

NATIONAL MARROW DONOR PROGRAM® BE THE MATCH®

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COUNCIL MEETING 2013

One Cord or Two? Results from Studies on Single vs. Multi Cord Blood Transplants

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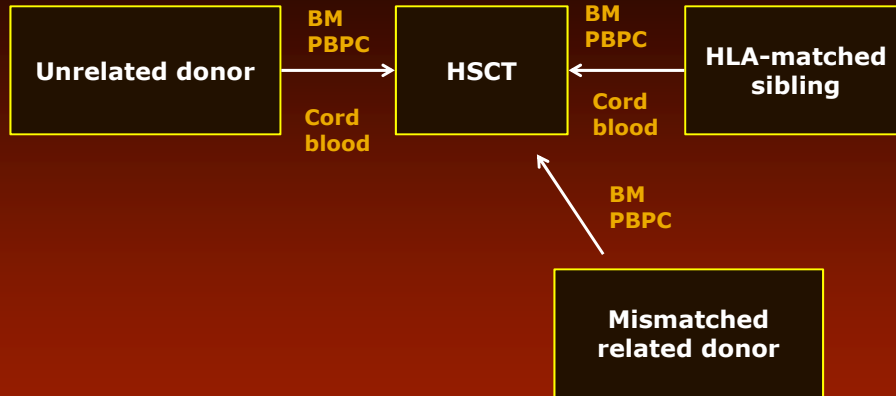
Financial Disclosures – None

COUNCIL MEETING 2013: SHARING OUR PASSION FOR LIFE

Learning Objectives

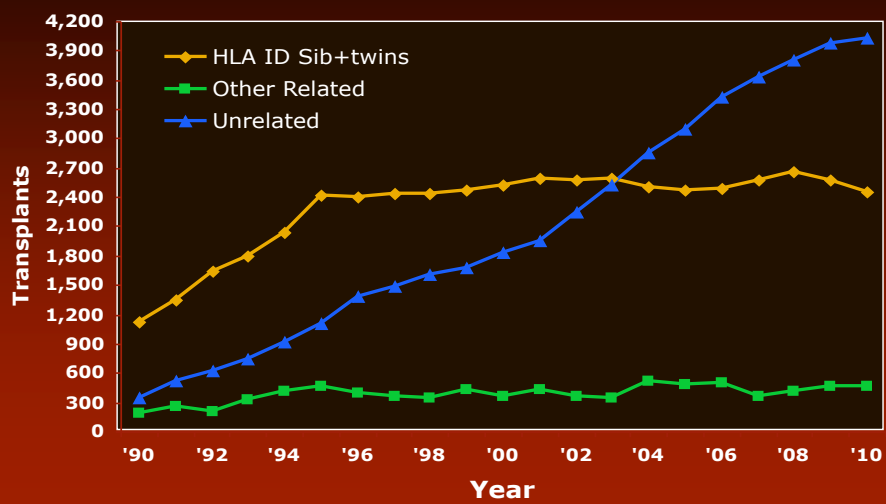
At the end of this session, you'll be able to:

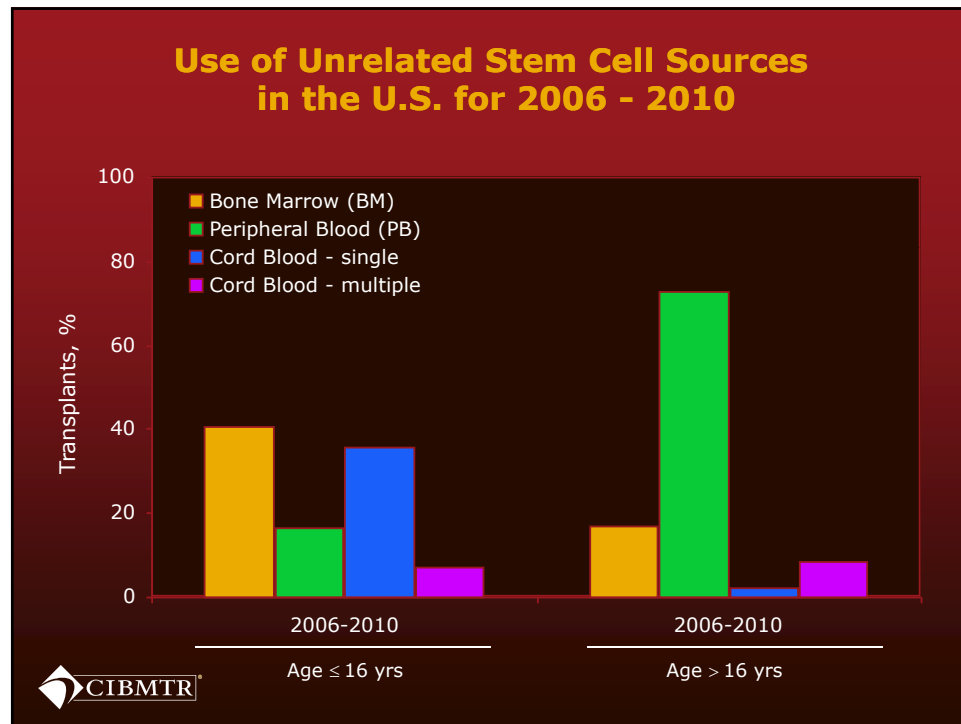
- 1. Describe the use of single and double umbilical cord blood transplants (UCBT) in pediatric and adult patients.
- 2. Recall the challenges faced during UCB selection in an effort to optimize the success of a UCBT.
- 3. State the importance of cell dose in the success of UCBT.



Donor Options for Hematopoietic Stem Cell Transplantation in 2013

Allogeneic Transplant Activity - U.S.





Advantages

- **Readily available**
 - Units are banked and readily available
 - Particular advantage when transplantation is needed urgently
- **Risks to the donor**
 - None
 - Cord blood is collected from the placenta after delivery

Obstacles

- **Cell dose**
 - Each unit contains a fixed cell dose
 - No subsequent collections
 - Delayed hematopoietic recovery
 - High early mortality from transplant-related complications
- **Donor-recipient HLA match**
 - Units are less well matched to recipients than when considering adult donor transplantation

Cord Blood Unit Selection

- Minimum cell dose (TNC) is needed to facilitate hematopoietic recovery and lower early mortality
- Donor-recipient HLA match
 - Minimum match criteria allows for mismatching at 2 HLA-loci
 - Matching is determined at resolution lower than for unrelated adult donors
 - Does not consider matching at allele-level at Class I

Guidelines for unit selection

- **Single CB transplants**
- **6/6 HLA-matched transplants**
 - Outcome not associated with TNC
- **5/6 HLA-matched transplants**
 - $\text{TNC} \geq 2.5 \times 10^7/\text{kg}$
- **4/6 HLA-matched transplants**
 - $\text{TNC} \geq 5.0 \times 10^7/\text{kg}$
- **Double CB transplants**
 - $\text{TNC} \geq 2.0 \times 10^7/\text{kg}$ for each unit
 - Preference for HLA-match

Barker JN Blood 2007; 2011

Guidelines for unit selection

- **Single CB transplants**
- **6/6 HLA-matched transplants**
 - $\text{TNC} \geq 3 \times 10^7/\text{kg}$
- **5/6 HLA-matched transplants**
 - $\text{TNC} \geq 4 \times 10^7/\text{kg}$
- **4/6 HLA-matched transplants**
 - $\text{TNC} \geq 6 \times 10^7/\text{kg}$
- **If a single UCB unit with adequate TNC is not available → 2 UCB units**
 - $\geq 1.5 \times 10^7/\text{kg}$ for each unit
 - At least 4/6 HLA-match to recipient

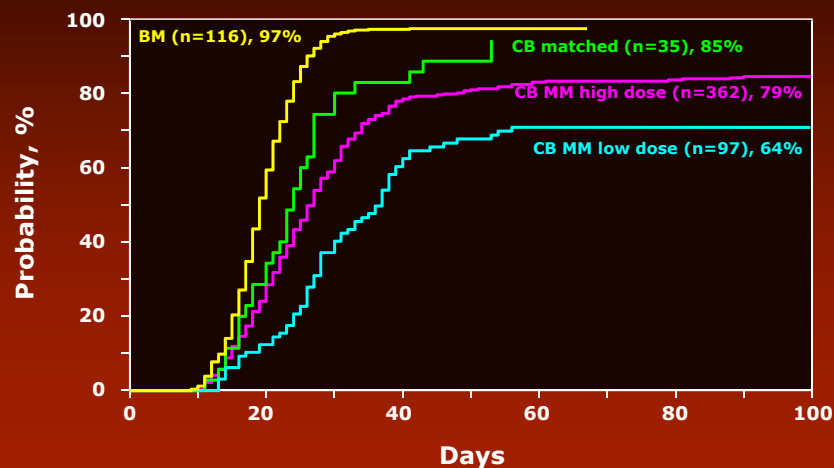
Delaney C B J Haematol 2009

Guidelines for unit selection

- **Single CB transplants**
- **6/6 HLA-matched transplants**
 - $\text{TNC} \geq 3 \times 10^7/\text{kg}$
- **5/6 HLA-matched transplants**
 - $\text{TNC} \geq 4 \times 10^7/\text{kg}$
- **4/6 HLA-matched transplants**
 - $\text{TNC} \geq 5 \times 10^7/\text{kg}$
- **If a single UCB unit with adequate TNC is not available → 2 UCB units; target TNC $\geq 3 \times 10^7/\text{kg}$; $\geq 1.5 \times 10^7/\text{kg}$ for each unit**
 - **At least 4/6 HLA-match to recipient**

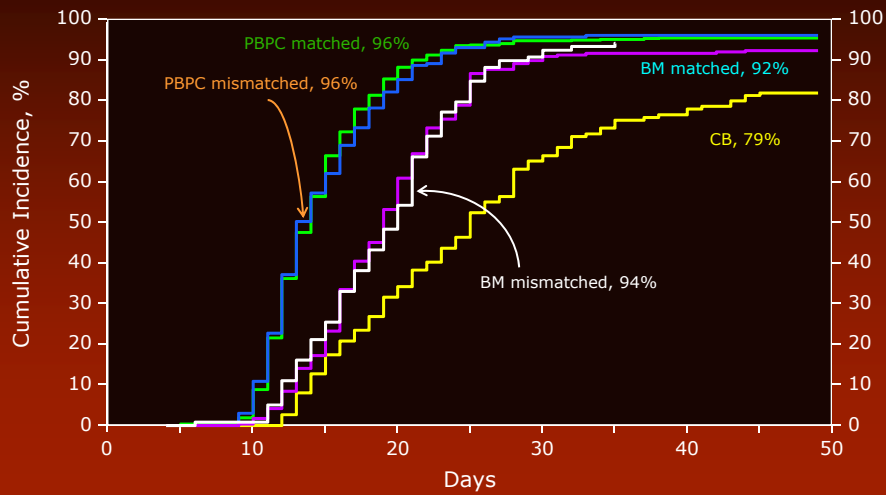
Brunstein Blood 2007; Verneris M Blood 2009

Neutrophil Recovery - Children -



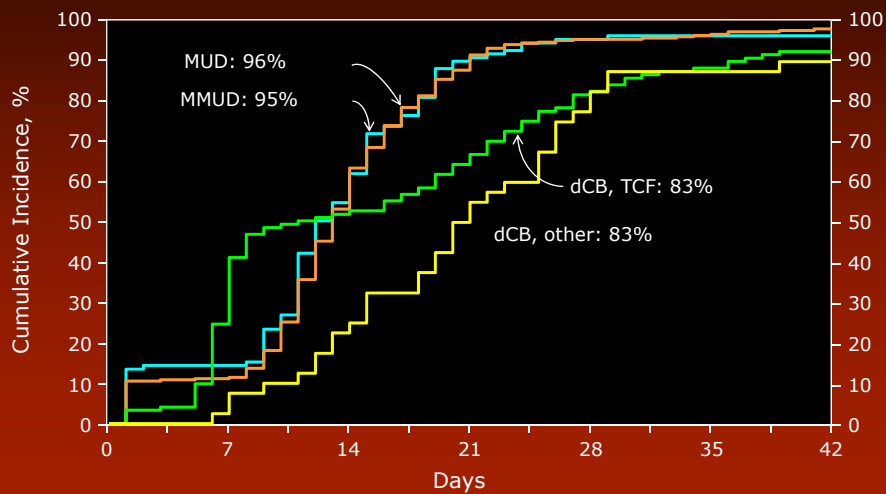
Eapen M et. al. Lancet 2007

Neutrophil Recovery - Adults; Myeloablative Conditioning -



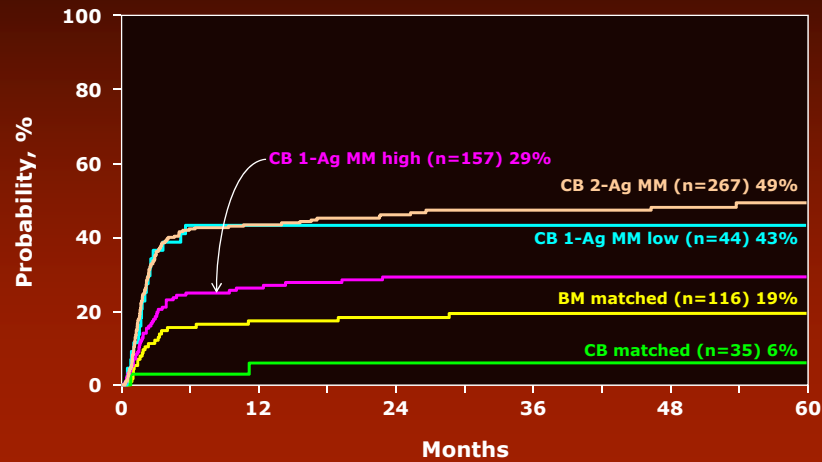
Eapen M; Lancet Oncol 2010

Neutrophil Recovery - Adults; Reduced Intensity Conditioning -



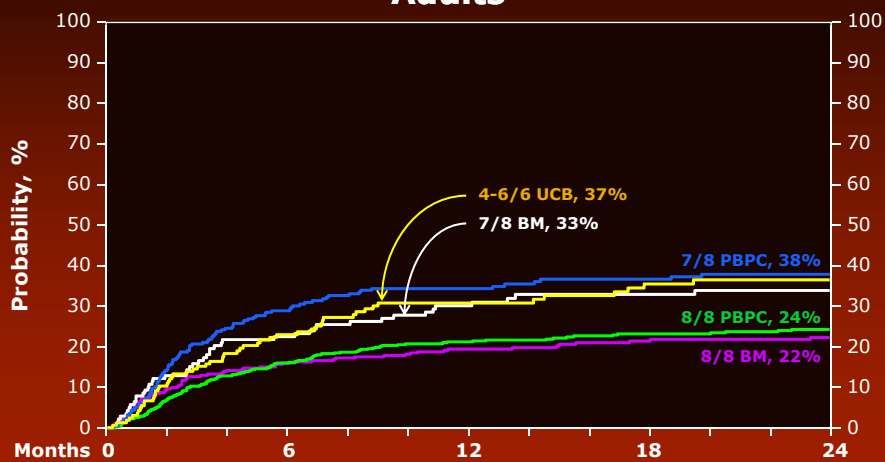
Brunstein C; Blood 2012

Treatment-related Mortality - Children -



Eapen M et al; Lancet 2007

Transplant-related Mortality - Myeloablative Conditioning - - Adults -

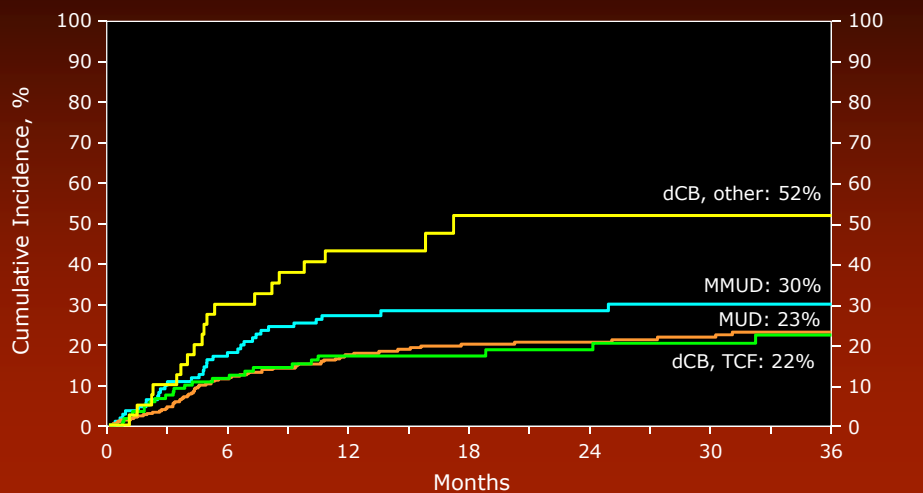


Eapen M; Lancet Oncol 2010

Transplant-related Mortality

- Reduced Intensity Conditioning -

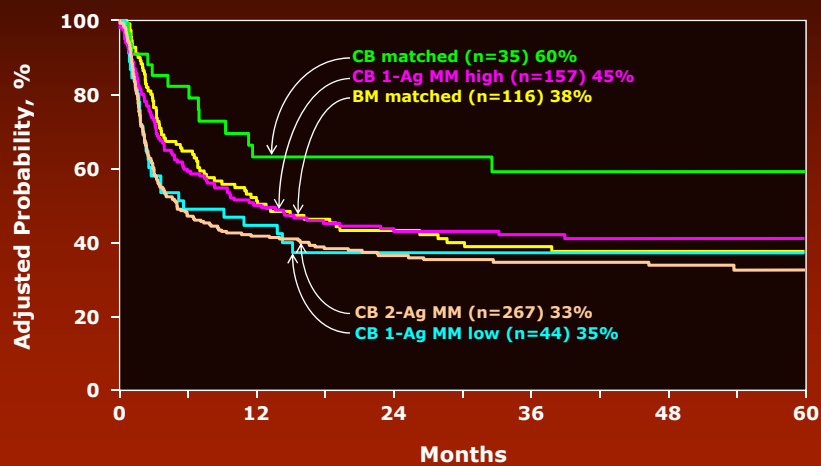
- Adults -



Brunstein C et al; Blood 2012

Leukemia-free Survival

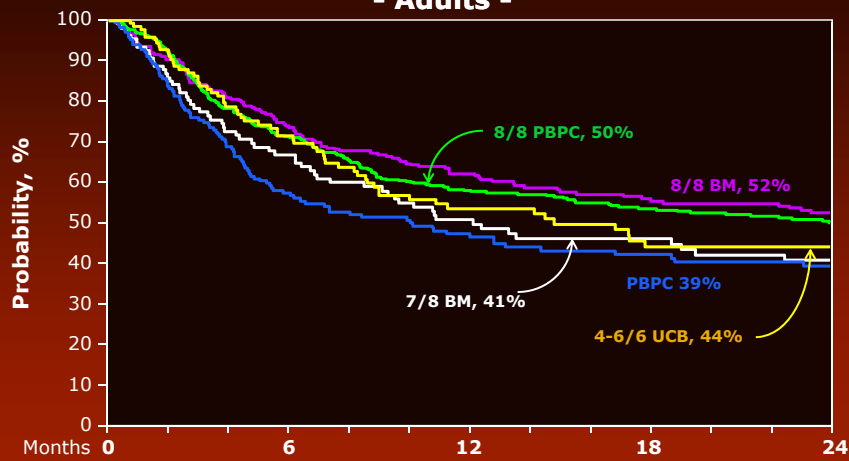
- Children -



Eapen M; Lancet 2007

Leukemia-free Survival

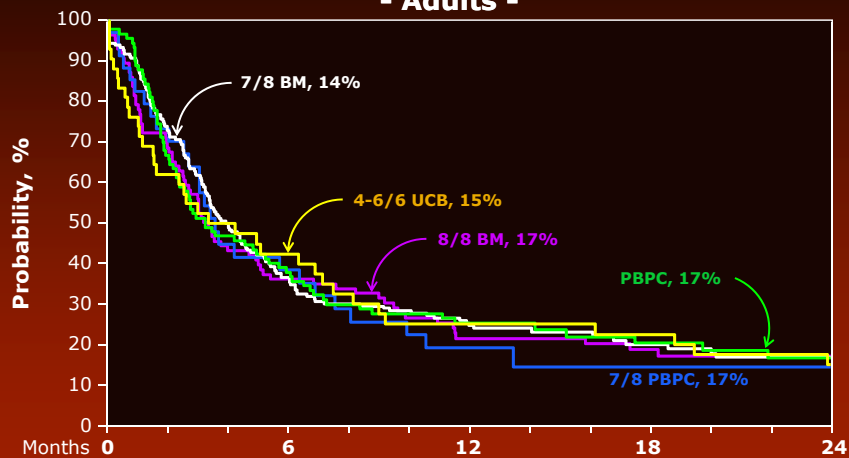
- Transplantation in Remission -
- Adults -



Eapen M; Lancet Oncol 2010

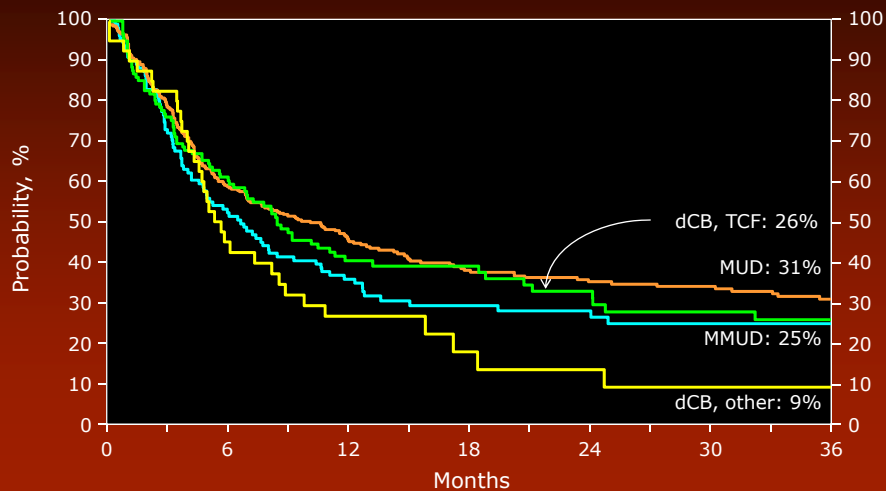
Leukemia-free Survival

- Not in Remission at Transplantation -
- Adults -



Eapen M; Lancet Oncol 2010

Leukemia-Free Survival - Reduced Intensity Conditioning - - Adults -



Brunstein C; Blood 2012

Should Transplantation of Two Cord Blood Units be the Standard for Adults?

- Approximately 80 - 85% of cord blood transplants in the U.S., infuse two units
- Practice variation
 - Likely that some of these patients may have had an adequately dosed single unit
 - Majority with TNC (sum of unit 1 & 2) in excess of $3 \times 10^7/\text{kg}$

Should Transplantation of Two Cord Blood Units be the Standard for Adults?

- **Study Objective**
 - Address the question of whether infusing 2 units could effectively create an adequately dosed graft for those without access to an adequately dosed single unit
 - Compared hematopoietic recovery, GVHD and survival after transplantation of 2 UCB units to that after 1 UCB unit with an adequate cell dose

Should Transplantation of Two Cord Blood Units be the Standard for Adults?

- **Ideal study design**
 - Randomized trial
 - Each patient has an adequately dosed single unit
 - Randomized to receive one or two units
- **Randomized trial in children/ adolescents**
 - 2007 – 2011
 - All younger patients will have a single unit with adequate TNC – **feasible**
- **None planned in adults – not feasible**

Study Design

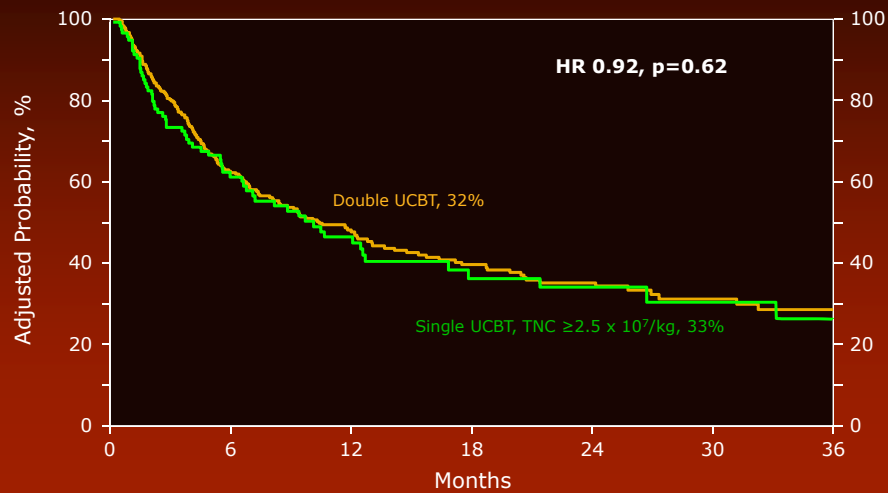
- Used data reported to observational registries
 - CIBMTR; N = 327
 - NYBC; N = 79
- All single units contained
 - $\text{TNC} \geq 2.5 \times 10^7/\text{kg}$
- Lower TNC limit for 1 unit CBTs: BMT CTN 0501
- Almost all two UCB unit transplants
 - $\text{TNC} \geq 3 \times 10^7/\text{kg}$
 - $\approx 10\%$ of 1 unit $\text{TNC} < 1.5 \times 10^7/\text{kg}$

Study Population

- N = 303 recipients of double UCBT
- N = 106 recipients of single UCBT
- AML or ALL
- Transplant period: 2002 – 2009
- Several differences b/w two groups
 - **Single UCB recipients** were younger, more likely to be in relapse, MAC conditioning regimen, 6/6 or 5/6 HLA-matched to donor, lower TNC and transplanted prior to 2005

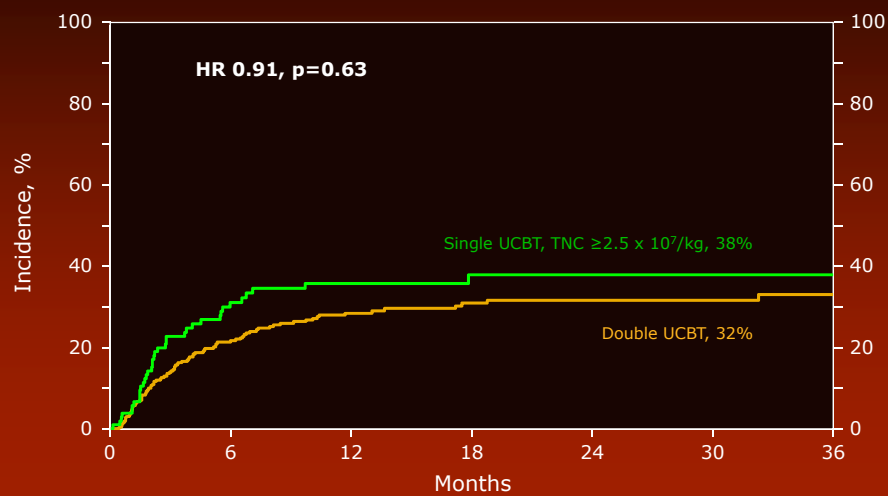
Overall Survival

- Adequate Dose Single vs. Double UCBT -



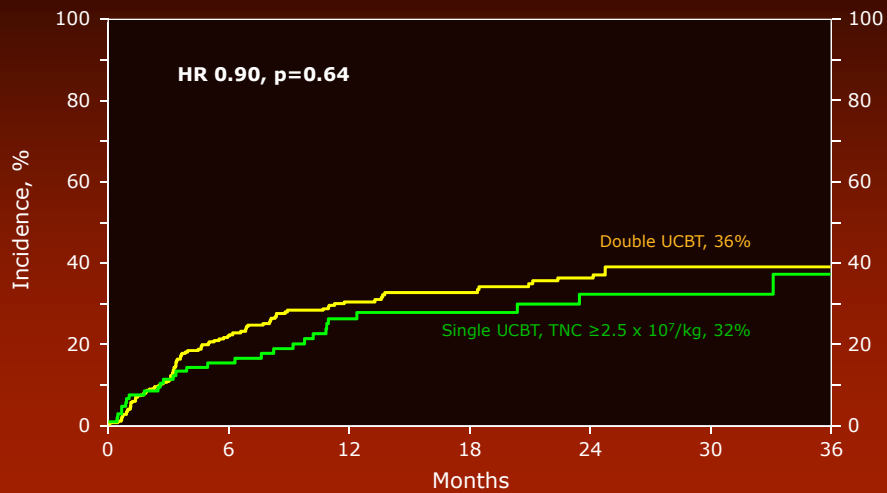
Transplant-related Mortality

- Adequate Dose Single vs. Double UCBT -



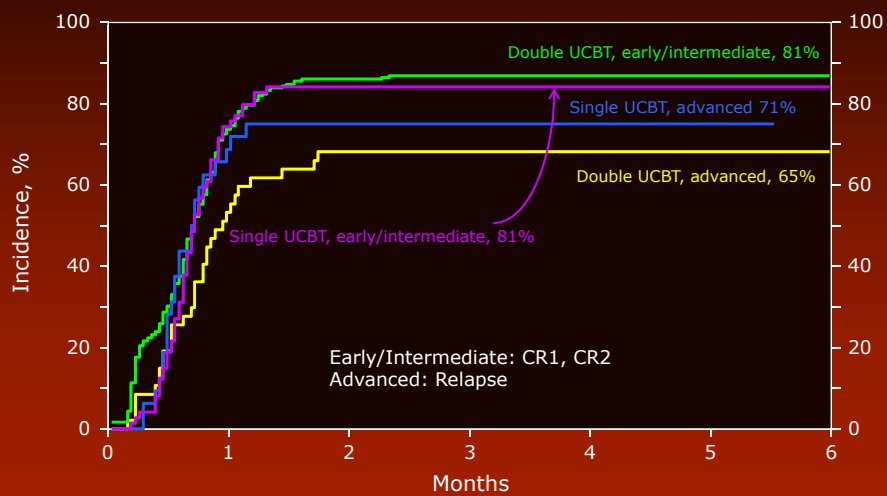
Relapse

- Adequate Dose Single vs. Double UCBT -



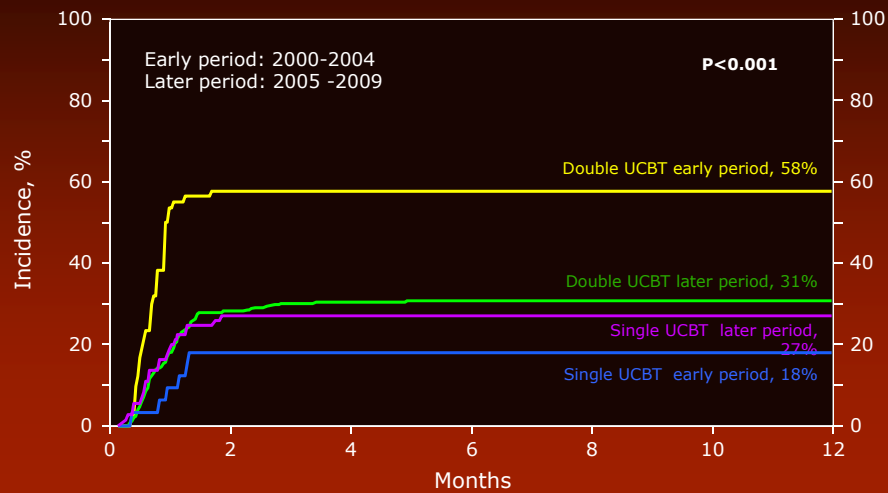
Neutrophil Recovery

- Adequate Dose Single vs. Double UCBT -



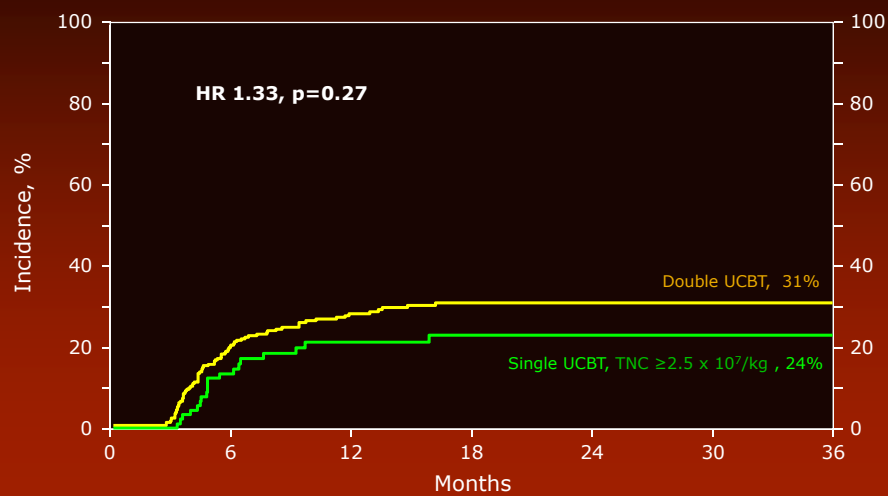
Grade II-IV Acute GVHD

- Adequate Dose Single vs. Double UCBT -



Chronic Graft vs. Host Disease

- Adequate Dose Single vs. Double UCBT -



SUMMARY

- **These data confirm**
 - Infusing 2 UCB units overcomes the cell dose barrier
 - Thereby making this treatment accessible to a substantial number of adults
 - Survival after transplantation using a single unit (adequate dose) is comparable to that after two units
- **Not addressed**
 - Are outcomes superior with better donor-recipient HLA match?

SUMMARY

- Infusing 2 UCB units overcomes the cell dose barrier
- Transplantation of 1 or 2 UCB units results in survival rates comparable to that after HLA-matched adult donor grafts for acute leukemia
- Longer follow-up (>5 years) will determine whether lower GVHD risks associated with UCB transplants translate to long-term survival advantage compared to adult donor grafts

Is there a Survival Advantage after Double Umbilical Cord Blood Compared to Single UCB Transplant in Children with Hematologic Malignancy?



JE Wagner, M Eapen, SL Carter, P Haut, E Perez, K Schultz, J Thompson, D Wall and J Kurtzberg



Background

- Pilot data suggested that infusion of two partially HLA-matched UCB units is safe.

Parameter	COBLT	Minnesota
Total pts	191	40
Study interval	2000-2003	2000-2004
Conditioning	TBI CY ATG	FLU CY TBI
GVHD proph	CSA MP	CSA MMF
Median age	7.7 (0.9-18.9)	24 (13-53)
Median weight	25.1 (7.5-118)	77 (48-120)
Median TNC	$5.2 \times 10^7/\text{kg}$	$4.3 \times 10^7/\text{kg}$
Engraftment	75% (CI 69-81)	100%
DFS at 1 year	50% (CI 43-56)	57% (CI 35-79)



- Cell dose is an important factor influencing engraftment and survival (threshold $2.5 \times 10^7/\text{kg}$).

Hypothesis

Increased cell dose in recipients of double UCBT will be associated with improved survival

Primary Objective

Compare 1-year overall survival after double and single UCB transplant using an intent-to-treat analysis



Treatment Schema

Eligibility

- Age
- Disease
- Performance status
- Organ function
- Two adequate UCB units

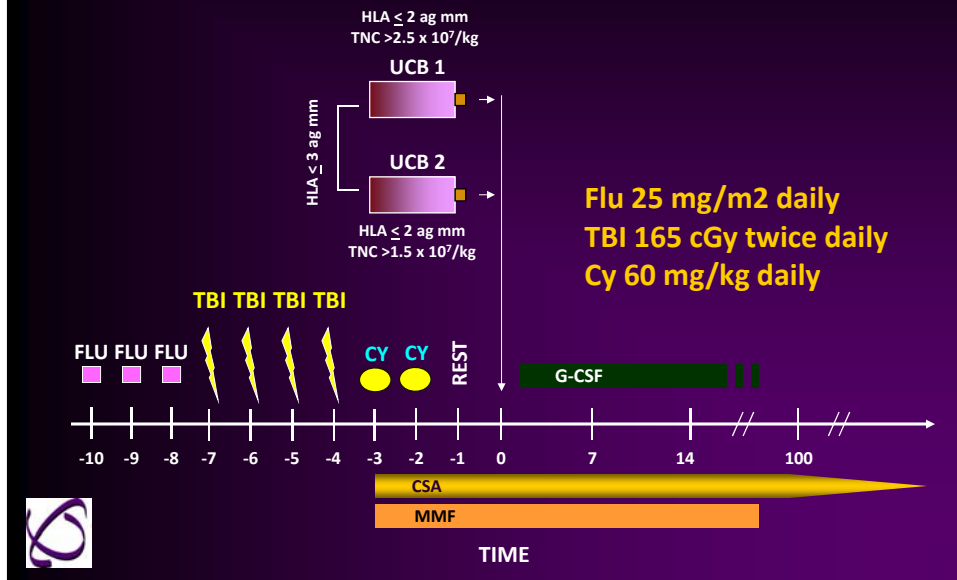
Randomization

One UCB unit
Target N = 110

Two UCB units
Target N = 110



Treatment Schema



Patients

- 224 patients enrolled over 32 transplant centers between 12/2006 – 02/2012
 - 111 were randomized to receive double UCBT
 - 113 were randomized to single UCBT
- **Compliance >95%**
 - Cross-over
 - 2.7% single UCB → double UCB
 - 1% double UCB → single UCB
 - 1.8% in both groups were not transplanted

Inclusion Criteria

- Age: 1 – 21 years old
- Performance score ≥ 70
- Diseases:
 - ALL, AML, NK leukemia
 - First, second or subsequent complete remission
 - First relapse (BM blasts $<25\%$)
 - Minimal residual disease positive
 - CML: chronic or accelerated phase
 - MDS: any stage



Diseases

	Double UCB N = 111	Single UCB N = 113
AML	38 (34%)	39 (35%)
ALL	58 (52%)	61 (54%)
Other AL	2 (2%)	7 (6%)
MDS	13 (12%)	5 (4%)
CML	—	1 (1%)

- Groups were well matched for age, gender, race, performance status, and disease status



Donor-Recipient HLA Match

	Double UCB N = 111	Single UCB N = 110
HLA match grade*		
6/6	12 (11%)	16 (14%)
5/6	46 (42%)	50 (45%)
4/6	49 (45%)	44 (40%)
3/6	2 (2%)	1 (1%)

* Presented as the worst matched unit for double UCBT

HLA match criteria: HLA A and B at **antigen** level

HLA DRB1 at **allele** level

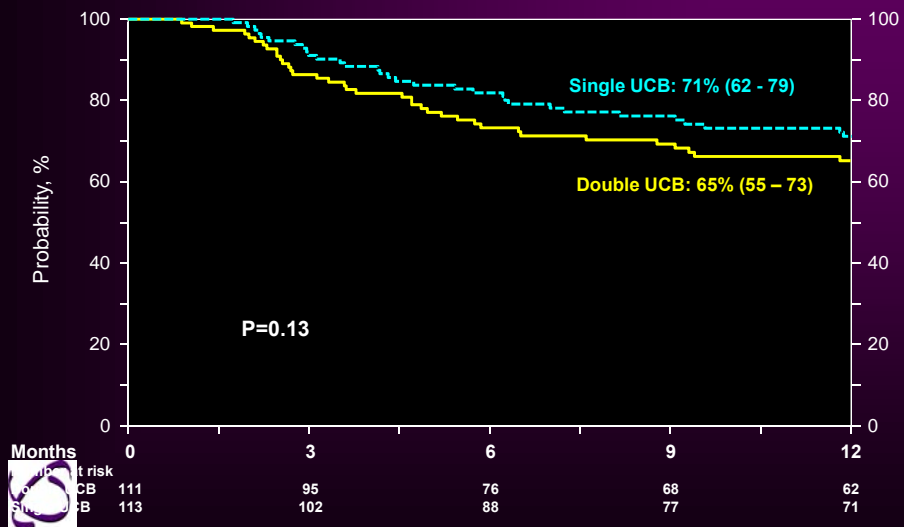


Cell Doses

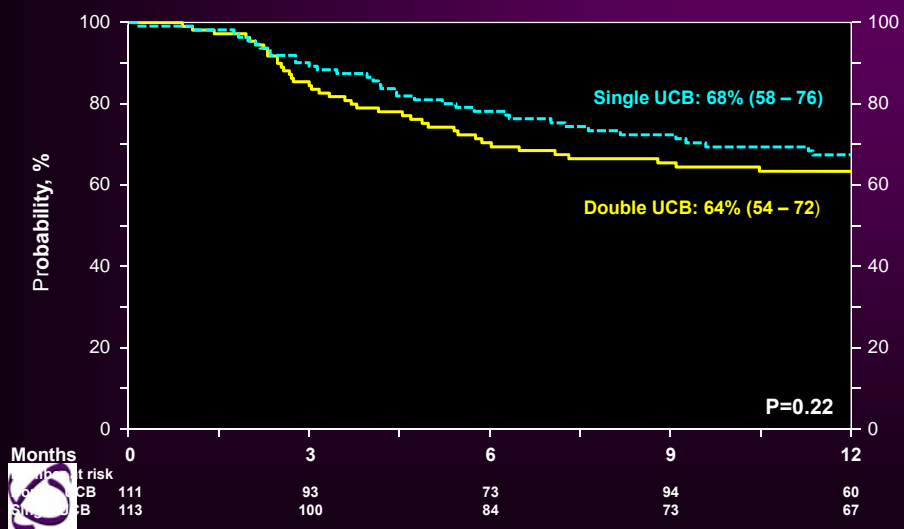
	Double UCB N = 111	Single UCB N = 113
TNC (cryo)	8.9×10^7	4.8×10^7
TNC (thaw)	7.2×10^7	3.9×10^7
CD34 (thaw)	3.7×10^5	1.9×10^5



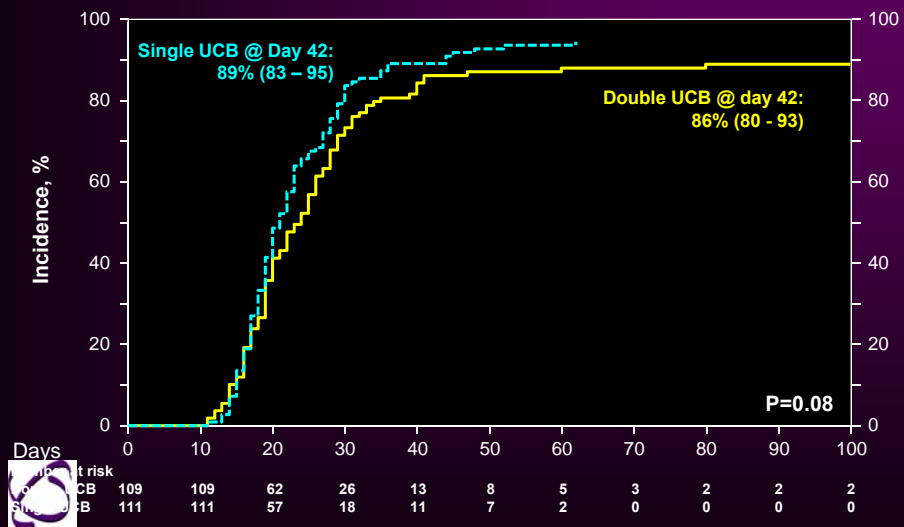
Overall Survival - Intent-to-Treat -



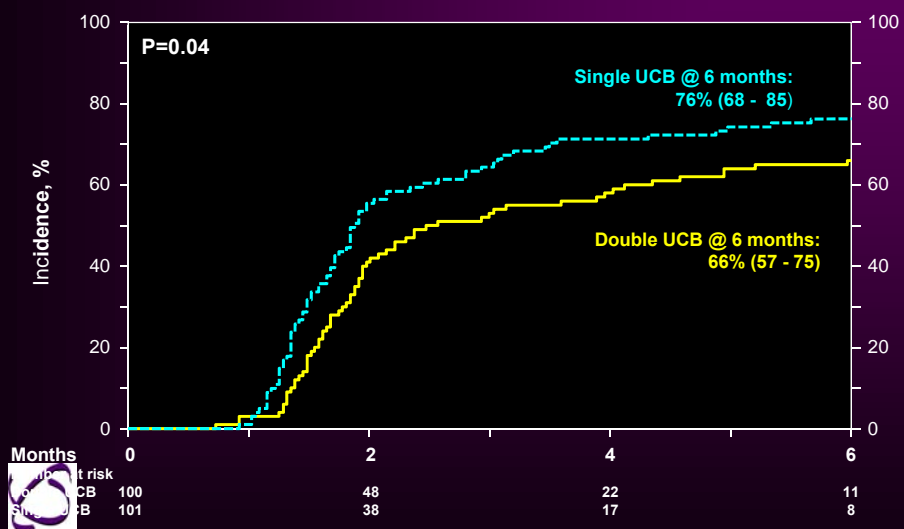
Disease-free Survival - Intent-to-Treat -



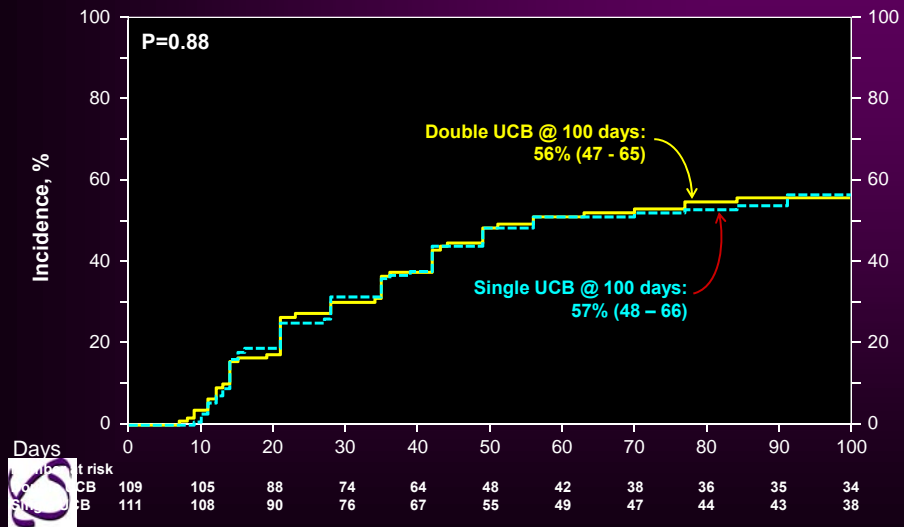
Neutrophil Recovery - Transplanted -



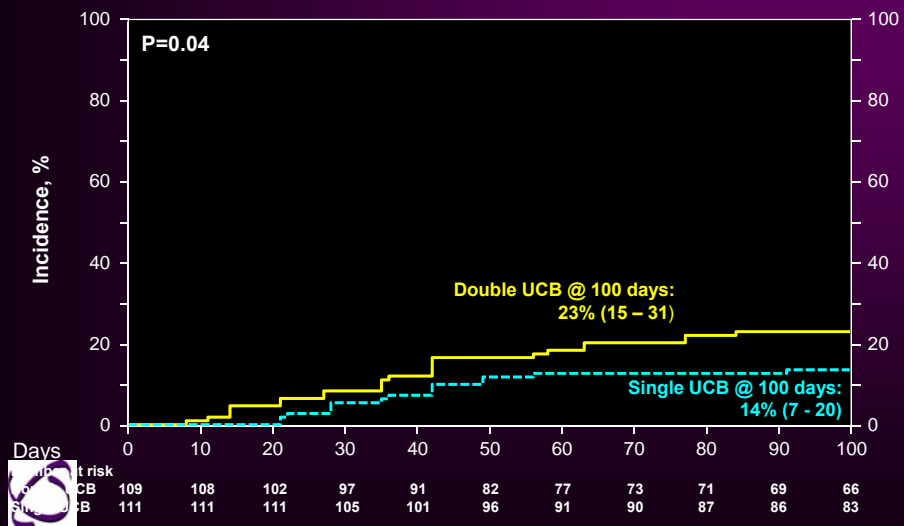
Platelet Recovery - Transplanted -



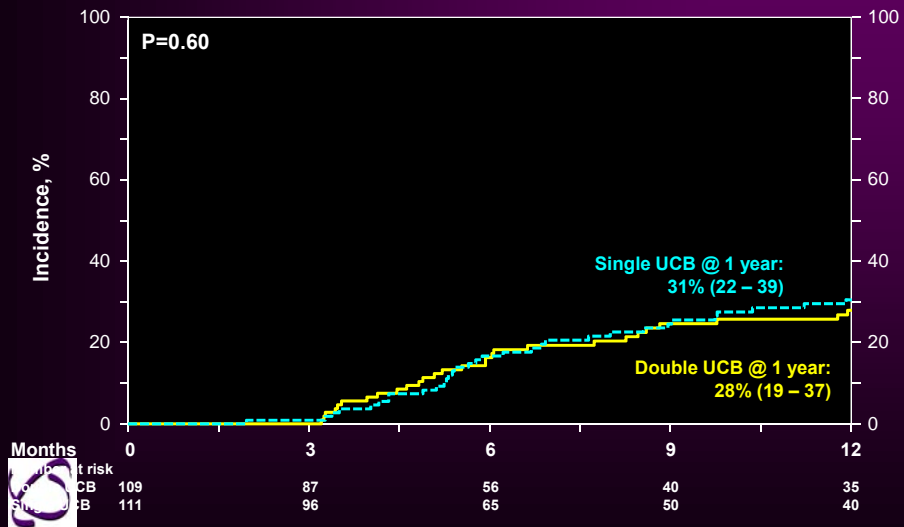
Grade II – IV Acute GVHD - Transplanted -



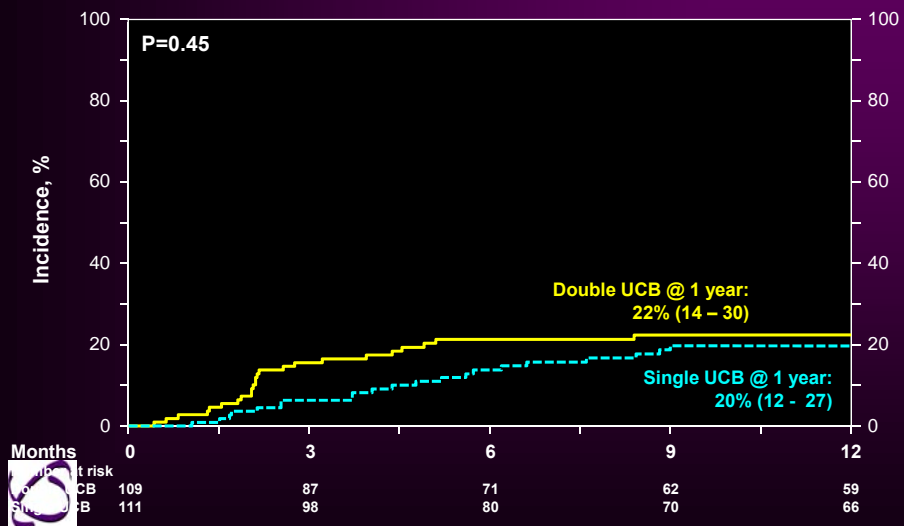
Grade III-IV Acute GVHD - Transplanted -



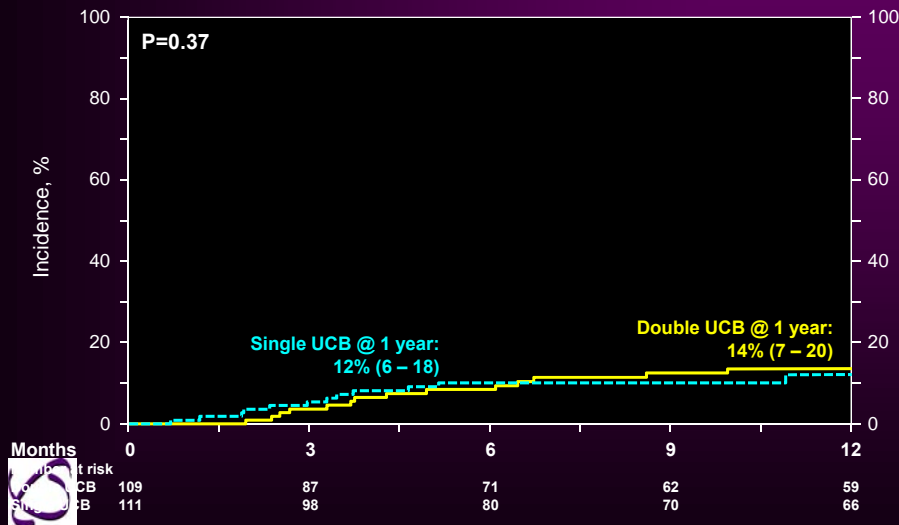
Chronic GVHD - Transplanted -



Non-relapse Mortality - Transplanted -



Relapse - Transplanted -



Summary



- Survival after double UCBT in children is not enhanced compared to those transplanted with an adequately dosed single UCB unit
- All outcomes were similar between the two groups except for a lower incidence of platelet recovery and higher incidence of grade III-IV aGVHD in recipients of two units
- Single UCB should be considered the standard graft for children undergoing UCBT; the use of a double UCB graft should be reserved for those without a suitable single UCB unit



Is Allele-Level HLA-Matching Relevant for Single Umbilical Cord Blood Transplants?

**Eurocord and Center for International
Blood and Marrow Transplant Research**

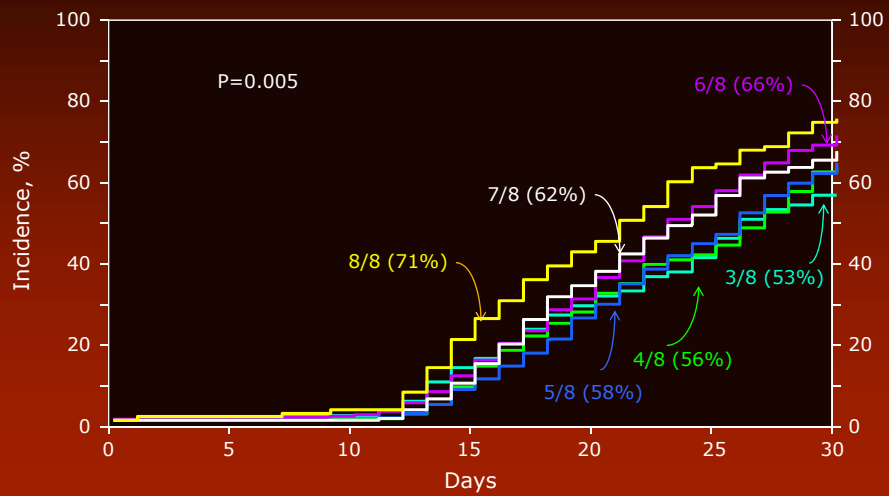
**M Eapen, JP Klein, A Ruggeri, S Spellman, W Arcese, LA
Baxter-Lowe, M Fernandez-Vina, MM Horowitz,
SJ Lee, F Locatelli, A Paolo Lori, S Marino, G Michel, GF
Sanz, E Gluckman and V Rocha**

Study Population

- **N = 1568 donor – recipient pairs**
- **Hematologic malignancy**
 - **AML (38%), ALL (52%), MDS (10%)**
- **Transplant period: 2000 - 2010**
- **Single UCB unit**
- **Myeloablative conditioning regimen**
- **Calcineurin inhibitor GVHD prophylaxis**
- **Median follow-up: 4 years**

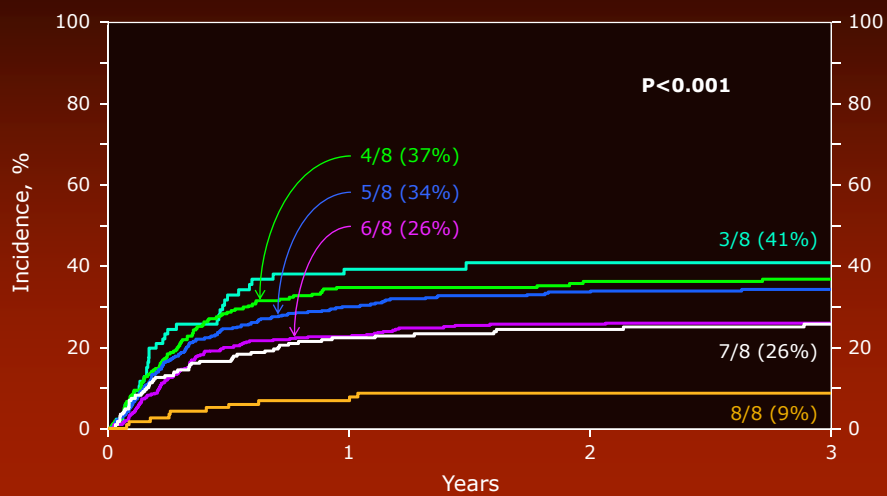
Neutrophil Recovery

- Allele-level Matched at A, B, C, DRB1 -



Non-Relapse Mortality

- Allele-level Matched at A, B, C, DRB1 -

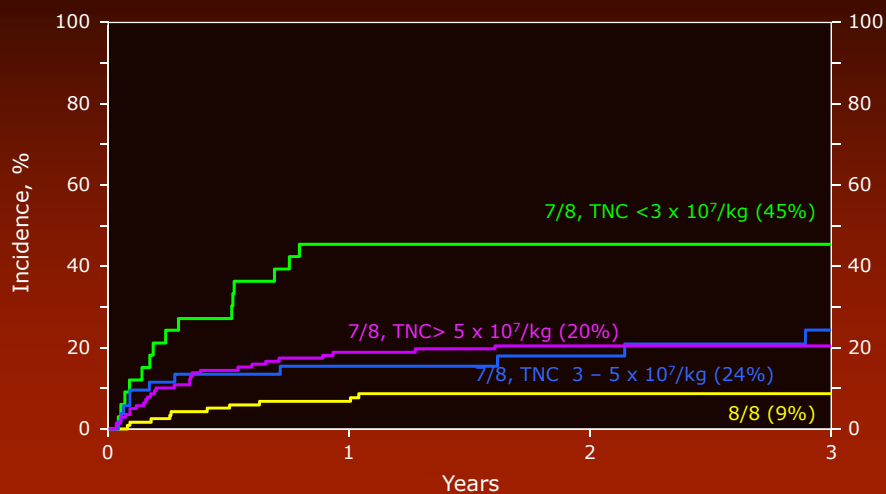


DONOR AVAILABILITY

Inventory Size	Current			X 3 current		
	8/8	7/8	6/8	8/8	7/8	6/8
African American	5%	33%	80%	7%	43%	87%
South East Asian	7%	33%	75%	13%	45%	85%
Alaskan Native	11%	42%	83%	16%	54%	91%
Native American Indian	10%	44%	85%	17%	59%	91%
Caucasian	36%	81%	98%	48%	88%	99%

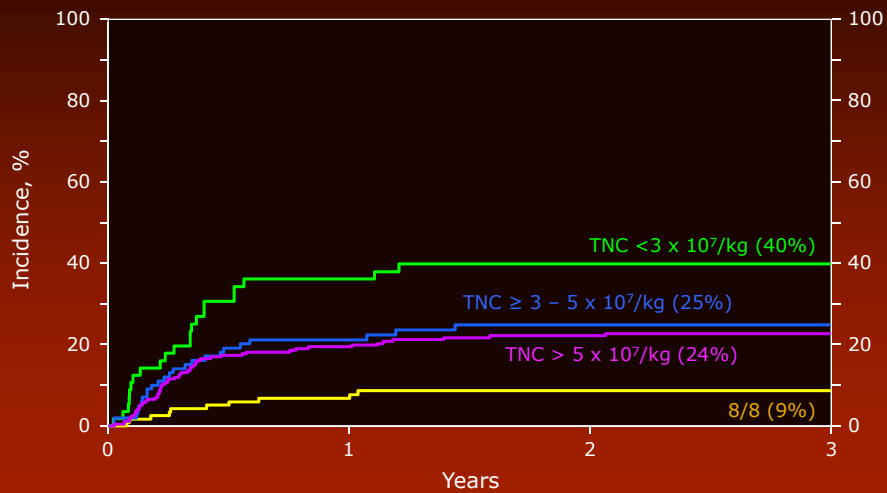
Non-Relapse Mortality

- 7/8 Allele-level HLA-Matched: Effect of TNC -



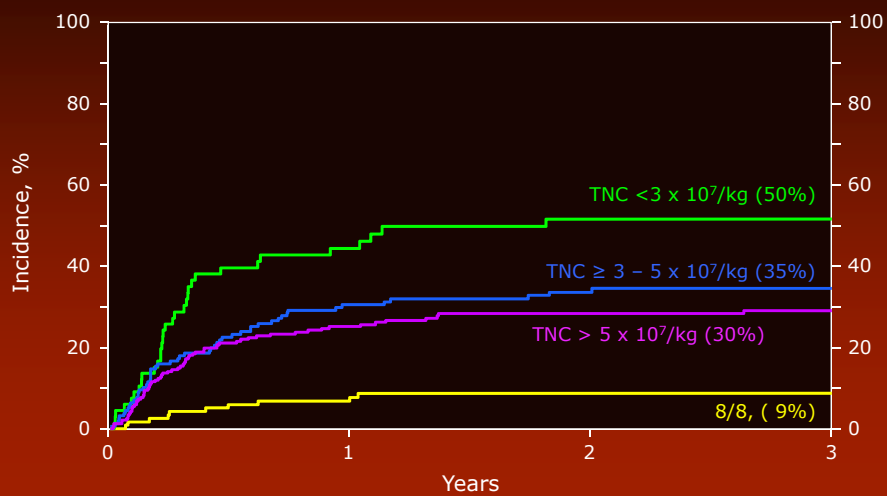
Non-Relapse Mortality

- 6/8 Allele-level HLA-Matched: Effect of TNC -



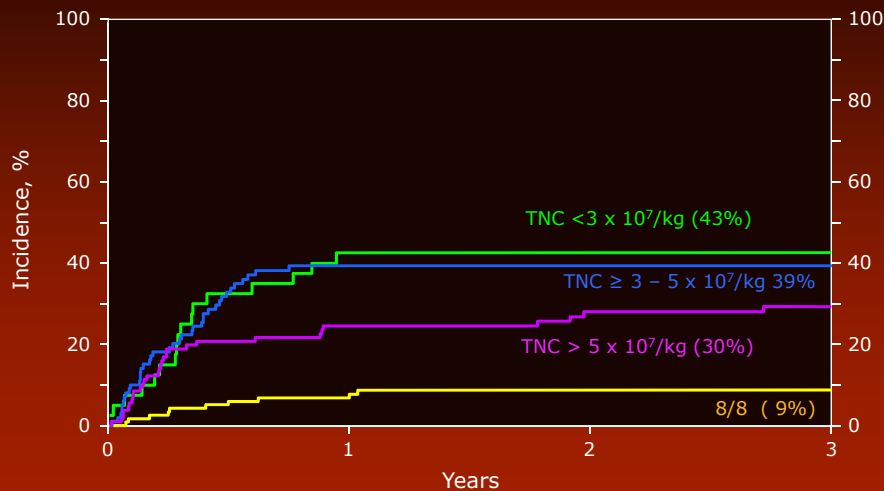
Non-Relapse Mortality

- 5/8 Allele-level HLA-Matched: Effect of TNC -



Non-Relapse Mortality

- 4/8 Allele-level HLA-Matched: Effect of TNC -



What have we learned?

- Large single UCB units are being selected
 - Median TNC is in excess of $3 \times 10^7/\text{kg}$
- Co-infusion of two units is acceptable for larger patients - minimum TNC required
- Increasing TNC in excess of the minimum required does not lower TRM
- HLA-match between the unit and recipient is important – lower TRM with better matched and adequately dosed units



Select units with minimum TNC $3 \times 10^7/\text{kg}$
TNC in excess of minimum required does not lower NRM

Best HLA-match

Allele-level match at HLA-A, -B, -C and -DRB1

Avoid 5/8, 4/8 and 3/8
HLA-matched transplants

7/8 and 6/8 HLA-
matched transplants
are better tolerated
than other mismatches

