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Phase I/II trial assessing bendamustine plus bortezomib combination therapy for the treatment of patients with relapsed or refractory multiple myeloma

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Summary

Bendamustine, active in multiple myeloma (MM), is a bifunctional mechlorethamine derivative with alkylating properties. Bortezomib, approved to treat MM, is effective in combination with alkylators. The tolerability and efficacy of bendamustine plus bortezomib in relapsed/refractory MM was assessed in an open-label, dose-escalating, phase I/II study. Patients aged ≥ 18 years received intravenous bendamustine 50, 70, or 90 mg/m^2 (days 1 and 4) plus bortezomib 1·0 mg/m^2 (days 1, 4, 8, and 11) for up to eight 28-day cycles. No dose-limiting toxicity was observed after cycle 1; bendamustine 90 mg/m^2 plus bortezomib 1·0 mg/m^2 was designated the maximum tolerated dose (MTD). The most common grade 3/4 adverse events were leucopenia (58%), neutropenia (50%), lymphopenia (45%), and thrombocytopenia (30%). Primary efficacy measure was overall response rate (ORR), which was the combined complete response (CR), very good partial response (VGPR), partial response (PR), and minimal response (MR). ORR was 48% (one CR, two VGPR, nine PR, and seven MR) for all 40 enrolled patients, 52% (16/31) at the MTD (90 mg/m^2), and 42% and 46% for prior use of bortezomib ($n = 31$) or alkylators ($n = 28$) respectively. Bendamustine plus bortezomib was well tolerated with promising efficacy in this heavily pretreated population.

Keywords: bendamustine, bortezomib, multiple myeloma, alkylator, phase I/II.

Multiple myeloma (MM) is an aggressive haematological malignancy that remains incurable. Significant improvements in response rates have recently occurred (Kumar, 2010) but most patients experience disease progression requiring additional therapeutic options (Altekruse *et al*, 2010). Thus, there remains a need for effective alternative treatments for these patients.

Historically, melphalan plus prednisone (MP) was the standard treatment for MM (Gregory *et al*, 1992; Rajkumar

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et al, 2002; Anderson, 2003; Kyle *et al*, 2003). High-dose chemotherapy followed by autologous stem cell transplant (ASCT) demonstrated improved survival compared with conventional chemotherapy (Attal *et al*, 1996; Child *et al*, 2003; http://nccn.org/professionals/physician_gls/f_guidelines.asp) in some but not all trials (Bladé *et al*, 2005). Moreover, ASCT is not an option for most patients with this disease (Cavo *et al*, 2011). The incorporation of recently approved agents, such as bortezomib, lenalidomide and thalidomide, in the treatment of MM has also improved response rates and overall survival (OS) (Richardson *et al*, 2005; Brinker *et al*, 2006; Dimopoulos *et al*, 2007; Gay *et al*, 2010; Mateos *et al*, 2010; Roussel *et al*, 2010).

The proteasome inhibitor (PI) bortezomib may be used alone to treat relapsed MM (Richardson *et al*, 2005, 2007; Berenson *et al*, 2006). *In vitro*, bortezomib sensitized MM cell lines that were highly resistant to melphalan (Ma *et al*, 2003). In clinical studies, bortezomib plus the alkylating agent melphalan with or without ascorbic acid (without glucocorticosteroids) demonstrated response rates of 68–74% with manageable toxicity among patients with relapsed/refractory (R/R) and previously untreated MM (Berenson *et al*, 2006, 2009). A phase III study of previously untreated MM patients who were ineligible for high-dose therapy showed that bortezomib-MP significantly prolonged OS *versus* MP alone (San Miguel *et al*, 2008). Retreatment with bortezomib-based regimens in these patients was also effective (Mateos *et al*, 2010). However, one concern with bortezomib-based regimens is the relatively high incidence of peripheral neuropathy (PN; Richardson *et al*, 2003, 2005; Jagannath *et al*, 2004; Palumbo *et al*, 2010). Our clinical trials, which used a longer 4-week cycle and lower dose (1·0 mg/m^2) of this PI, appear to reduce the occurrence and severity of PN without sacrificing efficacy (Berenson *et al*, 2006, 2009, 2011).

Bendamustine is a bifunctional mechlorethamine derivative with a multifaceted mechanism of action that distinguishes it fom other alkylators (Strumberg *et al*, 1996; Leoni *et al*, 2008; Cheson & Rummel, 2009). Bendamustine has shown incomplete cross-resistance with other alkylators (Strumberg *et al*, 1996) and has delivered more extensive and durable DNA damage than other alkylators (Strumberg *et al*, 1996). It elicits cell death via apoptosis or mitotic catastrophe and, unlike other alkylating agents that act on the alkyltransferase DNA repair pathway, bendamustine acts on the base excision repair DNA damage response pathway (Leoni *et al*, 2008).

Used for the treatment of chronic lymphocytic leukaemia and refractory indolent B cell non-Hodgkin lymphoma, bendamustine monotherapy has demonstrated efficacy in achieving remission in patients with MM (Pönisch & Niederwieser, 2002). A phase III study showed that bendamustine plus prednisone elicited a higher complete response (CR) rate and prolonged time to treatment failure compared with MP for newly diagnosed MM patients (Pönisch *et al*, 2006). In a recently published phase I/II trial, a partial response (PR) or better was achieved in 52% of 25 evaluable patients with R/R MM who received a maximum tolerated dose (MTD) of combination therapy with bendamustine (75 mg/m^2 on days 1 and 2 of a 28-d cycle) and oral lenalidomide (10 mg/d on days 1–21) with a fixed weekly dose of 40 mg of oral dexamethasone (Lentzsch *et al*, 2012).

In vitro, the sensitivity of MM cells to bendamustine is enhanced by bortezomib (Zhang *et al*, 2008). Combining this agent with bortezomib may allow the effective use of lower doses of the PI, potentially reducing PN, as observed when combining other alkylators with bortezomib (Berenson *et al*, 2009). Furthermore, neither of these agents has extensive renal elimination nor leads to nephrotoxicity (Owen *et al*, 2010; Piro & Molica, 2011); and renal impairment commonly occurs in MM patients, limiting and complicating the use of some anti-MM agents, including lenalidomide. In this study, we determined the MTD of bendamustine that can be combined with bortezomib in R/R MM patients and then assessed the tolerability and efficacy of that combination for an expanded cohort of similar patients at the MTD.

Methods

Study design and drug administration

This was an open-label, multicentre, nonrandomized, dose-escalating, phase I/II study conducted from May 2009 to August 2011 for patients with R/R MM. The study was conducted in accordance with the Guideline for Good Clinical Practice approved by the International Conference on Harmonisation and local ethics committees. All patients provided written informed consent.

During phase I of the study, patients received bendamustine 50 (cohort 1), 70 (cohort 2), or 90 mg/m^2 (cohort 3), infused intravenously over 1 h on days 1 and 4. Per protocol, patients also received intravenous bortezomib 1·0 mg/m^2 over 3–5 s on days 1, 4, 8, and 11 of each 28-d treatment cycle, a regimen that the Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST) showed to be clinically active (CR + PR 30%) but with a lower incidence of PN (21%) than the standard 1·3 mg/m^2 dose (62%) (Jagannath *et al*, 2004; Berenson *et al*, 2006).

The schedule in this study was chosen to enable bendamustine and bortezomib to be administered at the same clinic visit rather than on days 1 and 2, as the alkylator is given for patients with other B cell malignancies. The MTD was defined as the highest dose at which <33% of recipients had unacceptable dose-limiting toxicities (DLTs), which were defined as grade 4 haematological toxicity regardless of treatment relationship, grade 3 thrombocytopenia with grade 3/4 haemorrhage, grade 3 febrile neutropenia, grade 3/4 nausea and vomiting refractory to antiemetic therapy, any study drug-related grade 3/4 nonhaematological toxicity, or any drug-related death. Three patients were planned for each initial cohort, but up to five were allowed to be enrolled if they were in screening before enrolment of the third patient. If a

DLT was identified in one of the first three patients, additional patients were recruited to that dose level, up to a maximum of six patients. Dose escalation was performed only if the first three patients at the previous level received one cycle without an unacceptable DLT, or if a DLT occurred in only one patient among a total of six patients who received that dose. Based on a log-normal tolerance distribution, the probability of having a DLT as a function of dose was calculated to derive four possible conclusions: the MTD of bendamustine is <50, 50 or 70 mg/m^2, or it is $\geq$90 mg/m^2. The sample size in phase II was selected to provide for derivation of an estimate and confidence interval of the probability of obtaining a DLT, should any DLTs be observed.

Once the MTD was established, the phase II study was initiated with enrolment expanded to a total of 40 patients for the entire study. Response criteria in the phase II part of the trial were based on changes in the amount of monoclonal protein in the blood and 24 h urine collection and assessment of the size or number of lytic bone lesions and any extramedullary plasmacytomas (Bladé *et al*, 1998).

For patients with bortezomib-related neuropathic pain and/or PN, bortezomib doses were reduced to 0·7 mg/m^2 for grade 1 events with pain or grade 2 events; delayed and then reduced for grade 2 events with pain or grade 3 events; and discontinued for grade 4 events. For DLTs (excluding death), both bendamustine and bortezomib were discontinued up to 4 weeks (or until the toxicity resolved to $\leq$1 grade) and were reinitiated but reduced, respectively, by a dose of 20 or 0·3 mg/m^2 (discontinued if the DLT did not resolve to $\leq$1 grade within 4 weeks at the lower dose, or discontinued bortezomib 0·7 mg/m^2 if it was not tolerated).

Treatment was continued for two cycles beyond the maximum response (defined as the lowest paraprotein level), up to eight cycles without progressive disease (PD) or DLT. Final assessment was at 28 d after the end of treatment and follow-up thereafter at 3-month intervals until another therapy was started or death occurred.

Table I. Baseline patient demographics and clinical characteristics.

Total patients (*N*)	40
Age, median (range), years	67 (43–89)
Gender, *n* (%)	
Male	23 (58)
Female	17 (43)
Median weight, kg (range)	74·3 (47–116)
Median height, cm (range)	172 (145–187)
Race, *n* (%)	
White	32 (80)
Black	6 (15)
Asian	1 (3)
Other	1 (3)
Baseline disease characteristics, median (range)	
Haemoglobin, g/l	110 (70–150)
Creatinine clearance, ml/min	77 (13–134)
ECOG performance status score, *n* (%)	
0	21 (53)
1	16 (40)
2	3 (8)
ISS status *n* (%)	
I	12 (30)
II	17 (43)
III	10 (25)
Missing	1 (3)
24-h protein >300 mg, *n* (%)	13 (33)
History of renal dysfunction/failure, *n* (%)	6 (15)
Prior therapies, *n* (%)	
Number of prior antimyeloma therapies	
1–3	10 (25)
4–6	13 (33)
$\geq$7	17 (43)
Prior bortezomib	31 (78)
Prior alkylator	28 (70)
Prior bortezomib and alkylator	23 (58)
Prior radiotherapy	13 (33)
Prior stem cell transplantation	12 (30)

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.

Patients

Eligible patients, per protocol, were aged $\geq$18 years and had R/R MM, a serum monoclonal protein $\geq$10 g/l and/or urine monoclonal protein spike $\geq$200 mg/24 h and PD from prior MM treatment (excluding bendamustine). Eastern Cooperative Oncology Group (ECOG) performance status was $\leq$2 and International Staging System scores were I (30%), II (43%), III (25%), and missing (3%) at the time of enrolment on the study (Table I). Patients had a life expectancy >3 months; platelets $\geq$ 75 $\times$ 10^9/l and absolute neutrophil count (ANC) $\geq$ 1·5 $\times$ 10^9/l (platelets $\geq$ 50 $\times$ 10^9/l and ANC $\geq$ 1·0 $\times$ 10^9/l with extensive bone marrow infiltration); hepatic aminotransferase levels $\leq$3 times upper limit of normal (ULN); serum bilirubin $\leq$2 times ULN; and creatinine clearance $\geq$30 ml/min ($\geq$10 ml/min if due to myeloma-related involvement of the kidneys).

Exclusion criteria included plasma cell leukaemia or another type of malignancy besides nonmelanomatous skin cancer within 5 years; grade $\geq$2 PN; other severe and/or uncontrolled medical or psychiatric conditions, including abnormal laboratory values; treatment with corticosteroids (>10 mg/d prednisone or equivalent) or chemotherapy within 3 weeks before enrolment (nitrosoureas within 6 weeks) or immunotherapy, antibody, or radiation therapy within 4 weeks; and use of any investigational drug within 1 month before screening. Supportive therapy (e.g. administration of bisphosphonates, erythropoietin, and immunoglobulins) was permitted during study treatment.

Assessments

The primary objective of phase I was to assess the tolerability of bendamustine with bortezomib for patients with R/R MM.

The primary objective of phase II was assessment of efficacy, with the overall response rate (ORR) as the primary measure. Adverse events (AEs) were evaluated per the National Cancer Institute Common Terminology Criteria for AEs, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

The per-protocol study design defined ORR as the rates of combined CR, very good partial response (VGPR), PR, and minimal response (MR). Secondary efficacy measures included duration of response (DOR); time to progression (TTP; defined as the time from initiation of therapy to PD); progression-free survival (PFS; defined as the time from initiation of therapy to PD or death); time to first response (defined as the time from initiation of therapy to the first evidence of a confirmed response); and OS (defined as the time from initiation of therapy to death or last follow-up visit). Response was assessed by modified Bladé criteria (Bladé *et al*, 1998) prior to the first day of drug administration on each cycle and at the end-of-treatment visit. Assessment was repeated 4 weeks later to confirm any response.

Data analysis

The safety analysis included all patients who received ≥ 1 dose of both study drugs. The efficacy analysis included all patients who had ≥ 1 post-baseline primary efficacy assessment.

The ORR was also based on all patients treated in the study. The other variables (DOR, TTP, PFS, and OS) were estimated using Kaplan–Meier methodology. Exact binomial 95% confidence intervals (CIs) were reported for responses.

For all variables, only observed data were used in the statistical analyses. Patients without a valid response assessment were assigned a best overall response of 'not evaluable' and those lost to follow-up before reaching an endpoint in any of the time-to-event analyses or without an event (e.g. PD for DOR and TTP, and PD or death for PFS) were censored.

Results

Patient characteristics and disposition

Of the 40 patients in the study, five enrolled received a mean of 3·0 (standard deviation 1·7) cycles of bendamustine 50 mg/m^2, four received 4·0 (2·9) cycles of 70 mg/m^2 and 31 (five enrolled in phase I, 26 in phase II) received 4·6 (2·7) cycles of 90 mg/m^2. Patient disposition is shown in Fig 1. Overall, the mean and median durations of treatment were 15·5 (10·8) and 12·9 weeks respectively.

At baseline, patients had received a mean of six prior therapies and many showed decreased creatinine clearance (Table I).

Tolerability

As no DLTs were observed at any dose level in phase I, bendamustine 90 mg/m^2 (plus bortezomib 1·0 mg/m^2) was designated as the MTD and selected as the regimen for phase II.

Dose delays were reported in 19 (47·5%) patients across all bendamustine treatment cohorts, occurring in one, three,

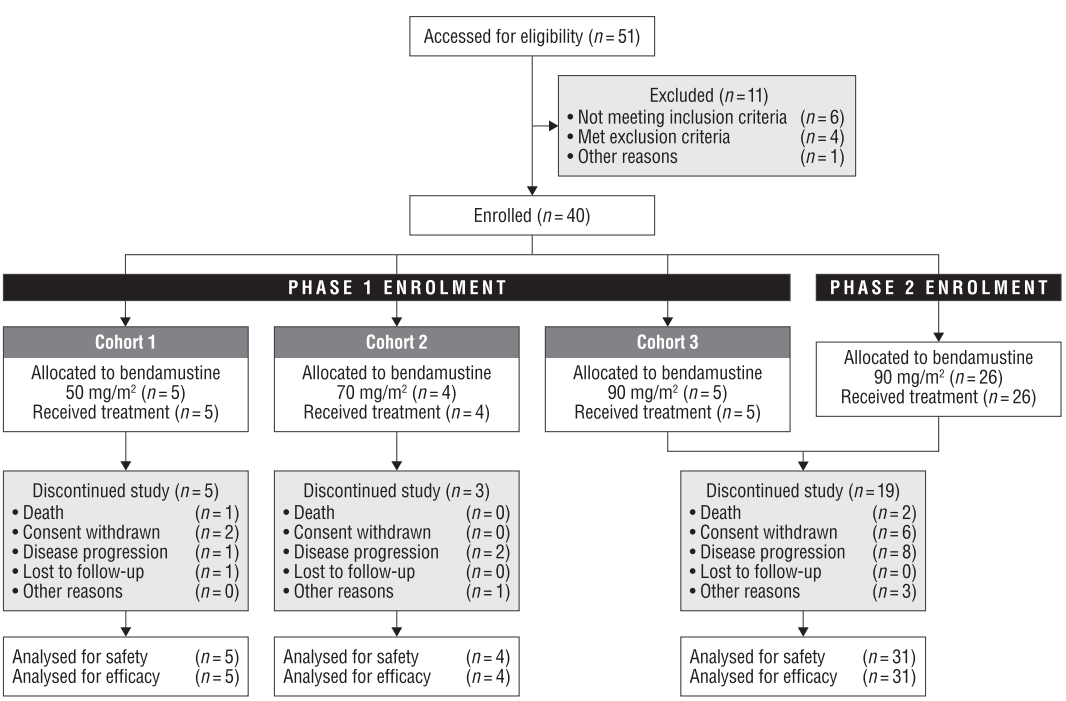

Fig 1. Patient disposition.

and 15 patients in the 50, 70, and 90 mg/m^2 cohorts respectively. Dose changes occurred in one patient treated at 70 mg/m^2 (bendamustine changed) and among 15 patients treated at 90 mg/m^2; in the latter cohort, bendamustine and bortezomib doses were changed in 10 and five patients respectively. One patient treated at 50 mg/m^2, one at 70 mg/m^2, and four at 90 mg/m^2 discontinued treatment due to AEs.

Overall, bendamustine plus bortezomib was well tolerated. Among all 40 patients, 34 (85%) had grade 3/4 haematological toxicities: 3/5 patients (60%) receiving bendamustine 50 mg/m^2, 4/4 (100%) receiving 70 mg/m^2, and 27/31 (87%) receiving 90 mg/m^2 (Table II). The most common grade 3/4 haematological AEs were leucopenia (23/40 patients, 58%), neutropenia (20/40, 50%), lymphopenia (18/40, 45%), thrombocytopenia (12/40, 30%), and anaemia (8/40, 20%). Grade 3/4 nonhaematological AEs were uncommon (Table II). Although 31 patients (77·5%) had a history of PN, only one patient experienced grade 3/4 PN in cohort 3 and 12 patients (30%) experienced grade 1/2 PN during the study.

The most common nonhaematological AEs ($\geq$28%) for all cohorts were nausea (25/40, 63%); fatigue (24/40, 60%); constipation (16/40, 40%); PN (13/40, 33%); diarrhoea (12/40 30%); and vomiting, upper respiratory tract infection and decreased appetite (11/40, 28% each).

One patient in Cohort 2 developed two serious AEs, pneumonia and renal failure. Two serious cases of pyrexia and one each of anaemia, febrile neutropenia, thrombocytopenia, cystitis, pneumonia, sepsis syndrome, dehydration, and renal failure were reported. Back or musculoskeletal chest pain occurred in seven patients receiving bendamustine 90 mg/m^2. One patient who received bendamustine 50 mg/m^2 died from unknown causes. Two deaths occurred among patients receiving bendamustine 90 mg/m^2, from disease progression and septic shock.

Efficacy

Among all 40 enrolled patients, the ORR, as defined by the study protocol, was 48% (19 patients; 95% CI, 32–64%) at the end of the treatment period and included one CR at 90 mg/m^2, two VGPR at 90 mg/m^2, nine PR (one at 50 mg/m^2 and eight at 90 mg/m^2), and seven MR (one each in Cohorts 1 and 2 and five at 90 mg/m^2). A *post hoc* calculation of response rate, using the definition of the International Myeloma Working Group's International Uniform Response Criteria for Multiple Myeloma (CR + VGPR + PR), (Durie *et al*, 2006) was determined to be 30%.

An additional 17 patients (43%) experienced stable disease and 4 (10%) showed PD (Table III). At 90 mg/m^2 (n = 31), the ORR was 52%. Among patients who had received bortezomib (n = 31) or alkylators (n = 28), the ORRs were 42% and 46% respectively.

The median time to first response was 1·9 months (range, 0·7–6·9); however, the median DOR could not be estimated due to the many censored observations (78·9% of responding patients; 95% CI minimum, 6·5). The median TTP for all patients (n = 40) was 8·4 months [95% CI, minimum 4·0 months, maximum not available due to many censored

Table II. Grade 3/4 haematological toxicities (laboratory results)* and non-haematological adverse events† occurring in $\geq$2 patients.

n (%)	Bendamustine 50 mg/m^2 (n = 5)	Bendamustine 70 mg/m^2 (n = 4)	Bendamustine 90 mg/m^2 (n = 31)	Total (N = 40)
Haematological				
Thrombocytopenia	2 (40)	2 (50)	8 (26)	12 (30)
Leucopenia	1 (20)	3 (75)	19 (61)	23 (58)
Neutropenia	1 (20)	3 (75)	16 (52)	20 (50)
Lymphopenia‡	1 (20)	3 (75)	14 (45)	18 (45)
Anaemia	2 (40)	1 (25)	5 (16)	8 (20)
Non-haematological				
Infection and infestations	0	1 (25)	3 (10)	4 (10)
Pneumonia	0	1 (25)	1 (3)	2 (5)
Metabolism and nutrition disorders	0	1 (25)	4 (13)	5 (13)
Hyponatraemia	0	1 (25)	2 (7)	3 (8)
Musculoskeletal and connective tissue disorders	1 (20)	1 (25)	1 (3)	3 (8)
Back pain	0	1 (25)	1 (3)	2 (5)
Renal and urinary disorders	0	1 (25)	2 (7)	3 (8)
Renal failure	0	1 (25)	2 (7)	3 (8)

*Graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0: Thrombocytopenia: platelet count $<50 \times 10^9$/l; Leucopenia: leucocyte count $<2{\cdot}0 \times 10^9$/l; Neutropenia: neutrophil/granulocyte counts $<1{\cdot}0 \times 10^9$/l; Lymphopenia: lymphocyte count $<0{\cdot}5 \times 10^9$/l; Anaemia: haemoglobin <80 g/l.

†Patients are counted only once in each preferred term category and only once in each system organ class category.

‡Data for lymphocyte count available for 3/5 patients receiving bendamustine 50 mg/m^2 and 15/31 patients receiving bendamustine 90 mg/m^2.

Table III. Objective responses to treatment with bendamustine and bortezomib ($n = 40$).*

n (%)	Bendamustine 50 mg/m^2 ($n = 5$)	Bendamustine 70 mg/m^2 ($n = 4$)	Bendamustine 90 mg/m^2 ($n = 31$)	Total ($N = 40$)
ORR	2 (40)	1 (25)	16 (52)	19 (48)
CR	0	0	1 (3)	1 (3)
VGPR	0	0	2 (7)	2 (5)
PR	1 (20)	0	8 (26)	9 (23)
MR	1 (20)	1 (25)	5 (16)	7 (18)
SD	2 (40)	2 (50)	13 (42)	17 (43)
PD	1 (20)	1 (25)	2 (7)	4 (10)

ORR, overall response rate (CR + VGPR + PR + MR); CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.
*Efficacy evaluable patients.

patients (65%); Fig 2A] at a median follow-up time of 3·7 months (range, 0·7–8·6); median PFS was 8·4 months (95% CI, 5·2–16·6 months; Fig 2B) at a median follow-up time of 3·9 months (range, 0·7–16·6).The median OS was 13·3 months (95% CI, 13·3–16·6 months) for all patients (three with an event and 37 censored) at the median follow-up time of 5·0 months (range, 0·7–16·6; Fig 2C).

Discussion

Bendamustine was evaluated at doses of 50, 70, or 90 mg/m^2 on a novel days 1 and 4 schedule with bortezomib at 1·0 mg/m^2 on days 1, 4, 8, and 11 on a longer 4-week cycle for patients with R/R MM. The combination was well tolerated at all bendamustine dose levels and an expanded cohort was studied at 90 mg/m^2. The most common grade 3/4 haematological toxicities included leucopenia and thrombocytopenia; grade 3/4 nonhaematological AEs, including hyponatraemia, pneumonia, back pain, and renal failure, were uncommon.

Notably, myelosuppression and PN as DLTs were not observed. Indeed, the MTD was not reached as no DLTs occurred. PN has been reported as a grade 3/4 toxicity in studies of intravenous bortezomib, alone and in combination therapy, in the treatment of R/R MM (Jagannath *et al*, 2004; Richardson *et al*, 2005; Berenson *et al*, 2006); however, in this study, a majority of patients had PN at baseline and in most cases its occurrence during the study was not considered related to treatment. The occurrence of any PN in this study, whether deemed treatment-related or not, was 32·5% (13 of 40 patients), a similar percentage (31%) as observed in our prior clinical trial, also involving previously treated MM patients using the same lower bortezomib dose with the longer 4-week schedule (Berenson *et al*, 2006). Another way to reduce PN with bortezomib is to administer the drug subcutaneously (Arnulf *et al*, 2012). Comparing the subcutaneous to intravenous administration of the drug at the 1·3 mg/m^2 dose when administered on the standard days 1, 4, 8, and 11 of a 3-week schedule, both routes of administration provided equivalent efficacy (ORR 52% in each arm) for R/R MM patients, but the incidence of PN was significantly lower in patients receiving the subcutaneous route of administration (38% vs. 53%; $P = 0·044$) with rates of grade ≥ 3 PN also reduced in incidence (6% vs. 16%; $P = 0·026$).

The tolerability of steroid-based regimens has recently been explored in several studies of R/R MM. Bortezomib, dexamethasone, and then bendamustine, given in a multistep fashion to minimize toxicity from steroids in R/R MM patients, showed overall AE profiles that were comparable among the treatment groups and toxicity was limited to 14% of nonresponding patients (Fenk *et al*, 2007). Dose-dependent toxicity from steroids was seen in the ECOG comparison of standard-dose *versus* low-dose dexamethasone with lenalidomide in previously untreated MM patients (Rajkumar *et al*, 2010). In our study, use of an effective steroid-free regimen, bendamustine plus bortezomib, offers an option for patients who do not tolerate glucocorticosteroids.

The present study also demonstrated promising efficacy for bendamustine and bortezomib in R/R MM, producing responses in nearly half of these heavily pretreated patients and in more than half of patients who received bendamustine at 90 mg/m^2. In addition, the ORRs for patients who had previously received alkylating therapy or bortezomib were 46% and 42% respectively. In a study of bendamustine, thalidomide, and dexamethasone salvage therapy, a response rate of 43% (CR of 4%, PR of 22%, MR 17%) was attained. Ninety-one percent of patients had received prior bortezomib therapy (Grey-Davies *et al*, 2011). In another trial of bortezomib and bendamustine that also included dexamethasone, patients with R/R MM had an ORR (CR + VGPR + PR) of 60%; the response rate among those previously exposed to bortezomib was 58% (Ludwig *et al*, 2011). In a study conducted among patients with a history of autologous stem-cell transplantation or standard chemotherapy, bendamustine, thalidomide, and prednisolone salvage therapy demonstrated an ORR of 86% (CR + PR) (Pönisch *et al*, 2008). All pretreated patients had received corticosteroids or alkylating agents; 14% had previously received bortezomib.

The findings suggest that progression from bortezomib in combination with chemotherapy does not preclude clinical efficacy of this PI with another chemotherapeutic agent, even an agent in the same class of drugs as used in the prior

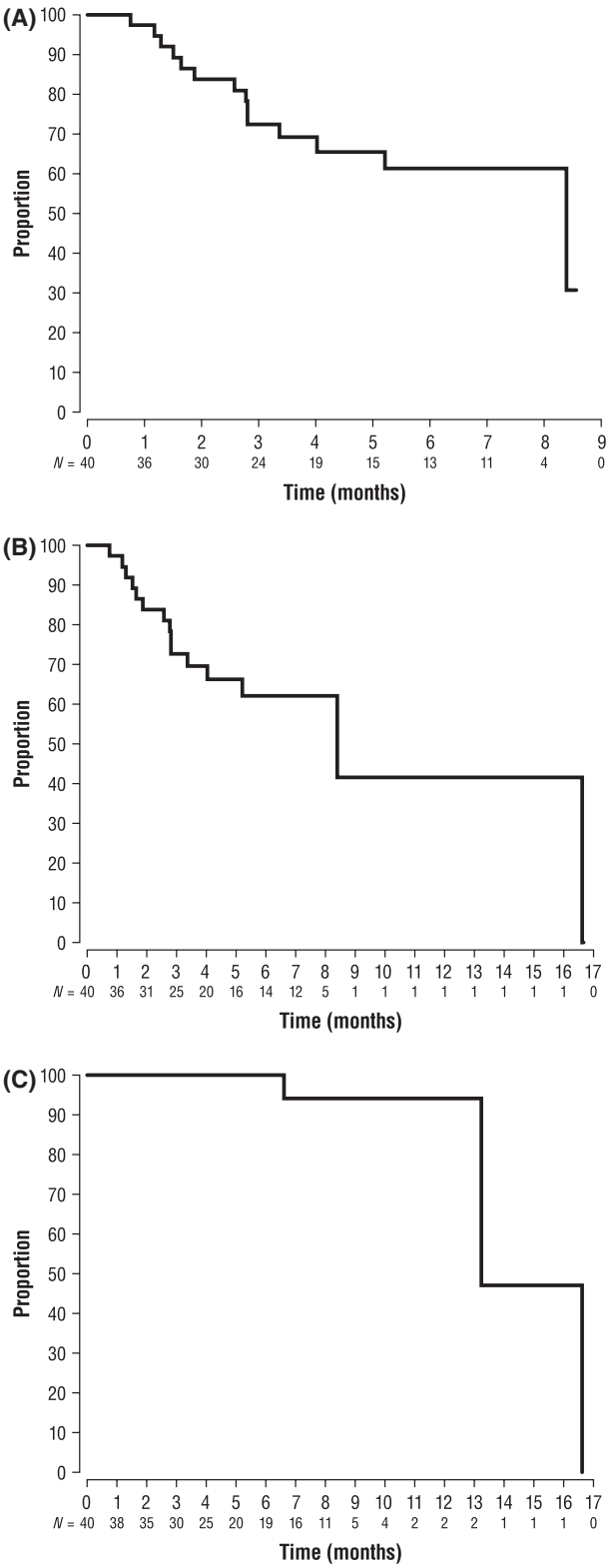

Fig 2. (A) Time to progression for all evaluable patients (n = 40). (B) Progression-free survival for all evaluable patients (n = 40). (C) Overall survival for all evaluable patients (n = 40).

bortezomib-containing combination. Indeed, bendamustine may confer increased bortezomib sensitivity and little cross-resistance with other alkylators via distinct mechanisms of action, including inhibition of mitotic checkpoints and effects on different DNA repair pathways than other nitrogen mustard-containing compounds (Strumberg *et al*, 1996; Leoni *et al*, 2008; Cheson & Rummel, 2009).

Responses were durable across treatment cohorts in the present study, with a median TTP and PFS of 8·4 months and a median OS of 13·3 months. Two randomized, phase III studies of bortezomib monotherapy in bortezomib-naïve patients with R/R MM demonstrated a median DOR of 7·0–7·8 months and median TTP of 6·2–6·5 months using a higher dose (1·3 mg/m^2) and a shorter 3-week cycle length (Orlowski *et al*, 2007; Richardson *et al*, 2007). In one of these studies, bortezomib with or without pegylated liposomal doxorubicin was used to treat bortezomib-naïve MM patients who were less heavily pretreated than in the current study, the median PFS was 6·5 months for single-agent bortezomib (Orlowski *et al*, 2007). In a phase I/II study, treatment with lower doses of melphalan and bortezomib (0·7–1·0 mg/m^2) without steroids in heavily pretreated MM patients (including bortezomib-experienced individuals) resulted in a median PFS of 8 months (2–18 months) (Berenson *et al*, 2006). An OS of 13 months was also reported for bendamustine, thalidomide, and dexamethasone salvage therapy (Grey-Davies *et al*, 2011); however, median PFS was 3 months. In the study of bortezomib and bendamustine plus dexamethasone, a median PFS of 10·9 months and OS of 12·2 was achieved (Ludwig *et al*, 2011).

The results of this clinical trial suggest several potential avenues of further research. Substantial efficacy and tolerability of bendamustine were shown in this study involving heavily pretreated MM patients. Results of other recent studies of bendamustine-based salvage therapy (Pönisch *et al*, 2007, 2008; Grey-Davies *et al*, 2011; Ludwig *et al*, 2011) have also rendered promising results, as have results of studies of bendamustine combinations in newly diagnosed patients with MM, including patients with renal dysfunction, in which ORRs (PR or greater) of up to 88% have been reported (Berdeja *et al*, 2011; Ramasamy *et al*, 2011; Pönisch *et al*, 2012). These results support a possible role for this alkylator as first-line treatment in MM patients as well.

It will be interesting to determine whether bendamustine plus bortezomib shows superior outcomes to other alkylators, such as melphalan or cyclophosphamide, with bortezomib when treating R/R or previously untreated MM patients. Moreover, it will also be important to determine whether patients who are refractory to these other alkylators plus bortezomib remain responsive to treatment with bendamustine plus bortezomib, adding another treatment option for this incurable B cell malignancy.

Other areas for investigation might include combining bendamustine with other PIs in development or immunomodulatory agents, such as lenalidomide or thalidomide. The

recent phase I/II trial that showed promising results of bendamustine, lenalidomide, and dexamethasone (BLD) in the treatment of R/R MM patients supports the use of bendamustine with immunomodulatory drugs (Lentzsch *et al*, 2012). In addition, we have recently shown a high response rate with excellent tolerability when bortezomib (at the same lower dose and longer 4-week cycle as in our present study) was combined with lenalidomide, dexamethasone, and pegylated liposomal doxorubicin (DVD-R) for R/R MM patients (Berenson *et al*, 2012). However, results from the recent, randomized, phase II EVOLUTION trial suggested that there was little improvement in response rates when the alkylator cyclophosphamide was combined with bortezomib, lenalidomide, and dexamethasone *versus* combination therapies of three of these drugs (i.e. bortezomib, dexamethasone, and cyclophosphamide; bortezomib, dexamethasone, and lenalidomide; Kumar *et al*, 2012).

Given the promising results of DVD-R and BLD, as well as the combination of bendamustine and bortezomib in our current study, for R/R MM patients, it will be important to evaluate whether the alkylator bendamustine combined with bortezomib, lenalidomide, and dexamethasone will prove more effective and as well tolerated compared with other three-drug combinations in a similar patient population.

In summary, bendamustine plus bortezomib was well tolerated and showed promise as a therapeutic option for R/R MM patients. Larger, well-designed clinical studies will need to confirm the suitability of this combination for patients who have failed to respond to or relapsed following previous treatment, including treatment with bortezomib plus other alkylators.

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Conflict of interest

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Author contributions

JRB and OY conceived and designed the study. AB, RVB, SJN, DSG, DP-D, RSS, TK, EJG, YN, RAS, and DM collected and assembled the data. JRB, OY, AB, RVB, DSG, EJG, and DM analysed and interpreted the data. All authors wrote and approved the manuscript.

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