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New approaches to prevent or reduce complications and disability following Hematopoietic Cell Transplantation

Steven Devine M.D.
Chief Medical Officer
National Marrow Donor Program (NMDP)

Disclosures

Full time employee of NMDP/Be The Match

Research support from Magenta, Vor Bio, Orca Bio

Advisor to Janssen, BMS, Sanofi, Orca Bio, Vor Bio

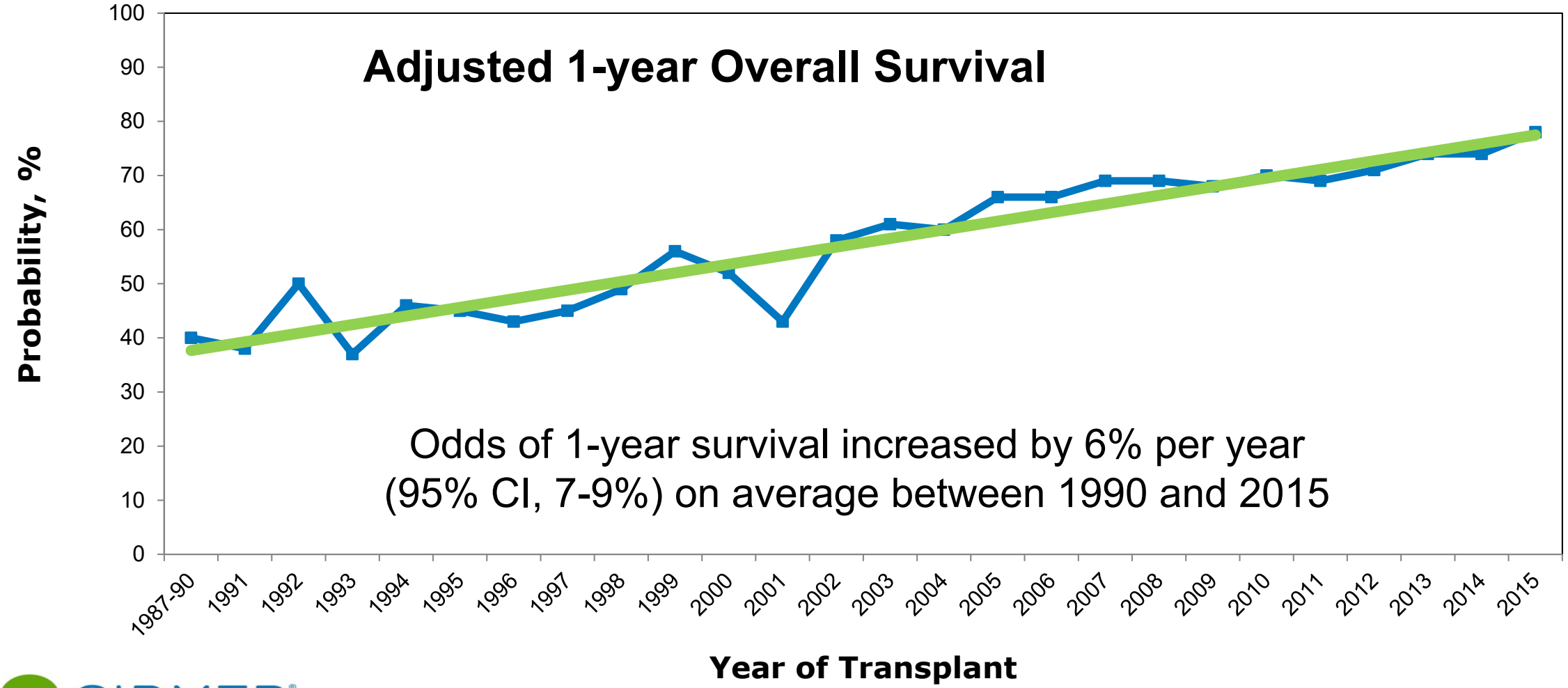
NMDP has equity interest in Magenta and Tmunity

Objectives

- Outline efforts by NMDP/CIBMTR and other partners to improve outcomes of Hematopoietic cell transplantation (HCT)
- Describe recent efforts to address disparities in access to BMT by NMDP and others
- Recognize there are very important efforts in search of progress by multiple investigators globally that cannot be covered by this talk

Survival After Unrelated Donor Transplantation

Age <50 years, myeloablative conditioning, acute leukemia in remission or MDS



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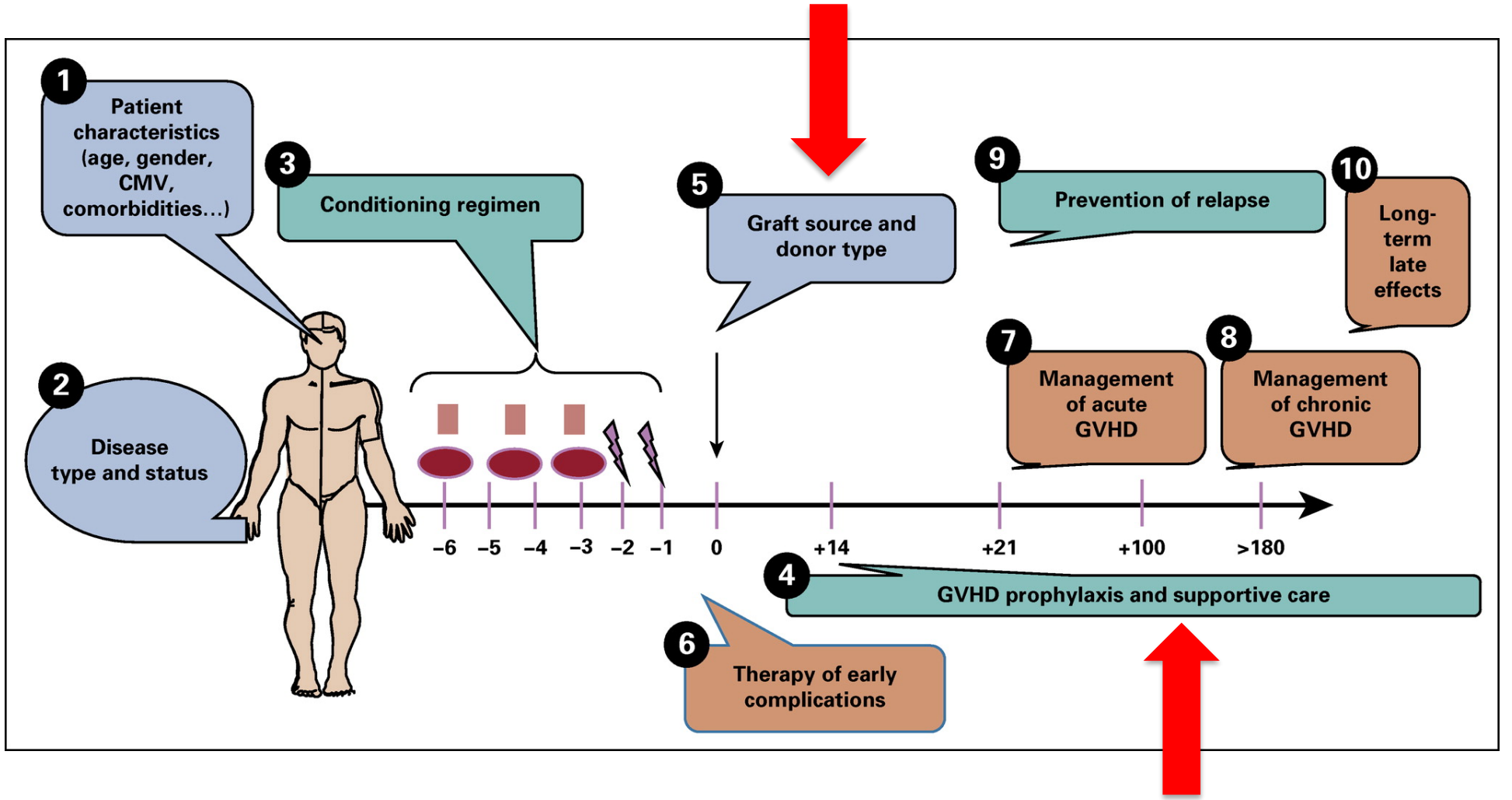
How can we provide allogeneic HCT for all patients?

EXISTENCE



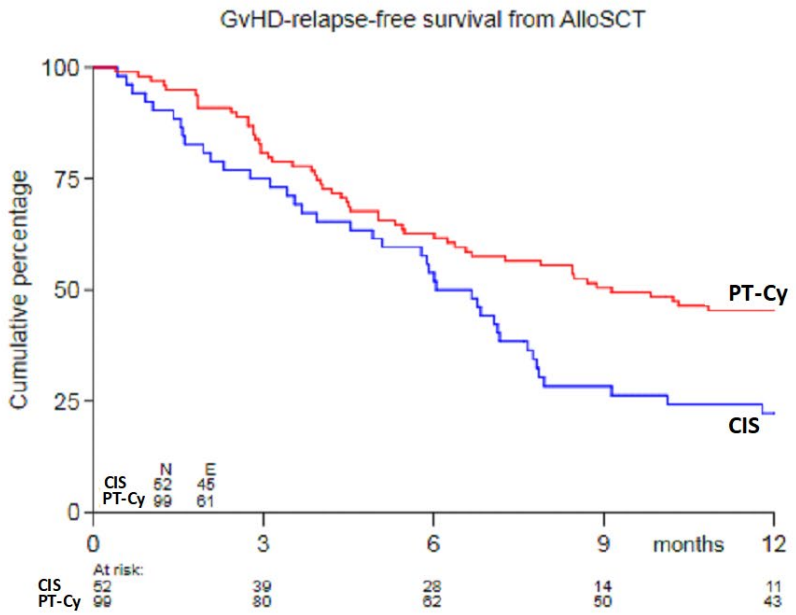
OBTAINABILITY

J Clin Oncol 2021;39(18):1951

Prevention of GVHD

- To be widely applicable, newer approaches must:
  - Increase access to HCT by mitigating impact of HLA mismatching
  - Be less toxic; not contribute to late toxicity (e.g renal toxicity of CSA/Tac)
  - Less influence on immune reconstitution
  - Predict who is at greatest risk of GVHD
- General approaches to prevent GVHD
  - **Pharmacological:** CNI-based, **Post transplant cyclophosphamide, CD28 blockade (abatacept),** monoclonal and polyclonal antibodies (e.g. ATG)
    - ➢ Not a single drug yet FDA-approved for GVHD prophylaxis!
  - **Physical/graft manipulation:** CD34+ cell selection, naïve T-cell depletion, α/β T-cell depletion, other novel approaches (e.g. graft engineering)
    - ➢ **One device (CliniMACS) approved for GVHD prophylaxis via humanitarian device exemption (HDE)**

Post-Transplantation Cyclophosphamide after Allogeneic Hematopoietic Stem Cell Transplantation: Results of the Prospective Randomized HOVON-96 Trial in Recipients of Matched Related and Unrelated Donors



- PTCy compared to cyclosporine based GVHD prophylaxis
- Randomized Trial
- Matched related and Unrelated donors
- Peripheral blood graft source
- Better GVHD, relapse free survival (GRFS) with PTCy based prophylaxis

De Jong et al, ASH Plenary, 2019

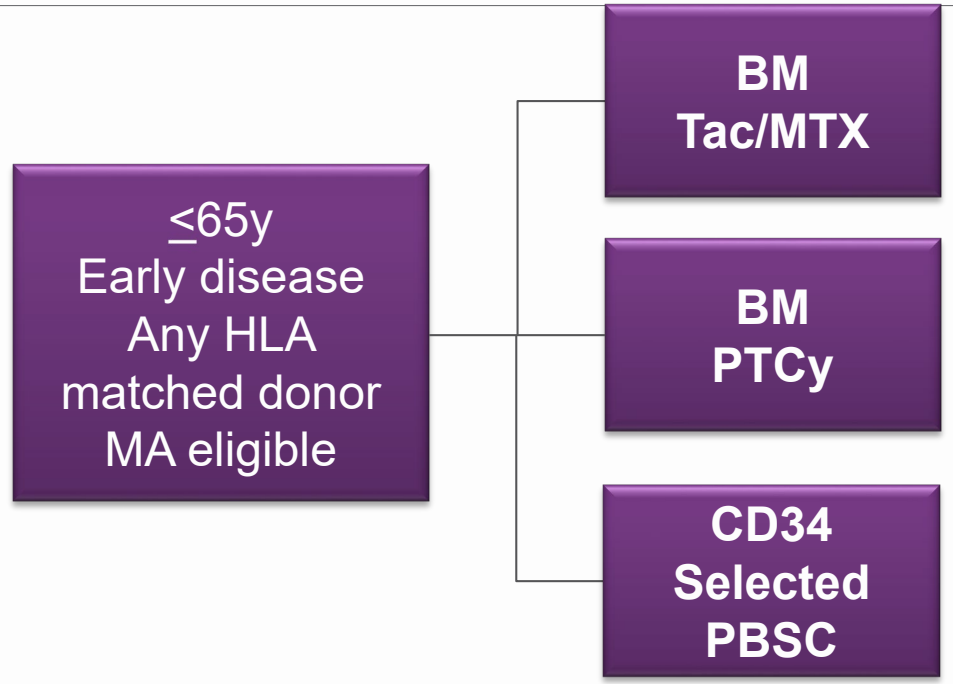
BMT CTN 1301

A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus Host-Disease

PROGRESS II trial
Prevention and Reduction Of GVHD and Relapse and Enhancing Survival after Stem cell transplantation

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1301 CNI free Trial: 3-arm Phase III



- 345 (115/arm): 85% power to detect a 20% difference over the 22% baseline of the chronic GVHD/relapse-free survival [CRFS] primary endpoint.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Completed accrual; results likely in CY2020

Progress
Prevention and Reduction Of Gvhd and Relapse and Enhancing Survival after Stem cell transplantation

BMT CTN 1703

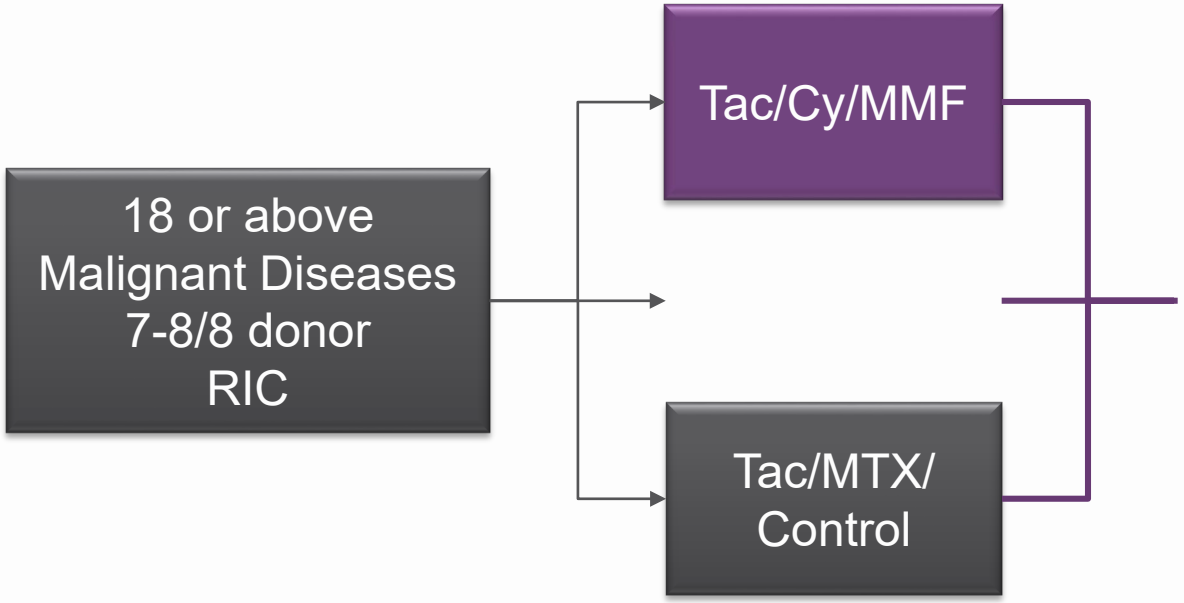
A Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation

PROGRESS III trial

Prevention and Reduction Of GVHD and Relapse and Enhancing Survival after Stem cell transplantation

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN #1703: Study Outline



1^0 Endpoint: GRFS at 1 year

N= 428 over 3 years

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

PROGRESS
Prevention and Reduction Of Gvhd and Relapse and Enhancing Survival after Stem cell transplantation

Increasing use of post transplant cyclophosphamide (PTCy) in US

Year		
Donor source	**2016**	**2020**
Matched sibling	7%	24%
Haploidentical related	85%	94%
Matched unrelated	6%	28%
Mismatched unrelated	14%	63%

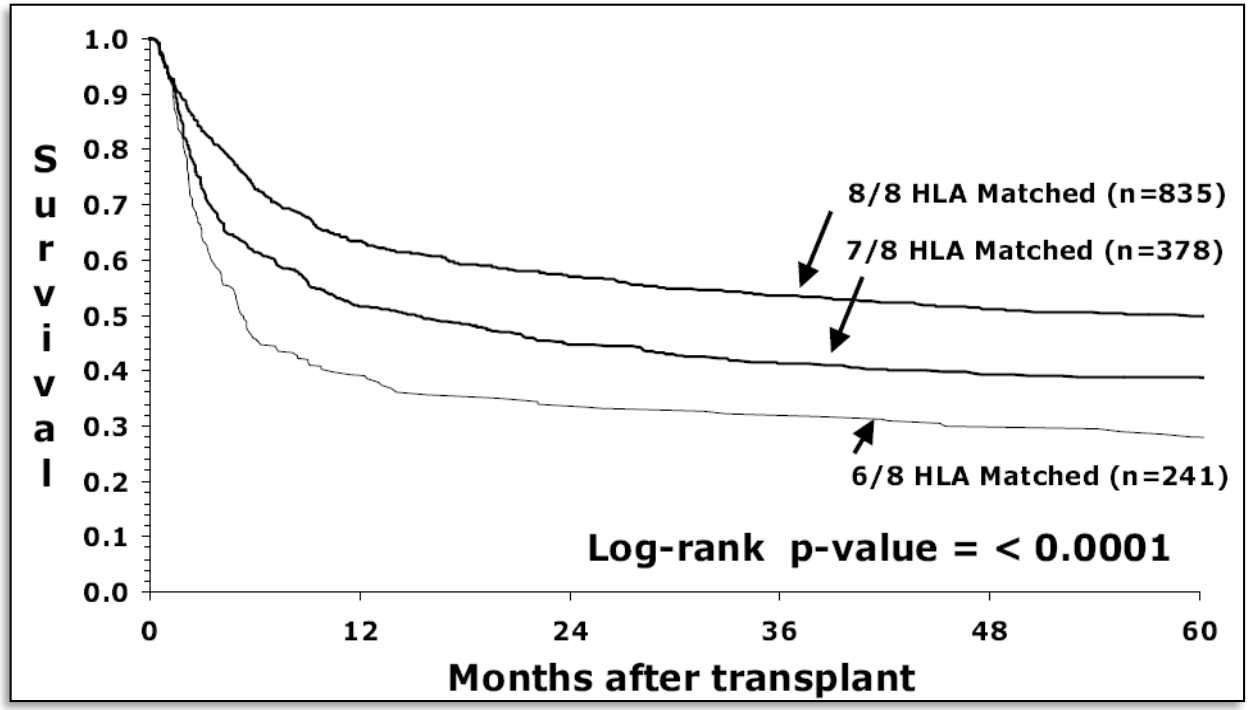
- **Source:** CIBMTR Activity report from US transplant centers
- Preliminary data during pandemic that PTCy use in matched unrelated donors has increased to 35-40%
- Awaiting results of BMT CTN 1703 study to determine impact on patient outcomes

The HLA Barrier: Historical Need for an HLA-matched donor

High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

Stephanie J. Lee,[1] John Klein,[2] Michael Haagenson,[3] Lee Ann Baxter-Lowe,[4] Dennis L. Confer,[5] Mary Eapen,[2] Marcelo Fernandez-Vina,[6] Neal Flomenberg,[7] Mary Horowitz,[2] Carolyn K. Hurley,[8] Harriet Noreen,[9] Machteld Oudshoorn,[10] Effie Petersdorf,[1] Michelle Setterholm,[5] Stephen Spellman,[5] Daniel Weisdorf,[11] Thomas M. Williams,[12] and Claudio Anasetti[13]

[1]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; [2]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee; [3]Center for International Blood and Marrow Transplant Research, Minneapolis, MN; [4]Department of Surgery, University of California, San Francisco; [5]National Marrow Donor Program, Minneapolis, MN; [6]M. D. Anderson Cancer Center, Houston, TX; [7]Thomas Jefferson University Hospital, Philadelphia, PA; [8]Department of Oncology, Georgetown University Medical Center, Washington, DC; [9]Immunology/Histocompatibility Laboratory, University of Minnesota Medical Center, Fairview; [10]Europdonor Foundation, Leiden, the Netherlands; [11]Blood and Marrow Transplantation (BMT) Program, University of Minnesota, Minneapolis; [12]Department of Pathology, University of New Mexico, Albuquerque; and [13]H. Lee Moffitt Cancer Center, Tampa, FL

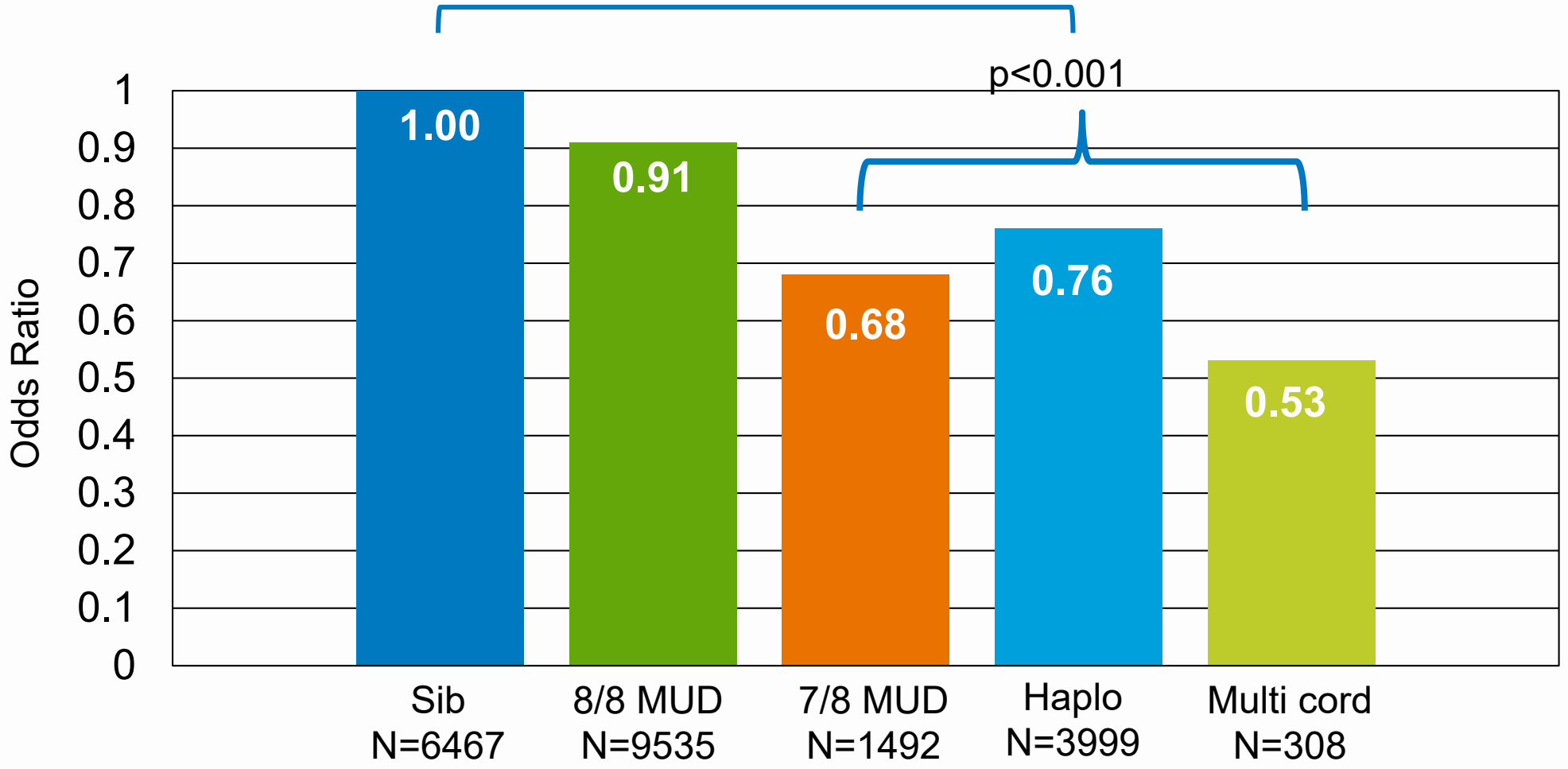


- Historically, mismatched URD transplants associated with worse survival
- Roughly 10% decrease in survival for each HLA mismatch

Lee et al, Blood 2007;110:4576

Real world data: outcomes using mismatched donor products are worse than using matched donors……..

Impact of donor type on one-year mortality (5-15%) after HCT done in 2016-2018



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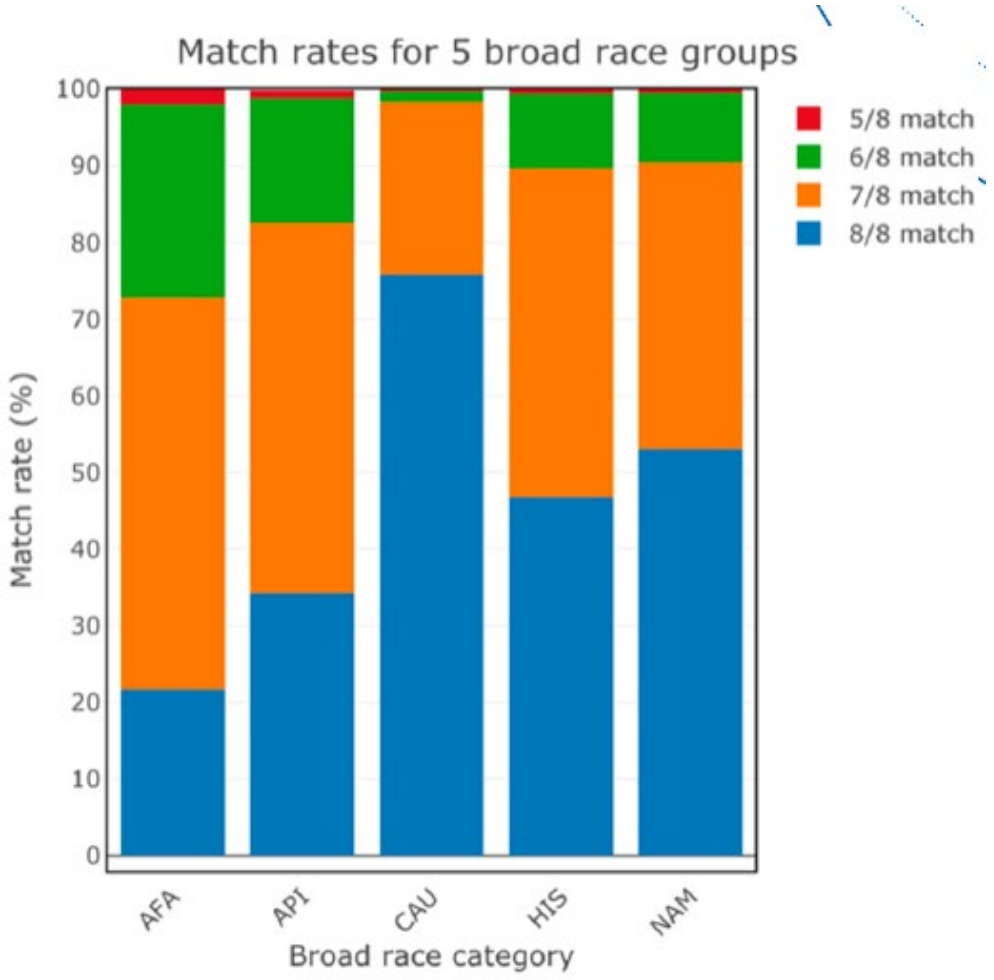
Mismatched grafts close the disparity gap

- Registry modeling from NMDP Bioinformatics
- Successful 7/8 transplants increase donor availability to **72% for AFA pts**
- Successful 6-7/8 transplants increase donor availability to **97% for AFA pts**



AFA = African American
API = Asian Pacific
CAU = Caucasian
HIS = Hispanic/Latino
NAM = Native American

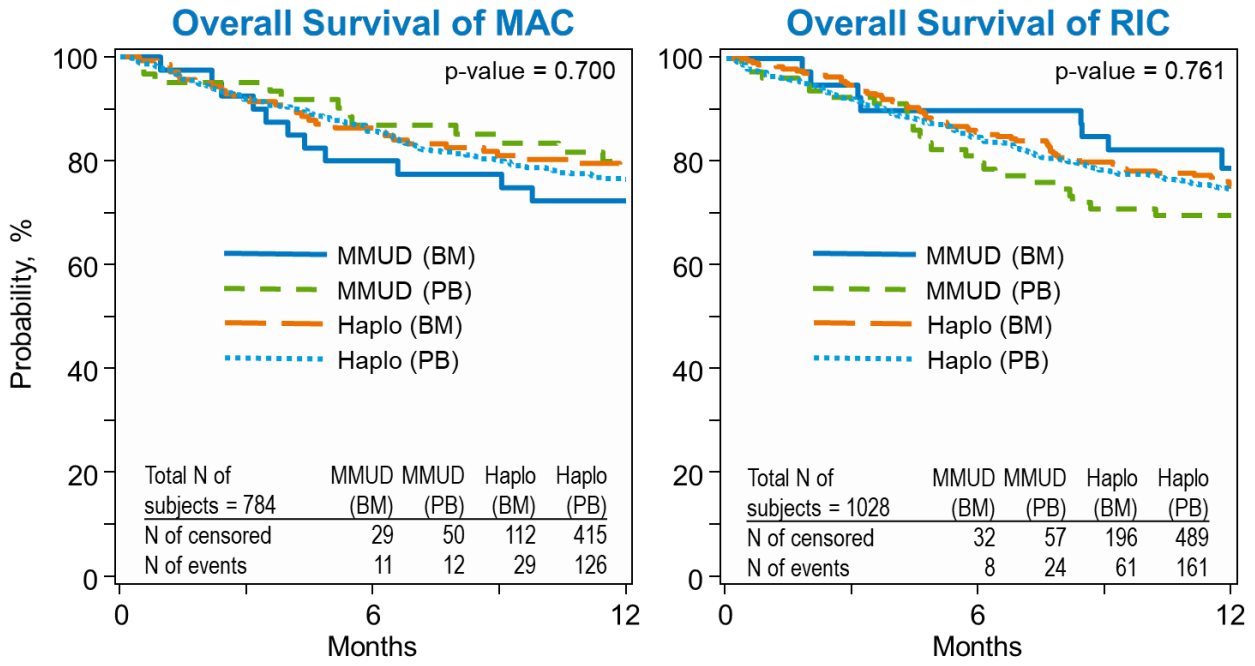
National Marrow Donor Program–Sponsored Multicenter, Phase II Trial of HLA-Mismatched Unrelated Donor Bone Marrow Transplantation Using Post-Transplant Cyclophosphamide

Bronwen E. Shaw, MD, PhD[1]; Antonio Martin Jimenez-Jimenez, MD, MS[2]; Linda J. Burns, MD[1]; Brent R. Logan, PhD[1]; Farhad Khimani, MD[3]; Brian C. Shaffer, MD[4]; Nirav N. Shah, MD[1]; Alisha Mussetter, BS[5]; Xiao-Ying Tang, MPH[1]; John M. McCarty, MD[6]; Asif Alavi, MD[7]; Nosha Farhadfar, MD[8]; Katarzyna Jamieson, MD[8]; Nancy M. Hardy, MD[10]; Hannah Choe, MD[10]; Richard F. Ambinder, MD, PhD[11]; Claudio Anasetti, MD[3]; Miguel-Angel Perales, MD[4]; Stephen R. Spellman, MBS[5]; Alan Howard, PhD[5]; Krishna V. Komanduri, MD[2]; Leo Luznik, MD[11]; Maxim Norkin, MD, PhD[12]; Joseph A. Pidala, MD, PhD[3]; Voravit Ratanatharathorn, MD[13]; Dennis L. Confer, MD[5]; Steven M. Devine, MD[5]; Mary M. Horowitz, MD, MS[1]; and Javier Bolaños-Meade, MD[11]

- Ph II MMUD = Mismatched unrelated donor
- RIC and MAC conditioning (non-randomized, TC choice)
- GvHD prophylaxis: PTCy (D3&4), Sirolimus, MMF
- BM graft
- **48% (38) enrolled patients were racial or ethnic minorities**
- **1 y OS 76%**
- **OS did not differ by HLA match or conditioning intensity**
- **19 deaths (7 primary disease, 4 MOF)**

Race, No. (%)			
American Indian or Alaska Native	1 (3)	0	1 (1)
Asian	1 (3)	1 (3)	2 (3)
Black or African American	9 (23)	6 (15)	15 (19)
White	29 (73)	31 (78)	60 (75)
Not reported or unknown	0	2 (5)	2 (3)

J Clin Oncol 2021;39(18):1971



- Real-life comparator dataset (CIBMTR)
- All consented first allo HCT in the U.S. (2016-2019)
- Met all main eligibility criteria for MMUD phase II trial
- Received PTCy as GVHD prophylaxis
- Total numbers:
  - MMUD receiving PBSC grafts (n=143)
  - Haplo receiving BM grafts (n=398)
  - Haplo receiving PBSC grafts (n=1191)
- Cox modeling of outcomes to compare against other benchmark mismatched related or unrelated groups receiving PTCy from CIBMTR

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ACCESS: A Multi-Center, Phase II Trial of HLA-Mismatched Unrelated Donor Hematopoietic Cell Transplantation with Post-Transplantation Cyclophosphamide for Patients with Hematologic Malignancies

Resource for Clinical Investigation in Blood and Marrow Transplantation (RCI BMT)

Version 1.0
January 28, 2021

NMDP Protocol Chair
Steven Devine, MD[1]

CIBMTR Protocol Officers
Bronwen Shaw[2] (adult)
Larisa Broglie[2] (pediatric)

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

Primary Objective

To determine overall survival (OS) at one year following transplantation of a PBSC product from a MMUD using PTCy-based GVHD prophylaxis.

Hypothesis

Transplantation of a PBSC or BM product from a HLA-mismatched unrelated donor (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.

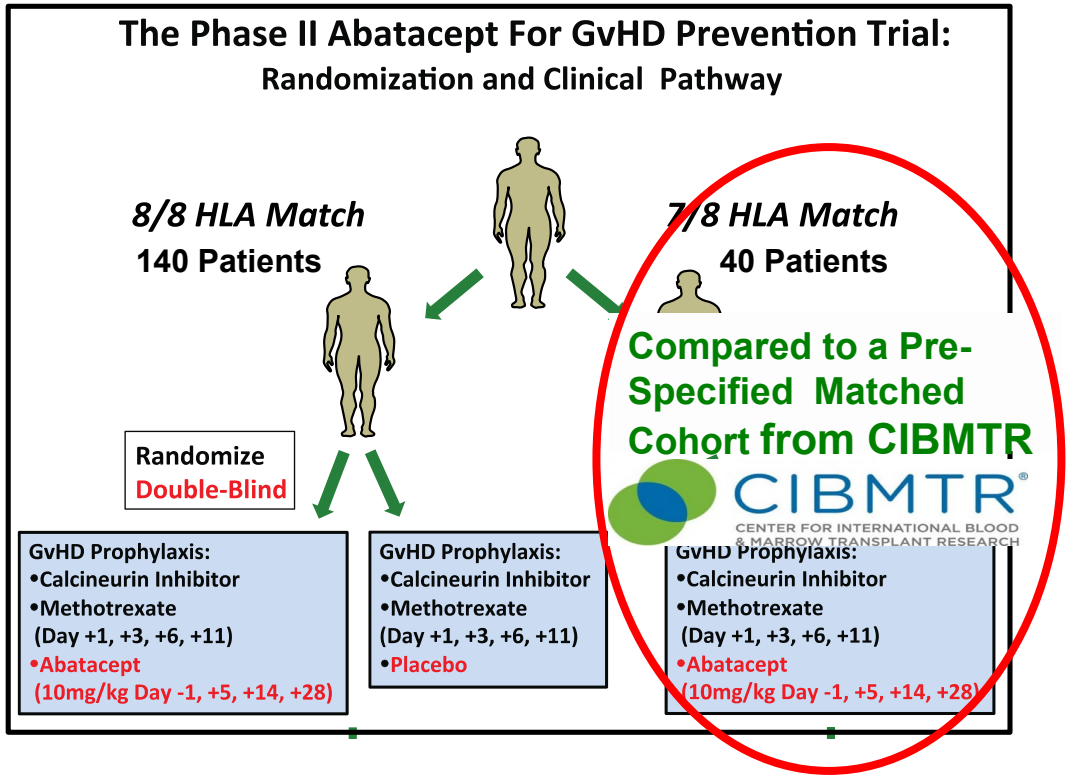
Study Population	Patients with eligible diagnosis receiving a MMUD PBSC or BM (pediatric strata only) product at participating transplant centers
Study Design/Phase	This is a multi-center Phase II study with three strata (two adult strata based on conditioning intensity and one pediatric) designed to estimate the one year OS following MMUD PBSC or BM (pediatric stratum only) transplantation.

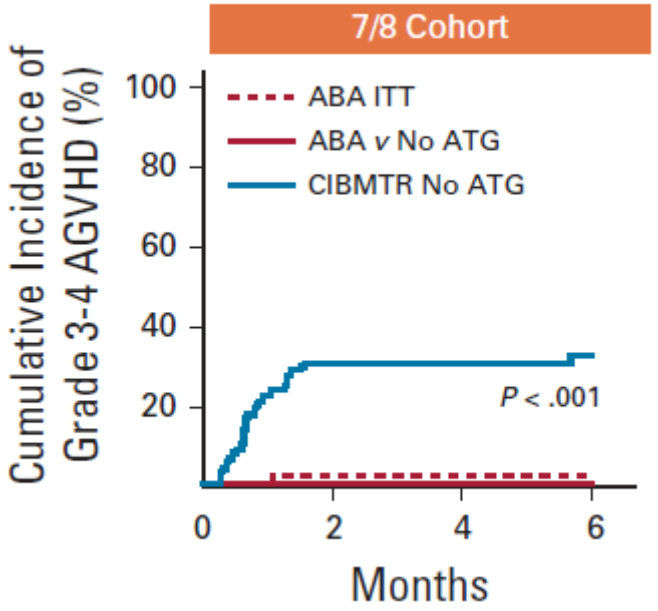
Primary Endpoint: 1 y OS following HCT in each adult strata

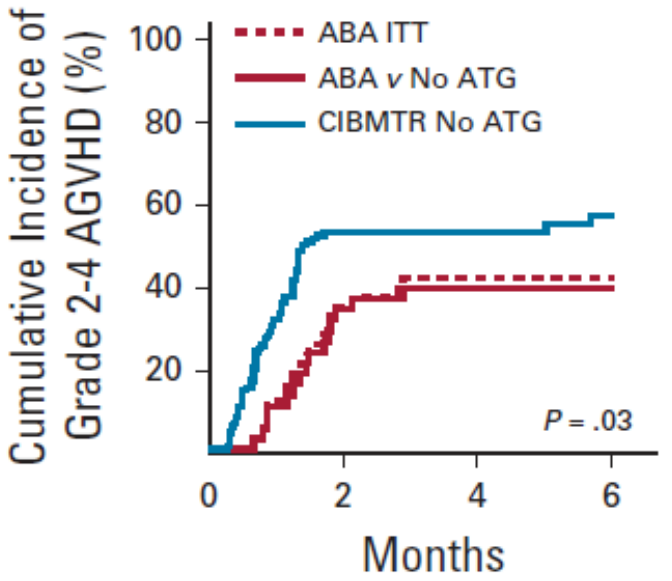
original reports

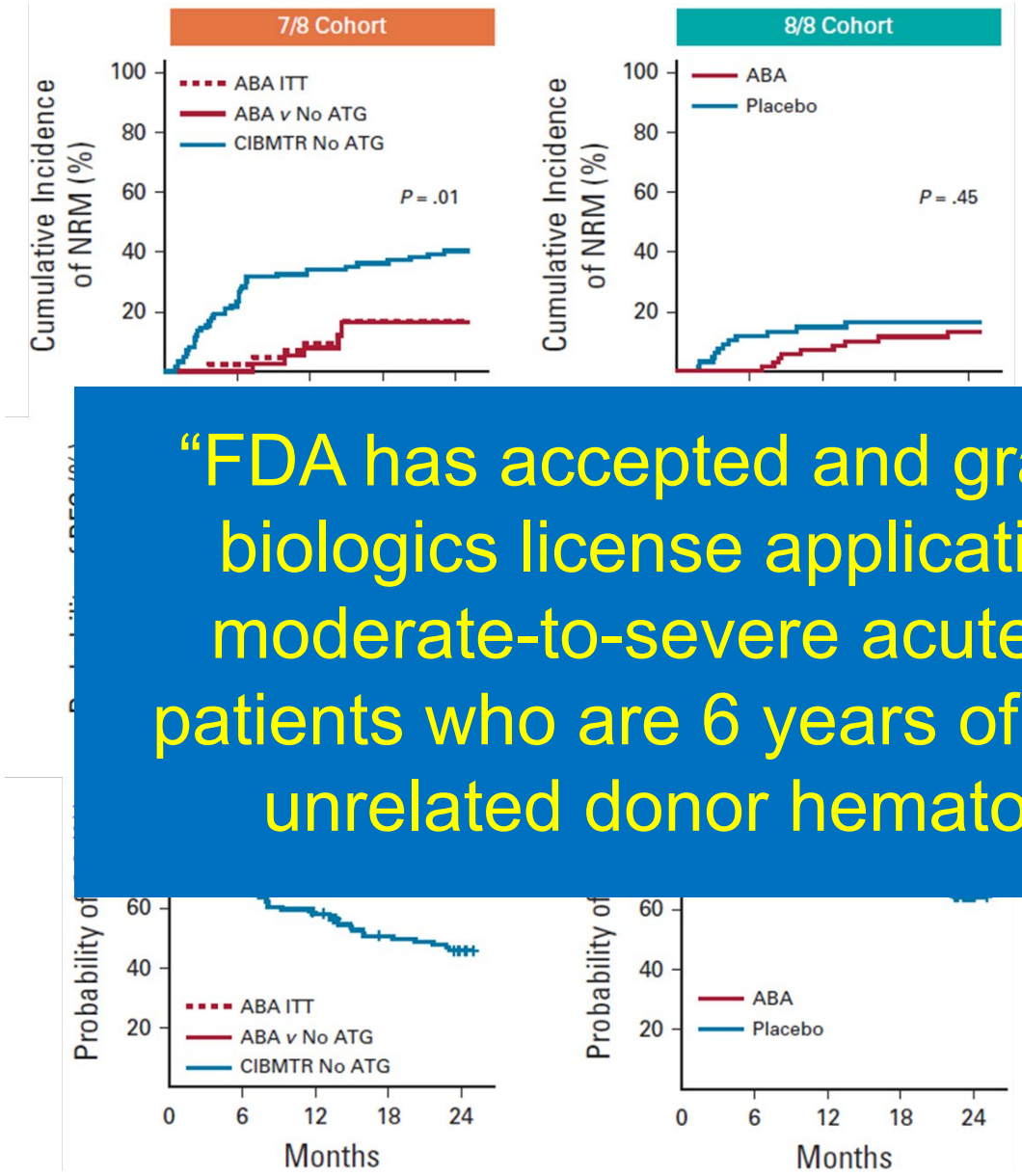
Phase II Trial of Costimulation Blockade With Abatacept for Prevention of Acute GVHD

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]

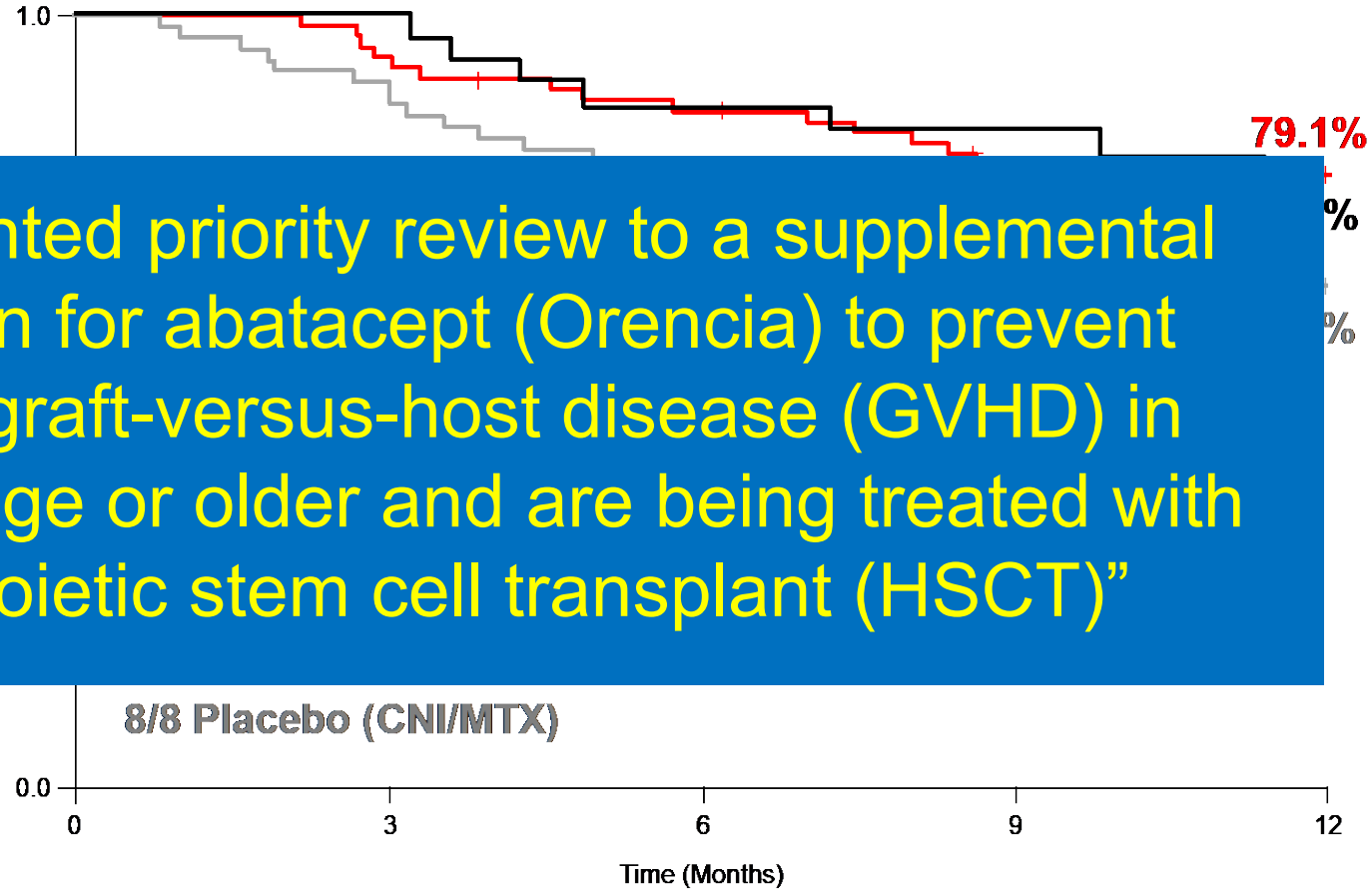








Relapse-Free Survival



"FDA has accepted and granted priority review to a supplemental biologics license application for abatacept (Orencia) to prevent moderate-to-severe acute graft-versus-host disease (GVHD) in patients who are 6 years of age or older and are being treated with unrelated donor hematopoietic stem cell transplant (HSCT)"

Strategies to prevent acute GVHD

Pharmacological treatment of recipient

- Conventional immunosuppression
- Novel agents
- In vivo T-cell depletion (ATG, Campath, Post Transplant Cy)

Graft manipulation

- Ex vivo
  - T-cell depletion (CD34 selection, αβ TCD, selective TCD, graft engineering, immunomodulation)

RCI BMT Supported Graft Engineering Studies

16-NTCD (NCT03779854)

- PTCTC Developed (Marie Bleakley: PI); FHCRC sponsored
- Funding: St Baldrick's, Jeff Gordon FDN, Miltenyi

OrcaGraft (NCT03802695)

- Graft engineering to improve post transplant outcomes
- Phase I study sponsored by Orca and coordinated by RCI BMT

Treg graft (NCT04013685)

- Defined doses of Tregs and Tcons to mitigate GVHD without reducing GVL (Phase 1b study)
- Sponsored by Orca and coordinated by RCI BMT

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Summary

- Encouraging data are being generated that suggest access to transplantation may be greatly enhanced by innovative pharmacological and physical approaches to mitigate GVHD
- We may be on the cusp of first FDA approval for GVHD prophylaxis (abatacept)
- Graft manipulation in particular seems to be gaining traction
- Improvements in access will increase opportunities for patients with serious non-malignant disorders and will allow us to focus more attention on preventing relapse in patients with cancer
- NMDP/Be The Match and CIBMTR view research as critical to making progress in HCT and provides scientific input, infrastructure and $$$ to support its successful conduct

Unresolved question for the HCT community

As we make HCT more accessible to an increasingly diverse set of patients (older, racially/ethnically), will we encounter unique toxicities and disabilities (physical/mental/social/financial) that we have not previously observed or considered?