

Updated survival analyses after prolonged follow-up of the phase 2, multicenter CREST study of bortezomib in relapsed or refractory multiple myeloma

Sundar Jagannath,¹ Bart Barlogie,² James R. Berenson,³ David S. Siegel,⁴ David Irwin,⁵ Paul G. Richardson,⁶ Ruben Niesvizky,⁷ Raymond Alexanian,⁸ Steven A. Limentani,⁹ Melissa Alsina,¹⁰ Dixie-Lee Esseltine,¹¹ Kenneth C. Anderson⁶

¹St. Vincent's Comprehensive Cancer Center, New York, NY; ²Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR; ³Oncotherapeutics, West Hollywood, CA; ⁴Hackensack University Medical Center, Hackensack, NJ; ⁵Alta Bates Cancer Center, Berkeley, CA; ⁶Dana-Farber Cancer Institute, Boston, MA; ⁷Weill-Cornell Medical College of Cornell University, New York Presbyterian Hospital, NY; ⁸University of Texas M. D. Anderson Cancer Center, Houston, TX; ⁹Carolinas Hematology/Oncology Associates, Charlotte, NC; ¹⁰H. Lee Moffitt Cancer Center Research Institute, Tampa, FL; ¹¹Millennium Pharmaceuticals, Inc., Cambridge, MA

BACKGROUND

- Bortezomib (VELCADE®) is approved for the treatment of multiple myeloma (MM) patients who have received at least one prior therapy.¹
- Accelerated approval in the United States was based on the results of the phase 2 SUMMIT^{2,3} and CREST⁴ trials.
- Final approval was based on the results of the phase 3 APEX trial.^{5,6}
- CREST is the only phase 2 study of two doses of bortezomib as second-line therapy, and it established the activity of bortezomib 1.0 mg/m² and 1.3 mg/m² in comparable patient populations.⁴
- Here, we present updated data from the CREST study after prolonged follow-up (median 5 years).

OBJECTIVE

- To evaluate overall survival (OS) in the CREST⁴ phase 2 trial of bortezomib ± dexamethasone after prolonged follow-up (median >5 years) in patients who received:
 - Bortezomib 1.0 mg/m²
 - Bortezomib 1.3 mg/m²

METHODS

Study design

- Patients were enrolled to receive bortezomib as second-line therapy.
- Patients had relapsed following chemotherapy or were refractory to front-line chemotherapy.
 - Front-line therapy could be composed of more than one regimen, defined as a single drug or combination therapy.
- Patients were randomized to receive bortezomib 1.0 mg/m² or 1.3 mg/m² on days 1, 4, 8, and 11 of a 21-day cycle for up to 8 cycles.
 - To ensure that the two dose levels were studied in similar patient populations, a center-specific randomization was used, based on disease stage and previous chemotherapy.
- Patients with suboptimal response to bortezomib alone (progressive disease after 2 cycles or stable disease after 4 cycles) were eligible to add

dexamethasone 20 mg on the day of and day after each bortezomib dose.

- Patients who, in the investigator's opinion, could benefit or continue to benefit from treatment or retreatment could continue receiving bortezomib in an extension study.⁸

Assessments

- Response and progression were assessed according to the European Group for Blood and Marrow Transplantation (EBMT) criteria.⁹
 - Also included near CR (nCR) – 100% M-protein reduction but with positive immunofixation.
- Secondary efficacy endpoints assessed included time to progression (TTP), duration of response, and OS.
 - Time-to-event analyses were performed using the Kaplan-Meier method.
- Adverse events (AEs) were assessed at each visit and graded according to the National Cancer Institute Common Toxicity Criteria version 2.
 - Bortezomib dose reductions were required for drug-related grade ≥3 non-hematologic and grade 4 hematologic toxicities.
- The study was prospectively designed to determine whether the rate of response to bortezomib alone was at least 20% ($\alpha=0.05$), with at least 80% power to conclude a response rate of 40% or more.

RESULTS

- 54 patients were enrolled:
 - 28 received bortezomib 1.0 mg/m²
 - 26 received bortezomib 1.3 mg/m².
 - Patient demographics and baseline characteristics are shown in Table 1.
 - Patients were balanced with respect to demographics and prior therapies across the two arms.
 - Exposure to treatment in CREST and the extension study for each dose group are summarized in Table 2.
- ### Efficacy
- Of the 54 patients enrolled, 53 were evaluable for response.
 - One patient with non-secretory myeloma was not evaluable.

Table 1. Patient demographics and baseline characteristics

	Bortezomib dose group	
	1.0 mg/m ² (n=28)	1.3 mg/m ² (n=26)
Mean age, years (range)	64 (39–82)	60 (30–84)
Male, n (%)	14 (50)	9 (35)
IgG/IgA/other MM, %	54/29/18	65/23/12
Karnofsky Performance Status \leq 70, n (%)	3 (11)	4 (15)
β 2-microglobulin \geq 4 mg/L, n/N (%)	14/24 (58)	11/23 (48)
Platelets $<$ 75 \times 10 ⁹ /L, n/N (%)	5/26 (19)	0/25 (0)
Abnormal cytogenetics, n/N (%)	7/24 (29)	11/23 (48)
Durie-Salmon Stage III, n/N (%)	15/27 (56)	16/26 (62)
Median time since diagnosis, years	2.0	2.0
Median no. of prior regimens, n (range)	3 (1–7)	3 (1–7)
Prior ASCT/other high-dose therapy, n (%)	15 (54)	11 (42)

Table 2. Exposure to treatment with bortezomib ± dexamethasone in CREST and the extension study

	Bortezomib dose group	
	1.0 mg/m ² (n=28)	1.3 mg/m ² (n=26)
Median duration of treatment in CREST, months (range)	4.7 (0.03–7.6)	3.9 (0.4–5.7)
Patients completing \geq 4 cycles, n (%)	24 (86)	19 (73)
Patients completing 8 cycles, n (%)	17 (61)	7 (27)
Median number of cycles	8	6
Patients requiring dose reductions due to AEs, n (%)	3 (11)	9 (35)
Patients receiving added dexamethasone, n (%)	16 (57)	12 (46)
Patients continuing in extension study, n (%)	12 (43)	5 (19)

- The study objective was met. In the 1.0 mg/m² dose group, 30% of the patients achieved CR+PR and 33% achieved CR+PR+MR.
- Both the 1.0 mg/m² and 1.3 mg/m² doses were active and induced durable responses, as shown in Table 3.
- Median treatment duration in the 1.3 mg/m² group is similar to that in the APEX phase 3 trial of bortezomib 1.3 mg/m².

Table 3. Response rates and TTP by bortezomib dose group

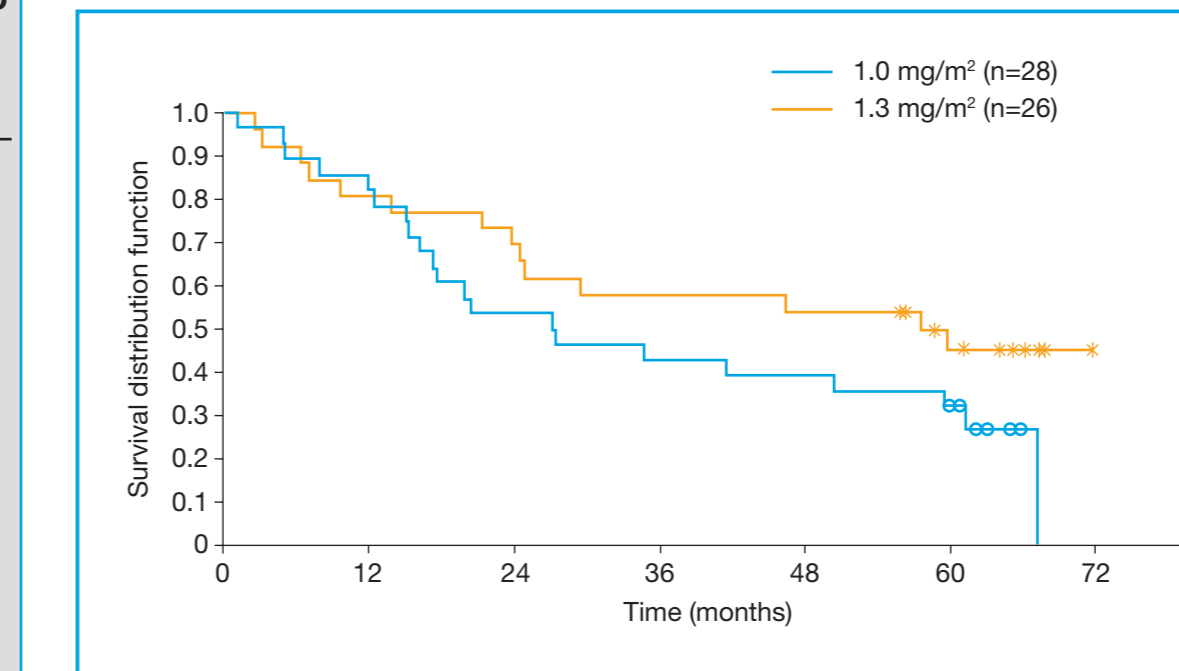
	Bortezomib dose group	
	1.0 mg/m ² (n=27)	1.3 mg/m ² (n=26)
Overall response rate (CR+PR+MR), n (%)		
To bortezomib alone	9 (33)	13 (50)
To bortezomib ± dexamethasone	12 (44)	16 (62)
CR+PR rate, n (%)		
To bortezomib alone	8 (30)	10 (38)
To bortezomib ± dexamethasone	10 (37)	13 (50)
Median time to first response, months	1.3	1.5
Median duration of response (CR/PR/MR), months	9.5	13.7
Median TTP, months	7.0	11.0

- Median follow-up was:
 - 61 (59–65) months in the 1.0 mg/m² dose group
 - 65 (55–71) months in the 1.3 mg/m² dose group.
- OS at the 5-year mark was 32% and 45% for the 1.0 mg/m² and 1.3 mg/m², respectively.
- Kaplan-Meier distributions of OS in the two dose groups are shown in Figure 1.
 - Survival rates are summarized in Table 4.

Table 4. Survival rates by bortezomib dose group

	Bortezomib dose group	
	1.0 mg/m ² (n=28)	1.3 mg/m ² (n=26)
1-year survival rate, %	82	81
2-year survival rate, %	54	69
3-year survival rate, %	43	58
4-year survival rate, %	36	54
5-year survival rate, %	32	45
Number of patients who have died, n (%)	21 (75)	14 (54)
Median follow-up, months	61	65

Figure 1. Kaplan-Meier analyses of OS in patients who received bortezomib 1.0 mg/m² or 1.3 mg/m² ± dexamethasone



Safety⁸

- Toxicities were manageable.
- AEs reported at \geq 20% greater rate with the 1.3 mg/m² dose compared with the 1.0 mg/m² dose included:
 - Diarrhea, vomiting, anxiety, peripheral neuropathy, night sweats, myalgia, blurred vision, and dyspnea.
- A higher proportion of patients at the 1.3 mg/m² dose level required dose reductions due to AEs compared with the 1.0 mg/m² dose level (35% vs 11%).
 - Patients' final bortezomib dose was the same as their starting dose in 82% of patients in the 1.0 mg/m² dose level and 65% in the 1.3 mg/m² dose level.
 - The median dose intensity (% of dose expected) was 95% and 86.9% for the 1.0 mg/m² dose level and 1.3 mg/m² dose level, respectively.
- Thirteen patients (23%) discontinued due to AEs, including three (11%) at the 1.0 mg/m² dose level and ten (38%) at the 1.3 mg/m² dose level.
 - Of these AEs resulting in discontinuation, two and six, respectively, were considered related to bortezomib.

Subsequent therapy

- Comprehensive data on subsequent therapies received for MM is not available.
- Some patients received retreatment with bortezomib-based therapy, which has been shown to be active in patients with relapsed MM.^{10–12}
- Some patients received treatment with other novel therapies, including thalidomide and lenalidomide.
- Subsequent therapy with bortezomib and other novel agents may have contributed to the prolonged survival reported here.

CONCLUSIONS

- Long-term follow-up confirms the survival benefit conferred by bortezomib ± dexamethasone after a first relapse:
 - 1.3 mg/m²: 3-year survival rate is 58%
 - 1.0 mg/m²: 3-year survival rate is 43%.
- Bortezomib demonstrated substantial activity at both dose levels:
 - 1.3 mg/m²: CR+PR = 38%
 - 1.0 mg/m²: CR+PR = 30%.
- The 1.0 mg/m² dose is associated with better tolerance compared with the 1.3 mg/m² dose:
 - 1.3 mg/m²: 27% of patients completed eight cycles; 35% had dose reductions and 35% discontinued due to AEs
 - 1.0 mg/m²: >60% of patients completed eight cycles; 11% had dose reductions and 11% discontinued due to AEs.
- A starting dose of 1.3 mg/m² is the preferred dose for bortezomib;⁷ patients should be closely monitored for AEs, especially neuropathy. In cases of toxicity, bortezomib dose can be reduced to 1 mg/m² and retain acceptable efficacy.
- A starting dose of 1.0 mg/m² is acceptable in special circumstances where patients may not be able to tolerate the higher dose.

REFERENCES

- Kane RC, et al. Clin Cancer Res 2006;12:2955–60.
- Richardson PG, et al. N Engl J Med 2003;348:2609–17.
- Richardson PG, et al. Cancer 2006;106:1316–9.
- Jagannath S, et al. Br J Haematol 2004;127:165–72.
- Richardson PG, et al. N Engl J Med 2005;352:2487–98.
- Richardson PG, et al. Blood 2007;110:3557–60.
- Millennium Pharmaceuticals, Inc. VELCADE® (bortezomib) for injection. Prescribing Information. Rev 7. October 2007.
- Berenson JR, et al. Cancer 2005;104:2141–8.
- Bladé J, et al. Br J Haematol 1998;102:1115–23.
- Conner TM, et al. Blood 2006;108:1007a (abstract 3531).
- Sood R, et al. Ann Oncol 2006;17:ix205–6 (abstract 679P).
- Wolf JL, et al. Blood 2006;108:1008a (abstract 3532).

ACKNOWLEDGMENTS

The authors thank Steve Hill, Sarah Maloney, and Jane Saunders for their assistance in drafting the poster. Steve Hill and Sarah Maloney are Medical Writers, and Jane Saunders is a Medical Editor with Gardiner-Caldwell London.

DISCLOSURES

- Employment: Millennium Pharmaceuticals (DLE)
- Consultancy: Millennium Pharmaceuticals (JB, RN, KA), Celgene (RN, KA), Novartis (KA)
- Ownership interest: Millennium Pharmaceuticals (DLE)
- Research funding: Millennium Pharmaceuticals (JB, RN, KA), Celgene (RN, KA), Novartis (KA)
- Honoraria: Millennium Pharmaceuticals (SJ, BB, RA, PR, RN, KA), Celgene (BB, PR, RN, KA), Novartis (KA), Johnson & Johnson (PR)
- Membership: Millennium (SJ, BB, JB, DS, PR), Celgene (SJ, BB, PR), Johnson & Johnson (PR)