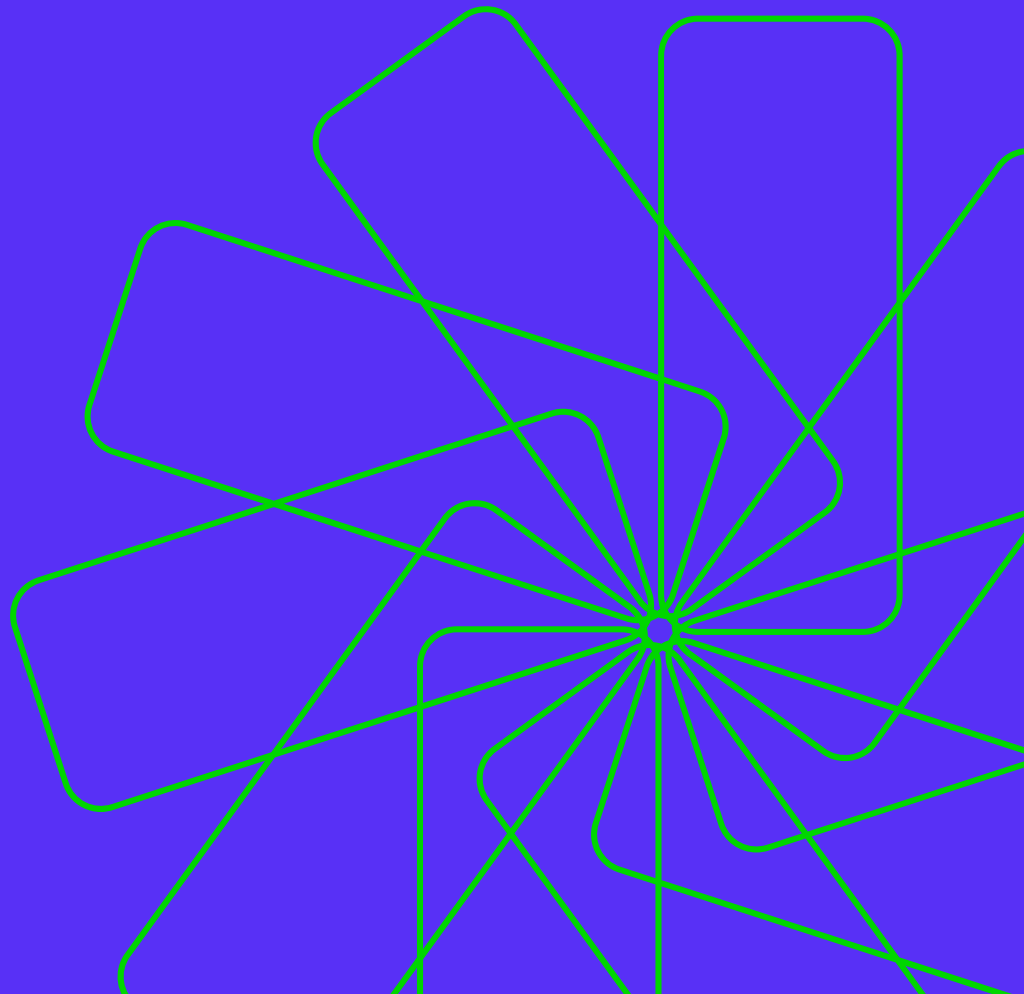
Which alternative donor should I pick?

DR CHLOE ANTHIAS

September 2024



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My Background…

- Clinical transplanter Royal Marsden Hospital and donor health consultant at Anthony Nolan
- RMH 60-70 adult allos/year
- Diverse population – lots of alternative donor transplants
- High risk population (cancer centre)
- Biggest cord centre in the UK but also do haplos (5-10/yr) and in last year have started MMUDs with PTCy

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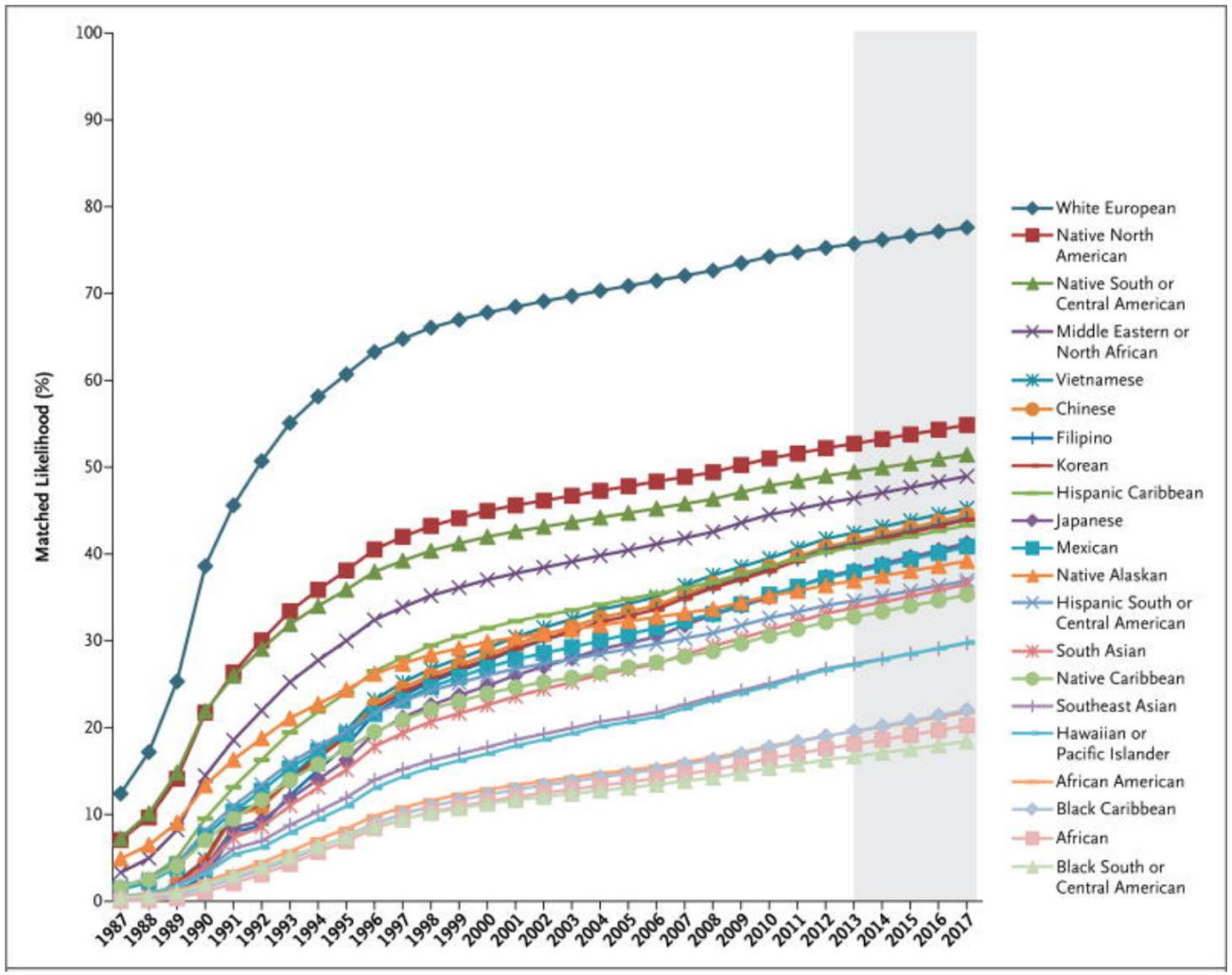
Why we will always need alternative donors



Expanding unrelated donor registries will never be enough to find everyone a well matched donor

This is despite strategies to target recruitment of donors from ethnic minority groups

Gragert et al, NEJM 2014

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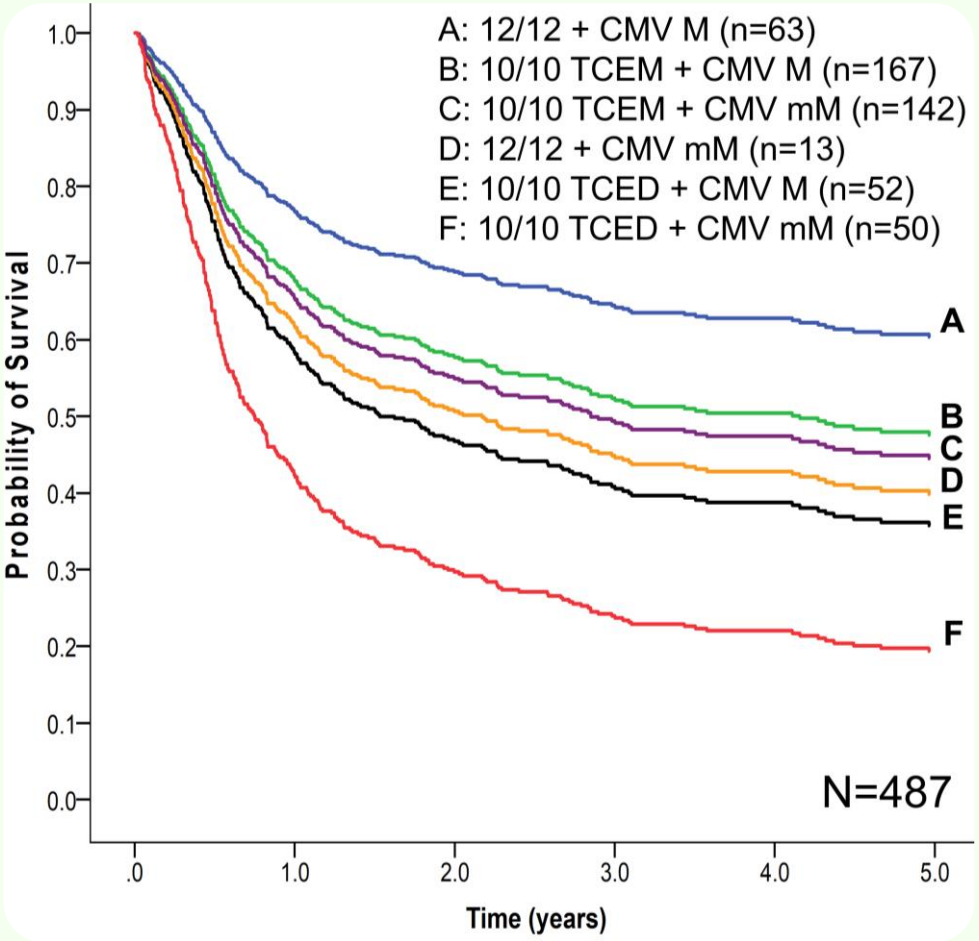
Not all 10/10 matches are equal or optimal!



A: 12/12 + CMV M

vs

F: 10/10 TCED + CMV mM

HR 3.252 (1.90-5.55)

P< 0.001

5yr OS

A: 62.5%

F: 17.5%

Mayor et al BBMT 2019

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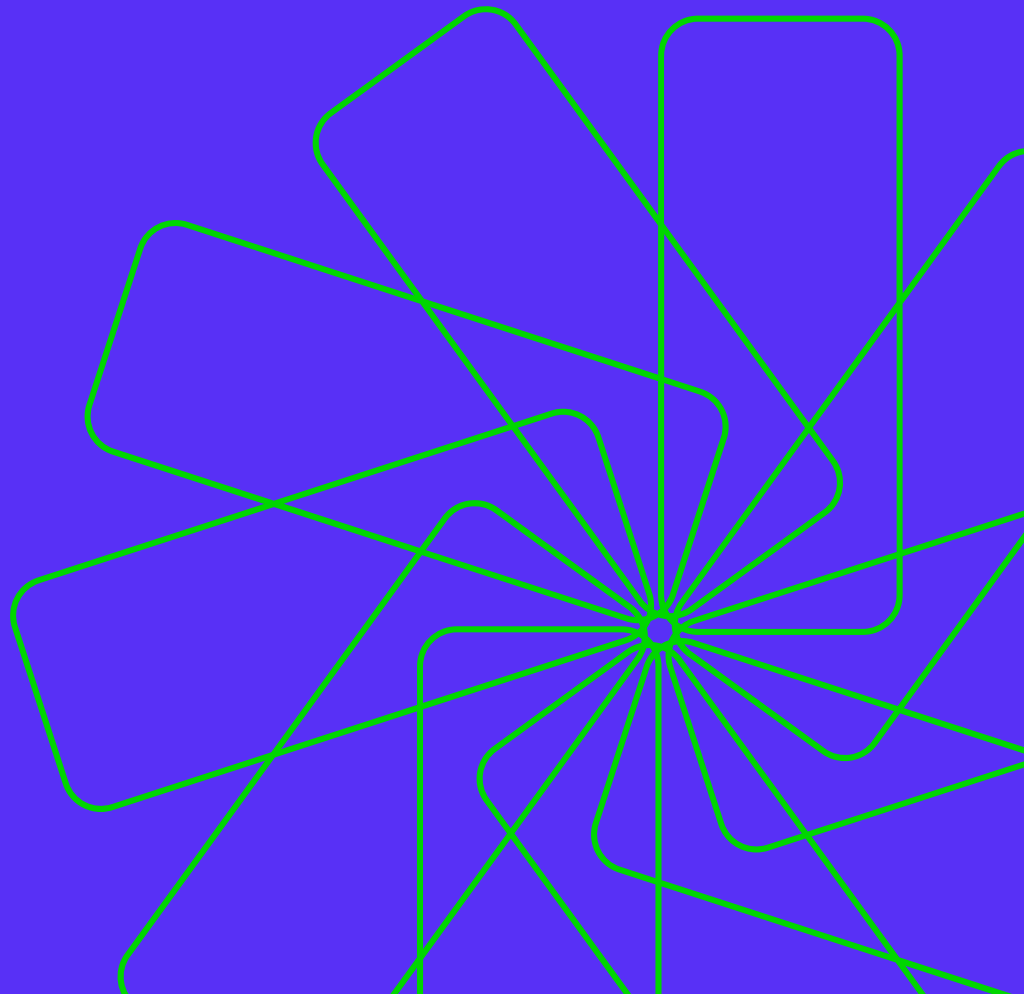
Cord: who benefits?



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What is unique about cord?

- Fastest available cell source
- Can be given T replete due to lower cGVH risk
- Low cell dose and mismatch means more concern re graft failure and need for high dose immune suppression at start

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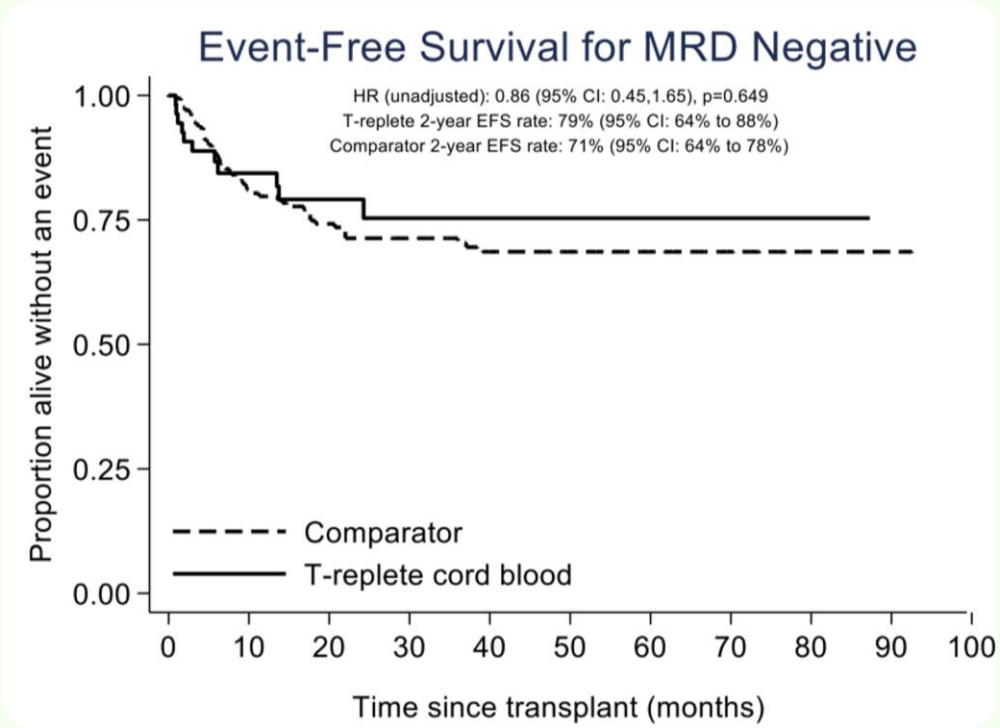
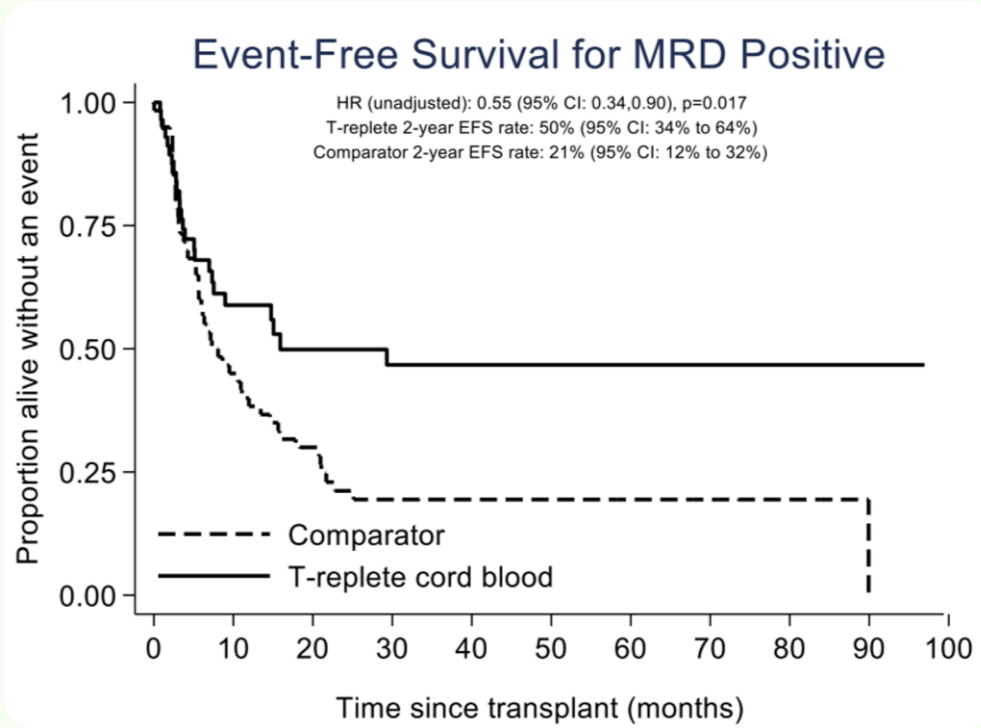
Cord is Superior for Highest Risk Paediatric Patients





UK paediatric study 2014-2021. n=112 (cord) 255 (other graft sources) AML/MDS.

CBT recipients' higher risk (46% refractory disease)

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Hogan et al, Blood Adv, 2023

Cord is Superior for Highest Risk Paediatric Patients

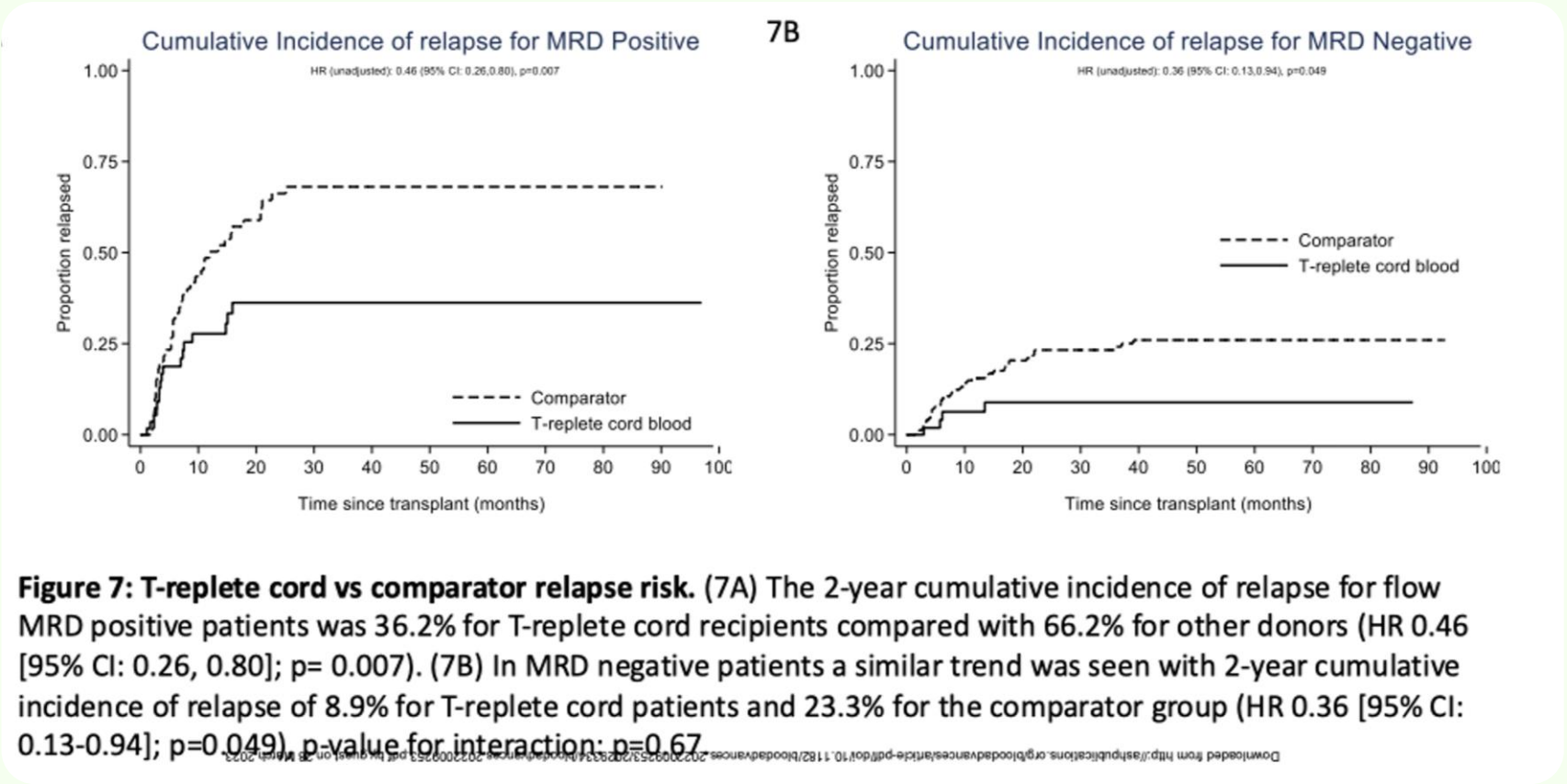

Figure 7: T-replete cord vs comparator relapse risk. (7A) The 2-year cumulative incidence of relapse for flow MRD positive patients was 36.2% for T-replete cord recipients compared with 66.2% for other donors (HR 0.46 [95% CI: 0.26, 0.80]; p= 0.007). (7B) In MRD negative patients a similar trend was seen with 2-year cumulative incidence of relapse of 8.9% for T-replete cord patients and 23.3% for the comparator group (HR 0.36 [95% CI: 0.13-0.94]; p=0.049). p-value for interaction: p=0.67

Hogan et al, Blood Adv, 2023

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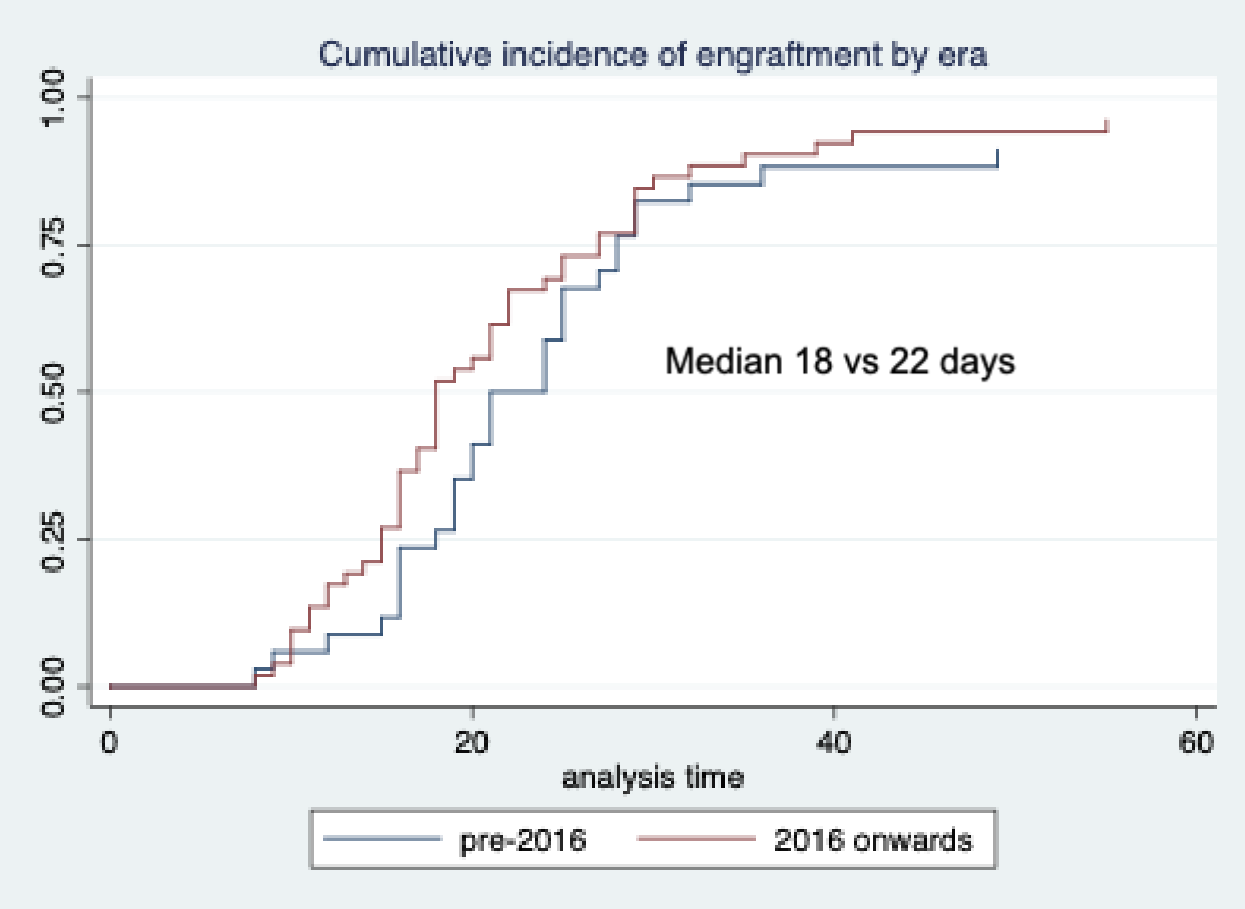
Engraftment slow but improving compared to initial analyses



n=96

haematological malignancies

Transplanted 2009-2021

Median age 42 (18-70)

5% primary graft failure

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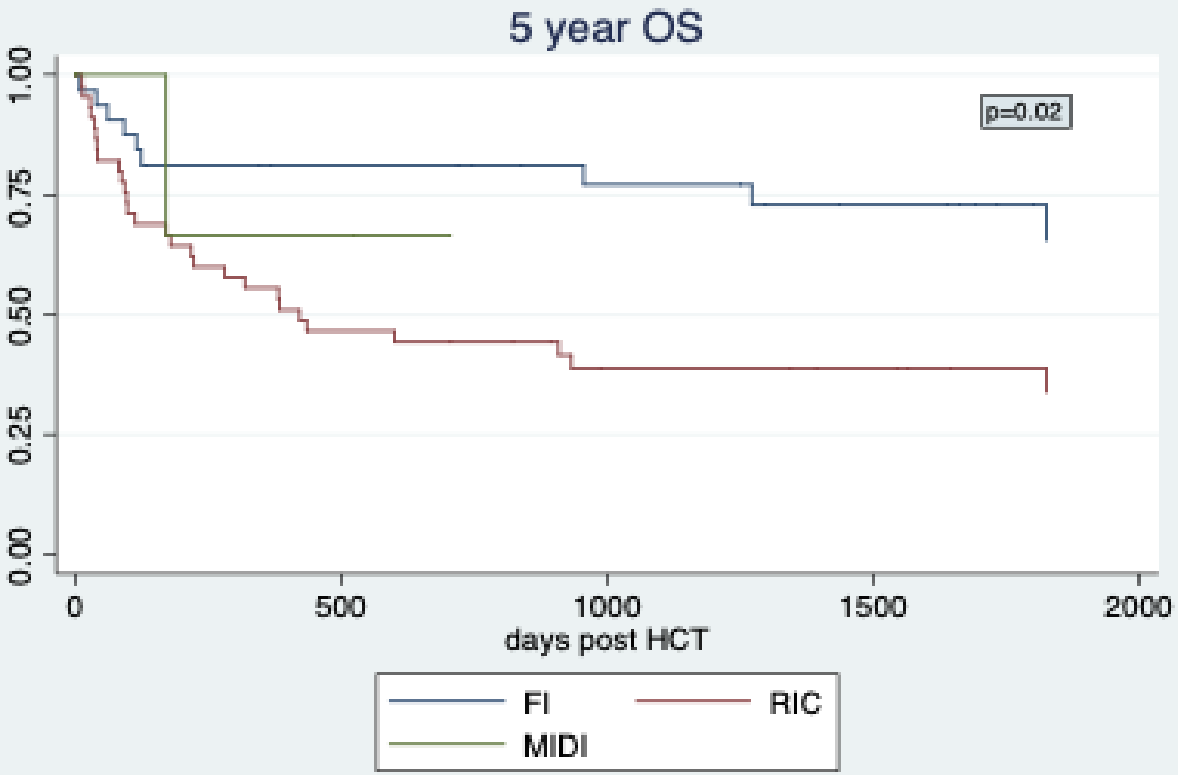
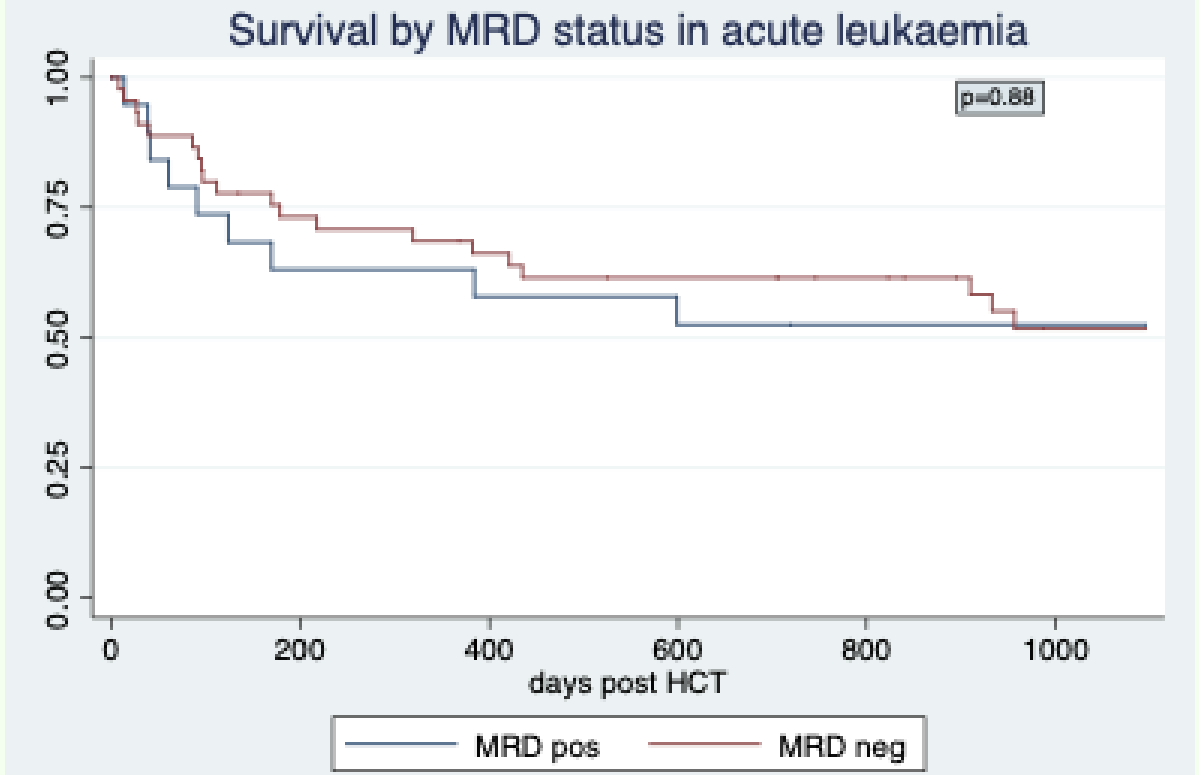
Cord can overcome MRD in adults too





RMH data

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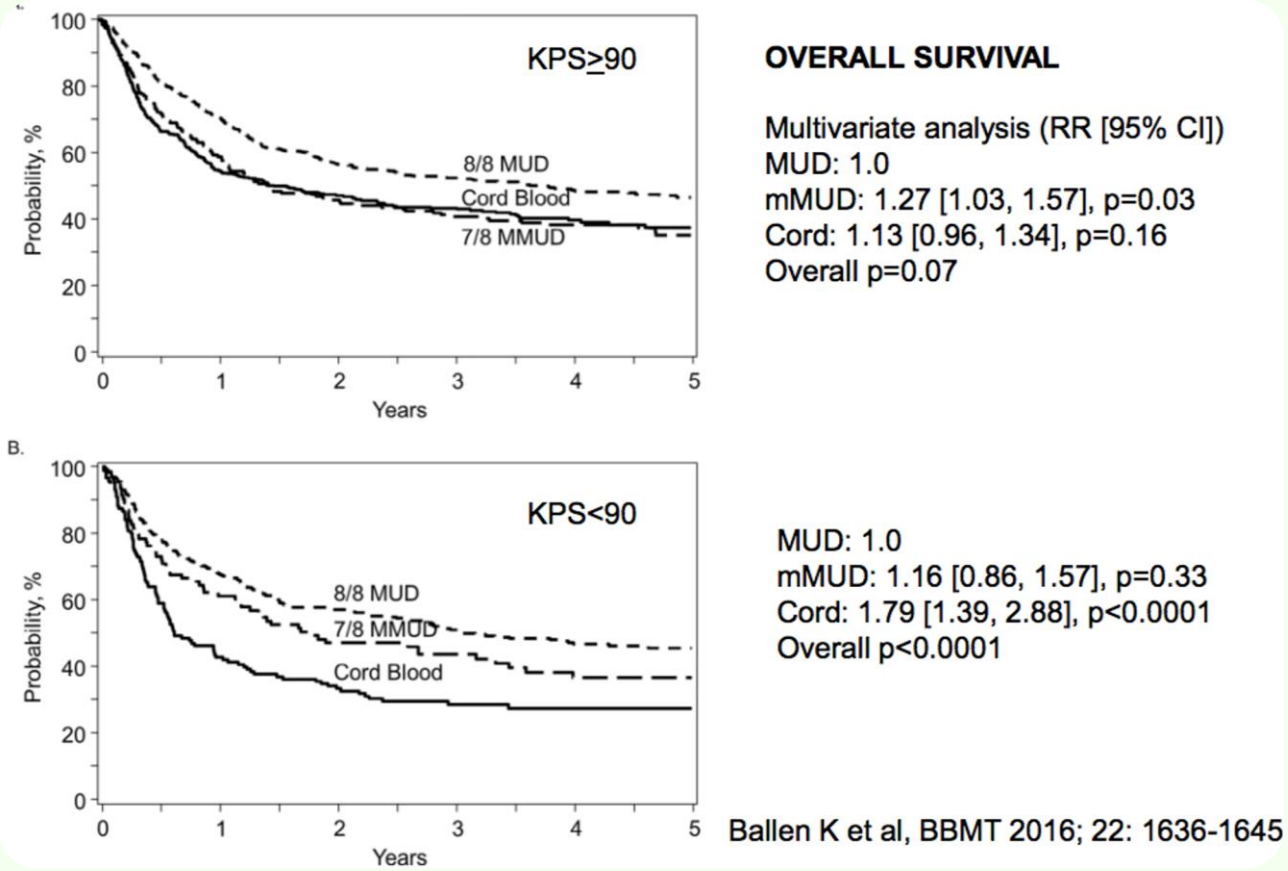
Challenges: Poor performance status patients do badly



OVERALL SURVIVAL

Multivariate analysis (RR [95% CI])
MUD: 1.0
mMUD: 1.27 [1.03, 1.57], p=0.03
Cord: 1.13 [0.96, 1.34], p=0.16
Overall p=0.07

MUD: 1.0
mMUD: 1.16 [0.86, 1.57], p=0.33
Cord: 1.79 [1.39, 2.88], p<0.0001
Overall p<0.0001

Ballen K et al, BBMT 2016; 22: 1636-1645

Retrospective CIBMTR analysis

N=1781 adults with Acute Leuk

Ballen et al, BBMT 2016

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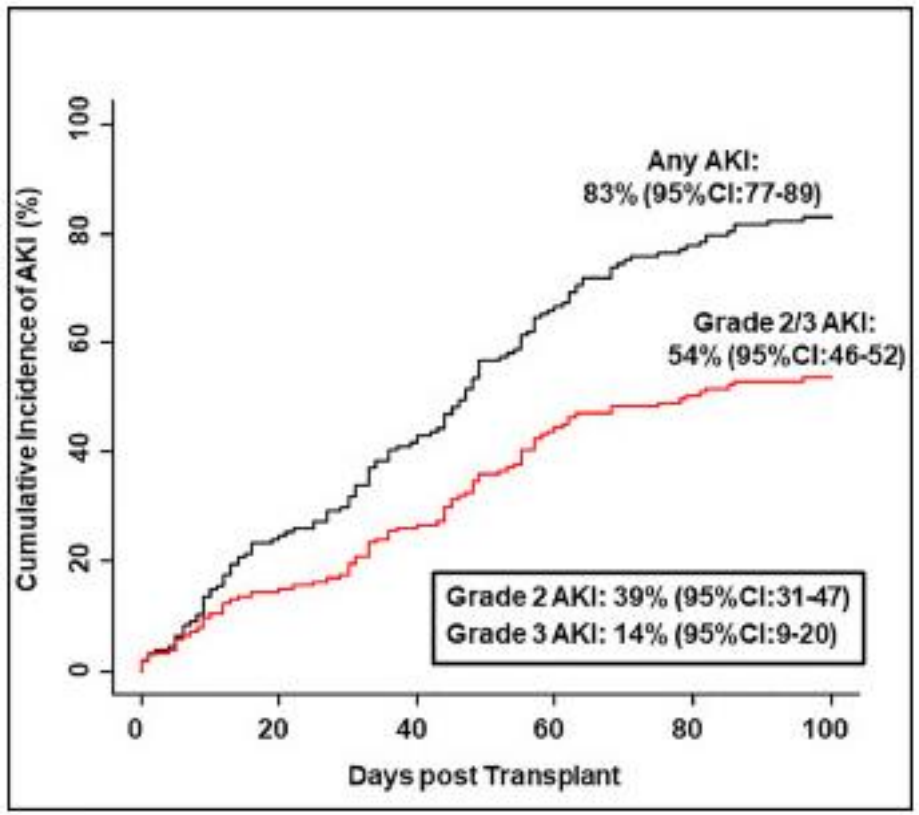
Challenges in Cord Transplants

D100 acute kidney injury is high post cord
1/3 of these will have chronic kidney disease
at 2 years



Gutarts et al BBMT 2020

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Case study- patient CP

32yo female 51kg. high risk B-ALL with TP53 mutation
Treated with UKALL 2019 chemo
MRD pos post cycle 1 then in remission.
Fit and coped well with chemo.

Donor options

- 3 sibs in Philappines.
  - 1 refused UK visa
  - Tried to arrange typing and potential collection in Singapore but logistics failed
- UD search: 2x 11/12 DPB1 permissive
- Cord search: 6/8 single cord

- Young CMV matched 11/12 permissive selected Nov 2022

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Case study- patient CP

23rd December 2022: Selected UD failed medical
Other 11/12 became uncontactable

17th Jan : Decision to switch to cord
6/8 unit with TNC 6.9x10^7/kg and CD34 5.2x10%5/kg selected

2nd Feb: 77% TNC viability 98% CD34 viability CFU growth

Admitted 2/2/23 for full intensity cord allograft

Engrafted Day+12 . Discharged 6th March
Post transplant issues with infections but remains well and leukaemia free.

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Who benefits most

High risk acute leukaemia esp MRD positive
Fit patients
Small patients
Rescue option when initial donor fails

Not so good for ….
Poor renal function
Less fit pts
Active infections/plt refractory/multiple comorbidities
Patients with high risk of graft failure

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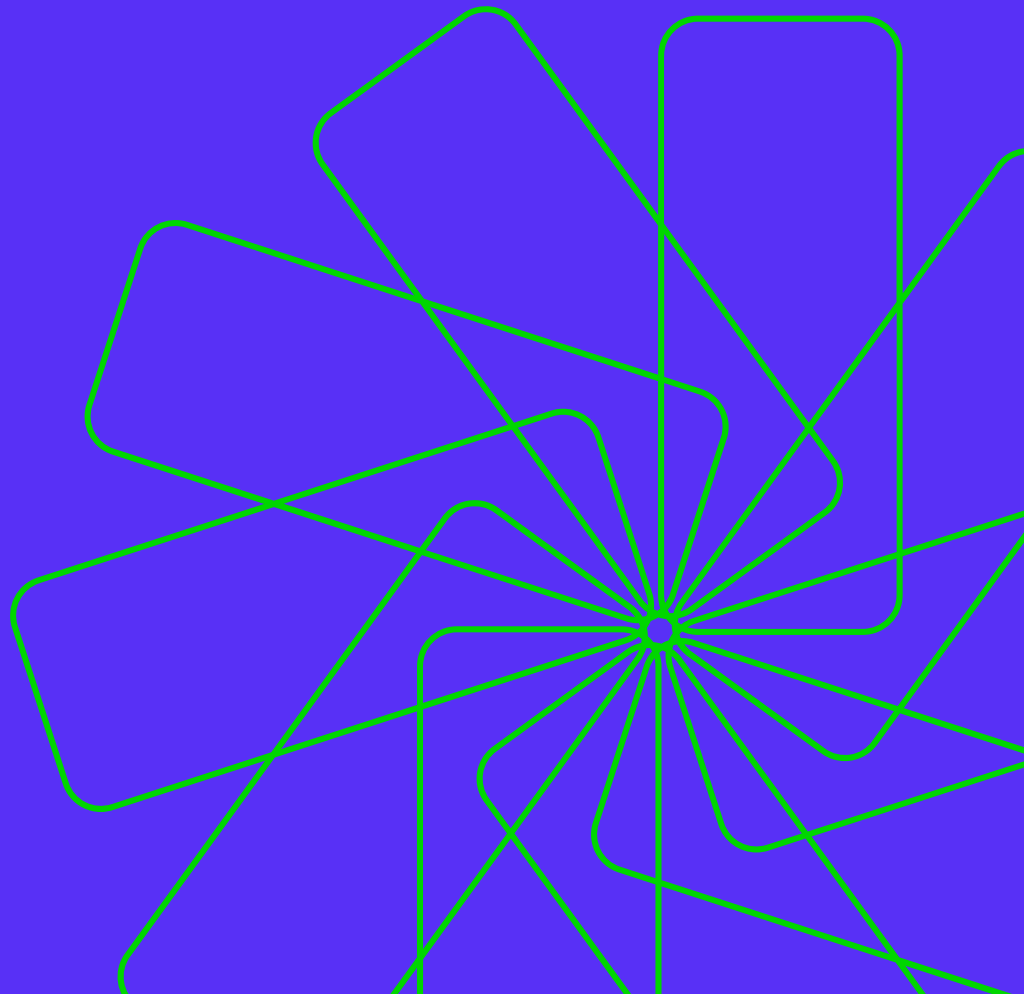
Haplo: who benefits?



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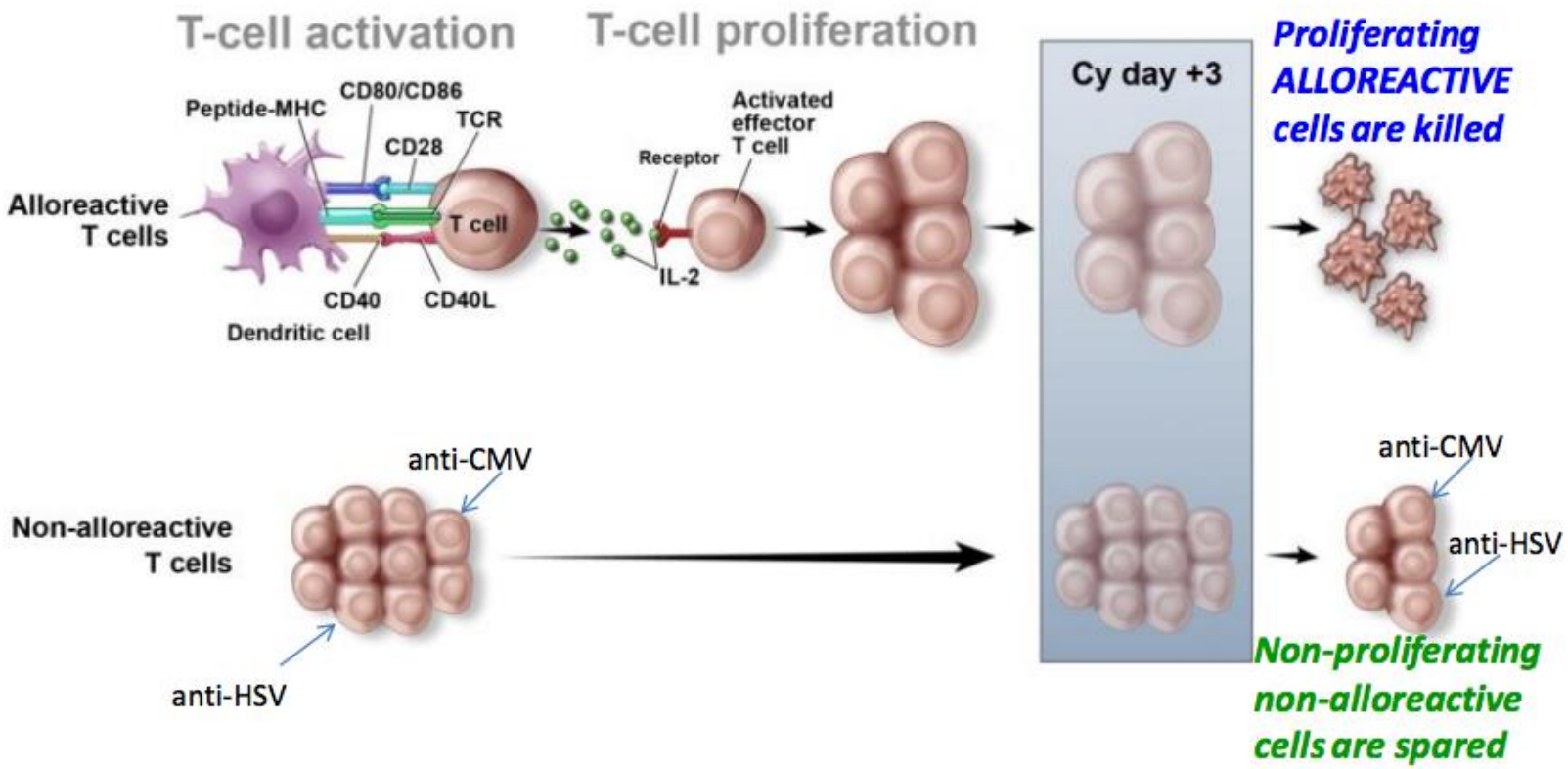
Selective allodepletion with high dose, post-transplantation cyclophosphamide (PT/Cy)



Luznik L et al Blood 2001

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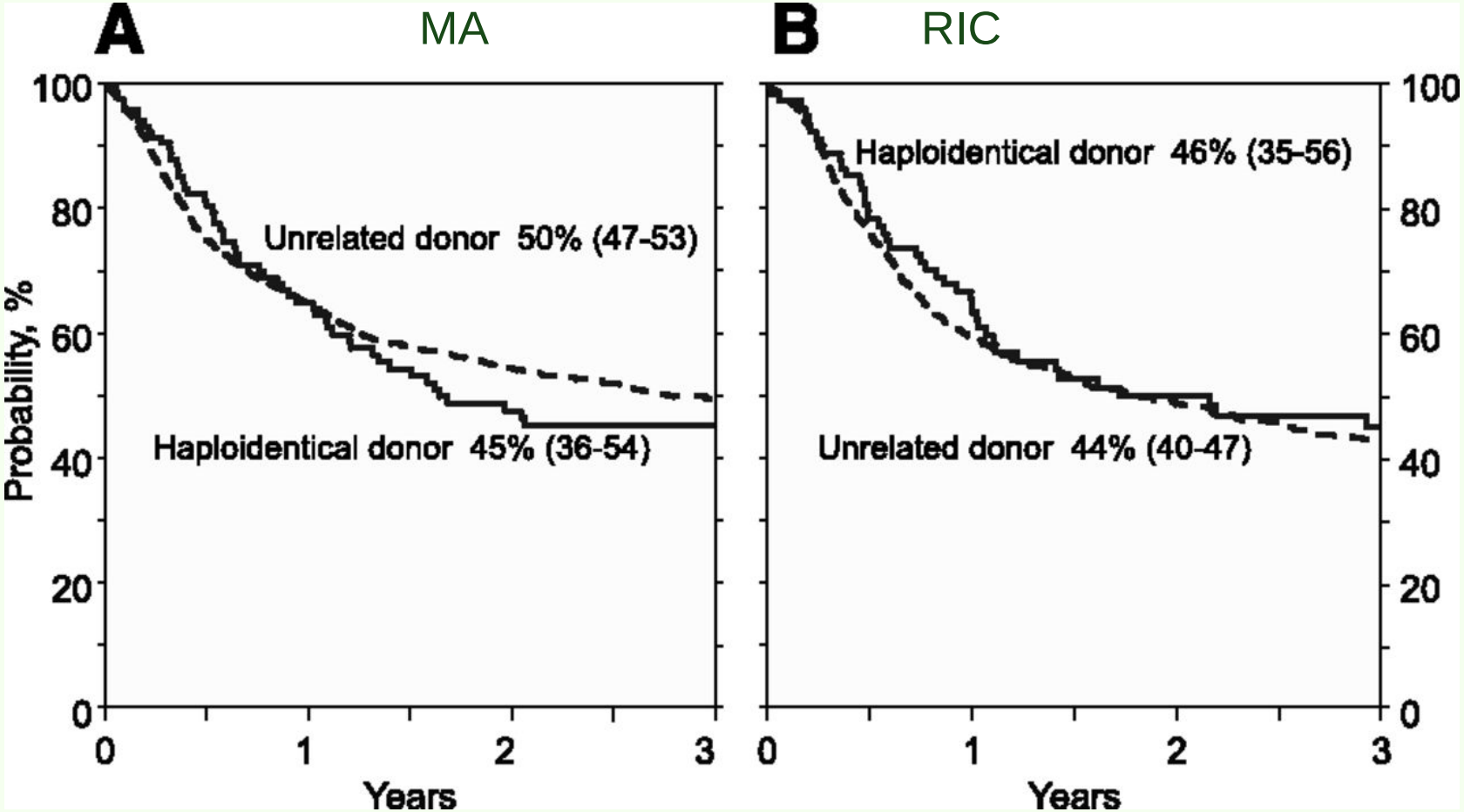
Haplo vs MUD: OS



Retrospective CIBMTR study

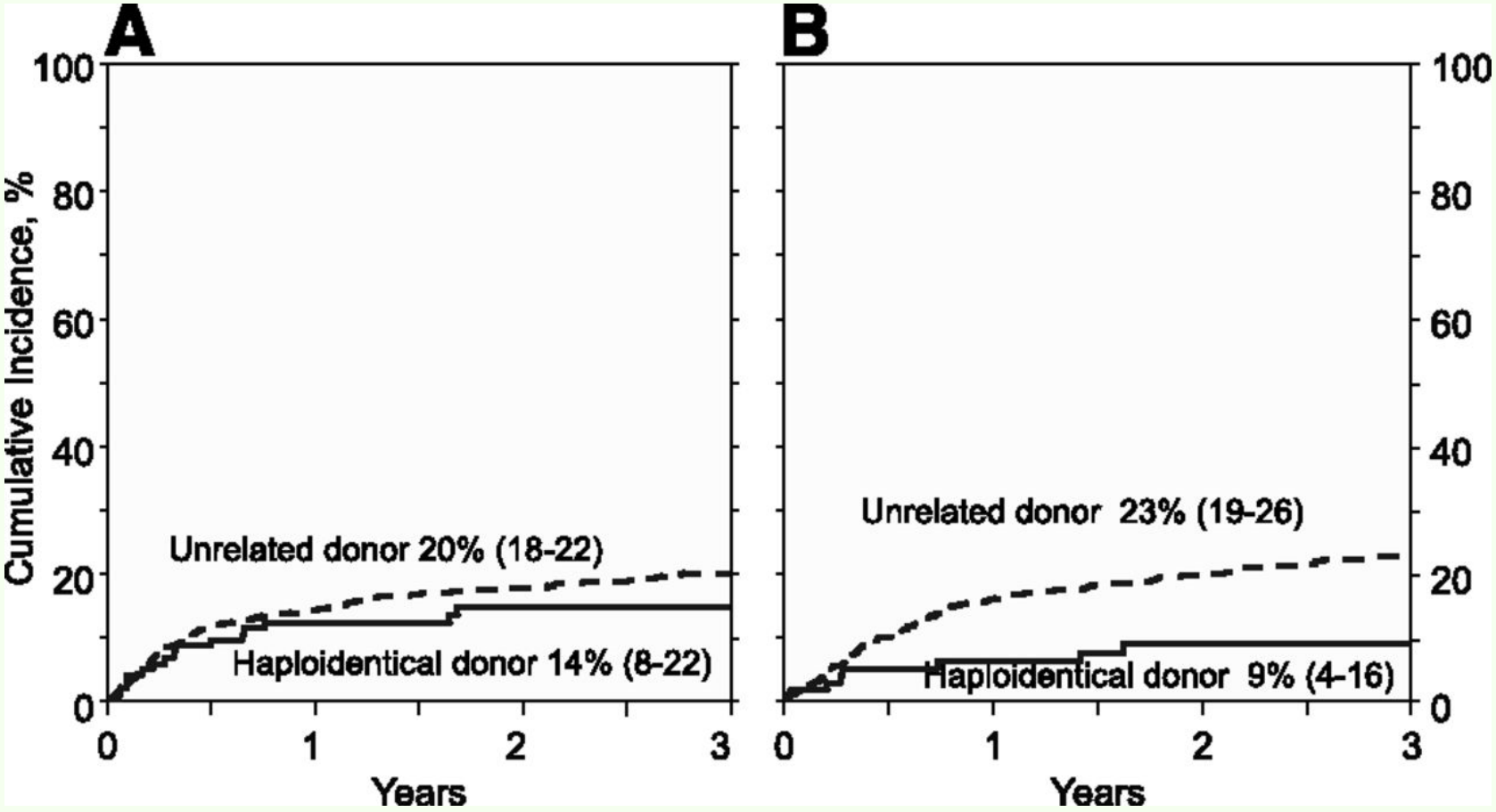
n = 1982 patients
192 haplo with PTCy vs
1790 8/8 UDs without PTCy

10% primary graft failure in haplo
But 82% BM in haplo

Ciurea et al, Blood 2015

Haplo vs UD: NRM

MA RIC



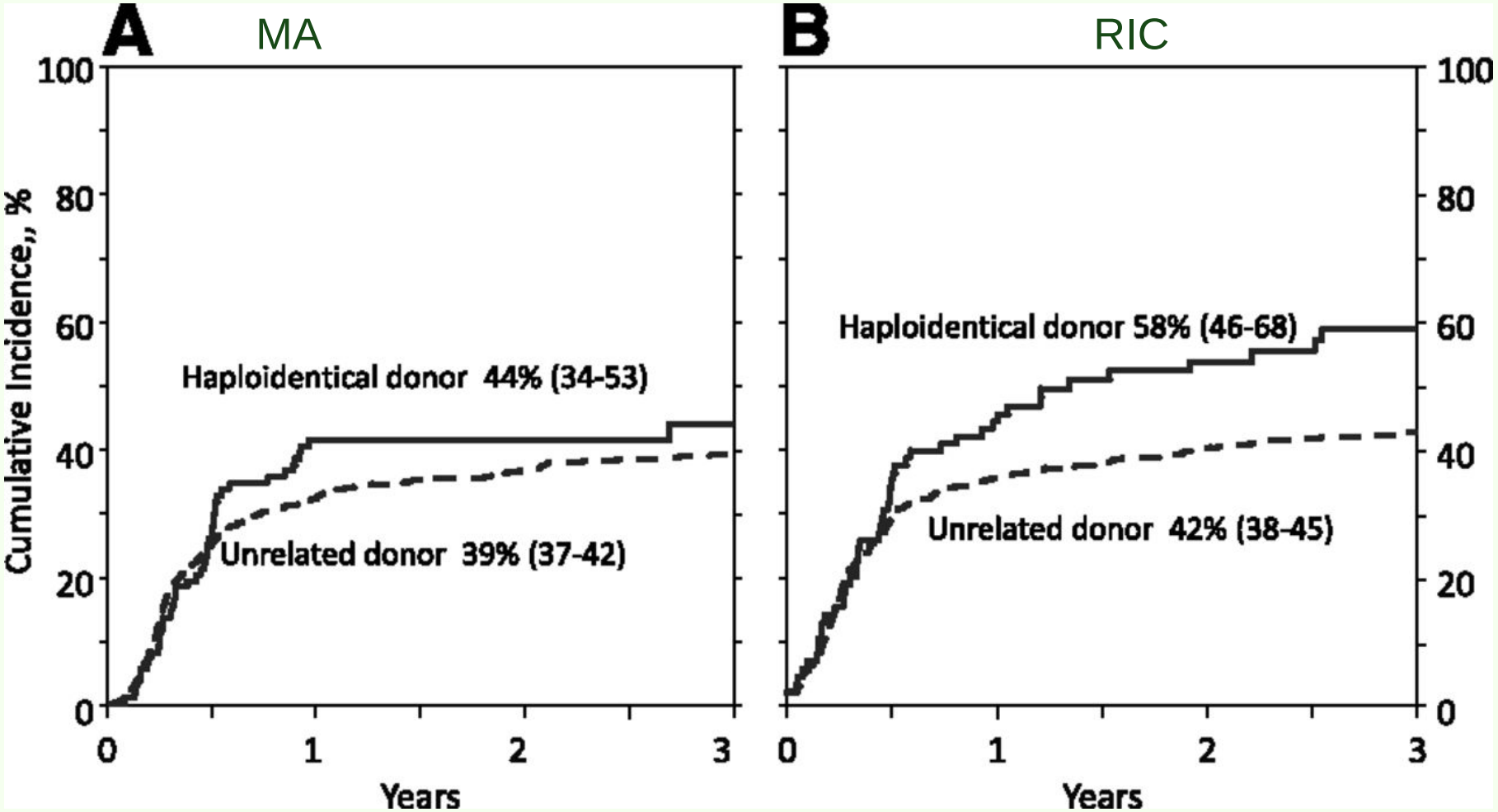
Retrospective CIBMTR study

n = 1982 patients
192 haplo with PTCy vs
1790 8/8 UDs without PTCy

Higher NRM in RIC UD.

Ciurea et al, Blood 2015

Haplo vs UD: Relapse



Retrospective CIBMTR study

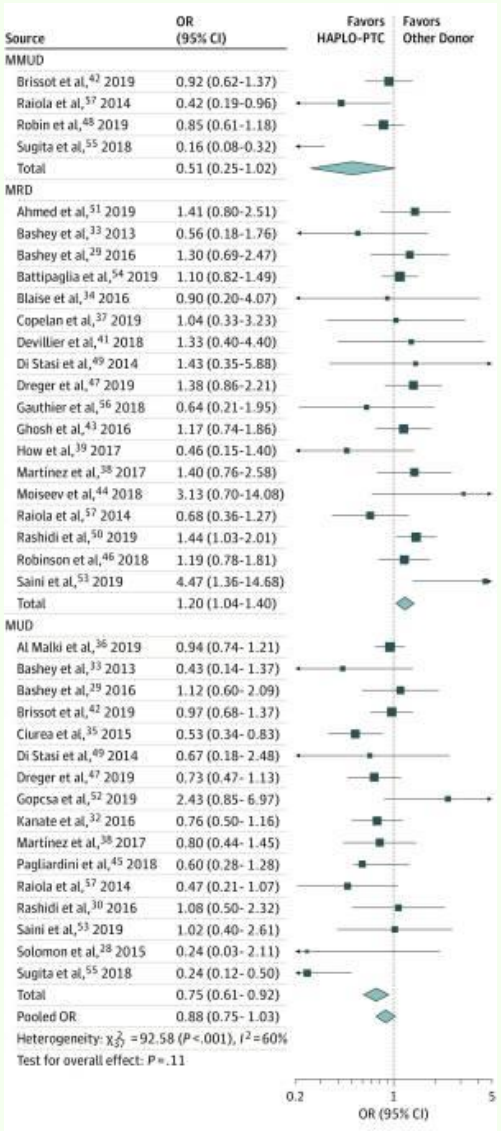
n = 1982 patients
192 haplo vs 1790 8/8 UD

Higher relapse in Haplo RIC (but 82%BM)

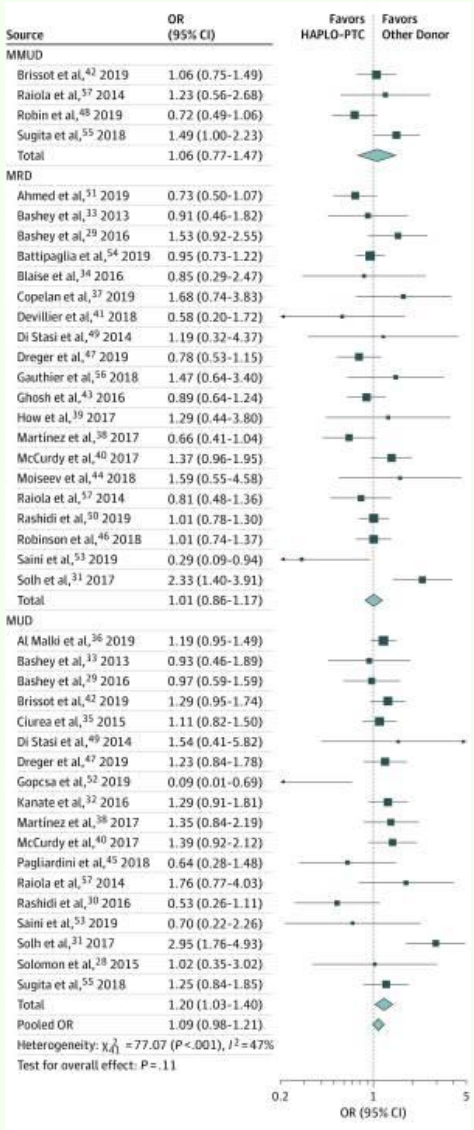
Ciurea et al, Blood 2015

Haplo vs other donor sources

NRM



Relapse



Metanalysis 30 studies
22974 adult patients haem cancers
MRD vs MUD vs MMUD vs Haplo
5 haplo studies used PBSC, 3 used BM

OS pooled ORs were
MRDs OR= 1.17 (95% CI, 1.05-1.30; I^2 = 1%)
MUD OR=1.06 (95% CI, 0.96-1.18; I^2 = 0%)
MMUD OR=0.79 (95% CI, 0.65-0.97; I^2 = 0%).

Gagelmann N et al JAMA oncol 2023

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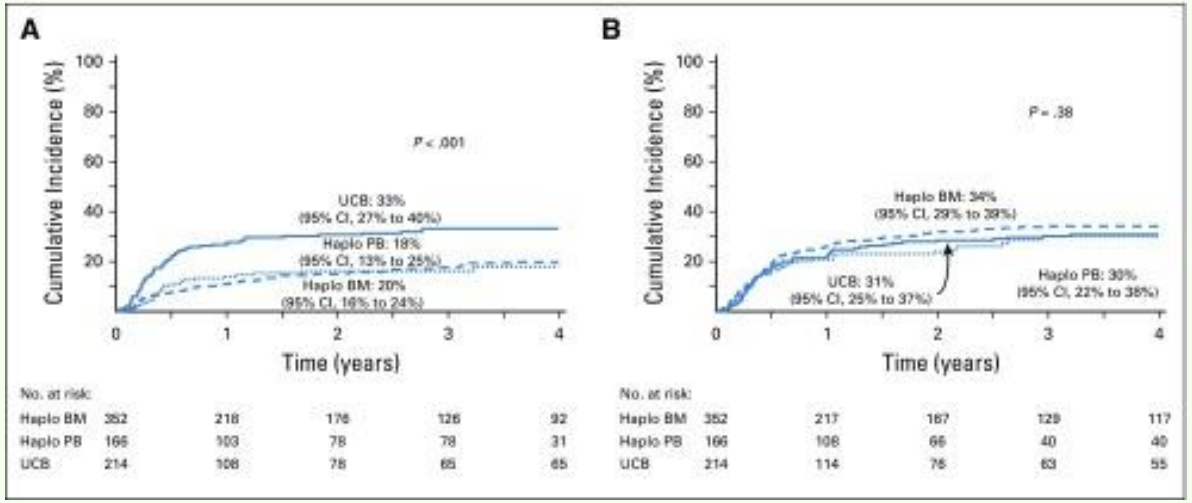
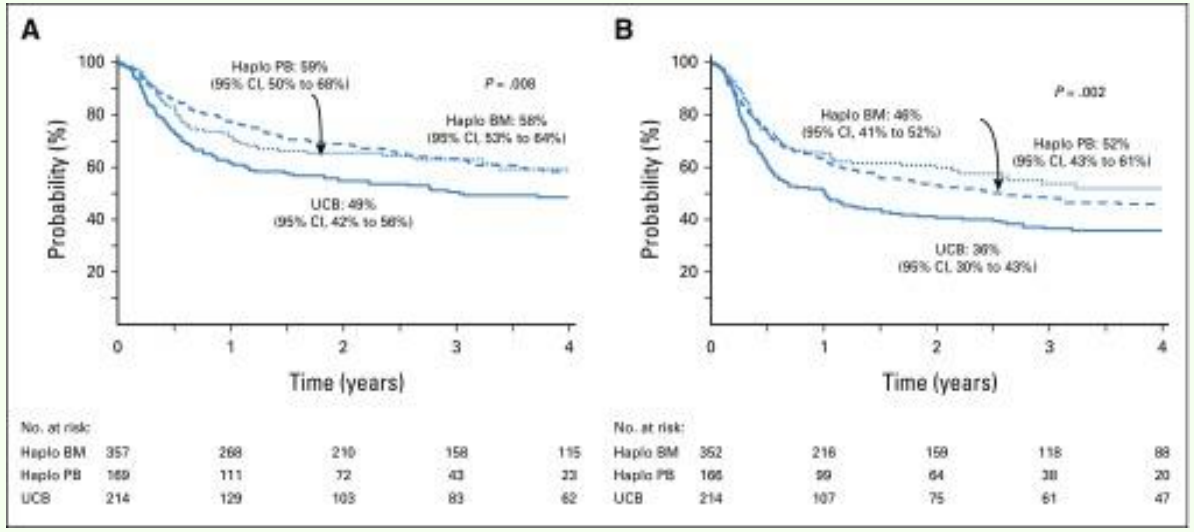
Haplo vs Cord in Lymphoma

TRM



Relapse

OS



PFS

Retrospective
EBMT/Eurocord/CIBMTR study
2009-2016
n = 740 patients
RIC

Fatobene et al, JCO 2020

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Challenges of Haplo: CRS and Cardiotoxicity

Early cardiotoxicity is higher in PTCy transplants
Linked to age, previous Cy exposure and Cy dose
Most improve with appropriate treatment

n=331 mix of MA and RIC

TABLE 2 Cumulative Incidences of Cardiac Events Within 100 Days After Transplantation

	No PT-Cy		PT-Cy		
	n (%)	% (95% CI)	n (%)	% (95% CI)	p Value
Left ventricular systolic dysfunction	6 (2.1)	2.1 (0.7–4.9)	20 (14.3)	(8.3–19.8)	0.001
Acute pulmonary edema	4 (2.1)	2.1 (0.7–4.9)	9 (6.7)	(3.3–11.8)	0.036
Arrhythmia	7 (3.1)	3.1 (1.3–6.3)	5 (3.1)	(1–7.1)	0.95
Pericarditis	2 (0.5)	0.5 (0–2.7)	5 (3.8)	(1.4–8.1)	0.09
Acute coronary syndrome	1 (0.5)	0.5 (0–2.7)	2 (1.5)	(0.3–4.8)	0.36

Cumulative incidence was used to estimate all early cardiac events, with relapse and death being the competing events.
CI = confidence interval; PT-Cy = post-transplant cyclophosphamide.

CRS occurs very frequently D+2 to D+4
Severe CRS (Grade 3) has been associated with worse NRM and OS
Tocilizumab can be used BUT some studies have suggested an impact on engraftment and chronic GVHD
Viral reactivation also remains an issue

Dulery et al JACC 2021

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Case study- patient PT

64 yo female. Afrocaribbean.

- Diabetes on 3 agents.
- Hypertension.
- Osteoarthritis with limited mobility
- Palpitations with recording loop
- Asthma

Diagnosed with TPLL July 2024.
Treated with campath which she is tolerating ok except CMV reactivation.

Donor search

- No suitable sib.
- UD search No 10/10. Has 9/10 DPB1 NP 37 yo/46 yo/49 yo options.
- 3 Children

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Case study- patient PT

Children

- 1 Daughter in US. Haplo match. CMV match
- 1 Son in UK Haplo match CMV neg
- 1 daughter in UK – not typed as needlephobic.

Cords

1x 5/8, some 4/8s. All slightly borderline cell doses.

Decision to work up daughter via NMDP.

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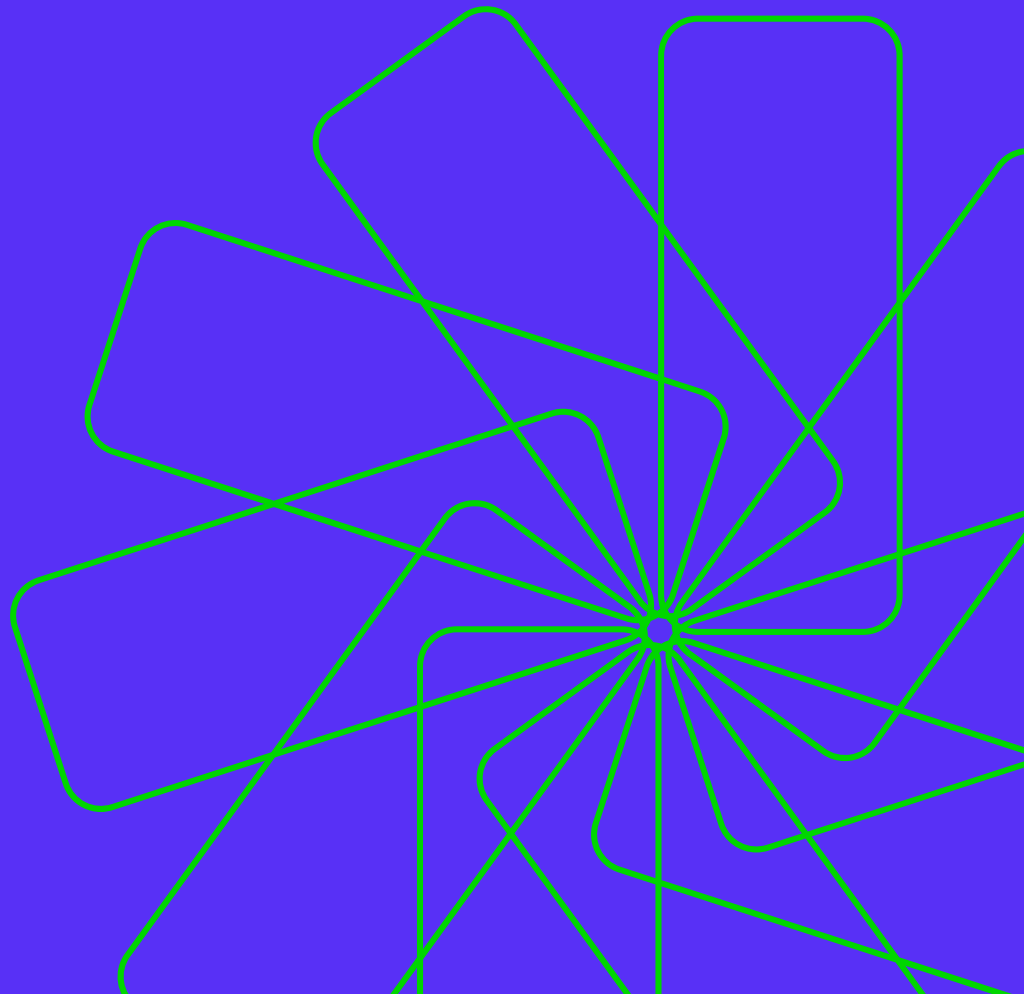
Who benefits

A broad range of patients in remission (possibly without the worst disease risk for RIC)
Patients lacking good cord options
Patients with young haplo options
Rescue option when first choice donor fails and there is time to organise a related donor

Less optimal if....
V high risk leukaemia
HLA antibodies
Only BM available
Patients at high risk of cardiac tox.

Mismatched unrelated donor PTCy Transplants



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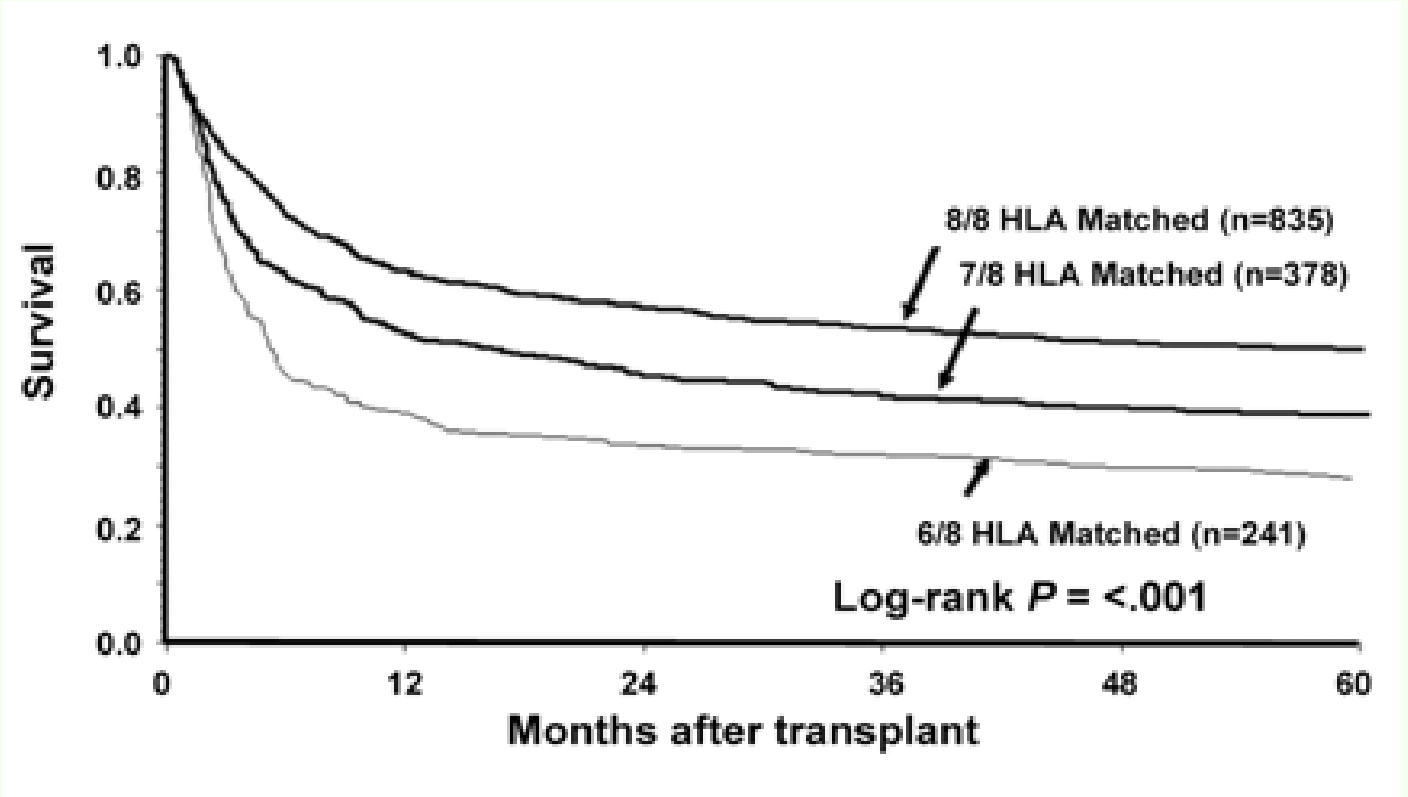
Historically poor results from <7/8 transplants

N=1545 URD pairs
T replete
Retrospective



50%

39%

28%

Lee et al, Blood 2007

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3yr results NMDP sponsored prospective study MMUD

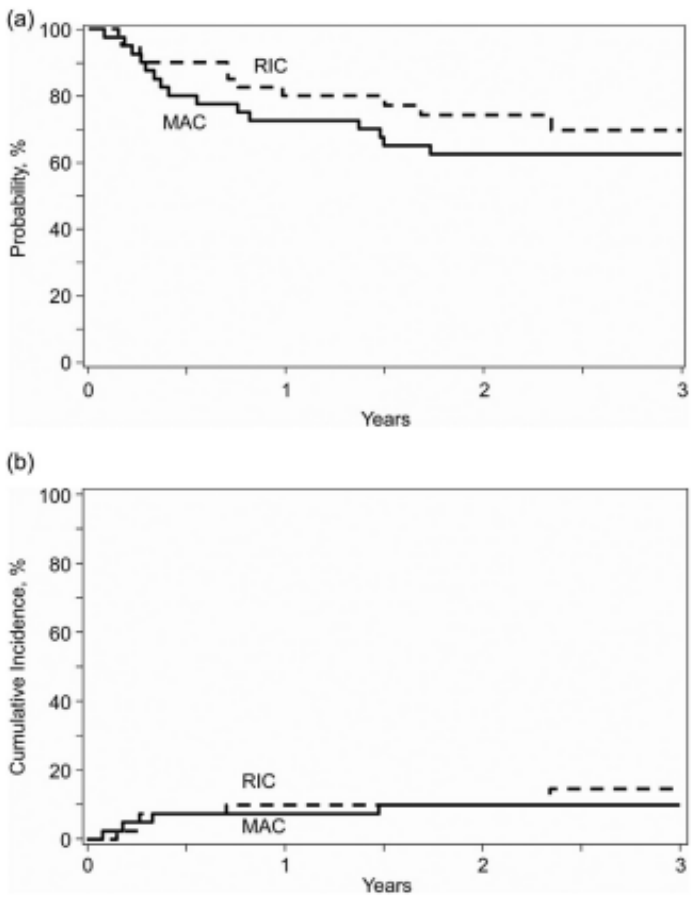


Figure 1. Three-year OS (A) and NRM (B) by conditioning intensity.

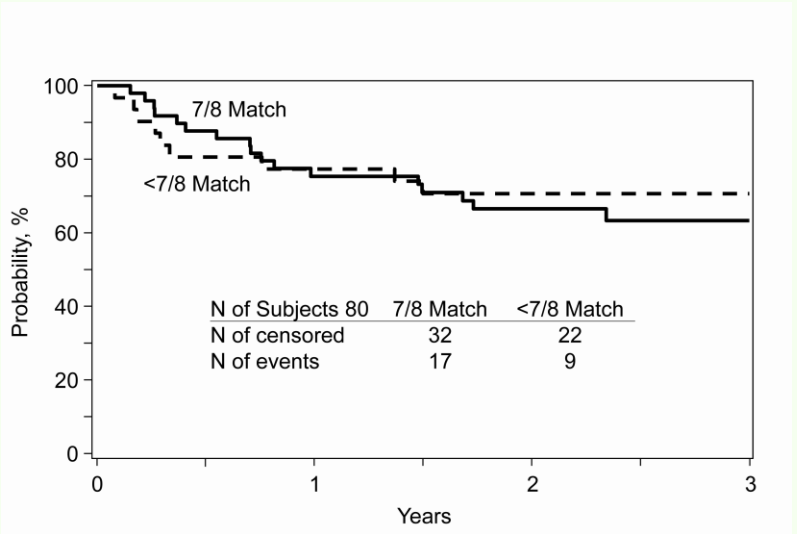
N=80 Mismatched UDs with PTCy

BM infused

39% donors <7/8 match
48% pts from ethnic miniorities
54% had HCT-CI >2

1 yr OS 76%

No outcome difference by HLA match grade



Shaw et al, JCO 2021

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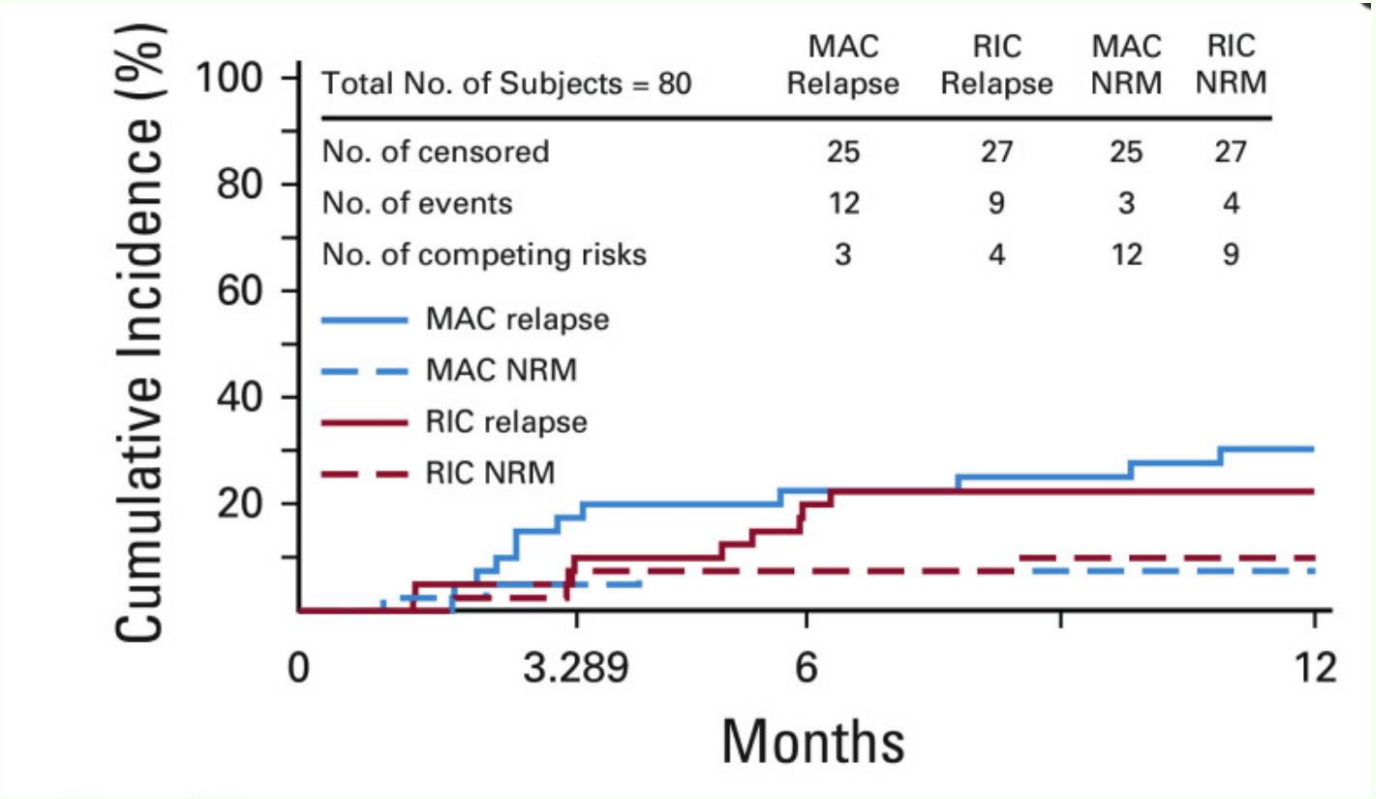
3yr results NMDP sponsored prospective study



RIC relapse of 29% at 3 years

MAC 51% at 3 years

NRM is low but relapse at 12 months is relatively high

MAC doesn't appear protective against relapse

Shaw et al, JCO 2021

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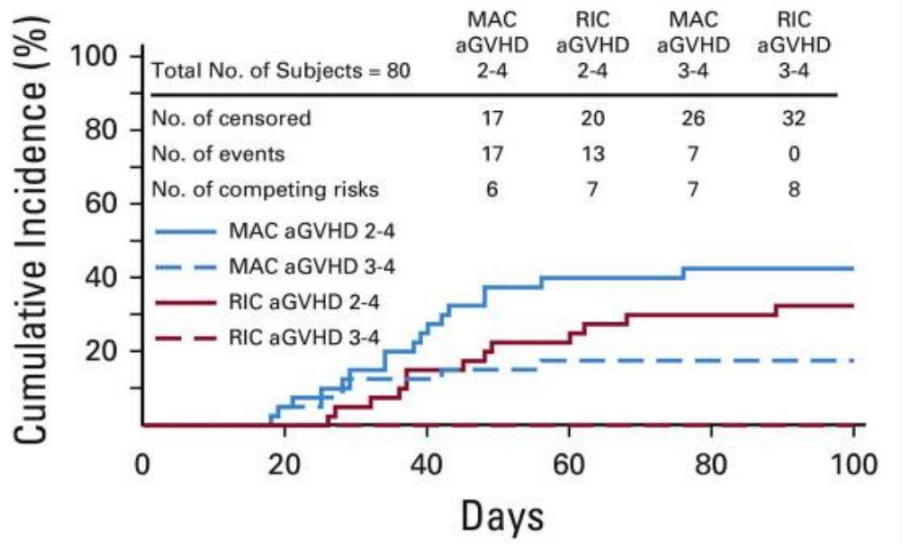
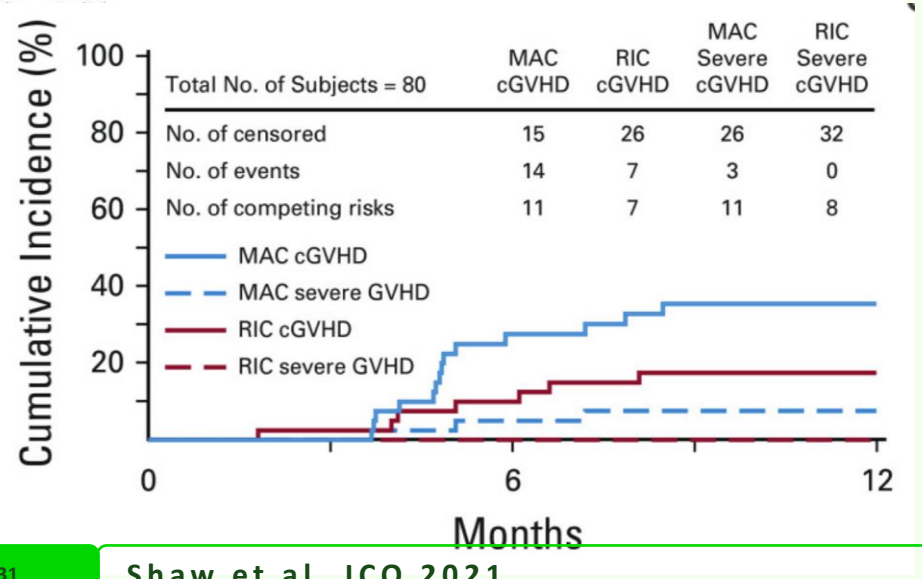
3yr results NMDP sponsored prospective study





Low risk of severe aGVHD

Similar to Haplo PTCy studies

5% graft failure (but BM)

Low cGVHD

Shaw et al, JCO 2021

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MMUD vs MUD with PTCy vs CNI: US data

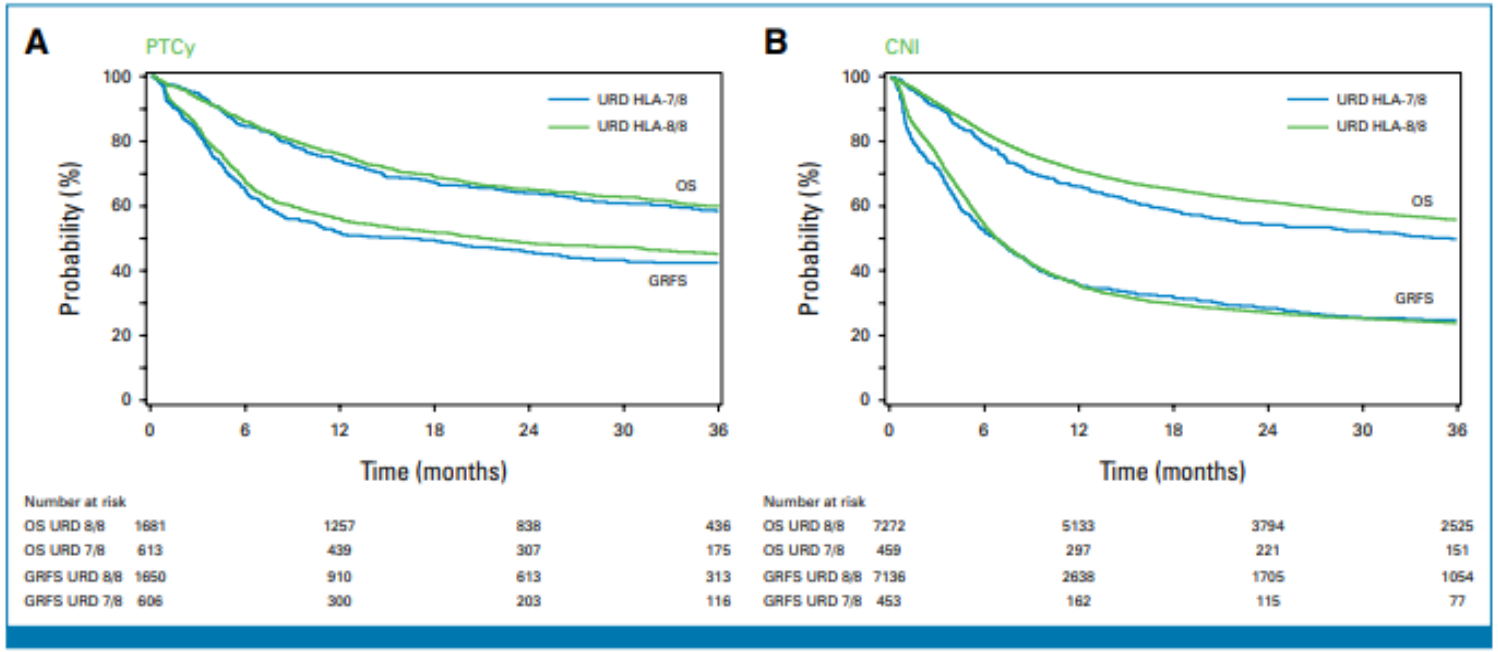
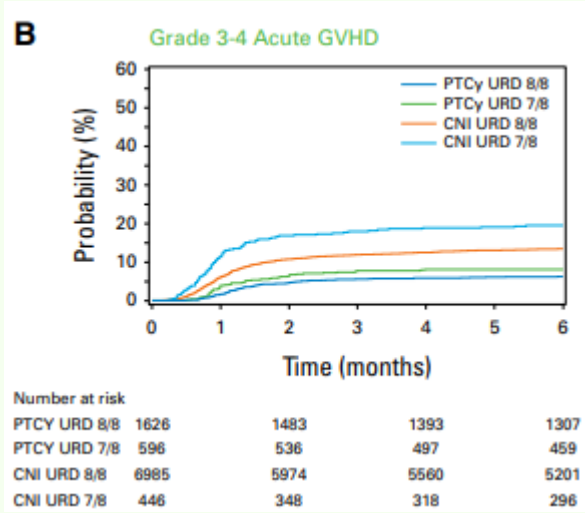
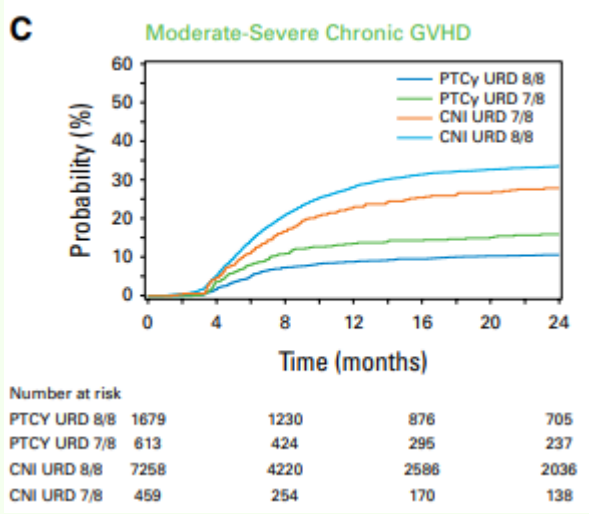


FIG 1. Adjusted Kaplan-Meier estimates of GRFS and OS in recipients of (A) PTCy and (B) CNI. CNI, calcineurin inhibitor; GRFS, graft-versus-host disease-free, relapse-free survival; HLA, human leukocyte antigen; OS, overall survival; PTCy, post-transplant cyclophosphamide; URD, unrelated donor.

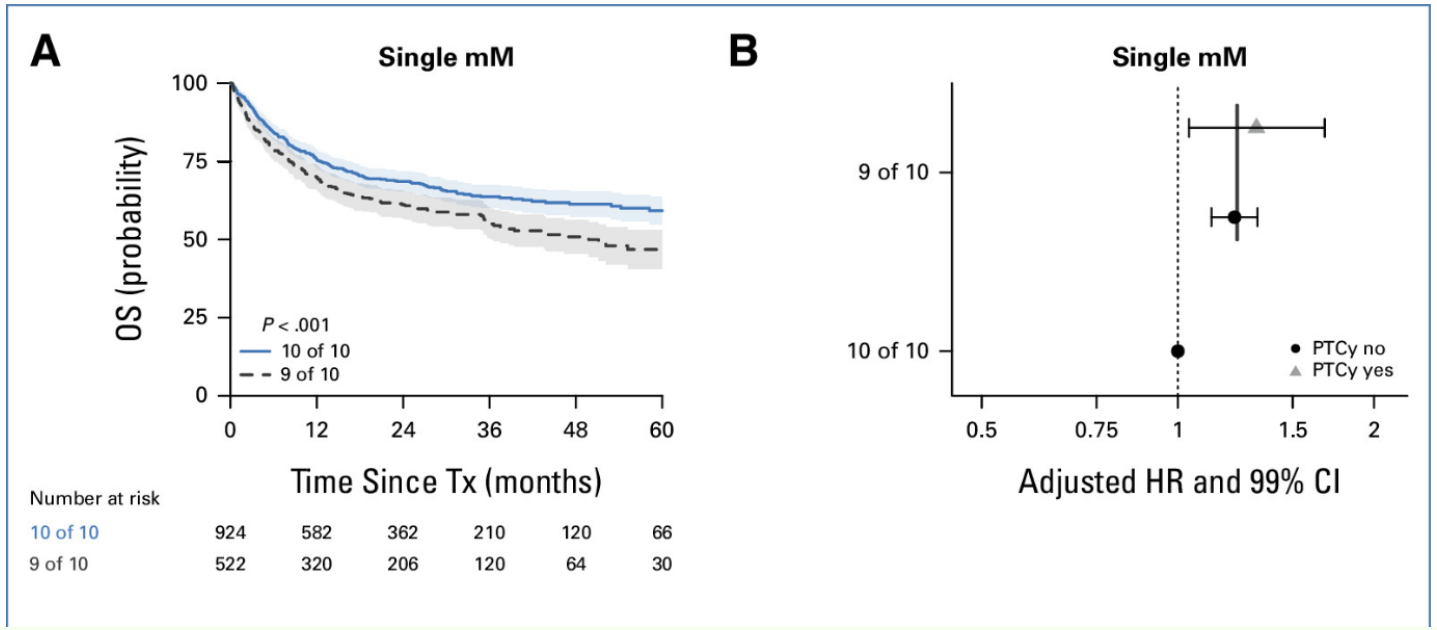




N=10,025
Retrospective
MMUD with PTCY/CNI
MUD with PTCY/CNI

Shaffer et al JCO 2024

EBMT PTCY UD Retrospective Data



N=17,200

MUD or MMUD.

24% UDs 8-9/10 match

Lower OS in MMUD with or without PTCy.

PTCy better GRFS in all

Arrieta-Bolaños et al, JCO 2024

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Case study- Patient AA

68 yo 80kg female self-paying patient
High risk AML. Negative HLA ab screen

2 x 11/12 donors failed/uncontactable
1x10/12 NP donor awaiting VT Turkish registry

2 sons in Dubai- visa issues

Cords available 5-6/8 but concerns about patient fitness and ability to afford upfront graft costs

19 yo UK 9/10 CMV mm
24yo German 9/10 CMV mm

Final decision awaiting discussion re costs and pre-transplant investigations

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Who benefits from MMUD PTCy

Patients without good cord or haplo options

Patients with HLA antibodies (easier to find MMUD than haplo/cord without DSAs)

Patients who need a back-up donor

To allow us to select on secondary donor characteristics (Age/Virology matching status) ...More data needed

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Conclusions

There is no single best donor source for all patients.

Cord has good anti-leukaemic activity but high NRM in unfit patients

Haplo has a solid evidence base, particularly in the less high risk setting but viral infections and cyclophosphamide toxicites remain an issue

We need results of prospective studies to confirm effect of PTCy on overcoming HLA barrier in MMUD transplants

Access trial (phase II MMUD PBSC PTCy NMDP sponsored 180 pts)
MoTD (UK Phase II)
GRAPPA (PTCy vs ATG)

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QUESTIONS

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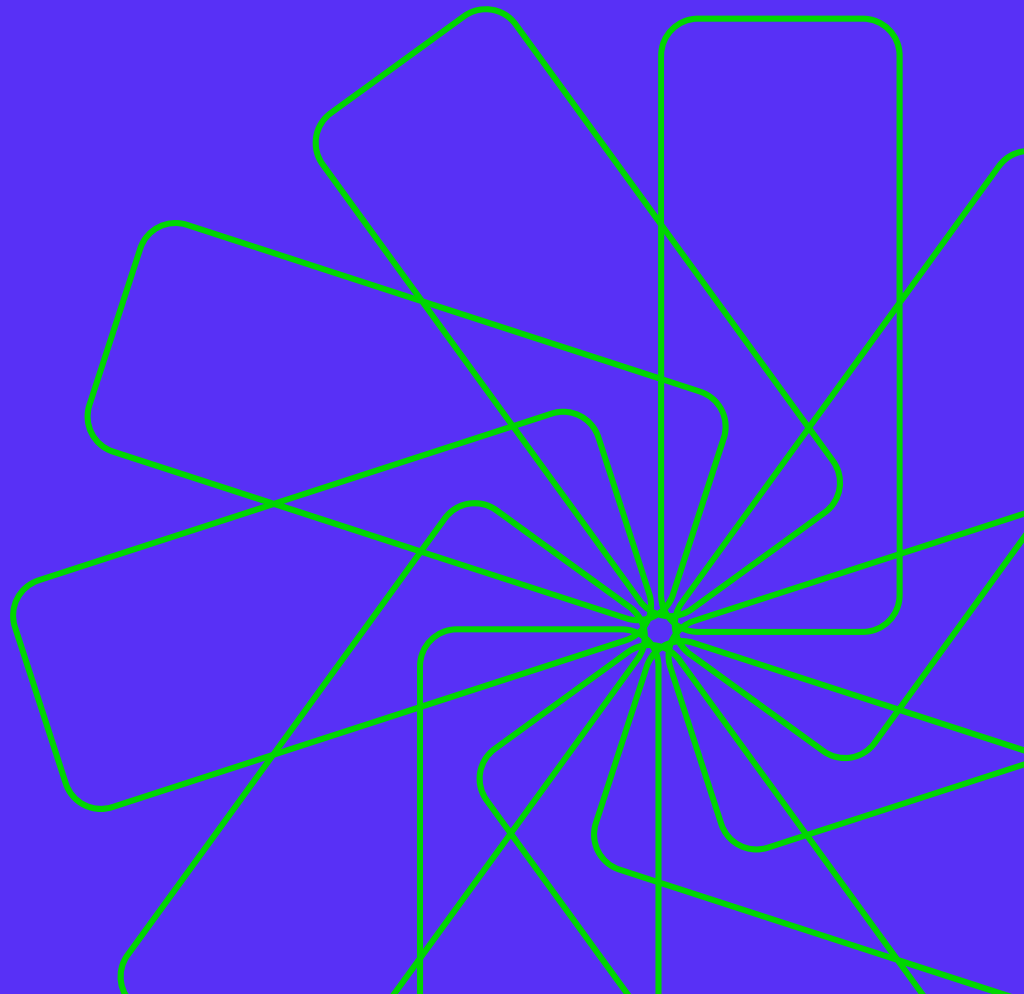

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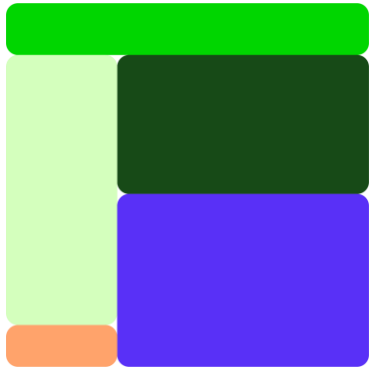
Expert fundamentals

Our expert mindset helps us communicate our pioneering, world-leading research and scientific know how to a wide audience. Whether we're sharing commercial findings, medical information, B2B collateral or research projects – this calm and technical approach underlines our credibility.

Using selective colours and more detailed, outline styles it helps us appear precise and defined in everything we do. A more scientific, controlled approach to photography inspires trust and reinforces the message that Anthony Nolan is home to some of the world's most pioneering and progressive experts.

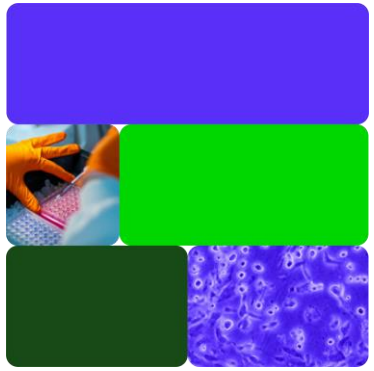
01

More use of the darker shades in palette



02

Slightly more controlled use of cell block system



03

More use of microscopic / zoomed in photography