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Rapid and Robust CD4+ and CD8+ T-, NK-, B- and Monocyte Cell Reconstitution after Nicotinamide-Expanded Cord Blood Transplantation

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Disclosures

- DMC member / chair (consulting):
 - Magenta, Chimerix, Bluebird Bio
- Consulting:
 - Avrobio, Takeda
- Grants: Sanofi (unrestricted)



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Today messages

- CD4+ reconstitution after Nicotinamide-expanded CBT is **at least as fast as unmanipulated CBT and BMT** in adolescents and young adults
- Immune reconstitution after NiCord transplantation was associated with recovery of a broad spectrum of T-, B- and NK-cell subsets



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Cord blood as Hematopoietic (Stem) Cell Source (HCS)

Advantages

Readily available HSC

Some mismatch is allowed (donor available for many patients)

Less chronic GvHD vs. Matched

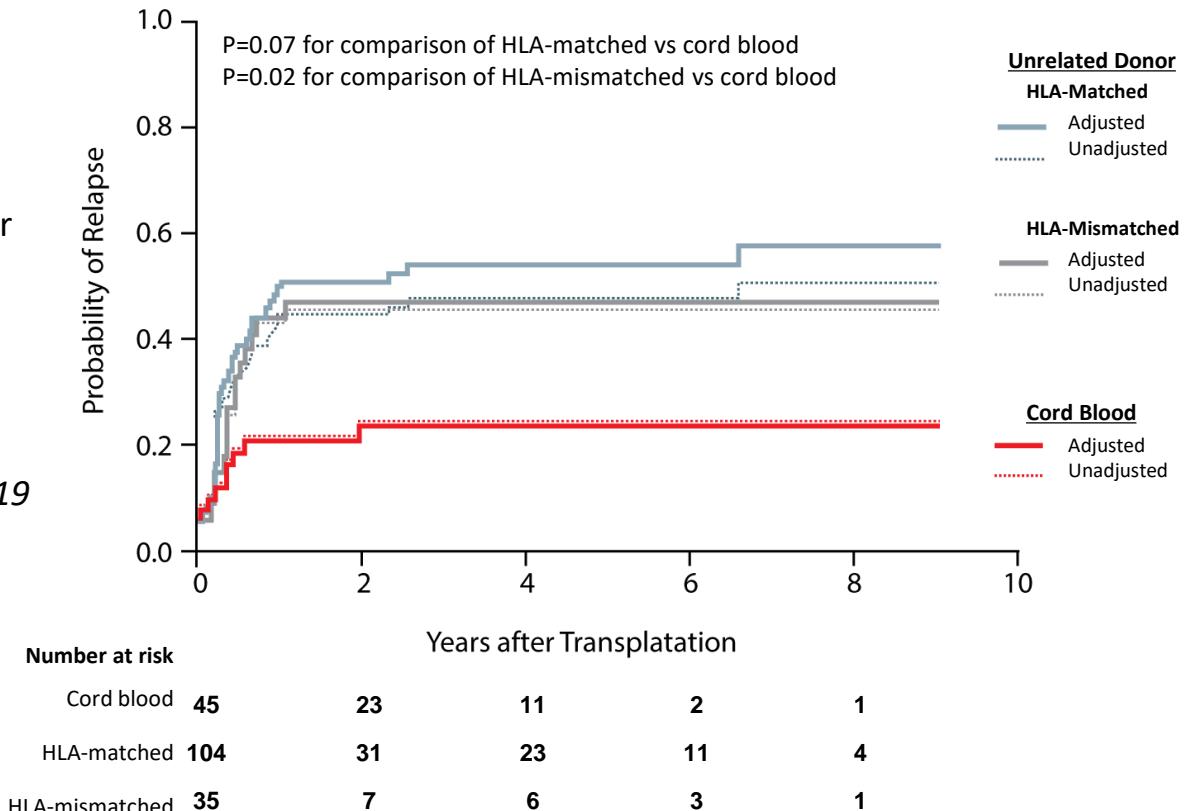
Unrelated donor

Eapen M et al Lancet 2010

Langenhorst, Blood Advances 2019

Potent anti-tumor activity

Milano F et al NEJM 2016

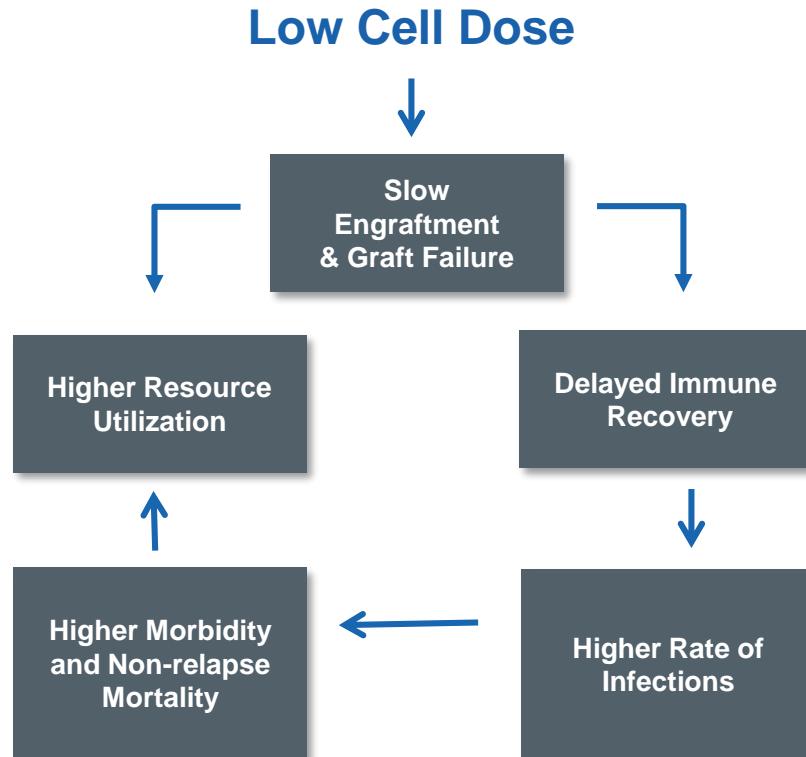


Cord blood as HCS

Disadvantages

Low cell dose leads to delayed hematopoietic recovery

Increased resource utilization



Solution:

Nicotinamide expansion of uCB-unit

- *Ex-vivo* expansion from entire uCB unit
 - CD133+ cultured fraction
 - CD133- non-cultured
 - T-cell containing fraction is cryopreserved until transplantation
- Culture system:
 - Culture media + **Nicotinamide** + cytokines:
 - TPO, IL-6, FLT-3 ligand and SCF
- Culture length: 21 +/- 2 days



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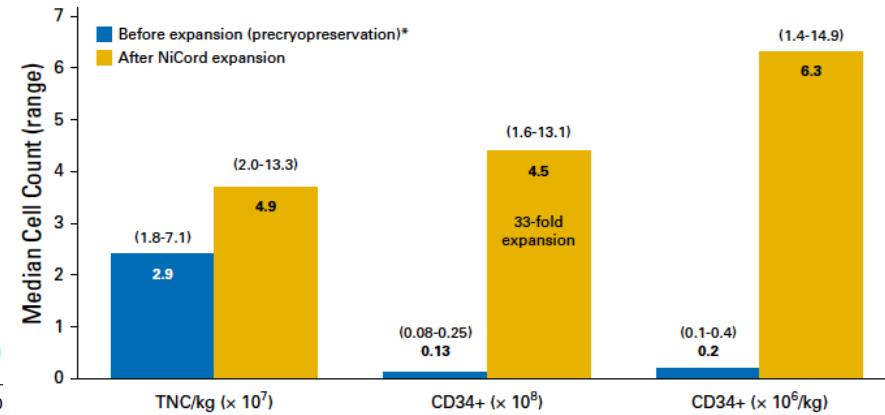
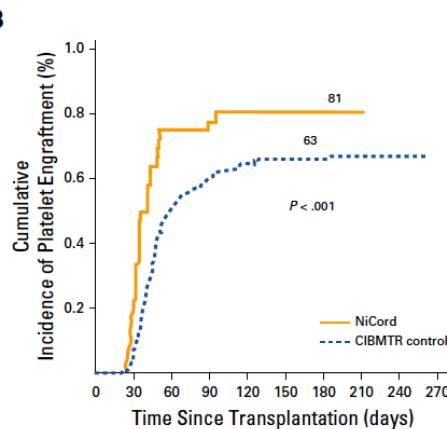
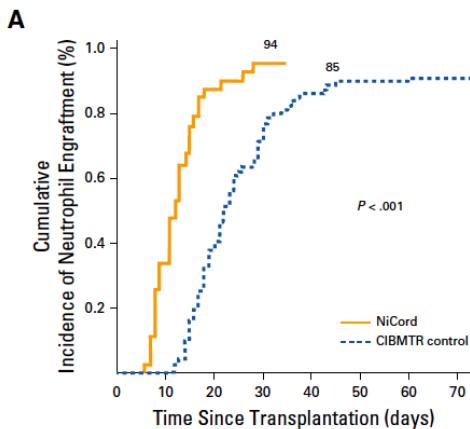
Phase I/II Study of Stem-Cell Transplantation Using a Single Cord Blood Unit Expanded Ex Vivo With Nicotinamide

Mitchell E. Horwitz, Stephen Wease, Beth Blackwell, David Valcarcel, Francesco Frassoni, Jaap Jan Boelens, Stefan Nierkens, Madan Jagasia, John E. Wagner, Jurgen Kuball, Liang Piu Koh, Navneet S. Majhail, Patrick J. Stiff, Rabi Hanna, William Y.K. Hwang, Joanne Kurtzberg, Daniela Cilloni, Laurence S. Freedman, Pau Montesinos, and Guillermo Sanz

JOURNAL OF CLINICAL ONCOLOGY

Dec 2018

N=36, med.age 44 (13-63) yrs



Phase I/II median CD34+ cells infused: $6.4 \times 10^6/kg$
Phase I/II median CD34+ cells infused: $2.3 \times 10^6/kg$

Challenges in HCT for upcoming years

Unmet needs

1. Reducing the Toxicity of HCT:

1. Short term toxicity: viral reactivation, TRM, GvHD
2. Long term toxicity

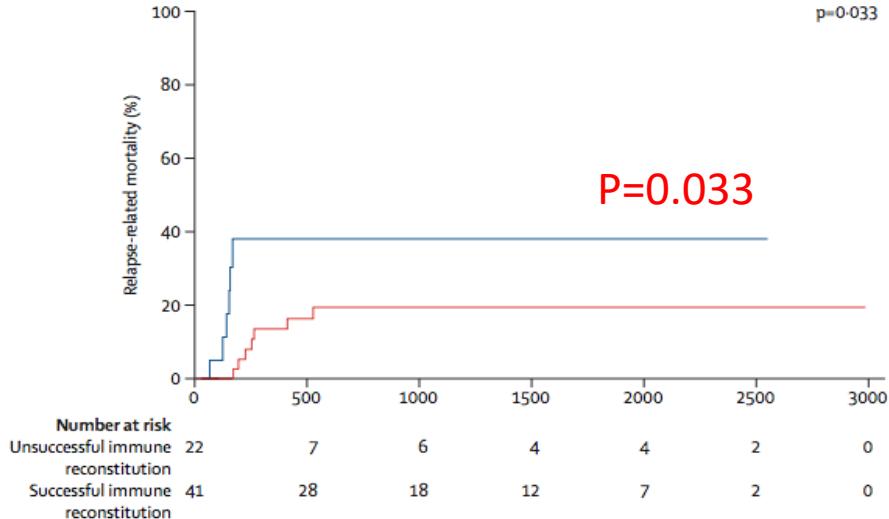
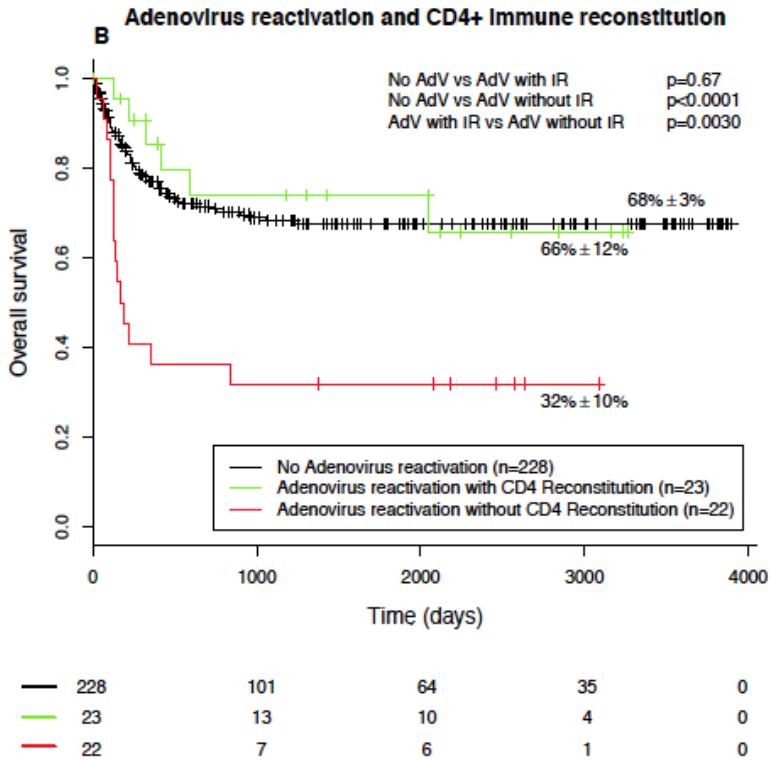
2. Better disease control

**Balanced & Predictable T-cell (CD4+) Reconstitution essential
(e.g. Lancet H 2015, 2017, Blood 2016, JACI 2017)**



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OS according to Adeno and AML-relapse and CD4+ reconstitution



IR definition:

>50/uL, twice within 100 days

Lancet Haem; 2015

JACI 2017

ig

Immune Reconstitution “add on” Study at Central Laboratory

Primary endpoint:

Comparison of probability of CD4 immune reconstitution

Secondary endpoint:

Reconstitution over time of CD4+, CD8+, monocytes, natural killer (NK)- and B-cells, including subsets, TRECs, recent thymic emigrants

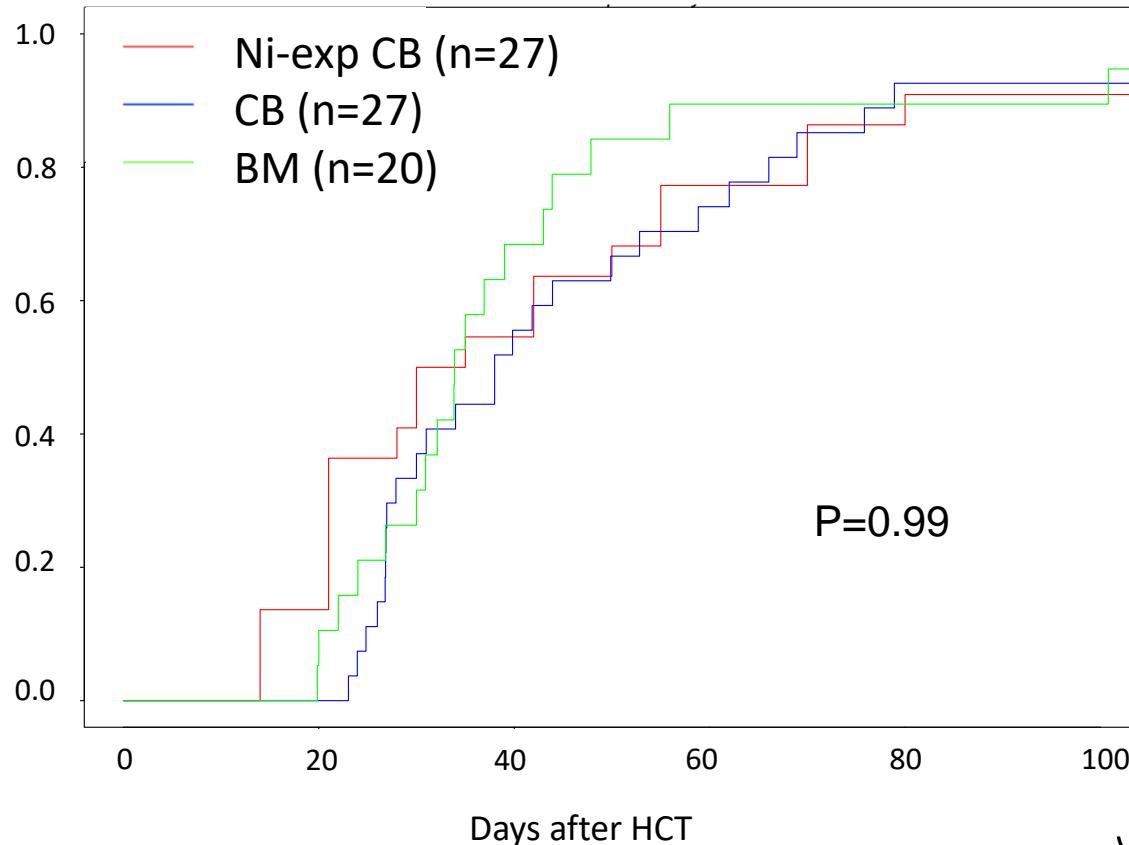
Controls:

UMCU CBT (n=27); median age = 16 (12-28); 100% CloFluBu, malignancy
UMCU BMT (n=20); median age = 14 (12-20); 100% CloFluBu, malignancy



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CD4 immune reconstitution According to Cell Source



>90% IR

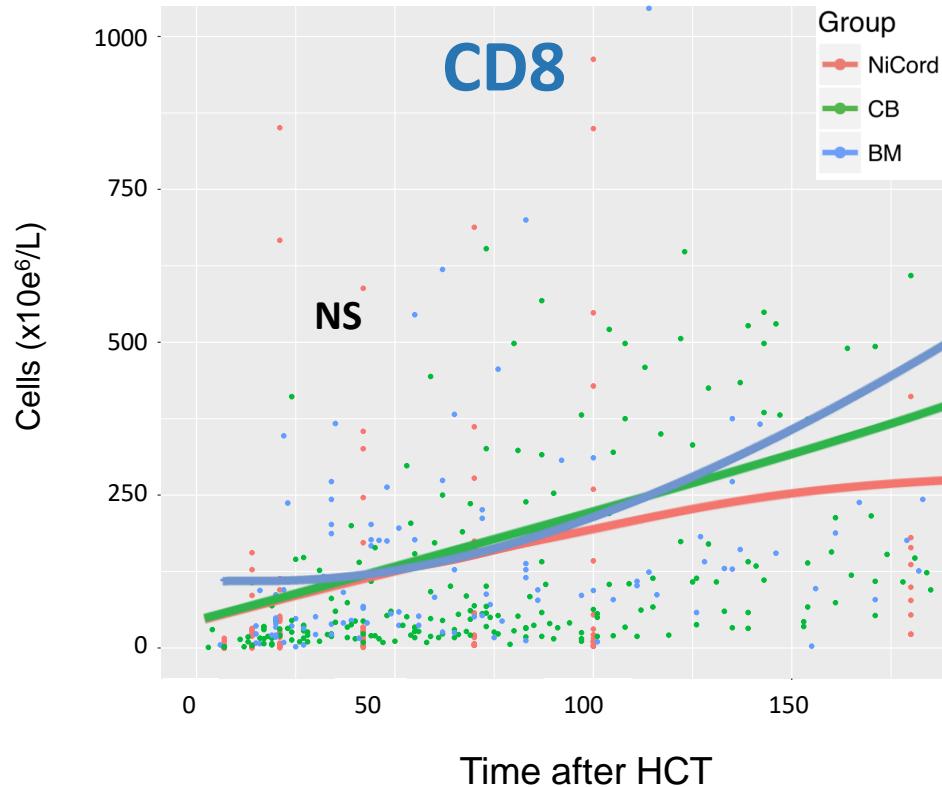
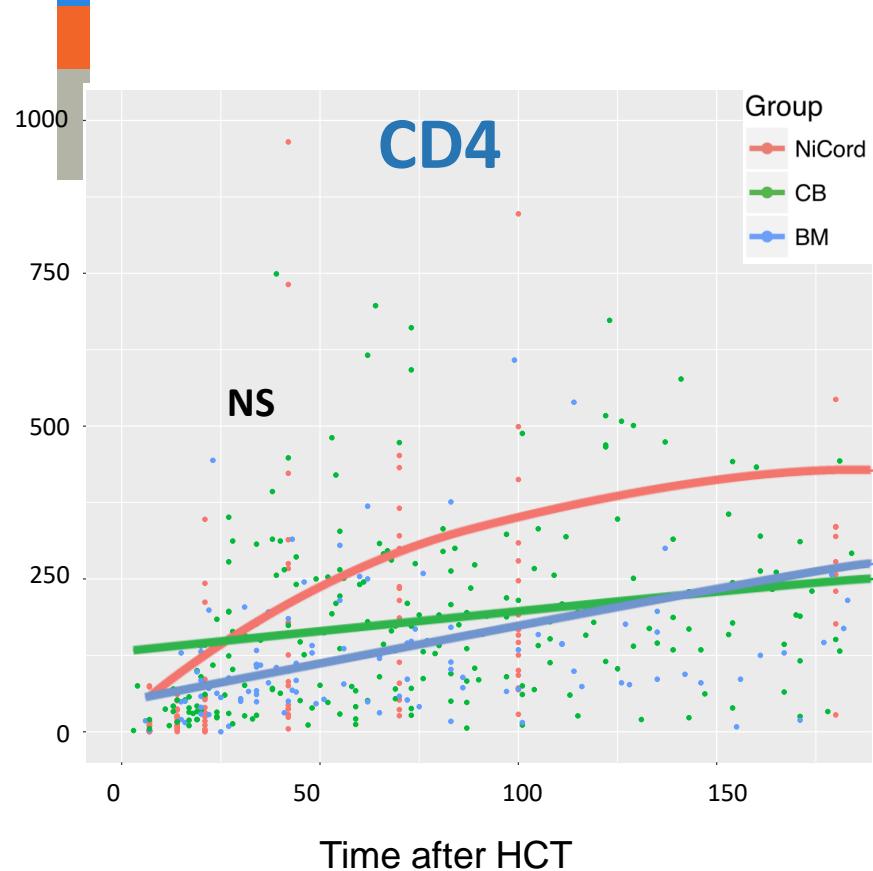
IR = > $50 \times 10^6 / L$
within 100 days

P=0.99



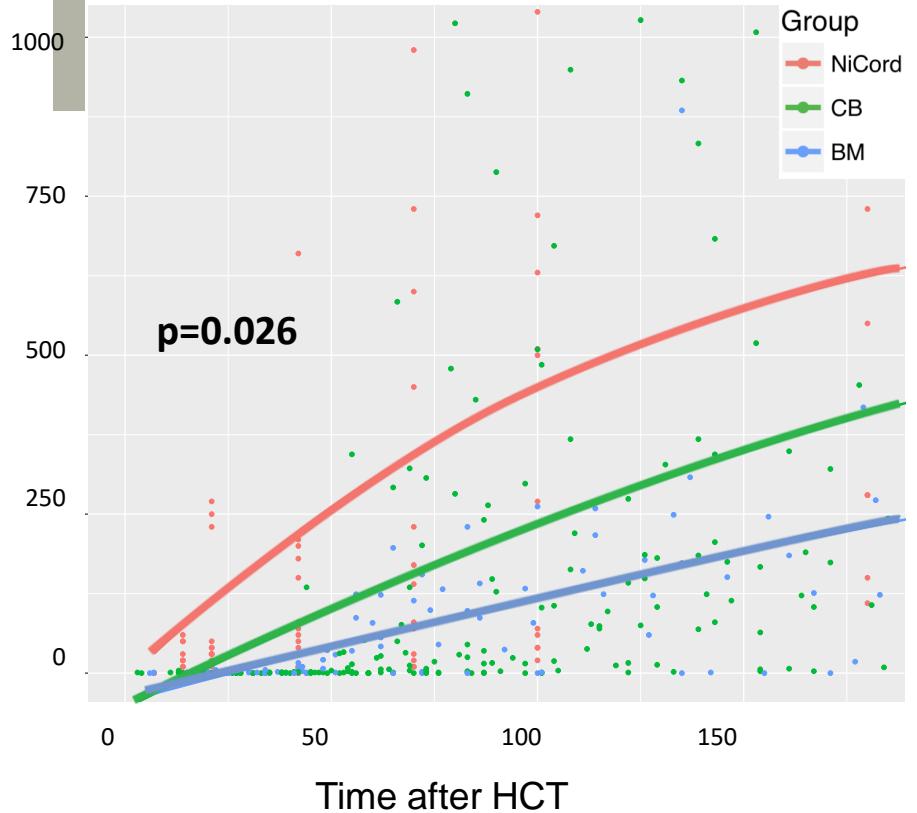
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Ni-exp CB: CD4 and CD8 T cell Reconstitution

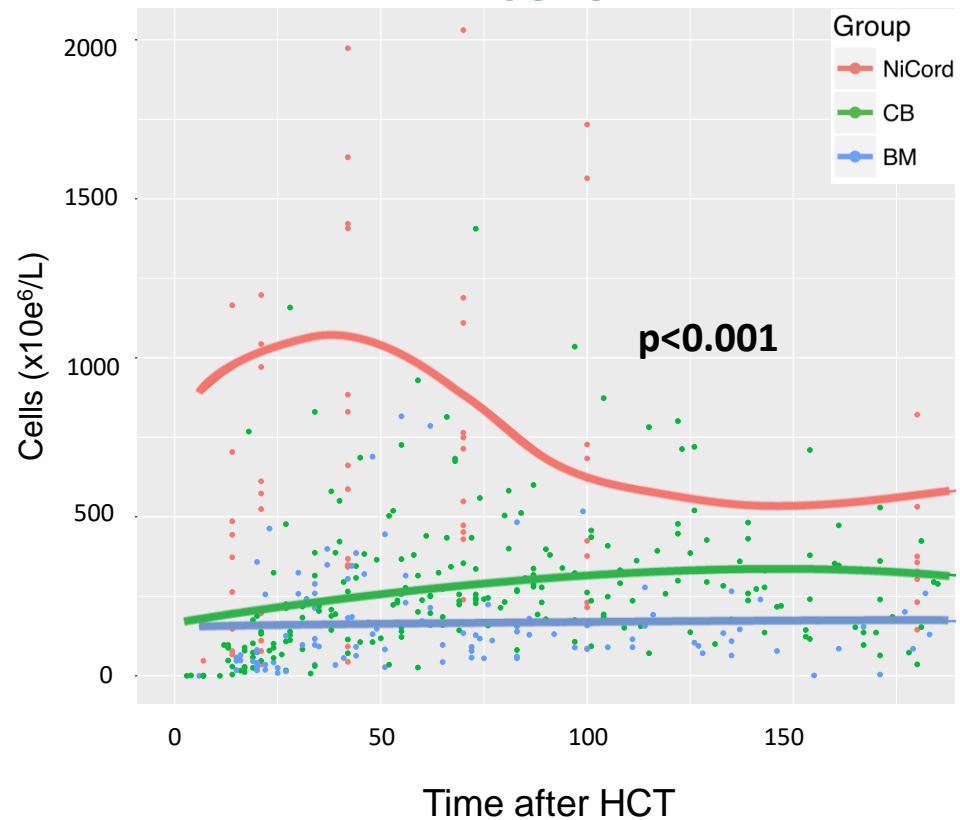


B- and NK-cell Reconstitution according to Cell Source

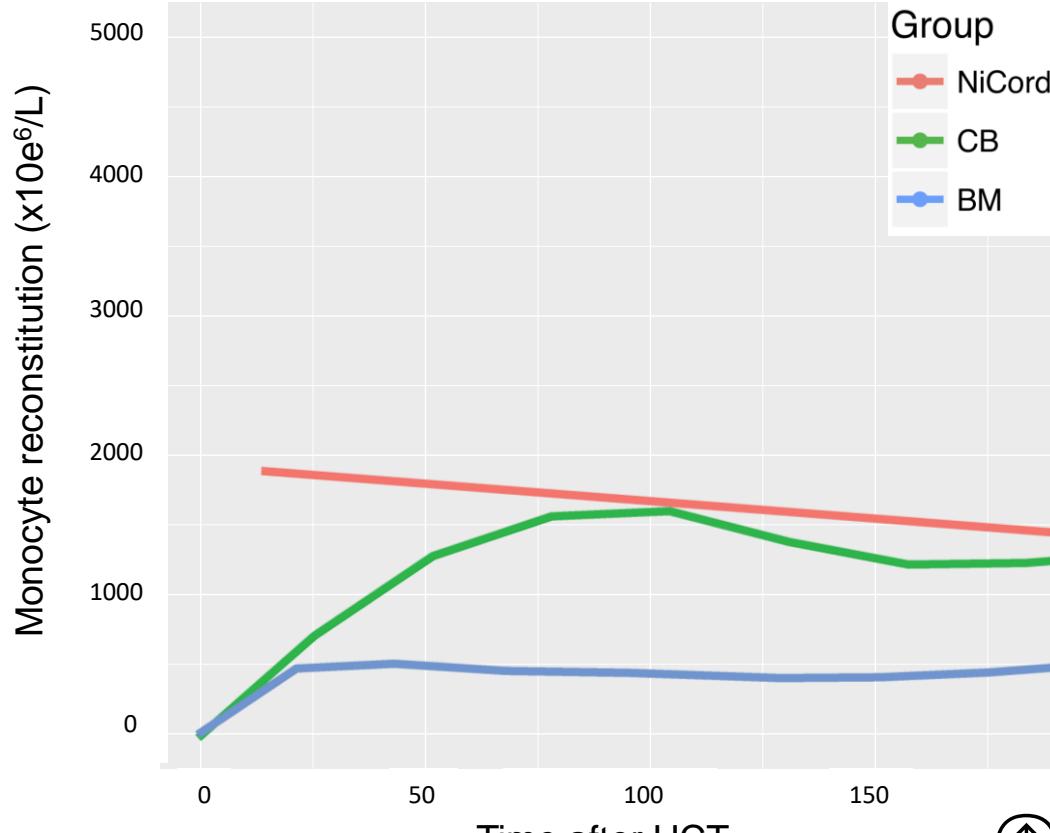
B cells



NK cells

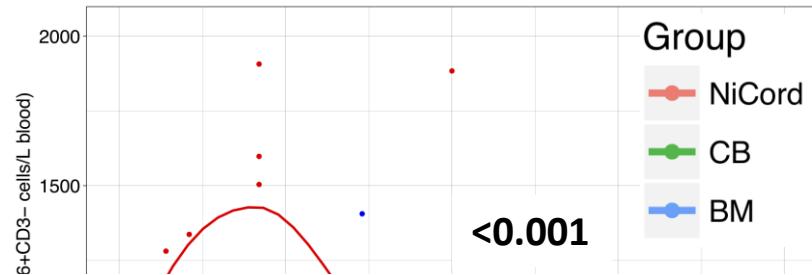


Monocyte immune reconstitution according to Cell source

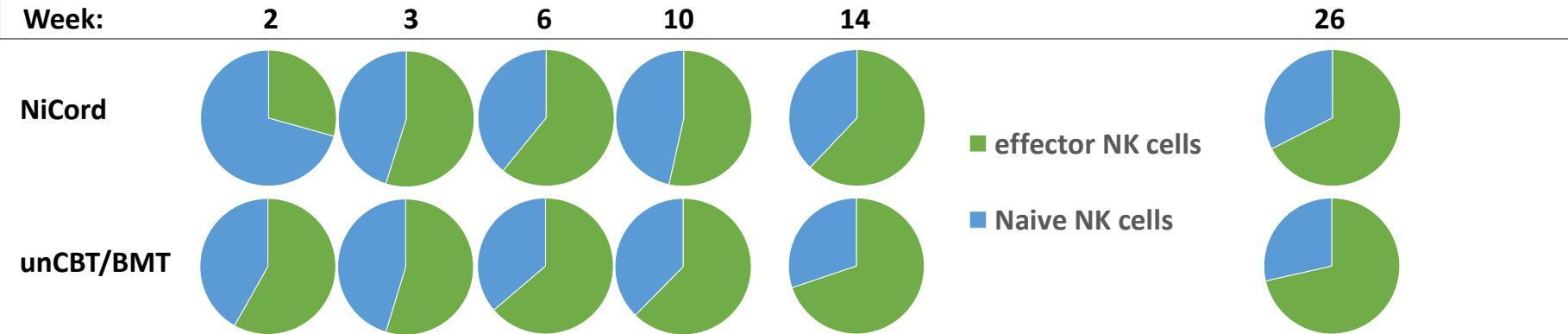


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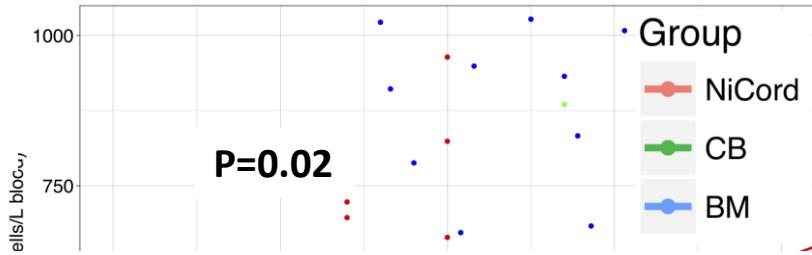
NK cell Reconstitution



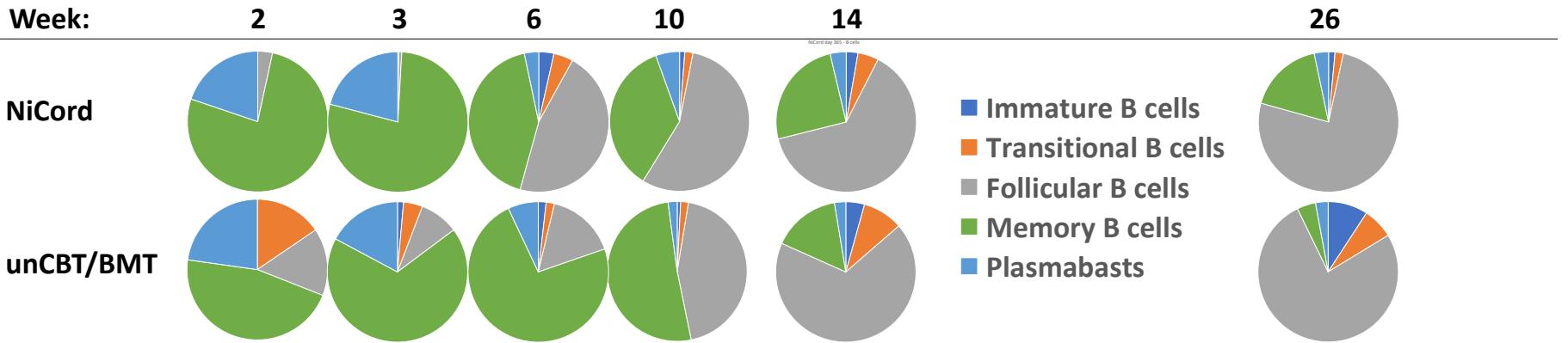
Week:



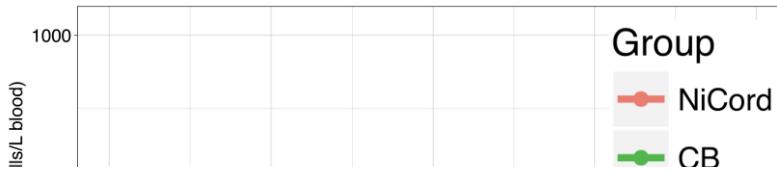
B cell Reconstitution



Week:

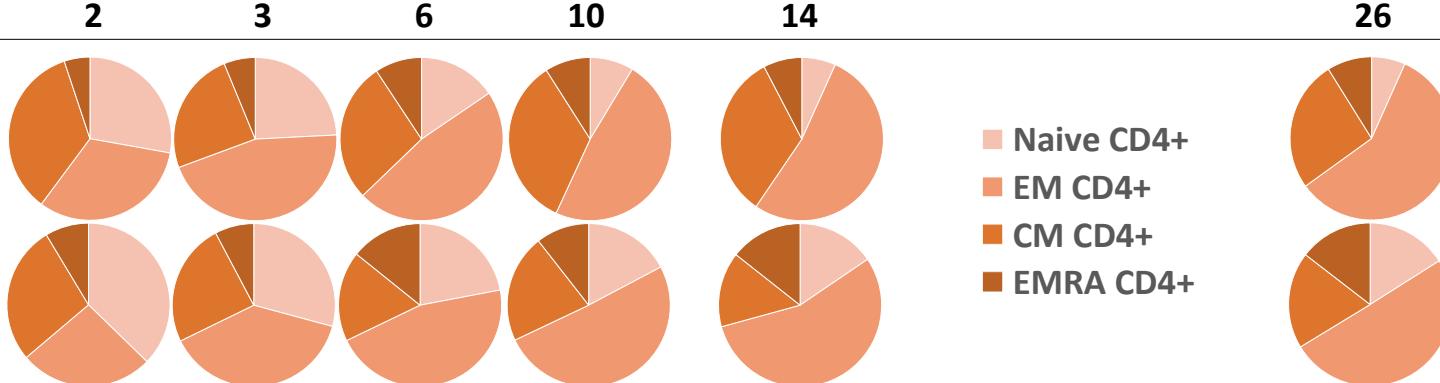


CD4+ cell Reconstitution



Week:

NiCord

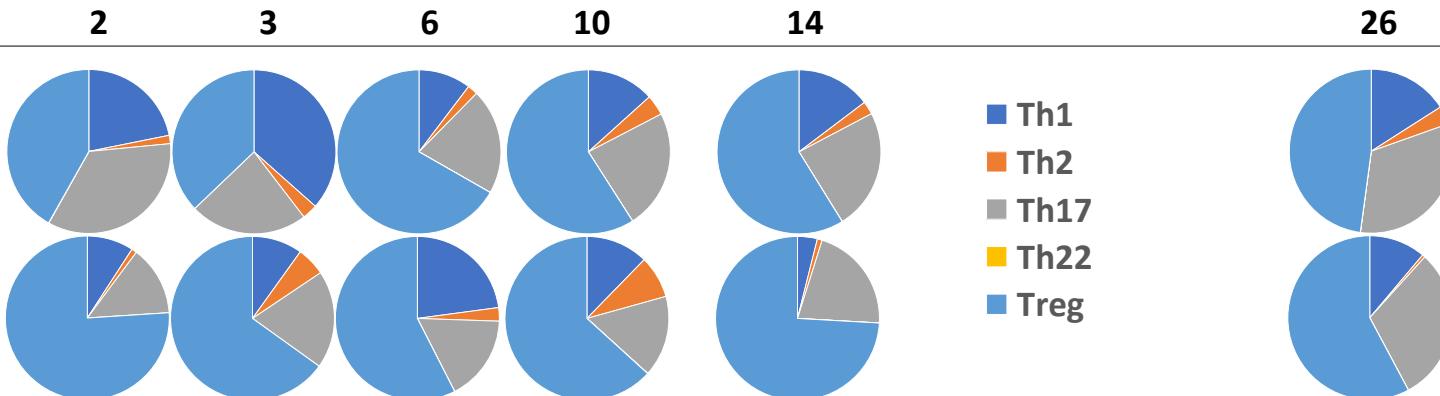


unCBT/BMT

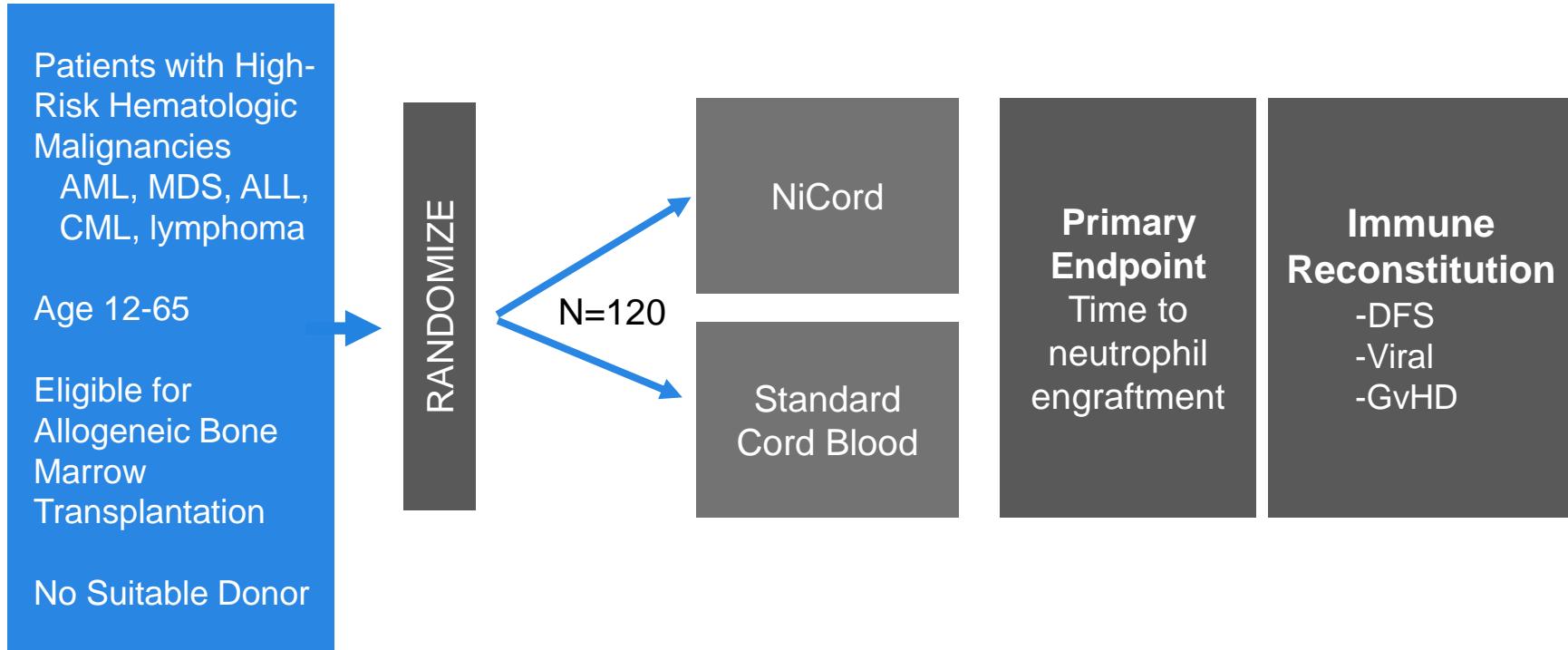
Week:

NiCord

unCBT/BMT



Phase III Study of Nicotinamide-Expanded Cord Blood for Allogeneic Transplantation in Patients with Hematologic Malignancies



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- Immune reconstitution after Nicotinamide-expanded CBT was associated with recovery of a broad spectrum of T-, B- and NK-cell subsets
- Optimal comparison of IR in a randomized controlled Phase III trial is underway



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Participating transplant centers

M Horwitz- Duke University
G. Sanz, P. Montesinos- Valencia
Pau Montesinos- Valencia
P. Stiff- Chicago
D. Valcarcel- Barcelona
M. Jagasia- Nashville
D. Cilloni- Turin
J. Boelens, J. Kuball- Utrecht
R. Hanna- Cleveland
L. Piu, W. Hwang- Singapore
J. Wagner, C. Brunstein- Minnesota



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Characteristics UMCU CBT and BMT patients

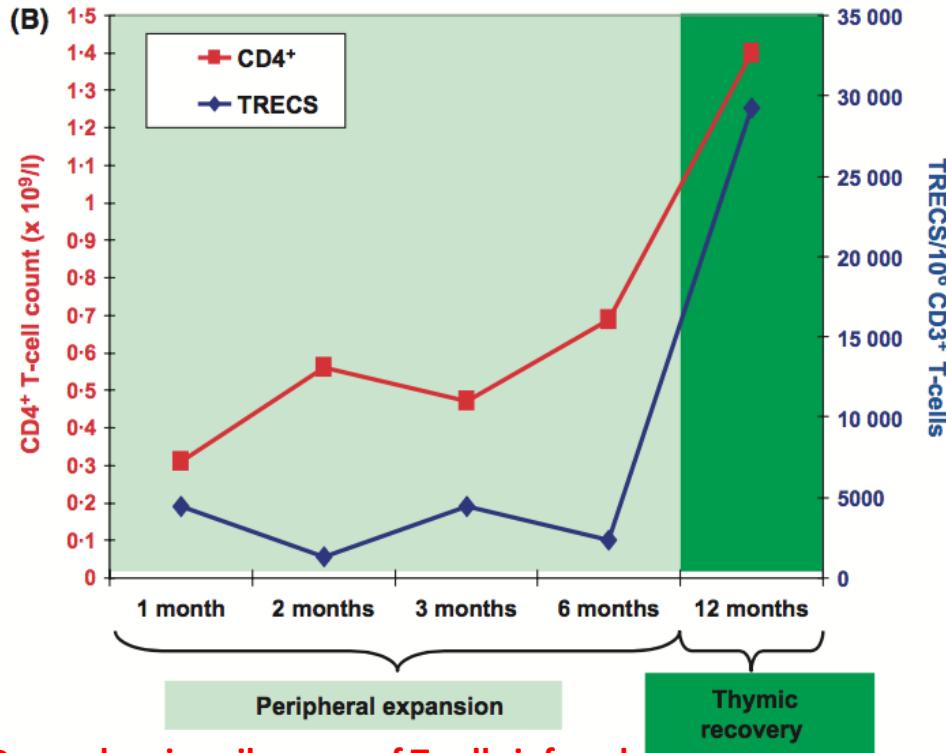
		CB (n=27)	BM (n=20)
Age	13-18	27	19
	19-39	0	1
	40+	0	0
	Median (range)	15 (12-18)	14 (12-20)
HLA Match score	4/6	8	0
	5/6	9	0
	6/6	8	0
	8/8	0	0
	8/10	1	0
	9/10	0	0
	10/10	1	19
Conditioning regimen	(Clo)BuFlu	27	20
Weight (kg)	Median (range)	21-74	32-88



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2 Phases of T cell Immune Reconstitution

“homeostatic peripheral expansion” and “thymic recovery”



Depends primarily on nr of T cells infused
and “in vivo” depleting agents

What Immune Marker is Best Predictor for Outcome?

Cohort of 273 HCTs: pediatric/young adult

	CD3 >100	CD4 >50	CD8 >50	B-cell	NK cell
CMV	0.56	0.31	0.74	0.13	0.18
HHV6	0.51	0.02*	0.33	0.37	0.66
BK-virus	0.82	0.27	0.93	0.87	0.23
Adenovirus	0.26	0.02*	0.66	0.54	0.24
EBV	0.45	0.03*	0.8	0.16	0.35
AML	0.53	0.012	0.7	0.8	0.42

MV P-values

Twice above cutt-off <100days after HCT

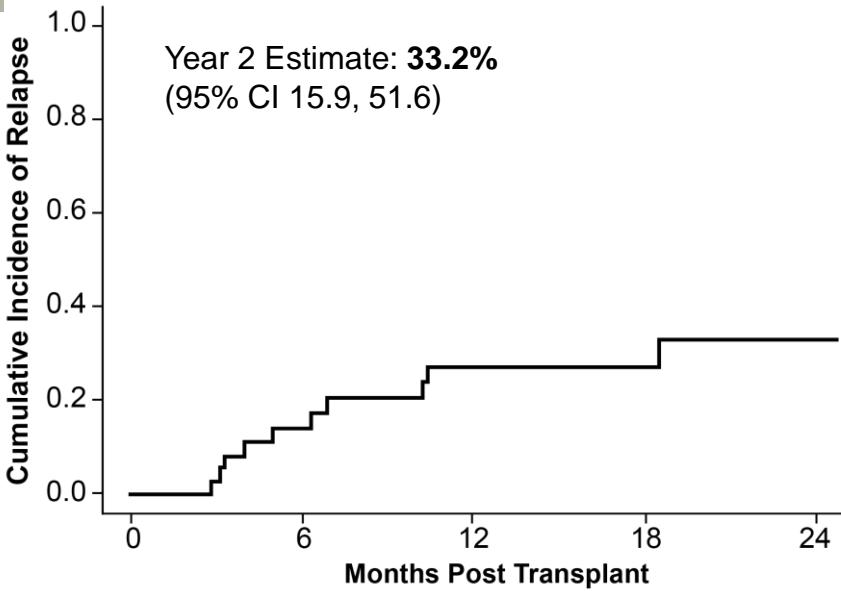
Admiraal and Koning: JACI 2017
Lancet Haematology 2015



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NiCord Phase I/II Outcome

Relapse



N at Risk 36

22

11

6

4

NRM: Year 2 Estimate: **23.8%**; (95% CI 10.9, 39.5)

Estimated Disease-Free Survival

1yr: 49.1% (95% CI 32.2%, 64.8%)
2yr: 43.0% (95% CI 24.2%, 60.5%)

Estimated Overall Survival

1yr: 51.2% (95% CI 32.9%, 66.8%)
2yr: 51.2% (95% CI 32.9%, 66.8%)

aGvHD grade II-IV: 44.0% (95% CI: 27.7%, 59.9%)

aGvHD grade III-IV: 11.1% (95% CI: 3.4%, 23.8%)

cGvHD (mild/moderate/severe): Month 12 Estimate 40.5%

(95% CI: 23.7%, 56.7%)

cGvHD (moderate/severe) Month 24 Estimate 9.8%
(95% CI: 2.4%, 23.7%)



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Demographic and Other Baseline Characteristics

		NiCord N (%)
Primary Diagnosis	Acute Lymphoblastic Leukemia	9 (25)
	High risk first complete morphologic remission (CR1)	5
	Second Remission	4
	Acute Myelogenous Leukemia	17 (47)
	First complete morphologic remission (CR1)	13
	Second Remission	4
	Myelodysplastic Syndrome	7 (19)
	Chronic Myelogenous Leukemia	2 (6)
	Hodgkin's Disease	1 (3)
Disease Risk	Low	8 (22)
	Intermediate	15 (42)
	High	13 (36)



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