Multicenter, Phase I, Dose-Escalation Trial of Lenalidomide Plus Bortezomib for Relapsed and Relapsed/Refractory Multiple Myeloma

Paul G. Richardson, Edie Weller, Sundar Jagannath, David E. Avigan, Melissa Alsina, Robert L. Schlossman, Amitabha Mazumder, Nikhil C. Munshi, Irene M. Ghobrial, Deborah Doss, Diane L. Warren, Laura E. Lunde, Mary McKenney, Carol Delaney, Constantine S. Mitsiades, Teru Hideshima, William Dalton, Robert Knight, Dixie-Lee Esseltine, and Kenneth C. Anderson

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From the Department of Medical Oncology, Dana-Farber Cancer Institute; and Beth Israel Deaconess Medical Center, Boston; and Millennium Pharmaceuticals, Cambridge, MA; St Vincent's Comprehensive Cancer Center, New York, NY; H. Lee Moffitt Cancer Center, Tampa, FL; and Celgene, Summit, NJ.

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Corresponding author: Paul G. Richardson, MD, Dana-Farber Cancer Institute, 44 Binney St, Dana 1B02, Boston, MA 02115; e-mail: paul_richardson@dfci.harvard.edu.

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ABSTRACT

Purpose

Lenalidomide and bortezomib are active in relapsed and relapsed/refractory multiple myeloma (MM). In preclinical studies, lenalidomide sensitized MM cells to bortezomib and dexamethasone. This phase I, dose-escalation study (ie, NCT00153933) evaluated safety and determined the maximum-tolerated dose (MTD) of lenalidomide plus bortezomib in patients with relapsed or with relapsed and refractory MM.

Patients and Methods

Patients received lenalidomide 5, 10, or 15 mg/d on days 1 through 14 and received bortezomib 1.0 or 1.3 mg/m² on days 1, 4, 8, and 11 of 21-day cycles. Dexamethasone (20mg or 40 mg on days 1, 2, 4, 5, 8, 9, 11, and 12) was added for progressive disease after two cycles. Primary end points were safety and MTD determination.

Results

Thirty-eight patients were enrolled across six dose cohorts. The MTD was lenalidomide 15 mg/d plus bortezomib 1.0 mg/m². Dose-limiting toxicities (n = 1 for each) were grade 3 hyponatremia and herpes zoster reactivation and grade 4 neutropenia. The most common treatment-related, grades 3 to 4 toxicities included reversible neutropenia, thrombocytopenia, anemia, and leukopenia. Among 36 response-evaluable patients, 61% (90% CI, 46% to 75%) achieved minimal response or better. Among 18 patients who had dexamethasone added, 83% (90% CI, 62% to 95%) achieved stable disease or better. Median overall survival was 37 months.

Conclusion

Lenalidomide plus bortezomib was well tolerated and showed promising activity with durable responses in patients with relapsed and relapsed/refractory MM, including patients previously treated with lenalidomide, bortezomib, and/or thalidomide. The combination of lenalidomide, bortezomib, and dexamethasone is being investigated in a phase II study in this setting and in newly diagnosed MM.

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INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy; 19,920 new cases of MM occurrences are predicted in the United States during 2008, with an estimated 10,690 deaths as a result of MM also predicted to have occurred in the same year.¹ New treatment options, including the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and its analog lenalidomide, have improved outcomes for patients with MM during the last decade.² Lenalidomide

plus dexamethasone and bortezomib alone are approved for the treatment of MM in patients after at least one prior therapy has been administered,³⁻⁶ and bortezomib is approved for treatment in patients with newly diagnosed MM.⁷

Preclinical studies have shown that both thalidomide and lenalidomide potentiate the activity of bortezomib and dexamethasone (Fig 1).^{8,9} Bortezomib has demonstrated synergistic or additive antitumor activity with agents commonly used in the treatment of MM, including dexamethasone, as well as activity in MM cells resistant

Fig 1. Putative mechanistic basis for the use of the lenalidomide-bortezomib-dexamethasone combination. Lenalidomide and dexamethasone have been shown to trigger myeloma cell apoptosis via caspase-8 and caspase-9, respectively. Bortezomib can activate both of these pathways and also can counteract the inhibitory effect of nuclear factor- κ B (NF- κ B) on the antimyeloma activity of dexamethasone (Dex). These molecular events potentiate the induction of a dual caspase-8 and caspase-9-mediated apoptotic cascade with poly(ADP-ribose) polymerase (PARP) cleavage, leading to enhanced antimyeloma activity.

to these agents.^{10,11} Anticipated overlapping toxicities are primarily hematologic.^{5,12}

In the phase I, dose-escalation study reported here (ie, NCT00153933), the combination of lenalidomide plus bortezomib was evaluated in patients with relapsed or relapsed/refractory MM. Objectives were to assess safety, to determine the maximum-tolerated dose (MTD), and to derive a recommended dose for phase II studies. Secondary objectives included assessment of the efficacy of the combination, and of the tolerability and efficacy of adding dexamethasone if progression occurred on the regimen of lenalidomide combined with bortezomib alone.

PATIENTS AND METHODS

Eligibility

Eligible patients were age 18 years or older; had relapsed or relapsed/refractory MM after one or more prior therapies (including lenalidomide, bortezomib, or thalidomide); and had an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients were considered refractory if they had progressive disease (PD; $> 25\%$ increase in serum and/or urine M-protein; absolute increases of ≥ 5 g/L in serum or ≥ 200 mg/24 hours in urine) on prior therapy or within 60 days of salvage treatment, subsequent to relapse.

Patients were excluded if they had grade 3 or greater or had painful grade 2 peripheral neuropathy (PNY); serum creatinine greater than 2.0 mg/dL; evidence of mucosal or internal bleeding; platelets less than 50,000/ μ L; absolute neutrophil count less than 1,000/ μ L; hemoglobin less than 8.0 g/dL; AST or ALT at least twice the upper limit of normal; prior chemotherapy within 3 weeks or nitrosoureas within 6 weeks of day 1, cycle 1; previous intolerance to

lenalidomide or bortezomib; or known hypersensitivity to thalidomide. Concomitant radiation therapy, anti-MM chemotherapy, and corticosteroids (except as indicated for other conditions to a maximum of prednisone 10 mg/d or equivalent, or as premedication for other medications or blood products) were not permitted.

Study Design

This open-label, dose-escalation study was conducted at four centers in the United States and enrolled patients between August 2004 and April 2006. Review boards at all centers approved the study, which was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Determination of the MTD

Patients were assigned to a dose level in the order of study entry. In the dose-escalation scheme, lenalidomide was given at 5, 10, or 15 mg, and bortezomib was given at 1.0 or 1.3 mg/m²; bortezomib was escalated before the lenalidomide. Cohorts of three patients were sequentially enrolled at each dose level, and dose-escalation proceeded on the basis of the dose-limiting toxicity (DLT) experienced during the first treatment cycle. The first cohort of three patients received lenalidomide 5 mg/d and bortezomib 1 mg/m². If one of the first three patients in a dose level experienced a DLT, an additional three patients were enrolled at that dose level. If none of the first three patients in the cohort or one of the six patients experienced DLT during the first treatment cycle, the subsequent three patients received the same dose of lenalidomide plus bortezomib 1.3 mg/m² at the next dose level. If two or more patients experienced DLTs, dose escalation was halted. A DLT was defined as any grade 3 or higher nonhematologic toxicity, grade 4 thrombocytopenia on more than one occasion despite transfusion support, grade 4 neutropenia for more than 5 days and/or that resulted in neutropenic fever (temperature $\geq 101^\circ\text{F}$) confirmed on two occasions, or inability to proceed to cycle 2 because of toxicity. The MTD was defined as the dose level immediately below that at which two or more patients experienced DLTs; an additional 10 patients were enrolled at this dose level for additional characterization of safety and efficacy. Patients who experienced DLTs could continue treatment if the toxicity resolved to grade 2 or lower.

Study Treatment

Patients received oral lenalidomide on days 1 through 14 and intravenous bortezomib on days 1, 4, 8, and 11 of a 21-day cycle. Dexamethasone (20 or 40 mg on days 1, 2, 4, 5, 8, 9, 11, and 12) could be added at the investigator's discretion at any time after cycle 2 if the patient experience progression on the combination of lenalidomide and bortezomib. After January 2006, all patients could receive dexamethasone up to 40 mg, although some still initially received dexamethasone 20 mg. Patients with stable disease (SD) or responding disease at the end of cycle 8 could continue therapy. Patients discontinued therapy if they experienced PD (after two additional cycles if dexamethasone was added), relapse, no additional benefit, unacceptable toxicity, or by patient/investigator decision.

Dose modifications for attributable toxicities were allowed; bortezomib could be reduced from 1.3 mg/m² to 1.0 mg/m² to 0.7 mg/m², and lenalidomide could be reduced from 20 mg/d to 15 mg/d to 10 mg/d. Dexamethasone could be reduced from 40 mg/dose to 20 mg/dose to 10 mg/dose. No dose re-escalation was allowed.

Patients received supportive therapy, including bisphosphonates, erythropoietin, and granulocyte colony-stimulating factor (G-CSF), as clinically indicated. Prophylactic acyclovir and antithrombotic agents were also recommended and were administered at the investigator's discretion.

Safety and Efficacy Assessments

Toxicities were monitored throughout the study and for up to 30 days after the last dose of study drug. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).¹³ In addition, neuropathy symptoms were assessed by using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neuropathy questionnaire (version 4.0)¹⁴; PNY was assessed on days 1 and 8 of each treatment cycle.

Responses were determined at the end of cycle 2 and at every cycle thereafter by using European Group for Blood and Marrow Transplantation criteria,¹⁵ modified to include near-complete response (nCR; defined as complete response [CR] but also immunofixation positive for M-protein).^{16,17} Assessments of response, relapse, and progression were based on serum and urine M-protein quantification and on bone marrow evaluation, skeletal survey, and assessment of plasmacytomas, as required clinically and by the modified European Group for Blood and Marrow Transplantation criteria. Response was defined as minimal response (MR) or better.

Statistical Analysis

Patient baseline characteristics were summarized as the number and percent of patients or as the median and range of values. Exact binomial 90% CIs were reported for toxicity and responses. The median time-to-response (TTR) and the duration-of-response (DOR) were reported among the responders. TTR was measured from treatment initiation to the date the response was first observed. DOR was measured from response to first PD or death and was censored at the date patients were last known to be event free or alive for those who had not experienced treatment failure. Time-to-progression (TTP), progression-free survival (PFS), and overall survival (OS) were measured from the time of treatment initiation to event (ie, PD for TTP; PD or death for PFS; death for OS). Patients without an event were censored at the date they were last known to be in remission for TTP, in remission and alive for PFS, and alive for OS. If nonprotocol therapy, excluding bisphosphonates or erythropoietin, was added before an event, patients were censored in the time-to-event (TTE) analyses at the initiation of nonprotocol therapy. The Kaplan-Meier method was used for TTE and OS analyses.

RESULTS

Patient Characteristics, Disposition, and Determination of MTD

A total of 38 patients were enrolled, including 12 patients (32%) with relapsed and 26 patients (68%) with relapsed/refractory MM. Baseline patient characteristics are listed in Table 1; the median number of prior treatments was five (range, one to 14). Prior therapies, received at any time point, included dexamethasone (89%), thalidomide (87%), bortezomib (55%), stem-cell transplantation (61%), and lenalidomide (18%). Among 38 patients, 24 (63%) were refractory to thalidomide, 16 (42%) were refractory to bortezomib, and six (16%) were refractory to lenalidomide.

Patient disposition is detailed in Table 2. Two patients (one each from dose levels 3 and 5) experienced rapid disease progression within cycle 1 and were not evaluable for response, assessment for DLT, and determination of the MTD; an additional patient was enrolled at each of these dose levels. One patient experienced DLT (transient grade 3 asymptomatic hyponatremia) in dose level 4, and two experienced DLT in dose level 6 (one grade 3 herpes zoster virus reactivation in a patient who was noncompliant with antiviral prophylaxis, and one grade 4 neutropenia that was reversed with dose reduction and G-CSF support). The MTD, therefore, was determined to be lenalidomide 15 mg/d plus bortezomib 1.0 mg/m².

Drug Exposure and Safety

Patients received a median of 10.5 treatment cycles of lenalidomide (range, one to 74 cycles) and a median of 10 cycles of bortezomib (range, one to 74 cycles). Dexamethasone was added on occurrence of progression for 18 patients (47%); the median duration of dexamethasone therapy was six cycles (range, one to 29 cycles). Thirteen patients (34%) received lenalidomide and bortezomib for more than 1 year. At data cutoff in November 2008, one patient remained on treatment

Table 1. Patient Demographic and Baseline Clinical Characteristics

Characteristic	Patients (N = 38)	
	No.	%
Age, years		
Median	59	
Range	38-79	
Sex		
Male	24	63
Ethnicity		
White	35	92
Durie-Salmon stage at diagnosis		
I	10	26
II	12	32
III	16	42
Eastern Cooperative Oncology Group performance status		
0	22	58
1	15	39
2	1	3
Myeloma subtype*		
IgG	24	68
IgA	8	23
Biclonal	1	3
Light chain only, κ/λ	2	6
Disease status		
Relapsed	12	32
Relapsed/refractory	26	68
Soft tissue plasmacytoma	3	8
Presence of lytic bone disease	24	63
Serum albumin, g/dL		
< 3.5	9	24
≥ 3.5-5.5	29	76
Median hemoglobin, g/dL		
Median	11.5	
range	8.1-15.5	
Platelet count, k/ μ L		
Median	176.5	
Range	62-350	
Prior therapies		
Median	5	
Range	1-14	
Prior therapy		
Thalidomide	33	87
Lenalidomide	7	18
Bortezomib	21	55
Dexamethasone	34	89
Stem cell transplantation: autologous or allogeneic	23	61
Melphalan	8	21
Melphalan plus prednisone	5	13
Time from diagnosis to study entry, months		
Median	45	
Range	9.3-129.5	

*Among the 35 patients positive for serum M-protein.

after having received 74 cycles of lenalidomide and bortezomib. Treatment was discontinued in the remaining patients because of PD (n = 22; 58% of all patients), completion of protocol treatment (n = 4; 11% of all patients), unacceptable toxicity (n = 4; 11% of all patients), withdrawal of consent (n = 4; 11% of all patients), physician decision (n = 1; 3% of all patients), death as a result of aspiration pneumonia

Table 2. Patient Disposition per Dose Level

Dose Level	Lenalidomide (mg)	Bortezomib (mg/m ²)	No. of Patients (N = 38)
1	5	1.0	3
2	5	1.3	3
3	10	1.0	4*
4	10	1.3	6
5	15	1.0	15†
6	15	1.3	7‡

*Two patients (one each in dose levels 3 and 5) were not evaluable for response because of rapid disease progression during cycle 1 and were not included in assessment of dose-limiting toxicity or determination of maximum-tolerated dose.

†Includes five initial patients plus 10 patients added at the level of the maximum-tolerated dose; this provided a total of 15 patients at dose level 5. Because of rapid disease progression, one of the three initial patients enrolled at dose level 5 came off study and was replaced by another patient who, because of a protocol violation, remained on study but was replaced by an additional patient; thus, in total, there were five initial patients.

‡Because of a dose-limiting toxicity with one of the three initial patients enrolled in dose level 6, three additional patients were enrolled. One of these additional patients had a protocol violation, so that patient remained on study but was replaced by an additional patient; thus, in total, there were seven patients.

not considered treatment-related ($n = 1$; 3% of all patients), and reason unspecified ($n = 1$; 3% of all 38 patients).

Treatment-related AEs that occurred with a frequency of 25% or greater are listed in Table 3. Sensory PNY was reported in 16 patients (42%; 90% CI, 29% to 57%), including seven patients (18%) with grade 1 PNY and nine patients (24%) with grade 2 PNY. No grades 3

or 4 sensory PNY occurrences were observed. The most common grade 3 or greater toxicities include neutropenia (63%; 90% CI, 49% to 76%), thrombocytopenia (45%; 90% CI: 31% to 59%), anemia (18%; 90% CI, 9% to 32%), and leukopenia (18%; 90% CI, 9% to 32%). Other treatment-related, grades 1 or 2 toxicities (in 25% or more of patients) included diarrhea (39%), pruritus (29%), musculoskeletal/soft tissue conditions (specifically, cramps; 26%), and nausea (26%). One patient experienced deep-vein thrombosis (DVT) while receiving lenalidomide alone plus low-molecular-weight heparin (LMWH).

Four patients discontinued treatment because of the following unacceptable toxicities: one dexamethasone-related toxicity, one occurrence of pneumonitis considered possibly related to lenalidomide therapy, and two persistent occurrences of cytopenias that also were possibly related to lenalidomide therapy. Four patients required dose reductions for lenalidomide, 14 for bortezomib, 11 for both agents, and six for dexamethasone. Ninety-five percent of the lenalidomide dose modifications and 82% of the bortezomib dose modifications occurred within the first eight cycles.

For those patients who experienced sensory PNY, supplements, including folate, B-complex vitamins, and amino-acids, were administered. Analgesics used included duloxetine, acetaminophen, gabapentin, and pregabalin. Eighteen patients (47%) received treatment (or prophylaxis) for sensory neuropathy that was present or that developed during the study. Fifteen patients (39%) received thromboprophylaxis; nine patients received aspirin (81 to 325 mg/d), one received warfarin alone, one received LMWH alone, and four patients received aspirin and warfarin, either simultaneously ($n = 2$) or warfarin followed by aspirin ($n = 2$).

Efficacy

Thirty-six patients were included in the response-evaluable population. MR or better to lenalidomide combined with bortezomib was observed in 61% of the patients (90% CI, 46% to 75%), which included an 8% CR/nCR rate (Table 4); 36% of patients achieved MR or greater at the MTD. Among the 22 responders, the median TTR was 1.4 months (range, 0.7 to 39 months), and the median DOR was 10.8 months (95% CI, 1.1 to 33.3 months). Among 18 patients who received dexamethasone because of PD, 83% (90% CI, 62% to 95%) had at least SD with PR in three patients (17%), MR in two patients (11%), and SD in 10 patients (56%); the median TTR was 0.9 months.

Among the 24 patients who were refractory to prior bortezomib, lenalidomide, and/or thalidomide, six (25%; 90% CI, 12% to 44%) achieved at least PR, and 12 (50%; 90% CI, 32% to 68%) achieved at least MR on this trial. Among the seven patients refractory to thalidomide, two achieved CR/nCR, one achieved PR, one achieved MR, and three had SD. Among two patients refractory to bortezomib, one achieved an MR, and one had PD. Among nine patients refractory to bortezomib and thalidomide, one achieved PR, three achieved MR, four had SD, and one was unevaluable for response. Among three patients refractory to lenalidomide and thalidomide, one achieved a PR, one achieved MR, and one had PD. Among three patients refractory to all three agents, one achieved nCR, and two had SD.

TTE and OS Data

For the 36 response-evaluable patients who received lenalidomide plus bortezomib, the median TTP was 7.7 months (Fig 2A); an estimated 42% (95% CI, 25% to 59%) and 18% (95% CI, 5% to 31%)

Table 3. Summary of Treatment-Related Adverse Events

Adverse Event	No. of Patients by Event Grade (N = 38)				Total Patients	
	1	2	3	4	No.	%
Treatment-related in $\geq 25\%$ of patients						
Neutropenia	1	2	18	6	27	71
Thrombocytopenia	4	3	10	7	24	63
Fatigue	9	10	2	0	21	55
Anemia	5	5	6	1	17	45
Sensory neuropathy	7	9	0	0	16	42
Diarrhea	9	6	0	0	15	39
Leukopenia	1	4	6	1	12	32
Constipation	7	3	1	0	11	29
Pruritus	11	0	0	0	11	29
Muscle cramps	5	5	0	0	10	26
Nausea	7	3	0	0	10	26
Additional grades 3 to 4						
Vomiting	1	3	1	0	5	13
Limb edema	2	0	1	0	3	8
Lymphopenia	0	0	3	0	3	8
Blurred vision	1	1	1	0	3	8
Fever without neutropenia	1	0	1	0	2	5
Hypertension	0	1	0	1	2	5
Hypokalemia	1	0	1	0	2	5
Skin infection	0	1	0	1	2	5
Ocular, other	0	1	1	0	2	5
Hyponatremia	0	0	1	0	1	3
Deep-vein thrombosis	0	0	0	1	1	3

Table 4. Best Response to Lenalidomide Plus Bortezomib Combination Therapy

Table 1: Best Response to Lenalidomide Plus Bortezomib Combination Therapy														
Treatment Dose			Patients by Response Type											
Cohort	Lenalidomide (mg)	Bortezomib (mg/m ²)	CR		nCR		PR		MR		SD		PD	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	5	1.0	0		0		2		0		1		0	
2	5	1.3	1		0		1		1		0		0	
3	10	1.0	0		1		2		0		0		0	
4	10	1.3	0		0		2		2		1		1	
5	15	1.0	0		0		1		4		7		2	
6	15	1.3	0		1		3		1		2		0	
Total*†			1	2	2	6	11	31	8	22	11	31	3	8

Abbreviations: CR, complete response; nCR, near-complete response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

*One patient (3%) who qualified for the response-evaluable population (n = 36) was not evaluable by European Group for Blood and Marrow Transplantation/paraprotein criteria.¹⁷

†Total CR + nCR = 8%; total CR + nCR + PR = 39% (90% CI, 25% to 54%). Overall response rate (ie, CR + nCR + PR + MR) = 61% (90% CI, 46% to 75%) per modified European Group for Blood and Marrow Transplantation criteria.⁴

of patients had not experienced progression at 1 and 2 years, respectively. Median PFS was 6.9 months (Fig 2B), and the estimated 1-year and 2-year PFS rates were 44% (95% CI, 27% to 60%) and 20% (95% CI, 7% to 34%), respectively. During a median follow-up of 36 months, 19 patients have died and 17 remain alive, as of November 2008. The median OS was 37 months (Fig 2C), and the estimated 1-year and 2-year OS rates were 77% (95% CI, 63% to 91%) and 50% (95% CI, 33% to 67%), respectively. All nine patients with follow-up of 24 to 37 months are currently alive and censored; therefore, median OS may change with additional follow-up.

To date, 13 of the 18 patients who received dexamethasone have subsequently experienced progression, and the median TTP was 6.1 months (95% CI, 2.7% to 14.6%) from the time of dexamethasone addition.

DISCUSSION

This phase I study is the first prospective study to evaluate lenalidomide in combination with bortezomib in patients with relapsed and relapsed/refractory MM. The MTD was established as lenalidomide 15 mg/d plus bortezomib 1.0 mg/m². However, this MTD was established on inclusion of one DLT (ie, herpes zoster viral reactivation) in the setting of noncompliance with prophylactic acyclovir treatment and one episode of grade 4 neutropenia. Both DLTs were reversible and proved readily manageable, which suggests that additional dose-escalation studies of this combination may be warranted. Although front-line studies cannot be used to inform treatment decisions for patients with relapsed or relapsed/refractory MM, the combination of lenalidomide and bortezomib plus dexamethasone has been successfully dose escalated further and currently is being studied at higher doses of lenalidomide and bortezomib (ie, 1.3 mg/m² and 25 mg/d, respectively) for the initial treatment of MM.¹⁸

Lenalidomide and bortezomib combined was well tolerated, had few treatment-related discontinuations, and had manageable toxicities. Treatment-related toxicities were consistent with established toxicity profiles of lenalidomide^{12,19,20} and bortezomib²¹⁻²³ in relapsed MM. Importantly, combined lenalidomide and bortezomib did not appear to substantially increase hematologic toxicity compared with single-agent lenalidomide.¹⁹ Furthermore, low rates of neurotoxicity were reported, and no grades 3 to 4 sensory PNY were reported; this

may be due to the lower-than-standard doses of bortezomib used or may reflect an effect of the combination with lenalidomide.²⁴ Also of note was the low rate of DVT (with only one occurrence reported); thromboprophylaxis may have reduced the risk of this complication,^{25,26} and bortezomib may have additionally abrogated it.^{23,27-29}

Lenalidomide plus bortezomib was active in this patient population, which included patients who had received prior thalidomide, bortezomib, and lenalidomide therapy. Importantly, the responses were durable; the median TTP was 7.7 months in a patient population in which 87% received prior thalidomide, 55% received prior bortezomib, and 18% received prior lenalidomide. These findings support the notion of dual-apoptotic signaling (Fig 1) and suggest that the use of these two agents in combination may resensitize patients with relapsed/refractory MM.

Importantly, overall response rates obtained with this combination were superior to single-agent response rates in this setting.^{16,19,24} At the MTD, 36% of patients previously exposed to lenalidomide and bortezomib had MR or better. In addition, when patients from the cohort escalated higher than the DLT at a dose of bortezomib of 1.3 mg/m² were included, 48% of patients had MR or better. These results offer additional evidence that re-treatment with bortezomib-containing combinations can be successful despite prior use and/or failure of bortezomib.^{30,31} As previously noted, studies in the front-line setting have dose escalated this combination beyond the MTD described and have found it well tolerated. Finally, the addition of dexamethasone in the subgroup of 18 patients with PD resulted in 28% of patients experiencing response (MR or better) and an additional 56% achieving SD, which suggests that the addition of dexamethasone to lenalidomide plus bortezomib results in improved activity (Fig 1); moreover, rates were similar to those seen with the addition of dexamethasone to single-agent bortezomib in the SUMMIT and CREST studies.³²

The median survival of 37 months seen in this study suggests that this combination is promising, particularly because overall response rates not only were higher than those achieved with some bortezomib-based and lenalidomide-based therapies in studies of heavily pre-treated patients, but also appeared more durable.^{12,16,24,33}

Future analyses will include exploratory pharmacogenomic analysis of molecular markers associated with response to lenalidomide

Fig 2. Kaplan-Meier estimates (in months) and 95% CIs of (A) time to progression, (B) progression-free survival, and (C) overall survival in 36 patients.

plus bortezomib and identification of surrogate markers to help define the mechanisms of this drug combination.

There are now clinical trial data that suggest that novel-agent regimens that combine lenalidomide and bortezomib may be promising therapeutic options for patients with newly diagnosed MM.^{7,18,28,34-36} Several phase III trials have been reported for bortezomib versus previous or existing standards of care in patients both eligible and not eligible for high-dose therapy and transplantation.^{7,28,36} The combination of lenalidomide and bortezomib plus dexamethasone is being evaluated additionally in a multicenter, phase II trial in patients with relapsed and relapsed/refractory disease,³⁷ and there is a recently com-

pleted, phase I/II study in patients with newly diagnosed MM.¹⁸ Preliminary data from these two studies each show a response rate of 84% in patients with relapsed disease (MR or better) and rates of 100% (for PR or better) and 44% (for CR/nCR) in newly diagnosed patients. A multicenter, phase I/II study of bortezomib and dexamethasone plus cyclophosphamide and of lenalidomide, bortezomib, dexamethasone, and cyclophosphamide³⁸ is ongoing, and phase III studies to compare lenalidomide, bortezomib, and dexamethasone with other combinations as well as with or without transplantation are planned.

In conclusion, the combination of lenalidomide and bortezomib with the addition of dexamethasone is feasible, tolerable, and active. Survival in this study was especially encouraging, as the regimen showed efficacy even in heavily pretreated patients who were previously exposed to immunomodulatory agents and to bortezomib. This combination may provide an important new platform for the treatment of advanced MM, and results may also provide the rationale for its use earlier in the disease course.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Paul G. Richardson, Edie Weller, Constantine S. Mitsiades, Teru Hideshima, William Dalton, Robert Knight, Dixie-Lee Esseltine, Kenneth C. Anderson

Provision of study materials or patients: Paul G. Richardson, Sundar Jagannath, David E. Avigan, Melissa Alsina, Robert L. Schlossman, Amitabha Mazumder, Nikhil C. Munshi, Irene M. Ghobrial, Deborah Doss, Mary McKenney, William Dalton, Kenneth C. Anderson

Collection and assembly of data: Paul G. Richardson, Sundar Jagannath, David E. Avigan, Melissa Alsina, Robert L. Schlossman,

Deborah Doss, Diane L. Warren, Laura E. Lunde, Carol Delaney, Kenneth C. Anderson

Data analysis and interpretation: Paul G. Richardson, Edie Weller, Laura E. Lunde, Kenneth C. Anderson

Manuscript writing: Paul G. Richardson, Edie Weller, Constantine S. Mitsiades, Kenneth C. Anderson

Final approval of manuscript: Paul G. Richardson, Edie Weller, Sundar Jagannath, David E. Avigan, Melissa Alsina, Robert L. Schlossman, Amitabha Mazumder, Nikhil C. Munshi, Irene M. Ghobrial, Deborah Doss, Diane L. Warren, Laura E. Lunde, Mary McKenney, Carol Delaney, Constantine S. Mitsiades, Teru Hideshima, William Dalton, Robert Knight, Dixie-Lee Esseltine, Kenneth C. Anderson

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