Phase I Study of Carfilzomib and Panobinostat for Patients With Relapsed and Refractory Myeloma: A Multicenter MMRC Clinical Trial

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Study Rationale

- Multiple myeloma (MM) remains a disease with a need for new treatments for patients with relapsed and refractory disease
- Carfilzomib is a selective proteasome inhibitor that has demonstrated significant activity in patients with relapsed and refractory myeloma
- Panobinostat is a pan-deacetylase inhibitor that can overcome resistance in combination with bortezomib in refractory multiple myeloma patients.
- Based on data showing synergistic cytotoxicity of pan-deacetylase and proteasome inhibitors, we hypothesized that carfilzomib and panobinostat would be safe and effective for the treatment of relapsed/refractory multiple myeloma.

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Study Design
Objectives and Assessments

Primary endpoint:

- Determine MTD and optimal schedule of the combination

Secondary endpoints:

- Adverse event incidence, frequency and severity
- Response data including response rates, duration, progression free and overall survival

Multi-center, open-label, Phase 1 study:

- Dose escalation phase:
  - Standard 3 + 3 design to determine MTD
  - MTD based on DLT during cycle 1
  - Patients assigned to one of 4 cohorts
- Expansion phase:
  - 12 additional patients treated at the MTD to support the secondary objectives

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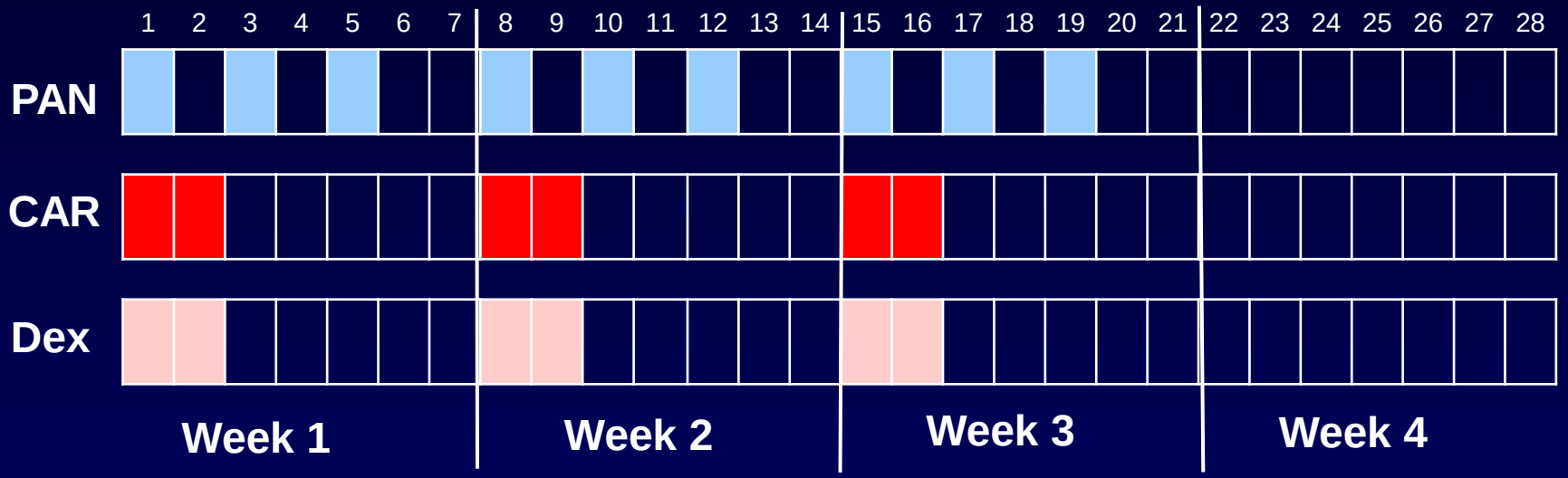
Carfilzomib/Panobinostat

Dosing schedule



- **PAN: Panobinostat 15-20 mg orally**
- **CAR: Carfilzomib 20-45 mg/m^2; all doses of carfilzomib over 27mg/m^2 were infused over 30 minutes**
- **Dex: Dexamethasone 4 mg oral for first cycle, optional thereafter**

If 3 out of 4 week dosing was not tolerable a change to 2 of 4 week dosing was planned

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Dose Escalation Schedule

Cohort	Panobinostat (oral TIW 3 out of 4 weeks	Carfilzomib (IV Days 1/2, 8/9, and 15/16 every 4 weeks)	Dexamethasone (oral prior to carfilzomib)
1	15 mg	C1D1/2: 20 mg/m^2 thereafter: 27 mg/m^2	4 mg (Cycle 1: thereafter as clinically indicated)
2	20 mg	C1D1/2: 20 mg/m^2 thereafter: 27 mg/m^2	4 mg (Cycle 1: thereafter as clinically indicated)
3	20 mg	C1D1/2: 20 mg/m^2 thereafter: 36 mg/m^2	4 mg (Cycle 1: thereafter as clinically indicated)
4	20 mg	C1D1/2: 20 mg/m^2 thereafter: 45 mg/m^2	4 mg (Cycle 1: thereafter as clinically indicated)

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Patient Characteristics

	N = 26*
Female, %	50
Median age, in years (range)	65 (49-75)
ECOG performance status, %	
0-1 / 2	96 / 4
Bortezomib (BTZ) refractory (%)	16 (62)
IMiD refractory (%)	22 (85)
Median lines of therapy (range)	3 (1-7)
Prior Auto (%)	23 (88)

- Patients received multiple prior regimens, including multiple prior BTZ combinations
- *20 patients in the dose escalation phase and 6 patients in the dose expansion phase

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Results: Cohorts, DLTs and MTD

Cohort	Evaluable	DLT	Non evaluable
1	3	0	1 - progression
2	3	0	1 - missed doses, non toxicity related
3	6	1 - Acute kidney injury, thrombocytopenia	1 - progression
4	5	1 – thrombocytopenia 2 - diarrhea	

One grade 5 cardiac event (sudden cardiac arrest) in cohort 1 was possibly related to study medications

MTD is Cohort 3: Carfilzomib 20/36 mg/m^2 and panobinostat 20 mg TIW 3 of 4 weeks

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Adverse Events

Occurring in ≥ 20% (All Grades) of Patients (n = 26)

All	26 (100%)	Pan/Bor/Dex[1]
Nausea	17 (65%)	60%
Anemia	14 (54%)	47%
Diarrhea	13 (50%)	71%
Thrombocytopenia	13 (50%)	66%
Fatigue	10 (38%)	69%
Vomiting	9 (35%)	
Hypokalemia	8 (31%)	22%
Pyrexia	8 (31%)	
Decreased appetite	7 (27%)	
Hypocalcemia	7 (27%)	
Insomnia	6 (23%)	

1. Richardson et al; Panorama 2; Blood: 122 (14), 2013.

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Adverse Events
Occurring in ≥5% (Grade 3/4) of Patients (n = 26)

AE, regardless of relationship to study drugs	Grade 3/4	
Number of Subjects with at Least One Event	20 (77%)	Pan/ Bor/Dex[1]
Anemia	10 (38%)	15%
Thrombocytopenia	10 (38%)	64%
Neutropenia	5 (19%)	15%
Fatigue	3 (12%)	20%
Decreased appetite	2 (8%)	
Diarrhea	2 (8%)	20%
Elevated creatinine	2 (8%)	
Hyperglycemia	2 (8%)	
Hypertension	2 (8%)	
Hyponatremia	2 (8%)	

1. Richardson et al; Panorama 2; Blood: 122 (14), 2013.

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Relative Dose Intensity

	Cohort	1	2	3	4
Carfilzomib		20/27	20/27	20/36	20/45
	N	4	4	13	5
	Mean (%)	100	96	98	89
Panobinostat		15	20	20	20
	Mean (%)	94	92	93	90

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Preliminary Efficacy Data

Best confirmed response	N = 26 (%)	BTZ refractory N = 16 (%)
Overall response (CR + VGPR + PR)	**12 (46)**	**7 (44)**
Complete response	1 (4)	1 (6)
VGPR	5 (19)	1 (6)
Partial response	6 (23)	5 (31)
MR	3 (12)	1 (6)
SD	4 (15)	3 (19)
PD	6 (23)	4 (25)

- All responses occurred in the first 2 cycles
- Two patients maintained response for 18 months
- Median DOR is 7.5 months and 8 patients remain on treatment
- 1 patient was not evaluable for response

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Patient Disposition
Prolonged Study Participation

	N = 26
Patients ongoing	8 (31%)
Off treatment	18 (69%)
In follow-up	12 (46%)
Off study	6 (23%)
Death	5 (19%)
Withdrew consent	0 (0%)
Lost due to follow up	1 (4%)

- Patients have been on study an average of 4.6 months (range <1-20)
- 14 (78%) patients discontinued treatment secondary to progression
- 4 (22%) patients discontinued to AE; 1 death; 2 asthenia; 1 GI toxicity

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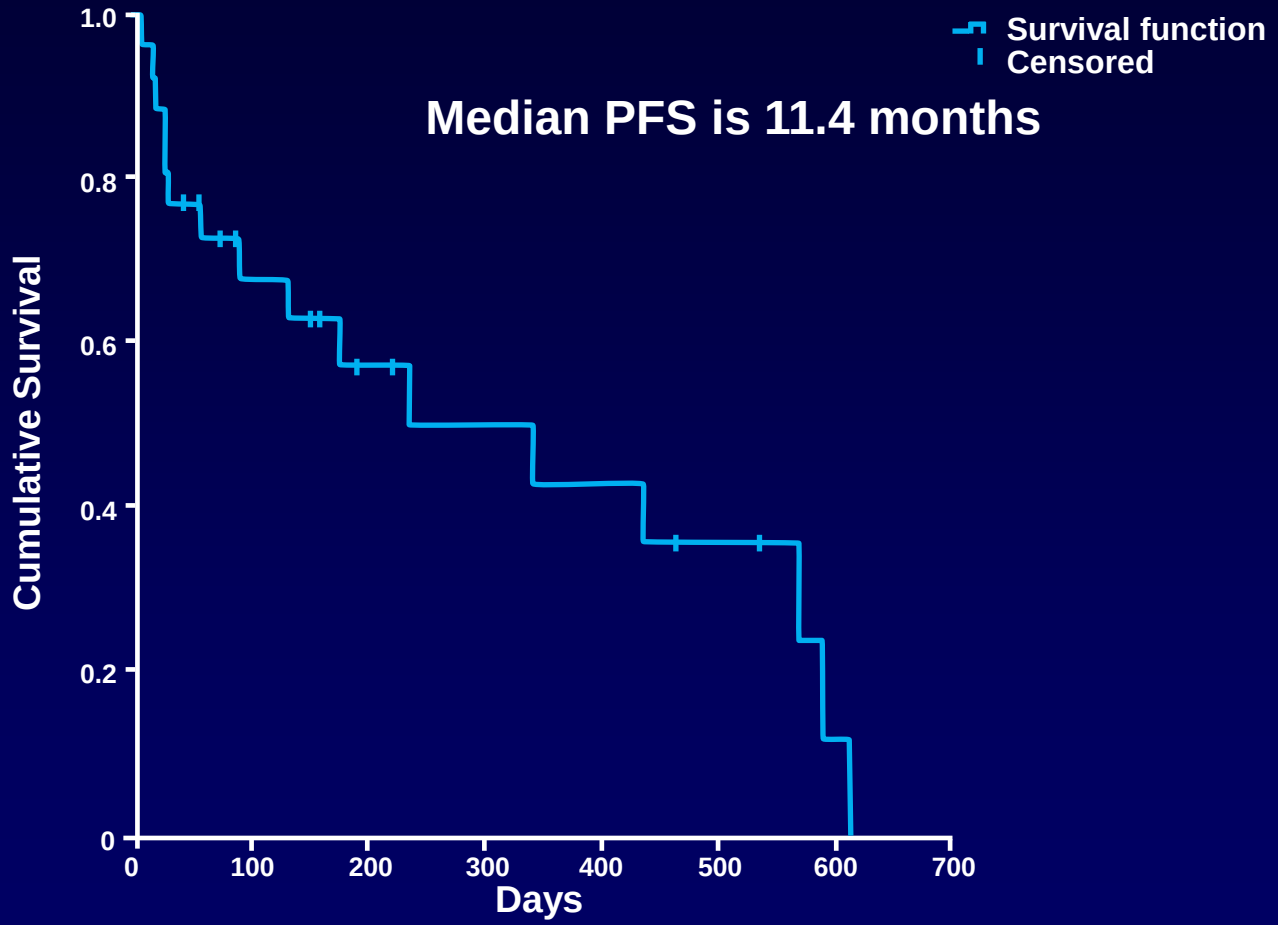
Progression-Free Survival Entire Cohort



Median PFS is 11.4 months (95% CI is 6.8-16 months)

With a median f/u of 8.7 months over 80% of patients are alive

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Conclusions & Future Directions

- The combination of carfilzomib and panobinostat is safe and effective with manageable adverse events in patients with relapsed and refractory myeloma
- The MTD of the combination in this study is carfilzomib 36mg/m^2 3 of 4 weeks and panobinostat at 20 mg TIW 3 of 4 weeks
- No unexpected toxicities were seen
- At the MTD patients were able to tolerate more than 90% of the planned doses
- Tolerance, response rate, DOR, PFS and OS are favorable when compared to similar studies using different dosing strategies, Shah et al (ASH 2012) and Berdeja et al (ASH 2013)

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