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ORIGINAL REPORT

Multicenter Phase II Study of Bortezomib in Patients With Relapsed or Refractory Mantle Cell Lymphoma

Richard I. Fisher, Steven H. Bernstein, Brad S. Kahl, Benjamin Djulbegovic, Michael J. Robertson, Sven de Vos, Elliot Epner, Amrita Krishnan, John P. Leonard, Sagar Lonial, Edward A. Stadtmauer, Owen A. O'Connor, Hongliang Shi, Anthony L. Boral, and André Goy

From the University of Rochester, James P. Wilmot Cancer Center, Rochester; Weill Medical College of Cornell University/New York Presbyterian Hospital; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Wisconsin, Madison, WI; H. Lee Moffitt Cancer Center, Tampa, FL; Indiana University Medical Center, Indianapolis, IN; University of California Los Angeles School of Medicine, Los Angeles; City of Hope National Medical Center, Duarte, CA; Oregon Health and Science University, Portland, OR; Winship Cancer Institute, Emory University, Atlanta, GA; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Millennium Pharmaceuticals Inc, Cambridge, MA; and the Cancer Center at Hackensack University Medical Center, Hackensack, NJ.

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Address reprint requests to Richard I. Fisher, MD, University of Rochester Medical Center, 601 Elmwood Avenue, Box 704, Rochester, NY 14642; e-mail: Richard_Fisher@urmc.rochester.edu.

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ABSTRACT

Purpose
Evaluate response rate, duration of response (DOR), time-to-progression (TTP), overall survival (OS), and safety of bortezomib treatment in patients with relapsed or refractory mantle cell lymphoma (MCL).

Patients and Methods
Bortezomib 1.3 mg/m^2 was administered on days 1, 4, 8, and 11 of a 21-day cycle, for up to 17 cycles. Response and progression were determined using International Workshop Response Criteria, both using data from independent radiology review and by the investigators. Primary efficacy analyses were based on data from independent radiology review.

Results
In total, 155 patients were treated. Median number of prior therapies was one (range, one to three). Response rate in 141 assessable patients was 33% including 8% complete response (CR)/unconfirmed CR. Median DOR was 9.2 months. Median TTP was 6.2 months. Results by investigator assessments were similar. Median OS has not been reached after a median follow-up of 13.4 months. The safety profile of bortezomib was similar to previous experience in relapsed multiple myeloma. The most common adverse events grade 3 or higher were peripheral neuropathy (13%), fatigue (12%), and thrombocytopenia (11%). Death from causes that were considered to be treatment related was reported for 3% of patients.

Conclusion
These results confirm the activity of bortezomib in relapsed or refractory MCL, with predictable and manageable toxicities. Bortezomib provides significant clinical activity in terms of durable and complete responses, and may therefore represent a new treatment option for this population with usually very poor outcome. Studies of bortezomib-based combinations in MCL are ongoing.

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INTRODUCTION

Mantle cell lymphoma (MCL), an aggressive, generally incurable subtype of non-Hodgkin's lymphoma (NHL),[1] accounts for approximately 5% to 6% of all NHL cases.[1-3] With an estimated 59,000 new cases of NHL diagnosed annually in the US[4] and 62,000 in the European Union,[5] this represents approximately 3,000 to 4,000 new MCL cases annually in each region. Most patients are male, age older than 60 years, and present with advanced disease.[6,7]

MCL has one of the poorest prognoses of all NHL subtypes.[1,8,9] Despite response rates of up to 97% with first-line standard or high-intensity chemotherapy, with or without stem-cell transplantation,[6,10-16] most patients relapse. Median failure-free survival is approximately 8 to 20 months with standard therapies,[6,16-19] although longer survival has been reported with high-intensity regimens.[11-14,16,18] Median survival is approximately 3 to 4 years with standard treatment.[6,7,18-20] After first relapse, prognosis is considered very poor, with median survival of approximately 1 to 2 years.[6,18] There is no generally accepted therapeutic approach, treatment options are often limited,[1] and chemoresistance is common.[21] Therefore, novel therapies are required for relapsed and/or refractory MCL.[20,21]

MCL is characterized by overexpression of cyclin D1, resulting from the t(11;14)(q13;q32) translocation.[1,20-22] Nuclear factor-κB (NF-κB) and B-lymphocyte stimulator are constitutively expressed in MCL cells[23,24]; increased proteasome degradation of p27 and *p53* mutation are associated with poor survival.[25,26] Bortezomib (VELCADE; Millennium Pharmaceuticals Inc and Johnson & Johnson Pharmaceutical Research and Development LLC) is a first-in-class proteasome inhibitor approved in the

US and European Union for treatment of multiple myeloma (MM) patients who have received at least one prior therapy. Bortezomib's antineoplastic effect probably involves several different mechanisms, including inhibition of cell-cycle progression, induction of apoptosis, NF-κB blockade, and inhibition of angiogenesis,[27-30] suggesting it should be active in MCL. Bortezomib inhibits constitutive NF-κB expression and cyclin D1 expression,[23] and upregulates the proapoptotic Noxa protein, which interacts with Mcl-1 and promotes release of Bak,[31] leading to apoptosis of MCL cells. Preclinical studies have demonstrated activity in MCL cell lines, ex vivo MCL cells, and MCL xenograft models.[23,31-33] Small single center and national multicenter phase I and II clinical studies have demonstrated activity in MCL patients,[34-38] confirming these findings.

This study was designed to confirm the activity of bortezomib in an international, multicenter study of patients with relapsed or refractory MCL. The objectives were to evaluate response rate (complete response [CR], unconfirmed CR [CRu], and partial response [PR]) according to International Workshop Response Criteria (IWRC),[39] duration of response (DOR), time-to-progression (TTP), and overall survival. The intended primary end point was a formal comparison of TTP with historical controls, which could not be accomplished (see Discussion).

PATIENTS AND METHODS

Eligibility

Eligibility criteria included: age 18 years or older; pathologically confirmed MCL including overexpression of cyclin D1 or evidence of t(11;14); documented relapse or progression after one to two prior lines of antineoplastic therapy (including an anthracycline or mitoxantrone, and rituximab, each in ≥ 1 line); one or more measurable or assessable disease sites; and Karnofsky performance status (KPS) 50% or higher. Toxicities from previous therapy had to have resolved to grade 2 or lower (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], version 3.0). At screening, patients required: absolute neutrophil count ≥ 1,000 cells/μL; platelets ≥ 50,000 cells/μL; aspartate transaminase ≤ 3× upper limit of normal (ULN); alanine transaminase ≤ 3× ULN; total bilirubin ≤ 2× ULN; and creatinine ≤ 2 mg/dL (or creatinine clearance ≥ 50 mL/min). All patients provided written informed consent.

Exclusion criteria included: prior bortezomib; prior chemotherapy within 3 weeks, nitrosoureas within 6 weeks, therapeutic antibodies within 4 weeks, radio- or toxin immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks, of day 1, cycle 1. Patients diagnosed with or treated for a malignancy other than MCL within 5 years before day 1, cycle 1 were excluded, except patients having complete resection of basal cell carcinoma, squamous cell carcinoma of the skin, or in situ malignancy, or definitively treated, low-risk prostate cancer.

Supportive therapy for MCL ongoing at baseline was allowed; platelet and RBC transfusions were permitted. Concomitant corticosteroid therapy was prohibited, except prednisone ≤ 15 mg/d or equivalent for adrenal insufficiency. Granulocyte colony-stimulating factor was permitted after cycle 1.

Study Design

This phase II, prospective, single-arm study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki at 35 centers in the United States, United Kingdom, and Germany from June 2003. Data cut off for this analysis was December 1, 2005. The study was approved by all independent review boards. Patients received bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle, for up to 17 cycles or four cycles beyond initial reporting of CR/CRu, discontinuing for progressive disease (PD) or unacceptable toxicity, or by patient/investigator decision. A three-stage design allowed early evaluation of activity to determine study continuation. At stages one and two, 19 and 48 patients were assessed for response, with response rates of at least 16% (4 of 19 patients) and 26% (13 of 48 patients) required for continuation. These criteria were met in February 2004 and June 2004, respectively. The original primary analysis was a formal comparison of TTP between study population and historical controls; however, an appropriate historical control cohort of sufficient size could not be identified.

Efficacy and Safety Assessments

At screening, assessments and procedures included full medical history, physical examination, KPS, computed tomography scan of chest, abdomen, and pelvis, radiologic evaluation of other disease sites, bone marrow aspirate and biopsy, and blood samples for hematology and clinical chemistry. During treatment, efficacy assessments were conducted every 6 weeks for 18 weeks, then every 12 weeks until PD or use of alternative antineoplastic therapy. Efficacy assessments included computed tomography scans of chest, abdomen, and pelvis, radiologic evaluation of other disease sites, physical examination, review of clinical laboratory results, and other procedures as required. KPS was assessed and physical examination performed on day 1 of each cycle, with hematology assessment before each bortezomib dose.

Disease response (CR, CRu, PR, stable disease, PD) was assessed according to the IWRC.[39] Scans were examined by an independent radiologist to ensure consistency across study sites. Adverse events (AEs) were monitored throughout, and toxicities assessed by NCI CTCAE version 3.0. At the end of treatment visit, 28 days after last bortezomib dose or earlier if patients required alternative antineoplastic therapy, disease response was assessed if there was no prior evidence of PD.

Patients discontinuing for reasons other than PD received short-term follow-up every 6 weeks until week 18, then every 12 weeks until PD or use of alternative antineoplastic therapy. All patients received long-term follow-up every 3 months to assess survival. Dosing was held or modified for grade 3 or higher neutropenia with fever, grade 4 neutropenia lasting longer than 7 days, platelets less than 10,000 cells/μL, or any grade 3 or higher nonhematologic toxicity that was considered to be bortezomib related.

Statistical Analysis

A sample size of 152 patients was determined. This was large enough for a three-stage design allowing for decisions on study continuation based on response rate. The three-stage design was based on a one-sided test ($\alpha = .025$; 95% power; undesirable response rate, 25%; desirable response rate, 40%). Data cut off for this analysis was selected to allow 6 months or longer follow-up after first bortezomib dose in every patient, determined to be adequate for TTP and DOR evaluation.

Patient populations included the all-treated population (ATP; patients who received any amount of bortezomib), response population for final analysis (RP-Final; ATP patients who had measurable disease at screening and at least one postbaseline tumor assessment), and refractory population (ATP patients who had not responded to their last line of therapy or responded with TTP of < 6 months). Safety and efficacy data (except response) were analyzed for ATP; response and DOR were analyzed for RP-Final; and all efficacy parameters were analyzed for the refractory population.

Response, date of response, and PD were determined using a computer algorithm that applied the IWRC with a minor modification to correlate more closely with application of these criteria in clinical practice, and used tumor measurements from independent radiology review of patient scans. The IWRC modification was incorporated when it became clear that small changes in nodes smaller than 1 cm in size were assessed as PD by algorithm but not by investigator. The definition of PD, which required 50% or higher increase in the product of the longest perpendicular dimensions of any previously identified, measurable site of lymphoma, or 50% or higher increase in the longest dimension of any previously identified site of lymphoma that was larger than 1 cm in the longest transverse dimension (ie, measurable at baseline), was modified to specify that the lesion should be larger than 1 cm in both perpendicular dimensions at the time of PD and that the absolute increase in either dimension, or in the longest dimension, respectively, should be at least 0.5 cm. This better reflects the recently updated IWRC.[40]

Response and disease progression were derived using this algorithm, and assessed by investigators using the IWRC. Kaplan-Meier methods were used to estimate distribution of DOR, TTP, and survival. Additional nonprotocol-specified analyses included DOR, TTP, and survival assessment by response status, and assessment of response, DOR, and TTP for patient subgroups based on time since diagnosis of MCL, number of prior lines of therapy, and prior high-intensity chemotherapy (defined as stem-cell transplantation, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine [Hyper-CVAD]; ifosfamide, carboplatin, and etoposide [ICE]; etoposide, methylprednisolone, high-dose cytarabine, and cisplatin [ESHAP]; or dexamethasone, high-dose cytarabine, and cisplatin [DHAP]; all with/without rituximab).

RESULTS

Patient Characteristics and Disposition

In total, 155 patients were enrolled and received 1 or more doses of bortezomib. Baseline characteristics are presented in Table 1; median number of prior therapies was one. At data cut off, 100 patients remained on the study (12 on treatment, 16 on short-term follow-up, and 72 on long-term follow-up). Of 55 who discontinued from the study, 52 had died, two were lost to follow-up, and one withdrew consent. Treatment was discontinued by 130 of 155 patients (84%). Reasons included lack of efficacy (72; 46%), AEs (41; 26%), patient decision (7; 5%), and other reasons (10; 6%).

The median number of treatment cycles was four in all patients and eight in responding patients; 59% of patients received four or more cycles, 31% received eight or more. The median total bortezomib dose was 20.7 mg/m^2 (range, 1.3 to 87.5); median percentage of expected bortezomib received during time on therapy was 90.4%.

Table 1. Baseline Patient and Disease Characteristics (N = 155)

Characteristic	Patients No.	Patients %
Sex		
Male	125	81
Race/ethnicity		
White	142	92
Black	6	4
Hispanic	4	3
Asian or Pacific Islander	3	2
Age, years		
Median	65	
Range	42-89	
KPS, < 90%	44/153	29
IPI, ≥ 3	65/147	44
LDH > ULN	54/149	36
Stage IV MCL	119	77
Time from diagnosis, years		
Median	2.3	
Range	0.2-11.2	
Diagnosed < 3 years prior to first dose	103	66
Positive bone marrow evaluation	84/154	55
No. of prior lines of therapy for MCL		
1	84	54
2	65	42
3*	6	4
Received prior regimen		
Anthracycline/mitoxantrone	152	98
Alkylating agents	150	97
Rituximab	149	96
At least 2 of 3 of the above	155	100
All 3 of the above	141	91
Prior high-intensity therapy†	58	37
Prior radioimmunotherapy	8	5
Prior radiation therapy (not including radioimmunotherapy)	29	19

Abbreviations: KPS, Karnofsky performance status; IPI, International prognostic index; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; ULN, upper limit of normal.
*Protocol deviation: eligibility violation exemption granted.
†High-intensity regimens defined as stem cell transplantation, Hyper-CVAD, ICE, ESHAP, or DHAP, all with or without rituximab (see Patients and Methods section for definitions of regimens).

Efficacy

In total, 141 of 155 patients (91%) were assessable for response; of 14 patients excluded, five did not have measurable disease and nine had no postbaseline measurements. Best responses are presented in Table 2. Response rate was 33% (8% CR/CRu) by algorithm, and 40% (8% CR/CRu) by investigator assessment (30% and 37%, respectively, intent-to-treat analysis, n = 155). Median time to first response was 1.3 months (within two cycles). Figure 1 shows changes in lesion size from baseline to best response. Table 3 shows DOR, TTP, and overall survival. Median DOR by algorithm was 9.2 months (Fig 2A) and 13.5 months in patients with CR/CRu. Median TTP by both assessments was 6.2 months. By algorithm, median TTP was 14.6, 7.4, 6.8, and 1.2 months for patients with CR/CRu, PR, stable disease, and PD, respectively, and 10.6 months for all responders (Fig 2B). At data cut off, median overall survival had not been reached (Fig 2C); with median follow-up of 13.4 months, 103 of 155 patients (66%) were alive. One-year survival probability was 69.3% for all patients, 94.3% in responding patients, and 100% in patients achieving CR/CRu.

In the refractory population (n = 58; 50 did not respond to last prior therapy, eight responded with TTP < 6 months), among 51 patients assessable for response, the response rate by algorithm was 31% (6% CR/CRu). Median DOR was 4.9 months (based on six events). For all 58 patients, median TTP was 3.8 months, median survival was 14.4 months, and 1-year survival probability was 54%.

Bortezomib showed efficacy in all patient subgroups. Response rate was lower in patients diagnosed fewer than 3 years before study entry (25%) compared with 3 years or longer (50%), although DOR (9.4 *v* 9.2 months) and TTP (6.2 *v* 6.1 month) were similar. DOR was lower in patients with more than one prior line of therapy (6.1

Table 2. Best Response to Treatment (N = 141) by Algorithm and by Investigator Assessment

Response	By Algorithm No.	By Algorithm %	By Algorithm 95% CI	By Investigator No.	By Investigator %	By Investigator 95% CI
CR + CRu + PR	47	33	26 to 42	57	40	32 to 49
CR + CRu	11	8	4 to 14	11	8	4 to 14
CR	9	6	3 to 12	8	6	2 to 11
PR	36	26	19 to 34	46	33	25 to 41
SD	47	33	26 to 42	46	33	25 to 41
PD	35	25	18 to 33	37	26	19 to 34
No postbaseline assessment	12	9	4 to 14	1	< 1	0 to 4

Abbreviations: CR, complete response; CRu, unconfirmed CR; PD, progressive disease; PR, partial response; SD, stable disease.

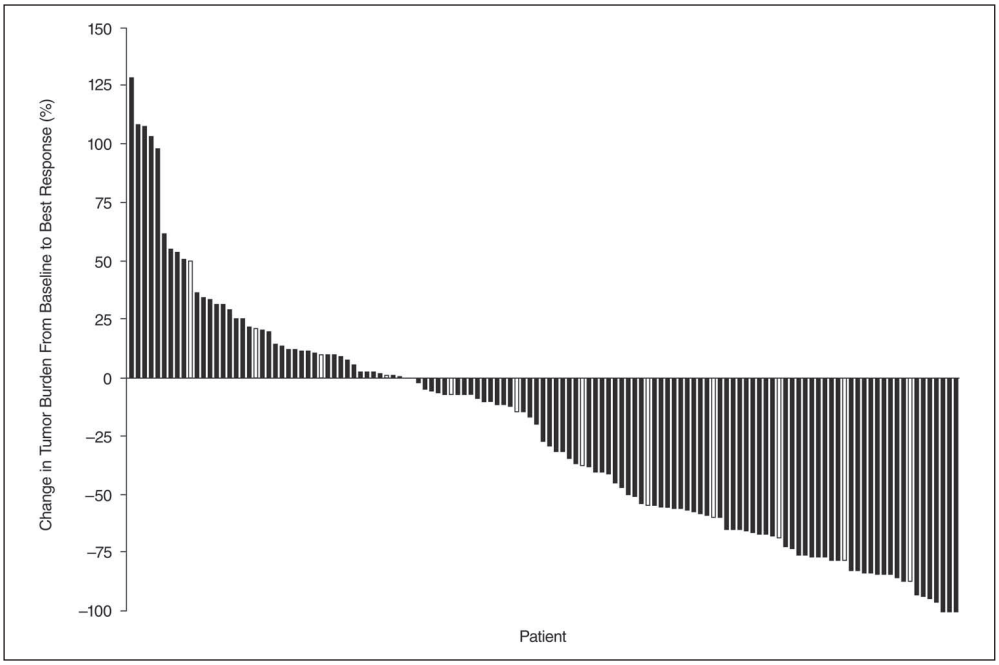

Fig 1. Percentage changes in tumor burden, measured as sum of the products of perpendicular diameters (SPD) of all measurable sites of disease from baseline to best response in response-assessable patients (N = 141); data are shown for 127 patients, as 12 patients had no postbaseline measurements, and two patients had responses based only on assessable disease sites or bone marrow assessment. Each line represents one patient; the white lines indicate every tenth patient.

months) compared with one prior line (9.4 months), although response rate (38% *v* 30%) and TTP (5.4 *v* 6.5 months) were similar. Response rate (27% *v* 37%) and TTP (4.2 *v* 6.7 months) were lower in patients who had prior high intensity therapy versus those who did not, although DOR was similar (9.2 *v* 9.4 months).

Safety

All 155 patients were assessable for safety. As would be expected, almost all (152; 98%) experienced at least one AE; 108 (70%) experienced at least one grade 3 or higher AE, and 145 (94%) experienced at least one drug-related AE. The most common AEs were fatigue, peripheral neuropathy, and gastrointestinal events. Overall incidences are presented in Table 4, including grade 3 or higher and drug-related incidences. Other grade 3 or higher AEs reported in 5% or more of patients and not shown in the table were disease progression (7%), weakness (6%), abdominal pain, syncope, pneumonia, and dehydration (5% each). Grade 4 or higher AEs were reported in 26 patients (17%). The most common grade 4 AEs were thrombocytopenia (4%), sepsis and disease progression (3% each), and neutropenia (2%). Serious AEs (SAEs; AEs that result in death, are life-threatening, require inpatient hospitalization, or result in persistent or significant disability/incapacity) were reported in 60 patients (39%; drug-related in 32; 21%). Incidences of individual SAEs were low; most frequent were disease progression and pneumonia (6% each). An AE was the primary reason for treatment discontinuation in 41 patients (26%). The most common AEs leading to treatment discontinuation were peripheral neuropathy (10%) and fatigue (6%).

Table 3. DOR, TTP, Time to Alternative Therapy, and Survival

Parameter	By Algorithm		By Investigator	
	Median	95% CI	Median	95% CI
DOR, months*	9.2	4.9 to 13.5	8.9	6.2 to 11.8
In patients achieving CR/CRu†	13.5	13.5 to NE	15.5	11.5 to 23.3
TTP, months‡	6.2	4.0 to 6.9	6.2	4.3 to 6.9
In responding patients (CR/CRu/PR)*	10.6	7.3 to 15.2	12.7	7.7 to 14.6
In patients achieving CR/CRu†	14.6	7.3 to NE	18.2	13.1 to 24.7
Overall survival, months‡				
Median		NE		
95% CI		19.8 to NE		
Estimated 1-yr survival probability‡§		69.3%		
In responding patients (CR/CRu/PR)*	94.3%		93.7%	
In patients achieving CR/CRu†	100%		100%	

Abbreviations: CR, complete response; CRu, unconfirmed complete response; DOR, duration of response; NE, not estimable; TTP, time-to-progression.
*In responders only; n = 47 by algorithm, n = 57 by investigator.
†n = 11 by both algorithm and investigator; however, patient groups differ between assessment methods.
‡In all patients, N = 155 by both algorithm and investigator.
§One-year survival probability based on Kaplan-Meier estimates.

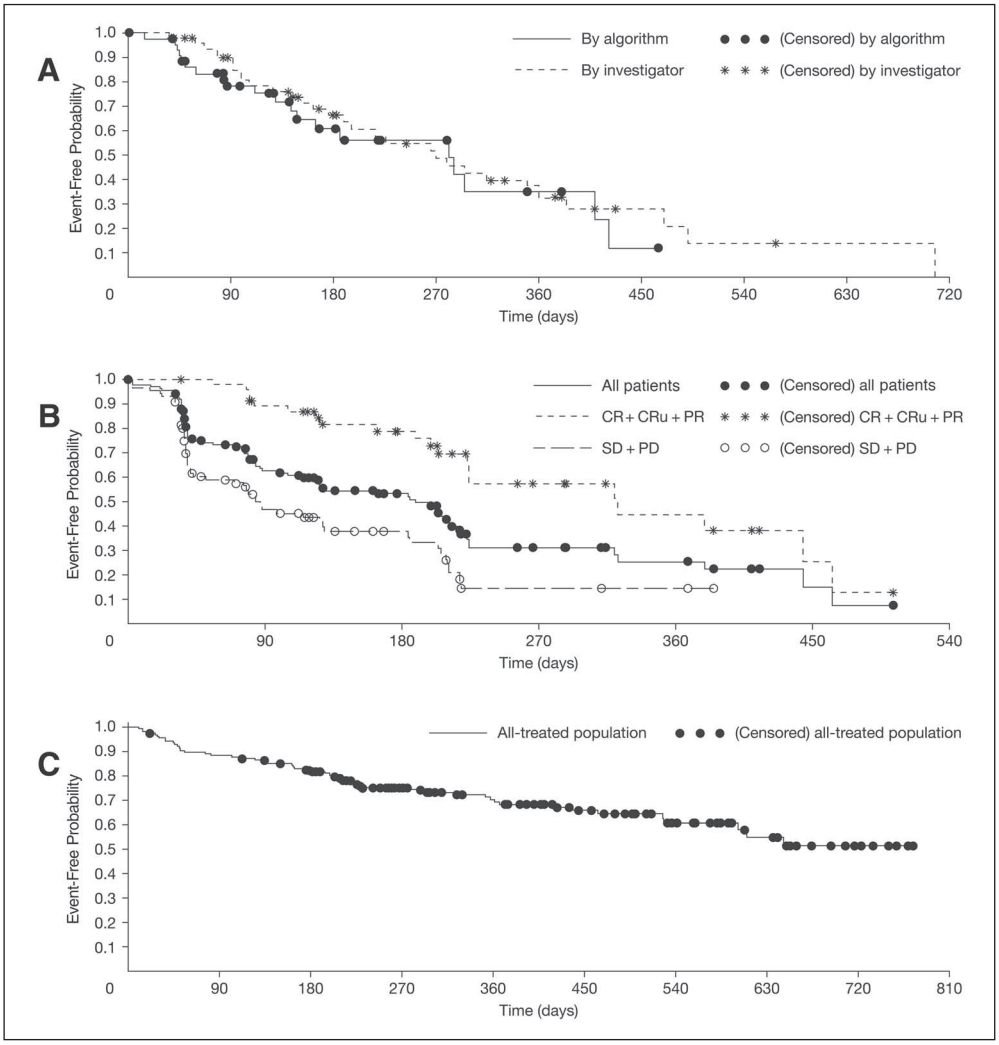

Fig 2. Kaplan-Meier curves of (A) duration of response in all patients responding to bortezomib, by algorithm and by investigator; (B) time to progression for all patients (N = 155), for patients achieving a response, and for patients with stable disease or progressive disease, by algorithm; and (C) overall survival for all patients (N = 155).

Twelve patients died within 28 days after their last dose of bortezomib. The SAEs reported as leading to death were disease progression (six patients), sepsis (three patients; in association with cardiac arrest in one patient, and with fungal pneumonia, pulmonary alveolar hemorrhage and multiorgan failure in one patient), respiratory failure (two patients), and intestinal obstruction (one patient); these included grade 5 (fatal) AEs in five patients (3%; three disease progression, one respiratory failure, one intestinal obstruction). The cause of death was considered related to bortezomib in five patients, three deaths due to sepsis, and one death due to respiratory failure; one patient died unwitnessed in the setting of PD, and the investigator could not rule out a potential contribution of bortezomib.

DISCUSSION

This study represents the largest prospective study to date in patients with relapsed MCL. In a population typical of the relapsed MCL population, the results demonstrate that bortezomib is effective, with a 33% response rate, including 8% CR/CRu. The median DORs in all responding patients (9.2 months) and patients achieving CR/CRu (13.5 months) are considerable given the median expected survival of 1 to 2 years after initial relapse, suggesting important clinical benefit. Similarly, median TTP was 10.6 months among responders, 14.6 months in patients achieving CR/CRu, and 6.2 months in all patients. These data are supported by similar results from phase I and II studies of single-agent bortezomib in relapsed MCL.[34-38,41]

After a median follow-up of 13.4 months, median survival has not been reached. Notably, bortezomib was active in patients with aggressive (diagnosed $<$ 3 years before study entry) and less aggressive (diagnosed $\geq$ 3 years before study entry) disease, and demonstrated activity in patients with MCL refractory to last prior therapy. These results in patient subgroups indicate that bortezomib is active in the whole MCL population; therefore the observed activity should translate to the clinical setting, outside of clinical trials.

As described, the intended primary end point was a formal comparison of TTP with historical controls; however, an appropriate cohort of sufficient size could not be identified. Critical data on disease-assessment intervals, response criteria, and prior therapies in three academic research databases of MCL patients were absent. Consequently, only 15 of 258 patients were considered valid comparators, preventing the planned analysis. A comprehensive literature review was conducted of studies of single-agent therapies in relapsed

Table 4. AEs Reported in ≥ 20% Total Patients (N = 155), Plus Incidences of Grade ≥ 3 and Drug-Related AEs

Event	Any Grade		Grade ≥ 3		Drug Related	
	No.	%	No.	%	No.	%
Fatigue	95	61	19	12	81	52
Peripheral neuropathy	85	55	20	13	84	54
Constipation	77	50	4	3	52	34
Diarrhea	73	47	11	7	60	39
Nausea	68	44	4	3	56	36
Rash	43	28	4	3	36	23
Vomiting	42	27	4	3	35	23
Anorexia	36	23	5	3	22	14
Dizziness (excluding vertigo)	36	23	5	3	28	18
Dyspnea	35	23	7	5	10	6
Insomnia	33	21	1	< 1	15	10
Thrombocytopenia	33	21	17	11	25	16
Musculoskeletal pain	31	20	3	2	15	10
Edema lower limb	31	20	1	< 1	13	8

Abbreviation: AE, adverse event.

MCL.[42-49] None of these studies, of rituximab,[42,47,48] fludarabine,[45,46] gemcitabine,[44] and the investigational agent flavopiridol,[43] involved patients with a comparable extent of prior therapies to that required in our study. Nonetheless, our 33% response rate compares favorably with 33%, 37%, and 28% with rituximab,[42,47,48] 17% and 31% with fludarabine,[45,46] 27% with gemcitabine,[44] and 11% with flavopiridol.[43] The patients in a recent temsirolimus study[49] were more comparable with those in our study; however, sample size was small (N = 34) and of the 38% response rate, CR/CRu rate was only 3%.[49] Our median DOR of 9.2 months compares favorably with 3.3 months with flavopiridol,[43] 4 to 8 months with fludarabine,[46] 6.9 months with temsirolimus,[49] and 6 to 14 months with rituximab.[47,48] Similarly, our median TTP of 6.2 months is comparable with TTP/time to treatment failure of 3.0 months with flavopiridol,[43] 6.1 months with fludarabine,[45] and 6.5 months with temsirolimus,[49] and our overall survival compared with 12 months median overall survival with temsirolimus.[49]

The safety profile of bortezomib was predictable and manageable, and similar to that in relapsed or refractory MM.[50-52] The incidence of peripheral neuropathy was higher compared with the Assessment of Proteasome Inhibition for Extending Remissions phase III study in MM,[51] perhaps due to inherent differences between the diseases or differences in prior therapy. Baseline neuropathy data were not collected. However, an examination of peripheral neuropathy in two MM studies found no correlation between overall incidence and baseline neuropathy or type of prior therapy, though severe neuropathy was more frequent in the presence of baseline neuropathy.[53]

Hematologic AEs were less frequent in this study than in MM studies,[50-52] which may reflect more significant disease-related bone marrow suppression in MM than MCL. Patients with positive baseline bone marrow evaluation experienced grade 3/4 hematologic AEs more frequently than bone-marrow–negative patients. Thrombocytopenia and neutropenia were cyclical and transient, as in MM studies.[54,55]

In conclusion, the results of this study confirm the activity of bortezomib, including CRs and durable responses, in relapsed/refractory MCL, with a manageable toxicity profile. Activity compares favorably with other studies of single-agent therapies in this setting. Bortezomib may therefore represent an important new treatment option for this population with usually poor outcome. Based on preclinical findings of additive/synergistic activity in lymphoma, studies are also investigating combinations of bortezomib with standard therapeutic agents in patients with untreated, relapsed, and refractory MCL, with promising early results.[56-58]

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Richard I. Fisher			Millennium (A)		Millennium (A)			
Steven H. Bernstein			Millennium (A)		Millennium (A)			
Brad S. Kahl			Millennium (A)		Millennium (A)			
Sven de Vos			Millennium (A)					
Elliot Epner					Millennium (A)			
Amrita Krishnan			Celgene (A); Genetech (A); Millennium (A)	Celgene (A)	Celgene (A); Genetech (A)	Biogen Idec (A)		
John P. Leonard			Millennium (A); Johnson & Johnson (A)		Millennium (A)			
Sagar Lonial			Millennium (A)		Millennium (A)			
Edward A. Stadtmauer					Millennium (A)	Millennium (A)		
Owen A. O'Connor					Millennium (B)	Millennium (C)		
Hongliang Shi	Millennium (N/R)			Millennium (A); Millennium (A)				
Anthony L. Boral	Millennium (N/R)			Millennium (C)				
André Goy					Millennium (B)			

Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required

Author Contributions

Conception and design: Richard I. Fisher, Steven H. Bernstein, Michael J. Robertson, Amrita Krishnan, John P. Leonard, Sagar Lonial, Owen A. O'Connor, Hongliang Shi, Anthony L. Boral, André Goy
Provision of study materials or patients: Richard I. Fisher, Steven H. Bernstein, Brad S. Kahl, Benjamin Djulbegovic, Sven de Vos, Elliot Epner, André Goy
Collection and assembly of data: Benjamin Djulbegovic, Sven de Vos
Data analysis and interpretation: Richard I. Fisher, Steven H. Bernstein, Benjamin Djulbegovic, Michael J. Robertson, Sven de Vos, Amrita Krishnan, John P. Leonard, Sagar Lonial, Owen A. O'Connor, Hongliang Shi, Anthony L. Boral, André Goy
Manuscript writing: Richard I. Fisher, Sven de Vos, Edward A. Stadtmauer, Owen A. O'Connor, Anthony L. Boral, André Goy
Final approval of manuscript: Richard I. Fisher, Steven H. Bernstein, Brad S. Kahl, Benjamin Djulbegovic, Michael J. Robertson, Elliot Epner, Amrita Krishnan, John P. Leonard, Sagar Lonial, Edward A. Stadtmauer, Owen A. O'Connor, André Goy