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ORIGINAL REPORT

Single-Agent Bortezomib in Previously Untreated Multiple Myeloma: Efficacy, Characterization of Peripheral Neuropathy, and Molecular Correlations With Response and Neuropathy

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
To assess efficacy and safety of single-agent bortezomib in previously untreated patients with multiple myeloma, investigate prevalence of baseline and treatment-emergent polyneuropathy, and identify molecular markers associated with response and neuropathy.

Patients and Methods
Patients received bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, for up to eight 21-day cycles. A subset of patients underwent neurophysiologic evaluation pre- and post-treatment. Bone marrow aspirates were performed at baseline for exploratory whole-genome analyses.

Results
Among 64 patients, 41% had partial response or better, including 9% complete/near-complete responses; median duration of response was 8.4 months. Response rates did not differ in the presence or absence of adverse cytogenetics. After median follow-up of 29 months, median time to progression was 17.3 months. Median overall survival had not been reached; estimated 1-year survival was 92%. Thirty-two patients successfully underwent optional stem-cell transplantation. Bortezomib treatment was generally well tolerated. At baseline, 20% of patients had sensory polyneuropathy. Sensory polyneuropathy developed during treatment in 64% of patients (grade 3 in 3%), but proved manageable and resolved in 85% within a median of 98 days. Neurologic examination, neurophysiologic testing, and measurements of epidermal nerve fiber densities in 35 patients confirmed pretreatment sensory neuropathy in 20% and new or worsening neuropathy in 63%. Pharmacogenomic analyses identified molecular markers of response and treatment-emergent neuropathy, which will require future study.

Conclusion
Single-agent bortezomib is effective in previously untreated myeloma. Baseline myeloma-associated neuropathy seems more common than previously reported, and bortezomib-associated neuropathy, although a common toxicity, is reversible in most patients.

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INTRODUCTION

Novel agents have transformed the management of multiple myeloma (MM),[1,2] including the proteasome inhibitor bortezomib (VELCADE, Millennium Pharmaceuticals, Boston, MA and Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, NJ). Bortezomib is approved in the United States for the treatment of MM, having demonstrated substantial activity in combination in newly diagnosed patients[1,3,4] and alone and in combination in relapsed/refractory disease.[1,2,5] The safety profile of bortezomib has been well characterized in relapsed/refractory MM.[6-8] One of the key toxicities is peripheral neuropathy (PN),[6-8] which is reversible in most patients.[4,9-11] MM itself has also been associated with PN in 3% to 13% of patients.[12-16] Pharmacogenomic studies of patients with relapsed/refractory MM receiving bortezomib have identified gene sets associated with response and survival.[17] In addition, parameters intrinsic to MM (such as proinflammatory proteins and vasoactive mediators) might contribute to the emergence of PN with

bortezomib and be reflected in primary tumor cell gene expression profiles.

The present study is the first prospective investigation of single-agent bortezomib as induction therapy for MM and provides a unique setting for investigating disease-related and bortezomib-associated PN, as well as exploration of pharmacogenomic aspects of MM, without the heterogeneous molecular changes that may accumulate from previous treatments. Study objectives therefore included (1) evaluation of efficacy and safety of single-agent bortezomib; (2) assessment of prevalence, incidence, and severity of PN by standard toxicity criteria and modified consensus criteria based on extensive neurologic evaluation; (3) identification of candidate molecular markers associated with response to bortezomib and emergence of PN.

PATIENTS AND METHODS

Eligibility

Eligible patients were ≥ 18 years of age with previously untreated symptomatic MM and measurable disease. Other eligibility criteria included Karnofsky performance status ≥ 60%; platelets ≥ 50×10^9/L (≥ 30×10^9/L with extensive bone marrow infiltration), hemoglobin ≥ 8.0 g/dL, and absolute neutrophil count ≥ 0.5×10^9/L before bortezomib administration; and adequate liver function.

Patients were excluded if they had polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, more than grade 2 PN, were receiving more than 10 mg daily (prednisone equivalent) of corticosteroids for other medical conditions, or had creatinine clearance less than 30 mL/min within 14 days before enrollment.

Study Design

This open-label, phase II study was conducted at six centers in the United States between December 2003 and July 2007. The study was approved by all participating institutional review boards. Patients received bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 of 21-day cycles for up to eight cycles[8] or for two cycles beyond confirmed complete response (CR). Patients with progressive disease (PD) or unacceptable toxicity discontinued treatment. Candidates for high-dose therapy plus autologous stem-cell transplantation (ASCT) could be discontinued to undergo this procedure at the investigator's discretion. Patients ineligible for or who chose to defer ASCT and who experienced benefit from treatment after completing the planned eight cycles could continue bortezomib.

Dosing was delayed or modified for febrile neutropenia, grade 4 hematologic toxicity, or grade 3 or worse nonhematologic toxicity considered treatment-related by the investigator. Patients who experienced treatment-related neuropathic pain (NP) and/or PN were managed according to established dose-modification guidelines (Appendix Table A1, online only)[10]; step-wise pharmacologic interventions[18,19] were also recommended (Appendix, online only).

Treatment with bisphosphonates, hematopoietic growth factors, antiemetics, and antidiarrheals was permitted, as was concurrent local radiotherapy if indicated for bone disease or plasmacytoma, but not concomitant corticosteroids. Anti-viral prophylaxis using acyclovir against herpes zoster virus was recommended in all patients.

Efficacy and Safety Assessments

Blood and 24-hour urine samples were taken at screening and on day 11 of each cycle for serum/urine protein electrophoresis with M-protein quantitation and immunofixation. Bone marrow aspirate and biopsy were performed for assessment of CR. Response was assessed after every two cycles according to European Group for Blood and Marrow Transplantation criteria,[20] modified to include near CR (nCR; CR, but immunofixation-positive for M-protein).[7] Patients were also evaluated for very good partial response (VGPR; ≥ 90% M-protein reduction) per International Uniform Response Criteria.[21] Adverse events (AEs) were monitored throughout the study, using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. At the end-of-study visit, efficacy and safety assessments were repeated. Patients were observed thereafter for disease progression and toxicity, including PN.

Neurologic Assessments

Patients were examined by a neurologist at screening, at end-of-study visit, and during therapy if screening results were abnormal or if clinically indicated. Total neuropathy score was calculated for each visit.[10] Patients completed the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity questionnaire[22] on days 1 and 8 of each cycle and at study end.

Neurophysiologic testing, including motor and sensory nerve conduction studies (NCS), quantitative sensory testing (QST), and autonomic testing, were performed for all patients treated at the Dana-Farber Cancer Institute (Appendix). Skin biopsies were performed to measure intraepidermal nerve fiber (IENF) density, as a reduction in IENF density is the standard test.[23-25] Congo red staining was used to test for amyloid deposition. Presence or absence of PN was determined using modified consensus criteria.[26]

Cytogenetics and Pharmacogenomics

Bone marrow aspirate and biopsy were performed at baseline for morphology, cytogenetic assessment, and pharmacogenomics. Cytogenetics were processed using fluorescent in situ hybridization techniques according to each participating center's practice. Pharmacogenomic analyses were conducted using samples from patients who provided additional consent, according to algorithms described in the Appendix.

Statistical Analysis

Median time to response and duration of response (time from first evidence of response to progression; receipt of nonprotocol therapy, including ASCT or other therapies, except bisphosphonates or erythropoietin; or death) were reported among responding patients. Estimates of time to progression (TTP), progression-free survival (PFS), and event-free survival (EFS; event defined as progression, receipt of nonprotocol therapy, or death) were calculated using Kaplan-Meier methodology. TTP, PFS, EFS, and overall survival (OS) were assessed from start of treatment; patients receiving nonprotocol therapy without progression were censored in TTP/PFS analyses. Responses were assessed according to cytogenetic abnormalities, including chromosome 13 deletion (del(13)), using Fisher's exact test. Exploratory analyses included identification of gene expression profiles associated with response and emergence of PN. All reported *P* values are two-sided; no adjustments were made for multiple comparisons.

RESULTS

Patient Enrollment and Treatment

Sixty-six patients were enrolled; one withdrew consent and one came off study before receiving therapy for rapid PD with associated multisystem dysfunction requiring high-dose corticosteroids. Characteristics of 64 patients who received at least one bortezomib dose are listed in Table 1.

Thirty-nine patients (61%) had received nonprotocol therapy at the time of final analysis, including 11 patients who developed PD before additional therapy. Of these, 32 proceeded to high-dose treatment and ASCT; nine patients received additional treatment before ASCT. Median CD34$^+$ cells collected was 9.6×10^6/kg (range, 2.34 to 57.8); no difficulty in collection was reported. No unexpected toxicities during ASCT were described, with recoveries and clinical course considered otherwise unremarkable.

Efficacy

The CR plus partial response (PR) rate was 41%, including 9% CR/nCR (Table 2). Median time to response (n = 26) was 1.7 months,

Table 1. Patient Demographic and Baseline Characteristics

Characteristic	No. of Patients (N = 64)	%
Age, years		
Median	60	
Range	33-76	
Male sex	44	69
White race	59	92
KPS ≤ 90%	56	88
Myeloma type*		
IgG	36	56
IgA	15	24
Light chain disease	10	16
Durie Salmon stage		
I	5	8
II	27	42
III	32	50
ISS stage		
I	32	50
II	26	41
III	4	6
Unknown	2	3
Abnormal cytogenetics by FISH	34/62	55
Presence of lytic lesions	45	70
Serum β_2-microglobulin, mg/dL†		
Median	3.3	
Range	1.6-9.5	
β_2-microglobulin > 5.5 mg/dL	4	6
Serum albumin, g/dL		
Median	3.9	
Range	2.5-5.5	
Albumin ≥ 3.5 g/dL	50	78
LDH > ULN	3/54	6

Abbreviations: KPS, Karnofsky performance status; Ig, immunoglobulin; ISS, International Staging System[27]; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal.
*N = 61; data not available for three patients.
†N = 62.

Table 2. Response to Bortezomib Monotherapy

Outcome	No. of Patients (N = 64)	%
Best response to treatment		
CR	2	3
nCR	4	6
PR	20	31
VGPR	5	8
MR	14	22
NC	21	33
PD	2	3
Not evaluable	1	2
CR + PR	26	41
95% CI, %	30 to 52	
CR + PR + MR	40	63
95% CI, %	51 to 73	
≥ VGPR	11	17
TTR, months		
Median	1.7	
Range	0.3 to 5.4	
DOR, months		
CR + PR, n = 26*		
Median	8.4	
95% CI	6.2 to 13.4	
CR + PR + MR, n = 40†		
Median	7.1	
95% CI	5.2 to 10.9	

Abbreviations: CR, complete response; nCR, near complete response; PR, partial response; MR, minimal response; NC, no change; PD, progressive disease; VGPR, very good partial response; TTR, time to first response; DOR, duration of response.
*Twelve patients underwent autologous stem-cell transplantation (ASCT; n = 8) or other nonprotocol therapy (n = 4) without having experienced disease progression.
†An additional four patients with MR underwent ASCT (n = 2) or other nonprotocol therapy (n = 2) without having experienced disease progression. Receipt of ASCT/other nonprotocol therapy was treated as an event in these DOR analyses.

and median duration of response was 8.4 months. Fluorescent in situ hybridization cytogenetics were available from 62 assessable patients and were abnormal in 34 patients (55%). No correlation was detected between presence/absence of any cytogenetic abnormality and response ($P = .713$). Response rate did not seem to differ with presence versus absence of abnormalities (PR or better, 44% *v* 36%; minimal response [MR] or better, 65% *v* 64%); the proportions of patients with abnormal cytogenetics were not significantly different when patients were stratified by response of PR or better ($P = .606$) or MR or better ($P = 1.00$). Del(13) was present in 17 patients (27%); del(13) presence/absence was not correlated with response ($P = .867$). No difference was detected in response rates between those patients with versus without del(13) (PR or better, 41% *v* 40%; MR or better 59% *v* 67%), but rates of del(13) were not significantly different when patients were stratified by response of PR or better ($P = 1.00$) or MR or better ($P = .568$).

With a median follow-up of 29 months, 14 patients have died and 26 patients have experienced disease progression (six of whom subsequently died). Median TTP, PFS, and EFS (Fig 1A) were 17.3 months (95% CI, 10.6 to 23.0 months), 17.0 months (95% CI, 8.6 to 21.5 months), and 7.1 months (95% CI, 6.2 to 8.6 months), respectively. Median OS (Fig 1B) was not reached; estimated 30-month OS rate was 79% (95% CI, 68% to 91%) for all patients and 82% (95% CI, 66% to 98%) and 78% (95% CI, 63% to 92%) for patients who did and did not undergo transplantation, respectively.

Drug Exposure and Safety

Patients received a median of eight cycles (range, two to eight cycles); 36 patients (56%) completed treatment per protocol (33 patients received eight cycles and three patients who achieved CR received < eight cycles). Median duration of bortezomib therapy was 5.1 months (range, 0.8 to 6.1 months); median cumulative dose was 33.65 mg/m^2 (range, 7.80 to 41.60 mg/m^2). Reasons for early termination included PD (n = 9), unacceptable toxicity (n = 9), physician decision (n = 3), lack of response (n = 3), death (n = 2), patient withdrawal (n = 1), and initiation of nonprotocol therapy (n = 1).

Sixty-two patients (97%) experienced at least one AE; 33 patients (52%) experienced grade 3 or 4 AEs. Common AEs are shown in Table 3. Treatment was generally well tolerated, and side effects proved manageable. Dose modifications and delays were required in 19 (30%) and eight patients (13%), respectively, primarily for PN. No deep vein thrombosis was seen. Two deaths were reported within 30 days of last bortezomib dose, attributed to heart failure and sudden

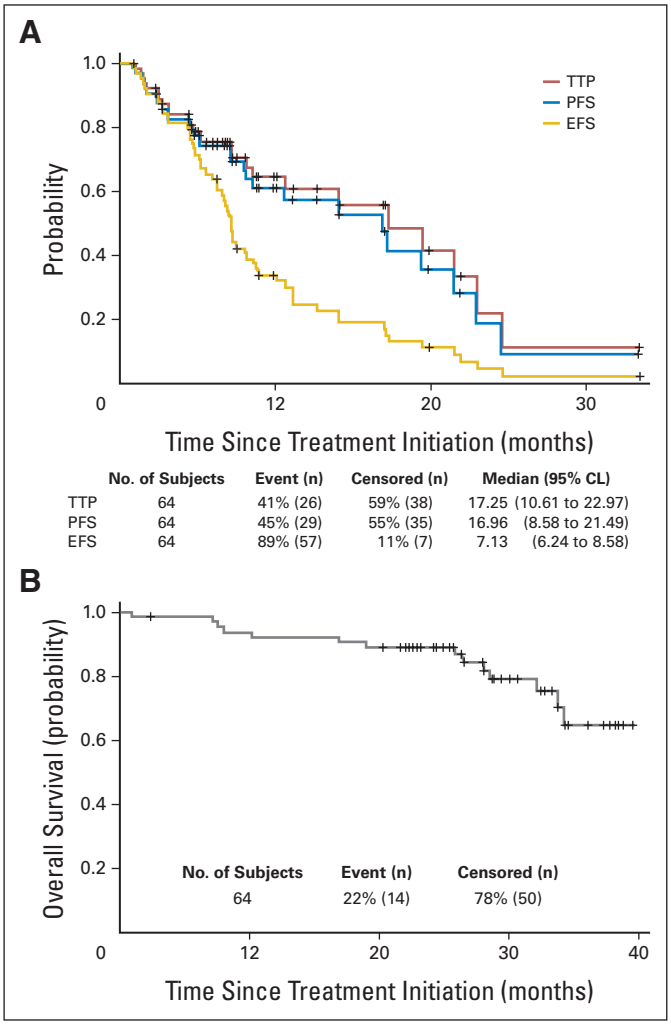

Fig 1. (A) Kaplan-Meier estimates of time to progression (TTP), progression-free survival (PFS), and event-free survival (EFS). (B) Kaplan-Meier estimates of overall survival.

death, both considered unrelated to bortezomib by the treating physician.

Assessment of Peripheral Neuropathy

NCI-CTCAE grading. At baseline, 13 patients (20%) had sensory PN per NCI-CTCAE (12 grade 1, one grade 2), three patients (5%) reported motor neuropathy (one grade 1, two grade 2), and one patient reported grade 1 NP. Treatment-emergent (new or worsening from baseline) sensory PN was reported in 41 patients (64%; 36% grade 1, 25% grade 2, 3% grade 3), with treatment-emergent NP reported in eight patients (13%; 3% grade 1, 5% grade 2, 5% grade 3) and motor neuropathy reported in seven patients (11%; 6% grade 1, 2% grade 2, 3% grade 3). Overall, five patients (8%) developed any grade 3 neuropathy (one sensory/NP, one sensory/motor, two NP only, one motor only). Baseline PN was present in both patients who developed grade 3 treatment-emergent PN.

Median time to onset of sensory PN of any grade was 63 days (range, 1 to 169 days). Median time to onset of grade 2 or 3 PN (n = 18) was 72 days (range, 10 to 154 days). At last follow-up, 35 (85%) of 41 patients had resolution of treatment-emergent sensory

Table 3. Most Common AEs Reported in All 64 Patients With Overall Incidence of ≥ 25% and/or Grade 3 or 4 Incidence of ≥ 5%

AE	Any Grade		Grade ≥ 3	
	No.	%	No.	%
Sensory neuropathy	41	64	2	3
Constipation	34	53	2	3
Nausea	34	53	1	2
Fatigue	28	44	2	3
Thrombocytopenia	28	44	3	5
Leukopenia	22	34	4	6
Lymphopenia	21	33	14	22
Diarrhea without prior colostomy	20	31	0	0
Rash/desquamation	16	25	1	2
Neutropenia	12	19	4	6
Neuropathic pain	8	13	3	5
Hypotension*	7	11	3	5
Dyspnea	6	9	3	5
Syncope	3	5	3	5

Abbreviation: AE, adverse event.
*Transient, not considered related to autonomic neuropathy.

PN during or after completion of therapy, including both patients with grade 3 PN. Median time to resolution from onset of most severe grade was 98 days (range, 7 to 665 days). Treatment-emergent NP had resolved in seven (88%) of eight patients at last follow-up.

Twelve patients required dose reductions for sensory PN or NP; one patient required a second dose reduction. Per protocol, pharmacologic interventions for neuropathy included multivitamins with B complex (n = 32), folic acid (n = 28), vitamin B_6 (n = 23), alpha-lipoic acid, acetyl-carnitine/L-carnitine (n = 19 each), vitamin E (n = 15), gabapentin (n = 14), magnesium (n = 10), and glutamine (n = 4).

Neurophysiologic and skin biopsy evaluations. Thirty-five patients underwent extensive testing to detect large- and small-fiber PN (Appendix Table A2, online only). At baseline, 19 patients (54%; 90% CI, 39% to 69%) had clinical symptoms or signs of PN or any single abnormal laboratory test (NCS, QST of temperature perception, autonomic studies, or IENF density). Seven patients (20%) had sensory PN, including six patients with pure small-fiber and one with mixed large- and small-fiber PN, based on modified consensus criteria.[26] Mean IENF density relative to age-matched normals was in the 25th percentile at study entry (Fig 2), whereas mean IENF density in seven patients with baseline PN was at the ninth percentile. Eight patients (23%) had abnormal IENF density (< fifth percentile) at baseline. There was no evidence of amyloid deposition in any skin biopsies before therapy.

In total, 22 (63%) of these 35 patients (90% CI, 48% to 76%) developed new (n = 15) or worsening (n = 7) PN by modified consensus criteria[26] during bortezomib treatment. Among the 15 patients with new PN, seven patients had pure small-fiber PN and eight patients had both large- and small-fiber involvement. The predominant symptoms were burning and tingling pain in the legs. None of the patients experienced weakness or autonomic symptoms, including orthostatic hypotension. Median total PN score increased significantly from baseline due to increases in sensory symptoms and signs ($P < .01$), as did Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity score ($P < .01$; Table 4).

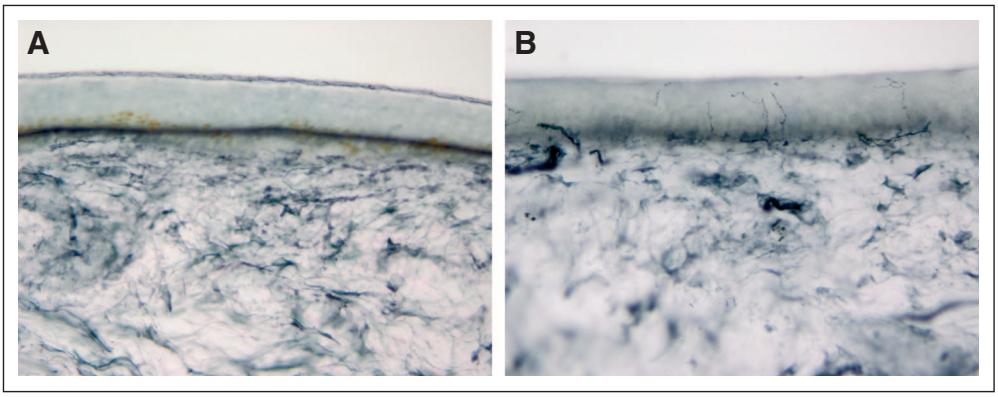

Fig 2. Representative PGP9.5 immuno-labeled pretreatment images of axons in vertically sectioned punch skin biopsies from patients; stratum corneum of the epidermis is uppermost with dermis below. (A) Biopsy from a 46-year-old man that is devoid of expected axonal innervation at baseline. Quantitation of intraepidermal nerve fibers identified a neurite density of 65/mm^2 skin surface area, at the third centile for age and diagnostic of small-fiber polyneuropathy. (B) Biopsy from a 54-year-old woman before therapy. Quantitation of intraepidermal nerve fibers identified a neurite density of 325/mm^2 skin surface area, at the 78th centile for age, which is within the normal range. These tissues were photographed using a Leica Microsystems (Wetzlar, Germany) DM/LS light microscope (40x objective) coupled to an Olympus (Tokyo, Japan) DP25 Microscope Digital Camera. No digital processing was performed.

On follow-up skin biopsies, there was no reduction in mean IENF density compared with baseline; unexpectedly, there was a trend toward increased density compared with baseline, but no new evidence of amyloid deposition.

Exploratory Pharmacogenomics

Baseline gene expression profiles were analyzed from 23 assessable patients who had achieved best response of CR (n = 2), nCR (n = 1), PR (n = 8), MR (n = 4), or stable disease (SD; n = 8). Transcripts were identified by pattern recognition analyses, which distinguished patients who achieved SD or PD from responders (MR or better). These include molecules implicated in tumorigenesis and/or bortezomib response, as well as molecules with an established role in protein translation. There was no difference ($P = .62$) in the expression-based proliferation index of myeloma cells from responding patients versus SD/PD and no correlation of response with the gene-expression signatures of activated NF-κB signaling reported by Schaffer et al[28] ($P = .86$) or Annunziata et al[29] ($P = .40$).

Baseline gene expression profiles were analyzed for 25 patients, nine patients with and 16 patients without treatment-emergent PN. Transcripts that distinguish patients with treatment-emergent PN from other patients were identified. These transcripts do not involve genes that are etiologically linked to the development of PN, but instead include distinct classes involved in protein translation, ribosomal proteins, and cell-surface markers. However, none of these transcriptional signatures showed a significant correlation with the presence of clinical and/or subclinical PN at baseline, presumably as a result of the small numbers involved.

DISCUSSION

The results of this phase II multicenter study demonstrate that single-agent bortezomib is active in newly diagnosed MM, with an overall response rate of 41%, including 9% CR/nCR and 17% ≥ VGPR. These data, notably the rate of VGPR or better, compare favorably with single-agent thalidomide or dexamethasone in frontline MM.[30-35] Consistent with other studies in frontline and relapsed MM, abnormal cytogenetics, including del(13), did not seem to lessen response to bortezomib.[36-39] Substantially enhanced activity has been reported with bortezomib-based combination regimens,[4,40-43] as reviewed recently.[1,3] Such combinations are therefore more likely to be used than single-agent bortezomib. Indeed, several bortezomib-based regimens are included as frontline treatment options in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Multiple Myeloma.[44] Even so, the benefit of a corticosteroid-sparing approach in selected patients remains an important consideration.

After a median follow-up of 29 months, median OS has not been reached, and the 30-month survival probability was 79%. Almost half the patients have proceeded to receive ASCT; our data on stem-cell collection support previous findings that use of bortezomib in induction therapy before ASCT has no adverse impact on stem-cell mobilization or collection.[45]

Toxicities were manageable, no unexpected AEs were seen, and the safety profile was similar to that seen with single-agent bortezomib in patients with relapsed and/or refractory MM.[6-8] Importantly, no thromboembolic events were reported, which can be a significant challenge both in the frontline and relapsed setting with certain combination approaches.[46,47]

As expected, PN was an important toxicity. This predominantly mild-to-moderate, sensory PN proved reversible in most patients, consistent with other studies of bortezomib in frontline and relapsed MM.[4,9-11] However, overall rates of both baseline and treatment-emergent PN by NCI-CTCAE seemed higher than previously reported.[6-8] This may have been due to the specific focus placed on this toxicity or due to differences in AE assessment criteria between the NCI Common Toxicity Criteria version 2.0, used in previous studies,[6-8] and NCI-CTCAE version 3.0. Importantly, rates of grade 3 sensory PN (3%) and NP (5%) were low and there was no grade 4 PN or NP, possibly due to rigorous monitoring and use of established dose-modification guidelines. Furthermore, the high degree of reversibility (85%) indicates another potential benefit of the use of the dose-modification guidelines. The pharmacologic interventions used may also have contributed to the low rates of grade 3 PN and NP and

Table 4. Neurologist Assessment Results for All Patients With Baseline and End-of-Study Evaluations (n = 28) and for Patients With (n = 21) or Without (n = 7) Treatment-Emergent Neuropathy per Consensus Criteria

Neurologic Assessment	All Patients*				Patients Without Treatment-Emergent Neuropathy†				Patients With Treatment-Emergent Neuropathy and No Baseline Neuropathy‡				Patients With Treatment-Emergent Neuropathy and Baseline Neuropathy§			
	Baseline		Change		Baseline		Change		Baseline		Change		Baseline		Change	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
Total neuropathy score	6	0-36	13‖	−10-40	11.0	0-24	7	−10-15	0	0-29	9.5‖	−2-30	10	0-36	26.5‖	12-40
Total sensory score	8	0-24	10‖	−9-29	11.0	0-20	7	−9-17	0	0-24	5‖	−2-20	11	4-21	18‖	8-29
FACT/GOG-Ntx score	1.0	0-8	2.5‖	−3-14	1.0	0-1.0	3‖	1-6	1.0	0-7	2‖	−3-14	4	0-8	8	2-10
Sural SNAP amplitude, μV; normal: > 5 μV	13.4	4-36.4	−3.7‖	−25.5-11.3	19.2	8.8-28.1	−3.5‖	−8.5 -−0.9	11.8	4.0-36.4	−3.6‖	−25.5-0.9	12.8	6-24	−5.8	−8.7-11.3
Ulnar SNAP amplitude, μV; normal: > 11 μV	21.5	4.5-61.1	−1.9‖	−23.3-3.5	24.9	15.3-44.3	−2.5	−10.4-0.7	22.4	6.4-61.1	−1.8‖	−23.3-3.5	19.8	4.5-41.8	−1.67‖	−9.90-−0.30
QSART, μL																
Foot, normal: > 0.55 μL	0.45	0.04-2.77	−0.29‖	−2.63-0.99	0.79	0.24-1.78	−0.21	−0.82-0.99	0.45	0.17-2.77	−0.36‖	−2.63-0.04	0.19	0.04-0.70	−0.13	−0.69-0.04
Distal leg, normal: > 0.73 μL	0.73	0.02-2.69	−0.35‖	−1.19-0.49	0.84	0.17-2.69	−0.36	−1.19-0.33	0.95	0.16-2.19	−0.36‖	−0.99-0.03	0.60	0.02-0.71	0.04	−0.65-0.49
Thigh, normal: > 0.60 μL	0.83	0.05-1.51	−0.05	−1.27-1.00	0.82	0.11-1.06	0.11	−0.75-1.00	0.97	0.10-1.51	−0.30	−1.27-0.45	0.75	0.05-0.87	−0.03	−0.60-0.35
Forearm, normal: > 0.66 μL	0.62	0.04-2.73	−0.24	−1.49-1.17	0.71	0.09-2.73	−0.05	−1.14-1.12	0.58	0.04-1.89	−0.28	−1.49-1.17	0.49	0.11-2.32	−0.18	−1.33-1.12

Abbreviations: FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity; SNAP, sensory nerve action potential; QSART, quantitative sudomotor axon reflex testing.

*n = 25 for total neuropathy score, n = 26 for total sensory score and FACT/GOG-Ntx score; n = 28 for ulnar SNAP amplitude, n = 27 for sural SNAP amplitude, and for QSART.

†n = 7 for total neuropathy score, total sensory score, and FACT/GOG-Ntx score; n = 8 for sural and ulnar SNAP amplitude, and for QSART.

‡n = 12 for total neuropathy score, n = 13 for total sensory score, n = 14 for FACT/GOG-Ntx score, sural SNAP amplitude, and QSART, n = 15 for ulnar SNAP amplitude.

§n = 6 for total neuropathy score, total sensory score, and ulnar SNAP amplitude, n = 5 for FACT/GOG-Ntx score and QSART.

‖*P* value < .05.

the reversibility. These findings are in contrast to thalidomide-related PN, which seems less reversible,[48] with both dose and duration contributing to neurotoxicity.[49]

PN caused by the disease itself may be under-recognized. In the current study, seven (20%) of 35 newly diagnosed patients had sensory PN by modified consensus criteria.[26] Moreover, the rate observed in patients with either clinical symptoms or signs on NCS, QST, autonomous study, or skin biopsy abnormalities alone was even higher (54%). Previous series have reported a prevalence of 3% to 13%,[12-16] and more recent data from Hulin et al[50] suggested underlying abnormalities in up to 38% of newly diagnosed patients by electromyographic testing. The prevalence may be higher in our study owing to more stringent screening and because most other reports have focused on large-fiber PN; in this study, six patients had pure small-fiber PN at baseline.

Despite the modest sample size for pharmacogenomic analysis, it was possible to identify a series of candidate markers of response to bortezomib and of bortezomib-associated treatment-emergent PN, which will require further preclinical and clinical studies for validation. The limited overlap between the candidate markers of response compared with those previously reported[17] could be due to differences in the molecular determinants of bortezomib response between newly diagnosed patients and those with relapsed/refractory MM. In addition, bortezomib primarily affects the degradation state of intracellular ubiquitinated proteins; its effect on transcription is secondary.[51] This may explain why transcriptional profiles of myeloma cells do not provide a clear picture of the mechanisms determining response to bortezomib. However, it is notable that no correlation with response was observed for gene expression–based signatures of cell proliferation or NF-κB activity; this suggests that the proliferation rate of myeloma cells or the level of NF-κB activity are not the sole determinants of the in vivo antimyeloma activity of bortezomib. Regarding the potential markers of treatment-emergent PN, one hypothesis is that the genes correlating with treatment-emergent PN may be enriched with molecules involved in the initiation and regulation of protein translation, reflecting the production and release by some MM cells of proteins that could be toxic to the peripheral nervous system. Such a process may contribute to the frequent development of PN in patients with MM at baseline, as well as its exacerbation with potentially neurotoxic drug therapy. Conversely, rational combination approaches may reduce this effect; for example, with bortezomib plus lenalidomide or tanespimycin, rates and degrees of treatment-emergent PN have been low.[52-55]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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