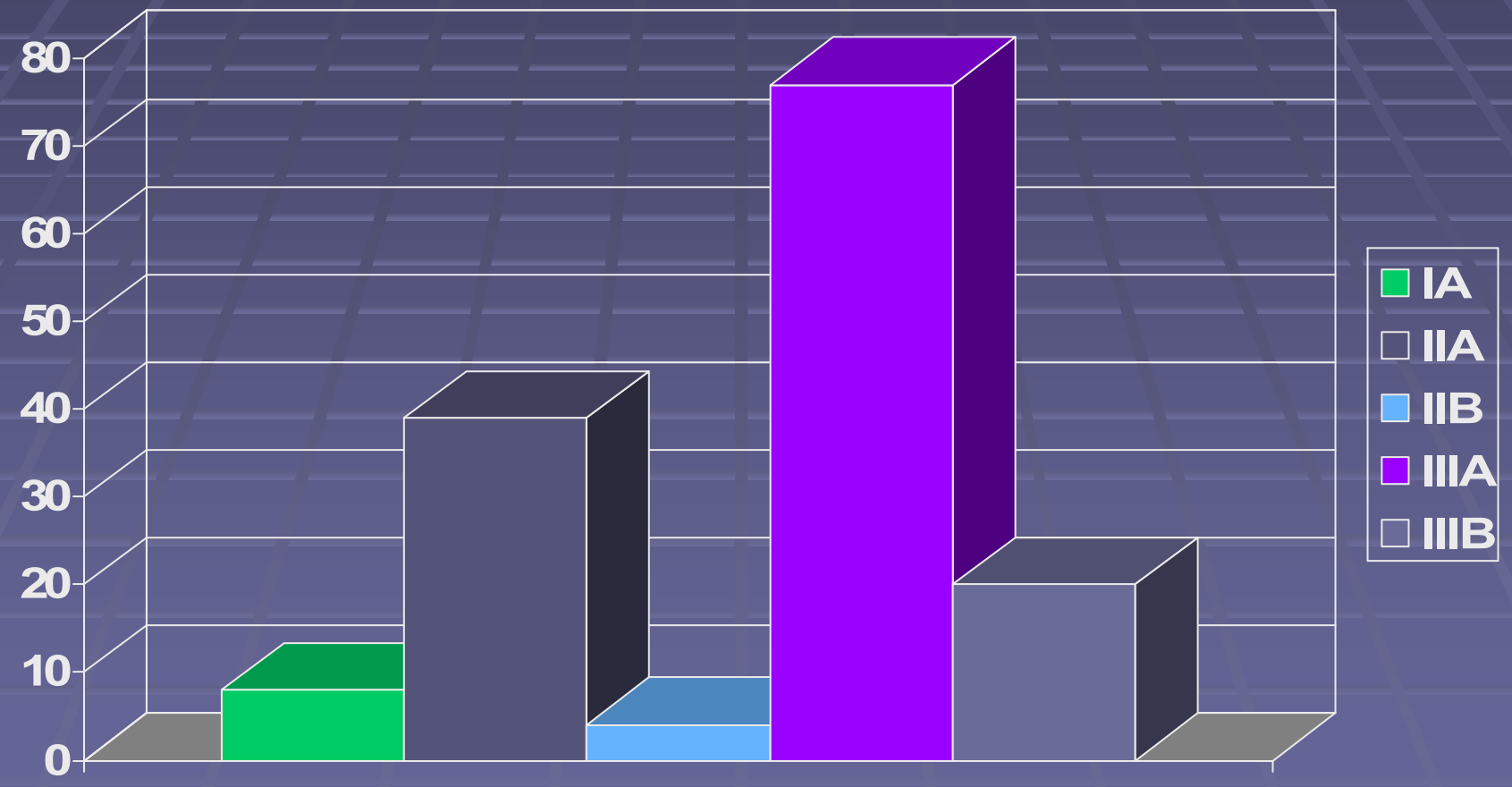
Bortezomib v léčbě MM ve 2. a dalších liniích. Výsledky v ČR a SR

CMG (I.Špička et al.) + SMS (P.Kotouček et al.)

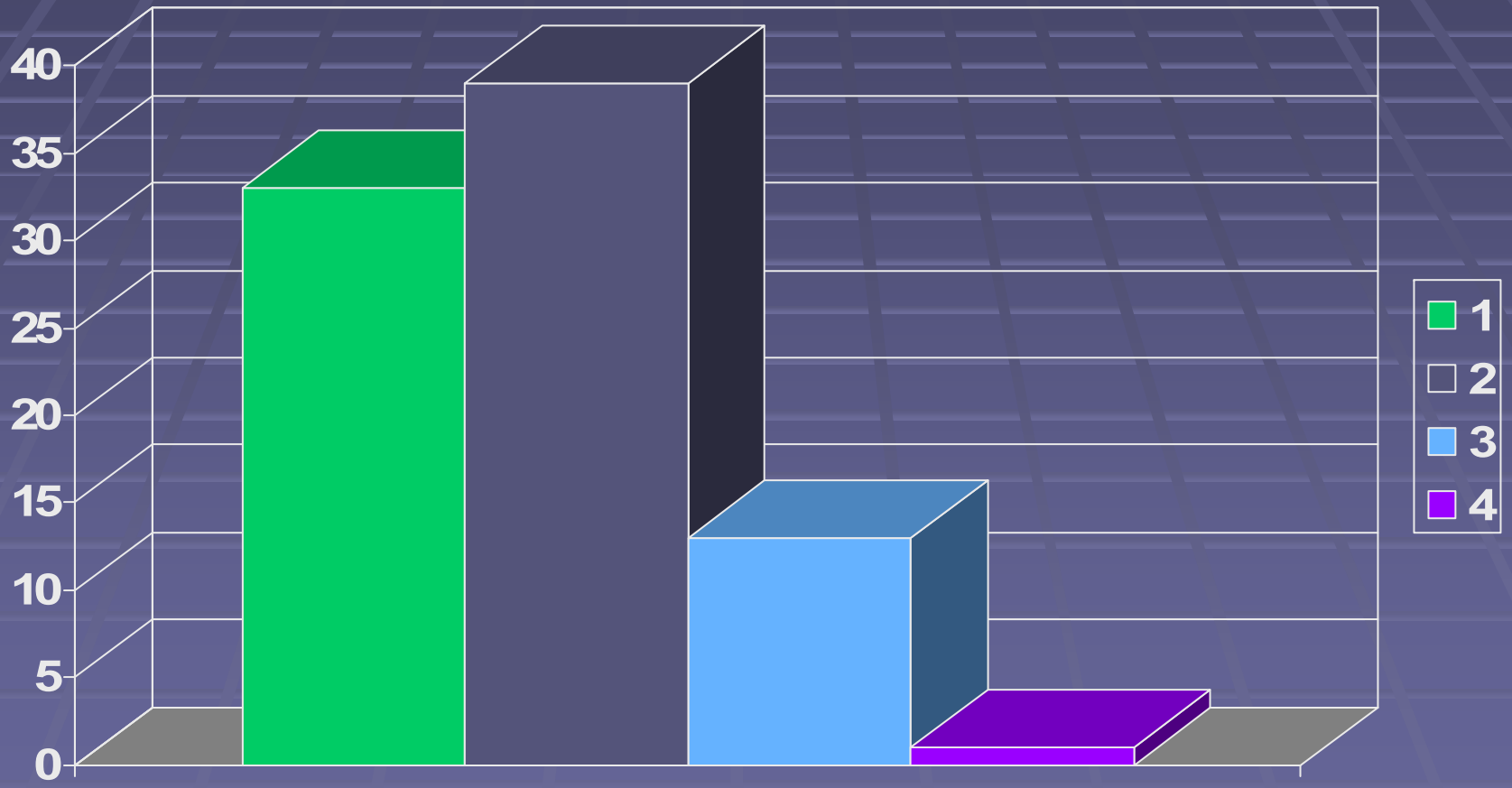
Soubor pacientů, základní charakteristiky

Věk	33 - 78
Sex	M 89 Ž 59
Předchozí linie	1 - 11 cyklů
Předchozí th.Thalid.: 58 pac.	
Celkem pac.	148

Klinické stádium



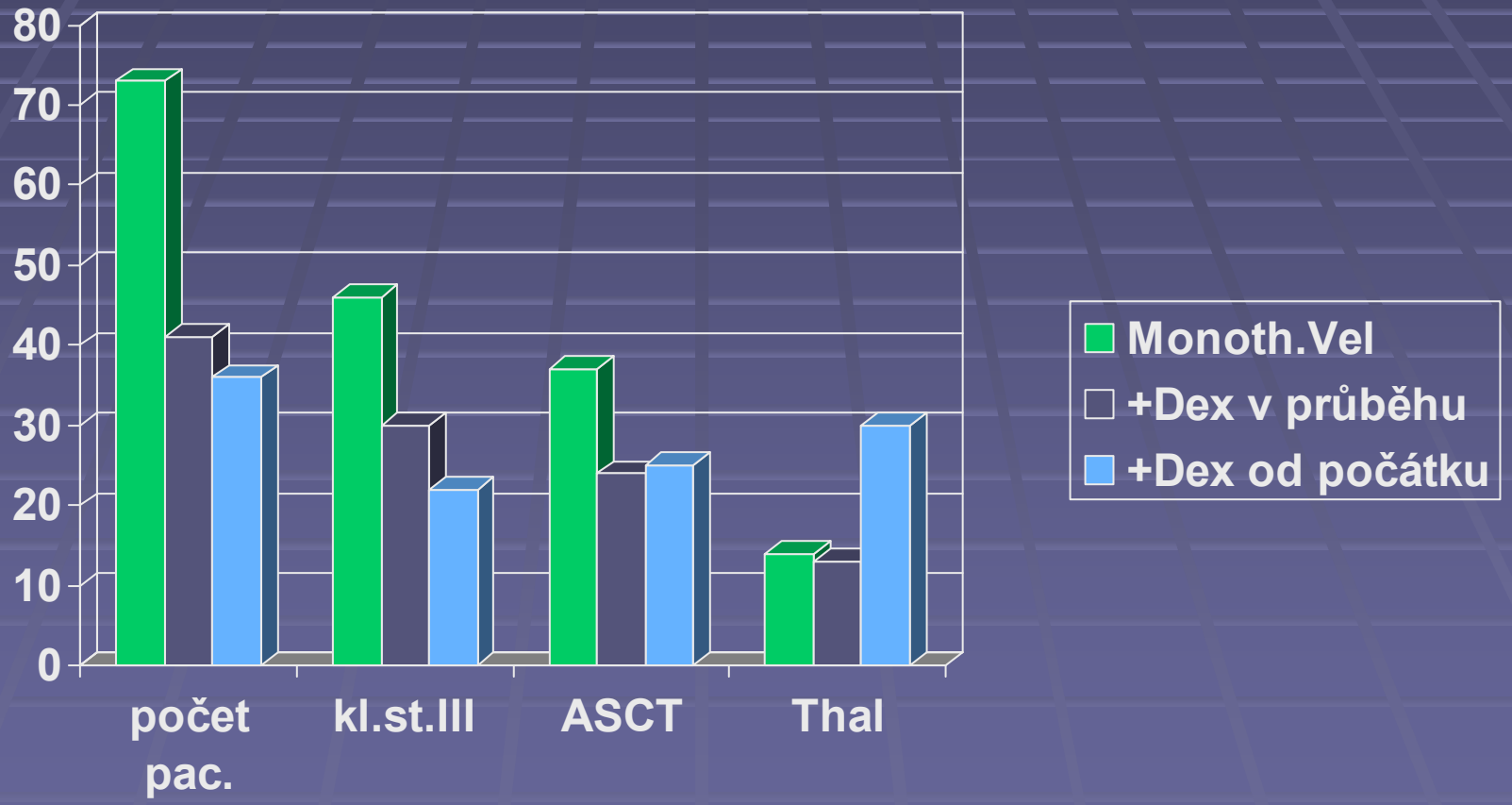
Předchozí ASCT (86 pac.)



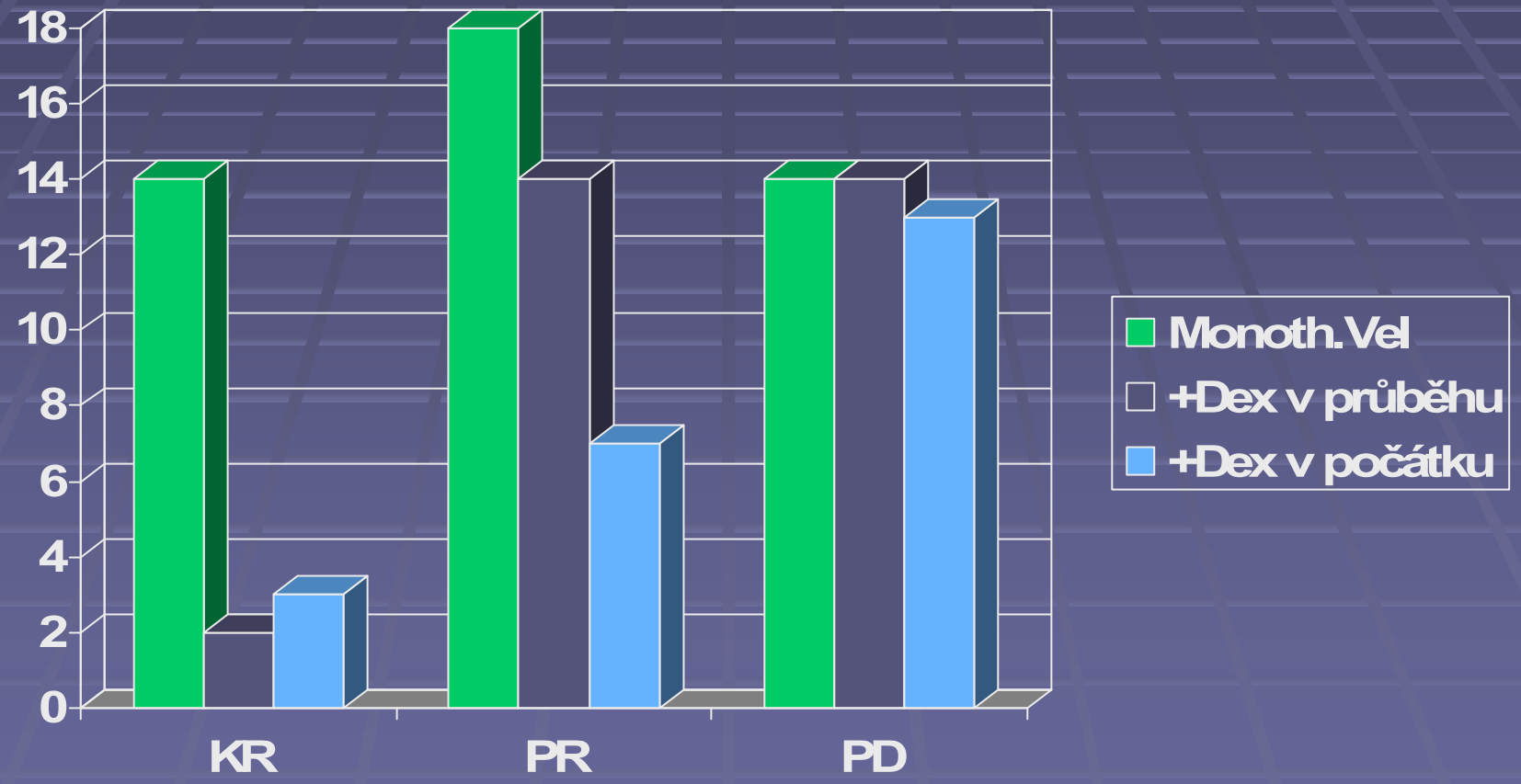
Výsledky léčby

KR	19(12.8%)
KR+PR	58(39.2%)
SD	25 (16.9%)
PD	41 (27.7%)

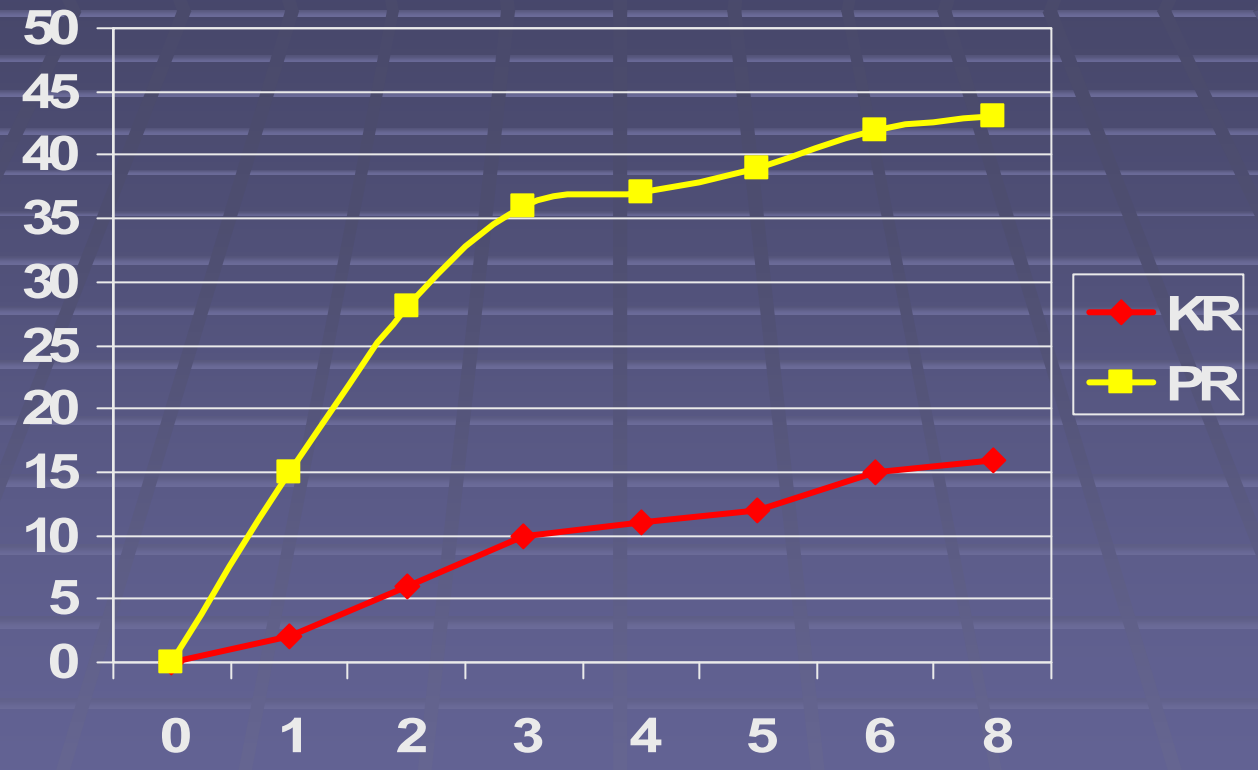
Rozdělení dle způsobu léčby – charakteristika souborů



Výsledky léčby dle skupin

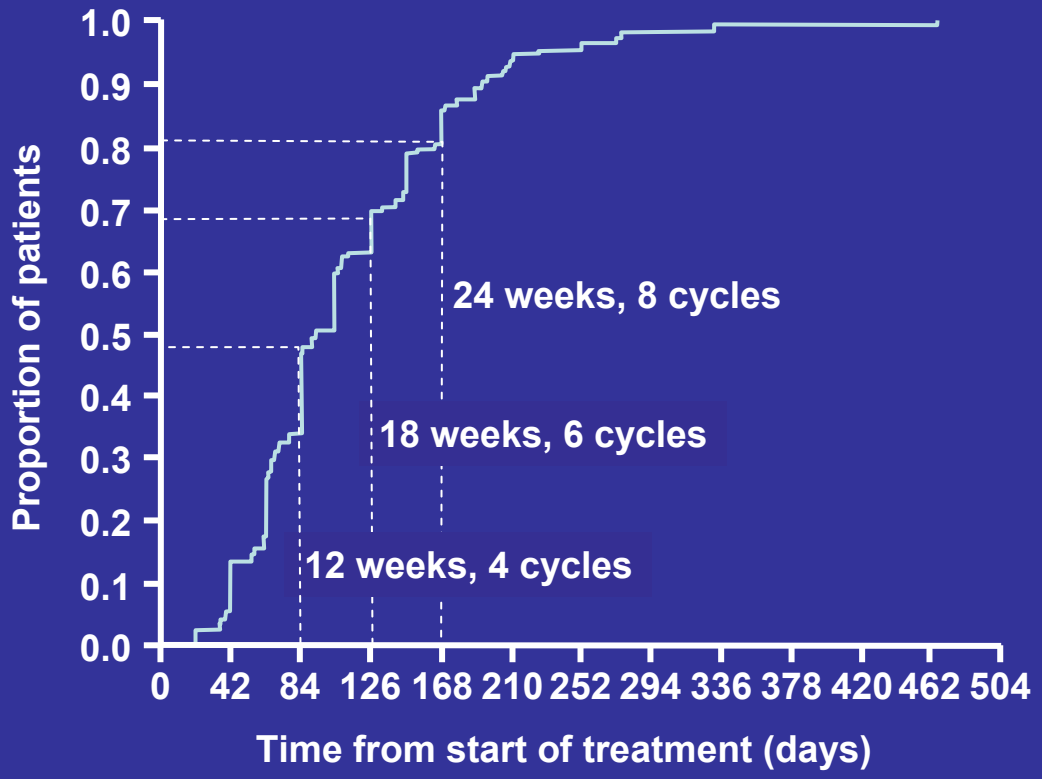


Odpověď po cyklech terapie



Best response achieved after longer duration of bortezomib therapy

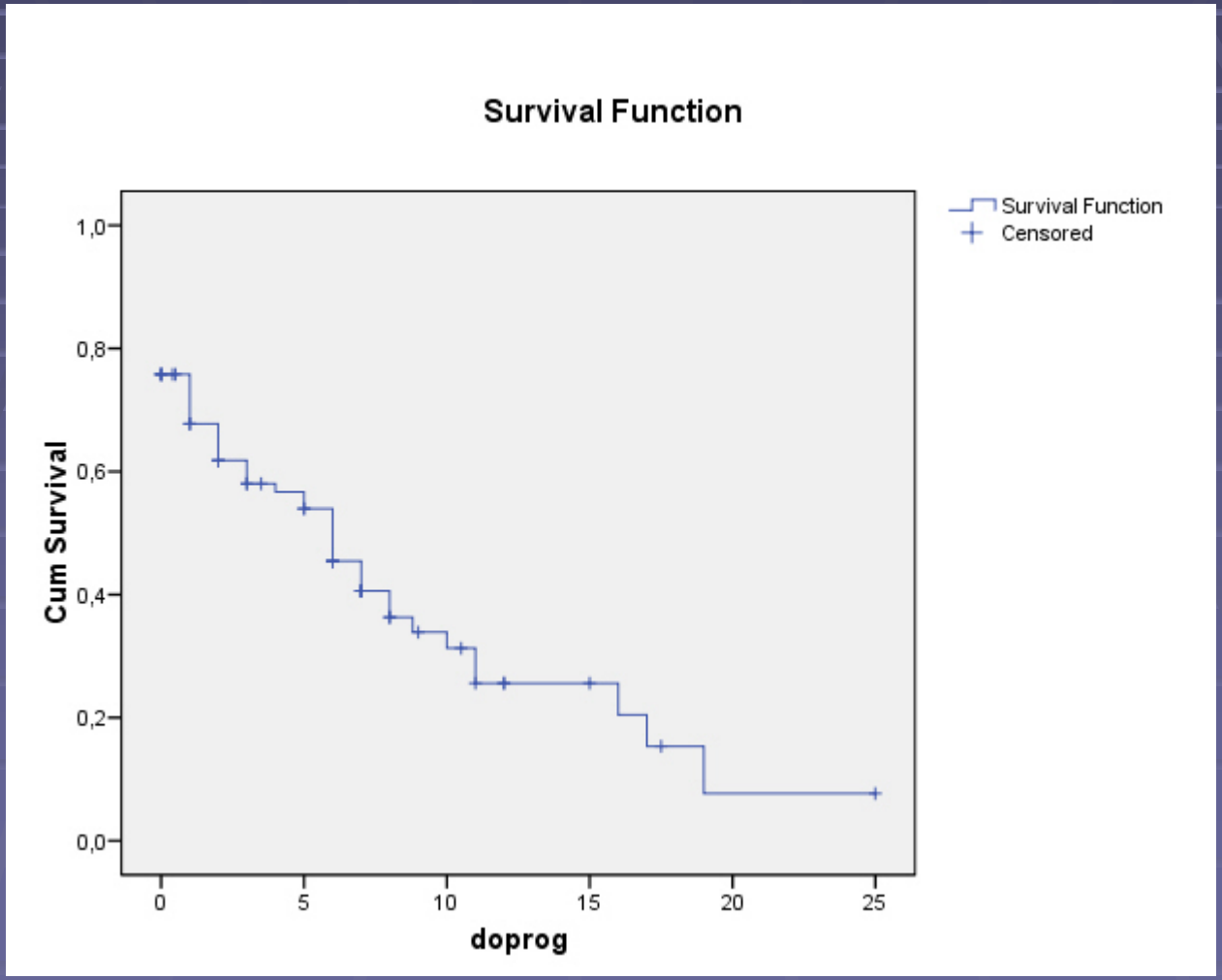
Time to maximal serum M-protein reduction in patients responding to bortezomib



Approximately 20% of patients responding to bortezomib achieved maximal M-protein reduction in cycle 8 or later

Richardson *et al. Blood* 2005;106 (Abstract 2547); Poster at ASH 2005

PFS


Survival Function
Survival Function
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Cum Survival
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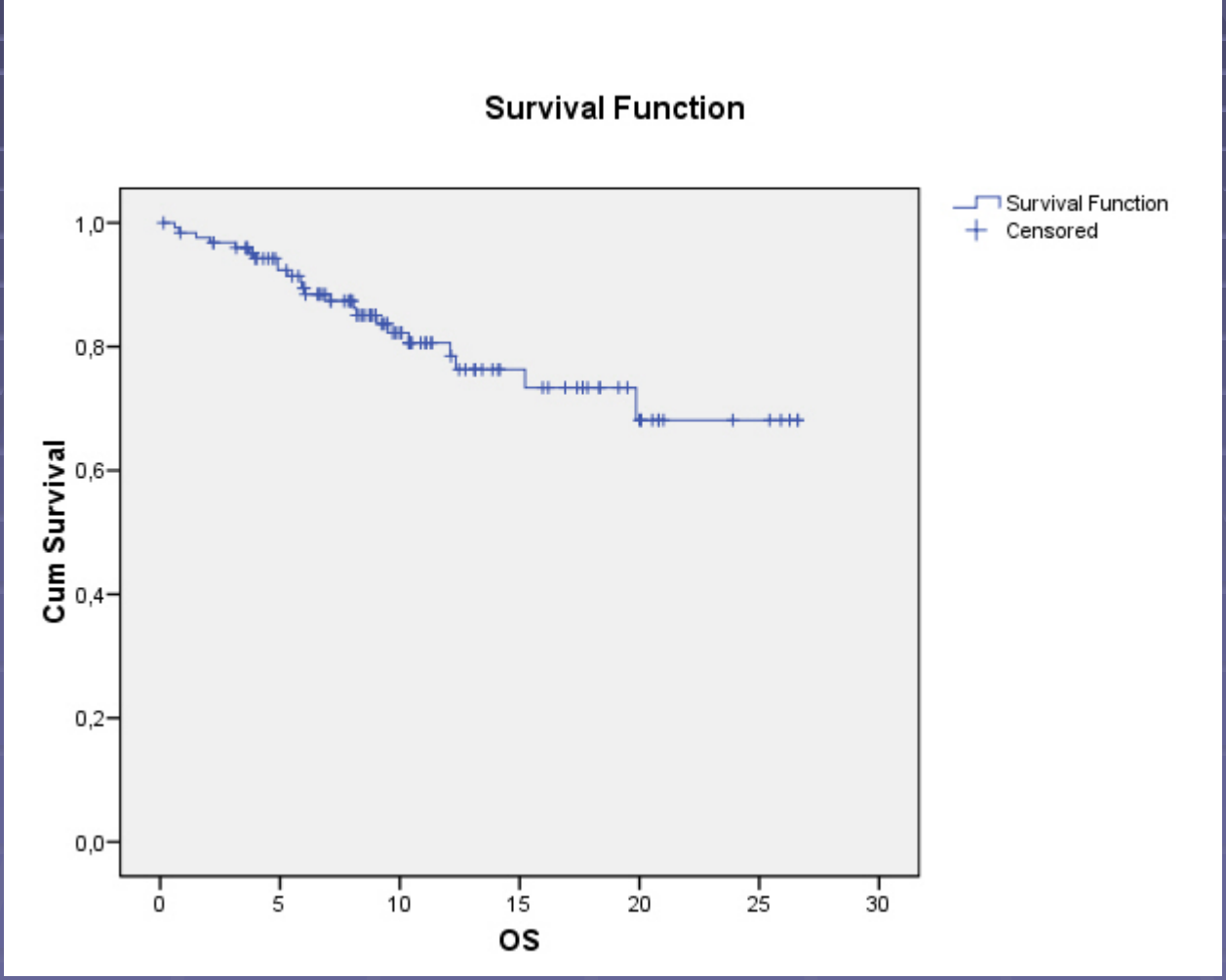
OS


Survival Function
Survival Function
Censored
Cum Survival
1,0
0,8
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0,2
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20
25
30
OS

Neuropathy (139 pts.)

Neuropathy at baseline (history, initial examin., gr.1,2): 43x

Total **78 pts. (56.1%)**

gr. 3,4 **28 pts. (20,1%)**

Analysis according to baseline involvement	Overall risk (%)	Grade 3/4 risk (%)
Neuropathy initially - NO	45,8	16,7
Neuropathy initially – YES	79,1	27,9

Thrombocytopenia (132 pts.)

Thrombocytopenia at baseline (gr.1,2) – 26x

Total **75 pts. (56.8%)**

gr. 3,4 **40 pts. (30.3%)**

Analysis according to baseline involvement	Overall risk (%)	Grade 3/4 risk (%)
Thrombocytopenia initially - NO	48.5	23.3
Thrombocytopenia initially - YES	86.2	55.2

Soubor pacientů předléčených thalidomidem, základní charakteristiky

Věk		33 - 75
Sex		M 42
		Ž 16
Předchozí linie		1 - 11 cyklů
Kl. stádium	I	5
	II	16
	III	37
Typ M-Ig	IgG	44
	IgA	9
	BJ	3
	biklon	1
	IgD	1
Celkem pac.		58

Výsledky léčby

KR	5 (8.6%)
KR+PR	20 (34,5%)
SD	10 (17.2%)
PD	21 (36.2%)

Odpověď dle předch. terapie

Odpověď	Celý soubor	Pac.po thalid.	Pac.bez thalid.
KR	12,8%	8,6%	18,3%
KR+PR	39,2%	34,5%	40.9%
KR+PR+MR	40%	29,8%	46,2%

Efficacy of single agents in relapsed/refractory MM

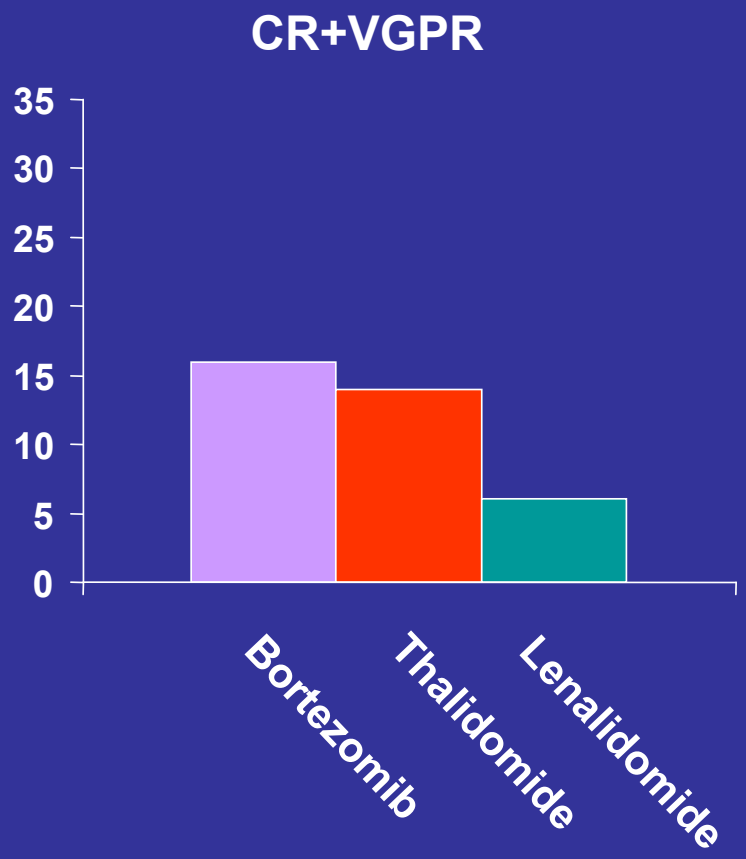
Regimen	Phase	n	CR + PR	CR + nCR	Reference
Bortezomib (APEX)	3	331	43%	16%	Richardson *et al.* *Blood* 2005;106 (abstract 2547)
Thalidomide	2	169	30%	14%	Barlogie *et al.* *Blood* 2001;98:492–4
		42	43%	-	Cibeira *et al.* *Eur J Haematol* 2006;77:486–92
Lenalidomide	2	222	27%	Not given	Richardson *et al.* *Blood* 2005;106 (abstract 1565)
		101	24%	6%	Richardson *et al.* *Blood* 2003;235a (abstract 825)

Bortezomib combinations for relapsed/ refractory MM presented in 2006 (+1agent)

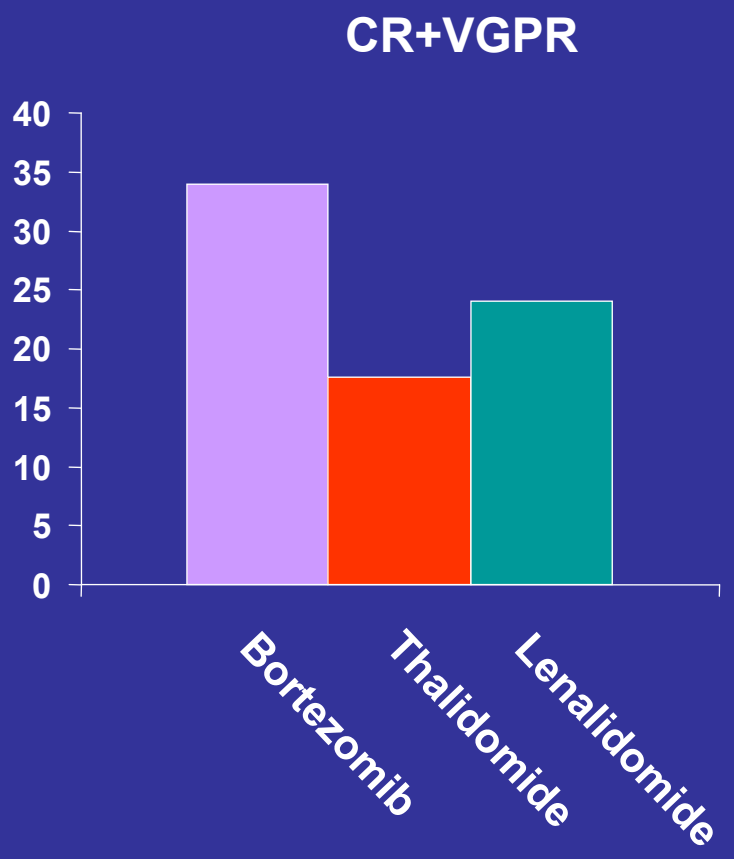
Bortezomib regimen	Phase	n	CR + PR	CR + nCR	Abstract
± Dexamethasone	3b	624	54%	35%*	Mikhael *et al.* *Blood* 2006;108 (abstract 3530)
+ Dexamethasone	1/2	32	67%	29% (CR only)	Solano *et al.* *Haematologica* 2006;91 (abstract 1210)
+ DOXIL	3	646	48%	14%	Orlowski *et al.* *Blood* 2006;108 (abstract 404)
+ Lenalidomide	1	38	39%	6%	Richardson *et al.* *Blood* 2006;108 (abstract 405)

Efficacy in relapsed/refractory MM

Single agents



In combination



Referenced from published literature

Bortezomib multi-drug combination – higher CR + nCR rate

Regimen	Phase	n	CR + PR	CR + nCR	Abstract
Bortezomib (1.3 mg/m^2) + adriamycin + dexamethasone (PAD)	2	21	**Pre-SCT 95%** **Post-SCT 95%**	**Pre-SCT 29%** **Post 57%**	**Oakervee *et al.* *Br J Haem* 2005;129:755–62**
Bortezomib (1.0 mg/m^2) + adriamycin + dexamethasone (reduced-dose PAD)	2	19	**Pre-SCT 89%** **Post-SCT 100%**	**Pre-SCT 16%** **Post-SCT 54%**	**Popat *et al*. *Blood* 2005;106 (abstract 2554)**
Bortezomib + pegylated doxorubicin	2	63	**Pre-SCT 58%**	**Pre-SCT 16%**	**Orlowski *et al.* ASH 2006 (abstract 797)**
Bortezomib + doxil + dexamethasone	2	30	**Pre-SCT 89%** **Post-SCT 96%**	**Pre-SCT 32%** **Post-SCT 54%**	**Jakubowiak *et al*. ASH 2006 (abstract 3093)**

Response rates are increased following transplantation

CR and overall outcome in MM

- 721 previously untreated patients < 65 years
- Treatment: high-dose dex-based combination (primary therapy) + ASCT (n=397)

Patient group	Median survival
CR after primary therapy	10–14 years
CR after intensive therapy of PR or NR	10–14 years
PR after primary treatment	4.3 years
PR after intensive therapy	5.9 years
Resistant disease	2 years

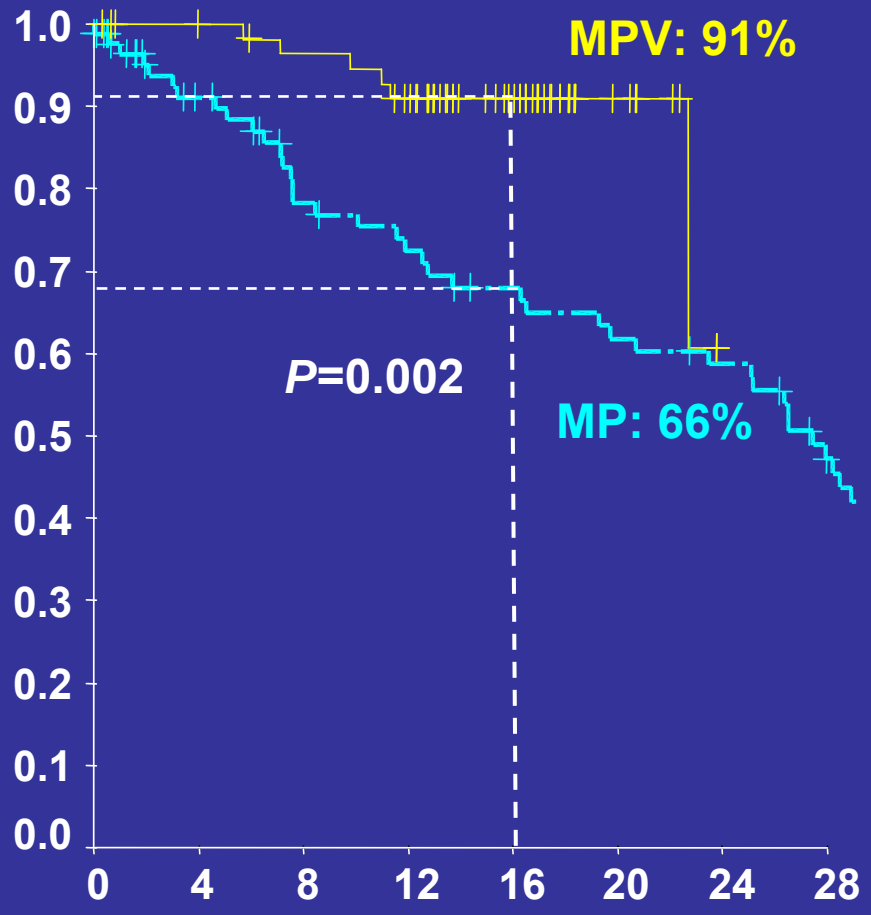
High-dose therapy: no additional benefit after CR at initial therapy

Randomized trials required to evaluate this further

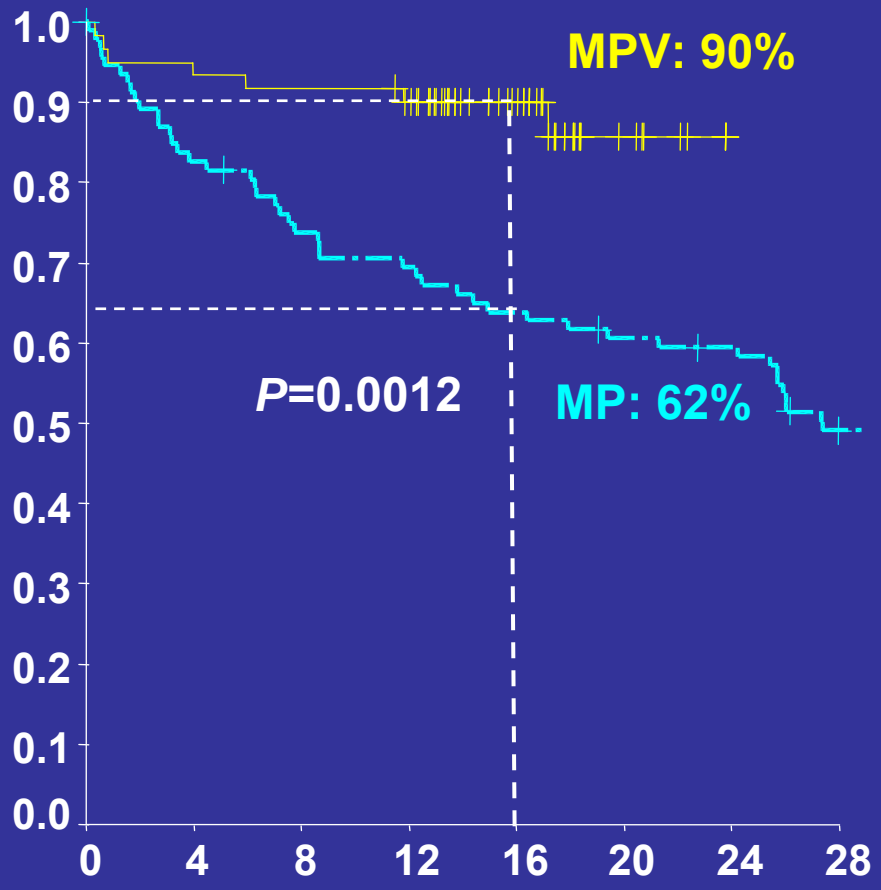
Wang *et al*. ASH 2006 (Abstract 403)

MPV

Progression-free survival



Overall survival

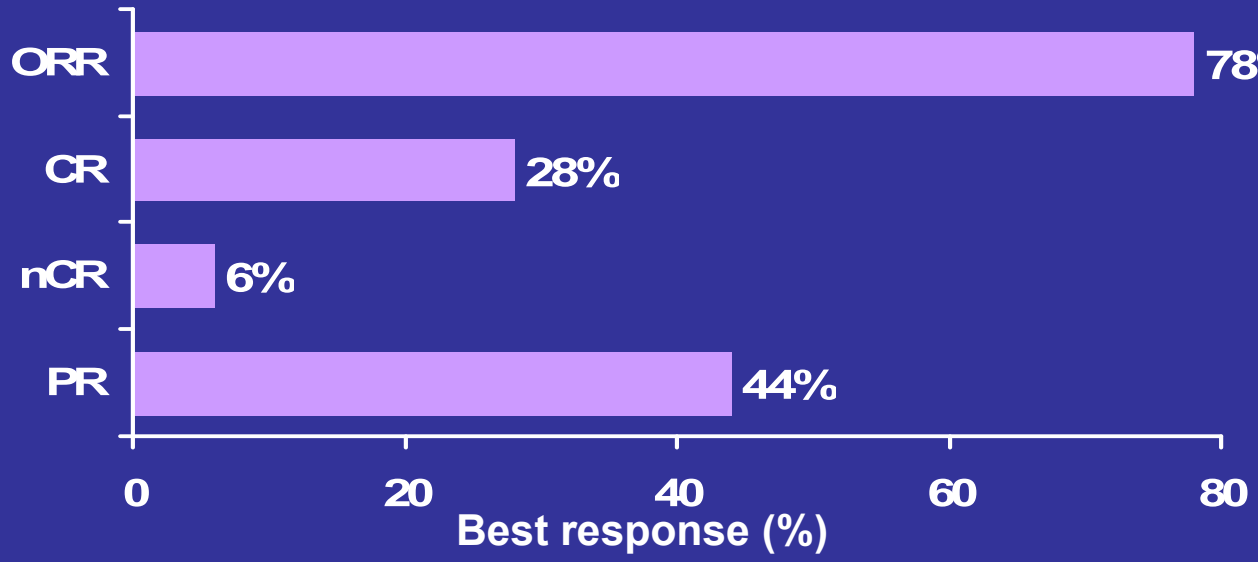


Median follow-up: 16 months (11–24)

Mateos *et al*. *Blood* 2006;108:2165–72

Bortezomib in patients with renal failure requiring dialysis

- Retrospective analysis of 24 patients treated with:
  - Single-agent bortezomib
  - Bortezomib combinations (+ dex + thal/dex + thal/doxorubicin)
- Number of therapies prior to bortezomib: median 2 (range 0–6)



Comparable response rates and toxicity profile of bortezomib in patients requiring renal dialysis

Chanan-Khan A *et al*. *Blood* 2006 Epub Nov30

Bortezomib – efekt na kostní chorobu.

ASH 2006:Preclinical studies

Author (abstract no.)	Results
Zavrski *et al*. ASH 2006 (abstract 1395)	Bortezomib inhibited osteoclastogenesis
Boissy *et al*. ASH 2006 (abstract 3508)	Bortezomib transiently inhibited osteoclast activity
Breitkreuz et al. ASH 2006 (abstract 3485)	Bortezomib inhibited osteoclast differentiation
Feng et al. ASH 2006 (abstract 507)	Synergistic inhibition of osteoclastogenesis by bortezomib and PXD101
Mukherjee *et al*. ASH 2006 (abstract 88)	Bortezomib promoted osteoblastogenesis
Giuliani *et al*. ASH 2006 (abstract 508)	Bortezomib increased osteoblast differentiation Bortezomib did not affect mature osteoblasts
Pennisi et al. ASH 2006 (abstract 509)	• Bortezomib increased BMD in responding mice • Bortezomib suppresses osteoclastogenesis through downregulation of NFκB activity in osteoclast precursors

ASH 2006: Clinical studies

Effect of bortezomib on markers of bone metabolism

	Baseline	After 4 cycles of bortezomib	*P* (vs baseline)	After 8 cycles of bortezomib	*P* (vs baseline)
Osteoblast inhibitor					
DKK-1 (ng/mL)	76.6	53.6	0.035	25.8	0.001
Osteoclast regulators					
sRANKL (pmol/L)	0.47	0.25	0.01	0.09	<0.001
OPG (pmol/L)	3.54	3.31	0.249	2.29	0.151
sRANKL/OPG	0.12	0.05	0.126	0.03	0.01
Markers of bone resorption					
CTX (ng/mL)					
TRACP-5b (U/L)	0.7	0.33	<0.001	0.25	0.001
	2.59	1.86	<0.001	2.04	0.003
Markers of bone formation					
bALP (U/L)					
OC (ng/mL)	17.3	23.7	<0.001	26	<0.01
	7.46	12.5	<0.01	19	<0.01

Terpos *et al*. ASH 2006 (Abstract 506)

IVIG u bortezomibem indukované neuropatie

Neuropatie (PNY)	**35%**
Redukce dávky/ukončení th.	**12/5%**
Asie - PNY (20 pac.)	**75%**
Redukce dávky/ukončení th.	**53/27%**

Gabapentin, L-carnitin, amitriptylin – prakticky bez efektu

IVIG, zlepšení PNY o aspoň 1 stupeň - 9/9 pac.

TeohG., et al., ASH 2006, abstr.5097

Poděkování