

Universitätsklinikum
Hamburg-Eppendorf

Chemotherapie vs. KMT beim Multiplen Myelom

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**Ist das Multiple Myelom
eine heilbare Erkrankung?**

TOTAL THERAPY CONCEPT IN MM

ADOPTED FROM ST JUDE APPROACH TO
CHILDHOOD ALL

IMPLIES UP-FRONT USE OF ALL KNOWN ACTIVE
AGENTS AND MODALITIES TOWARD CURE

MEL200 MTD – “TANDEM TRANSPLANT” LOGICAL
STEP TOWARD RAISING CR FROM <5% WITH MP
TO 50%?

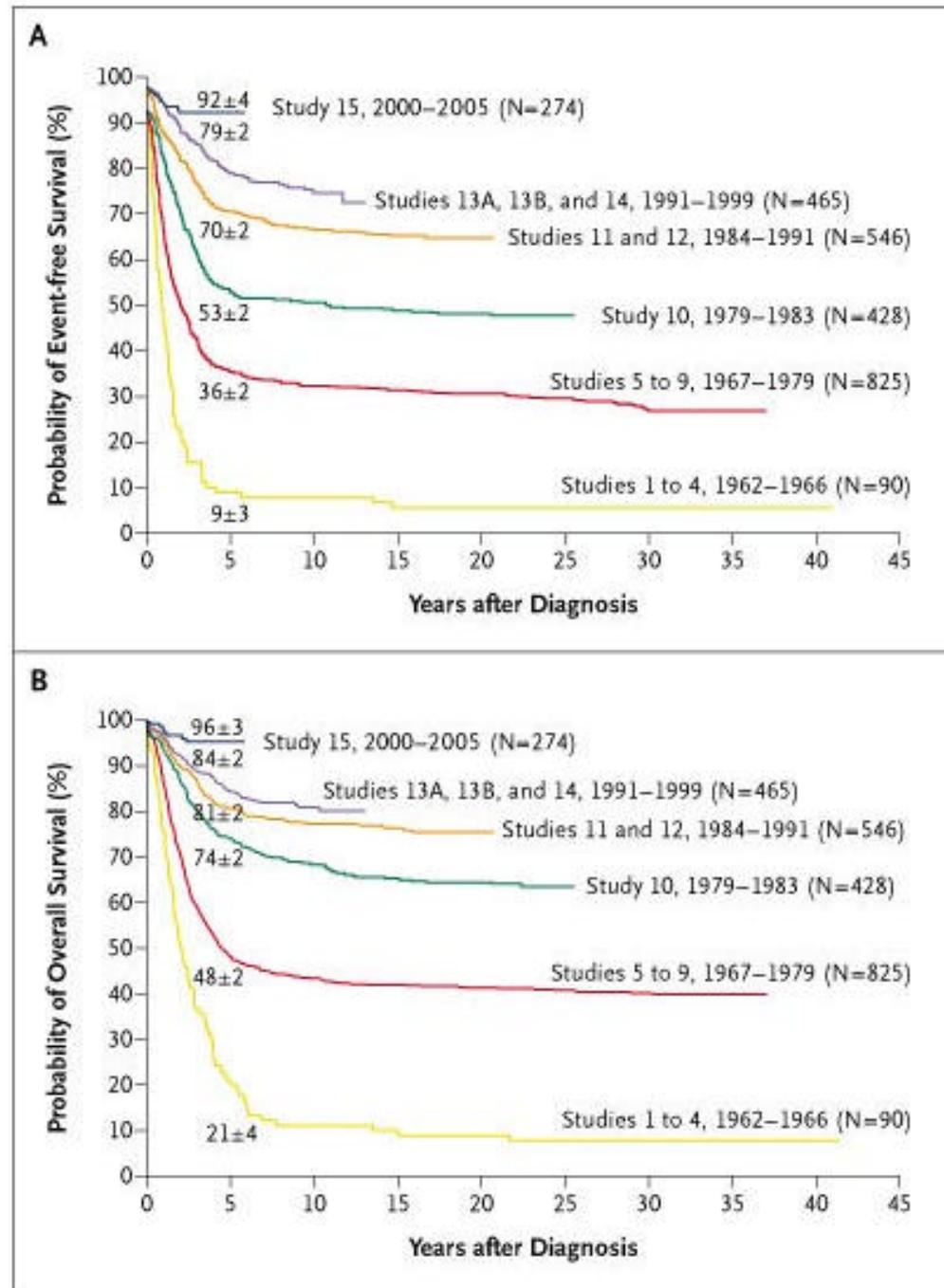
2628 CHILDREN WITH NEWLY DIAGNOSED ALL

Event-free Survival (Panel A)

A SUCCESS STORY PAR EXCELLENCE

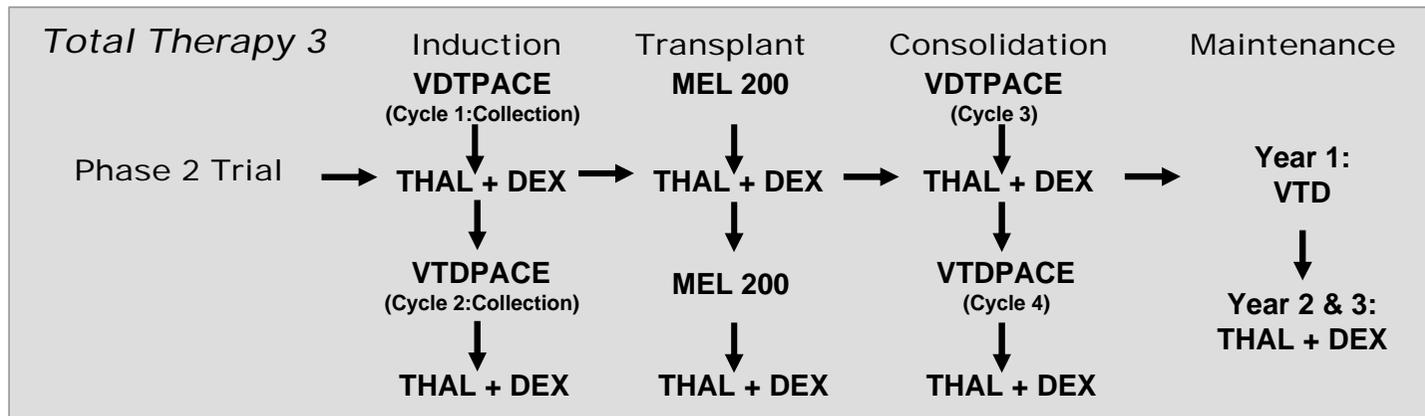
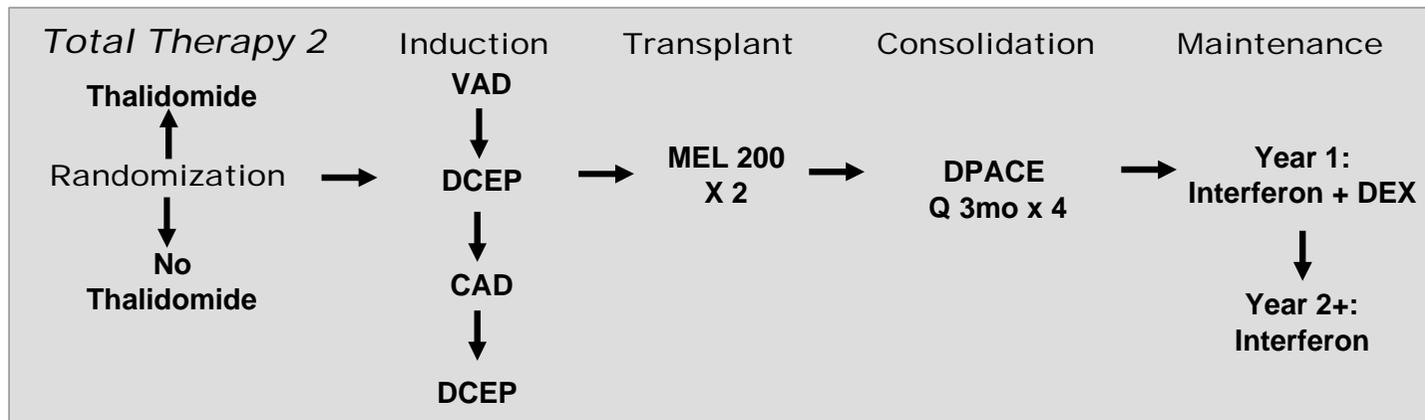
Overall Survival (Panel B)

Pui C-H and Evans E:
Treatment of acute lymphoblastic leukemia.
N Engl J Med 2006;354;166-178

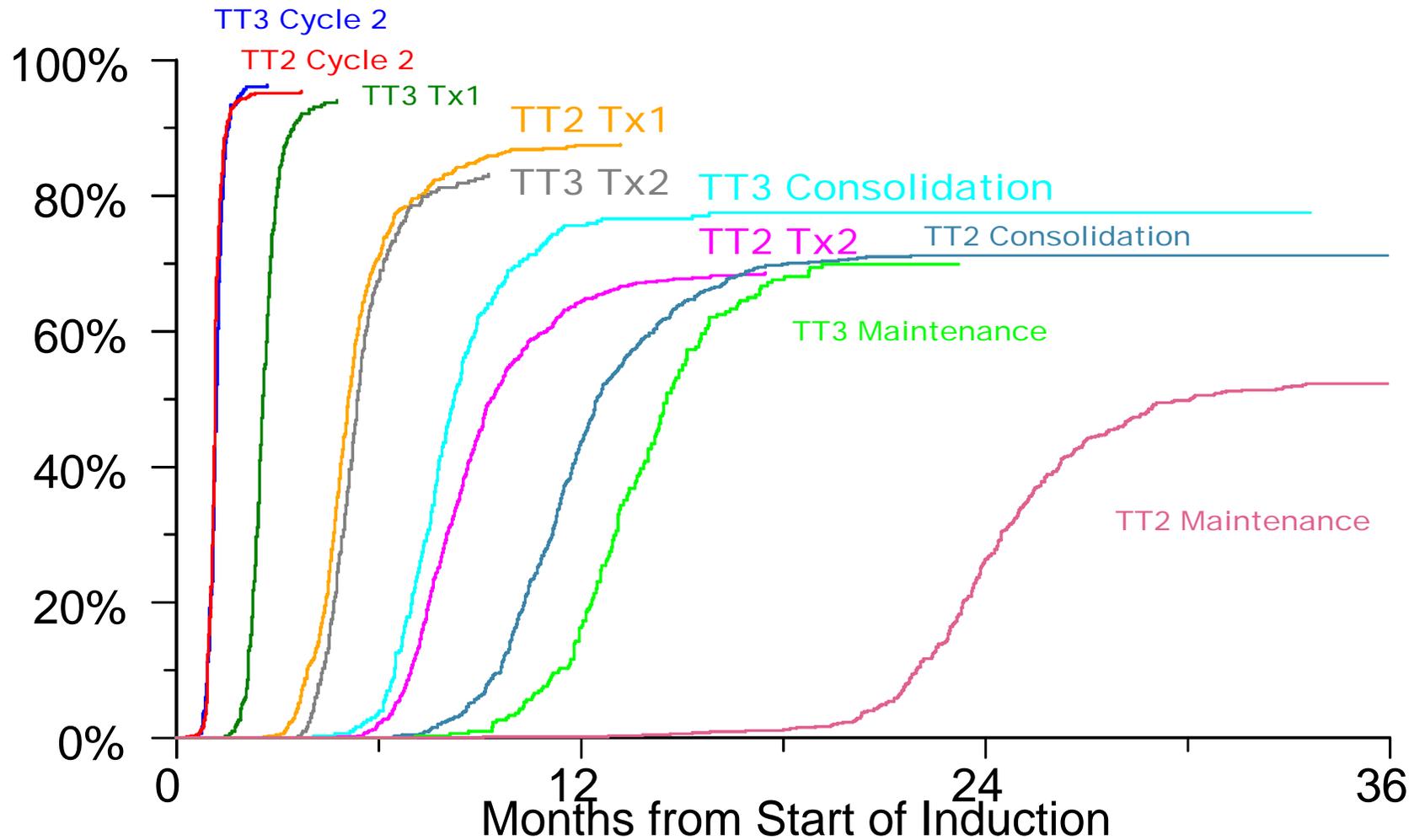


TREATMENT SCHEMA: TT3 V TT2

TT3: ADDED BORTEZOMIB & SHORTENED BOTH INDUCTION AND CONSOLIDATION

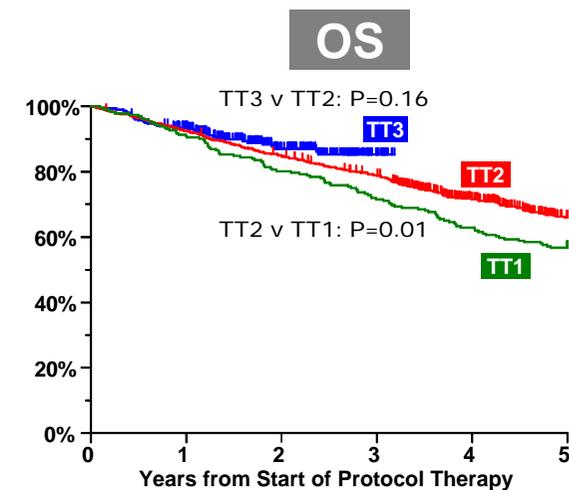
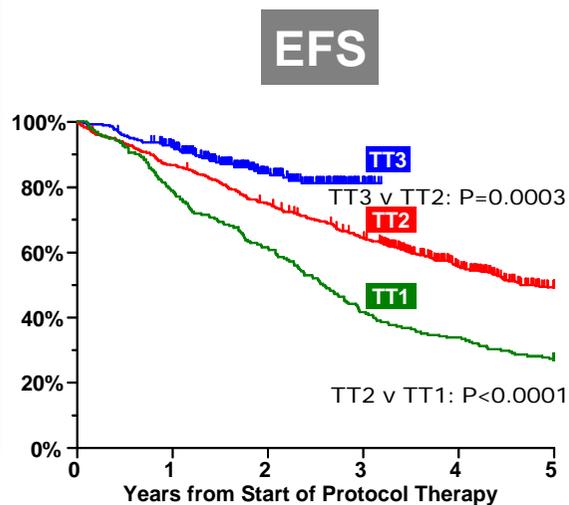
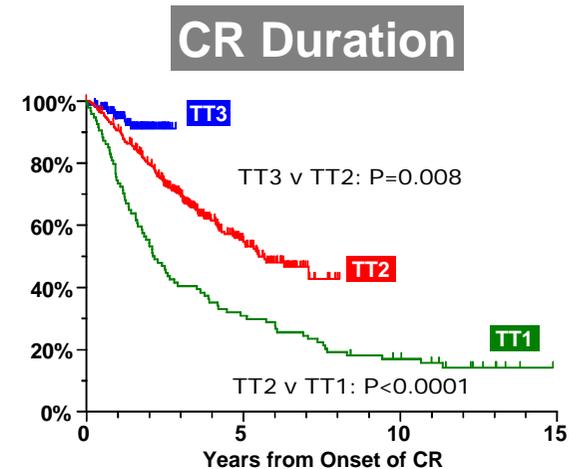
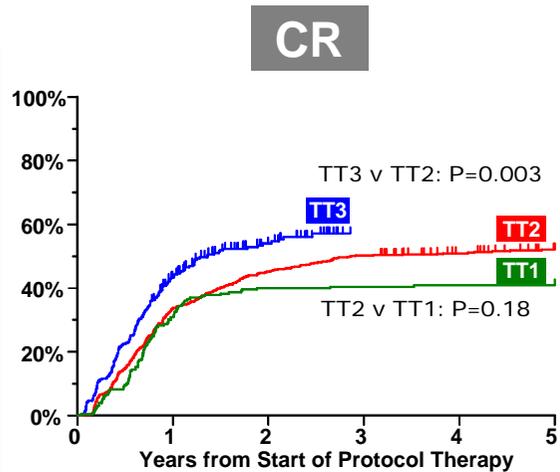


FASTER PROGRESSION THROUGH TREATMENT STEPS IN TT3 v TT2



TOTAL THERAPIES 1, 2, 3: STEADY IMPROVEMENT IN OUTCOMES BY BUILDING ON MEL200 TANDEM Tx BACKBONE

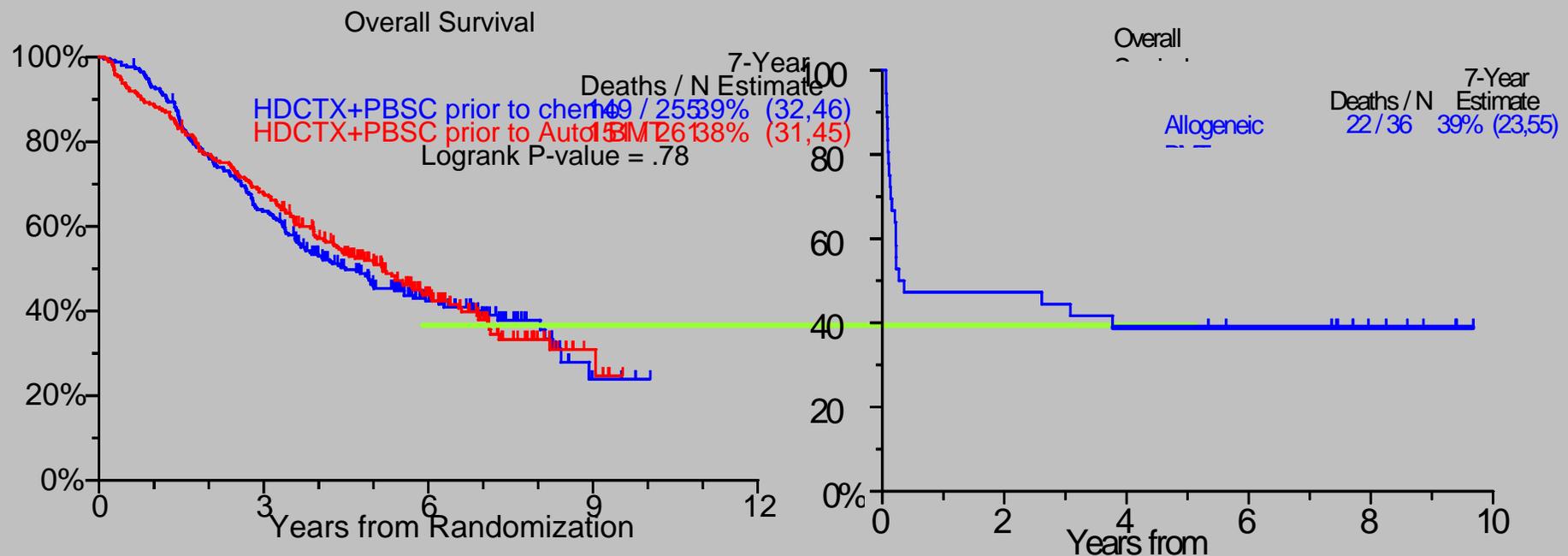
	TT1 N=231	TT2 N=668	TT3 N=303
Median mos of follow-up	12yr	5yr	2.5yr
Age >65 yr	9%	20%	28%
Abnormal Cytogenetics	32%	30%	33%
Completed Tx #1	84%	85%	94%
Completed Tx #2	71%	67%	83%



Autograft versus ablative allograft SWOG 9321

*Autologous SCT and
Conventional CT*

Allogeneic



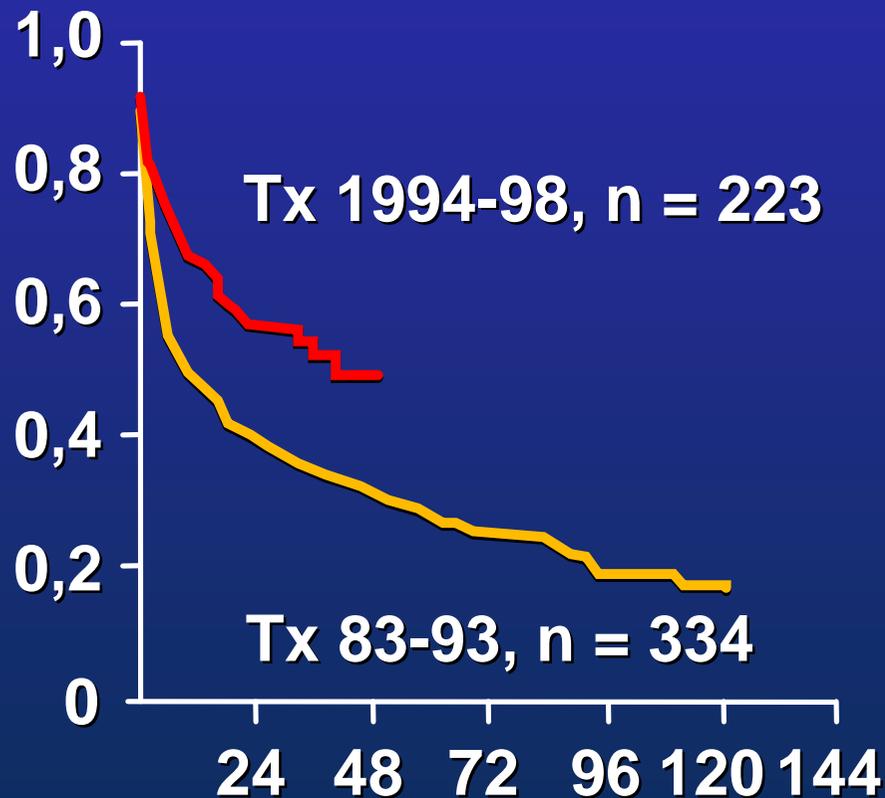
EBMT-Study

autologous vs allogeneic SCT

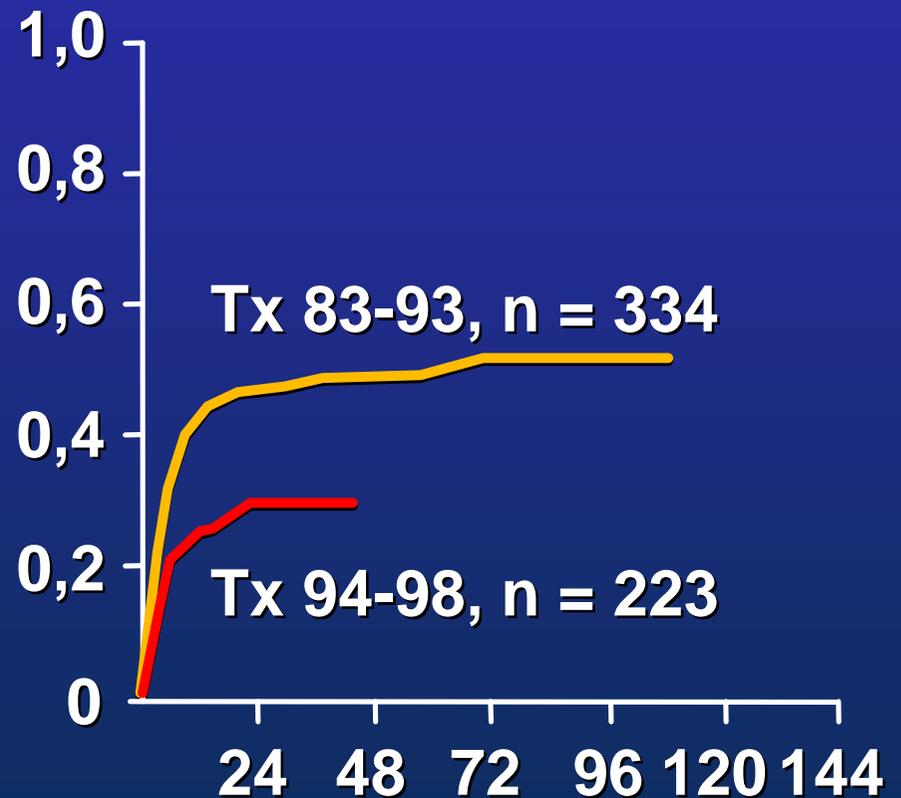
	Allo	Auto	p-value
TRM	41%	13%	p<0.001
Relapse (4 y.)	50%	70%	p=0.04

Allogeneic Transplantation

Survival

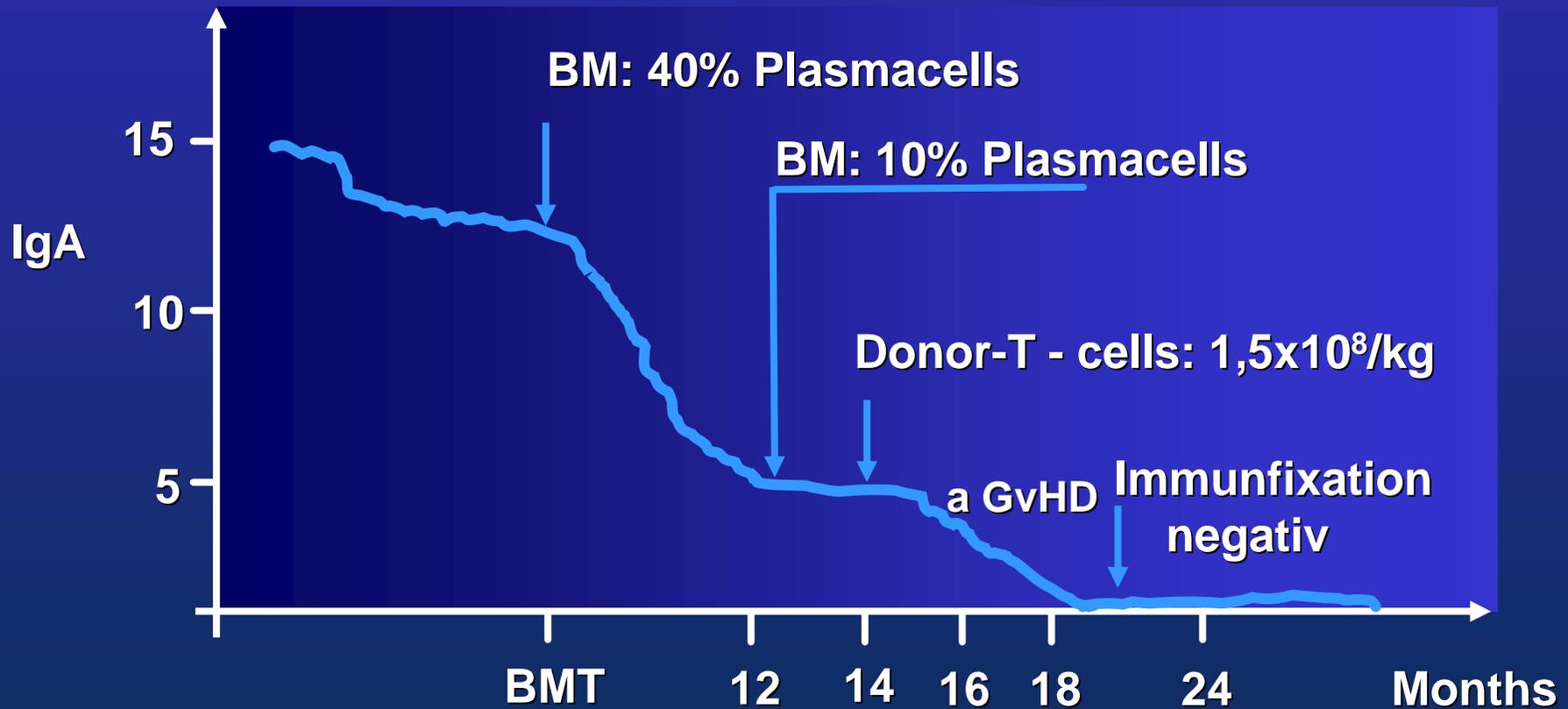


Mortality



Months after transplantation

Graft versus myeloma-effect



Reduction of treatment related mortality from allogeneic SCT

Standard-Allograft

High-dose
chemotherapy

+

Allogeneic
Immunotherapy

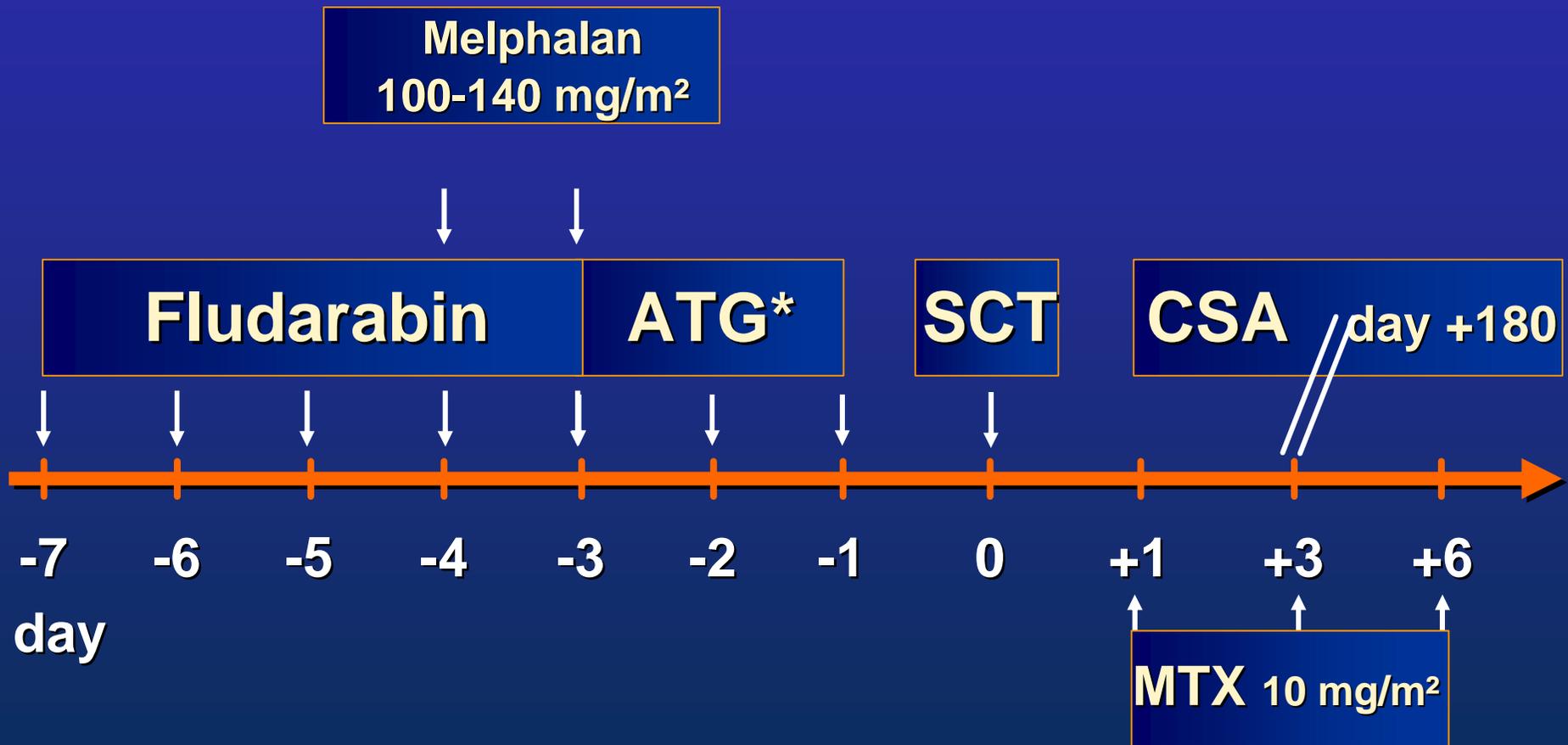
Autologous
SCT

2 - 3
Months

Allogeneic SCT
after reduced
intensity
conditioning

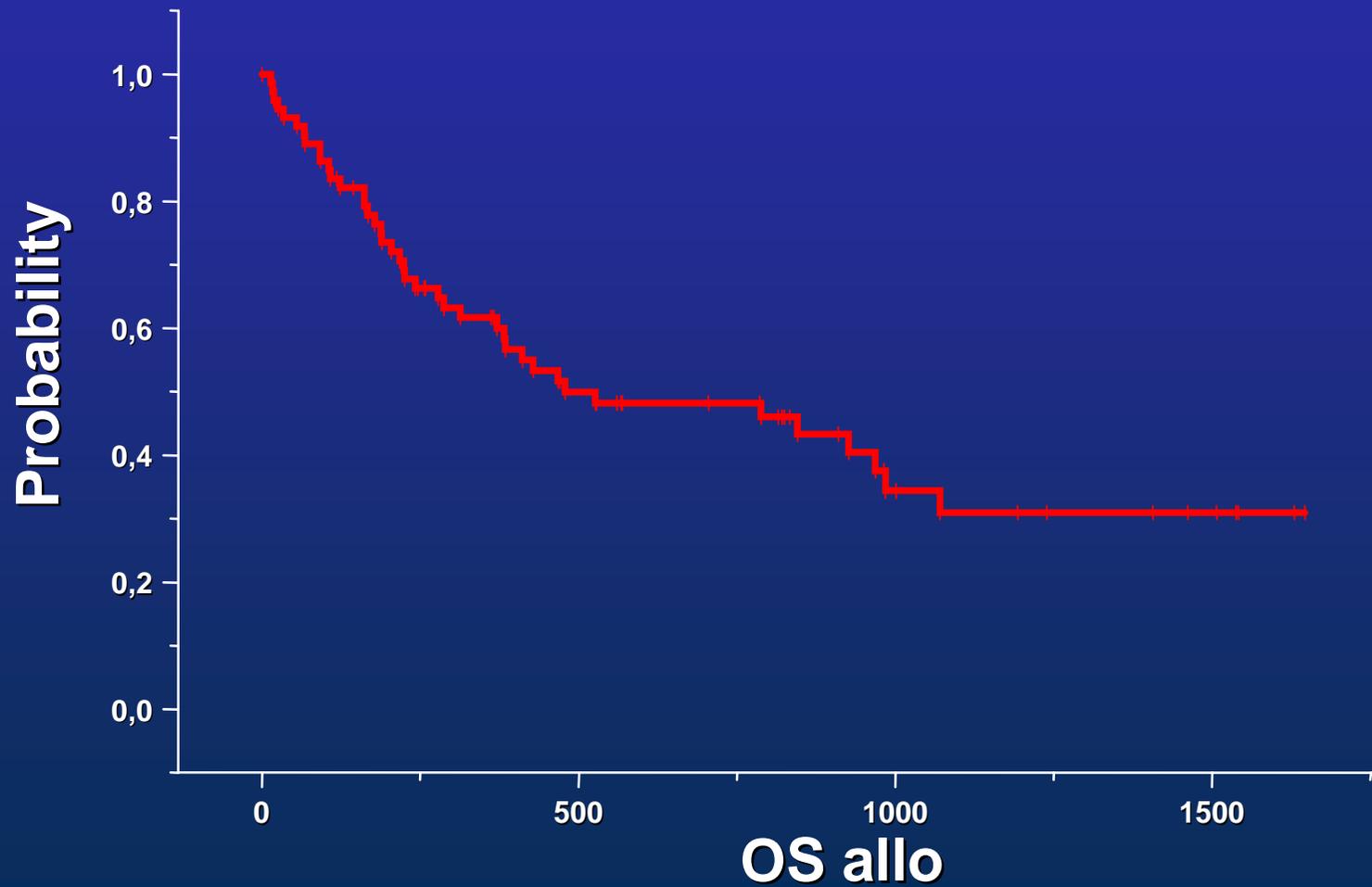
Adoptive
Immunotherapy
(DLI)

Dose-reduced Melphalan/Fludarabine in Multiple Myeloma

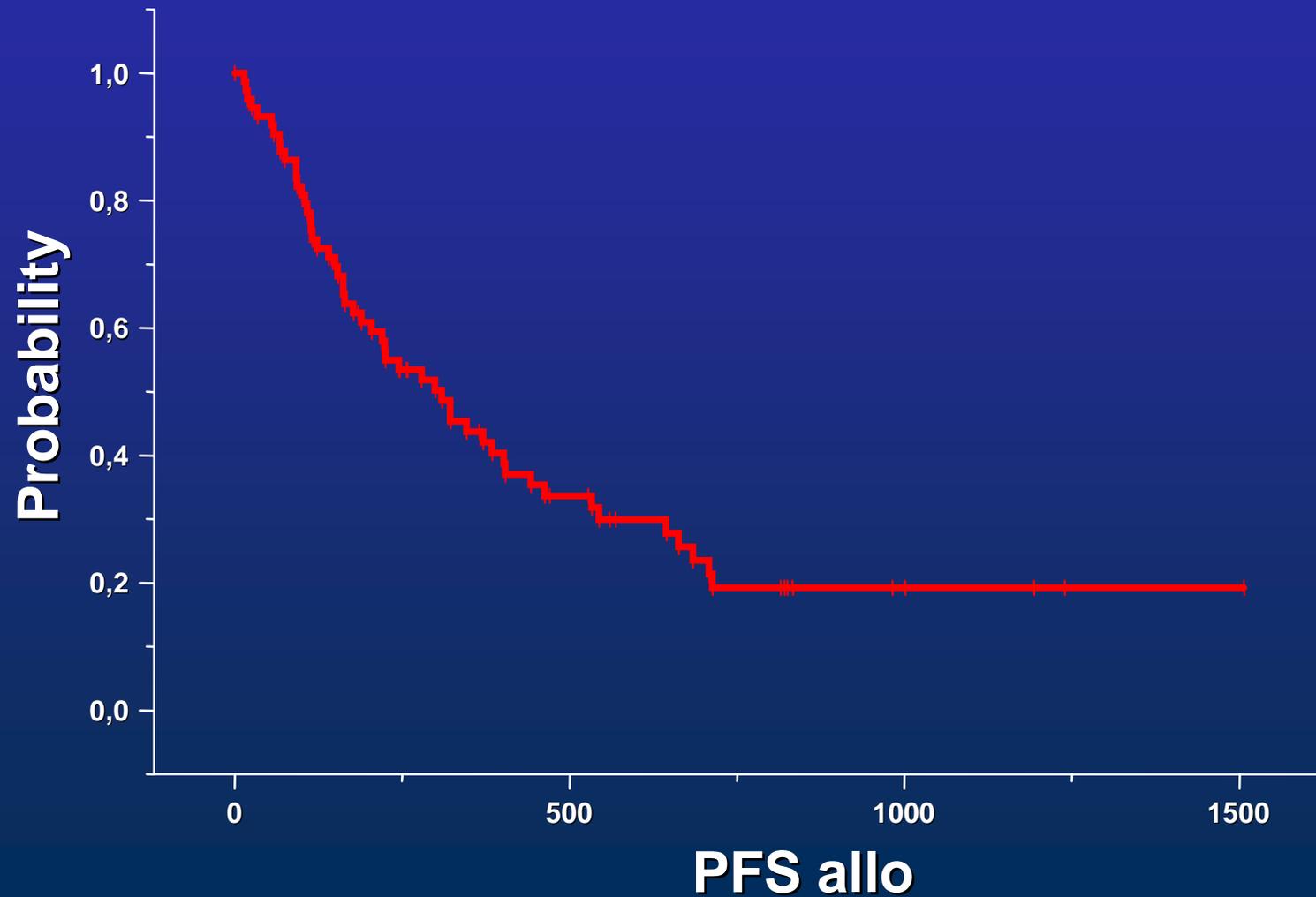


**optional in MRD*

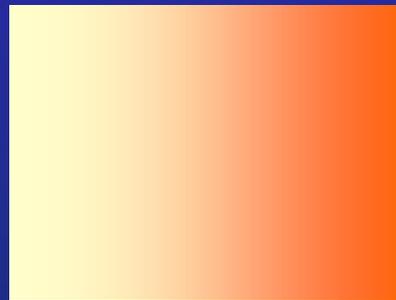
Allogeneic SCT as salvage therapy after failure to an autograft



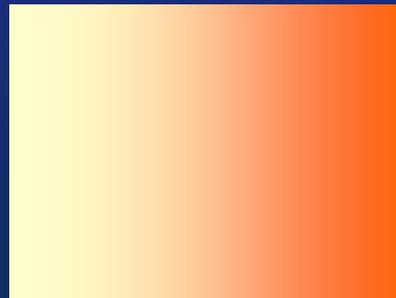
Allogeneic SCT as salvage therapy after failure to an autograft



Dose-reduced Melphalan/Fludarabin in Multiple Myeloma



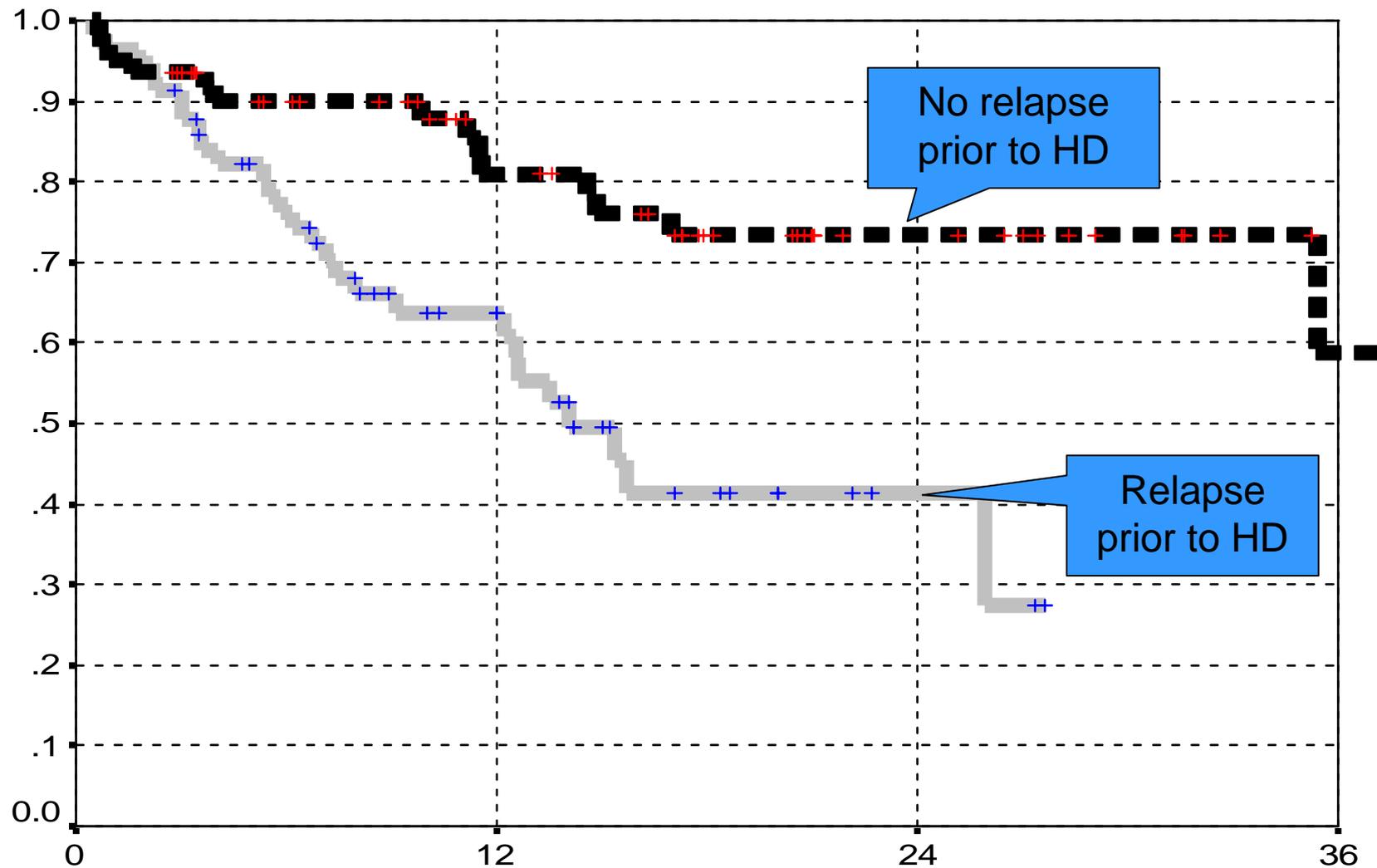
Strategy



1. Salvage therapy: For patients with relapse to autograft (n = 73)

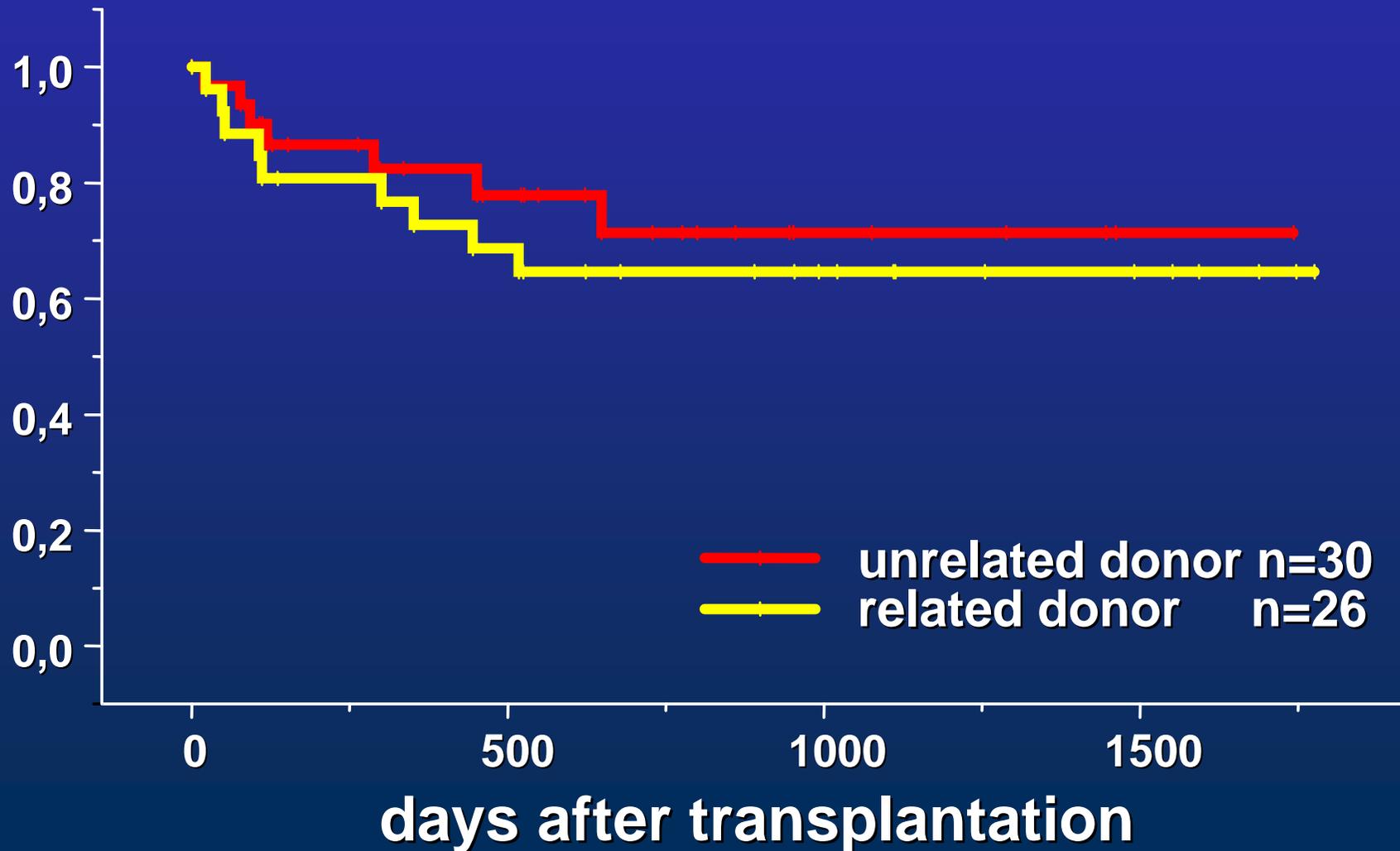
2. Auto-allo tandem approach mainly for newly diagnosed pts (n = 57)

Prognostic factor for allografting after melphalan/fludarabine: Overall survival



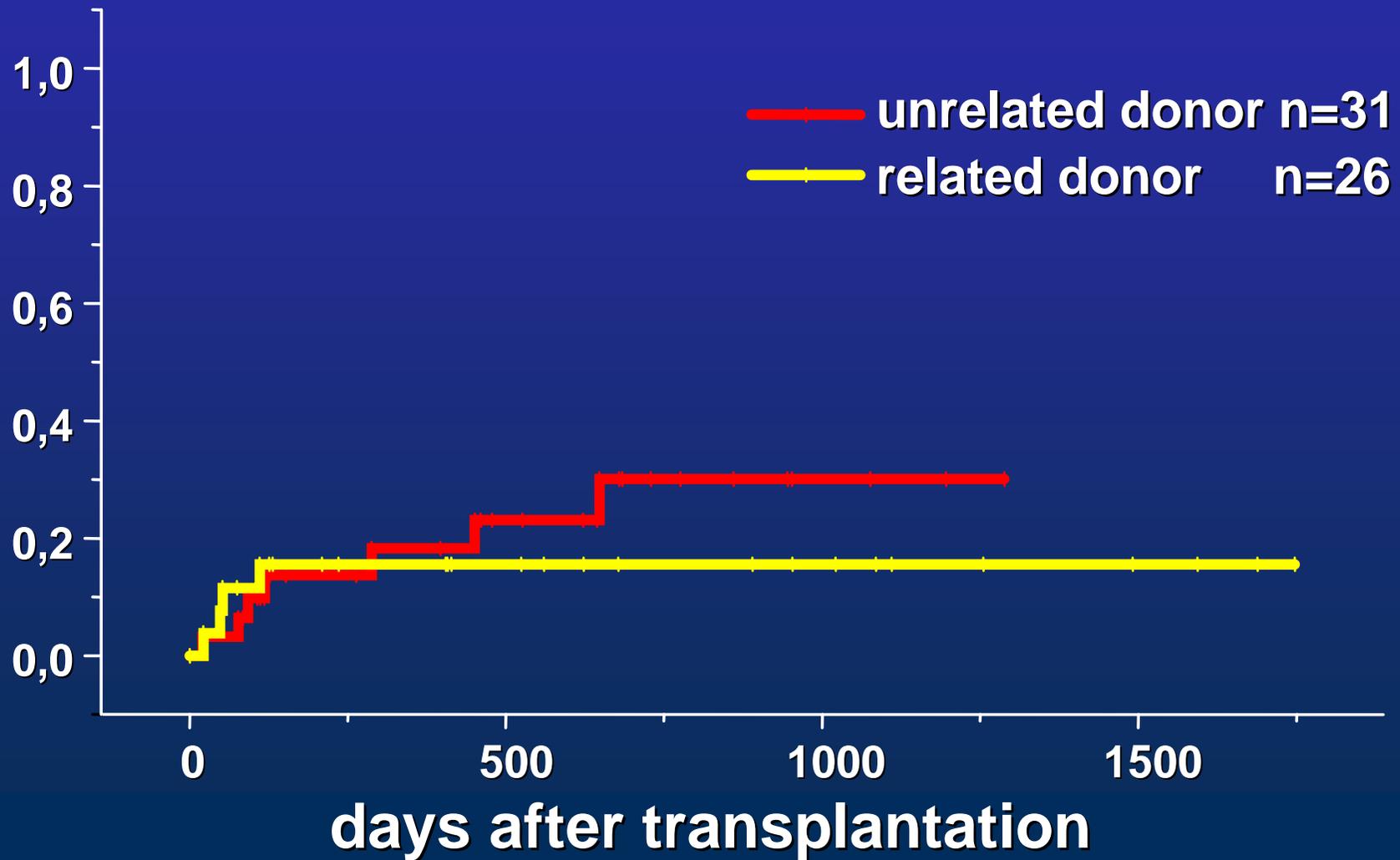
Update auto-allo tandem transplantation

probability of overall survival



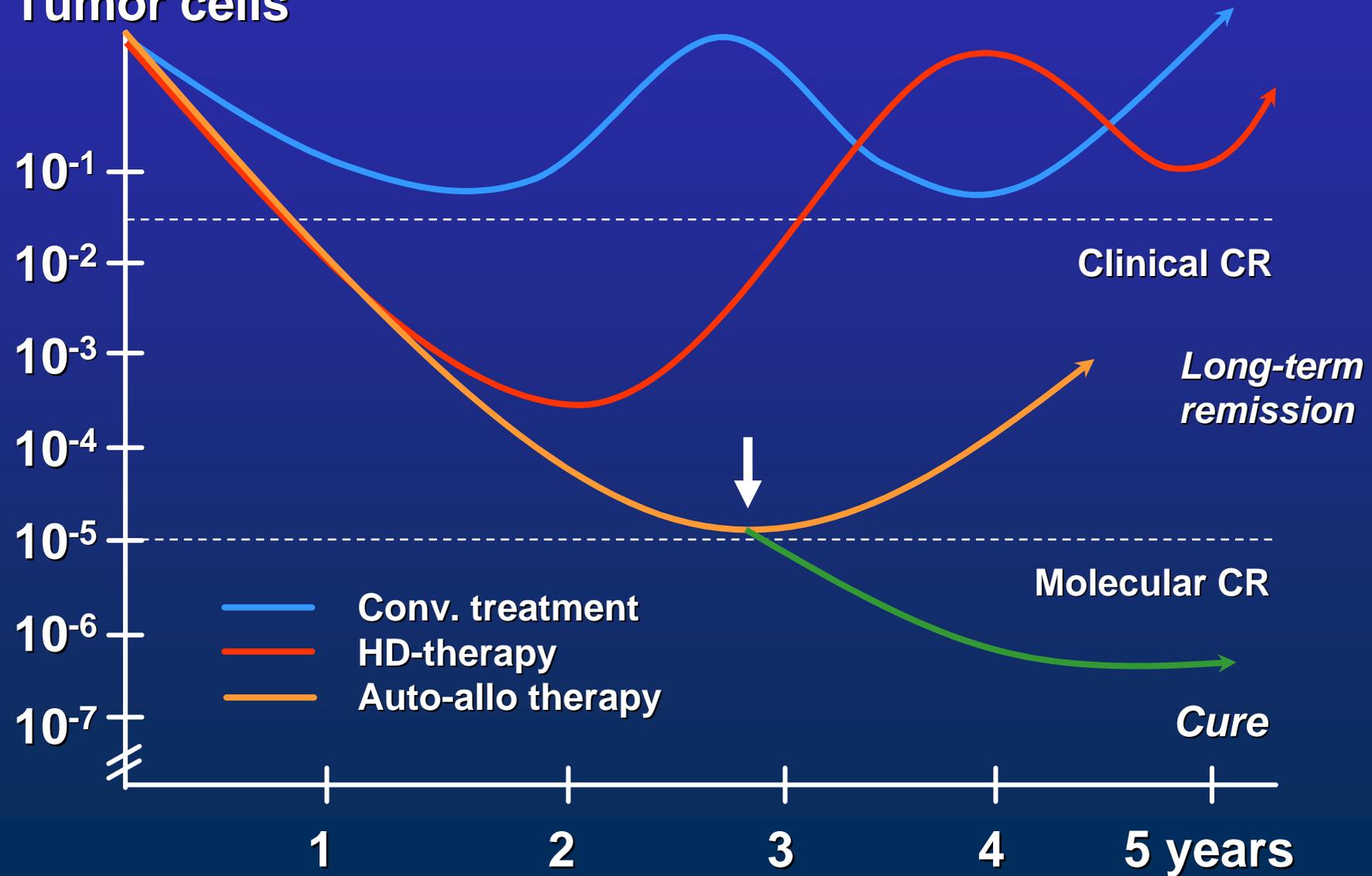
Treatment-related mortality

transplant-related mortality



Szenario of treatment of Multiple Myeloma

Tumor cells



Post Transplant Strategies

1. Thalidomid +/- DLI
2. Velcade
3. Revlimid

Chromosomal abnormalities and survival

Poor risk factors

Del(13)

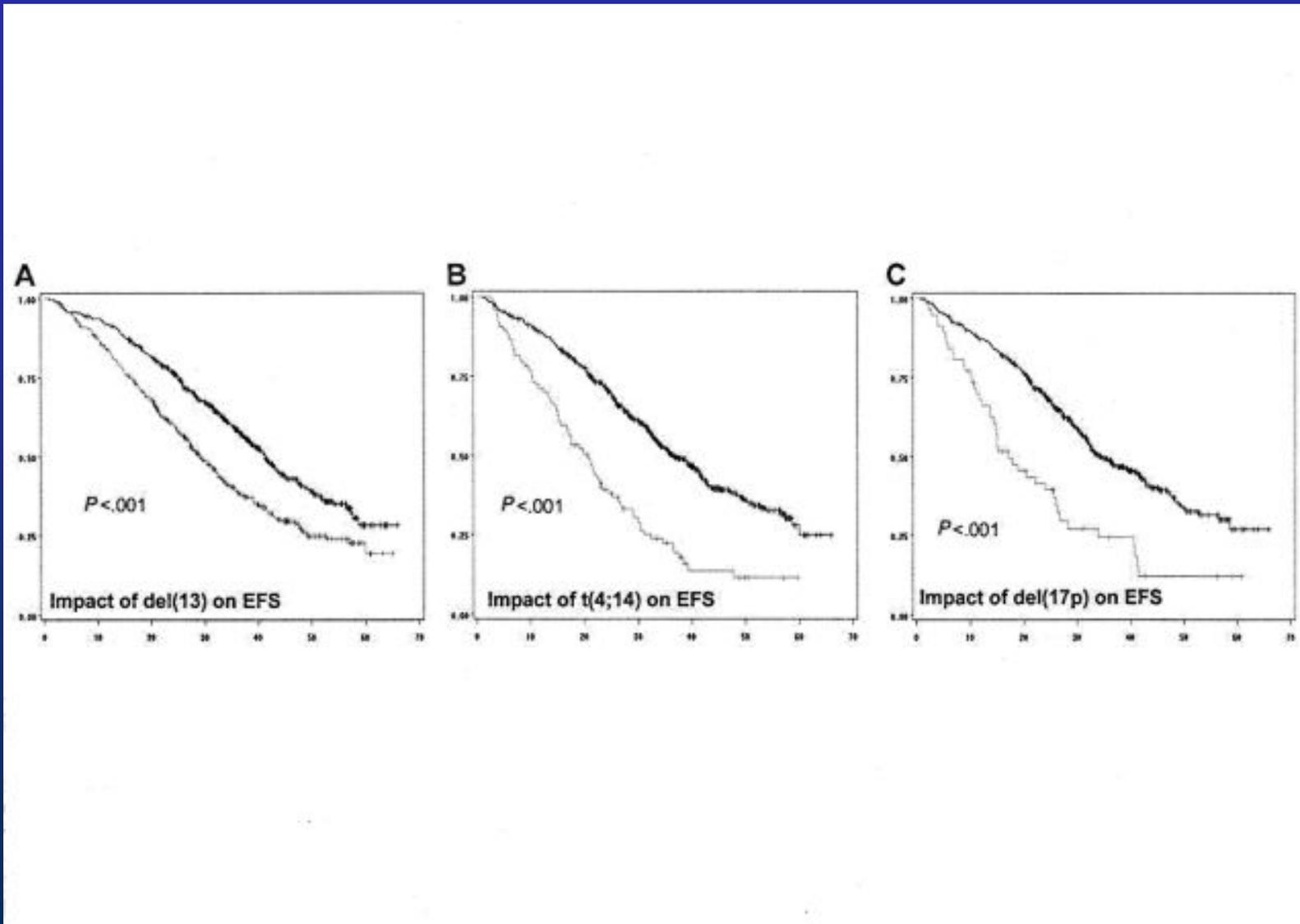
t(4;14)

hyperdiploidy

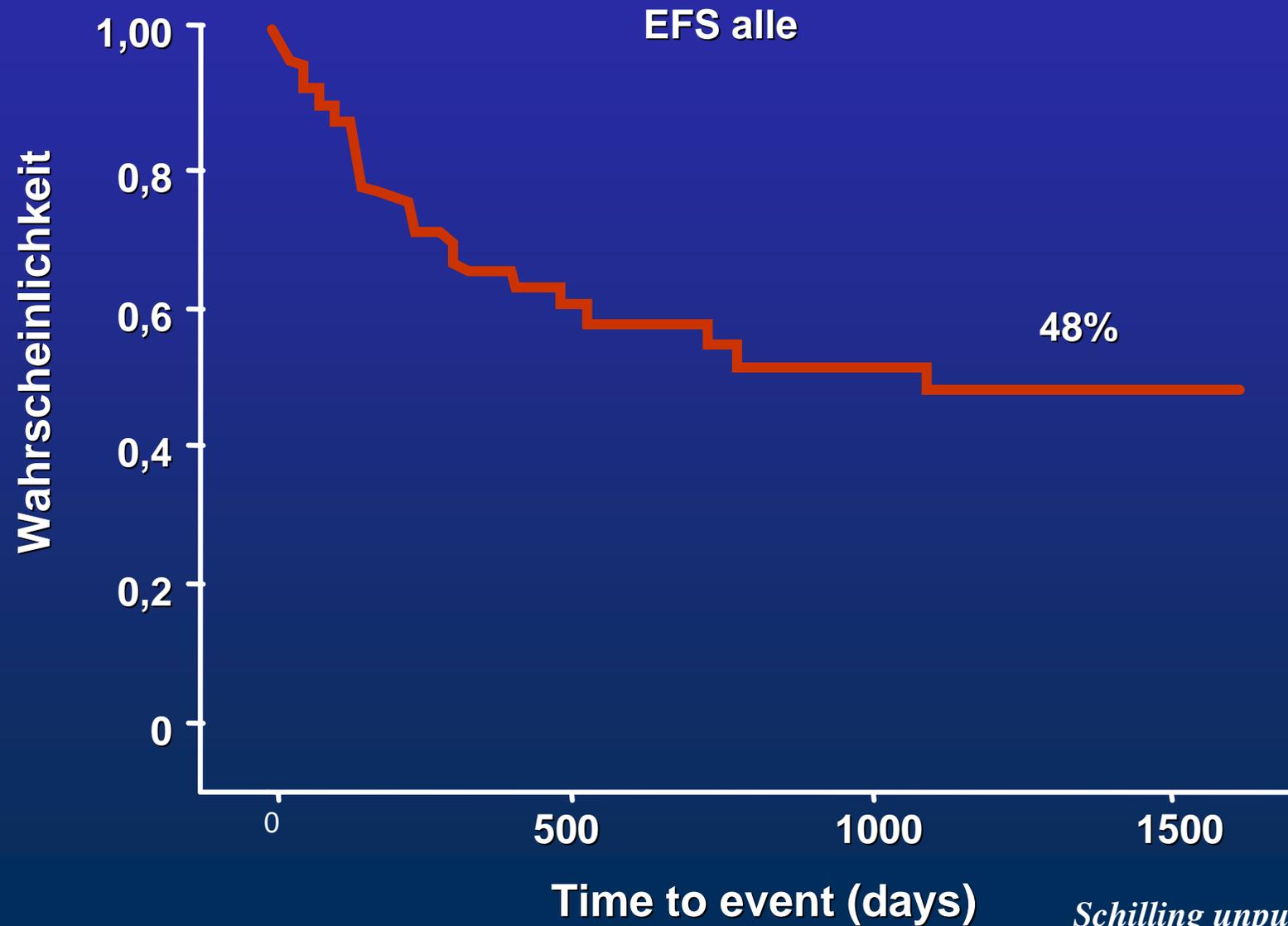
del(17p)

Avet-Loiseau et al. Blood.2007;109:3489

Chromosomal abnormalities and EFS

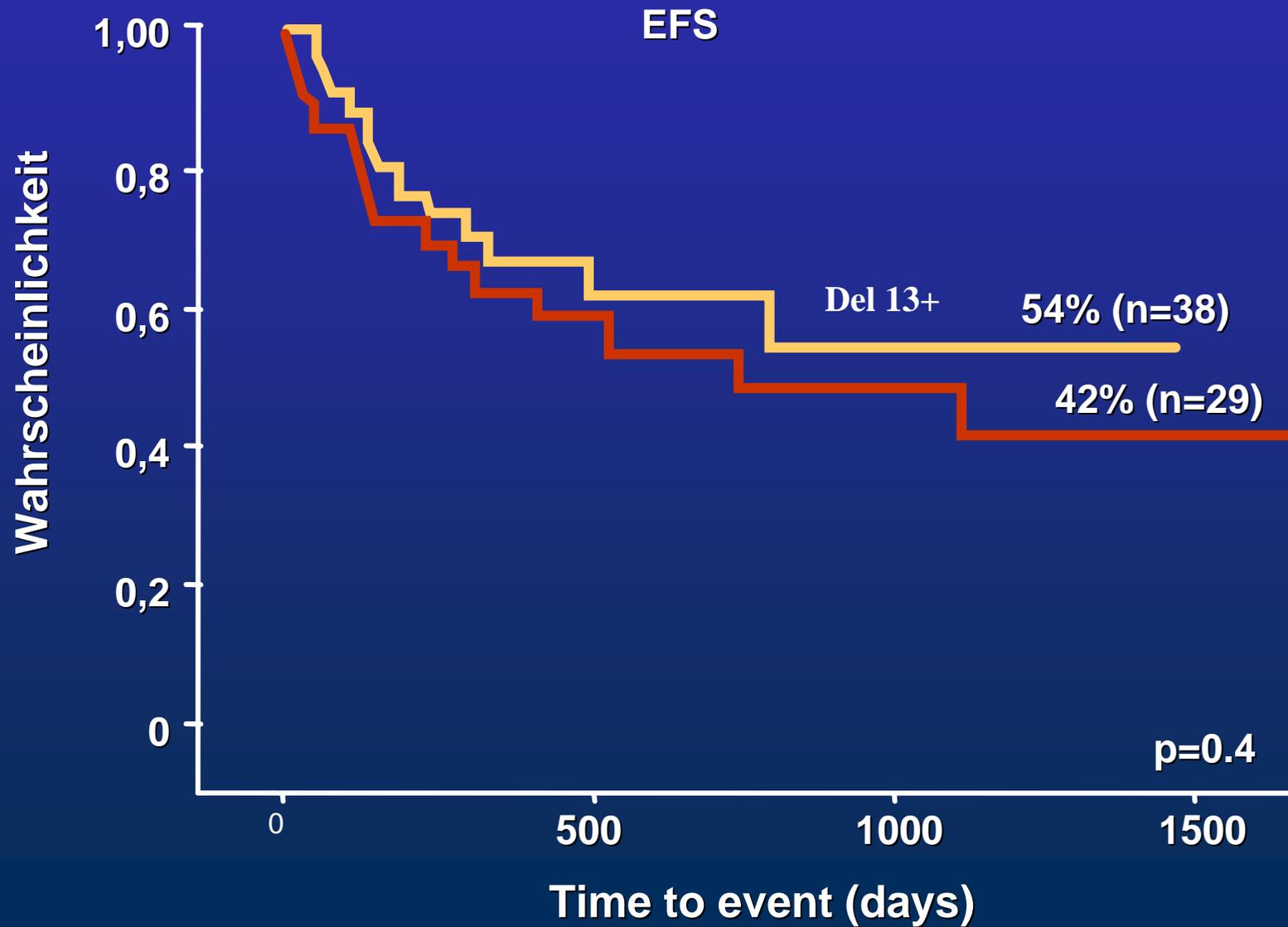


FISH Study allo Myelom: n=64

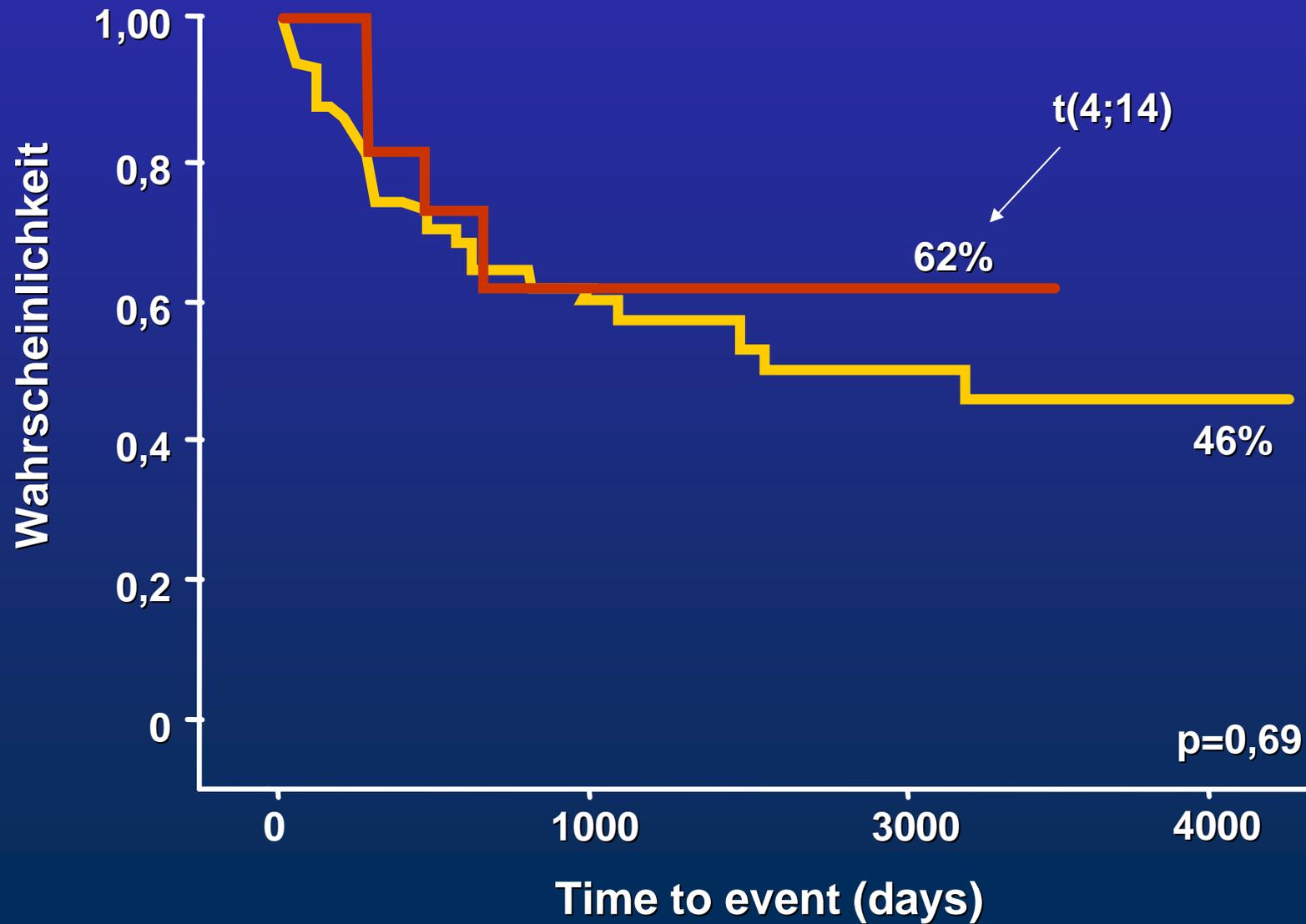


Schilling unpublished data

Del 13q14 (n=38)

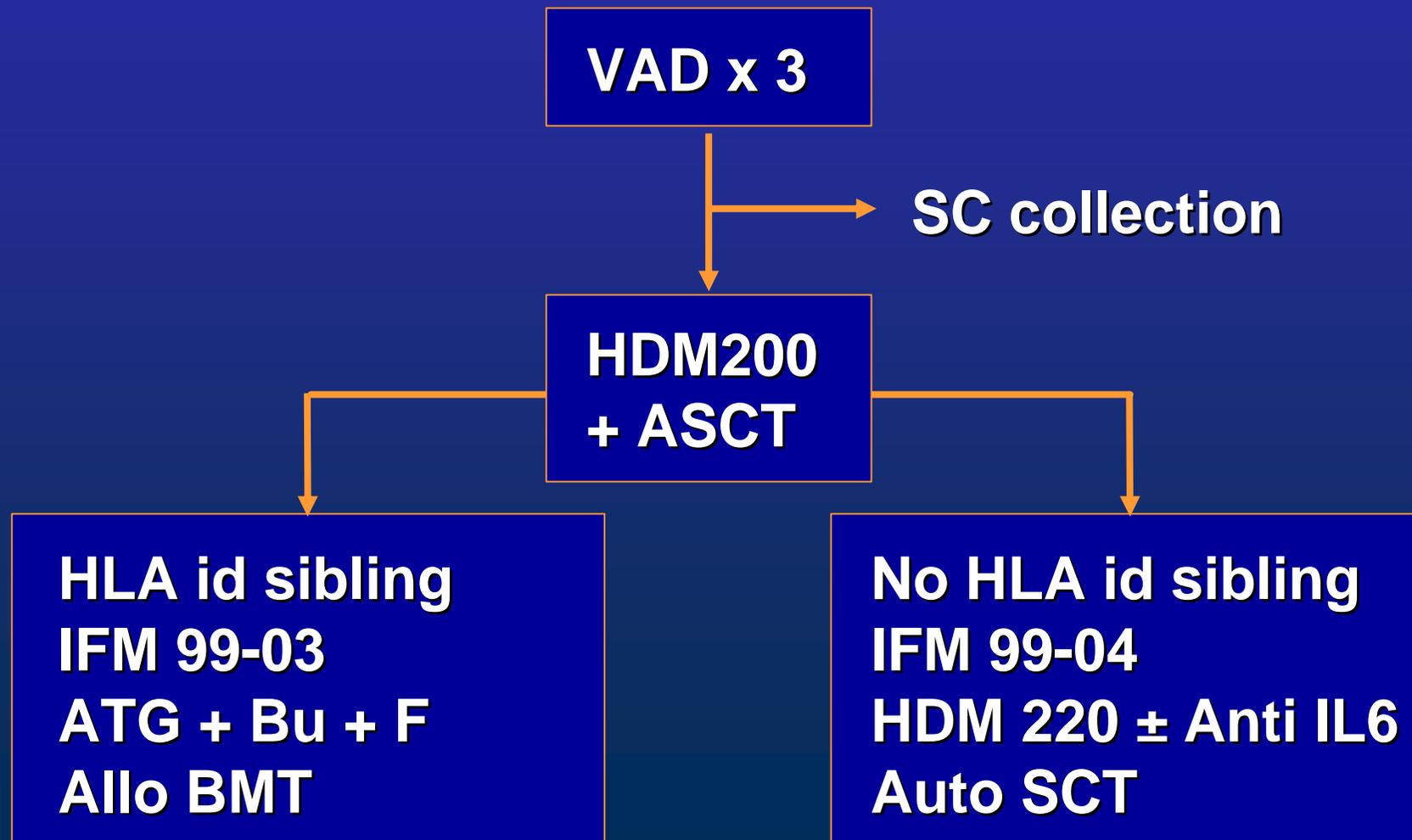


$t(4;14)$ $n=11$

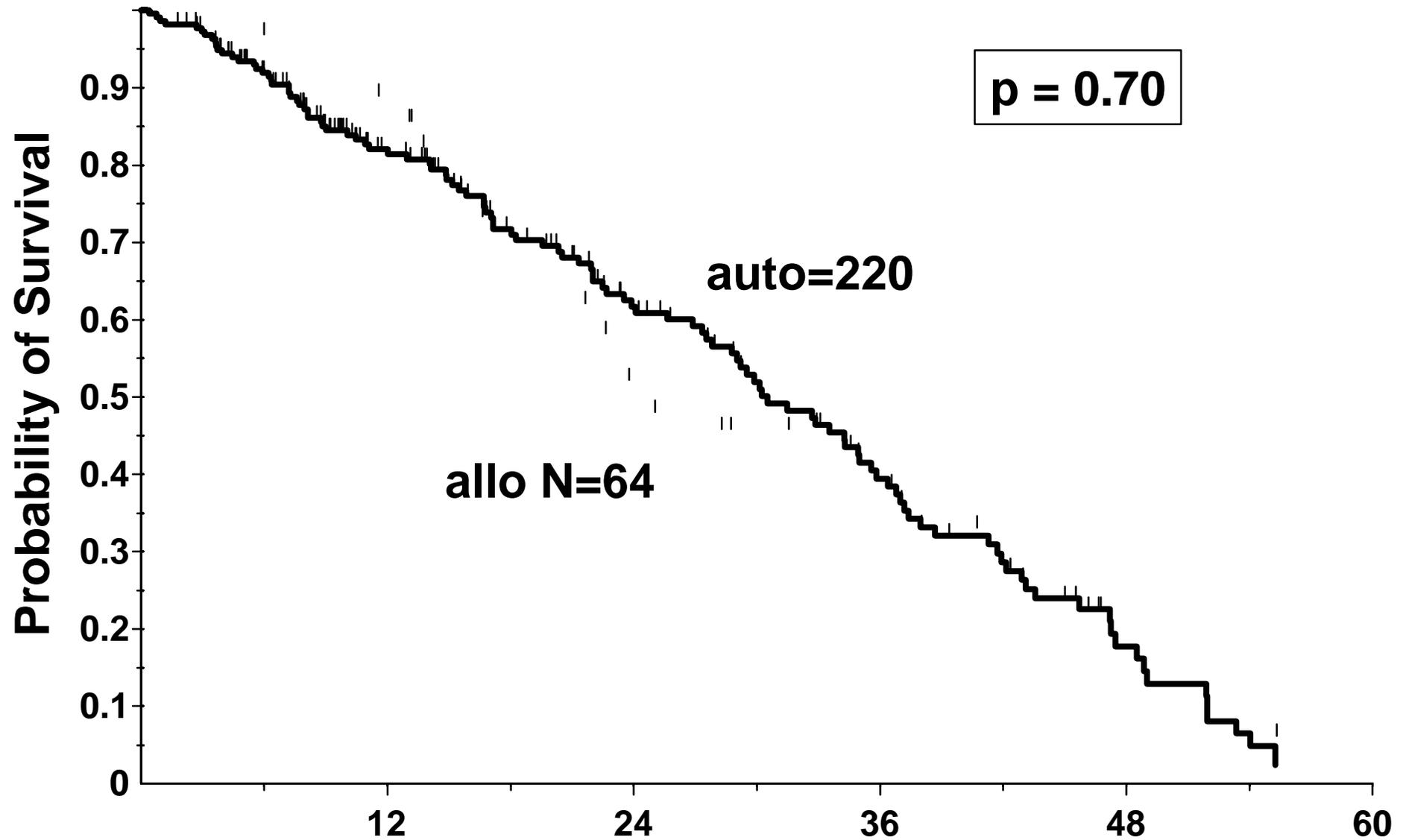


IFM 99-03 / 99-04

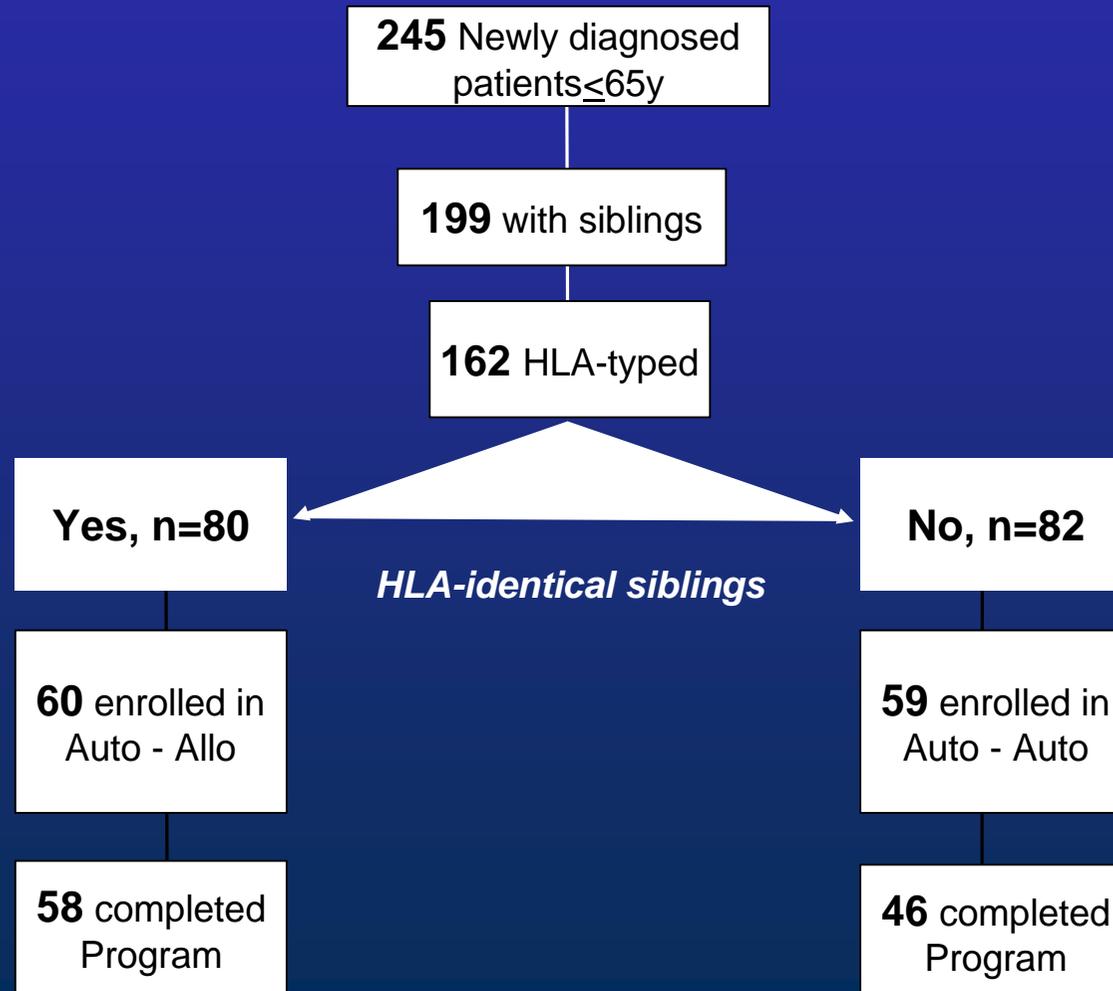
- = 65 years
- b2 microgl > 3 mg/l + D13 (FISH)



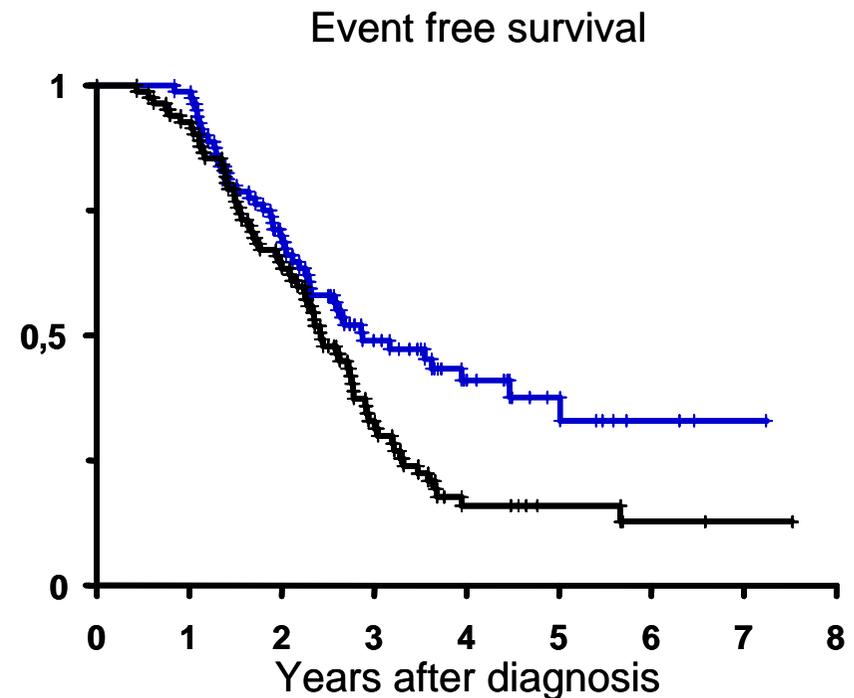
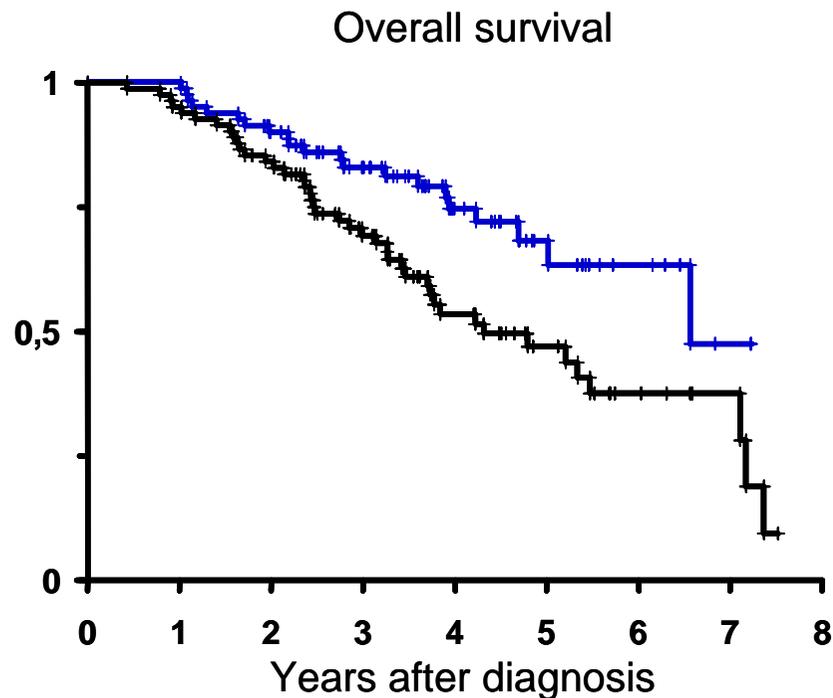
EFS intent-to-treat: IFM 99-03 VS 99-04



Multiple Myeloma auto-allo SCT Italian experience



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

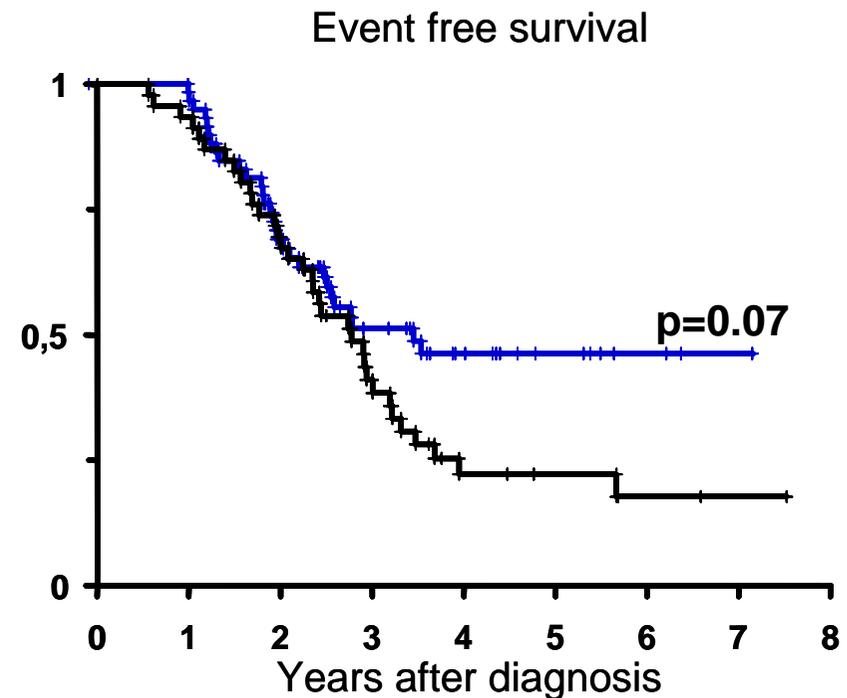
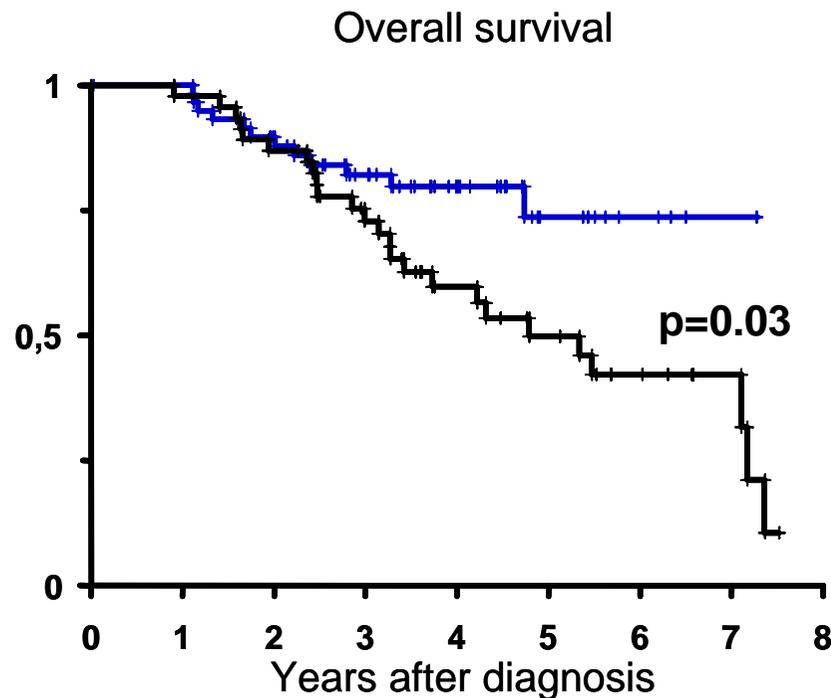


HLA-Id sibling:

YES —

NO —

Outcome according to completed treatment (n=104)



Auto – Allo n=58 —

Auto – Auto n=46 —

Multiples Myelom Stadium II/III nach Salmon + Durie Allo Intergroup (DSMM/GMMG)

Alter < 55 Jahre)

↓
Induktionstherapie
CR/PR/MR/PD max. 8 Zyklen

↓
Registrierung aller Patienten Stammzellmobilisation + Einleitung der
Spendersuche

↓
Melphalan (200 mg/m²) + autologe PBSCT

↓
2 Monate später: Melphalan (140
mg/m²) + Fludara/ATG+
allogene PBSCT

↓
Tag 120 nach allogener PBSCT:
Thalidomid 100 mg (max.
2 J. bis Progress bzw. nicht-
tolerabler Toxizität)

↓
Falls kein Spender gefunden wird (max.
4 Wo. nach autologer SCT) od. falls Pat.
Allo-SCT ablehnt: 2 Monate später
(200 mg/m²) + **autologe PBSCT**

↓
Tag 120 nach autologer PBSCT: Thal.
100 mg (max. 2 J. bis Progress bzw.
nicht-tolerabler Toxizität)

Rezidiv nach autologer SCT; Alter = 65 Jahre



Revlimid-Dexa x 4
(Spendersuche: HLA-ident. Geschwister, 10/10 HLA komp. MUD)
[CR, PR, SD] PD

off study

Spender gefunden:
allo RIC
(z.B. Treo, Fludarabin
oder TBI 2Gy / Flu)
Erhaltung: Revlimid x 4

Kein Spender:
Revlimid-Dexa bis
Progress

Primäres Studienziel: EFS

Acknowledgement

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United Kingdom

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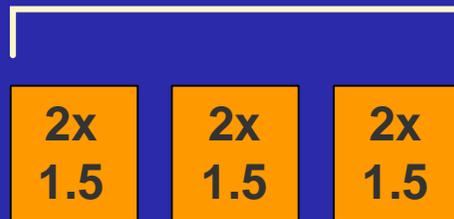
Israel

Nagler	Tel Hashomer
A. Shimoni	



Total Marrow Irradiation, Busulfan, Cyclophosphamide and ATG

TMI (Gy)



Busulfan (mg/kg)



Cyclo (mg/kg)



ATG (mg/kg)



Day

-9

-8

-7

-6

-5

-4

-3

-2

-1

0

Total Marrow Irradiation, Busulfan, Cyclophosphamide and ATG

Patients	n = 18
HLA-identical sibling:	18
Median age	44 years (29 - 53)
Male/female	14/ 4
Stage	II = 7 III = 11
Med. β_2 MG	3.1mg/dl (1.7- 11)
Prior chemotherapy cycles	6 (4-18)
Prior autologous transplant	n=1

Total Marrow Irradiation, Busulfan, Cyclophosphamide and ATG

Acute GvHD

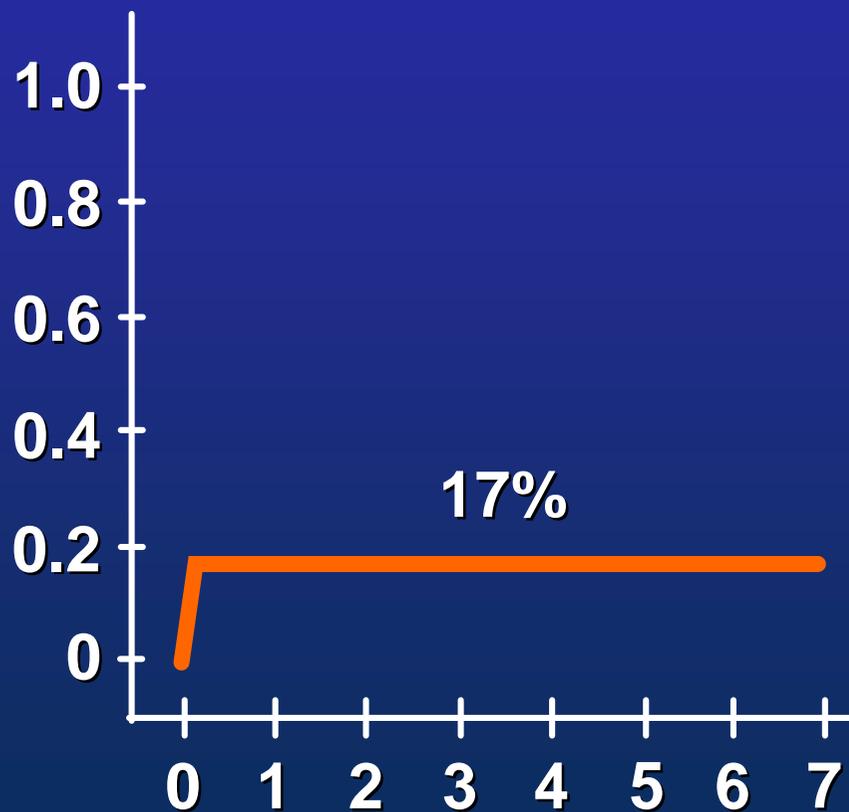
None	n = 7
II - IV	n = 6 (25%)
III / IV	n = 1 (6%)

Chronic GvHD

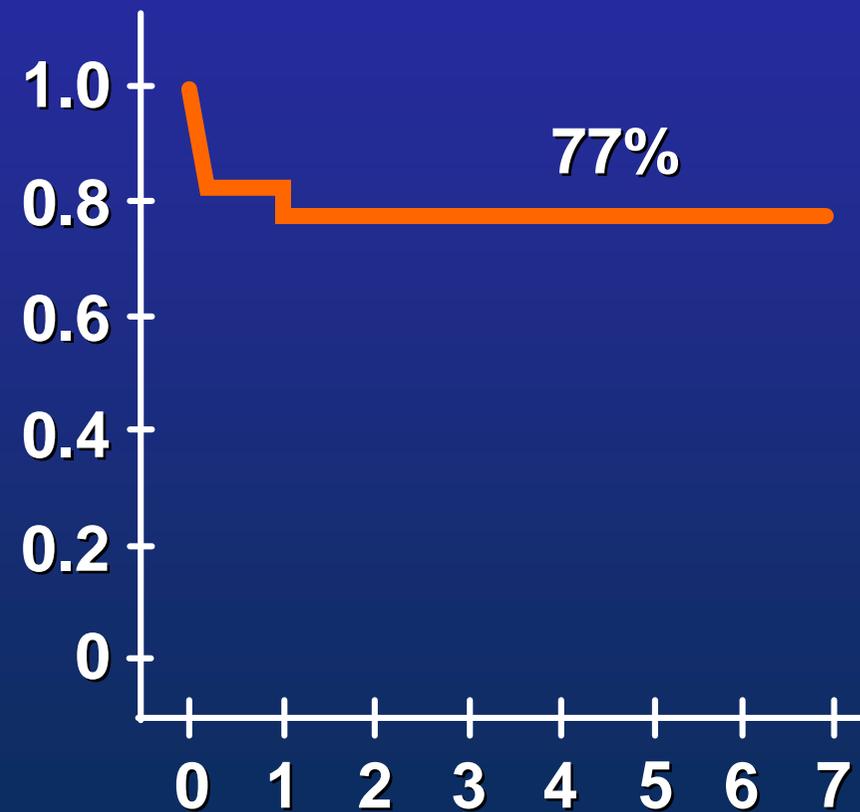
Lim.	n = 4 (27%)
Ext.	n = 1 (7%)

Total Marrow Irradiation, Busulfan, Cyclophosphamide and ATG

TRM



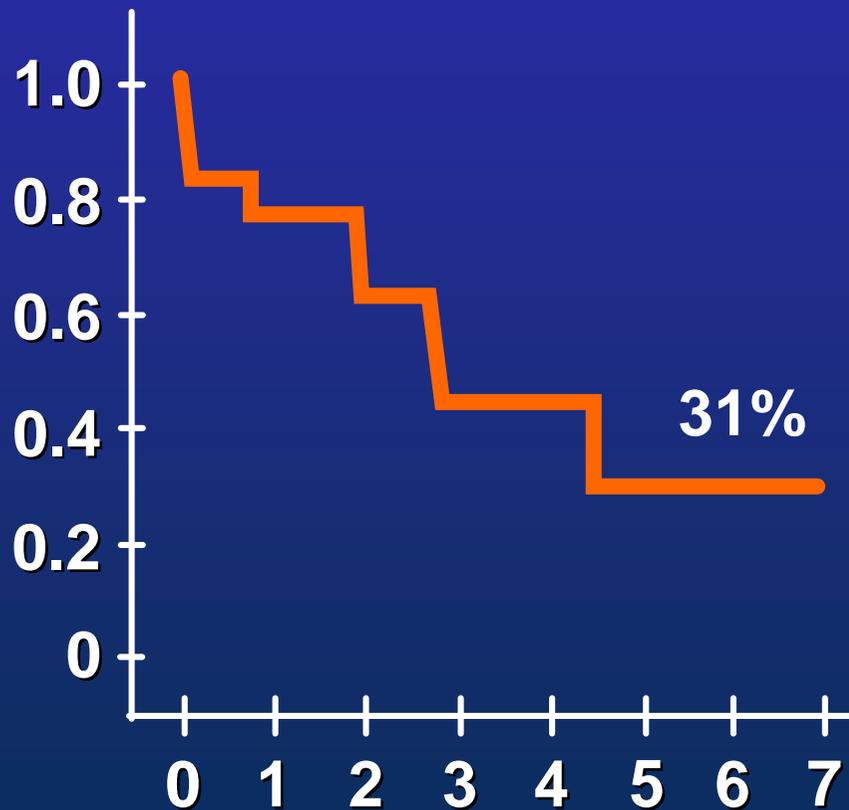
Probability of OS



Years after transplantation

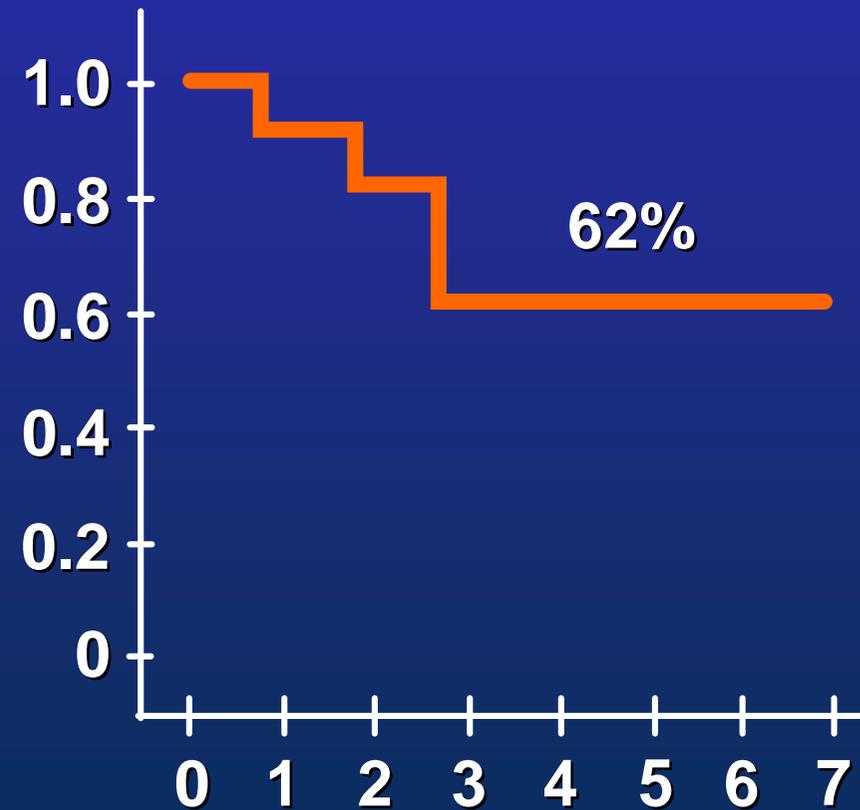
Total Marrow Irradiation, Busulfan, Cyclophosphamide and ATG

Progression-free survival



31%

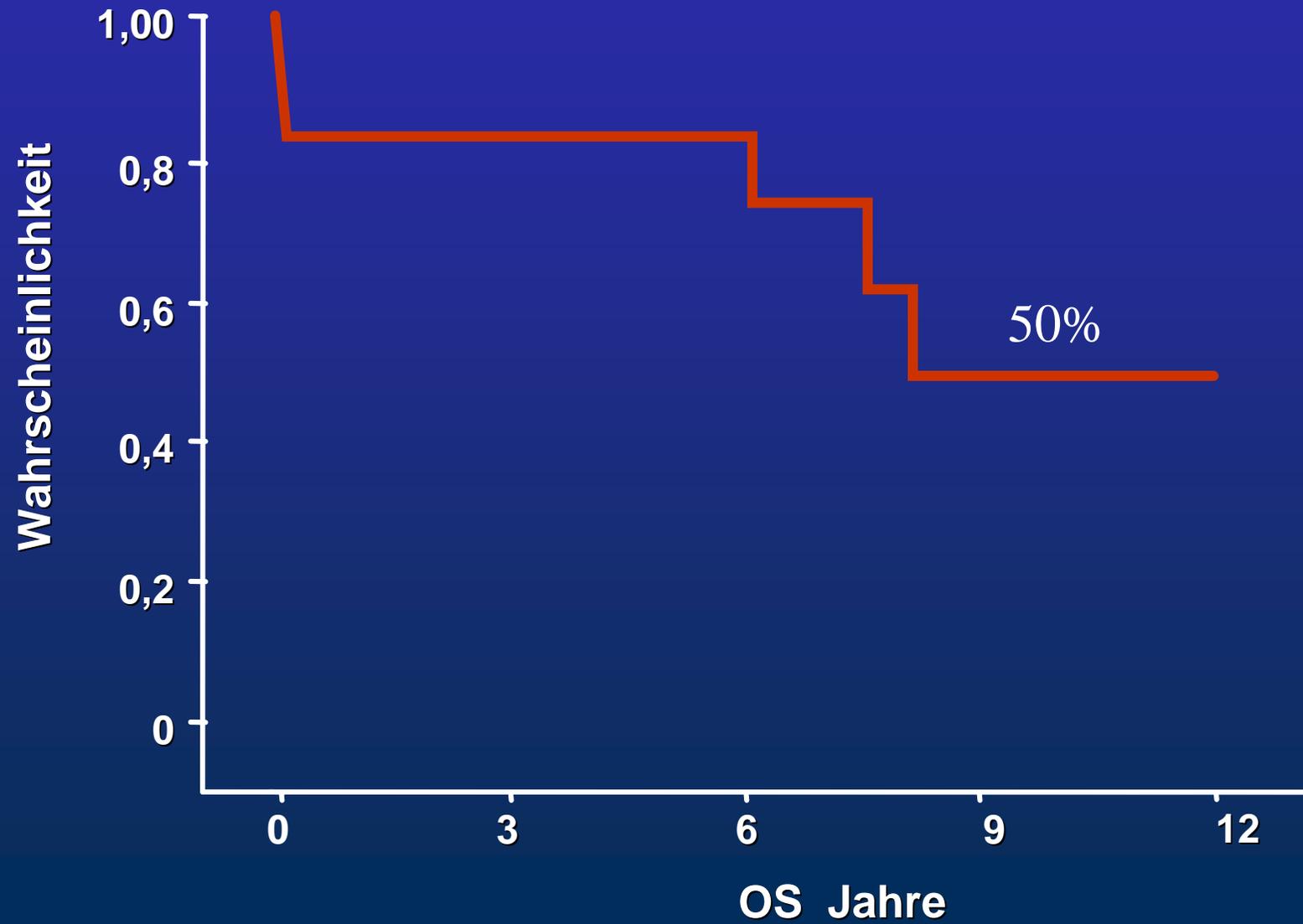
Complete remission



62%

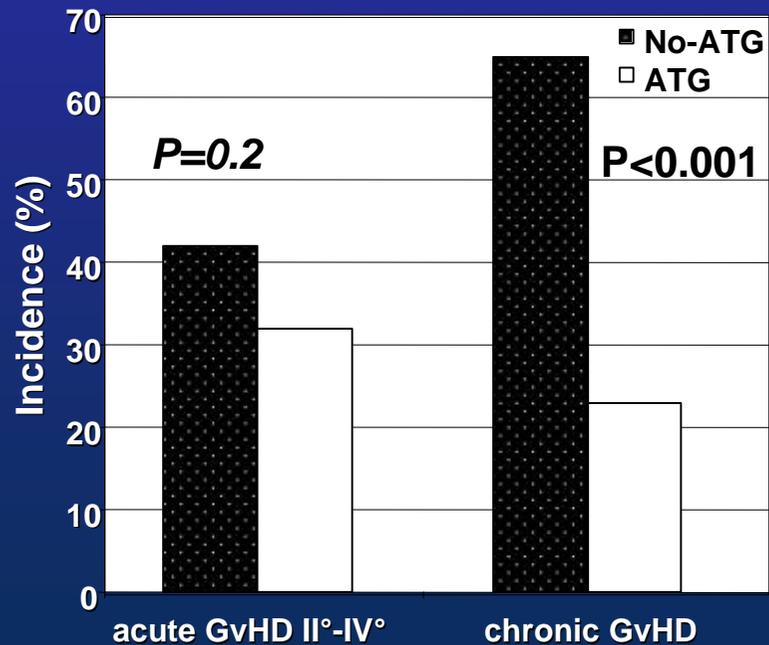
Years after transplantation

TMI/Bu/CY: update OS

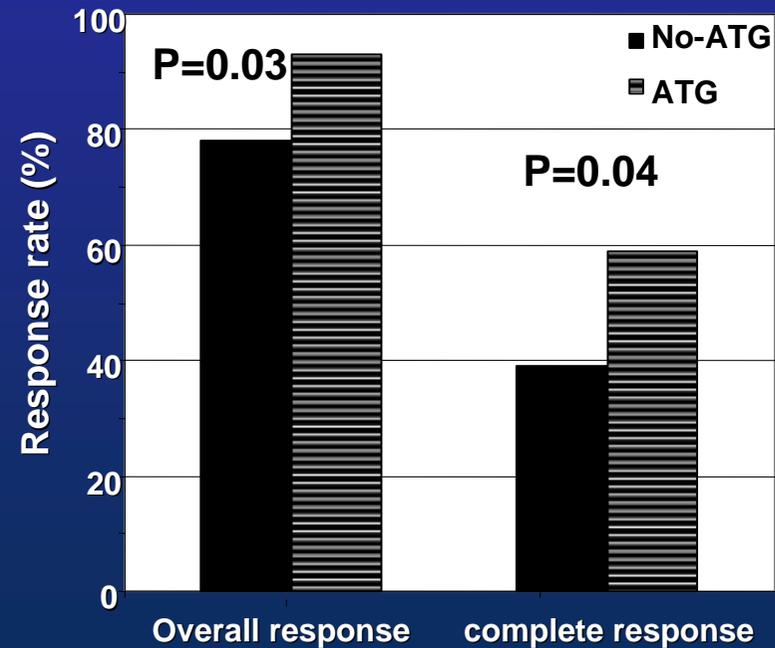


Less GvHD , higher CR without increase risk of relapse: The role of ATG

Effect of ATG on the incidence of acute and chronic GvHD



Effect of ATG on response in patients with multiple myeloma



Unpublished results

ATG induces complement-independent cytotoxicity in myeloma cell lines

