El trasplante de sangre de cordón umbilical (TSCU): pasado, presente y futuro

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Conferencia de ingreso como Académico Correspondiente

REIAL ACADÈMIA DE MEDICINA DE LA COMUNITAT VALENCIANA

Valencia, 2 mayo 2019

Hematopoietic Reconstitution in a Patient with Fanconi's Anemia by Means of Umbilical-Cord Blood from an HLA-Identical Sibling

Gluckman E, Broxmeyer HE, Auerbach AD, et al.

N Engl J Med 1989; 321:1174-1178

En 2018 se cumplieron 30 años del primer trasplante de sangre de cordón umbilical (TSCU)

Contenido de la presentación

- Introducción al TSCU
- Resultados y estado actual del TSCU de donante no emparentado (DNE) en adultos con neoplasias hematológicas
- Contribuciones relevantes del HUP La Fe
- Estrategias de mejora:
  - Expansión *ex vivo*
  - Mejora reconstitución inmune y tratamiento infecciones
- Actividad actual de TSCU
- Conclusiones

Introducción

Antecedentes

- El trasplante de progenitores hematopoyéticos (TPH) es el tratamiento de elección, en numerosas ocasiones el único curativo, de diversas enfermedades:
  - Neoplasias hematológicas (leucemia, linfoma y mieloma).
  - No neoplásicas (aplasia medular, errores congénitos del metabolismo e inmunodeficiencias).
- La sangre de cordón umbilical (SCU) es una de las potenciales fuentes de progenitores hematopoyéticos.

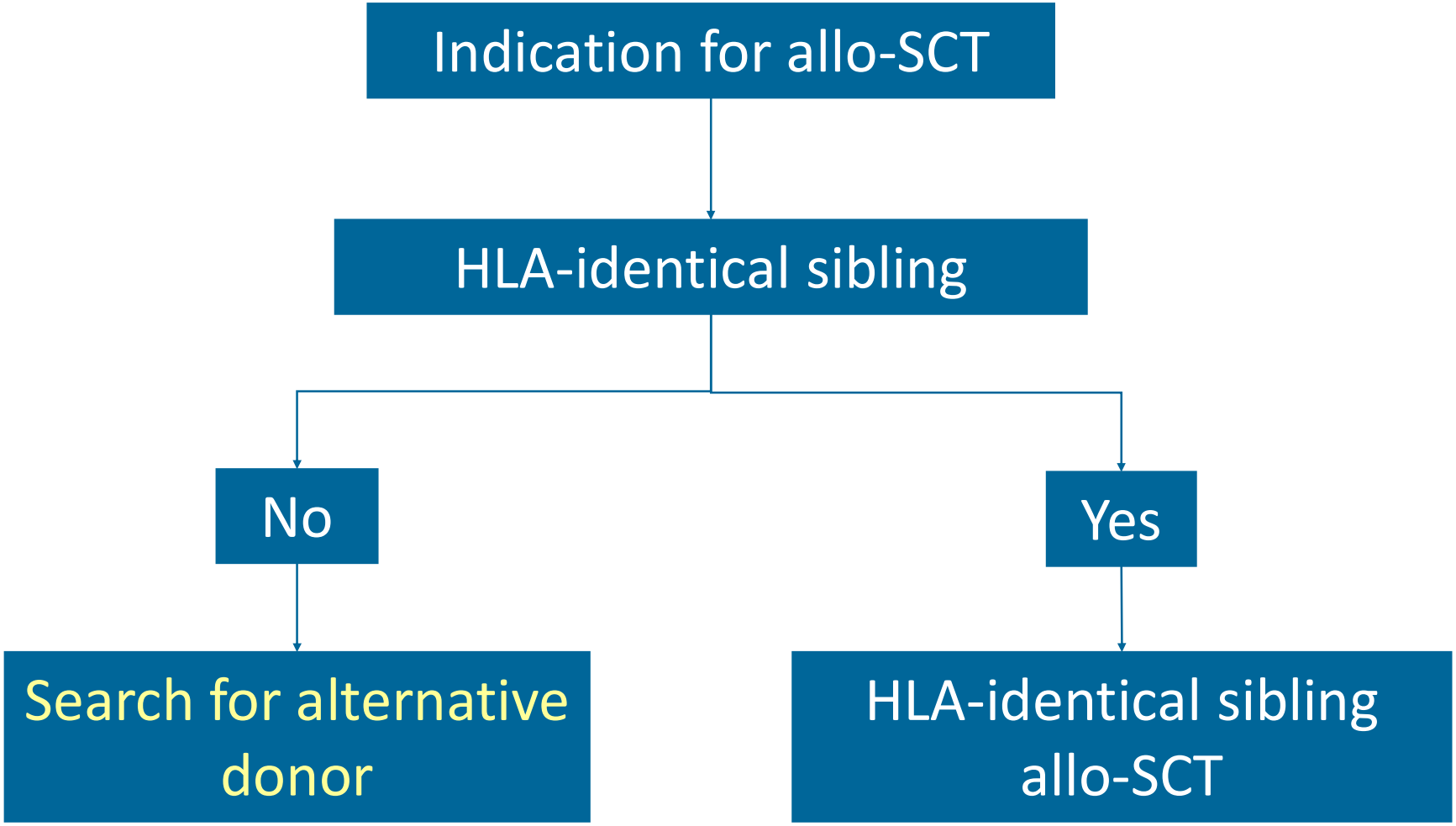
Características de las colonias granulocíticas macrofágicas en sangre de cordón umbilical

Juan Besalduch Vidal

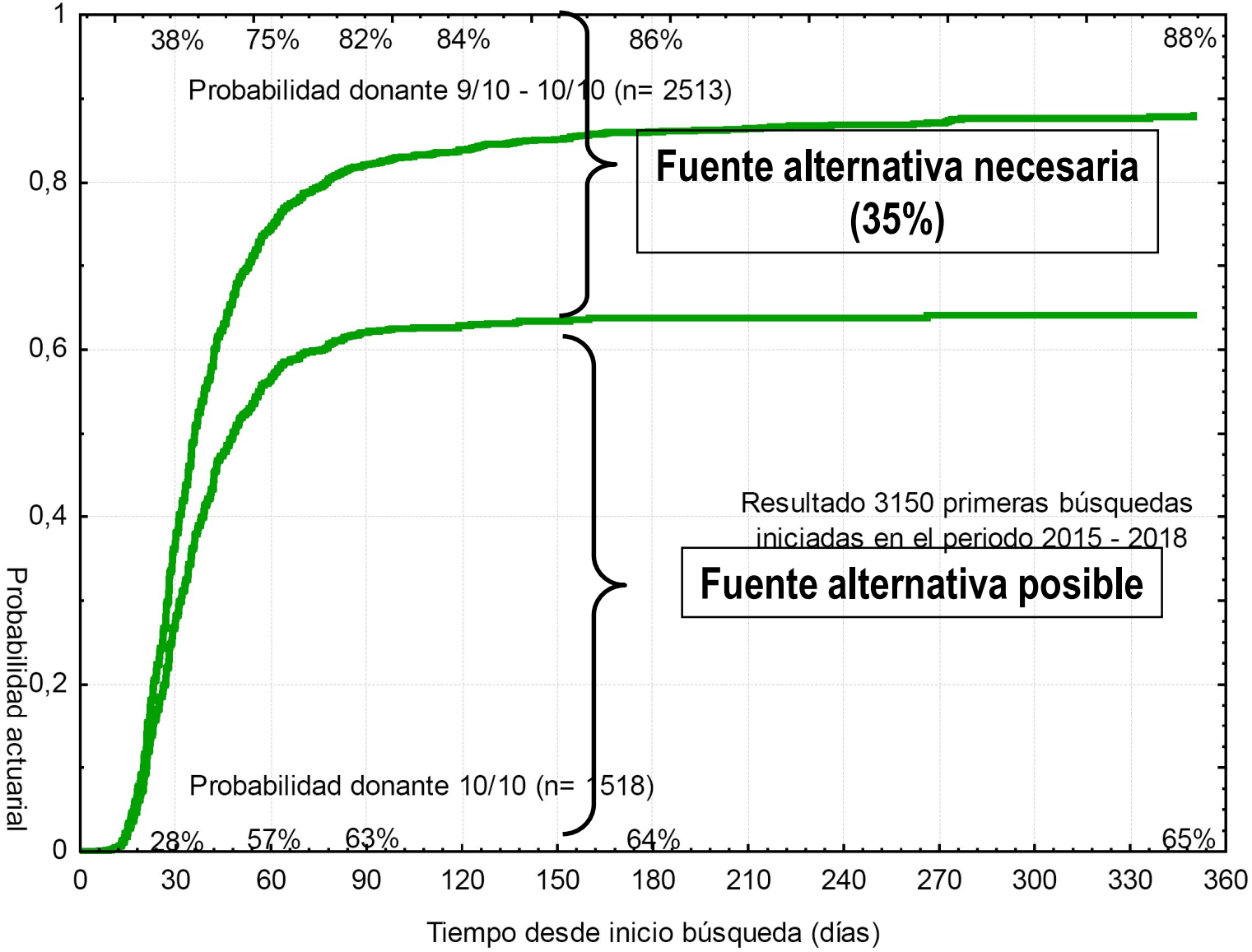
Tesis Doctoral. Universitat de València, 1985

La sangre de cordón umbilical (SCU) contiene progenitores hematopoyéticos que podrían usarse para trasplante

Decision-tree for allogeneic SCT



Actuarial probability of finding a 9 – 10/10 matched unrelated adult donor in Spain (REDMO)



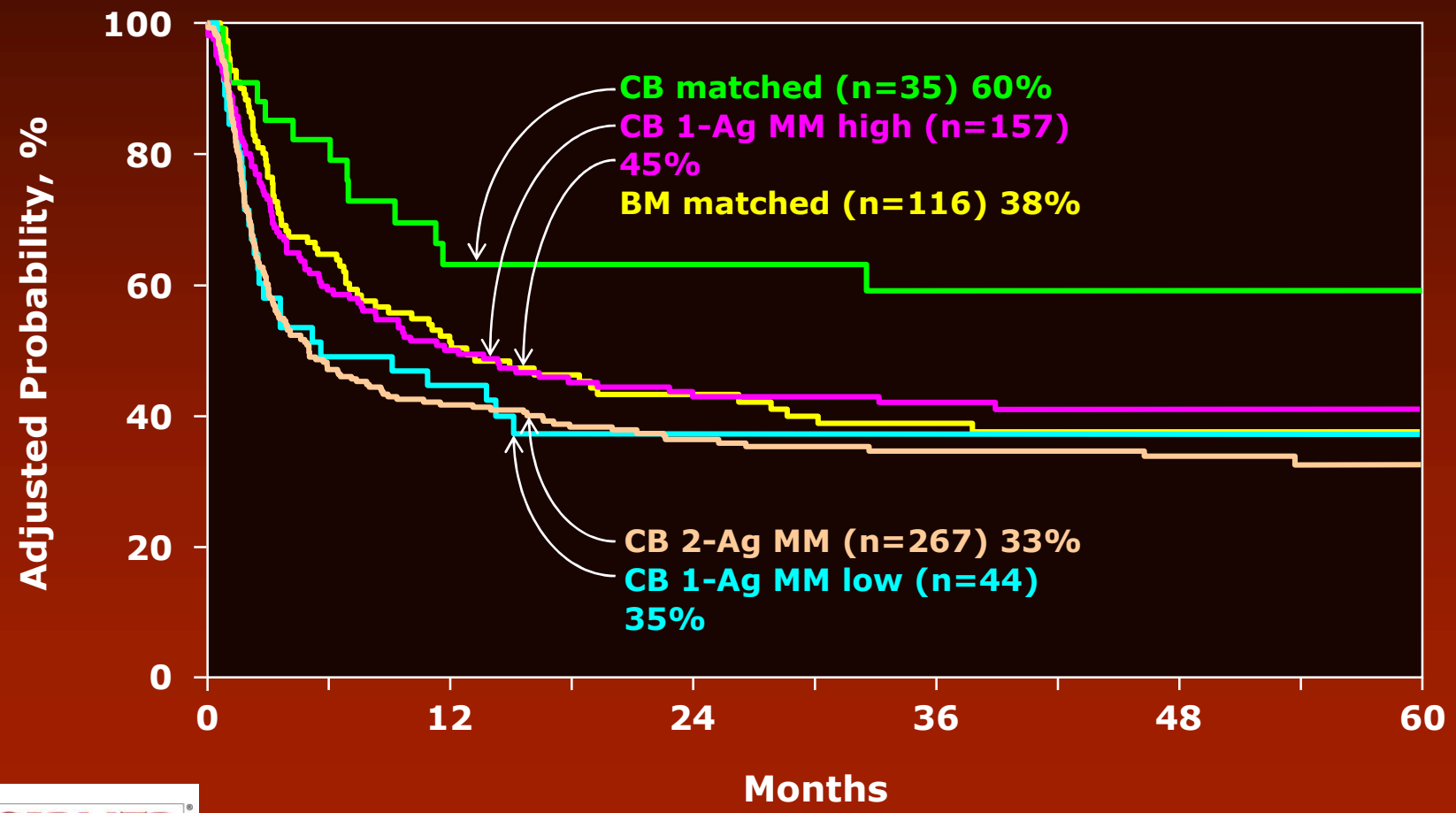
Pros and cons of UCB transplants

- **Advantage:** Urgent transplantation more likely
  - Fast availability (14 days to acquisition)
  - Great HLA disparity allowed (less GVHD)
  - Healthier stem cells (innate cell youth)
- **Disadvantage:** High TRM due to infections
  - Slow neutrophil engraftment
  - Delayed and impaired immune reconstitution

Expand access to transplant (chance, > 90%)

Resultados actuales del TSCU

Leukemia-free Survival in Children with Acute Leukemia

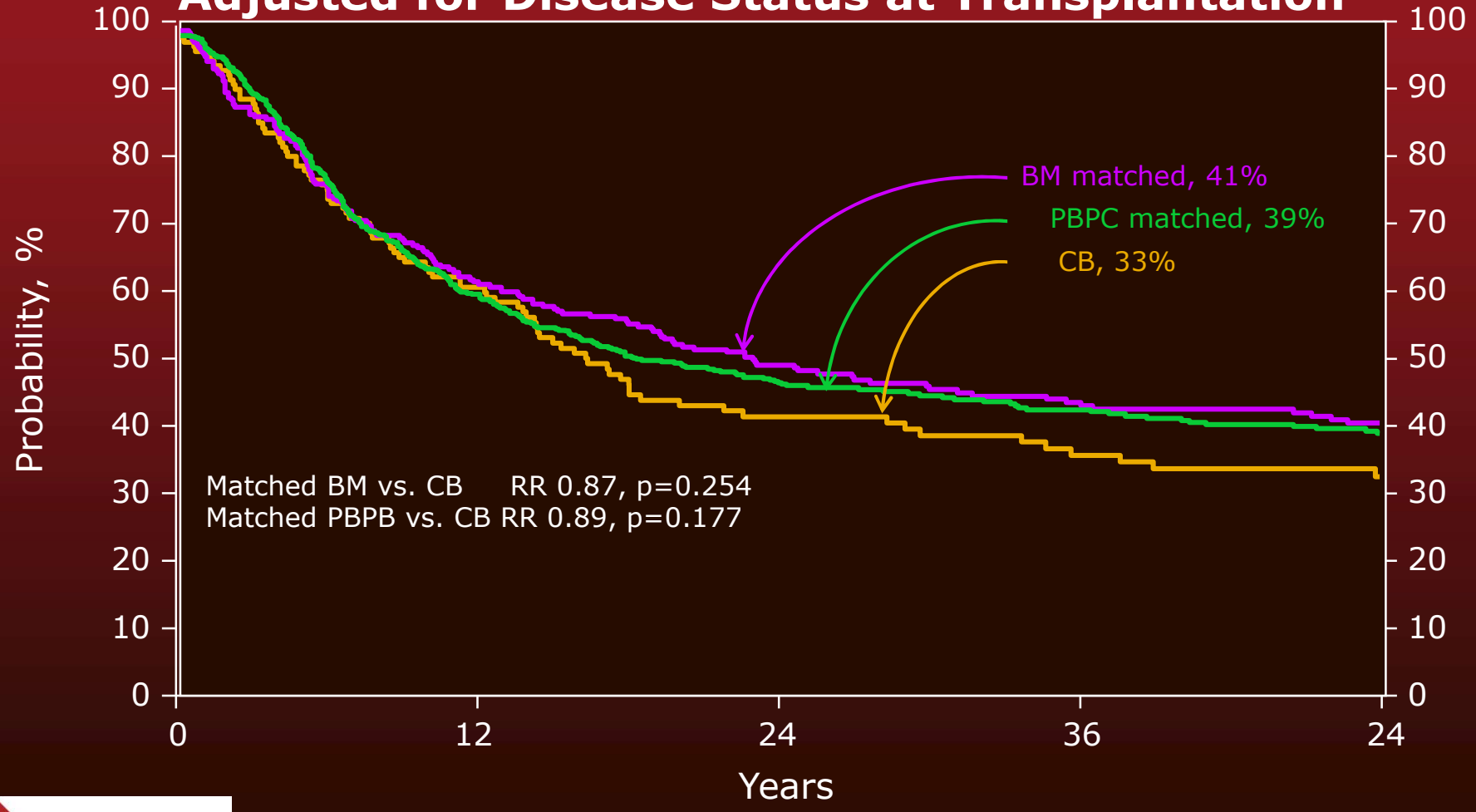


CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Eapen et al. Lancet 2007

Impact of Stem Cell Source in Adults with Acute Leukemia, n=1280

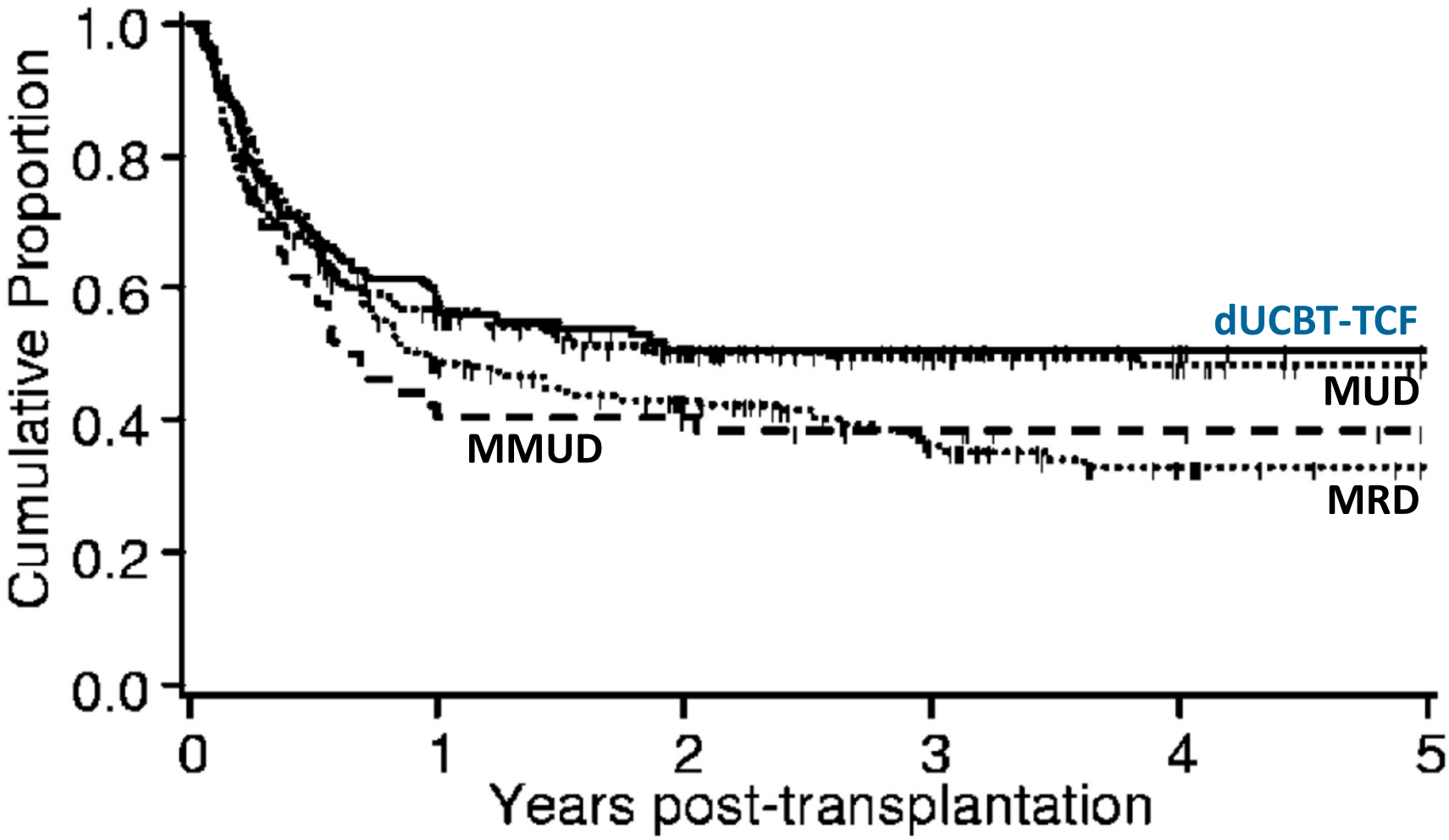
Leukemia-free Survival
-Adjusted for Disease Status at Transplantation-



Eapen M, Rocha V, Lancet Onc 2010

MAC transplants (FHCRC + Univ. Minnesota)

DFS by source (dUCBT with TCF conditioning)



Brunstein CG, et al. *Blood* 2010:116:4693-4699.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cord-Blood Transplantation in Patients with Minimal Residual Disease

Filippo Milano, M.D., Ph.D., Ted Gooley, Ph.D., Brent Wood, M.D., Ann Woolfrey, M.D., Mary E. Flowers, M.D., Kristine Doney, M.D., Robert Witherspoon, M.D., Marco Mielcarek, M.D., Joachim H. Deeg, M.D., Mohamed Sorror, M.D., Ann Dahlberg, M.D., Brenda M. Sandmaier, M.D., Rachel Salit, M.D., Effie Petersdorf, M.D., Frederick R. Appelbaum, M.D., and Colleen Delaney, M.D.

N Engl J Med 2016;375:944-53.

Characteristics of the patients

Characteristic	UBCT (N = 140)	HLA-matched (N = 344)	HLA-mism. (N = 98)
Median age (range), yr*	29 (1 – 64)	40 (1 – 67)	45 (2 – 64)
White race, no. (%)*	64 (46)	294 (85)	76 (78)
High/very high disease risk, no. (%)*	47 (34)	68 (20)	21 (21)
Presence of MRD, %	33	31	39
ALL	51 (36)	106 (31)	28 (29)
AML	73 (52)	175 (51)	52 (53)
MDS	16 (11)	63 (18)	18 (18)
FC-TBI conditioning, no. (%)*	97 (69)	0	0
CSA + MM GVHD prophylaxis, n (%)*	140 (100)	0	0

* *P* value < 0.001

Milano F. *N Engl J Med*. 2016; 375:944–53.

Adjusted Cox models for death and relapse by MRD

Table 2. Adjusted Cox Regression Models for Analyses of Death and Relapse, According to Minimal Residual Disease Status.*

Outcome	Hazard Ratio (95% CI)	P Value
Death		
Patients without minimal residual disease		
Cord-blood group	1.00	—
HLA-matched group	0.78 (0.48–1.28)	0.33
HLA-mismatched group	1.36 (0.76–2.46)	0.30
Patients with minimal residual disease		
Cord-blood group	1.00	—
HLA-matched group	1.69 (0.94–3.02)	0.08
HLA-mismatched group	2.92 (1.52–5.63)	0.001
Relapse		
Patients without minimal residual disease		
Cord-blood group	1.00	—
HLA-matched group	1.30 (0.65–2.58)	0.46
HLA-mismatched group	1.28 (0.51–3.25)	0.60
Patients with minimal residual disease		
Cord-blood group	1.00	
HLA-matched group	2.92 (1.34–6.35)	0.007
HLA-mismatched group	3.01 (1.22–7.38)	0.02

Lower risk of death and relapse with UCB in MRD-positive patients

Milano F. *N Engl J Med*. 2016; 375:944–53.

Adequate UCB *versus* BM from 8/8 matched VUD as graft sources for adults with acute leukemia

- Slower engraftment with UCB
- Lower incidence of GVHD with UCB
- Similar (or reduced) incidence of relapse
- Greater TRM (at least during 1st year)
- Similar LFS
- Better LFS without GVHD?

UCB *versus* haploidentical transplants for adults with acute leukemia

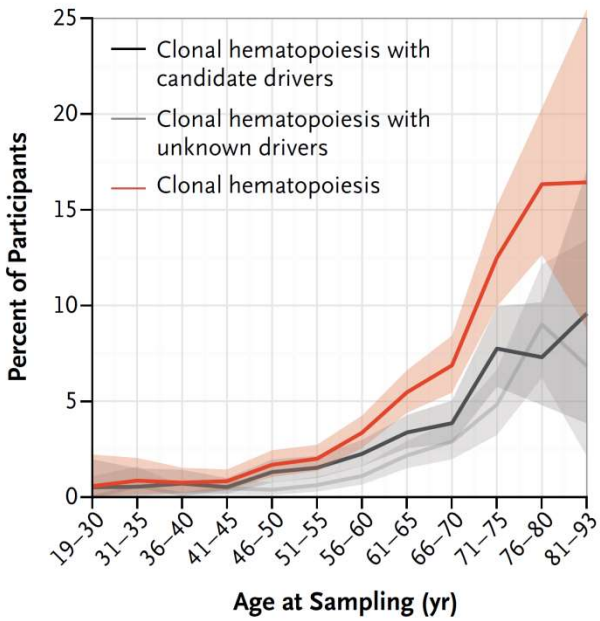
Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia.

Annalisa Ruggeri , Myriam Labopin, Guillermo Sanz, Simona Piemontese, William Arcese, Andrea Bacigalupo, Didier Blaise , Alberto Bosi, He Huang, Dimitrios Karakasis, Yener Koc, Mauricette Michallet, Alessandra Picardi, Jaime Sanz, Stella Santarone, Henrik Sengelov, Jorge Sierra, Laure Vince19, Fernanda Vol, Arnon Nagler, Eliane Gluckman, Fabio Ciceri, Vanderson Rocha, and Mohamad Mohty. A EUROCORD, ALWP-EBMT STUDY

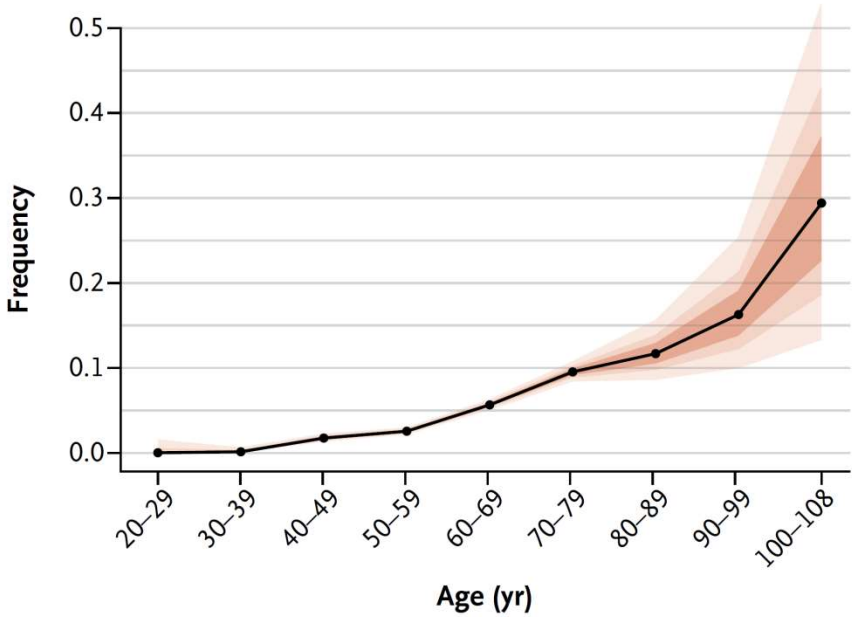
- UCBT (n=928) or Haplo (n=518) reported to EBMT centers.
- Major limitation: Great heterogeneity of patients.
- **No differences between Haplo and UCBT for RI (HR= 0.87; p=0.24) and LFS (HR= 1.06; p=0.47).**
- Factors independently associated with lower LFS were disease status at transplant (HR=2.69, p=<0.001), and use of ATG (HR=1.28, p=0.001).

Ruggeri A, et al. Leukemia 2015; 29(9):1891-900

Clonal hematopoiesis in apparently healthy people is age-related and associated with an increased risk of hematologic malignancies



Genovese G, et. al. *N Engl J Med* 2014:371:2477-87.



Jaiswal S, et. al. *N Engl J Med* 2014:371:2488-98.

UCB is the youngest source of hematopoietic cells

Contribuciones HUP La Fe

Actividad TPH, HUP La Fe (hasta 31 dic 2018)

Tipo de TPH	Número de TPH
Autólogo	*1.260*
Alogénico	*1.384*
- Singénico	7
- Hermano HLA-idéntico	707
- Familiar no HLA-idéntico	27
- Haploidéntico	122
- DNE adulto (HLA-idéntico)	120
- TSCU	401
Total	**2.644**

Standardized, unrelated donor cord blood transplantation in adults with hematologic malignancies

Guillermo F. Sanz, Silvana Saavedra, Dolores Planelles, Leonor Senent, Jose Cervera, Eva Barragán, Carmen Jiménez, Luis Larrea, Guillermo Martín, Jesús Martínez, Isidro Jarque, Federico Moscardó, Gemma Plumé, Rafael Andreu, Ana I. Regadera, Inmaculada García, Susana Mollá, Pilar Solves, Javier de la Rubia, Pascual Bolufer, Luis Benlloch, María A. Soler, María L. Marty, and Miguel A. Sanz

BLOOD, 15 OCTOBER 2001 • VOLUME 98, NUMBER 8

ORIGINAL ARTICLE

Transplants of Umbilical-Cord Blood or Bone Marrow from Unrelated Donors in Adults with Acute Leukemia

Vanderson Rocha, M.D., Ph.D., Myriam Labopin, M.D., Guillermo Sanz, M.D., William Arcese, M.D., Rainer Schwerdtfeger, M.D., Alberto Bosi, M.D., Niels Jacobsen, M.D., Tapani Ruutu, M.D., Marcos de Lima, M.D., Jürgen Finke, M.D., Francesco Frassoni, M.D., and Eliane Gluckman, M.D., for the Acute Leukemia Working Party of European Blood and Marrow Transplant Group and the Eurocord–Netcord Registry*

The NEW ENGLAND JOURNAL of MEDICINE

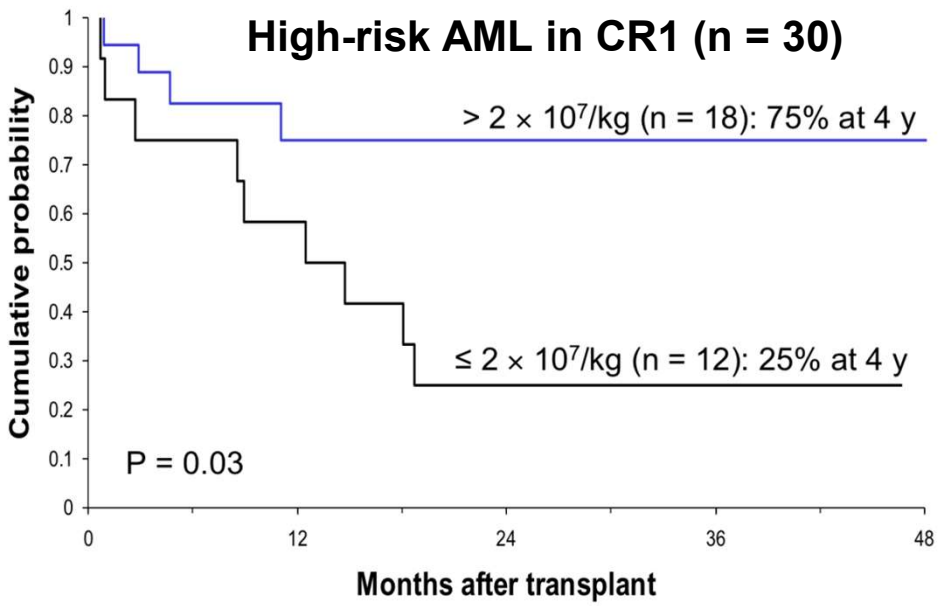
EDITORIALS

Cord-Blood Transplantation in Patients with Leukemia — A Real Alternative for Adults

Miguel A. Sanz, M.D., Ph.D.

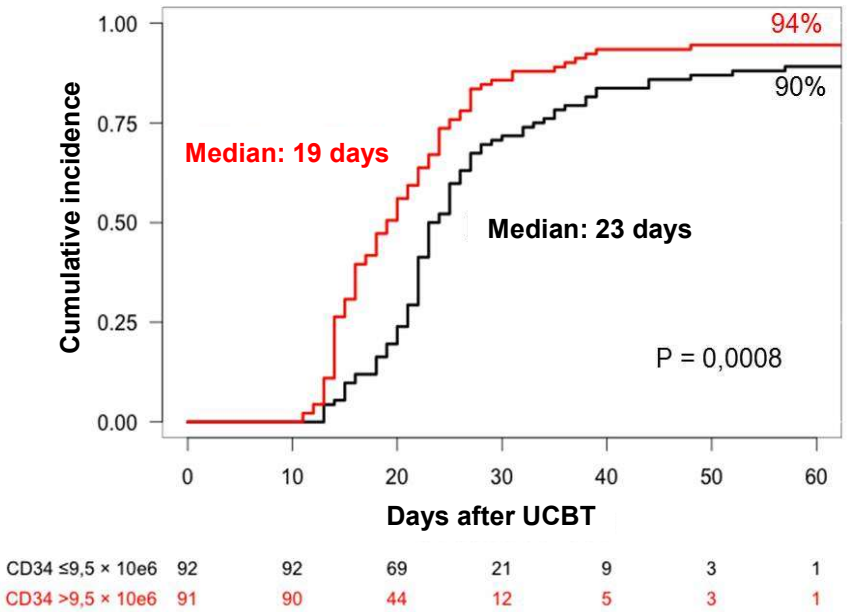
Impact of cell dose on outcome after UCBT

LFS by nucleated cell dose



Sanz J, *et al*. Biol Blood Marrow Transplant 2010;16:86-94

Myeloid engraftment by CD34 cell dose



Sanz J. Doctoral Thesis

UCBT program at Hospital La Fe, Valencia

Criteria for UCB unit choice by period

- **Minimum cell dose requirements** (at collection)

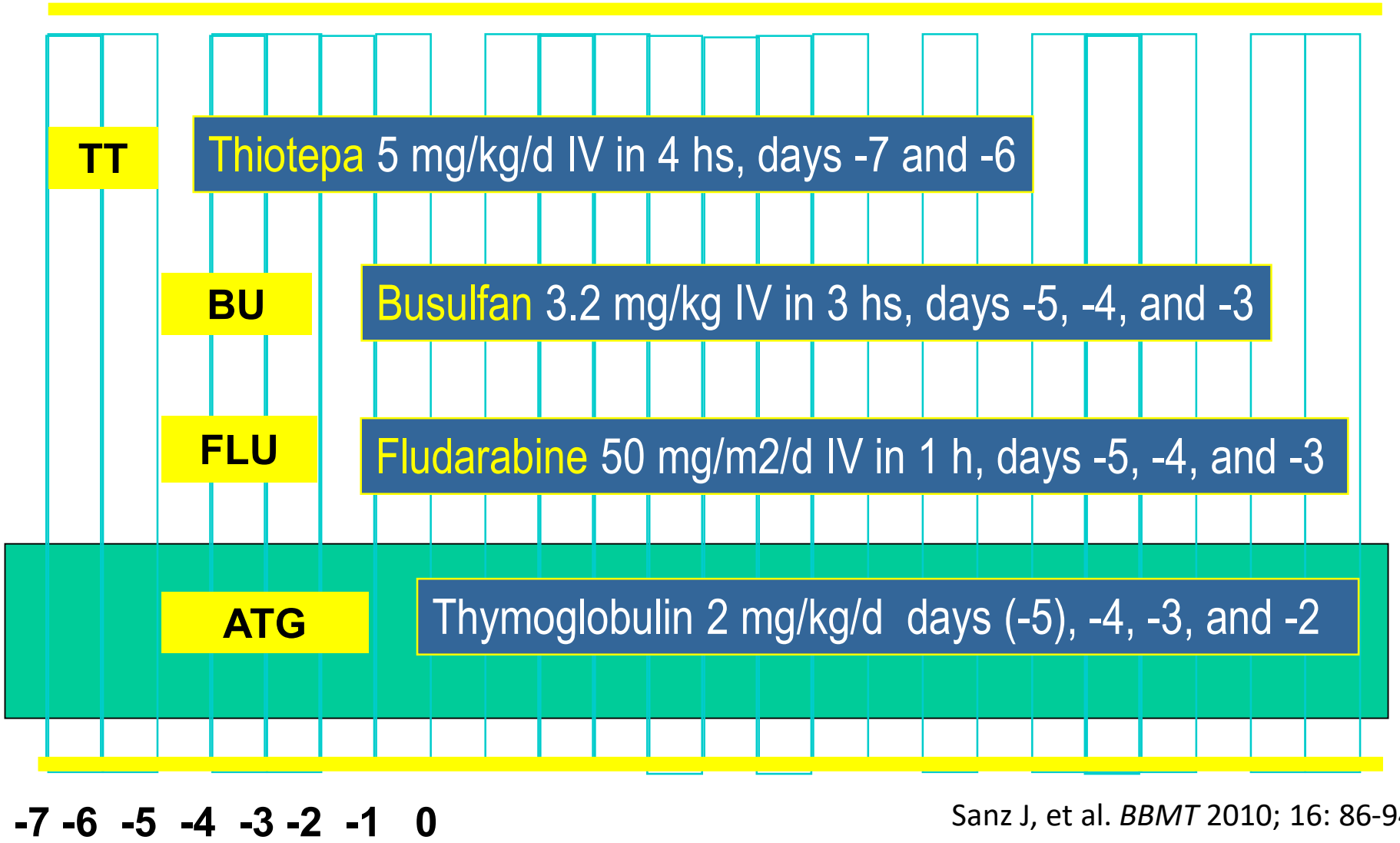
Cell dose	1997 – 2005	2005 – 2007	2007 – present
TNCs	> 1,5 x 10^7/kg.	> 2.0 x 10^7/kg	> 150 x 10^7
CD34+ cells	-	> 1.0 x 10^5/kg	> 70 x 10^5

- **HLA match**

≥ 4/6 (HLA-A and -B at antigen level and -DRB1 at allele level)

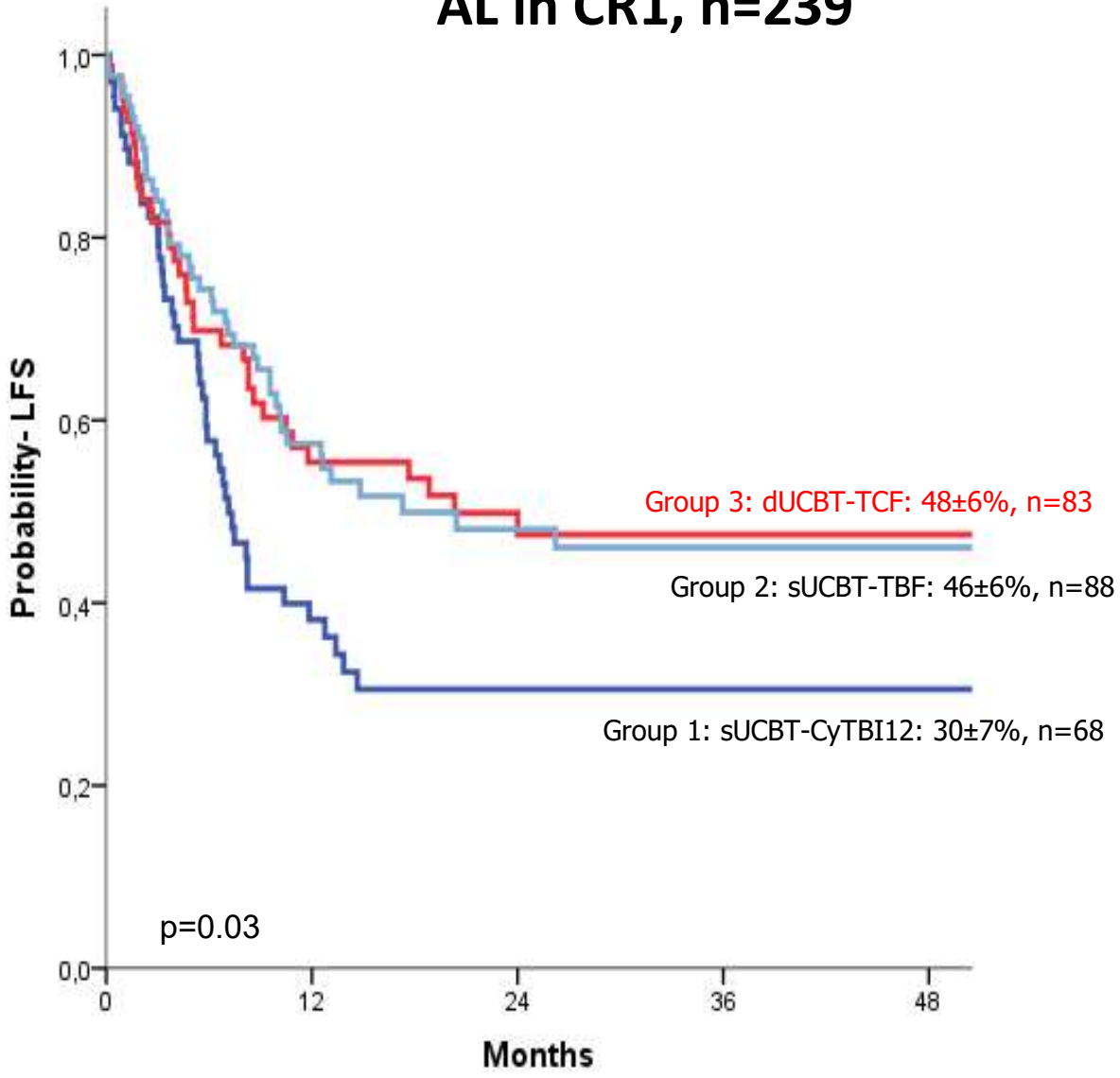
Conditioning regimens for UCBT

TBF regimen (Hospital La Fe, Valencia)



Sanz J, et al. *BBMT* 2010; 16: 86-94

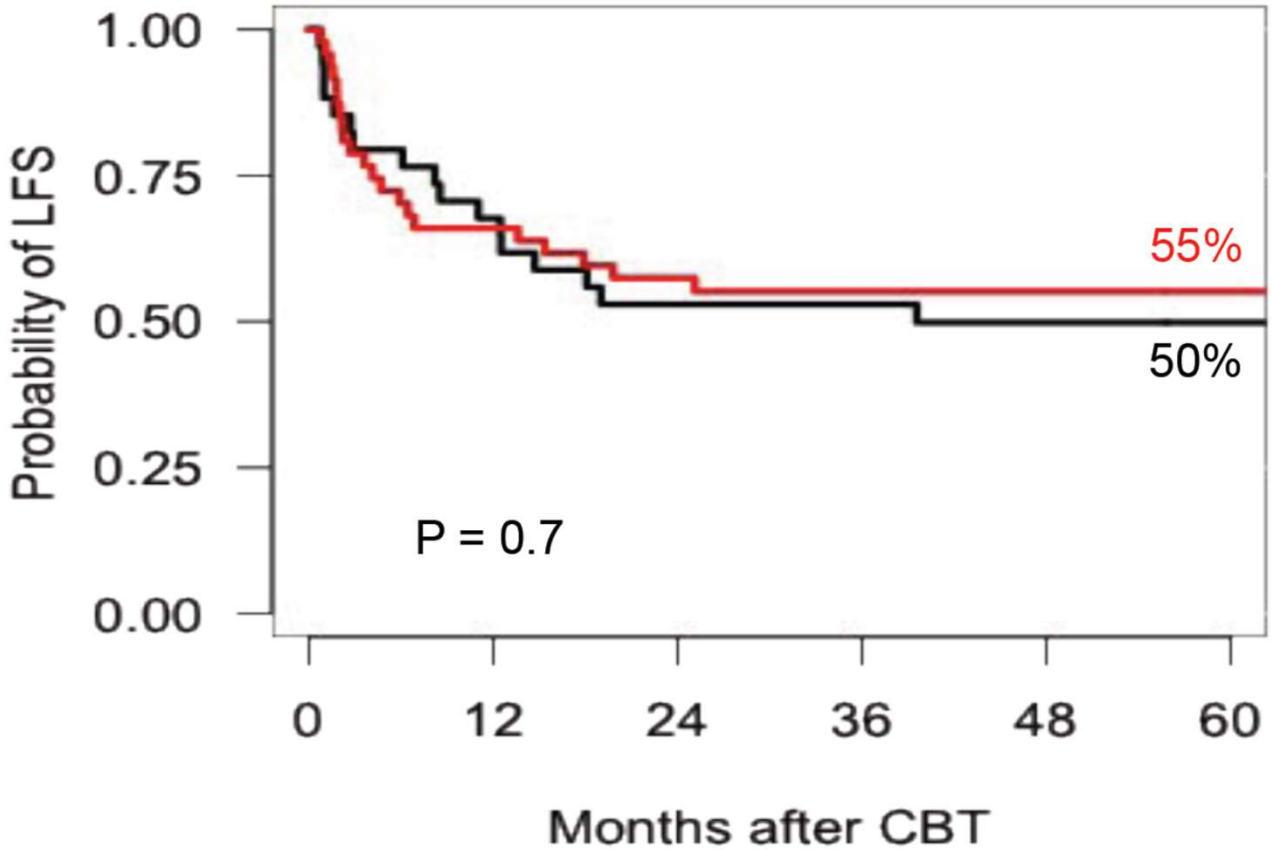
2 years- LFS after MAC sUCBT and dUCBT in adults with AL in CR1, n=239



Ruggieri A, et al. *Leukemia* 2013

UCBT after MAC in adults with acute leukemia: Comparison of two different transplant platforms

Leukemia-free survival in patients with AML in CR



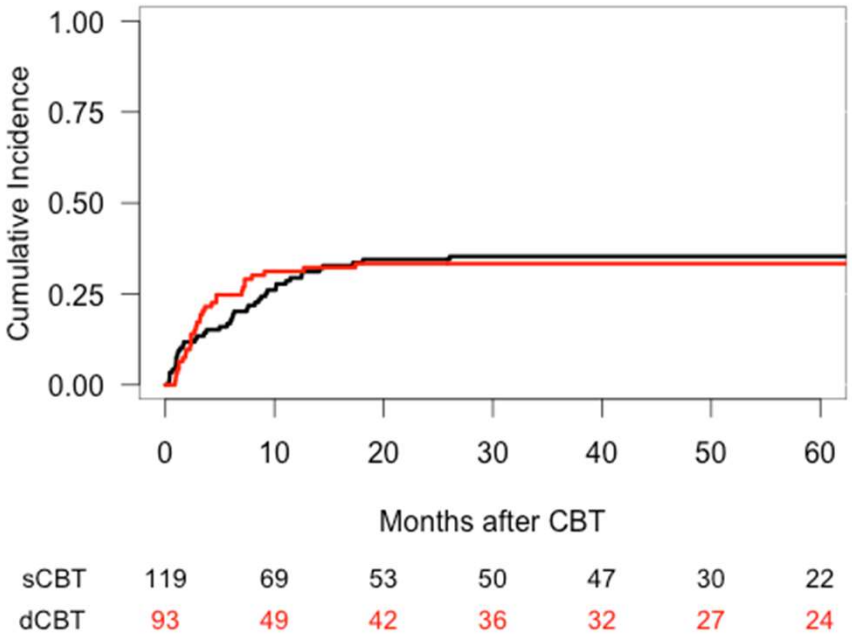
sCBT	34	23	18	18	14	10
dCBT	47	31	27	22	21	15

Sanz J, et al. BBMT 2013; 19: 1725-30.

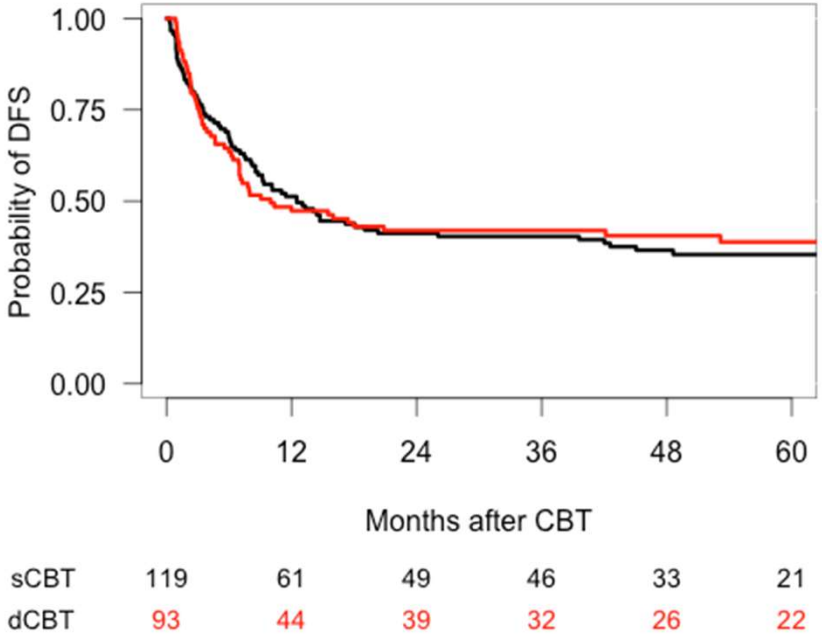
Single-unit UCBT (sCBT) versus Dual HSCT

Non-relapse mortality and leukemia-free survival

Non-relapse mortality



Leukemia-free survival



- In adults with acute leukemia both UCB platforms showed closely similar non-relapse mortality and leukemia-free survival.

Sanz, J et al. *Blood Adv*. 2017;1(15):1047-1055).

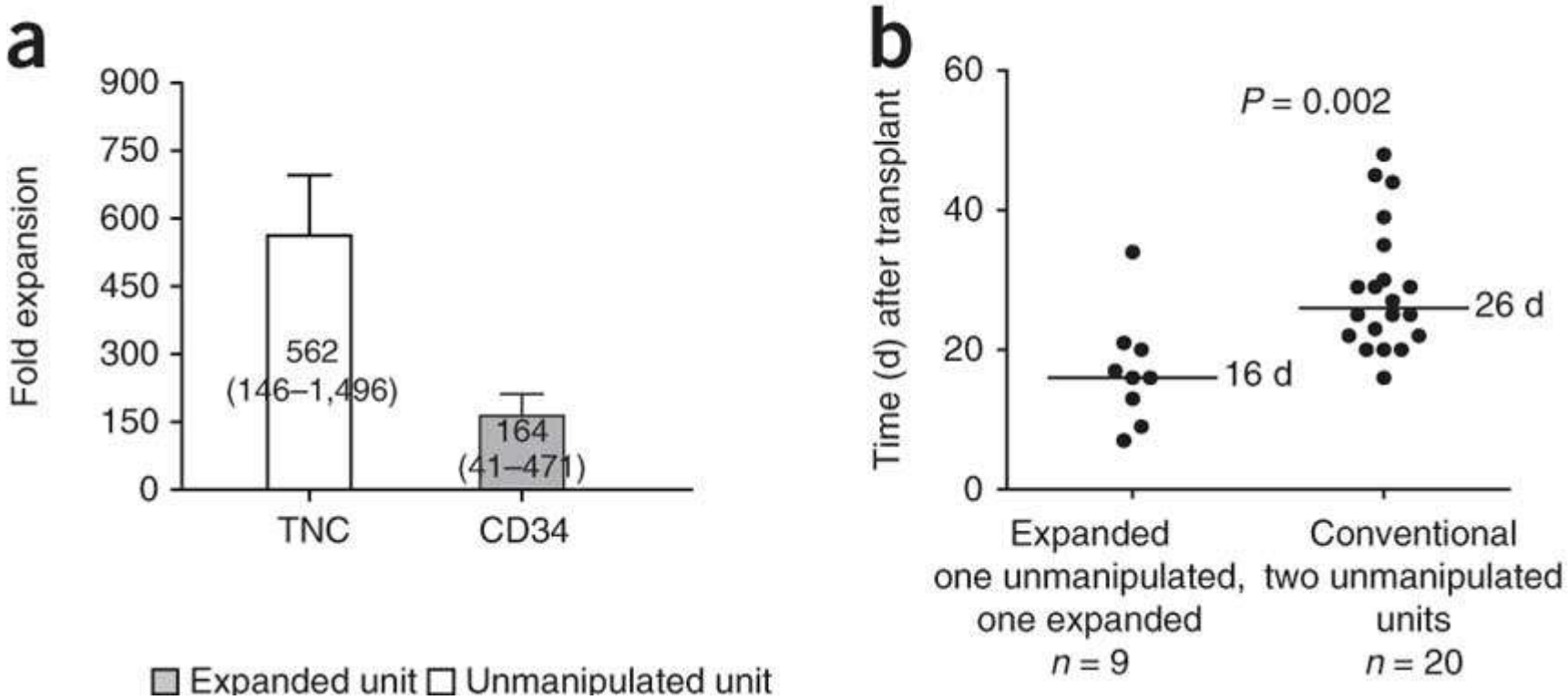
Estrategias de mejora: Expansión *ex vivo*

Current experiences on *ex vivo* expansion
Expansion efficiency

- CD34+ cell expansion: 20 – 200 fold expansion
- **CD34+ cells in final product : 1 – 20 x 10^6/kg**

In many instances similar or higher numbers than with mobilized peripheral blood from adult donors

Ex vivo expansion with Notch-ligand
Double-cord platform



- **Double UCBT configuration**, 16 days expansion of one of the units (**no T-cells**)
- **Median CD34+ cells: 6 × 10^6/kg**
- **Median days** (range) **to PMN engraftment**: **16** (7 – 34)
- **Winning unit: not expanded unit**

Delaney C et al. *Nature Med* 2010; 16: 232-6.

Ex vivo expansion with NiCord® product

NiCord® (nicotinamide cultured cells)

Cord Blood Unit

↓

CliniMACS separation:
Enrichment of
CD133^{+} cells

Cultured fraction (CF)

The CD133 positive cell fraction - Cultured for 21±2 days using NAM technology

+

Non-cultured fraction (NF)

The CD133 negative cell fraction Is kept frozen till the day of transplantation

- **NiCord®** is an ***ex vivo* expanded cell product** from an **entire** UCB unit treated **with nicotinamide** that increase stem and progenitors cells, inhibit differentiation and increase migration, BM homing, and engraftment efficiency.

Horwitz ME, et al. *J Clin Invest* 2014;124:3121-8.

Ex vivo expansion with NiCord® product

Phase I-II, double cord platform study

Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment

Mitchell E. Horwitz,[1] Nelson J. Chao,[1] David A. Rizzieri,[1] Gwynn D. Long,[1] Keith M. Sullivan,[1] Cristina Gasparetto,[1] John P. Chute,[1] Ashley Morris,[1] Carolyn McDonald,[1] Barbara Waters-Pick,[1] Patrick Stiff,[2] Steven Wease,[3] Amnon Peled,[4] David Snyder,[5] Einat Galamidi Cohen,[5] Hadas Shoham,[5] Efrat Landau,[5] Etty Friend,[5] Iddo Peleg,[5] Dorit Aschengrau,[5] Dima Yackoubov,[5] Joanne Kurtzberg,[6] and Tony Peled[5]

[1]Adult Blood and Marrow Transplant Program, Duke University Medical Center, Durham, North Carolina, USA. [2]Loyola University Medical Center, Maywood, Illinois, USA. [3]The EMMES Corporation, Rockville, Maryland, USA. [4]Goldyne Savad Institute of Gene Therapy, Hadassah - Hebrew University Medical Center, Jerusalem, Israel. [5]Gamida Cell Ltd., Jerusalem, Israel. [6]Pediatric Blood and Marrow Transplant Program, Duke University Medical Center, Durham, North Carolina, USA.

Horwitz ME, et al. *J Clin Invest* 2014;124:3121-8.

Ex vivo expansion with NiCord® product

Phase I-II, double cord platform study. Results

- **8 of 11 patients engrafted with NiCord® unit (> 2 yr)**
- **NiCord® shortens hematopoietic recovery**:

  - PMN > 500 (mean); 11 vs. 25 days Duke control (p=0.001)

  - Platelets > 20K (mean); 30 vs. 41 days Duke control (p=0.012)
- **NiCord® shortens hospitalization**:

  - Patients engrafted with NiCord®: 24 days (day +14 discharge)

  - Duke control cohort (n=17): 42 days (day +33 discharge)
- 8 patients alive in CR at a median follow-up of 20 months

Horwitz ME, et al. *J Clin Invest* 2014; 124: 3121-8.

ASCO

Journal of Clinical Oncology

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original report

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

Mitchell E. Horwitz, MD[1]; Stephen Wease, MPH[2]; Beth Blackwell, ScD[2]; David Valcarcel, MD, PhD[3]; Francesco Frassoni, MD[4]; Jaap Jan Boelens, MD, PhD[5]; Stefan Nierkens, PhD[5]; Madan Jagasia, MD[6]; John E. Wagner, MD[7]; Jurgen Kuball, MD[5]; Liang Piu Koh, MBBS, MRCP[8]; Navneet S. Majhail, MD[9]; Patrick J. Stiff, MD[10]; Rabi Hanna, MD[9]; William Y.K. Hwang, MBBS[11]; Joanne Kurtzberg, MD[1]; Daniela Cilloni, MD, PhD[12]; Laurence S. Freedman, PhD[13]; Pau Montesinos, MD[14]; and Guillermo Sanz, MD, PhD[14]

J Clin Oncol 37:367-374.

Ex vivo expansion with NiCord® product
Phase I – II, single cord platform study

- 36 patients (median age, 44 yr) were evaluable and their outcomes compared to those of 146 matched controls (CIBMTR; 80% double CBT).

Horwitz ME, et al. *J Clin Oncol* 2019; Feb 10;37(5):367-374..

Ex vivo expansion with NiCord® product

Phase I – II, single cord platform study

Patient characteristics (N = 36)

Characteristic	No.	%
Sex		
Male	20	55.6
Female	16	44.4
Median age, range	44	13-63
Primary diagnosis		
ALL	9	25.0
AML	17	47.2
MDS	7	19.4
Non-Hodgkin lymphoma	0	0.0
Hodgkin disease	1	2.8
CML	2	5.6
Adjusted disease risk index[6]		
Low	8	22.2
Intermediate	15	41.7
High	13	36.1
Performance status		
100	13	36.1
90	16	44.4
80	6	16.7
70	1	2.8

Characteristic	No.	%
Patient CMV status		
Positive	25	69.4
Negative	10	27.8
Indeterminate	1	2.8
HLA match score		
4/6	26	72.2
5/6	8	22.2
6/6	2	5.6
Conditioning regimen		
Regimen A (TBI 13.5 Gy, fludarabine, cyclophosphamide + or thiotepa)*	13	36.1
Regimen A.1 (TBI 13.2 Gy, fludarabine, cyclophosphamide)	2	5.6
Regimen B (thiotepa, busulfan, fludarabine)†	19	52.8
Regimen C (clofarabine, fludarabine, busulfan)‡	2	5.6
Median weight at enrollment, kg, range	75	42-127

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelomonocytic leukemia; CML, chronic myeloid leukemia; CMV, cytomegalovirus; MDS, myelodysplastic syndrome; TBI, total body irradiation.

*TBI 13.5 Gy over eight or nine fractions on days −9 to −6 or −5, and either cyclophosphamide, 60 mg/kg on days −4 and −3 or thiotepa 5 mg/kg administered on days −11 and −10.[7,8,9] The third agent in regimen A was fludarabine 40 mg/m^2 on days −5 to −2 when paired with thiotepa, or 25 mg/m^2 on days −8 to −6 when paired with cyclophosphamide.

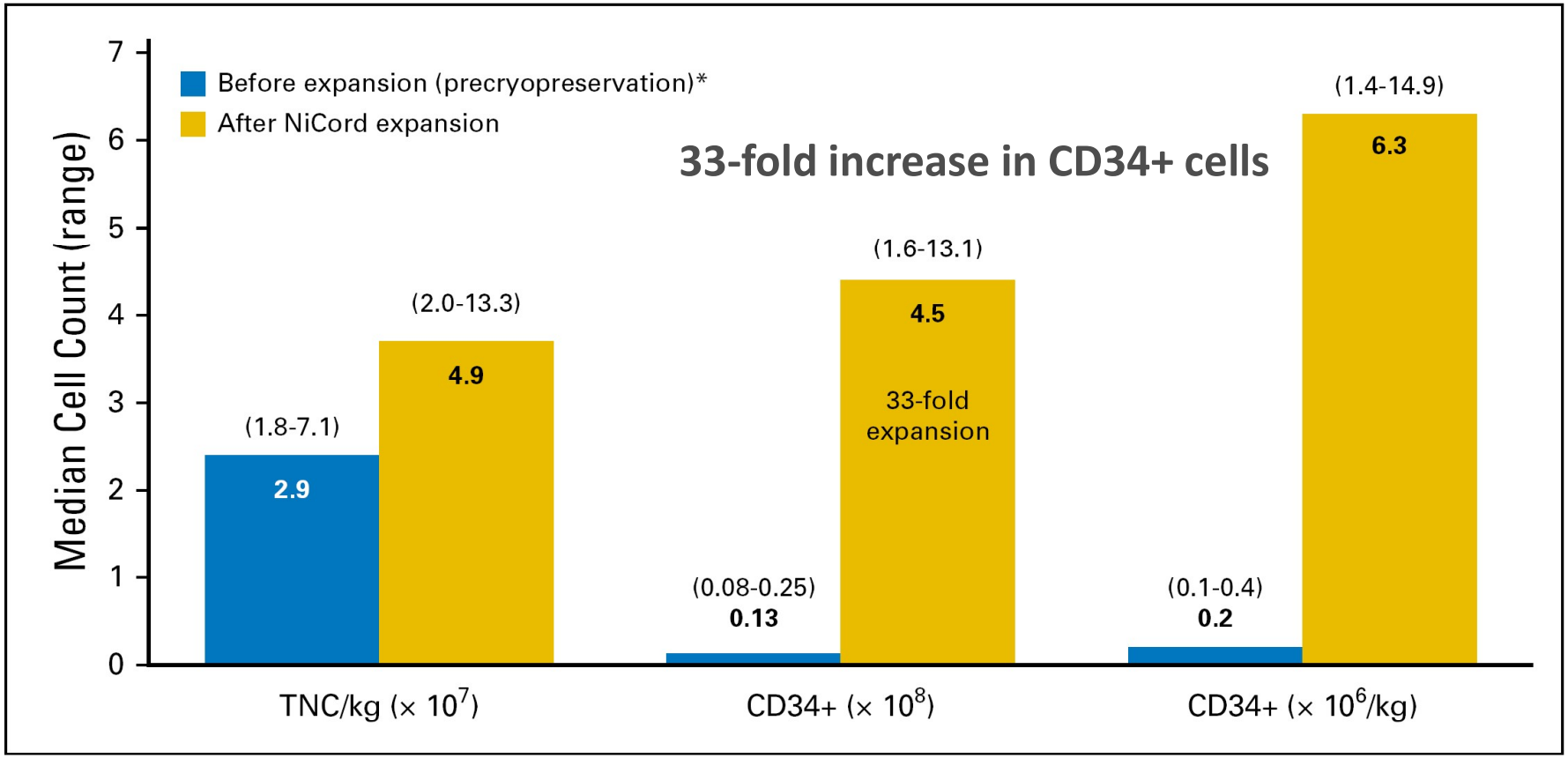
†Thiotepa 5 mg/kg over 4 hours on days −7 and −6, busulfan 3.2 mg/kg over 3-hour intravenous infusion on days −5 through −3, and fludarabine 50 mg/m^2 on days −5 through −3.

‡Clofarabine 30 mg/m^2 on days −5 through −2, fludarabine 10 mg/m^2 on days −5 through −2, and busulfan using weight based dosing as per Bartelink et al[10] on days −5 through −2.

Ex vivo expansion with NiCord® product

Phase I – II, single cord platform study

NiCord Graft Characteristics

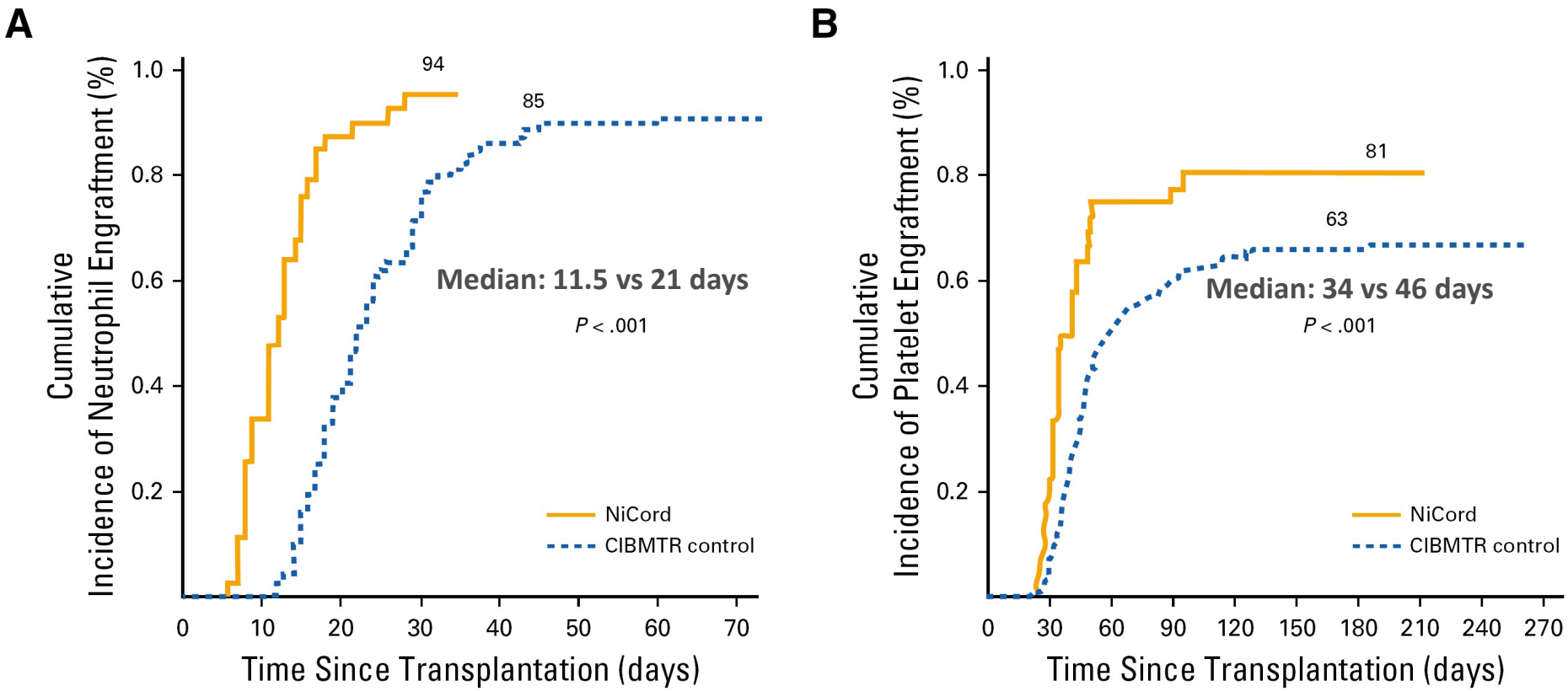


Horwitz ME, et al. *J Clin Oncol* 2019; Feb 10;37(5):367-374..

Ex vivo expansion with NiCord® product

Phase I – II, single cord platform study

Hematopoietic engraftment

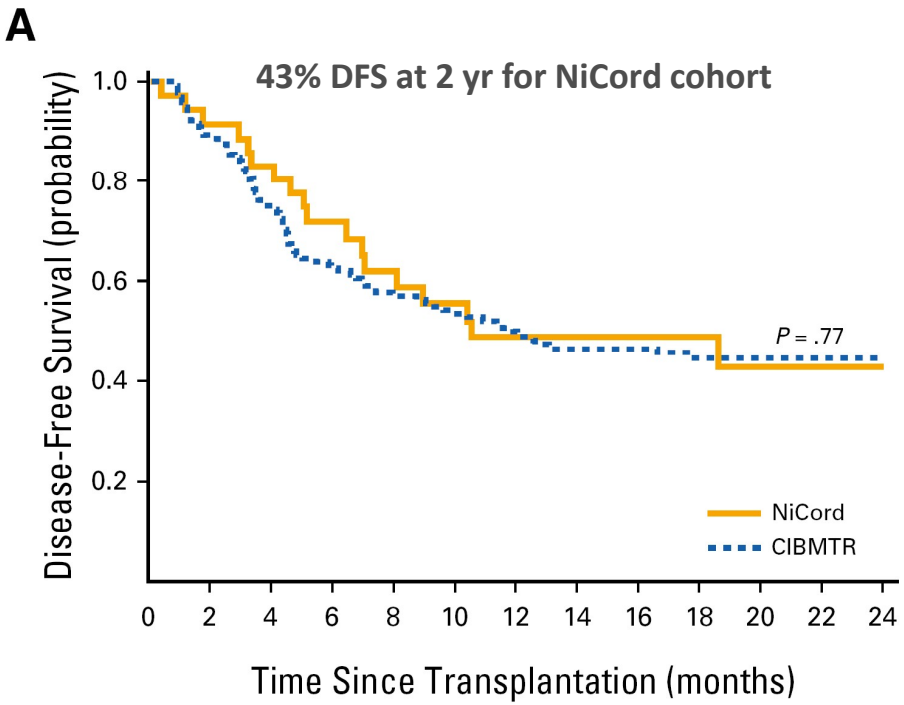


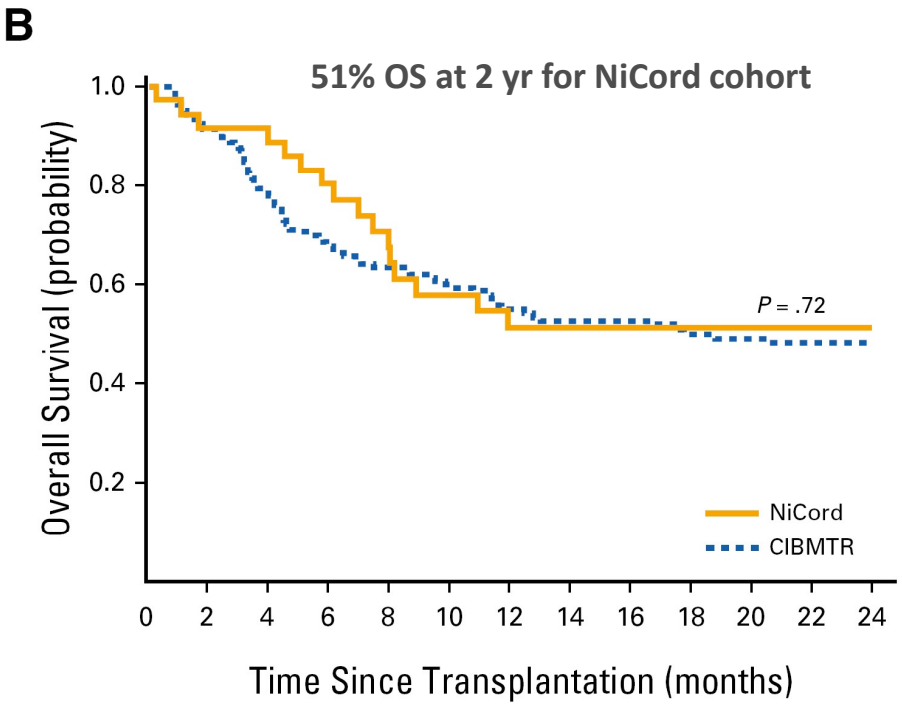
Horwitz ME, et al. *J Clin Oncol* 2019; Feb 10;37(5):367-374..

Ex vivo expansion with NiCord® product

Phase I – II, single cord platform study

A) Disease-free survival and B) Overall survival



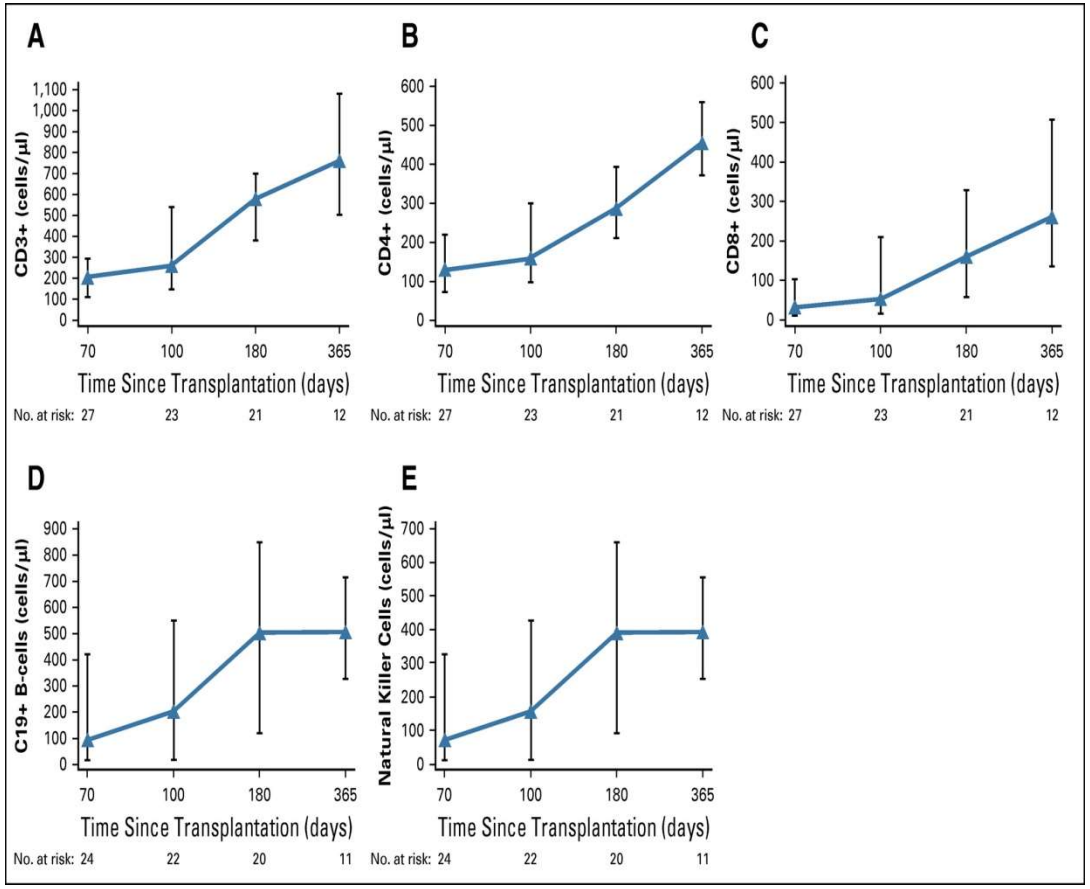


Horwitz ME, et al. *J Clin Oncol* 2019; Feb 10;37(5):367-374..

Ex vivo expansion with NiCord® product

Phase I – II, single cord platform study

Immune reconstitution in 27 patients



Quantitative recovery of (A) CD3, (B) CD4, (C) CD8, (D) CD19, and (E) natural killer cells measured at target day 70, day 100, 6 months, and 1 year after transplant with NiCord.

Horwitz ME, et al. *J Clin Oncol* 2019; Feb 10;37(5):367-374..

Ex vivo expansion with NiCord® product

Phase I – II, single cord platform study

Main conclusions

- This trial establishes the feasibility, safety, and efficacy of an ex vivo expanded UCB unit as a stand-alone graft capable of sustaining a robust and durable hematopoiesis.
- This study suggests that NiCord® obviates the need for a second UCB graft.

Horwitz ME, et al. *J Clin Oncol* 2019; Feb 10;37(5):367-374.

Ex vivo expansion with NiCord® product

Randomized phase III study (ongoing)

High-Risk Hematologic Malignancies
- AML
- MDS
- ALL
- CML
- Lymphoma

Age 12-65

Eligible for allogeneic HSCT

No suitable donor

RANDOMIZE

N=120

NiCord

Standard Cord Blood (single or double)*

* According to EBMT guidelines

Primary Endpoint:
Time to neutrophil engraftment

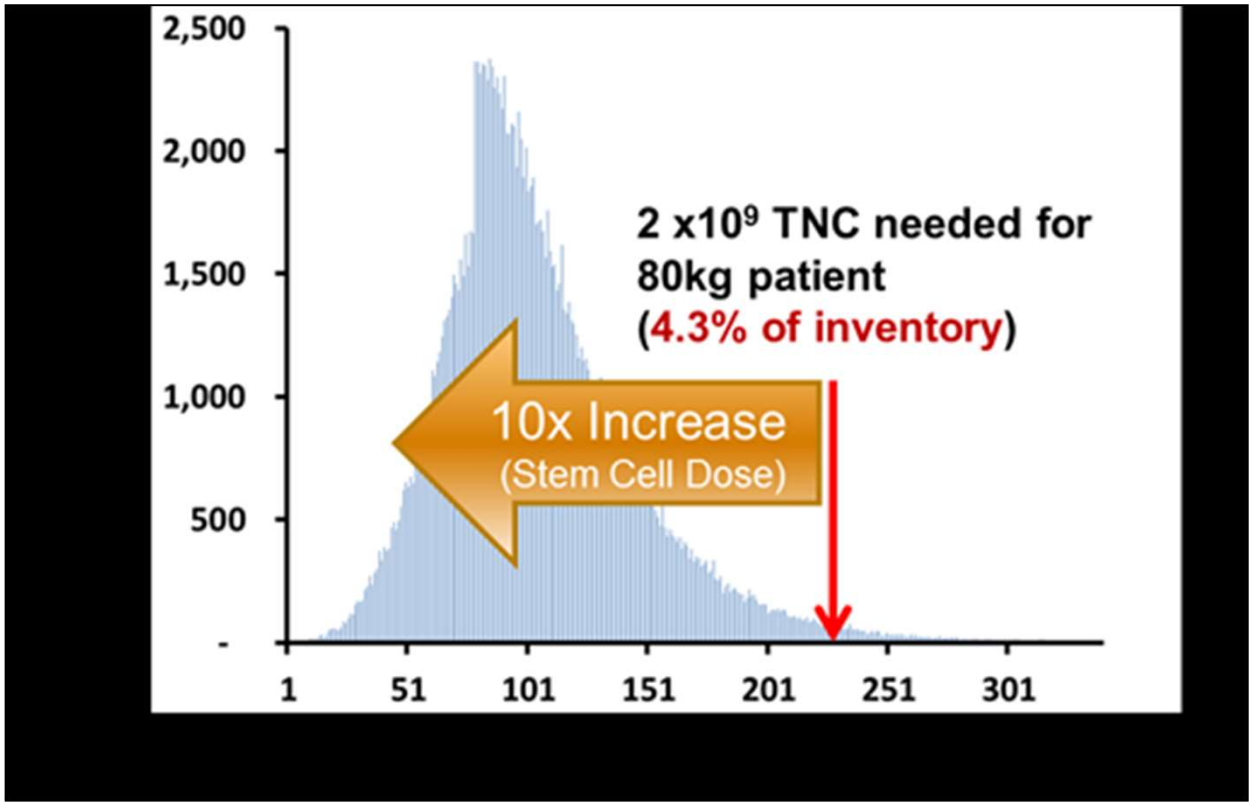
Secondary Endpoints:
Platelet engraftment
Infections
Hospitalization
Non-relapse mortality
Disease-free survival
Overall survival
Acute and chronic GvHD
Immune reconstitution

Sites in U.S., Europe and Asia

EudraCT Number: 2016-000704-28

ClinicalTrials.gov Identifier: NCT02730299

Potential advantages of *ex vivo* UCB expansion

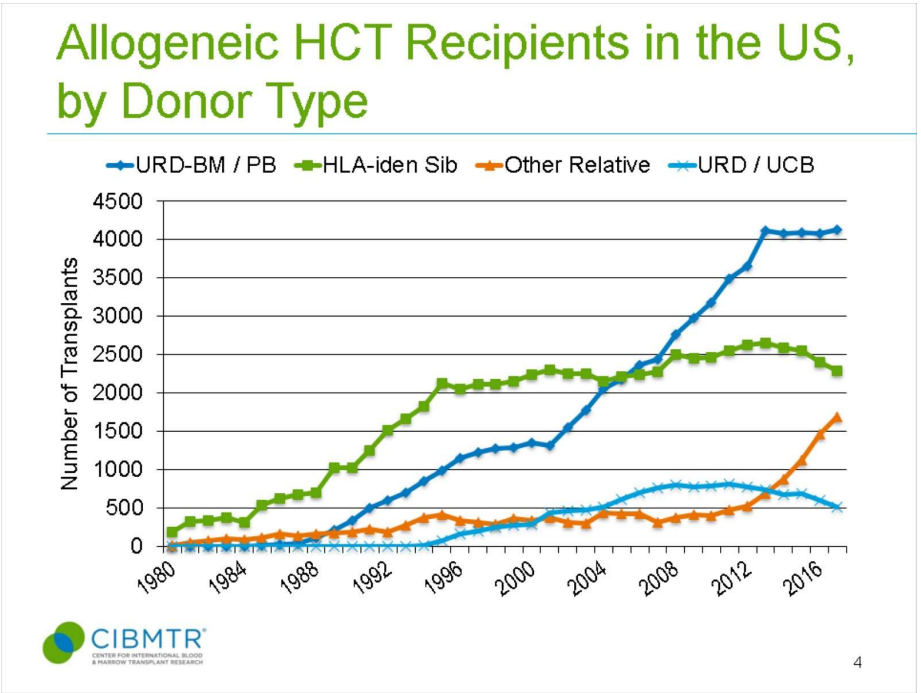


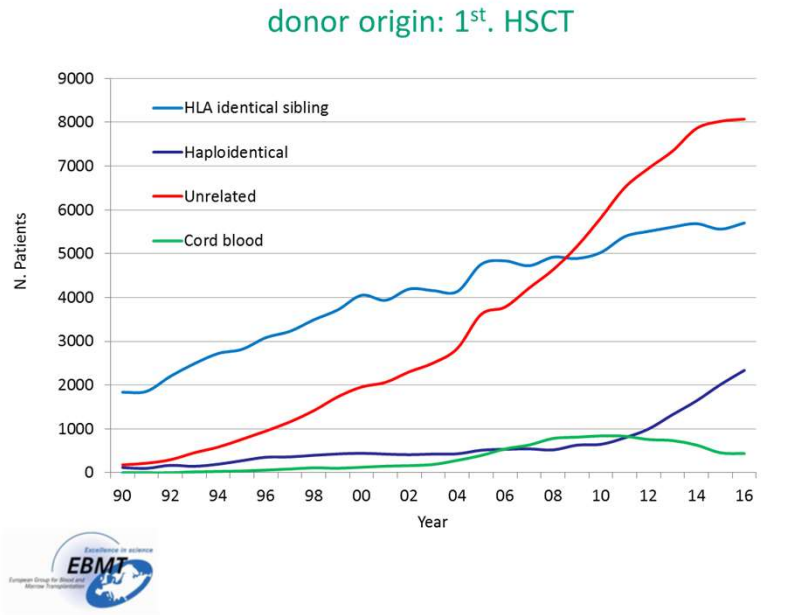
Cell dose will become less relevant:
Selection of better HLA-matched units most likely & less immunosuppression possible

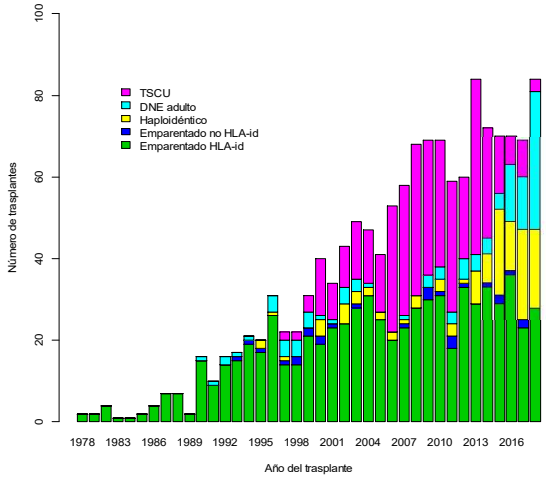
Actividad actual de TSCU

Fuentes TPH alogénico por año

Reducción número de TSCU







Actividad TPH alogénico, HUP La Fe (hasta 31 dic 2018)

Razones reducción del número de TSCU

- **Aumento del TPH haploidéntico**
  - *Búsqueda sencilla y disponibilidad de donante rápida y muy frecuente (90%).*
  - Resultados preliminares muy prometedores (especialmente con uso de ciclofosfamida post-trasplante).
  - Hospitalización inicial más corta.
  - ¿Menor coste?

Conclusiones

TSCU
Conclusiones

- Aumenta sustancialmente el acceso al trasplante.
- Sus resultados a largo plazo son similares a los de otras fuentes de progenitores hematopoyéticos de donantes alternativos.
- Puede ser preferible si hay EMR al trasplante.
- La expansión *ex vivo* acelera dramáticamente el prendimiento y reduce la estancia hospitalaria inicial pero su efecto beneficioso a largo plazo es incierto.
- Su situación actual es crítica y será una fuente marginal de progenitores hematopoyéticos si no se produce una mejora sustancial de sus resultados.

Agradecimientos

- Al Dr. Miguel Ángel Sanz Alonso
- A todo el equipo de trasplante y del servicio de Hematología y Hemoterapia
- A todo el personal facultativo, de enfermería y auxiliar de otros Servicios y Unidades del HUP La Fe
- Al CTCV, REDMO y ONT
- Al GETH, EBMT y EuroCord
- A nuestros pacientes, sus familias y cuidadores
- A ASLEUVAL