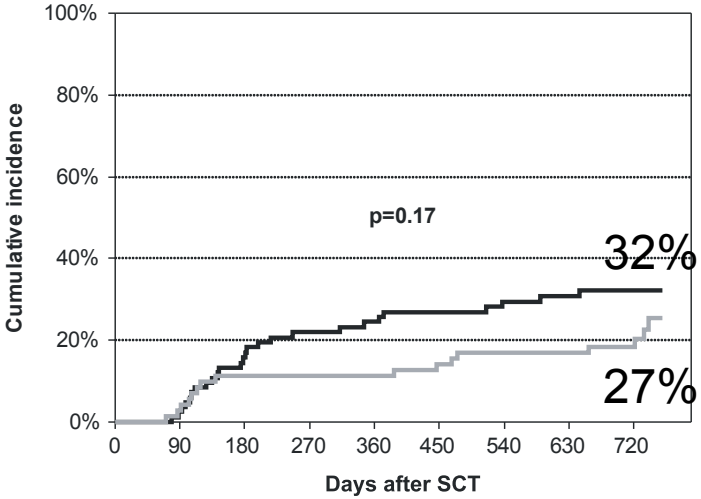
NRM



Number of patients at risk:

ATG	83	78	70	64	63	60	57	54	44
Non-ATG	72	68	65	63	61	60	59	56	42

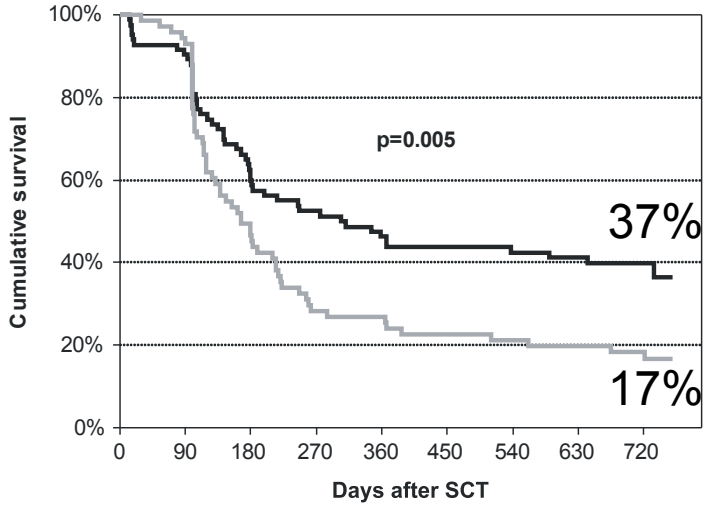
Relapse



Number of patients at risk:

ATG	83	76	63	59	57	54	51	48	40
Non-ATG	72	68	61	60	58	56	54	54	42

cGVHD/relapse free survival



Number of patients at risk:

ATG	83	75	49	42	37	35	33	32	27
Non-ATG	72	66	33	20	18	16	15	14	12

CsA d/C @ 1 yr 91% in the ATG arm
39% in the control arm

Ongoing cGVHD @ 2 yr 25% in the ATG arm
60% in the control arm

Kroger et al N Engl J Med 2016

PROTOCOL
ELECTRONIC DATABASE FOR THE FOLLOW UP OF THE ATG_FamilyStudy

STUDY TYPE: OBSERVATIONAL, ELECTRONIC DATABASE WITH A PROSPECTIVE PHASE AND RETROSPECTIVE PHASE
Acronym: AFF (ATG_FAMILYSTUDY_FOLLOW_UP)

PRINCIPAL INVESTIGATOR: Francesca Bonifazi, Bologna, Italy

NATIONAL COORDINATORS: Francesca Bonifazi, Bologna, Italy

Nicolaus Kroger, Hamburg, Germany

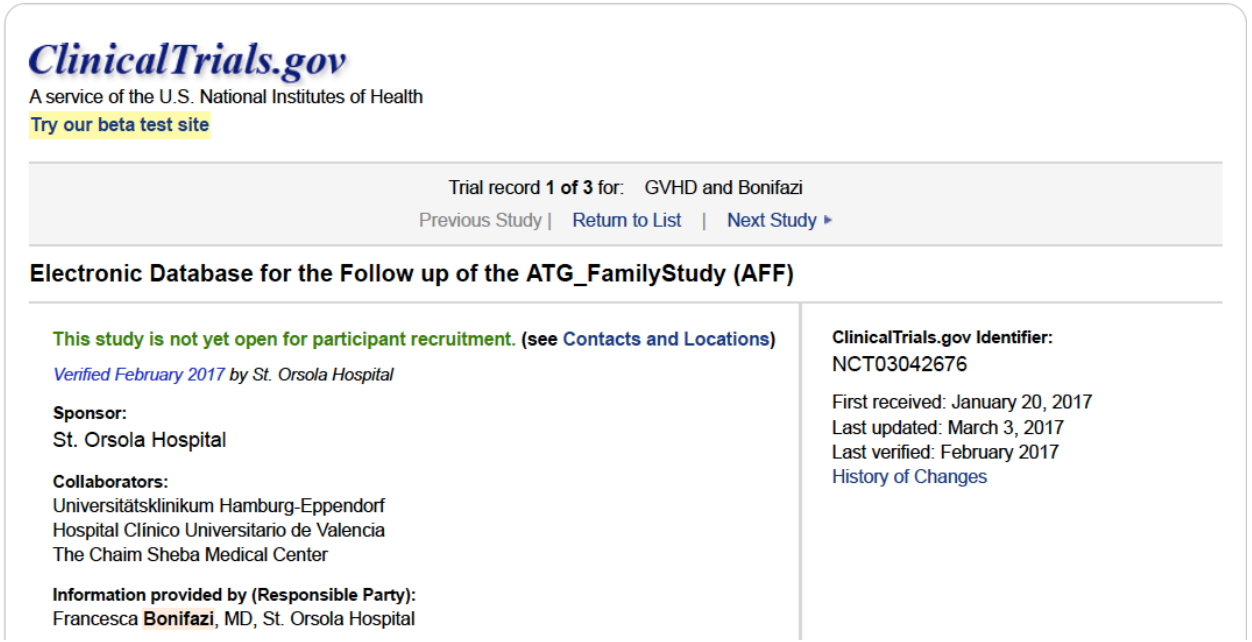
Carlos Solano, Valencia, Spain

Arnon Nagler, Tel Hashomer, Israel

ITALIAN COORDINATOR : A.O.U. S.Orsola-Malpighi Bologna – U.O. Ematologia - Dr.ssa Francesca Bonifazi

ITALIAN AND INTERNATIONAL SPONSOR : A.O.U. S.Orsola-Malpighi Bologna – U.O. Ematologia

WRITING COMMITTEE: Francesca Bonifazi, Carlos Solano, Maria Rosaria Sessa, Mario Arpinati, Arnon Nagler,



DEADLINE for data retrieval

JUNE 1st 2017

QoL evaluation

Analysis ongoing

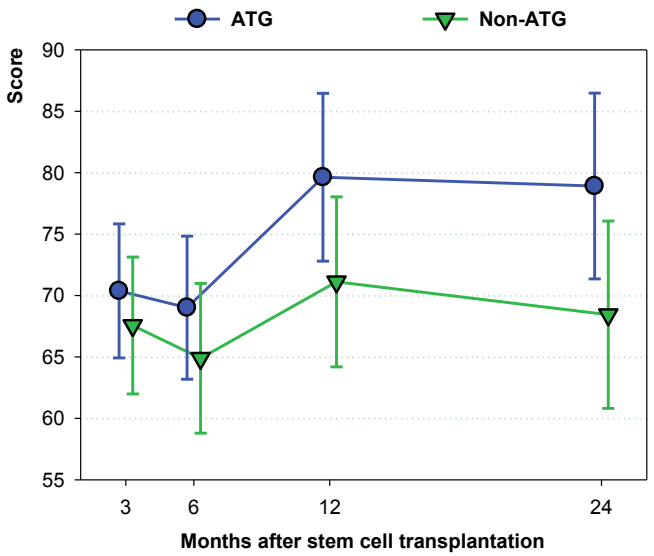
ATGfamilystudy (NCT 00612875)

Significant Improvement of QoL by using ATG as part of the conditioning regimen followed by HLA-identical peripheral stem cell transplantation in acute leukemia patients. Results from a prospective, randomized phase III study (ATGFamilyStudy)

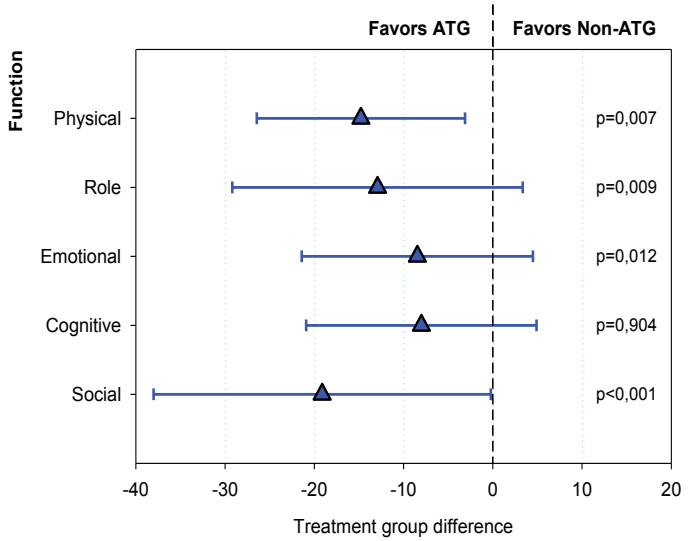
The study protocol included quality of life (QoL) questionnaires (EORTC QLQ-30 and HDC29) before and after SCT (day+ 100 6, 12 and 24 mos). The QLQ-C30 includes a global QoL scale, 5 functional scales (physical, role, emotional, cognitive and social function) and 9 symptom scales (fatigue, nausea-vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial problems). The QLQ-HDC29 includes 6 multi-item scales and 8 single items that describe impairment through high-dose treatment. Mixed models for repeated measures (MMRM) and linear mixed models (LMM) were used to analyze the time courses and the slopes of the outcomes depending on treatment arm (ATG vs non ATG), age, country, sex, and cGVHD.

In an MMRM model controlling for country, age, sex, and cGVHD, pts treated with ATG showed significantly more pronounced improvement of global health status / QoL over time compared to non-ATLG ($p=0.02$), with a treatment group difference of 2.8 ± 3.9 points (marginal mean ± SEM) at Day 100 and increasing to 10.5 ± 5.3 points at month 24 favoring ATG. Significant superiority of ATG ($p<0.05$) was also observed for 4 of the 5 functional scales as well as for several symptom scales scores including appetite loss, insomnia, nausea-vomiting and dyspnea.

QoL analysis: ATGfamilystudy (NCT 00612875)



Global health status / quality of life time course – marginal means 95% confidence intervals from MMRM analysis adjusted for baseline values (higher scores indicate a more favorable status)



QLQ-30 functional scores: differences between MMRM marginal means at 24 months after stem cell transplantation with 95% confidence intervals. p-values apply to the entire 24-month time course, adjusted for country, age, sex, and cGvHD

URD TRANSPLANT:

A STANDARD INDICATION

A STANDARD GVHD PROPHYLAXIS?

Antithymocyte globulin for graft-versus-host disease prophylaxis in transplants from unrelated donors: 2 randomized studies from Gruppo Italiano Trapianti Midollo Osseo (GITMO)

Bacigalupo A et al. Blood 2001

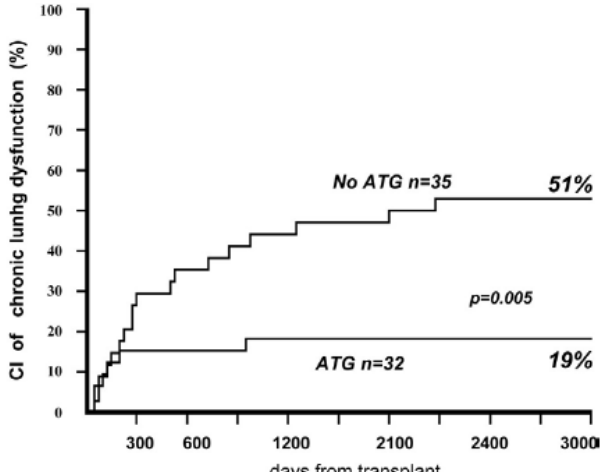
Andrea Bacigalupo, Teresa Lamparelli, Paolo Bruzzi, Stefano Guidi, Paolo Emilio Alessandrino, Paolo di Bartolomeo, Rosa Oneto, Barbara Bruno, Mario Barbanti, Nicoletta Sacchi, Maria Teresa Van Lint, and Alberto Bosi for Gruppo Italiano Trapianti Midollo Osseo (GITMO)

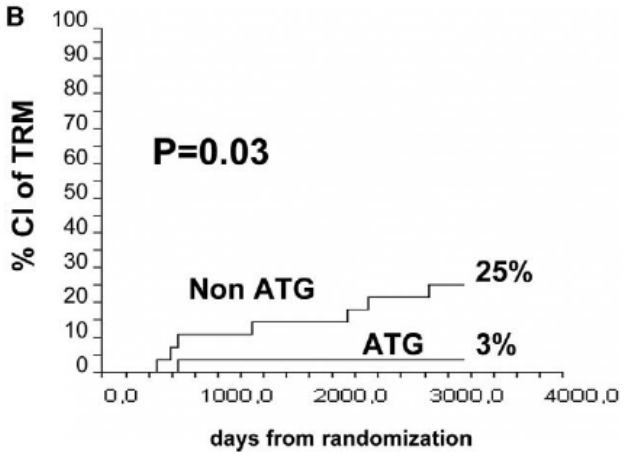
Thymoglobulin Prevents Chronic Graft-versus-Host Disease, Chronic Lung Dysfunction, and Late Transplant-Related Mortality: Long-Term Follow-Up of a Randomized Trial in Patients Undergoing Unrelated Donor Transplantation

Bacigalupo A et al. BBMT 2006

Table 1. *Clinical Data of Patients Receiving or Not Receiving ATG before Transplantation Who Were Alive on Day +100*

No. Patients	No ATG (n = 37)	ATG (n = 38)	P Value
No. of patients in trial 1	20	21	
No. of patients in trial 2	17	17	.60
Median age, y (range)	26 (13-51)	27 (16-44)	.80
% with early disease	60%	47%	.20
Diagnosis			
Acute leukemia	11	11	
Chronic myeloid leukemia	25	27	
Myelodysplasia	1	0	.90
Follow-up (d)			
Median	2078	2065	
Range	108-3159	108-3196	
Chronic GVHD (limited + extensive)	60%	37%	.05
Chronic GVHD (extensive)	41%	15%	.01
Chronic lung dysfunction	51%	19%	.005
% with Karnofsky ≥90% at 4 y	57%	89%	.03
Transplant-related deaths	11 (30%)	6 (16%)	.10
Chronic GVHD	9	4	
Respiratory failure	2	0	
Other	0	2	
Relapse-related deaths	7 (19%)	7 (18%)	.50
No. patients alive	19 (51%)	25 (66%)	.10



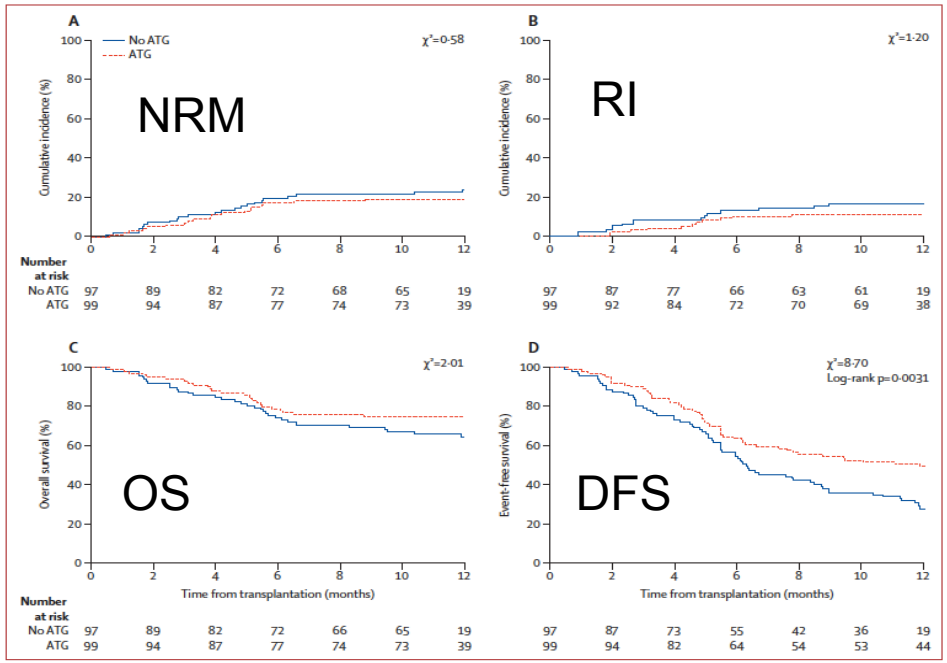


B, Actuarial 9-year survival of patients randomized to the ATG arm (n = 29) or non-ATG arm (n = 28) who were alive 1 year after transplantation.

Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in patients with haematological malignancies undergoing haemopoietic cell transplantation from unrelated donors: a randomised, controlled, open-label, phase 3, multicentre trial

Irwin Walker, Tony Panzarella, Stephen Couban, Felix Couture, Gerald Devins, Mohamed Elemary, Geneviève Gallagher, Holly Kerr, John Kuruvilla, Stephanie J Lee, John Moore, Thomas Nevill, Gizelle Popradi, Jean Roy, Kirk R Schultz, David Szwajcer, Cynthia Toze, Ronan Foley, on behalf of the Canadian Blood and Marrow Transplant Group

12-month IS withdrawal: 37% vs 16% p:0.0006
100-day aGvHD: 50% vs 65% p:0.0012
12-month cGVHD 22% vs 33% p:0.065

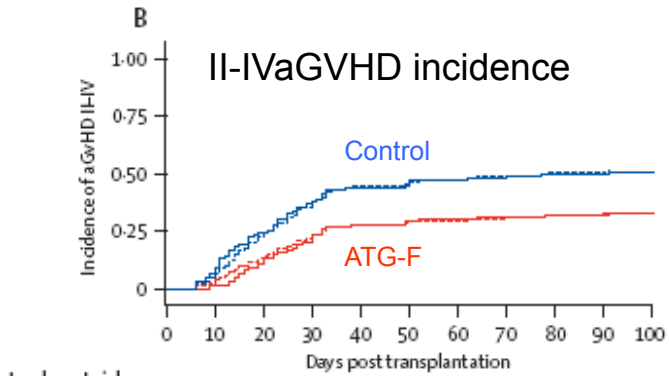


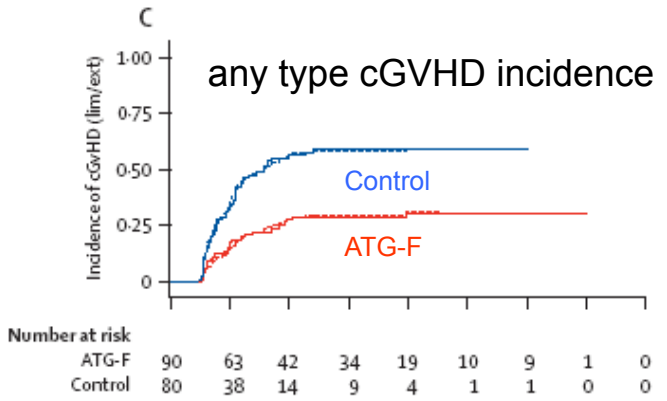
	No ATG (n=97)*	ATG (n=99)
Haematological disease		
Chronic myeloid leukaemia	5 (5%)	7 (7%)
Acute myeloid leukaemia	39 (40%)	39 (39%)
Acute lymphocytic leukaemia	16 (17%)	13 (13%)
Myelodysplastic syndrome	12 (12%)	11 (11%)
Chronic lymphocytic leukaemia	8 (8%)	8 (8%)
Lymphoma	13 (13%)	14 (14%)
Other	4 (4%)	7 (7%)
Disease stage		
Early	59 (61%)	57 (58%)
Late	34 (35%)	34 (34%)
Other	4 (4%)	8 (8%)
Preparative regimen		
Myeloablative	66 (68%)	66 (67%)
Non-myeloablative or reduced intensity conditioning	31 (32%)	33 (33%)
Graft cell type		
Blood	85 (88%)	88 (89%)
Marrow	12 (12%)	11 (11%)

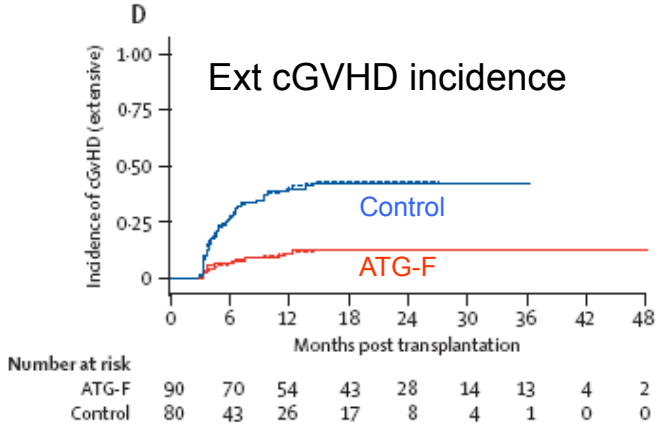
Standard graft-versus-host disease prophylaxis with or without anti-T-cell globulin in haematopoietic cell transplantation from matched unrelated donors: a randomised, open-label, multicentre phase 3 trial

Finke et al Lancet Onc 2009

	ATG-F (N=103)	Control (N=98)
Sex		
Male	58	58
Female	45	40
Median patient age (years; range)	40 (18–60)	39 (18–60)
≤25	12	23
26–39	35	27
≥40	56	48
Median donor age (years; range)*	35 (20–58)	37 (18–56)
≤25	11	13
26–39	51	51
≥40	32	30
Ethnic origin(white)	102	97
Karnofsky performance score		
50–80%	13	15
90%	43	35
100%	47	48
Diagnosis		
Acute lymphoid leukaemia	37	33
Acute myeloid leukaemia	55	46
Chronic myeloid leukaemia	6	11
Myelodysplastic syndrome	5	5
Osteomyelofibrosis	0	3
Disease status		
Early	64	43
Advanced	39	55
Conditioning regimen		
Total body irradiation/cyclophosphamide	54	48
Busulfan/cyclophosphamide	26	26
Total body irradiation/etoposide/cyclophosphamide	11	6
Total body irradiation/other	7	9
No total body irradiation/other	5	9
Stem-cell source		
Bone marrow	21	16
Peripheral blood	82	82



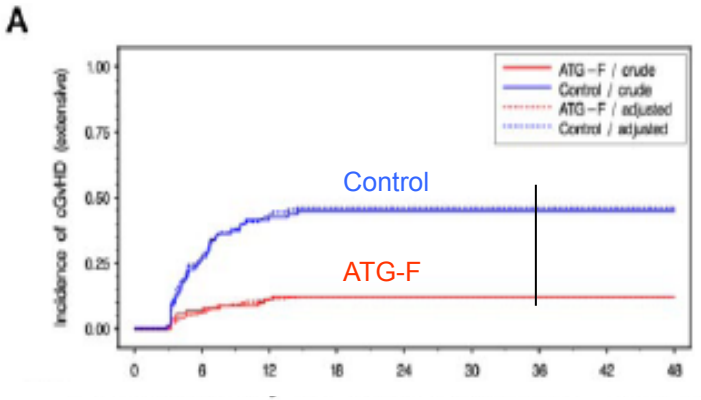




Socie et al Blood 2011

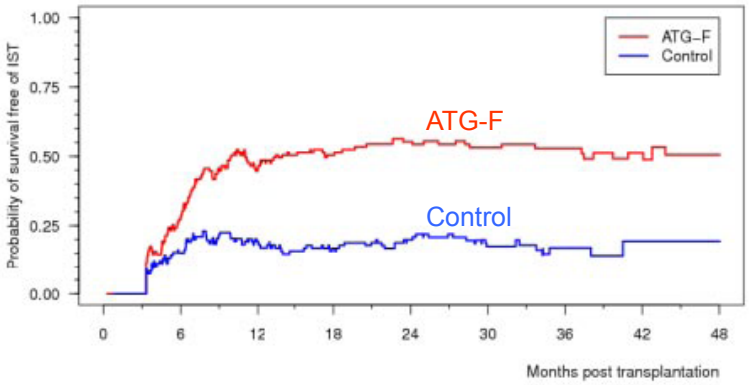
Confirmation of reduced cGVHD

12.2% vs 45.0% @ 3yrs p<0.0001



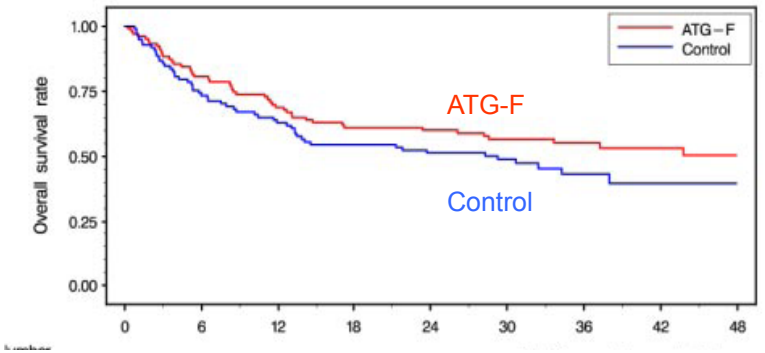
Lower probability of survival free of IST

52.9% vs 16.0% @ 3yrs p<0.0001



Non significant difference in survival

55.3% vs 43.3% @ 3yrs p<0.0001



- **The addition of ATG to the conditioning regimen of patients undergoing allogeneic transplantation from HLA identical PBSC should always be advised**

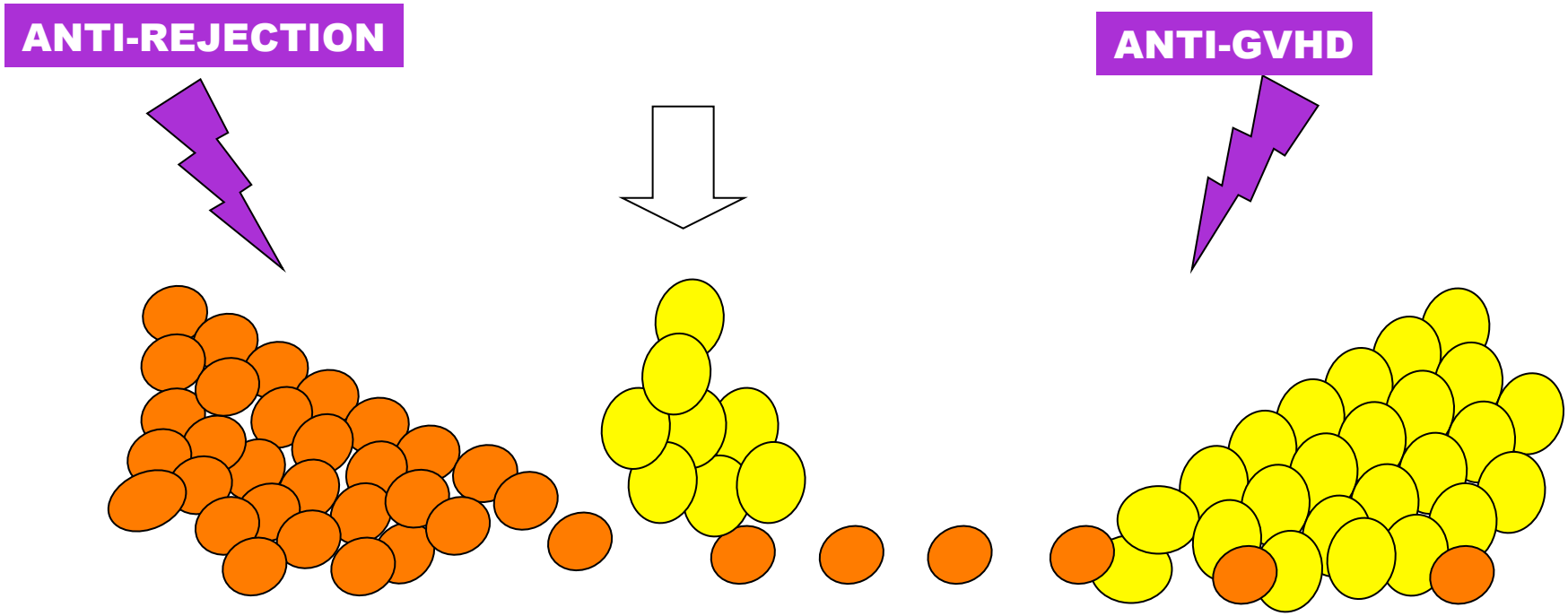
- **The addition of ATG to the conditioning regimen of patients undergoing allogeneic transplantation from unrelated donors should always be advised**
- **It represents a standard of care for GVHD prophylaxis in particular when the stem cell source is represented by G-CSF mobilised peripheral blood stem cells**

Rambaldi A et al. Lancet Oncology 2015

ATG: THE UNSOLVED PROBLEM OF THE DOSE AND THE TIMING (for each brand)

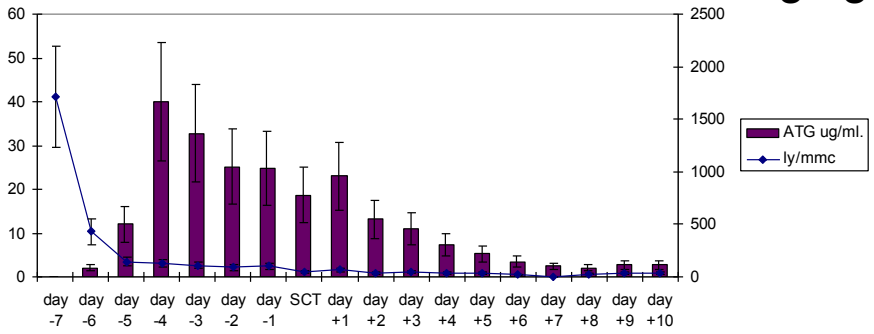
THE EFFECT DEPENDS ON BOTH DOSE & TIMING:

TARGET CELLS CAN BE DIFFERENT

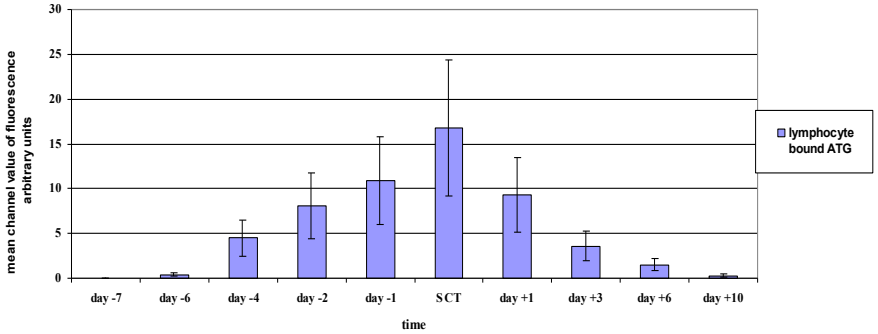


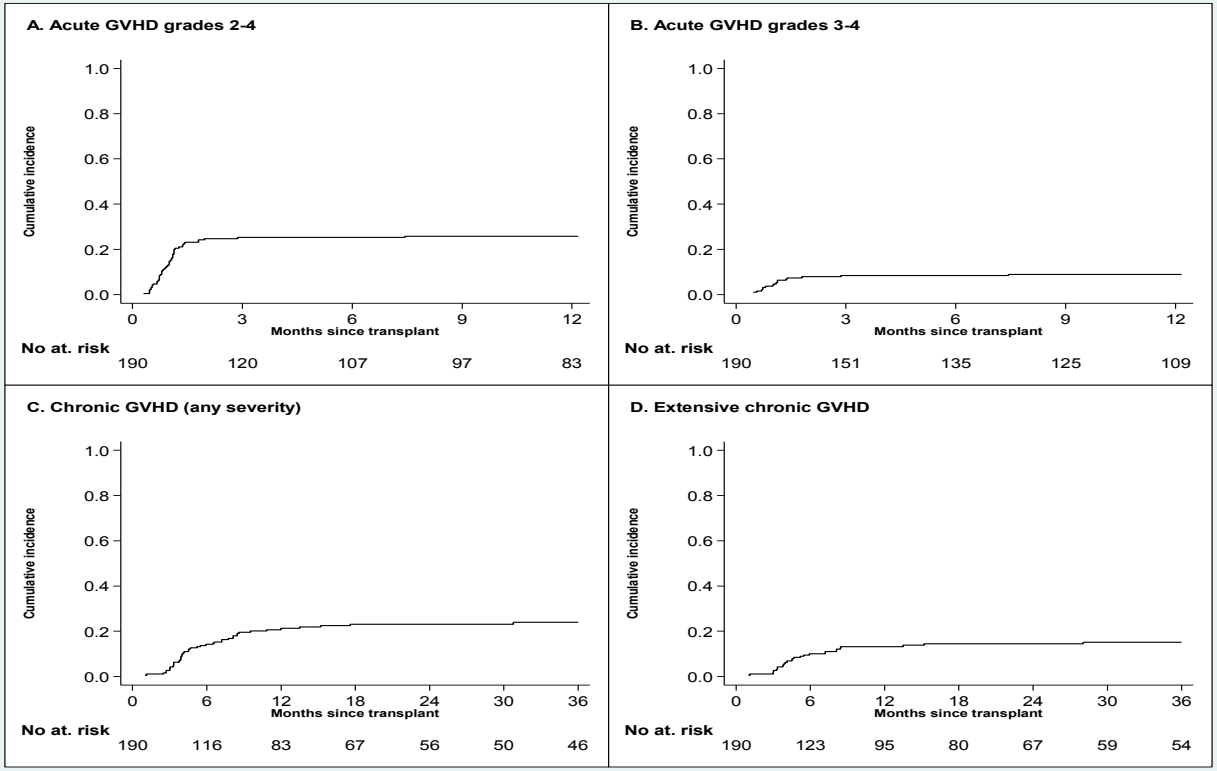
Levels of plasma ATG and peripheral blood lymphocytes

15 mg/kg dal -6 al -2



ATG bound to patients lymphocytes





Low doses ATG given with an aerly timing in allotransplants from URD in AL and MDS

15-30 mg /kg as total dose from day -6 to -2

Chronic GVHD	Number (%)	score ≥2
Overall cGVHD occurrence	46 (24.2)	
Severity according NIH		
Mild	17 (8.9)	
Moderate	18 (9.5)	
Severe	11 (5.8)	
Organ		
Eyes	23 (12.1)	3 (1.6)
Genitals	8 (4.2)	4 (2.1)
Gut	10 (5.3)	5 (2.6)
Joints and fascia	13 (6.8)	5 (2.6)
Liver	14 (7.4)	9 (5.6)
Lungs	11 (6.9)	6 (3.2)
Mouth	26 (13.7)	5 (2.6)
Skin	28 (14.7)	16 (10.0)

Bonifazi, EBMT 2017

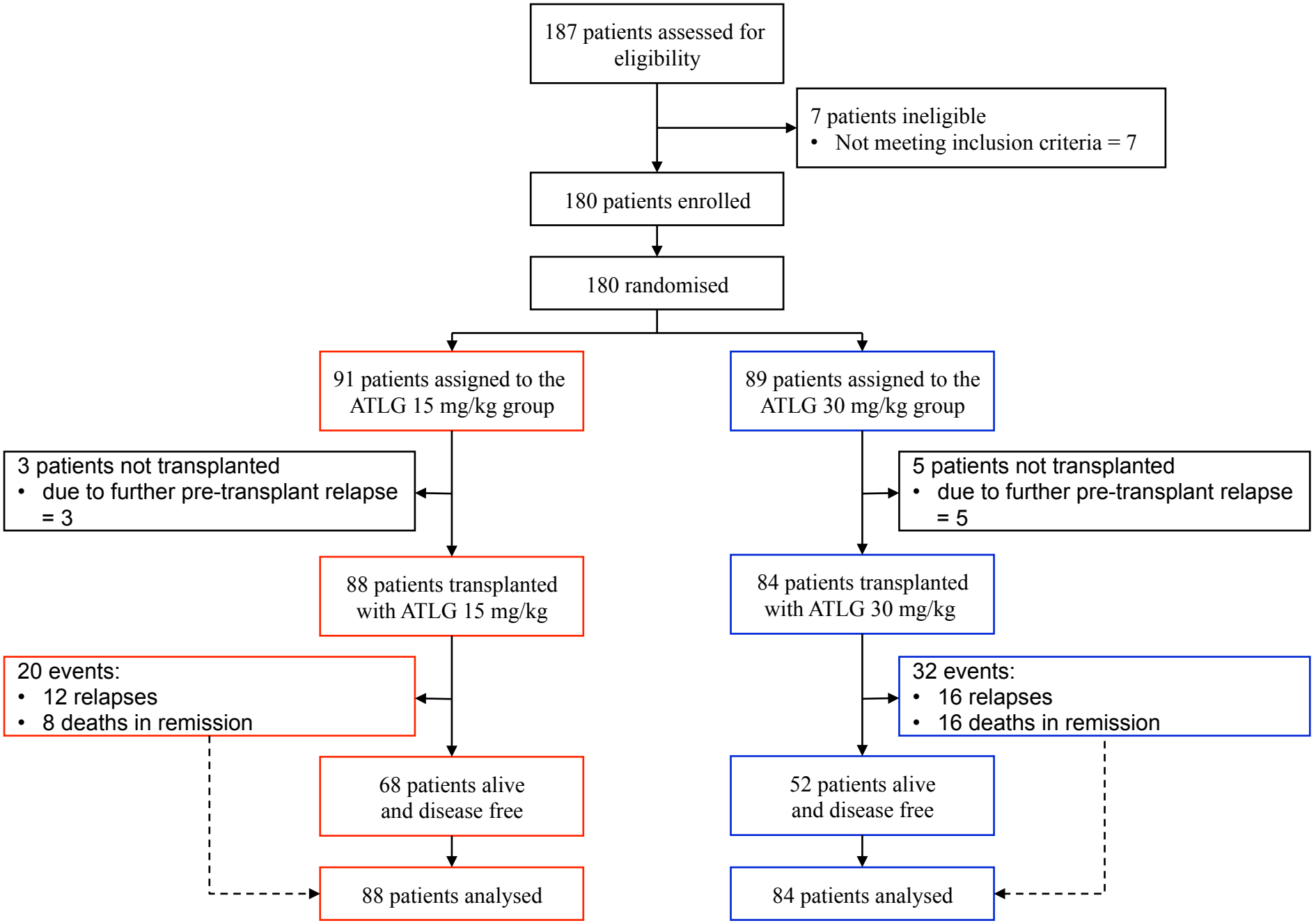
Randomized clinical trial on two different dosages of rabbit anti-T lymphocyte globulin (rATLG) in children with hematological malignancies given allogeneic HSCT from an unrelated volunteer

Eudract number 2008-000101-11; NCT 00934557

Principal Investigator: F. Locatelli

Primary end-point

To test whether high-dose rATLG (30 mg/Kg over days -4, -3 and -2) was superior to a lower dose (15 mg/Kg over the same days) in terms of grade II-IV acute GvHD prevention.


187 patients assessed for eligibility
7 patients ineligible
• Not meeting inclusion criteria = 7
180 patients enrolled
180 randomised
91 patients assigned to the ATLG 15 mg/kg group
89 patients assigned to the ATLG 30 mg/kg group
3 patients not transplanted
• due to further pre-transplant relapse = 3
5 patients not transplanted
• due to further pre-transplant relapse = 5
88 patients transplanted with ATLG 15 mg/kg
84 patients transplanted with ATLG 30 mg/kg
20 events:
• 12 relapses
• 8 deaths in remission
32 events:
• 16 relapses
• 16 deaths in remission
68 patients alive and disease free
52 patients alive and disease free
88 patients analysed
84 patients analysed

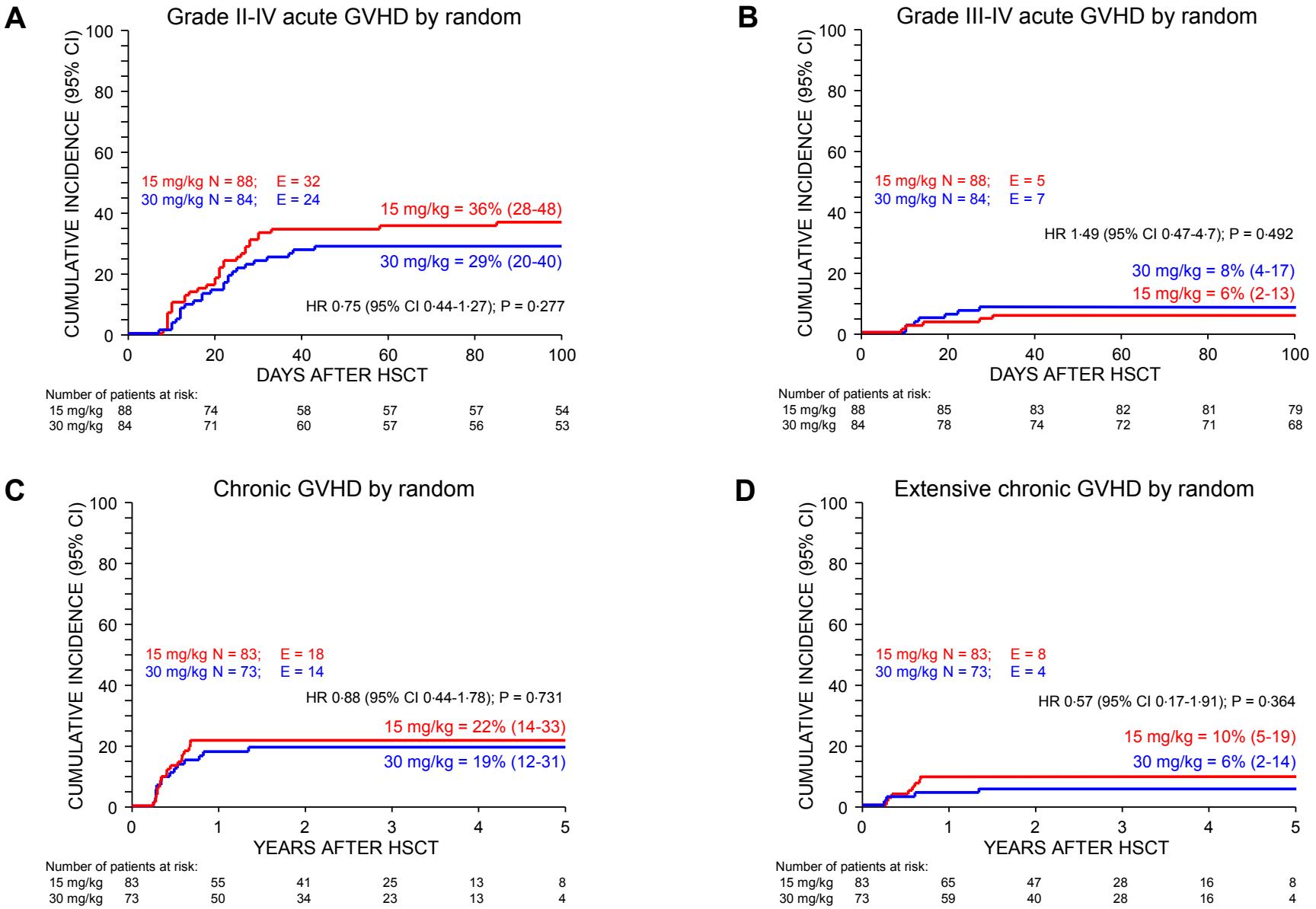
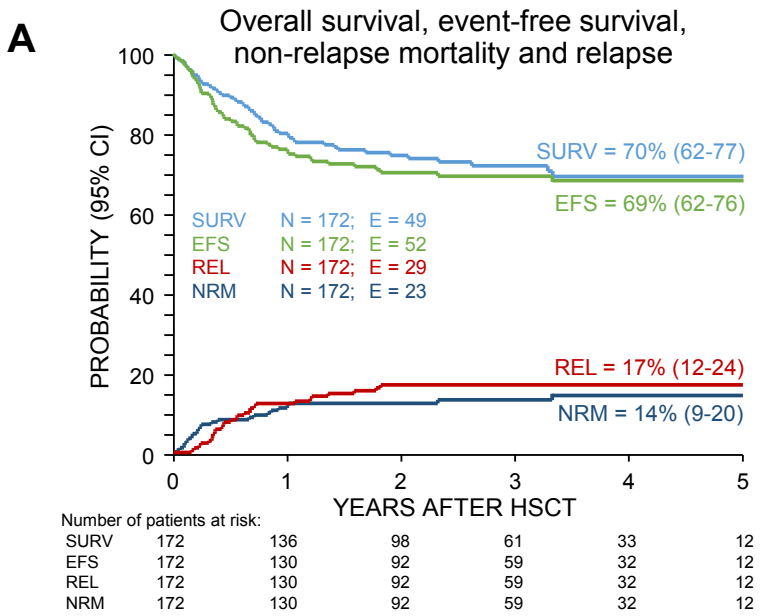
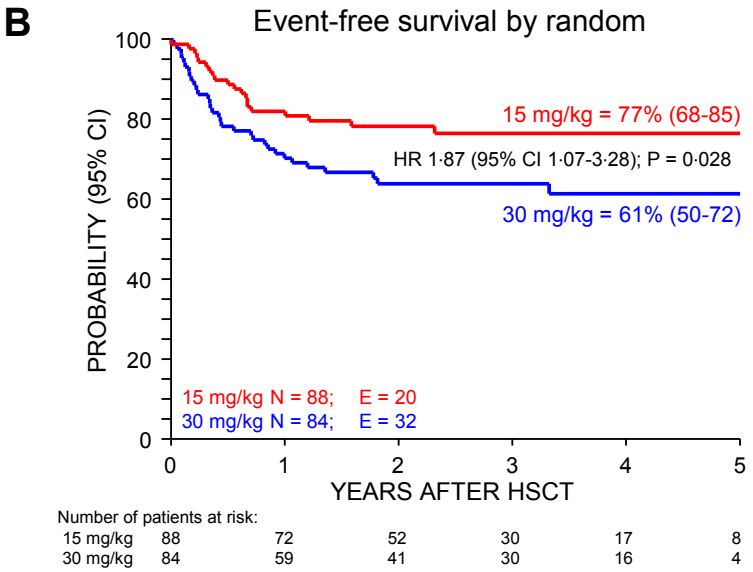
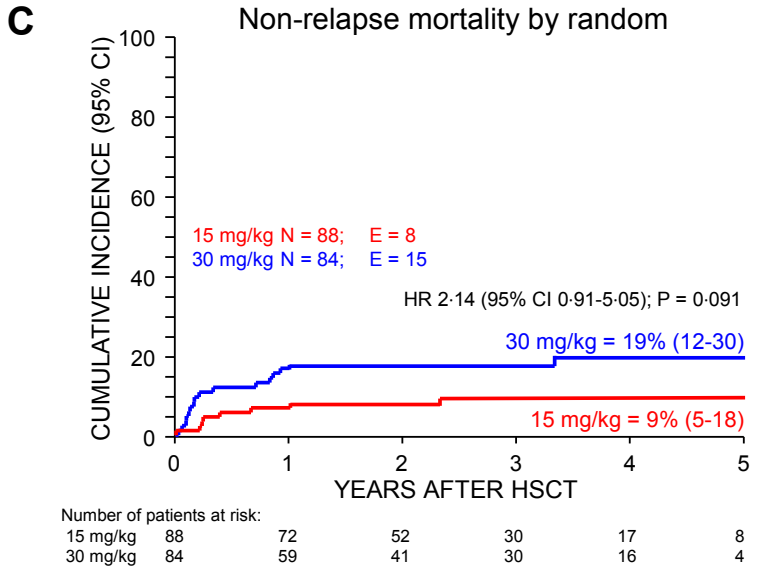

A
Grade II-IV acute GVHD by random
CUMULATIVE INCIDENCE (95% CI)
DAYS AFTER HSCT
15 mg/kg N = 88; E = 32
30 mg/kg N = 84; E = 24
15 mg/kg = 36% (28-48)
30 mg/kg = 29% (20-40)
HR 0·75 (95% CI 0·44-1·27); P = 0·277
Number of patients at risk:
15 mg/kg 88 74 58 57 57 54
30 mg/kg 84 71 60 57 56 53
B
Grade III-IV acute GVHD by random
CUMULATIVE INCIDENCE (95% CI)
DAYS AFTER HSCT
15 mg/kg N = 88; E = 5
30 mg/kg N = 84; E = 7
HR 1·49 (95% CI 0·47-4·7); P = 0·492
30 mg/kg = 8% (4-17)
15 mg/kg = 6% (2-13)
Number of patients at risk:
15 mg/kg 88 85 83 82 81 79
30 mg/kg 84 78 74 72 71 68
C
Chronic GVHD by random
CUMULATIVE INCIDENCE (95% CI)
YEARS AFTER HSCT
15 mg/kg N = 83; E = 18
30 mg/kg N = 73; E = 14
HR 0·88 (95% CI 0·44-1·78); P = 0·731
15 mg/kg = 22% (14-33)
30 mg/kg = 19% (12-31)
Number of patients at risk:
15 mg/kg 83 55 41 25 13 8
30 mg/kg 73 50 34 23 13 4
D
Extensive chronic GVHD by random
CUMULATIVE INCIDENCE (95% CI)
YEARS AFTER HSCT
15 mg/kg N = 83; E = 8
30 mg/kg N = 73; E = 4
HR 0·57 (95% CI 0·17-1·91); P = 0·364
15 mg/kg = 10% (5-19)
30 mg/kg = 6% (2-14)
Number of patients at risk:
15 mg/kg 83 65 47 28 16 8
30 mg/kg 73 59 40 28 16 4

Figure 2


A
Overall survival, event-free survival, non-relapse mortality and relapse
PROBABILITY (95% CI)
YEARS AFTER HSCT
SURV = 70% (62-77)
EFS = 69% (62-76)
REL = 17% (12-24)
NRM = 14% (9-20)
SURV N = 172; E = 49
EFS N = 172; E = 52
REL N = 172; E = 29
NRM N = 172; E = 23
Number of patients at risk:
SURV 172 136 98 61 33 12
EFS 172 130 92 59 32 12
REL 172 130 92 59 32 12
NRM 172 130 92 59 32 12


B
Event-free survival by random
PROBABILITY (95% CI)
YEARS AFTER HSCT
15 mg/kg = 77% (68-85)
HR 1·87 (95% CI 1·07-3·28); P = 0·028
30 mg/kg = 61% (50-72)
15 mg/kg N = 88; E = 20
30 mg/kg N = 84; E = 32
Number of patients at risk:
15 mg/kg 88 72 52 30 17 8
30 mg/kg 84 59 41 30 16 4


C
Non-relapse mortality by random
CUMULATIVE INCIDENCE (95% CI)
YEARS AFTER HSCT
15 mg/kg N = 88; E = 8
30 mg/kg N = 84; E = 15
HR 2·14 (95% CI 0·91-5·05); P = 0·091
30 mg/kg = 19% (12-30)
15 mg/kg = 9% (5-18)
Number of patients at risk:
15 mg/kg 88 72 52 30 17 8
30 mg/kg 84 59 41 30 16 4

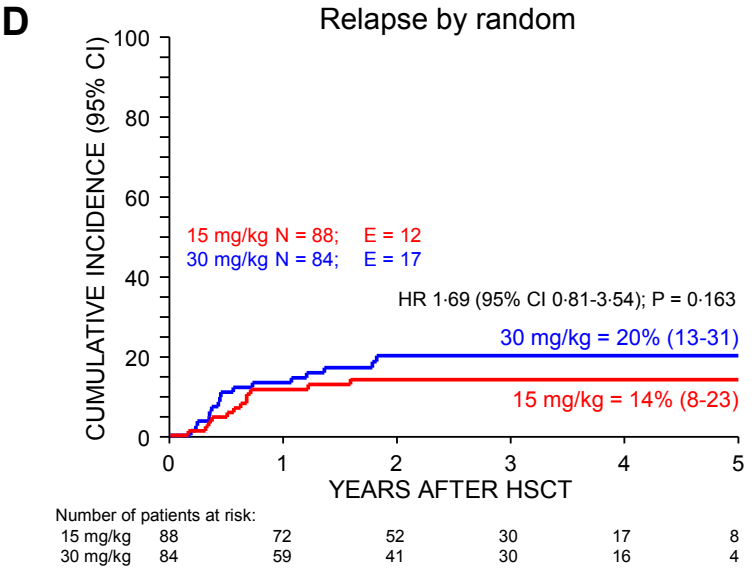

D
Relapse by random
CUMULATIVE INCIDENCE (95% CI)
YEARS AFTER HSCT
15 mg/kg N = 88; E = 12
30 mg/kg N = 84; E = 17
HR 1·69 (95% CI 0·81-3·54); P = 0·163
30 mg/kg = 20% (13-31)
15 mg/kg = 14% (8-23)
Number of patients at risk:
15 mg/kg 88 72 52 30 17 8
30 mg/kg 84 59 41 30 16 4

Figure 3

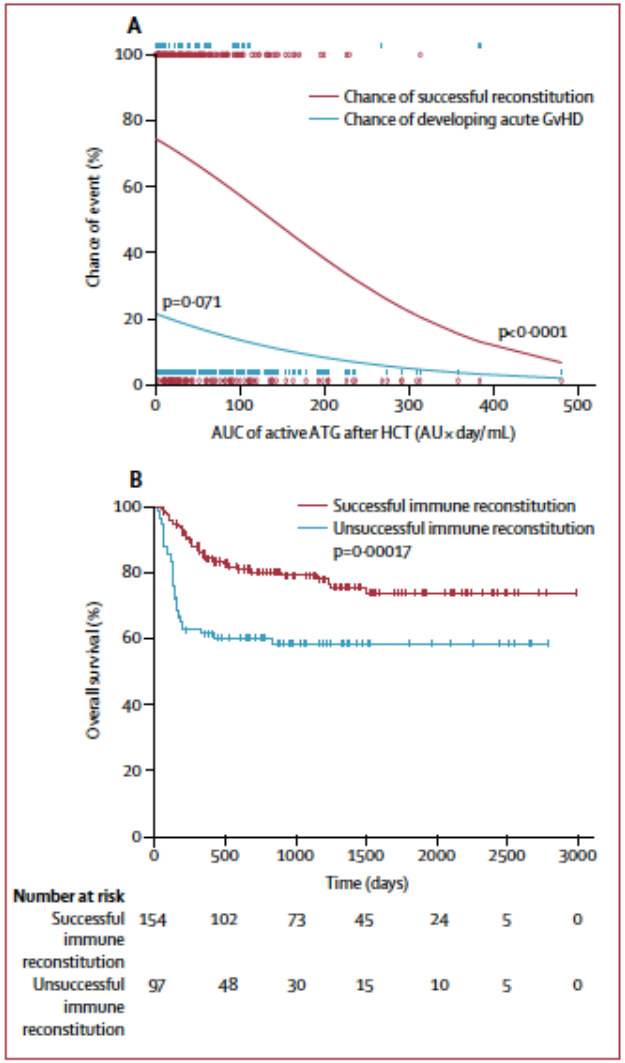
Association between anti-thymocyte globulin exposure and CD4+ immune reconstitution in paediatric haemopoietic cell transplantation: a multicentre, retrospective pharmacodynamic cohort analysis

Admiraal Lancet Onc 2015

Rick Admiraal, Charlotte van Kesteren*, Cornelia M Jol-van der Zijde*, Arjan C Lankester, Marc B Bierings, Toine C G Egberts, Maarten J D van Tol, Catherijne A J Knibbe, Robbert G M Bredius†, Jaap J Boelens†

251 pts
Retrospective
Pediatrics
Malign & non malignant
10 mg/kg Thymo started medianly 5 days (1 -19) before HCT
ATG-AUC both before and post HCT
Primary endpoint:
T cell immunorecovery (>0.05 x 109/L) at 100 d

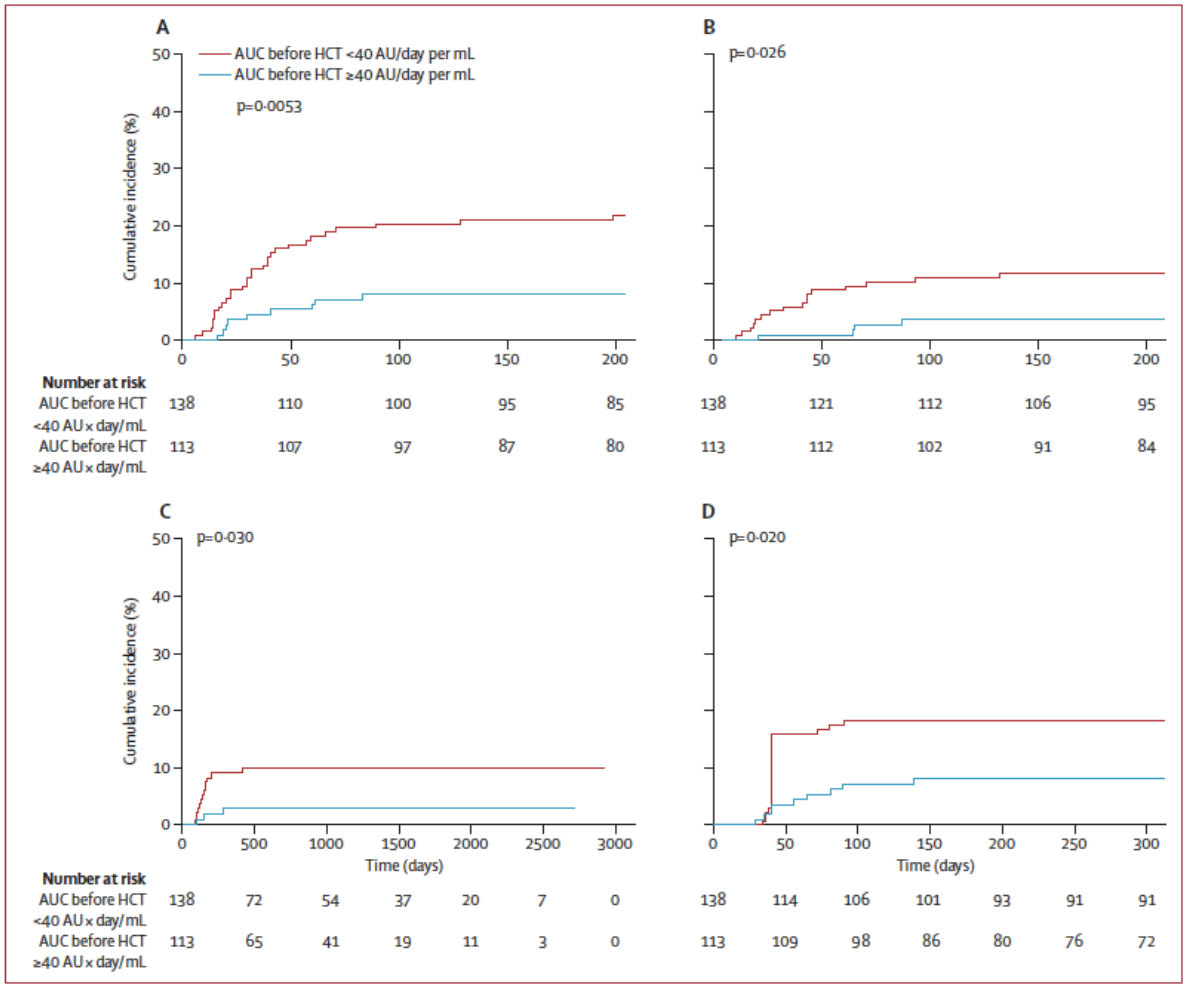
AUC after transplant correlated with IR and aGVHD
IR correlated with OS



Admiraal Lancet Onc 2015

Pretransplant exposure significantly correlated with

-aGVHD
-cGVHD
-Relapse
-graft failure



TRANSPLANTATION

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A COMPENDIUM OF REPORTED HUMAN BONE MARROW TRANSPLANTS[1]

MORTIMER M. BORTIN

May and Sigmund Winter Research Laboratory, Mount Sinai Hospital, and Department of Medicine, Marquette School of Medicine, Milwaukee, Wisconsin 53233

TABLE 1. Results of 203 reported human bone marrow transplants

Disease	No. of patients	No. with no engraftment	No. with secondary disease	No. of allogeneic chimeras
Aplastic anemia	73	66	5	0
Leukemia	84	33	32	3
Malignant disease	31	23	1	1
Immune deficiency	15	3	11	7
Total	203	125	49	11[a]

[a] Three alive at the time of this report.

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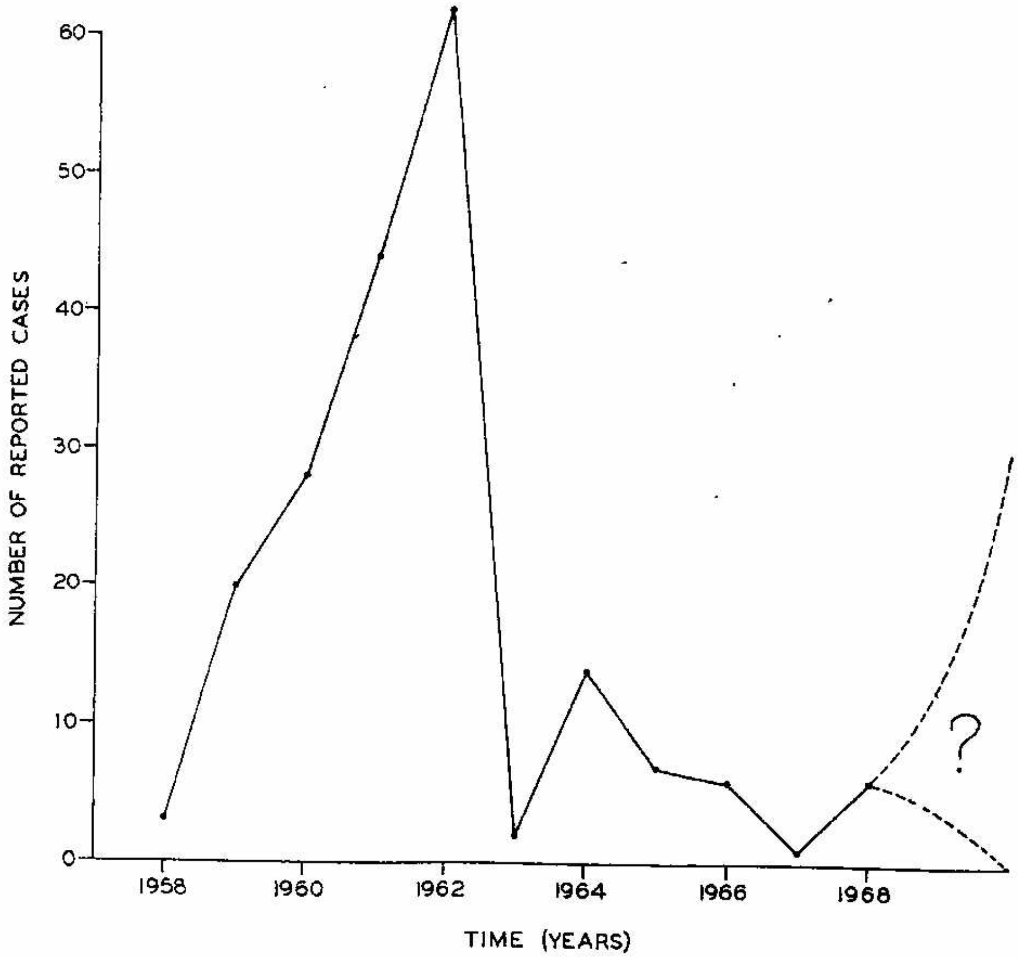

FIGURE 1. Reported human bone marrow transplants from 1958 to 1968.