HEMATOPOIETIC STEM CELL TRANSPLANTATION: STATE OF THE ART IN 2023

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BETHESDA MD

Dr. Richard W. Childs disclosures:

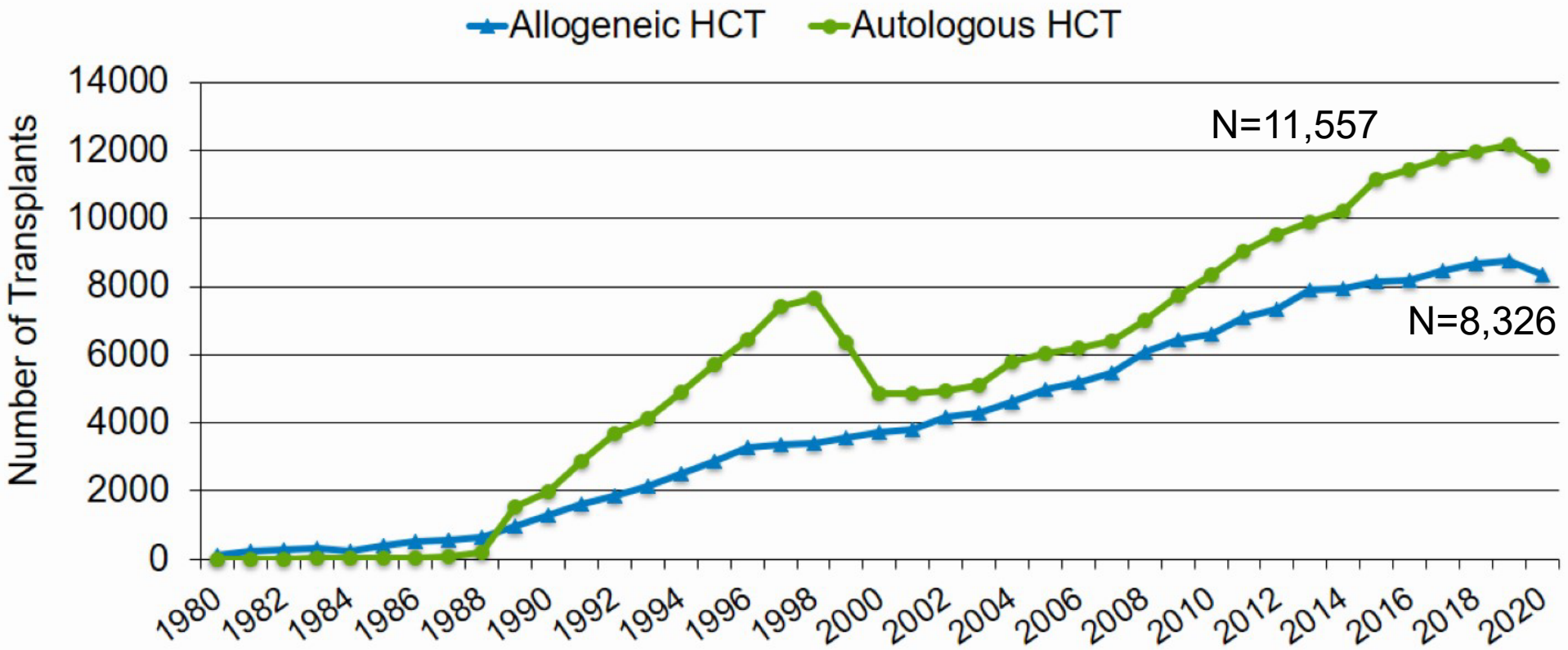
- None

Learning Objectives

- To Update the Field of Allogeneic Transplants in 2023
  - Improvements in managing Complications
    - CMV- prevention and treatment
    - GVHD- prevention and treatment
    - Safer Conditioning Regimens
  - Better Understanding of Who Benefits from RIC vs Myeloablative Conditioning
  - Improvements in Disease Specific Outcomes
- Alternative Donor Transplants
  - Trends for utilization
  - Cord versus Haplo
- Updates on strategies to prevent, treat and diagnose GVHD

GVHD= Graft vs host disease

Number of HCTs in the US Reported to CIBMTR by Transplant Type



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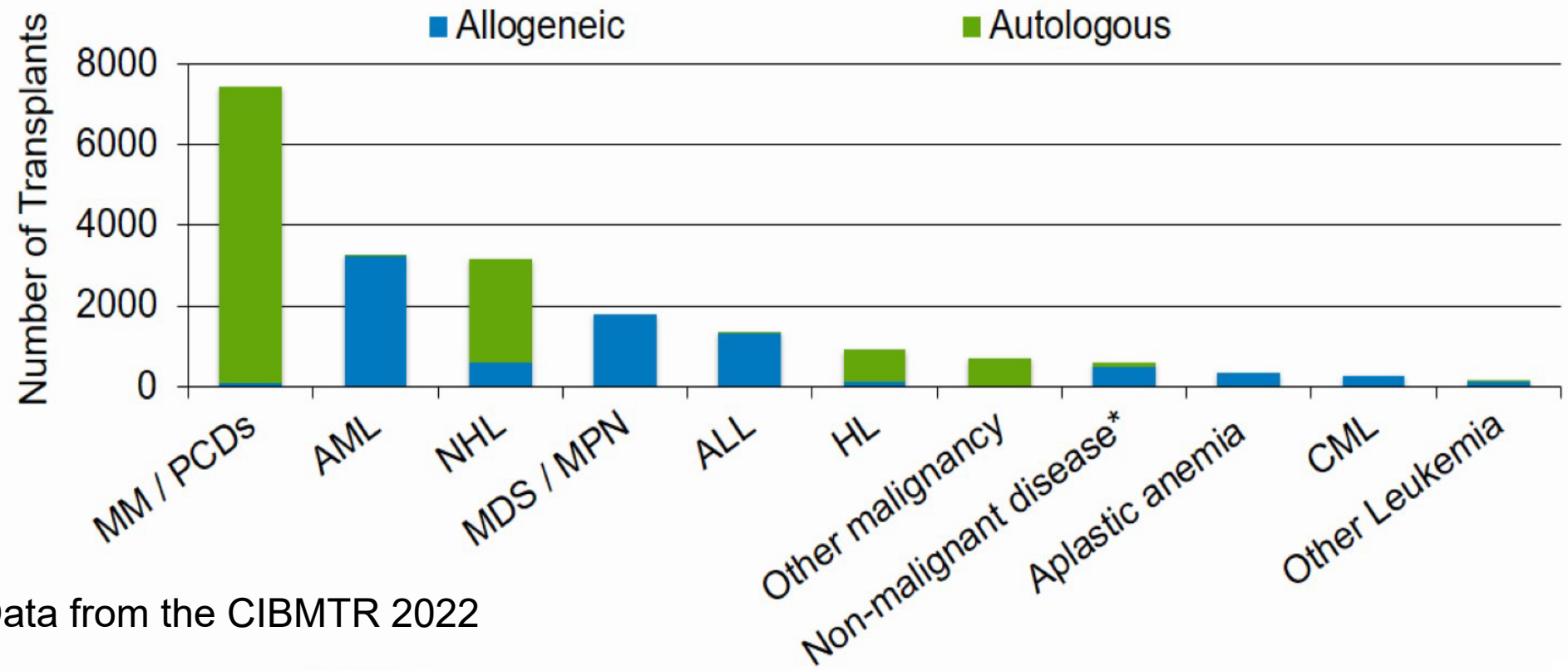
Data from the CIBMTR 2022

Number of HCTs by Indications in the US, 2020



Data from the CIBMTR 2022

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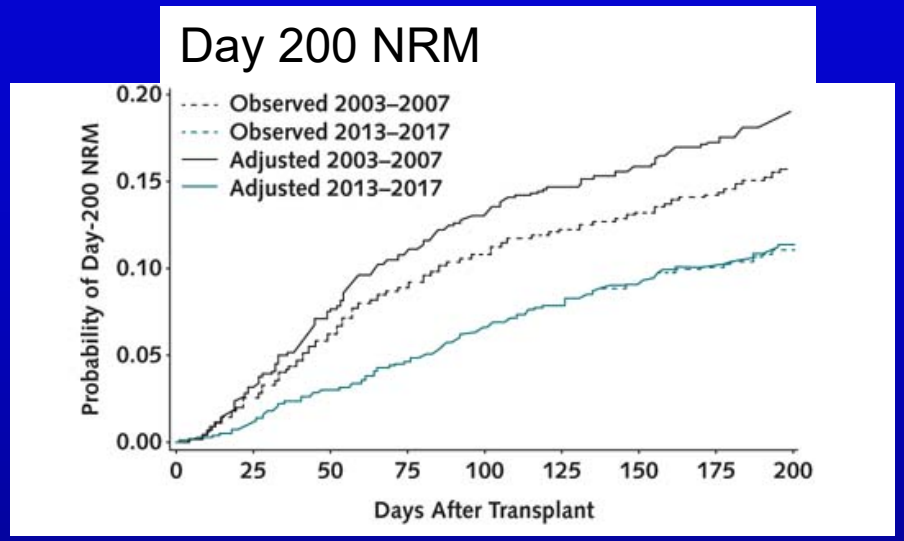
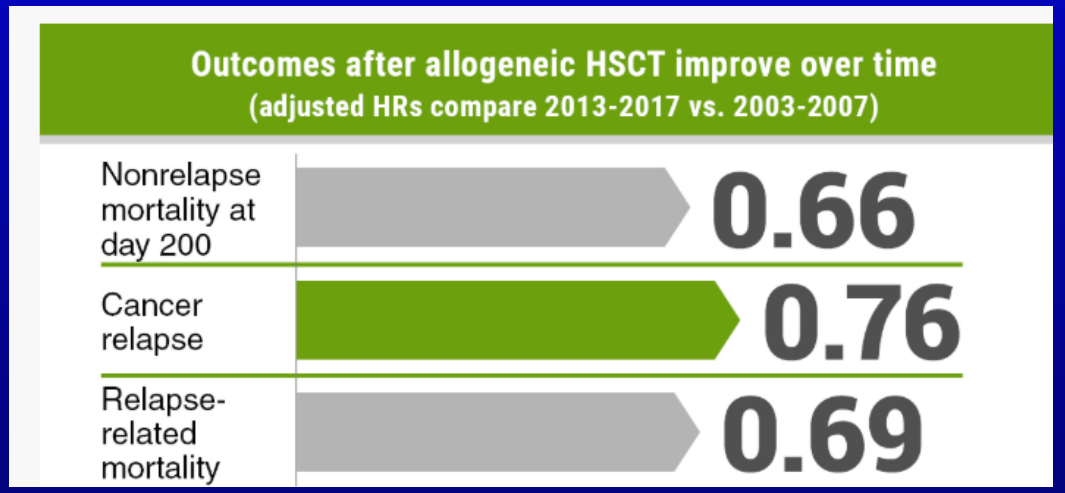
Abbreviations –
MM: Multiple myeloma;
PCDs: Plasma cell disorders;
AML: Acute myelogenous leukemia;
NHL: Non-Hodgkin lymphoma;
MDS: Myelodysplastic syndromes;
MPN: Myeloproliferative neoplasms;
ALL: Acute lymphoblastic leukemia;
HL: Hodgkin lymphoma;
CML: Chronic myeloid leukemia

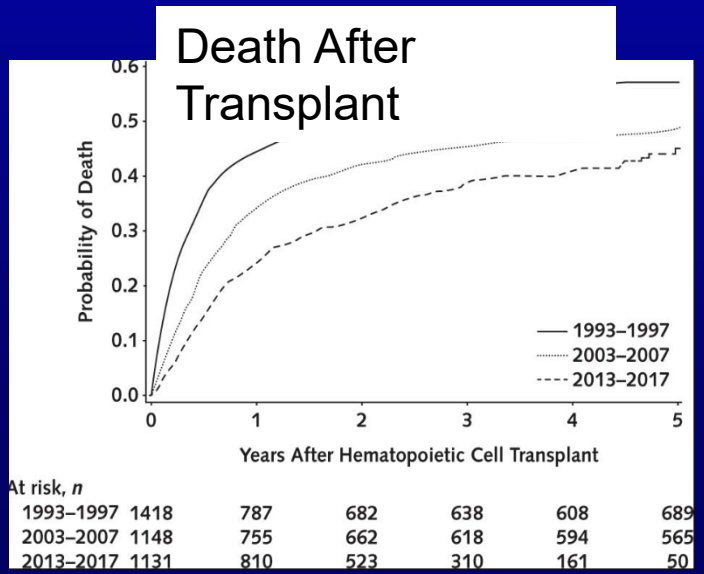
*excludes Aplastic anemia

Major Improvements in Transplant Safety Over the Past 2 Decades



2003-2007-n=1148
2013-2017- n=1131

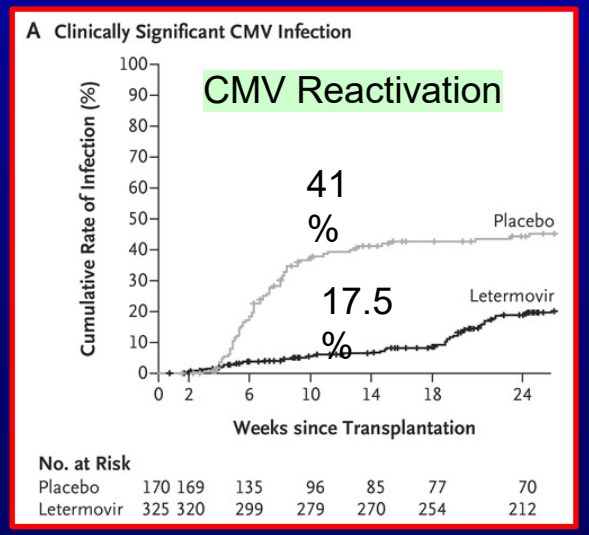


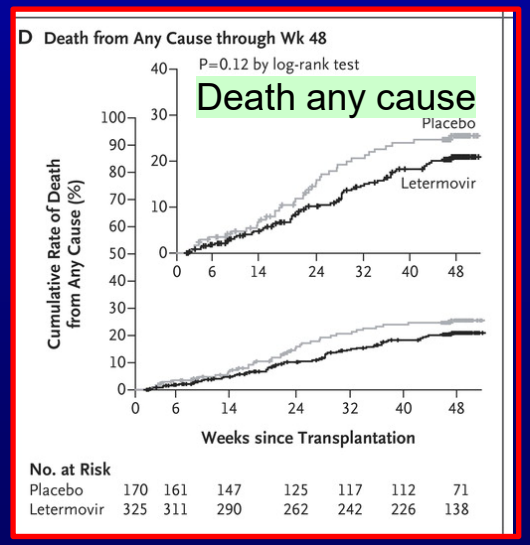


McDonald G.B. et al Annals Int Med 2020:Ann Intern Med. 2020;172:229-239.

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



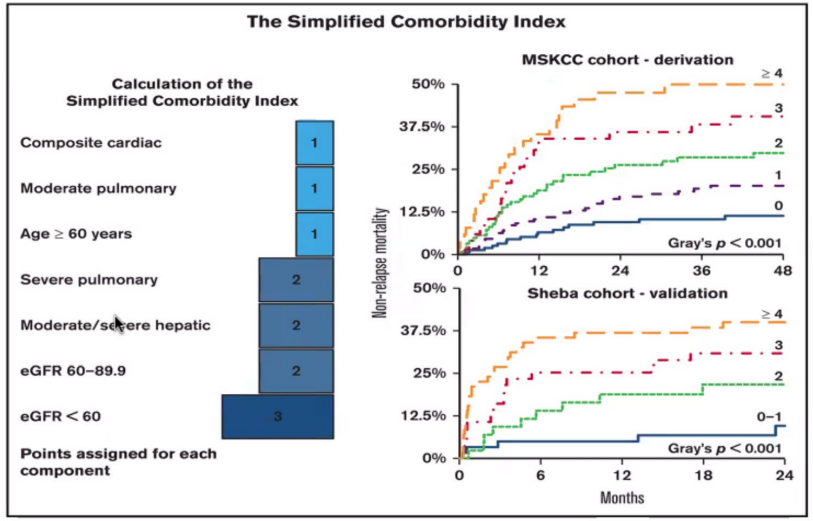


Marty F. et al. NEJM Dec 2017

Better Tools To Predict Risk of Transplant-Related Mortality (TRM)

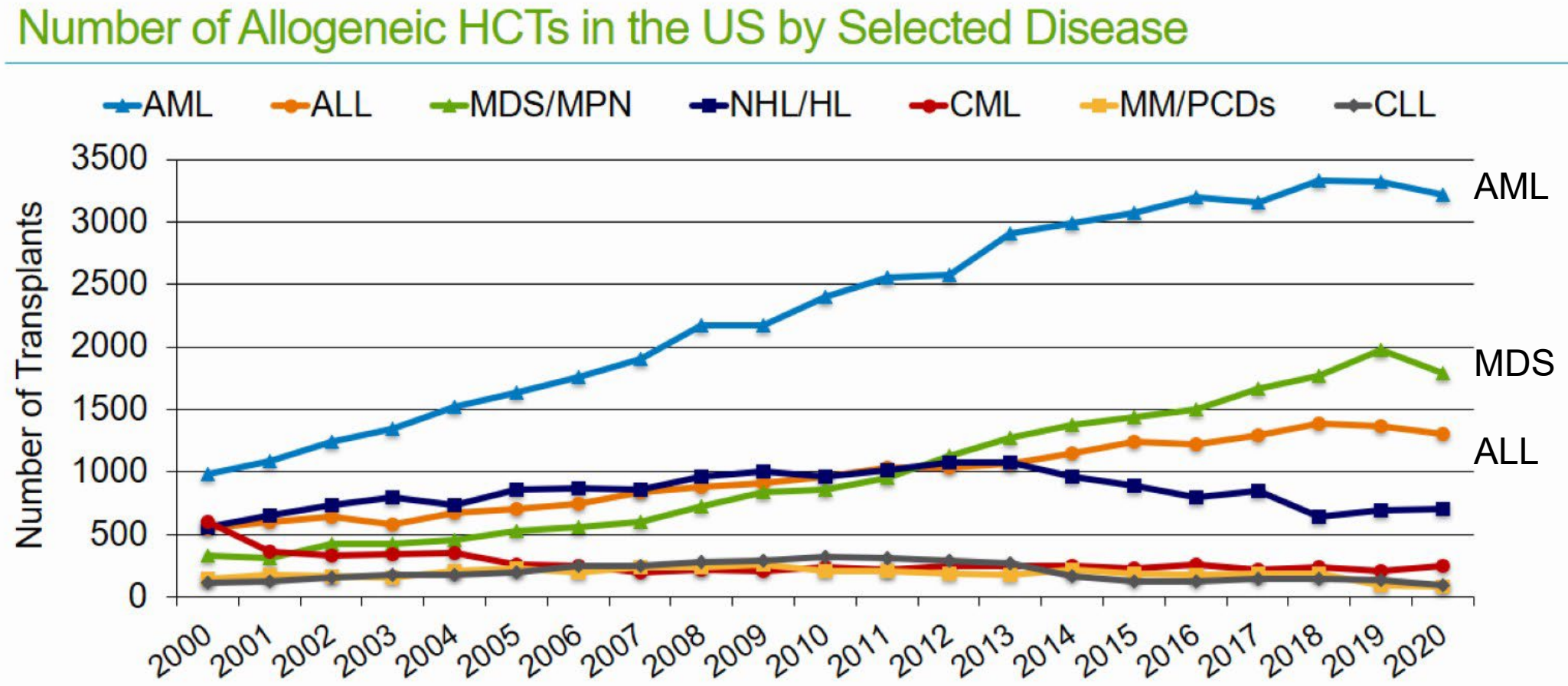
- Simplified Transplant Co-Morbidity Index
  - Can predict who does poorly with transplant
  - Cardiac, pulmonary, age, renal, hepatic status all factors that predict risk of mortality
  - Key question to always ask- What was the patient's level of fitness 3-6 months before they developed leukemia

The Simplified Comorbidity Index: a new tool for prediction of non-relapse mortality in allo-HCT



Shouval et al Blood Advances 2022

The Number of Allo-Transplants For AML, ALL and MDS Continue to Rise



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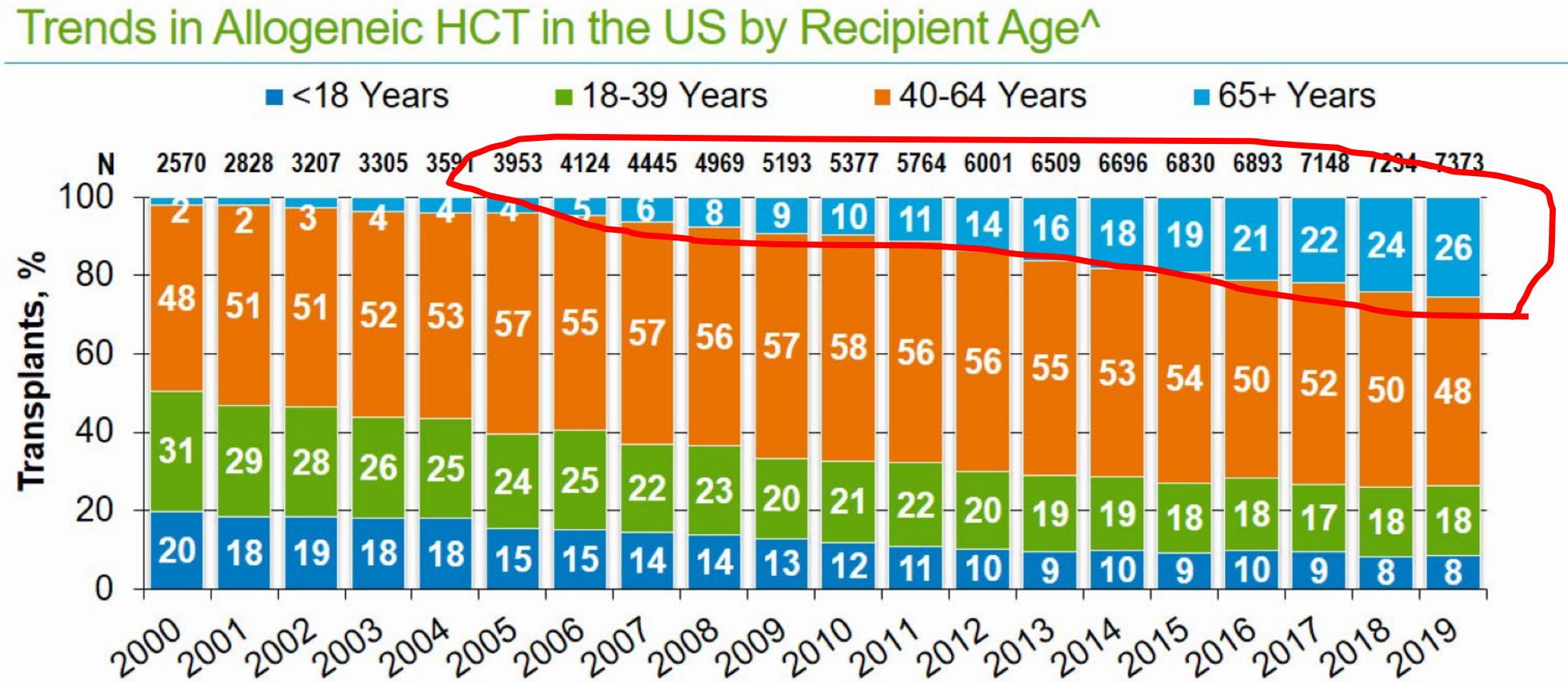
ALL: Acute lymphoblastic leukemia;
MDS: Myelodysplastic syndromes;
MPN: Myeloproliferative neoplasms;
NHL: Non-Hodgkin lymphoma;
HL: Hodgkin lymphoma;
CML: Chronic myeloid leukemia;
MM: Multiple myeloma;
PCDs: Plasma cell disorders;
CLL: Chronic lymphocytic leukemia

More Utilization of Allotransplants Amongst Older Patients



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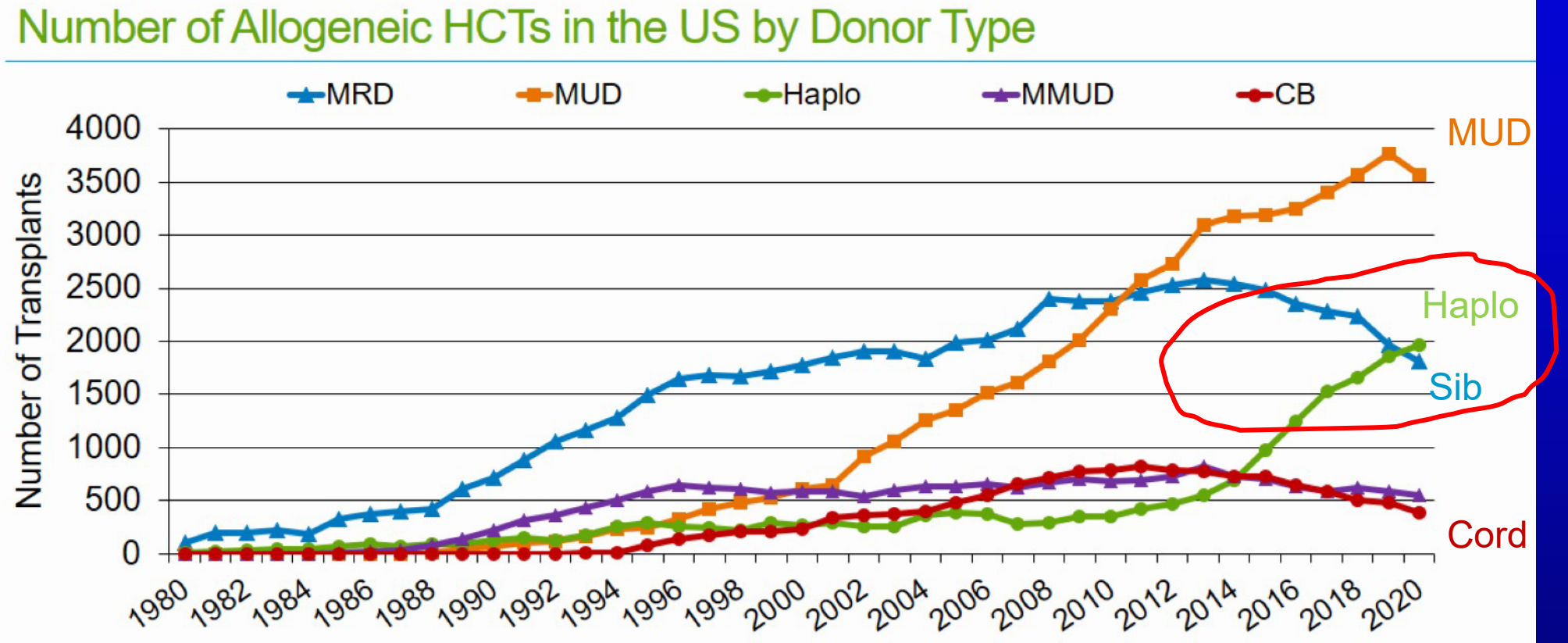
^Transplants for AML, ALL, MDS, NHL, HD, MM

Data from the CIBMTR 2022

Now More Haplo Transplants Than Sibling Transplants in the U.S.



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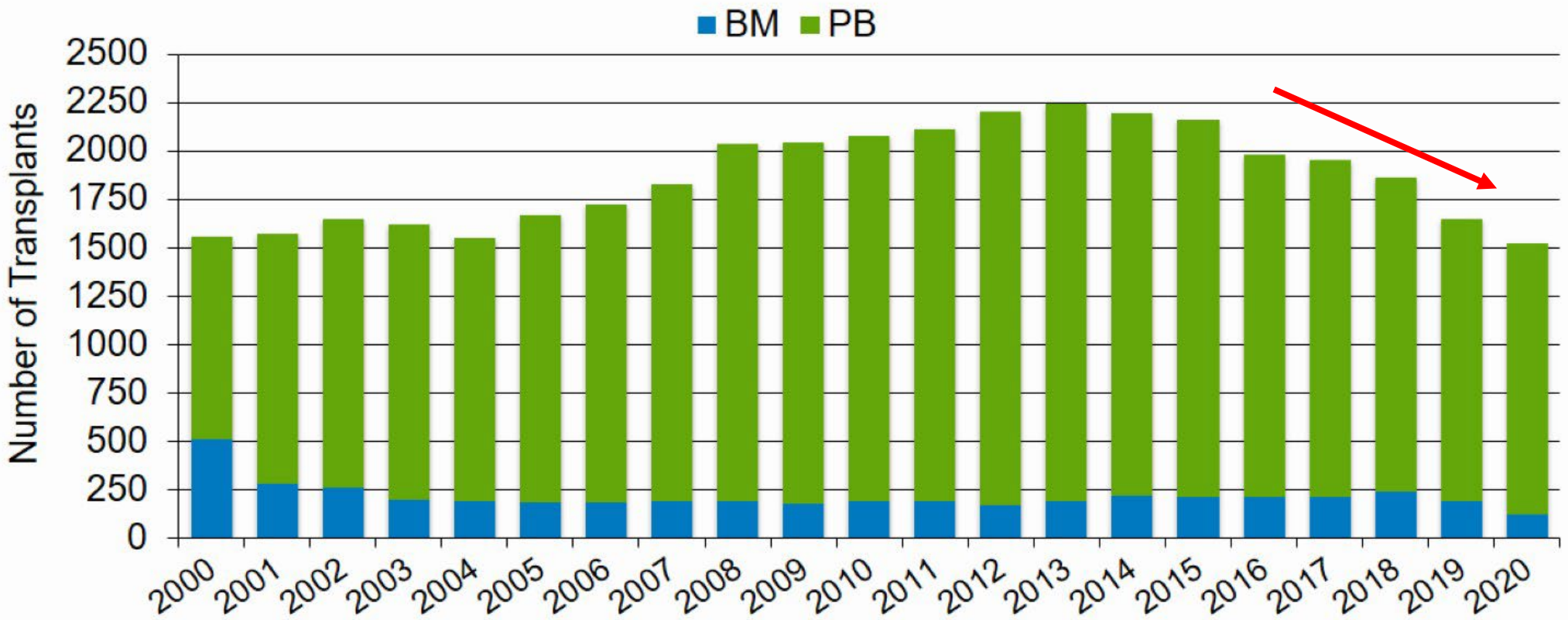
Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor;
Haplo: Haploidentical donor (includes all mismatched related donors); MMUD: Mismatched unrelated donor; CB: Cord blood

3

Data from the CIBMTR 2022

Fall In the Number Of Matched Related Donor HCTS

Number of Matched Related Donor HCTs in the US in Recipients Aged ≥18 Years by Graft Source



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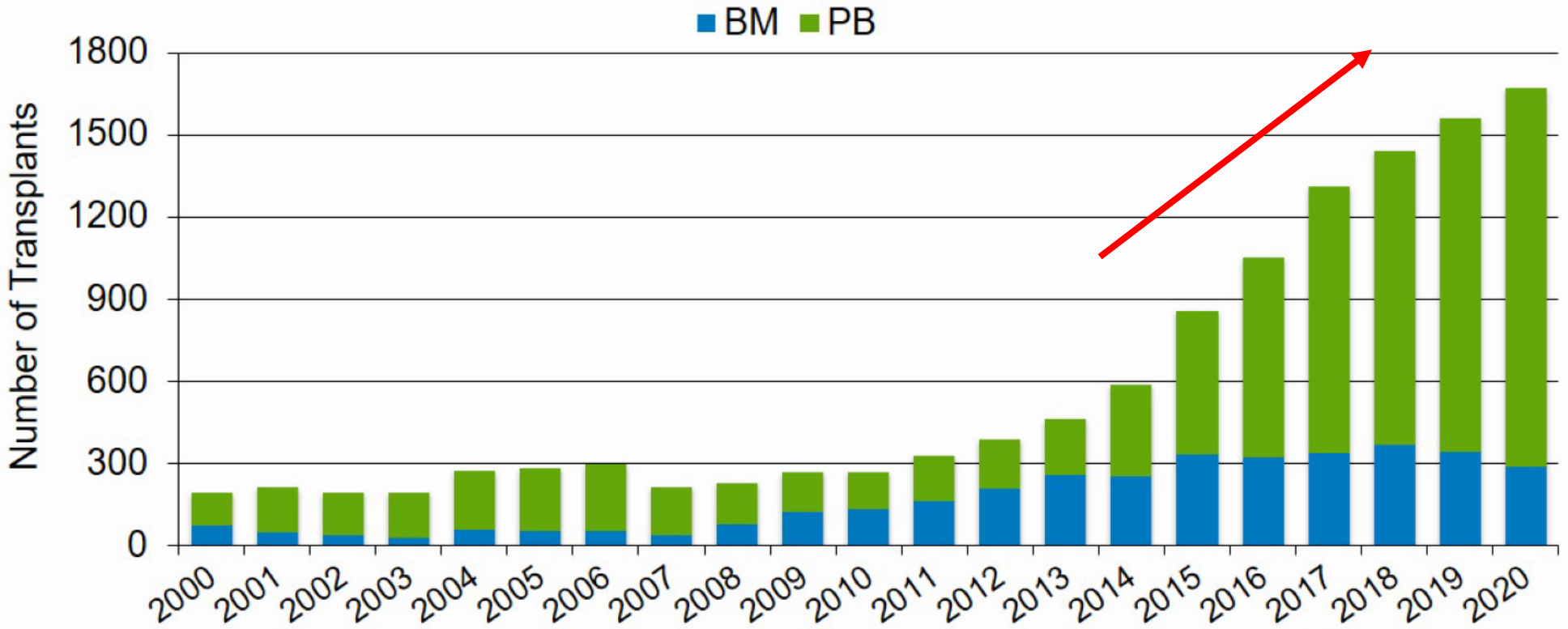
Abbreviations - BM: Bone marrow; PB: Peripheral blood

Data from the CIBMTR 2022

Number of Haploidentical Donor# HCTs in the US in Recipients Aged ≥18 Years by Graft Source



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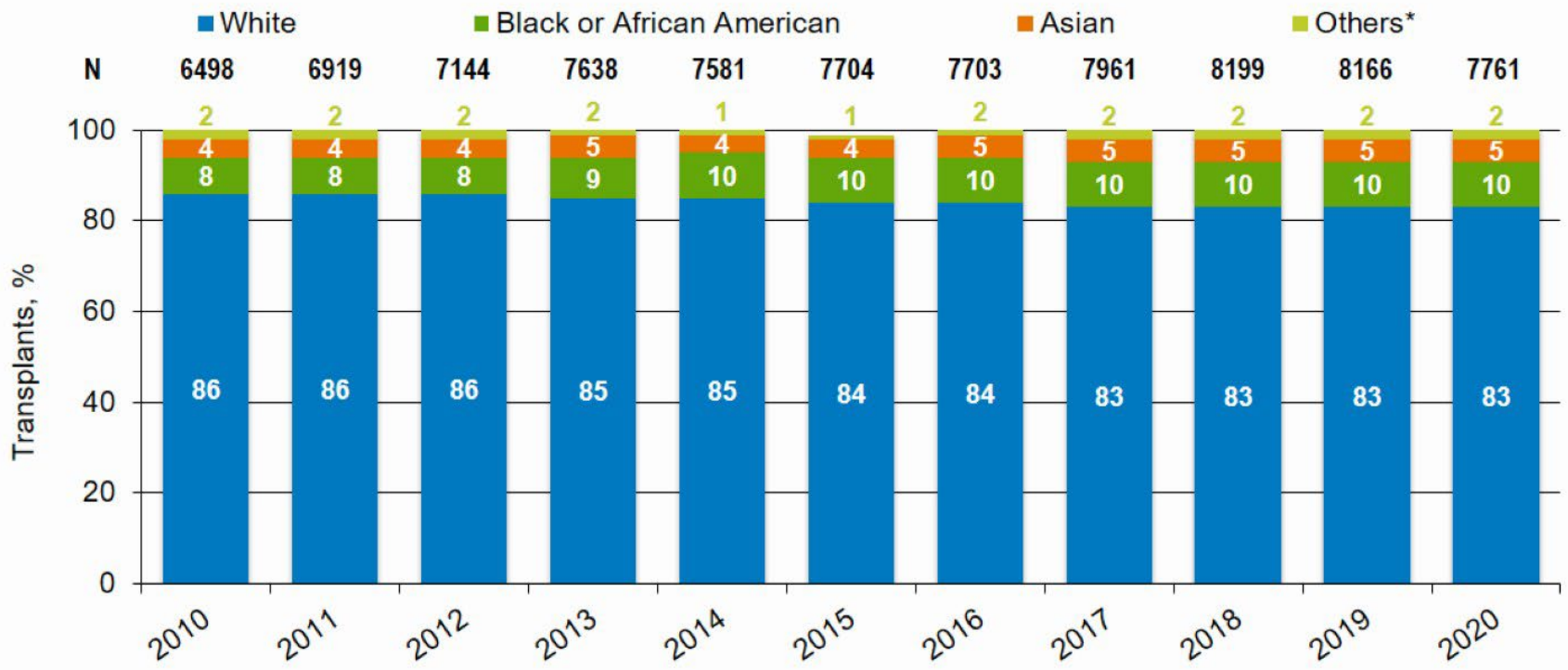
#includes all mismatched related donors; Abbreviations - BM: Bone marrow; PB: Peripheral blood

Relative Number of Allogeneic HCTs in UC by Race



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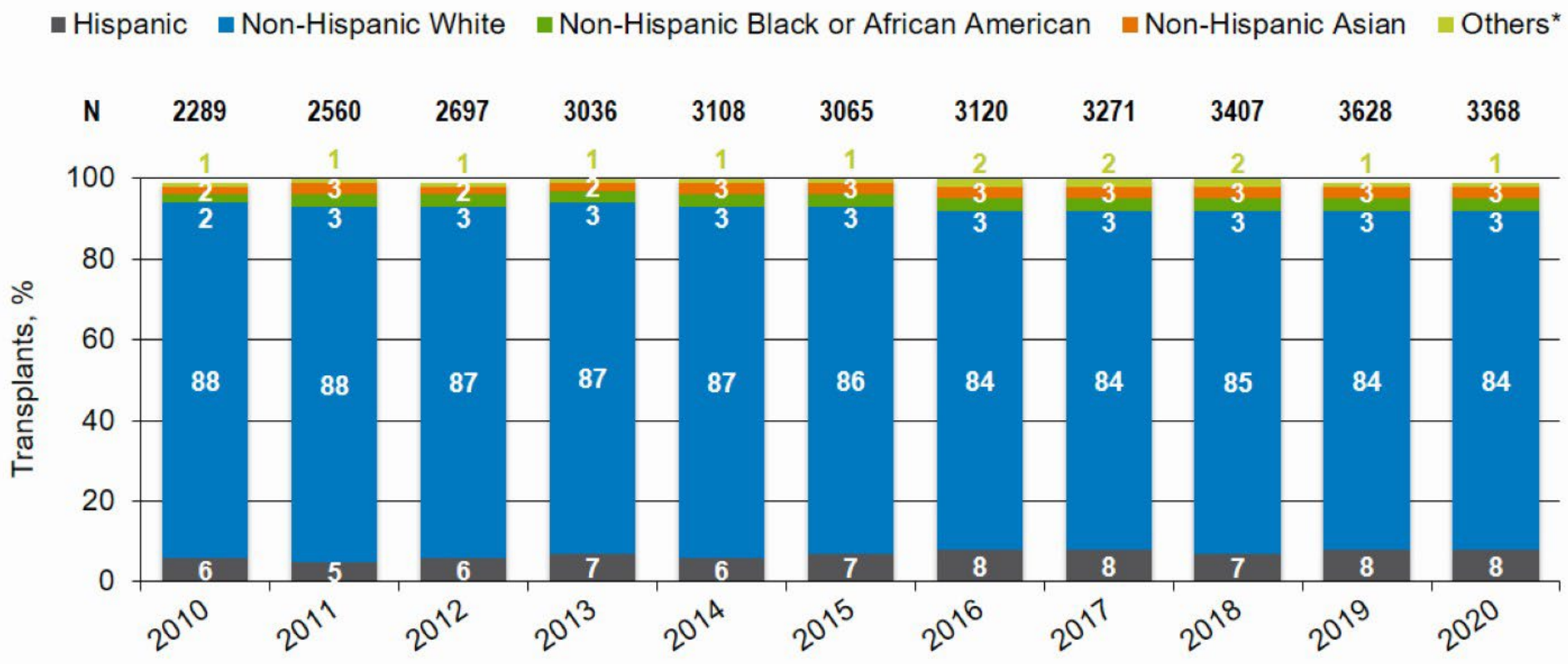
*includes Native Hawaiian or other Pacific Islander (n=23), American Indian or Alaska Native (n=43), and More than one race (n=76) in 2020

Relative Proportion of MUD Transplants in US by Race



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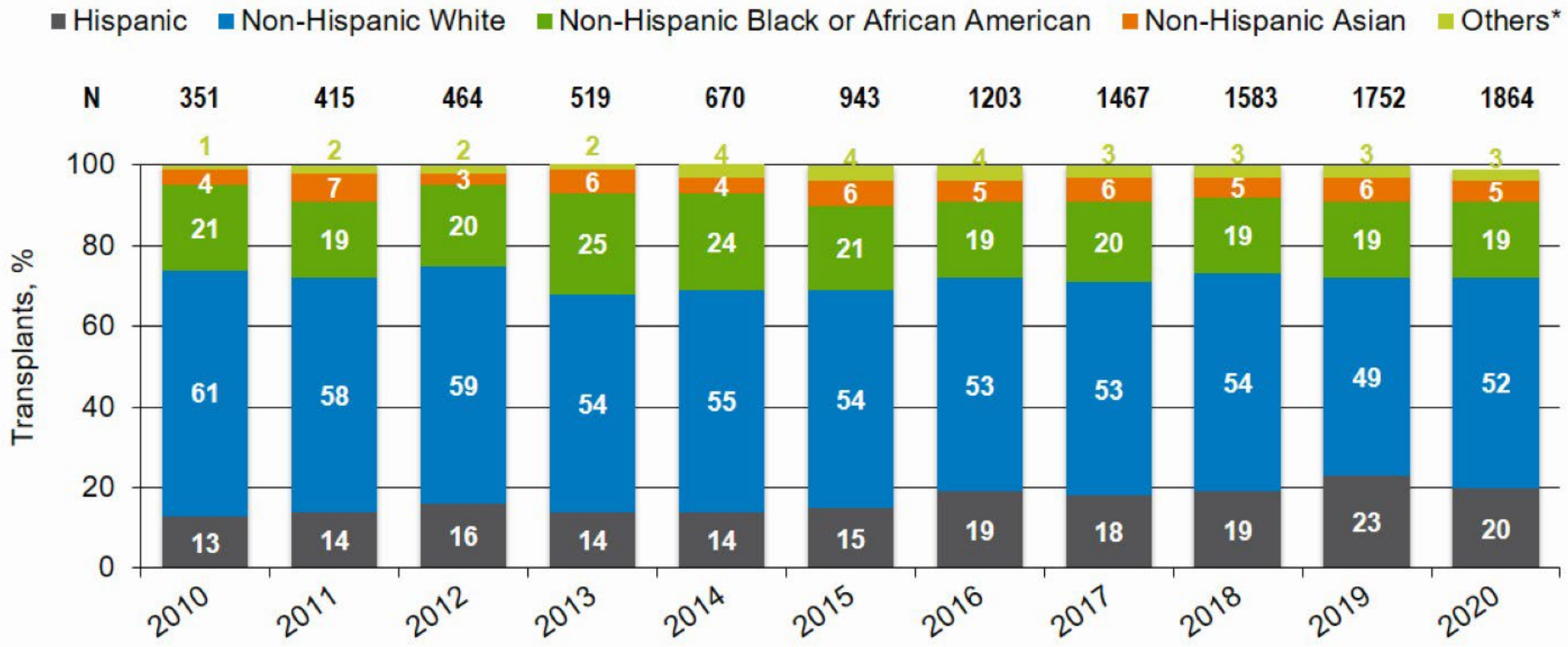
*includes non-Hispanic Native Hawaiian or other Pacific Islander (n=2), American Indian or Alaska Native (n=10), More than one race (n=17), and Non-resident of the US (n=20) in 2020

Relative Proportion of Haplo Transplants in US by Race



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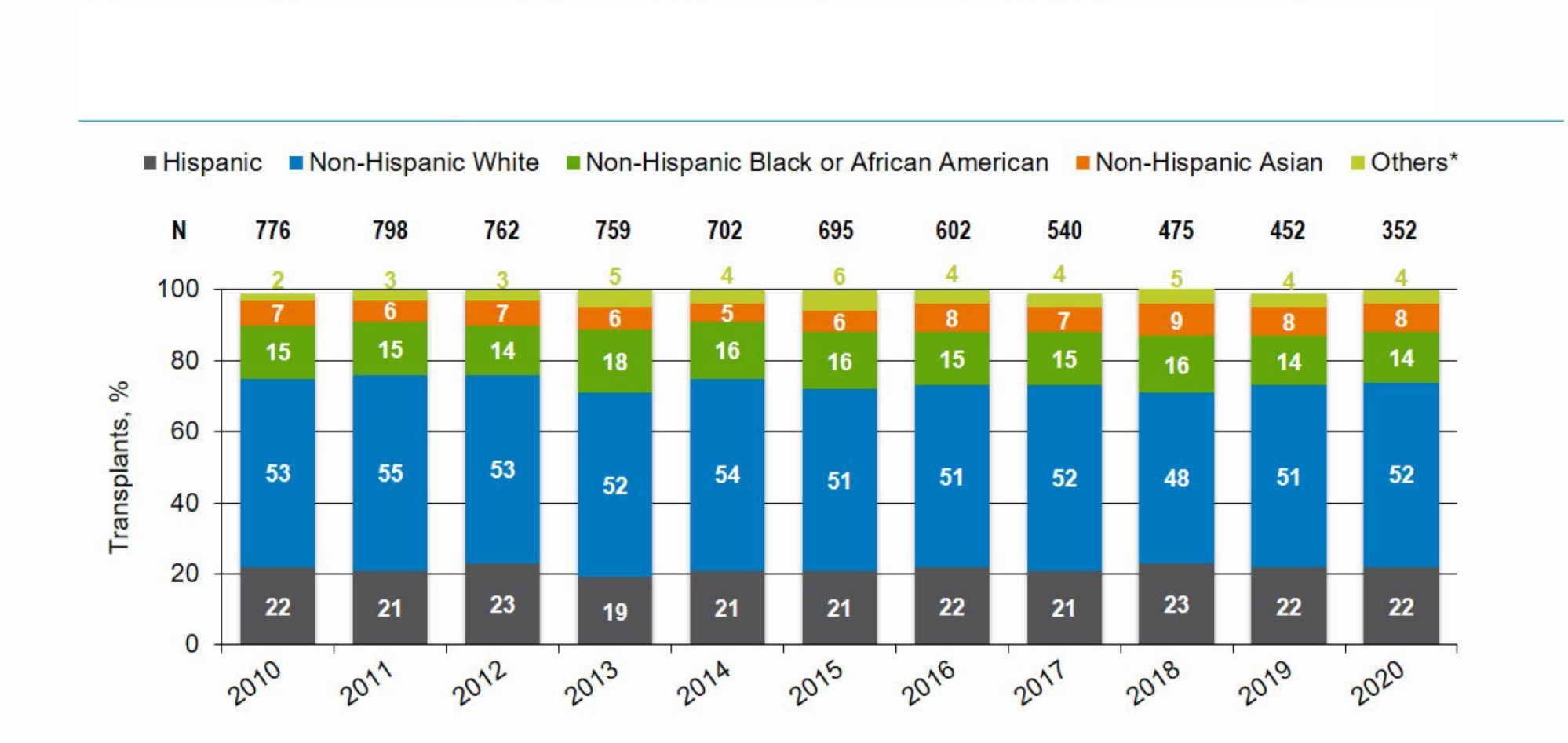
#includes all mismatched related donors
*includes non-Hispanic Native Hawaiian or other Pacific Islander (n=5), American Indian or Alaska Native (n=6), More than one race (n=16), and Non-resident of the US (n=27) in 2020

Relative Proportion of Cord Transplants in US by Race



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*includes non-Hispanic Native Hawaiian or other Pacific Islander (n=1), American Indian or Alaska Native (n=6), More than one race (n=3), and Non-resident of the US (n=3) in 2020

Cord vs Haplo: Which is Better?

Pros for Both Cords and Haplo Transplants

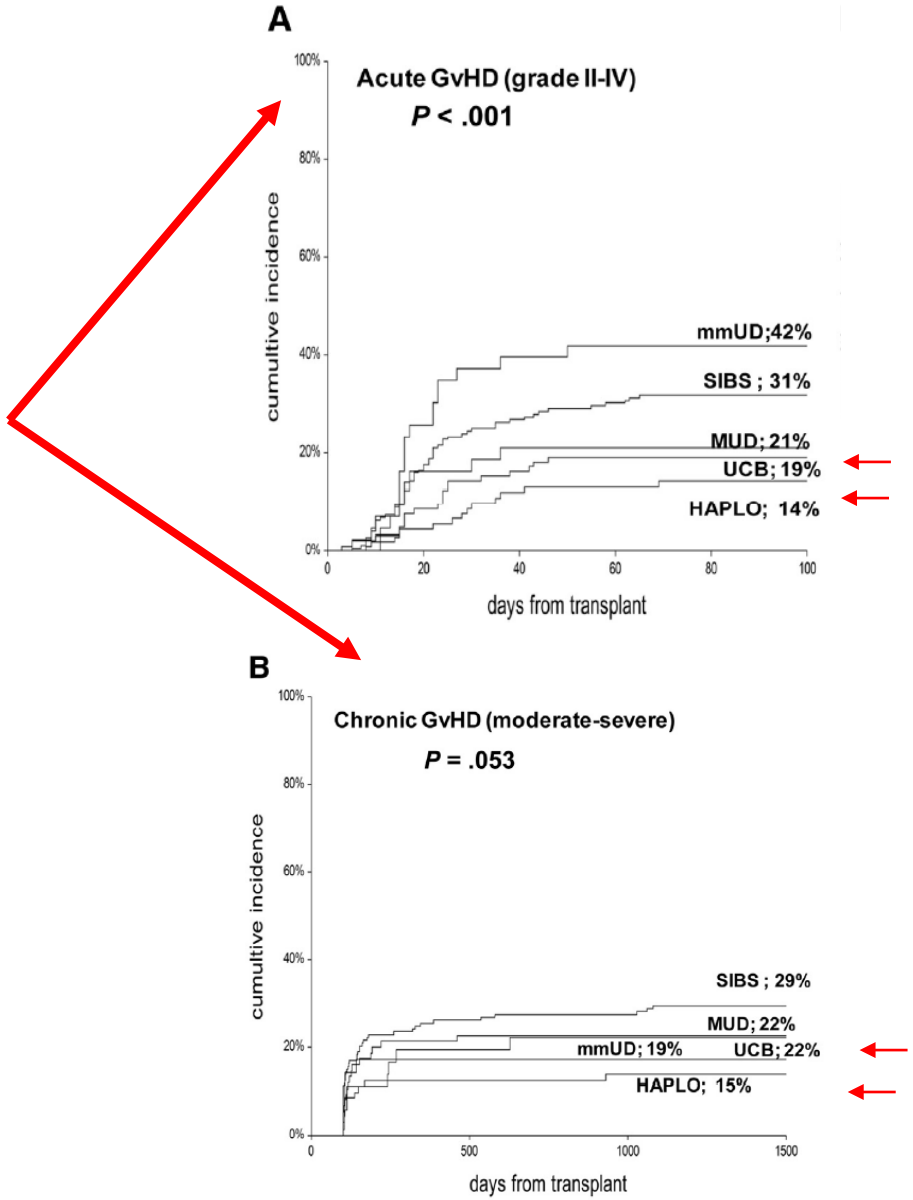
- Most adults will have a haplo donor or a cord unit for transplantation.
- Acute and chronic GVHD rates are very low with both approaches

Cons For Cords:

- Cost approx. $50,000 per graft
- Slow engraftment rates
- 15% graft failure rate
- Delayed recovery in T-cell immunity

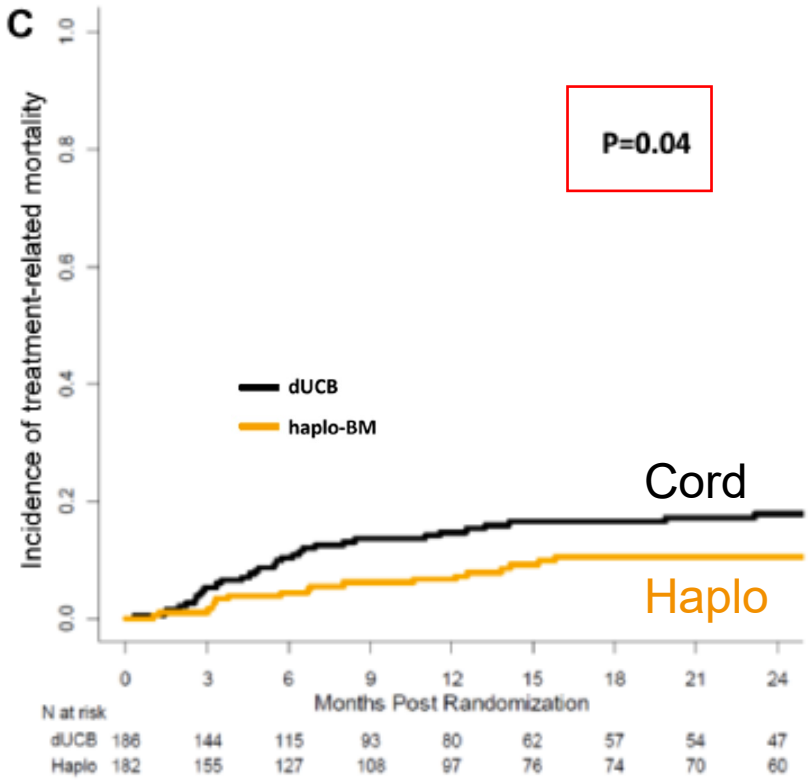
Cons for Haplos:

- Concern relapse rate may be higher??
- Graft rejection problematic for some diseases i.e SCA, SAA

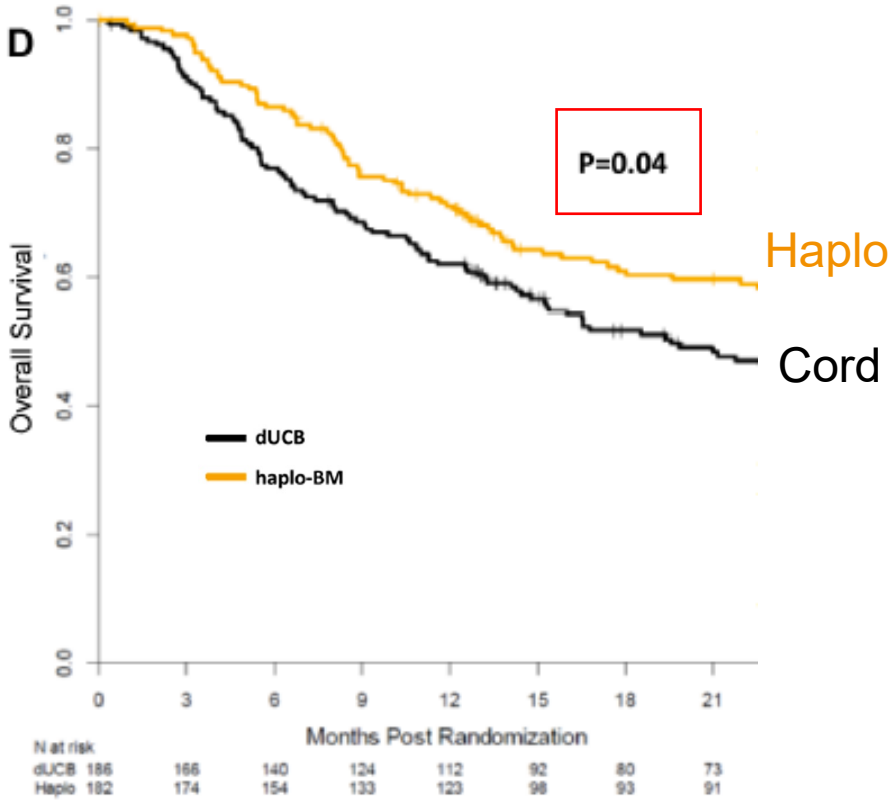


Cord vs. Haplo

Transplant related Mortality (TRM)



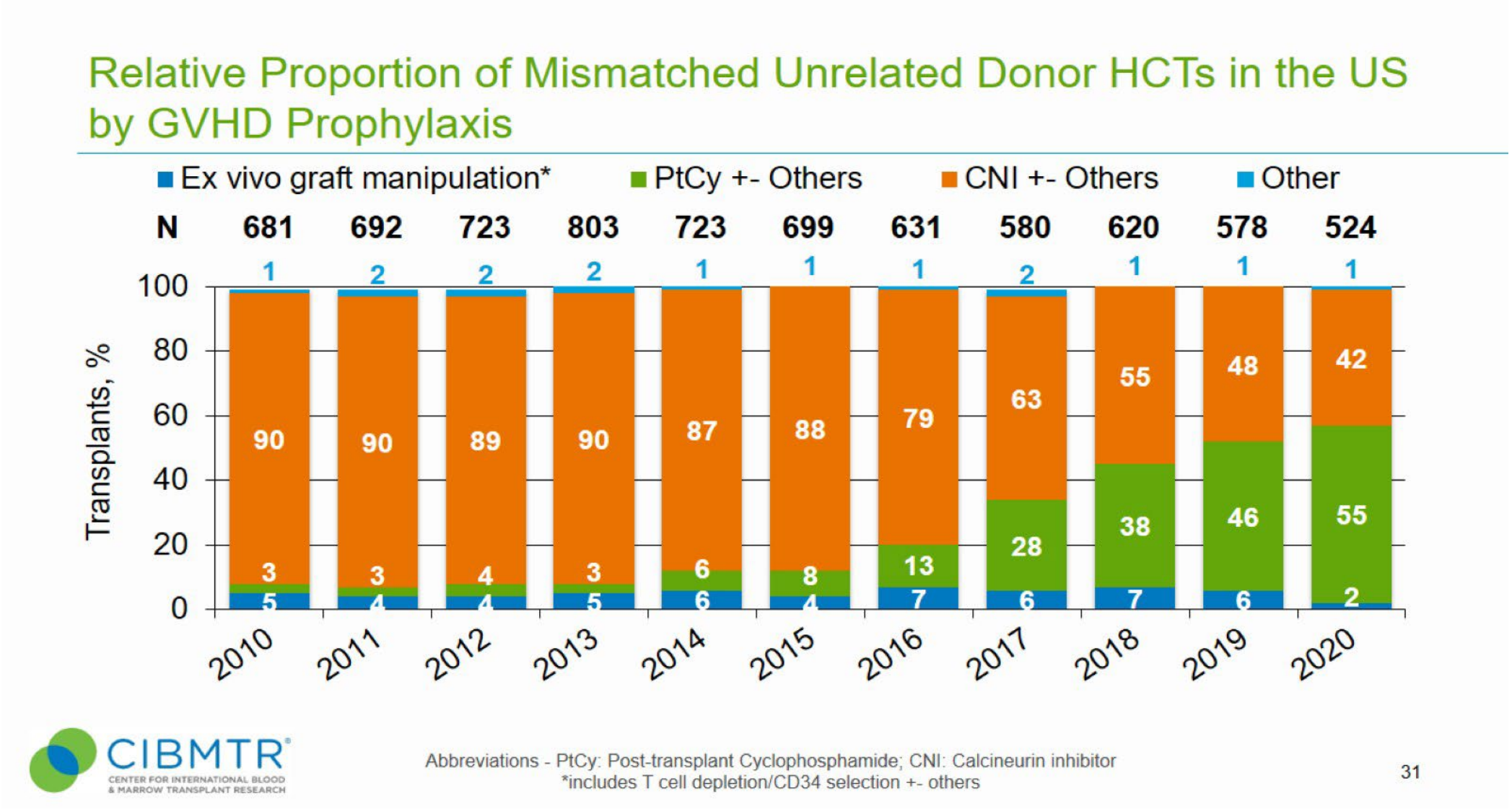
Overall Survival



- 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



Data from the CIBMTR 2022

CNI- Calcineurin Inhibitors

PtCy- post transplant cyclophosphamide

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

- These data support the concept that any haplo-identical family member can be used as a donor (avoiding Donor specific antibodies-DSA)

Younger Haplo Donors Have a Lower Risk of Causing Acute GVHD Compared To Older

Study

- CIBMTR Study 646 pts between 2013-2016

Results:

Acute GVHD not impacted by

- **degree of HLA match**
- **type of relative**
- **female into male**
- **CD3 dose**
- **Type of conditioning**
- **Graft source (PB vs BM**

- **Donor age >29 years associated with more acute GVHD**
- **Peripheral Blood RIC associated with more cGVHD**

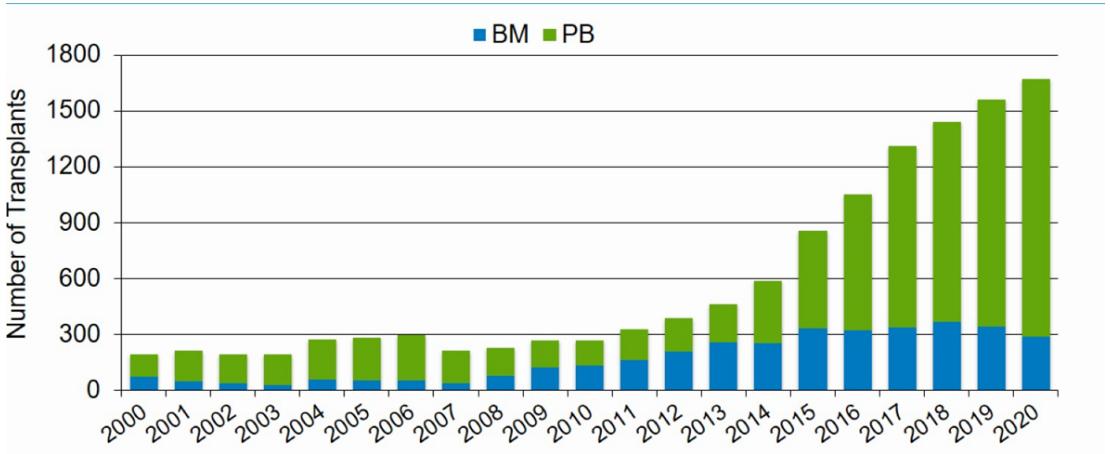
Donor Age

- G2-4: 30-49 years v <29 years
  - (HR 1.53, CI 1.11-2.12,
  - P=0.01)
- G3-4: 30-49 years v <29 years
  - (HR 3.89, CI 1.81-8.35,
  - P = 0.0005)

Im A, et al. Biol Blood Marrow Transplant. 2020 Aug;26(8):1459-1468.

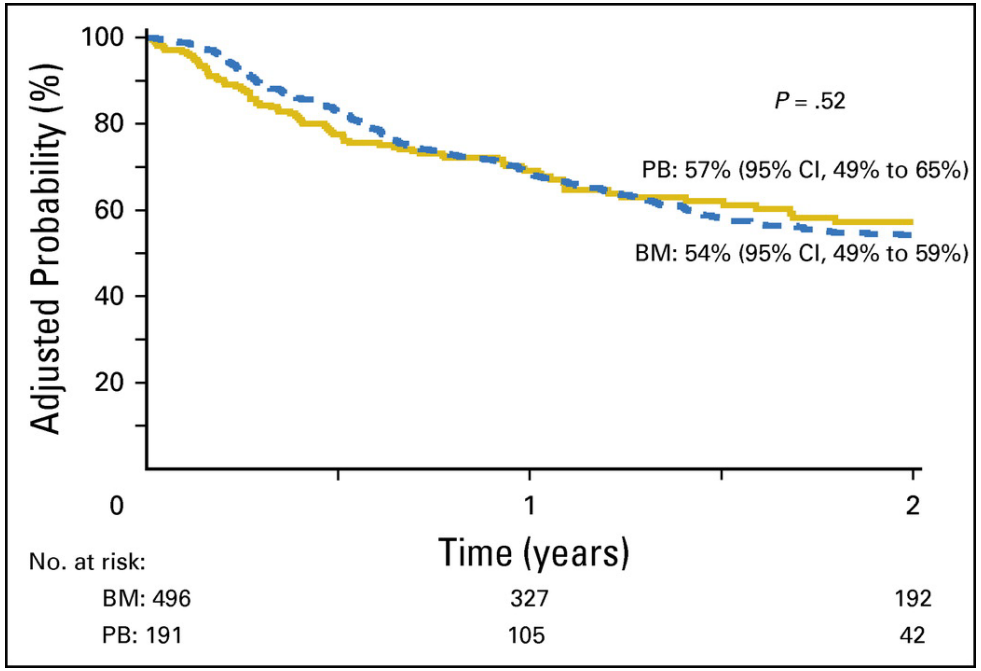
Haplo Transplants and Graft Source: More PBSC then BM With Similar Outcome

Haplo-Transplants and Graft Source



PBSC=Peripheral Blood Stem Cell
BM= Bone marrow

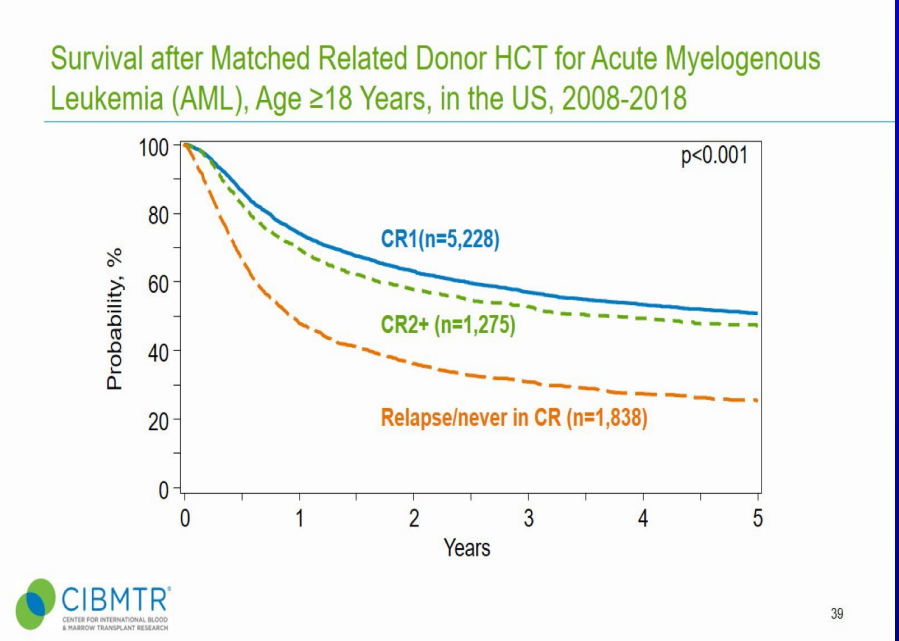
Haplo-Transplants and Graft Source and Survival



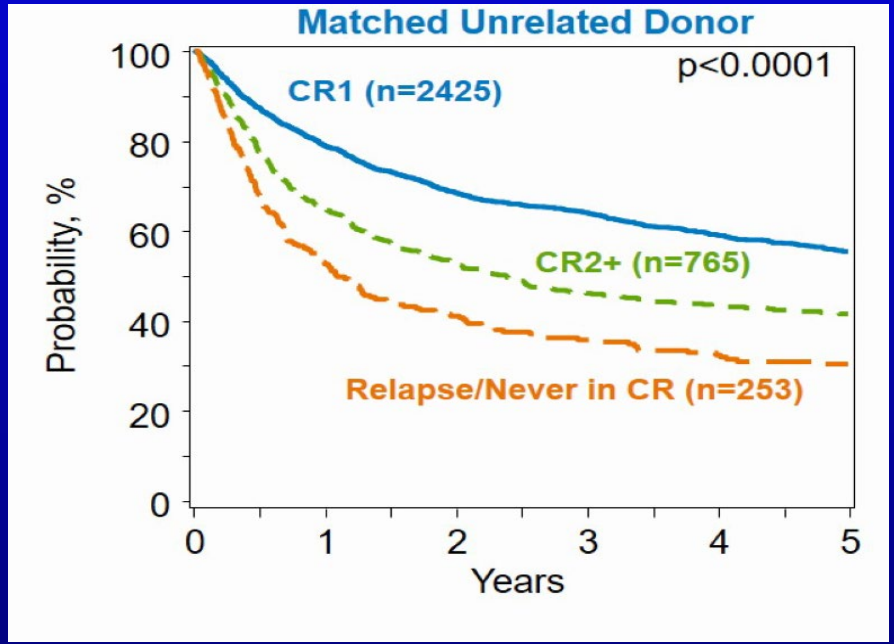
Bashey et al, JCO 2017

Allogeneic Transplant For Hematological Malignancies: The Earlier the Better

MRD Transplants For AML



MUD Transplants For ALL

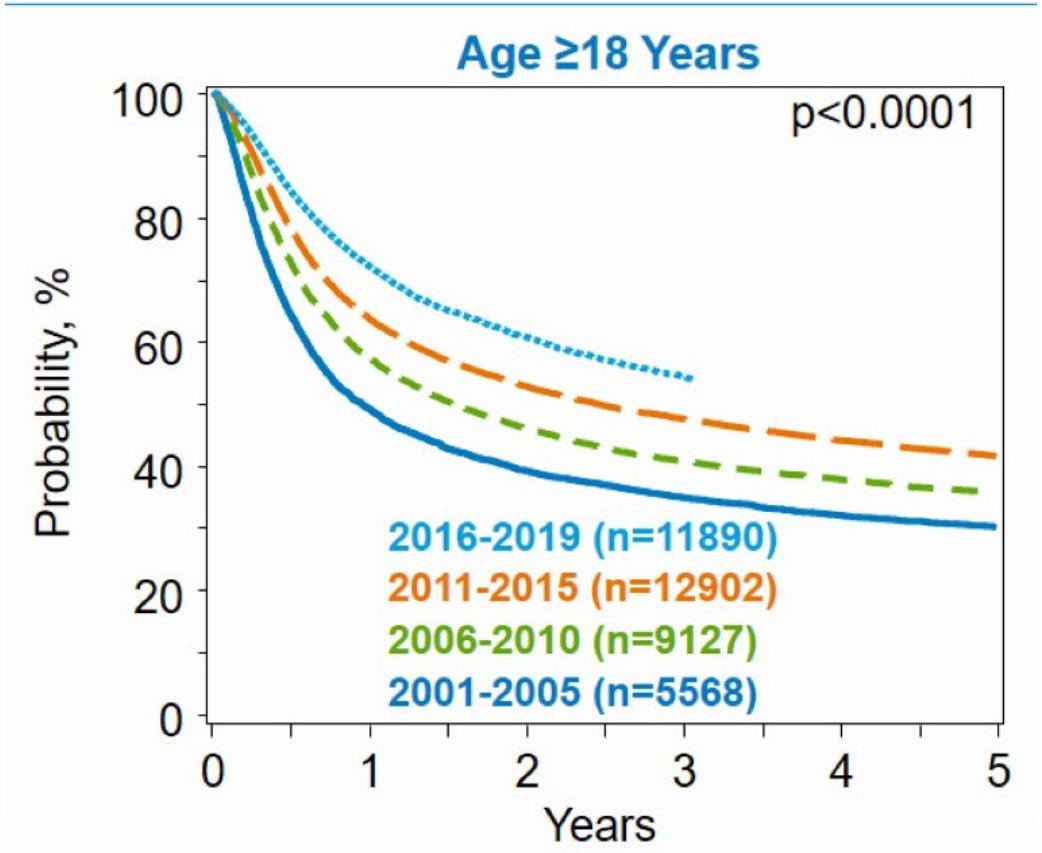


Reduced transplant-related mortality and lower relapse with the earlier use of transplants has led to an increasing use of allogeneic transplants upfront for leukemia in CR-1

CIBMTR Data 2020

Survival Improving In AML Patients Undergoing Allogeneic HCT Over The Past 2 Decades

Trends in Survival after Allogeneic HCTs for Acute Myelogenous Leukemia (AML), in the US, 2001-2019



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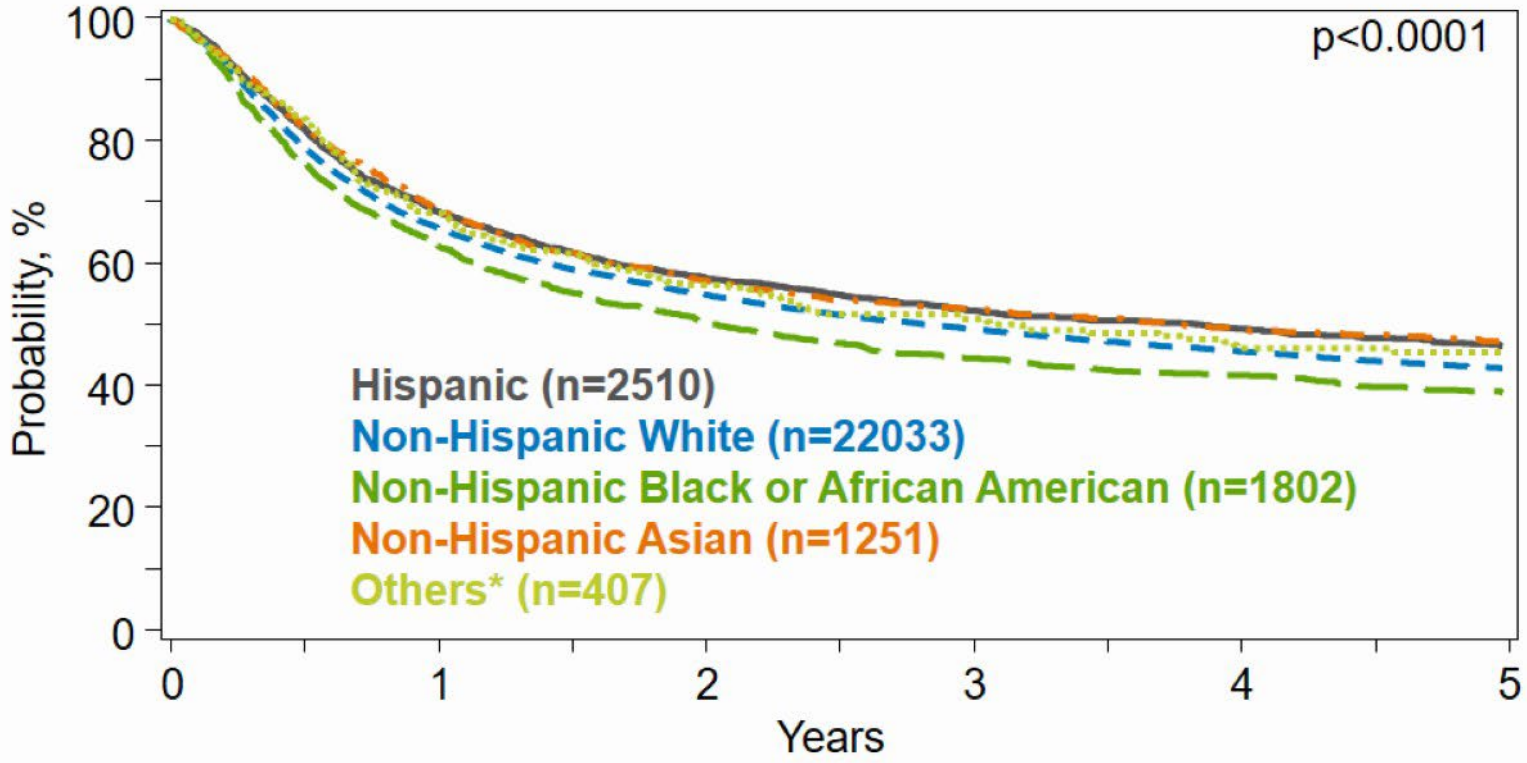
Race and Ethnicity And Survival Following Allo BMT for AML

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



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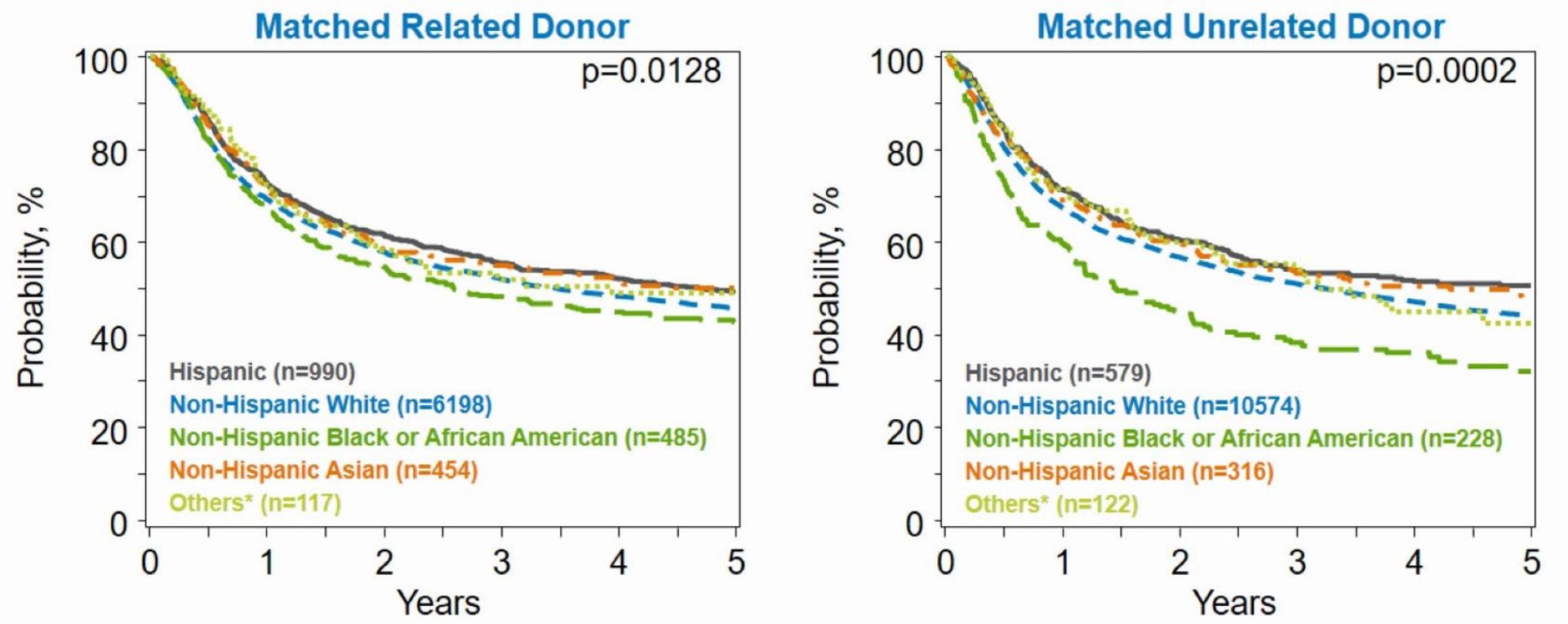
*includes Non-Hispanic Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, More than one race, and Non-resident of the US

Race and Ethnicity And Survival Following Allo 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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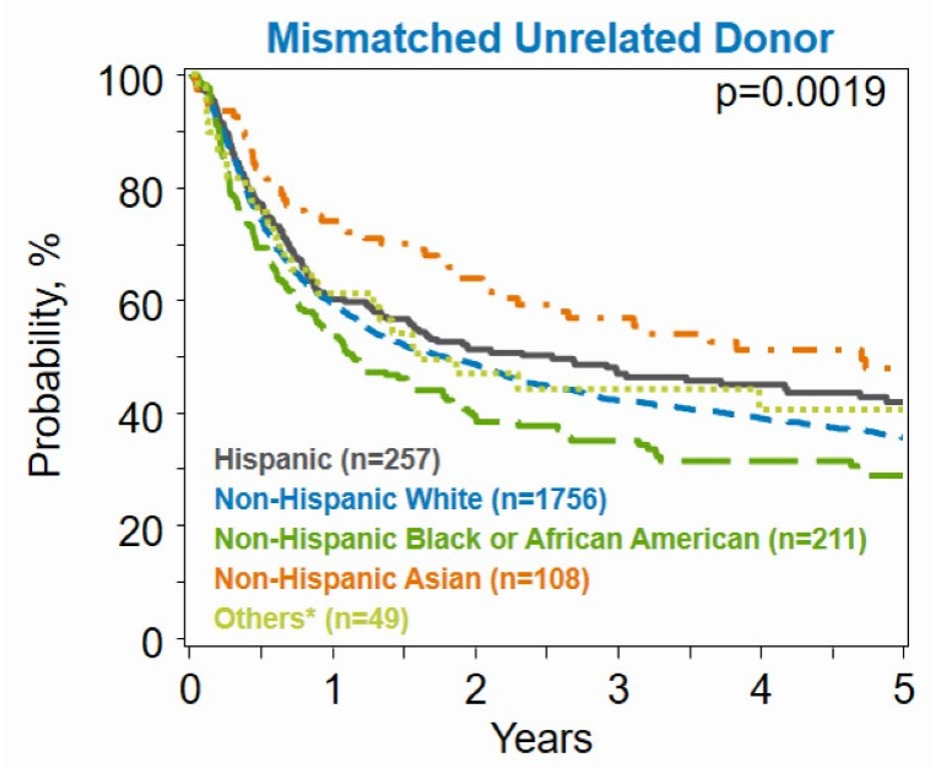

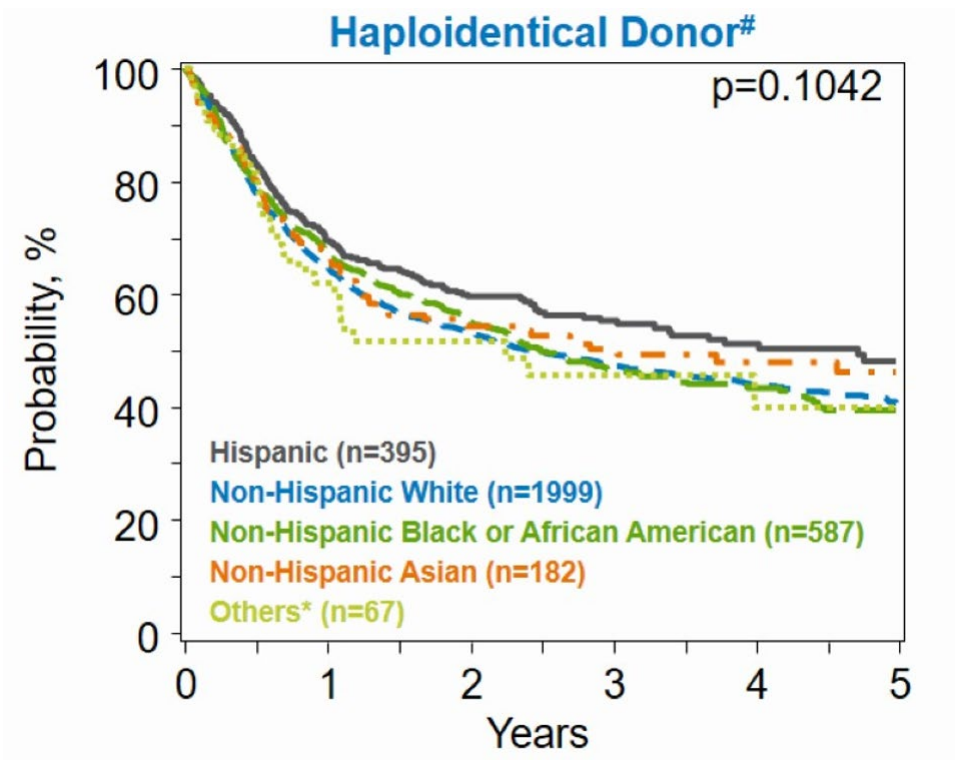

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Relapse Remains The Major Cause of Death After Allogeneic HCT

Age ≥18 years
Total transplants = 2985

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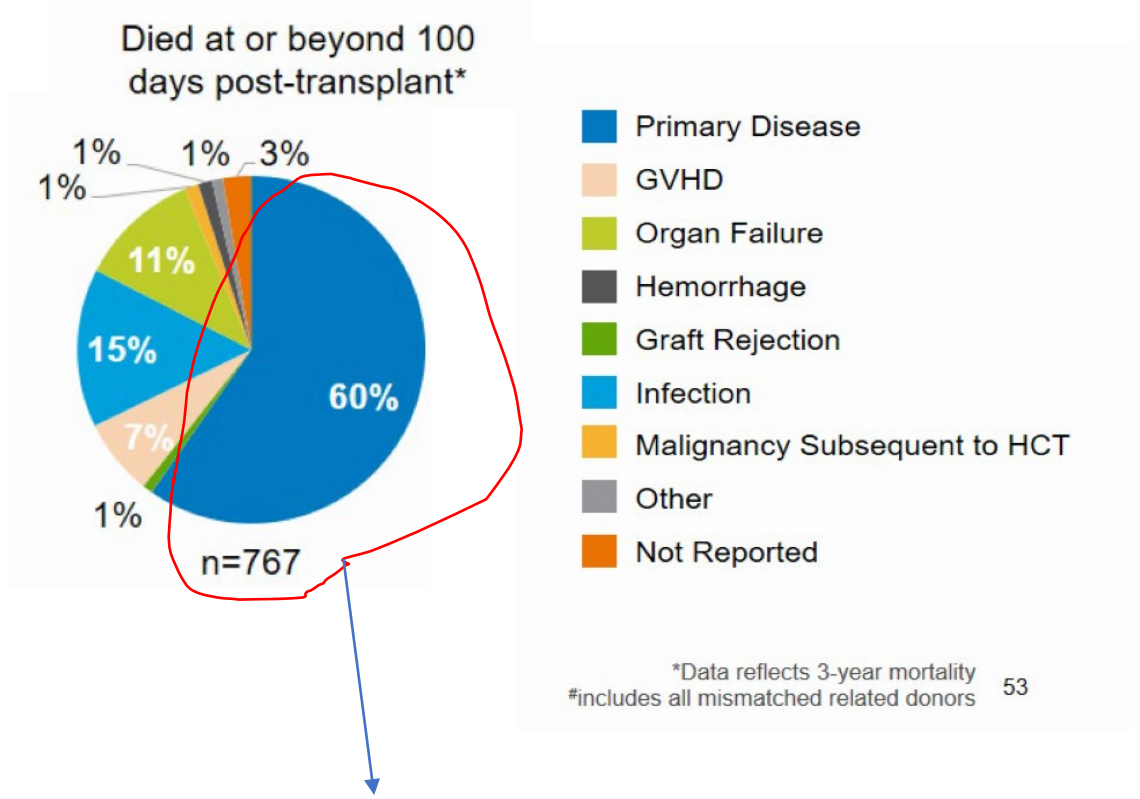
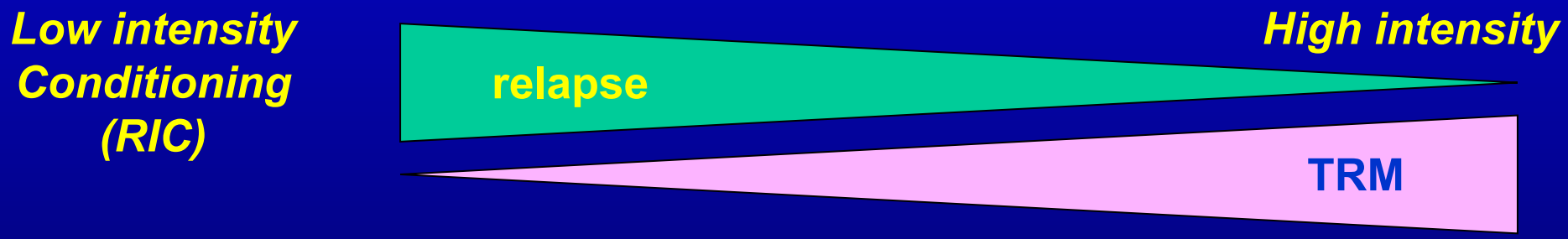


RELAPSE!!

Reduced Intensity Conditioning (RIC): Decreases Risk Of TRM But May Increase Risk of Relapse For Some Malignancies



Possibility of increased risk of relapse (i.e. AML, MDS) with reduced intensity transplants

TRM= Transplant Related Mortality

Trial: Myeloablative vs. Reduced Intensity Allogeneic Transplantation for AML/ MDS

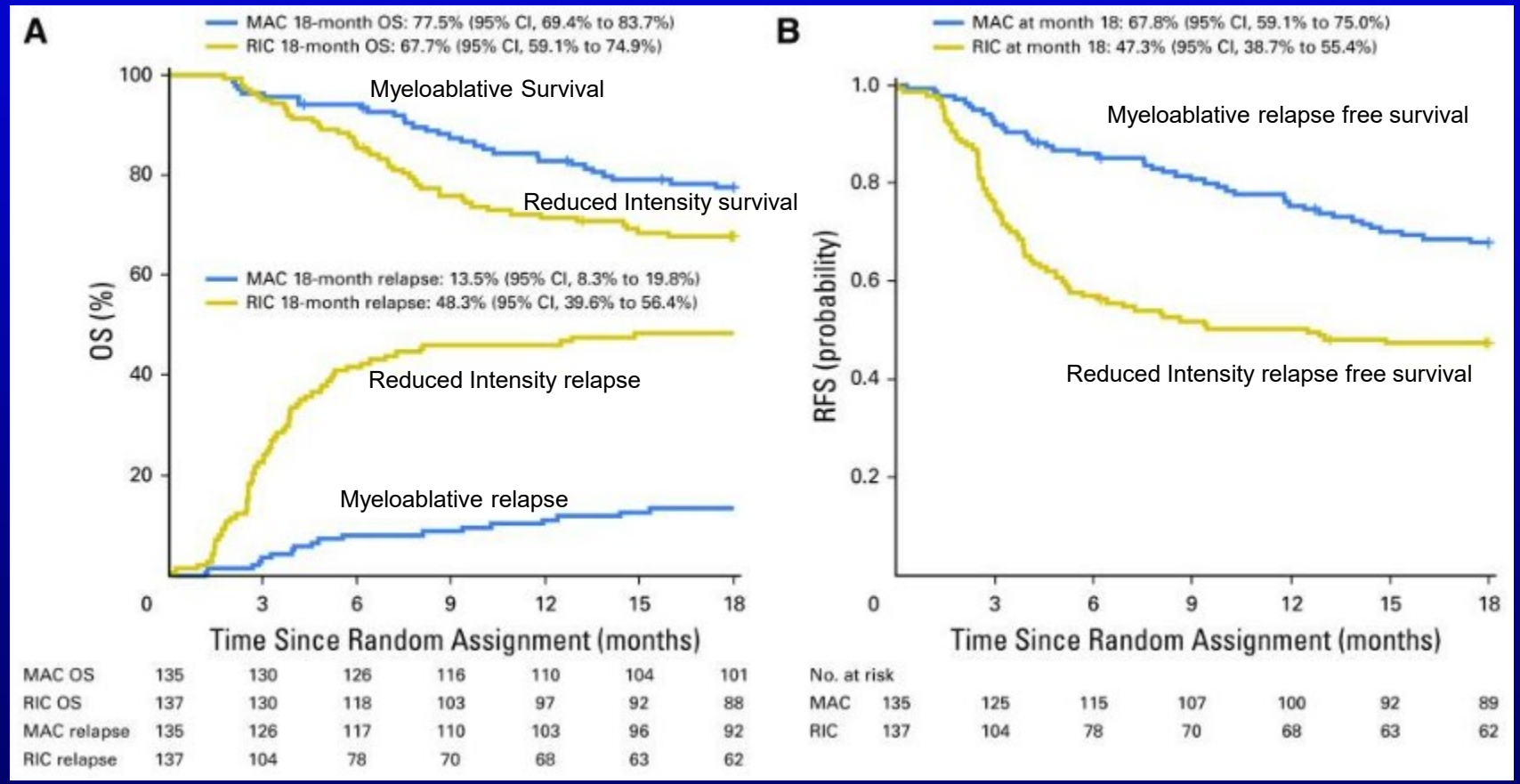
- **Hypothesis:**
  - **Alternative: The l**ower treatment-related mortality (TRM) with reduced-intensity conditioning (RIC) would result in improved overall survival (OS) compared with myeloablative conditioning (MAC).
  - Null: Higher relapse with reduced-intensity conditioning (RIC) would result in inferior overall survival (OS) compared with myeloablative conditioning (MAC).

- **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

Scott et al JCO 2017

Myeloablative Transplant For AML is Associated With A Reduced Risk of Disease Relapse For Acute Myeloid Leukemia and MDS



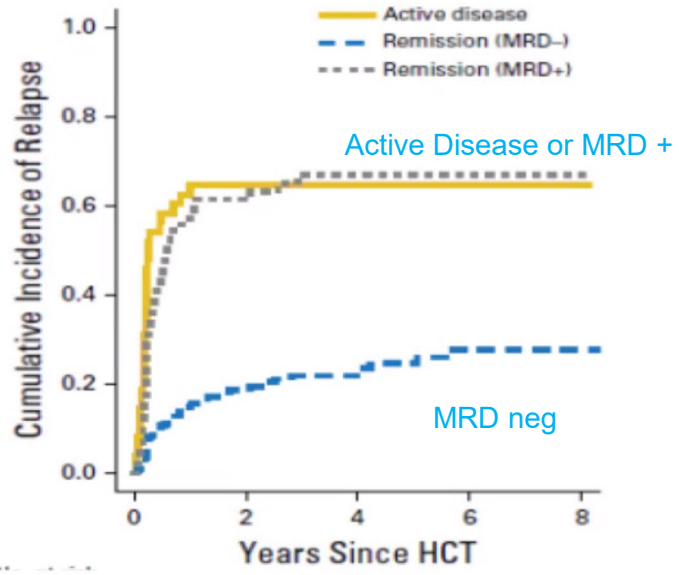
Scott et al JCO 2017

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

Impact of pre-transplant MRD on transplant outcome is related to conditioning regimen intensity

MRD+ result may alter decisions to transplant

Relapse by MRD status pre MAC SCT



Araki, et al. J Clin Oncol. 2015

Impact of Conditioning Intensity of Allogeneic Transplantation for AML With Genomic Evidence of Residual Disease

METHODS:

- Ultra-deep sequencing for 13 commonly mutated genes in AML was performed on preconditioning in adult patients with myeloid malignancy in morphologic complete remission to myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC).

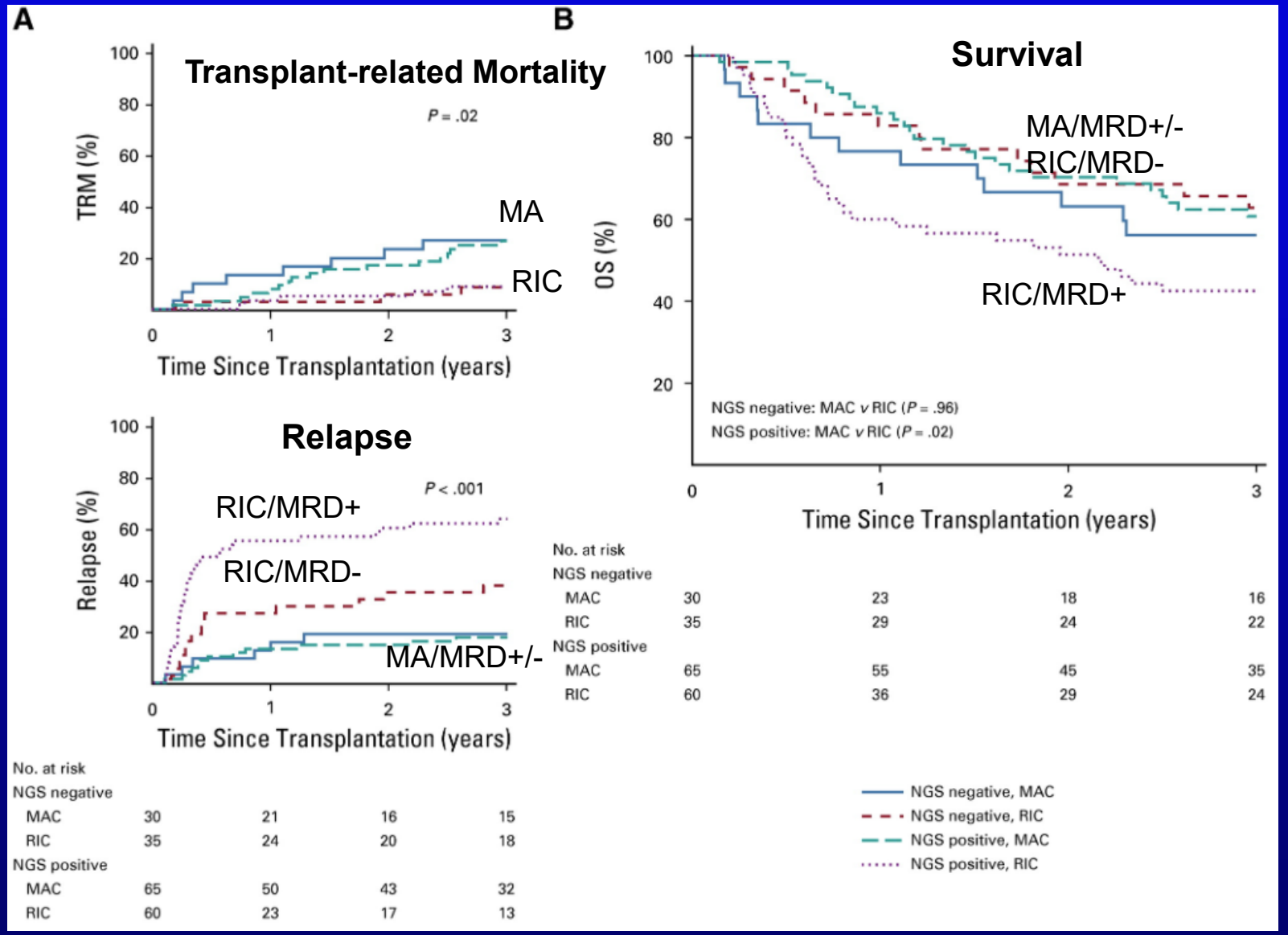
RESULTS:

- No mutations were detected in 32% of MAC and 37% of RIC recipients;
  - these groups had similar survival (3-year overall survival [OS], 56% *v* 63%; *P* = .96).
- In patients with a detectable mutation RIC was significantly associated with increased relapse (hazard ratio [HR], 6.38; 95% CI, 3.37 to 12.10; *P* < .001), decreased relapse-free survival (HR, 2.94; 95% CI, 1.84 to 4.69; *P* < .001), and decreased OS (HR, 1.97)

CONCLUSION:

In patients with AML with genomic evidence of MRD before alloHCT, MAC rather than RIC results in improved survival

Hourigan et al JCO 2019

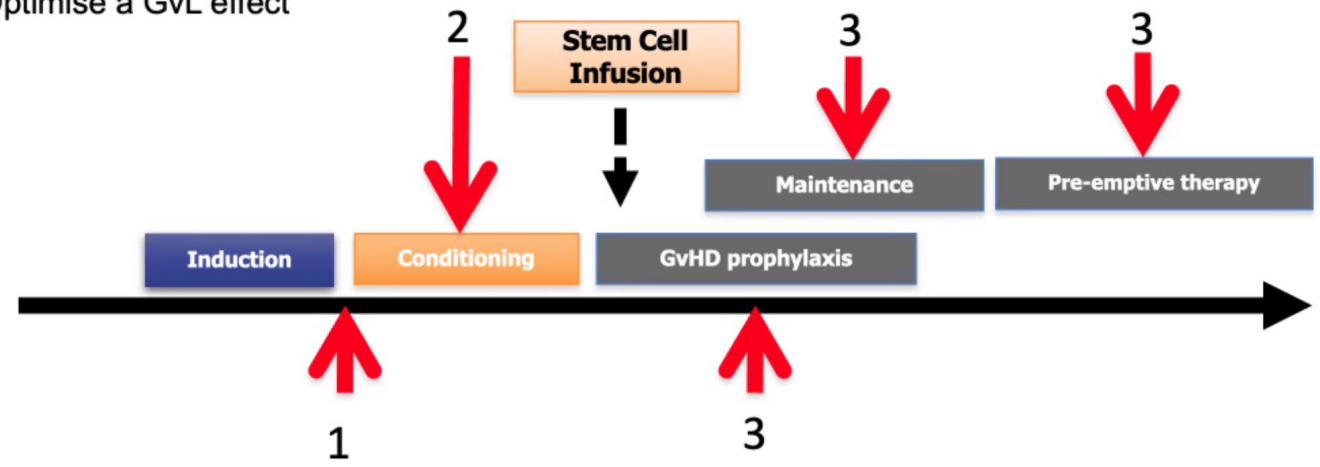


Hourigan et al JCO 2019

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



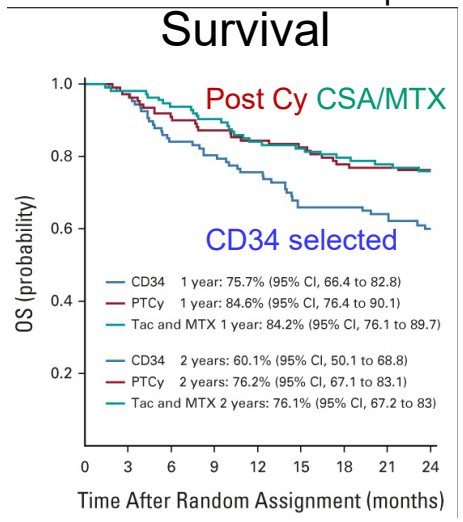
Craddock, et al. Bone Marrow Transplant. 2019

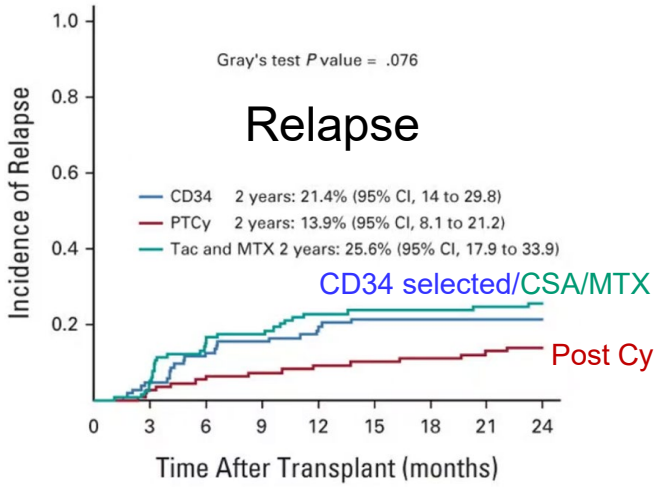
Post-Transplant Cytoxan to Reduce Relapse after HLA-Matched Allogeneic HCT

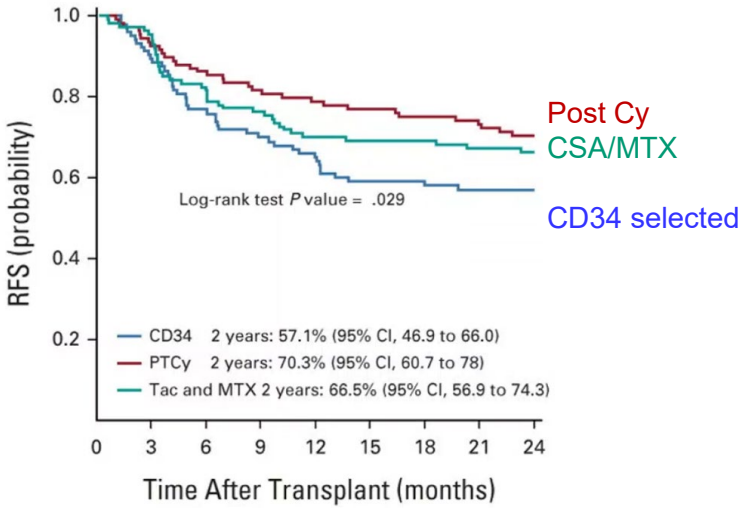
- Lower cyclosporine levels (AUCs) after transplant associated with lower risk of AML relapse (Craddock C. et al Haematologica 2010)

- 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

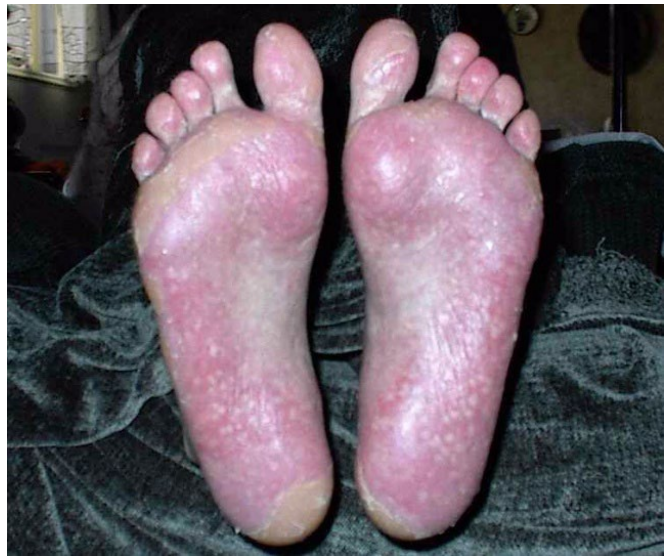


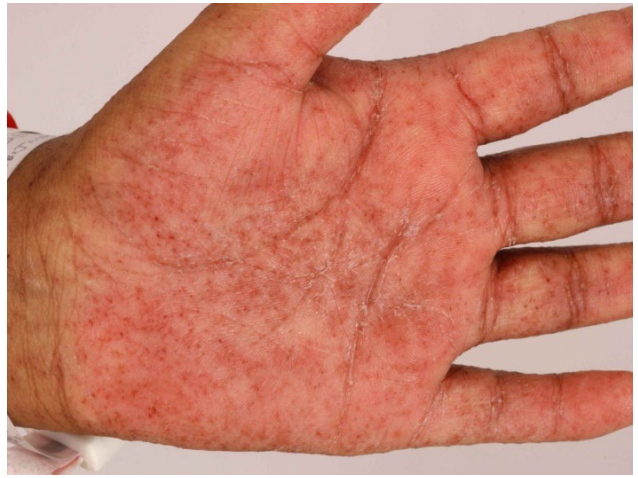


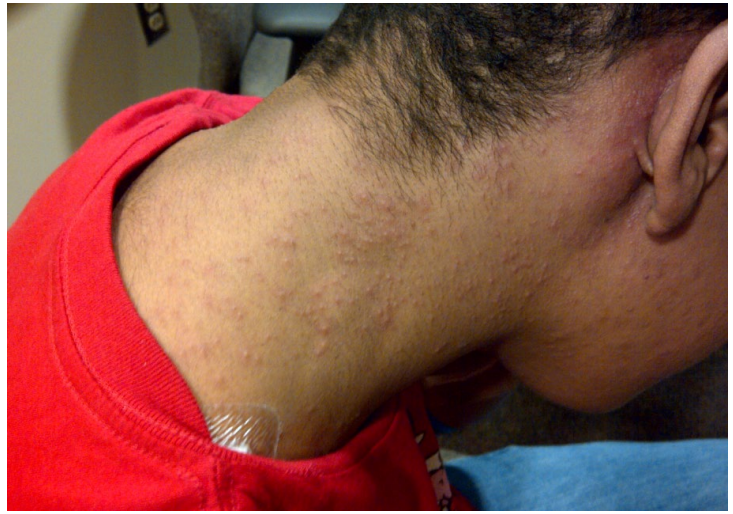


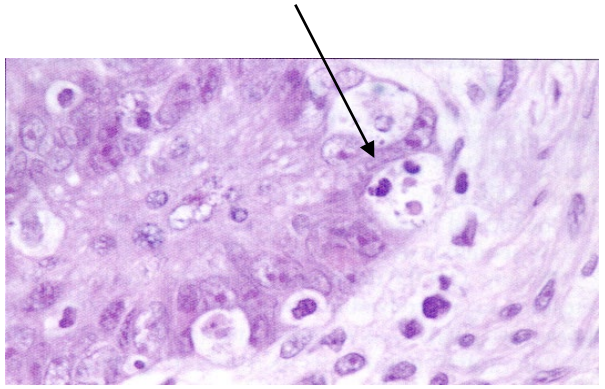
Luznik L. et al JCO 2022

GVHD Historically Has Been A Major Contributor to Transplant Related Mortality

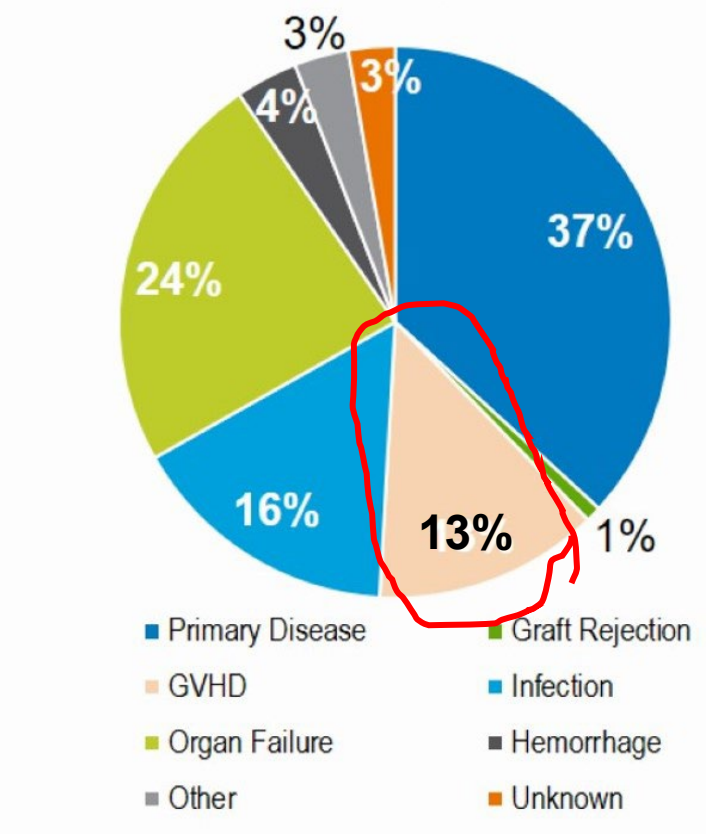








GVHD of the Colon



TRM by day 100
13% caused by GVHD

CIBMTR Data 2022

blood
Regular Article

TRANSPLANTATION

Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study

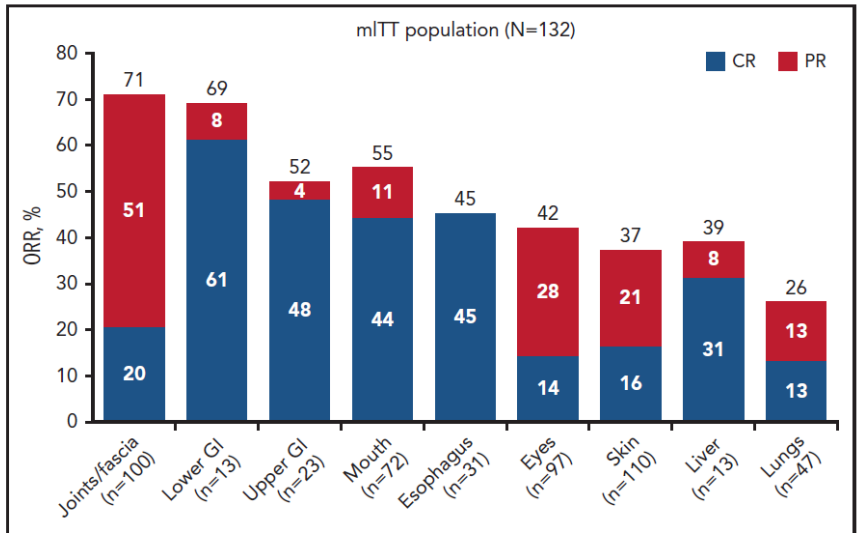
- Approximately 30% of pts develop chronic GVHD (CGVHD)
- Belumosudil is an oral selective inhibitor of Rho-associated coiled-coil-containing protein kinase 2 (ROCK2)
- It reduces type 17 and follicular T helper cells via downregulation of STAT3 and enhances regulatory T cells via upregulation of STAT5
- Phase 2 randomized multicenter registration study evaluated belumosudil 200 mg daily (n = 66) and 200 mg twice daily (n = 66) in subjects with cGVHD who had received 2 to 5 prior lines of therapy
- Primary end point was best overall response rate (ORR).

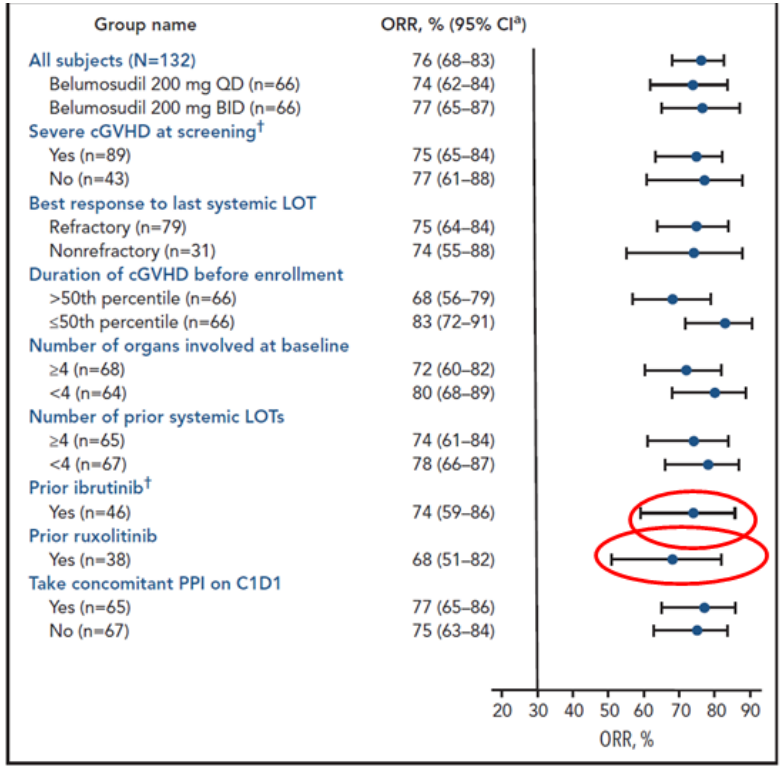
Cutler C. Et al Blood 2021

OUTCOME:

- ORR was 74% and 77% for belumosudil 200 mg daily and 200 mg twice daily
- High response were observed in all subgroups of cGVHD. All affected organs demonstrated complete responses.
- 59% and 62% of subjects reported reduction in symptoms respectively.
- Belumosudil appears to be a VERY promising therapy for cGVHD, was well tolerated with clinically meaningful responses.

Response By Organ System





Cutler C. Et al Blood 2021