Changing paradigm in GvHD prophylaxis and leukemia relapse

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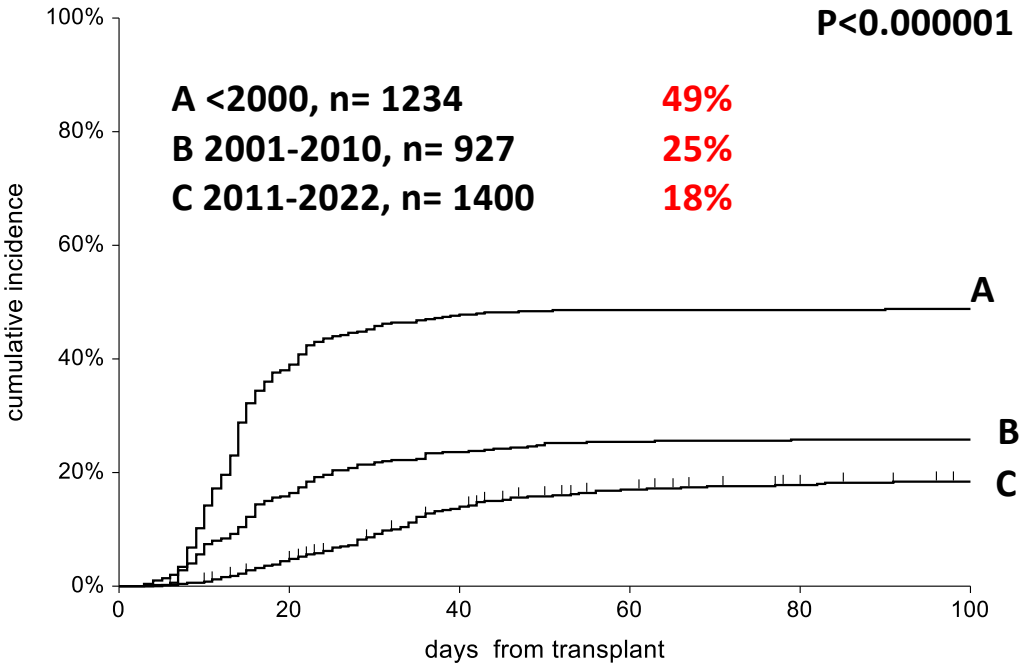
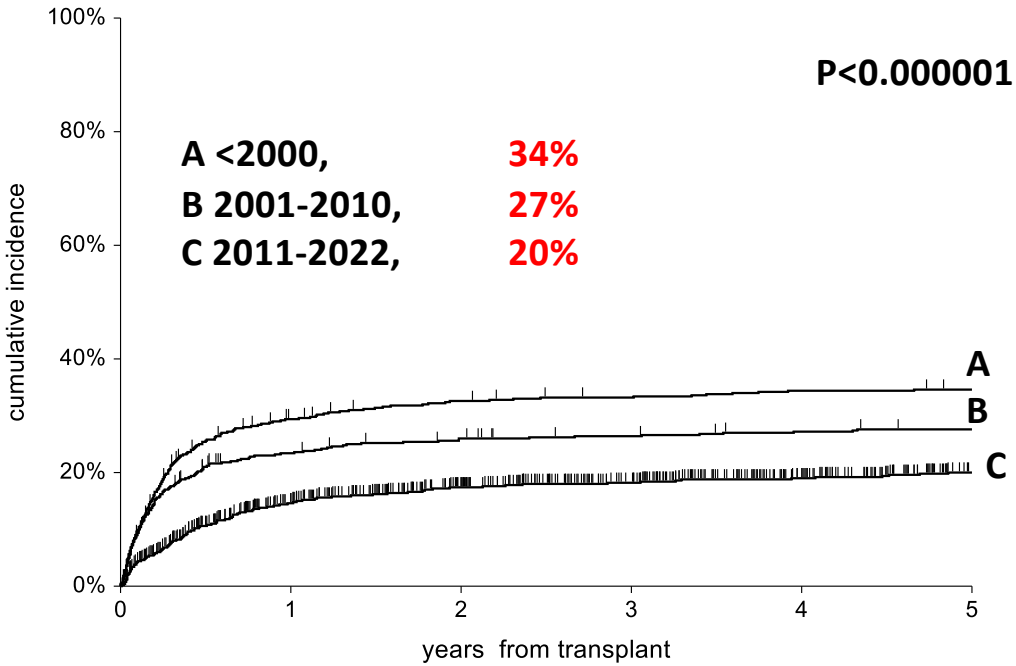
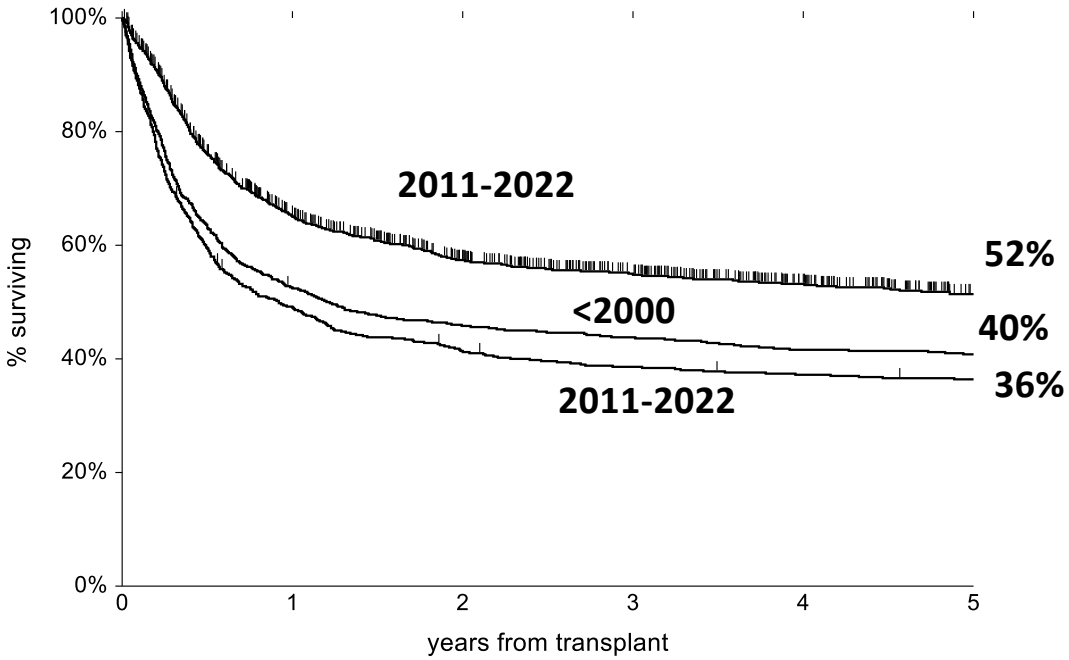
acute GvHD grade II-IV (n=3561)



TRM

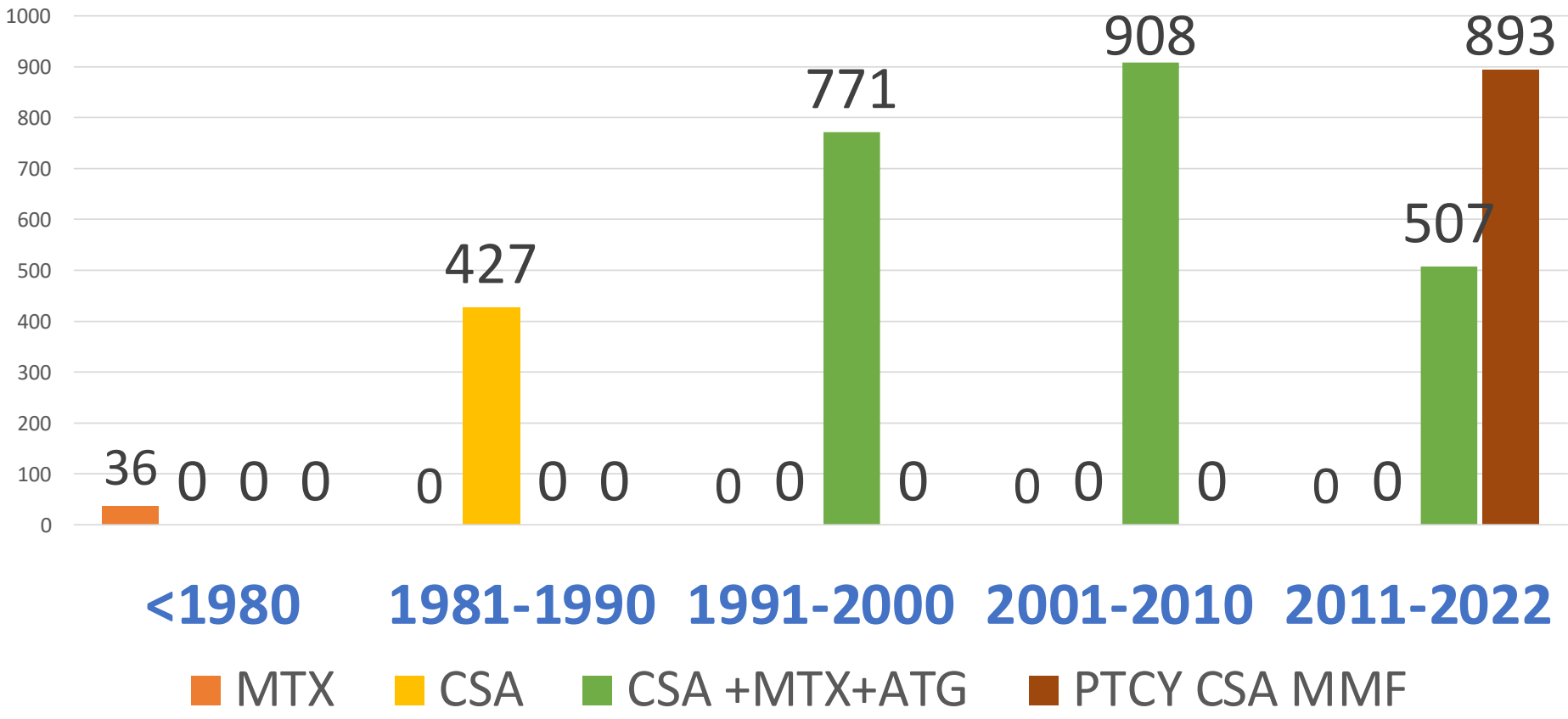


Disease Free Survival



relapse

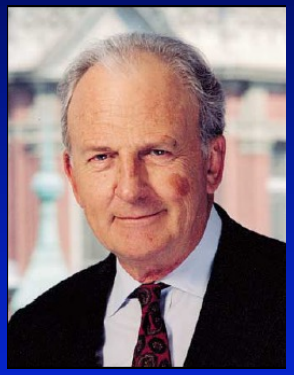
GvHD prophylaxis 3561 patients (GESM-GEM)



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)

HLA-Haploidentical Bone Mar… Transplantation for Hematologic Malignancies U… onmyeloablative Conditioning and High-Do… ansplantation Cyclophosphamide

Biol Blood Marrow … …008

Leo Luznik,[1]* Paul V. O'Donnell,… …en,[1] M. Susan Leffell,[1]
Marianna Zahurak,[1] Ted A. Go… …[1] Richard F. Ambinder,[1]
Carol Ann Huff,[1] William Ma… …[1] Jonathan D. Powell,[1]
Elizabeth Harrington,[2] Sand… …ky,[1] Brenda M. Sandmaier,[2,3]
Rainer F. Storb,[2,3] Richard…

Rejected by NEJM, Lancet, JCO, Blood

Accepted by BBMT

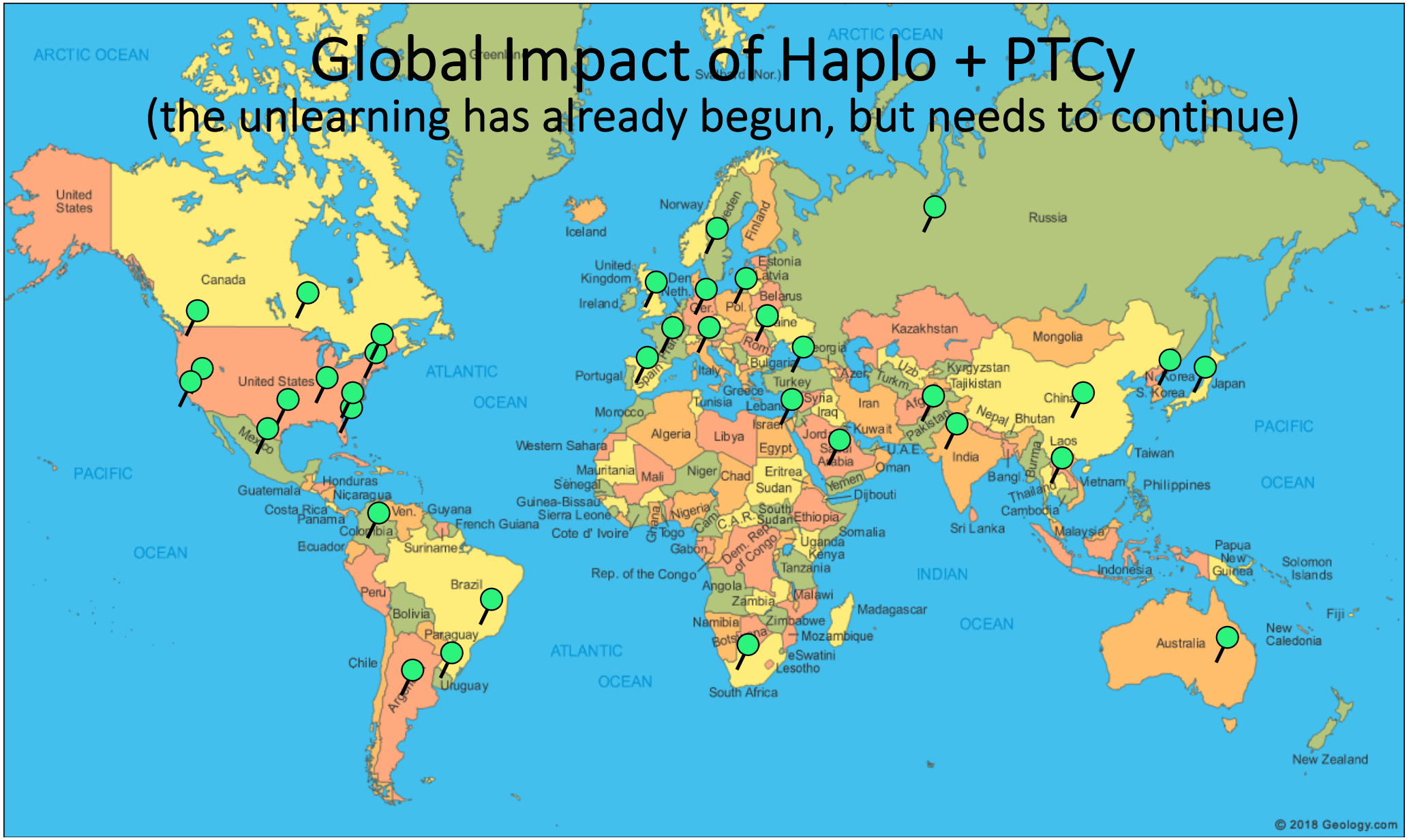
Transplant paper with highest numer of citations 2008-2018 !

Practice changing study !

- Cyc… …ve T cells maximally sensitive to Cy… …er BMT
  - HSCs … memory lymphs resistant due to high ALDH expression.

Global Impact of Haplo + PTCy

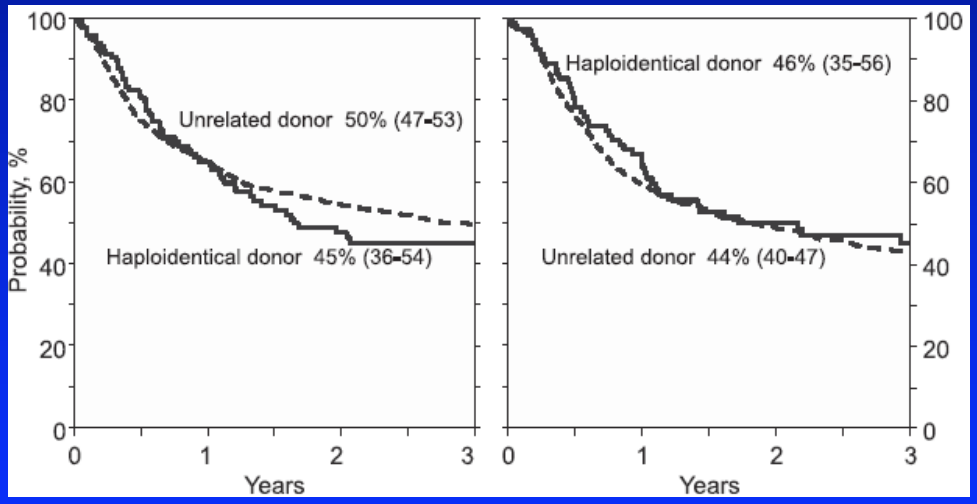
(the unlearning has already begun, but needs to continue)



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

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)	Transplant conditioning regimen intensity: 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

HAPLO and PTCY
comparable outcome vs
HLA matched and CSA/MTX/±ATG

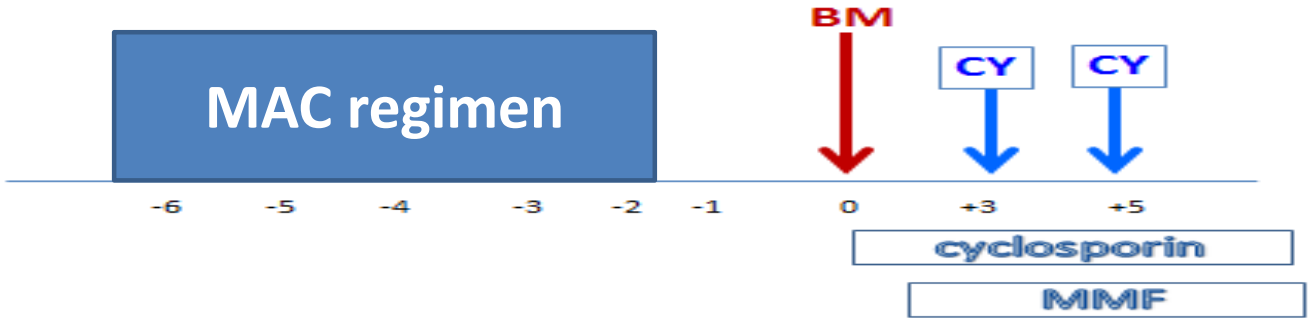
HAPLO + PTCY = A REVOLUTION

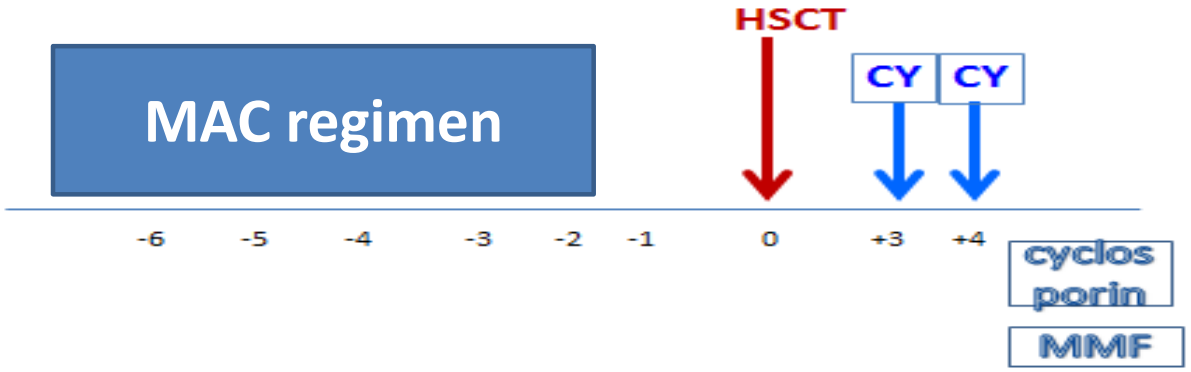
Thank you BALTIMORE-

particularly in countries with low income

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]

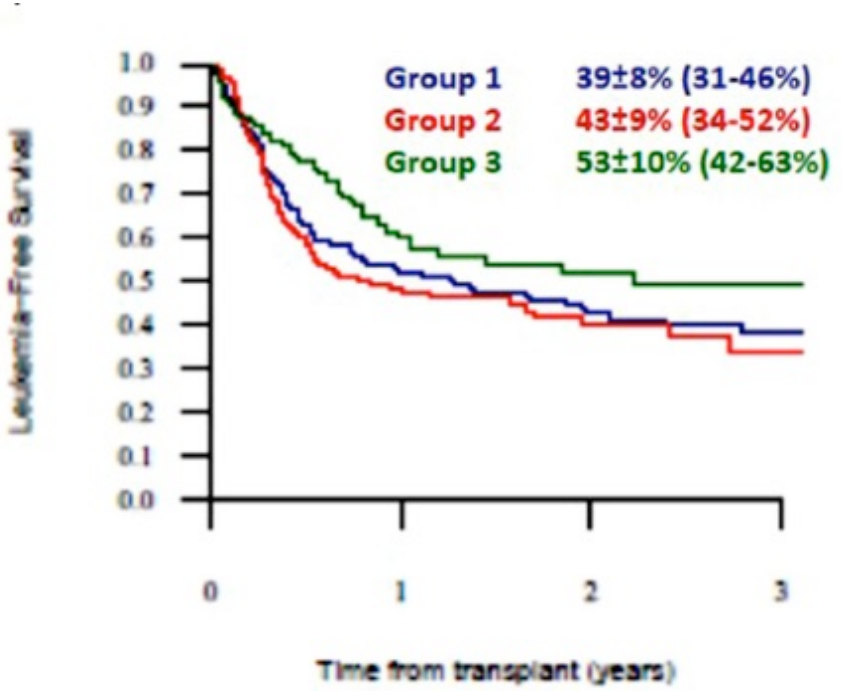
ACUTE LEUKEMIA

	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)

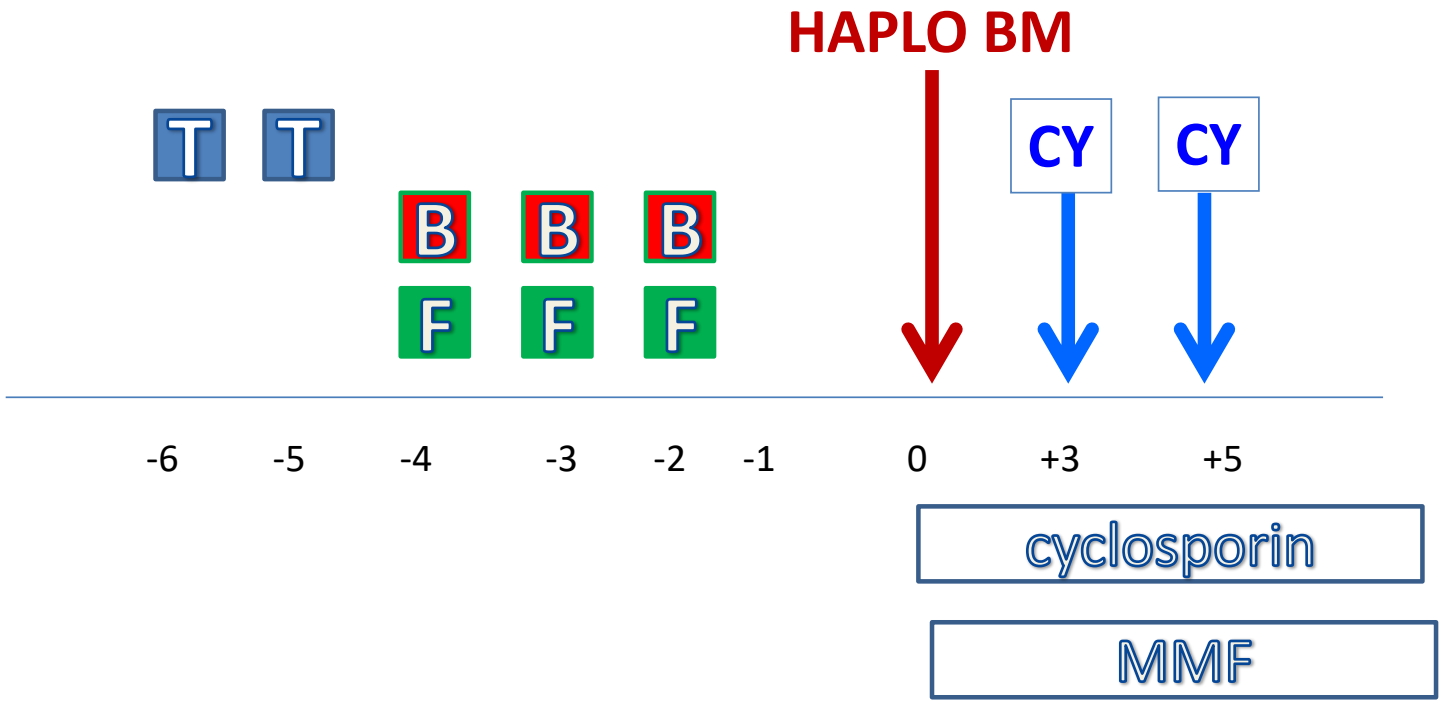
Not inferior to PTCY +3+4 (BM or PB)

Perhaps less relapse?

Long term outcome AML remission?

AML CR1/ CR2

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



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

AML

Age 44 (17-64)

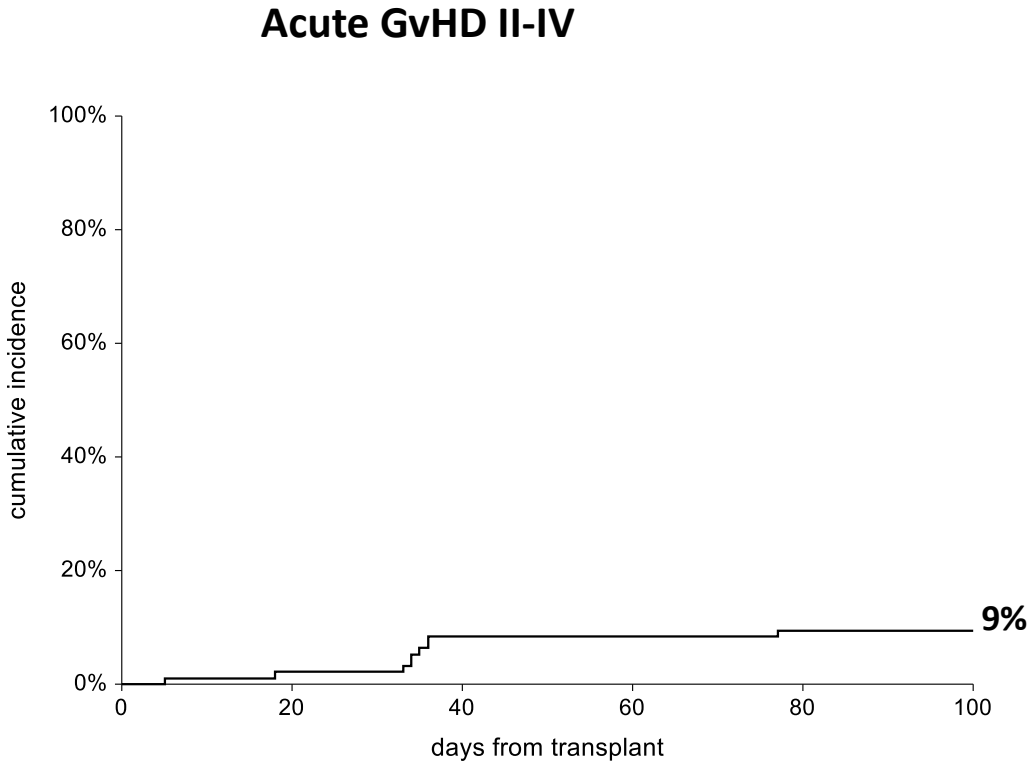
Donor age 34 (14-67)

CR1 78 CR2 20

Adverse risk factors (CR1) Pr Ind failure

Primary induction failure	18	MRD+	12
AML MRC	12	BPDCN	2
Hyperleukocytosis	17	t(6;9)	1
Flt3 ITD+	15	del 7	2
t(9;22)	1	del 5	1
		complex cytogenetics	6

I


Acute GvHD II-IV
100%
80%
60%
40%
20%
0%
cumulative incidence
0
20
40
60
80
100
days from transplant
9%

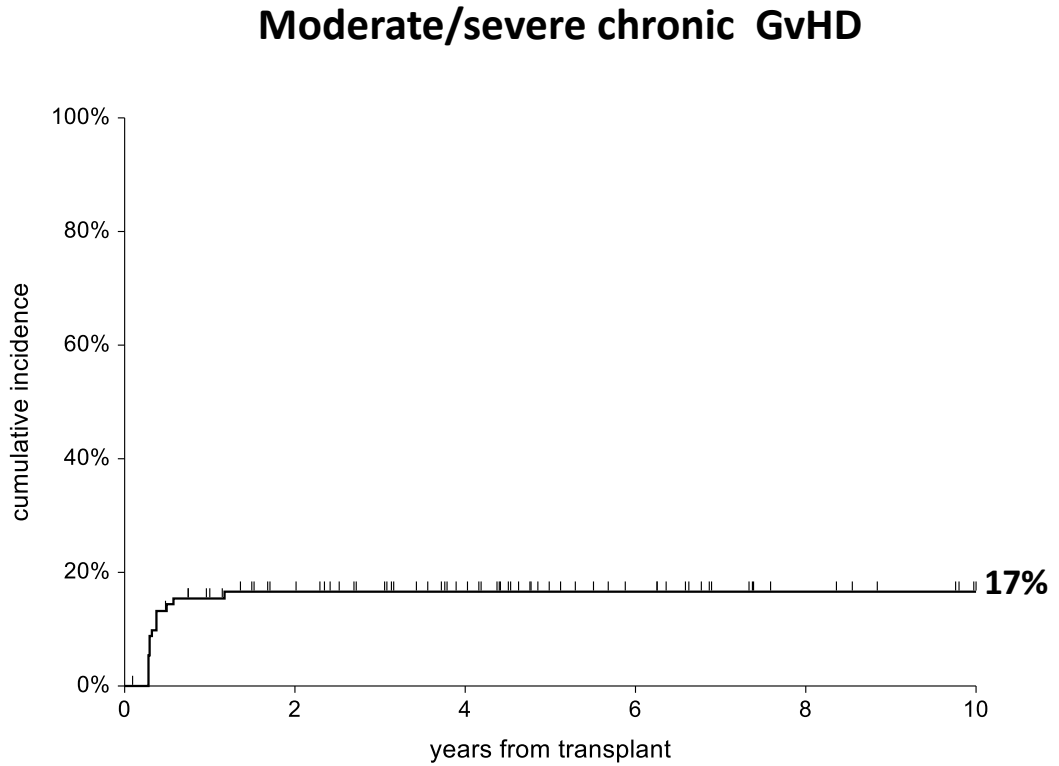
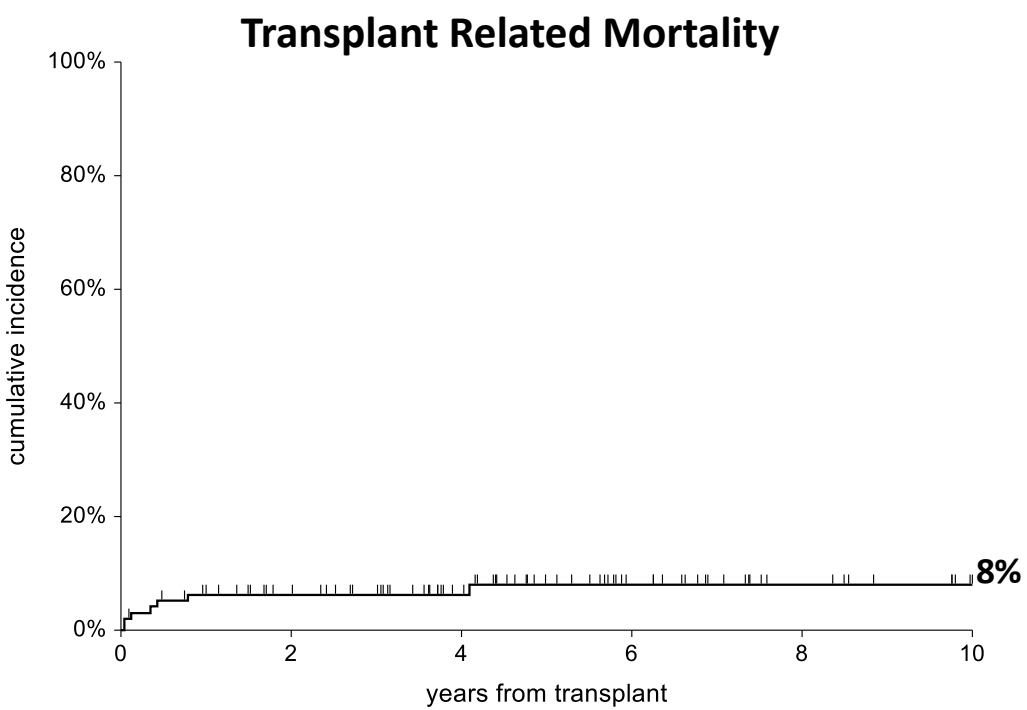

Moderate/severe chronic GvHD
100%
80%
60%
40%
20%
0%
cumulative incidence
0
2
4
6
8
10
years from transplant
17%

Fig.1


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

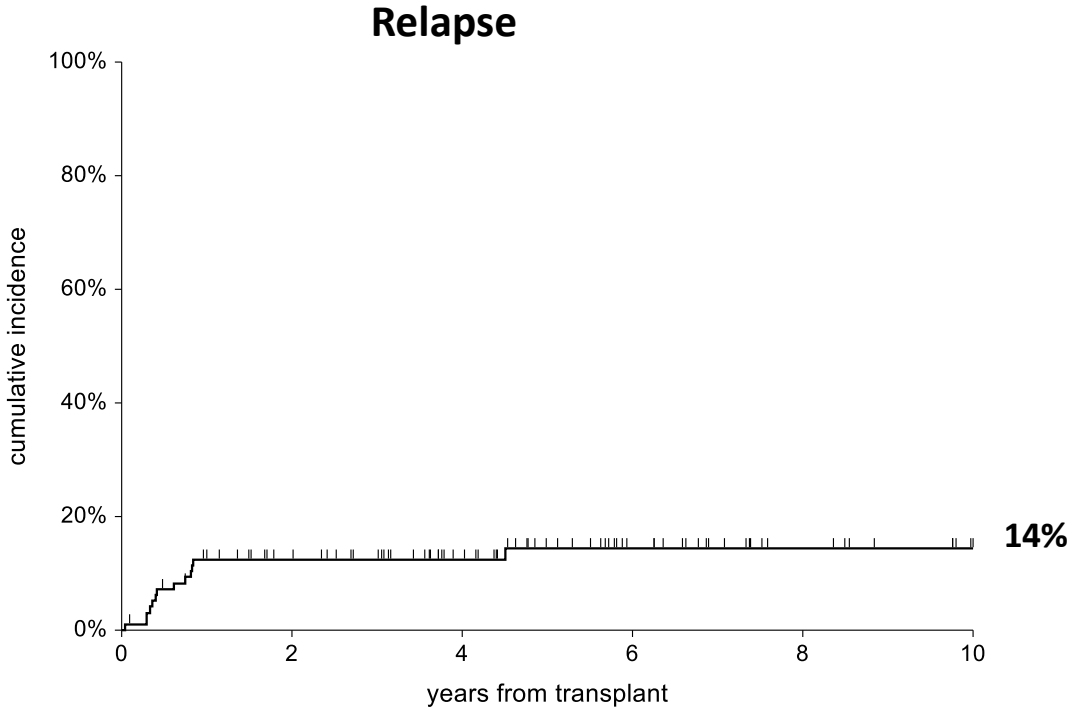

Relapse
100%
80%
60%
40%
20%
0%
cumulative incidence
0
2
4
6
8
10
years from transplant
14%

Fig.2

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

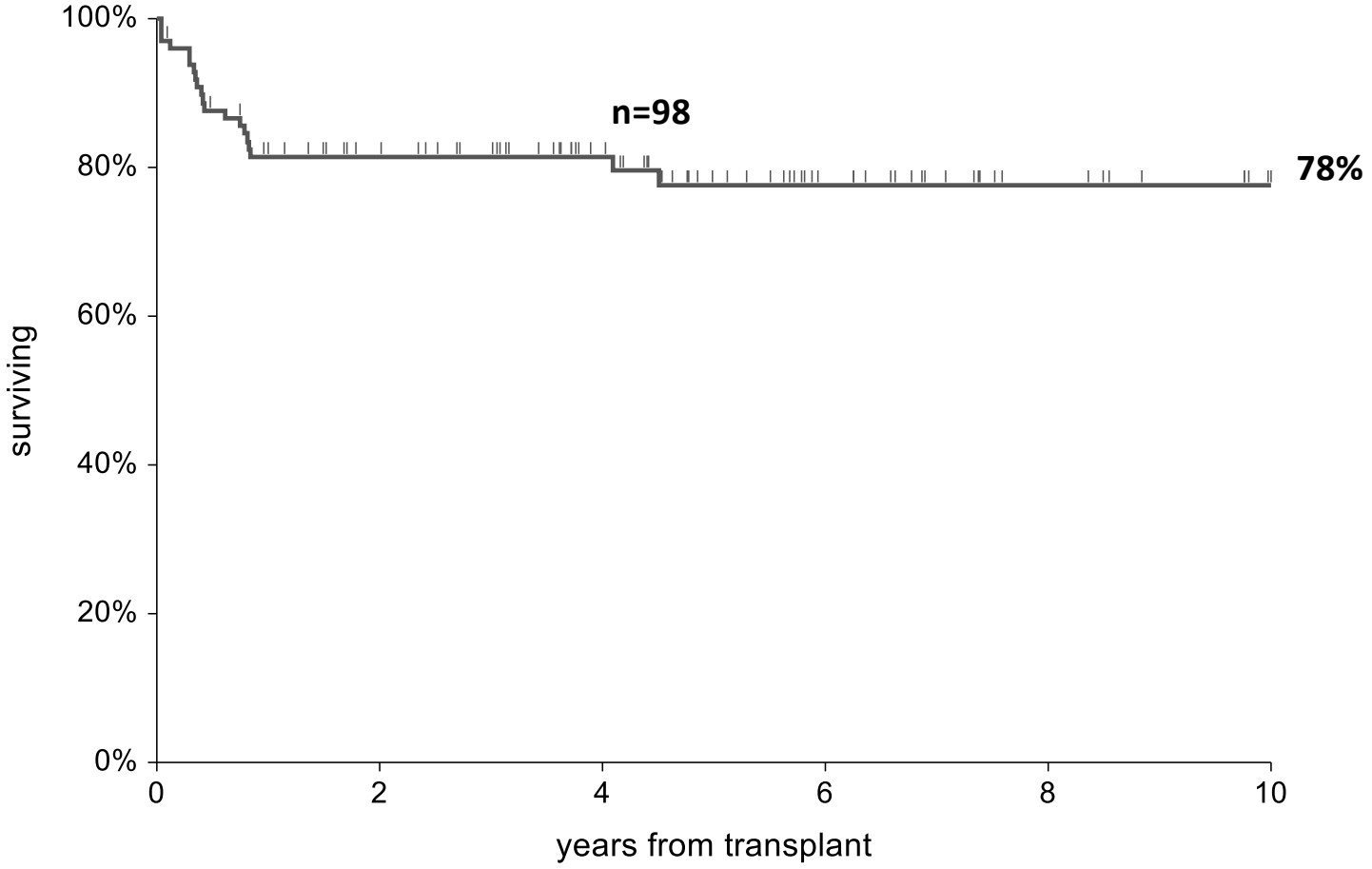
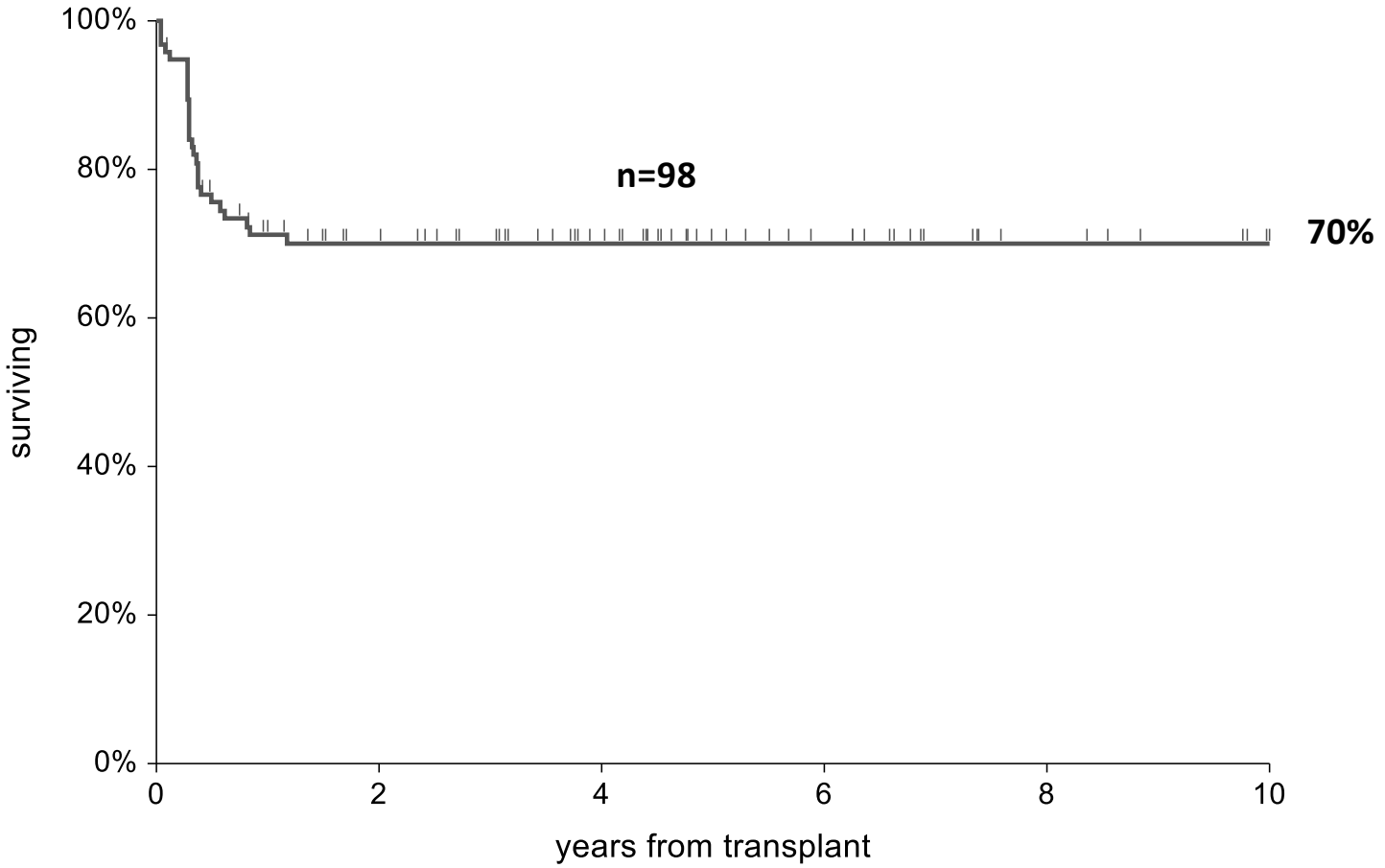


Fig.3

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



AML CR1+CR2: very encouraging

 # thiotepa busulfan fludarabine

 # HAPLO BM

 # PTCY +3+5 CSA day 0, MMF day 1

QUESTIONS:

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

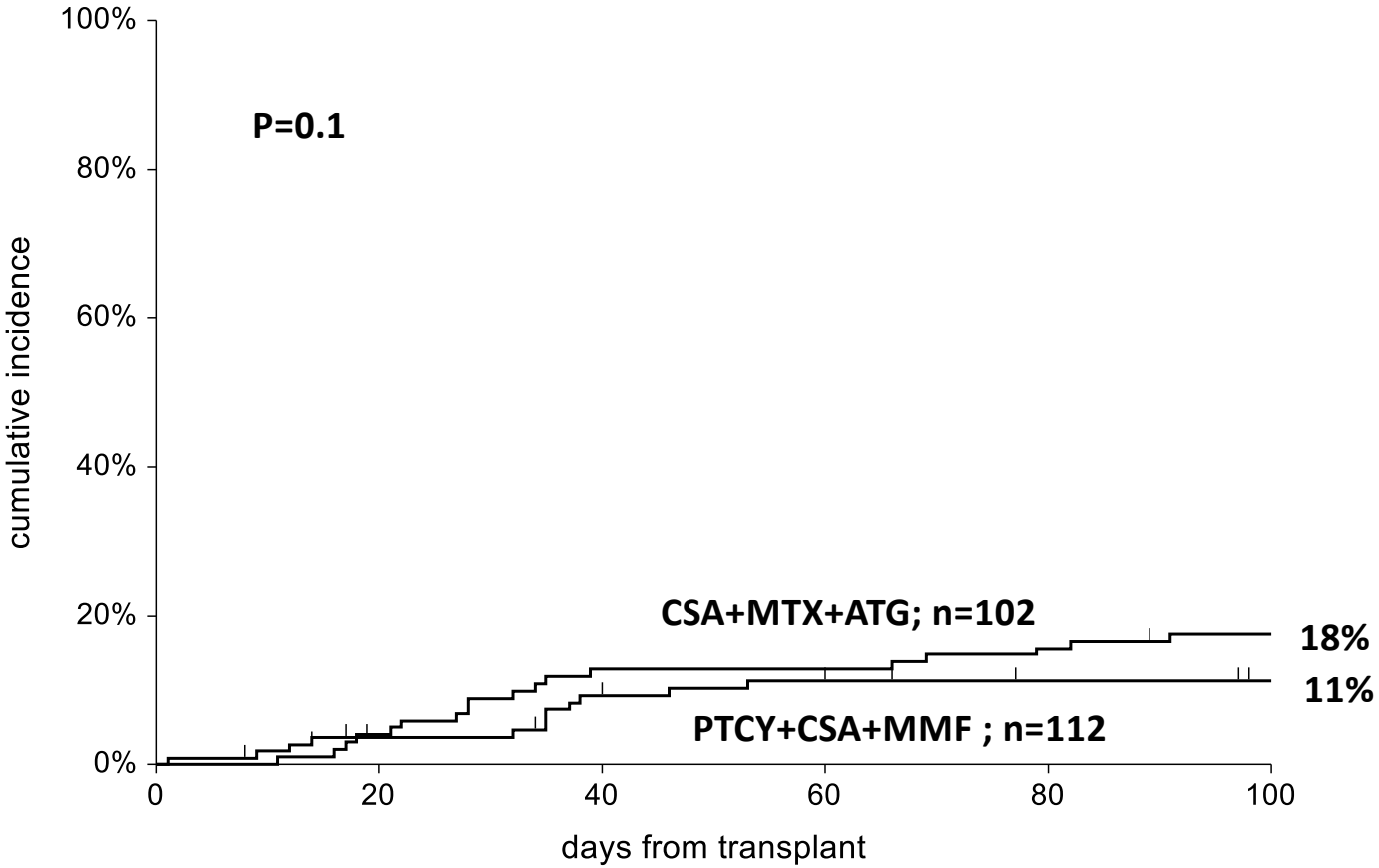
+3+5 with HAPLO BM

 # if PTCY is so good in HAPLO, why not use it in HLA identical Tx?

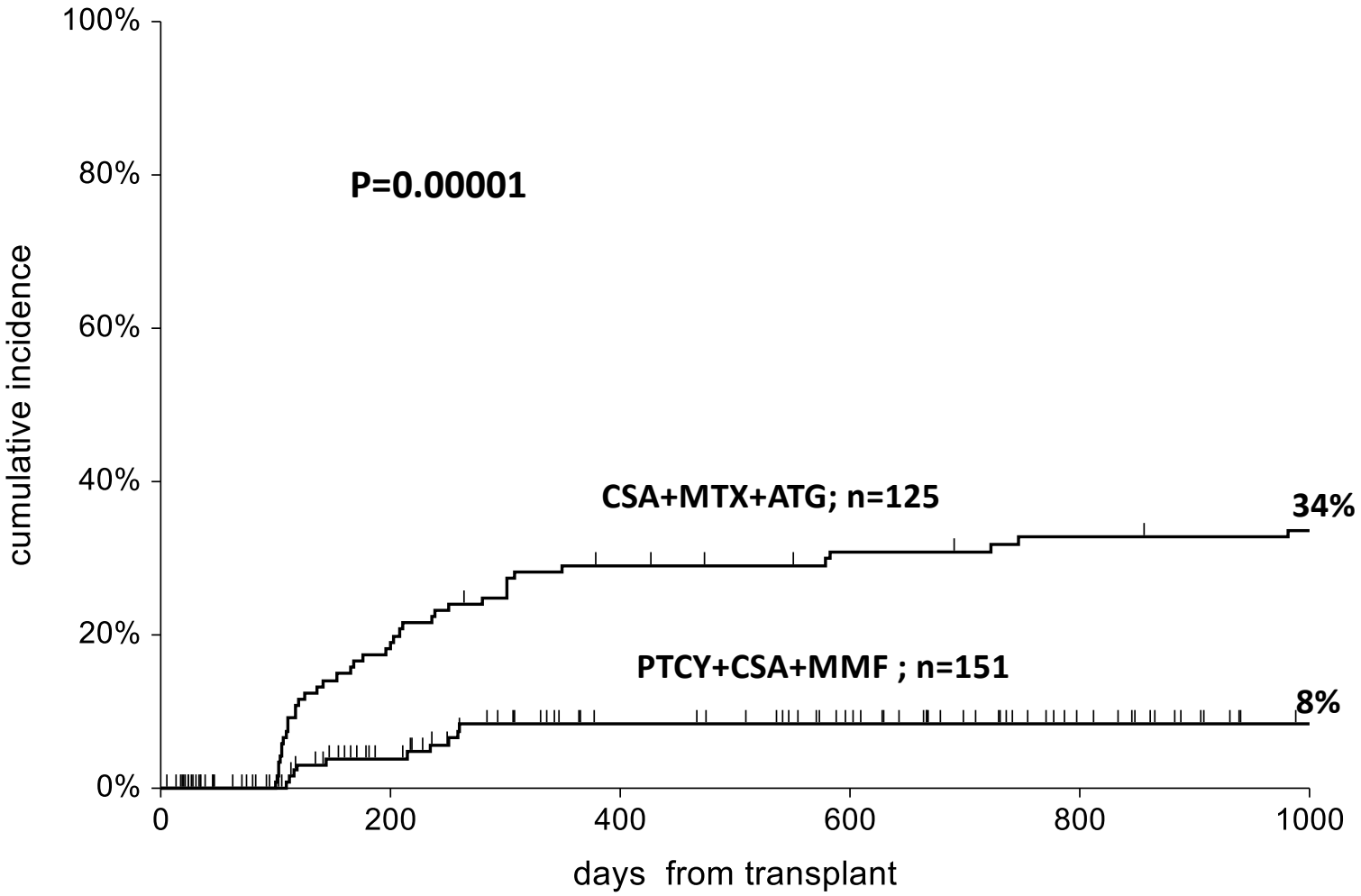
HLA = transplants 2015-2022 (Gemelli)

GvHD proph	CSA+MTX+ATG	PTCY+CSA+MMF	P
n.Patiens	125	151	
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

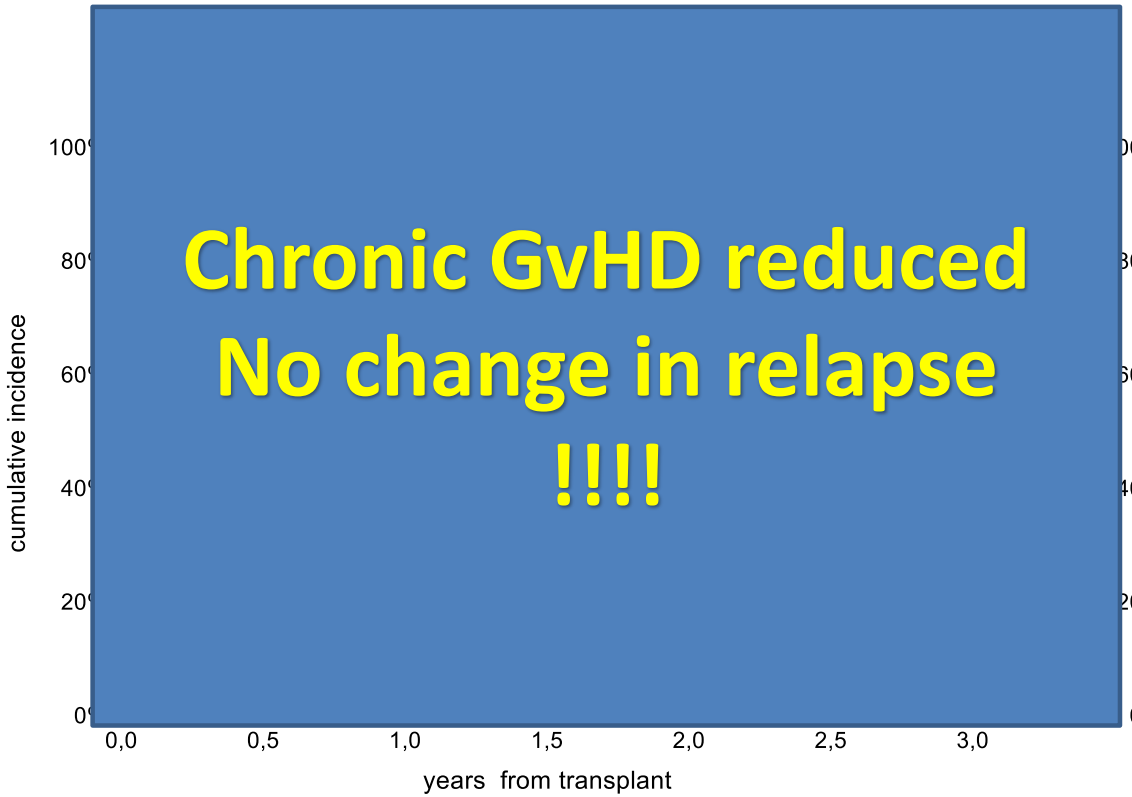
CI of grade II-IV acute GvHD : HLA matched grafts

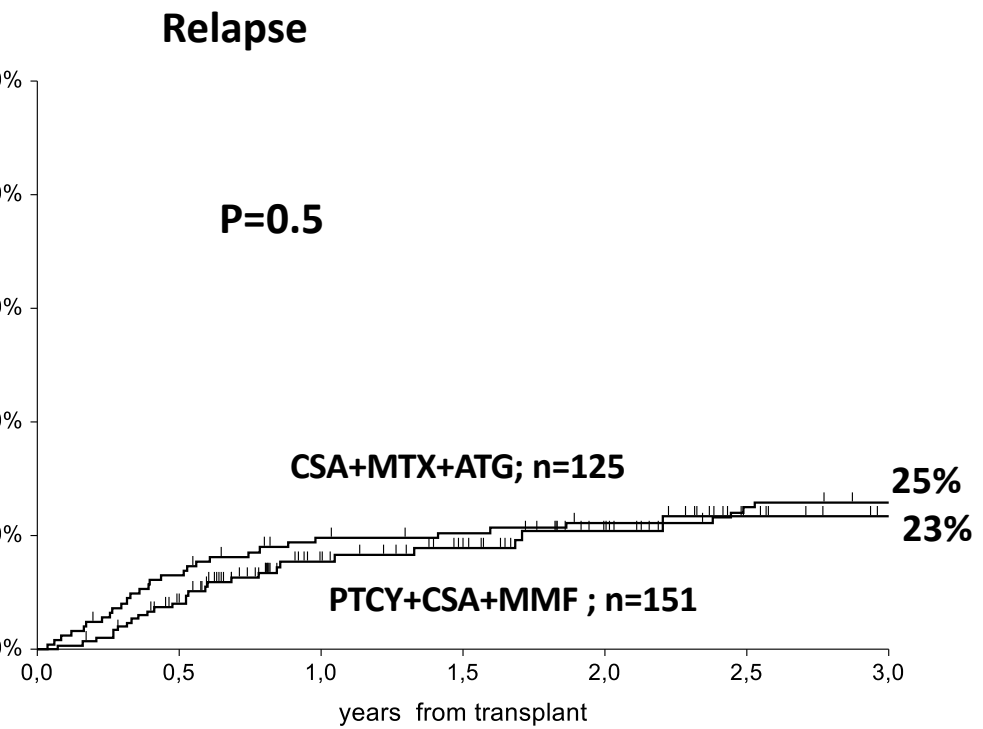


CI of moderate/severe chronic GvHD : HLA matched grafts

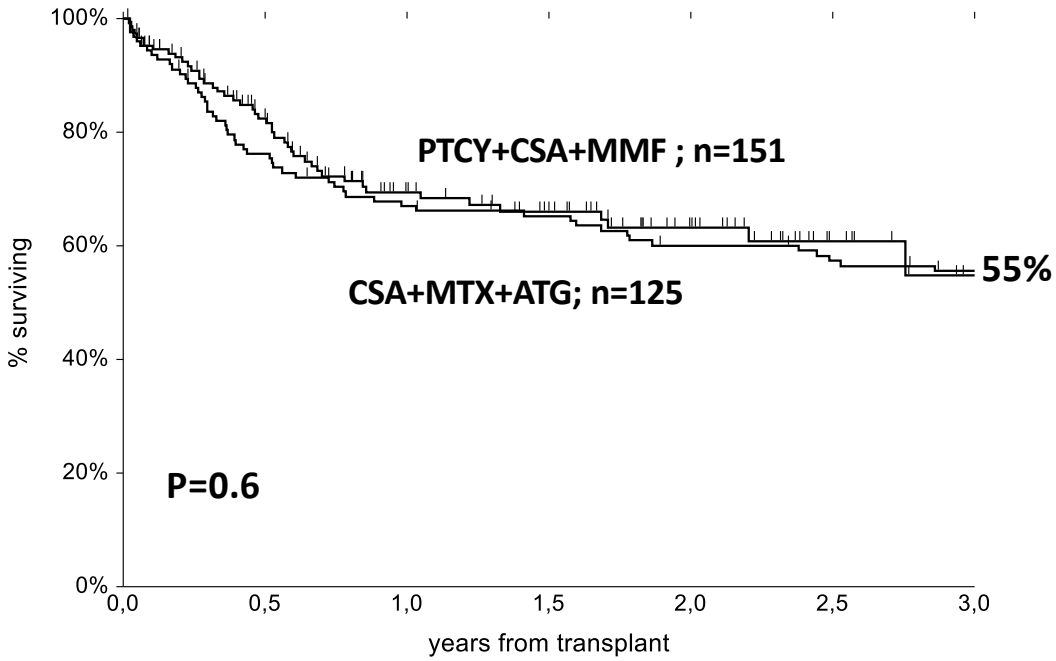


Chronic GvHD reduced
No change in relapse
!!!!

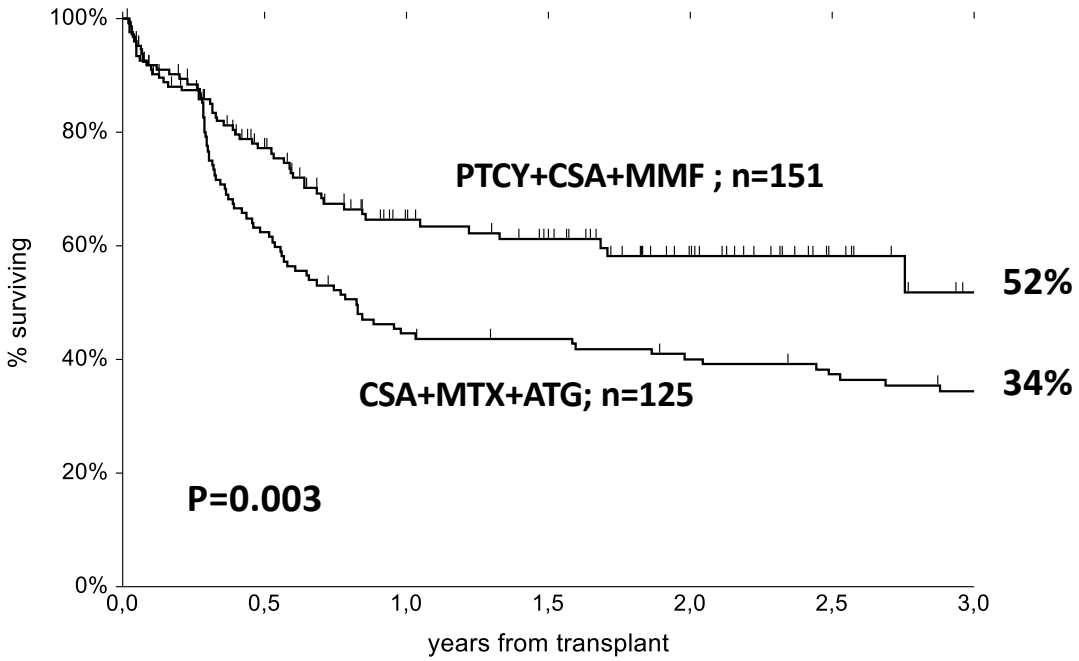




Disease free survival



Graft and relapse free survival



QUESTIONS:

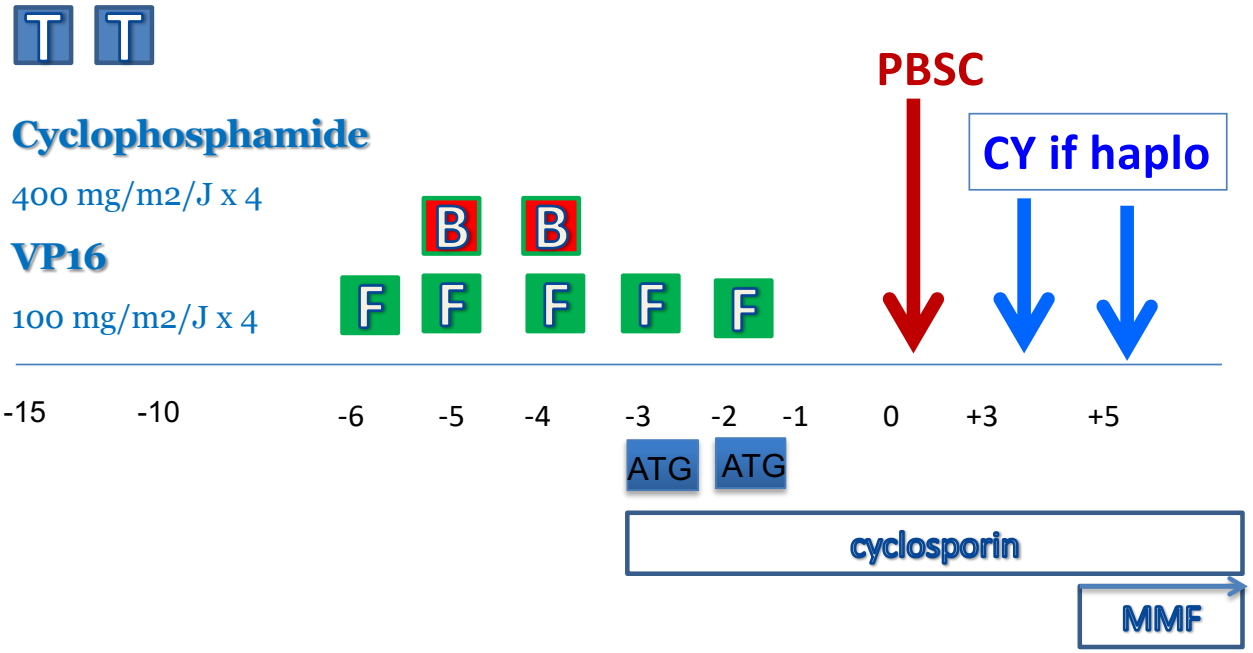
 # Can TIMING of PTCY +3+4 be changed =yes

 # 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

QUESTIONS:

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

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

less cGvHD, improved GRFS

 # can PTCY be combined with ATG =yes

MA condit + advanced leukemia

CONCLUSIONS:

 # we have reduced incidence of acute GvHD

 # we have reduced incidence of chronic GvHD

 # we have reduced transplant mortality (not enough)

 # DFS seems improved

 # RELAPSE ? Overall no change.

A combination of changes in conditioning regimens, donor type, GvHD prophylaxis , cell subtypes infused, targeted therapy (sorafenib) may have an impact on leukemia relapse

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