Phase 1, Multicenter, Open-label, Dose-escalation, Combination Study of Pomalidomide (POM), Marizomib (MRZ), and Dexamethasone (Lo-Dex) in Patients with Relapsed and Refractory Multiple Myeloma

Study NPI-0052-107

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PI Disclosures

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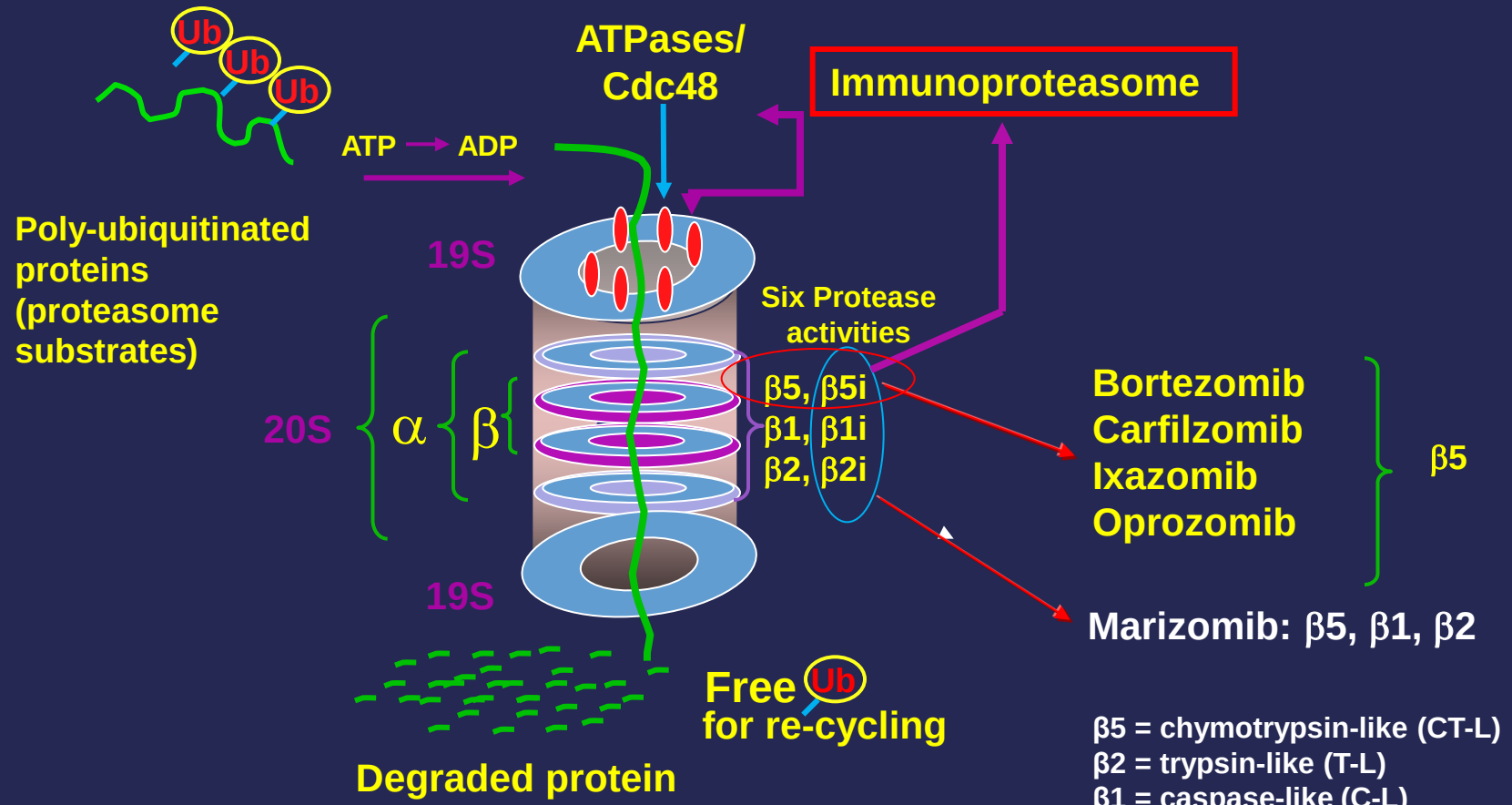
Proteasome Inhibitors: Marizomib is a First in Class Pan Proteasome Inhibitor

Adapted from Paul Richardson et al, IMWG, Kyoto, 2013

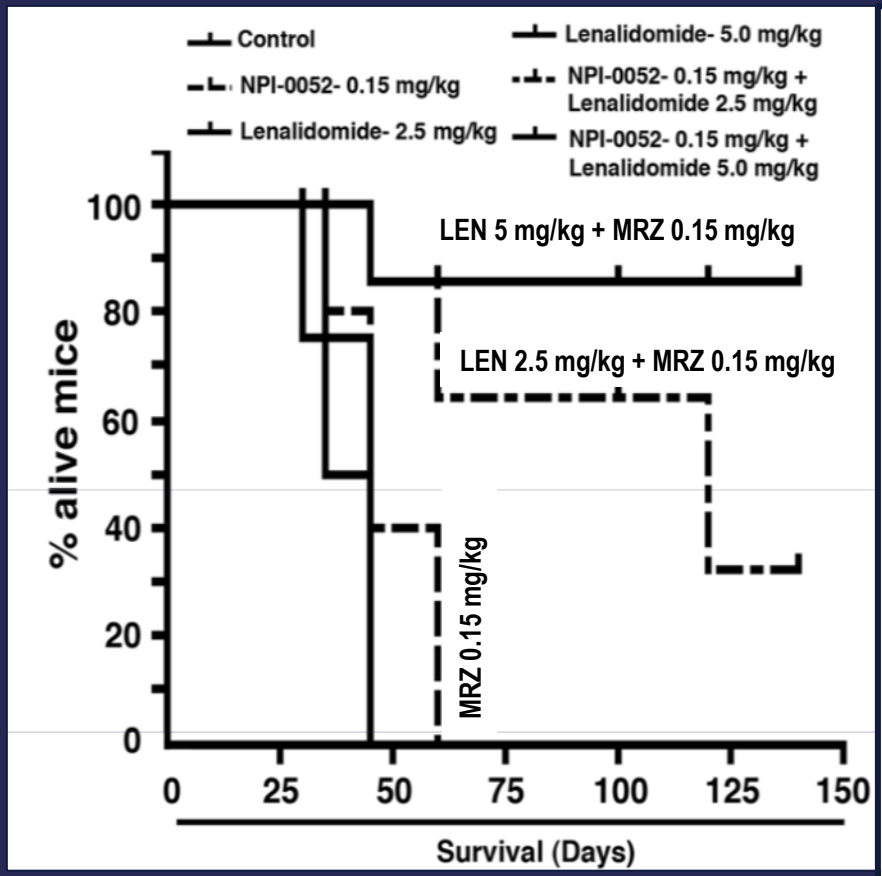


Ref: Lawasut P, Chauhan D et al. Curr Hematol Malig Rep. 2012: 258-66.

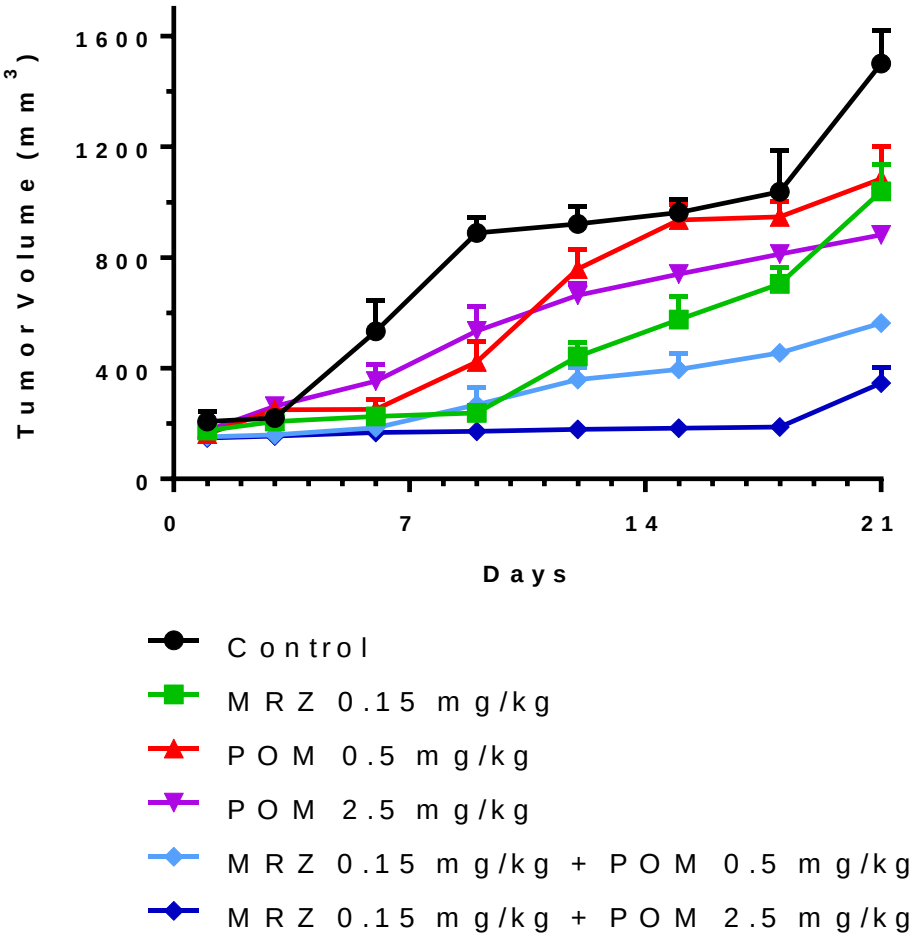
26S PROTEASOME

Synergistic Efficacy of Marizomib (MRZ) with IMiDs: MM1.S Myeloma Mouse Tumor Model

MRZ + Lenalidomide (LEN)



MRZ + Pomalidomide (POM)



Chauhan et al., 2010 Blood;115:834
Das et al., 2015 Br J Haematol; in press

Objectives

Primary Objective

- To determine the MTD and/or RP2D of pomalidomide + marizomib + low-dexamethasone (PMD)

Secondary Objectives

- To evaluate safety
- To characterize the clinical response using IMWG criteria

Exploratory

- To evaluate pharmacokinetics (PK)
- To assess pharmacodynamic (PD) activity
- To assess clinical response relative to genetic profile

Dose Cohorts

Cohort	POM (mg)	IV MRZ BIW (mg/m^2)	Lo-Dex	Patients Enrolled
Schedule	qd x 21	Days 1, 4, 8, 11 (120 min infusion)	10 mg qd on the day of and after MRZ and on Days 15, 16, 22, 23	
✓ 1	3	0.3	10 mg (5 mg if >75 years)	5*
✓ 2	3	0.4		3
✓ 3	4	0.4		3
✓ 4	4	0.5		3
RP2D Expansion	4	0.5		20**

* 2 patients in Cohort 1 were not evaluable for DLTs due to missed doses and were replaced

** RP2D dose-expansion enrollment as of Sept 15, 2015

Inclusion Criteria

- ≥18 years old
- Measurable disease
- Must have received prior lenalidomide (LEN) and bortezomib (BZ)
- Relapsed disease - must have achieved ≥ stable disease for at least one cycle then developed PD
- Refractory disease defined as progression during or within 60 days after last regimen
- Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2

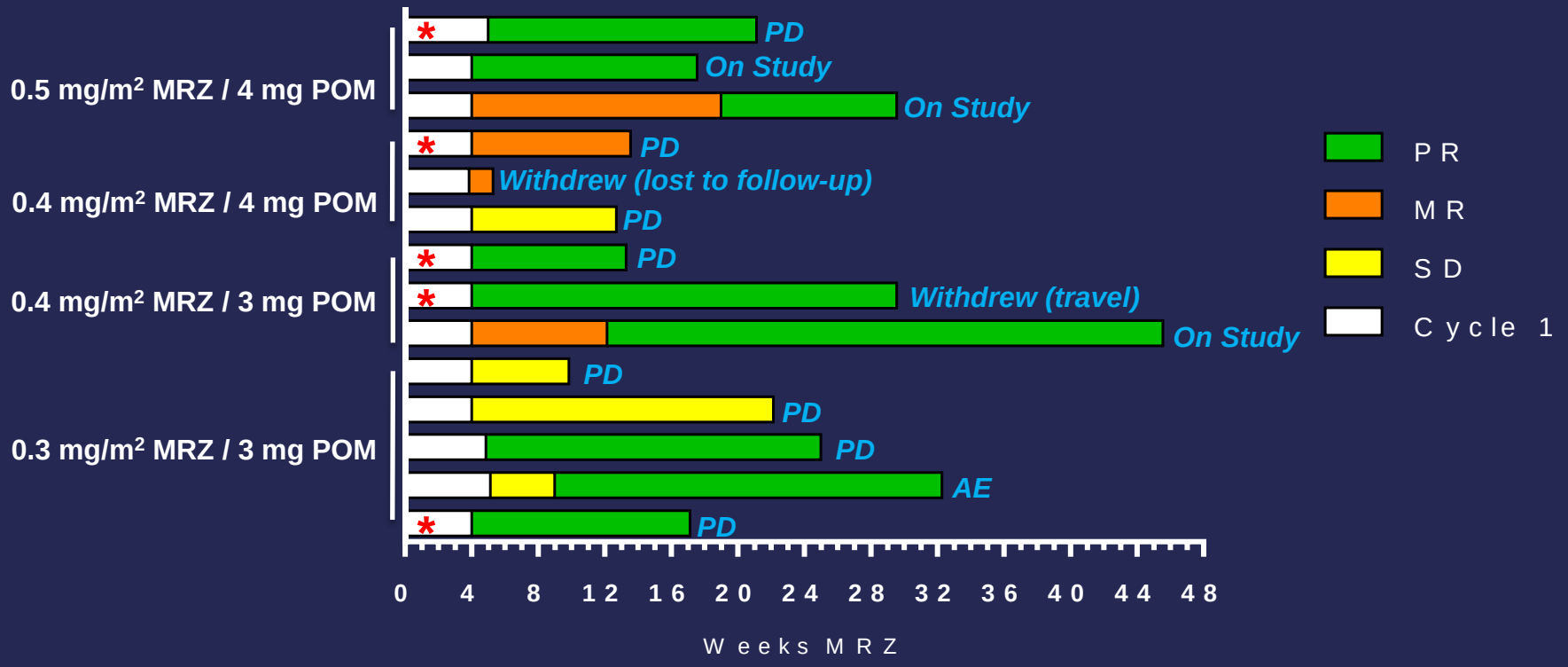
Baseline Characteristics

Parameter	n=14
Age (yrs, median, range)	61 (31-69)
Male, %	71%
Prior regimens (median, range)	4.5 (2-15)
Prior therapies (%)	
LEN	100% (14/14)
BORTEZOMIB (BZ)	100% (14/14)
CARFILZOMIB (CFZ)	50% (7/14)
Cytogenetic Profile, %	
High-risk*	36% (5/14)
Standard-risk	43% (6/14)
Missing	21% (3/14)

* High-risk defined as 17p deletion and/or t(4;14) translocation

Preliminary Data
Data Cut as of 22 July 2015

Weeks on MRZ by Patient and Response



*High risk cytogenetics as defined by 17p deletion and/or t(4;14) translocation

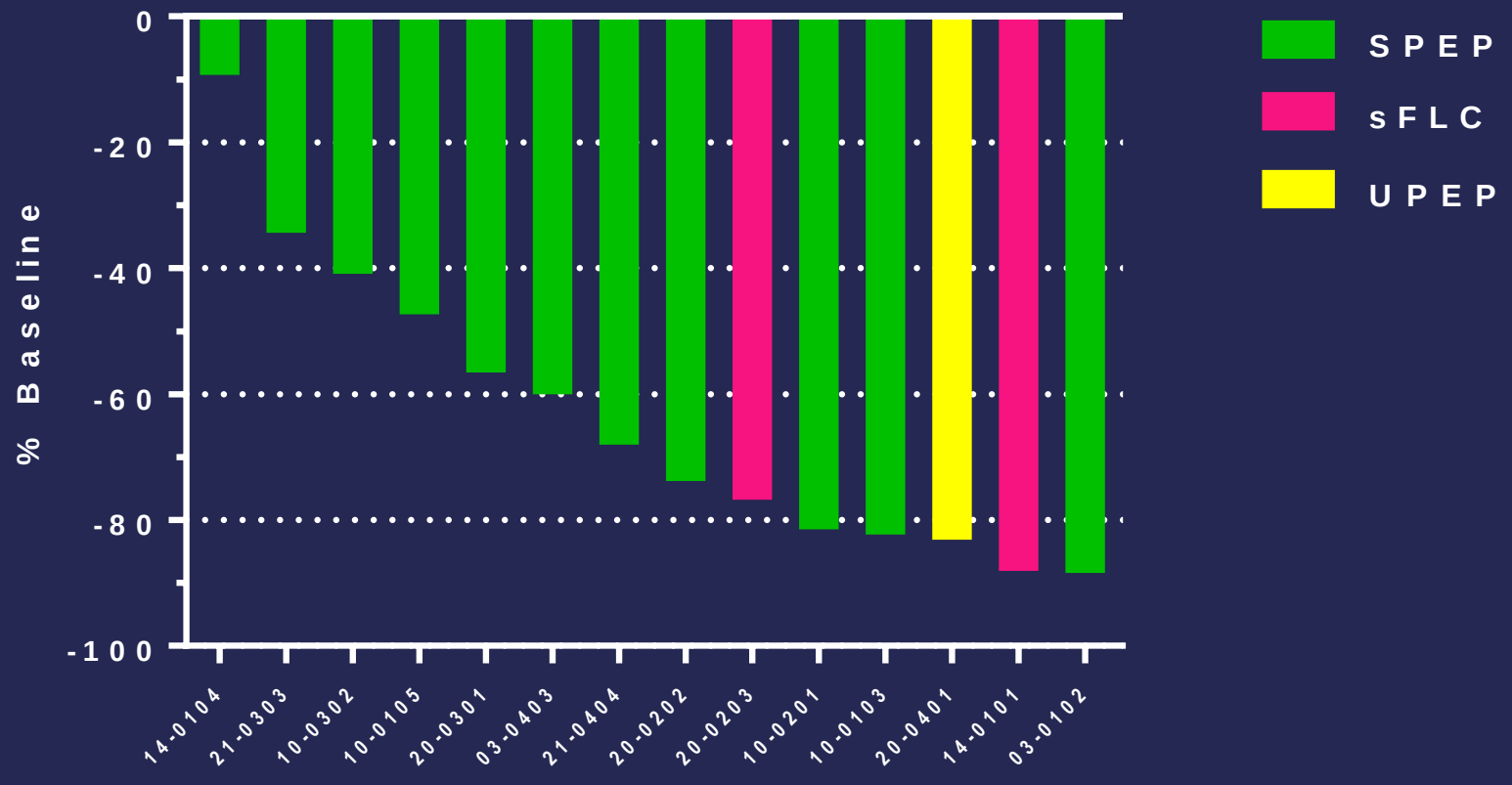
Preliminary Data
Data Cut as of 15 Sep 2015

AEs Related to Study Treatment

Number (%) of Related AEs in 2 or More Patients (N=14)		
Preferred Term	All AEs	Grade 3/4 AEs
Neutropenia	7 (50)	5 (36)
Fatigue	6 (43)	0
Anaemia	5 (36)	2 (14)
Thrombocytopenia	5 (36)	2 (14)
Oedema peripheral	3 (21)	0
Deep vein thrombosis	2 (14)	0
Dyspnoea	2 (14)	0
Insomnia	2 (14)	1 (7)
Muscle spasms	2 (14)	0
Nausea	2 (14)	0
Neuropathy peripheral	2 (14)	0
Urinary tract infection	2 (14)	0
White blood cell count decreased	2 (14)	1 (7)

- No DLTs during dose-escalation
- 1 patient with Grade 2 tumor lysis syndrome related to study treatment
- 1 patient with Grade 1 increased peripheral neuropathy related to POM
- 1 patient with Grade 1 peripheral neuropathy related to POM and MRZ
- 1 patient died 62 days after study treatment due to disease progression
- 1 patient died 95 days after study treatment, cause unknown

Change in Myeloma Protein and Best Response from Baseline for All Patients (N=14)



Preliminary Data
Data Cut as of 22 July 2015

Best Response (n=13 evaluable pts)

IMWG Best Response	PMD (N=13)
PR	62% (n=8)
MR	15% (n=2)
SD	23% (n=3)

ORR = 62%
CBR = 79%

Summary includes 13 patients with data through at least C3D1

All 13 patients had a decrease in myeloma protein by C2D1, while 6/8 patients with PR achieved PR by C2D1 – first time response assessed

Preliminary Data
Data Cut as of 22 July 2015

Response by Cytogenetics

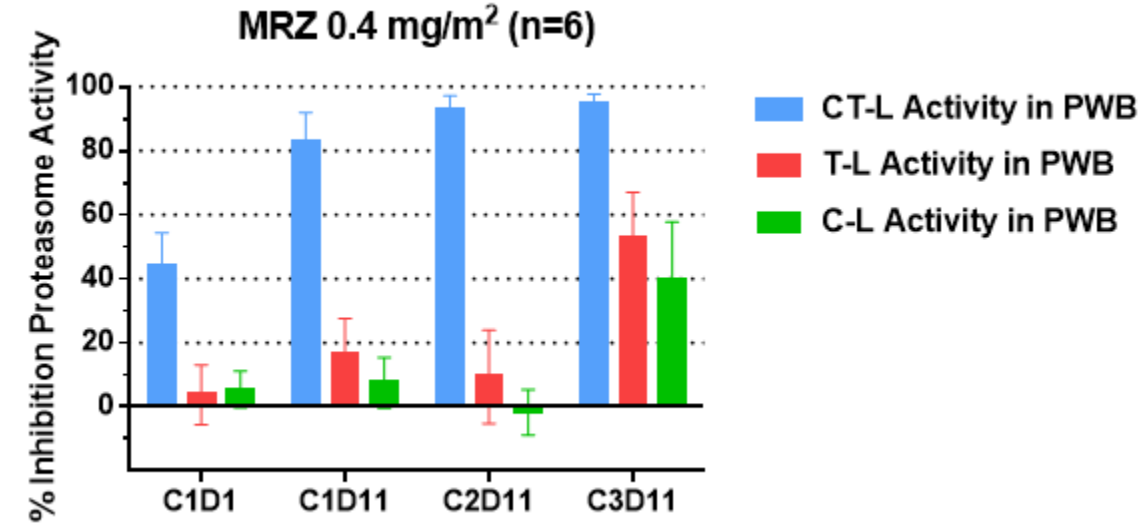
Cytogenetics	ORR PR or better	CBR MR or better
High Risk	4 / 5	5 / 5
Standard Risk	3 / 6	4 / 6
Unknown	1 / 2	1 / 2

High risk is 17p deletion and/or t(4;14) translocation

Preliminary Data
Data Cut as of 22 July 2015

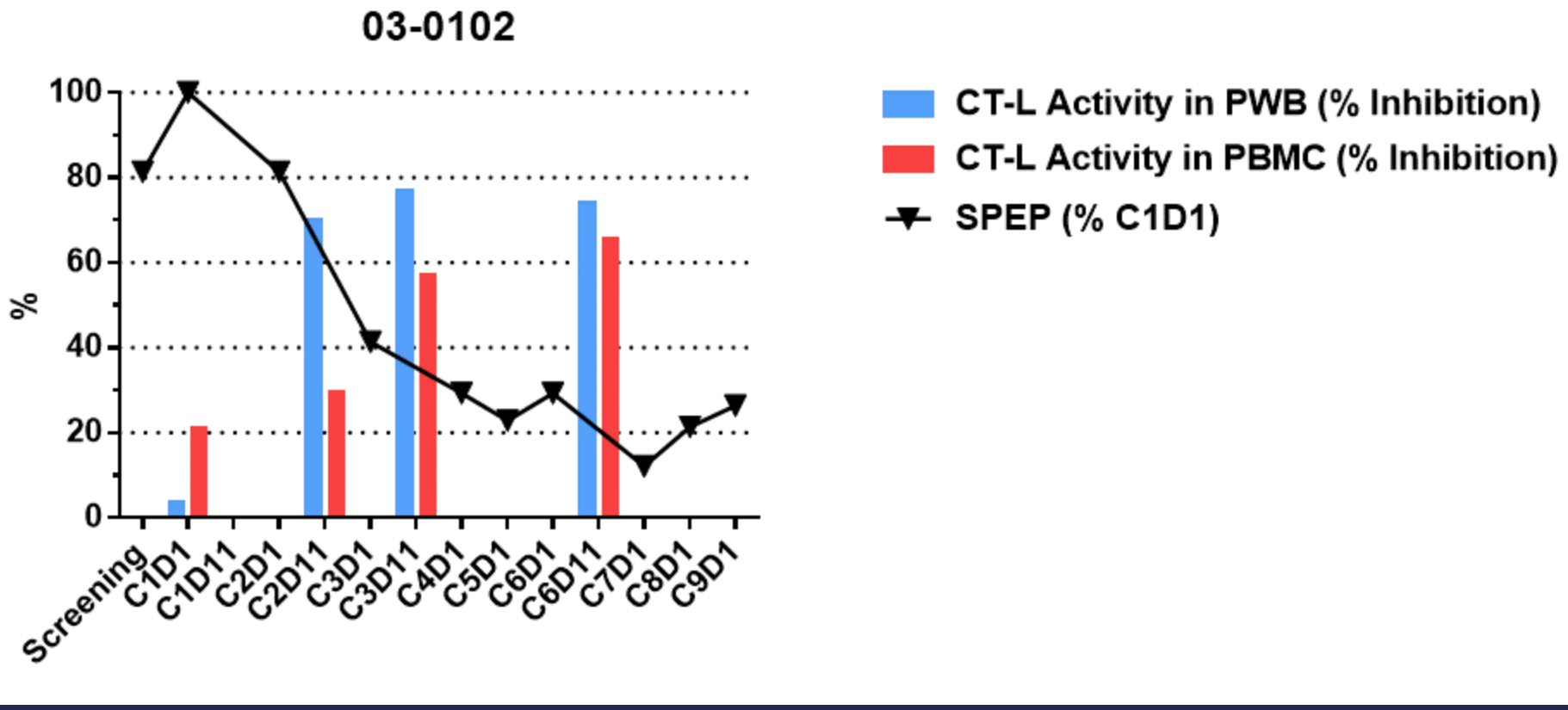
MRZ PK & PD: Short $T_{1/2}$ with Long PD

- **PK**
  - Short $T_{1/2}$ (< 30 min), C_{max} 1-14 ng/mL, T_{max} 40-125 min
  - MRZ PK parameters similar to previous clinical experience
  - No impact on POM or DEX PK
- **PD – Inhibition of Proteasome Activity**
  - Rapid and robust inhibition of CT-L activity
  - Evolving inhibition of T-L & C-L over time at MRZ 0.4 mg/m^2



PK data to 11Mar 2015
PD data to 31Jul 2015

Cohort 1
POM=3 mg / MRZ=0.3 mg/m^2 / Lo-DEX=10 mg



Best IMWG Response	**PR**
Cytogenetic Risk Status	**del13q (other markers not determined), normodiploid**
Prior Therapy	**5 regimens including BZ, LEN & BZ/DEX/ perifosine; last regimen CFZ/DEX refractory**

Dose-Expansion Stage Ongoing

- As of September 17, 2015

  14 escalation patients
  20 expansion patients
  34 patients total

- 17 of 34 patients have investigator-reported response data through C3D1

ORR	12/17 (71%)
CBR	14/17 (82%)

- 1 unconfirmed VGPR

Conclusions & Future Directions

- RP2D is POM 4mg + MRZ 0.5 mg/m2 + Lo-DEX 10 mg
  - Enrollment of expansion cohort ongoing
- PMD was generally well tolerated
  - No DLTs
  - Most common Grade 3 & 4 AEs related to study treatment were neutropenia, anemia, and thrombocytopenia
  - MRZ does not appear to increase the incidence or severity of POM/Lo-DEX AEs
- MRZ has a short elimination half life and long lasting PD effect
  - Clinically meaningful inhibition of all three proteasome subunits with about 100% inhibition of the CT-L subunit as early as C1D11
- PMD has a rapid onset of activity as early as C2D1
- PMD combination is demonstrating promising anti-myeloma activity in heavily pretreated patients
- Ongoing Study: MRZ + Avastin Phase 1 study in recurrent glioblastoma ongoing
- Planned Study: Phase 1 study with oral MRZ formulation in RR MM

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Triphase / MMRC	Investigational Sites					
Mo Trikha, PhD Steve Reich, MD Karl Cremer, PharmD Jennifer Ki Amanda Brown Lollie Nelson Sherri Taylor Daleen Herman Sofia Cendrawan Paul Bassett Karen Woolley Nancy Levin, PhD Mike White Steve Michelson Aura Fratian	Dana Farber Cancer Institute Jacob Laubach, MD Paul Richardson, MD Sara Tse Heidi DiPietro Kristen Cummings	University of Maryland Ashraf Badros, MD Pat Lesho Sunita Philips Emily Lederer	Karmanos Cancer Center Jeffrey Zonder, MD Colleen Neveux Kate Murphy Christy Houde Amanda Sehmera Silva Pregja	University of Chicago Todd Zimmerman, MD Cara Rosenbaum, MD Kyrsten Brooks, Erica Severson Jennifer Nam	Peter MacCallum Cancer Centre Simon Harrison, MD Amit Khot, MD Emma Nicholls Carrie Donohoe Alicia Snowden	Prince Alfred Hospital Andrew Spencer, MD Krystal Bergin, MD Sarah Nadjidai