CLINICAL TRIALS AND OBSERVATIONS

A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma

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Key Points

- Lenalidomide-bortezomib-dexamethasone resulted in partial response or better in nearly two-thirds of relapsed/refractory myeloma patients.
- The regimen had substantial activity despite high rates of prior bortezomib/thalidomide and regardless of poor prognostic characteristics.

In this prospective, multicenter, phase 2 study, 64 patients with relapsed or relapsed and refractory multiple myeloma (MM) received up to 8 21-day cycles of bortezomib 1.0 mg/m^2 (days 1, 4, 8, and 11), lenalidomide 15 mg/day (days 1-14), and dexamethasone 40/20 mg/day (cycles 1-4) and 20/10 mg/day (cycles 5-8) (days of/after bortezomib dosing). Responding patients could receive maintenance therapy. Median age was 65 years; 66% were male, 58% had relapsed and 42% had relapsed and refractory MM, and 53%, 75%, and 6% had received prior bortezomib, thalidomide, and lenalidomide, respectively. Forty-eight of 64 patients (75%; 90% confidence interval, 65-84) were alive without progressive disease at 6 months (primary end point). The rate of partial response or better was 64%; median duration of response was 8.7 months. Median progression-free and overall survivals were 9.5 and 30 months, respectively (median follow-up: 44 months). Common treatment-related toxicities included sensory neuropathy (53%), fatigue (50%), and neutropenia (42%); common grade 3/4 treatment-related toxicities included neutropenia (30%), thrombocytopenia (22%), and lymphopenia (11%). Grade 3 motor neuropathy was reported in 2 patients. Lenalidomide-bortezomib-dexamethasone appears effective and tolerable in patients with relapsed or relapsed and refractory MM, demonstrating substantial activity among patients with diverse prior therapies and adverse prognostic characteristics. This trial is registered with www.clinicaltrials.gov as #NCT00378209. (*Blood*. 2014;123(10):1461-1469)

Introduction

The introduction of the proteasome inhibitor bortezomib and the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide has transformed multiple myeloma (MM) treatment over the past decade and is associated with improved survival.[1,2] Both bortezomib[3,4] and lenalidomide-dexamethasone[5,6] have demonstrated superiority vs high-dose dexamethasone in phase 3 studies in relapsed MM. Preclinical studies indicate that lenalidomide sensitizes MM cells to bortezomib and dexamethasone[7] and that dexamethasone activity is also enhanced by bortezomib,[8] suggesting that combination therapy may enhance clinical activity. Combinations of bortezomib and/or lenalidomide plus dexamethasone have shown substantial clinical activity in treatment-naive MM,[9-14] and bortezomib-IMiD–based triplet regimens have shown improved activity vs bortezomib- or IMiD-dexamethasone doublets in the frontline and relapsed settings.[9,15-18]

The safety and maximum tolerated doses (MTD) of oral lenalidomide and intravenous (IV) bortezomib in combination (± dexamethasone 20 or 40 mg for progressive disease [PD] after cycle 2) were evaluated in a phase 1 study of 38 relapsed/refractory MM patients[19]; the MTD was lenalidomide 15 mg plus bortezomib 1.0 mg/m^2. The combination was well tolerated, with no significant peripheral neuropathy (PN) and only 1 case of deep vein thrombosis (DVT). The response rate (complete [CR] + partial [PR] + minimal [MR] response) by modified European Group for Blood and Marrow Transplantation (EBMT) criteria[20] was 61%. The addition of dexamethasone in patients with PD resulted in improved responses. In 24 patients who were refractory to previous bortezomib, thalidomide, and/or lenalidomide, 50% achieved at least MR. Median overall survival (OS) was 37 months.[19] This suggests that lenalidomide-bortezomib-dexamethasone may offer continued sensitivity to therapy in the relapsed setting,

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despite prior treatment with the individual agents. Indeed, studies of bortezomib retreatment in relapsed MM patients have shown that a substantial proportion remain sensitive to treatment,[21-24] indicating its utility as a component of subsequent lines of therapy.

Here we report the first prospective, multicenter, open-label, phase 2 study to evaluate the efficacy and safety of lenalidomide-bortezomib-dexamethasone, at the MTD established during the previous phase 1 study,[19] in patients with relapsed or relapsed and refractory MM.

Patients and methods

Patients

Patients aged ≥18 years with a Karnofsky performance status ≥60% and relapsed or relapsed and refractory MM after 1 to 3 prior regimens were eligible. Refractory MM was defined as development of disease progression during therapy or within 60 days of completing salvage therapy; patients with primary refractory disease were excluded. Prior use of bortezomib, thalidomide, and lenalidomide was permitted, either alone or in combination with dexamethasone; patients who had received prior bortezomib and lenalidomide in combination were excluded. Other exclusion criteria included: concomitant corticosteroids (>10 mg prednisone or equivalent), grade ≥2 PN (graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0), renal insufficiency (serum creatinine >2.5 mg/dL), platelets <50 000 cells/mm^3, absolute neutrophil count <1000 cells/mm^3, hemoglobin < 8.0 g/dL, and transaminases ≥2× the upper limit of normal.

The study was conducted per the International Conference on Harmonization for Good Clinical Practice and the Declaration of Helsinki. Institutional review board/independent ethics committee approval was obtained at each site; all patients provided written, informed consent.

Study design and treatment

The study (clinicaltrials.gov #NCT00378209) was conducted at 6 centers in the United States. Patients were enrolled between September 2006 and April 2008. The primary end point was the proportion of patients alive and progression-free at 6 months following lenalidomide-bortezomib-dexamethasone combination therapy. Secondary end points included objective response rate (CR, near-CR [nCR], very good PR [VGPR], and PR), duration of response (DOR), OS, and tolerability.

Patients were treated for up to 8 21-day cycles at the previously established bortezomib-lenalidomide MTD of bortezomib 1.0 mg/m^2 IV, days 1, 4, 8, and 11, and oral lenalidomide 15 mg/day, days 1 through 14, in combination with oral dexamethasone 40 mg/day (cycles 1-4) and 20 mg/day (cycles 5-8) on the days of and days after bortezomib dosing (days 1, 2, 4, 5, 8, 9, 11, and 12).[19] Following a protocol amendment based on data elucidated by the study indicating that dexamethasone 40 mg was not well tolerated, dexamethasone dosing was reduced to 20 mg/day in cycles 1 through 4 and 10 mg/day in cycles 5 through 8. Beyond cycle 8, responding patients and those with stable disease (SD) could receive maintenance therapy until disease progression or unacceptable toxicity. Maintenance therapy comprised bortezomib and lenalidomide at the doses tolerated on completion of cycle 8, with lenalidomide on days 1 through 14 and using an amended schedule of weekly bortezomib (days 1 and 8) and dexamethasone 10 mg on days 1, 2, 8, and 9. Patients could selectively discontinue treatment with specific agent(s) if required and continue to receive therapy with the remaining agent(s).

Dose modifications were implemented for specific drug-related adverse events (AEs), including grade 3/4 neutropenia, grade 3 thrombocytopenia with bleeding, and grade ≥3 venous thromboembolism. Bortezomib-associated PN was managed using established dose-modification guidelines.[25] Patients were required to take anticoagulation therapy (daily aspirin at 81 or 325 mg) and antiviral therapy as prophylaxis against herpes zoster. In patients for whom there was any concern regarding thrombotic risk, full-dose thromboprophylaxis (Coumadin [target International Normalized Ratio 2-3] or low-molecular-weight heparin) was recommended, followed by aspirin after 3 to 6 months after absence of thromboembolism was observed. Also recommended were vitamin supplements/amino acids for PN, prophylactic antibiotics, bisphosphonate therapy, and *Pneumocystis* pneumonia prophylaxis. The use of granulocyte-colony stimulating factor and erythropoietin was similarly permitted as clinically indicated.

Assessments

Response was assessed according to the EBMT criteria,[20] modified to include the additional response categories of nCR (as initially described in the Study of Uncontrolled Multiple Myeloma managed with proteasome Inhibition Therapy trial[26]) and VGPR (per the international uniform response criteria[27]). Patients were eligible for response evaluation after 1 cycle; 2 assessments at least 6 weeks apart were required for confirmation of response. Blood and urine samples were collected for M-protein quantification and immunofixation at baseline, at the start of each cycle, and at the end of cycle 8. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. Metaphase analysis of cytogenetics was performed, and fluorescence in-situ hybridization (FISH) was used to assess the presence of specific cytogenetic abnormalities including del13q, t(4;14), t(14;16), and del17p.

Statistical analysis

A 1-stage design was used, which required at least 31 of 58 eligible patients to be progression-free and alive at 6 months to consider the treatment promising. The design was selected to have high probability (0.90) of concluding the treatment to be effective when correct (defined as a true 6-month progression-free rate of 60%) and low probability (0.10) when not (true rate of 42%). Planned accrual was 64 patients allowing for 10% ineligibility. The trial accrued 65 patients within 18 months; 1 was ineligible. The proportion who were progression-free and alive at 6 months among the first 58 eligible patients was similar to that among all 64 eligible patients (43/58, 74% [90% confidence interval (CI): 63-83]; and 48/64, 75% [90% CI: 65-84]). Therefore, results are presented for all 64 eligible patients.

Exact binomial 90% CIs were reported for proportions. Kaplan-Meier methodology was used to estimate distributions of DOR (time of first response to progression or death, censoring at the date patients were last known to be alive and disease-free for patients who had not progressed or died), progression-free survival (PFS; time of treatment initiation to progression or death, censoring as for DOR), and OS (time of treatment initiation to death, censoring at the date patients were last known to be alive for those who had not died). Patients were censored at the date of initiation of nonprotocol therapy, excluding bisphosphonates and erythropoietin. The 95% CIs based on the log-log transformation are reported for time-to-event end points.

Post hoc analyses were performed to evaluate response rate, PFS, and OS by disease stage, baseline β_2-microglobulin, albumin, calcium, hemoglobin, and lactate dehydrogenase (LDH), baseline metaphase cytogenetics, and presence of specific cytogenetic abnormalities by FISH (for those with data available in >20 patients) by using Fisher's exact test and the Wald χ-square test from Cox proportional hazards model, respectively. Data reported here were as of June 2012; analyses were performed using SAS statistics software (SAS Software v8, SAS Institute Inc., Cary, NC).

Data were analyzed by P.G.R., W.X., and E.W., and all authors had access to the primary clinical trial data.

Results

Patients and treatment

Sixty-five patients were enrolled and 64 were treated. The ineligible patient was never treated because of rapid PD and renal failure, and was treated off-protocol with high-dose steroids plus bortezomib-based therapy. Table 1 shows patients' baseline characteristics and prior therapies; the median age at study entry was 65 years, 42% of

Table 1. Patient characteristics at baseline and prior therapies

Characteristic	N = 64
Median age, years (range)	65 (32-83)
Male, n (%)	42 (66)
Myeloma type, n (%)	
Immunoglobulin G	31 (48)
Immunoglobulin A	12 (19)
Immunoglobulin M	1 (2)
Immunoglobulin D	3 (5)
Biclonal	2 (3)
Serum-free light chain only	12 (19)
Light chain disease only	3 (5)
Durie-Salmon stage at diagnosis, n (%)	
I	9 (14)
II	16 (25)
III	38 (59)
Unknown	1 (2)
ISS stage at diagnosis, n (%)	
I	17 (27)
II	16 (25)
III	15 (23)
Unknown*	16 (25)
ECOG PS, n (%)	
0	28 (44)
1	32 (50)
2	4 (6)
Disease status, n (%)	
Relapsed	37 (58)
Relapsed/refractory	27 (42)
Metaphase cytogenetics, n (%)†	
Normal	44 (73)
Abnormal	16 (27)
Cytogenetic abnormalities by FISH, n (%)‡	
del13/13q	23 (36)
del17p	8 (13)
t(4;14)	4 (6)
del17p and/or t(4;14)	10 (16)
t(14;16)	2 (3)
del17p and/or t(4;14) and/or t(14;16)	12 (19)
Median β_2-microglobulin, mg/L (range)	3.3 (1.3-30.1)
Median albumin, g/dL (range)	3.9 (2.9-4.8)
Median prior therapies, n (range)	2 (1-3)
Patients receiving therapy at least once before study entry, n (%)	
Bortezomib	34 (53)
Thalidomide	48 (75)
Lenalidomide	4 (6)
Dexamethasone	58 (91)
ASCT	23 (36)

ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; PS, performance status.

*ISS stage not determined at diagnosis.

†60 patients provided samples for cytogenetic analysis.

‡Data on individual cytogenetic abnormalities by FISH not available for all patients; status was unknown in 23 (36%) patients for del13/13q, 28 (44%) patients for del17p, 27 (42%) patients for t(4;14), 31 (48%) patients for del17p and/or t(4;14), 51 (80%) patients for t(14;16), and 47 (73%) for del17p and/or t(4;14) and/or t(14;16).

patients had relapsed and refractory MM, the median time from diagnosis was 34.4 months (range 4.6-166.6), and 53%, 75%, and 6% of patients had received prior bortezomib, thalidomide, or lenalidomide, respectively. Five patients were refractory to prior bortezomib and 2 were refractory to prior lenalidomide.

The median treatment duration was 8.0 months (range 0.4-46.2), and 18 patients (28%) remained on study for >12 months. Patients received a median of 11 cycles of treatment (range 1-64), including medians of 11 (range 1-64), 9 (range 1-64), and 9 (range 1-64) cycles of lenalidomide, bortezomib, and dexamethasone, respectively. Dexamethasone dosing was initiated at 40 mg/day in 19 patients and at 20 mg/day in 45 patients. Forty-two patients (66%) completed at least 8 cycles of therapy with all 3 drugs, and 35 (55%) continued into the maintenance phase, including 26 (74%) with a response of PR or better and 9 (26%) who had MR or SD at the end of cycle 8. All patients are off treatment. Of 22 patients (34%) who discontinued before completing 8 cycles, 11 discontinued because of PD, 3 because of toxicity (rash from lenalidomide, PN, fungal pneumonia), 3 because of initiation of other therapy, 3 for patient/physician preference, 1 as a result of death from disease, and 1 because of other reasons (treatment delay of >6 weeks because of pneumonia, sepsis, and hospitalization in an intensive care unit).

Dose modifications were required in 42 patients (66%): 11 patients had 16 bortezomib dose modifications because of sensory neuropathy in 10 patients, motor neuropathy in 2, and fatigue, neuropathic pain, diarrhea, and neutropenia each in 1. Twenty-one patients had 66 lenalidomide dose modifications, with the most common reasons including diarrhea in 18 patients, neutropenia in 9, fatigue in 7, upper respiratory issues in 7, and thrombocytopenia in 3. Twenty-eight patients had 39 dexamethasone dose modifications, with the most common reasons including peripheral edema in 6 patients, hyperglycemia in 5, and agitation, anxiety, and insomnia each in 4. Fewer dose reductions were observed in patients receiving lower-dose dexamethasone (14/45 patients vs 14/19 patients in the higher-dose group; $P = .002$).

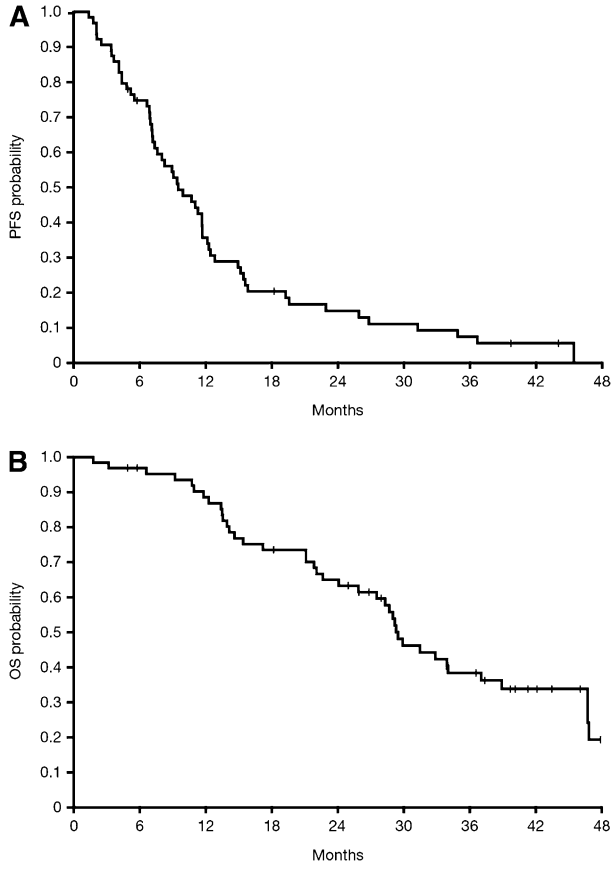

Figure 1. (A) PFS and (B) OS for all patients treated with lenalidomide-bortezomib-dexamethasone (censoring at time of transplant, n = 5). Estimated 6-, 12-, and 24-month PFS rates were 75% (95% CI, 62-84), 36% (95% CI, 24-48), and 15% (95% CI, 7-25), respectively. Estimated 12- and 24-month OS rates were 89% (95% CI, 77-84) and 65% (95% CI, 51-76), respectively.

Table 2. Best response to lenalidomide-bortezomib-dexamethasone

	N = 64		
Response	**n**	**%**	**90% CI**
CR	7	11	5-20
nCR	9	14	8-23
VGPR	2	3	1-10
PR	23	36	26-47
MR	10	16	9-25
SD	10	16	9-25
PD	1	2	0.1-7
Not evaluable*	2	3	1-10
CR+nCR	16	25	16-36
CR+nCR+VGPR	18	28	19-39
At least PR	41	64	53-74
At least MR	51	80	70-88

*Two patients were not evaluable for response; 1 received <1 cycle and 1 had nonmeasurable disease.

Outcomes

At data cutoff, after a median follow-up of 44 months, 42 patients had died, 37 (88%) because of disease and 5 from other causes. Fifty-eight patients had progressed, of whom 40 subsequently died; 2 patients died without PD. Five patients had undergone transplant: 2 progressed at 3 and 9 months' posttransplant and subsequently died; 1 progressed at 3 months' posttransplant, and 2 had not progressed. For the primary analysis of time-to-event outcomes (patients censored at time of transplant), there were 57 and 40 events for PFS and OS, respectively. The proportion of patients alive and without PD for ≥6 months (primary end point) was 75% (90% CI: 65-84; 48 of 64 eligible patients). Median PFS (Figure 1A) was 9.5 months (95% CI: 7.2-11.7), and median OS (Figure 1B) was 30 months (95% CI: 24-37).

The overall response rate was 64% (intent-to-treat population, Table 2). The median time to best response was 2.3 months (range 0.7-11.3), and the median DOR was 8.7 months (95% CI: 6.6-11.1).

Post hoc analyses compared response rate, PFS, and OS by baseline characteristics. Patient numbers were small for these analyses, which should be interpreted in this context. There were no significant differences ($P \geq .41$) in response rate according to patient subtypes (Table 3), including relapsed (62%) vs relapsed and refractory (67%) disease and abnormal (56%) vs normal (66%) metaphase cytogenetics. A marginal difference was detected between patients with or without chromosome 13 deletion (48% vs 78%, $P = .06$). Additionally, there were no significant differences seen in response rates according to prior bortezomib exposure ($P \geq .44$). No significant differences ($P \geq .19$) in PFS were observed according to patient/disease characteristics, with the exception of hemoglobin level (Table 4). This effect remained significant in a multivariate model (hazard ratio [HR] 0.23; 95% CI: 0.10-0.52; $P = .0004$) after adjusting for disease status, β_2-microglobulin, albumin, calcium, elevated LDH, and metaphase cytogenetics. For OS, differences in the risk for death were seen with hemoglobin level and elevated LDH (Table 4). After adjusting for other variables simultaneously in a multivariate model, only the effect of hemoglobin remained significant (HR 0.32; 95% CI: 0.13-0.79; $P = .01$).

Safety

Table 5 shows the most common treatment-related toxicities. Two patients (3%) had a DVT (possibly attributed to lenalidomide plus dexamethasone in one). Grade 3 atrial fibrillation was recorded in 2 patients (3%), was reversed with cardiac medication, and did not recur; these AEs were attributed to lenalidomide plus dexamethasone 40 mg, prompting dexamethasone dose reduction. Two on-study deaths occurred: 1 patient died after 3 cycles because of bronchopneumonia; the second died during cycle 18 (maintenance phase) because of acute stroke. The study site investigator attributed the first death as possibly related to immunosuppression by dexamethasone; the second death was not attributed to study drugs. No secondary malignancies were reported. Toxicities resulting in discontinuation were reported in 5 patients, including grade 3 motor PN (n = 2; attributed to bortezomib), grade 3 rash during cycle 1 (n = 1; attributed to lenalidomide), grade 3 myelodysplastic syndrome (n = 1; attributed to prior high-dose melphalan), and grade 2 nausea (n = 1; attributed to lenalidomide).

Thirty-four patients reported new or worsening PN (Table 5). Only 2 patients (3%) experienced any grade 3 PN (both grade 3 motor neuropathy, attributed to bortezomib). Despite bortezomib being held, and subsequent dose reduction upon improvement, both events eventually resulted in treatment discontinuation, although further improvement in PN was seen thereafter. No grade 3 sensory neuropathy or neuropathic pain was reported.

Discussion

In this first prospective phase 2 study in patients with relapsed or relapsed and refractory MM, lenalidomide-bortezomib-dexamethasone

Table 3. Comparison of response rate (PR or better) according to baseline characteristics

	Value	Patients, n	≥PR, n (%) [90% CI]	P*
Baseline characteristics				
ISS disease stage at diagnosis	I	17	12 (71) [48-88]	.99
	II/III	31	21 (68) [52-81]	
Durie-Salmon disease stage at diagnosis	I	9	6 (67) [35-90]	.99
	II/III	54	34 (63) [51-74]	
Current disease status	Relapsed	37	23 (62) [47-76]	.80
	Relapsed/ refractory	27	18 (67) [49-81]	
β_2-microglobulin, mg/L	<3.5	32	20 (63) [47-77]	.99
	≥3.5	29	19 (66) [49-80]	
Albumin, g/dL	<3.5	9	5 (56) [25-83]	.71
	≥3.5	54	36 (67) [55-77]	
Hemoglobin, g/dL	<12	42	25 (60) [46-72]	.41
	≥12	22	16 (73) [53-87]	
Serum calcium, g/dL	<10	53	34 (64) [52-75]	.99
	10-12	11	7 (64) [35-87]	
Elevated LDH	No	49	32 (65) [53-77]	.73
	Yes	10	6 (60) [30-85]	
Cytogenetics†				
Abnormal cytogenetics by metaphase karyotyping	Yes	16	9 (56) [33-77]	.55
	No	44	29 (66) [53-78]	
Presence of del13/13q by FISH	Yes	23	11 (48) [30-67]	.06
	No	18	14 (78) [56-92]	
Presence of del17p by FISH	Yes	8	4 (50) [19-81]	.42
	No	28	19 (68) [51-82]	
Presence of t(4;14) by FISH	Yes	4	2 (50) [10-90]	.60
	No	33	22 (67) [51-80]	
Presence of del17p and/or t(4;14) by FISH	Yes	10	5 (50) [22-78]	.43
	No	23	16 (70) [50-85]	

*Fisher's exact *P* value.

†Response rate not assessed according to presence/absence of t(14;16) because data were available in only 13 patients (unknown status in 51 patients).

Table 4. PFS and OS according to baseline characteristics, univariate comparison, and censoring at transplant

	PFS		OS	
	Crude HR (95% CI)	P*	Crude HR (95% CI)	P*
Baseline characteristics (reference† vs comparison)				
ISS disease stage at diagnosis (I vs II/III)	1.12 (0.60-2.12)	.71	1.96 (0.91-4.19)	.09
Durie-Salmon disease stage at diagnosis (I vs II/III)	1.51 (0.71-3.21)	.29	2.22 (0.79-6.26)	.13
Current disease status (relapsed vs relapsed/refractory)	1.16 (0.68-1.97)	.59	1.58 (0.85-2.96)	.15
β_2-microglobulin, mg/L (<3.5 vs ≥3.5)	1.08 (0.63-1.86)	.77	1.64 (0.85-3.13)	.14
Albumin, g/dL (<3.5 vs ≥3.5)	0.91 (0.44-1.88)	.80	1.27 (0.53-3.04)	.59
Hemoglobin, g/dL (<12 vs ≥12)	0.34 (0.18-0.63)	.0006	0.40 (0.20-0.82)	.01
Serum calcium, g/dL (<10 vs 10-12)	1.45 (0.72-2.92)	.29	0.92 (0.38-2.20)	.84
Elevated LDH (no vs yes)	1.61 (0.79-3.28)	.19	2.59 (1.22-5.52)	.01
Cytogenetics‡				
Abnormal cytogenetics by metaphase karyotyping (no vs yes)	1.04 (0.56-1.92)	.91	1.33 (0.63-2.80)	.45
Presence of del13/13q by FISH (no vs yes)	1.55 (0.78-3.10)	.21	2.59 (1.06-6.34)	.04
Presence of del17p by FISH (no vs yes)	0.85 (0.34-2.08)	.72	1.82 (0.65-5.04)	.25
Presence of t(4;14) by FISH (no vs yes)	0.56 (0.17-1.87)	.35	0.56 (0.13-2.37)	.43
Presence of del17p and/or t(4;14) by FISH (no vs yes)	0.89 (0.39-2.02)	.78	1.69 (0.67-4.22)	.26

*Wald χ-square *P* value.

†Reference groups: ISS stage I, Durie-Salmon stage 1, disease status-relapsed, β_2-microglobulin <3.5 g/dL, albumin <3.5 g/dL, hemoglobin <12 g/dL, calcium <10 g/dL, no elevated LDH, normal metaphase and FISH cytogenetics. Number of patients with missing clinical characteristics: ISS at diagnosis (N = 16), Durie-Salmon stage at diagnosis (N = 1), β_2-microglobulin (N = 3), albumin (N = 1), elevated LDH (N = 5). Number of patients with cytogenetics results are provided by abnormality type and noted in parentheses: metaphase cytogenetics (N = 60), del13q (N = 41), del17p (N = 36), t(4;14) (N = 37), t(11;14) (N = 38), t(14;16) (N = 13); other immunoglobulin H translocation (N = 34), del17p and/or t(4;14) (N = 33).

‡PFS and OS not assessed according to presence/absence of t(14;16) because data were available in only 13 patients (unknown status in 51 patients).

was active and well tolerated. The median PFS (per stringent modified EBMT criteria) was 9.5 months, and the 6-month PFS rate of 75% substantially exceeded that at which the regimen could be considered effective. Response rates were high, including 25% CR/nCR, and durable responses were observed (median DOR: 8.7 months). Median OS was 30 months, with 22 patients (34%) alive after a median follow-up of almost 3.7 years. These results were observed despite a high proportion of patients having received prior thalidomide (75%) and/or prior bortezomib (53%), although only 6% received prior lenalidomide; nonetheless, a substantial proportion of patients entered the study with disease that was relapsed and refractory to several agents.

Several other studies of IMiD-proteasome inhibitor-dexamethasone triplet regimens in patients with relapsed and/or refractory MM have been reported recently, including studies of bortezomb-thalidomide-dexamethasone[16] and carfilzomib-lenalidomide-dexamethasone.[28,29] Comparisons across studies should be interpreted with caution because of potential confounding factors such as differences in patient characteristics and prior therapies; it should also be noted that OS may be influenced by the availability and use of different subsequent therapies. Furthermore, it is important to note that the doses of lenalidomide (15 mg) and bortezomib (1.0 mg/m^2) used in the present triplet study were lower than in the other studies, in which each agent was dosed at 25 mg and 1.3 mg/m^2, respectively. Acknowledging this context, the phase 3 Multiple Myeloma Velcade at Relapse/Intergroupe Francophone du Myélome 2005-04 study of bortezomib-thalidomide-dexamethasone vs thalidomide-dexamethasone in MM patients who had relapsed after 1 or more stem cell transplant[16] demonstrated a response rate for the triplet regimen of 86%, including 45% CR/nCR, with a median DOR of 17.2 months and a median time to progression (TTP) of 19.5 months. Although these data seem superior to our findings, the 24-month OS rate of 71% appears similar to the 65% rate reported in our study. The patients in the Multiple Myeloma Velcade at Relapse/Intergroupe Francophone du Myélome 2005-04 study were less heavily pretreated than our patient population, with only 20% and 10% of those in the bortezomib-thalidomide-dexamethasone arm having receiving prior bortezomib and thalidomide, respectively.[16] It is also important to note the substantially higher rate of grade ≥3 PN reported with bortezomib-thalidomide-dexamethasone of 31%,[16] compared with 3% in the present study. In the PX-171-006 phase 2 dose-expansion study of carfilzomib-lenalidomide-dexamethasone in relapsed MM patients who had received 1 to 3 prior lines of therapy,[29] among 52 patients in the maximum planned dose cohort the overall response rate was 77%, including 42% VGPR or better, with a median DOR of 22.1 months and a median PFS of 15.4 months (OS data not reported). The regimen was associated with higher rates of grade 3/4 lymphopenia (48%) and anemia (19%) but a low rate of grade 3 PN (2%). None of the patients had received prior carfilzomib, but 81% and 73% had prior bortezomib and lenalidomide, respectively. Patients received carfilzomib at the approved dose of 20/27 mg/m^2 and lenalidomide at 25 mg on days 1 through 21 of 28-day cycles (in contrast to our dosing schedule of 15 mg on days 1-14 of 21-day cycles). It is possible that use of bortezomib at the approved dose of 1.3 mg/m^2 plus lenalidomide at 25 mg within the triplet regimen may have resulted in greater activity (and an altered toxicity profile) than seen in the present study.

Nevertheless, our results are noteworthy in the context of previous findings from comparable studies using standard doses of single-agent bortezomib and bortezomib or lenalidomide plus dexamethasone. In the phase 3 Assessment of Proteasome Inhibition for Extending Remissions trial (NCT #00048230),[4] the response rate with single-agent bortezomib was 43%, median TTP was 6.2 months, and median OS was 29.8 months. In the phase 3 MMY-3021 study (NCT #00722566) of IV vs subcutaneous bortezomib ± dexamethasone, the response rate was 52% in both arms, including 22% vs 23% CR/nCR, and the median PFS was 8.4 vs 9.3 months.[30,31] In the MM-009 (NCT00056160)[6] and MM-010 (NCT #00424047)[5] phase

Table 5. Treatment-related AEs reported in >15% of patients in the treated population (N = 64), plus all other events reported at grade 3-5 severity

	AEs, n (%)			
	All grades	Grade 3	Grade 4	Grade 5
Neuropathy, sensory*	34† (53)	–	–	–
Fatigue	32 (50)	3 (5)	–	–
Neutropenia	27 (42)	18 (28)	1 (2)	–
Diarrhea without prior colostomy	26 (41)	2 (3)	–	–
Muscle pain	25 (39)	–	–	–
Hyperglycemia	24 (38)	6 (9)	–	–
Edema, limb	22 (34)	2 (3)	–	–
Thrombocytopenia	21 (33)	8 (13)	6 (9)	–
Constipation	19 (30)	–	–	–
Insomnia	18 (28)	–	–	–
Pain in extremity	15 (23)	1 (2)	–	–
Anemia	15 (23)	1 (2)	–	–
Nausea	15 (23)	–	–	–
Leukopenia	11 (17)	6 (9)	–	–
Neuropathic pain	11 (17)	–	–	–
Neuropathy, motor	9 (14)	2 (3)	–	–
Rash/desquamation	9 (14)	1 (2)	–	–
Dizziness	9 (14)	1 (2)	–	–
Lymphopenia	7 (11)	7 (11)	–	–
Hyponatremia	7 (11)	5 (8)	–	–
Fever without neutropenia	7 (11)	1 (2)	–	–
Hypophosphatemia	6 (9)	5 (8)	1 (2)	–
Pulmonary/upper respiratory, other	4 (6)	2 (3)	1 (2)	1 (2)
Atrial fibrillation	3 (5)	2 (3)	–	–
Hypotension	3 (5)	1 (2)	–	–
Lung infection with grade 0-2 neutropenia	2 (3)	1 (2)	–	–
Confusion	2 (3)	–	1 (2)	–
Apnea	1 (2)	1 (2)	–	–
Psychosis	1 (2)	–	1 (2)	–

–, event did not occur at this grade.

*22 cases were grade 1, 12 cases were grade 2.

†PN was reported in 28 of 41 patients who had no PN at baseline (22 had grade 1, 6 grade 2) and 6 of 23 patients with grade 1 PN at baseline (increasing to grade 2 during the study). Sensory PN was manageable and 16 of the 34 patients had improvement or resolution of their PN, including resolution to grade 0 in 10 patients who had no PN at baseline and in 1 patient with grade 1 PN at baseline. However, 2 patients with grade 1 events that resolved to grade 0 and 2 patients with grade 2 events that improved to grade 1 subsequently experienced another PN event or worsening to grade 2, respectively.

3 studies of lenalidomide-dexamethasone, response rates were 61% and 60%, respectively, and in a combined updated analysis[32] the median TTP and median OS were 13.4 and 38.0 months, respectively. As with the present study, these studies included patients who had received 1 to 3 prior regimens, including 30% to 53% prior thalidomide/IMiD, 4.5% to 11% prior bortezomib, and ~0% prior lenalidomide. However, a higher proportion of patients in the present study had received prior novel agent-based therapy, including bortezomib and lenalidomide; notably, response to the lenalidomide-bortezomib-dexamethasone triplet regimen used in the present study was not significantly affected by prior bortezomib exposure. Also noteworthy for comparison are the findings of a phase 2 study of predominantly bortezomib plus dexamethasone as second-line MM therapy, which showed a response rate of 66% and a median TTP and median PFS of 9.5 and 8.6 months, respectively.[33]

A recent analysis evaluated outcomes in MM patients who were refractory to prior bortezomib and were relapsed following, refractory to, or ineligible to receive an IMiD; 32% of patients achieved a PR or better, and the median event-free survival and OS were 5 and 9 months, respectively.[34] In this context, our 64% response rate and outcomes data appear promising, albeit acknowledging that our study included fewer refractory patients and not all patients had received both prior bortezomib and an IMiD. Nevertheless, lenalidomide-bortezomib-dexamethasone has also shown notable activity in a more advanced population, with a response rate of 47% in a retrospective analysis of 30 more heavily pretreated relapsed/refractory MM patients with greater prior exposure to novel agents.[35] Activity of lenalidomide-bortezomib-dexamethasone (using doses of lenalidomide 25 mg and bortezomib 1.3 mg/m^2) has also been demonstrated in previously untreated MM patients,[13,36] with a 100% response rate and an estimated 18-month OS rate of 97% in a prospective phase 1/2 study.[13] Indeed, the widespread use of lenalidomide-bortezomib-dexamethasone as a frontline regimen in the United States may affect its use in relapsed/refractory patients who have previously received this triplet; nevertheless, data from our study suggest that the regimen represents an active option in this setting, both among patients not receiving this therapy as frontline treatment and also among patients previously exposed to the constituent components of the triplet.

Toxicities observed with lenalidomide-bortezomib-dexamethasone were manageable and consisted mainly of grade 1/2 myelosuppression. The lengthy median treatment duration (8.0 months) indicated that the combination was well tolerated. A low rate (3%) of grade 3 PN was observed (2 cases of reversible motor neuropathy), possibly reflecting usage of bortezomib 1.0 instead of 1.3 mg/m^2, which has previously been associated with fewer cases of, or less severe, PN.[9,37] Further, concomitant dexamethasone dosing may have contributed to a protective effect against bortezomib-associated PN.[38,39] In addition, IV bortezomib was used in this study, and subcutaneous administration may significantly further reduce PN as part of this combination,[30,31] but further studies with this combination are needed and are either planned or under way. Low rates of grade 3 or 4 PN have been seen in other studies of lenalidomide-bortezomib–containing regimens[11,13,19,36]; one hypothesis is that this might be associated with the immunomodulatory and cytokine-reducing properties of lenalidomide, with the caveats that the myalgia and low-grade PN sometimes associated with lenalidomide use can be confounding, and acknowledging that neurotoxicity with thalidomide-containing regimens remains a challenge.[16,38,40]

A low DVT rate (3%) was also recorded, which may be linked to the use of thromboprophylaxis, a 15-mg dose of lenalidomide, low-dose dexamethasone in 41 patients,[12] and/or a possible protective effect of bortezomib.[41] Further, cardiotoxicity was limited, with only 2 cases of grade 3 atrial fibrillation, which were attributed to lenalidomide plus the higher dose of dexamethasone (40 mg) and were reversible with cardiac medication and dose reduction; importantly, no attributable cases of significant cardiac dysfunction, cardiomyopathy, or ischemia were reported, and nor was otherwise unexplained dyspnea on exertion.

Although the dexamethasone dose was reduced in the present study because of tolerability issues, higher lenalidomide and bortezomib doses, in combination with dexamethasone 20 mg, may be tolerable in this setting among selected patients. Lenalidomide 25 mg, bortezomib 1.3 mg/m^2, and dexamethasone 20 mg as frontline therapy has demonstrated favorable tolerability[13]; however, this was in a different patient population (previously untreated, compared with relapsed or relapsed and refractory patients in the present study). Use of subcutaneous over IV bortezomib may also significantly improve the safety profile.[30,31] Furthermore, the phase 1 MTD used in the present study was defined based on reversible and readily manageable dose-limiting toxicities.[19] This suggests that higher doses of lenalidomide and bortezomib could have been used, which may have resulted in higher

activity, as indicated by noncomparative studies of bortezomib at 1.3 and 1.0 mg/m^2.[37,42]

Given the observed effectiveness and tolerability of lenalidomide-bortezomib-dexamethasone, there is potential for further development of this 3-drug regimen, including the addition of a fourth agent, as has been investigated with combinations of bortezomib and thalidomide.[43-47] Reports from phase 2 studies of lenalidomide-bortezomib-dexamethasone plus pegylated liposomal doxorubicin in frontline[11] and relapsed/refractory MM[48] have demonstrated the feasibility and activity of this 4-drug approach, although comparative studies are required to determine if efficacy is improved. Of interest in this context, frontline studies have suggested no additional benefit in adding cyclophosphamide to bortezomib, dexamethasone, and lenalidomide/thalidomide.[45,46] Finally, second-generation proteasome inhibitors such as carfilzomib and ixazomib citrate (MLN9708) in combination with lenalidomide-dexamethasone have shown great promise and important differences in toxicities, most notably less neurotoxicity, especially in newly diagnosed patients, offering yet another series of options as well as validating the importance of this combination approach.[29,49,50]

In conclusion, lenalidomide-bortezomib-dexamethasone appears an effective and tolerable combination in relapsed and relapsed/refractory MM patients, demonstrating substantial activity regardless of prior therapy or adverse prognostic characteristics.

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Authorship

Contribution: P.G.R. was the principal investigator; P.G.R., S.J., A.J., S.L., N.S.R., M.A., I.M.G., R.L.S., T.H., R.K., D.L.-E., C.S.M., and K.C.A. designed the research; P.G.R., S.J., A.J., S.L., N.S.R., M.A., I.M.G., R.L.S., N.C.M., A.M., D.H.V., J.L.K., K.C., M.M., L.E.L., J.F., M.E.M., D.W., D.F., T.H., C.S.M., and K.C.A. performed the research; W.X. and E.W. performed statistical analyses; P.G.R., W.X., S.J., A.J., S.L., N.S.R., M.A., I.M.G., R.L.S., N.C.M., A.M., D.H.V., J.L.K., E.W., and K.C.A. analyzed and interpreted the data; P.G.R., S.J., A.J., S.L., D.H.V., C.S.M., E.W., and K.C.A. wrote the manuscript; and all authors reviewed the draft manuscript and approved the final version for submission.

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