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A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Selection and Transplantation of Mismatched Unrelated Donors

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Chief Medical Officer, NMDP
Senior Scientific Director, CIBMTR

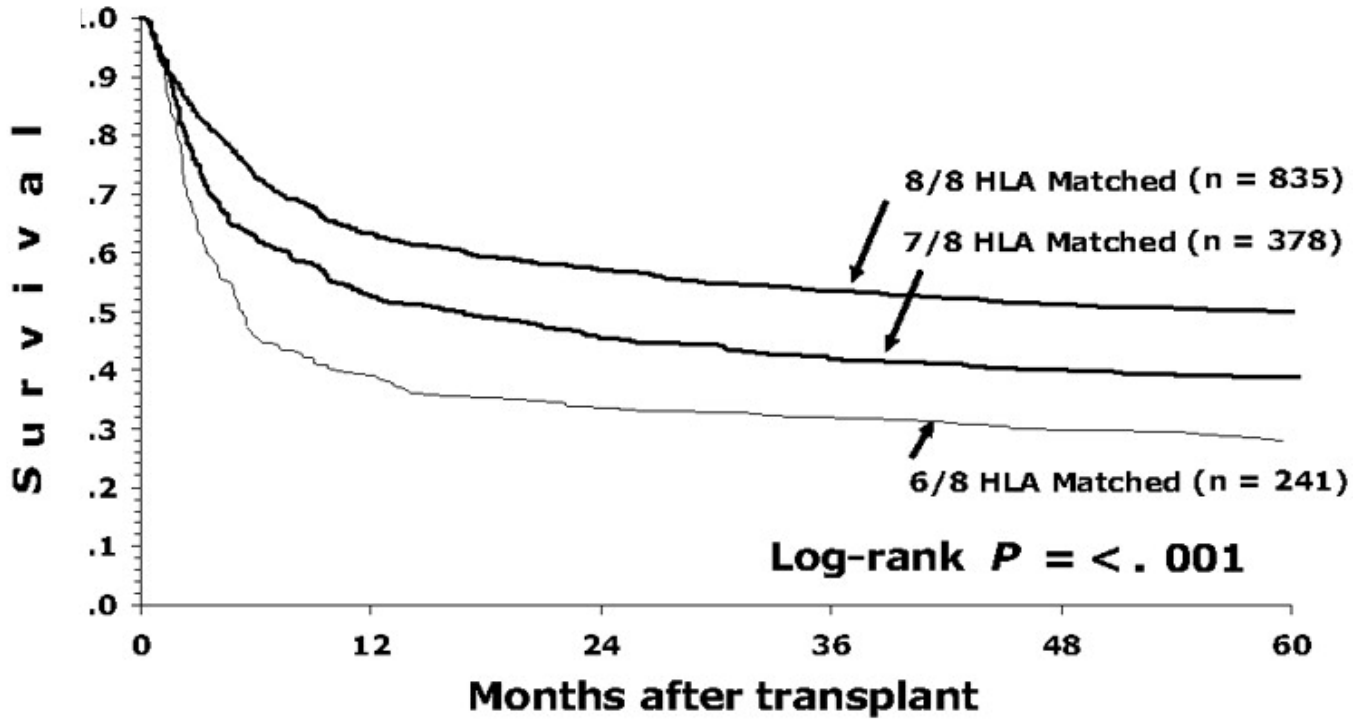
Disclosures

Full time employee of NMDP

Historically, overall survival (OS) has been inferior following MMUD (6-7/8) vs. MUD (8/8) HCT using CNI-based GvHD prophylaxis

Patient cohort:

- N=3,857
- ALL, AML, CML, MDS
- 1st alloHCT 1988-2003
- 84% MAC
- 94% BM grafts
- 78% T-cell replete
- **CNI GvHD prophylaxis**
- Median follow-up = 5y



50% 8/8
39% 7/8 **5y OS**
28% 6/8

Early stage-disease OS is shown.
Similar survival trends for intermediate and advanced-stage disease.

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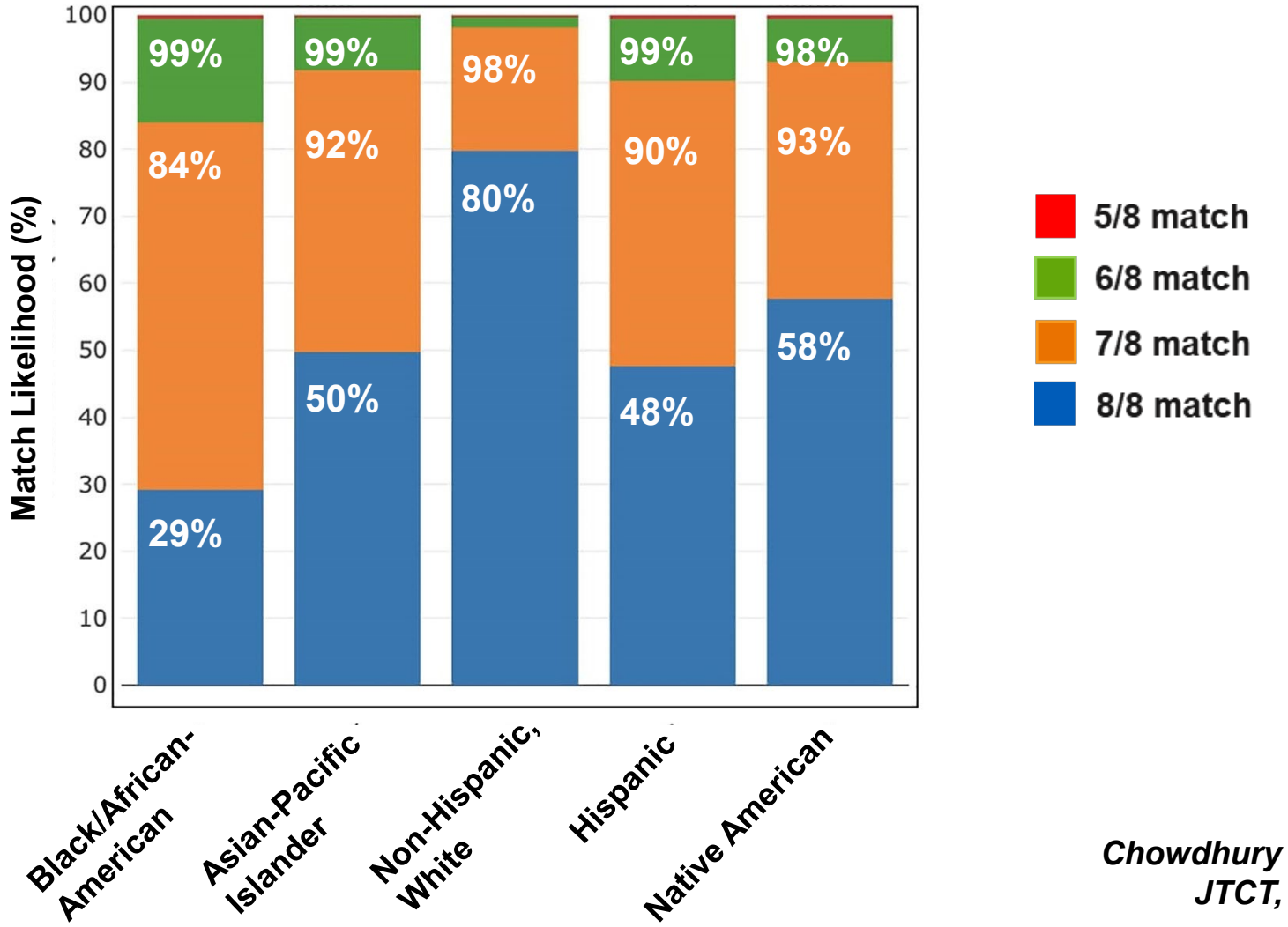
CNI = calcineurin inhibitor

Lee at al, Blood 2007;110(13):4576

8/8 unrelated donor unlikely for many patients, but 7/8 mismatched unrelated donor (MMUD) donors are likely

HLA match likelihoods (%) at 5/8-8/8 levels with donors of all ages in 5 broad race/ethnic groups



Chowdhury et al, JTCT, 2023

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original reports

Phase II Trial of Costimulation Blockade With Abatacept for Prevention of Acute GVHD

Benjamin Watkins, MD[1]; Muna Qayed, MD[1]; Courtney McCracken, PhD[2]; Brandi Bratrude, BA[3]; Kayla Betz, BS[3]; Yvonne Suessmuth, PhD[1]; Alison Yu, PhD[3]; Shauna Sinclair[4]; Scott Furlan, MD[5]; Steven Bosinger, PhD[6]; Victor Tkachev, PhD[3]; James Rhodes, PharmD[7]; Audrey Grizzle Tumlin, BS[7]; Alexandria Narayan, BA[5]; Kayla Cribbin, BS[4]; Scott Gillespie, MS[2]; Ted A. Gooley, PhD[5]; Marcelo C. Pasquini, MD[8]; Kyle Hebert, MS[8]; Urvi Kapoor, MD[9]; Andre Rogatko, PhD[10]; Mourad Tighiouart, PhD[10]; Sungjin Kim, MS[10]; Catherine Bresee, MS[10]; Sung W. Choi, MD[11]; Jeffrey Davis, MD[12]; Christine Duncan, MD[3]; Roger Giller, MD[13]; Michael Grimley, MD[14]; Andrew C. Harris, MD[15]; David Jacobsohn, MD[16]; Nahal Lalefar, MD[17]; Maxim Norkin, MD[18]; Nosha Farhadfar, MD[19]; Michael A. Pulsipher, MD[20]; Shalini Shenoy, MD[21]; Aleksandra Petrovic, MD[4]; Kirk R. Schultz, MD[12]; Gregory A. Yanik, MD[11]; Edmund K. Waller, MD[22]; John E. Levine, MD[9]; James L. Ferrara, MD[9]; Bruce R. Blazar, MD[23]; Amelia Langston, MD[22]; John T. Horan, MD[3]; and Leslie S. Kean, MD, PhD[3]

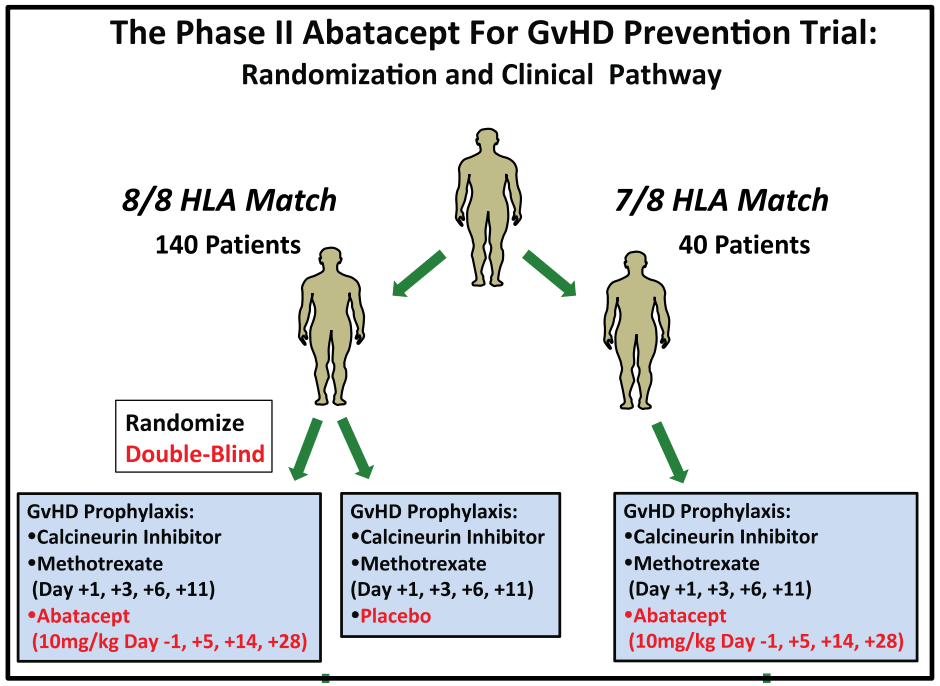
December 15, 2021

U.S. FOOD & DRUG ADMINISTRATION

FDA Homepage

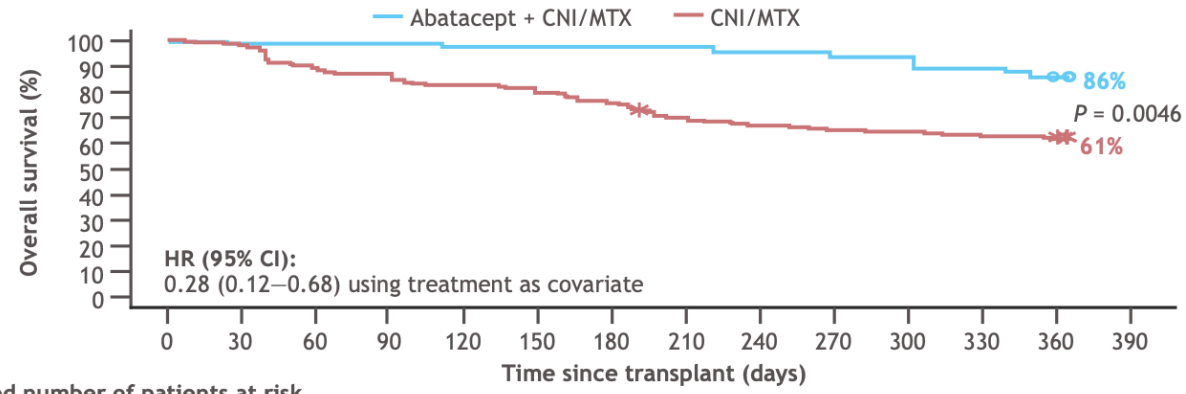
← Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases / Resources for Information | Approved Drugs / FDA approves abatacept for prophylaxis of acute graft versus host disease

FDA approves abatacept for prophylaxis of acute graft versus host disease



7/8 MMUD recipients

OS



Weighted number of patients at risk

Abatacept + CNI/MTX	54	53	53	53	53	53	53	53	52	51	51	48	45
CNI/MTX	161	158	144	140	133	131	122	112	107	104	103	100	98

Day 180 FDA prespecified primary endpoint: abatacept, 98% vs CNI/MTX, 75%; HR (95% CI): 0.06 (0.01–0.27); *P* = 0.0028; using treatment as covariate

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Watkins et al, J Clin Oncol, 2021

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Post-Transplant Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis Following Mismatched Unrelated Donor Peripheral Blood Stem Cell (PBSC) Transplantation (the ACCESS Study)

Monzr M. Al Malki, Stephanie Bo-Subait, Brent Logan, Janelle Olson, Erin Leckrone, Juan Wu, Heather E. Stefanski, Jeffery J. Auletta, Stephen R. Spellman, Craig Malmberg, Brian C. Shaffer, Dipenkumar Modi, Farhad Khimani, Mahasweta Gooptu, Mehdi Hamadani, Larisa Broglie, Bronwen E. Shaw, Steven Michael Devine, Antonio Martin Jimenez Jimenez

Study Sponsored by:

nmdp
FIND CURES. SAVE LIVES.

NCT04904588

ACCESS Study Design

Adults stratified by intensity and analyzed separately with one pediatric MAC stratum

Stratum 1	•Adult subjects undergoing HCT with a **PBSC** graft source and receiving a myeloablative conditioning **(MAC) regimen** and PTCy-based GVHD prophylaxis
Stratum 2	•Adult subjects undergoing HCT with a **PBSC** graft source and receiving a non-myeloablative (**NMA**) or reduced-intensity conditioning **(RIC) regimen** and PTCy-based GVHD prophylaxis
Stratum 3	•Pediatric and young adult subjects undergoing HCT from a **BM** graft source and receiving a **MAC** regimen and PTCy-based GVHD prophylaxis

- Initial design planned for for 70 adults in each strata
- Accrual in RIC stratum far exceeded expectations, leading to protocol amendment to increase to 190 in order to analyze impact of donors matched at <7/8
- Study activated August 2021
- Enrollment RIC cohort completed September 2022
- Follow-up completed September 2023
- **Initial statistical analysis plan included first 70 RIC patients**

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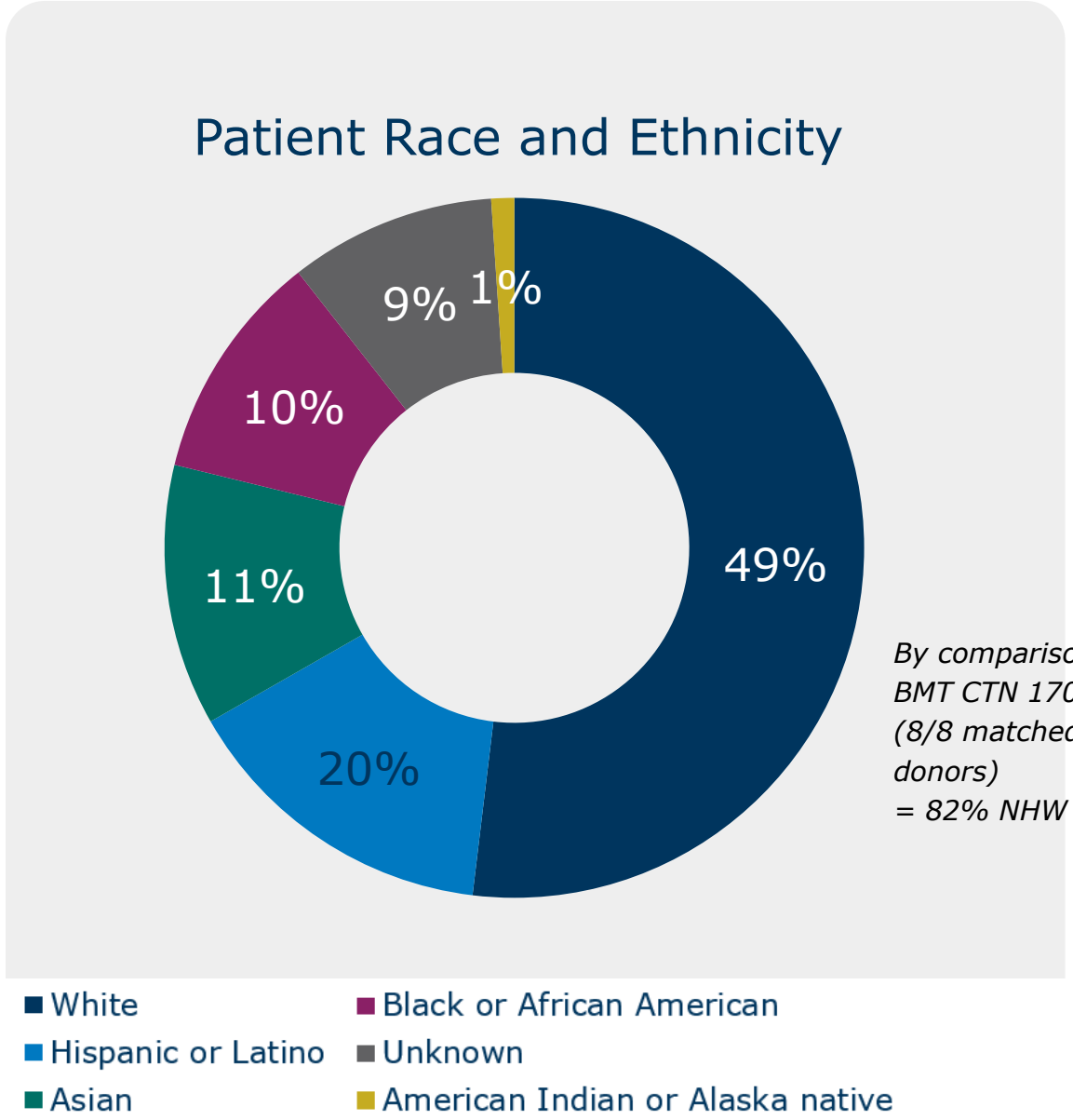
**Prospective, multi-center Phase II study (NCT04904588) to assess the impact of PTCy-based GVHD prophylaxis on transplantation in adults and children with advanced hematological malignancies.*

Results – Patient Demographics

Characteristic	n (%)
No. of patients	70
No. of centers	13
Age at HCT	
Median (min-max)	**65.0** (24.0-77.0)
Sex	
Male	35 (50.0)
Female	35 (50.0)
Cryopreservation	
Cryopreserved	60 (85.7)
Fresh	10 (14.3)



By comparison: BMT CTN 1703 (8/8 matched donors) = 82% NHW

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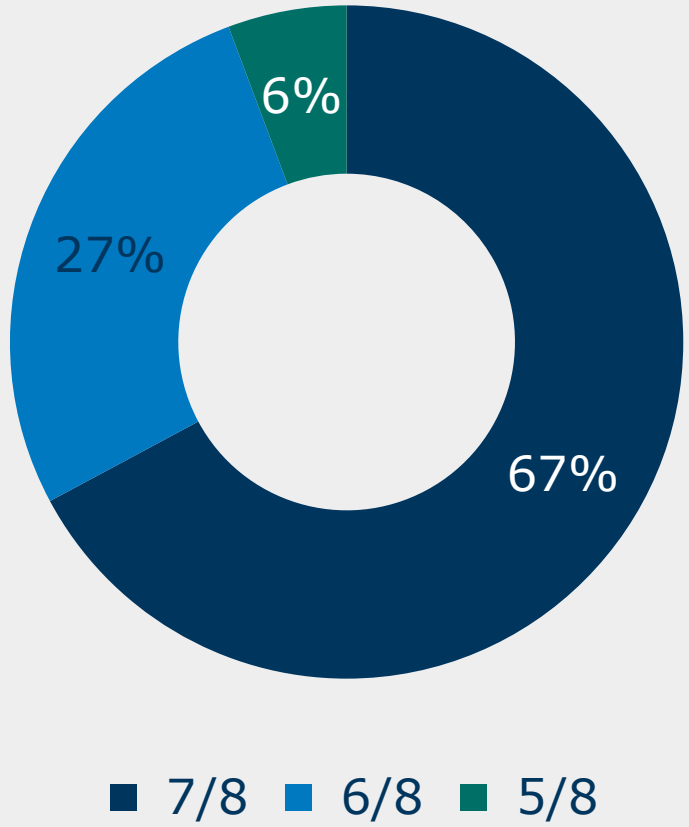
Results – Donor Characteristics

Characteristic	n (%)
Donor Age	
Median (min-max)	25.1 (18.7-35.3)
18-24	32 (45.7)
25-29	28 (40.0)
30-35	10 (14.3)
Donor Sex	
Male	31 (44.3)
Female	39 (55.7)



***One-third of donors matched at <7/8**

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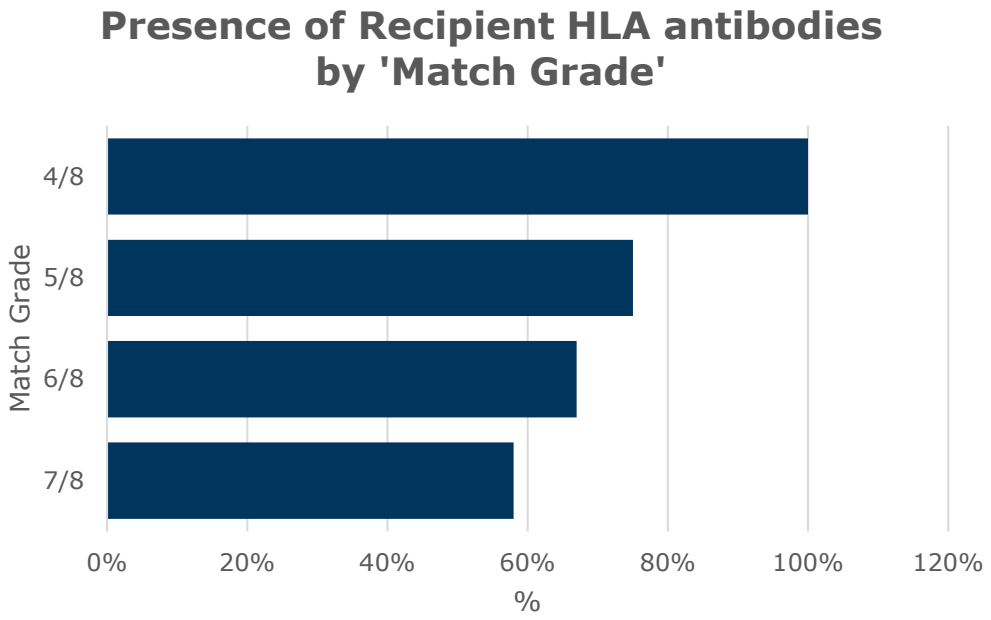
High Prevalence of HLA-Directed antibodies in ACCESS Recipients



Increasing prevalence of antibodies in recipients using less well matched donors

HLA Antibodies by recipient sex		
Patients with HLA-directed antibodies by Sex	Sum of %	Sum of n
Female	58%	93
Male	42%	68
Grand Total	100%	161

At least 56% of recipients has some level of HLA-directed antibodies reported, including children

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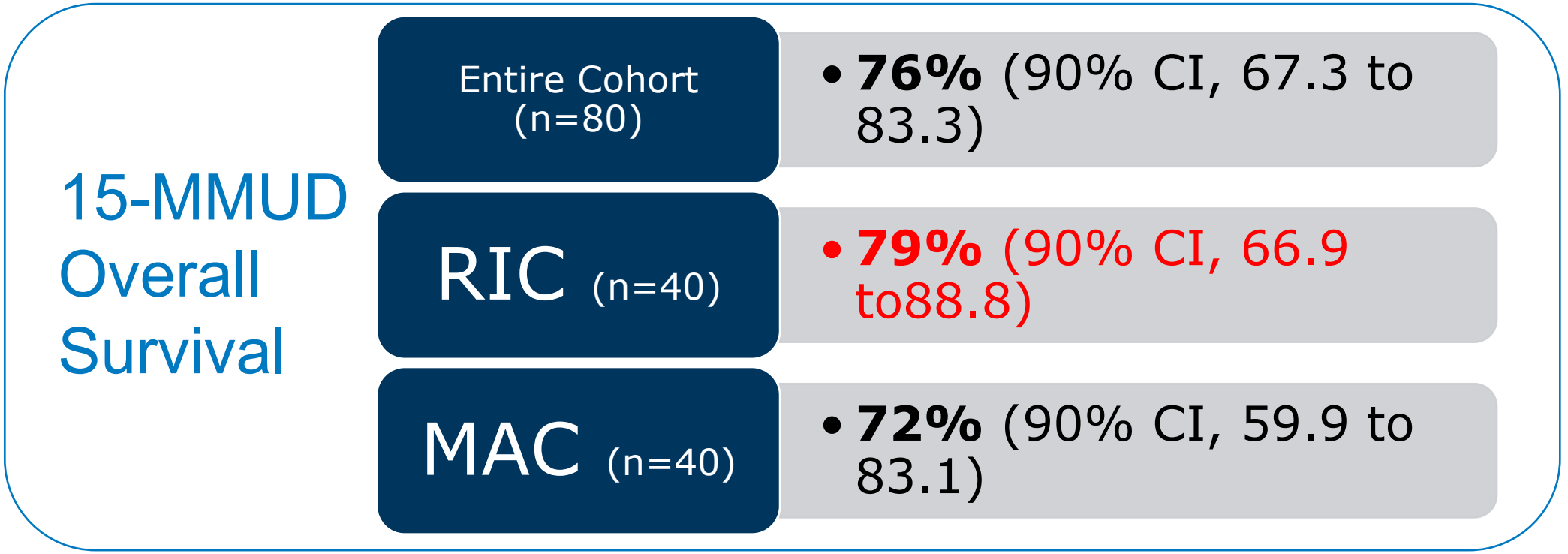
Hypothesis Testing for ACCESS Study

Transplantation of a PBSC product from a MMUD using PTCy-based GVHD prophylaxis will be safe and feasible and will result in a high likelihood of overall survival at one year following HCT.



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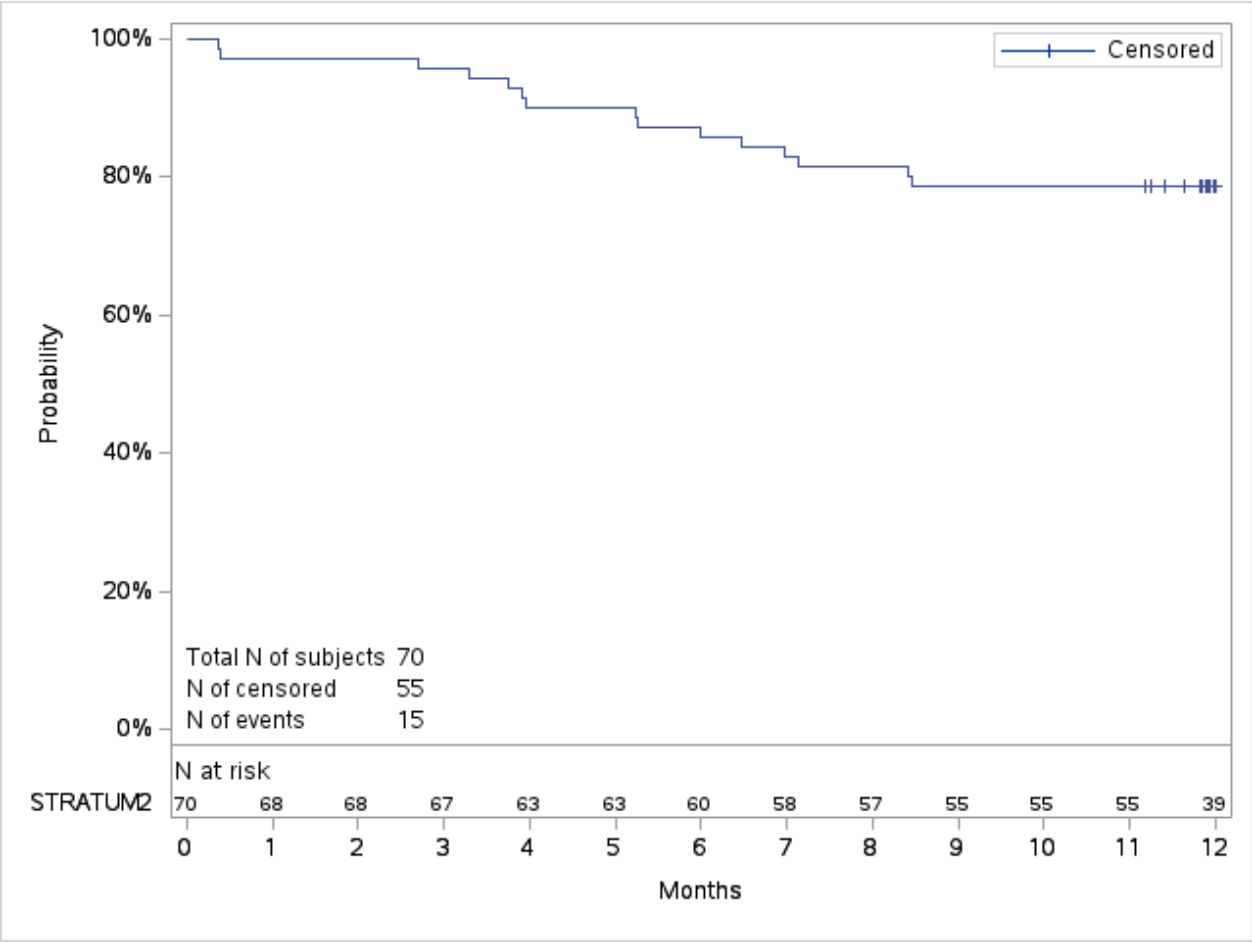
Shaw et al, J Clin Oncol, 2021

Primary Endpoint: Overall Survival



Kaplan-Meier estimates and 95% confidence intervals for overall survival

Outcomes	N/n eval	Prob (95% CI)
OS[1]	70	
1-year	39	79 (68-87) %

[1] Median follow-up (min-max), months: 12.0 (0.4-12.9)
Median follow-up (min-max) of survivors, months: 12.1 (11.2-12.9)

Impact of degree of HLA match (7/8 Vs <7/8) on OS

	HLA match: 7/8		HLA match: <7/8		
Outcomes	N/n eval	Prob (95% CI)	N/n eval	Prob (95% CI)	P-value[1]
OS	47		23		0.580
1-year	27	77 (64-87)%	12	83 (65-95)%	

[1] P-value from log-rank test.

Impact of donor age (above vs below median of 25) on OS

	> Median		≤ Median		
Outcomes	N/n eval	Prob (95% CI)	N/n eval	Prob (95% CI)	P-value[1]
OS	35		35		0.813
1-year	18	77 (62-89)%	21	80 (65-91)%	

[1] P-value from log-rank test.

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Results – Secondary Endpoints

Clinical Endpoint	One year estimate (%) (95% CI)#
GVHD-free, relapse free survival (GRFS)[1]	**51%** (39-62%)
Acute GVHD grade II-IV	**43%** (31-55%)*
Acute GVHD grade III-IV	**9%** (3-16%)*
NIH moderate/severe chronic GVHD	**9%** (3-17%)
Primary graft failure by Day 28	**6%** (2-14%)
Non-relapse mortality (NRM)	**13**% (6-22%)
Relapse	**21%** (13-32%)

*6-month estimate
GRFS using Kaplan-Meier method; GVHD, NRM and relapse using cumulative incidence method.
[1] Events include: acute GVHD Grade III-IV, chronic GVHD requiring systemic immunosuppression, relapse, or death by any cause

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Results: comparison to BMT CTN 1703

Clinical Endpoint	ACCESS Study (RIC Stratum; N=70)	BMT CTN 1703 PTCy Arm[1]
Overall Survival	79% (68-87%)	77% (71-82%)
GVHD-free, relapse free survival (GRFS)	51% (36-59%)	53% (46-39%)
Primary graft failure by Day 28	6% (2-14%)	3% (not reported)
Non-relapse mortality (NRM)	13% (6-22%)	12% (8-17%)
Relapse	21% (13-32%)	21% (16-27%)
Acute GVHD grade II-IV	43% (31-55%)*	56% (49-62%)*
Acute GVHD grade III-IV	9% (3-16%)*	8% (5-12%)*
NIH moderate/severe chronic GVHD	9% (3-17%)	7% (not reported)

One-year estimates (%) (95% CI); *6-month estimate

OS and GRFS using Kaplan-Meier method; NRM, relapse, and GVHD using cumulative incidence method.

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1. Bolanos-Meade et al, New Engl J Med, 2023

Results: Infections

		Overall #		First 100 days		100 days to 1 year	
Infection	CTCAE grade	# Infections	# recipients affected n (%)	# Infections	# recipients affected n (%)	# Infections	# recipients affected n (%)
By grade	Grade 2-Moderate	87	42 (60)	57	35 (50)	30	20 (28.6)
	Grade 3-Severe	47	21 (30)	27	15 (21.4)	20	7 (10)
	Grade 4-Life threatening or disabling	4	3 (4.3)	3	2 (2.9)	1	1 (1.4)
	Grade 5-Fatal	5	5 (7.1)	2	2 (2.9)	3	3 (4.3)

*77% of recipients with Grade 2-5 infections in the first 100 days post-transplant presents an opportunity to improve infection-free survival.

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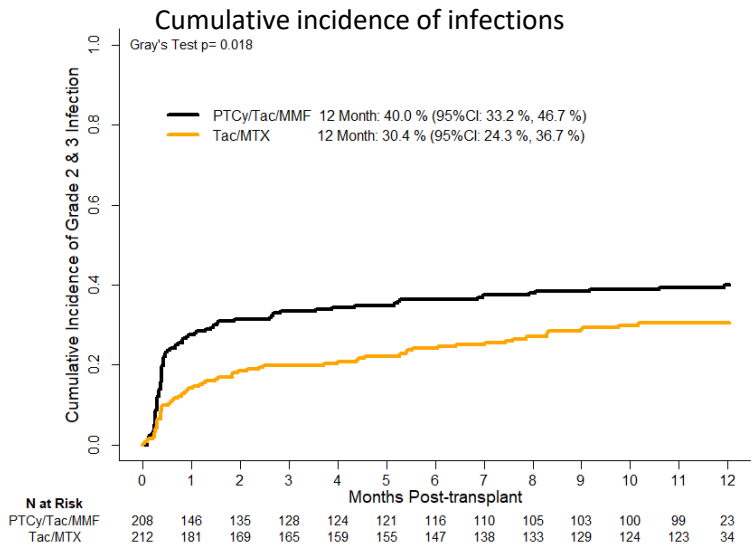
PTCy-based GVHD prophylaxis as the new standard in RIC HCT using HLA-matched donors

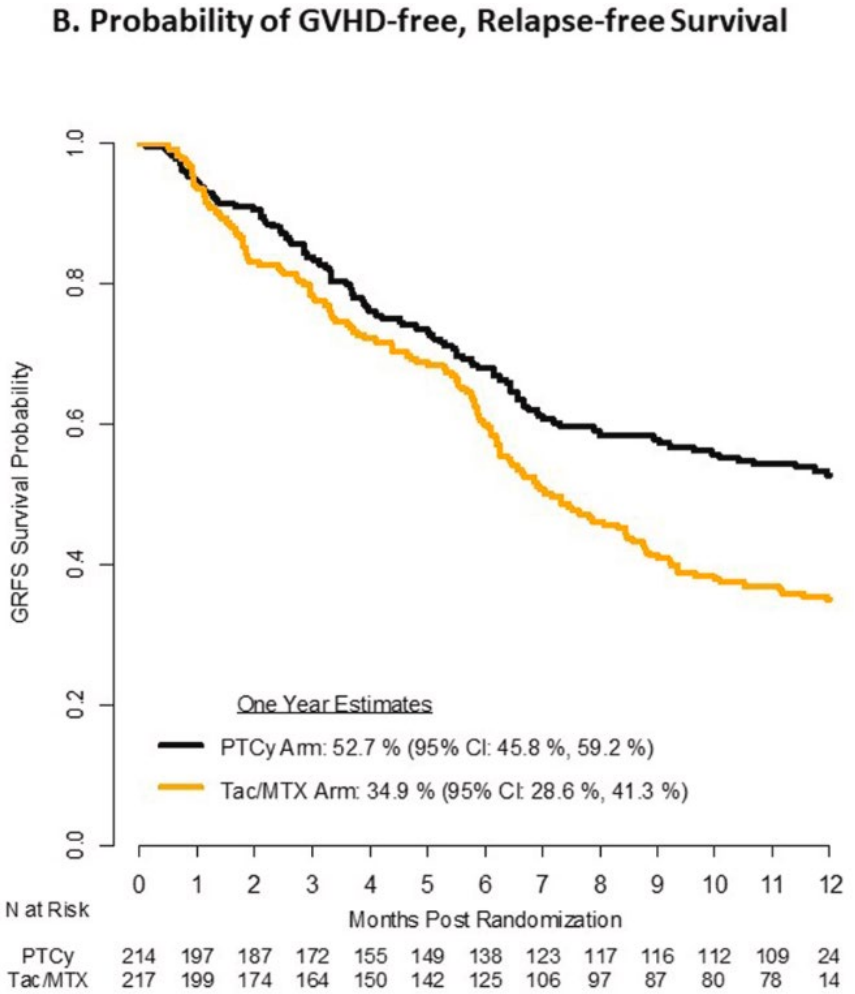
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis

J. Bolaños-Meade, M. Hamadani, J. Wu, M.M. Al Malki, M.J. Martens, L. Runaas, H. Elmariah, A.R. Rezvani, M. Gooptu, K.T. Larkin, B.C. Shaffer, N. El Jurdi, A.W. Loren, M. Solh, A.C. Hall, A.M. Alousi, O.H. Jamy, M.-A. Perales, J.M. Yao, K. Applegate, A.S. Bhatt, L.S. Kean, Y.A. Efebera, R. Reshef, W. Clark, N.L. DiFronzo, E. Leifer, M.M. Horowitz, R.J. Jones, and S.G. Holtan, for the BMT CTN 1703 Investigators*





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Bolanos-Meade et al, NEJM, 2023

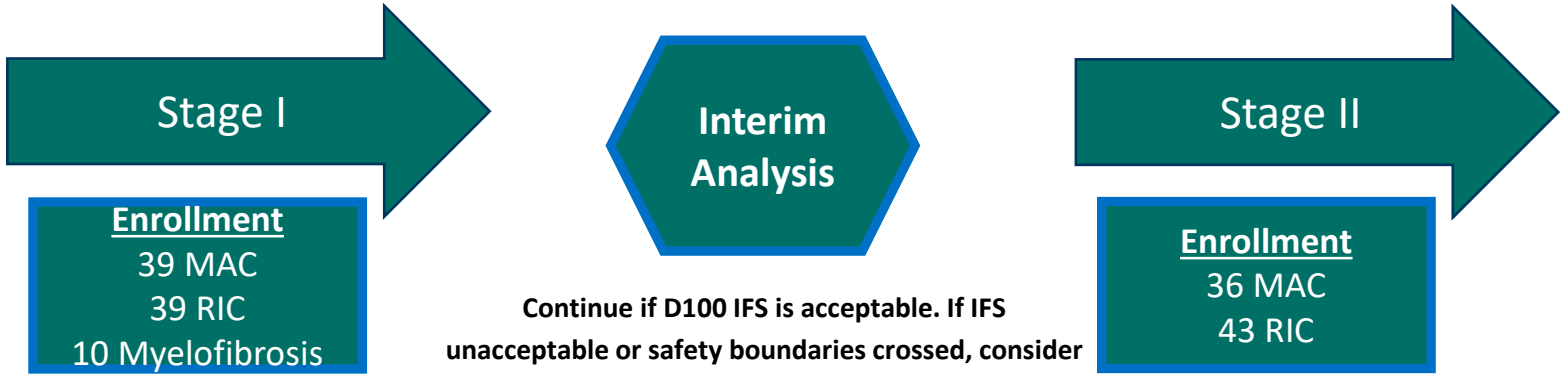
MMUD Prospective Clinical Trial Updates: OPTIMIZE Reduced-dose PTCy MMF, Tacrolimus

Patients:

- Adults age≥18y (n=157)
- ALL, AML, MDS, MF (limited)
- MAC (n=75) or RIC (n=82)

Protocol status:

- IRB approved
- 20 budgeted sites FY24
  - 6 expansion sites
  - 4 interested sites
- 5 SIVs completed
  - 6 nearing



Groups	PTCy	CNI Start / Wean / End	MMF Start / End
RIC	25 mg/kg D3, D4	D5 / D90 / D180	D5 / D35
MAC	25 mg/kg D3, D4	D5 / D90 / D180	D5 / D35
Safety Arm	37.5 mg/kg D3, D4	D5 / D90 / D180	D5 / D35

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Optimize Study Activity

Enrollment

Enrollment Summary

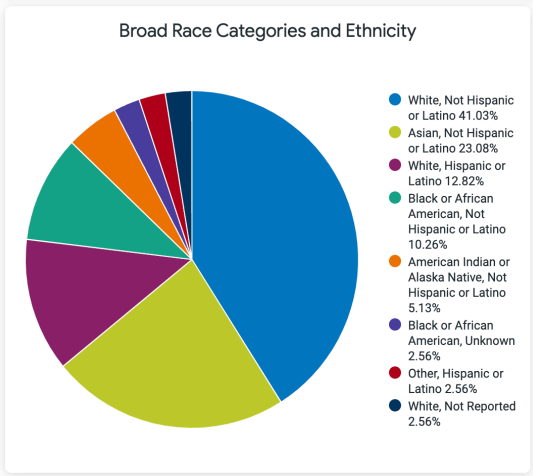
# of Patients

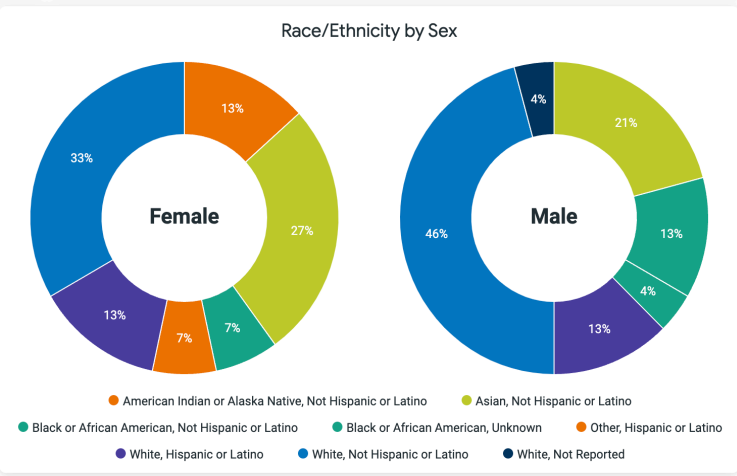
45 Enrolled	31 Enrolled and Infused	1 Completed Study
11 In Screening	1 Screen Failed	14 Consented, Eligible, Enrolled, not Treated

Enrollment by Stratum

8 # Enrolled in Run-In Phase	12 # Enrolled in Stage 1 MAC Stratum	20 # Enrolled in Stage 1 RIC Stratum	2 # Enrolled in Myelofibrosis Stratum
40% of 20 available slots filled	31% of 39 available slots filled	51% of 39 available slots filled	20% of 10 available slots filled

Demographics





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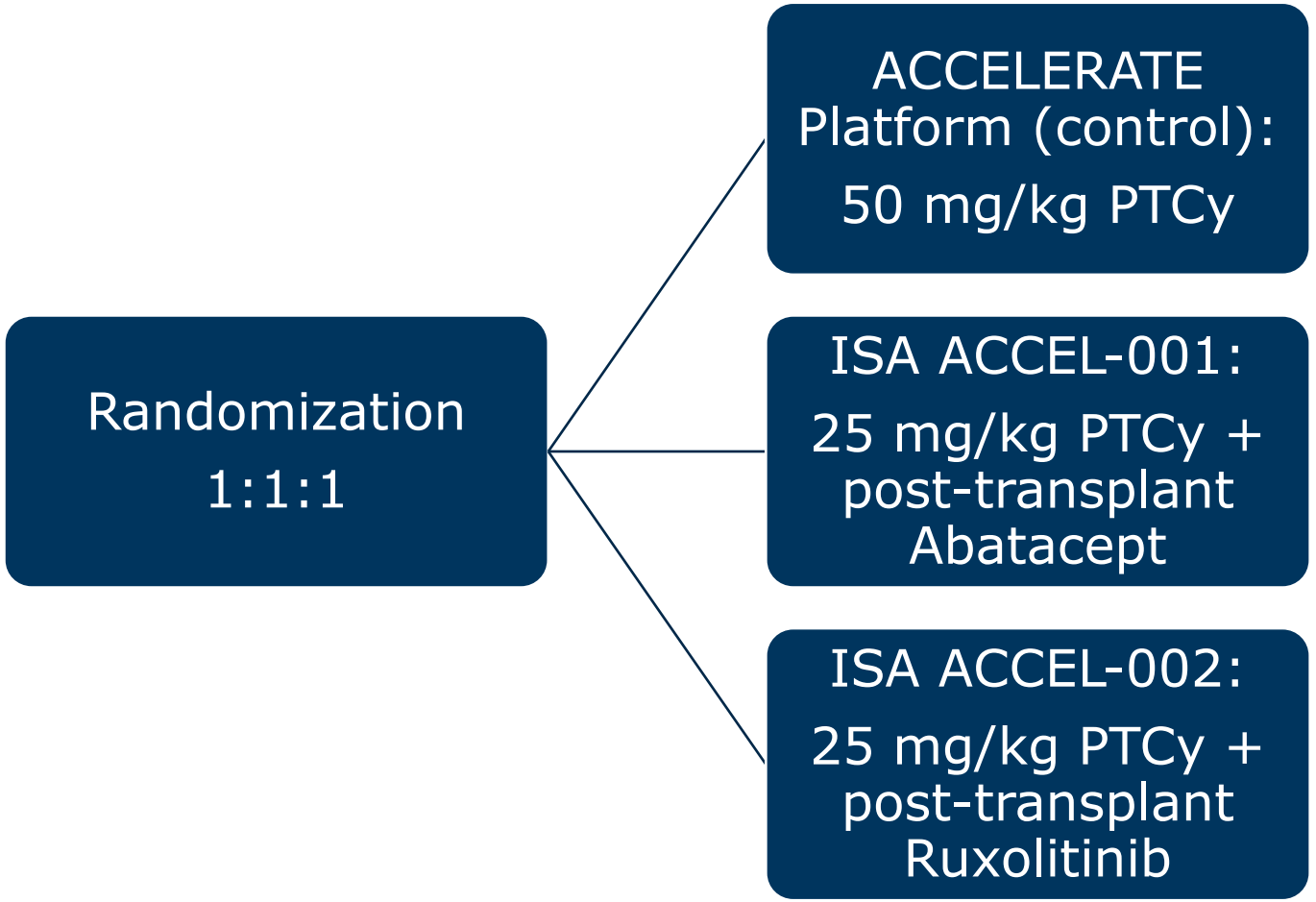
As of 6-24-24

ACCELERATE treatment arms

After safety lead-in:



Unified:

- Shared control
- Schedule of Assessments
- AE/SAE collection
- Data collection
- Stopping rules*

*Same/similar stopping rules for ISAs (separate monitoring)

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ISA = Intervention-specific appendix

CIBMTR CRO: MMUD Portfolio of NMDP Sponsored Prospective Trials

Feasible → Practical → Safer → Faster

15-MMUD

- Adults
- Bone Marrow
- PTCy-based GVHD prophylaxis
- 80 Patients
- ~50% ethnically diverse

- **Results: 76% OS at 1 year**

ACCESS

- Adults: PBSC (MAC & RIC)
- Peds: BM
- PTCy-based GVHD prophylaxis
- 271 Adult Patients + 40 Peds

- **Adult Enrollment Complete**

OPTIMIZE

- Adults: PBSC
- No peds
- Reduced dose PTCy
  - 25mg/kg
  - Safety run in 37.5 mg/kg <7/8
- 170 Patients
- Primary endpoint: infection-free survival

- **First patient enrolled Jan 2024**

MMUD Platform Protocol

- Large, ongoing study
- Collect foundational MMUD data on a standard arm
- Allow for amendments for new investigational arms

- **Concept in development**

* Protocol development/activation/accrual/completion have been rapid and exceeded expectations!

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Biological specimens/HLA data/selection algorithms or preferences

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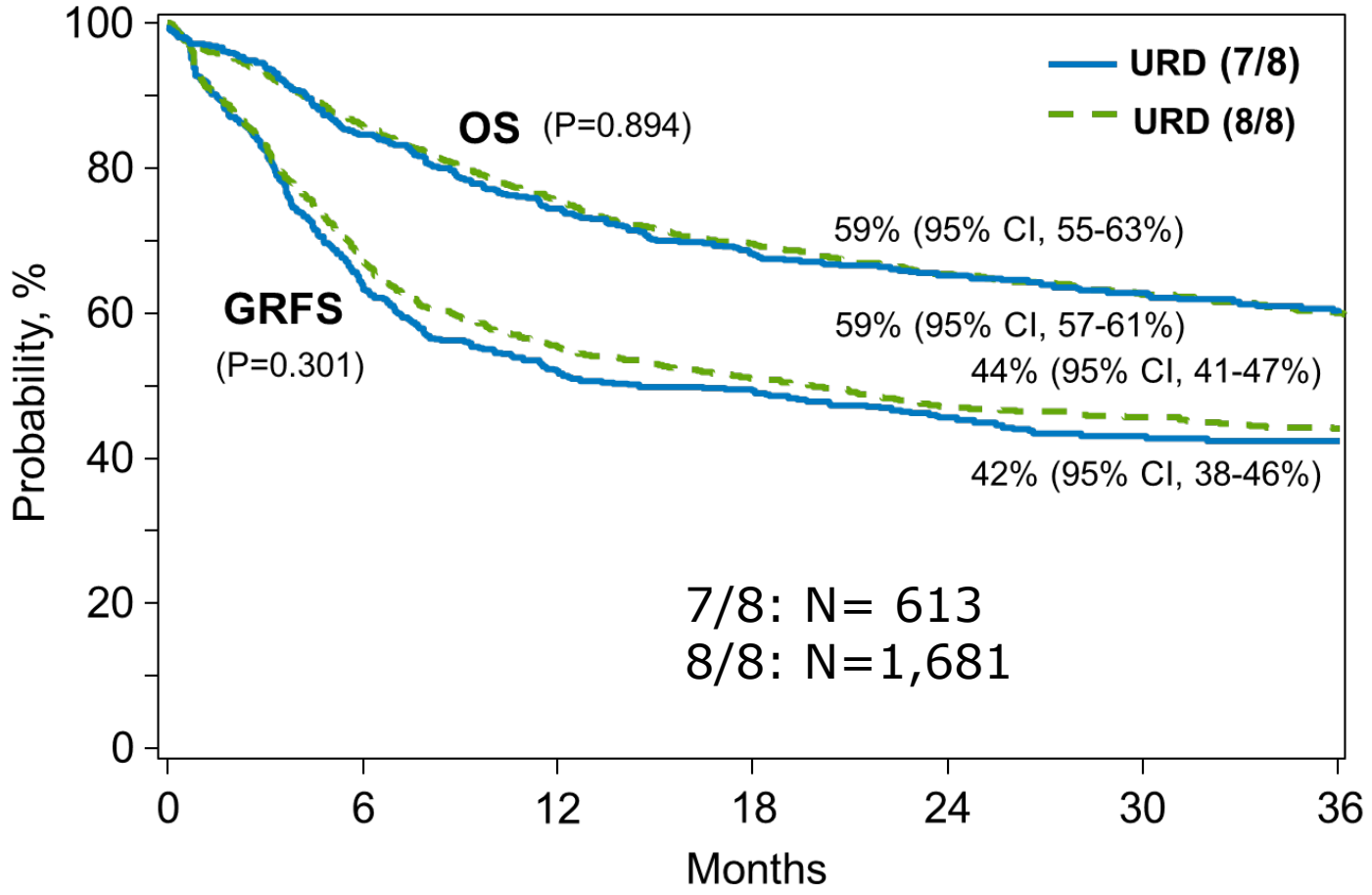
Impact of PTCy on Patient Outcomes

Updated CIBMTR Analysis of US data

No difference between 8/8 and 7/8 URD HCT with PTCy: Adjusted 3y OS and GRFS

First allogeneic HCT in adults with ALL, AML or MDS using PTCy GvHD prophylaxis (2017-2021)



	PTCy URD 8/8	CNI URD 8/8	PTCy URD 7/8	CNI URD 7/8
HLA Locus				
A mismatch	NA	NA	291 (47.5)	204 (44.4)
B mismatch	NA	NA	123 (20.0)	111 (24.2)
C mismatch	NA	NA	73 (11.9)	68 (14.8)
DRB1 mismatch	NA	NA	126 (20.6)	76 (16.6)
HLA DQB1				
Matched	1559 (92.7)	6904 (94.9)	515 (84.0)	429 (93.5)
Missing	35 (2.1)	50 (0.7)	4 (0.7)	6 (1.3)
HLA DPB1				
Matched	432 (25.7)	1751 (24.1)	107 (17.5)	69 (15.0)
Missing	43 (2.6)	605 (8.3)	45 (7.3)	52 (11.3)

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Shaffer et al, J Clin Oncol, in press

Is donor age more important than HLA Matching following PTCy?

TRANSPLANTATION

Younger unrelated donors may be preferable over HLA match in the PTCy era: a study from the ALWP of the EBMT

Jaime Sanz,[1] Myriam Labopin,[2] Goda Choi,[3] Alexander Kulagin,[4] Jacopo Peccatori,[5] Jan Vydra,[6] Péter Reményi,[7] Jurjen Versluis,[8] Montserrat Rovira,[9] Didier Blaise,[10] Hélène Labussière-Wallet,[11] Juan Montoro,[1] Simona Sica,[12] Ellen Meijer,[13] Maija Itälä-Remes,[14] Nicolaas Schaap,[15] Claude Eric Bulabois,[16] Simona Piemontese,[5] Mohamad Mohty,[17] and Fabio Ciceri[5,18]

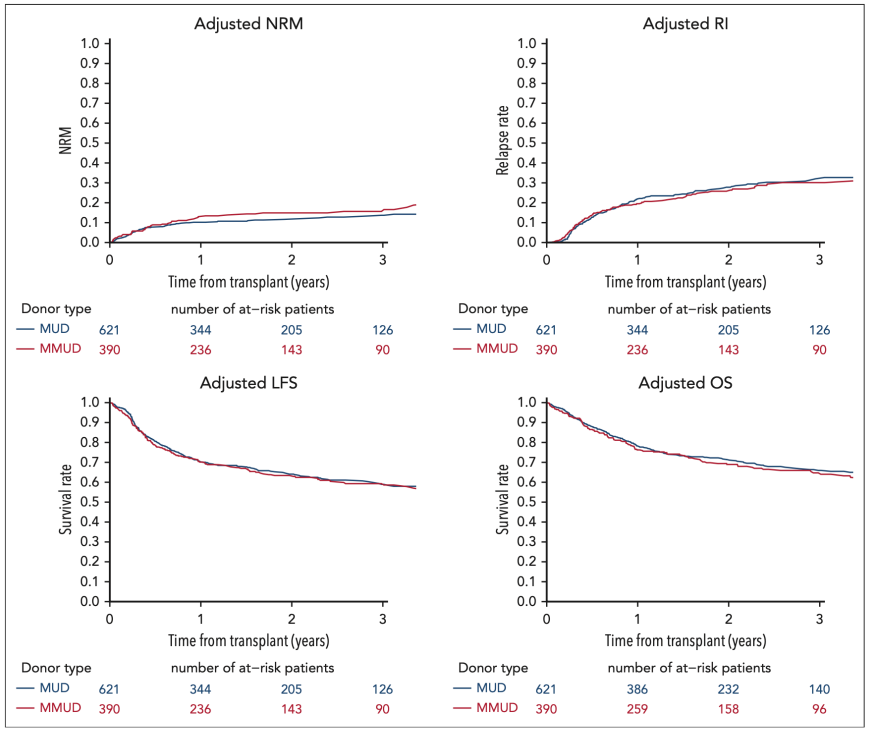

Figure 1. Adjusted cumulative incidence of NRM and relapse, and probability of LFS and OS for MUDs or MMUDs. RI, relapse.

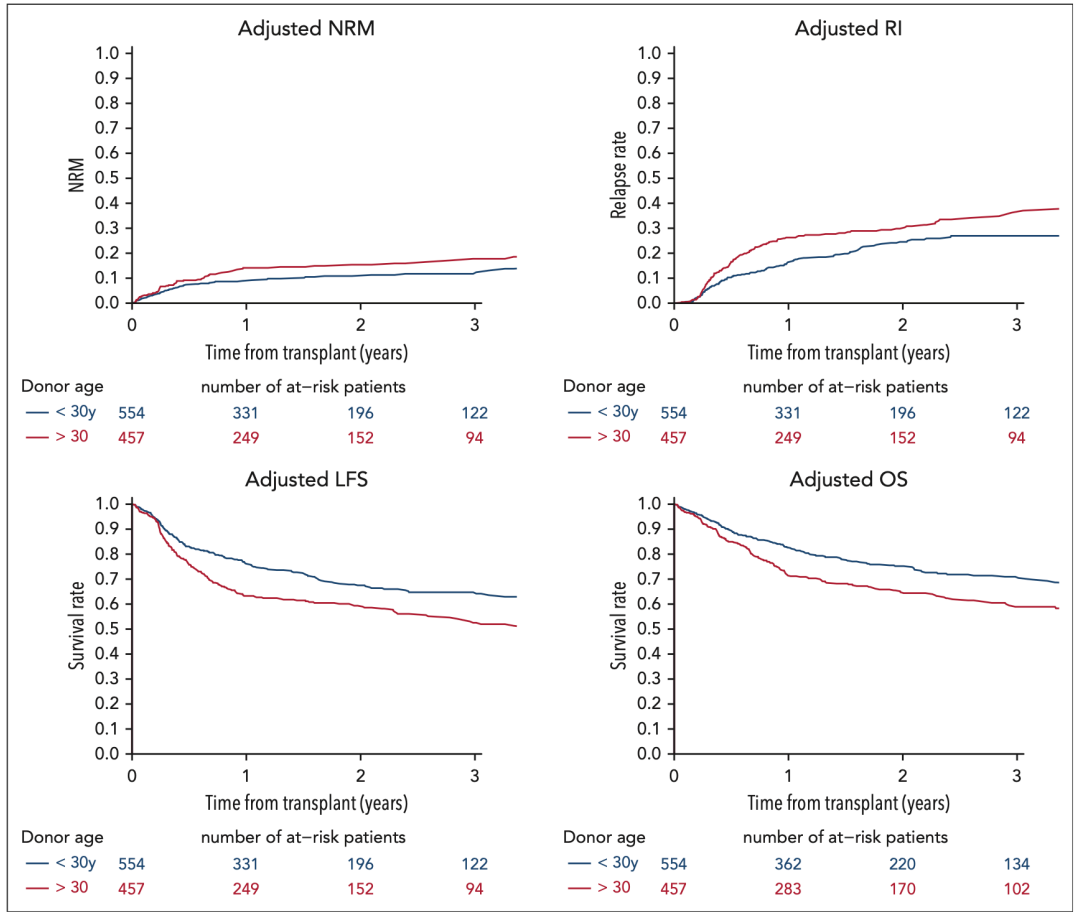

Figure 2. Adjusted cumulative incidence of NRM and relapse, and probability of LFS and OS according to donor age. RI, relapse.

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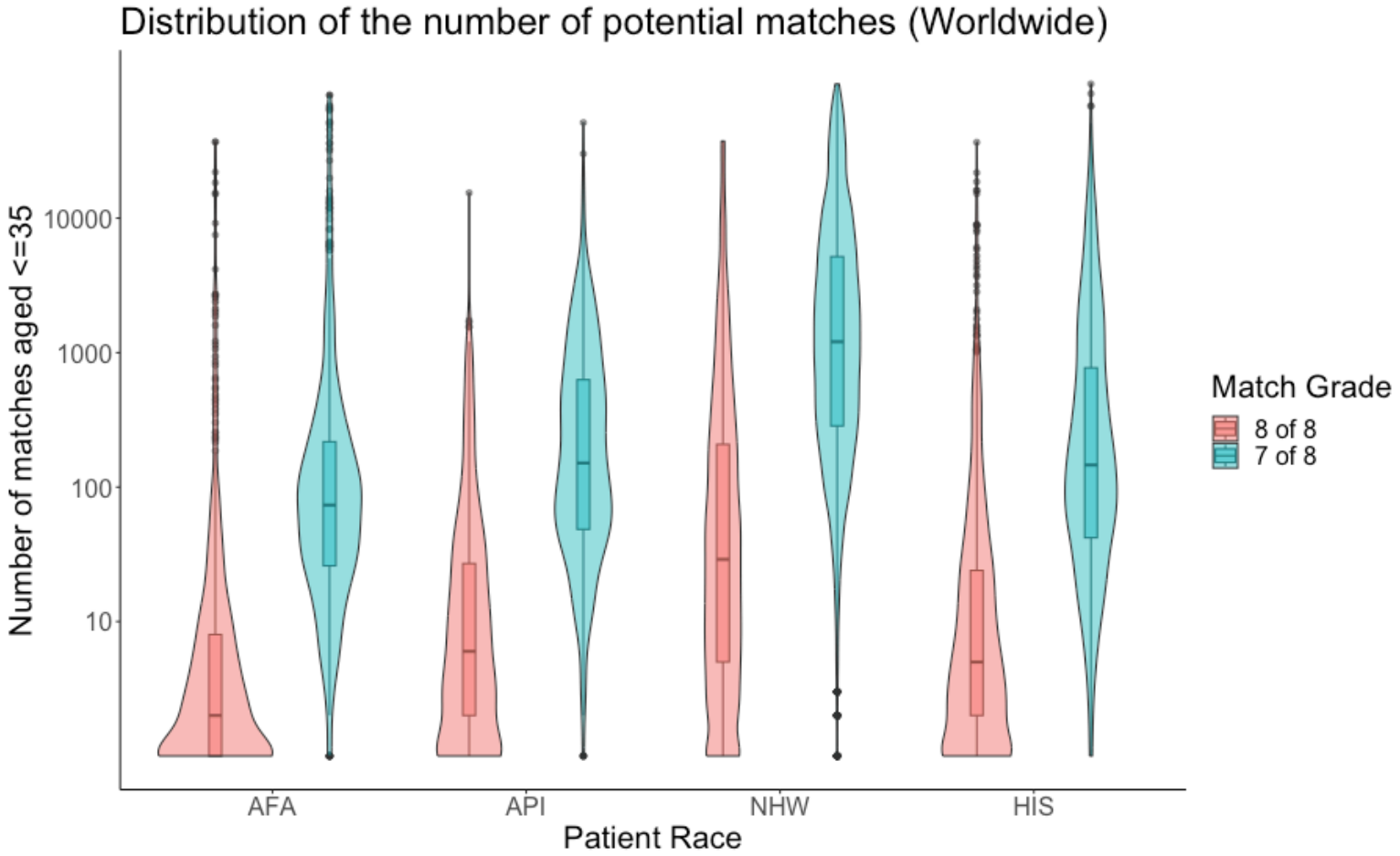
Sanz et al, Blood, 2024

Effect of MMUD on Donor Existence



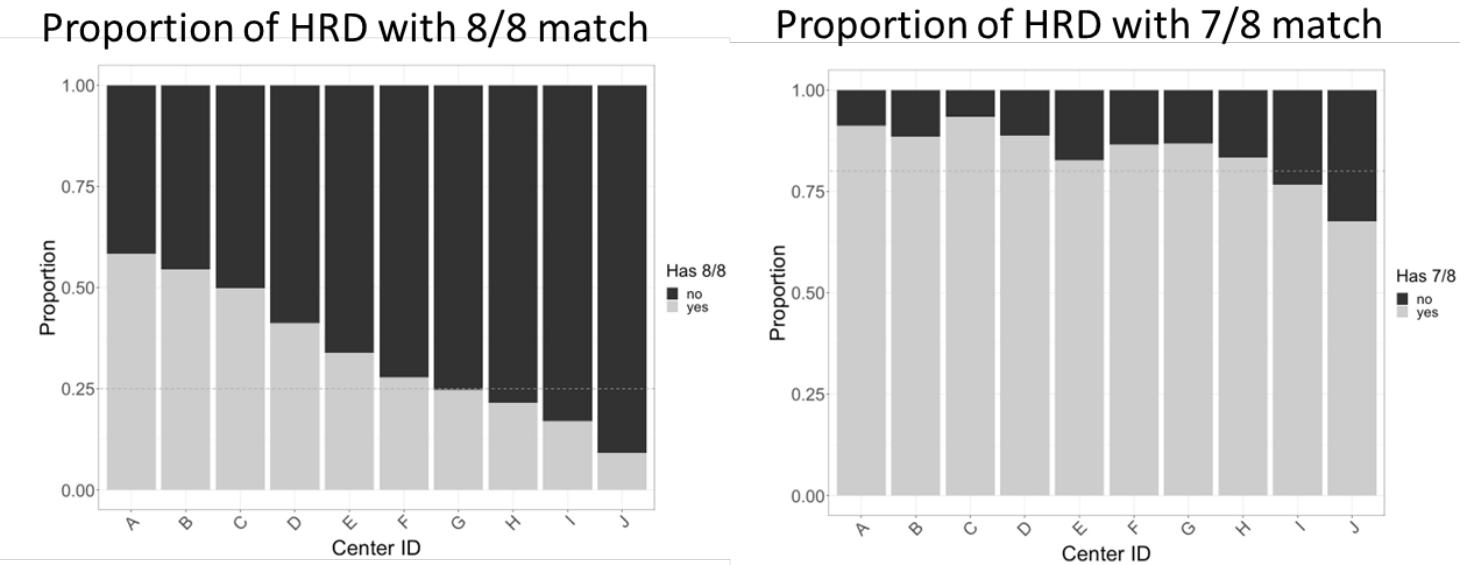
Existing donors Median:	**2**	**74**	**6**	**151**	**29**	**1226**	**5**	**147**

Shaffer et al, J Clin Oncol, in press

Haplo HCT recipients are highly likely to have 7/8 URD

- Existence of unrelated donors (URDs) on the NMDP Registry at the 8/8 or 7/8 match level for patients receiving HRD HCT in the US and reported to the CIBMTR from 2013-2020
- 9696 HRD HCT recipients (0-87 y)
- 34% of recipients had ≥1 8/8 URD and 84% had ≥1 7/8 URD
- Recipients of older HRDs (≥35y) had 20-65% likelihood of ≥5 existing 7/8 URDs age ≤35 years

U.S. center practice variation at top 10 HRD centers by volume



Search summary of HRD patients considering donors of all ages and ≤35 years old by race/ethnic group

Population	≥1 8/8 N (%)	≥1 Young 8/8 N (%)	≥1 7/8 N (%)	≥1 Young 7/8 N (%)
African American (n=1863)	275 (14.8%)	115 (6.2%)	1286 (69%)	895 (48%)
Asian and Pacific Islander (n=532)	108 (20.3%)	47 (8.8%)	414 (77.8%)	299 (56.2%)
Non-Hispanic White (n=5173)	2385 (46.1%)	1721 (33.3%)	4772 (92.3%)	4378 (84.6%)
Hispanic (n=1659)	393 (23.7%)	219 (13.2%)	1318 (79.4%)	1049 (63.2%)
Multiple Race (n=172)	30 (17.4%)	15 (8.7%)	121 (70.3%)	88 (51.2%)
Native American (n=41)	14 (34.1%)	7 (17.1%)	39 (95.1%)	29 (70.7%)
Unknown (n=257)	58 (22.6%)	41 (16%)	182 (70.8%)	150 (58.4%)

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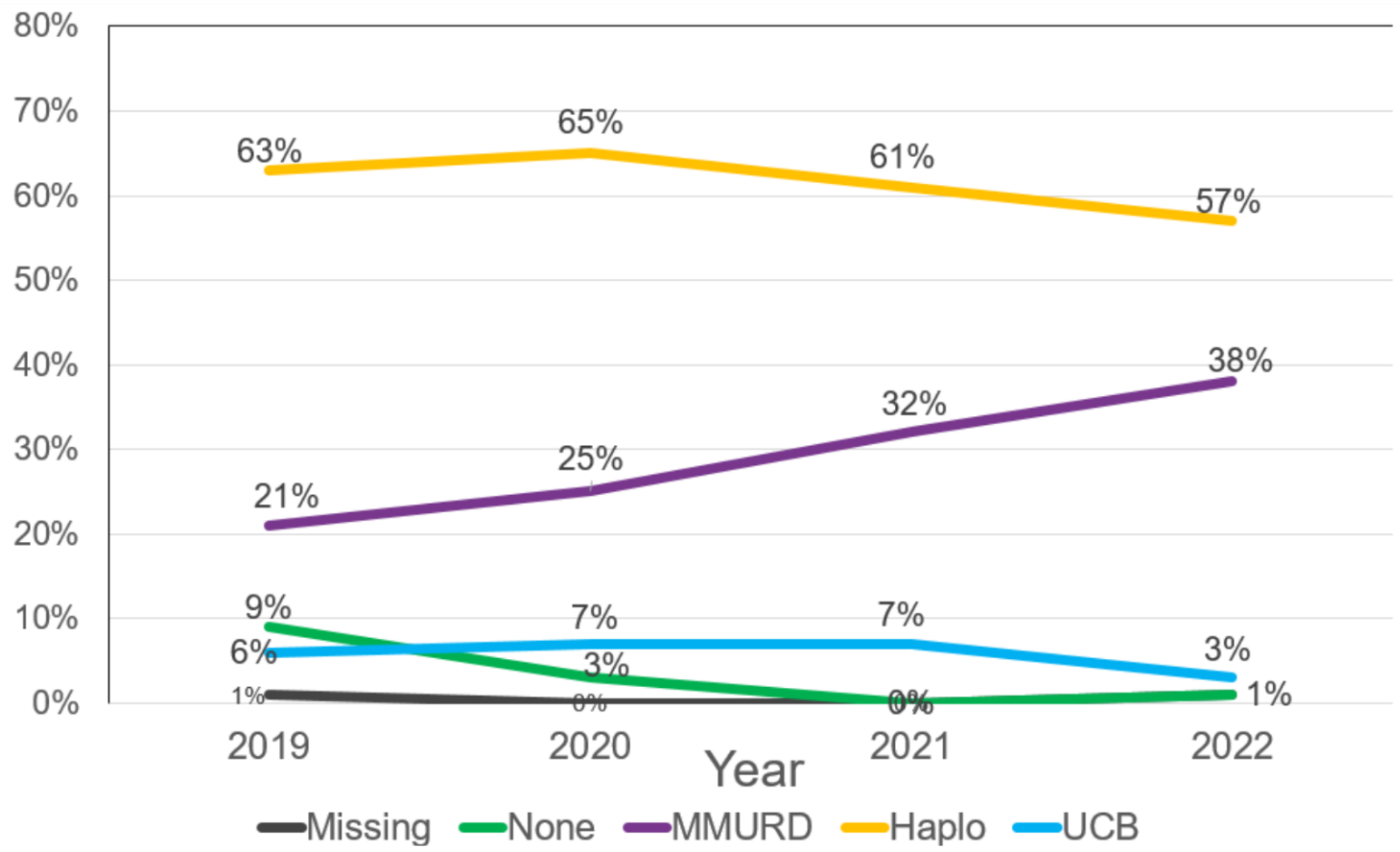
Fingerson et al, Blood Advances 2023

BMT CTN 1702: Change in alternative donor preference over course of study

Figure 3: First Preference of Donor Cell Source by Year of Enrollment



Dehn et al, EBMT annual meeting, 2023

Growth in US MMUD Transplants facilitated by NMDP

MMUD: Mismatched Unrelated Donors

Details of matched (8/8) and mismatched (anything less than 8/8) unrelated donor collection trends over time. Includes unrelated donor collections stored with cryo services. Excludes other fullfillment types.

NOTE: Date filter and Related filter do not apply to this visual. Includes all MMUD collections (fresh and cryo).

981

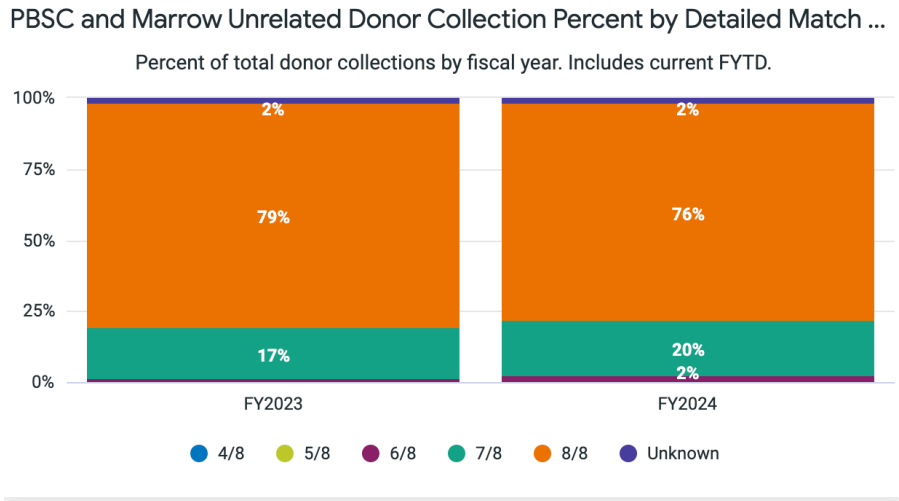
Marrow/PBSC MMUD FYTD

129% of 763 Marrow/PBSC MMUD FYTD

Monthly YoY Growth in MMUD Marrow and PBSC Collections

NOTE: This tile will show 1 less fiscal year that what is selected in the date filter. The 1st year selected is not displayed because it will always show no growth since it isn't populating the prior year for comparison.

Fiscal M	October	November	December	January	February	March	April	May	June	July	August
FY	YoY Growth	YoY Growth	YoY Growth	YoY Growth	YoY Growth	YoY Growth	YoY Growth	YoY Growth	YoY Growth	YoY Growth	YoY Growth
FY2024	38%	27%	57%	24%	24%	31%	35%	20%	-17%	∅	∅



~28-30% YoY growth in MMUDs facilitated for two consecutive fiscal years

MMUD grafts now close to 24% of all volunteer donor Products

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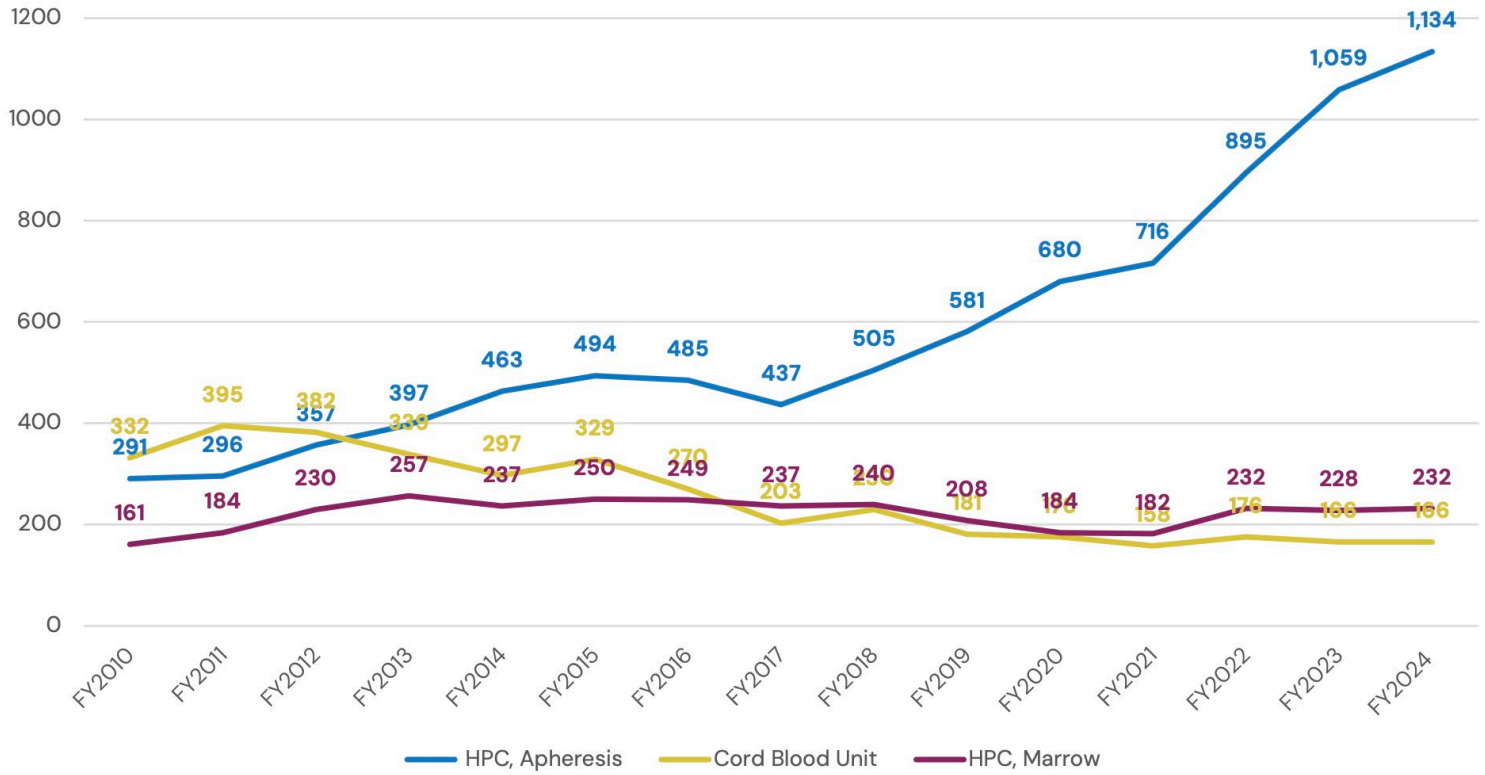
Source: NMDP Looker dashboard, 6/24/24

Ethnically Diverse patients: most significant impact from MMUD



*Data is inclusive of all TCs for ethnically diverse patients and all suppliers
*Data for FY24 includes actuals plus rest of year forecast

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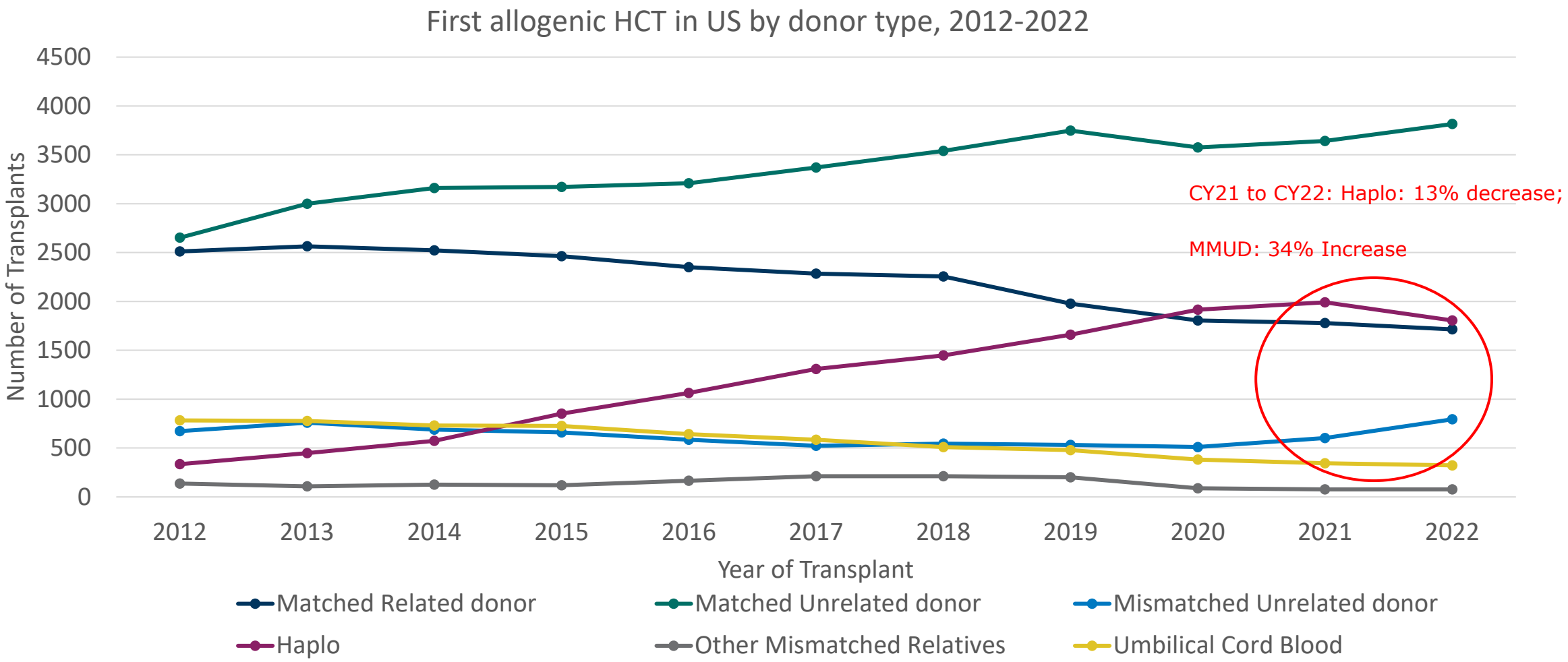
Source: NMDP Operations

CIBMTR registry data reflects the shift in practice



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CIBMTR U.S. Summary Slides, https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports

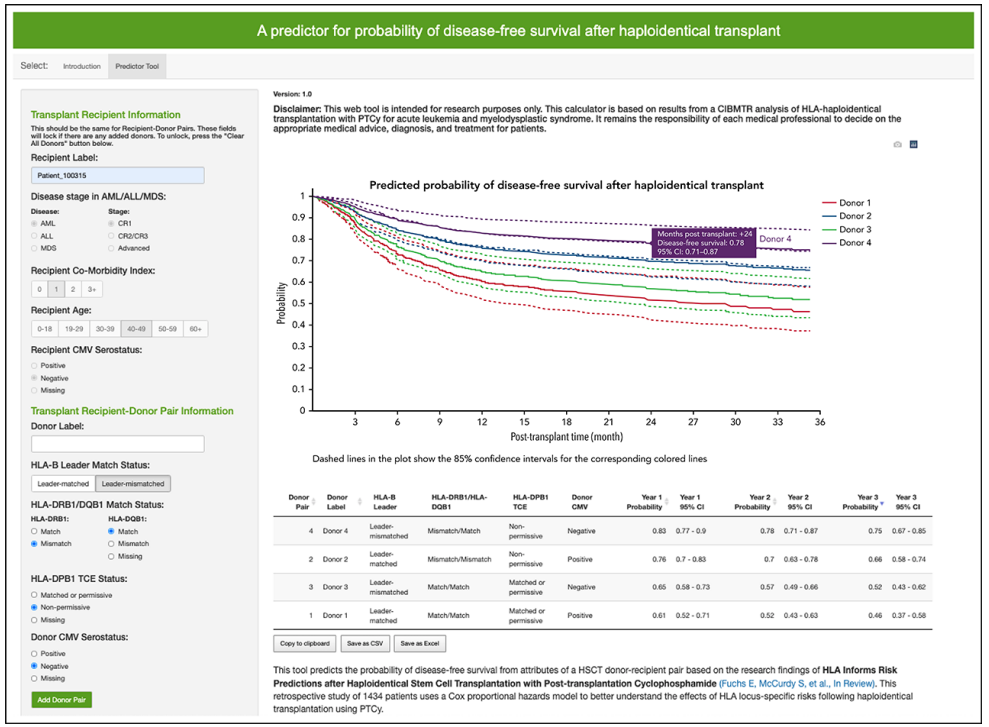
How should we select mismatched unrelated donors?

blood®
Plenary Paper

IMMUNOBIOLOGY AND IMMUNOTHERAPY

HLA informs risk predictions after haploidentical stem cell transplantation with posttransplantation cyclophosphamide

Ephraim J. Fuchs,[1,*] Shannon R. McCurdy,[2,*] Scott R. Solomon,[3] Tao Wang,[4,5] Megan R. Herr,[6] Dipenkumar Modi,[7] Michael R. Grunwald,[8] Taiga Nishihori,[9] Michelle Kuxhausen,[10] Stephanie Fingerson,[10] Caroline McKallor,[11] Asad Bashey,[3] Yvette L. Kasamon,[1] Yung-Tsi Bolon,[10] Ayman Saad,[12] Joseph McGuirk,[13] Sophie Paczesny,[14] Shahinaz M. Gadalla,[15] Steven G. E. Marsh,[16] Bronwen E. Shaw,[4] Stephen R. Spellman,[10] Stephanie J. Lee,[11,17] and Effie W. Petersdorf[11]



Do Haplo related donor rules apply to selection of mismatched unrelated donors?

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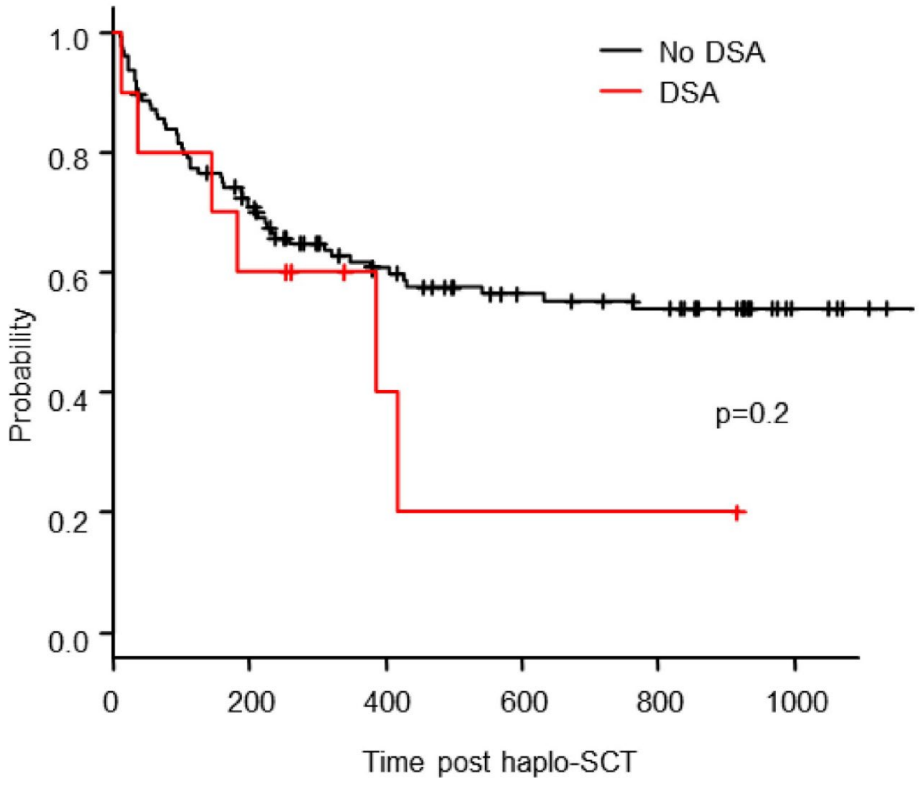
Fuchs et al, Blood, 2023

Does it matter whether the donor is related or unrelated? YES: MMUD allows for avoiding DSA and LOH relapse

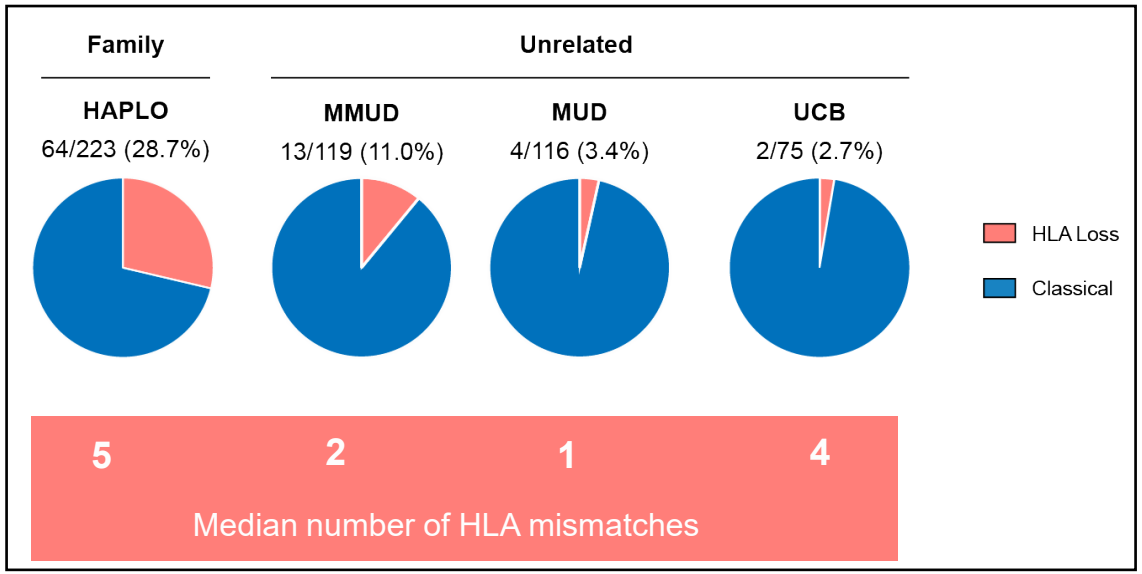
Overall Survival



OSPEDALE SAN RAFFAELE

HLA Loss Relapse

HLA Loss und Donor Type



A case for Unrelated HCT with Mismatches on both Haplotypes?

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Bramanti et al, Transplant Cell Ther 2019; Fleischhauer et al, L Vago under submission

Could targeted HLA-mismatching mitigate risk of relapse?

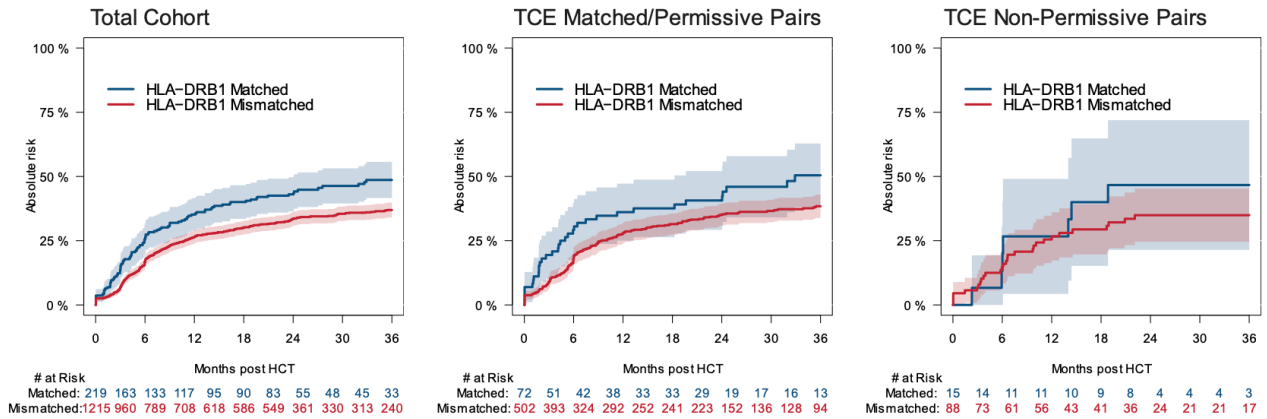

Figure 1: Incidence of relapse in subjects evaluated in IBWG 19-02 by the donor/recipient HLA-DPB1 T-cell Epitope Status. Left pane: Total cohort; middle pane: HLA-DPB1 matched or permissively mismatched; right pane: HLA-DPB1 non-permissively mismatched pairs.

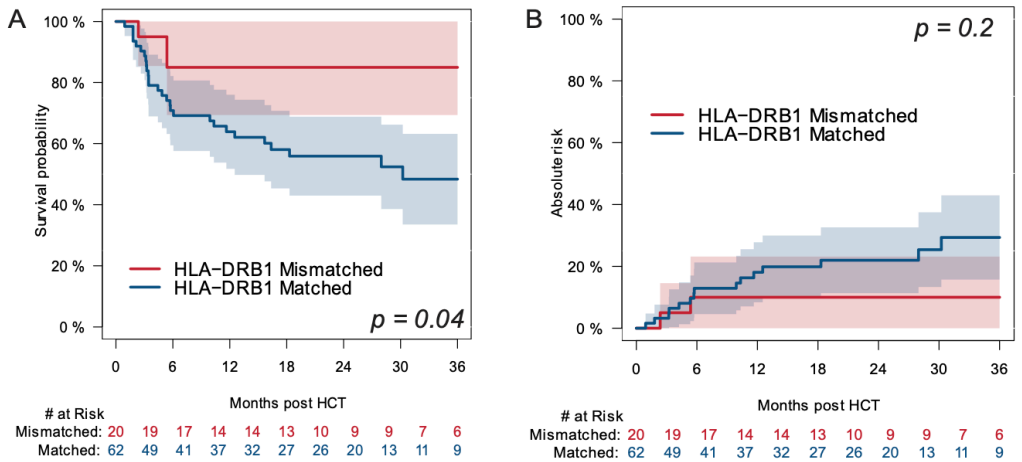

Figure 2: Outcomes in 82 subjects treated with mmURD allo HCT using PTCY based GVHD prophylaxis at MSKCC and the University of Miami. (A) Event-free survival, (B) Cumulative incidence of relapse.

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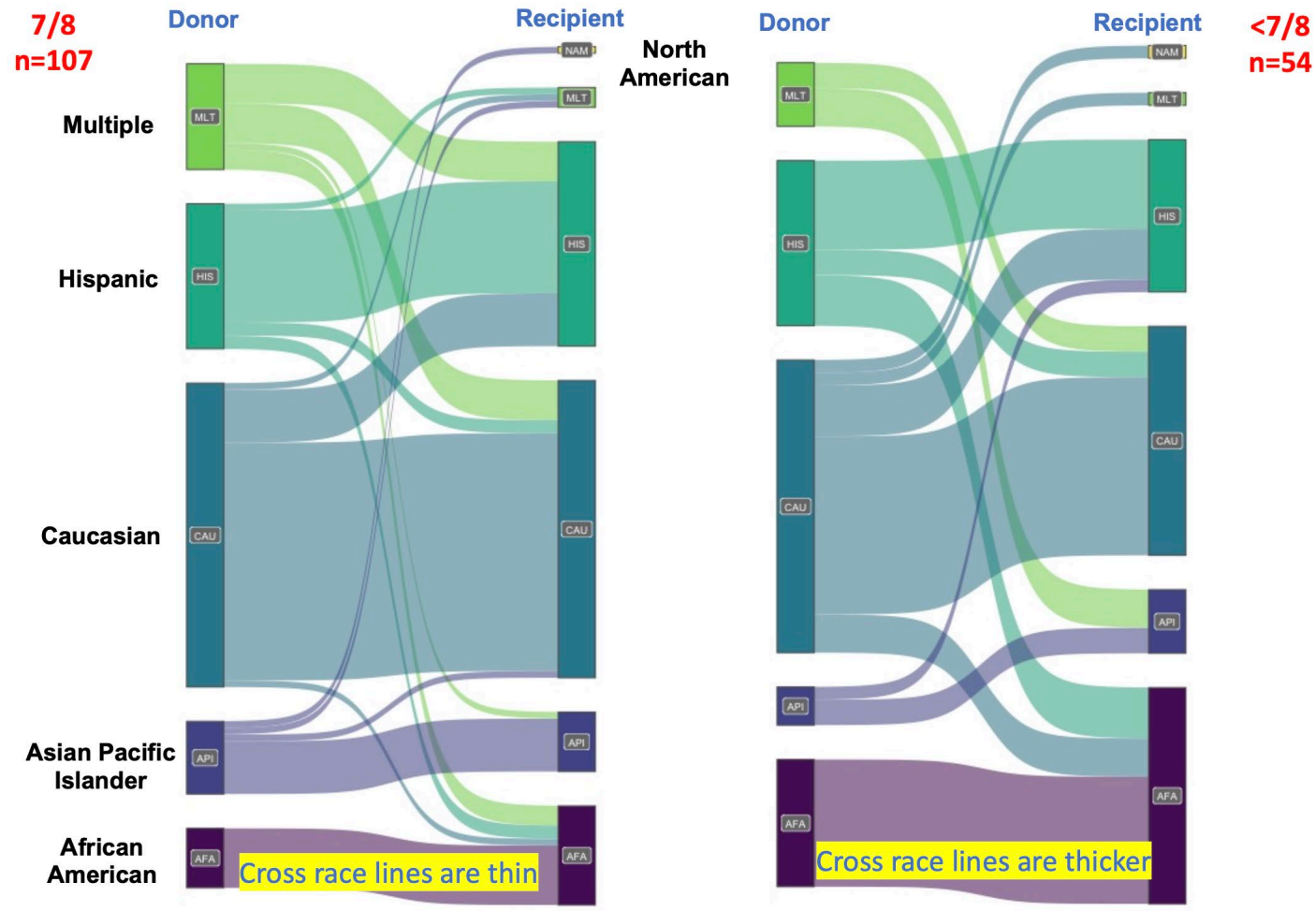
Shaffer and Jimenez, unpublished data

Increase in MMUD HCT will require donors with diverse ancestry



Most donors for ACCESS study patients have a similar broad racial/ethnic background as the recipient

This is because less so with increasing HLA-disparity

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Conclusions

- NMDP realized that disparities in access to HLA-matched donors based on race/ethnicity could not be solved **just** by increasing registry size or diversity

- This required committing resources to prospective clinical research designed to close the gap in outcomes between matched and mismatched URDs

- CIBMTR led studies sponsored by NMDP demonstrate that PTCy-based GVHD prophylaxis has mitigated impact of HLA-mismatching
    - 7/8 Donors using PTCy-prophylaxis now a standard of care at US transplant centers

- Next steps involve making MMUD HCT safer and more effective, so all will benefit

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