Inhibitory proteasomu

Roman Hajek

Novel agents in development

Agent	Mechanism of action		Stage of development
Carfilzomib	Proteasome inhibitors		Phase 2/3
MLN9708			Phase 1/2
Marizomib (NPI-0052)			Phase 1
Oprozomib			Phase 1b
Pomalidomide	Immunomodulator (IMiD)		Phase 2/3
Panobinostat	HDAC inhibitor		Phase 2/3
Vorinostat			Phase 3
Elotuzumab	Monoclonal antibody against:	CS1	Phase 2/3
Daratumumab		CD38	Phase 1/2
BHQ880		DKK1	Phase 2
BT062		CD138	Phase 1
Tabalumab		B cell activating factor (BAFF)	Phase 1

http://clinicaltrials.gov

Novel agents in development

Agent	Mechanism of action	Stage of development
Perifosine	Akt inhibitor	Phase 2/3
Temsirolimus	mTOR inhibitor	Phase 1/2
Plitidepsin (aplidin)	Jun N-terminal Kinase (JNK) activator, anti-angiogenic activity	Phase 2/3
Dinaciclib	Cyclin dependent kinase inhibitor	Phase 1/2
MLN8237	Aurora kinase inhibitor	Phase 1
ARRY-520	Kinesin spindle protein (KSP) inhibitor	Phase 2

http://clinicaltrials.gov

Novel agents in development

- Proteasome inhibitors and IMiDs remain key players in the treatment of Multiple Myeloma. Their combination offer probably the strongest therapy currently available

- Many new agents but only few with anti-MM efficacy as monotherapy

Key features of different proteasome inhibitors

Characteristic	Bortezomib	MLN9708	Carfilzomib	Marizomib
Active moiety	Boronate	Boronate	Epoxyketone	β-lactone
Subunits inhibited				
Constitutive proteasome	β5, β1	β5	β5	β5 and β2
Immunoproteasome	β5i	NR	β5i	NR
IC_{50}, nM				
Chymotrypsin	2.4-7.9	3.4	6	3.5
Trypsin	590-4200	3500	3600	28
Caspase	24-74	31	2400	430
IC_{50} against RPMI 8226 MM cell line, nM	5.7	NR	5	9.1
Binding kinetics	Slowly reversible	Reversible	Irreversible	Irreversible
Half-life, minutes	110	18	< 30	< 10-15
Route of administration	IV/SC	Oral/IV	IV	IV

Approval status

EMA: front-line non-transplant, relapse — Not approved

FDA: relapse — Not approved

FDA: all settings

Moreau et al. Blood 2012;120(5):947-59, http://www.fda.gov; http://www.ema.europa.eu

Phase 1/2: MLN9708 in newly diagnosed MM

- n=65, newly diagnosed MM

	Phase 1	Phase 2	Total
ORR	**100%**	**90%**	**92%**
≥ VGPR	**53%**	**58%**	**55%**
CR + nCR	**33%**	**29%**	**28%**

- Short time to response: < 1 month

- Most common AEs (all grades): rash, GI toxicity, fatigue
- Grade 3 AEs: mainly rash, GI toxicity
- Few grade 4 AEs
- PN: 21 pts (32%)
  - Grade 1: 13 pts, Grade 2: 6 pts, Grade 3: 2 pts
- 1 death
- 7 discontinuations due to AEs

Kumar et al. ASH 2012 (Abstract 332), oral presentation

Carfilzomib + Thal + Dex (CTD) as Induction and Consolidation in newly diagnosed MM

- n=50
- Treatment
  - 4 cycles induction CTD, transplant, 4 cycles consolidation CTD
  - Thal dose: 200 mg/d during induction, 50 mg/d during consolidation
- Results
  - 39/50 pts completed treatment according to protocol

Adverse events	Grade 1-2	Grade 3
PN	19%	2%
Azotemia	0	4%
GI	22%	6%
Skin	8%	12%
Cardiac	2%	6%

  - No DLTs

Sonneveld et al. ASH 2012 (Abstract 333), oral presentation

Carfilzomib + Thal + Dex (CTD) as Induction and Consolidation in newly diagnosed MM

- Response following induction
  - ORR 91%, VGPR 60%, CR 18%
- Median follow-up: 14 mos
- Responses are upgraded following consolidation

	High-risk MM	Standard-risk MM	All pts
CR/sCR	**55%**	**45%**	**44%**
≥ VGPR	**90%**	**77%**	**84%**
≥PR	**95%**	**92%**	**94%**

Sonneveld et al. ASH 2012 (Abstract 333), oral presentation

Carfilzomib + cyclophosphamide + Dex (CCd) for newly diagnosed MM

- Patients (n=58)
  - Median age 71 years (55-86), 16 pts ≥ 75 years
- Treatment
  - CCd (9 cycles), carfilzomib maintenance until progression
- Results
  - Improvement in response quality with treatment duration
    - Responses at cycle 9
      - sCR 23%, ≥ nCR 53%, ≥ VGPR 77%, ≥ PR 100%
  - Median time to PR < 1 month
  - Slight decrease in CR rate in ISS3 and high-risk cytogenetics
  - 1-year PFS 88%, 1-year OS 87%

Palumbo et al. ASH 2012 (Abstract 730), oral presentation

Update on Carfilzomib Phase 3 Trials

(Non-Confidential Overview)

- FOCUS (Protocol PX-171-011)
- ASPIRE (Protocol PX-171-009)
- ENDEAVOR (Protocol 2011-003)

Prepared for:
Czech Myeloma Group Meeting
April 2013

Version 18 April 2013

Overview of Studies

Study	Design
FOCUS (PX-171-011)	Randomized, Phase 3 Relapsed and refractory multiple myeloma 3 or more prior regimens Carfilzomib vs. best supportive care Primary endpoint: overall survival (OS)
ASPIRE (PX-171-009)*	Randomized, Phase 3 Relapsed multiple myeloma 1-3 prior regimens Lenalidomide/dexamethasone (Rd) vs. Rd plus carfilzomib (CRd) Primary endpoint: progression-free survival (PFS)
ENDEAVOR (2011-003)	Randomized, Phase 3 Relapsed multiple myeloma (1-3 prior regimens) Carfilzomib (higher dose)/dexamethasone vs. bortezomib/dexamethasone

***Onyx has an agreement with the U.S. Food and Drug Administration (FDA) for a Special Protocol Assessment (SPA) and has received Scientific Advice from the European Medicines Agency (EMA) on the design and planned analysis of the ASPIRE trial.**

Sources: Onyx Corporate Factsheet, January 2013; Onyx press releases; Q4 2011 Earnings Call Transcript (2/22/12)

Status of Studies

FOCUS (PX-171-011)

- Enrollment completed
- Phase 3 FOCUS interim analysis – 2H13*

ASPIRE (PX-171-009)

- Enrollment completed
- Phase 3 ASPIRE interim analysis – 4Q13+*

ENDEAVOR (2011-003)

- **Phase 3 ENDEAVOR ongoing**

***Interim analysis estimated (event driven)**

Sources: Onyx Corporate Presentation, April 2013

ENDEAVOR (2011-003) Study

Study Update

As of 18 April 2013

Study Start-Up *(as of 18 April 2013)*

- **Regulatory approvals to enroll in 22/30 (73%) countries**
- **116/221 (52%) sites activated**
- **Most of the currently identified sites will be activated by Q2 2013**
- **Additional countries (sites) to be brought on board: Argentina (n=5), Mexico (n=5), Hong Kong (n=4), Switzerland (n=3), and Thailand (n=4)**

Country	# of Activated/ Projected Sites	Country	# of Activated/ Projected Sites	Country	# of Activated/ Projected Sites
Australia	11/18	Germany	2/10	Russia	7/9
Austria	1/3	Greece	1/1	Singapore	2/3
Belgium	4/6	Hungary	4/6	Slovakia	1/1
Brazil	0/12	Israel	3/6	Spain	5/9
Bulgaria	3/5	Italy	9/12	Taiwan	4/6
Canada	7/8	New Zealand	4/5	Ukraine	3/7
Czech Rep	6/6	Poland	0/8	UK	2/8
France	10/10	Romania	3/5	USA	24/27

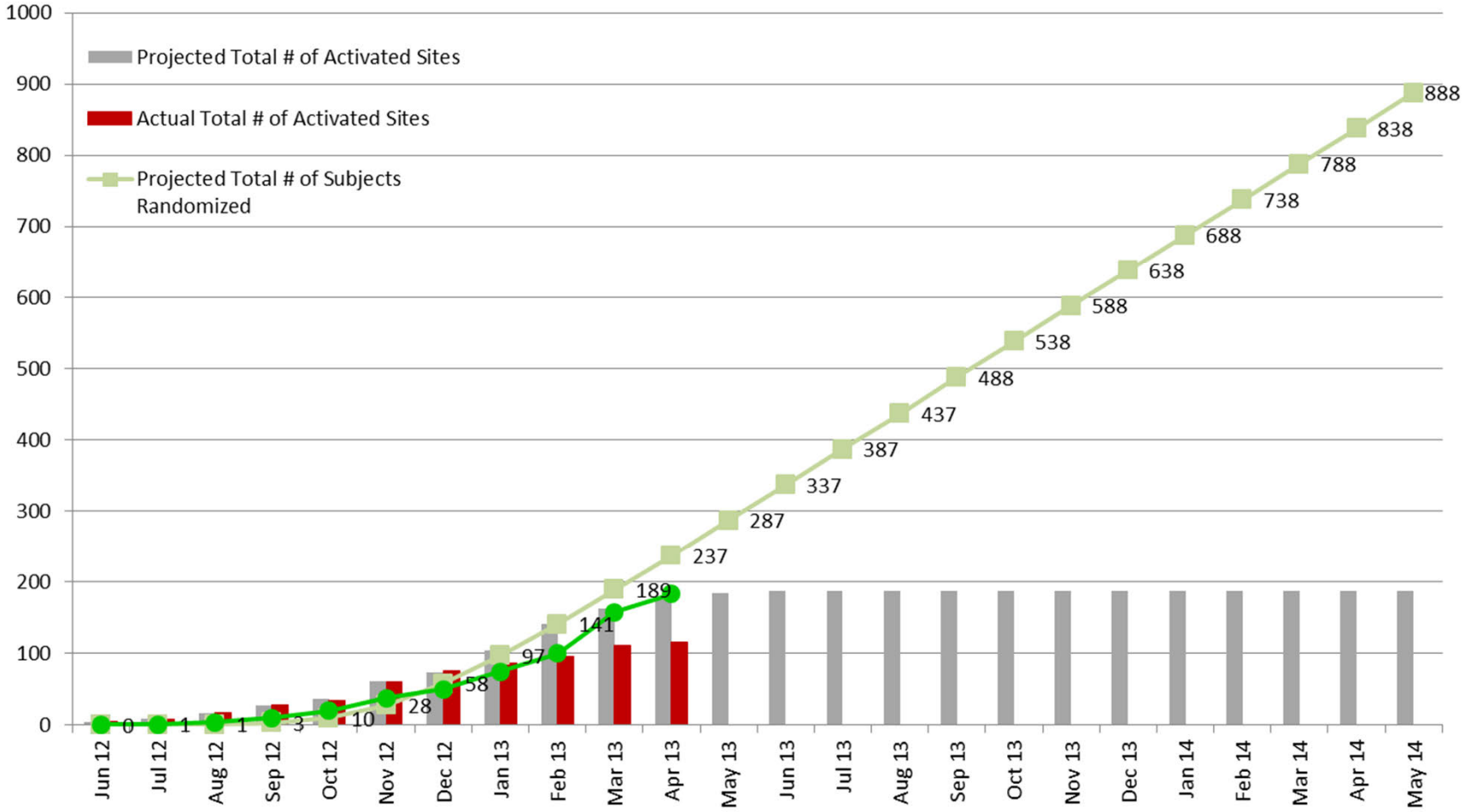
Note: South Korea is currently on hold and is therefore not listed here.

Goals for the Study

- Enroll 75% of patients (n=667) by 31 December 2013
- Complete enrollment (n=888) by May 2014

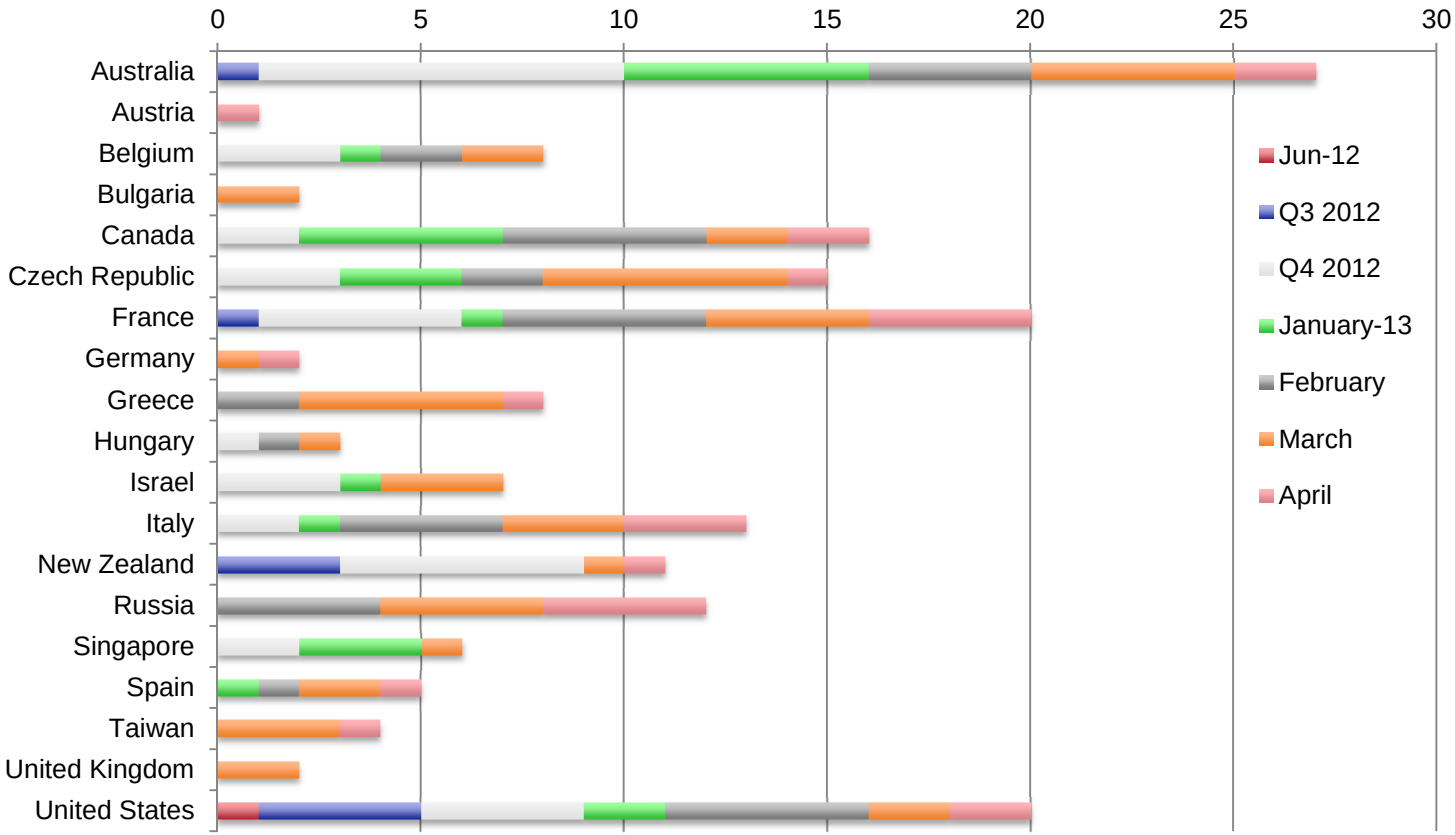
ENDEAVOR Enrollment Curve

(as of 18 April 2013)



Actual Enrollment by Country

(as of 18 Apr 2013)



Velcade
Czech republic

Statistical analysis of 1790 patients

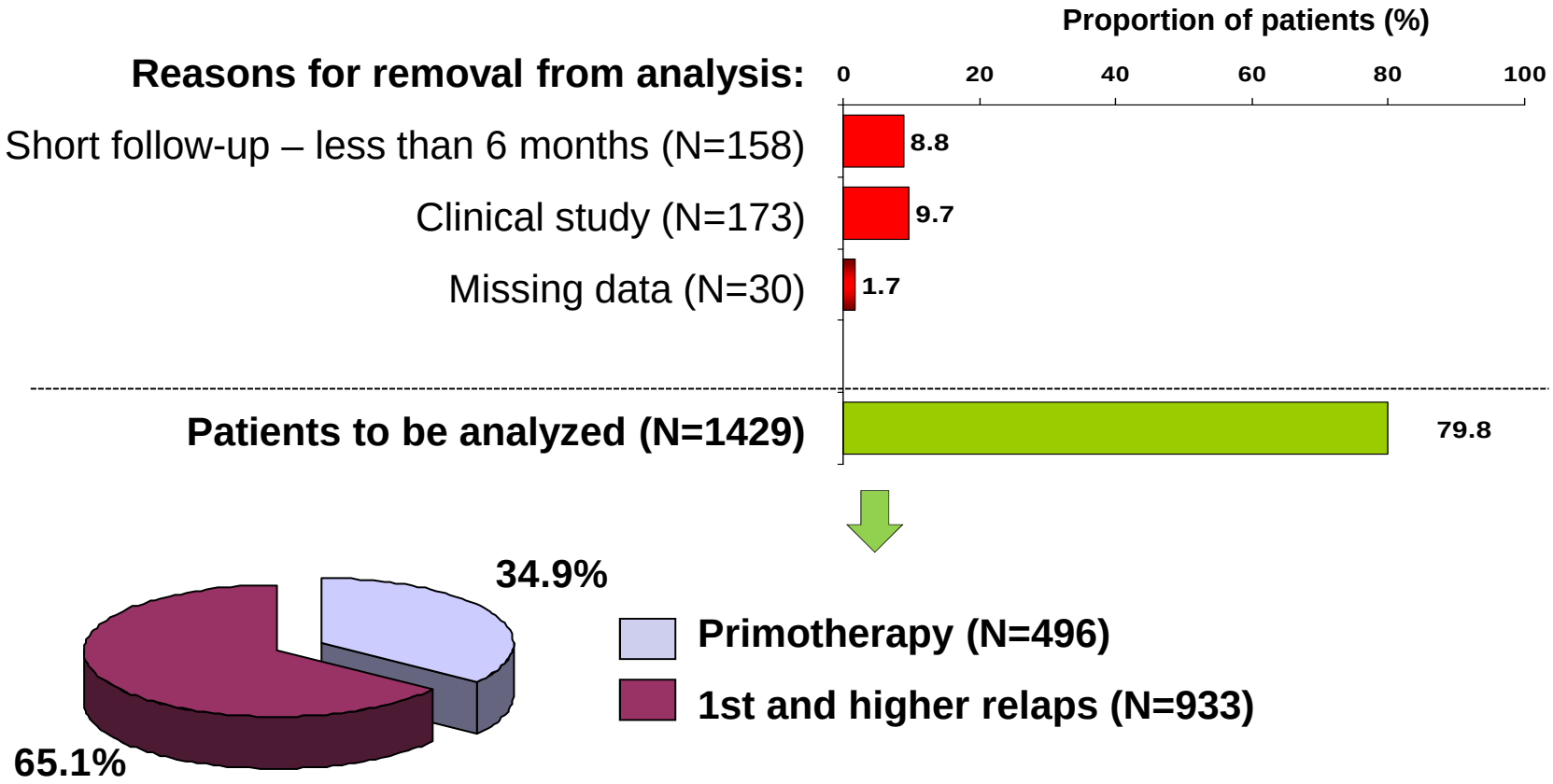
4/2013

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

ČESKÁ MYELOMOVÁ SKUPINA
CZECH MYELOMA GROUP
NADAČNÍ FOND

Suitable patients for analysis

Total number of records with velcade treatment: 1790

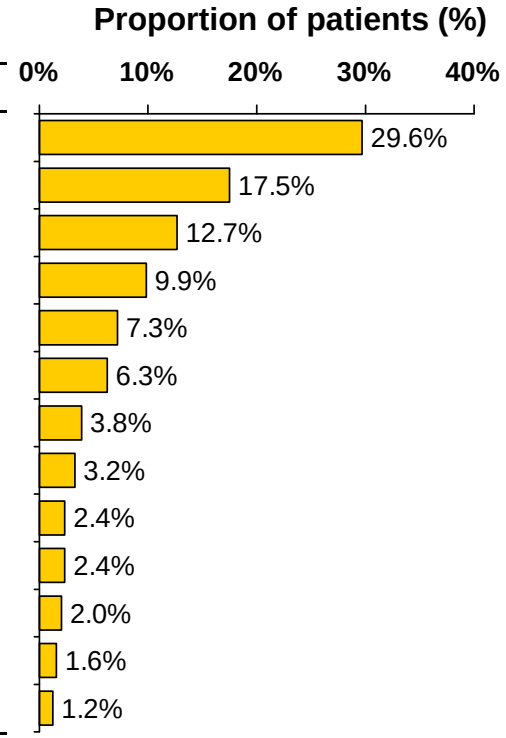


Primotherapy analysis

SITES

Base: N=496 patients in primotherapy

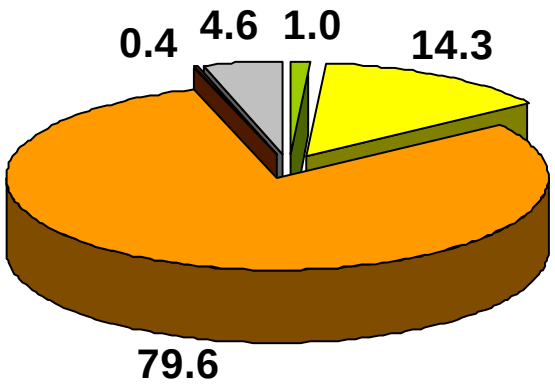
SITE	number	%
FN Brno - IHOK	147	29.6%
VFN Praha - I. Interní klinika	87	17.5%
FN Olomouc - III. interní klinika	63	12.7%
FNHK - OKH	49	9.9%
FNKV Praha - OKH	36	7.3%
Havířov - Hematologické odd.	31	6.3%
KN Liberec - OKH	19	3.8%
Nový Jičín - Onkologické centrum, HO	16	3.2%
Opava - Hematologické odd.	12	2.4%
ČB - OKH	12	2.4%
FN Ostrava - UKH	10	2.0%
Pelhřimov - OHT	8	1.6%
Mladá Boleslav - HTO	6	1.2%
Total	496	100.0%



Treatment procedure

Base: N=496 patients in primotherapy

Drug combination

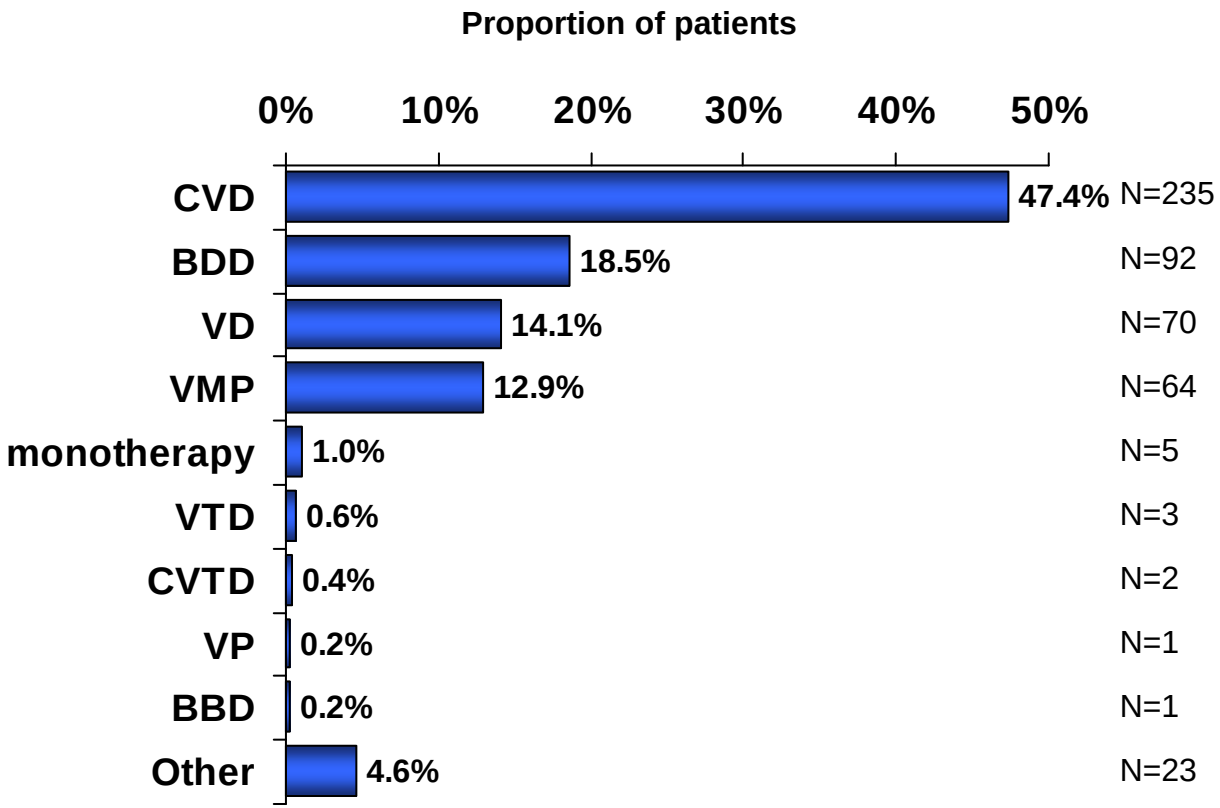


- **monotherapy** (N=5)
- **two-combination therapy** (N=71)
- **three-combination therapy** (N=395)
- **four-combination therapy** (N=2)
- **unknown Velcade combination therapy** (N=23)

Treatment procedure

Base: N=496 patients in primotherapy

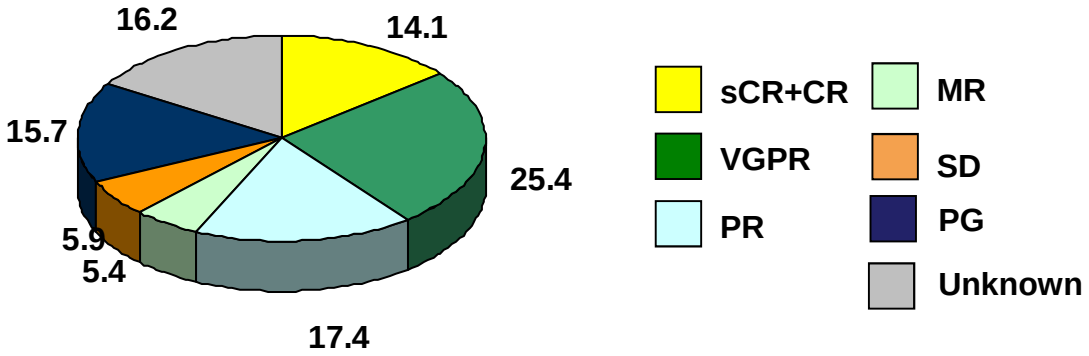
Treatment used



Treatment response

Base: N=426 patients in PT with completed treatment

Treatment response



Treatment response (N=426)	
sCR	15 (3.5%)
CR	45 (10.6%)
VGPR	108 (25.4%)
PR	74 (17.4%)
MR	23 (5.4%)
SD	25 (5.9%)
PG	67 (15.7%)
Unknown	69 (16.2%)

ORR	242 (56.8%)
CBR	265 (62.2%)

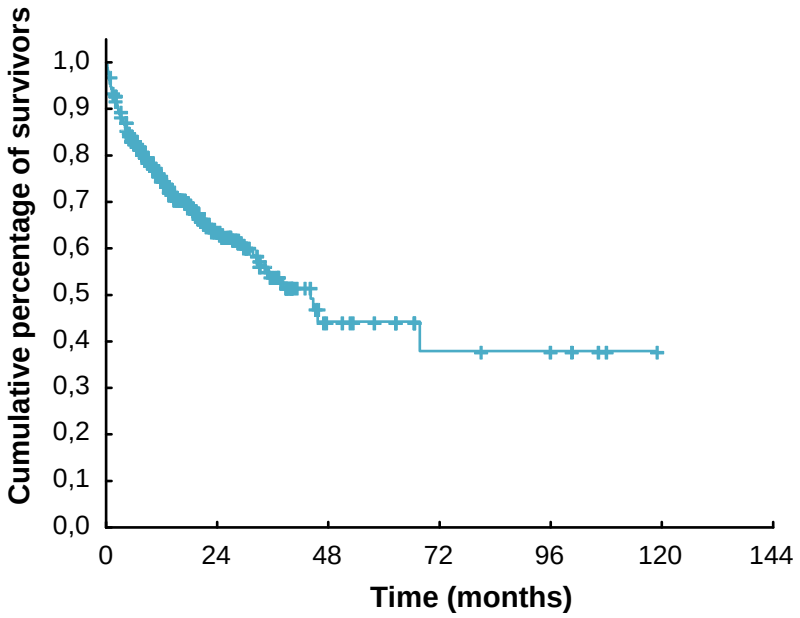
ORR = treatment response PR and better

CBR = treatment response MR and better

Survival analysis

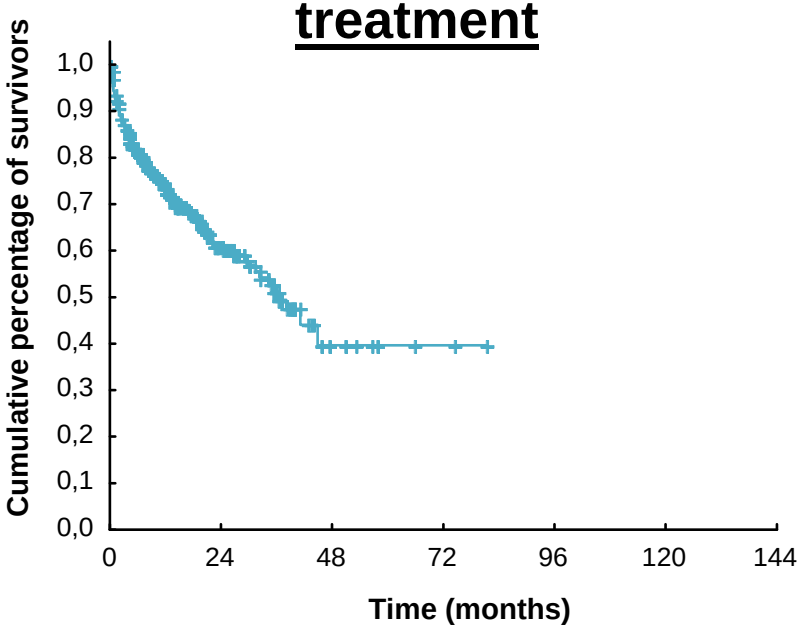
Base: N=496 patients in primotherapy

OS from diagnosis



	OS (%; 95% CI)
N	496
Median survival (months)	44.1 (35.5-52.7)
Survival 12 m. %(CI)	74.6 (34.7-92.2)
Survival 24 m. %(CI)	63.9 (25.8-86.3)
Survival 36 m. %(CI)	54.2 (15.6-81.8)

OS from beginning of treatment



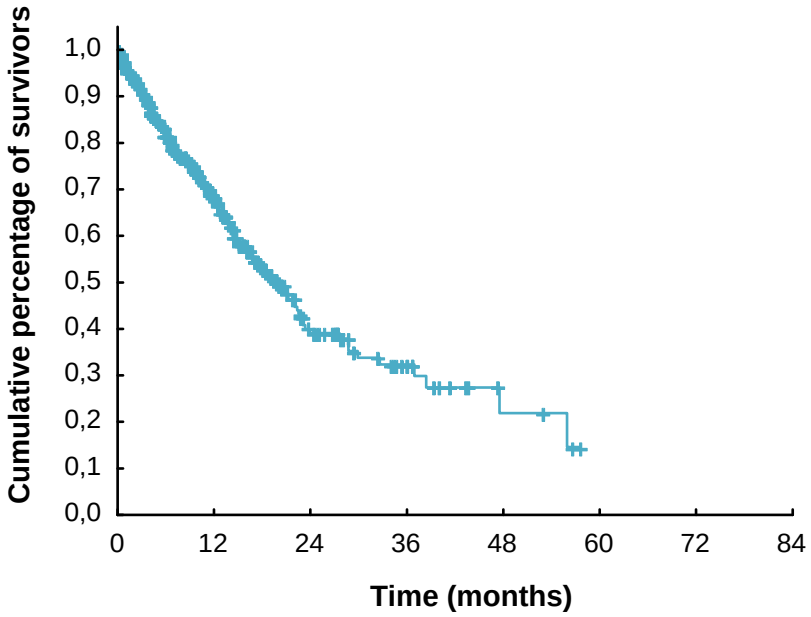
	OS (%; 95% CI)
N	496
Median survival (months)	36.5 (29.6-43.4)
Survival 12 m. %(CI)	72.6 (33.3-91.1)
Survival 24 m. %(CI)	60.7 (22.6-84.6)
Survival 36 m. %(CI)	51.2 (12.2-80.8)

Note: Dataset consists of patients with at least 6 months follow up!

Survival analysis

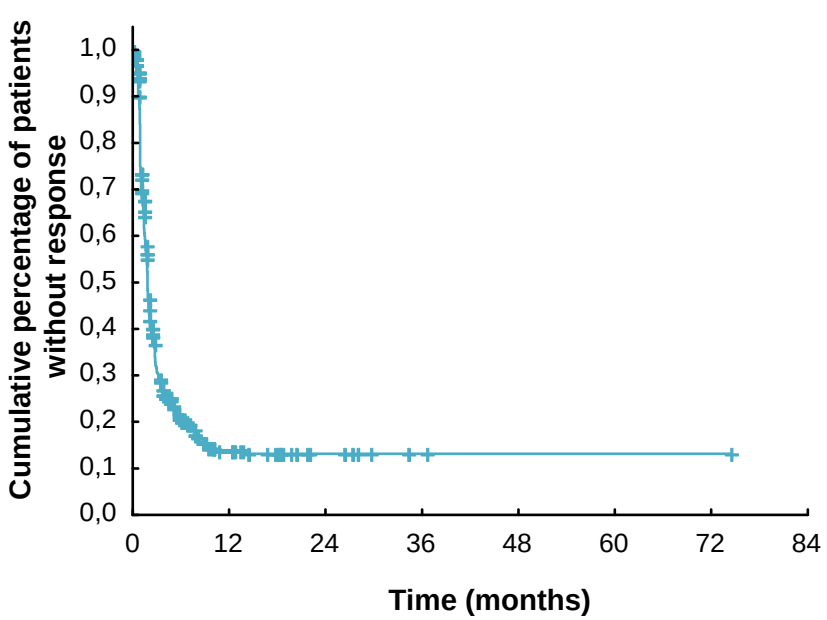
Base: N=496 patients in primotherapy

TTP (time to progress)



	TTP (%; 95% CI)
N	496
Median survival (months)	19.5 (16.4-22.7)
Survival 12 m. %(CI)	68.0 (29.3-88.6)
Survival 24 m. %(CI)	39.1 (7.8-70.8)
Survival 36 m. %(CI)	32.3 (3.6-68.0)

TTR (Time to response)

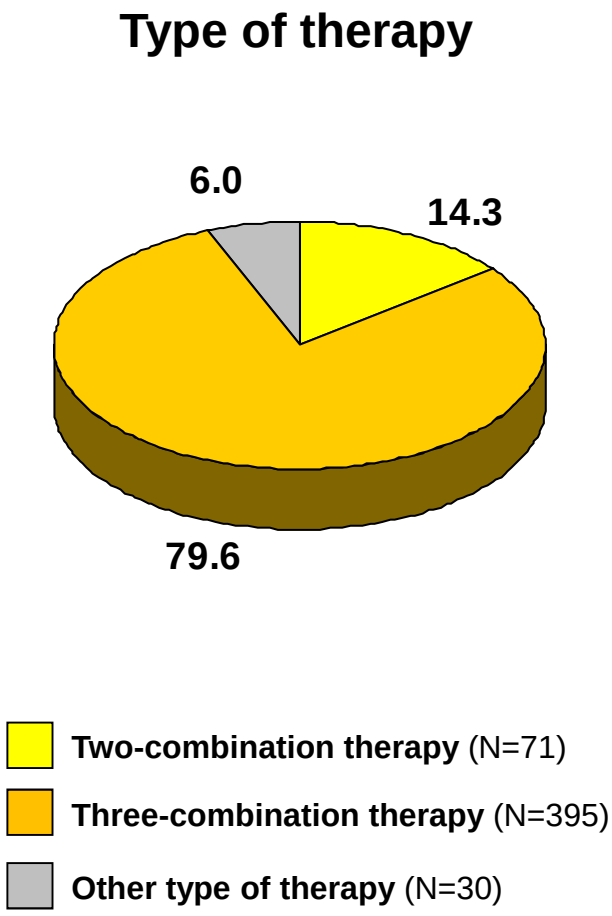


	TTR (%; 95% CI)
N	496
Median survival (months)	1.8 (1.7-1.9)
Survival 12 m. %(CI)	13.9 (0.5-48.1)
Survival 24 m. %(CI)	13.1 (0.3-48.4)
Survival 36 m. %(CI)	13.1 (0.3-48.4)

Note: Dataset consists of patients with at least 6 months follow up!

Treatment with two/three-combination therapy

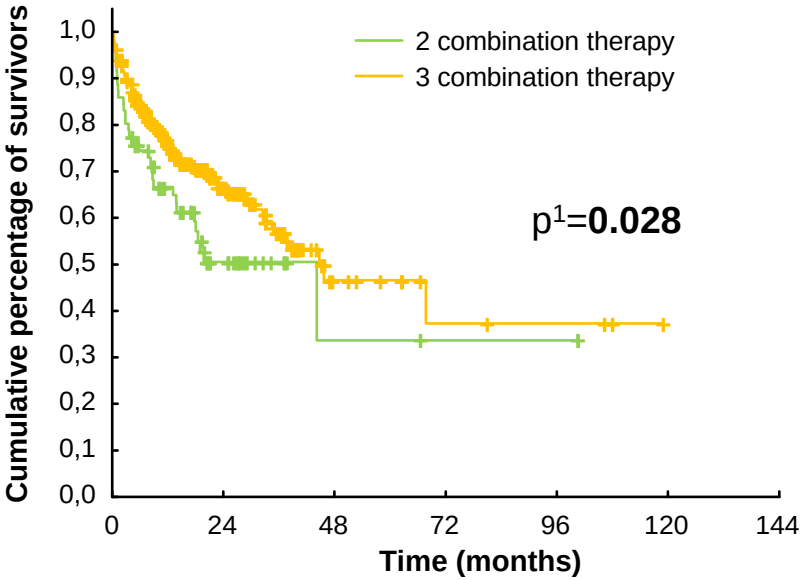
Base: N=496 patients in primotherapy



Treatment combination

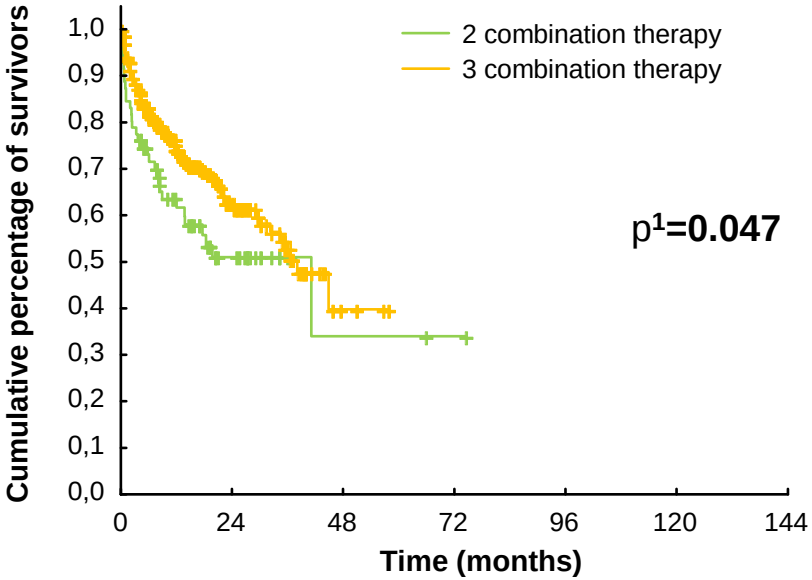
Base: N=466 patients in PT with two/three combination therapy

OS from diagnosis



	2 comb. therapy	3 comb. therapy
N	71	395
Median survival (months (95% CI))	44.1 (10.2-78.1)	45.7 (26.2-65.2)
Survival 12 m. %(CI)	66.6 (18.8-90.6)	75.4 (38.7-92.0)
Survival 24 m. %(CI)	50.5 (14.5-78.6)	66.8 (33.0-86.4)
Survival 36 m. %(CI)	50.5 (14.5-78.6)	56.6 (24.0-79.7)

OS from beginning of treatment



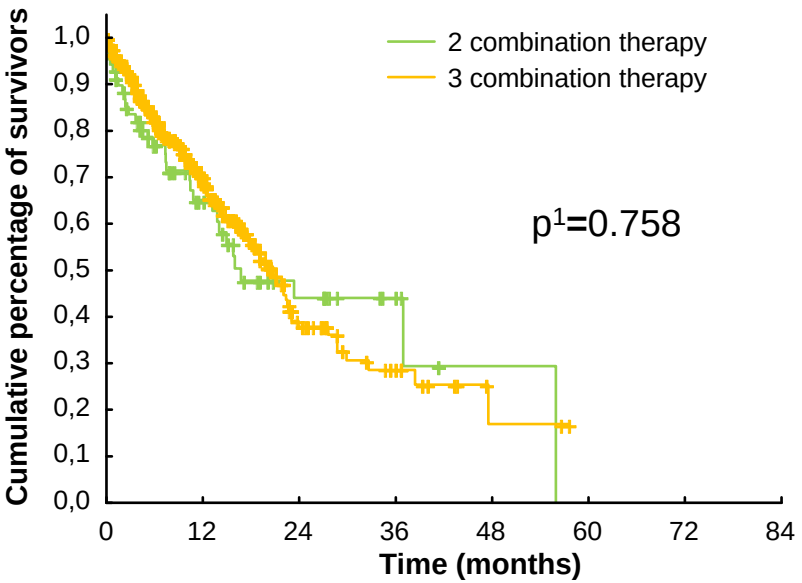
	2 comb. therapy	3 comb. therapy
N	71	395
Median survival (months (95% CI))	41.1 (10.3-72.0)	38.1 (30.2-46.0)
Survival 12 m. %(CI)	61.7 (18.1-87.2)	73.8 (37.9-90.9)
Survival 24 m. %(CI)	51.0 (14.6-79.0)	62.4 (29.4-83.4)
Survival 36 m. %(CI)	51.0 (14.6-79.0)	52.6 (20.2-77.2)

[1] Tested by log-rank test

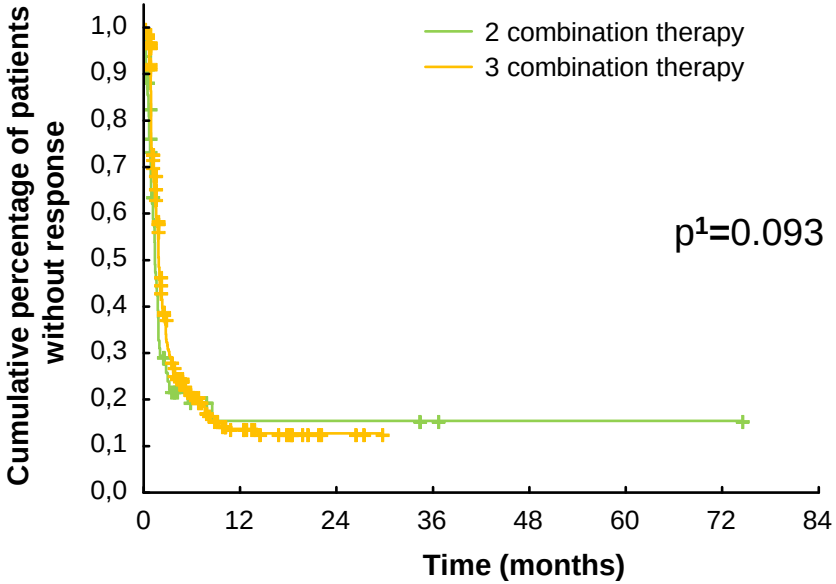
Treatment combination

Base: N=466 patients in PT with two/three combination therapy

TTP (time to progress)



TTR (Time to response)



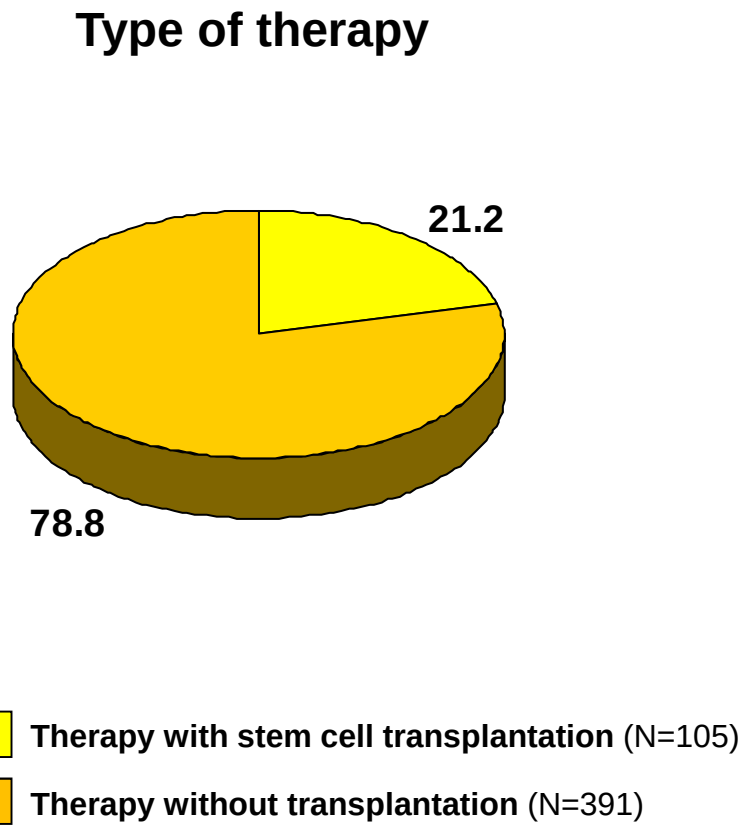
	2 comb. therapy	3 comb. therapy
N	71	395
Median survival (months (95% CI))	16.7 (6.4-27.0)	20.7 (18.0-23.4)
Survival 12 m. %(CI)	65.1 (16.9-90.2)	69.4 (35.1-88.0)
Survival 24 m. %(CI)	44.1 (10.9-73.8)	37.9 (14.9-60.9)
Survival 36 m. %(CI)	44.1 (10.9-73.8)	28.6 (9.2-51.7)

	2 comb. therapy	3 comb. therapy
N	71	395
Median survival (months (95% CI))	1.4 (1.1-1.7)	1.9 (1.8-2.0)
Survival 12 m. %(CI)	15.4 (3.0-36.8)	13.7 (5.3-26.0)
Survival 24 m. %(CI)	15.4 (3.0-36.8)	12.7 (4.7-24.9)
Survival 36 m. %(CI)	15.4 (3.0-36.8)	12.7 (4.7-24.9)

[1] Tested by log-rank test

Therapy with transplantation

Base: N=496 patients in primotherapy

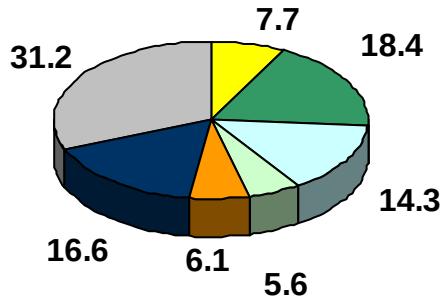


Therapy with transplantation – Treatment response

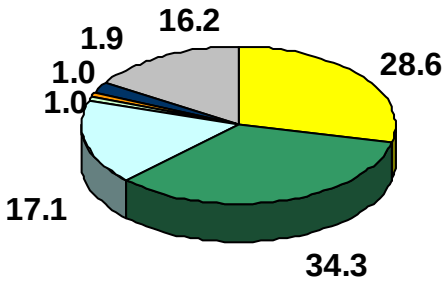
Base: N=496 patients in primotherapy

Treatment response

Therapy without AT (N=391)



Therapy with AT (N=105)



sCR+CR | VGPR | PR | MR | SD | PG | Unknown

Treatment response (N=391)	
sCR	4 (1.0%)
CR	26 (6.6%)
VGPR	72 (18.4%)
PR	56 (14.3%)
MR	22 (5.6%)
SD	24 (6.1%)
PG	65 (16.6%)
Unknown	122 (31.2%)

ORR	158 (40.4%)
CBR	180 (46.0%)

Treatment response (N=105)	
sCR	11 (10.5%)
CR	19 (18.1%)
VGPR	36 (34.3%)
PR	18 (17.1%)
MR	1 (1.0%)
SD	1 (1.0%)
PG	2 (1.9%)
Unknown	17 (16.2%)

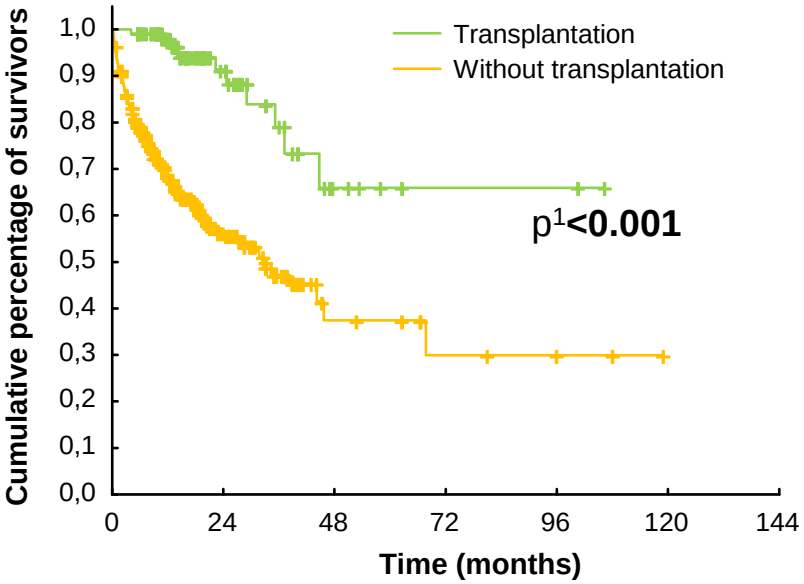
ORR	84 (80.0%)
CBR	85 (81.0%)

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

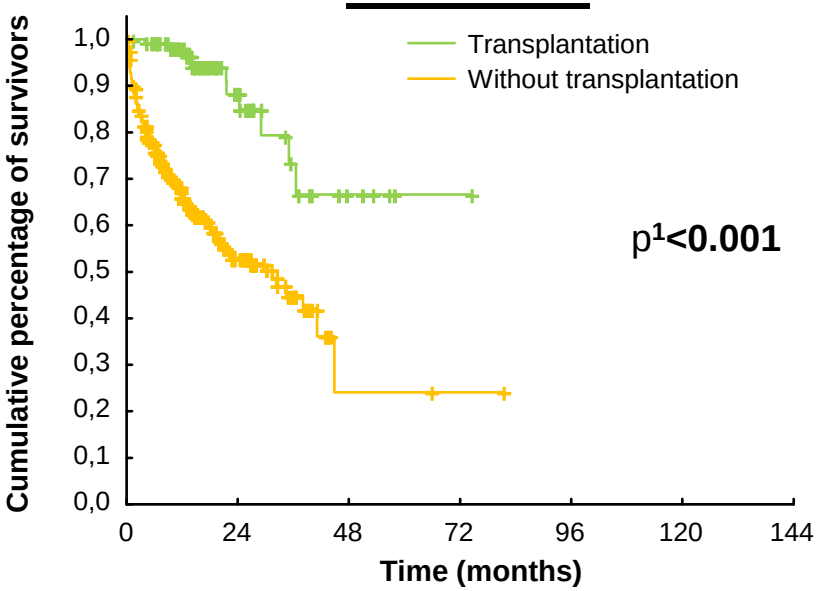
Transplantation during therapy

Base: N=496 patients in primotherapy

OS from diagnosis



OS from beginning of treatment



	Transplantation	Without transplantation
N	105	391
Median survival (months (95% CI))	-	32.5 (22.1-42.8)
Survival 12m. %(CI)	97.9 (-)	68.0 (35.9-86.5)
Survival 24 m. %(CI)	91.4 (0.1-99.9)	56.1 (27.9-77.0)
Survival 36 m. %(CI)	79.0 (4.6-98.2)	47.2 (20.3-70.3)

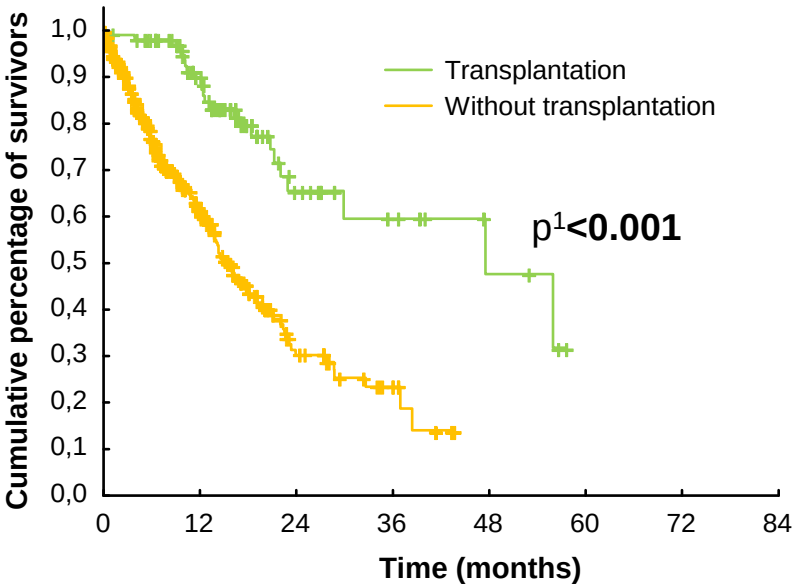
	Transplantation	Without transplantation
N	105	391
Median survival (months (95% CI))	-	31.6 (21.4-41.8)
Survival 12 m. %(CI)	97.9 (-)	65.3 (34.3-84.4)
Survival 24 m. %(CI)	88.2 (1.1-99.6)	53.0 (25.4-74.5)
Survival 36 m. %(CI)	73.2 (5.8-96.7)	44.9 (17.9-68.9)

[1] Tested by log-rank test

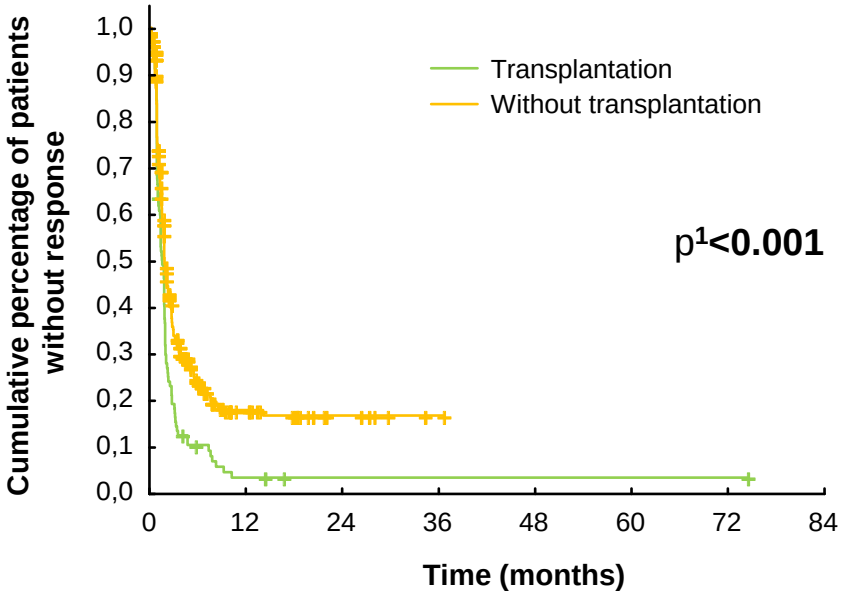
Transplantation during therapy

Base: N=496 patients in primotherapy

TTP (time to progress)



TTR (Time to response)



	Transplantation	Without transplantation
N	105	391
Median survival (months (95% CI))	47.5 (24.4-70.7)	14.9 (12.7-17.2)
Survival 12m. %(CI)	89.9 (3.1-99.7)	61.0 (30.8-81.2)
Survival 24 m. %(CI)	65.5 (14.8-91.1)	30.2 (11.6-51.4)
Survival 36 m. %(CI)	59.6 (11.5-88.3)	23.4 (7.5-44.2)

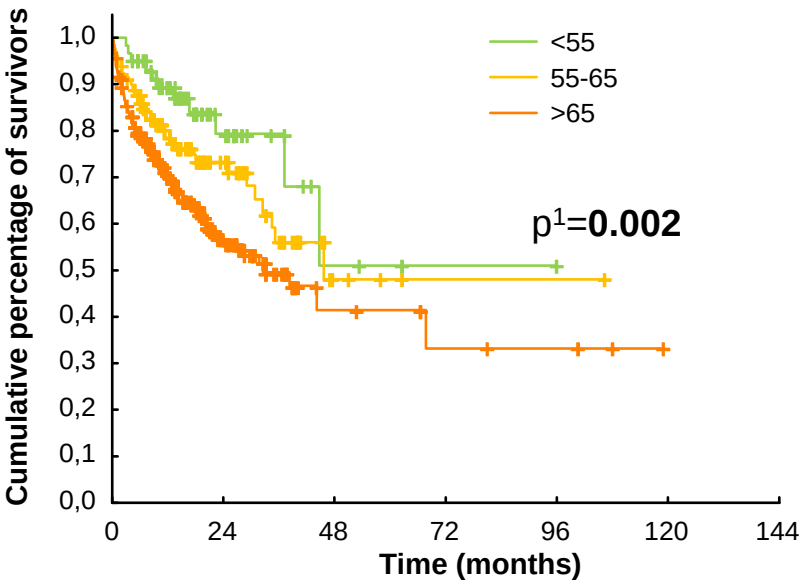
	Transplantation	Without transplantation
N	105	391
Median survival (months (95% CI))	1.6 (1.4-1.9)	1.9 (1.7-2.1)
Survival 12 m. %(CI)	3.5 (0.6-11.4)	18.0 (7.4-32.3)
Survival 24 m. %(CI)	3.5 (0.6-11.4)	16.9 (6.6-31.2)
Survival 36 m. %(CI)	3.5 (0.6-11.4)	16.9 (6.6-31.2)

[1] Tested by log-rank test

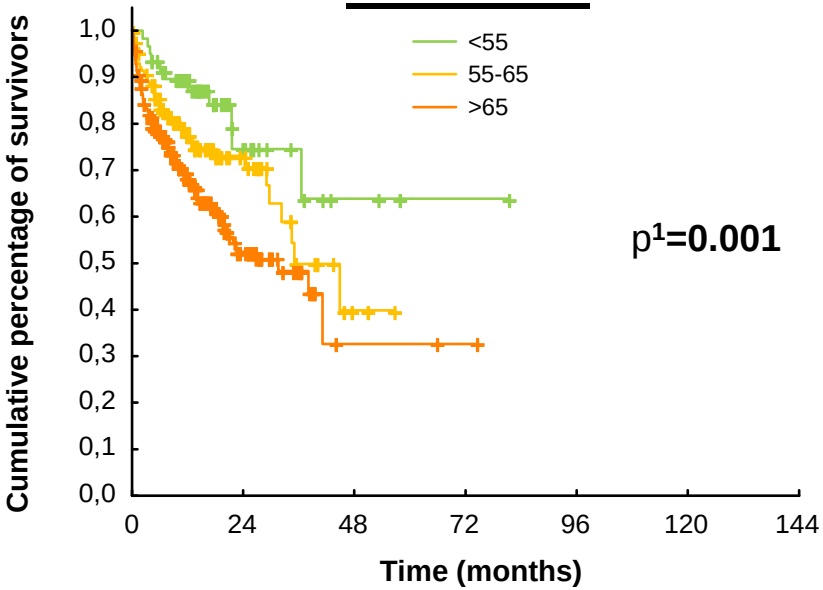
Age

Base: N=496 patients in primotherapy

OS from diagnosis



OS from beginning of treatment



	Age<55	Age: 55-65	Age >65
N	61	130	305
Median survival (months (95% CI))	-	45.7 (-)	32.6 (20.7-44.5)
Survival 12 m. %(CI)	89.3 (0.9-99.7)	78.5 (23.9-96.0)	69.9 (34.5-88.7)
Survival 24 m. %(CI)	79.4 (6.3-98.1)	73.3 (23.6-93.6)	56.7 (26.2-78.6)
Survival 36 m. %(CI)	79.4 (6.3-98.1)	56.1 (14.6-84.0)	49.5 (20.0-73.6)

	Age<55	Age: 55-65	Age >65
N	61	130	305
Median survival (months (95% CI))	-	35.0 (23.9-46.2)	31.6 (18.6-44.6)
Survival 12 m. %(CI)	87.3 (2.6-99.5)	77.2 (24.1-95.4)	67.5 (33.2-86.9)
Survival 24 m. %(CI)	74.5 (7.4-96.7)	73.1 (23.4-93.5)	52.5 (23.1-75.3)
Survival 36 m. %(CI)	74.5 (7.4-96.7)	49.8 (10.6-80.5)	48.3 (18.9-72.8)

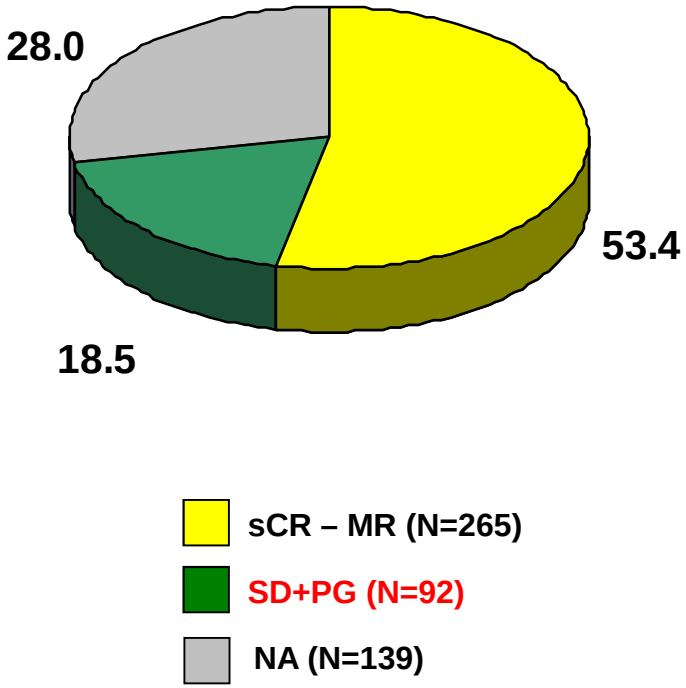
[1] Tested by log-rank test

Next therapy of patients with SD+PG

SD+PG

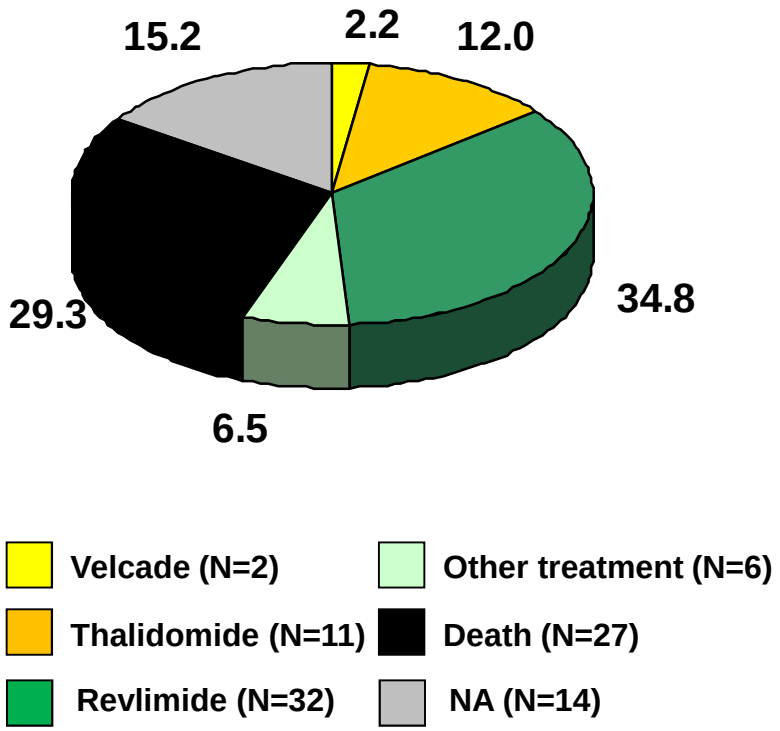
Base: N=496 patients in primotherapy

Treatment response



SD+PG – Next treatment

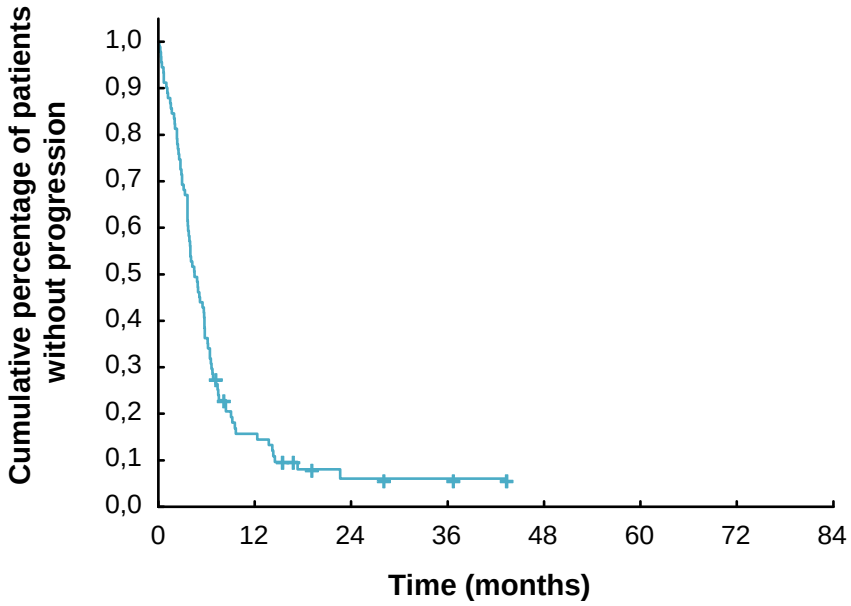
Base: N=92 patients in PT with treatment response SD or PG



SD+PG

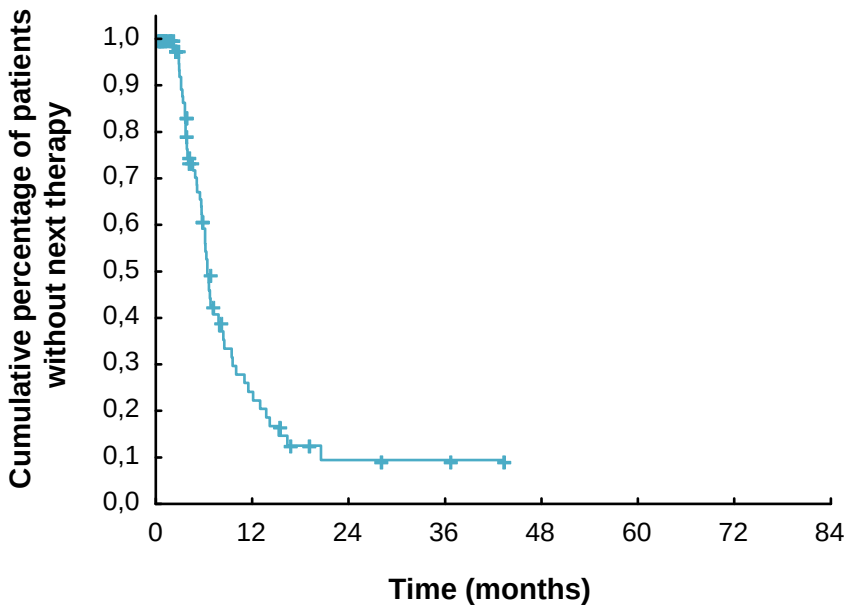
Base: N=92 patients in PT with treatment response SD or PG

PFS (progression free survival)



	PFS (%; 95% CI)
N	92
Median survival (months)	4.5 (3.4-5.6)
Survival 12 m. %(CI)	15.7 (0.1-61.3)
Survival 24 m. %(CI)	6.0 (0.0-67.3)
Survival 36 m. %(CI)	6.0 (0.0-67.3)

TNT (Time to next therapy)



	TNT (%; 95% CI)
N	92
Median survival (months)	6.4 (5.8-7.1)
Survival 12 m. %(CI)	24.1 (0.4-69.3)
Survival 24 m. %(CI)	9.4 (0.0-68.6)
Survival 36 m. %(CI)	9.4 (0.0-68.6)

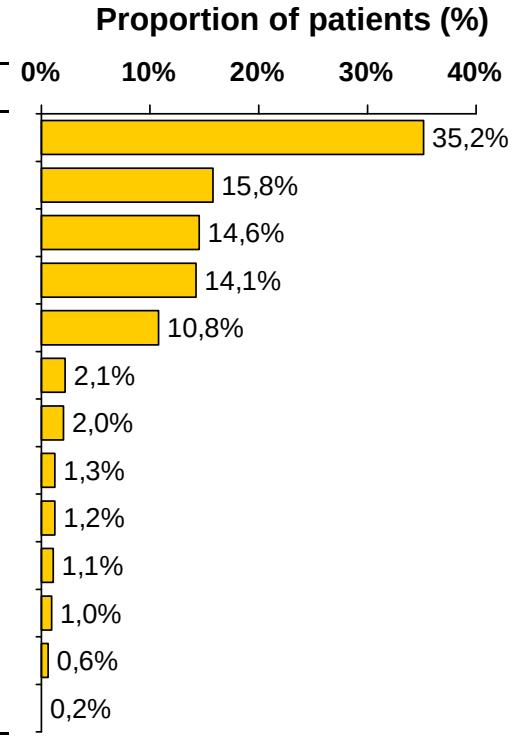
*Dataset consists of patients with at least 6 months follow up!

Basic characteristics for patients in relaps

SITES

Base: N=933 patients in relaps

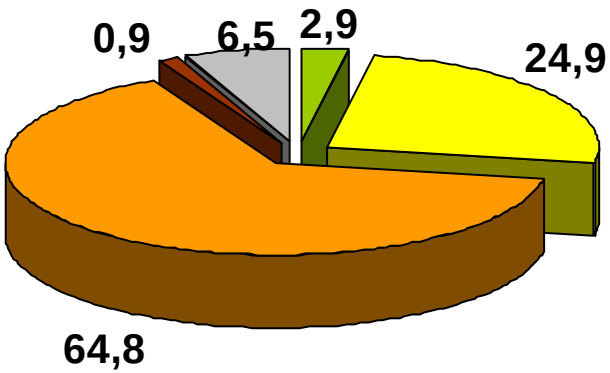
SITE	number	%
FN Brno - IHOK	328	35.2%
VFN Praha - I. Interní klinika	147	15.8%
FN Olomouc - III. interní klinika	136	14.6%
FNHK - OKH	132	14.1%
FNKV Praha - OKH	101	10.8%
Havířov - Hematologické odd.	20	2.1%
KN Liberec - OKH	19	2.0%
Nový Jičín - Onkologické centrum, HO	12	1.3%
Opava - Hematologické odd.	11	1.2%
ČB - OKH	10	1.1%
FN Ostrava - UKH	9	1.0%
Pelhřimov - OHT	6	0.6%
Mladá Boleslav - HTO	2	0.2%
Total	933	100.0%



Treatment procedure

Base: N=933 patients in relaps

Drug combination

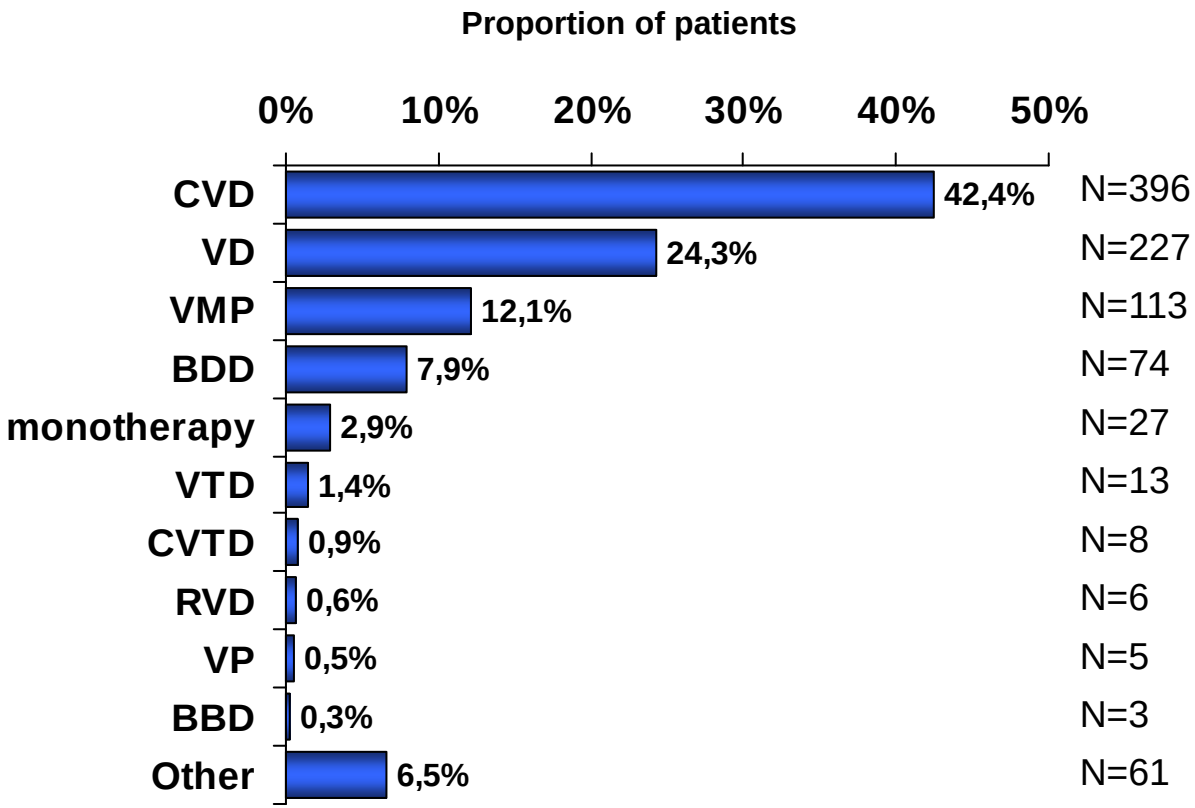


- **monotherapy** (N=27)
- **two-combination therapy** (N=232)
- **three-combination therapy** (N=605)
- **four-combination therapy** (N=8)
- **unknown Velcade combination therapy** (N=61)

Treatment procedure

Base: N=933 patients in relaps

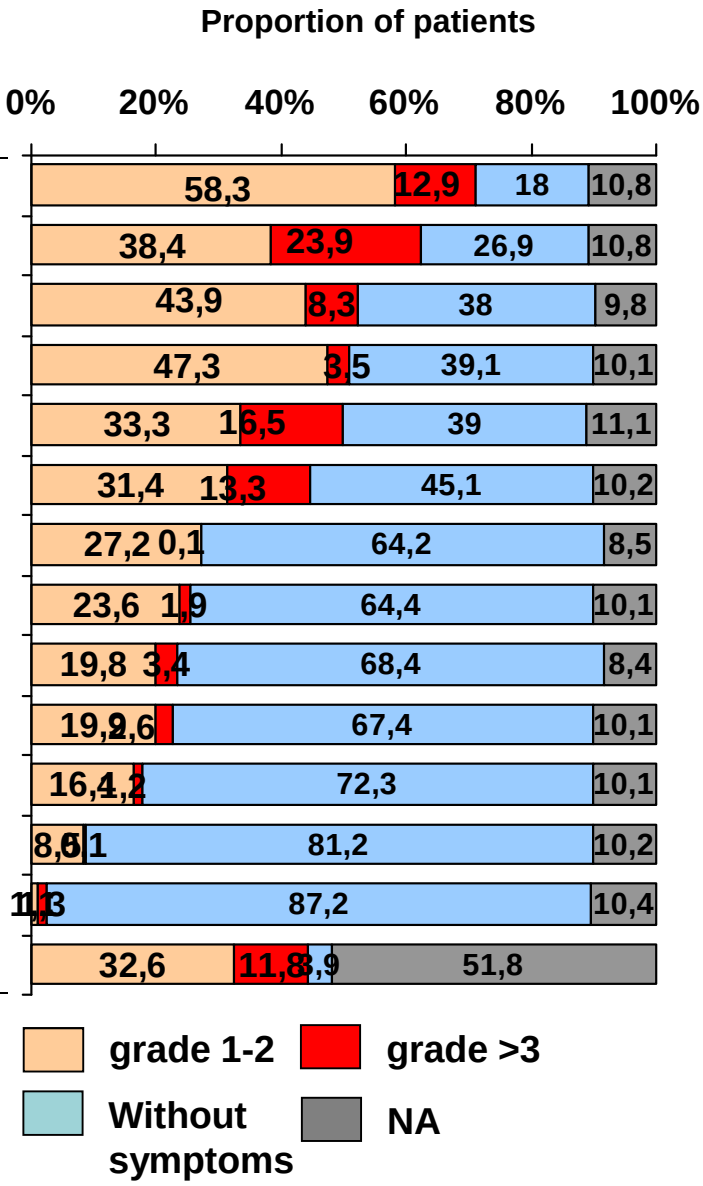
Treatment used



Toxicity

Base: N=933 patients in relaps ; each patient can suffer from more than one toxicity

Toxicity	Number of patients grade 1-2/>3/without/NA
Anemia	544/120/168/101
Thrombocytopenia	358/223/251/101
Neuropathy	410/77/355/91
Fatigue	441/33/365/94
Neutropenia	311/154/364/104
Infection	293/124/421/95
Neuropathy before treatment	254/1/599/79
Nausea	220/18/601/94
Thrombocytopenia before treatment	185/32/638/78
Diarrhoea	186/24/629/94
Anorexia	153/11/675/94
Constipation	79/1/758/95
Thrombosis	10/12/814/97
Other	304/110/36/483



Toxicity

Base: N=933 patients in relaps ; each patient can suffer from more than one toxicity

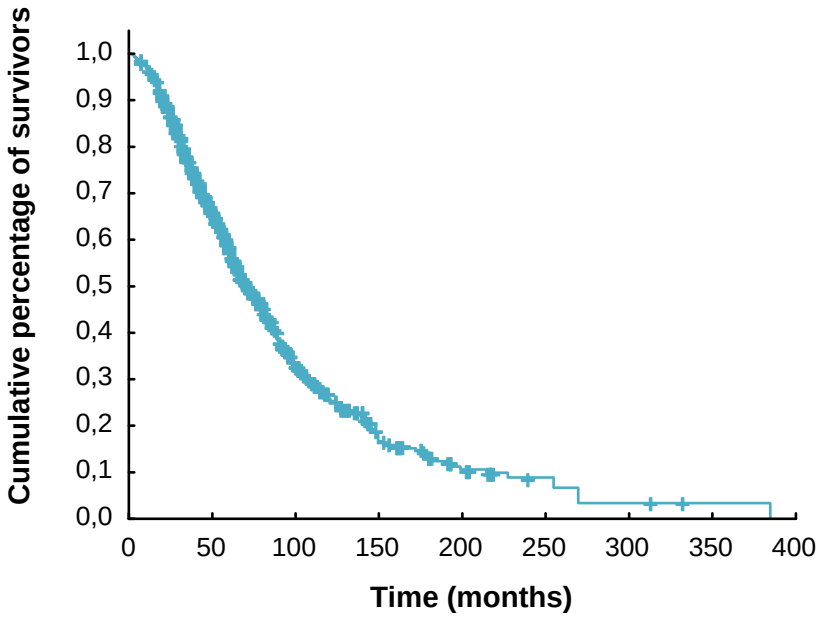
The most observed toxicity

	grade	N(%)
Fatigue	1	313 (33.5%)
Anemia	1	293 (31.4%)
Thrombocytopenia	1	254 (27.2%)
Neuropathy	1	227 (24.3%)
Neuropathy before treatment	1	215 (23.0%)
Infection	2	201 (21.5%)
Neutropenia	2	172 (18.4%)
Nausea	1	171 (18.3%)
Thrombocytopenia before treatment	1	169 (18.1%)
Anorexia	1	140 (15.0%)
Diarrhoea	1	130 (13.9%)
Constipation	1	125 (13.4%)
Thrombosis	1	57 (6.1%)
Other	2	9 (1.0%)

Survival analysis

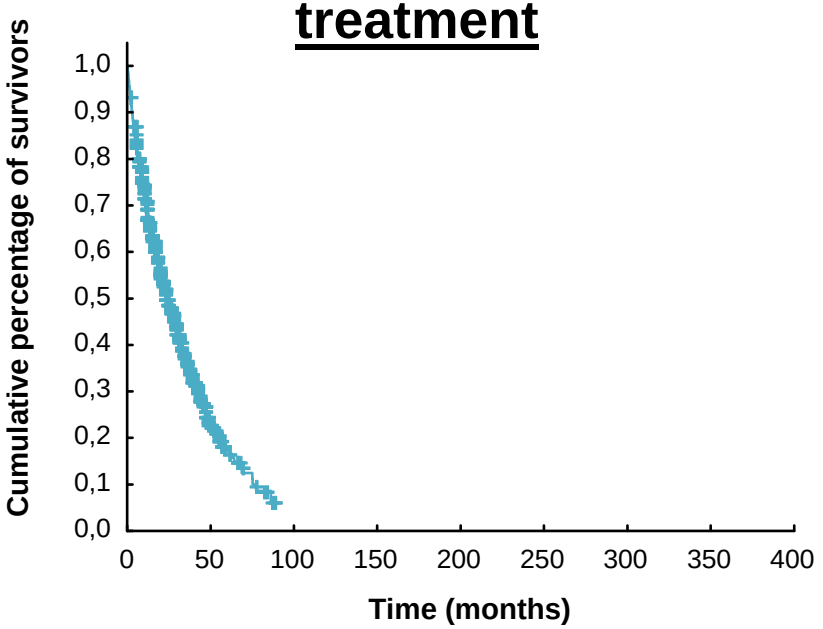
Base: N=933 patients in relaps

OS from diagnosis



	OS (%; 95% CI)
N	933
Median survival (months)	70.0 (64.0-76.0)
Survival 12 m. %(CI)	96.0 (94.6-97.1)
Survival 24 m. %(CI)	87.2 (84.9-89.2)
Survival 36 m. %(CI)	75.8 (72.8-78.4)

OS from beginning of treatment



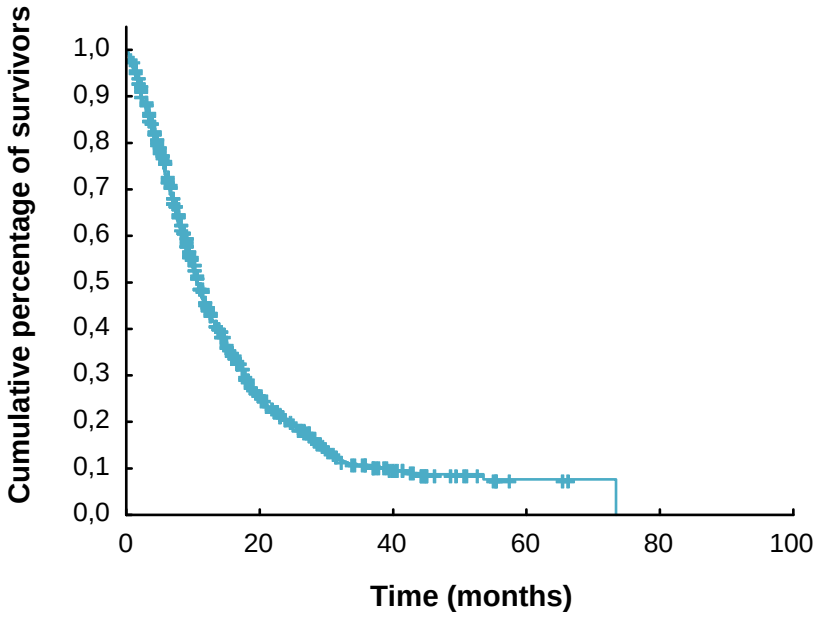
	OS (%; 95% CI)
N	933
Median survival (months)	23.2 (20.3-26.0)
Survival 12 m. %(CI)	66.9 (63.7-69.8)
Survival 24 m. %(CI)	49.0 (45.5-52.4)
Survival 36 m. %(CI)	35.6 (32.0-39.2)

Note: Dataset consists of patients with at least 6 months follow up!

Survival analysis

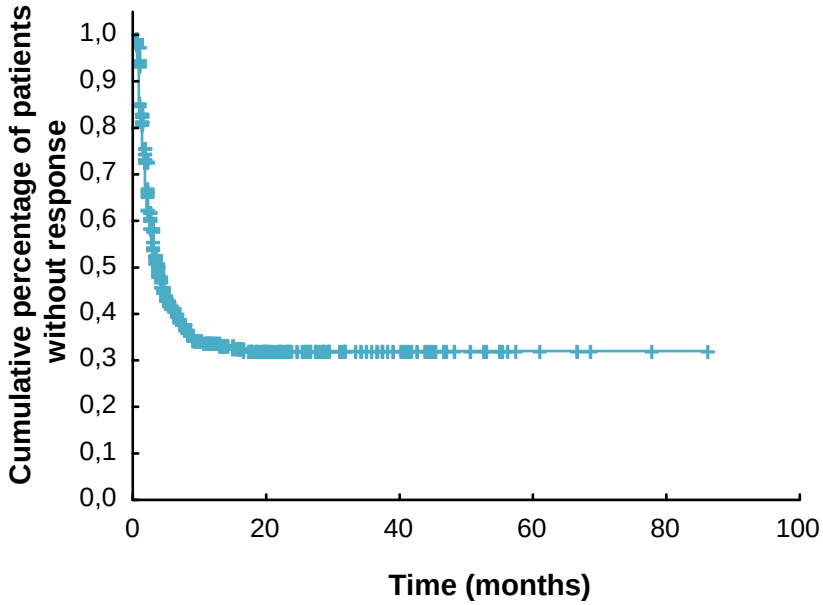
Base: N=933 patients in relaps

TTP (time to progress)



	TTP (%; 95% CI)
N	933
Median survival (months)	10.6 (9.8-11.4)
Survival 12 m. %(CI)	44.8 (41.4-48.1)
Survival 24 m. %(CI)	20.7 (17.8-23.7)
Survival 36 m. %(CI)	10.8 (8.3-13.5)

TTR (Time to response)



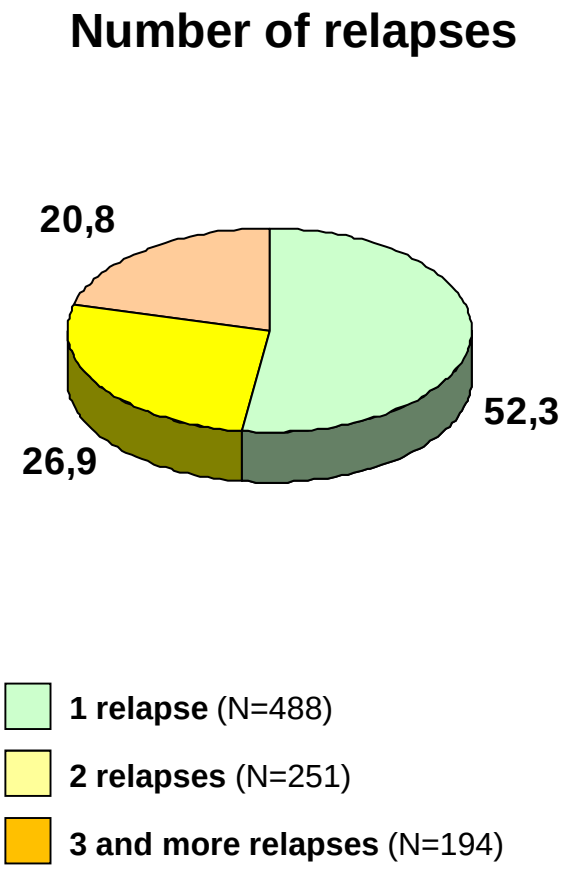
	TTR (%; 95% CI)
N	933
Median survival (months)	3.7 (3.2-4.2)
Survival 12 m. %(CI)	33.8 (30.4-37.2)
Survival 24 m. %(CI)	32.0 (28.5-35.5)
Survival 36 m. %(CI)	32.0 (28.5-35.5)

Note: Dataset consists of patients with at least 6 months follow up!

Analysis according to preceding line of treatment for patients in relaps

Preceding line of treatment

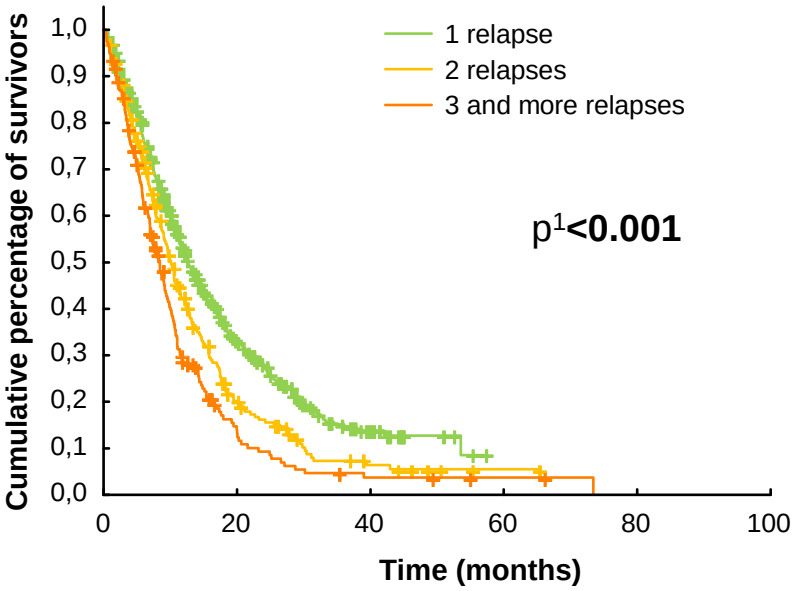
Base: N=933 patients in relaps



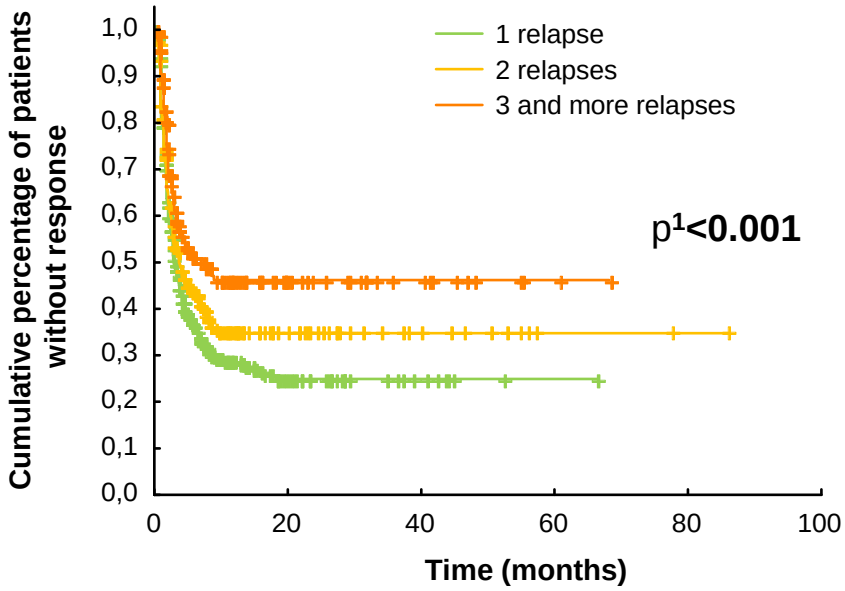
Relapses

Base: N=933 patients in relaps

TTP (time to progress)



TTR (Time to response)



	1 relapse	2 relapses	≥3 relapses
N	488	251	194
Median survival (months (95% CI))	12.7 (11.2; 14.1)	10.1 (9.0; 11.3)	8.4 (7.1; 9.7)
Survival 12 m. %(CI)	52.6 (47.9-57.2)	42.2 (35.8-48.5)	28.2 (21.7-35.1)
Survival 24 m. %(CI)	27.7 (23.2-32.4)	16.1 (11.4-21.6)	9.3 (5.2-14.8)
Survival 36 m. %(CI)	15.1 (11.1-19.7)	7.3 (3.9-12.0)	4.6 (1.9-9.1)

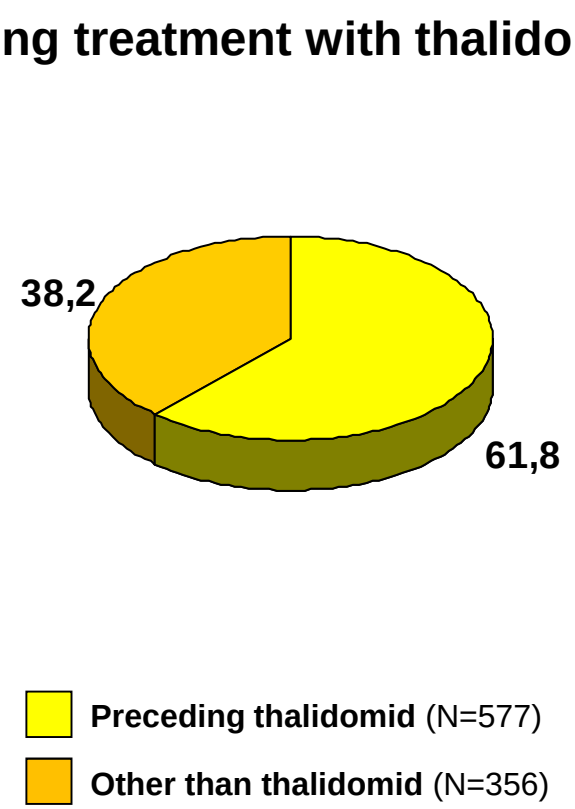
	1 relapse	2 relapses	≥3 relapses
N	488	251	194
Median survival (months (95% CI))	3.0 (2.5; 3.4)	3.7 (2.5; 5.0)	6.3 (-)
Survival 12 m. %(CI)	28.5 (24.1-33.1)	34.8 (28.3-41.3)	46.2 (38.1-53.8)
Survival 24 m. %(CI)	24.9 (20.2-29.8)	34.8 (28.3-41.3)	46.2 (38.1-53.8)
Survival 36 m. %(CI)	24.9 (20.2-29.8)	34.8 (28.3-41.3)	46.2 (38.1-53.8)

[1] Tested by log-rank test

Analysis according to type of preceding treatment for patients in relaps

Preceding treatment with thalidomid

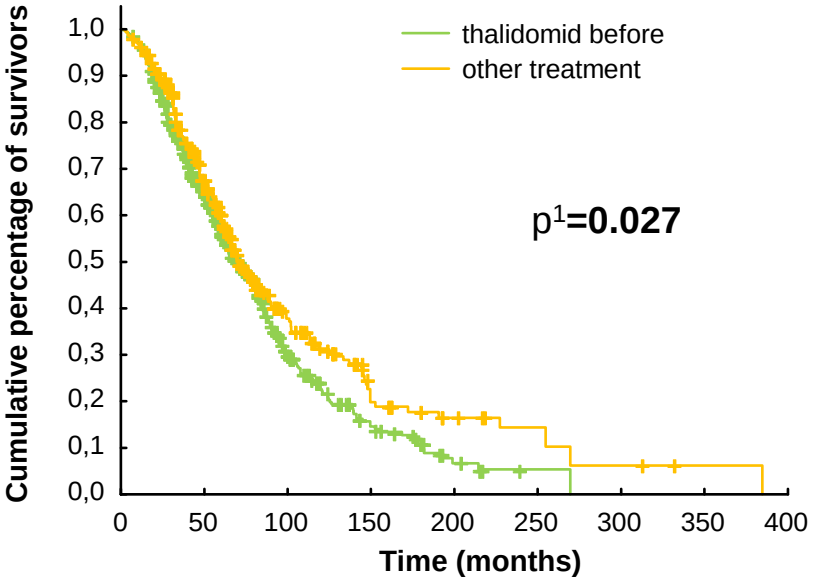
Base: N=933 patients in relaps



Preceding treatment with thalidomid

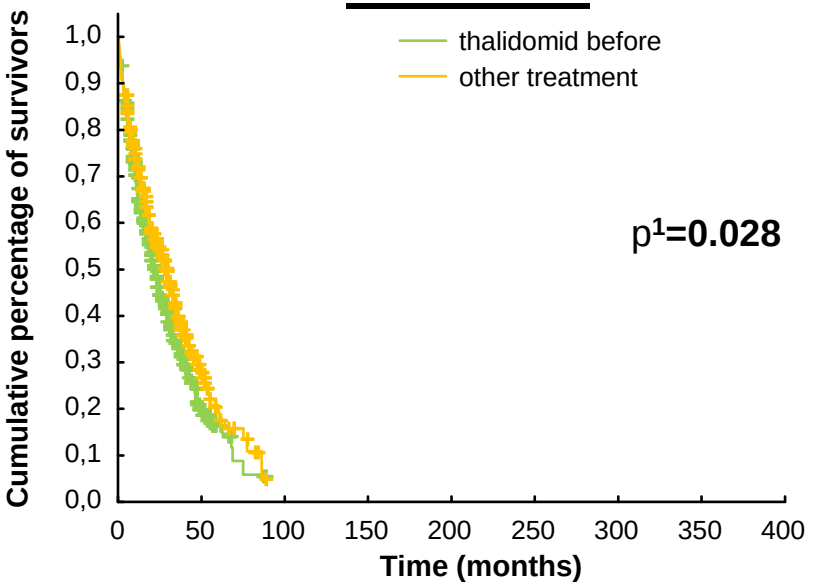
Base: N=933 patients in relaps

OS from diagnosis



	Thalidomid before	Other treatment
N	577	356
Median survival (months (95% CI))	70.6 (62.0; 79.2)	70.0 (61.8; 78.2)
Survival 12 m. %(CI)	96.2 (94.3-97.5)	95.8 (93.1-97.4)
Survival 24 m. %(CI)	85.5 (82.4-88.1)	90.1 (86.4-92.8)
Survival 36 m. %(CI)	75.0 (71.2-78.3)	77.0 (72.2-81.2)

OS from beginning of treatment

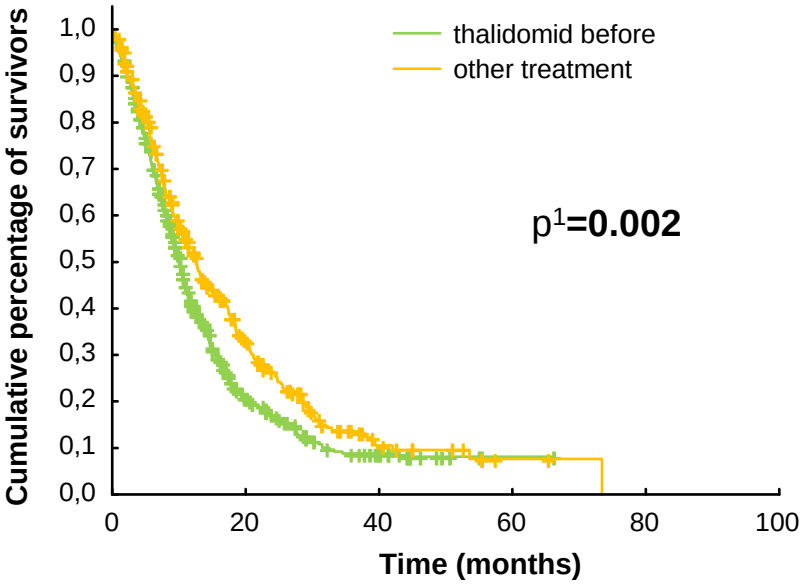


	Thalidomid before	Other treatment
N	577	356
Median survival (months (95% CI))	21.4 (19.0; 23.8)	28.3 (23.5; 33.1)
Survival 12 m. %(CI)	64.9 (60.8-68.7)	69.9 (64.8-74.5)
Survival 24 m. %(CI)	45.0 (40.5-49.4)	55.1 (49.6-60.4)
Survival 36 m. %(CI)	33.0 (28.6-37.6)	39.5 (33.7-45.3)

[1] Tested by log-rank test

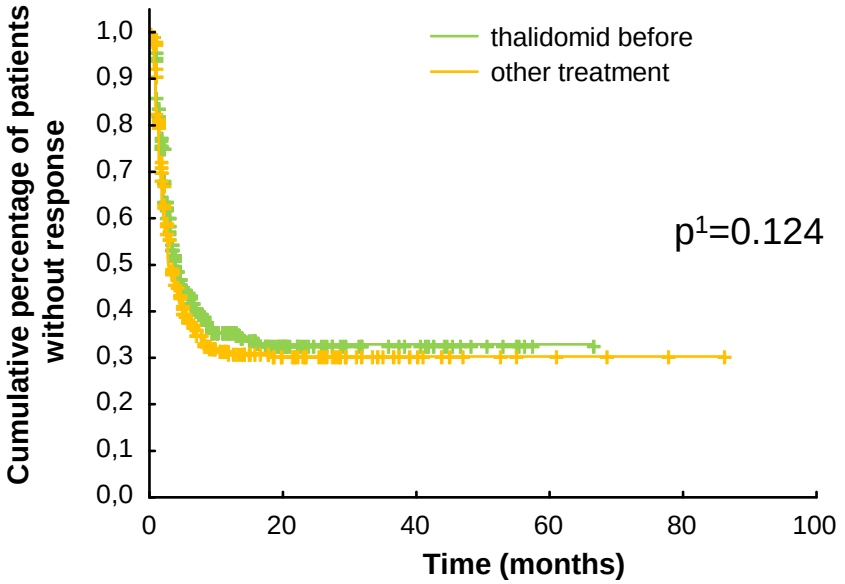
Preceding treatment with thalidomid

TTP (time to progress)



	Thalidomid before	Other treatment
N	577	356
Median survival (months (95% CI))	9.9 (9.2; 10.7)	12.6 (11.0; 14.3)
Survival 12 m. %(CI)	40.1 (35.9-44.3)	52.0 (46.5-57.2)
Survival 24 m. %(CI)	16.9 (13.5-20.7)	26.4 (21.4-31.6)
Survival 36 m. %(CI)	8.8 (6.1-12.2)	13.8 (9.6-18.7)

TTR (Time to response)

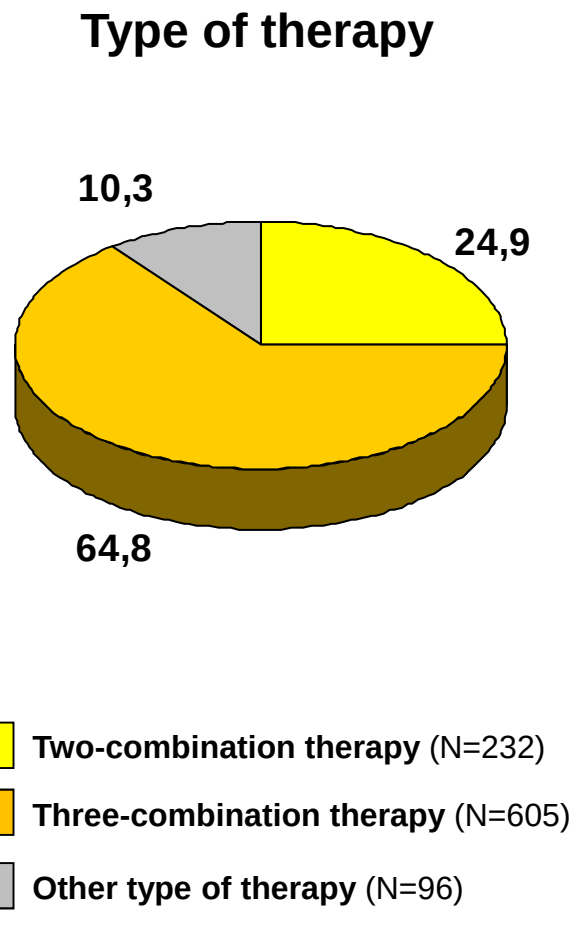


	Thalidomid before	Other treatment
N	577	356
Median survival (months (95% CI))	3.8 (3.0; 4.6)	2.9 (2.2; 3.6)
Survival 12 m. %(CI)	35.5 (31.1-39.9)	31.0 (25.8-36.4)
Survival 24 m. %(CI)	32.9 (28.3-37.5)	30.3 (25.0-35.7)
Survival 36 m. %(CI)	32.9 (28.3-37.5)	30.3 (25.0-35.7)

[1] Tested by log-rank test

Treatment with two/three-combination therapy

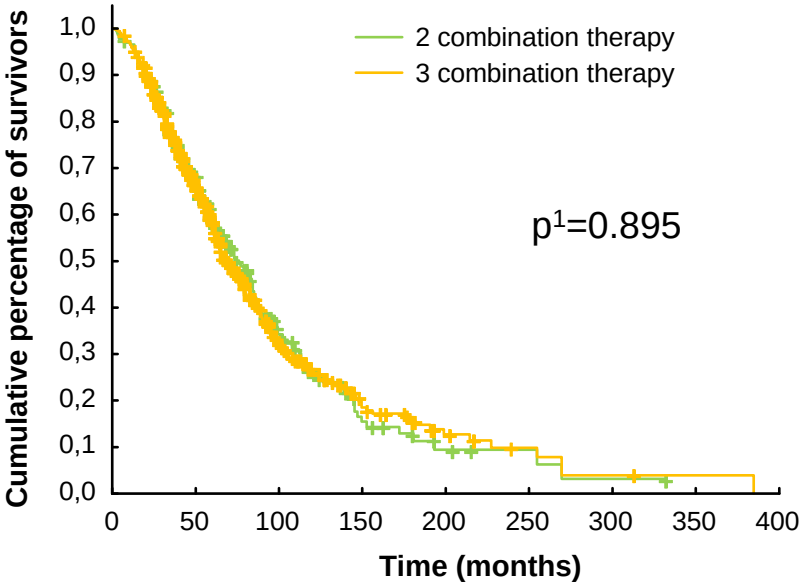
Base: N=933 patients in relaps



Treatment combination

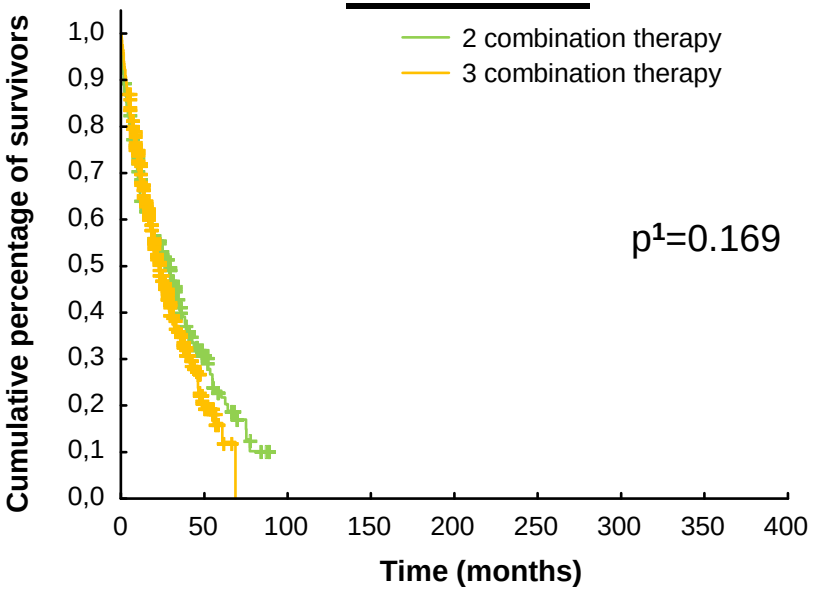
Base: N=837 patients in relaps with two/three combination therapy

OS from diagnosis



	2 comb. therapy	3 comb. therapy
N	232	605
Median survival (months (95% CI))	76.2 (63.4; 88.9)	67.2 (60.2; 74.2)
Survival 12 m. %(CI)	96.5 (93.2-98.3)	95.9 (93.9-97.2)
Survival 24 m. %(CI)	87.9 (82.9-91.5)	86.8 (83.8-89.3)
Survival 36 m. %(CI)	75.0 (68.8-80.1)	76.5 (72.8-79.7)

OS from beginning of treatment



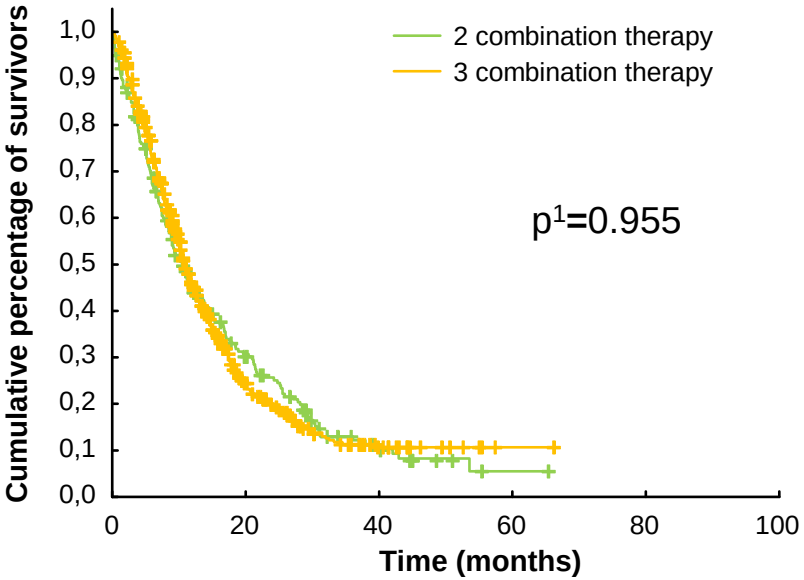
	2 comb. therapy	3 comb. therapy
N	232	605
Median survival (months (95% CI))	28.5 (20.6; 36.3)	22.6 (19.5; 25.7)
Survival 12 m. %(CI)	64.5 (58.0-70.4)	67.6 (63.6-71.2)
Survival 24 m. %(CI)	53.9 (47.1-60.3)	46.8 (42.4-51.1)
Survival 36 m. %(CI)	40.4 (33.5-47.2)	34.6 (30.1-39.1)

[1] Tested by log-rank test

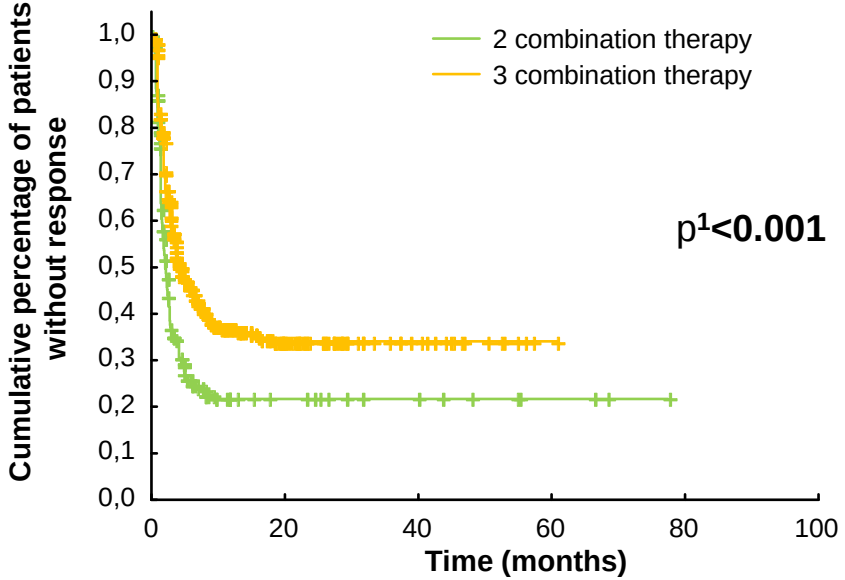
Treatment combination

Base: N=837 patients in relaps with two/three combination therapy

TTP (time to progress)



TTR (Time to response)



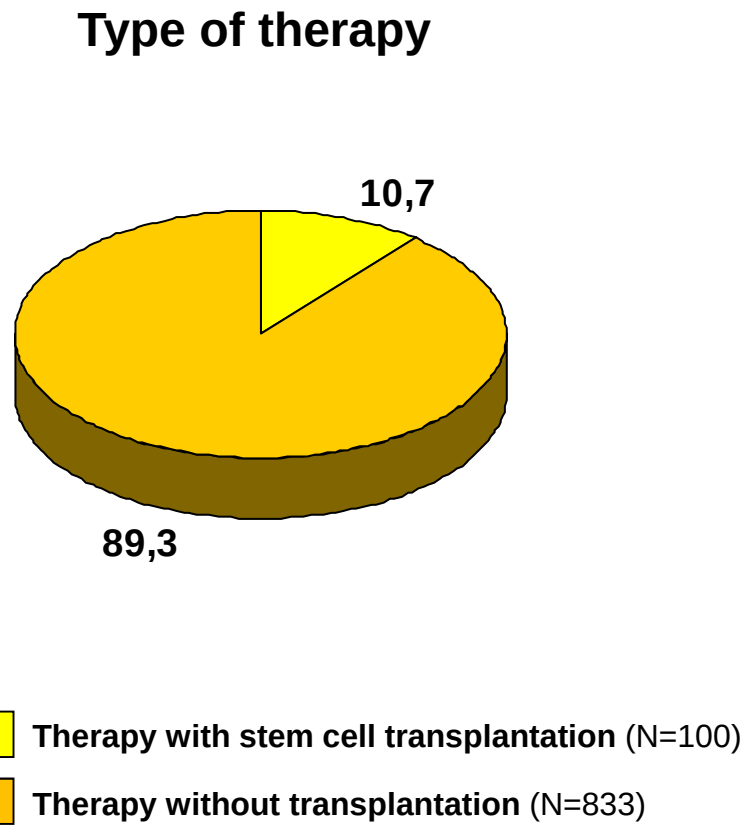
	2 comb. therapy	3 comb. therapy
N	232	605
Median survival (months (95% CI))	10.5 (8.6; 12.4)	10.7 (9.7; 11.6)
Survival 12 m. %(CI)	45.3 (38.6-51.8)	45.2 (41.0-49.4)
Survival 24 m. %(CI)	25.7 (19.8-31.9)	20.1 (16.5-24.0)
Survival 36 m. %(CI)	13.0 (8.5-18.5)	11.3 (8.2-15.0)

	2 comb. therapy	3 comb. therapy
N	232	605
Median survival (months (95% CI))	2.1 (1.7; 2.4)	4.2 (3.3; 5.2)
Survival 12 m. %(CI)	21.7 (15.9-28.1)	36.6 (32.4-40.9)
Survival 24 m. %(CI)	21.7 (15.9-28.1)	34.0 (29.6-38.5)
Survival 36 m. %(CI)	21.7 (15.9-28.1)	34.0 (29.6-38.5)

[1] Tested by log-rank test

Therapy with transplantation

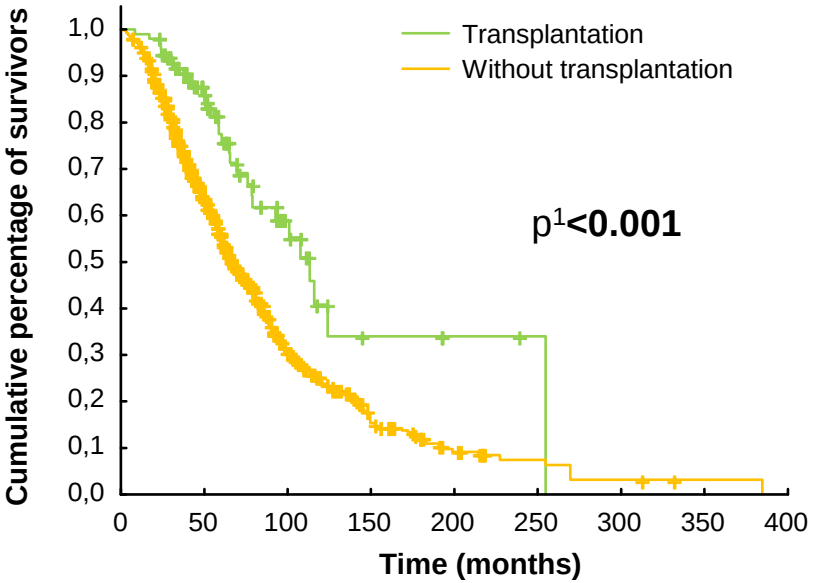
Base: N=933 patients in relaps



Transplantation during therapy

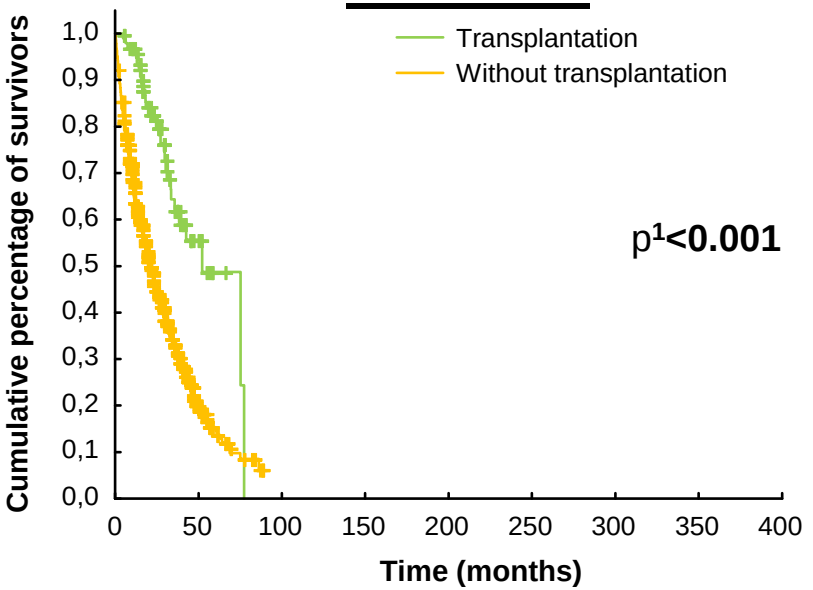
Base: N=933 patients in relaps

OS from diagnosis



	Transplantation	Without transplantation
N	100	833
Median survival (months (95% CI))	113.2 (95.6; 130.8)	65.6 (59.6; 71.6)
Survival 12m. %(CI)	99.0 (93.1-99.9)	95.7 (94.0-96.9)
Survival 24 m. %(CI)	97.0 (90.9-99.0)	86.1 (83.5-88.3)
Survival 36 m. %(CI)	90.4 (82.3-94.9)	74.1 (70.9-76.9)

OS from beginning of treatment



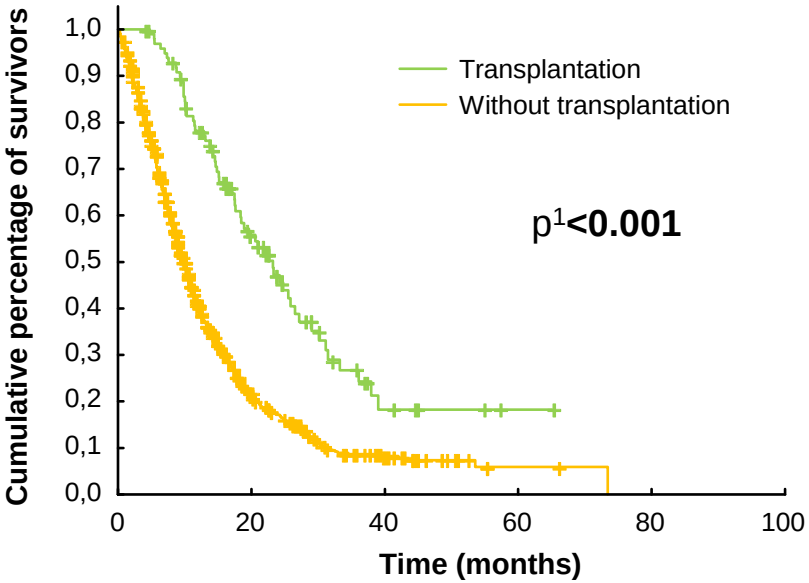
	Transplantation	Without transplantation
N	100	833
Median survival (months (95% CI))	52.2 (33.8; 70.6)	20.5 (18.3; 22.8)
Survival 12 m. %(CI)	95.9 (89.4-98.4)	63.3 (59.9-66.6)
Survival 24 m. %(CI)	81.4 (71.3-88.2)	45.1 (41.5-48.7)
Survival 36 m. %(CI)	62.2 (48.7-73.1)	32.4 (28.8-36.1)

[1] Tested by log-rank test

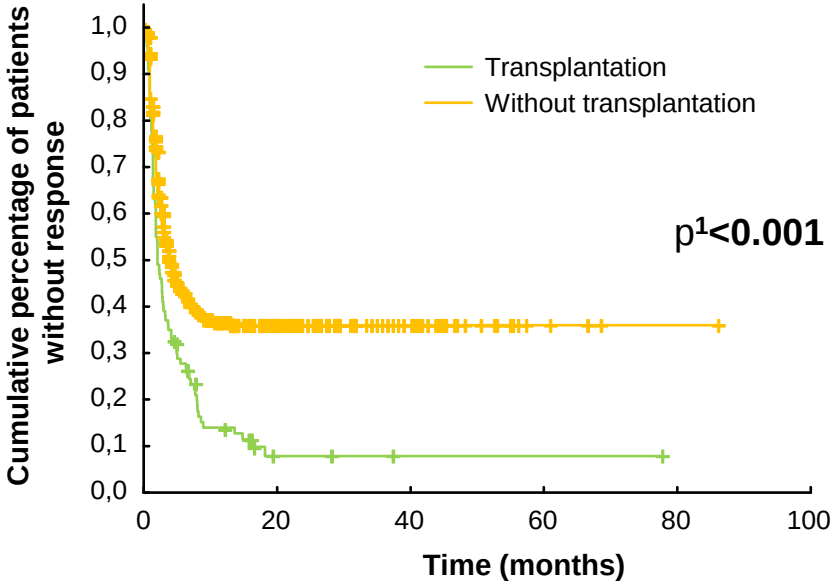
Transplantation during therapy

Base: N=933 patients in relaps

TTP (time to progress)



TTR (Time to response)



	Transplantation	Without transplantation
N	100	833
Median survival (months (95% CI))	23.2 (18.6; 27.9)	9.7 (8.9; 10.4)
Survival 12m. %(CI)	78.2 (68.6-85.2)	40.5 (37.0-44.0)
Survival 24 m. %(CI)	47.2 (36.0-57.5)	17.1 (14.3-20.2)
Survival 36 m. %(CI)	26.7 (16.4-38.2)	8.6 (6.4-11.3)

	Transplantation	Without transplantation
N	100	833
Median survival (months (95% CI))	2.1 (1.2; 2.9)	3.8 (3.1; 4.4)
Survival 12 m. %(CI)	14.0 (7.8-21.9)	36.7 (33.0-40.3)
Survival 24 m. %(CI)	7.8 (3.1-15.4)	36.0 (32.3-39.7)
Survival 36 m. %(CI)	7.8 (3.1-15.4)	36.0 (32.3-39.7)

[1] Tested by log-rank test

Souhrn

Výsledky je nutné srovnávat s výsledky jak klinických studií, tak podobných registrů.

Analýzy pro transplantované a netransplantované soubory je nutné připravit zvlášť.

V České republice používáme nejčastěji režim CVD jak v primoléčbě tak relapsu MM.

Trojkombinace má pozitivní vliv na OS v primoléčbě, ne však v relapsu onemocnění.

Pacienti, kteří v relapsu onemocnění mají indikovanou transplantaci, mají delší přežití.

Přestože je bortezomib dobrým lékem, je potřeba hledat účinnější kombinace a postupy léčby.

Nová generace inhibitorů proteasomu nezpůsobuje vážnější polyneuropatii. Jsou k dispozici i formy p.o.

Thank you for your attention