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ADVISORY COUNCIL ON BLOOD STEM CELL TRANSPLANTATION (ACBSCT)

U.S. Department of Health and Human Services

CIBMTR/NMDP Update on Clinical Trials using Mismatched unrelated Donors

Dr Steven Devine; 10/24/24

Disclosures

Full time employee of NMDP

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CIBMTR/NMDP Prospective Clinical Trials Focused on Improving Outcomes in Mismatched Unrelated Donor HCT

Rationale for NMDP Focus on MMUD HCT

- Increasing racial/ethnic diversity of patients in US who need HCT
- NMDP realized diversifying the registry was necessary, but that alone would not allow us to meet our equity goals
- Patients need more options: Haplo related and UCB help, but many gaps remain
- A significant proportion of patients do not have a suitable haplo donor or UCB graft available
- Advent of PTCy created an opportunity to determine if good outcomes in haploidentical setting could be translated to MMUD

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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

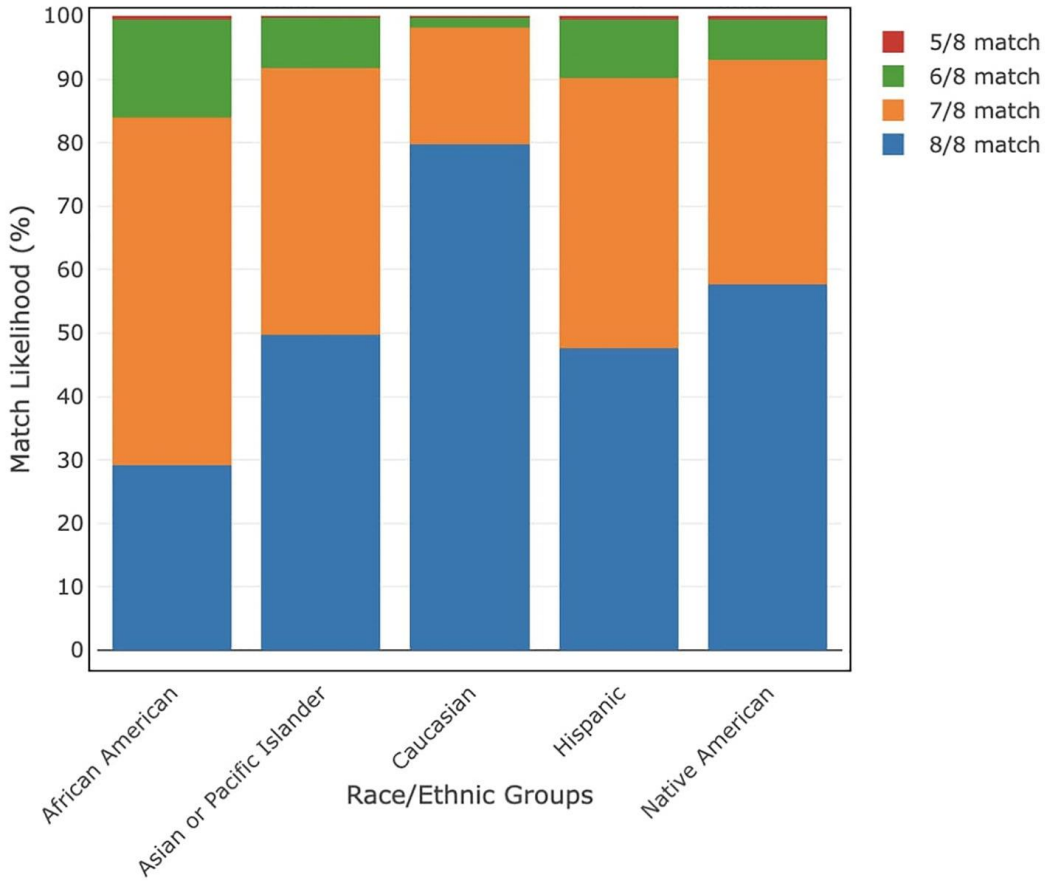
Study Sponsored by:

nmdp
FIND CURES. SAVE LIVES.

NCT04904588

Background

HLA match likelihood (%) at 5/8 to 8/8 levels with donors of all ages[1]



Matching Requirement Impacts Demographics

- In recent CIBMTR analysis of 8/8 URD recipients from 2017-2021, 86% were Non-Hispanic white (NHW)[2]
- In BMT CTN 1703 randomized study evaluating PTCy-based versus standard CNI-based GVHD prophylaxis, 82% were NHW[3]

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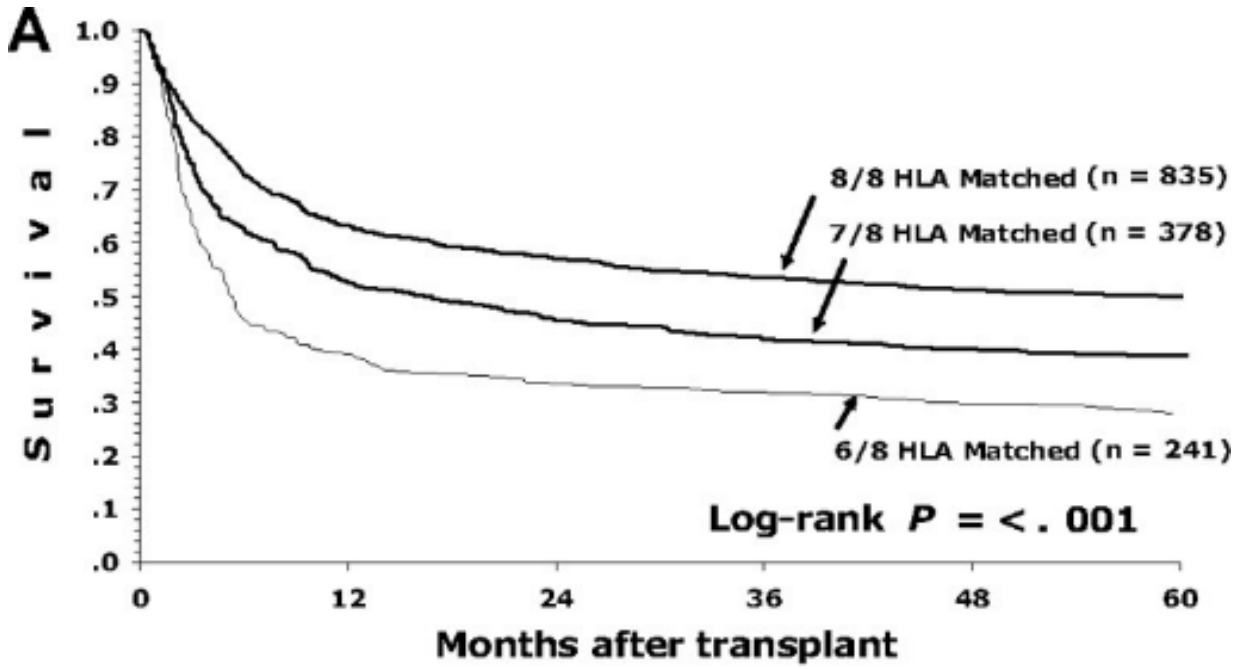
1. Chowdhury A et al. Transplant Cell Ther 2023 Nov;29(11):686; 2. CIBMTR unpublished data; 3. Bolanos-Meade, New Engl J Med, 2023

Background:

*Historically, unrelated donor HLA mismatching associated with clinically important and statistically significantly worse survival using standard calcineurin-based GVHD prophylaxis**



Overall Survival	One year	Five year
Match level		
8/8	63%	50%
7/8	52%	39%
6/8	39%	28%

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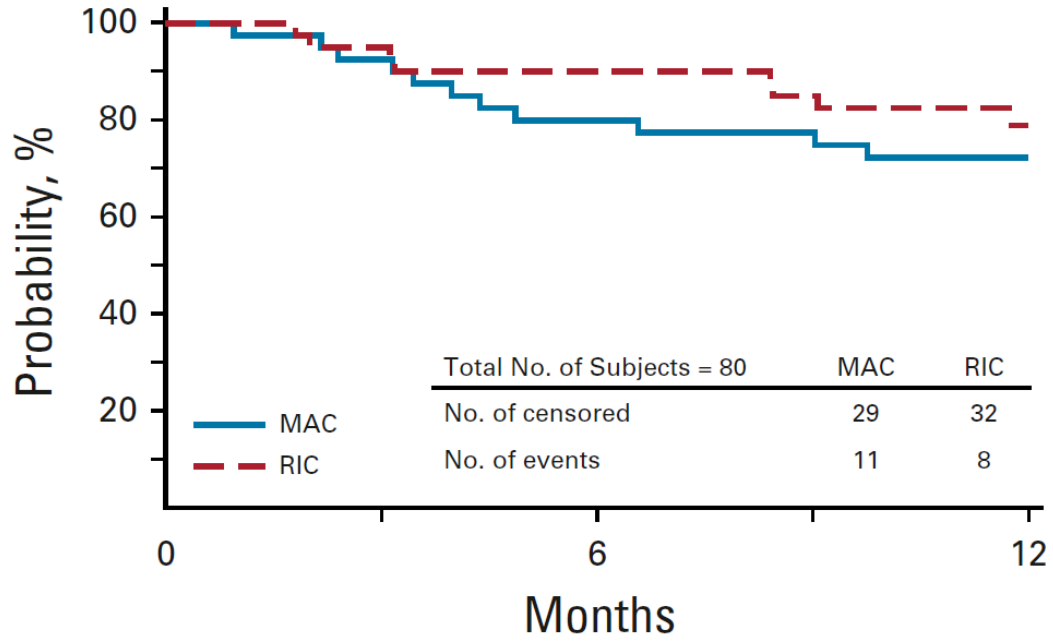
***Lee et al. Blood. 2007 Dec 15;110(13):4576-83**

Background: 15-MMUD trial results

- **Study description:**
  Patients: 80
  Conditioning Regimens: Standard RIC and MA (non-randomized, TC choice)
  Donor: MMUD (4-7/8 allowed)
  Graft: Bone marrow
  GvHD prophylaxis: PTCy, Sirolimus, MMF



1-year outcomes:

- **76%** survival rate after one year
- **11%** aGVHD III-IV at 100 days
- **>90%** engraftment
- 19 deaths (7 relapse, 4 MOF)

- ***48% of Patients were racially/ethnically diverse***

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Shaw et al J Clin Oncol 2021 Jun 20;39(18):1971-1982

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
- Adult strata enrollment completed almost one year ahead of plan
- **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.*

ACCESS eligibility criteria

Key Inclusion Criteria	Key Exclusion Criteria
Hematological malignancy requiring HCT HCT-CI: 0-4 (MAC); any (RIC) PBSC donor product Patient age ≥ 18 years KPS of ≥ 60% Available partially HLA-MMUD (4/8-7/8 at HLA-A, -B, -C, and -DRB1) with age ≤ 35 years Estimated creatinine clearance > 60 mL/min	Availability of a suitable HLA-matched related or 8/8 high resolution matched URD Presence of donor-specific HLA antibodies to any mismatched allele/antigen with mean fluorescence intensity > 3000 Prior allogeneic HSC transplant Primary myelofibrosis Concurrent enrollment on other interventional GVHD clinical trial

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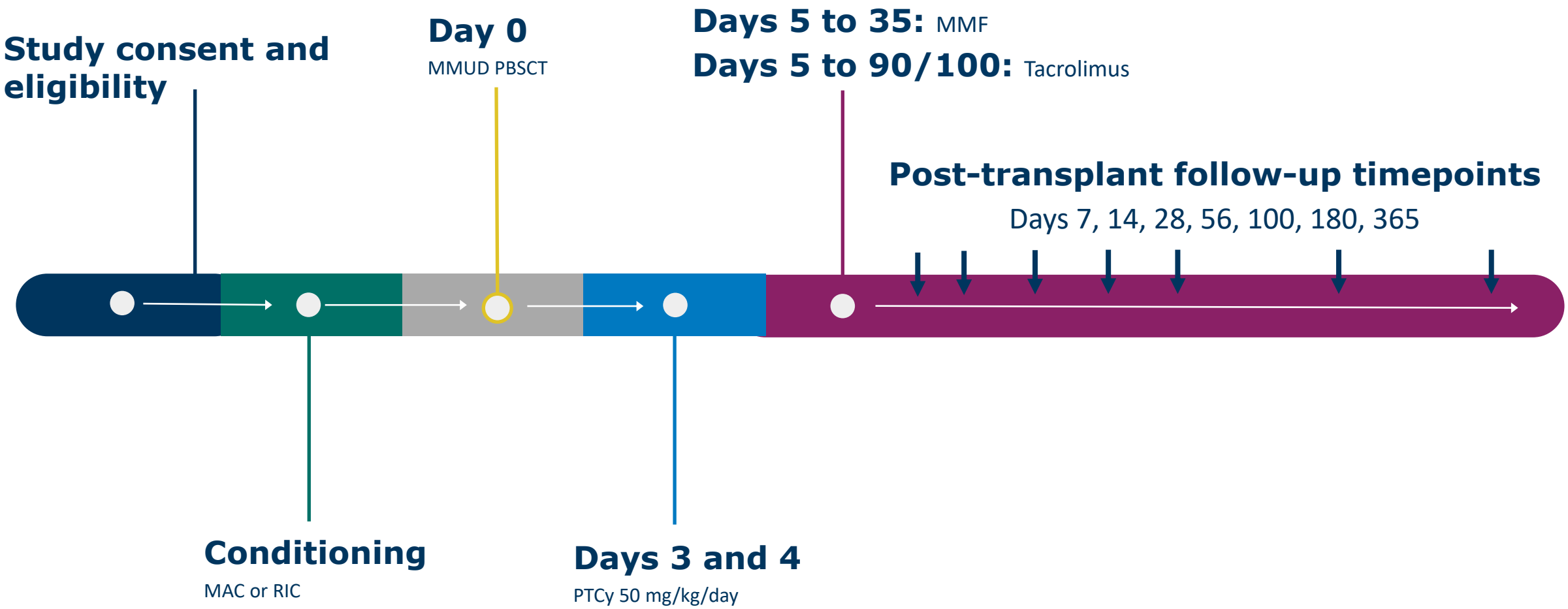
ACCESS treatment scheme



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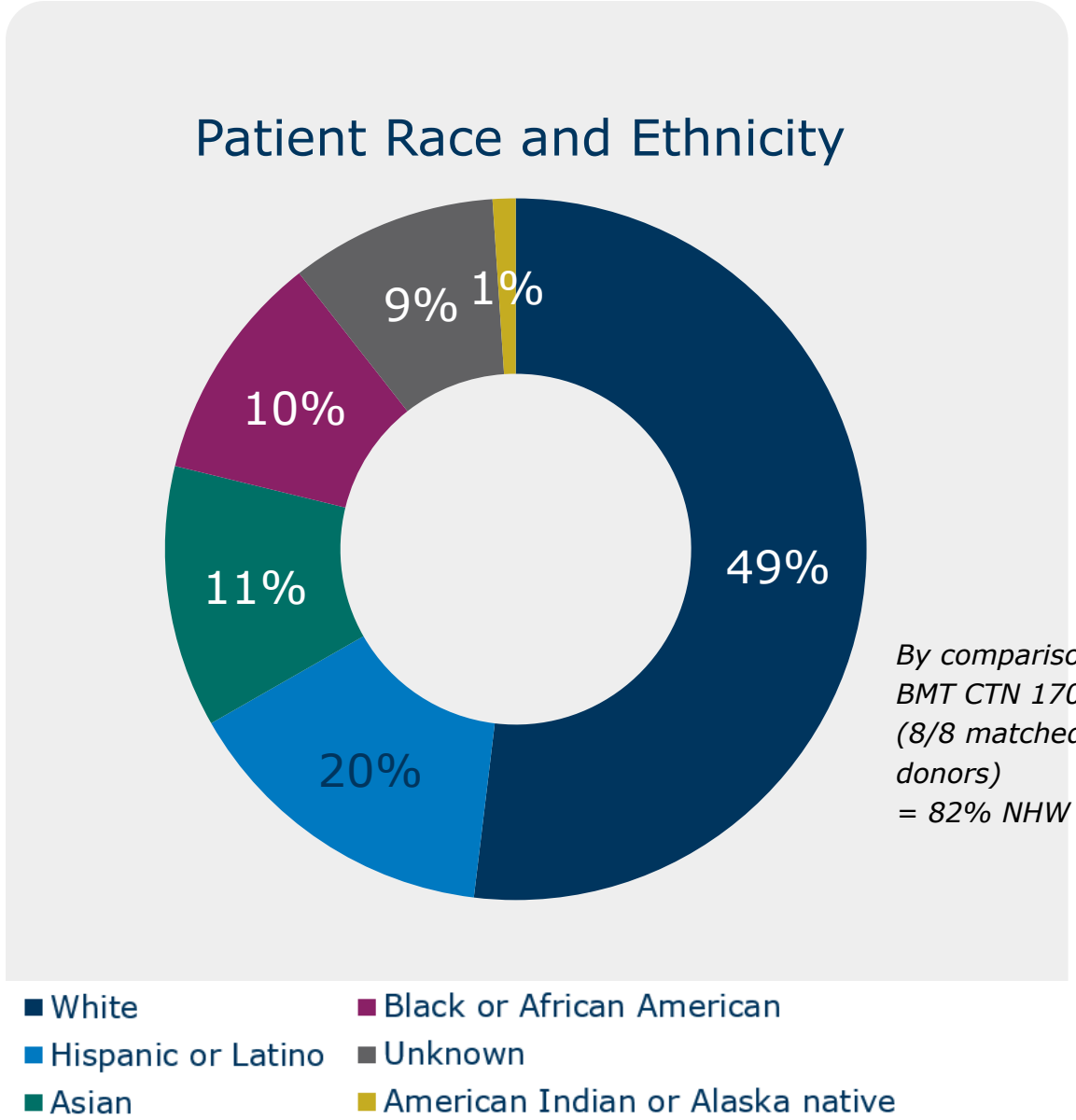
Patient Demographics (RIC)

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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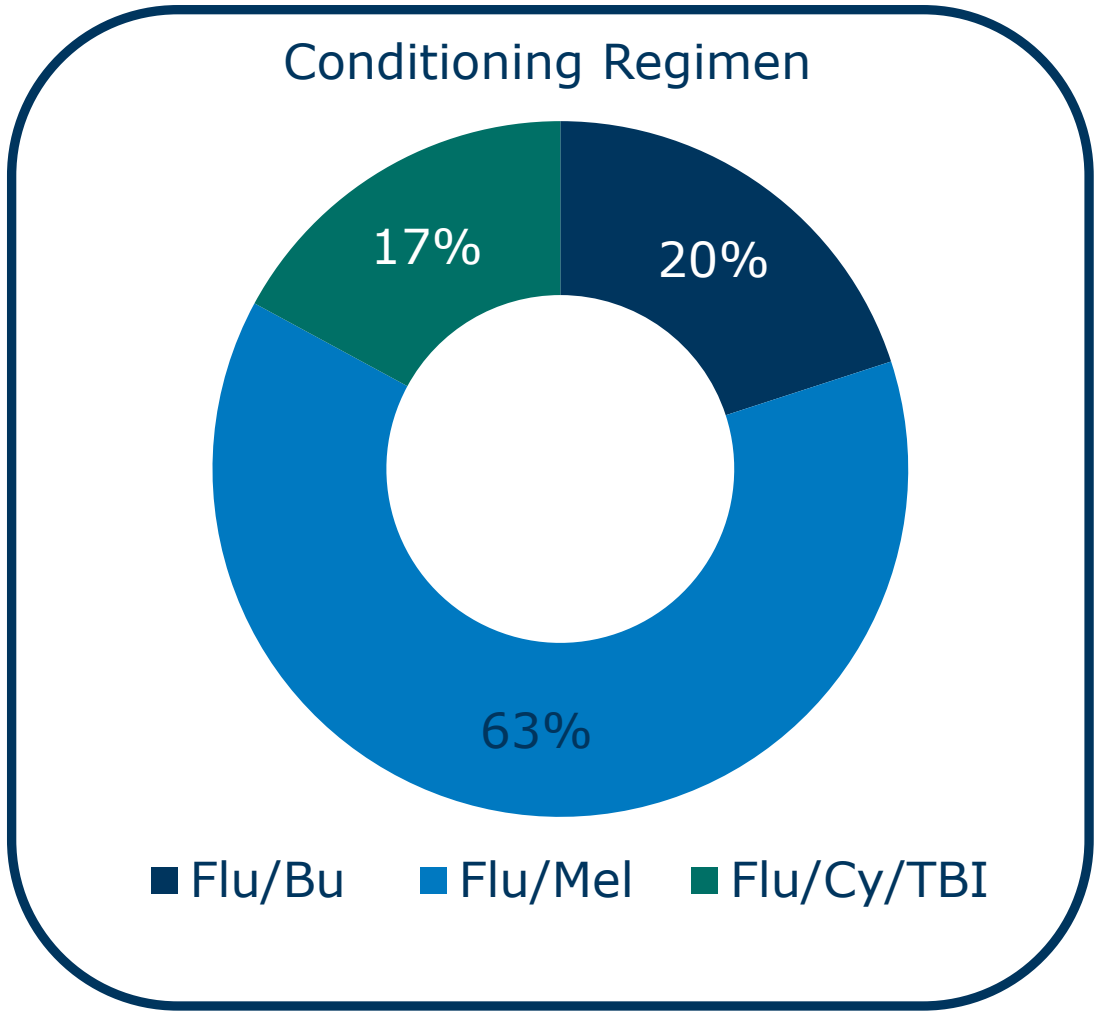
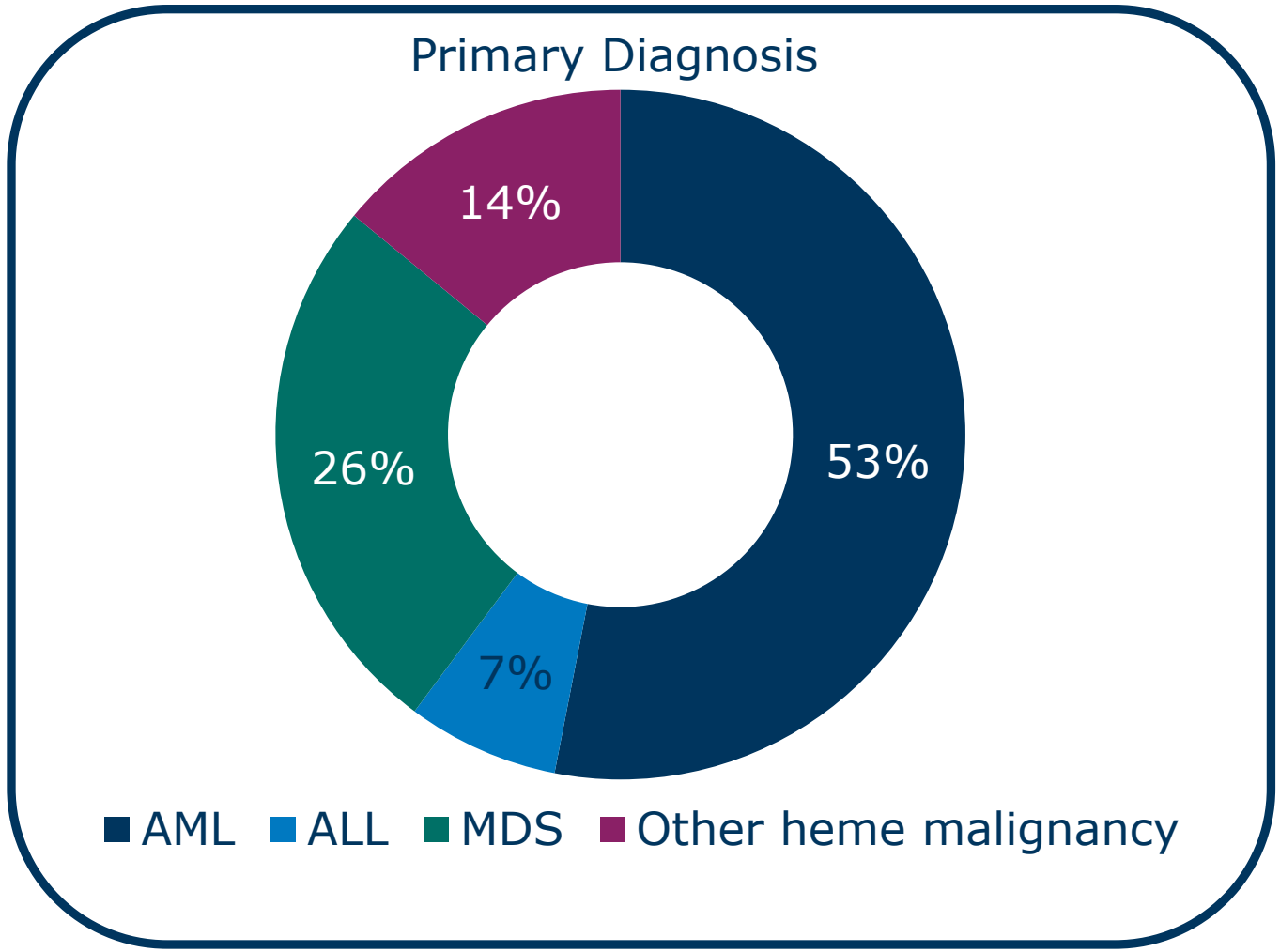
Results – Patient Characteristics (RIC)





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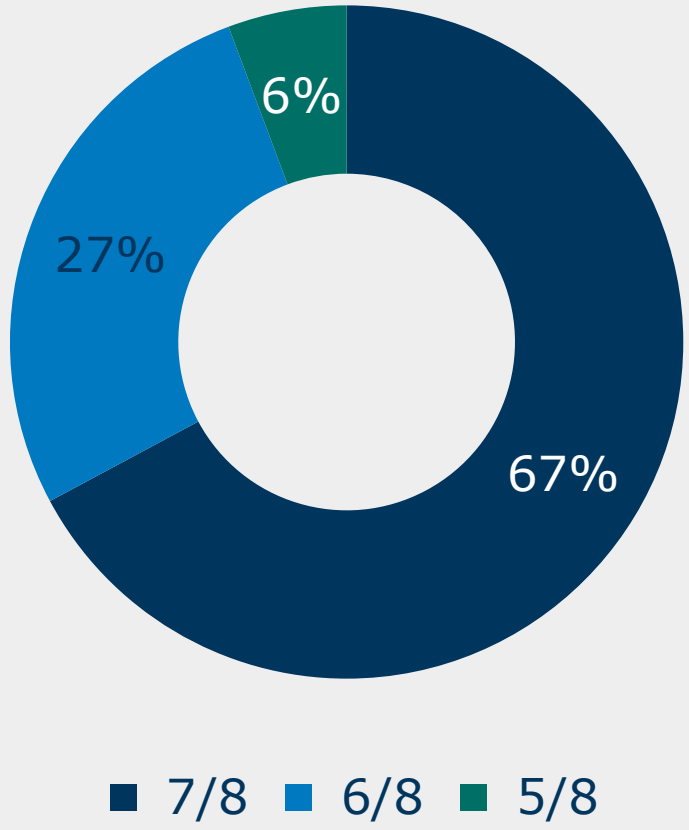
Results – Donor Characteristics

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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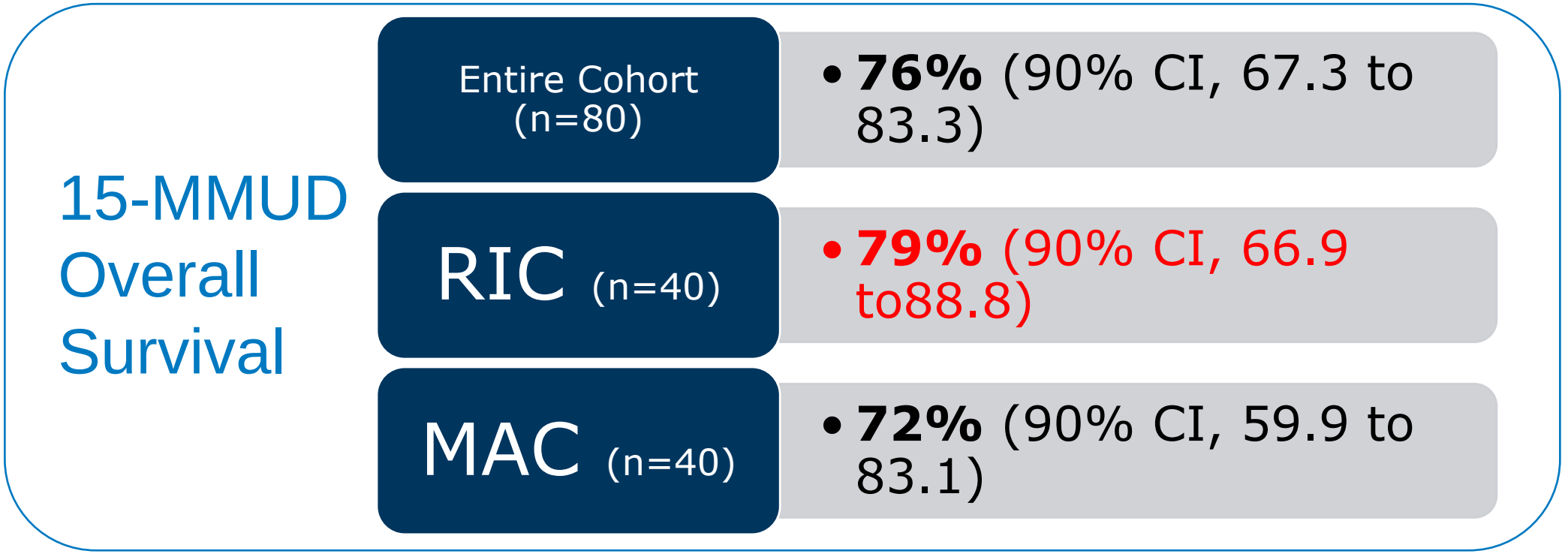
Hypothesis Testing for ACCESS Study

- 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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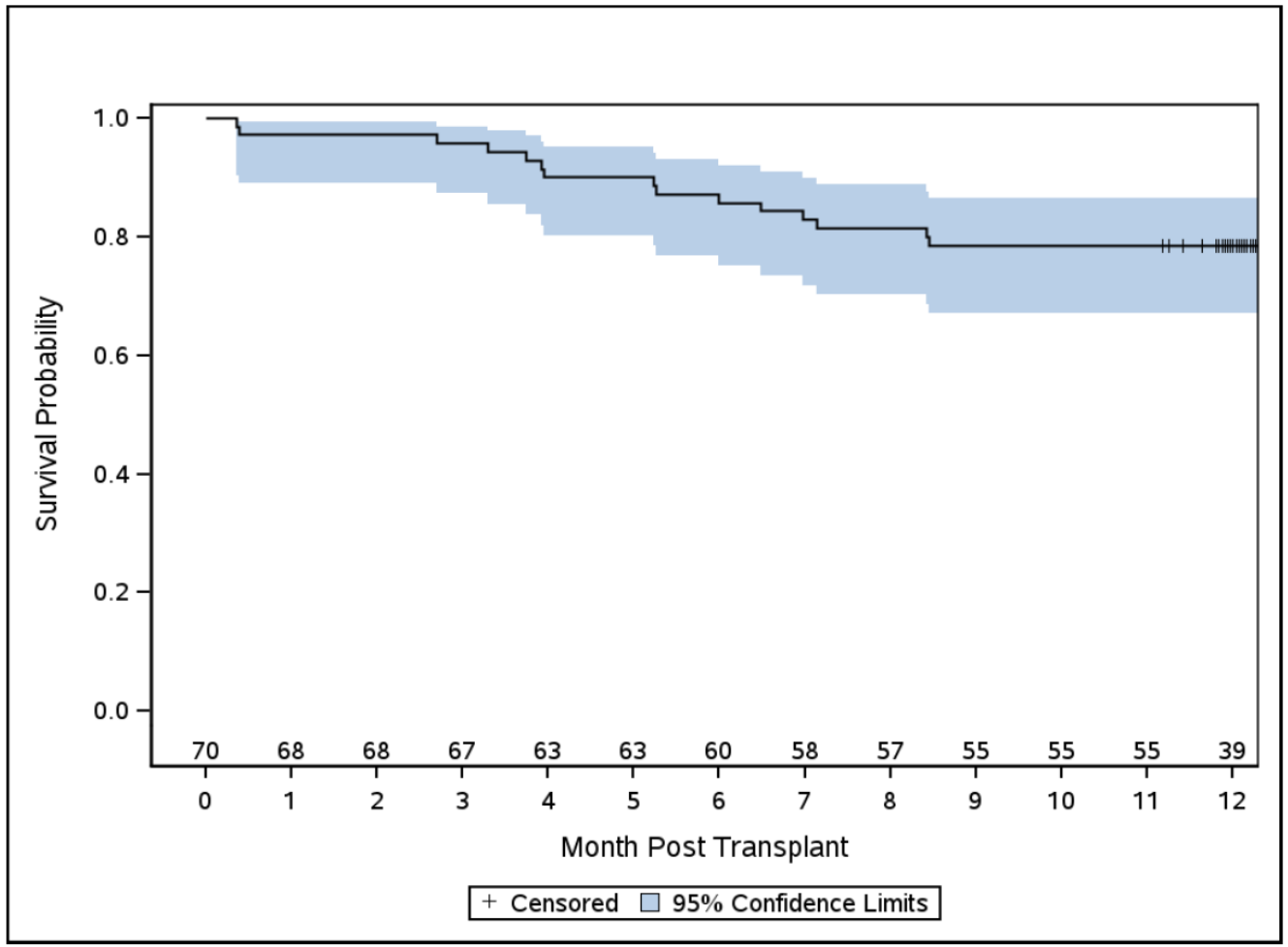
Shaw et al, J Clin Oncol, 2021

Results – Primary Endpoint



Overall Survival at 1-year post-HCT = **79%**

Overall Survival at 1- year post-HCT in 15-MMUD study RIC cohort = ***79%***
(Shaw et al J Clin Oncol 2021 Jun 20;39(18):1971-1982)

95% confidence interval: 68-87%
Median follow-up (min-max) of survivors, months: 12.1 (11.2-12.9)

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Results – Overall Survival by match grade (exploratory)

	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		**76.6** (61.7-86.3)%		**82.6** (60.1-93.1)%	

[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 on RIC Stratum

		Total		First 100 days		D100 to 1 year	
Infection	CTCAE grade	Infections n	Recipients affected n (%)	Infections n	Recipients affected n (%)	Infections n	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)

*50% of recipients with Grade 2 infections in the first 100 days post-transplant presents an opportunity to improve infection-free survival.

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ACCESS: Anti-HLA directed antibodies (Ab)

By Patient Gender

N=153	n	%
Female	89	58%
Male	64	42%

By Conditioning Intensity

Intensity	Total	Positive for HLA-directed Ab	%
MAC	66	35	53%
RIC	181	118	65%

Excludes adult unknowns

Summary:

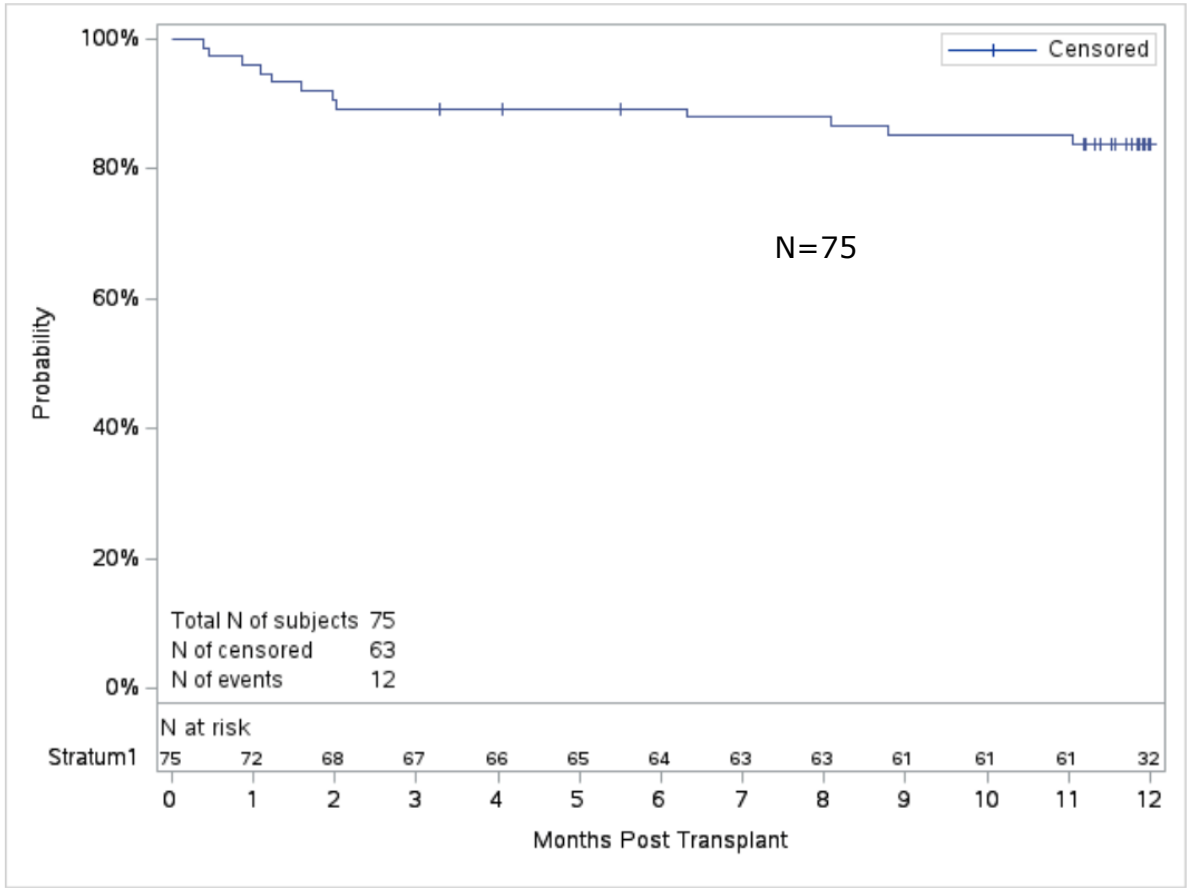
- Of 153 patients with anti-HLA Ab, 89 (53%) were female
- Higher incidence of anti-HLA Ab noted in patients utilizing MMUD with higher degree of HLA mismatch
- May allow highly alloimmunized females access to HCT when UCB and Haplo donors not suitable due to HLA antibodies

By Donor Match Level

	n	n with HLA-directed Ab	%
7/8	165	96	58%
6/8	67	45	67%
5/8	12	9	75%
4/8	3	3	100%

Excludes adult unknowns

Primary Endpoint (MAC): Overall Survival



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

	Stratum1 (N = 75)	
	N	Prob (95% CI)
Overall survival	75	
6 months	64	89.3 (79.8-94.5)%
1-year	32	83.8 (73.1-90.4)%

Median (range) follow-up is 12.0 (3.3-12.9) months.
Median (range) follow-up of survivors who did not exit study early: 12.0 (11.2-12.9)

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

	7/8 (N = 52)		<7/8 (N = 23)		
	N	Prob (95% CI)	N	Prob (95% CI)	P-Value[1]
Overall survival	52		23		0.278
6 months	44	86.5 (73.8-93.3)%	20	95.7 (72.9-99.4)%	
1-year	22	80.6 (67-89.1)%	10	90.9 (68.1-97.6)%	

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

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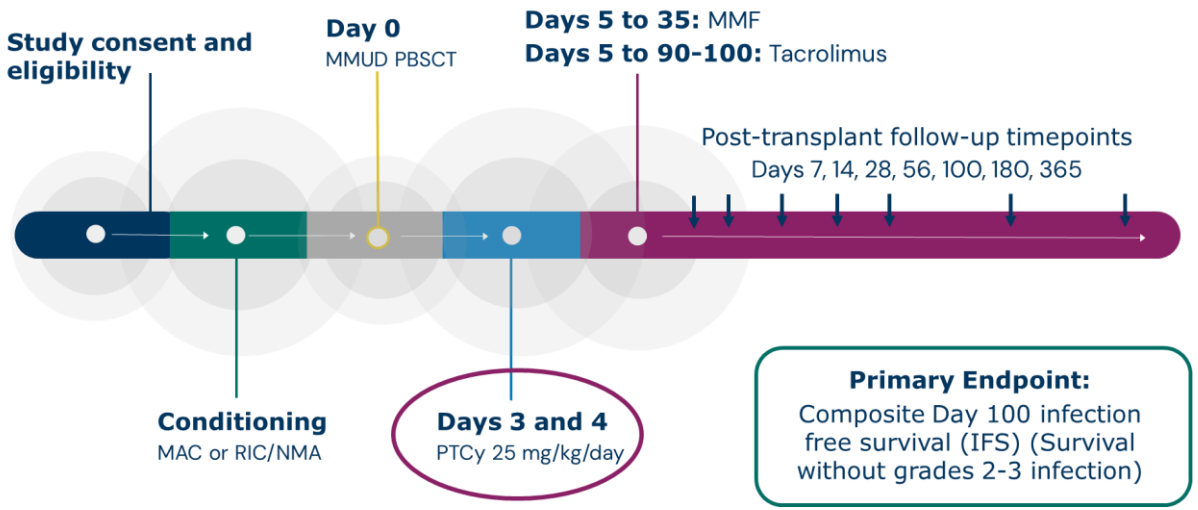
OPTIMIZE: Primary Objective and Endpoints

- **Primary Objective:**
  - To estimate **infection-free survival (IFS)** and determine safety of combination reduced-dose PTCy, MMF, and tacrolimus as GvHD prophylaxis for patients with hematologic malignancies receiving mismatched unrelated donor (MMUD) peripheral blood stem cells (PBSC) following myeloablative or reduced-intensity conditioning.

- **Primary Endpoints:**
  - Composite D100 infection free survival (IFS) (survival without grades 2-3 infection)

- **Safety Endpoints:**
  - D28 Primary graft failure
  - D14 Grade 3-4 CRS
  - D100 Grades 3-4 acute GvHD
  - D100 Non-relapse mortality (NRM)



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OPTIMIZE: Patients (As of October 9, 2024)

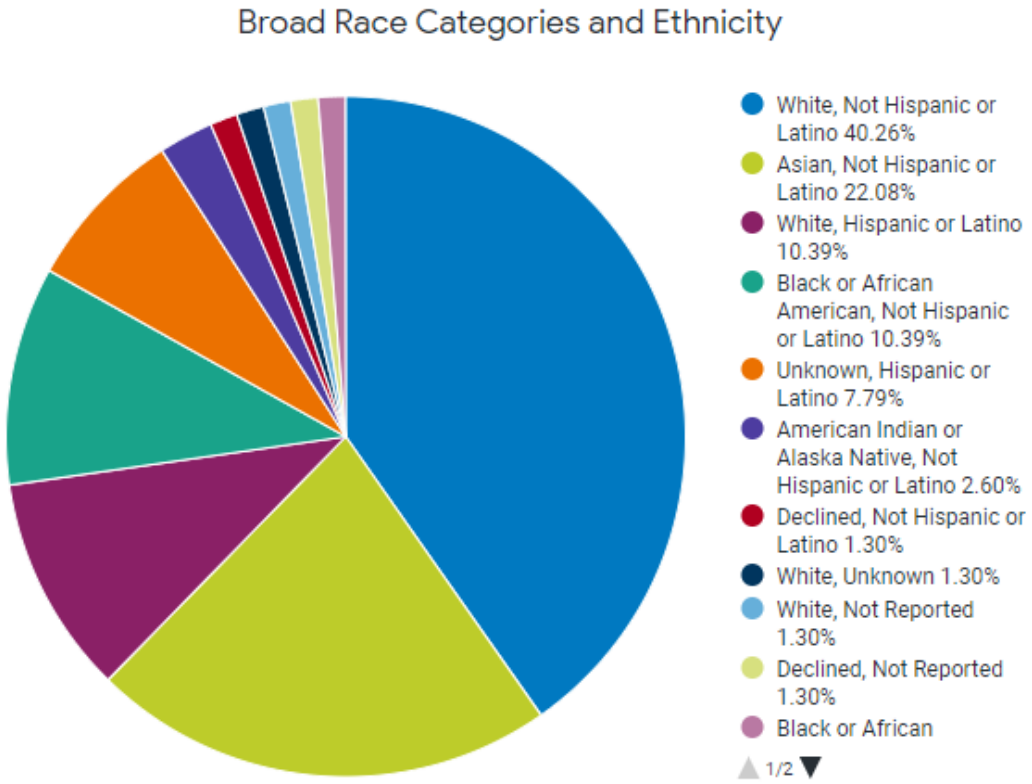
Brisk enrollment: exceeding expectations by 50%

Projected enrollment: 82 (RIC): 75 (MAC)

90 Enrolled	80 Enrolled and Infused	10 Consented, Eligible, Enrolled, not ...	0 Completed Study
16 In Screening	9 Screen Failed	6 Off Protocol	3 Early Terminated

Enrollment by Stratum

16 # Enrolled in Run-In Phase	24 # Enrolled in Stage 1 MAC Stratum	40 # Enrolled in Stage 1 RIC Stratum	5 # Enrolled in Myelofibrosis Stratum
80% of 20 available slots filled	62% of 39 available slots filled	103% of 39 available slots filled	50% of 10 available slots filled



59% of Enrolled subjects report Non-white, non-Hispanic or Latino Race/Ethnicity

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First interim analysis in RIC stratum completed; on to stage II

MMUD Clinical Trial Portfolio

Conventional

Design → Conduct → Analyze

Feasible

15-MMUD
n=80 adults

Study development: 2015
Study opened: Dec 2016
Study closed: Mar 2019
Results presented: Feb 2020
Results published: Apr 2021

Practical

ACCESS
n=268 adults

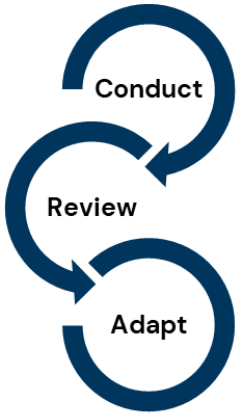
Study development: 2020
Study opened: Sept 2021
Study closed: Dec 2023
Results presented: Mar 2024
Results published: TBD

Safer

OPTIMIZE
n=187 adults

Study development: 2022
Study opened: Dec 2023
Study closed: TBD

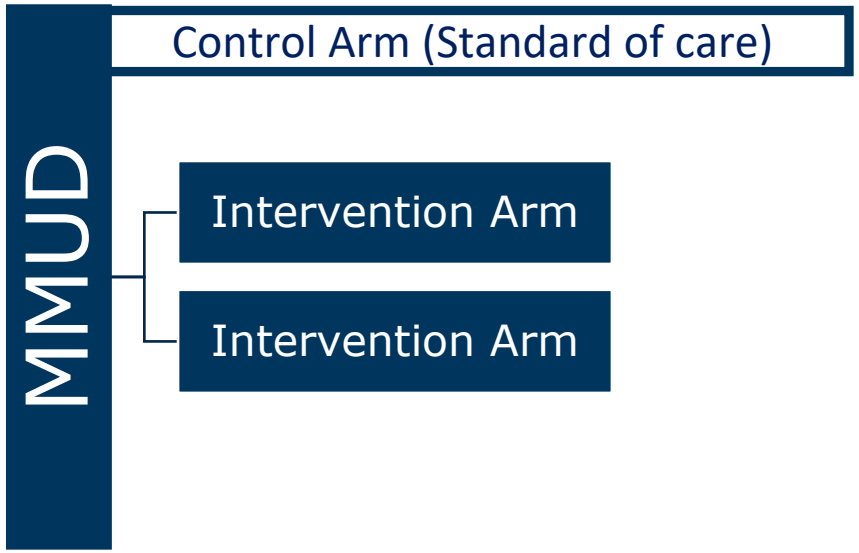
Platform



Faster

ACCELERATE
n=318 adults

Study development: 2023
Study opened: 2025
Study closed: TBD



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A MMUD Platform Protocol: ACCELERATE

Evaluates several interventions against a perpetual common control group ("ACCESS").

Multiple study questions are addressed under a single protocol (added as protocol appendix)

Has pre-specified rules to allow dropping of ineffective intervention(s) and flexibility of adding new intervention(s) during the trial.

Improve outcomes by reducing complications seen in MMUD donor transplants:

- **Acute and Chronic GvHD**
- **Infections**
- **Relapse**
- **Primary Graft Failure**

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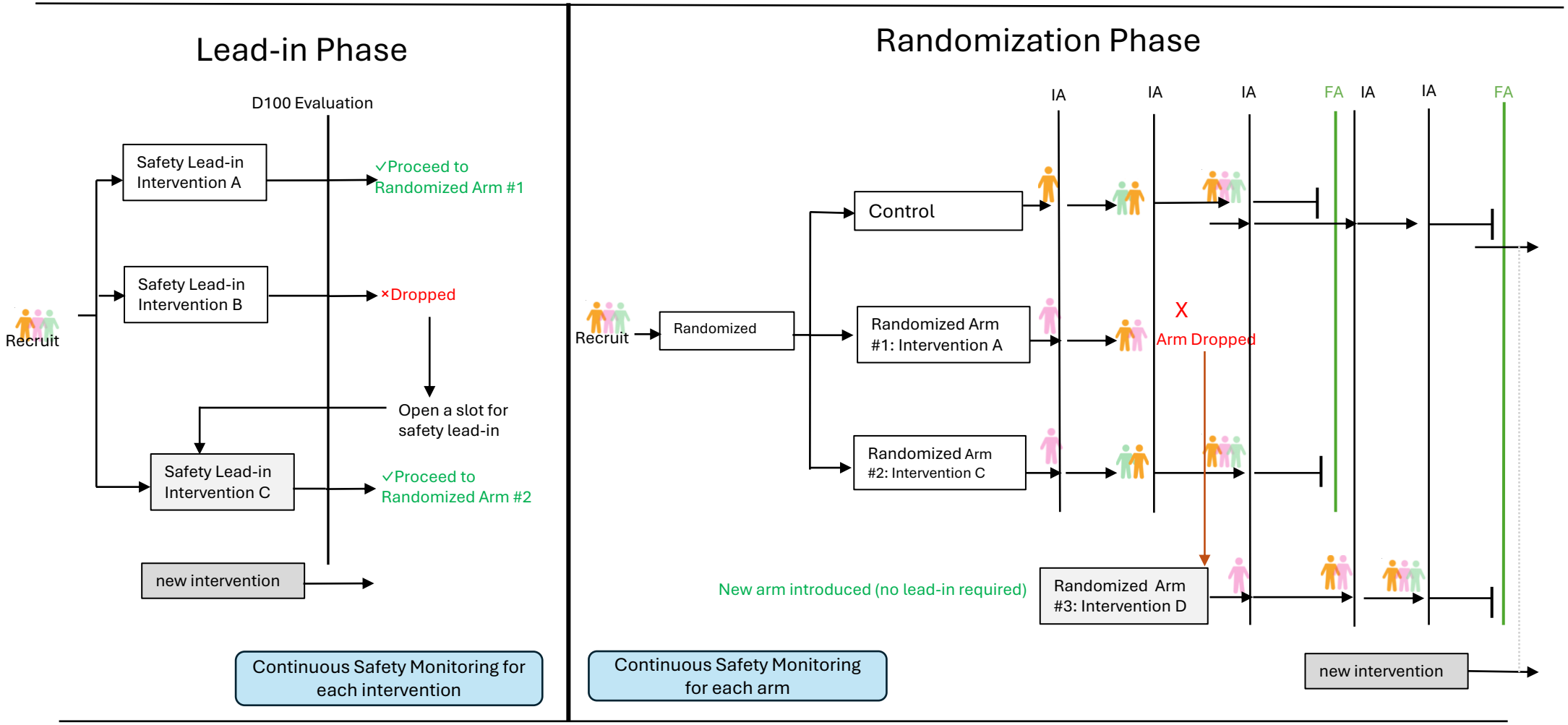
ACCELERATE: Study design schema



D28: Day 28 post HCT; D100: Day 100 post HCT. IA=Interim Analysis; FA=Final Analysis

Continuous Safety Monitoring :
- PGF by D28 (if treatment starts before D28)
- D100 Grades 3-4 aGVHD
- D100 Overall Mortality

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ACCELERATE Treatment Scheme

SAME ACROSS THE PLATFORM

Study consent and eligibility

Day 0
MMUD PBSCT

Days 5 to 90-100: Tacrolimus

Conditioning
MAC or RIC/NMA

Days 3 and 4
PTCy

Post-transplant follow-up timepoints
Days 7, 14, 21, 28, 56, 100, 180, 270, 365

VARIES

Platform Arm	PTCy	MMF	Investigational Drug
Control	50 mg/kg	Day 5 to 35	--
ACCEL-001	25 mg/kg	--	Abatacept
ACCEL-002	25 mg/kg	Day 5 to 35	Ruxolitinib

Primary Endpoint:
GRFS: Graft-versus-host disease-free, relapse-free survival

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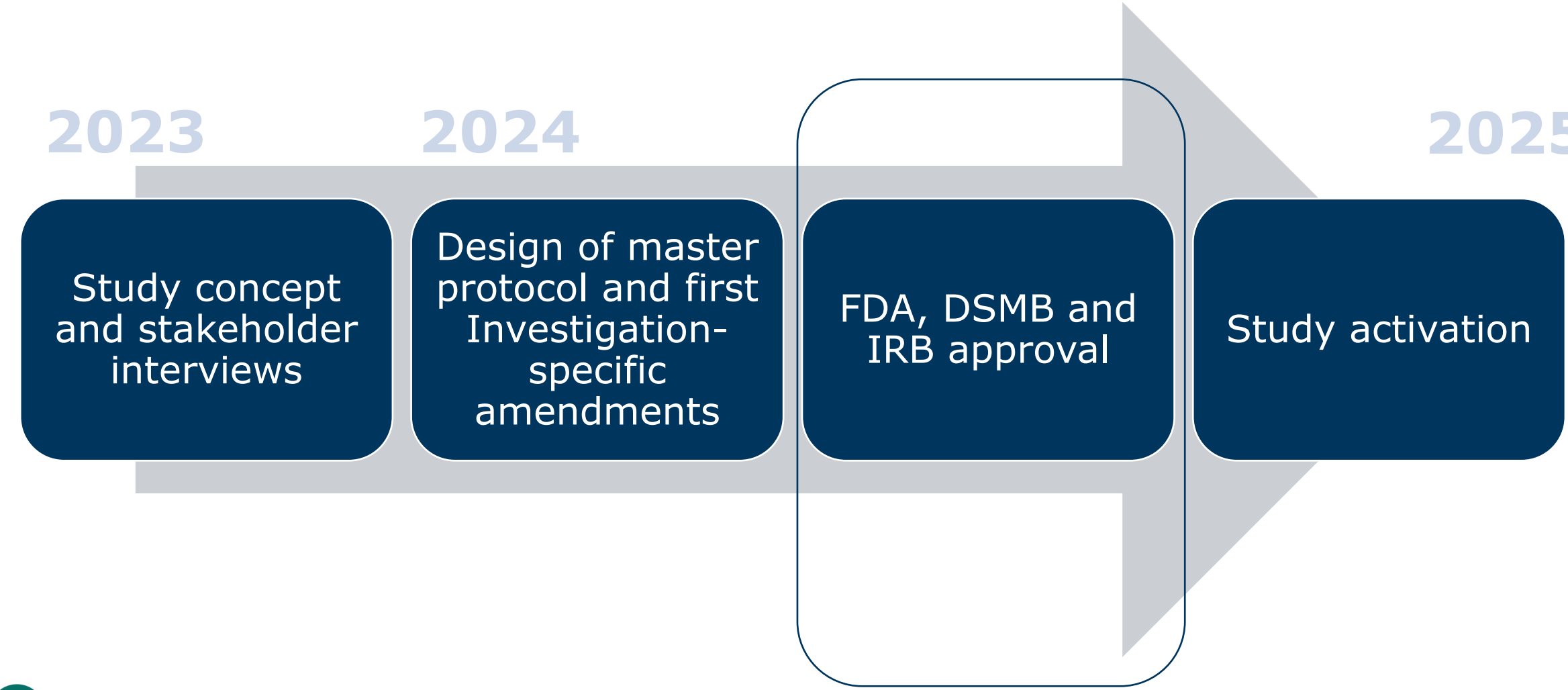
Where are we now?



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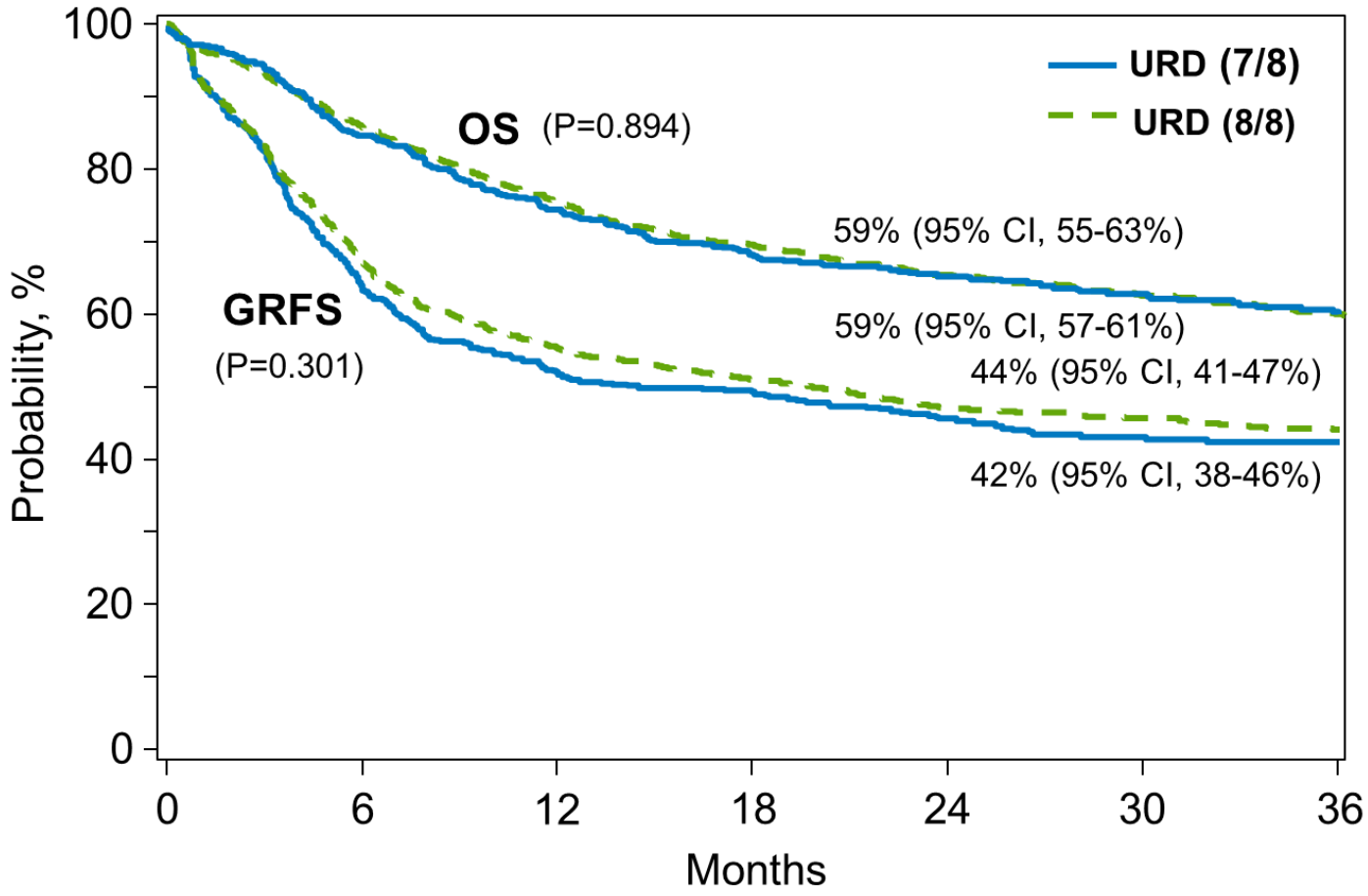
No difference between 8/8 and 7/8 URD HCT with PTCy: Adjusted 3y OS and GRFS

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



7/8: N= 613
8/8: N=1,681

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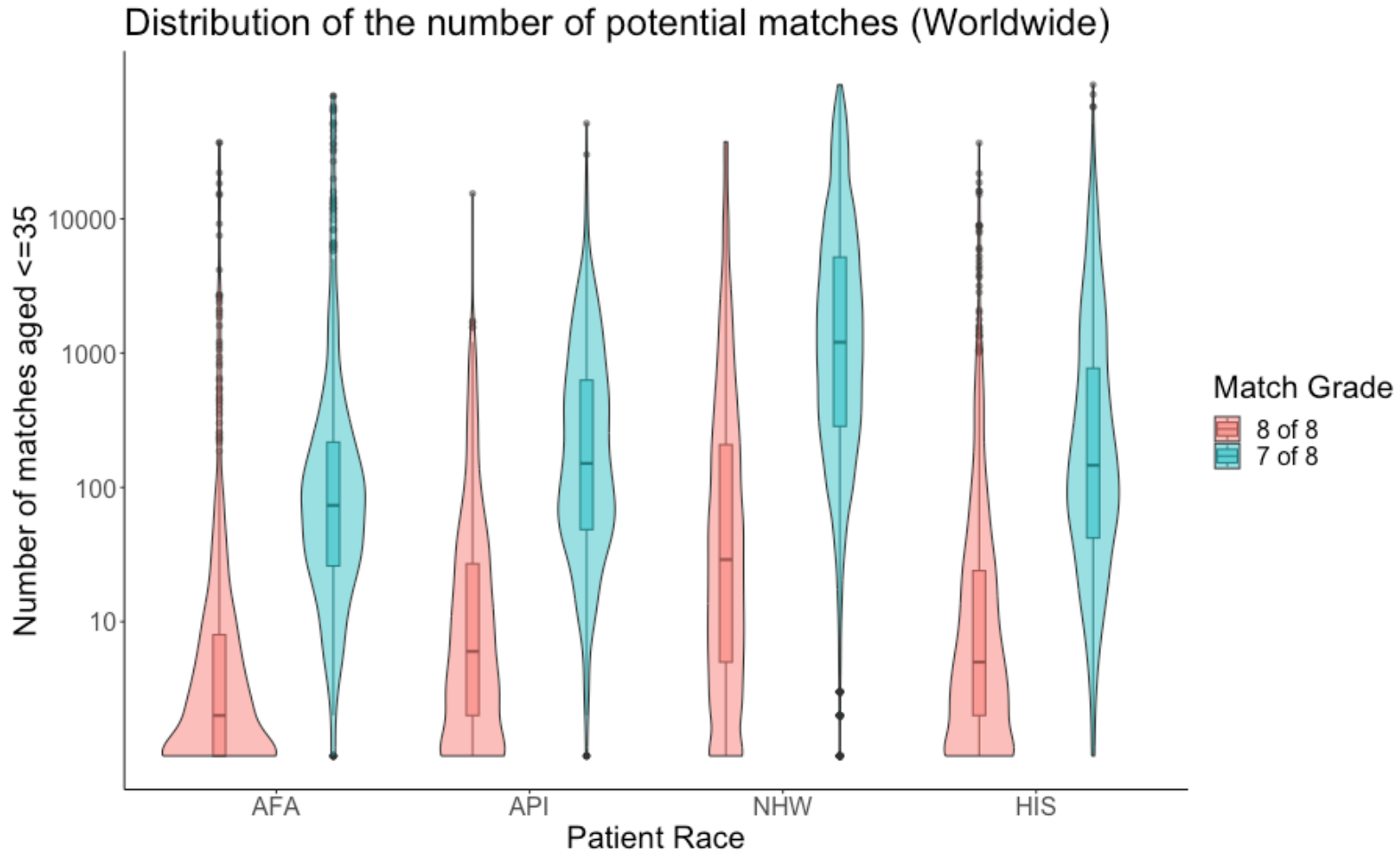
Shaffer et al, J Clin Oncol, 2024

Effect of MMUD on Donor Existence



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

Shaffer et al, J Clin Oncol, 2024

Conclusions

- Encouraging OS was observed at one year following MMUD PBSC in patients receiving RIC or MAC and PTCy. OS was similar to our prior study using BM grafts.
- Rates of GVHD and other complications appear comparable to those in HLA-matched donor recipients, suggesting MMUD HCT expands access to a potentially life-saving therapy.
- PRO and QoL data collected on ACCESS and will be analyzed and reported shortly.
- **No obvious difference in OS using 5-6/8 donors, but more data needed.**
- Ongoing (OPTIMIZE; NCT06001385) and future studies will target improvements in acute and chronic GVHD, infection rate, and relapse rate.
- Randomized Phase II studies (ACCELERATE) will be activated in 2025

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