The role of bone marrow transplantation in aplastic anemia : 2022

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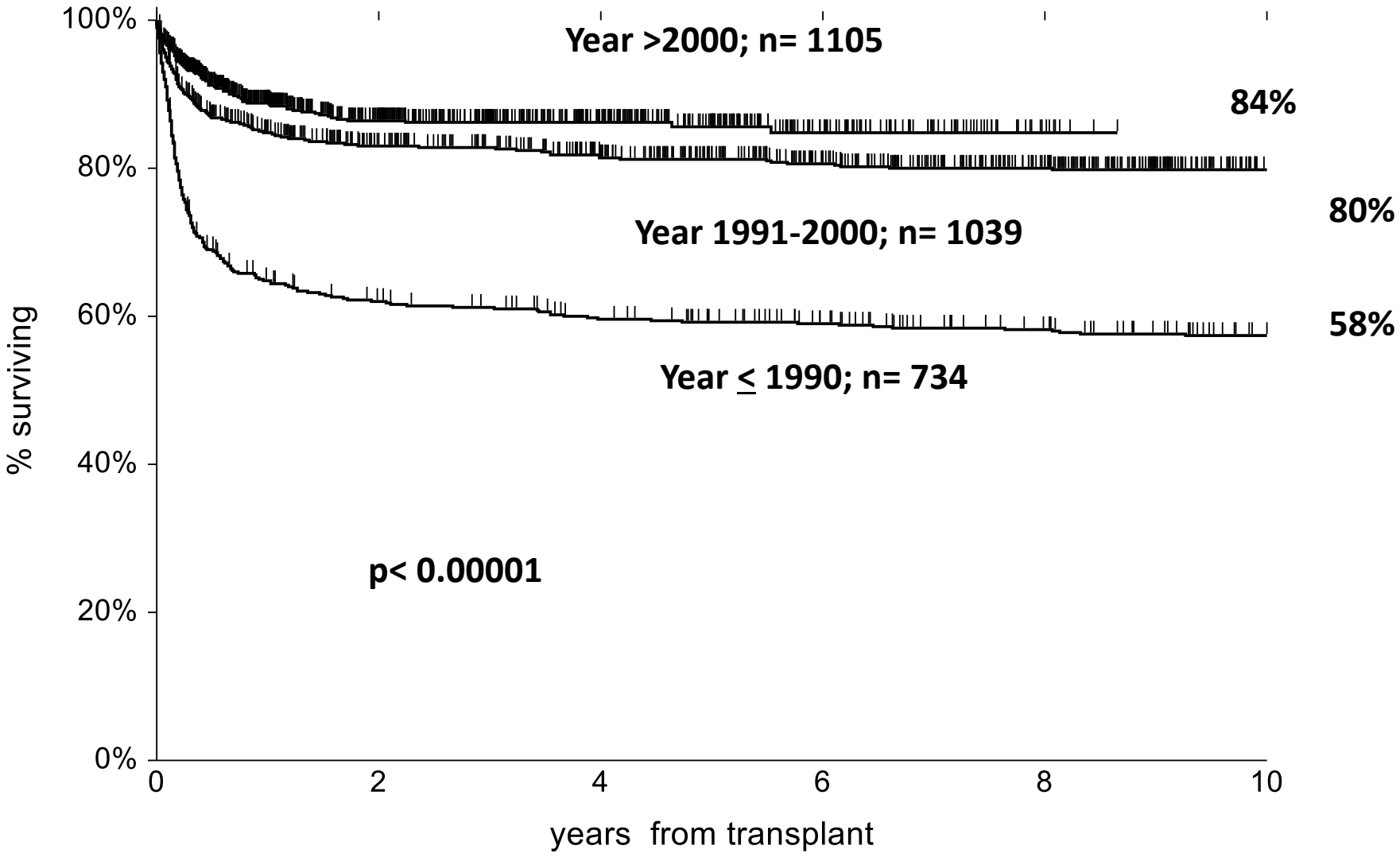
Universita' Cattolica- Policlinico Gemelli
Rome , Italy

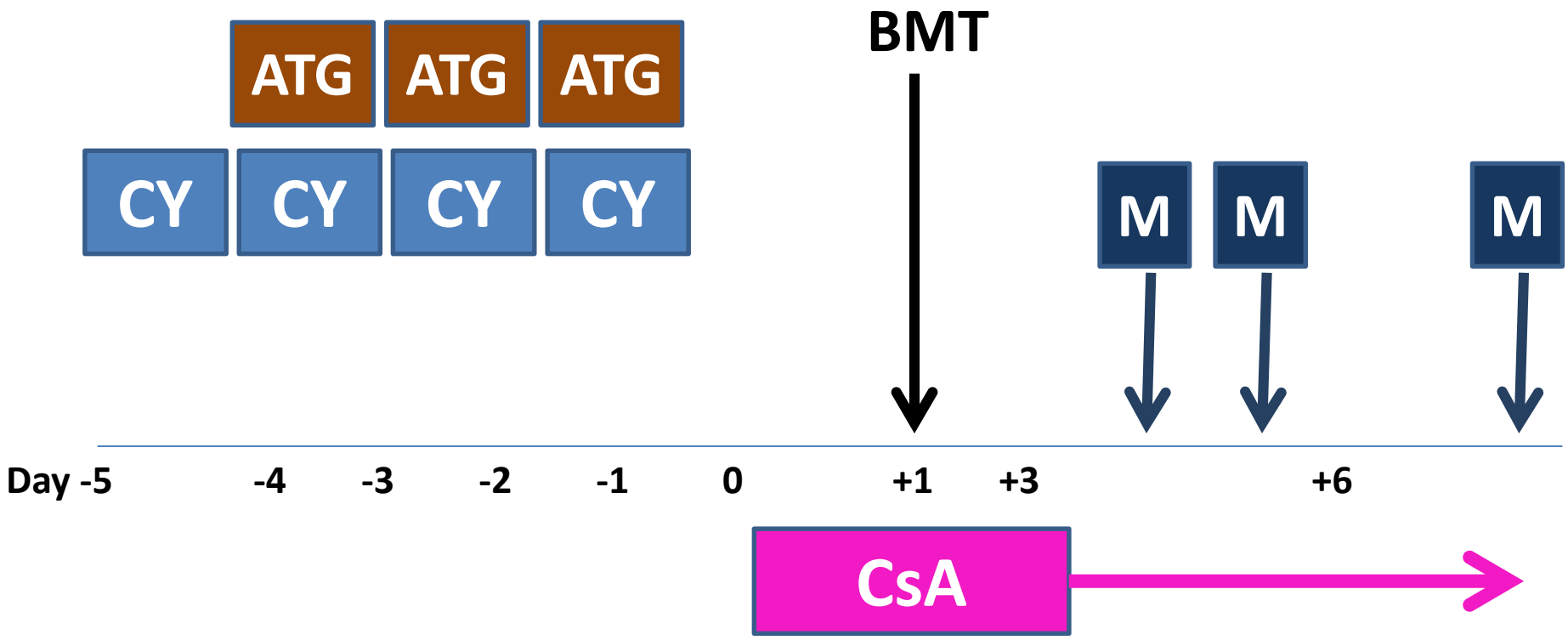
HLA typing should be performed at diagnosis in a patient with acquired aplastic anemia

Certainly under the age of 60

Together with family members

First line HLA id sib BMT for SAA; AGE ≤40



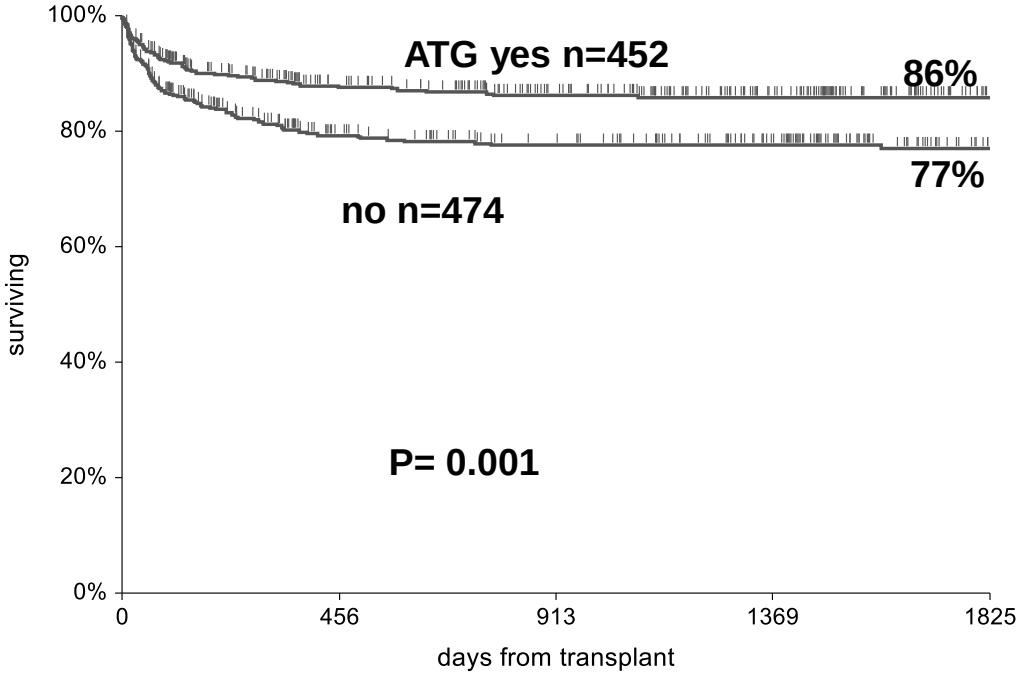


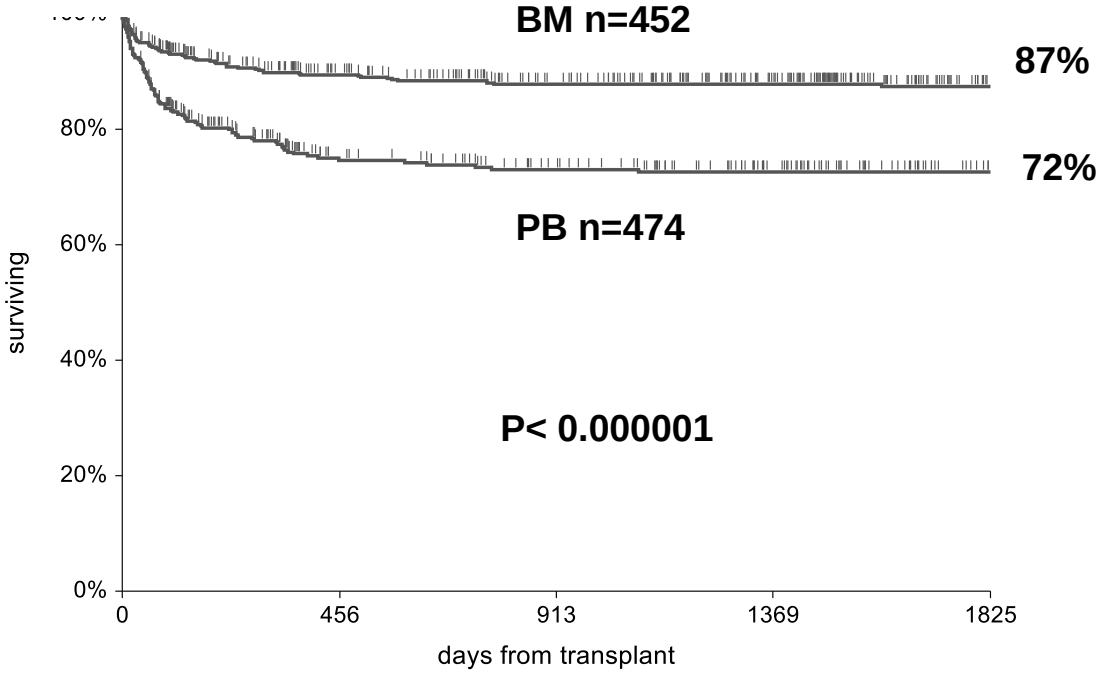
CY Cyclophosphamide 50 mg/kg

ATG Rabbit ATG 2.5 mg/kg

Figure 2B

HLA identical SIB transplants





First line HLA identical sibling BMT for SAA; (EBMT 2001-2010) <40 yy

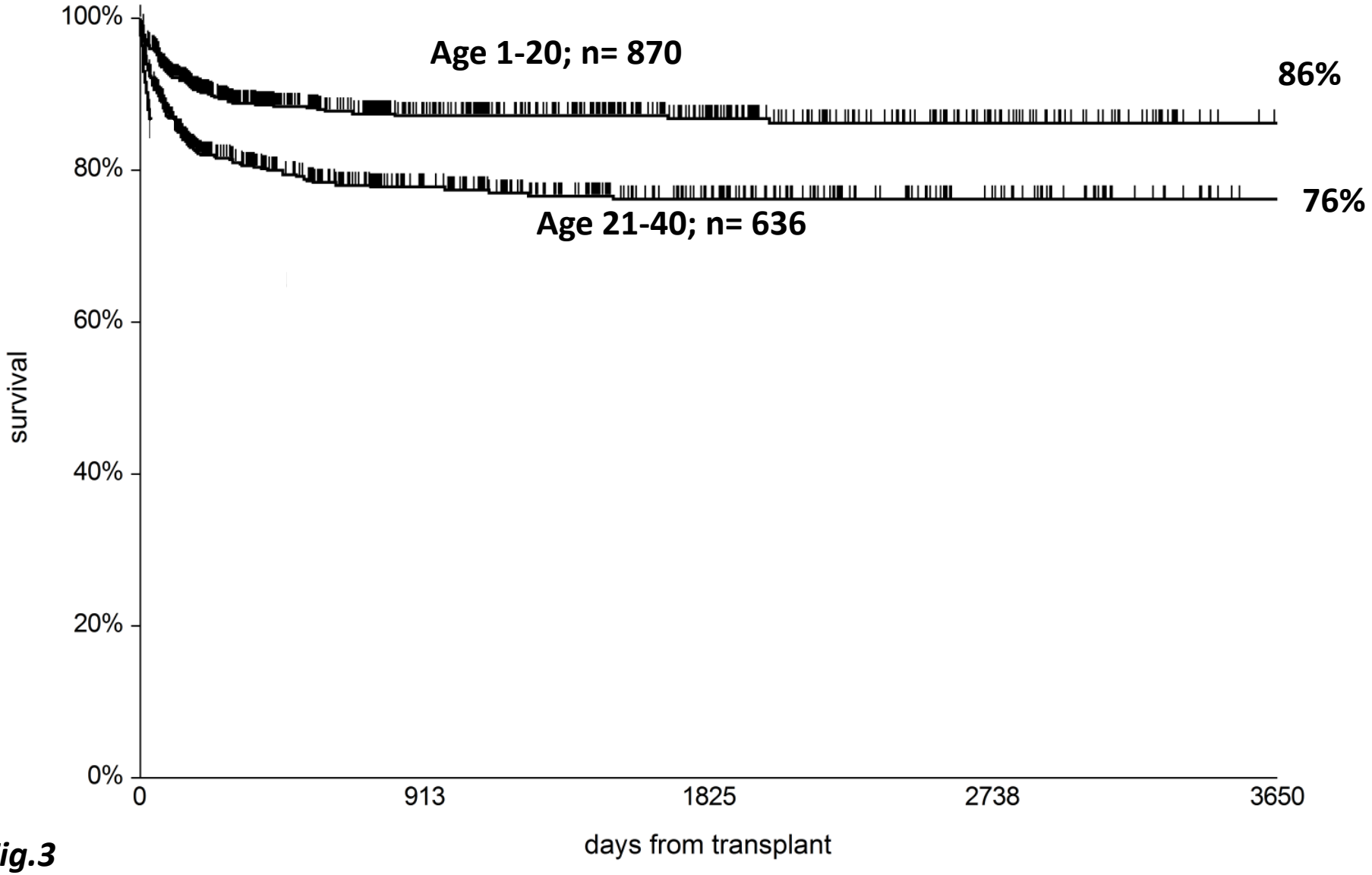
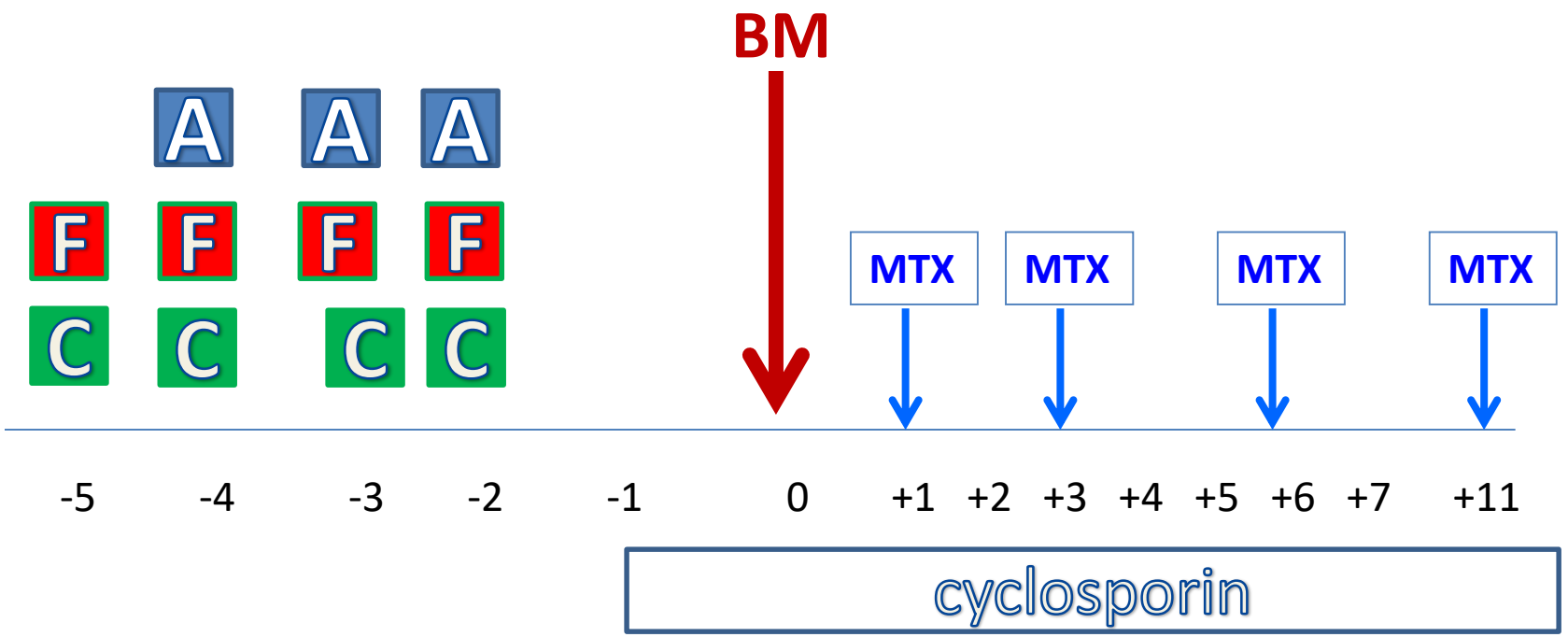


Fig.3

conditioning regimen for SIB transplants > 30 years of age



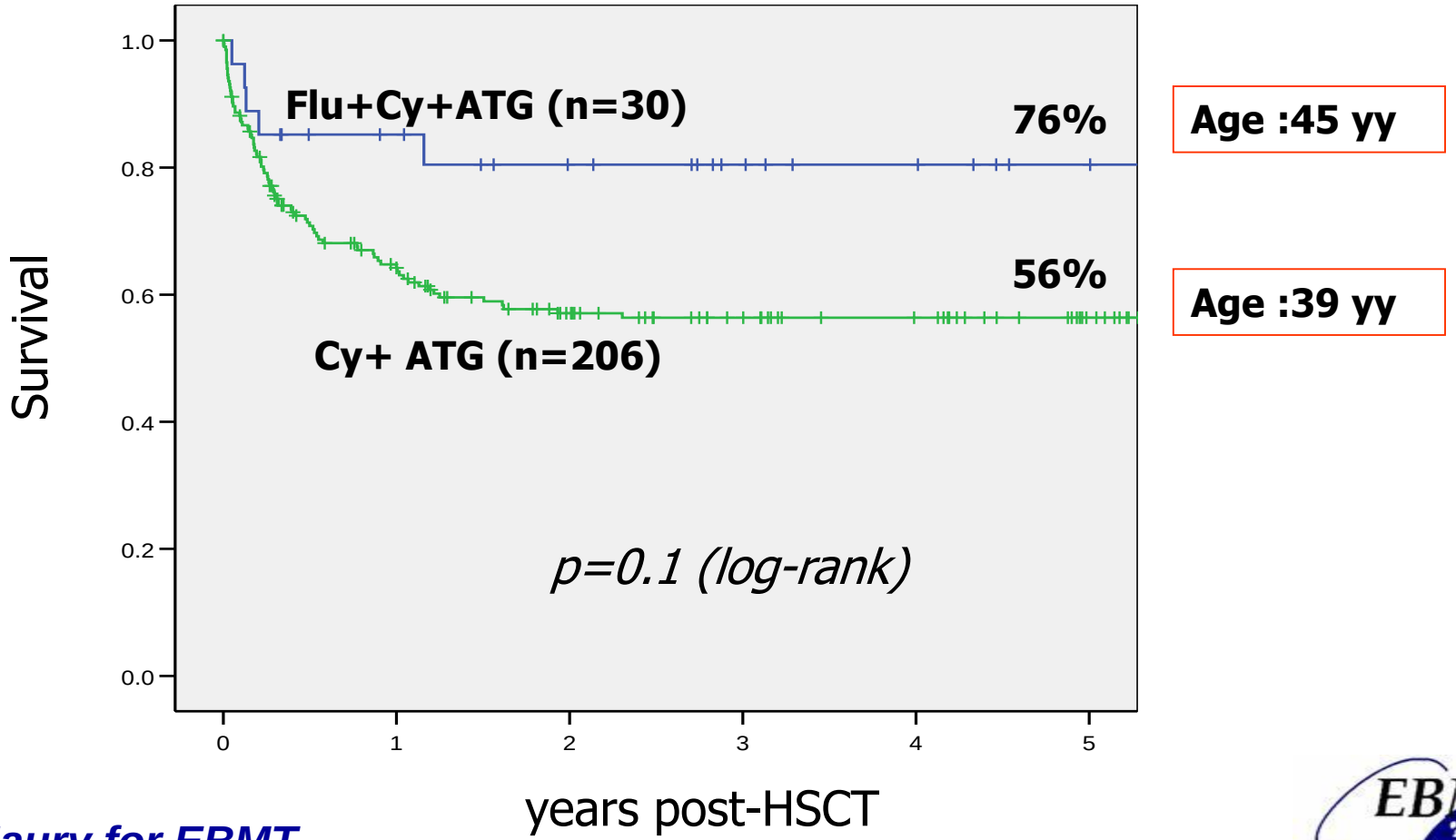
F FLUDARABINE 30 mg/m^2/day x4

C CYCLOPHOSPHAMIDE 30 mg/kg/day x4

A ATG : 2.5 mg/kg/day

HLA id SIBS; Age > 30 yy

Difference is Graft Failure 0% vs 11% (p=0.01)



S Maury for EBMT

BMT in young patients

 # significant improvement with time

 # transplant platform has remained unchanged

ATG+CY 200 /kg + BM+CSA+MTX

ATG+FLUCY for patients 30-40 yy

 # better supportive care

young patients

 # and older patients >40 years?

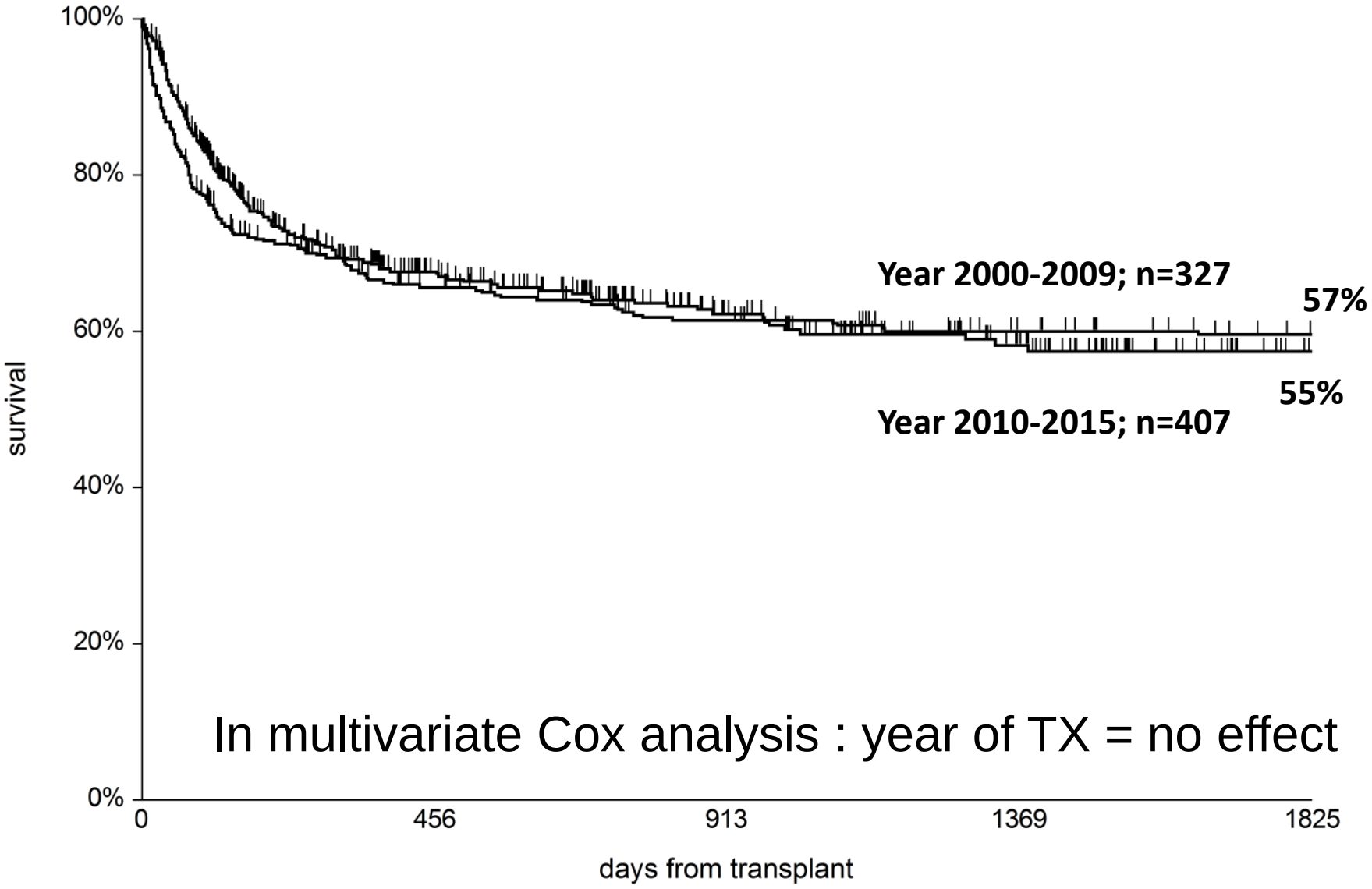
First line HLA identical sibling BMT for SAA; (EBMT 2001-2010)

Have results changed > 2010 ?

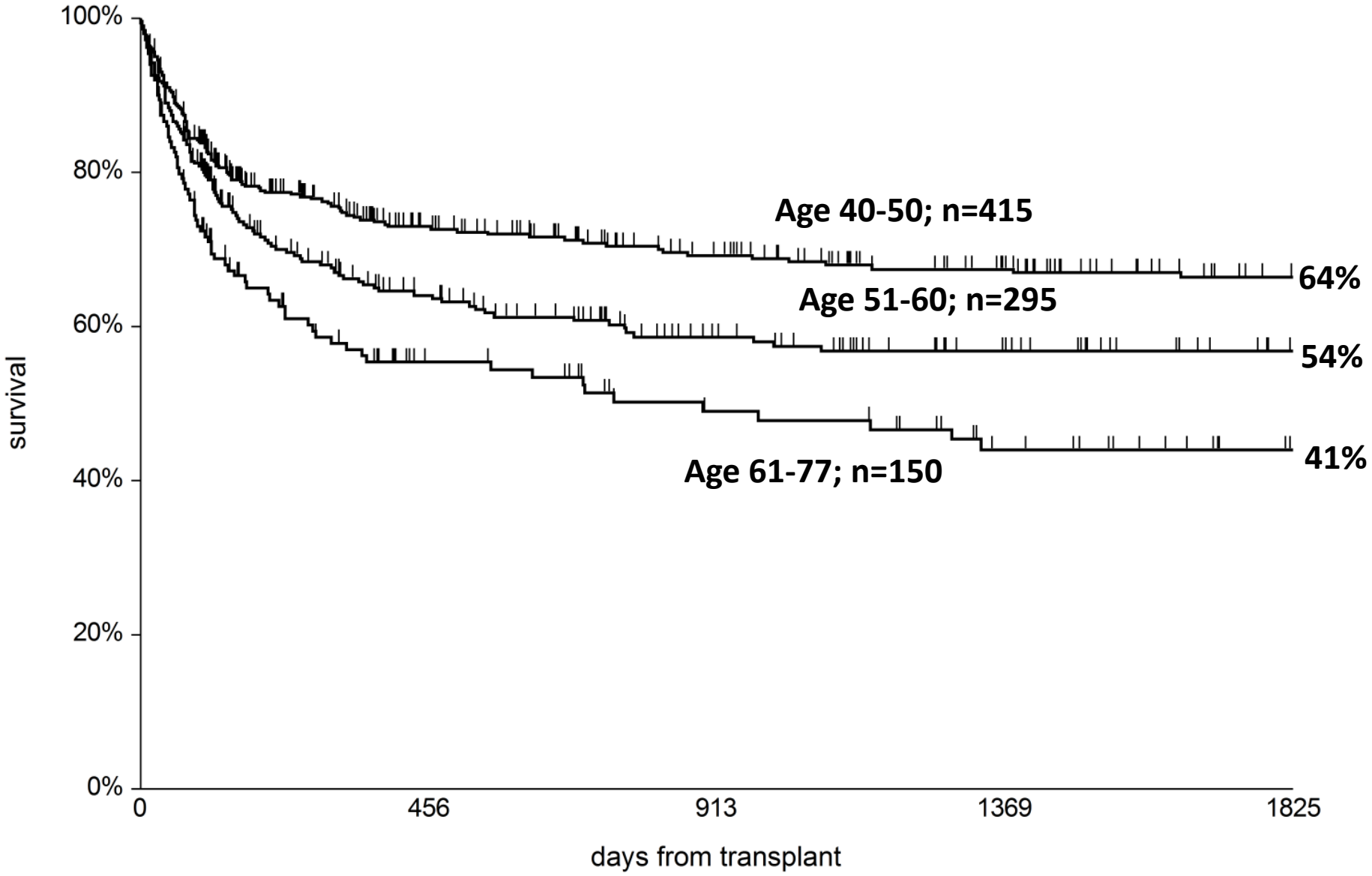
Fig.3

Blood 2018; 131: 1989

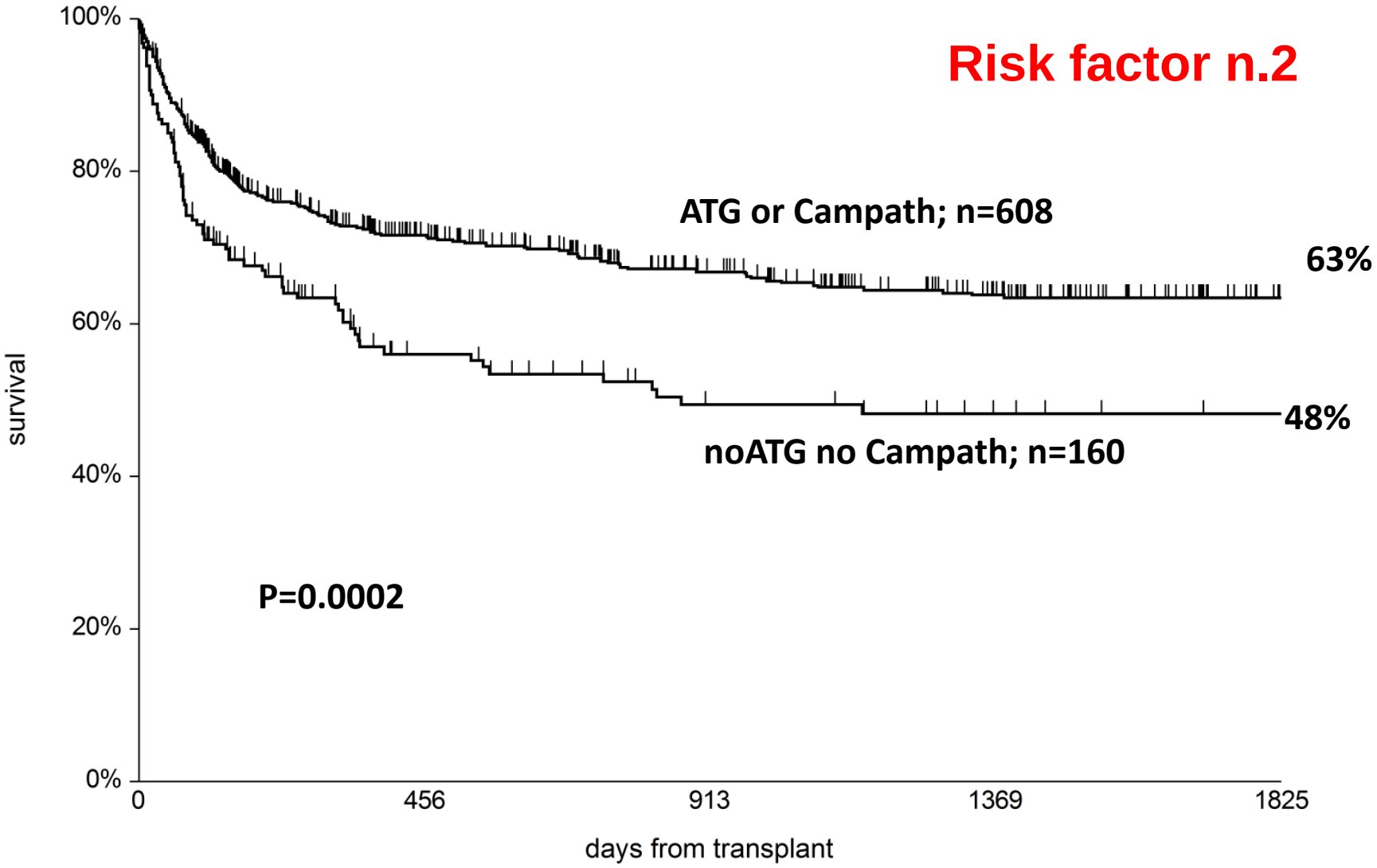
Outcome of acquired SAA aged ≥ 40 years : 2000-2009 (327) and 2010-2015 (407)



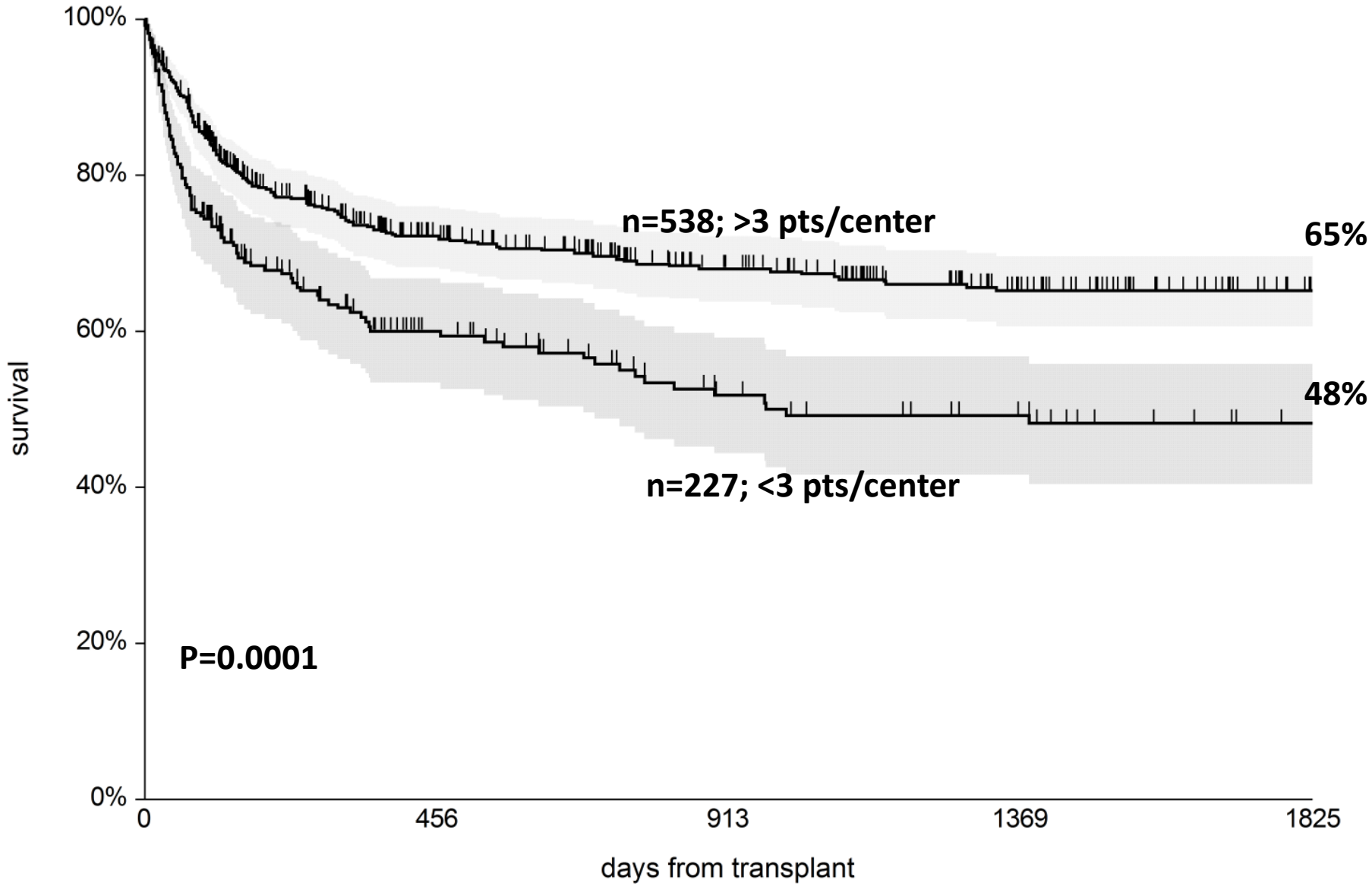
Risk factor n.1



SAA- EBMT : over 40 years of age; all patients



Risk factor n.3

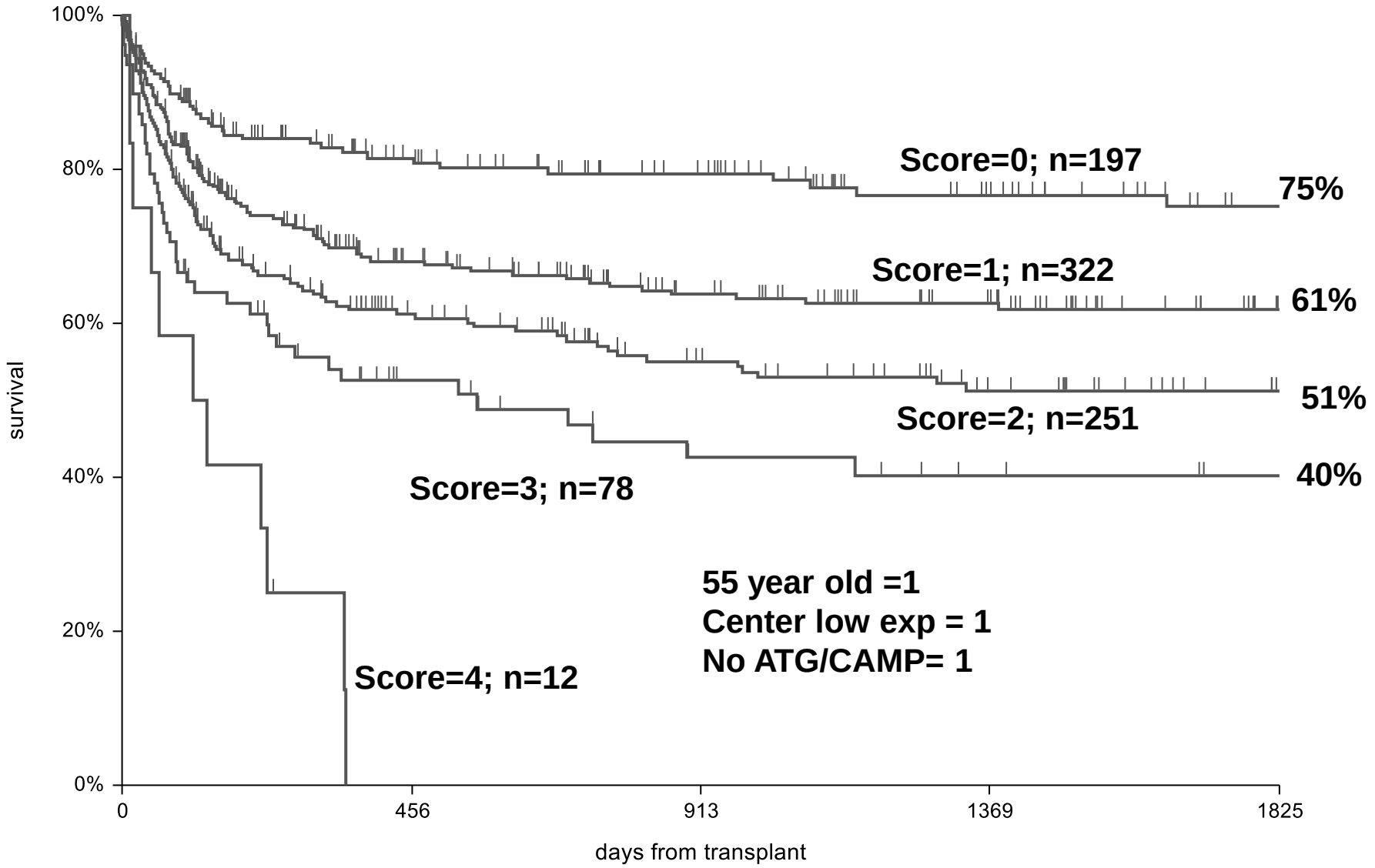


EBMT WPSAA data 2001-2015
Cox analysis

		HR	*P*
Center	>3 pts	0.59	0.0001
Age	50-59	1.3	0.05
	>60	2.0	0.0001
ATG/C	yes	0.3	0.0001
Year	≥2010	0.9	0.5
DxTx	>180	1.17	0.2
Donor	UD	1.24	0.1

Blood 2018; 131: 1989

Risk factors for older SAA patients;
age (<50=0,50-59=1,>60=2); ATG/CAMP(no=1); centers < 3pts =1



Age > 40 remains a significant risk factor for BMT

results have not improved over the past years

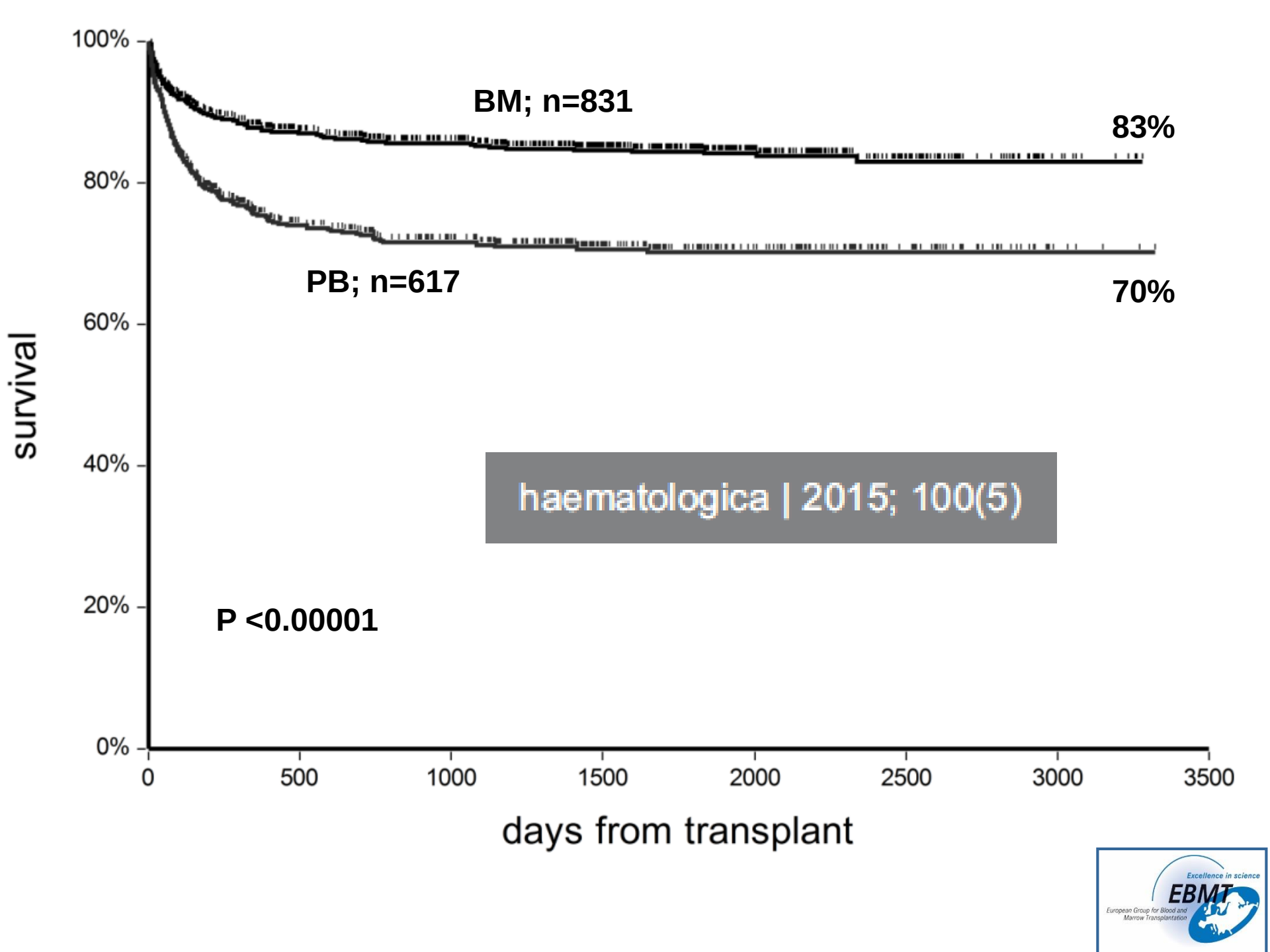
additional risk factors are

. No ATG/CAMP

. Unexperienced centers

different transplant platform needed

young patients
and older patients >40 years?
and stem cell source?


100%
80%
60%
40%
20%
0%
survival
BM; n=831
83%
PB; n=617
70%
haematologica | 2015; 100(5)
P <0.00001
0
500
1000
1500
2000
2500
3000
3500
days from transplant

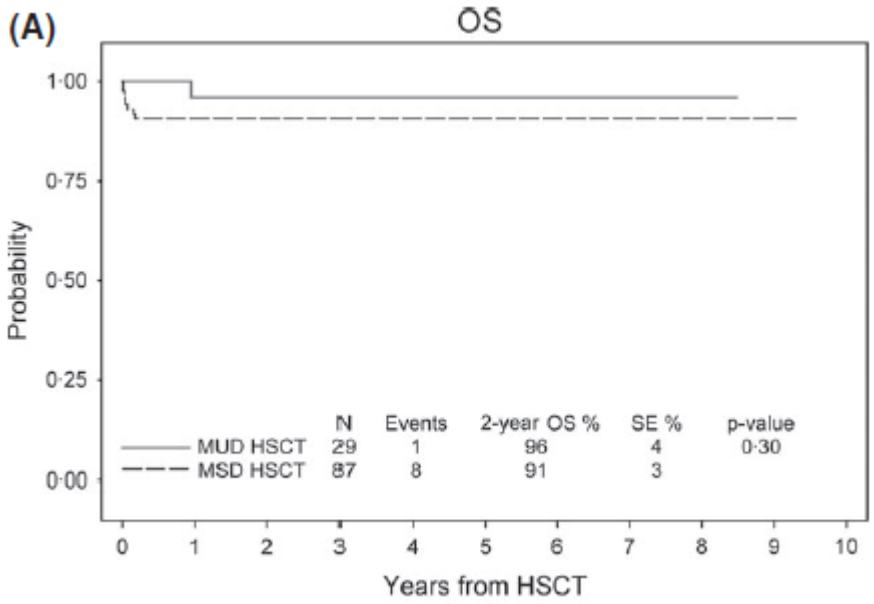
young patients
and older patients >40 years?
and stem cell source?
 # and UD transplants?

Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia. A study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT

British Journal of Haematology, 2015, **171**, 585–594

N=29

Median Age
8 yy (1-19)



Biol Blood Marrow Transplant 000 (2019) 1–9

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

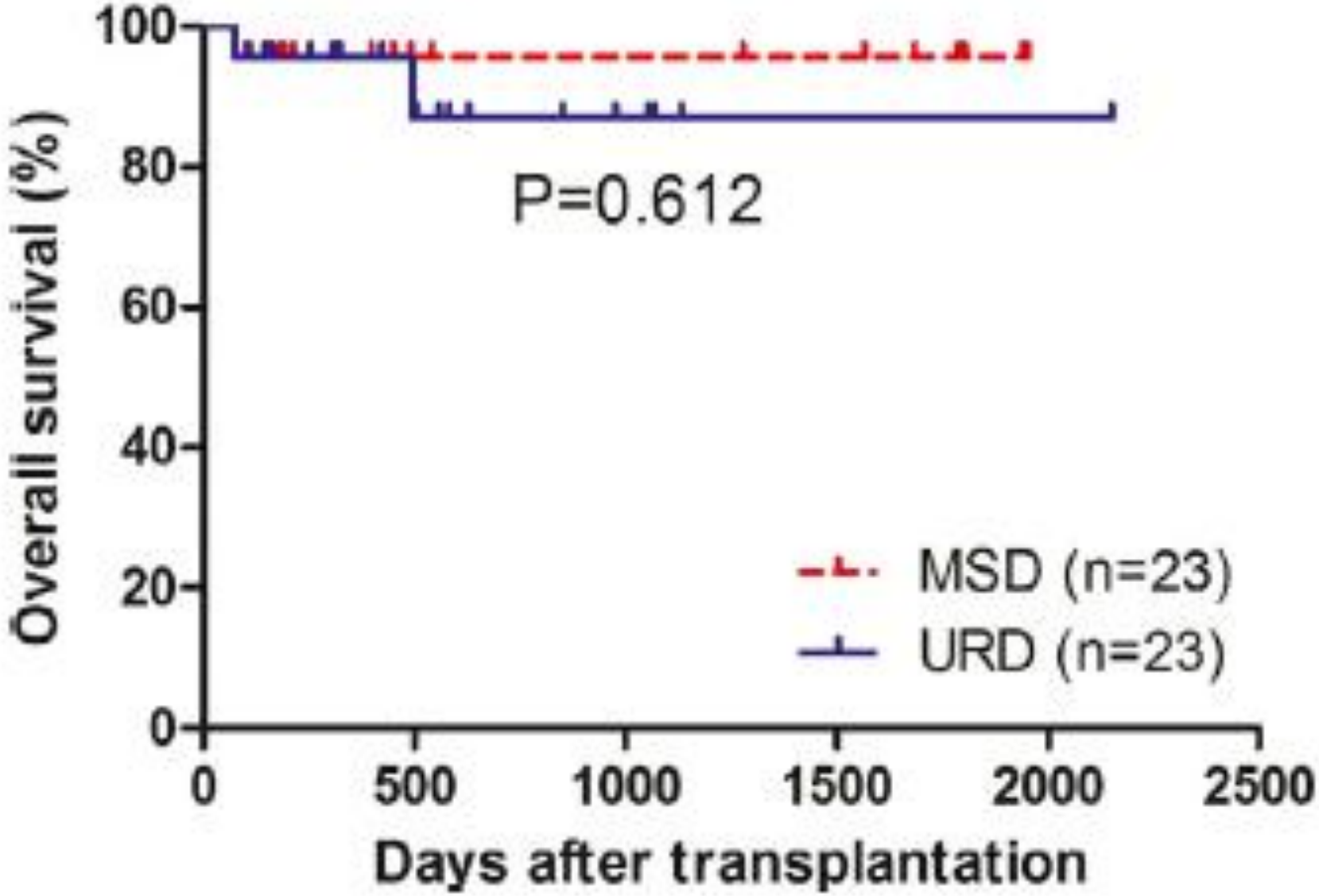
ASBMT American Society for Blood and Marrow Transplantation

Comparable Outcomes of First-Line Hematopoietic Stem Cell Transplantation from Unrelated and Matched Sibling Donors in Adult Patients with Aplastic Anemia: A Retrospective Single-Center Study

Yuping Zhang[1,2,a], Liangliang Wu[1,2,a], Wenjian Mo[1,2], Ming Zhou[1,2], Yumiao Li[1,2], Xiaowei Chen[1,2], Caixia Wang[1,2], Shiyi Pan[1,2], Shilin Xu[1,2], Wei Zhou[1,2], Ruiqing Zhou[1,2], Shunqing Wang[1,2,*]

[1] *Department of Hematology, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou, Guangdong, China*
[2] *Department of Hematology, Guangzhou First People's Hospital, Guangzhou Medical University, Guangzhou, Guangdong, China*

	MSD	UD
N=	23	23
Age	30 (17-43)	26 (14-49)

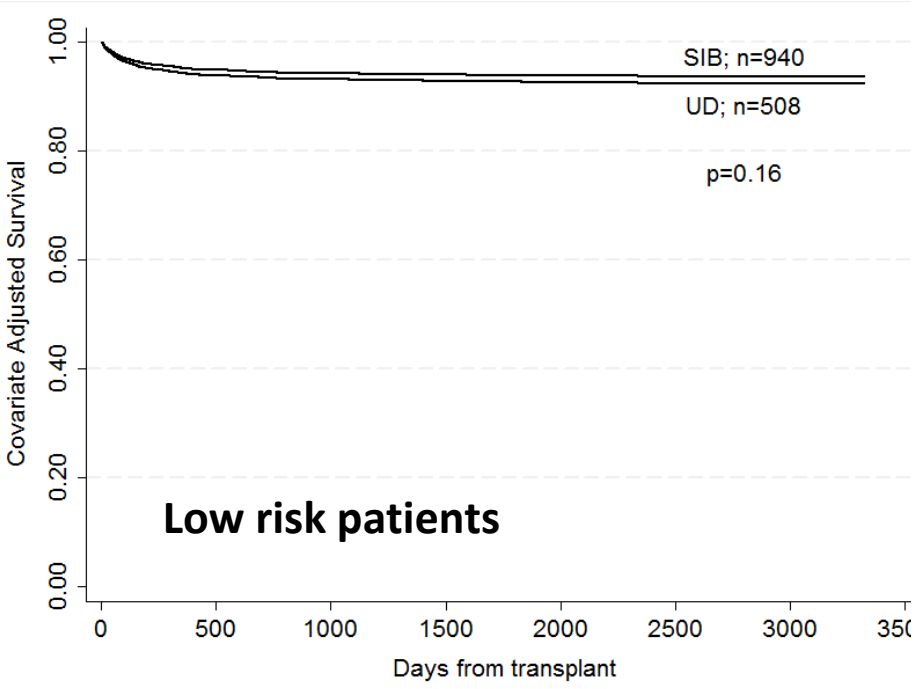

100
80
60
40
20
0
Overall survival (%)
P=0.612
MSD (n=23)
URD (n=23)
0
500
1000
1500
2000
2500
Days after transplantation

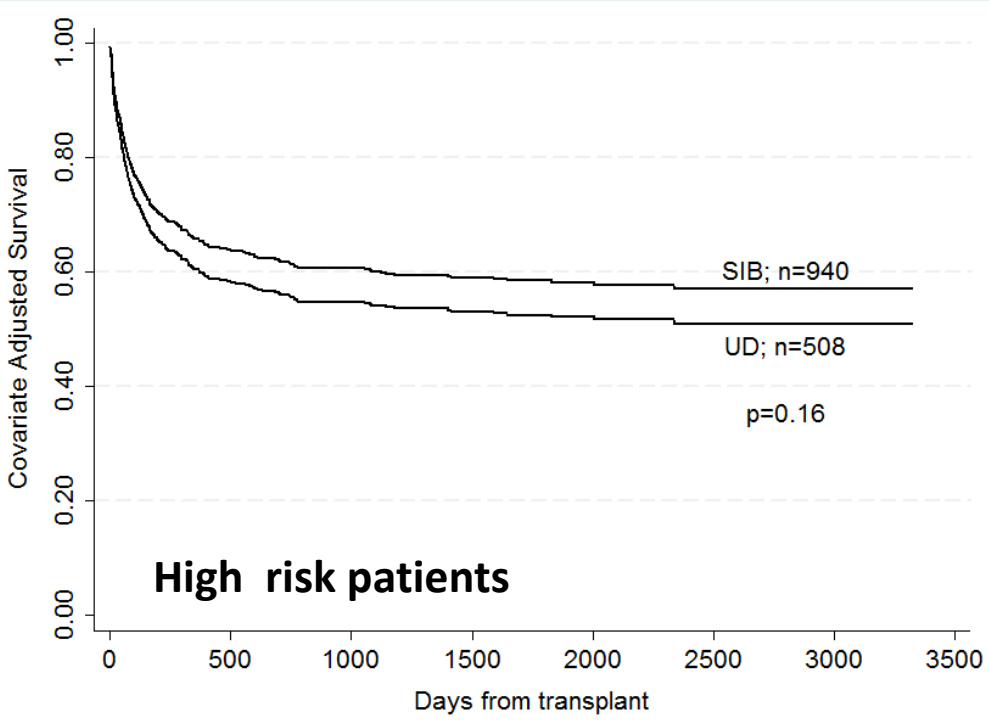
ALLOGENEIC TRANSPLANTS FOR APLASTIC ANEMIA

Haematologica 2015; 100; 696

EBMT analysis 2014: **1448 patients**

Adjusted effect of donor type (UD vs SIB) derived from the multivariate analysis
After adjusting for AGE, interval DxTx, use of ATG, use of BM/PB, and CMV status)





Low risk= age<20; ATG; BM; DxTx <180 dd
CMV D-/R-

High risk: Age ≥20; no ATG; PB; DxTx ≥180
CMV other than D-/R-

Fig. 1a Acute II-IV GvHD

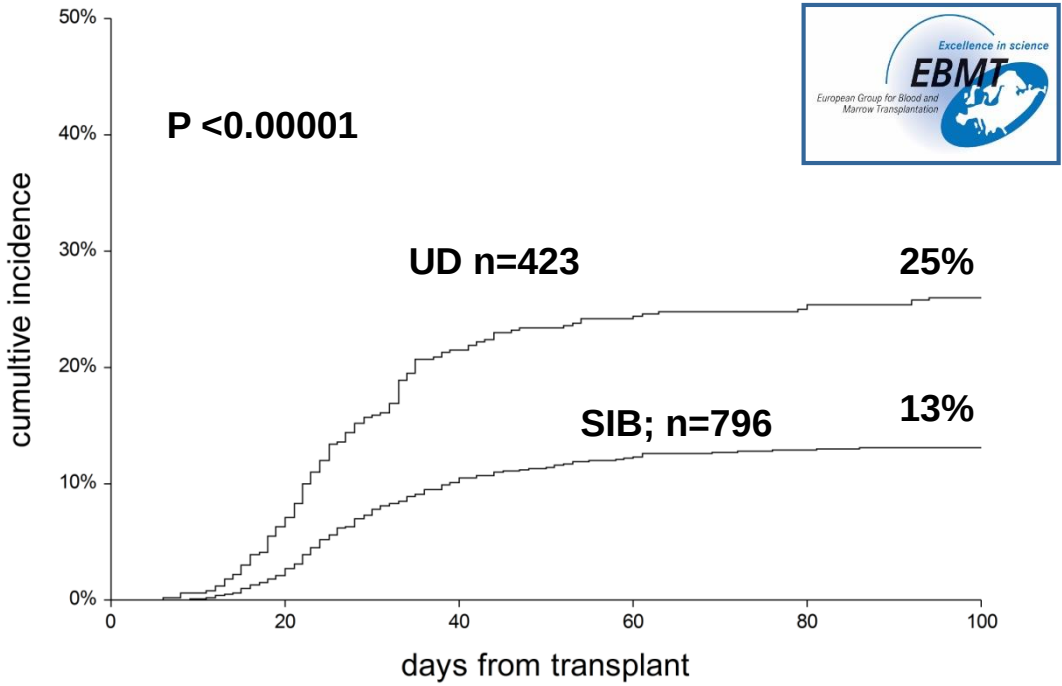
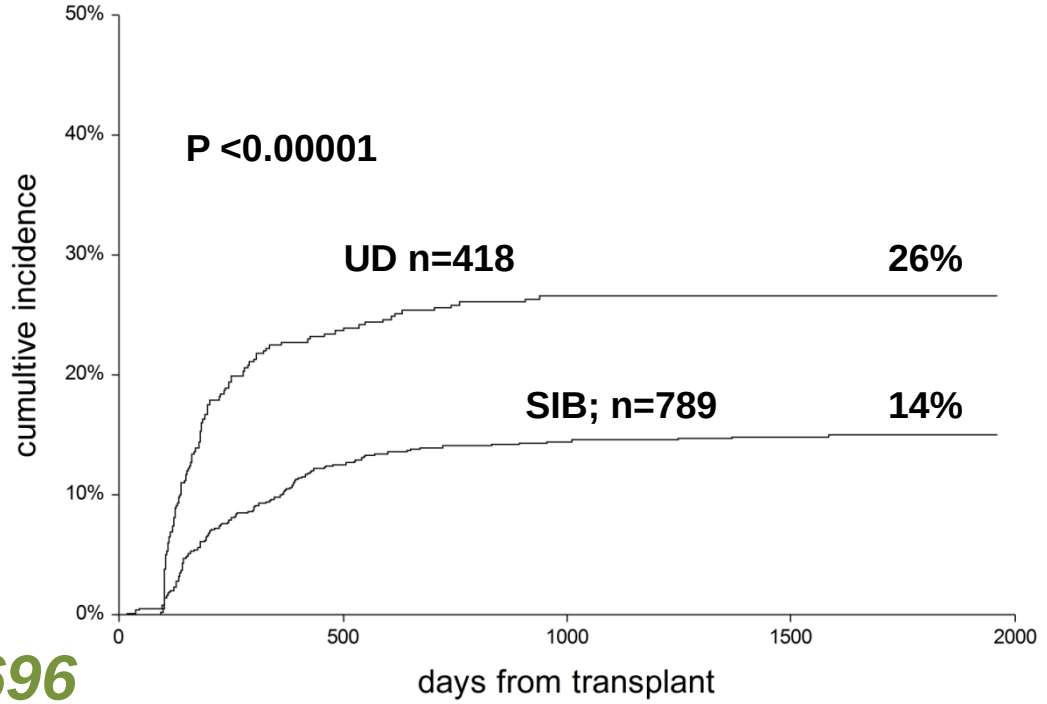


Fig. 1b Chronic GvHD

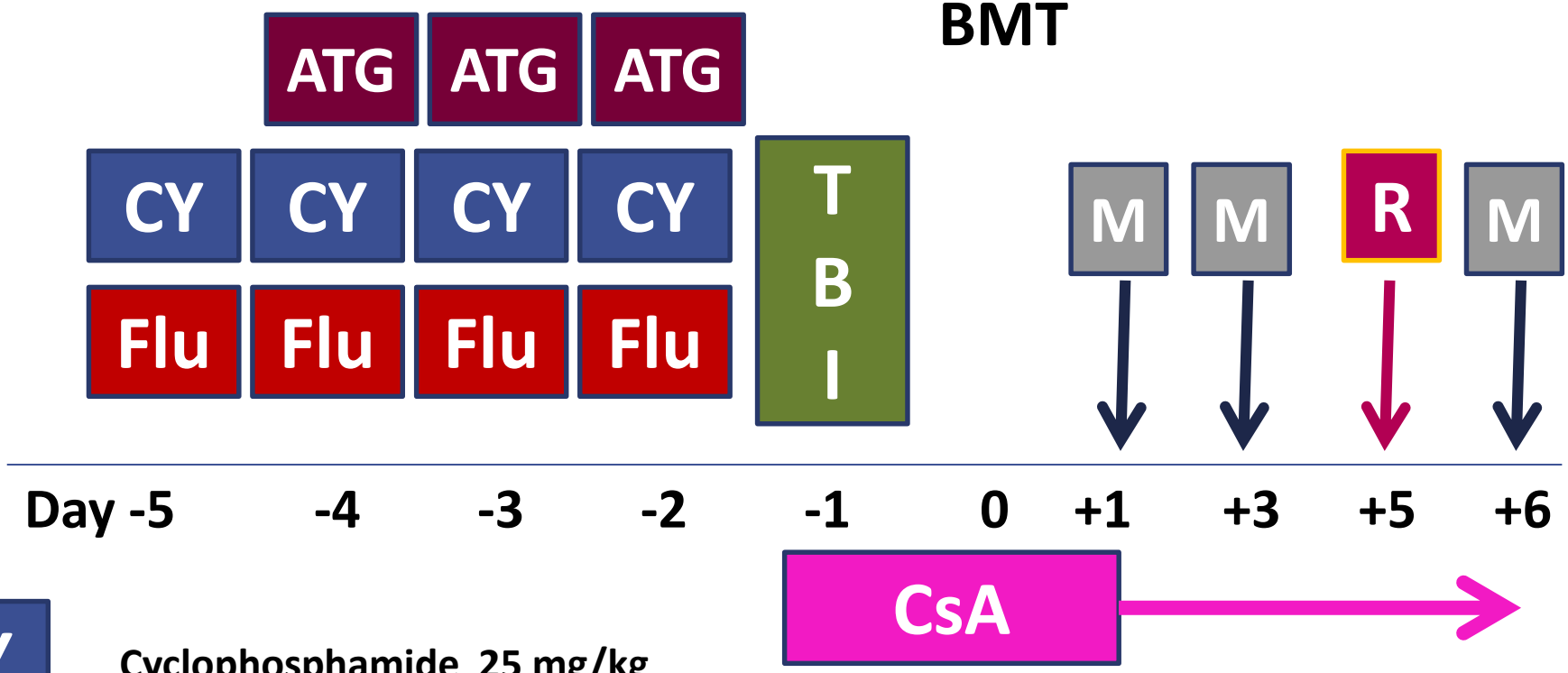


Haematologica 2015; 100; 696

Prevalence of late effects in SAA patients transplanted 1995-2006 (CIBMTR)

- Increasing number of late effects with longer follow-up
- Unrelated HSCT more late effects than related HSCT
  - GVHD and its treatment more relevant in unrelated HSCT?

Buchbinder D. et al. BBMT. 2012.18:1776-1784



CY — Cyclophosphamide 25 mg/kg

Flu — Fludarabine 30 mg/m^2

ATG — Rabbit ATG 2.5 mg/kg

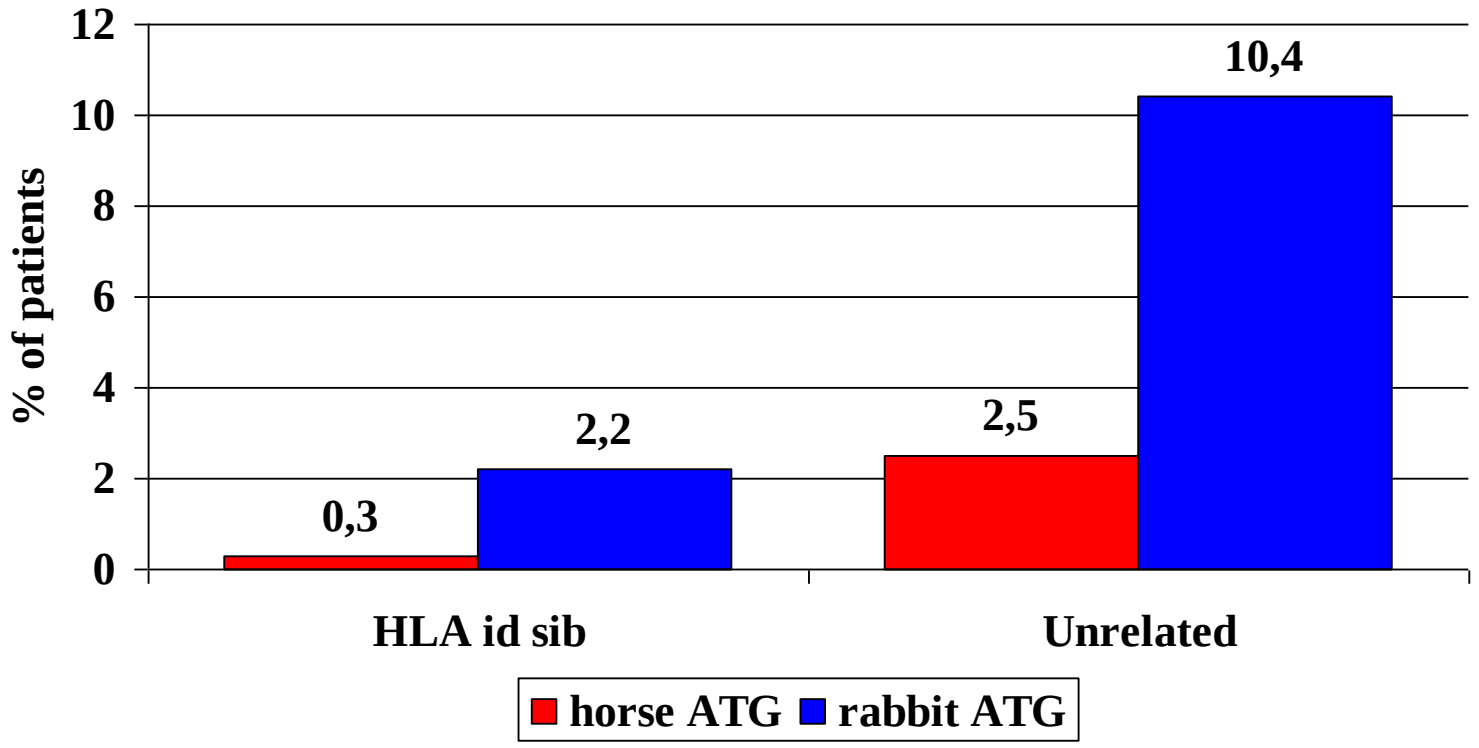
TBI — Total Body Irradiation 2 Gy

M — Methotrextae 10 mg/m^2

R — Rituximab 200 mg

Figure 2A

EBV reactivation after allo-Tx for SAA: CIBMTR , Haematologica 2017



Bone Marrow Transplantation (2011), 1–6

www.nature.com/bmt

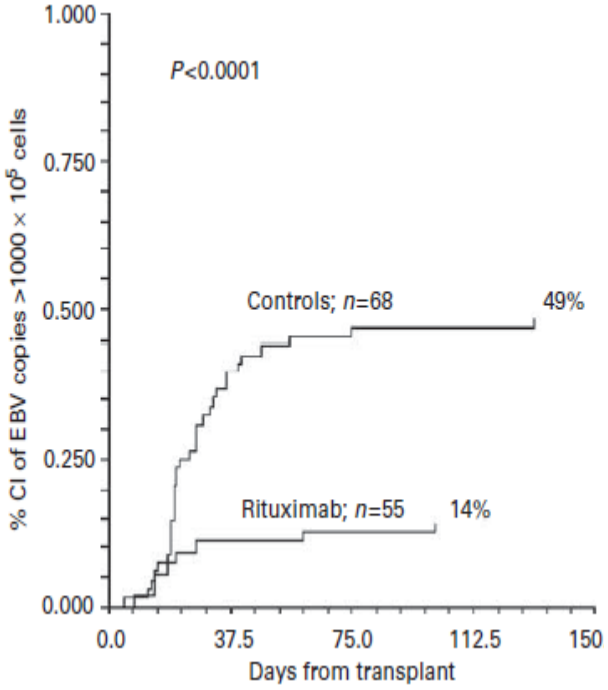
ORIGINAL ARTICLE

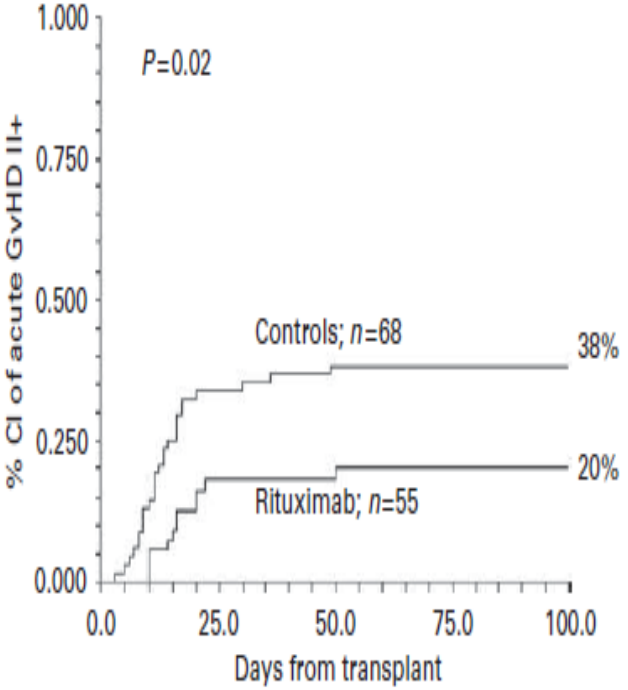
In vivo B-cell depletion with rituximab hemopoietic SCT

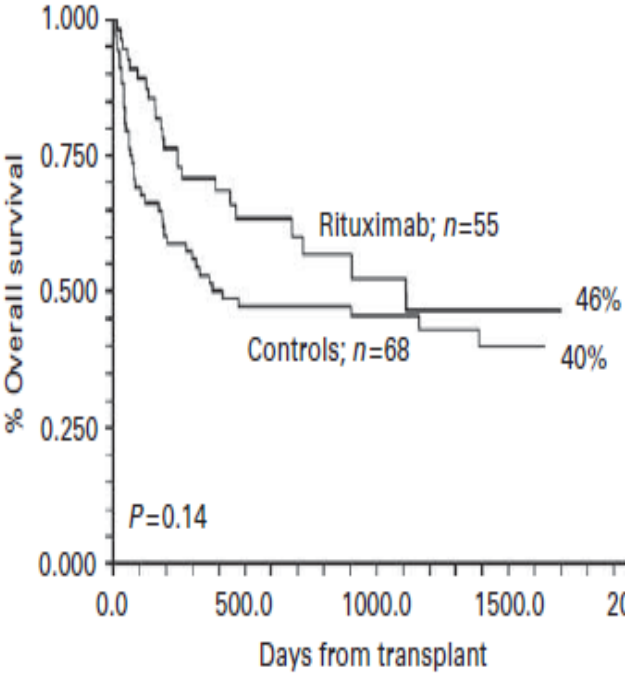
Rituximab
200 mg fixed dose
Day +5

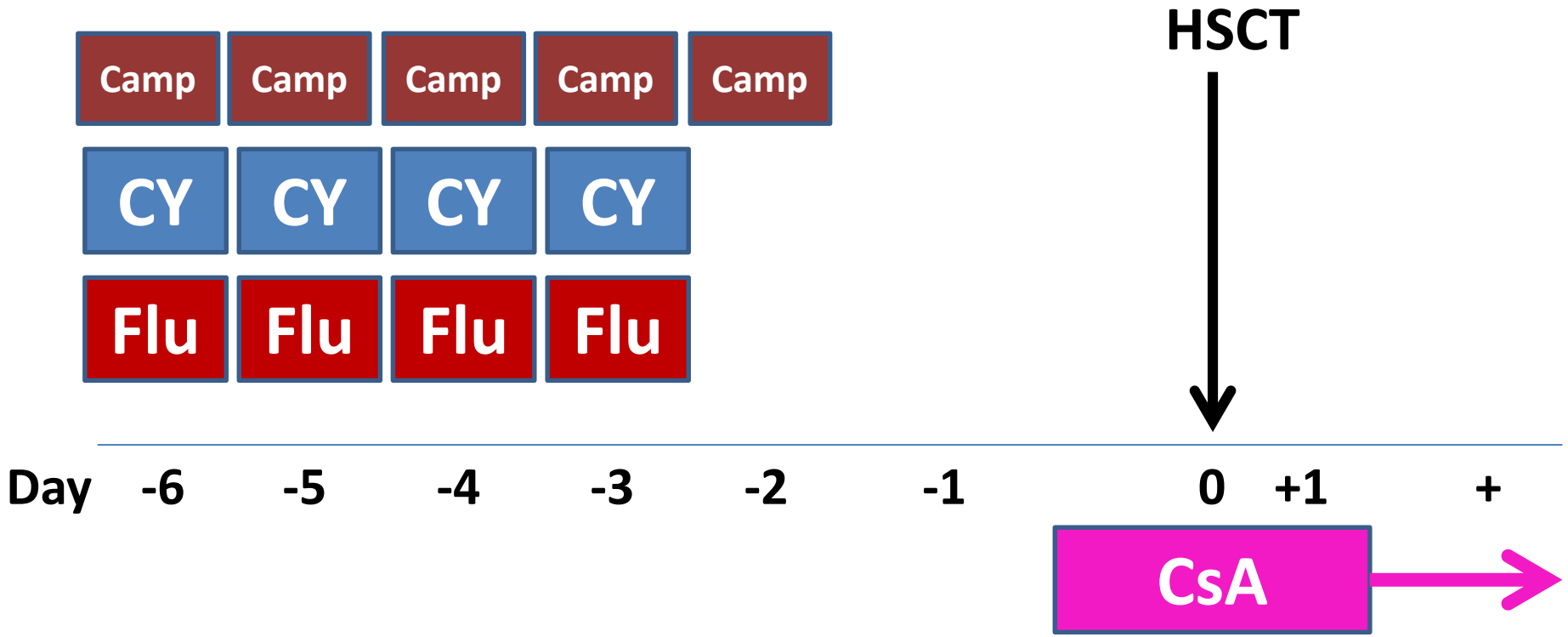
A Dominietto, E Tedone, M Soracco, B Bruno, AM [illegible] mparelli, B Galano, F Gualandi, F Frassoni and A Bacigalupo

Divisione Ematologia e Trapianto di Midollo Osseo, Ospedale San Martino, Genova, Italy









CY — Cyclophosphamide 300 mg/m^2

Flu — Fludarabine 30 mg/m^2

Camp — CAMPATH 0.2 mg/kg

Figure 3

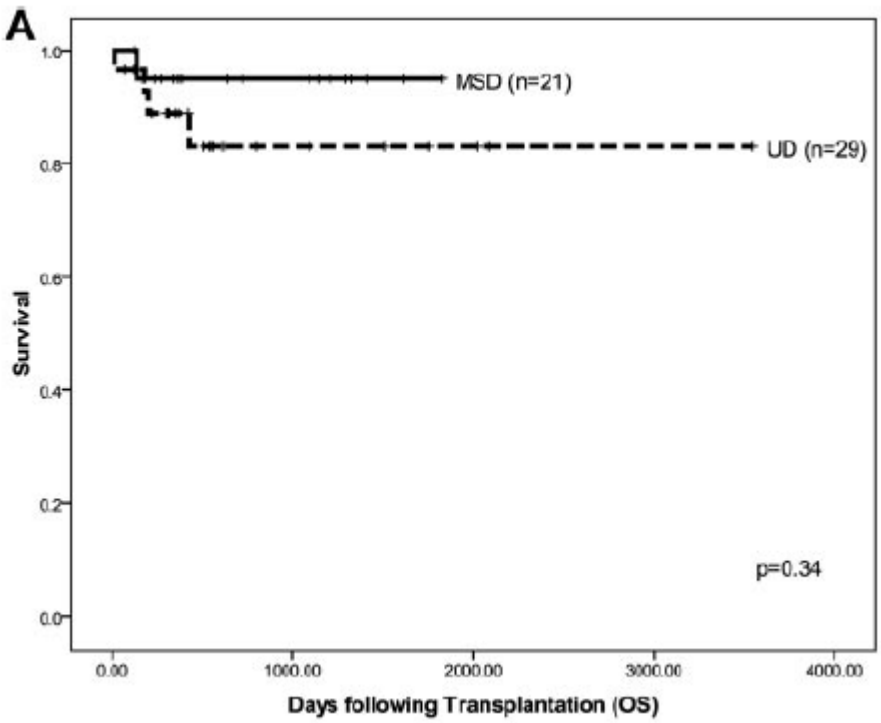
blood
2011 118: 2351-2357
doi:10.1182/blood-2010-12-327536 originally published online April 25, 2011

Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after allogeneic stem cell transplantation for acquired aplastic anemia

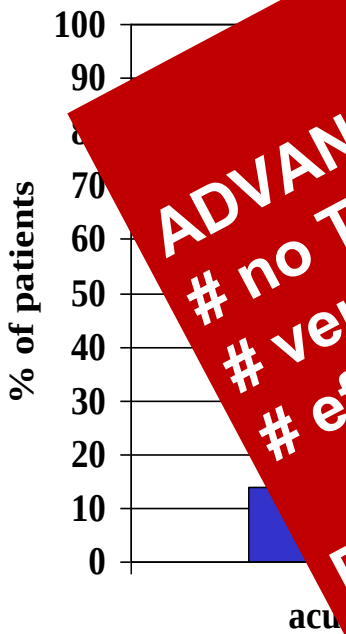
Judith C. Marsh, Vikas Gupta, ZiYi Lim, Aloysius Y. Ho, Robin M. Ireland, Janet Hayden, Victoria Potter, Mickey B. Koh, M. Serajul Islam, Nigel Russell, David I. Marks, Ghulam J. Mufti and Antonio Pagliuca

FCC (FLU CY CAMP 100)
UD n=29
SIB n=21

Age 35 (8-62)
DxTX 6mm (SIB) 10mm (UD)



FCC for aplastic anemi



ADVANTAGES of FCC

- # no TBI (= no sec tum)
- # very little acute and chronic GvHD
- # effective in both SIB and UD Tx

DISADVANTAGES of FCC

- # Campath difficult to get
- # infections
- # mixed chimeris
- # autoimmune cytopenias

Conditioning regimen UD transplants

FLU CY CAMPATH (UK)

FLU CY ATG +TBI 2Gy (EBMT-USA-JAPAN)

Outcome of UD and SIB transplants
For SAA

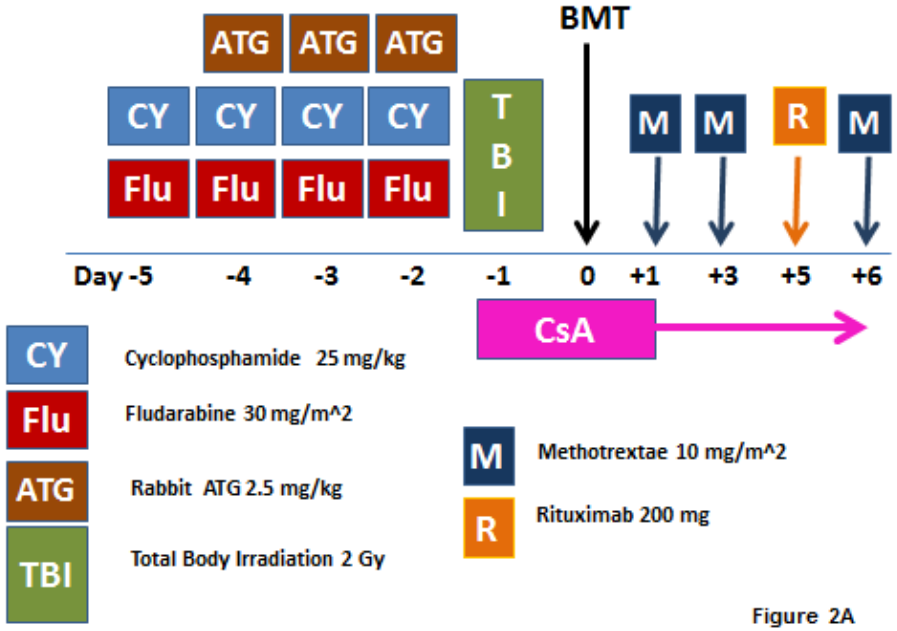
Currently almost superimposable
GvHD and late effects
still more frequent in UD TX

young patients
and older patients >40 years?
and stem cell source?
and UD transplants?
 # and CB transplants?

blood®
2018 132: 750-754
doi:10.1182/blood-2018-01-829630 originally published online May 14, 2018

Unrelated cord blood transplantation in patients with idiopathic refractory severe aplastic anemia: a nationwide phase 2 study

Regis Peffault de Latour, Sylvie Chevret, Charlotte Jubert, Anne Sirvent, Claire Galambrun, Annalisa Ruggeri, Virginie Gandemer, Jérôme Cornillon, Fanny Rialland, Jean-Hugues Dalle, Edouard Forcade, Benedicte Bruno, Catherine Paillard, Pierre S. Rorlich, Alexandra Salmon, Sabine Fürst, Flore Sicre de Fontbrune, Marie Therese Rubio, Jacques-Olivier Bay, Mohamad Mohty, Jerome Larghero, Eliane Gluckman and Gerard Socié



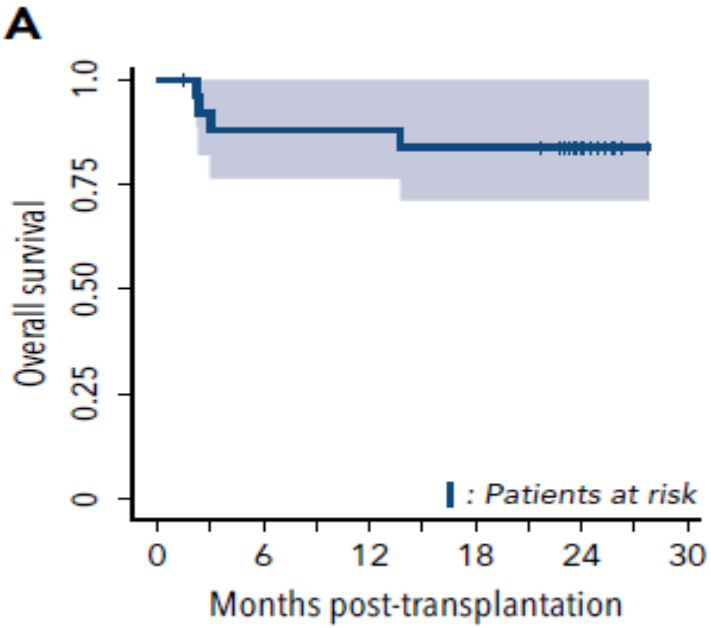


Figure 2A

and Unrelated Transplants?
and older patients >40 years?
and stem cell source?
an UD transplants?
and CB transplants?
HAPLO transplants?

Xu et al. Journal of Hematology & Oncology (2017) 10:25
DOI 10.1186/s13045-017-0398-y

Journal of Hematology & Oncology

RESEARCH Open Access

Upfront haploidentical transplant for acquired severe aplastic anemia: registry-based comparison with matched related transplant

Lan-Ping Xu[1†], Song Jin[4†], Shun-Qing Wang[5†], Ling-Hui Xia[6], Hai Bai[7], Su-Jun Gao[8], Qi-Fa Liu[9], Jian-Min Wang[10], Xin Wang[11], Ming Jiang[12], Xi Zhang[13], De-Pei Wu[4†] and Xiao-Jun Huang[1,2,3*†]

158 patients upfront HSCT 2012-2015

89 HAPLO

69 SIB=

Conditioning

	HAPLO	SIB
CY	50mg/kg x4	50 mg/kgx2
ATG	2.5 mg/kgx4	2.5 mg/kgx4
BU	**3.2 mg/kgx4**	
FLU		30 mg/m^2X4

Table 1 Patient and graft characteristics

Variable	Haploidentical $N = 89$	Matched related $N = 69$	P
Age (years), median (range)	22 (4–51)	33 (7–61)	<0.001
Children, no. (%)	33 (37.1%)	7 (10.1%)	<0.001
Adult, no. (%)	56 (62.9%)	62 (89.9%)	
Median follow-up among alive patients, mo. (range)	21.4 (7.1–47.6)	26.0 (7.5–47.6)	0.258
Neutrophil engraftment, median (range)	12 (9–20)	11 (8–19)	0.151
Platelet engraftment, median (range)	15 (6–91)	14 (7–36)	0.484

TRM 6% 8% !!

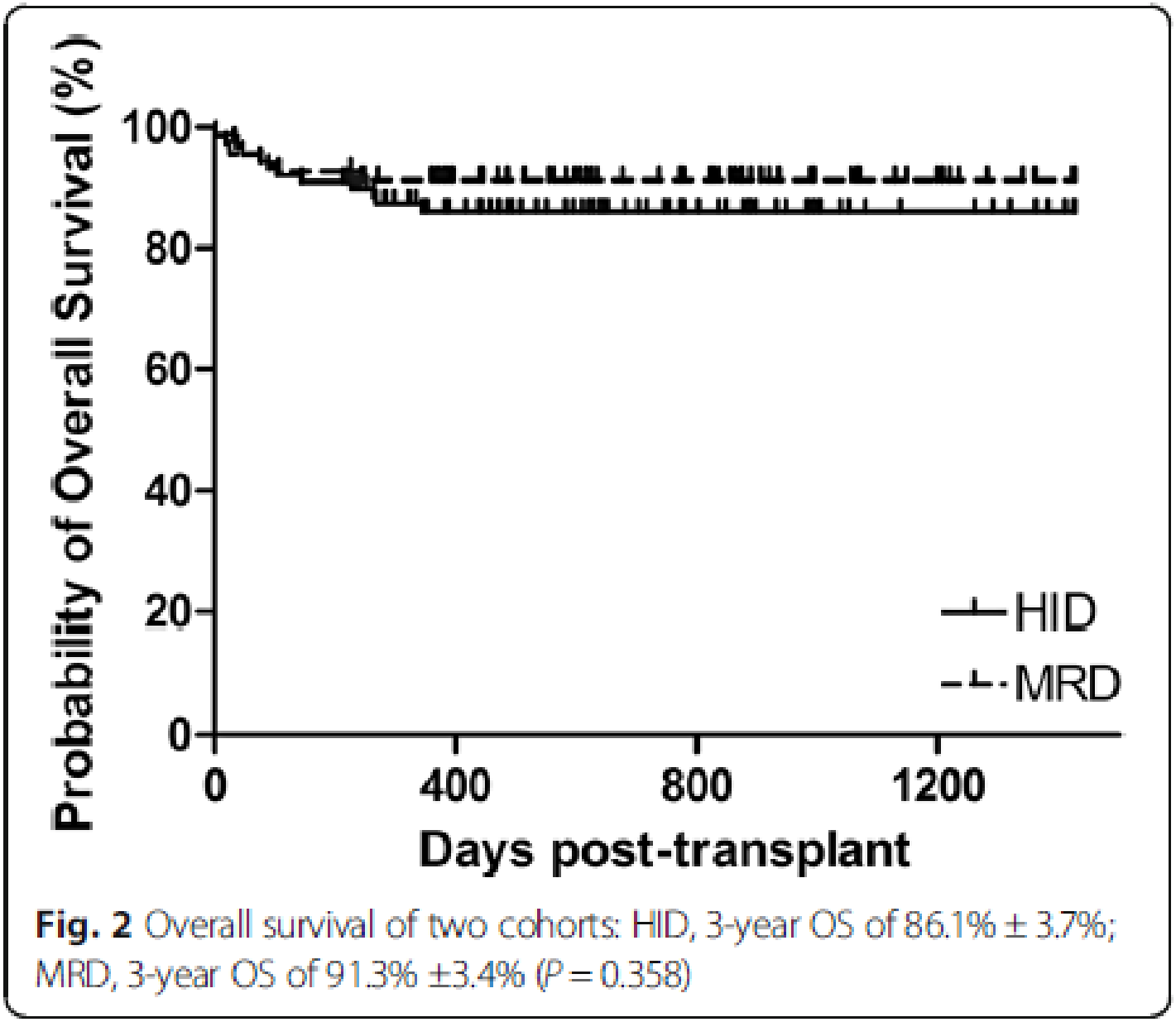


Fig. 2 Overall survival of two cohorts: HID, 3-year OS of 86.1% ± 3.7%; MRD, 3-year OS of 91.3% ±3.4% ($P = 0.358$)

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Biology
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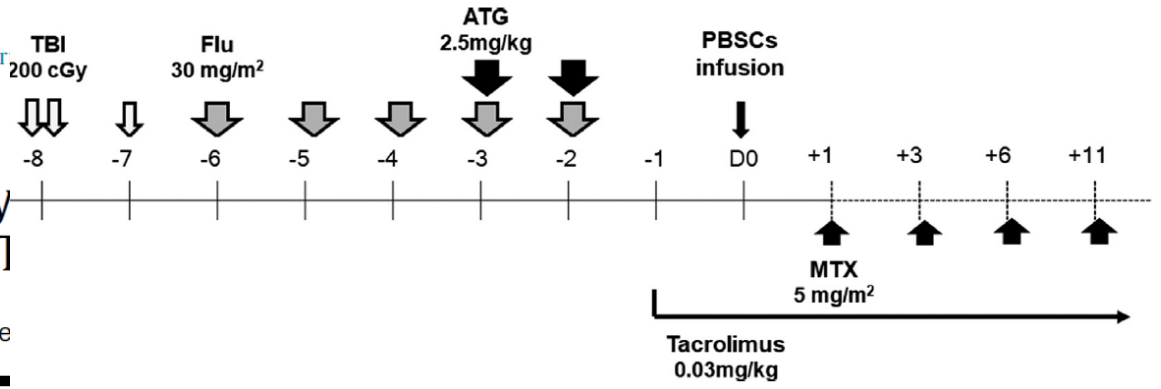
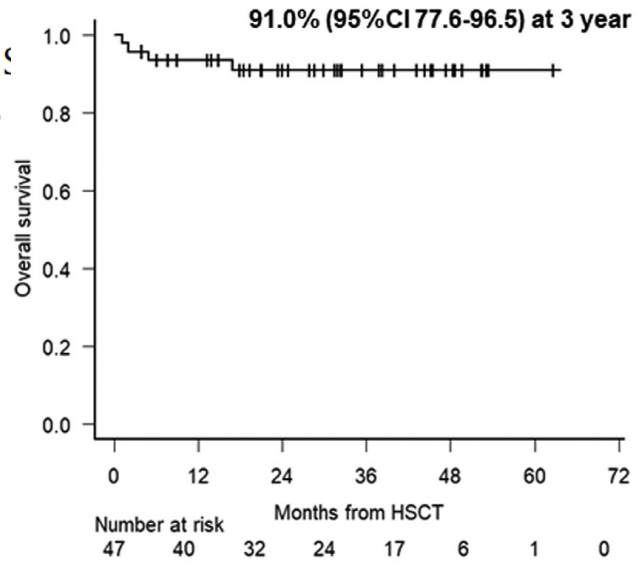
ELSEVIER



Haploidentical

Outcomes of Haploidentical Stem Cell Transplantation using Total Body Irradiation (600 cGy) and Fludarabine with Antithymocyte Globulin in Adult Patients with Severe Aplastic Anemia: A Prospective Phase II Study

Sung-Eun Lee[1], Gi June Min[1], Sung-Soo Park[1], Silvia Park[1], Jae-Ho Yoon[1], S
Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Seok Lee[1], Chang-Ki Min[1],
Seok-Goo Cho[1], Jong Wook Lee[1,*]



47 pts age 36 (17-61)
3 yy OS 91%

HAPLO

 # amazing results from the Chinese/Korean group with survival over 80% in young adults - same thoughts as after the 2006 Blood publication showing same outcome of HAPLO and SIBS.

 # and the Baltimore platform?

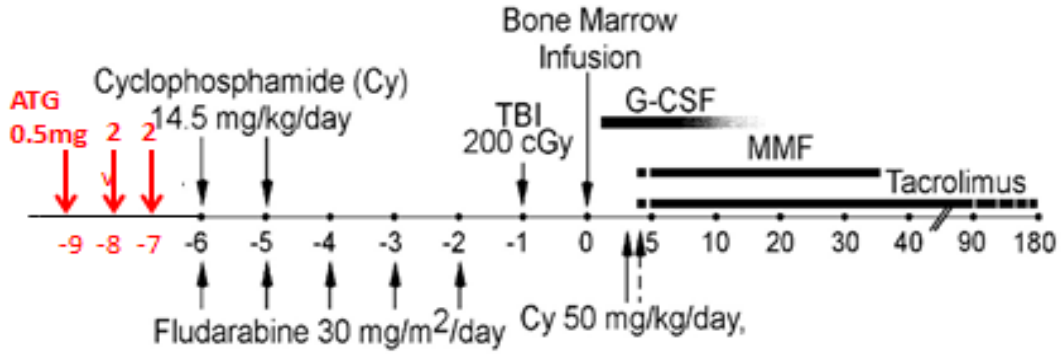
Biol Blood Marrow Transplant 23 (2017) 498–504

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

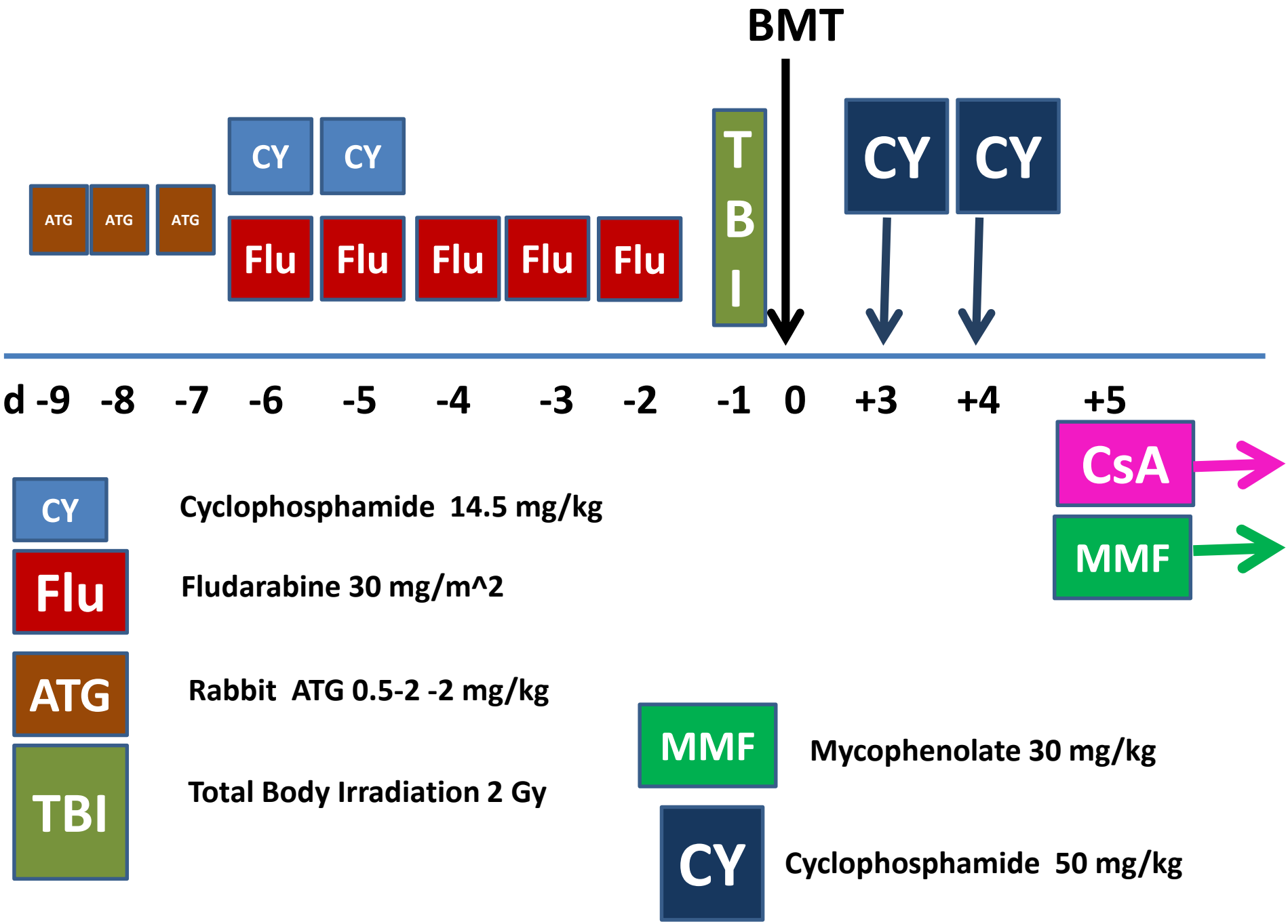
Alternative Donor Transplantation with High-Dose Post-Transplantation Cyclophosphamide for Refractory Severe Aplastic Anemia

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


BMT
ATG
ATG
ATG
CY
CY
Flu
Flu
Flu
Flu
Flu
TBI
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

blood advances

American Society of Hematology
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Non-myeloablative transplantation with post-trans cyclophosphamide for Severe Aplastic Anemia

22 alive
15 alive

Tracking no: ADV-2020-001729-T

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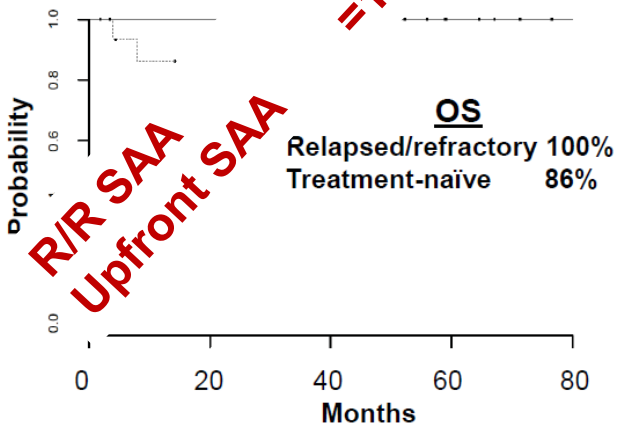
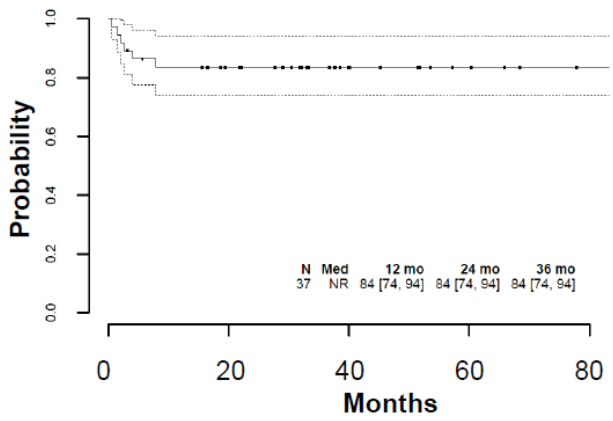
HAPLO
HAPLO

n=22
=17



R/R SAA
Upfront SAA



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Biol Blood Marrow Transplant 000 (2020) 1–7

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Impact of CD34 Cell Dose and Conditioning Regimen on Outcomes after Haploidentical Donor Hematopoietic Stem Cell Transplantation with Post-Transplantation Cyclophosphamide for Relapsed/Refractory Severe Aplastic Anemia

Leonardo Javier Arcuri[1,*], Samir Kanaan Nabhan[2], Renato Cunha[3], Samantha Nichele[2], Andreza Alice Feitosa Ribeiro[1], Juliana Folloni Fernandes[1,4], Liane Esteves Daudt[5], Ana Luiza Melo Rodrigues[6], Celso Arrais-Rodrigues[7], Adriana Seber[8], Elias Hallack Atta[9], Jose Salvador Rodrigues de Oliveira[7], Vaneuza Araujo Moreira Funke[10], Gisele Loth[2], Luiz Guilherme Darrigo Junior[3], Alessandra Paz[5], Rodolfo Froes Calixto[11], Alessandra Araujo Gomes[12], Carlos Eduardo Sa Araujo[13], Vergilio Colturato[14], Belinda Pinto Simoes[3], Nelson Hamerschlak[1], Mary Evelyn Flowers[15], Ricardo Pasquini[2], Vanderson Rocha[4,16], Carmem Bonfim[2]

N= 87 HAPLO Tx for SAA
BRASIL
Heavily transfused
All pts had failed IST

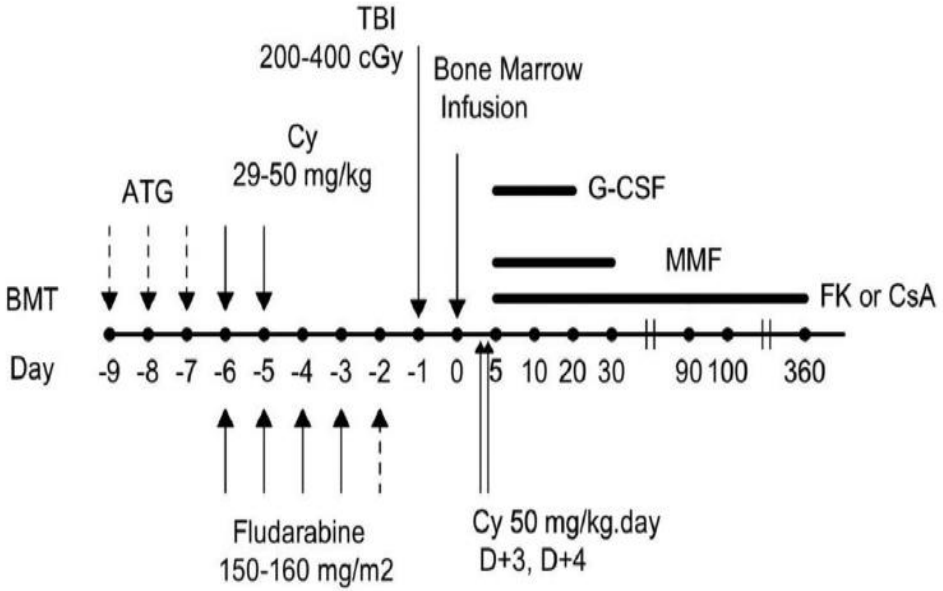
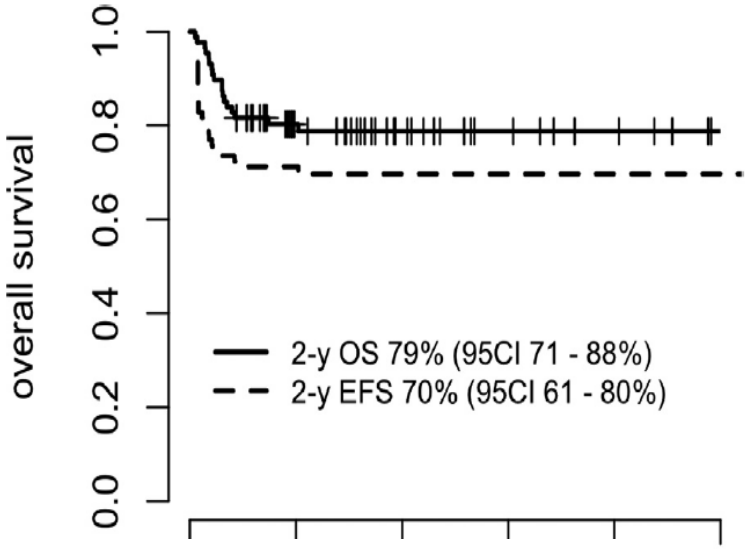
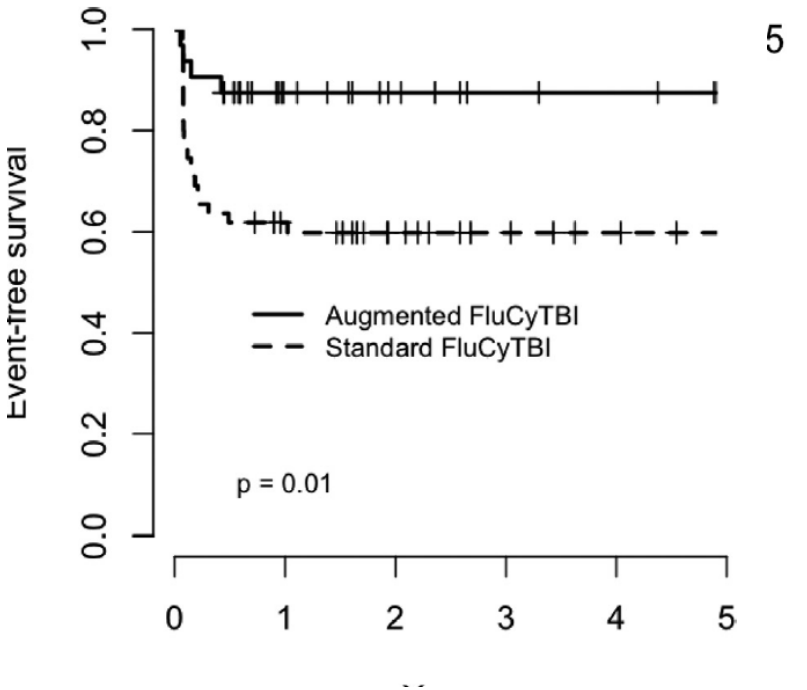


Figure 1. Conditioning regimens and GVHD prophylaxis.





The Baltimore protocol

 # excellent for HAPLO; results confirmed in Curitiba

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

 # possibly the new platform for UD TX

Biol Blood Marrow Transplant 26 (2020) e222–e226

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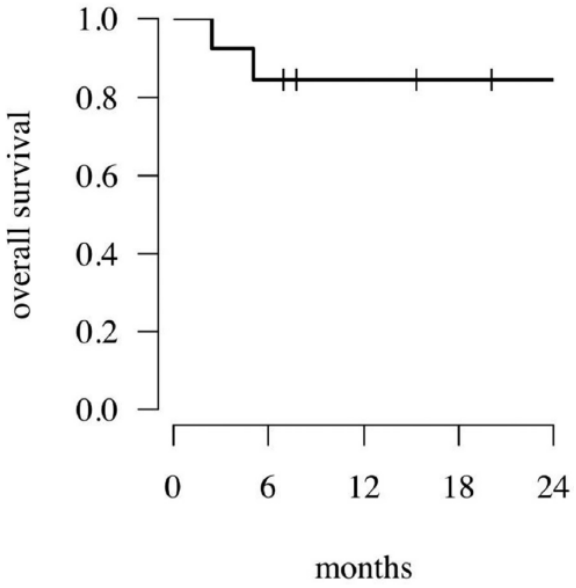
Brief Articles

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 – BMT : Have me made progress?

 # YES

- **more donor types**
- **more transplant platforms**
- **better supportive care**

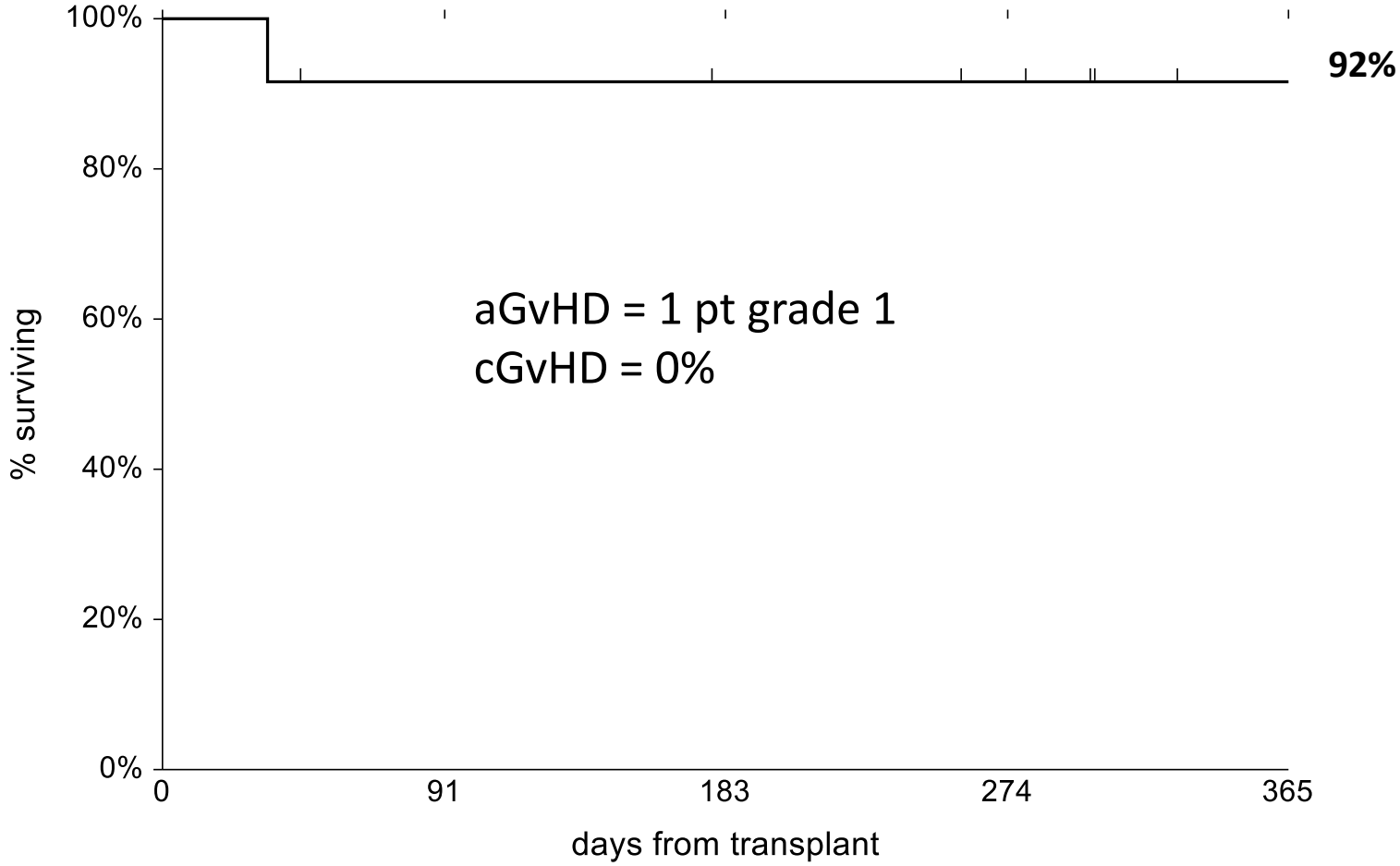
SAA – BMT : Have me made progress?

 # NO

in older patients >40 >50 >60

we need to test the Baltimore platform (ATG+PTCY) in older patients receiving HLA matched or mismatched grafts

ATG-FLU-CY-TBI200 /PTCY CSA MMF:
Protocol DZ for SAA: UD / HAPLO/eld SIB; n=12




Thank you
M20