Vall d'Hebron
Hospital
Servei d'Hematologia

SOCIEDAD ESPAÑOLA DE HEMATOLOGÍA Y HEMOTERAPIA

PROGRAMA DE FORMACIÓN

FEHH
FUNDACIÓN ESPAÑOLA DE HEMATOLOGÍA Y HEMOTERAPIA

Altas dosis de quimioterapia y trasplante de progenitores hematopoyéticos

TRATAMIENTO ANTINEOPLÁSICO EN HEMATOLOGÍA: MUCHO QUE APRENDER, MUCHO QUE RECORDAR

ORGANIZADO POR LA FEHH
COORDINADORES: Dr. Francesc Bosch y Dra. Dolores Caballero
FECHA: 23 y 24 de octubre 2014
LUGAR CELEBRACIÓN: Colegio Oficial de Médicos de Madrid

David Valcárcel
SCT Unit
Hematology Department
Hospital Vall d´Hebron

Index

- General Concepts
- Commonest Schemes
- The Introduction of RIC

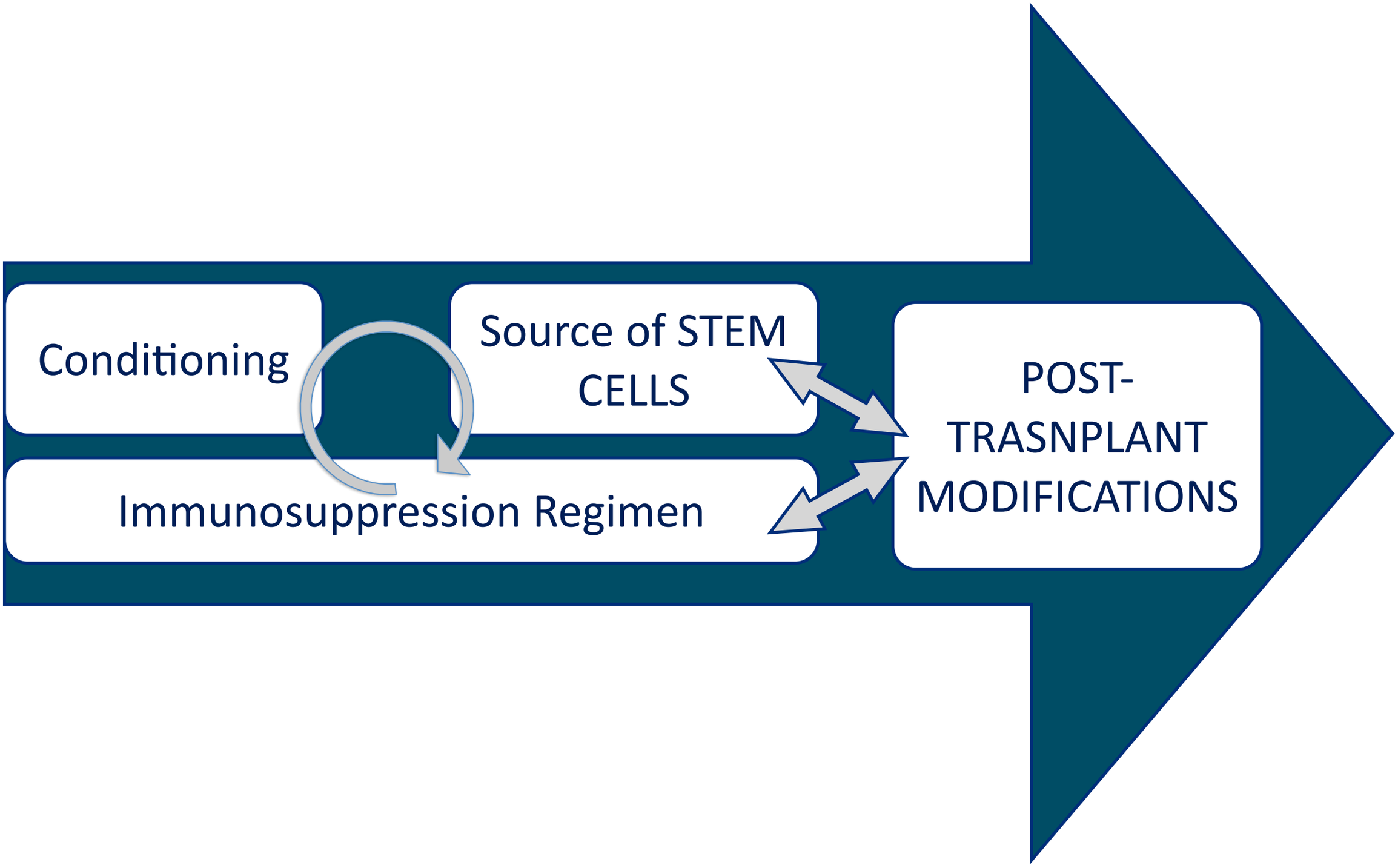
Definition and Objectives

Conditioning is the preparation of the patient to receive the transplant. It includes the drugs and/or radiotherapy that the patient receives before the cells infusion

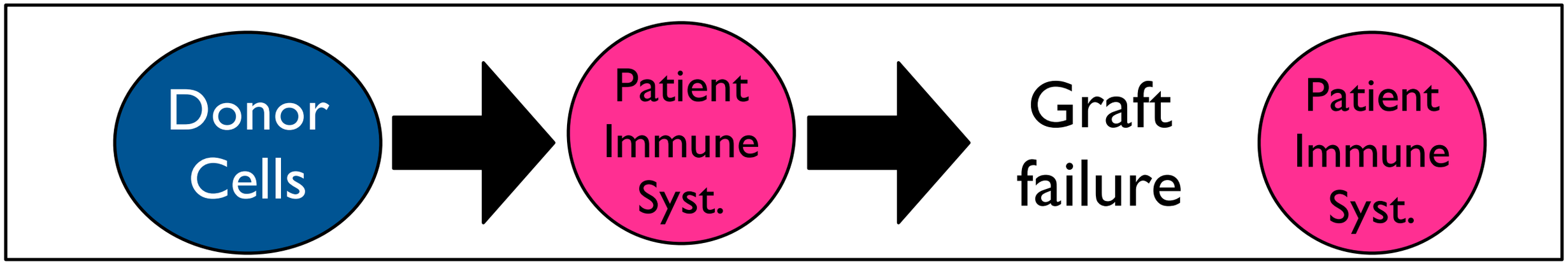
Objectives

- To eliminate the Disease
- To create space
- Host Immunosuppression

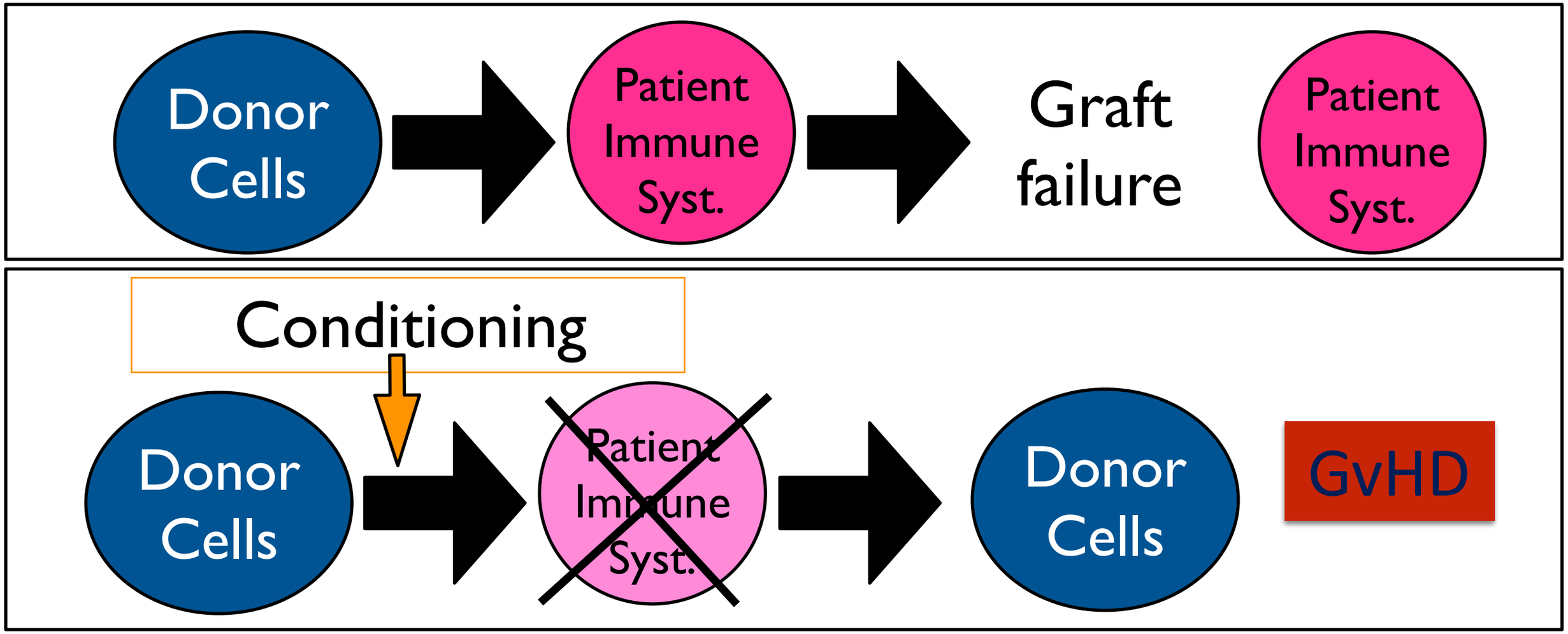
Transplant Platform



The transplant procces



The transplant procces



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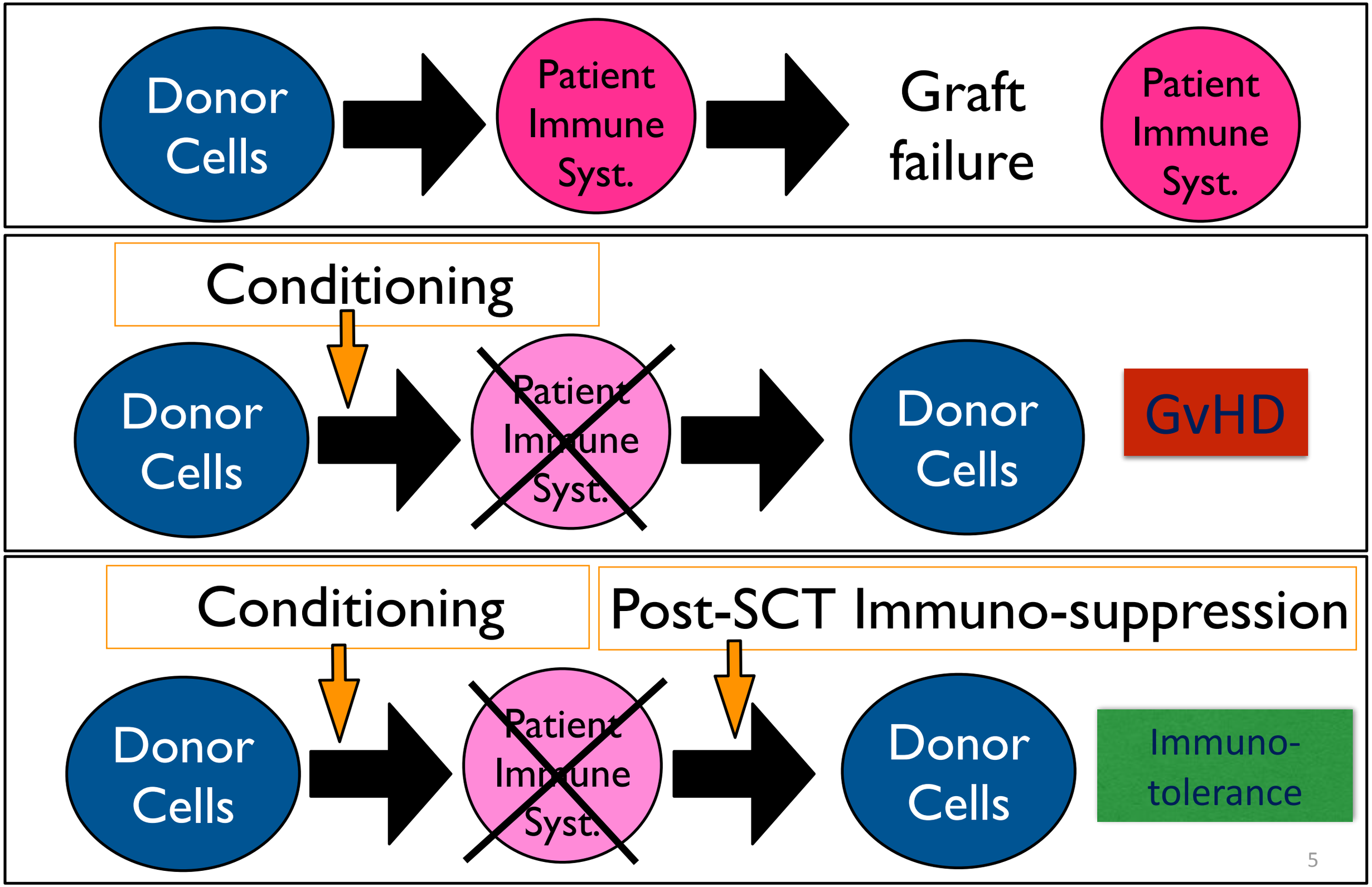
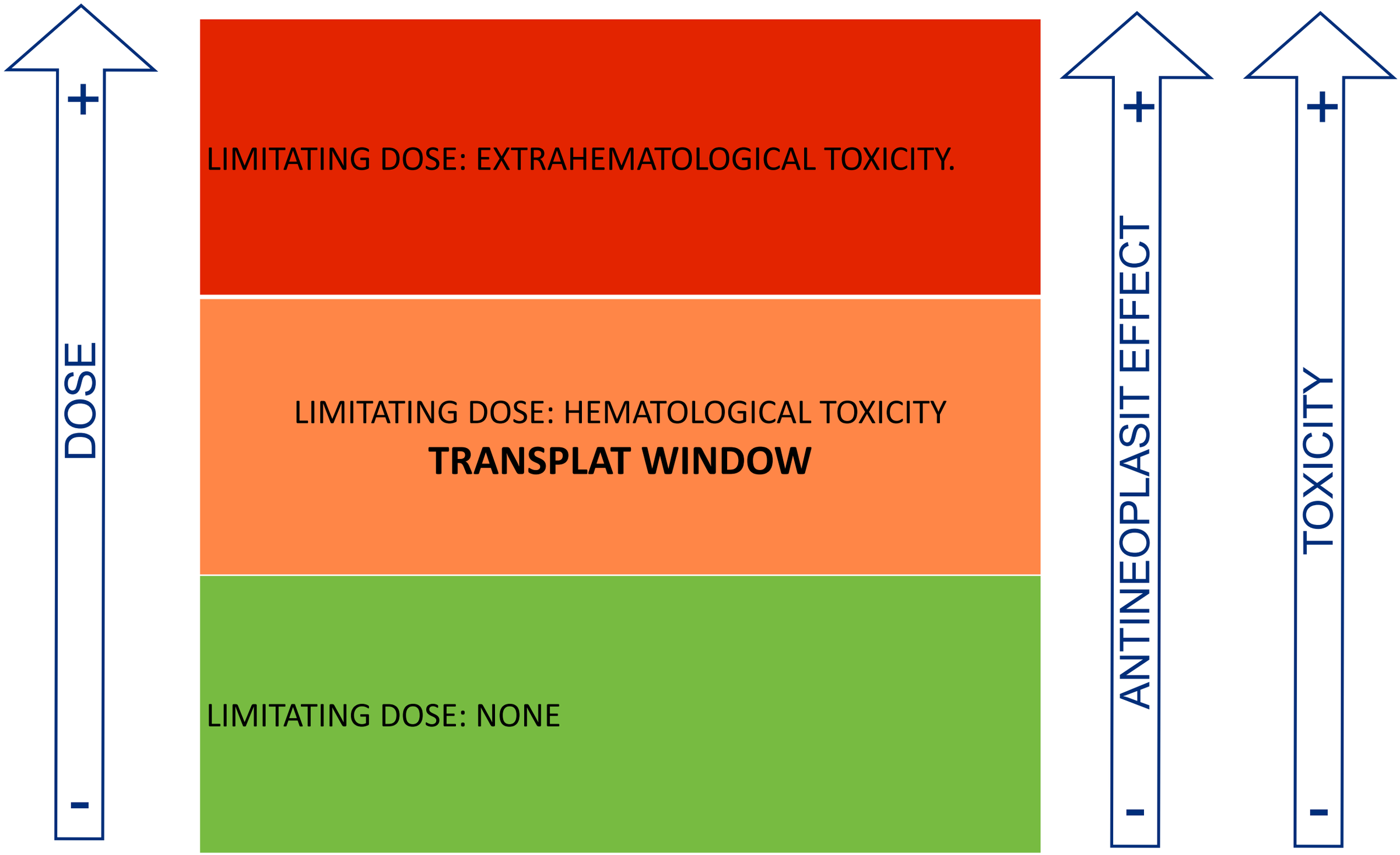
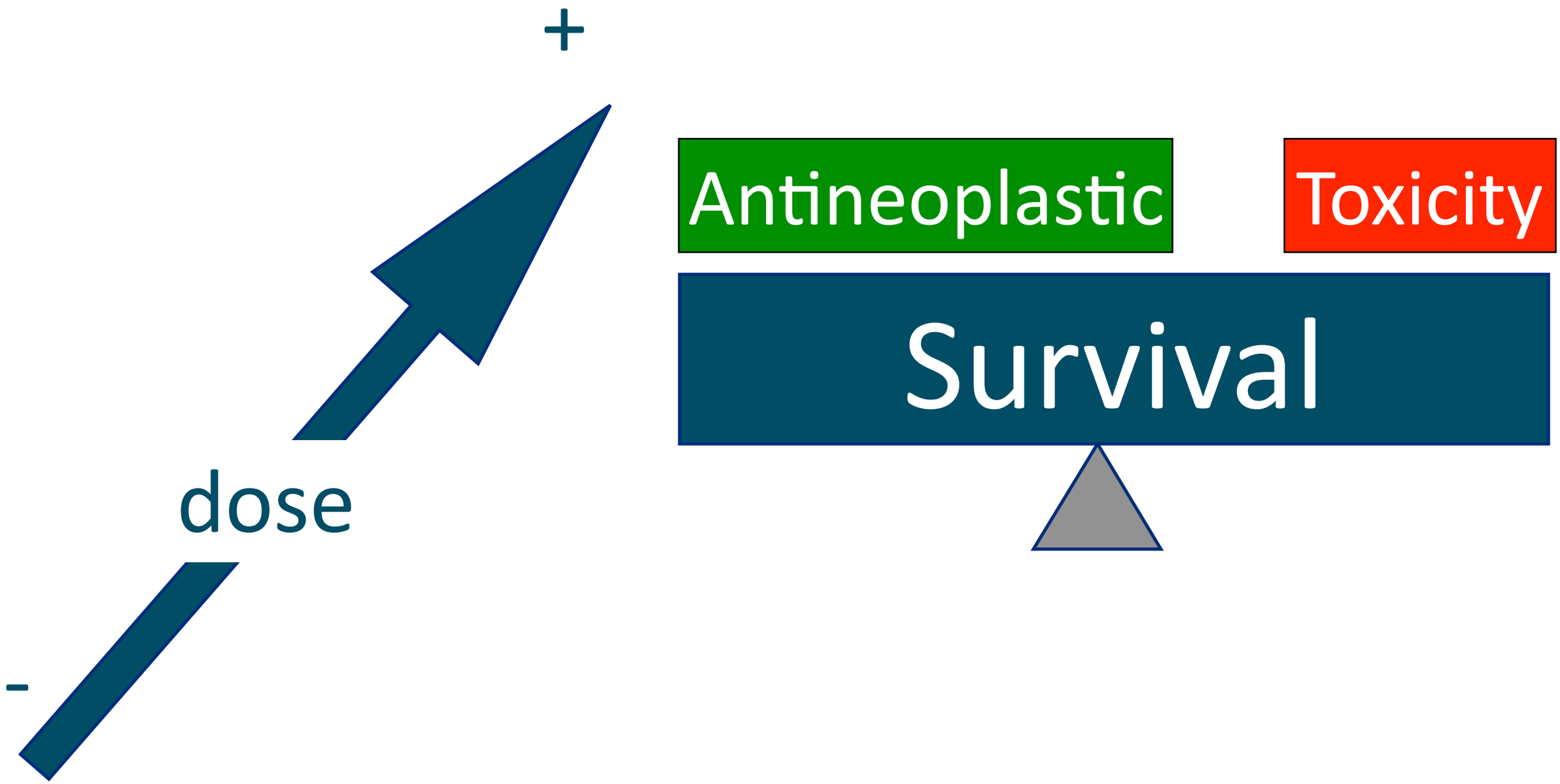
The transplant procces



Antineoplastic Effect



High Dose Paradox



Transplant types

Transplant types

ACONDICIONAMIENTO
CONVENCIONAL
INTENSIDAD REDUCIDA

Transplant types

ACONDICIONAMIENTO	PROCEDENCIA CÉLULAS
CONVENCIONAL	AUTOLOGO
	ALOGÉNICO
INTENSIDAD REDUCIDA	
	SINGÉNICO

Transplant types

ACONDICIONAMIENTO	PROCEDENCIA CÉLULAS	
CONVENCIONAL	AUTOLOGO	
	ALOGÉNICO	FAMILIAR
		NO EMPARENTADO
		HAPLOIDÉNTICO
INTENSIDAD REDUCIDA	SINGÉNICO	

Transplant types

<table>
<tr><th>ACONDICIONAMIENTO</th><th colspan="2">PROCEDENCIA CÉLULAS</th><th>FUENTE PROGENITORES</th></tr>
<tr><td rowspan="2">CONVENCIONAL</td><td colspan="2">AUTOLOGO</td><td>MEDULA ÓSEA</td></tr>
<tr><td rowspan="3">ALOGÉNICO</td><td>FAMILIAR</td><td rowspan="3">SANGRE PERIFÉRICA</td></tr>
<tr><td rowspan="3">INTENSIDAD REDUCIDA</td><td>NO EMPARENTADO</td></tr>
<tr><td>HAPLOIDÉNTICO</td></tr>
<tr><td colspan="2">SINGÉNICO</td><td>CORDÓN UMBILICAL</td></tr>
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Main Drugs Used in Conditioning

TBI

12-13 Gy
2 Gy
8 Gy
.....

Drugs

Cyclophosphamide
Busulfan
Melphalan
BCNU
Etoposide
Cytarabine
Cysplatine
Fludarabine

Bendamustine
Clofarabine
Thiotepa
Clofarabine
Zevalin
Rituximab

Factors Influencing Conditioning

Disease (Type and Status)

BEAM: NHL, HD
HD Mel: MM
BuCy: AML, ALL, others
TBI: ALL, AML
HD Cy/ATG: Aplasia
Flu/Bu: Myeloid
Flu/Mel: Lymphoid
.....
CR, Low Risk: RIC
PR, High Risk: Stand

Patient Age/ Comorbidities

Age:
Children
Young adult
Old adult

Comorbidities:
Sorror: 3 points

Prior Therapies

Different drugs
Prior Radiotherapy?

Center Experience/ Disponibility

Center protocols
Radiotherapy availability

Immunosuppressive regimens

Calcineurin inhibitors: cyclosporine vs. tacrolimus

T-CELL DEPLETION
CD 34 SELECTION
ATG
CAMPATH

MTX vs. MMF

Prednisone

Sirolimus

Cyclophsphamide

New strategies: HDACi, AZA, Photoapheresis....

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Myeloablative Conditioning in AML

Ciclofosfamida
120 mg/kg
+
TBI 12-13 Gy

¿?

Ciclofosfamida
120 mg/kg
+
Busilvex
12.8 mg/kg

Fludarabina
150 mg/m^2
+
Busilvex
12.8 mg/kg

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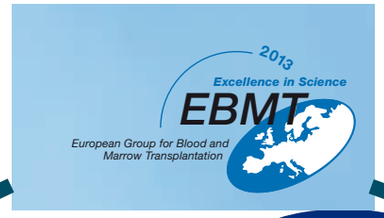
Myeloablative Conditioning in AML



Ciclofosfamida
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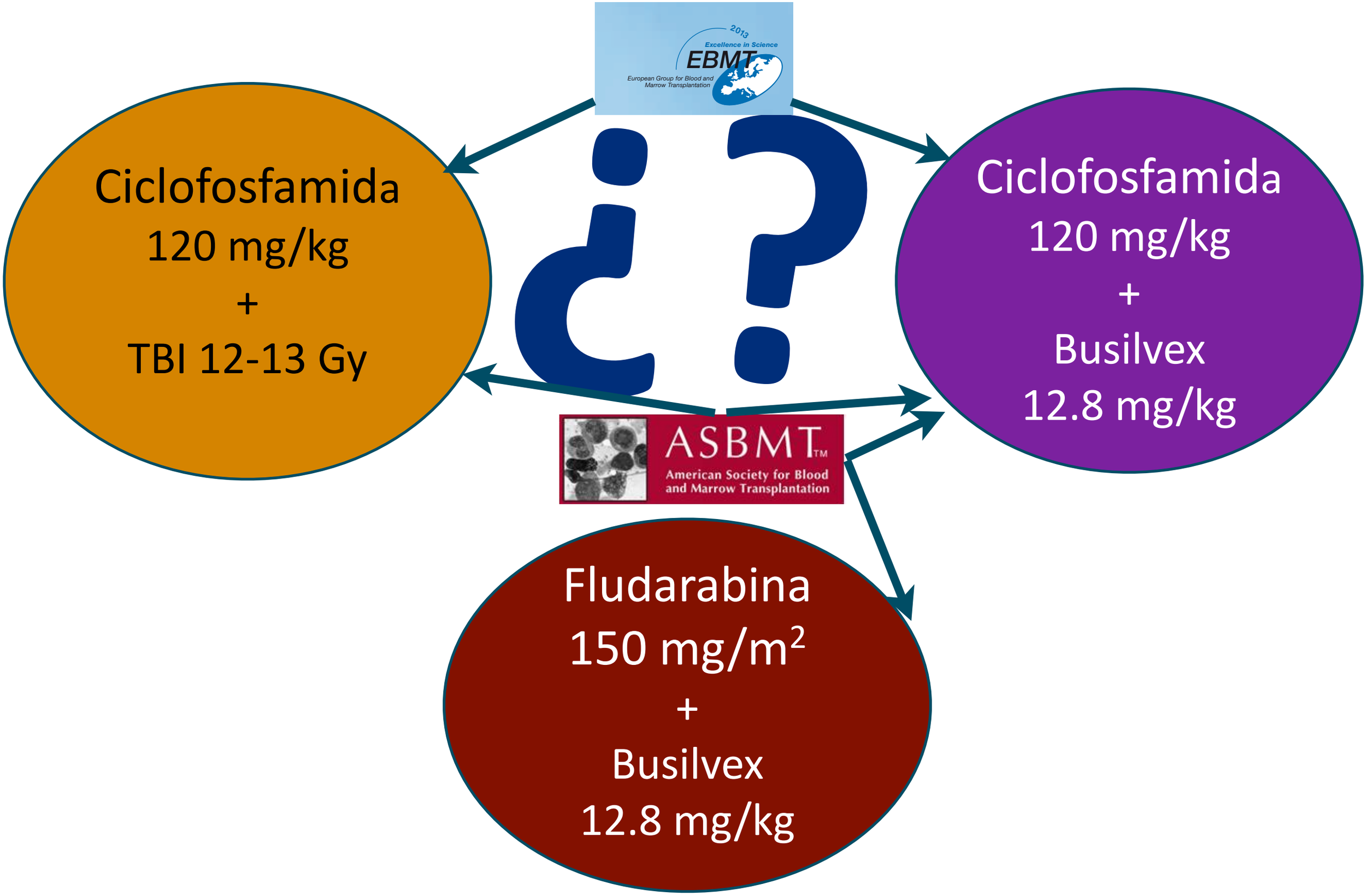
Myeloablative Conditioning in AML



Acute Leukemias (Bu-Cy) (Cy-TBI)

CY-BU (BU-CY)

Busulfan 12.8 mg/kg (iv)
16 mg/kg (vo)
(-7 to -4) (-5 to -2)

Cyclophosphamide120 mg/kg
(-3,-2) (-7,-6)

BU-FLU

Busulfan (as before)

FLUDARABINE 150 mg/m^2

VS.

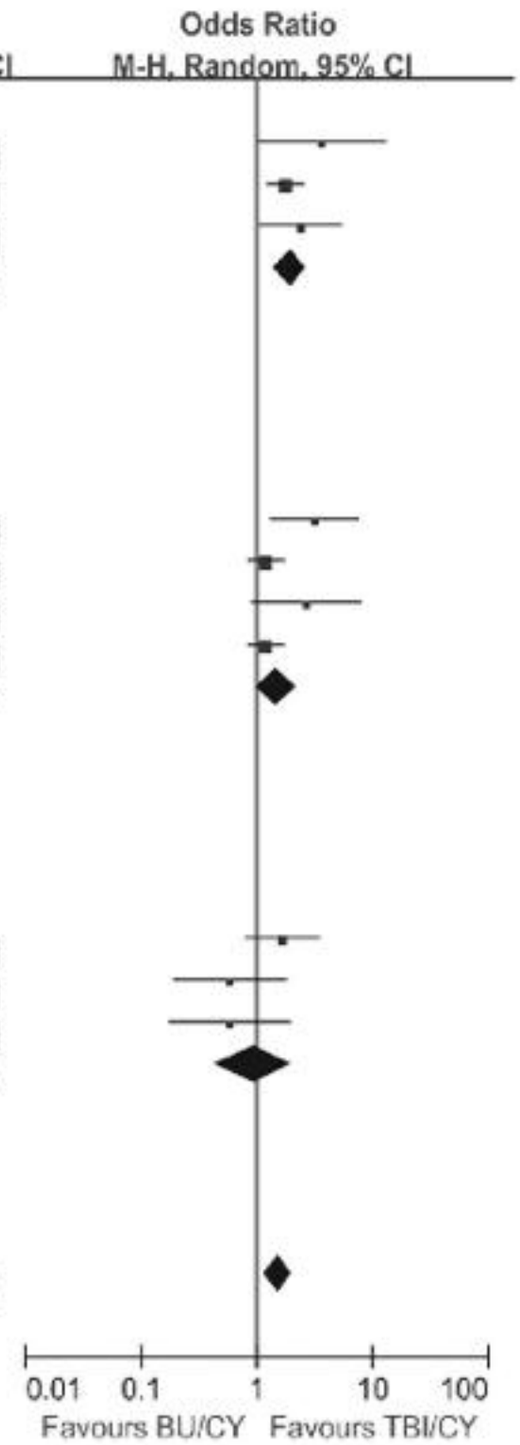
CY-TBI

Cyclophosphamide120 mg/kg
(-6 to -5)

TBI 13 Gy (-3 to -1)

BuCy *vs.* CyTBI

Study or Subgroup	TBI/CY Events	TBI/CY Total	BU/CY Events	BU/CY Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 ALL						
Bunin	13	22	6	21	4.0%	3.61 [1.01, 12.89]
Davies	276	451	83	176	18.6%	1.77 [1.24, 2.51]
Granados	49	114	10	42	8.3%	2.41 [1.08, 5.37]
Subtotal (95% CI)		**587**		**239**	**30.9%**	**1.93 [1.42, 2.64]**
Total events	338		99			
Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 4.14 (P < 0.0001)						
1.1.2 AML						
Blaise	39	50	27	51	7.4%	3.15 [1.33, 7.49]
Litzow	114	196	205	380	18.7%	1.19 [0.84, 1.68]
Michel G	26	32	26	42	5.3%	2.67 [0.90, 7.89]
Ringden	169	269	158	269	18.7%	1.19 [0.84, 1.68]
Subtotal (95% CI)		**547**		**742**	**50.1%**	**1.49 [1.01, 2.20]**
Total events	348		416			
Heterogeneity: Tau² = 0.07; Chi² = 6.21, df = 3 (P = 0.10); I² = 52%						
Test for overall effect: Z = 2.01 (P = 0.04)						
1.1.3 CML						
Devergie	28	55	25	65	9.4%	1.66 [0.80, 3.43]
Kim I	14	26	18	27	5.1%	0.58 [0.19, 1.77]
Kröger	15	25	18	25	4.6%	0.58 [0.18, 1.91]
Subtotal (95% CI)		**106**		**117**	**19.0%**	**0.93 [0.44, 1.98]**
Total events	57		61			
Heterogeneity: Tau² = 0.20; Chi² = 3.54, df = 2 (P = 0.17); I² = 44%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Total (95% CI)		**1240**		**1098**	**100.0%**	**1.53 [1.16, 2.02]**
Total events	743		576			
Heterogeneity: Tau² = 0.08; Chi² = 16.58, df = 9 (P = 0.06); I² = 46%						
Test for overall effect: Z = 3.01 (P = 0.003)						



Shi-Xia X et al. Leuk&Lymph, 2010

Cy/TBI vs. i.v. BuCy for AML in CR: Transplantation Outcome (n = 1659)

i.v.BuCy (n=795)		Cy/TBI (n=864)
Engraftment: 98%		Engraftment: 99%
ANC > $0.5x10^9$/L – d16		ANC > $0.5x10^9$/L – d16
aGVHD^ ≥ Grade II-IV: 20%	P <0.0001	aGVHD ≥ Grade II-IV: 31%
≥ Grade III-IV: 6%	P <0.0001	≥ Grade III-IV: 11%
cGVHD (2y) 38±2%	P =0.003	cGVHD (2y) 50±2%
Limited - 111		Limited – 146
Extensive - 105		Extensive - 171
VOD^^: 5.9% (3-gr III)	P =0.66	VOD: 4.7% (5-gr III)

^ In multivariable analysis acute and chronic GVHD were found to be higher with Cy/TBI: HR-2.63, p<0.0001; and HR 1.24, p=0.002
aGVHD more prevalent in older patients; cGVHD more prevalent with PB and F donors to M pts

^^ VOD was available for 273 pts. transplanted before 2008

Courtesy of Dr Nagler.

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IV BU-CY vs CY-TBI (EBMT experience)

	IV BU-CY	CY/TIB	P
NON-RELAPSE MORTALITY (2 Y)	12 +/-1	15 +/- 2	0.14
RELAPSE (2 Y)	26 +/-2	21 +/-1	0,012
LEUKEMIA FREE SURVIVAL (2 Y)	61 +/-2	64 +/-2	0.27
OVERALL SURVIVAL (2 Y)	68 +/-2	69 +/-2	0.84

Courtesy of Dr Nagler.

Comparison of Conditioning Regimens Using Intravenous Busulfan versus Total Body Irradiation for Allogeneic Hematopoietic Stem Cell Transplantation in Hematologic Malignancies

CIBMTR Study SC09-01

Prospective

CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Patient Characteristics

Characteristics	IV Bu (N=1025) %	TBI (N=458) %
Age		
<20 yrs	16	11
20-49 yrs	44	60
>=50 yrs	40	29
Female	50	48
Performance Score ≥ 90	69	67
AML	68	78
MDS	21	10
CML	11	12
HCI-CI ≤3	81	83
Advanced disease	31	29

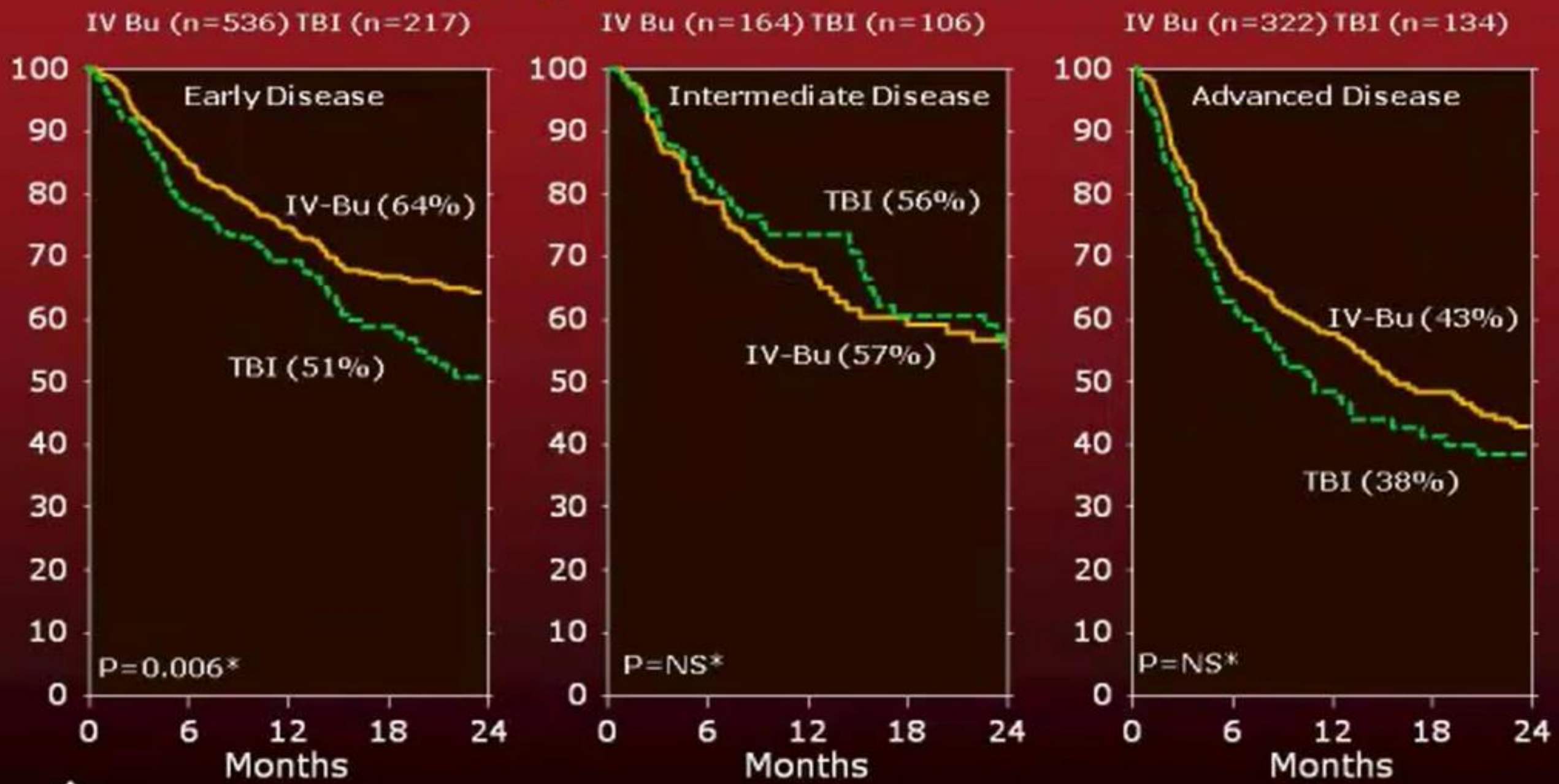
CIBMTR®

Morbidity

Complication	IV Bu 1025 %	TBI 458 %	P-value
VOD/SOS	5	1	<0.01
IPN	4	6	0.05
Dialysis @ 1yr	6	7	0.24
Acute GVHD			
Grade II-IV	46	51	0.17
Grade III-IV	18	23	0.05
Chronic GVHD @1y	50	48	0.45

CIBMTR

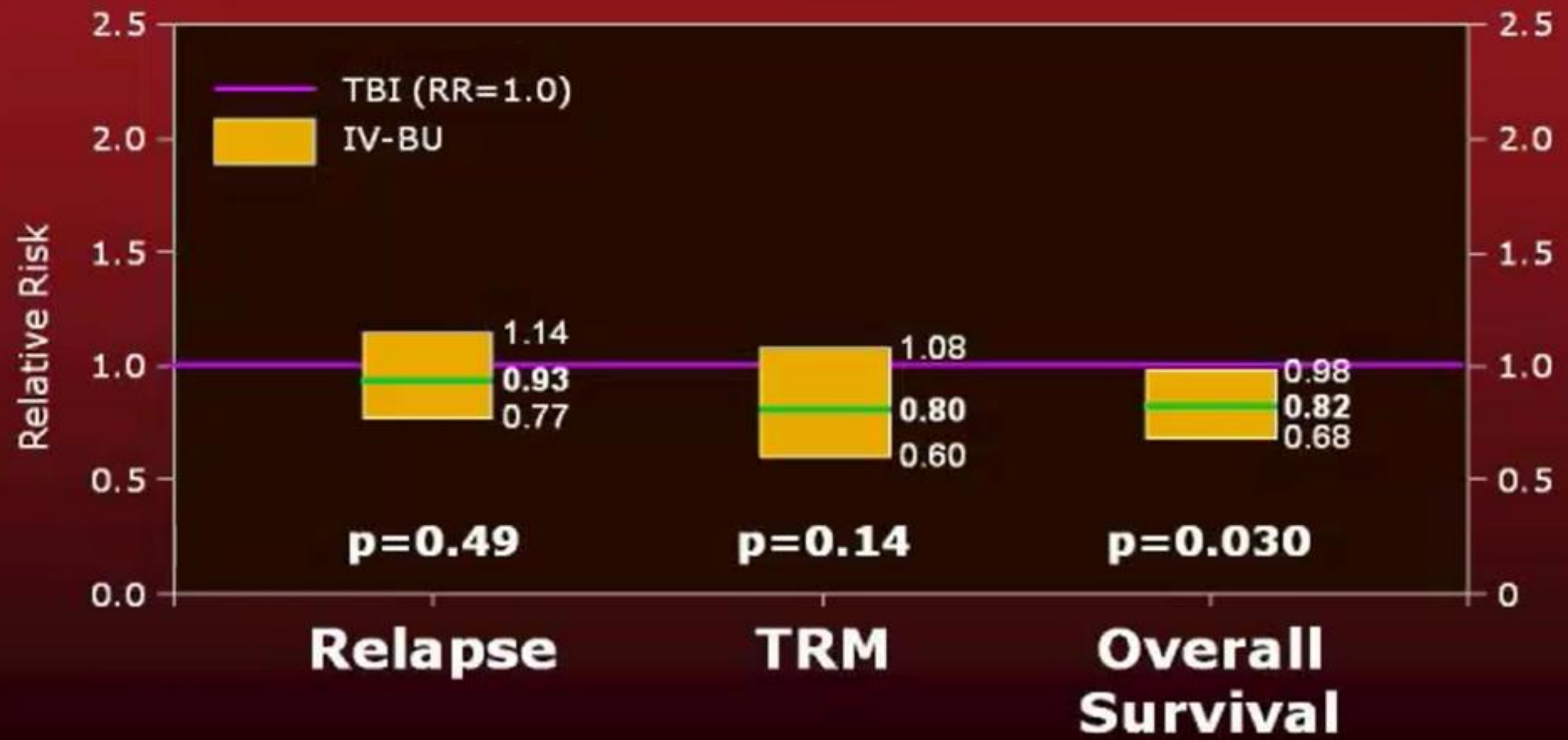
Overall Survival of Recipients of IV-BU Compared to TBI-based Myeloablative Conditioning by Disease Status at Transplant



CIBMTR®

***pointwise p-value at 2 years**

Multivariate Analysis: Bu vs.TBI



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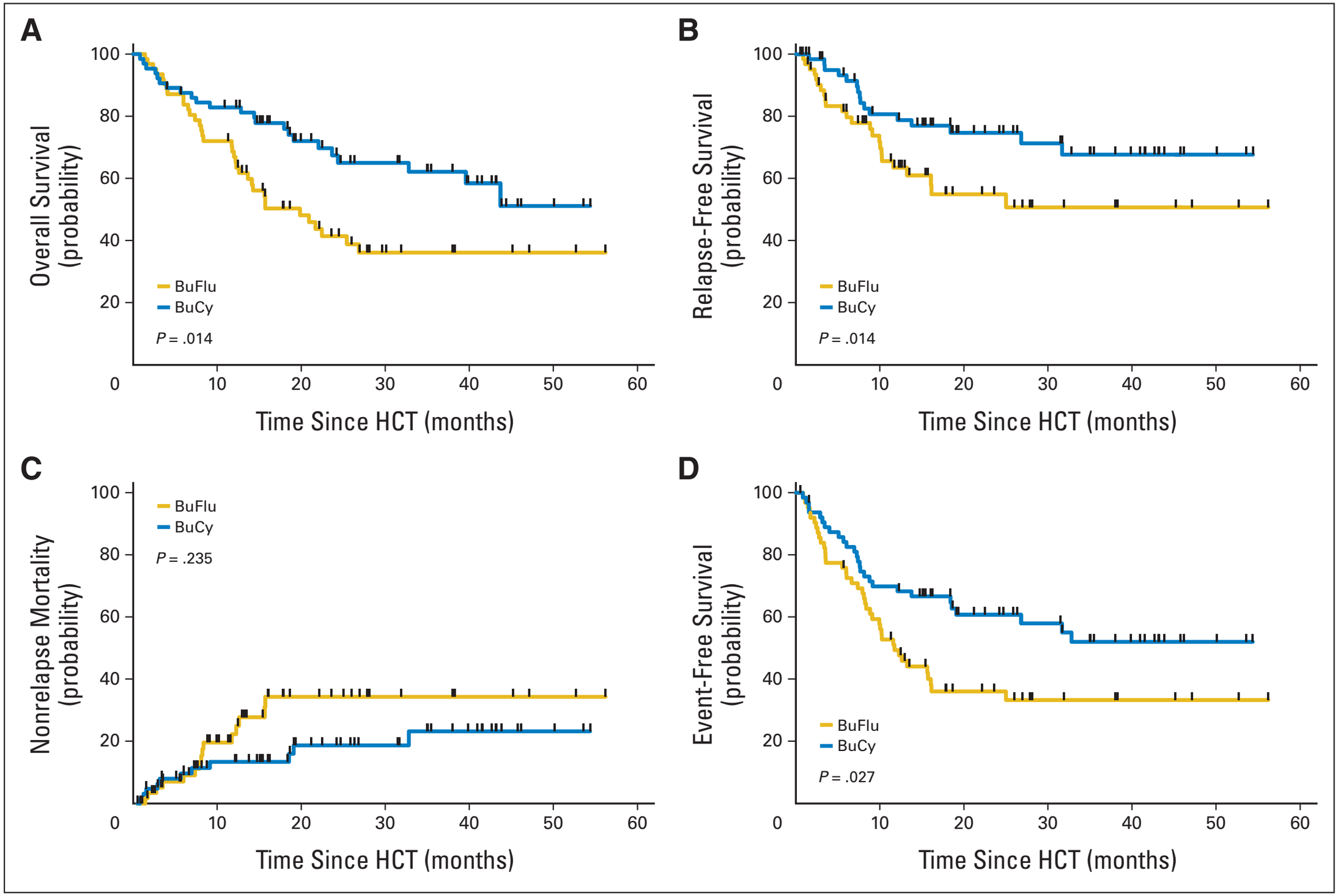
BuCy *vs.* FluBu: Randomized Trial including AML, ALL

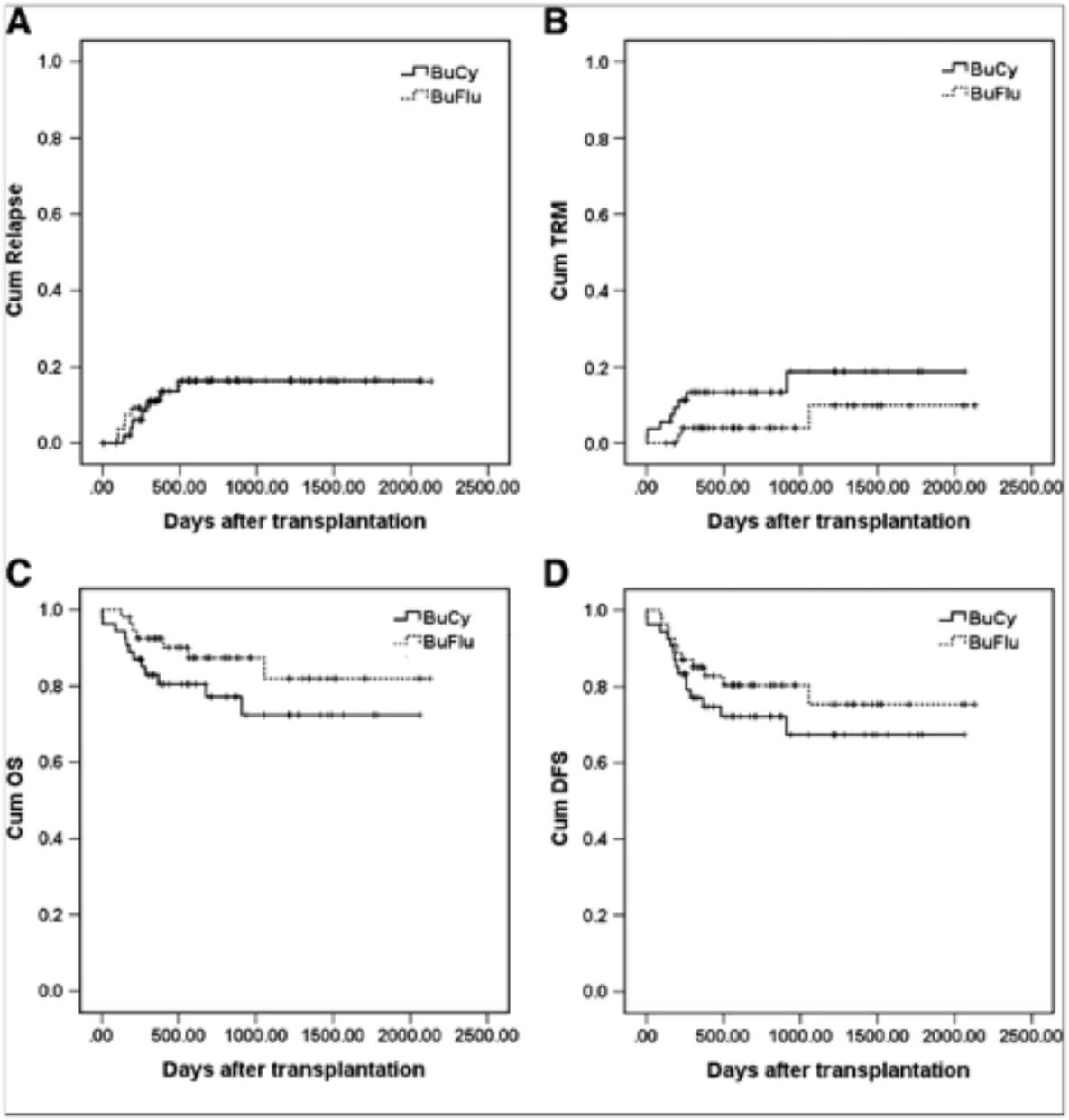


Lee JH, et al, JCO 2013

BuCy *vs.* FluBu: Randomized Trial in AML in first CR

	Grade I or II		Grade III or IV		
	BuCy	BuFlu	BuCy	BuFlu	P value
Heart (single/multiple)	4/8	2/4	2/0	0/0	0.048
Bladder	5/8	2/4	0/1	0/0	0.010
Kidneys	0/2	0/1	0/0	0/0	0.500
Lungs	0/0	0/0	0/0	0/0	
Liver	4/10	4/5	0/1	0/0	0.165
CNS	0/0	0/1	0/3	0/0	0.618
Mucosa	16/20	15/9	0/0	0/0	0.020
Gut	1/24	10/6	0/2	0/0	0.018

Abbreviations: *BuCy*, busulfan-cyclophosphamide; *BuFlu*, busulfan-fludarabine; *CNS*, central nervous system.



Liu H, et al. Journal of hematology and oncology, 2013

Lymphomas: BEAM

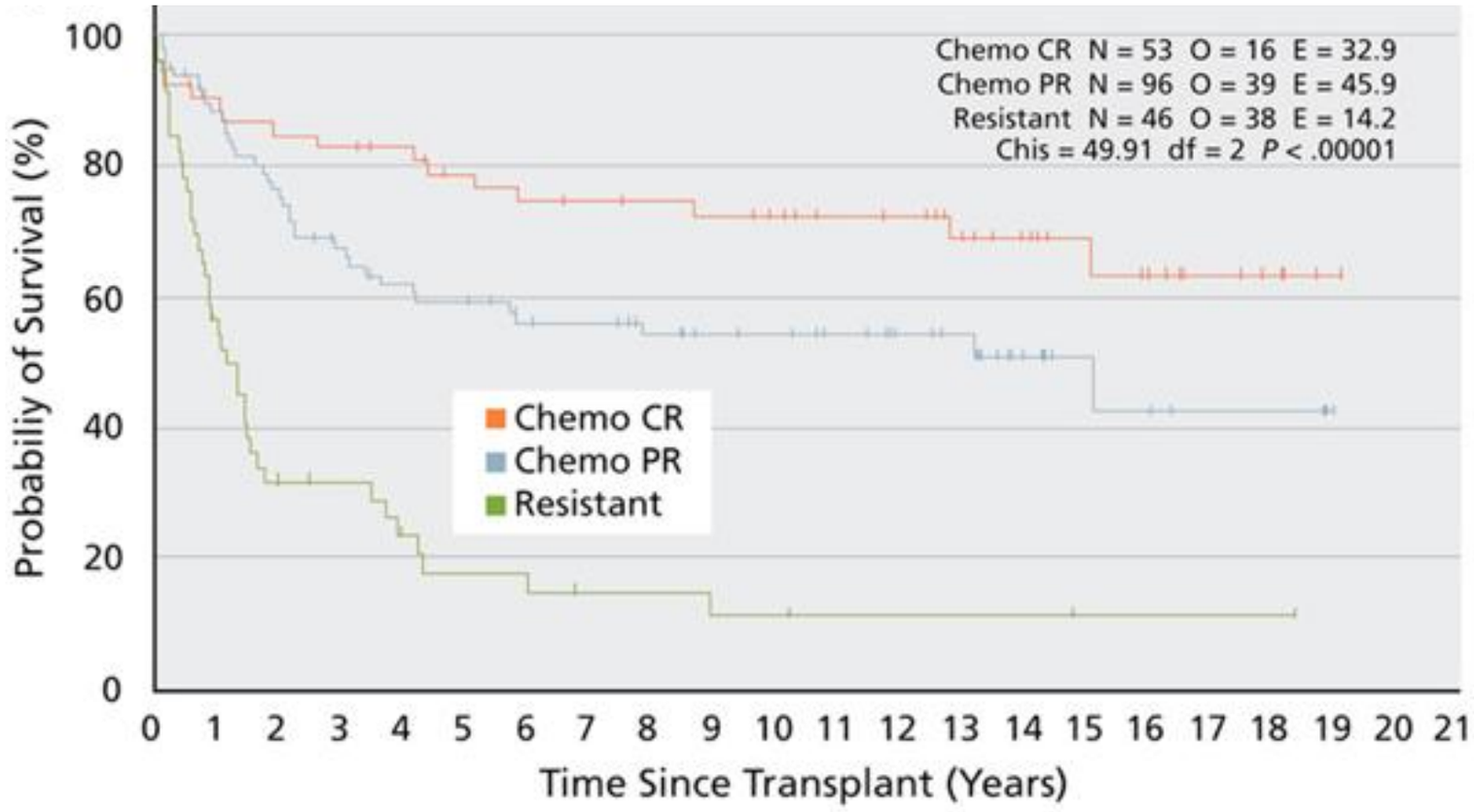
BCNU 300 mg/m^2
(-6)

ETOPOSIDE 800 mg/m^2
(-5 to -2)

CYTARABINE 800 mg/m^2
(-5 to -2)

MELPHALAN 140 mg/m^2
(-1)

Hodgkin Lymphoma



BEAM....Modifications

BENDAMUSTINE 160-200 mg/m^2 (-7,-6)

THIOTEPA 300 mg/m^2 (-6)

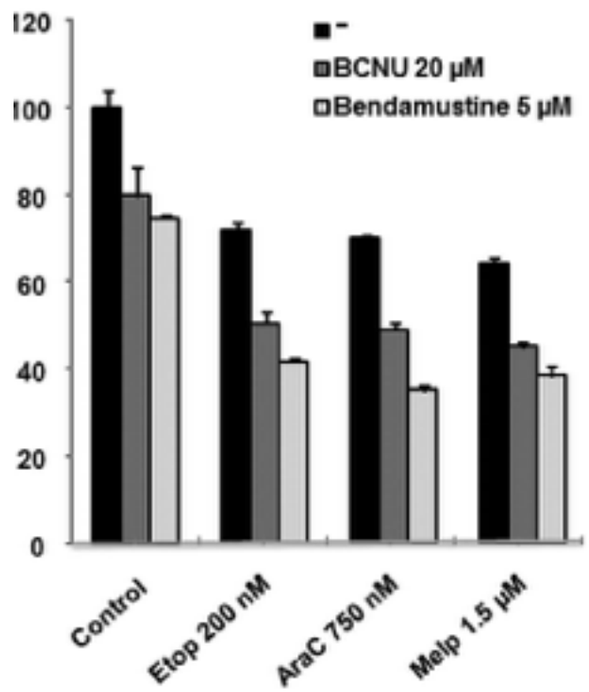
BCNU 300 mg/m^2 (-6)

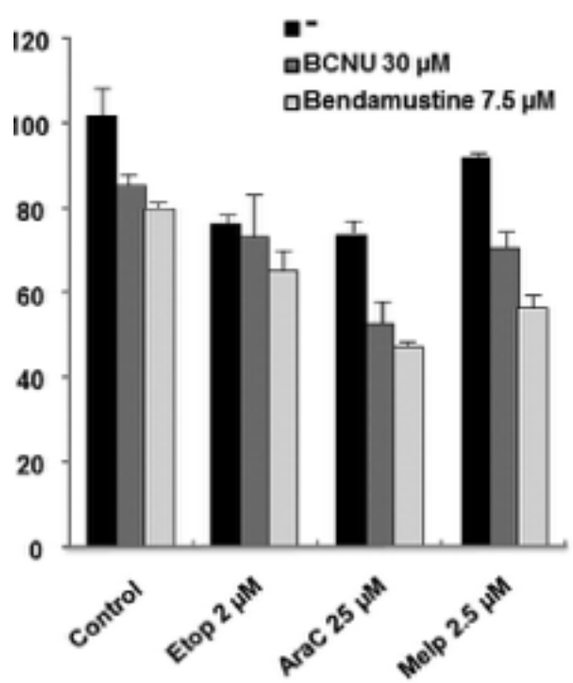
ETOPOSIDE 800 mg/m^2 (-5 to -2)

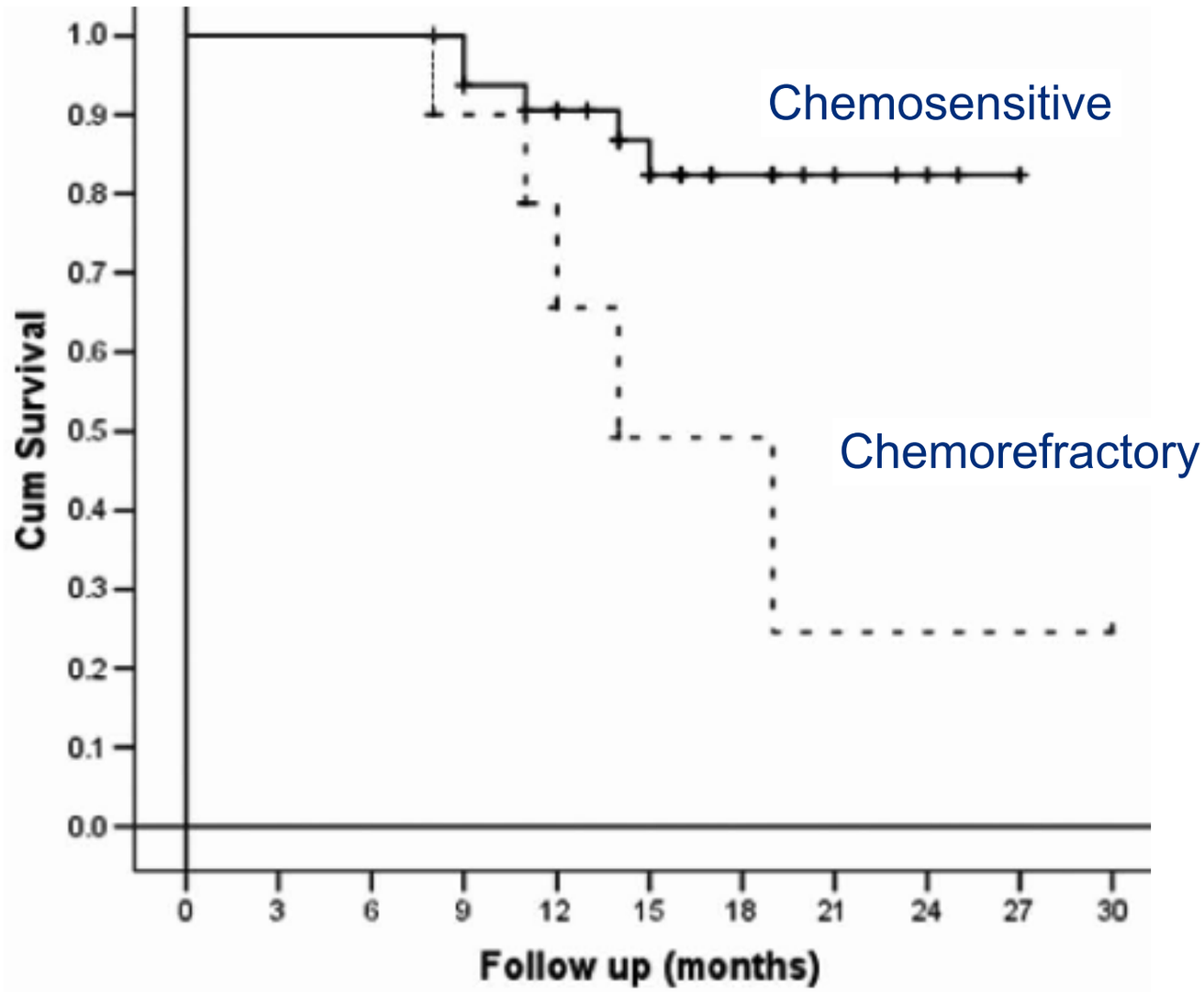
CYTARABINE 800 mg/m^2 (-5 to -2)

MELPHALAN 140 mg/m^2 (-1)

Be-EAM



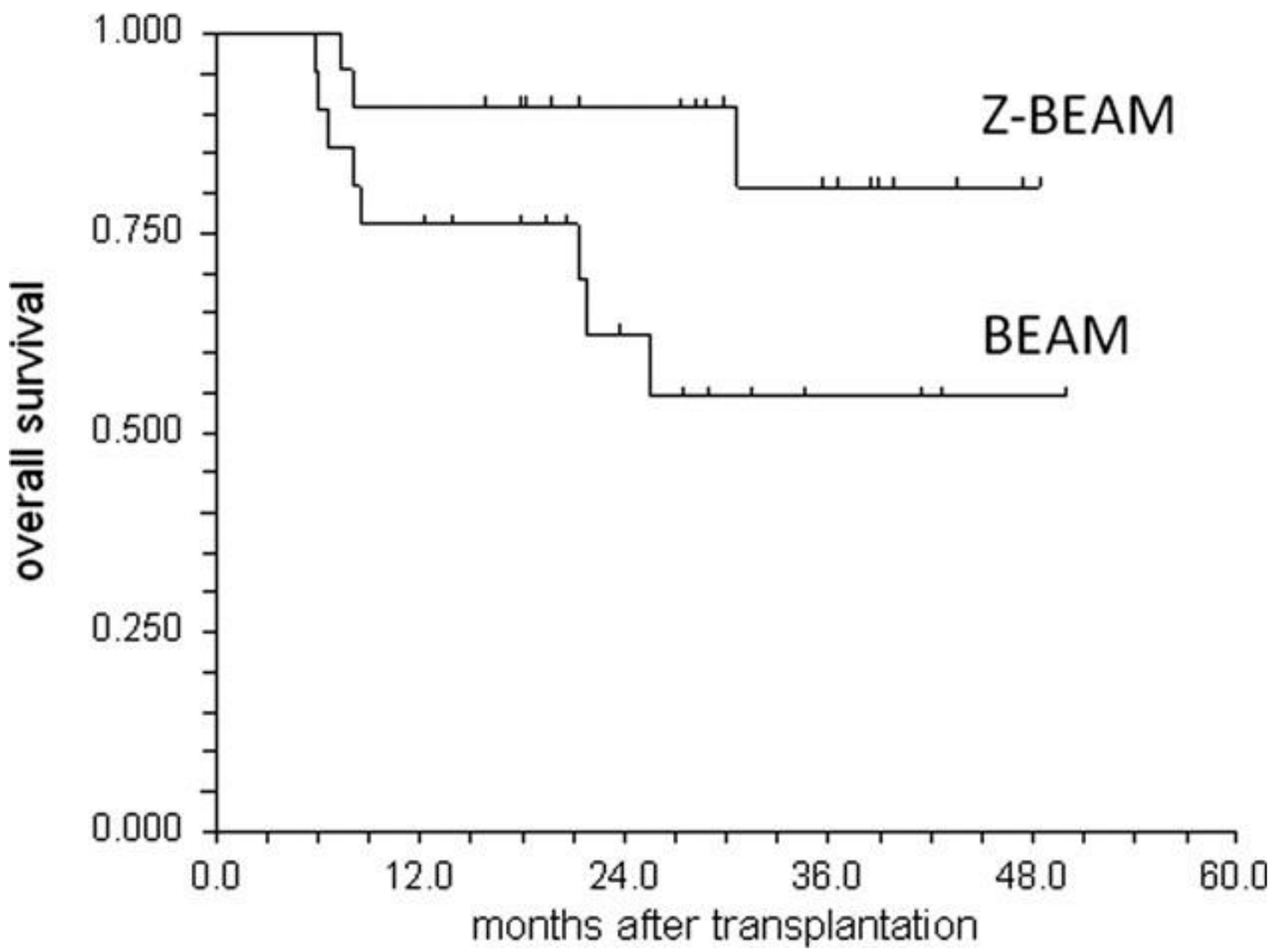




Visapi G, et al. Blood 2011.

Zevalin in the conditioning (Z-BEAM)

rituximab 250 mg/m^2 followed by **ibritumomab tiuxetan** 0.4 mCi/kg (capped at 32 mCi) on day -14 before + BEAM



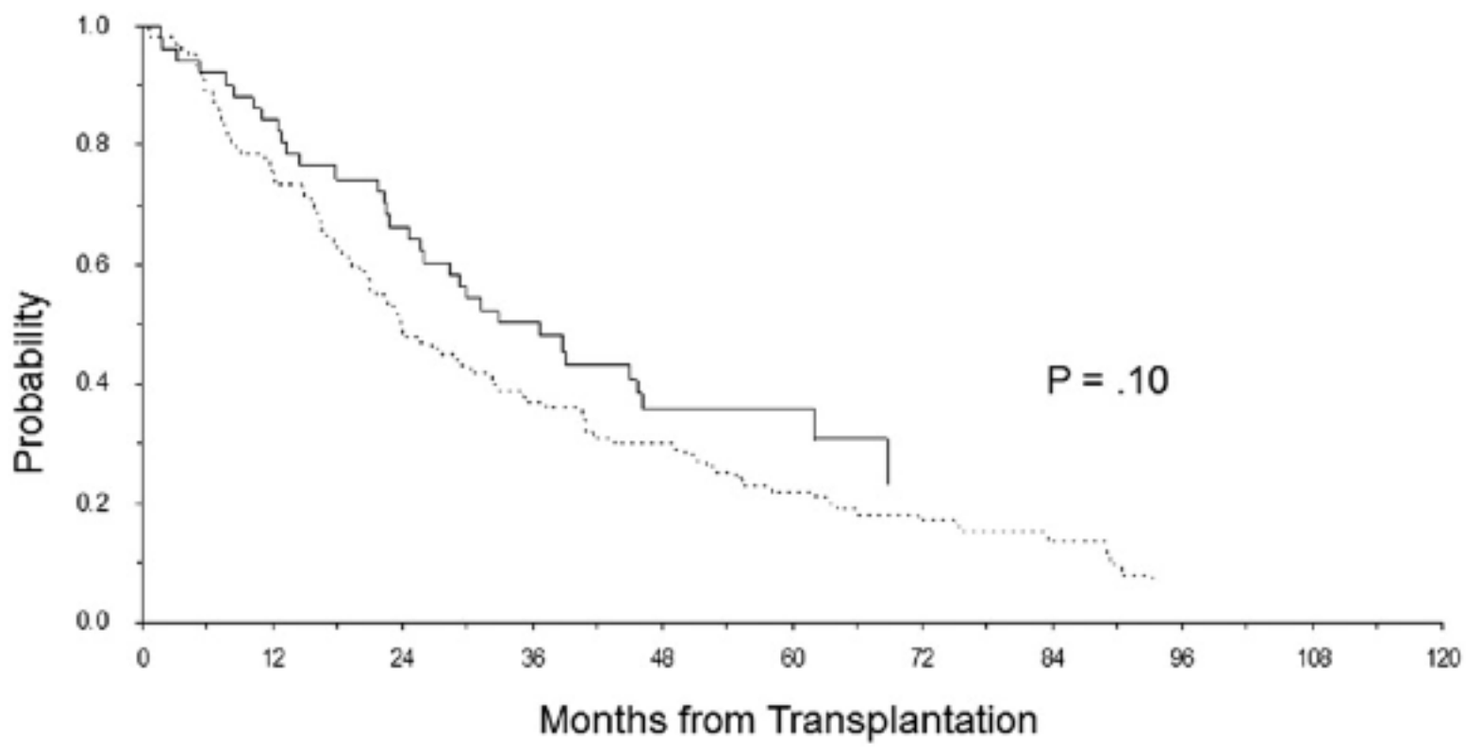
Shimoni. A, et al. Cancer 2012

Myeloma: High Dose Melphalan

Melphalan 200 mg/m^2 (-3,-2)

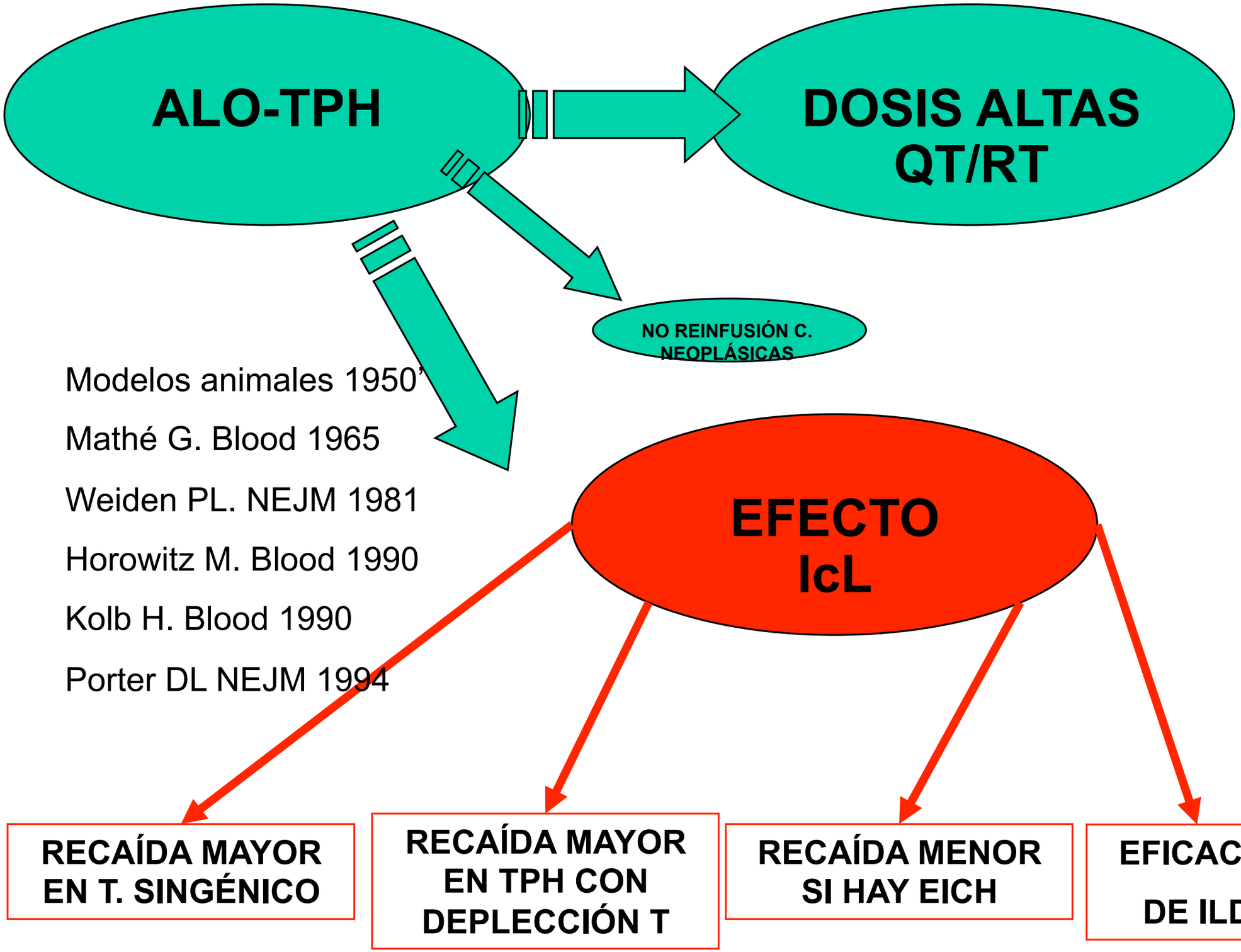
Melphalan 140 mg/m^2

Busulphan 9.6 mg/kg (-5, -3)



Blanes M, et al. BBMT 2013

Efecto injerto contra tumor



Modelos animales 1950'

Mathé G. Blood 1965

Weiden PL. NEJM 1981

Horowitz M. Blood 1990

Kolb H. Blood 1990

Porter DL NEJM 1994

The Introduction of RIC

blood 1997 89: 4531-4536

Engraftment of Allogeneic Hematopoietic Progenitor Cells With Purine Analog-Containing Chemotherapy: Harnessing Graft-Versus-Leukemia Without Myeloablative Therapy

Sergio Giralt, Elihu Estey, Maher Albitar, Koen van Besien, Gabriela Rondón, Paolo Anderlini, Susan O'Brien, Issa Khouri, James Gajewski, Rakesh Mehra, David Claxton, Borje Andersson, Miloslav Beran, Donna Przepiorka, Charles Koller, Steve Kornblau, Martin Körbling, Michael Keating, Hagop Kantarjian and Richard Champlin

Nonmyeloablative Stem Cell Transplantation and Cell Therapy as an Alternative to Conventional Bone Marrow Transplantation With Lethal Cytoreduction for the Treatment of Malignant and Nonmalignant Hematologic Diseases

By Shimon Slavin, Arnon Nagler, Ella Naparstek, Yossi Kapelushnik, Memet Aker, Gabriel Cividalli, Gabor Varadi, Mark Kirschbaum, Aliza Ackerstein, Simcha Samuel, Avraham Amar, Chaim Brautbar, Ofira Ben-Tal, Amiram Eldor, and Reuven Or

Blood, Vol 91, No 3 (February 1), 1998: pp 756-763

¿Qué es un acondicionamiento de intensidad reducida (AIR)?

- Acond. no mieloablativo:
  - recuperación hematopoyética autóloga en < 28 días. Quimerismo mixto al prendimiento
- Acond. mieloablativo:
  - requiere TPH para recuperación hematopoyética. Quimerismo completo al prendimiento
- Acond. de intensidad reducida:
  - mieloablación con reducción de dosis y toxicidad. Quimerismo al prendimiento variable según intensidad

Definición.....

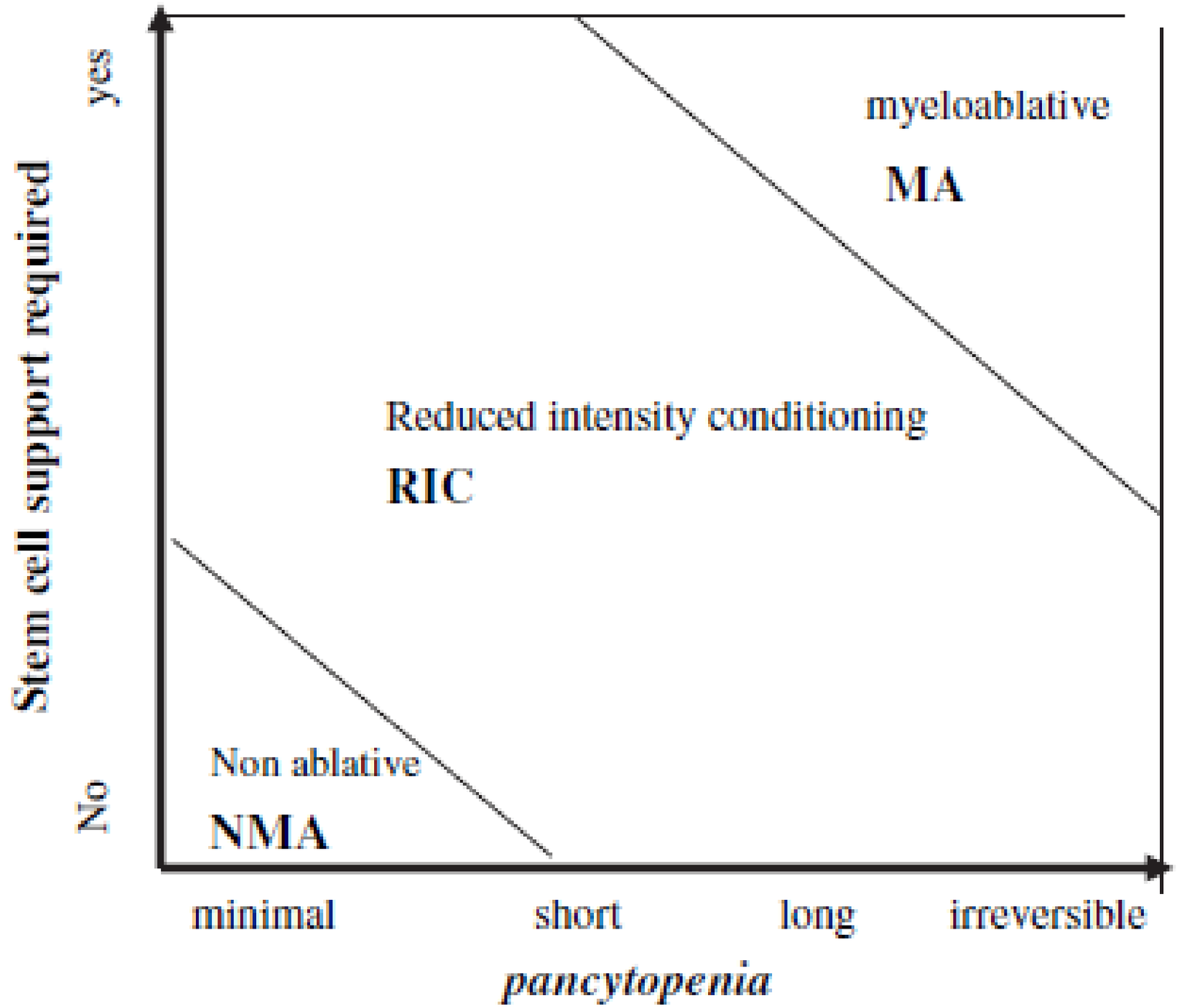
Reduced-Intensity Conditioning Regimens for Hematologic Malignancies: What Have We Learned over the Last 10 Years?

Sergio Giralt

In practice, based on both published experience and expert opinion, the Center for International Blood and Marrow Research (CIBMTR) and the National Marrow Donor Program have used one or more of the following criteria to define an RIC regimen:[10-12]

a) ≤ 500 cGy total-body irradiation;
b) ≤ 9 mg/kg total busulfan dose;
c) ≤ 140 mg/m^2 total melphalan dose;
d) ≤ 10 mg/kg total thiotepa dose;

Reduced Intensity Conditioning



Bacigalupo A. Biol Blood Marrow Transplant.2009;15:1628-33

En la práctica diaria

TBI (10-14.4 Gy) + Cy 120

Bu 16 + Cy 120-200

Bu16 + Mel140

TBI12 + Mel140

BEAM

CONVENCIONAL

Fluda 125 + Cy120

INT. REDUCIDA

Fluda 180 + ATG20 + Bu8

Fluda120 + Mel140 + C1H100

Fluda120 + Ida42 + AraC8

Fluda150 + Mel140

Fluda150 + Bu10

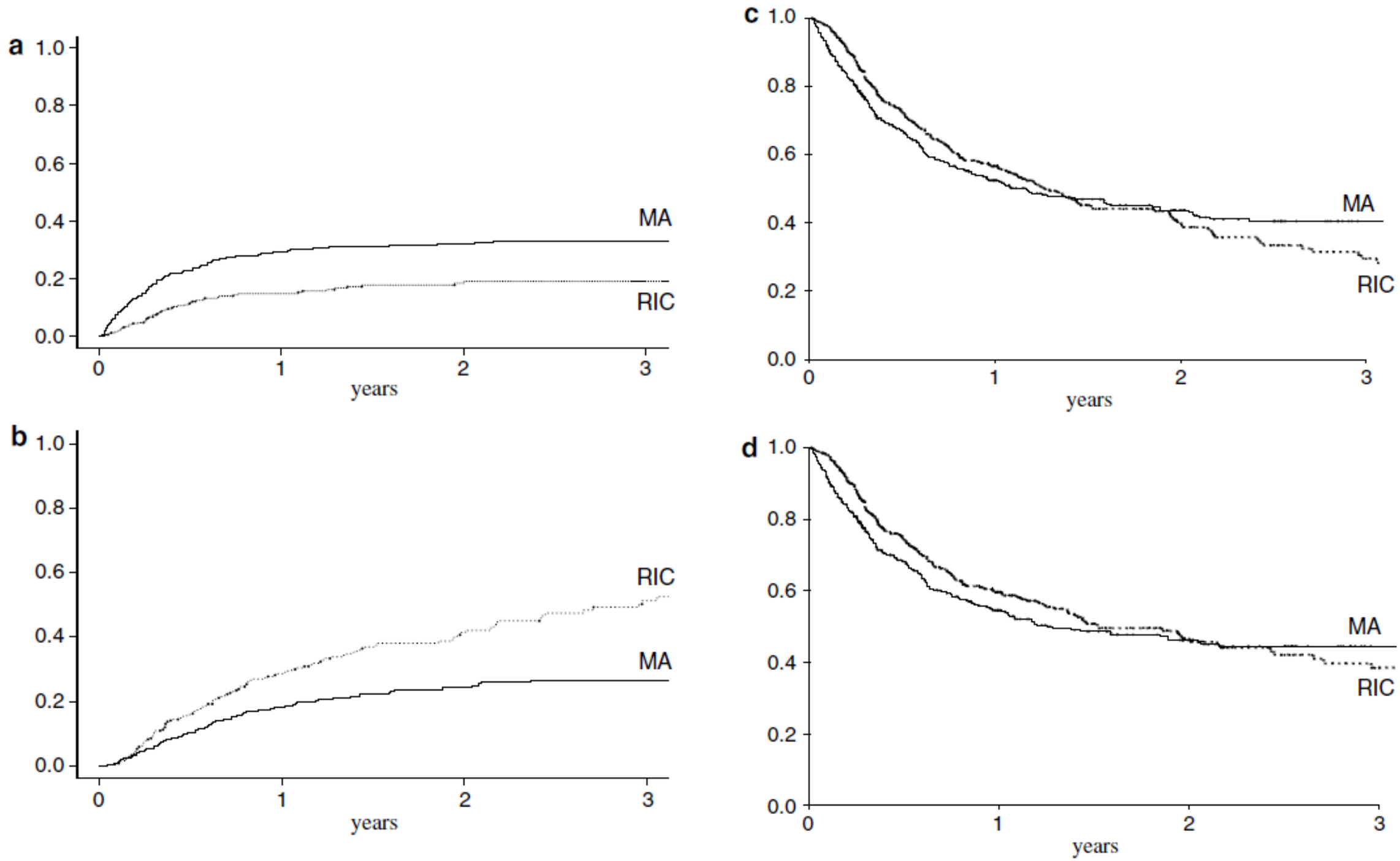
NO MIELOABLATIVO

TBI 200 cGy

El efecto injerto contra tumor es básico para eliminar la enfermedad

Las dosis altas de acondicionamiento no son imprescindibles para conseguir el injerto

MAC *vs.* RIC



Aoudjhane M.Leukemia.2005;19:2304-12

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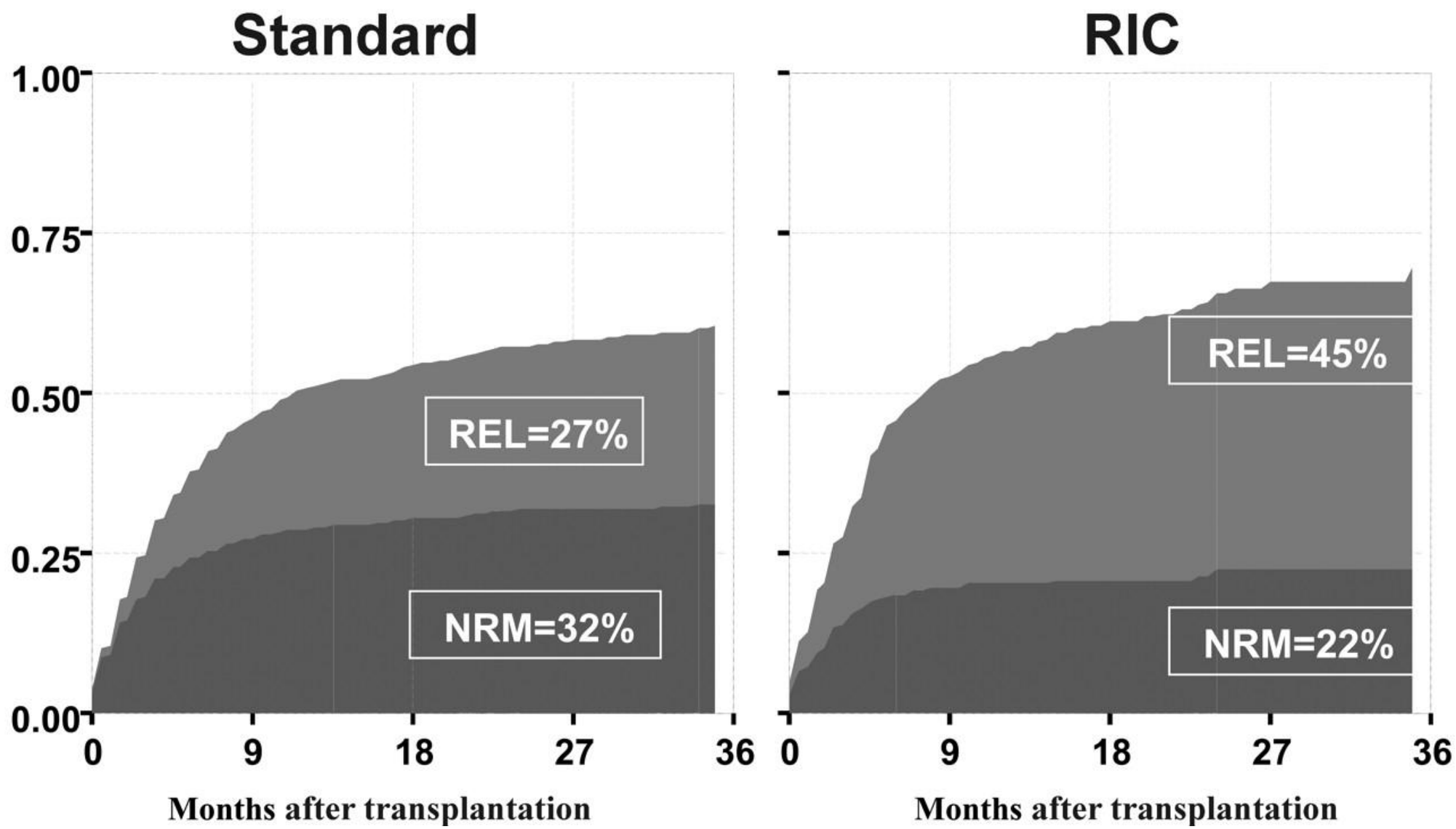
MAC *vs.* RIC



Martino R et al. Blood 2006;108:836-846

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Reduced Intensity Conditioning

Purine Analogues

Fluda
Cladri
Clofa

+

Alquilating (and other) Agents

Bu
Mel
Thio
Ara-C
Cy

+/-

Low Dose TBI

+/-

Anti-T Agents

ATG
Campath

+

Immunosuppressive Drugs

CsA
MTX
MMF
Rapa

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RIC *vs.* STANDARD (RICMAC Study) Prospective Randomized Trial

N. Kroger et al. EBMT. Chronic Malig WP

	Bu (12.8 mg/kg) Cy (120 mg/kg) n= 64	Fluda 150 mg/m n=65
Edad (años)	50	51
Blastos (%)	4	5
Dx (%)		
MDS	79 (53% IPSS low/int-1; 38% Int-2/High)	89 (53% IPSS low/Int-1; 47% Int-2/High)
CMML	5	3
sAML	14	6
Don (%)		
HLA Sib	15	14
HLA id URD	24	24
MM Rel	-	2
MM URD	11	11
Resto de características basales también homogéneas entre los grupos: Fase enfermedad, uso ATG/ Campath, Uso de Quimioterapia pre-trasplante		

Profilaxis EICR: CsA/MTX (ATG/Campath en URD o MM donor)

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RICMAC Study: Global Results

N. Kroger et al. EBMT. Chronic Malig WP

	Bu (12.8 mg/kg) Cy (120 mg/kg) n= 64	Fluda 150 mg/m n=65
Injerto Neut	14 d	15 d
Injerto Plaq	14 d	15 d
EICR Ag (%) I-IV II-IV III-IV	 44 32 14	 47 29 11
EICR Cr (%) Limitada Extensa	 22 20	 32 26
TRM 1 y 2 a	24 y 30%	13 y 18 %
Recidiva 2 a	10%	19%
RFS 2 a	60%	63%
OS 2 a	65%	77%
Recidiva Vivo	5%	14%

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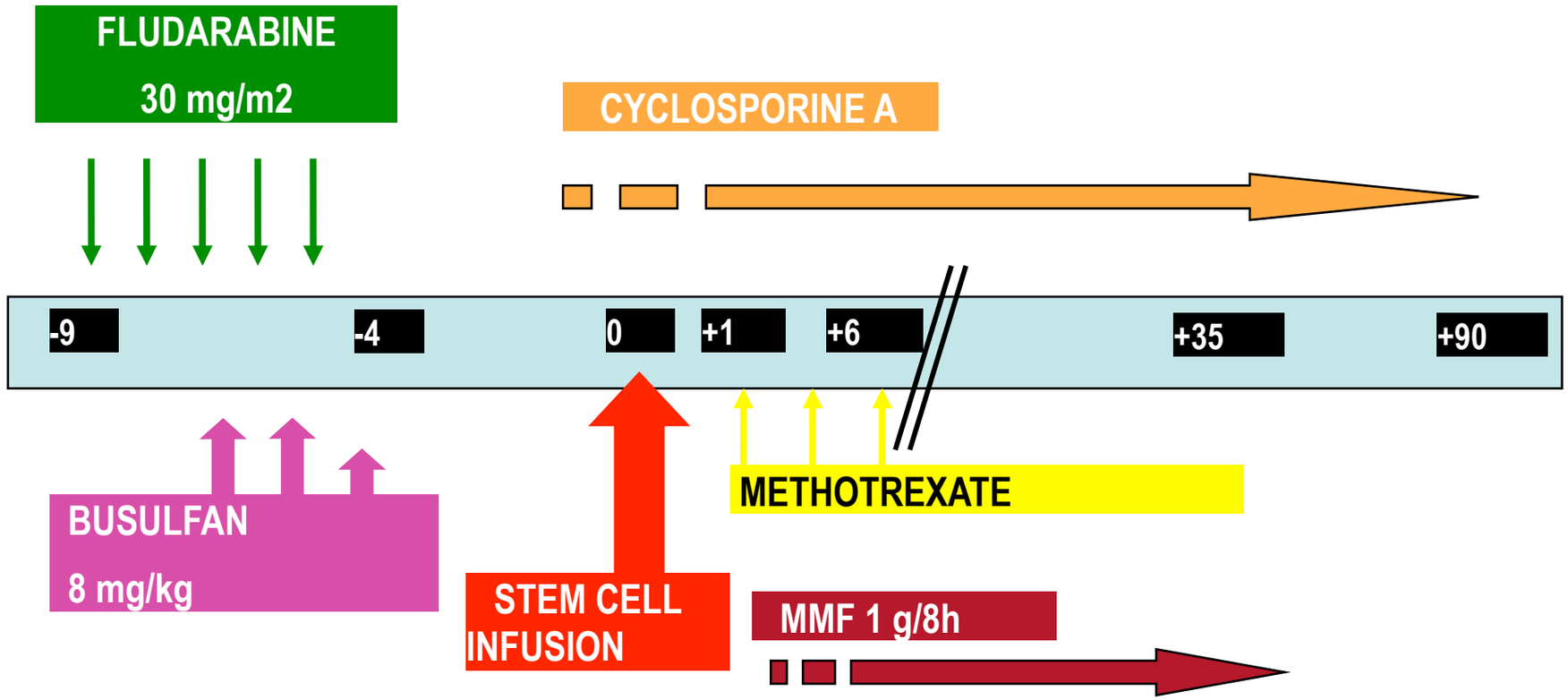
RICMAC Study: Cox Model Results

N. Kroger et al. EBMT. Chronic Malig WP

	OS HR (P)	RFS (HR)	Relapse (HR)	NRM (HR)
RIC	0.5 (0.06)	0.7 (0.4)	1.39 (0.5)	0.54 (0.1)
Blasts 5%	0.6 (0.3)	1.08 (0.8)	1.95 (0.2)	0.67 (0.38)
MUD	2.6 (0.04)	1.6 (0.2)	0.9 (0.9)	2.7 (0.07
Age	1.05 (0.13)	1.036 (0.06)	1.001 (0.1)	1.01 (0.02)

"Spanish" RIC

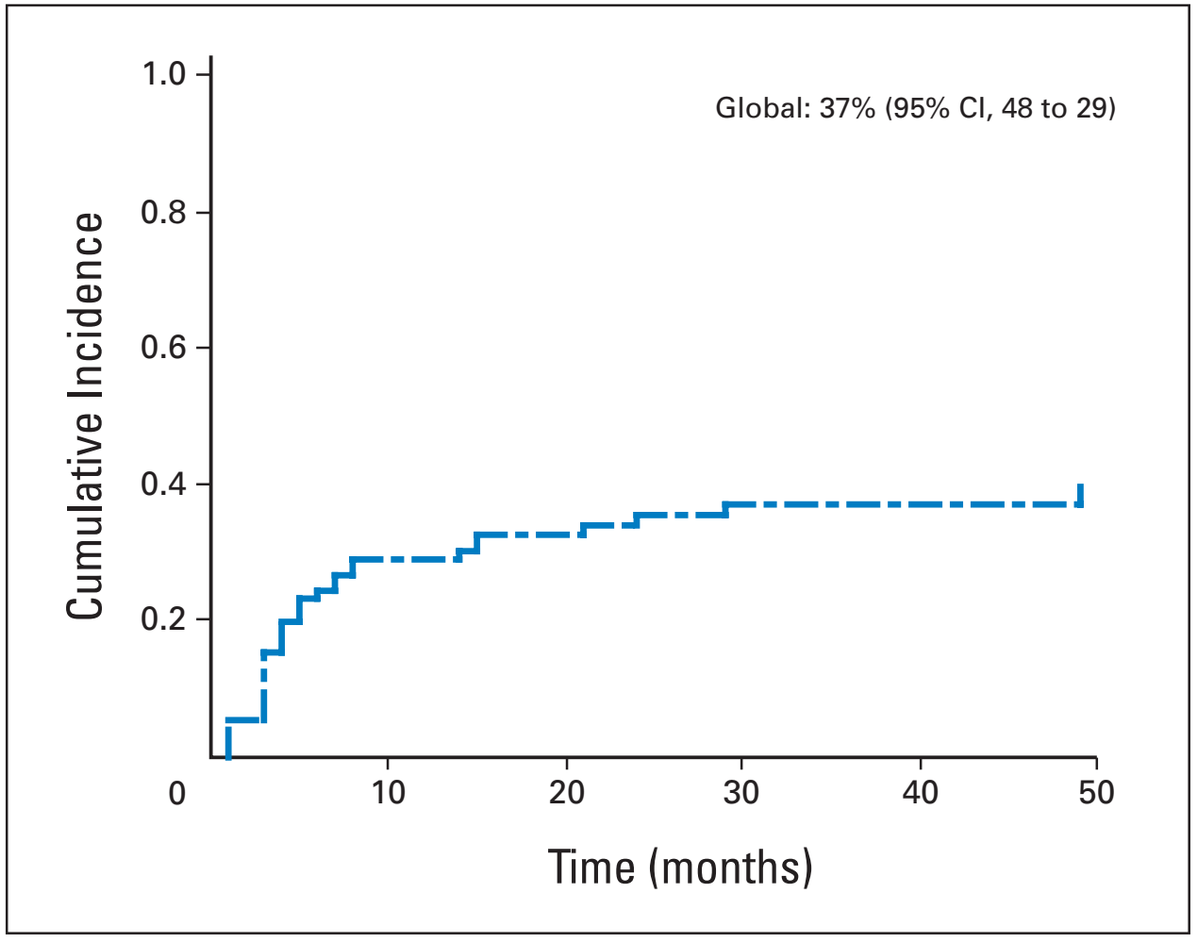


Very good feasibility
"Acceptable" Non-Relapse mortality

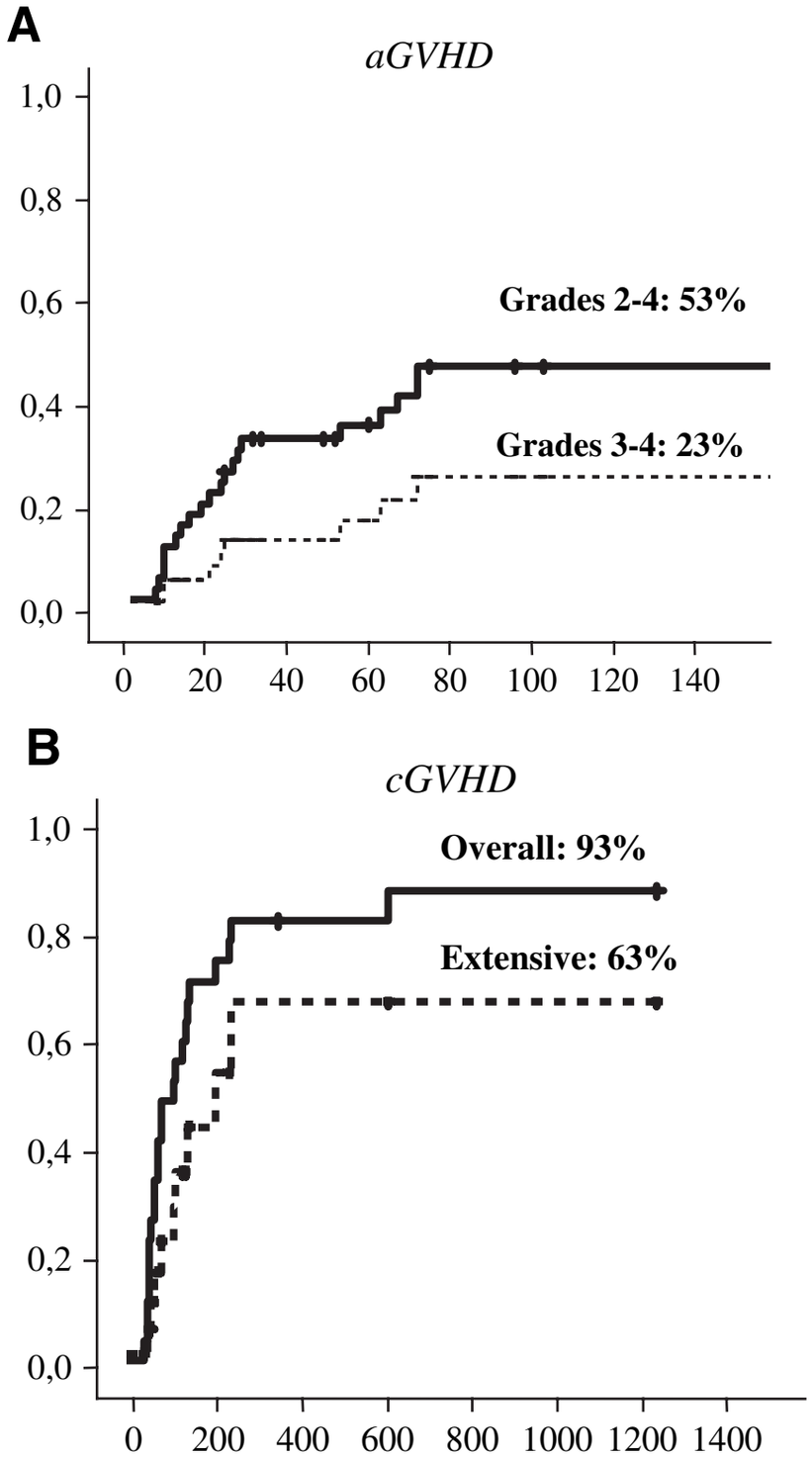
but.....

High Incidence of Relapse
GVHD remains a problem

Main RIC Problems



Valcárcel D, et al. JCO, 2008



Perez-Simón JA, et al. BBMT, 2008

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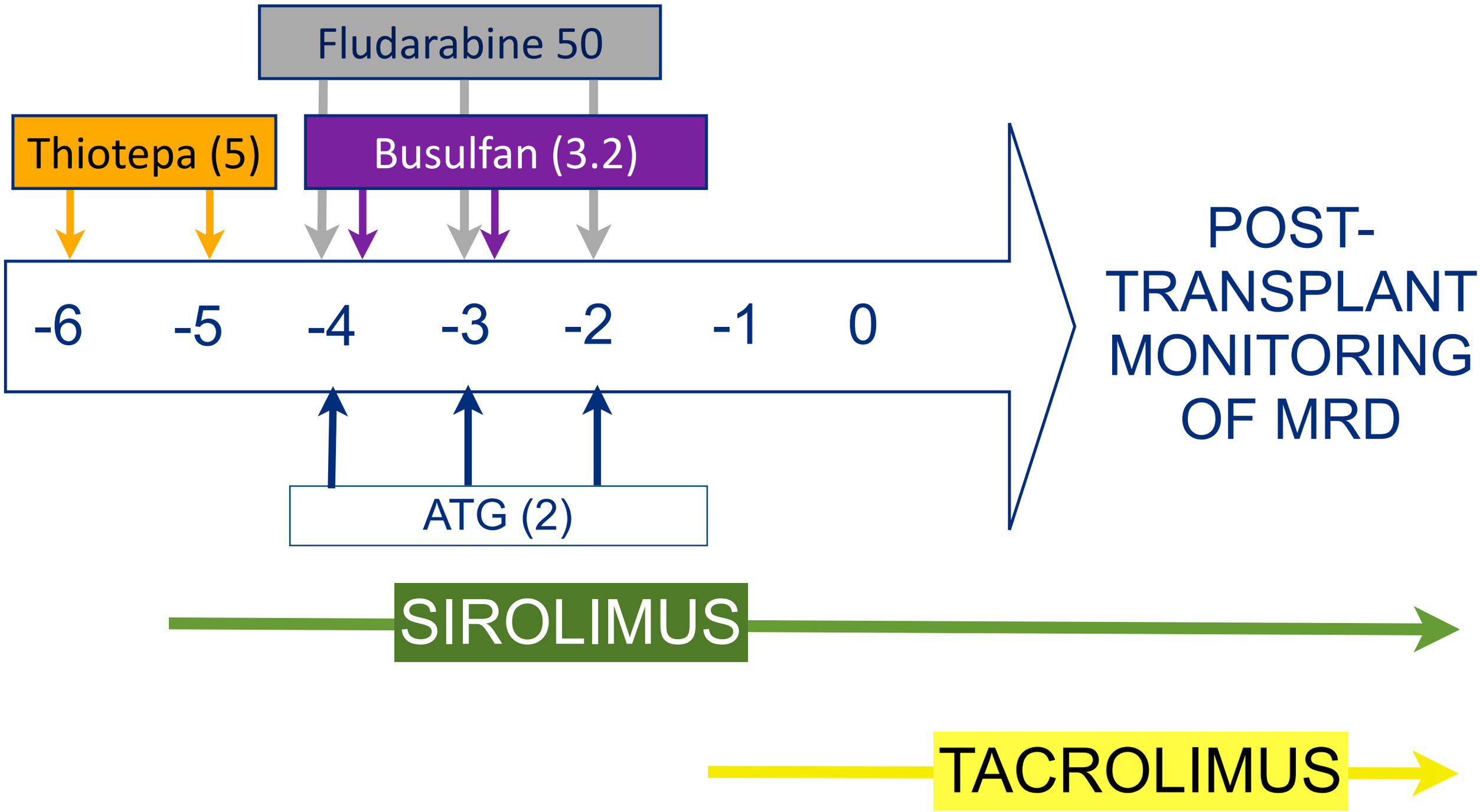
"New" RIC Platform



BASES de CICLOFOSFAMIDA dosis altas en profilaxis de EICH

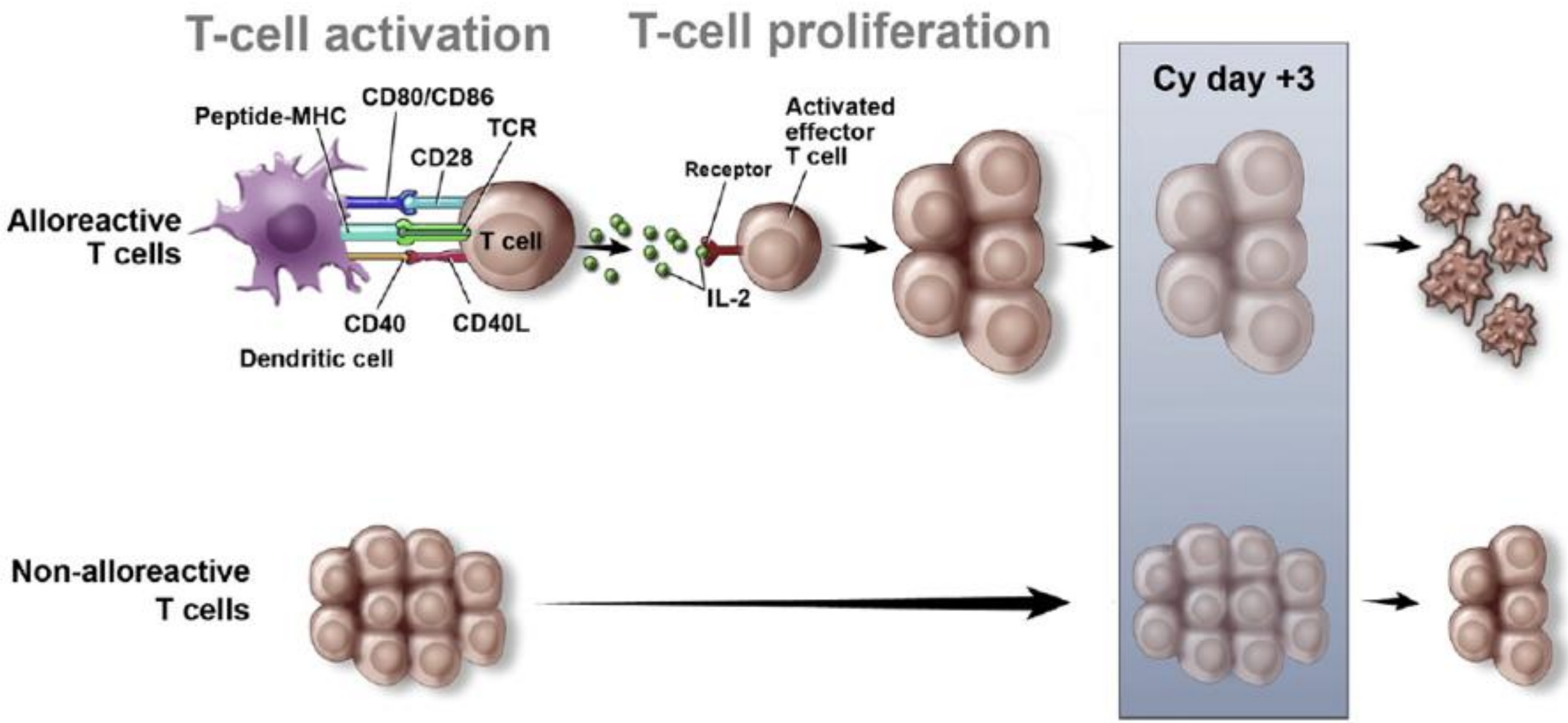


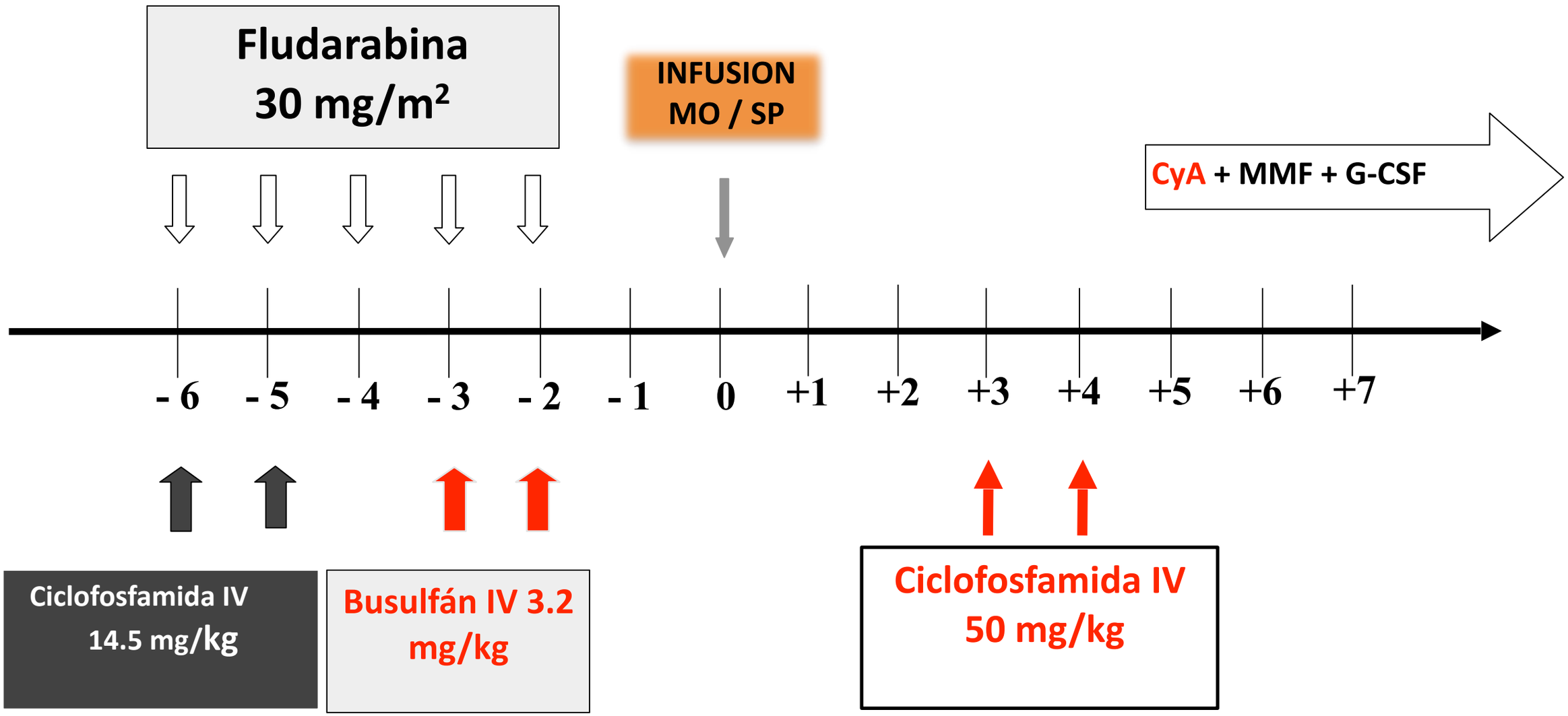
Figure 1. Activated T cells are relatively more sensitive to the effects of cyclophosphamide compared to resting T cells. Following nonmyeloablative conditioning, both donor and host T cells are exposed to alloantigens, resulting in activation and proliferation of T cells capable of host-versus-graft and graft-versus-host reactions. Expansion of the alloreactive clones occurs in the first 3 days after transplant, at which point cyclophosphamide is given to deplete activated T cells. Hematopoietic stem cells and resting T cells are relatively resistant to cyclophosphamide, which preserves T cells that recognize viral antigens and enhances immune reconstitution.

Courtesy of Dr. Jorge Gayoso

Eva Guinan,[1] Leo Luzmik,[2] Rupert Handgretinger,[3] Ann Woolfrey[4]

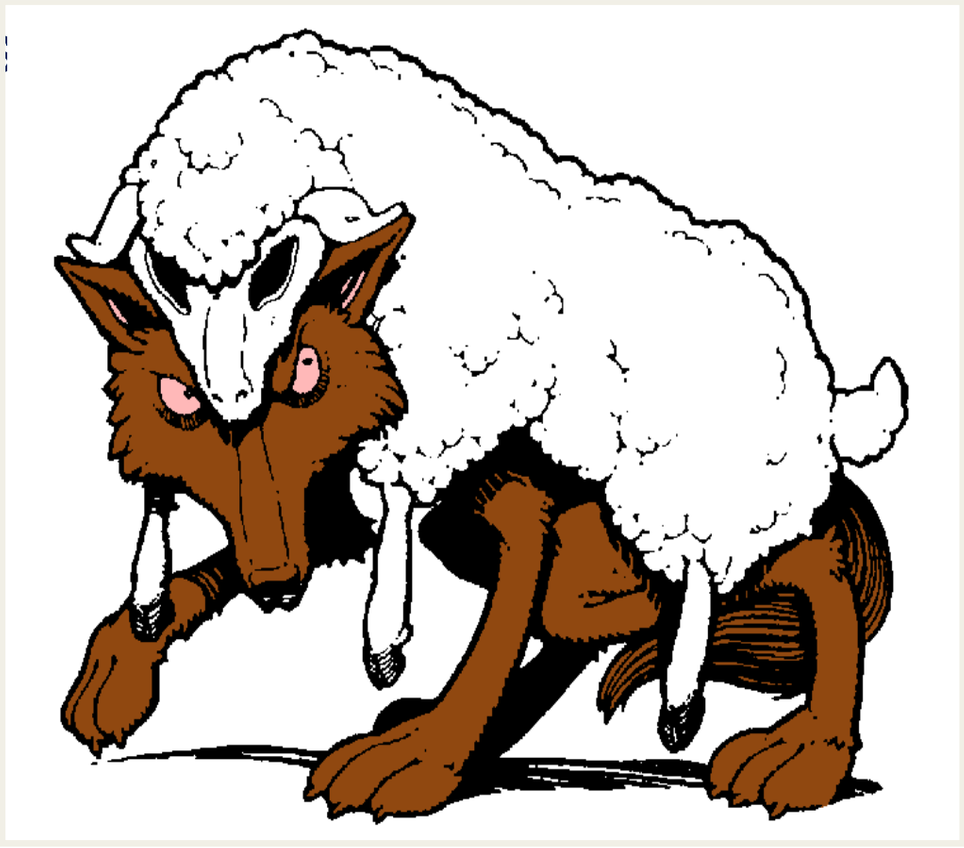
Biol Blood Marrow Transplant 16:S68-S74, 2010

NUEVO ESQUEMA DE ACONDICIONAMIENTO y PROFILAXIS de EICH en HGUGM (2011)



"take home" message

- The Conditioning regimens are the combination of drugs +/- radiotherapy used before SCT with the aim of:
  - erradicating disease
  - allow engraftment

- The type of conditioning depends of:
  - The patient´s age an performance status
  - the disease

- Not always more is best: RIC