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GVHD prophylaxis in matched sibling donor transplant

The case for "post-cyclophosphamide

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TRANSPLANTATION

Comment on Kanakry et al, page 1389

How much immunosuppression do we need?

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GvHD prevention

Peri-transplant
- Immunosuppr. drugs
- Antiproliferative drugs
- Lymphodepletion

+

Post-transplant
- No IS
- Time restricted IS
- Longer IS

=

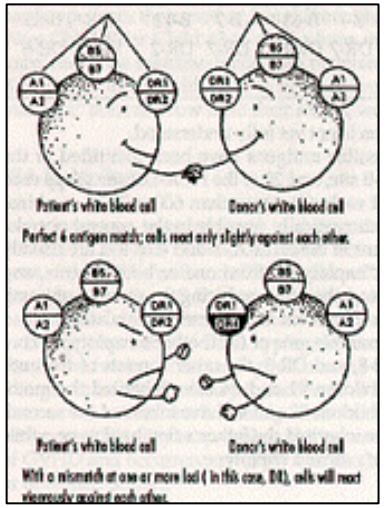
Total
(NRM, REL, OS)

CNI/mTOR
MTX/MMF
ATG / CD34
PTCY

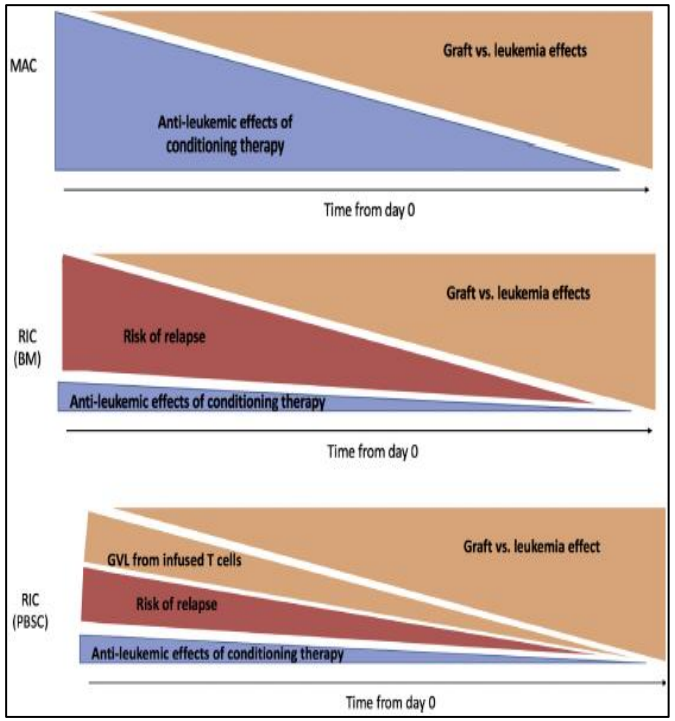
+

CNI

HLA-match

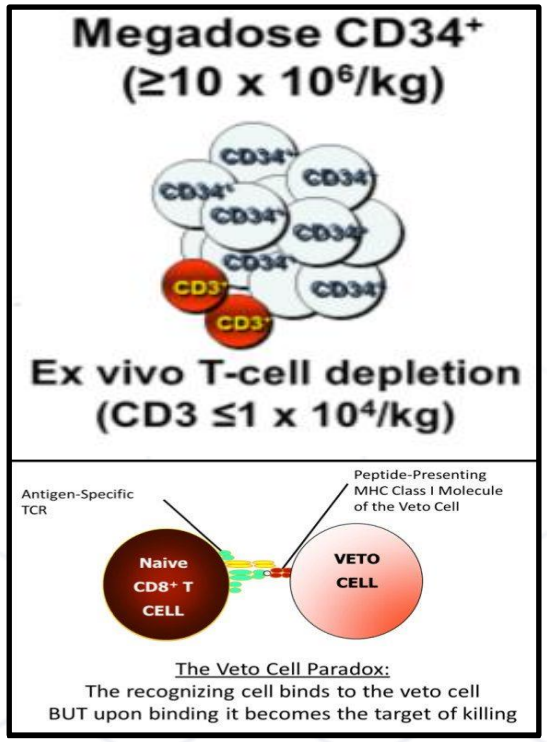


Graft, conditioning

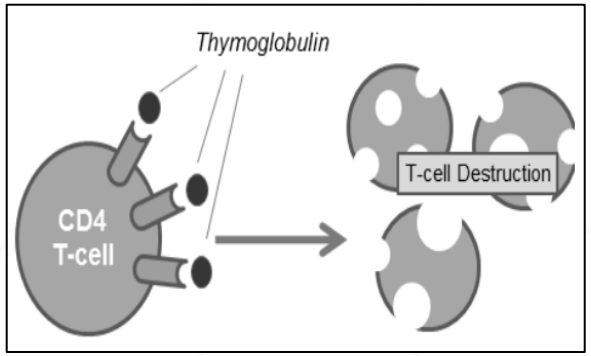


Transplant across HLA barriers: PTCY is the winner

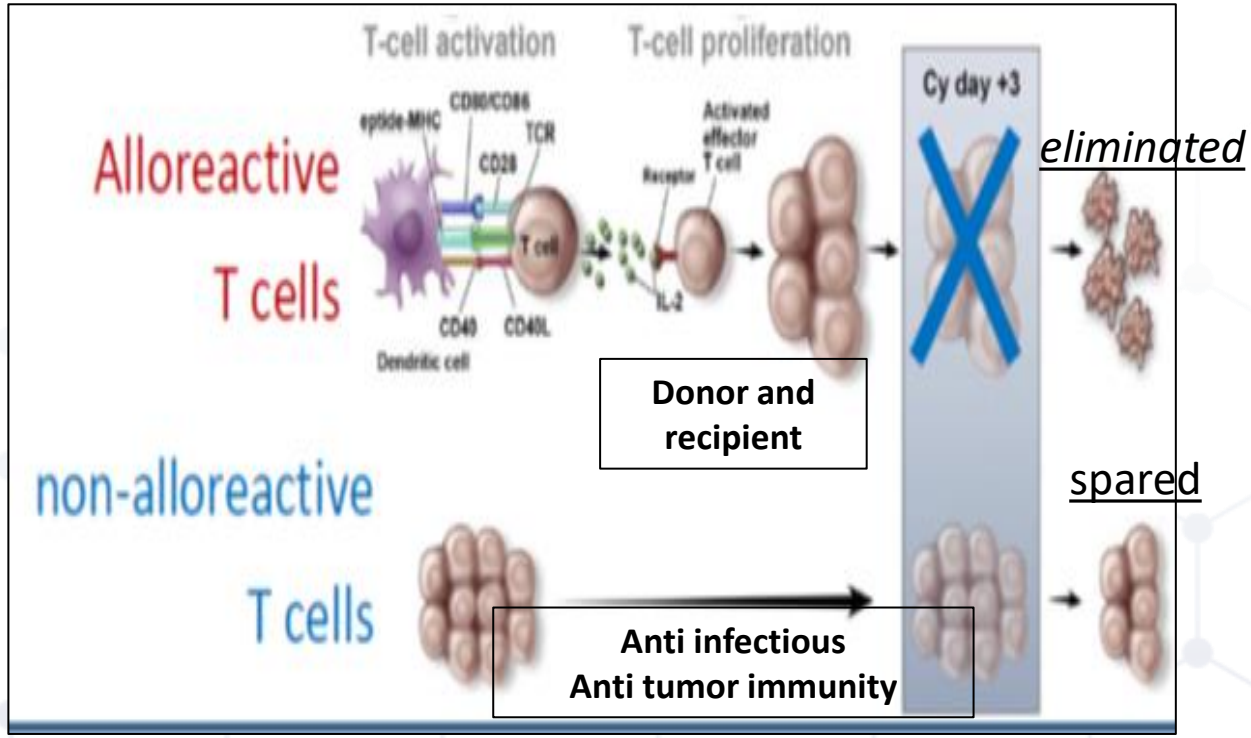
CD34 megadose:
Ex vivo TCD (graft)
+ veto suppression (host)



ATG: In vivo TCD
(graft and host)



Putative Mechanism of PTCy:
in vivo selective (clonal) TCD of alloreactive cells
(graft and host)



1. Aversa et al. JCO. 2005;23:3447-54, 2. Huang X jun, Beijing Protocol. 2004 Jun 18;36(3):229–33.3. 3. Luznik L. et al. BBMT 2008;14:1641-50

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PTCy has Markedly Changed the Field of GVHD prophylaxis

- Already a standard of care for HLA-haploidentical HCT (EU and USA)
- Low rates of severe acute and chronic GVHD and NRM
- Allows Haplo-related donors to be used about as safely as HLA-matched donors
- Enables even “haplo” - MMUD (4/8 to 7/8) transplant (better results as historical serological HLA class I matched UD HCT)

Ciurea et al. Blood. 2015, Ghosh et al. JCO. 2016, Gagelmann et al. JAMA Oncology. 2019; Kanakry CG et al. Blood. 2014, Kanakry CG et al. JCO. 2014, Kanakry CG et al. Blood. 2017, McCurdy et al Blood. 2015, Kanakry CG et al. Nat Rev Clin Oncol. 2016; Shaw BE et al. JCO 2021; 39;1971-82

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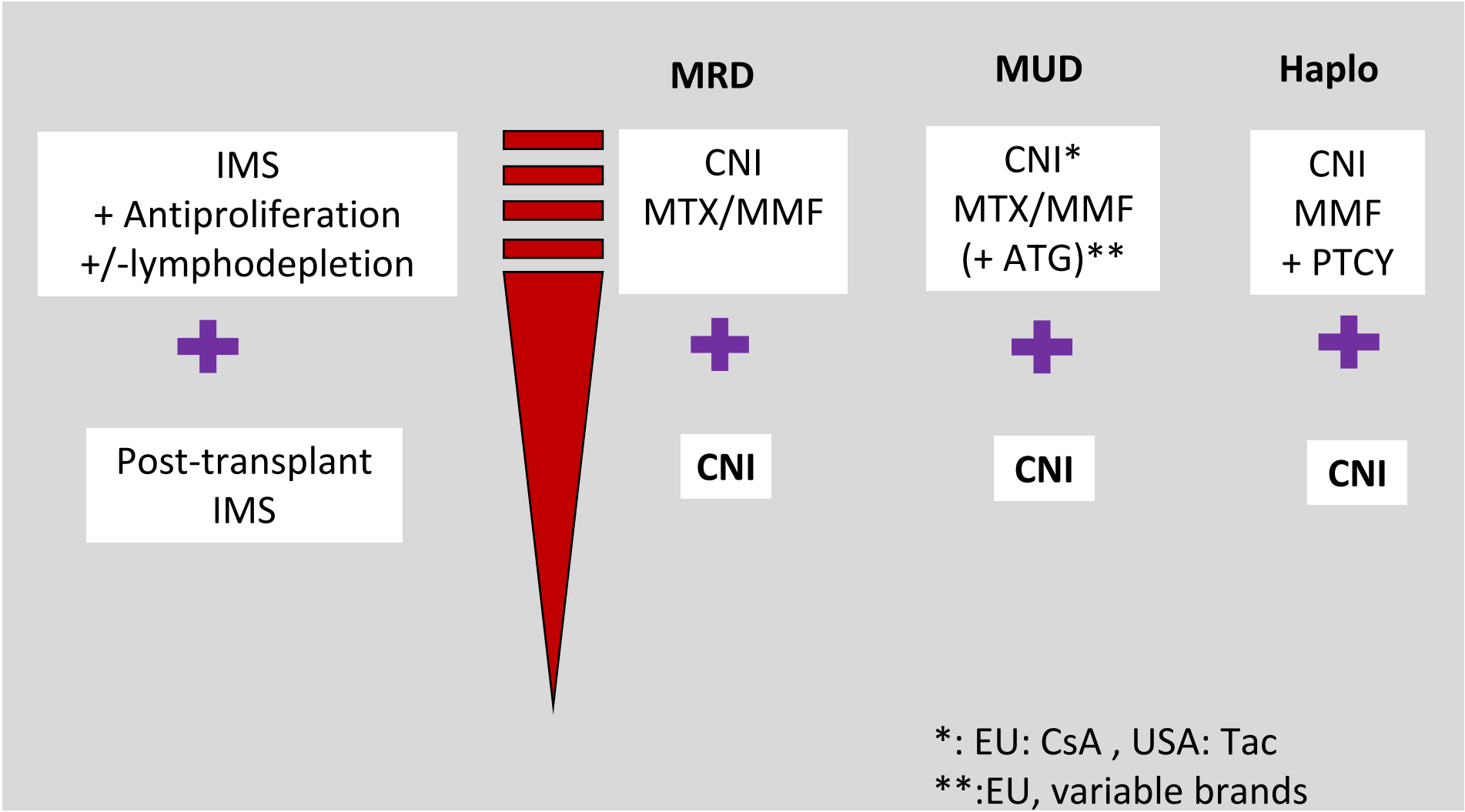
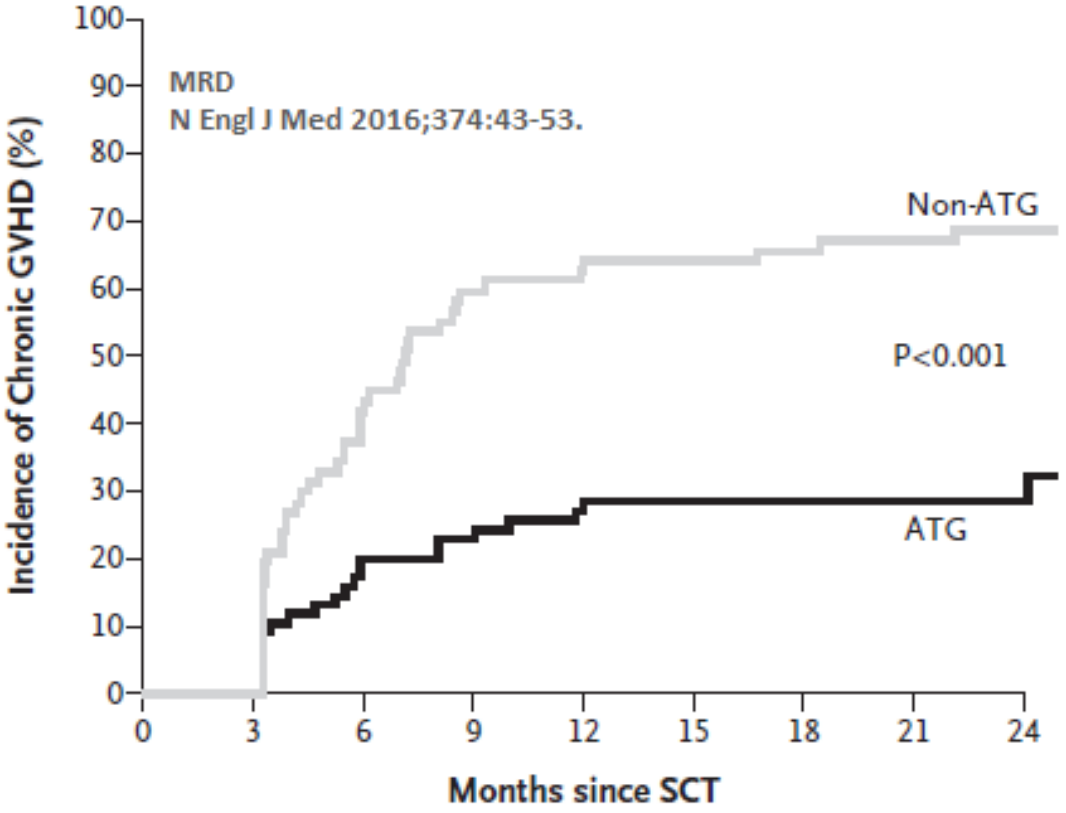
Standard (?) GvHD prophylaxis in 2023

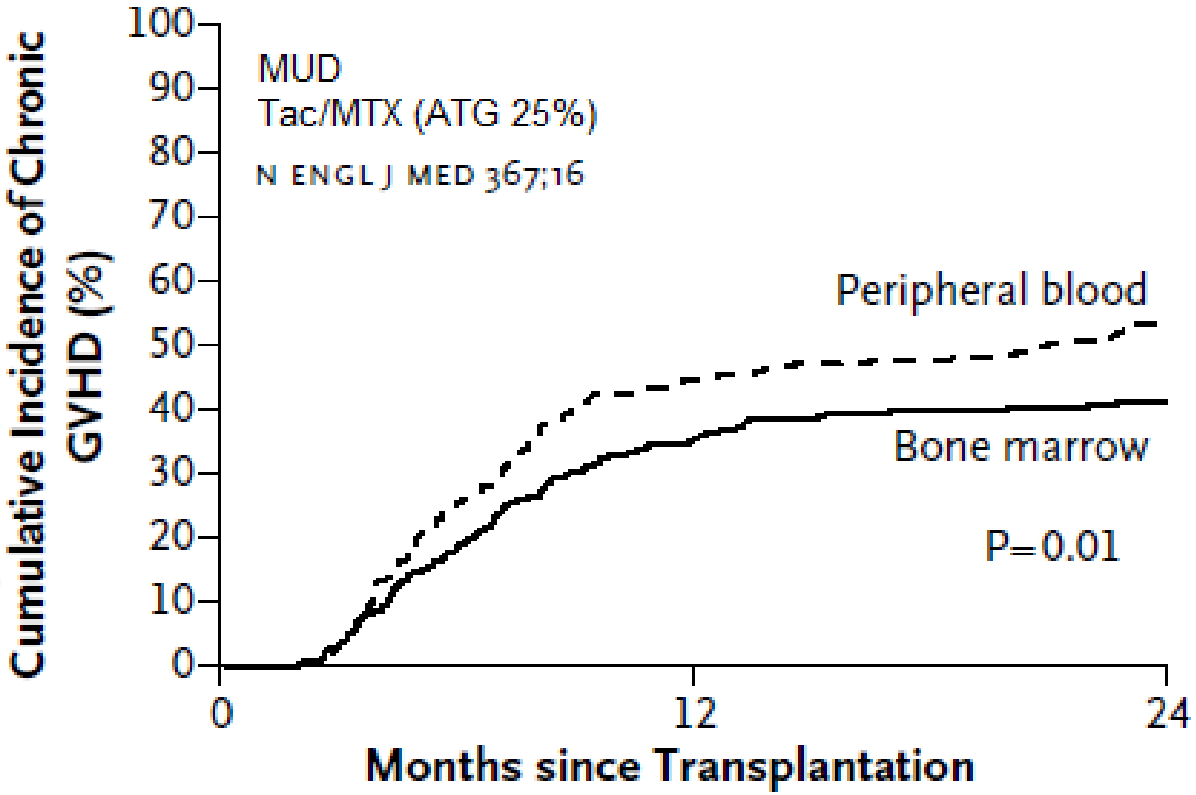


Should we change our standard GVHD prophylaxis in HLA-matched HCT?

CsA/ MTX is not enough

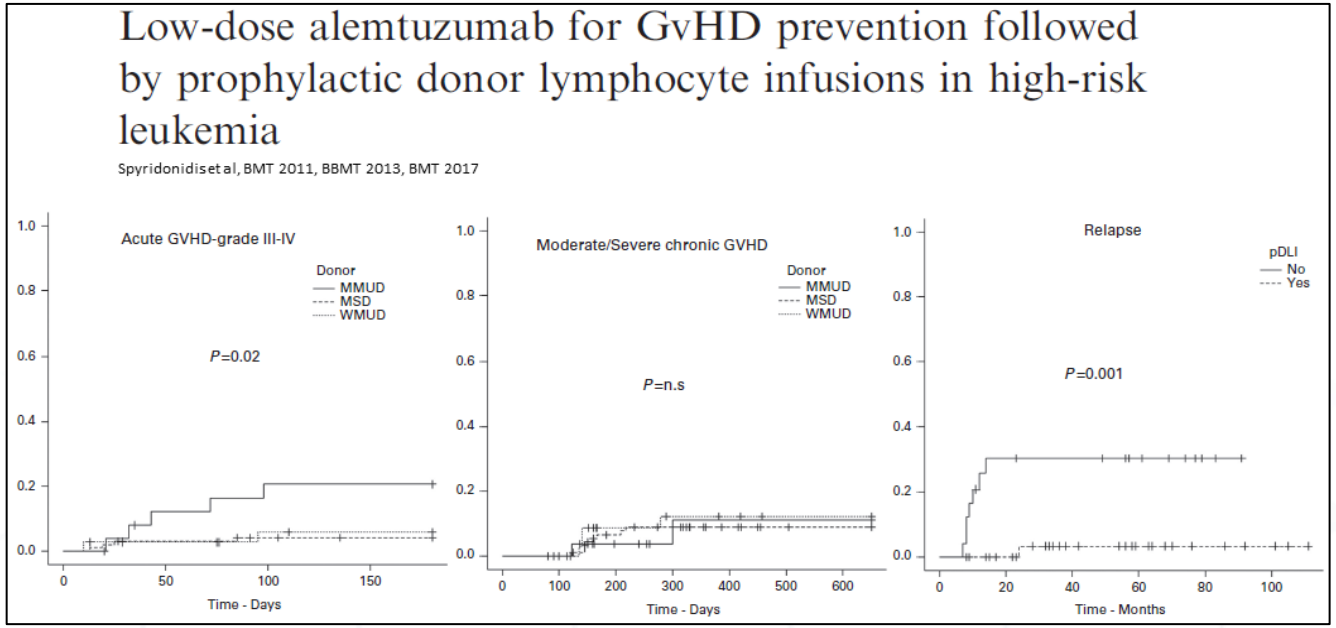


Tac/MTX is not enough



What to add/ change for GVHD prophylaxis in HLA-matched HCT?

- ❑ **ATG**
  - Europe: Standard for MUD, viable option for MRD
  - Various doses, Various formulations
  - Improves GVHD, GRFS, may increase relapse when RIC is used
- ❑ **PTCY**
- ❑ **PTCY + ATG**
- ❑ **Other** (abatacept, vedolizumab, JAKI, Treg)



EudraCT Number: 2021-006367-26 **Sponsor Protocol Number:** IGTRegs **Start Date*:** 2023-01-03

Sponsor Name: Πανεπιστήμιο Πατρών

Full Title: Phase I / II study of HLA-G + induced T-regulatory cells (iG-Tregs) in patients after allogeneic hematopoietic stem cell transplantation from HLA compatible sibling / donor.

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PTCY is increasingly used in HLA –Matched HCT

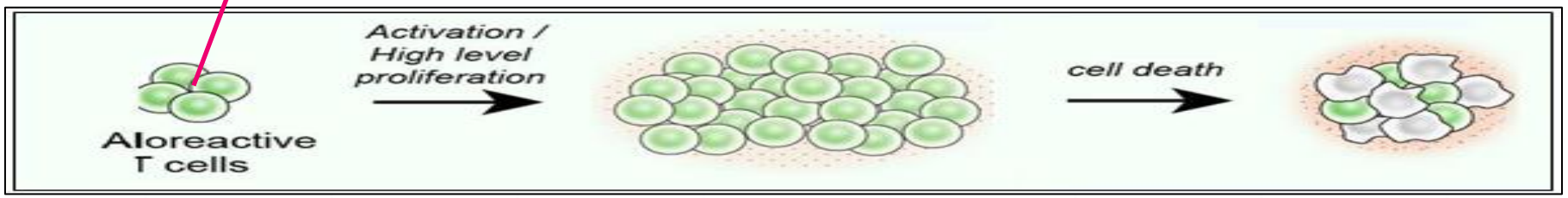
- Is it safe?
- Is it efficient?
- Is it better than the standard GVD prophylaxis?
- Endpoints? (GVHD outcomes, REL, OS, GRFS)
- Other outcomes: Engraftment, toxicity, infections,
- How to use and optimize clinically ? (dose, timing etc)
- Preferrable in specific cases?

Ciurea et al. Blood. 2015, Ghosh et al. JCO. 2016, Gagelmann et al. JAMA Oncology. 2019; Kanakry CG et al. Blood. 2014, Kanakry CG et al. JCO. 2014, Kanakry CG et al. Blood. 2017, McCurdy et al Blood. 2015, Kanakry CG et al. Nat Rev Clin Oncol. 2016

Concerns for the efficacy of PTCY in the HLA- matched setting

Direct recognition of foreign major antigens of haploidentical recipient: burst of proliferation

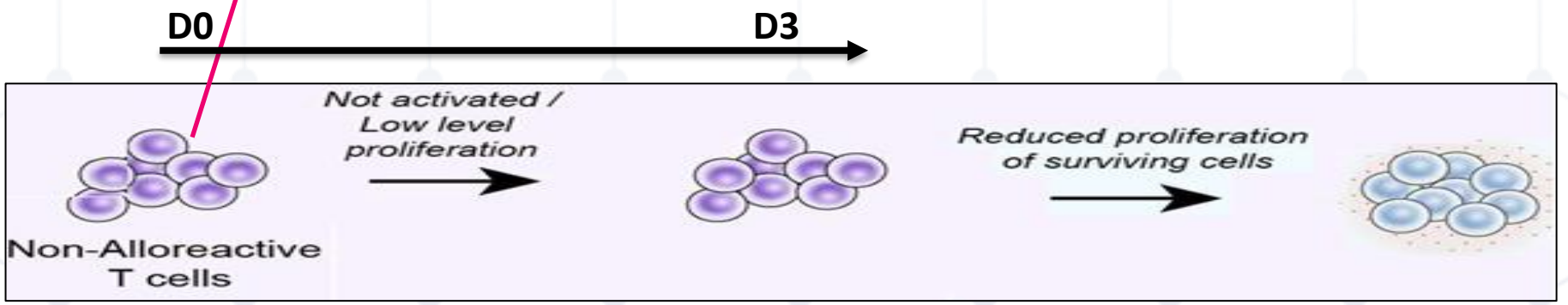
PTCY in mismatch



clonal depletion

Recognize foreign minor antigens presented in the context of "self" HLA: proliferation later and not so fast

PTCY in match?

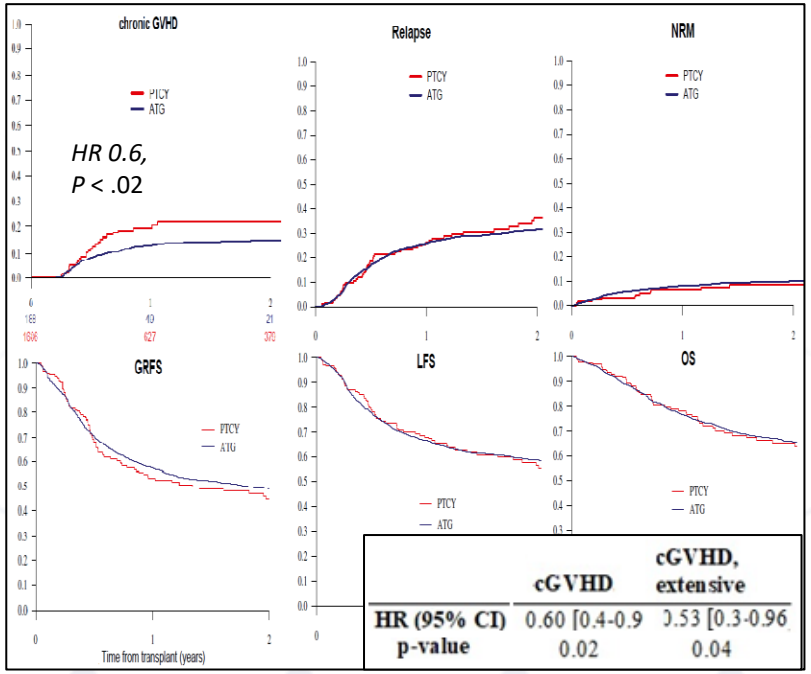


Antiprolife-rative drug? (as MTX /MMF?)

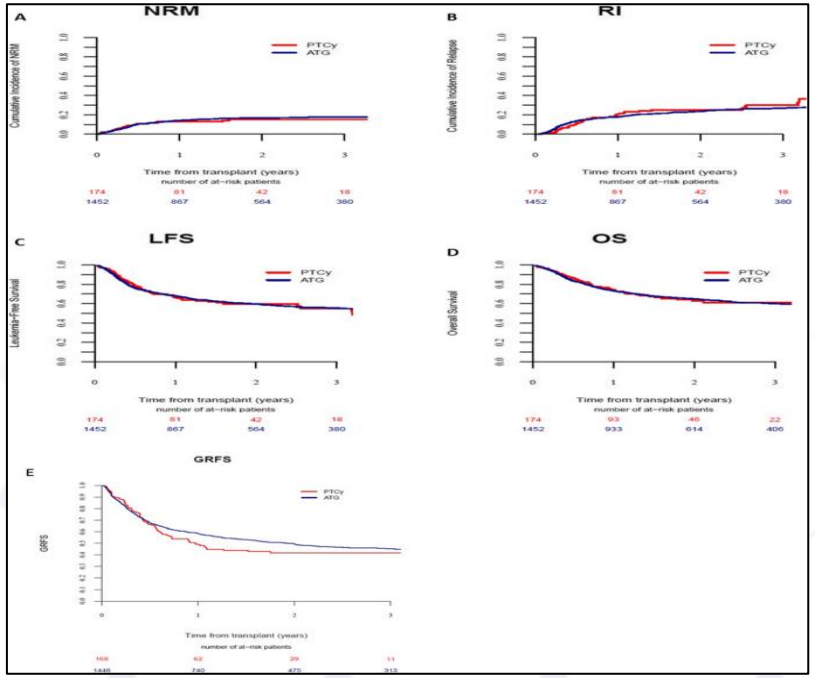
Support for the classical model of PTCY: PTCy efficacy predominantly in mismatch

PTCY vs ATG (EBMT, matched-paired)

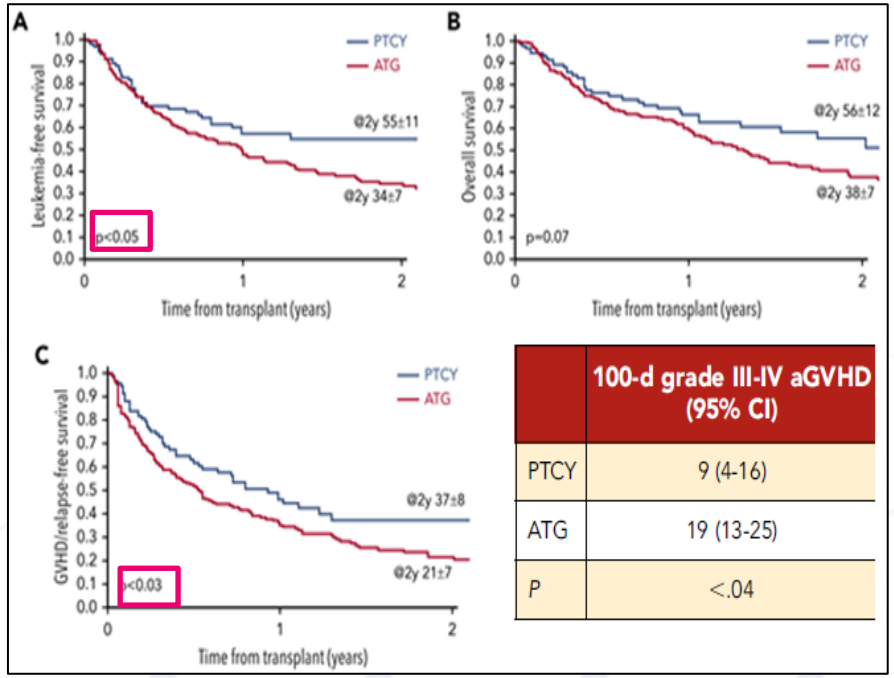
MRD
ATG better for cGVHD



WMUD (10/10)
ATG= PTCY



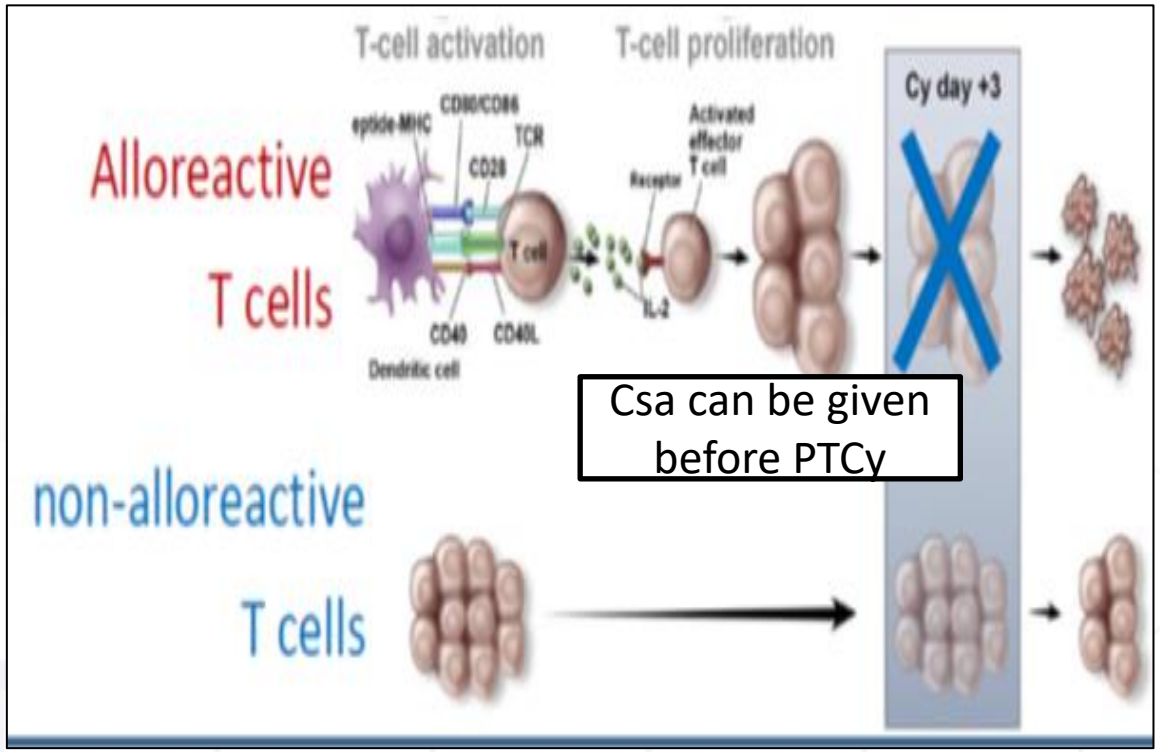
MMUD (9/10)
PTCY better for aGVHD



	100-d grade III-IV aGVHD (95% CI)
PTCY	9 (4-16)
ATG	19 (13-25)
P	<.04

Battipaglia G, *Cancer 2021;127:209-218* Brissot J. Hematol OncolJ Hematol Oncol. 2020;13:87. Battipaglia G, *Blood* (2019) 134 (11): 892–899.

Clinical Observations that do not support the Classical Model of PTCY



Alloreactive T cells
SURVIVE (incomplete elimination)

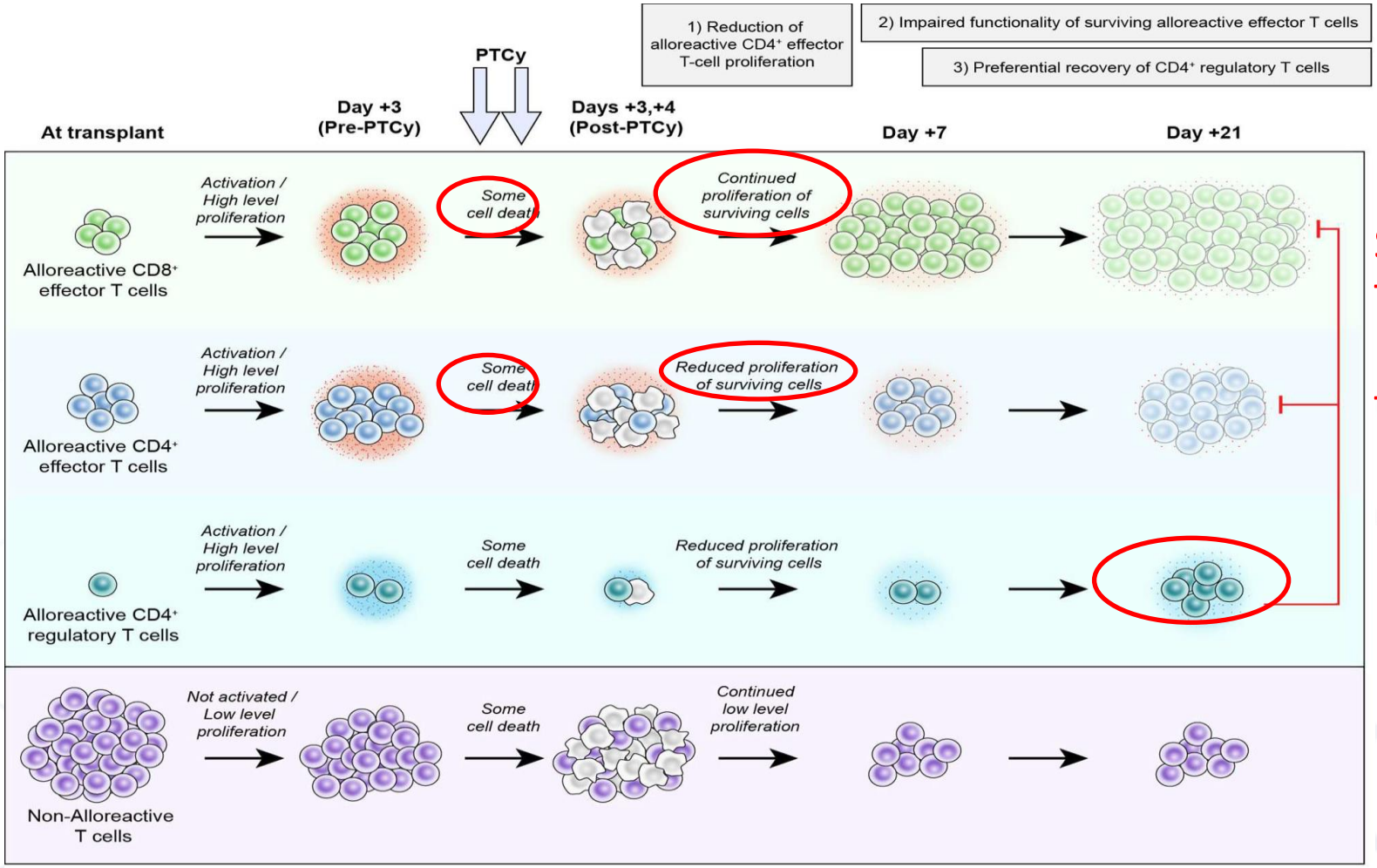
- Grade II acute GVHD is frequent despite PTCy (~30-80%)

DYSFUNCTIONAL (Impaired functionality)

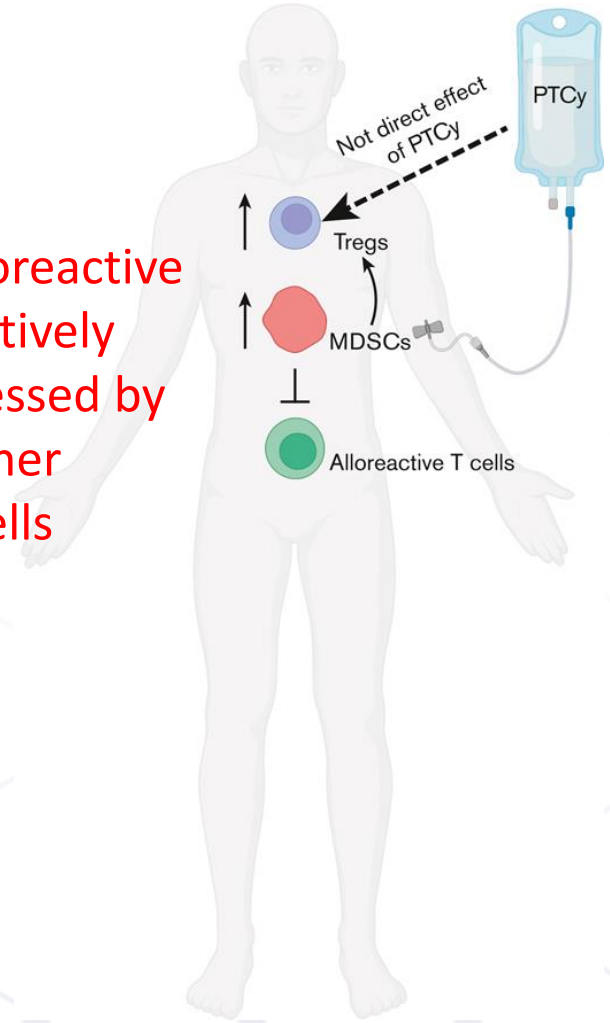
- Severe GVHD is still Prevented (10-20%)

Luznik L, Immunol Res. (2010) 47:65–77; Luznik L, Semin Oncol. (2012) 39:683–93; Nunes NS and Kanakry CG (2019) Front. Immunol. 10:2668.

How does PTCY work? preferential recovery of regulatory cells



Surviving alloreactive T cells are actively being suppressed by Tregs and other regulatory cells



Wachsmuth LP. JCI. 2019; 2Kanakry CG et al. Science TM. 2013; Ganguly et al. Blood. 2014.Nunes NS and Kanakry CG (2019) Front. Immunol. 10:2668. Fletcher RE et al.. Blood Adv. 2023.

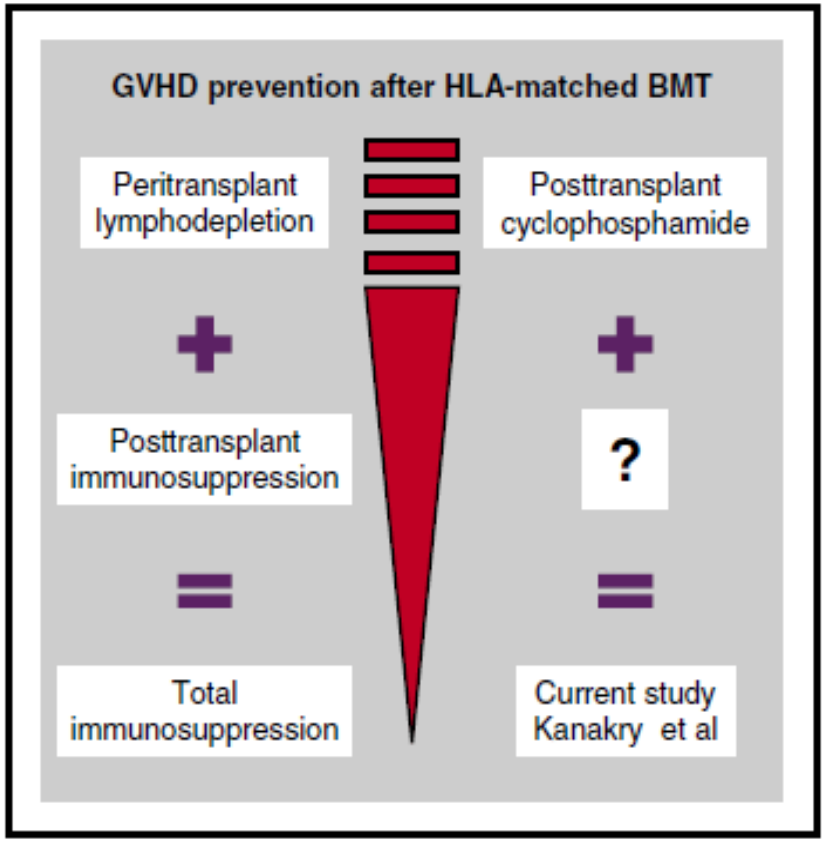
Can PTCY be used as Single Agent in HLA matched HCT (CNI-free HCT)?

PTCy in MRD/MUD BMT.

Single and multi-institutional cohorts

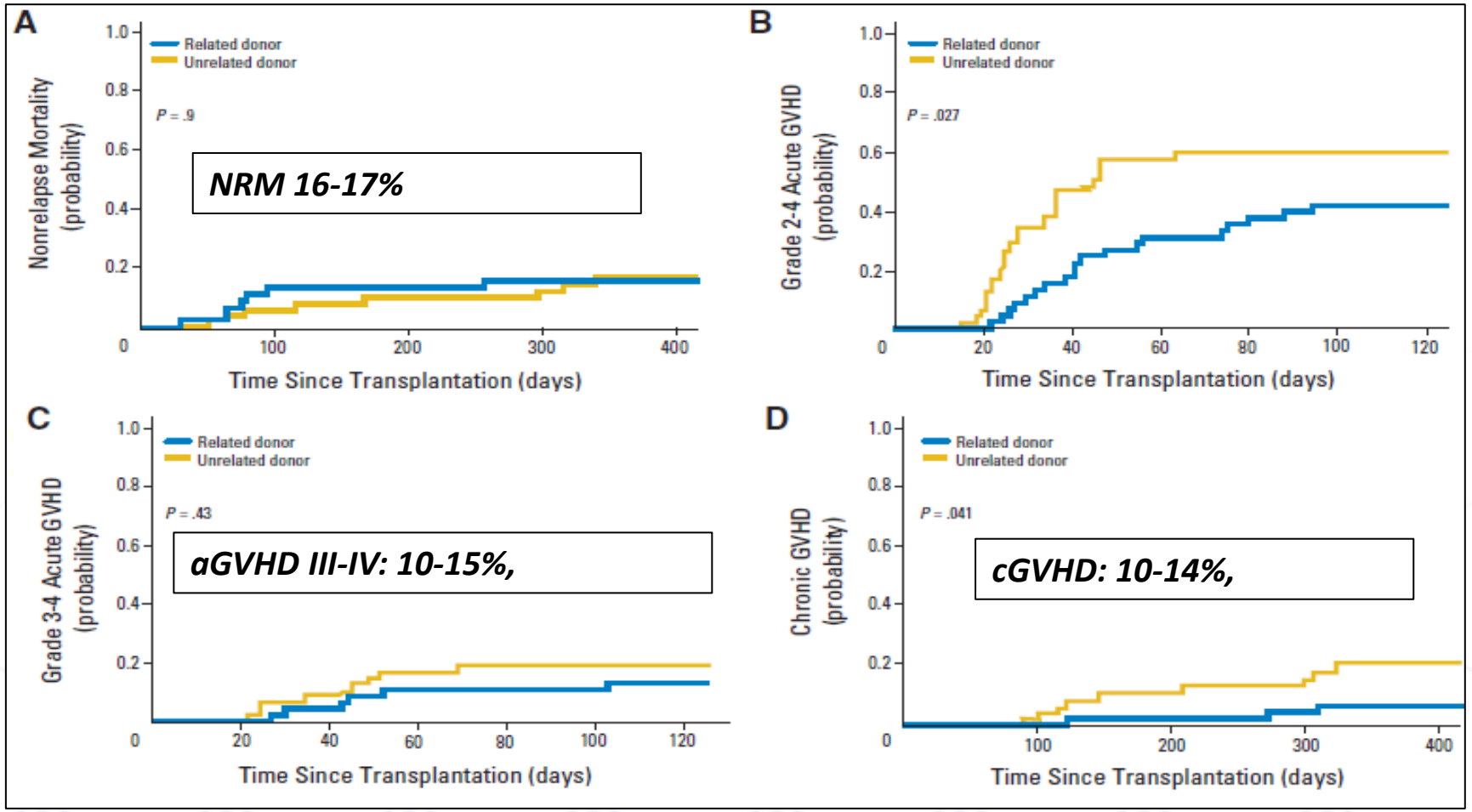
N=117 (1), N=92 (2), N=209 (3),
N=339 (4), N=298 (5)

MAC BMT,
MRD 30% , MUD approx. 70%
PTCY single agent,
no further ISD as prophylaxis



1.Luznik L, Blood. 2010;115: :3224-3230, 2. Kanakry C. J Clin Oncol 2014 32:3497-3505, 3. Kanakry C Blood. 2014; 24:3817-3827, 4. Kanakry C Blood. 2017;129(10):1389-1393, 5. Shannon R McCurdy BBMT 2019 Jun;25(6):1128-1135

PTCy Single Agent in MRD/MUD BMT is Safe and Effective



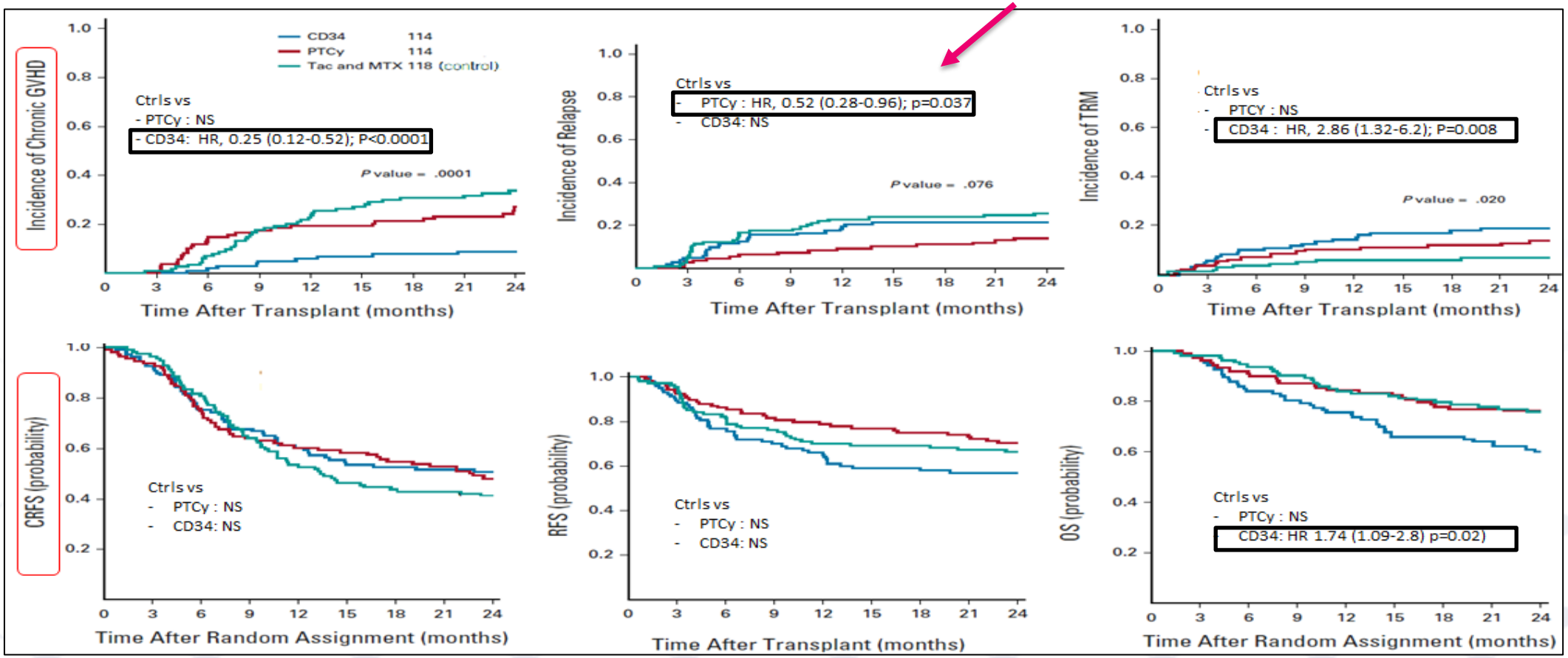
Low IS burden

- 50% MRD / 30% MUD never required any further IS
- Rest 1-2 IS drugs med 5 mo
- nearly all with no IMS at 1y
-
- aGVHD GII→ improved OS

1.Luznik L, Blood. 2010;115: :3224-3230, 2. Kanakry C. J Clin Oncol 2014 32:3497-3505, 3. Kanakry C Blood. 2014; 24:3817-3827, 4. Kanakry C Blood. 2017;129(10):1389-1393, 5. Shannon R McCurdy BBMT 2019 Jun;25):1128-35

PTCy Single Agent is not superior vs Tac/MTX in MRD/MUD MAC-BMT

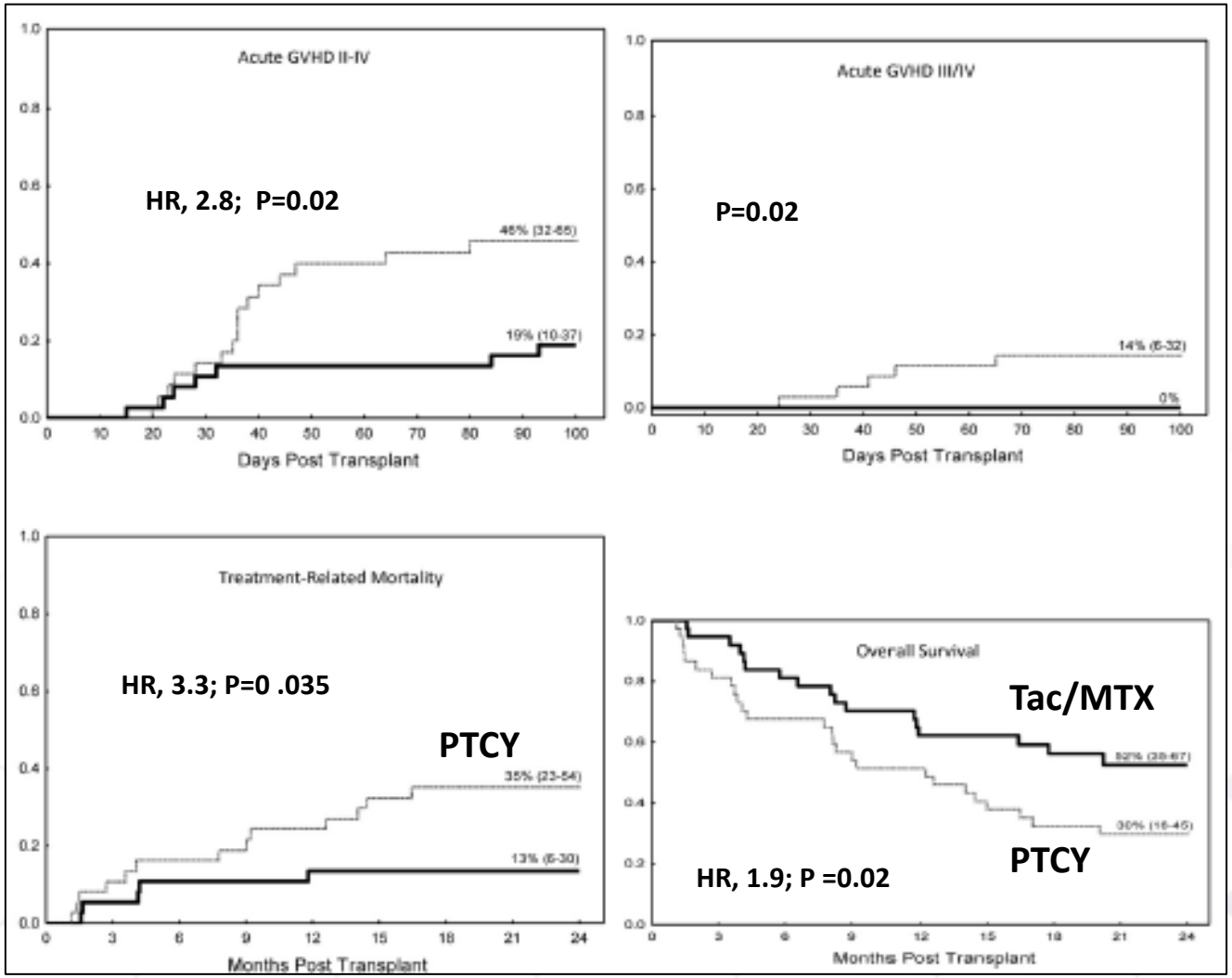
Phase III, BMT CTN 1301, n=346, MRD: 38%, MUD: 62% (CNI-free interventions, peak the winner)



Luznik et al. J Clin Oncol 2021; 40:356-368

PTCy Single Agent in MRD/MUD is probably Not Sufficient

- N=49, PTCy mono
- BM:38, PBSCT:11
- vs matched historical TAC/MTX
- cGVHD 20% vs 22% (NS)



Alousi A.M. BBMT; 21 (2015) 906e912

PTCy in MRD/MUD RIC- PBSCT

PTCY single agent: not safe

Increased rates of life threatening aGVHD

- Bradstock et al: 4/5 pts aGVHD III-IV (6)
- Holtick et al: TRM 36%, principally attributable to severe intestinal aGVHD (7)

PTCY + ISD : safe and effective

PTCY+CNI

N=43, aGVHD III-IV 0%, cGVHD: 16%, NRM 14% (1)

N=35, aGVHD III-IV 0%, cGVHD: 7%, NRM: 3 % (2)

PTCY+ mTORI

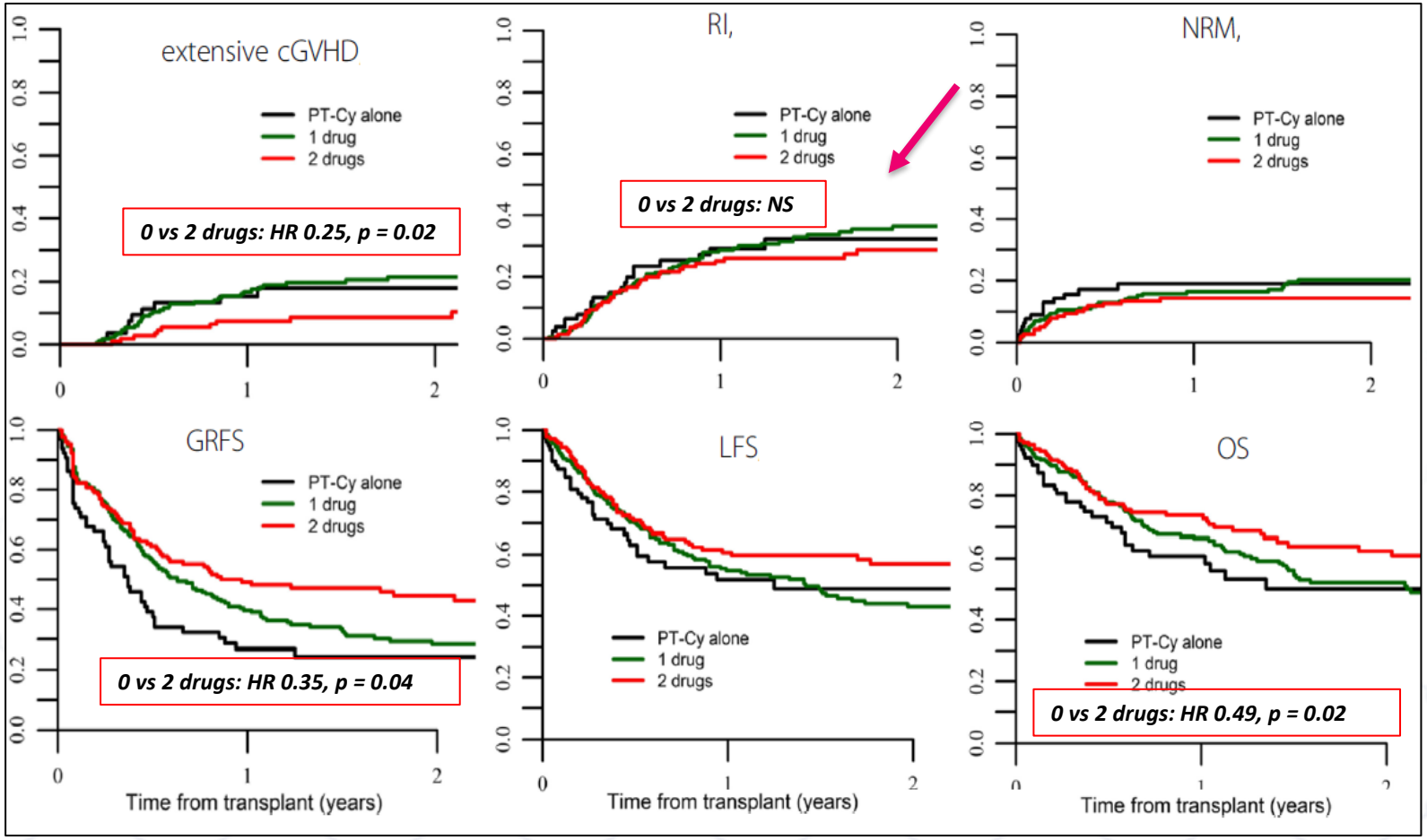
N=28, aGVHD III-IV 4%, cGVHD: 13%, NRM 14 % (4)

N=26, aGVHD III-IV 15%, cGVHD: 31%, NRM 4% (5)

1.Mielcarek M, Blood 2016:127:1502-8, 2. Carnevale-Schianca F BBMT 23 (2017) 459–466, 3. Moisseev IS BBMT 2016; 22:1037, 4. Greco R, Blood 2016, 128:1528-31, 5. Solomon SR , BBMT 2014;
6. Bradstock et al. BBMT 21 (2015) 934e953, 7. Holtick et al. Eur J Haematol. 2016 January ; 96(1): 27–35.

PTCY in MRD/MUD: The role of additional IS (EBMT)

	PTCy alone (n = 78)	1 drug (n = 204)	2 drugs (n = 141)
MSD	63 (81%)	114 (56%)	64 (45%)
UD	15 (19%)	90 (44%)	77 (54%)
BM	58 (74%)	25 (12%)	25 (18%)
PB	20 (26%)	179 (88%)	116 (82%)

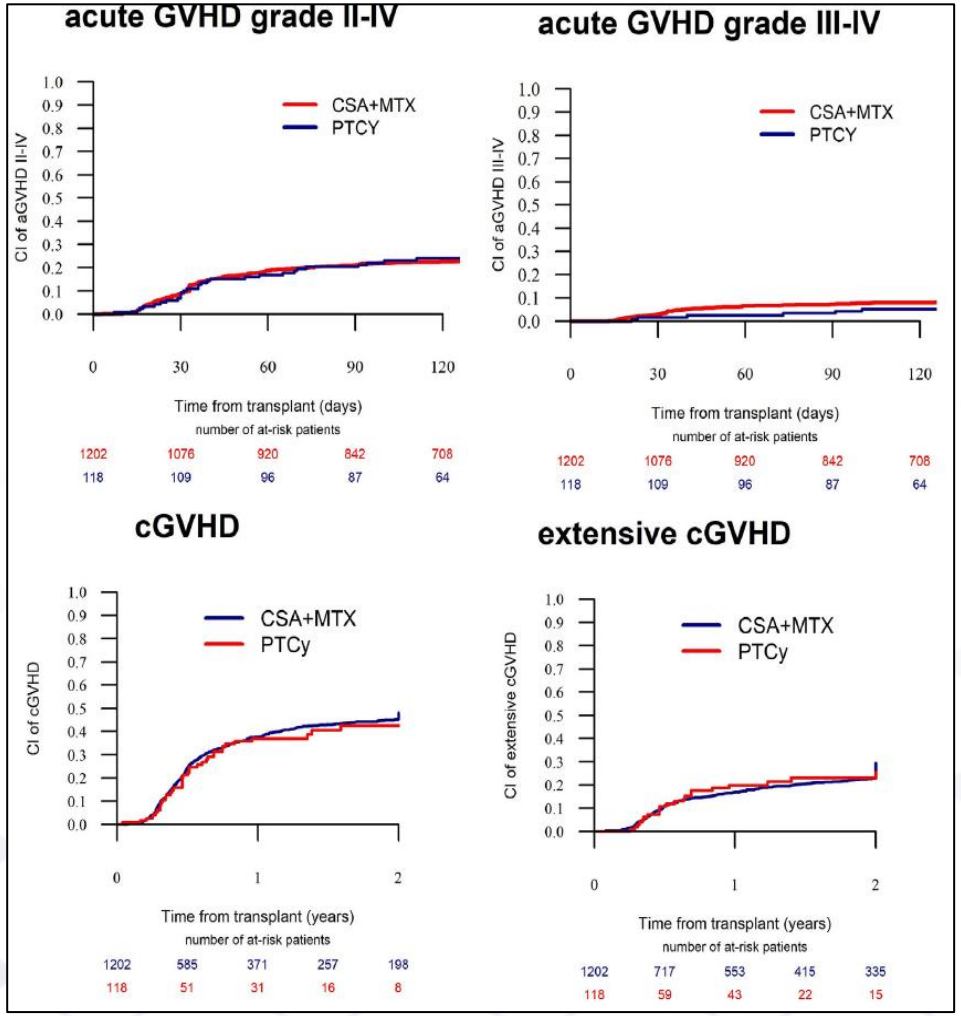


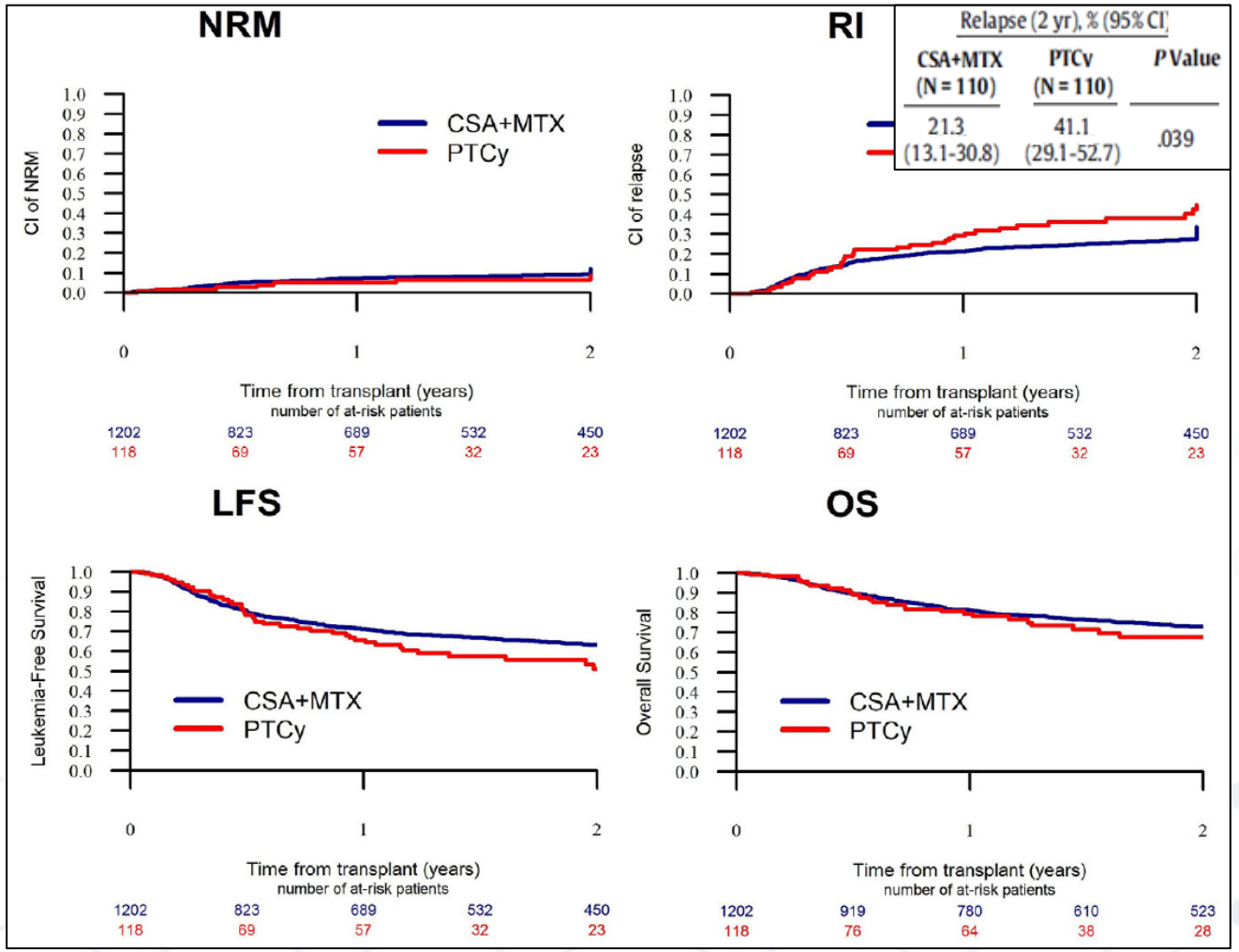
Ruggeri A. *J Hematol Oncol*. 2018;11:40.

The case for PTCY in the HLA-matched setting

1. **PTCy in BMT**
   - Can be used as single agent GvHD prophylaxis
   - PTCY mono = Tac/MTX: Equal GvHD, GRFS, OS, LFS, less Rel? (CTN 1301)
2. **PTCY in PBSCT**
   - Inadequate as monotherapy
   - Viable option as PTCY + CNI
   - PTCY+CNI vs standard?

PTCY + CNI comparable as CsA + MTX in MRD PBSCT (EBMT)

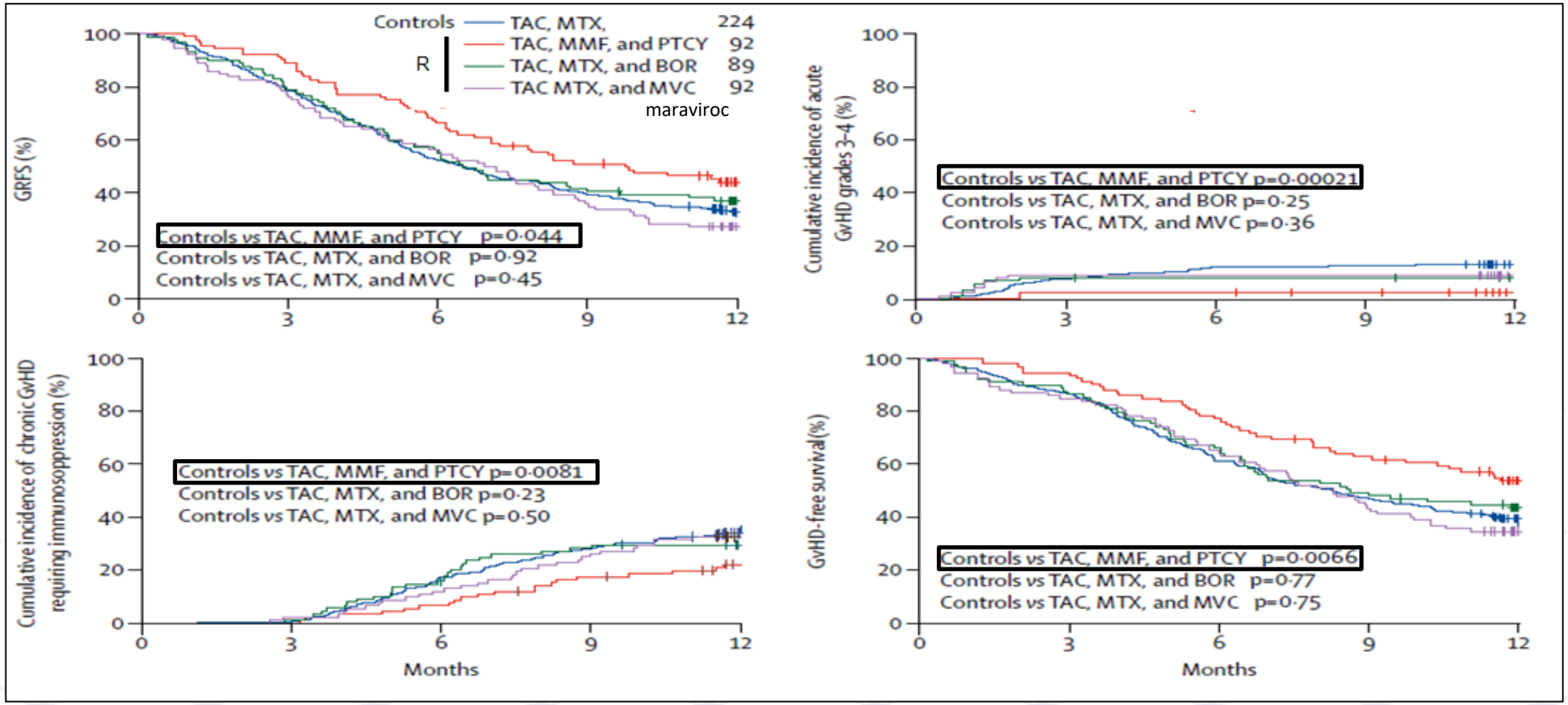




A. Nagler et al. / Transplantation and Cellular Therapy 28 (2022) 86.e186.e8

PTCy+Tac/MMF Favorable vs Tac/MTX

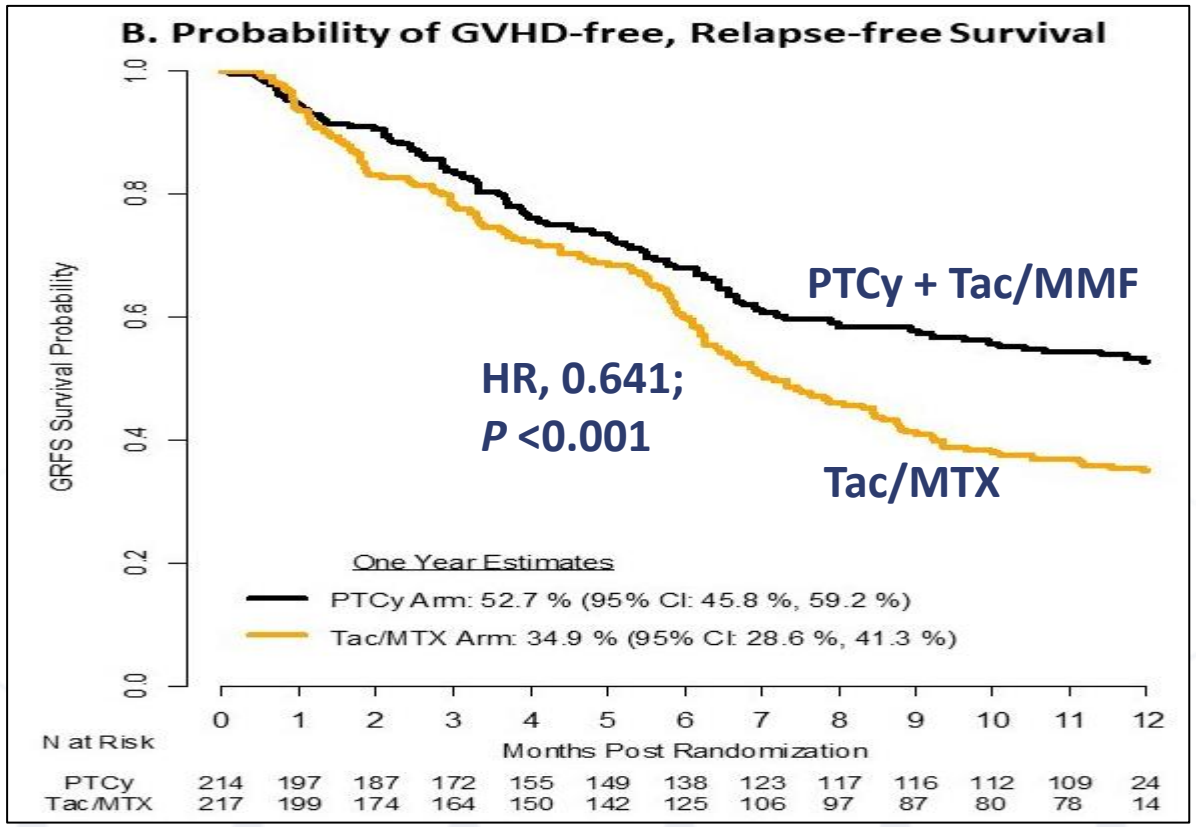
BMT-CTN 1203 (rand. Ph. II, including prospective Ctrls, MRD/MUD RIC- PBSCT)



Bolanos-Meade, LancetHaematol. 2019 March ; 6(3): e132–e143.

PTCy+Tac/MMF Superior vs Tac/MTX

Phase III BMT CTN 1703, N=431, MRD/WMUD RIC-PBSCT
MRD ~30% in both arms

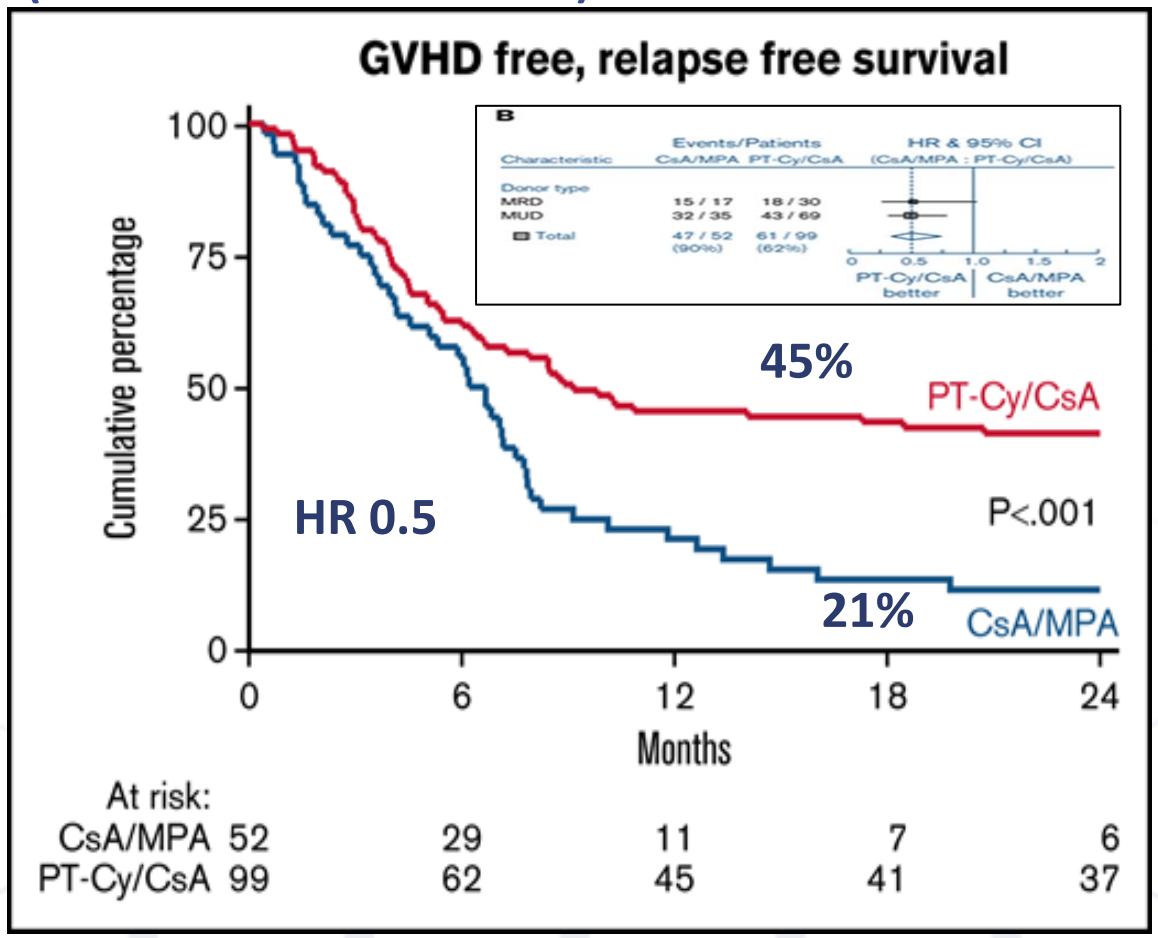


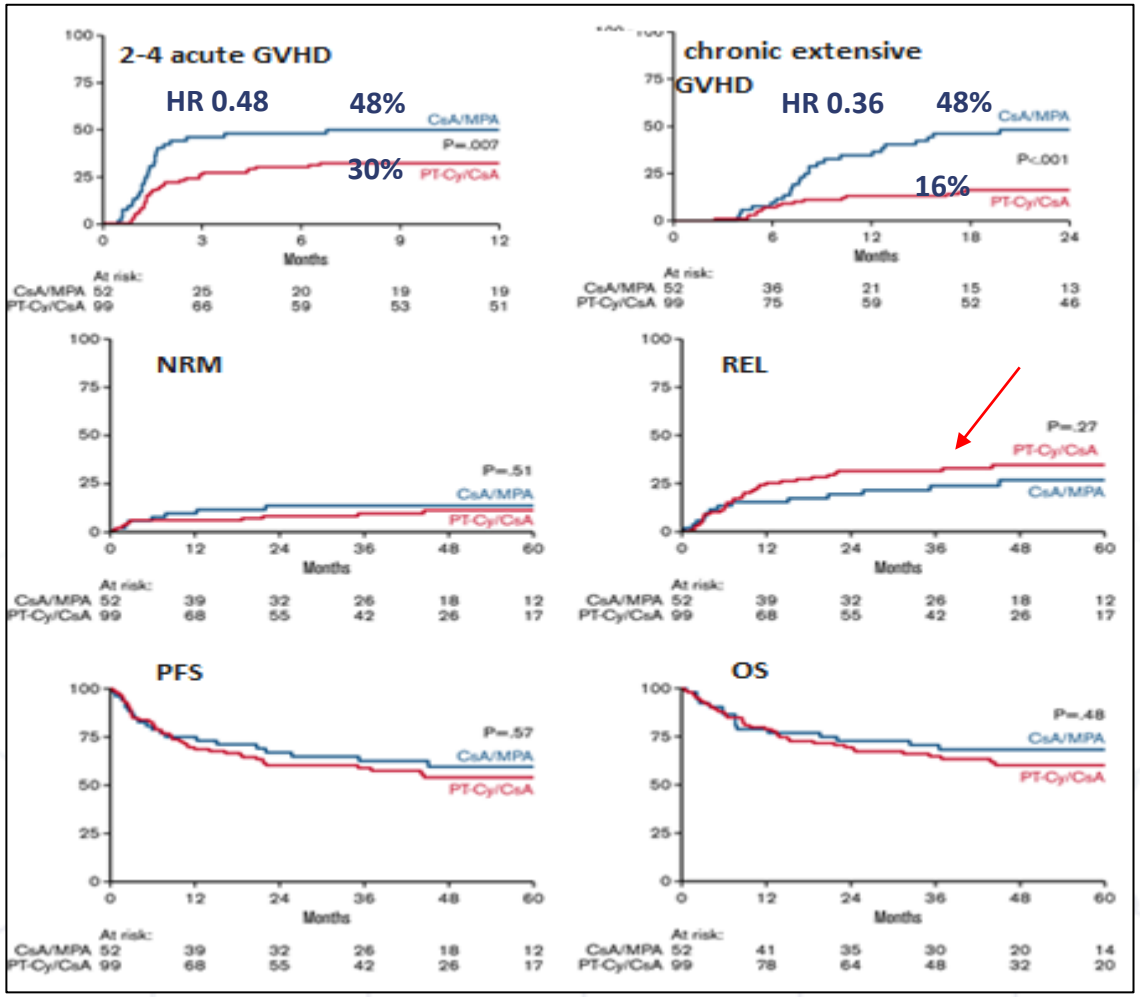
- The improvement in GRFS was driven primarily by a reduction in severe acute and chronic GVHD.
- aGVHD III-IV: 6.3% vs 14.7% **(P =0.001)**
- >=mod. cGVHD 12.5% vs 25% **(P =0.001)**
- IMPROVED GVHD outcomes not at expense of REL or NRM,
- REL: 20.8% vs 20.2%, p=0.906
- NRM: 12.3% vs 17.2%, (P =.167).
- PTCy/Tac/MMF should be the standard GVHD prophylaxis in well matched RIC PBSCT

Holtan et al. *ASH. 2022, Late-Breaking Abstracts Session*

PTCY + CsA Superior vs CsA/MMF

Phase III HOVON NL2128, MRD/WMUD NMA-PBSCT (MRD ~30% in both arms)





Broers et al. *Blood Adv* (2022) 6 (11): 3378–3385.

The case for PTCY in the HLA-matched setting

1. **PTCy single agent**
   - Can be used with BMT
   - Inadequate in PBSCT
2. **Add PTCY to CNI > CNI based**
   - Better GVHD outcomes, not at expense of Rel (?)
   - PTCY+ Tac/MMF > Tac/MTX (CTN 1203 and 1703, RIC-PBSCT)
   - PTCY + CsA > CsA/MMF (Hovon, NMA-PSBCT)

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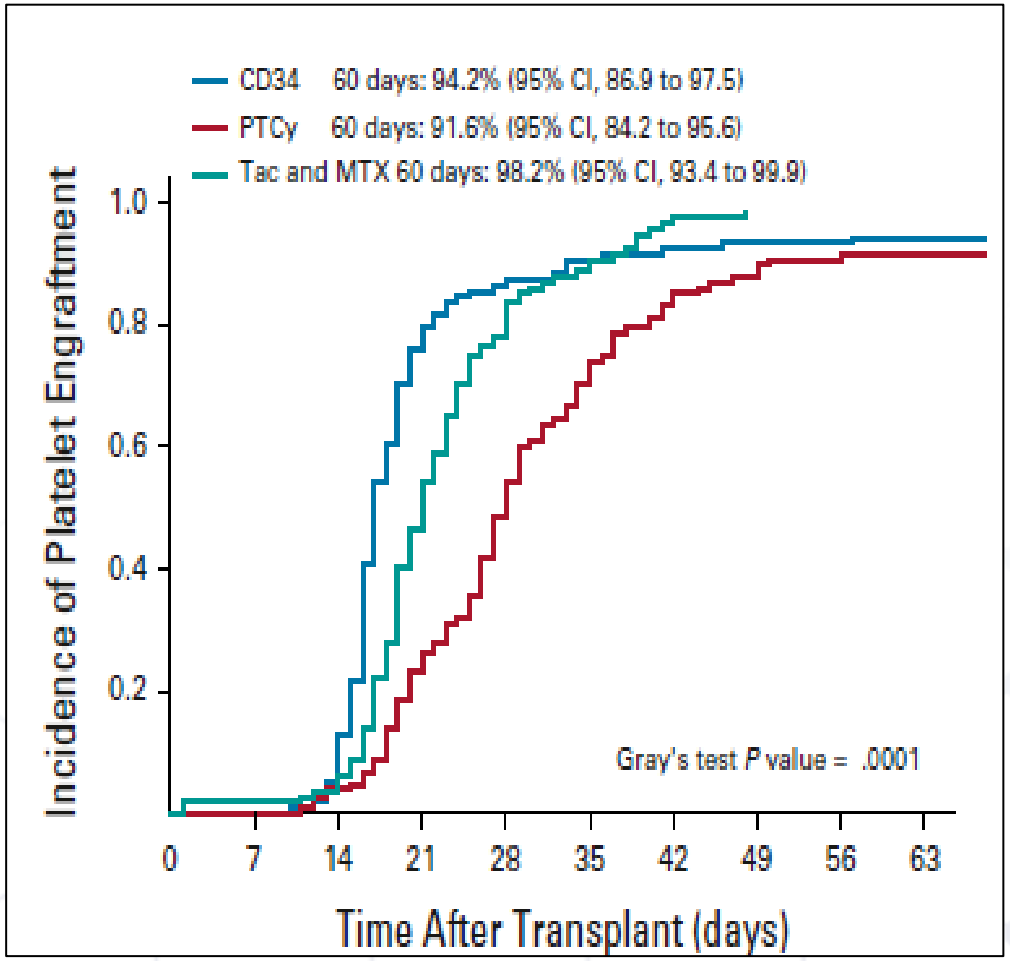
Is PTCY + CNI the new standard in HLA matched HCT?

Side Effects of PTCY

BMT CTN 1301, (BMT)



Holtan et al. *ASH. 2022, Late-Breaking Abstracts Session*

BMT CTN 1703, PTCy + Tac/MMF vs Tac/MTX (RIC-PBSCT)

Slightly poorer graft function with PTCY

- Graft rejection 3% vs 0.5% (*P* =.198)
- D28 Neutrophil recovery 90.3 vs 93.4% (*P* =.032)
- D100 PLT >20.000: 90.3 vs 92.8% **(*P* <.001)**
- secondary GF 2.9% vs 0.9% (*P* =.172)

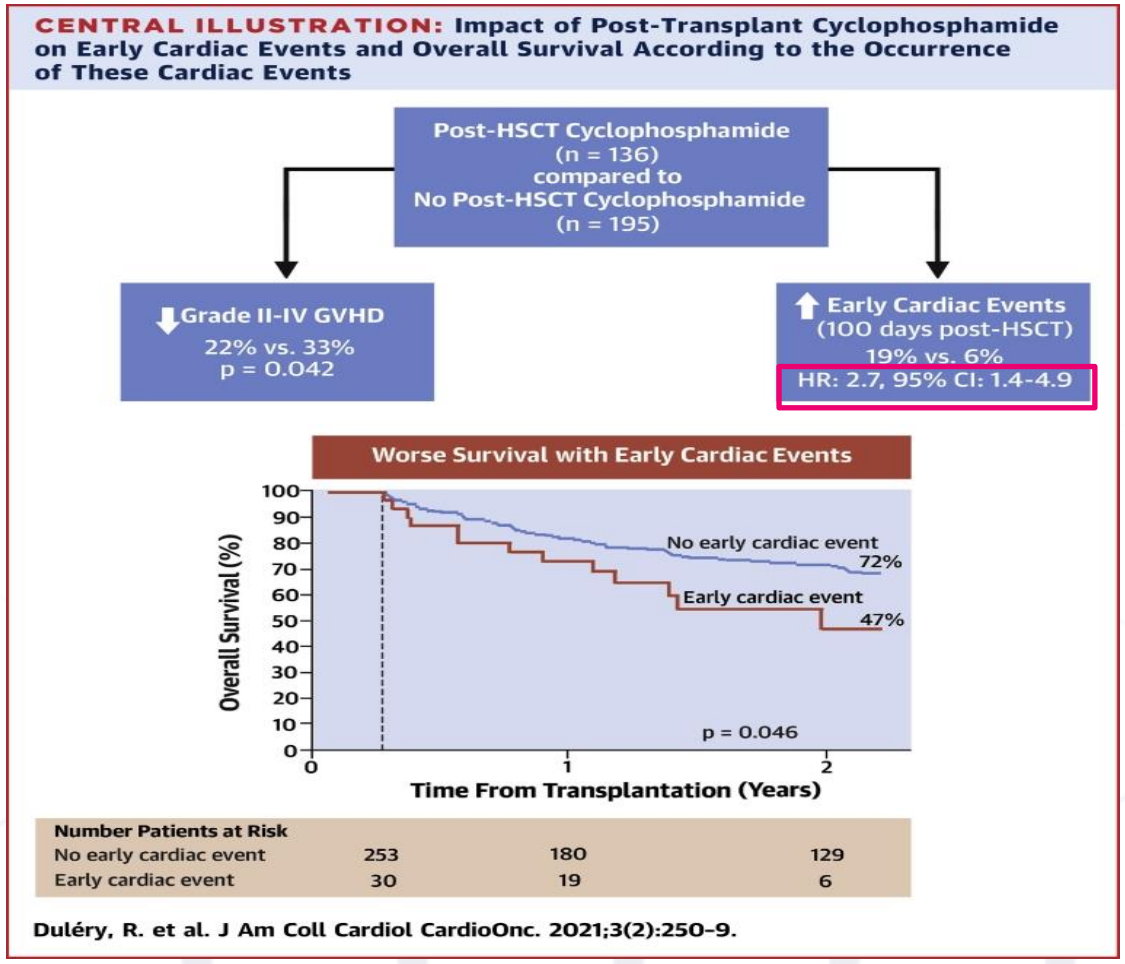
Infections

- Gr 2-3: PTCY 40% vs 30% (P =0.018), GR3: NS
- CMV reactivation 7% vs 7% (letermovir)
- No PTLD

TRM Deaths

- due to aGVHD more common in Ctrl (14.3% vs 4.2%)
- due to organ failure more common in PTCy (23 vs 11%

Specific toxicities of PTCY



PTCy can be Optimized Clinically (Haplo)

- ❑100 mg/kg → 80mg/kg (1)
- ❑100 mg/kg → 50 → 25 (2) (NCT03983850)
  - sufficient for GVHD
  - faster NEU and PLT recovery,
  - less severe mucositis,
  - less Hemorrhagic cystitis,

Duléry, R.,Bone Marrow Transplant (2022)., Kanakry et a TCT 2023,Pleanry talkl

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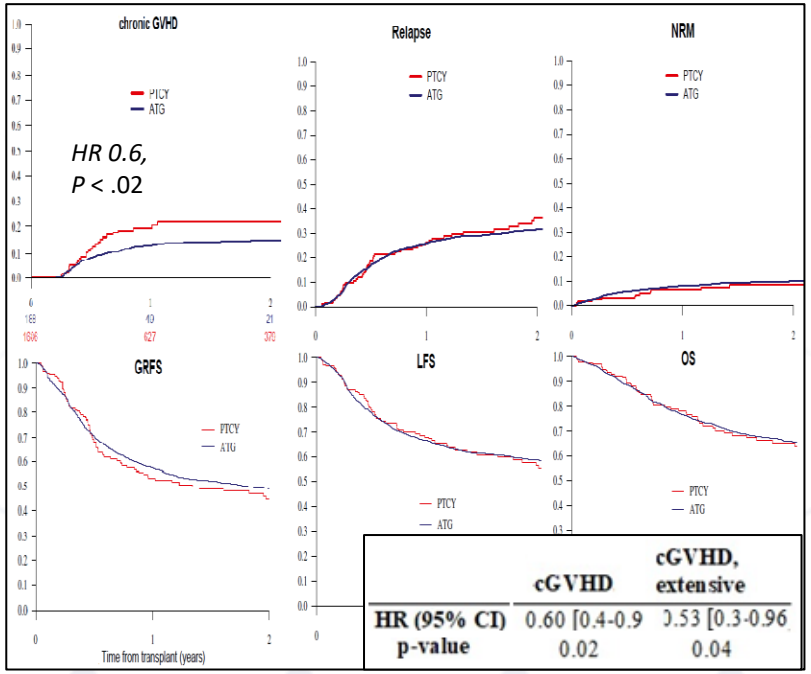
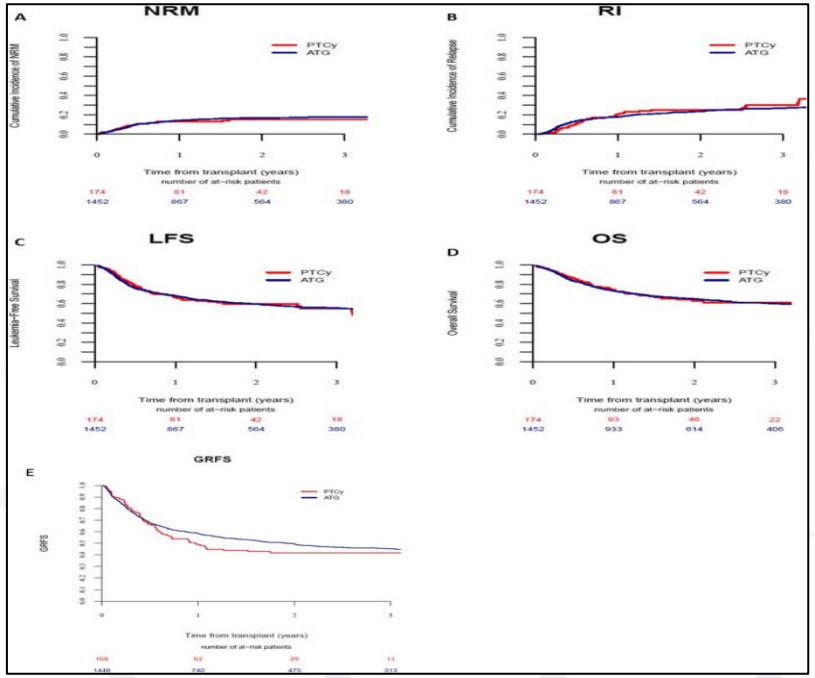
Should PTCY replace (or add to) ATG?

PTCY vs ATG (EBMT)

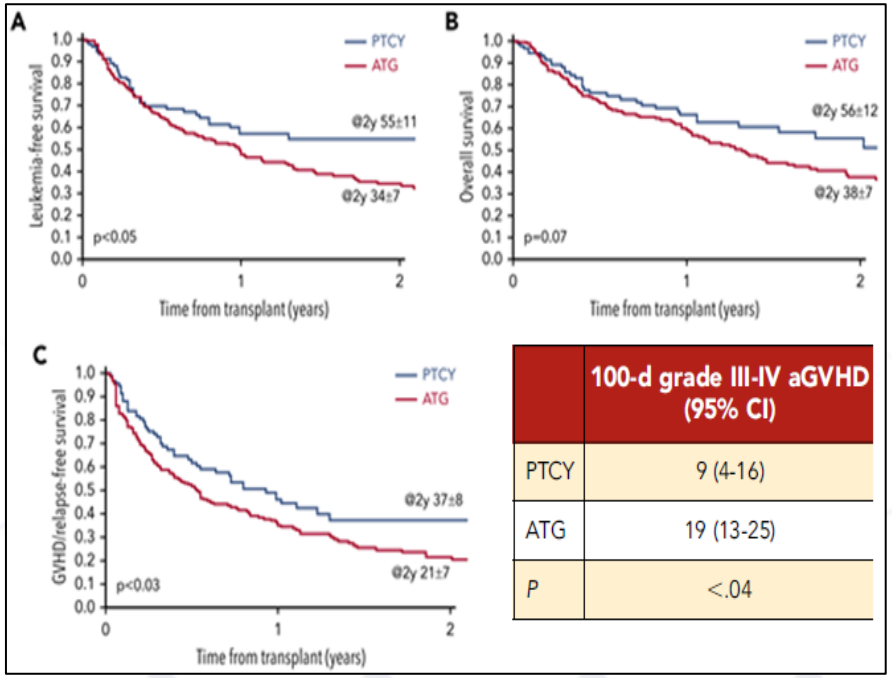
MRD
ATG better for cGVHD



WMUD (10/10)
ATG= PTCY



MMUD (9/10)
PTCY better for aGVHD

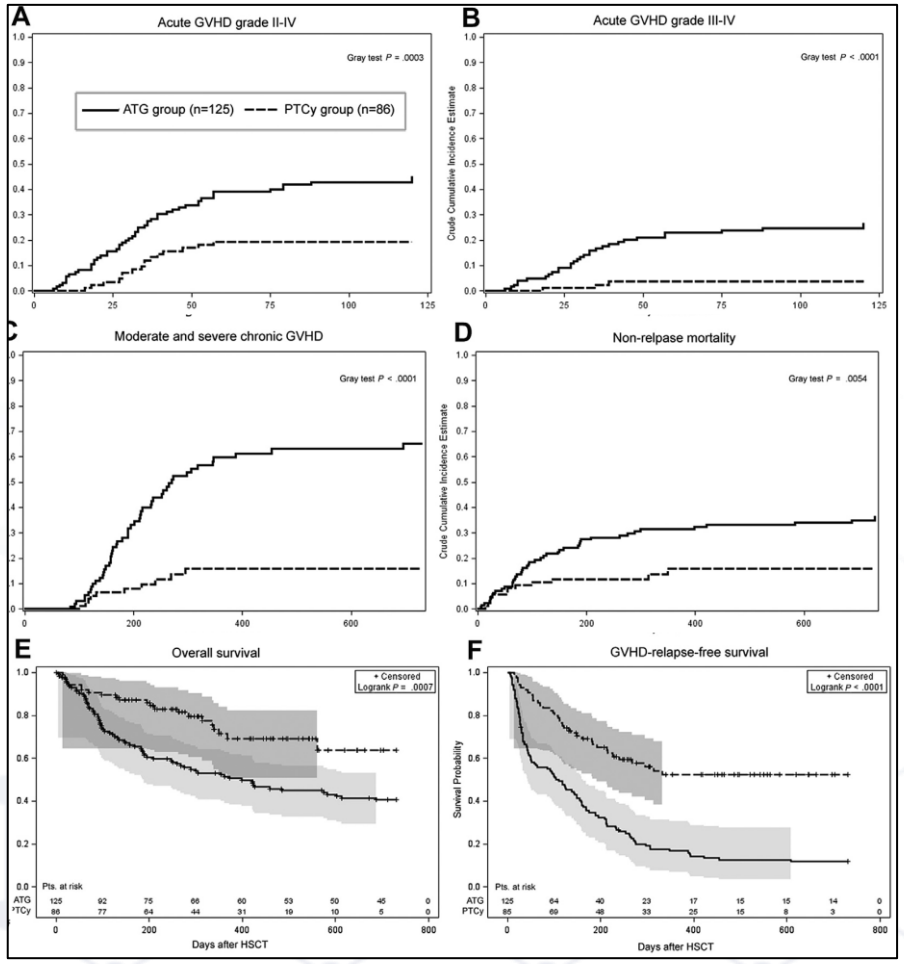


	100-d grade III-IV aGVHD (95% CI)
PTCY	9 (4-16)
ATG	19 (13-25)
P	<.04

Battipaglia G, *Cancer 2021;127:209-218* Brissot J. Hematol OncolJ Hematol Oncol. 2020;13:87. Battipaglia G, *Blood* (2019) 134 (11): 892–899.

PTCy favorable vs ATG in MUD PBSCT (Historical, single center)

PTCY+ IS (MUD 79% / MMUD 21%) N=86, vs historical ATG+IS

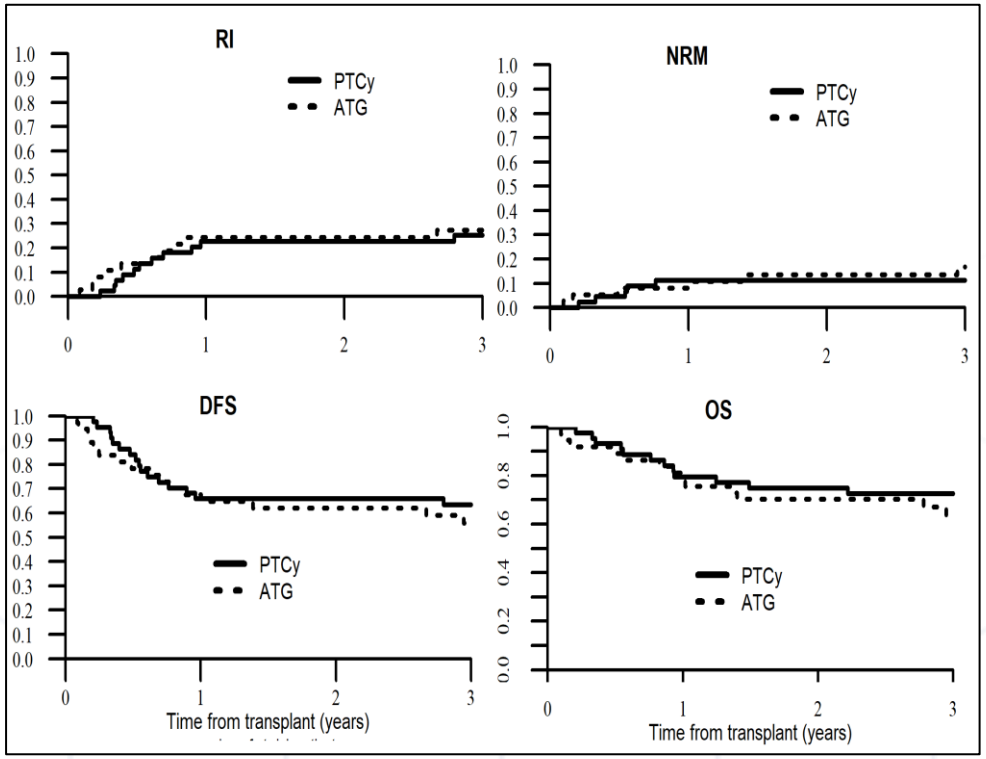


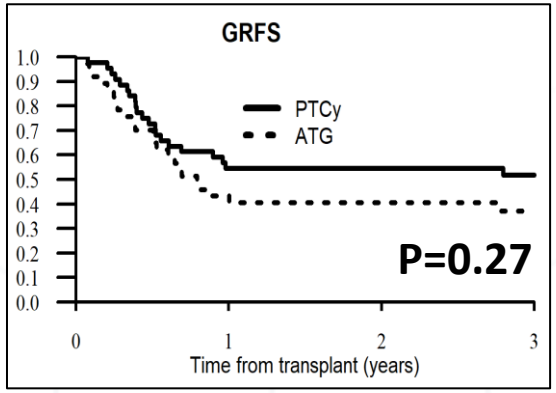
Factor	HR, 95% CI	HR (95% CI)	*P*-value
Acute GVHD grade II-IV			
ALL vs AML		1.33 (0.77-2.27)	.304
Age		1.06 (0.84-1.32)	.645
CMV status		0.78 (0.55-1.11)	.169
RIC vs MAC		0.48 (0.27-0.86)	.014
Female donor for male		0.52 (0.20-1.37)	.521
Disease status		1.07 (0.77-1.50)	.672
HLA-mismatch		0.66 (0.33-1.30)	.225
PTCy vs ATG		0.31 (0.17-0.56)	<.0001
Moderate and severe chronic GVHD			
ALL vs AML		0.78 (0.42-1.45)	.430
Age		1.01 (0.79-1.29)	.959
CMV status		0.88 (0.57-1.34)	.538
RIC vs MAC		0.85 (0.43-1.70)	.652
Female donor for male		0.61 (0.21-1.75)	.358
Previous aGVHD		3.87 (1.71-8.74)	.001
HLA-mismatch		1.21 (0.53-2.77)	.659
PTCy vs ATG		0.39 (0.19-0.81)	.011
Event-free survival			
ALL vs AML		1.00 (0.64-1.56)	.992
HCT-CI		1.35 (1.08-1.69)	.008
Age		1.08 (0.89-1.32)	.423
CMV reactivation		0.82 (0.54-1.23)	.338
Cytogenetic risk		1.24 (0.85-1.80)	.262
RIC vs MAC		0.70 (0.43-1.17)	.174
CD34+> 3.0x10*6/kg		0.35 (0.16-0.76)	.007
Disease status		2.60 (2.02-3.35)	<.0001
HLA-mismatch		0.79 (0.46-1.35)	.380
PTCy vs ATG		0.49 (0.31-0.78)	.003

Moisseev IS BBMT 2016; 22:1037,

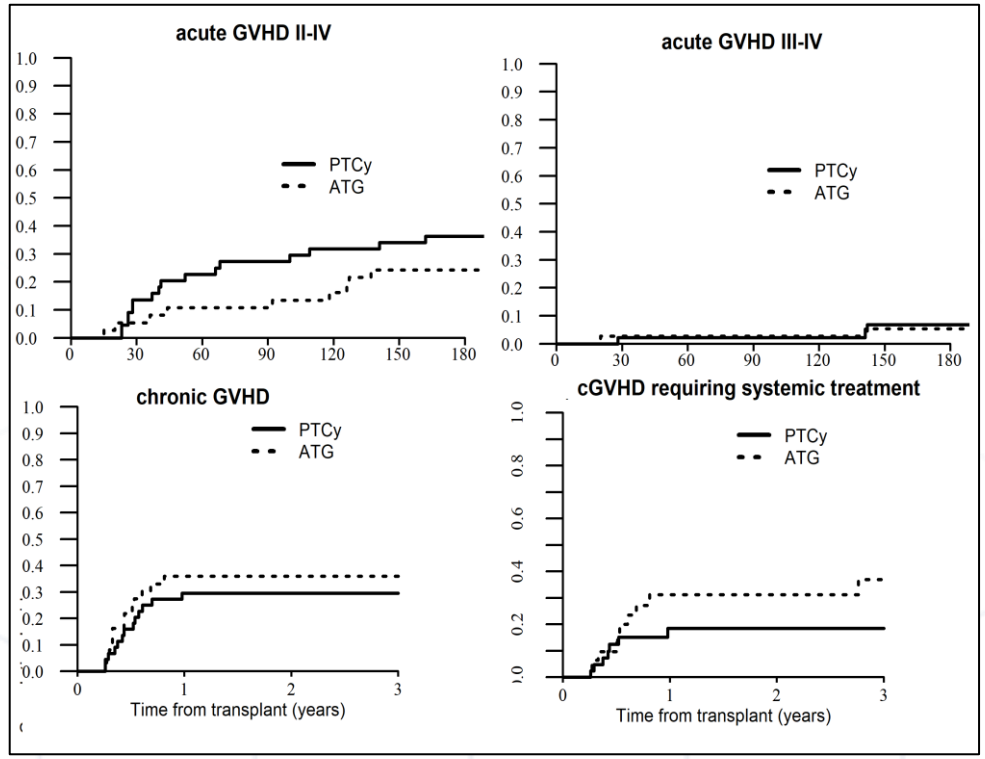
PTCy comparable vs ATG in MRD/ MUD PBSCT (rand)

ATG+IS vs PTCY+ IS, MRD 40% / WMUD 60%, FluBu2, PBSC, median 64y, N=89 (randomized, NCT02876679)





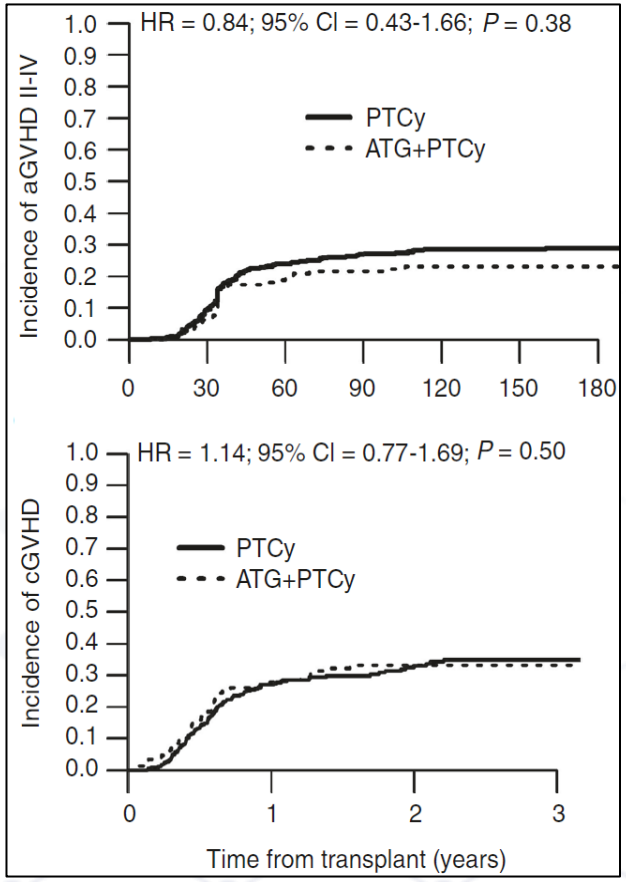
EORTC QLQ-C30

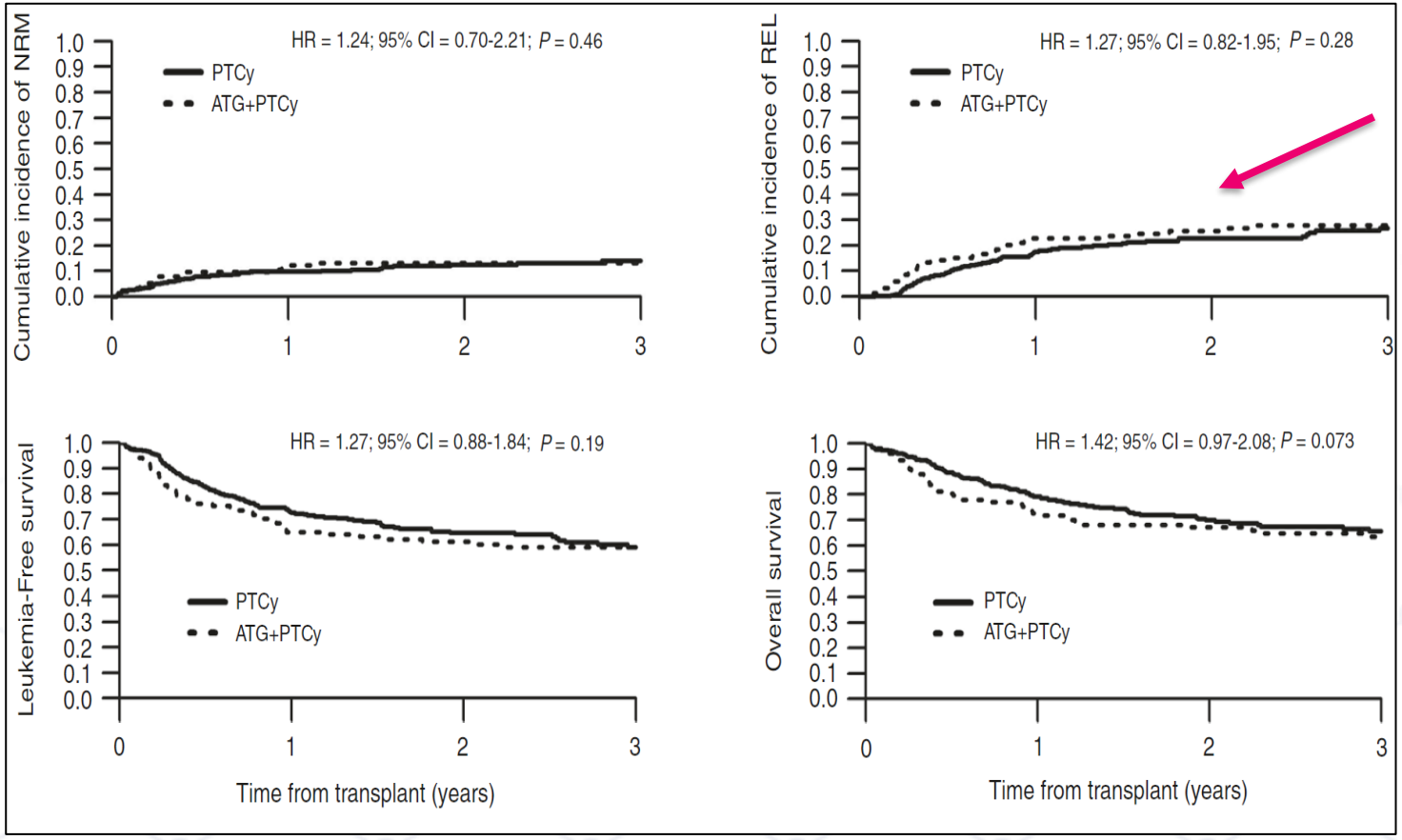


Courtesy Eolia Brissot, unpublished data, do not post

PTCY platform (MUD PSBCT): add ATG

PTCy+ATG vs PTCy: feasible but does not provide any extra benefit (EBMT)

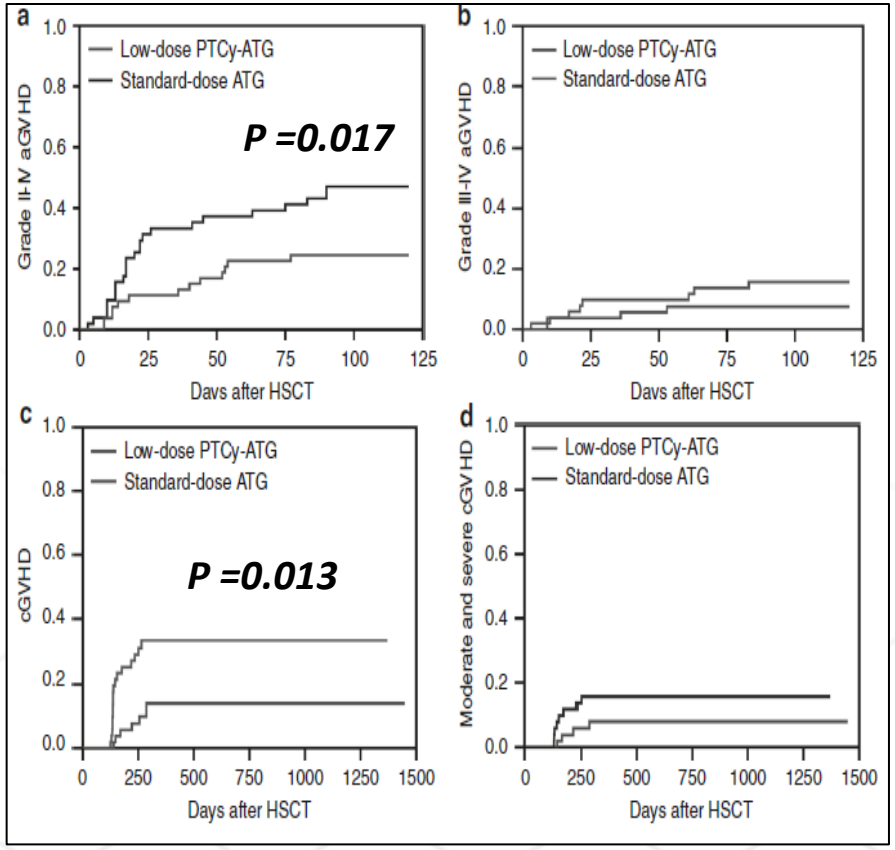


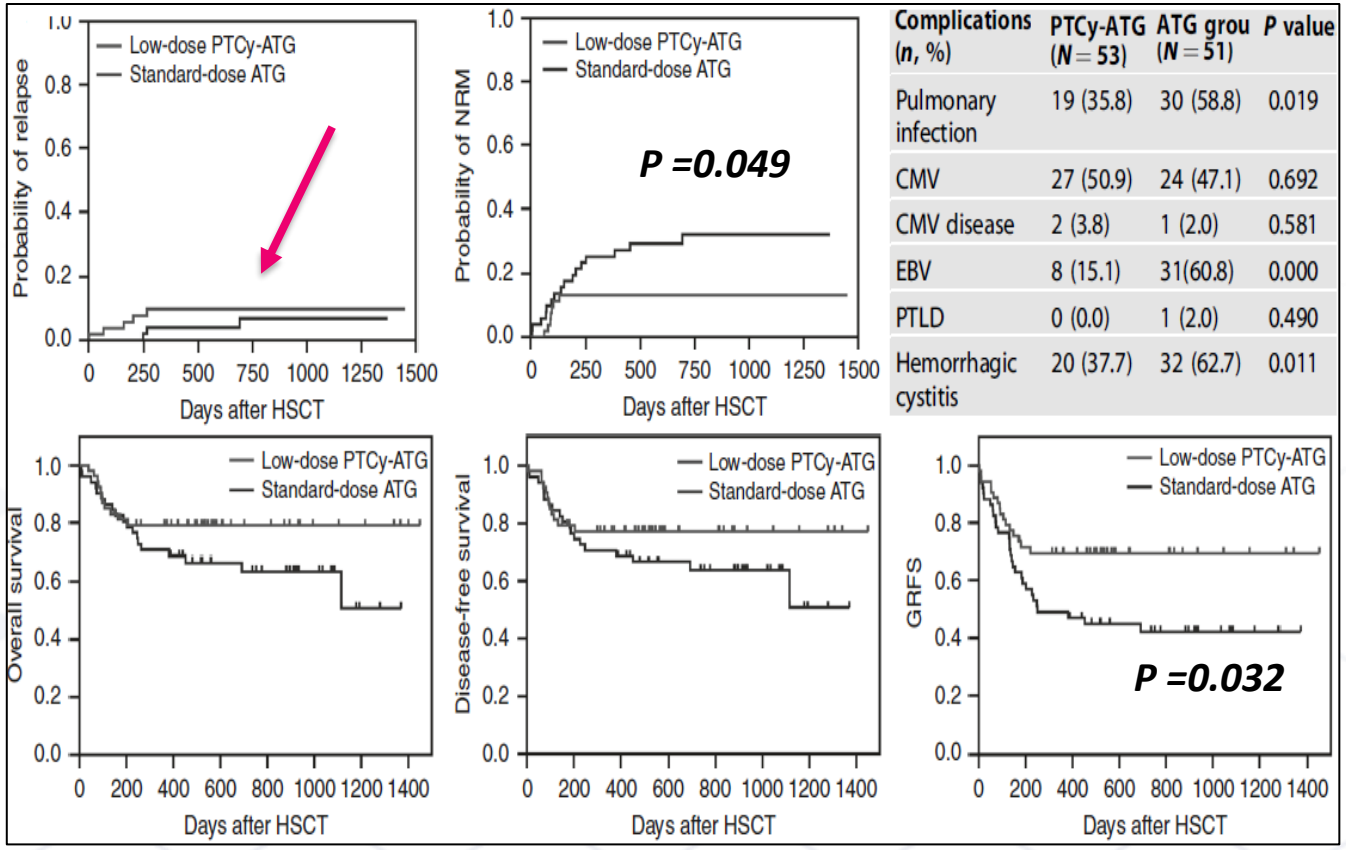


Spyridonidis A. Bone Marrow Transplantation (2022) 57:1774–1780.

ATG platform (WMUD, PBSCT): Add PTCY

LD PTCY (40mg) + LD ATG favorable vs ATG (rand., WMUD, single center)





Complications (*n*, %)	PTCy-ATG (*N* = 53)	ATG grou (*N* = 51)	*P* value
Pulmonary infection	19 (35.8)	30 (58.8)	0.019
CMV	27 (50.9)	24 (47.1)	0.692
CMV disease	2 (3.8)	1 (2.0)	0.581
EBV	8 (15.1)	31(60.8)	0.000
PTLD	0 (0.0)	1 (2.0)	0.490
Hemorrhagic cystitis	20 (37.7)	32 (62.7)	0.011

Zu Y, BMT. 2022 Oct;57(10):1573–80.

PTCy preferrable in specific cases (?)

Previously exposure to checkpoint inhibitors

1. Increased severe GVHD after PD-1 pretreatment (1)
2. Clinical observations suggested reduced GVHD rates in CPI recipients when PTCY was used as GVHD prophylaxis (2,3,4)
3. PTCy ameliorates GVHD by restoring regulatory and effector T-cell homeostasis after PD-1 blockade (5)
4. PTCY based GVHD prophylaxis became standard following CPI pretreatment

1. Merryman RW, Blood 2017; 129:1380-8, 2. Schoch LK et al. Blood Adv 2018; 2: 2226-9, 3. Paul S et al. BBMT 2020; 26:1679-88, 4. Oran et Cancer 2020; 126:2193-205. 5. Shuntaro Ikegawa Blood Adv (2019) 3 (23): 4081–4094

The case for PTCY in the HLA-matched setting

1. **PTCy single agent**
   - Can be used in BMT, comparable with Tac/MTX
   - Inadequate in PBSCT
2. **Add PTCY to CNI > CNI**
   - Better GVHD outcomes, no effect on Rel (?)
   - PTCY+ Tac/MMF > Tac/MTX, PTCY + CsA > CsA/MMF
3. **PTCY based vs ATG based**
   - Evtl. PTCY> ATG in mismatched 7/8 MUD (EBMT)
   - One prospective analysis MRD / WMUD: comparable results (NCT02876679)
   - Rand. PTCY vs ATG (NCT05153226, NCT03852407)
4. **PTCY + ATG?**
   - feasible
   - Enables long term free IS? (with PTCY is safe to d/c CNI at day 60 (MRD) and day 90 (MUD)
   - Rand PTCy + ATG vs ATG (NCT04202835)

EBMT European Society for Blood and Marrow Transplantation

Should we change to PTCY in HLA matched HCT?

1. PTCY has a role in MRD/MUD HCT, improves GVHD outcomes
2. There is room for clinical optimization
3. Has the potential to replace ATG-based GVHD prophylaxis
4. Combination of PTCY and ATG may enable CNI-free / long term IS-free HCT
5. Concerns that PTCY increase REL (not true), unknown
6. Infections (?)
7. Effects of PTCY on Microbiome/ Immunobiome are awaited (companion study CTN 1703)

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GVHD prophylaxis in matched sibling donor transplant
The case for "post-cyclophosphamide"

"In the current world of drug development, the real work often begins after a drug is approved"

Mark Levis, Blood Commentary 2022

EBMT European Society for Blood and Marrow Transplantation

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Statisticians	Myriam Labopin Maud Ngoya Jacques-Emmanuel Galimard Christophe Peczynski

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ΕΥΔΕ ΕΤΟΚ

ΕΣΠΑ 2014-2020

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