4220 Phase 1, Multicenter, Open-Label, Combination Study (NPI-0052-107; NCT02103335) of Pomalidomide (POM), Marizomib (MRZ), and Low-Dose Dexamethasone (Lo-DEX) in Patients with Relapsed and Refractory Multiple Myeloma (RRMM) – Preliminary Results

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Abstract

Marizomib (MRZ) is a novel, irreversible, pan subunit proteasome inhibitor (PI). The combination of POM and MRZ has demonstrated synergistic antimyeloma activity *in vitro* and *in vivo* (Das et al., 2015 Br J Haematol; epub ahead of print). This study was designed to evaluate the safety and antimyeloma activity of POM, MRZ and Lo-DEX (PMD) in patients with RRMM.

Thirty-eight heavily pretreated patients with relapsed and refractory multiple myeloma (RRMM) were enrolled [dose-escalation (n=14); RP2D (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 5 prior lines of therapy; 100% received prior lenalidomide (LEN) and bortezomib (BZ), 32% carfilzomib (CFZ), and 50% thalidomide (THAL).

There were no DLTs in the study. The most common treatment related Grade 3 AEs were neutropenia (9 pts), pneumonia (4 pts), anemia (3 pts), thrombocytopenia (2 pts), and febrile neutropenia (2 pts). The ORR and CBR for the 29 response evaluable pts was 59% and 66%, respectively; for high risk cytogenetic patients (n=6), ORR and CBR were 67% and 83%; for double refractory patients (n=15), ORR and CBR were 67 and 73%; for triple refractory patients (n=6), ORR and CBR were both 83%. MRZ was cleared rapidly but exhibited a robust pharmacodynamic impact due to its irreversible binding to all three proteasome subunits.

In summary, MRZ in combination with POM and Lo-DEX was well tolerated and demonstrated promising activity in heavily pretreated RRMM patients.

Study Objectives

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

Secondary: Evaluate safety and IMWG best response

Exploratory: Pharmacokinetics (PK), pharmacodynamic (PD) activity, and clinical response relative to cytogenetic profile

Study Design and Methods

- Phase 1, multicenter, open-label study
- 3+3 dose-escalation; expansion cohort at RP2D

Treatment Regimens

IV MRZ (twice weekly)

0.3 to 0.5 mg/m^2 over 120 minutes

POM

3 or 4 mg once daily

Lo-DEX

10 mg once daily (5 mg if > 75 yr old)

Key Eligibility Criteria

- ≥18 years old
- Measurable disease
- Received prior LEN and BZ
- Relapsed disease: Achieved ≥ stable disease for at least 1 cycle before developing PD
- Refractory disease: Progression during or within 60 days after last regimen

Analysis

Safety population: Patients who received at least 1 MRZ dose

Best response population: Investigator IMWG response assessment in response evaluable patients with data at least through C3D1

Adverse events (AEs) and laboratory parameters: Assessed according to NCI CTCAE (v4.03) grading for severity; "related" refers to any one of the 3 study treatments

Results (unaudited data through 23 Nov 2015)

Demographics and Baseline Characteristics

Parameter	N = 38
Age (yrs, median, range)	61 (31-76)
Male, %	27 (71%)
Median prior regimens (range)	5 (2-14)
Prior LEN	38 (100%)
Prior BZ	38 (100%)
Prior CFZ	12 (32%)
Prior THAL	19 (50%)
Prior Oprozomib	3 (8%)
Cytogenetic Profile	
High-risk*	9 (24%)
Standard-risk	19 (50%)
Unknown	10 (26%)

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

Most common AEs (≥5% of patients) and Grade 3 AEs (≥2% of patients) (N=38)

Preferred Term n (%)	All AEs	All AEs Related	Grade 3 AEs	Grade 3 AEs Related
Dyspnoea	14 (37)	5 (13)	1 (3)	0
Constipation	13 (34)	3 (8)	0	0
Fatigue	13 (34)	10 (26)	0	0
Neutropenia*	12 (32)	11 (29)	9 (24)	9 (24)
Anaemia	8 (21)	8 (21)	4 (11)	3 (8)
Back pain	8 (21)	0	3 (8)	0
Nausea	8 (21)	5 (13)	0	0
Diarrhoea	7 (18)	3 (8)	1 (3)	0
Oedema peripheral	7 (18)	6 (16)	0	0
Thrombocytopenia	7 (18)	6 (16)	2 (5)	2 (5)
Insomnia	6 (16)	6 (16)	1 (3)	1 (3)
Muscle spasms	6 (16)	4 (11)	0	0
Upper respiratory tract infection	6 (16)	2 (5)	0	0
Hypokalaemia	5 (13)	1 (3)	1 (3)	0
Pneumonia	4 (11)	4 (11)	4 (11)	4 (11)
Febrile neutropenia	2 (5)	2 (5)	2 (5)	2 (5)

DLTs: There were no DLTs in the study

AEs of Interest:

- *1 Grade 4 neutropenia related to POM
- Grade 2 tumor lysis syndrome, related PMD
- Grade 1 peripheral neuropathy, related POM and Grade 1 peripheral neuropathy, related POM/MRZ)

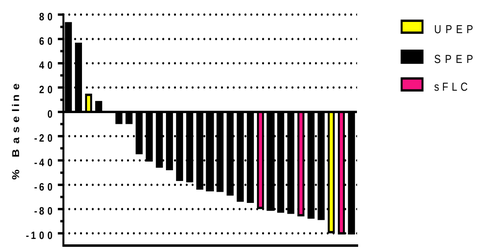
9 Deaths:

5 patients: Disease progression
2 patients: Sepsis 4-5 months after study
1 patient: Unknown cause 95 days after treatment
1 patient: Cardiopulmonary arrest in Cycle 1, possibly related to POM, no autopsy

MRZ PK Parameters

Parameter (Units)	0.3 mg/m^2 (SD, n)	0.4 mg/m^2 (SD, n)	0.5 mg/m^2 (SD, n)
$T_{1/2}$ (min)	14.9 (n=1)	7.12 (1.2, 2)	14.2 (11, 13)
T_{max} (min)	92.3 (46,3)	103.4 (36, 5)	112 (19, 17)
C_{max} (ng/mL)	2.35 (0.72, 3)	4.47 (5.7, 5)	18.9 (40, 17)
AUC_{last} (min*ng/mL)	126 (48, 3)	136 (48, 5)	731 (1200, 17)
Vz (mL/m^2)	44246 (n=1)	35111 (11680, 2)	37903 (40658, 13)
CL (mL/min/m^2)	2064 (n=1)	3555 (1713, 2)	2303 (1706, 13)

Myeloma Protein: Maximum Change from Baseline in Efficacy-Evaluable Patients (data ≥ C3D1, n=29)

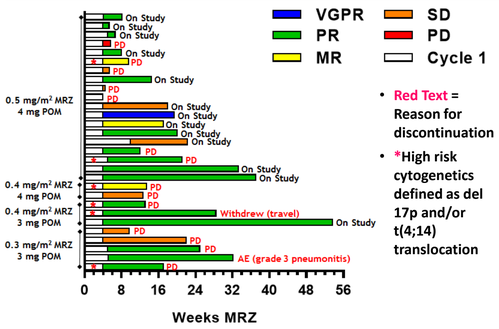


23/29 pts had decrease in myeloma protein by C2D1

Best Response in Efficacy Evaluable Patients (data through at least C3D1, n=29)

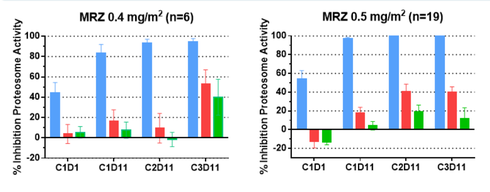
IMWG Best Response	Number (%)
VGPR	1/29 (3)
PR	16/29 (55)
MR	2/29 (7)
SD	8/29 (28)
PD	2/29 (7)
ORR (PR or Better)	17/29 (59)
CBR (MR or Better)	19/29 (66)

Best Response by Dose (n=29)



- Red Text = Reason for discontinuation
- *High risk cytogenetics defined as del 17p and/or t(4;14) translocation

Proteasome Inhibition



Packed Whole Blood (PWB) samples drawn 1 hr post MRZ infusion

Best Response in Efficacy Evaluable Patients by Cytogenetics (n=29)

Cytogenetic Status n (%)	ORR PR or better	CBR MR or better
High risk	4/6 (67)	5/6 (83)
Standard risk	10/16 (62)	10/16 (62)
Unknown	3/7 (43)	4/7 (57)

Best Response by Prior Therapy

Prior Antimyeloma Therapy n (%)	ORR PR or Better	CBR MR or Better
Refractory to LEN	12/23 (52)	14/23 (61)
Refractory to BZ	12/17 (71)	13/17 (76)
Refractory to CFZ	8/10 (80)	8/10 (80)
Double Refractory (LEN & BZ)	10/15 (67)	11/15 (73)
Triple Refractory (LEN, BZ, & CFZ)	5/6 (83)	5/6 (83)
Refractory to LEN in Last Regimen	6/13 (46)	7/13 (54)
Refractory to BZ in Last Regimen	4/5 (80)	4/5 (80)
Refractory to CFZ in Last Regimen	6/7 (86)	6/7 (86)

Conclusions & Future Directions

- RP2D = POM 4 mg + MRZ 0.5 mg/m^2 + Lo-DEX 10 mg
  - Treatment and follow-up ongoing
- PMD was well tolerated; no DLTs
  - Most common Grade 3 treatment related AEs were neutropenia (9 pts), pneumonia (4 pts), anemia (3 pts), thrombocytopenia (2 pts), and febrile neutropenia (2 pts)
  - MRZ does not appear to increase the incidence or severity of 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
- Clinically meaningful inhibition of all 3 proteasome subunits
- PMD has a rapid onset of activity (as early as C2D1)
- PMD is demonstrating promising antimyeloma activity in heavily pretreated, high risk, and double/triple refractory patients
- Ongoing clinical study of MRZ + Avastin in recurrent glioblastoma
- Clinical study with oral MRZ formulation in RRMM is planned