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A phase 1 clinical trial evaluating marizomib, pomalidomide and low-dose dexamethasone in relapsed and refractory multiple myeloma (NPI-0052-107): final study results

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Summary

Marizomib (MRZ) is an irreversible, pan-subunit proteasome inhibitor (PI) in clinical development for relapsed/refractory multiple myeloma (RRMM) and glioma. This study analysed MRZ, pomalidomide (POM) and low-dose dexamethasone (Lo-DEX) [PMD] in RRMM to evaluate safety and determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D). Intravenous MRZ (0·3–0·5 mg/m^2) was administered over 2 h on days 1, 4, 8, 11; POM (3–4 mg) on days 1–21; and Lo-DEX (5 or 10 mg) on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 16, 22 and 23 of every 28-day cycle. Thirty-eight patients were enrolled that had received a median of 4 (range 1–10) prior lines of therapy; all patients received prior lenalidomide and bortezomib. No dose-limiting toxicities (DLTs) were observed and 0·5 mg/m^2 MRZ was determined to be the RP2D. The most common treatment-related ≥Grade 3 adverse events were: neutropenia (11/38 patients: 29%), pneumonia (4/38 patients 11%), anaemia (4/38 patients; 11%) and

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Authorship contribution

A.S., S.H., J.Z., A.B., J.L., K.B., A.K., T.Z. D.C. and P.R. were responsible for acquisition of data. M.T. and S.R. were responsible for the development of the protocol for the study. S.R. was the medical monitor responsible for study supervision. N.L. analysed and interpreted the pharmacokinetic and pharmacodynamic data for the study. A.M. was responsible for analysis and interpretation of the clinical study efficacy data, and for writing the manuscript. All authors contributed to review of the manuscript.

Conflict of interest disclosure

A.M. N.L. and M.T. are employees of Triphase Accelerator. S.R. is a consultant to Triphase Accelerator. All other authors declare no competing financial interests.

thrombocytopenia (4/38 patients; 11%). The overall response rate and clinical benefit rate was 53% (19/36) and 64% (23/36), respectively. In conclusion, PMD was well tolerated and demonstrated promising activity in heavily pre-treated, high-risk RRMM patients.

Keywords

marizomib; proteasome inhibitor; pomalidomide; low-dose dexamethasone; relapsed/refractory multiple myeloma

Marizomib (MRZ) is a novel second-generation, irreversible, pan proteasome inhibitor (PI) whose bicyclic β-lactone γ-lactam structure is distinct from other peptide-based PIs. MRZ is a potent, broad-spectrum, irreversible-binding PI that has been shown to inhibit all three proteasome activities in cells, animals and patients (Chauhan et al, 2008). The inhibitory potency for MRZ at each catalytic subtype is chymotrypsin-like (CT-L) > trypsin-like (T-L) > caspase-like (C-L) with a 50% inhibitory concentration (IC_{50}) of 3·5 ± 0·3 nmol/l, 29 ± 2 nmol/l and 430 ± 34 nmol/l, respectively, in 20S proteasomes purified from red blood cells (Chauhan et al, 2005). MRZ rapidly enters cells and covalently binds to all 3 enzyme sites (Groll et al, 2006). The irreversible nature of this binding means that continued proteasome activity requires either cell replacement and/or proteasome re-synthesis, which may confer some distinct advantages over the approved and emerging agents in this class. While Velcade® (bortezomib, BTZ) and Ninlaro® (ixazomib, IXZ) inhibit the CT-L and, to a lesser extent, the C-L subunits, their effects are temporary due to reversible binding (Teicher & Tomaszewski, 2015). By contrast, Kyprolis® (carfilzomib, CFZ) and its oral formulation, oprozomib, bind irreversibly and mediate long lasting proteasome inhibition, but are entirely specific for CT-L activity (Zhou et al, 2009; Rocarro et al, 2010). One additional differentiating feature of MRZ is its ability to cross the blood brain barrier (BBB). Preclinical studies have demonstrated that MRZ crosses the BBB, inhibits proteasome activity in the brain and has anti-tumour effects in intracranial glioma xenograft models (Di et al, 2016).

In the last 10 years, a number of agents have been approved for use in multiple myeloma (MM) with 4 being approved in 2015. These agents, with diverse mechanisms of action, including proteasome inhibition, have significantly improved efficacy and are often better tolerated than first generation novel agents. Clinical trials evaluating these agents have demonstrated that combining a PI with an immunomodulatory agent and dexamethasone (DEX) delivers clinical benefit in both the frontline and relapsed setting in MM (Richardson et al, 2010, 2014a). Pomalyst® (pomalidomide, POM), a potent immunomodulatory agent, in combination with DEX has been approved for relapsed and refractory MM (RRMM) in patients who have received at least two prior lines of therapy including the immunomodulatory agent Revlimid® (lenalidomide, LEN) and a PI (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204026lbl.pdf). Darzalex® (daratumumab), a CD38-targeting antibody, has demonstrated single agent activity in patients with prior immunomodulatory agent and PI exposure (Lokhurst et al, 2015). In spite of the plethora of agents recently added to the MM armamentarium, patients do not universally respond to these agents, and continued use often results in the development of

either refractory disease or evolving treatment-related toxicity. It is reasonable to hypothesize that relapse to CT-L catalytic subunit-specific PIs in MM patients may, in part, be due to compensatory hyperactivation of the other catalytically active proteasome subunits (Levin et al, 2016). This highlights the remaining unmet need for novel agents that can offer benefit in the relapsed and refractory setting to patients with prior PI and immunomodulatory agent exposure, the most commonly used drugs in MM. MRZ has distinct advantages due to its irreversible binding and pan proteasome activity, which may confer clinical benefit in patients that are relapsed or refractory to prior PIs. In the Phase 1 multicentre, open label, dose escalation combination study described herein, we evaluate the safety and efficacy of MRZ with POM and low-dose DEX (Lo-DEX) [PMD] in patients with RRMM.

Methods

Patient selection

Adults with RRMM with measurable disease in serum or urine and who had received ≥2 prior anti-myeloma therapies were eligible. All patients had received prior LEN and BTZ, given separately or in combination. Patients had to achieve at least stable disease or better for at least one cycle of prior anti-myeloma regimen before progressing, with refractoriness to last anti-myeloma therapy and have an Eastern Cooperative Oncology Group performance score ≤2. Exclusion criteria included Grade ≥2 peripheral neuropathy; absolute neutrophil count $<1{\cdot}0 \times 10^9$/l; platelet count $<50 \times 10^9$/l or $<30 \times 10^9$/l for patients with ≥50% bone marrow plasmacytosis; creatinine clearance <35 ml/min; serum liver transaminase levels >3 × upper limit of normal (ULN); serum bilirubin >1·5 × ULN; congestive heart failure (New York Heart Association class III–IV); and prior exposure to POM and/or MRZ. The institutional review board at each centre approved the study, which was conducted in accordance with Good Clinical Practice and the provisions of the Declaration of Helsinki. All patients provided informed consent prior to study enrolment.

Study design

This was an international, multicentre, Phase 1, open label, dose-finding study that had a primary endpoint of determining the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of patients with RRMM. The secondary endpoints were to evaluate safety, efficacy, overall survival (OS), time to response (TTR) and duration of response (DOR).

Dose-limiting toxicity (DLT) was evaluated during Cycle 1 using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). A DLT was defined as the occurrence of any of the following treatment-emergent toxicities that were assigned to at least one of the study drugs: Grade 4 infection; Grade 4 neutropenia; febrile neutropenia; Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with significant bleeding; Grade ≥3 non-haematological toxicity including Grade ≥3 nausea, vomiting, constipation and/or diarrhoea with optimal antiemetic/antidiarrheal therapy; and Grade ≥3 fatigue present for >7 days.

Intravenous (IV) hydration (~350 ml/h) with normal saline was given for 1 h prior and 2 h following MRZ infusion. MRZ was dosed on days 1, 4, 8 and 11 of a 28-day cycle as a 2 h IV infusion. Dexamethasone was dosed orally on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 16, 22 and 23 as 10 mg (≤75 years) or 5 mg (>75 years). POM was dosed orally once daily on days 1–21 of each cycle at either 3 mg or 4 mg. Treatment continued until disease progression or unacceptable toxicity.

As the MTD of both MRZ (Harrison et al, 2016) and POM (Schey et al, 2004) were known at the start of this study, the objective of the protocol was to ensure that both drugs given at their MTD was safe, and if so to get a preliminary estimate of the efficacy of these combinations. To accomplish this objective, both drugs were started below the MTD and increased one at a time until the MTD of each drug was reached in the combination, as detailed in Table I. A standard 3 + 3 dose-escalation schedule was used for this study, as similar 3 + 3 designs have been evaluated for PIs in combination with immunomodulatory agents, such as LEN or POM, and did not result in any tolerability concerns in the RRMM patient population (Richardson et al, 2009; Shah et al, 2015; Krishnan et al, 2016). Dosing started at Cohort 1 with up to 4 dose-escalation cohorts of 3–6 patients in each cohort (Table I). Additional patients were enrolled at the RP2D with a maximum of 22 response-evaluable patients planned.

Pharmacokinetics

Blood pharmacokinetic (PK) sampling was performed for MRZ on Cycle 1 Day 8 pre-dose, during infusion at 40, 80 and 120 min, then 2, 5, 10, 15, 30, 45, 60 and 90 min after infusion completion for MRZ. POM and DEX PK sampling was performed pre-dose, 2 h and 24 h following dosing on Cycle 1 Day 8. Non-compartmental PK analyses were independently performed by PKPD Bioscience (Exton, PA) using validated PK analysis software (Phoenix WinNonlin 6.3, Pharsight Corp., Sunnyvale, CA).

Pharmacodynamics

Pharmacodynamics samples from packed whole blood (PWB) and peripheral blood mononuclear cells (PBMC) were collected at screening, pre-dose and 1 h post-dose on Cycle 1 Day 1 and then pre- and post-dose on Day 11 for Cycles 1, 2 and 3 and every third cycle thereafter. PWB and PBMC samples were processed to analyse the CT-L, T-L and C-L catalytic activities of the proteasome as previously described (Levin et al, 2016).

Response and safety assessment

Responses were assessed on Day 1 of each cycle using International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Rajkumar et al, 2011) and required two consecutive assessments to confirm response. The overall response rate (ORR) was defined as the percentage of patients who achieved ≥ partial response (PR), and the clinical benefit rate (CBR) was defined as those patients who achieved ≥ minimal response (MR). TTR was defined as the time (months) from the study treatment start to the first occurrence of ≥PR. DOR was defined as the time from ≥PR to disease progression or death due to any cause. Progression-free survival (PFS), an exploratory endpoint, was defined as the number of months between start of treatment and first documented disease progression according to

IMWG-URC or death. OS was defined as the time (months) from the date of first study drug dose to date of death due to any cause. Adverse event (AE) data was collected until 28 days after last administration of study drug, and was graded according to the NCI-CTCAE v4.03. Serious AEs (SAEs) were to be collected after the 28-day period, if there was a reasonable possibility that they were related to one or more of the study drugs.

Statistical design and analysis

The sample size of 36 patients was chosen based on recruitment projections and methods to determine DLT and MTD. It was assumed that 3–6 evaluable patients per dose cohort would provide data to assess the toxicity profile of MRZ, followed with up to 24 patients at the RP2D to confirm the safety and activity of MRZ prior to proceeding to the next clinical trial. The RP2D of single agent MRZ had been determined from a prior study (Harrison et al, 2016) and that dose, of 0·5 mg/m^2 administered as a 2-h IV infusion, was not to be exceeded. The approved dose of POM (4 mg for 21 days of a 28-day) cycle was not to be exceeded. The dose of DEX was fixed dependent upon the patient's age. Patients who received at least 1 dose of study drug (intent to treat population, ITT) were analysed for safety. Response evaluable (RE) patients were defined as all enrolled patients who took at least one dose of any of the study treatments and who had measurable disease at baseline and had at least one post-baseline efficacy assessment. Toxicities were summarized by tabulating maximum grade for each unique AE per patient. All time to events analyses were determined using the Kaplan-Meier method except TTR, for which descriptive statistics were employed.

Results

Patients & demographics

Thirty-eight patients with RRMM were recruited across 4 US and 2 Australian sites between July 2014 and September 2015. The ITT population comprised all 38 patients. The RE population was 36 patients, as 2 patients from the RP2D cohort discontinued treatment during Cycle 1 prior to receiving a post-baseline efficacy assessment. One patient discontinued prior to Cycle 1 Day 4 treatment due to Grade 3 pneumonia that was subsequently attributed to plural plasmacytomas. The second patient had a Grade 5 cardio-respiratory arrest on Cycle 1 Day 15 that was attributed to POM by the investigator.

The median age was 62 years (range 31–76), with 71% of patients <65 years, and the population was predominantly male (71%). The median number of prior treatment regimens was 4 (range 1–10) with median time from diagnosis of 5·5 years (range 1–15). Twenty-nine percent of patients had high-risk cytogenetics, defined as 17p deletion and/or t(4;14) translocation. All patients had prior BTZ, LEN and DEX exposure, and 87% had prior haematopoietic progenitor cell transplants (Table II). A high proportion of patients were refractory to LEN (84%) and BTZ (61%), with 29% of patients CFZ refractory. Fifty-three percent of patients were double refractory to LEN/BTZ and 21% refractory were triple refractory to LEN/BTZ/CFZ as per IMWG-URC criteria (Rajkumar et al, 2011).

Dose escalation

The first dosing cohort was expanded to 5 patients as 2 patients missed doses of study treatment during Cycle 1, and thus were not evaluable for DLT as per protocol. One patient was hospitalized for a bowel obstruction unrelated to study drug, and the second patient was hospitalized for a sacral skin infection unrelated to study drug. Three patients each were enrolled in Cohorts 2, 3 and 4 and no DLTs were observed, leading to the dose expansion Cohort 5, where 24 additional patients were enrolled to further evaluate the safety and efficacy profile of PMD.

Safety

The safety population, which consisted of all patients receiving at least one dose of study drug, was 38 patients. The last patient was dosed in the study on 27 September 2016 and the safety analysis was performed on the locked database. Treatment-emergent adverse events accounted for 16% (6 patients) of discontinuations, 2 patients withdrew consent/were lost to follow-up (5%), and 2 patients (5%) discontinued due to closure of the study. Two deaths occurred on study, one Grade 5 cardio-respiratory arrest attributed to POM by the investigator, and a second due to gastro-intestinal bleeding due to a plasmacytoma, which was attributed to progressive disease (PD) and not related to study treatment.

The median duration of treatment was 16 weeks (range 0·1–88). Thirty-five patients (92%) had a treatment-related AE (TRAE) with 25 (66%) of patients experiencing AEs ≥Grade 3. Analysis of the most common TRAEs by cohort demonstrated that the frequency of the most common AEs did not increase with dose escalation, confirming that the MTD of MRZ and POM was tolerated as a combination treatment in this patient population (Table III). Table IV summarizes all TRAEs and TRAEs ≥Grade 3. The most common AEs were haematological, with neutropenia, thrombocytopenia and anaemia being most frequent. TRAEs from ≥Grade 3 haematological events were as follows: 11 (29%) neutropenia, 7 (18%) thrombocytopenia, 4 (11%) anaemia and 2 (5%) febrile neutropenia. Non-haematological AEs of note included fatigue (26%, 10/38), dyspnoea (18%, 7/38), pneumonia (13%, 5/38), nausea (16%, 6/38) and peripheral oedema (21%, 8/38). Infections were also common, as expected in the immune-suppressed RRMM population. No DLTs were observed during this study, therefore the MTD was not determined. In the RP2D dose cohort, one grade 5 AE occurred, cardio-respiratory arrest from a suspected pulmonary embolism, an event that occurred after Cycle 1 MRZ dosing was completed. The event was judged by the investigator to be related to POM. Three patients experienced Grade 4 AEs during study treatment; neutropenia related to POM (Cohort 4), thrombocytopenia related to POM and MRZ (Cohort 5), and picornavirus infection related to DEX (Cohort 5). Insomnia was the most common central nervous system (CNS) AE in 4 patients, with only 1 Grade 3 event. Other CNS AEs were infrequent and of a lower grade.

Pharmacokinetics

The half-life of MRZ in this study was short, in the range of 6·3–11 min. This was expected, as rapid hydrolysis occurs at physiological pH with irreversible binding to proteasomes. Volume of distribution (Vd) was high (range of 41–86 l) suggesting extensive tissue distribution of MRZ or partitioning of the drug in blood cells. MRZ clearance was also high

(range 252–564 l/h), significantly higher than liver blood flow, which is suggestive of extrahepatic metabolism. No dose proportionality was observed in this study and this is most likely due to the narrow dose range that was tested and high inter-subject variability. Overall, the lack of dose proportionality observed in the current study aligns with previous PK observations in the preclinical and clinical settings (Potts et al, 2011; Harrison et al, 2016).

Pharmacodynamic activity

The pharmacodynamic effects of MRZ on three proteasome subunits were measured in PWB and PBMC. Partial or complete proteasome subunit inhibition in PWB was achieved at the dosing schedule used in this clinical study (Fig 1A, B). The sensitivity of subunit inhibition was consistent with the documented biochemical potency of MRZ [CT-L > T-L > C-L] (Teicher & Tomaszewski, 2015). Additionally, hyperactivation of the T-L and C-L subunits was observed prior to subsequent gradual inhibition once CT-L activity was fully inhibited. These results align with previous observations by other groups (Altun et al, 2005; Chauhan et al, 2006) and prior MRZ clinical studies (Levin et al, 2016). In general, CT-L inhibition was more effectively suppressed between MRZ dosing in anucleated samples (PWB) compared to nucleated cells (PBMC). This is probably reflective of the active re-synthesis of proteasomes in nucleated cells. Meaningful correlations between any proteasome subunit inhibition and either clinical response or best reduction in myeloma protein were not observed, suggesting that proteasome inhibition in peripheral blood did not function as a surrogate biomarker for tumour proteasome inhibition.

Efficacy

Thirty-six patients were evaluable for efficacy as per protocol definition. The median number of cycles of PMD was 4 (range 1–23). Response status was determined by investigator using IMWG-URC criteria (Rajkumar et al, 2011). The ORR (≥PR) was 53% and the CBR (≥MR) was 64% in the response evaluable population. Two of 36 (6%) patients achieved a very good partial response (VGPR), 17 of 36 (47%) patients achieved a PR, 4 of 36 (11%) patients had a MR, 10 of 36 (28%) patients had stable disease (SD) and 3 of 36 (8%) had PD (Table V). Thirty-one of 36 patients (81%) had reductions in paraprotein following PMD treatment (Fig 1C). Analysis of the paraprotein levels in individual patients revealed that PMD treatment resulted in a rapid decline in serum M protein levels (Fig 1D, E). Of note, one of the patients achieved and maintained a VGPR on MRZ alone, after POM (Cycle 2) and DEX (Cycle 4) discontinuation (Fig 1E). The rapid decline in M protein is also reflected in the median time to response (≥PR patients) of 1 month (range 1–4 months). The swimmer plot of the time on MRZ in all patients demonstrates the range of duration and depths of responses observed in patients (Fig 1F). Five patients achieved PRs and maintained them ≥10 months; one patient achieved a PR by Cycle 4 and maintained this PR through to Cycle 23.

The median duration of response (DOR) was 7·5 months (95% confidence interval [CI] 4·1–11·1) with a median follow up of 12·9 months. The median PFS was 4·0 months (95% CI 2·8–5·6 months) after a median follow up of 11·2 months (Fig 2A). Patients achieving ≥PR had a significantly longer PFS than patients with ≤MR responses (6·7 months vs. 2·6 months respectively, $P < 0·0001$) [Fig 2B]. After a median follow-up of 15·7 months (95% CI 12–

19·6 months), the median OS was 13·6 months (95% CI 7·5 months–not reached) [Fig 2C]. Similar to PFS analysis, significantly longer median OS was evident in patients that achieved either a PR or VGPR compared to those that achieved a MR, SD or PD (P = 0·0392) [Fig 2D].

The activity of PMD was also analysed in subpopulations. ORR was 56% (10/18) in double refractory (LEN/BTZ) patients and 71% (5/7) in triple refractory (LEN/BTZ/CFZ) patients (Table V). The median DOR, median PFS and median OS were not significantly different in double refractory (LEN/BTZ) patients compared to the total study population (5·8, 3·8 and 13·6 months, respectively, data not presented). In triple refractory (LEN/BTZ/CFZ) patients, median DOR, median PF and median OS were similar to the total patient population (data not presented). Eight of 10 (80%) CFZ-refractory patients had PRs. Patients with high risk cytogenetics had an ORR (50%) comparable to the total patient population (Table V), but shorter median DOR (2·8 months), median PFS (3·3 months) and median OS (10·6 months).

Discussion

Proteasome inhibitors, including BTZ, CFZ and IXZ, have demonstrated clinical activity and been approved in MM (Kane et al, 2003; Stewart et al, 2015; Moreau et al, 2016). They are commonly used in combination with DEX and immunomodulatory agents, such as LEN and POM (National Comprehensive Cancer Network, 2015). MRZ has been extensively evaluated pre-clinically in MM models as a single agent and in combination with POM (Chauhan et al, 2005; Das et al, 2015). Given its novel pan subunit proteasome inhibitory activity, MRZ was investigated in combination with POM and DEX in the current study.

The RP2D of MRZ in this study was 0·5 mg/m^2 when administered on the study schedule (days 1, 4, 8 and 11 of a 28-day cycle, infused over 2 h), with 4 mg POM (days 1–21) and 5 or 10 mg DEX (days 1, 2, 4, 5, 8, 9, 11, 12, 15, 16, 22 and 23). This is a similar MRZ RP2D as determined in previous studies evaluating MRZ monotherapy in a Phase 1 solid tumour study (Harrison et al, 2016) and in RRMM patients (Richardson et al, 2016). While a small number of MM patients demonstrated clinical benefit in these earlier studies, it was anticipated and confirmed here that MRZ in combination with POM and Lo-DEX would result in more robust responses.

The PMD combination was well tolerated in this study. The Grade ≥3 haematological toxicities observed in this study were comparable in type and reduced in frequency compared with those observed with POM/Lo-DEX. In a Phase 3 study evaluating POM/Lo-DEX, Grade ≥3 neutropenia events were 48% (San Miguel et al, 2013) whereas in the current study they were 29%. Similar trends were also observed for thrombocytopenia (22% for POM/Lo-DEX vs. 11% for PMD) and anaemia (33% for POM/Lo-DEX vs. 11% for PMD). Historical studies with MRZ have also demonstrated low levels of haematological toxicity (Millward et al, 2012; Harrison et al, 2016; Richardson et al, 2016). These data imply that MRZ does not add additional haematological toxicity to the POM/Lo-DEX regimen. A lower rate of treatment-related infections and infestations were observed in this study compared with historical POM/Lo-DEX studies, 18% vs. 34% respectively (San Miguel et al, 2013), with the caveat that a small number of patients was assessed in the

current study, and larger studies are required to more accurately compare PMD safety to POM/Lo-DEX Phase 3 safety data. The approved PIs have pharmacological class toxicity that includes cardiac events, peripheral neuropathy and haematological toxicity (Lonial et al, 2005; Richardson et al, 2006; Atrash et al, 2015). Analysis of the PMD AE dataset revealed that these pharmacological class toxicities were not observed and that MRZ had a safety profile that was distinct from other agents in this class. Historical studies with MRZ described both renal and CNS toxicity at higher dose levels and infusion over shorter durations (Harrison et al, 2016; Richardson et al, 2016). In this study, no significant renal or CNS AEs were observed, suggesting that this dosing strategy and infusion duration is well tolerated in RRMM.

The ORR observed with PMD was substantially higher than POM/Lo-DEX alone (San Miguel et al, 2013), 53% vs. 31% respectively, suggesting that MRZ added clinical benefit to this combination. A high ORR was also observed in patients in the high-risk cytogenetics group. In the current study a 50% ORR was observed compared to 27% in the same patient population in the POM/Lo-DEX Phase 2 study (Richardson et al, 2014b). Of note, the ORR was also high in patients that were either double (LEN/BTZ) or triple (LEN/BTZ/CFZ) refractory (56% and 71%) and refractory to CFZ (80%), further demonstrating that PMD had activity in heavily pre-treated patients. Although the number of patients treated with CFZ is small ($N = 10$), PMD had activity in patients who were refractory to other PIs, and even in patients who were refractory to two prior PIs. Studies evaluating the combination of CFZ with POM/DEX have also demonstrated comparable ORR in patients that are refractory to LEN and BTZ (Shah et al, 2015). In contrast, recent data has demonstrated that CFZ in combination with melphalan and prednisolone did not show any significant PFS benefit over BTZ with melphalan and prednisolone in newly diagnosed MM (Facon et al, 2017). This suggests that irreversible inhibition of the CT-L subunit of the proteasome is not sufficient to add clinical benefit over that observed with reversible CT-L inhibition in the newly diagnosed setting. In contrast, IXZ is approved in less heavily pre-treated patients, with one prior therapy (Shirley, 2016). This uniquely positions MRZ as demonstrating activity in combination with POM and Lo-DEX in CFZ failures and refractory patients. The pan subunit inhibitory activity of MRZ probably contributes to its activity in patients that have failed two prior PIs. Together, the current clinical experience with PIs suggests that there is still room for a better agent in both front line and heavily pre-treated patient settings.

The DOR, PFS and OS of PMD were comparable to the Phase 3 POM/Lo-DEX data (San Miguel et al, 2013), suggesting that, despite a higher ORR, there was not a significant gain in response duration with the current schedule of PMD. PK analysis in this study aligned with historical studies demonstrating a short half-life of 6–10 mins with a high volume of distribution reflective of the irreversible binding to proteasomes (Harrison et al, 2016). The short half-life of MRZ in plasma precluded any assessments of exposure/response relationships. Analysis of PD activity in peripheral blood also aligned well with historical MRZ experience (Levin et al, 2016). Importantly, we observed significantly more CT-L inhibition in peripheral blood than has been observed with BTZ (Cortes et al, 2004; Dy et al, 2005; Moreau et al, 2008), probably due to the irreversible binding of MRZ. An ongoing study evaluating MRZ in recurrent glioma () using higher doses of MRZ with shorter infusion times has demonstrated more significant T-L and CL inhibition than those observed

here (Bota et al, 2016). This would suggest that MRZ did not maximally inhibit all 3 proteasome subunits in the current study. Taken together, the lack of renal and CNS toxicity observed in this study and the lack of any DLTs with the PMD combination demonstrate that MRZ could be dosed above 0·5 mg/m^2. Recently, higher doses of MRZ infused for a shorter duration (0·8 mg/m^2, 10 min IV infusion) have been administered under compassionate use in a limited number of MM patients with CNS relapse (CNS-MM). This dosing schedule, which is identical to the schedule being evaluated in glioma, appears to be well tolerated in CNS-MM patients and is showing promising signs of clinical benefit (Badros et al, 2017).

Conclusions

PMD was well tolerated in RRMM patients and demonstrated activity in heavily pre-treated patients. The rapid time to response in this study (1·0 month) demonstrates that MRZ is clinically active, when compared with a POM/Lo-DEX time to response of 1·9–2·7 months (Leleu et al, 2013; Richardson et al, 2014b). Collectively, the current data provide the basis for further evaluation of a MRZ-based therapy for RRMM using higher doses and a shorter infusion schedule, similar to those evaluated in glioma and CNS-MM.

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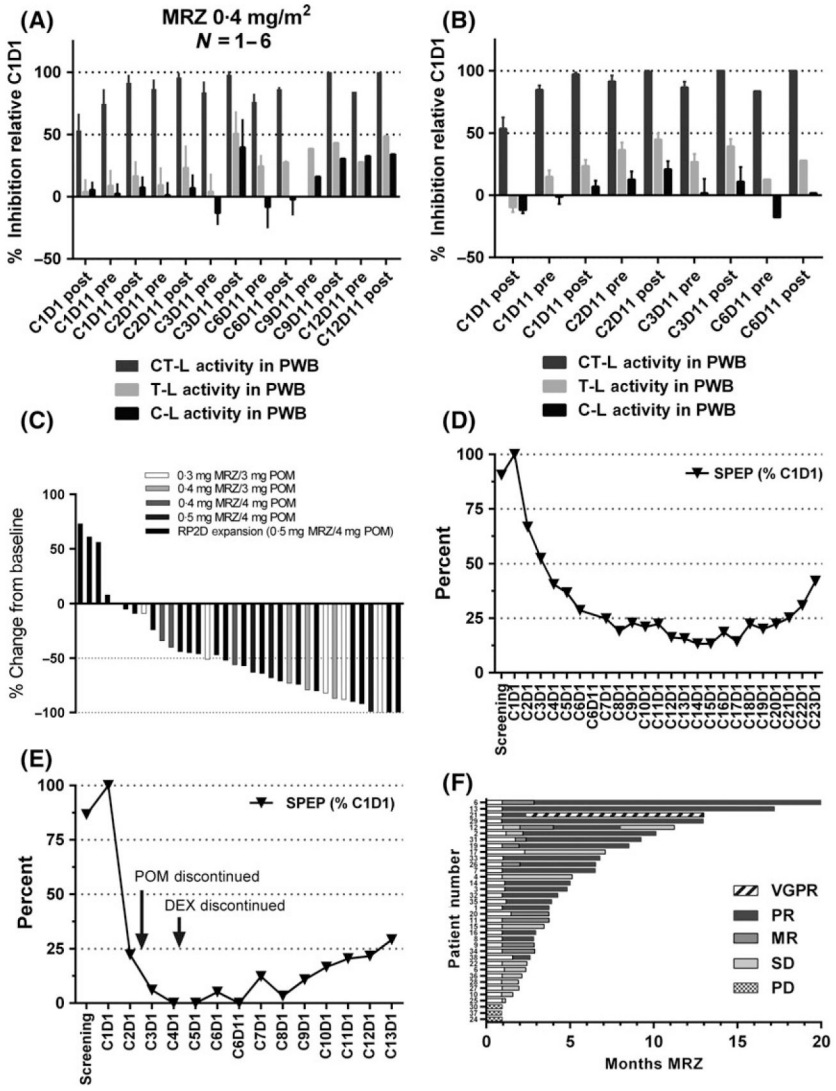

Fig 1.

(A) Pharmacodynamic inhibition of proteasome activity in PWB at 0·4 mg/m^2 MRZ. Data are presented as mean with standard error of the mean (SEM). (B) Pharmacodynamic inhibition of proteasome activity in PWB at 0·5 mg/m^2 MRZ cohorts. Data are presented as mean with SEM. (C) Waterfall plot: Best percentage change in paraprotein from baseline. (D) SPEP reduction in Patient 6 by cycle relative to baseline measurements. (E) SPEP reduction in Patient 12 by cycle relative to baseline measurements. (F) Swimmer plot showing responses with time on MRZ. C-L, caspase-like; CT-L, chymotrypsin-like; CxDx, Cycle x, Day x; DEX, dexamethasone; MR, minimal response; MRZ, marizomib; PD, progressive disease; POM, pomalidomide; PR, partial response; PWB, packed whole blood; RP2D, recommended Phase 2 dose; SD, stable disease; SPEP, serum protein electrophoresis; T-L, trypsin-like; VGPR, very good partial response.

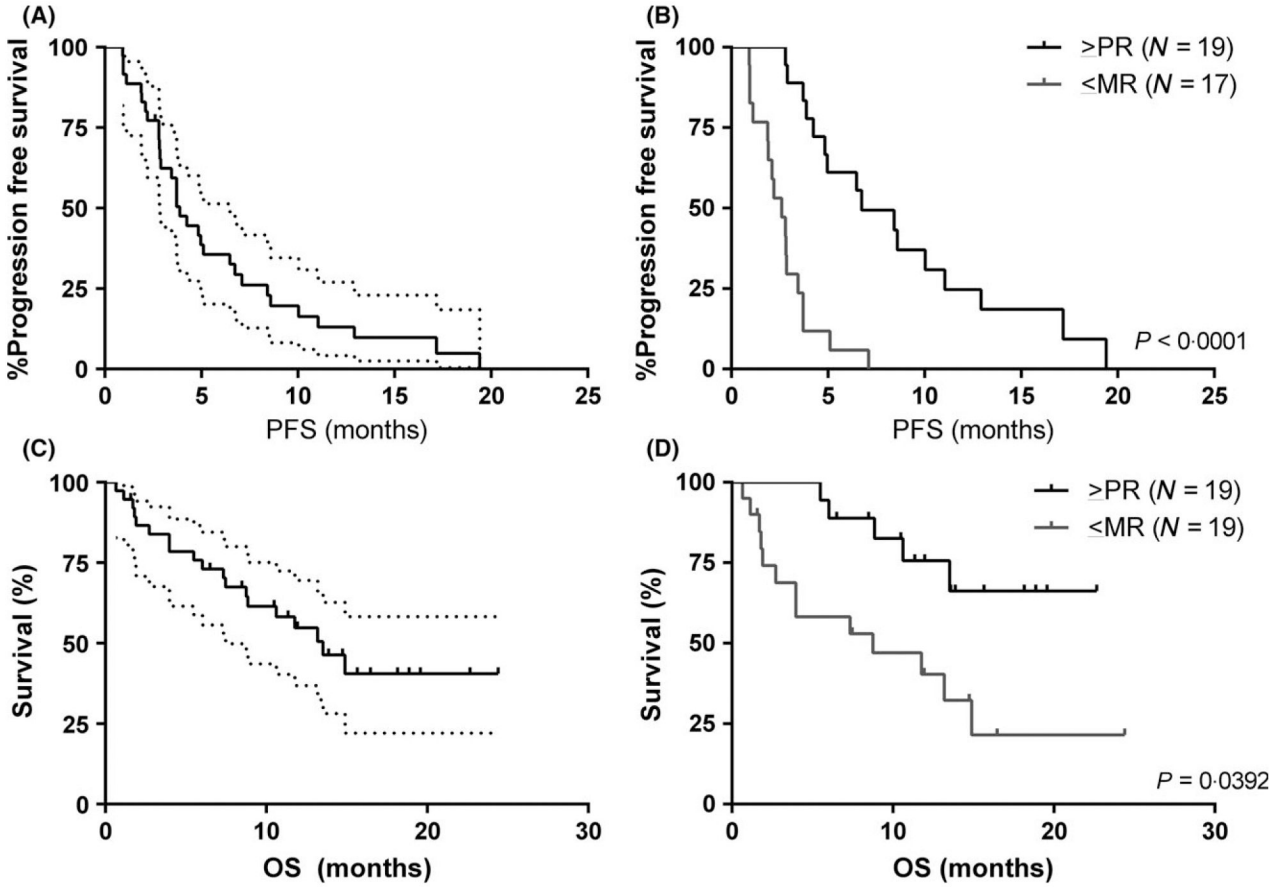

Fig 2.

PFS and OS. (A) PFS in response evaluable population ($N = 36$) with 95% confidence intervals (CI), and (B) PFS by subpopulation analysis. (C) OS in ITT population ($N = 38$) with 95% CI, and (D) OS by subpopulation analysis. ITT, intent-to-treat; MR, minimal response; OS, overall survival; PFS, progression-free survival; PR, partial response.

Table I.

Planned dose cohorts.

Cohort	Oral POM (mg)	IV MRZ (mg/m^2)	Oral DEX	Patients enrolled
1	3	0·3	10 mg (≤75 years)	5
2	3	0·4	OR	3
3	4	0·4	5 mg (>75 years)	3
4	4	0·5		3
RP2D	4	0·5		24

DEX, dexamethasone; IV, intravenous; MRZ, marizomib; POM, pomalidomide; RP2D, recommended Phase 2 dose.

Table II.

Baseline patient characteristics (*N* = 38).

Parameter	*N* = 38
Median age, years (range)	62 (31–76)
Age <65 years, %	71
Age ≥65 years, %	29
Male, %	71 (27/38)
Median number prior lines of therapy (range)	4 (1–10)
Number of prior therapies (%)	
≤2	21
>2	79
Median time from diagnosis, years (range)	5·5 (1–15)
ECOG performance score (%)	
0	32
1	63
2	5
Prior Therapies (%)	
LEN	100% (38/38)
BTZ	100% (38/38)
DEX	100% (38/38)
CFZ	34% (13/38)
THAL	50% (19/38)
Refractory to LEN	84% (32/38)
Refractory to BTZ	61% (23/38)
Refractory to CFZ	29% (11/38)
Refractory to LEN/BTZ	53% (20/38)
Refractory to LEN/BTZ/CFZ	21% (8/38)
Prior Transplant	87% (33/38)
Extramedullary disease	21% (8/38)
Cytogenetic Profile, %	
High-risk del 17p and/or t(4;14)translocation	29% (11/38)
Standard risk	50% (19/38)
Unknown	21% (8/38)

BTZ, bortezomib; CFZ, carfilzomib; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; THAL, thalidomide.

Table III.

Summary of the most frequent adverse events related to study treatment in ≥10% of the safety population (*N* = 38).

Preferred Term	Cohort 1 (*N* = 5)	Cohort 2 (*N* = 3)	Cohort 3 (*N* = 3)	Cohort 4 (*N* = 3)	RP2D (*N* = 24)	Pooled MTD/RP2D* (*N* = 27)	Total (*N* = 38)
Neutropenia	4 (80%)	0	1 (33%)	2 (67%)	6 (25%)	8 (30%)	13 (34%)
Fatigue	4 (80%)	1 (33%)	1 (33%)	1 (33%)	3 (13%)	4 (15%)	10 (26%)
Peripheral oedema	2 (40%)	1 (33%)	0	2 (67%)	3 (13%)	5 (19%)	8 (21%)
Thrombocytopenia	3 (60%)	0	1 (33%)	1 (33%)	3 (13%)	4 (15%)	8 (21%)
Dyspnoea	2 (40%)	1 (33%)	0	0	4 (17%)	4 (15%)	7 (18%)
Anaemia	3 (60%)	0	0	1 (33%)	2 (8%)	3 (11%)	6 (16%)
Muscle spasms	2 (40%)	0	0	1 (33%)	3 (13%)	4 (15%)	6 (16%)
Nausea	2 (40%)	0	1 (33%)	0	3 (13%)	3 (11%)	6 (16%)
Constipation	1 (20%)	0	0	0	4 (17%)	4 (15%)	5 (13%)
Diarrhoea	2 (40%)	0	1 (33%)	0	2 (8%)	2 (7%)	5 (13%)
Pneumonia	1 (20%)	0	0	0	4 (17%)	4 (15%)	5 (13%)
Insomnia	1 (20%)	0	1 (33%)	0	2 (8%)	2 (7%)	4 (11%)
Leukopenia	3 (60%)	0	0	0	1 (4%)	1 (4%)	4 (11%)
Upper respiratory tract infection	0	1 (33%)	0	0	3 (13%)	3 (11%)	4 (11%)

MTD, maximum tolerated dose; RP2D, recommended Phase 2 dose.

*Pooled MTD/RP2D = Cohort 4 + RP2D cohorts pooled.

Table IV.

Summary of the most frequent adverse events (AEs) related to study treatment in ≥3% of the safety population (*N* = 38) and all study treatment related adverse events ≥Grade 3.

Preferred Term	All related AEs in ≥3 patients, *n* (%)	Grade 3 AEs, *n* (%)	Grade 4 AEs, *n* (%)	Grade 5 AEs, *n* (%)
Neutropenia	13 (34%)	10 (26%)	1 (3%)	
Thrombocytopenia	8 (21%)	3 (8%)	1 (3%)	
Anaemia	6 (16%)	4 (11%)		
Leucopenia	4 (11%)	2 (5%)		
Febrile Neutropenia	2 (5%)	2 (5%)		
Platelet count decreased	–	1 (3%)		
Fatigue	10 (26%)	–		
Dyspnoea	7 (18%)	–	–	–
Pneumonia	5 (13%)	4 (11%)	–	–
Device-related infection	–	1 (3%)	–	–
Upper respiratory tract infection	4 (11%)	–	–	–
Clostridium difficile infection	–	1 (3%)	–	–
Picornavirus	–	–	1 (3%)	–
Urinary tract infection	–	1 (3%)	–	–
Pneumonitis	–	1 (3%)	–	–
Muscle spasms	6 (16%)	–	–	–
Oesophagitis	–	1 (3%)	–	–
Constipation	5 (13%)	1 (3%)	–	–
Diarrhoea	5 (13%)	1 (3%)	–	–
Nausea	6 (16%)	–	–	–
Peripheral oedema	8 (21%)	–	–	—
Oedema	–	1 (3%)	–	–
Deep vein thrombosis	3 (8%)	–	–	–
Depression	3 (8%)	–	–	–
Insomnia	4 (11%)	1 (3%)	–	–
Peripheral neuropathy	–	1 (3%)	–	–
Atrial fibrillation	–	1 (3%)	–	–

Preferred Term	All related AEs in ≥3 patients, *n* (%)	Grade 3 AEs, *n* (%)	Grade 4 AEs, *n* (%)	Grade 5 AEs, *n* (%)
Cardio-respiratory arrest	–		–	1 (3%)
Hypertension	–	1 (3%)	–	–
Hypophosphatemia	–	1 (3%)	–	–
Hyperglycaemia	–	1 (3%)	–	–

Table V.

Best response in response evaluable patients by cohort and by refractory status.

	ORR	CBR
Cohort 1	3/5 (60%)	3/5 (60%)
Cohort 2	3/3 (100%)	3/3 (100%)
Cohort 3	0	2/3 (67%)
Cohort 4	3/3 (100%)	3/3 (100%)
Dose Expansion	10/22 (45%)	12/22 (55%)
Pooled MTD/RP2D patients	13/25 (52%)	15/25 (60%)
All response-evaluable patients	19/36 (53%)	23/36 (64%)
High risk cytogenetics *	5/10 (50%)	7/10 (70%)
Standard risk cytogenetics	10/18 (56%)	11/18 (61%)
Prior LEN/BTZ	19/36 (53%)	23/36 (64%)
Prior CFZ	9/11 (82%)	10/11 (91%)
Refractory to LEN	15/30 (50%)	19/30 (63%)
Refractory to BTZ	12/21 (57%)	13/21 (62%)
Refractory to CFZ	8/10 (80%)	9/10 (90%)
Refractory to LEN/BTZ	10/18 (56%)	12/18 (67%)
Refractory to LEN/BTZ/CFZ	5/7 (71%)	6/7 (87%)
Refractory to LEN in last regimen	7/15 (47%)	10/15 (67%)
Refractory to BTZ in last regimen	3/7 (43%)	4/7 (57%)
Refractory to CFZ in last regimen	6/7 (86%)	6/7 (86%)

BTZ, bortezomib; CBR, clinical benefit rate; CFZ, carfilzomib; LEN, lenalidomide; MTD, maximum tolerated dose; ORR, overall response rate; RP2D, recommended Phase 2 dose.

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