Division of Transplantation and Cellular Therapy

Department of Medicine

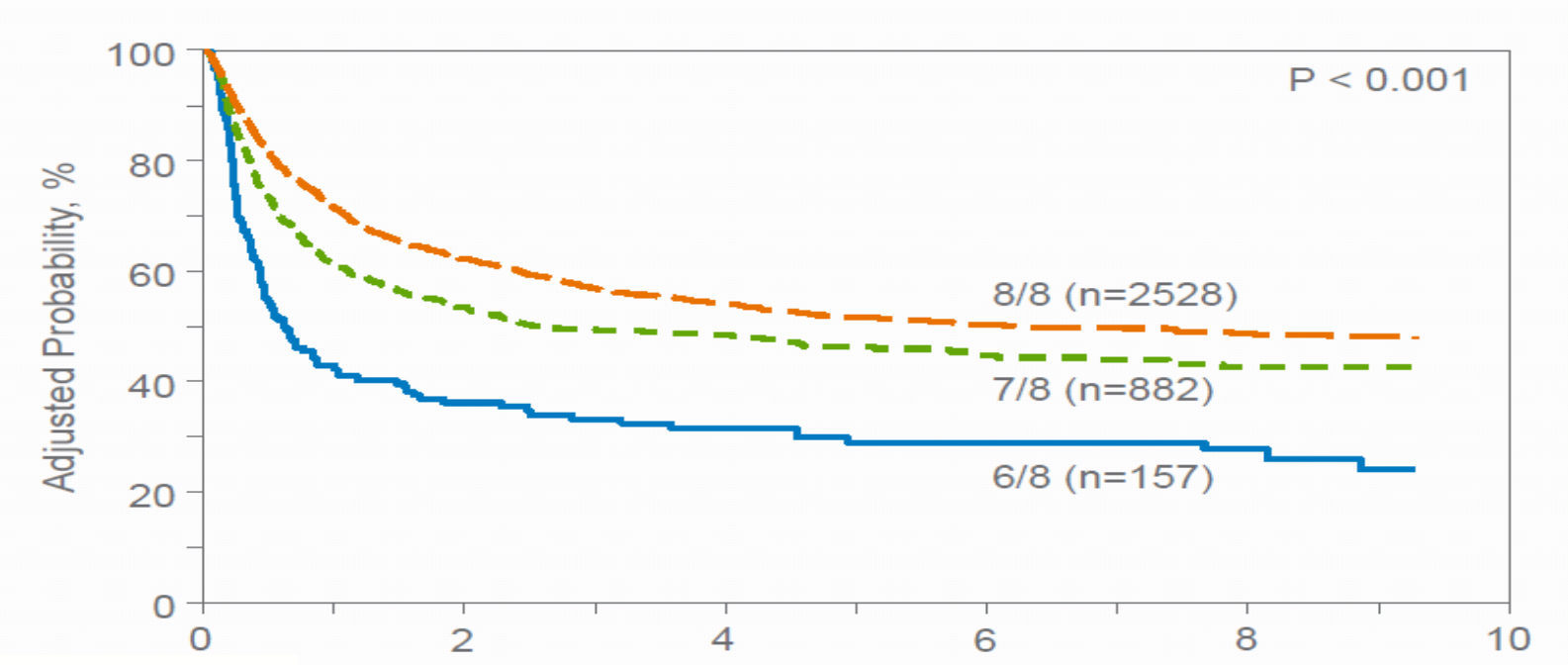
Updates in Stem Cell Transplantation and CAR-T Therapy for Heme Malignancies

Krishna Komanduri, MD, FASCT
Kalish Family Chair in Stem Cell Transplantation
Chief, Division of Transplantation and Cellular Therapy
Professor of Medicine, Microbiology & Immunology

Allogeneic SCT in 2022

- Remains the standard of care for many patients with high-risk MDS, high-risk or relapsed AML and ALL, high-risk myelofibrosis, many patients with severe aplastic anemia and subsets of patients with refractory lymphoid malignancies
- We now recognize that immunologic graft vs. tumor effects are critical for the success of alloSCT, which have led to utilization of lower intensity conditioning regimens for many
- Early mortality has dramatically declined (from 30-40% 25 years ago to 5-10% now)
- AlloSCT (including for those with well matched unrelated donors) now routinely performed for patients up to age 75, even with modest comorbidities common with aging
- Access remains a problem, with outcomes compromised for non-white patients, especially for those lacking a suitable matched related sibling

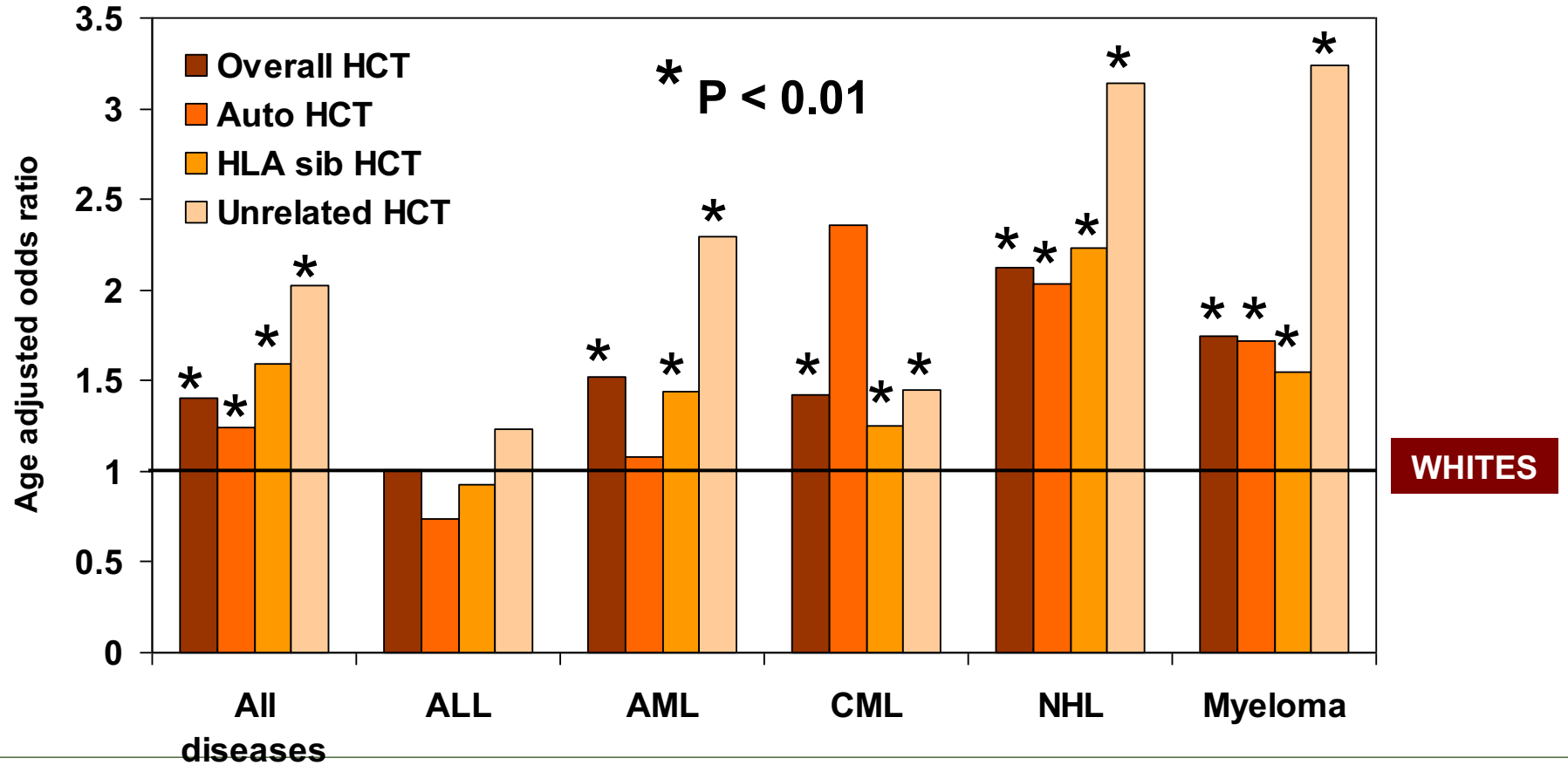
Impact of HLA Matching: Race and ethnicity matter



NMDP/HRSA Report, 2017
Pidala et al., Blood 2014

CIBMTR Study: Race and Access to HCT

African-Americans less likely to receive HCT compared to Whites



T Joshua et al, Cancer

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

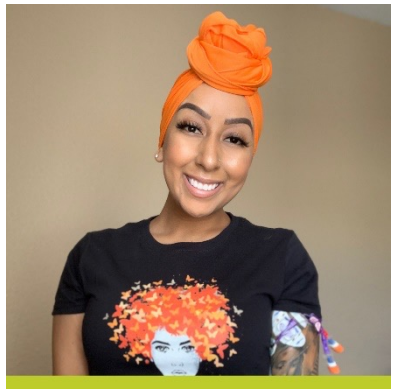
However, a MUD is not available for every patient.

29%

Black or African American

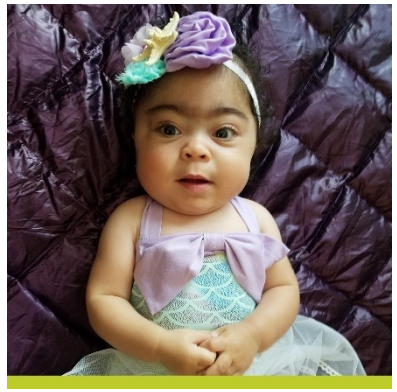
47%

Asian or Pacific Islander



48%

Hispanic or Latino



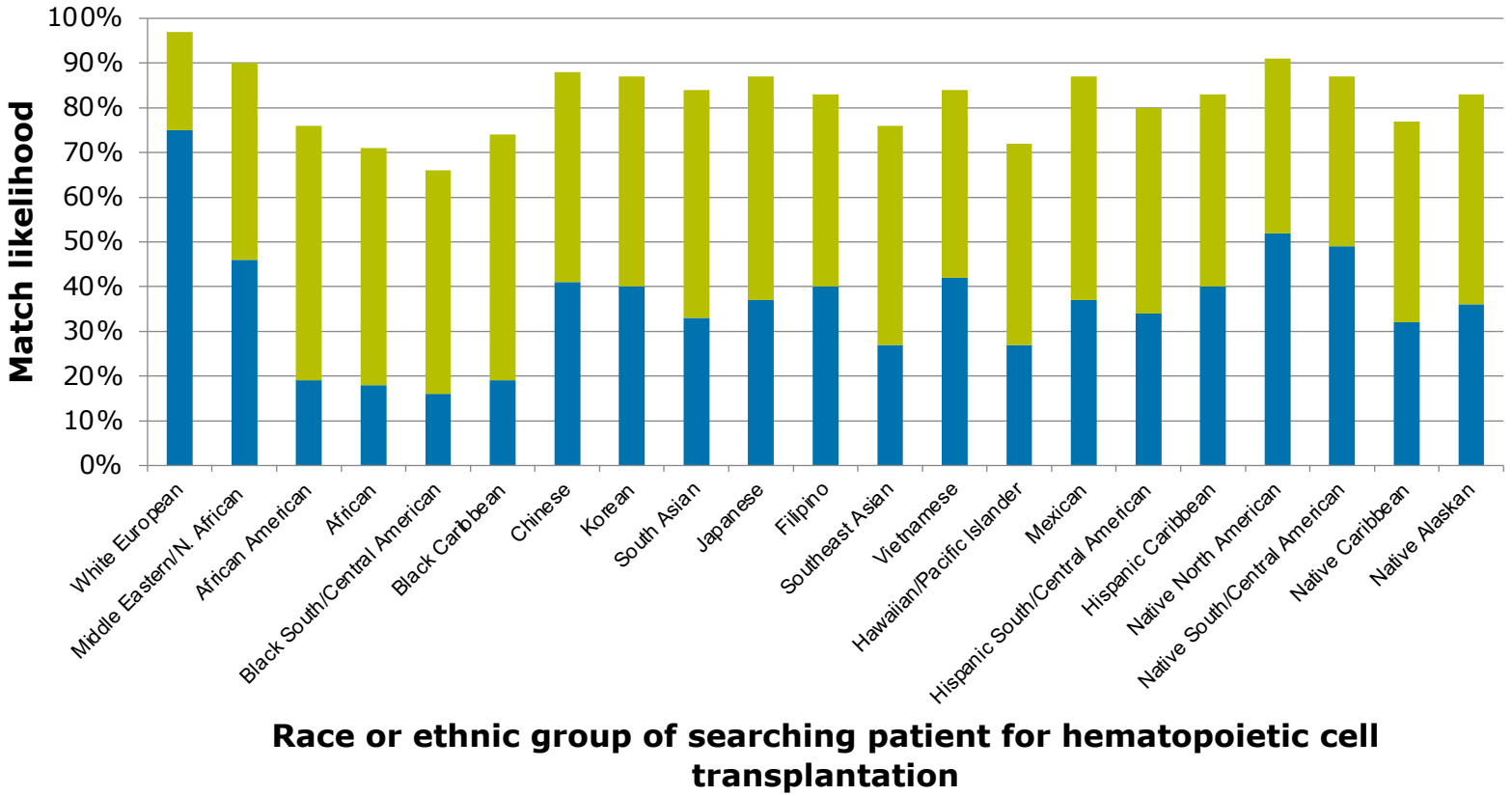
60%

American Indian and Alaska Native

79%

White

Likelihood of HLA Matching: Race and ethnicity matter



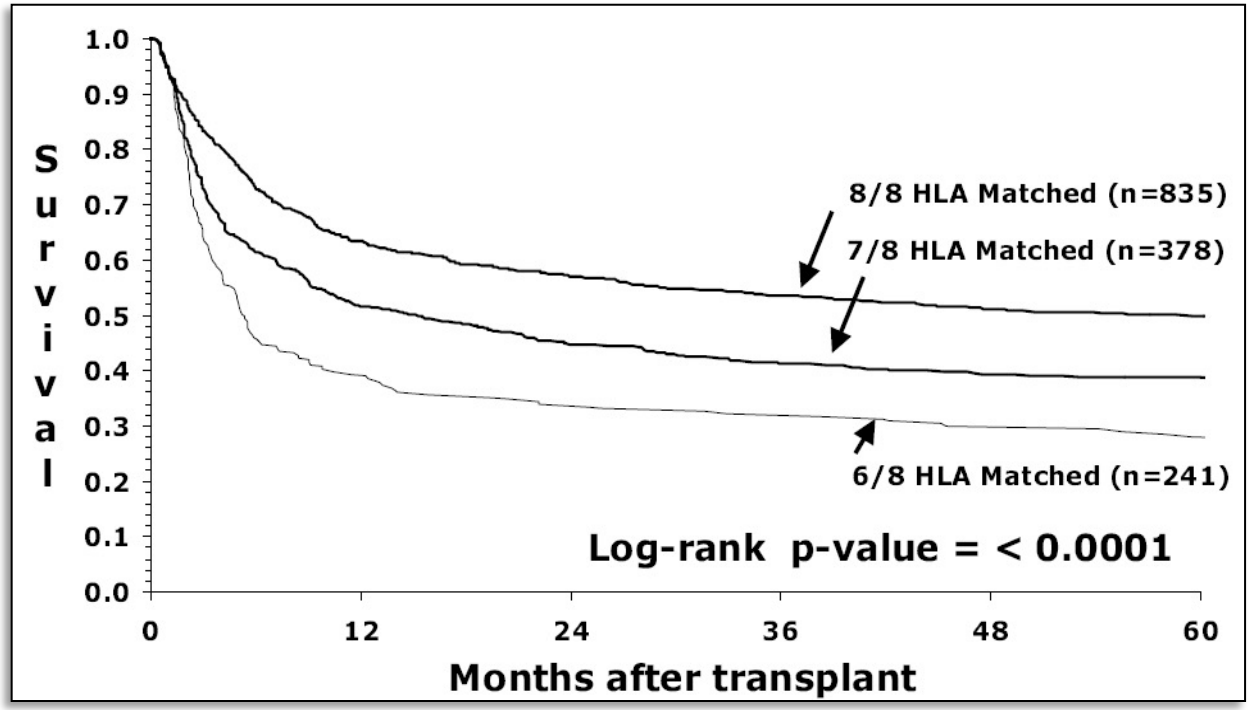
Gragert L, et al. N Engl J Med. 2014; 371(4): 339-348.

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

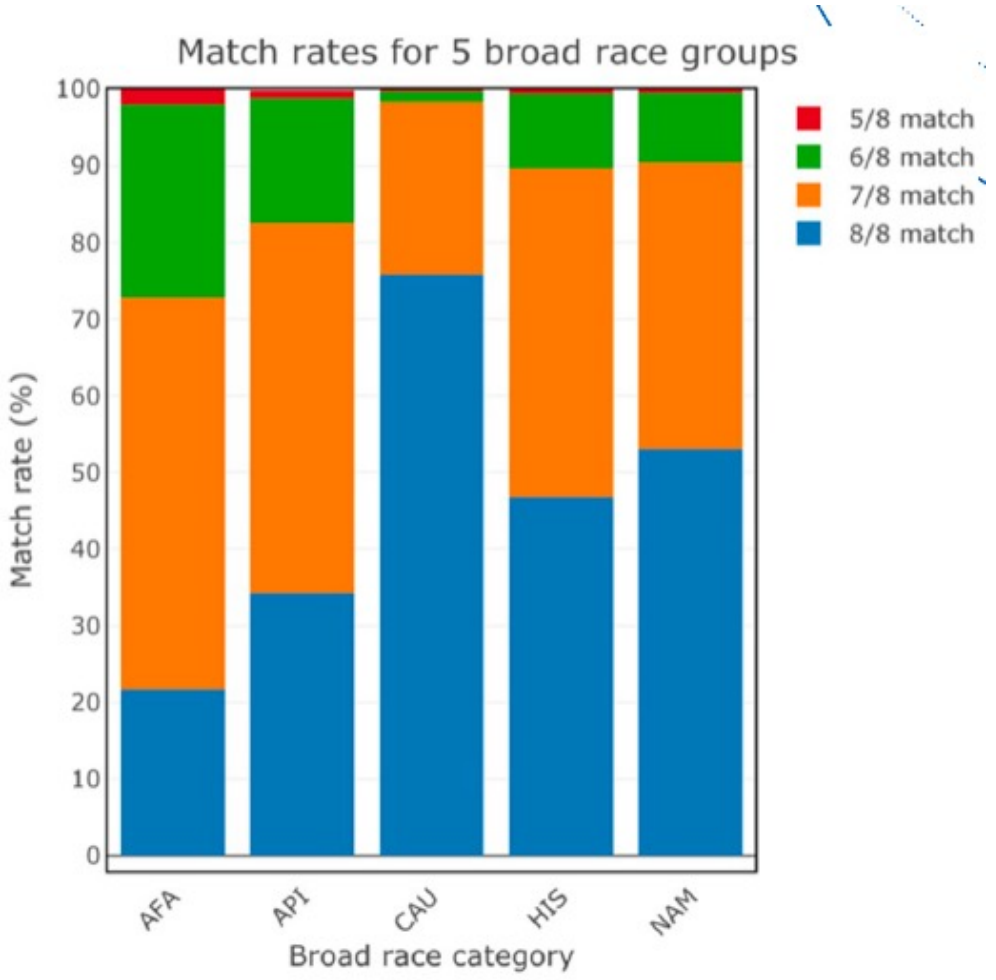


- **Historically, mismatched URD transplants associated with worse survival**
- **Roughly 10% decrease in survival for each HLA mismatch**

Lee et al, Blood 2007;110:4576

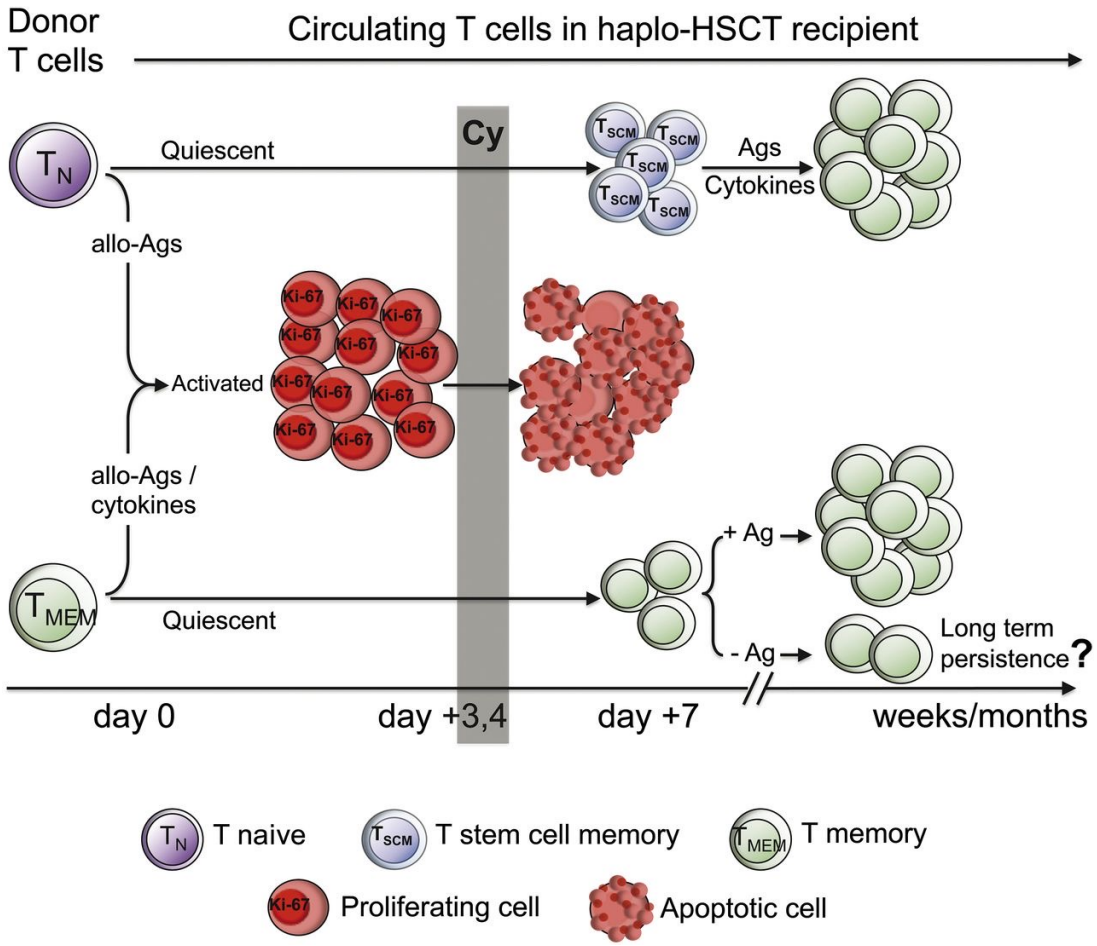
Mismatched grafts close the disparity gap

- 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**

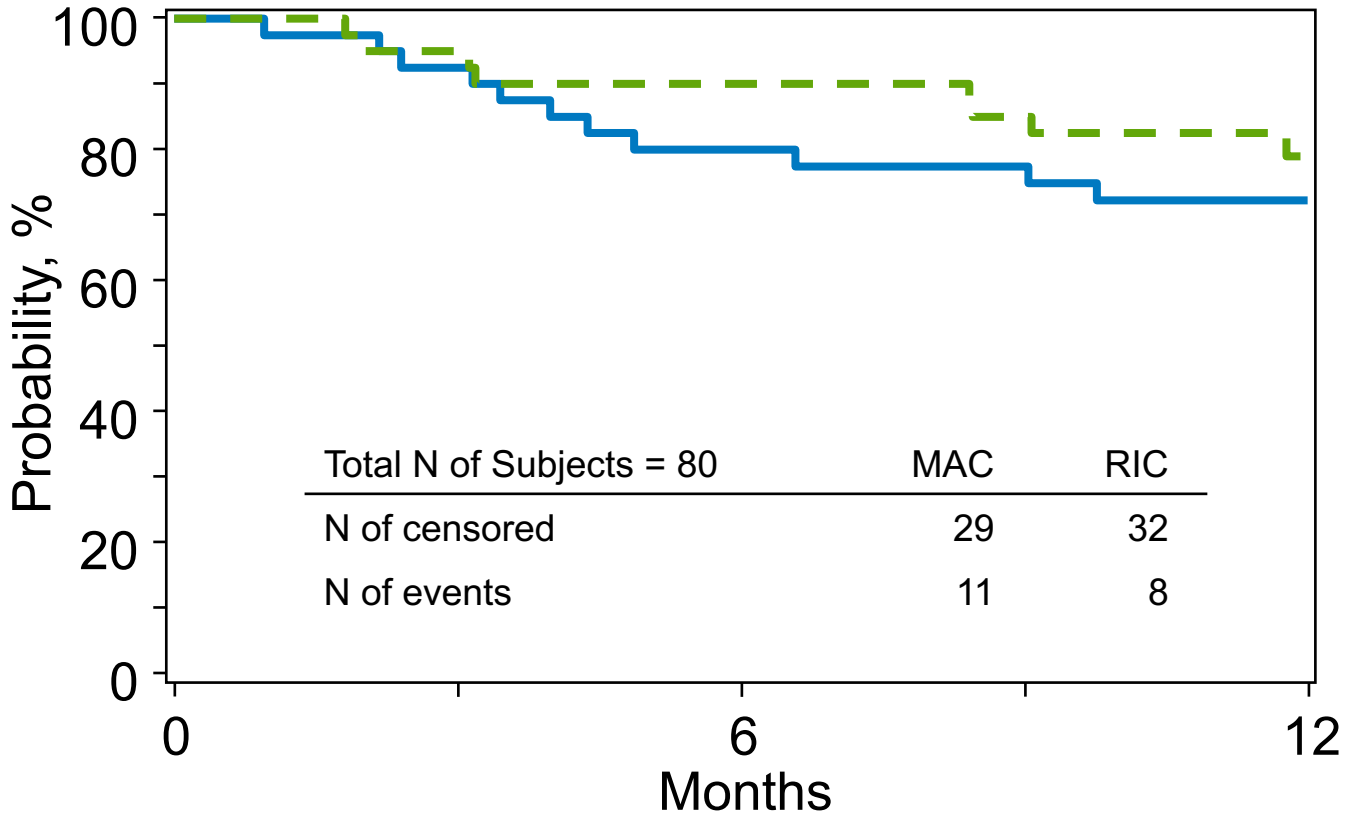


AFA = African American
API = Asian Pacific
CAU = Caucasian
HIS = Hispanic/Latino
NAM = Native American

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



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

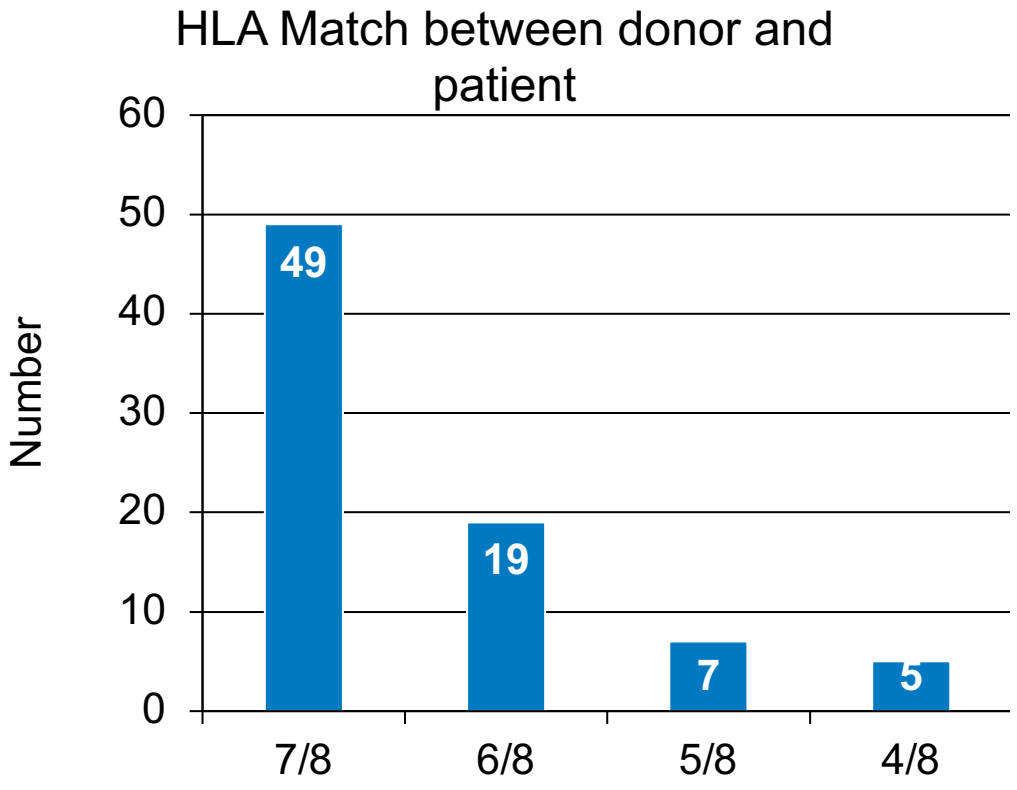


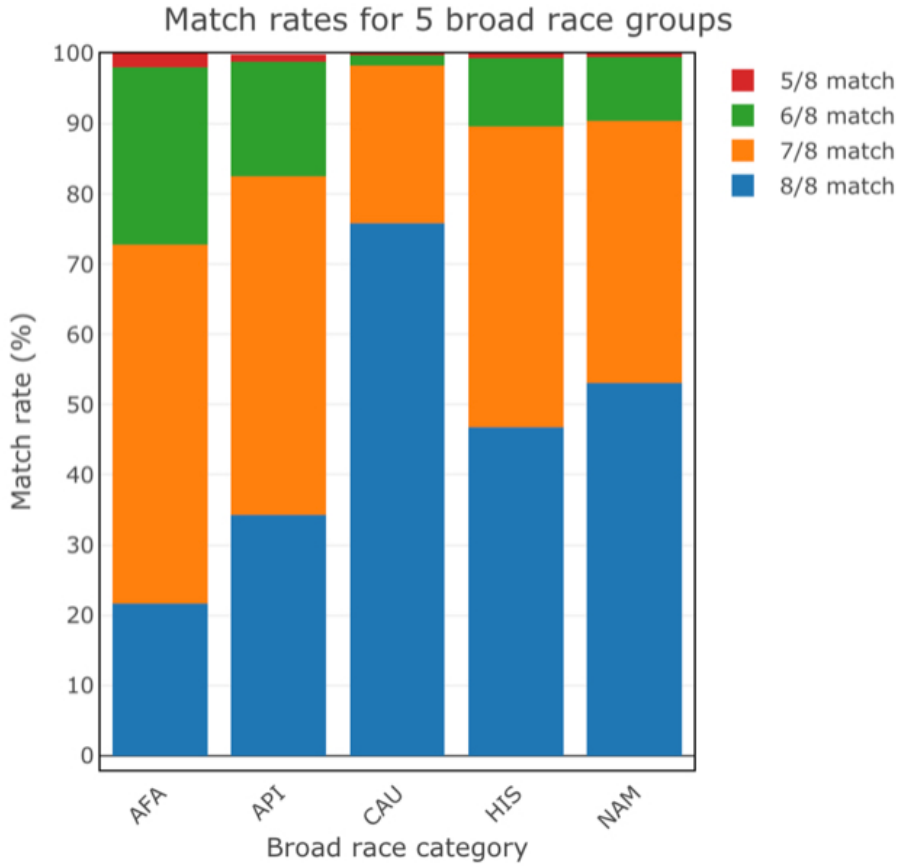
original reports

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]

Everyone has a ≤6/8 donor





CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM
NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

15-MMUD Conclusions

- This approach is feasible and safe, and outcomes are similar to other settings using PTCy
- 48% of patients enrolled were racial/ethnic minority groups: MMUD PTCy broadens access to transplant
- Manuscript accepted for publication (2/2021): Journal of Clinical Oncology
  - Antonio Jimenez-Jimenez (Sylvester) co-first author

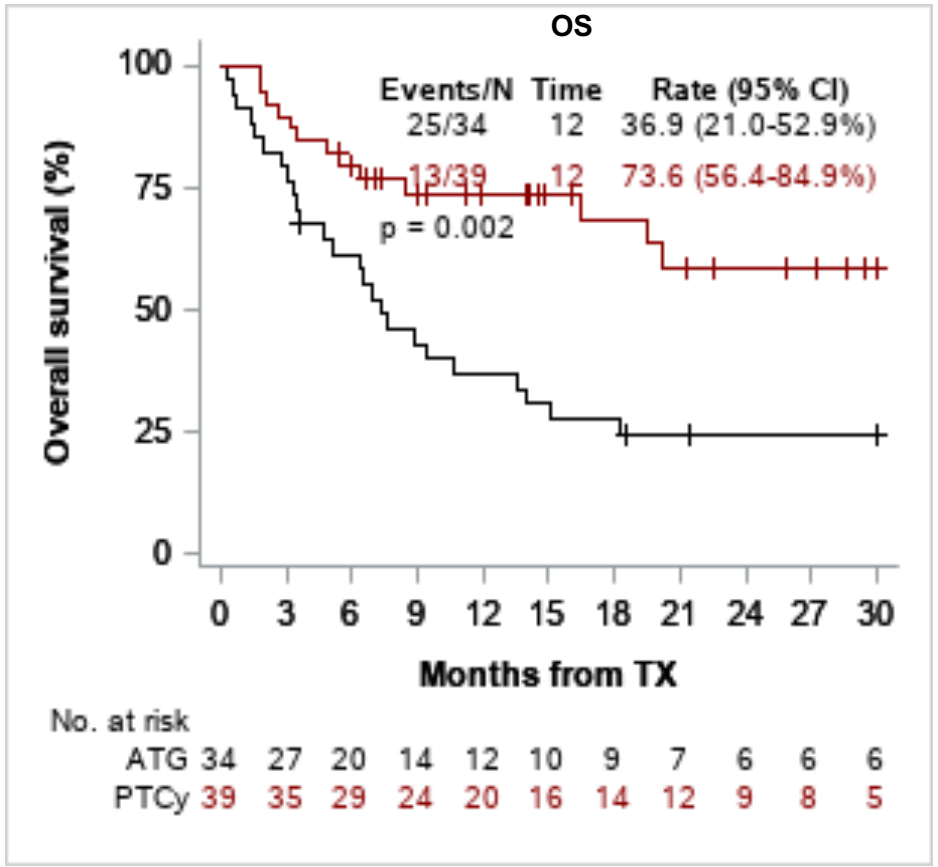
Post-Transplant Cyclophosphamide (PTCy) Is Associated with Improved Clinical Outcomes in HLA-MMUD Hematopoietic Cell Transplantation (HCT): The University of Miami Experience

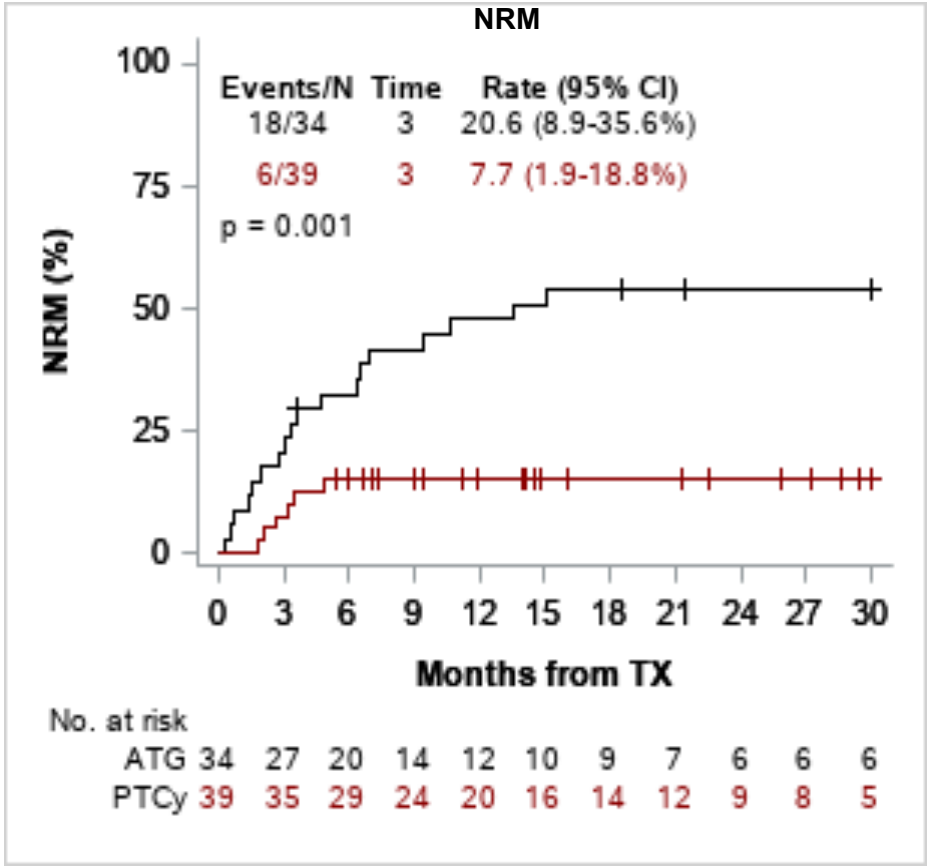
- UM established the leading mismatched unrelated donor transplant program in the US

- Trial Highlights:
  - 73 patients, ≥18 years s/p MMUD s/p HCT 1/2016 and 12/2019
  - Post-HCT GvHD prophylaxis: PTCy vs. historical SOC ATG
  - 70% Hispanic and Afro-Caribbean patients
  - 30% Highly mismatched grafts in experimental arm

Jimenez Jimenez A, Komanduri K *et al*., The TCT Meetings of ASTCT and CIBMTR.

Results





Jimenez Jimenez A, Komanduri K *et al*., The TCT Meetings of ASTCT and CIBMTR.

Future Directions

The 15-MMUD study will be followed by a multicenter NMDP-sponsored clinical trial using peripheral blood stem cell grafts:

- ACCESS: A Multi-Center, Phase II Trial of HLA-Mismatched Unrelated Donor Hematopoietic Cell Transplantation (HCT) with Post-Transplantation Cyclophosphamide for Patients with Hematologic Malignancies (21-MMUD) (Jimenez Jimenez A, Devine S, Al-Maki M et al.)
- 40 sites, ~180 patients.
- University of Miami/Sylvester activated and currently leading national accrual

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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 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.

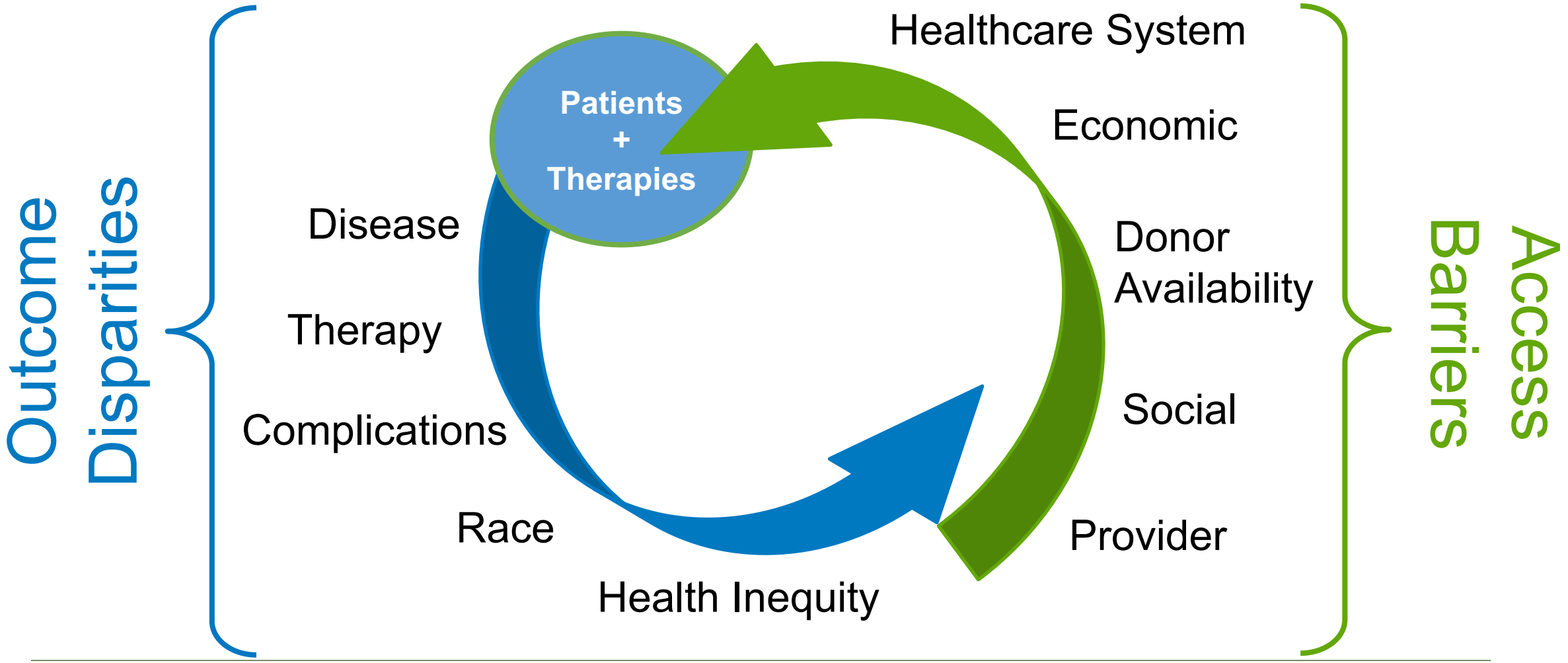
Study Population	Patients with eligible diagnosis receiving a MMUD PBSC or BM (pediatric strata only) product at participating transplant centers
Study Design/Phase	This is a multi-center Phase II study with three strata (two adult strata based on conditioning intensity and one pediatric) designed to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

Conclusions: PTCy to improve MMUD HCT

- Despite a higher degree of HLA-mismatch, PTCy following MMUD HCT resulted in superior OS, RFS, GRFS and lower NRM when compared to ATG-based GvHD prophylaxis.
- Outcomes following PTCy appear to be approaching historically excellent outcomes with matched unrelated donor HCT, as the utility of this platform continues to be explored prospectively.
- MMUD with PTCy appears to be a safe and effective alternative graft source for individuals without matched sibling or registry donors and significantly levels the playing field for underrepresented minorities.

Access Barriers and Outcome Disparities

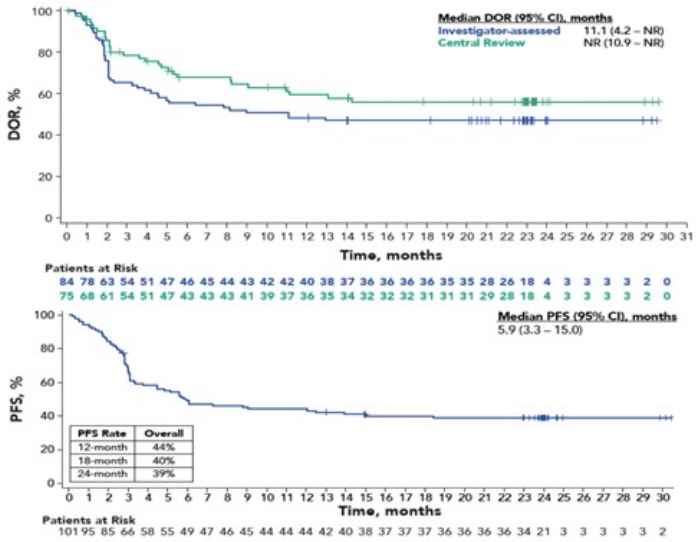


Conclusions

- Autologous and allogeneic HCT remain the standard of care for many patients with high risk and/or relapsed malignancies, including myeloma, relapsed lymphoma and many patients with MDS and AML
- Significant disparities exist, with lower referral and utilization rates based on gender and race
- Biological barriers (e.g., increasing ethnic diversity with underrepresentation in registries) also exist, but can be addressed with steadily improving outcomes with approaches including mismatched transplantation using PTCy
- Approaches to address disparities must be holistic, with attention to bias, financial access barriers, cultural barriers, education and biological factors

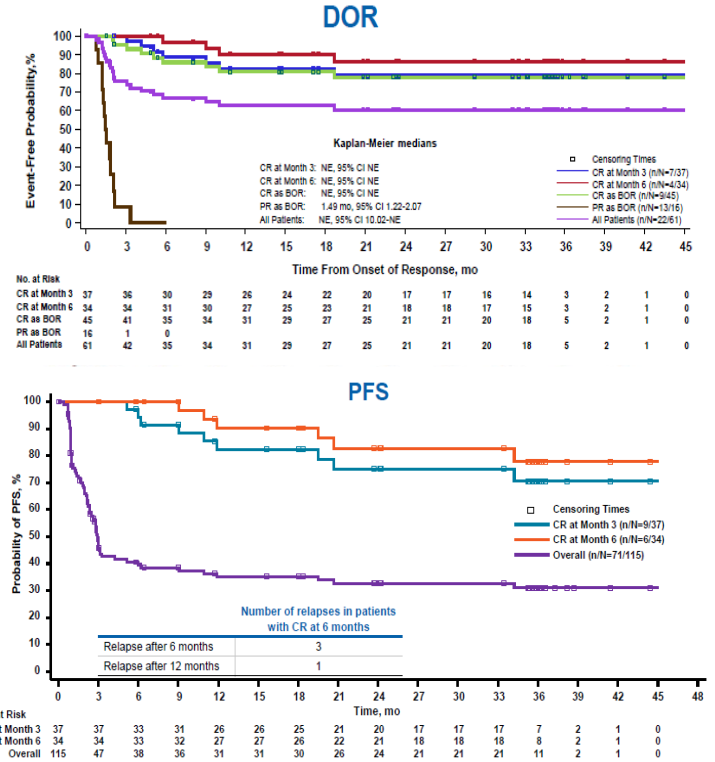
CD19 CAR T-cells Yield Durable Remission in ~40%

ZUMA-1

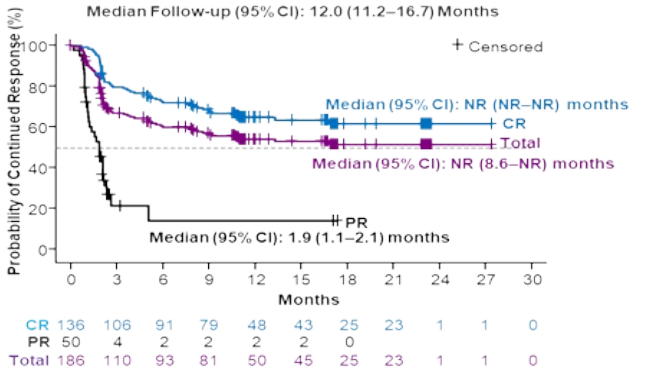


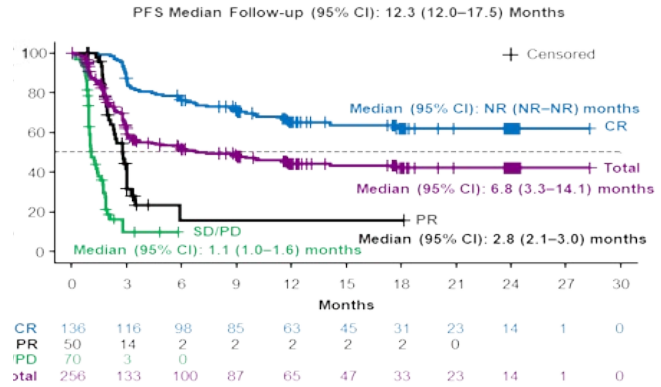
Locke et al Lancet Oncology 2019;20:31
Schuster et al NEJM 2018
Abramson et al ASH 2019, Lancet 2020

JULIET



TRANSCEND-001



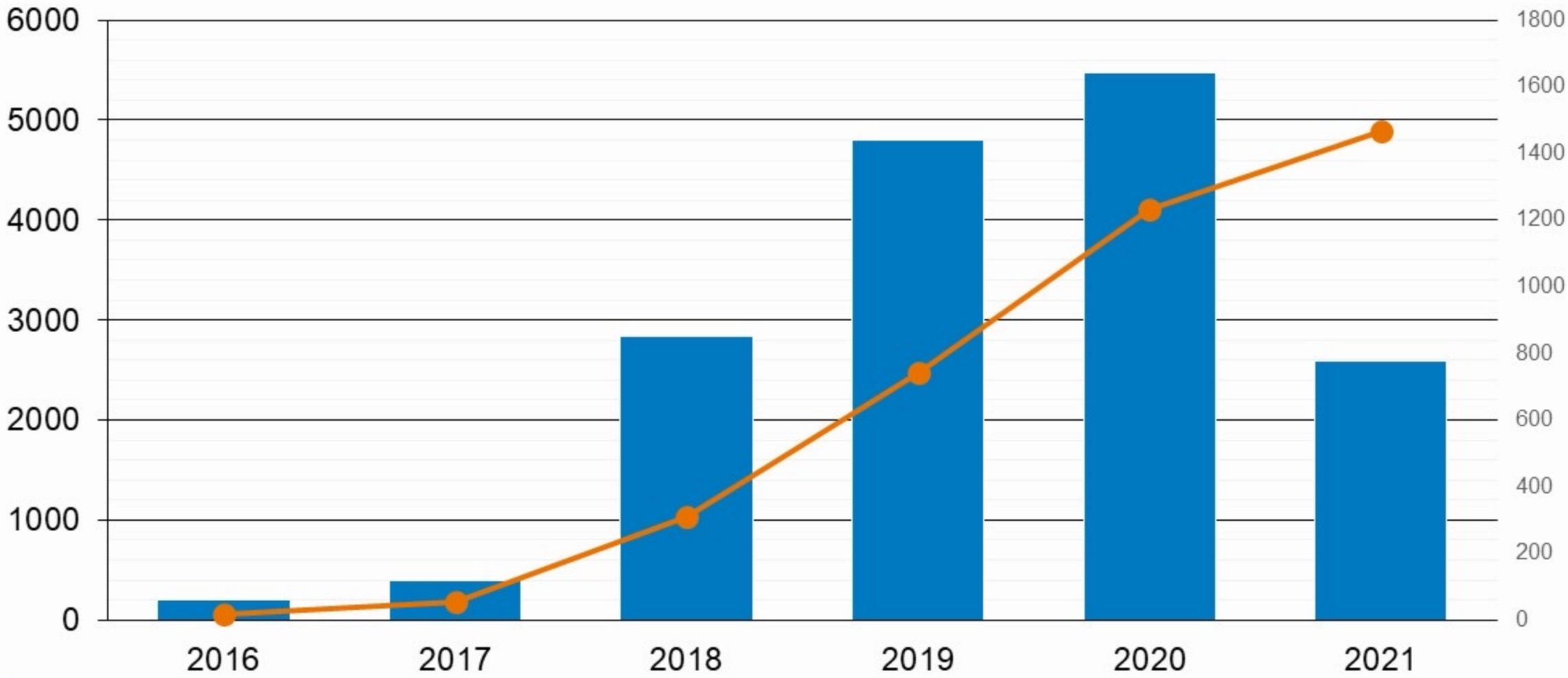


SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Number of CAR T cell infusions: 2016-2021 (4,886 patients and 5,129 infusions)

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE



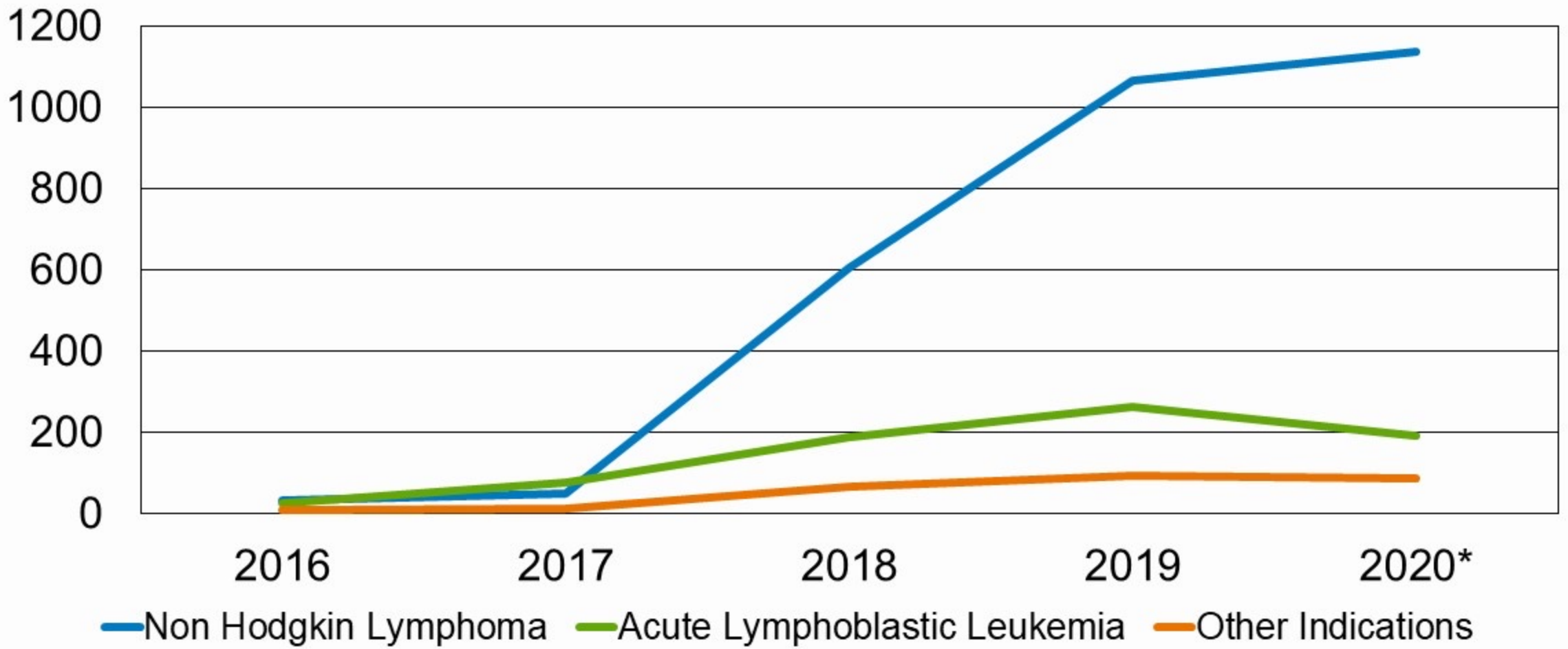
CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Cumulative

Data Incomplete for 2020 & 2021

CAR T cell Indications Annually: 2016-2020

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE

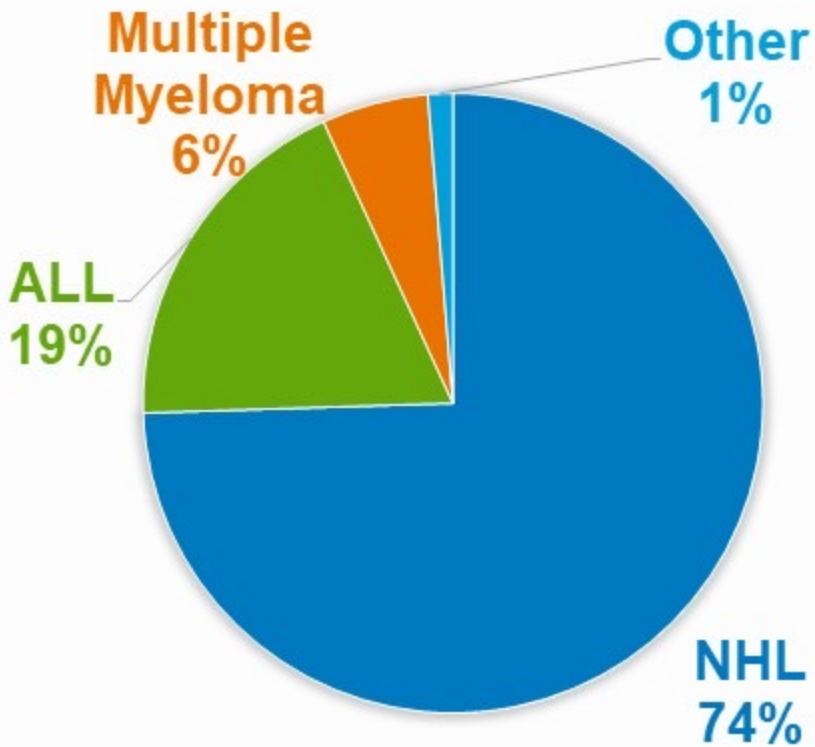


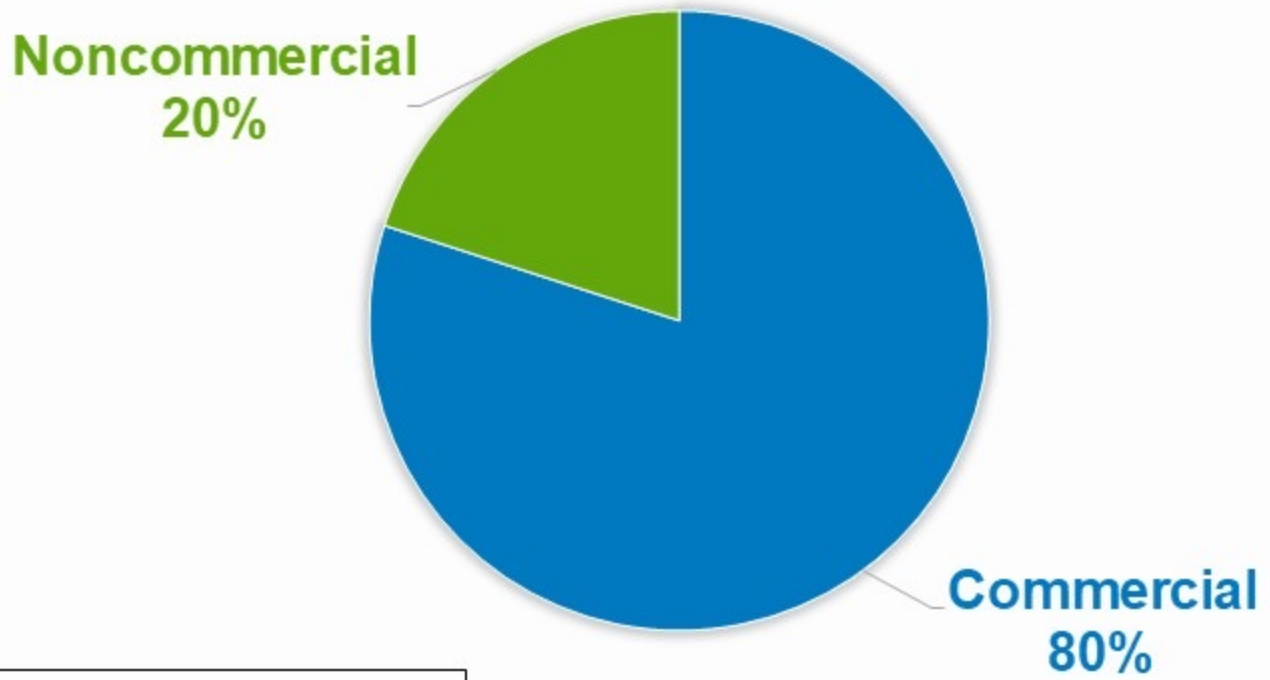
CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

*Data incomplete

CAR T Cell Indications: 2016-2021 (N=4,886)

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE





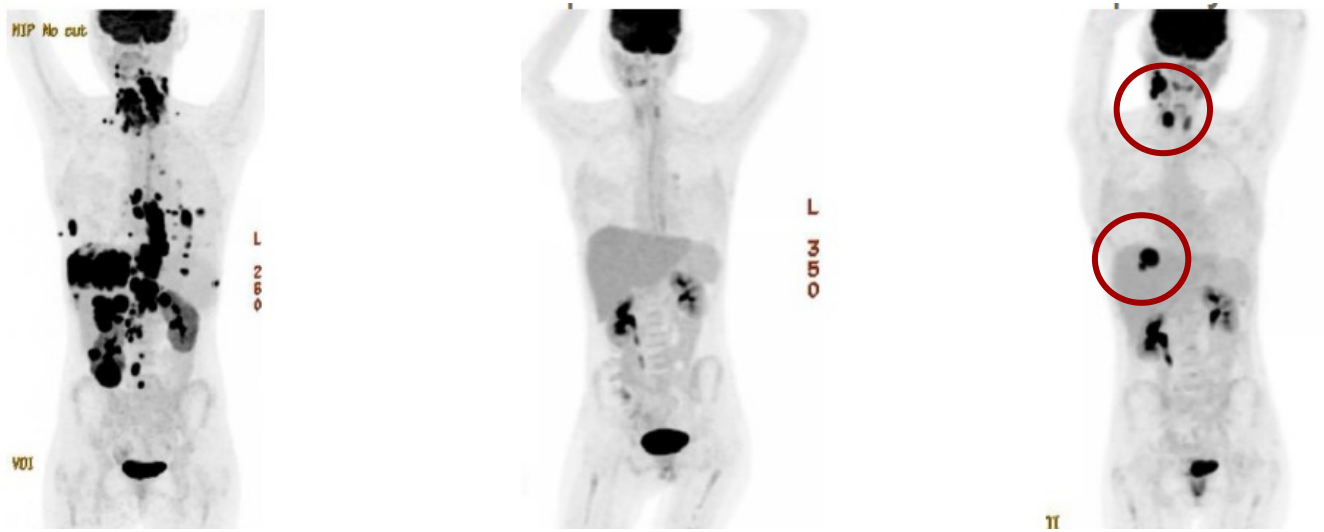
Centers: 159
Median age: 59 y (<1-91)y
Prior HCT: 33%

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

CD19 Antigen Loss is a Common Cause of treatment failure after CAR19 Therapy

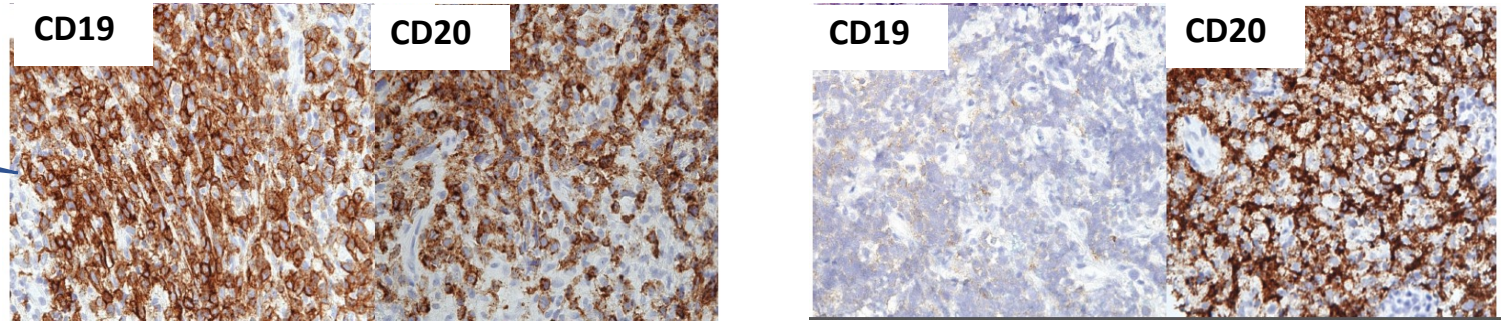
- 7/21 (33%) ZUMA-1 patients w/ disease progression after therapy were CD19 negative#
- 34 patients treated with commercial Axi-Cel at Stanford*
  - 16 developed disease progression
  - 12 were biopsied at time of progression
  - Six showed CD19 loss

PRE-INFUSION ***DAY 28*** ***DAY 60***



Lymph node analysis pre-CAR and at Day 60 highlighted loss of CD19 but preservation of CD20 expression

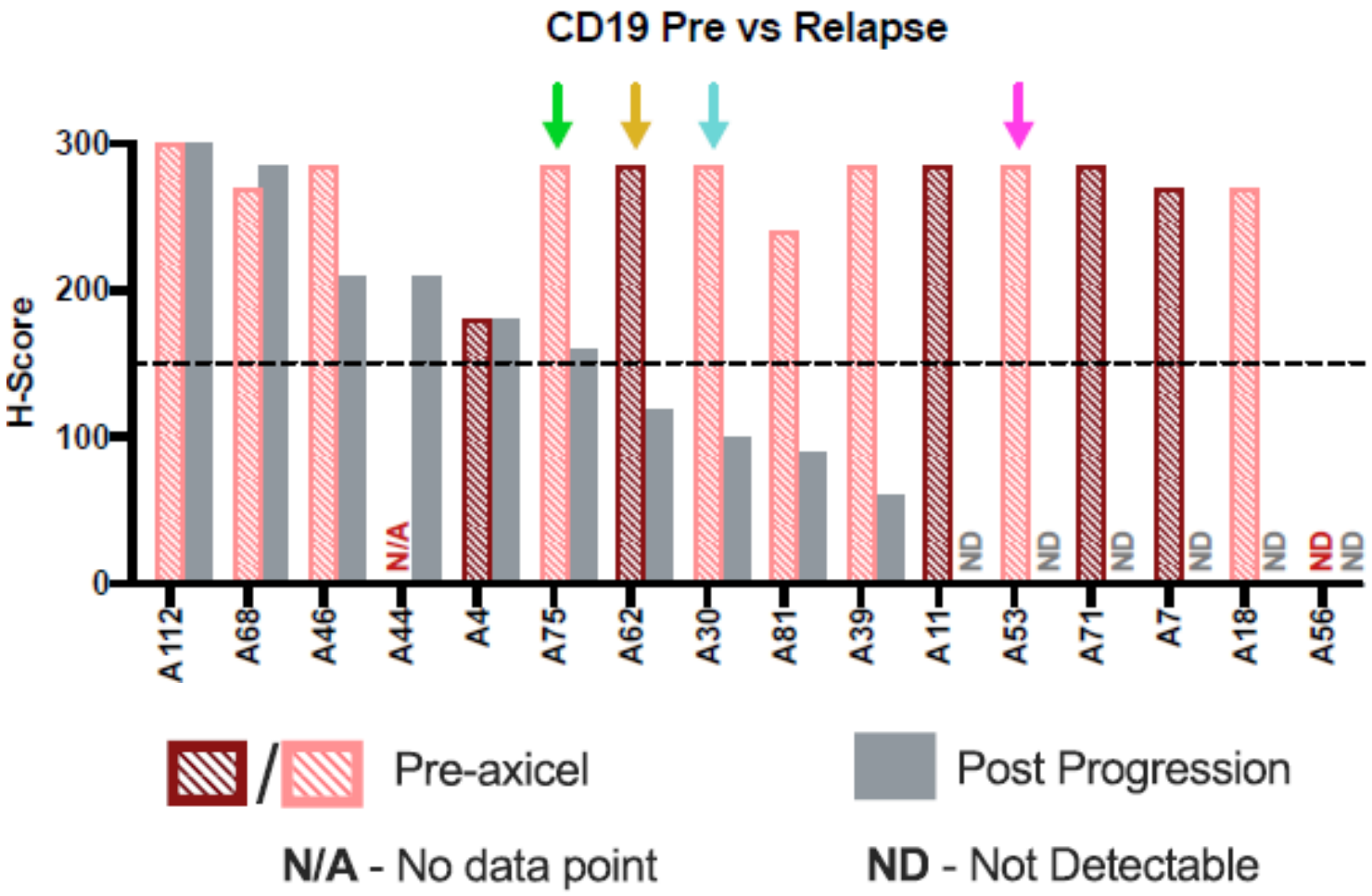
PRE-THERAPY ***DAY 60 RELAPSE***

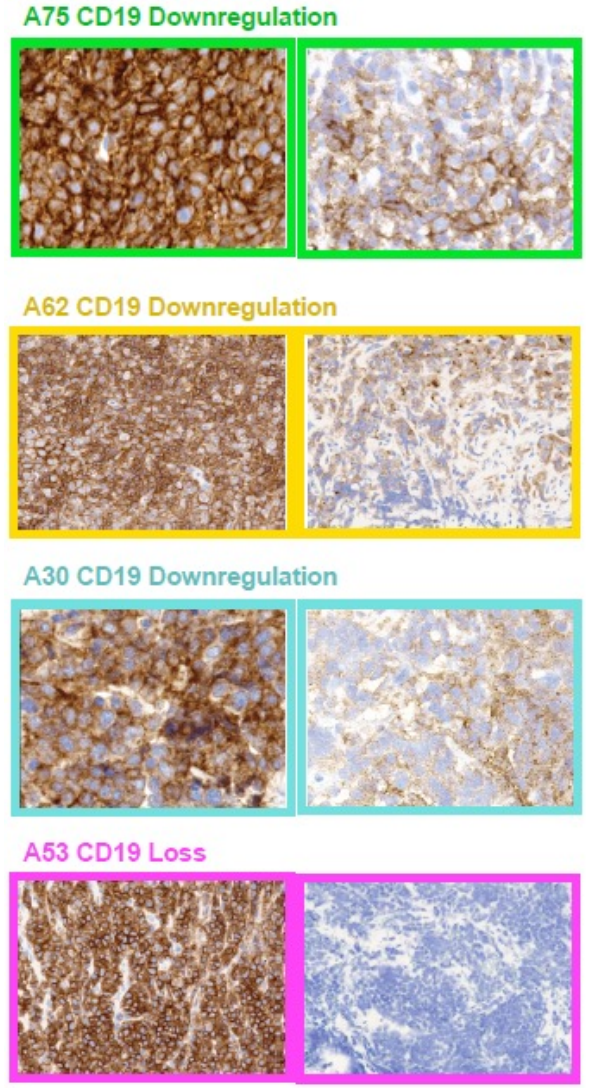


#Neelapu et al, ASH2017 Abstract #578

*Jean Oak et. al, ASH2018 Abstract #4656

CD19 loss or down-regulation occurs after axi-cel





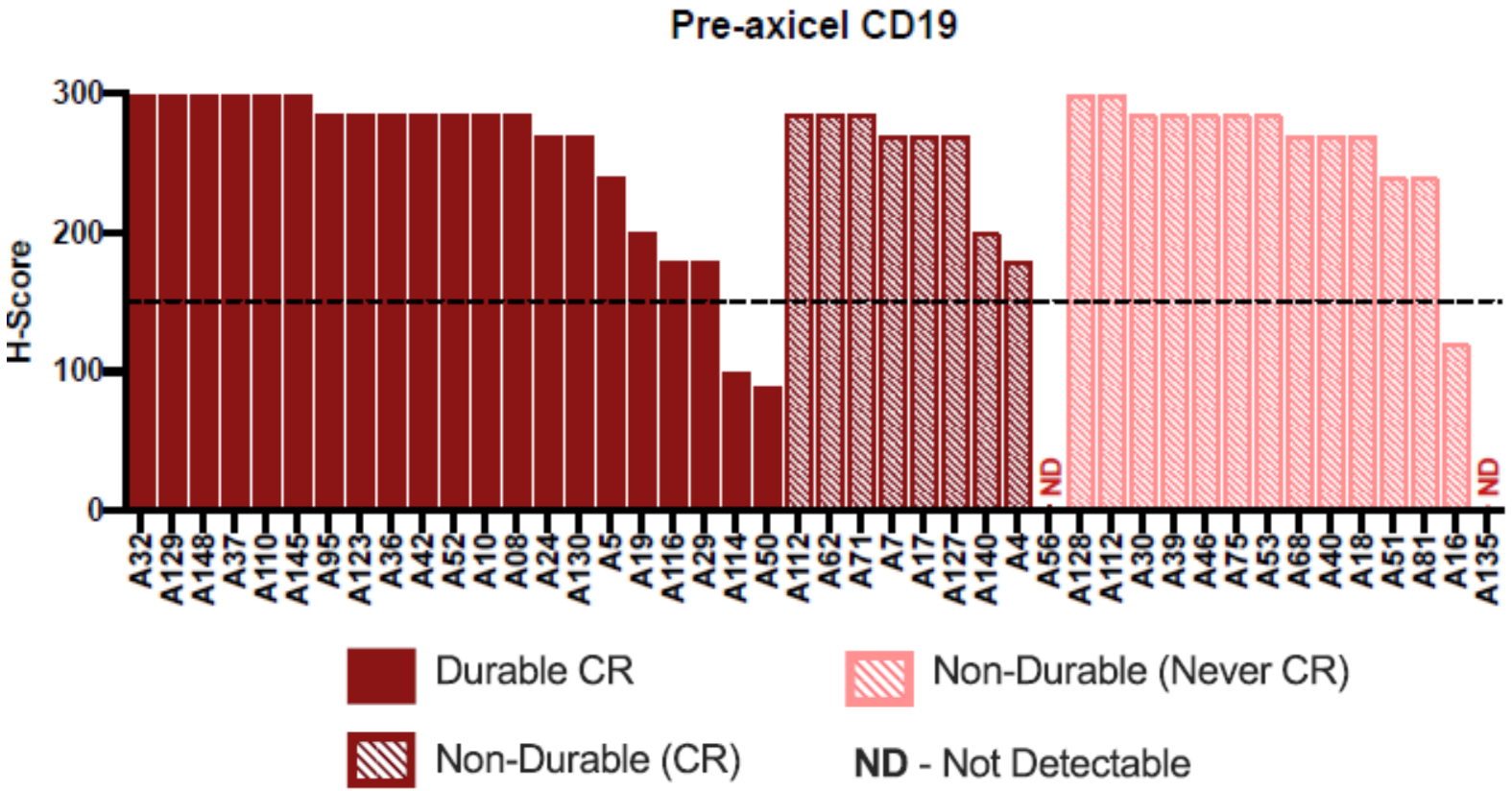
SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Spiegel, *Nat Medicine* 2021

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Pre-treatment CD19 by IHC is not associated with Clinical Outcomes

H-score = %tumor cells positive (0-100) x staining intensity (0-3)

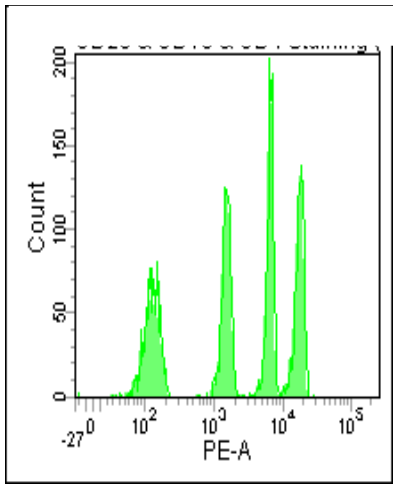


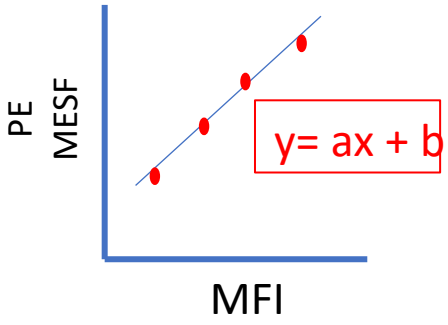
Spiegel, *Nat Medicine* 2021

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

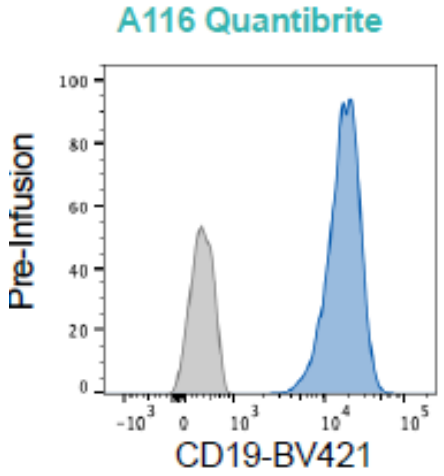
NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

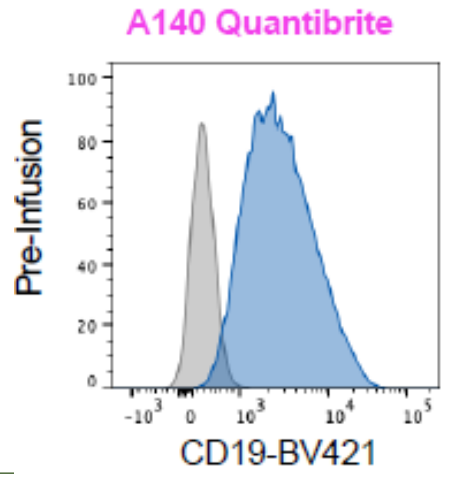
Pre-treatment quantitative flow may identify patients at risk for treatment failure

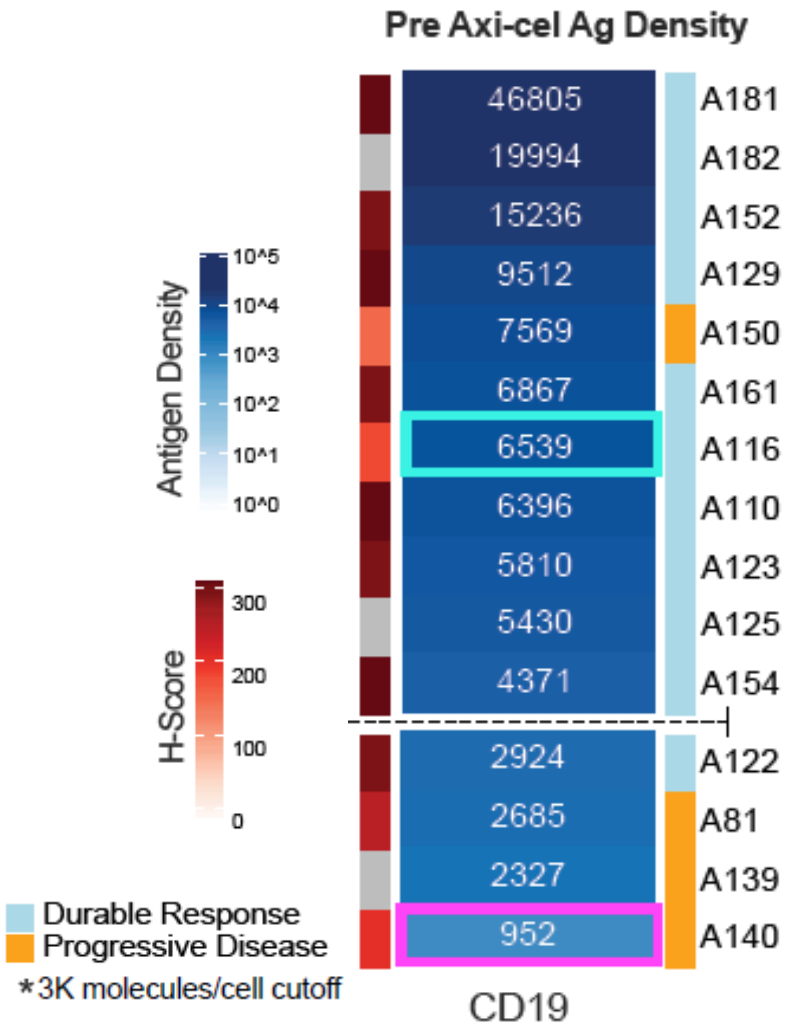




Bead population	PE Molecules
High	81,345
Med-High	29,683
Med-Low	6,573
Low	355







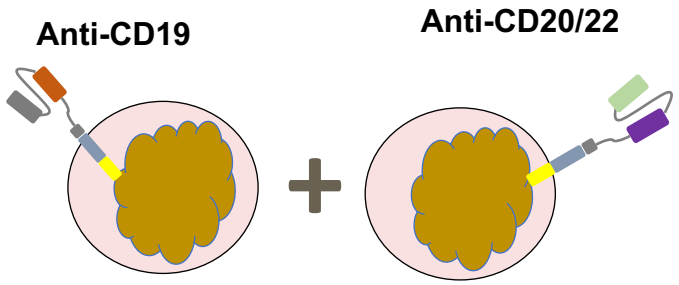
Spiegel, *Nat Medicine* 2021

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Simultaneous targeting of two tumor antigens may overcome antigen loss and improve efficacy

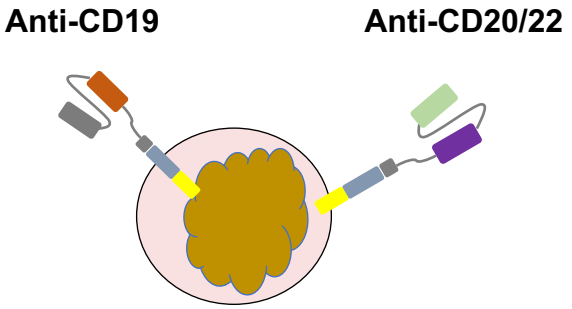
Co-administration



Pros:
- Defined dose for each CAR

Cons:
- Multiple production runs
- Potential competition
- When to infuse 2nd dose

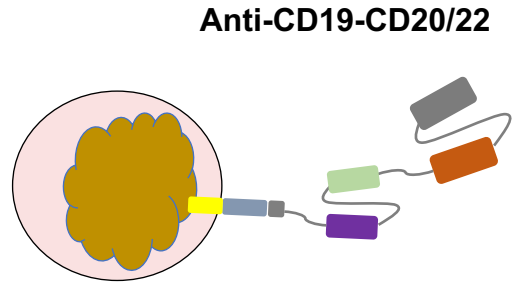
Co-expression
(co-transfection or bicistronic)



Pros:
- Each CAR molecule signals independently
- Reduces steric concerns

Cons:
- Can generate multiple CAR populations

Bivalent-bispecific receptor



Pros:
- Each cell expresses both scFVs

Cons:
- Distal scFV may have signalling deficiencies

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Cronk RJ, *Cancers* 2020 12:2523

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Phase I Dose Escalation Study of CAR19-22 in Adults with Relapsed/Refractory DLBCL or B-ALL

Primary Objectives

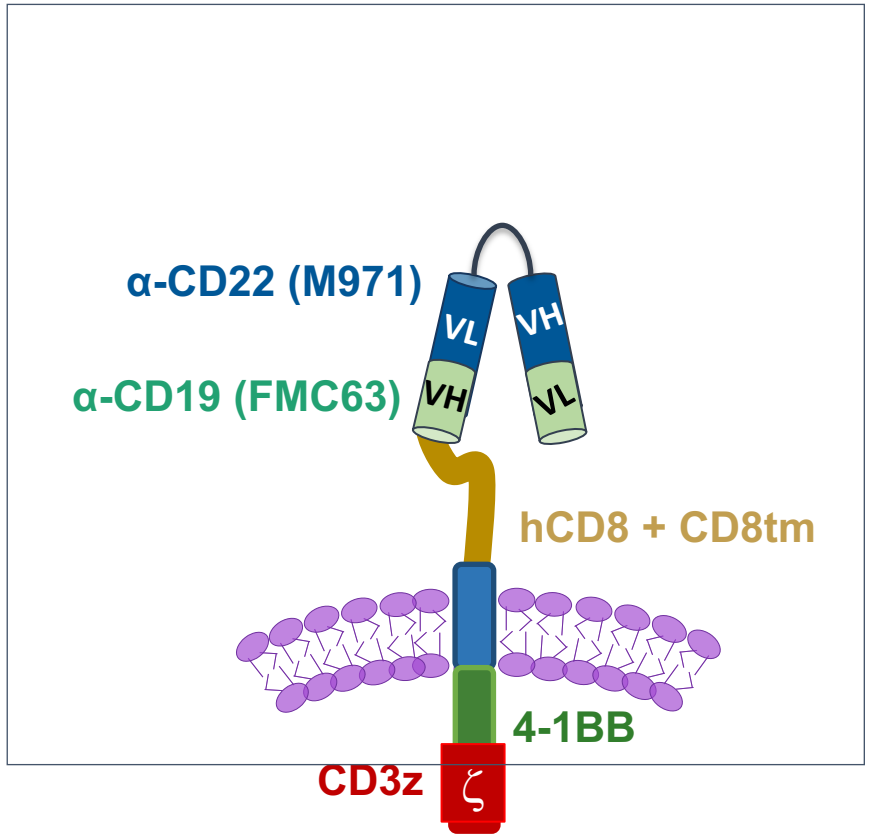
- Determine feasibility of production
- Assess safety

Secondary Objectives

- Response rate and clinical efficacy

Exploratory Objectives

- CAR19-22 persistence
- Antigen remodeling at Relapse



Spiegel, Muffly, Mackall, et al., *Nat Medicine* 2021

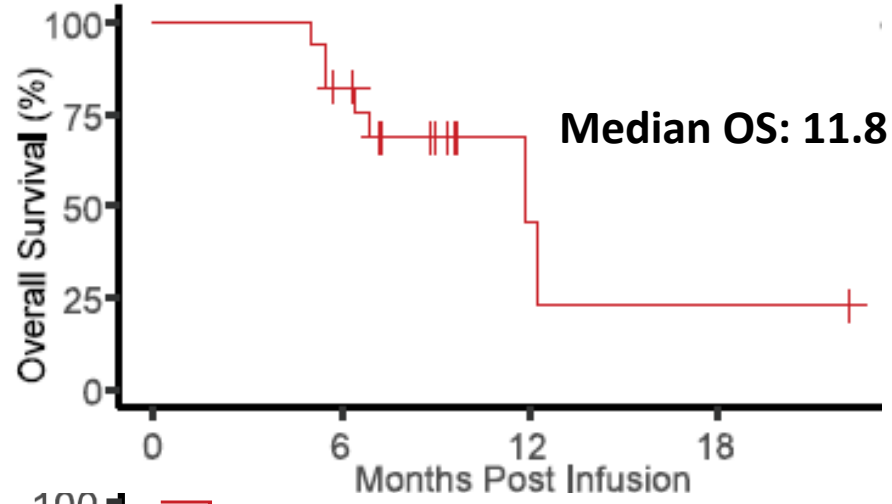
ClinicalTrials.gov NCT03233854

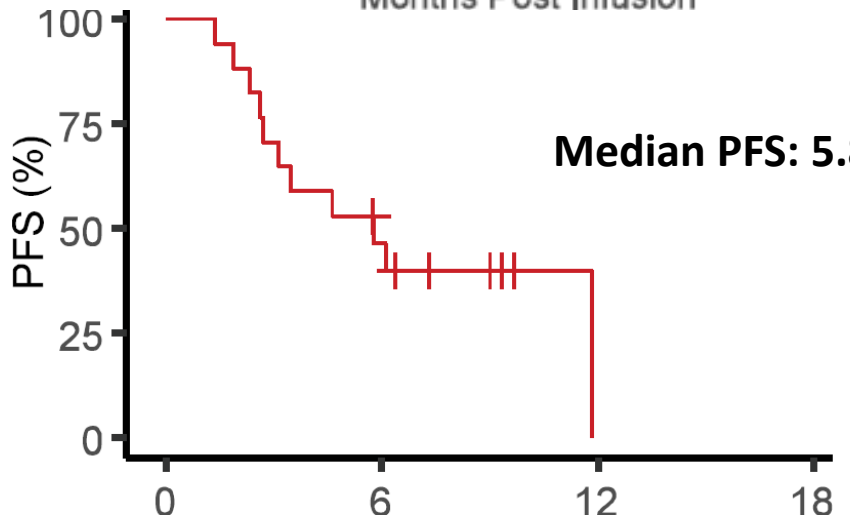
SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Clinical Outcomes

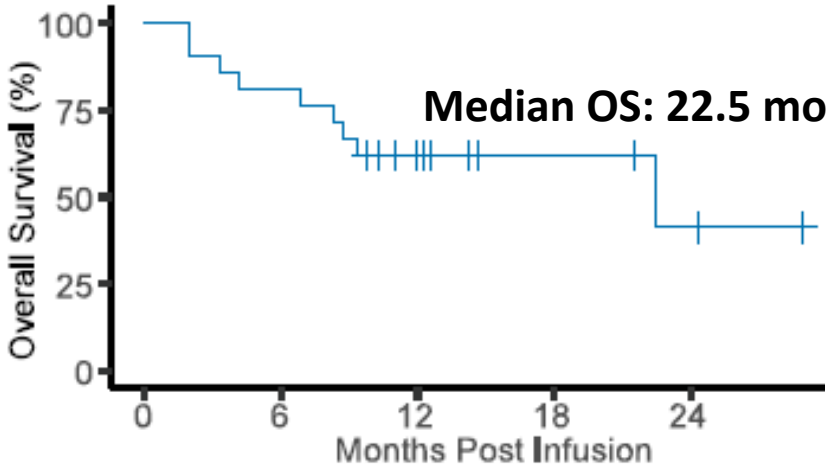
ALL : 100% ORR, 88% CR

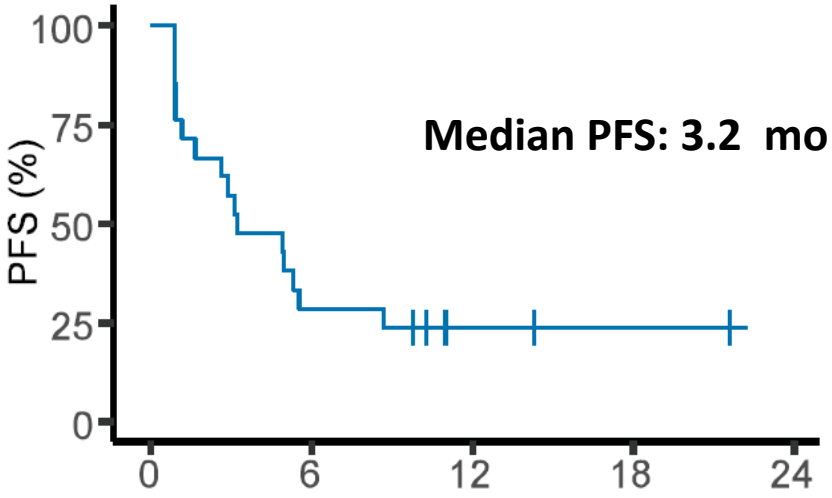




ALL n=17

Lymphoma : 62% ORR, 29% CR





LBCL n=21

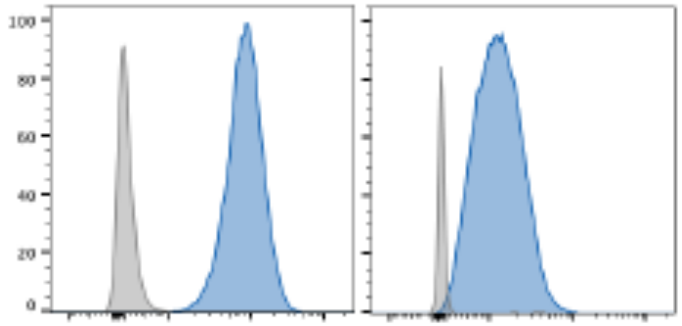
Spiegel et. al, Nature Medicine 2021

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

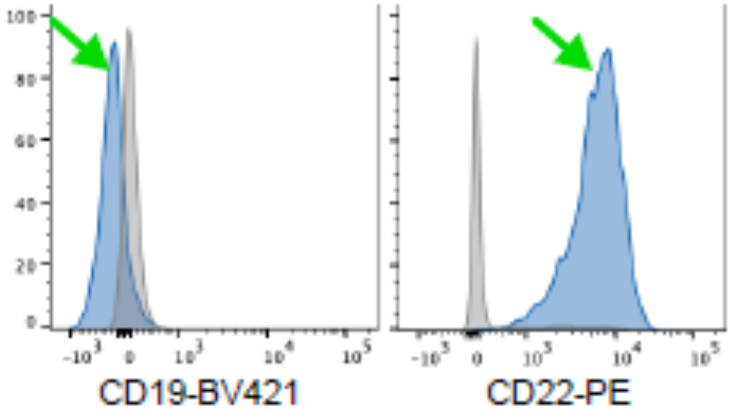
NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

CD19 Negative Relapse Occurs after Treatment with CAR19-22

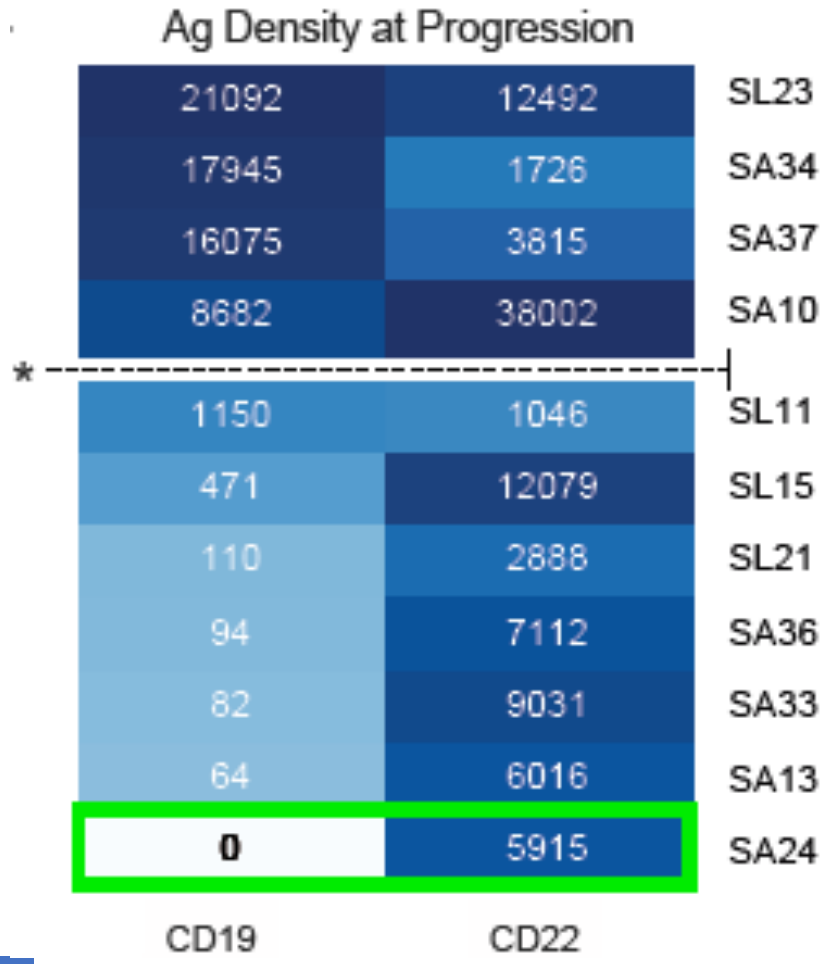
Before Therapy



Relapse after CAR19-22



CD19 expression is lost, whileCD22 expression is maintained



Relapsed Patients (n= 26)	CD19 Positive	CD19 Negative
DLBCL (n= 16)	9/14 (2 not bx)	5/14
ALL (n=10)	5/10	5/10

Spiegel, *Nat Medicine* 2021

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

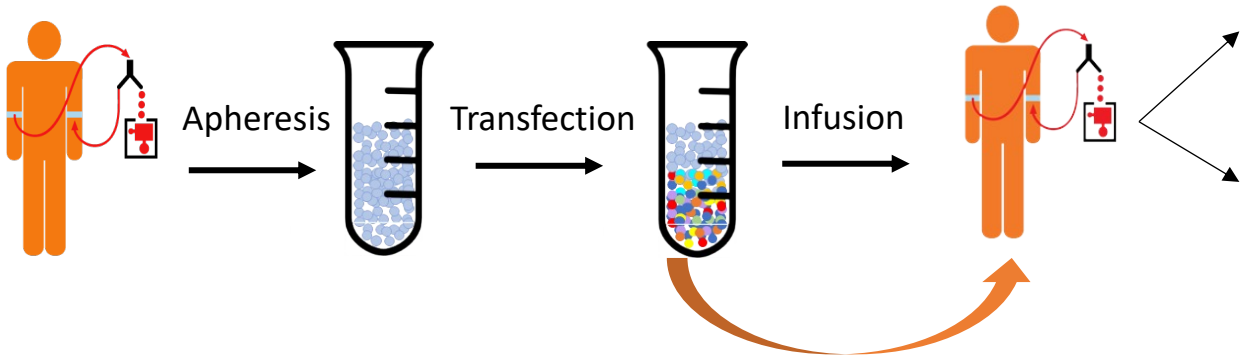
CD19-CD22 Bispecific CAR-T Summary

- Closed system manufacturing with the prodigy is feasible
- CAR19-22 had limited toxicity, one DLT grade 4 CRS and ICANS
  - Beneficial Clinical Outcomes: Overall Response: 69%
    - 20 DLBCL and 2 PMBCL: ORR: 62% → **29%CR**
    - 17 ALL patients: ORR:100% → **88% CR**
- Unfortunately, 36% DLBCL and 50% ALL subjects have relapsed CD19- CD22+, thus multi-antigen targeting will require new constructs and strategies
- Brexu-cel now the only available therapy for Adults with R/R ALL
- Stanford (Mackall, et al) manufacturing for a more balanced CD4/CD8 cell product and have reopened the trial to treat another 15-20 ALL patients

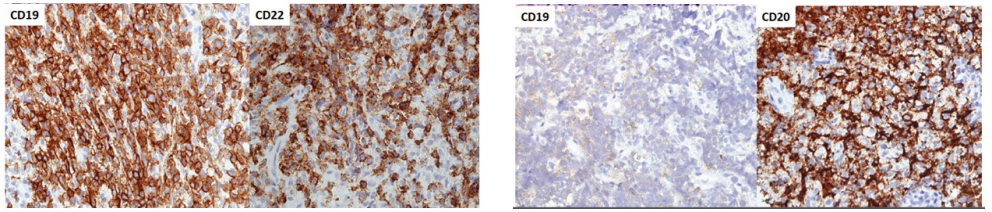
Optimizing CAR-T Therapy: Model by Spiegel and Miklos

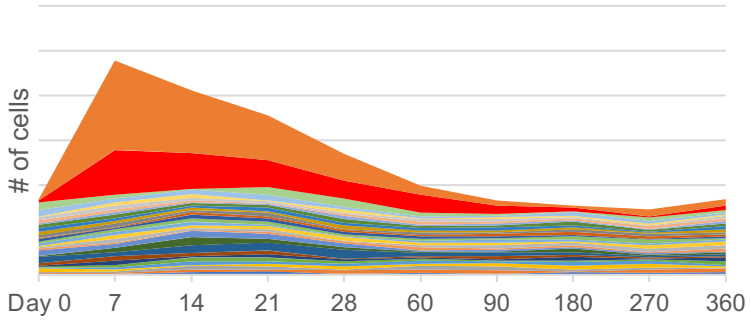
Tumor Biology:
- Tumor Antigen Density
- Tumor microenvironment

Patient **CAR-T Product**



PRE-THERAPY ***DAY 60 RELAPSE***





CAR-T Product Fitness:
- Patient T cell fitness
- CAR-T construct
- CAR-T manufacturing

CAR-T Pharmacokinetics and Pharmacodynamics
- Characterize which CAR-T localize to tumor
- Immune Phenotype of CAR-T blood expansion

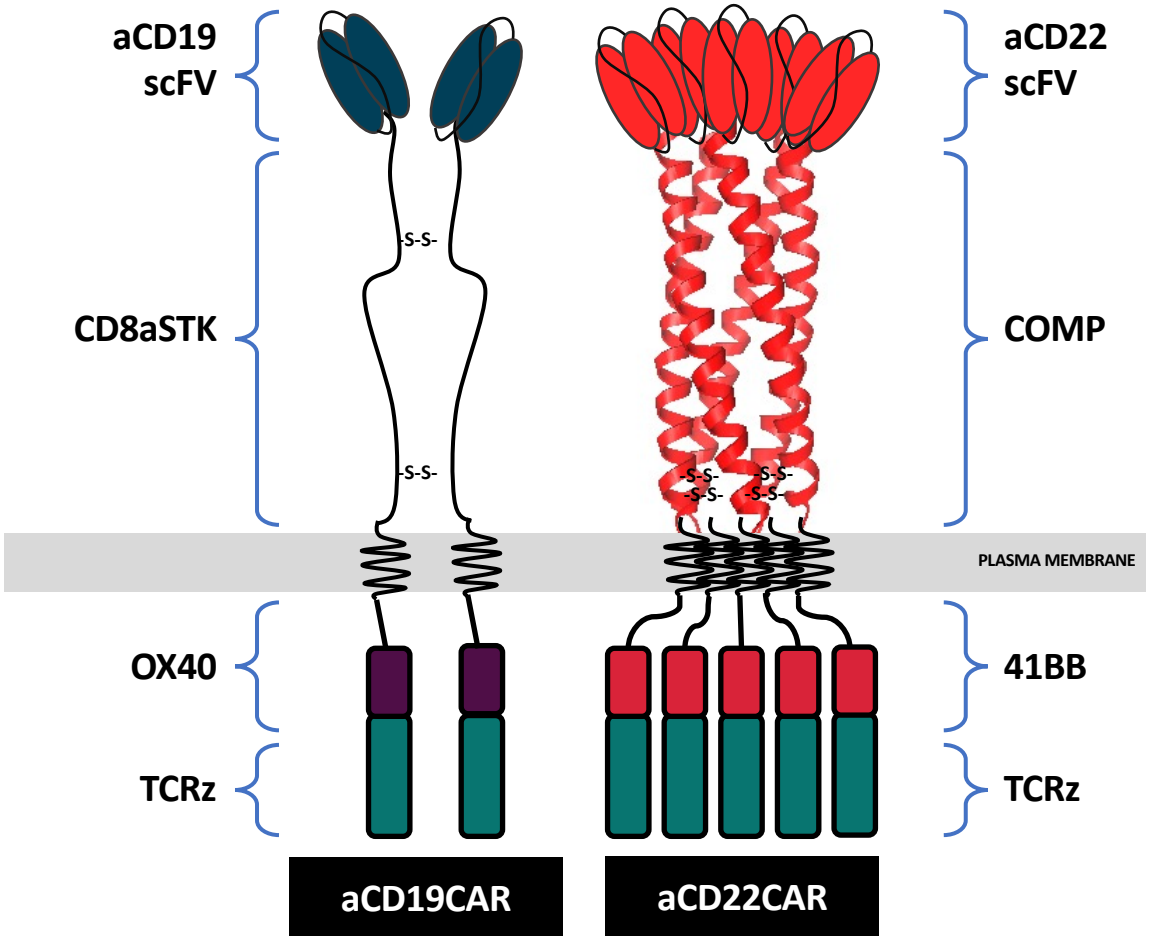
SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

AUTO3: First CD19 and CD22 Targeting Bicistronic CAR

Gamma Retroviral-Based Vector with RD114 Pseudotype

- Dual antigen targeting
- Two independent CARs delivered in single retroviral vector
- Humanized binders
- CD22 CAR with novel pentameric spacer
- OX40/41BB costimulatory domains designed to improve persistence
- Independently target CD19 and CD22



Phase 1/2 study of AUTO3, the first bicistronic chimeric antigen receptor (CAR) targeting CD19 and CD22, followed by an anti-PD1 in patients with relapsed/refractory (r/r) Diffuse Large B Cell Lymphoma (DLBCL): Results of Safety Cohorts of the ALEXANDER study

Aravind Ramakrishnan, MD , Kirit M. Ardeshna , Connie Lee Batlevi, MD, PhD , Maria A V Marzolini, Wendy Osborne, MBBS , Eleni Tholouli, MD, MRCPath , Carlos Bachier, MD, Peter A. McSweeney MD, Elizabeth Budde MD, Nancy L. Bartlett MD, Muhammad Al-Hajj, PhD, Yiyun Zhang, PhD , Simon Thomas, PhD, Martin Pule, MD , Vijay G R Peddareddigari MD, Nushmia Z Khokhar, MD , Maud Jonnaert PhD, Robert Chen, MD, and Lazaros Lekakis, MD.

	Total (N=49)	50 x 10^6 AUTO3 (N=7)	150 x 10^6 AUTO3 (N=16)	300 x 10^6 AUTO3 (N=10)	450 x 10^6 AUTO3 (N=16)
All Grades	17 (35%)	1 (14%)	4 (25%)	2 (20%)	10 (63%)
Grade 1	10 (20%)	1 (14%)	2 (13%)	2 (20%)	5 (31%)
Grade 2	6 (12%)	0	1 (6%)	0	5 (31%)
≥ Grade 3	1 (2%)	0*	1 (6%)	0	0

Low rates of CRS

Neurotoxicity (NT/ICANS)

Low rates of NT

	Total (N=49)	50 x 10^6 AUTO3 (N=7)	150 x 10^6 AUTO3 (N=16)	300 x 10^6 AUTO3 (N=10)	450 x 10^6 AUTO3 (N=16)
All Grades	3 (6%)	1 (14%)	2 (13%)	0	0
≥ Grade 3	2 (4%)	1 (14%)	1 (6%)	0	0

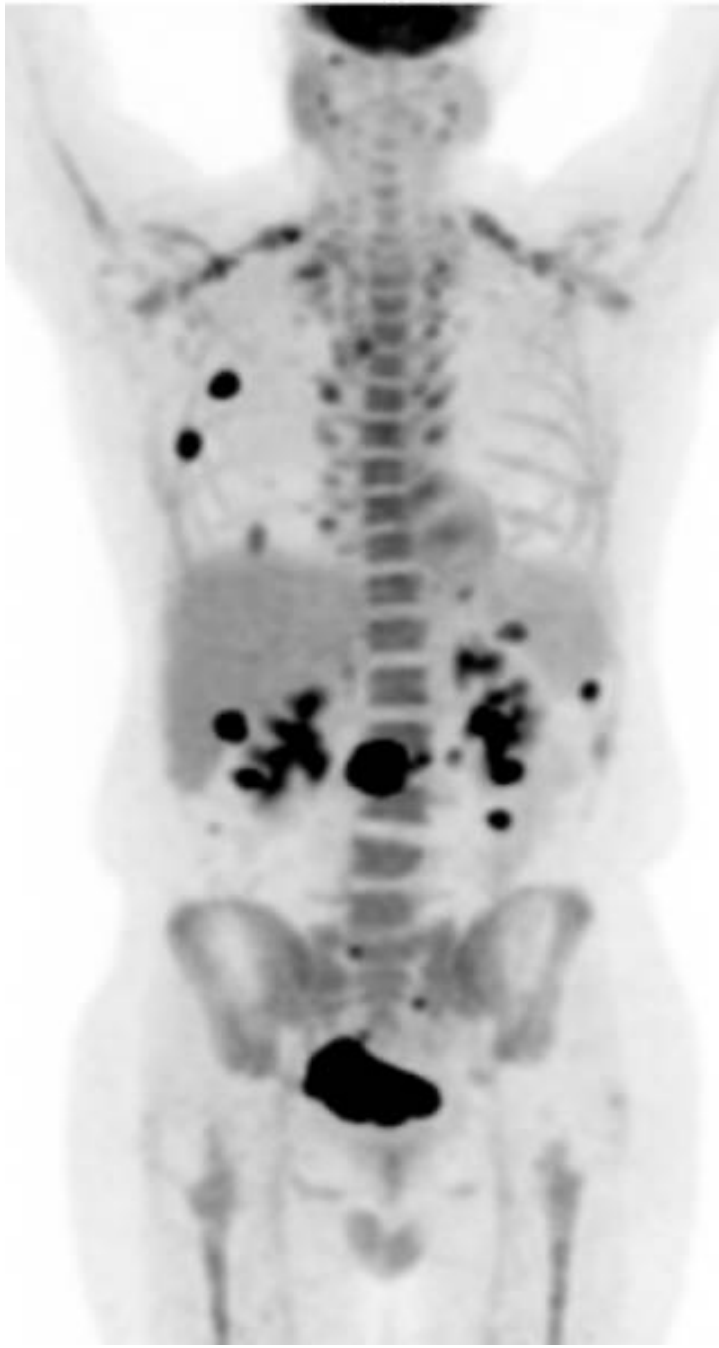
RESPONSES

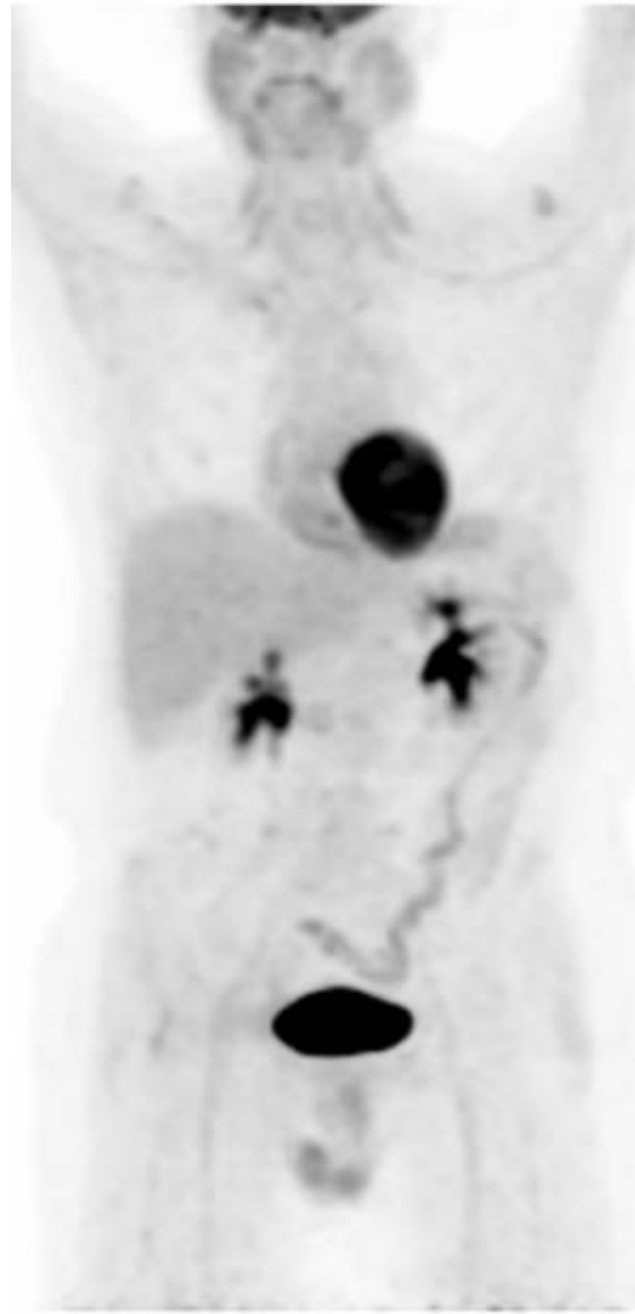
	Total (N=49)	50 x 10^6 AUTO3 (N=7)	150 x 10^6 AUTO3 (N=16)	300 x 10^6 AUTO3 (N=10)	450 x 10^6 AUTO3 (N=16)
N Evaluable*	43	6	13	9	15
ORR	28 (65%)	4 (67%)	4 (31%)	7 (78%)	13 (87%)
CR	22 (51%)	2 (33%)	4 (31%)	5 (56%)	11 (73%)
PR	6 (14%)	2 (33%)	0	2 (22%)	2 (13%)

First-in-Human Data of ALLO-501A, an Allogeneic Chimeric Antigen Receptor (CAR) T Cell Therapy and ALLO-647 in Relapsed/Refractory Large B Cell Lymphoma (R/R LBCL): ALPHA2 Study.

Frederick Lundry Locke, Shahbaz Malik, Michael Timothy Tees, Sattva Swarup Neelapu, Leslie Popplewell, Jeremy S. Abramson, Jennifer T. McDevitt, Chu Ri Shin, Eren Demirhan, Cyril Konto, Lazaros J. Lekakis, H. Lee Moffitt Cancer Center &

- Off the shelf allogeneic CAR-T
- TCR is KO to avoid GVHD.
- CD52 is also KO and anti-CD52 Ab is added to Flu-CTX to avoid rejection.
- Still suboptimal expansion
- Viral reactivations: letermovir to prevent CMV





Primary Analysis of ZUMA-7: a Phase 3 Randomized Trial of Axicabtagene Ciloleucel Versus Standard-of-Care Therapy in Patients With Relapsed/Refractory Large B-Cell Lymphoma

Frederick L. Locke, MD[1]; David B. Miklos, MD, PhD[2]; Caron A. Jacobson, MD, MMSc[3]; Miguel-Angel Perales, MD[4]; Marie José Kersten MD, PhD[5]; Olalekan O. Oluwole, MBBS, MPH[6]; Armin Ghobadi, MD[7]; Aaron P. Rapoport, MD[8]; Joseph P. McGuirk, DO[9]; John M. Pagel, MD, PhD[10]; Javier Muñoz, MD, MS, MBA, FACP[11]; Umar Farooq, MD[12]; Tom van Meerten, MD, PhD[13]; Patrick M. Reagan, MD[14]; Anna Sureda, MD, PhD[15]; Ian W. Flinn, MD, PhD[16]; Peter Vandenberghe, MD, PhD[17]; Kevin W. Song, MD, FRCPC[18]; Michael Dickinson, MBBS, D Med Sci, FRACP, FRCPA[19]; Monique C. Minnema, MD, PhD[20]; Peter A. Riedell, MD[21]; Lori A. Leslie, MD[22]; Sridhar Chaganti, MD[23]; Yin Yang, MS, MD[24]; Simone Filosto, PhD[24]; Marco Schupp, MD[24]; Christina To, MD[24]; Paul Cheng, MD, PhD[24]; Leo I. Gordon, MD[25]; and Jason R. Westin, MD, MS, FACP[26], on behalf of all ZUMA-7 investigators and contributing Kite members

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Stanford University School of Medicine, Stanford, CA, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [5]Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, on behalf of HOVON/LLPC; [6]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [7]Washington University School of Medicine, St Louis, MO, USA; [8]The Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA; [9]University of Kansas Cancer Center, Kansas City, KS, USA; [10]Swedish Cancer Institute, Seattle, WA, USA; [11]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [12]University of Iowa, Iowa City, IA, USA; [13]University Medical Center Groningen, Groningen, Netherlands; [14]University of Rochester School of Medicine, Rochester, NY, USA; [15]Hematology Department, Institut Català d'Oncologia-Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, S… Institute and Tennessee Oncology, Nashville, TN, USA; [17]University Hospitals Leuven, Leuven, Belgium; [18]Division of Hematology, University of British Columbia and Leukemia/BMT… Hospital, Vancouver, BC, Canada; [19]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Victoria, Australia; [20]UMC, Univers… behalf of HOVON/LLPC; [21]The University of Chicago Medical Center, Chicago, IL, USA; [22]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; … University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [24]Kite, a Gilead Company, Santa Monica, CA, USA; [25]Northwestern… Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; and [26]The University of Texas MD An… Center, Houston, TX, USA

Fred Locke, et al

LBA#6

Michael R. Bishop, MD
mbishop@medicine.bsd.uchicago.edu

Tisagenlecleucel vs Standard of Care as Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III BELINDA Study

Michael R. Bishop,[1] Michael … Duncan Purtill[3], Pere Barba[4], Armando Santoro[5], Nada Hamad[6], Koji Kato[7], Anna Sureda[8], Richard Greil[9], Catherine Thieblemont[10], … Martin Janz[12], Ian Flinn[13], Werner Rabitsch[14], Yok Lam Kwong[15], Marie José Kersten[16], Monique C. Minnema[17], … Esther Hian Li Chan[19], Joaquin Martinez-Lopez[20], Antonia M.S. Mueller[21], Richard T. Maziarz[22], Joseph P. … Emmanuel … Le Gouill[25,#], Martin Dreyling[26], Hideo Harigae[27], David Bond[28], Charalambos Andreadis[29], Peter Mc… Mohamed Kha…[30], Simon Newsome[31], Evgeny Degtyarev[31], Christopher del Corral[32], Giovanna Andreola[33], Aisha Mas… Stephen J. Schuster[34], … eger[34], Peter Borchmann[35,*], Jason R. Westin[36,*]

[1]The … Jonas Center for Cellular … sity of Chicago, Chicago, IL, USA; [2]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia; [3]Fiona Stanley Hosp… h, WA, Australia; [4]Hospital U… Hebron and Universitat Autonoma de Barcelona, Barcelona, Spain; [5]Department of Biomedical Sciences, Humanitas University and IRCCS Hum… search Hospital-Humanitas Cance… Italy; [6]Department of Haematology, St Vincent's Hospital Sydney, Australia and St Vincent's Clinical School, Sydney, University of New South Wa… e, [7]Hematology, Oncology, and C… Medicine, Kyushu University Hospital, Fukuoka, Japan; [8]Clinical Hematology Department, Institut Català d'Oncologia – Hospitalet de Llobregat, Ba… pain; [9]Third Medical Department, Pa… al University; Salzburg Cancer Research Institute-CCCIT and Cancer Cluster Salzburg, Salzburg, Austria; [10]APHP, Hemato-Oncology, Hôpital S… Paris, France; [11]Centre Hospitalier R… taire de Lille, Lille, France; [12]Hematology, Oncology and Tumorimmunology, Charité, University Hospital Berlin, Campus Benjamin Franklin, …many; [13]Sarah Cannon Research Insti… e Oncology, Nashville, TN, USA; [14]Internal Medicine I, BMT-Unit, Vienna General Hospital-Medical University of Vienna, Vienna, Austria; …ment of M… Queen Mary Hospital, … ong, China; [16]Department of Oncology, Oslo University Hospital, Oslo, Norway and KG Jebsen Center for B-cell Malignancies, Oslo, Norway; …al U… Institute Singapore, Singapore; [18]Hematology Department, Hospital 12 De Octubre, Complutense University, i+12, CNIO, Madrid, Spain; [19]Department of Medical Oncology and …ital, Zurich, Switzerland; [20]Center for Hematologic Malignancies, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [21]Division of Hematologic …therapeutics, The University of Kansas Cancer Center, Westwood, KS, USA; [22]Hospices Civils de Lyon and Université Claude Bernard Lyon 1, Lyon, France; [23]CRCINA, INSERM …, Nantes, France; [24]Medizinische Klinik III, LMU Klinikum, Munich, Germany; [25]Tohoku University Hospital, Sendai, Japan; [26]The Ohio State University, Columbus, OH, USA; …ensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [28]Division of Hematology-Oncology and Blood and Marrow Transplantation and Cellular …yo Clinic, Jacksonville, FL, USA; [30]Novartis Pharma AG, Basel, Switzerland; [31]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [32]Lymphoma Program, Abramson Cancer …ty of Pennsylvania, Philadelphia, PA, USA; [34]Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Vienna General Hospital – Medical University of Vienna, Vienna, …-Clinic I for Internal Medicine, University Hospital Cologne, Cologne, Germany; [36]Department of Lymphoma & Myeloma, M.D. Anderson Cancer Center, Houston, TX, USA; *Dr. Borchmann and Dr. …restin are co-senior authors. #At the time of the present work, now affiliated with Institut Curie, Paris, France

Scan to obtain

https://bit.ly/BishopMR123

Copies of this presentation obtained through Quick Response (QR) code are for personal use only and may not be reproduced without permission of the authors.

Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021; Georgia World Congress Center – Atlanta, GA

Michael Bishop, et al

ASH 2021

Lisocabtagene Maraleucel, a CD19-Directed Chimeric Antigen Receptor T Cell Therapy, Versus Standard of Care with Salvage Chemotherapy Followed by Autologous Stem Cell Transplantation as Second-Line Treatment in Patients with Relapsed or Refractory Large B-Cell Lymphoma: Results from the Randomized Phase 3 TRANSFORM Study

Manali Kamdar,[1] Scott R. Solomon,[2] Jon Arnason,[3] Patrick B. Johnston,[4] Bertram Glass,[5] Veronika Bachanova,[6] Sami Ibrahimi,[7] Stephan Mielke,[8] Pim Mutsaers,[9] Francisco Hernandez-Ilizaliturri,[10] Koji Izutsu,[11] Franck Morschhauser,[12] Matthew Lunning,[13] David G. Maloney,[14] Alessandro Crotta,[15] Sandrine Montheard,[15] Alessandro Previtali,[15] Lara Stepan,[16] Ken Ogasawara,[16] Timothy Mack,[16] Jeremy S. Abramson[17]

[1]University of Colorado Cancer Center, Aurora, CO, USA; [2]Northside Hospital Cancer Institute, Atlanta, GA, USA; [3]Beth Israel Deaconess Medical Center, Boston, MA, USA; [4]Mayo Clinic, Rochester, MN, USA; [5]Helios Klinikum Berlin-Buch, Berlin, Germany; [6]University of Minnesota, Minneapolis, MN, USA; [7]University of Oklahoma Stephenson Cancer Center, Oklahoma City, OK, USA; [8]Center of Allogeneic Stem Cell Transplantation and Cellular Therapy (CAST), Karolinska Institutet and University Hospital, Stockholm, Sweden; [9]Erasmus University Medical Center, Rotterdam, The Netherlands, on behalf of HOVON/LLPC; [10]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [11]National Cancer Center Hospital, Tokyo, Japan; [12]Université de Lille, Centre Hospitalier Universitaire de Lille. ULR 7365, GRITA – Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France; [13]University of Nebraska Medical Center, Omaha, NE, USA; [14]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [15]Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]Massachusetts General Hospital Cancer Center, Boston, MA, USA

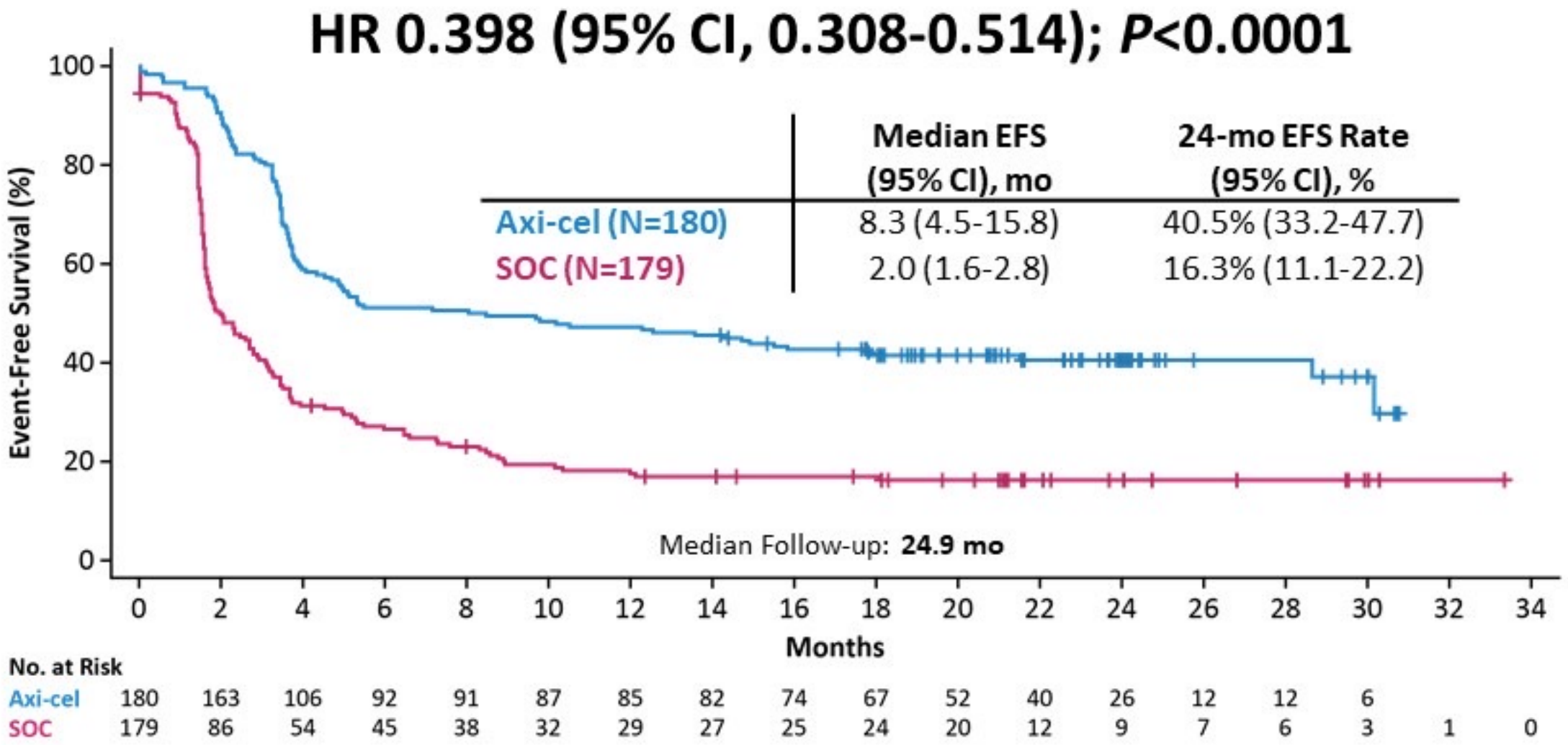
Manali Kamdar, et al

@DrMiguelPerales

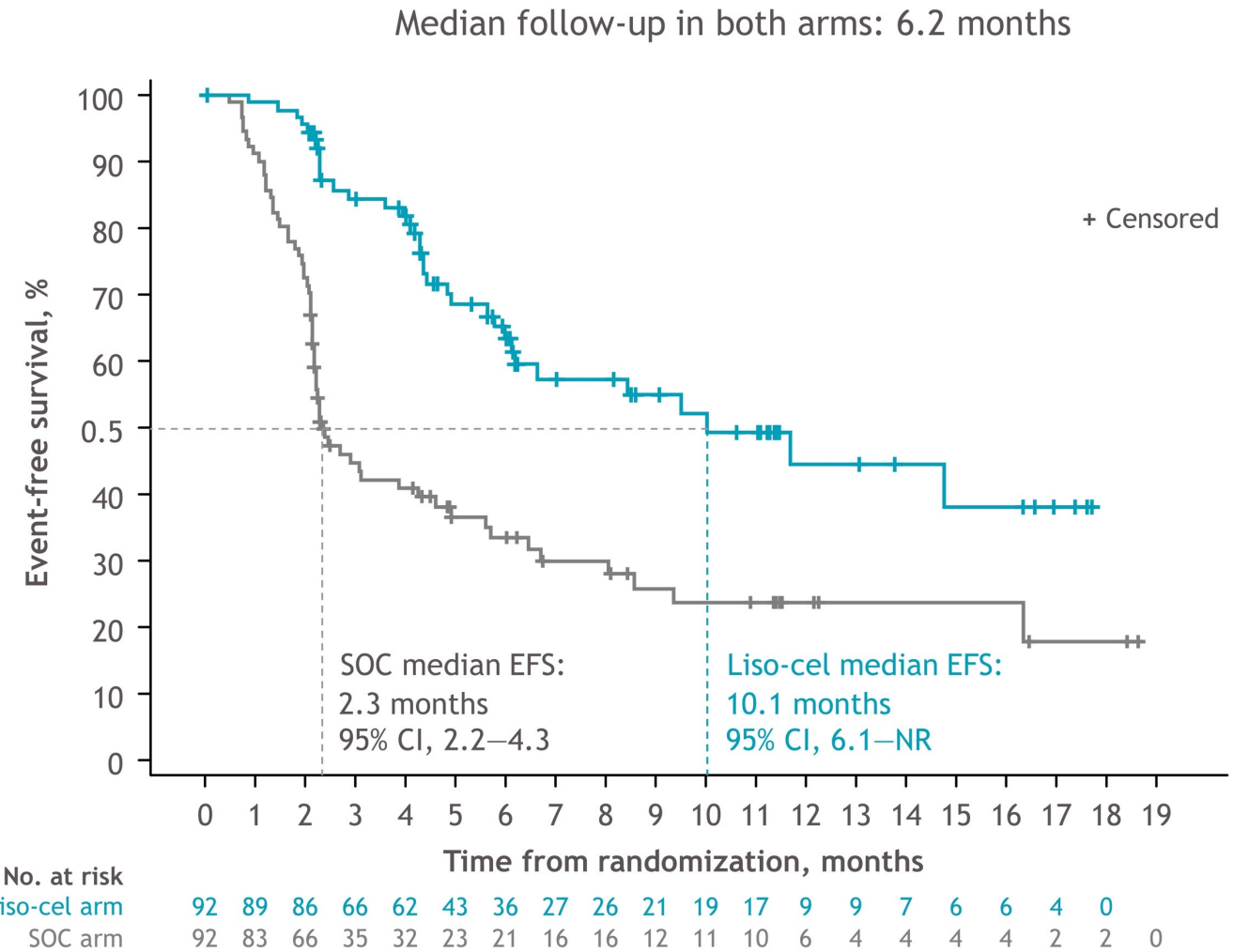
ASH 2021, Presentation Number 91

Primary EFS Endpoint: Axi-cel is Superior to SOC

ZUMA-7



TRANSFORM: Event-free survival per IRC (ITT set; primary endpoint)



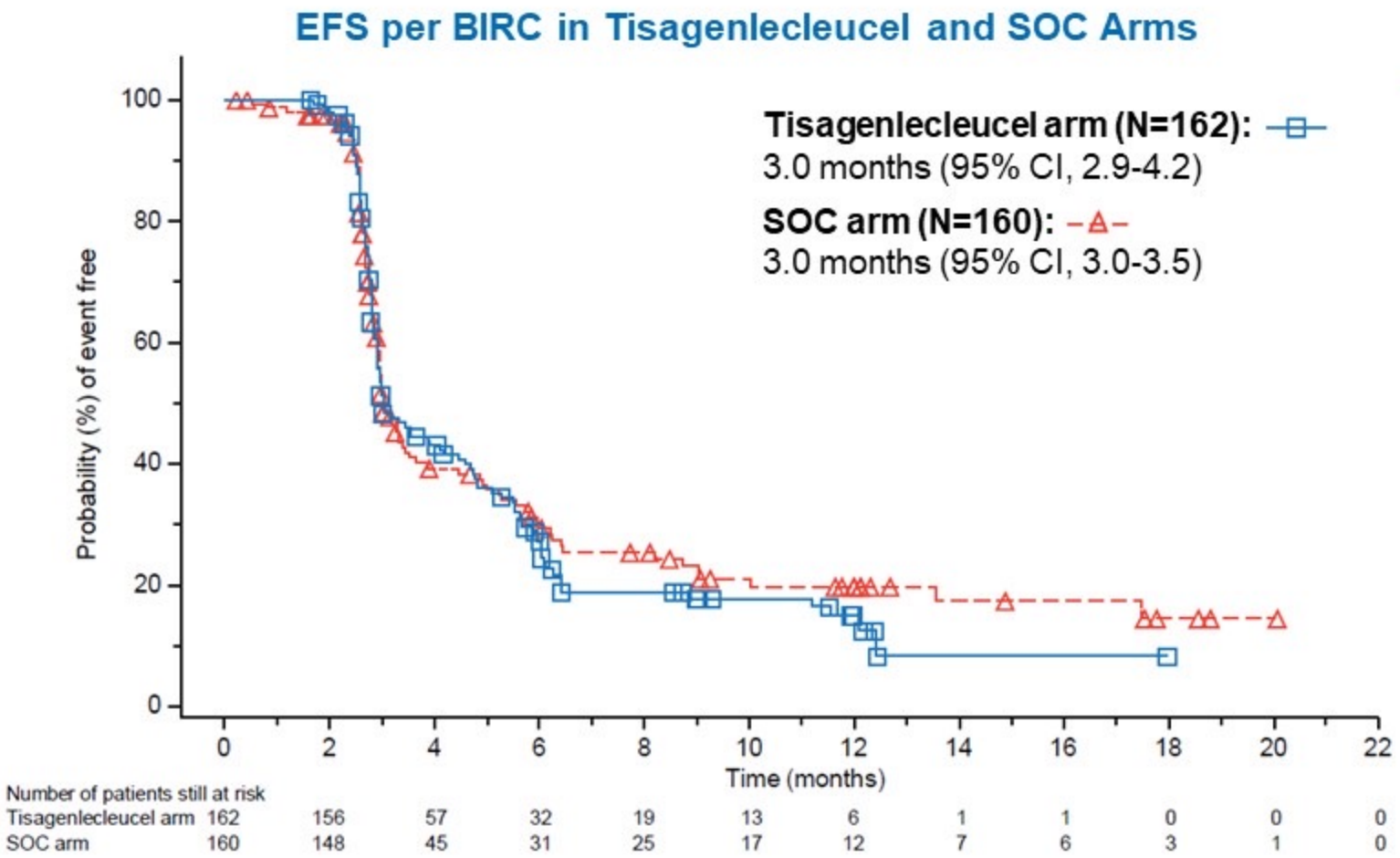
	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	**0.349** (0.229—0.530) *P* < 0.0001	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0—74.7	23.0—43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4—59.6	13.4—34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.
CI, confidence interval; HR, hazard ratio; NR, not reached; SE, standard error.

Kamdar M, et al. ASH 2021 [Abstract #91]

No Difference in EFS Between Treatment Arms



- EFS[a] was not significantly different between treatment arms
  - Primary analysis: Stratified unadjusted HR: 1.07 (95% CI, 0.82-1.40, p[b]=0.69)
  - Supportive analysis: Stratified adjusted[c] HR: 0.95 (95% CI, 0.72-1.25)
  - 6 patients responded to tisagenlecleucel infusion, but were captured as an EFS event due to SD/PD before or soon after infusion[d]

[a]EFS events defined as PD/SD after day 71 or death at any time. [b]p-value derived from 1-sided stratified log-rank test. [c]Adjusted for for potential imbalances in patient characteristics with pre-specified covariates of age, sex, race, ECOG performance status, histological subgroup, disease stage, and disease subtype. [d]Stratified adjusted HR accounting for delayed responses in both arms yield HR of 0.84 (95% CI: 0.63, 1.12).

BIRC, blinded independent review committee; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; PD, progressive disease; SD, stable disease; SOC, standard of care.

Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021; Georgia World Congress Center - Atlanta, GA

TRIAL	ZUMA-7		BELINDA		TRANSFORM	
	Axi-Cel	SOC	Tisa-Cel	SOC	Liso-Cel	SOC
	N=180	N=179	N=162	N=160	N=92	N=92
Patient disposition						
CAR T infusion (%)	94	N/A	96	N/A	98	N/A
Bridging (%)	65[b]	N/A	83	N/A	68	N/A
Median days to infusion	13	N/A	52	N/A	NR	N/A
ASCT (%)	N/A	36	N/A	33	N/A	47
Crossover to CAR T (%)	N/A	56	N/A	51	N/A	55
Efficacy						
Median follow-up (months)	25	25	10	10	6	6
ORR (%)	83	50	46	43	86	48
CR (%)	65	32	28	28	66	39
EFS median (months)	8.3	2	3	3	10.1	2.3
PFS median (months)	14.7	3.7	NR	NR	14.8	5.7
OS median (months)	Not reached	35.1	NR	NR	Not reached	16.4

ZUMA-7 only allowed corticosteroids for bridging.

Locke et al, Bishop et al, Kamdar et al, ASH 2021
Locke et al, NEJM 2022; Bishop et al, NEJM 2022

Varying definitions of EFS in 2nd line CAR-T trials

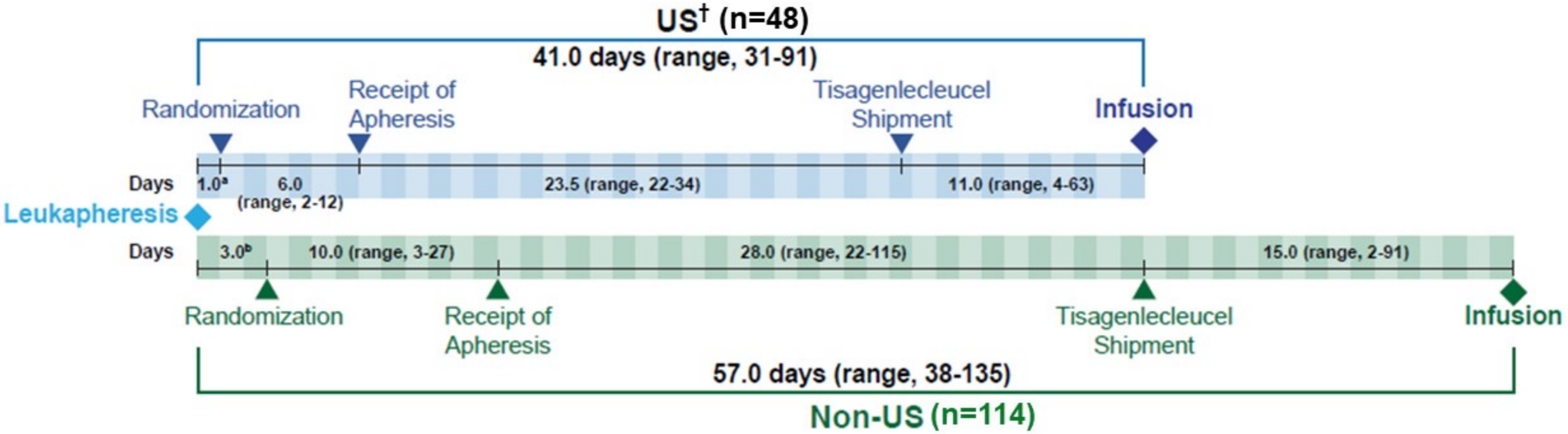
- **ZUMA-7**: time from randomization to the earliest date of disease progression, commencement of new therapy for lymphoma, death from any cause, or a best response of stable disease up to and including the response on the day 150 assessment.

- **BELINDA**: time from randomization to stable or progressive disease at or after the week 12 assessment.

- **TRANSFORM**: time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post randomization, or start of new antineoplastic therapy, whichever occurs first.

Time to Tisagenlecleucel Infusion

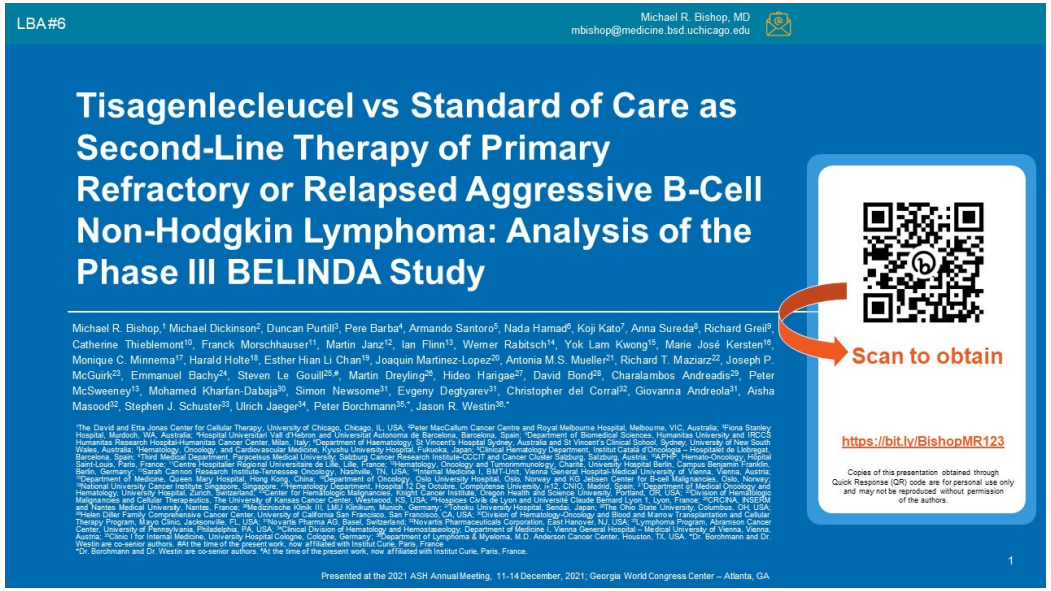
- Median time to infusion for all patients on the Tisagenlecleucel arm was 52 days (range, 31-135)



†North America was a stratification factor, and all enrolled patients in this group were from the United States (US).
[a]range, 1-6 days. [b]range, 1-17 days

Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021; Georgia World Congress Center - Atlanta, GA

Potential explanations for BELINDA Outcomes


LBA#6

Michael R. Bishop, MD
mbishop@medicine.bsd.uchicago.edu

Tisagenlecleucel vs Standard of Care as Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III BELINDA Study

Michael R. Bishop,[1] Michael Dickinson[2], Duncan Purtill[3], Pere Barba[4], Armando Santoro[5], Nada Hamad[6], Koji Kato[7], Anna Sureda[8], Richard Greil[9], Catherine Thieblemont[10], Franck Morschhauser[11], Martin Janz[12], Ian Flinn[13], Werner Rabitsch[14], Yok Lam Kwong[15], Marie José Kersten[16], Monique C. Minnema[17], Harald Holte[18], Esther Hian Li Chan[19], Joaquin Martinez-Lopez[20], Antonia M.S. Mueller[21], Richard T. Maziarz[22], Joseph P. McGuirk[23], Emmanuel Bachy[24], Steven Le Gouill[25,#], Martin Dreyling[26], Hideo Harigae[27], David Bond[28], Charalambos Andreadis[29], Peter McSweeney[13], Mohamed Kharfan-Dabaja[30], Simon Newsome[31], Evgeny Degtyarev[31], Christopher del Corral[32], Giovanna Andreola[31], Aisha Masood[32], Stephen J. Schuster[33], Ulrich Jaeger[34], Peter Borchmann[35,*], Jason R. Westin[36,*]

[1]The David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, IL, USA; [2]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia; [3]Fiona Stanley Hospital, Murdoch, WA, Australia; [4]Hospital Universitari Vall d'Hebron and Universitat Autonoma de Barcelona, Barcelona, Spain; [5]Department of Biomedical Sciences, Humanitas University and IRCCS Humanitas Research Hospital-Humanitas Cancer Center, Milan, Italy; [6]Department of Haematology, St Vincent's Hospital Sydney, Australia and St Vincent's Clinical School, Sydney, University of New South Wales, Australia; [7]Hematology, Oncology, and Cardiovascular Medicine, Kyushu University Hospital, Fukuoka, Japan; [8]Clinical Hematology Department, Institut Català d'Oncologia – Hospitalet de Llobregat, Barcelona, Spain; [9]Third Medical Department, Paracelsus Medical University, Salzburg Cancer Research Institute-CCCIT and Cancer Cluster Salzburg, Salzburg, Austria; [10]APHP, Hemato-Oncology, Hôpital Saint-Louis, Paris, France; [11]Centre Hospitalier Régional Universitaire de Lille, Lille, France; [12]Hematology, Oncology and Tumorimmunology, Charité, University Hospital Berlin, Campus Benjamin Franklin, Berlin, Germany; [13]Sarah Cannon Research Institute-Tennessee Oncology, Nashville, TN, USA; [14]Internal Medicine I, BMT-Unit, Vienna General Hospital-Medical University of Vienna, Vienna, Austria; [15]Department of Medicine, Queen Mary Hospital, Hong Kong, China; [16]Department of Oncology, Oslo University Hospital, Oslo, Norway and KG Jebsen Center for B-cell Malignancies, Oslo, Norway; [17]National University Cancer Institute Singapore, Singapore; [18]Hematology Department, Hospital 12 De Octubre, Complutense University, n12, CNIO, Madrid, Spain; [19]Department of Medical Oncology and Hematology, University Hospital, Zurich, Switzerland; [20]Center for Hematologic Malignancies, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [21]Division of Hematologic Malignancies and Cellular Therapeutics, The University of Kansas Cancer Center, Westwood, KS, USA; [22]Hospices Civils de Lyon and Université Claude Bernard Lyon 1, Lyon, France; [23]CRCINA, INSERM and Nantes Medical University, Nantes, France; [24]Medizinische Klinik III, LMU Klinikum, Munich, Germany; [25]Tohoku University Hospital, Sendai, Japan; [26]The Ohio State University, Columbus, OH, USA; [27]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [28]Division of Hematology-Oncology and Blood and Marrow Transplantation and Cellular Therapy Program, Mayo Clinic, Jacksonville, FL, USA; [29]Novartis Pharma AG, Basel, Switzerland; [30]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [31]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [32]Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Vienna General Hospital – Medical University of Vienna, Vienna, Austria; [33]Clinic I for Internal Medicine, University Hospital Cologne, Cologne, Germany; [34]Department of Lymphoma & Myeloma, M.D. Anderson Cancer Center, Houston, TX, USA. *Dr. Borchmann and Dr. Westin are co-senior authors. #At the time of the present work, now affiliated with Institut Curie, Paris, France

Scan to obtain

https://bit.ly/BishopMR123

Copies of this presentation obtained through Quick Response (QR) code are for personal use only and may not be reproduced without permission of the authors.

Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021; Georgia World Congress Center – Atlanta, GA

1

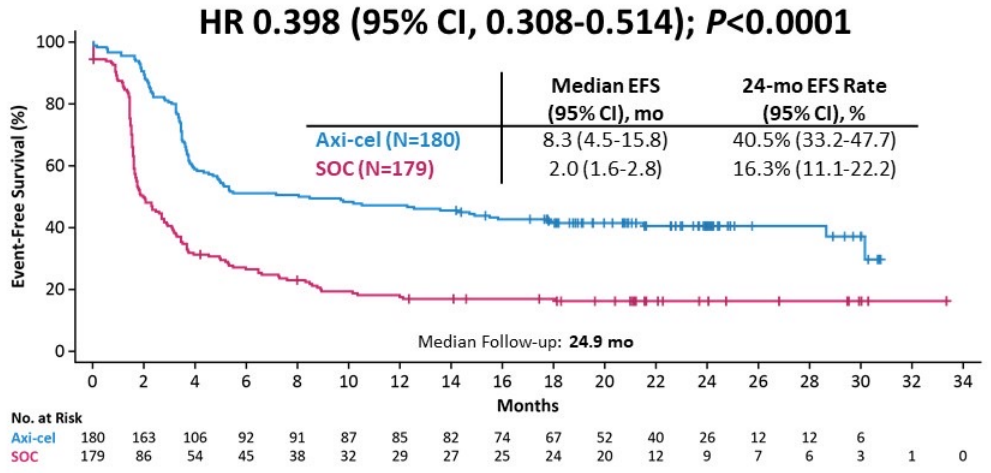
- Design:
  - EFS definition
  - SOC allowed 2 lines of salvage
- Patient factors?
- Product:
  - Manufacturing time
  - Lower ORR/CR

@DrMiguelPerales

ZUMA-7

EFS vs. OS as a primary endpoint for 2nd line CAR-T Trials

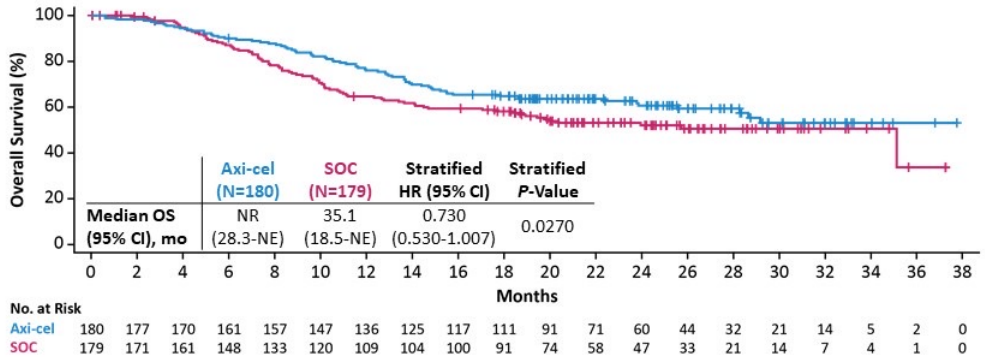
Primary EFS Endpoint: Axi-cel is Superior to SOC



7 Locke et al ASH 2021 Plenary Presentation

VS

Median OS, Evaluated as an Interim Analysis, Was Not Reached for Axi-cel Versus 35.1 Months for SOC



- 56% of SOC patients received subsequent cellular immunotherapy (off protocol)
- Preplanned sensitivity analysis[a] suggests an OS benefit, likely confounded by SOC treatment switching

[a] Analysis utilized the validated and commonly used Rank Preserving Structural Failure Time model, which preserves randomization as described by Robins and Tsiatis (*Commun Stat Theory Methods.* 1991;2609-2631), and revealed the difference in treatment effect if SOC patients did not receive subsequent cellular immunotherapy. Stratified hazard ratio was 0.580 (95% CI, 0.416-0.809).

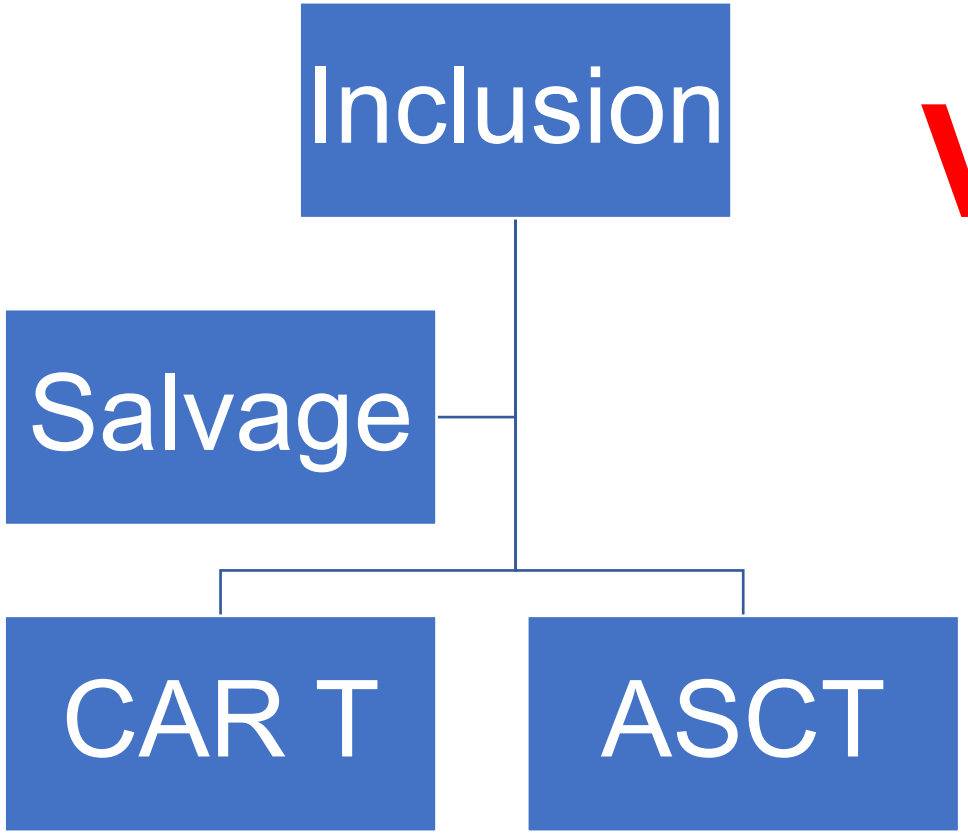
12 Locke et al ASH 2021 Plenary Presentation

@DrMiguelPerales

Locke et al, ASH 2021; Locke et al, NEJM 2022

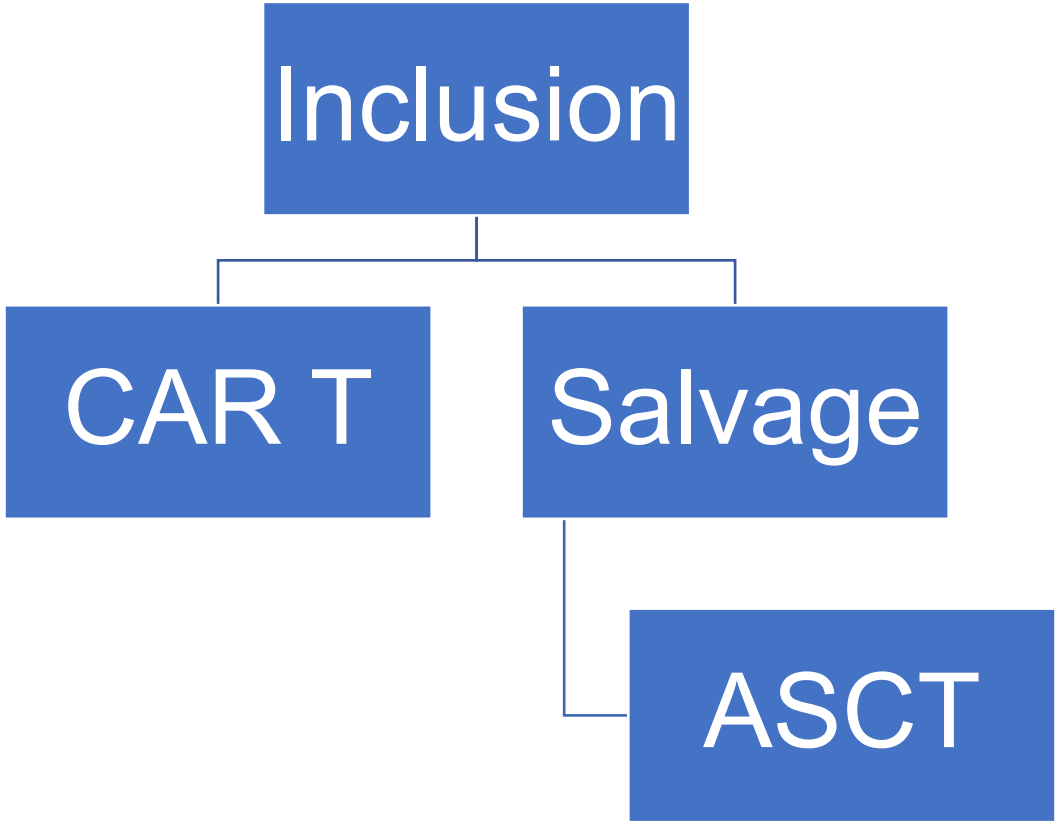
Which is the better study design?

CAR T vs. ASCT



VS

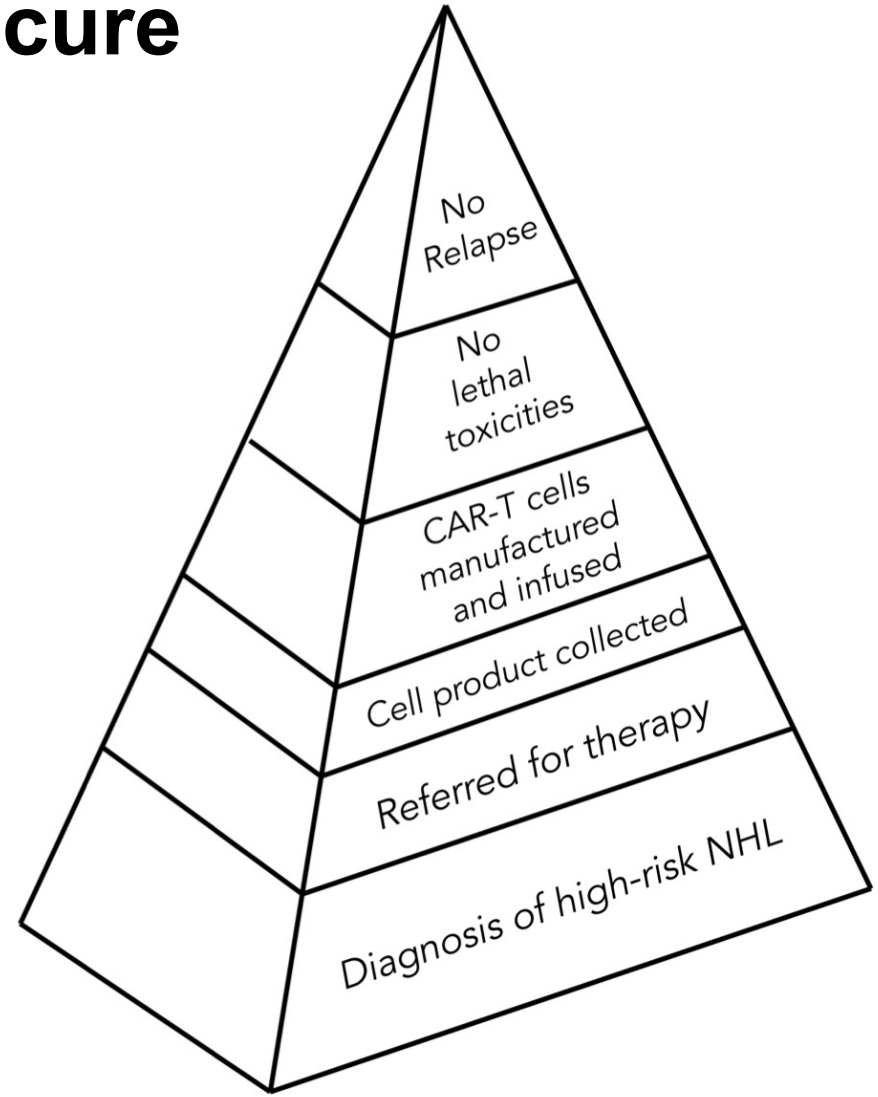
CAR T vs. Salvage CIT



Are CAR-T therapies reaching enough patients?

- Short answer is (for most)….NO!
- Estimate of DLBCL cases in the US is approximately 25K/year
- Probably 10K patients eligible per FDA label (~5K relapsed, 5K refractory)
- *Probably <2500 patients per year treated* ***<25% of patients who qualify***
- Likely similar underutilization rates to what we already see for both autologous and allogeneic transplantation

From diagnosis to cure



Komanduri, *J Clinical Oncology, 2021*

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Where is CAR-T therapy for lymphoma in 2022?

- CAR-T therapies have truly shifted our treatment paradigm with unprecedented success in relapsed and refractory CD19+ lymphoma/leukemia
- *However…*treatments are associated with significant relapse rates, non-relapse mortality and cost
- Two of three 2nd line trials for high-risk are positive, but ASCT may still have benefit for those with chemosensitive relapse
- Dual targeting in lymphoma (eg., CD19/22) is theoretically promising but still unproven
- Bispecific antibody and other non-cellular technologies continue to improve
- With high costs (both for products and for care) access is limited even in the United States *a key challenge will be finding ways to sustainably provide access and develop new therapies*

Acknowledgments

•Antonio Jimenez (Sylvester)
•Jay Spiegel (Sylvester)
•Lazaros Lekakis (Sylvester)
•Miguel Perales (MSKCC)

•Physicians, staff and patients of the Sylvester Comprehensive Cancer Center