Haploidentical Transplantation: The Answer to our Donor Problems?

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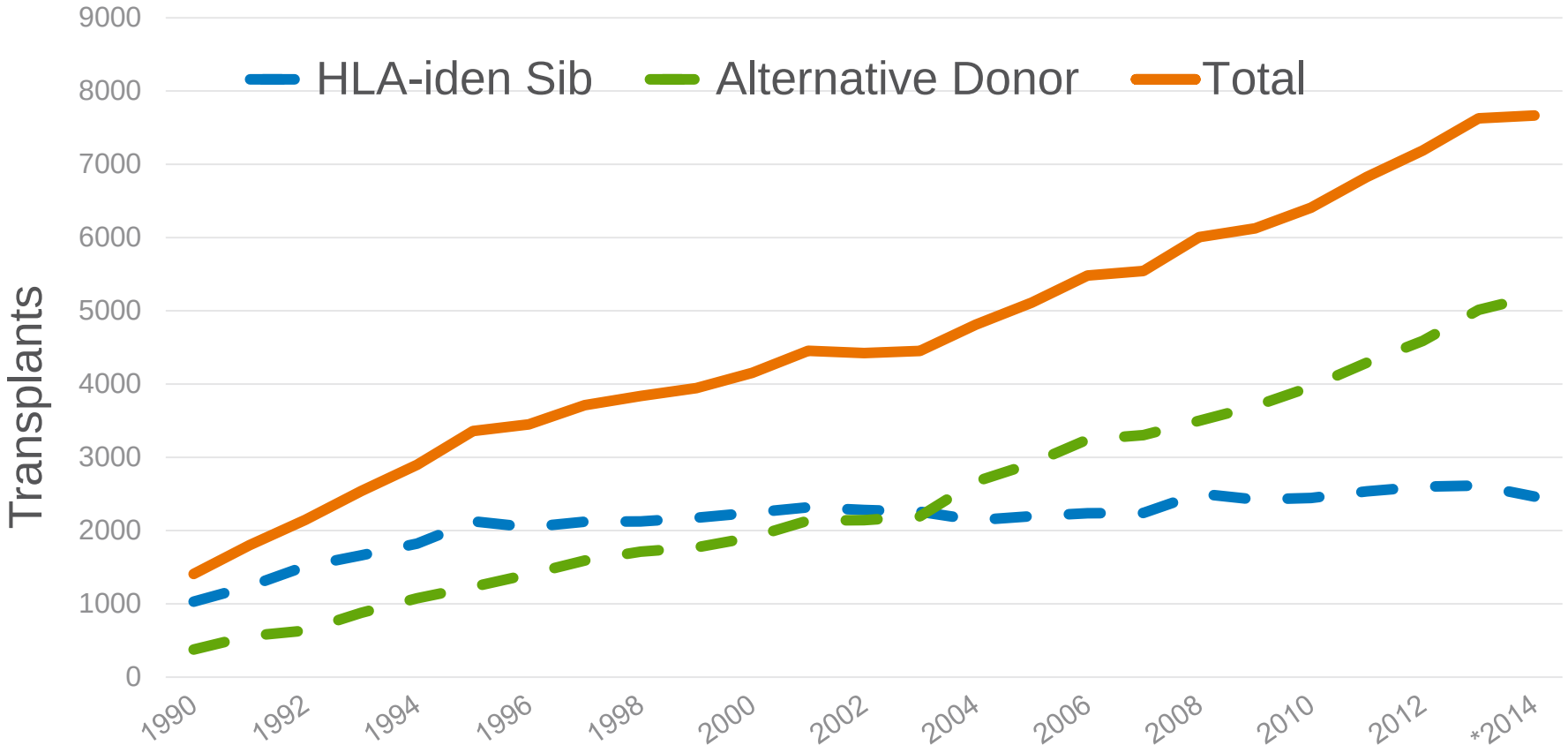
A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

Allogeneic Transplant Recipients in the US, by Donor Type



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*2014 Data incomplete

Donor Availability

- HLA-matched relative 25-30%
- Unrelated donor 40-90%
  - Optimally selected* 10-60%

*HLA-matched, permissive DP mismatch, age <30, (ABO, CMV, sex)

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Patients Without an Adult Donor May be Helped by Banked Umbilical Cord Blood

- Advantages:
  - Immediately available (important for patients with rapidly progressive diseases)
  - No risk to donor
  - Allows more HLA-mismatch with lower risk of GVHD
- Disadvantages:
  - Low cell numbers - inadequate cell dose for many adults, requiring two units (expensive)
  - Slow hematopoietic recovery and higher risk of graft failure
  - High cost

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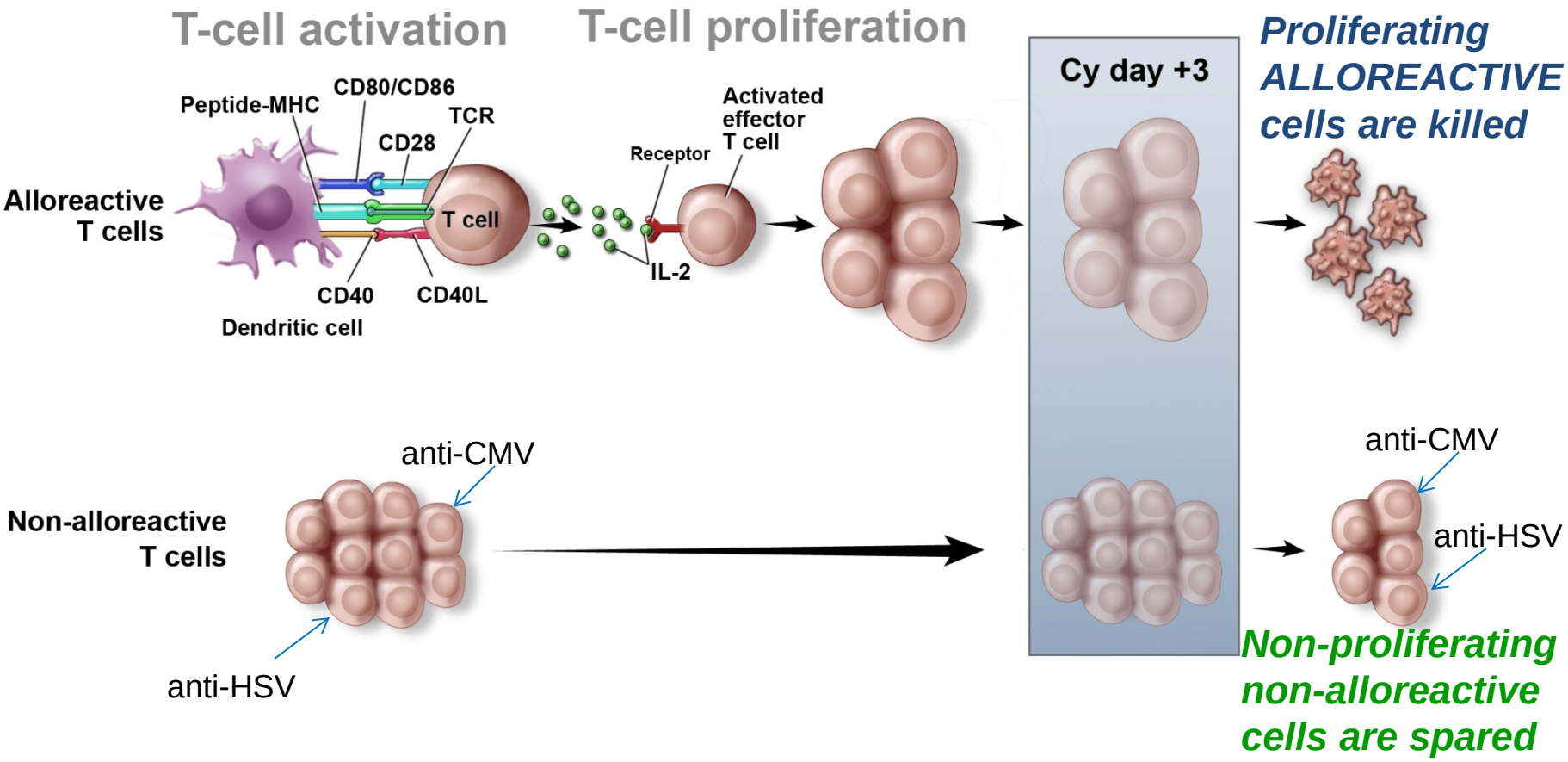
The “New” Alternative – Haploidentical

- In Europe, haploidentical transplants using T-cell depleted peripheral blood grafts have been used for a small but important proportion of transplants
- In the US, very few haploidentical transplants were performed until the last five years
  - No approved CD34 selection or T-cell depletion device available
- Introduction of the Hopkins approach using posttransplant cyclophosphamide increased interest
  - Technically simple
  - Costs similar to HLA-identical sibling transplant

Cyclophosphamide-induced tolerance



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BMT CTN PROTOCOL #0603

A Phase II Trial of Reduced Intensity Conditioning and Transplantation of Partially HLA-Mismatched Bone Marrow for Patients with Hematologic Malignancies

BMT CTN PROTOCOL #0604

A Phase II Trial of Reduced Intensity Conditioning and Transplantation of Umbilical Cord Blood from Unrelated Donors in Patients with Hematologic Malignancies

Brunstein, Fuchs, et al Blood 2011

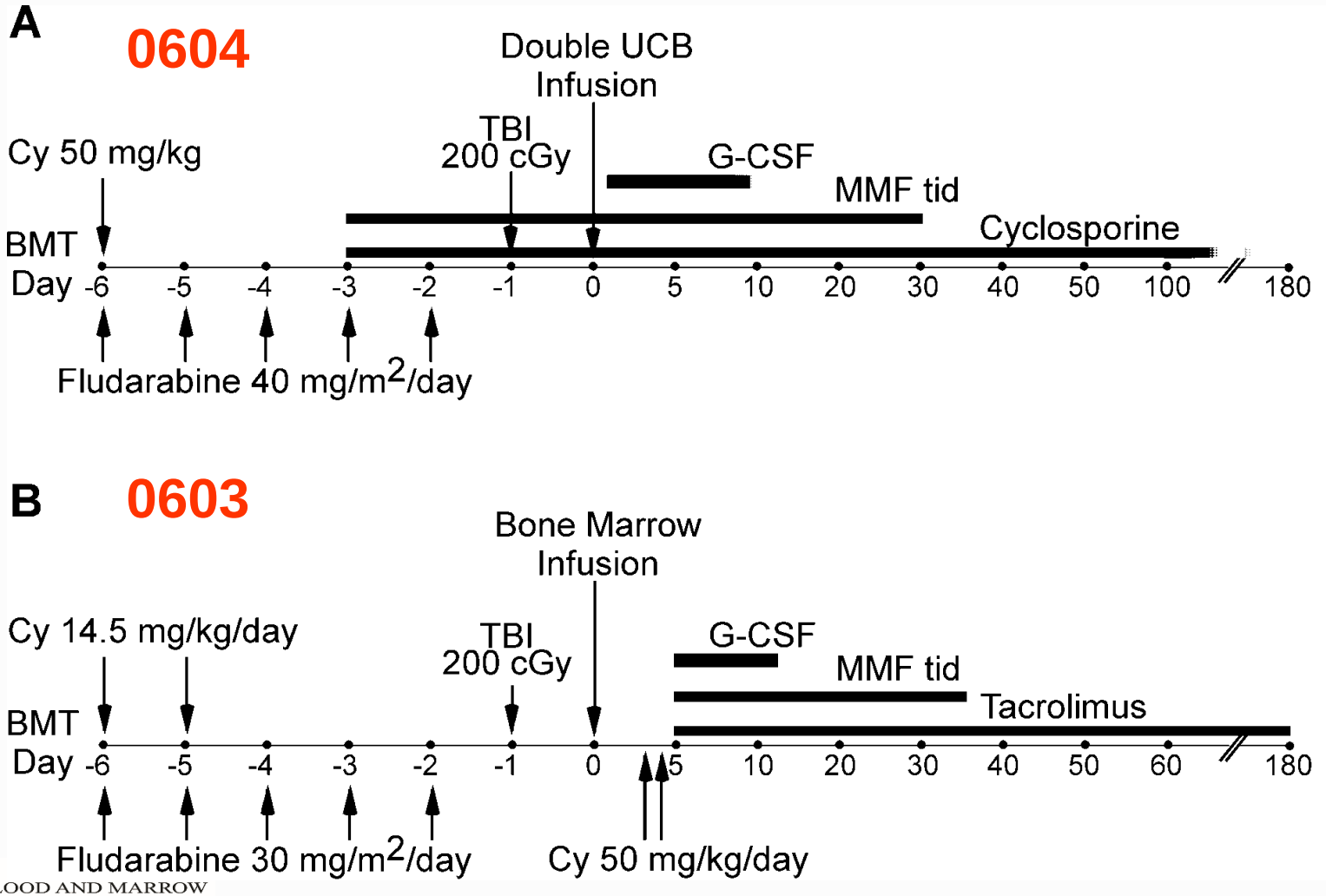
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

The precursors to BMT CTN 1101: BMT CTN 0603 (haplo) and BMT CTN 0604 (double cord)

- Parallel phase II trials (n=50/trial) of alternative donor stem cell transplantation after fludarabine/200 cGy TBI-based conditioning
- Acute leukemia in CR, lymphoma
- Hypothesis: Survival at six months is >60% (CIBMTR benchmark for unrelated donor HCT with reduced intensity conditioning)
- Trials conducted at 16 or 17 centers each, completed within 18 months

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Treatment Regimens

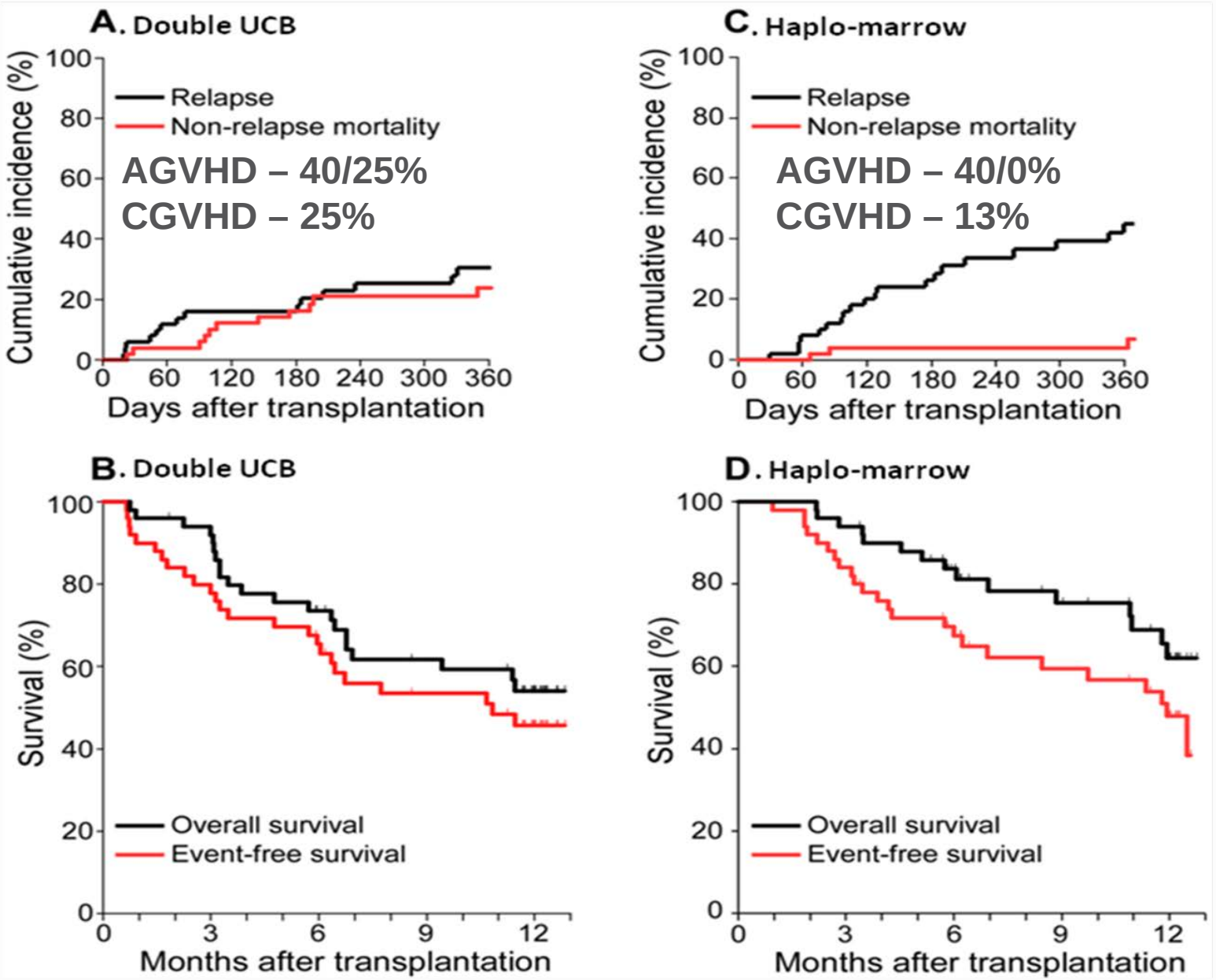


BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 0603 and 0604 demographics
Cord blood patients older, more AML

Table 1. Patient and disease characteristics

	CTN 0604 dUCB	CTN 0603 Haplo-marrow
Number of patients	50	50
Age, y		
Median	58	48
Range	16-69	7-70
Primary disease		
Acute lymphoblastic leukemia	6 (12%)	6 (12%)
Acute myelogeneous leukemia	29 (58%)	22 (44%)
Biphenotypic/undifferentiated leukemia	1 (2%)	3 (6%)
Burkitt lymphoma	1 (2%)	0
Hodgkin lymphoma	5 (10%)	7 (14%)
Large-cell lymphoma	3 (6%)	8 (16%)
Marginal zone B-cell lymphoma	1 (2%)	1 (2%)
Follicular non-Hodgkin lymphoma	4 (8%)	3 (6%)



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Brunstein, et al 2011

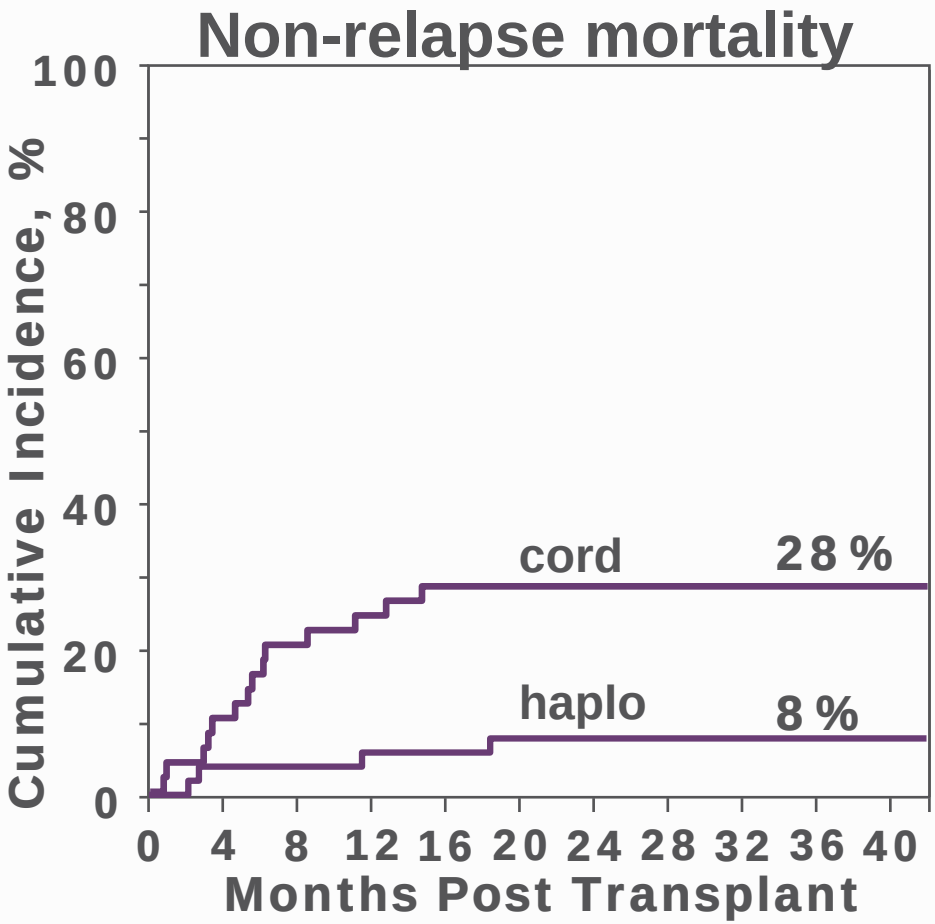
BMT CTN Trials 0603/0604

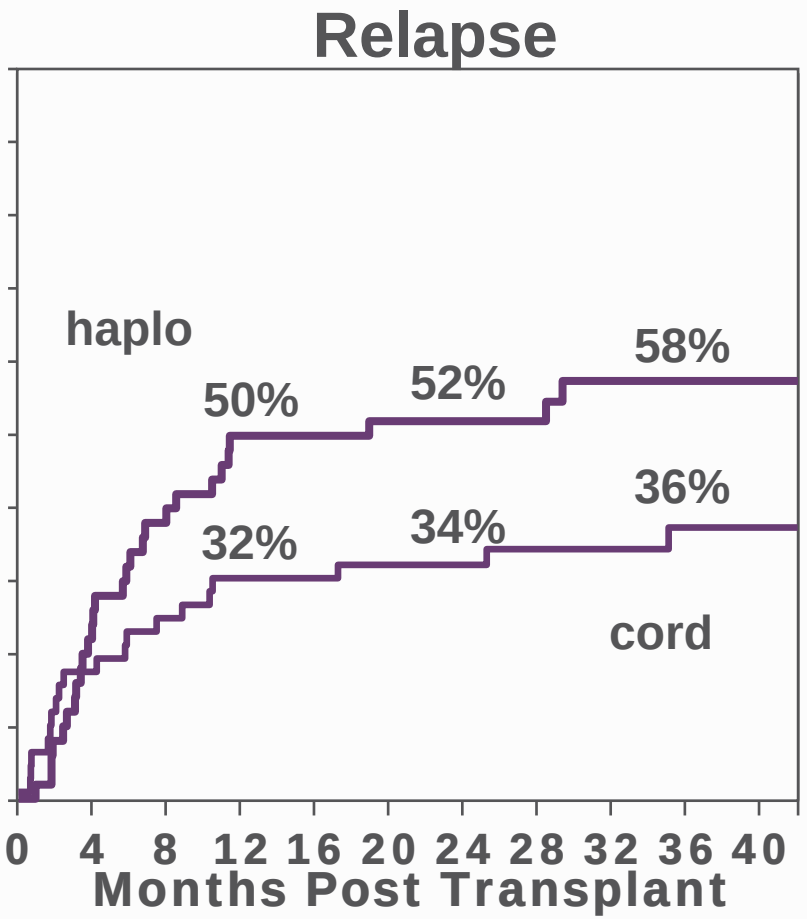
Extended Follow-up

Biol Blood Marrow Transplant, 2014; 20(10): 1485-92

BMT CTN 0603/0604

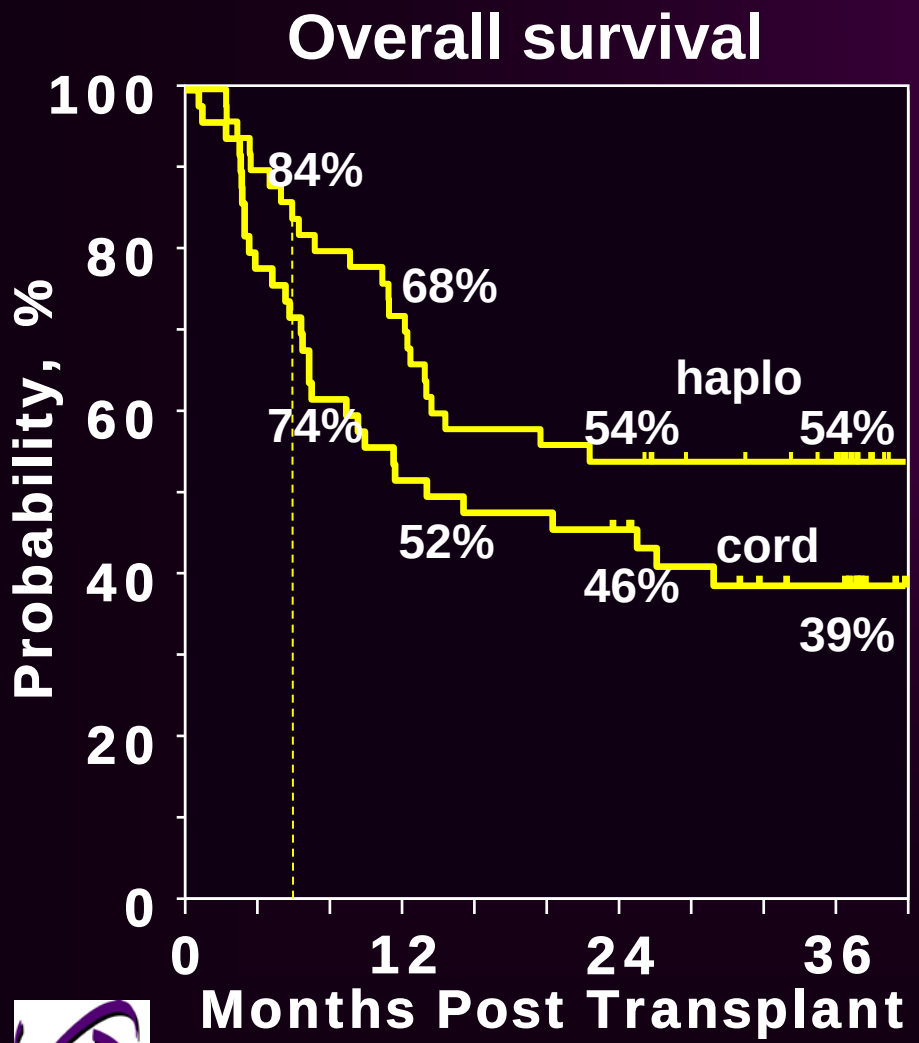
Non-relapse mortality and relapse

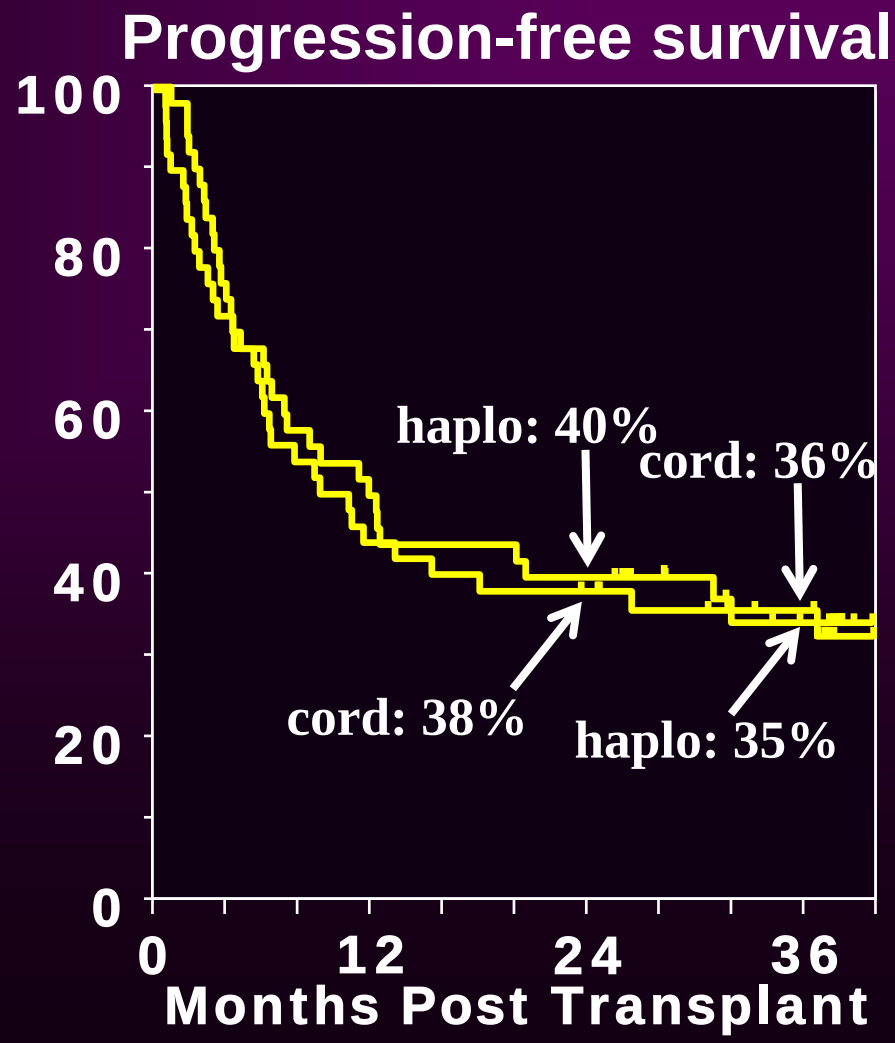




BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Comparisons of clinical outcomes: UCB vs Haplo (BMT CTN 0603/0604)





The results of BMT CTN 0603 and 0604 established the following

A. The trials were not intended to be compared directly to each other
B. Progression-free and overall survival rates are similar after haplo and cord blood transplants
C. Pattern of treatment failure differed by donor source
   - Non-relapse mortality is higher after cord blood than after haplo transplants
   - Relapse is higher after haplo than after cord blood transplant

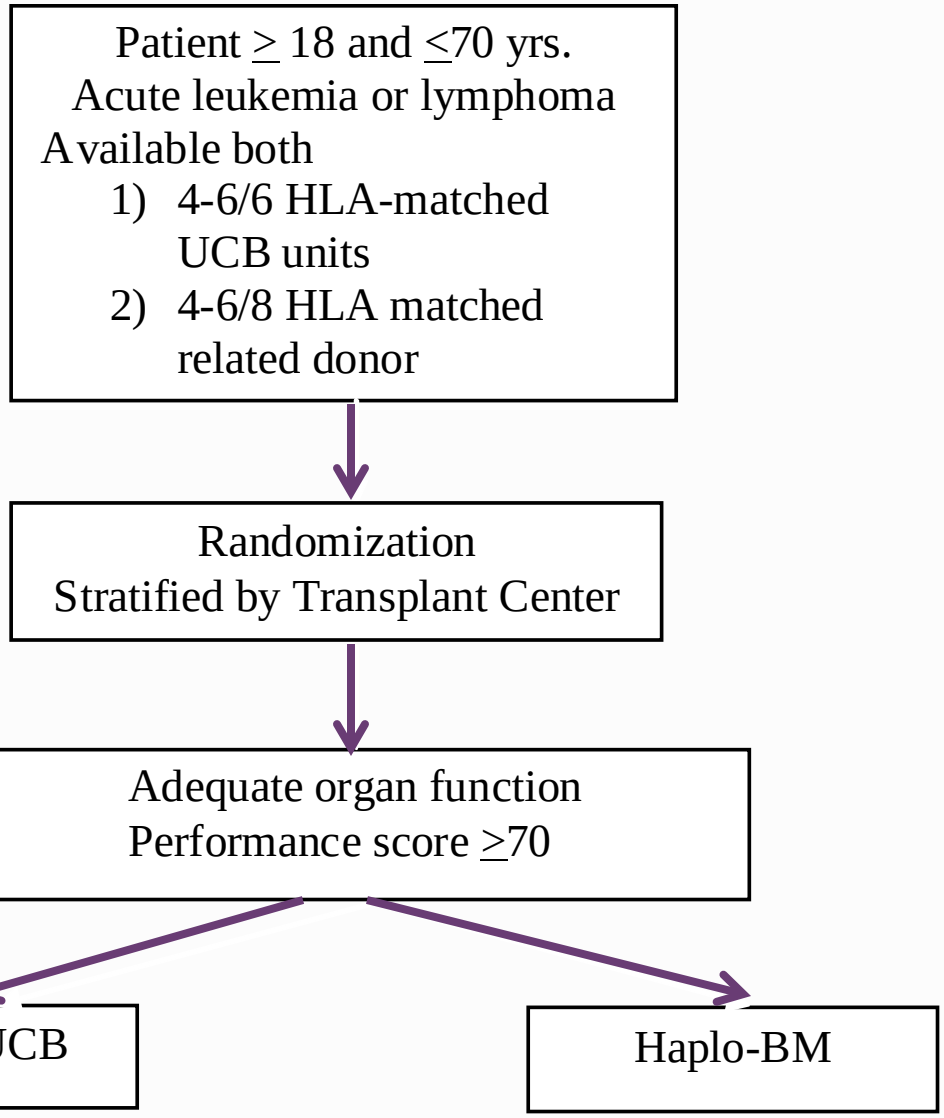
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

The results of BMT CTN 0603 and 0604 provided equipoise for a randomized phase III clinical trial with progression-free survival as the primary endpoint

BMT CTN 1101 Hypothesis: Two year PFS is similar after related haplo-BM donor transplantation or after double UCB transplantation.

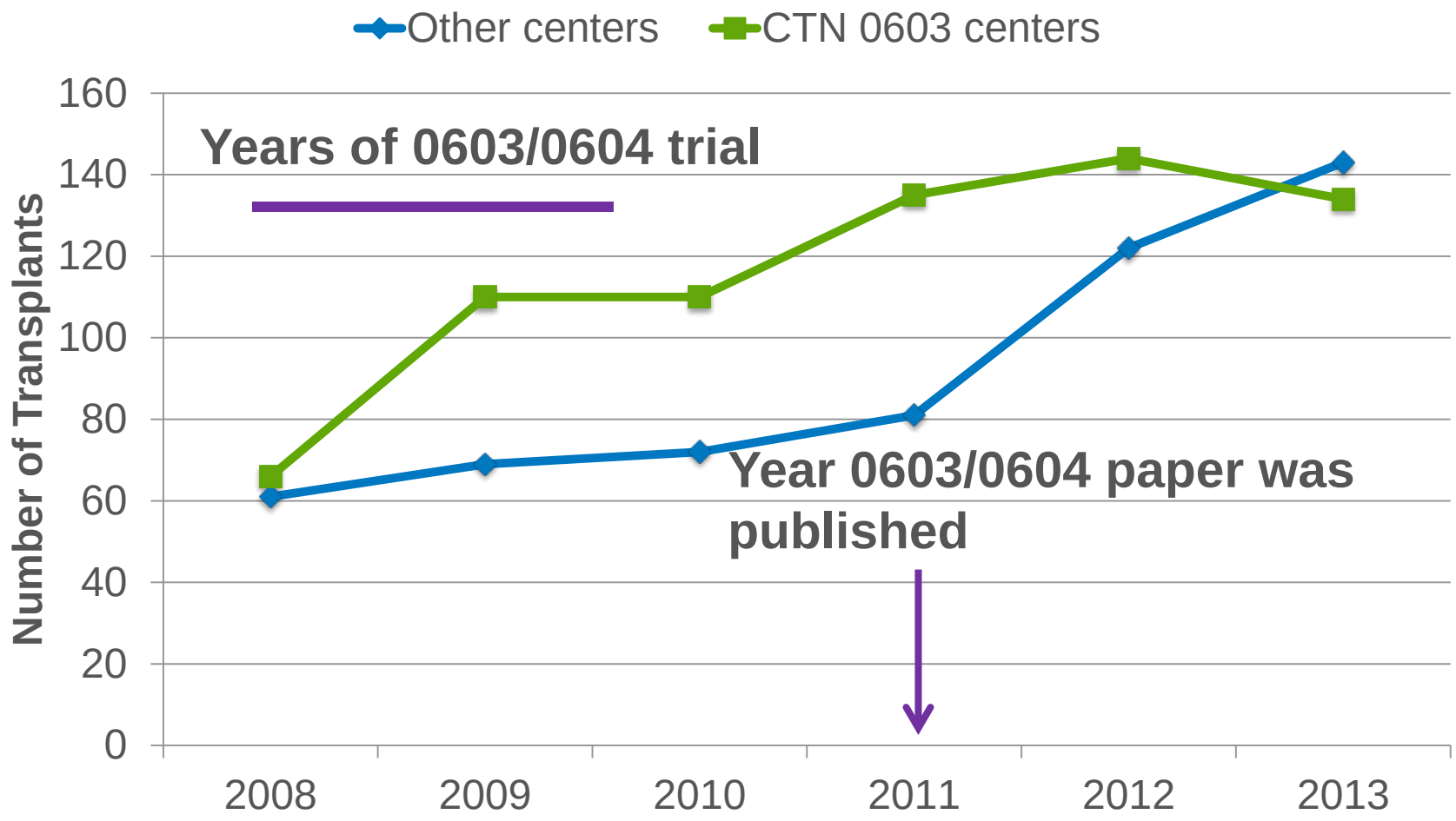
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1101 Schema



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Haploidentical Transplantations for Hematologic Malignancy



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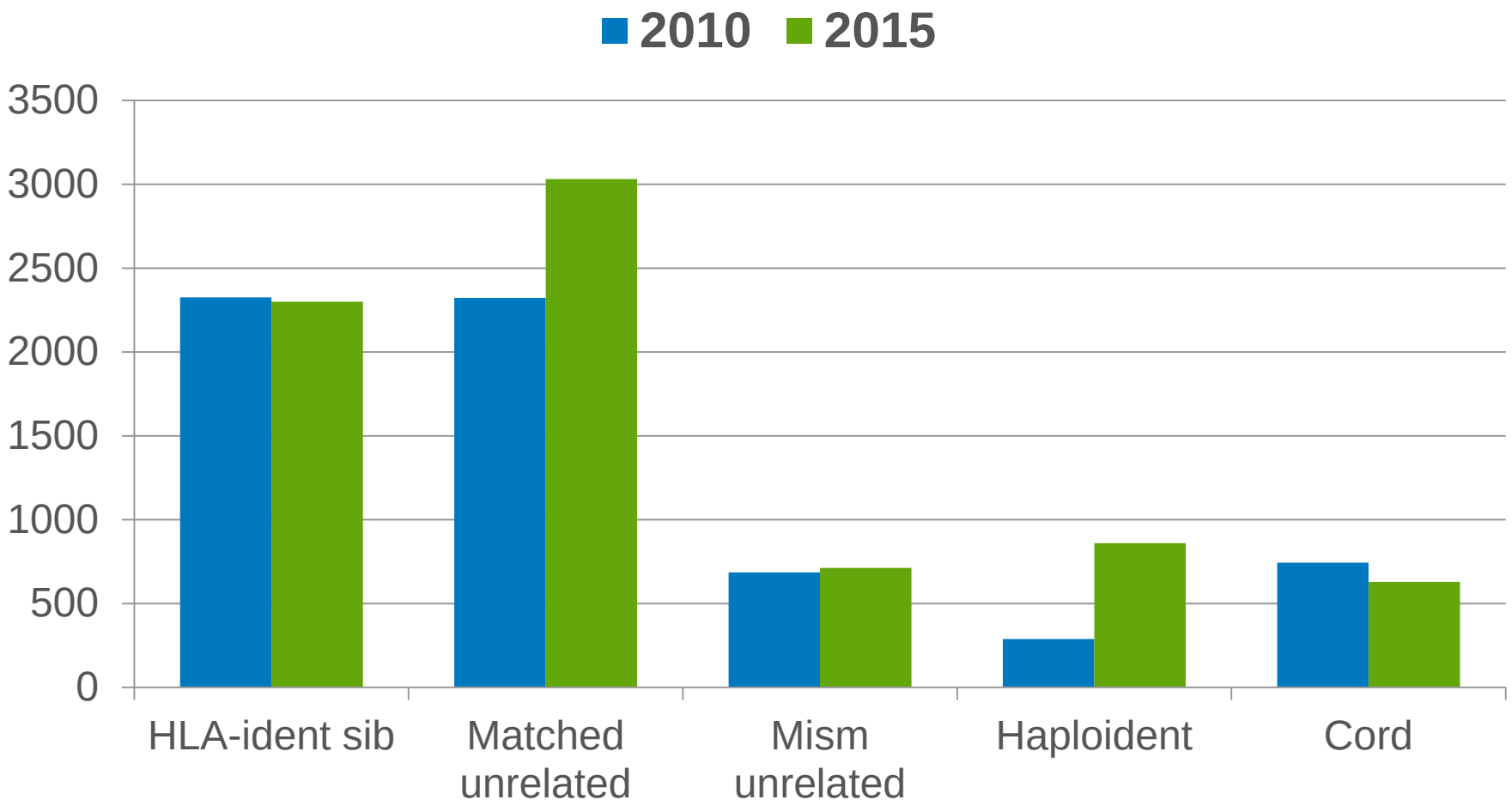
Distribution of Graft Sources in the US: 2015 vs 2010



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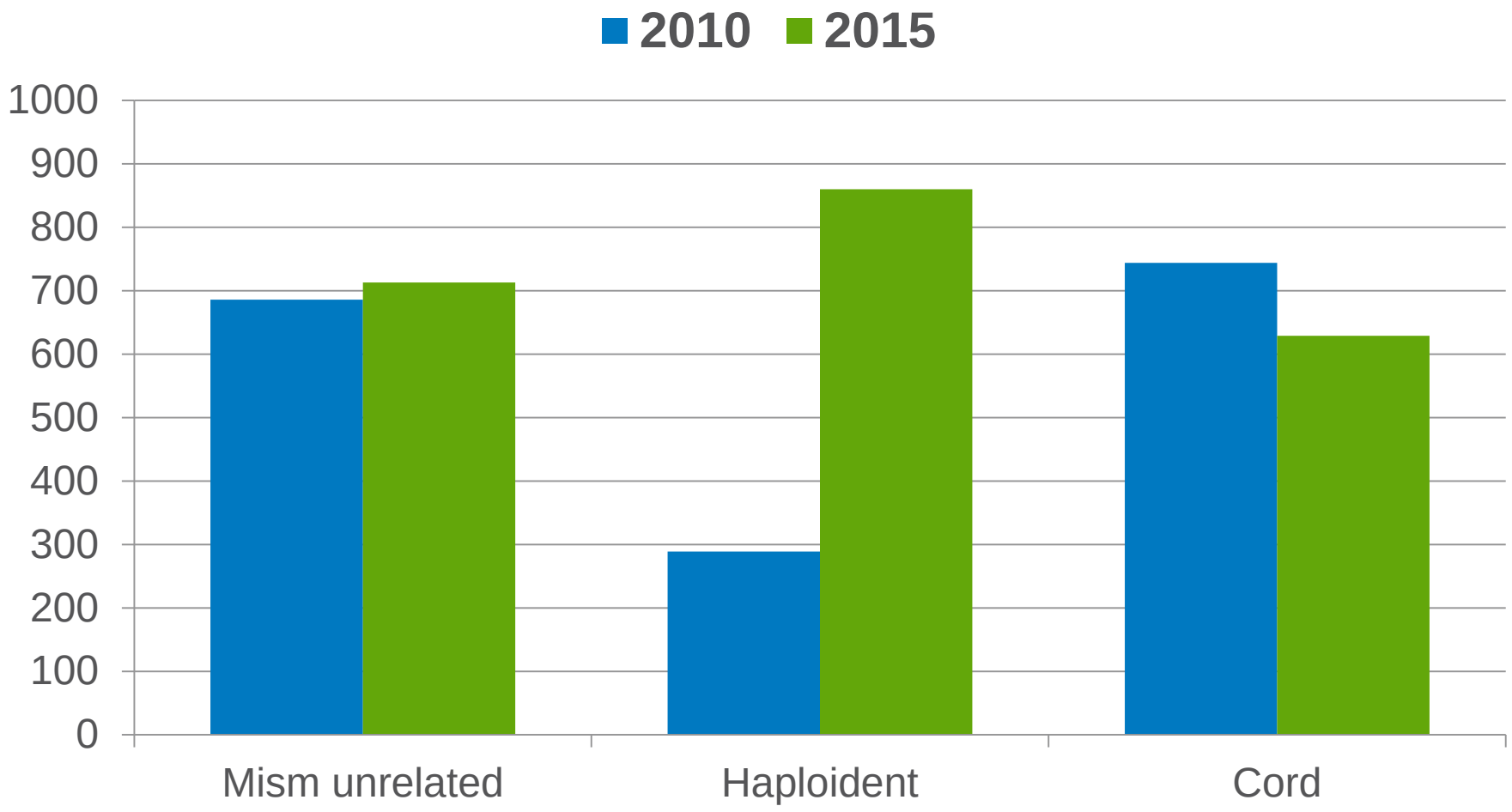
Distribution of Alternative (not an HLA-matched adult donor) Graft Sources



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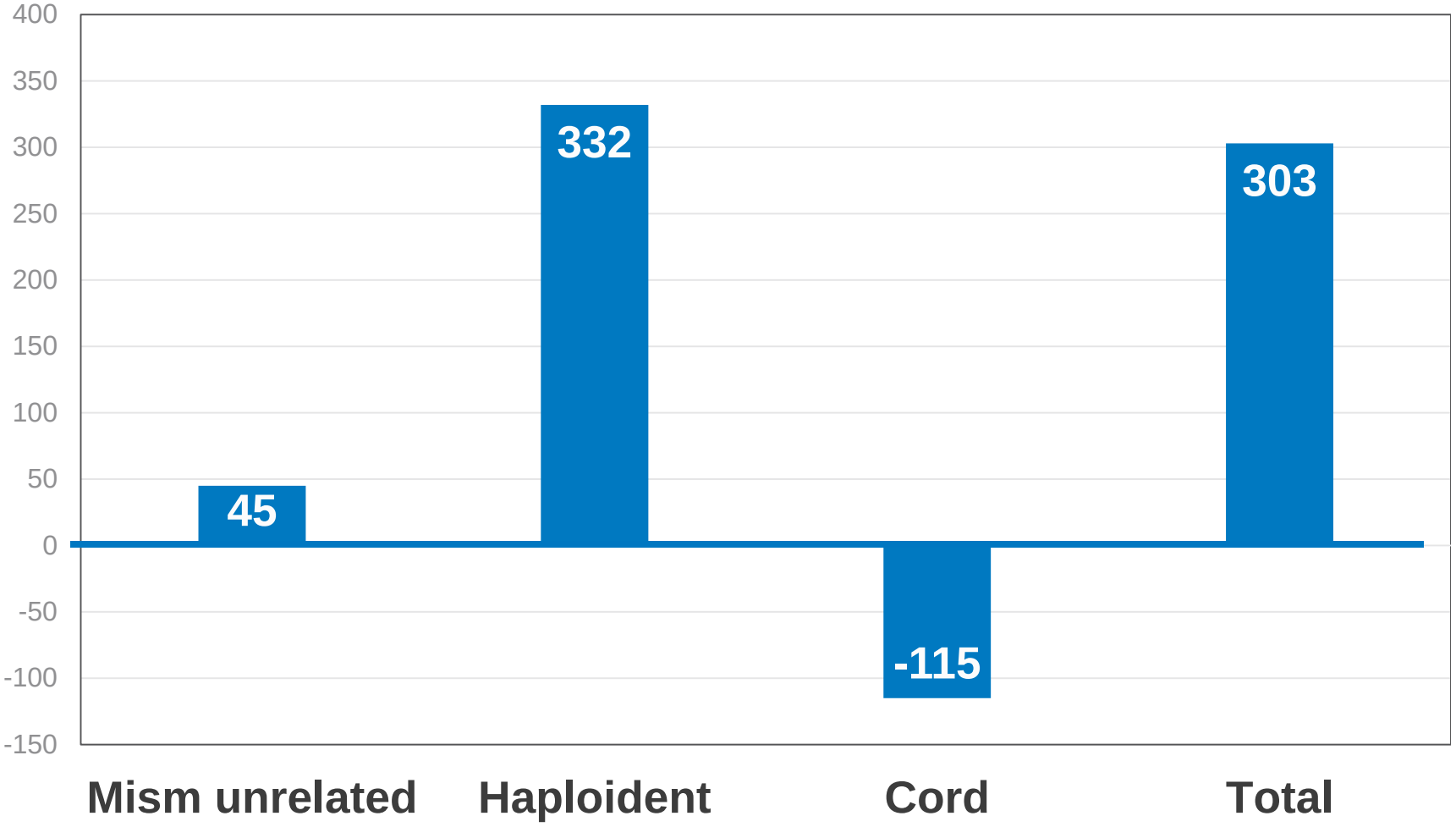
Change From 2010 to 2015



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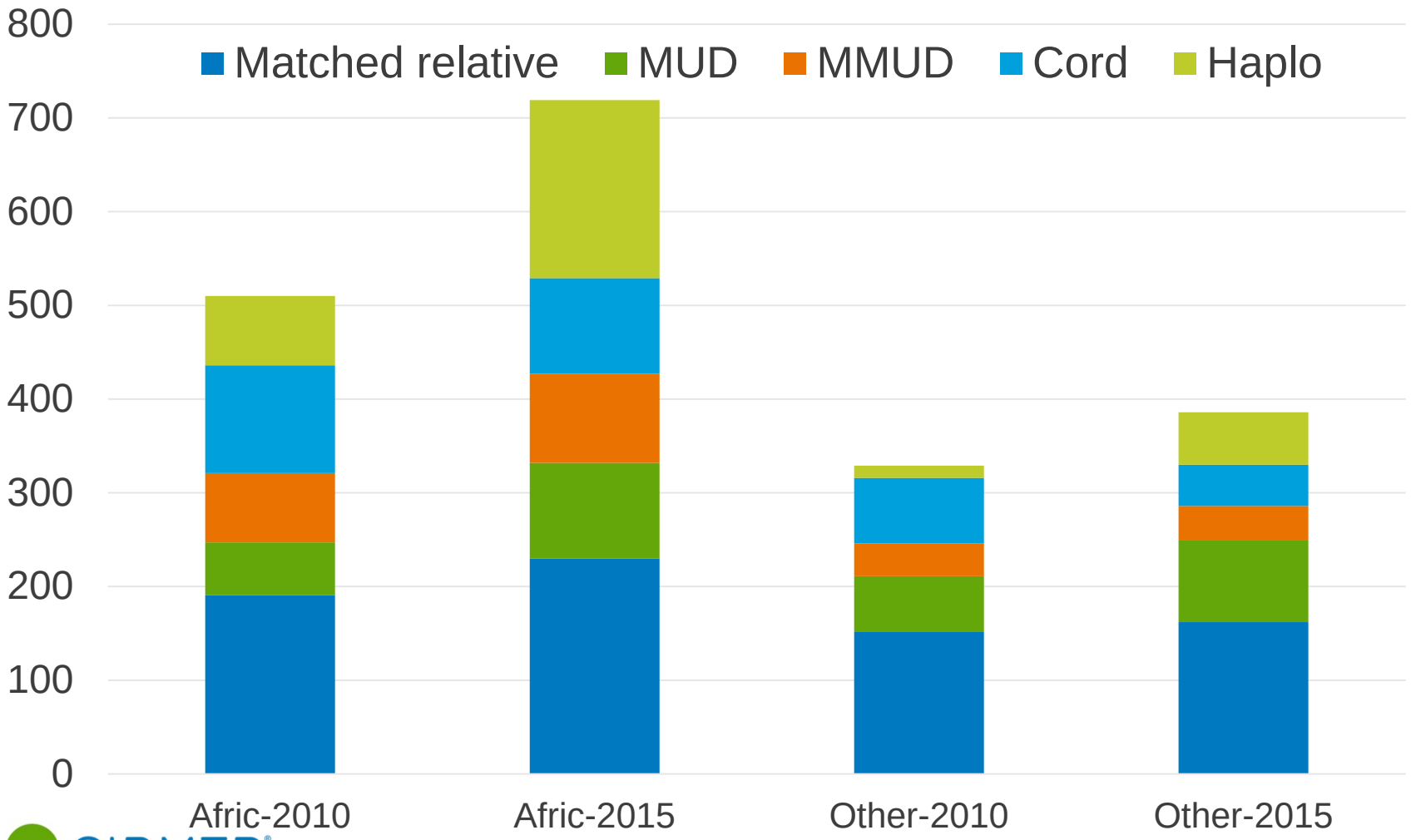
US Transplants in non-Caucasians by Year and Donor Type



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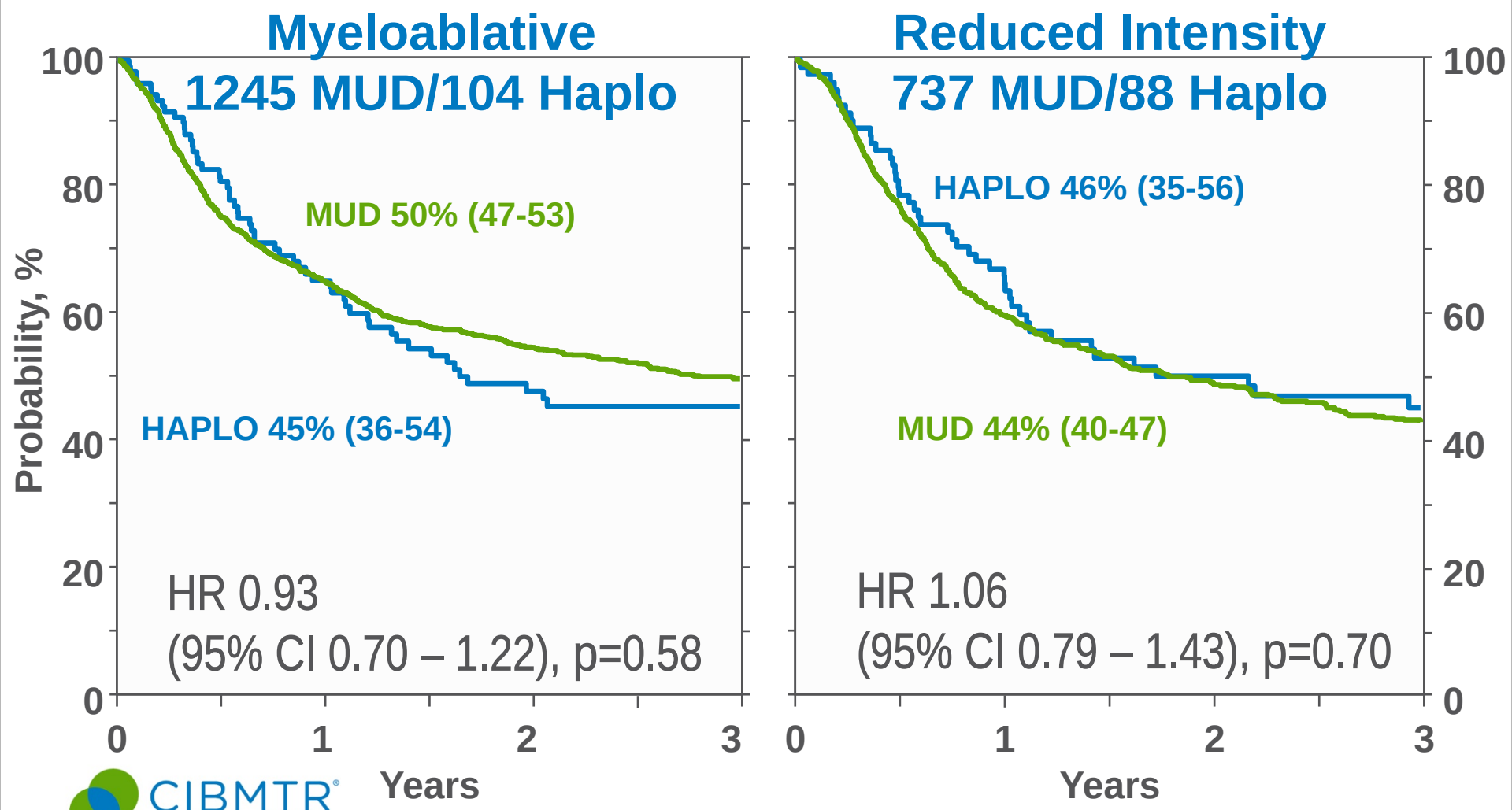
Overall Survival
Adjusted for Age, Disease Risk, Secondary AML



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Ciurea, Blood, 2015

Limitation of this Analysis - POWER

COMPARISONS OF 3-Year SURVIVAL						
	Myeloablative: **1245** MUD/**104** Haplo			Reduced Intensity: **737** MUD/**88** Haplo		
	Point Estimate	Lower Bound	Upper Bound	Point Estimate	Lower Bound	Upper Bound
Matched Unrelated	50%	47%	53%	44%	40%	47%
Haploidentical	45%	**36%**	**54%**	46%	**35%**	**56%**

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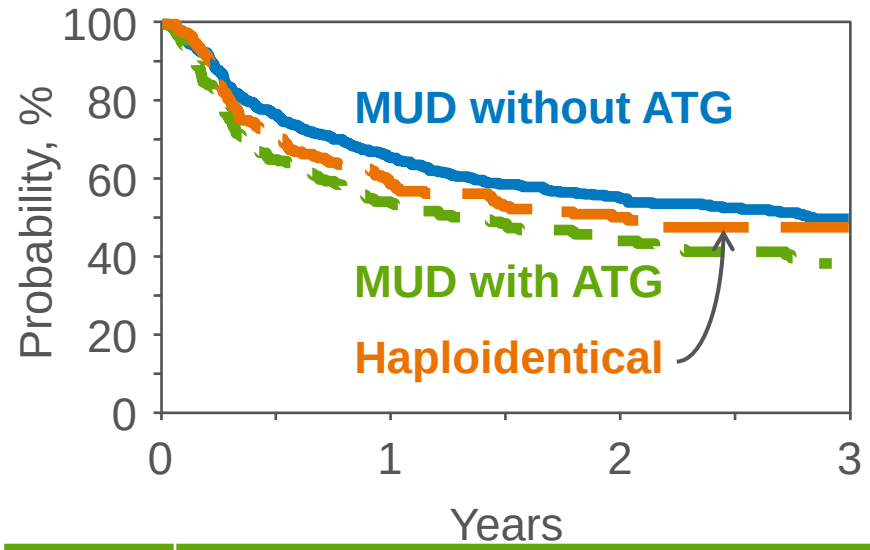
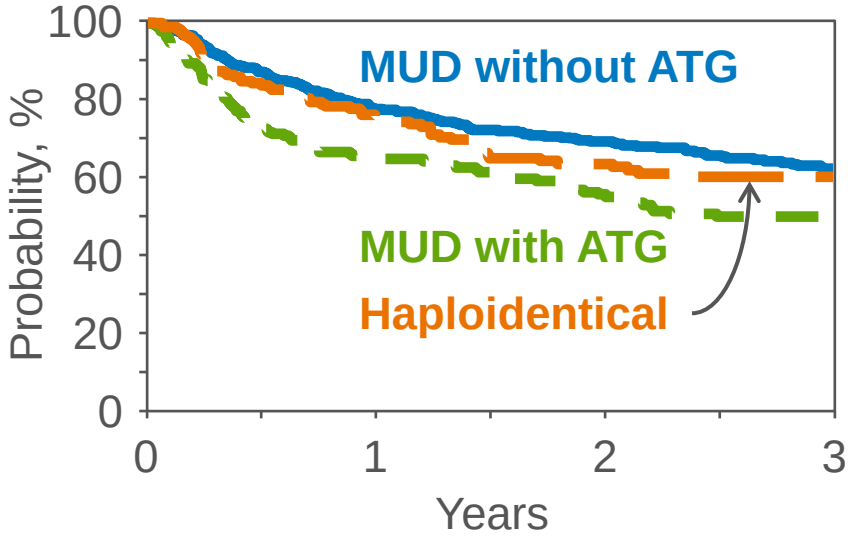
Progression-free Survival



Overall Survival

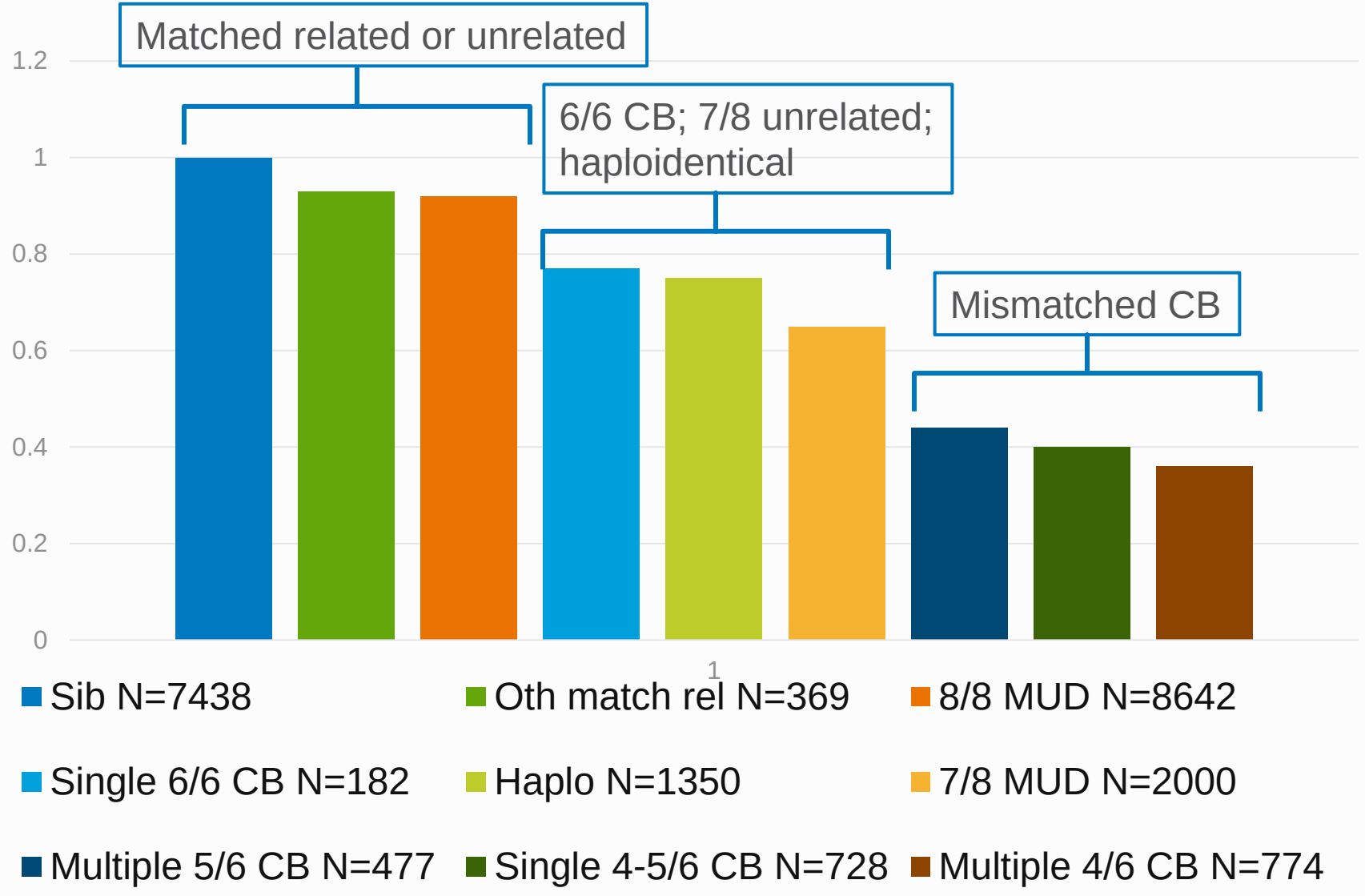


	1-year (95% CI)			3-years (95% CI)		
	Haplo	URD w/o ATG	URD w/ ATG	Haplo	URD w/o ATG	URD w/ ATG
PFS	58 (51-65)	65 (61-70)	53 (47-60)	47 (40-55)	49 (44-54)	38 (31-45)
OS	76 (69-81)	78 (74-81)	65 (58-71)	60 (52-67)	62 (57-67)	50 (42-57)

Haplo with Posttx Cy vs MUD with Calcineurin Inhibitor for Lymphoma

Relative Risk of Mortality and Treatment Failure						
	Mortality			Treatment Failure (Prog or Death)		
	Relative Risk	Lower Bound	Upper Bound	Relative Risk	Lower Bound	Upper Bound
Haplo (N=184)	1.00	--	--	1.00	--	--
MUD – No ATG (N=491)	0.83	0.62	1.11	0.90	0.71	1.16
MUD – ATG (N=291)	1.25	0.92	1.69	1.16	0.92	1.69

Impact of Donor Type on one-year mortality after HCTs done in 2012-2014



What Do We Know About Haplos with Post-tx Cyclophosphamide?

- Haploidentical HCT can be performed with low GVHD and low early TRM and acceptable 2-3 year overall mortality, when used with postCy
- Haploidentical HCT is increasingly used, predominantly for adult patients who do not have an HLA-matched adult donor – and for some who do

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Some Unknowns About Haplos with Post-tx Cyclophosphamide

- Long-term control of malignancy
- Engraftment in non-malignant diseases
- Optimal graft type (PB or BM) or conditioning regimen
- Suitability of Older Donors
  - More graft failure
  - Clonal hematopoiesis more common with older donors – uncertain significance
- Optimal HLA-matching
- Efficacy relative to other graft sources

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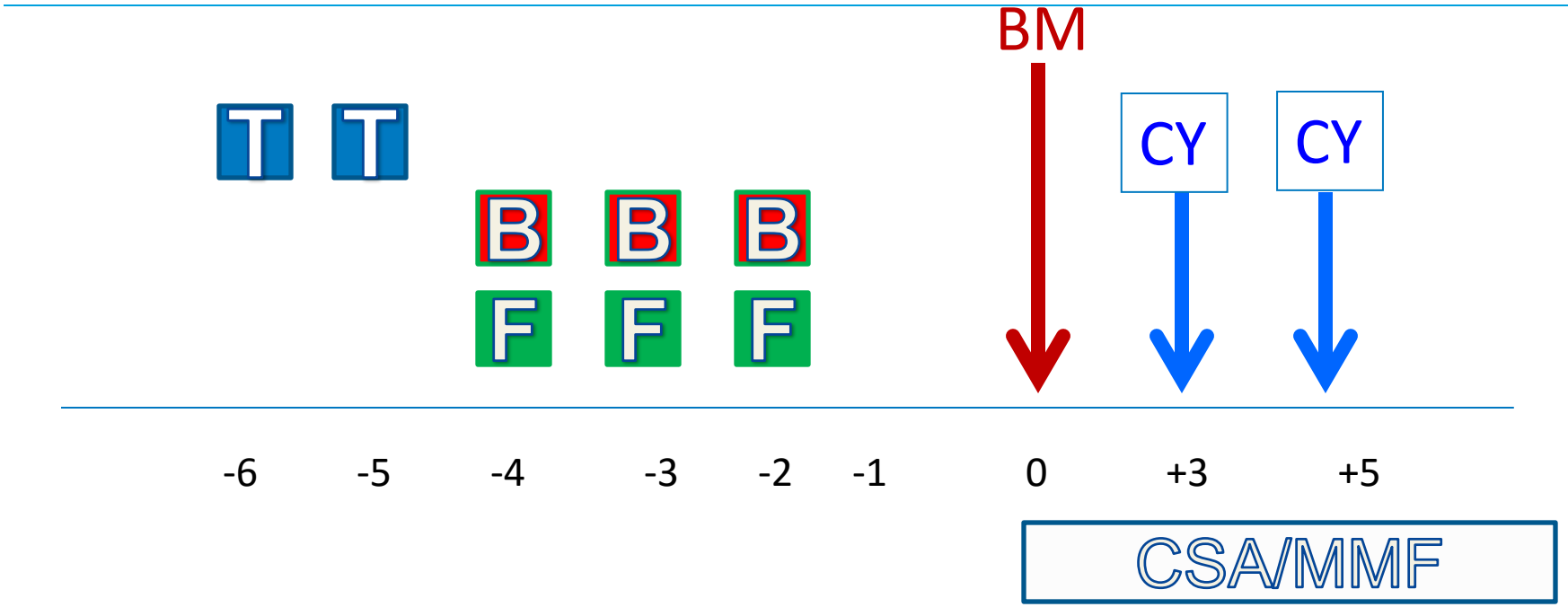

Thiotepa 5 mg/kg
Fludarabine 50 mg/mE+2
Busulfan 3.2 mg/kg

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TBF (N=214)

Age	56 (17-64)
AML	60
ALL	29
MF	29
RAEB	48
Other	48
CR1	70

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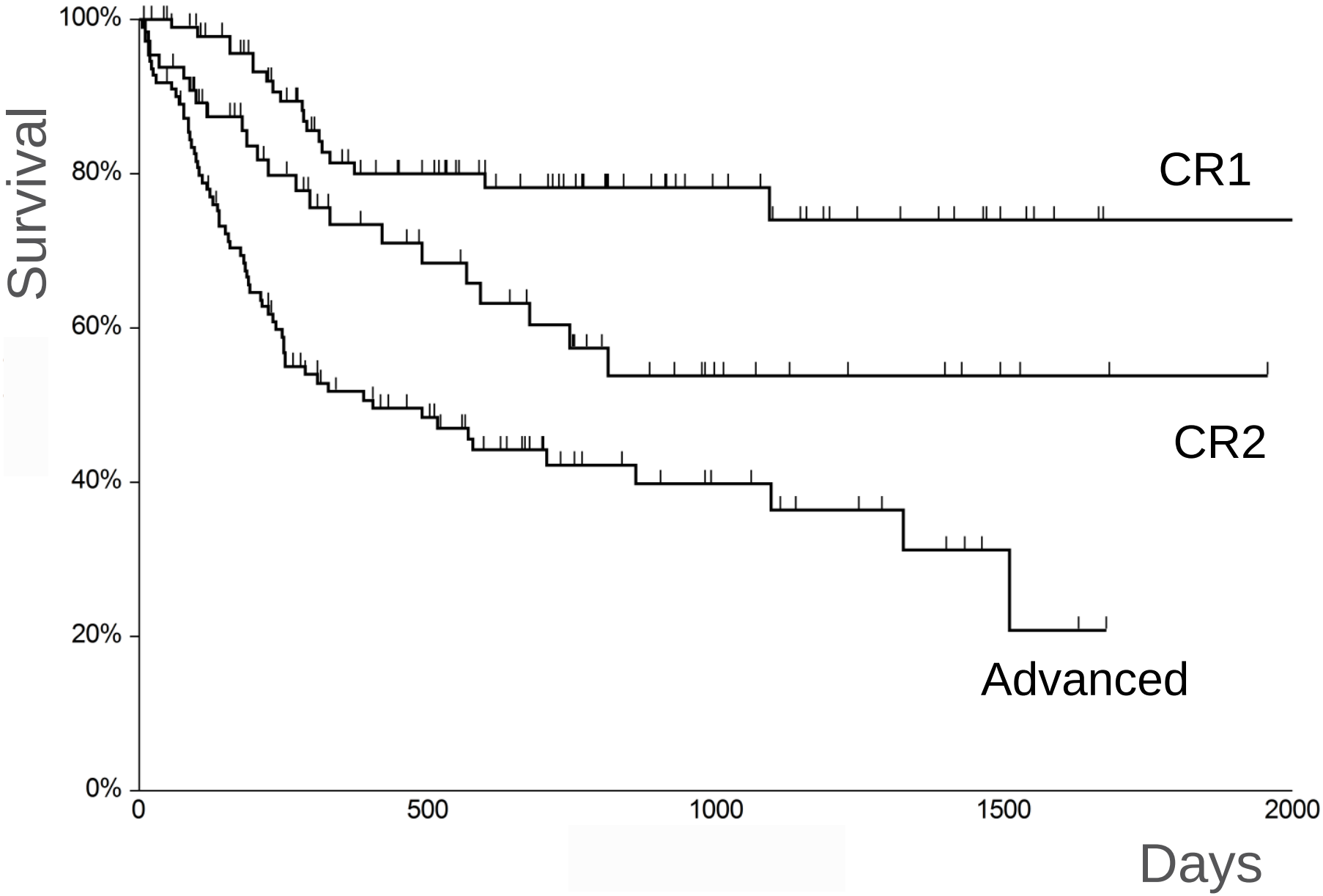
Survival
100%
80%
60%
40%
20%
0%
0
500
1000
1500
2000
Days
CR1
CR2
Advanced

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Some Other Important Unknowns About Post-tx Cyclophosphamide

- Roles in HLA-mismatched unrelated donor transplantation: could allow selection of donors bases on other characteristics (e.g. age) from small donor pool
- Role in HLA-matched related and unrelated donor transplantation
- Viral immunity
- Graft versus tumor effects
- Are the same donor and recipient risk factors important for TRM, relapse and survival

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Relative risks and benefits of different cell sources: acquisition issues

	UD	Cord	Haplo
Suitable HLA match available	90% Caucasian 16% ethnic minority	Majority	Almost always – but donor-specific HLA antibodies a problem
Availability	Variable	Predictable	Generally predictable
Speed of acquisition	**Medium**	**Fastest**	**Usually Fast**
Cell dose	**High**	**Low**	**High**
2nd donations/ DLI	**Possible**	**Not possible**	**Possible**
Cost	**Higher than sibling**	**Much higher**	**Equal to sibling**

Relative risks and benefits of different cell sources: Clinical Outcomes

	UD	Cord	Haplo*
Engraftment	Fast	Slow	Fast
Graft failure	Rare	More common	Slightly more common
GVHD	High (esp with mismatch)	Lower than expected with mismatch	Low due to techniques used
Relapse	Possibly lower than sibling	Possibly lower than sibling	Higher
Experience	>30 years	>20 years	**<10 years**

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*** In adults with malignancy**

US National Trials Addressing Some of These Issues

- BMT CTN 1101: Haplo vs Cord with **reduced intensity conditioning**
- BMT CTN 1203: PostCy as GVHD prophylaxis with **matched** donors and **reduced intensity** conditioning
- BMT CTN 1301: PostCy as GVHD prophylaxis with **matched** donors and **myeloablative** conditioning
- BMT CTN 1502: Haplo with PostCy and UCB for **aplastic anemia**
- BMT CTN 1507: Haplo with PostCy in **Sickle Cell Disease**
- RCI BMT MMUD: PostCy as GVHD prophylaxis with **multiply mismatched unrelated donors**

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Conclusions

- **Few patients lack an acceptable donor**
- All donors (8/8, 7/8 adult, haplo, cord) produce outcomes that, if not identical, are in same range
  - Maximum differences in survival, compared to 8/8 adult donor, are in the range of 10%-15%
  - Outcomes more driven by patient and disease factors
  - Donor choice may depend on other factors

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Conclusions

- Important to track the outcomes of haploidentical transplantation in an organized way so that we can address the many unknowns

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