Trasplante de progenitores hematopoyéticos en SMD

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Opciones terapéuticas: TPH alogénico

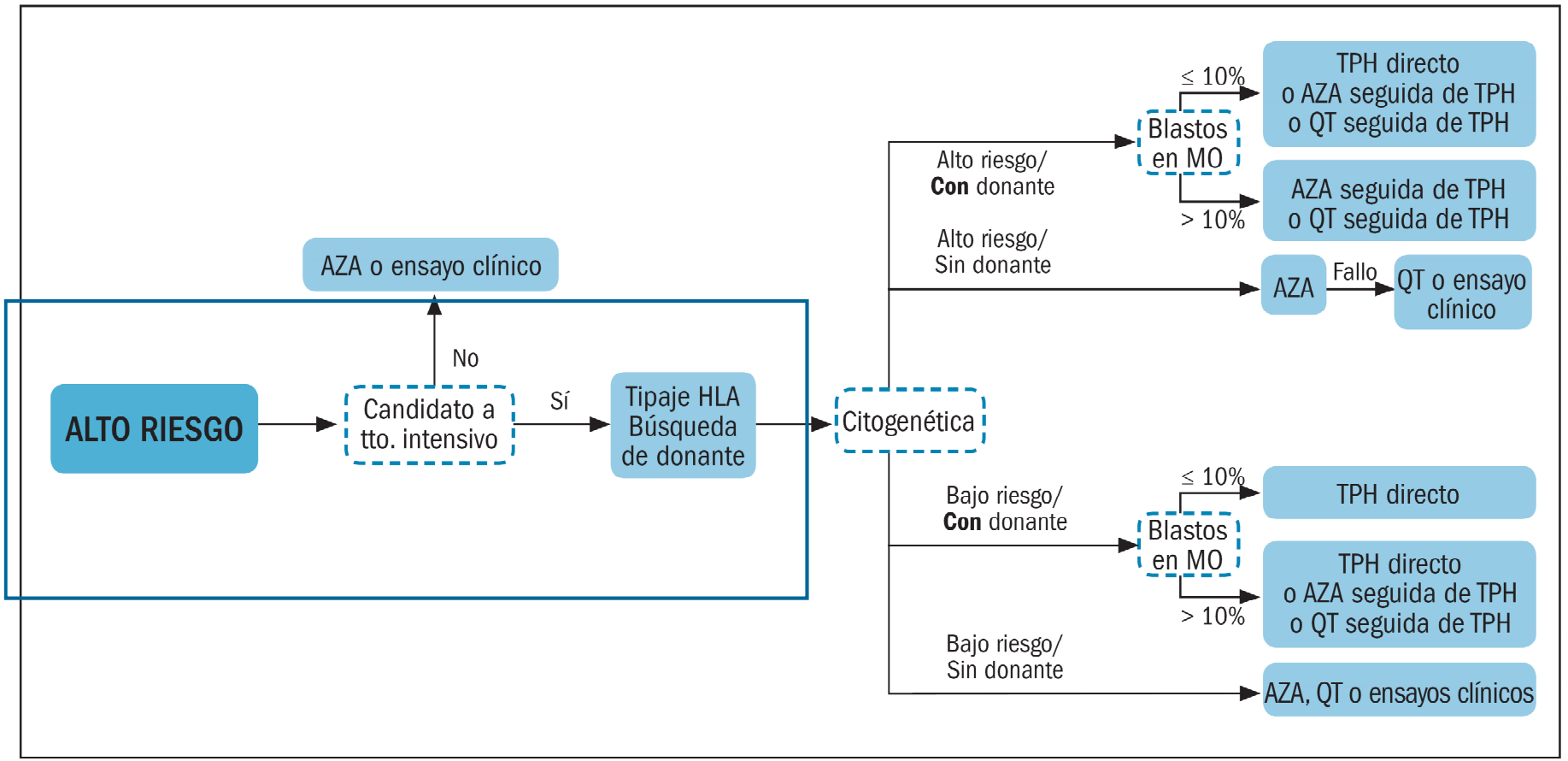
Indicaciones

- El **TPH alogénico** es el **tratamiento de elección** para SMD alto riesgo candidatos al mismo.
- Todos los pacientes de alto riesgo deben ser evaluados para **definir si son candidatos** a un tratamiento intensivo incluyendo TPH alogénico.
  - **No existen criterios objetivos** de edad y comorbilidad para decidir elegibilidad.

Guías de diagnóstico y tratamiento de los SMD y de la LMMC. *Haematologica* 2012; 97 (suppl 5): 1 – 58.

Recomendaciones del GESMD

Algoritmo terapéutico SMD alto riesgo



Guías de diagnóstico y tratamiento de los SMD y de la LMMC. *Haematologica* 2012; 97 (suppl 5): 1 – 58.

TPH alogénico en SMD

Resultados históricos en grandes series

Tipo TPH	RR	MRT	SLE
Hermano HLA-id	23%	37%	40%
DNE	14%	54%	29%

Sierra J et al. *Blood* 2002; 100: 1997-2004.

Castro-Malaspina H et al. *Blood* 2002; 99: 1943-51.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Significant Improvement in Survival After Allogeneic Hematopoietic Cell Transplantation During a Period of Significantly Increased Use, Older Recipient Age, and Use of Unrelated Donors

Theresa Hahn, Philip L. McCarthy Jr, Anna Hassebroek, Christopher Bredeson, James L. Gajewski, Gregory A. Hale, Luis M. Isola, Hillard M. Lazarus, Stephanie J. Lee, Charles F. LeMaistre, Fausto Loberiza, Richard T. Maziarz, J. Douglas Rizzo, Steven Joffe, Susan Parsons, and Navneet S. Majhail

Hahn T et al. *JCO* 2013 (in press)

TPH alogénico en SMD

Mejoría resultados en años recientes

Hermano HLA-id	1994 – 95	2004 – 06	P
OS al día 100	71%	88%	< 0,001
OS al año	54%	64%	0,04

Resultados similares de AIR y MAC aunque no mejoría de AIR a lo largo del tiempo

Hahn T et al. *JCO* 2013 (in press)

TPH alogénico en SMD

Mejoría resultados en años recientes

DNE HLA-id	1994 – 95	2004 – 06	P
OS al día 100	64%	78%	< 0,001
OS al año	41%	57%	0,01

Resultados similares de AIR y MAC

Hahn T et al. *JCO* 2013 (in press)

TPH alogénico en SMD

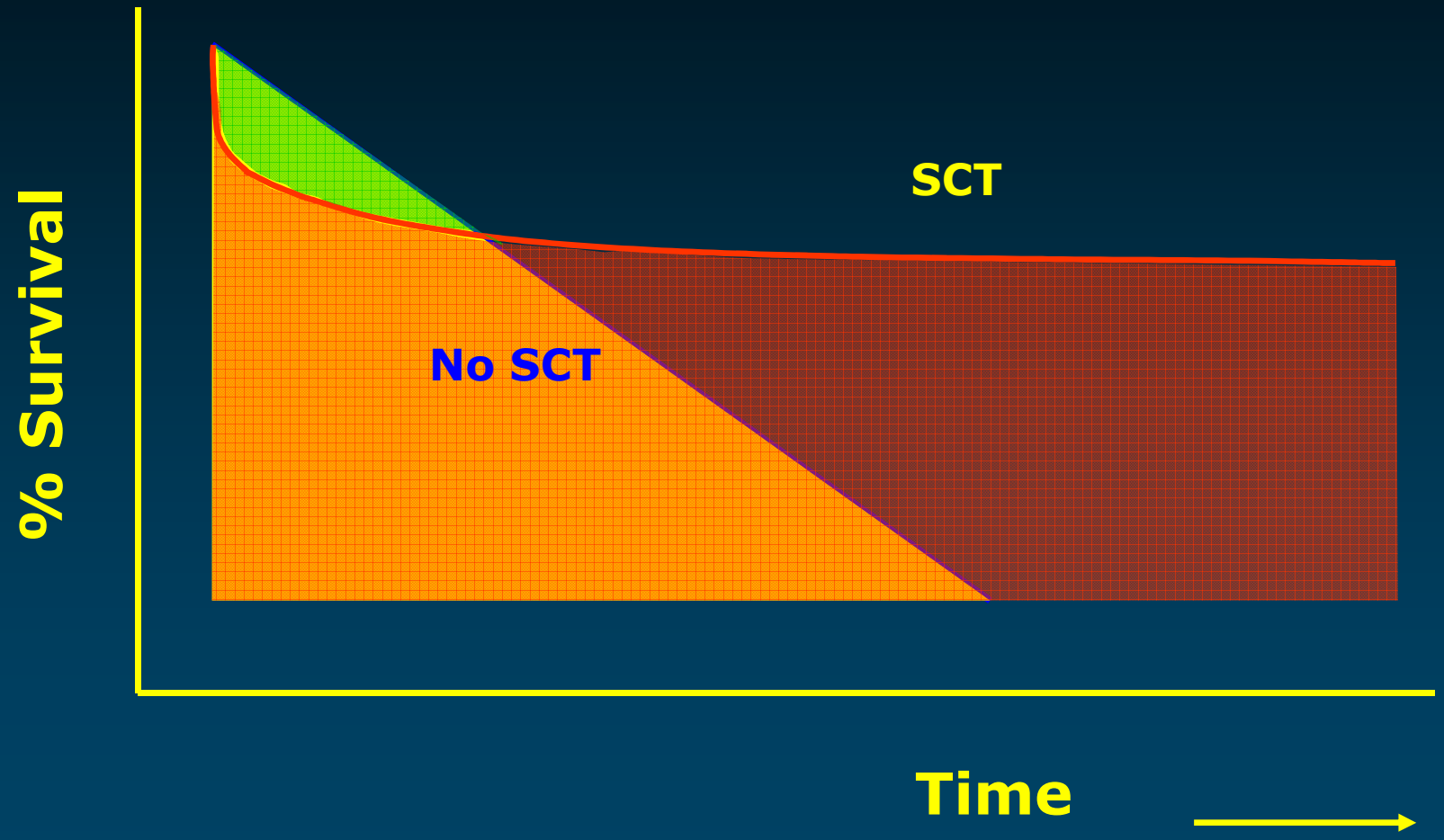
Temas a debate

- Momento del trasplante
  - Al diagnóstico o a la progresión
- Fuente de células
  - Hermano HLA-idéntico ó DNE
  - MO, SP ó SCU
- Acondicionamiento
  - MAC o AIR
  - Drogas y esquema
- Tratamiento pre-trasplante
  - Necesidad y tipo

Momento del trasplante

TMO Alogénico Hermano HLA-idéntico

¿Cuándo trasplantar?



Cutler et al. *Blood* 2004; 104: 579-85

TMO Alogénico Hermano HLA-idéntico

¿Cuándo trasplantar?

Approximation of Life Expectancy (Years)

IPSS	Immediate Transplant	Transplant in 2 Years	Transplant at Progression
Low	6.51	6.86	7.21
Int-1	4.61	4.74	5.16
Int-2	4.93	3.21	2.84
High	3.20	2.75	2.75

Cutler et al. *Blood* 2004; 104: 579-85

TPH alogénico en SMD

Momento del TPH

- No consideración de
  - Edad
  - Influencia del tiempo al TPH en resultados
  - Otros factores pronósticos

Cutler et al. *Blood* 2004; 104: 579-85

TPH alogénico en SMD

Momento del TPH

- Preferible al diagnóstico en
  - IPSS intermedio-2 y alto riesgo
  - Jóvenes con IPSS intermedio-1

Alessandrino P et al (GITMO). *ASH* 2011

Recomendaciones del GESMD
Grupos de riesgo

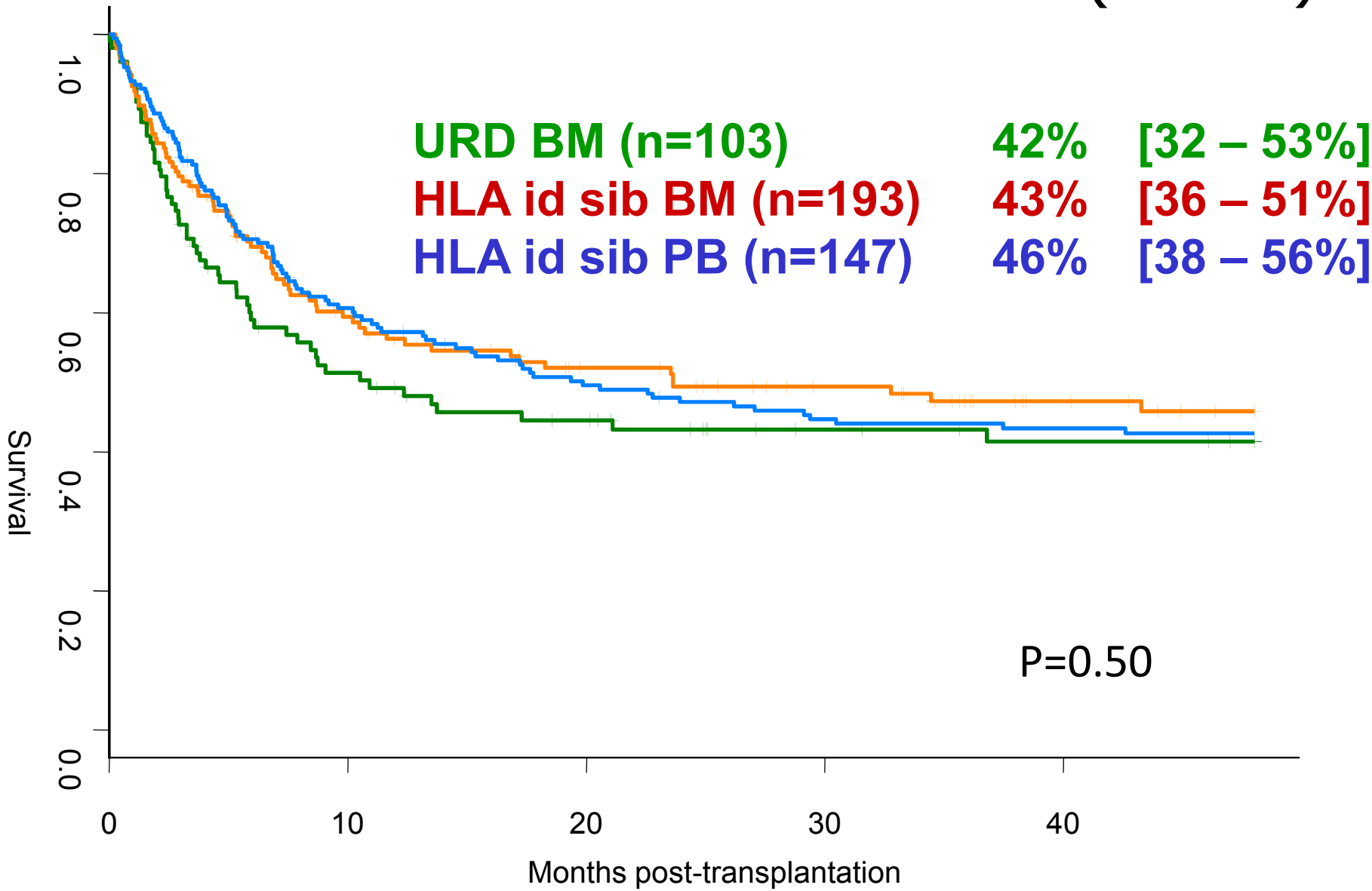
- **Pacientes de alto riesgo**
  - IPSS de riesgo intermedio-2 y alto y/o WPSS y/o IPSS-R de riesgo alto y muy alto
  - **IPSS intermedio-1 y/o WPSS y/o IPSS-R de riesgo intermedio con 1 ó más de las siguientes características:**
    - **Anomalía citogenética de riesgo alto o muy alto del IPSS-R**
    - **Plaquetas < 30 × 10^9/L**
    - **PMN < 0,5 × 10^9/L**
    - **Mielofibrosis (grados 2-3 del consenso europeo)**

Guías de diagnóstico y tratamiento de los SMD y de la LMMC. *Haematologica* 2012; 97 (suppl 5): 1 – 58.

Fuente de células

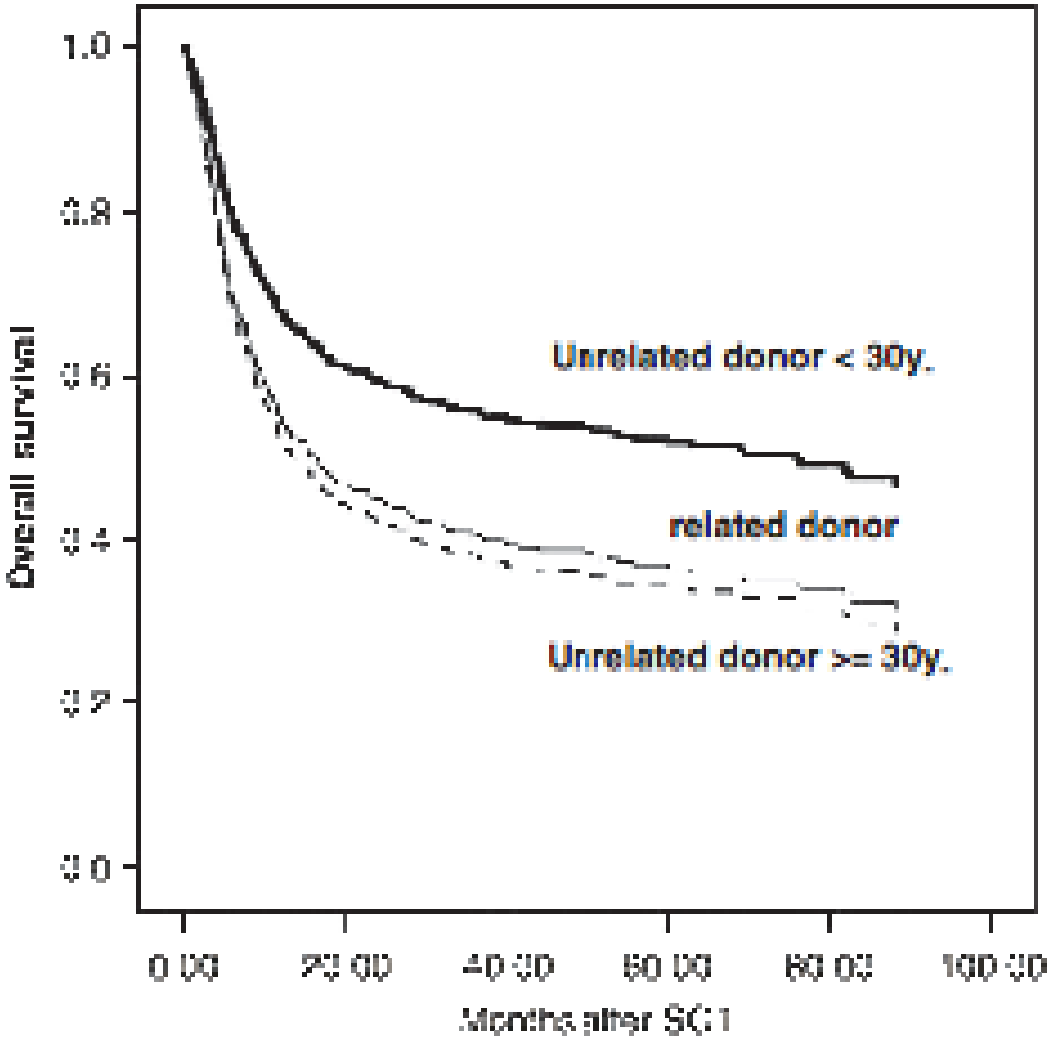
TPH alogénico en SMD

Resultados en series recientes (EBMT)



TPH alogénico en SMD

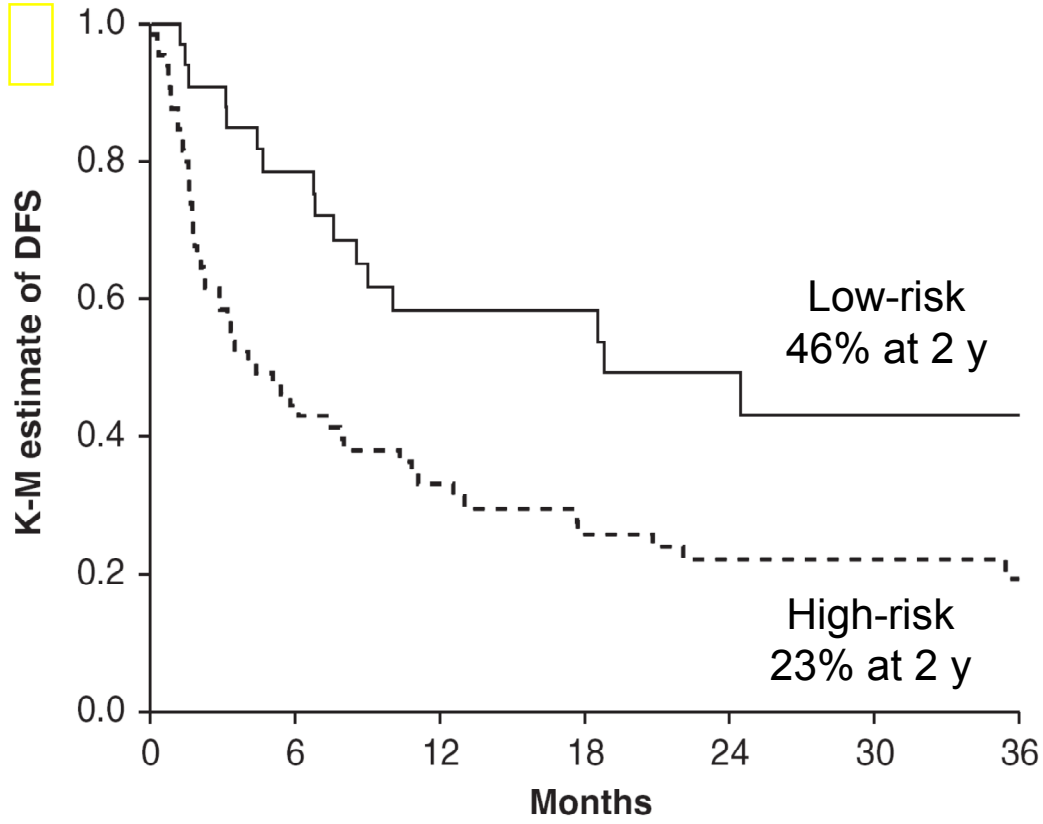
Hermano de edad avanzada o DNE joven



Kroger N et al. *Leukemia* 2013

UCB transplantation for MDS
Eurocord/EBMT (N = 108)

DFS by risk disease at transplant

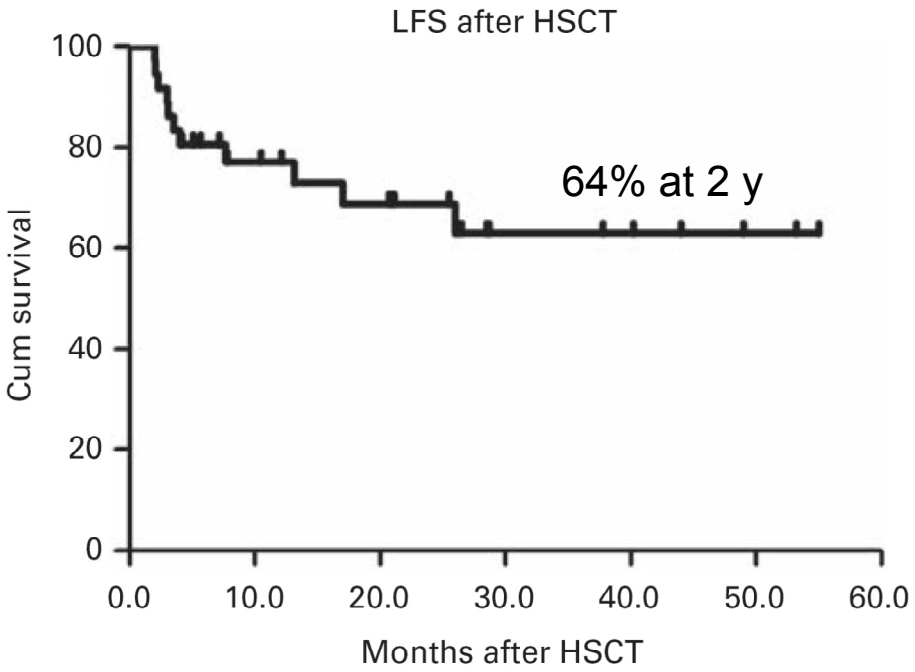


- High-risk disease at transplant
  - AML not in remission
  - IPSS int-2 or high-risk
  - >5% blasts in BM
- Low-risk disease at transplant
  - All others

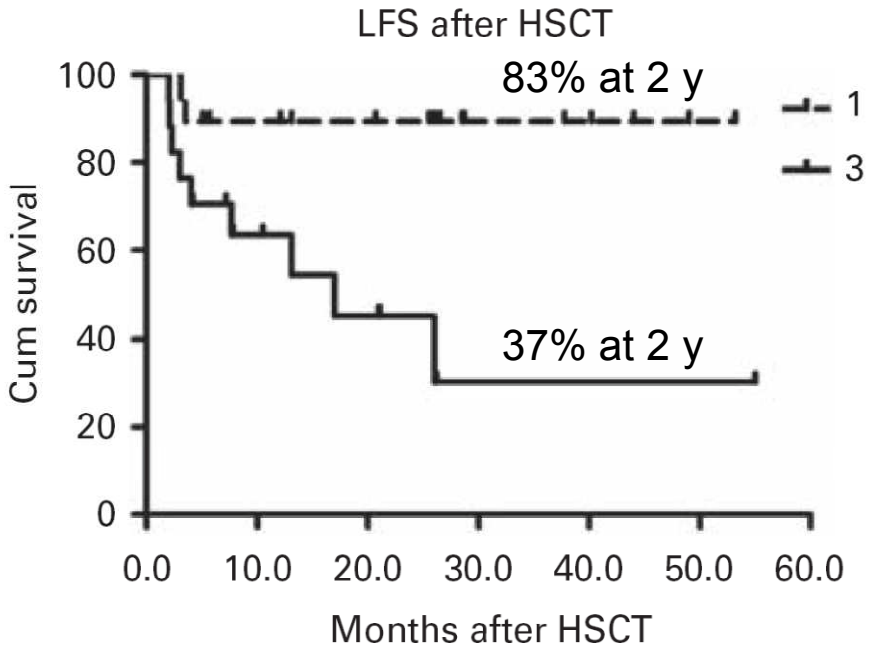
Robin M et al. Leukemia 2011; 25:75-81.

Haploidentical transplantation for MDS

Disease-free survival



Overall series



By no. of HLA mismatches

Chen Y et al. Bone Marrow Transplant 2010; 45:1333-1339.

TPH alogénico en SMD

Fuente de células

- ¿Mejor DNE HLA-idéntico joven que hermano de edad avanzada?
- SPM probablemente preferible a MO en enfermedad avanzada (pero mayor EICH)
- Experiencia con SCU y donante haploidéntico limitada

Opciones terapéuticas: TPH alogénico

Momento y tipo de trasplante

- El trasplante se deberá realizar **tan pronto se localice un donante apropiado**.
  - Realizar **tipaje HLA al diagnóstico**.
  - **Búsqueda inmediata y simultánea de DNE y unidades de SCU** si no hay donante familiar HLA-idéntico.
    - Limitar a pacientes de menos de 65 años.
    - Entre 55 y 65 años es preferible un DNE adulto.
  - Realizar en centro con experiencia

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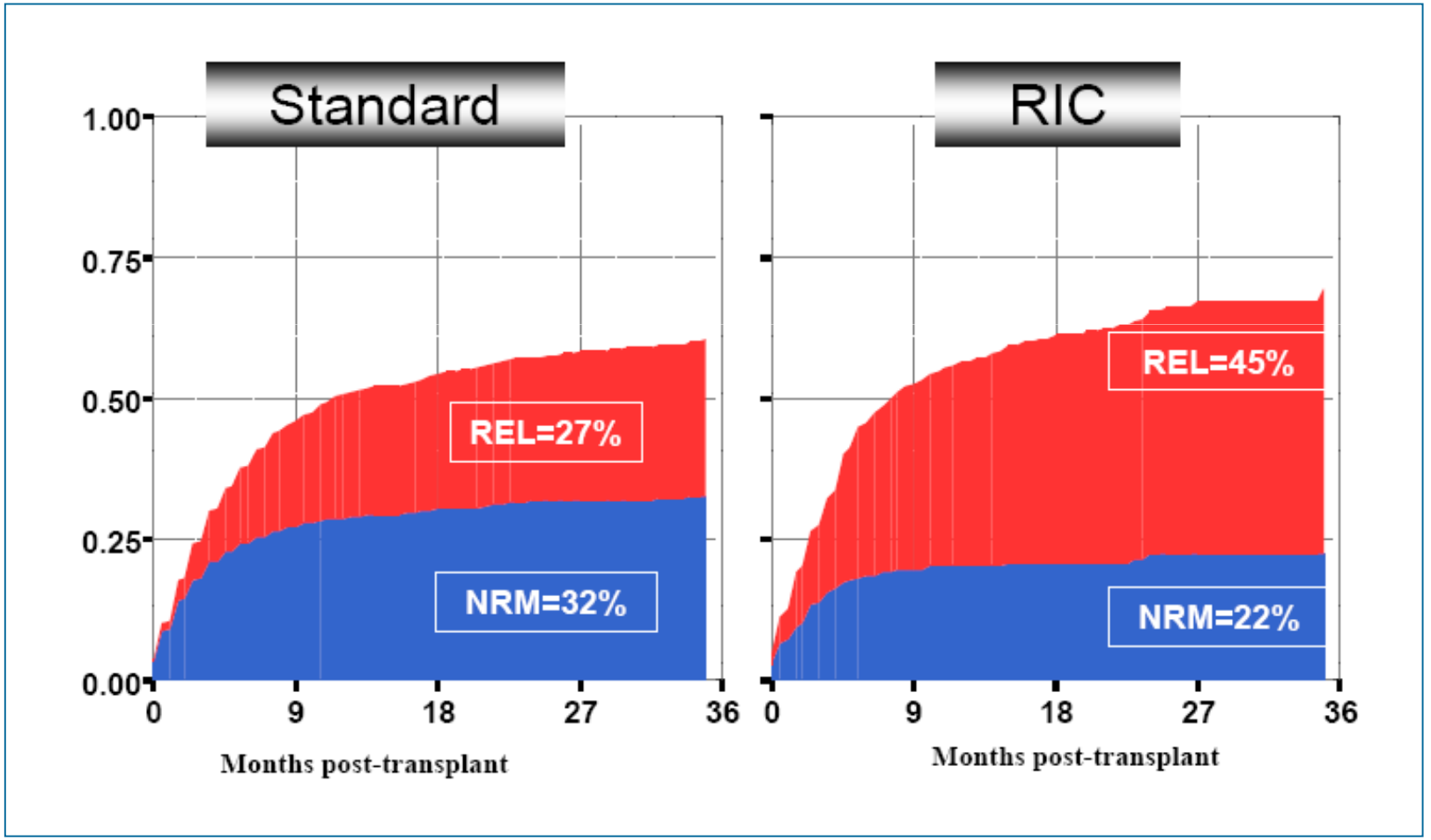
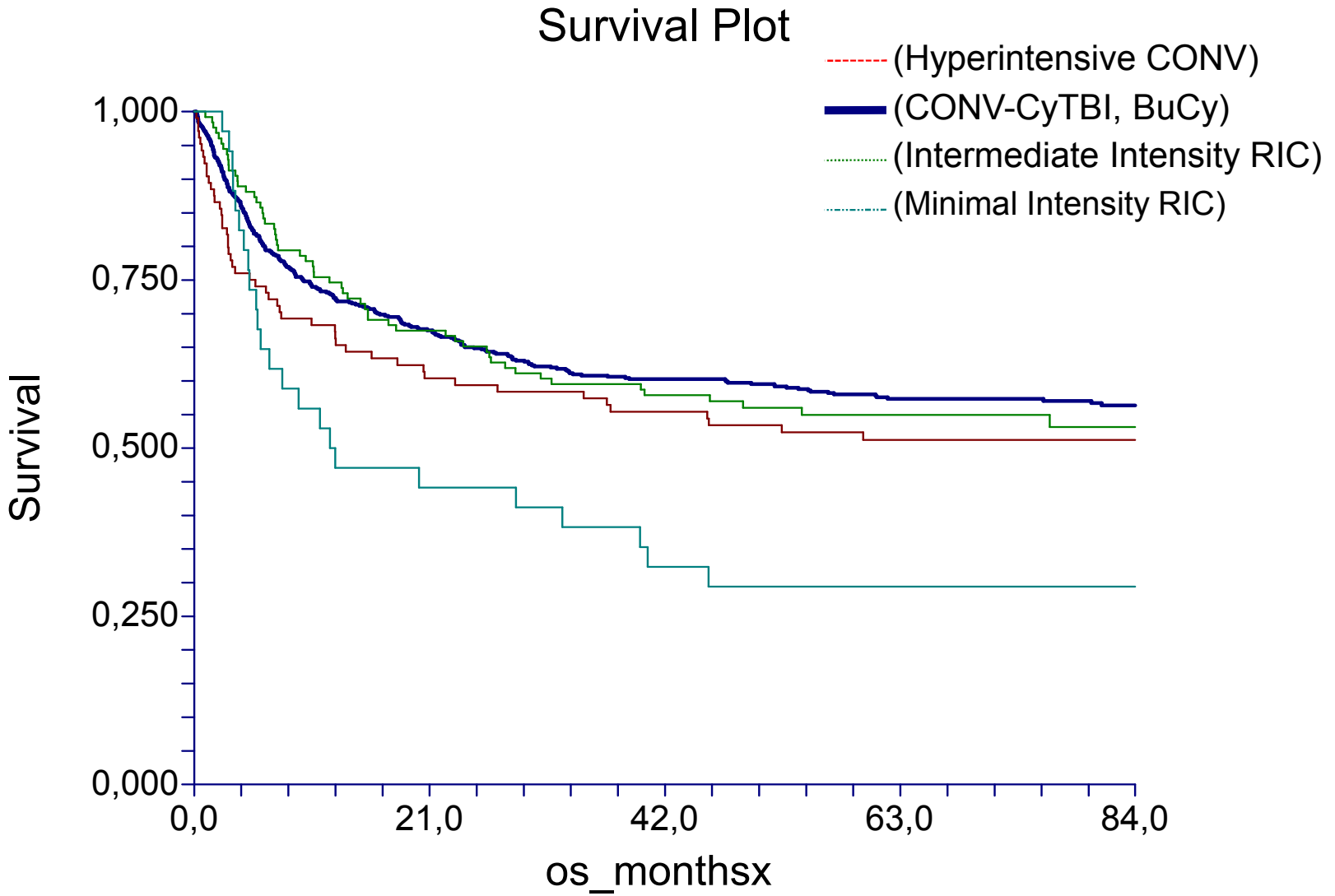
Acondicionamiento

Impacto del régimen de acondicionamiento (MAC versus AIR)



Martino R et al. *Blood* 2006

Survival at 7 year for RIC vs standard conditioning



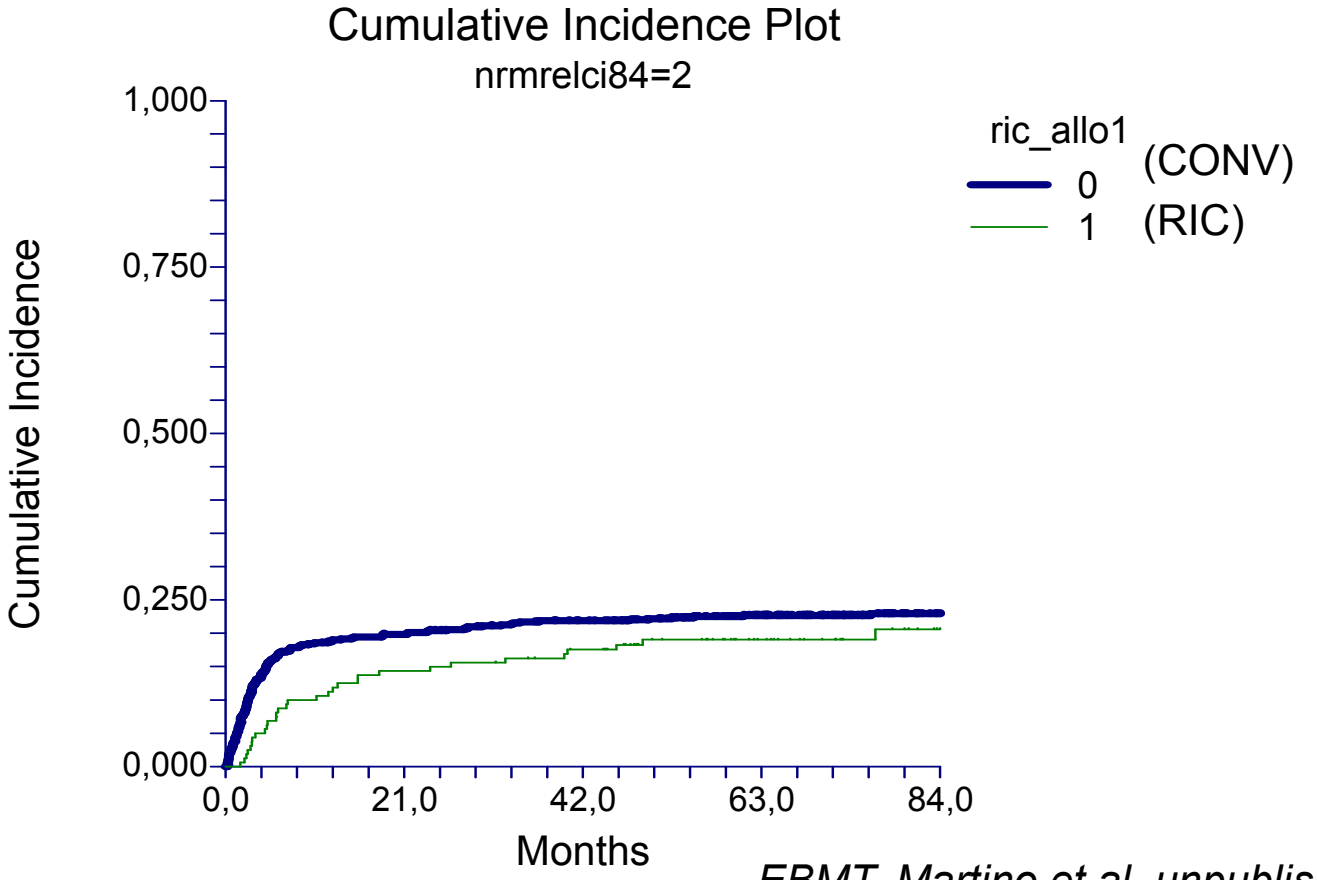
Martino et al.,unpublished update

NRM at 7 y for RIC vs standard conditioning

HLA-id sibling, MDS or AML with < 10% blasts

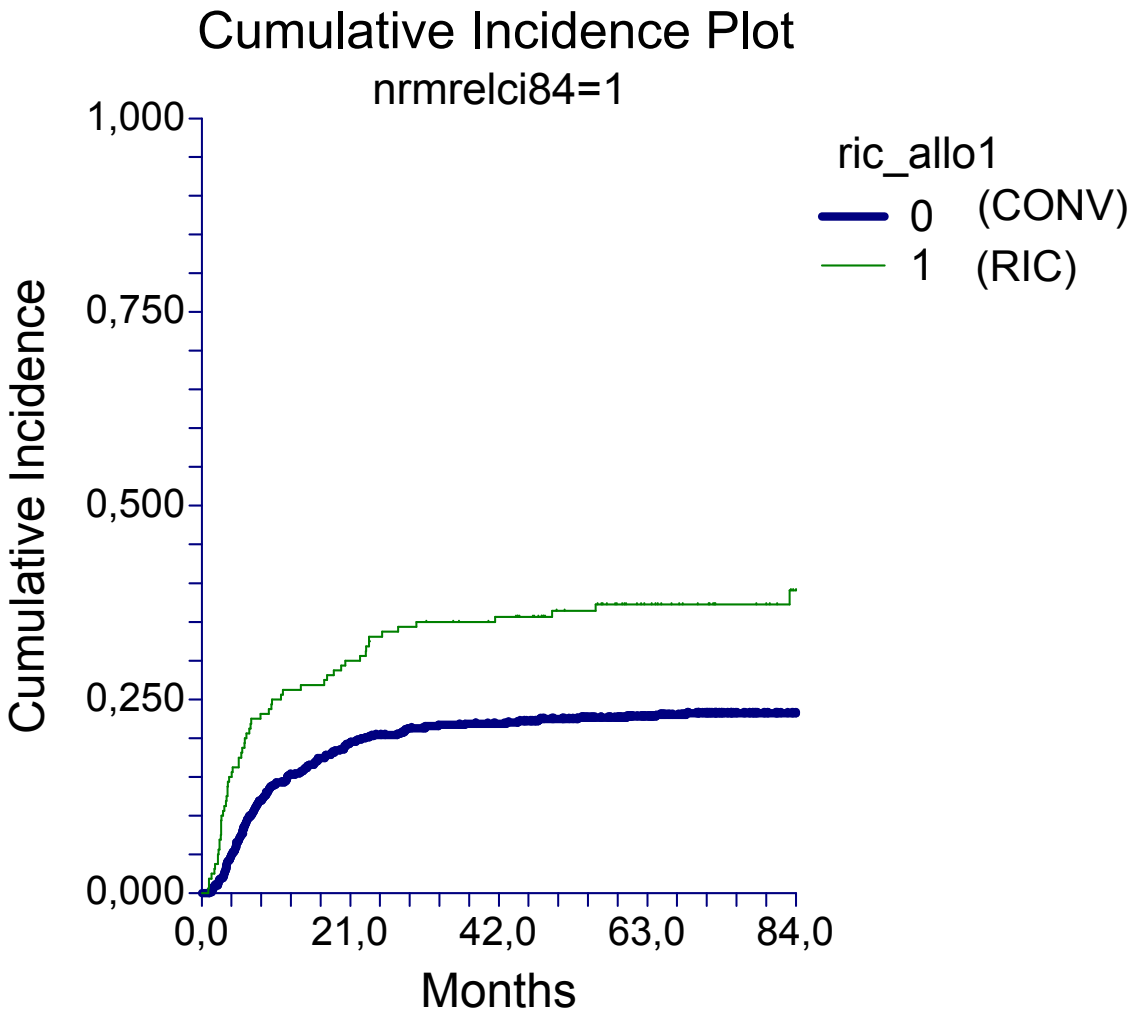
Myeloablative conditioning: n = 718

Reduced intensity n = 160



EBMT, Martino et al.,unpublished update

Relapse incidence at 7 year for RIC vs standard conditioning



EBMT, Martino et al.,unpublished update

RICMAC Study: Cox Model Results

	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)

N. Kroger et al. EBMT 20013. Chronic Malignant WP

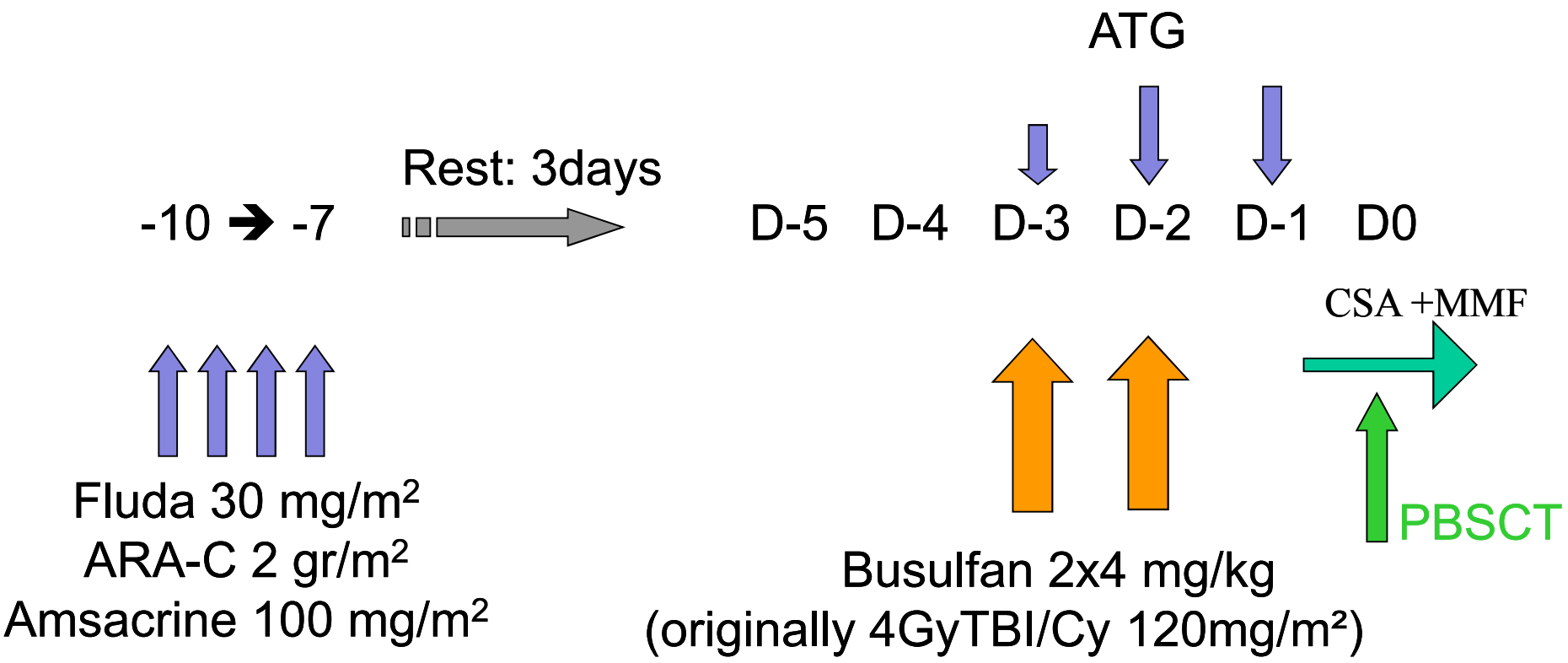
Opciones terapéuticas: TPH alogénico

Régimen de acondicionamiento

- **Mieloablativo estándar**
  - Edad < 55 años y no comorbilidades, especialmente si proporción medular de blastos elevada o citogenética adversa.
- **De intensidad reducida**
  - Edad > a 55 años o comorbilidades.

Guías de diagnóstico y tratamiento de los SMD y de la LMMC. *Haematologica* 2012; 97 (suppl 5): 1 – 58.

Induction followed by immediate conditioning (FLAMSA protocol)



Resultados muy preliminares

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

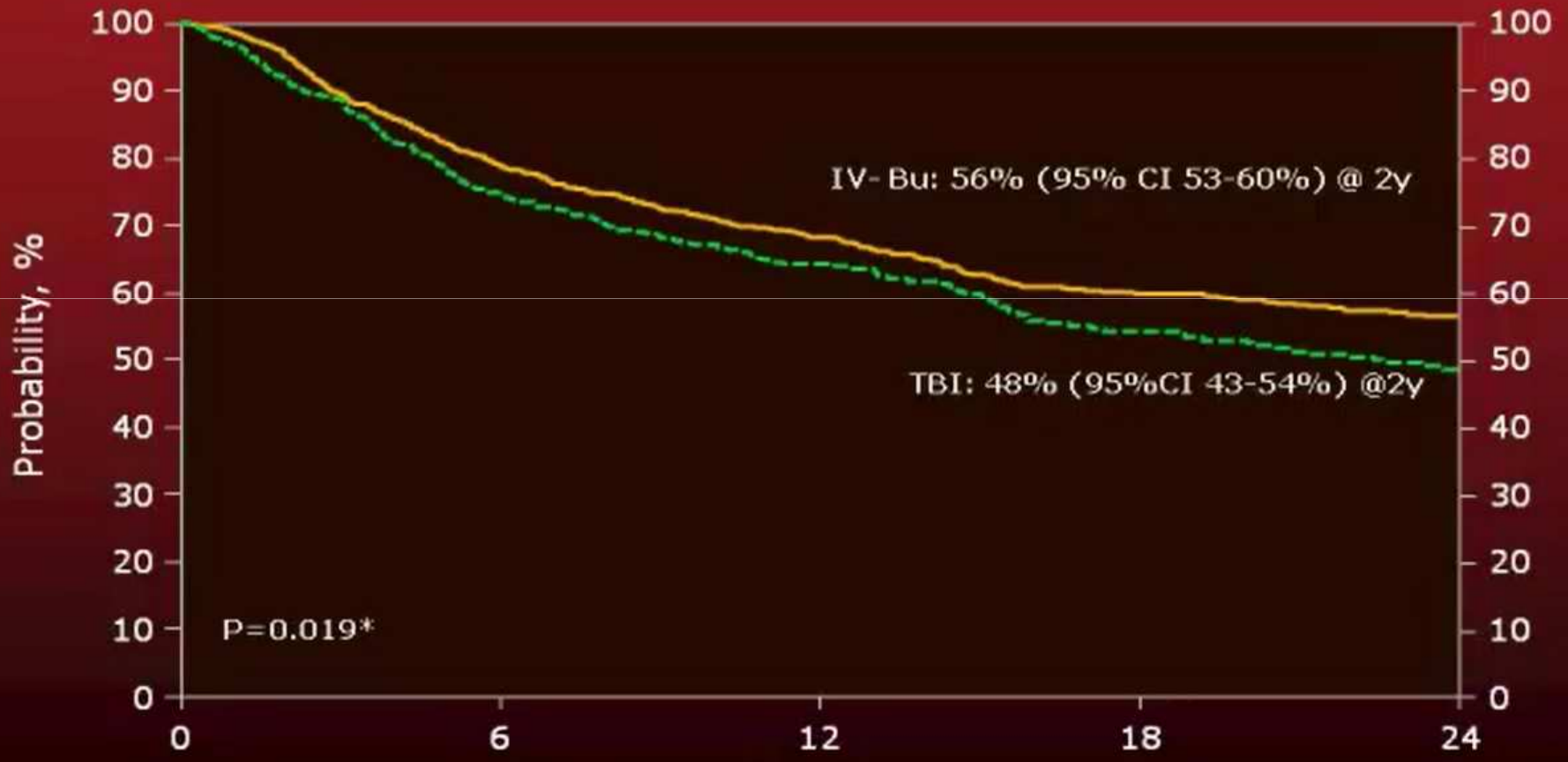
CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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

Overall Survival of Recipients of IV-BU Compared to TBI-based Myeloablative Conditioning



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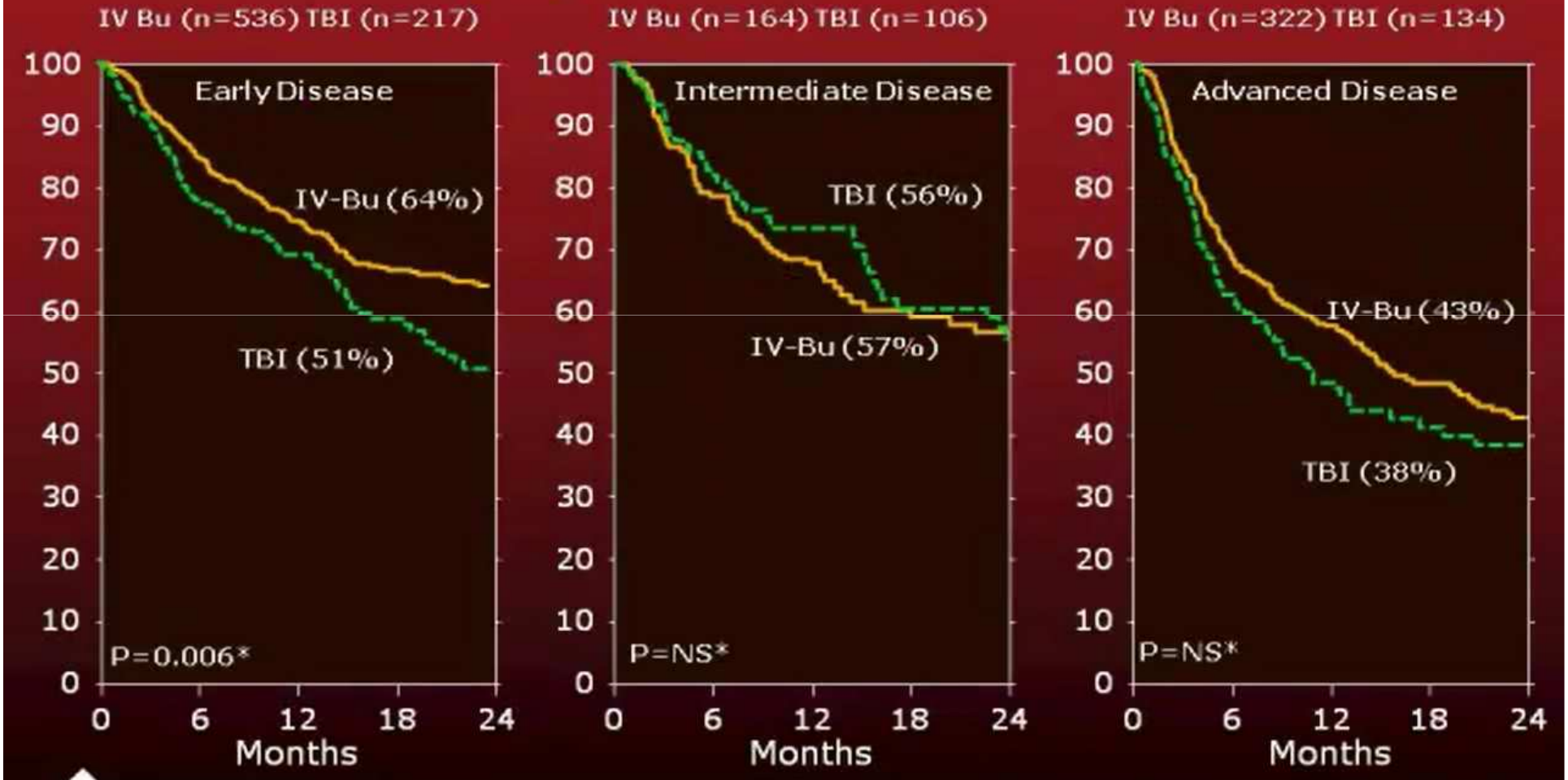
*pointwise p-value at 2 years

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



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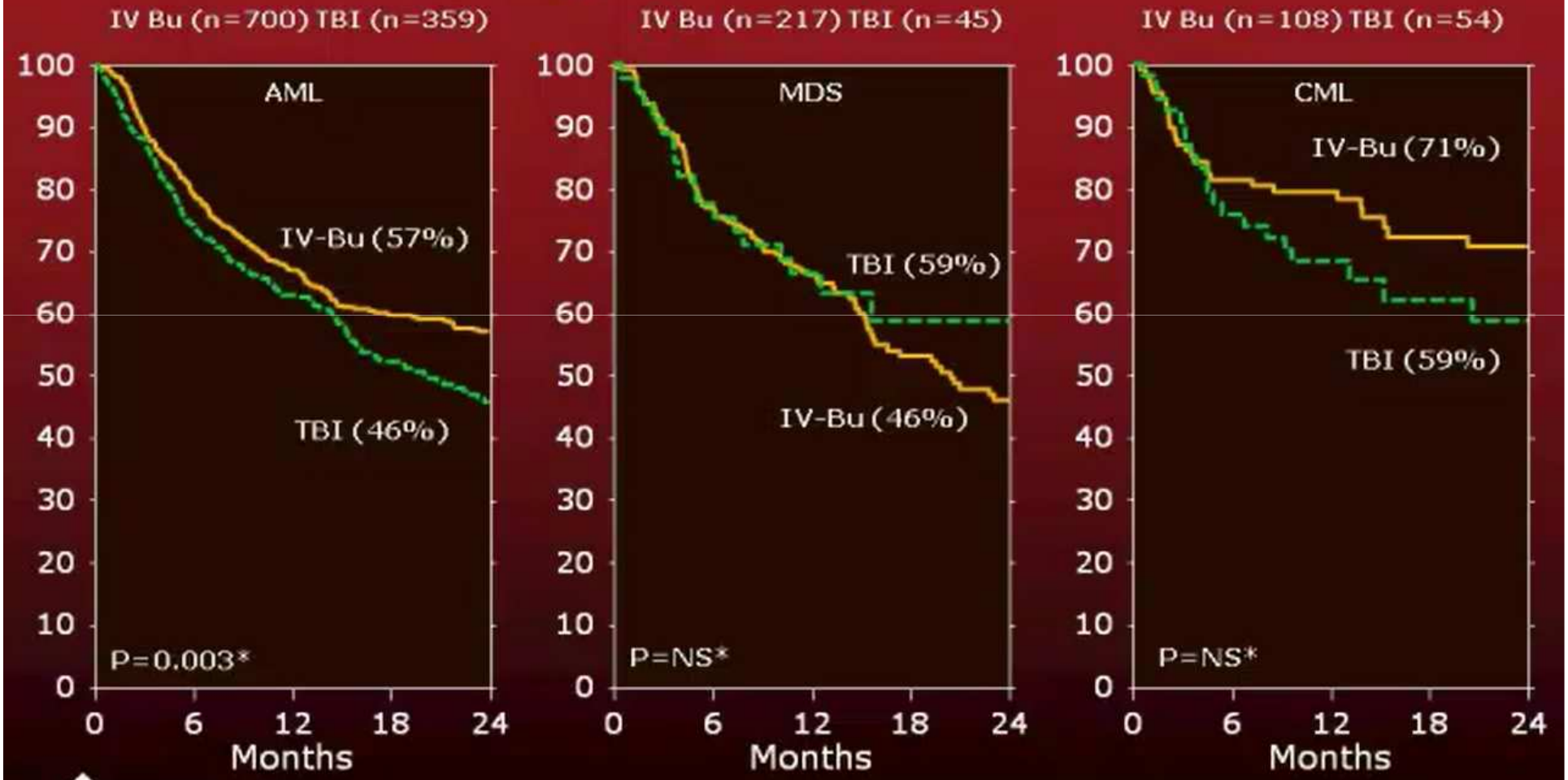
*pointwise p-value at 2 years

Overall Survival of Recipients of IV-BU Compared to TBI-based Myeloablative Conditioning by Transplant Indication



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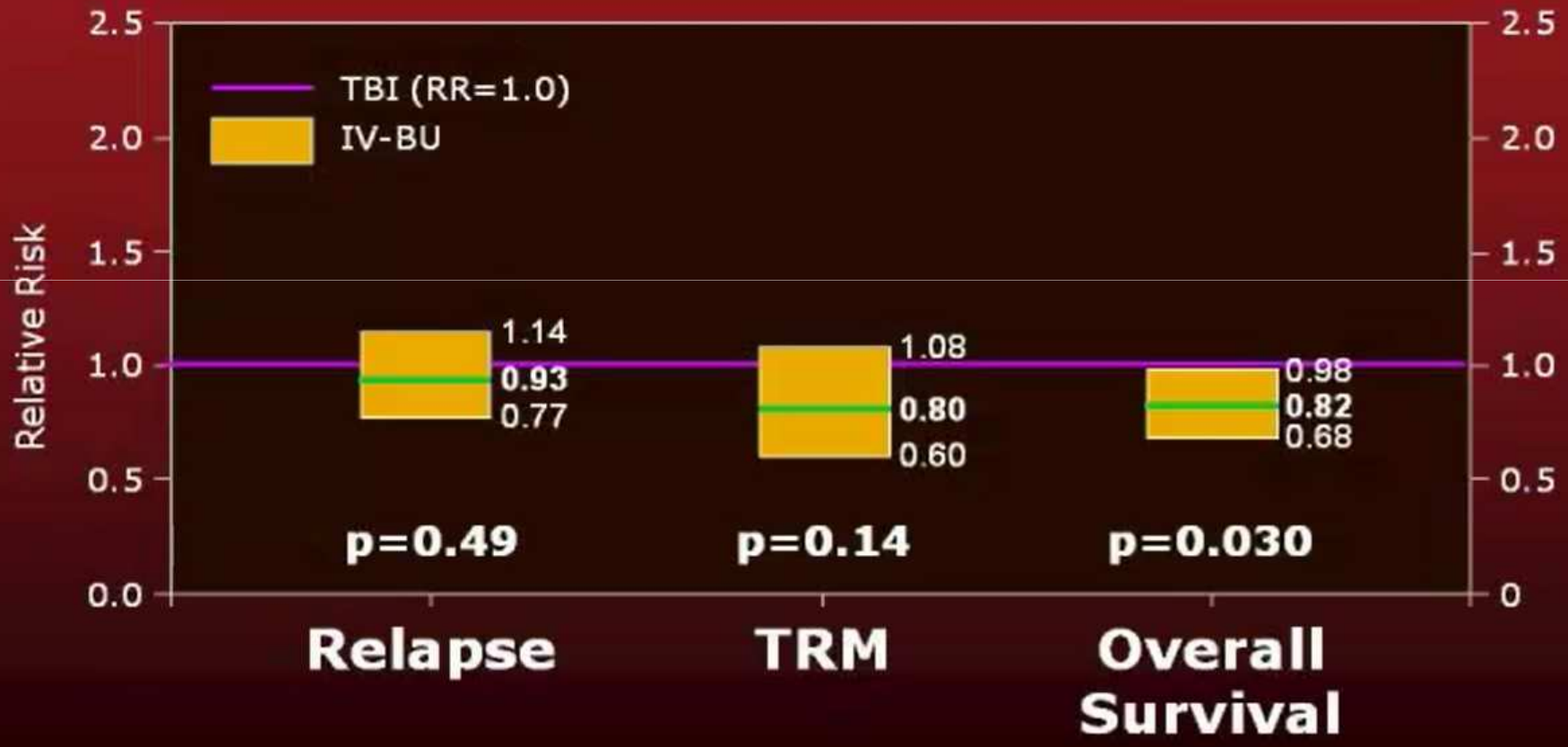
*pointwise p-value at 2 years

Multivariate Analysis: Bu vs.TBI



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Tratamiento pre-trasplante

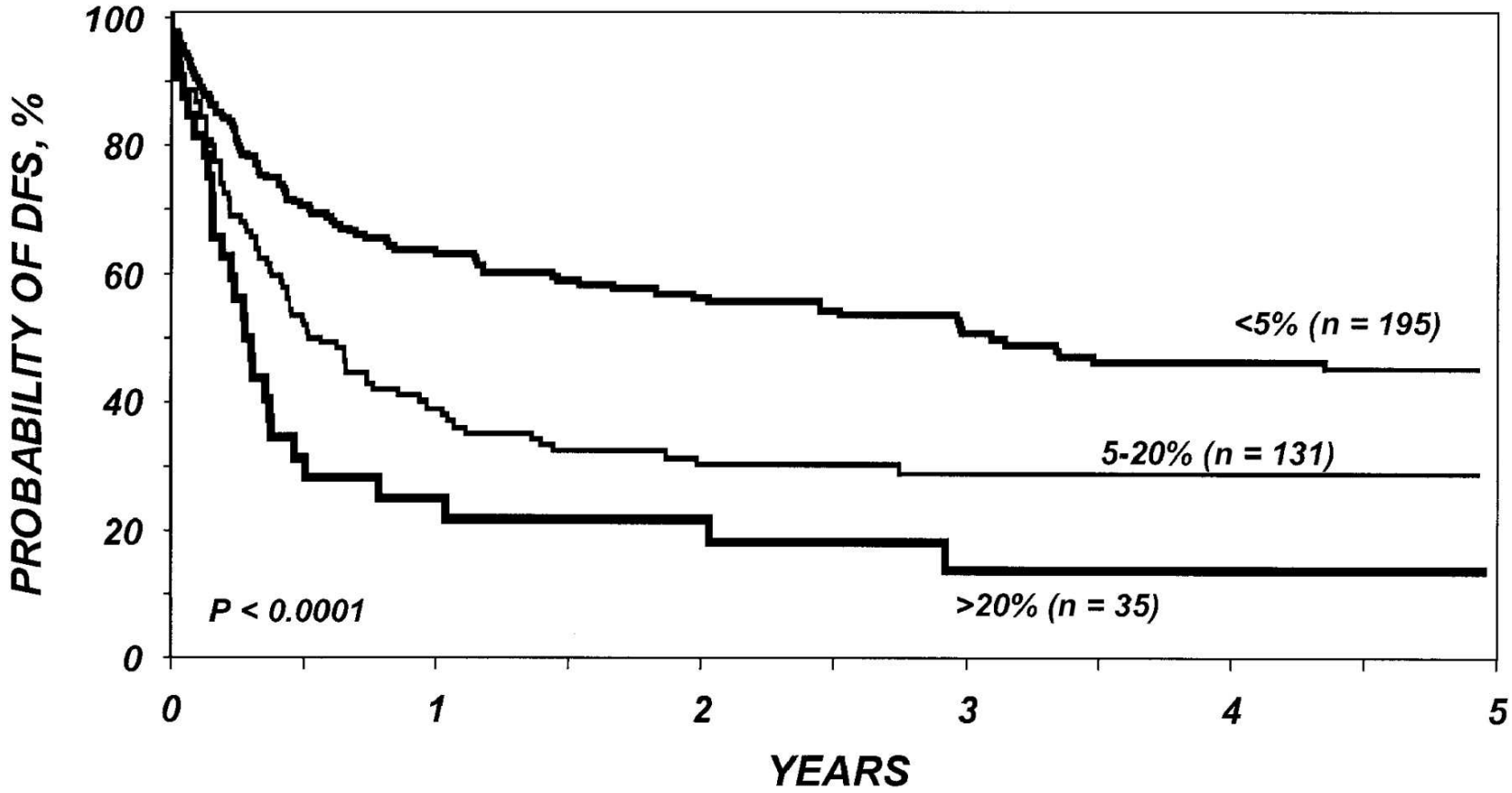
Pre-treatment

Main reasons for preconditioning therapy

- Lower the burden of disease
  - Aim: To reduce relapse risk and improve survival
  - Classical indications:
    - Excess of blasts (usually > 10%; > 5% if RIC)
    - Poor-risk cytogenetics
- Logistic
  - Aim: To stabilize the disease while waiting for the transplant
  - Classical indication:
    - Search for an unrelated donor

Allo-SCT for MDS

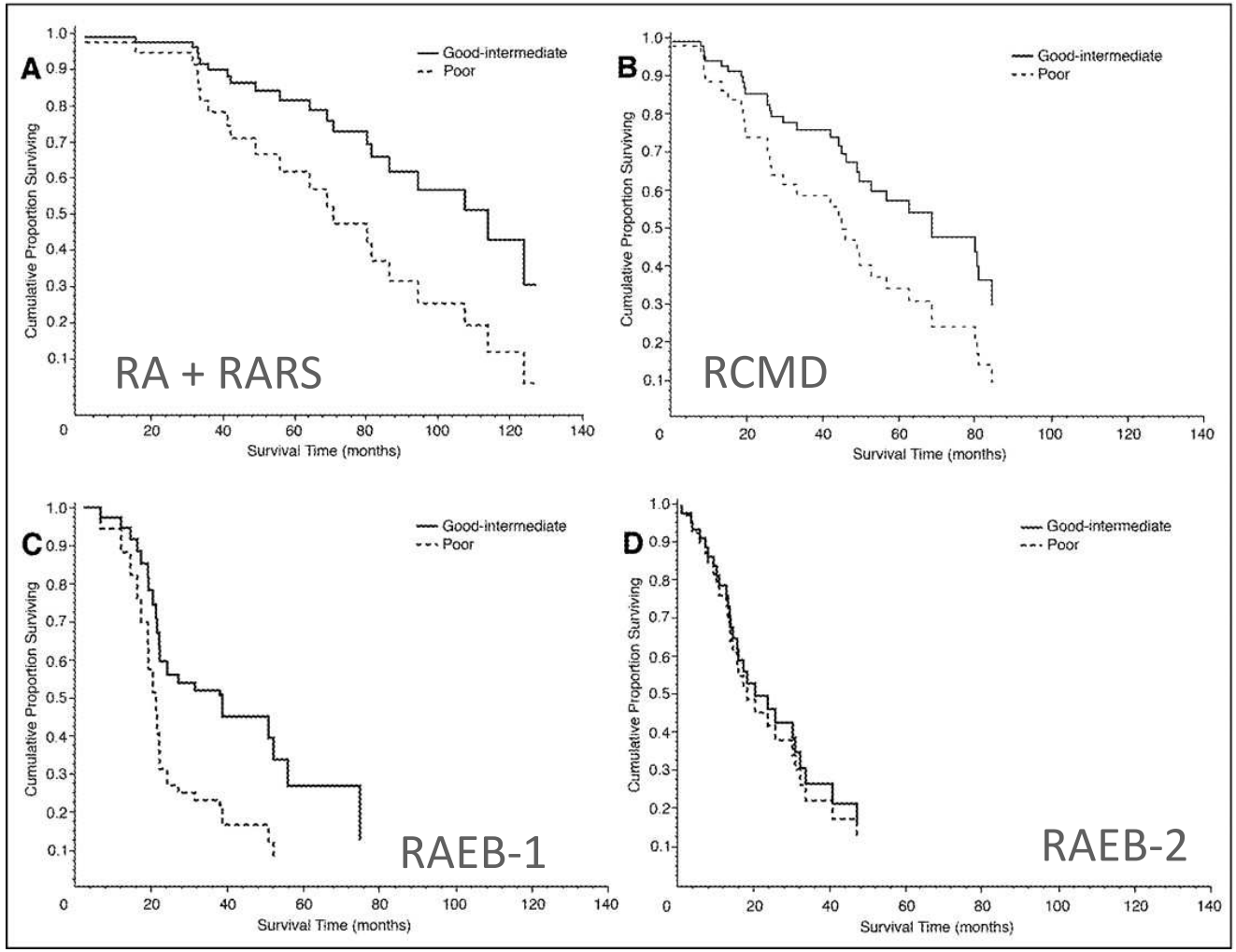
Impact of bone marrow blasts at transplant in outcome



Sierra J et al. *Blood* 2002;100:1997-2004.

Allo-SCT for MDS

Impact of cytogenetic risk in transplant outcome



~ 85% of marrow cells in MDS bear somatic mutations

Malcovati L et al. *J Clin Oncol* 2005;23:7594-7603

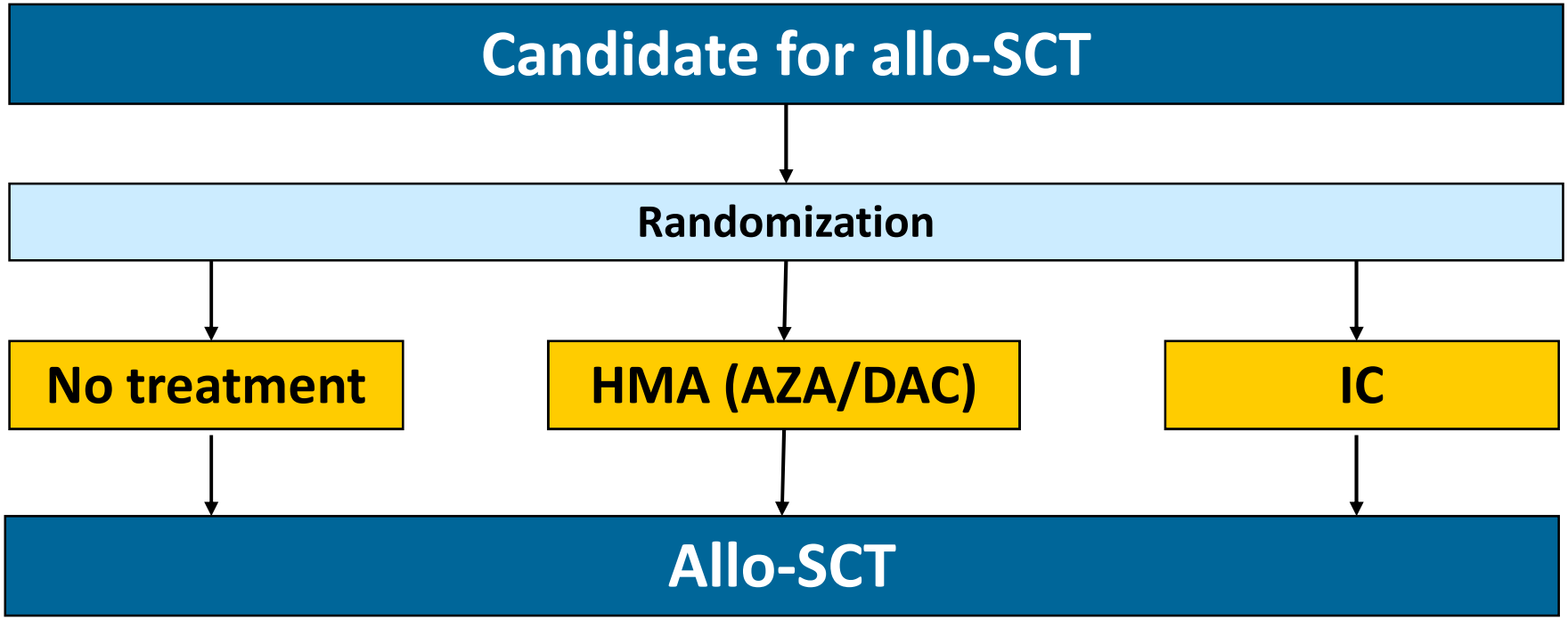
Pre-treatment
Main factors to take into account

- Characteristics of the disease
  - Percentage of BM blasts
  - Cytogenetic risk group
- Characteristics of the patient
  - Age
  - Comorbidity
- Characteristics of the transplant
  - Conditioning: Standard myeloablative / RIC
  - Donor: Family / Unrelated donor

Pre-treatment
Disadvantages of preconditioning therapy

- Prevent the patient from reaching the transplant or increase NRM after SCT
  - Death or serious adverse events
    - Intensive chemotherapy (~ 20 – 30%)
    - Hypomethylating drugs (unknown, likely < 10%)
- Failure to reduce burden of disease
  - Refractory disease or progression
    - Intensive chemotherapy (~ 25 – 30%)
    - Hypomethylating drugs (unknown, likely > 40%)

Pre-treatment
Randomized prospective comparative trial required



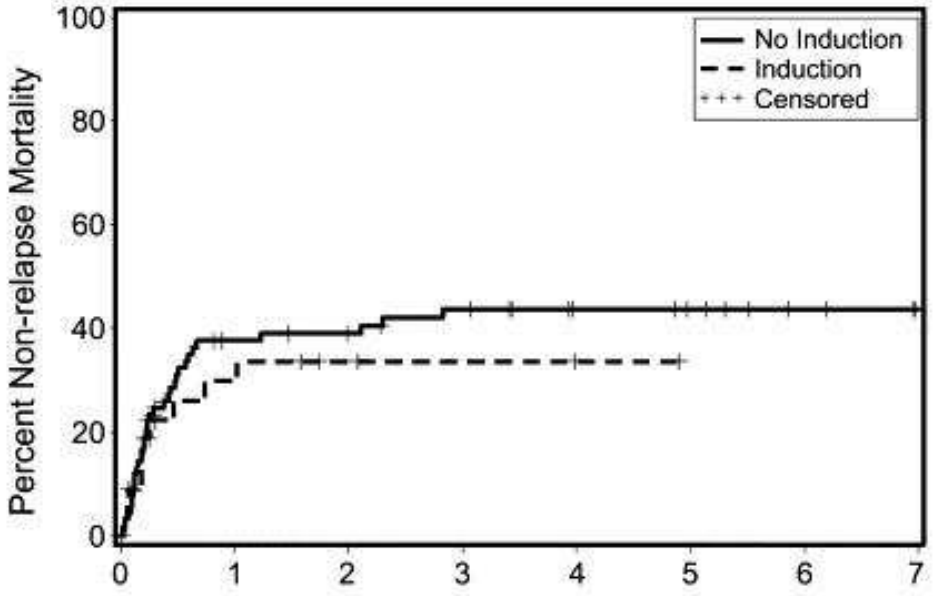
- Difficult to perform and unlikely to occur
  - Large number of patients required, especially if subset analysis required

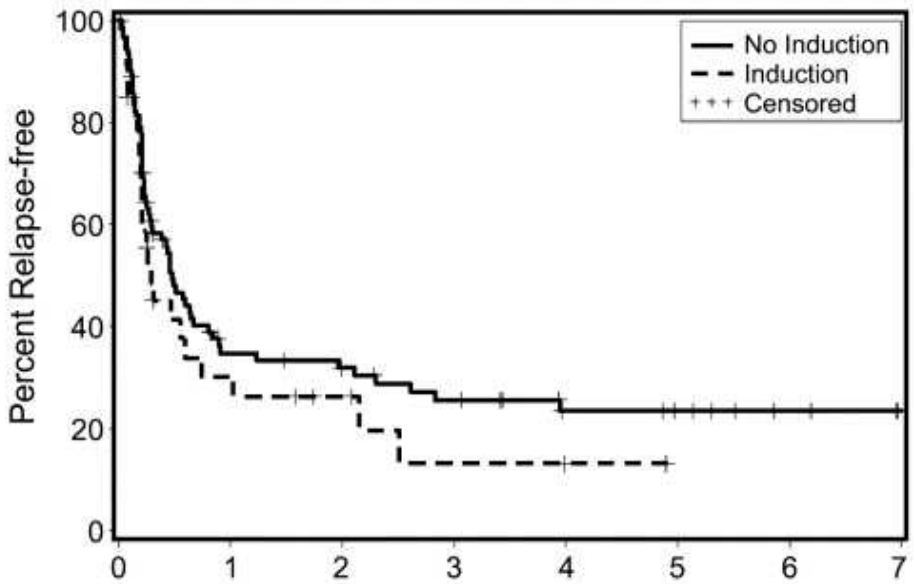
Pre-treatment
Retrospective comparative data

- Very few studies available
- Small sample size: low statistical power to detect differences in outcomes
- Studies do not include patients who fail pre-treatment and are not referred to transplantation: potential bias

Pre-treatment
IC versus no treatment before MAC

- 125 patients: IC (n = 33), no IC (n = 92)
- All received myeloablative conditioning
- No differences in RR, NRM, and RFS

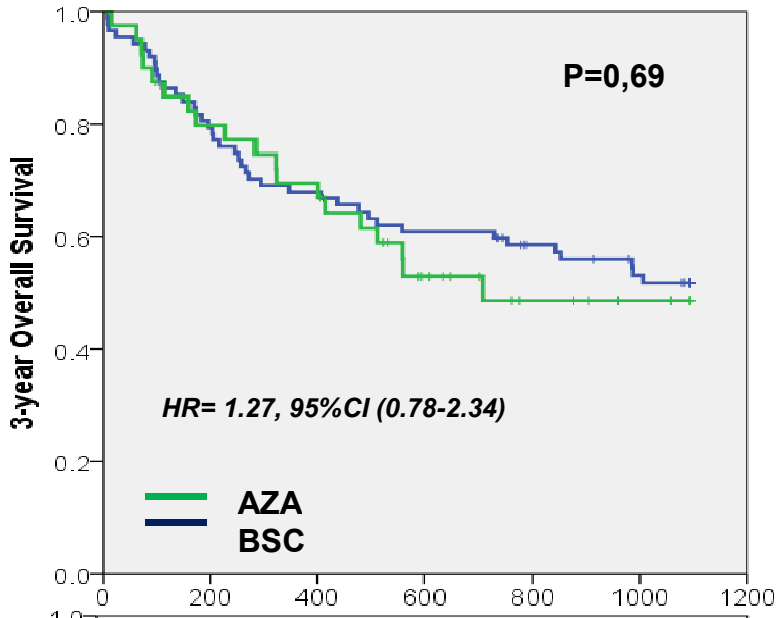


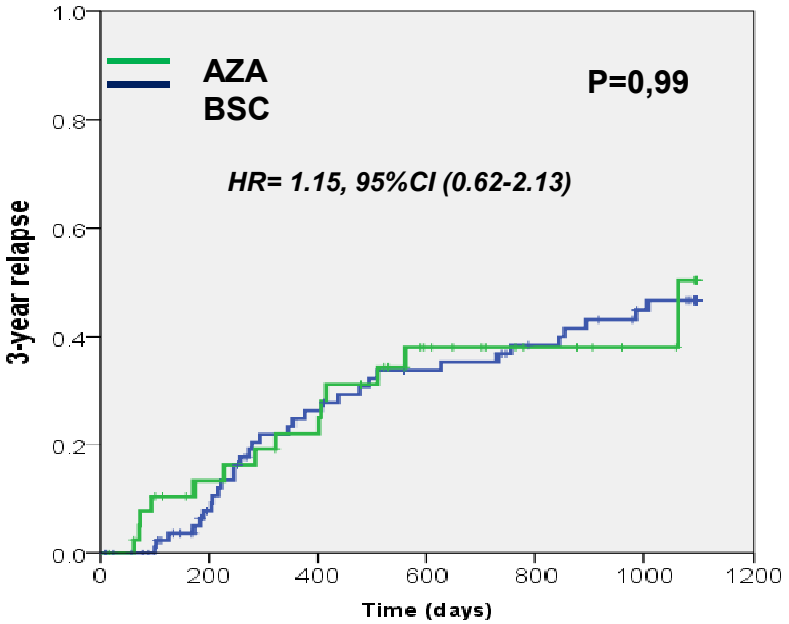


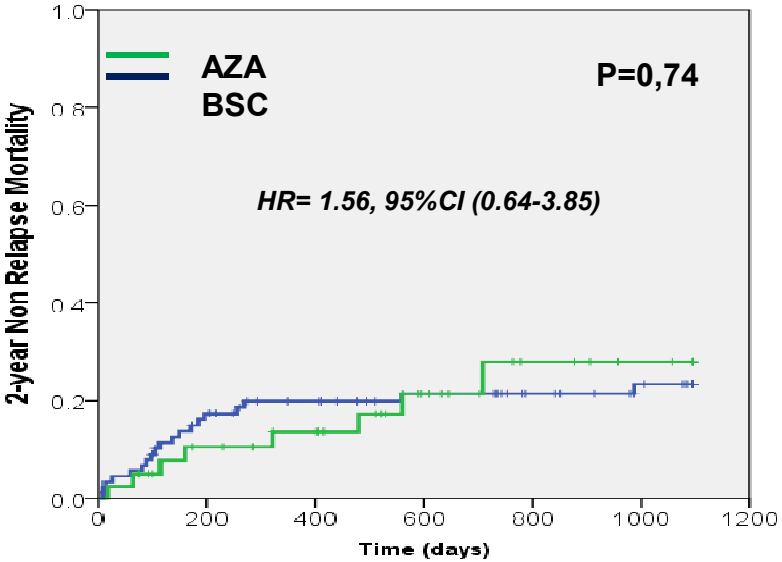
- Conclusion: No evidence of a benefit for IC before transplant

Scott BL et al. *Biol Blood Marrow Transplant* 2005;11:65-73

Pre-treatment
Azacitidine versus no treatment before RIC







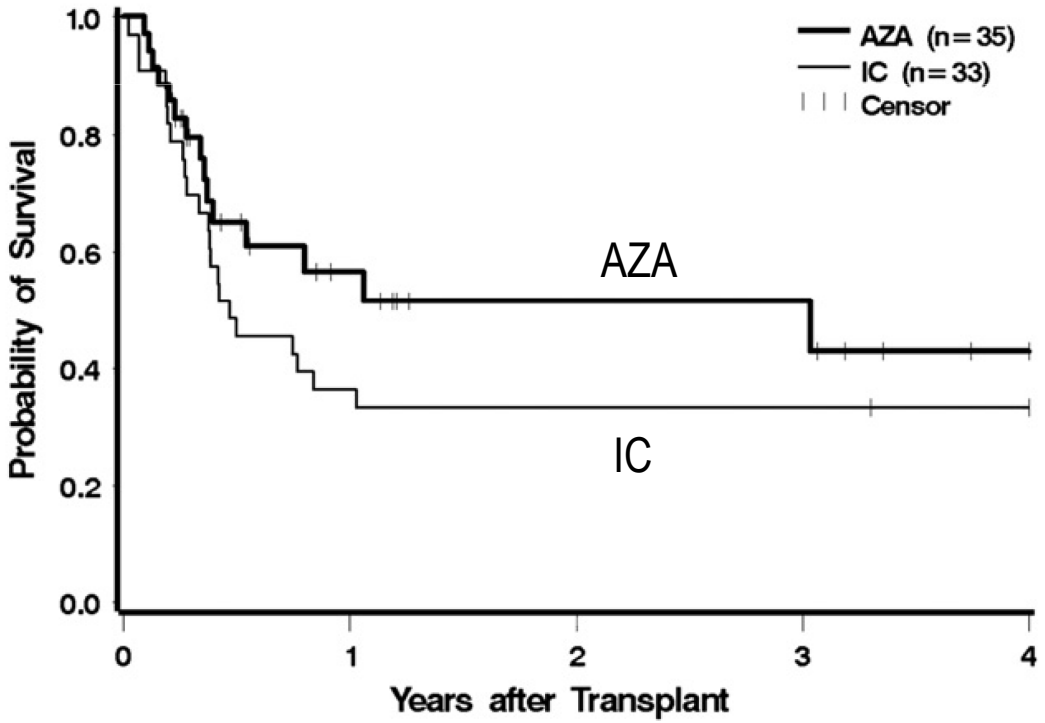
- Conclusion: Absence of treatment before RIC did not alter outcomes after transplant

Damaj G et al (SFGM-TC/GFM). *12th International Meeting on MDS, Berlin* 2013; Best abstracts session. O-014

Pre-treatment
Azacitidine versus intensive chemotherapy

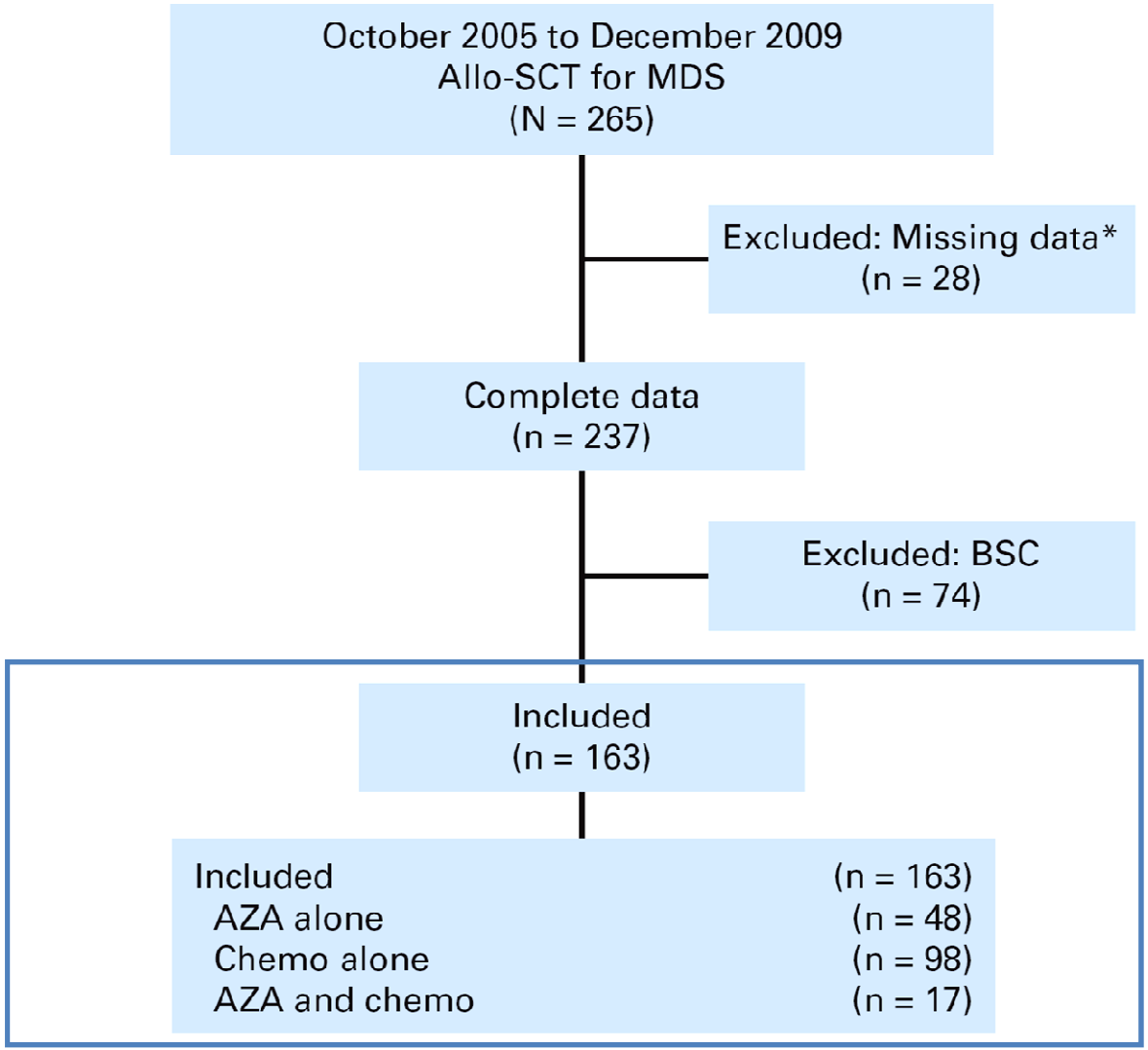
- 68 patients: IC (n = 33, all myeloablative), AZA (n = 35, 60% RIC)
- AZA patients were older (median age, 60 y vs 47 y), had less advanced disease, and had more frequently an URD (P = .002)
- No significant differences in RR, NRM, and OS were evident in multivariate analysis

- Conclusion: AZA may allow similar transplant outcomes than IC with less toxicity



Gerds AT, et al. *Biol Blood Marrow Transplant* 2012;18:1211-8.

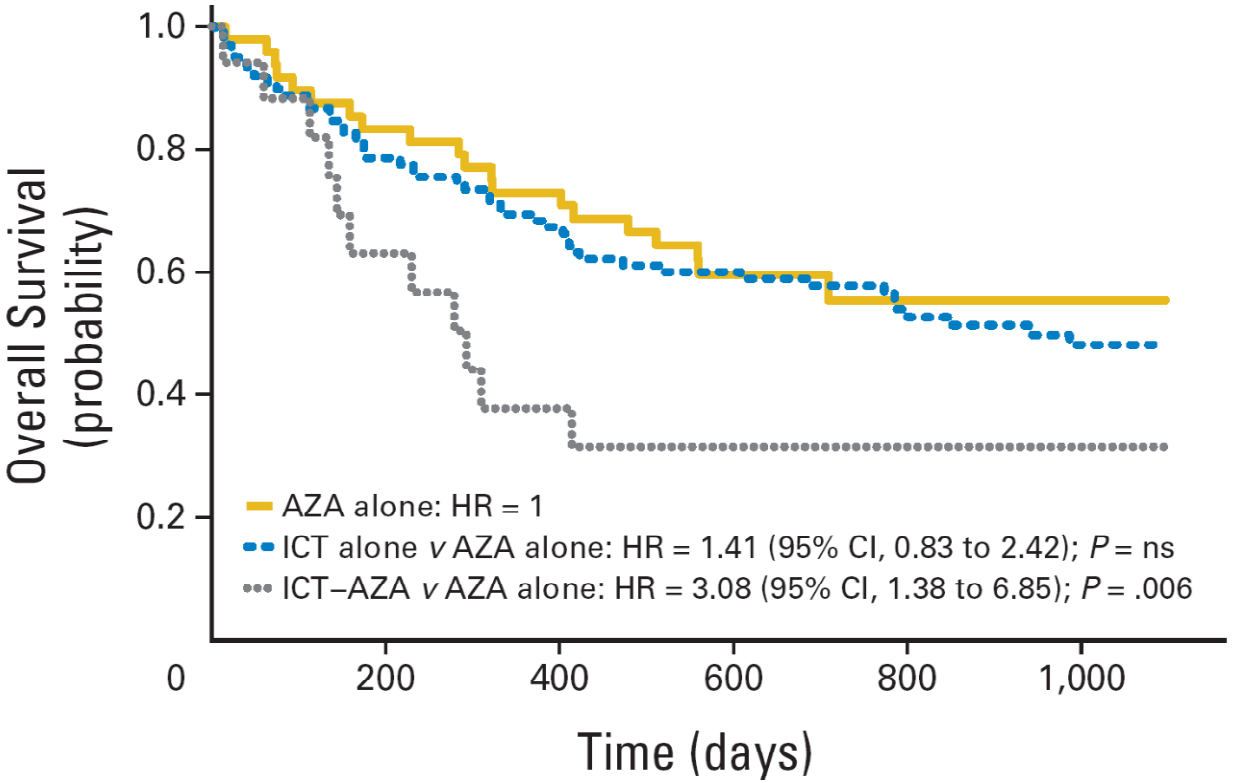
Pre-treatment
Azacitidine versus intensive chemotherapy



Damaj G, et al. *J Clin Oncol* 2012;30:4533-40.

Pre-treatment
Azacitidine versus intensive chemotherapy

- Absence of statistically significant differences in OS, EFS, RR, and NRM in uni- or multivariable analyses
- Conclusion: AZA and ICT led to similar outcomes



Damaj G, et al. J Clin Oncol 2012; 30: 4533-40.

Pre-treatment
Conclusions

- Available data do not allow to make definite recommendations on the usefulness and best type of pre-conditioning therapy for allo-SCT
- Preliminary data suggest that outcomes after azacitidine and intensive chemotherapy are similar
- At present, subsets of patients who could benefit from one of these treatment alternatives cannot be properly defined

Pre-treatment
Iron chelation

- Iron overload is clearly associated to poorer outcomes after allo-SCT in MDS and AML due to higher NRM
- Currently available treatment guidelines recommend early iron chelation in patients considered candidates for allo-SCT
- There are no data on the clinical benefit of iron chelation before allo-SCT in MDS patients

Opciones terapéuticas: TPH alogénico

Tratamiento pre-trasplante

- **Uso de QT tipo LMA ó azacitidina (AZA) aceptable**, **aunque de eficacia no probada**, en pacientes con blastos en MO >10% y/o citogenética de alto riesgo.
  - **No** existe **evidencia para inclinarse por el uso de AZA ó QT tipo LMA** en este contexto.
- El **tratamiento quelante del hierro** antes del trasplante recomendable si dependencia transfusional y sobrecarga de hierro.

Guías de diagnóstico y tratamiento de los SMD y de la LMMC. *Haematologica* 2012; 97 (suppl 5): 1 – 58.

TPH alogénico en SMD

Conclusiones

- El TPH alogénico es el tratamiento de elección en SMD de alto riesgo candidatos al mismo.
- El empleo de acondicionamientos de menor toxicidad y fuentes alternativas al hermano HLA-idéntico ha aumentado el acceso al TPH pero su empleo sigue siendo limitado (<10%).
- Cuestiones de gran relevancia continúan sin respuesta.