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Auto-TPX beim Multiplen Myelom

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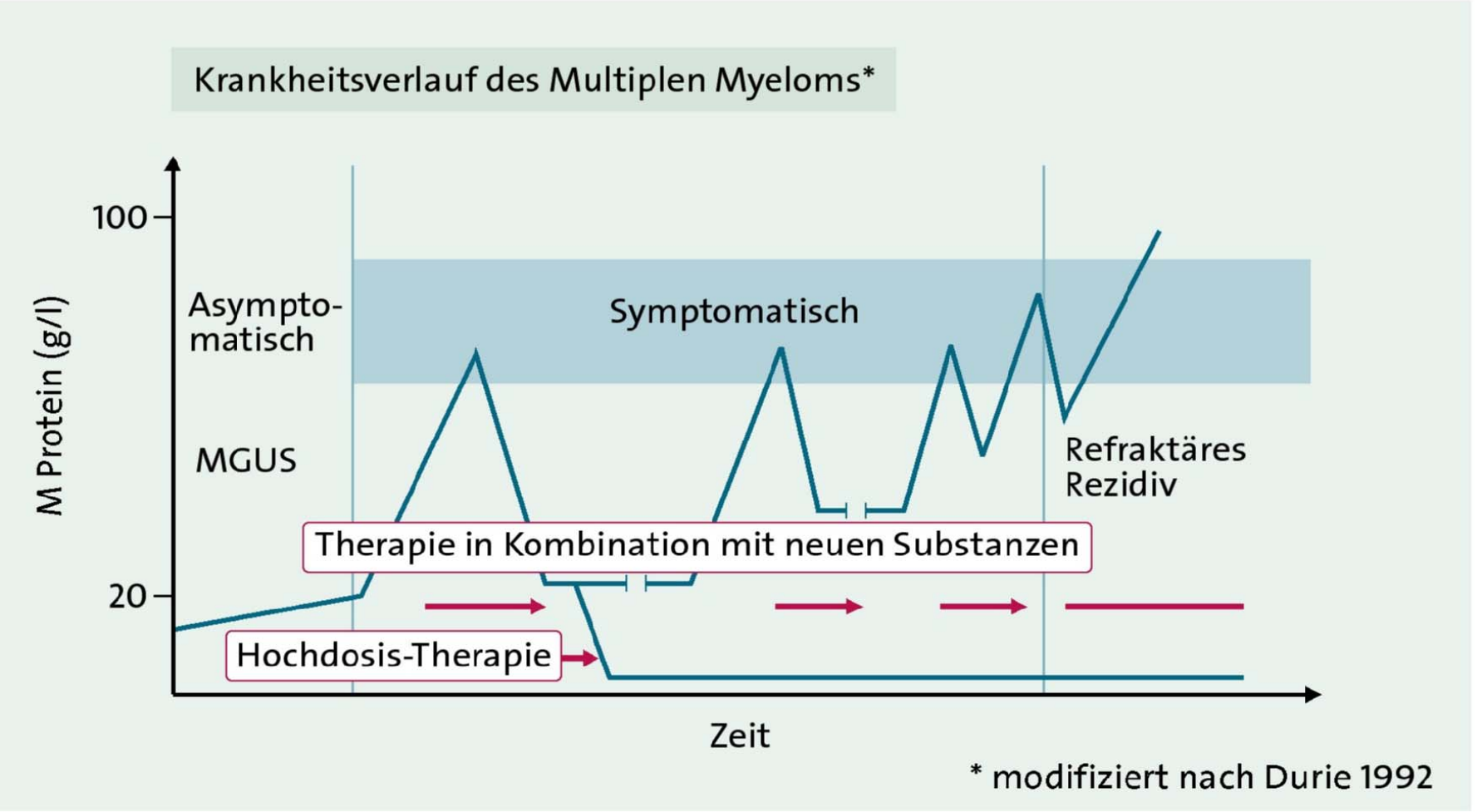
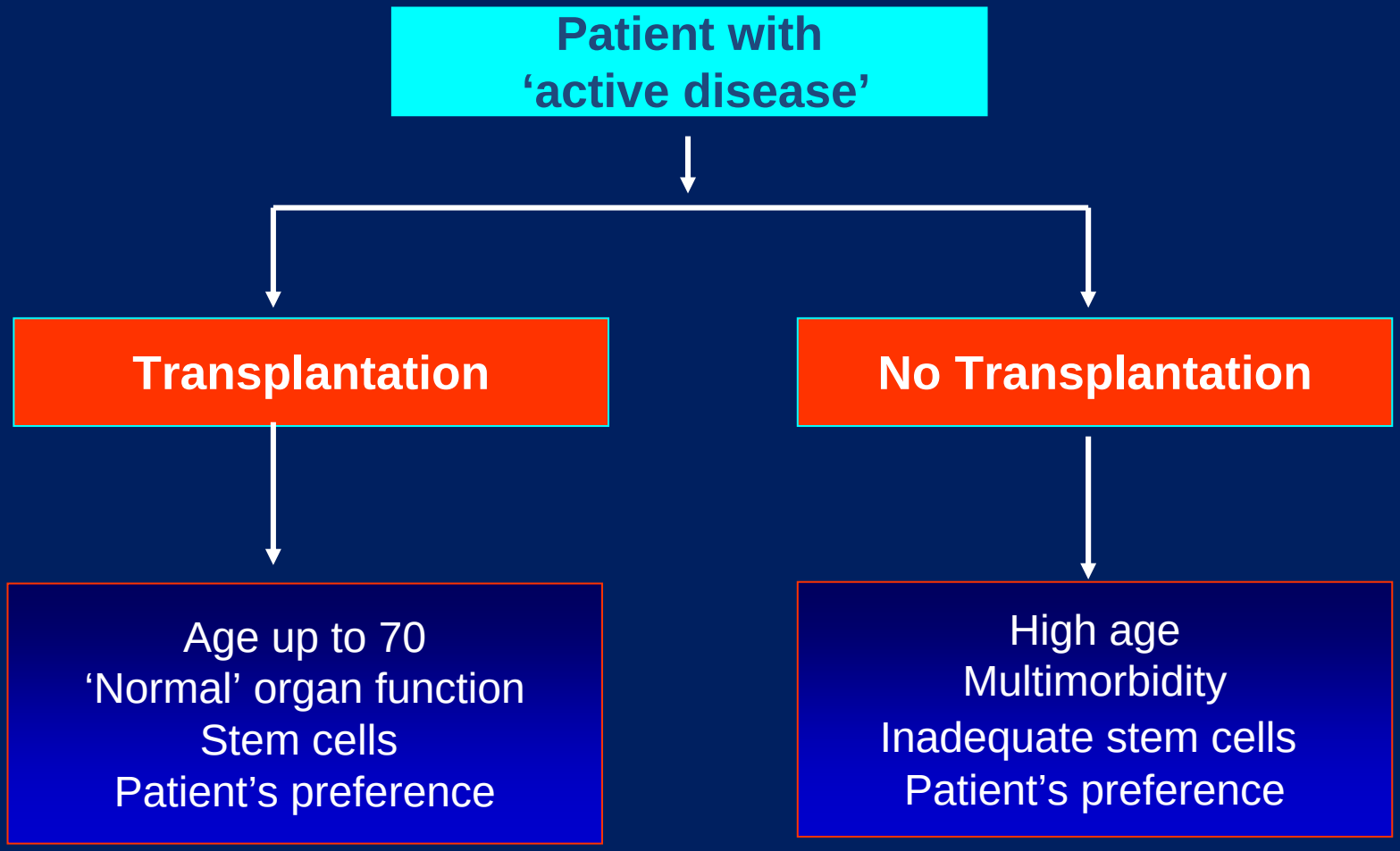
1 Myelom Krankheitsverlauf - Hochdosistherapie

Rezidiv-Therapie des Multiplen Myeloms
Krankheitsverlauf



modifiziert nach: Durie BG (1992) Multiple Myeloma: A concise review of the disease and treatment options (booklet). Los Angeles, CA, International Myeloma Foundation

Multiple Myeloma: First line treatment



Adapted from Ludwig 2009; Post ASH-Slides

Improving the response quality / Increasing CR rate after SCT

Induction

Vel-Dex (VD)
Vel-Cyclo-Dex (VCD)
Vel-ADM-Dex (PAD)

VRD
VTD

Len-Dex
RAD

Mel 200 **Mel 200**

Consolidation Maintenance

VTD
VRD
Bortezomib
Len 25

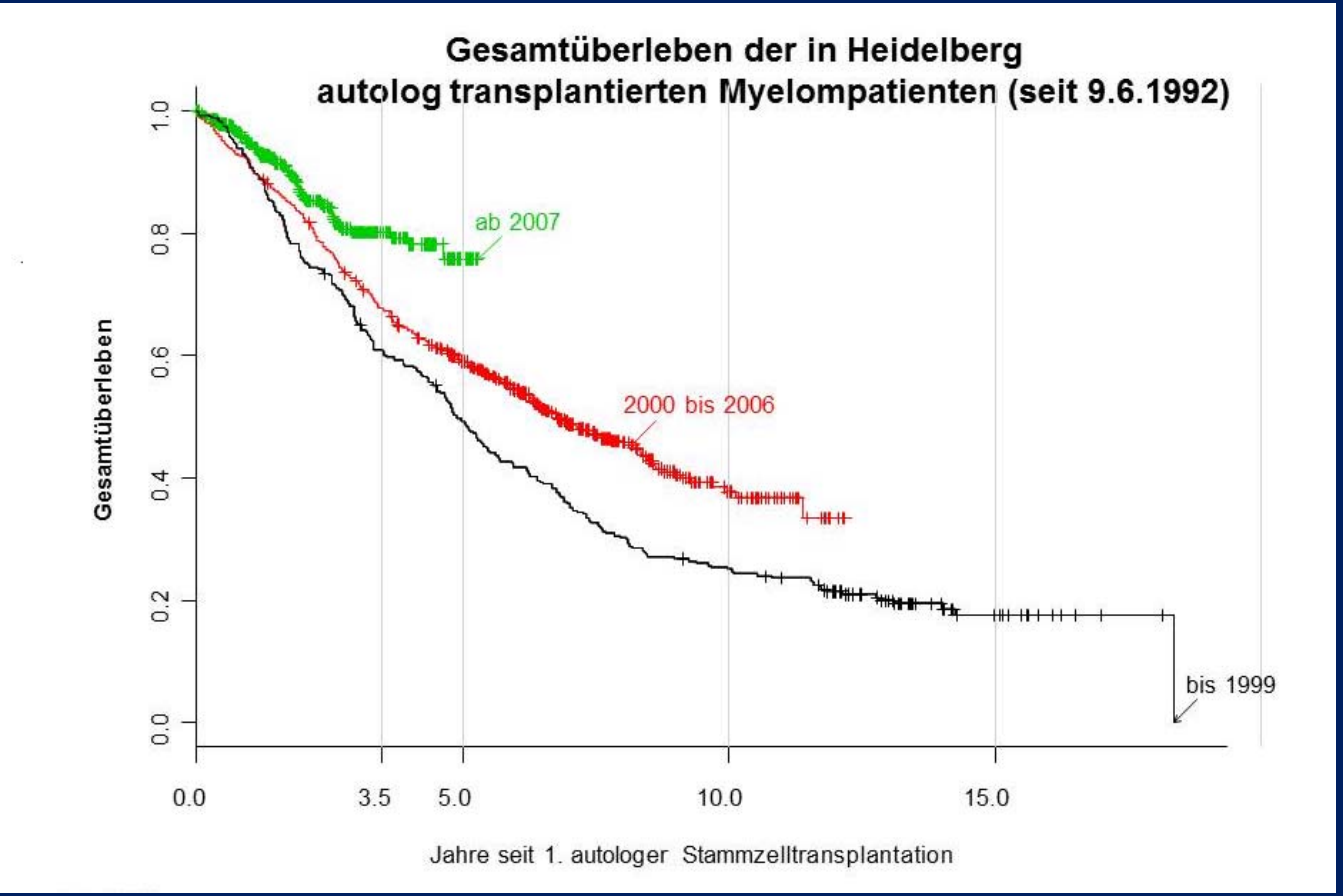
Thalidomide
IMF 99/02

Lenalidomide
IMF 2005-02,
CALGB

Bortezomib
Hovon/GMMG
DSMM XI
PETHEMA/GEM

Einsele 2012

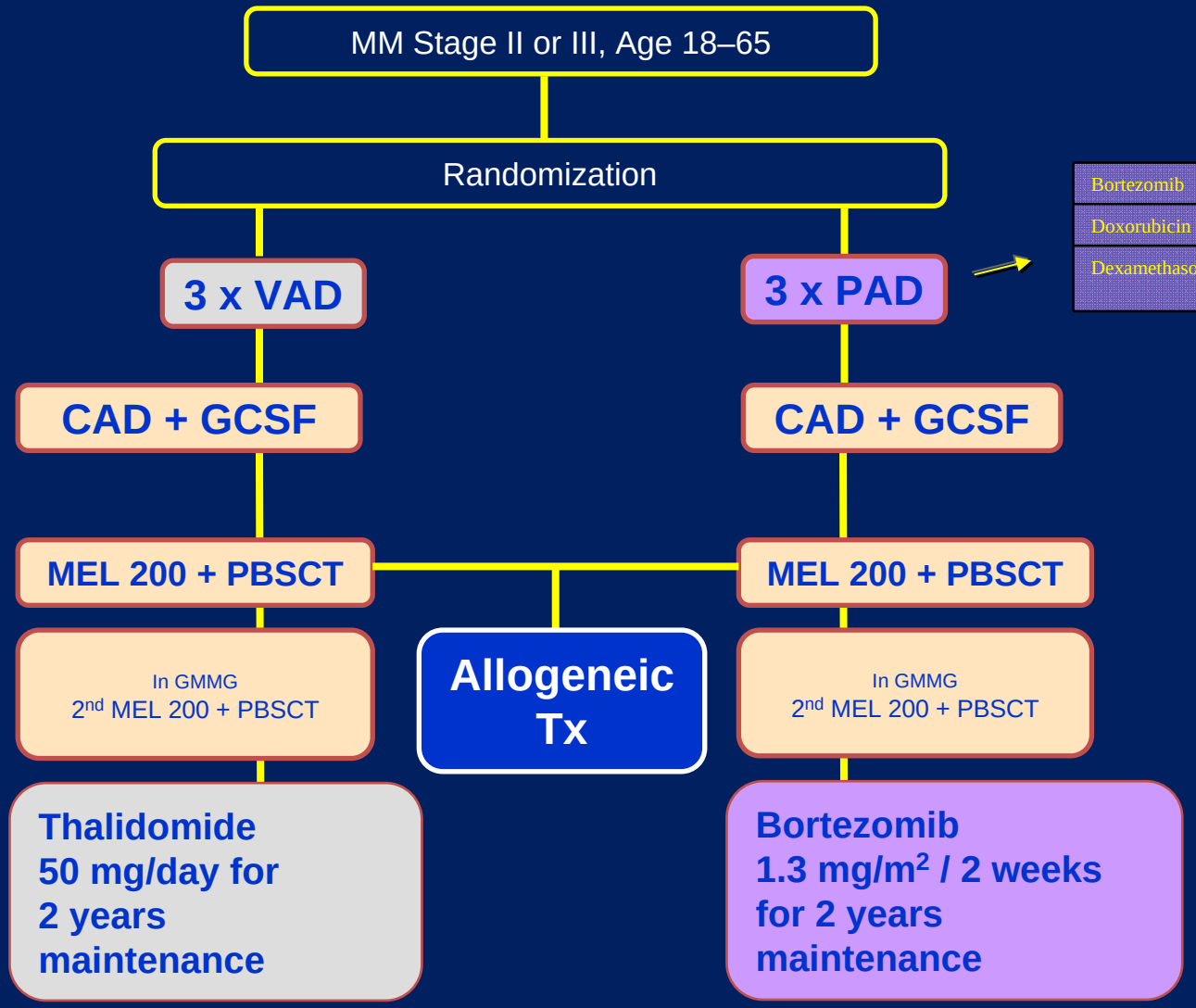
Multiple Myeloma – Heidelberg Center
20 Years ABSCT (n = 1486 pts.)



Unpublished data

2 GMMG-Ergebnisse

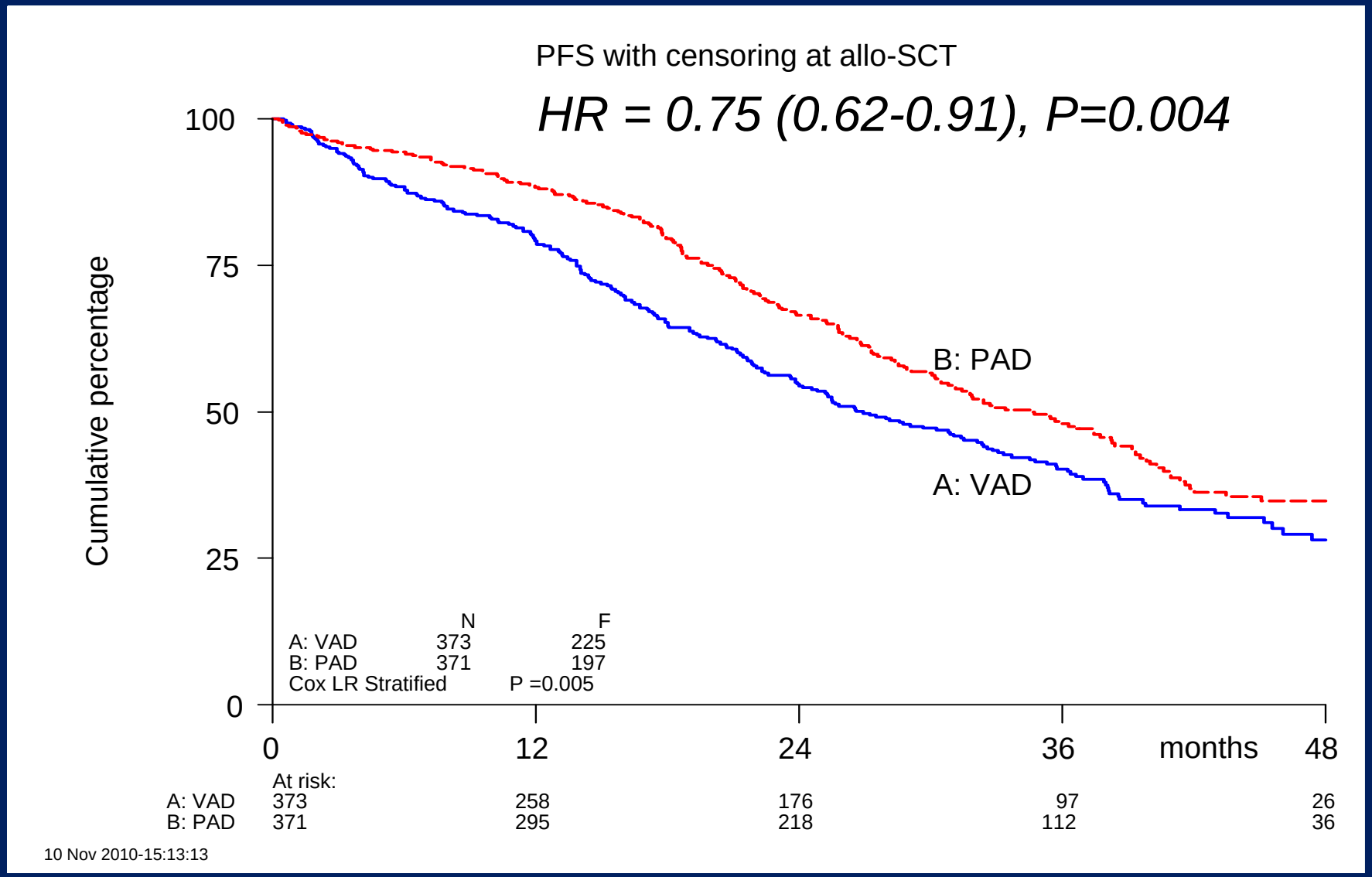
HOVON 65 MM / GMMG-HD4 Trial



Bortezomib	1.3 mg/m²
Doxorubicin	9 mg/m²
Dexamethasone	40 mg HDD

P. Sonneveld et al., JCO 2012

Progression-free survival with censoring at allo-SCT: primary endpoint



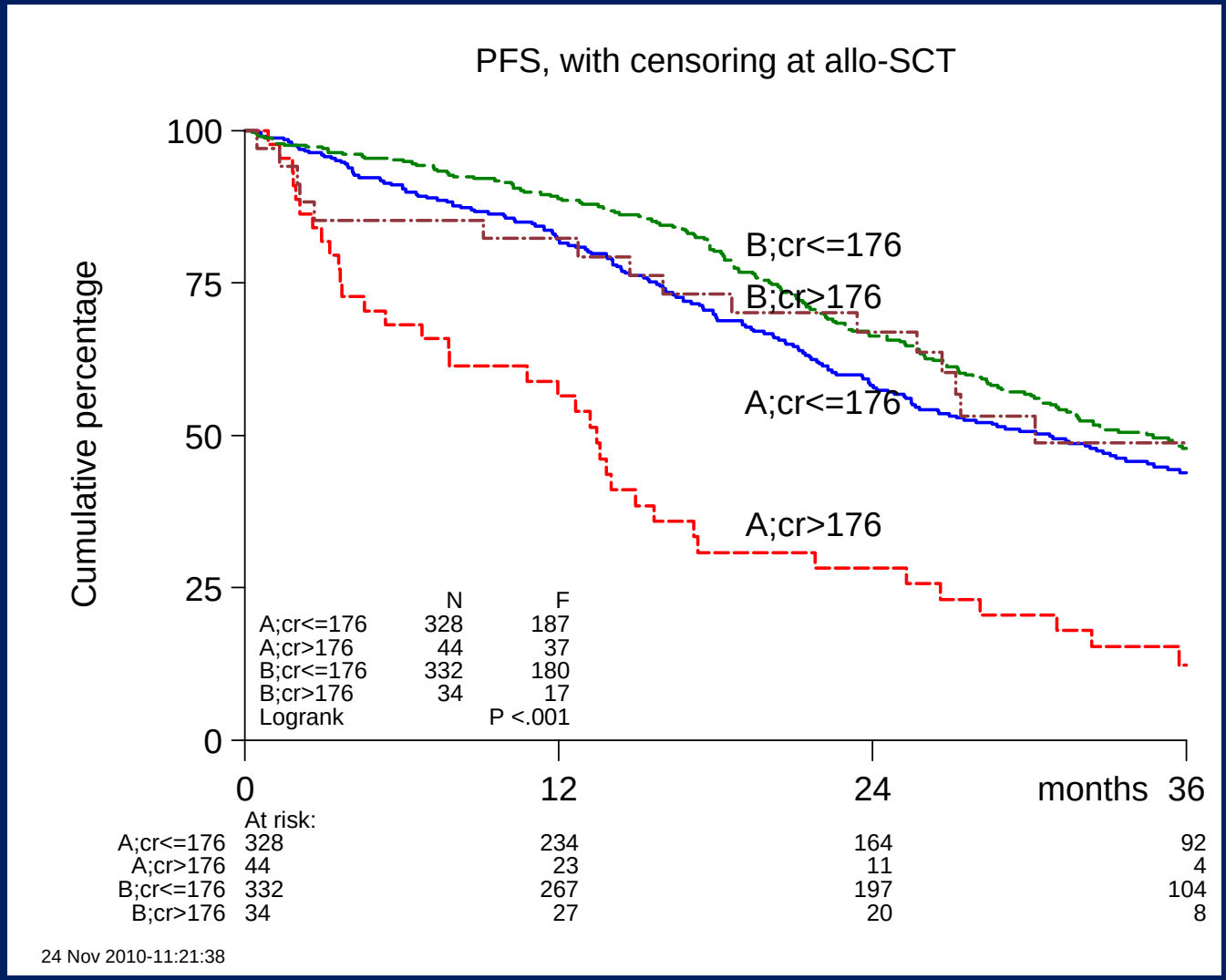
P. Sonneveld et al., JCO 2012

Multivariate Cox regression analysis

PFS (allo censored)				OS		
t	HR	*p*		t	HR	*p*
Arm	0.74	.002		Arm	0.70	.013
WHO	1.22	.005		WHO	1.49	<.001
IgA	1.62	.002		IgA	1.82	.01
IgG	1.33	.041		IgG	1.71	.008
LDH	1.25	.10		LDH	1.59	.006
ISS	1.25	.001		ISS	1.47	<.001
13q-	1.43	.001		13q-	1.62	.002
SG	0.81	.039		SG	0.73	.031

P. Sonneveld et al., JCO 2012

HO65/HD4: Impact of kidney function



C. Scheid et al.,Haematologica 2013

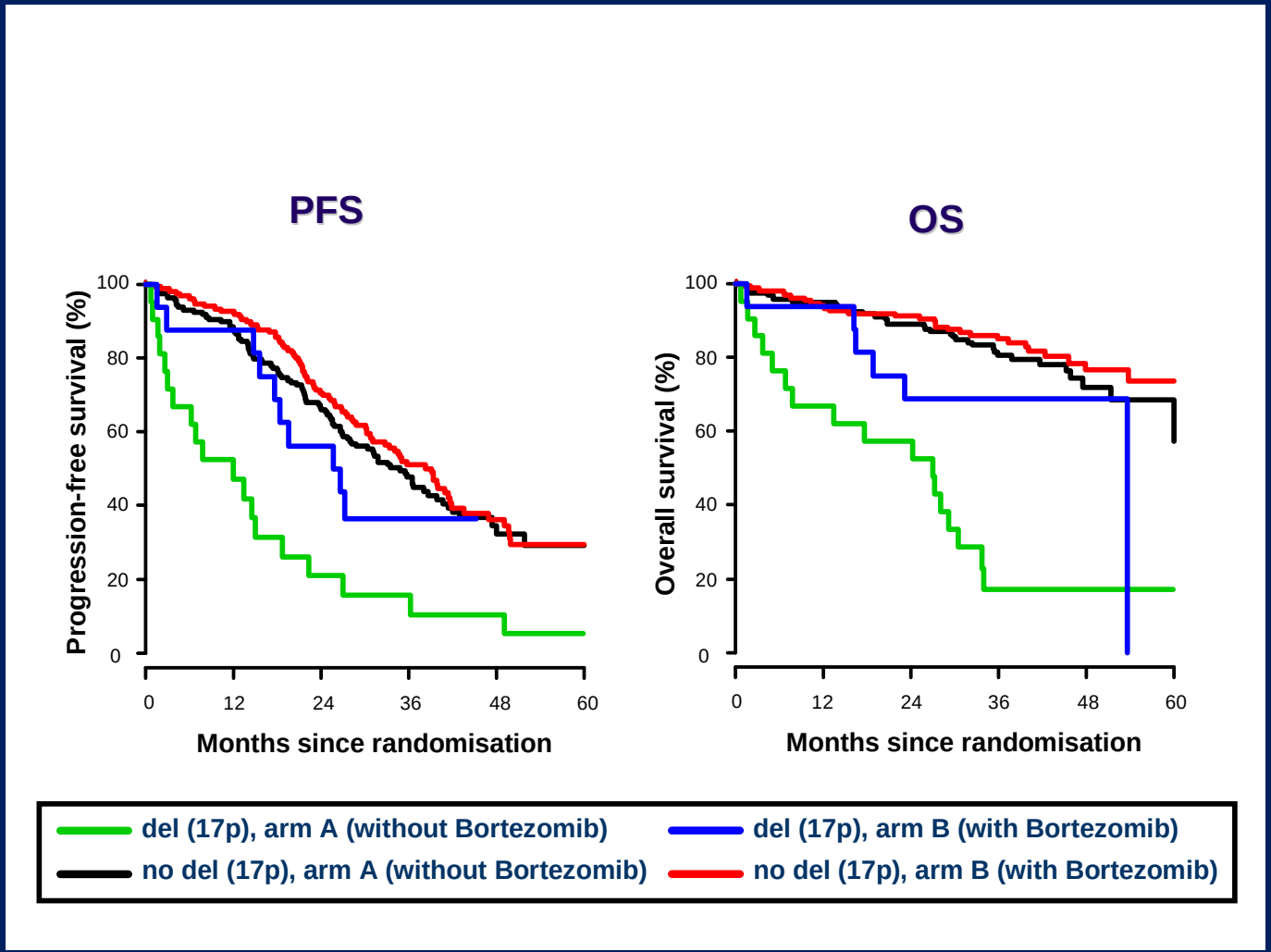
Comparison between both treatment arms HD4

	Median PFS (months)			OS at 36 months (%)		
	Arm B	Arm A	p-value	Arm B	Arm A	p-value
del(8p21)	33	25	0.37	78	65	0.16
del(13q14)	27	25	0.27	81	61	0.072
del(17p13)	26	12	0.024	69	17	0.028
+1q21	28	24	0.22	77	62	0.10
+11q23	39	33	0.27	83	75	0.11
+19q13	38	35	0.41	85	80	0.26
HD*	36	33	0.21	84	78	0.21
t(4;14)	25	22	0.12	66	44	0.37
t(11;14)	40	35	0.33	87	79	0.37

*HD, hyperdiploid

K. Neben et al., Blood 2012

Comparison between both study arms HD4
Deletion 17p13



K. Neben et al., Blood 2012

JOURNAL OF CLINICAL ONCOLOGY

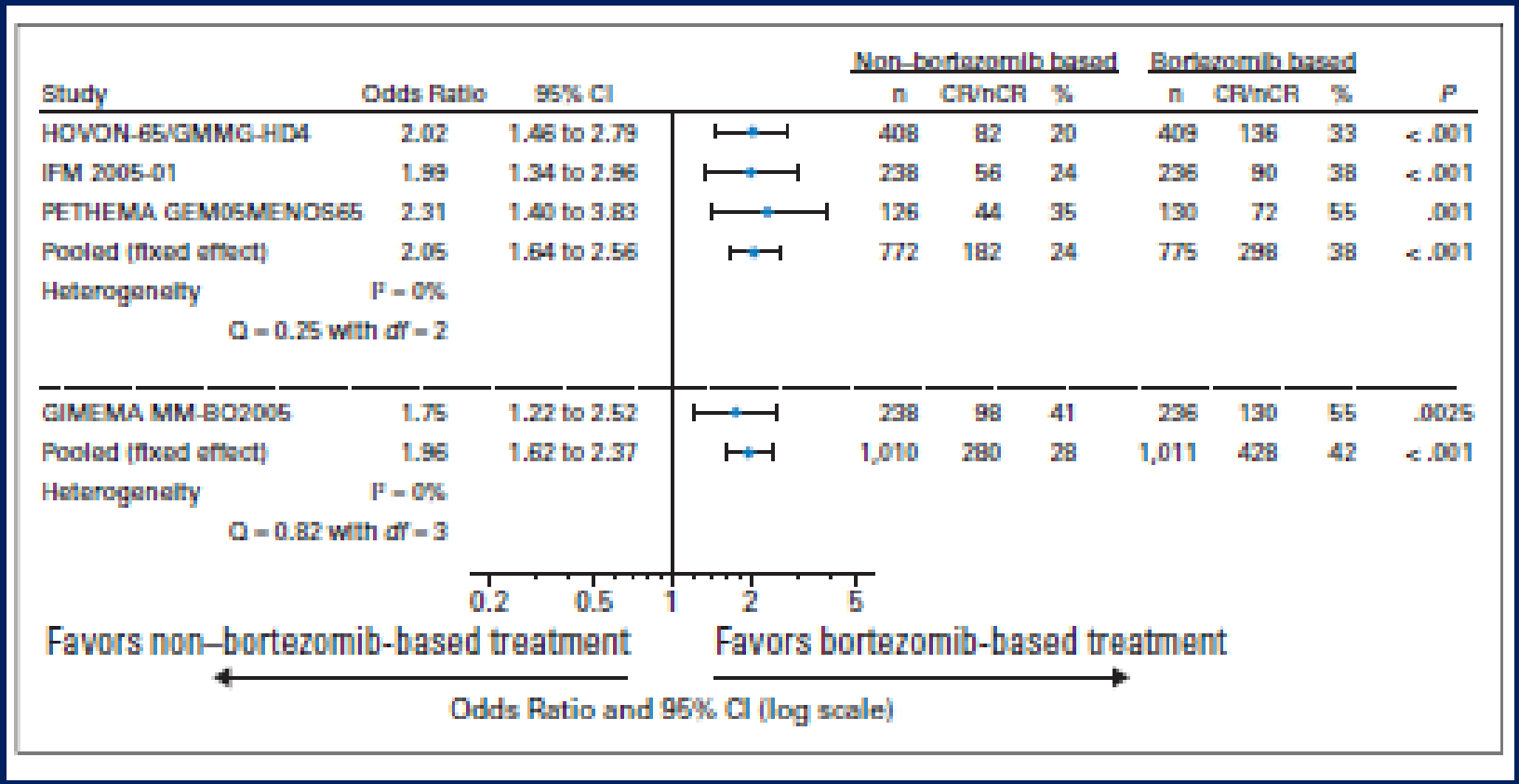
ORIGINAL REPORT

Bortezomib-Based Versus Nonbortezomib-Based Induction Treatment Before Autologous Stem-Cell Transplantation in Patients With Previously Untreated Multiple Myeloma: A Meta-Analysis of Phase III Randomized, Controlled Trials

Pieter Sonneveld, Hartmut Goldschmidt, Laura Rosiñol, Joan Bladé, Juan José Lahuerta, Michele Cavo, Paola Tacchetti, Elena Zamagni, Michel Attal, Henk M. Lokhorst, Avinash Desai, Andrew Cakana, Kevin Liu, Helgi van de Velde, Dixie-Lee Esseltine, and Philippe Moreau

Sonneveld et al, J Clin Oncol, 2013

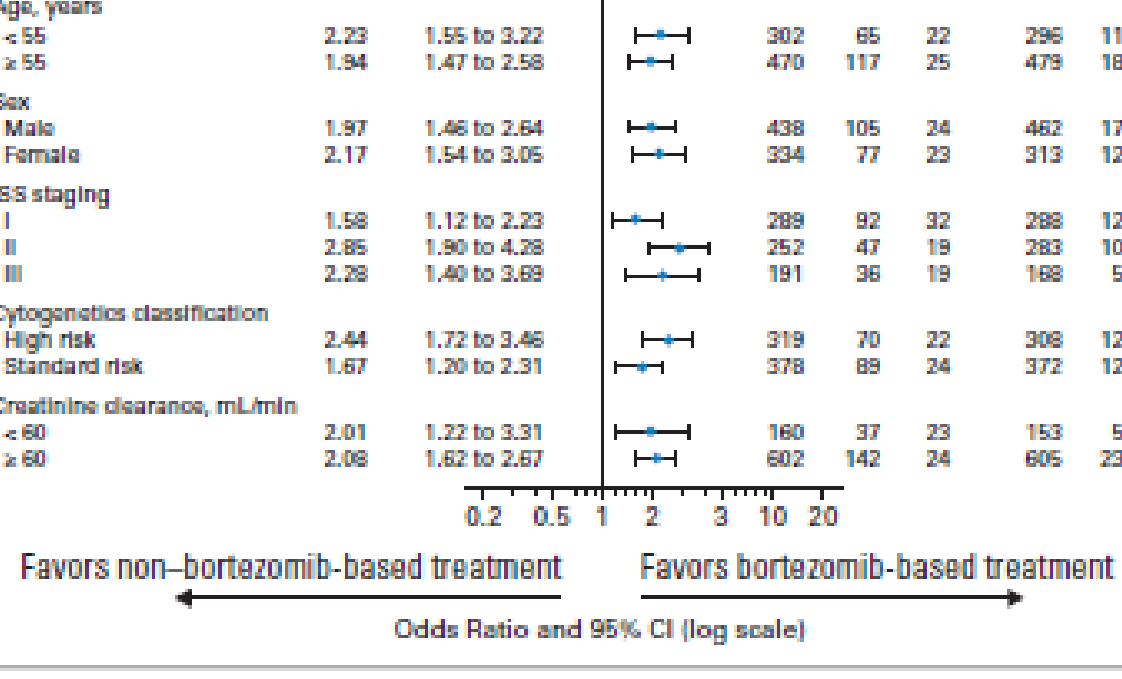
Efficacy endpoint of post-transplantation complete response (CR) plus near complete response (nCR) rate



Sonneveld et al, J Clin Oncol, 2013

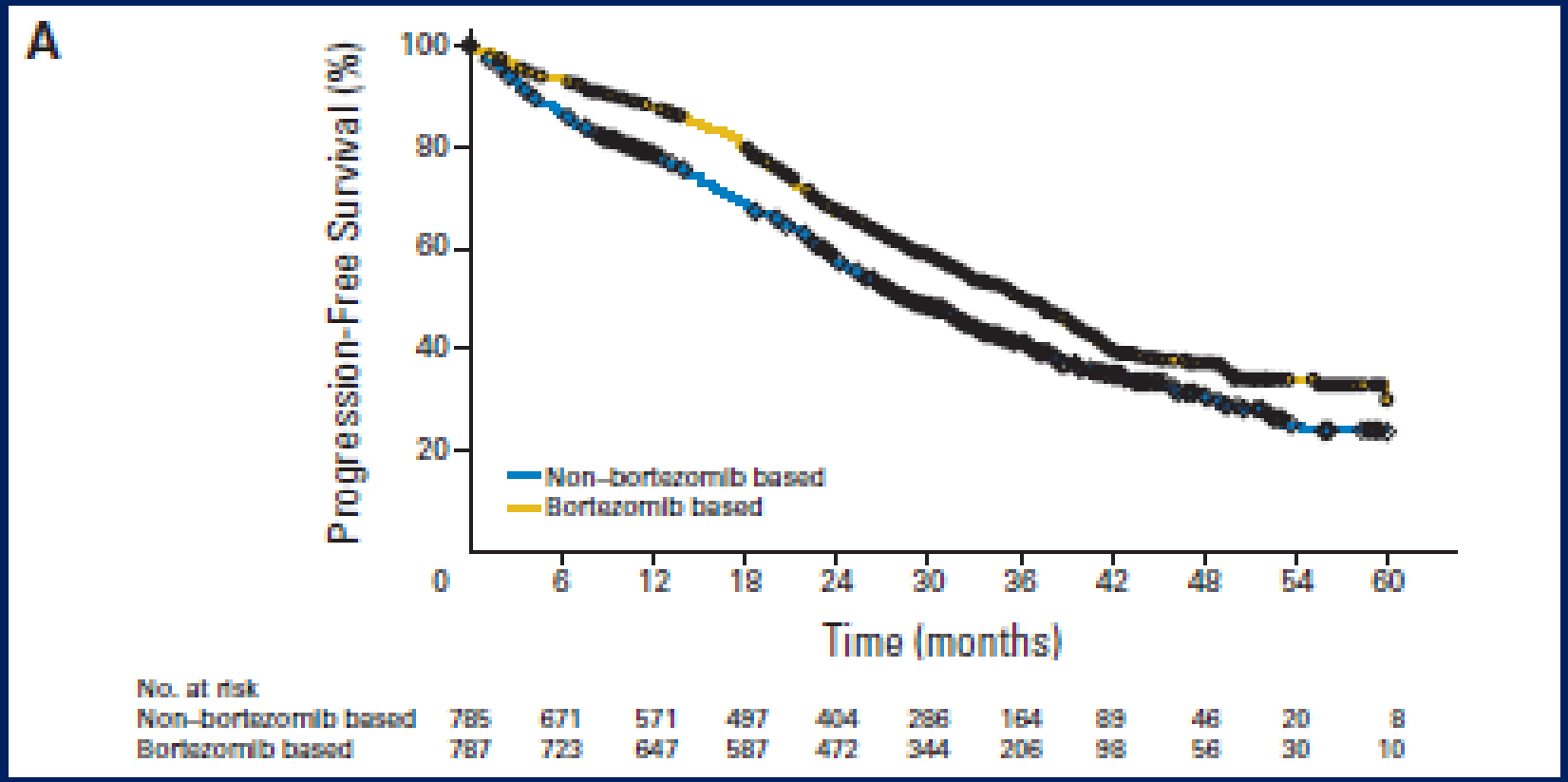
Post-transplantation complete response plus near-complete response rate by patients subgroup

Group	Odds Ratio	95% CI	Non–bortezomib based n	Non–bortezomib based Response	Non–bortezomib based %	Bortezomib based n	Bortezomib based Response	Bortezomib based %
All patients	2.05	1.64 to 2.56	772	182	24	775	298	38
Age, years								
< 55	2.23	1.55 to 3.22	302	65	22	296	111	38
≥ 55	1.94	1.47 to 2.58	470	117	25	479	187	39
Sex								
Male	1.97	1.46 to 2.64	438	105	24	462	175	38
Female	2.17	1.54 to 3.05	334	77	23	313	123	39
ISS staging								
I	1.58	1.12 to 2.23	289	92	32	288	121	42
II	2.85	1.90 to 4.28	252	47	19	283	109	39
III	2.28	1.40 to 3.69	191	36	19	188	58	35
Cytogenetics classification								
High risk	2.44	1.72 to 3.46	319	70	22	308	126	41
Standard risk	1.67	1.20 to 2.31	378	89	24	372	124	33
Creatinine clearance, mL/min								
< 60	2.01	1.22 to 3.31	160	37	23	153	58	38
≥ 60	2.08	1.62 to 2.67	602	142	24	605	235	39



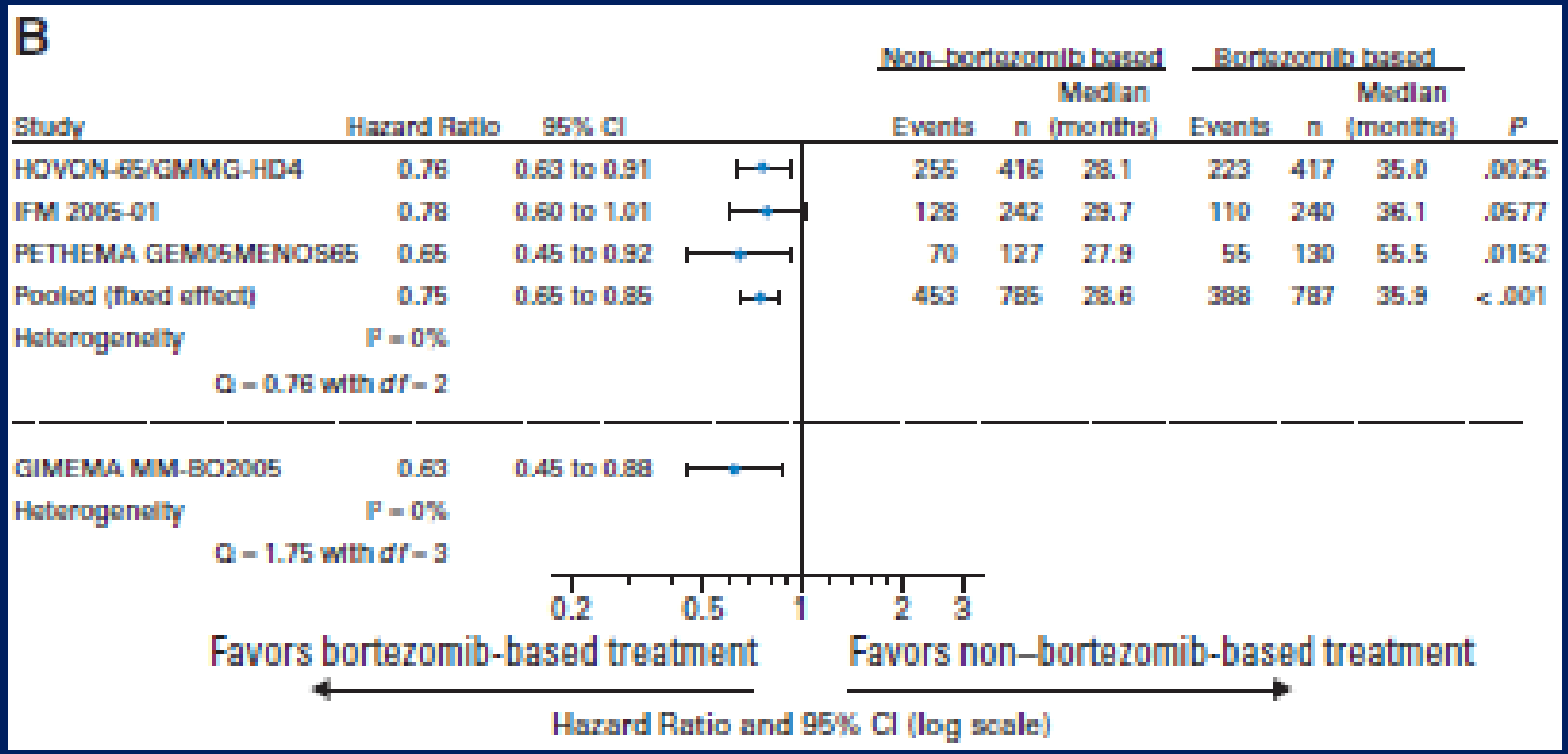
Sonneveld et al, J Clin Oncol, 2013

Kaplan-Meier curve end point of progression-free survival



Sonneveld et al, J Clin Oncol, 2013

Hazard ratios for progression free survival, for the individual studies and the integrated analysis



Sonneveld et al, J Clin Oncol, 2013

IFM 2005-02: Study design

Phase III randomized, placebo-controlled trial
N= 614 patients, from 78 centers, enrolled between 7/2006 and 8/2008

Patients < 65 years, with non-progressive disease, ≤ 6 months after ASCT in first line

Randomization: stratified according to Beta-2m, del13, VGPR

Consolidation:
Lenalidomide alone 25 mg/day p.o.
days 1-21 of every 28 days for 2 months

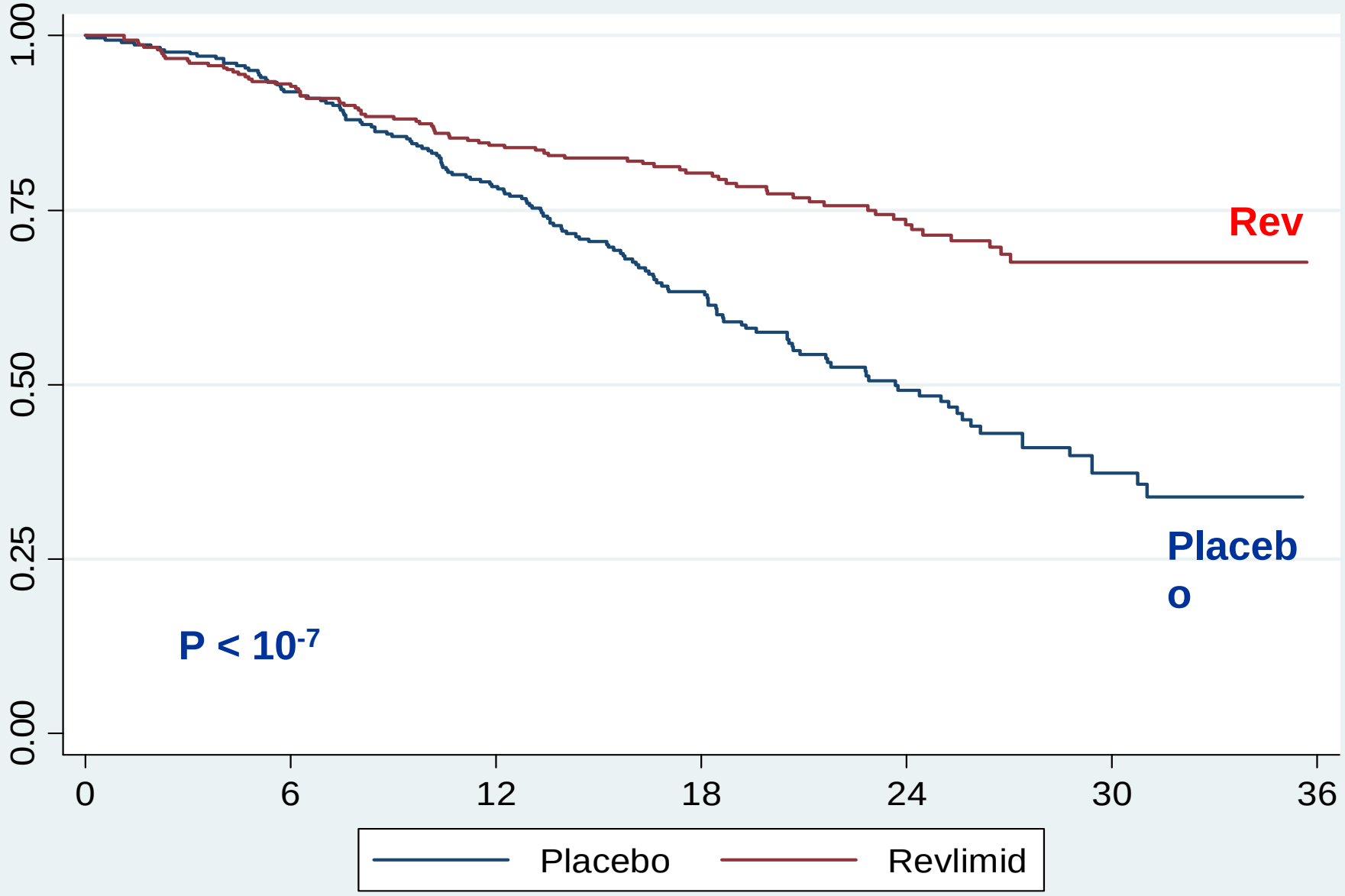
Arm A=
Placebo
(N=307)
until relapse

Arm B=
Lenalidomide
(N=307)
10-15 mg/d until relapse

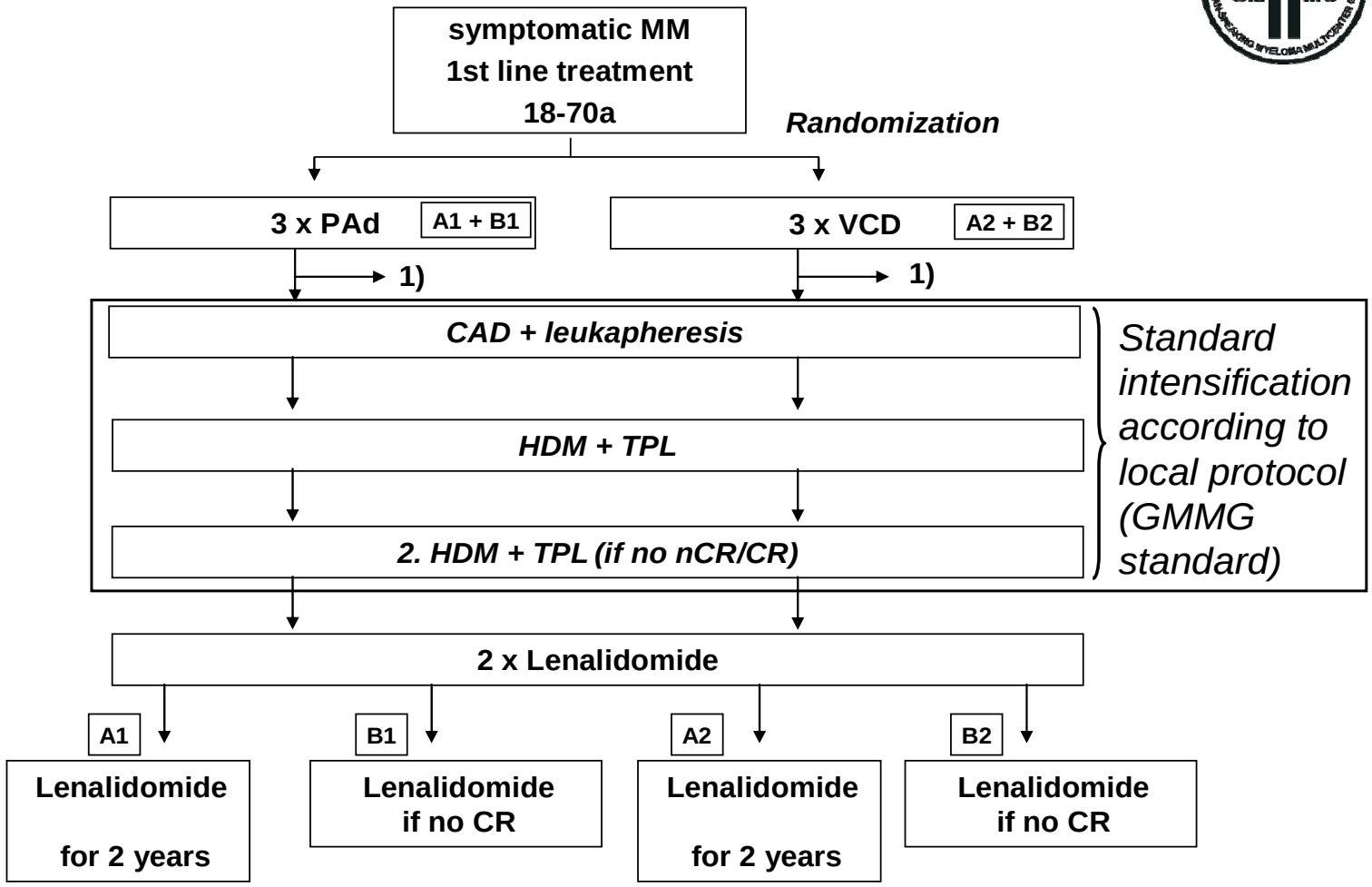
Primary end-point: PFS.
Secondary end-points: CR rate, TTP, OS, feasibility of long-term lenalidomide….

ASCT = autologous stem cell transplant. IFM = Intergroupe Francophone du

IFM 2005-02 : PFS from randomization



MM5 Trial



1) High Risk Patients, optional in Phase II trial

3 Auto-TPX >65 Jahre

Übersicht

- *Auto TPL in Kombination mit neuen Medikamenten ist Standard für Patienten <65 Jahre*
- *Vergangene retrospektive Studien haben gezeigt, dass Auto TPL für > 65jährige möglich ist*
- *Meisten Studien jedoch mit MEL 100 mg/m^2 statt 200 mg/m^2 und ohne neue Medikamente in der Induktionstherapie und ohne Erhaltungstherapie*
- *Daher Stellenwert unklar*
- *MPT sogar MEL 100 mg/m^2 überlegen*

  (Facon et al. Lancet 2007)

Auto TPL von 2007-09/2012 > 60 in Heidelberg

		60-64		65-69		70+		Overall	
		n		*n*		*n*		*n*	
No. of Patients		83		93		26		202	
Age	(Median)	62		67		71		65	
Sex	male	42	51%	46	49%	13	50%	101	50%
	female	41	49%	47	51%	13	50%	101	50%
Ig subtype	Ig G	50	60%	59	63%	14	54%	123	61%
	Ig A	16	19%	18	19%	8	31%	42	21%
	Bence Jones	14	17%	14	15%	3	12%	31	15%
	IgD / M / asecr.	3	4%	2	2%	1	4%	6	3%
ISS	I	46	58%	39	44%	12	55%	97	51%
	II	17	22%	29	33%	5	23%	51	27%
	III	16	20%	21	24%	5	23%	42	22%
Cytogenetic	standard-risk	56	88%	69	87%	16	73%	141	85%
	high-risk	8	13%	10	13%	6	27%	24	15%
Combined risk score	low	32	52%	28	36%	9	43%	69	43%
	intermediate	27	44%	45	58%	9	43%	81	50%
	high	3	5%	5	6%	3	14%	11	7%

Auto TPL von 2007-09/2012 > 60 in Heidelberg

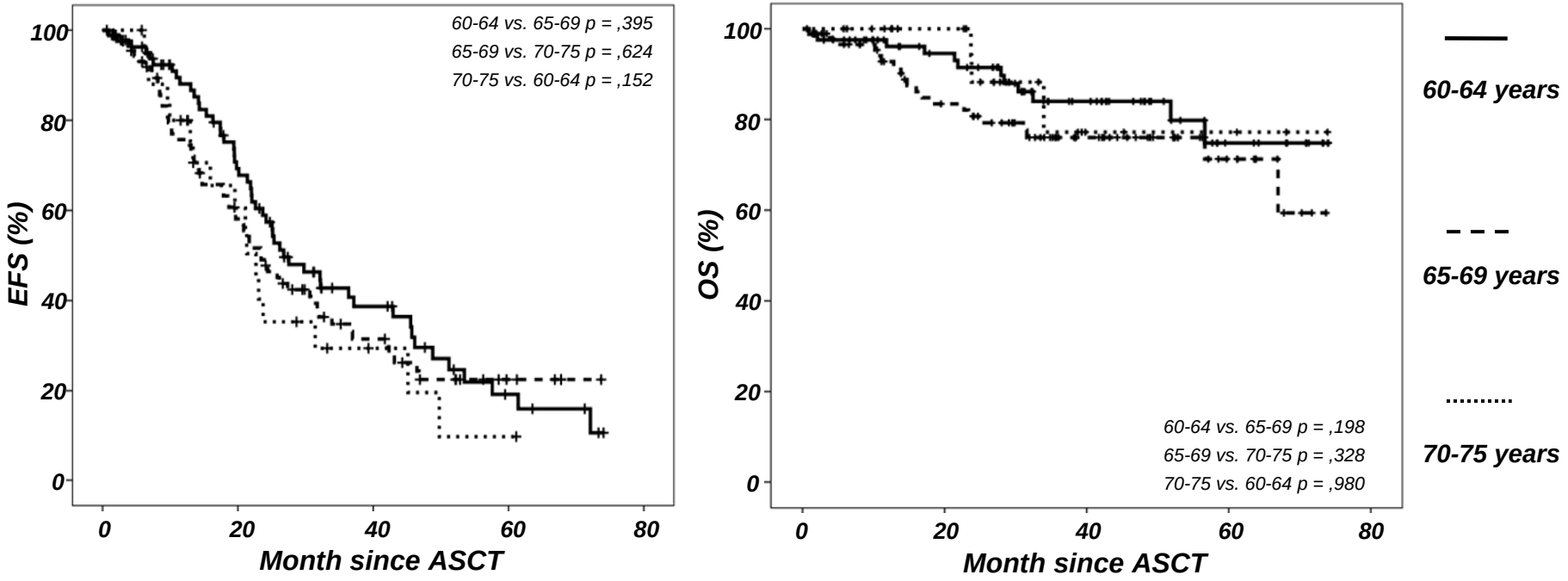
			60-64		65-69		70+		Overall	
			n		*n*		*n*		*n*	
Induction therapy	Novel agent	overall	56	67%	58	62%	14	54%	128	63%
		Bortezomib	52	63%	47	51%	13	50%	112	55%
		IMiD	4	5%	11	12%	1	4%	16	8%
	no novel agent		27	33%	35	38%	12	46%	74	37%
HDT	MEL 200		80	96%	89	96%	26	100%	195	97%
	Tandem MEL200		29	35%	12	13%	2	8%	43	21%
	MEL 100		3	4%	4	4%	0	0%	7	3%
Maintenance therapy	Novel agent	overall	35	42%	27	29%	7	27%	69	34%
		Bortezomib	9	11%	2	2%	0	0%	11	5%
		IMiD	26	31%	25	27%	7	27%	58	29%
	Interferon		5	6%	16	17%	4	15%	25	12%
	no		43	52%	50	54%	15	58%	108	53%

Auto TPL von 2007-09/2012 > 60 in Heidelberg

Safety

		60-64	65-69	70+	Overall
Trans-fusions	thrombocytes	1 (0-3)	1 (0-6)	1 (0-15)	1 (0-15)
	erythrocytes	1 (0-6)	2 (0-11)	2 (0-24)	1 (0-24)
Engraftment (days to)	leucocytes > 1000/µl	13 (0-17)	13 (0-23)	13 (10-18)	13 (0-23)
	thrombocytes > 20000/µl	11 (6-16)	11 (7-16)	11 (8-16)	11 (6-16)
	thrombocytes > 50000/µl	12 (0-26)	12 (0-26)	14 (0-23)	12 (0-26)
Hospitalization (days)	in hospital	21 (16-36)	23 (17-99)	22 (16-56)	22 (16-99)
	fever >38.5°C	3 (0-25)	4 (0-20)	3 (0-10)	4 (0-25)
	intravenous antibiotics	8 (0-25)	9 (0-90)	9 (0-42)	8 (0-90)
	intravenous antimycotics	1 (0-13)	2 (0-84)	2 (0-30)	2 (0-84)
TRM (n)	patients admitted to ICU	3 (4%)	1 (1%)	1 (4%)	5 (3%)
	patients deceased in first 100 days	2 (2%)	1 (1%)	0 (0%)	3 (2%)

EFS und OS



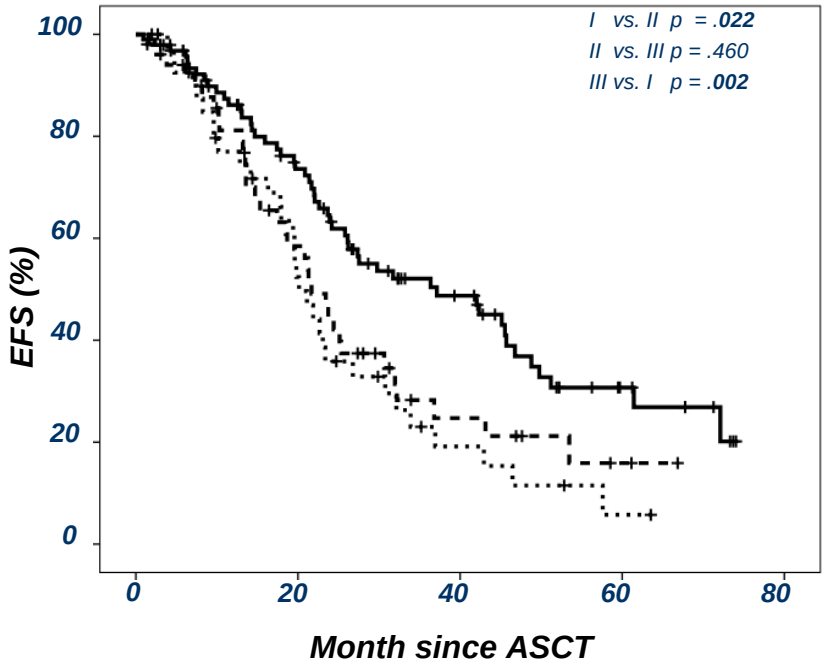
median EFS: *60-64: 27months 65-69: 23months 70-75: 23mo*
median OS: *not reached*

Uni- und multivariate Analyse

		Event-free survival				Overall survival			
		multivariate		univariate		multivariate		univariate	
		HR	*p*	HR	*p*	HR	*p*	HR	*p*
Age	60-64	1,0		1,0		1,0		1,0	
	65-69	1,0	*,918*	1,2	*,391*	1,3	*,532*	1,6	*,204*
	70-75	0,8	*,521*	1,4	*,219*	0,7	*,626*	0,9	*,888*
ISS	I	1,0	-	1,0		1,0		1,0	
	II	1,5	*,127*	***1,7***	***,022***	1,5	*,948*	2,4	*,052*
	III	***1,7***	***,044***	***2,0***	***,002***	***3,7***	***,001***	***4,2***	***,001***
Cytogenetic	low-risk	1,0		1,0		1,0		1,0	
	high-risk	***4,0***	***,000***	***2,6***	***,001***	***5,5***	***,001***	***3,5***	***,005***
Remission before HDT	nCR + CR	1,0		1,0		1,0		1,0	
	PR - VGPR	1,6	*,288*	1,6	*,115*	1,1	*,791*	2,5	*,210*
	SD or PD	1,5	*,392*	1,3	*,387*	1,7	*,644*	3,2	*,136*
Tandem ASCT	no	1,0		1,0		1,0		1,0	
	yes	0,5	*,050*	***0,5***	***,003***	1,1	*,917*	0,5	*,149*
Remission after HDT	nCR + CR	1,0		1,0		1,0		1,0	
	PR - VGPR	***2,5***	***,002***	***2,1***	***,001***	4,3	*,570*	***3,7***	***,016***
	SD or PD	2,4	*,058*	***2,1***	***,043***	7,0	*,610*	***4,6***	***,045***
Maintenance therapy	no	1,0		1,0		1,0		1,0	
	Interferon-α	***0,4***	***,006***	0,7	*,119*	0,8	*,750*	1,3	*,599*
	Novel agent	***0,5***	***,005***	***0,6***	***,013***	0,5	*,213*	0,6	*,186*

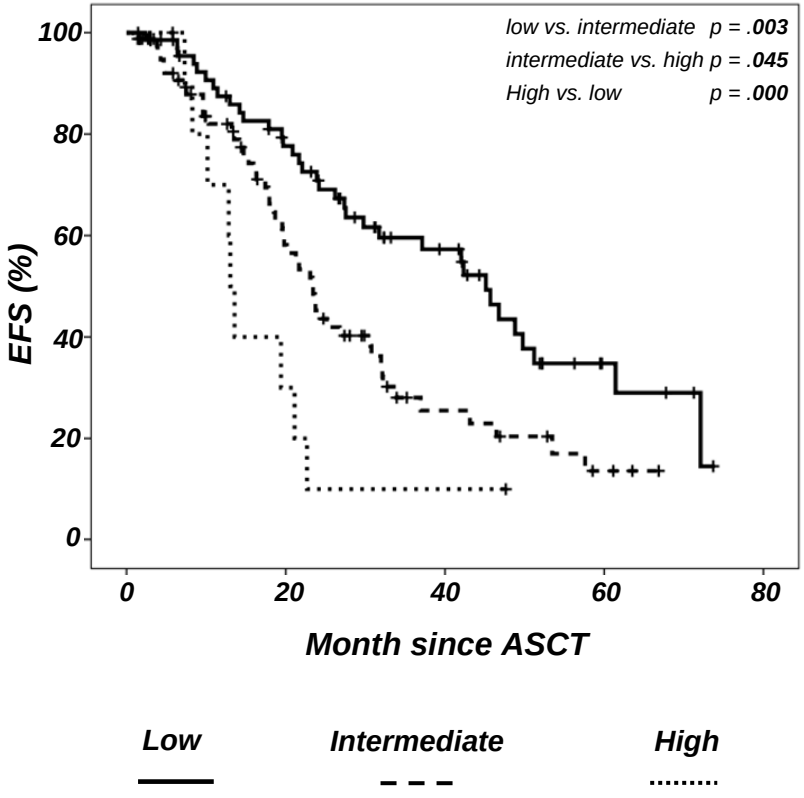
Risikostratifizierung

ISS



ISS und Zytogenetik kombiniert

(nach Neben et al. Blood 2012)



Zusammenfassung

- ***Im Zeitalter der neuen Medikamente ist die Auto TPL >65 Jahre sicher***
- ***Ergebnisse vergleichbar mit 60-65jährigen***
- ***Erhaltungstherapie mit klarem EFS Vorteil***
- ***Risikostratifizierung mittels Zytogenetik sinnvoll***
- ***Limitationen der aktuellen Daten: vermehrt Tandem TPL bei <65jährigen***

4 Überlegungen zur Auswahl der Rezidivtherapie

Rezidiv-Therapie des Multiplen Myeloms
Grundsätzliche Überlegungen

Auswahl der Rezidivtherapie

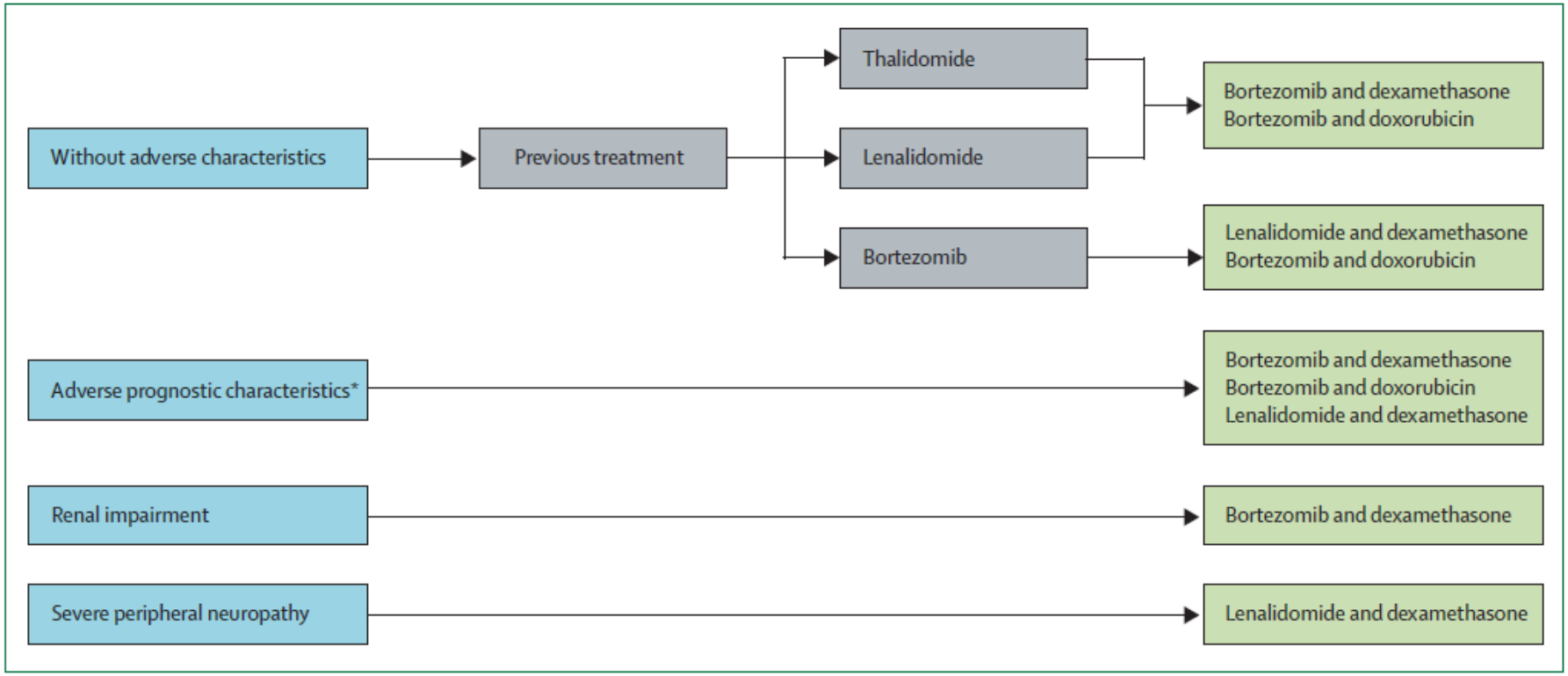


Figure 3: **Treatment considerations of relapsed and refractory disease**

*Adverse characteristics such as short progression-free survival, extramedullary disease, immunoglobulin light chain disease, IgA isotype, and unfavourable cytogenetics.

Raab MS, *et al.*, Lancet, 2009

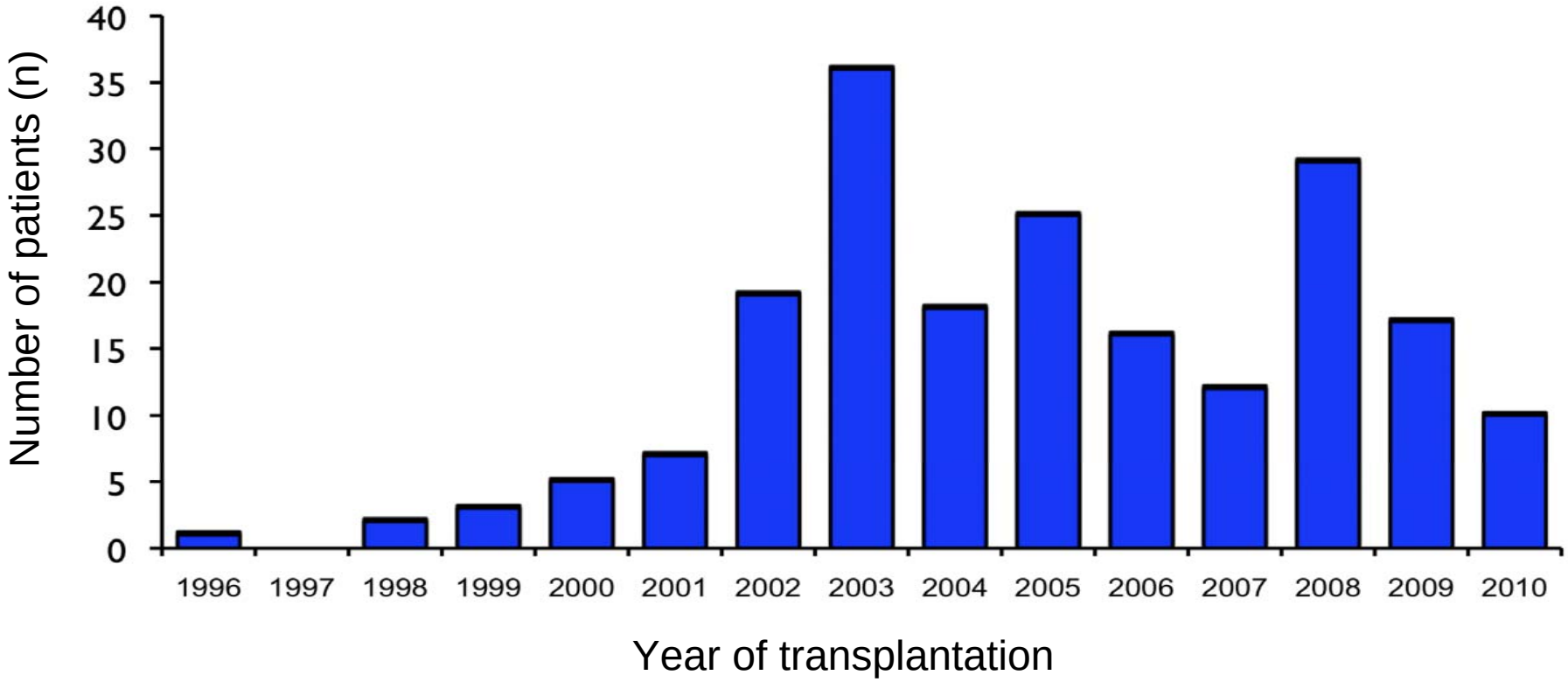
5 Autologe Re-Transplantation

Rezidiv-Therapie des Multiplen Myeloms
Autologe Re-Transplantaton (Uniklinik Heidelberg)

Clinical parameter (n=200)	N (%)
Isotype (IgG / IgA / BJ / others)	55 / 26 / 18/ 1
Gender (male / female)	58 / 42
ISS at diagnosis (I / II / III)	60 / 26 / 14
No. of upfront ASCT (single / tandem)	63 / 37
Age at salvage ASCT (>65 years)	80 / 20
Treatment with Thal prior to salvage ASCT	59
Treatment with Bortezomib prior to salvage ASCT	17
Treatment with Lenalidomide prior to salvage ASCT	27
ISS at salvage ASCT (I / II / III)	69 / 19 / 11

Sellner / Neben, *et al*., Cancer, 2013

Rezidiv-Therapie des Multiplen Myeloms
Autologe Re-Transplantaton (Uniklinik Heidelberg)

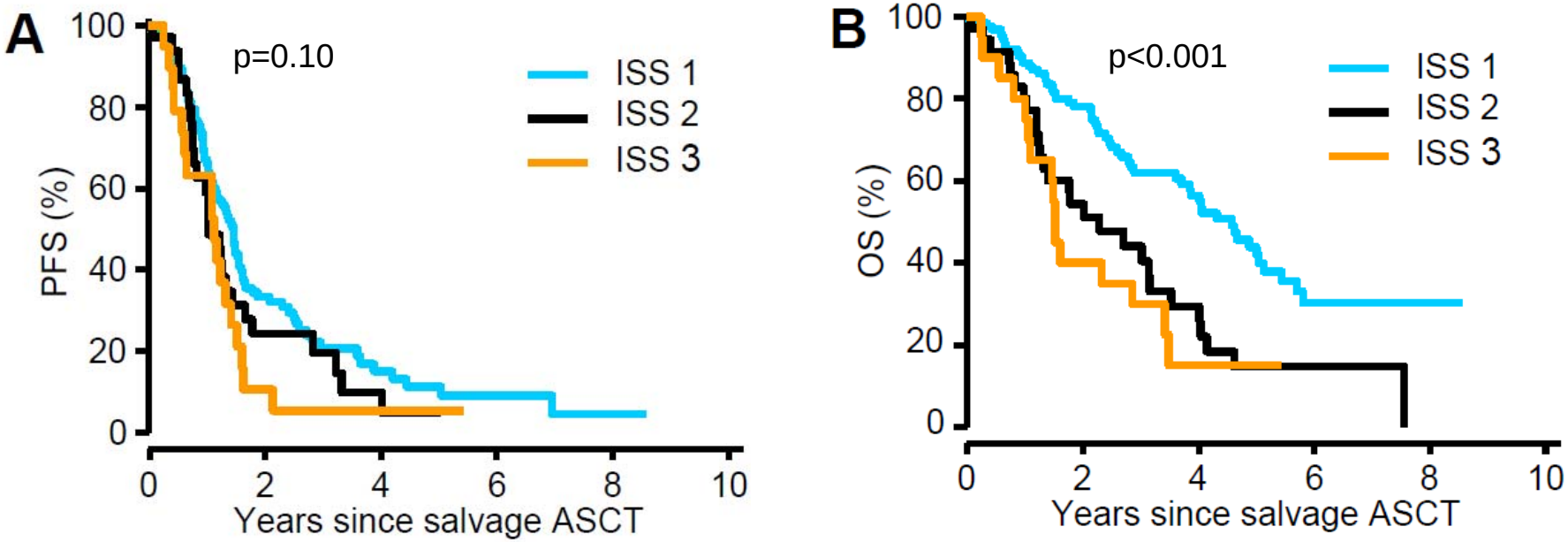


→ **Median follow-up time after salvage ASCT was 57.1 months (95% CI, 52.7- 63.6)**

Sellner / Neben, *et al*., Cancer, 2013

Rezidiv-Therapie des Multiplen Myeloms
Autologe Re-Transplantaton (Uniklinik Heidelberg)

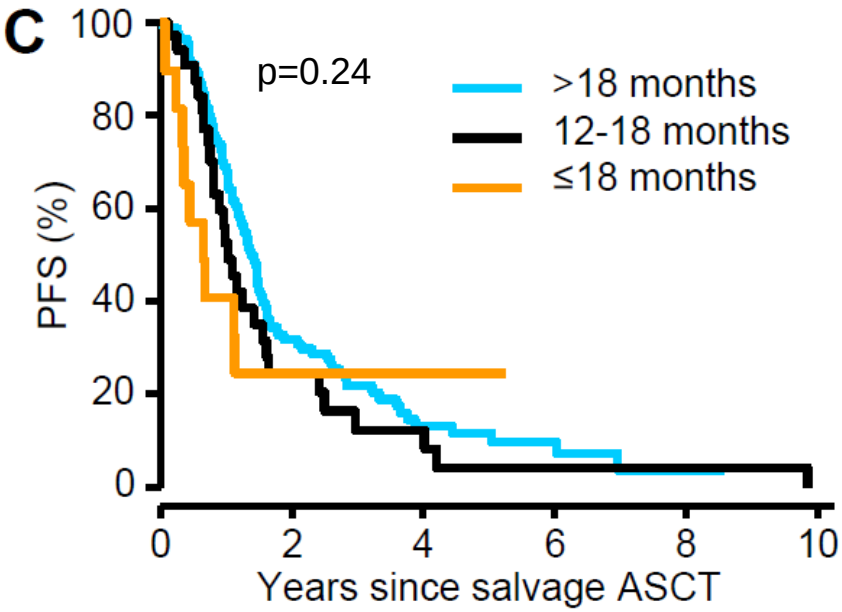
ISS-Stadium vor Re-Transplantation

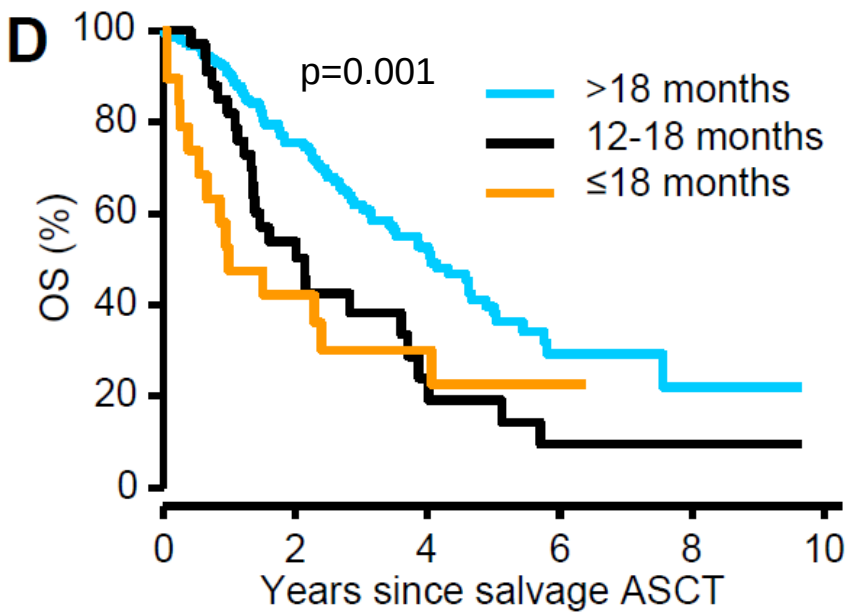


Sellner / Neben, *et al*., Cancer, 2013

Rezidiv-Therapie des Multiplen Myeloms
Autologe Re-Transplantaton (Uniklinik Heidelberg)

Remissionszeit nach Upfront-Transplantation

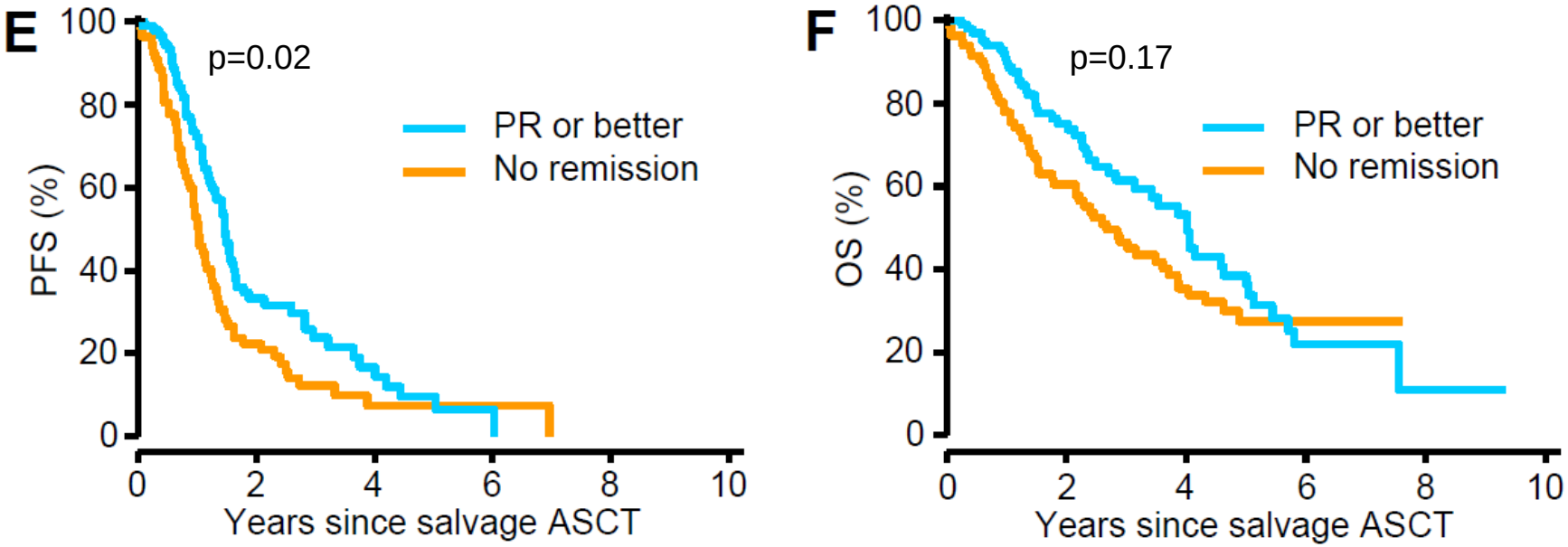




Sellner / Neben, *et al*., Cancer, 2013

Rezidiv-Therapie des Multiplen Myeloms
Autologe Re-Transplantaton (Uniklinik Heidelberg)

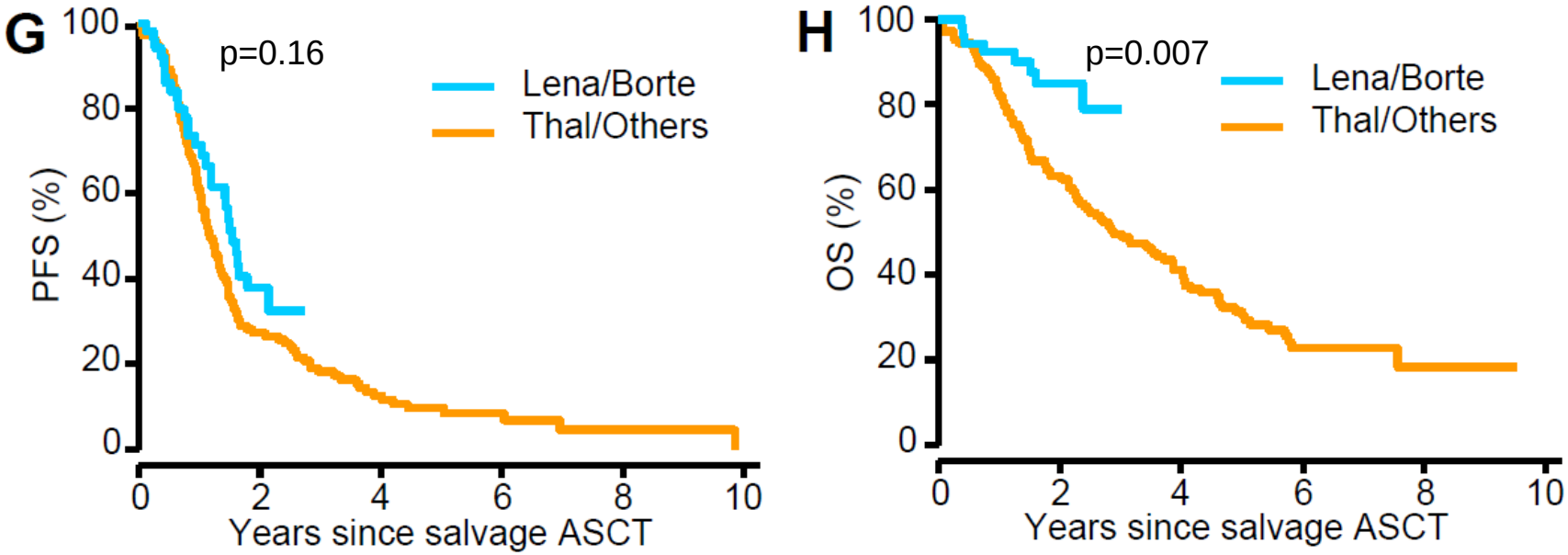
Remissionstatus vor Re-Transplantation



Sellner / Neben, *et al*., Cancer, 2013

Rezidiv-Therapie des Multiplen Myeloms
Autologe Re-Transplantaton (Uniklinik Heidelberg)

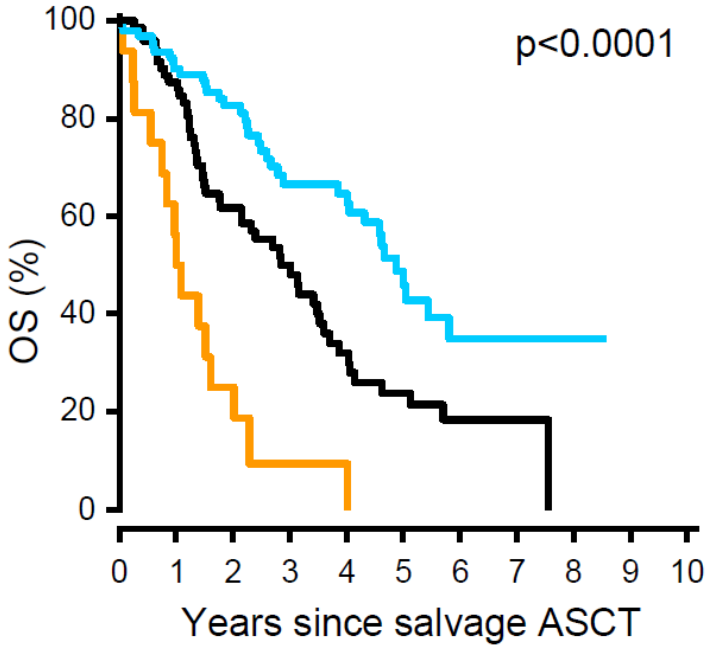
Einsatz von Lena / Borte zur Re-Induktion



Sellner / Neben, *et al*., Cancer, 2013

Rezidiv-Therapie des Multiplen Myeloms
Autologe Re-Transplantaton (Uniklinik Heidelberg)

ISS- und PFS-basierter Prognosescore (OS)



Line	Score	ISS	PFS time after 1st ASCT	OS	
				HR	Median time
	Low risk (n=96)	I	>18 months	1	58.5 months
	Intermediate risk (n=74)	I II/III	≤ 18 months > 18 months	2.03	33.9 months
	High risk (n=16)	II/III	≤ 18 months	6.83	13.5 months

Sellner / Neben, *et al*., Cancer, 2013

Rezidiv-Therapie des Multiplen Myeloms
Autologe Re-Transplantaton

Study	N	NRM (%)	Median TTP after 1st ASCT	Median PFS after salvage ASCT	Median OS after salvage ASCT
Sellner / Neben, 2012	200	2.5	65 mo	15 mo	42 mo
Jimenez-Zepeda, 2011	81	2.6	39 mo	16 mo	53 mo
Fenk, 2011	55	5	23 mo	14 mo	52 mo
Shah, 2011	44	2	?	12 mo	32 mo
Blimark, 2011	66	0	NA	9 mo	24 mo
Olin, 2009	41	7	21 mo	9 mo	21 mo
Burzynski, 2009	25	8	NA	12 mo	19 mo
Elice , 2006	26	0	NA	15 mo	38 mo
Quazilbash, 2006	14	7	NA	7 mo	30 mo

UniversitätsKlinikum Heidelberg

ReLApsE-Studie

Randomisierte, offene, multizentrische Phase III Studie zum Vergleich von Lenalidomid/Dexamethason versus Lenalidomid/Dexamethason mit anschließender autologer Blutstammzelltransplantation und Lenalidomid Erhaltungstherapie für Patienten mit rezidiviertem Multiplen Myelom

Jana Schlenzka

ReLApsE-Studie

282 Patienten

Multiples Myelom, 1.-3. Rezidiv
18-70 Jahre

Randomisation

3 Zyklen Rd

1) Cyclophosphamid
+ G-CSF
+ Stammzellsammlung

Rd
bis Progress

bei Progress
Hochdosistherapie + Auto Tx empfohlen
(außerhalb dieser Studie)

3 Zyklen Rd

1) Cyclophosphamid
+ G-CSF
+ Stammzellsammlung

HD Mel 200mg/m²
+ autologe Transplantation

2) R-Erhaltungstherapie
bis Progress

1) Stammzellmobilisierung und -sammlung wenn kein geeignetes Transplantat von früheren Mobilisierungen vorhanden
2) Revlimid-Erhaltungstherapie 10mg/d kontinuierlich
R-Revlimid ® (Lenalidomid), d-Dexamethason, HD Mel-Hochdosis Melphalan

Primäre Fragestellung

- **progressionsfreies Überleben**

Sekundäre Fragestellungen

- Gesamtüberleben
- Ansprechraten
- Toxizitätsanalyse

Zentren

- 18 Zentren initiiert

Berlin Charité Campus Benjamin Franklin
Helios Klinikum **Berlin-Buch**
Med. Univ.-Klinik **Bonn**
Klinikum **Bielefeld**
Städt. Klinikum **Braunschweig**
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Franziskuskrankenhaus **Mönchengladbach**
Universitätsklinikum **Tübingen**


Vielen Dank für Ihre Aufmerksamkeit!