HEMATOPOIETIC STEM CELL TRANSPLANTATION: UPDATING THE OLD CLOSET

RICHARD W. CHILDS M.D.
BETHESDA MD

Learning Objectives

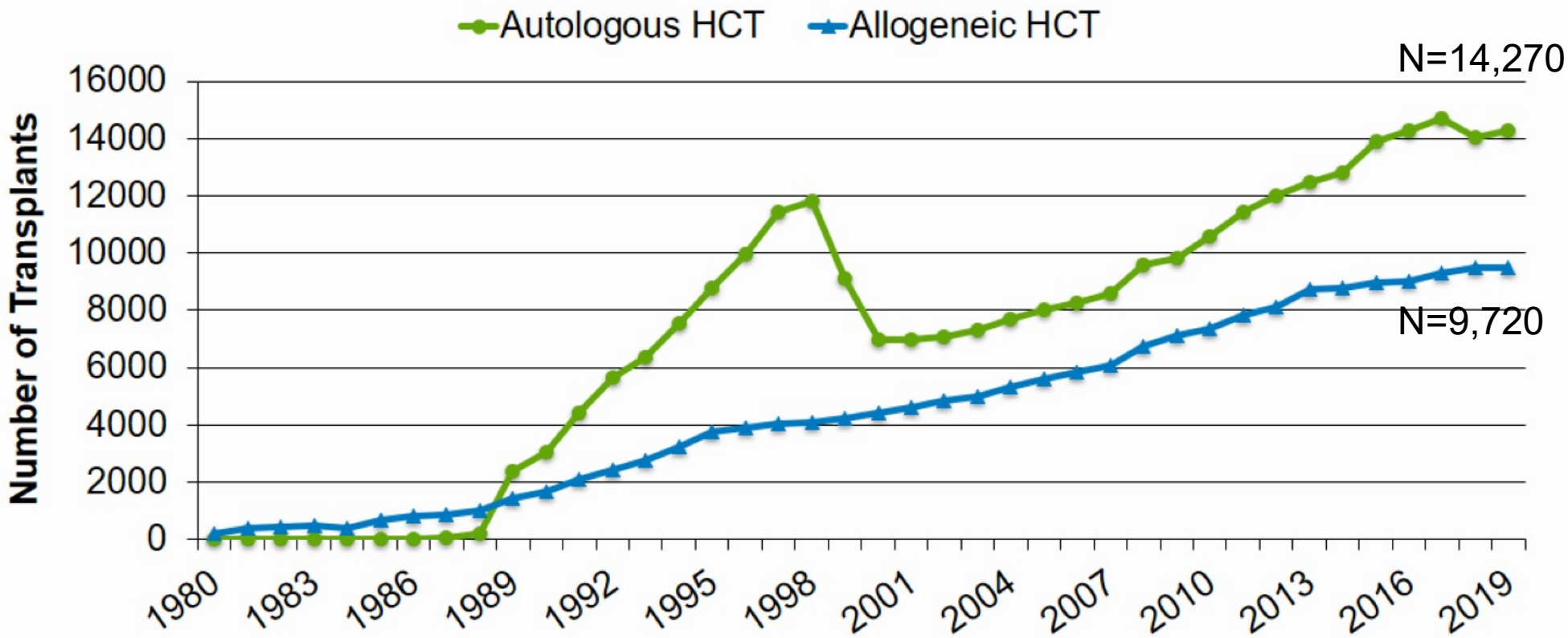
- To review Allogeneic Transplants in 2021
  - State of the art
  - Transplant types, outcomes and trends
- To update the status of Haplo-transplants- Everything you need to know
- To review outcomes with Cord Blood transplants compared to Haplo Transplants- which is better
  - CTN1101 tells us…….
- To update strategies to prevent and treat GVHD:
  - New transplant approaches to prevent acute GVHD
  - New approaches besides steroids for managing acute GVHD
  - New approaches to managing steroid refractory GVHD and chronic GVHD

GVHD= Graft vs host disease

Dr. Richard W. Childs disclosures:

- None

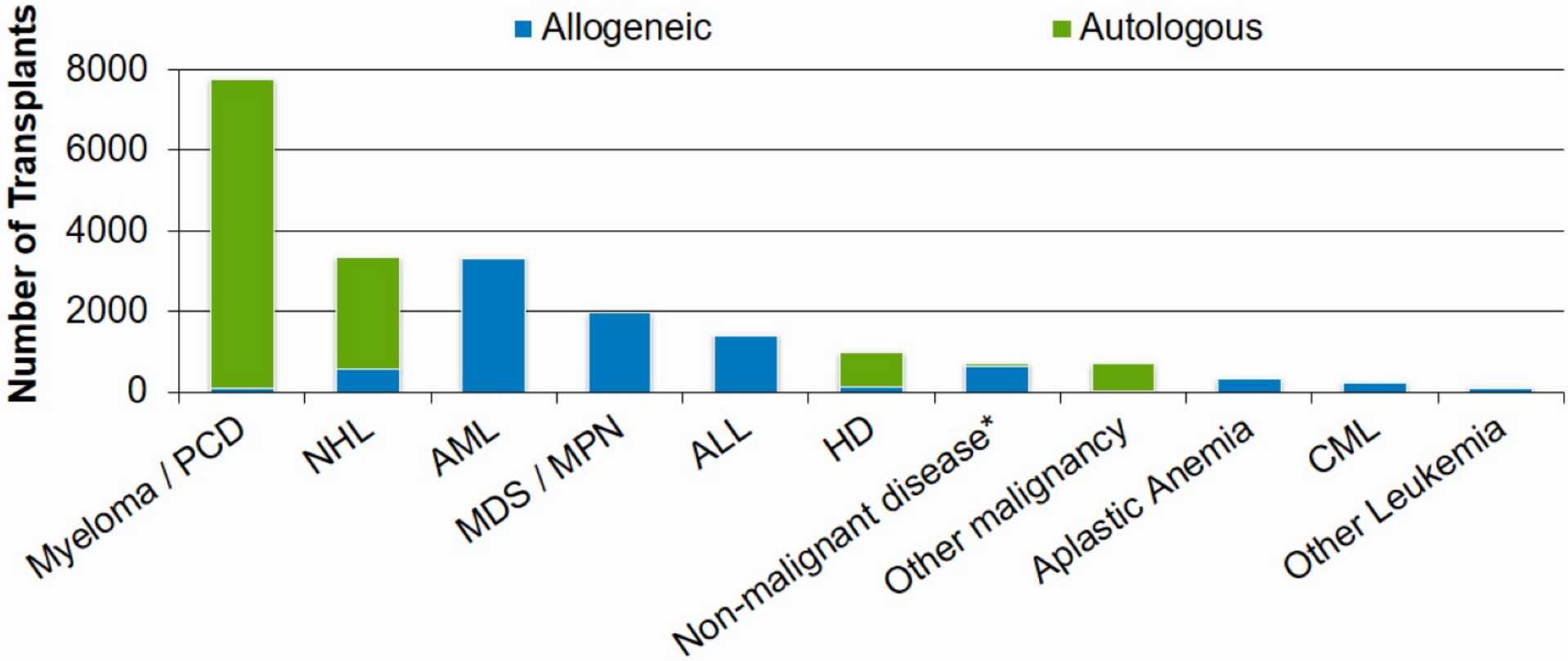
Estimated Annual Number of HCT Recipients in the US by Transplant Type



CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Data from the CIBMTR 2021

Indications for Hematopoietic Cell Transplant in the US, 2019

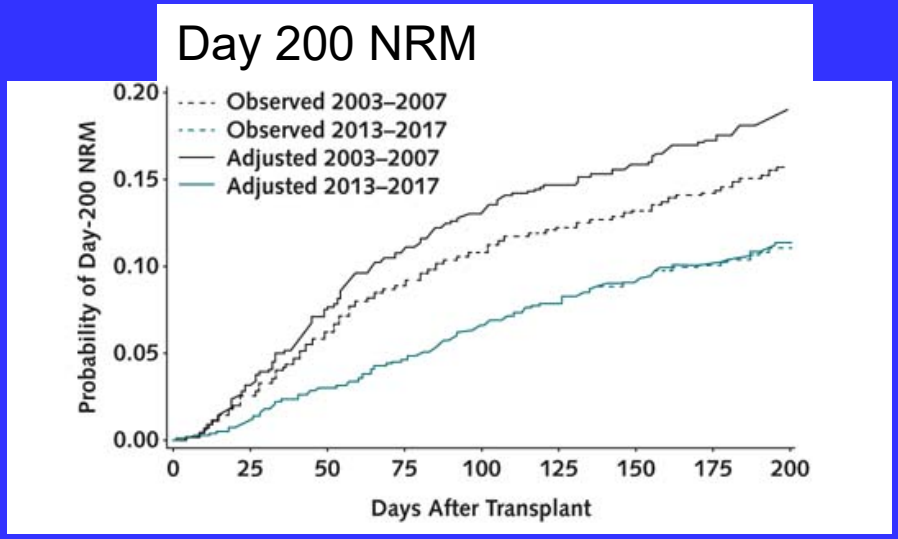


CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

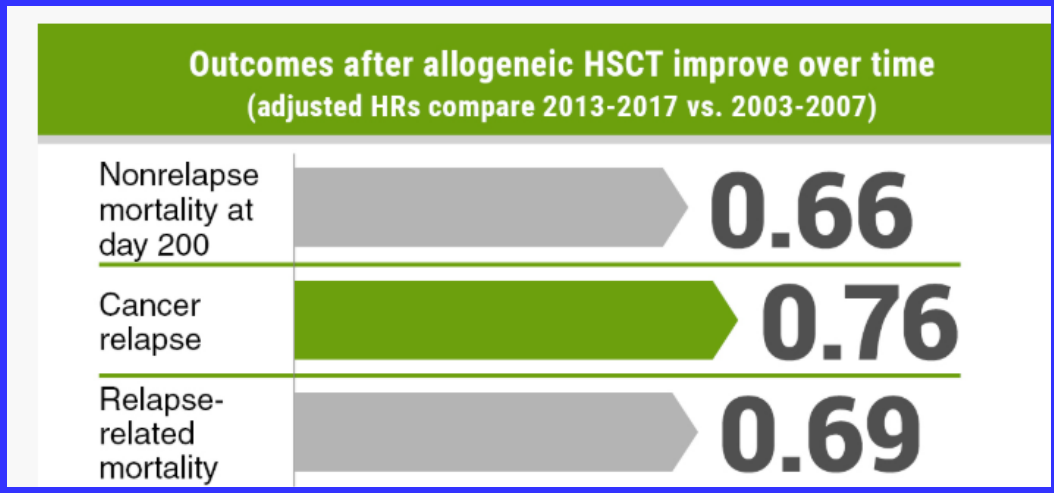
*excludes aplastic anemia

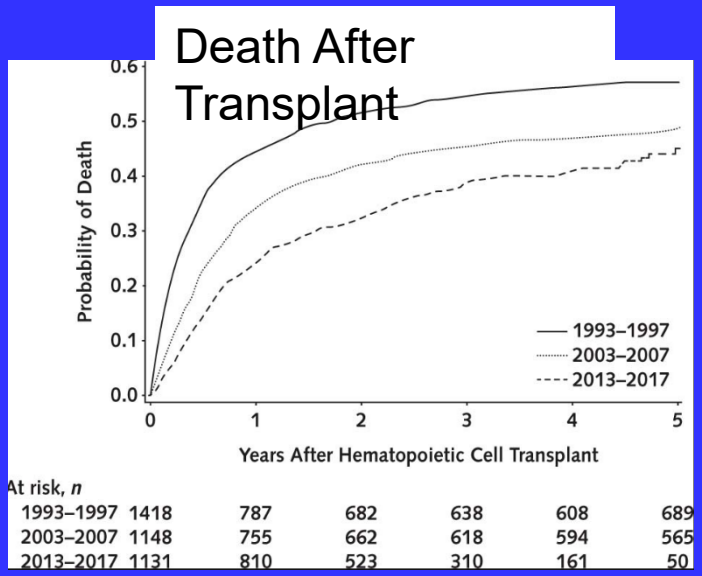
Data from the CIBMTR 2021

Major Improvements in Transplant Safety Over the Past 2 Decades



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

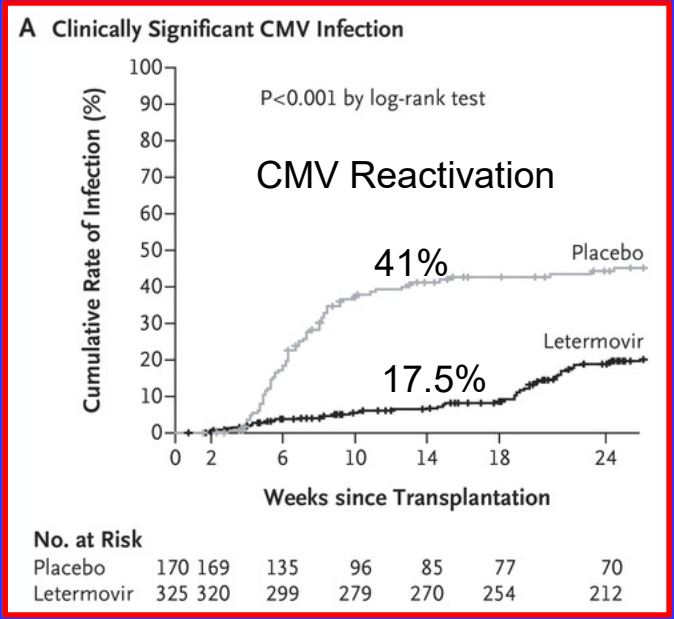


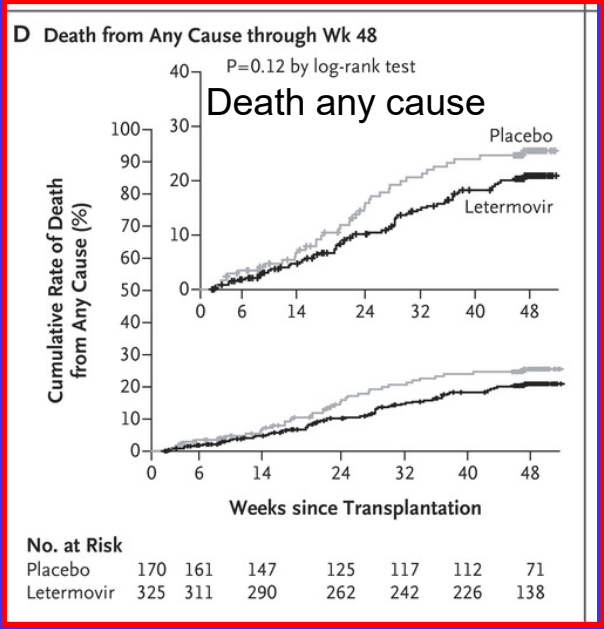


McDonald G.B. et al Annals Int Med 2020:Ann Intern Med. 2020;172:229-239.

Major Improvements in Transplant Outcomes Over the Past 2 Decades

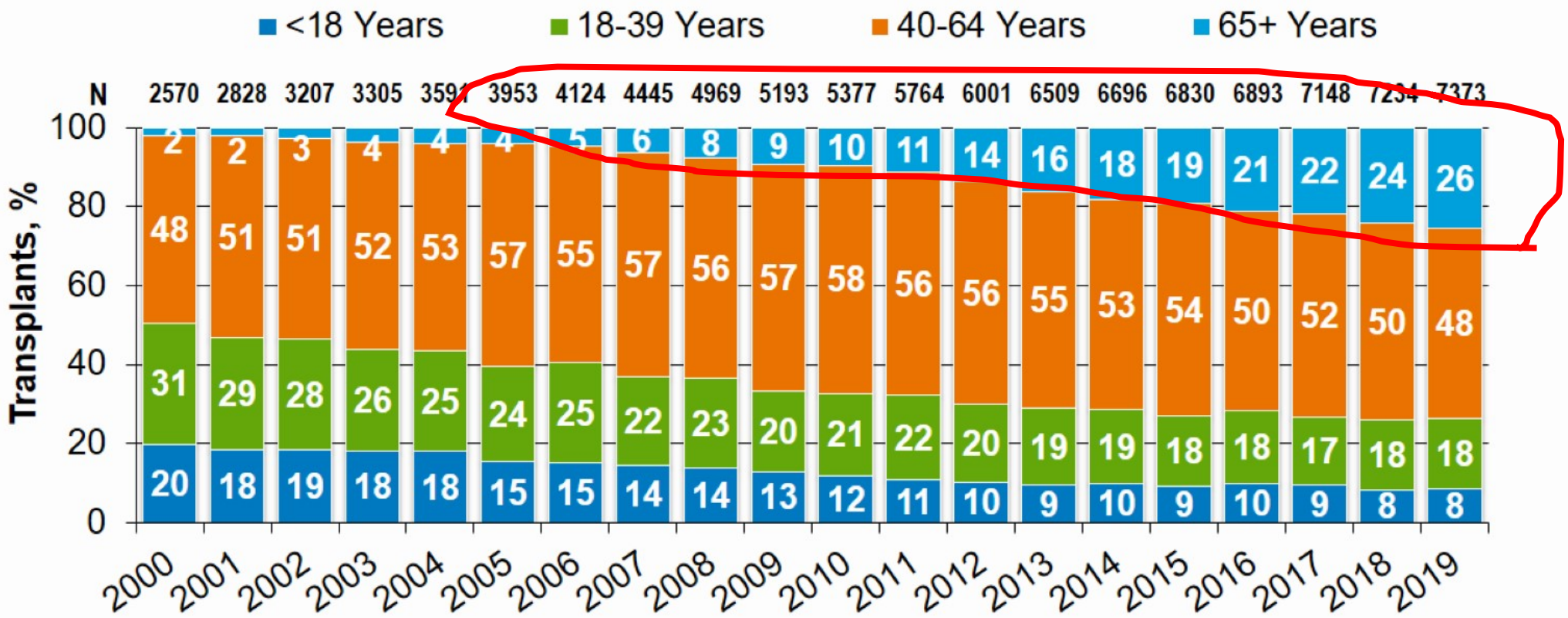
- **First FDA approved drugs to treat GVHD**
  - **Ibrutinib** demonstrated ORR 67% cGVHD (CR=21%, PR=45%)
    - Miklos, D et al, Blood-Sept 2017
  - **Ruxolitinib** 73% response for SR acute GVHD- FDA approved May 24, 2019
- **Letermovir approved (2017) to prevent CMV reactivation post-HCT**
  - **Reduced risk of CMV reactivation from 41% to 17% compared to placebo**





Marty F. et al. NEJM Dec 2017

Trends in Allogeneic HCT in the US by Recipient Age^

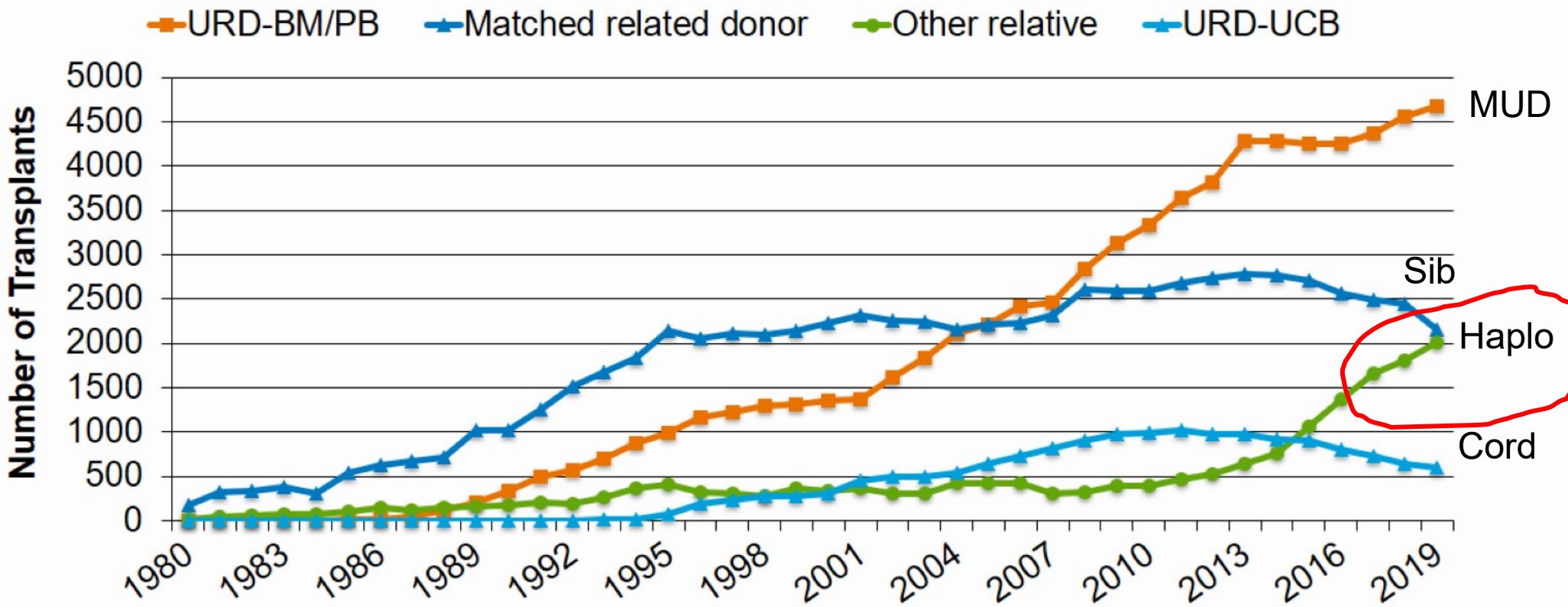


CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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

Data from the CIBMTR 2021

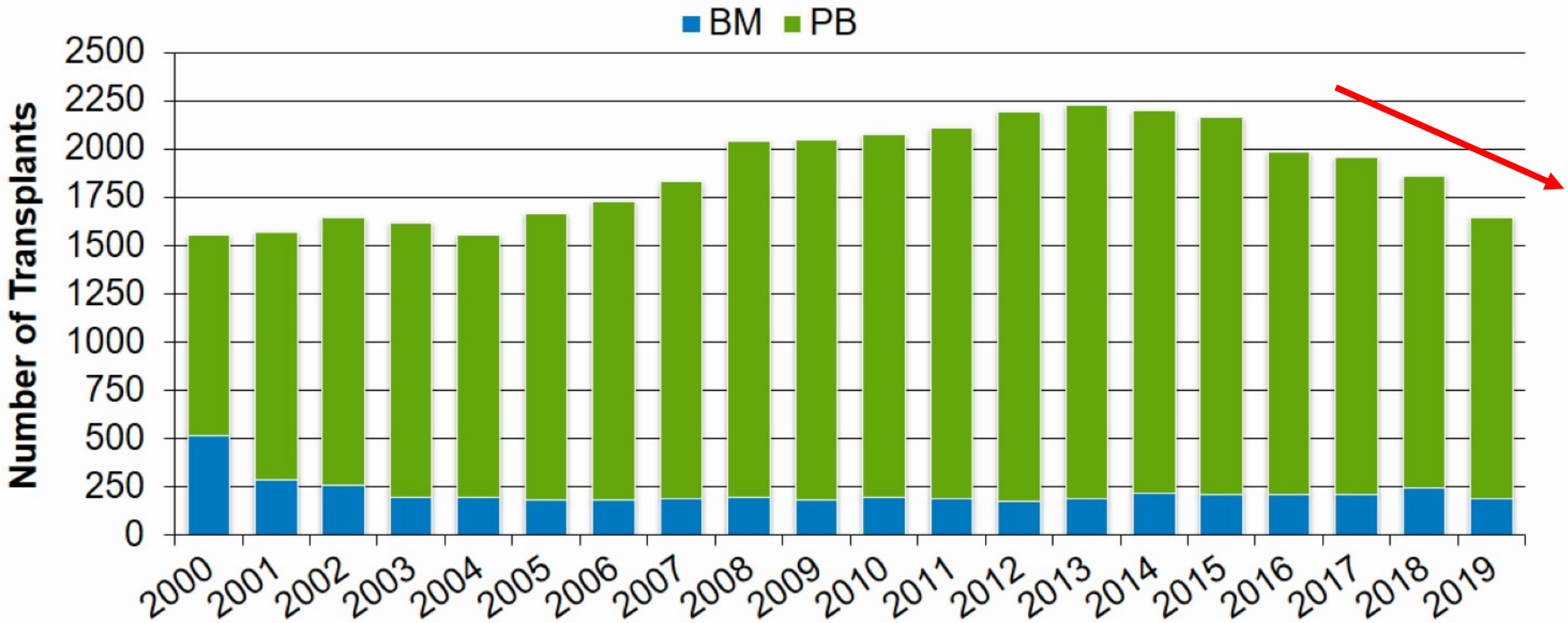
Estimated Allogeneic HCT Recipients in the US by Donor Type



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Data from the CIBMTR 2021

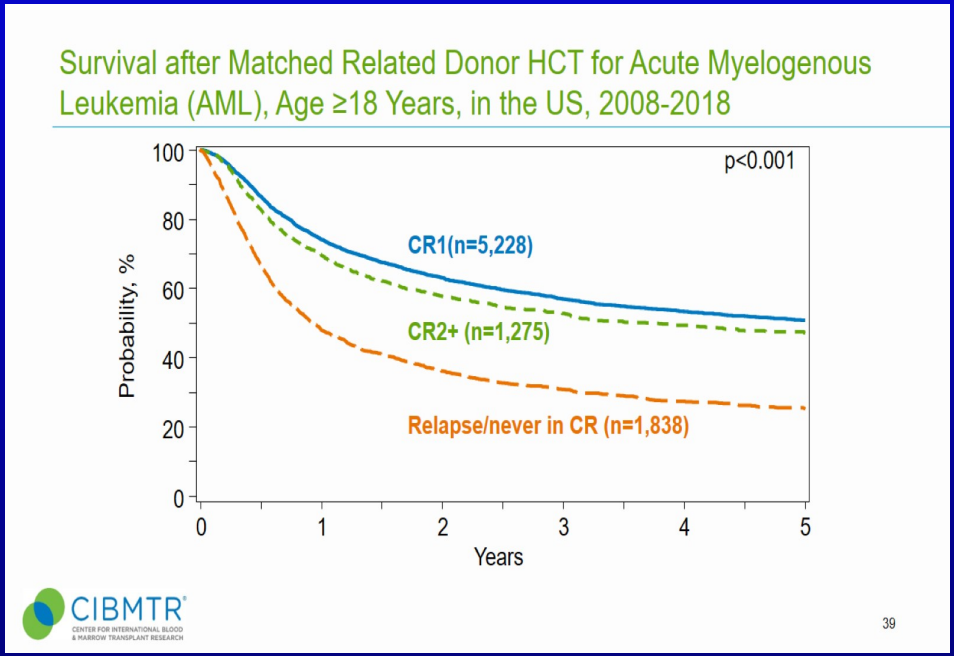
Matched Related Donor Allogeneic HCT in the US in Patients ≥18 Years

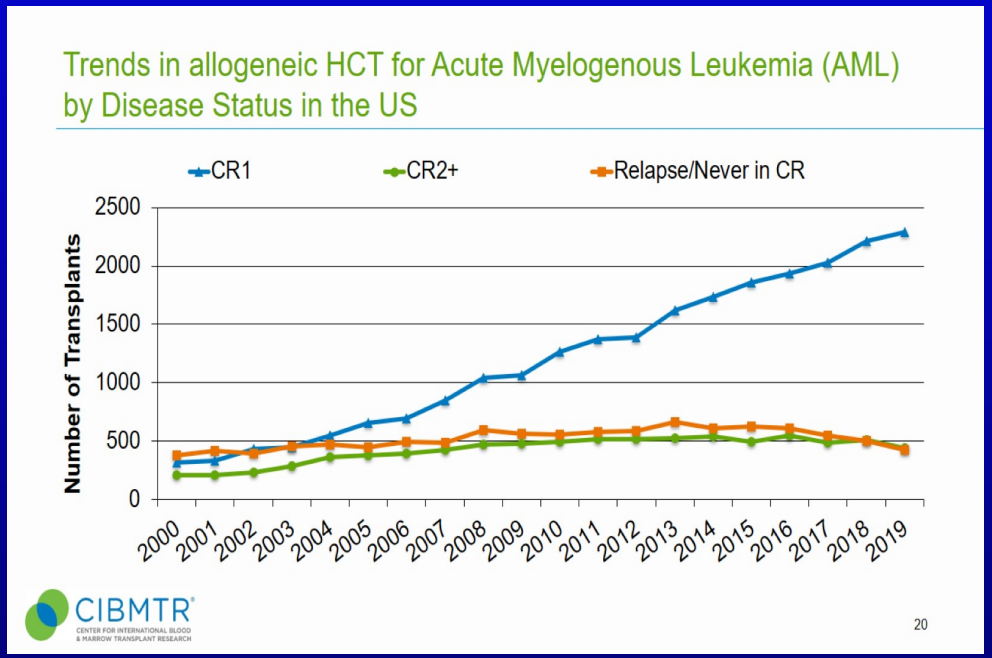


CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Data from the CIBMTR 2021

Allogeneic Transplant For Hematological Malignancies: The Earlier the Better !!





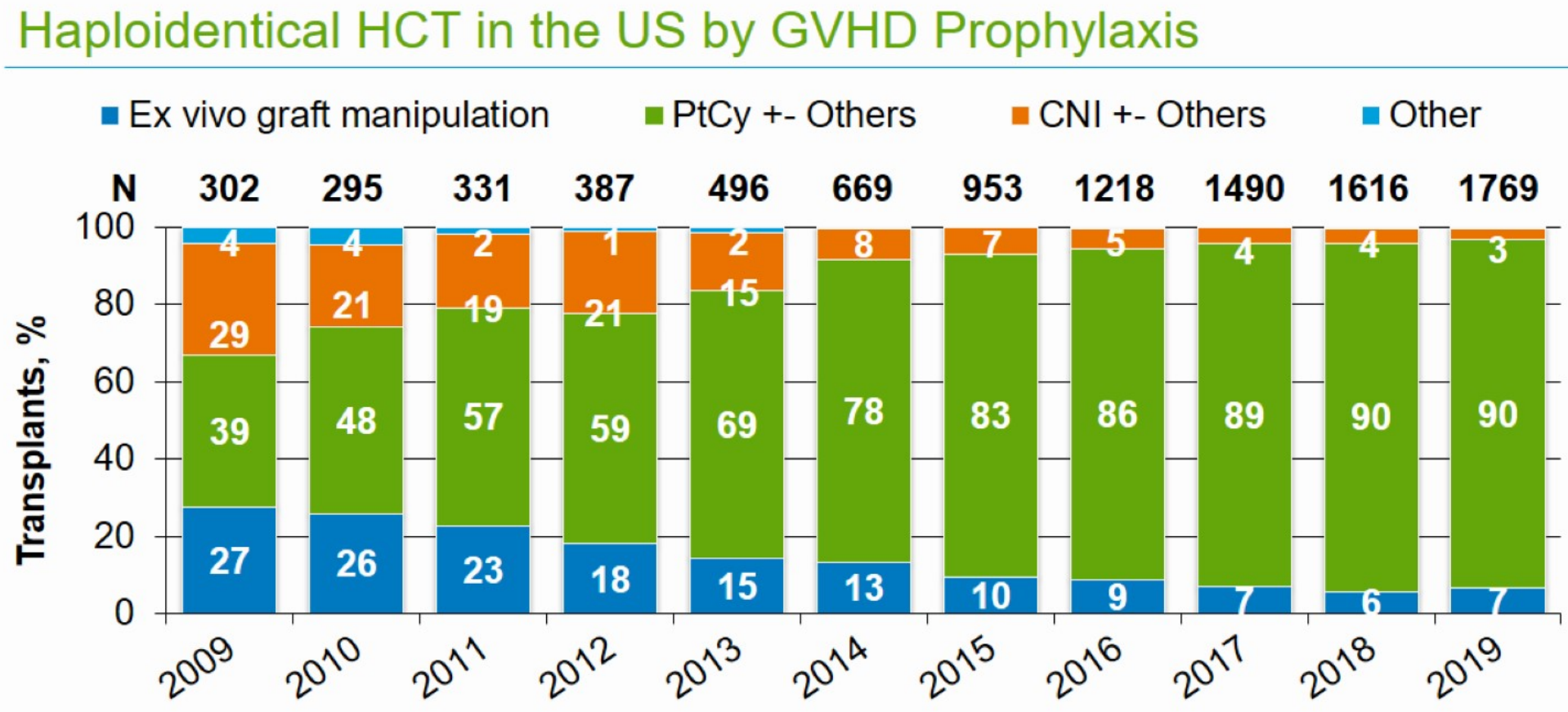
Reduced transplant-related mortality and lower relapse with the earlier use of transplants has led to an increasing use of allogeneic transplants upfront for AML in CR-1

CIBMTR Data 2020

Haplo-Transplants: Current Status and Trends

Post-Transplant Cyclophosphamide Has
Revolutionized Haplo Transplants

Most Haplo-Transplants Use Post Transplant Cytoxan



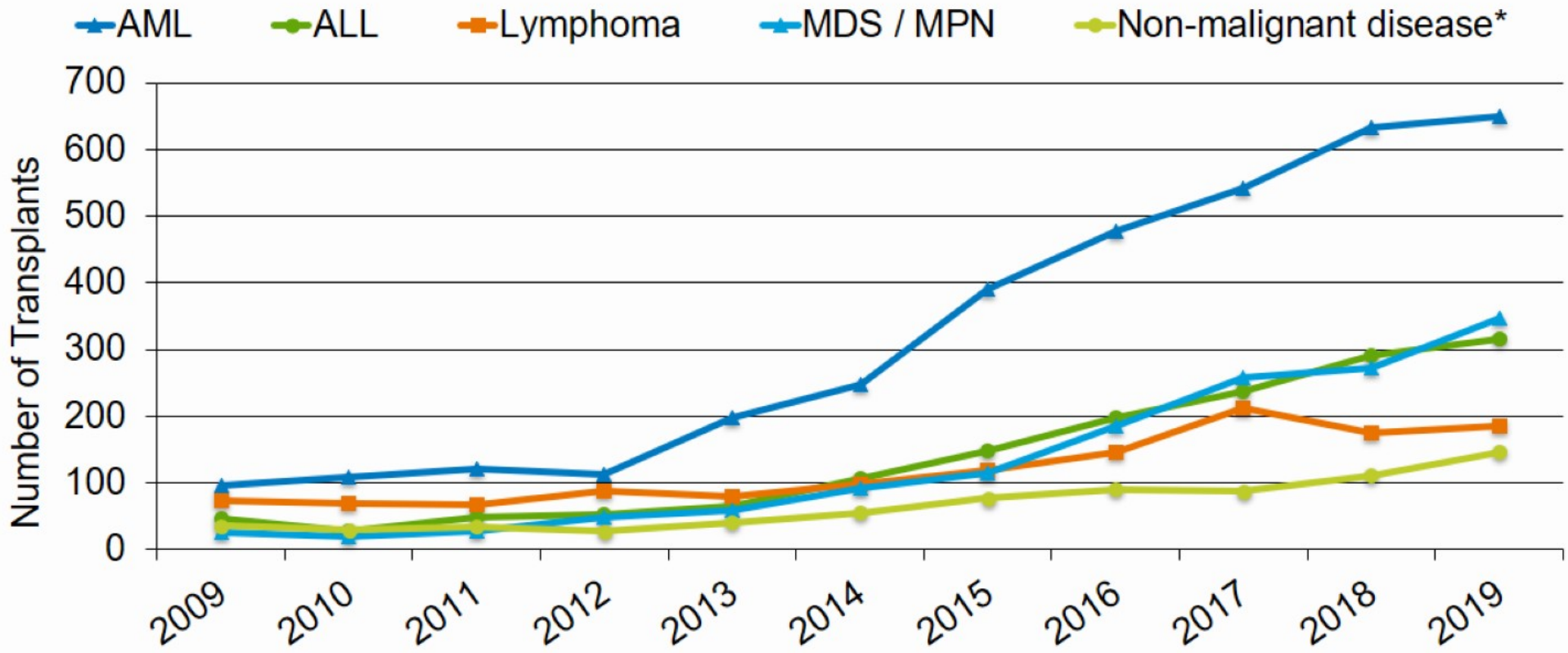
CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Abbreviations - PtCy: Post-transplant cyclophosphamide; CNI: calcineurin inhibitor

Data from the CIBMTR 2021

Use Of Haplo-Transplants Increasing For Multiple Disease Categories

Haploidentical HCT in the US by Disease

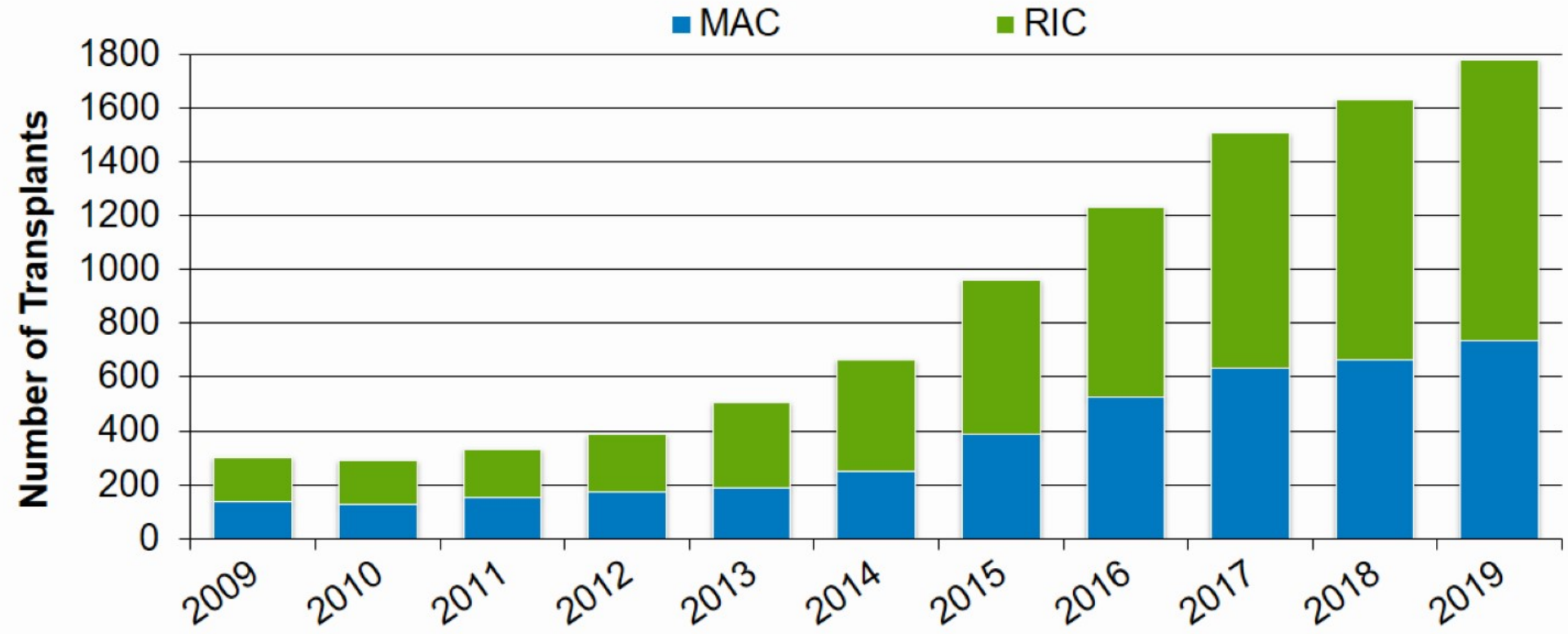


CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

*Not including aplastic anemia

Data from the CIBMTR 2021

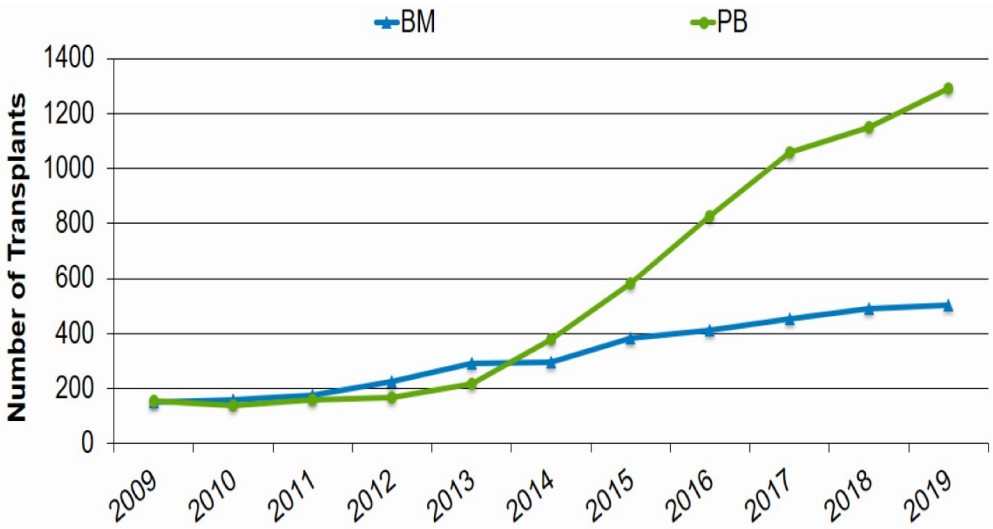
Slightly More RIC Haplo-Transplants Than Myeloablative Transplants



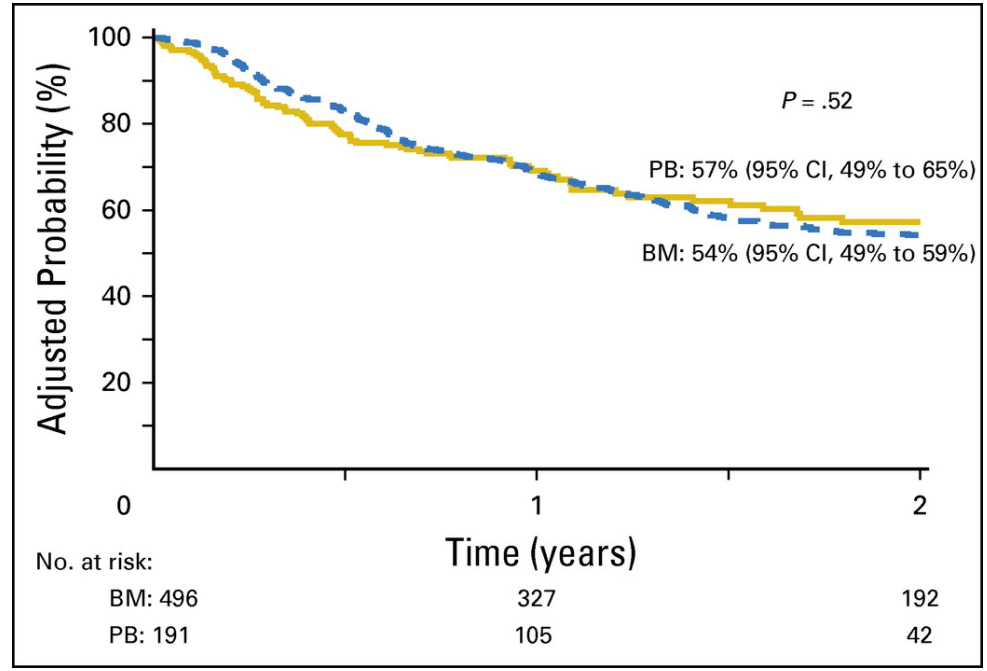
Data from the CIBMTR 2021

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

Haplo-Transplants and Graft Source



Haplo-Transplants and Graft Source and Survival



Bashey et al, JCO 2017

PBSC=Peripheral Blood Stem Cell BM= Bone marrow

Who IS the Optimal Donor To Choose For Haplo Transplants 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 donor age, 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).

Multivariate Analysis of Risk Factors for Acute Grade II-IV GVHD 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 v <29
  - (HR 1.53, CI 1.11-2.12,
  - P=0.01)
- G3-4: 50 v <29
  - (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.

Cord vs Haplo: Which is Better?

Pros for Both Cords and Haplo Transplants

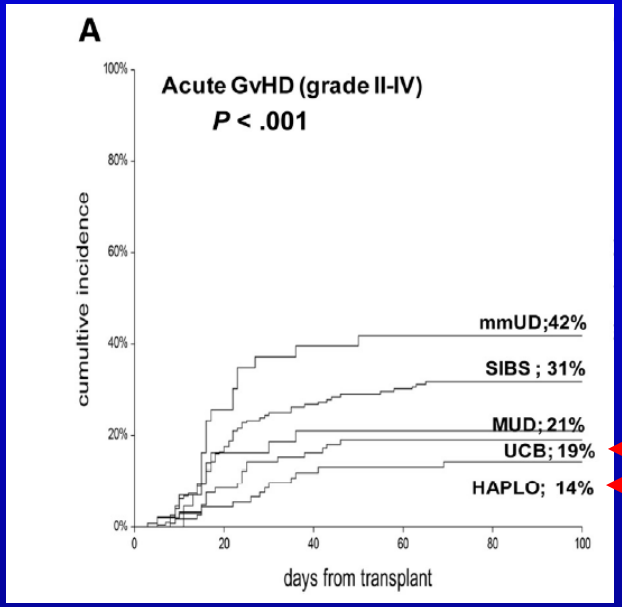
- Almost all Adults will have a haplo donor available or a cord unit that is suitable for transplantation.
- Acute and chronic GVHD rates are very low with both approaches

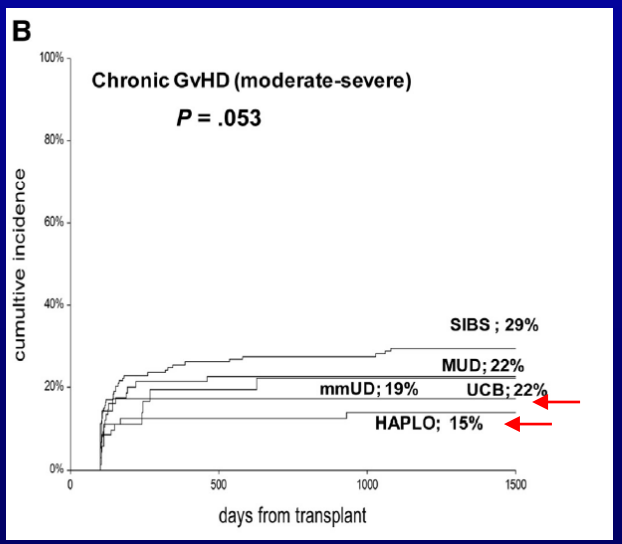
Cons For Cords:

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

Cons for Haplos:

- Relapse rate may be higher??
- Graft rejection problematic for some diseases

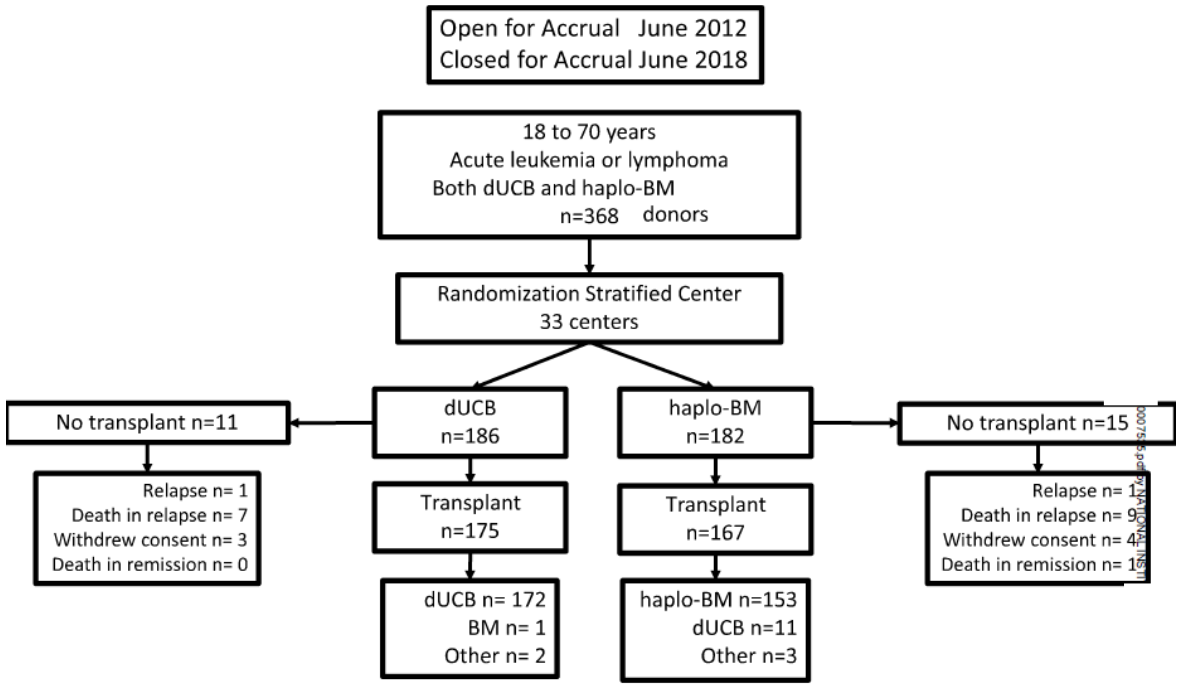


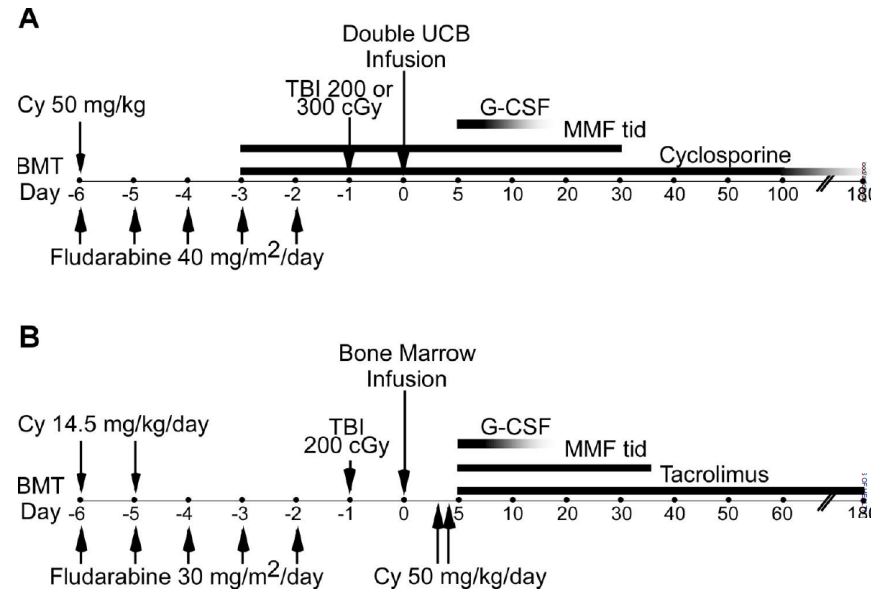


CTN 1101: Cord vs. Haplo

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

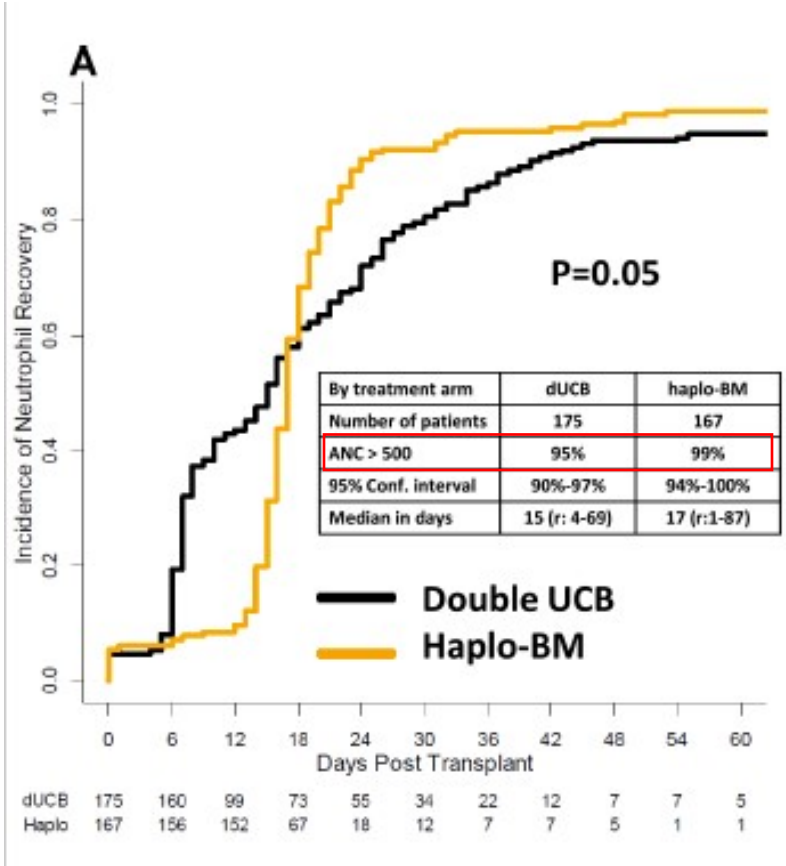




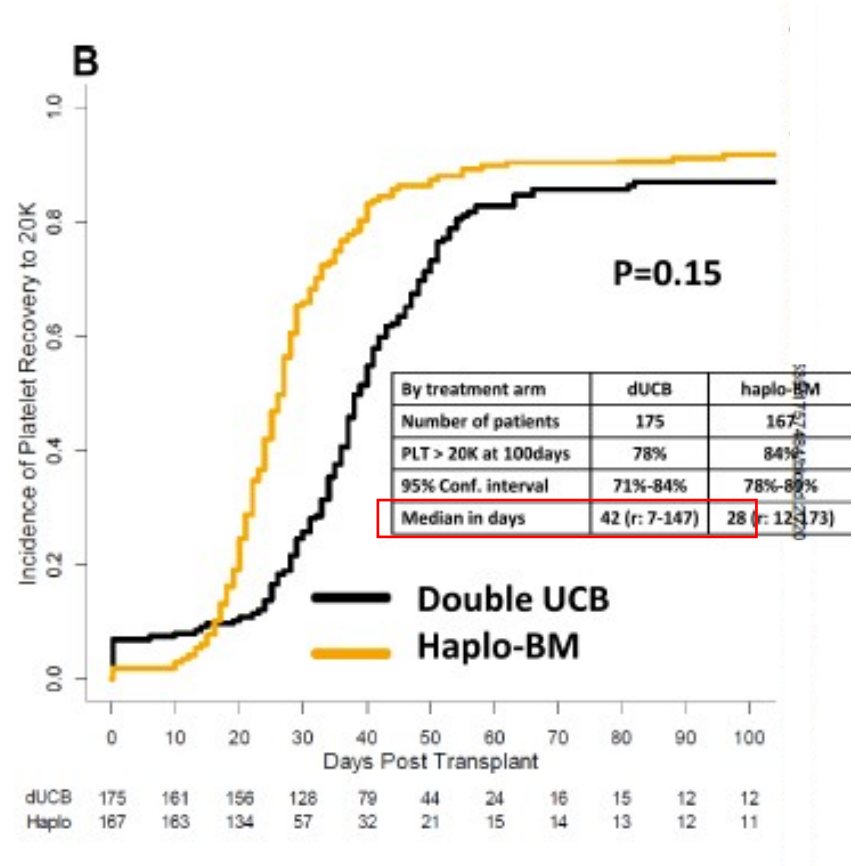
Fuchs E. et al Blood 2021: 137:420428

CTN 1101: Cord vs. Haplo

Neutrophil Recovery



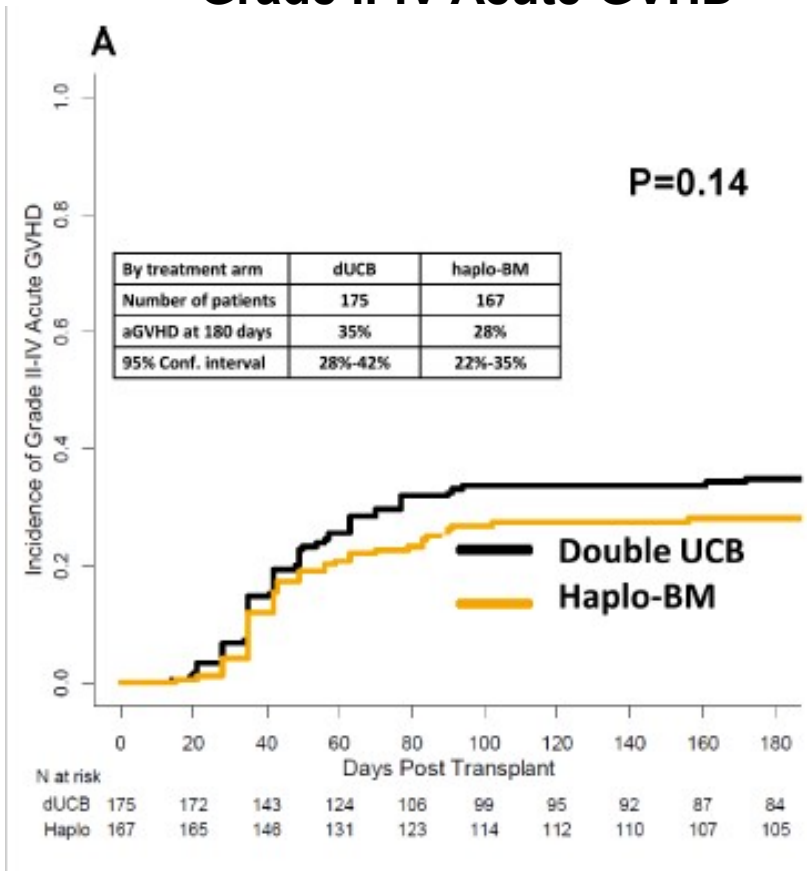
Platelet Recovery



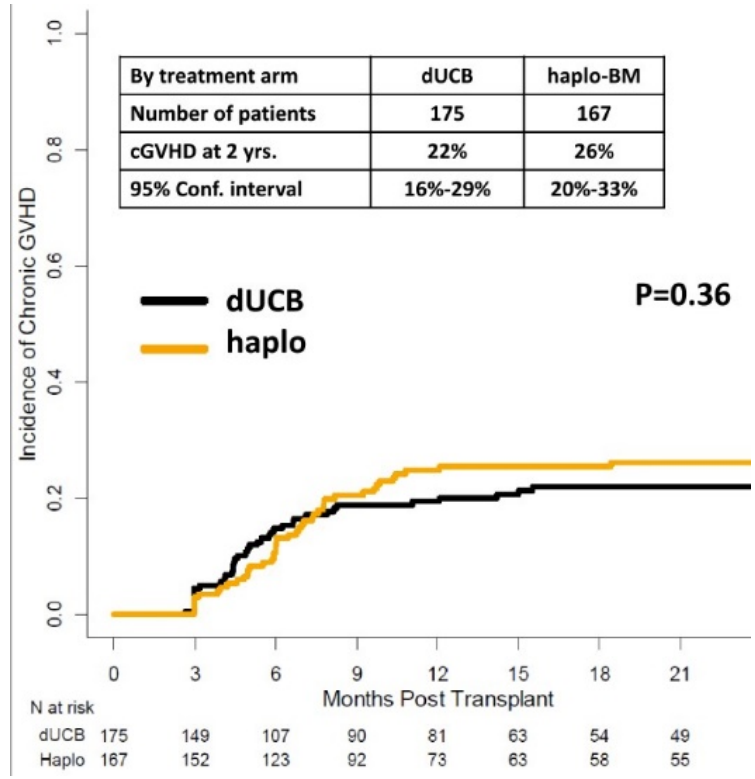
Fuchs E. et al Blood 2021: 137:420428

CTN 1101: Cord vs. Haplo

Grade II-IV Acute GVHD



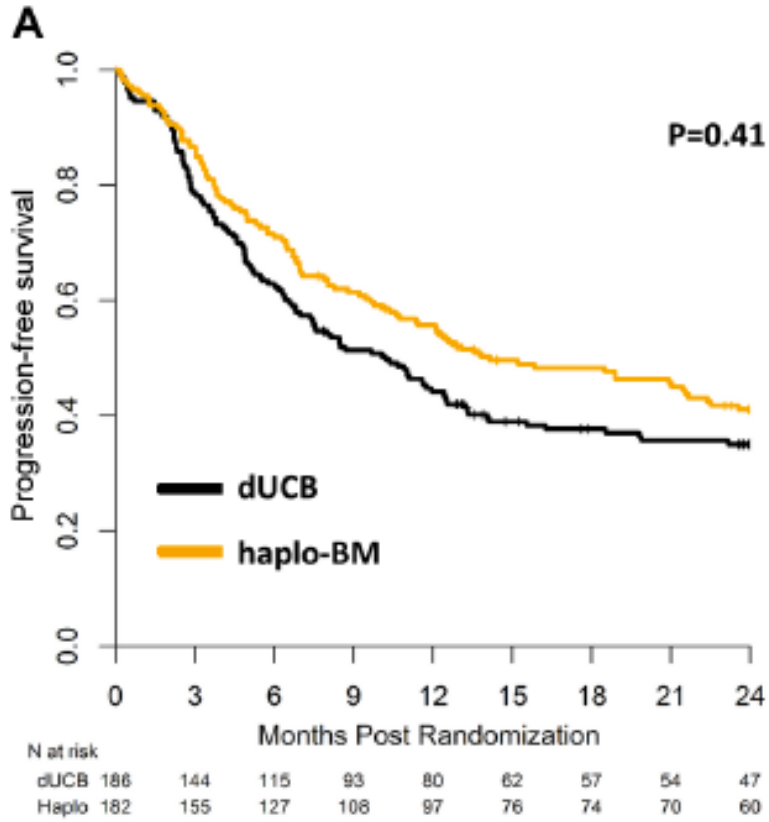
Chronic GVHD



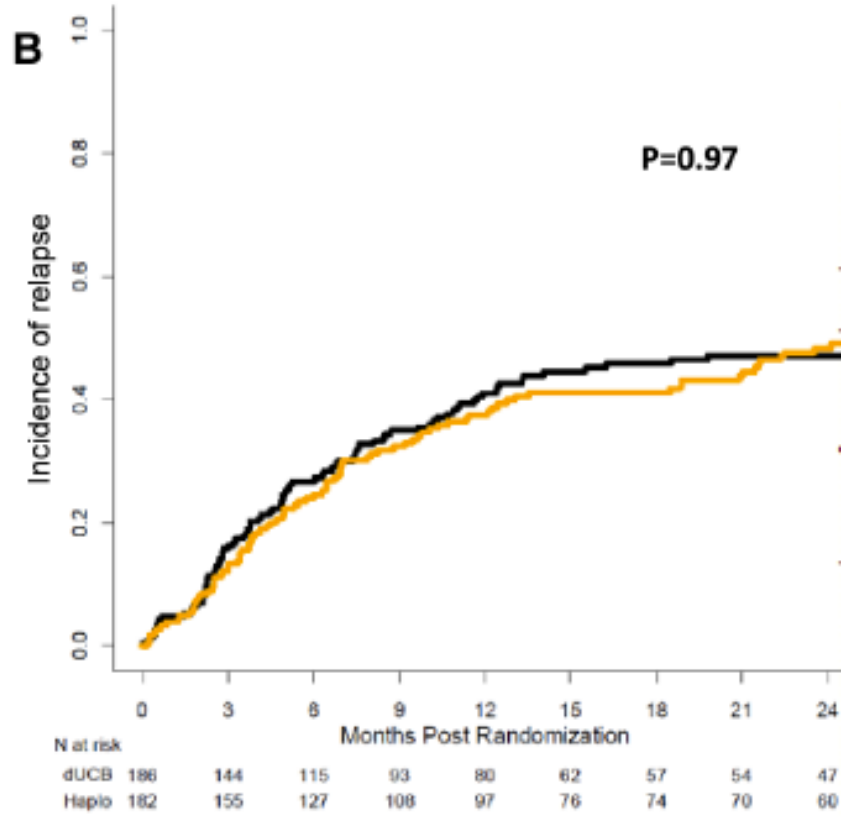
Fuchs E. et al Blood 2021: 137:420428

CTN 1101: Cord vs. Haplo

Progression Free Survival



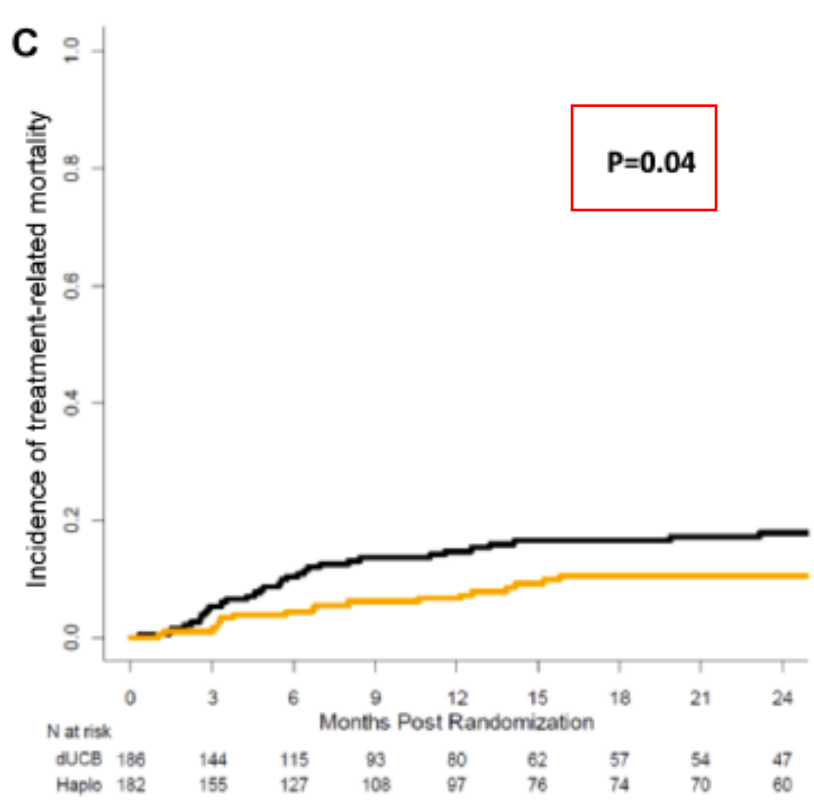
Relapse



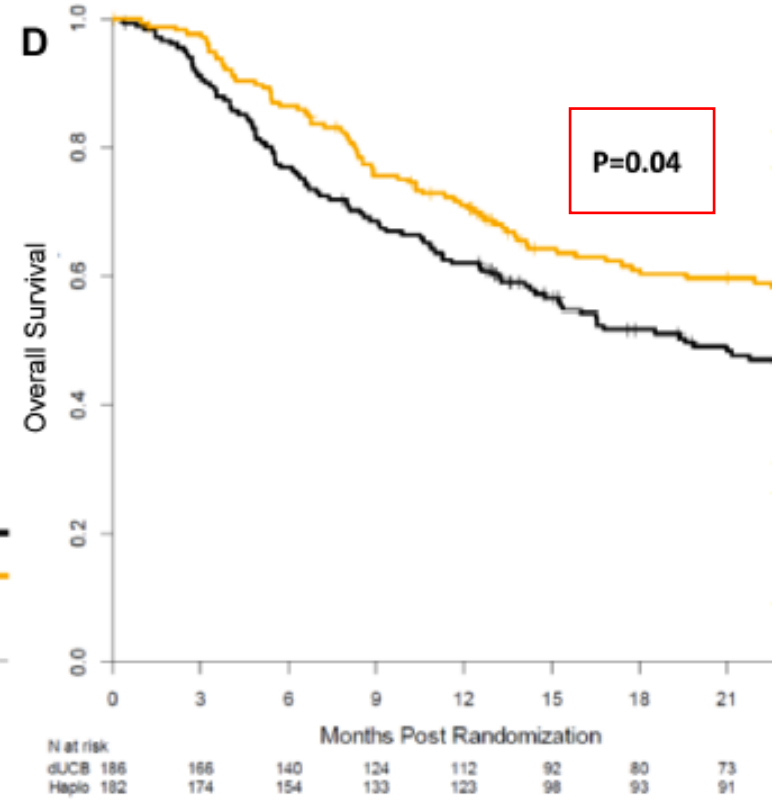
Fuchs E. et al Blood 2021: 137:420428

CTN 1101: Cord vs. Haplo

Transplant related Mortality



Overall Survival



Fuchs E. et al Blood 2021: 137:420428

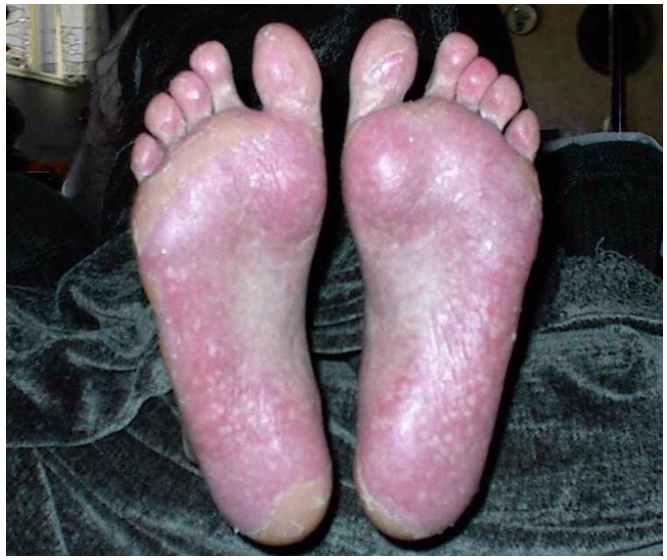
CTN 1101: Cord vs. Haplo

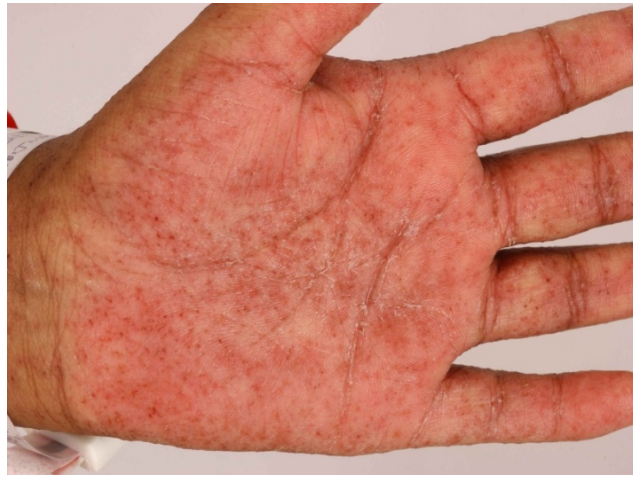
Conclusions:

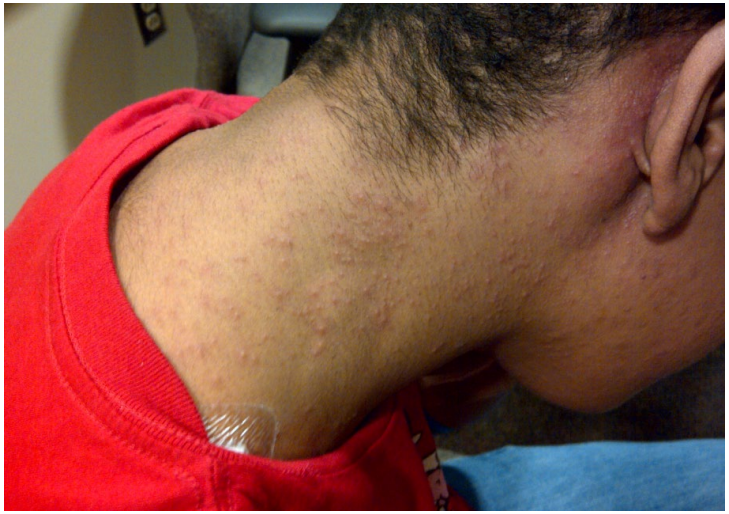
- There was no significant difference in progression-free survival between cord blood and haploidentical transplantation for leukemia or lymphoma
- Engraftment rates and relapse were similar between transplant approaches
- Haplo transplants had lower non-relapse mortality rates which resulted in superior overall survival
- These data favor the use of haploidentical marrow over cord blood transplantation

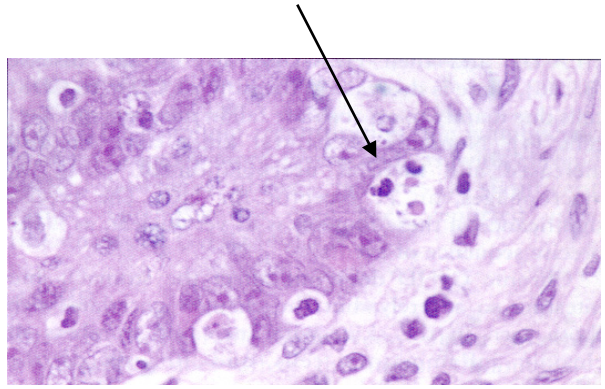
Fuchs E. et al Blood 2021: 137:420428

GVHD Historically Has Been A Major Contributor to Transplant Related Mortality









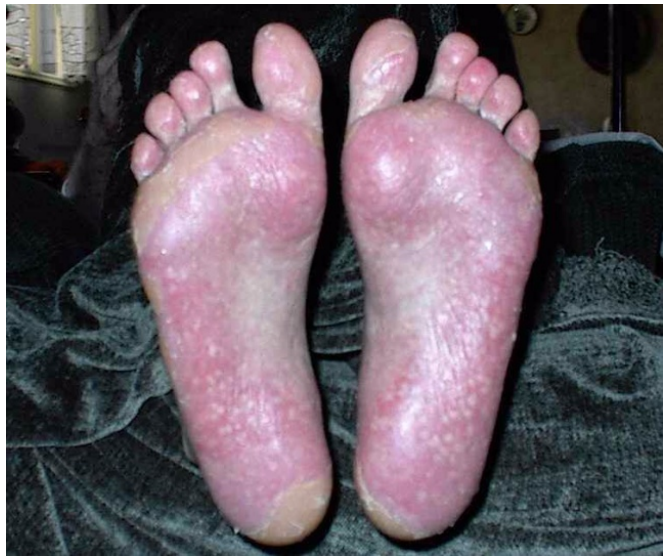
GVHD of the Colon

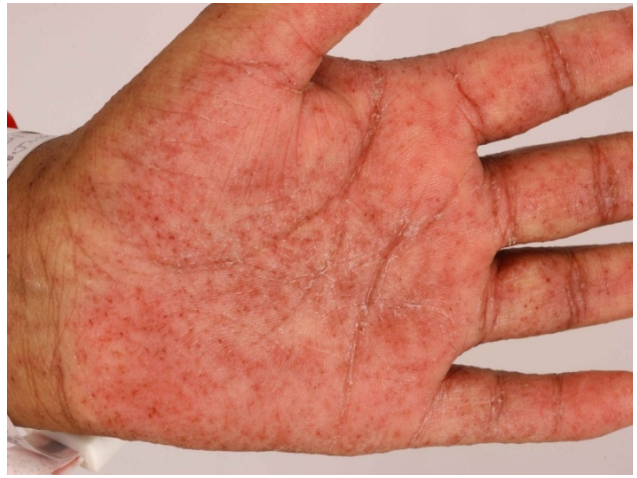
Acute GVHD

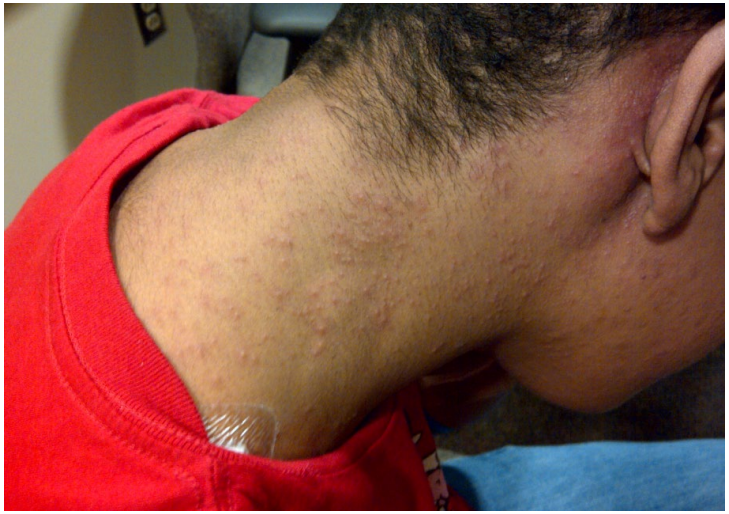
1. GI Tract: Diarrhea
2. Liver: Jaundice
3. Skin: Rash

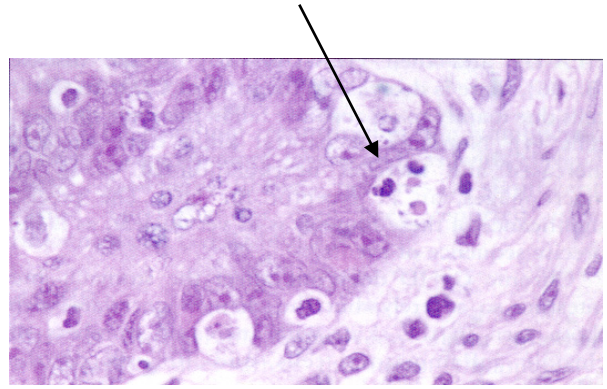
Pictures from the files of Dr. Richard Childs

GVHD Historically Has Been A Major Contributor to Transplant Related Mortality

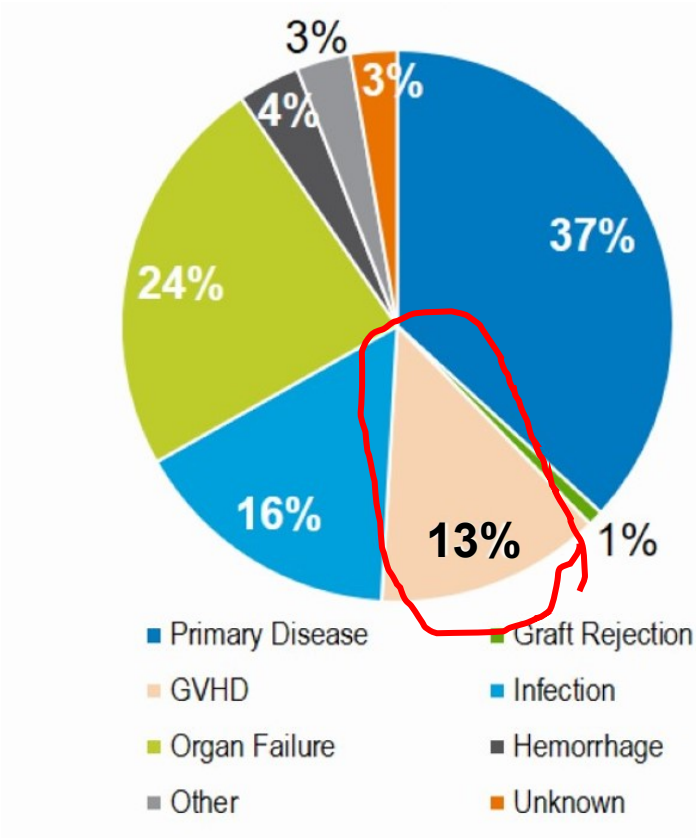








GVHD of the Colon



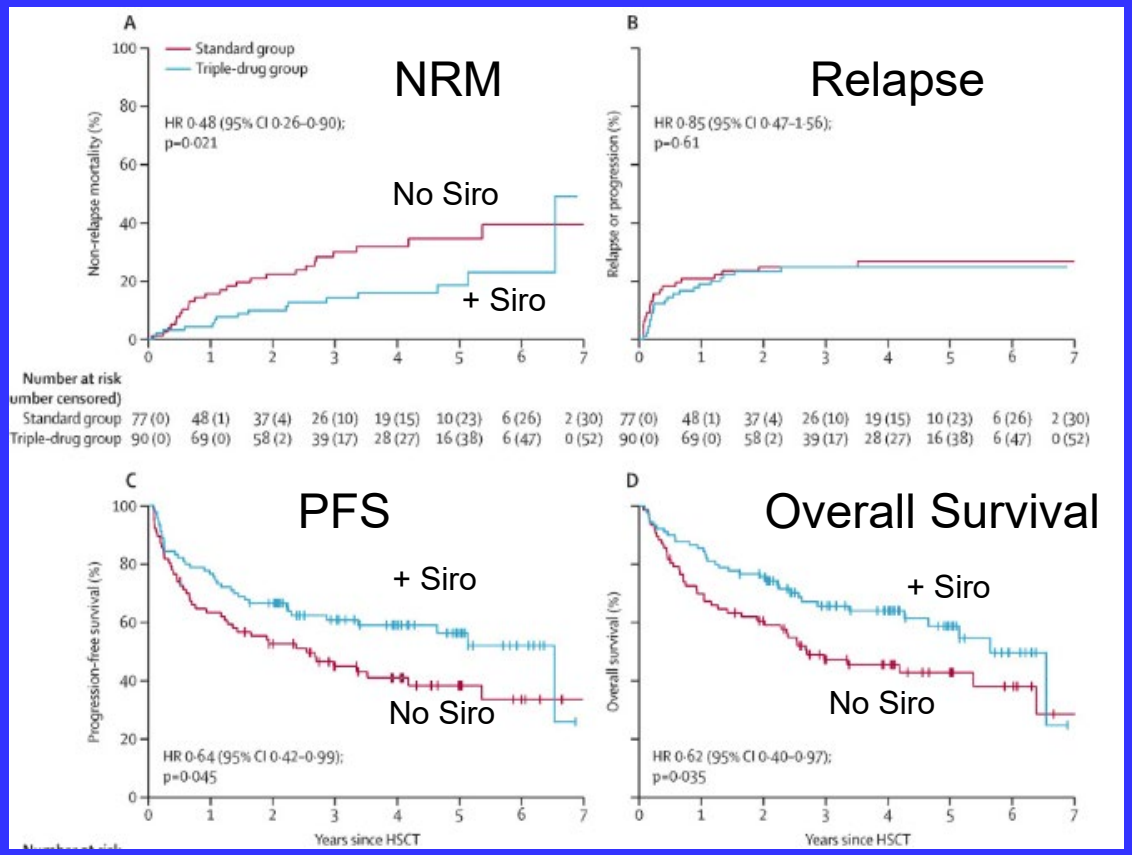
TRM by day 100
13% caused by GVHD

CIBMTR Data 2021

Prevention of GVHD: Adding Sirolimus to Standard CSA/MMF Reduces GVHD and Improves Survival After RIC Allo HCT

Post-Transplant Cytoxan resulted in

1. Lower grade III-IV GVHD (9% vs 19%; P<0.04)
2. Trend towards less NRM (16% vs 29%; p=0.06)
3. Improved LFS (55% vs 34%; p<0.05)
4. Trend towards improved OS (56% vs 38%;p=0.07)
5. Improved GVHD free/Relapse free survival (37% vs 21%; p<0.03)



Sandmaier B. et al. Lancet Haema 2019; 6(8)

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

Pros:

- Rapid onset of action: <24 hours

Cons:

- Only 50%-70% Response Rate
- Substantial morbidity related to use
  - Opportunistic infection: Lethal fungal infections
  - Hypertension
  - Diabetes
  - Osteopenia
  - Cataracts
  - Myalgia

Hypothesis -pts presenting with acute GVHD can be effectively treated with sirolimus as opposed to steroids: **CTN BMT 1501**

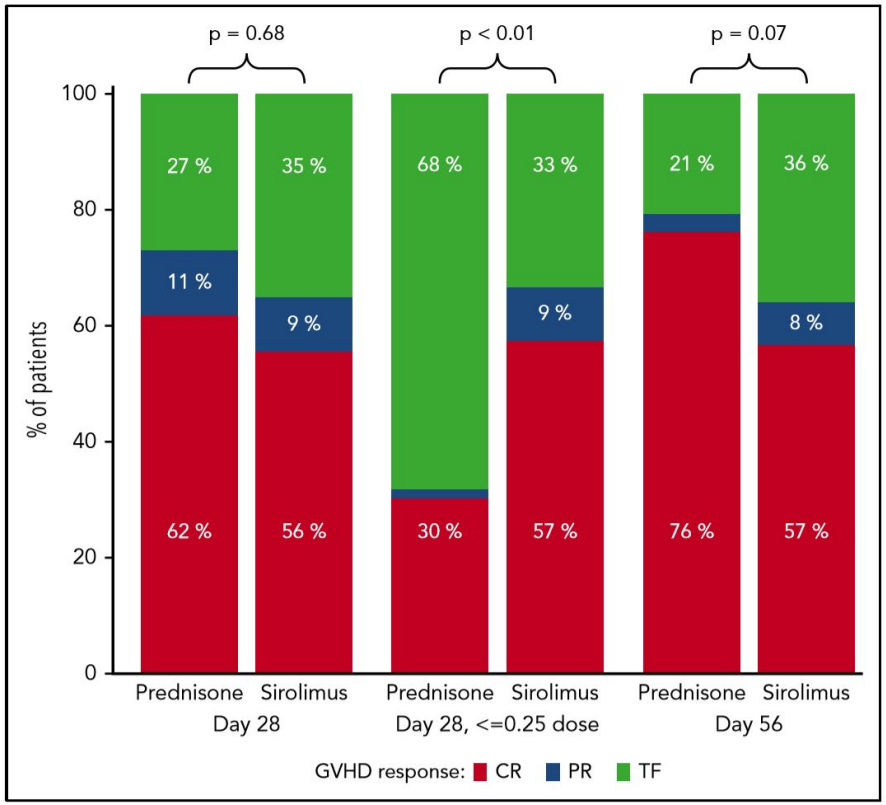
BMT CTN 1501 Trial

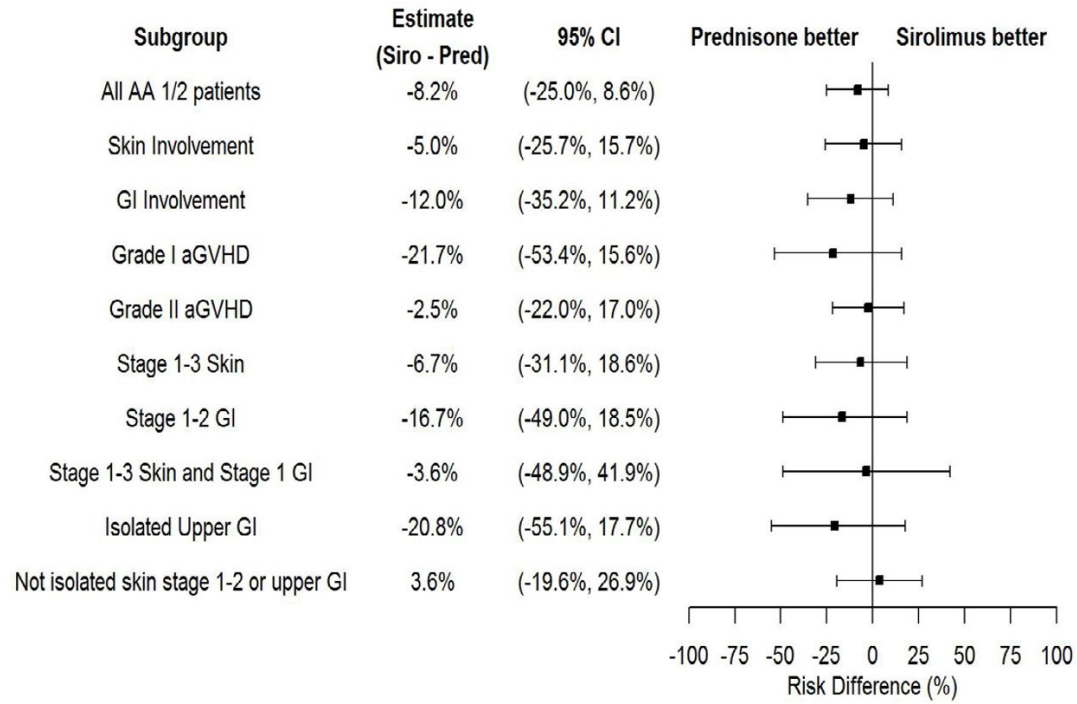
Study Design:

- **Patients**: standard-risk acute GVHD
- **Intervention:**
  - Study Drug: sirolimus (goal 10-14 ng/mL until GVHD resolution, then 5-10 ng/mL after resolution until day 56), followed by taper x less than 3 months. Can have concurrent calcineurin inhibitors.
  - Control: prednisone 2 mg/kg/day, required to be on for at least 3 days, followed by taper. Suggested taper x 7 weeks.
- **Objectives:**
  - Primary endpoint: difference between day 28 CR/PR rates in aGVHD
  - Secondary endpoints: the rate of day 28 CR/PR with prednisone dose 0.25 mg/kg/day or less (treatment failure rate), chronic GVHD incidence, infection, EFS, relapse, death, DFS and OS, NRM
- **Target sample size**: 120, to achieve a 90% confidence interval (CI) half width of 15% for the difference in day 28 CR/PR rates between groups

Pidala et al Blood 2020;135:2

BMT CTN 1501 Trial

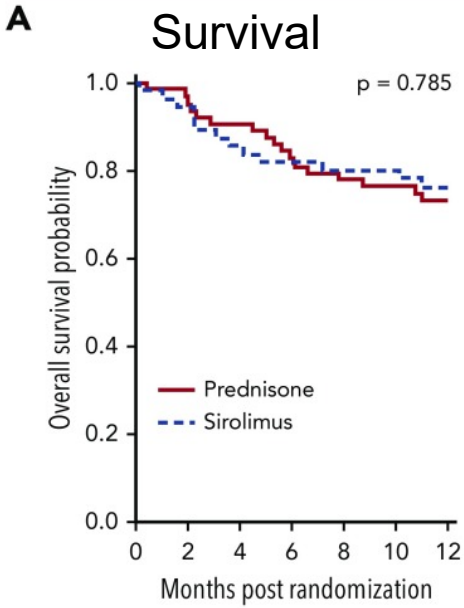


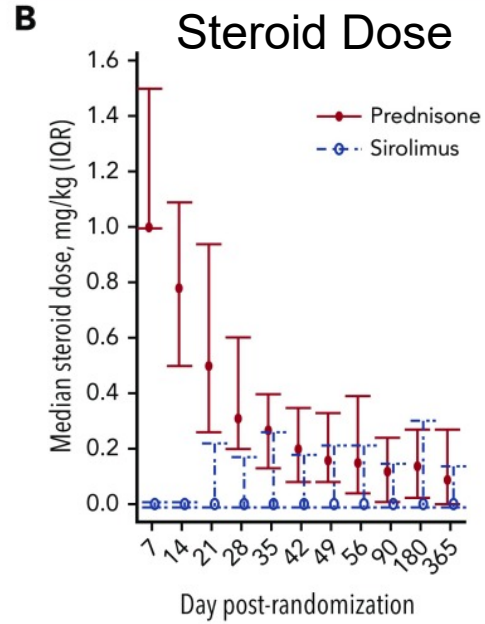


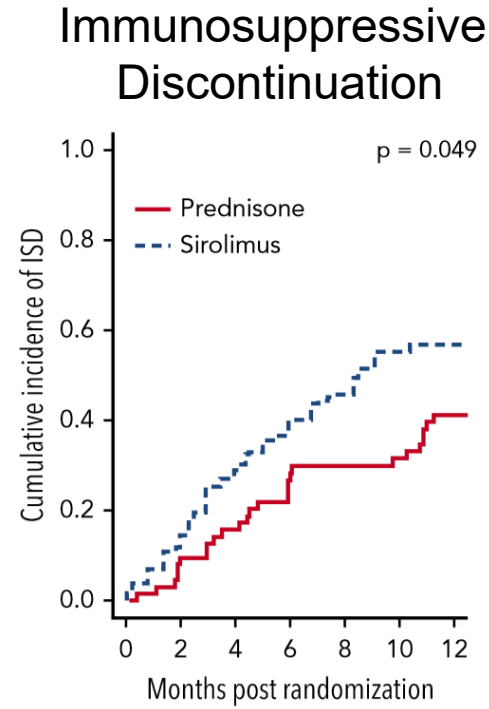
RESULTS:

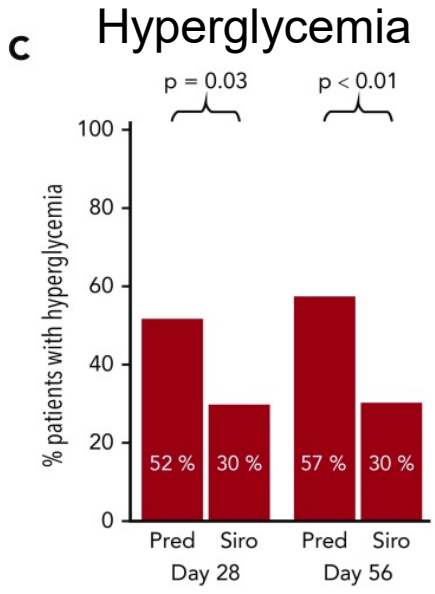
- Day 28 CR rates for sirolimus vs prednisone similar
- Day 28 CR rates for sirolimus vs < 0.25 mg/kg higher with sirolimus
- Day 56- Nonresponse was significantly higher in the sirolimus group
  - 84% of Sirolimus non-responders salvaged with steroids

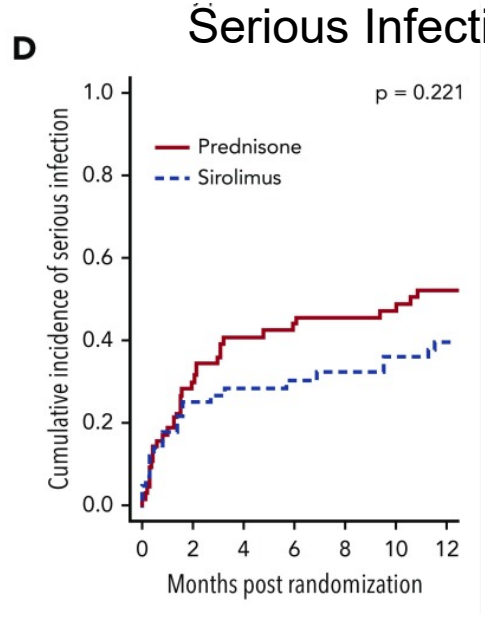
Pidala et al Blood 2020;135:2











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

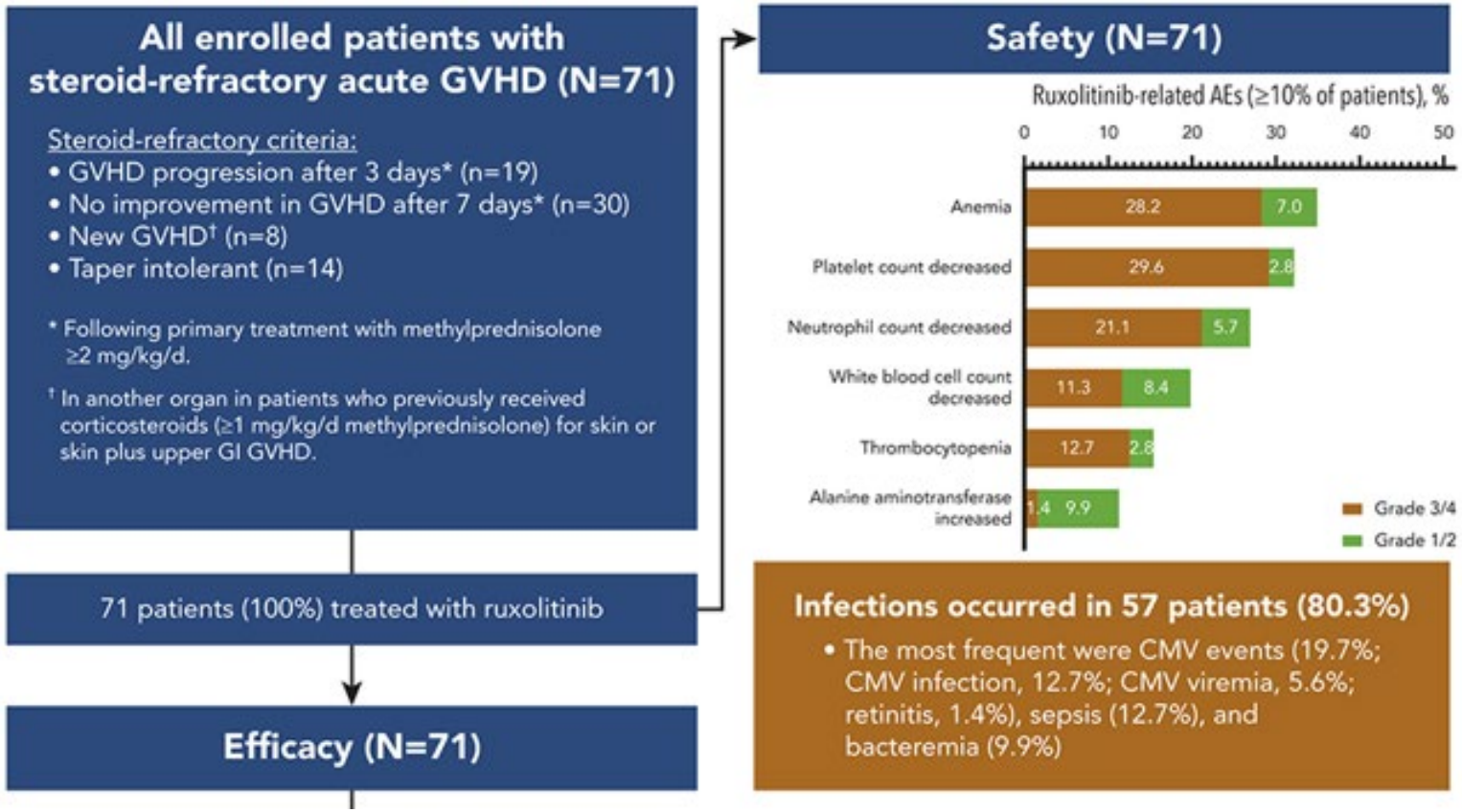
Pidala et al Blood 2020;135:2

blood
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial

Madan Jagasia,[1] Miguel-Angel Perales,[2,3] Mark A. Schroeder,[4] Haris Ali,[5] Nirav N. Shah,[6] Yi-Bin Chen,[7] Salman Fazal,[8] Fitzroy W. Dawkins,[9]



Overall response

Day 28 overall response rate: 54.9%

- 26.8% complete response
- 9.9% very good partial response
- 18.3% partial response

Overall response rate at any time: 73.2%

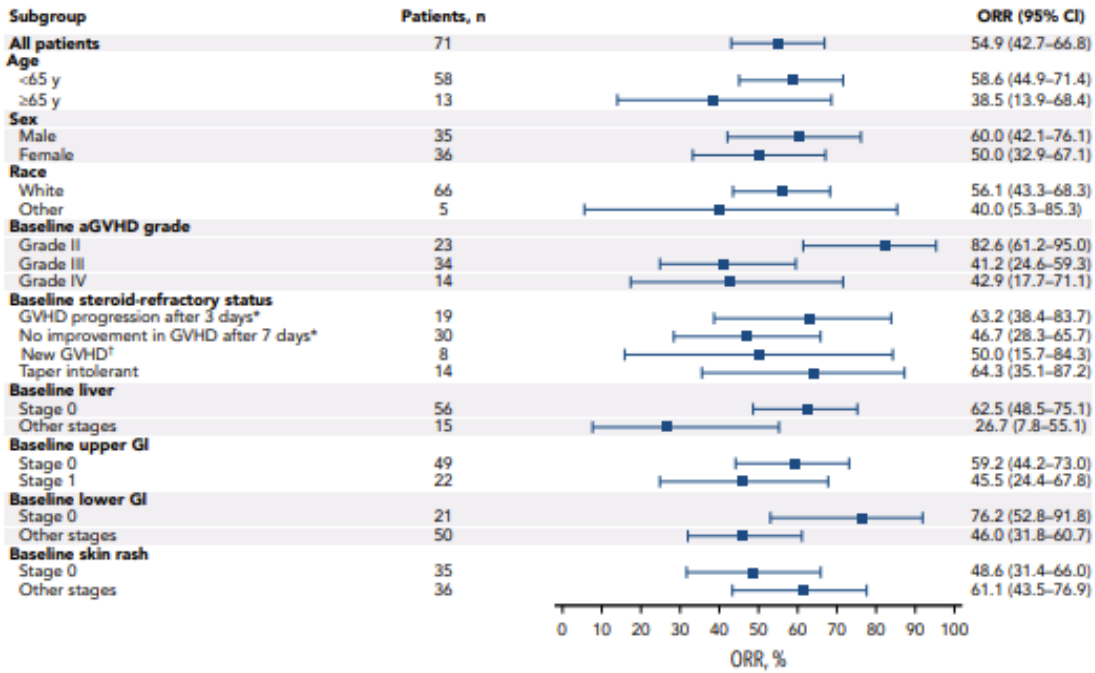
Duration of response at 6 months: median, 345 days

blood Regular Article

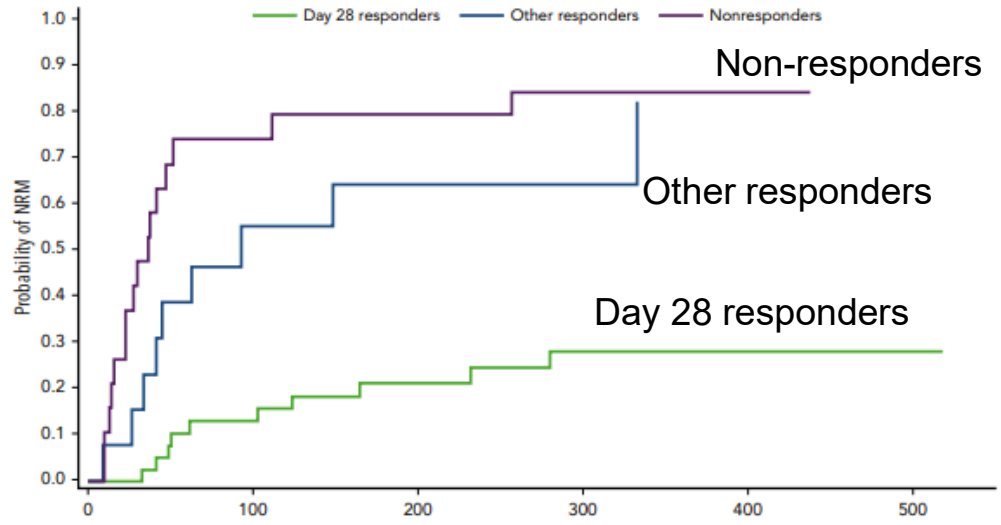
CLINICAL TRIALS AND OBSERVATIONS

Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial

Madan Jagasia,[1] Miguel-Angel Perales,[2,3] Mark A. Schroeder,[4] Haris Ali,[5] Nirav N. Shah,[6] Yi-Bin Chen,[7] Salman Fazal,[8] Fitzroy W. Dawkins,[9]



Non-Relapse Mortality



Jagasia M. et al Blood 2020 135:1739-1749

Overall response

Day 28 overall response rate: 54.9%

- 26.8% complete response
- 9.9% very good partial response
- 18.3% partial response

Overall response rate at any time: 73.2%

Duration of response at 6 months: median, 345 days

blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial

Madan Jagasia,[1] Miguel-Angel Perales,[2,3] Mark A. Schroeder,[4] Haris Ali,[5] Nirav N. Shah,[6] Yi-Bin Chen,[7] Salman Fazal,[8] Fitzroy W. Dawkins,[9]

Conclusions:

- Ruxolitinib is an effective treatment option for patients with steroid-refractory aGVHD.
- Responses to ruxolitinib seen at day 28 were durable and were associated with improved survival when compared with survival rates among non-responders
- Ongoing REACH2 phase 3 randomized study of ruxolitinib vs best available therapy in patients with steroid-refractory aGVHD (NCT02913261) will further establish the role of JAK inhibitors in the treatment of steroid-refractory aGVHD

Jagasia M. et al Blood 2020 135:1739-1749


NIH