Phase 1 Clinical Trial of Marizomib in Patients with Advanced Malignancies Including Multiple Myeloma: Study NPI-0052-102 Final Results

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Introduction
Marizomib (MRZ, NPI-0052; salinosporamide A) is a proteosome inhibitor derived from a marine actinomycete. MRZ enters cells within seconds and forms covalent chemical bonds within minutes both in vitro and in vivo inducing irreversible inhibition at all three active enzyme sites in the proteosome.
- β1 (casepase-like; C-L)
- β2 (trypsin-like; T-L)
- β5 (chymotrypsin-like; CT-L).
MRZ induces a broader spectrum of proteosome inhibition than bortezomib or carfilzomib.

Proteosome inhibition by MRZ is only reversed through cell replacement and/or proteosome reactivation.

At pharmacological concentrations MRZ does not demonstrate toxicity to bone marrow derived progenitor cells of any lineage and exhibits marked synergistic antitumor activity when combined with lenalidomide and pomalidomide in vitro and in vivo models of myeloma. Herein we report the results of a Phase 1 study of MRZ [NPI-0052-102 (NCT00629473)] conducted in Australia and Estonia, which explored both the weekly and twice-weekly dosing schedule in patients with solid tumors, lymphoma, chronic lymphocytic leukemia (CLL), Waldenström's macroglobulinaemia, and relapsed and/or refractory (RR) multiple myeloma (MM).

Study objectives

Primary
- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) for 2 schedules in patients with advanced malignancies
- To evaluate the blood pharmacokinetics (PK) of MRZ

Secondary
- To evaluate the safety and toxicity profile of repeated dosing
- To assess the biological activity (using laboratory correlation studies)
- To describe and assess anti-tumor activity

Patients and methods

Study design
Phase 1, multicenter, open-label study:
- Explored 2 dosing schedules (Schedules A = once-weekly dosing, Schedule B = twice-weekly dosing).
- Classic 3+3 Phase 1 design with expansion cohorts
- Once RP2D was determined additional cohorts of patients with chronic lymphocytic leukemia (CLL), lymphoma, or multiple myeloma were treated

Key eligibility criteria
- Histologically-confirmed advanced malignancy
- Measurable disease by disease specific criteria
- No standard approved therapy available
- Adequate bone marrow, liver, and kidney function
- RP2D restricted to CLL, lymphoma, or RR MM

Drug treatment
Schedule A: Once-weekly dosing (Days 1, 8, 15 of 4-week cycle).
Schedule B: Twice-weekly dosing (Days 1, 4, 8, 11 of 3-week cycle). For patients with MM, dexamethasone (20 mg PO or IV) was given the day before and the day of DEX infusion

Pharmacokinetics and Pharmacodynamics
- PK parameters and concentrations of MRZ estimated by non-compartamental analysis.
- Proteosome subunit activity was assayed in packed whole blood (PBWB) and peripheral blood mononuclear cell (PBMC) samples.

Results

Baseline characteristics of Patients with RR MM

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Schedule A</th>
<th>Schedule B</th>
<th>MM Subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Since Initial Primary Diagnosis (months)</td>
<td>n</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>n</td>
<td>75.5 (37.10)</td>
<td>71.4</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>21.2, 161.1</td>
<td></td>
</tr>
<tr>
<td>Number of Relapses</td>
<td></td>
<td>2 (12)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>17 (49%)</td>
<td></td>
</tr>
<tr>
<td>Multiple Myeloma Status at Screening</td>
<td></td>
<td>36 (86%), 0.075 mg/m²</td>
<td>38 (86%), 0.7 mg/m²</td>
</tr>
<tr>
<td>Relapsed</td>
<td></td>
<td>23 (66%)</td>
<td></td>
</tr>
<tr>
<td>Relapsed/Refractory</td>
<td></td>
<td>12 (34%)</td>
<td></td>
</tr>
<tr>
<td>Primary Resistant</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Prior Treatment with Bortezomib</td>
<td></td>
<td>28 (60%)</td>
<td></td>
</tr>
<tr>
<td>Prior Bortezomib Regimens (median)</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Refractory to Prior Bortezomib</td>
<td></td>
<td>5/16 (30%)</td>
<td></td>
</tr>
</tbody>
</table>

Marizomib treatment received on study

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Regimen</th>
<th>Days 1, 4, 8, 11 infusions</th>
<th>Days 1, 4, 8, 11 infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule A</td>
<td>Once-weekly 1–10 minute IV infusion N=42</td>
<td>1 (6), 2 (3)</td>
<td>1 (6), 2 (3)</td>
</tr>
<tr>
<td>Schedule B</td>
<td>Twice-weekly 1-minute 2-hour infusion N=44</td>
<td>1 (6), 2 (3)</td>
<td>1 (6), 2 (3)</td>
</tr>
</tbody>
</table>

Dose-related proteasome inhibition

- Inhibition of CT-L is maximal at a cumulative dose-intensity equivalent to one cycle of weekly dosing at 0.5mg/m²
- The cumulative dose responsiveness in % T-L inhibition with repeated dosing starting at ~1.6mg/m² (when CT-L target to be 100% inhibited)

Pharmacokinetics
- Short mean half-life 2.5 to 33 minutes
- Large mean volume of distribution (15.0 to 418.8 L)
- High mean clearance (0.9 to 22.3 L/min)

Related treatment-emergent adverse events (TEAEs) in >10% of patients in at least 1 schedule and all related Grade 3 TEAEs

- No on-study deaths; no Grade 4 MRZ-related AEs

Summary
- RP2D of the weekly regimen (Day 1, 4 and 15) in 4-week cycles: 0.7 mg/m² as 10-minute infusion
- RP2D of biweekly regimen (Day 1, 4, 8 and 11) in 3-week cycles: 0.5 mg/m² as 2-hour infusion with dexamethasone
- Infusion length increased to 2 hours to ameliorate CNS toxicities observed with a 10 minute infusion that are thought to be related to the maximum concentration which occurs at the end of the infusion.
- PK data indicate that the half-life is short with rapid clearance and a large volume of distribution.
- MRZ inhibits binds irreversibly to all three proteasome subunits and maintains a long duration of inhibition despite its short exposure. MRZ inhibits C-T-L, T-L and C-L activities
- MRZ does not induce the bortezomib- and carfilzomib-associated toxicities of peripheral neuropathy, thrombocytopenia, and neutropenia