Aplasie Midollari: che c’e’ di nuovo

Andrea Bacigalupo
Universita’ Cattolica- Policlinico Gemelli
Rome , Italy

02 dicembre 2023

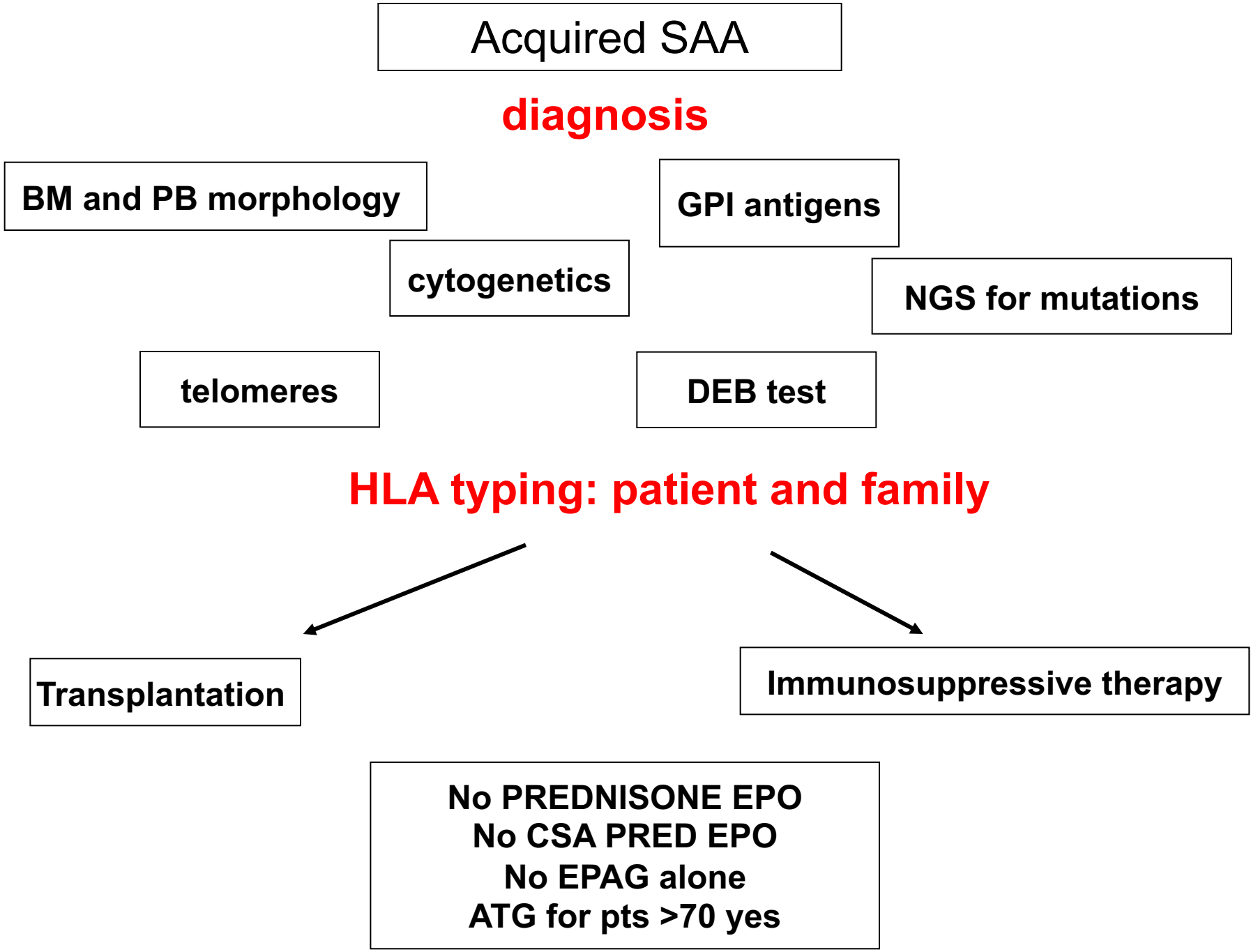
Excellence in science
EBMT
European Group for Blood and Marrow Transplantation

APBMT

CIBMTR

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE


Acquired SAA
diagnosis
BM and PB morphology
GPI antigens
cytogenetics
NGS for mutations
telomeres
DEB test
HLA typing: patient and family
Transplantation
Immunosuppressive therapy
No PREDNISONE EPO
No CSA PRED EPO
No EPAG alone
ATG for pts >70 yes

Survival of patients with acquired SAA (N=6263) , receiving 1° line BMT or IST;

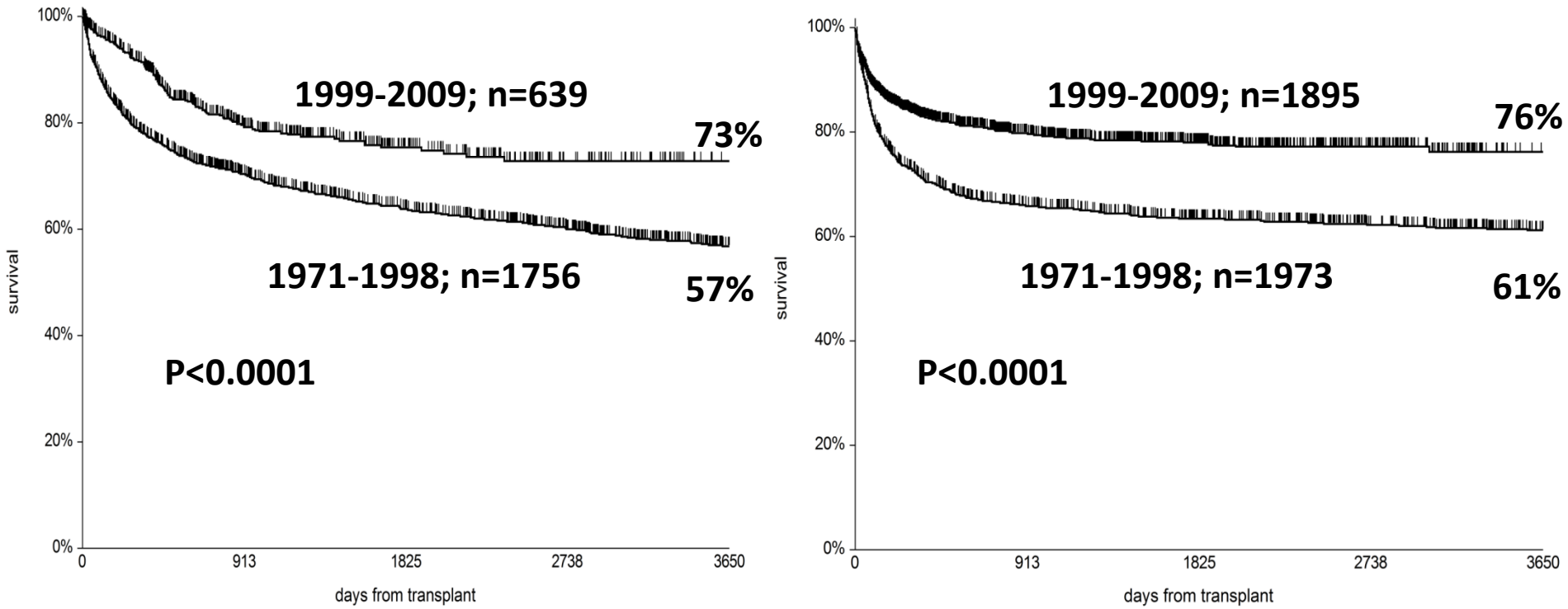
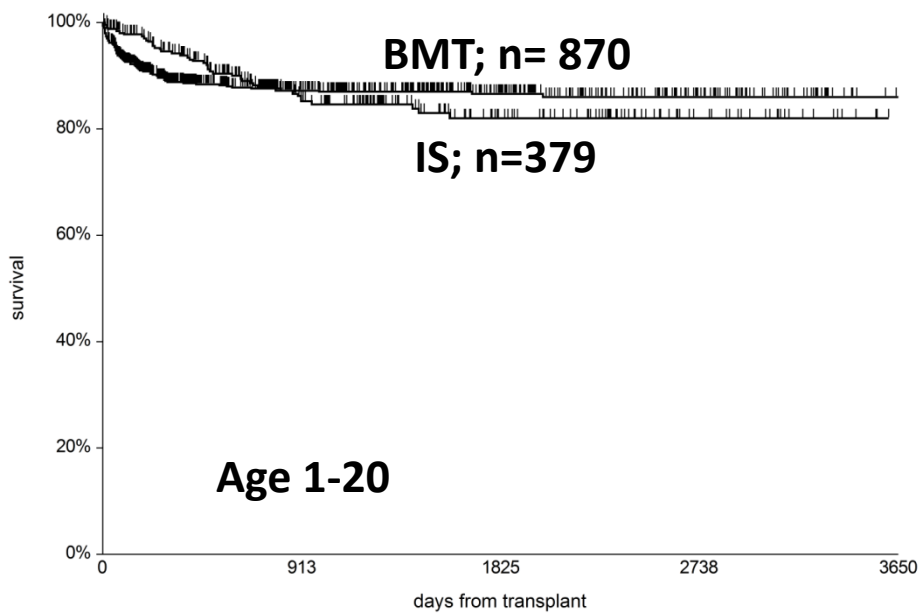
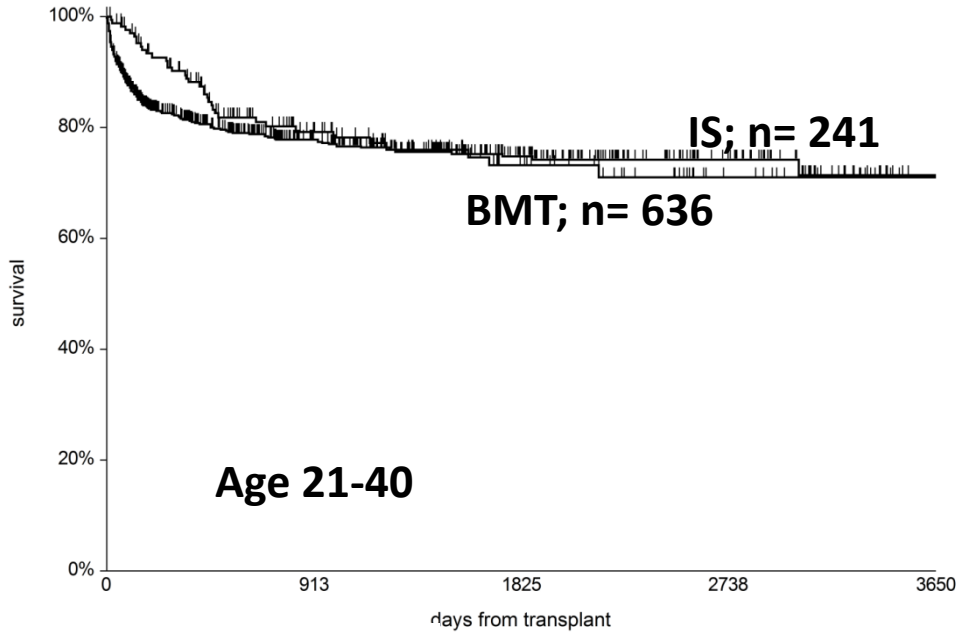
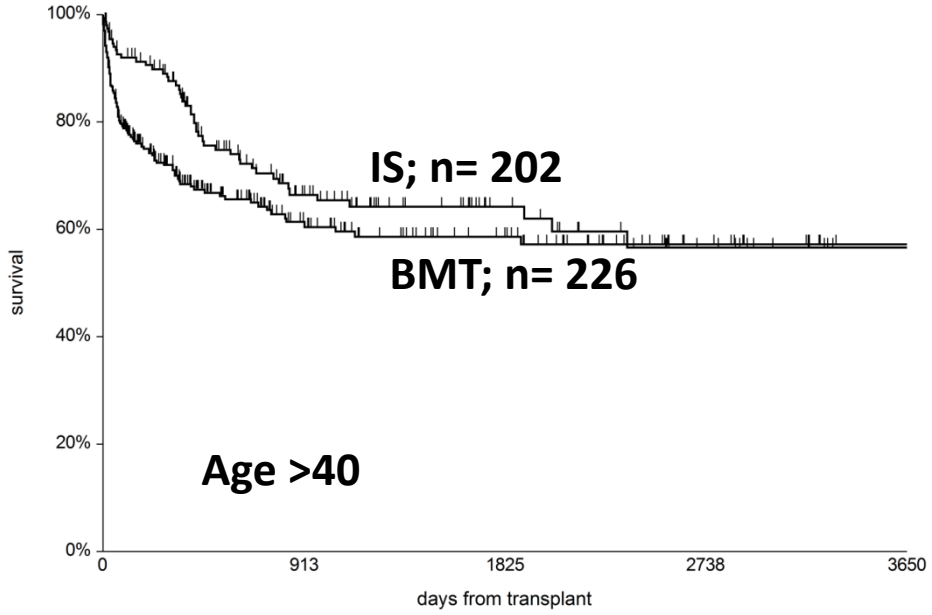


Fig.1

Survival of patients with acquired SAA (N=6293) , receiving 1° line BMT or IST;







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SAA 1

 # OS after 1° line treatment with either BMT or IS, comparable at 10 years

results: age dependent

First line IST for SAA; (EBMT 2001-2010)

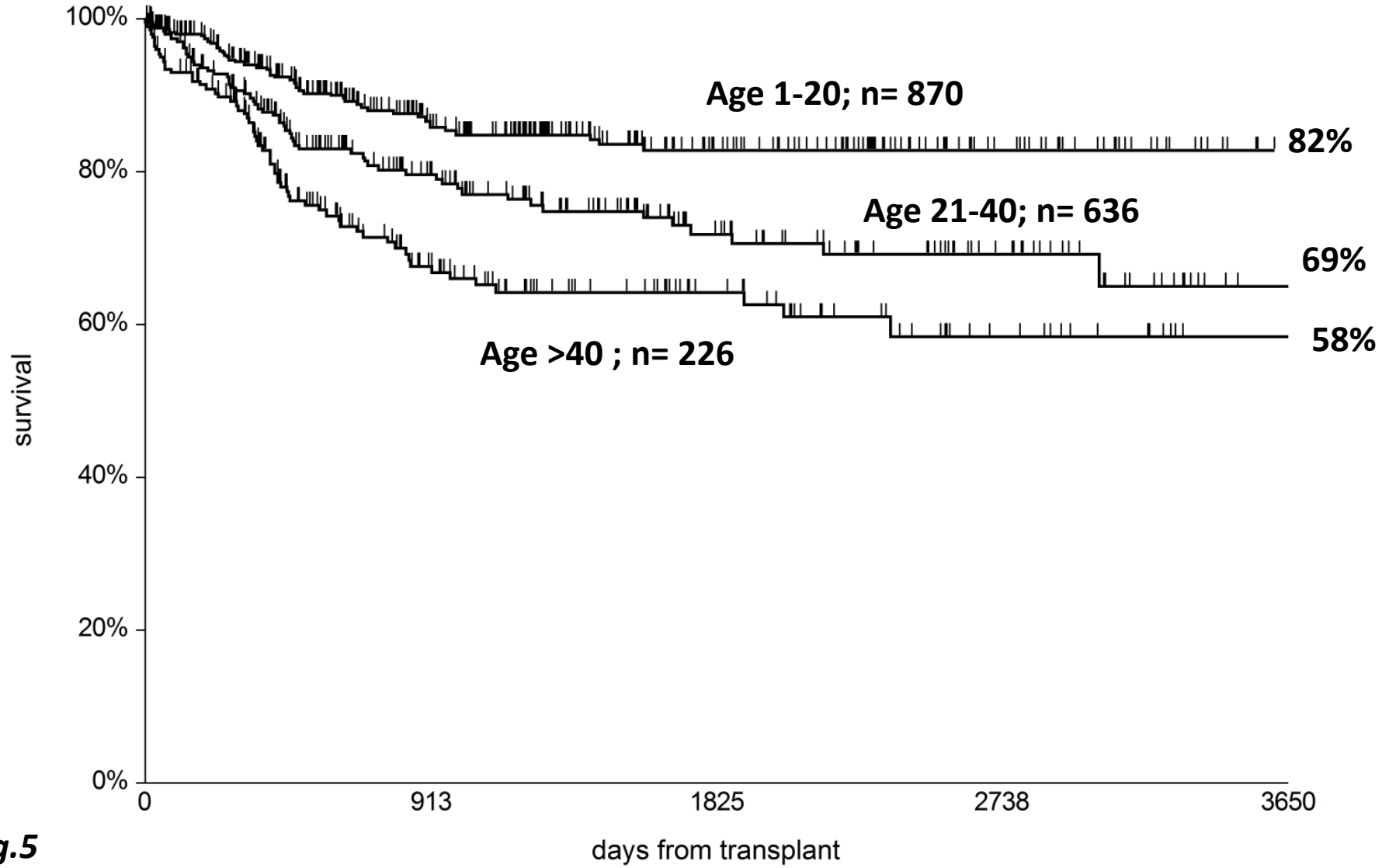


Fig.5

SAA 2

strong age effect in pts receiving ATG+CSA

predictive factors : age , PMN counts, int DxTx, response to ATG

can growth factors be helpful?

Haematologica. 2019; 104

haematologica
Journal of The Ferrata Storti Foundation

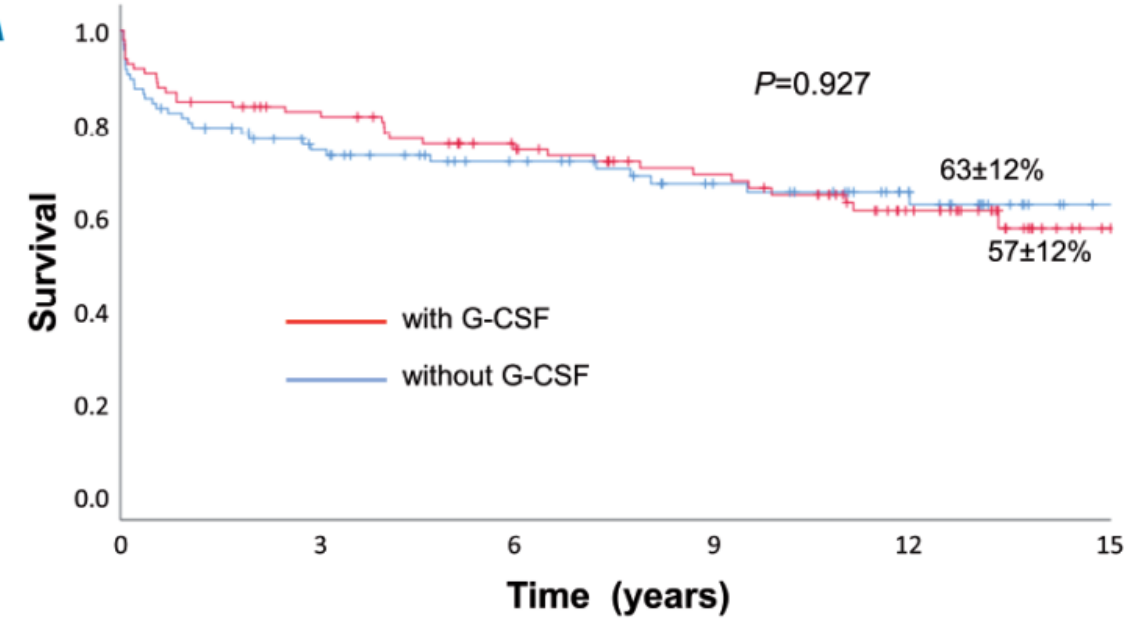
Long-term outcome of a randomized controlled study in patients with newly diagnosed severe aplastic anemia treated with antithymocyte globuline, cyclosporine, with or without G-CSF: a Severe Aplastic Anemia Working Party Trial from the European Group of Blood and Marrow Transplantation

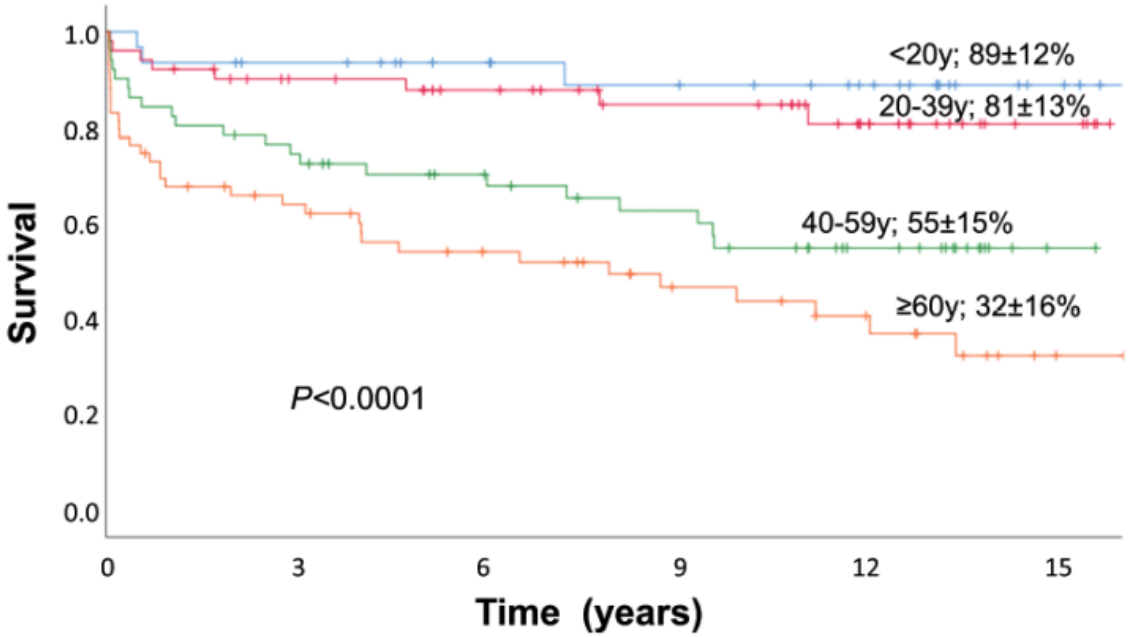
by André Tichelli, Régis Peffault de Latour, Jakob Passweg, Cora Knol-Bout, Gérard Socié, Judith Marsh, Hubert Schrezenmeier, Britta Höchsmann, Andrea Bacigalupo, Sujith Samarasinghe, Alicia Rovó, Austin Kulasekararaj, Alexander Röth, Dirk-Jan Eikema, Paul Bosman, Peter Bader, Antonio Risitano, and Carlo Dufour. Collaborative Groups: Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation)

Randomization
hATG+CSA

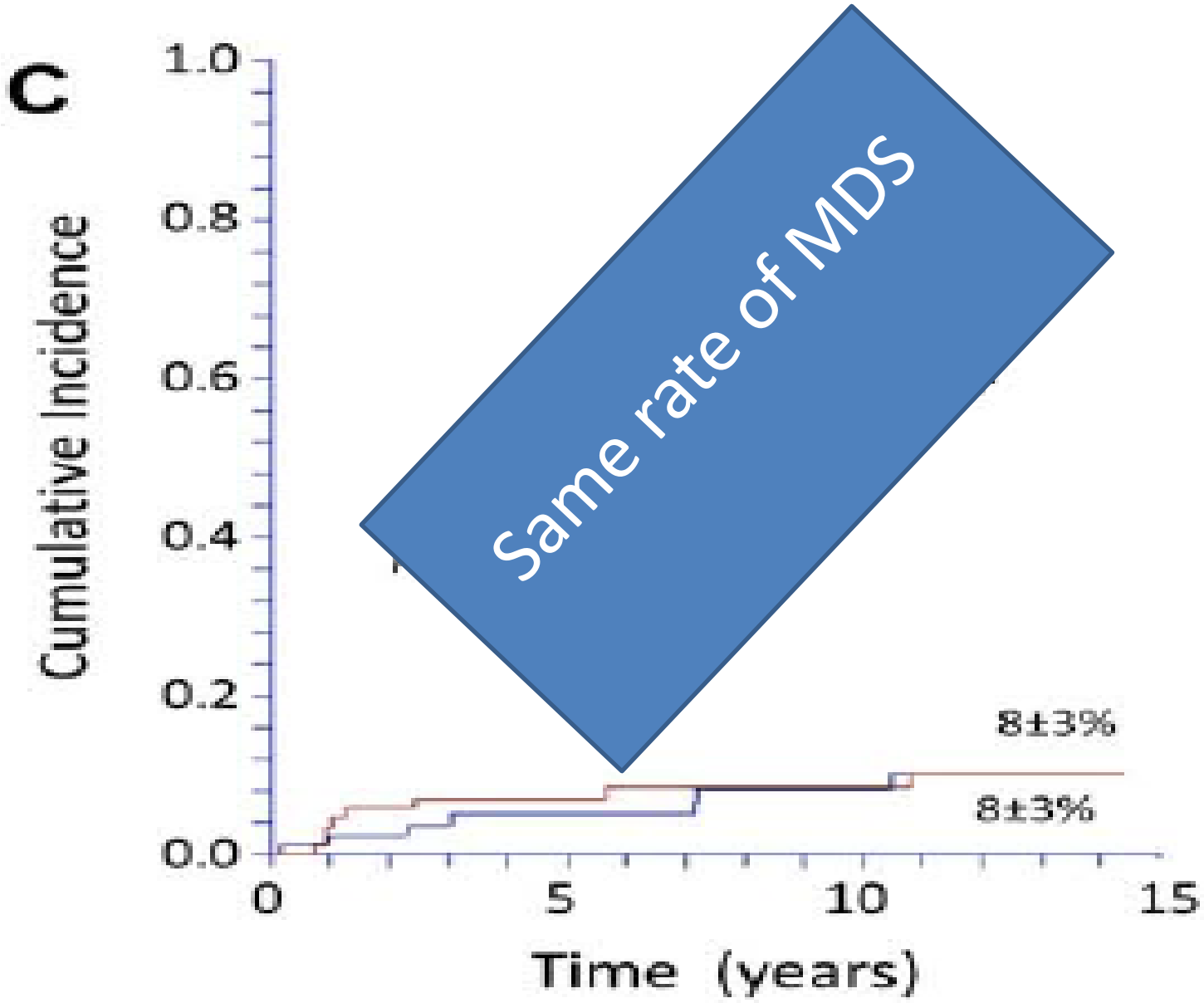
hATG+CSA+
GCSF
150 ug/m^2
day +8 day +240
Or untill response

BMT
14% GCSF
24% no GCSF





Clonal disease, (cytogenetic abn, MDS, AML)



Clinical PNH
10% GCSF
13% no GCSF

RELAPSE
30% GCSF
25% no GCSF

GCSF (4-8 months) does NOT cause leukemia (relevant for healthy donors)

Does not improve response/ survival

Reduces infections
Reduces hospital stay
Day +30 PMN level (500) predicts responders

 # survival >80% at 15 years in patients <30yy!

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 6, 2022 VOL. 386 NO. 1

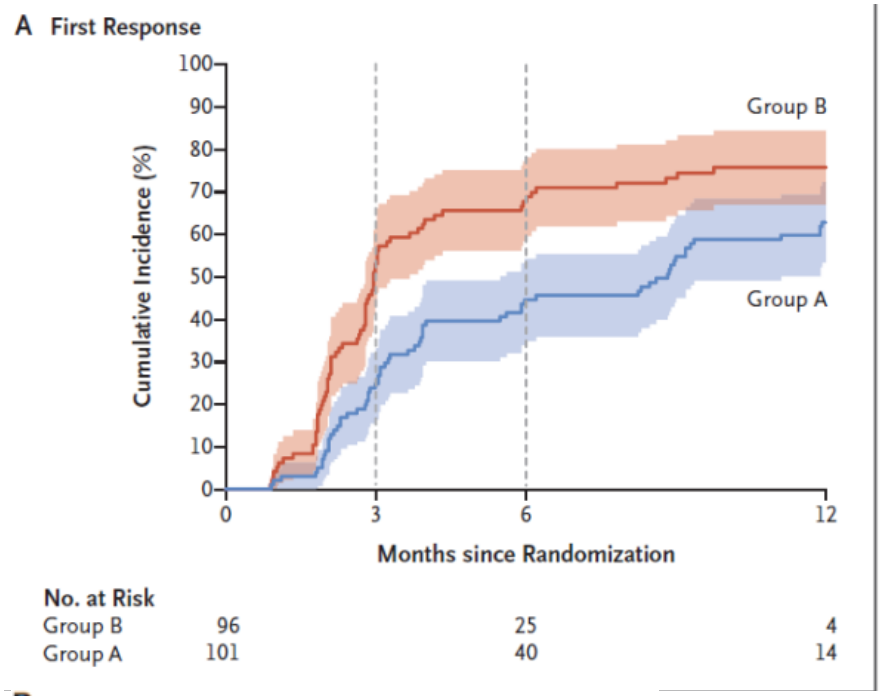
Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia

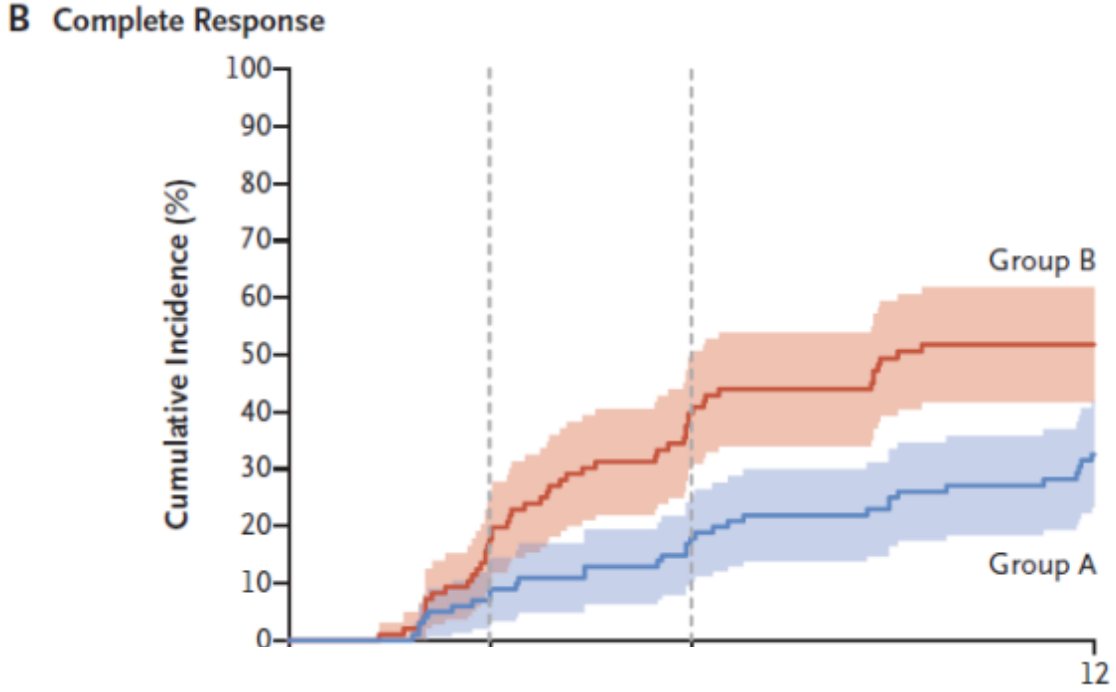
R. Peffault de Latour, A. Kulasekararaj, M. Griffin, C.J.M. Halkes, C. Recher, F. Barraco, E. Forcade, J.-C. Valle, E. Angelucci, R.A.P. Raymakers, M.R. de Latour, E. Nur, W. Barcellini, N.H. Russell, L. Terriou, A.-P. Iori, U. La Rocca, A. Sureda, I. Sán coy, I. Jarque, J. Cavenagh, F. Sicre de Fontbrune, S. Marotta, T. Munir, J.M.L. Tjon, S. Tavitian, A. Praire, L. Clement, F. Rabian, L. Marano, A. Hill, F. Palmisani, P. Muus, F. Cacace, C. Frieri, M.-T. van Lint, J.R. Passweg, J.C. A.M. Risitano, for the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation*

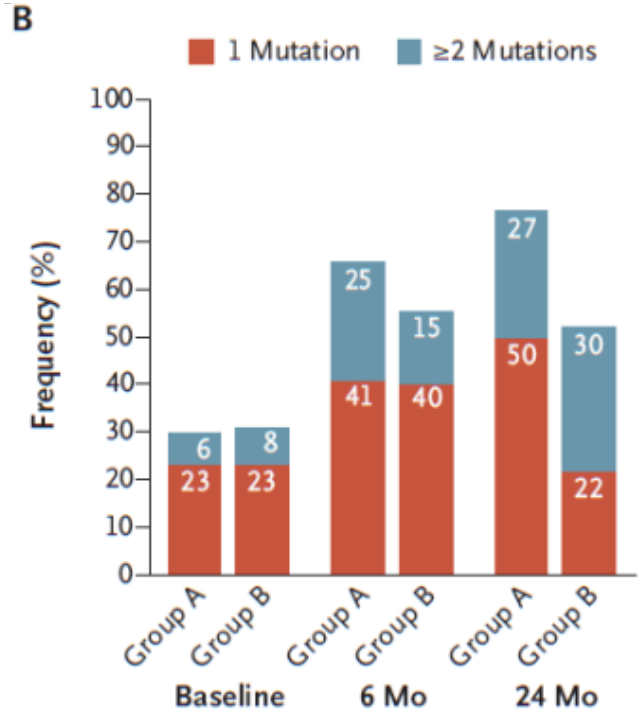
Random

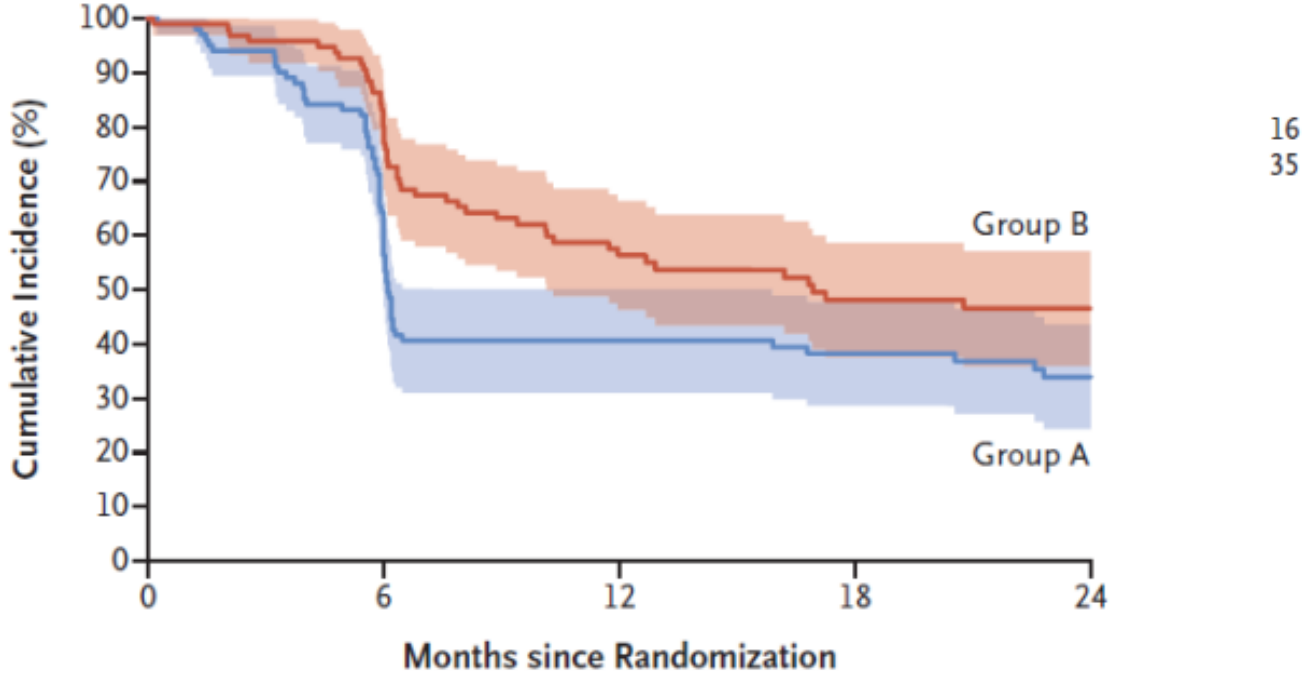
ATG horse+ CSA

ATG horse+ CSA + EPAG


A First Response
Cumulative Incidence (%)
Group B
Group A
Months since Randomization
No. at Risk
Group B 96 25 4
Group A 101 40 14


B Complete Response
Cumulative Incidence (%)
Group B
Group A
12


B
1 Mutation
≥2 Mutations
Frequency (%)
Group A
Group B
Baseline
6 Mo
24 Mo


Cumulative Incidence (%)
Group B
Group A
16
35
Months since Randomization

RACE : EBMT 2021

	ATG+CSA	**ATG+CSA+EPAG**	
N=	101	96	
Age	52(15-81)	55 (16-77)	
>40 years	42%	40%	
CR 3 mm	**10%**	**22%**	**0.01**
OR 6 mm	**45%**	**72%**	**0.01**

ESH EBMT BMF Meeting 18-20/11/2022

 # ACE (ATG +CSA+EPAG) is considered standard first line IST therapy in SAA

 # the recommended dose is 150 mg/day

 # EPAG should be given for 6 months, and tapered very slowly. EPAG dependence is described

Acquired SAA

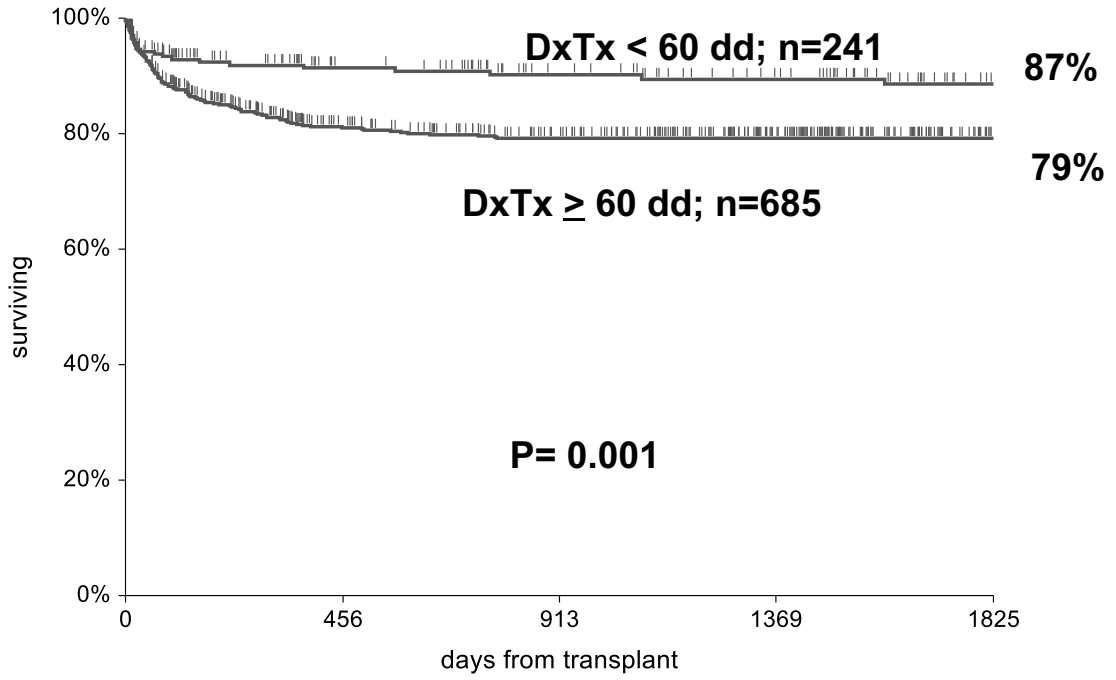
HLA typing

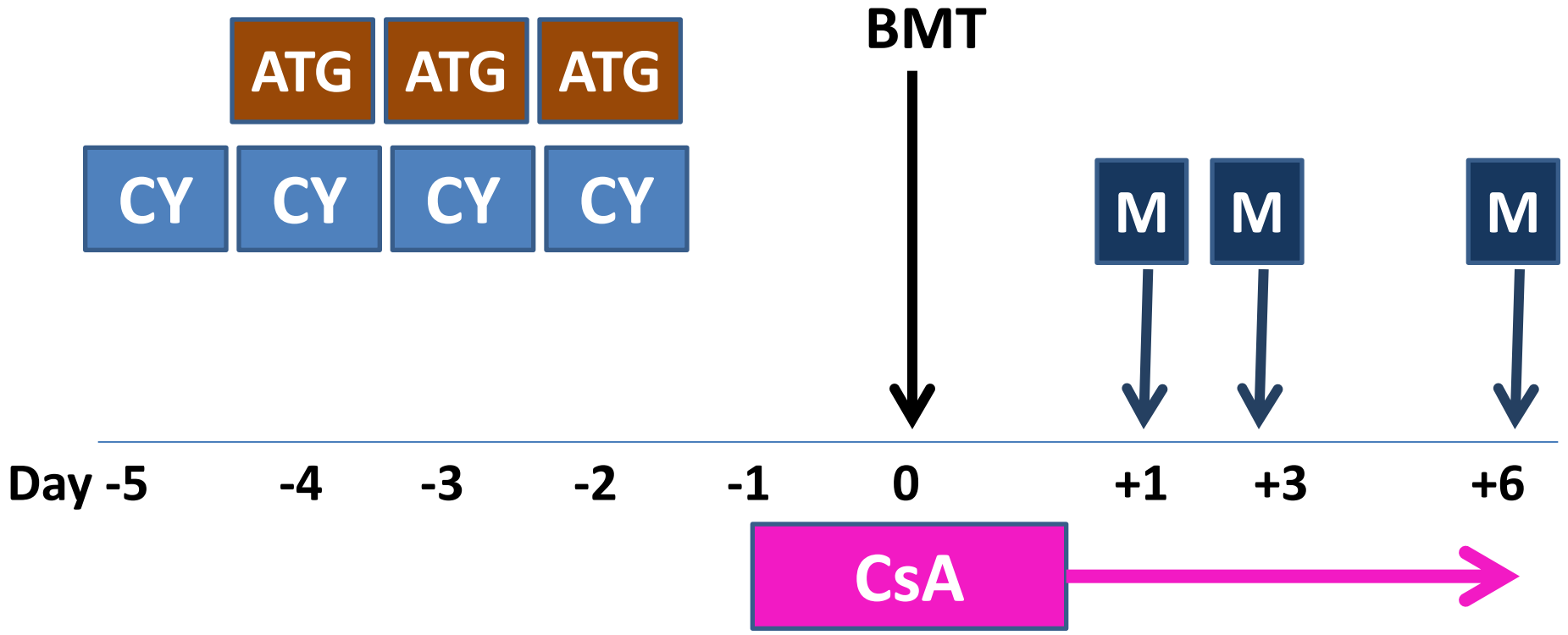
HLA = Sib

≤40 yy

Sib BMT

As soon as possible



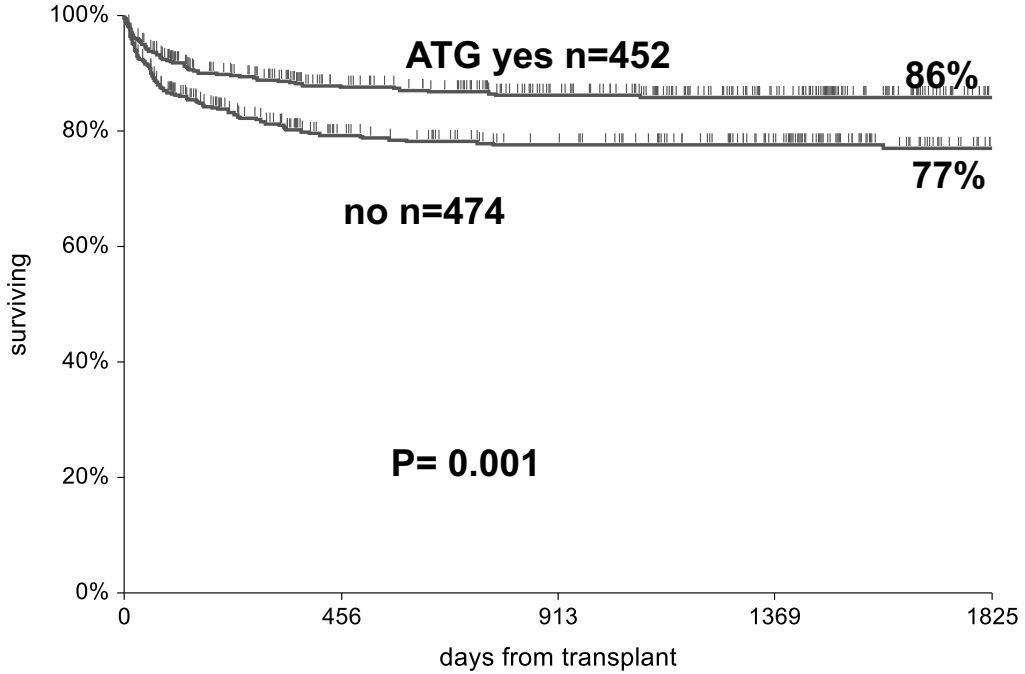


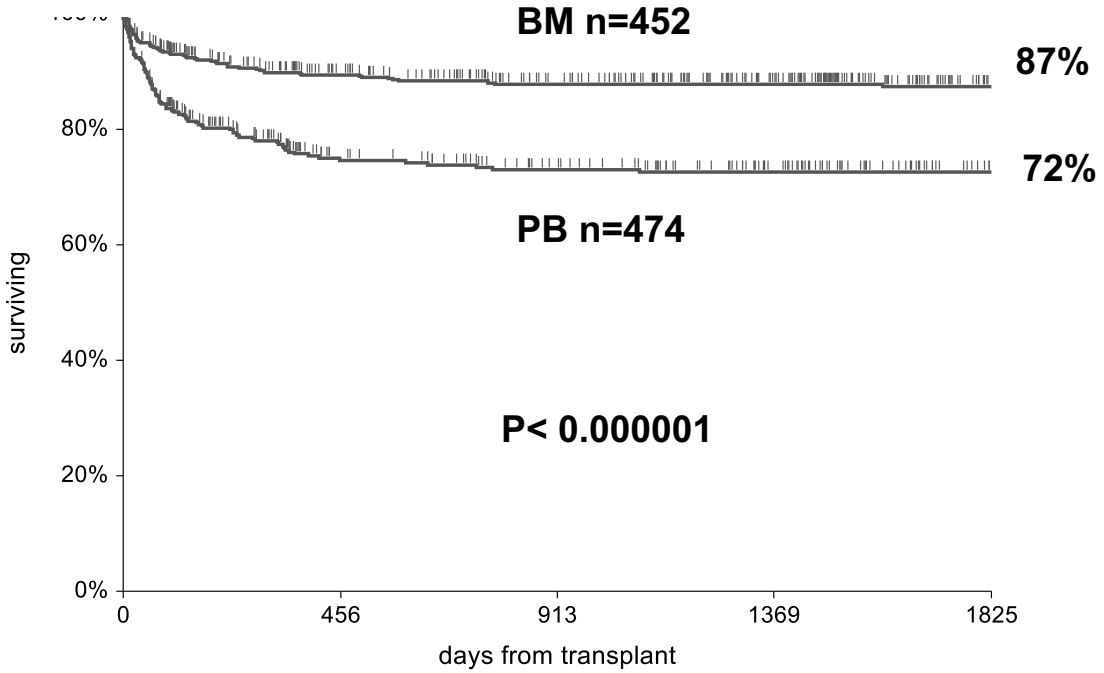
CY Cyclophosphamide 50 mg/kg

ATG Rabbit ATG 2.5 mg/kg

Storb et al , Blood 1974

HLA identical SIB transplants





Nakamura et al, Int J Hematology, 15 nov 2022

Outcome of peripheral blood stem cell transplantation , from HLA identic al siblings, in patients with SAA

94 adults with SAA; engtraftment 94%
24% ac GvHD II-IV **20% extensive chronic GvHD**

5 year OS 74%

In conclusion, PBSCT from HLA-identical sibling donors for aplastic anemia would result in acceptable outcomes. Several risk factors identified in our study should be considered when selecting a stem cell source.

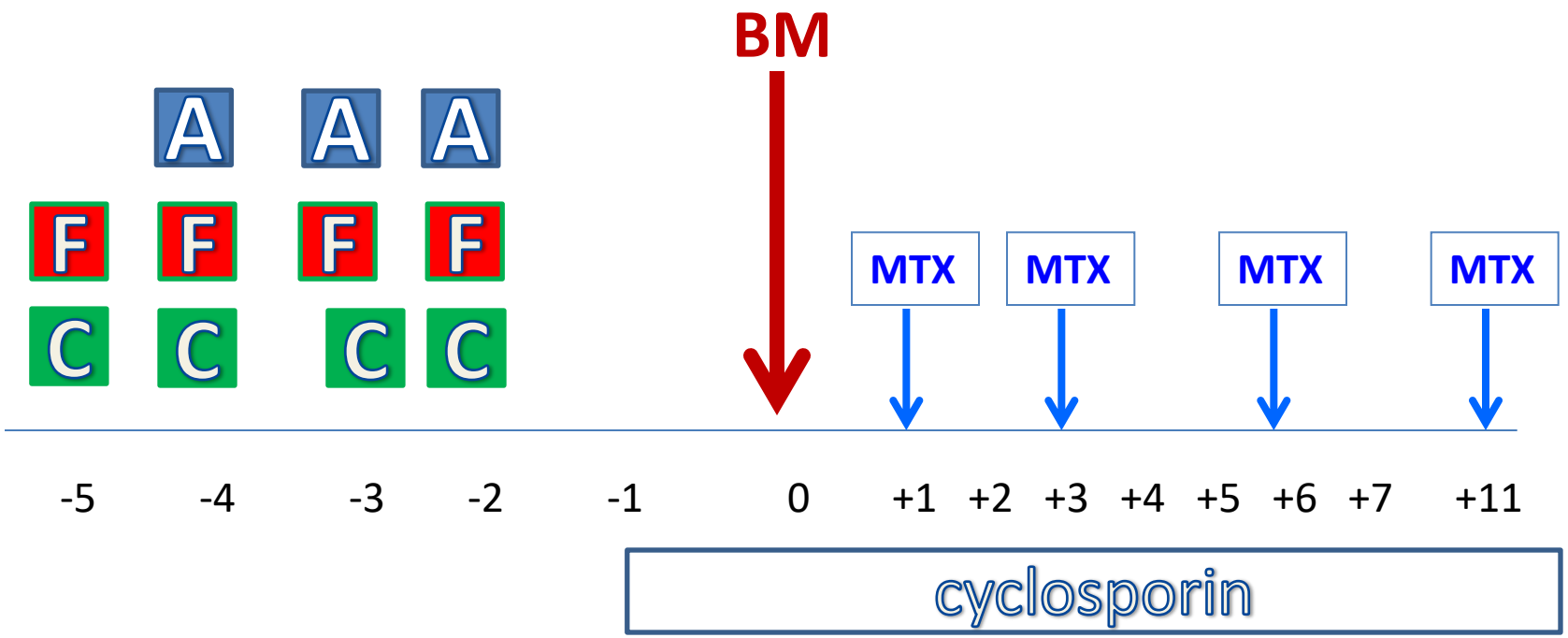
 # SAA <40 years old :

id SIB BMT first line; Excellent outcome

Please use BM (do you know how to harvest?

 # CY 200 for patients over 30 yy?

conditioning regimen for SIB transplants 30-40 years of age



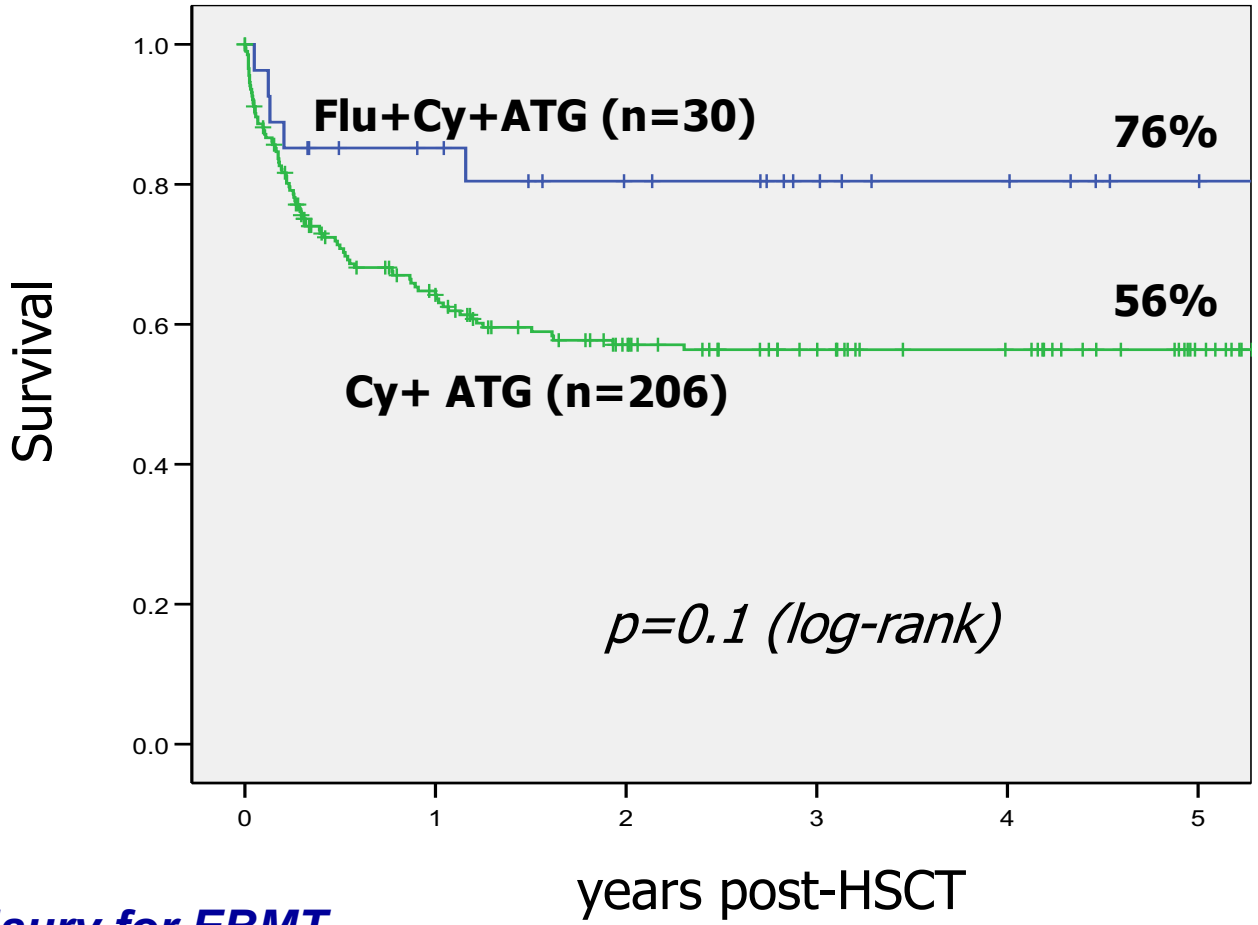
F **FLUDARABINE 30 mg/m^2/day x4**

C **CYCLOPHOSPHAMIDE 30 mg/kg/day x4**

A **ATG : 2.5 mg/kg/day**

HLA id SIBS; Age > 30 yy

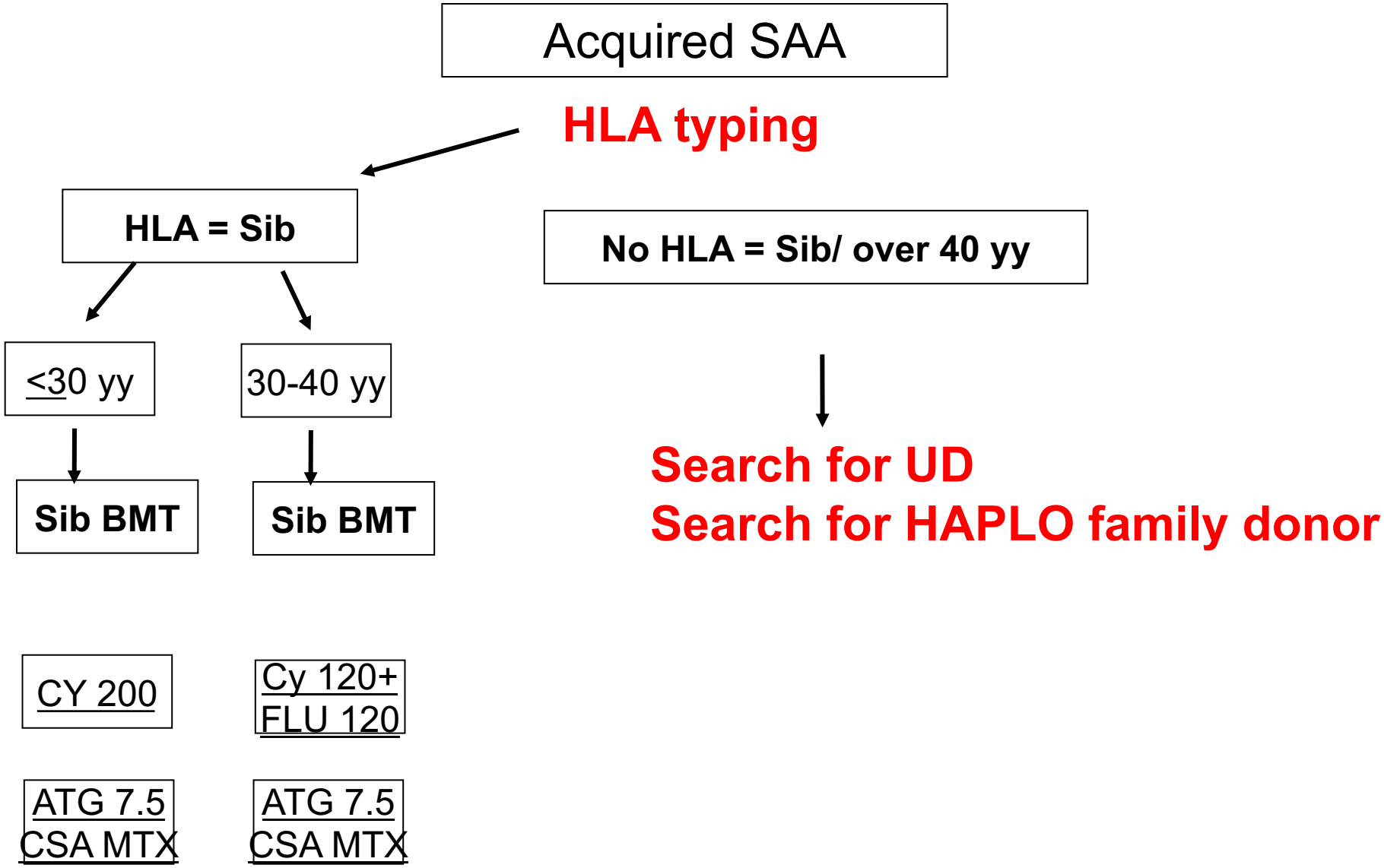
Difference is Graft Failure 0% vs 11% (p=0.01)



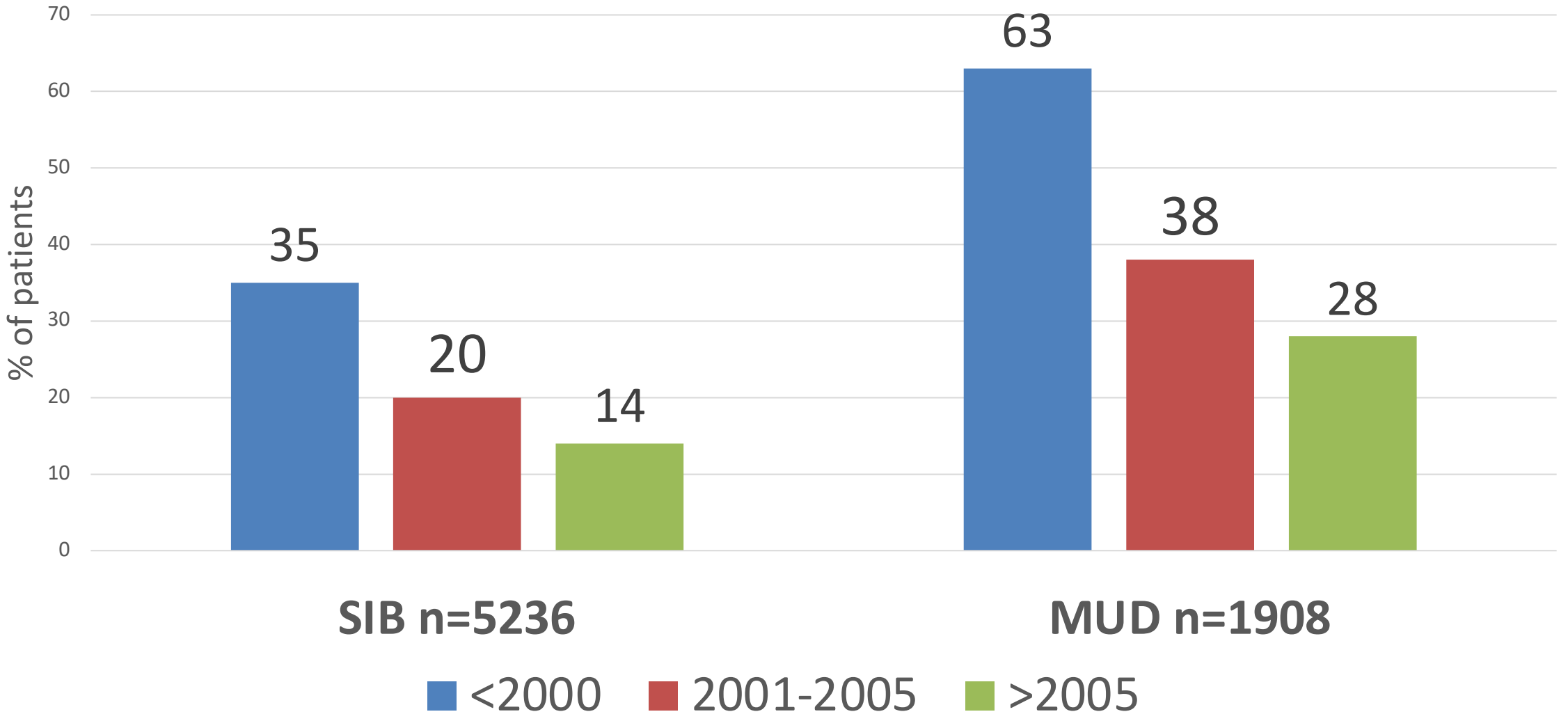
Age :45 yy

Age :39 yy

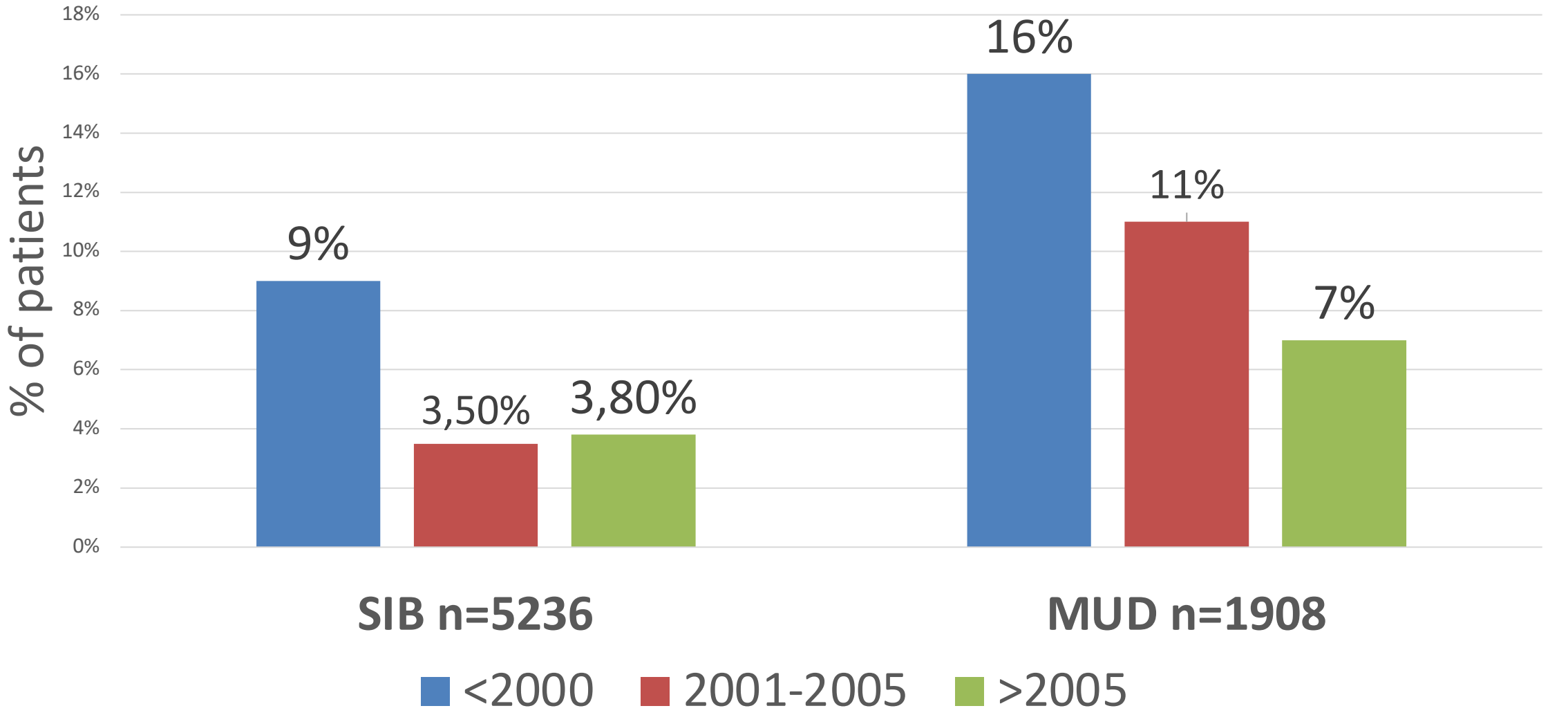
S Maury for EBMT


Acquired SAA
HLA typing
HLA = Sib
No HLA = Sib/ over 40 yy
<30 yy
30-40 yy
Search for UD
Search for HAPLO family donor
Sib BMT
Sib BMT
CY 200
Cy 120+
FLU 120
ATG 7.5
CSA MTX
ATG 7.5
CSA MTX

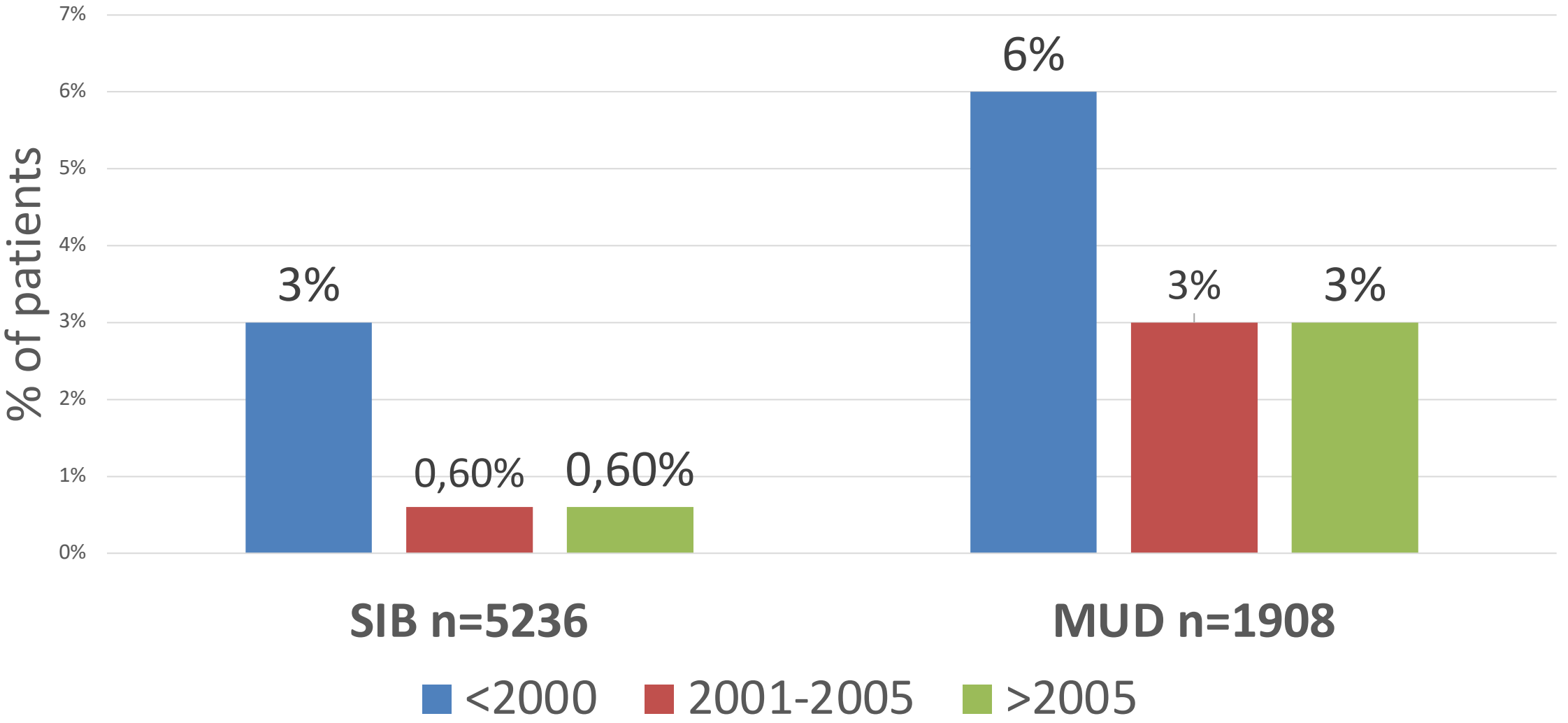
SAA: Transplant related mortality

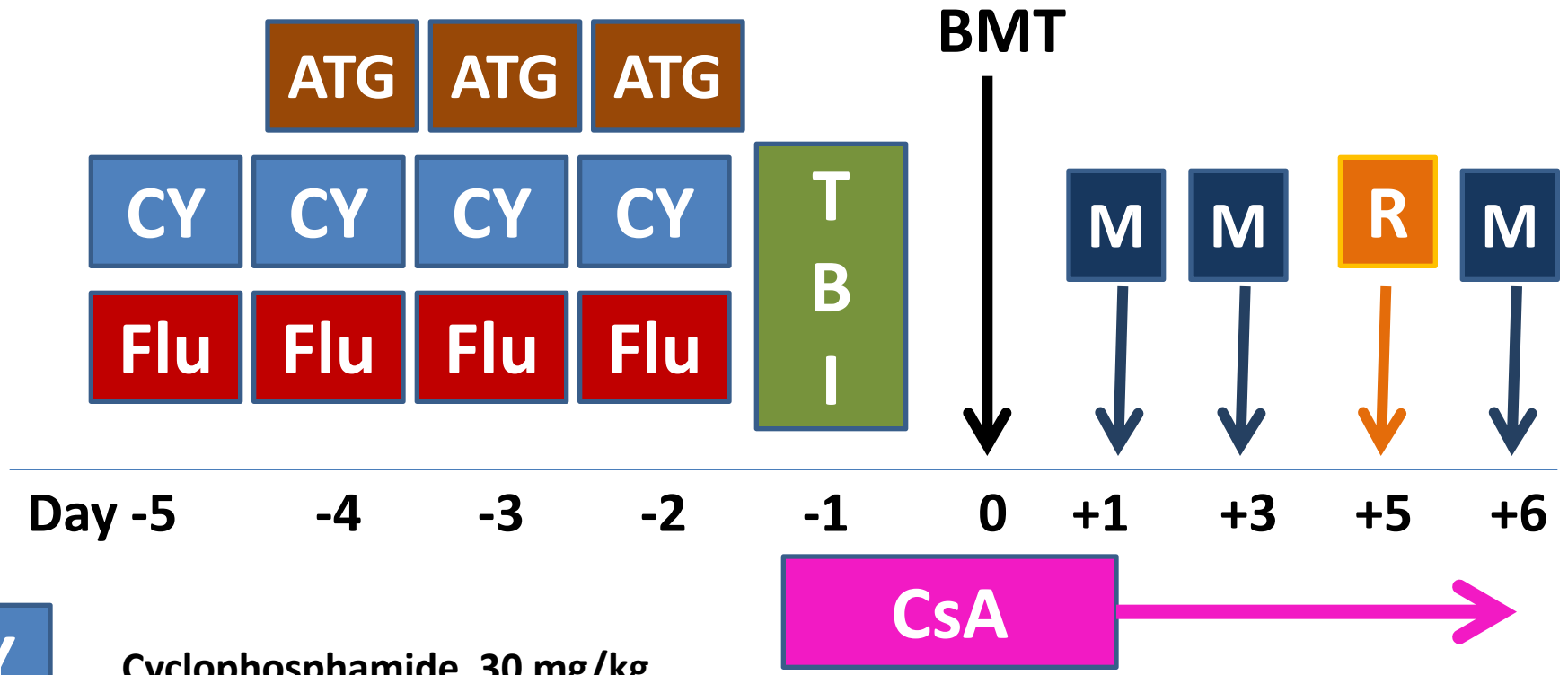


SAA: death due to aGvHD



SAA: death due to chronic GvHD





CY — Cyclophosphamide 30 mg/kg

Flu — Fludarabine 30 mg/m^2

ATG — Rabbit ATG 2.5 mg/kg

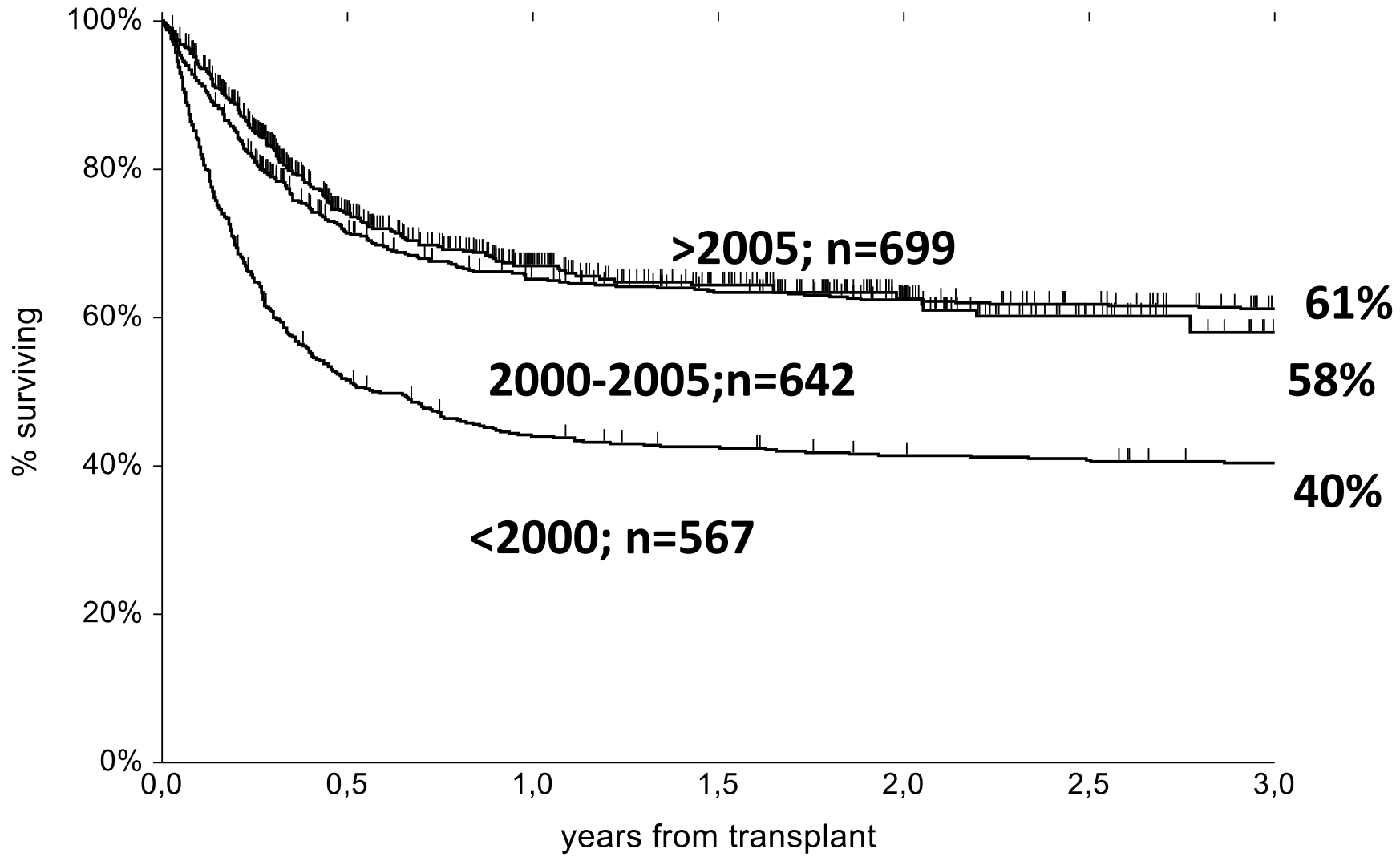
TBI — Total Body Irradiation 2 Gy

M — Methotrextae 10 mg/m^2

R — Rituximab 200 mg

Figure 2A

SAA: MUD transplants



MUD grafts for SAA

 # improved outcome with time
 # in 2015 :too much
graft failure and infections
aGvHD , cGvHD

 # have we improved > 2015?

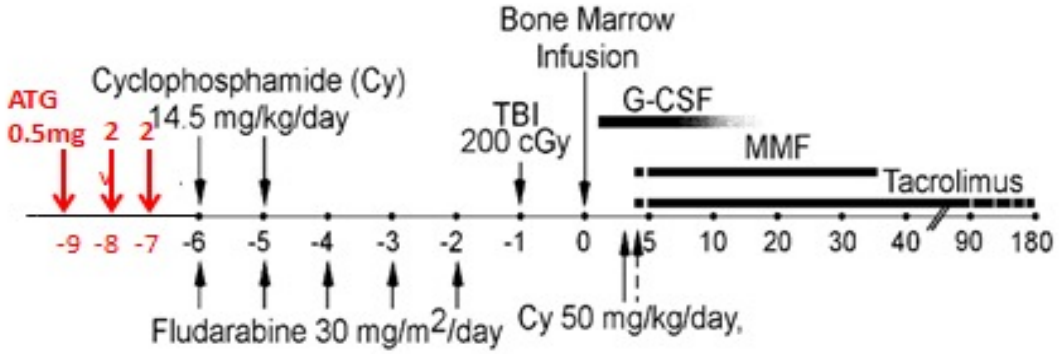
Biol Blood Marrow Transplant 23 (2017) 498–504

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

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

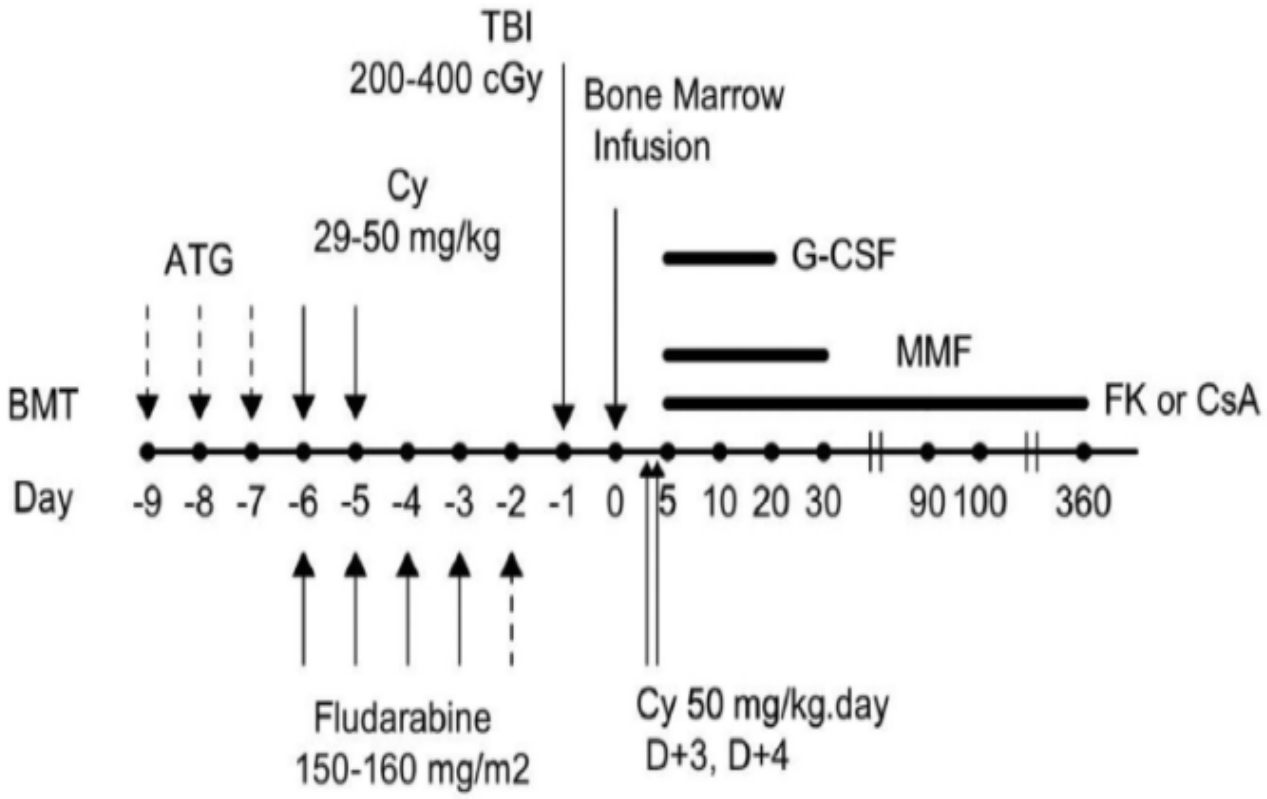
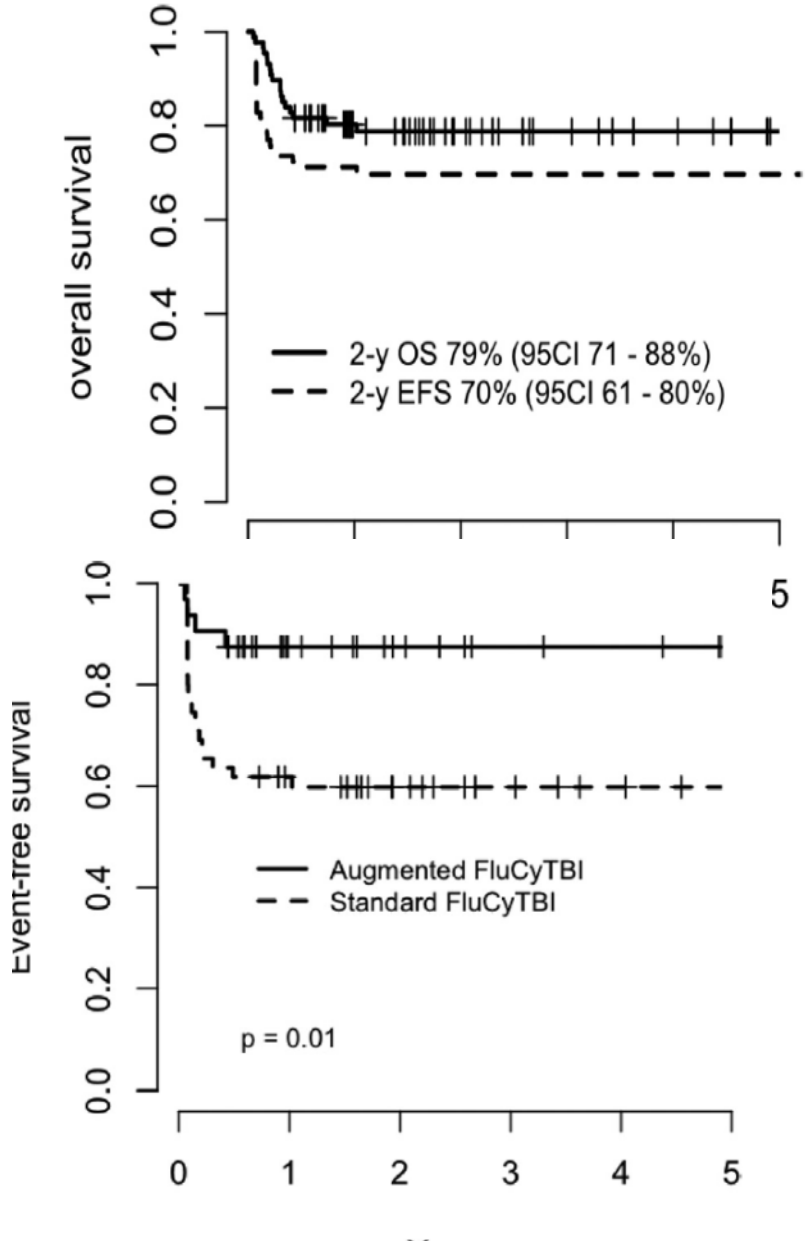
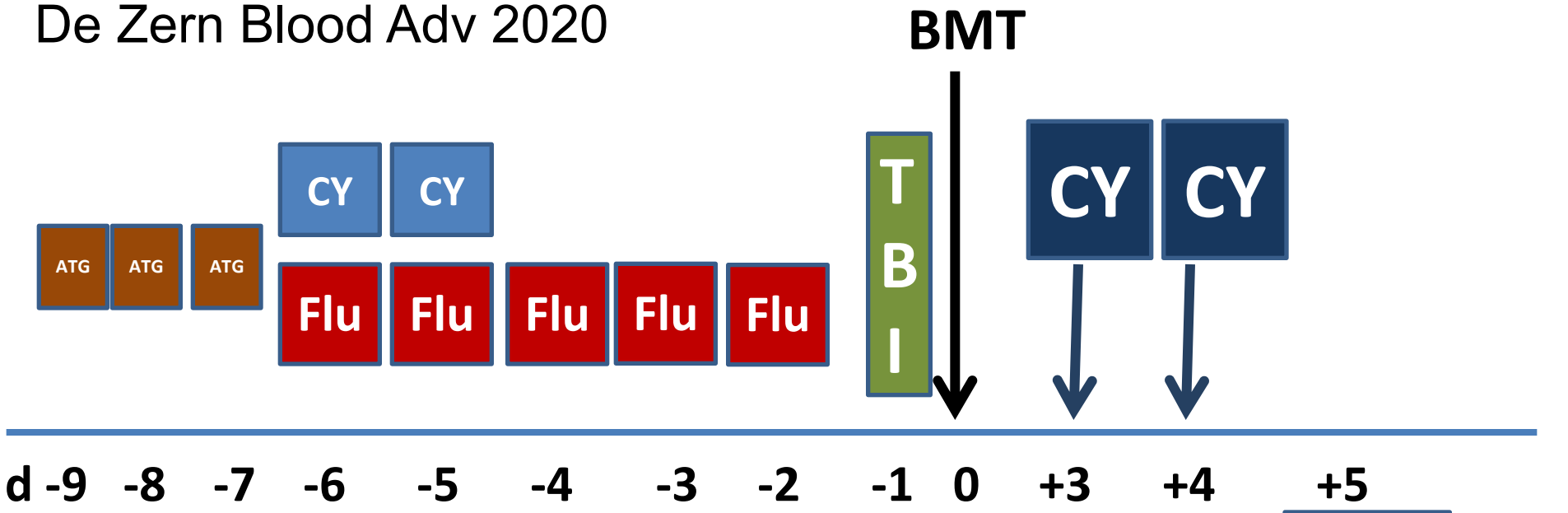


Figure 1. Conditioning regimens and GVHD prophylaxis.



Arcuri BBMT 2020

De Zern Blood Adv 2020



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 4 Gy

MMF Mycophenolate 30 mg/kg

CY Cyclophosphamide 50 mg/kg

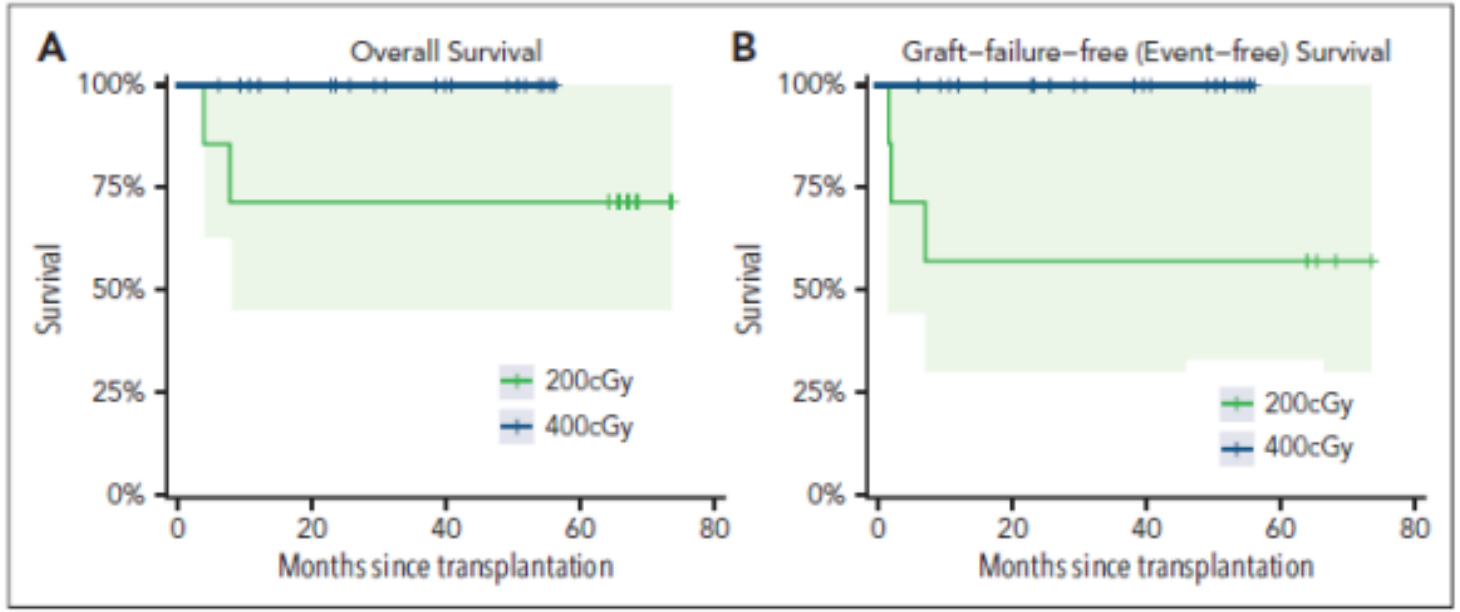
CLINICAL TRIALS AND OBSERVATIONS

Alternative donor BMT with posttransplant cyclophosphamide as initial therapy for acquired severe aplastic anemia

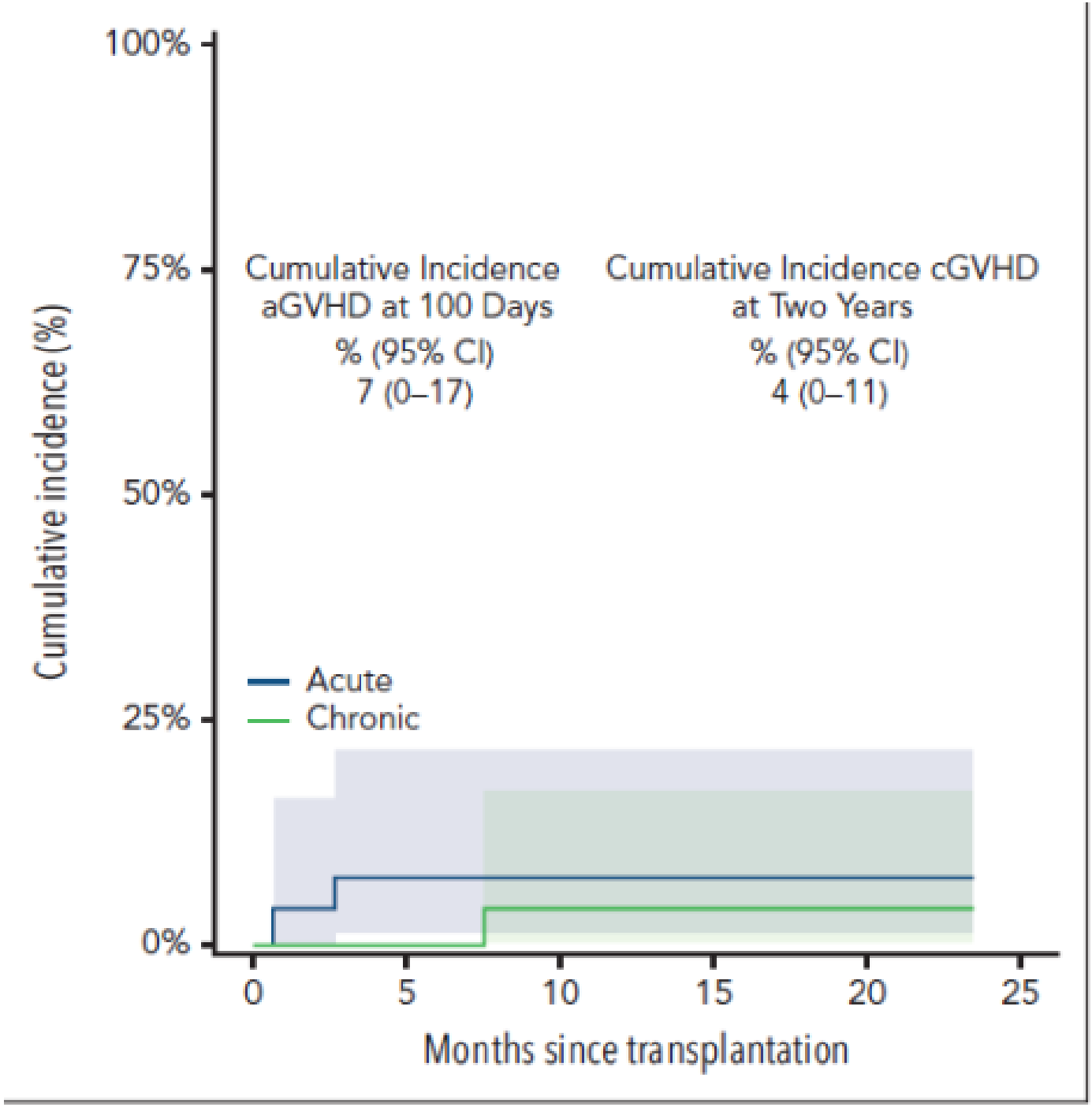
Amy E. DeZern,[1,2] Marianna Zahurak,[1,3] Heather J. Symons,[1,4] Kenneth R. Cooke,[1,4] Carol Ann Huff,[1] Tania Jain,[1] Lode J. Swinnen,[1] Philip H. Imus,[1] Nina D. Wagner-Johnston,[1] Richard F. Ambinder,[1] Mark Levis,[1] Leo Luznik,[1] Javier Bolaños-Meade,[1] Ephraim J. Fuchs,[1] Richard J. Jones,[1] and Robert A. Brodsky[1,2]

blood® 22 JUNE 2023 | VOLUME 141, NUMBER 25 3031

Upfront BMT 27 patients
HAPLO donors
BMT
7 pts TBI 200 (GF 3)
20 pts TBI 400 (GF 0)



GvHD free platform



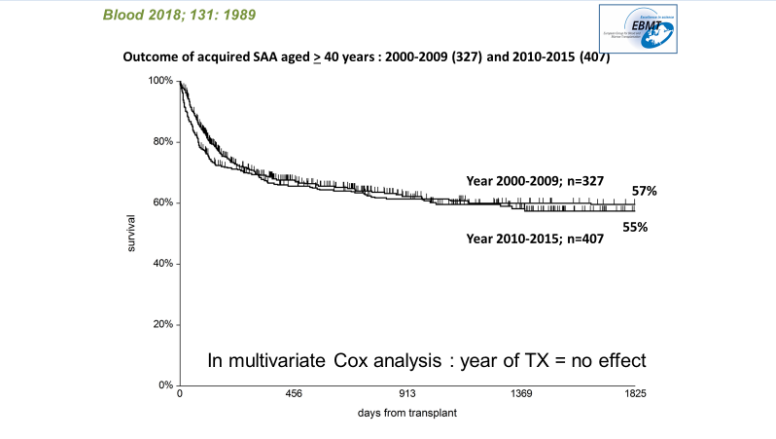
Baltimore DZ for UD and older patients

good engraftment

very low acute and chronic GvHD: GvHD free (?) also with PB

cardiac toxicity in older patients? Should we reduce the dose of PTCY?

# could we use DZ for HLA matched U
HLA= BMT?



Biol Blood Marrow Transplant 26 (2020) e222–e226

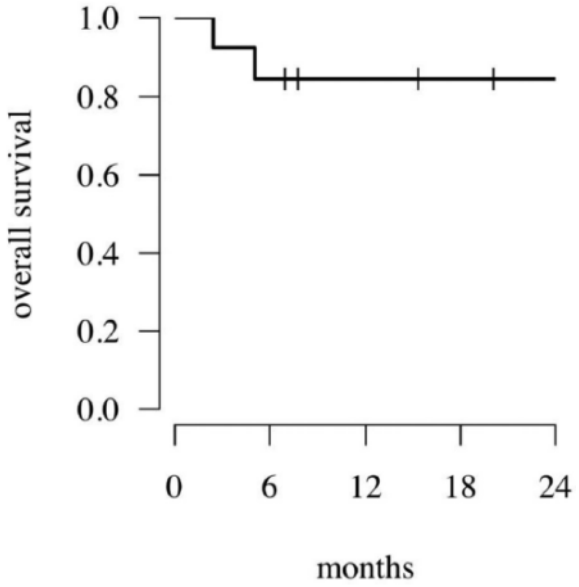
Biology of Blood and Marrow Transplantation

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]



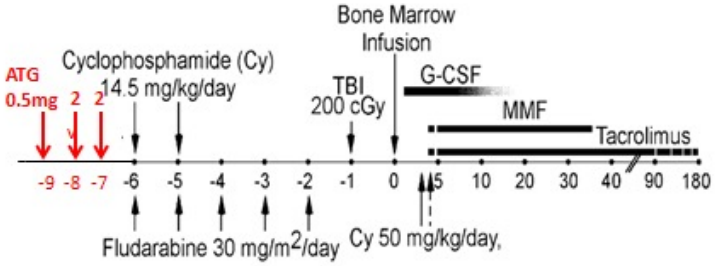
13 patients; all pts engrafted
2 died infections
11 surviving

SAA; GITMO 2020-2022

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

Age : 40 (19-70)

MUD (8/8) n=16
mmUD (7/8) n=6
SIB n=1
APLO n=2



ATG-FLU-CY-TBI200 / PTCY CsA MMF; DZ Baltimore (n=25)

BM n=17 (%)
PB n=8 (%)

Engr PMN day 19 (16-27)
Engr Plt day 22 (13-38

4 early deaths septic thromb day+10
cardiac failure day+30
infection day+34
infection day +84

Donor Chimerism day+50 100% full donor

SAA; GITMO 2020-2022

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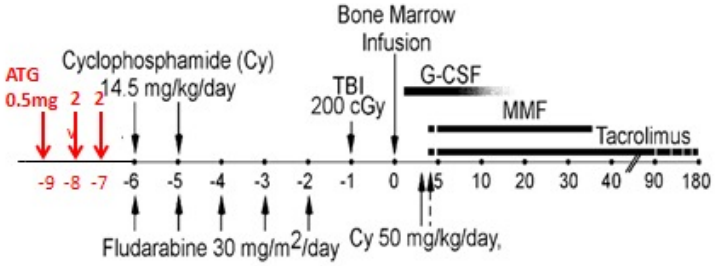

ATG-FLU-CY-TBI200 / PTCY CsA MMF; DZ Baltimore (n=25)

Acute GvHD grade I n=2
grade II n=1

Chronic GvHD minimal n=3

CE n.23 born 1953
ATG CSA 2022 NR Tx dependent
MUD 8/8 male/male 0+/A+ PB 10x10^8
Day +180: off IS, no GvHD;
Hb 13, WBC 5.0 Plt 180

SAA; GITMO 2020-2023

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Alessandria, Bolzano
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Age : 40 (19-70)

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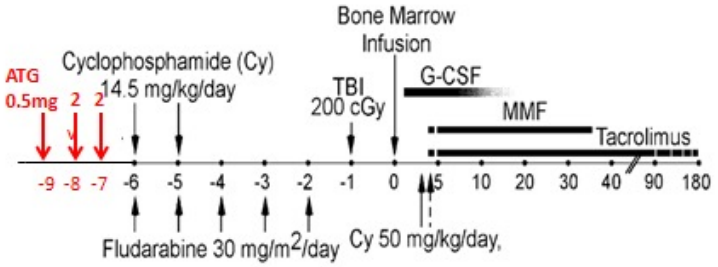
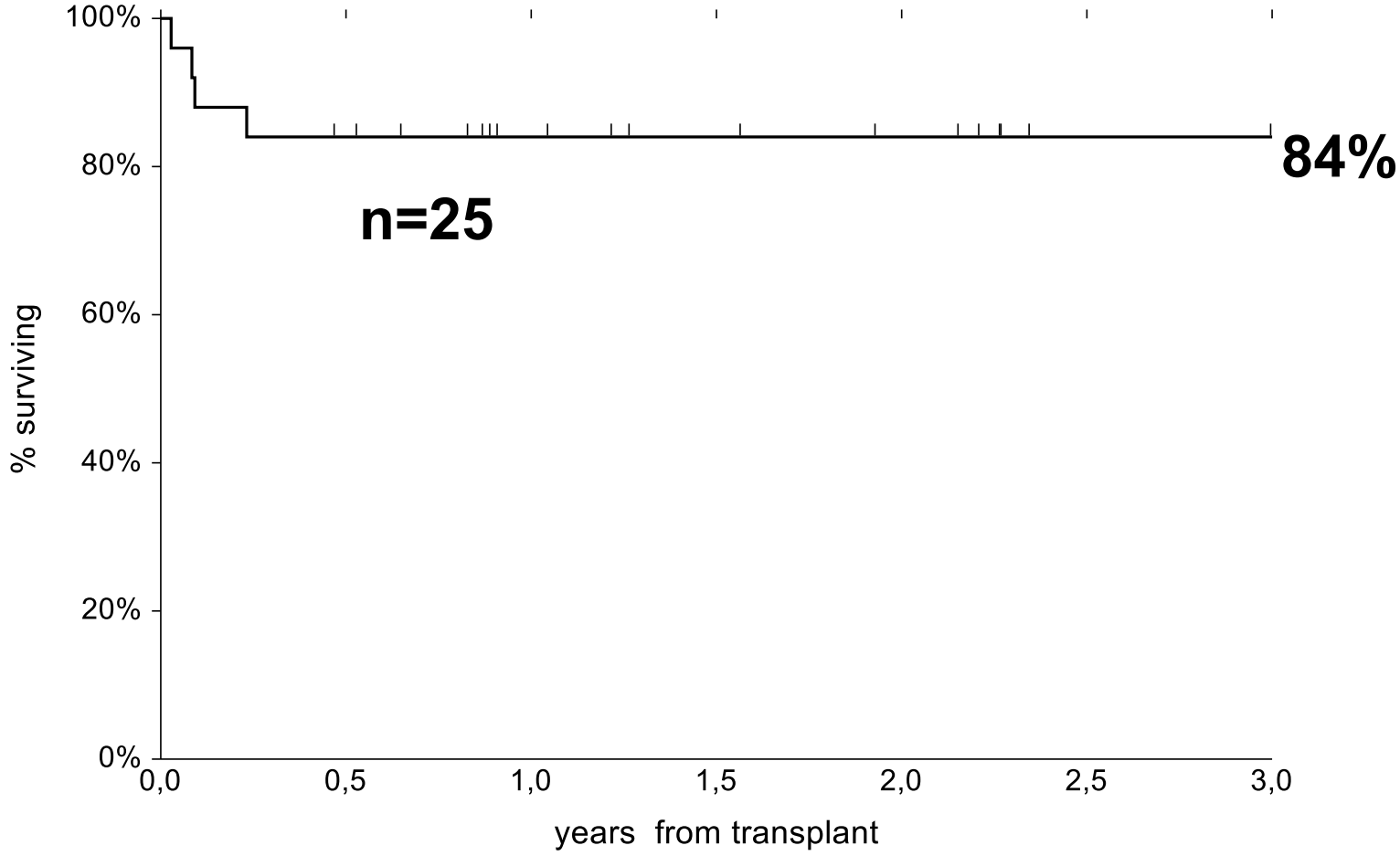
SIB n=2
APLO n=3



ATG-FLU-CY-TBI200 / PTCY CsA MMF; DZ Baltimore protoco

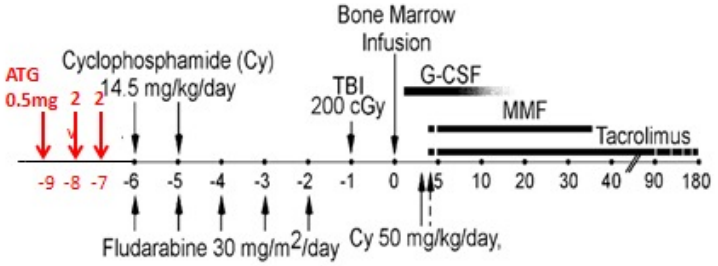


SAA; GITMO 2020-2023

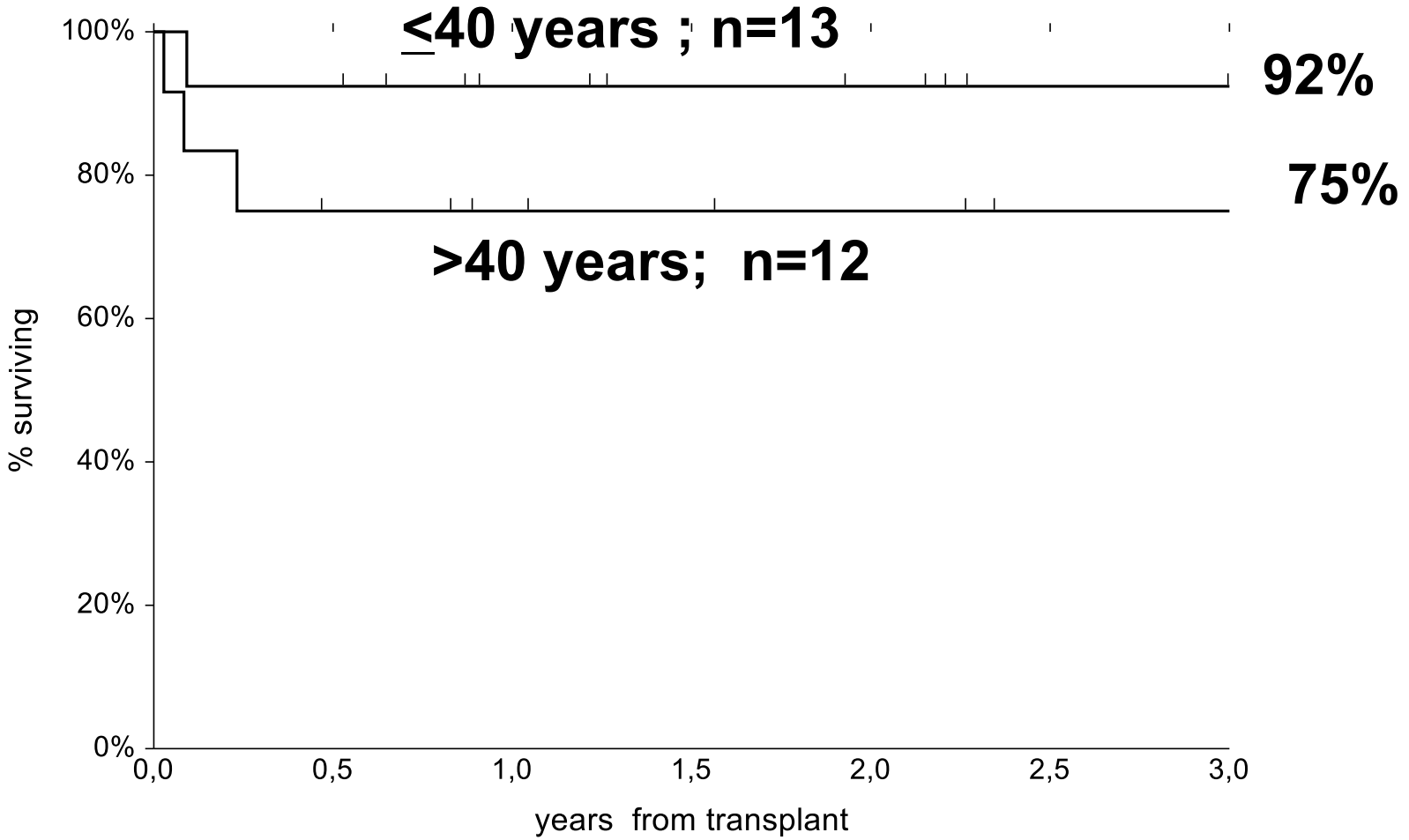
Gemelli, Cuneo, Udine,Palermo
Alessandria, Bolzano
Torino, Verona,Perugia, Milano

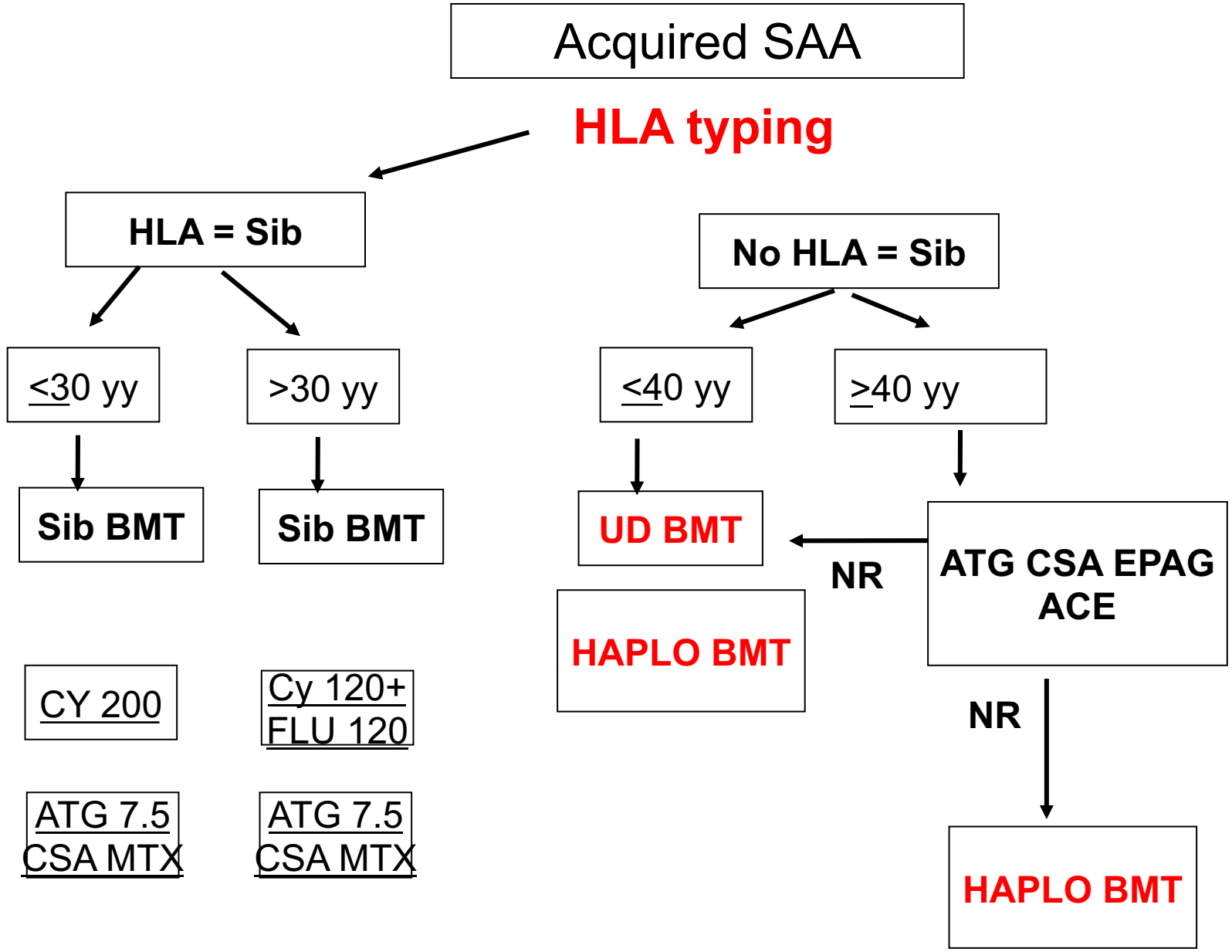
Age : 40 (19-70)

MUD (8/8) n=11
mmUD (7/8) n=8
SIB n=1
APLO n=2



ATG-FLU-CY-TBI200 / PTCY CsA MMF; DZ Baltimore (n=25)




Acquired SAA
HLA typing
HLA = Sib
No HLA = Sib
≤30 yy
>30 yy
≤40 yy
≥40 yy
Sib BMT
Sib BMT
UD BMT
ATG CSA EPAG ACE
NR
HAPLO BMT
CY 200
Cy 120+ FLU 120
NR
ATG 7.5 CSA MTX
ATG 7.5 CSA MTX
HAPLO BMT

TRANSPLANTS IN SAA 2023

≤40 years , with HLA=SIB → MSD BMT

≤40 years , no HLA=SIB →UD BMT /HAPLO?

> 40 years → ACE → NR → UD or HAPLO BMT

Baltimore DZ being tested in UD and older patients

TBI 200

TREATMENT of SAA 2028???

If we overcome the issue of AGE and donor, then Indications for HSCT will be like we have today for MDS

≤75 years allogeneic HSC transplantation
the donor is not an issue

ACE for pts who are ineligible for BMT

- SAA WP
- Regis Peffault de la Toutr and Antonio Risitano
- Carlo Dufour, Anna Locasciulli, Franco Locatelli, Christina Peters, Rosi Oneto, Jacob Passweg,
- Maria Teresa Van Lint, Gérard Socié, Andre Tichelli , Judith Marsh, Hubert Schrezenmeier, Carlos Vallejo

- N Young, P Scheinberg, J Deeg, S Nakao , S Kojima ,
- Xiaofan Zhu, Xiaojuan Chen, Surapol Issaragrisil, Suporn Chuncharunee , Dae Chul Jeong , Yizhou Zheng

Excellence in science
EBMT
European Group for Blood and Marrow Transplantation