

NEW DEVELOPMENTS IN

# **MULTIPLE MYELOMA**

MADRID, SPAIN

MAY 16 – MAY 17, 2008

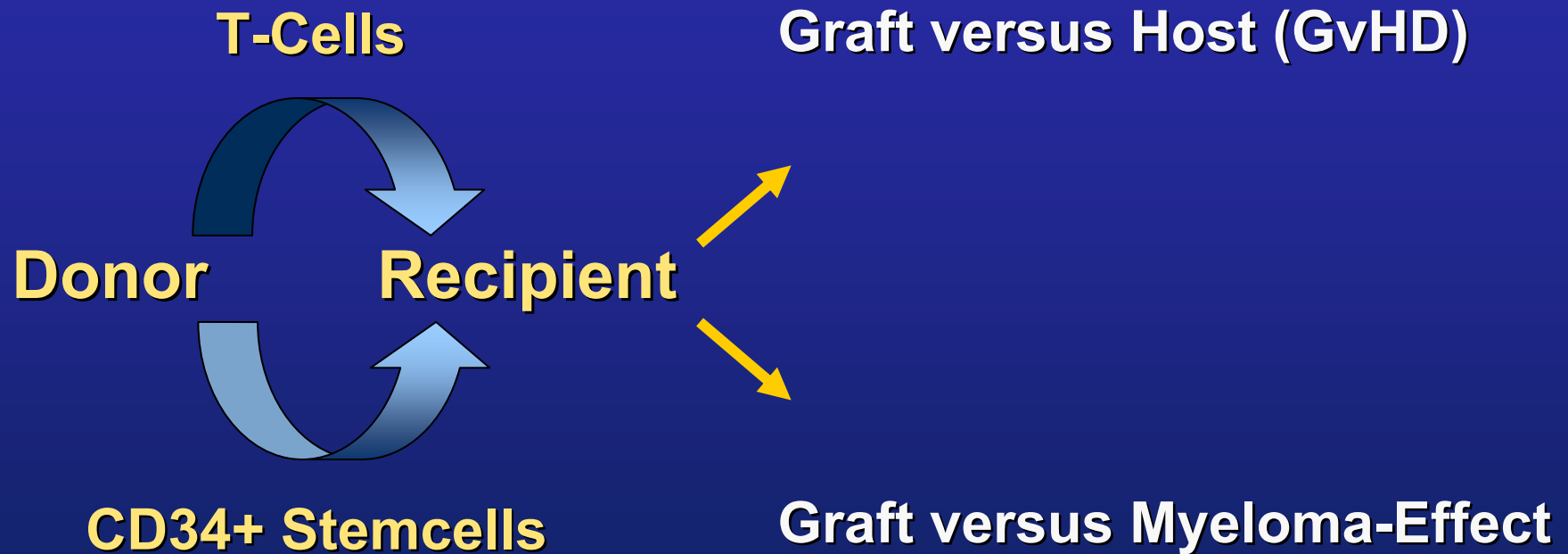
## **The Role and Timing of Allogeneic Stem Cell Transplantation in Multiple Myeloma**

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University Hospital Hamburg  
Hamburg, Germany*



**NOVARTIS**

# Allogeneic Stem Cell Transplantation



# Allogeneic SCT in Myeloma



*upfront*



*salvage*  
(e.g. after effective failure to autologous SCT)

# Allogeneic SCT in Myeloma

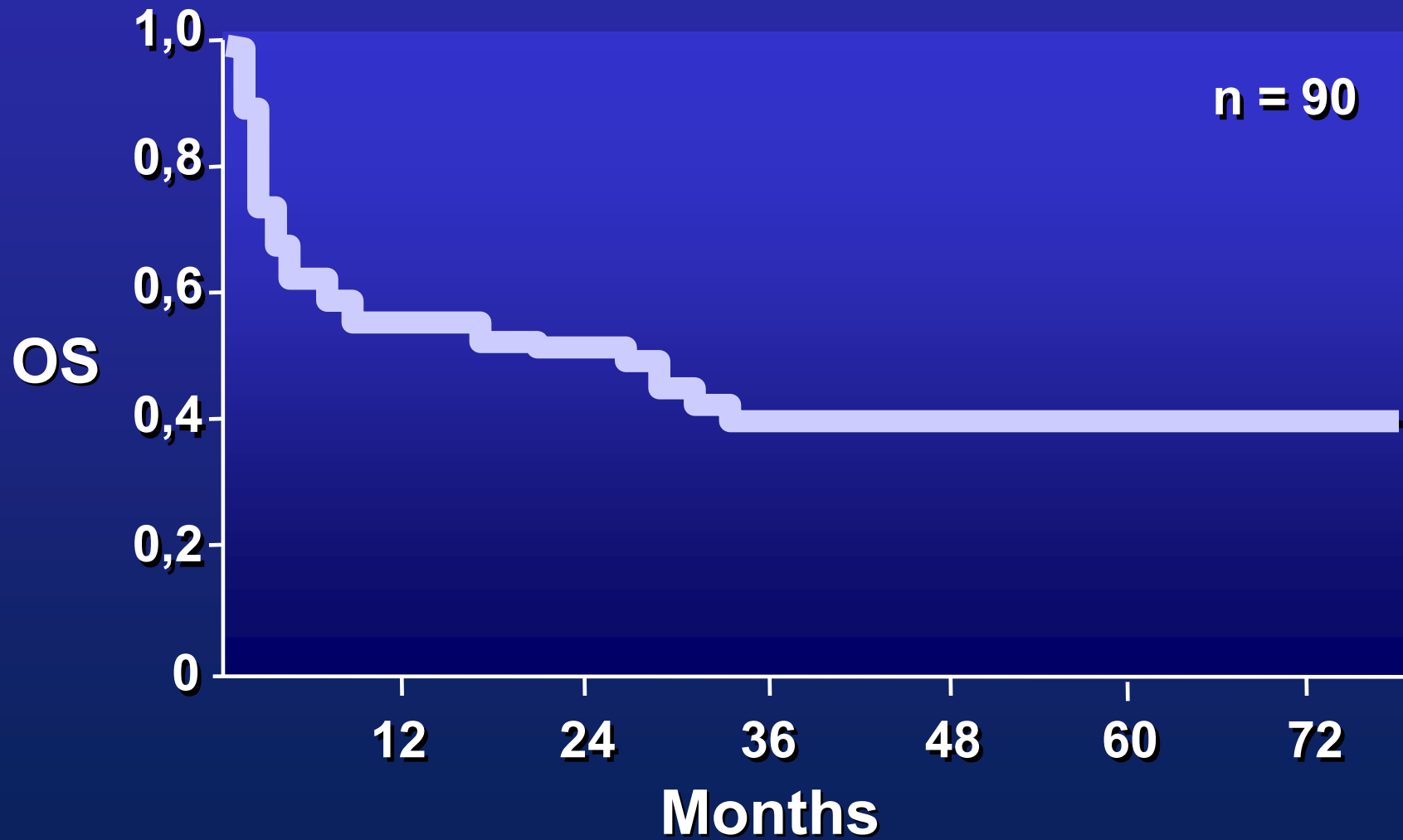
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standard  
myeloablative  
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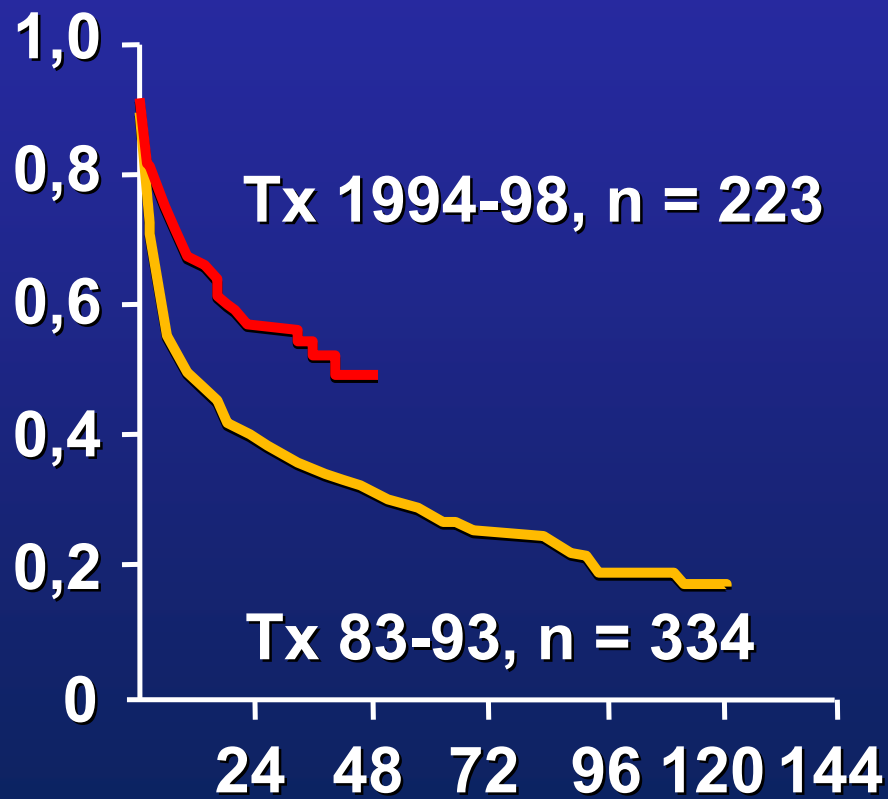


# Allogeneic stem cell transplantation

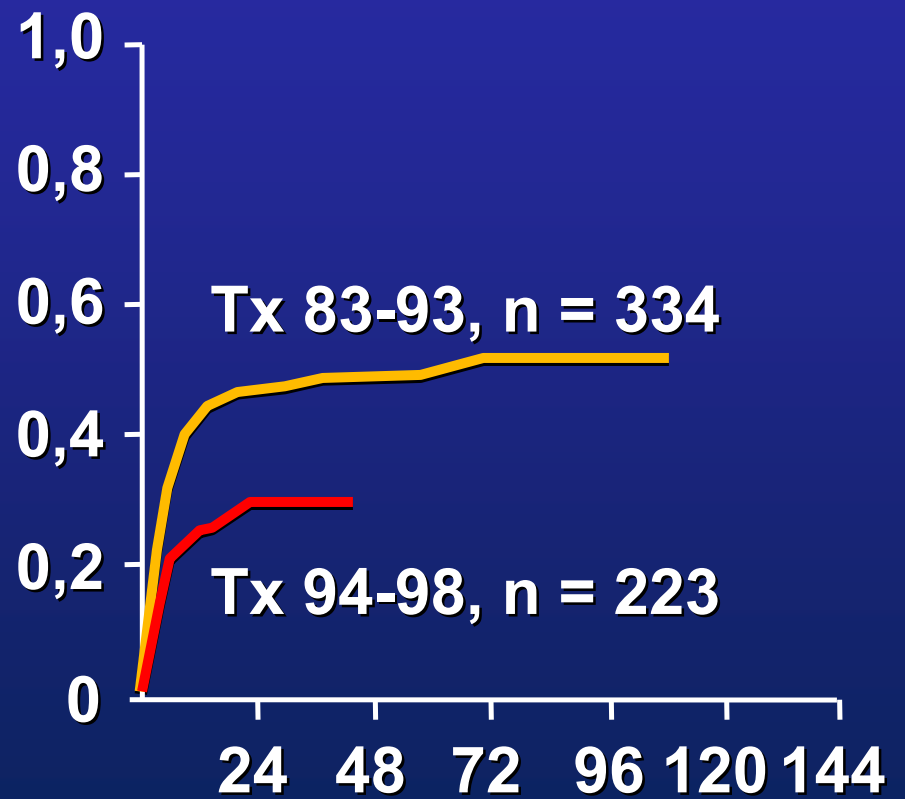


# Allogeneic Transplantation

## Survival



## Mortality



Months after transplantation

# Comparison of standard myeloablative allogeneic SCT and autologous SCT

		TRM	Relapse	OS
<b>EBMT</b> (n=378)	<b>auto</b>	<b>13%</b>	<b>70%</b>	<b>34 months (med.)</b>
	<b>allo</b>	<b>41%</b>	<b>50%</b>	<b>18 months (med.)</b>
<b>Boston</b> (n=232)	<b>auto</b>	<b>6%</b>	<b>56%</b>	<b>41% (4 years)</b>
	<b>allo</b>	<b>24%</b>	<b>46%</b>	<b>39% (4 years)</b>
<b>Vancouver</b> (n=158)	<b>auto</b>	<b>14%</b>	<b>70%</b>	<b>31% (10 years)</b>
	<b>allo</b>	<b>22%</b>	<b>47%</b>	<b>40% (10 years)</b>

*Data from: Björkstrand et al., 1996; Alyea et al., 2003;  
Kuruvilla et al., 2007*

# Rate of molecular remission based on rearranged immunoglobulin heavy chain genes

**In CR:**      **after allograft: 50% molecular CR**  
                 **after autograft: 7% molecular CR**

*Corradini et al., JCO 1999*

**In CR:**      **after allograft: 50% molecular CR**  
                 **after autograft: 16% molecular CR**

*Martinelli et al., JCO 2000*

# Minimal residual disease after allogeneic stem cell transplantation

## *Multiple Myeloma (EBMT-Studie): Pat with CR*

	PCR neg	PCR mixed	PCR pos
No. of pts	16	19	13
5 year cumulative risk of relapse	0%	33%	100%

*Corradini et al., Blood 2003*

# Allogeneic SCT in Myeloma

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(e.g. after effective failure to autologous SCT)

**standard  
myeloablative  
allograft**

*advantage:*  
potential cure, molecular remission

*disadvantage:*  
high TRM

*notice:*  
improvement of TRM

# Allogeneic SCT in Myeloma

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**standard  
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allograft**

**reduced  
intensity  
allograft**

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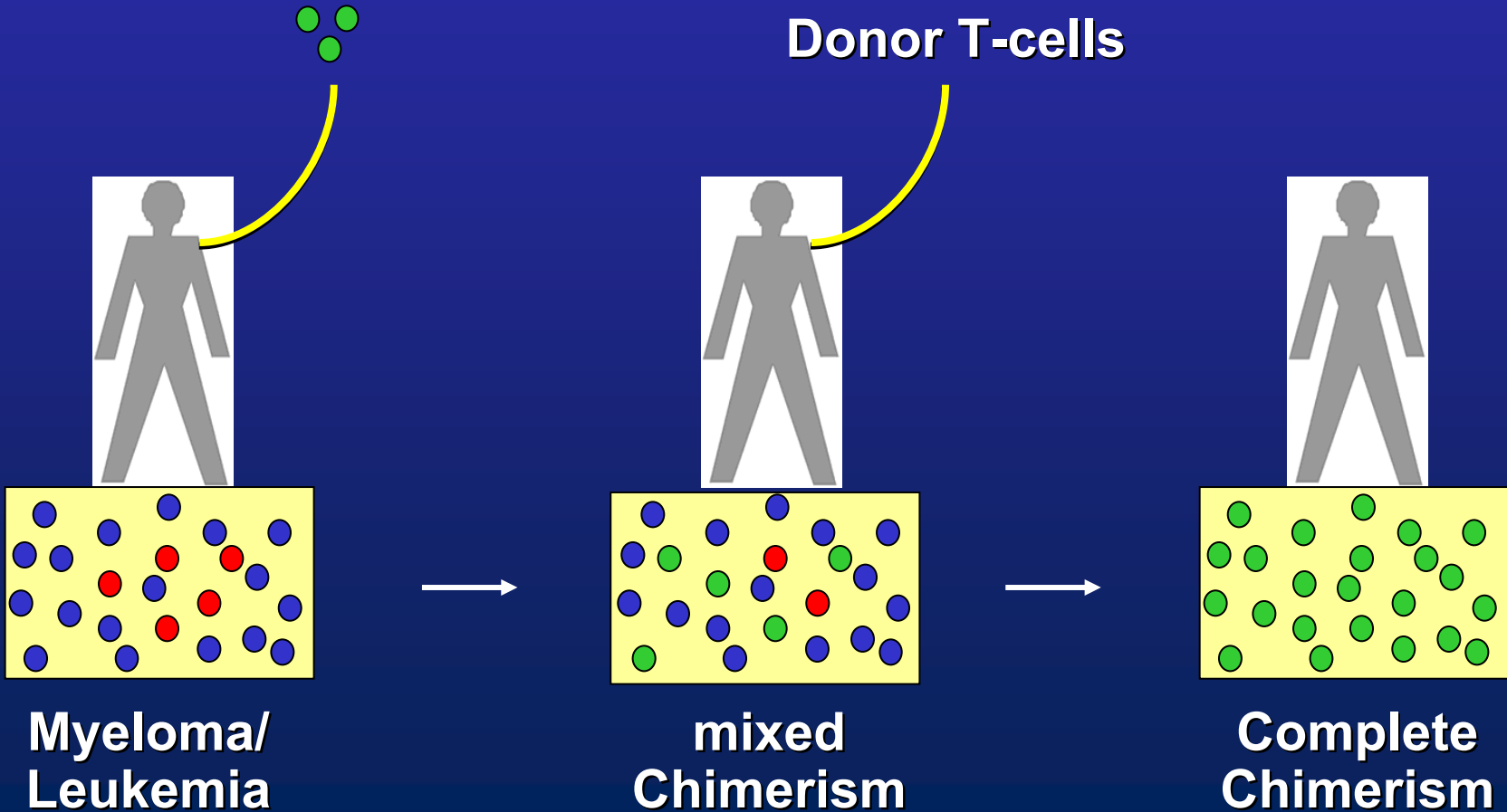
*disadvantage:*  
high TRM

*notice:*  
improvement of TRM more recent years

# Dosis-reduced conditioning

TBI 2 Gy/Busulfan 8mg/kg  
Fludarabine  
+ CD34+ stem cells

Donor T-cells

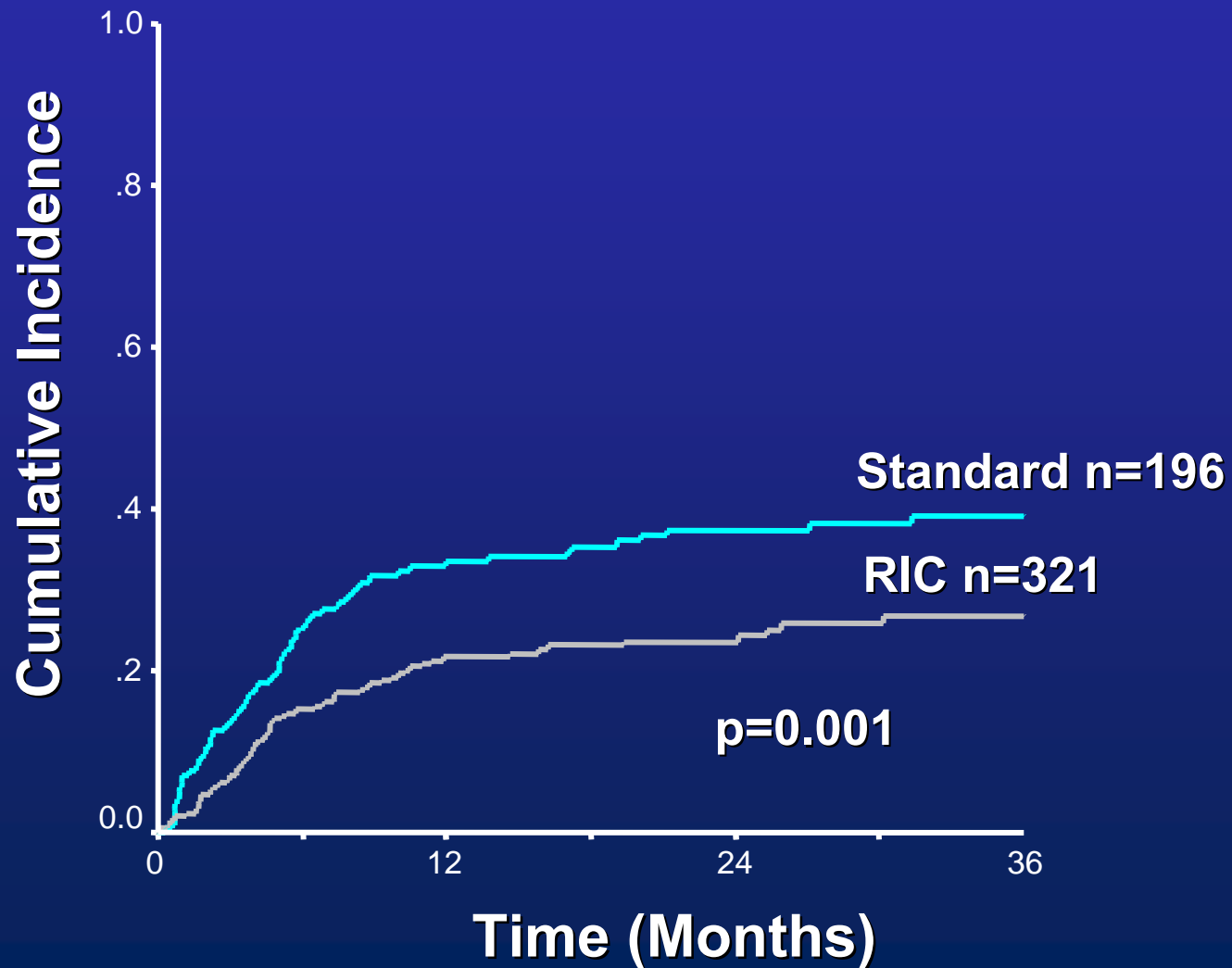


# RIC for advanced myeloma

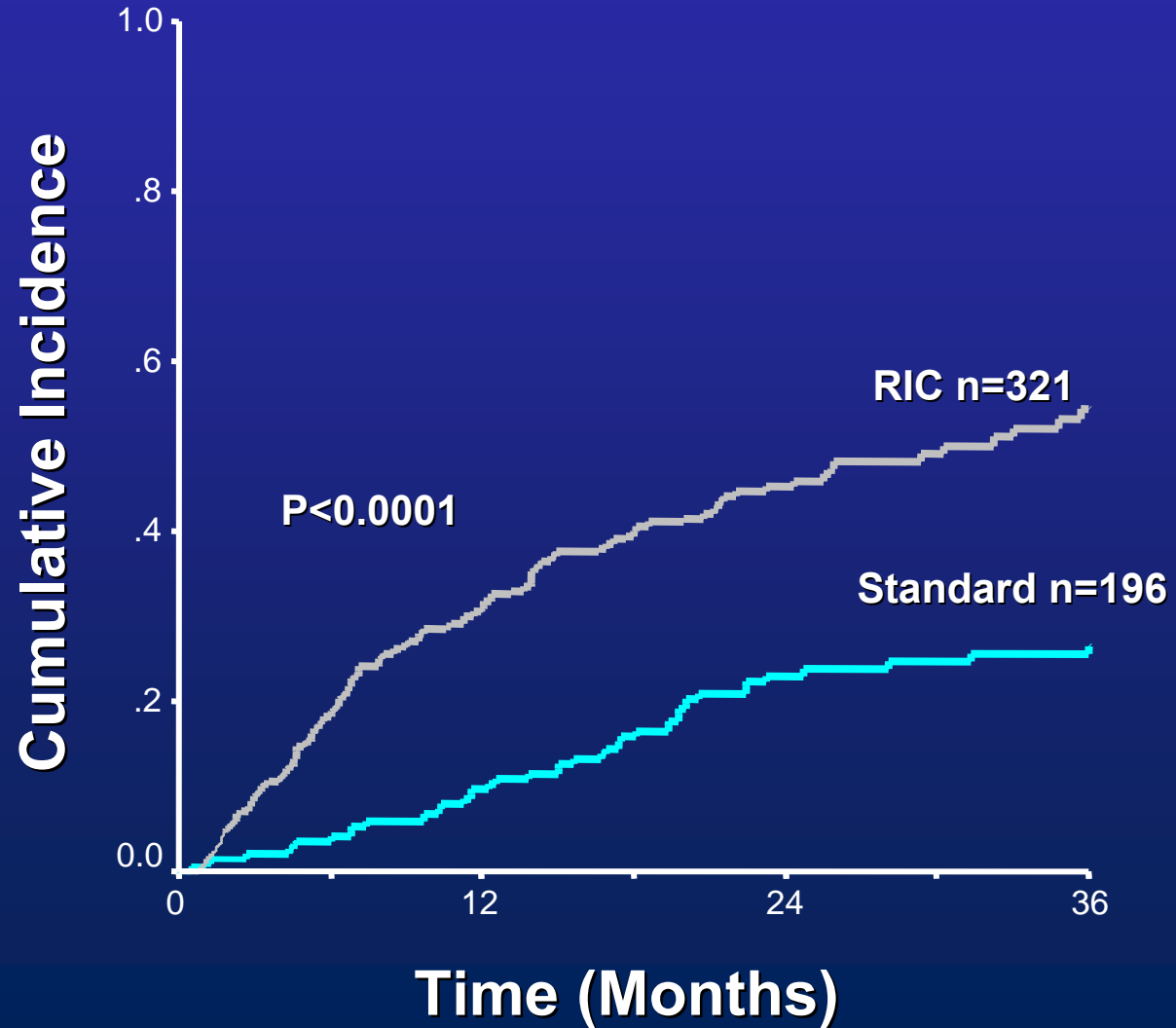
<i>Intensity</i> ⇒	<i>Mini</i>	<i>Midi</i>		<i>Maxi</i> <i>Standard cond</i>
<b>Regimen</b> ⇒	<b>2 Gy TBI +/- Fludara (n=52)</b>	<b>Busulfan 4-8 mg/kg + Fludarabine (n=41)</b>	<b>Mel 100-160 mg/m<sup>2</sup> + Fludarabine (n=111)</b>	<b>After 2000 (n=239)</b>
<b>CR</b>	<b>27 %</b>	<b>24 %</b>	<b>32 - 49 %</b>	<b>50-60 %</b>
<b>TRM</b>	<b>17 %</b>	<b>17 %</b>	<b>20 - 25%</b>	<b>25-30 %</b>
<b>Survival</b>	<b>41 % (1,5 years)</b>	<b>62 % (2 years)</b>	<b>30 % - 71 % (2 years)</b>	<b>28 - 77 %</b>

*Data from: Gerull 2005; Mohty 2004; Badros 2002; Giralt 2002;  
Kröger 2004; Hunter 2005; Lokhorst 2003*

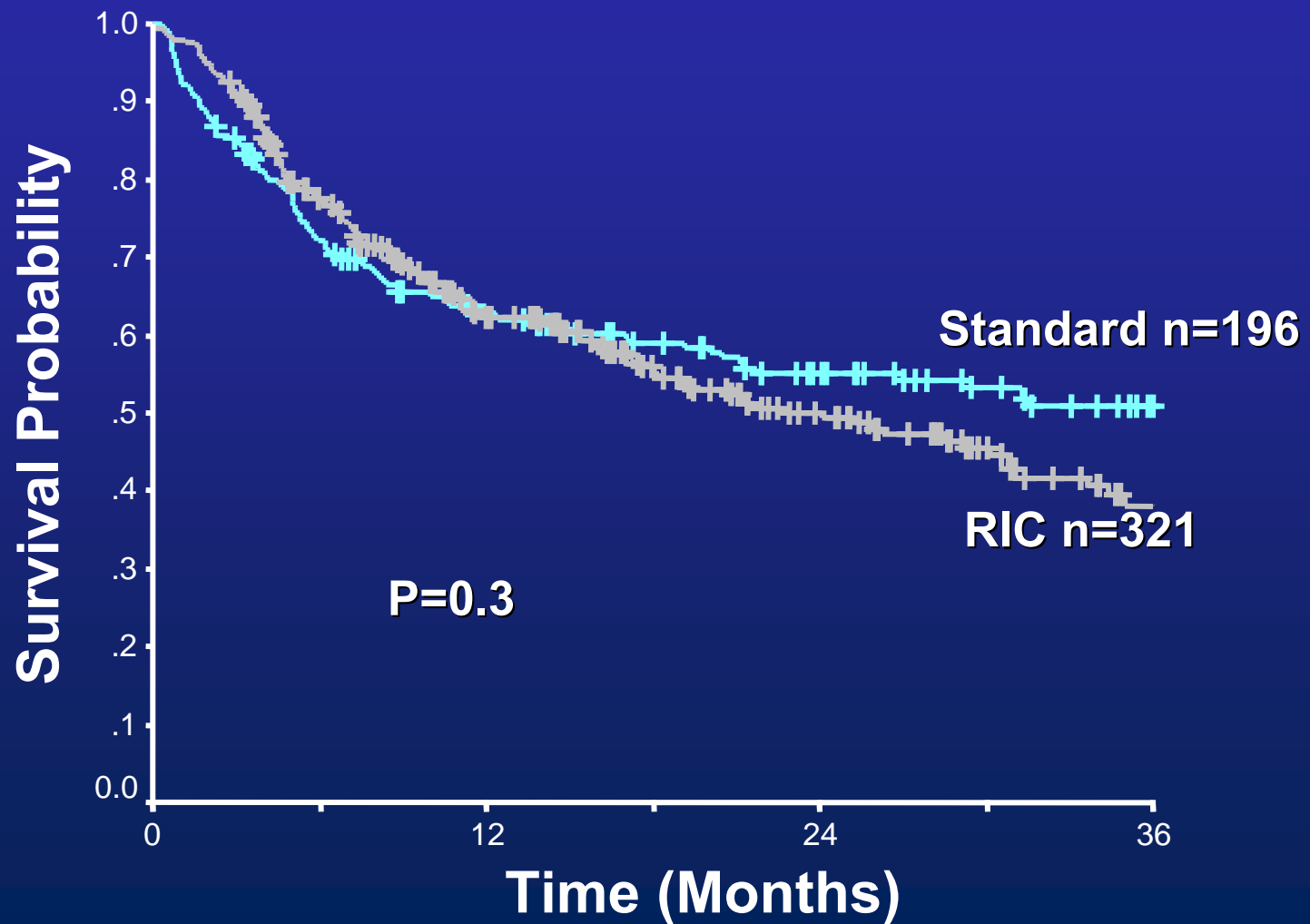
# Transplant Related Mortality



# Relapse



# Overall Survival



## Retrospective comparison between RIC and Standard allograft in myeloma: EBMT-Data (since 1998)

	<i>RIC</i> n = 321	<i>Standard</i> n = 196
Prior transplants	↑	-
Less PR/CR more SD/PD	↑	-
More unrelated donors	↑	-
Longer interval for diagn. to transplant	↑	-
More T-cell depletion (incl. Campath)	↑	-
Median age	↑ (51 y.)	(45 y.)

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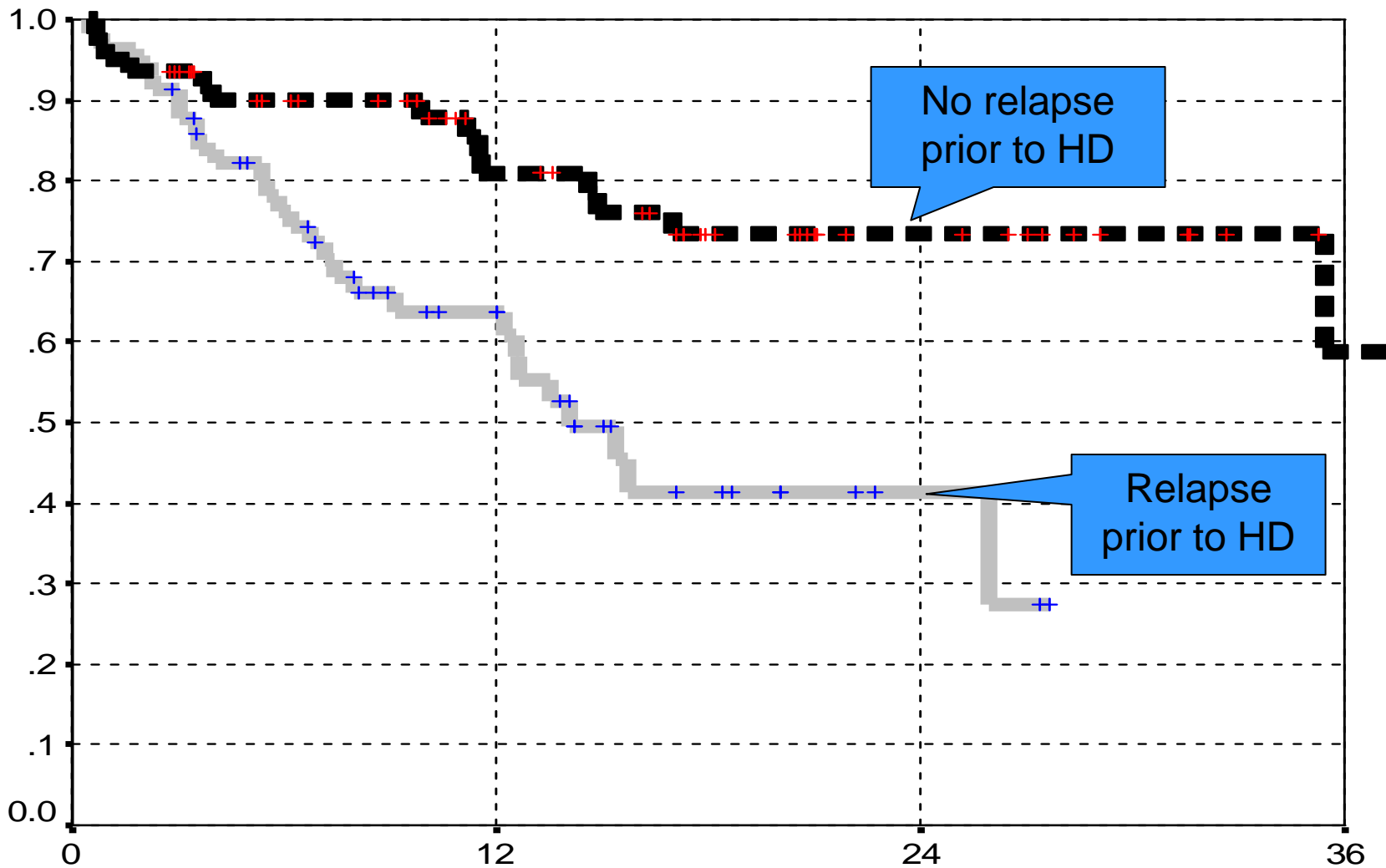
**reduced  
intensity  
allograft**

*advantage:*  
potential cure, molecular remission

*disadvantage:*  
high TRM

*notice:*  
improvement of TRM more recent years

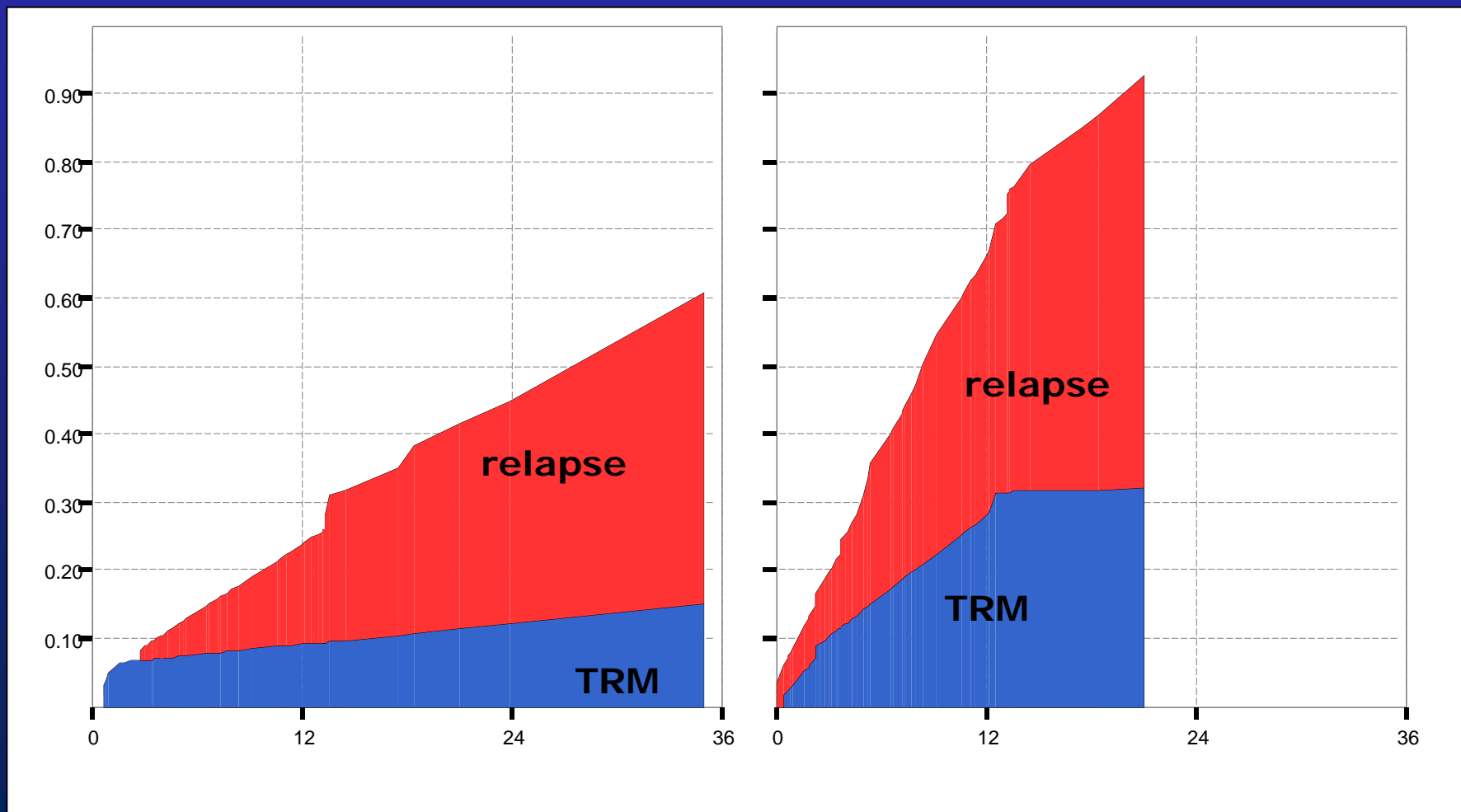
# Timing of RIC Transplantation: before or after failure to autologous transplantation



# Cumulative incidence of relapse and TRM in a competing risk model

*No relapse to HD-therapy*

*relapse to HD-therapy*



# Allogeneic SCT in Myeloma

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*advantage:*  
less TRM

*disadvantage:*  
probably higher risk of relapse

*notice:*  
patient-selection  
no prospective randomized trial

# Allogeneic SCT in Myeloma

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# Reduction of treatment related mortality from allogeneic SCT

## Standard-Allograft

High-dose  
chemotherapy

+

Allogeneic  
Immunotherapy

Autologous  
SCT

*2 - 3  
Months*

Allogeneic SCT  
after reduced  
intensity  
conditioning

Adoptive  
Immunotherapy  
(DLI)

# Auto-Allo Tandem Transplantation

	<i>n</i> = 109	<i>n</i> = 59	<i>n</i> = 16	<i>n</i> = 46
<b>Auto-Regimen</b> ⇒	Melphalan 200 mg/m <sup>2</sup>	Melphalan 200 mg/m <sup>2</sup>	Melphalan 140 mg/m <sup>2</sup>	Melphalan 200 mg/m <sup>2</sup>
<b>Allo-Regimen</b> ⇒	2 Gy TBI +/- Fludarabine	Melphalan 100-150 mg/m <sup>2</sup> + Fludarabine (1)	2 Gy TBI + Fludarabine	Busulfan 4 mg/kg BW + Fludarabine (2)
<b>CR</b>	52 - 58 %	55 - 83 %	62 %	33 %
<b>TRM</b>	16 - 17 % (1 year)	0 - 17 % (1 year)	16 % (1 year)	11 % (1 year)
<b>OS</b>	78 % (2 years)	70 % - 100 % (2 years)	62 % (3 years)	57 % (2 years)

*Data from Maloney 2003; Bruno 2007; Carella 2004,  
Kröger 2002; Garban 2006, Soek 2003*

# Auto-allo (RIC) vs standard allo SCT

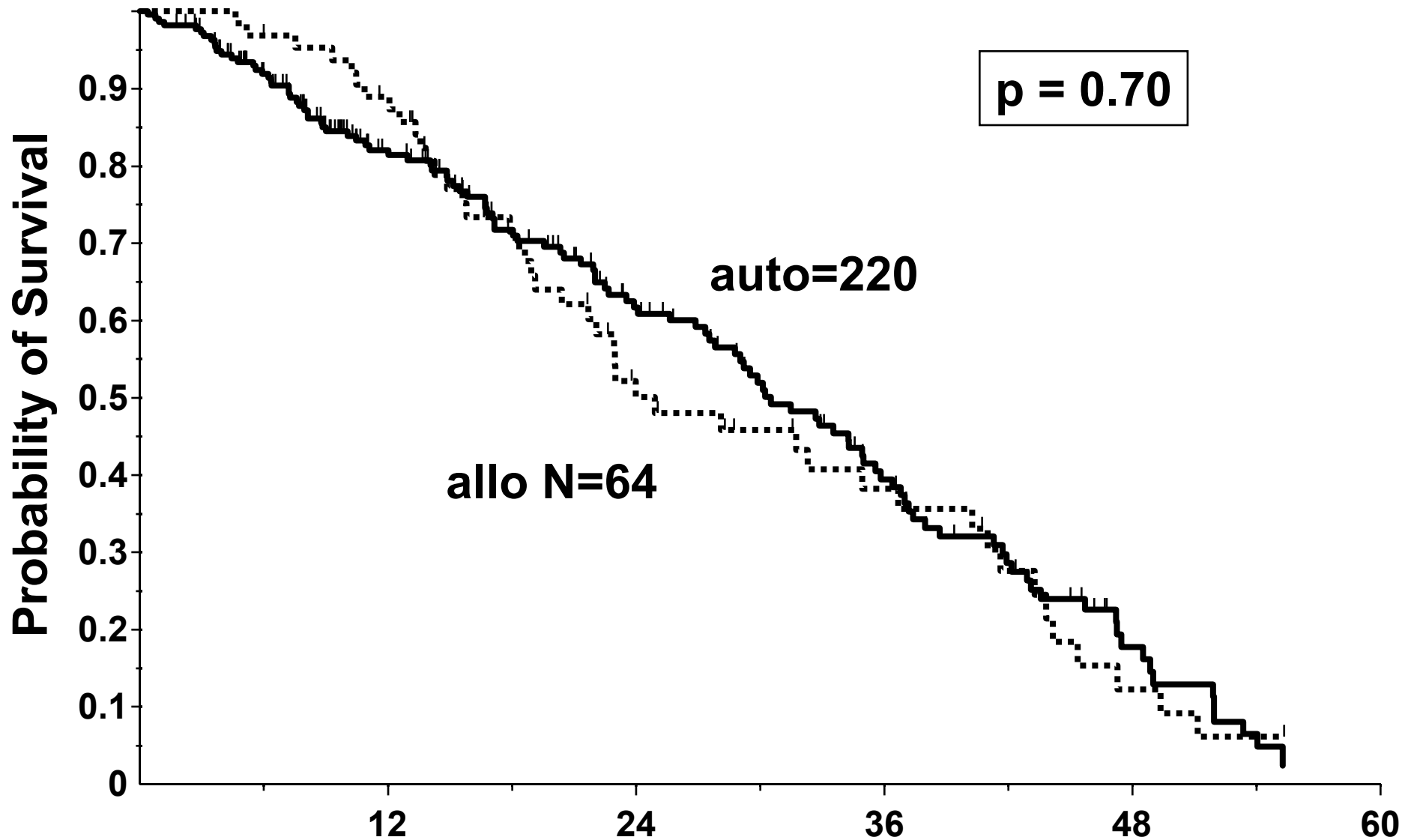
	<i>Auto-allo</i>	<i>Allo Standard (after 2000)</i>
<b>Regimen =&gt;</b>	<b>Mel 200 mg/m<sup>2</sup> → Mel 140/ oder 2 Gy TBI + Fludarabine</b>	<b>Melphalan 200 mg/m<sup>2</sup>/ 12 GyTBI</b>
<b>CR</b>	<b>~ 55 %</b>	<b>~ 50-60 %</b>
<b>Relapse</b>	<b>~ 35-40 %</b>	<b>~ 35-40 %</b>
<b>TRM</b>	<b>~ 15 %</b>	<b>~ 25-30 %</b>

*Daten aus: Maloney 2003; Bruno 2007; Carella 2004,  
Kröger 2002; Garban 2006, Soek 2003, Lokhorst 2003*

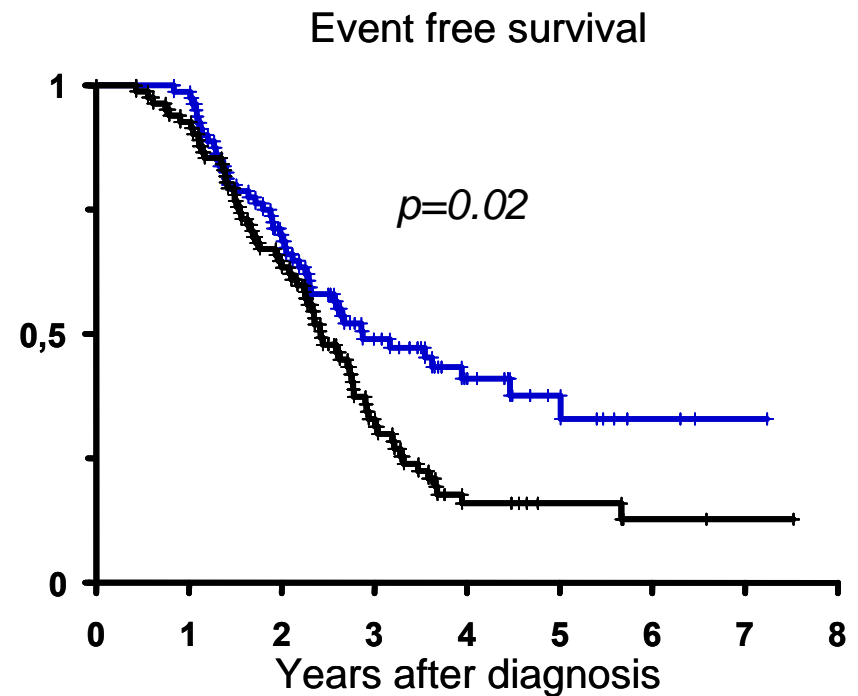
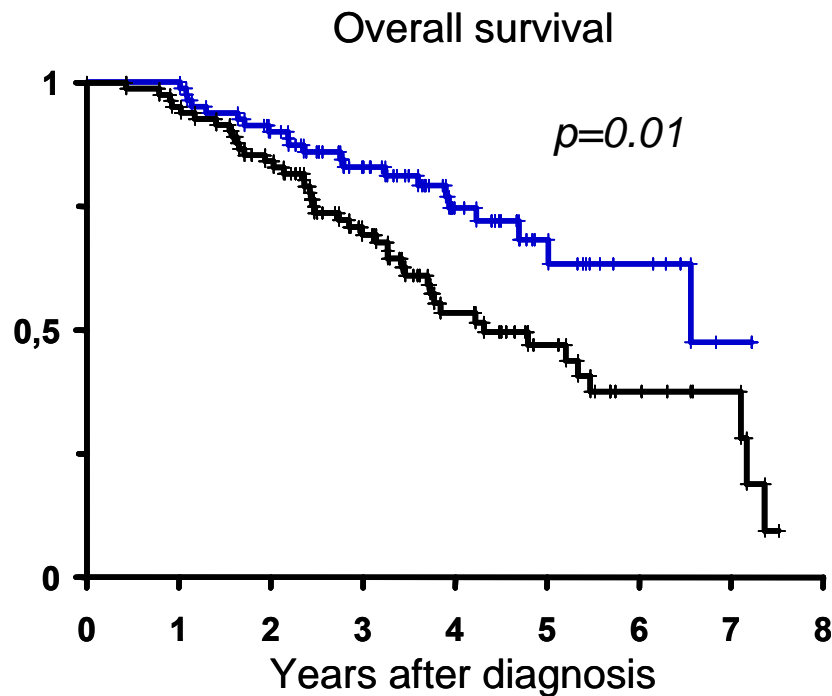
# Randomised studies comparing tandem-autologous SCT vs. auto-allo (RIC) in myeloma

<i>Author</i>	<i>number Patients</i>	<i>Regime</i>	<i>TRM</i>	<i>Response (CR)</i>	<i>DFS</i>	<i>OS</i>
Garban <i>et al.</i> , 2006	n = 219	<b>auto-auto:</b> Melphalan (200 mg/m <sup>2</sup> ) / Melphalan (220 mg/m <sup>2</sup> )	5 %	33 %	0 % (at 5 years)	44 % (at 5 years)
High risk (del13/β2)	n = 65	<b>auto-allo:</b> Melphalan (200 mg/m <sup>2</sup> ) / Busulfan (4 mg/kg BW) Fludarabine ATG (Thymoglobulin)	11 %	33 %	0 % (at 5 years)	33 % (at 5 years)
Bruno <i>et al.</i> , 2007	n = 80	<b>auto-auto:</b> Melphalan (200 mg/m <sup>2</sup> ) / Melphalan (200 mg/m <sup>2</sup> )	4 %	26 %	20 % (at 4 years)	53 % (at 4 years)
All risk	n = 82	<b>auto-allo:</b> Melphalan (200 mg/m <sup>2</sup> ) / 2 Gy TBI	10 %	55 %	42 % (at 4 years)	75 % (at 4 years)

# EFS intent-to-treat: IFM 99-03 VS 99-04



# Outcome according to presence of HLA-identical siblings (n=162), Median follow up from diagnosis: 45 months, range 21-90

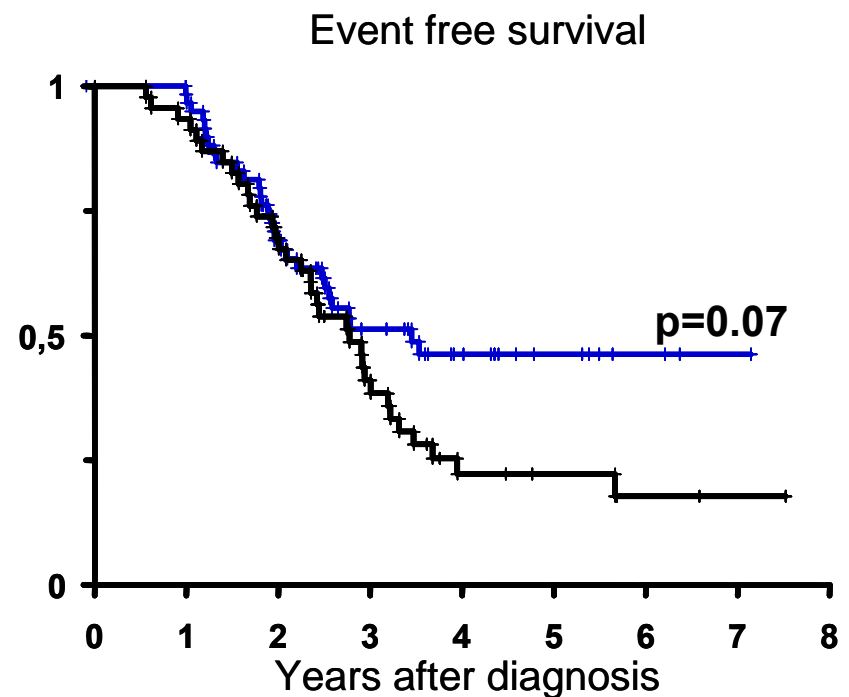
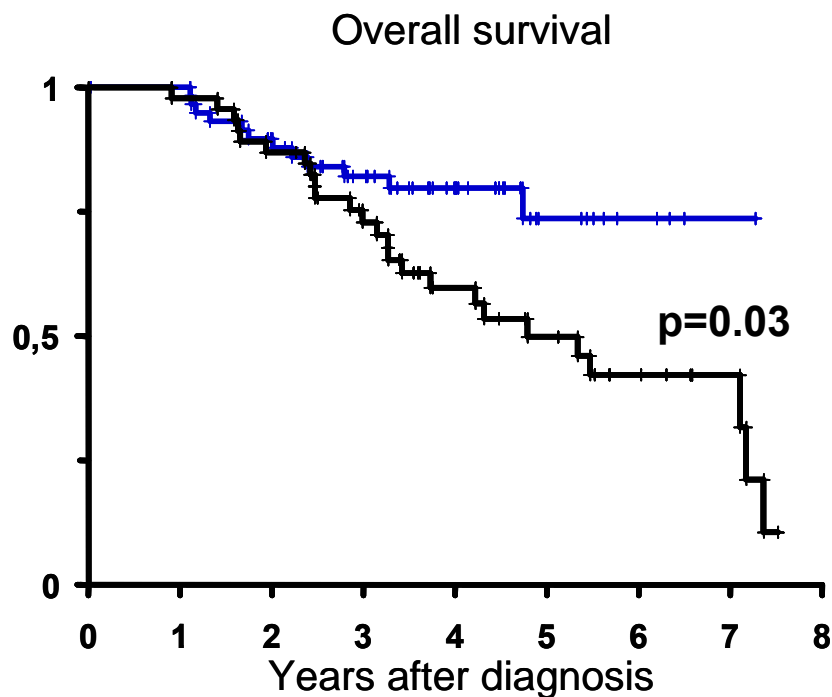


HLA-Id sibling:

YES —

NO —

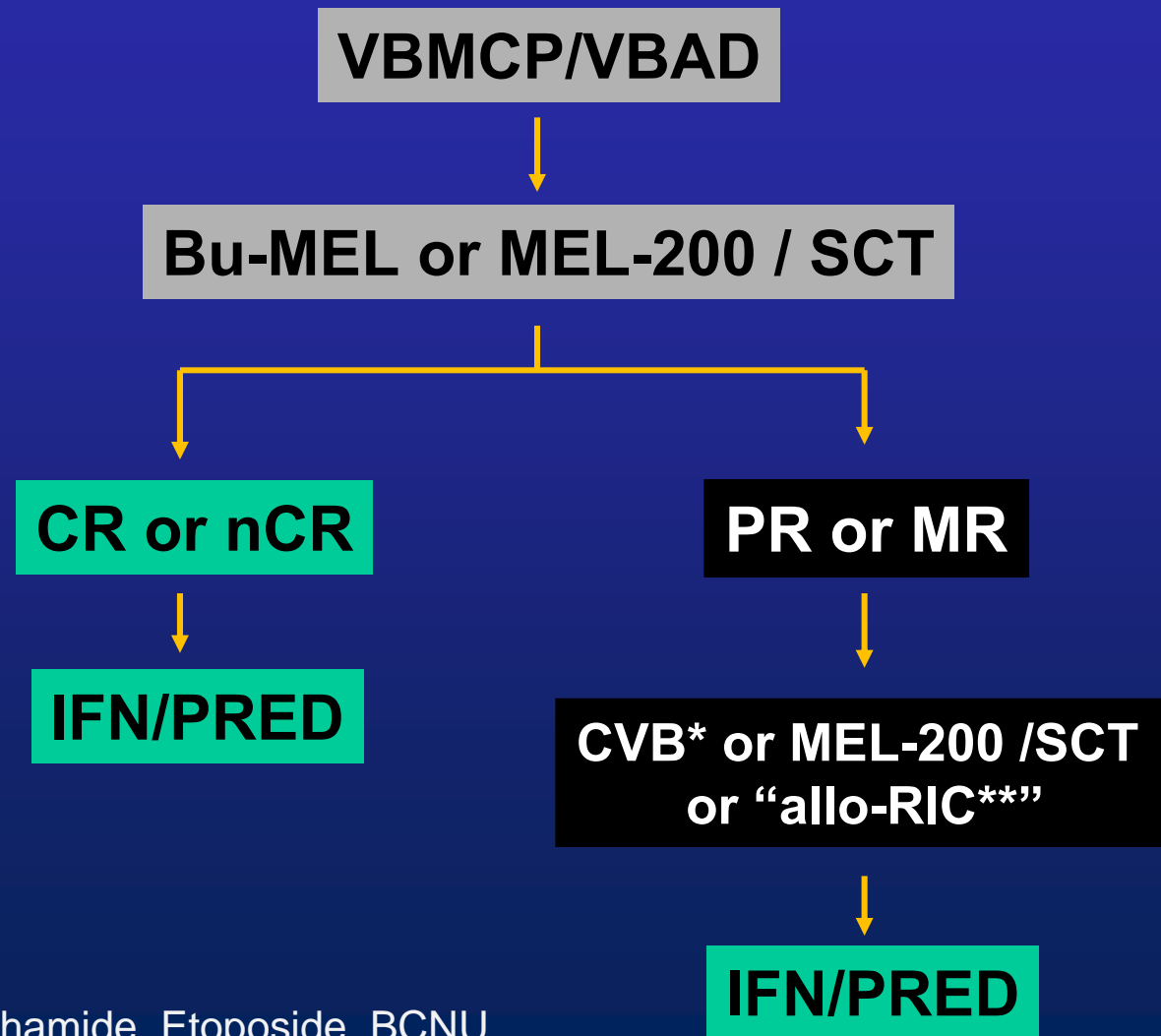
# Outcome according to completed treatment (n=104) CR: 55% vs 26% p= 0.004



Auto – Allo      n=58      —

Auto – Auto      n=46      —

# Spanish PETHEMA/GEM-2000 Trial



\*Cyclophosphamide, Etoposide, BCNU

\*\* Fludarabine/Melphalan-140

Blade ASH 2007

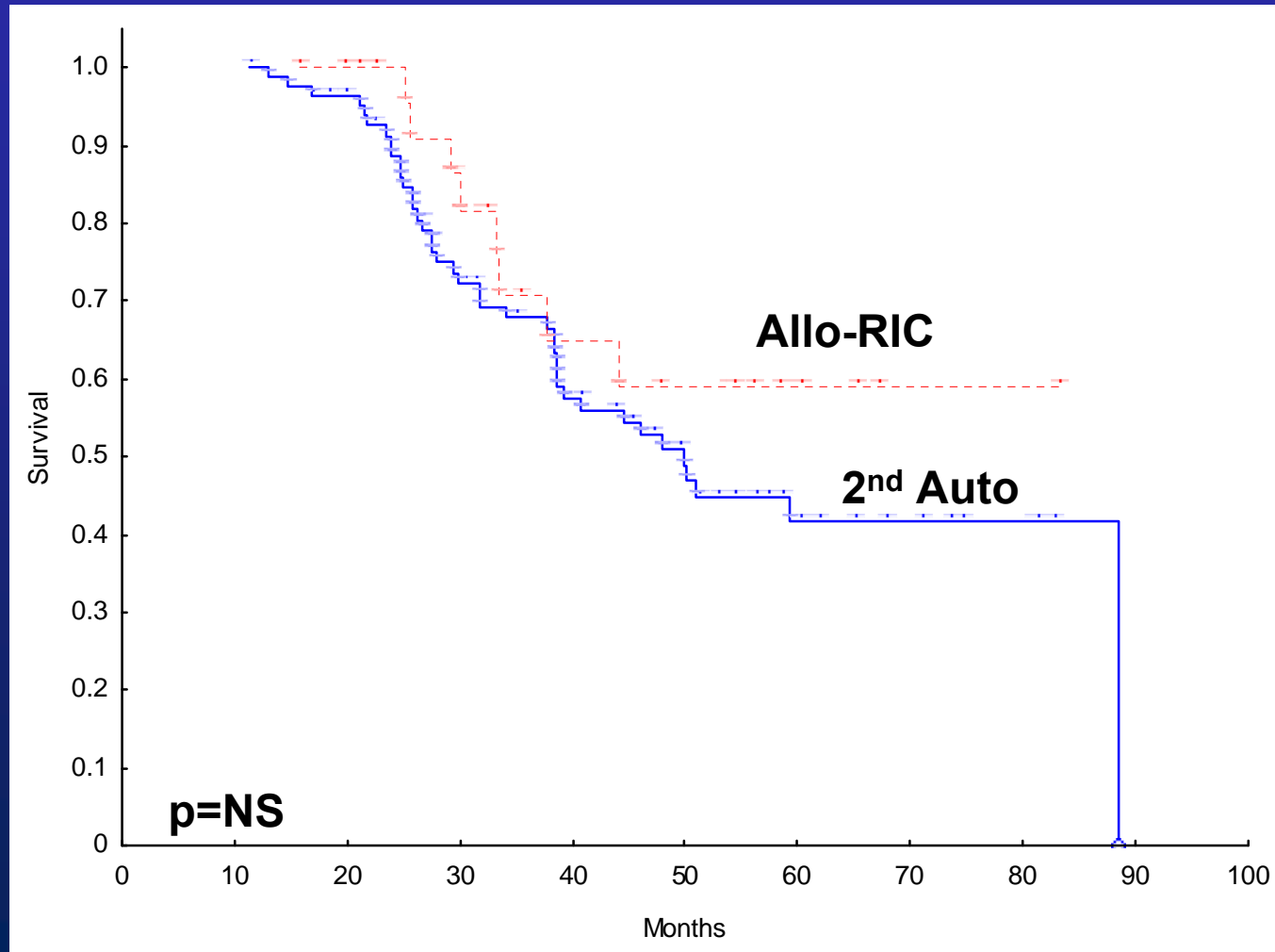
# Response Up-grading with Second HDT “Auto” vs. “Allo-RIC”

<i>Response</i>	<i>2<sup>nd</sup> Auto (n=85)</i>	<i>Allo-RIC (n=26)</i>
Non-evaluable	1 (1%)	-
CR (IF-) <sup>#</sup>	<b>9 (10%)*</b>	<b>9 (35%)*</b>
n-CR (EP-) <sup>†</sup>	7 (8%)	-
PR	8 (9%)	2 (8%)
MR	9 (10%)	2 (8%)
No change	<b>45 (53%)</b>	<b>9 (35%)</b>
Progressive disease	2 (2%)	-
TRM	<b>4 (5%)**</b>	<b>4 (15%)**</b>

\*p=0.01 \*\* p=0.08 #IF: immunofixation †: electrophoresis

# EFS

## 2nd Auto vs. Allo-RIC



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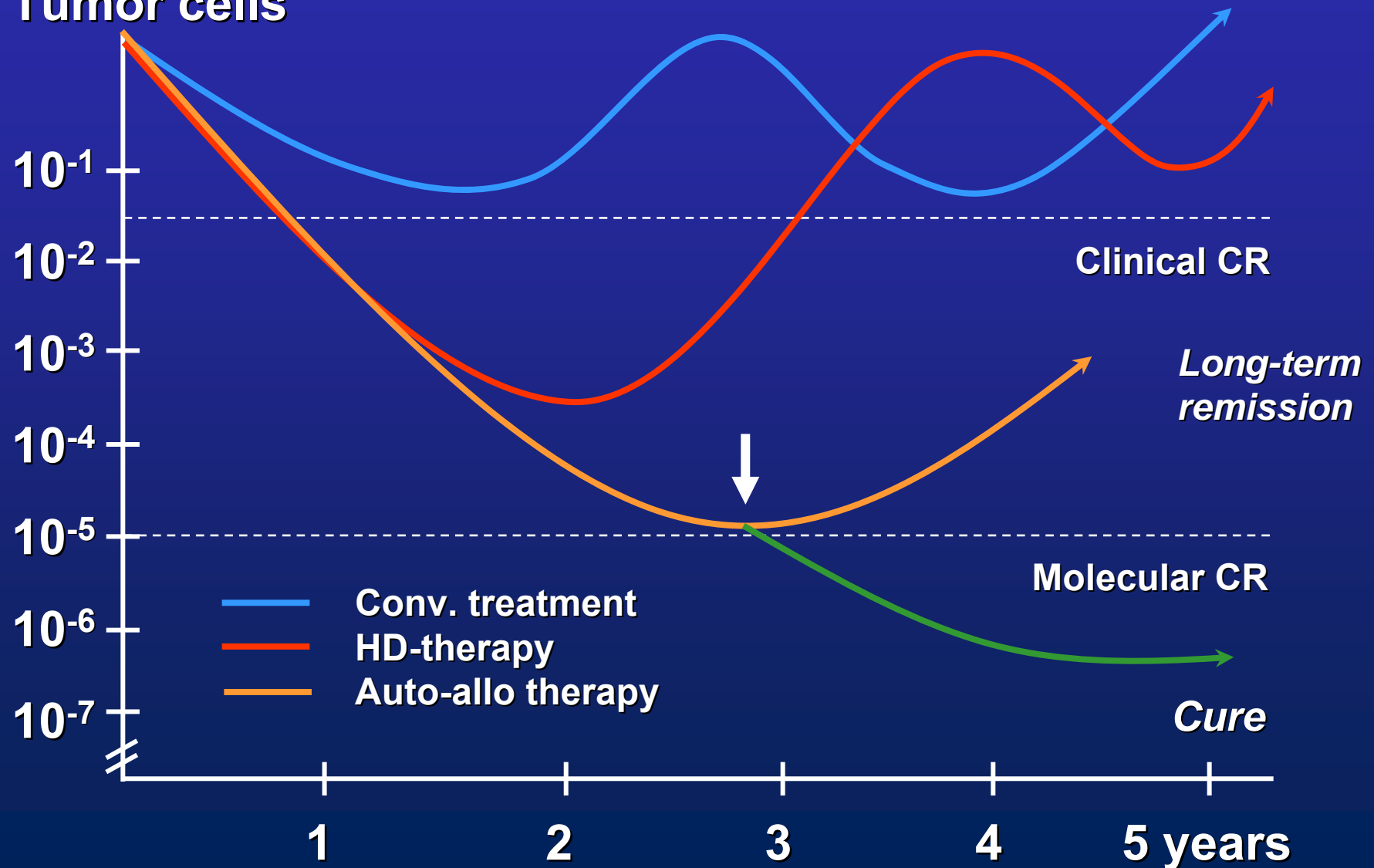
*notice:*  
patient-selection  
no prospective randomized trial

*advantage:*  
effective as standard allograft, but less TRM,  
may be better than tandem autograft

*disadvantage:*  
still high risk of relapse

# Scenario of treatment of Multiple Myeloma

Tumor cells



# Targeting residual disease after transplantation in myeloma

Induction with new agents



Cytoreduction (autologous SCT)



RIC allograft

## Platform for MRD-targeting Posttransplantat-strategies



### *Drug-based:*

- Thalidomid
- Bortezomib
- Revlimid



### *Adoptive Immunotherapy:*

- DLI: CD 8 depleted CD3+ cells
- Alloreactive NK-Cells
- Myeloma-specific CTL`s



### *Vaccination:*

- mHag
- Cancer testis antigen
- Donor vaccination (idiotypic)

# Donor lymphocyte infusion in combination with novel agents

## *Treatment plan*

Thalidomide 100 mg

↓ 14 days

DLI:  $1 \times 10^6$  CD3+/kg (MUD)  
or:  $5 \times 10^6$  CD3+/kg (related)

No response:

escalating Thalidomide (200 → 300 → 400 mg)

And/or: further DLI

# Thalidomide and DLI

## *Response rate*

<b>CR:</b>	<b>6/18</b>	<b>33%</b>	}	<b>67% (ORR)</b>
<b>PR:</b>	<b>4/18</b>	<b>22%</b>		
<b>MR:</b>	<b>2/18</b>	<b>12%</b>		
<b>SD/NC:</b>	<b>5/18</b>	<b>28%</b>		
<b>PD:</b>	<b>1/18</b>	<b>5%</b>		

**Med. time to response: 108 days (36 – 266)**

# Thalidomide and DLI

	after SCT	after DLI	after Thal/DLI
<b>No. of patients</b>	<b>18</b>	<b>11</b>	<b>18</b>
<b>acute GvHD I-IV</b>	<b>10 (55%)</b>	<b>5 (46%)</b>	<b>2 (11%)</b>
<b>acute GvHD II-IV</b>	<b>4 (22%)</b>	<b>3 (27%)</b>	<b>0</b>
<b>chr.GvHD lim</b>	<b>4 (22%)</b>	<b>4 (36%)</b>	<b>7 (39%)</b>
<b>chr.GvHD ext</b>	<b>1 (6%)</b>	<b>0</b>	<b>0</b>

# Post-allo Transplant Strategies

		<i>ORR</i>	<i>CR</i>
1.	Donor lymphocyte infusion	40 - 67 %	19 - 30 %
2.	CD8-depleted donor-lymphocyte infusion	71 %	43 %
3.	Thalidomide	29 - 83 %	0 - 22 %
4.	Bortezomib	80 - 100 %	29 - 30 %
5.	Interferon- $\alpha$	80 %	80 %
6.	Thalidomide plus donor-lymphocyte infusion	67 %	22 %
7.	Donor vaccination		3 out of 5 after allograft

*Data from Lokhorst 2004; Salama 2000; Ayuk 2004; Byrne 1998; Kröger 2004, 2004; Bruno 2006; Neelapu 2005; Alyea 2001*

**Multiple Myeloma  
Age  $\leq$  55 y, Stage II/III**

**Induction  
chemotherapy  
max. 8 cycles  
(new agents)**

**Registration**

**CD34+ cell harvesting  
+ Donorsearch (Sibling  
and MUD)**

**Melphalan 200 mg/m<sup>2</sup>  
+ auto PBSC**

**Donor available**

**Melphalan 140 mg/m<sup>2</sup>  
/Fludarabin/ ATG (MUD)  
+ allo PBSC**

**Thalidomide 100 mg until  
Rel/PD,  
max. 2 years + DLI**

**no donor**

**Melphalan 200 mg/m<sup>2</sup>  
+ auto PBSC**

**Thalidomide 100 mg until  
Rel/PD,  
max. 2 years**

**\*9/10 Allele**

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