Il superamento della barriera HLA nel trapianto allogenico : la rivoluzione della ciclofosfamide post trapianto (PTCY)

Andrea Bacigalupo, Istituto di Ematologia,
Fondazione Universitaria Policlinico Gemelli IRCCS
Universita' Cattolica,
Roma- Italy

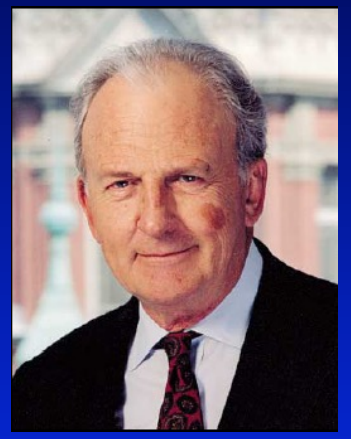
Conflict of interest

- Speakers Bureau/ Advisory Board
  - JAZZ, Pfizer, Therakos, Sanof, Adienne, Novartis

Development of Post-Transplant Cy

Back to the future (Santos & Owens, 1960s-70s)

- Cy post alloBMT prevented GVHD in mice (Santos/Owens – 1960s)
  - Only high doses (150-300 mg/kg) effective
  - Lower doses - limited activity



- Standard Hopkins prophylaxis (1975-1984)
  - Low dose - 7.5 mg/kg/d x 4 because of hematologic toxicity fears

- Randomized trial - less effective than CsA (Santos *et al Clin Transplant* 1986)

Cyclophosphamide and cancer: golden anniversary

Nat Rev Clin Oncol 6:638-647, 2009

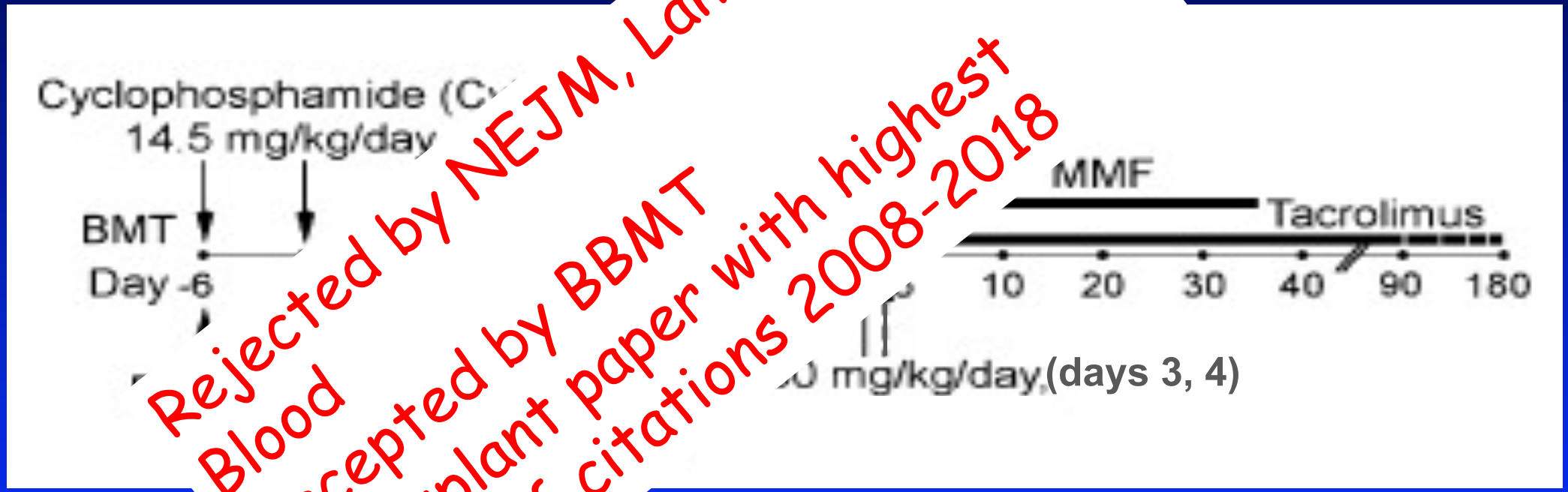
Ashkan Emadi, Richard J. Jones and Robert A. Brodsky

- Unique pharmacology responsible for PTCy's effectiveness
  - Prodrug activated by hepatic P450 enzymes
  - Tissue ALDH1 fully responsible for it inactivation
- ALDH1 generates retinoic acid (RA) from vitamin A
  - ALDH1 also known as retinaldehyde dehydrogenase
  - HSCs and other stem cells, including memory lymphs, require RA and highly express ALDH1 to generate RA
- Cells expressing high ALDH1 resistant to Cy
  - By serendipity, the Cy metabolic intermediate aldophosphamide is a substrate for ALDH1

HLA-Haploidentical Bone Marro Transplantation for Hematologic Malignancies Usir nmyeloablative Conditioning and High-Dose ansplantation Cyclophosphamide

Biol Blood Marrow Trar 008

Leo Luznik,[1] Paul V. O'Donnell,[2,3]* F
Marianna Zahurak,[1] Ted A. Gooley,[2,3]
Carol Ann Huff,[1] William Matsui,[1]
Elizabeth Harrington,[2] Sandy Wa
Rainer F. Storb,[2,3] Richard J. Jo
en,[1] M. Susan Leffell,[1]
[1] Richard F. Ambinder,[1]
[1] Jonathan D. Powell,[1]
ey,[1] Brenda M. Sandmaier,[2,3]

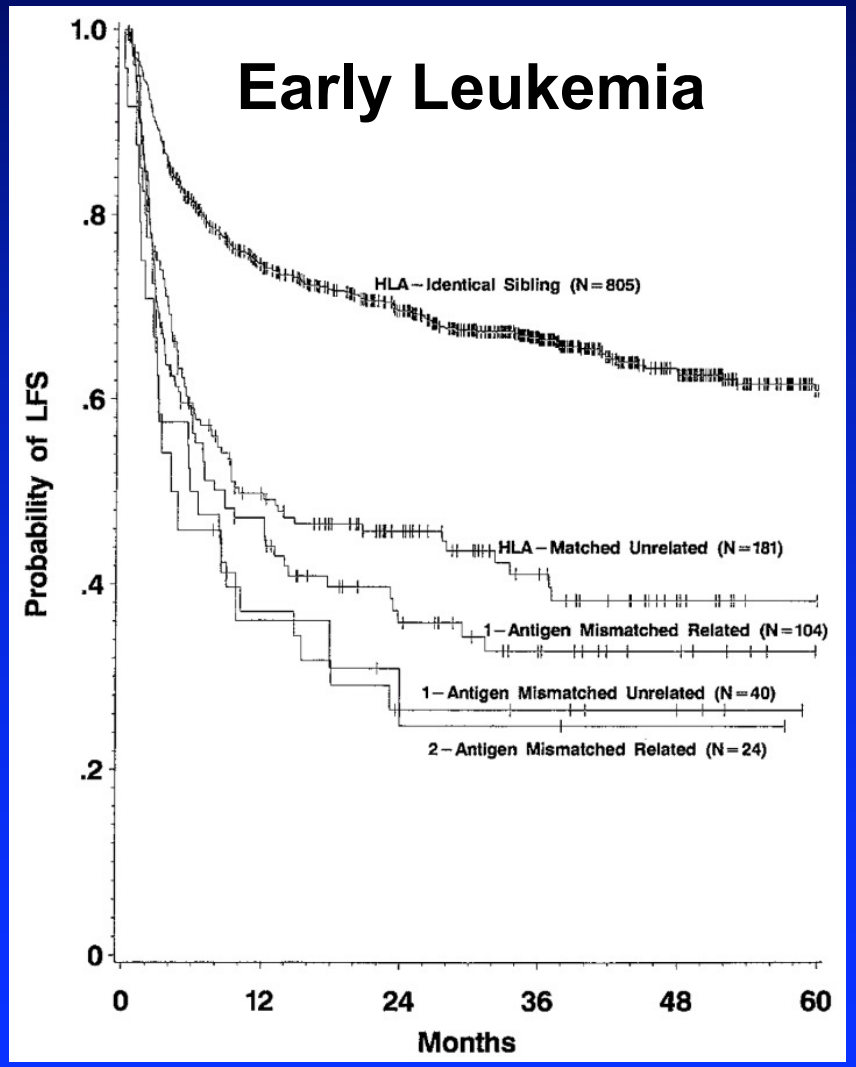


Rejected by NEJM, Lancet, JCO, Blood
Accepted by BBMT
Transplant paper with highest numer of citations 2008-2018

- Cyc ive T cells maximally sensitive to Cy after BMT
  - HSCs and memory lymphs resistant due to high ALDH expression.

What We Learned Over the Decades

HLA mismatches are prohibitively toxic



Disease State/Type of Donor†	No.	TRM (%)	P*
Early			
HLA-identical sibling	805	21 ± 2	—
1-Antigen mismatched related	104	53 ± 5	< .001
2-Antigen mismatched related	24	55 ± 11	< .001
Matched unrelated	181	53 ± 4	< .001
1-Antigen mismatched unrelated	40	69 ± 8	< .001

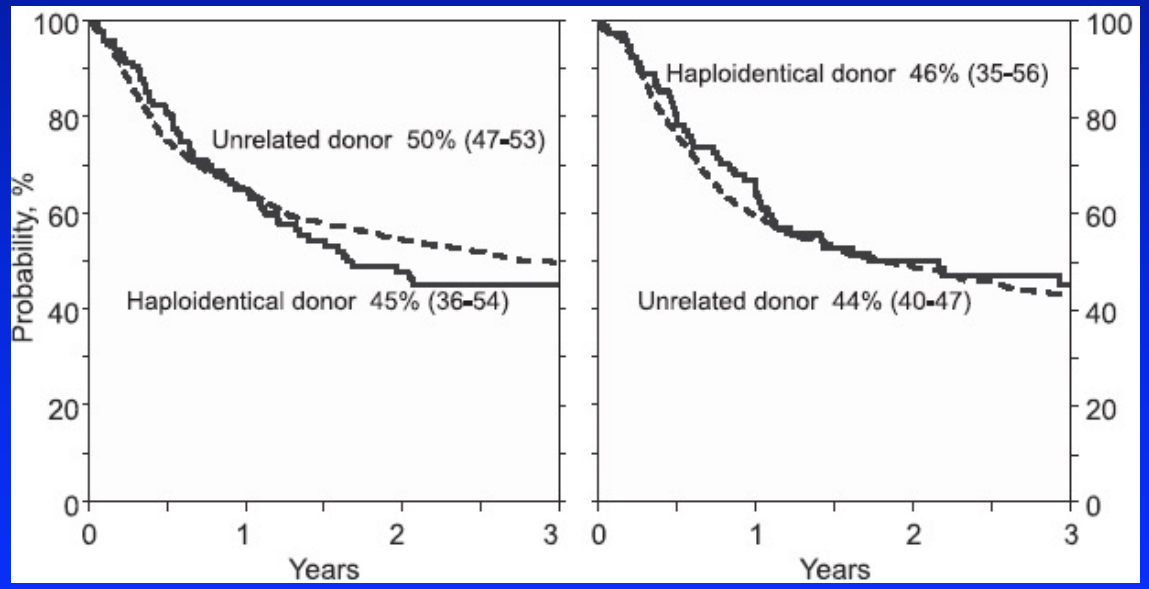
IBMTR
Szydlo et al *JCO* 1997

Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia

Stefan O. Ciurea,[1] Mei-Jie Zhang,[2,3] Andrea A. Bacigalupo,[4] Asad Bashey,[5] Frederick R. Appelbaum,[6] Omar S. Aljitawi,[7] Philippe Armand,[8] Joseph H. Antin,[8] Junfang Chen,[2] Steven M. Devine,[9] Daniel H. Fowler,[10] Leo Luznik,[11] Ryotaro Nakamura,[12] Paul V. O'Donnell,[6] Miguel-Angel Perales,[13] Sai Ravi Pingali,[1] David L. Porter,[14] Marcie R. Riches,[15] Olle T. H. Ringdén,[16] Vanderson Rocha.[17] Ravi Vii.[18] Daniel J. Weisdorf.[19] Richard E. Champlin,[1] Mary M. Horowitz,[2] Ephraim J. Fuchs,[11] and Mary Eapen[2] *Blood.* 2015;126(8):1033-1040

However, it is time to unlearn

No survival difference



Myeloablative RIC

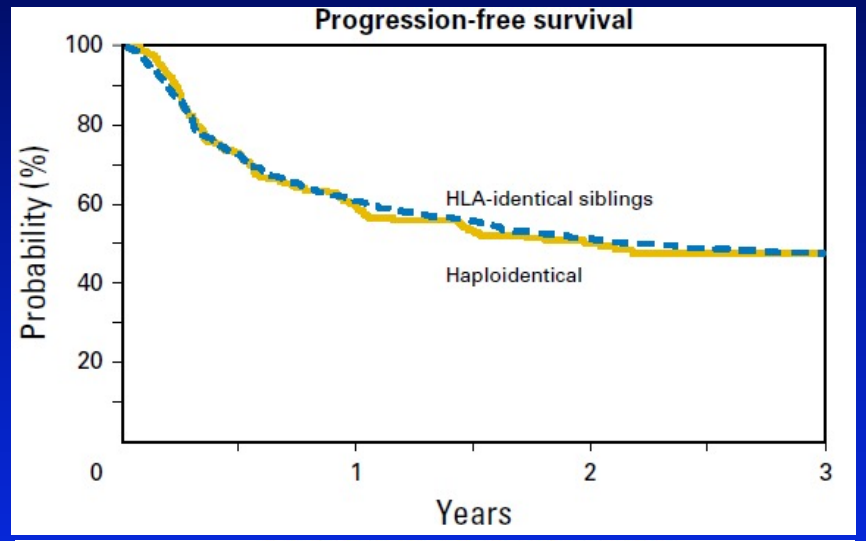
Less GVHD with Haplo/PTCy

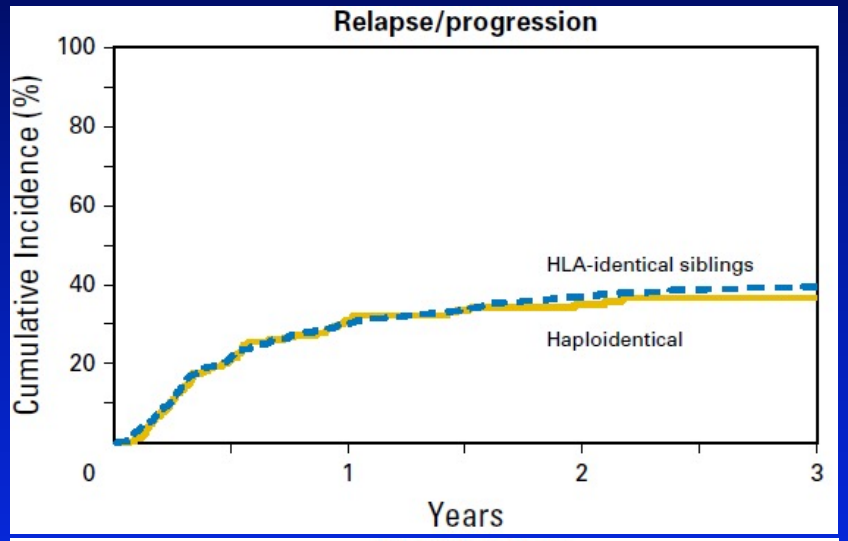
Table 5. Multivariate analysis (subset): risks of acute and chronic GVHD, nonrelapse mortality, relapse, and OS by donor type

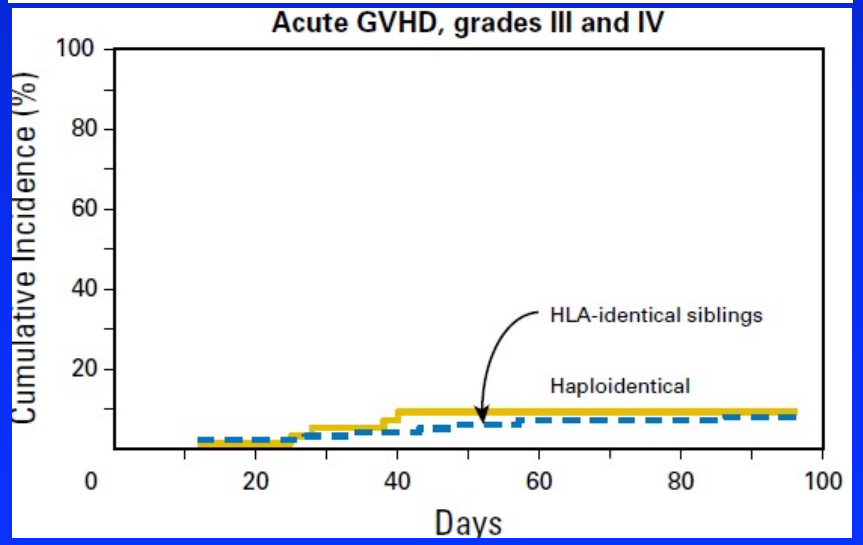
Outcome	Transplant conditioning regimen intensity: Myeloablative* Hazard ratio (95% CI)	Reduced intensity† Hazard ratio (95% CI)
Grade 2-4 acute GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.37 (0.23-0.61) *P* = .0001	0.71 (0.44-1.15) *P* = .16
Grade 3-4 acute GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.33 (0.14-0.81) *P* = .02	0.21 (0.05-0.86) *P* = .03
Chronic GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.44 (0.29-0.66) *P* = .0001	0.45 (0.28-0.71) *P* = .0006

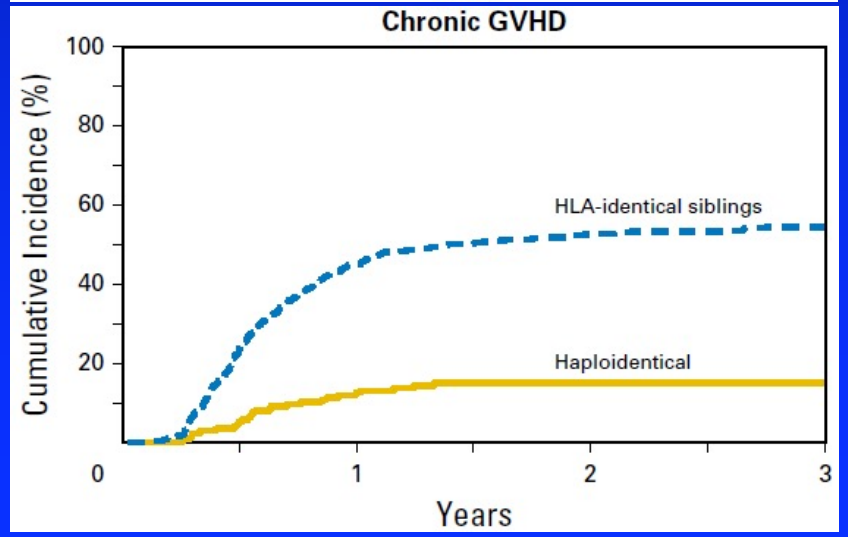
Reduced-Intensity Transplantation for Lymphomas Using Haploidentical Related Donors Versus HLA-Matched Sibling Donors: A Center for International Blood and Marrow Transplant Research Analysis *JCO* 34:3141-49, 2016

Nilanjan Ghosh, Reem Karmali, Vanderson Rocha, Kwang Woo Ahn, Alyssa DiGilio, Parameswaran N. Hari, Veronika Bachanova, Ulrike Bacher, Parastoo Dahi, Marcos de Lima, Anita D'Souza, Timothy S. Fenske, Siddhartha Ganguly, Mohamed A. Kharfan-Dabaja, Tim D. Prestidge, Bipin N. Savani, Sonali M. Smith, Anna M. Sureda, Edmund K. Waller, Samantha Jaglowski, Alex F. Herrera, Philippe Armand, Rachel B. Salit, Nina D. Wagner-Johnston, Ephraim Fuchs, Javier Bolaños-Meade, and Mehdi Hamadani









HAPLO and PTCY

comparable outcome vs

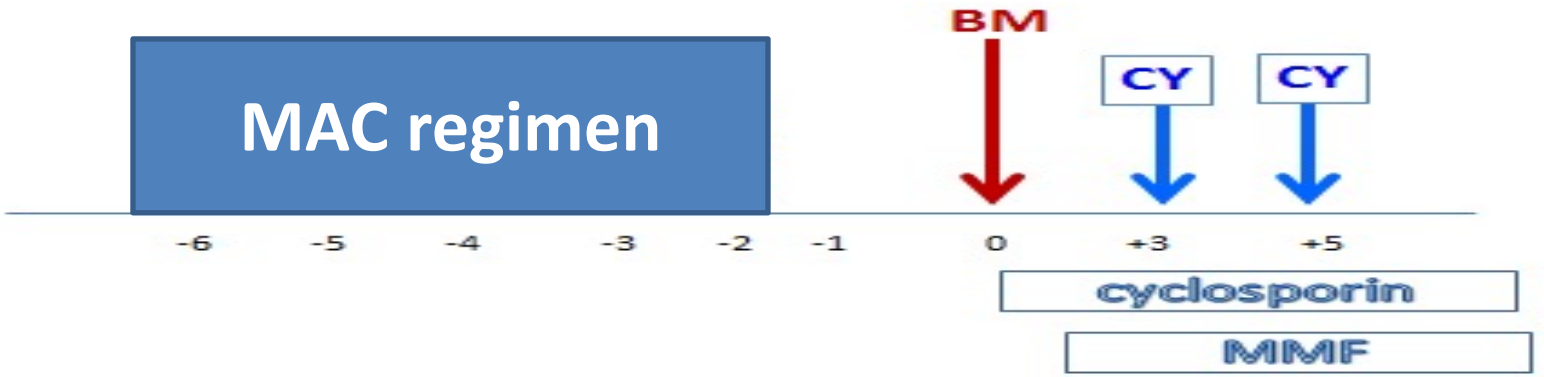
HLA matched and CSA/MTX/±ATG

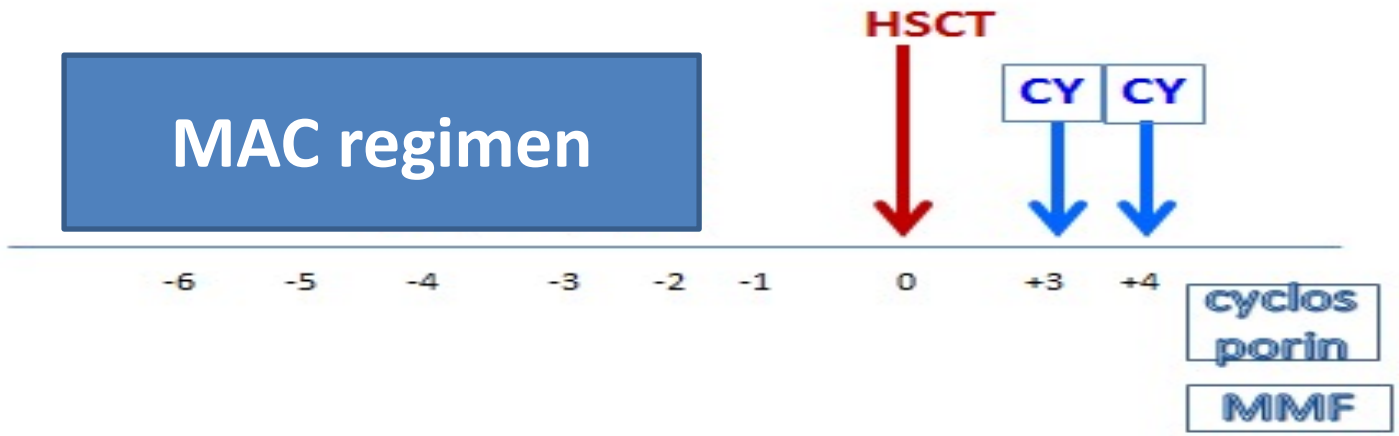
HAPLO + PTCY = A REVOLUTION

Thank you BALTIMORE!!

QUESTIONS:

 # Can TIMING of PTCY +3+4 be changed?


MAC regimen
BM
CY
CY
-6
-5
-4
-3
-2
-1
0
+3
+5
cyclosporin
MMF


MAC regimen
HSCT
CY
CY
-6
-5
-4
-3
-2
-1
0
+3
+4
cyclos
porin
MMF

Biol Blood Marrow Transplant 26 (2020) 1915–1922

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Timing of Post-Transplantation Cyclophosphamide Administration in Haploidentical Transplantation: A Comparative Study on Behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Annalisa Ruggeri[1,*], Myriam Labopin[2,3,4], Giorgia Battipaglia[5], Patrizia Chiusolo[6], Johanna Tischer[7], Jean Luiz Diez-Martin[8], Benedetto Bruno[9], Luca Castagna[10], Ivan Sergeevich Moiseev[11], Antonin Vitek[12], Montserrat Rovira[13], Fabio Ciceri[1], Andrea Bacigalupo[6], Arnon Nagler[3,14], Mohamad Mohty[2,3,4]

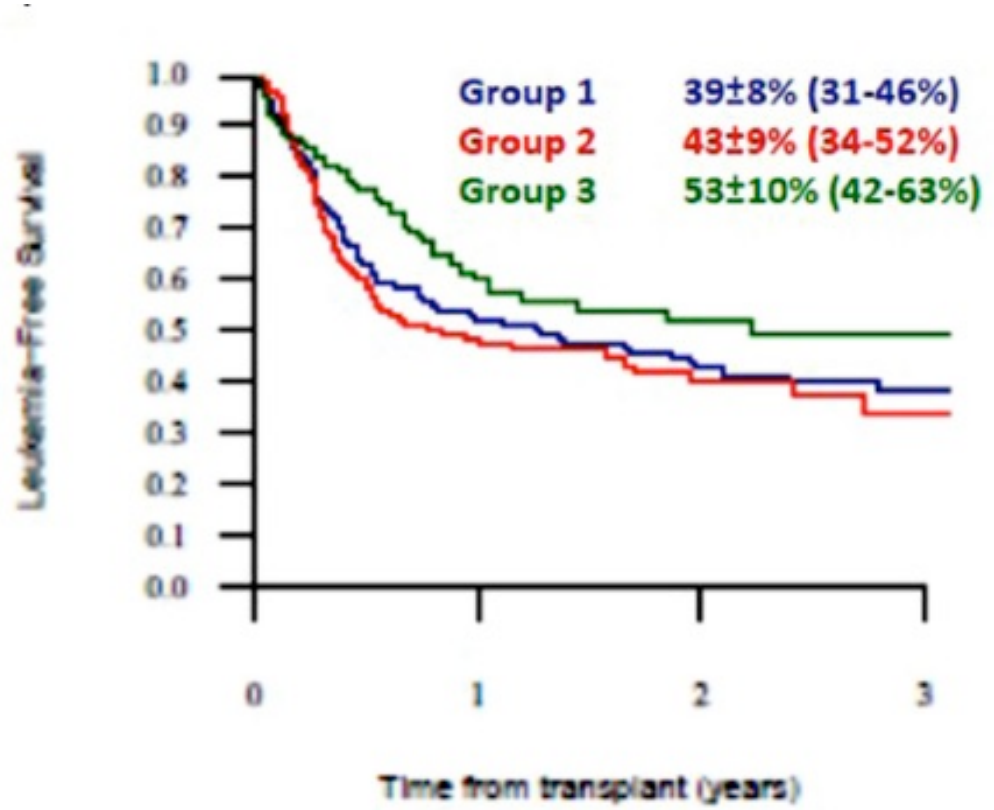
ACUTE LEUKEMIA

	timing	added	pts	BM	CR1
Group 1	PTCY +3+4	Tacro MMF	n=217	54%	42%
Group 2	PTCY +3+4	CSA MMF	n=170	17%	48%
Group 3	**PTCY +3+5**	**CSA MMF**	**n=124**	**77%**	**46%**

	GR1	**GR2**	**GR3**	**p=**
aGvHD II-IV	25%	39%	18%	0.01
cGvHD	25%	21%	24%	0.5

COX mult analysis

	relapse	LFS	rGRFS
GR1	1	1	1
GR2	1.02	0.98	0.96
GR3	0.49	0.58	0.62
p=	0.03	0.02	0.03



The use of CSAon day 0 and MMF on day+1 reduces relapse and improves LFS and rGRFS

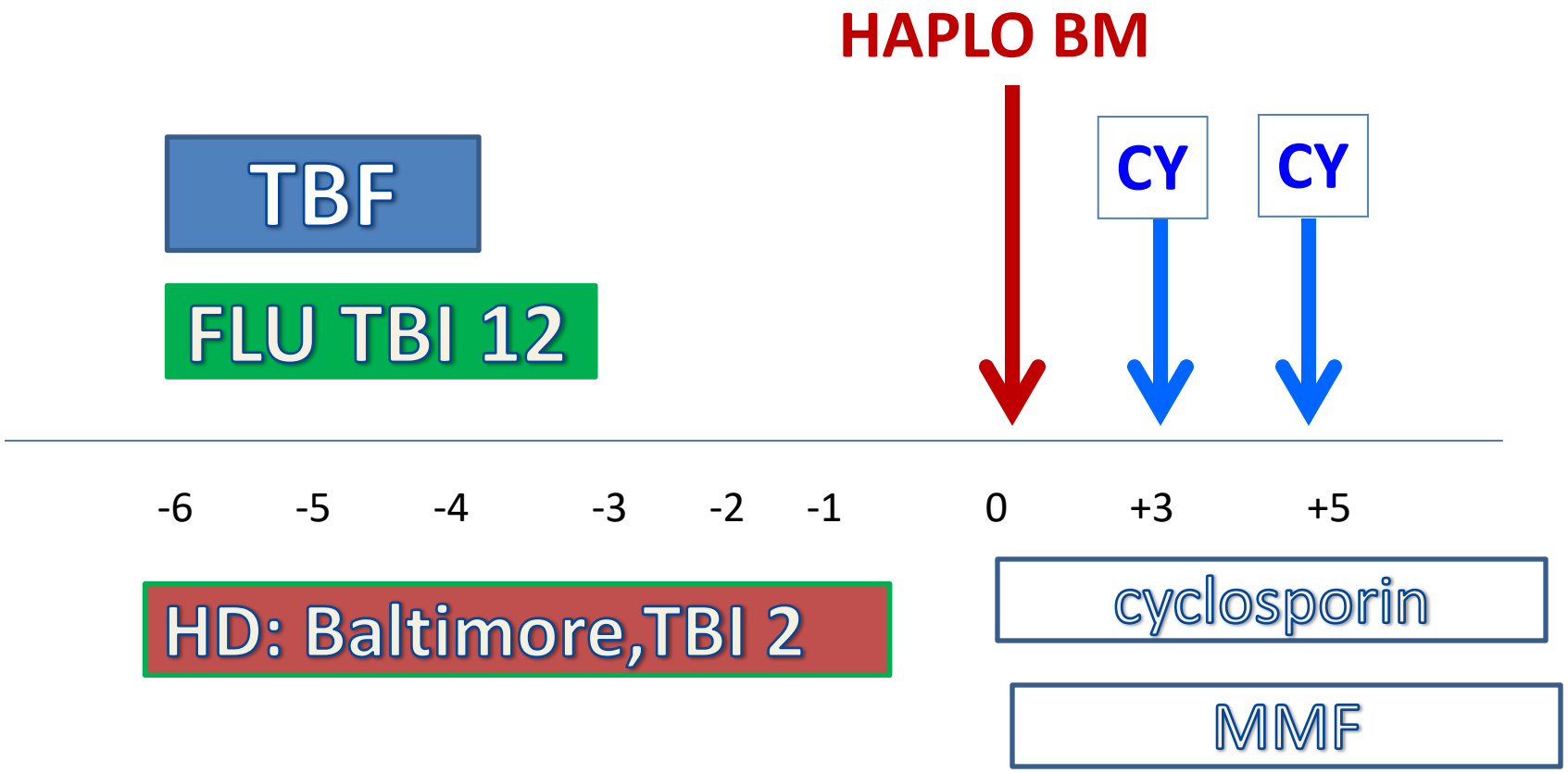
PTCY +3+5 (BM)

Not inferior to PTCY +3+4 (BM or PB)

Perhaps less relapse?

Myelo Ablative Regimen

Sanz , BMT 2012, 47; 12897
Raiola, BBMT 2013; ; 19:117



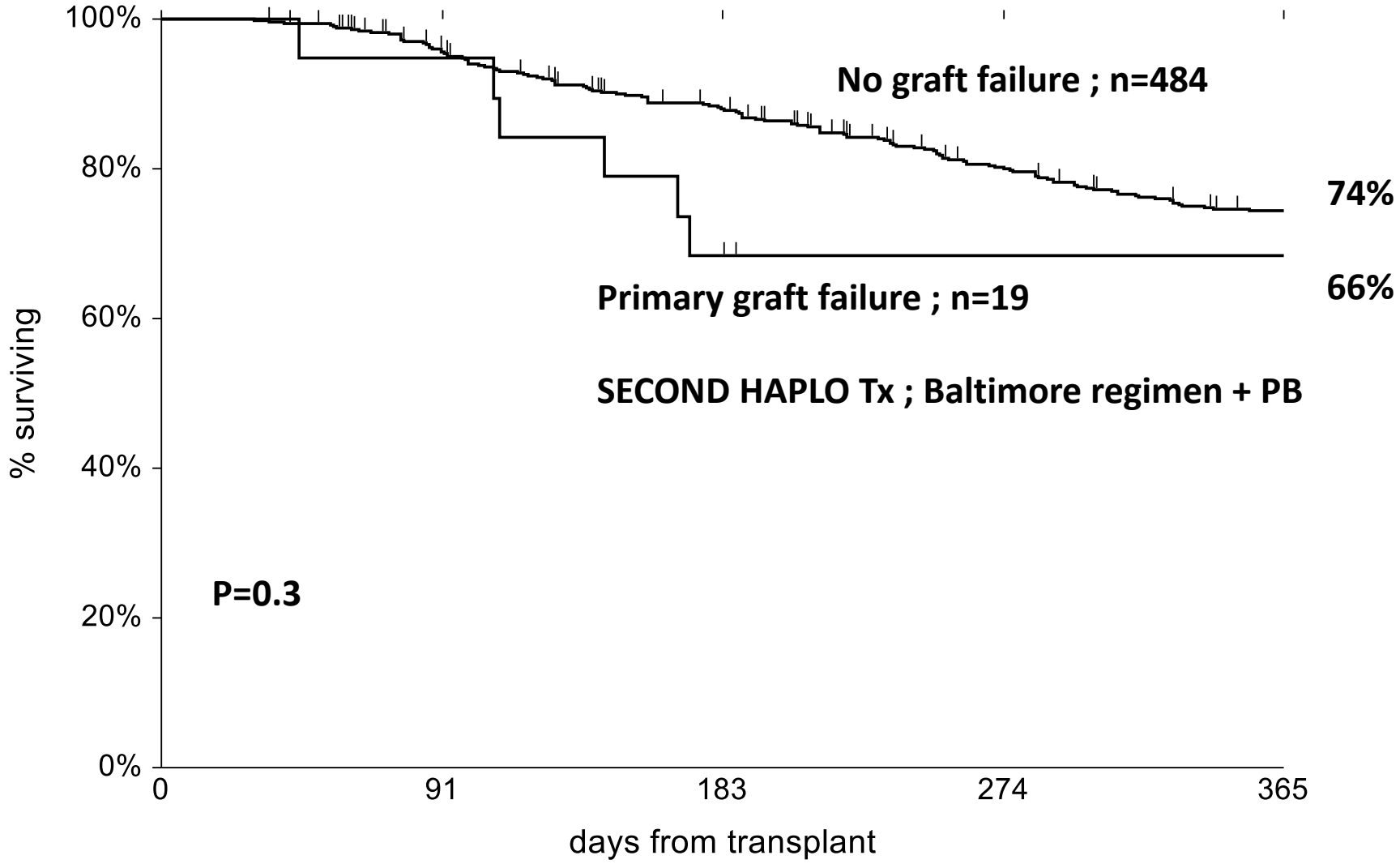
503 patients for engraftment after TBI 12Gy or TBF

	ENGR	PrGF	P
N=	484	19 (3.8%)	
Age	54 (17-70)	57 (19-69)	0.4
Don Age	34 (10-67)	36 (20-63)	0.8
Diagnosis Ac Leuk	55%	53%	
Myelofibrosis	12%	21%	0.7
Median Cellx10^8/kg	3.4 (1.1-9.3)	3.2 (1.4-5.3)	0.3
FU dd (range)	601(2-3050)	530 (45-1965)	0.5

Intensity of the conditioning regimen and PrGF

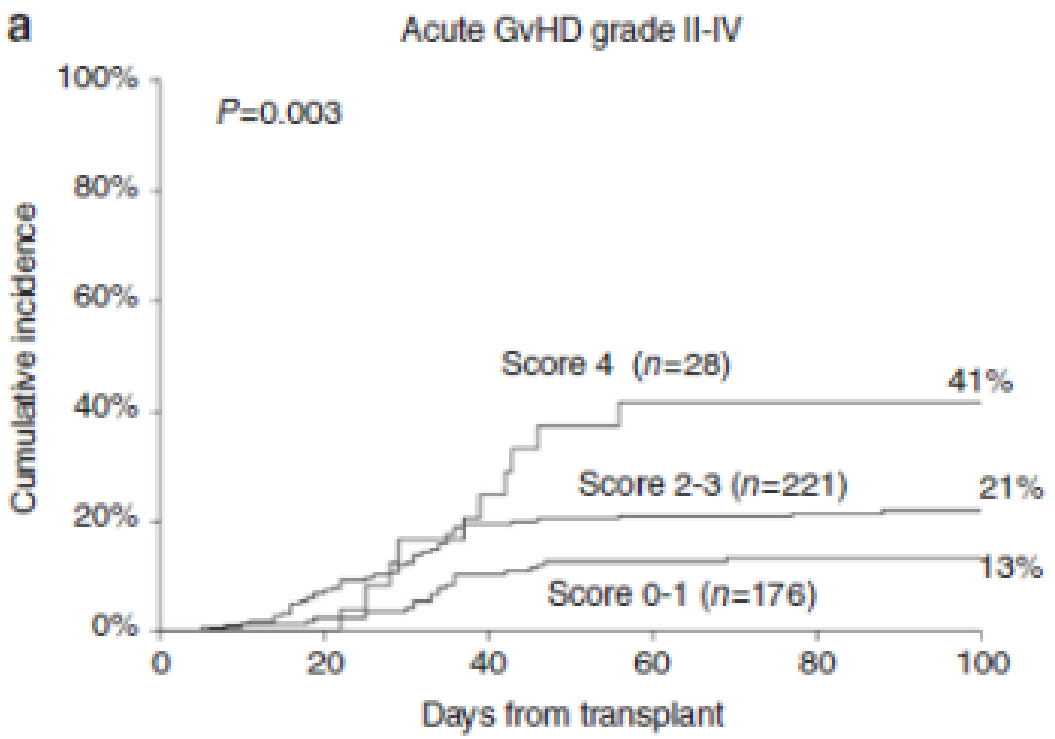
	With PrGF
N=	**19= 3.8%**
•FLU-TBI 12Gy (n=74)	1 (1.4%)
•TBF (BU3) (n=213)	6 (2.9%)
•TBF (BU2) (n=208)	11 (5.3%)
•TBF (BU1) (n=8)	1 (12.5%)

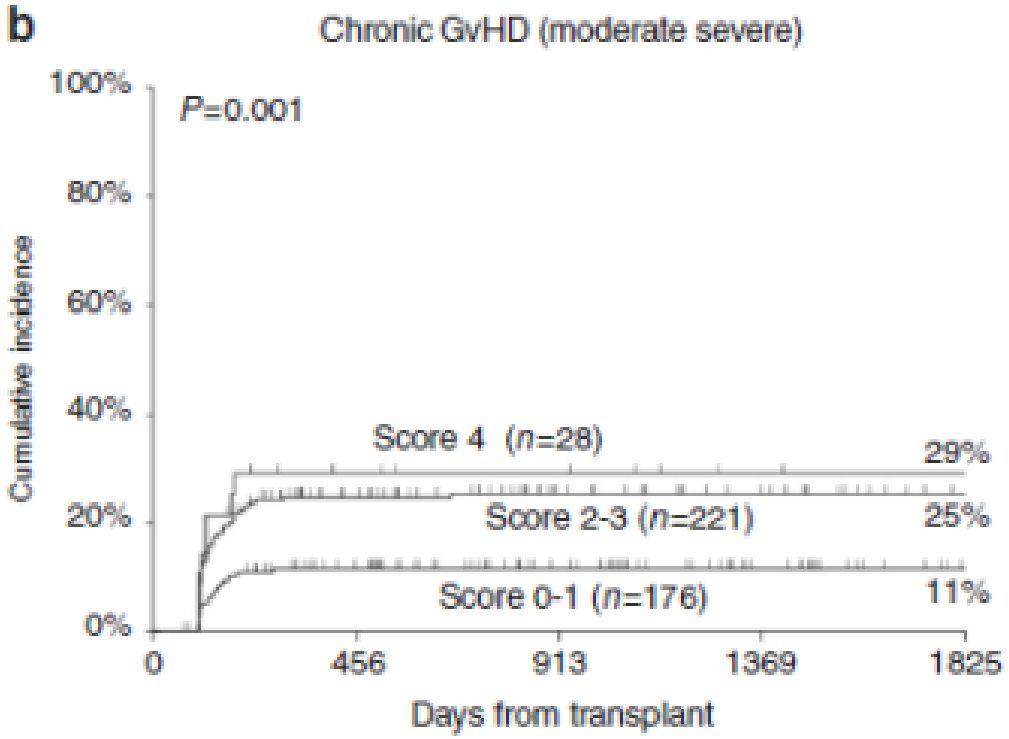
Survival


100%
80%
60%
40%
20%
0%
% surviving
0
91
183
274
365
days from transplant
No graft failure ; n=484
74%
Primary graft failure ; n=19
66%
SECOND HAPLO Tx ; Baltimore regimen + PB
P=0.3

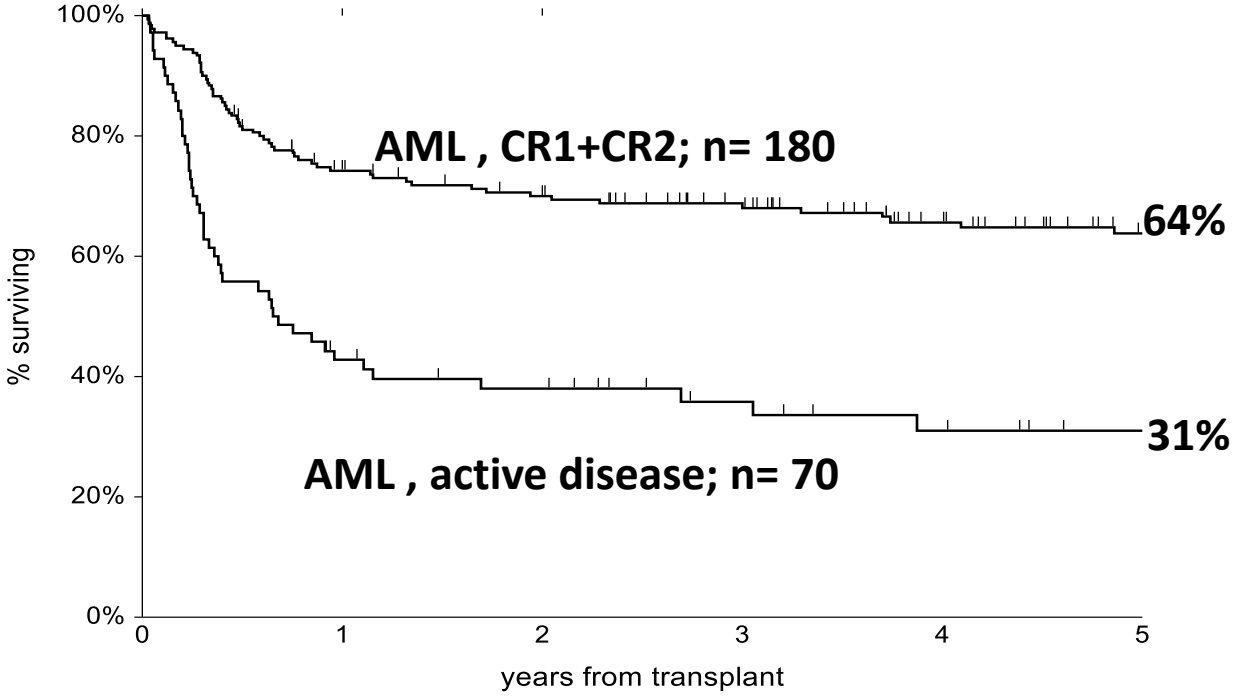
AGE SCORE:

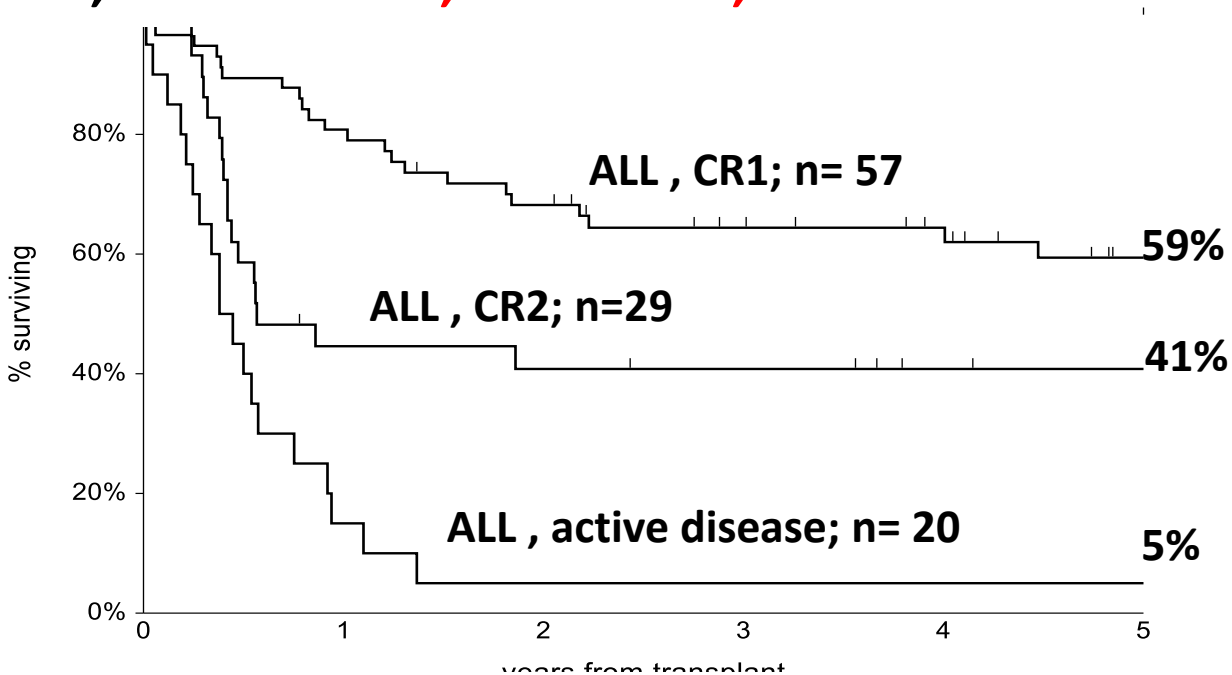
Donor age (yy)		<30	31-40	>40
Recipient age	<40	0	1	2
Recipient	41-60	1	2	3
Recipient	>60	2	3	4

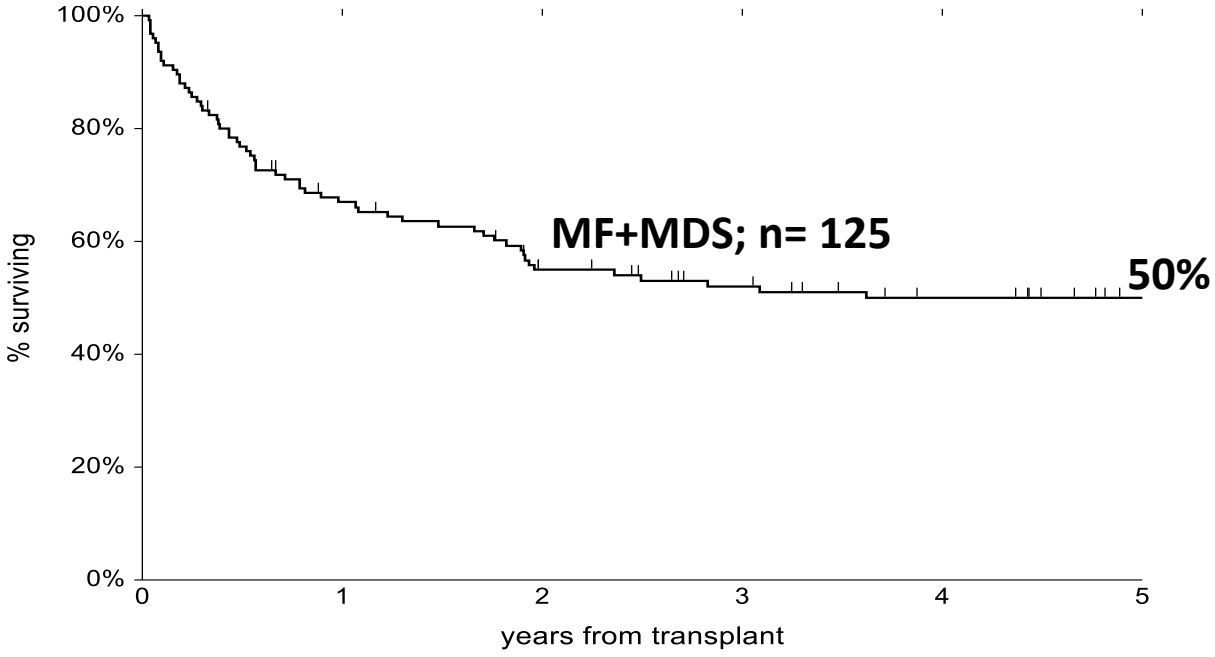


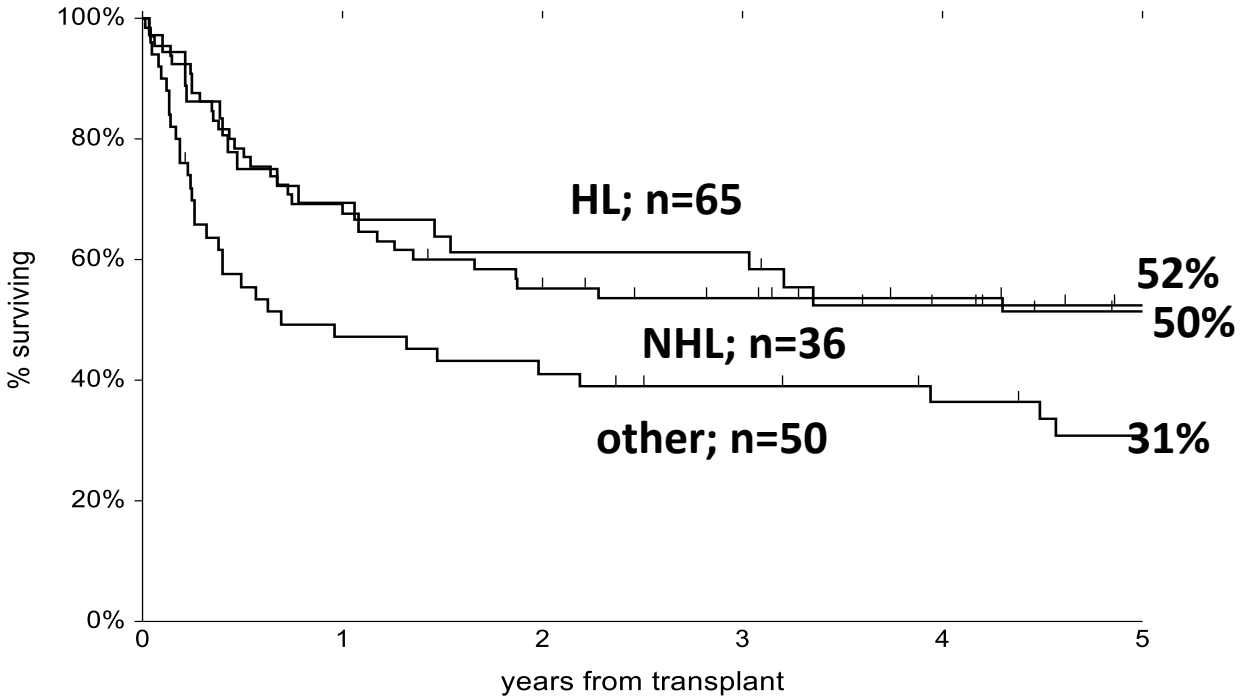


DISEASE FREE SURVIVAL ; HAPLO BMT; PTCY+3+5; n=632

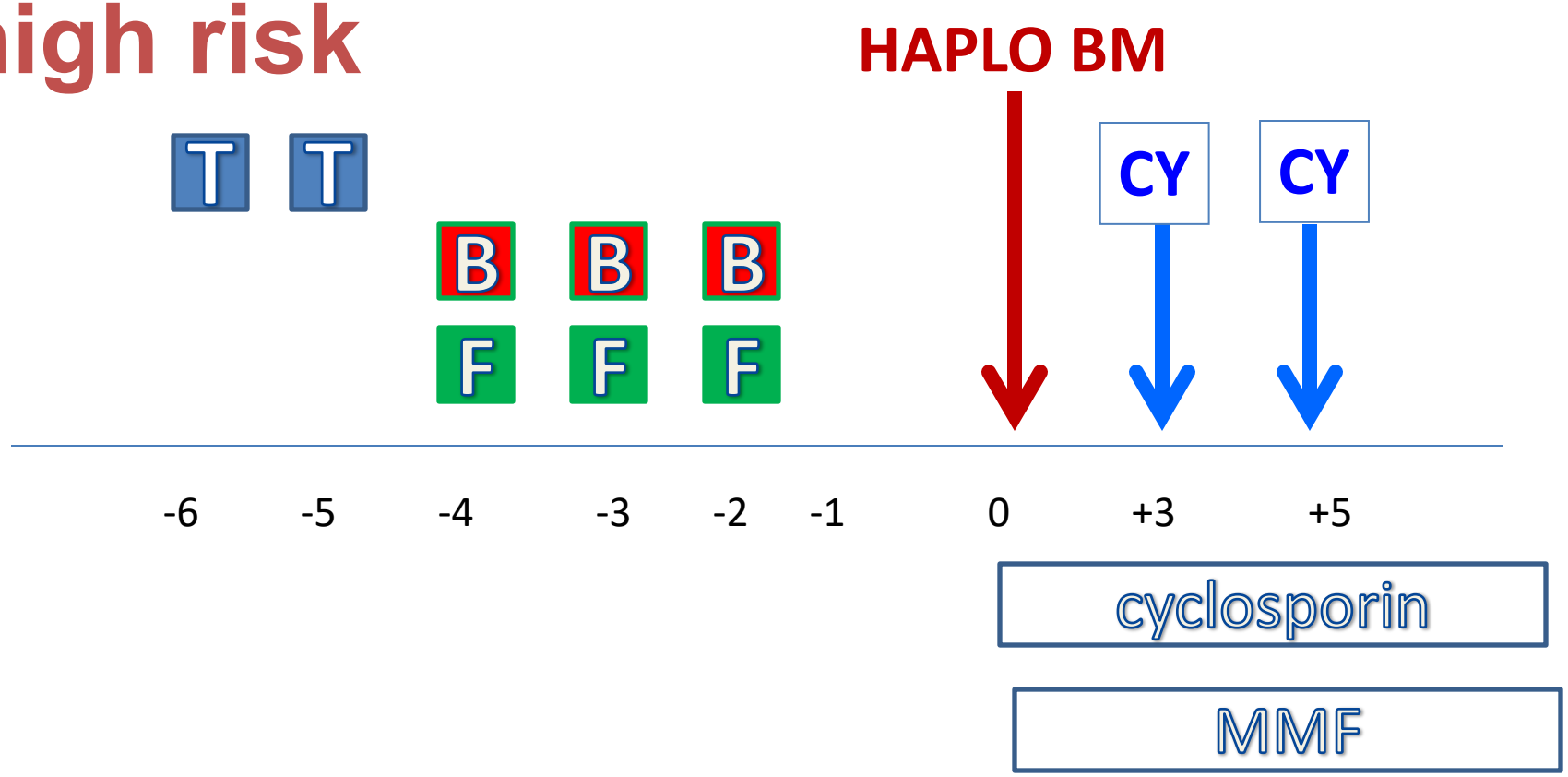






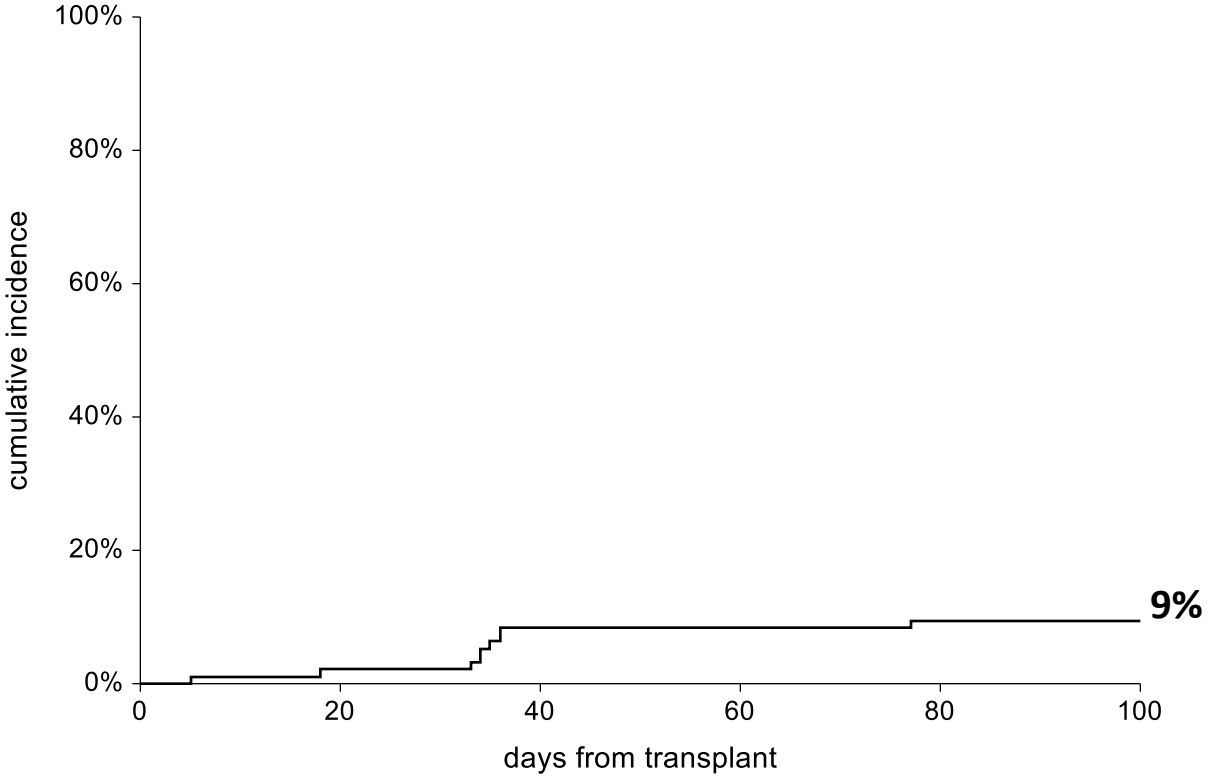


AML CR1/ CR2 int/high risk



Thiotepa 5 mg /kg day -6-5 tot 10 mg/kg
Fludarabine 50 mg/m^2 day 4-3-2 tot 150 mg/m^2
Busulfan 3.2 mg/kg q24h day -4-3-2 tot 9,6 mg/kg

Acute GvHD II-IV



Moderate/severe chronic GvHD

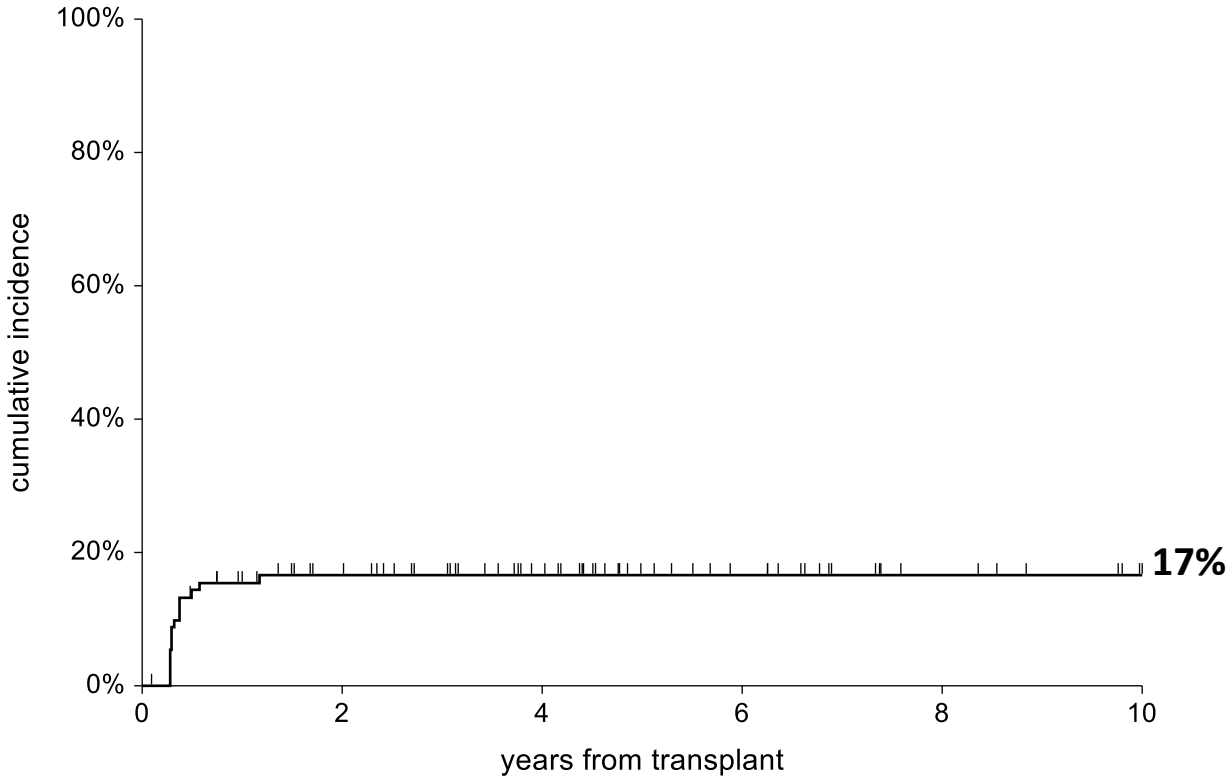
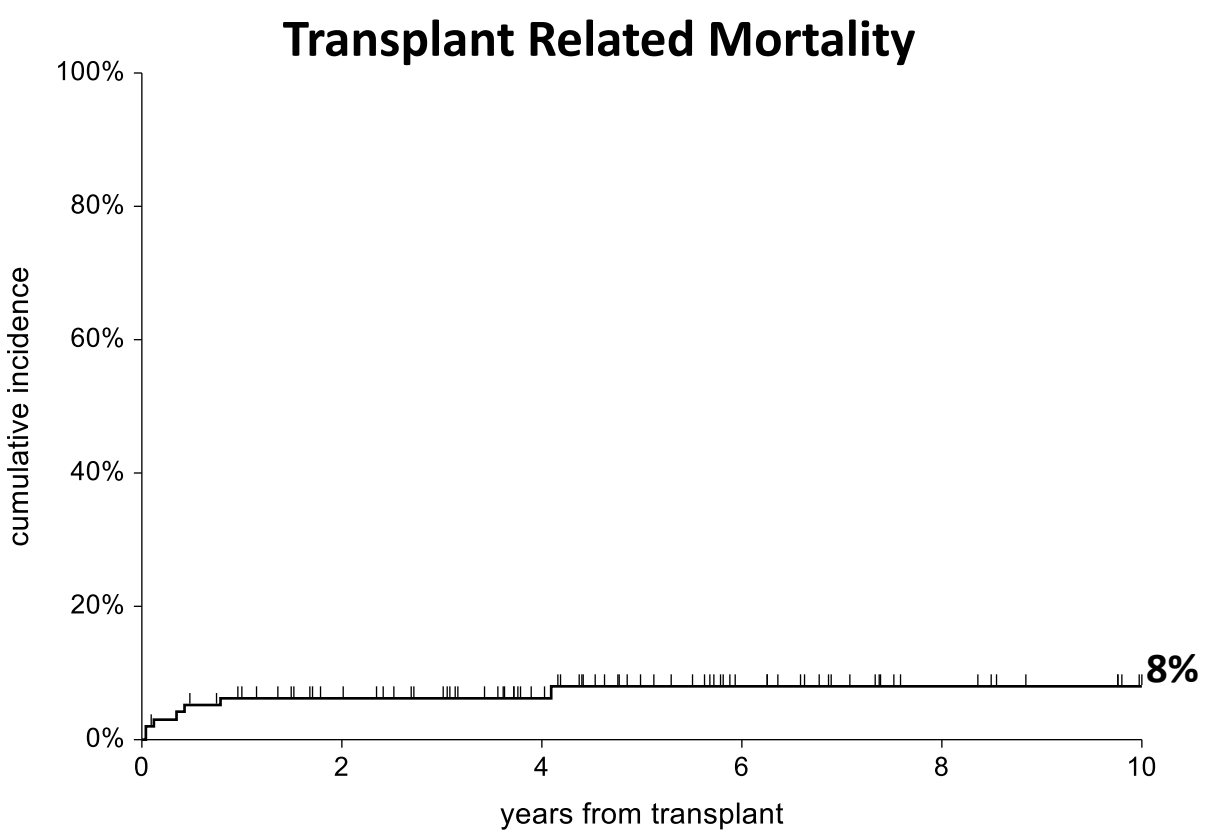


Fig.1


Transplant Related Mortality
100%
80%
60%
40%
20%
0%
cumulative incidence
0
2
4
6
8
10
years from transplant
8%

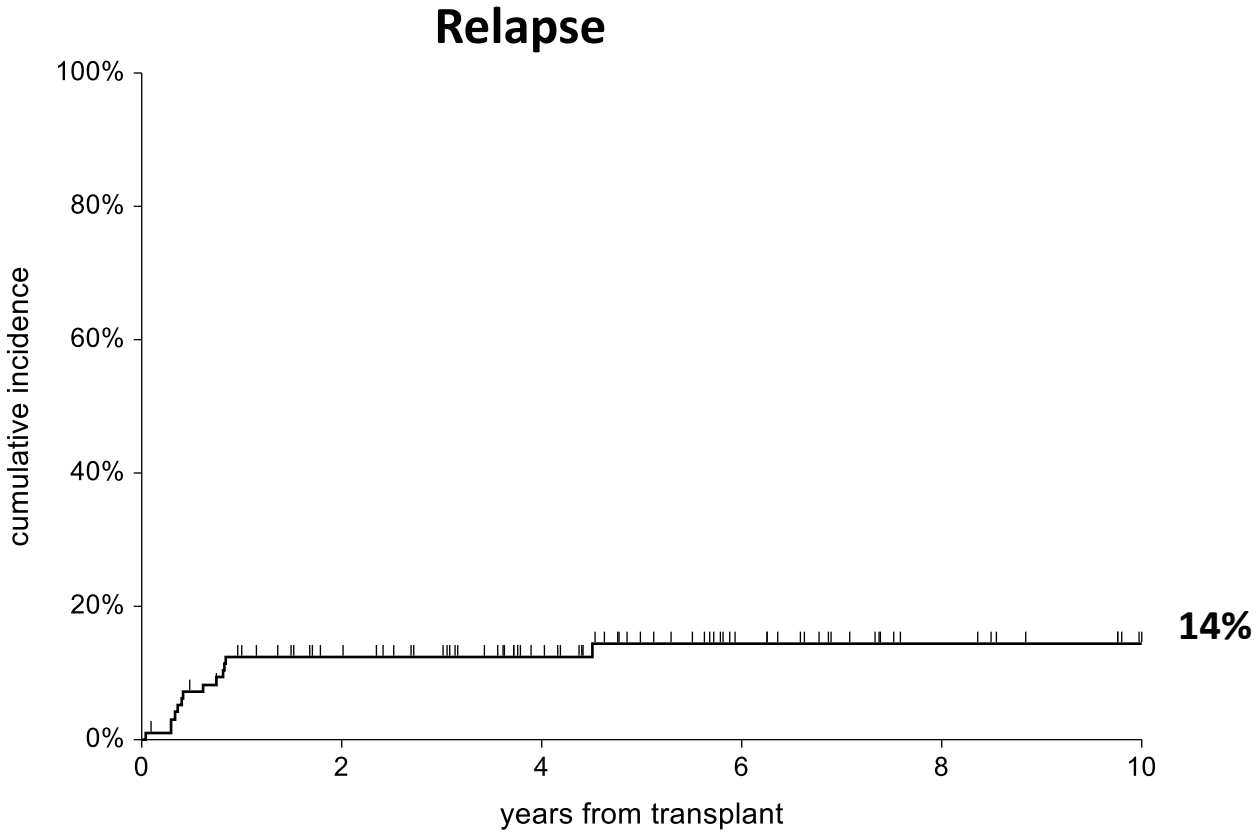

Relapse
100%
80%
60%
40%
20%
0%
cumulative incidence
0
2
4
6
8
10
years from transplant
14%

Fig.2

Disease Free Survival : HAPLO BMT for remission AML; PTCY+3+5; CSA day 0

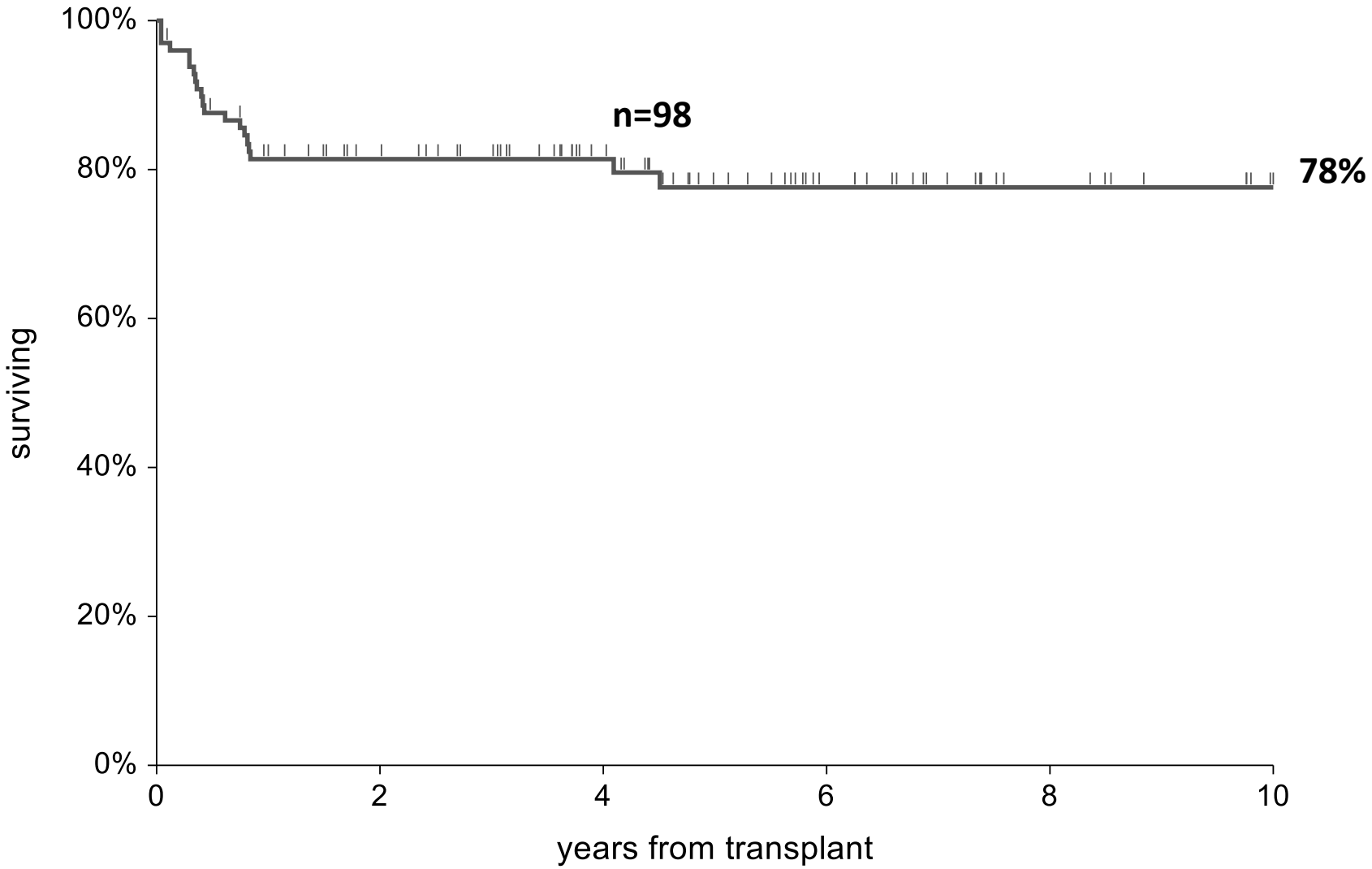
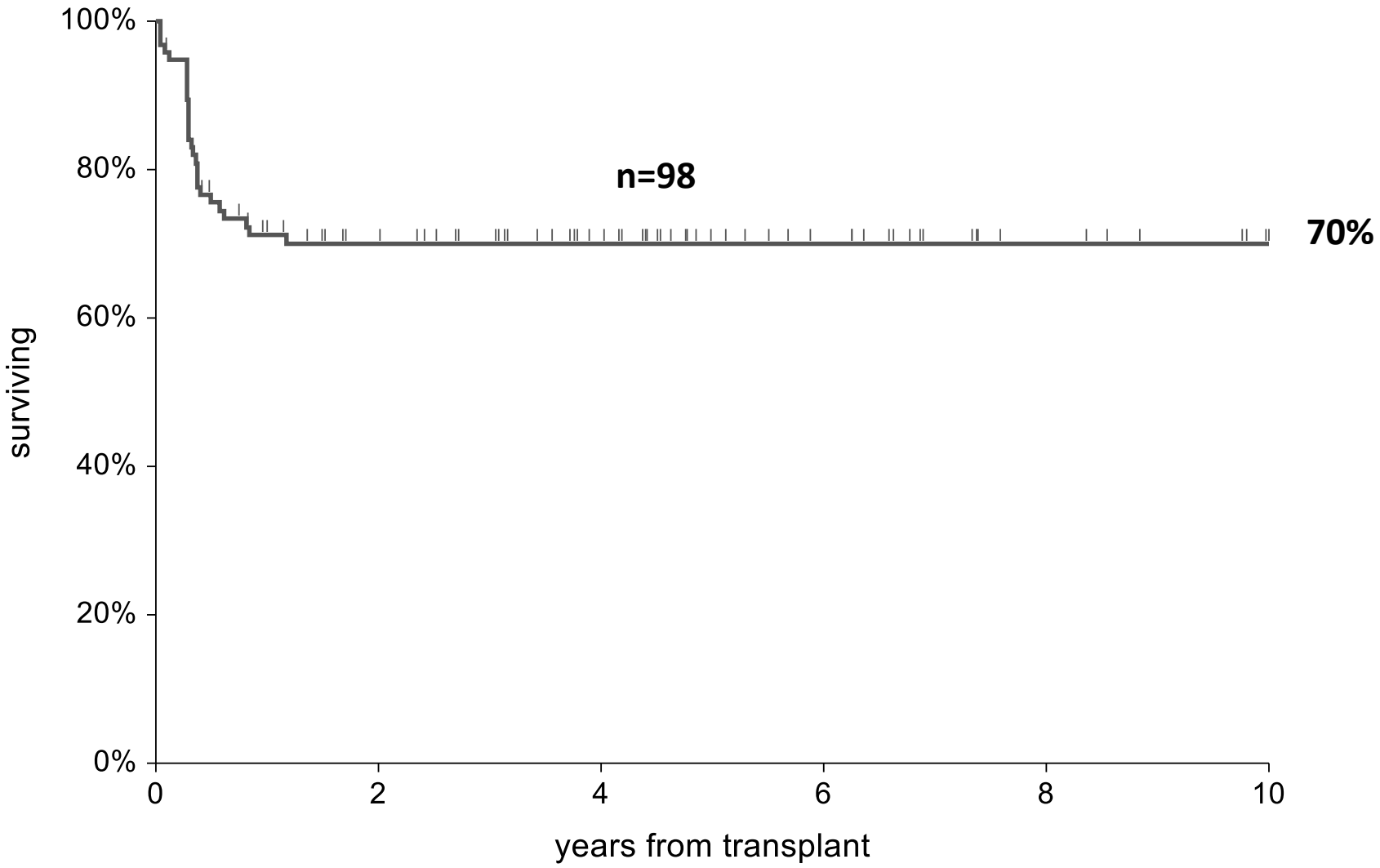


Fig.3

GvHD and relapse free survival : HAPLO BMT for remission AML; PTCY+3+5; CSA day 0



QUESTIONS:

 # Can TIMING of PTCY +3+4 be changed =yes

+3+5 with HAPLO BM

 # is PTCY better than ATG in HAPLO Tx?

PTCy vs. ATG in T-replete Haplo Multivariate analysis

		p	HR	CI	
LFS	ATG vs PT-Cy	**0.03**	1.48	1.03	2.12
	Nb haplo/centre	**<0.001**	0.97	0.96	0.99
GRFS	ATG vs PT-Cy	**0.03**	1.45	1.04	2.02
	Nb haplo/centre	**0.04**	0.99	0.97	1.00
OS	ATG vs PT-Cy	**0.06**	1.43	0.98	2.09
	Nb haplo/centre	**<0.001**	0.97	0.95	0.98

MV Adjusted for: type of AML, disease status, age, stem cell source and conditioning regimen

QUESTIONS:

 # Can TIMING of PTCY +3+4 be changed =yes

 # is PTCY better than ATG in HAPLO Tx =yes

 # is PTCY better than ATG in mmUD Tx?

blood® Regular Article

TRANSPLANTATION

Posttransplant cyclophosphamide vs antithymocyte globulin in HLA-mismatched unrelated donor transplantation

Giorgia Battipaglia,[1,2] Myriam Labopin,[1,3,4] Nicolaus Kröger,[5] Antonin Vitek,[6] Boris Afanasyev,[7] Inken Hilgendorf,[8] Johannes Schetelig,[9] Arnold Ganser,[10] Didier Blaise,[11] Maija Itälä-Remes,[12] Jakob R. Passweg,[13] Francesca Bonifazi,[14] Jurgen Finke,[15] Annalisa Ruggeri,[16] Arnon Nagler,[3,17] and Mohamad Mohty[1,3,4]

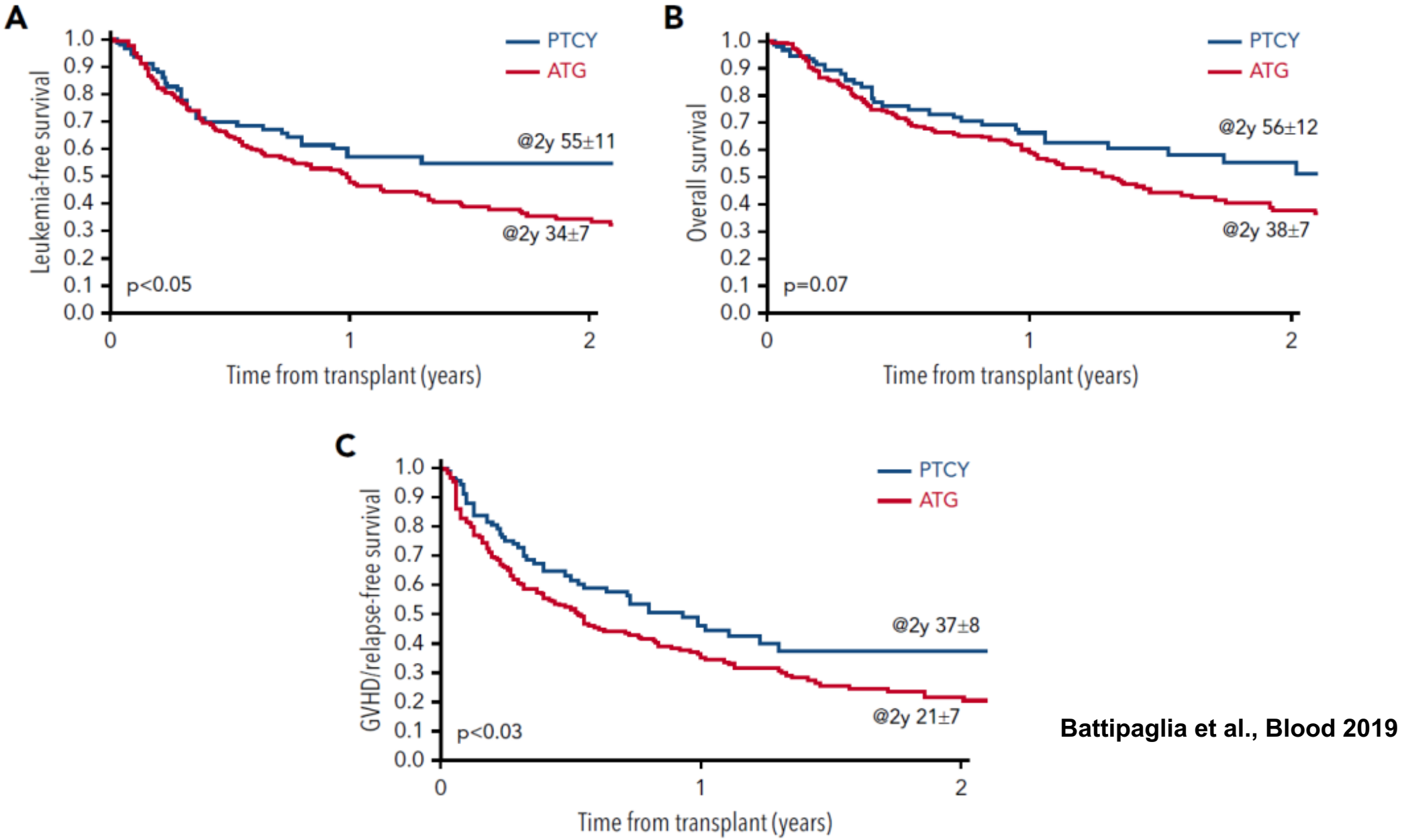
blood® 12 SEPTEMBER 2019 | VOLUME 134, NUMBER 11

KEY POINTS

- **PTCY results in a lower incidence of severe acute GVHD compared with ATG in patients transplanted from 9/10 MMUD for acute myeloid leukemia.**
- **PTCY results in better survival compared with ATG in patients transplanted from 9/10 MMUD for acute myeloid leukemia.**

Table 3. Two-year survival outcomes after matched-pair analysis

	LFS (95% CI)	OS (95% CI)	GRFS (95% CI)	RI (95% CI)	NRM (95% CI)
PTCY	55 (43-66)	56 (43-68)	37 (25-49)	29 (20-40)	16 (9-25)
ATG	34 (27-42)	38 (30-46)	21 (14-28)	37 (29-44)	29 (22-36)
P	<.05	.07	<.03	.31	.06



Battipaglia et al., Blood 2019

QUESTIONS:

 # Can TIMING of PTCY +3+4 be changed =yes

 # is PTCY better than ATG in HAPLO Tx =yes

 # is PTCY better than ATG in mmUD Tx =yes

 # is PTCY better than ATG in HLA= Tx ?

Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203)

Javier Bolaños-Meade, Ran Reshef*, Raphael Fraser, Mingwei Fei, Sunil Abhyankar, Zaid Al Kate Bickett, Yi-Bin Chen, Lloyd E Damon, Yvonne A Efebera, Nancy L Geller, Sergio A Giralt, Mary M Horowitz, David A Jacobsohn, Richard J Jones, Jane L Liesveld, Brent R Logan, Marg Joseph Pidala, David L Porter, Iskra Pusic, Ronald Sobecks, Scott R Solomon, Daniel J Weisdo*

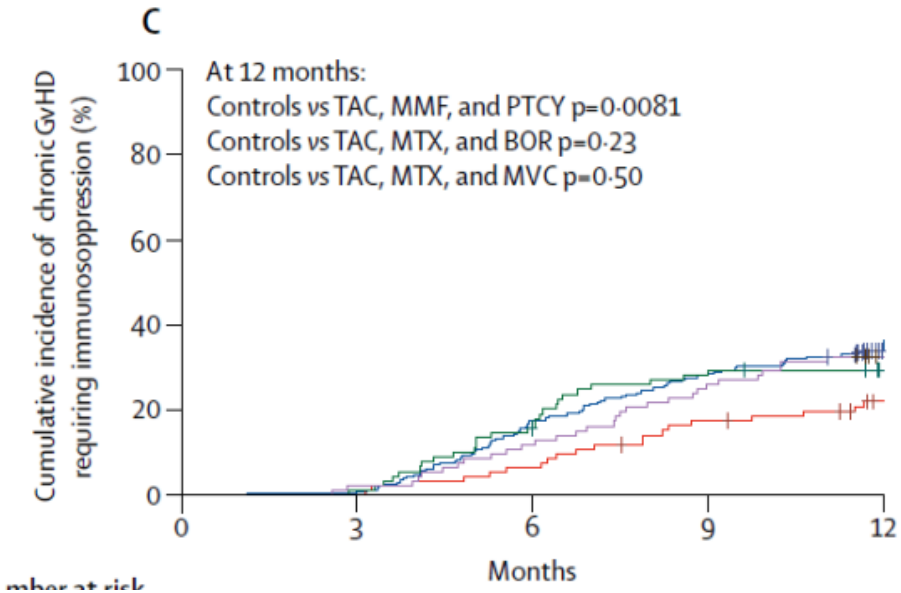
Lancet Haematol 2019; 6: e132–43

Random **TAC MMF PTCY**

TAC MTX BOR

TAC MTX MVC

Control TAC MTX



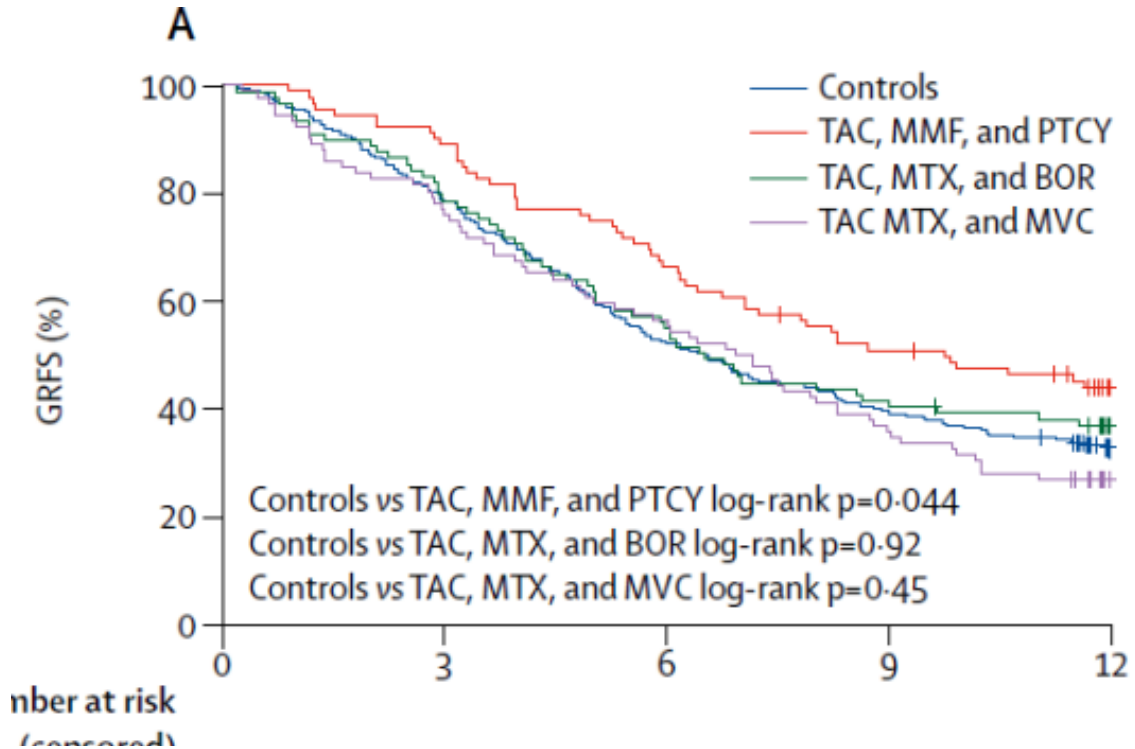
Relapse

28% **TAC MMF PTCY**

24% **TAC MTX BOR**

31% **TAC MTX MVC**

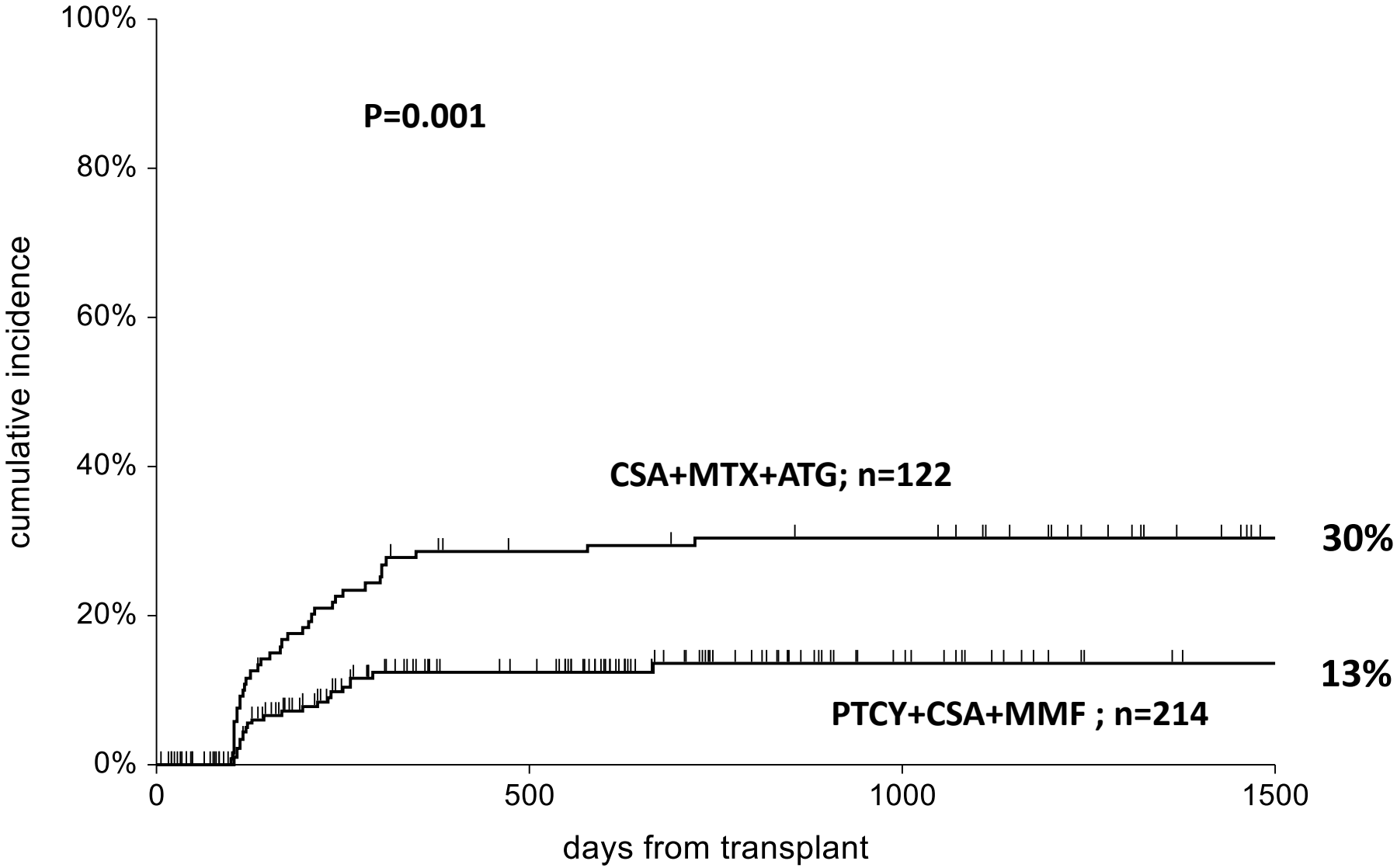
25% **TAC MTX**



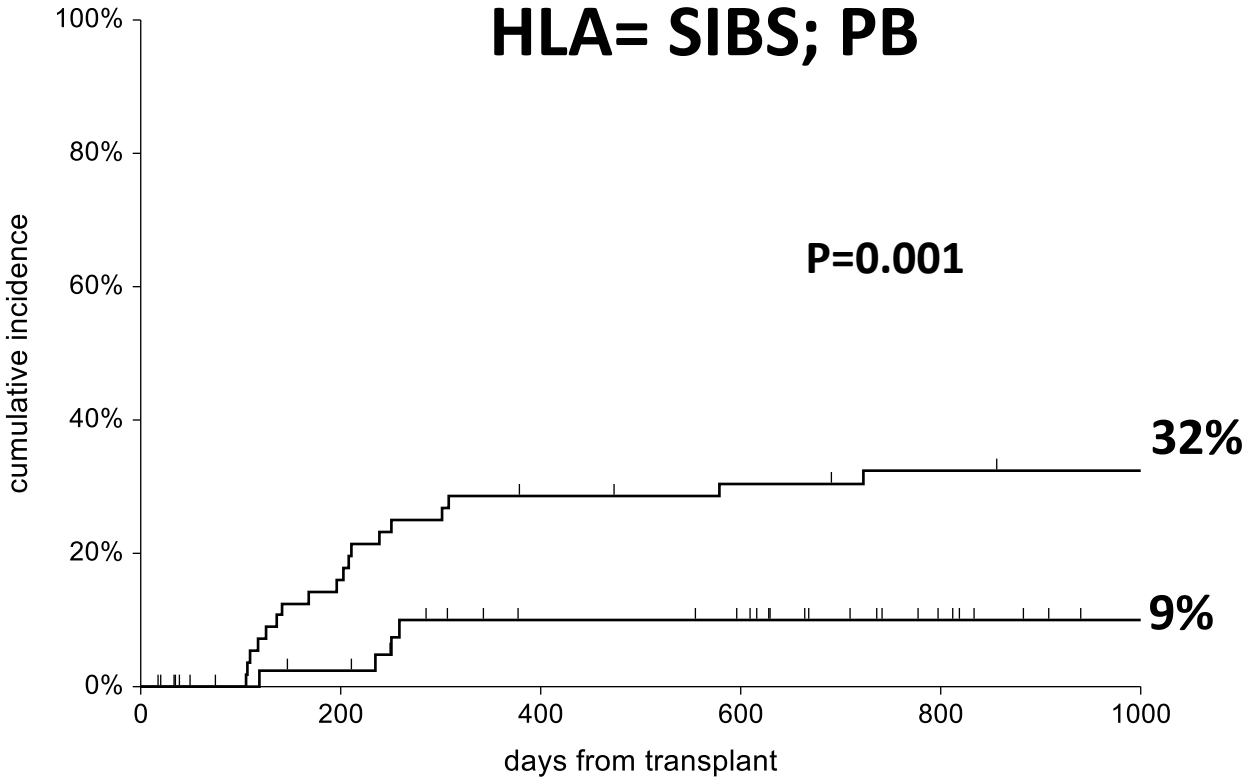
HLA = transplants 2015-2022 (Gemelli)

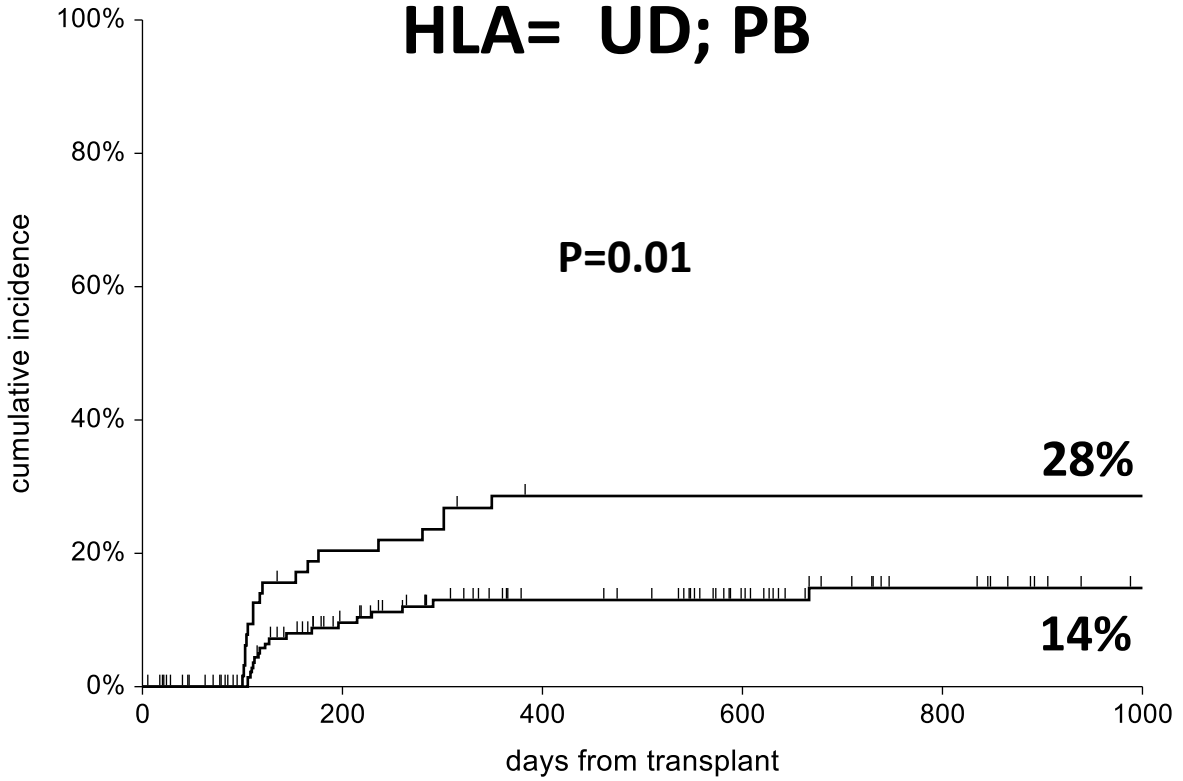
GvHD proph	CSA+MTX±ATG	PTCY+CSA+MMF	P
n.Patiens	122	214	
HLA= SIBs	46%	23%	<0.01
MUD	54%	67%	
AGE (yy)	51 (13-73)	55 (14-74)	<0.01
AML	35%	30%	
ALL	9%	15%	0.007
MF	12%	23%	
MDS	15%	12%	
CR1/CR2	46%	46%	NS
Conditioning reg	48%	73%	<0.01

Chronic GvHD ; HLA matched grafts (Gemelli 2015-2022)

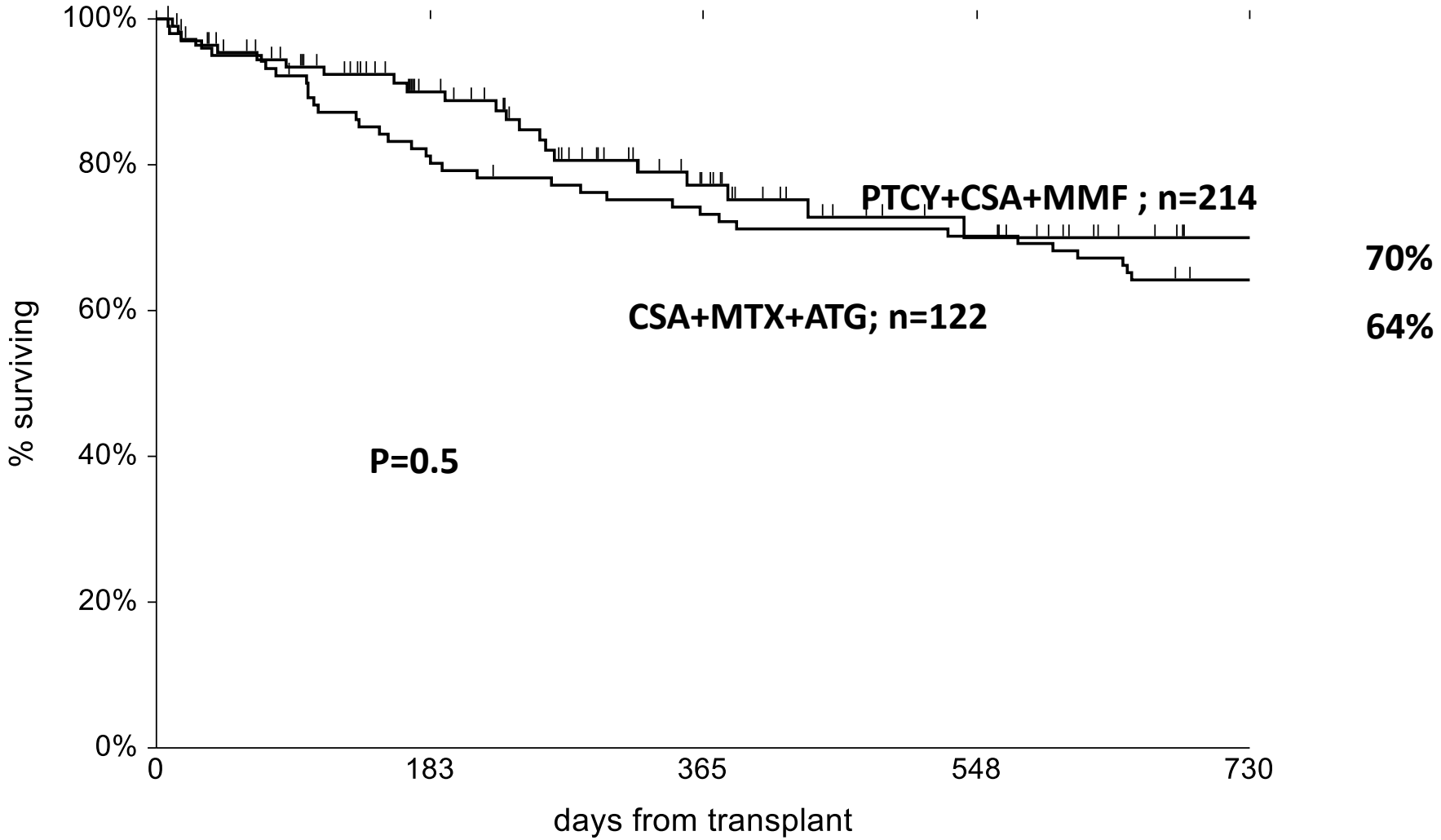


No ATG / low dose ATG 2.5

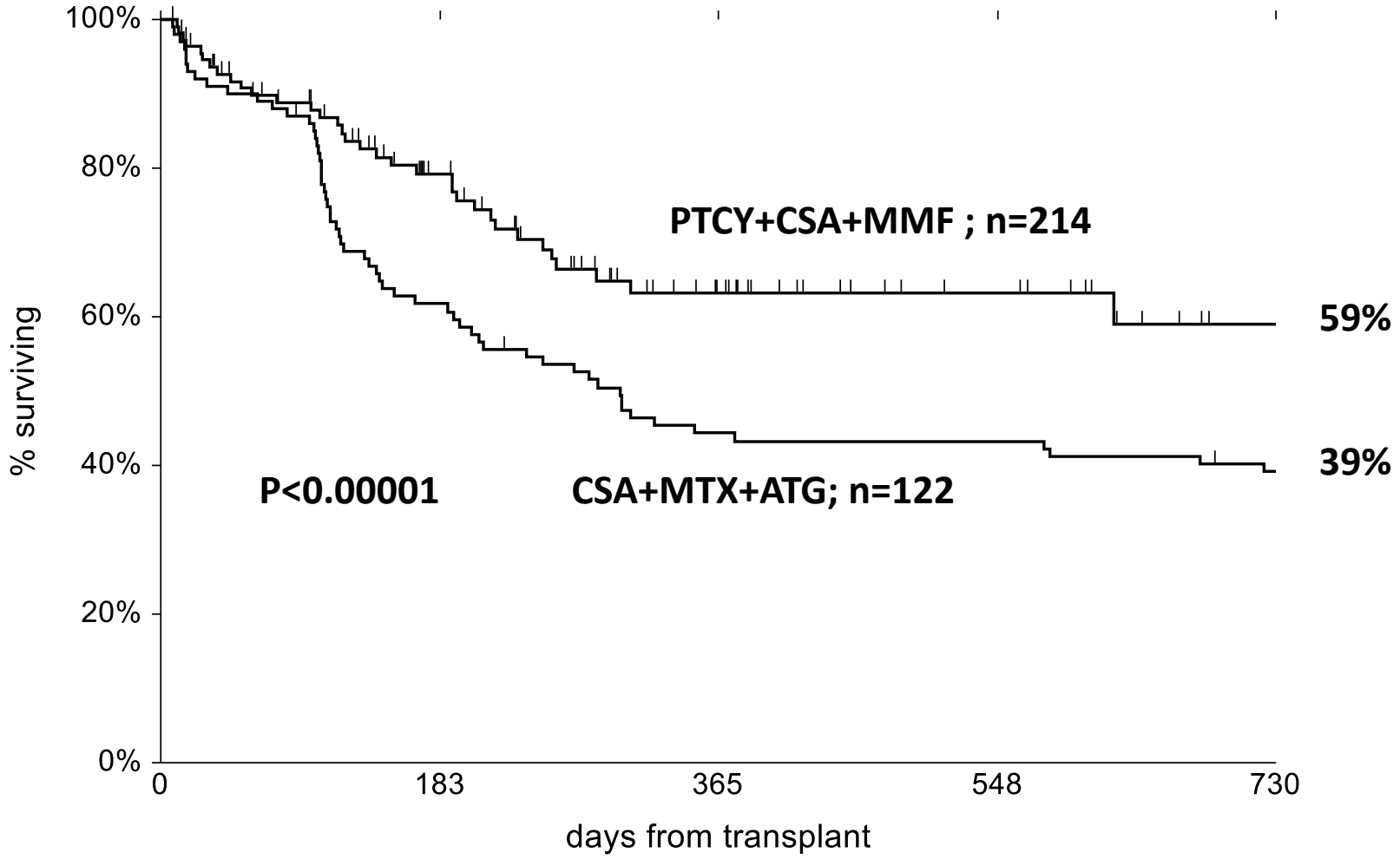




Overall Survival : HLA matched grafts (Gemelli 2015-2022)



GRFS : HLA matched grafts



QUESTIONS:

 # Can TIMING of PTCY +3+4 be changed =yes

 # is PTCY better than ATG in HAPLO Tx =yes

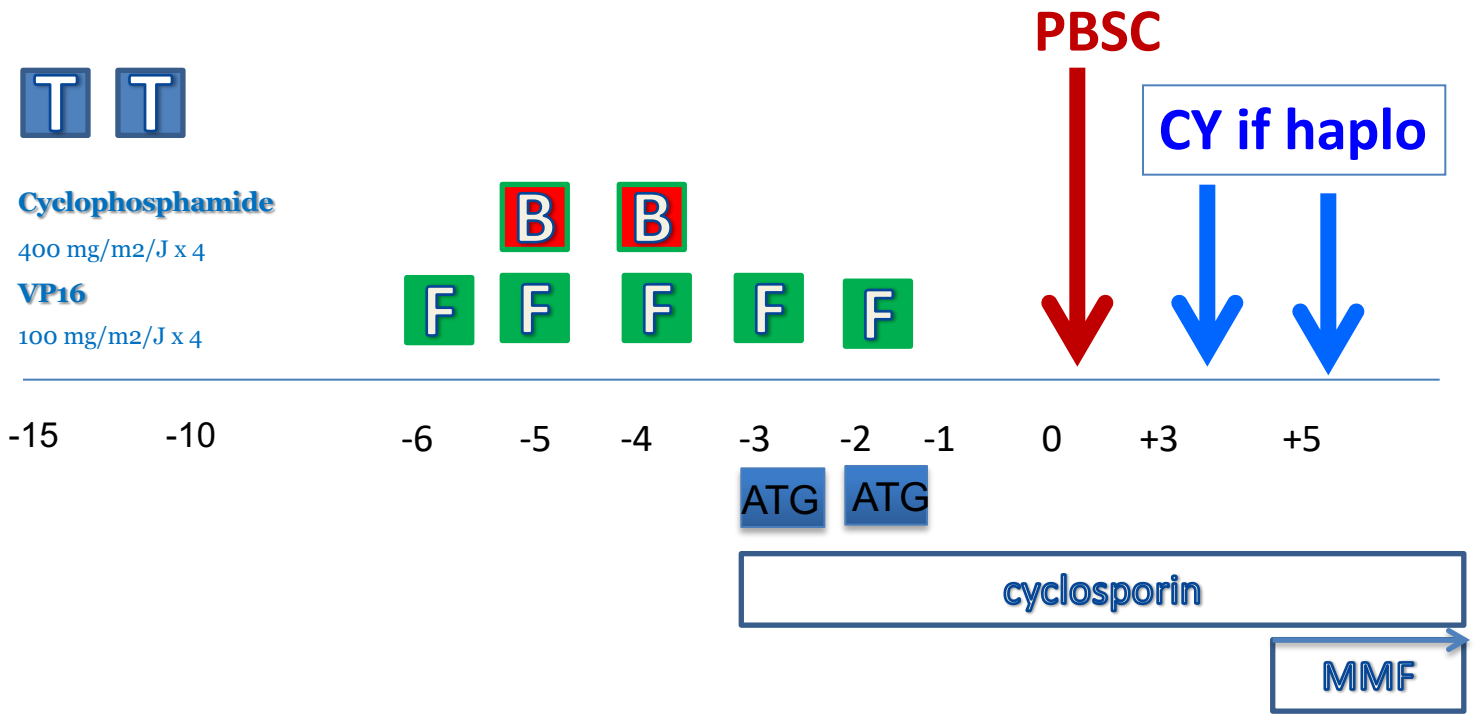
 # is PTCY better than ATG in UD Tx =yes

 # is PTCY better than ATG in HLA=Tx =yes

less cGvHD, improved GRFS

 # can PTCY be combined with ATG?

ATG *and* PtCy combination (Hopital St Antoine Paris)



Thiotepa 5 mg /kg	day -15-14	tot 10 mg/kg
Cyclophosphamide 400 mg/m2/d	day -13 to -10	tot 1600 mg/m2
VP16 100 mg/m2/d	day -13 to -10	tot 400 mg/m2
Fludarabine 30 mg/m2	day -6-5-4-3-2	tot 150 mg/m2
Iv Busulfan 3.2 mg/kg/24h	day -5-4	tot 9,6 mg/kg
ATG (Thymoglobuline) 2.5 mg/Kg/24h	day -3-2	total 5 mg/kg

Dulery et al., Biol Blood Marrow Transplant 2018

ATG *and* PtCy combination

	Total (n=72) n (%)	Haplo (n=27) n (%)	MRD (n=16) n (%)	UD (n=29) n (%)
Relapse incidence	23.6	22.4	31.2	21.5
NRM	23.5	16.7	20.5	31.3
Acute GVHD II-IV	23.6	11.1	12.5	41.4
Chronic GVHD	50.7	45.4	55.3	53

Dulery et al., Biol Blood Marrow Transplant 2018

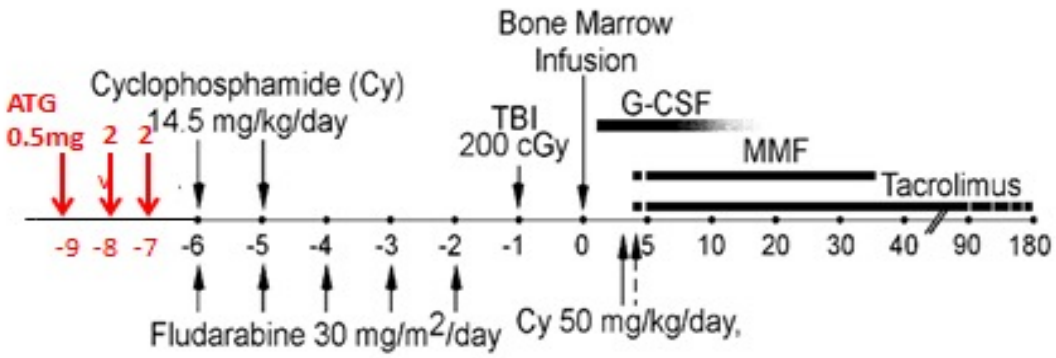
Biol Blood Marrow Transplant 23 (2017) 498–504

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Alternative Donor Transplantation with High-Dose Post-Transplantation Cyclophosphamide for Refractory Severe Aplastic Anemia

Amy E. DeZern [1,2,*], Marianna Zahurak [1,3], Heather Symons [1,4], Kenneth Cooke [1,4],



Patients = 16
13 HAPLO 3 UD
Median age 30 (13-69)

Survival 16/16

R/R SAA	**n=22**	**HAPLO**	**22 alive**
Upfront SAA	**=17**	**HAPLO**	**15 alive**

blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-
bloodadvances@hematology.org

Non-myeloablative transplantation with post-trans cyclophosphamide for Severe Aplastic Anemia

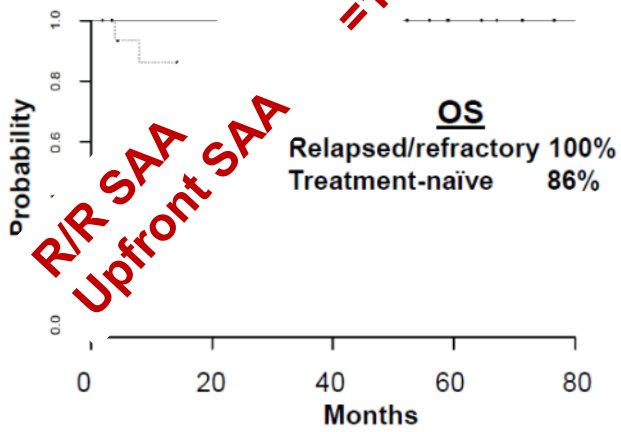
22 alive
15 alive

Tracking no: ADV-2020-001729-T

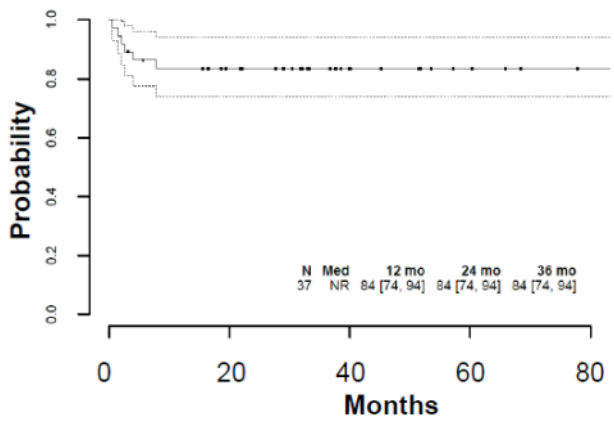
Amy DeZern (The Sidney Kimmel Comprehensive Cancer C Hopkins, United States) Marianna Zahurak (Johns Hopkins University, United States) Heather Symons (Johns Hopkins, United S Cooke (Johns Hopkins University School of Medicine, United States) Gary Rosner (Johns Hopkins University, United States) one (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, United States) Carol Ann Huff (Johns Hopkins Unive tes) Lode Swinnen (Johns Hopkins University, United States) Philip Imus (Johns Hopkins Medical Institute, United States) J ohns Hopkins University, United States) Nina Wagner-Johnston (Johns Hopkins University, United States) Richard Ambinder (J niversity, School of Medicine,) Leo Luznik (Johns Hopkins University, United States) Javier Bolaños Meade (Johns Hopkir ited States) Ephraim Fuchs (Sidney Kimmel Cancer Center at Johns Hopkins, United States) Richard Jones (Johns Hopkins On United States) Robert Brodsky (Johns Hopkins University School of Medicine, United States)

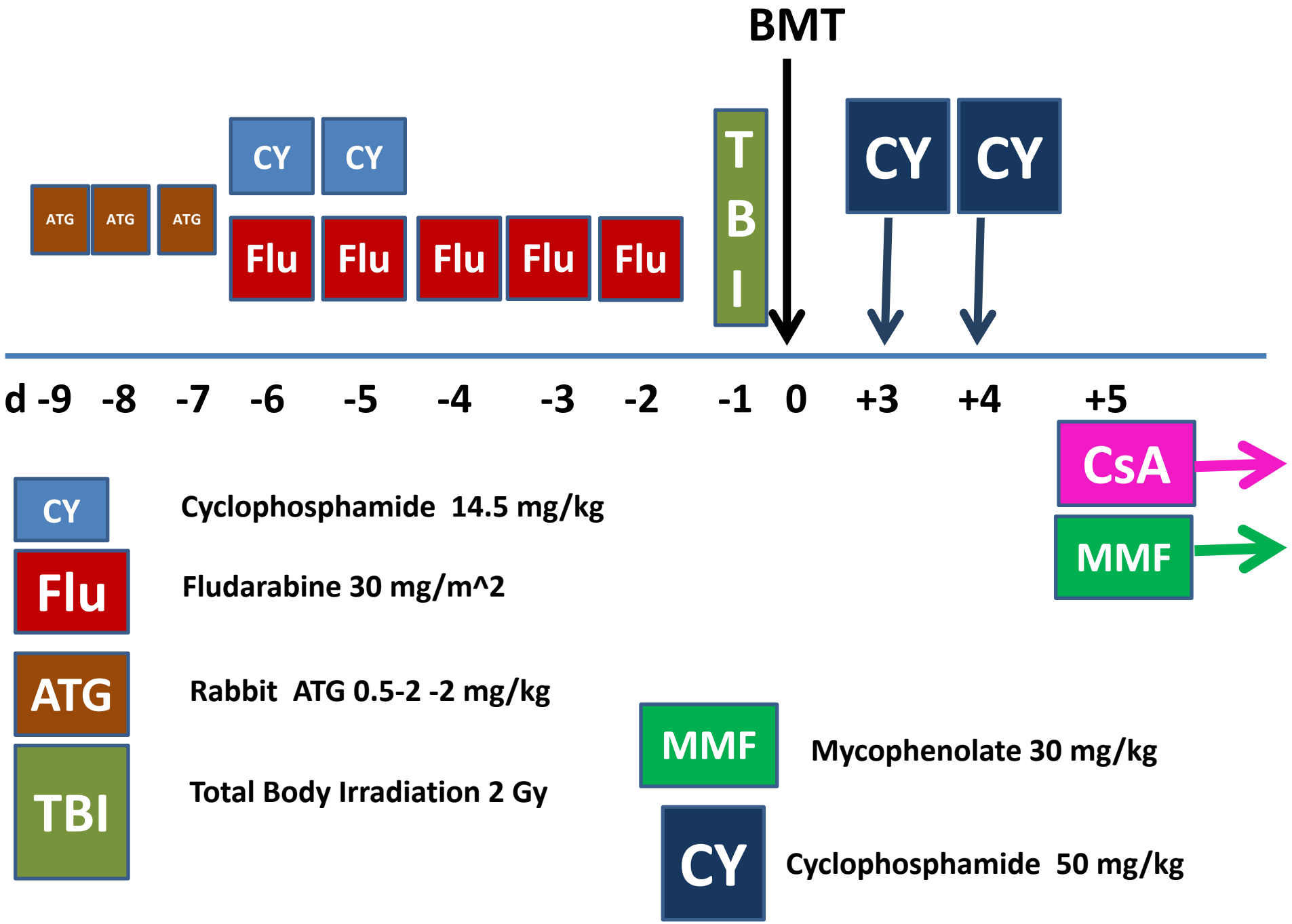
HAPLO
HAPLO

n=22
=17



R/R SAA
Upfront SAA




BMT
ATG
ATG
ATG
CY
CY
Flu
Flu
Flu
Flu
Flu
T
B
I
CY
CY
d -9
-8
-7
-6
-5
-4
-3
-2
-1
0
+3
+4
+5
CsA
MMF
CY
Cyclophosphamide 14.5 mg/kg
Flu
Fludarabine 30 mg/m^2
ATG
Rabbit ATG 0.5-2 -2 mg/kg
TBI
Total Body Irradiation 2 Gy
MMF
Mycophenolate 30 mg/kg
CY
Cyclophosphamide 50 mg/kg

The Baltimore protocol (PTCY+ATG) for SAA

 # excellent for HAPLO; results confirmed in a multicenter study in Brazil

 # if we can control GvHD and rejection in a HLA HAPLO setting, why not use it in an HLA= setting?

Biol Blood Marrow Transplant 26 (2020) e222–e226

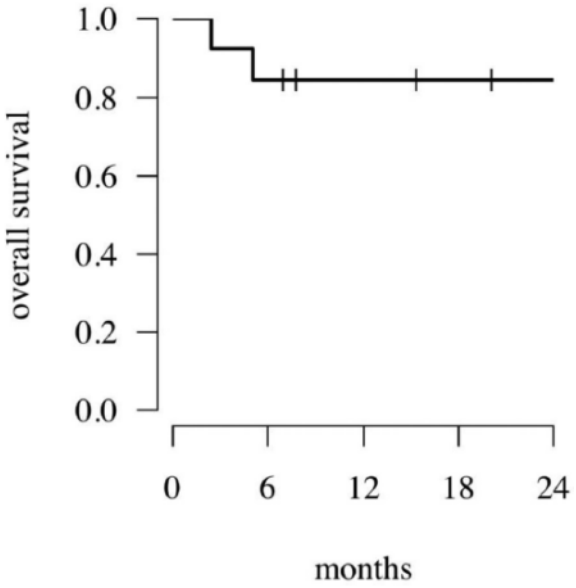
Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

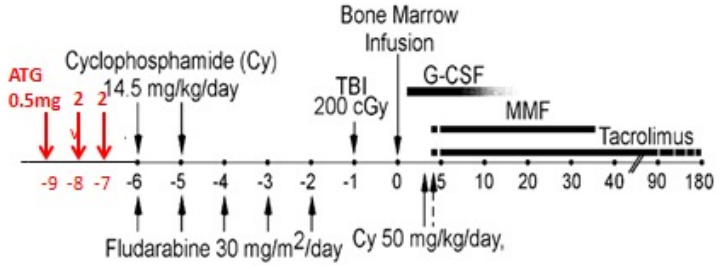
Brief Articles

A Case Series of Post-Transplantation Cyclophosphamide in Unrelated Donor Hematopoietic Cell Transplantation for Aplastic Anemia

Leonardo Javier Arcuri[1,*], Samir Kanaan Nabhan[2], Gisele Loth[2], Elias Hallack Atta[1], Michel Oliveira[2], Samantha Nichele[2], Renato de Castro Araujo[1], Carmem Bonfim[2]



13 patients; all pts engrafted
2 died infections
11 surviving

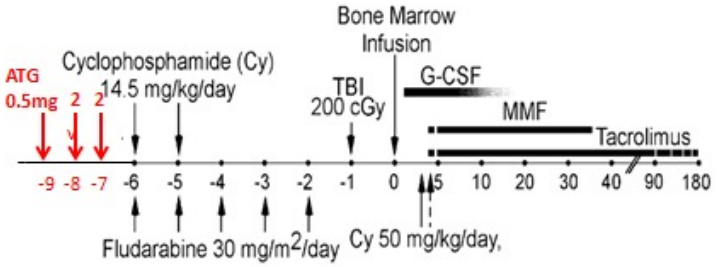


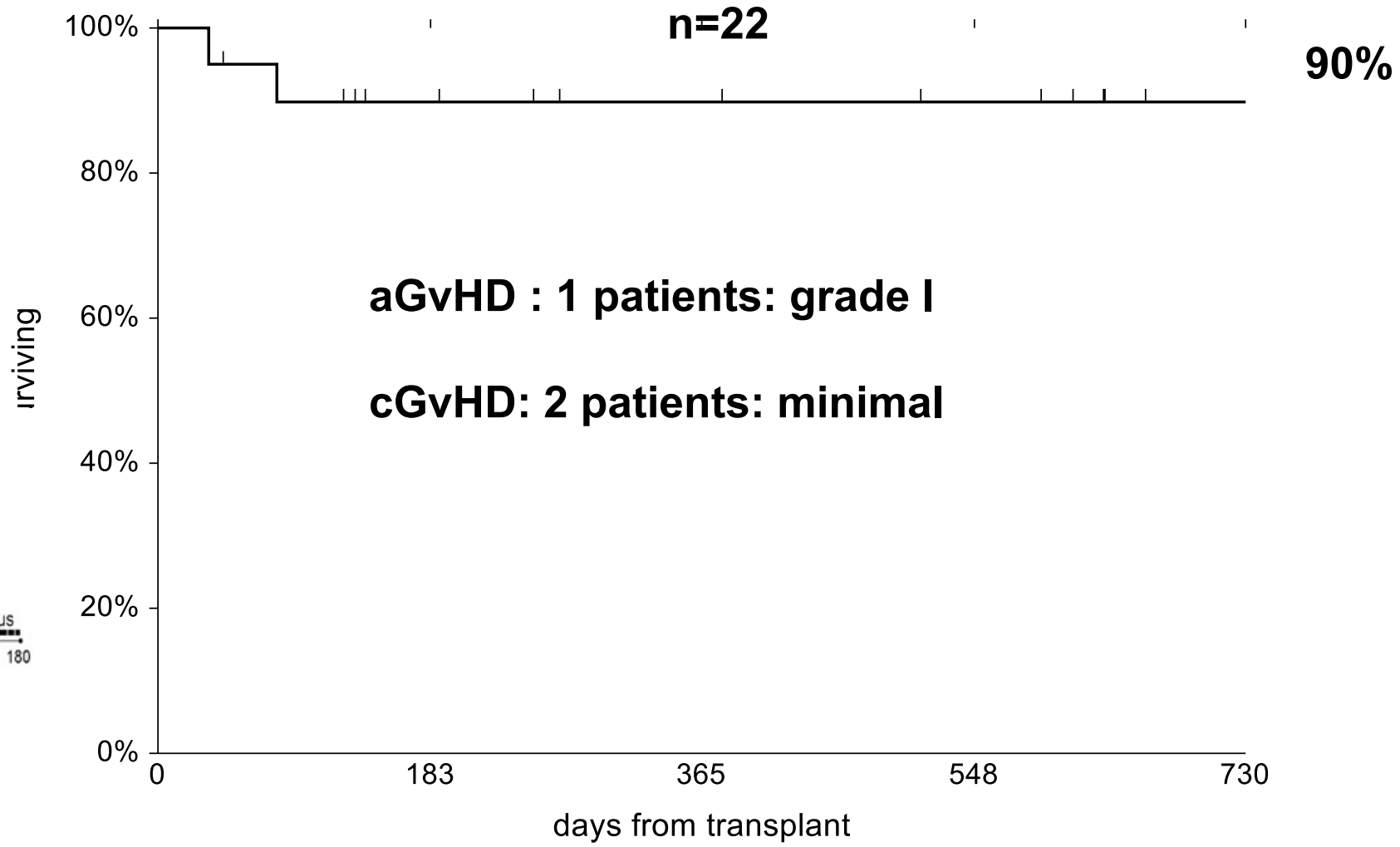
SAA; GITMO 2020-2022

Gemelli, Cuneo, Milano
Alessandria, Bolzano
Torino, Verona, Perugia

Age : 39 (21-60)

MUD (8/8) n=12
mmUD (7/8) n=6
SIB n=1
APLO n=3





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less cGvHD, improved GRFS

 # can PTCY be combined with ATG =yes

MA condit + advanced leukemia

NMA condit + SAA

CONCLUSIONS:

 # PTCY allows for safe HAPLO Tx

 # PTCY schedule can be modified (timing, dose?)

 # PTCY being used in HLA = transplants
less cGvHD, improved GRFS

BMT Unit Genova

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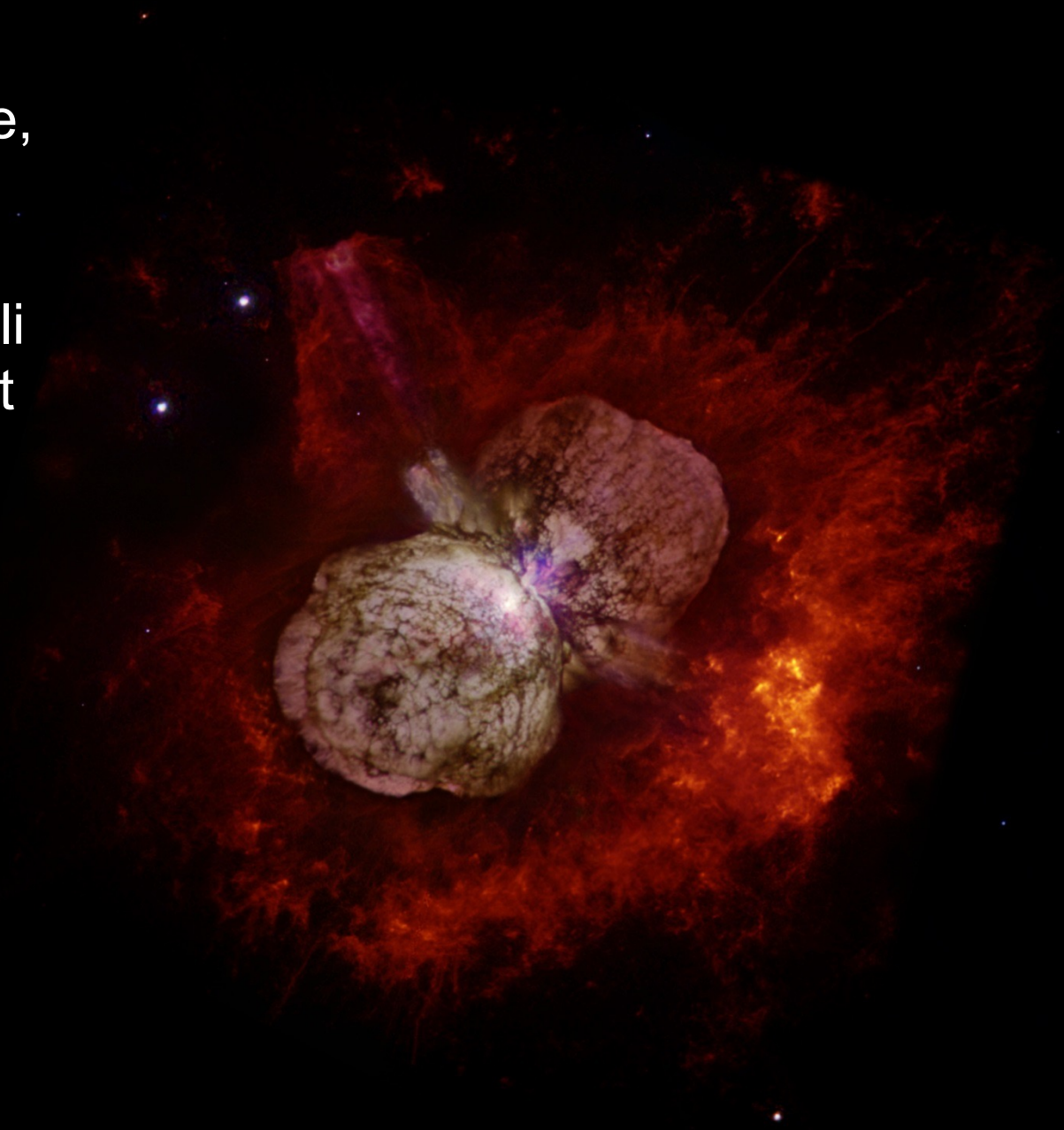
C Di Grazia
A Dominietto, A Ghiso
F Gualandi, T Lamparelli
AM Raiola, M T Van Lint
R Varaldo



Data Center

Rosi Oneto
M Daneri
C Frau

BMT Unit

S Sica, P
L Laurenti,
F Sora', I I
Autore, E M
G Zini, L Te
Bianchi, N