Introduction

Proteasome inhibition in myeloma

The proteasome is a multisubunit enzyme complex that is responsible for degradation of a wide variety of protein 3-ubiquitin conjugates within normal and transformed cells. It is a well validated target in multiple myeloma (MM), and two proteasome inhibitors are currently approved for the treatment of MM (bortezomib and carfilzomib), and several others are currently in development. Although bortezomib and carfilzomib therapies are very important advances, they are associated with off-target toxicities1,2, and the development of acquired resistance3.

Marizomib (MRZ; also known as NPI-0012 or Selinexor) is an irreversible proteasome inhibitor that displays antimalarial activity in vitro and in vivo. MRI inhibits 3 separate enzyme activities of isolated proteasomes, chymotrypsin-like (CT-L), trypsin-like (T-L), and caspase-like (CL) with half-maximal inhibitory concentrations (IC50) values of 5.3, 26, and 430 nM, respectively.4 MRI is active in MM cells that are resistant to a variety of clinical drugs, including bortezomib (BZ), thalidomide, and lenalidomide (Dex). In vivo, MRI inhibits proteasome activity in whole blood, solid tissues, and human MM tumors when administered to nude mice by either intravenous (IV) or oral routes, and exerts antitumor activity in various MM models both alone5 or in combination with BZ, lenalidomide (LEN), or pomalidomide6.7. On-target mechanisms of acquired resistance to proteasome inhibitors that have been described include resynthesis and upregulation of the dominant g 5 (CT-L) subunit, and constitutive proteasome upregulation in the activity of the g 1 (CL) and g 2 (T-L) subunits.8,9 Due to its pan-proteasome inhibitory activity in MM cells and irreversible binding,10 MRI has the potential to overcome both of these adaptive mechanisms clinically and to improve patient outcomes.

Study objectives

Primary

To determine the maximum tolerated dose (MTD) and/or recommended Phase 1 dose (RP2D) in patients with relapsed or refractory multiple myeloma (RRMM).

Secondary

Safety and toxicity profile of repeated dosing

Pharmacokinetics (PK)

Biological activity (using laboratory correlative studies)

Dose for future study

Anti-tumor activity (using modified European Group for Bone Marrow Transplantation and International Working Group Uniform Response Criteria (MIWG-URC))

Study design

Phase 1, multicenter, open-label, dose escalating

Exploration of 2 dosing schedules (once- and twice-weekly)

Key eligibility criteria

Pathological diagnosis of multiple myeloma (MM), bortezomib and carfilzomib

- Received 2 or prior regimens

- Prior cytotoxic chemotherapy

- Received at least 2 cycles of LEN and 2 cycles of BZ, either in separate regimens or the same regimen (RP2D cohorts only)

- Relapsed or refractory to last therapy

Treatment regimens

MRZ Schedule A: Once-weekly, 1-10 minute IV infusion, Days 1, 8, 15 of 4-week cycles

MRZ Schedule B: Twice-weekly, 1-2 hour IV infusion, Days 1, 4, 8, 11 of 4-week cycles

Dex: Beginning with Protocol Amendment 5, concomitant Dex (20 mg) was allowed for patients who did not achieve at least minimal response (MR) after Cycle 2 (determined day of and day after MRZ; Protocol Amendment 10 revised this Dex allowance to begin after Cycle 2).

Pharmacokinetic and pharmacodynamic analyses

PK parameters and concentrations of MRZ and were estimated by non-compartmental analysis using Phosimet WinNonlin program version 6.3. Schedule A samples were collected at the first and third infusions in Cycle 1 (Days 1 and 15); Schedule B samples were collected at the first and fourth infusions in Cycle 1 (Days 1 and 11). Proteasome subunit activity was assayed in packed whole blood (PWB) and peripheral blood mononuclear cell (PBMC) samples.

Safety and efficacy

All patients who received one dose of MRZ were evaluated. All adverse events (AEs) and abnormal laboratory values apart from cardiac failure (NYHA Classification) were assessed and coded using modified EBMFT and MMW-URC Criteria.