

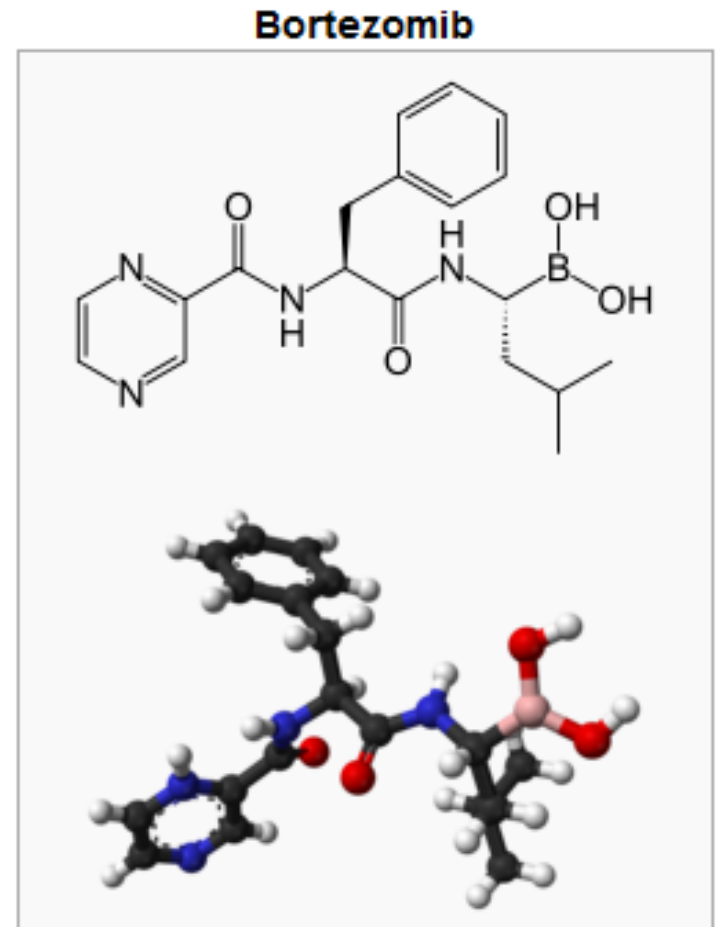
Vliv způsobu podání bortezomibu na účinnost a bezpečnost léčby pacientů s mnohočetným myelomem

MUDr. P. Pavlíček
FN KV a 3. LF UK Praha

*Tato prezentace vznikla
s finanční podporou společnosti
Johnson & Johnson, s.r.o. - div. Janssen*

Bortezomib

- **Proteazomový inhibitor**
působící cíleně na proteolýzu
ubiquitních proteinů proteazomu
- 1995 - PS 341
- 2003 - FDA
- 2012 - S.C.
- S.C.:
stejná látka, stejná dávka
jiná koncentrace
(1,0 mg/ml i.v. x 2,5 mg/ml s.c.)



THE LANCET **Oncology**

- Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study

P. Moreau et al. 2011

- 53 léčebných center v Evropě, Asii a Jižní Americe, publikováno v květnovém vydání *Lancet Oncology*

P. Moreau et al. 2011

- 222 pacientů, randomizace 2:1 (s.c. : i.v.)
- 1,3 mg/m²; D 1, 4, 8, 11; cyklus 21 dnů
- Bez stat. významného rozdílu v ORR, TTP, 1Y OS
- Toxicita: u některých org. systémů až o 10% nižší u s.c.
- S.C. podání: lokálně dobře tolerováno

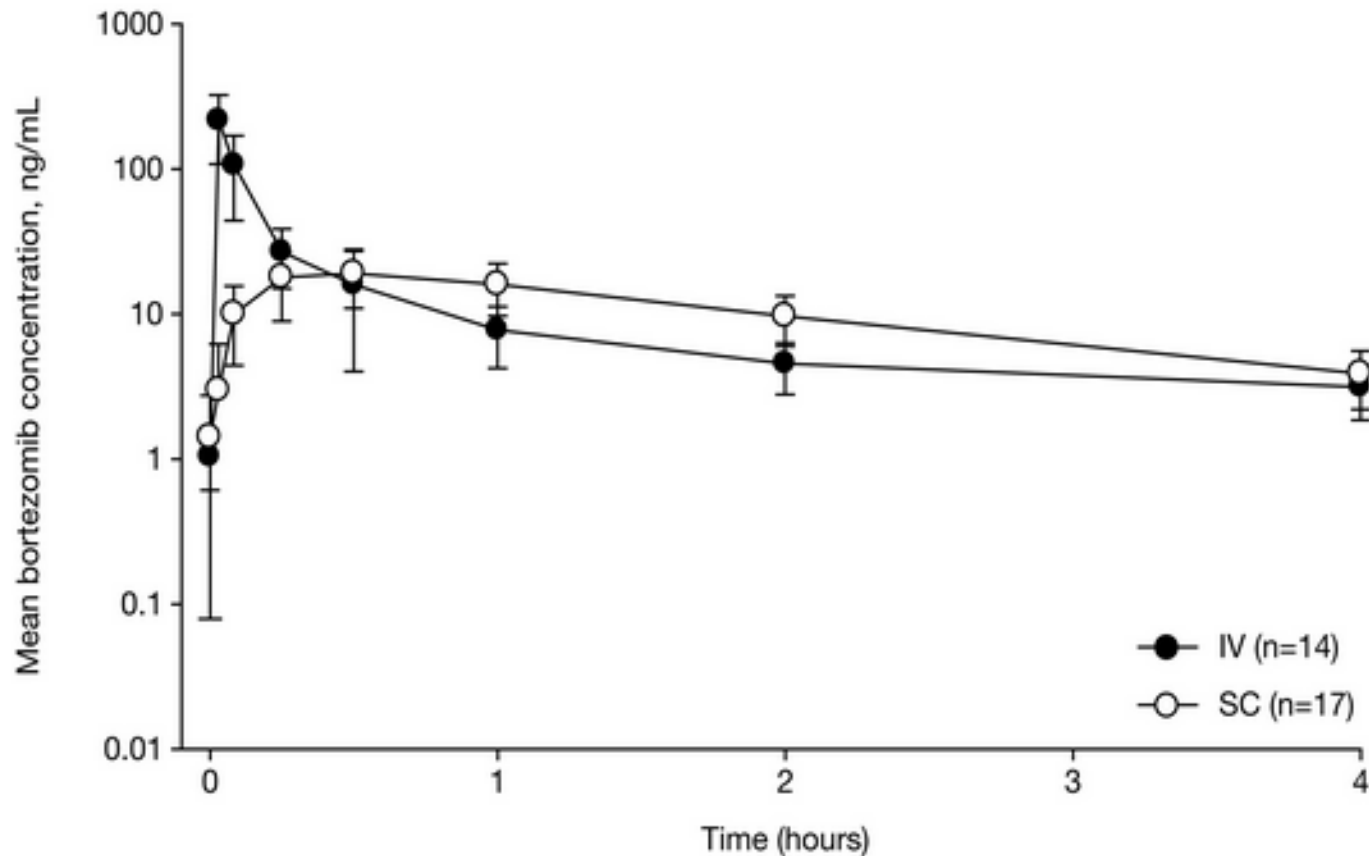
Polyneuropatie

P. Moreau et al. 2011

	S.C. (%)	I.V. (%)
Gr. 1-4	38	53
Gr. 2, 3, 4	24	41
Gr. 3, 4	6	16

S.C. x I.V.

Mean (SD) plasma bortezomib concentration-time profile following IV or SC injection of 1.3 mg/m² on day 11

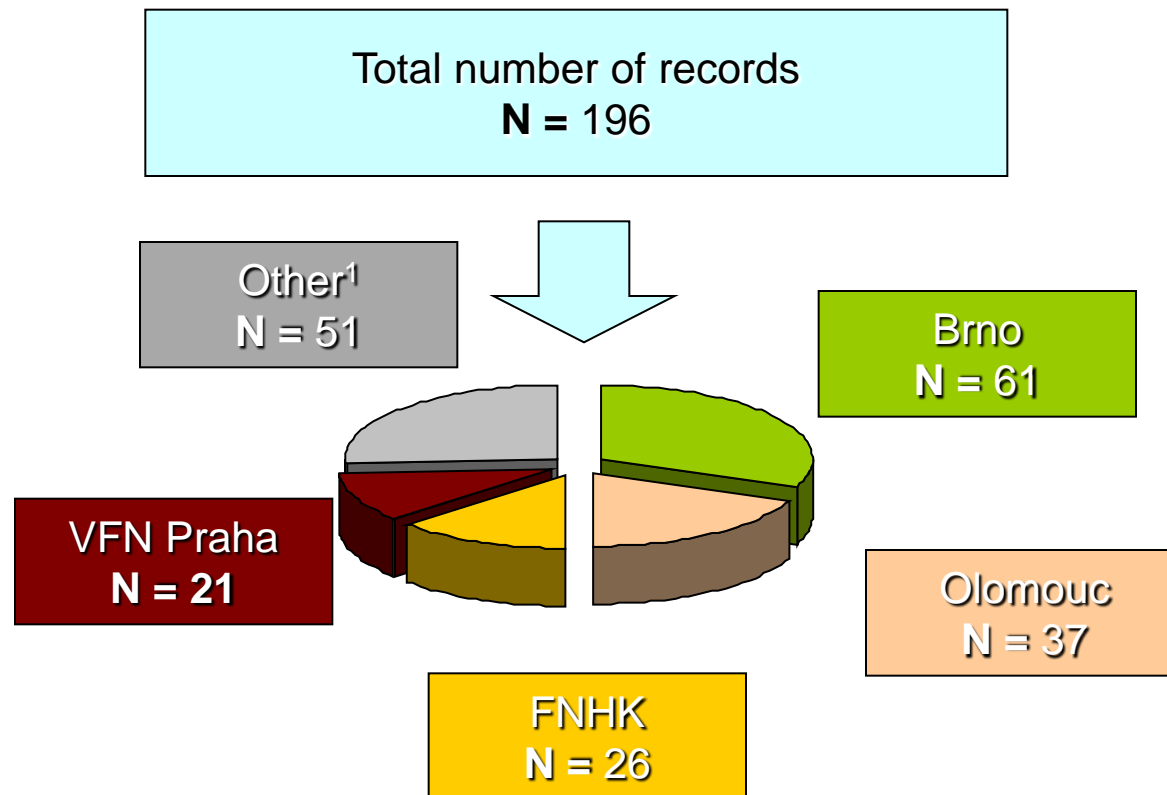


Velcade v ČR - 2013

- Celkový počet zahájených léčeb Velcade..... 363
- Způsob podání vyplněn140

- S.C.:.....109 (77.9%)
- I.V.:.....19 (13.6%)
- I.V. ad S.C.:11 (7.9%)
- S.C. ad I.V.:..... 1 (0.7%)

Centra ČR

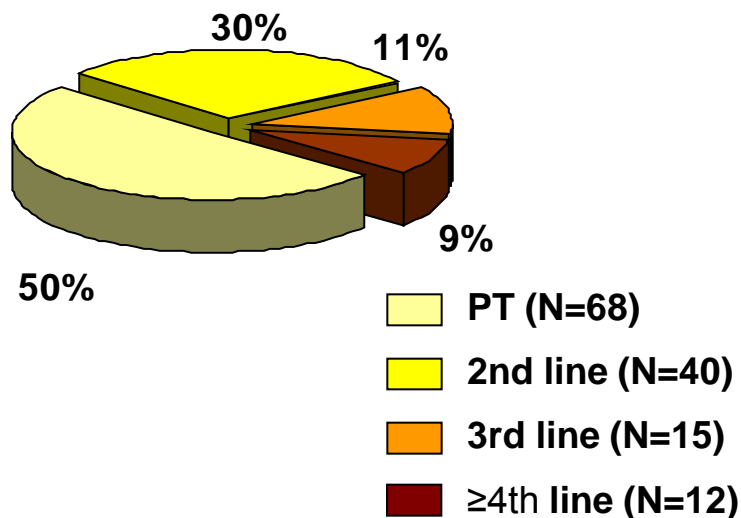


Centre	Total (N=196)	IV (N=135)	SC (N=61)
FN Brno - IHOK	61 (31.1%)	50 (37.0%)	11 (18.0%)
FN Olomouc - III. interní klinika	37 (18.9%)	25 (18.5%)	12 (19.7%)
FNHK - IV. interní hematologická klinika	26 (13.3%)	10 (7.4%)	16 (26.2%)
VFN Praha - I. Interní klinika	21 (10.7%)	16 (11.9%)	5 (8.2%)
Other ¹	51 (26.0%)	34 (25.2%)	17 (27.9%)

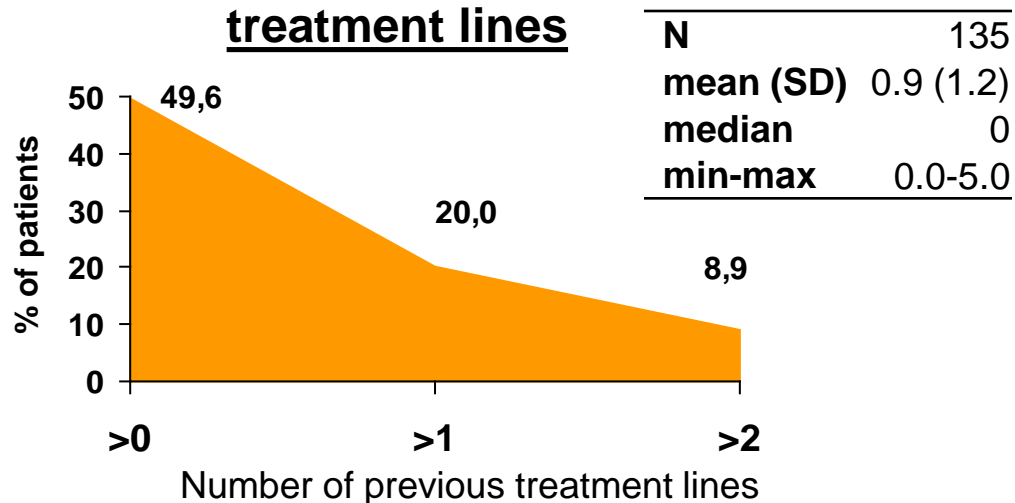
¹ Centres with less than 15 records

Počet léčebných linií

IV (N=135)

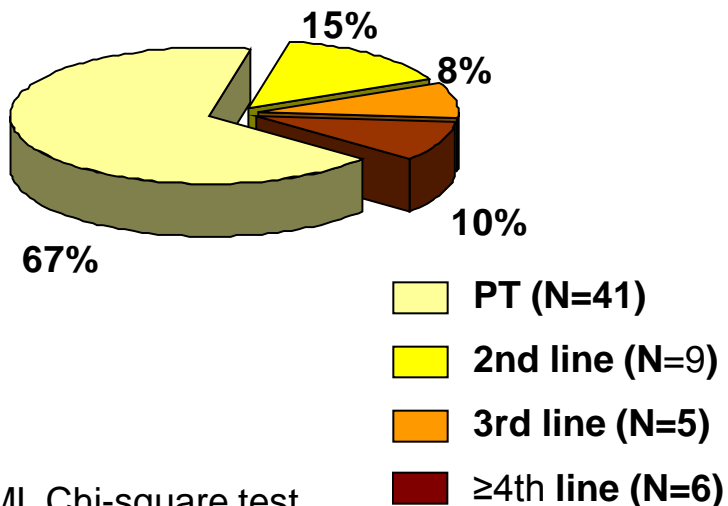


Number of previous treatment lines

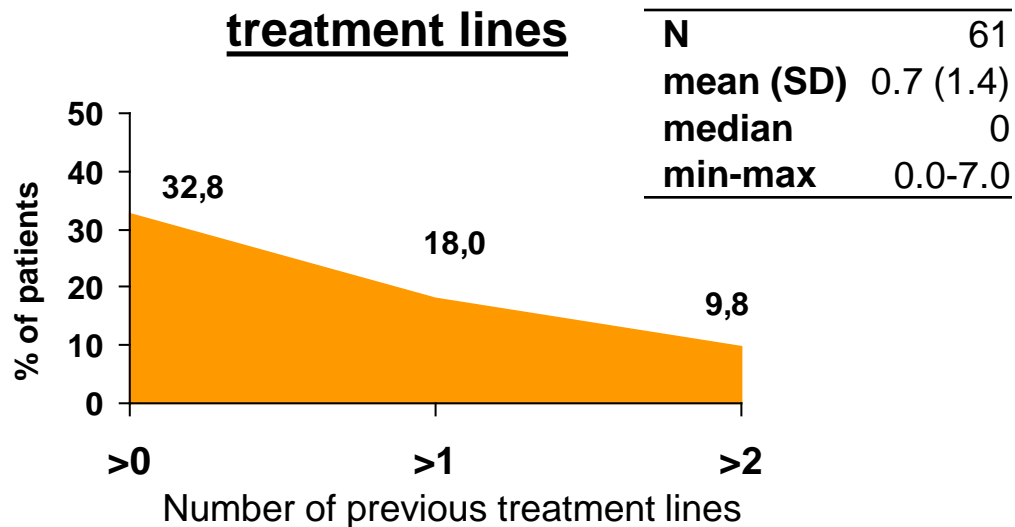


SC (N=61)

$p^1 = 0.087$



Number of previous treatment lines

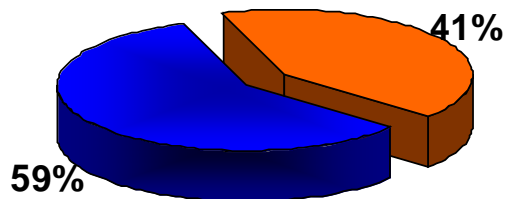


¹ ML Chi-square test

Pohlaví a věk

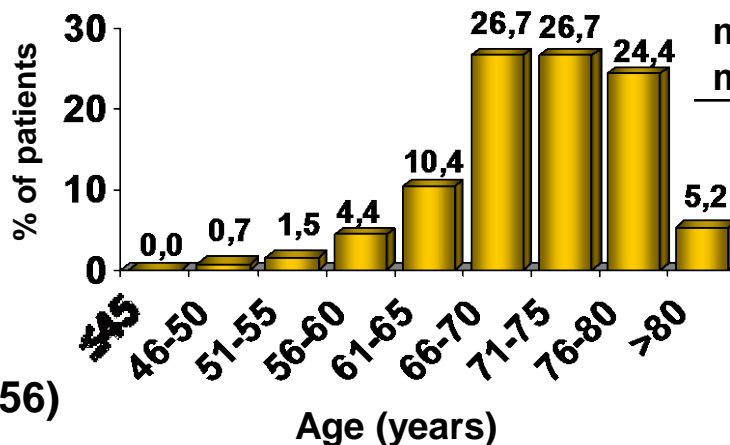
IV (N=135)

Sex



Men (N=79) Women (N=56)

Age

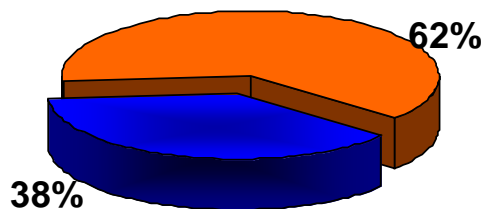


N	135
mean (SD)	71.3 (6.8)
median	72
min-max	46.0-86.0

$p^1 = 0.007$

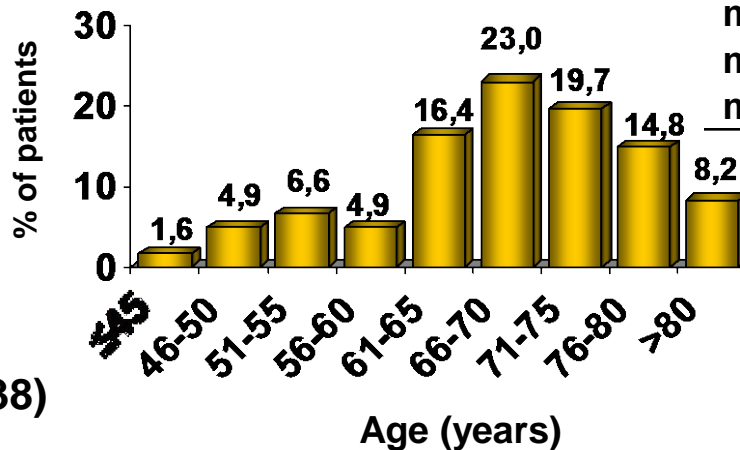
SC (N=61)

Sex



Men (N=23) Women (N=38)

Age

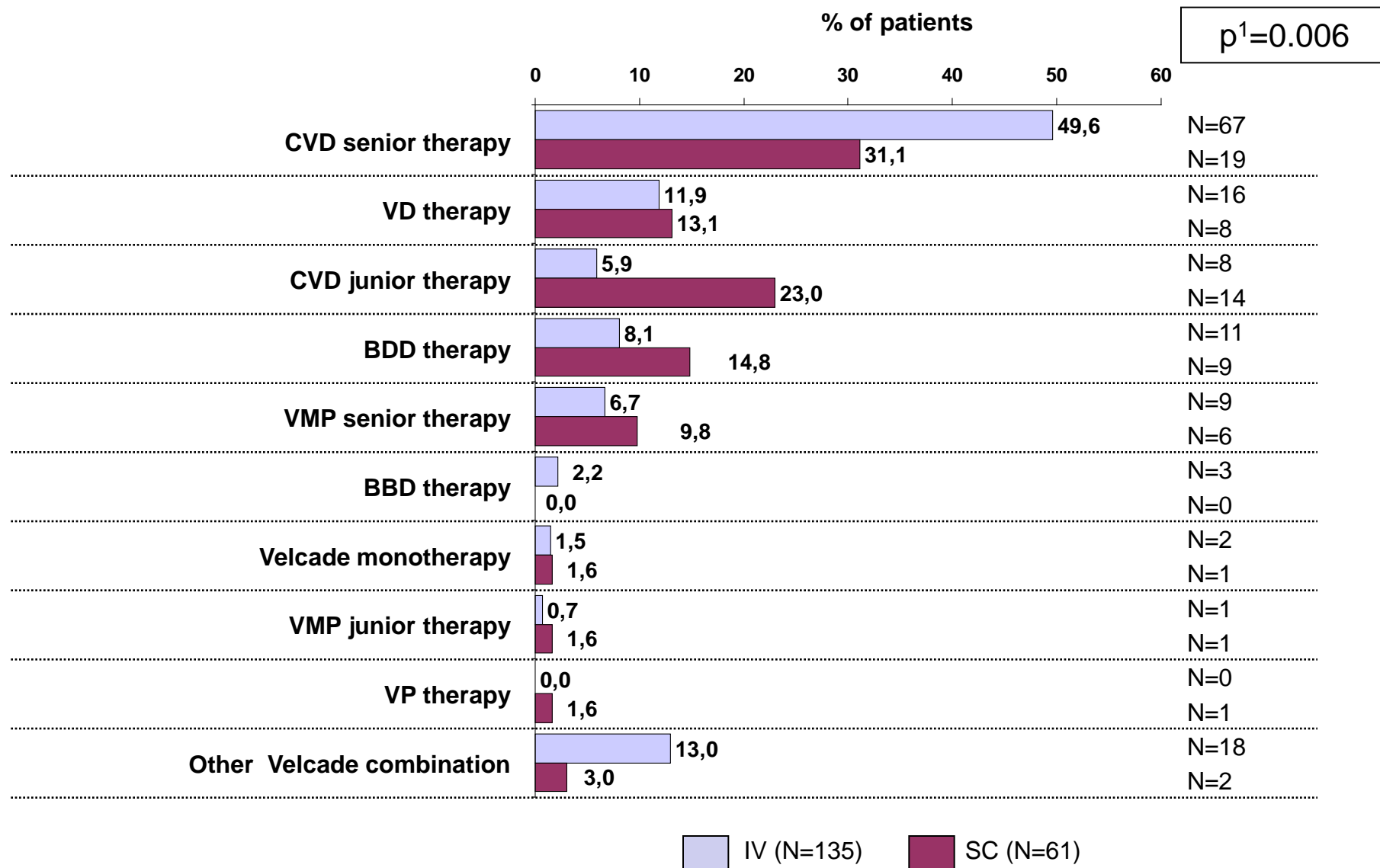


N	61
mean (SD)	67.9 (9.5)
median	69
min-max	41.0-84.0

$p^2 = 0.024$

¹ ML Chi-square test, ² Mann-Whitney U test

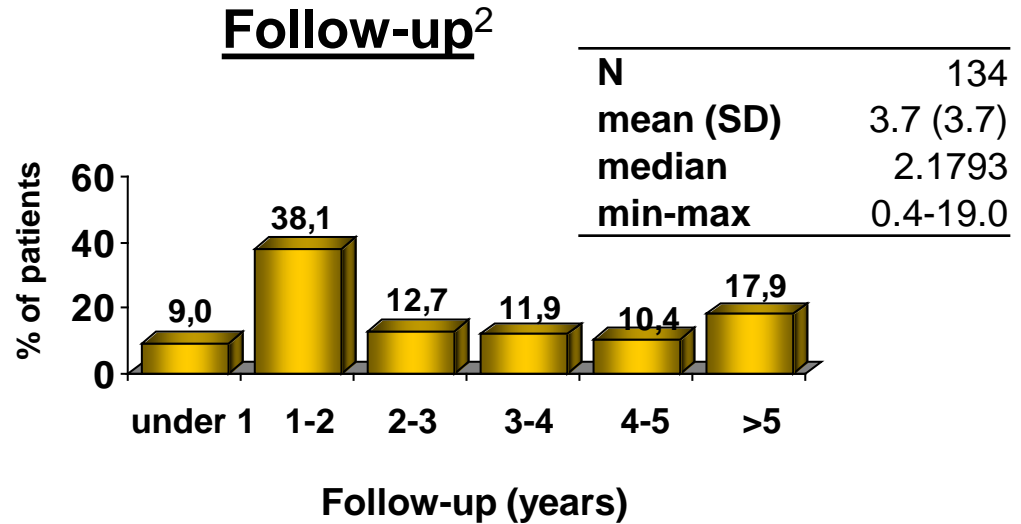
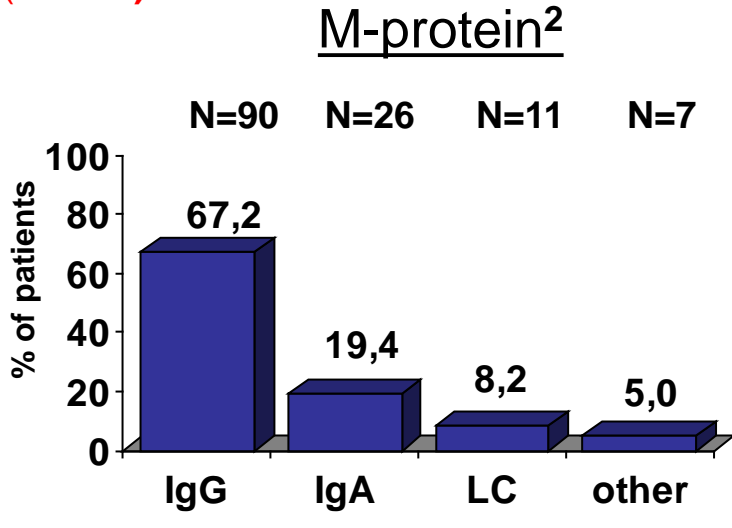
Léčebné režimy



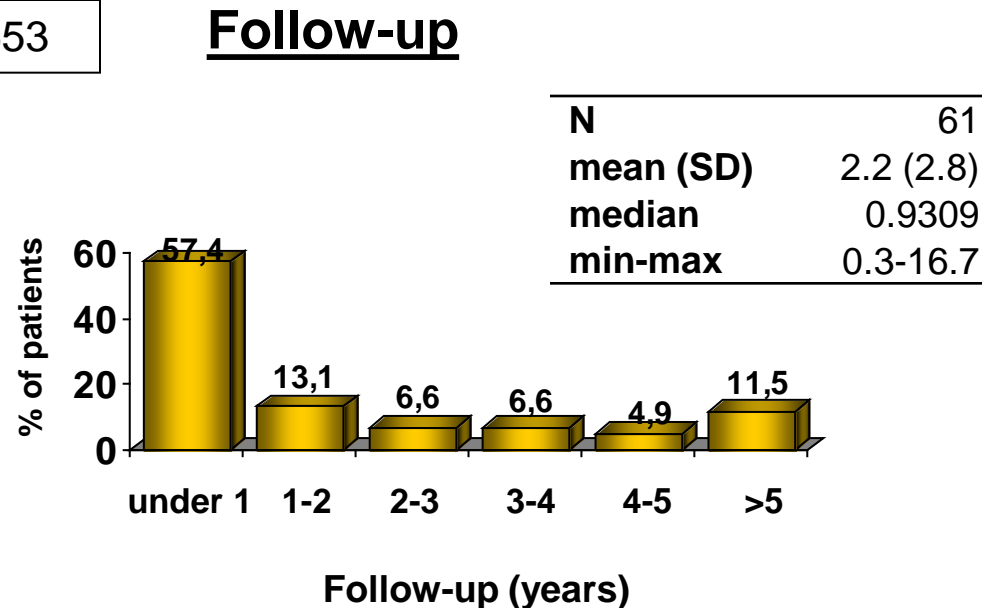
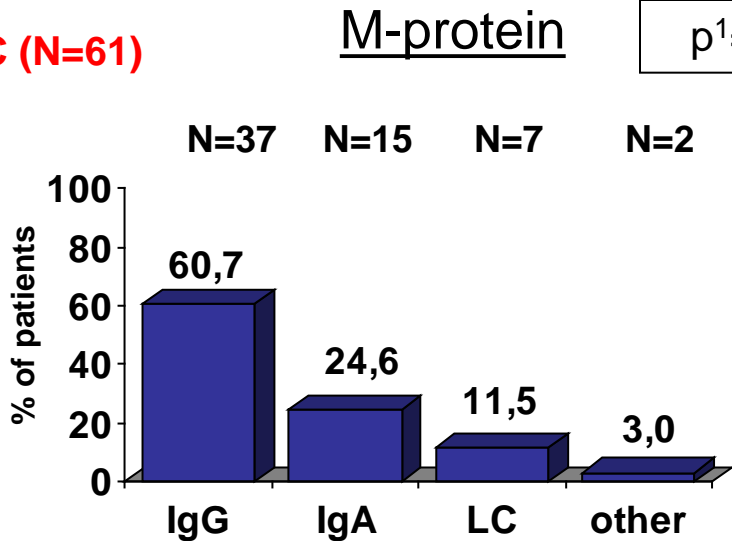
¹ ML Chi-square test, categories with count in total lower than 10 added to Other Velcade combination

M-protein typ a follow-up

IV (N=135)



SC (N=61)

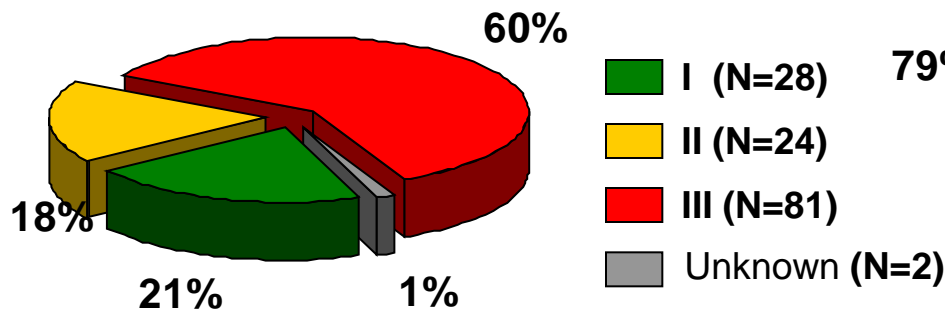


¹ ML Chi-square test, ² missing for 1 patient

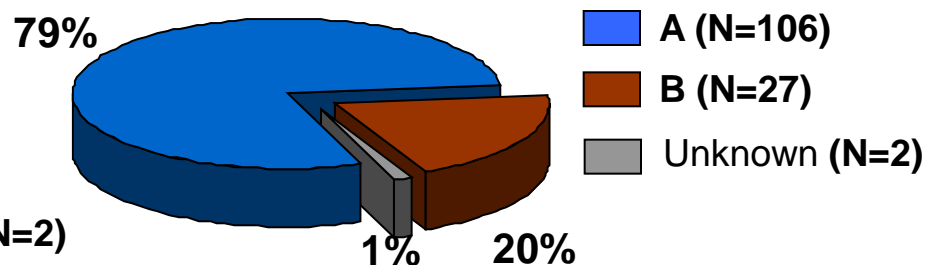
D-S stadium (při diagnóze)

IV (N=135)

D-S stage



A-B substage

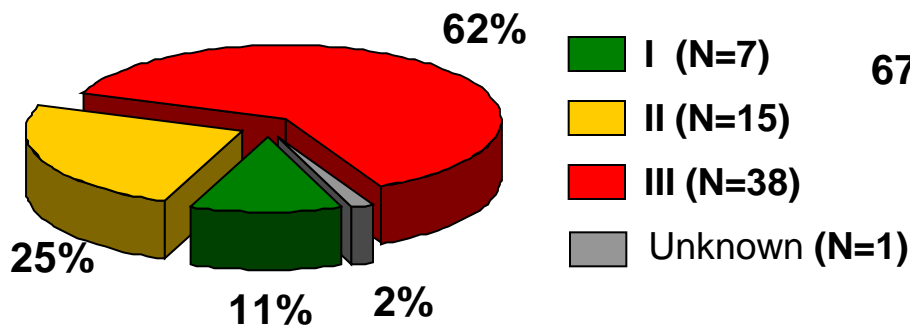


$p^1 = 0.205$

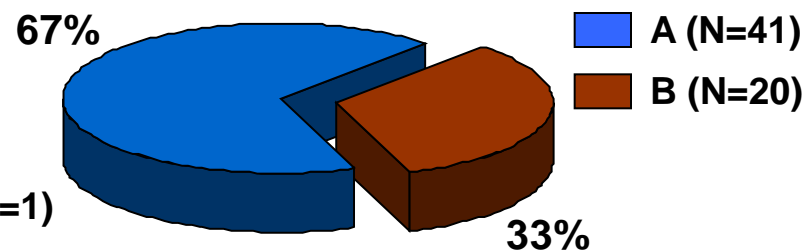
$p^1 = 0.064$

SC (N=61)

D-S stage



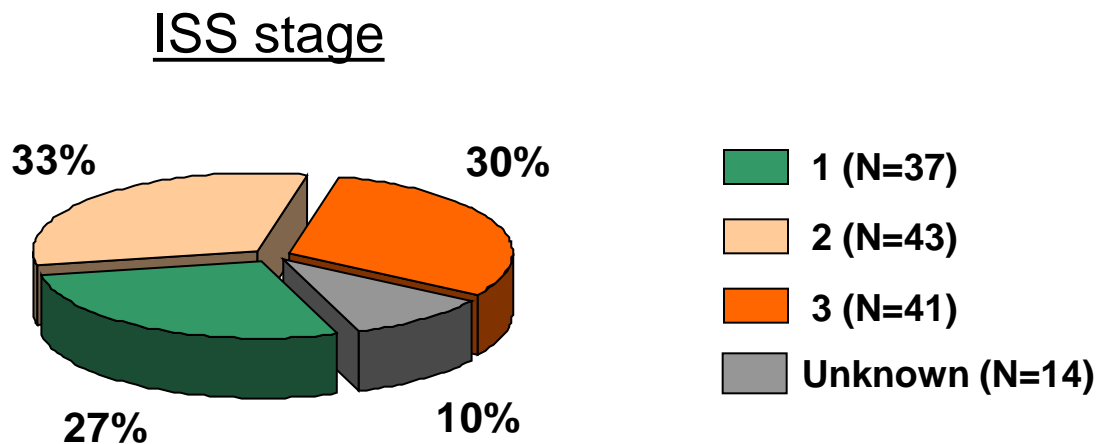
A-B substage



¹ ML Chi-square test

ISS stadium (při diagnóze)

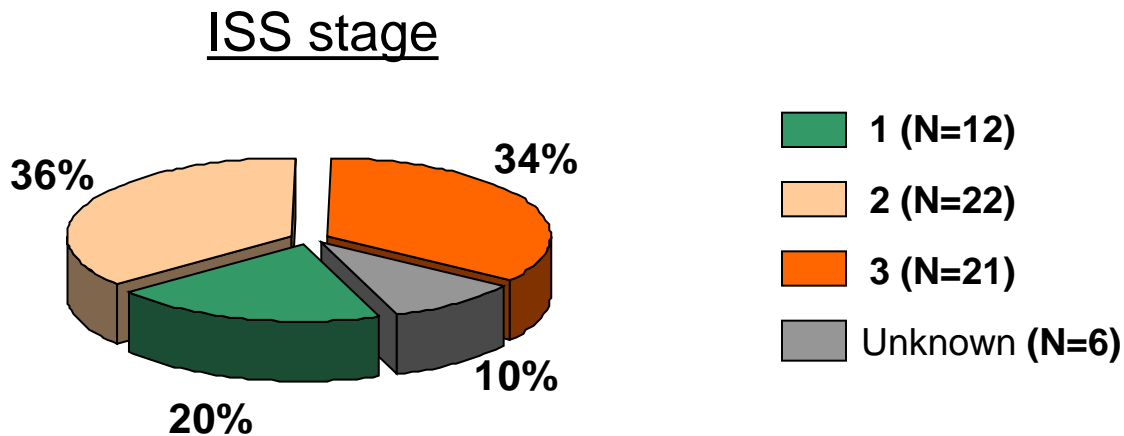
IV (N=135)



- 1 (N=37)
- 2 (N=43)
- 3 (N=41)
- Unknown (N=14)

$p^1 = 0.476$

SC (N=61)



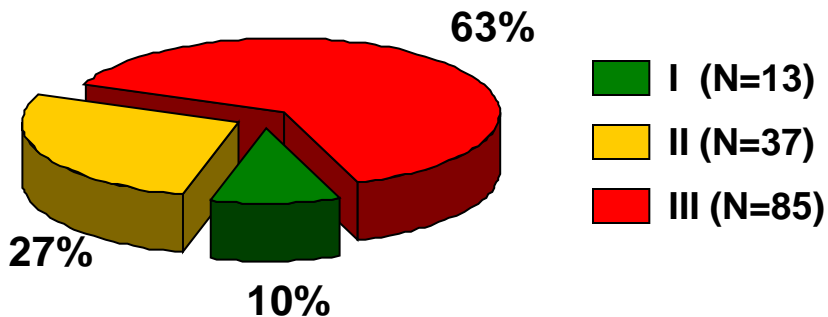
- 1 (N=12)
- 2 (N=22)
- 3 (N=21)
- Unknown (N=6)

¹ ML Chi-square test

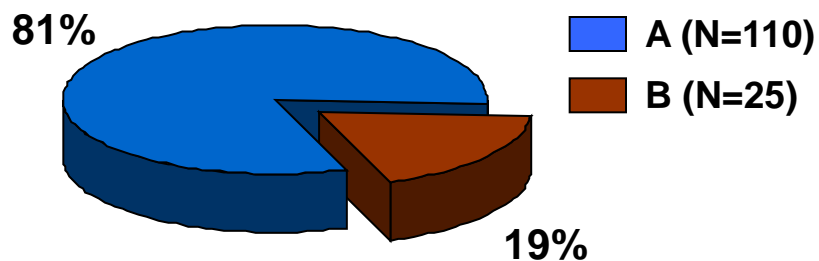
D-S stadium (při zahájení léčby)

IV (N=135)

D-S stage



A-B substage

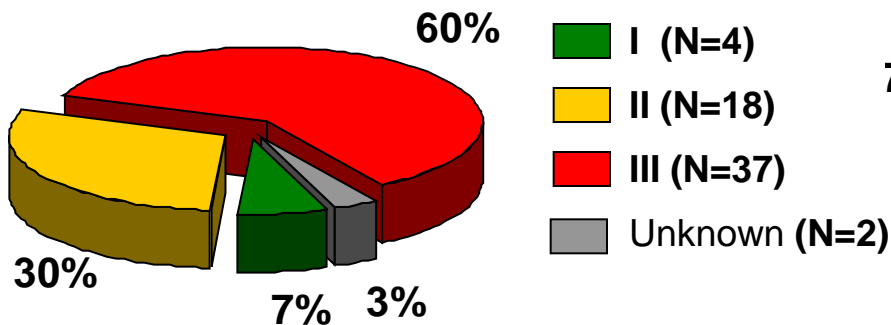


$p^1 = 0.764$

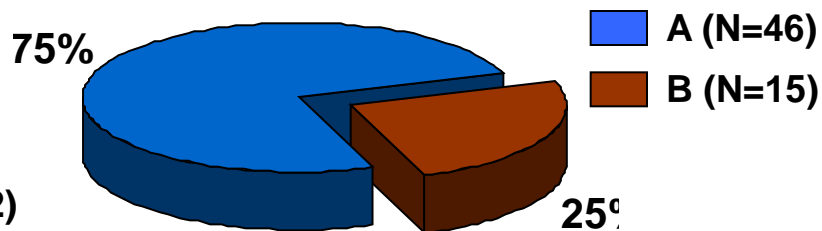
$p^1 = 0.335$

SC (N=61)

D-S stage



A-B substage

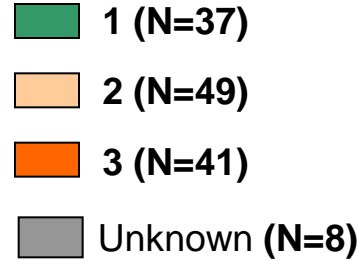
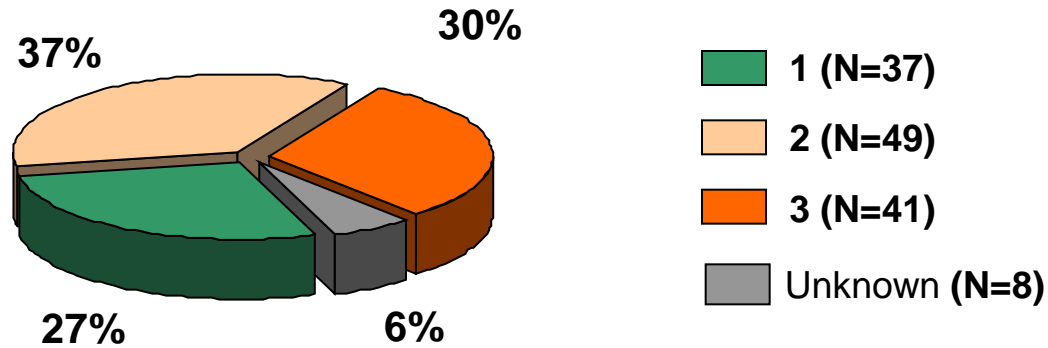


¹ ML Chi-square test

ISS stadium (při zahájení léčby)

IV (N=135)

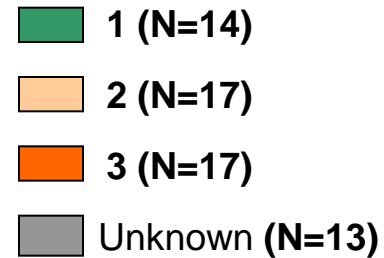
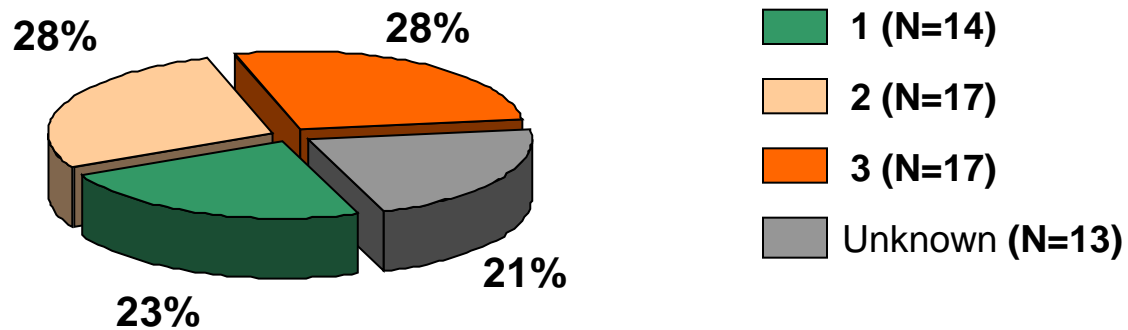
ISS stage



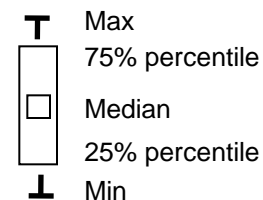
$p^1 = 0.907$

SC (N=61)

ISS stage



Před léčbou I



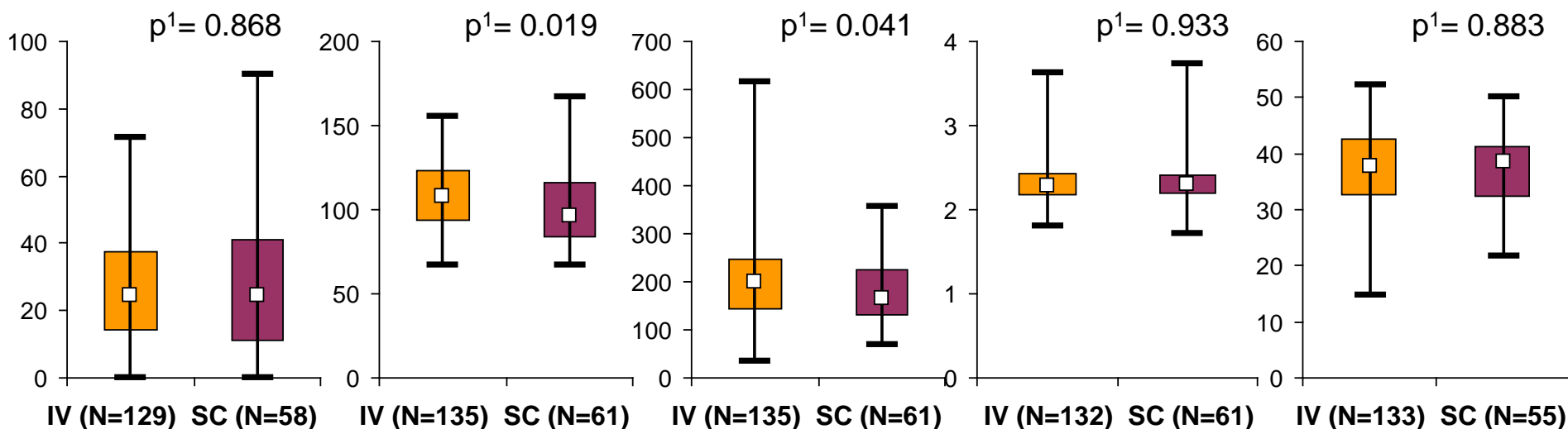
Serum M-protein
(g/l)

Hemoglobin
(g/l)

Thrombocytes
(10E9/l)

Calcium
(mmol/l)

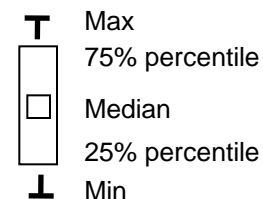
Albumin
(g/l)



	Serum M-protein		Hemoglobin		Thrombocytes		Calcium		Albumin	
	IV	SC	IV	SC	IV	SC	IV	SC	IV	SC
N	129	58	135	61	135	61	132	61	133	55
mean (SD)	26.4 (17.0)	27.5 (20.0)	108.8 (20.1)	102.1 (23.0)	198.7 (80.5)	175.4 (65.0)	2.3 (0.2)	2.3 (0.3)	37.0 (7.1)	37.1 (6.2)
median	24.7	24.4	108.0	96.2	199.0	166.0	2.3	2.3	37.9	38.6
min-max	0.0-71.6	0.0-90.4	67.0-155.0	67.0-167.0	35.7-615.0	70.0-355.0	1.8-3.6	1.7-3.7	14.6-52.1	21.7-50.0

¹ Mann-Whitney U test

Před léčbou II



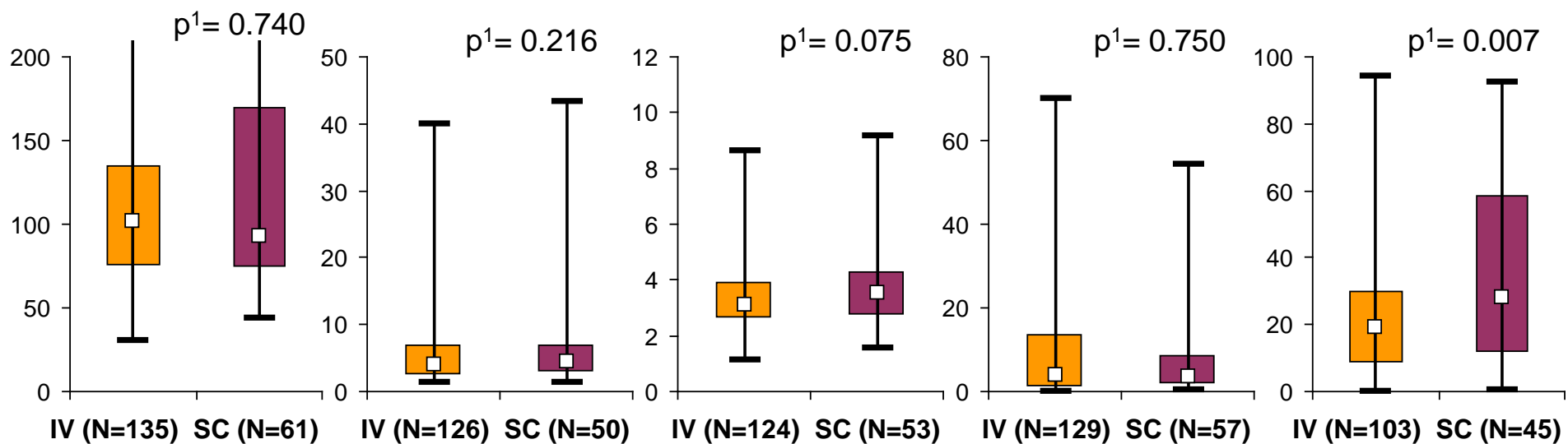
Creatinine
($\mu\text{mol/l}$)

Beta2 microglobulin (mg/l)

LDH (ukat/l)

CRP (mg/l)

Plasmocytes
count (%)

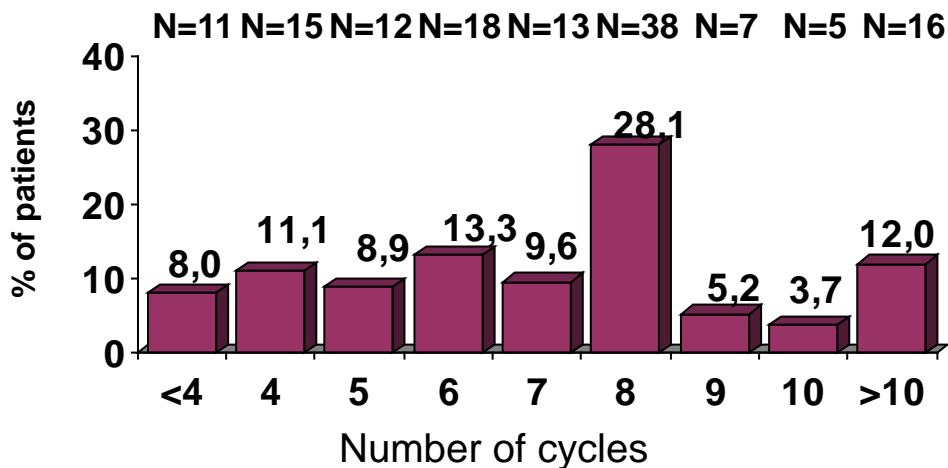


	Creatinine		Beta2 microglobulin		LDH		CRP		Plasmocytes count	
	IV	SC	IV	SC	IV	SC	IV	SC	IV	SC
N	135	61	126	50	124	53	129	57	103	45
mean (SD)	143.0 (131.0)	215.9 (291.8)	6.2 (6.2)	8.0 (9.6)	3.4 (1.2)	3.8 (1.5)	9.9 (14.0)	6.8 (9.0)	22.7 (19.2)	34.8 (25.9)
median	102.0	93.0	3.9	4.5	3.1	3.6	4.0	3.7	19.2	28.0
min-max	30.0-831.0	44.0-1666.0	1.4-40.0	1.4-43.4	1.1-8.6	1.6-9.2	0.0-69.9	0.2-54.3	0.0-94.2	0.6-92.4

¹ Mann-Whitney U test

Počet léčebných cyklů

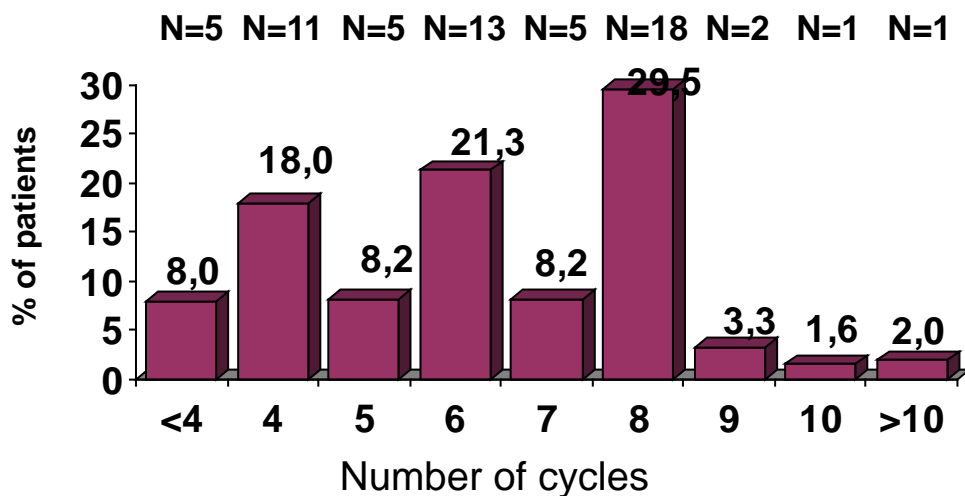
IV (N=135)



N	135
mean (SD)	7.0 (2.8)
median	7
min-max	0.0-13.0

$p^1 = 0.039$

SC (N=61)



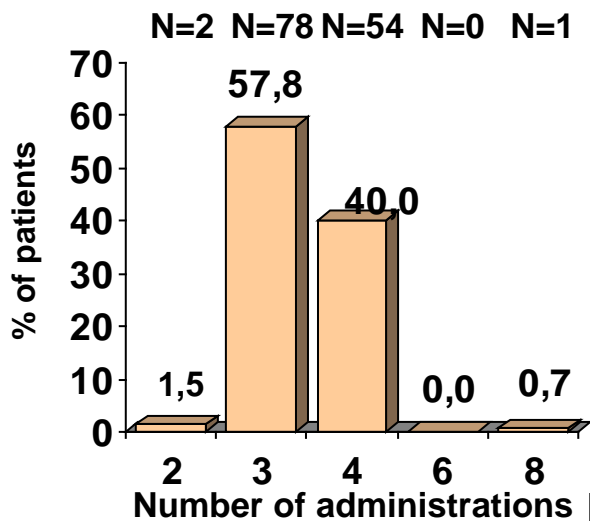
N	61
mean (SD)	6.2 (2.1)
median	6
min-max	1.0-11.0

¹ Mann-Whitney U test

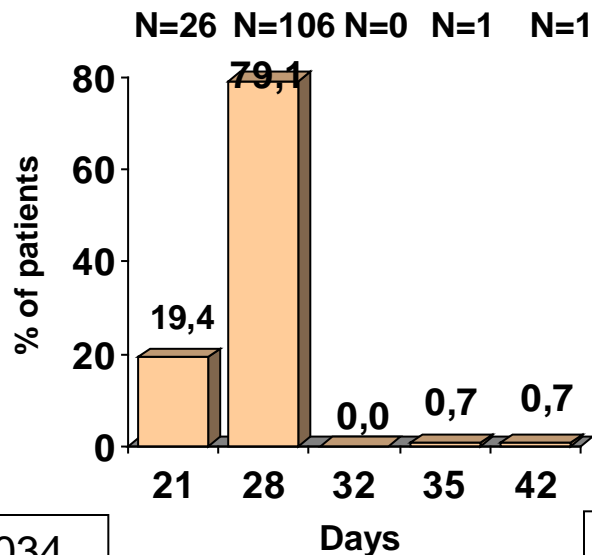
Počet aplikací v cyklu

IV (N=135)

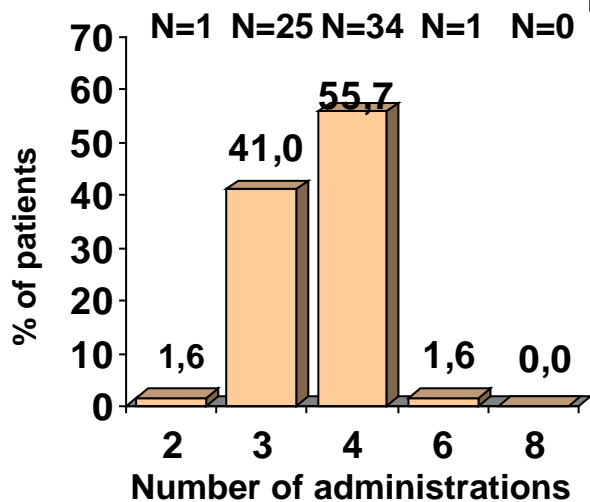
Počet aplikací v cyklu



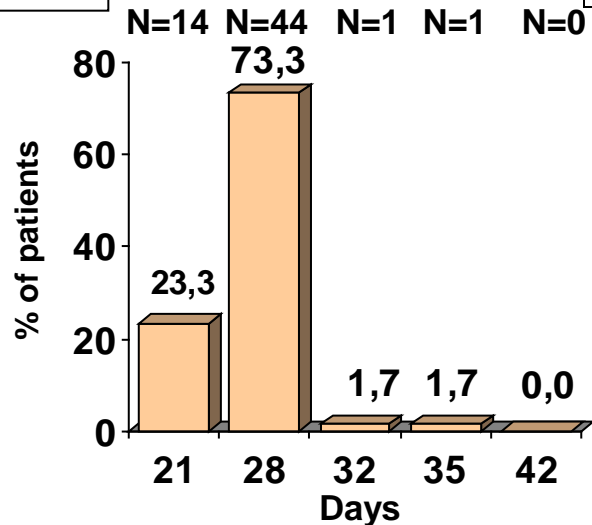
Délka cyklu



SC (N=61)



$p^1 = 0.034$

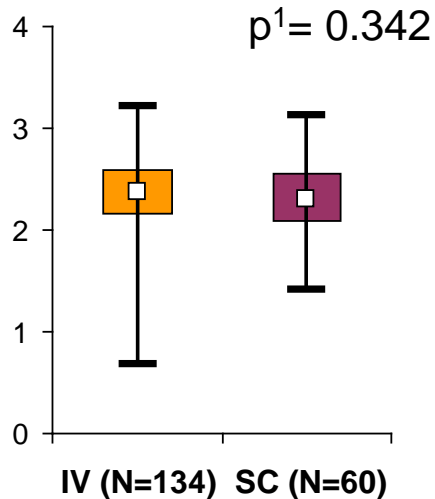


$p^1 = 0.711$

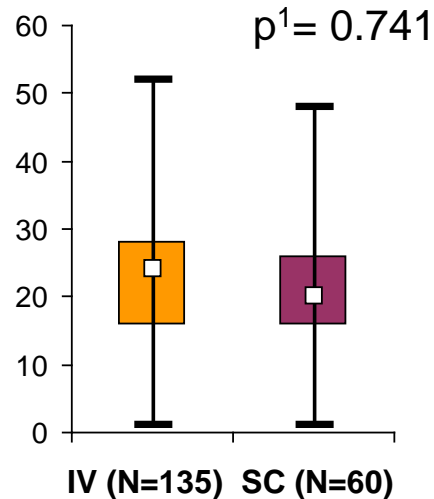
¹ Mann-Whitney U test, ² missing for 2 patients

Charakteristika léčby

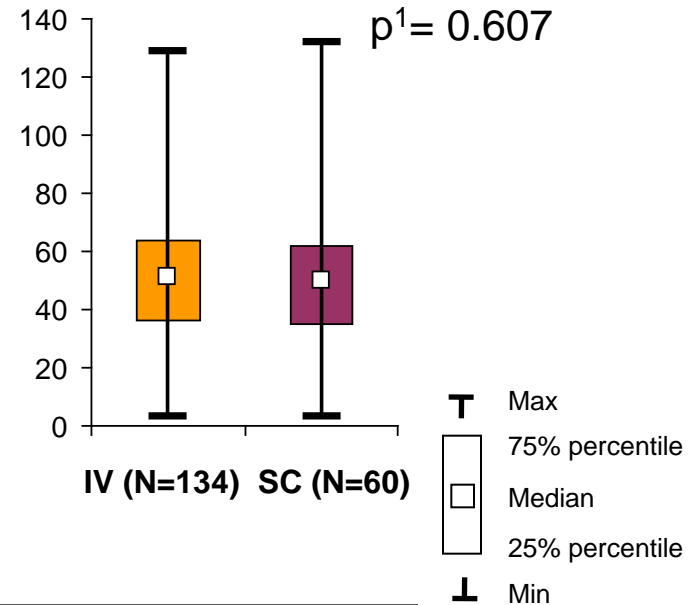
Mean dose of drug for one administration



Total number of administrations



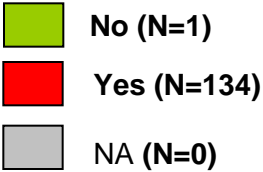
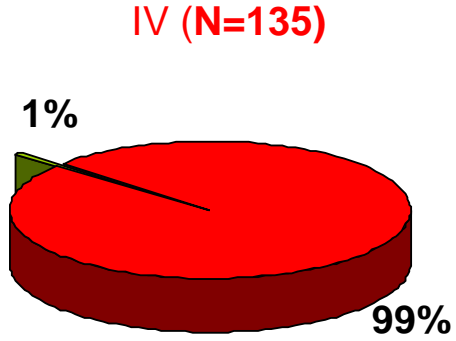
Total cumulative dose (mg)



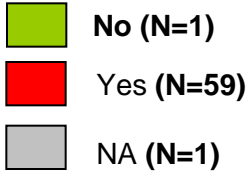
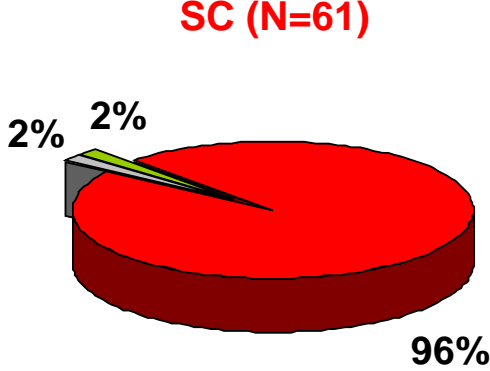
	Mean dose of drug for one administration		Total number of administrations		Total cumulative dose (mg)	
	IV	SC	IV	SC	IV	SC
N	134	60	135	60	134	60
mean (SD)	2.4 (0.4)	2.3 (0.3)	22.0 (9.4)	22.2 (10.3)	51.5 (23.8)	50.5 (23.7)
median	2.4	2.3	24	20	51	50
min-max	0.7-3.2	1.4-3.1	1.0-52.0	1.0-48.0	3.0-129.0	3.0-132.0

¹ Mann-Whitney U test

Toxicita



$p^1 = 0.569$



¹ ML Chi-square test

Toxicita (bez TX)

IV (N=134)

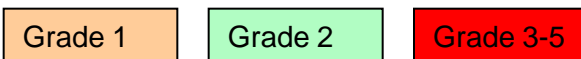
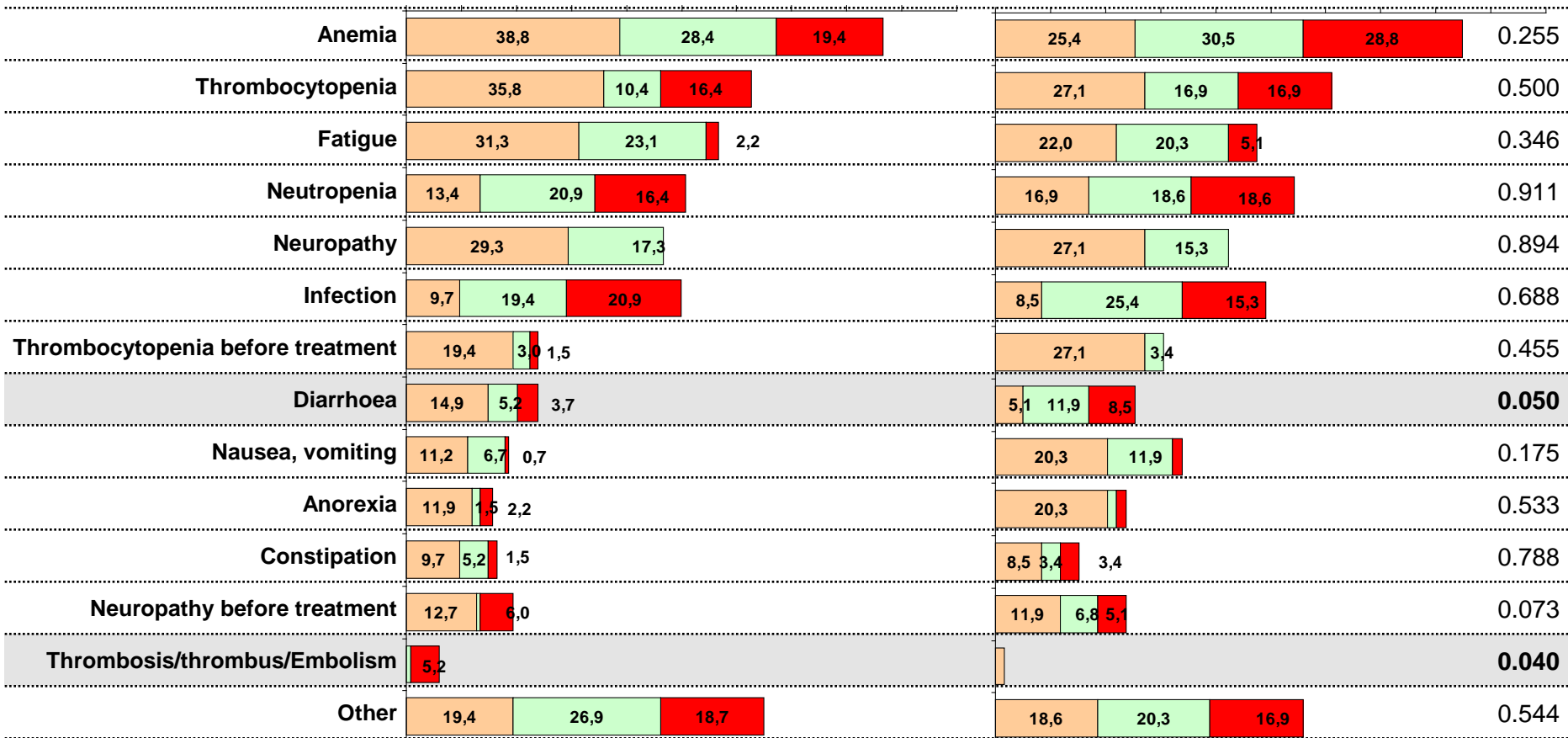
SC (N=59)

% of patients

% of patients

p¹

0 10 20 30 40 50 60 70 80 90 100 0 10 20 30 40 50 60 70 80 90 100



¹ ML Chi-square test

Toxicita (s TX)

IV (N=174)

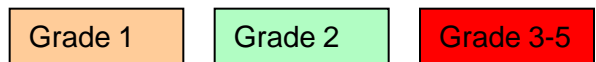
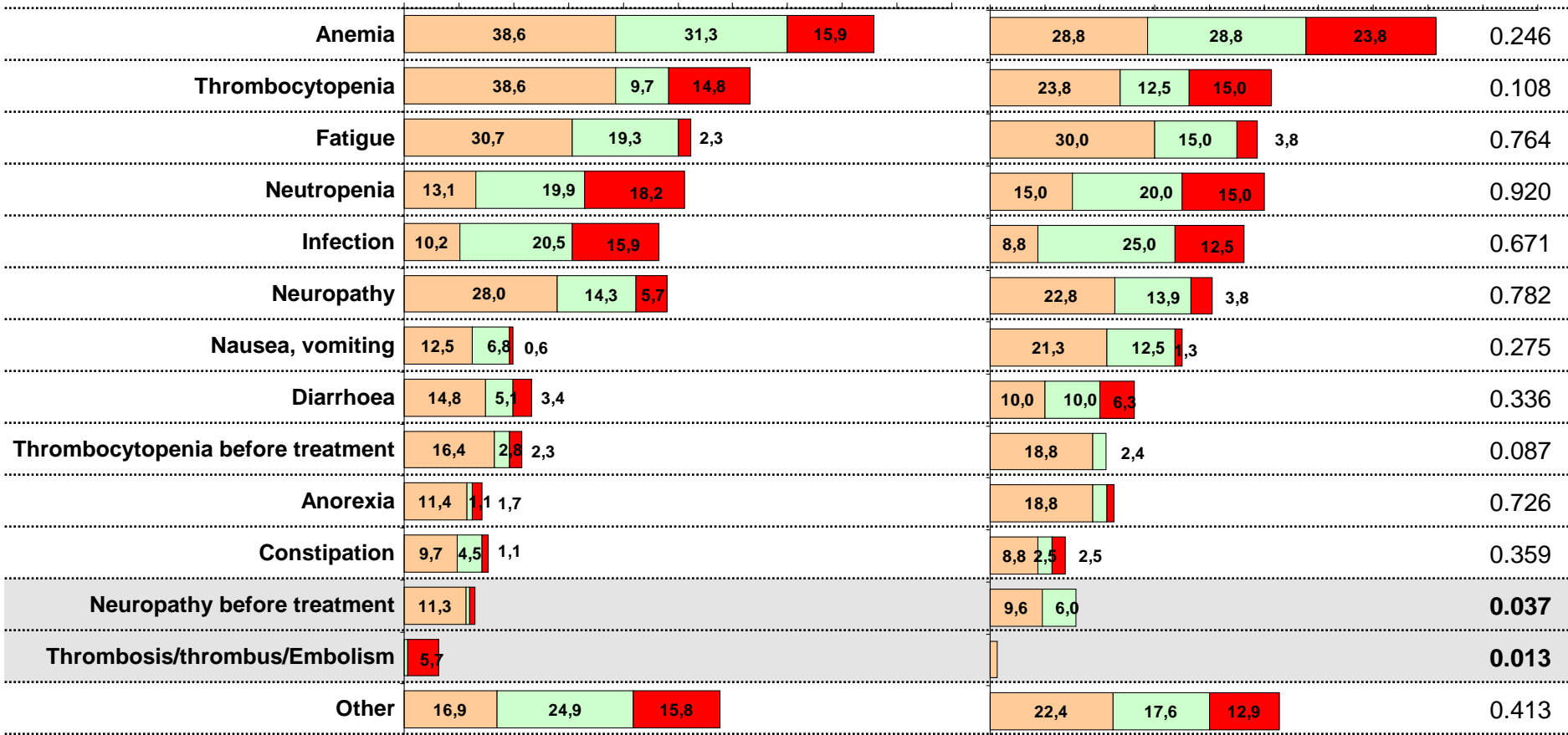
SC (N=78)

% of patients

% of patients

p¹

0 10 20 30 40 50 60 70 80 90 100 0 10 20 30 40 50 60 70 80 90 100

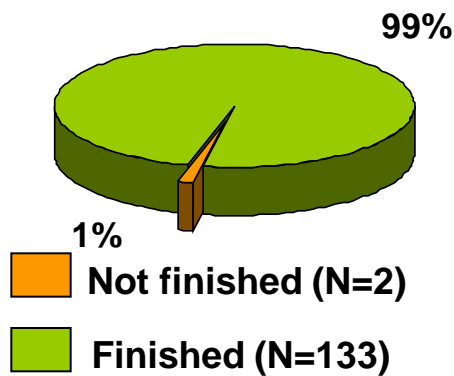


¹ ML Chi-square test

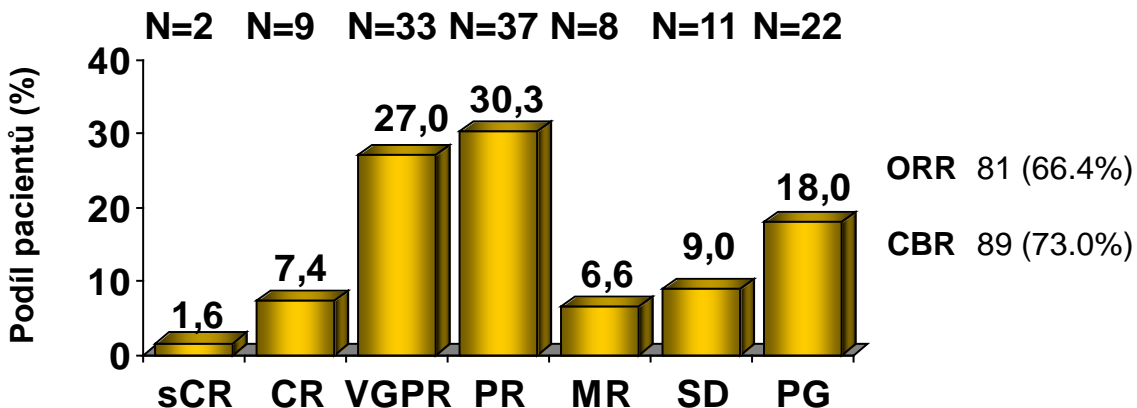
Výsledná léčebná odpověď' (bez TX)

IV (N=135)

Treatment

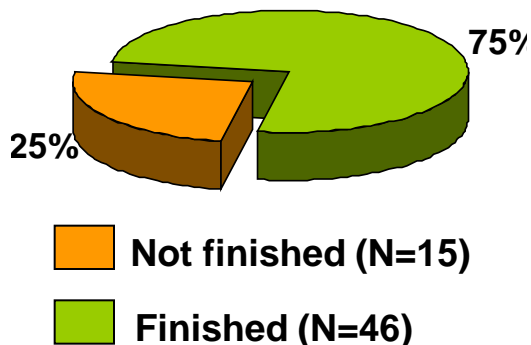


Treatment response²

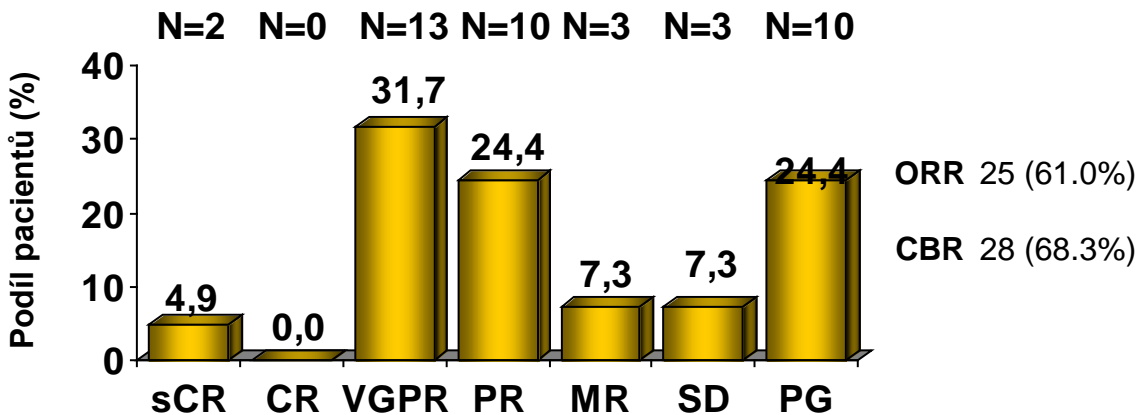


SC (N=61)

Treatment



Treatment response³



$p^1 = 0.261$

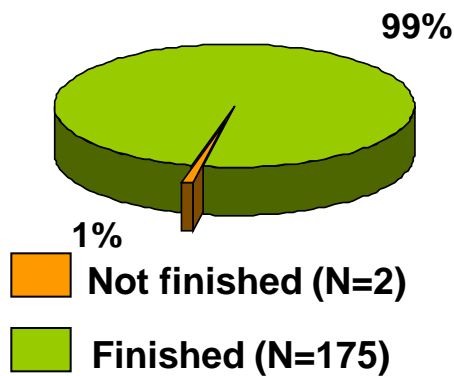
ORR= treatment response PR and better
CBR= treatment response MR and better

¹ ML Chi-square test, ² Missing for 11 patients, ³ Missing for 5 patients

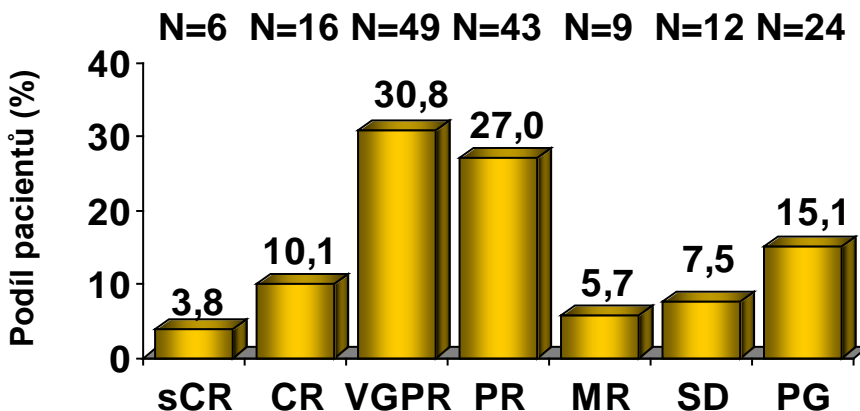
Výsledná léčebná odpověď' (s TX)

IV (N=177)

Treatment



Treatment response²

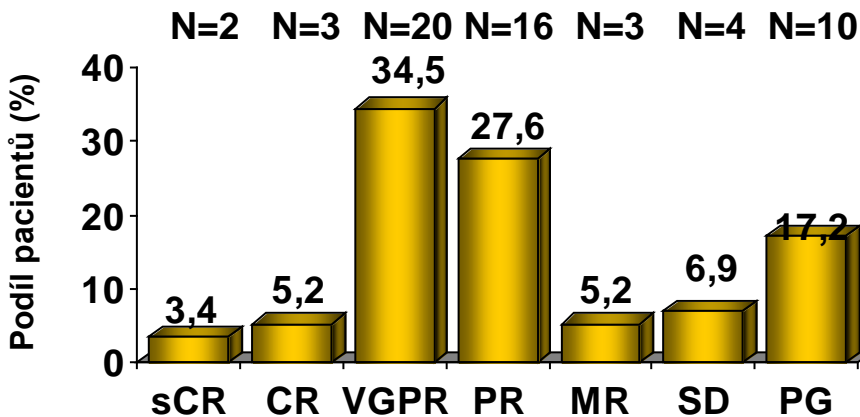


ORR 114 (71.7%)

CBR 123 (77.4%)

$p^1 = 0.949$

Treatment response³



ORR 41 (70.7%)

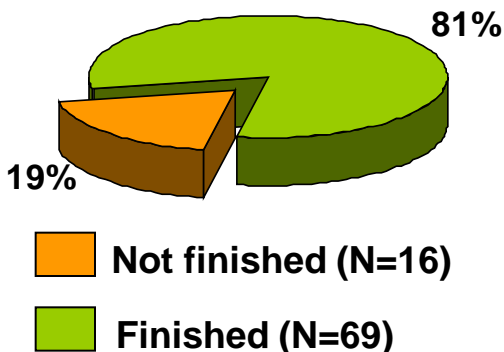
CBR 44 (75.9%)

ORR= treatment response PR and better

CBR= treatment response MR and better

SC (N=85)

Treatment



¹ ML Chi-square test, ² Missing for 16 patients, ³ Missing for 11 patients

Závěr: S.C. x I.V.

S.C. výhody

- Komfort pacienta
- Komfort personálu
- Méně nežádoucích účinků, zejm. NP (P. Moreau et al. 2011)

S.C. nejistoty

- Nezralá data? (1, 4, 8, 11 á 21D)
- Konstantní s.c. dostupnost?
- Lok. snášlivost?

Závěr: S.C. x I.V.

- Základní charakteristiky účinnosti terapie bortezomibem jsou nezávislé na použití aplikační cesty (i.v. x s.c.)
- Četnost NÚ v případě s.c. aplikace je nižší

Děkuji za pozornost !