HEMATOPOIETIC STEM CELL TRANSPLANTATION IN 2024: WHAT EVERY HEMATOLOGIST NEEDS TO KNOW

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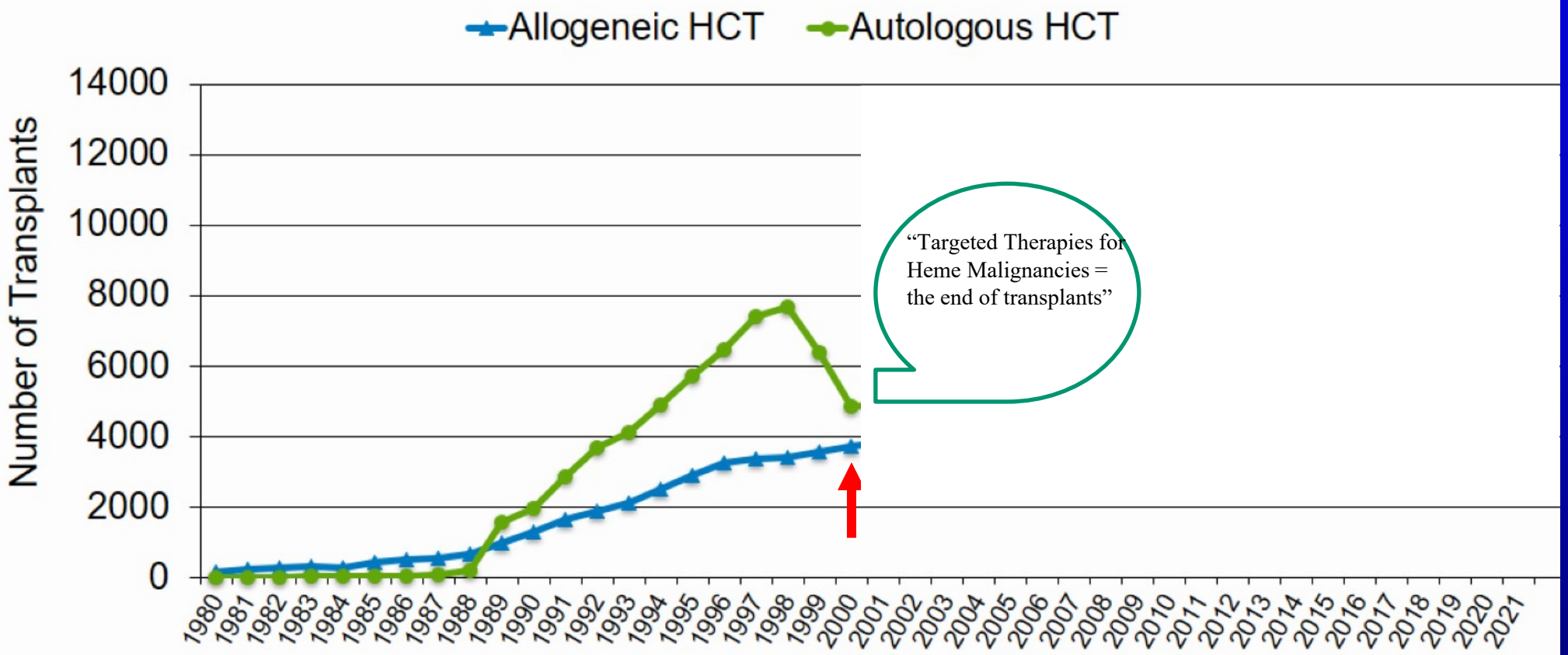
Learning Objectives

- To Update the Field of Allogeneic Transplants in 2024
  - Improvements in transplant outcomes
  - Improvements in managing Complications
    - CMV- prevention and treatment
    - GVHD- prevention and treatment
  - Better Understanding of Who Benefits from RIC vs Myeloablative Conditioning
  - Importance of pretransplant MRD status
- Alternative Donor Transplants
  - Trends for utilization and outcomes
- CRISPR Editing donor CD34+ stem cells to prevent AML relapse
- New treatment for cGVHD

GVHD= Graft vs host disease

Number of 1st HCTs reported to CIBMTR in the U.S.



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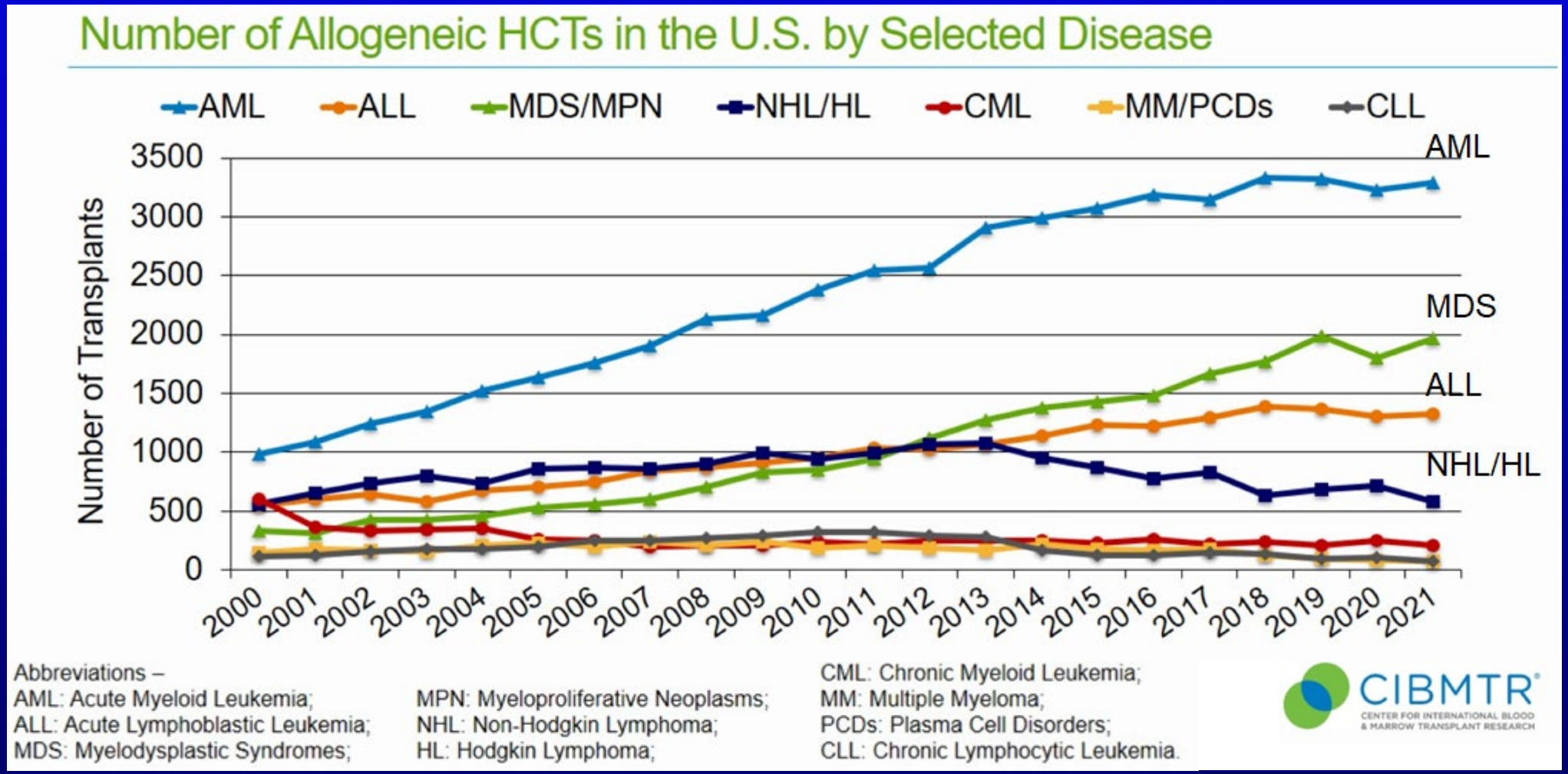
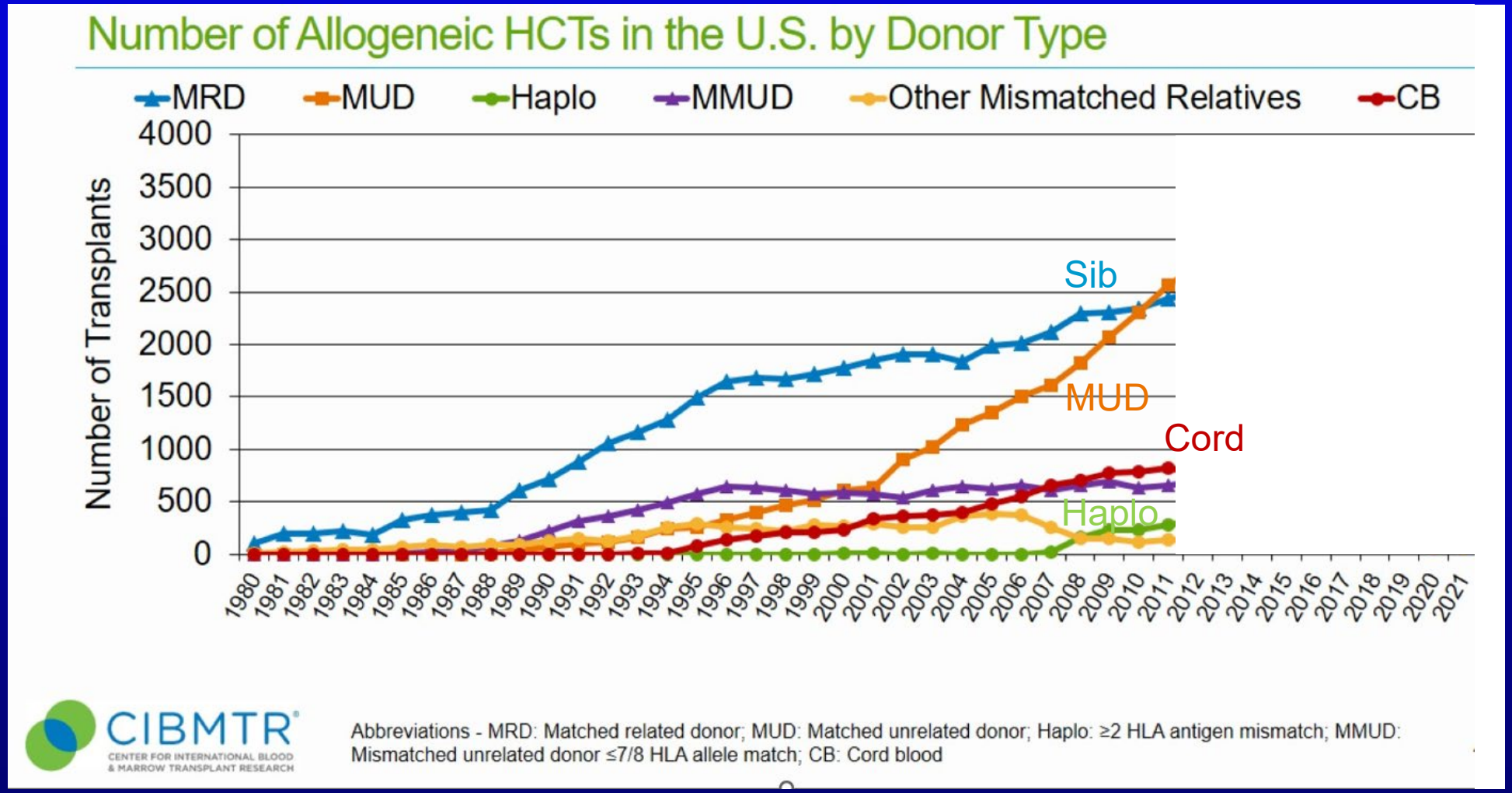
Data from the CIBMTR 2023

Stable Number of Allo-Transplants For AML, ALL and MDS



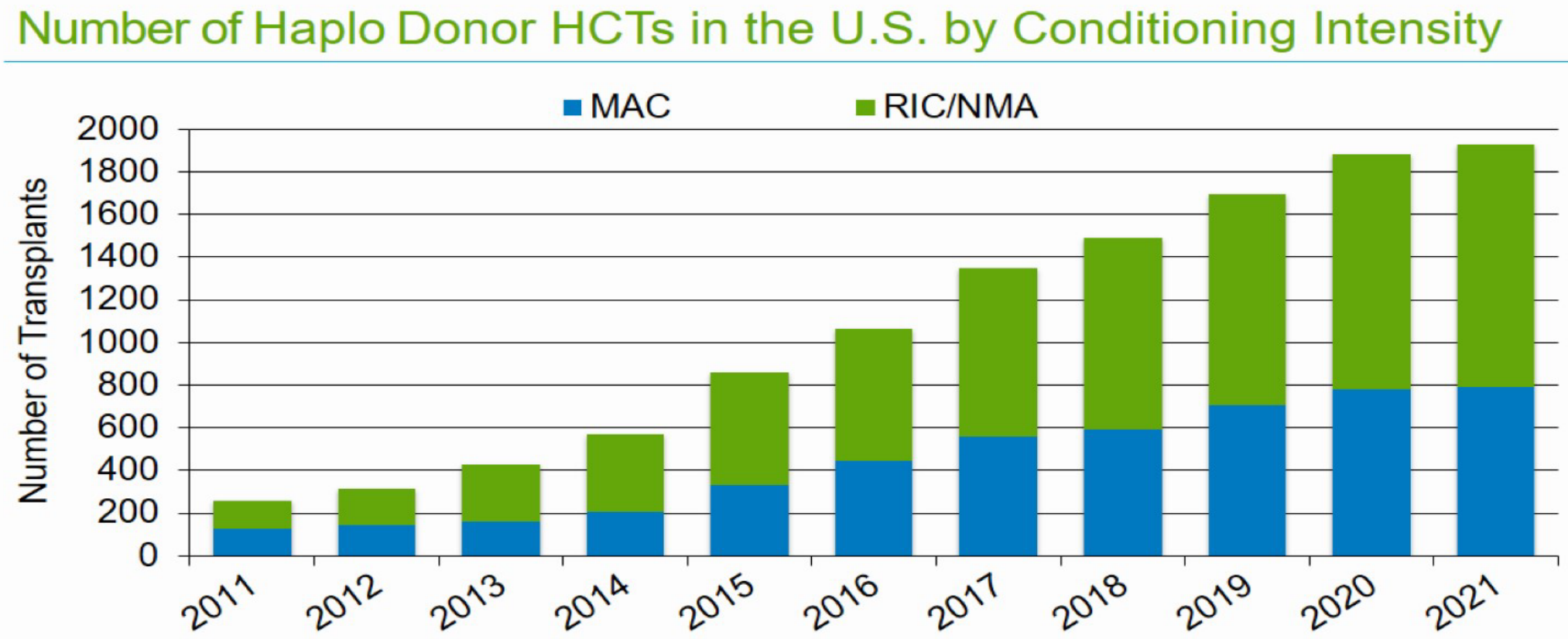
CIBMTR Data 2023

Dramatic Change in Use of Transplant Donors Over the Past 10 Years



Data from the CIBMTR 2023

Increase in Reduced Intensity Transplants Over Myeloablative Transplants



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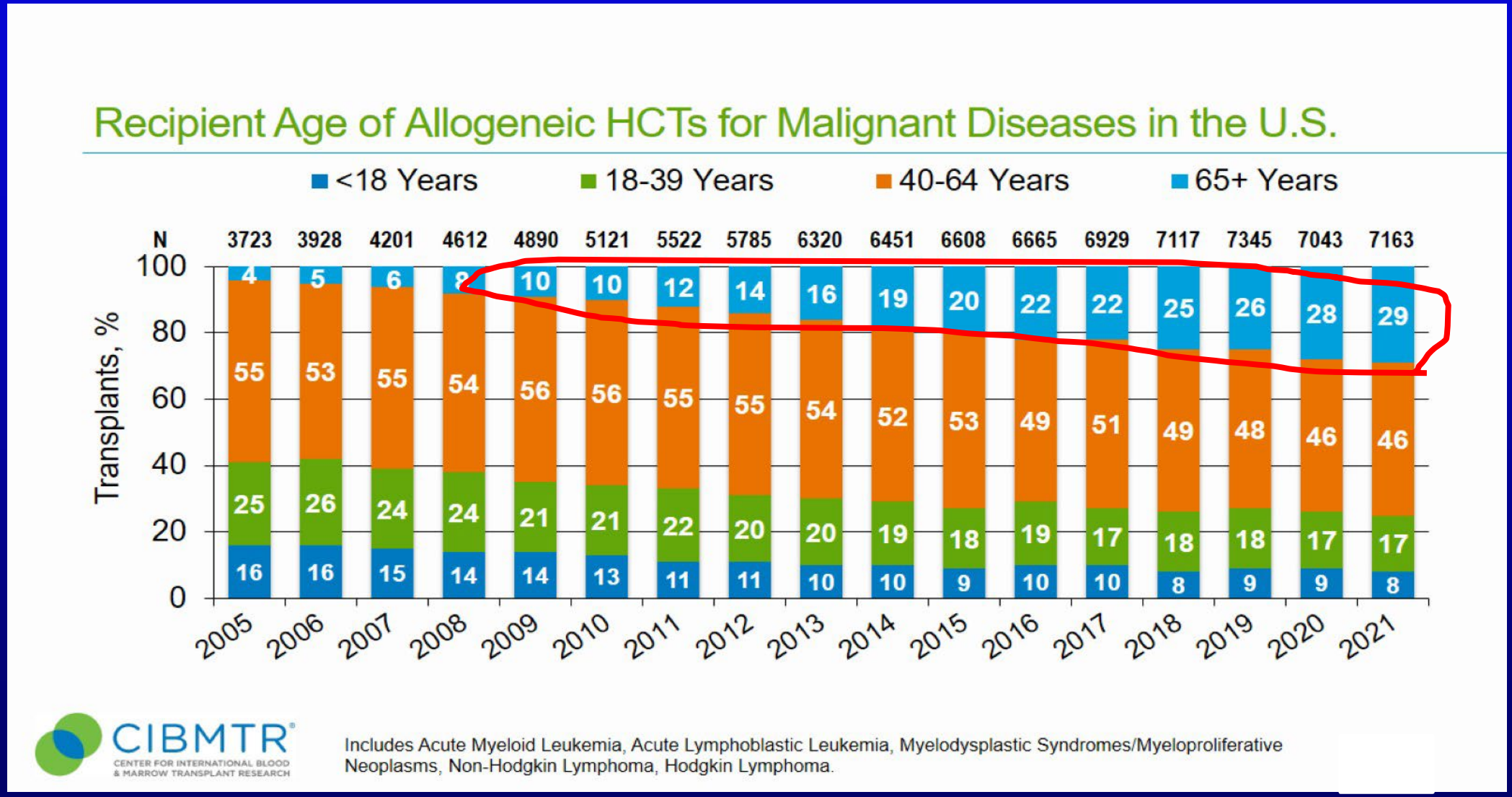
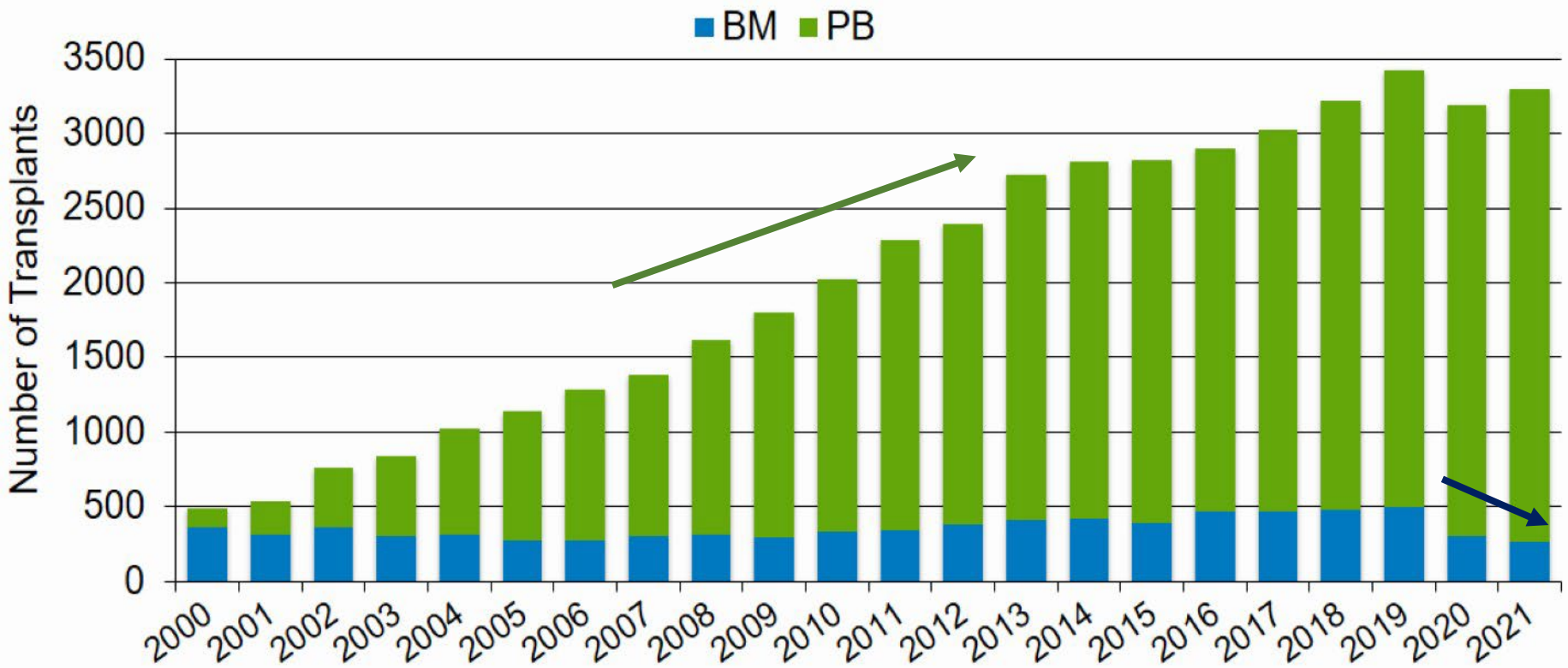
Abbreviations - MAC: Myeloablative conditioning; RIC/NMA: Reduced intensity conditioning/Non-Myeloablative regimen. Haplo: ≥2 HLA antigen mismatch donors.

More Utilization of Allotransplants Amongst Older Patients



Data from the CIBMTR 2023

Increase in MUD Transplants Using PBSC Over Bone Marrow in the U.S.



Abbreviations - BM: Bone marrow; PB: Peripheral blood.

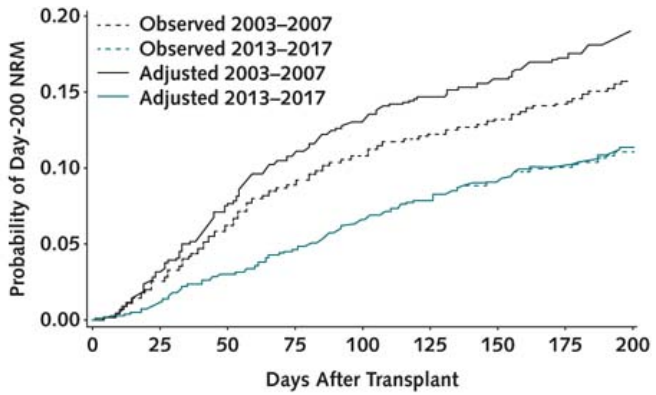
Data from the CIBMTR 2023

Transplants Dramatically Safer Over Past 2 Decades

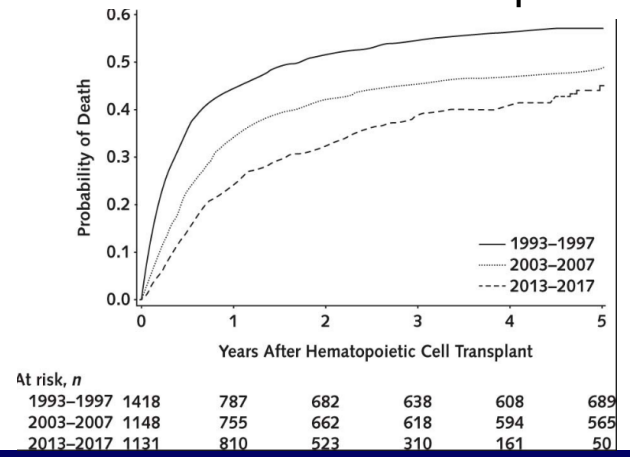
2003-2007 vs 2013-2017

- **34% reduction in NRM**
- **24% reduction in cancer relapse**

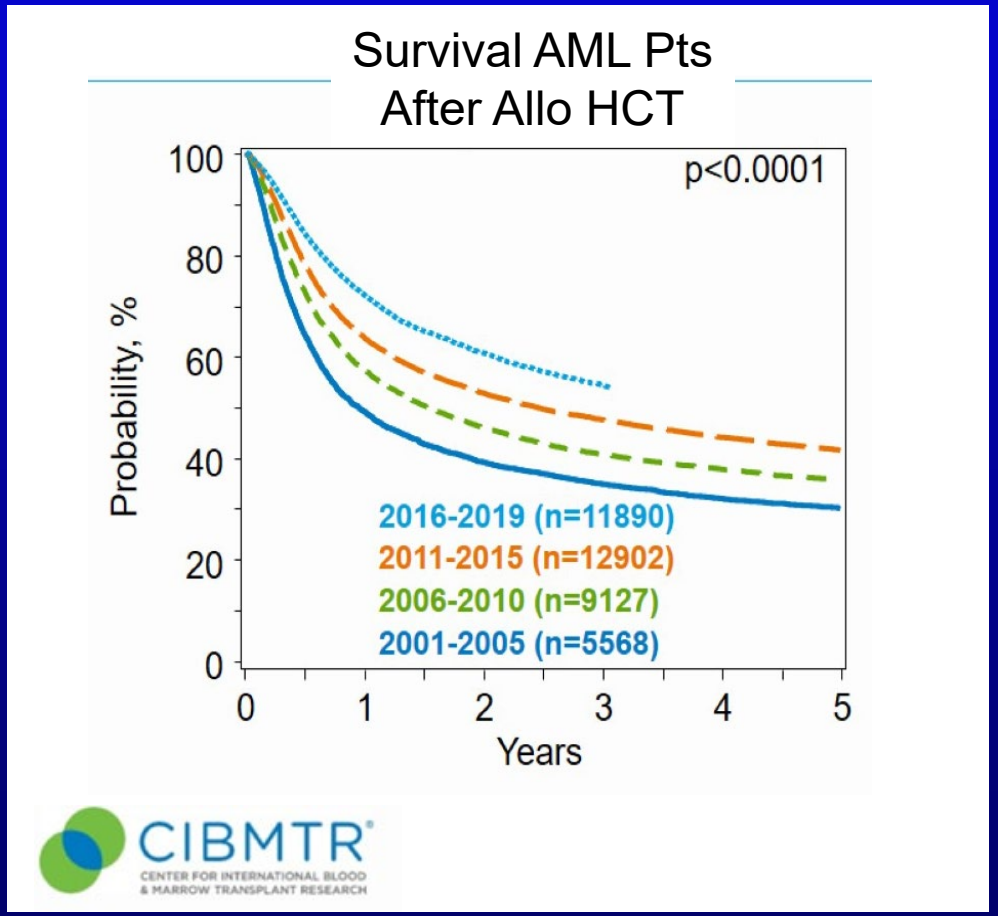
Day 200 NRM



Death After Transplant



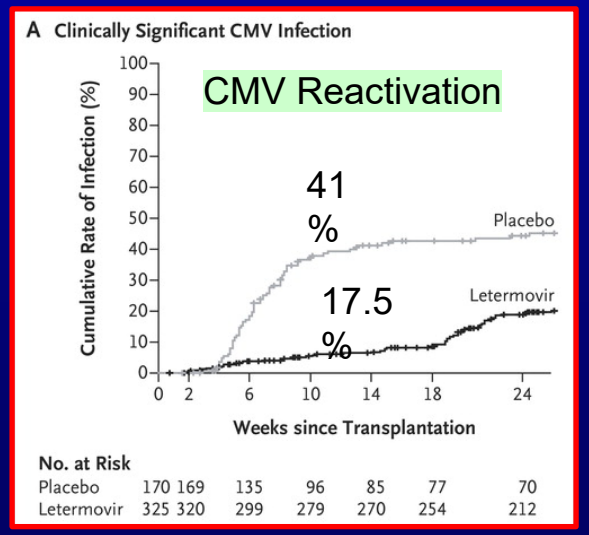
AML and Allogeneic Transplant: Survival Improving

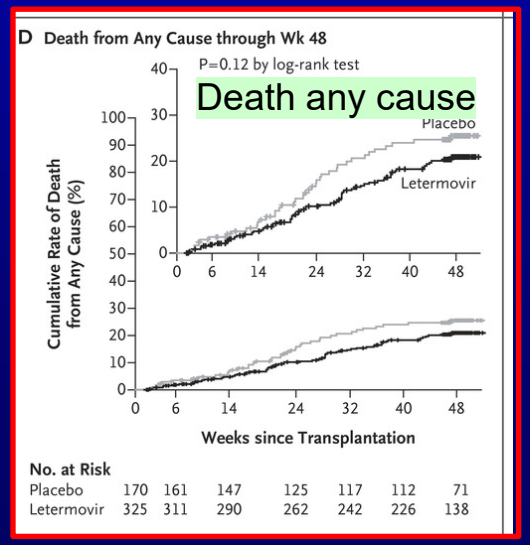


Wong F.L. et al JNCI 2020 (112:11)
McDonald G.B. et al Annals Int Med 2020:Ann Intern Med. 2020;172:229-239.

Major Improvements in Transplant Outcomes Over the Past 2 Decades

- **First FDA approved drugs to treat GVHD**
  - **Ibrutinib** demonstrated ORR 67% cGVHD (CR=21%, PR=45%)
    - Miklos, D et al, Blood-Sept 2017
  - **Ruxolitinib** 73% response for SR acute GVHD- FDA approved 2019
  - **Rezurock** – 74%-77% response rate- FDA approved 2021 for pts who have received ≥ 2 lines of systemic therapy
- **Letermovir approved (2017) to prevent CMV reactivation post-HCT**
  - ✓ **Reduced risk of CMV reactivation from 41% to 17% compared to placebo**
- **Maribavir- FDA approved 2022 for patients with post-transplant refractory CMV infection**
  - ✓ 57% viral clearance rate compared to best standard therapies
  - ✓ No marrow suppression or renal toxicity

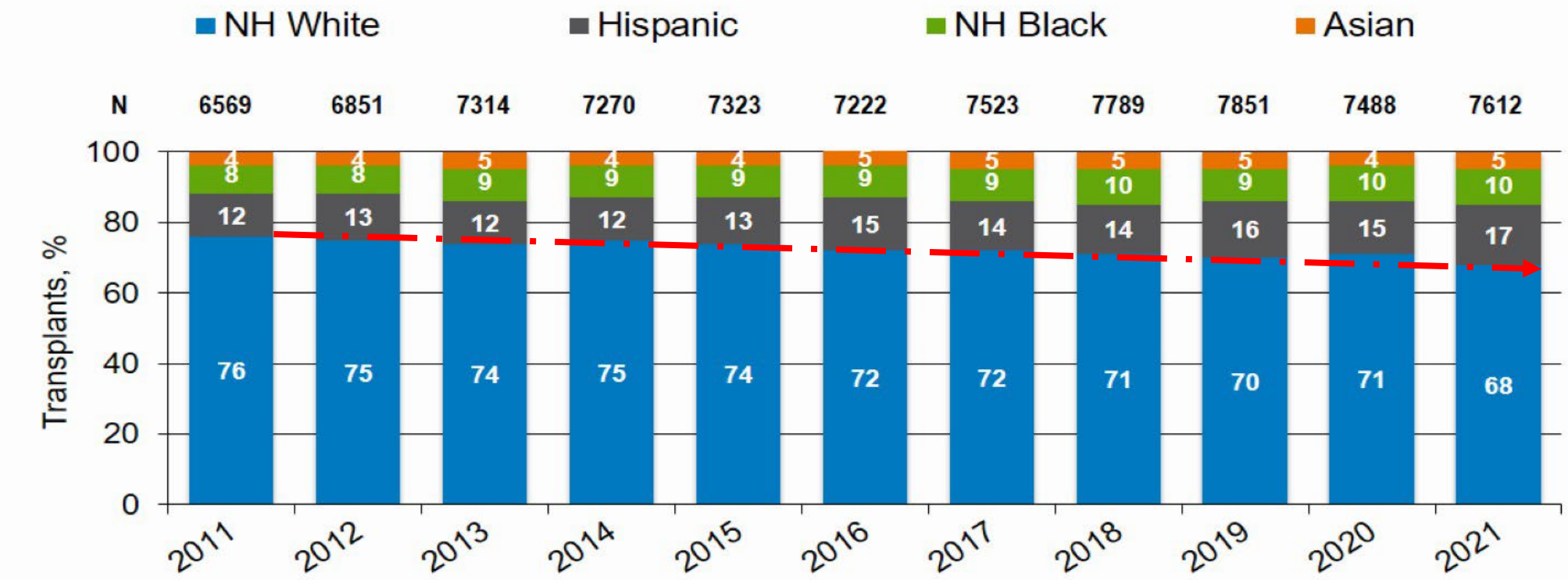




Cutler C. et al, Blood 2021
Maertens J. et al, NEJM 2019: 381(12)
Marty F. et al. NEJM Dec 2017

Increase In Proportion of Minorities Being Transplanted

Relative Proportion of Allogeneic Transplants in US by Race



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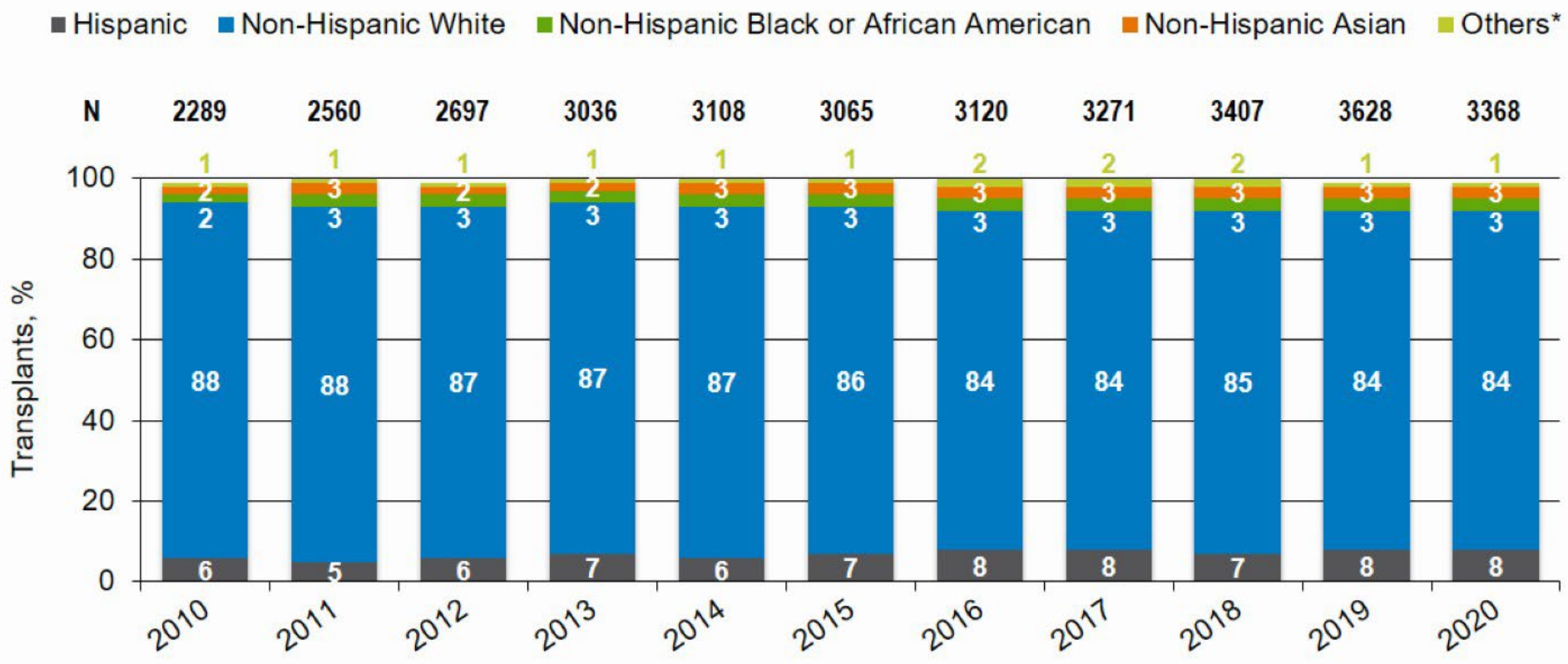
Abbreviation – NH: Non-Hispanic.

Relative Proportion of MUD Transplants in US by Race



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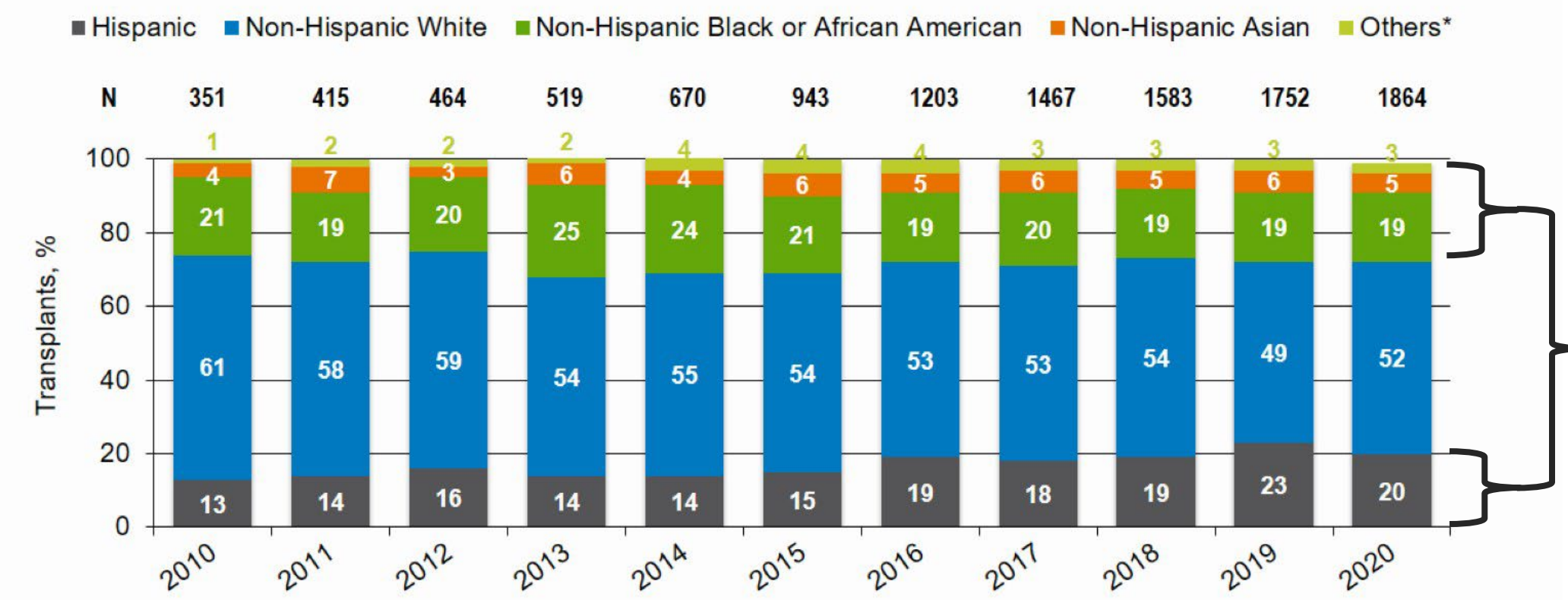
*includes non-Hispanic Native Hawaiian or other Pacific Islander (n=2), American Indian or Alaska Native (n=10), More than one race (n=17), and Non-resident of the US (n=20) in 2020

Haplo Transplants Particularly Useful For Racial Groups That Are Least Likely to Have MUD Donors Available

Relative Proportion of Haplo Transplants in US by Race



47% Haplo HCTs
- Asian
- Hispanic
- Black or African American

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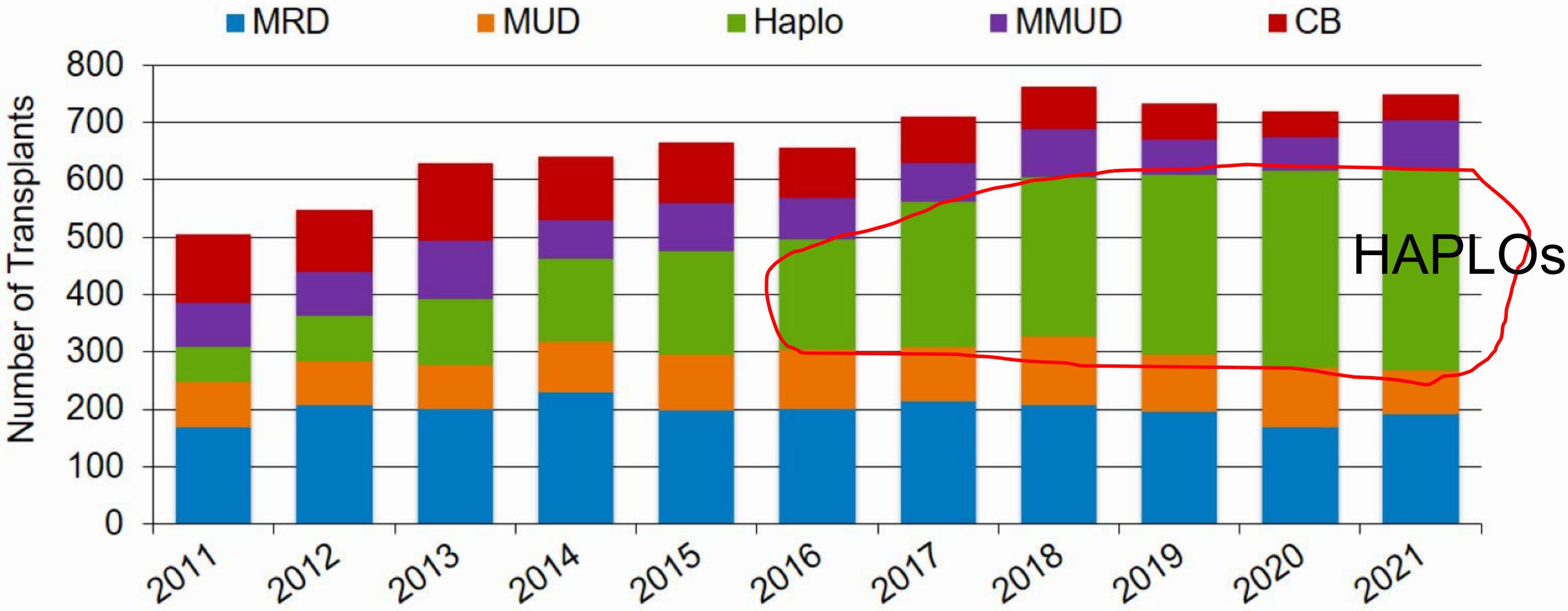
#includes all mismatched related donors
*includes non-Hispanic Native Hawaiian or other Pacific Islander (n=5), American Indian or Alaska Native (n=6), More than one race (n=16), and Non-resident of the US (n=27) in 2020

Allogeneic Transplants in U.S. For Black or African American By Donor Type



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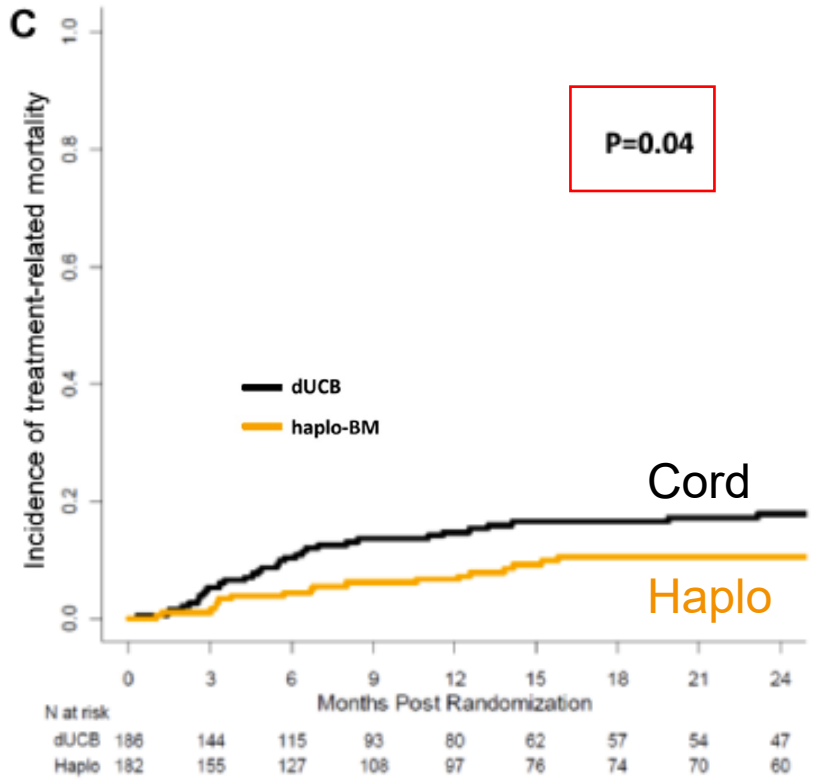
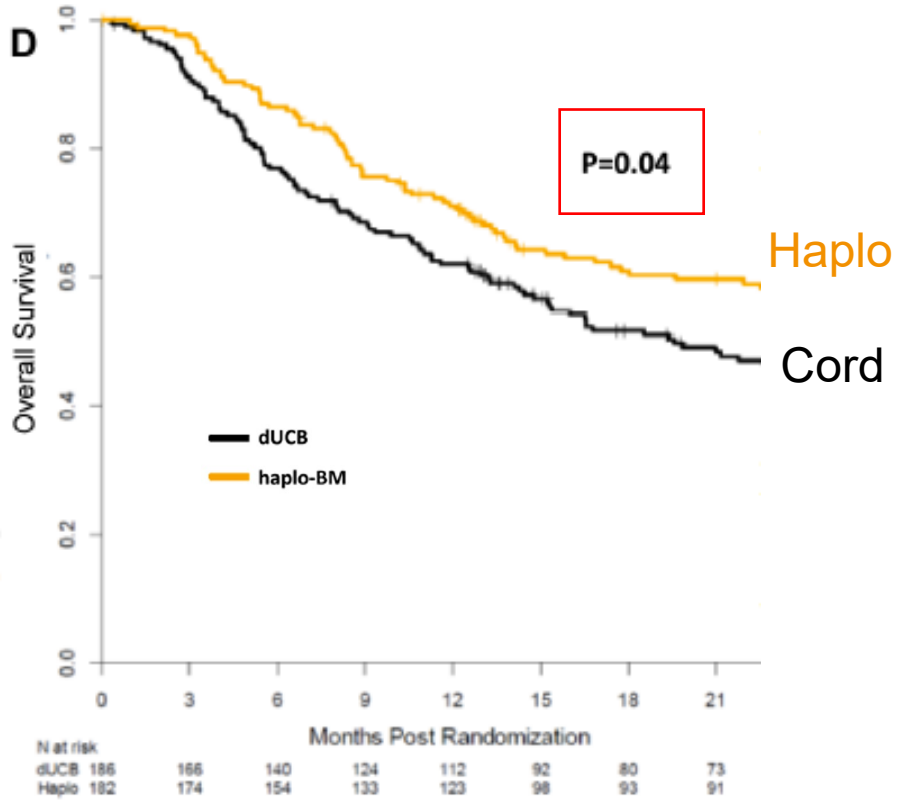
Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor; Haplo: ≥2 HLA antigen mismatch; MMUD: Mismatched unrelated donor ≤7/8 HLA allele match; CB: Cord blood.

CTN 1101-Cord vs. Haplo: Haplo Wins

Transplant related Mortality (TRM)



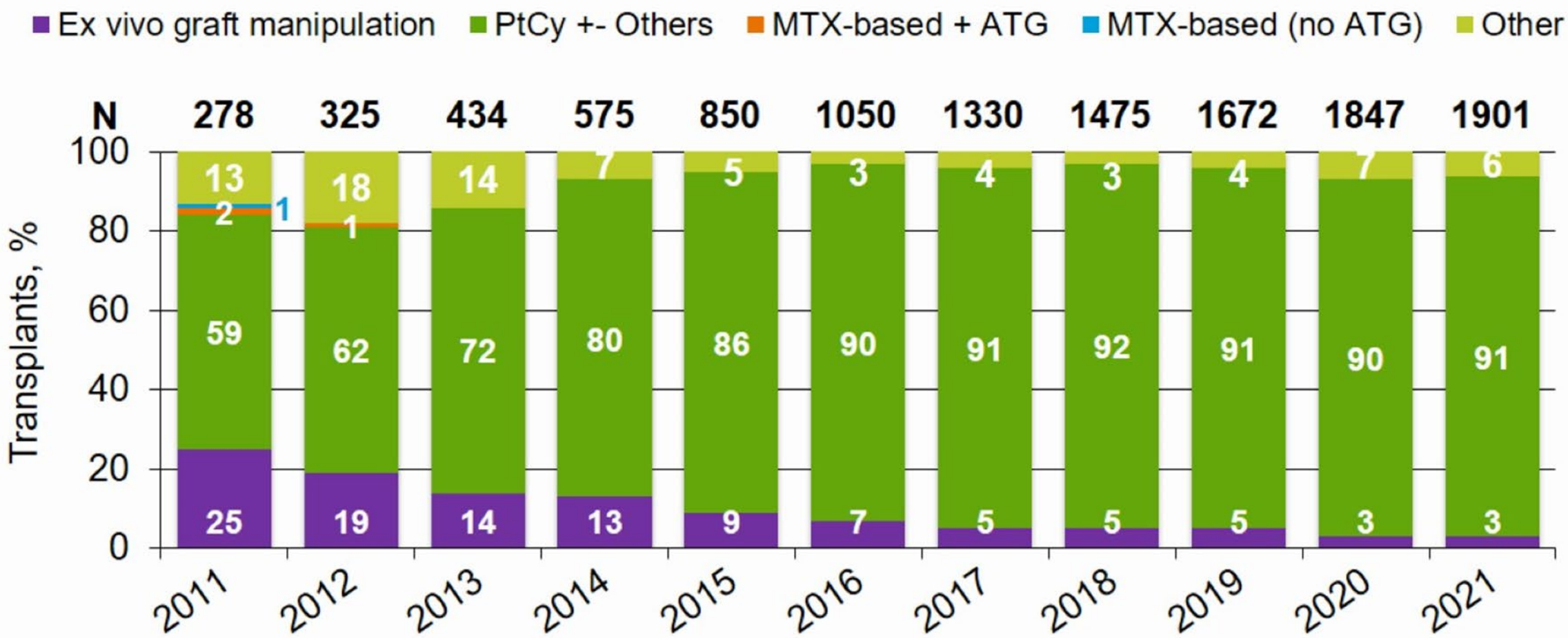
Overall Survival



- Engraftment, relapse and progression-free survival were similar between cohort
- Haplo transplants had lower TRM which resulted in superior overall survival
- These data favor the use of haploidentical marrow over cord blood transplantation

Fuchs E. et al Blood 2021: 137:420428

Most Haplo-Transplants Utilize Post Transplant Cytoxan



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Abbreviations - PtCy: Post-transplant Cyclophosphamide. Ex vivo graft manipulation includes T cell depletion/CD34 selection +- others. Haplo: ≥2 HLA antigen mismatch donors. Many regimens include Calcineurin Inhibitors.
GVHD Other includes: CNI + MMF +/- others; CNI +/- others; Other. ATG includes alemtuzumab (Campath).

Choosing the Best Haplo Transplant Relative

Fact: In transplants from HLA matched donors (related and unrelated), best outcomes are associated with

- Donors that have the best HLA match
- Donors who are younger (<30 years MUD)
- Avoiding a female donor into a male recipient (results in less GVHD)

Fact: Recipients of Haplo Transplants typically have many potential family donors to choose from

Choosing the best Donor:

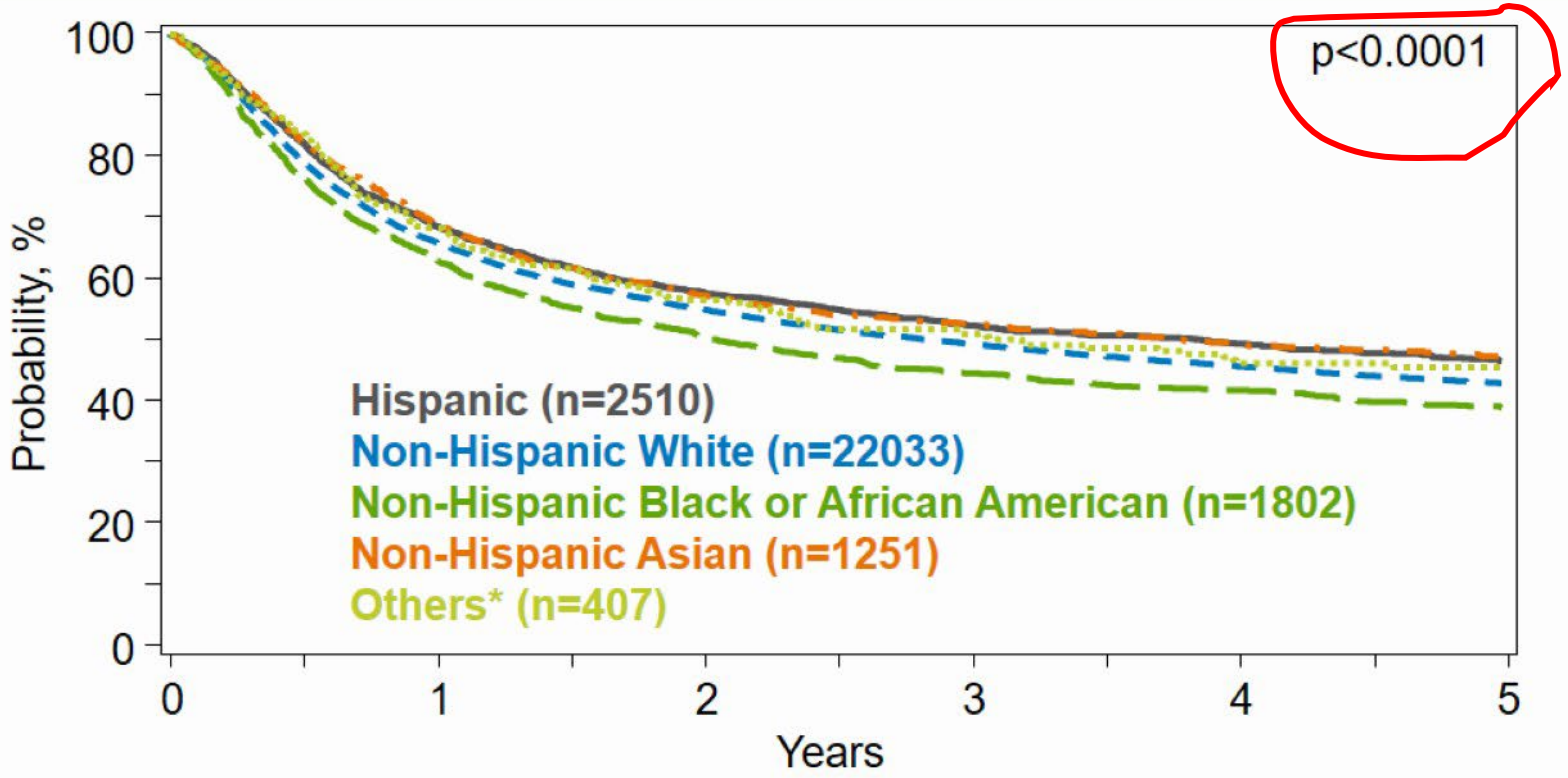
- PFS and survival not impacted by gender, relationship of the donor to the recipient, degree of HLA mismatch or ABO incompatibility, prior donor pregnancy
- Avoid DSA to Haplo Donor

- Donors <30 have a sustainably lower chance of causing severe acute GVHD

Im A, et al. Biol Blood Marrow Transplant. 2020 26(8)

Inferior Survival Amongst Non-Hispanic Black or African American Patients Following Following Allo BMT for AML

Survival after Allogeneic HCTs for Acute Myelogenous Leukemia (AML), Age ≥18 Years, in the US, 2009-2019



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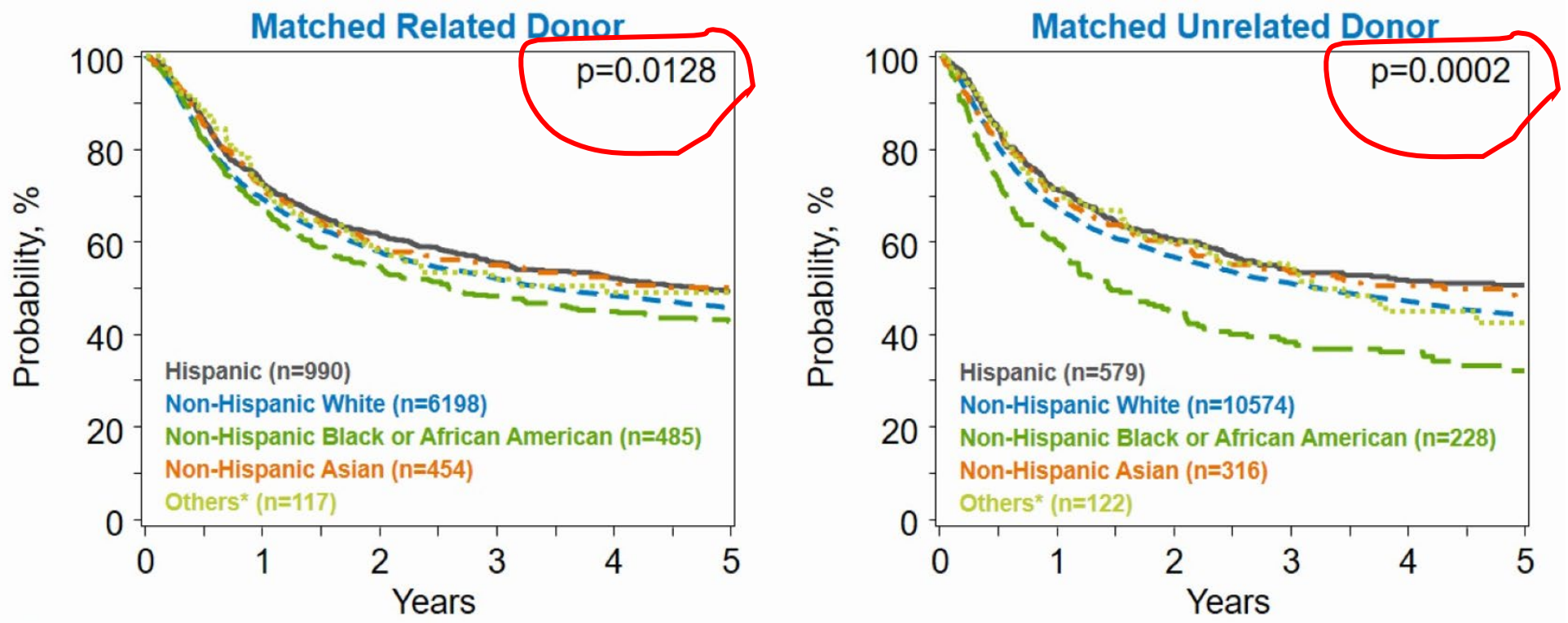
Inferior Survival Amongst Non-Hispanic Black or African American Patients Following Following HLA Matched Allo BMT

Survival after Allogeneic HCTs for Acute Myelogenous Leukemia (AML), Using Matched Donors, Age ≥18 Years, in the US, 2009-2019



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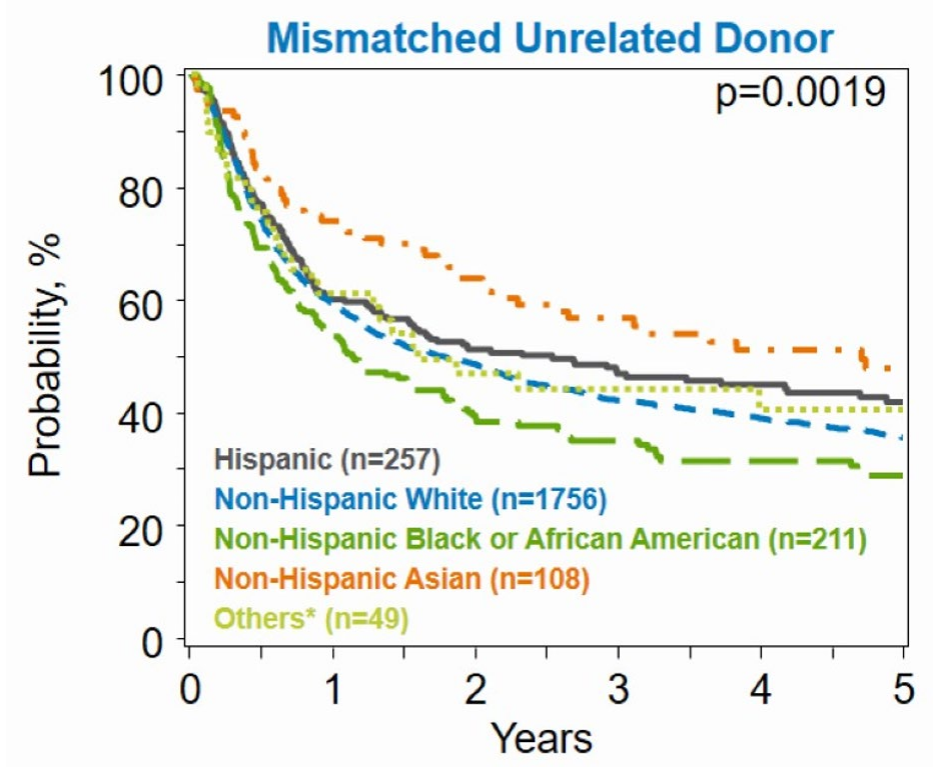
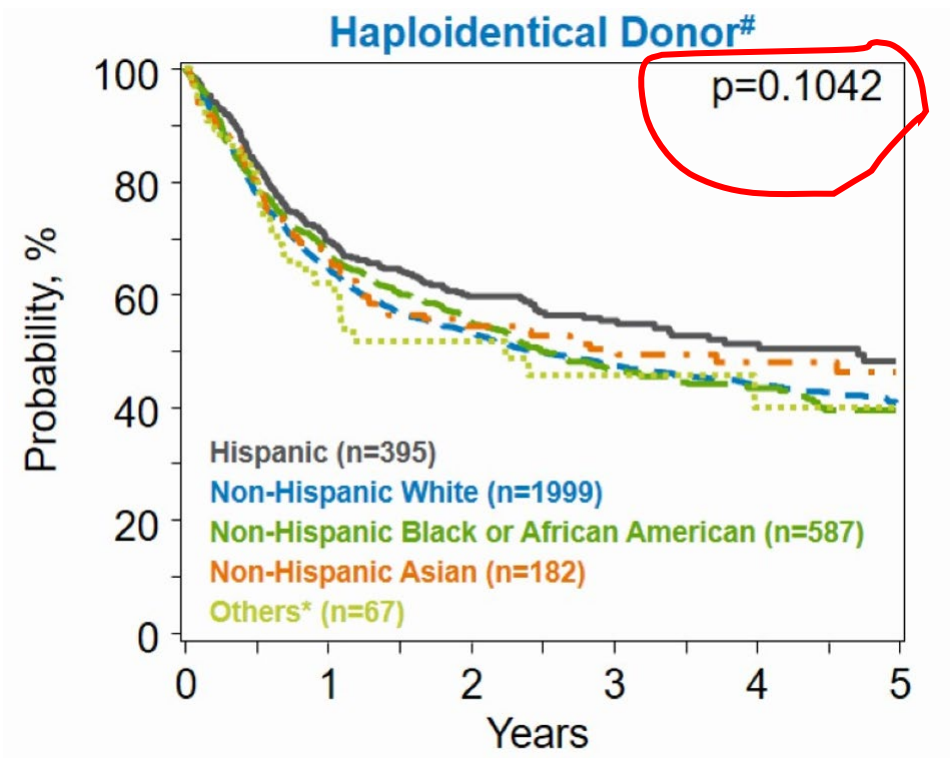
Comparable Survival Amongst Non-Hispanic Black or African American Patients Following Haplo/Post Cy BMT for AML

Survival after Allogeneic HCTs for Acute Myelogenous Leukemia (AML), Using Matched Donors, Age ≥18 Years, in the US, 2009-2019





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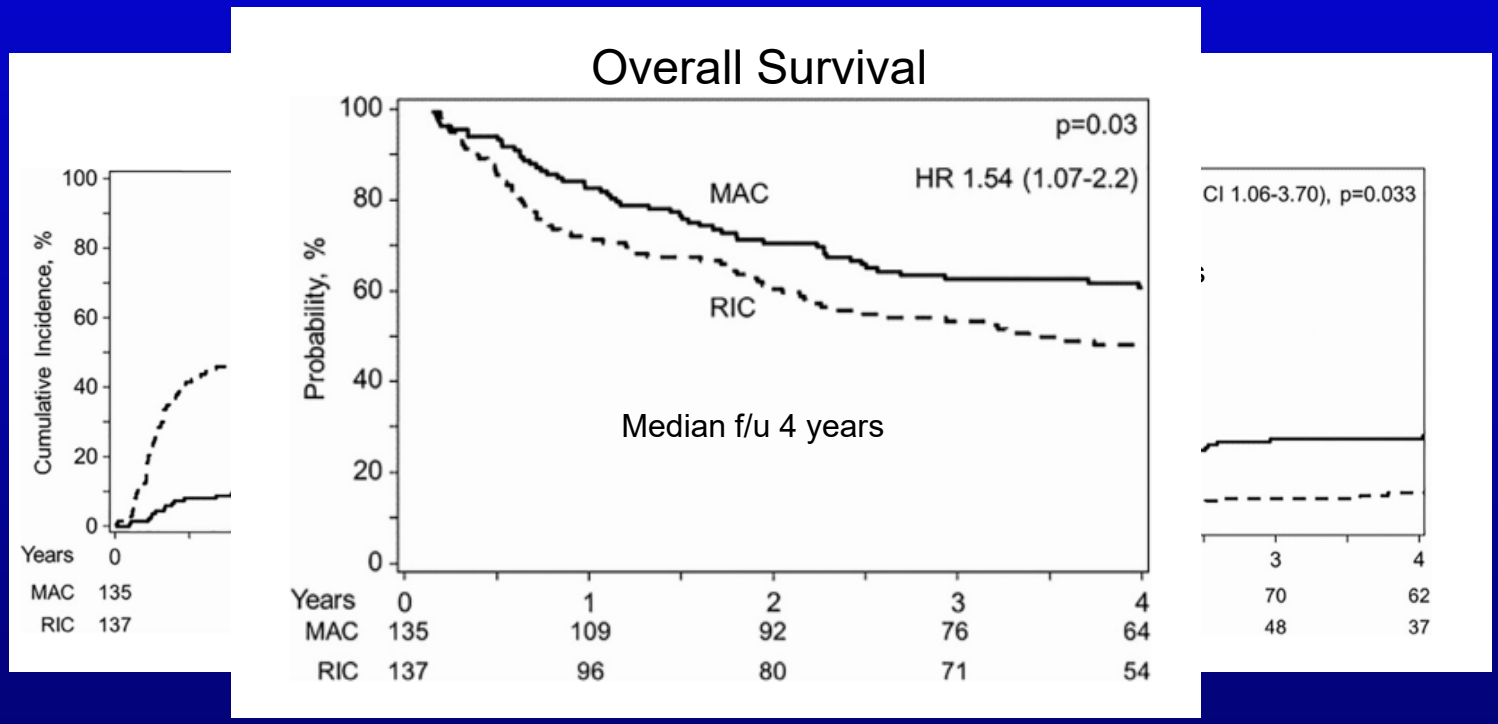
Update on BMT 0901: Myeloablative Conditioning (MAC) Superior to Reduced Intensity Conditioning (RIC) For AML/ MDS

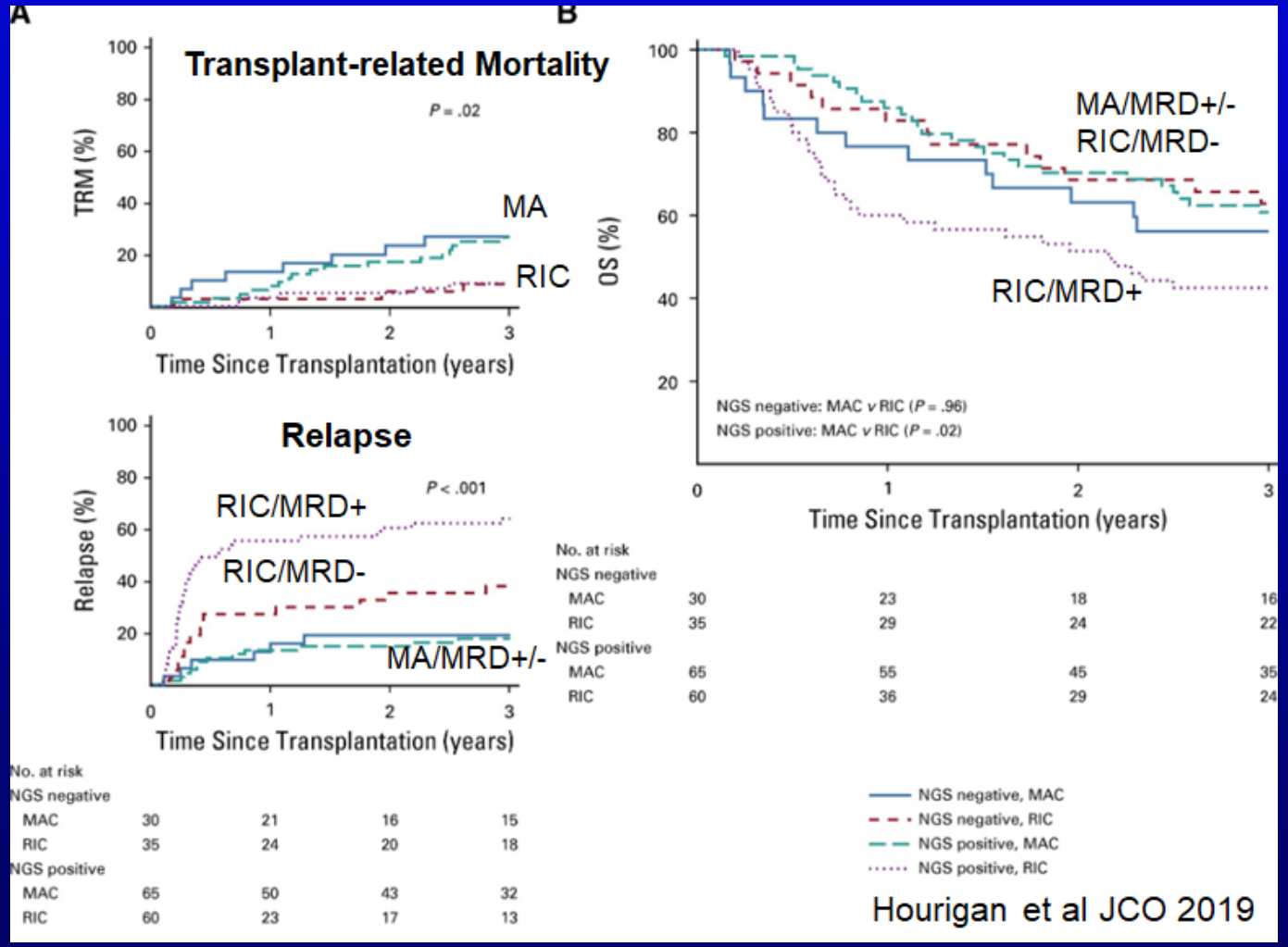
- **Study Design:**
  - Phase III randomized trial comparing MAC with RIC in patients with acute myeloid leukemia or myelodysplastic syndromes.
- **Patients:**
  - age 18 to 65 years
  - HCT comorbidity index ≤ 4
  - < 5% marrow myeloblasts pre-HCT
- **Outcomes**
  - TRM MAC 25% vs 10% RIC
  - Relapse higher RIC (HR 4.06 CI 2.6-6.35 P<0.001)
  - Survival superior in pts that received MAC



Scott B. et al, Trans Cell Ther 2021 27(6)
Scott B. et al, JCO 2017

The Greatest Benefit of MAC Is Seen in Patients Who Have Genomic Evidence of MRD Before alloHCT

- Used ultra-deep sequencing for 13 commonly mutated genes in AML
- RIC was significantly associated with increased relapse (hazard ratio [HR], 6.38; CI, 3.37 to 12.1; *P* < .001), and decreased OS (HR, 1.97)



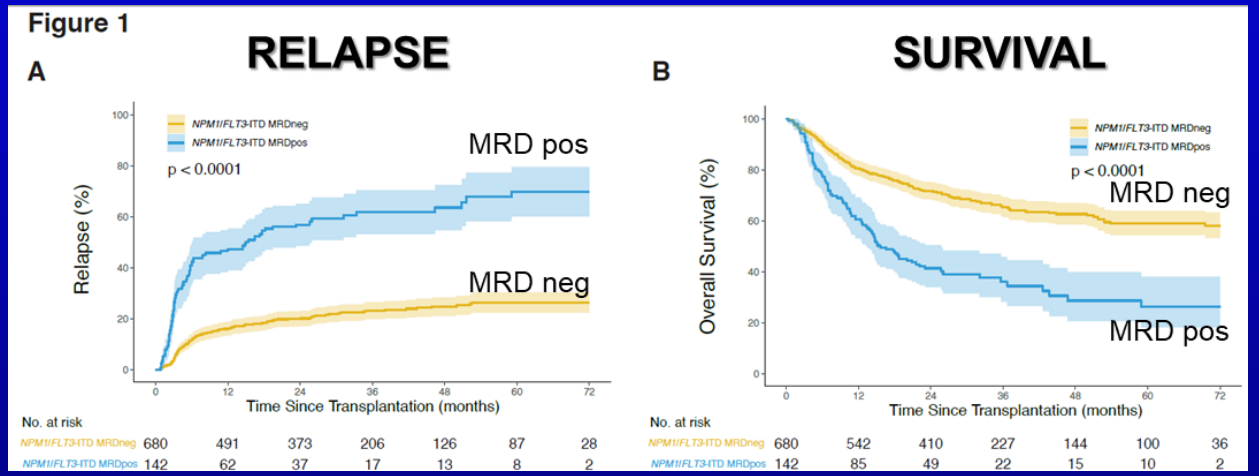
Hourigan et al JCO 2019

Predicting Relapse for AML After Allogeneic HCT:

Pre-Transplant MRD Positivity Increases Risk of Relapse After Allogeneic HCT

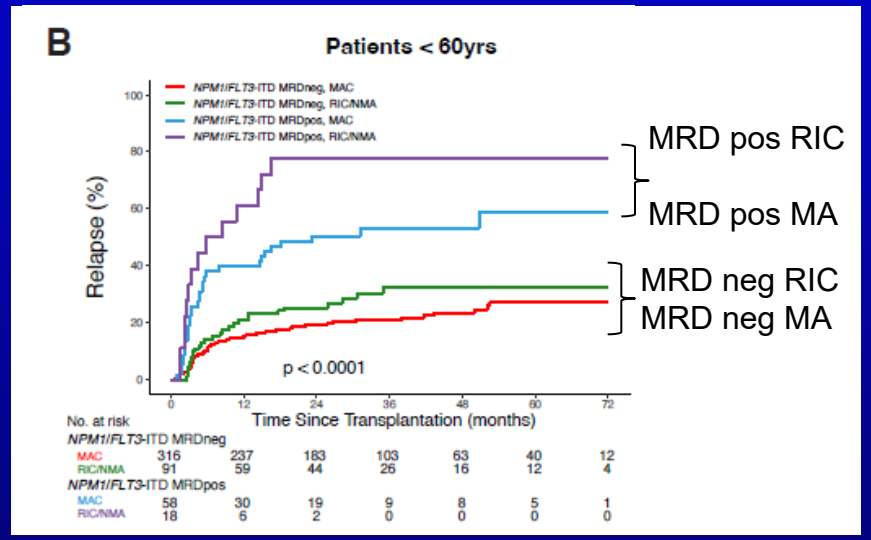
PRE-MEASURE STUDY: Confirmed Higher Rates of Relapse And Decreased Survival in Pts With Detectable NPM1 and/or FLT3-ITD Mutated AML Before Allogeneic HCT

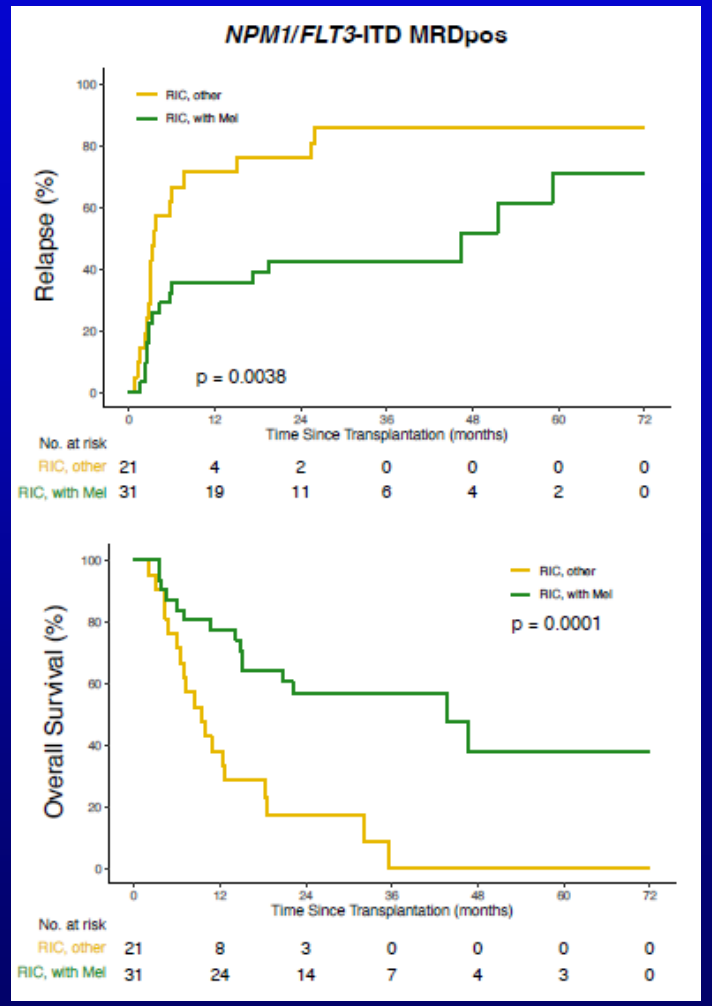
- **1075 patients** with *NPM1, FLT3, IDH1, IDH2* and/or *KIT* mutated AML in CR1 undergoing allogeneic HCT
- Targeted error-corrected DNA sequencing was performed on 500ng of genomic DNA using a custom panel covering hotspot regions within the five genes of interest.
- 454 were transplanted between March 2013 and December 2017 (discovery cohort)
- 621 were transplanted between January 2018 and February 2019 (validation cohort)



Dillon L.W. et al JAMA 2023:745-755

PRE-MEASURE STUDY: The Use of Melphalan Decreased Relapse and Increased Survival In *NPM1* and/or*FLT3*-ITD Mutated AML Positive Pts Receiving RIC





Conclusions:

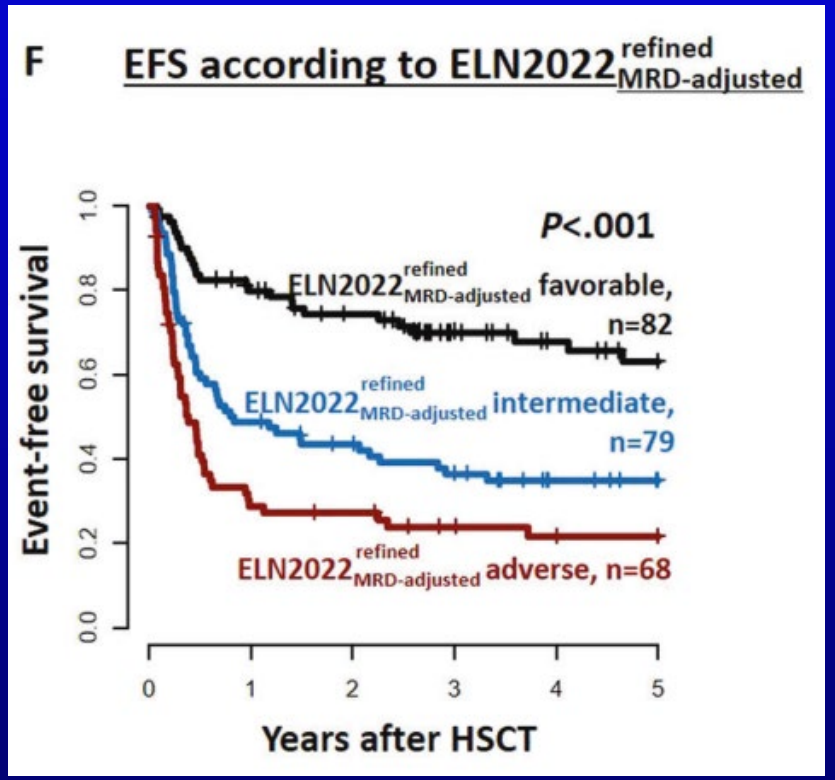
Among AML patients in first remission prior to allogeneic HCT

- The persistence of *FLT3* internal tandem duplication or *NPM1* variants in the blood at an allele fraction of 0.01% or higher was associated with increased relapse and worse survival
- Myeloablative and melphalan-containing reduced intensity conditioning regimens may partially mitigate this risk
- Novel therapeutic approaches to decrease the risk of relapse in MRD positive patients undergoing allogeneic HCT are needed.

Dillon L.W. et al JAMA 2023:745-755
ASH Abstract 4325- Similar data using a commercially available NGS test

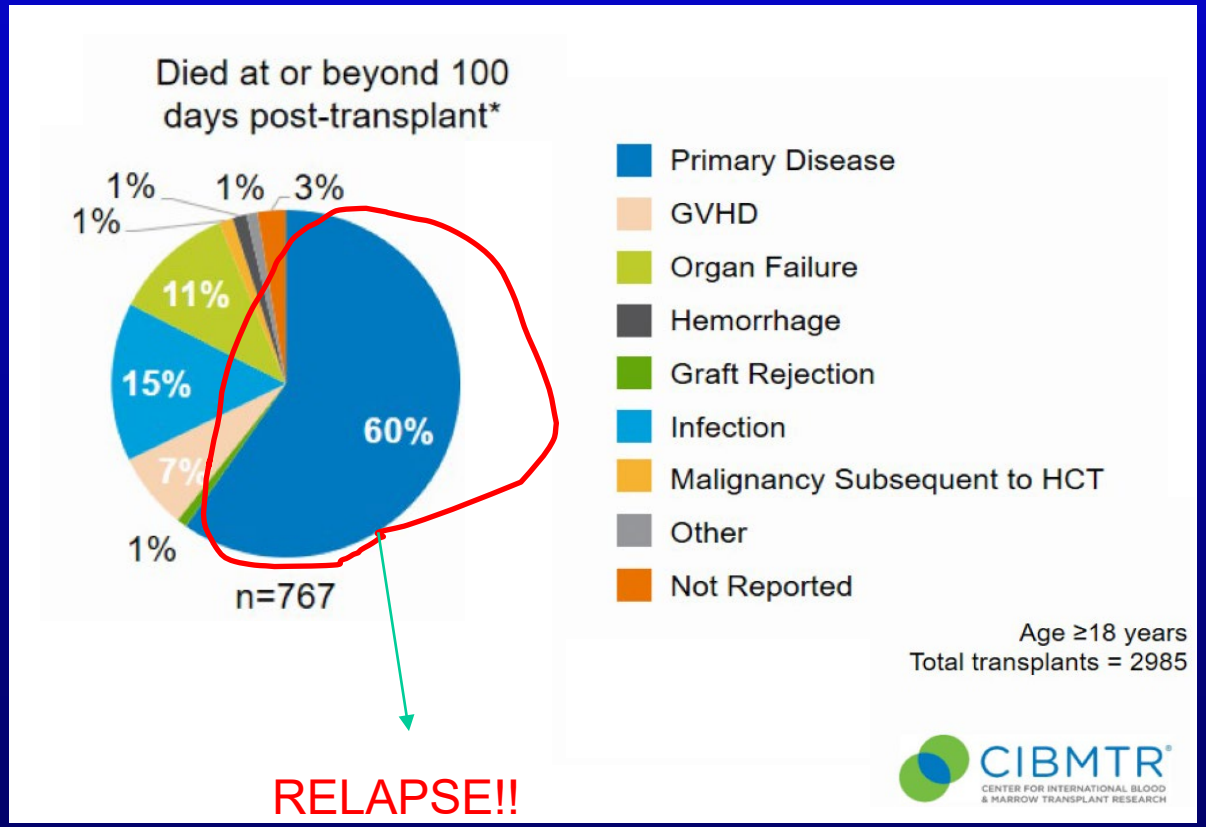
European LeukemiaNet Revised Risk Classification for AML (ELN2022) Predicts Relapse and Survival After Allogeneic Transplant

- 552 AML pt undergoing allogeneic HSCT median 59 yrs (16-76)
  - 229 had MRD status was evaluated
- ELN2022 risk was 22% favorable, 26% intermediate, 52% adverse
- ELN2022 risk status was associated with the risk of relapse and overall survival
- MDS-related gene mutations did not have adverse transplant outcomes
- When Reclassifying all these MDS patients as intermediate risk and adjusting for MRD status led to a refined and improved risk stratification



Jentzsch et al Blood Cancer Journal 2022

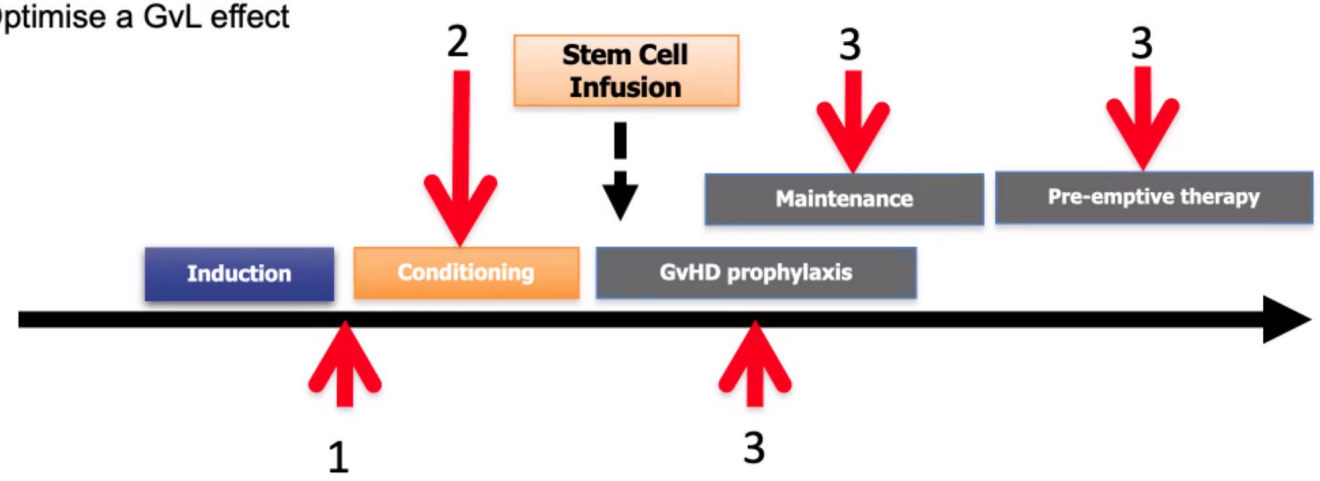
Relapse Continues To Be THE Major Cause Of Death After Allogeneic



How Do We Prevent Transplant Relapse

Strategies to reduce relapse risk in patients allografted for AML- the impact of pre-transplant MRD

1) Minimise pre-transplant disease burden
2) Optimise cytotoxic properties of the conditioning regimen
3) Maintenance drug or cellular therapies which:
   - Target residual leukaemic stem/progenitors
   - Optimise a GvL effect



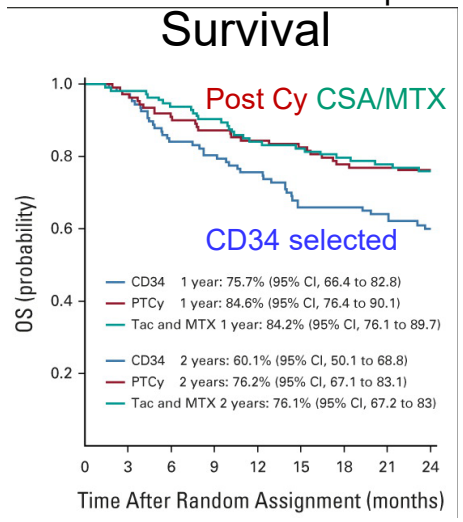
Craddock, et al. Bone Marrow Transplant. 2019

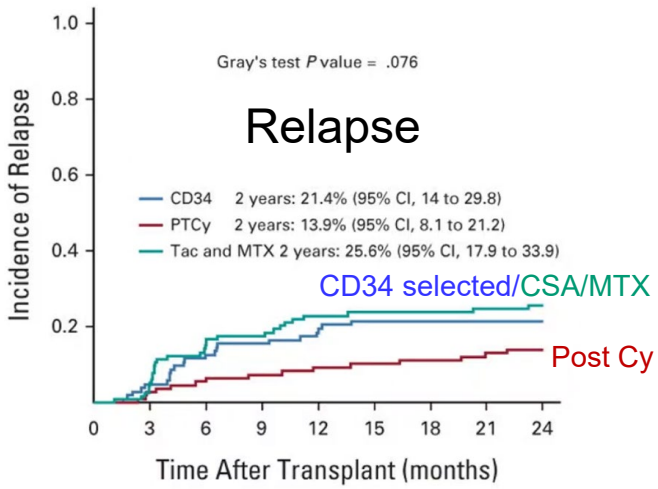
Post-Transplant Cytoxan to Reduce Relapse after HLA-Matched Allogeneic HCT

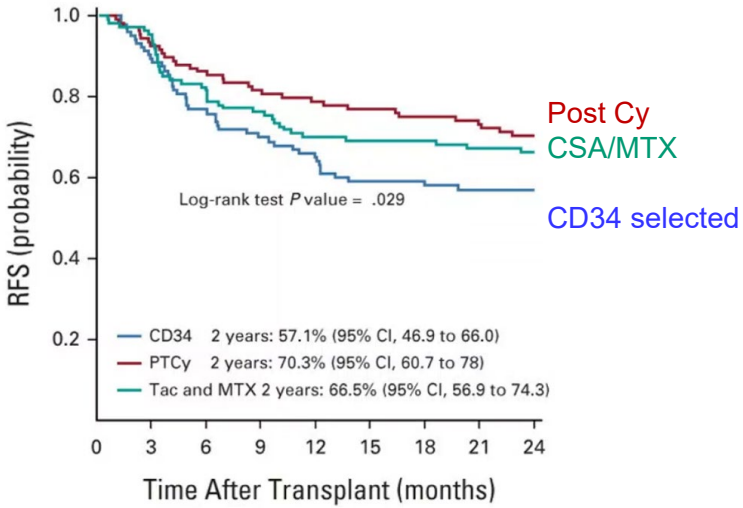
- Lower cyclosporine levels (AUCs) after transplant associated with lower risk of AML relapse (Craddock C. et al Haematologica 2010)

- Post-Transplant Cytoxan after HLA matched Transplant may obviate the need for post-transplant CSA/Tacro
  - Potentially allows for increased graft-vs-leukemia effects decreasing relapse risk
  - CTN Phase III trial-Better RFS in leukemia patients receiving post HCT Cy compared to CSA/MTX or CD34 selected transplants

327 pts leukemia in remission randomized to post HCT CY vs CSA/MTX vs CD34 selection

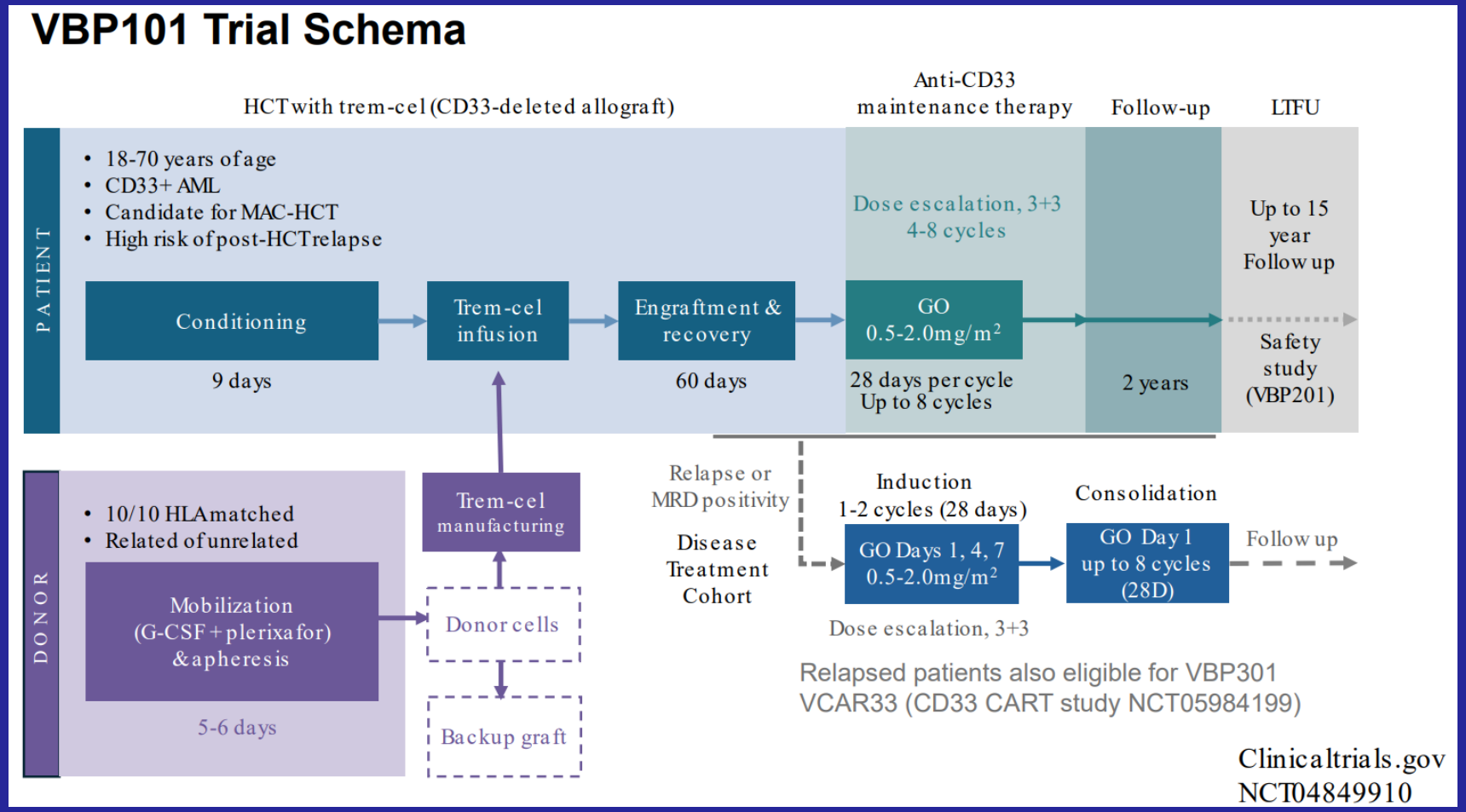






Luznik L. et al JCO 2022

CRISPR Deletion of CD33 in Donor Stem Cells To Protect Them From Anti-CD33 Targeting Therapies Given Post Allo-HCT To Prevent AML Disease Relapse



Dipersio J. et al #486

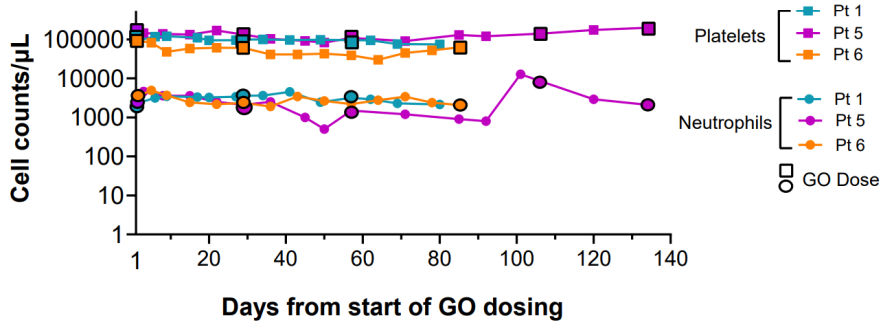
CRISPR Deletion of CD33 in Donor Stem Cells To Protect Them From Anti-CD33 Targeting Therapies Given Post Allo-HCT To Prevent AML Disease Relapse

8 Patients Treated to Date
Transplanted CD34+ cells
- **Median 87.5% CD33 negative**
- **100% engrafted**
- **no ANC reduction in first 3 pts treated with GO**
- **rise in %CD33 neg myeloid cells in GO treated pts**

Pt	Age/ Sex	10/10 Donor	Dose (×10^6 CD34 cells/kg)	CD33 Gene Editing
1	64/F	Unrelated	7.6	88%
2	32/M	Unrelated	3.2	87%
3	55/F	Unrelated	2.6	80%
4	68/M	Related	5.8	89%
5	66/M	Unrelated	4.6	85%
6	63/F	Unrelated	5.7	91%
7	67/F	Unrelated	9.4	87%
8	57/M	Unrelated	9.5	91%

- **Platform could be used to protect from other CD33-targeting therapies such** as CD33 CART

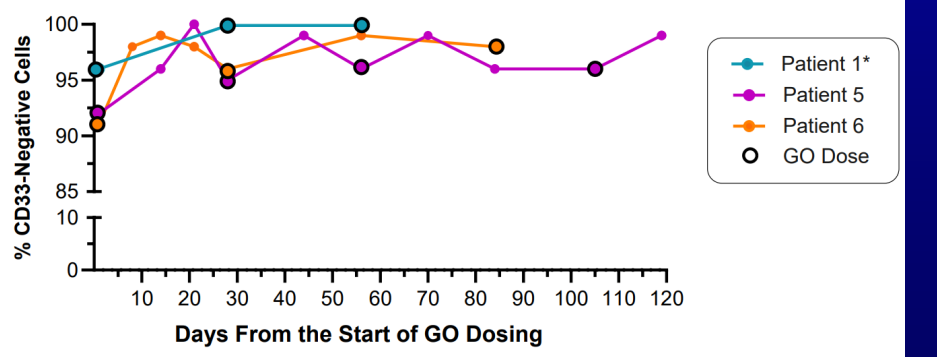
Neutrophil and platelet counts after GO dosing: Cohort 1 (0.5 mg/m^2)



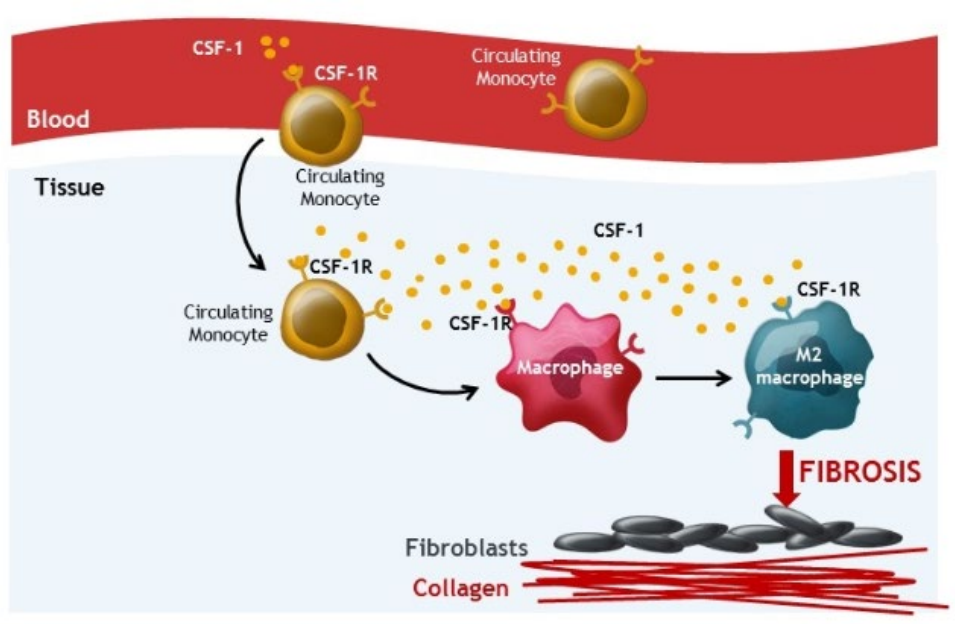
- No dose-limiting toxicity criteria met
- No increase in liver function tests above upper limit of normal. No SOS/VOD
- Dose Escalation Committee recommended increasing to 1 mg/m^2 dose

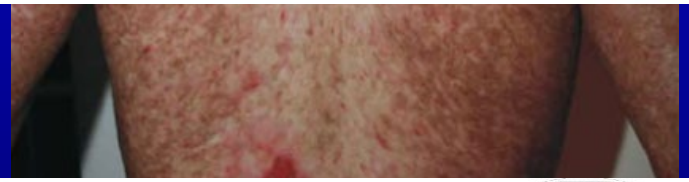
Trending Increase in CD33 Negative Myeloid Cells during GO dosing

- Editing of CD33 persists over time
- Treatment with GO selects for CD33 negative cells



Axatilimab For cGVHD

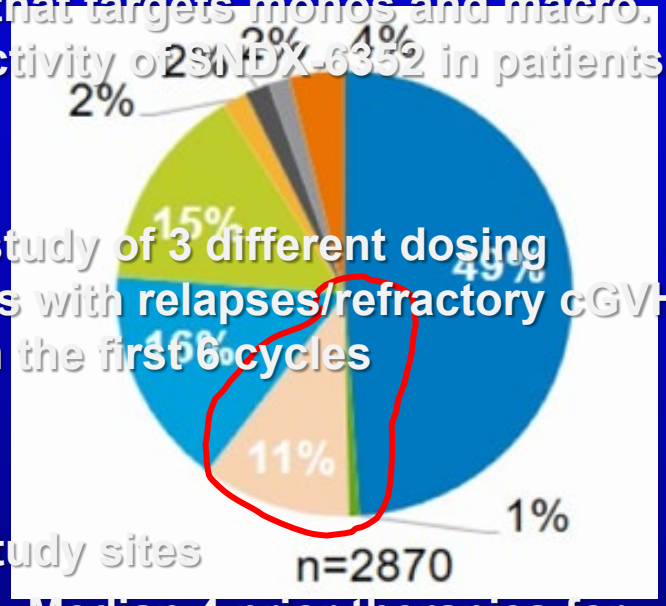




- **Background**- Preclinical data suggest colony-stimulating factor 1 receptor dependent monos/macros may drive cGVHD inflammation and fibrosis. Axatilimab (SNDX-6352) is an investigational CSF-1R mAb that targets monos and macro. Phase I data demonstrated activity of SNDX-6352 in patients with cGVHD

- **Method**: Phase 2 open label study of 3 different dosing schedules of Axatilimab in pts with relapses/refractory cGVHD. Primary outcome was ORR in the first 6 cycles

- **Outcomes:**
  - 241 pts enrolled at 121 study sites
  - Heavily pretreated cohort- Median 4 prior therapies for cGVHD
  - Activity seen at all dose levels with 0.3 mg/kg IV q 2 weeks most active
  - 74% ORR rate observed in pts who had failed ruxolitinib (74%) and belumosidil (23%)
  - Drug discontinuation in 6% due to TRAEs (infection)



Death After Day 100:
11% caused by cGVHD

cGVHD= Chronic graft vs host disease