3326 PMD-107: Marizomib, Pomalidomide and Low-dose Dexamethasone Combination Study in Relapsed/Refractory Multiple Myeloma (NCT02103335): Full Enrollment Results from a Phase 1, Multicenter, Open Label Study

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Abstract

Marizomib (MRZ) is a novel, irreversible, pan subunit proteasome inhibitor (PI) with preclinical evidence demonstrating *in vitro* and *in vivo* activity in multiple myeloma (MM). This study was designed to evaluate the safety and antimyeloma activity of pomalidomide (POM), MRZ and low dose dexamethasone (Lo-DEX) (PMD) in patients with relapsed and refractory multiple myeloma (RRMM).

Thirty-eight heavily pretreated patients with RRMM were enrolled [dose-escalation cohort (n=14); recommended Phase 2 dose (RP2D) cohort (n=24)]. IV MRZ (0.3 to 0.5 mg/m^2) was administered on Days (D) 1, 4, 8, 11; POM (3 or 4 mg) on D1 through 21; and Lo-DEX (5 or 10 mg) on D1, 2, 4, 5, 8, 9, 11, 12, 15, 16, 22, 23 of every 28-D cycle. Patients received a median of 4 (range 1-9) prior lines of therapy; 100% received prior lenalidomide (LEN) and bortezomib (BTZ), 34% carfilzomib (CFZ), and 50% thalidomide. 53% of patients were refractory to both LEN and BTZ and 21% were refractory to LEN, BTZ, and CFZ. There were no dose limiting toxicities during the study. The most common study treatment related ≥Grade 3 adverse events (AEs) were neutropenia (11/38 pts: 29%), pneumonia (4/38 pts 11%), anemia (4/38 pts; 11%), thrombocytopenia (4/38 pts; 11%), and febrile neutropenia (2/38 pts; 5%), with three grade 4 AEs (neutropenia related to POM, thrombocytopenia related to POM/MRZ, and viral infection related to DEX), and one grade 5 AE (cardio-respiratory arrest from a suspected PE related to POM). Overall, MRZ was well tolerated, did not add to the incidence or severity of POM/Lo-DEX AEs and the regimen may have fewer hematological and infectious AEs compared to that observed with POM/Lo-DEX.

MRZ pharmacokinetic analysis revealed that it was rapidly cleared with a short $T_{1/2}$ (6.2-11 mins) and a large volume of distribution (41-86 L) suggesting extensive tissue distribution. Pharmacodynamic analysis demonstrated rapid and robust inhibition of chymotrypsin-like (CT-L) activity in both packed whole blood (PWB) and peripheral blood mononuclear cells (PMBCs), reflecting the irreversible binding nature of MRZ. Evolving inhibition of trypsin-like (T-L) and caspase-like (C-L) proteasome activity was also observed in PWB and PBMC with continued dosing.

The overall response rate (ORR) and clinical benefit rate (CBR) for the 36 response evaluable patients was 53% (19/36) and 64% (23/36), respectively. Subpopulation analysis demonstrated an ORR of 50% (5/10) in high risk cytogenetic patients, 56% (10/18) in LEN/BTZ refractory patients, 71% (5/7) in LEN/BTZ/CFZ refractory patients and 80% (8/10) in CFZ refractory patients. These data compare favorably against POM/Lo-DEX with a near doubling of ORR in both the total patient population and the double refractory patients. Substantial activity in high-risk patients that are triple refractory and in patients that are refractory to CFZ in prior last regimen was observed. MRZ activity in RRMM patients exposed and/or refractory to multiple PIs is likely a consequence of its unique pan proteasome subunit inhibitory actions. In conclusion, MRZ in combination with POM and Lo-DEX was well tolerated and demonstrated promising activity in heavily pretreated, high-risk RRMM patients.

Study Objectives

Primary: To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D)

Secondary: Evaluate safety and best response using IMWG uniform response criteria

Exploratory: Pharmacokinetics (PK), pharmacodynamic (PD) activity and assess response relative to genetic profile

Key Eligibility Criteria

- ≥18 years old
- Measurable disease
- Received prior LEN and BTZ
- Achieved ≥ stable disease for at least 1 cycle before developing progressive disease
- Documented refractory disease ≤ 60 days after most recent therapy

Treatment Regimens

IV MRZ 0.3 to 0.5mg/m^2 / 2hr infusion

POM 3 or 4mg / daily

Lo-DEX 10mg / daily (5mg if >75yrs)

Dosing by Cohort

Cohort	Oral POM (mg)	IV MRZ (mg/m^2)	Oral DEX (mg)
1	3	0.3	10mg (≤75 years) OR 5mg (≥75)
2	3	0.4	
3	4	0.4	
4	4	0.5	
RP2D	4	0.5	

Results (unaudited data through 28 Jun 2016)

Demographics and Baseline Characteristics

Parameter	N = 38
Age (yrs, median, range)	61 (31-76)
Male, %	27 (71%)
Median prior regimens (range)	4 (1-9)
Prior LEN	38 (100%)
Prior BZ	38 (100%)
Prior CFZ	13 (34%)
Prior THAL	19 (50%)
Prior Oprozomib	3 (8%)
Refractory to LEN	30 (79%)
Refractory to BTZ	23 (61%)
Refractory to CFZ	11 (29%)
Refractory to BTZ/LEN	20 (53%)
Refractory to BTZ/LEN/CFZ	8 (21%)
Cytogenetic Profile • High-risk (17p deletion and or t(4:14)translocation) • Standard-risk • Unknown	 11 (29%) 19 (50%) 8 (21%)

Most common treatment related AEs (≥5% of patients) and ≥Grade 3 AEs (≥3% of patients) (N=38)

Preferred Term n (%)	All TRAEs	≥Grade 3 TRAEs
Neutropenia	13 (34)	11 (29)
Fatigue	10 (26)	0
Thrombocytopenia	8 (21)	4 (11)
Oedema peripheral	8 (21)	0
Anaemia	7 (18)	4 (11)
Dyspnoea	6 (16)	0
Nausea	6 (16)	0
Muscle spasms	6 (16)	0
Pneumonia	5 (13)	4 (11)
Constipation	5 (13)	1 (3)
Diarrhoea	5 (13)	1 (3)
Insomnia	5 (13)	1 (3)
Leukopenia	4 (11)	2 (5)
Upper respiratory tract infection	4 (11)	0
Deep vein thrombosis	3 (8)	0
Depression	3 (8)	0
Febrile Neutropenia	2 (5)	2 (5)

AEs assessed according to NCI CTCAE v4.03

DLTs: There were no DLTs in the study

4 ≥Grade 4 AEs:

- 1 Grade 5 cardio-respiratory arrest (POM)
- 1 Grade 4 neutropenia (POM)
- 1 Grade 4 thrombocytopenia (POM/MRZ)
- 1 Grade 4 picornavirus infection (DEX)

2 Deaths on study:

- Cardio-respiratory arrest in cycle 1 (POM)
- GI bleeding from plasmacytoma (PD) in cycle 2

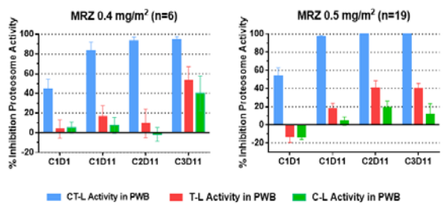
MRZ Pharmacokinetics & Pharmacodynamics

Pharmacokinetic Summary

- MRZ has a short $T_{1/2}$ (6.2-11 mins), high volume of distribution (41-86 L) and high clearance (252-564 L/hr) similar to previous trials
- PK data is supportive of rapid hydrolysis of MRZ and irreversible binding to proteasomes
- No effect of co-administration of MRZ on DEX or POM PK

Pharmacokinetic Summary

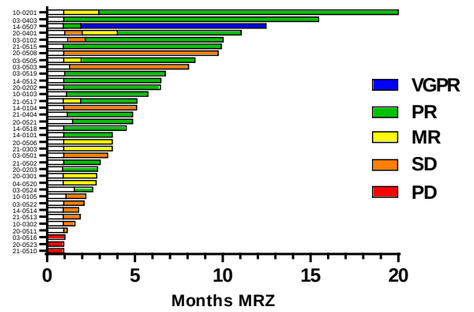
- Rapid inhibition of CT-L activity with evolving inhibition of T-L and C-L activity over time



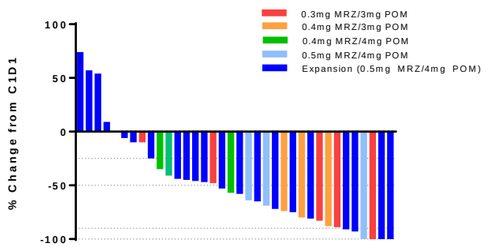
Best Response in Response-Evaluable Patients (N=36)

IMWG Best Response	Number (%)
ORR (≥ PR)	19/36 (53)
CBR (≥ MR)	23/36 (64)
VGPR	1/36 (3)
PR	18/36 (50)
MR	4/36 (11)
SD	10/36 (28)
PD	3/36 (8)

Best Response by Patient (N=36)



Myeloma Protein: Maximum Change from Baseline in Response-Evaluable Patients (N=36)



Best Response in Response-Evaluable Patients by Cytogenetics

Cytogenetic Status n (%)	ORR (≥ PR)	CBR (≥ MR)
High risk	5/10 (50)	7/10 (70)
Standard risk	10/18 (56)	11/18 (61)
Unknown	3/8 (38)	4/8 (50)

Best Response in Response-Evaluable Patients by Prior Therapy

Prior Antimyeloma Therapy n (%)	ORR (≥ PR)	CBR (≥ MR)
Refractory to LEN	15/30 (50)	19/30 (63)
Refractory to BTZ	12/21 (57)	13/21 (62)
Refractory to CFZ	8/10 (80)	9/10 (90)
Double Refractory (LEN & BTZ)	10/18 (56)	12/18 (67)
Triple Refractory (LEN, BTZ, & CFZ)	5/7 (71)	6/7 (86)
Refractory to LEN in Last Regimen	7/15 (47)	10/15 (67)
Refractory to BTZ in Last Regimen	4/7 (57)	6/7 (86)
Refractory to CFZ in Last Regimen	6/7 (86)	7/7 (100)

PMD Progression Free Survival (PFS) & Overall Survival (OS)

Parameter (Months)	ITT (N=38)	LEN/BTZ Refractory	LEN/BTZ/ CFZ Refractory	High-Risk Cytogenetics
Median DOR (≥ PR)	5.8	N.D.	N.D.	N.D.
Median PFS	4.6	4.0	3.7	3.3
Median OS	13.3	13.3m	13.3	13.6

N.D: Not Determined

Conclusions & Future Directions

- PMD was well tolerated; no DLTs
  - Most common Grade 3 TRAEs were similar to those observed with POM/Lo-DEX and were not increased in incidence or severity compared to POM/Lo-DEX AEs
- MRZ has a short $T_{1/2}$ and large V_D; MRZ does not affect the PK of POM or Lo-DEX
- Robust pan proteasome inhibition observed in most patients within 2 dosing cycles
- PMD has a rapid onset of activity (as early as C2D1) with a higher ORR compared to historical POM/Lo-DEX studies, but comparable DOR, PFS and OS to POM/Lo-DEX
- MRZ, which has the ability to cross the blood brain barrier, has demonstrated activity in WHO Grade IV recurrent glioma in combination with bevacizumab in CNS-MM (Badros et al., ASH Abstract #2118) , and is currently being evaluated in combination with radiotherapy and temozolomide in frontline WHO Grade IV glioma
- PMD is demonstrating promising antimyeloma activity in heavily pretreated, high risk, and double/triple refractory patients suggesting that it should be further evaluated in RRMM