Indian Society of Hematology & Blood Transfusion

EUROPEAN HEMATOLOGY ASSOCIATION

5th ISHBT-EHA Tutorial

01st - 03rd March 2024

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EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology

March 1-3, 2024 |
Hyderabad, India

Overview of Stem Cell Transplantation – Focus on Haplo-identical SCT

Speaker:
Alexandros Spyridonidis
Prof. of Hematology

Disclosures

- 2023/ 2024: Research support: Novartis, AbbVie
- 2023/2024: Honoraria for advisory membership and travel grants:

  Gilead, MSD, Novartis, Amgen, Bristol, Genesis, AbbVie, Servier
- Nothing related to this talk

Few words about me

UNIVERSITY OF PATRAS
ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ

The 4 pillars of the Cell Therapy Program

Director Prof. A. Spyridonidis

We treat patients	*We recruit donors*	*We innovate*	*We shape scientists*
			
www.bmtpatra.gr	www.xarisezoi.gr	www.ictpatras.gr	www.mastercgt.com
BMT Unit Establ. *1997 auto/ 2006 allo* Jacie, ISO for clinical trials	**CBMDP Donor Center** Establ. 2010 *WMDA Cert*	**Institute Cell Therapy** Establ. 2021 GMP certified	**MSc Cell and Gene Therapies** Establ. 2022 International Students

EBMT
European Society
for Blood and Marrow Transplantation

Leader RIC Committee
Acute Leukemia WP

JACIE
Joint Accreditation Committee
ISCT | EBMT

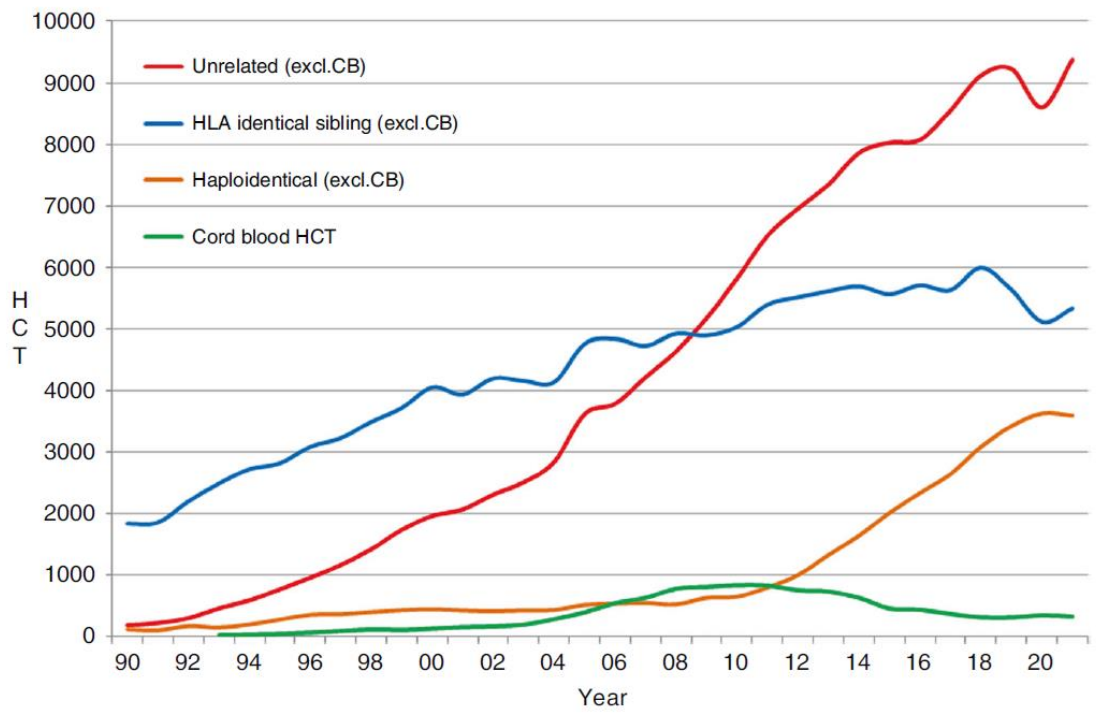
JACIE Inspector
CGT and GMP

EU

Hellenic Representative
Section "Tissues-Cells"

Remarkable progress in the field of allogeneic SCT

- Expanded patient pool (e.g. older pts)
  - NRM declines
  - antimicrobial strategies / support
  - modern conditioning
  - Modern GvHD prophylaxis
- Expanding the donor pool
  - WMDA 42 Mio unrelated donors
  - Transplant across HLA barriers (Haplo donors)

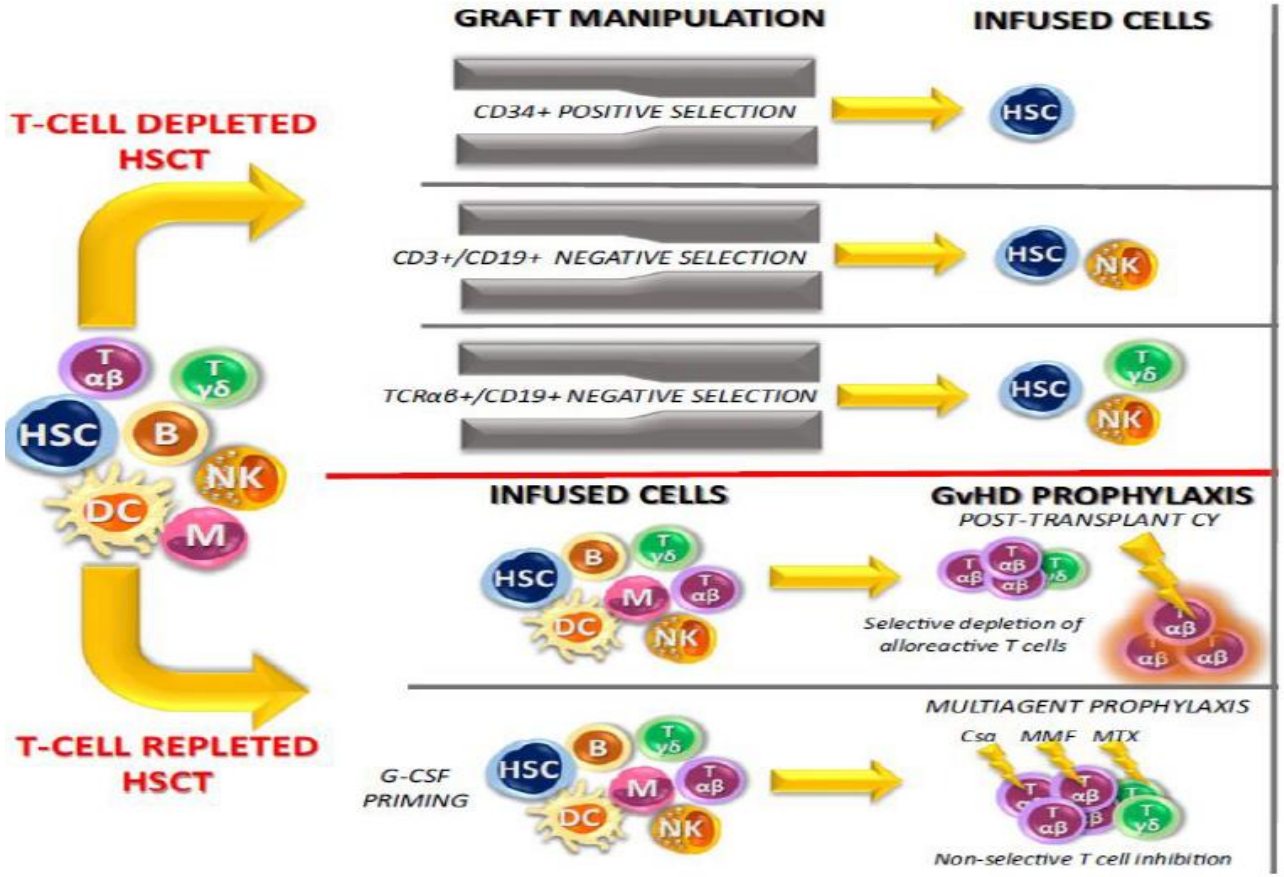


Passweg J et al. Hematopoietic cell transplantation and cellular therapies in Europe 2021. The second year of the SARS-CoV-2 pandemic. A Report from the EBMT Activity Survey. Bone Marrow Transplantation (2023) 58:647–658, Joseph Rimando et al. Blood (2023) 141 (1): 49–59.

Learning Objectives

- ❑Understand the platforms of haploidentical HSCT
- ❑Understand the current status of haplo-PTCY in comparison to matched HSCT
- ❑Adopt a strategy to choose donor, graft source and conditioning in haplo-PTCY HSCT
- ❑Recognize the unique aspects of haplo-PTCY HSCT
- ❑Adopt a strategy to treat relapse after haplo-PTCY HSCT
- ❑Understand the unknowns and potential challenges in haplo-PTCY HSCT

Haplo-SCT: Transplant across HLA barriers



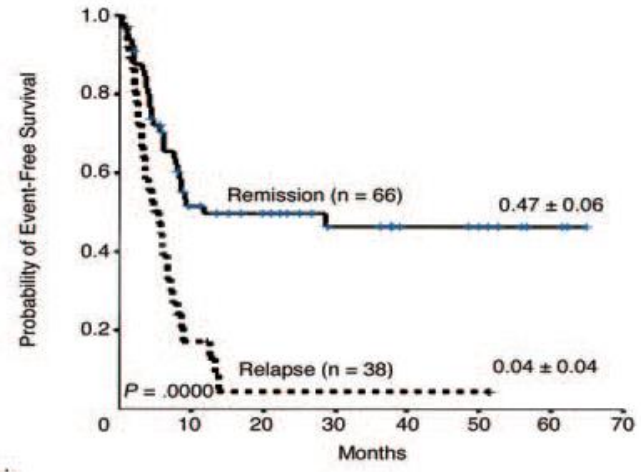
Without post-infusion immunesuppression

With post-infusion immunesuppression

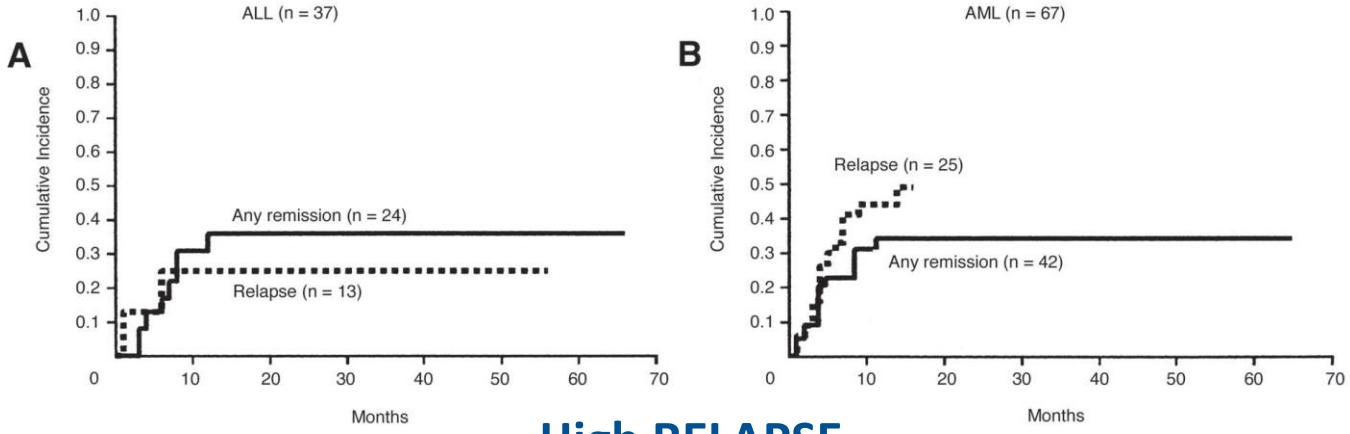
adapted from Bertaina, Curr Hematol Malig Rep 2017

T-cell depleted Haplo-SCT with CD34 selected “megadose” (veto effect) (Perugia)

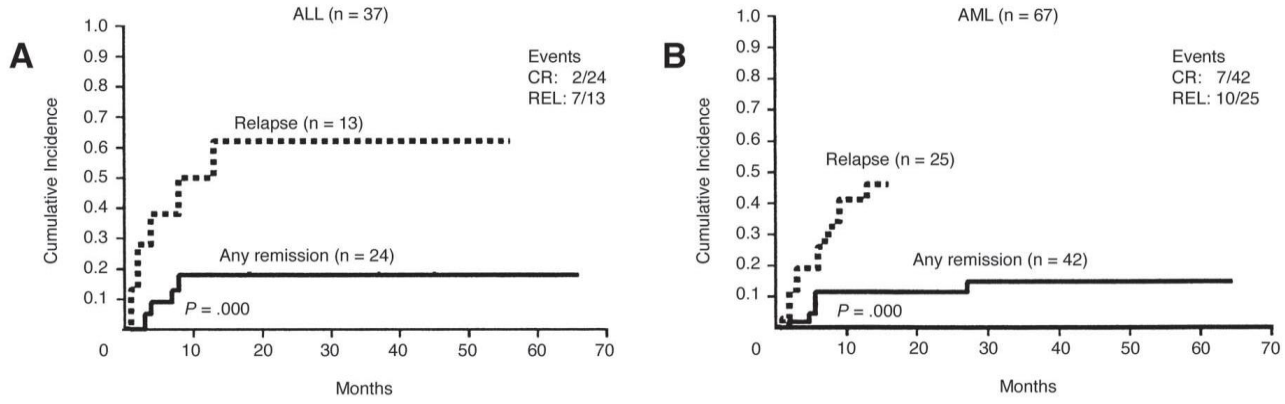
- slow immune reconstitution
- Expensive
- expertise in graft manipulation
- have in place a strategy for adoptive immunotherapy to reduce risk of infections



High TRM



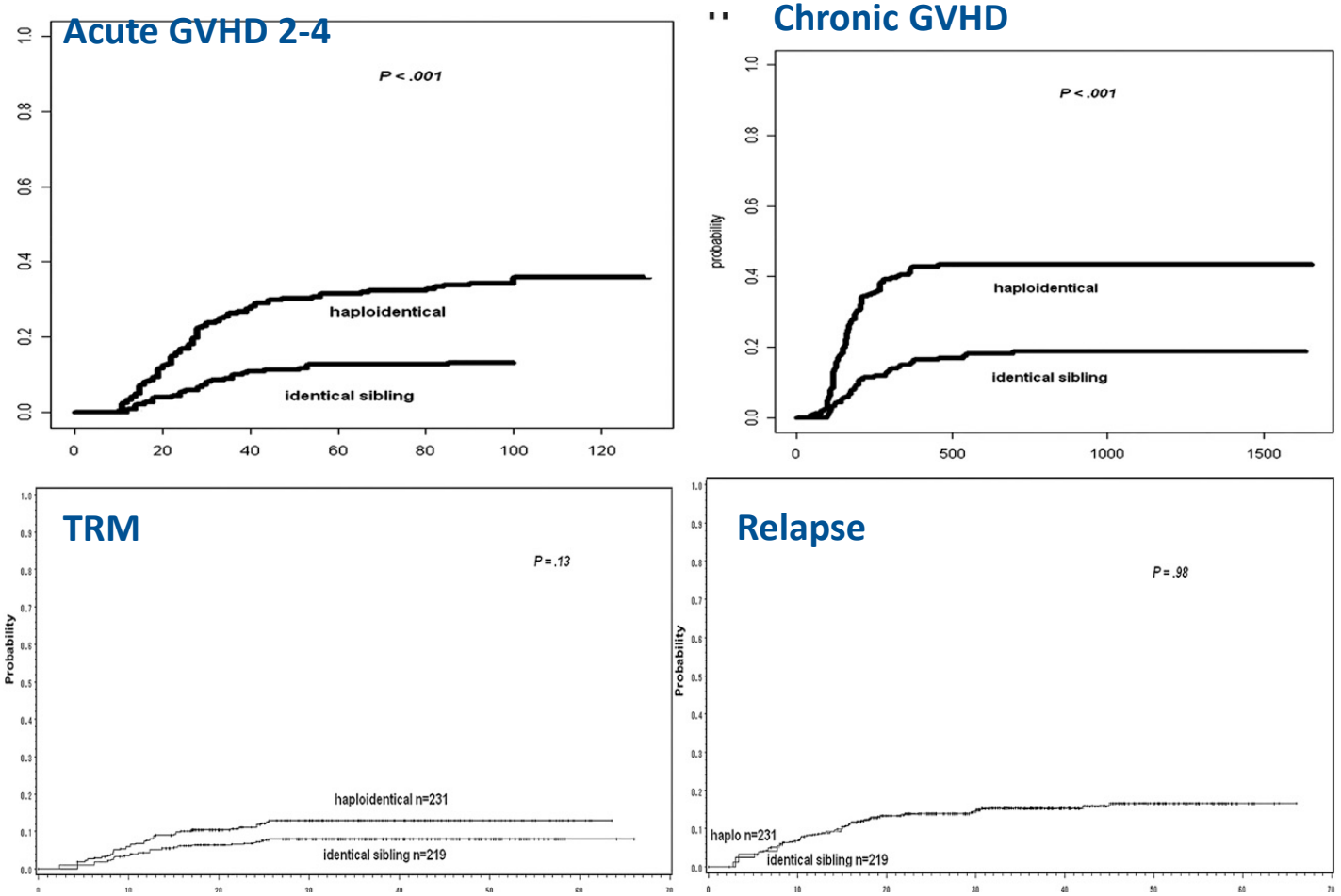
High RELAPSE



1. Aversa et al. JCO. 2005;23:3447-54,

Haplo-SCT with GIAC: G-CSF priming donor, intensive IMS, ATG, Combination PBSCT+BM. (China)

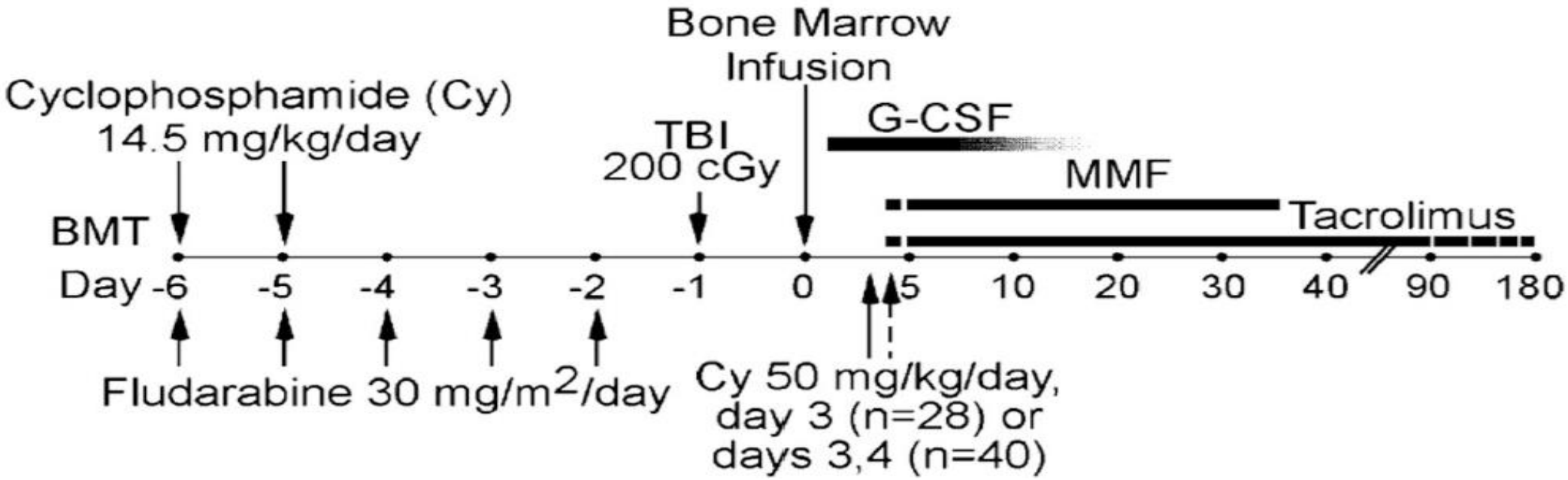
- Relatively inexpensive
- requires no expertise in graft manipulation
- Limited experience outside of China
- relatively high rates of severe acute and chronic GVHD are associated with this approach
- Italy: add basiliximab, use only BM



Lu et al Blood. 2006;107(8):3065, Wang Y, Blood. 2015 Jun;125(25):3956-62

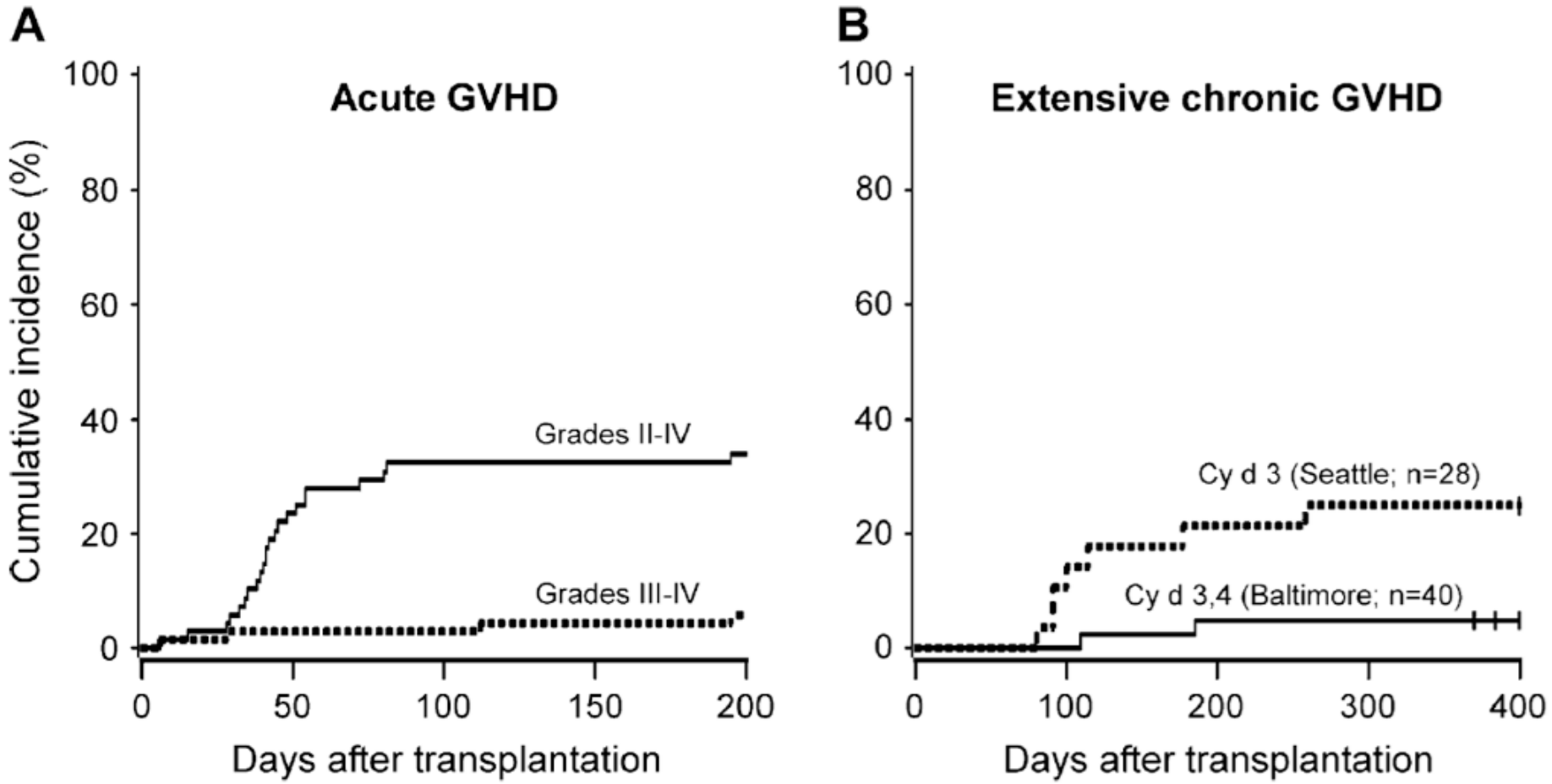
Haplo- SCT: PTCY is the winner

Low cost, simple, no extra instrumentation and training needed, utilization around the world



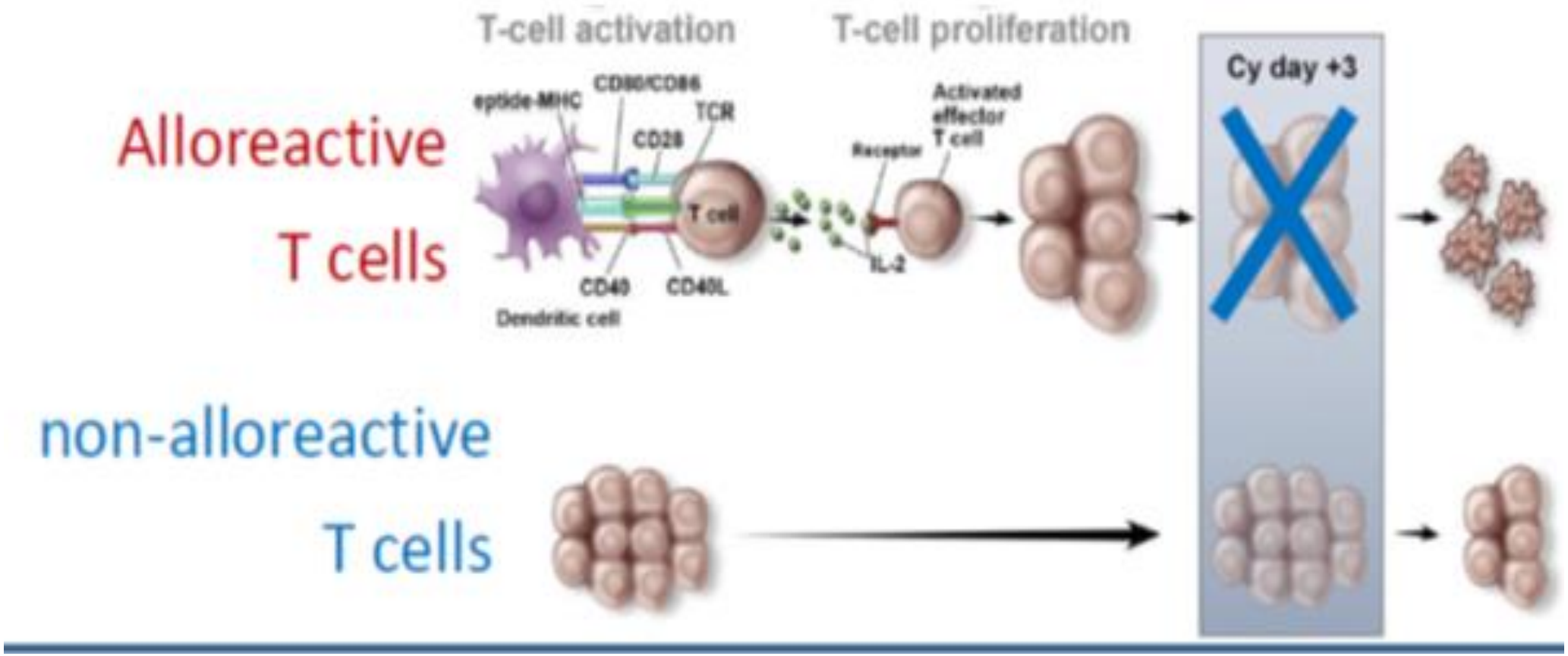
Luznik et al. BBMT 2008: 14; 641-650, Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation Nat Rev Clin Oncol. 2016;13(1):10-24

Early clinical studies of Haplo-BMT PTCY



Luznik et al. BBMT 2008: 14; 641-650

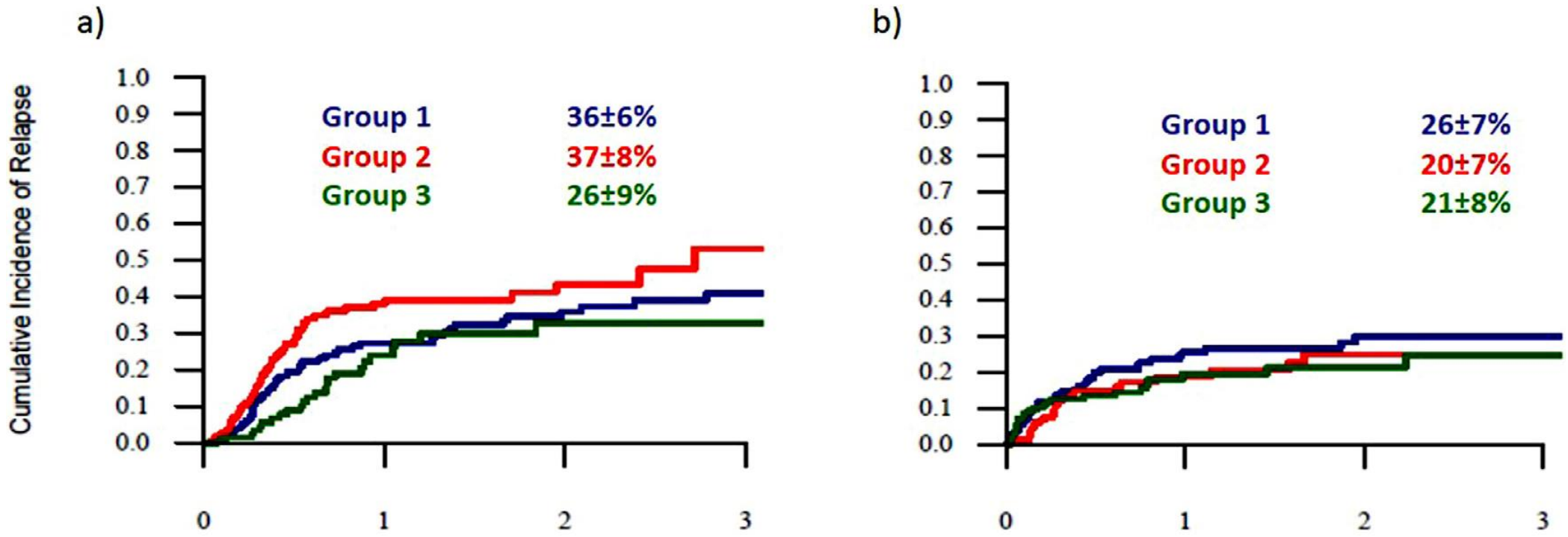
PTCY Haplo-HSCT : Depletion of in vivo alloreactive T cells



Luznik et al. Blood. 2001;98:3456-3464), Luznik L, Immunol Res. (2010) 47:65–77; Nunes NS and Kanakry CG (2019) Front. Immunol. 10:2668 Wachsmuth LP. JCI. 2019;

When to start CNI?

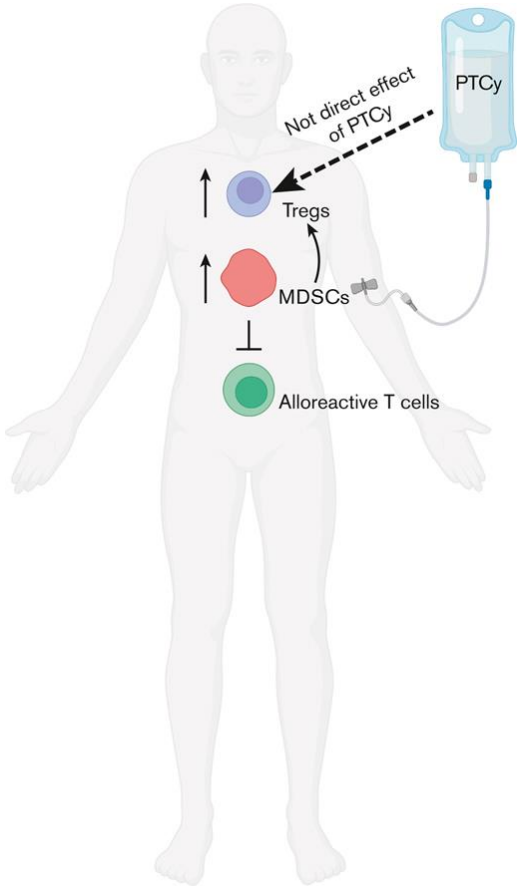
- EBMT retrospective



Ruggeri et al. BBMT 2020: 26, 1915-1922

PTCY Haplo-HSCT : preferential recovery of regulatory cells

- Surviving alloreactive T cells are actively being suppressed by Tregs and other regulatory cells
- Reduced cGVHD incidence

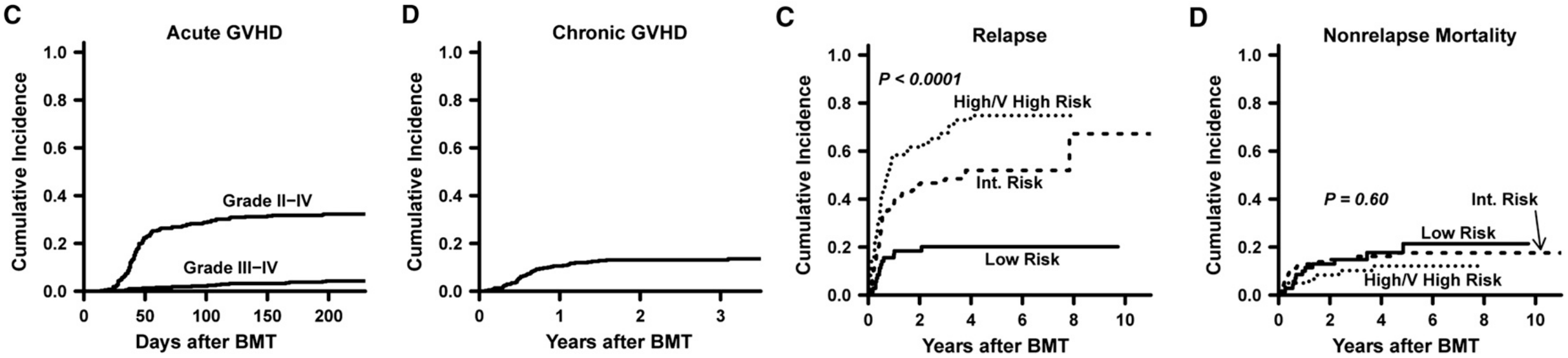


Fletcher RE et al.. Blood Adv. 2023

Haplo-SCT with PTCY: Confirmation of early clinical studies

N=372, Haplo-BMT, NMA

REL on parallel with other graft sources when DRI is factored in



Mc Curdy SR et al. Blood 2015; 125: 3024-3031

Haplo- SCT with PTCY

- Changed the field in performing SCT
- Already a standard of care for HLA-haploidentical HCT (EU and USA)
- Now everyone has a donor [Indian 700.000 donors, challenges in unrelated donor search e.g., minorities, population with extreme genetic diversity (novel alleles, unique haplotypes)
- Greece also a population with unique haplotypes, now with a poll of 250.000 donors about 30% of UD transplants are from Greek donors

Indian J Hum Genet. 2010 Sep-Dec; 16:105–107. WMDA: *DATRI Blood Stem Cell Donors Registry (528.000 donors), DKMS BMST Foundation India (110,393), MDR Marrow Donor Registry India Mumbai (53,275), GeneBandhu New Delhi (7847), Be The Cure Registry by Jeevan Stem Cell Foundation (13,167), The Arjan Vir Foundation (709)*

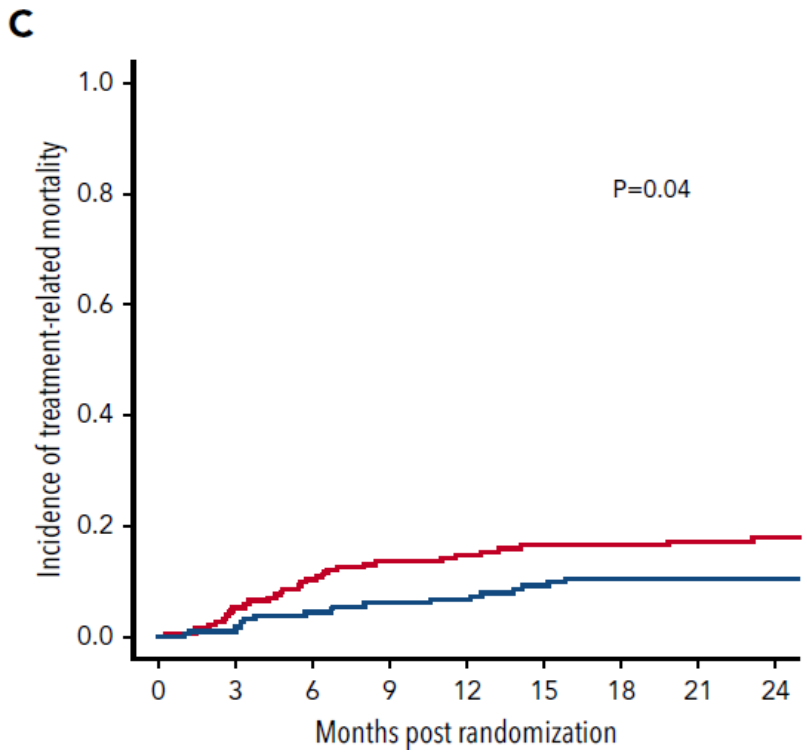
Haplo-SCT with PTCY: What we have learned

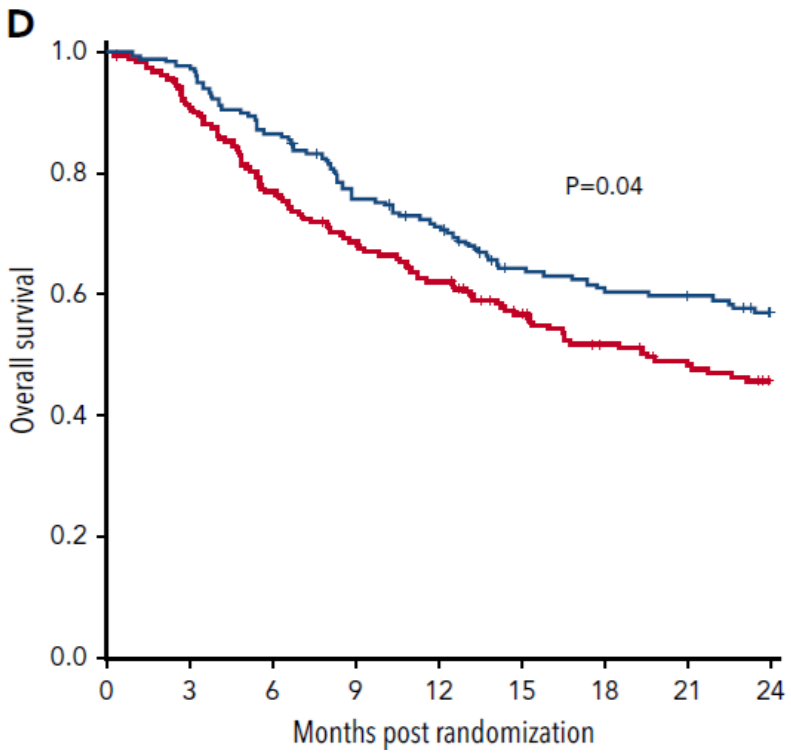
Haplo-PTCY > CB

Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial

KEY POINTS

- **There is no significant difference in PFS between UCB and haploidentical transplantation for leukemia or lymphoma.**
- **Lower nonrelapse mortality and superior OS favor haploidentical marrow over UCB transplantation.**

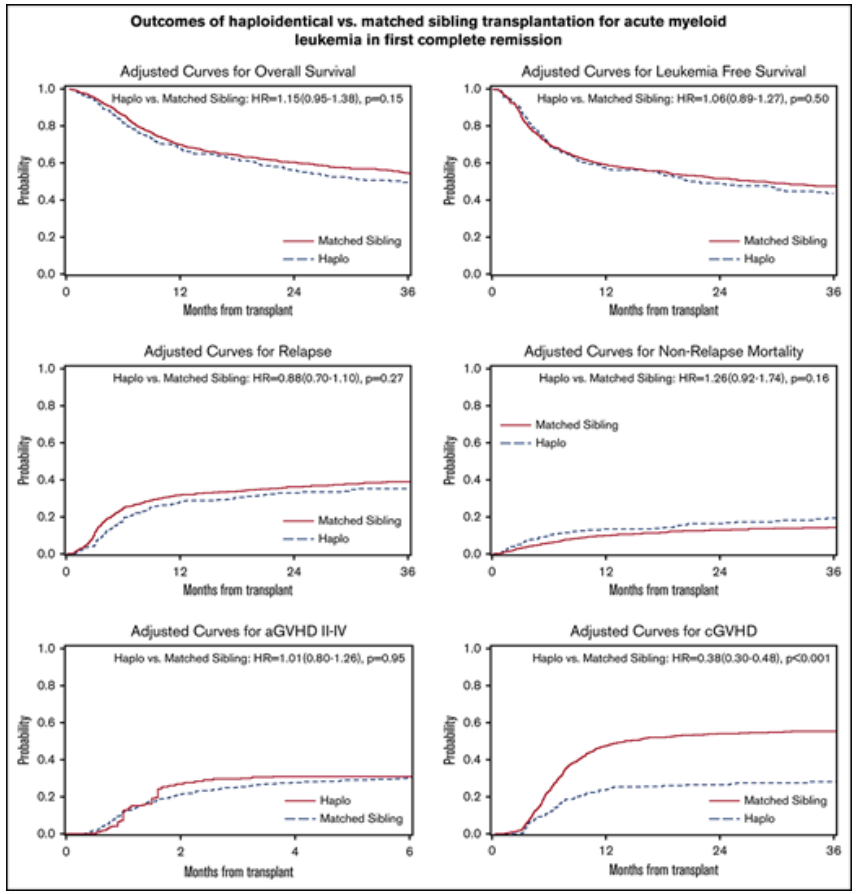




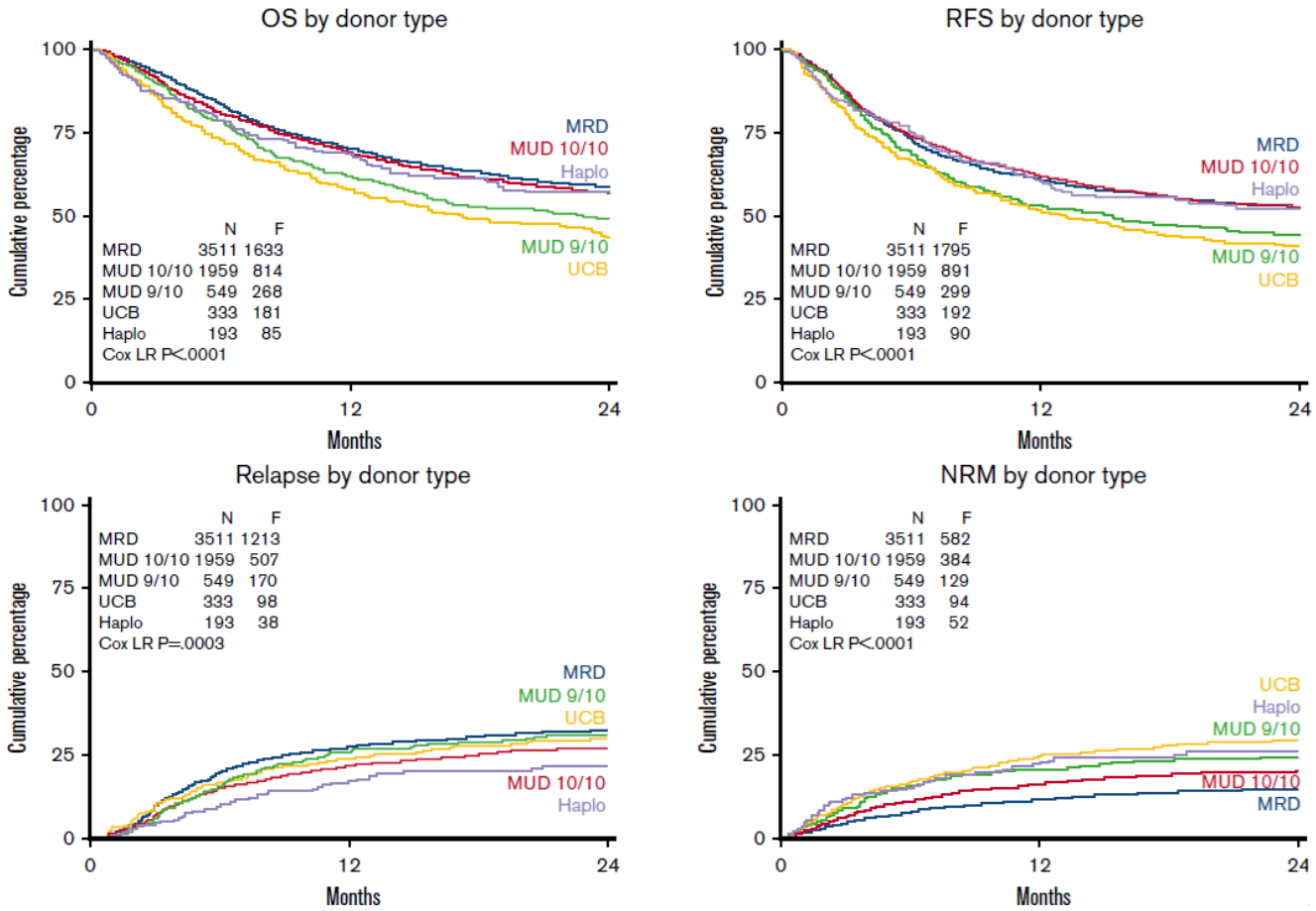
Ephraim J. Fuchs et al. Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation: the BMT CTN 1101 trial.. *Blood* (2021) 137 (3): 420–428.

Haplo-PTCY challenges matched CNI-based SCT

CIBMTR: AML in CR1.

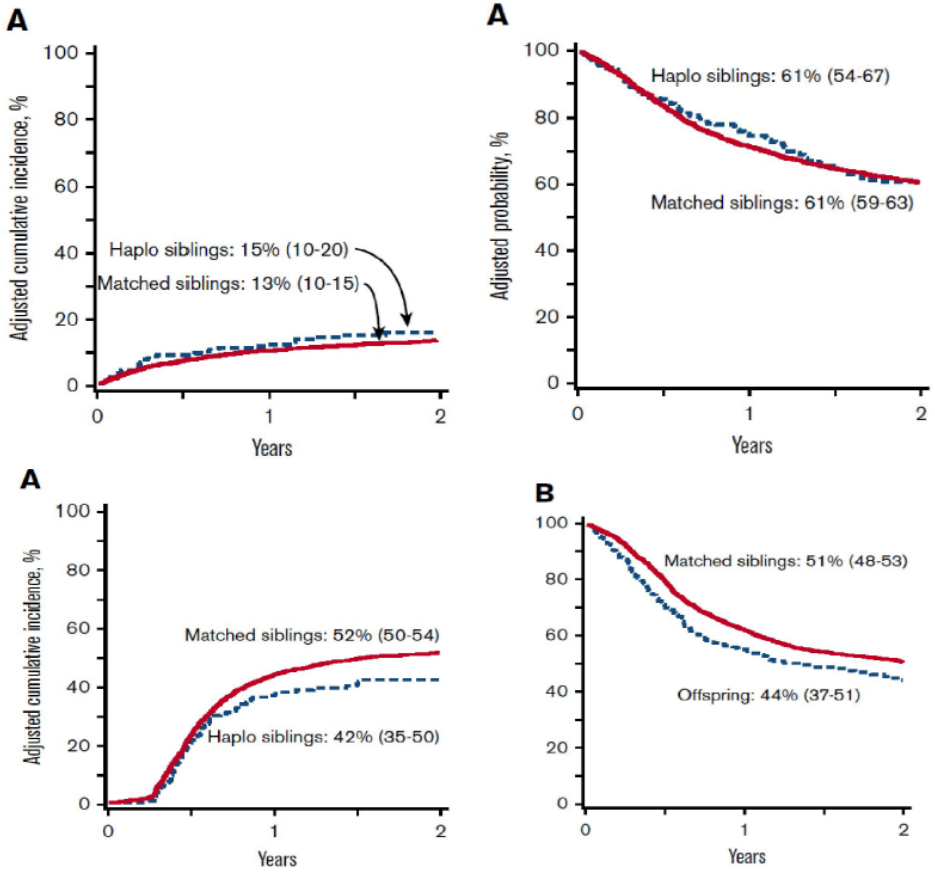


EBMT: poor risk AML in CR1.

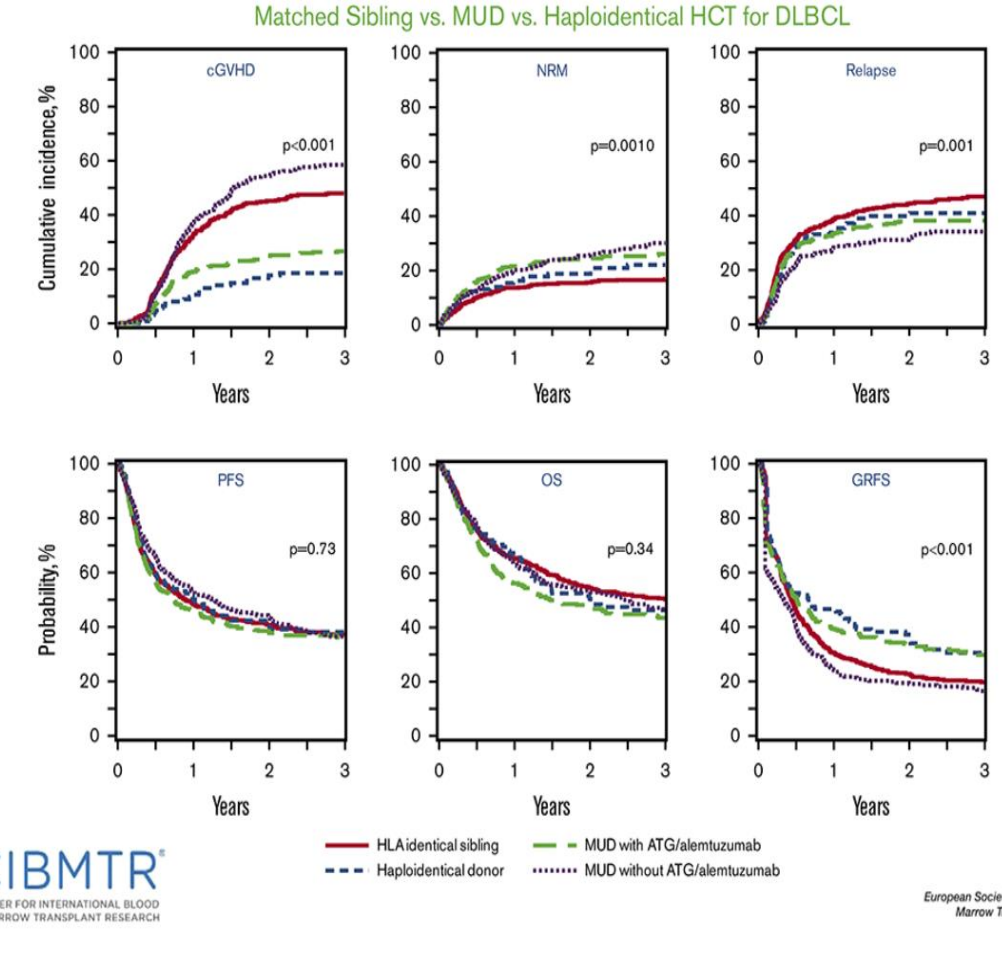


Rashidi et al Blood Advances 2019;3:1826-1836, Versluis J et al Blood Adv 2017;1:477-485

Haplo-PTCY challenges matched CNI-based SCT



Robinson, Blood Adv 2019



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

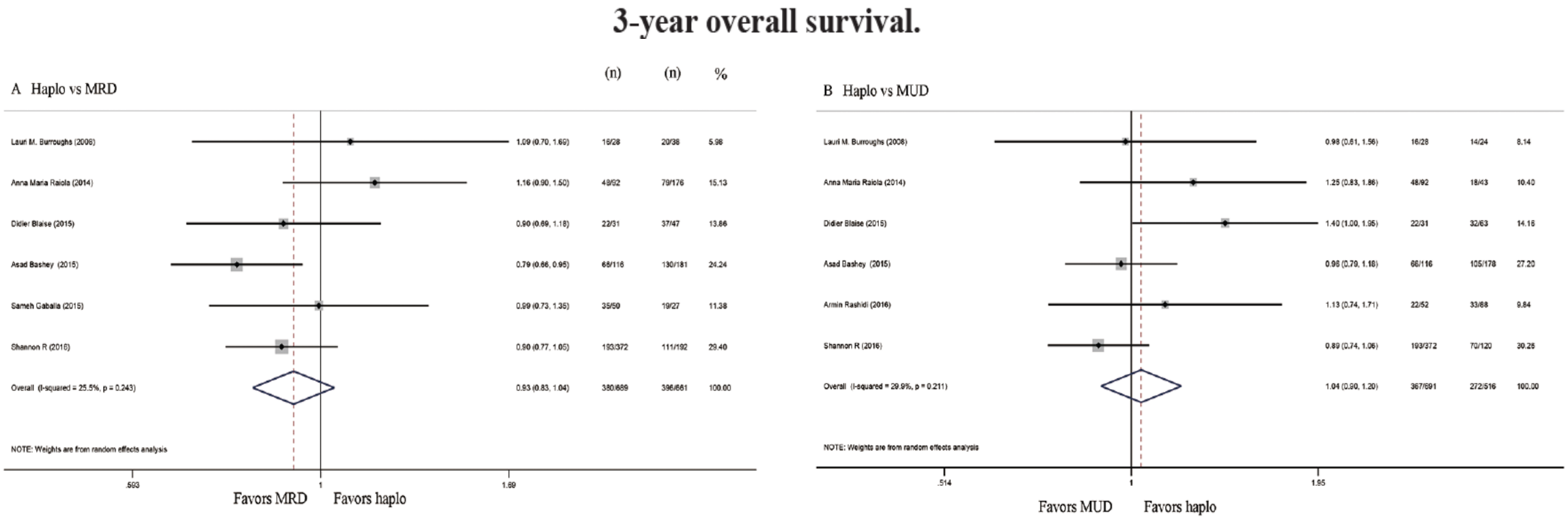
EBMT
European Society for Blood and Marrow Transplantation

Robinson, Blood Advances, 2019, Dreger at al. Blood Adv (2019) 3 (3): 360–369.

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Haplo-PTCY challenges matched CNI-based SCT

a meta-analysis of case-control studies



Gu et al. Oncotarget 2017; 8: 63574-63586

Donor selection in haplo-PTCY

- Donor must be medically, socially, and psychologically fit to donate
- Matched CMV serostatus between donor and recipient (though donor CMV serostatus is not associated with survival (letermovir prophylaxis?)
- Avoid major ABO incompatibility, use an ABO compatible donor over a minor ABO incompatible donor
- Donor age <40 years preferred over donor age ≥40 years
- Prefer male over females

McCurdy SR, Blood Adv. 2018;2(3):299-307. Elmariah H,Biol Blood Marrow Transplant. 2018;24(5):1099-1102.

Anti-HLA Donor Specific Antibodies (DSA)

- DSA in the recipient at transplant are the most important aspects of haplo-donor selection
- Increased DSA in parous females or pts with high transfusion burden (30-50%) vs 11% in males
- DSA against HLA Class I and II equal,
- what constitutes a prohibitive DSA level is unclear, mean fluorescence intensity (MFI) values can differ between laboratories
- MFI > 2.000 / > 5.000 / 10.000 → graft dysfunction, late engraftment / graft failure / very high risk of graft failure

McCurdy SR, Blood Adv. 2018;2(3):299-307. Elmariah H,Biol Blood Marrow Transplant. 2018;24(5):1099-1102.

DSA Desensitization

- Goal (arbitrarily) → reduce DSA to MFI < 3.000
- 3 to 6 every-other-day therapeutic plasma exchange (TPE) with post-TPE/IV immunoglobulin (IVIG) starting 2 weeks before conditioning
- Sop up the DSA by administer to the recipient irradiated “buffy coat” prepared from 1 unit of blood before transplantation

McCurdy SR, Blood Adv. 2018;2(3):299-307. Elmariah H,Biol Blood Marrow Transplant. 2018;24(5):1099-1102.

Donor- Recipient Relationship

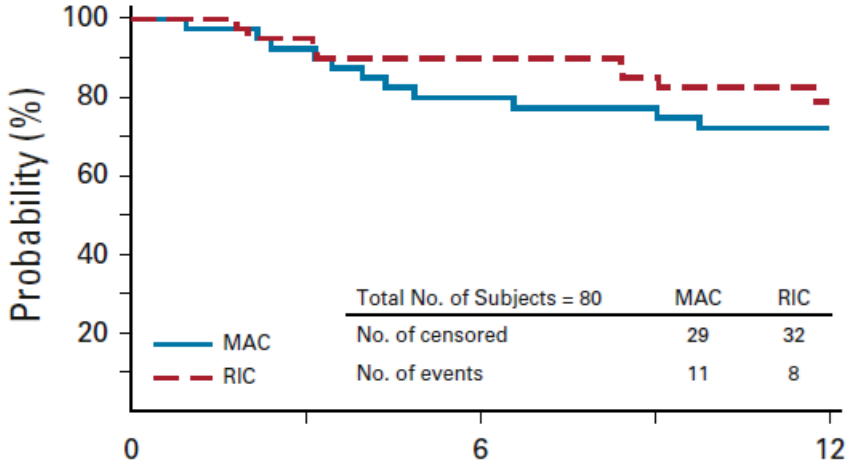
- ❑Absence of a negative effect of increasing HLA mismatched on outcomes (reports that DRB1 or epitope mismatching may decrease RR
- ❑avoid parent donors (14% graft failure vs 6% siblings and offsprings)
- ❑Prefer younger children than older sibling
- ❑2nd or even 3rd degree relatives (eg uncle, aunt, cousins, grandchildren) are safe alternatives
- ❑Q: younger nephew vs older sibling?

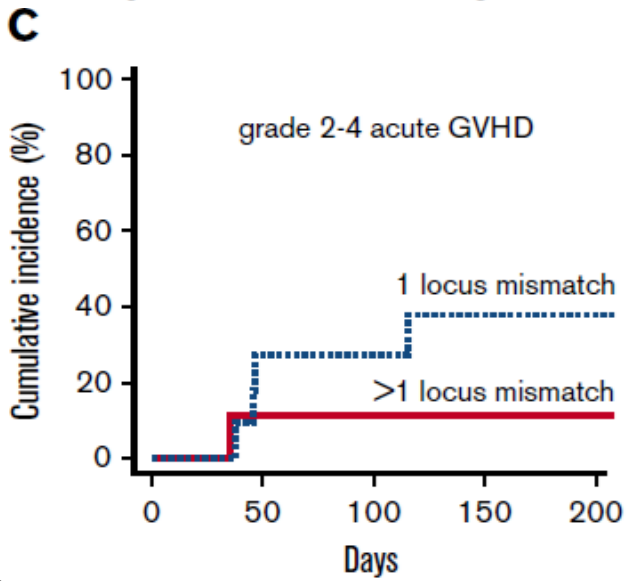
Kasamon YL et al. BBMT 2010; 16:482-489, Rimando J et al. Blood Advances 2018; 2: 3590-3601,McCurdy SR et al Blood Adv 2018; 2: 299-307, Elmariah H et. BBMT 218; 24: 1099-1102; Mariotti J. BMT 57, 1758–1764 (2022), Canaani J, Am J Hematol 2018; 93:246-253 Fuchs EJ et al. Blood 2022;139:1452-1468, Elmariah H BBMT. 2018;24(5):1099-1102.

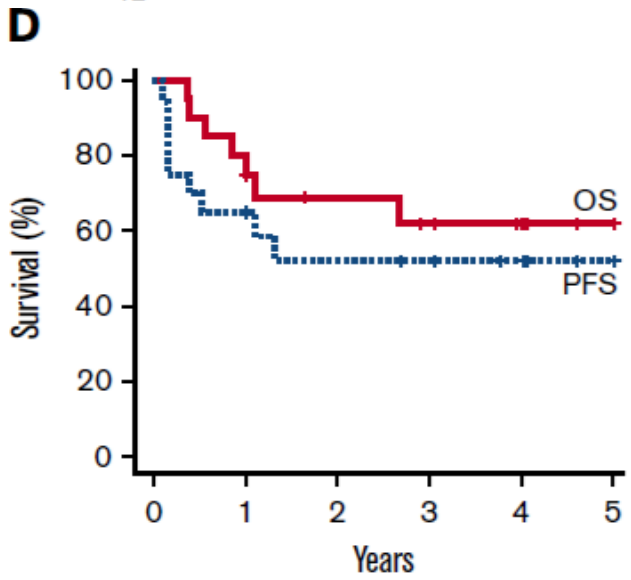
PTCY in UD with >1 mismatches (haplo UD?)

HLA match, No. (%)	
7 out of 8	49 (61)
6 out of 8	19 (24)
5 out of 8	7 (9)
4 out of 8	5 (6)

Unrelated grafts		
HLA matches§		
5/10 (1 locus mismatch at A, B, Cw, DRB1, DQB1)	1	(5%)
6/10 (1 A, 1 Cw, both B loci mismatched)	1	(5%)
7/10 (1 locus mismatch at class I, DRB1, DQB1)	3	(15%)
8/10	4‖	(20%)
9/10	11¶	(55%)







Shaw wt al. JCO 2021; 39:1971-1982, Kasamon YL, Blood Advances 2017; 1:288-292

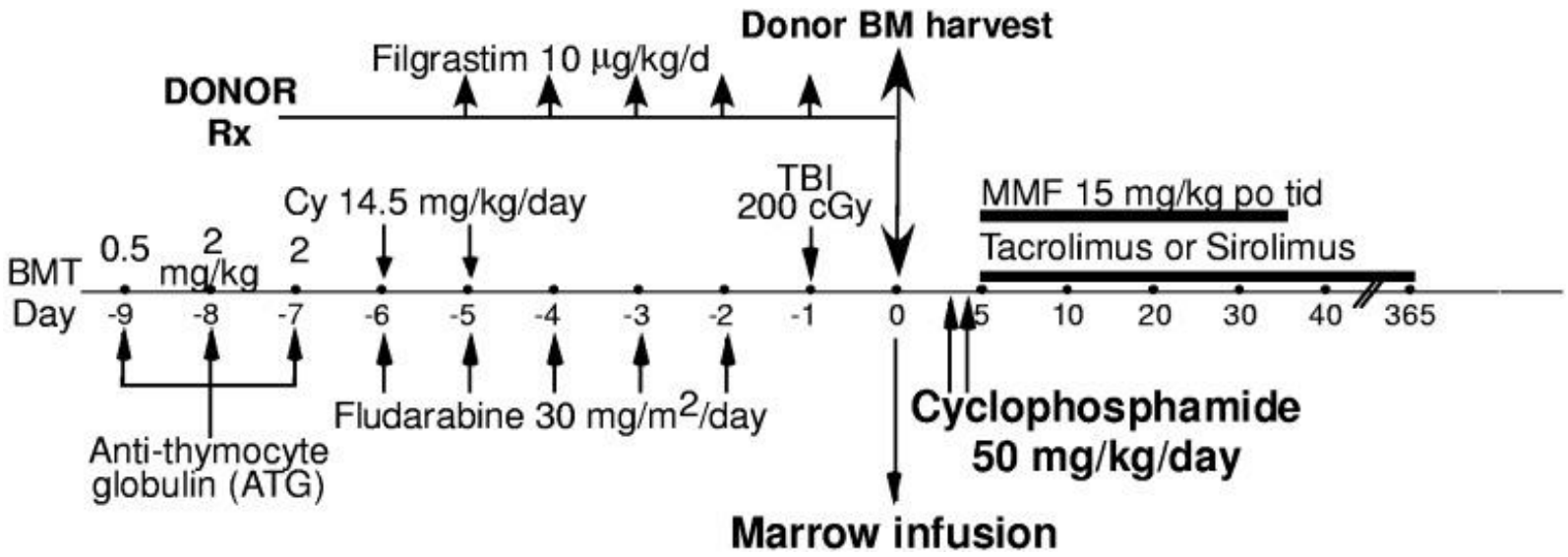
PBSC or BM?

- Initial studies with BM, European experience with PBSCT
- Initial concerns that GVHD with PBSCT greater
- PBSCT vs BM RIC-Haplo (CIBMTR)
  - neutrophil engraftment 1 to 2 days earlier with PBSCT
  - aGVHD and cGVHD risk was greater
  - relapse risk was less
- Use of PTCY + ATG with PBSCT
- BM: higher nucleated cell graft dose has been associated with improved PFS and OS
- PBSCT preferable for HR pts

McCurdy SR et al. BBMT 2018; 24: 343-352, Bashey A et al. JCO 2017; 35: 3002-3009

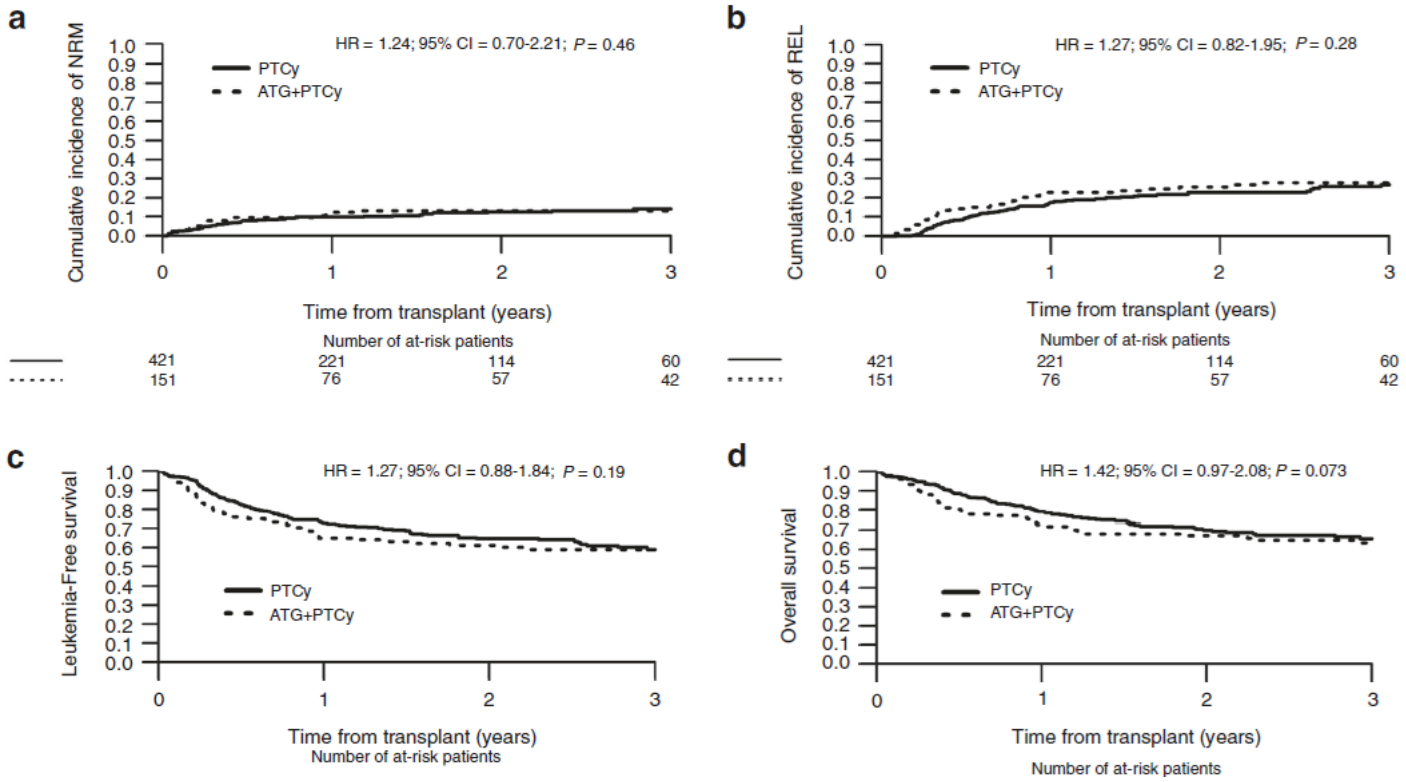
Haplo-PTCY in Non-malignant disorders

- Haplo-HCT with PTCY facilitates access to pts with no donor (minorities) and benign hematological disorders
- Sickle cell disease
- Thalassemia
- Fanconi anemia
- Aplastic anemia



Bolanos Meade, Blood 2012; 120:4285-4291, Bolanos Meade et al. Lancet Haematol 2019; 6:e183-e193

Should anti-thymocyte globulin be added in post-transplant cyclophosphamide based matched unrelated donor peripheral blood stem cell transplantation for acute myeloid leukemia? A study on behalf of the Acute Leukemia Working Party of the EBMT



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

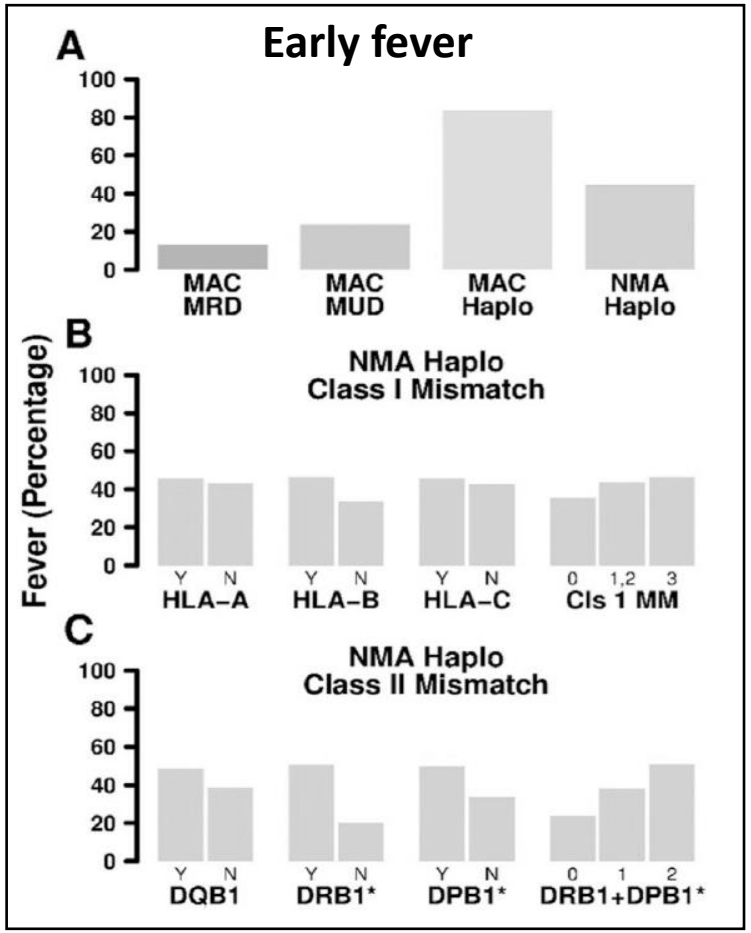
Unique concerns in haplo-SCT with PTCY

- Unique adverse events (CRS)
- Unique toxicities (Hemorrhagic cystitis, Cardiac etc)
- Unique relapses (HLA loss), more relapses?
- Unique immune reconstitution
- Increased CMV reactivation (but not worse survival)
- No PTLD with antibody free platforms
- TMA as in non PTCY transplants

Fayard et al BMT 2019; Irene et al BMT 2021; Goldsmith et al Blood 2021; Luznik et al J Clin Oncol 2021, Slade et al Transpl Infect Dis Off J Transplant Soc 2017; Fayard et al BMT 2019; Irene et al BMT 2021, Ruggeri et al Transpl Infect Dis 2015; Gutierrez-Aguirre et al Hematol Transfus Cell Ther 2020; Arango et al BBMT 2020

Unique AEs after haplo-PTCY: CRS

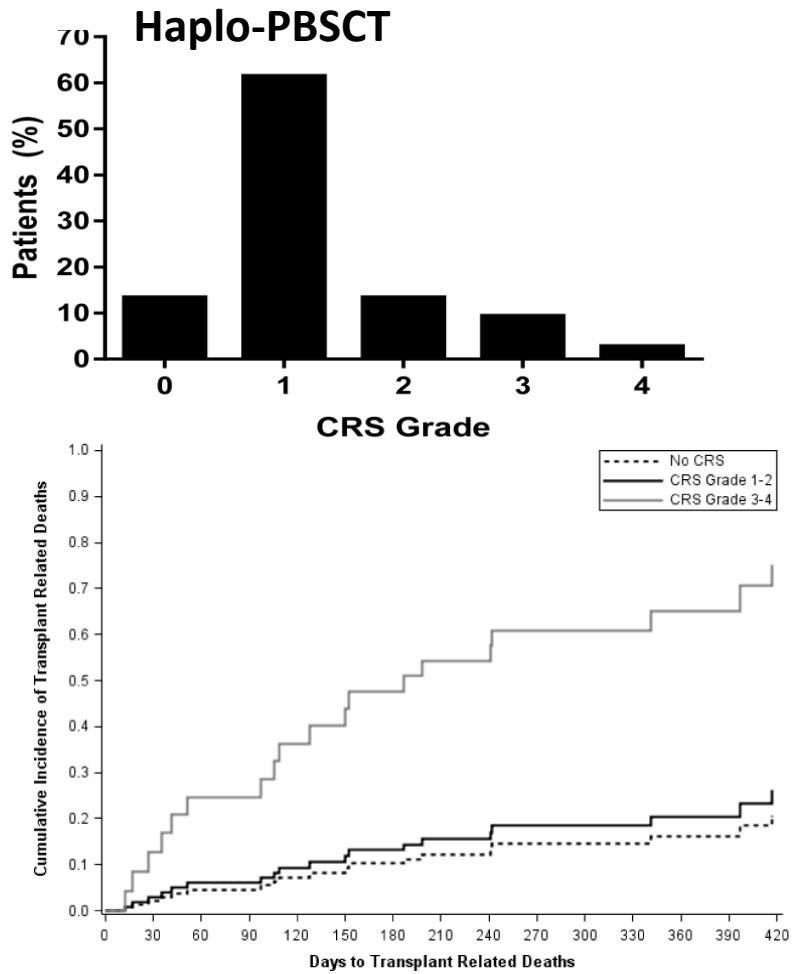
- related to the intense alloreactivity occurring as a result of the HLA mismatch between donor and recipient
- associated with class II mismatching
- Associated with higher CD3 graft cell dose (PBSCT > BM)
- between days 0 and 6
- severe



McCurdy SR, Blood Adv. 2018;2(3):299-307, Abboud R et al., BBMT 2016; 22:1851-1860

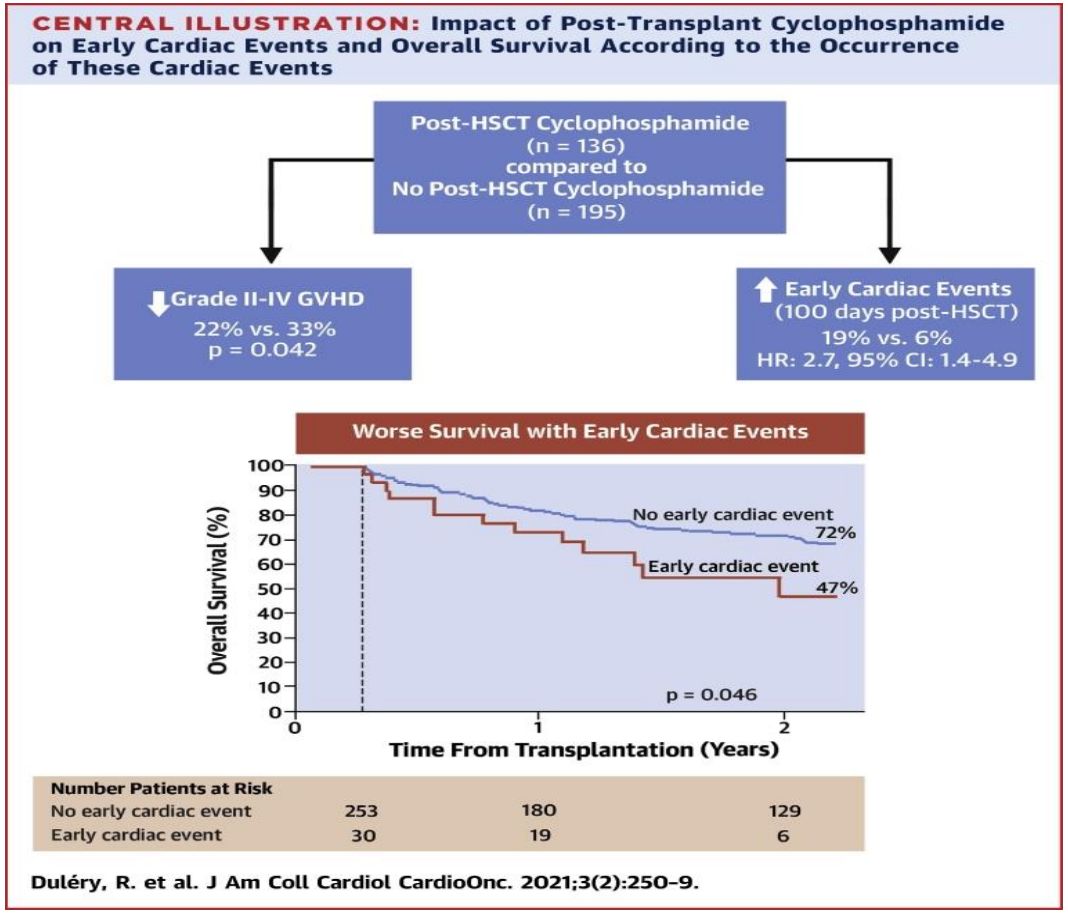
Unique AEs after haplo-PTCY: CRS

- ❑Noninfectious early fevers44% to 80%
- →Antipyretics, antibiotics, avoid steroids → typically resolve soon after completion of PTCY
- →no effect on survival
- →May decrease RR
- ❑Severe 3-4 CRS 19.5% PBSCT vs 4.9% BM ,
- →tocilizumab or corticosteroids
- →May influence TRM
- →May decrease RR



McCurdy SR, Blood Adv. 2018;2(3):299-307, Abboud R et al., BBMT 2016; 22:1851-1860, Abboud R et al. BMT 2021;56:2763-2770

Unique toxicities after haplo-PTCY: cardiotoxicity



Oral EBMT Glasgow (ALWP study)

- 5883 adult AML pts, median 58 y
- PTCY
- Haplo 61% /MUD 28% / MRD 11%

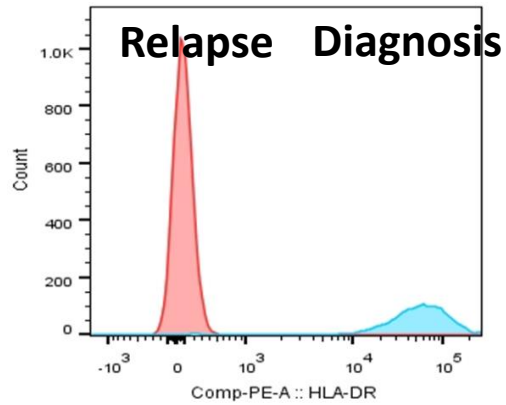
Cardiac disease (MV analysis)

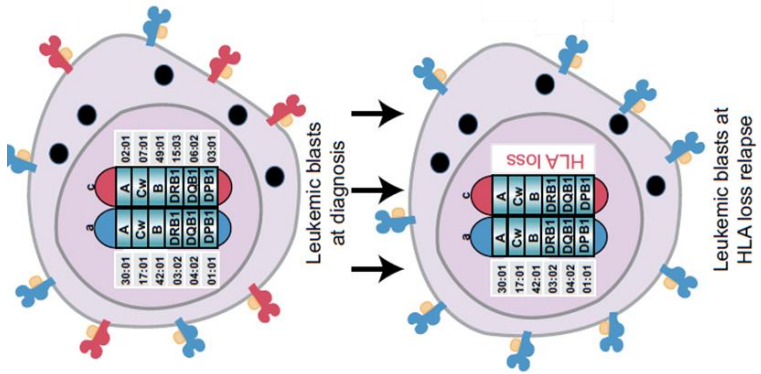
- NRM HR 1.47, p<0.0001
- reduced OS HR 1.3, p=0.0002

Lin CJ et al Cancer 2017;123:1800-1809, Yeh J et al. Blood Adv 2021; 5: 5599-5607, Dulery R et al JACC CardioOncol 2021; 3: 250-259, Spyridonidis et al The impact of individual comorbidities on NRM risk following PTCY allogeneic hematopoietic stem cell transplantation: An ALWP-EBMT study. EBMT 2023, Glasgow (oral)

Unique aspects of relapse after haplo-HSCT.

- ❑Initial concerns that PTCY increases relapse rate not true
  - Initial reports with relapsed/ refractory leukemia and use RIC regimens
  - HLA matched data suggest comparable relapses with MTX/CNI when DRI is factored in
- ❑HLA class II downregulation
- ❑**HLA Loss of the mismatched HLA haplotype**
  - PTCY haplo: 33% of patients with relapsed AML
  - ATG based haplo: 50% of relapses, > 180d after Tx





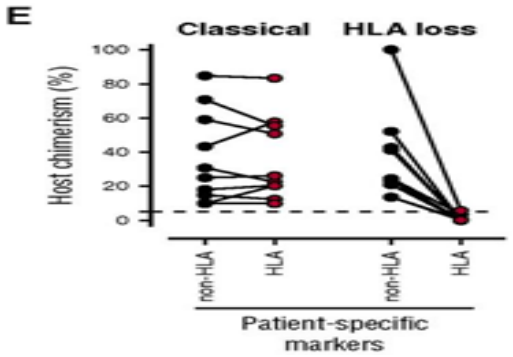
Vago L. et al New Eng. J. Med. **361**, 478-488 (2009), Christopher MJ N. Eng. J. Med. 379, 2330-2341 (2018), Zeiser et al. Blood. 2019 Mar 21;133(12):1290-1297. Crucitti L, Leukemia. 2015;29(5):1143-1152, Vago et al. *Blood* (2018) 132 (Supplement 1): 818. JAMA Network Open. 2022;5(4):e226114.

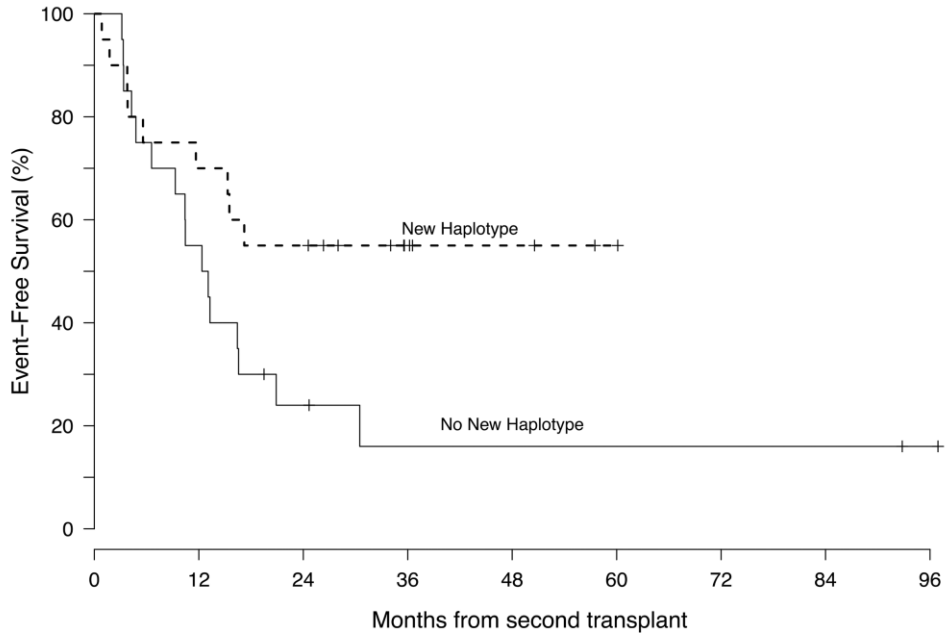
HLA loss relapse

- Diagnosis: purification of HLA blasts, or HLA-KMR PCR (combination of chimerism and HLA)

- Choice of salvage treatment

  - Same donor (DLI, second HCT) is not anticipated to be effective in treating HLA loss relapse
  - use a different haplotype-mismatched donor, the second donor's T cells should be alloreactive to the mismatched HLA molecules retained on the leukemic blasts





Ahci M et al. Blood (2017) 130 (10): 1270–1273., . Immus P et al. BBMT 2017: 23:1887-1894

Haplo-PTCY: Summaries, knowns and unknowns

- Low cost, simple, no extra instrumentation and training needed
- Low rates of acute and chronic GVHD and non-relapse mortality
- REL on parallel with other graft sources when DRI is factored in
- All conditioning intensities possible
- Haplo-PTCY outcomes are >= cord blood and >+ other Haplo platforms
- Safe and efficacious for malignant and non-malignant disorders
- Equivalent outcomes between haplo-PTCY and both MUD-SCT and MSD-SCT
- # of mismatches does not matter, Can use 2nd or 3rd degree relatives
- Can discontinue CNI at day 60 (BM) 90 (PBSC) safely
- Low rate of infections and rapid immune reconstitution
- Unique toxicities and relapses

McCurdy SR, Blood Adv. 2018;2(3):299-307. Elmariah H,Biol Blood Marrow Transplant. 2018;24(5):1099-1102.

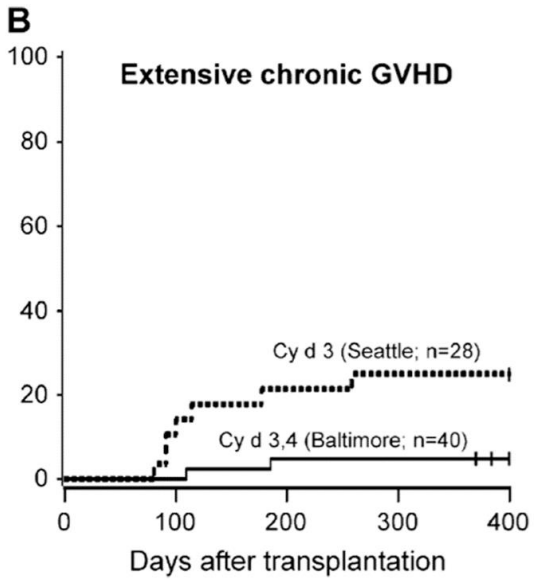
Haplo-PTCY: Summaries, knowns and unknowns

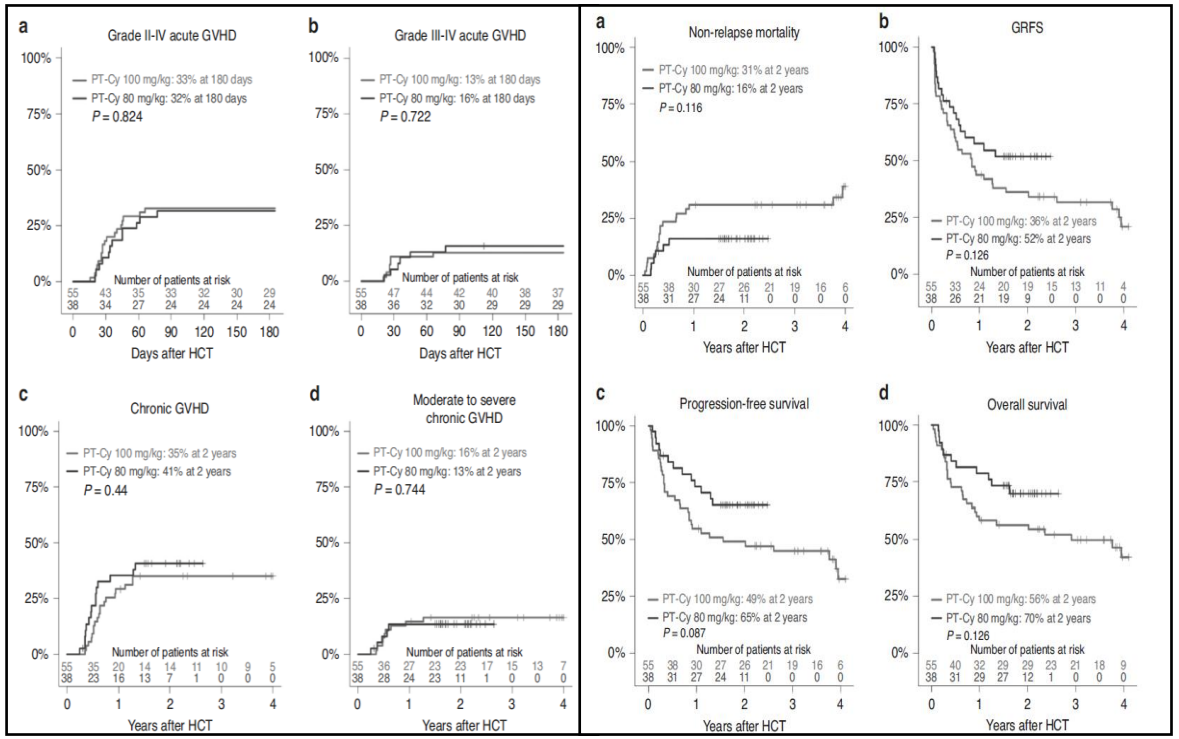
- Haplo-PTCY outcomes are >= cord blood and >+ other Haplo platforms
- Equivalent outcomes between haplo-PTCY and both MUD or MSD-SCT
- Comparison between PTCY Haplo vs PTCY-MUD or PTCY-MSD unknown
- Preferable in urgency in pts with high-risk disease (haplo donor immediate available)
- Preferable in Hodgkin / PD-1 pretreated pts. (Increased severe GVHD after PD-1 pretreatment, PTCy ameliorates GVHD by restoring regulatory and effector T-cell homeostasis after PD-1 blockade)

Shuntaro Ikegawa Blood Adv (2019) 3 (23): 4081–4094

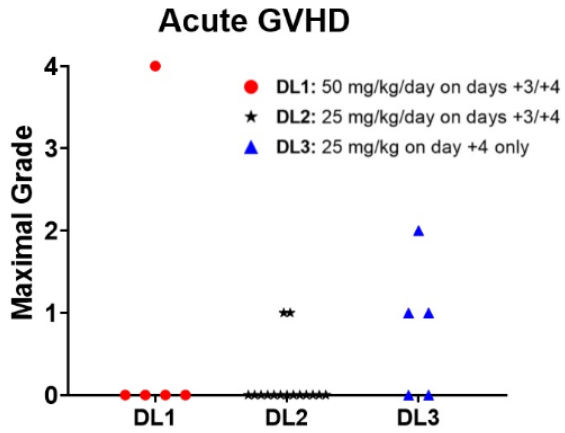
Haplo-PTCY: Can PTCY 100 mg/kg dose decreased ?

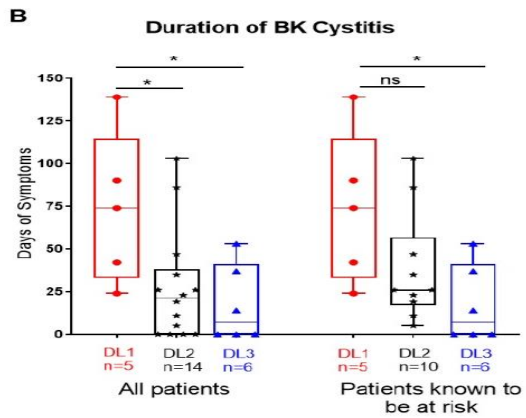
Single center Haplo PBSCT, elderly, 80,g/kg vs 100 mg/kg historical comparison





Phase I/II Haplo-BMT
NCT03983850





Dulery et al . Bone Marrow Transplantation (2023) 58:386–392; McAdams MJ et al. Blood 2021; 138 (suppl), abstract 101

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MOHTY	Mohamad	Vice-Chair
GIEBEL	Sebastian	Secretary
BRISSOT	Eolia	secretary

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PERIC	Zina	Acute Lymphoblastic Leukaemia	Co-leader
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BAZARBACHI	Ali	Post-transplant pharmacologic modulation	Co-leader
SANZ	Jaime	Alternative donor	Leader
PIEMONTESE	Simona	Alternative donor	Co-leader

PEOPLE

DONORS

FUNDING / SUPPORTERS

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