A Phase 1b Multicenter Dose Escalation Study of Carfilzomib plus Lenalidomide and Low-dose Dexamethasone in Relapsed Multiple Myeloma

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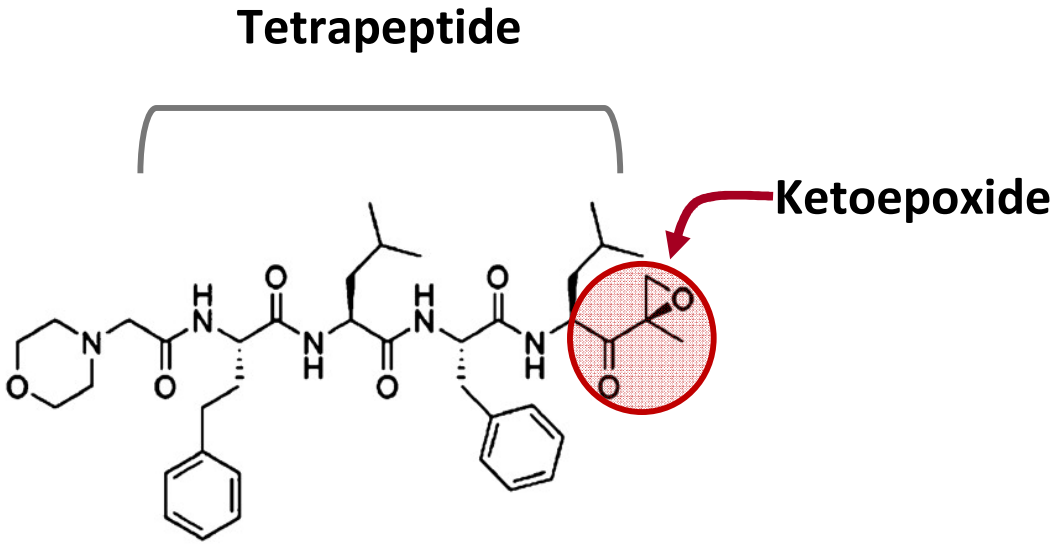
Carfilzomib:
Selective and Irreversible Proteasome Inhibitor

Carfilzomib is the first in a new class of selective and irreversible proteasome inhibitors that are associated with prolonged target suppression, improved antitumor activity and low neurotoxicity



Rationale for Carfilzomib + Len/Dex (CRd)

- **Carfilzomib is active as a single-agent in relapsed MM**
  - **At 20 mg/m²**
    - Bortezomib naïve: ORR 46 %, TTP 7.6 months
    - Bortezomib pre-treated: ORR 18 % TTP 5.3 months
  - **At 27 mg/m²**
    - Bortezomib naïve: ORR 53%

- **Len + Dex is a current standard of care for relapsed MM**

- **Bortezomib + Len/Dex (VRD) active in relapsed or refractory patients but has toxicity limitations (n=62)***
  - BTZ 1 mg/m² + Len 15 mg + High dose Dex
  - Prior therapies: 8% Len, 55% Btz, 77% Thal, 36% SCT
  - ORR (≥PR) 69%, (≥MR) 84%

- **Carfilzomib/Len/Dex should provide superior activity to Len/Dex alone**
  - Lack of overlapping toxicities and neuropathy should allow long term dosing

**Richardson, ASCO 2009 # 8536*

Study Objectives

Primary Objective:

- To evaluate safety and determine the maximum tolerated dose (MTD) of carfilzomib with lenalidomide and low dose dexamethasone in patients with relapsed MM

Secondary Objectives:

- To observe early evidence of efficacy and determine PK parameters of carfilzomib

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Dose Schedule

Study Design: Phase 1b, multi-center, escalation trial

Population: Relapsed multiple myeloma: 1 to 3 prior treatments

Study Treatment :

- Up to 6 dose escalation cohorts
- Expansion cohort at MTD or highest protocol dose (if MTD not established)
- 28 day cycles

	Days of Administration (dose escalation cohorts)		
Agent	Cycles 1-4	Cycles 5-8	Cycles 9-16
CFZ	1, 2, 8, 9, 15, 16	1, 2, 8, 9, 15, 16	1, 2, 15, 16
Len	1-21	1-21	1-21
Dex	1, 8, 15, 22	1	1

For the Expansion cohort:

- Dexamethasone weekly from C1-C18
- CFZ on days 1,2,8,9,15,16 from C1-C12

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Protocol Definitions

- Eligibility
  - Relapsed or progressive disease after 1- 3 prior therapies
  - Neuropathy (Grade 1/2 without pain) allowed at baseline
  - Platelets > 50,000/mm^3; ANC > 1,000/mm^3
  - Creatinine < 2 mg/dL or CrCl ≥ 50 mL/min
- Response criteria
  - IMWG, EBMT, NCI-CTC v3.0
- Dose limiting toxicity (DLT) defined as:
  - Grade (G) ≥3 non-hematologic
  - G4 neutropenia for > 7 d and / or neutropenic fever
  - G4 thrombocytopenia > 7 d
  - G3-G4 thrombocytopenia in association with bleeding
- MTD = Dose level prior to that resulting in ≥ 2/6 DLTs

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Baseline Characteristics (N=32*)

Characteristic		Median (range)
Age, years		60.3 (43-81)
Time since diagnosis, years		3.0 (0.35-21.5)
		n (%)
Gender	**Male**	15 (47)
	Female	17 (53)
Immunoglobulin subclass	**IgG**	24 (75)
	IgA	5 (16)
Baseline evaluation	**History of neuropathy**	24 (82)

***Includes all subjects enrolled in first 5 dose escalation cohorts**

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Prior Therapies (N=32)

Prior Therapies	Median (range)
Number	2.5 (1-3)
	%
Bortezomib	73
Immunomodulatory Agents	90
Lenalidomide	63
Thalidomide	43
Corticosteroid	100
Alkylating Agents	69
Anthracycline	30
Stem Cell Transplant	80
Relapse Refractory Status	50

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Enrollment Overview

Cohort	CFZ / LEN (mg/m^2 /mg)	Enrolled	DLTs	Duration on Therapy (# of 28 day-cycles)
1	15 / 10	6	0	17+, 9, 4, 3, 2, 1
2	15 / 15	6	0	14+, 14+, 11, 8, 1, 1
3	15 / 20	8	0	11+, 11+, 10+, 10+, 10+, 8, 7, 0
4	20 / 20	6	0	8+, 8+, 5, 3, 2, 1
5	20 / 25	6	0	5+, 5+, 5+, 4+, 3, 1
6	20-27* / 25	8	0	
Expansion	20-27* / 25	16		

***CFZ 20 mg/m^2 for days 1 & 2 in first cycle; 27 mg/m^2 thereafter**

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Adverse Events and Toxicity (N=27*)

Adverse Events	n (%) All Grades ≥ 20%	n (%) Grade 3 / 4 ≥ 5%
Fatigue	12 (44)	
Diarrhea	9 (33)	
Neutropenia	9 (33)	6 (22)
Anemia	7 (26)	4 (15)
Back Pain	7 (26)	
Cough	7 (26)	
Dyspnea	7 (26)	
Thrombocytopenia	6 (22)	6 (22)
Arthralgia	6 (22)	
Rash	6 (22)	
U Respiratory Infection	6 (22)	
Hyperglycemia	5 (18)	3 (11)

No DLTs or deaths through Cohort 5

No fatigue ≥ G3 or thrombotic events

G1 neuropathy in 2 cases with pre existing PN:

- Thalidomide-related
- Bortezomib-related

*27/32 subjects enrolled in first 5 dose escalation cohorts evaluable for safety

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Drug-related SAEs (N=32)

TO BE DISCUSSED

Cohort	SAE	Cycle Day	Treatment
2	Transient, G3 sinus bradycardia	C10 D9	Continued
3	G3 Upper respiratory tract infection	C7 D18	Delayed
3	Febrile neutropenia	C9 D8	Discontinued
4	G3 diarrhea and G3 urinary infection	C4 D1	Discontinued

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Drug-Discontinuation* (N=32)

TO BE DISCUSSED

Cohort	Cause	Relationship	Cycle Day
1	PD Renal failure	NR	C1 D23
2	PD Bone disease	NR	C2 D1
3	Fever Unknown Origin	NR	C1D2
3	Febrile neutropenia	Possibly	C9 D8
4	G3 Pneumonia	NR	C2 D1
4	G4 Soft tissue subglottic mass	NR	C1 D16
4	G3 diarrhea and G3 urinary infection	Possibly	C4 D1

*7/32 subjects enrolled in first 5 dose escalation cohorts evaluable for safety

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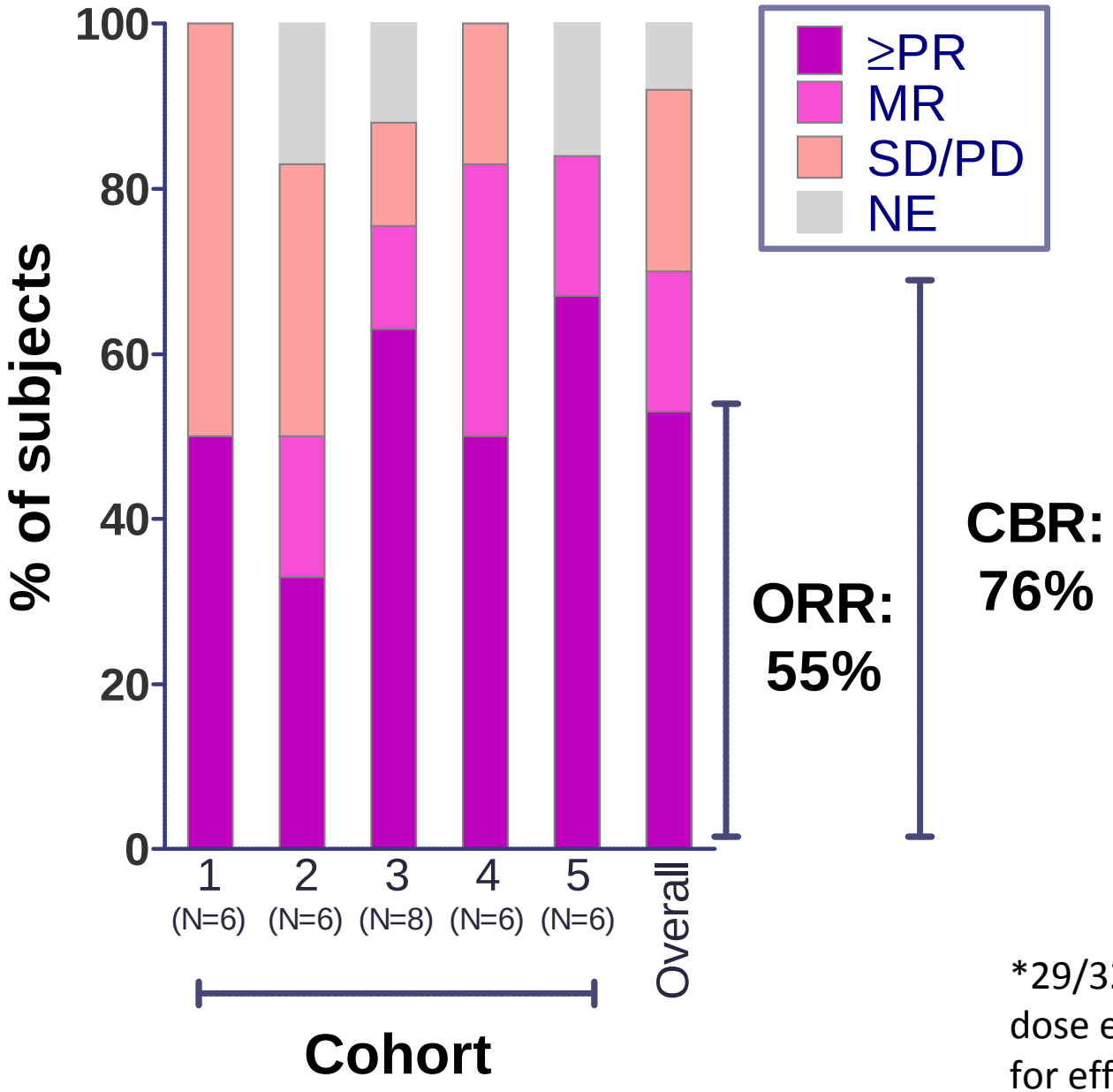
Activity in Evaluable Patients (N = 29)



*29/32 subjects enrolled in first 5 dose escalation cohorts evaluable for efficacy

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Activity in Evaluable Patients (N = 29)

CRd: Cohorts 1-5 CFZ: 15 to 20 mg/m^2 LEN: 10 to 25 mg	
Response	**N (%)**
CR/nCR	6 (21)
VGPR	5 (17)
PR	5 (17)
MR	6 (21)
SD	5 (17)

≥PR : 55%

≥MR : 76%

≥SD : 93%

- All responses observed at sub-MTD CFZ doses
- Responses improve with continuing therapy (≥3 months)
- Cohort 6 and expansion using CFZ 27 mg m^2 / LEN 25 mg

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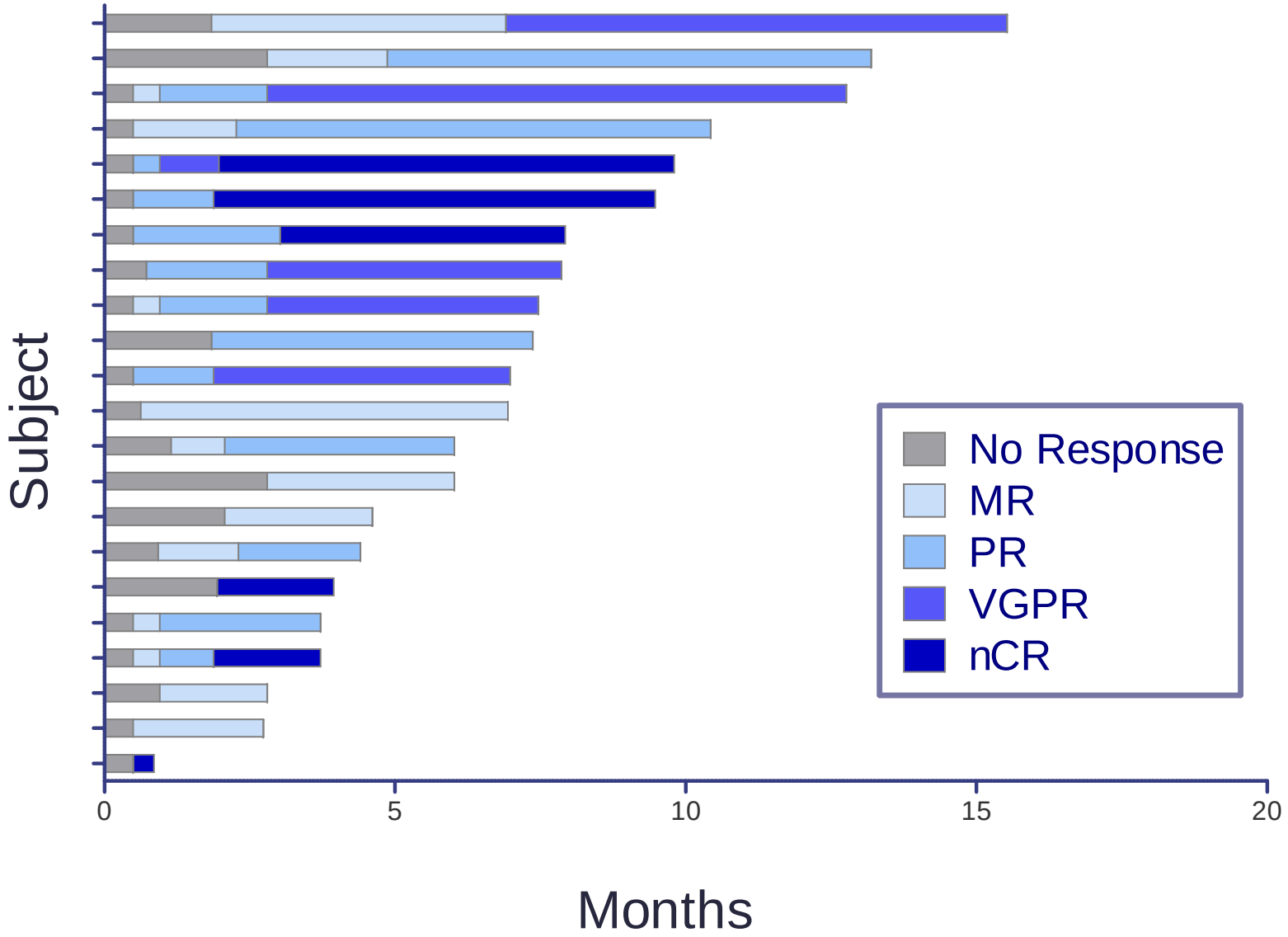
Response improves with prolonged treatment



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Activity in Evaluable Patients (N = 29)

	CRd: Cohorts 1-5 CFZ 10-20 / LEN 10-25 N (%)	
	Relapsed N= 13	Refractory N= 16
≥ CR/nCR	4 (31)	2 (13)
≥ VGPR	5 (38)	6 (38)
≥PR	6 (46)	10 (63)
≥MR	10 (77)	12 (75)

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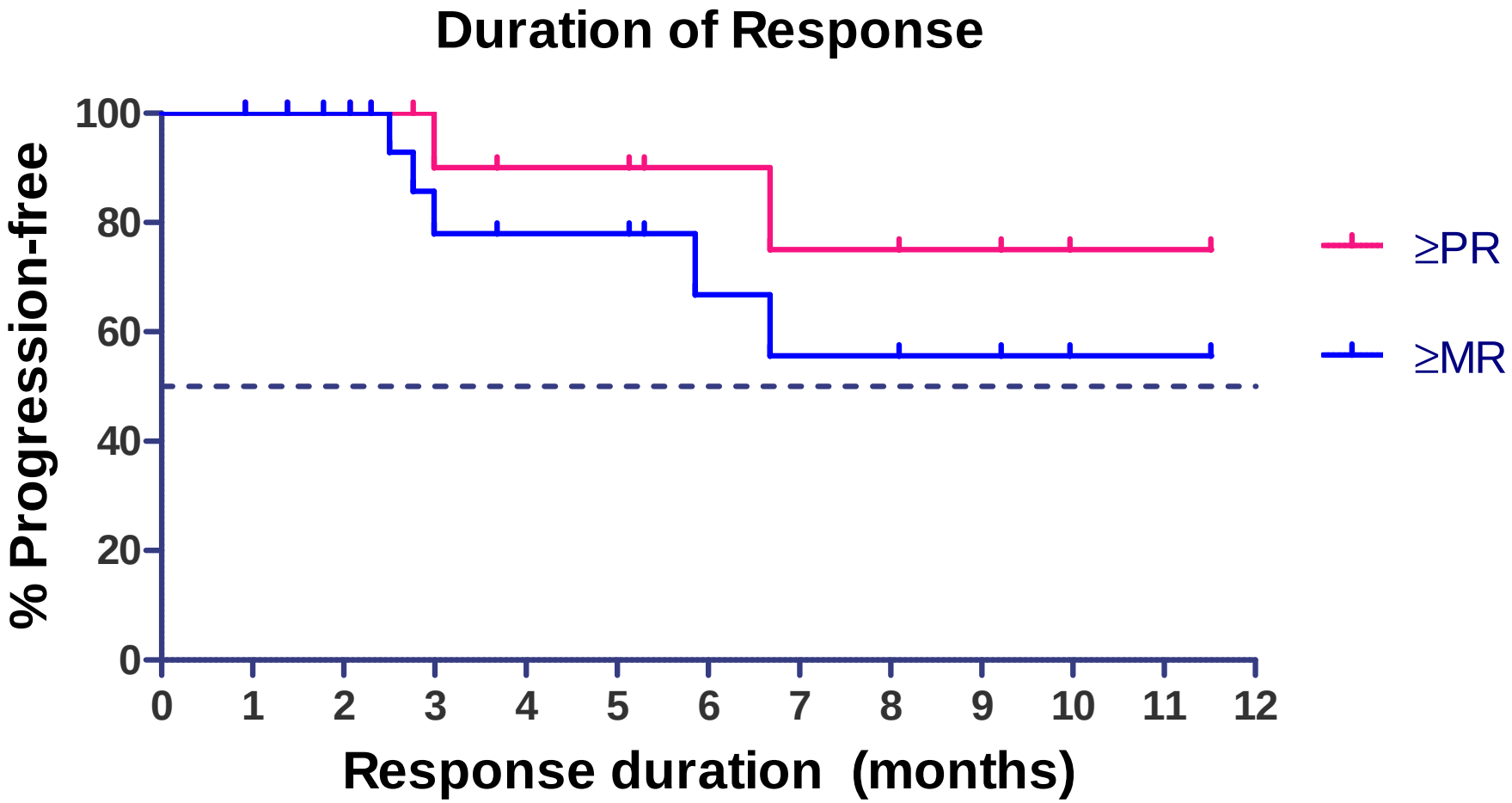
Duration of Response in Cohorts 1-5 (N=16)



- Median DOR not yet reached

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Conclusions

- **Carfilzomib + Len/Dex is well tolerated in subjects heavily pre-treated with BTZ and IMIDs**
  - MTD not reached - No DLTs up to cohort 6
  - Manageable expected hematological events
  - Peripheral neuropathy and DVT not observed
  - Prolonged administration possible (> 16 months)
- **Carfilzomib + Len/Dex yielded responses in the majority of subjects**
  - ORR: 55% (≥PR); 76% (≥MR)
  - Disease control rate = 93%
  - Responses improve with continuing therapy (≥ 3 months)
- **Expansion cohort currently enrolling**
  - 20→27 mg/m2 CFZ + 25 mg/day Len

Len/dex ± CFZ Phase 3 trial to be initiated in 2010

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