Optimizing Proteasome Inhibition in Myeloma

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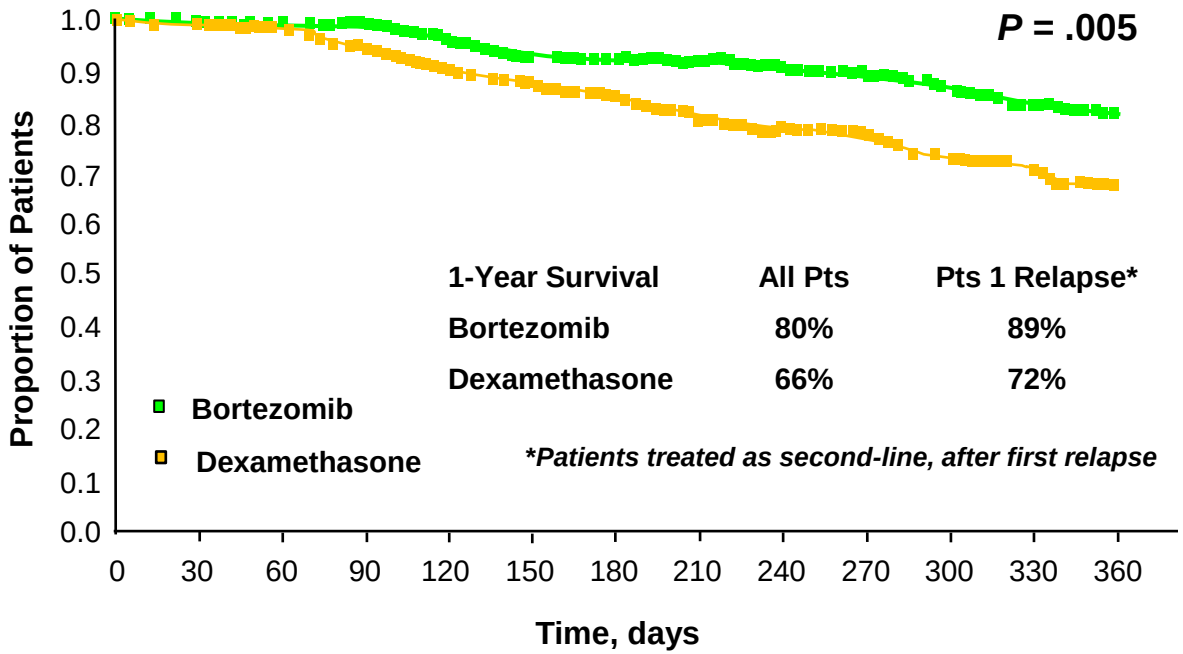
Objectives

- Review the role of proteasome inhibition in myeloma
- Proteasome inhibition in the context of other approaches
- Role in special patient populations
- Approaches to reducing toxicity
- New proteasome inhibitors

Bortezomib vs. High-Dose Dexamethasone in Relapsed Myeloma

APEX Study, International Phase III

Response rate (RR)	**38%**
Complete response (CR)	**6%**
Near CR (nCR)	**7%**
Partial response (PR)	**32%**
Median time to progression (TTP), months	**6.2**



Richardson PG, et al. *N Engl J Med.* 2005;352(24):2487-2498.

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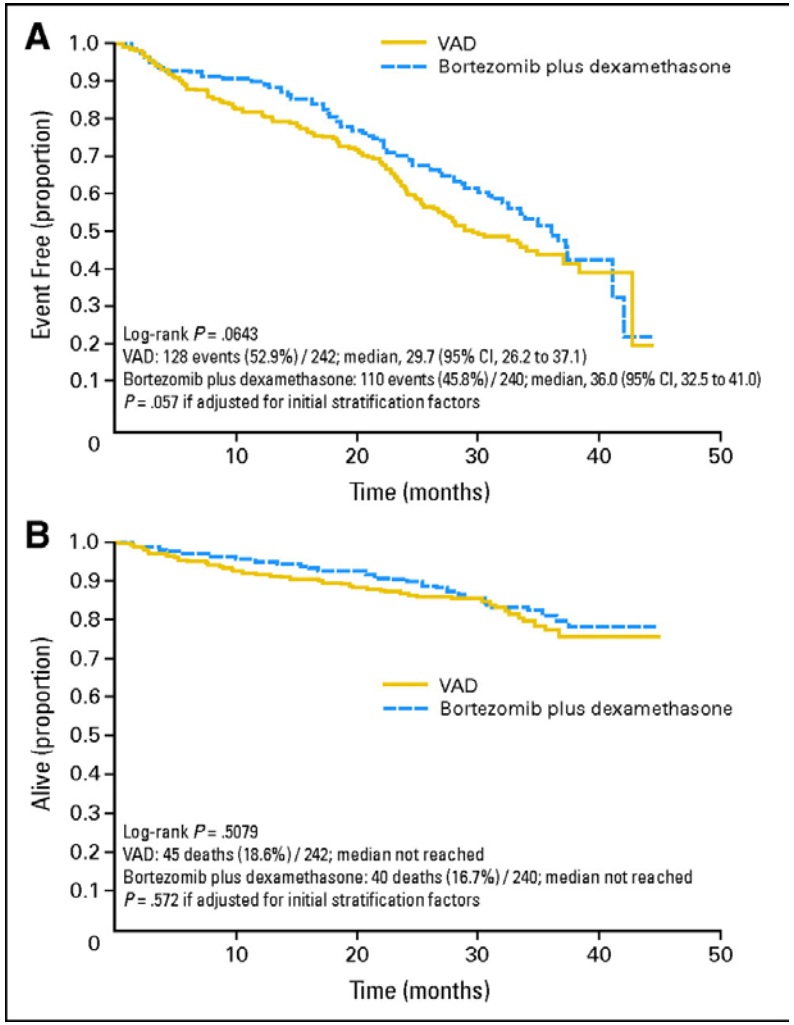
Bortezomib Plus Dexamethasone vs. VAD (IFM 2005-01)

Patients	VAD (A1 + A2) (n = 242)		Bortezomib Plus Dexamethasone (B1 + B2) (n = 240)		*P*
	No.	%	No.	%	
ORR (at least PR)	137	62.8	175	78.5	<.001
At least VGPR	33	15.1	84	37.7	<.001
CR	3	1.4	13	5.8	.012



ORR, overall response rate; VAD, vincristine/doxorubicin/dexamethasone; VGPR, very good PR

Harousseau J, et al. *J Clin Oncol.* 2010;28(30):4621-4629.

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Enhancing Activity With Combinations

	ORR, %	≥VGPR, %	≥CR, %
VTD[1]	93	62	19
VRD[2,3]	~73	11-32	6-9
VDD[4]	96	57	21
VCD[2]	82	41	24

***4 cycle responses**

VCD, bortezomib/cyclophosphamide/dexamethasone; VDD, bortezomib/pegylated liposomal doxorubicin/ dexamethasone; VRD, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone

1. Cavo M, et al. *Lancet.* 2010;376(9758):2075-2085. 2. Kumar S, et al. *Blood.* 2012;119(19):4375-4382. 3. Richardson PG, et al. *Blood.* 2010;116(5):679-686. 4. Jakubowiak AJ, et al. *Blood.* 2011;118(3):535-543.

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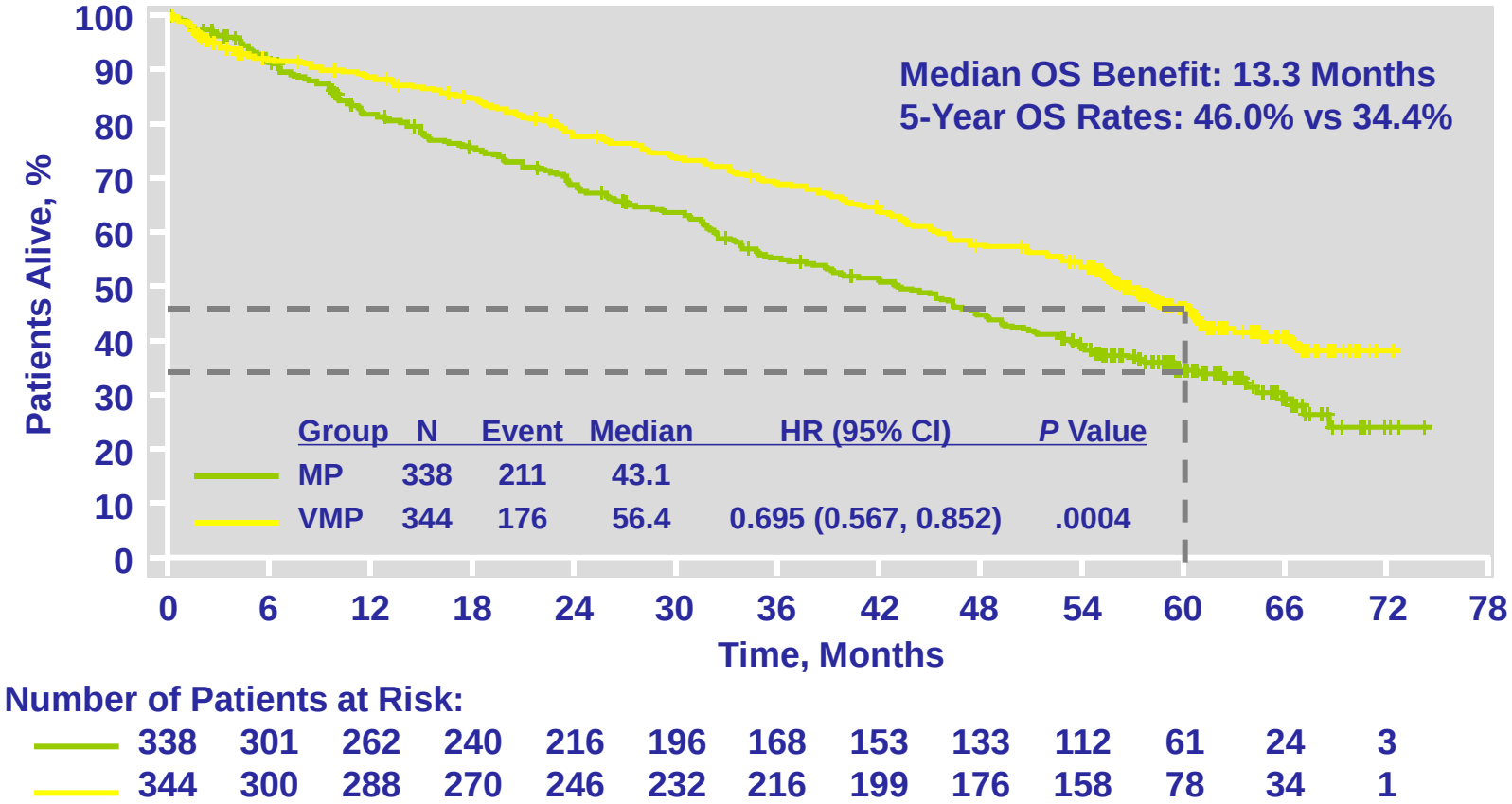
VMP vs. MP in Transplant Ineligible Population



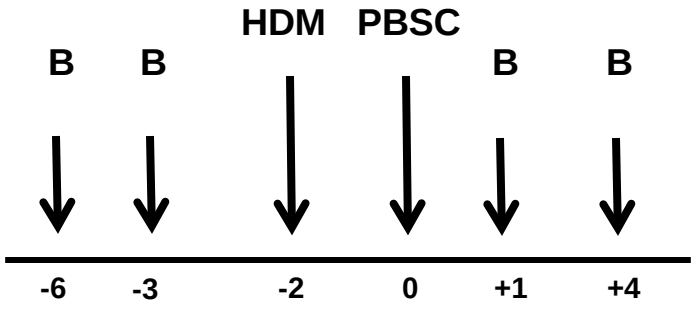
Number of Patients at Risk:

338	301	262	240	216	196	168	153	133	112	61	24	3
344	300	288	270	246	232	216	199	176	158	78	34	1

CI, confidence interval; OS, overall survival

San Miguel JF, et al. *Blood.* 2011;118: Abstract 476.

Bortezomib in Conditioning



B = Bortezomib 1 mg/m^2
HDM = Melphalan 200 mg/m^2

Response, n (%)	All Patients			VAD Induction			Bor/Dex Induction		
	IFM 2005-01 (n = 115)	Bor-HDM (n = 46)	*P*	IFM 2005-01 (n = 70)	Bor-HDM (n = 28)	*P*	IFM 2005-01 (n = 45)	Bor-HDM (n = 18)	*P*
CR	13 (11)	16 (35)	.001	7 (10)	9 (32)	.013	6 (13)	7 (39)	.038
VGPR	49 (43)	16 (35)		23 (33)	10 (36)		26 (58)	6 (33)	
PR	50 (43)	12 (26)		38 (54)	7 (25)		12 (27)	5 (28)	
SD	3 (3)	2 (4)		2 (3)	2 (7)		1 (2)	0	
CR + VGPR	62 (54)	32 (70)	.078	30 (43)	19 (68)	.043	32 (71)	13 (72)	

PBSC, peripheral blood stem cell; SD, stable disease
Roussel M, et al. *Blood.* 2010;115(1):32-37.

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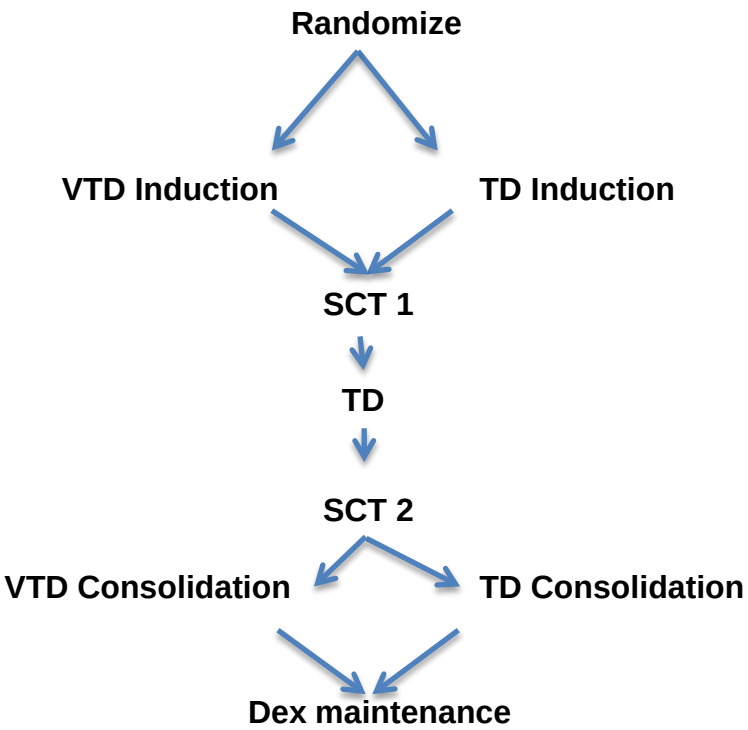
VTD vs. TD followed by Tandem SCT



	VTD (n = 226)	TD (n = 234)	*P* Value
Induction			
CR + nCR, %	31	11	<.001
VGPR, %	62	28	<.001
PR, %	93	79	<.001
Post-SCT			
CR + nCR, %	55	41	.0024
CR, %	42	30	.0105
VGPR, %	82	64	<.001

SCT, stem cell transplant; TD, thalidomide/dexamethasone
Cavo M, et al. *Lancet.* 2010;376(9758):2075-2085.

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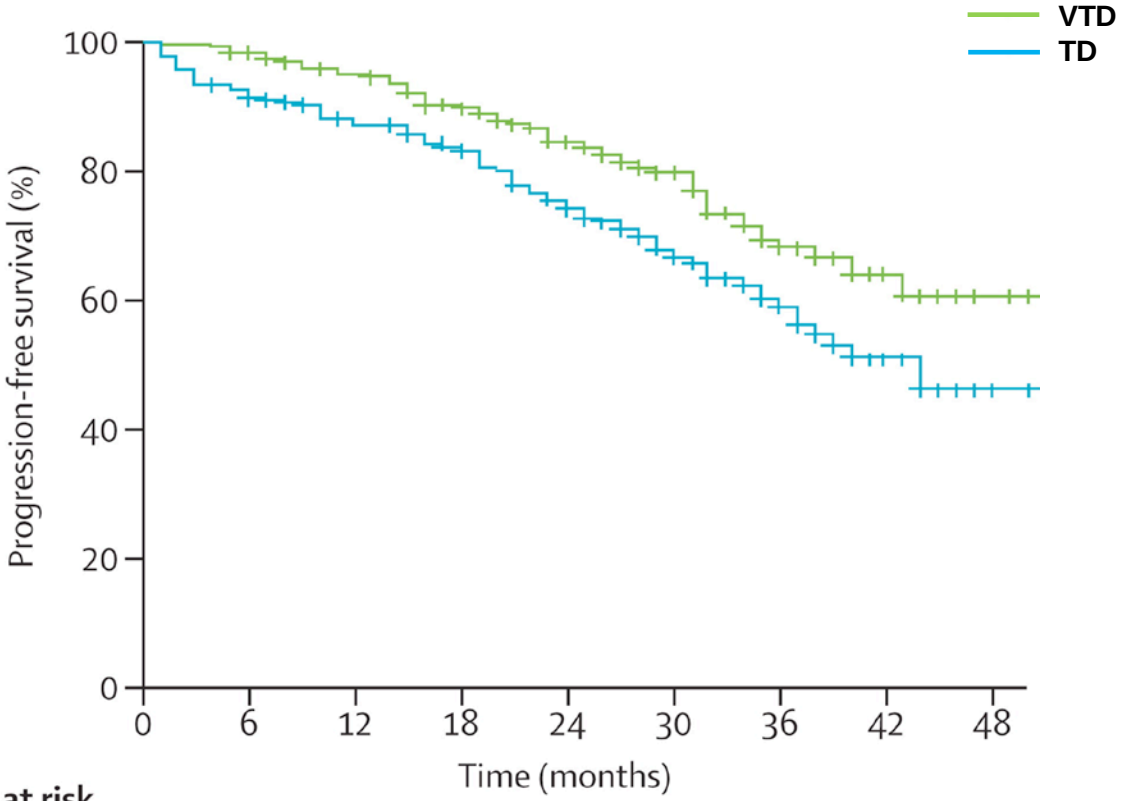
VTD vs. TD Followed by Tandem SCT

Progression-Free Survival



Number at risk

VTD	236	230	212	195	159	111	55	21	2
TD	238	218	200	185	158	99	51	13	2

The estimated 3-year rate of overall survival was 86% in the VTD group and 84% in the TD group (*P* = .30)

Cavo M, et al. *Lancet.* 2010;376(9758):2075-2085.

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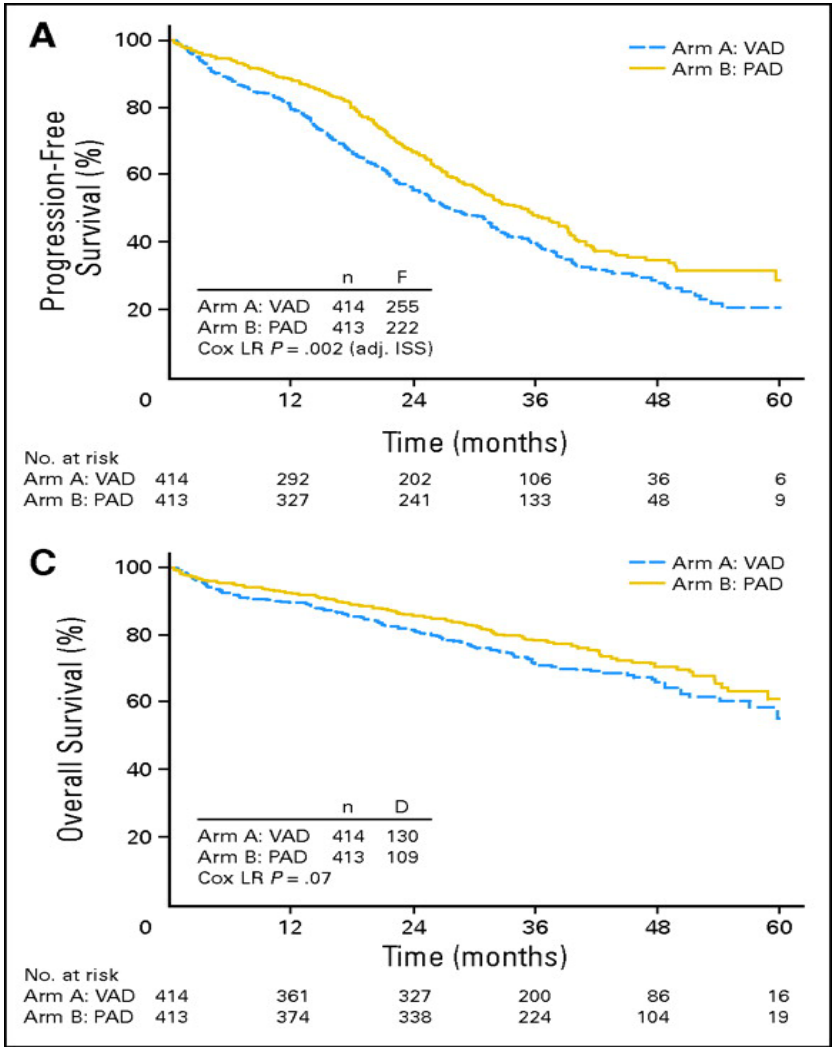
Bortezomib Maintenance

Response	VAD (n = 414)		PAD (n = 413)		*P*
	No.	%	No.	%	
Response after induction					
CR	7	2	29	7	<.001
≥VGPR	59	14	174	42	<.001
≥PR	222	54	322	78	<.001
Response after HDM					
CR	37	9	85	21	<.001
≥VGPR	150	36	254	62	<.001
≥PR	312	75	363	88	<.001
Response overall					
CR	99	24	147	36	<.001
≥VGPR	230	56	312	76	<.001
≥PR	343	83	373	90	.002



PAD, bortezomib/doxorubicin/dexamethasone
Sonneveld P, et al. *J Clin Oncol.* 2012;30(24):2946-2955

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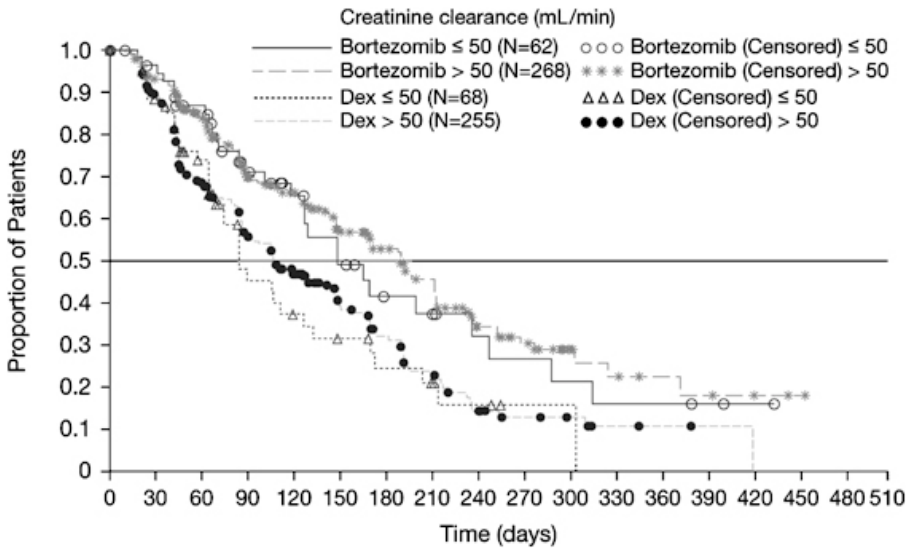
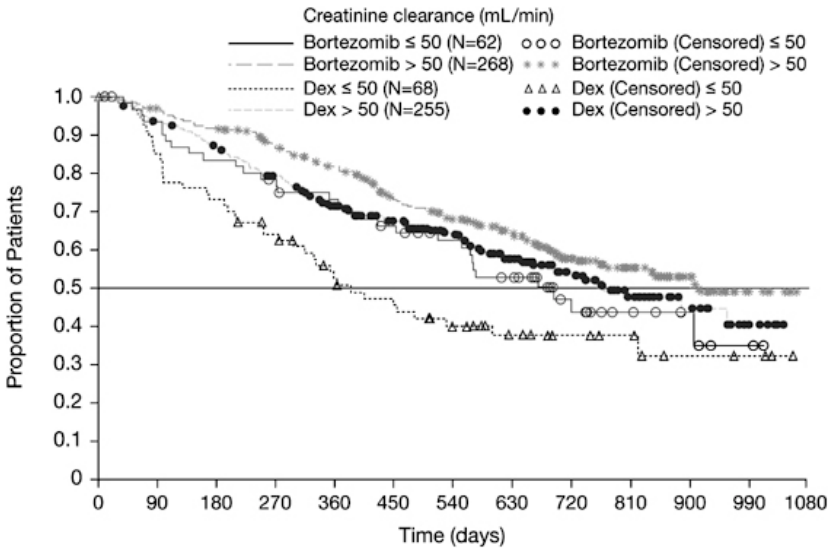
Bortezomib in Renal Failure

Analysis of APEX Data



PFS



OS

San-Miguel JF, et al. *Leukemia.* 2008;22(4):842-849.

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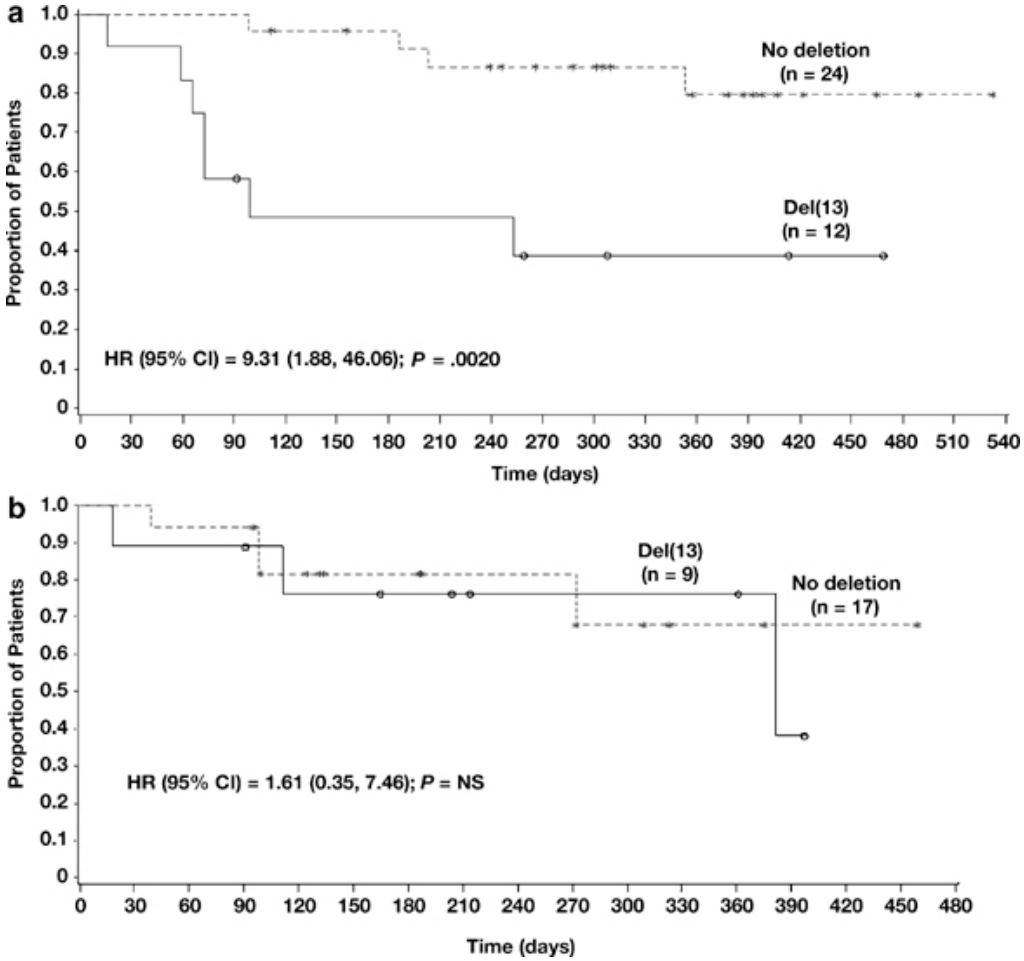
Bortezomib and Del(13)



- Matched pair analysis of patient with or without del(13) by cytogenetics in the Apex trial
- While Dex has not effect, bortezomib treated patients have similar outcome despite del(13)

Jagannath S, et al. *Leukemia.* 2007;21(1):151-157.

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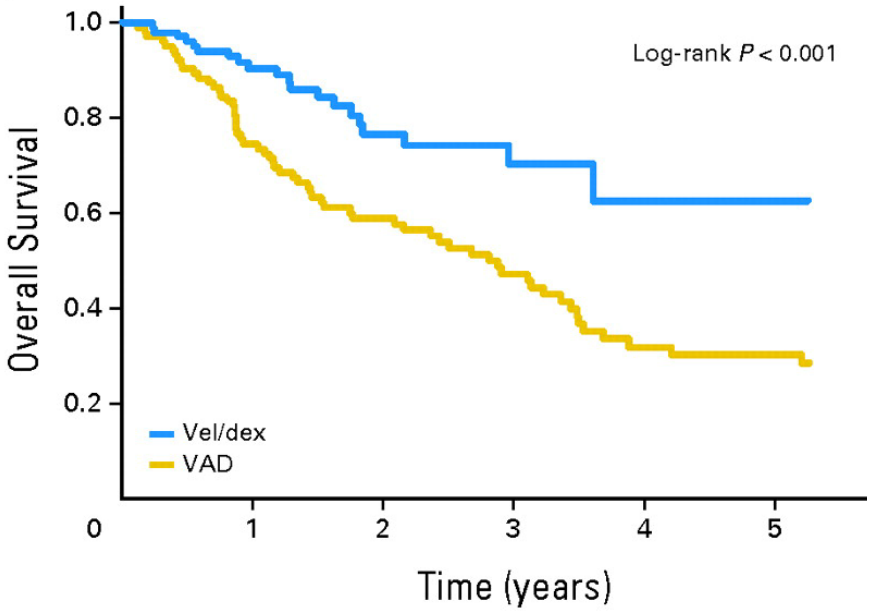
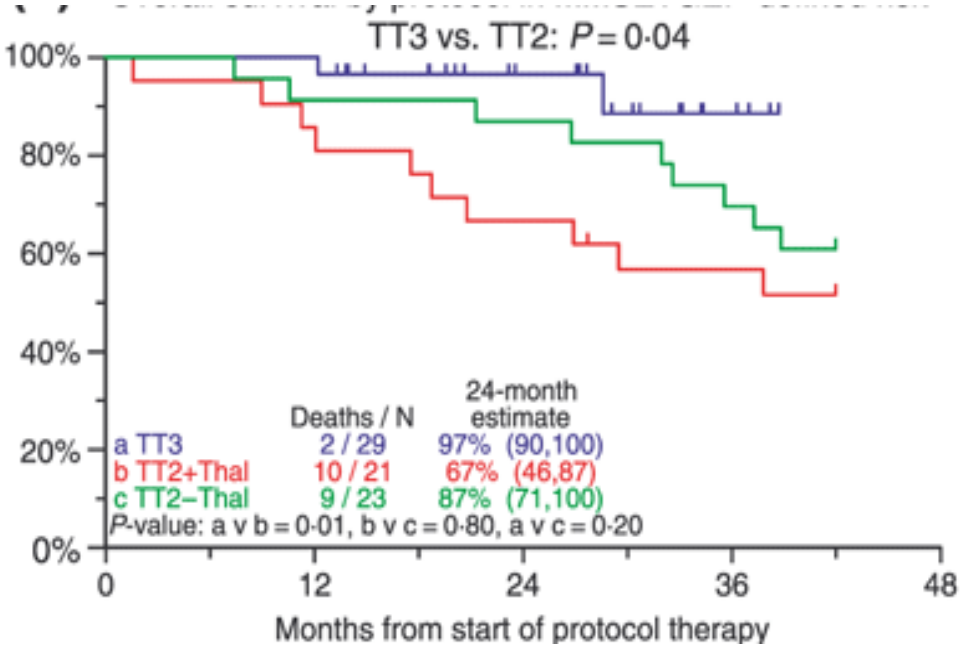
Bortezomib and t(4;14)





Avet-Loiseau H, et al. *J Clin Oncol.* 2010;28(30):4630-4634. Pineda-Roman M, et al. *Br J Haematol.* 2008;140(6):625-634.

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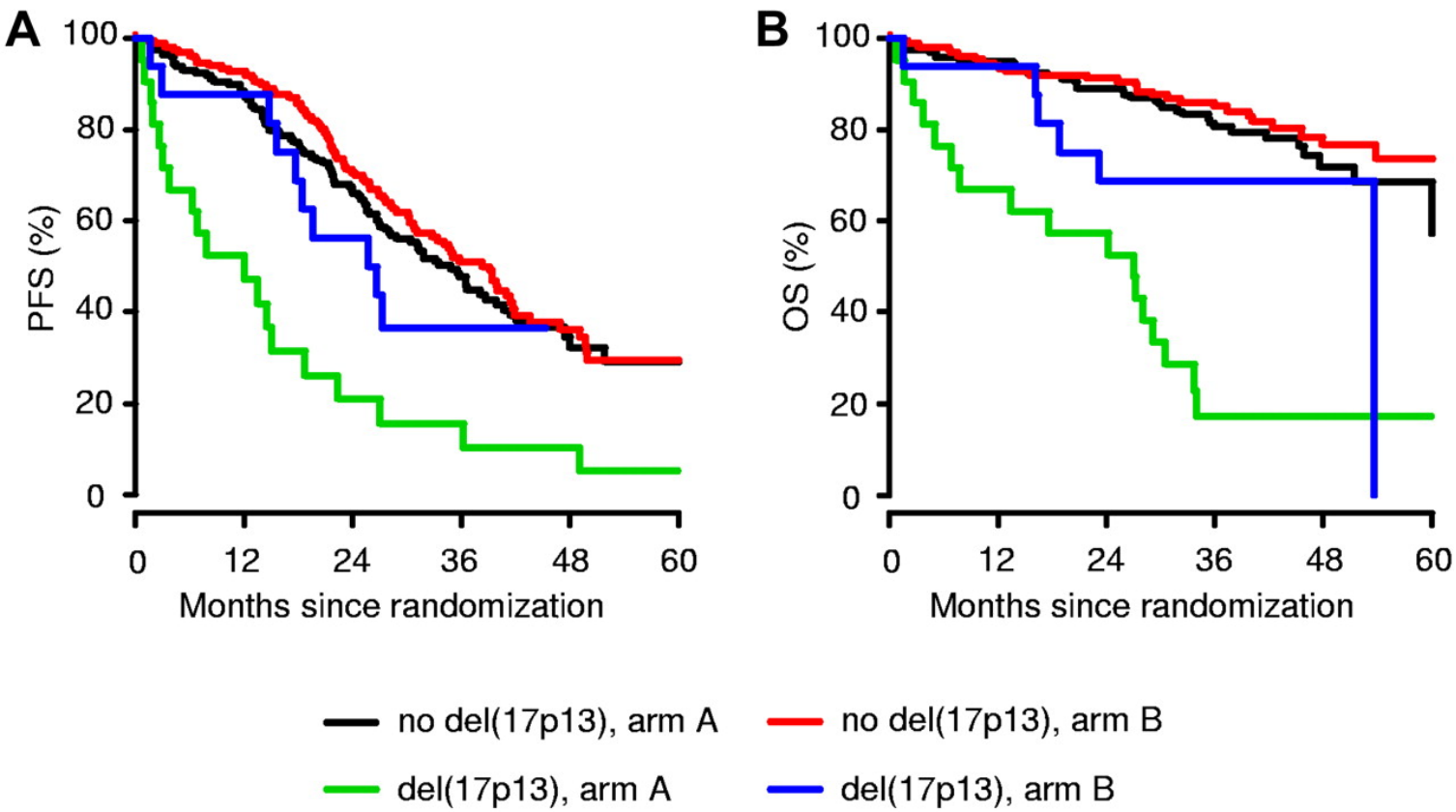
Bortezomib and Del(17p)



HOVON-65/GMMG-HD4: VAD induction, tandem SCT, and thalidomide maintenance vs PAD induction, tandem SCT, and bortezomib maintenance

Neben K, et al. *Blood.* 2012;119(4):940-948.

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Bortezomib Combinations in Relapse

- V + Thalidomide Dex
- V + Lenalidomide Dex
- V + Pomalidomide Dex
- V + Cyclophosphamide Dex
- V + Melphalan Dex/Pred
- V + Liposomal Doxorubicin Dex

Bortezomib Retreatment

Best Confirmed Response to Prior Bortezomib Therapy	Single Best Response to Bortezomib Retreatment, n (%)*				
	CR	PR	MR	NC	PD
Any prior bortezomib treatment					
CR (n = 32)	1 (3)	19 (59)	4 (13)	6 (19)	1 (3)
PR (n = 94)	0	49 (52)	21 (22)	10 (11)	6 (6)
Single-agent bortezomib					
CR (n = 14)	1 (7)	6 (43)	3 (21)	4 (29)	0
PR (n = 32)	0	15 (47)	9 (28)	2 (6)	3 (9)
Bortezomib in combination					
CR (n = 18)	0	13 (72)	1 (6)	2 (11)	1 (6)
PR (n = 62)	0	34 (55)	12 (19)	8 (13)	3 (5)

Median PFS 8.4 months (95% CI; 7-9 – 9.7)

MR, minor response; NC, no change; PD, progressive disease

Petrucci MT, et al. *Br J Haematol.* 2013;160(5):649-659.

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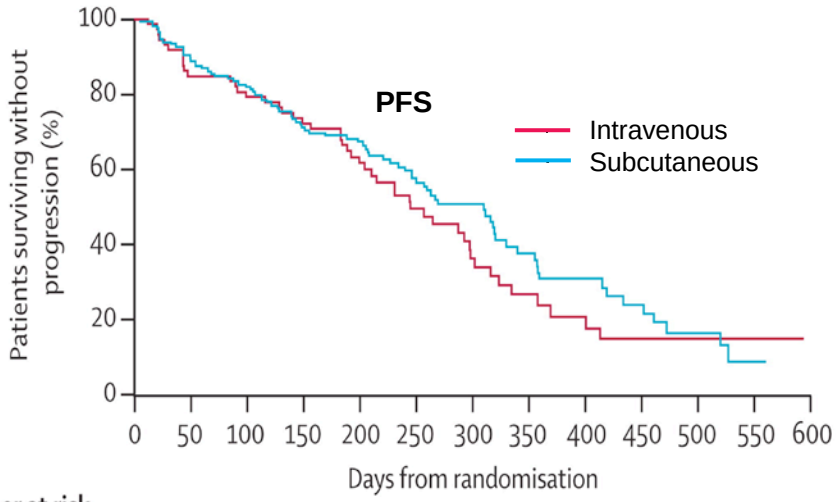
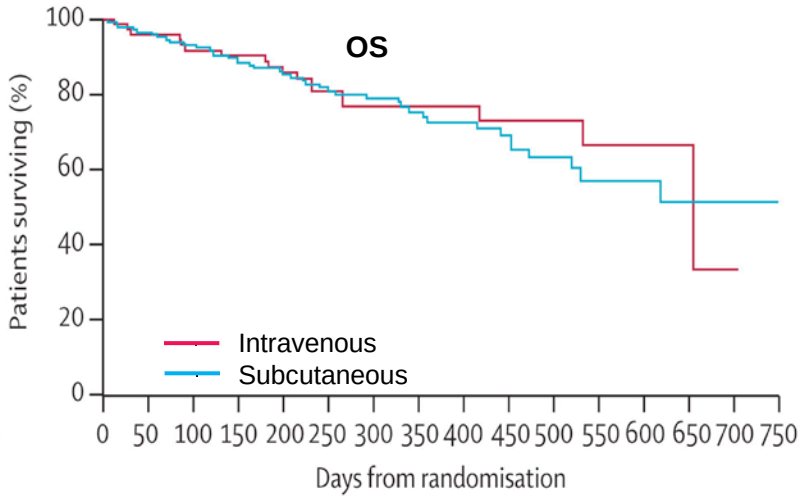
Bortezomib Subcutaneous (SQ)

Response After 4 Cycles (Single-Agent Bortezomib), Primary Endpoint		
	Subcutaneous (N = 145)*	**Intravenous (N = 73)**
ORR (CR+PR)	61 (42%)	31 (42%)
CR	9 (6%)	6 (8%)
>Minor response	81 (56%)	41 (56%)





Number at risk

Intravenous	74	61	57	51	38	24	16	10	7	5	4	3	1	74	70	67	64	53	42	33	29	26	19	12	9	4	2	1	0
Subcutaneous	148	129	116	97	76	55	36	22	16	10	6	2	1	148	141	136	125	107	88	71	59	47	37	26	15	12	4	2	0

Moreau P, et al. *Lancet Oncol.* 2011;12(5):431-440.

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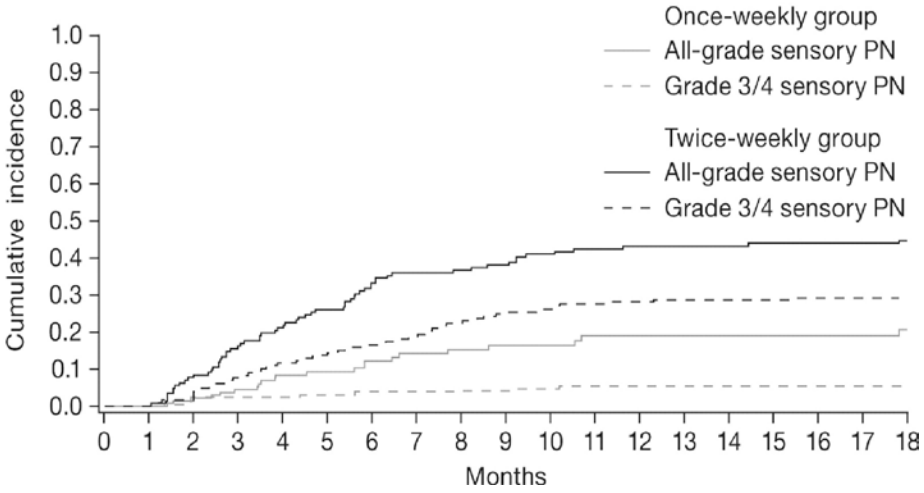
Bortezomib Once Weekly

Best Response, n (%)	Once-Weekly (n = 369)	Twice-Weekly (n = 134)	*P*
Overall response rate	312 (85)	115 (86)	0.78
Complete response	109 (30)	47 (35)	0.27
Very good partial response	93 (25)	25 (19)	0.15
Partial response	110 (30)	43 (32)	0.66
Stable disease	47 (13)	12 (9)	0.27
Progressive disease	4 (1)	1 (1)	0.61

Bortezomib Exposure	Once-Weekly (n = 369)	Twice-Weekly (n = 134)	*P*
Percentage of planned dose delivered, %	84	59	
Patients who received ≥ 90% of planned dose, n (%)	144 (39)	17 (13)	<.001



Bringhen S, et al. *Blood.* 2010;116(23):4745-4753.

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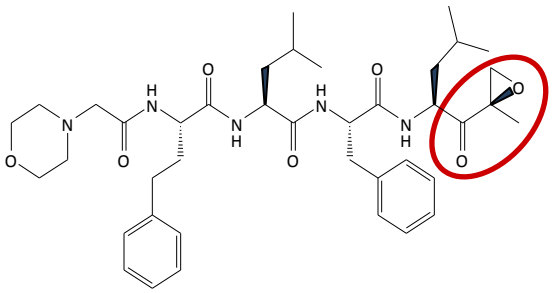
Carfilzomib

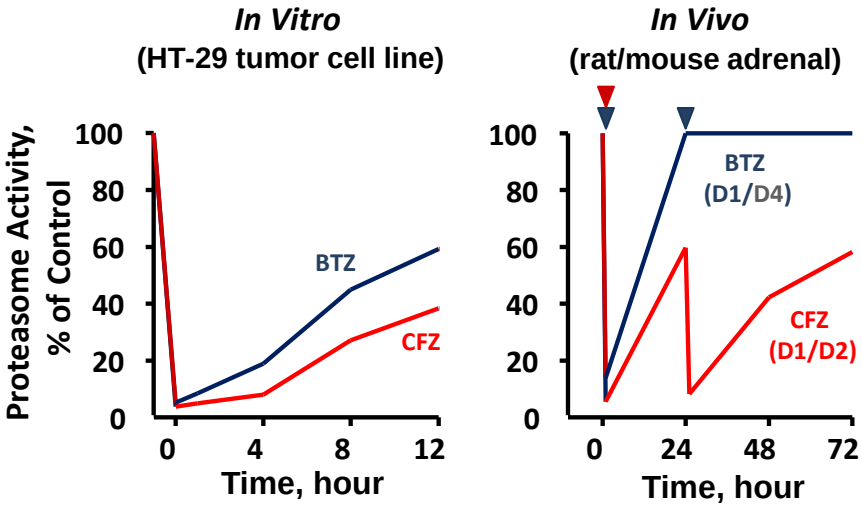
Peptide
Selective for proteasome chymotrypsin-like activity

Epoxyketone
Specific and irreversible target inhibition



Carfilzomib (CFZ)

Duration of Proteasome Inhibition



Selective Inhibition
- Targets one subunit within the proteasome
- Minimal inhibition of off-target proteases

Prolonged Inhibition
- Irreversible mechanism → delays recovery
- Consecutive day dosing with >80% maximum inhibition

Demo SD, et al. *Cancer Res*. 2007;67(13):6383-6391. Kuhn DJ, et al. *Blood*. 2007;110(9):3281-3290. Kirk CJ, et al. *Blood.* 2008;112: Abstract 2765). Arastu-Kapur S, et al. *Blood.* 2008;112: Abstract 2657.

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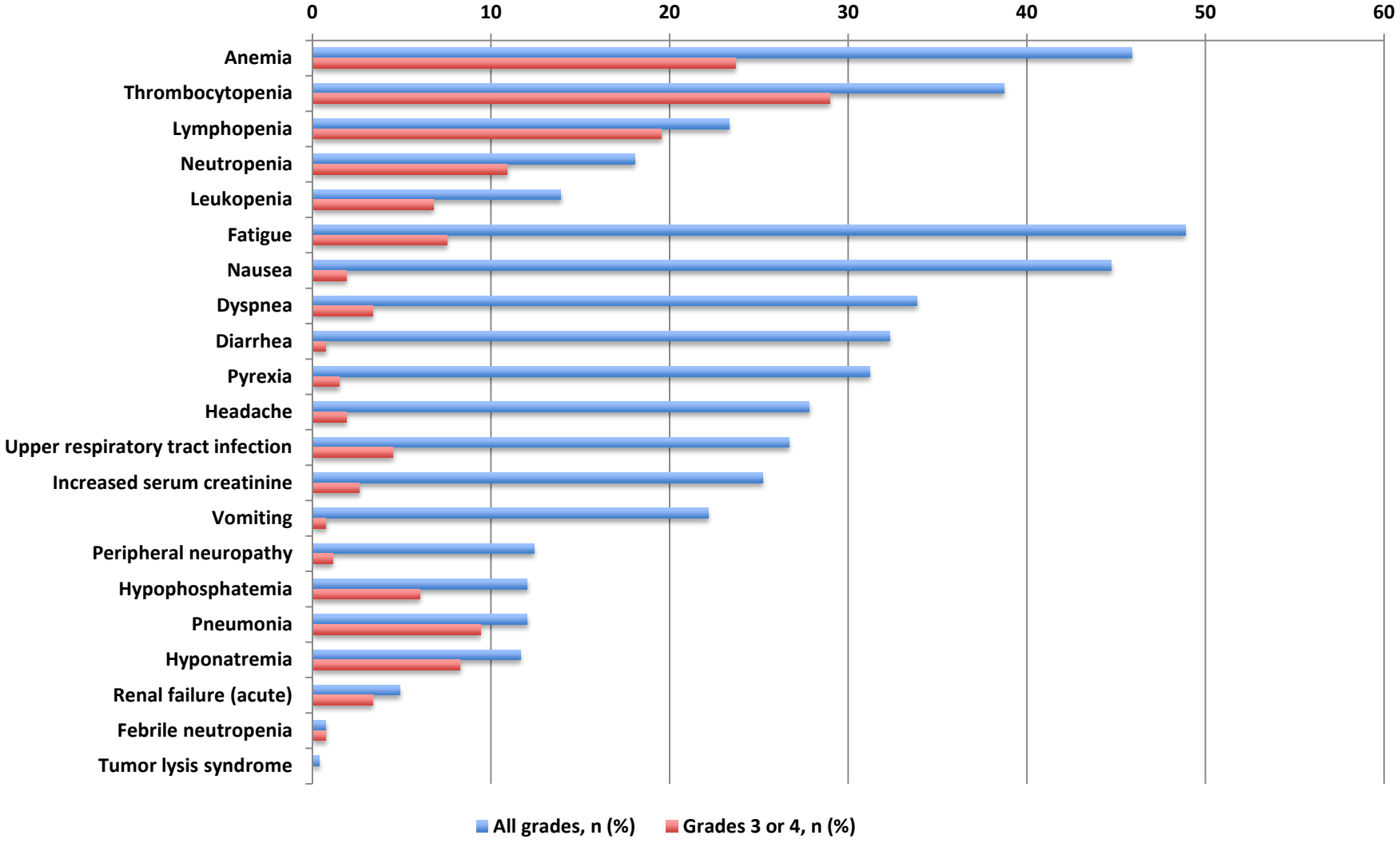
Carfilzomib

Trial	N	Population	Number Prior Lines	Overall Response Rate, %	MR/SD, %	Median TTP, months
003-A0[1]	39	Refractory	5	18	8/41	5.1
003-A1[2]	257	Refractory	5	24	13/32	3.7 (PFS)
004 (Bz exposed)[3]	35	Relapsed	1-3	17	12/35	4.6
004 (Bz naïve)[4]	126	Relapsed	1-3	47.6	14/18	54% @ 9 mos
006 (Combo with len/dex)[5]	40	Relapsed	1-3	62.5	--/15	10.2 (PFS)

1. Alsina M, et al. *Clin Cancer Res*. 2012;18(17):4830-4840. 2. Siegel DS, et al. *Blood*. 2012;120(14):2817-2825. 3. Vij R, et al. *Br J Haematol*. 2012;158(6):739-748. 4. Vij R, et al. *Blood*. 2012;119(24):5661-5670. 5. Niesvizky R, et al. *Clin Cancer Res.* 2013 Feb 27 [Epub ahead of print].

Adverse Events



Siegel DS, et al. *Blood*. 2012;120(14):2817-2825.

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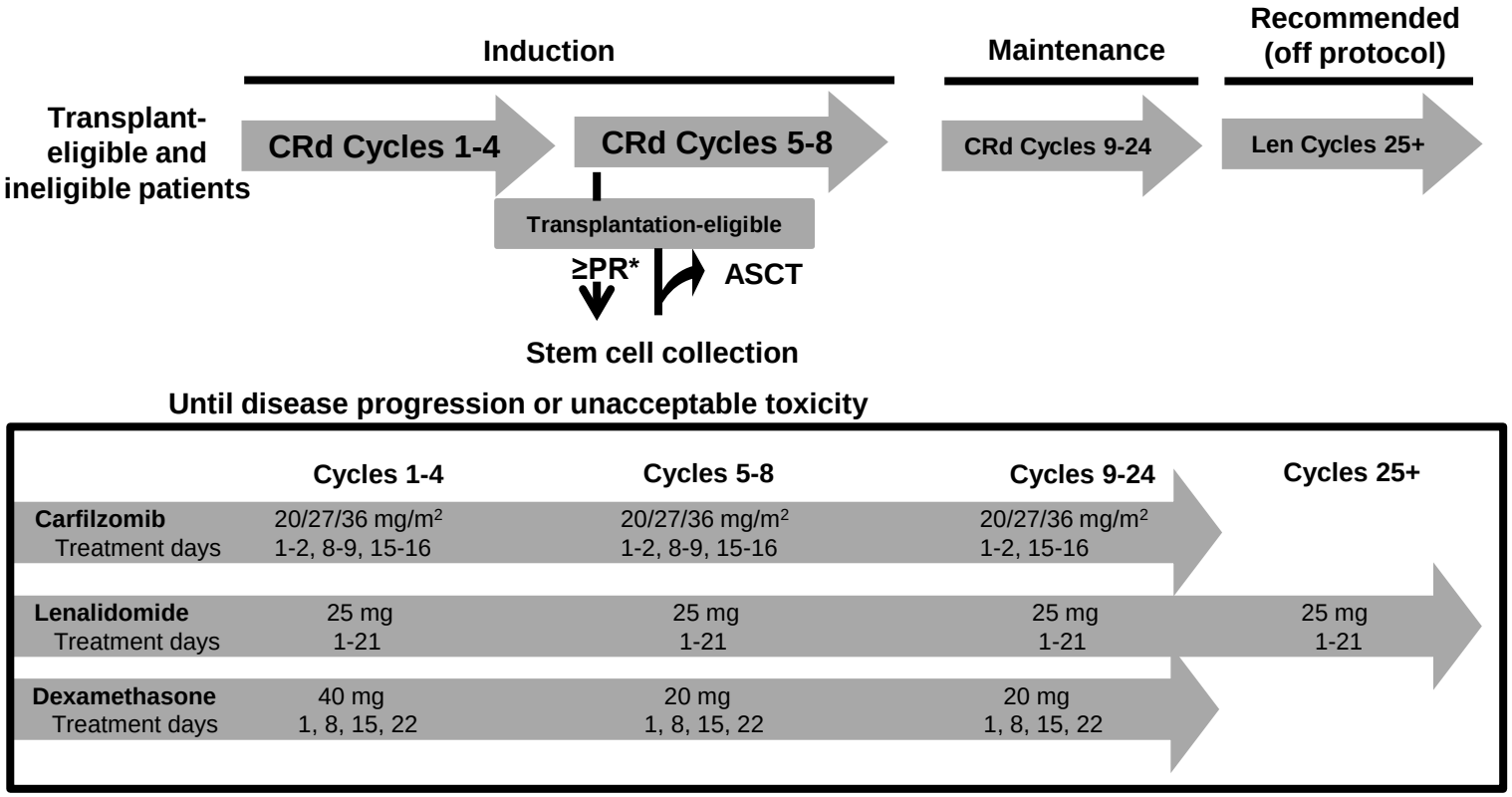
Carfilzomib-RD



Jakubowiak AJ, et al. *Blood.* 2012;120(9):1801-1809.

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Carfilzomib-Rev-Dex

Best Response to Treatment in Evaluable Patients

	Response, n (%)			
	≥PR	≥VGPR	≥nCR	sCR
All patients (N = 53)	52 (98)	43 (81)	33 (62)	22 (42)
Treatment duration				
4+ cycles (n = 49)	49 (100)	43 (88)	33 (67)	22 (45)
8+ cycles (n = 36)	36 (100)	33 (92)	28 (78)	22 (61)
12+ cycles (n = 29)	29 (100)	25 (86)	21 (72)	18 (62)

Jakubowiak AJ, et al. *Blood.* 2012;120(9):1801-1809.

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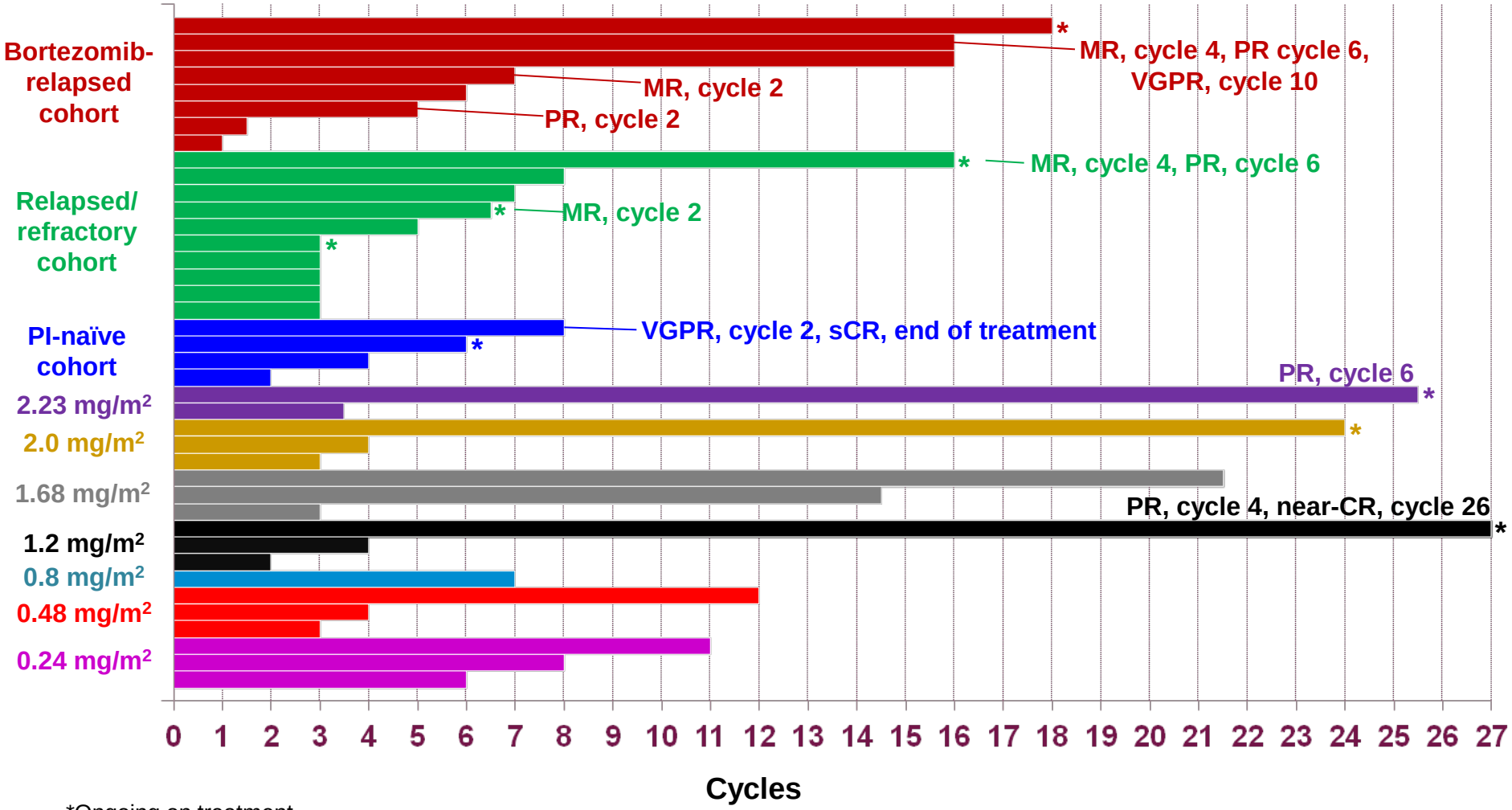
MLN9708

- MLN9708 is the citrate ester of the biologically active form, MLN2238, orally bioavailable
- Small molecule modified dipeptide boronic acid analog similar to bortezomib
- MLN2238 preferentially binds the β5 site of the 20S proteasome
- Rapidly dissociation from blood but sustained effects on marrow and tumor proteasome
- Excellent preclinical activity in several models

MLN9708: Biweekly Dosing, Relapsed Multiple Myeloma



*Ongoing on treatment

Response assessed every cycle after 2 cycles/at end of treatment

Lonial S, et al. *J Clin Oncol.* 2012;30(suppl): Abstract 8017.

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Drug-related AEs in >20% of patients overall

AE	Dose-escalation cohorts (n=26)	Expansion cohorts (n=38)*	Total (N=58)
Fatigue, %	42	42	45
Thrombocytopenia, %	31	50	41
Nausea, %	38	37	36
Rash,† %	31	24	28
Vomiting, %	31	21	26
Diarrhea, %	31	16	21

*Includes 6 patients from MTD dose-escalation cohort.

†Rashes, eruptions, and exanthems NEC, including rash macular, rash, and rash macro-papular

- 6 (10%) patients had drug-related PN
  - Grade 1 in 3 patients; grade 2 in 3 patients
- All 6 patients had grade 1 PN as baseline at study entry

Lonial S, et al. *J Clin Oncol.* 2012;30(suppl): Abstract 8017.

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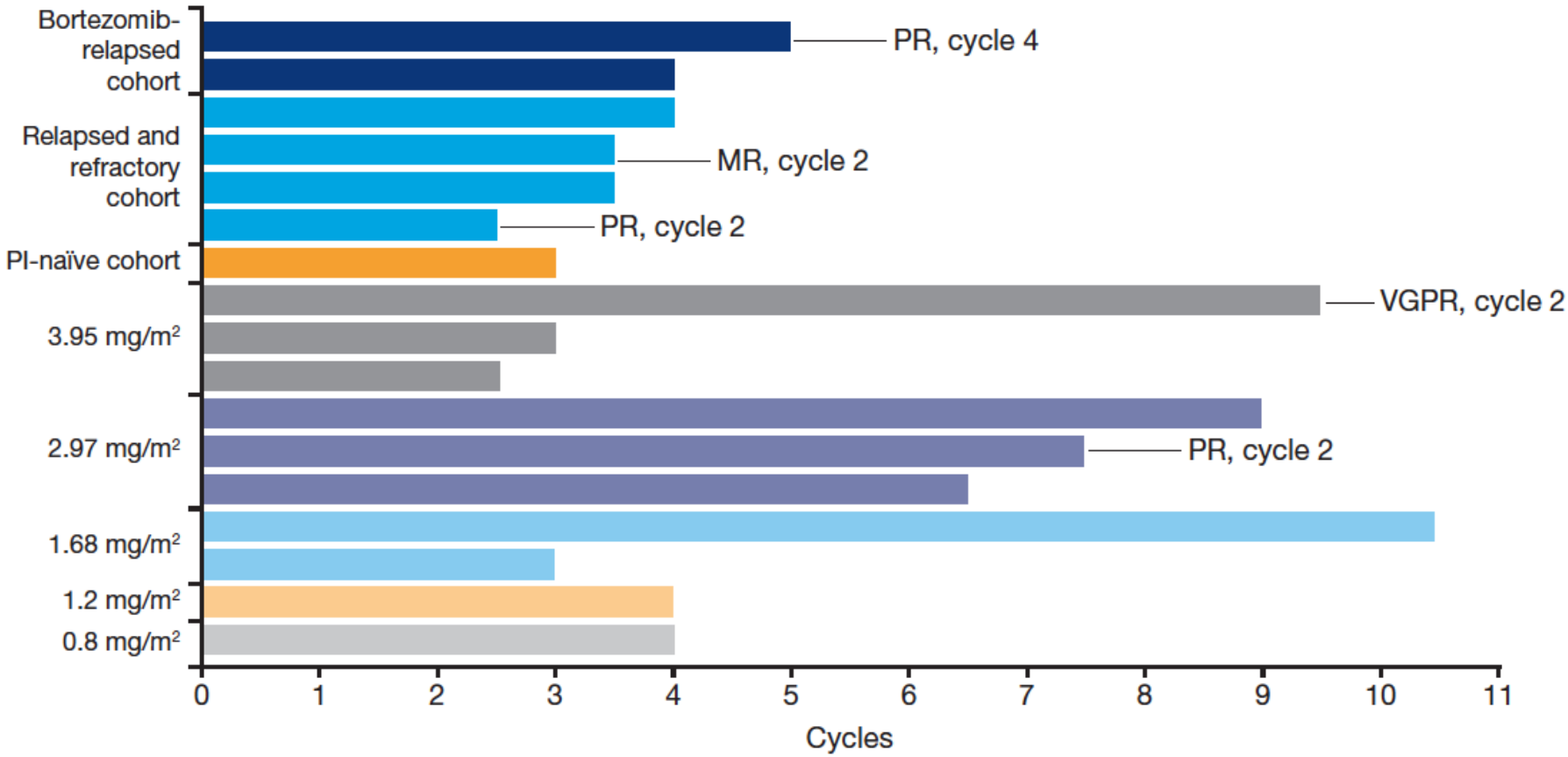
MLN9708: Weekly Dosing, Relapsed Multiple Myeloma



Kumar, SK, et al. *J Clin Oncol.* 2012;30(suppl): Abstract 8033.

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Drug-related AEs in >10% of patients

AE, n (%)	Dose-escalation cohorts (n=32)	Expansion cohorts (n=23)*	Total (n=52)
Thrombocytopenia	13 (41)	12 (52)	23 (44)
Diarrhea	11 (34)	10 (43)	19 (37)
Fatigue	11 (34)	9 (39)	18 (35)
Nausea	11 (34)	7 (30)	17 (33)
Vomiting	9 (28)	7 (30)	15 (29)
Decreased appetite	3 (9)	9 (39)	11 (21)
Anemia	2 (6)	5 (22)	6 (12)
Dehydration	3 (9)	4 (17)	6 (12)
Leukopenia	2 (6)	4 (17)	6 (12)
Lymphopenia	2 (6)	4 (17)	6 (12)
Neutropenia	3 (9)	3 (13)	5 (10)

*Includes 3 patients from MTD dose-escalation cohort.

Kumar, SK, et al. *J Clin Oncol.* 2012;30(suppl): Abstract 8033.

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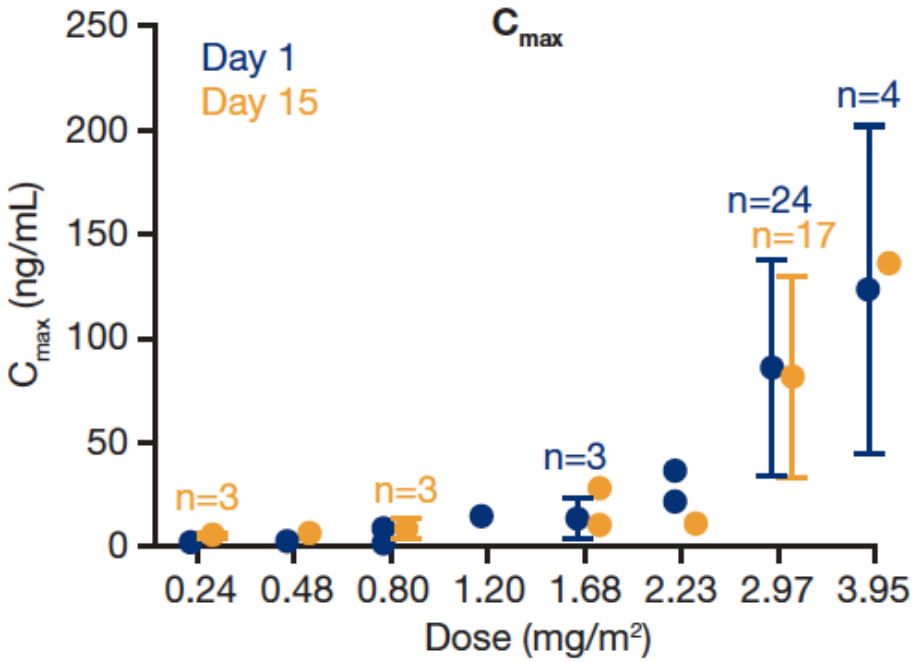
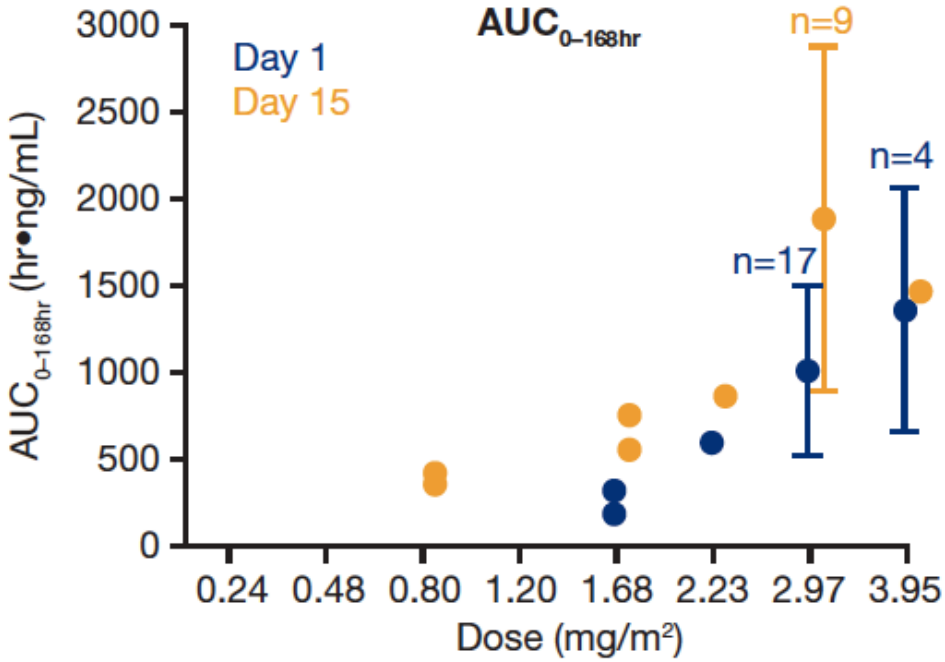
MLN9708 Pharmacokinetics





Kumar SK, et al. *IMW 2013*.

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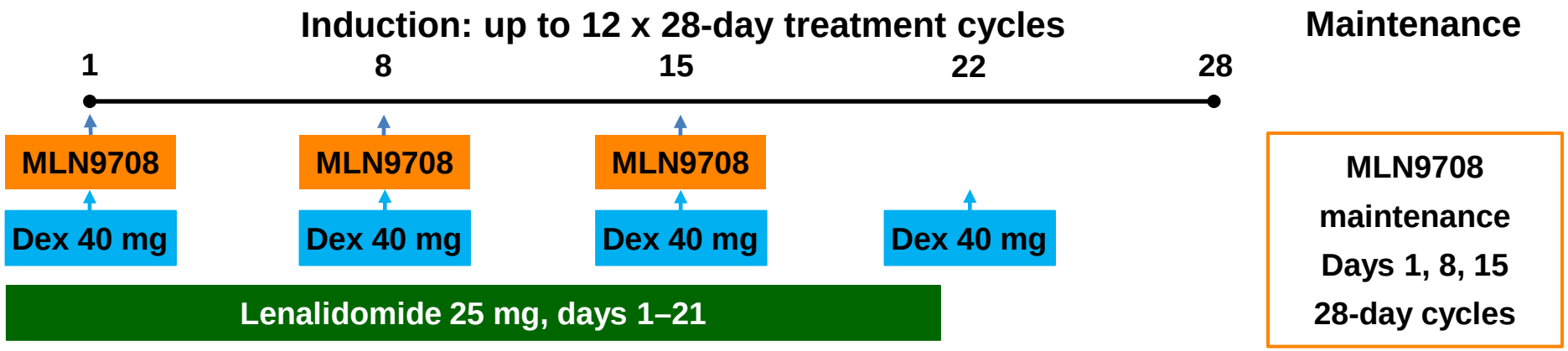
MLN9708 Phase 1 MTDs

- Based on this and other safety data, the MTD of oral MLN9708 on a once-weekly schedule was determined to be 2.97 mg/m2.
- The MTD is 2.0 mg/m2 with twice-weekly oral MLN9708 in a similar patient population
- Based on PK studies, the does were converted to flat dosing for future studies

MLN9708 + Len Dex (Rd)



- Phase I: oral MLN9708 dose-escalation
  - Standard 3+3 schema, 33% dose increments, based on cycle 1 dose-limiting toxicities (DLTs)
- Phase II: oral MLN9708 at the RP2D from phase I
- Stem cell collection allowed after 3 cycles, with autologous stem cell transplantation (ASCT) deferred until after 6 cycles
- MLN9708 maintenance continued until progression or unacceptable toxicity

Kumar SK, et al. *Blood.* 2012;120: Abstract 332.

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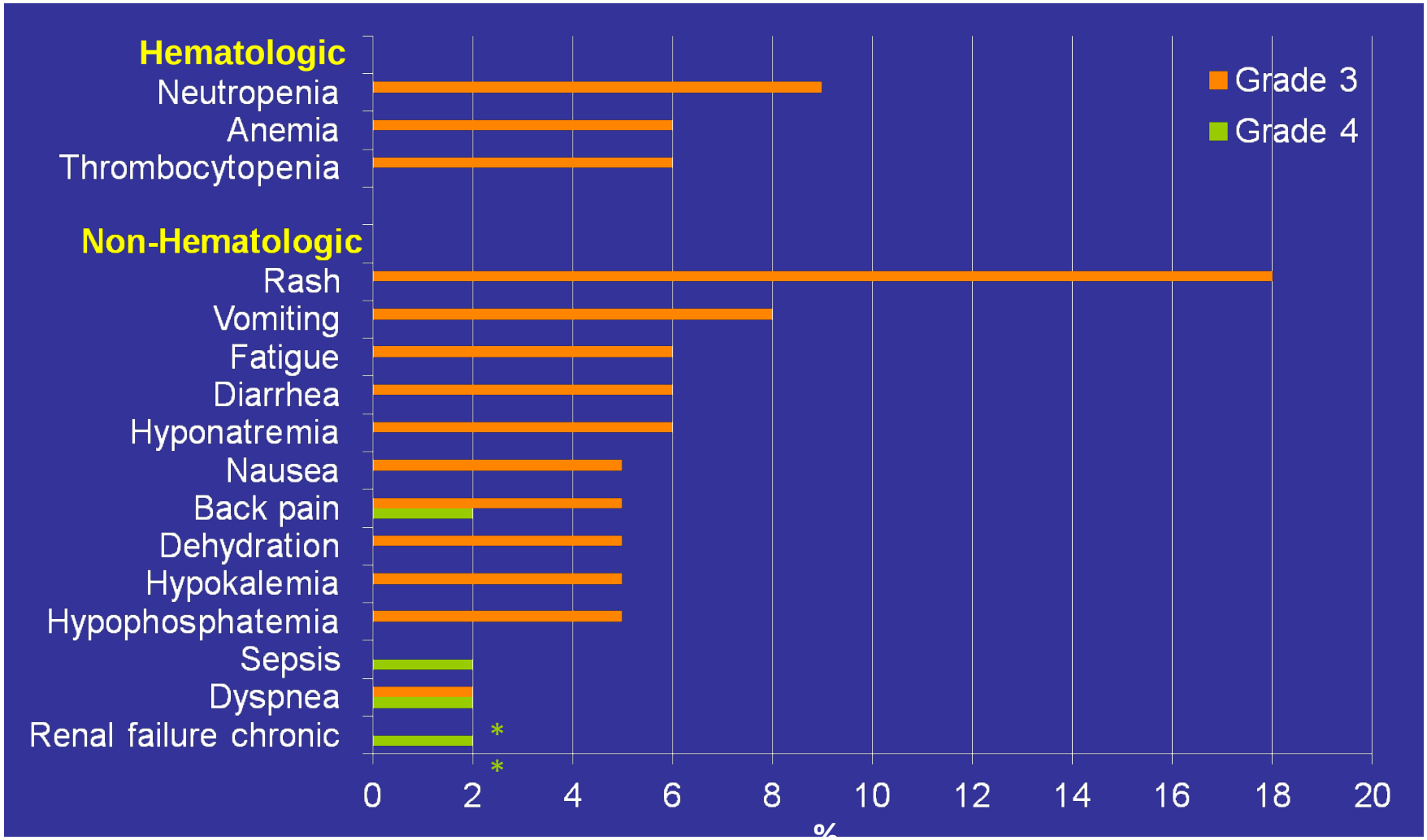
MLN9708+Rd: Grade 3 and 4 Adverse Events



Kumar SK, et al. *Blood.* 2012;120: Abstract 332.

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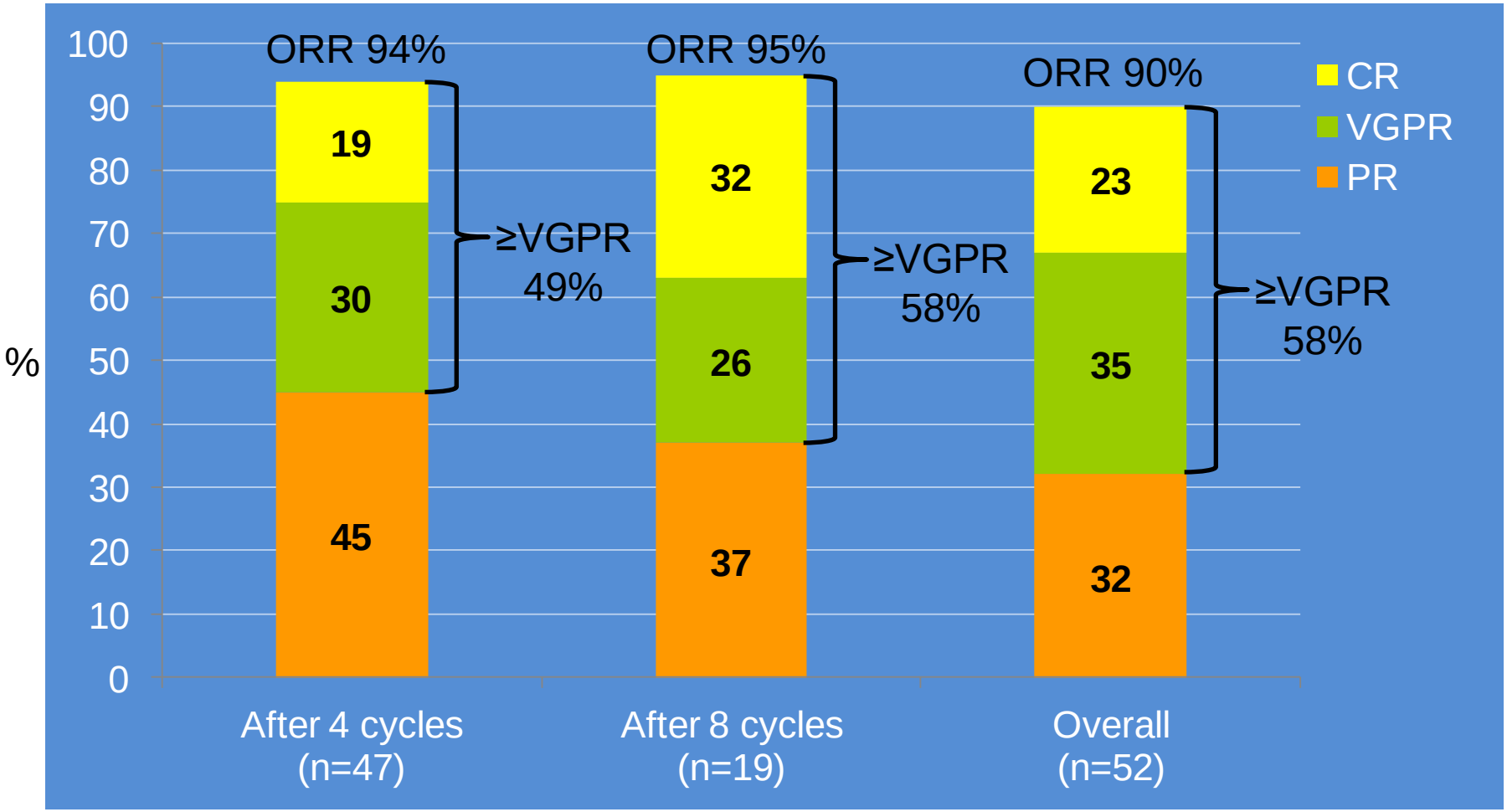
MLN9708-Rd: Response Rates

Previously Untreated Patients



- Of 3 response-evaluable patients who completed 12 cycles, 2 achieved CR and 1 VGPR

Kumar SK, et al. *Blood.* 2012;120: Abstract 332.

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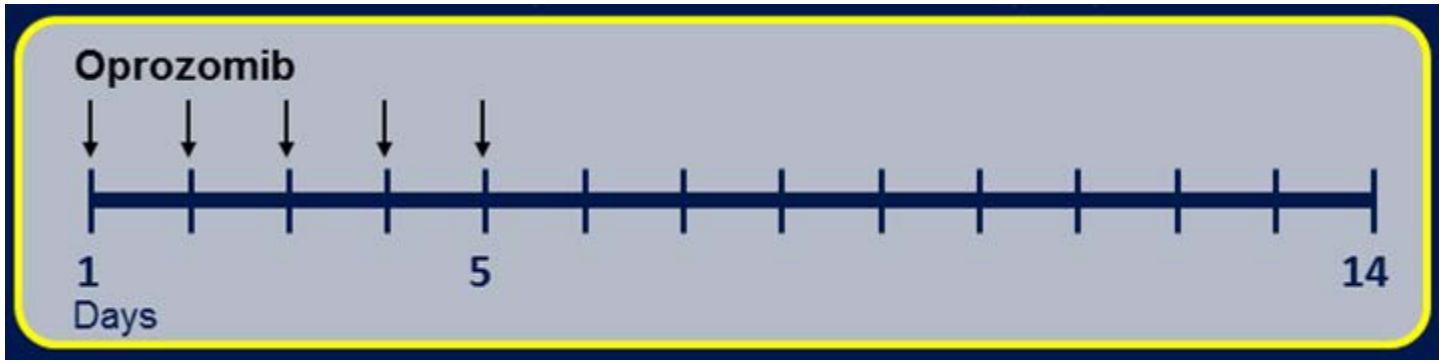
Oprozomib Phase Ib Dose-Escalation Study: Dosing and Schedule

- Starting total daily dose 120 mg/d
  - Given as 2 doses, 4-6 hours apart
  - Antiemetics ± 4 mg dexamethasone

Cohort	1st Daily Dose, mg	2nd Daily Dose, mg	Total Daily Dose, mg/d
1	60	60	120
2	90	60	150
3	90	90	180
4	120	90	210

- Administered on days 1-5 of a 14-day cycle



Prior therapies: median 4 chemotherapy regimens (range 2-8)

Savona MR, et al. *Blood.* 2012;120: Abstract 203.

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Oprozomib: Clinical Activity

- 9 patients with myeloma, and 1 with chronic lymphocytic leukemia (CLL) had post baseline assessments

Response	Patients	Cohorts
PR	3	Cohorts 1*, 3, 4
MR	2	Cohort 2
SD	4	Cohorts 1, 2, 3, 4
PD	1	Cohort 4

*CLL

Savona MR, et al. *Blood.* 2012;120: Abstract 203.

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Adverse Events in ≥2 Patients in Any Cohort

	Cohort 1	Cohort 2	Cohort 3
Diarrhea	2	2	3*
Nausea	2	3*	2
Vomiting	2	3	1
Fatigue	1*	2	2
Anemia	1*	2	1
Hypoalbuminemia	2	1	0
Pyrexia	2	1	0
Cognitive disorder	0	0	2

*Includes one grade 3 event, rest grade 1/2

Savona MR, et al. *Blood.* 2012;120: Abstract 203.

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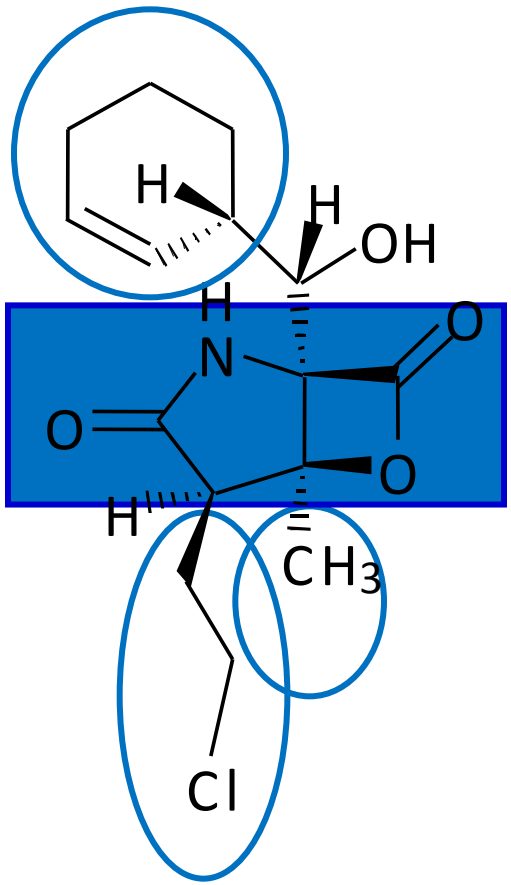
Marizomib: NPI-0052

Marizomib (NPI-0052)



- Exhibits high levels of proteasome inhibition without toxicities associated with bortezomib
- Active in bortezomib and IMiD resistant myeloma preclinically

<u>Phase I study</u>

Twice weekly x 4 doses, 21 day cycles, infusions of 1, 10, 60 and 120 min

Dexamethasone: 20 mg administered day before and day of marizomib dose.

Day	MZ	MZ	MZ	MZ		MZ	MZ	MZ	MZ	
	1	4	8	11	15	1	4	8	11	15
	Cycle 1					Cycle 2				

Chauhan D, et al. *Cancer Cell.* 2005;8(5):407-419.

Richardson PG, et al. *Blood.* 2011;118: Abstract 302.

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Responses to Marizomib +/- Dexamethasone (≥0.4 mg/m^2) Twice Weekly (n = 21**)

All Pts		
≥SD	12/21	57%
PR + VGPR	4/21	19%

Pts Refractory to Bortezomib		
≥SD	8/12	67%
PR + VGPR	2/12	17%

Pts Exposed to Bortezomib		
≥SD	11/19	58%
PR + VGPR	3/19	16%

Pts Refractory to Lenalidomide		
≥SD	9/14	64%
PR + VGPR	4/14	29%

Median Duration of Response (all patients) = 133 days (~ 5 months)

Richardson PG, et al. *Blood.* 2011;118: Abstract 302.

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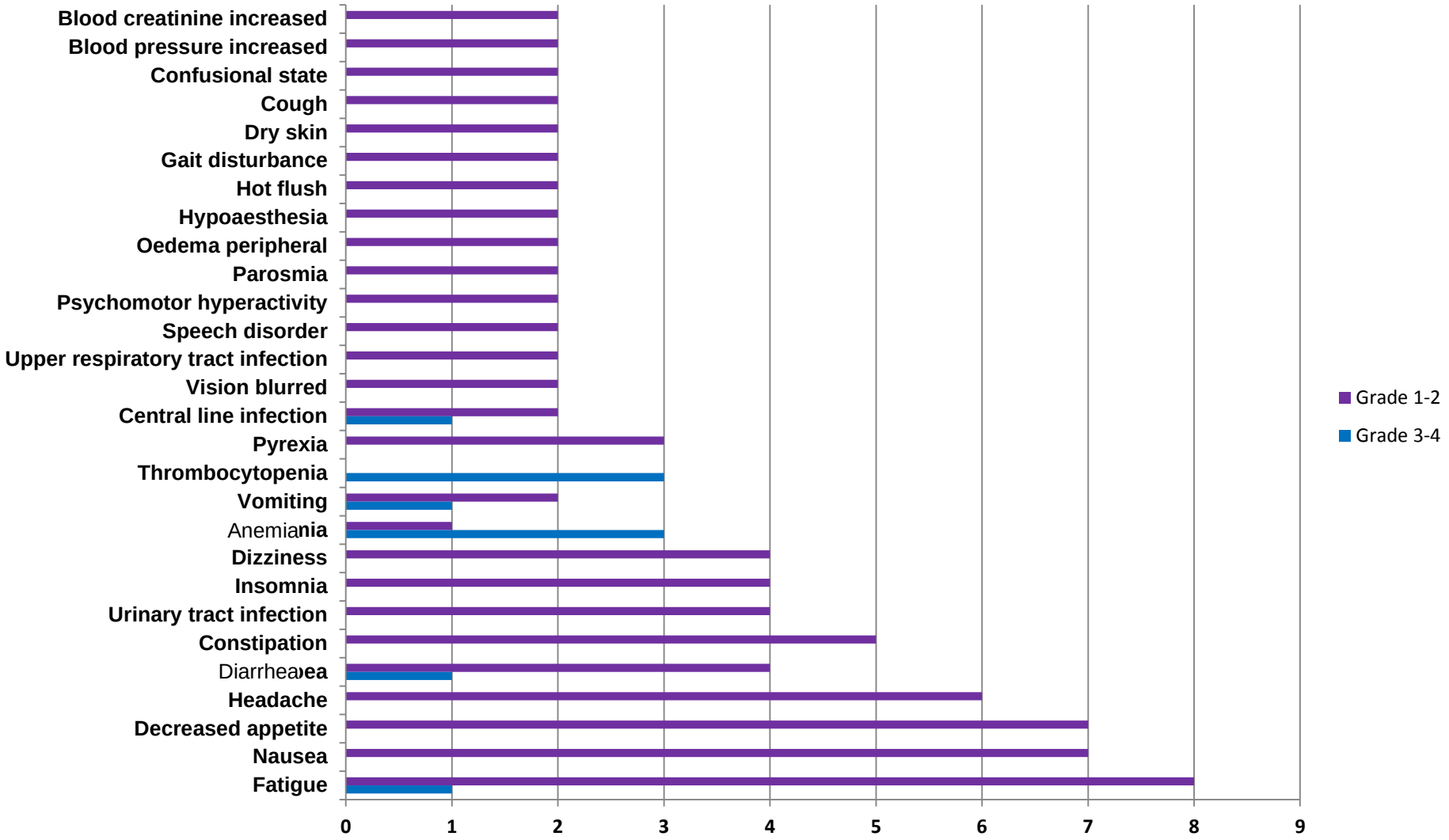
Marizomib Twice Weekly (NPI-0052-101) Adverse Events in >10% of Patients (n = 12)



Richardson PG, et al. *Blood.* 2011;118: Abstract 302.

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Thank You

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Summary

- Proteasome inhibition is a critical component of myeloma therapy today
- It has a role in different stages of therapy
- It is important for management of high risk MM and patients with renal insufficiency
- Strategies have evolved to make this strategy less toxic
- Oral proteasome inhibitors results in convenience and allows long term therapy more convenient