Post-transplant cyclophosphamide is the most effective GVHD prophylaxis for allogeneic stem cell transplant recipients

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Conflicts of interest (ORCA is relevant to this talk)

Consultant

- Verastem
- Allovir
- CRISPR
- Novartis
- CSL

Research Funding

- Novartis
- CSL
- ORCA
- BMS
- Sanofi
- NCI R01
- Verastem
- Secura
- Partners

Start-ups

- Cambium Medical Technologies
- Cambium Oncology

Why is GvHD prophylaxis needed?

- Donor T cells are critical to successful engraftment and graft-versus-leukemia effects
- Donor T cells cause damage to normal tissues, a condition called “graft-versus-host-disease”, as well as eliminating cancer cells.
- In the beginning of the transplant field, transplants were limited to HLA-matched donor recipient pairs as the risk of GvHD mortality was unacceptably high after conventional pharmacological immuno-suppression
- Post-transplant cyclophosphamide has allowed safe and successful transplantation across the HL barrier and has “democratized” transplantation, making a donor available to every patient with a low cost of therapy

GvHD is a major contributor to death among allo-transplant patients with conventional GvHD prophylaxis

Table 2. Primary Causes of Death among Patients Who Underwent Transplantation.*

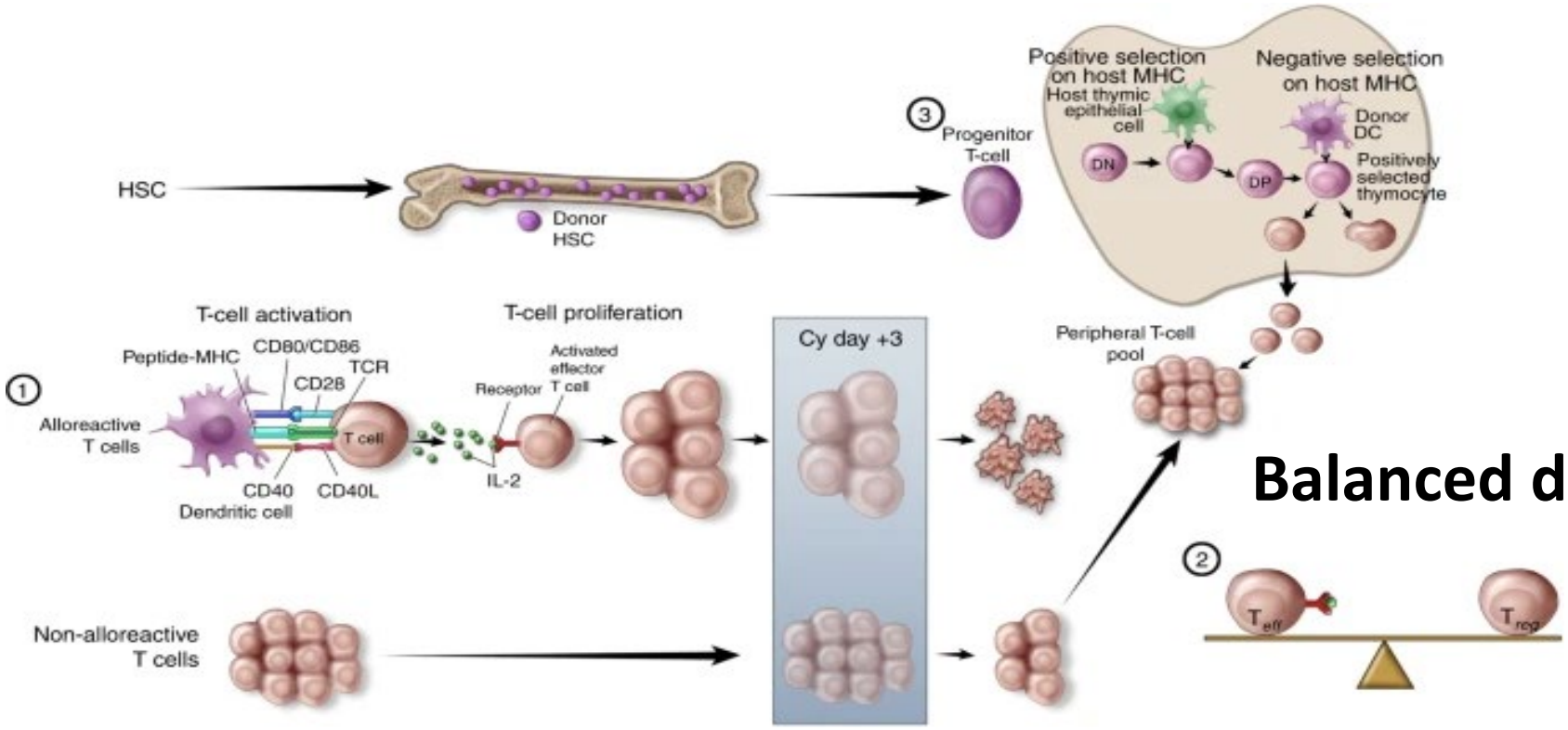
Cause of Death	Bone Marrow (N=145)	Peripheral-Blood Stem Cells (N=145)
	number (percent)	
Relapse	73 (50)	69 (48)
Infection	13 (9)	8 (6)
Graft failure	11 (8)	0
Acute GVHD	20 (14)	24 (17)
Chronic GVHD	14 (10)	30 (21)
Other	14 (10)	14 (10)

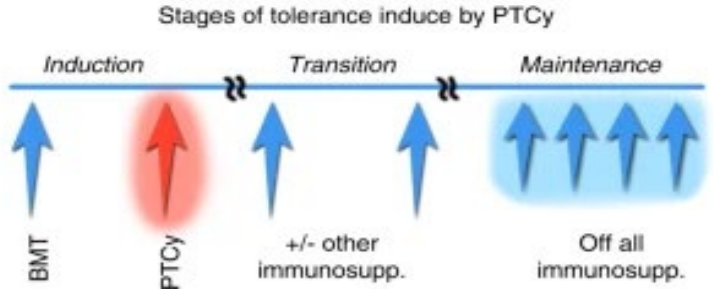
* P=0.002 for the overall comparison between the groups. Percentages do not add up to 100 because of rounding.

Death secondary to GvHD
24% (BM)
38% (PBSC)

Anasetti C, Logan BR, Lee SJ, Waller EK…NEJM 2012

Post-Transplant Cyclophosphamide eliminates most of the donor T cells that cause GvHD





McCurdy & Luznik BMT 2019

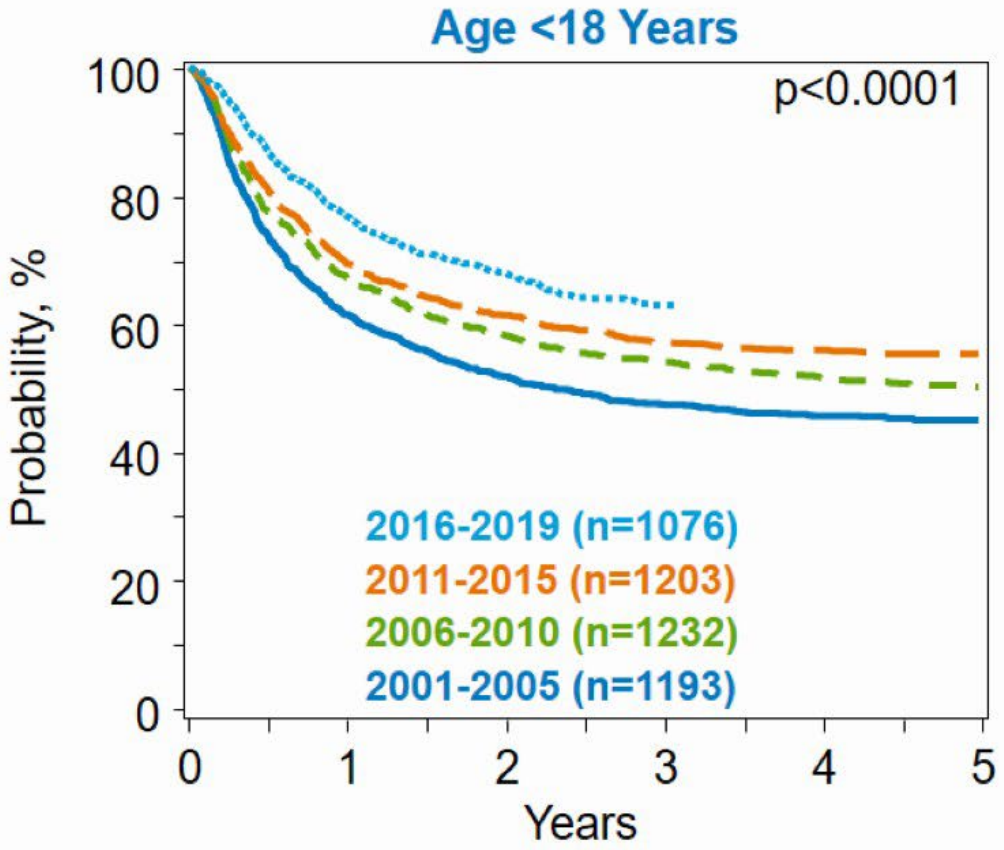
Types of GvHD prophylaxis and rates of grade 3-4 acute GvHD

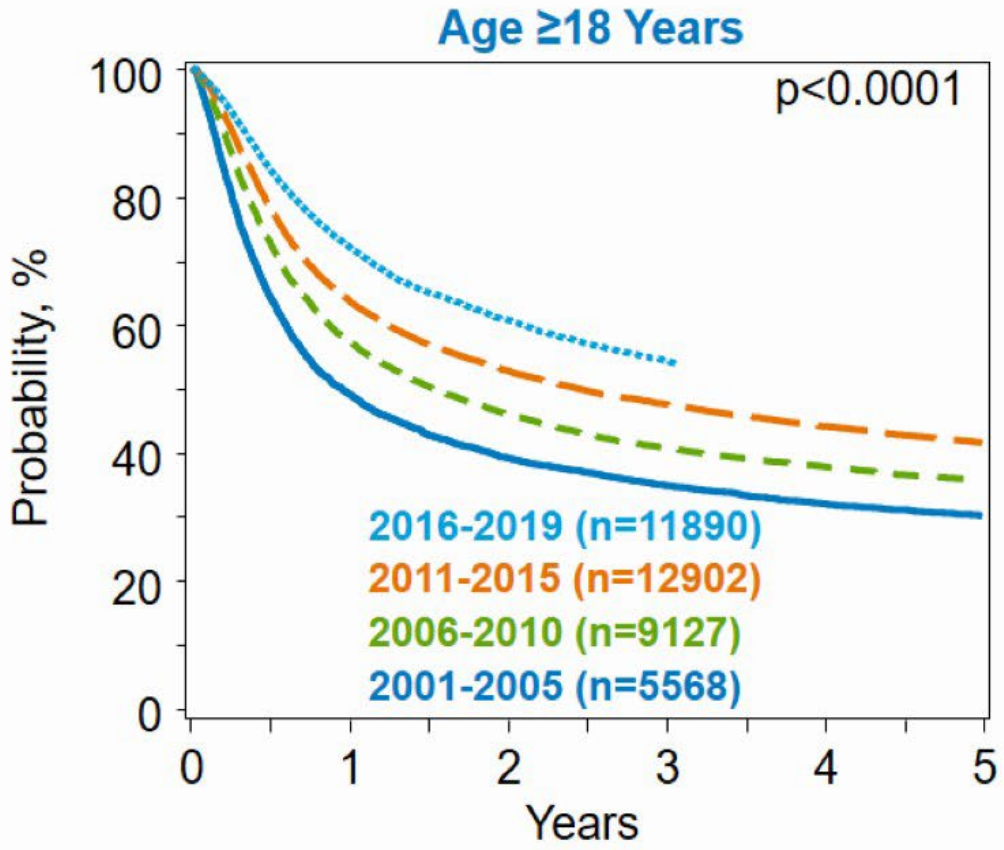
	CNI/Mtx	CNI/Mtx/Aba	ORCA ex vivo graft enginer.	Post-transplant Cy only	Post-transplant Cy/Tac/MMF
HLA-matched related or unrelated	14% (2)	7% (2)	2% (3)	21% (5)	
Mis-matched unrelated	32% (2)	2% (2)			
Haplo-Identical	60%		2% (4)		3% (6)

1. Anasetti NEJM 2012
2. Watkins JCO 2021
3. Olia ASH 2023
4. Salhotra ASH 2022
5. Bourgeois Clin Trans Med 2023
6. Quelol Ann Hematol. 2020

Survival after allo-transplants is now increasing

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





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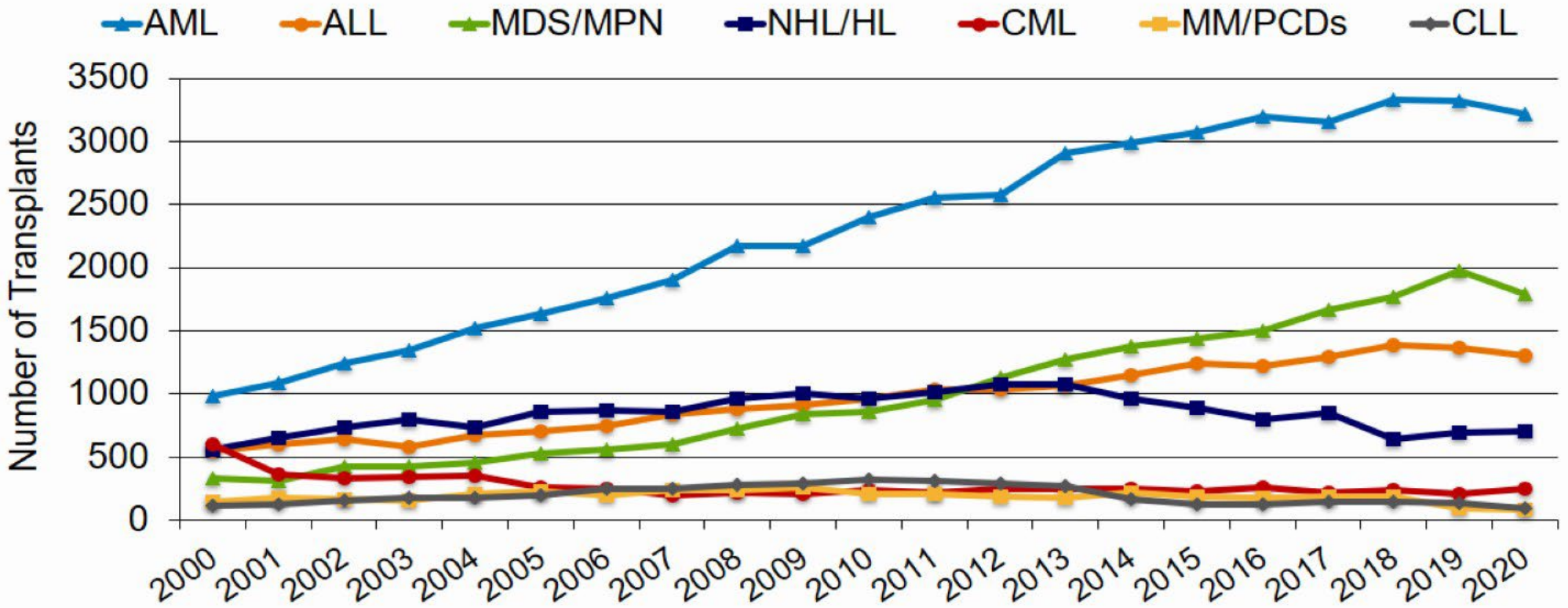
Numbers of allo- transplants performed for AML/MDS and ALL are rising

Number of Allogeneic HCTs in the US by Selected Disease



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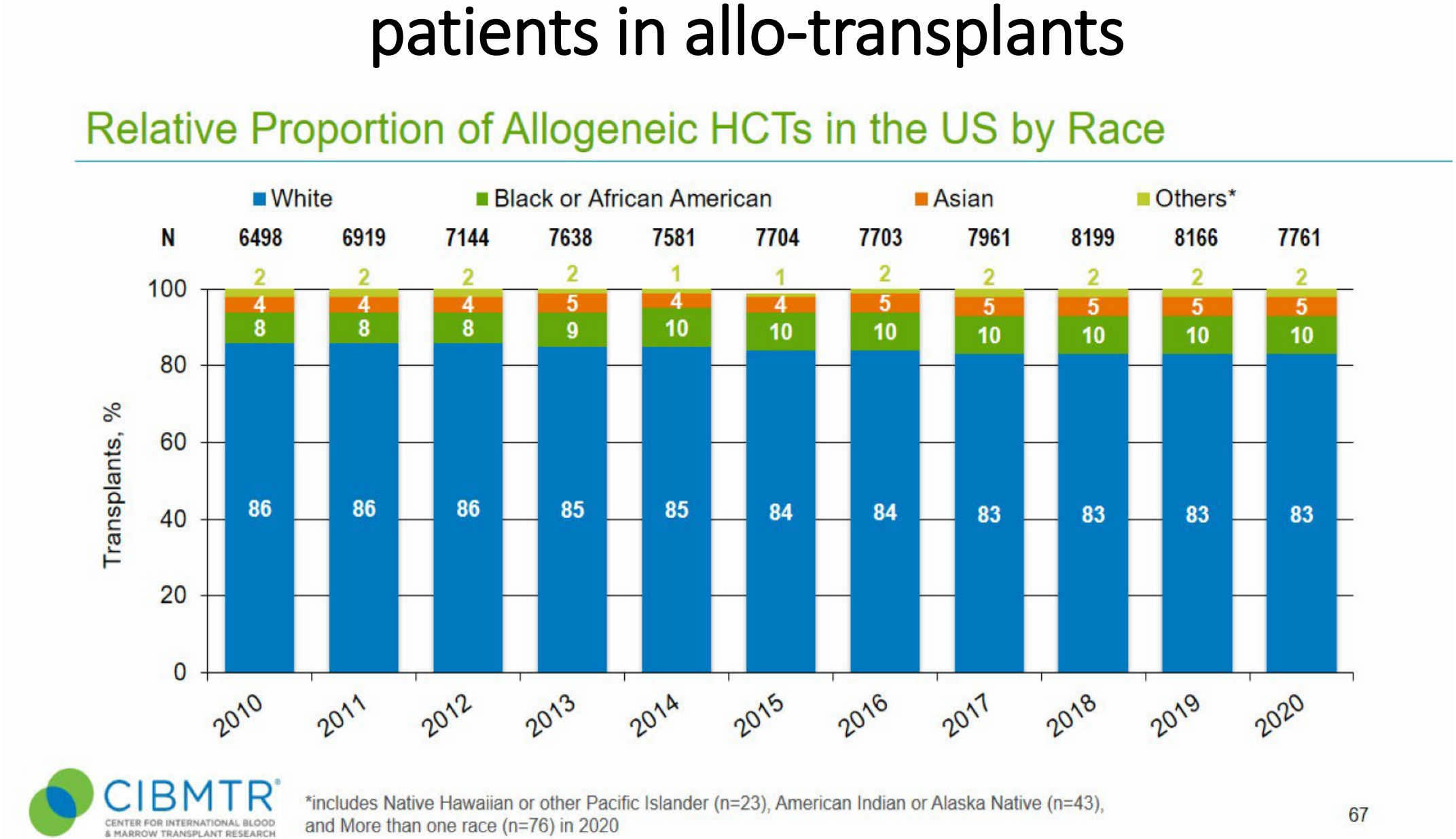
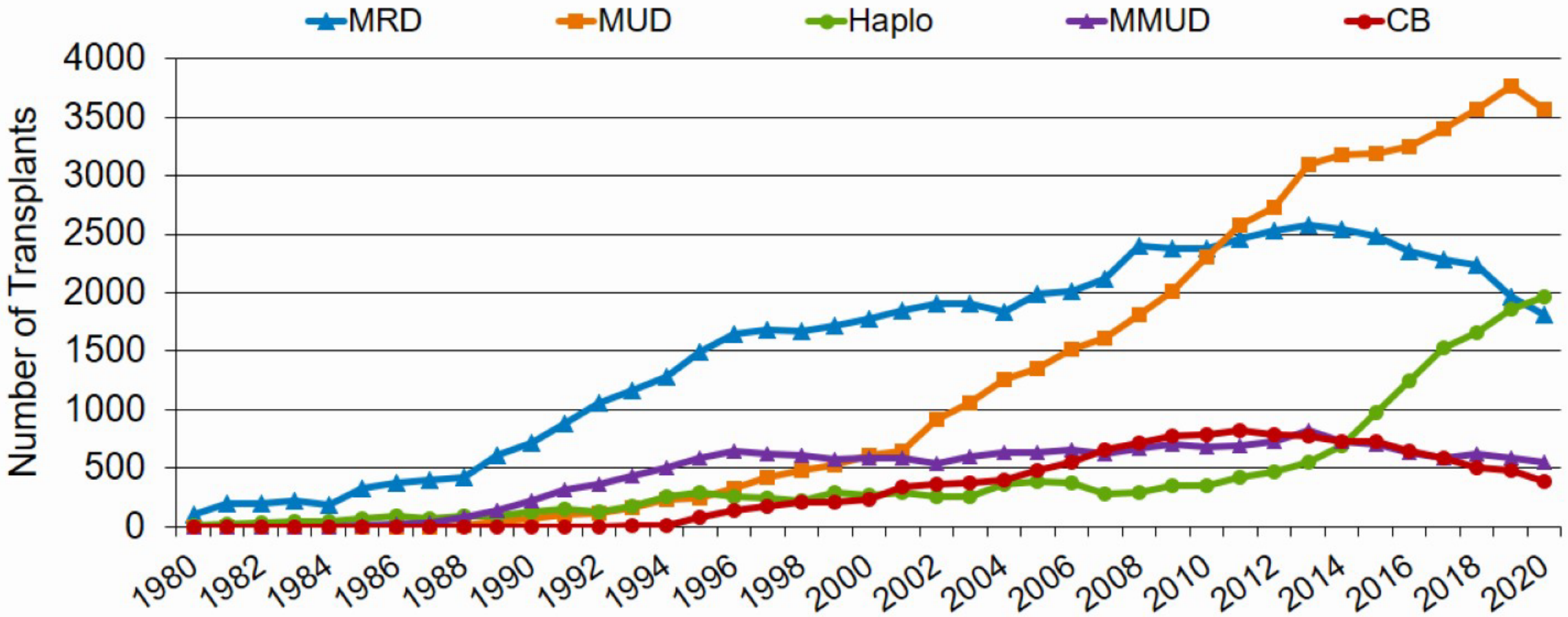
Abbreviations –
AML: Acute myelogenous leukemia;
ALL: Acute lymphoblastic leukemia;
MDS: Myelodysplastic syndromes;
MPN: Myeloproliferative neoplasms;
NHL: Non-Hodgkin lymphoma;
HL: Hodgkin lymphoma;
CML: Chronic myeloid leukemia;
MM: Multiple myeloma;
PCDs: Plasma cell disorders;
CLL: Chronic lymphocytic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

Under-representation of Black or African-American patients in allo-transplants



Haplo-identical transplants are increasing

Number of Allogeneic HCTs in the US by Donor Type



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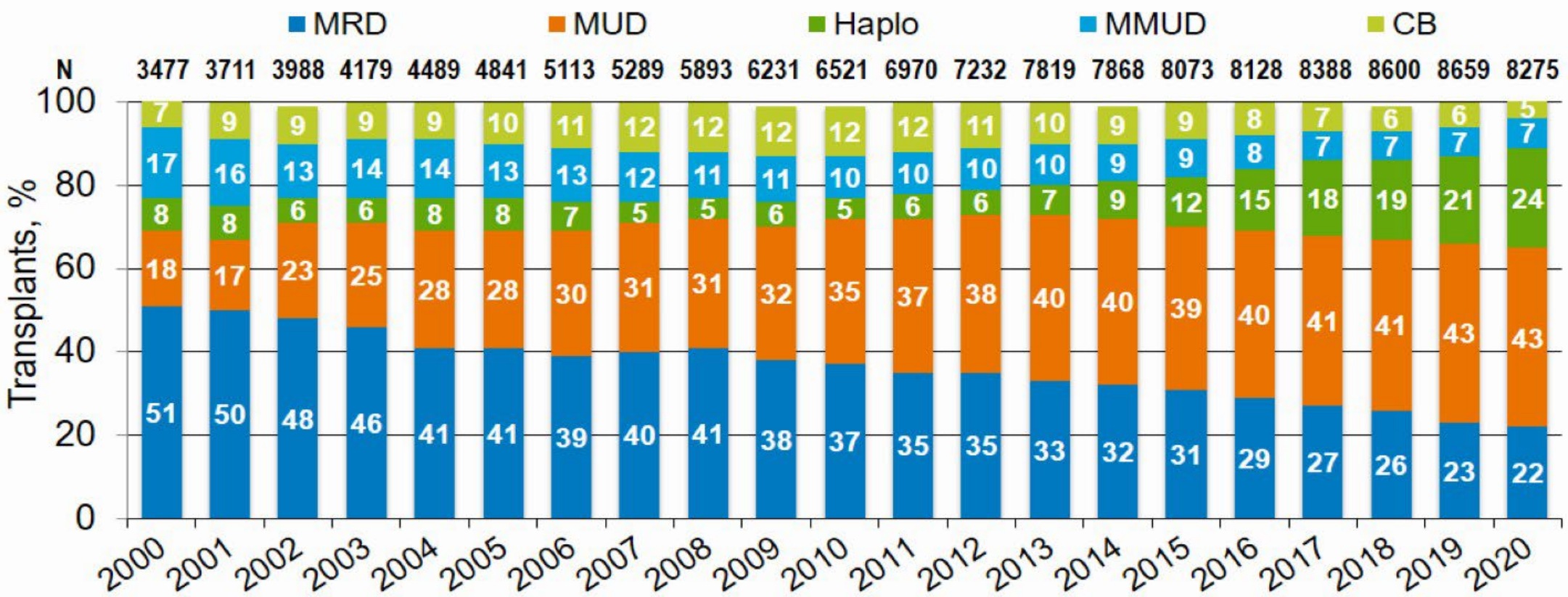
Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor;
Haplo: Haploidentical donor (includes all mismatched related donors); MMUD: Mismatched unrelated donor; CB: Cord blood

Haplo-identical transplantation is available for patients without matched sibling or rare HLA haplotypes

Relative Proportion of Allogeneic HCTs in the US by Donor Type



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Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor;
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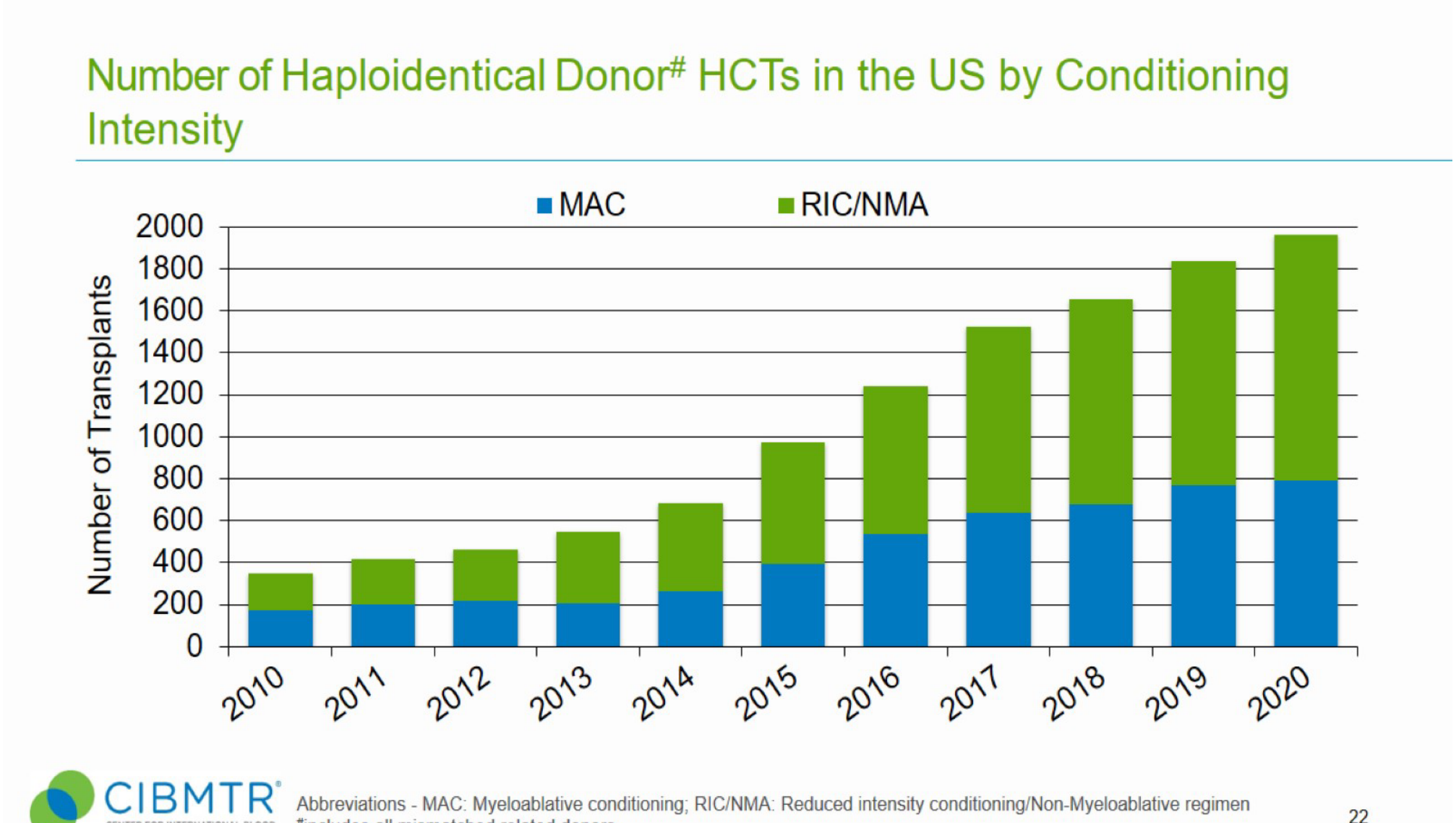
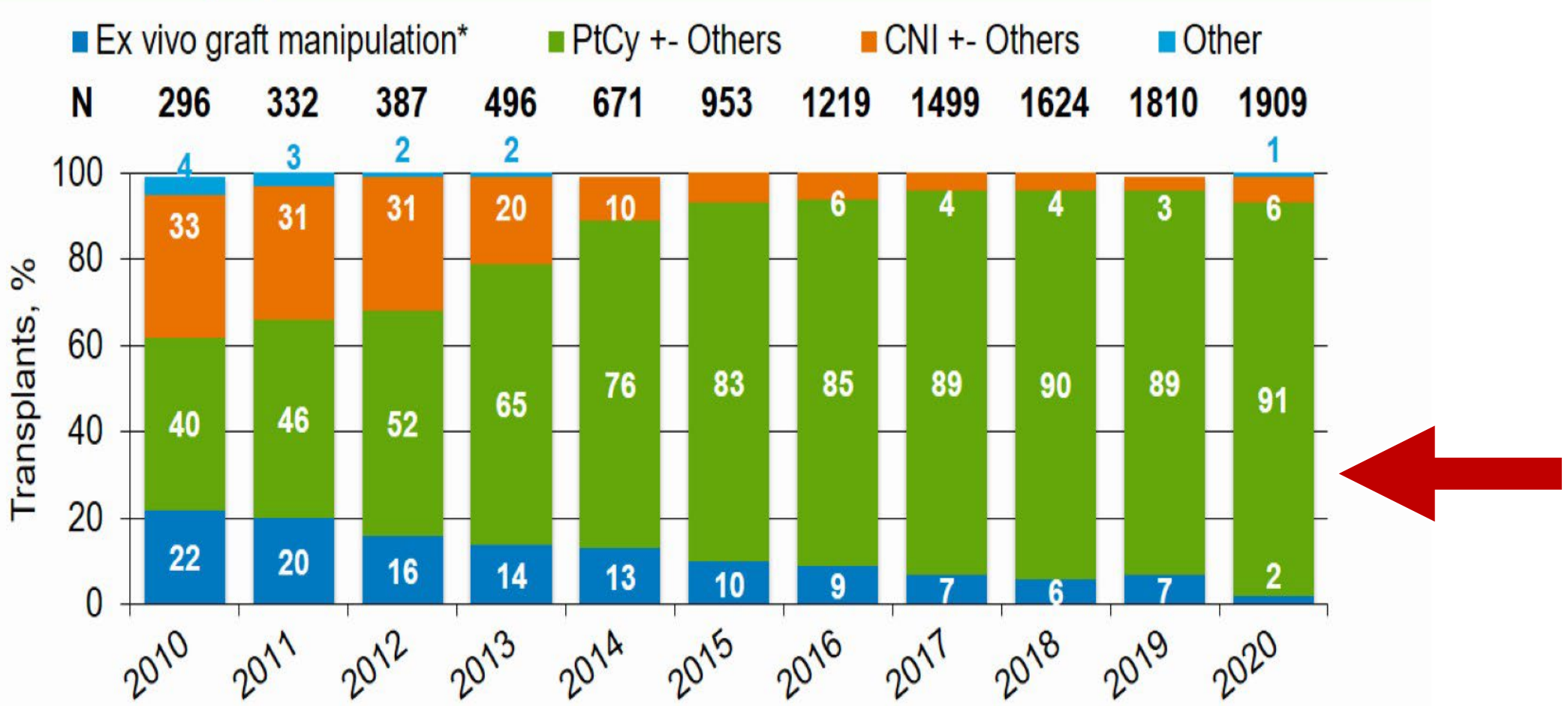
Haplo-identical transplants performed for myeloablative and reduced intensity conditioning regimens



Nearly all haplo-identical transplant recipients received post-transplant cyclophosphamide as GvHD prophylaxis



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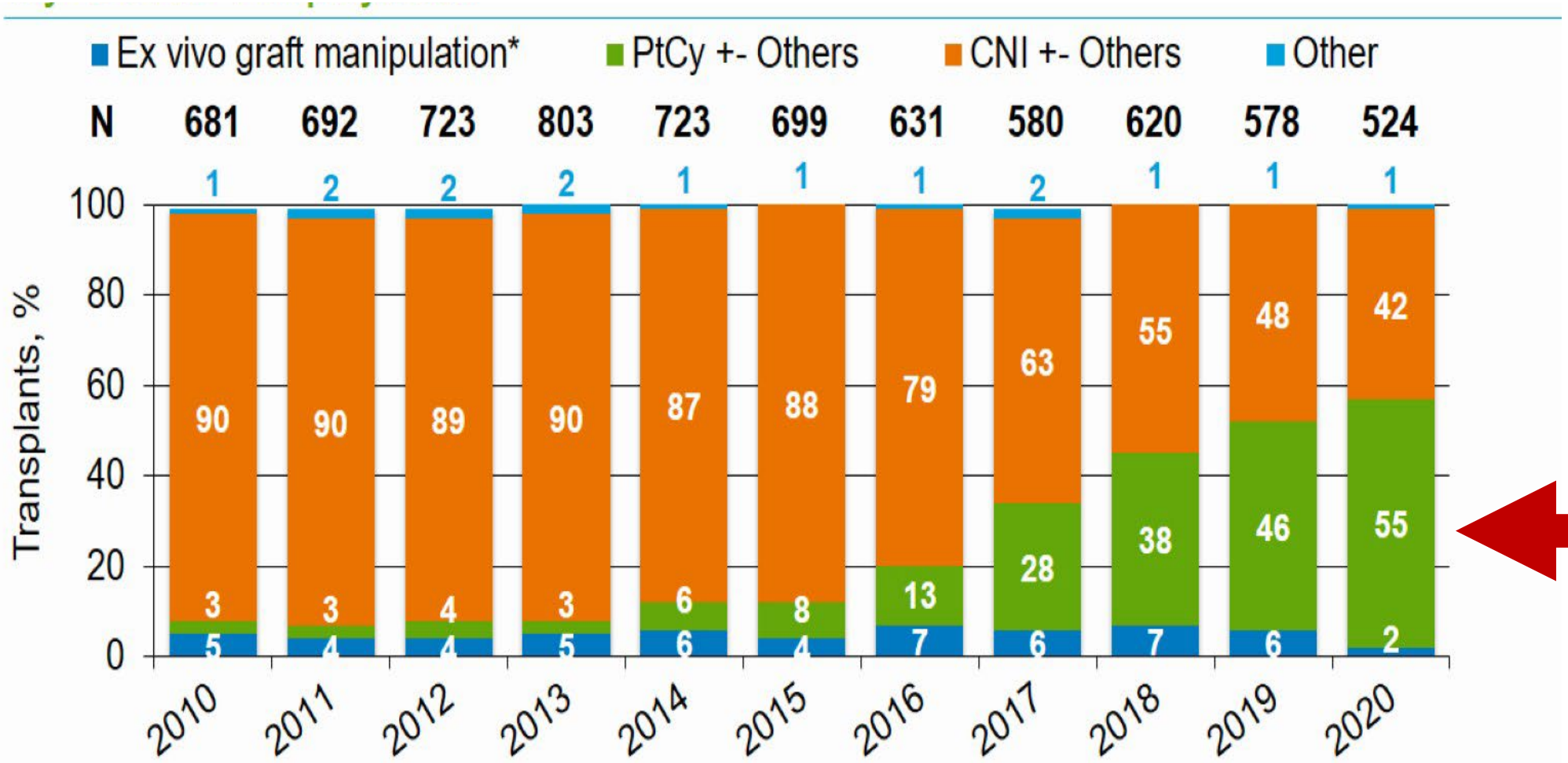
Abbreviations - PtCy: Post-transplant Cyclophosphamide; CNI: Calcineurin inhibitor
*includes T cell depletion/CD34 selection +- others; #includes all mismatched related donors

The majority of recipients of mis-matched unrelated donor grafts received post-transplant cyclophosphamide



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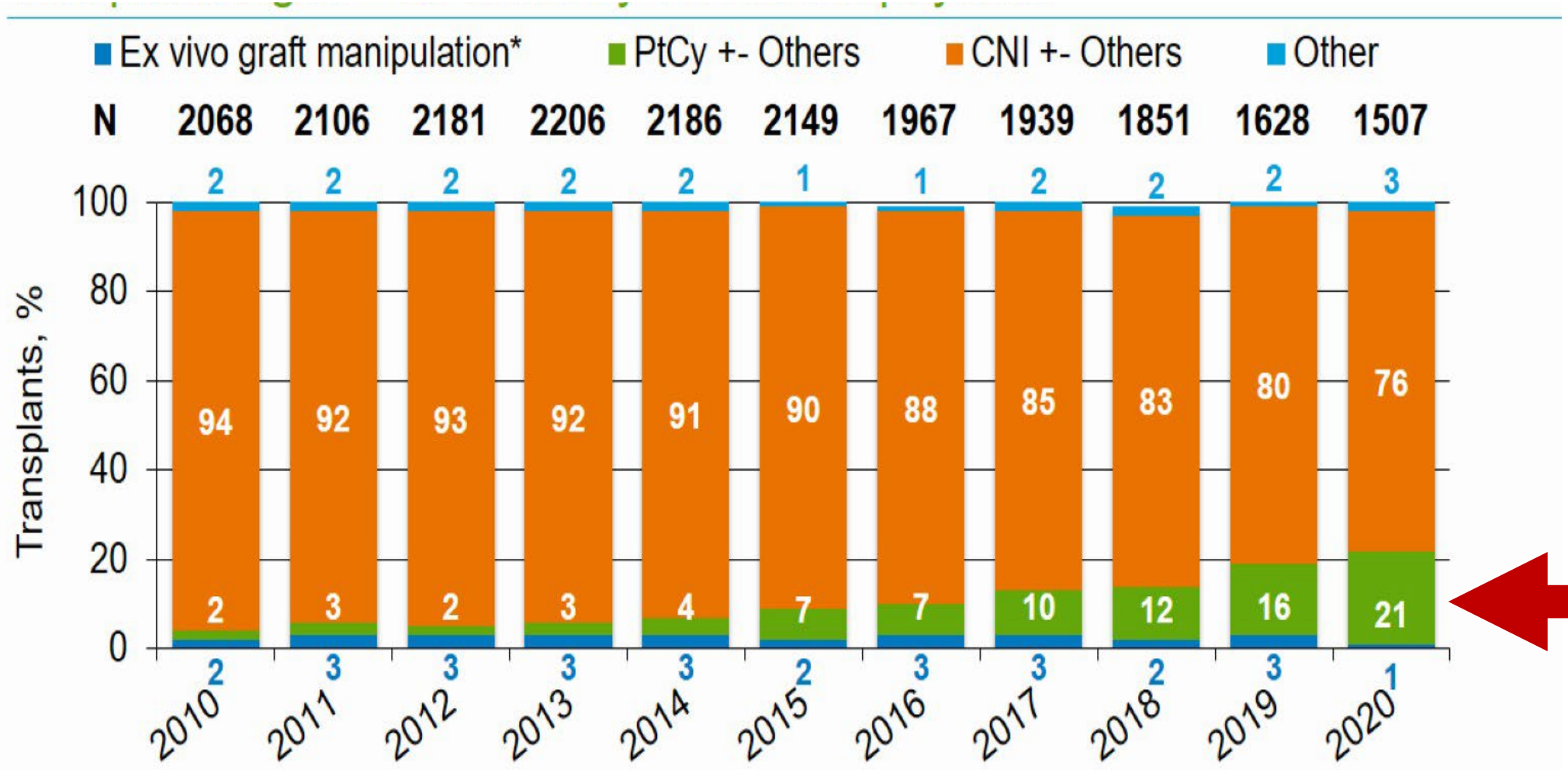
Increasing numbers of of recipients of matched related donor grafts received post-transplant cyclophosphamide



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Abbreviations - PtCy: Post-transplant Cyclophosphamide; CNI: Calcineurin inhibitor
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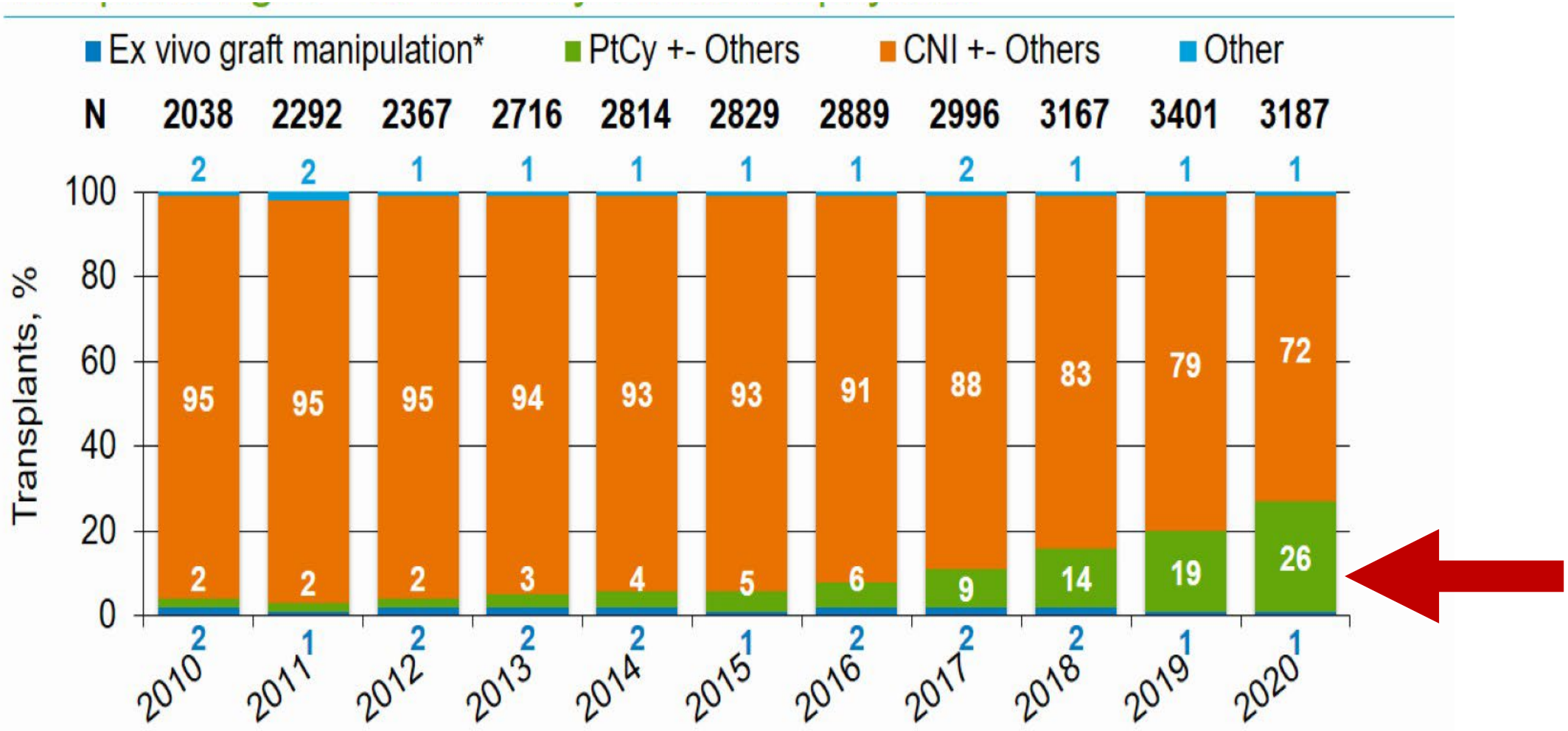
Increasing numbers of of recipients of matched unrelated donor grafts received PTCy



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*includes T cell depletion/CD34 selection +- others

Haplo-identical transplant recipients have the lower death rates from acute GvHD in the first 100 days vs. other graft sources

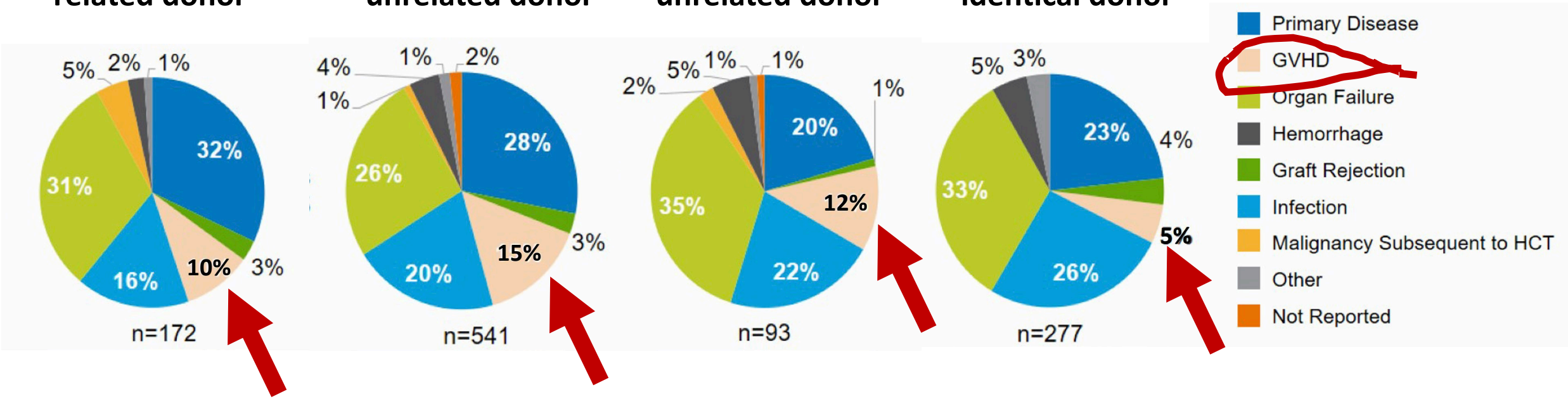
Post-transplant cyclophosphamide saves lives in allo-transplant

10%: Matched related donor

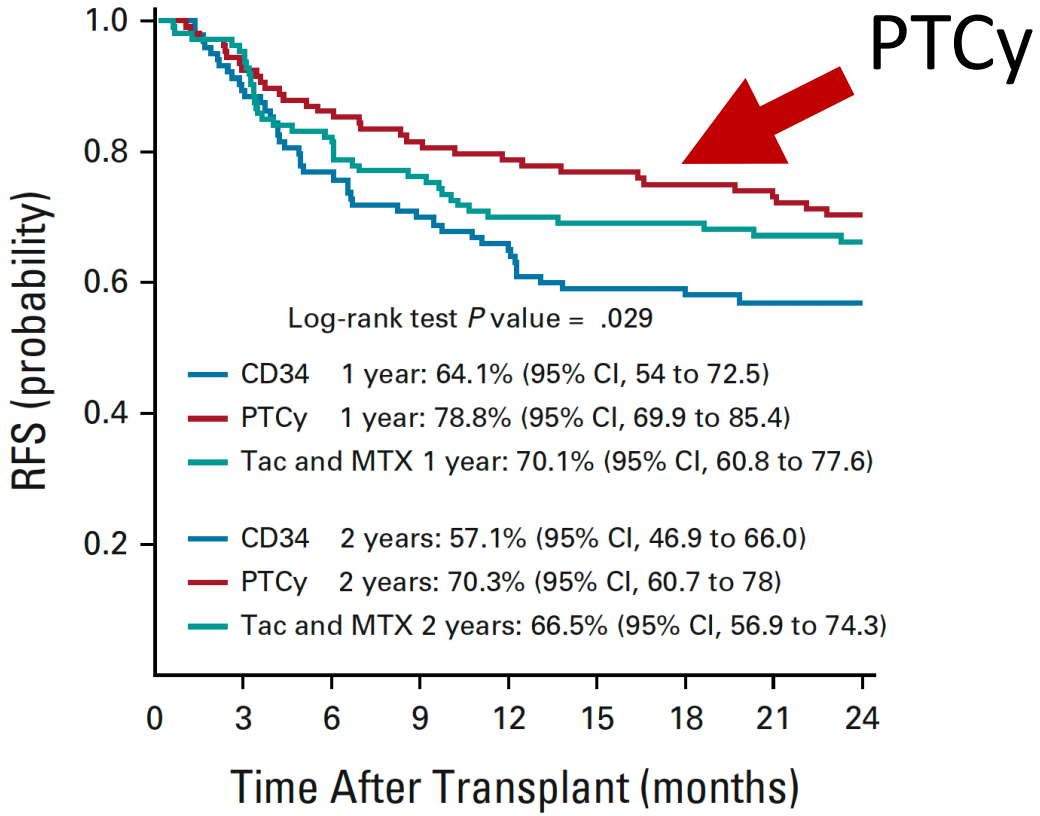
15%: Matched unrelated donor

12%: Mis-matched unrelated donor

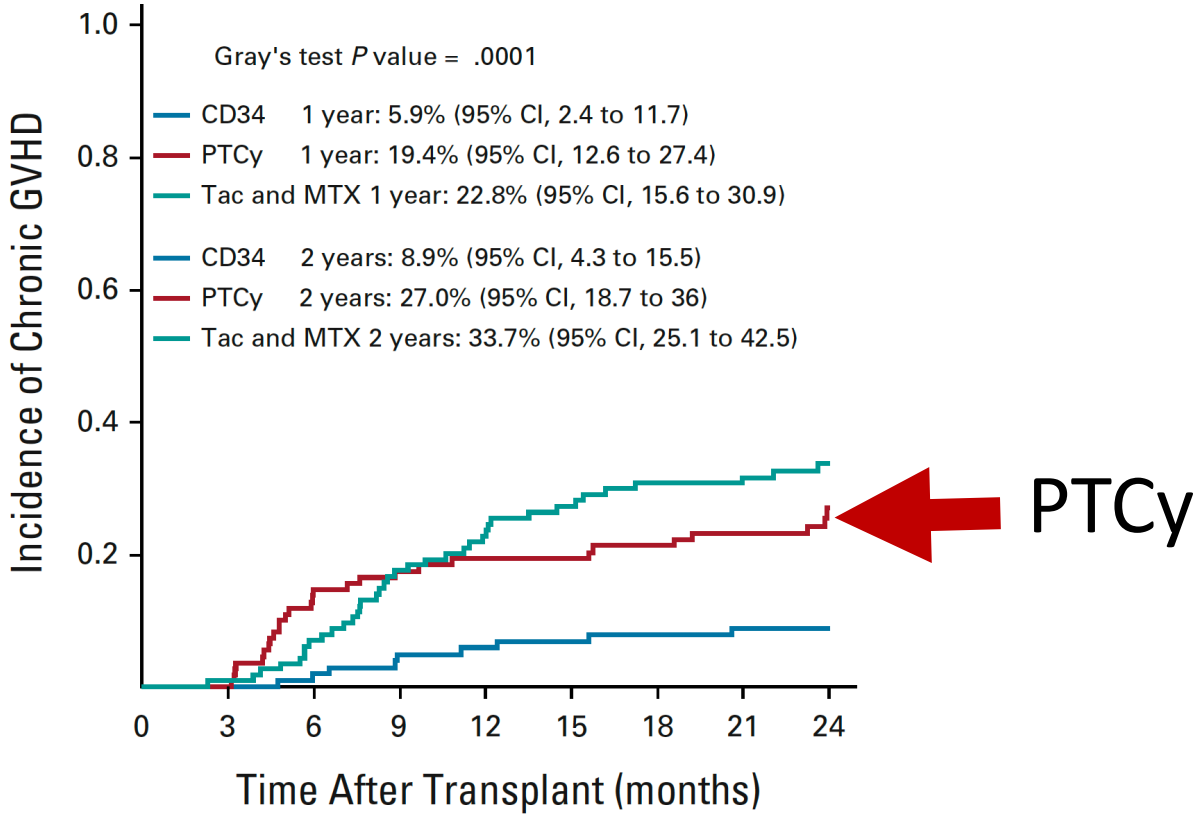
5%: Haplo-identical donor



Superior RFS and less relapse without increased cGvHD using PTCy myeloablative conditioning: randomized phase 2 study



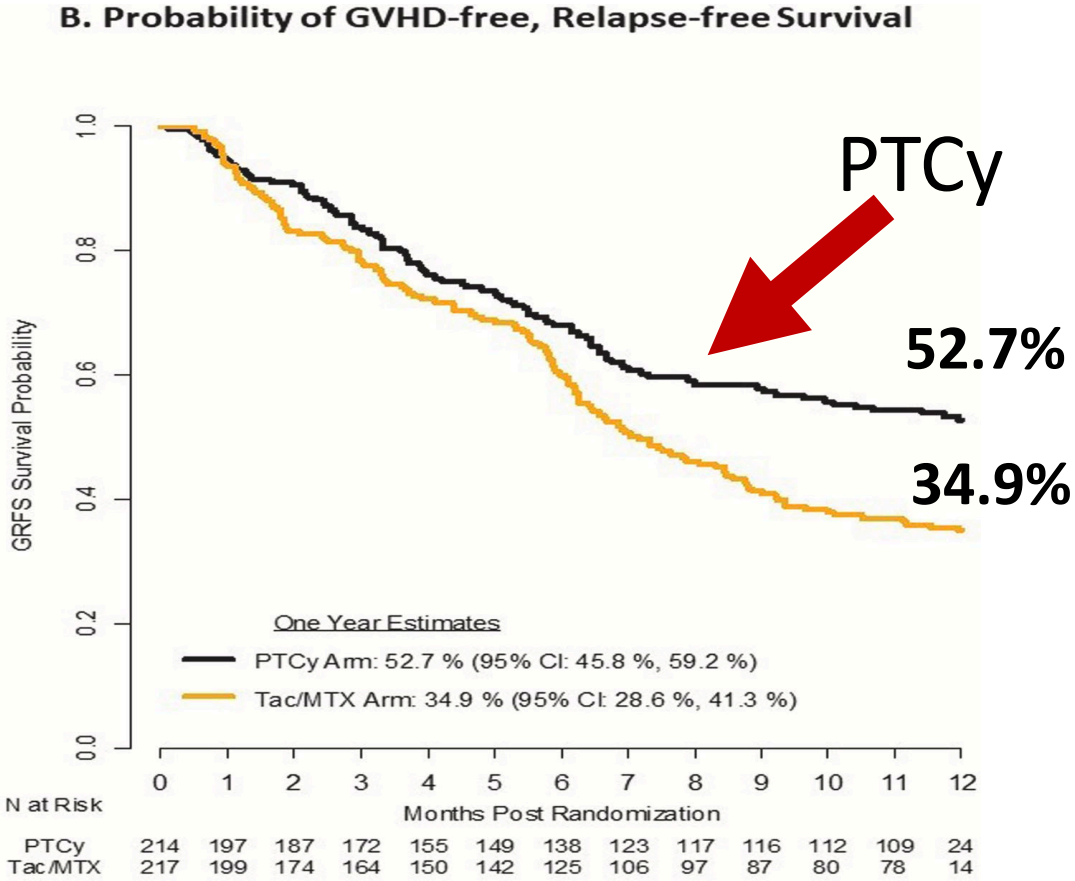
No. at risk:									
CD34	104	92	78	71	65	59	57	55	34
PTCy	109	101	93	88	85	82	80	78	47
Tac and MTX	114	106	90	87	79	77	77	75	44



No. at risk:									
CD34	104	97	84	76	71	64	61	57	34
PTCy	109	104	82	74	70	67	62	60	31
Tac and MTX	114	111	98	82	71	64	57	54	28

BMT CTN 1302

BMTCTN 1703: Post-transplant cyclophosphamide with Tac/MMF is superior to Tac/methotrexate in allo-transplantation after reduced intensity conditioning



J. Bolaños-Meade 2023 NEJM

431 patients with myeloid malignancies, ALL and lymphoma randomized to PTCy or Tac/Mtx

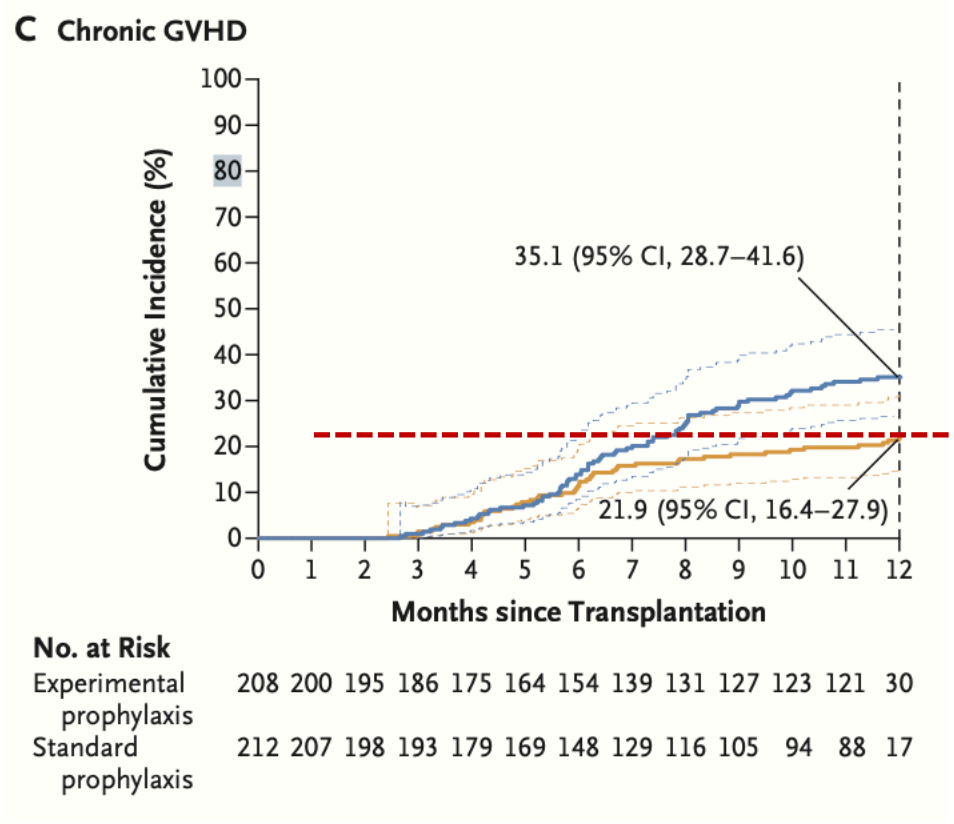
Most common conditioning regimen was Flu/Mel

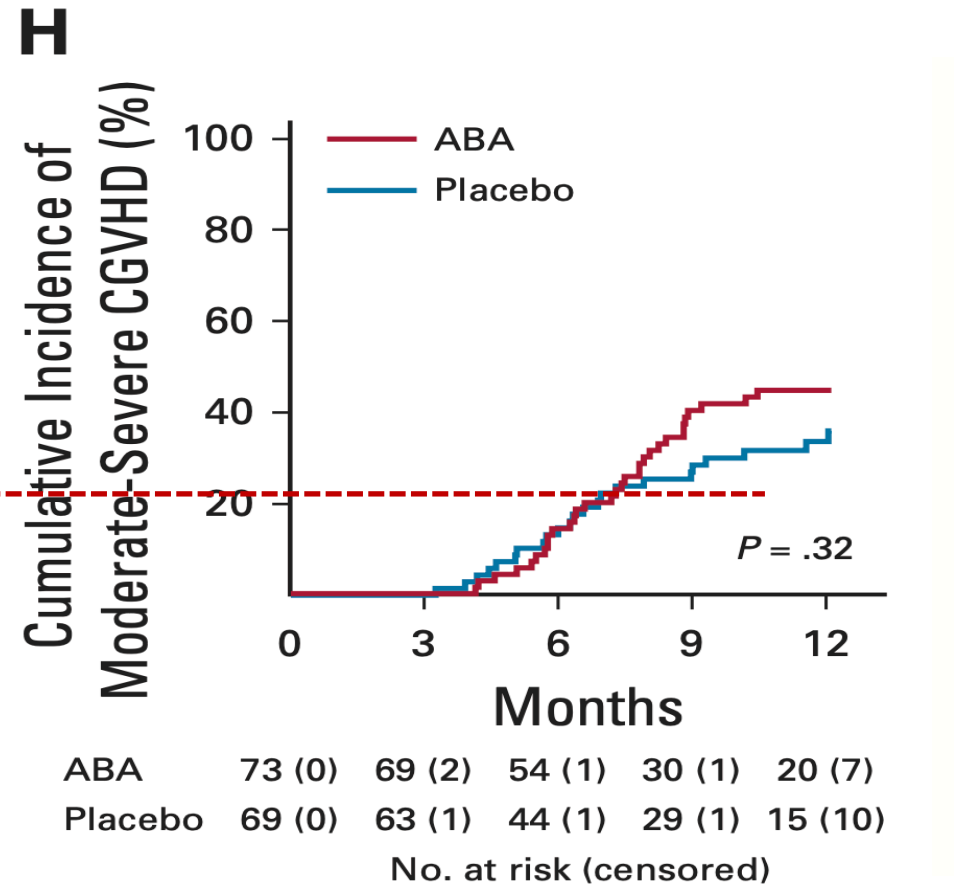
Less severe acute GVHD (6.3% vs. 14.7%) and less chronic GVHD requiring systemic treatment (12.5% vs. 25.0%) with PTCy.

Similar overall rates of non-relapse mortality, disease relapse, progression-free survival, and overall survival

BMTCTN1703: Post-transplant cyclophosphamide with Tac/MMF is superior to Tac/methotrexate in allo-transplantation after reduced intensity conditioning

Less chronic GvHD





J. Bolaños-Meade 2023 NEJM; Watkins 2021 JCO

Conclusions/take-aways

- The use of grafts from Haplo-identical related and HLA mis-matched unrelated donors is increasing based upon the addition of post-transplant cyclophosphamide as GvHD prophylaxis
- PTCy decreases rates of severe acute GvHD and allows patients with uncommon HLA haplo-types, including minority populations who undergo allo-transplant
- Randomized clinical trials conducted by the BMTCTN show superior GvHD-free survival in patients receiving RIC and and better overall survival in patients receiving MAC
- The cost of post-transplant Cy is $3000 versus $10,000 for abatacept and ~$300,000 for ORCA-T

Conclusions/take-aways

- Post-transplant cyclophosphamide GvHD prophylaxis is:
  - Faster
  - Better
  - Cheaper