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 antitumor 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 antitumor 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=16); RP2D (n=24)]. IV MRZ (0.3 to 0.5 mg/m²) 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, 4, 8, 11, 15, 12, 15, 16, 22.23, 27, 28, 31, 32, every 4 weeks. Patients received a median of 5 prior lines of therapy; 100% received prior lenalidomide (LEN) and bortezomib (BZ); 32% carfilzomib (CFZ), and 50% thalidomide (THD).

There were no DLTs in the study. The most common related treatment Grade 3 AEs were neutropenia (9 pts), pneumonia (3 pts), thrombocytopenia (2 pts), and febrile neutropenia (2 pts). The CBR and CFB for the 29 response evaluable pts was 99% and 66%, respectively; for high risk cytogenetic patients (n=8), ORR and CFB were 67% and 83%; for double refractory patients (n=15), ORR and CFB were 67% and 73%; for triple refractory patients (n=6), ORR and CFB were both 83%. MRZ was cleared rapidly but exhibited a long terminal half-life, which may be 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/m² over 120 minutes

- 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 achieved at least 1 MRZ dose
Best response population: Investigator IMWG response requirements in 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

Best Response in Efficacy Evaluable Patients by Prior Therapy

Conclusions & Future Directions

- RP2D = POM 4 mg + MRZ 0.5 mg/m² + Lo-DEX 10 mg
- Treatment and follow-up ongoing
- POM is 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 lebile neutropenia (2 pts)
- MRZ does not appear to increase the incidence or severity of POM-Lo-DEX AEs
- MRZ has a short T1/2 and large Vd; MRZ does not affect the PK of POM or Lo-DEX
- Clinical meaningful inhibition of all 3 proteasome subunits
- POM has a rapid onset of action (as early as G2/M)
- PDM is demonstrating promising antitumor 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