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.

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.

A B S T R A C T

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.

J Clin Oncol 24:4867-4874. © 2006 by American Society of Clinical Oncology

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 evalua-

tion 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 (α = .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; me-

dian 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%.

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

Characteristic	No.	%
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).

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

Response	By Algorithm			By Investigator		
	No.	%	95% CI	No.	%	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.
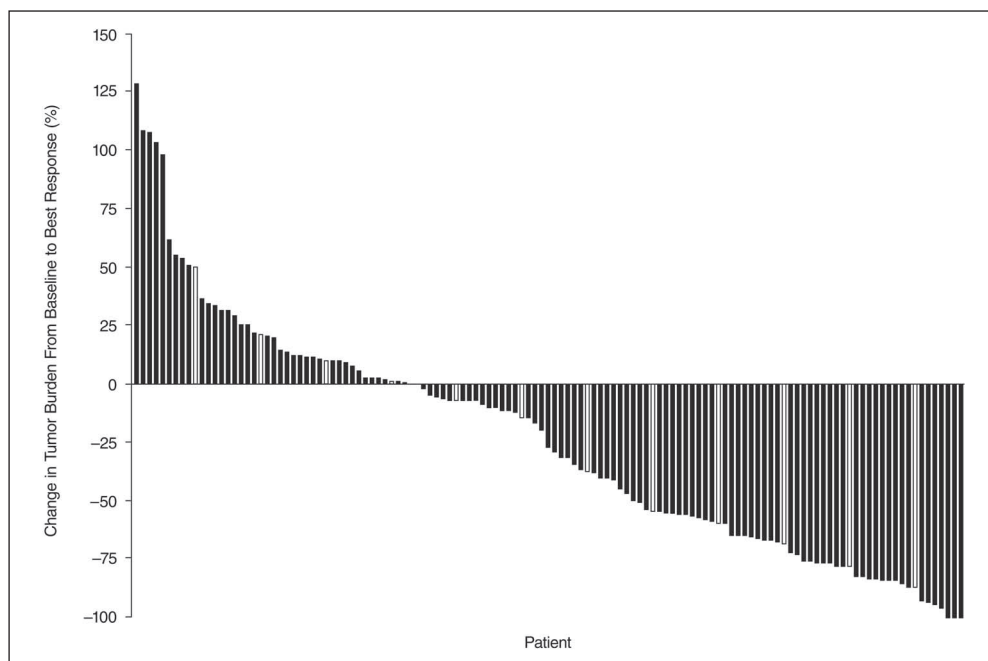
Fig 1. Percentage changes in tumor burden, measured as sum of the products of perpendicular diameters (SPD) of all measurable sites of disease from baseline to best response in response-assessable patients (N = 141); data are shown for 127 patients, as 12 patients had no postbaseline measurements, and 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%).

	By Algorithm		By Investigator	
Table 3. DOR, TTP, Time to Alternative Therapy, and Survival				
Parameter	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.
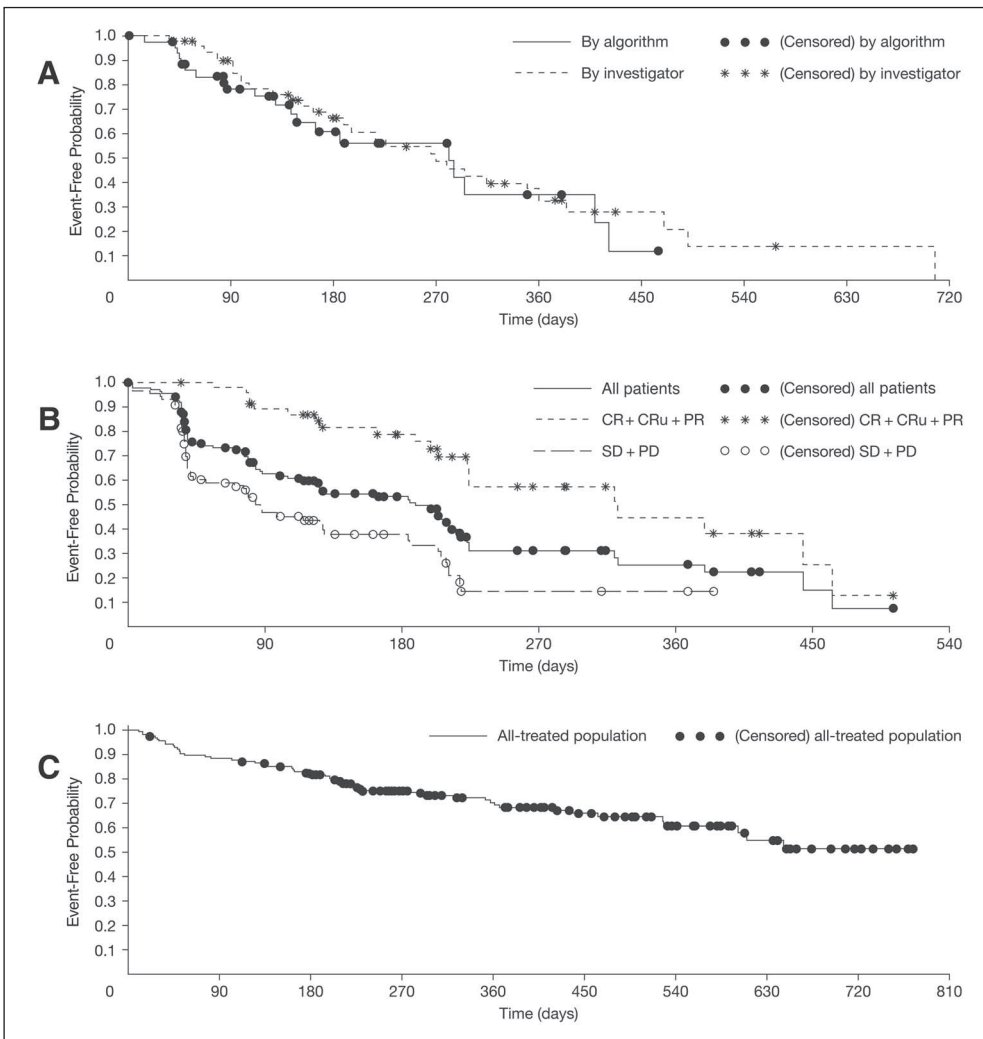§One-year survival probability based on Kaplan-Meier estimates.

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 ≥ 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]

REFERENCES

1. Williams ME, Densmore JJ: Biology and therapy of mantle cell lymphoma. Curr Opin Oncol 17:425-431, 2005

2. The Non-Hodgkin's Lymphoma Classification Project: A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 89:3909-3918, 1997

3. Argatoff LH, Connors JM, Klasa RJ, et al: Mantle cell lymphoma: A clinicopathologic study of 80 cases. Blood 89:2067-2078, 1997

4. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2006. CA Cancer J Clin 56:106-130, 2006

5. Boyle P, Ferlay J: Cancer incidence and mortality in Europe, 2004. Ann Oncol 16:481-488, 2005

6. Hiddemann W, Unterhalt M, Herrmann R, et al: Mantle-cell lymphomas have more widespread disease and a slower response to chemotherapy compared with follicle-center lymphomas: Results of a prospective comparative analysis of the German Low-Grade Lymphoma Study Group. J Clin Oncol 16:1922-1930, 1998

7. Lenz G, Dreyling M, Hiddemann W: Mantle cell lymphoma: Established therapeutic options and future directions. Ann Hematol 83:71-77, 2004

8. Fisher RI: Mantle cell lymphoma: At last, some hope for successful innovative treatment strategies. J Clin Oncol 23:657-658, 2005

9. Bertoni F, Rinaldi A, Zucca E, et al: Update on the molecular biology of mantle cell lymphoma. Hematol Oncol 24:22-27, 2006

10. Bauwens D, Maerevoet M, Michaux L, et al: Activity and safety of combined rituximab with chlorambucil in patients with mantle cell lymphoma. Br J Haematol 131:338-340, 2005

11. Romaguera JE, Fayad L, Rodriguez MA, et al: High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 23:7013-7023, 2005

12. Vigouroux S, Gaillard F, Moreau P, et al: High-dose therapy with autologous stem cell transplantation in first response in mantle cell lymphoma. Haematologica 90:1580-1582, 2005

13. Pott C, Schrader C, Gesk S, et al: Quantitative assessment of molecular remission after high-dose therapy with autologous stem cell transplantation predicts long-term remission in mantle cell lymphoma. Blood 107:2271-2278, 2006

14. Khouri IF, Romaguera J, Kantarjian H, et al: Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: An active regimen for aggressive mantle-cell lymphoma. J Clin Oncol 16:3803-3809, 1998

15. Forstpointner R, Dreyling M, Repp R, et al: The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) signif-icantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 104:3064-3071, 2004

16. Lenz G, Dreyling M, Hoster E, et al: Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 23:1984-1992, 2005

17. Howard OM, Gribben JG, Neuberg DS, et al: Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: Molecular complete responses are not predictive of progression-free survival. J Clin Oncol 20:1288-1294, 2002

18. Khouri IF, Lee MS, Saliba RM, et al: Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. J Clin Oncol 21:4407-4412, 2003

19. Fisher RI, Dahlberg S, Nathwani BN, et al: A clinical analysis of two indolent lymphoma entities: Mantle cell lymphoma and marginal zone lymphoma (including the mucosa-associated lymphoid tissue and monocytoid B-cell subcategories): A Southwest Oncology Group study. Blood 85:1075-1082, 1995

20. Witzig TE: Current treatment approaches for mantle-cell lymphoma. J Clin Oncol 23:6409-6414, 2005

21. Leonard JP, Schattner EJ, Coleman M: Biology and management of mantle cell lymphoma. Curr Opin Oncol 13:342-347, 2001

22. Bogner C, Peschel C, Decker T: Targeting the proteasome in mantle cell lymphoma: A promising therapeutic approach. Leuk Lymphoma 47:195-205, 2006

23. Pham LV, Tamayo AT, Yoshimura LC, et al: Inhibition of constitutive NF-kappa B activation in mantle cell lymphoma B cells leads to induction of cell cycle arrest and apoptosis. J Immunol 171:88-95, 2003

24. Fu L, Lin-Lee YC, Pham LV, et al: Constitutive NF-kappaB and NFAT activation leads to stimulation of the BLyS survival pathway in aggressive B-cell lymphomas. Blood 107:4540-4548, 2006

25. Greiner TC, Dasgupta C, Ho VV, et al: Mutation and genomic deletion status of ataxia telangiectasia mutated (ATM) and p53 confer specific gene expression profiles in mantle cell lymphoma. Proc Natl Acad Sci U S A 103:2352-2357, 2006

26. Chiarle R, Budel LM, Skolnik J, et al: Increased proteasome degradation of cyclin-dependent kinase inhibitor p27 is associated with a decreased overall survival in mantle cell lymphoma. Blood 95:619-626, 2000

27. Rajkumar SV, Richardson PG, Hideshima T, et al: Proteasome inhibition as a novel therapeutic target in human cancer. J Clin Oncol 23:630-639, 2005

28. Voorhees PM, Dees EC, O'Neil B, et al: The proteasome as a target for cancer therapy. Clin Cancer Res 9:6316-6325, 2003

29. Myung J, Kim KB, Crews CM: The ubiquitin-proteasome pathway and proteasome inhibitors. Med Res Rev 21:245-273, 2001

30. Adams J: The proteasome: A suitable antineoplastic target. Nat Rev Cancer 4:349-360, 2004

31. Perez-Galan P, Roue G, Villamor N, et al: The proteasome inhibitor bortezomib induces apoptosis in mantle-cell lymphoma through generation of ROS and Noxa activation independent of p53 status. Blood 107:257-264, 2006

32. Pastore A, Rieken M, Weigert O, et al: Inhibition of proteasome is associated with early alterations of cell cycle regulators and induces synergistic antitumour activities in mantle cell lymphoma in a sequence dependent manner. Blood 106:677a, 2005 (abstr 2409)

33. Weinkauf M, Rieken M, Pastore A, et al: Altered cellular protein levels of tumor suppressor genes and heat shock elements (TRAP1) indicate sensitivity to the proteasome inhibitor bortezomib (Velcade) in mantle cell lymphoma. Blood 106:681a, 2005 (abstr 2424)

34. Goy A, Younes A, McLaughlin P, et al: Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 23:667-675, 2005

35. O'Connor OA, Wright J, Moskowitz C, et al: Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. J Clin Oncol 23:676-684, 2005

36. Orlowski RZ, Stinchcombe TE, Mitchell BS, et al: Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. J Clin Oncol 20:4420-4427, 2002

37. Strauss SJ, Maharaj L, Hoare S, et al: Bortezomib therapy in patients with relapsed or refractory lymphoma: Potential correlation of in vitro sensitivity and tumor necrosis factor alpha response with clinical activity. J Clin Oncol 24:2105-2112, 2006

38. Belch A, Kouroukis C, Crump M, et al: Phase II trial of bortezomib in mantle cell lymphoma. Blood 104:175a, 2004 (abstr 608)

39. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol 17:1244-1253, 1999

40. Cheson BD, Pfistner B, Juweld ME, et al: Recommendations for revised response criteria for malignant lymphoma. J Clin Oncol 24:423s, 2006 (abstr 7507)

41. O'Connor O, Wright J, Moskowitz C, et al: Targeting the proteasome pathway with bortezomib in patients with mantle cell (MCL) and follicular lymphoma (FL) produces prolonged progression free survival among responding patients: Results of a multicenter phase II experience. Ann Oncol 16:66, 2005 (abstr 99)

42. Coiffier B, Haioun C, Ketterer N, et al: Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study. Blood 92:1927-1932, 1998

43. Kouroukis CT, Belch A, Crump M, et al: Flavopiridol in untreated or relapsed mantle-cell lymphoma: Results of a phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 21:1740-1745, 2003

44. Dumontet C, Morschhauser F, Solal-Celigny P, et al: Gemcitabine as a single agent in the treatment of relapsed or refractory low-grade non-Hodgkin's lymphoma. Br J Haematol 113:772-778, 2001

45. Tobinai K, Watanabe T, Ogura M, et al: Phase II study of oral fludarabine phosphate in relapsed indolent B-Cell non-Hodgkin's lymphoma. J Clin Oncol 24:174-180, 2006

46. Decaudin D, Bosq J, Tertian G, et al: Phase II trial of fludarabine monophosphate in patients with mantle-cell lymphomas. J Clin Oncol 16:579-583, 1998

47. Foran JM, Rohatiner AZ, Cunningham D, et al: European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. J Clin Oncol 18:317-324, 2000

48. Ghielmini M, Schmitz SF, Cogliatti S, et al: Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: A study of the Swiss Group for Clinical Cancer Res (SAKK). J Clin Oncol 23:705-711, 2005

49. Witzig TE, Geyer SM, Ghobrial I, et al: Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. J Clin Oncol 23:5347-5356, 2005

50. Richardson PG, Barlogie B, Berenson J, et al: A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 348:2609-2617, 2003

51. Richardson PG, Sonneveld P, Schuster MW, et al: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 352:2487-2498, 2005

52. Jagannath S, Barlogie B, Berenson J, et al: A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol 127:165-172, 2004

53. Richardson PG, Briemberg H, Jagannath S, et al: Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol 24:3113-3120, 2006

54. Lonial S, Richardson P, Sonneveld P, et al: Hematologic profiles in the phase 3 APEX trial. Blood 106:970a, 2005 (abstr 3474)

55. Lonial S, Waller EK, Richardson PG, et al: Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed, refractory multiple myeloma. Blood 106:3777-3784, 2005

56. Leonard JP, Furman RR, Cheung Y-K, et al: Phase I/II trial of bortezomib + CHOP-rituximab in diffuse large B cell (DLBCL) and mantle cell lymphoma (MCL): Phase I results. Blood 106:147a, 2005 (abstr 491)

57. Drach J, Kaufmann H, Pichelmayer O, et al: Marked activity of bortezomib, rituximab, and dexamethasone (BORID) in heavily pretreated patients with mantle cell lymphoma. J Clin Oncol 24:681s, 2006 (suppl; abstr 17522)

58. Wiestner A, Dunleavy K, Rizzatti EG, et al: Potent single agent activity and tumor selectivity of bortezomib in mantle cell lymphoma: First impressions from a randomized phase II study of EPOCH-rituximab-bortezomib in untreated mantle cell lymphoma. Blood 106:266b, 2005 (abstr)

■ ■ ■

Acknowledgment

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