# HEMATOPOIETIC STEM CELL TRANSPLANTATION: UPDATING THE OLD CLOSET

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# Learning Objectives

- To Update the Field of Allogeneic Transplants in 2022
  - State of the art
    - Drugs to Prevent CMV Reactivation
    - New Drugs to Treat GVHD
  - Transplant types and their utilization
  - Disease specific outcomes

- Alternative Donor Transplants
  - Trends for utilization
  - Cord versus Haplo

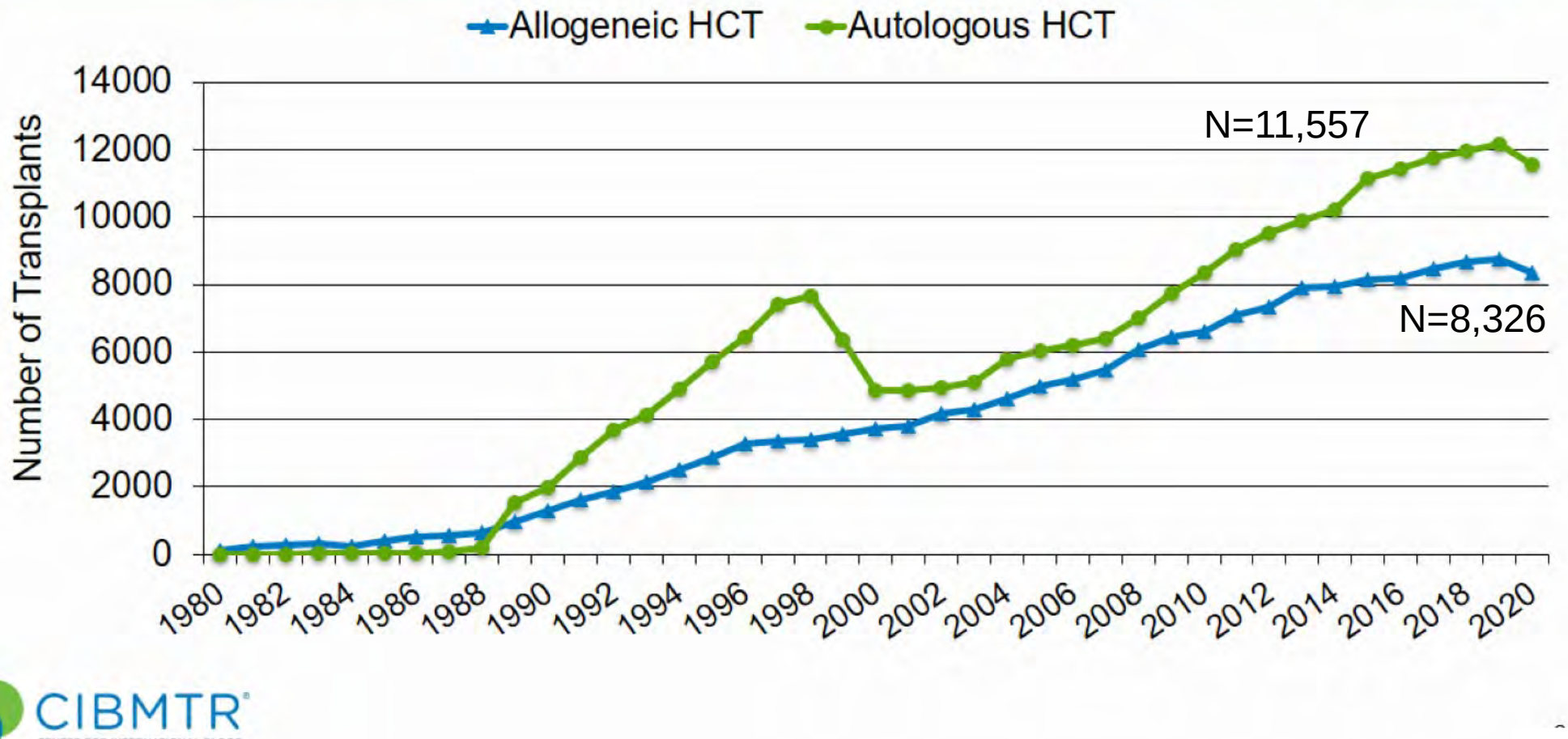
- Updates on strategies to prevent, treat and diagnose GVHD

GVHD= Graft vs host disease

Dr. Richard W. Childs disclosures:

- None

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

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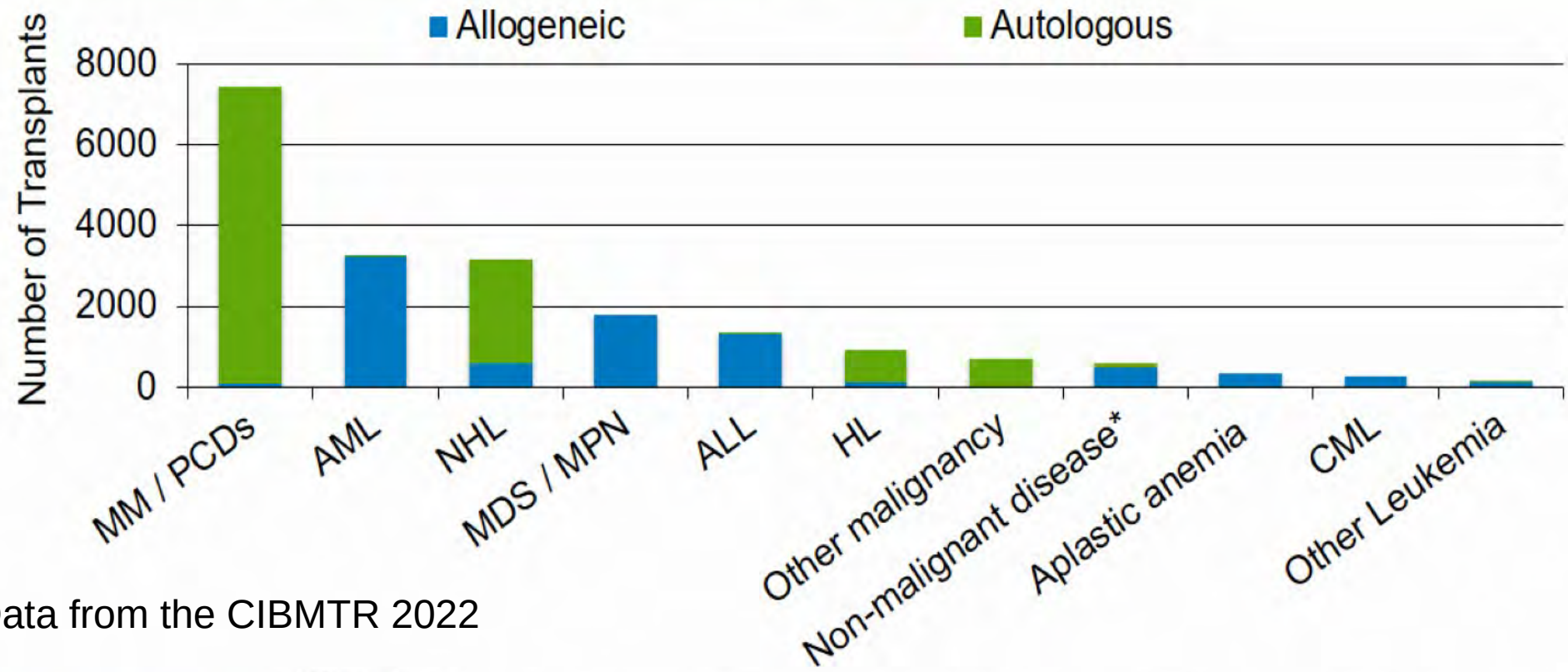
Data from the CIBMTR 2022

# Number of HCTs by Indications in the US, 2020




Data from the CIBMTR 2022

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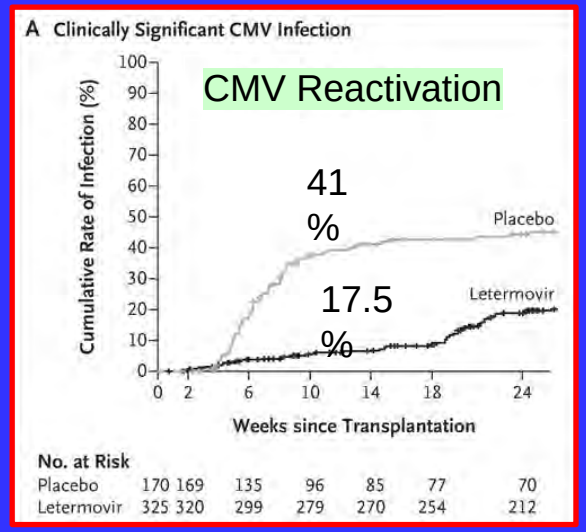
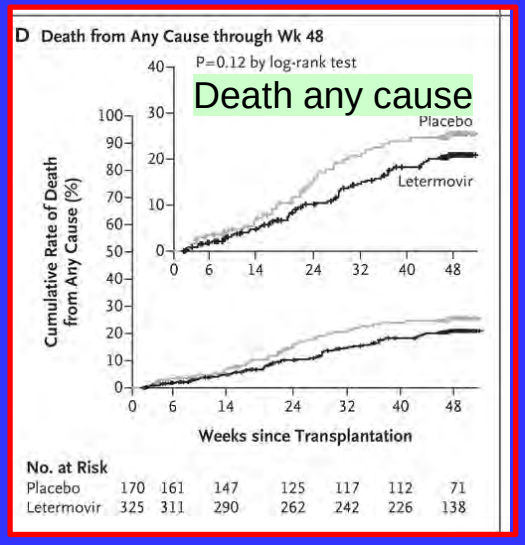
Abbreviations –
MM: Multiple myeloma;
PCDs: Plasma cell disorders;
AML: Acute myelogenous leukemia;
NHL: Non-Hodgkin lymphoma;
MDS: Myelodysplastic syndromes;
MPN: Myeloproliferative neoplasms;
ALL: Acute lymphoblastic leukemia;
HL: Hodgkin lymphoma;
CML: Chronic myeloid leukemia

*excludes Aplastic anemia

# Major Improvements in Transplant 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 May 24, 2019
  - **Rezurock** – 74%-77% response rate- FDA approved July 16, 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**

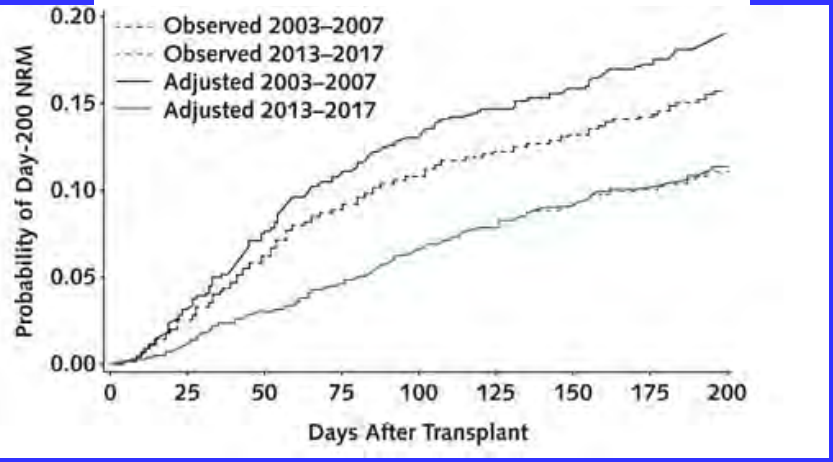


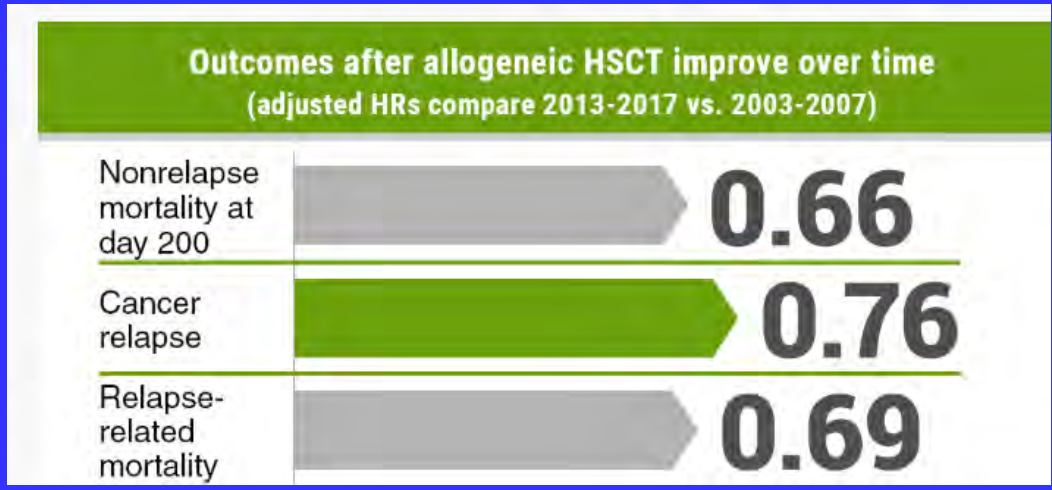

Marty F. et al. NEJM Dec 2017

# Major Improvements in Transplant Safety Over the Past 2 Decades

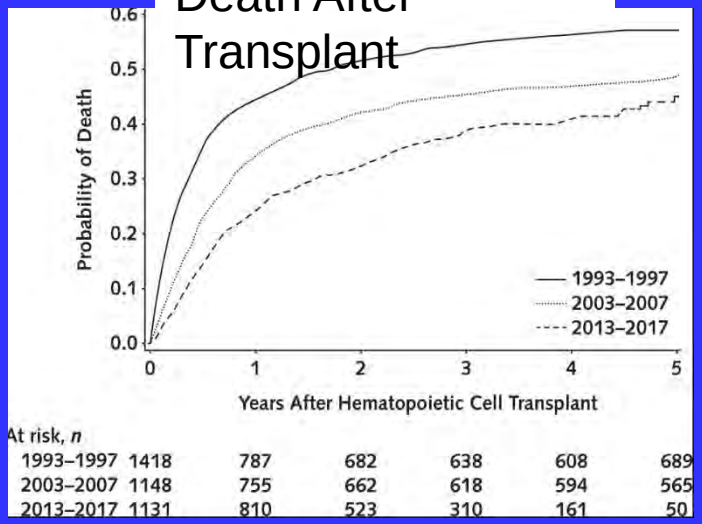
Day 200 NRM




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

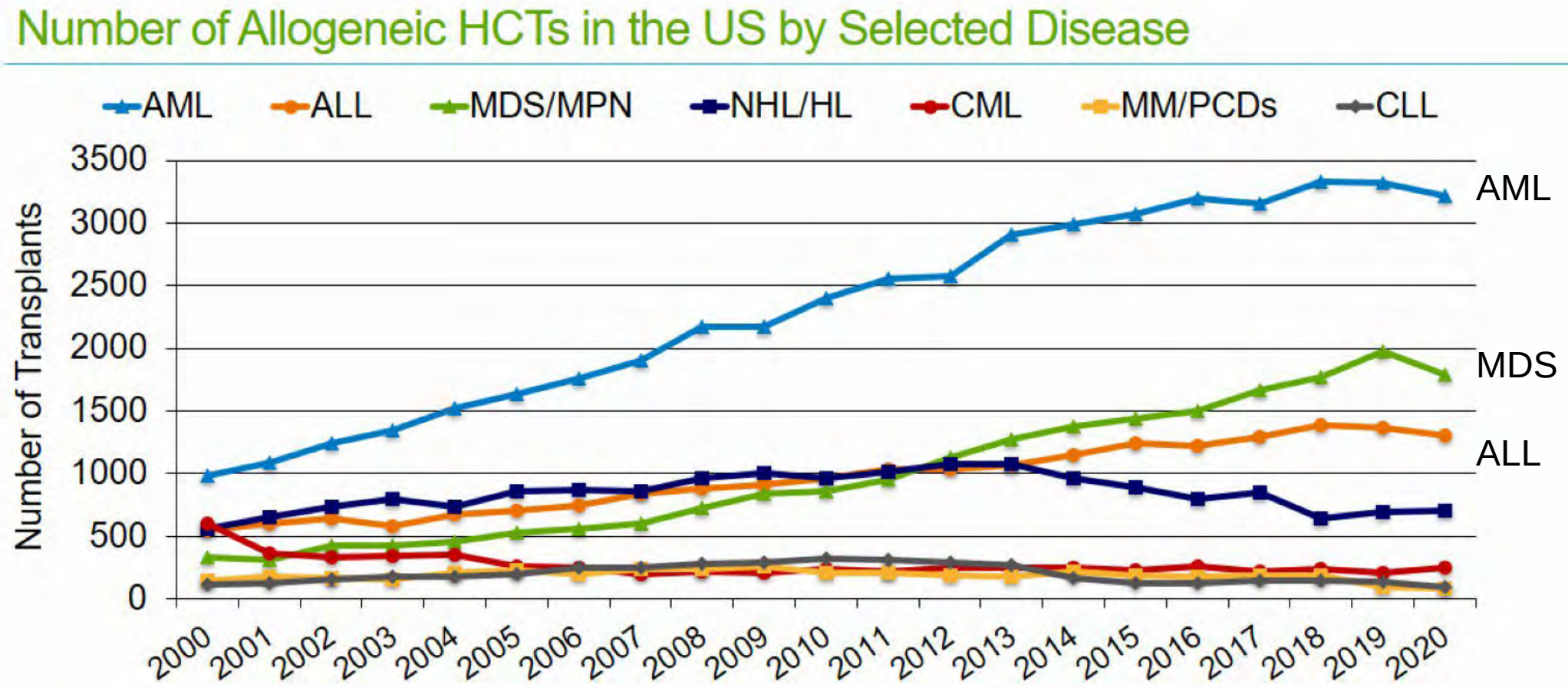



Death After Transplant




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

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

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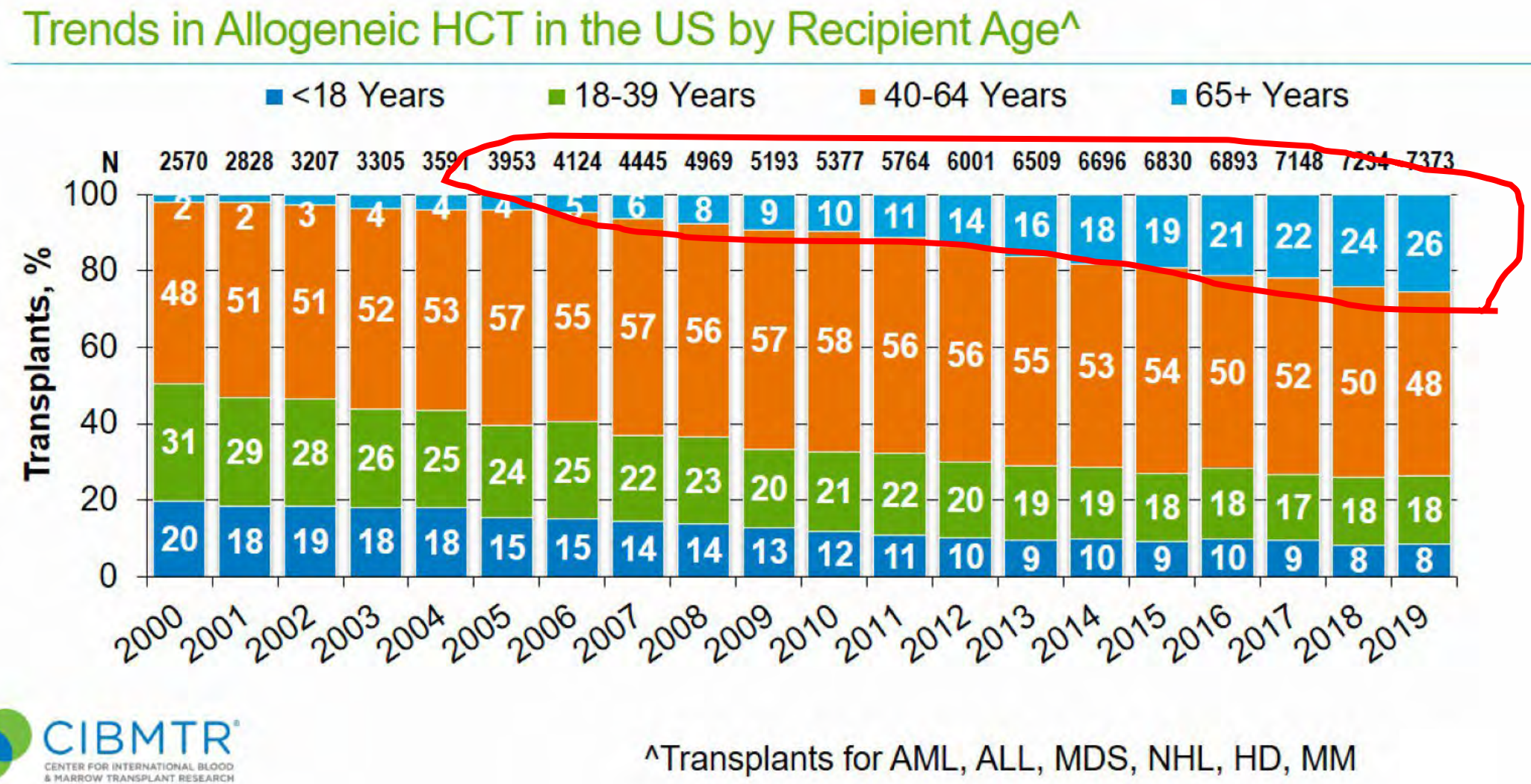
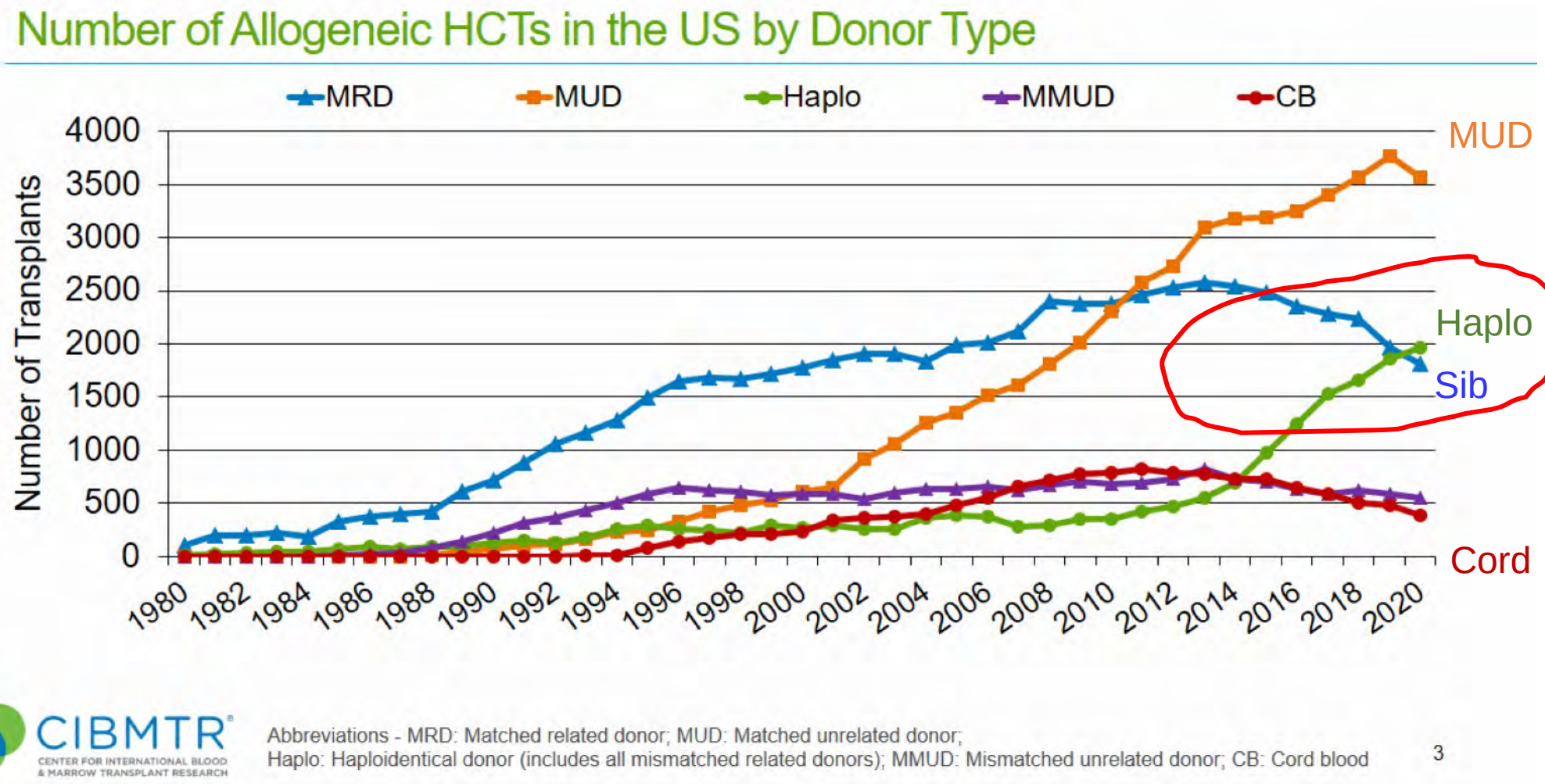
# More Utilization of Allotransplants Amongst Older Patients




Data from the CIBMTR 2022

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




Data from the CIBMTR 2022

# Cord vs Haplo: Which is Better?

**Pros for Both Cords and Haplo Transplants**

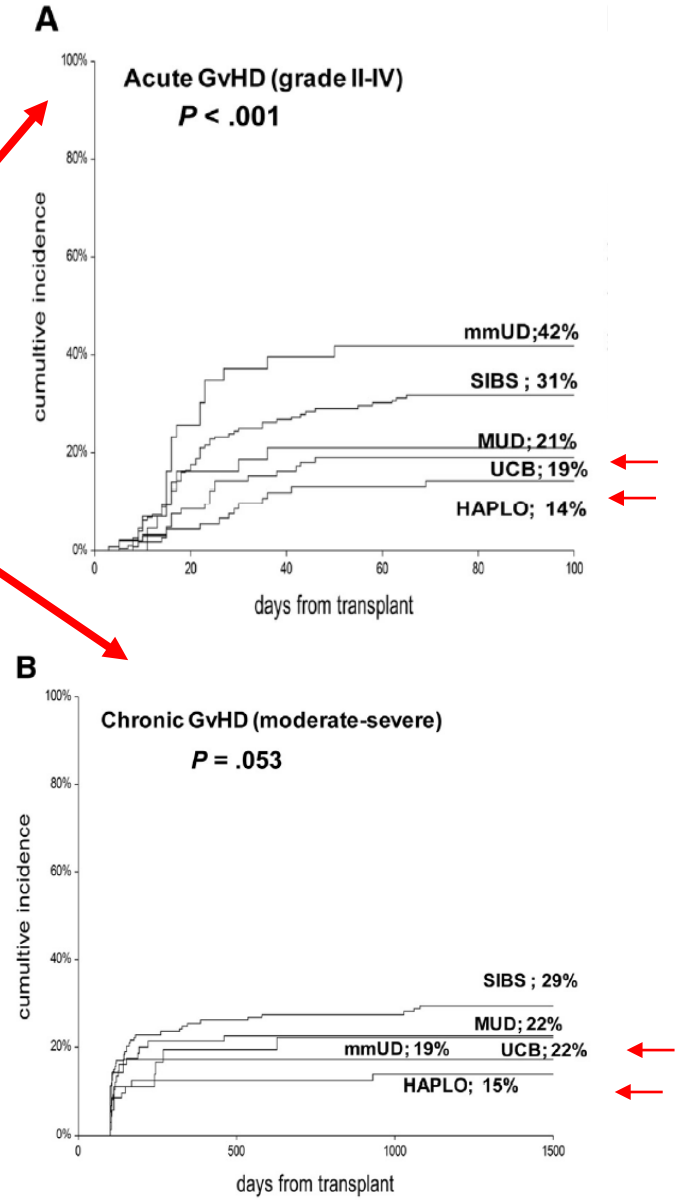
- Almost all adults will have a haplo donor available or a cord unit that is suitable for transplantation.
- Acute and chronic GVHD rates are very low with both approaches

**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



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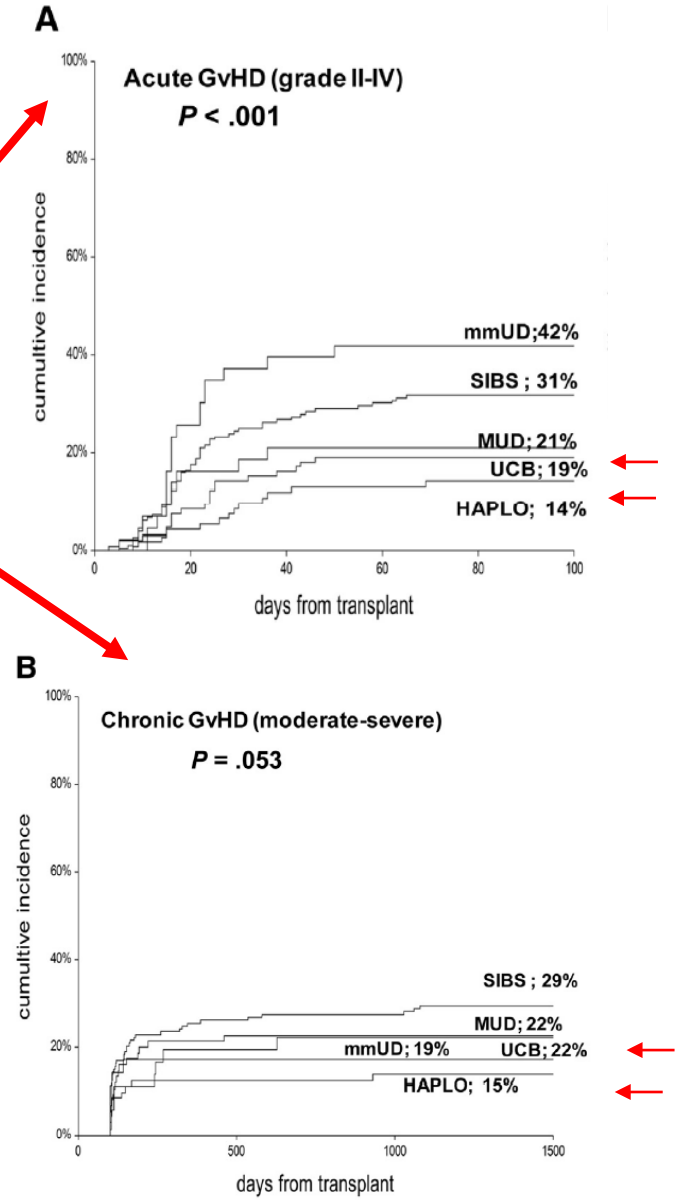

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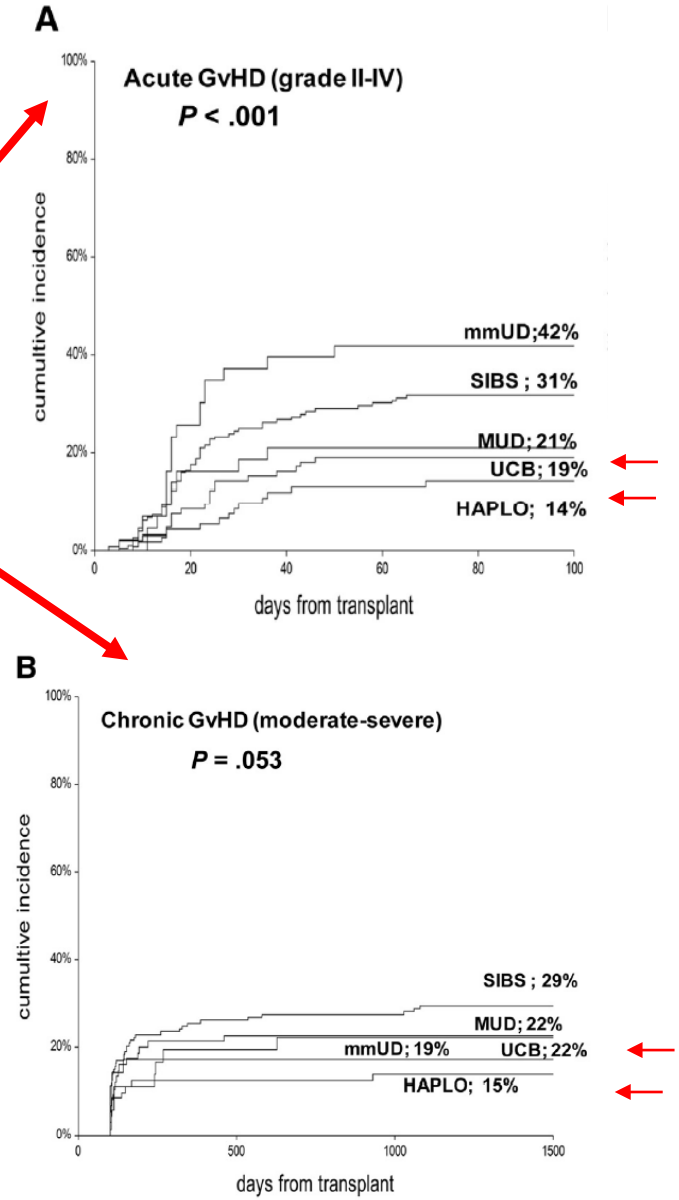
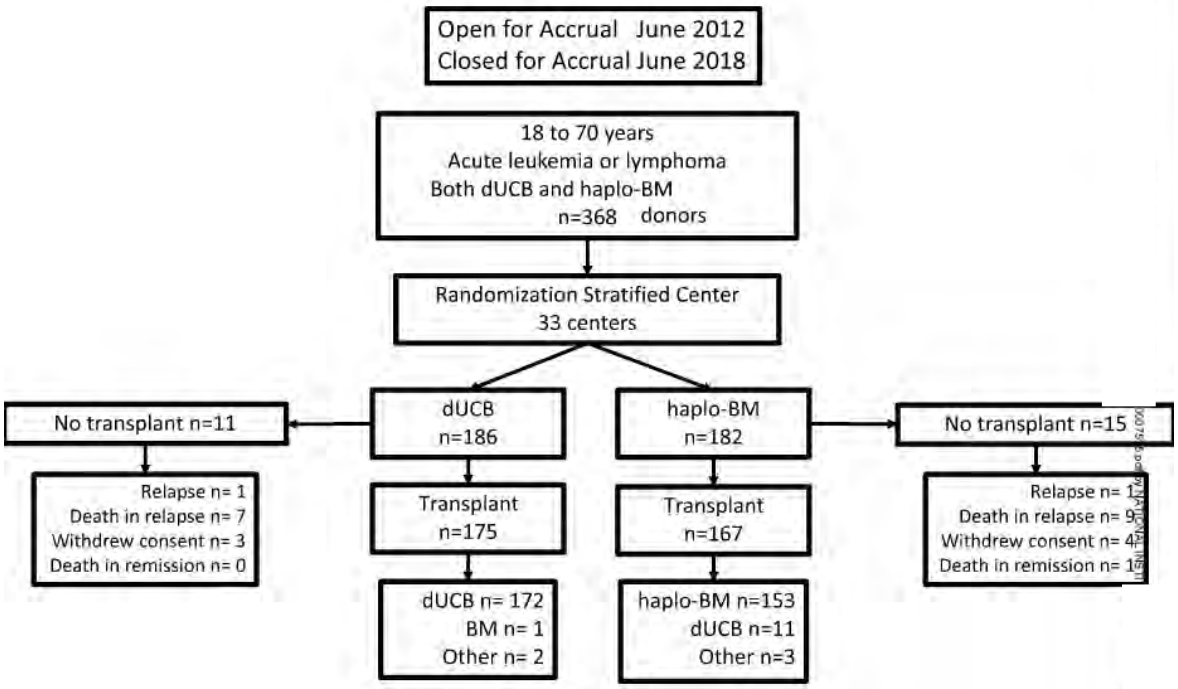
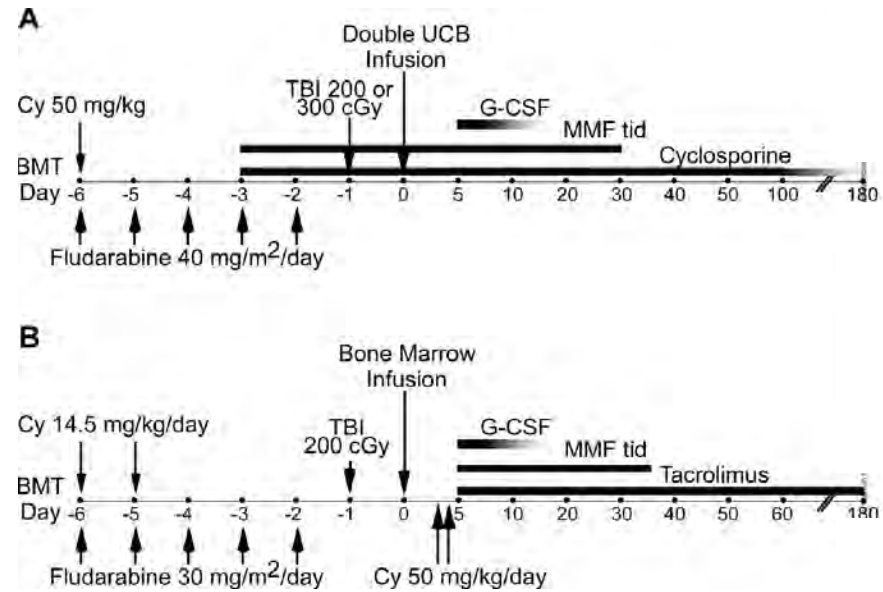


# CTN 1101: Cord vs. Haplo

Study:

- June 2012- through June 2018
- 368 pts randomized to dual cord transplant vs haplo-Cy transplant using RIC
- Age 18-70 years
- Diseases: acute leukemia in remission or chemotherapy sensitive lymphomas

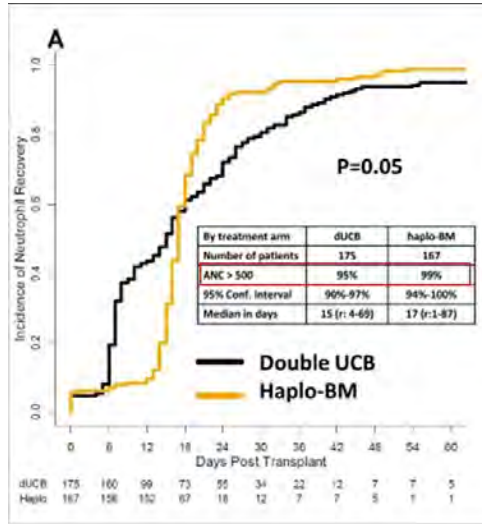


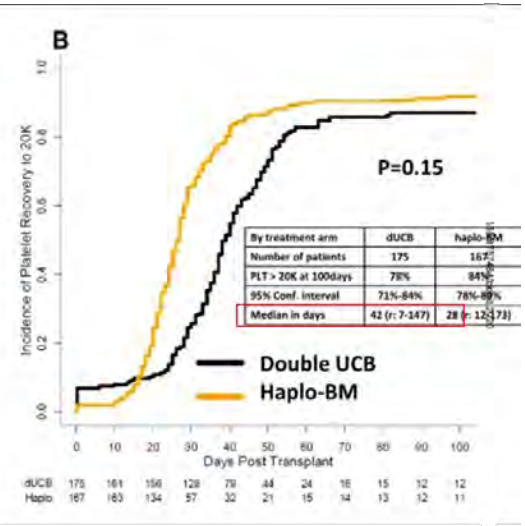

Fuchs E. et al Blood 2021: 137:420428

# CTN 1101: Cord vs. Haplo

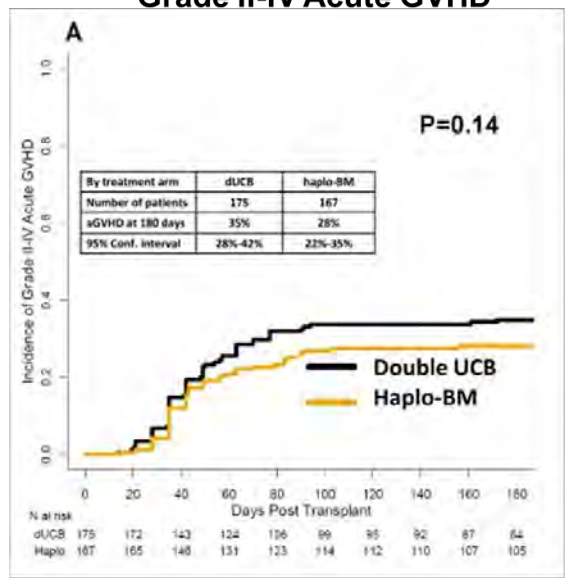
**Neutrophil Recovery**



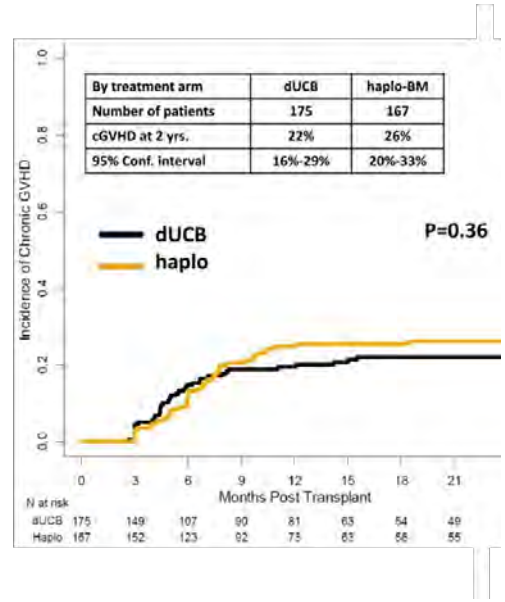

**Platelet Recovery**




**Grade II-IV Acute GVHD**




**Chronic GVHD**

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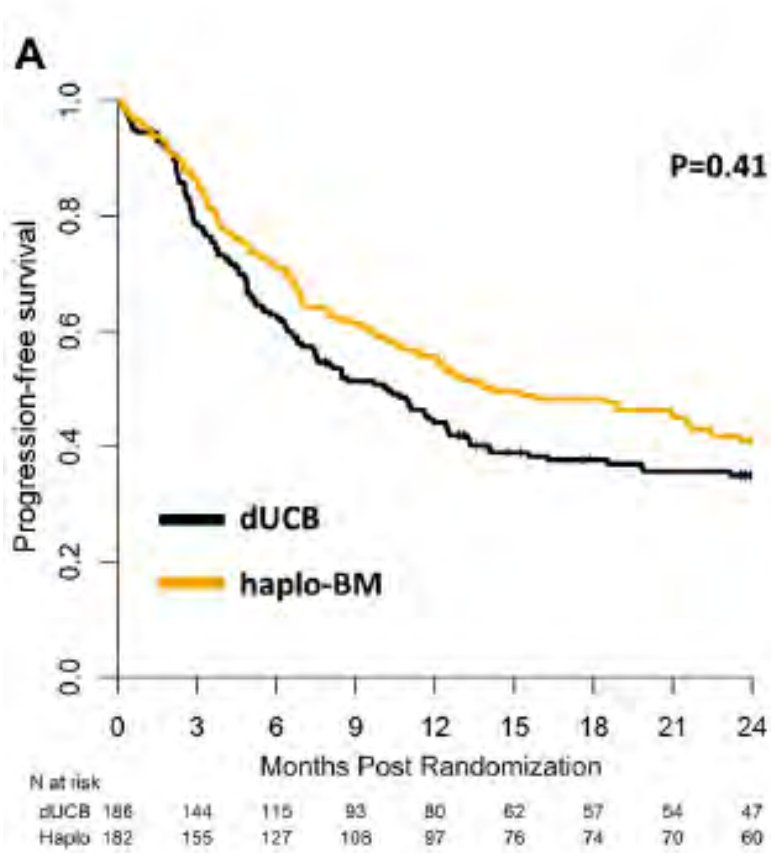
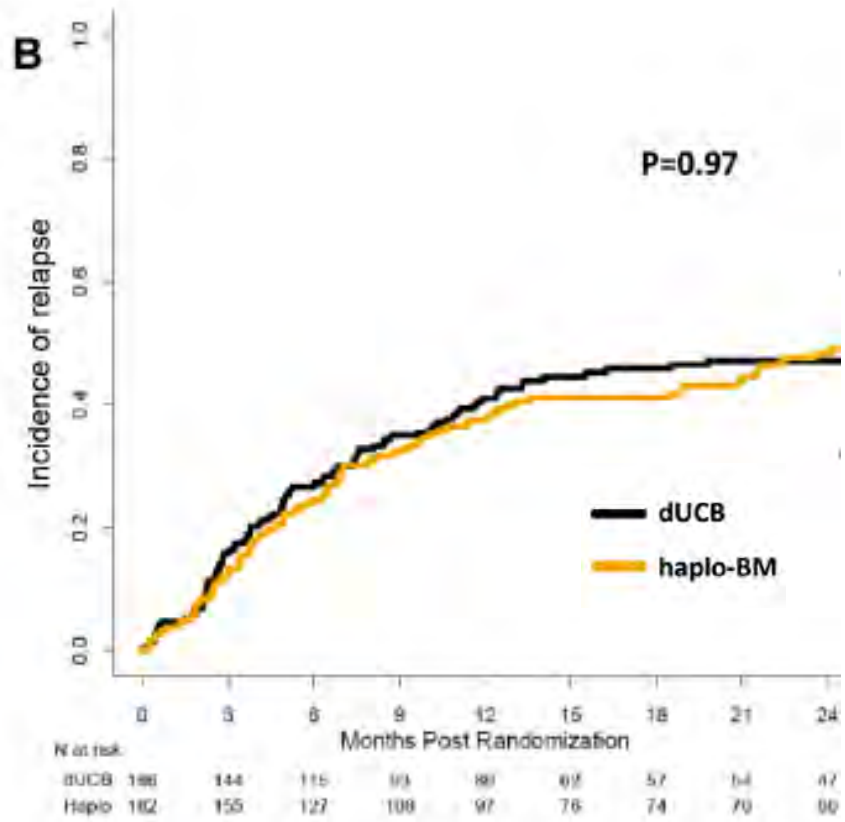
# CTN 1101: Cord vs. Haplo

## Progression Free Survival



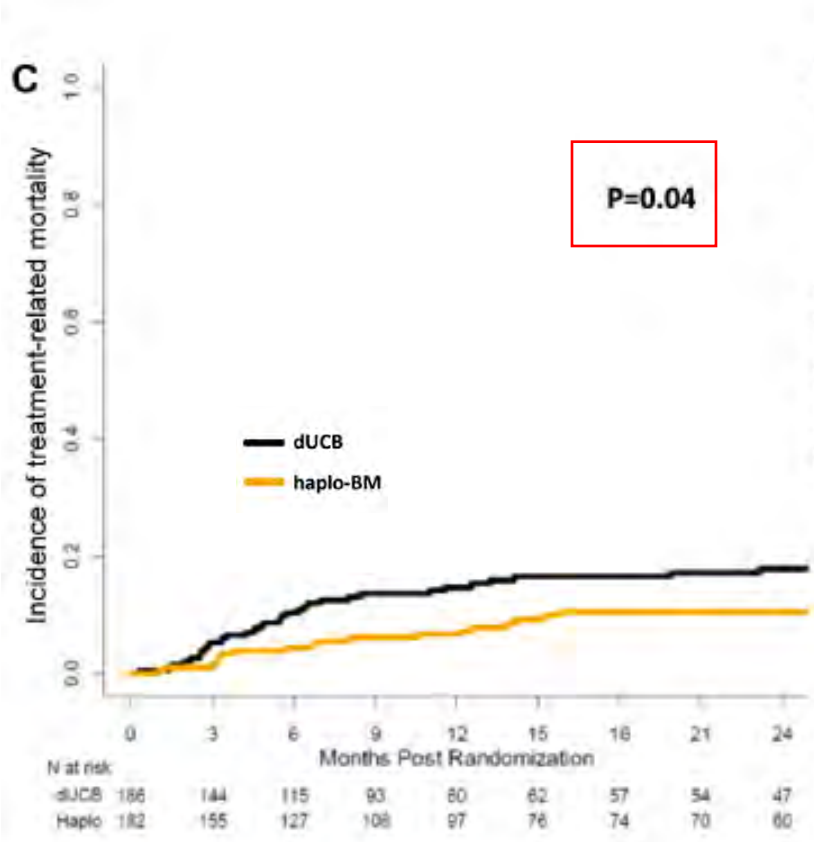

## Relapse



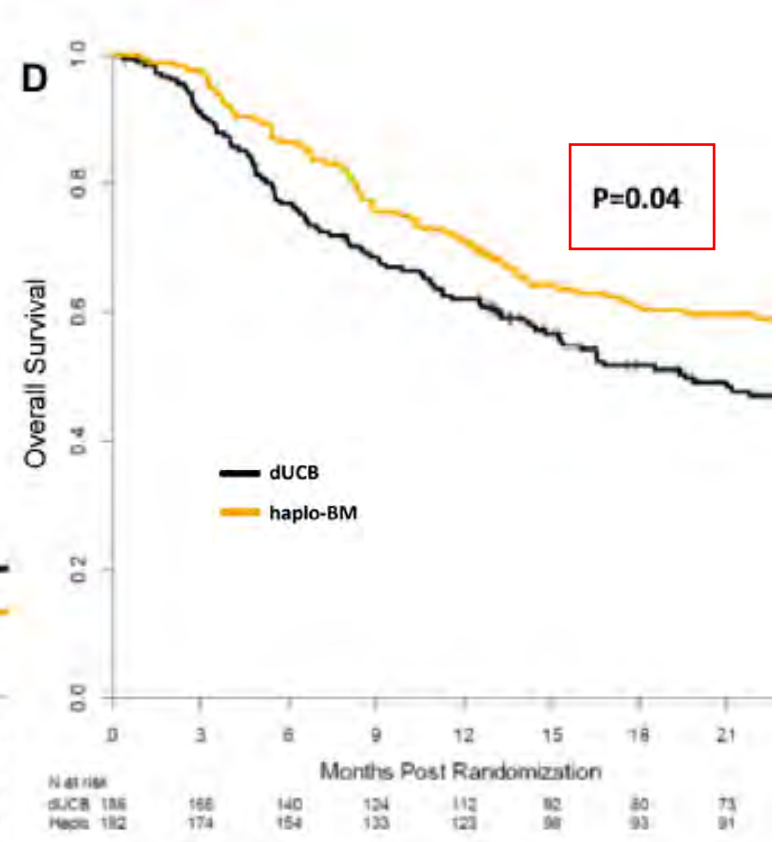

Fuchs E. et al Blood 2021: 137:420428

# CTN 1101: Cord vs. Haplo

## Transplant related Mortality




## Overall Survival




Fuchs E. et al Blood 2021: 137:420428

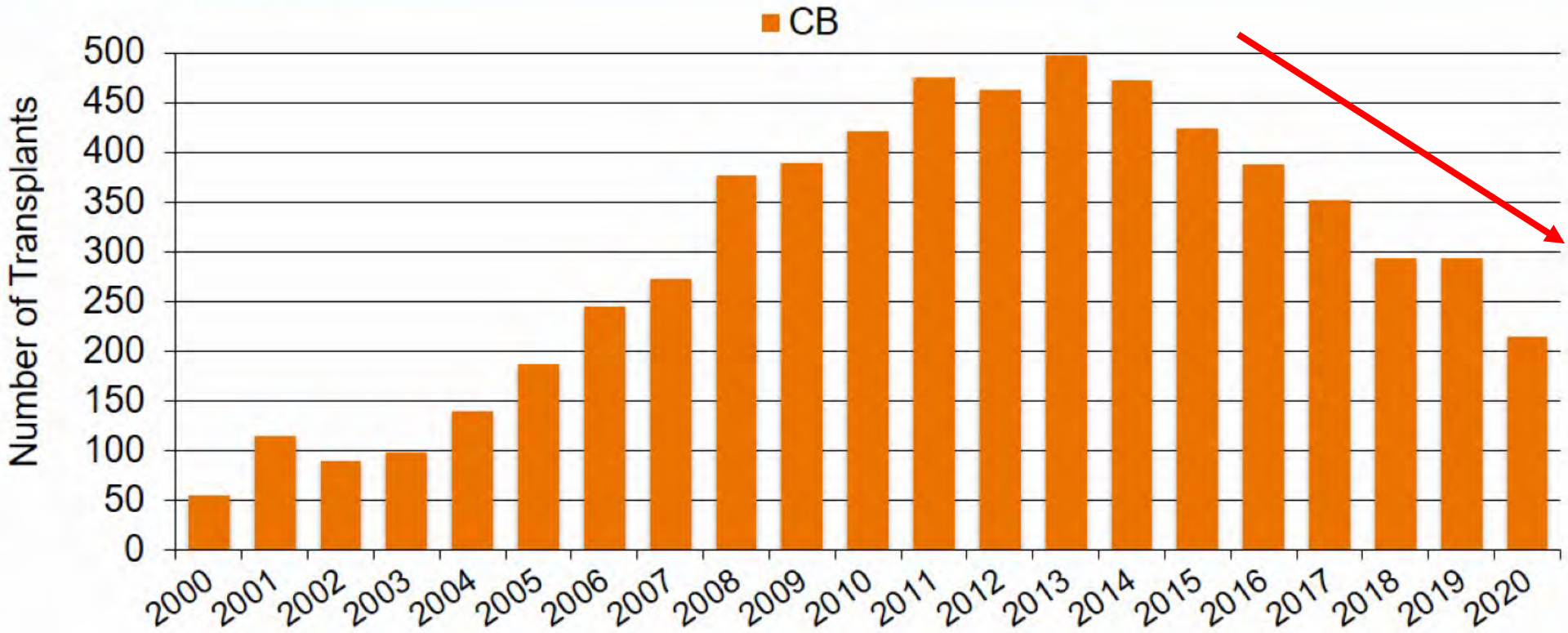
# CTN 1101: Cord vs. Haplo

## Conclusions:

- Engraftment rates, relapse and progression-free survival were similar between transplant approaches
- Haplo transplants had lower non-relapse mortality rates 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

# Trends in the Use of Cord Blood Allogeneic HCTs in the US in Recipients Aged ≥18 Years

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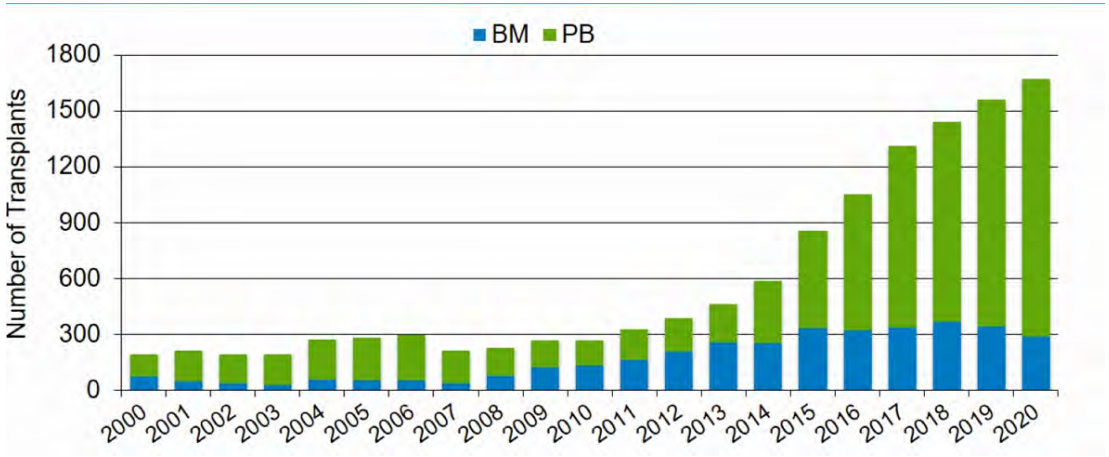
Abbreviation - CB: Cord blood



CB= Cord Blood

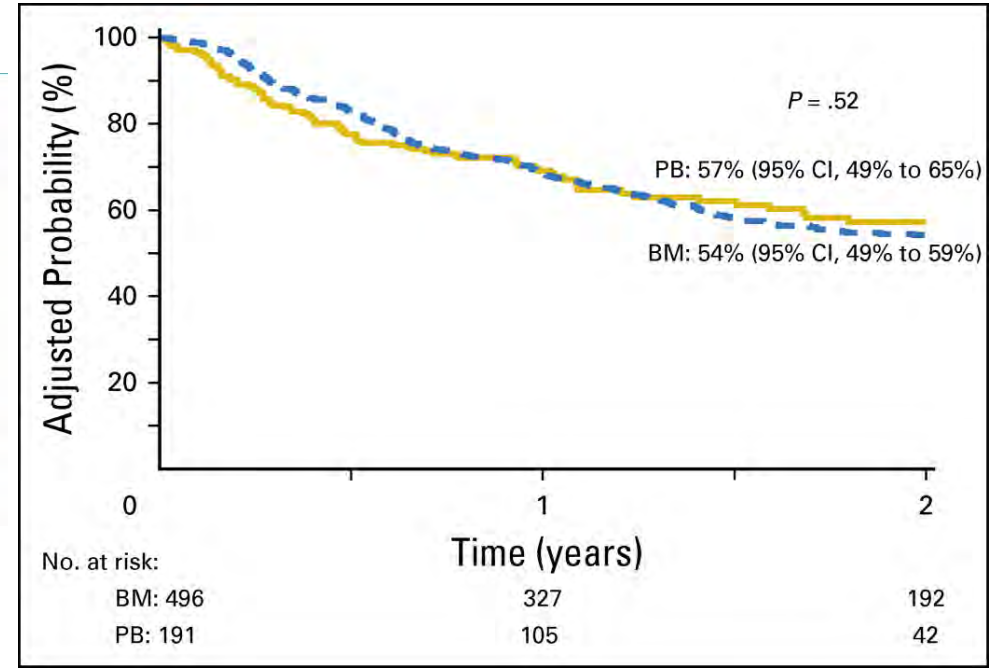
# Haplo Transplants and Graft Source: More PBSC then BM With Similar Outcome

Haplo-Transplants and Graft Source



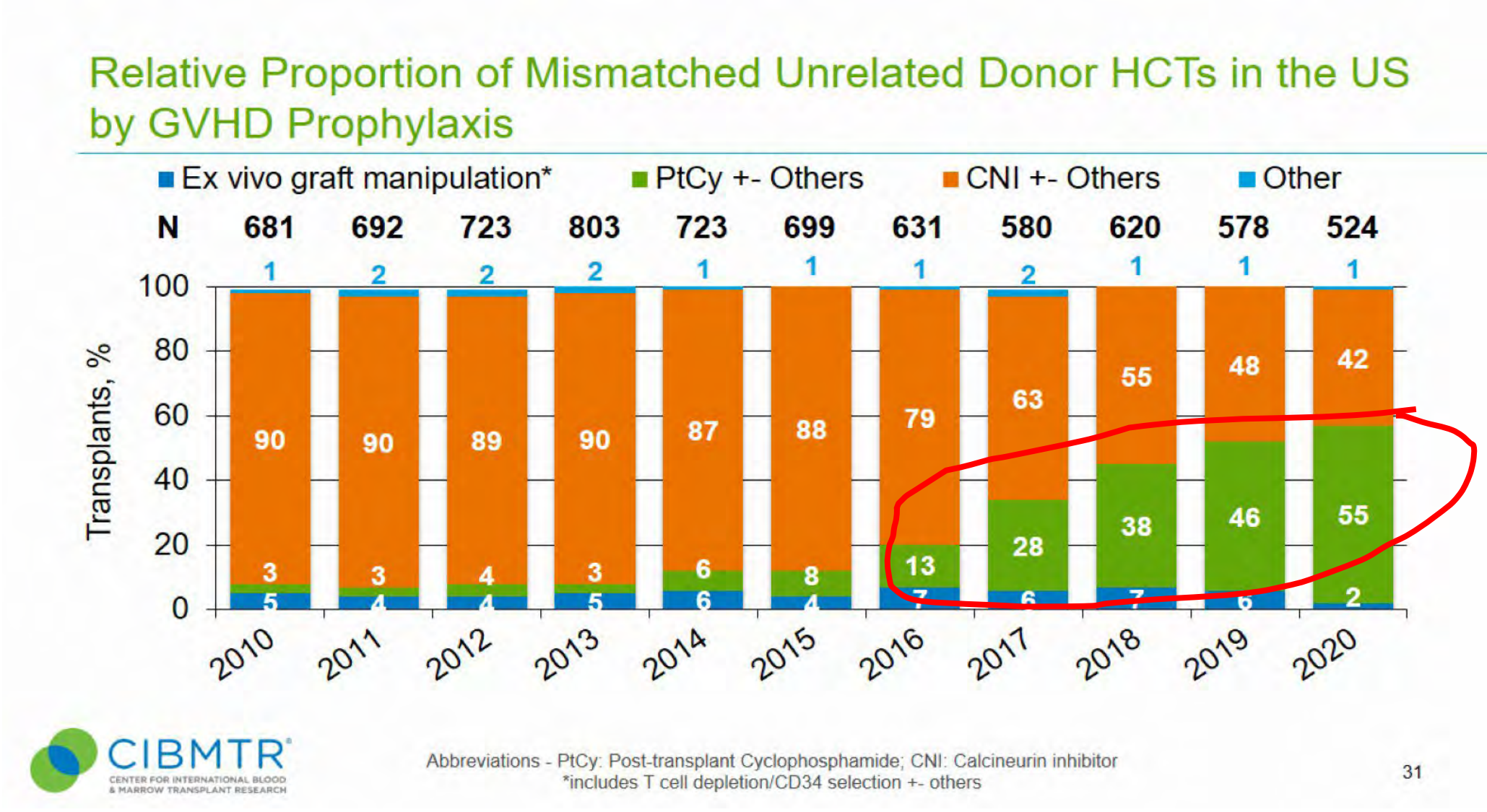

PBSC=Peripheral Blood Stem Cell
BM= Bone marrow

Haplo-Transplants and Graft Source and Survival




Bashey et al, JCO 2017

# 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 DSA).

# Younger Haplo Donors Better than Older: Analysis of Risk Factors for Acute and Chronic GVHD After Haplo-transplant

**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 or graft source (PB vs BM
- Donor age >29 years associated with more acute GVHD- so chose haplo-donors under 29 if possible
- Peripheral Blood RIC associated with more cGVHD

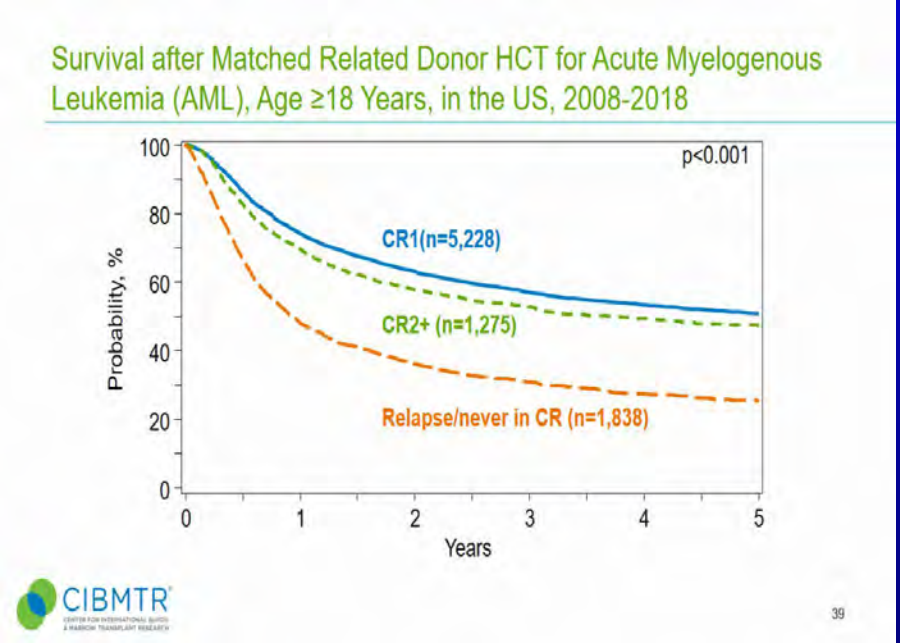
**Donor Age**

- 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)

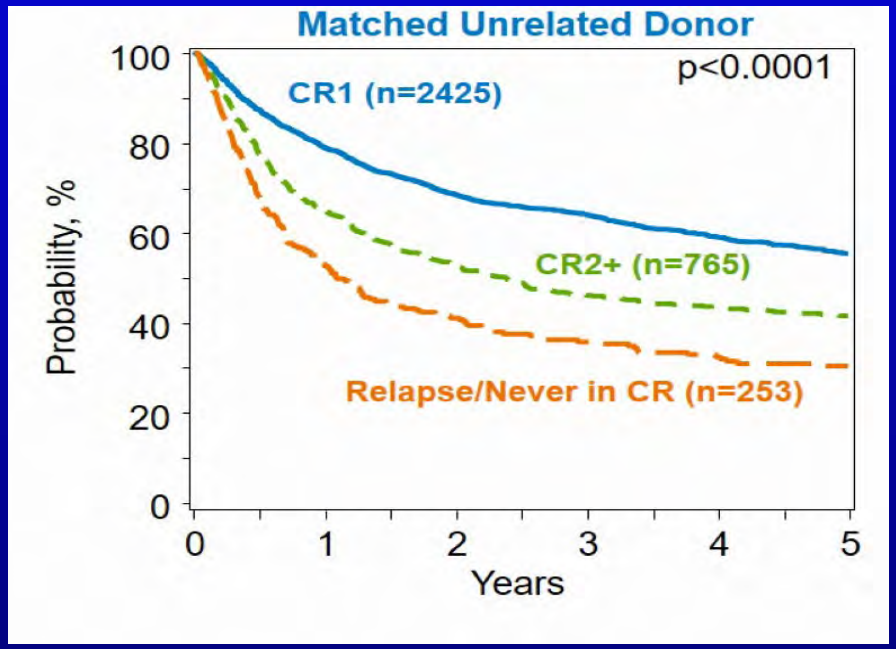
Im A, et al. Biol Blood Marrow Transplant. 2020 Aug;26(8):1459-1468.

# Allogeneic Transplant For Hematological Malignancies: The Earlier the Better

## MRD Transplants For AML




## MUD Transplants For ALL

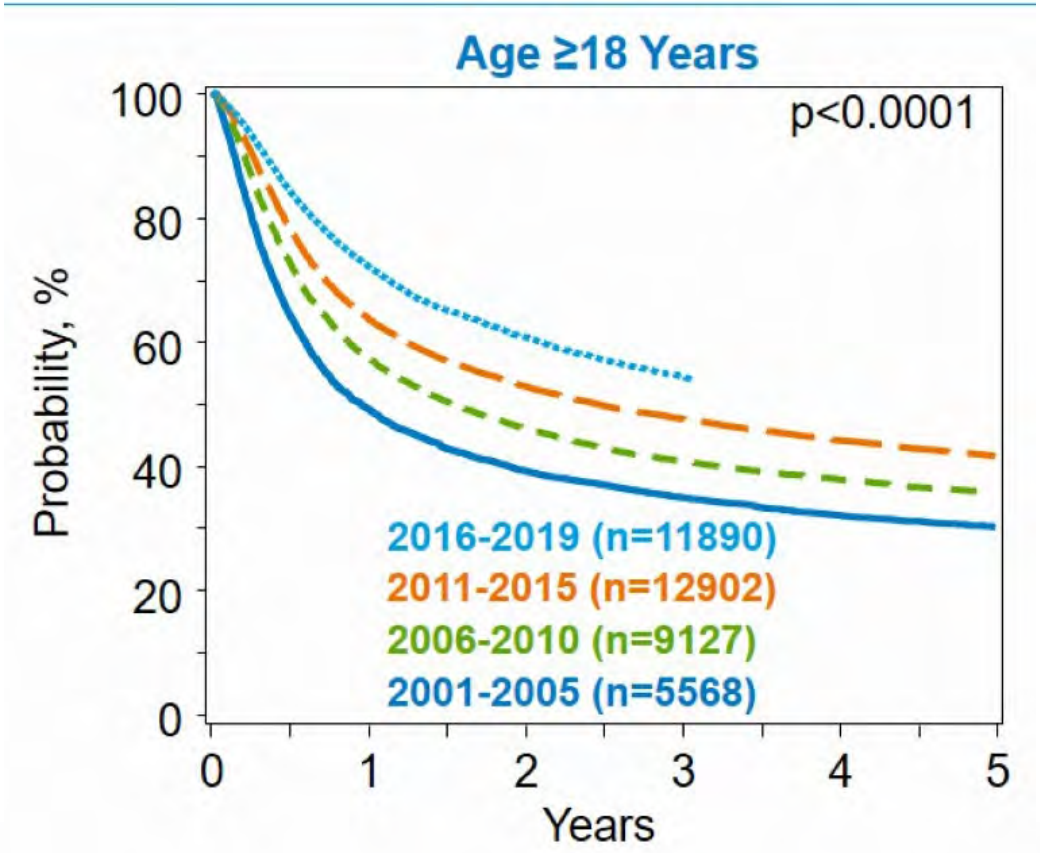



Reduced transplant-related mortality and lower relapse with the earlier use of transplants has led to an increasing use of allogeneic transplants upfront for leukemia in CR-1

CIBMTR Data 2020

# Survival Improving In AML Patients Undergoing Allogeneic HCT

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

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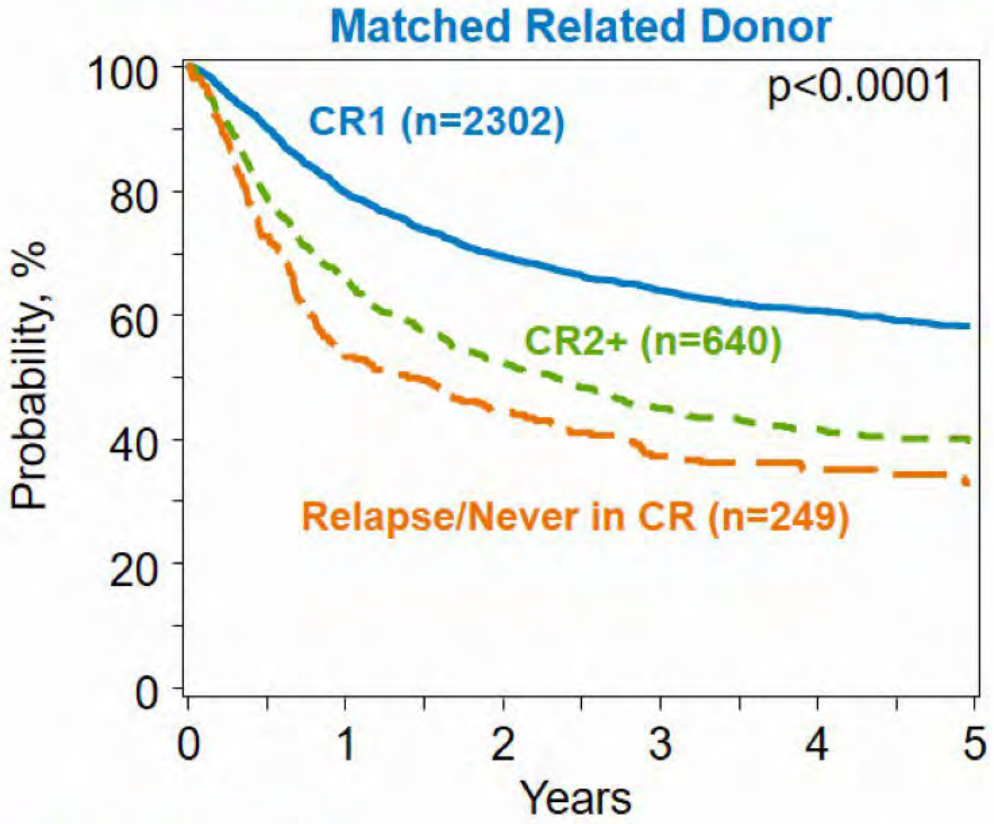
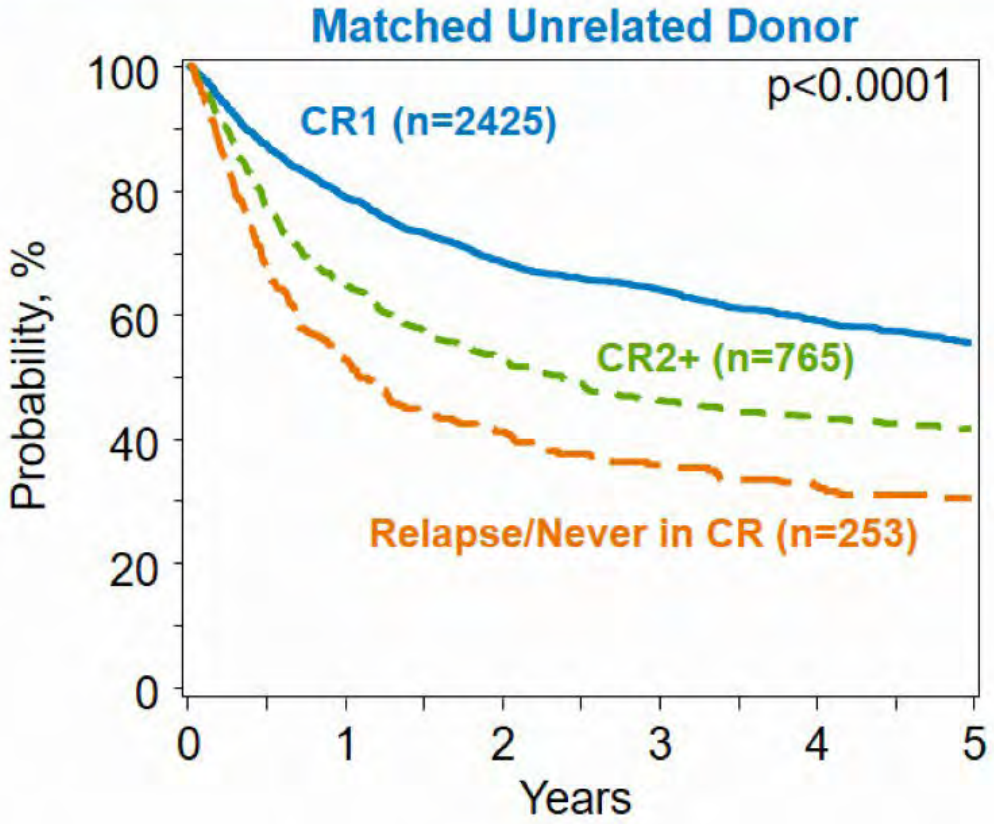
# Survival after Allogeneic HCTs for Acute Lymphoblastic Leukemia (ALL), Using Matched Donors, Age ≥18 Years, in the US, 2009-2019

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Abbreviation – CR: Complete remission

# Survival Improving In ALL Patients Undergoing Allogeneic HCTs

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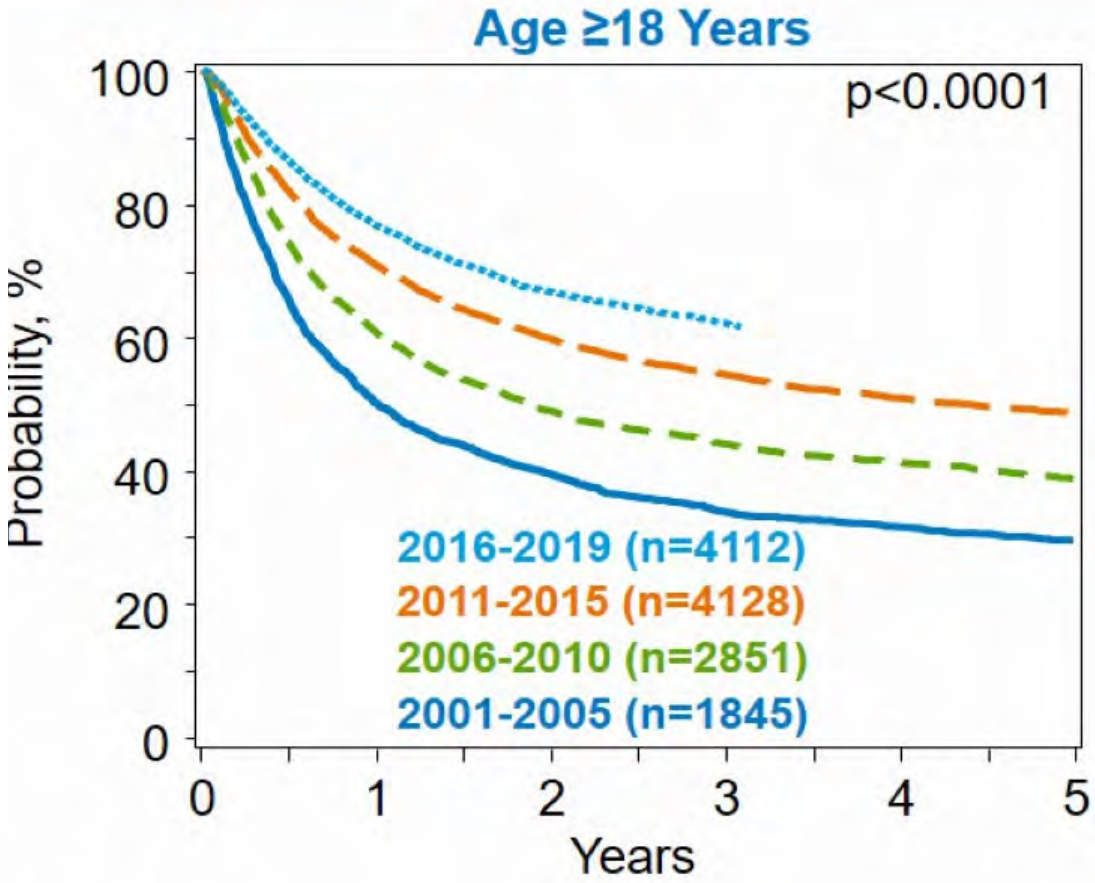


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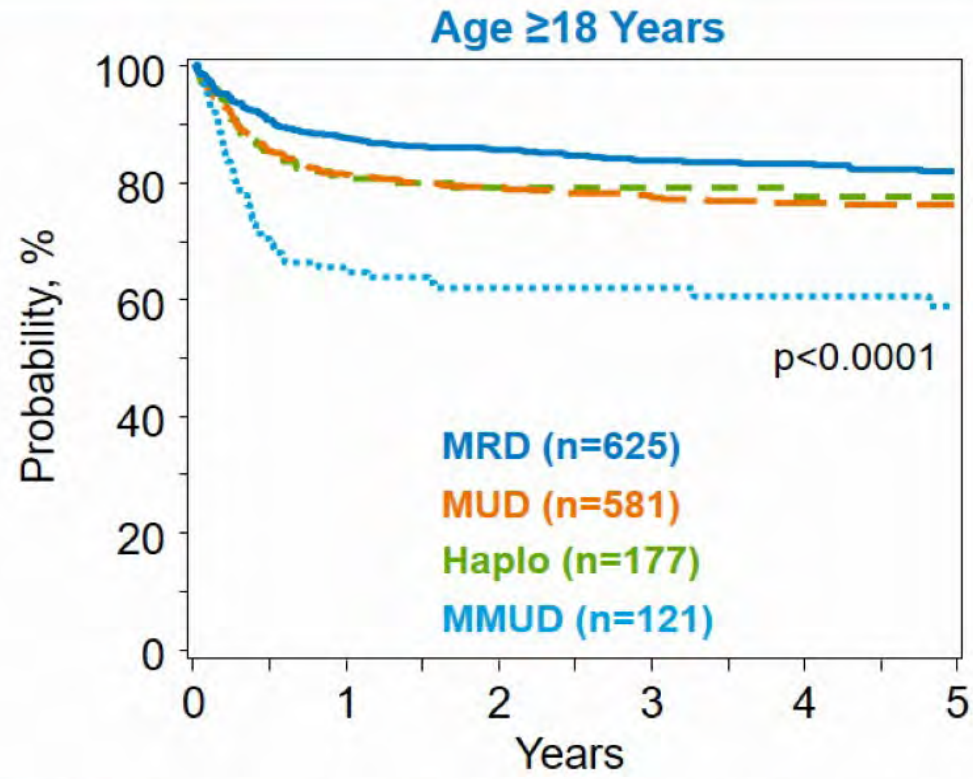
# Survival for SAA Based on Transplant Type

## Survival after Allogeneic HCTs for Severe Aplastic Anemia (SAA), in the US, 2009-2019

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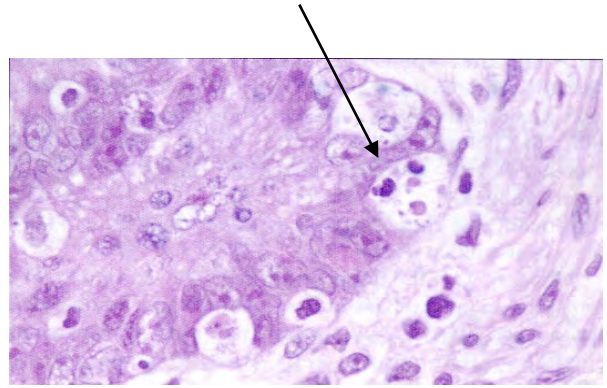
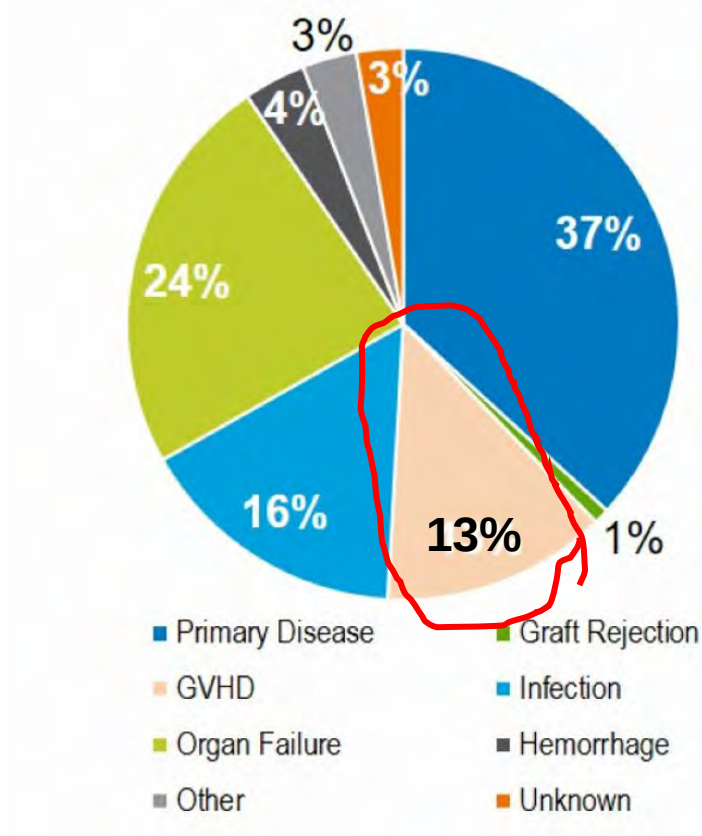
Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor; Haplo: Haploidentical donor (includes all mismatched related donors); MMUD: Mismatched unrelated donor; CB: Cord blood

# 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

# Treatment of Acute And Chronic GVHD: Steroids Represent Mainstay of Therapy

**Pros of Steroids:**

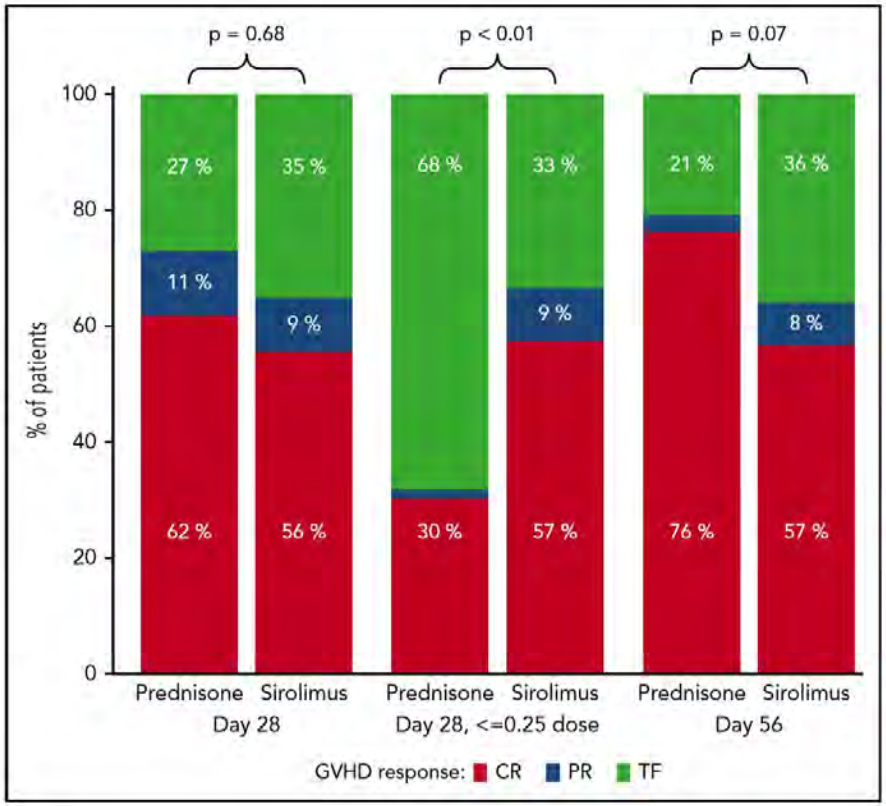
- Rapid onset of action: <24 hours

**Cons of Steroids:**

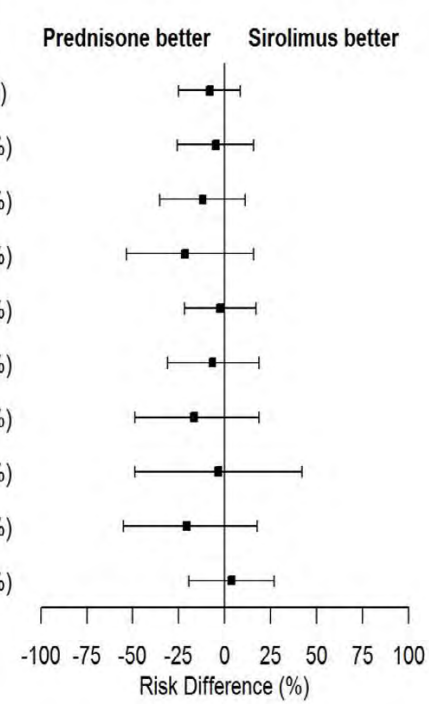
- Up to 30% don't respond
- Substantial morbidity related to use
  - Opportunistic infection: Lethal fungal infections
  - Hypertension
  - Diabetes
  - Osteopenia
  - Cataracts
  - Myalgia

- **Recent data show sirolimus for treatment of acute GVHD is as effective as steroids (CTN BMT 1501)**

# BMT CTN 1501 Trial: Sirolimus vs. Steroids for Acute GVHD



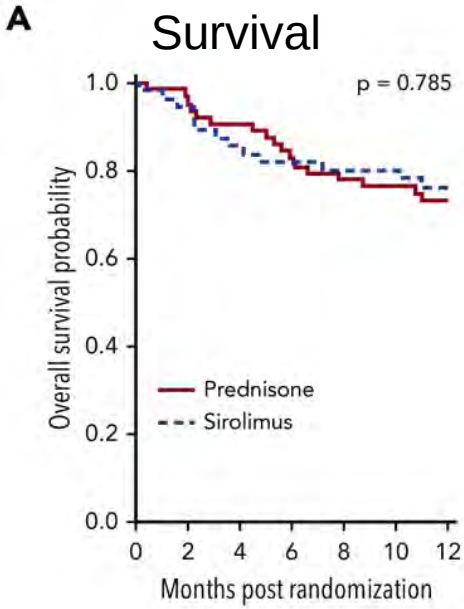

| Subgroup | Estimate (Siro - Pred) | 95% CI |
|---|---|---|
| All AA 1/2 patients | -8.2% | (-25.0%, 8.6%) |
| Skin Involvement | -5.0% | (-25.7%, 15.7%) |
| GI Involvement | -12.0% | (-35.2%, 11.2%) |
| Grade I aGVHD | -21.7% | (-53.4%, 15.6%) |
| Grade II aGVHD | -2.5% | (-22.0%, 17.0%) |
| Stage 1-3 Skin | -6.7% | (-31.1%, 18.6%) |
| Stage 1-2 GI | -16.7% | (-49.0%, 18.5%) |
| Stage 1-3 Skin and Stage 1 GI | -3.6% | (-48.9%, 41.9%) |
| Isolated Upper GI | -20.8% | (-55.1%, 17.7%) |
| Not isolated skin stage 1-2 or upper GI | 3.6% | (-19.6%, 26.9%) |

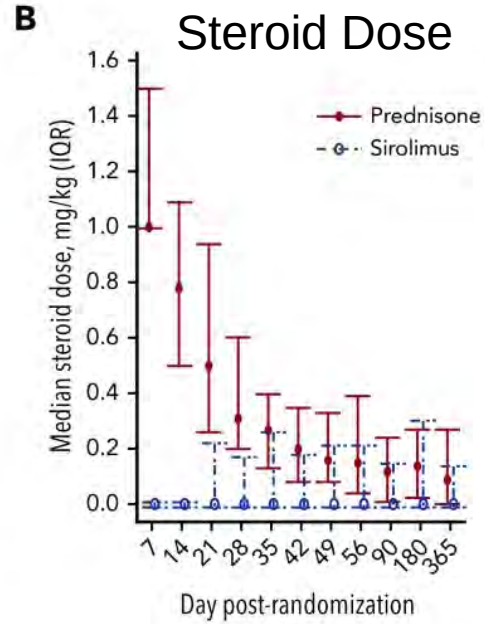


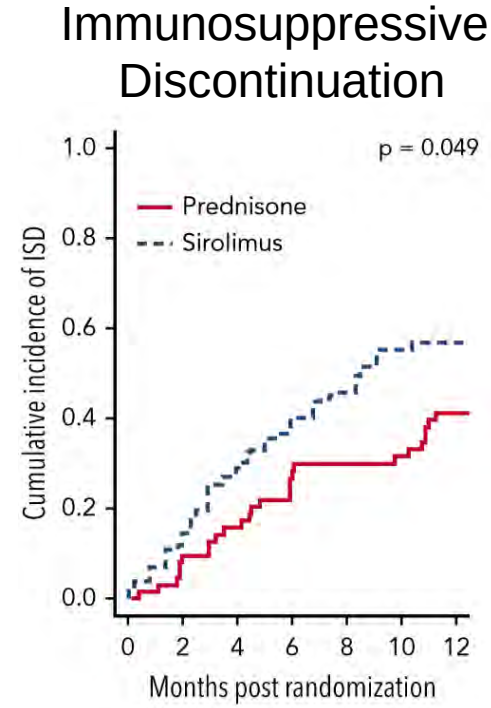

RESULTS:

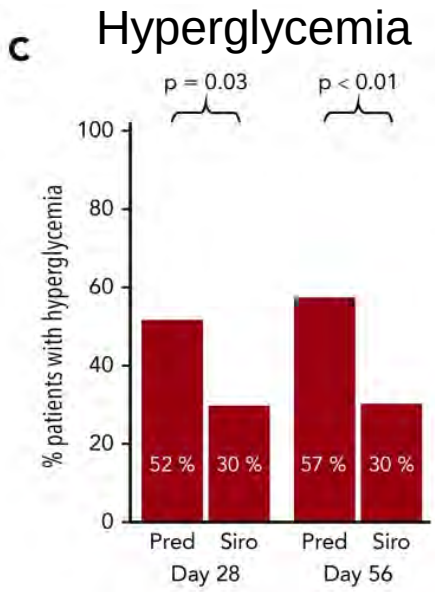
- Day 28 CR rates for sirolimus vs prednisone similar
- Day 28 CR rates for sirolimus vs < 0.25 mg/kg higher with sirolimus
- Day 56- Nonresponse was significantly higher in the sirolimus group
  - 84% of Sirolimus non-responders salvaged with steroids

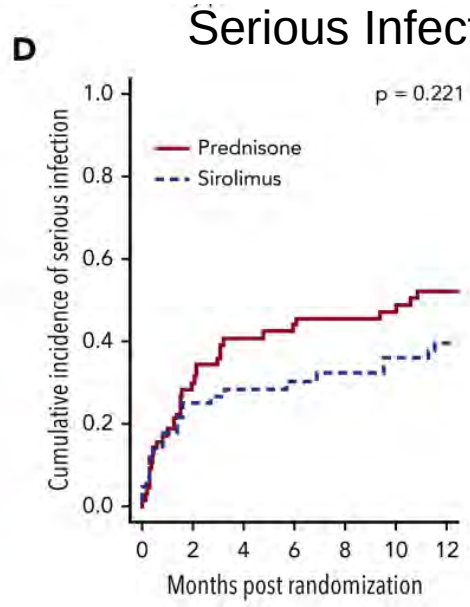
Pidala et al Blood 2020;135:2




**Sirolimus**

- is a viable option for front-line treatment of acute GVHD
- Non-responders can be salvaged with steroids
- Associated with quicker complete discontinuation of immunosuppressants and better quality of life
- Phase III study indicated

Pidala et al Blood 2020;135:2

original reports

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

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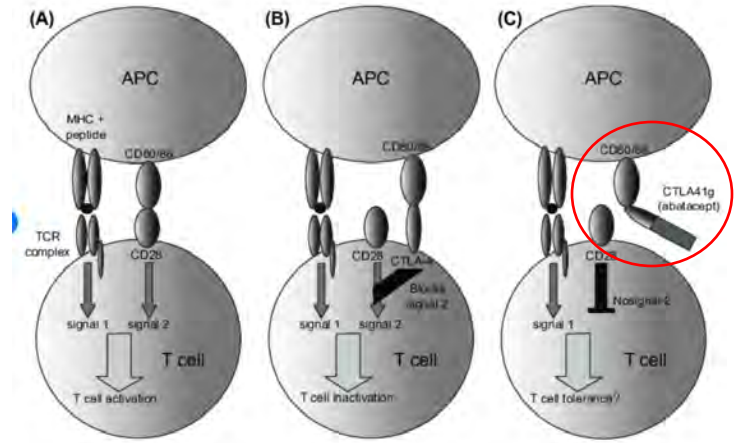
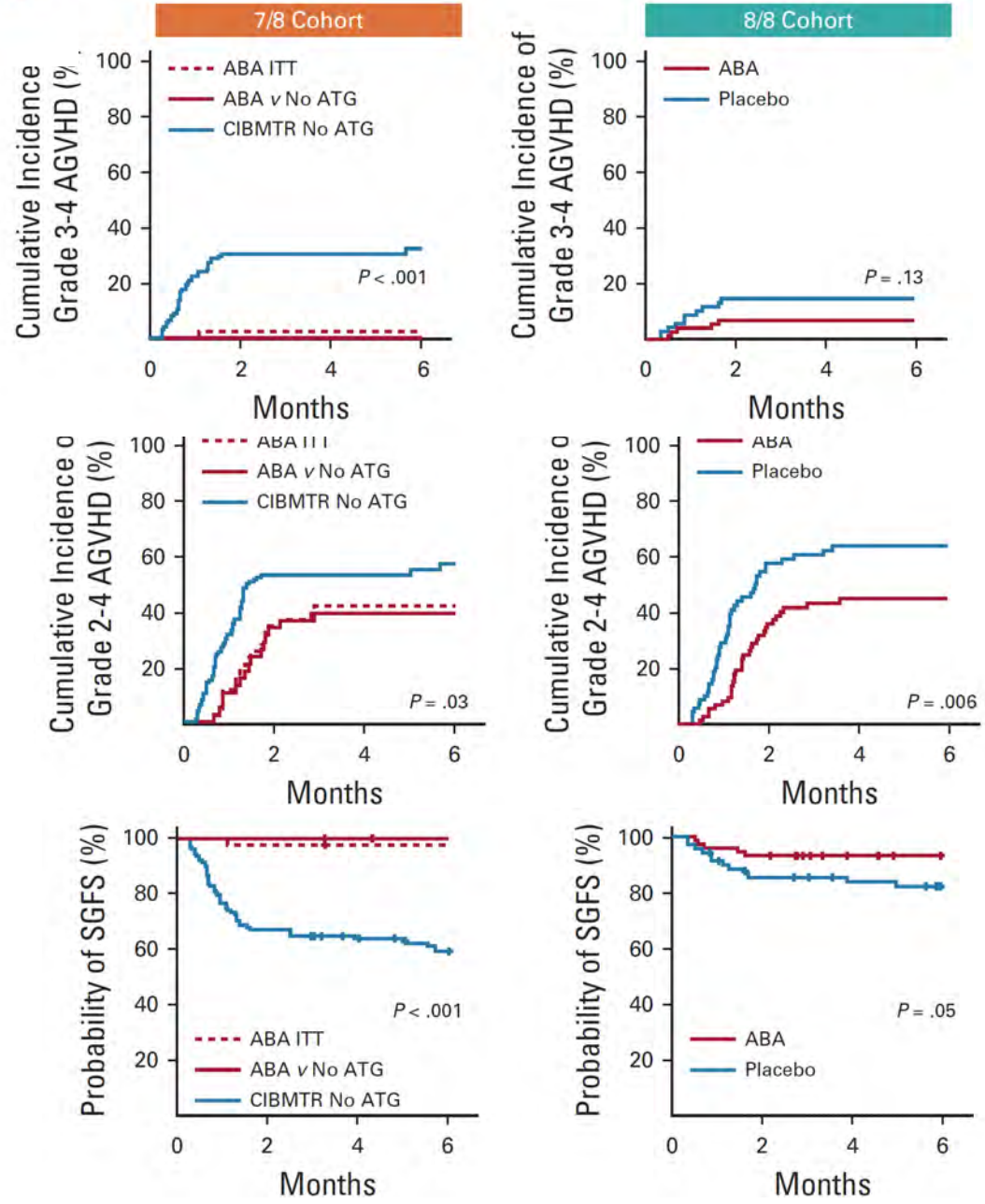
- Abatacept binds CD80 and CD86 (B7.1/2) on APCs preventing T-cell 2nd signalling through CD28
- FDA approved for rheumatoid arthritis
- Preclinical data suggest T-cell co-stimulation blockade when added to CSA/or tacro prevent T-cell alloreactivity and GVHD
- 2 Component Trial evaluated
  - In 8/8 matched recipients of an unrelated donor transplant- randomized/placebo-controlled trial evaluated incidence grade ¾ acute GVHD in pts receiving abatacept (ABA2) + csa/MTX vs CSA/MTX and
  - In 7/8 mismatched recipients of URD transplants- single arm trial evaluating the incidence of grade ¾ acute GVHD in pts receiving ABA2 + csa/MTX vs historical controls
- ABA2 (10 mg/kg/dose) given on days -1, +5, +14, +28



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

- In 8/8 transplants, grade 3-4 aGVHD occurred in 6.8% vs 14.8% of pts(p=0.13). Day 180 steroid free GVHD survival was 93.2% vs 82% (p=0.05)

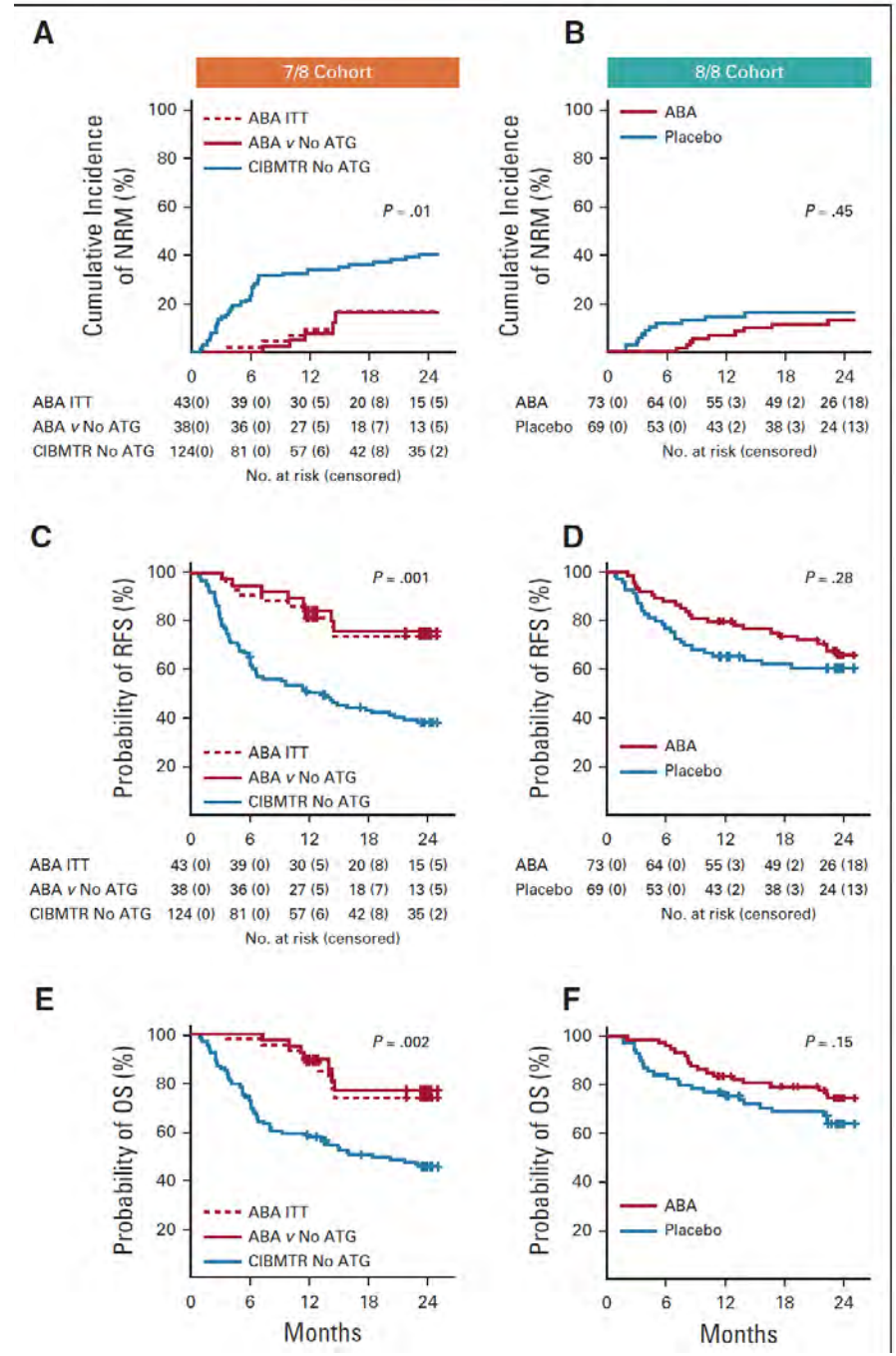
- In 7/8 transplants, grade 3-4 aGVHD occurred in 2.3% oif pts versus 30.2% in historical controls (p<0.001) and Day 180 steroid free GVHD survival was 97.7% vs 58.7% (p<0.001)



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

- **NRM**: Significantly lower in 7/8 mismatched recipients
- **Relapse:** Not increased in recipients of ABA2
- **Survival**: Significantly improved in recipients of mismatched 7/8 transplants.

**Conclusion**- adding abatacept to URD transplants is safe and reduces steroid free acute GVHD survival, particularly in recipients of mismatched unrelated donor transplants without increasing relapse risk or risk of infection.



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).

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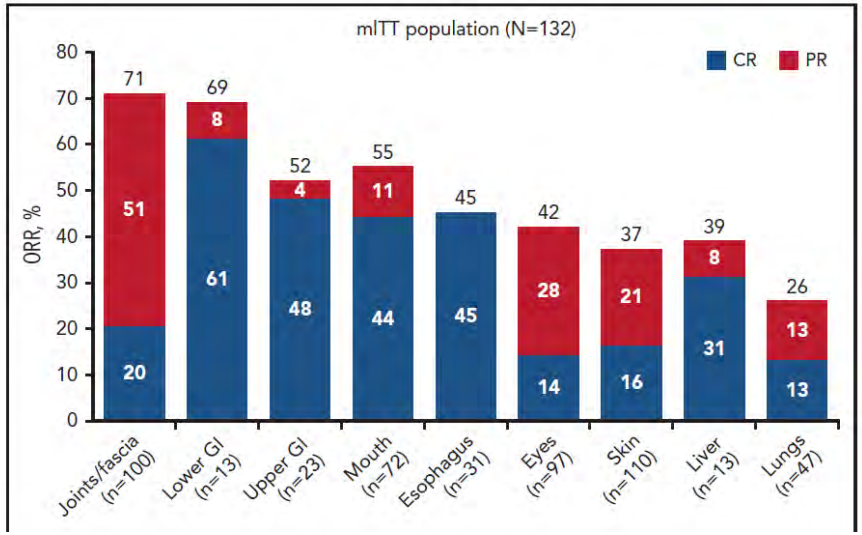
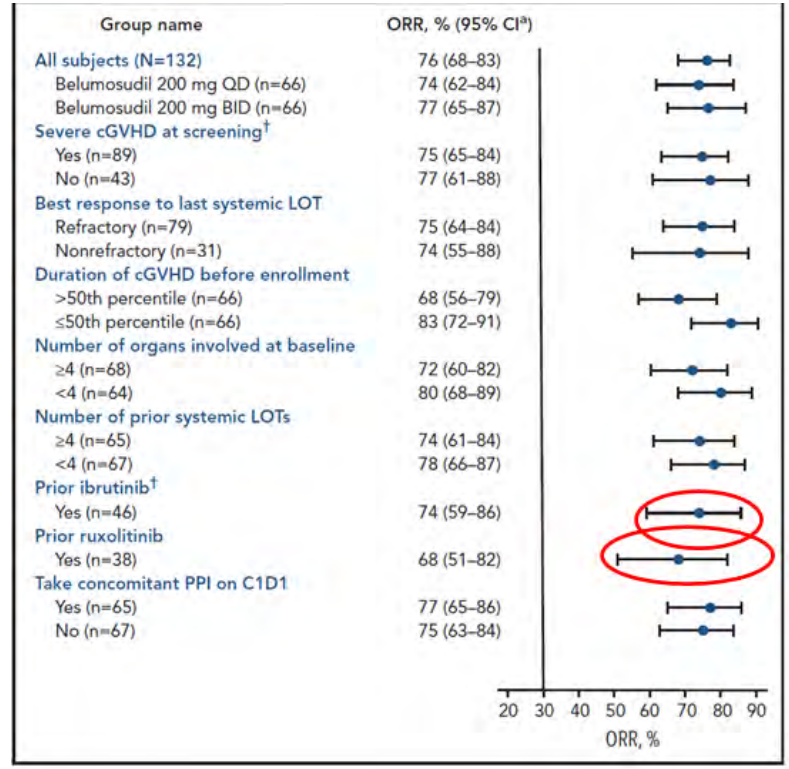
# **OUTCOME**:

- 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

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