UCSF Helen Diller Family Comprehensive Cancer Center

Cellular therapy for myeloma and Hematologic Malignancies: Disparities in access and outcomes to cellular therapies

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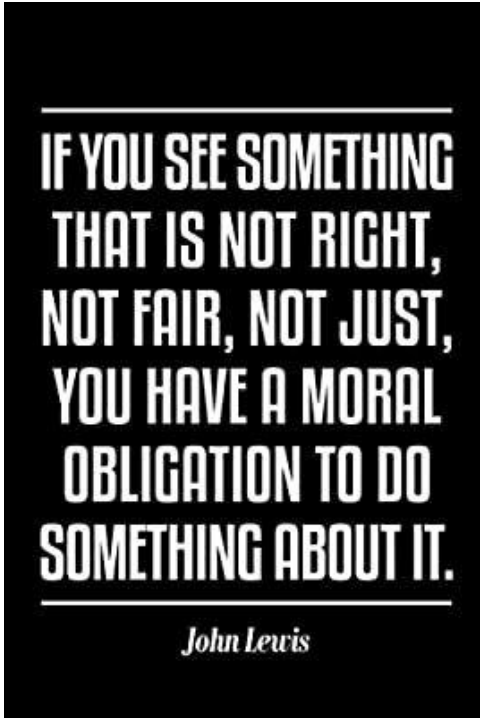
Disclosures

- *Ad hoc* Consulting: Iovance, Incyte, Syncopation Life Sciences, CRISPR therapeutics, Genentech/Roche
- Scientific Advisory Board: Aegle Therapeutics, Avacta Therapeutics


IF YOU SEE SOMETHING THAT IS NOT RIGHT, NOT FAIR, NOT JUST, YOU HAVE A MORAL OBLIGATION TO DO SOMETHING ABOUT IT.
John Lewis

Stem cell transplants: disparities in access to curative therapies

Evolution of allogeneic stem cell transplantation

- Since the 1980s, alloSCT has evolved from ablation to immunotherapy
- The use of *less intensive* conditioning expanded eligibility from <55 to 75 (or older)
- Peripheral blood HCT and improved supportive care have substantially decreased non-relapse mortality (from ~30-40% to 5-10% in the first 100 days after alloHCT)
- Typical results for AML: 5-10% 100-day and 30% one-year mortality (~50:50 NRM:relapse)

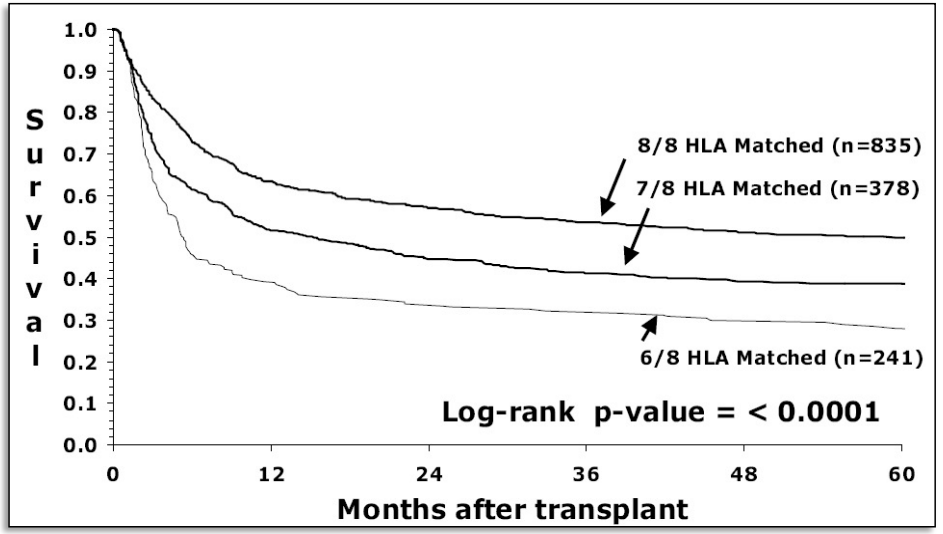
The HLA Barrier: Need for an HLA-matched donor

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**

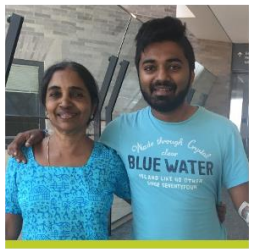


Lee et al, Blood 2007;110:4576

However, a MUD is still not available for every patient.

29%

Black or African American



47%

Asian or Pacific Islander

48%

Hispanic or Latino

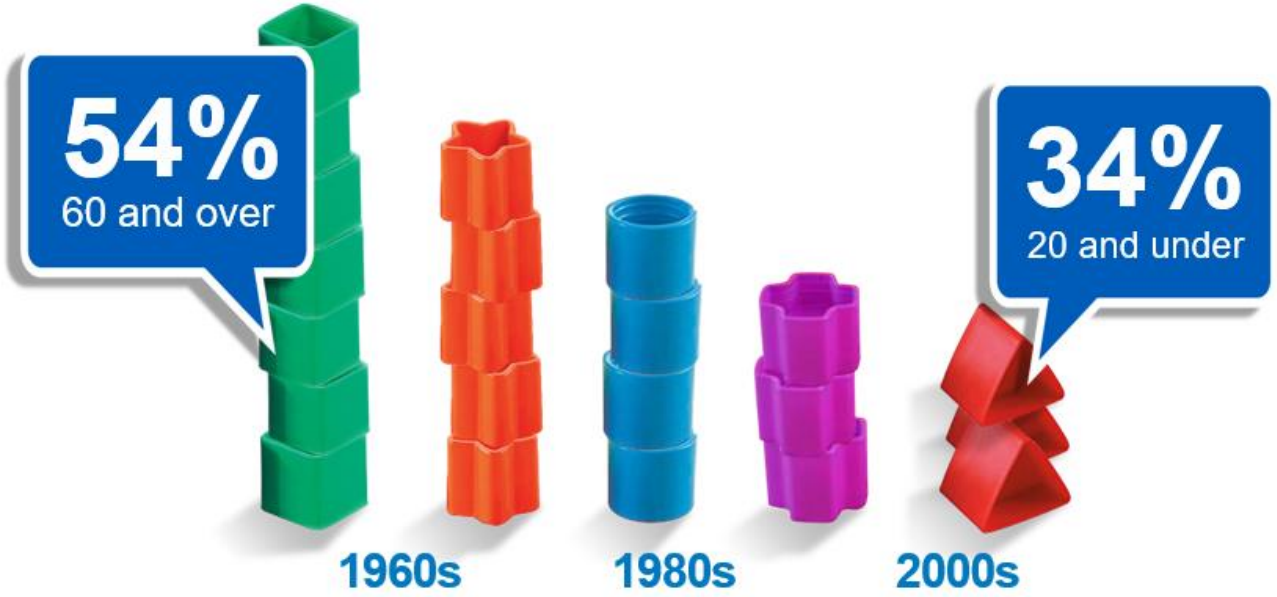
60%

American Indian and Alaska Native

79%

White

And, it's getting MORE DIFFICULT to match over time



BE THE MATCH

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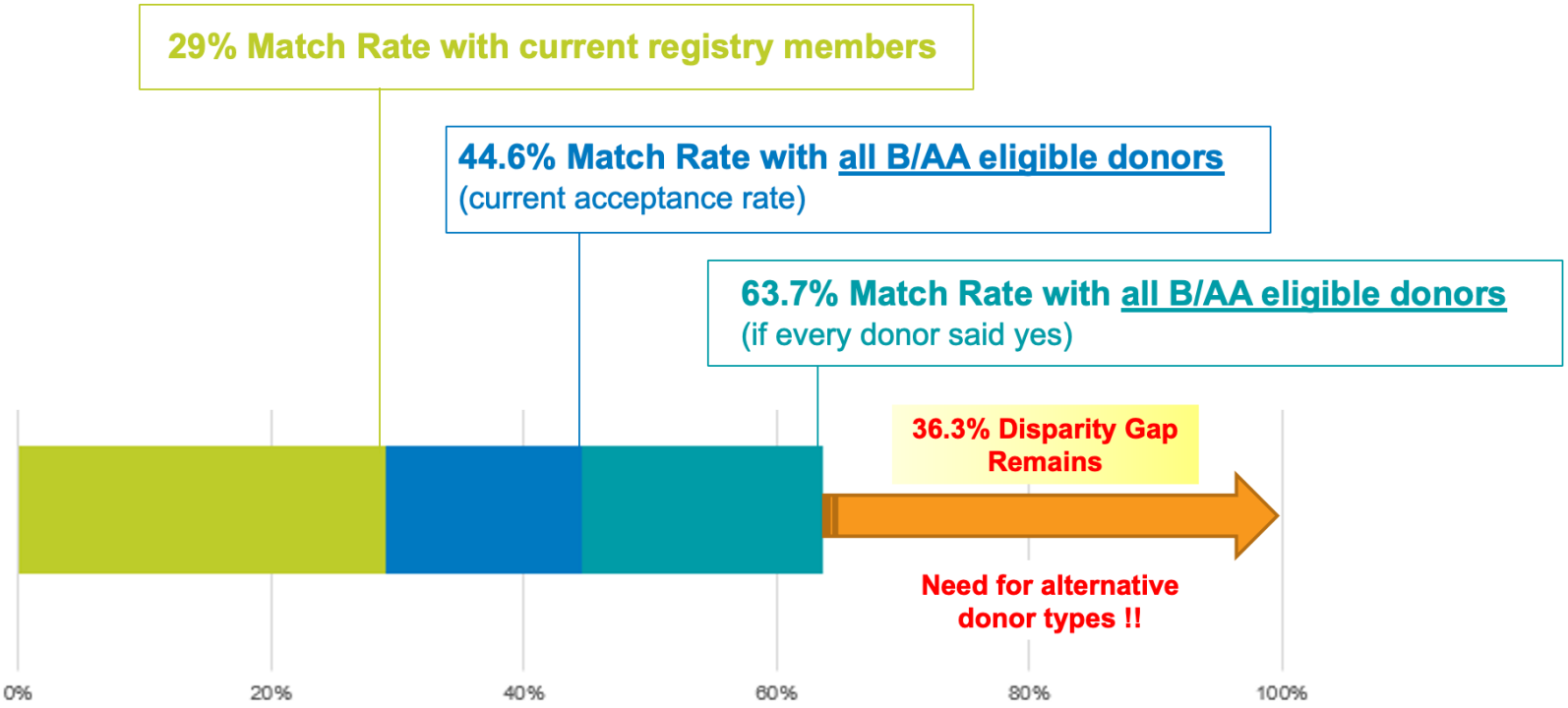
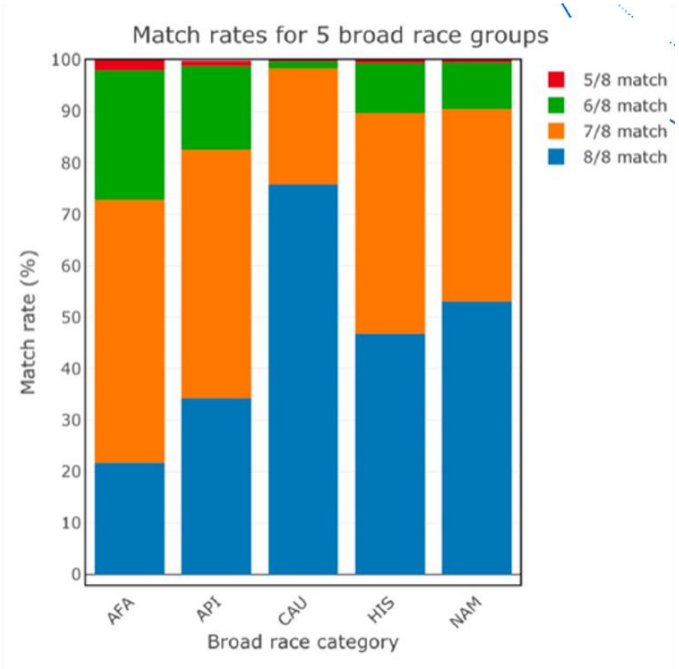
What if every eligible B/AA donor joined the registry?



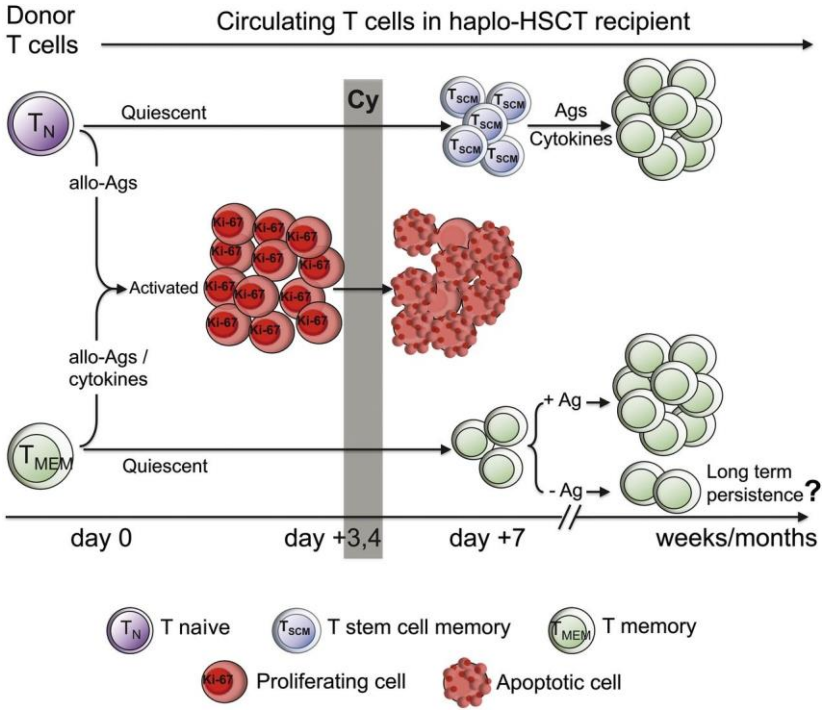
Mismatched grafts close the disparity gap

- Registry modeling from BTM 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

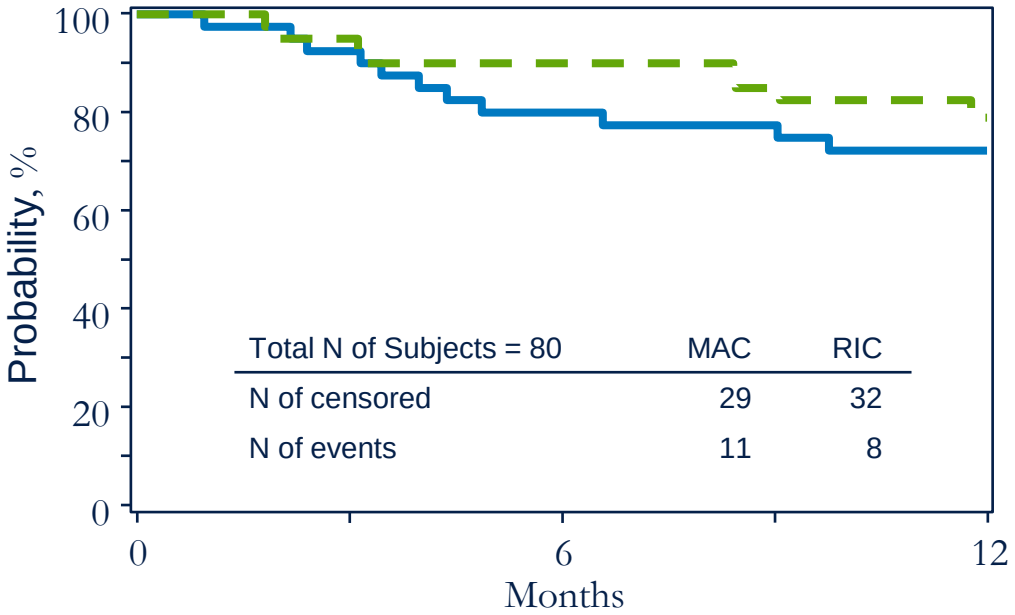


Post-transplant cyclophosphamide (PTCy) enhances GvHD prevention in the haploidentical setting



Blood 2015;125:2855

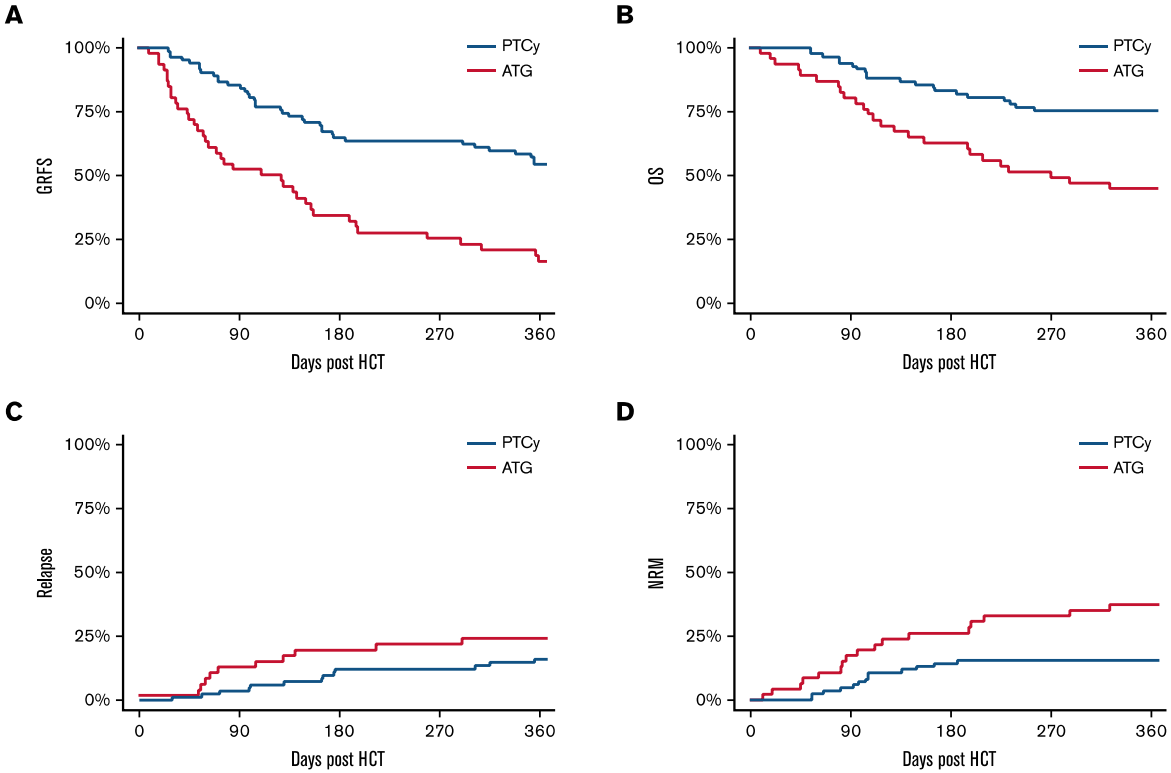
15-MMUD Study
Primary Endpoint: Overall Survival
72% MAC and 79% RIC



original reports

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[5]; Alisha Mussetter, BS[6]; Xiao-Ying Tang, MPH[1]; John M. McCarty, MD[7]; Asif Alavi, MD[8]; Nosha Farhadfar, MD[9]; Katarzyna Jamieson, MD[10]; Nancy M. Hardy, MD[11]; Hannah Choe, MD[12]; Richard F. Ambinder, MD, PhD[13]; Claudio Anasetti, MD[3]; Miguel-Angel Perales, MD[4]; Stephen R. Spellman, MBS[6]; Alan Howard, PhD[6]; Krishna V. Komanduri, MD[2]; Leo Luznik, MD[13]; Maxim Norkin, MD, PhD[14]; Joseph A. Pidala, MD, PhD[3]; Voravit Ratanatharathorn, MD[8]; Dennis L. Confer, MD[6]; Steven M. Devine, MD[6]; Mary M. Horowitz, MD, MS[1]; and Javier Bolaños-Meade, MD[13]



Improved GRFS after posttransplant cyclophosphamide-based vs ATG-based HLA-mismatched unrelated donor transplant

blood advances
9 AUGUST 2022 • VOLUME 6, NUMBER 15

Antonio Jimenez Jimenez,[1] Krishna Komanduri,[1] Samantha Brown,[2] Trent Wang,[1] Denise Pereira,[1] Mark Goodman,[1] Amer Beitinjaneh,[1] Lazaros Lekakis,[1] Stephanie Chinapen,[3] Sean Devlin,[2] Doris Ponce,[3,4] Craig Sauter,[3,4] Miguel-Angel Perales,[3,4] and Brian C. Shaffer[3,4]

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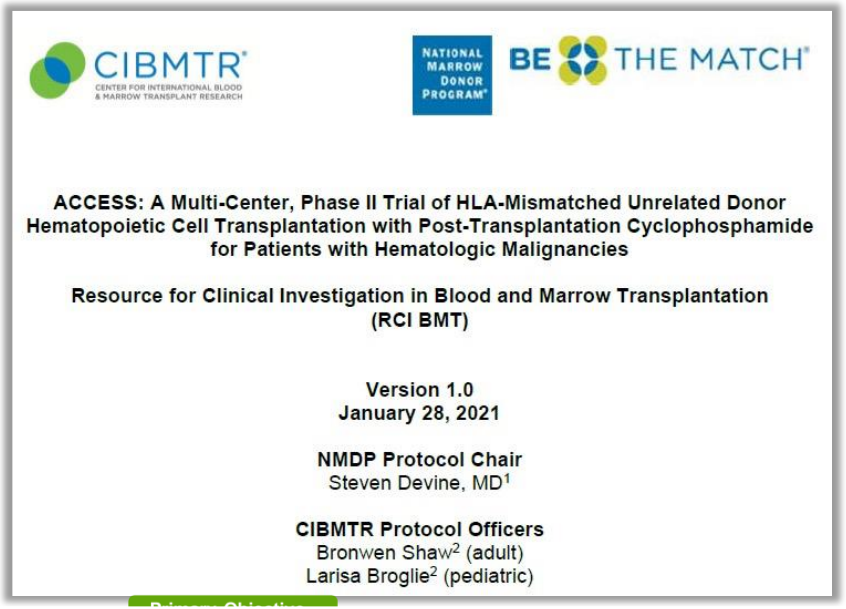

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NATIONAL MARROW DONOR PROGRAM

BE THE MATCH

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)

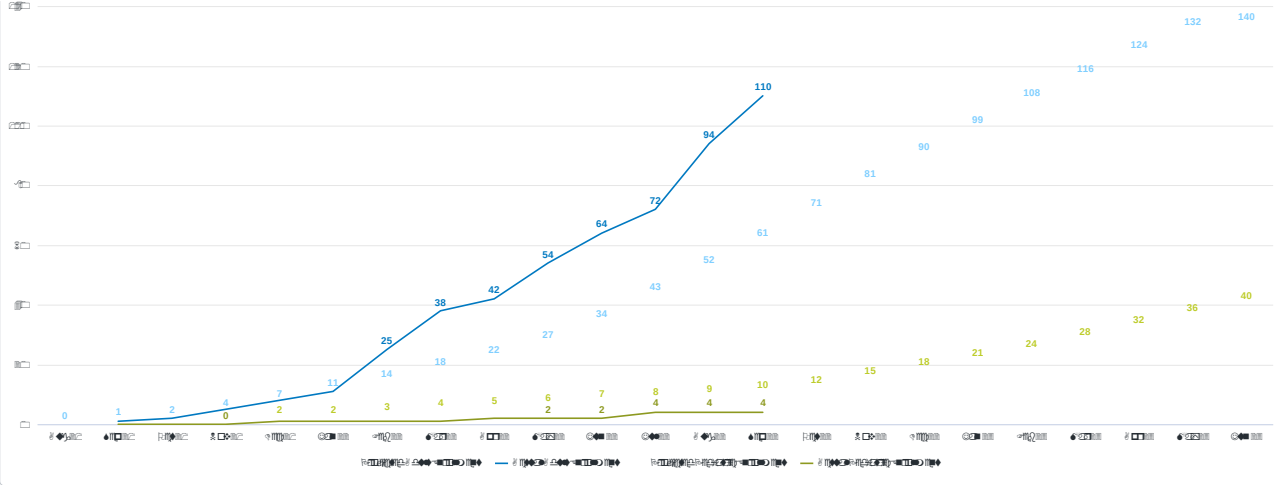
Stratum 1
- Adult subjects undergoing HCT with a PBSC graft source and receiving a myeloablative conditioning (MAC) regimen and PTCy-based GVHD prophylaxis

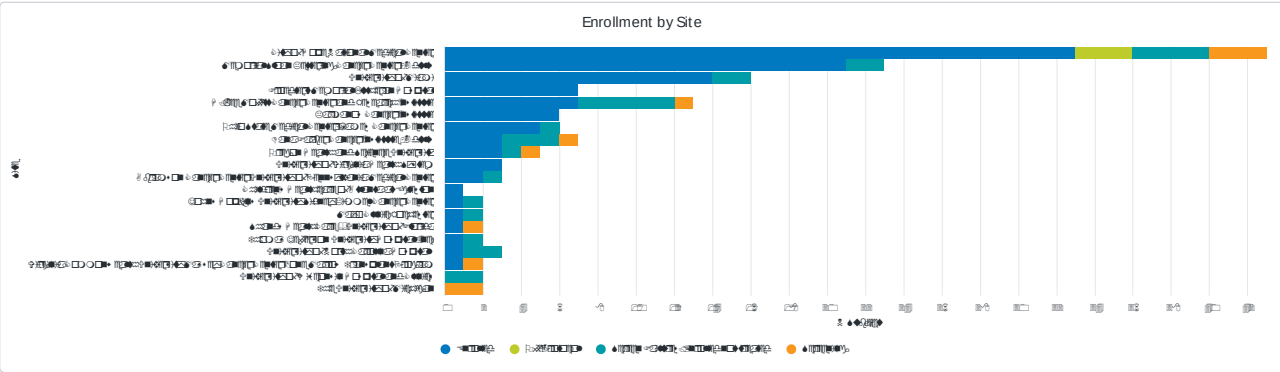
Stratum 2
- Adult subjects undergoing HCT with a PBSC graft source and receiving a non-myeloablative (NMA) or reduced-intensity conditioning (RIC) regimen and PTCy-based GVHD prophylaxis

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 endpoint is 1 year OS in each adult cohort

ACCESS trial: rapid accrual





Access Barriers to HCT: Race and Poverty

ELSEVIER

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

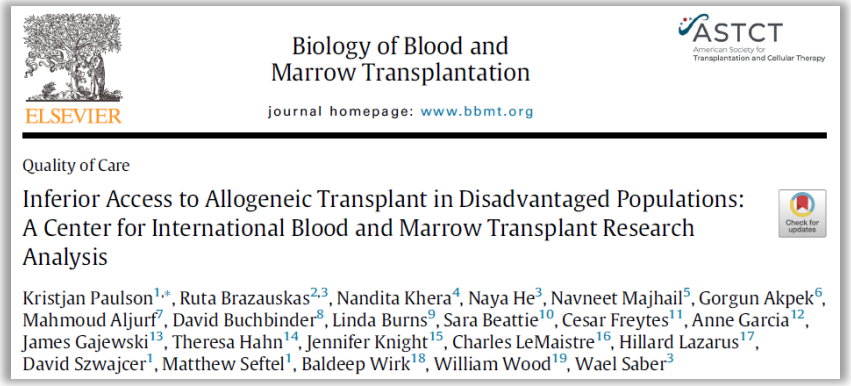
ASTCT American Society for Transplantation and Cellular Therapy

Analysis

Likelihood of Proceeding to Allogeneic Hematopoietic Cell Transplantation in the United States after Search Activation in the National Registry: Impact of Patient Age, Disease, and Search Prognosis

Jason Dehn[1,*], Pintip Chitphakdithai[2], Bronwen E. Shaw[3], Abby A. McDonald[1], Steven M. Devine[1,2], Linda J. Burns[1,2], Stephen Spellman[2]

- To identify likelihood of patient progression from initiation of an active search for an URD/UCB to HCT and to evaluate factors associated with proceeding to HCT within 6 months
- Retrospective cohort of US donor searches of the NMDP/Be The Match Registry from Jan-December 2016
  - TC's request of donor/cord blood unit testing; N=8816
- Adult UD search prognosis score (HLA type, race/ethnicity)
  - Good, fair, poor
- At 6 months: 3744 (42%) pt received HCT (Median for URD: 86d)
- **White patients were more likely to receive HCT (45%, n=2590/5687) vs. B/AA patients (27%, n=187/700; p<0.001)**



ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASTCT American Society for Transplantation and Cellular Therapy

Quality of Care

Inferior Access to Allogeneic Transplant in Disadvantaged Populations: A Center for International Blood and Marrow Transplant Research Analysis

Kristjan Paulson[1,*], Ruta Brazauskas[2,3], Nandita Khera[4], Naya He[3], Navneet Majhail[5], Gorgun Akpek[6], Mahmoud Aljurf[7], David Buchbinder[8], Linda Burns[9], Sara Beattie[10], Cesar Freytes[11], Anne Garcia[12], James Gajewski[13], Theresa Hahn[14], Jennifer Knight[15], Charles LeMaistre[16], Hillard Lazarus[17], David Szwajcer[1], Matthew Seftel[1], Baldeep Wirk[18], William Wood[19], Wael Saber[3]

- Data from the Surveillance, Epidemiology and End Results Program (SEER) and the Center for International Blood and Marrow Transplant Research (CIBMTR) were integrated to determine the rate of unrelated donor (URD) alloHCT for AML, ALL and MDS performed between 2000 and 2010 in the 612 counties covered by SEER
- **Patients from areas with higher poverty rates diagnosed with ALL, AML, and MDS are less likely than patients from wealthier counties to undergo URD alloHCT**

Biol Blood Marrow Transplant 2019;25:2086
Transplant Cell Ther 2021;27:184.e1

Autologous HCT rates are different based on race/ethnicity

Estimated autologous stem cell transplant utilization rates (STUR) for myeloma using CIBMTR data 2008-2014 (N=28,450) and incidence rates from SEER

Year	All patients	Non-Hispanic Whites	Hispanics	Blacks
2008	**19.1%**	**22.6%**	**12.2%**	**8.6%**
2014	**30.8%**	**37.8%**	**20.5%**	**16.9%**

Schriber JS et al. Cancer, 2017

ACCESS Initiative: Purpose and Vision

- **PURPOSE:**
  - To reduce barriers to hematopoietic cell therapy and transplantation through implementation of changes in practice and policy by active, sustained engagement of the cell therapy ecosystem

- **VISION:**
  - To advance, measure and sustain progress toward universal access in the initial focus areas of **awareness, poverty** and **racial inequality**

ASTCT Working Group Chair

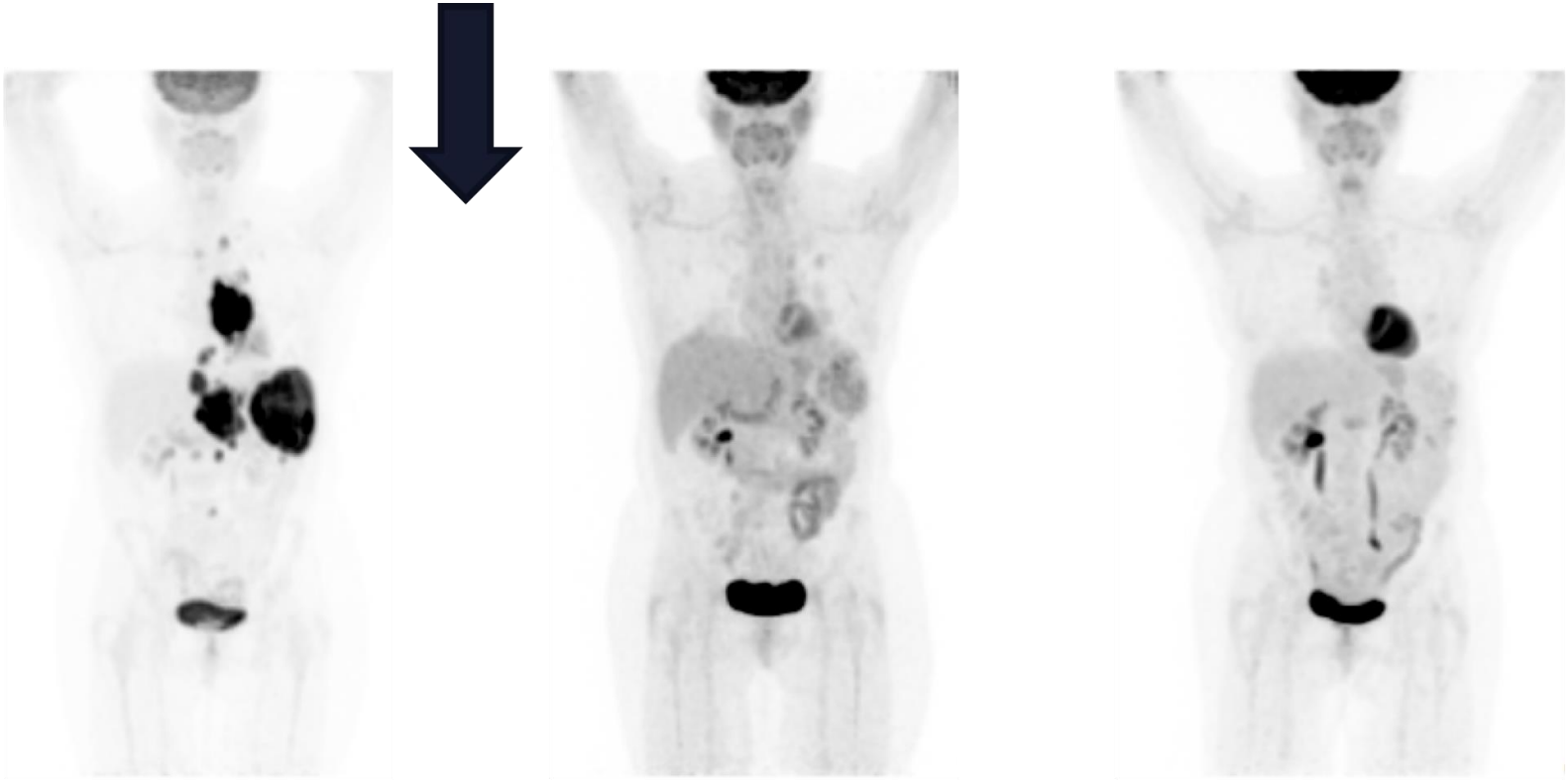
Stella Davies

NMDP Working Group Chair

Jeff Auletta

CAR-T therapies: present and future

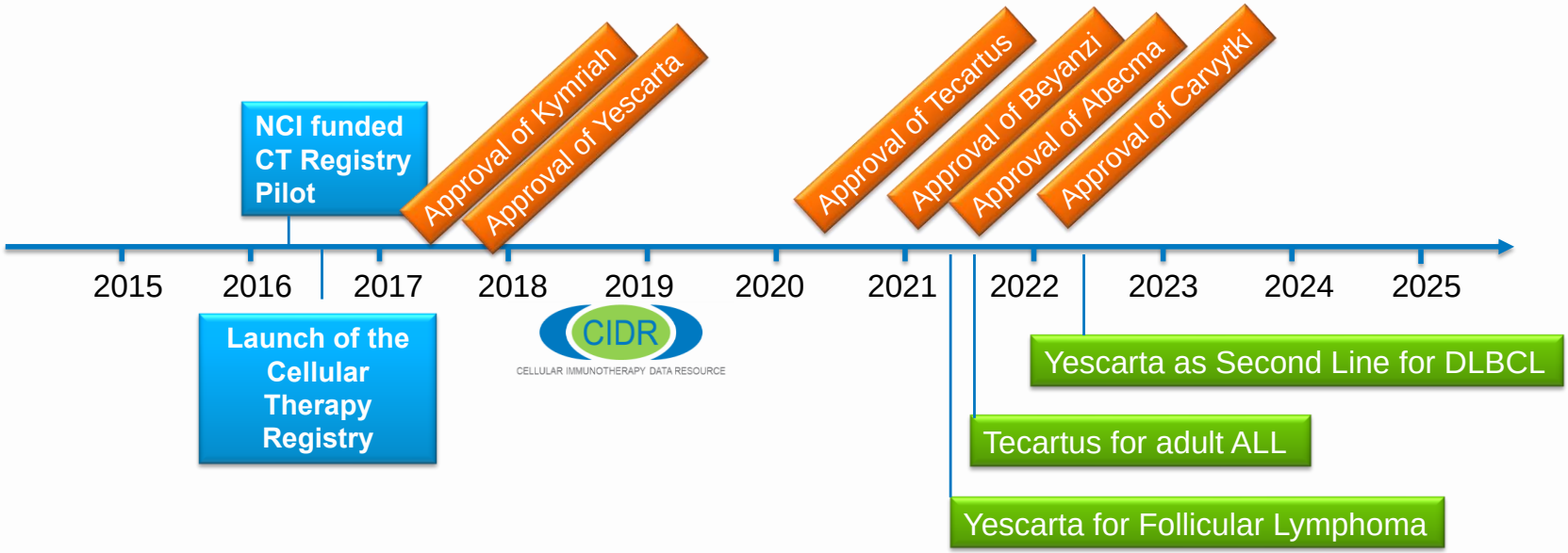
CAR-T therapy after six prior lines of therapy



December 2015 February 2016 April 2016

Lazaros Lekakis, MD

The Development of the Registry Parallel to the Expansion of the Field of Cellular Immunotherapy



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CIDR CELLULAR IMMUNOTHERAPY DATA RESOURCE

Cellular Immunotherapy Registry at a Glance

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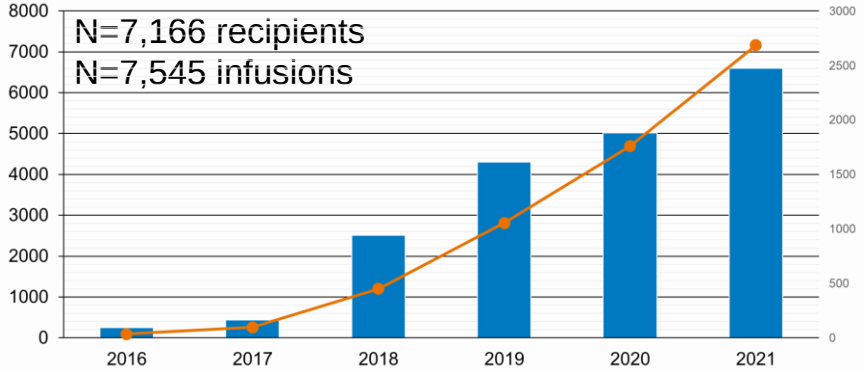

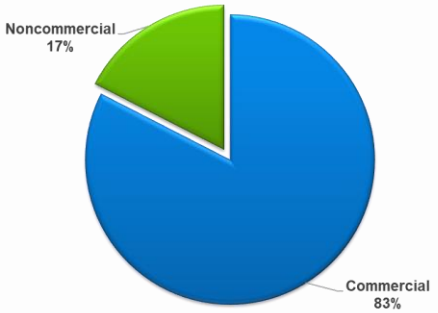

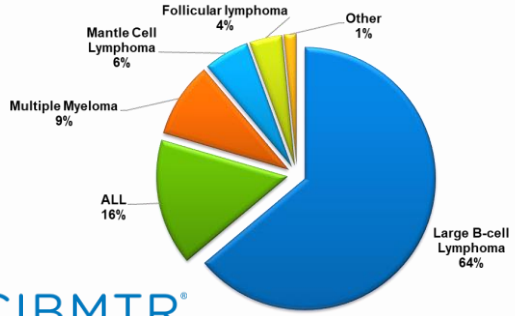

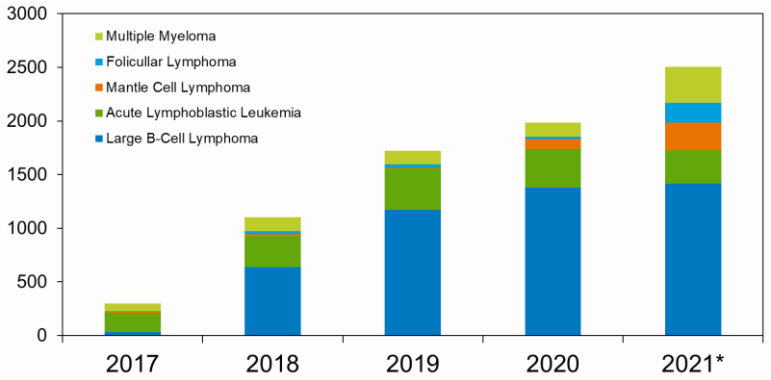

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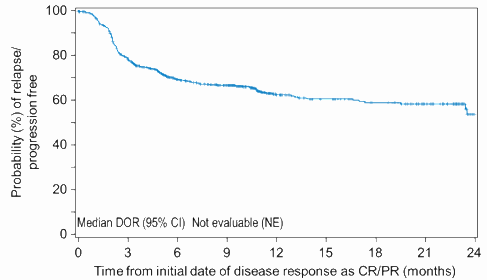
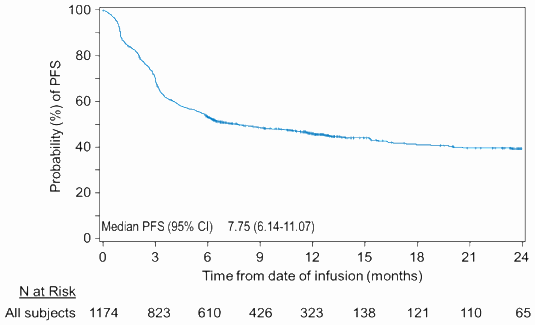
Comparable data between the CIBMTR and the pivotal trials: Axi-cel

Axi-cel PASS - CIBMTR

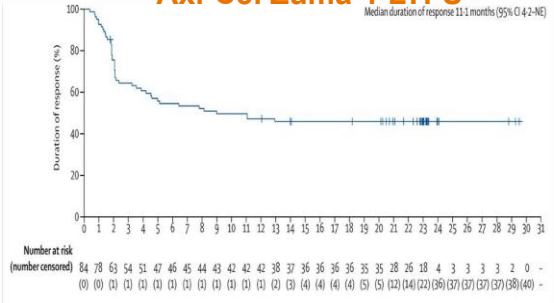


Patients who did not achieve CR/PR as best response during the follow-up period were excluded.

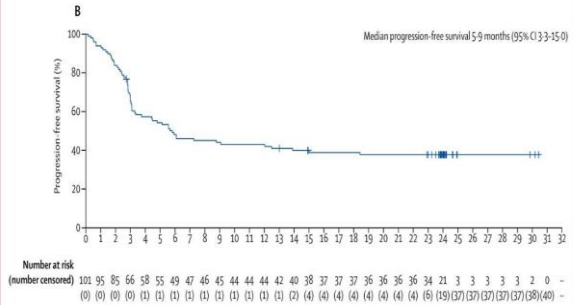


Axi-Cel Zuma-1 LTFU

Duration of response



Progression-free Survival



Jacobson C. et al ASCO 2021, Locke F et al Lancet Oncology 2019

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CD19 CAR T-cells in DLBCL: Earlier Lines

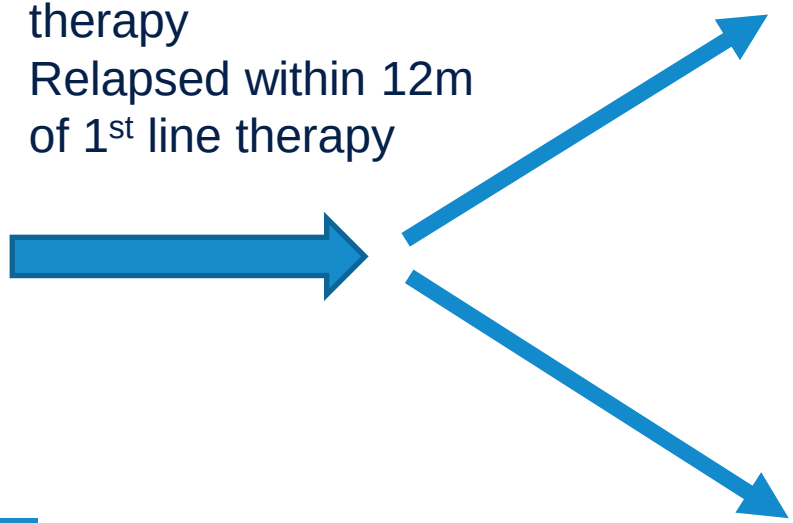
ZUMA-7
Axi-cel

BELINDA
Tisa-cel

TRANSFORM
Liso-cel

High Risk DLBCL:

- Refractory to 1st line therapy
- Relapsed within 12m of 1st line therapy



CAR T

Salvage /Auto

Is CAR-T therapy the 2nd line DLBCL standard?

- Two of three RCTs favored CAR-T therapy in the second line setting (ZUMA-7 and TRANSFORM)
- RCTs demonstrated traditional salvage therapies are suboptimally effective (<40% achieved PR and had AutoSCT)
- Retrospective analyses suggest individuals who achieved a PR can do quite well with AutoSCT
- Additional data (including from registries) needed but for patients with early relapse (< 1 year) 2nd line CAR-T is the new SOC
- Additional RCTs would be helpful (but very unlikely)

What about fourth line? First line?

- We need better therapies following CAR-T failure
- Long-term results of all three commercial products suggest only 30-40% cure rates
- CAR-T trials (including CD19/22) demonstrate ≤30% ORR
- Secondary (after first CAR-T failure) cellular therapies are needed
- First-line studies promising (ZUMA-12, Neelapu, et al.) but demonstrate responses similar to R-CHOP in highly selected patients

Do we have access barriers to CAR-T therapies?

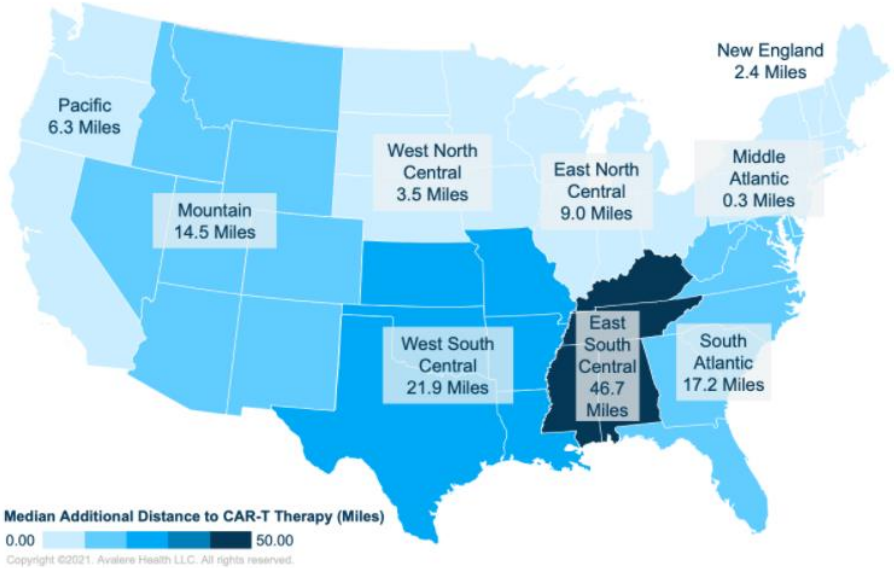
Is CAR-T therapy reaching everyone?

- Short answer is NO!
- ~30,000 DLBCL patients diagnosed annually
- 10K relapsed/refractory
- On the basis of available market/registry data probably no more than 30% of this eligible population has received an approved product

Access Barriers to CAR-T cells

- **Method:**
  - Medicare fee-for-service DLBCL claims analysis from 2017-2019
  - 64 accredited U.S. CAR T centers
  - Distance traveled from home zip code to center
- **Results:**
  - Geographic disparities in access exist
  - Patients in South travel considerable farther
  - Also likely some patients in remote areas have significant underutilization

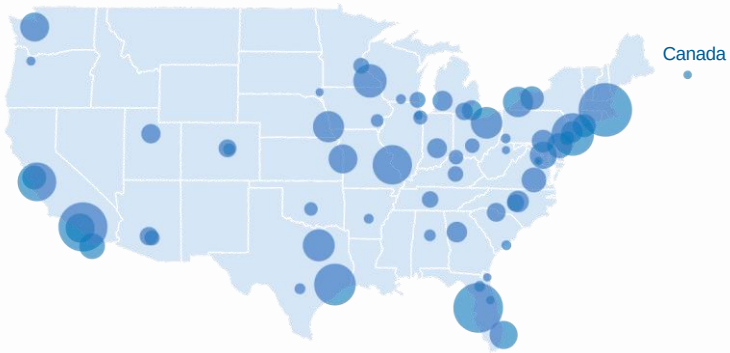
Figure 1. US Census Division Median Additional Distance to CAR-T Site of Care*



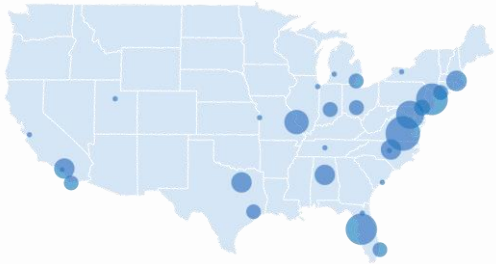
*Analysis specific for DLBCL indication.

Patient Geographic Distribution

Distribution of All Patients (N=1389)

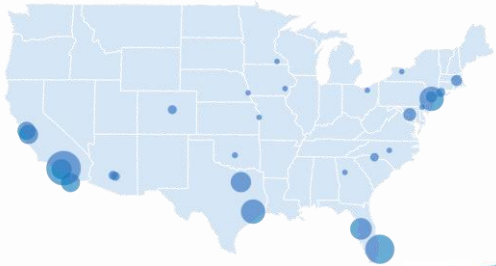


Distribution of African American Patients (n=70)



*12.7% of US Population in 2020 Census

Distribution of Hispanic or Latino Patients (n=152)



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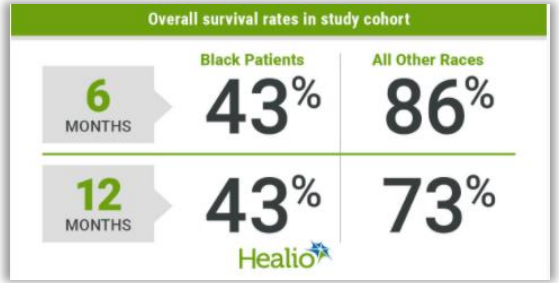
CIDR CELLULAR IMMUNOTHERAPY DATA RESOURCE

from Locke, Pasquini et al, *ASCO 2022*

Disparities in CAR T-cell Outcomes: Race



- Pediatric Real World CAR Consortium (15 U.S. Centers)
- Data on children and adolescents with R/R preB-ALL receiving Kymriah™
  - Outcomes of younger Black patients with ALL receiving Kymriah™
- 200 patients, 93 (46.5%) non-Hispanic white
  - Hispanic (37.5%), **Black (5.5%)**, Asian (4.5%), multiracial (2.5%), unknown (3.5%)
- Black vs other patients:
  - **More previous lines of therapy (median, 5 vs. 2, p<0.0001)**
  - **More relapses before CAR-T (median, 2 vs. 1, p=.0105)**
  - **Higher rate of prior stem cell transplantation (71% vs. 24%, p=0.0122)**
- 15 patients did not undergo infusion of Kymriah™
  - 36.4% of Black patients in the cohort (four of 11) compared with only 5.8% of patients (11 of 189) of other races and ethnicities (p=.005)
- Black vs. other patients:
  - **Lower CR (57% vs. 86%, p=0.007)**
  - **Lower OS at 6 months (43 vs. 86%, 0.026) and 1 year (43 vs. 73%, p=0.026)**
  - **MVA identified Black race as predictor of OS (HR=3.36, p=0.05)**

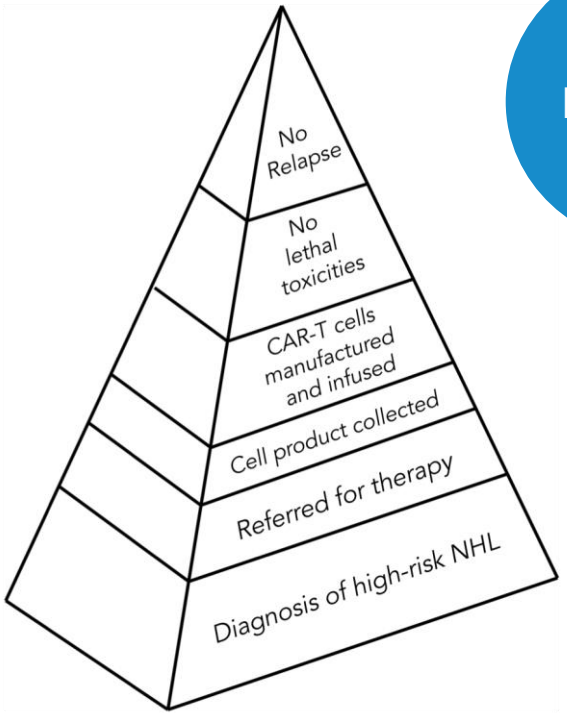
What do we know about CAR-T access and equity?

- All CAR-T therapies, in aggregate, are underutilized
- High cost, tertiary/quaternary therapies tend to maximize historical barriers to access (racial, socioeconomic, logistical)
- Early data suggest that African American patients are less likely to receive CAR-T therapy, and may have lower ORR, CR rates
- Unique access issues exist for pediatric patients, for whom fewer options exist
- High cost and complexity of access and care compound historic barriers

How can we improve access and equity in cellular therapy?

From diagnosis to cure

Better educate patients and referring physicians

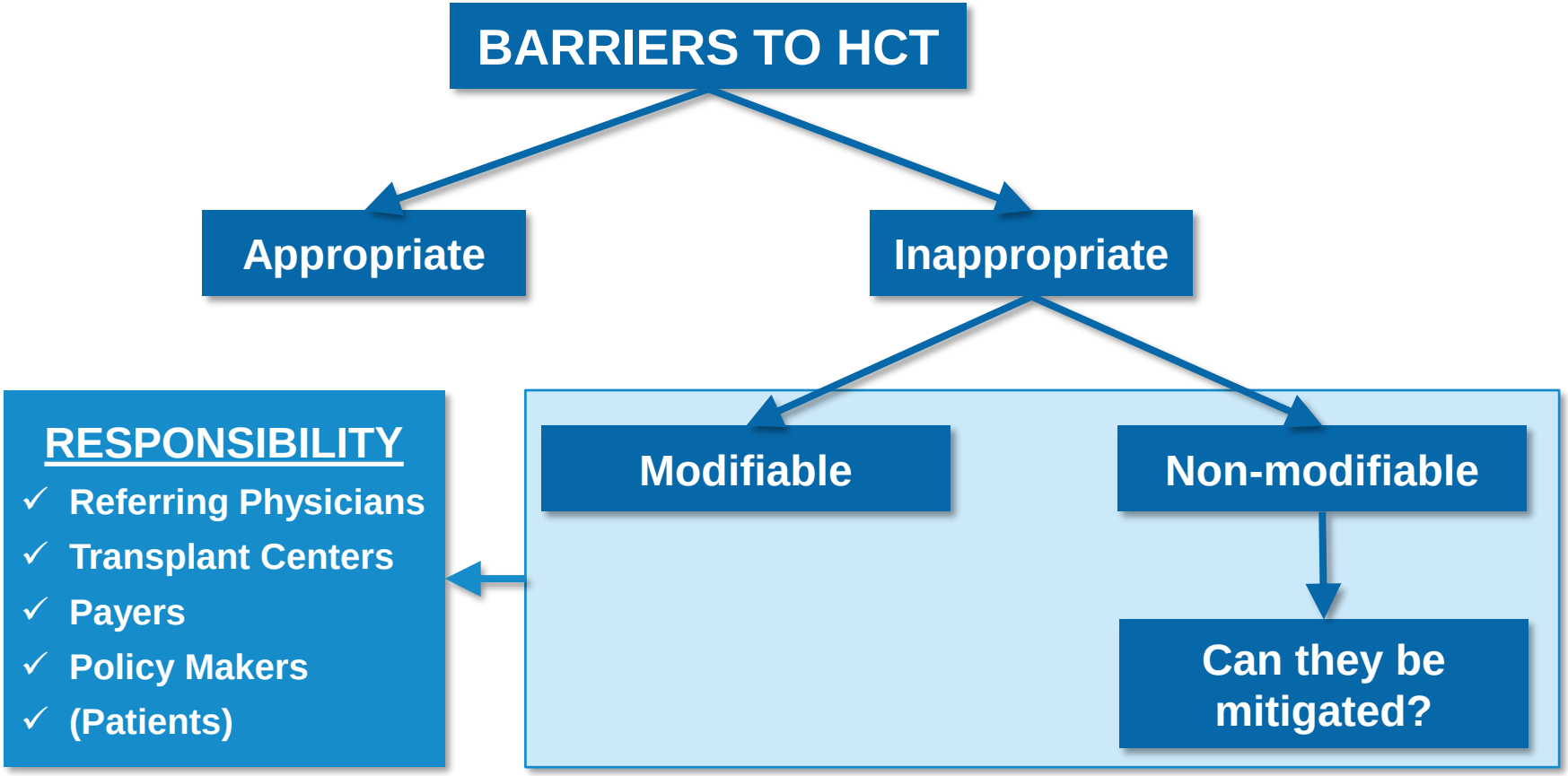


Develop less costly therapies

Streamline and scale manufacturing

Measure and advocate for value

Komanduri, *J Clinical Oncology, 2021*


BARRIERS TO HCT
Appropriate
Inappropriate
RESPONSIBILITY
✓ Referring Physicians
✓ Transplant Centers
✓ Payers
✓ Policy Makers
✓ (Patients)
Modifiable
Non-modifiable
Can they be mitigated?

Recurring themes warrant action across our ecosystem!

Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org

Quality of Care

Inferior Access to Allogeneic Transplant in Disadvantaged Populations: A Center for International Blood and Marrow Transplant Research Analysis

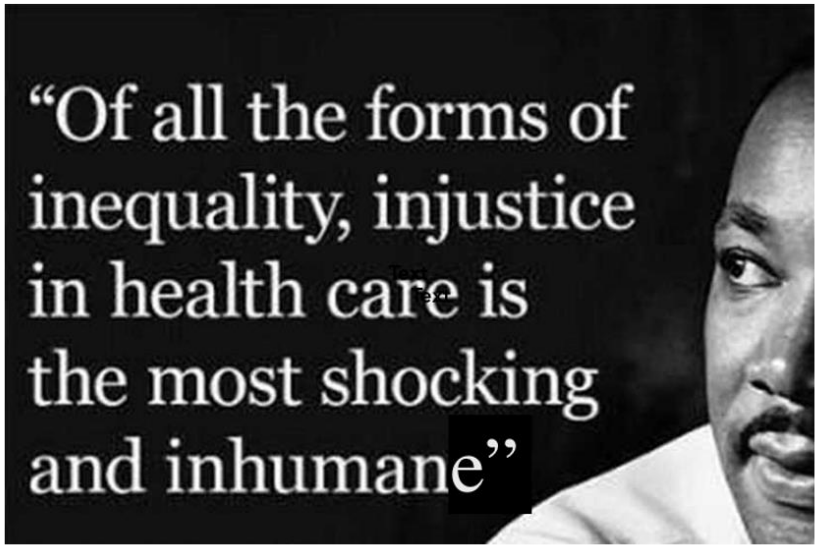
Kristjan Paulson[1,*], Ruta Brazauskas[2,3], Nandita Khera[4], Naya He[3], Navneet Majhail[5], Gorgun Akpek[6], Mahmoud Aljurf[7], David Buchbinder[8], Linda Burns[9], Sara Beattie[10], Cesar Freytes[11], Anne Garcia[12], James Gajewski[13], Theresa Hahn[14], Jennifer Knight[15], Charles LeMaistre[16], Hillard Lazarus[17], David Szwajcer[1], Matthew Seftel[1], Baldeep Wirk[18], William Wood[19], Wael Saber[3]

Transplantation and Cellular Therapy
journal homepage: www.tctjournal.org

Full Length Article
Cellular Therapy

Socioeconomic and Racial Disparity in Chimeric Antigen Receptor T Cell Therapy Access

Nausheen Ahmed[1,*], Moazzam Shahzad[2], Ernie Shippey[3], Rajat Bansal[1], Muhammad Umair Mushtaq[1], Zahra Mahmoudjafari[1], Muhammad Salman Faisal[4], Marc Hoffmann[1], Al-Ola Abdallah[1], Clint Divine[1], Mehdi Hamadani[5], Joseph McGuirk[1], Leyla Shune[1]



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Jeff Auletta (NMDP)

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