Phase I/Ib study of carfilzomib and panobinostat with or without dexamethasone in patients with relapsed/refractory multiple myeloma

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SUPPLEMENTARY MATERIAL

METHODS

Inclusion Criteria

1. Relapsed/refractory myeloma. Male or female patients aged ≥ 18 years old
2. Ability to provide written informed consent obtained prior to participation in the study and any related procedures being performed
3. Presence of the following laboratory criteria within 28 days prior to starting therapy:

- ANC ≥ 1.0 x 109/L
- Hemoglobin ≥ 8 g/dl (transfusions are permitted)
- Platelet count > 70,000 cells/mm3 for patients with < 50% of bone marrow plasma cells OR platelet count > 25,000 cells/mm3 for patients in whom > 50% of the bone marrow nucleated cells were plasma cells
- AST and ALT ≤ 2.5 x ULN
- Serum bilirubin ≤ 2 x ULN

4. ECOG Performance Status of ≤ 2
5. Creatinine clearance (CrCl) ≥ 30 mL/minute within 28 days prior to registration, either measured or calculated using a standard formula (e.g., Cockcroft and Gault)
6. MUGA or echocardiography must demonstrate LVEF ≥ 45%.
7. Female patients who: Are postmenopausal for at least 1 year before the screening visit, OR Are surgically sterile, OR If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, or agree to completely abstain from heterosexual intercourse. Male patients, even if surgically sterilized (i.e., status postvasectomy), who: Agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug, OR Agree to completely abstain from heterosexual intercourse.

Exclusion Criteria

1. Valproic acid for the treatment of cancer
2. Patients who will need valproic acid for any medical condition during the study or within 5 days prior to first panobinostat treatment
3. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:

- History or presence of sustained ventricular tachyarrhythmia. (Patients with a history of atrial arrhythmia are eligible)
- Any history of ventricular fibrillation or torsade de pointes
- Bradycardia defined as HR< 50 bpm. Patients with pacemakers are eligible if HR ≥ 50 bpm.
- Screening ECG with a QTc OR QTcf > 450 msec
- Right bundle branch block + left anterior hemiblock (bifascicular block)

• Patients with myocardial infarction or unstable angina ≤ 6 months prior to starting study drug

• Other clinically significant heart disease (e.g., CHF NY Heart Association class III or IV, uncontrolled hypertension, history of labile hypertension or history of poor compliance with an antihypertensive regimen)

4. Impairment of GI function or GI disease that may significantly alter the absorption of panobinostat

5. Patients with diarrhea > CTCAE grade 2

Definition of DLT

A dose-limiting toxicity (DLT) is defined as any of the below treatment emergent toxicities with attribution to one or more of the study drugs that occur during Cycle 1. Toxicities that occur in subsequent cycles will be handled through dose modifications but will not figure into the definition of MTD.

A DLT will be defined as follows:

• Hematologic dose-limiting toxicity will be defined as either
- o Grade 4 neutropenia lasting for ≥ 7 days in duration,
- o Febrile neutropenia (ANC < 1.0 x 109/L with a fever ≥ 38.3ºC)
- o Grade 4 thrombocytopenia lasting ≥ 7 days despite dose delay
- o Grade 3-4 thrombocytopenia associated with bleeding
- o Grade 5 hematologic toxicity.

At least three patients in each cohort must be evaluable for hematologic toxicity.

• Non-hematologic dose-limiting toxicity will be defined as any Grade 3, 4 or 5 non-hematologic toxicity, with the specific exception of:
- o grade 3 hyperglycemia
- o grade 3 fatigue
- o Isolated Grade 3 elevation of liver function tests (LFTs) without associated clinical symptoms, lasting for ≤ 7 days in duration.
- o Isolated Grade 3 elevation of amylase without associated clinical symptoms
- o Grade 3 hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hyphosphatemia which responds to medical intervention.
- o ≥ Grade 3 nausea, vomiting, or diarrhea despite maximal antiemetic/ antidiarrheal therapy
- o Any non-hematologic toxicity requiring a dose reduction within Cycle 1
- o Greater than 4 week delay in Day 1 dose of Cycle 2 due to drug related toxicity persisting from Cycle 1

Treatment Schedule

Applying the 3+3 design, the first cohort of 3 patients was treated at dose level 1 and evaluated for DLT at the end of first cycle. The algorithm used is as follows: (1) If 0 out of 3 patients experiences DLT, the next cohort of 3 patients will be treated at the next higher dose level. (2) If 1 out of 3 patients develop a DLT, an additional 3 patients will be treated at the same dose level. If no more DLTs develop at this dose, i.e. 1 out of a total of 6 patients

develops a DLT, the dose escalation continues for the next cohort of 3 patients. (3) At any given dose, if greater than 1 out 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose.

Role of funding source

The trial collaborator Amgen provided financial support but was not involved in study design, data collection, analysis, interpretation, writing of this report or decision to submit the manuscript for publication. The trial collaborator reviewed this report for accuracy. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Table S1: Baseline Patient Characteristics

			Patients treated at maximum recommended dose			
Characteristic	**All patients**	**(n= 47[1])**	**with dexamethasone (n= 17)**		**without dexamethasone (n= 12[1])**	
Age median (range), years	63	(41-76)	64	(41-76)	62	(44-72)
Gender, n (%)						
Female	16	34.0	5	29.4	5	41.7
Male	31	66.0	12	70.6	7	58.3
Race, n (%)						
African American	15	31.9	4	23.5	7	58.3
Asian	2	4.3	1	5.9	0	0.0
Caucasian	25	53.2	10	58.8	4	33.3
Hispanice or Latino	5	10.6	2	11.8	1	8.3
ECOG, , n (%)						
0	6	12.8	3	17.6	0	0.0
1	32	68.1	12	70.6	8	66.7
2	9	19.1	2	11.8	4	33.3
ISS stage, n (%)						
1	10	21.3	6	35.3	2	16.7
2	9	19.1	4	23.5	2	16.7
3	12	25.5	4	23.5	3	25.0
Unknown/Missing	16	34.0	3	17.6	5	41.7
FISH, n (%)**						
Normal	26	55.3	8	47.1	8	66.7
CKS1B amp <4 copies	5	10.6	4	23.5	1	8.3
CKS1B amp ≥ 4 copies*	2	4.3	2	11.8	0	0.0
t(4;14)*	4	8.5	1	5.9	0	0.0
t(11;14)	8	17.0	3	17.6	2	16.7
t(14;16)*	0	0.0	0	0.0	0	0.0
monosomy 13	14	29.8	6	35.3	2	16.7
17p del*	6	12.8	1	5.9	1	8.3
MYC t(8;14)	1	2.1	1	5.9	0	0.0
Cytogenetics, n (%)						
Normal	24	51.1	9	52.9	8	66.7
Hyperdiploid	6	12.8	1	5.9	3	25.0
Complex	15	31.9	7	41.2	2	16.7
t(11;14)	5	10.6	2	11.8	3	25.0
del(13)	5	10.6	1	5.9	3	25.0
del (17)	4	8.5	1	5.9	1	8.3
t(4;14)	3	6.4	0	0.0	0	0.0
High risk patients*, n (%)	10	21.3	4	23.5	1	8.3
Type of myeloma, n (%)						
IgA kappa	11	23.4	4	23.5	1	8.3
IgA lambda	6	12.8	3	17.6	1	8.3
IgG kappa	16	34.0	4	23.5	6	50.0
IgG lambda	4	8.5	2	11.8	2	16.7
Kappa	7	14.9	3	17.5	1	8.3
Lambda	2	4.3	1	5.6	0	0.0
Oligosecretory	1	2.1	0	0	1	8.3
Median number of prior therapies	**4**	**(2-16)**	**4**	**(2-16)**	**4**	**(2-7)**
Prior therapies , n (%)						
IMiD	47	100.0	17	100.0	12	100.0
Proteasome inhibitors (PI)[&]	45	95.7	17	100.0	12	100.0
Either IMiD or PI	47	100.0	17	100.0	12	100.0
Both IMiD and PI	45	95.7	17	100.0	12	100.0
Stem cell transplantation	41	87.2	16	94.1	9	75.0
Refractory to prior therapies , n (%)						
Both IMiD and PI	31	66.0	12	70.6	11	91.7
Either IMiD or PI	47	100.0	17	100.0	12	100.0
Bortezomib	32	68.1	15	88.2	11	91.7
Carfilzomib	13	27.7	11	64.7	1	8.3
IMiD	42	89.4	14	82.4	12	100.0

[1] includes one consent withdrawal during cycle 1

* High risk: FISH with more than 4 copies of GSK1B and/or t(4;14), and/or t(14;16), and/or 17p deletion. [&]PI: includes both bortezomib and/or carfilzomib

** 13 patients have more than one abnormality on FISH and 2 patients have more than one high risk abnormality on FISH

** 6 patients have more than one abnormality on FISH

[1] includes one consent withdrawal during cycle 1

** 2 patients have more than one abnormality on FISH

Table S2. Best response for patients at maximum recommended dose (MRD) with and without dexamethasone (dex) by subgroups

Response assessment	MRD with dex	MRD with dex Prior Bortezomib	MRD with dex Refractory to Bortezomib	MRD with dex Refractory to IMiD	MRD with dex Dual* Refractory	MRD with dex High risk	MRD with dex Standard risk
	n=17	n=17	n=13	n=14	n=12	n=4	n=13
ORR, n	9	9	7	6	4	2	7
(%)	*52.9*	*52.9*	*53.8*	*42.9*	*33.3*	*50.0*	*53.8*
CBR, n	11	11	9	8	6	2	9
(%)	*64.7*	*64.7*	*69.2*	*57.1*	*50.0*	*50.0*	*69.2*
CR, n	1	1	1	0	0	0	1
(%)	*5.9*	*5.9*	*7.7*	*0.0*	*0.0*	*0.0*	*7.7*
VGPR, n	2	2	1	2	1	1	1
(%)	*11.8*	*11.8*	*7.7*	*14.3*	*8.3*	*25.0*	*7.7*
PR, n	6	6	5	4	3	1	5
(%)	*35.3*	*35.3*	*38.5*	*28.6*	*25.0*	*25.0*	*38.5*
MR, n	2	2	2	2	2	0	2
(%)	*11.8*	*11.8*	*15.4*	*14.3*	*16.7*	*0.0*	*15.4*
SD, n	2	2	1	2	2	0	2
(%)	*11.8*	*11.8*	*7.7*	*14.3*	*16.7*	*0.0*	*15.4*
PD n	4	4	3	4	4	2	2
(%)	*23.5*	*23.5*	*23.1*	*28.6*	*33.3*	*50.0*	*15.4*

Response assessment	MRD no dex	MRD no dex Prior Bortezomib	MRD no dex Refractory to Bortezomib	MRD no dex Refractory to IMiD	MRD no dex Dual* Refractory	MRD no dex High risk	MRD no dex Standard risk
	n=11	n=10	n=8	n=11	n=10	n=1	n=10
ORR, n	2	2	1	2	1	0	2
(%)	*18.2*	*20.0*	*12.5*	*18.2*	*10.0*	*0.0*	*20.0*
CBR, n	4	4	2	4	3	0	4
(%)	*36.4*	*40.0*	*25.0*	*36.4*	*30.0*	*0.0*	*40.0*
CR, n	0	0	0	0	0	0	0
(%)	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
VGPR, n	1	1	0	1	0	0	1
(%)	*9.1*	*10.0*	*0.0*	*9.1*	*0.0*	*0.0*	*10.0*
PR, n	1	1	1	1	1	0	1
(%)	*9.1*	*10.0*	*12.5*	*9.1*	*10.0*	*0.0*	*10.0*
MR, n	2	2	1	2	2	0	2
(%)	*18.2*	*20.0*	*12.5*	*18.2*	*20.0*	*0.0*	*20.0*
SD, n	2	1	1	2	2	1	1
(%)	*18.2*	*10.0*	*12.5*	*18.2*	*20.0*	*100.0*	*10.0*
PD n	5	5	5	5	2	0	5
(%)	*45.5*	*50.0*	*62.5*	*45.5*	*20.0*	*0.0*	*50.0*

ORR = CR+VGPR+PR; CBR = CR+VGPR+PR+MR

*IMiD and PI

Table S3: Treatment-related toxicities

	Phase 1a n=24				Phase 1b n=23					MRD with dexamethasone n=17					MRD without dexamethasone n=12			
Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Abdominal pain	1	1			1										2	1		
Acute kidney injury							1		1*			1		1*				
Agitation					1					1								
Alanine aminotransferase increased	1				5					5								
Alkaline phosphatase increased	7	1			7	1				6	1				4	1		
Anemia		6	10	2*		7	13				4	10				3	7	
Anorexia	3				3		1*			3		1*			1			
Anxiety					1					1								
Aspartate aminotransferase increased	5		1		13	1				11	1				5			
Back pain	1																	
Blood bilirubin increased	4		1			4					3				2	1		
Blurred vision	4				4	3				4	3				1			
Bronchopulmonary hemorrhage					1					1								
Cardiac disorders - (Other)					1					1								
Chest pain - cardiac		1																
Chills	1				1					1								
Confusion					1		1*			1		1*						
Constipation	4		1		5	1				4	1				4			
Cough	2				3					3								
Creatinine increased	4	5		2#**	4	8	4			4	5	4			1	4		1*
Dehydration	1	1	1															
Diarrhea	12	4	2		9	6	1			8	5	1			5	2		
Dizziness	6	1			5	2	1			5	2	1			2			
Dry eye					4	1				4	1							
Dyspepsia		1																
Dyspnea	6	4*			5	7				3	7				5			
Edema limbs		2			11	3				9	3				2	2		
Prolonged Electrocardiogram QT					1					1								
Epistaxis	**3**					1					1				1			
Eye disorders - (Other)					1					1								
Fatigue	3	5	6		3	10	2			2	9	1			1	3	2	
Fever	1				7	1	1			5	1	1			2			
Gastroesophageal reflux disease	1				1					1					1			
General disorders and administration site					1					1								
Generalized muscle weakness	1				2					2								
Headache					1	1				1						1		
Heart failure							1*					1*						
Hematuria	1																	
Hiccups	1				1					1					1			
Hypercalcemia	1														1			
Hyperglycemia	2				2	1				2	1				1			
Hyperkalemia			1		6	1	1*			6	1	1*						
Hypermagnesemia					1		1			1		1						
Hypernatremia						1					1							
Hypertension			2				1										1	
Hyperuricemia	2				8		2	1		6		2	1		2			
Hypoalbuminemia	2				8	11				7	9				3	2		
Hypocalcemia	5	1			5	5		1		5	4				1	1		1
Hypoglycemia					2					1					1			
Hypokalemia	6				7	1	3			6	1	2			3		1	
Hypomagnesemia	5				13					9					6			
Hyponatremia	4				8		2			6		2			3			
Hypophosphatemia	3	1	1			3	2				2	2				2		
Hypotension		1			1					1								
Insomnia					2					2								
Left ventricular systolic dysfunction						1	1*				1	1*						
Lethargy					1					1								
Lung infection		1	1*	1*			4***					3**					1*	
Memory impairment	1	3			7					6					1	1		
Metabolism and nutrition disorders - (Other)					1										1			
Mucosal infection		1																
Mucositis oral	2				7	1				5					2	1		
Muscle weakness lower limb		1																
Muscle weakness upper limb						1										1		
Myalgia	**4**	2	1#		4	5	1			3	5	1			1	1	1	
Nasal congestion		1																
Nausea	5	7	1		5	9				4	7				4	3		
Neck pain	1				1										2			
Neutropenia	1	4	6	3		7	7	3			4	5	3			4	4	
Paresthesia						1										1		
Paroxysmal atrial tachycardia		1																
Peripheral sensory neuropathy	2	1			1	2				1	2					1		
Photophobia					1					1								
Thrombocytopenia	3	5	6	7	4	2	7	9		4	2	4	7			2	4	4
Thrombocytopenia with bleeding				2##														1
Rash maculo-papular	2														1			
Renal and urinary disorders - (Other)							1					1						
Respiratory, thoracic and mediastinal disorder		1				1					1							
Sinus bradycardia	1														1			
Sinus tachycardia					1					1								
Skin and subcutaneous tissue disorders - (Other)						1					1							
Skin infection						1					1							
Sore throat					1					1								
Supraventricular tachycardia						1					1							
Syncope			1*															
Tremor					1					1								
Upper respiratory infection		2																
Urinary tract infection		1				1					1							
Vitreous hemorrhage	1																	
Vomiting	7	4			3	4	2			3	3	1			3	2	1	
Watering eyes					4	1				4	1							
Weight loss	2				1					1					1			
Lymphocytopenia	1			1	5	11	6			4	8	5			1	3	1	

* represents one serious adverse event (SAE)

represents one dose limiting toxicity (DLT)

Table S4: Common toxicities expected with panobinostat and carfilzomib

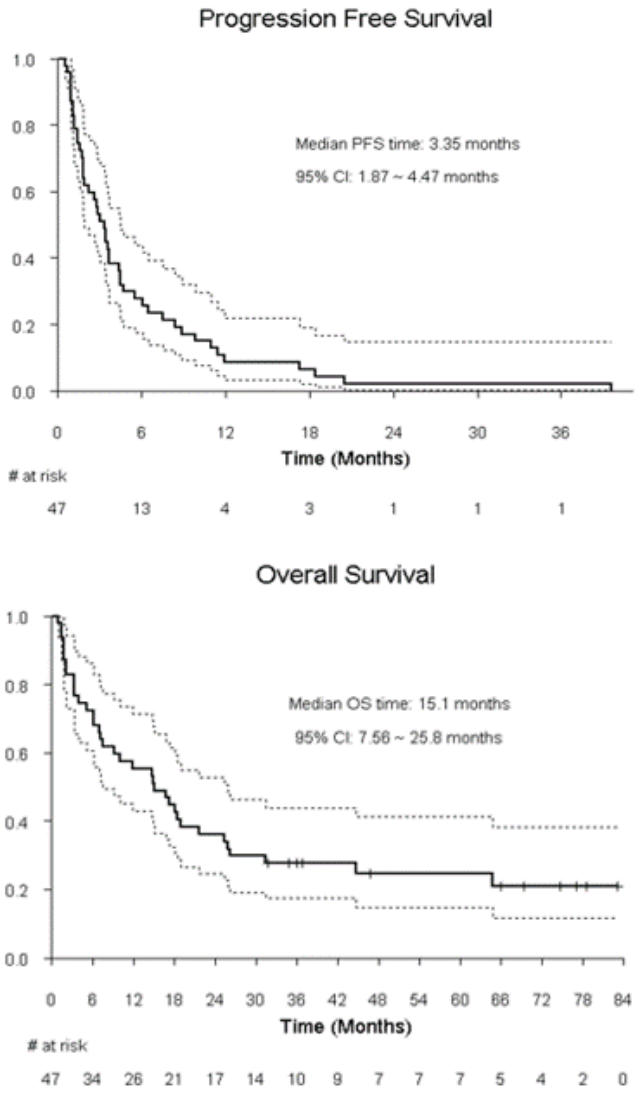
	Phase Ia								Phase Ib							
Toxicity	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
	n=24								**n=23**							
	GRADE 1		**GRADE 2**		**GRADE 3**		**GRADE 4**		**GRADE 1**		**GRADE 2**		**GRADE 3**		**GRADE 4**	
Diarrhea	12	*52.2*	4	*17.4*	2	*8.7*			9	*37.5*	6	*25.0*	1	*4.2*		
Nausea	5	*21.7*	7	*30.4*	1	*4.3*			5	*20.8*	9	*37.5*				
Vomiting	7	*30.4*	4	*17.4*					3	*12.5*	4	*16.7*	2	*8.3*		
Thrombcytopenia	3	*13.0*	5	*21.7*	6	*26.1*	9**	*39.1*	4	*16.7*	2	*8.3*	7	*29.2*	9	*37.5*
Neuropathy	2	*8.7*	1	*4.3*					1	*4.2*	2	*8.3*				
Cardiac Toxicity	1	*4.3*	2	*8.7*	3	*13.0*			3	*12.5*	2	*8.3*	3	*12.5*		
Dyspnea	6	*26.1*	4	*17.4*					5	*20.8*	7	*29.2*				

	MRD without dexamethasone								MRD with dexamethasone							
Toxicity	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
	n=12								**n=17**							
	GRADE 1		**GRADE 2**		**GRADE 3**		**GRADE 4**		**GRADE 1**		**GRADE 2**		**GRADE 3**		**GRADE 4**	
Diarrhea	5	*41.7*	2	*16.7*					8	*47.1*	5	*29.4*	1	*5.9*		
Nausea	4	*33.3*	3	*25.0*					4	*23.5*	7	*41.2*				
Vomiting	3	*25.0*	2	*16.7*	1	*8.3*			3	*17.6*	3	*17.6*	1	*5.9*		
Thrombcytopenia			2	16.7	4	33	5*	*41.7*	4	*23.5*	2	*11.8*	4	*23.5*	6	*35.3*
Neuropathy			1	*8.3*					1	*5.9*	2	*11.8*				
Cardiac Toxicity	1	*8.3*			1	*8.3*			3	*17.6*	2	*11.8*				
Dyspnea	5	*41.7*							3	*17.6*	7	*41.2*				

each * represents one case of thrombocytopenia with bleeding included

Figure S1

A



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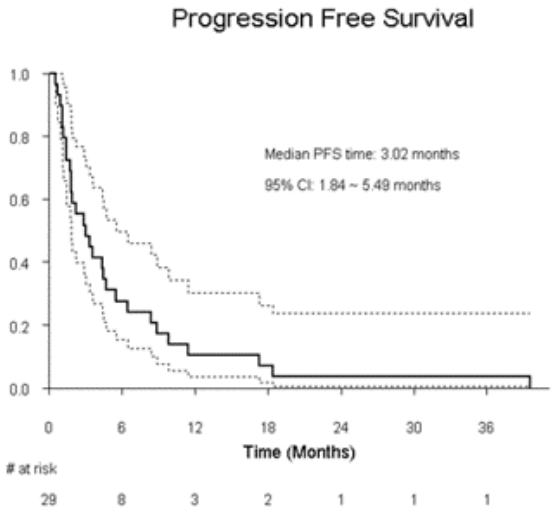


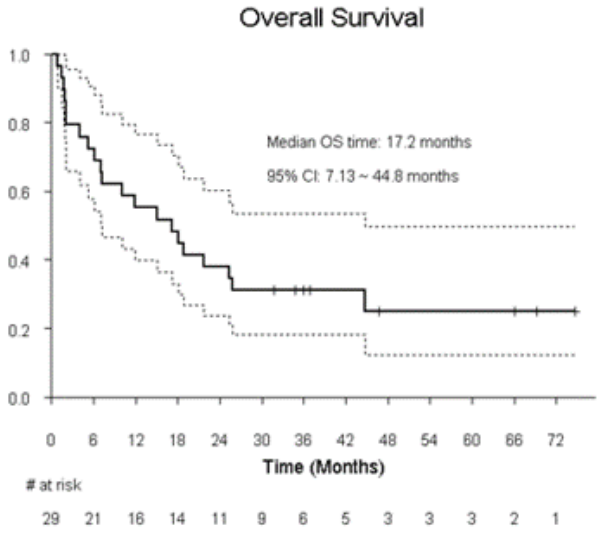


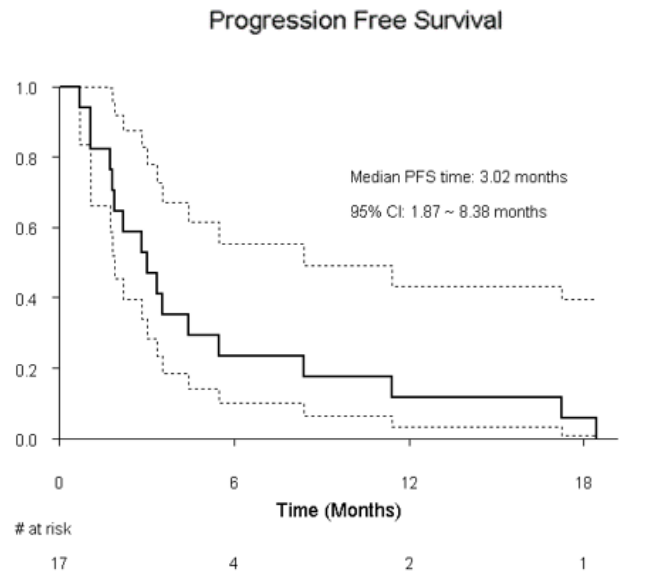
Figure S1: Progression-Free Survival and Overall Survival.

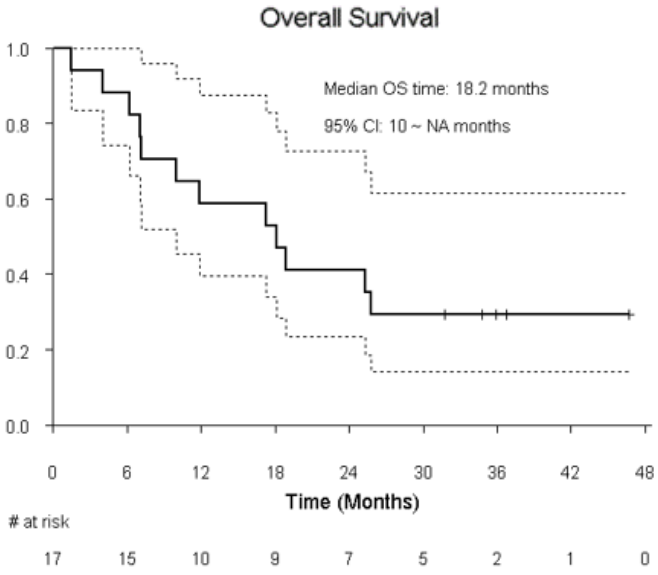
(A) Progession-free survival (top) and overall survival (bottom) in all 47 patients

(B) Progession-free survival (top) and overall survival (bottom) in 29 patients treated at the maximum recommended dose

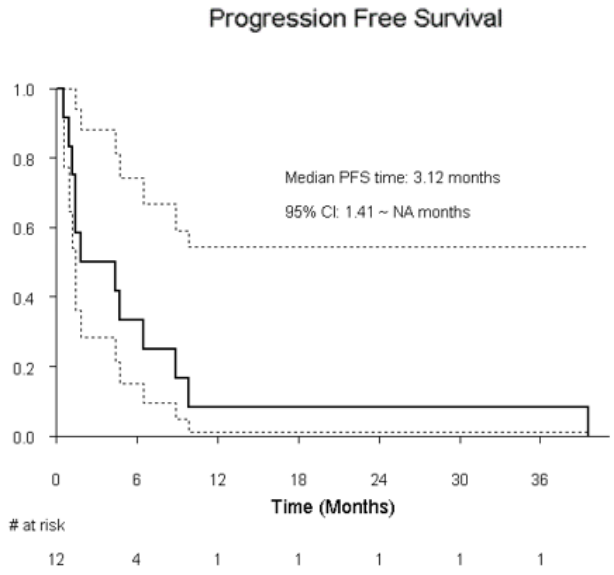
Figure S2

A





B



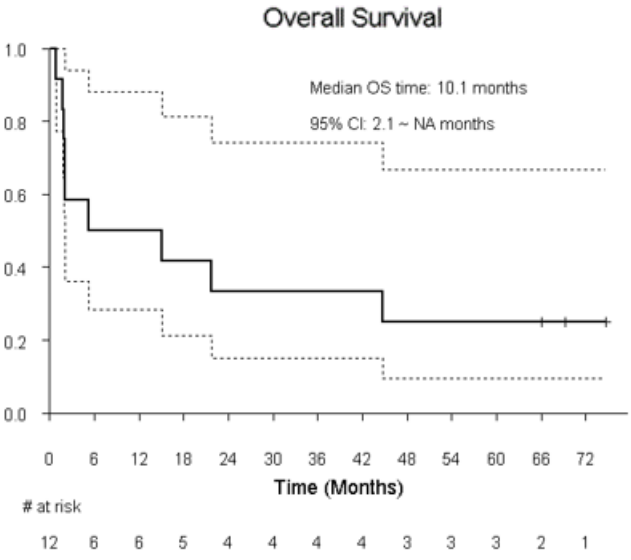


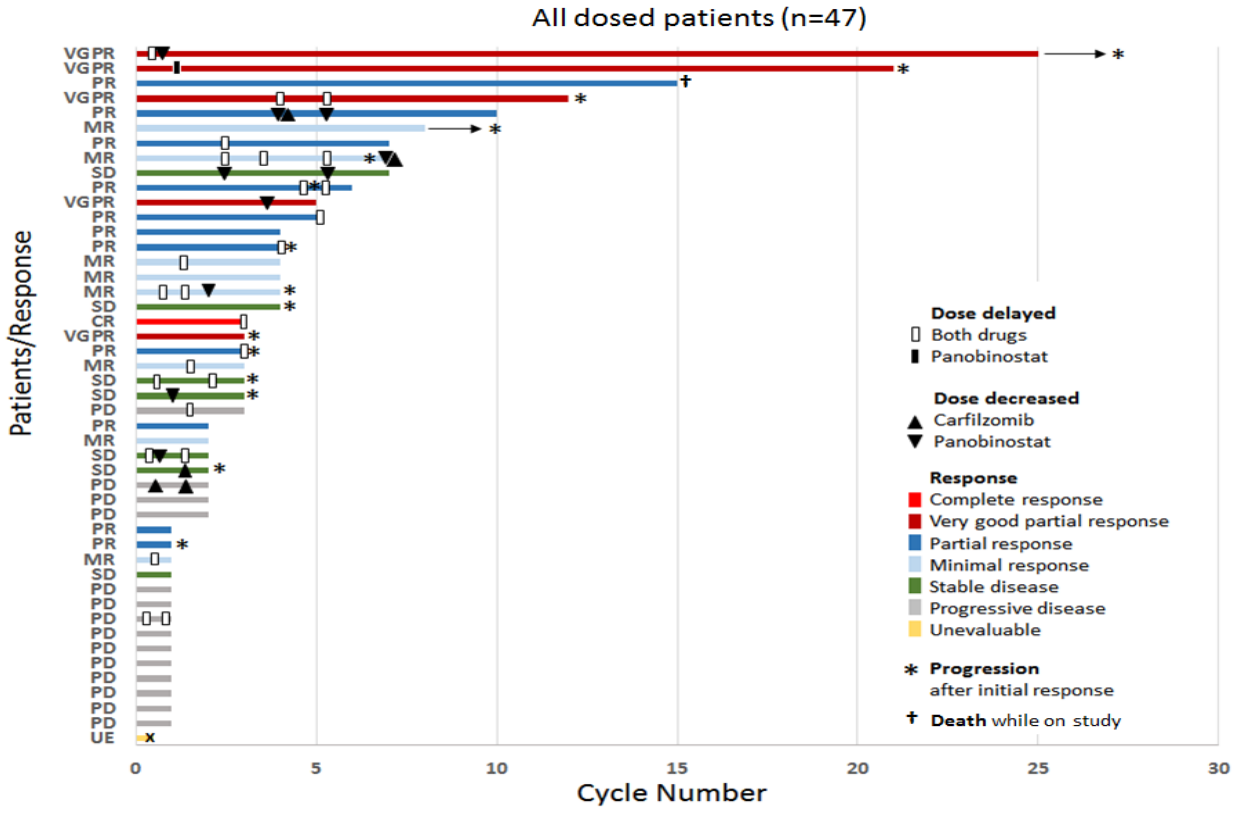
Figure S2: Progression-Free Survival and Overall Survival in patients at maximum recommended dose (MRD).

(A) Progession-free survival (top) and overall survival (bottom) in 17 patients treated at MRD with dexamethasone

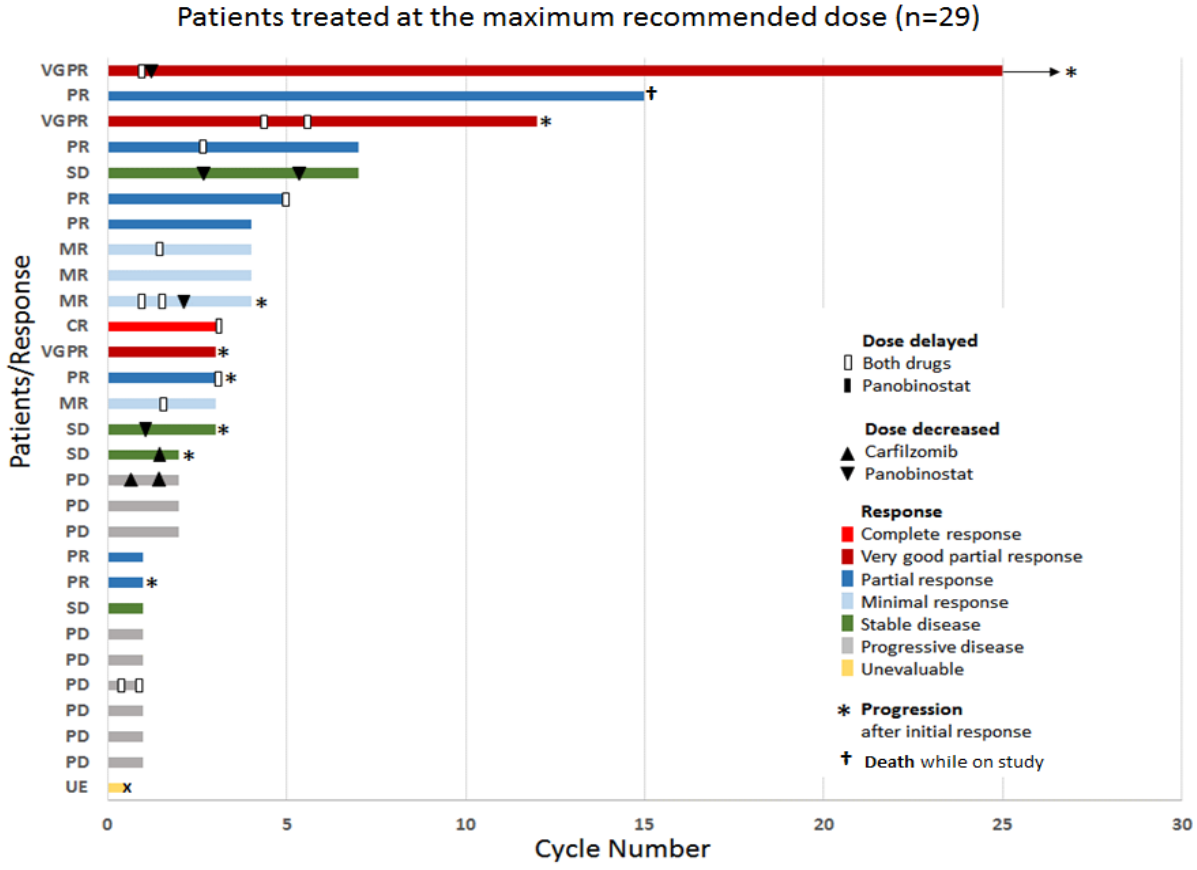
(B) Progession-free survival (top) and overall survival (bottom) in 11 patients treated at MRD without dexamethasone

Figure S3

A


All dosed patients (n=47)
Patients/Response
VGPR
PR
MR
SD
CR
PD
UE
Cycle Number
0
5
10
15
20
25
30
Dose delayed
Both drugs
Panobinostat
Dose decreased
Carfilzomib
Panobinostat
Response
Complete response
Very good partial response
Partial response
Minimal response
Stable disease
Progressive disease
Unevaluable
Progression after initial response
Death while on study

B


Patients treated at the maximum recommended dose (n=29)
Patients/Response
VGPR
PR
MR
SD
CR
PD
UE
Cycle Number
0
5
10
15
20
25
30
Dose delayed
Both drugs
Panobinostat
Dose decreased
Carfilzomib
Panobinostat
Response
Complete response
Very good partial response
Partial response
Minimal response
Stable disease
Progressive disease
Unevaluable
Progression after initial response
Death while on study

C

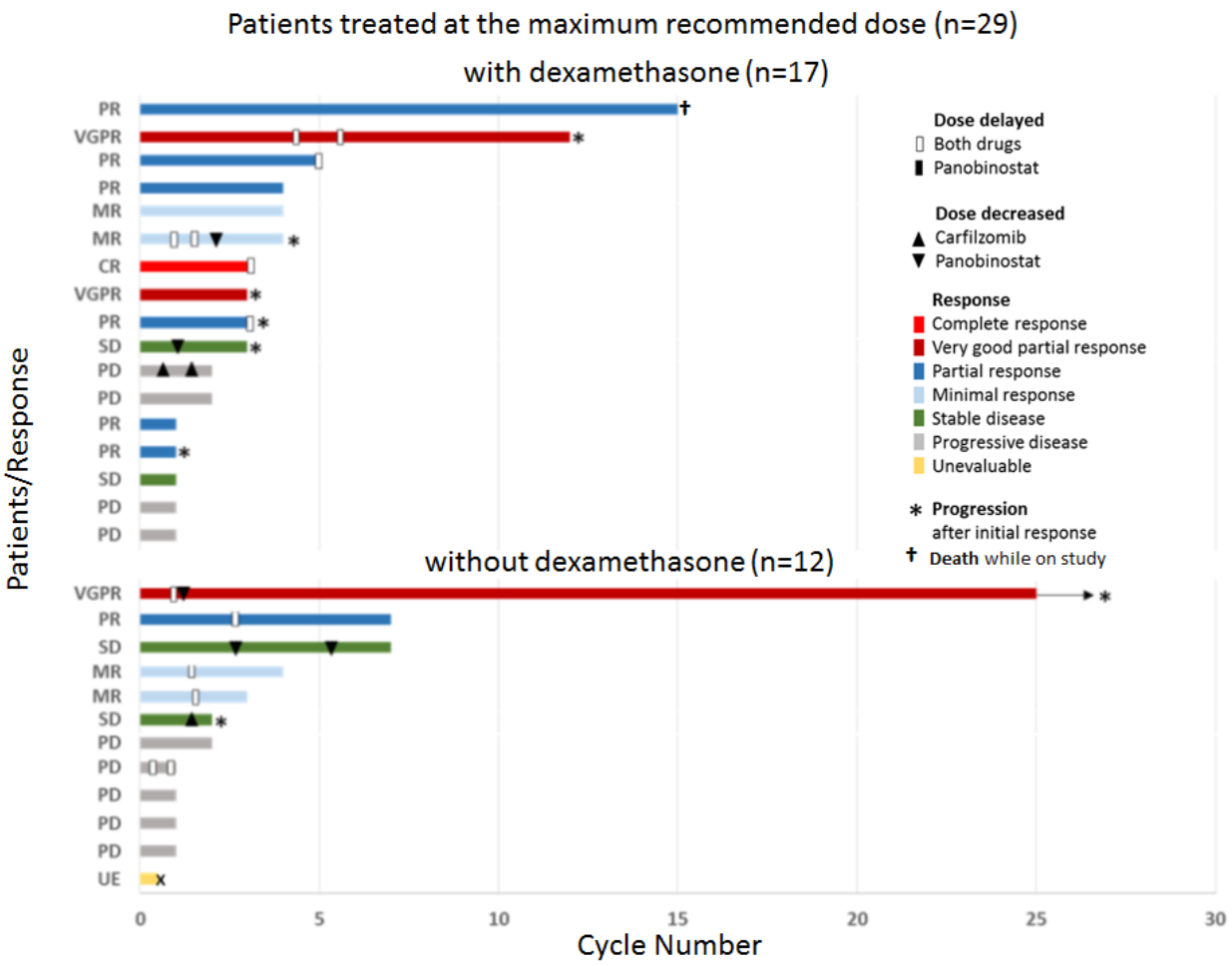


Figure S3: Dose delays and alterations.

(A) In all treated patients

(B) In patients treated at the maximum recommended dose

(C) In patients treated at the maximum recommended dose with (top) or without dexamethasone (bottom)