Allogeneic Hematopoietic Stem Cell Transplantation: State of the Art in 2020

RICHARD W. CHILDS M.D.
BETHESDA MD

Overview of Talk:

Updates on Transplant Trends/Approaches and Disease Specific Survival after Transplantation

- Focus on methods to reduce GVHD after transplant
  - Post Tx Cytoxan outside the context of Haplo transplant
    - GVHD prophylaxis following 9/10 match URD transplant
    - GVHD prophylaxis following MSD/MUD tx

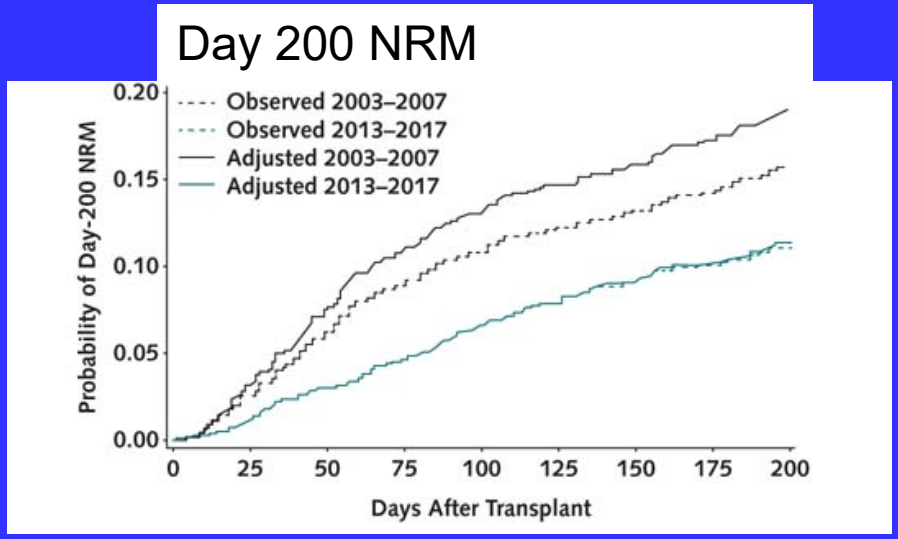
- Myeloablative vs Reduced intensity transplantation for AML/MDS-
  - MAC superior survival in MRD positive Pts compared RIC
  - Role of MRD to determine MAC vs RIC

- Haplo transplants using posttransplant cyclophosphamide
  - Updates on outcomes and transplant trends

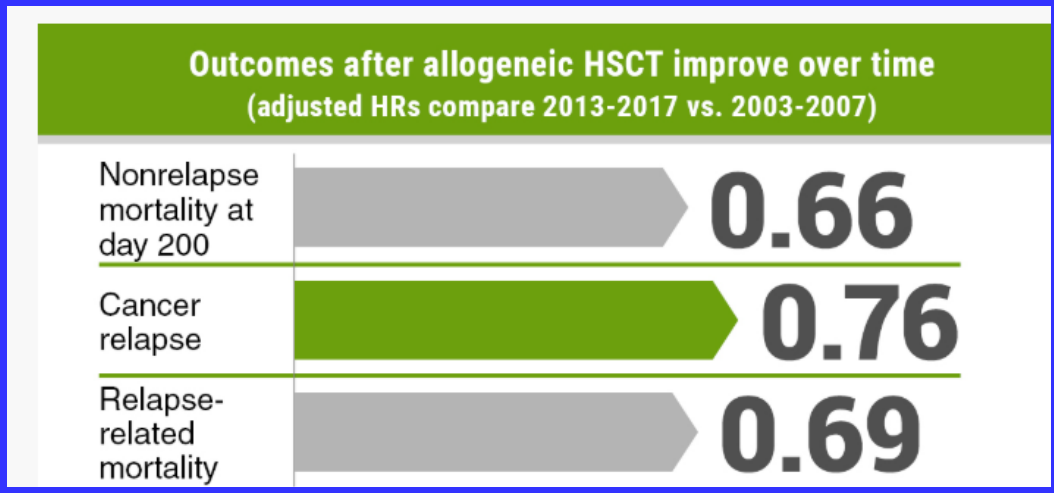
There Have Been Major Improvements in Transplant Outcomes Over the Past 2 Decades

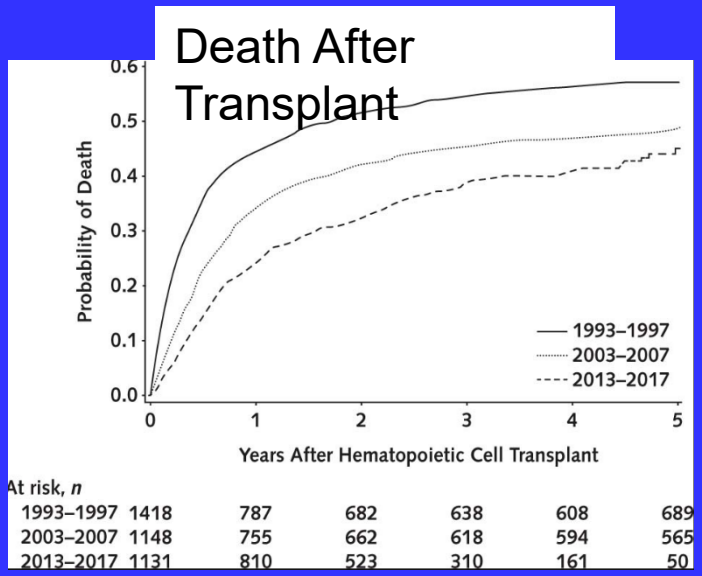
Historical Problem	Solution
• Conditioning regimens too toxic	• Development of safer conditioning regimens (IV busulfan)/use of lung shielding
• Older patients ineligible due to prohibitive risk of mortality	• Development of reduced intensity conditioning regimens
• Death from invasive fungus and CMV	• Advent of voriconazole, posaconazole-PCR to detect early CMV-Letermovir for CMV prophy
• Lack of donors precludes the use of the procedure	• Growth of unrelated registry, increasing use MUDS, cord transplants and haplo-identical donors

Major Improvements in Transplant Safety Over the Past 2 Decades



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

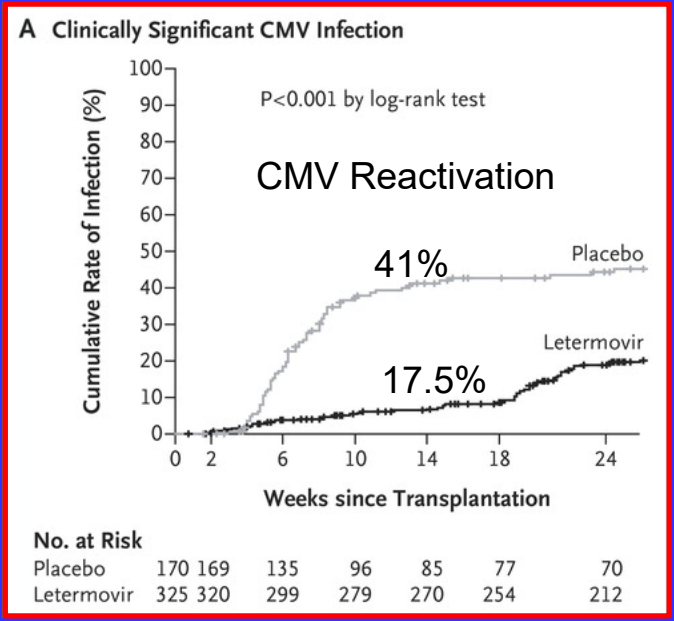


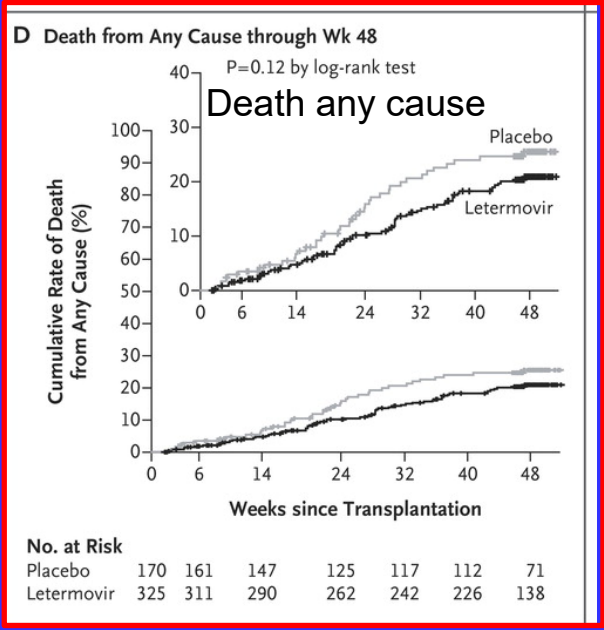


McDonald G.B. et al Annals Int Med 2020:Ann Intern Med. 2020;172:229-239.

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** 40% response for SR grade IV 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

Major Improvements in Transplant Outcomes Over the Past 2 Decades

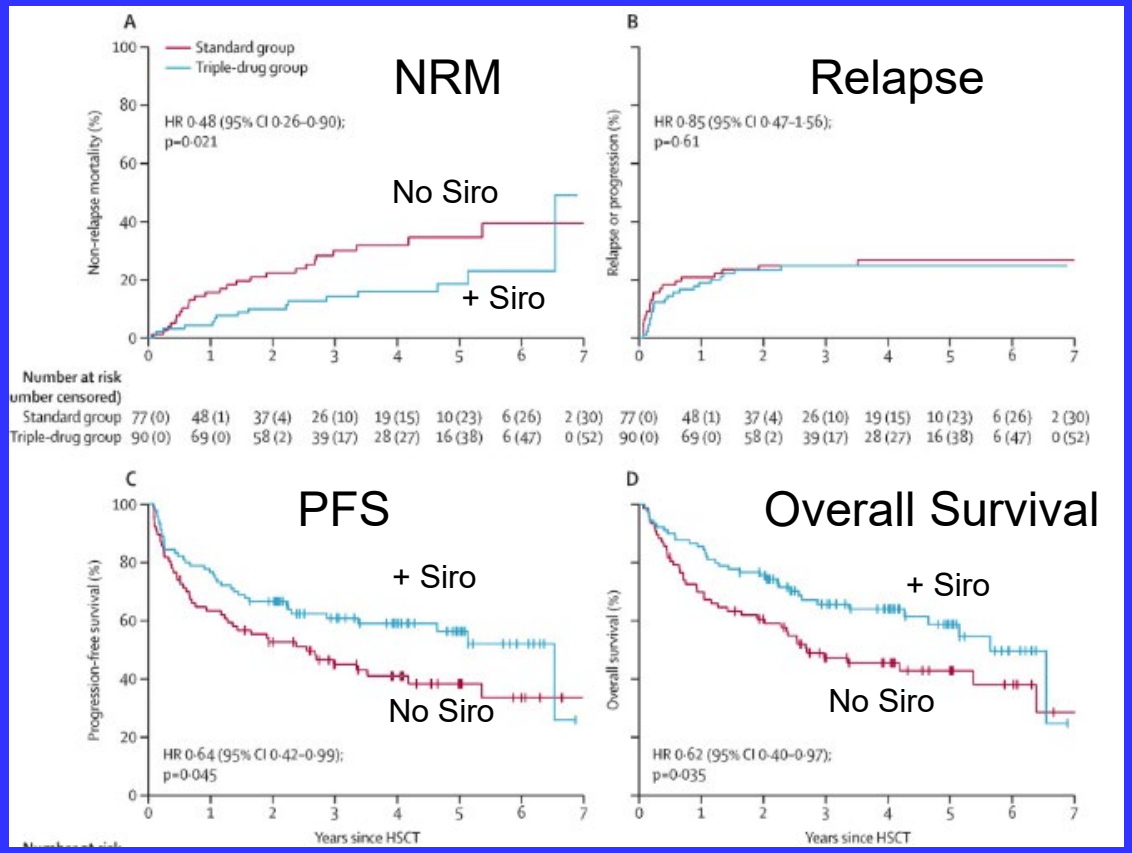
Adding Sirolimus to Standard CSA/MMF Reduces GVHD and Improves Survival After RIC Allo HCT

- Multicenter Study: 180 Subjects randomized to either the standard GVHD prophylaxis regimen (cyclosporine and mycophenolate mofetil) or the triple-drug combination regimen (cyclosporine, mycophenolate mofetil, and sirolimus).
- All received low dose TBI and Fludarabine
- The primary endpoint was the cumulative incidence of grade 2-4 acute GVHD at day 100 post-transplantation.
- Acute Grade II-IV was lower at day 100 was lower in the triple-drug group compared with the standard GVHD prophylaxis group (**26%** [95% CI 17-35] vs **52%** [41-63]; HR 0·45 [95% CI 0·28-0·73]; p=0·0013)

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

Major Improvements in Transplant Outcomes Over the Past 2 Decades

- **Adding Sirolimus to Standard CSA/MMF Reduces GVHD and Improves Survival After RIC Allo HCT**



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

Post-Transplant Cyclophosphamide Has Revolutionized Haplo Transplants

New Data Show Post Transplant Cyclophosphamide also improves transplant outcomes for

- recipients of mismatched unrelated transplants
- recipients of transplants from HLA matched donors

HLA Mismatched Unrelated Donor Transplantation: Superior Outcomes with Posttransplant Cyclophosphamide vs Anti-thymocyte Globulin (ATG)

EBMT Study:

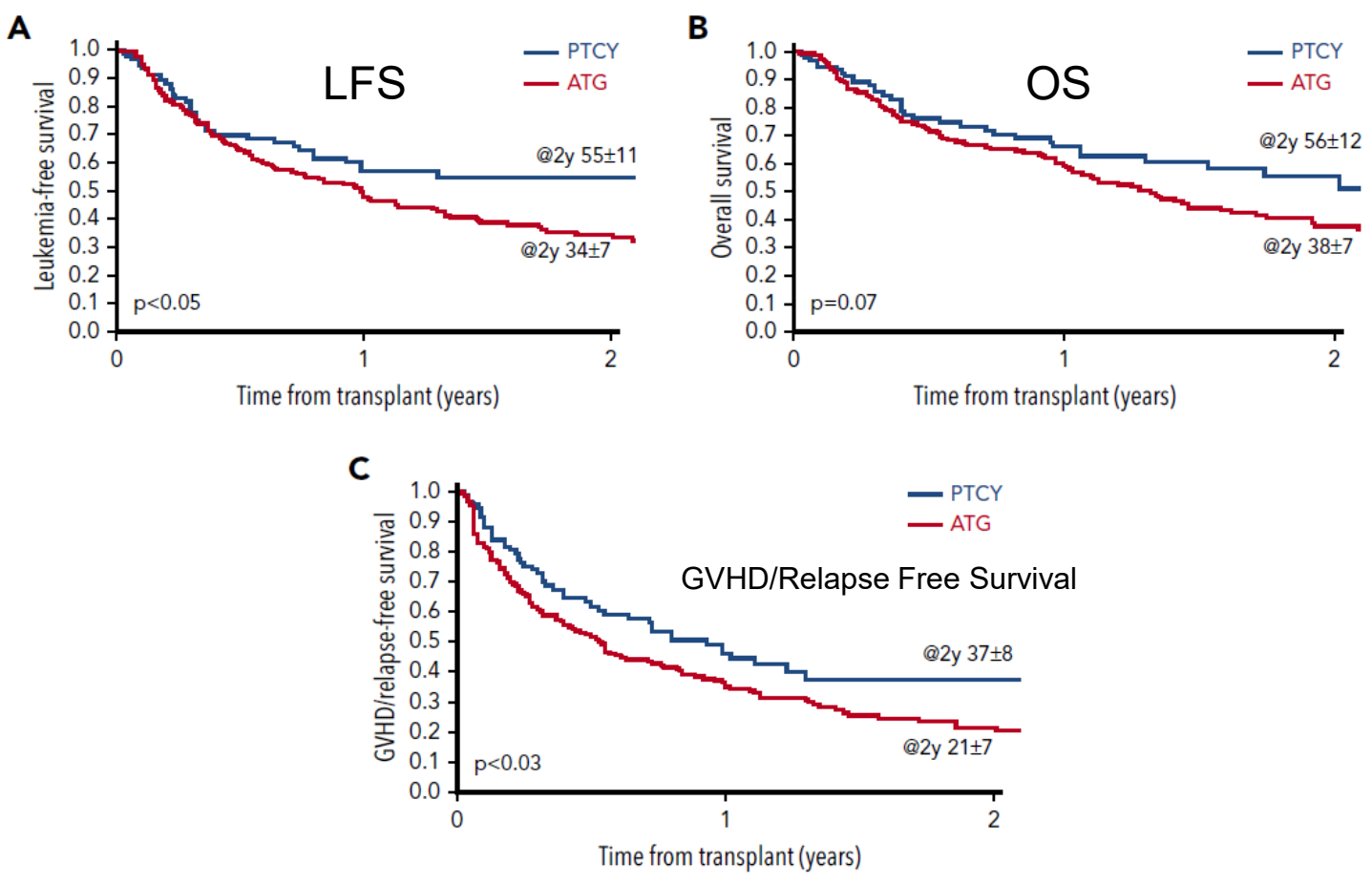
- 272 patients heme malignancies receiving 9/10 mismatched URD transplants
- 179 received ATG vs 93 received post-transplant Cytoxan

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)

Battipaglia et al Blood 2019; 134(11)

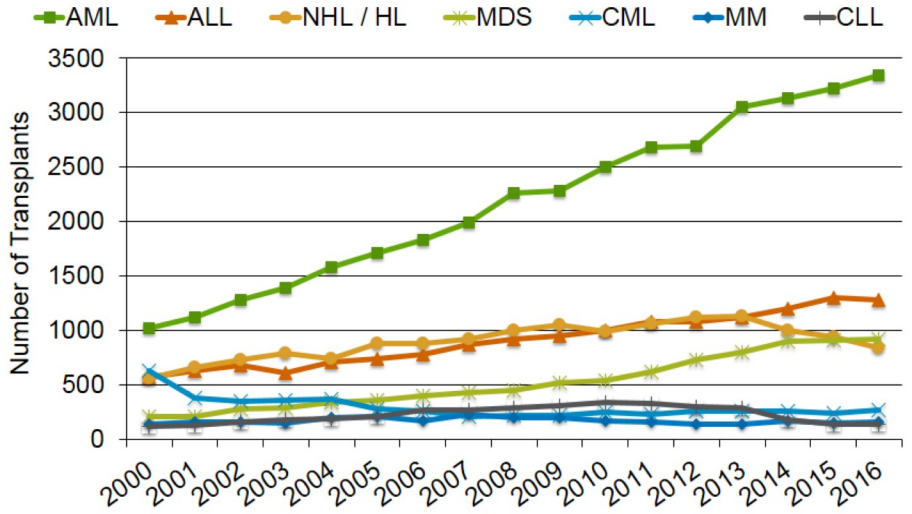
HLA Mismatched Unrelated Donor Transplantation: Superior Outcomes with Posttransplant Cyclophosphamide vs Anti-thymocyte Globulin (ATG)



Battipaglia et al Blood 2019; 134(11)

Indications for an Hematopoietic Cell Transplant (HCT) and Donor Source in the U.S.

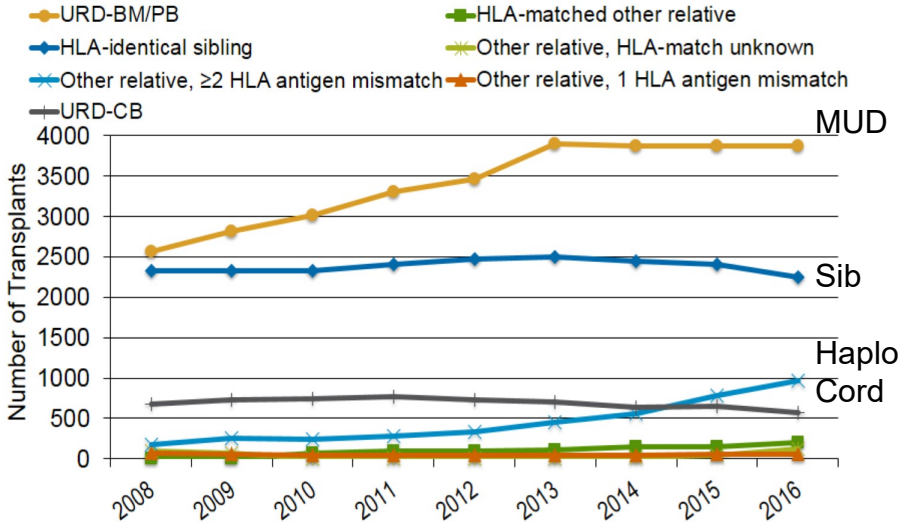
Selected Disease Trends for Allogeneic HCT in the US



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

14

Allogeneic HCT Recipients in the US, by Donor Type



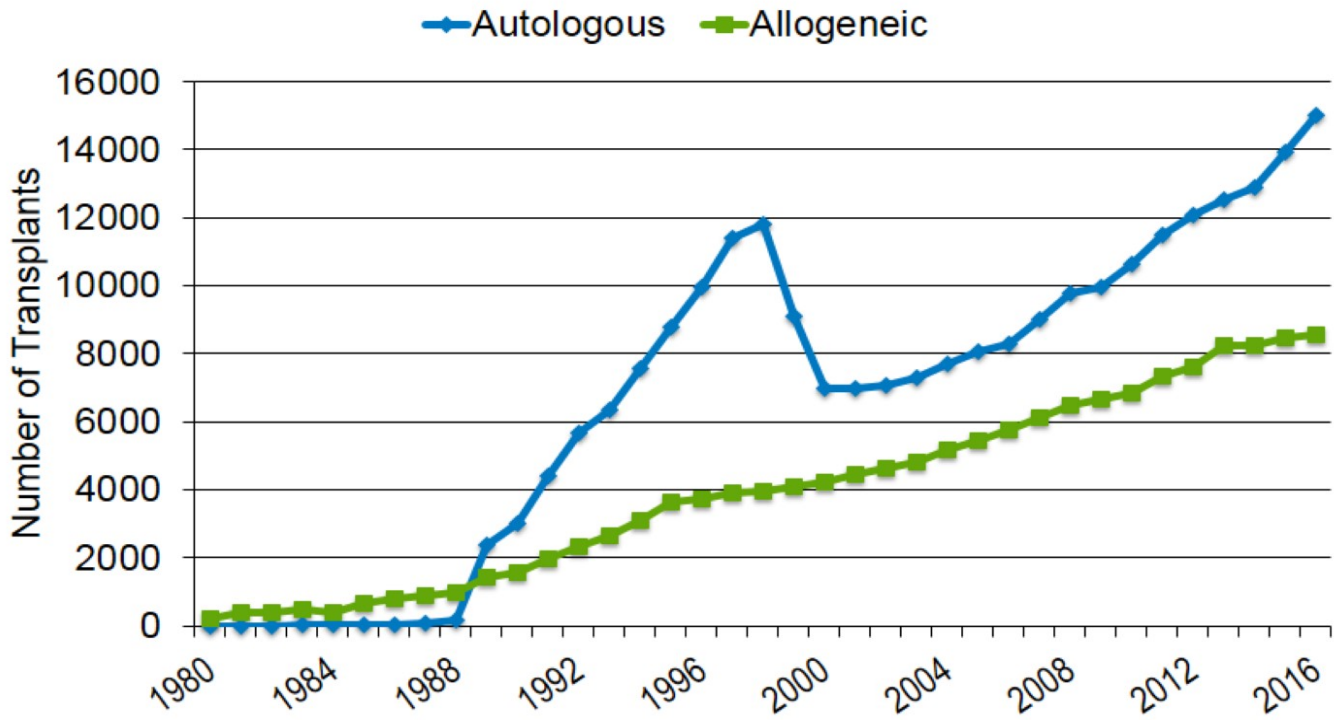
CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

5

CIBMTR Data 2019

Transplant Numbers Continue to Increase in the U.S.

Annual Number of HCT Recipients in the US by Transplant Type

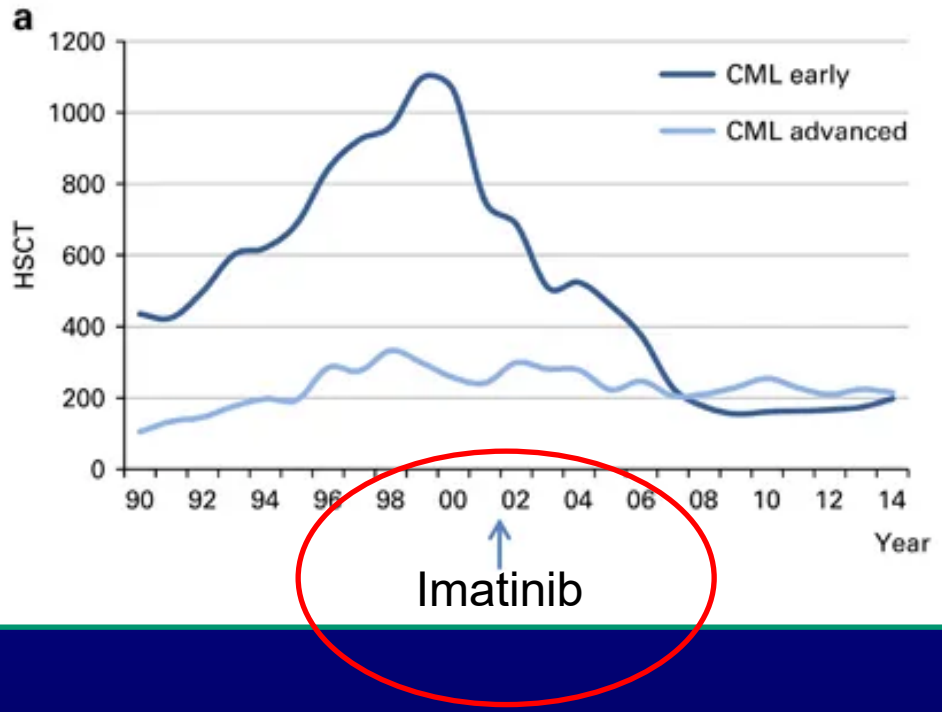


CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

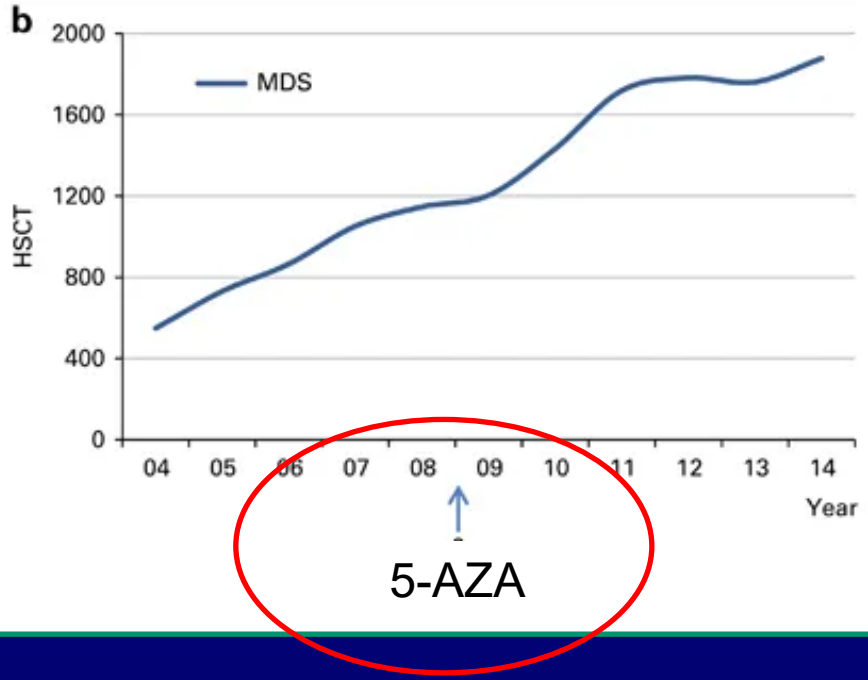
CIBMTR Data 2019

Impact of Drug Advances On Transplant Numbers

CML

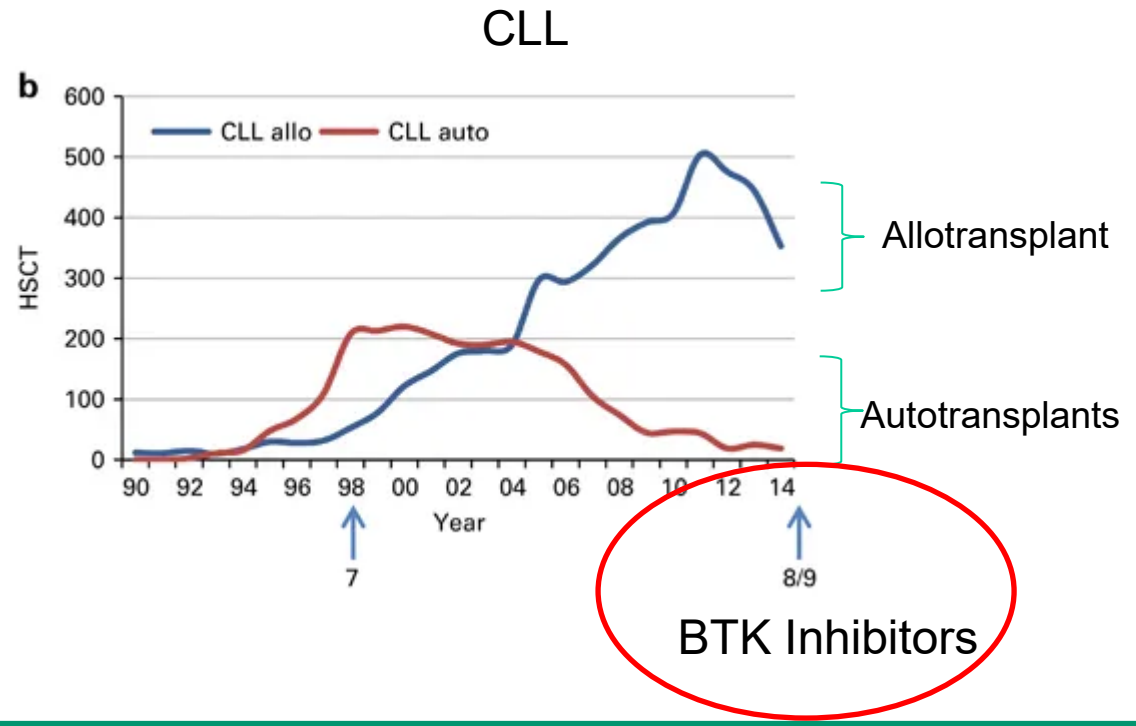


MDS



Passweg et al BMT 2017:Feb;52(2):191-196

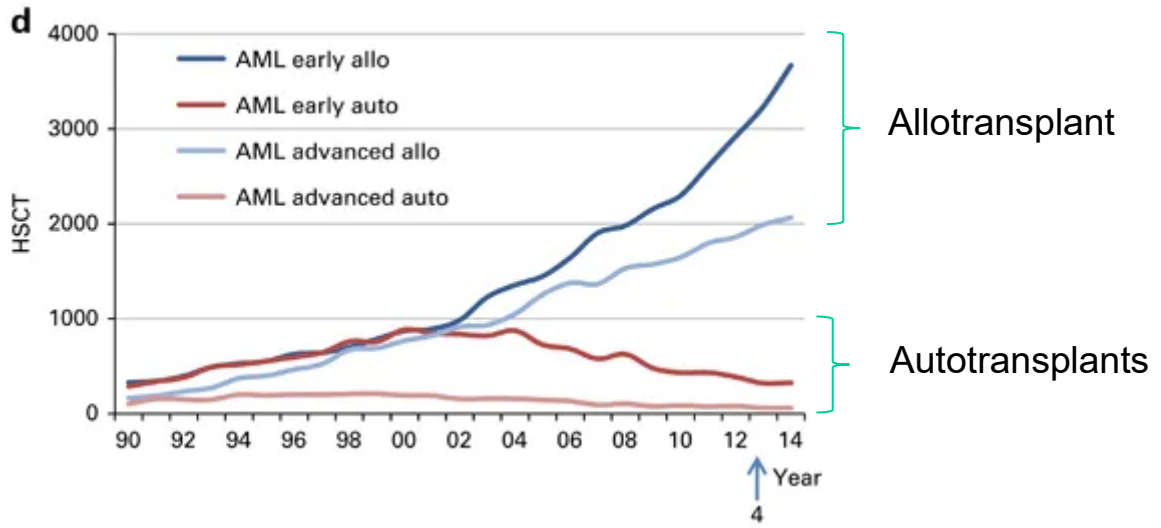
Impact of Drug Advances On Transplant Numbers



Passweg et al BMT 2017:Feb;52(2):191-196

Efficacy of Non-Transplant Therapies Impact Transplant Numbers

AML



Passweg et al BMT 2017:Feb;52(2):191-196

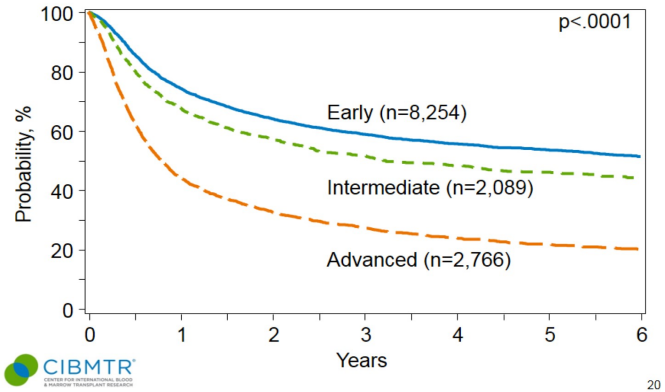
In the era of precision medicine, why do we still perform these dangerous allogeneic transplants?

- **Remains only curative modality for certain diseases associated with short survival with conventional therapy**
  - **Relapsed AML**
  - **Relapsed ALL**
  - **High Risk MDS**

- **Is the only curative modality for many non-malignant debilitating diseases**
  - Sickle cell Anemia
  - Aplastic Anemia- Relapsed refractory to IST

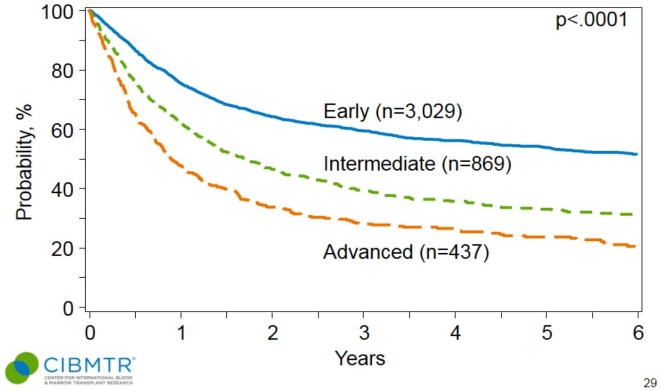
Allogeneic Transplant For Hematological Malignancies

Survival after HLA-Matched Sibling Donor HCT for AML, 2005-2015



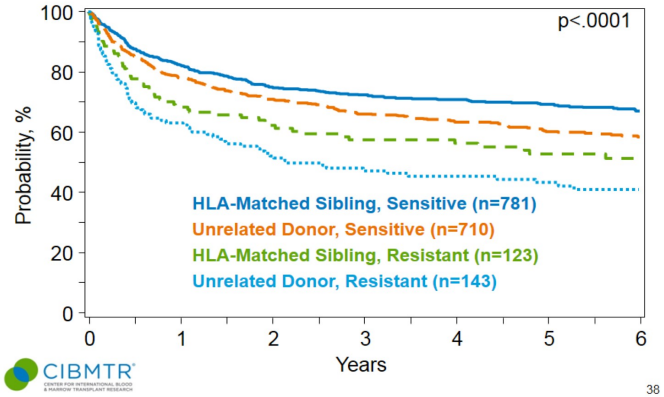
20

Survival after HLA-Matched Sibling Donor HCT for ALL, Age ≥18 Years, 2005-2015



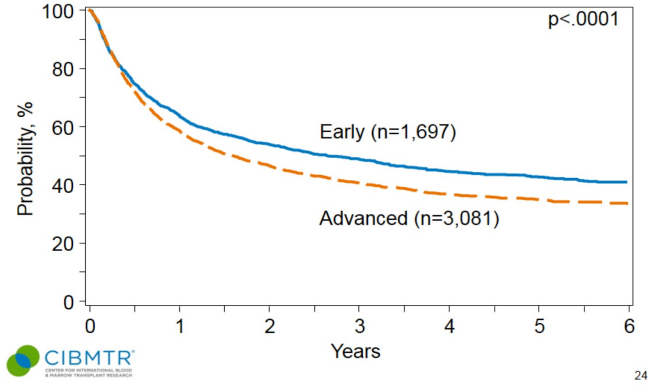
29

Survival after Allogeneic HCT for Follicular Lymphoma, 2005-2015



38

Survival after Unrelated Donor HCT for Myelodysplastic Syndrome (MDS), 2005-2015

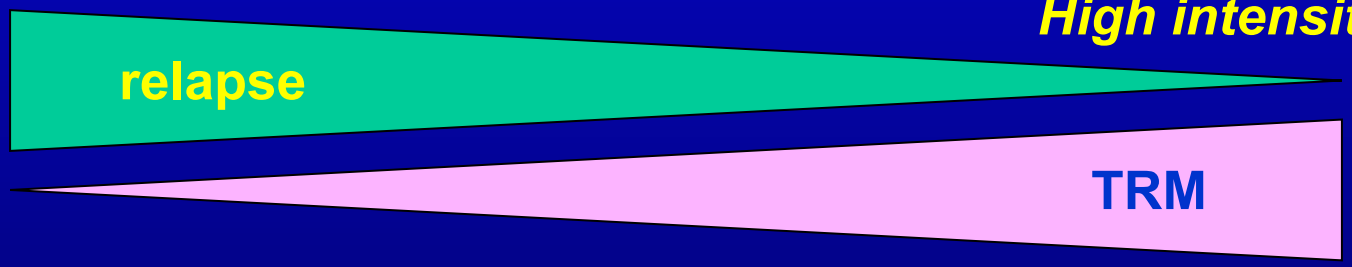


24

CIBMTR Data 2019

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

Low intensity Conditioning (RIC)



High intensity

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

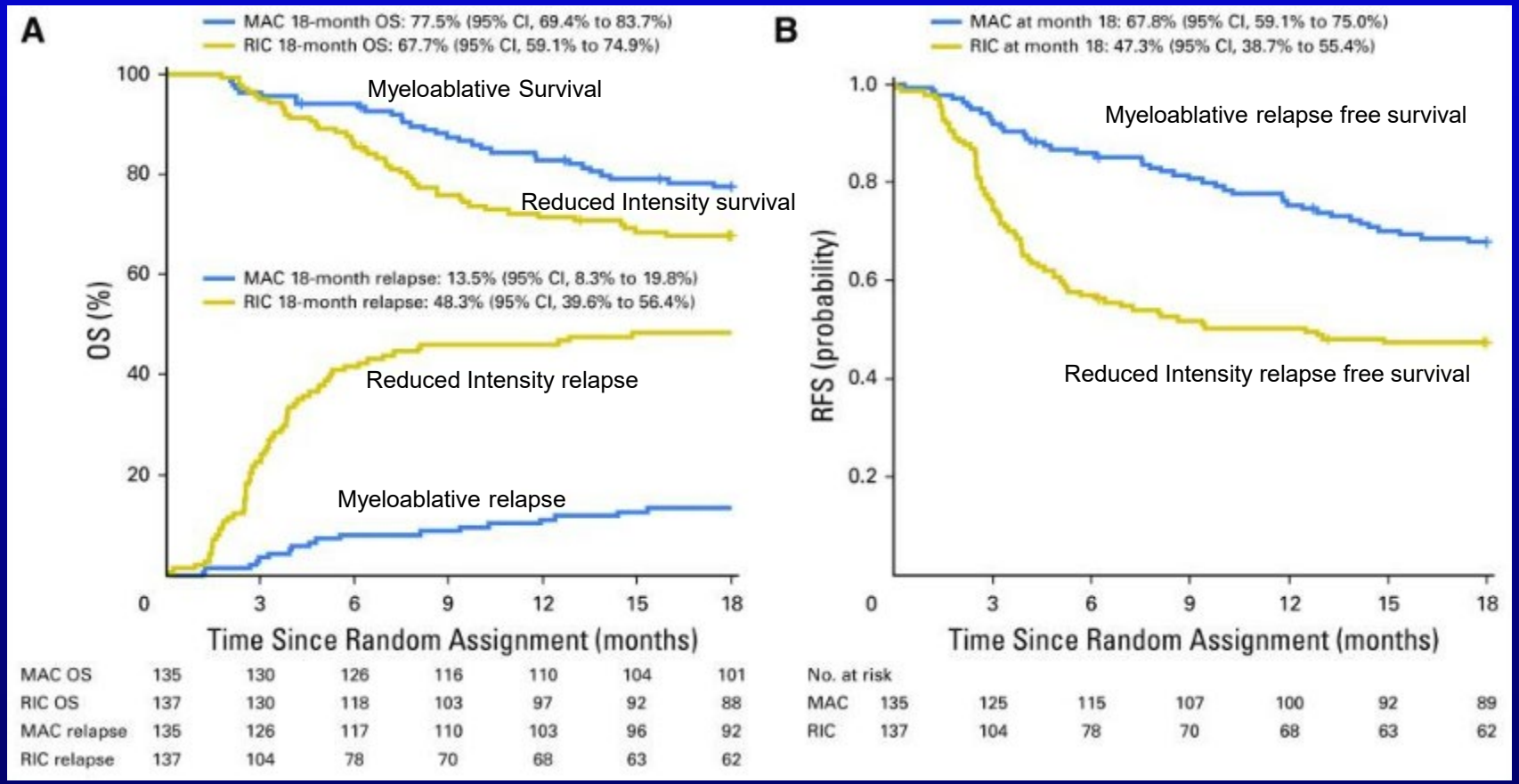
- **Hypothesis:**
  - **Alternative: The l**ower treatment-related mortality (TRM) with reduced-intensity conditioning (RIC) would result in improved overall survival (OS) compared with myeloablative conditioning (MAC).
  - Null: Higher relapse with reduced-intensity conditioning (RIC) would result in 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 Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes



Scott et al JCO 2017

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

METHODS:

- Ultra-deep, error-corrected sequencing for 13 commonly mutated genes in AML was performed on preconditioning blood from patients treated in a phase III clinical trial that randomly assigned adult patients with myeloid malignancy in morphologic complete remission to myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC).

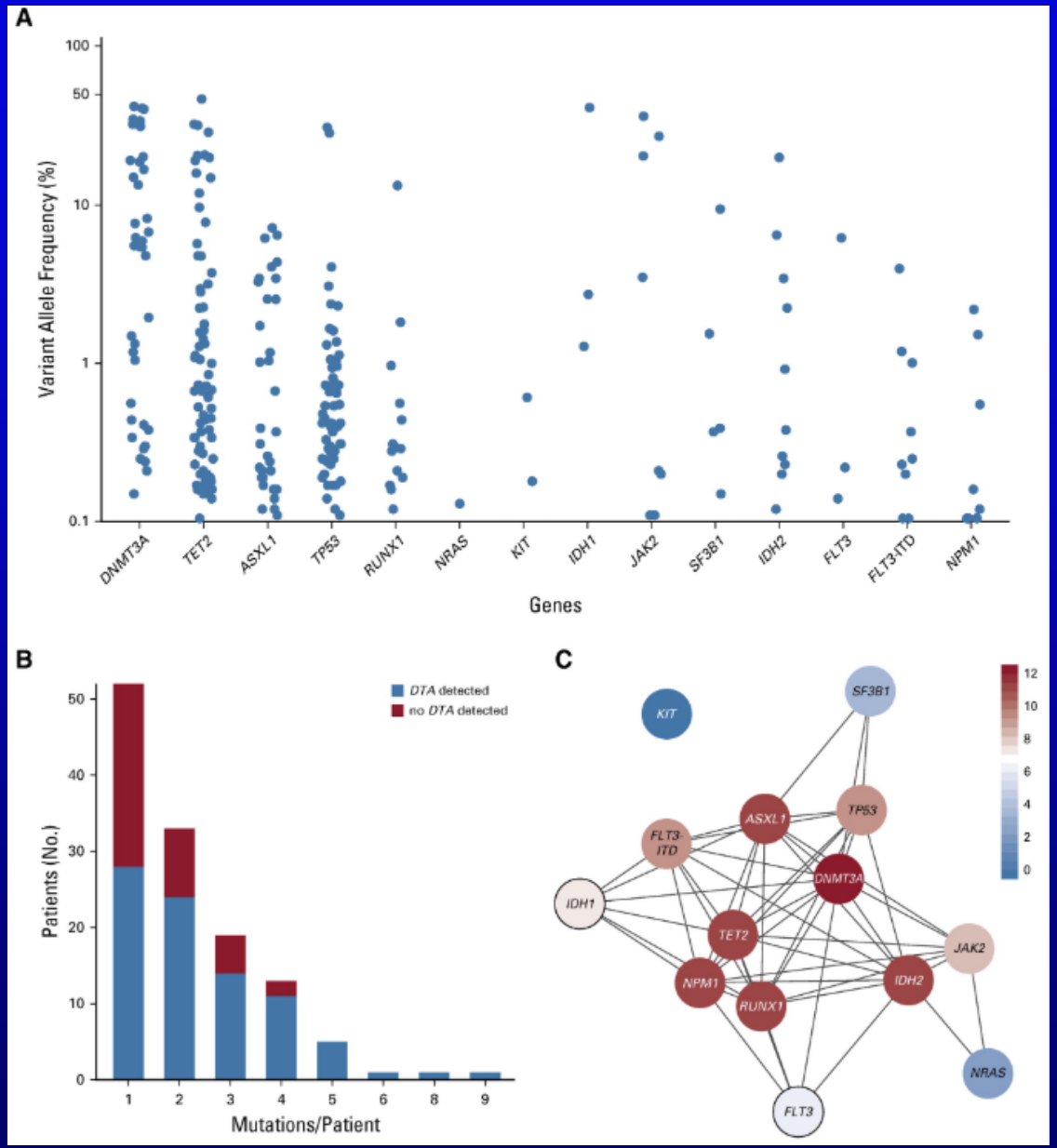
RESULTS:

- 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 (next-generation sequencing [NGS] positive), relapse (3-year cumulative incidence, 19% *v* 67%; *P* < .001) and survival (3-year OS, 61% *v* 43%; *P* = .02) was significantly different between the MAC and RIC arms, respectively. In multivariable analysis for NGS-positive patients, 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

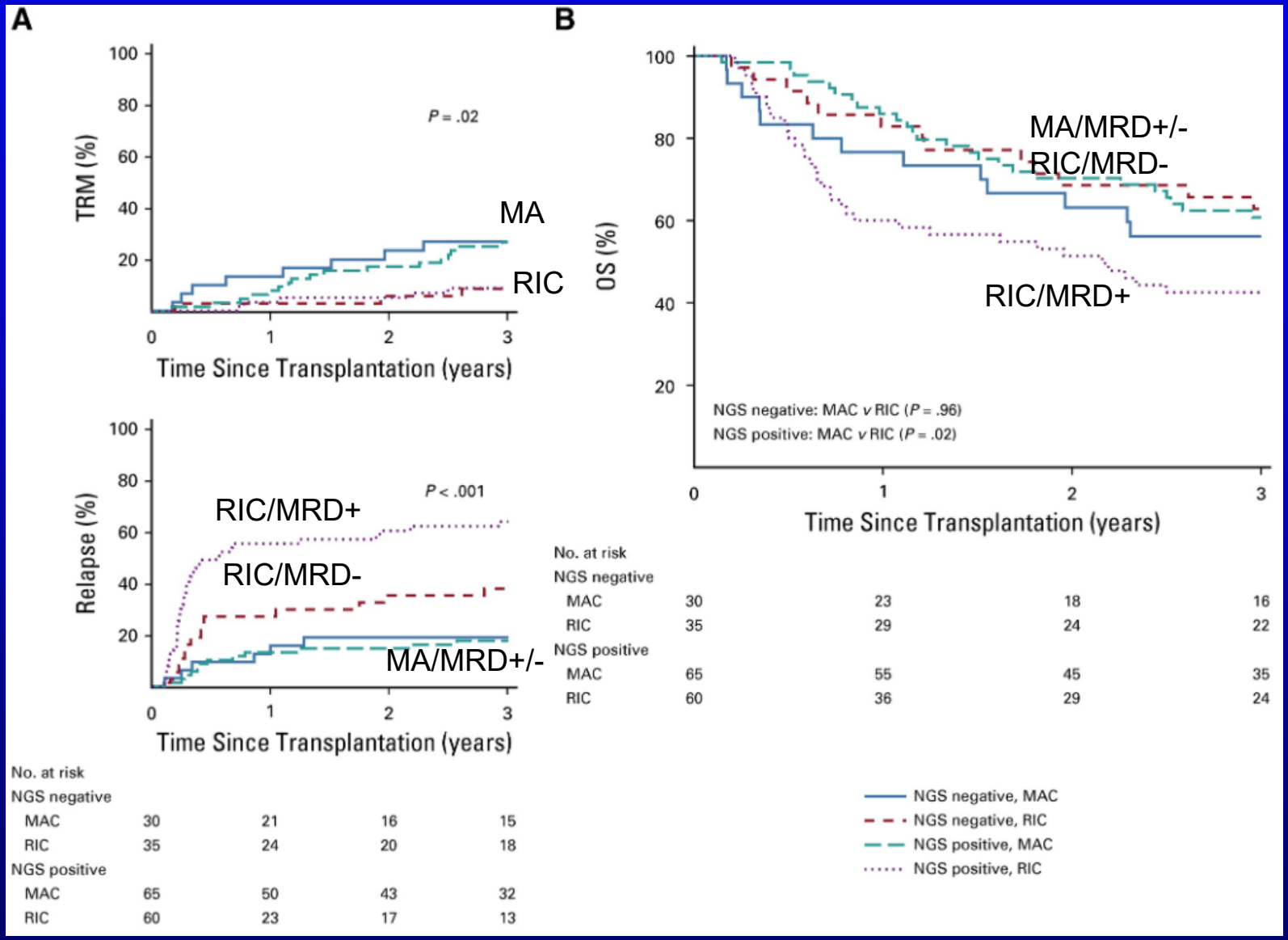


A- Detection of mutations in the blood of patients with acute myeloid leukemia (AML) during complete remission (CR).

(B) The total number of mutations detected per patient and the distribution across patients Pts with at least 1 mutation detectable in DNMT3A, TET2, or ASXL1 (DTA) genes

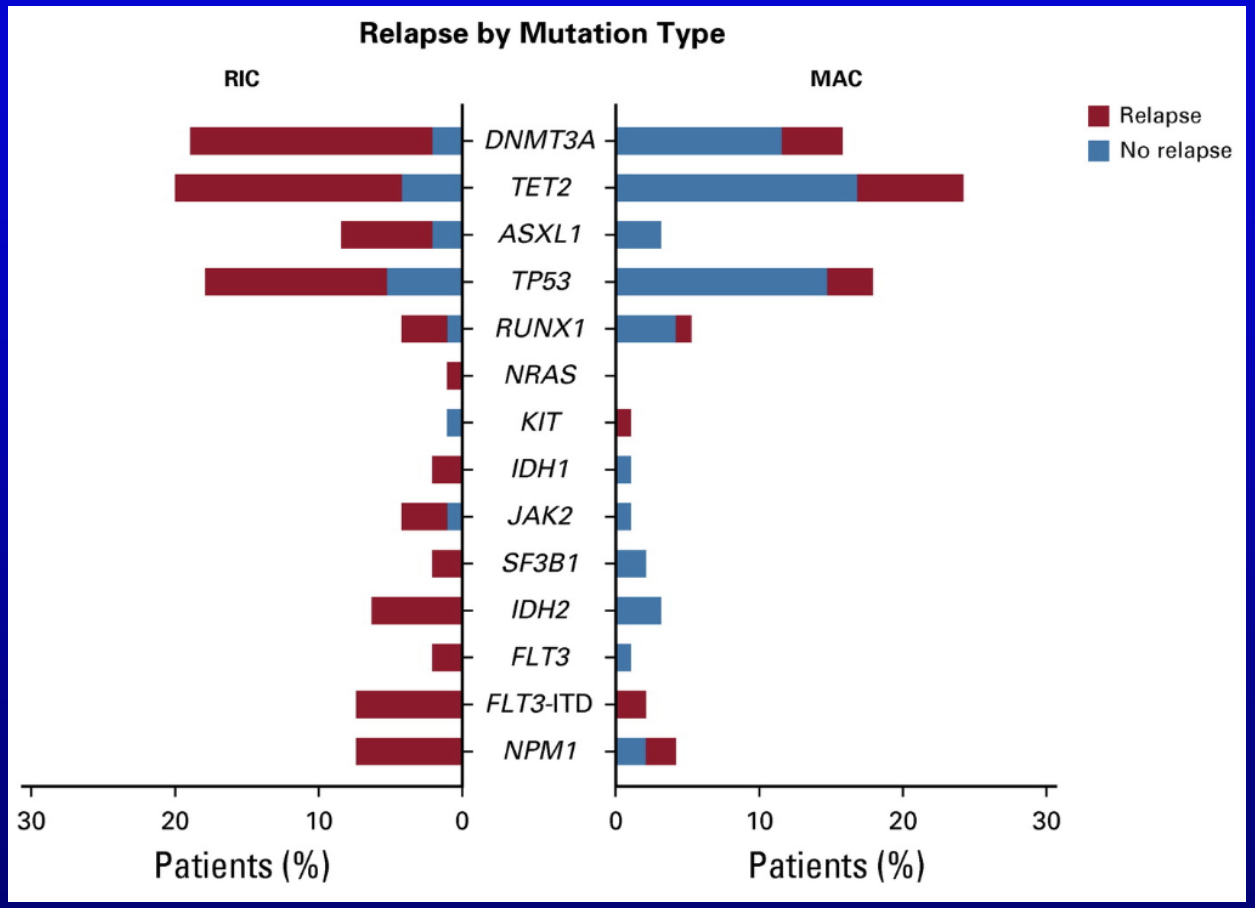
(C) A network analysis of the co-occurrence of mutations on the gene level within patient samples is shown.

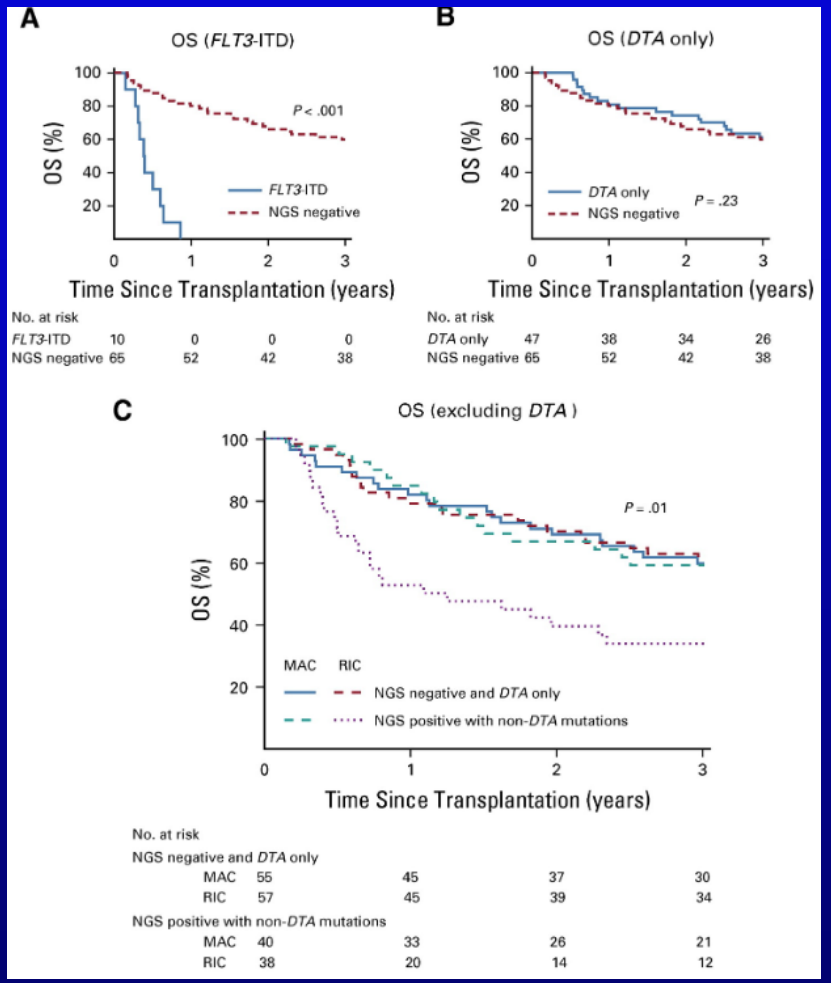
Hourigan et al JCO 2019



Hourigan et al JCO 2019

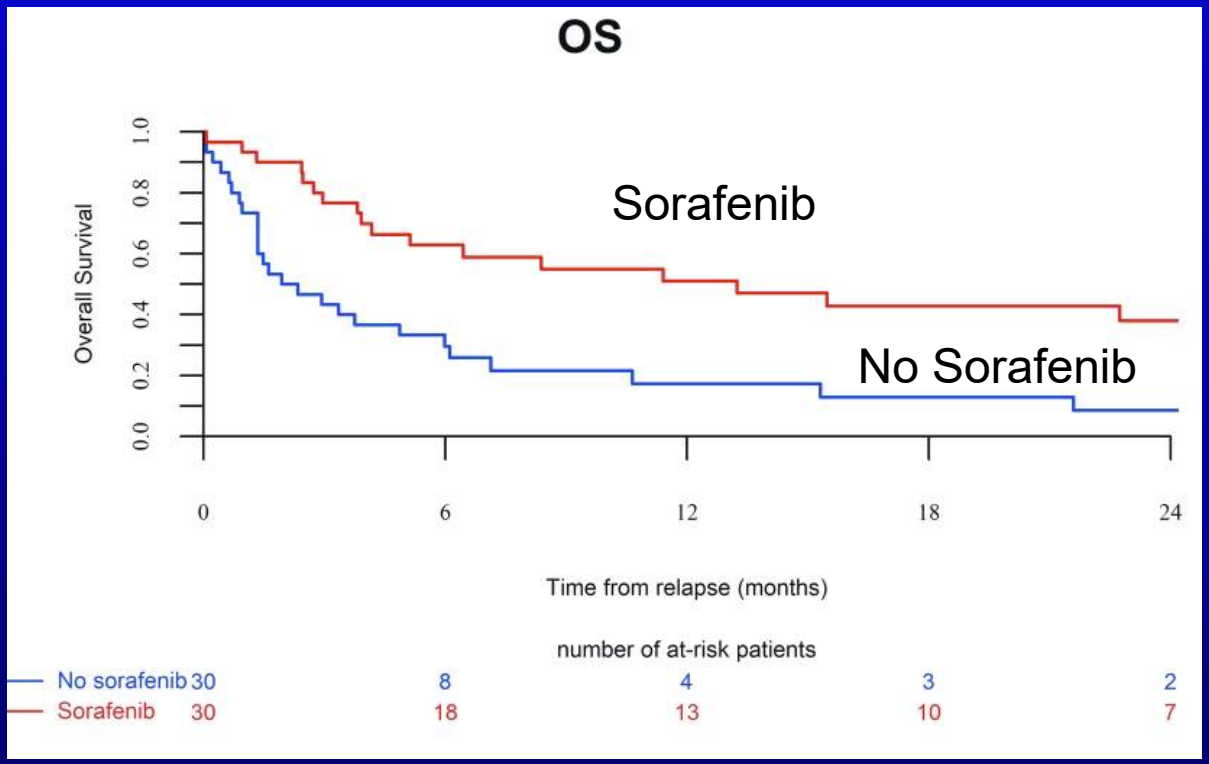
Impact of Conditioning Intensity of Allogeneic Transplantation for AML With Genomic Evidence of Residual Disease





Hourigan et al JCO 2019

Sorafenib Improves Survival of FLT3-mutated AML Relapse after Allogeneic HSCT: A Report of the EBMT Acute Leukemia Working Party



Sorafenib 400 BID

Bazarbachi A. et al Haematologica 2019: 104(9)

Retrospective EBMT study;
Sorafenib after relapse improved OS [HR=0.44 (0.26-0.75); *P*=0.001] compared to matched control not receiving sorafenib with relapse:
39% achieved a CR with Sorafenib: 1 and 2 year survival 51% and 38% vs 17% and 9% (p=0.001)

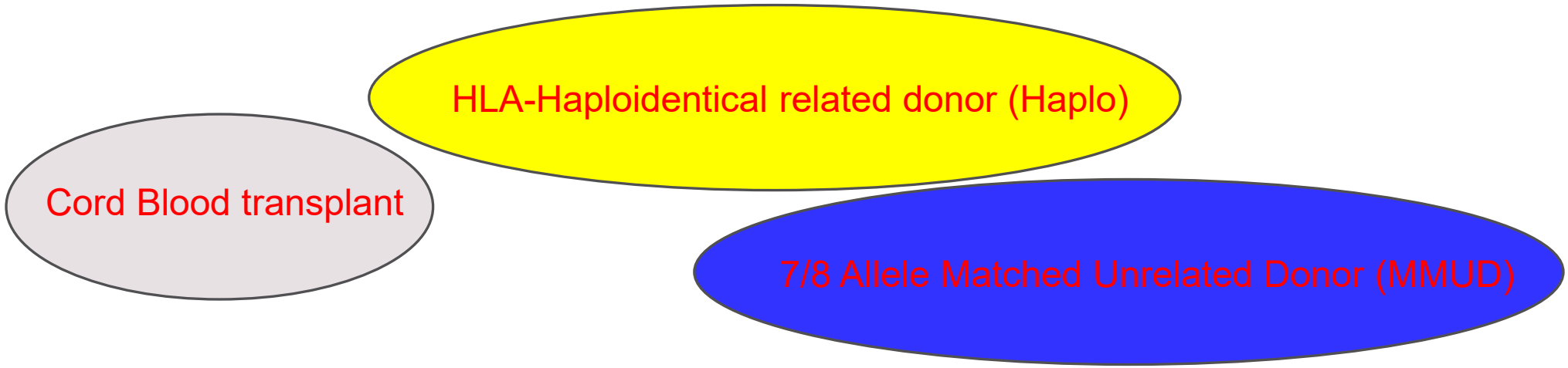
Gilteritinib now being tested as post-transplant maintenance for FLT3-ITD AML- Clinical Trial Ongoing
Clinical trial.gov:02997202

Graft Donor Sources- who to choose?

1) HLA Identical Sibling (SIB)- still best

2) 8/8 Allele Matched Unrelated Donor (MUD)- maybe still 2nd best

3) alternative donors:

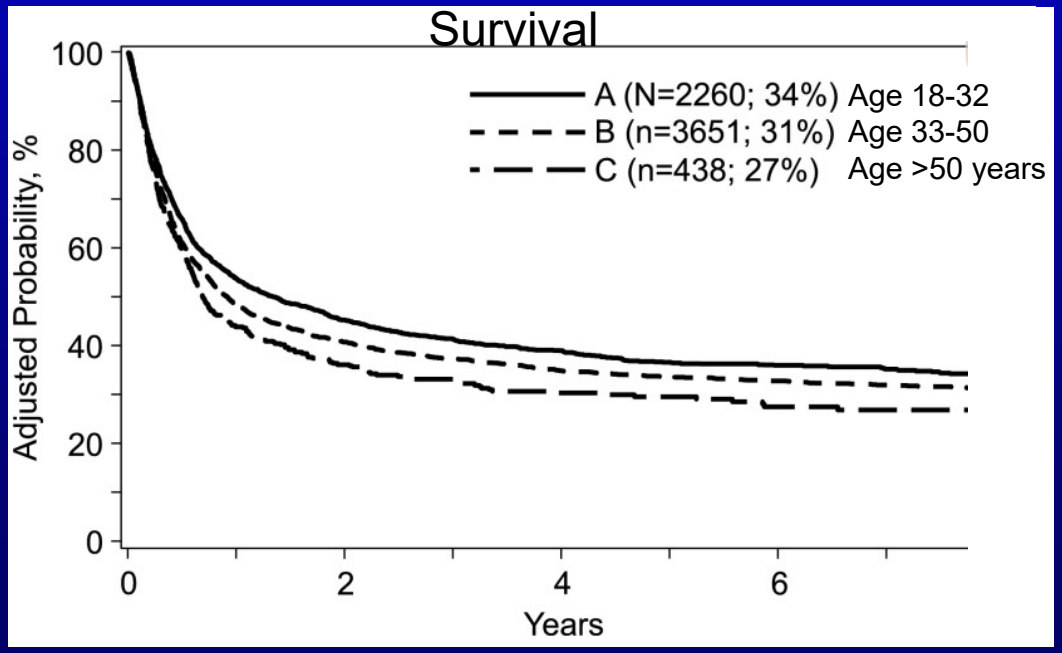


Choosing the Best Matched Unrelated Donors

2 most important variables on outcome

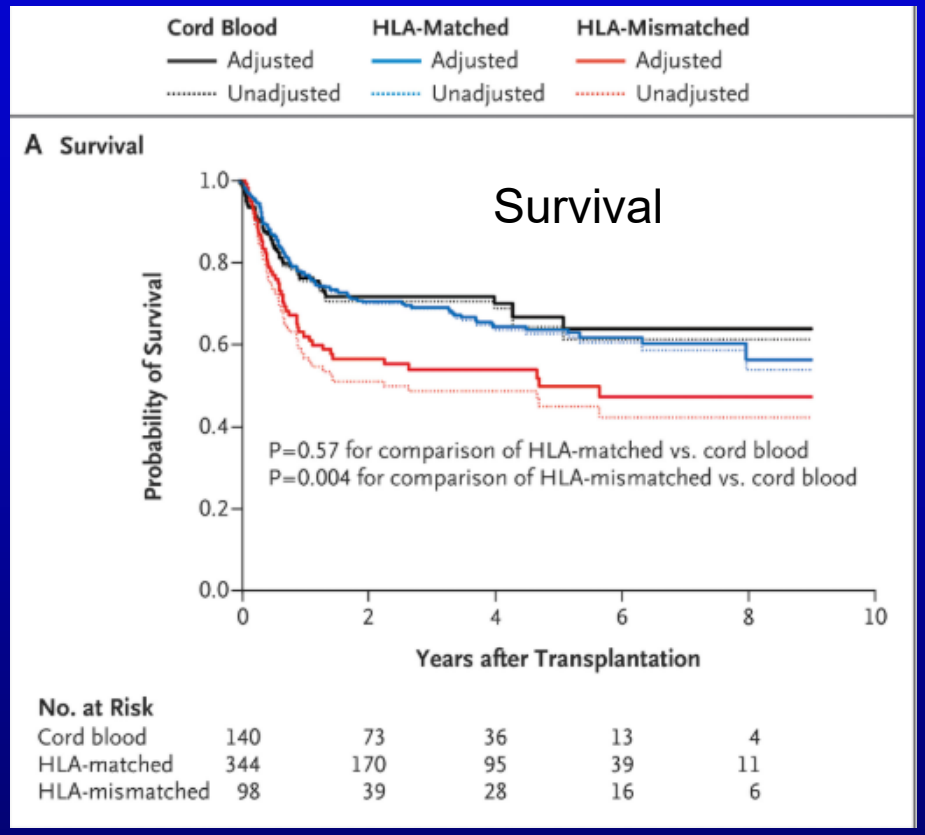
1) HLA Match: Best HLA Match 10/10 superior outcome to 9/10

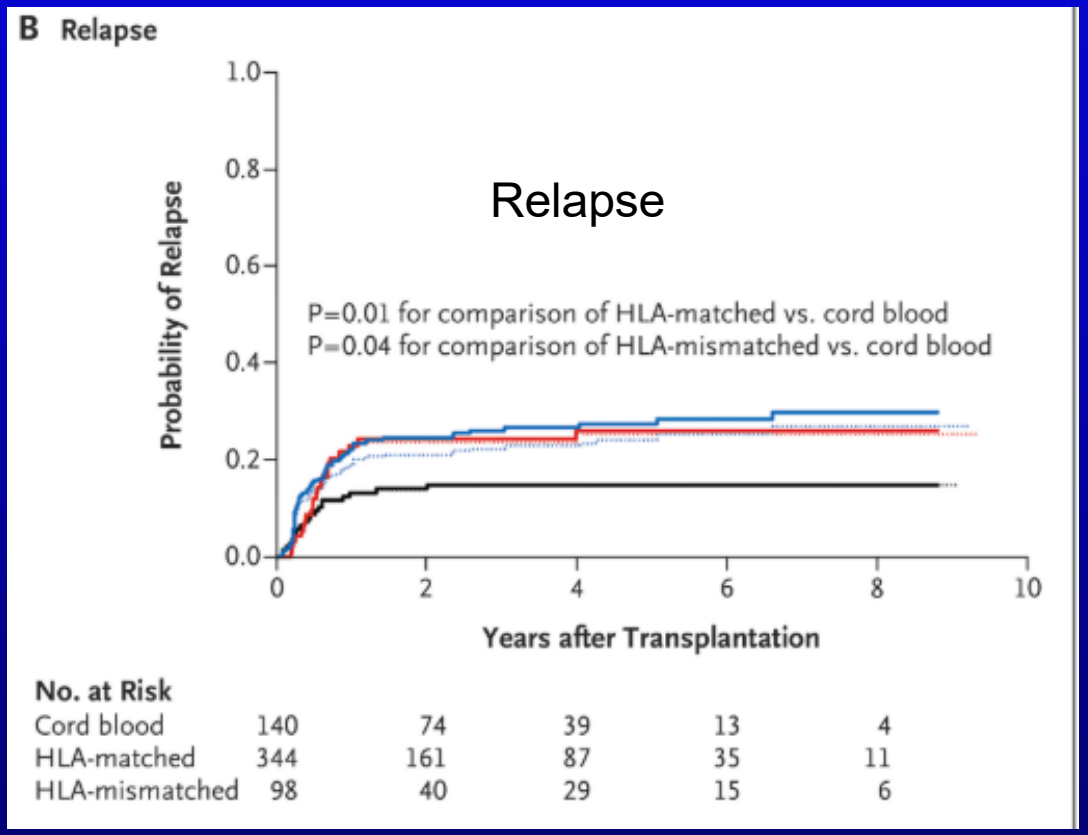
2)Donor Age: Younger aged donors improved outcome



Kollman C. et al Blood 2016;127(2)

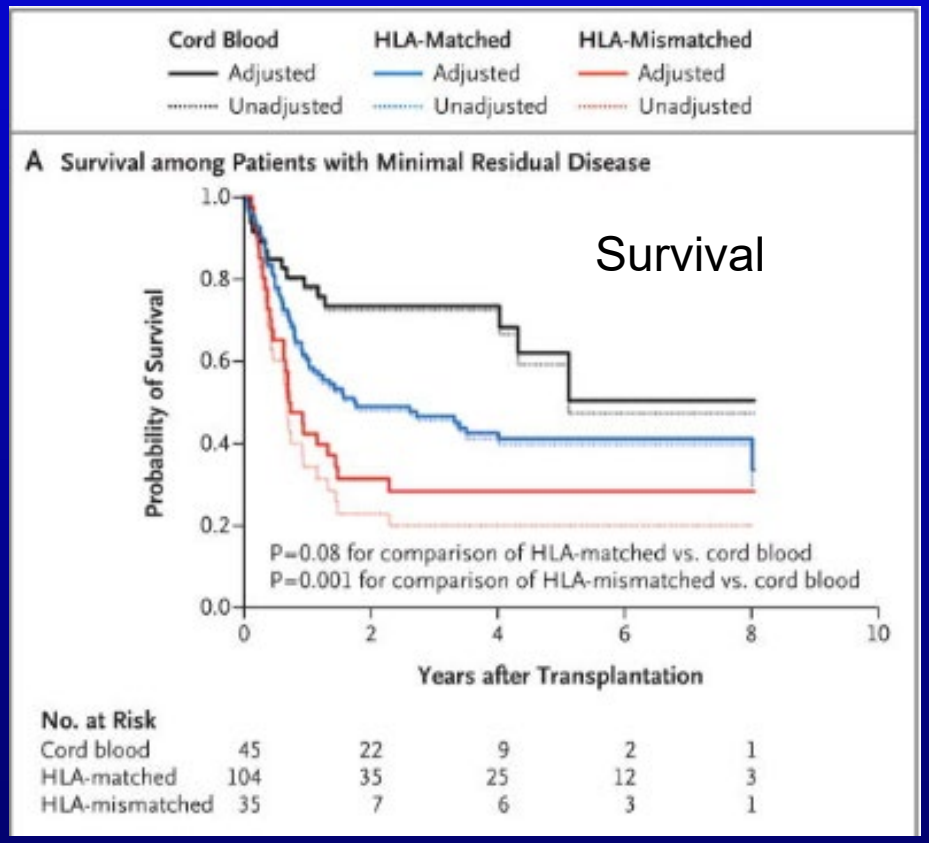
Cord Transplants Compares Favorably with Matched Unrelated Donor Transplants

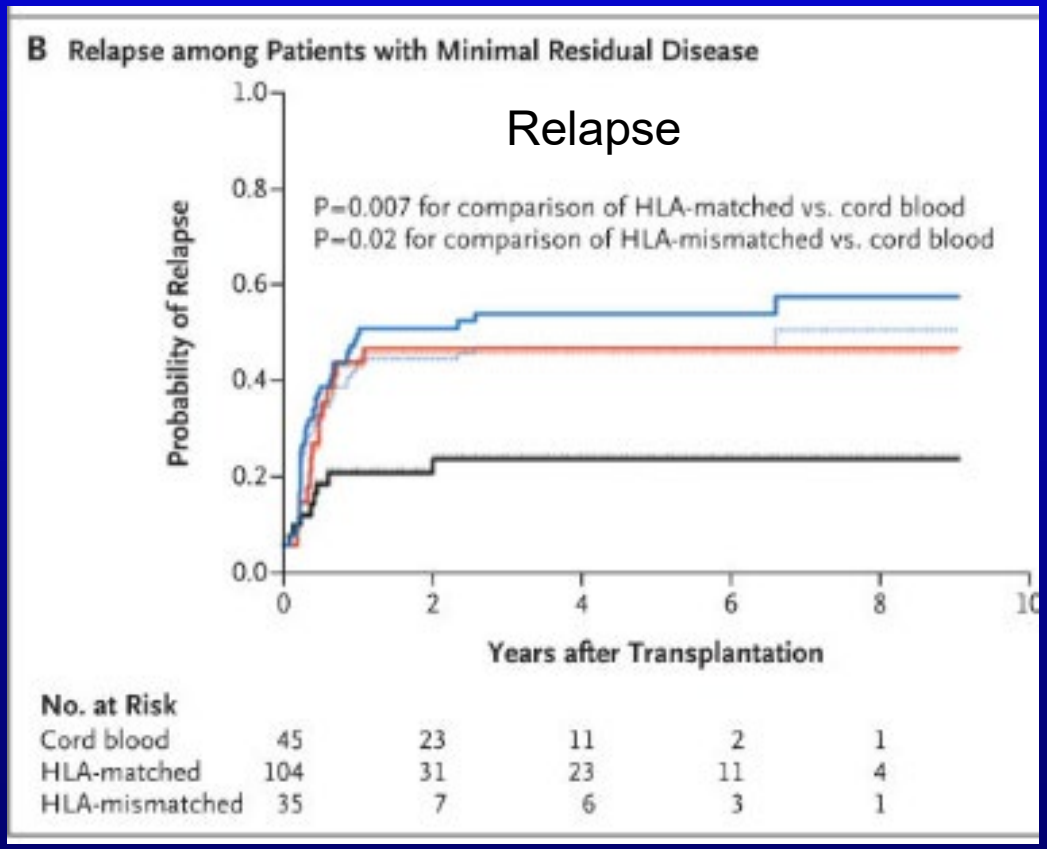




Milano et al NEJM 2016;375(10)

Cord Transplants Associated Superior Outcome in MRD + Patients Compared To Matched Unrelated Donor Transplants





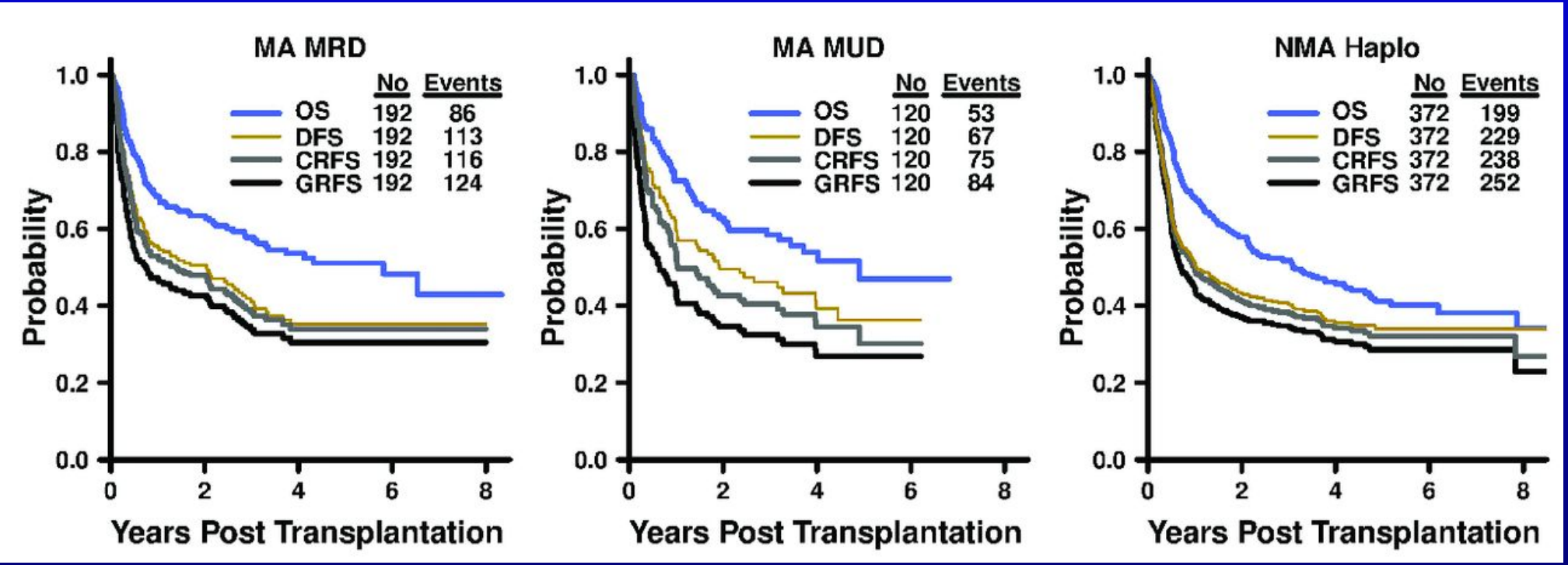
Milano et al NEJM 2016;375(10)

Haplo/Cy Transplants Compares Favorably with Matched Unrelated Donor Transplants

Reference	Population	Donor	N	MAC/RIC,%	OS	LFS	RI	NRM
Ciurea SO, 2015 (CIBMTR)	AML, all disease status	Haplo MUD	192 1982	15/85 41/59	46% 44%	- -	44% 39%	14% 20%
Piemontese S, 2017 (EBMT)	AML or ALL, CR1/2	Haplo MUD mMUD	265 2490 813	52/48 59/41 60/40	46% 56% 48%	41% 50% 46%	30% 29% 25%	29% 21% 29%
Santoro N, 2017 (EBMT)	Age > 60y AML, all disease status	Haplo MUD	250 2589	27/73 23/77	39% 42%	35% 40%	28% 32%	38% 28%
Lorentino F, 2018 (EBMT)	Adverse Karyo AML, CR1/2	Haplo MUD mMUD	74 433 123	53/47 49/51 54/46	59% 50% 50%	53% 43% 44%	27% 39% 37%	19% 17% 18%
Brissot E, 2019 (EBMT)	Rel/Ref AML	Haplo MUD mMUD	199 1111 383	53/47 42/58 38/62	29% 35% 28%	23% 28% 22%	52% 46% 51%	25% 26% 27%
Shem-Tov N, 2019 (EBMT)	B or T ALL, CR1	Haplo MUD mMUD	136 809 289	79/21 79/21 83/17	54% 62% 62%	49% 53% 55%	28% 28% 25%	23% 19% 20%

McCurdy S.,…Luznik L. Haematologica 2017: Volume 102(2):391-400

Haplo/Cy Transplant Compares Favorably with Matched Related Donor or Matched Unrelated Donor Transplants



McCurdy S.,…Luznik L. Haematologica 2017: Volume 102(2):391-400

No Impact Of Conditioning Intensity on Outcomes After Haplo-Transplantation with Post-transplant Cytoxan

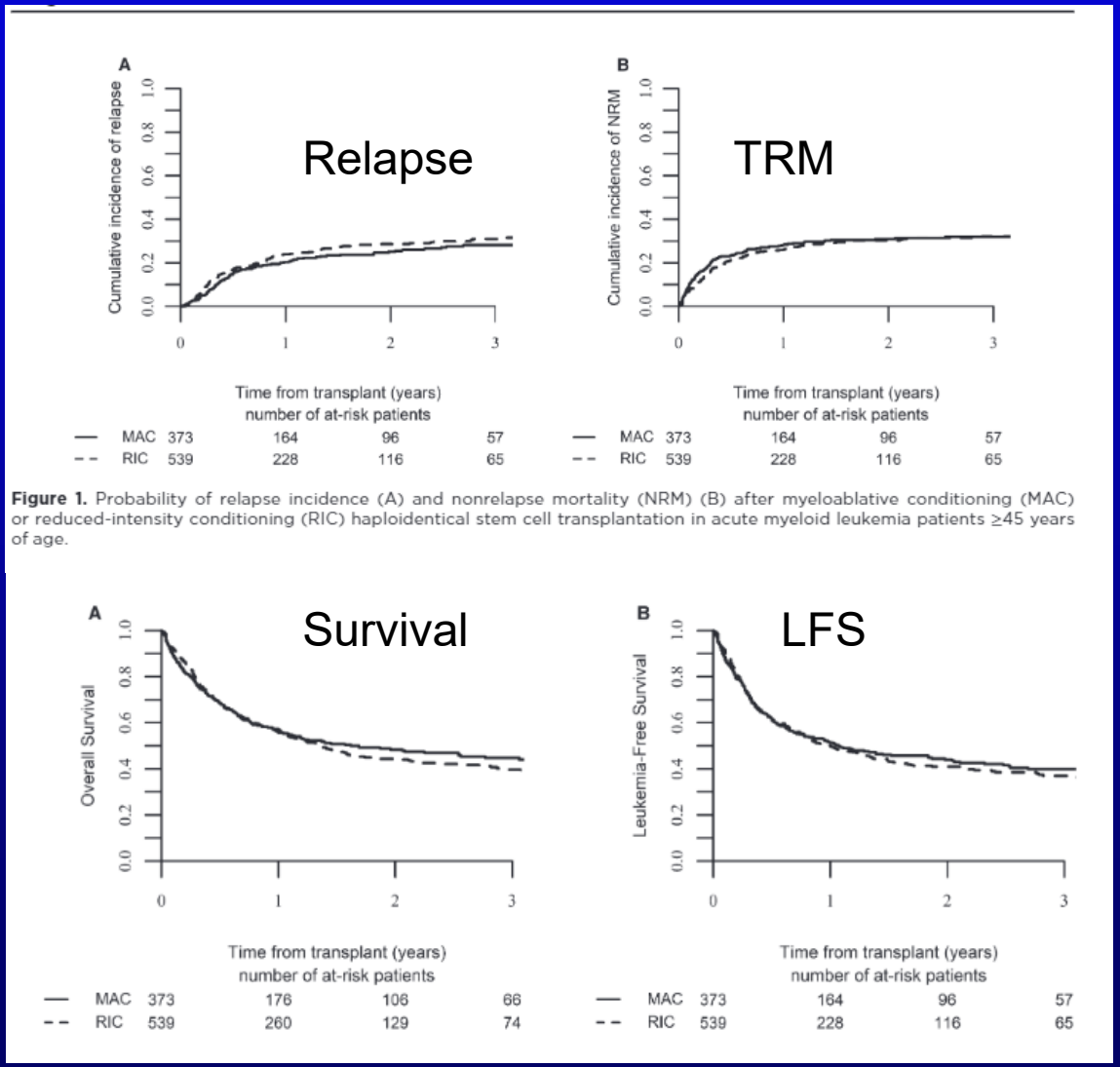


Figure 1. Probability of relapse incidence (A) and nonrelapse mortality (NRM) (B) after myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) haploidentical stem cell transplantation in acute myeloid leukemia patients ≥45 years of age.

- **912 pts AML >45 yrs MAC vs RIC**
- **No differences were found between MAC and RIC**

Santoro N. Cancer : 2019;125(9)

Choosing the Optimal Haplo 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)

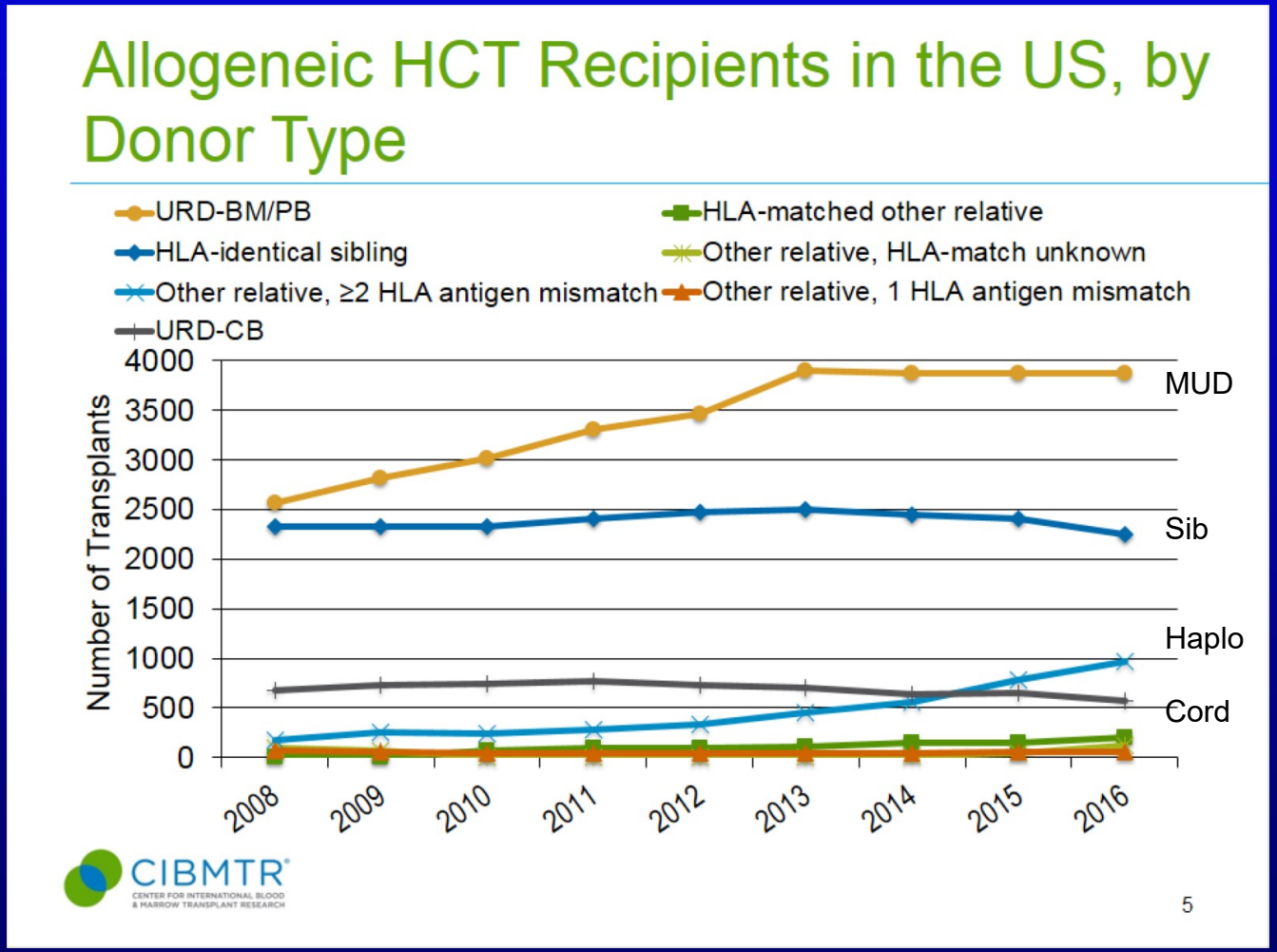
Fact: Recipients of Haplo Transplants may have many potential family donors to choose from

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).

Use of Haplo Transplants is Increasing



CIBMTR Data 2019