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

Simon J. Harrison[1], Laurence Catley[2], Timothy Price[3], Michael J. Millward[4], Peeter Padrik[5], Craig R. Underhill[6], Paul K. Cannell[7], Francis J. Burrows[8], Steven D. Reich[8], Mohit Trikha[8], and Andrew Spencer[9]

[1]The Peter MacCallum Cancer Centre; [2]Mater Adult Hospital; [3]Queen Elizabeth Hospital; [4]Sir Charles; [5]Tartu University Hospital; [6]Border Medical Oncology and University of New South Wales; [7]Royal Perth Hospital; [8]Triphase Accelerator; [9]Alfred Health-Monash University

Introduction

Marizomib (MRZ, NPI-0052; salinosporamide A) is a proteasome 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 proteasome.

- **β1 (caspase-like; C-L)**
- **β2 (trypsin-like; T-L)**
- **β5 (chymotrypsin-like; CT-L).**

MRZ induces a broader spectrum of proteasome inhibition than bortezomib or carfilzomib.

Proteasome inhibition by MRZ is only reversed through cell replacement and/or proteasome resynthesis.

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 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), Waldenstrom's macroglobuinemia, 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 correlative 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**
- **Measureable 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 cycles)

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

Pharmacokinetics and Pharmacodynamics

- **PK parameters and concentrations of MRZ estimated by non-compartmental analysis.**
- **Proteasome subunit activity was assayed in packed whole blood (PWB) and peripheral blood mononuclear cell (PBMC) samples.**

Results

Baseline characteristics

Characteristic	Schedule A	Schedule B	MM Subset
n	42	44	35
Age Median (range)	63.5 yrs (23-80)	62.5 yrs (38-79)	63.0 yrs (38-79)
Male	22 (52%)	26 (59%)	19 (54%)
Race Asian White Other	2 (5%) 33 (79%) 7 (17%)	1 (2%) 40 (91%) 3 (7%)	1 (3%) 32 (91%) 2 (6%)
Median Time Since Initial Diagnosis (months)	43.2 (11.1-177.5)	68.2 (14.8-161.1)	71.4 (21.2-161.1)
Median Karnofsky Performance Status (KPS) Score	90 (70-100)	90 (70-100)	90 (70-100)
Median Number of Prior Oncology Treatments	4 (1-15)	6 (2-13)	7 (2-13)

Baseline characteristics of Patients with RR MM

Time Since Initial Primary Diagnosis (months)	MM Subset
n	35
Mean (SD)	75.5 (37.10)
Median	71.4
Min, Max	21.2, 161.1
Number of Relapses	
1	4 (11%)
2	12 (34%)
3	17 (49%)
Multiple Myeloma Status at Screening	
Relapsed	23 (66%)
Relapsed/Refractory	12 (34%)
Primary Resistant	0
Prior Treatment with Bortezomib	28 (80%)
Prior Bortezomib Regimens (median)	1
Refractory to Prior Bortezomib	5/26 (19%)

Marizomib treatment received on study

Schedule	Regimen	Dose level achieved	Patients dosed
Schedule A: Once-weekly 1–10 minute IV infusion N=42	Days 1, 8, 11 4-week cycles	0.1 mg/m²	5
		0.15 mg/m²	4
		0.3 mg/m²	5
		0.45 mg/m²	3
		0.55 mg/m²	5
		0.7 mg/m²	3
		0.8 mg/m²	3
		0.9 mg/m²	2
Schedule A RP2D	10 minute infusion	0.7 mg/m²	12
Schedule B: Twice-weekly 1 minute–2 hour IV infusion N=44	Days 1, 4, 8, 11 3-week cycles	0.075 mg/m²	6
		0.15 mg/m²	3
		0.3 mg/m²	3
		0.4 mg/m²	6
		0.5 mg/m²	12*
		0.6 mg/m²	4
Schedule B RP2D	2 hour infusion	0.5 mg/m²	10

*Includes introduction of a new formulation

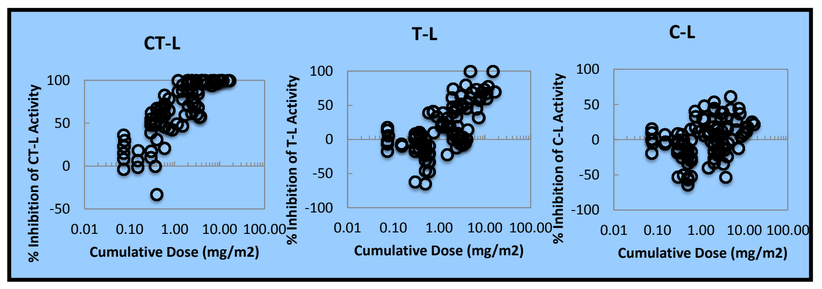
Efficacy

Response	Rate	
SD	44% (12/27)	
MR	15% (4/27)	Clinical Benefit Rate = 30%
PR/VGPR	15% (4*/27)	Overall Response Rate = 15%

Percentages are for 27 patients with computed response.
***Includes 1 very good partial response (VGPR)**
SD = Stable Disease; MR = Minimal Response; PR = Partial Response;

Schedule A: only response was a compete response in a patient with transformed marginal zone lymphoma
Schedule B: Only patients with MM had responses.

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 ~1.6 mg/m² (when CT-L starts to be 100% inhibited)**

Pharmacokinetics

- **Short mean half-life 2.5 to 33 minutes**
- **Large mean volume of distribution (15.0 to 415.8 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

Adverse Event MedDRA Preferred Term	Schedule A (N = 42)		Schedule B (N = 44)	
	All Grades	Grade 3	All Grades	Grade 3
Patients with ≥ 1 related AE-n (%)	40 (95)	11 (26)	39 (89)	11 (25)
Fatigue	23 (55)	0	16 (36)	2 (5)
Application/infusion/ injection site pain	23 (55)	3 (7)	8 (18)	0
Nausea	19 (45)	0	9 (21)	1 (2)
Diarrhoea	13 (31)	0	8 (18)	1 (2)
Dizziness	10 (24)	2 (5)	2 (5)	0
Headache	9 (21)	0	3 (7)	0
Vomiting	9 (21)	0	3 (7)	1 (2)
Dysgeusia	8 (19)	0	3 (7)	0
Insomnia	8 (19)	2 (5)	5 (11)	0
Anorexia	6 (14)	0	4 (9)	0
Hallucination (not otherwise specified, visual, auditory)	4 (10)	3 (7)	7 (16)	2 (5)
Delirium/confusional state/feeling drunk/ disorientation	3 (7)	2 (5)	4 (9)	2 (5)
Gait disturbance	3 (7)	3 (7)	3 (7)	1 (2)
Anaemia	3 (7)	1 (2)	3 (7)	0
Coordination abnormal	2 (5)	1 (2)	4 (9)	1 (2)
Asthenia	2 (5)	1 (2)	1 (2)	0
Dyspnoea	2 (5)	1 (2)	3 (7)	0
Convulsion	1 (2)	1 (2)	0	0
Loss of consciousness	1 (2)	1 (2)	0	0
Elevated mood	1 (2)	1 (2)	0	0
Pneumonia	1 (2)	1 (2)	1 (2)	0
Cognitive disorder	1 (2)	0	2 (5)	2 (5)
Aphasia	0	0	1 (2)	1 (2)
Thrombocytopenia	0	0	2 (5)	2 (5)
Lymphopenia	0	0	1 (2)	1 (2)

Summary

- **RP2D of the weekly regimen (Day 1, 8 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-TL, T-L and C-L activities**
- **MRZ does not induce the bortezomib- and carfilzomib-associated toxicities of peripheral neuropathy, thrombocytopenia, and neutropenia**