

# Final Overall Survival Results of a Randomized Trial Comparing Bortezomib Plus Pegylated Liposomal Doxorubicin With Bortezomib Alone in Patients With Relapsed or Refractory Multiple Myeloma

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**BACKGROUND:** Previous results from an interim analysis of an open-label, randomized, phase 3 study demonstrated that bortezomib combined with pegylated liposomal doxorubicin (PLD) was superior to bortezomib monotherapy in patients with relapsed/refractory multiple myeloma who had previously received one or more lines of therapy. Protocol-defined final survival data from that study are provided here. **METHODS:** Patients were randomized (1:1) to receive either bortezomib alone (1.3 mg/m<sup>2</sup> intravenously on days 1, 4, 8, and 11 of every 21-day cycle) or bortezomib-PLD (bortezomib plus PLD 30 mg/m<sup>2</sup> intravenously on day 4). The primary endpoint was the time to progression. Secondary efficacy endpoints included overall survival (OS), progression-free survival, and the overall response rate. **RESULTS:** In total, 646 patients (bortezomib-PLD, n = 324; bortezomib alone, n = 322) were randomized between December, 2004, and March, 2006. On the clinical cutoff date (May 16, 2014) for the final survival analysis, at a median follow-up of 103 months, 79% of patients had died (bortezomib-PLD group: 253 of 324 patients; 78%; bortezomib alone group: 257 of 322 patients; 80%). The median OS in the bortezomib-PLD group was 33 months (95% confidence interval [CI], 28.9-37.1) versus 30.8 months (95% CI, 25.2-36.5) in the bortezomib alone group (hazard ratio, 1.047; 95% CI, 0.879-1.246; *P* = .6068). Salvage therapies included conventional and novel drugs, which were well balanced between the two treatment groups. **CONCLUSIONS:** Despite inducing a superior time to progression, long-term follow-up revealed that PLD-bortezomib did not improve OS compared with bortezomib alone in patients with relapsed/refractory multiple myeloma. The inability to sustain the early observed survival advantage may have been caused by the effects of subsequent lines of therapy, and underscores the need for long-term follow-up of phase 3 trials while recognizing the challenge of having adequate power to detect long-term differences in OS. *Cancer* 2016;122:2050-6. © 2016 American Cancer Society.

**KEYWORDS:** bortezomib, doxorubicin, multiple myeloma, pegylated liposomal doxorubicin, survival.

## INTRODUCTION

Multiple myeloma (MM), the second most common hematologic malignancy, affects terminally differentiated plasma cells,<sup>1</sup> and is characterized by the overproduction of monoclonal immunoglobulins, osteolytic bone lesions, renal disease, and immunodeficiency.<sup>2</sup> Although patients with MM often respond to initial therapy, the disease eventually relapses and

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becomes refractory to further treatment. However, with the advent of new and more effective drugs for the treatment of MM, both alone and in combination with established anti-MM agents, there is now a rapid increase in the number of therapeutic options available to patients with MM, particularly in the relapsed/refractory setting.

The combination of bortezomib and pegylated liposomal doxorubicin (PLD) is considered an important therapeutic option for patients with relapsed or refractory MM who have received 1 or more prior therapies. Initial therapy with novel combinations that included bortezomib and/or PLD demonstrated high overall response rates (which ranged from 80% to 100%), complete response rates (range, 20%-30%), and very good partial response rates (range, 30%-50%) in previously untreated patients with MM.<sup>3-7</sup>

The results from the interim analysis of the study demonstrated that the bortezomib-PLD combination significantly reduced the risk of developing disease progression by 45% and prolonged the median time to progression (TTP) by 3 months in patients with relapsed or refractory MM.<sup>8</sup> An early overall survival (OS) benefit from treatment with bortezomib-PLD was observed compared with bortezomib monotherapy (hazard ratio [HR], 1.41; 95% confidence interval [CI], 1.002-1.97;  $P = .0476$ ).<sup>8</sup> Here, we report results from the protocol-defined, long-term follow-up for survival analysis of the study. The study is registered at clinicaltrials.gov as National Clinical Trial NCT00103506.

## MATERIALS AND METHODS

### Patients

Patients (aged  $\geq 18$  years) with confirmed MM whose disease had progressed after an initial response to at least 1 line of prior therapy or had been refractory to initial treatment were eligible. Patients who had an Eastern Cooperative Oncology Group performance status of 0 or 1, a life expectancy of at least 3 months, platelets  $\geq 75,000/\text{mm}^3$ , hemoglobin  $\geq 8.0$  g/dL, an absolute neutrophil count  $\geq 1000/\text{mm}^3$ , creatinine clearance  $\geq 30$  mL/minute, total bilirubin  $\leq 1.5$  times the upper limit of normal, and corrected serum calcium  $< 12$  mg/dL (3.0 mM/L) or ionized calcium  $< 6.5$  mg/dL (1.6 mmol/L) were enrolled in the study. Patients were bortezomib-naive and were excluded if they had previous disease progression while receiving anthracycline-containing therapy. Additional exclusion criteria included prior doxorubicin or other anthracycline exposure  $> 240$  mg/m<sup>2</sup>, clinically significant cardiac disease, a left ventricular ejection fraction less than institu-

tional normal limits, and grade 2 or higher peripheral neuropathy.

The study protocol was approved by local independent ethics committees, and the study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the protocol. All participants provided written informed consent to participate in the study.

### Study Design and Treatment

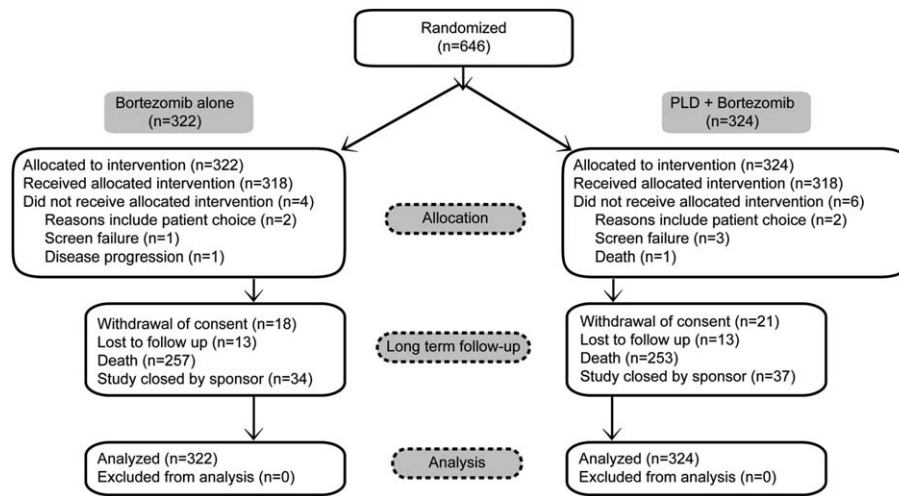
This was a phase 3, open-label, randomized, active-controlled, multicenter study. The eligible patients were randomized (1:1) to receive either bortezomib monotherapy (1.3 mg/m<sup>2</sup> intravenously on days 1, 4, 8, and 11 of every 21-day cycle;  $n = 322$ ) or bortezomib-PLD combination therapy (the same bortezomib monotherapy with PLD, 30 mg/m<sup>2</sup> as a 1-hour intravenous infusion on day 4 of each 21-day cycle;  $n = 324$ ) (Fig. 1). Before randomization, patients were stratified according to their serum  $\beta 2$  microglobulin levels ( $\leq 2.5$ ,  $> 2.5$  and  $\leq 5.5$ , or  $> 5.5$  mg/L) and response to previous treatment (response followed by progression or primary refractory disease). Study treatment was continued until disease progression, unacceptable treatment-related toxicity, or up to 8 cycles. Patients who were still responding after 8 cycles and had acceptable tolerability to the drug continued the treatment. Crossover to combination therapy from monotherapy was disallowed. Details of the study, including results from the interim analysis data, were published in 2007.<sup>8</sup> The final survival analysis presented here was based on the clinical cutoff date (May 16, 2014) upon final study closure.

### Endpoint

OS was defined as the interval from randomization to death from any cause. Data were censored at the last date the patient was known to be alive (for patients who were not known to have died).

### Statistical Method

Long-term follow-up survival data were collected until approximately 80% of enrolled patients had died. The distribution of OS was estimated for each treatment group using the Kaplan-Meier method. The log-rank test, stratified by enrollment strata, was used to compare the 2 treatment groups. A stratified Cox proportional-hazards model was used to estimate HRs (bortezomib monotherapy vs bortezomib-PLD: HR  $> 1$  indicates a treatment



**Figure 1.** This is a Consolidated System for Reporting Trials (CONSORT) diagram for the intent-to-treat analysis set. PLD indicates pegylated liposomal doxorubicin.

effect in favor of bortezomib-PLD) and 95% CIs. The effects of other prognostic factors were examined in a separate Cox proportional-hazards model. Subgroup analysis was performed to obtain HR estimates in each subgroup along with associated 95% CIs.

## RESULTS

### Patients and Treatments

Of 646 enrolled patients, 324 were randomized to the bortezomib-PLD group and 322 were randomized to the bortezomib monotherapy group. The baseline demographics and other characteristics were well balanced, and the groups were similar in the number and type of prior systemic therapy for MM.<sup>8</sup>

### OS Analysis

At the clinical cutoff, 79% of patients had died (bortezomib-PLD, 253 patients [78%]; bortezomib, 257 patients [80%]), 6% withdrew consent, 4% were lost to follow-up, and 11% were still alive (bortezomib-PLD, 37 patients [11%]; bortezomib, 34 patients [11%]). The median follow-up for survival was 103 months (8.6 years). The median OS for patients in the bortezomib-PLD group was 33.0 months (95% CI, 28.9-37.1 months) versus 30.8 months (95% CI, 25.2-36.5 months) for those in the bortezomib monotherapy group (HR, 1.047; 95% CI, 0.879-1.246;  $P = .6068$ ). This 2-month difference in median survival in favor of the bortezomib-PLD group over the bortezomib monotherapy group was not statistically significant (Fig. 2).

### Subgroup Analysis

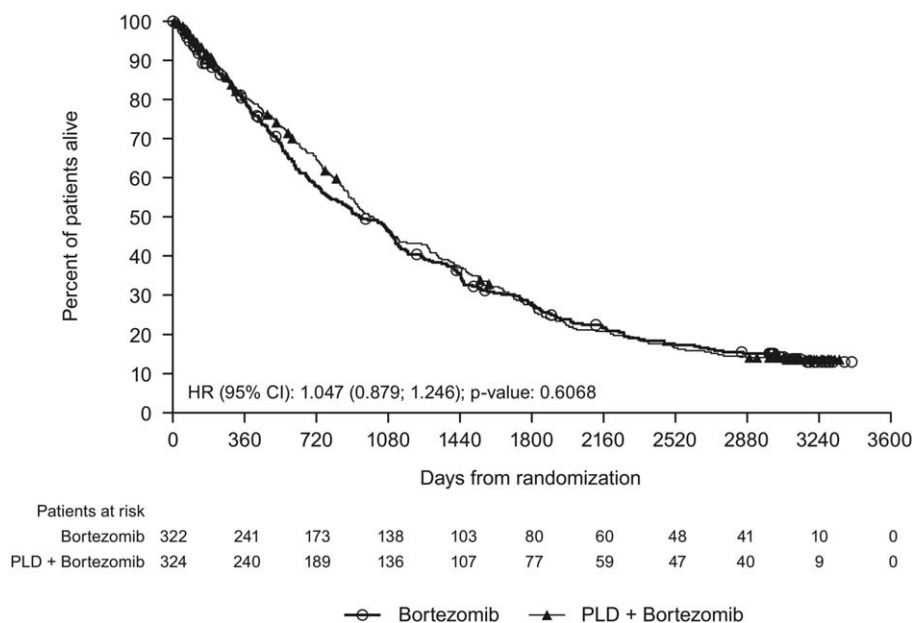
Subgroup analyses based on baseline variables were performed to evaluate their impact on the overall results. The results from the survival analysis by subgroup were generally consistent with the overall results except among those patients who had no response to initial treatments (Fig. 3).

### Subsequent Therapy

Patients in both groups received salvage therapies (78% in the bortezomib-PLD group vs 80% in the bortezomib monotherapy group), which were well balanced (Table 1). The most frequent salvage therapies (received by >10% patients in any group) in the bortezomib-PLD group versus the bortezomib monotherapy group included dexamethasone (47% vs 51%), thalidomide (31% vs 31%), cyclophosphamide (26% vs 31%), melphalan (24% vs 22%), lenalidomide (23% vs 21%), bortezomib (23% vs 18%), and doxorubicin (6% vs 11%). No tumor assessment data were collected after subsequent therapy.

## DISCUSSION

Results from this randomized, phase 3, final survival analysis report suggest a similar OS for the bortezomib-PLD combination therapy versus bortezomib monotherapy after a long-term median follow-up of 8.6 years. At the clinical cutoff of May 16, 2014, for the current analysis, a mortality rate of 79% was reported. This study represents the first long-term follow-up report of this combination regimen in patients with relapsed/refractory MM. The median OS for patients who received bortezomib-PLD patients was 33.0 months compared with 30.8 months for those who received bortezomib monotherapy.



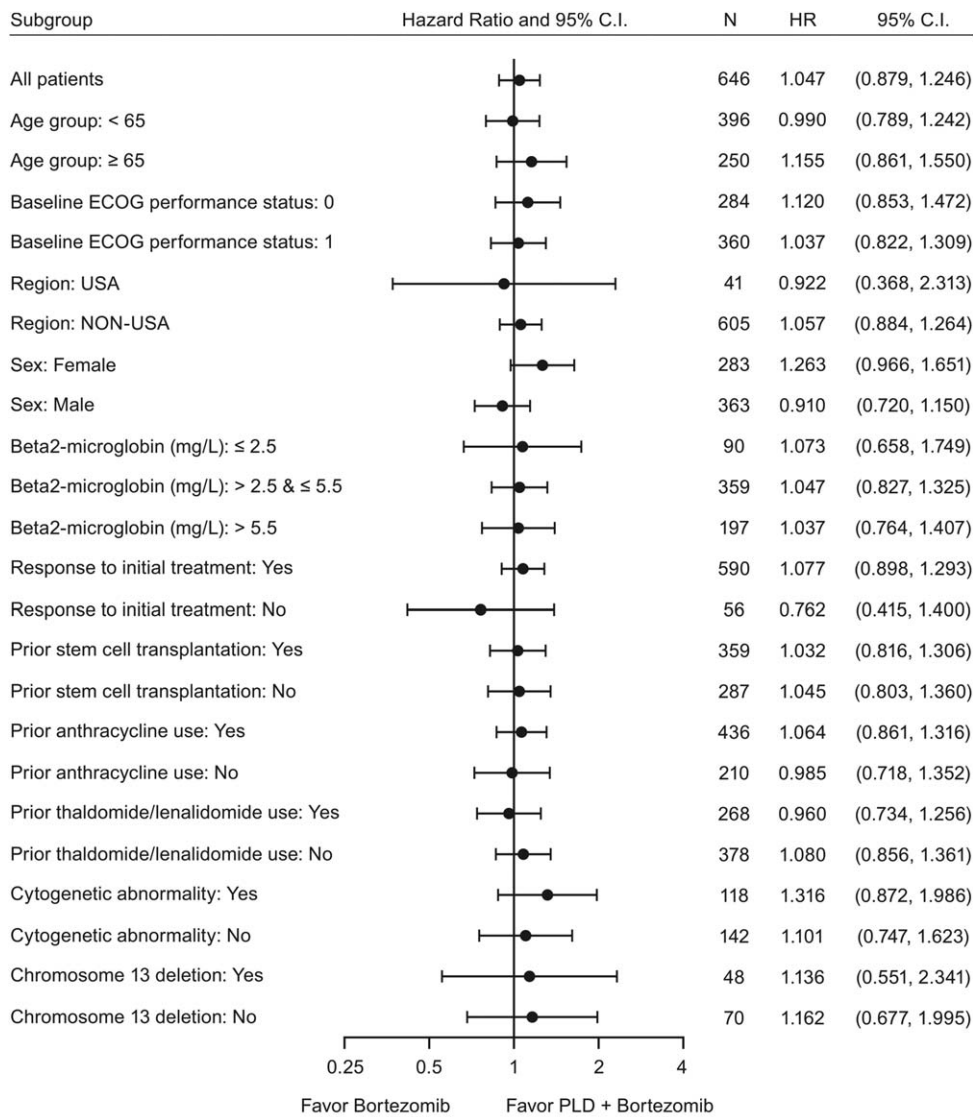
**Figure 2.** This Kaplan-Meier curve illustrates overall survival in the intent-to-treat analysis set. CI indicates confidence interval; HR, hazard ratio; PLD, pegylated liposomal doxorubicin.

On the basis of observations from *in vitro* studies of synergistic activity between bortezomib and anthracyclines<sup>9</sup> and phase 1 data,<sup>10</sup> a phase 3 study compared single-agent bortezomib with bortezomib plus PLD in patients with relapsed/refractory MM.<sup>8</sup> The results from the study demonstrated that bortezomib-PLD was superior to bortezomib monotherapy in treating patients with relapsed or refractory MM whose disease had failed 1 or more lines of prior therapy. Both the TTP and the overall response rate were in favor of the combination therapy compared with monotherapy.<sup>8</sup> Furthermore, an interim analysis also demonstrated a trend toward an OS benefit favoring bortezomib-PLD combination therapy.<sup>8</sup> A secondary analysis of that phase 3 study demonstrated that the therapeutic advantage of prolonged TTP attributed to the PLD-bortezomib combination, compared with bortezomib as a single agent, was maintained regardless of exposure to immunomodulatory drug therapy in prior lines of treatment.<sup>11</sup> Bortezomib-PLD was also active in patients whose disease was refractory to other antimyeloma agents<sup>11</sup> and was safe and effective in patients with renal compromise.<sup>12</sup>

However, despite the superiority in TTP and an early trend in OS favoring the combination therapy in the interim analysis, the long-term follow-up results revealed similar OS for bortezomib-PLD combination therapy and bortezomib monotherapy. Results from a subgroup analysis are generally consistent with the overall finding, while

patients who were aged  $\geq 65$  years, who had Eastern Cooperative Oncology Group performance status of 0, who had cytogenetic abnormalities, or who were women appeared to have outcomes in favor of the combination therapy.

The lack of any difference in the results from the final OS analysis could be because the majority of patients in this study received subsequent therapy. The advancements in treatment options for MM and the availability of new therapies, such as immunomodulators (eg, lenalidomide), other proteasome inhibitors, etc, have led to longer life expectancy for patients with MM. Indeed, the original design assumed that median survival in the bortezomib group would be only 20 months, which was exceeded by 50%, suggesting the benefits of novel agents. With an armamentarium of treatment options available, it would be unlikely to observe a difference in survival between the treatment groups in this study after prolonged follow-up. Several studies demonstrating a survival advantage in patients with myeloma have used the approach of continuing therapies until disease progression; whereas, in this study, the median number of treatment cycles received by patients was only 5 in both groups. Therefore, in retrospect, it is perhaps overly optimistic to expect that 5 cycles of PLD given over approximately 3.5 months would induce a sustained improvement in long-term OS. Results from this update underscore a general need for the long-term follow-up of phase 3 oncology trials and the practical challenge of having adequate power for long-



C.I. = confidence interval; HR = hazard ratio.

**Figure 3.** Overall survival analysis is illustrated by subgroup (intent-to-treat analysis set). ECOG indicates Eastern Cooperative Oncology Group; PLD, pegylated liposomal doxorubicin.

term survival as a primary endpoint if effective subsequent therapies are available.

Regardless of the significant improvement in patient’s overall outcomes with recent advances in treatment options, MM remains incurable in the majority of patients, prompting a continued search for additional therapeutic options, including multidrug-combinations. A prospective comparison of bortezomib-thalidomide-dexamethasone versus thalidomide-dexamethasone in patients who relapsed after high-dose therapy plus autologous stem cell transplantation demonstrated that the median TTP was significantly longer with bortezomib-thalidomide-

dexamethasone than with thalidomide-dexamethasone, with a trend in favor of a survival benefit.<sup>13</sup> This study demonstrated that a triplet bortezomib-based combination was superior to a 2-drug thalidomide-based regimen for patients with relapsed MM in terms of significantly greater response rate and longer TTP. Currently, other novel agents are being evaluated in combination with bortezomib in phase 3 trials with longer follow-up. Multiple other bortezomib-based combinations have also been studied in clinical trials, with steroids plus alkylators, immunomodulatory drugs, monoclonal antibodies, heat-shock protein-90, histone deacetylase inhibitors, pan-Bcl-2 family

**TABLE 1.** Subsequent Antimyeloma Therapy by Therapeutic Subgroup in >5% of Patients (Intent-to-Treat Analysis Set)

Variable	No. of Patients (%)		
	Bortezomib	Bortezomib + PLD	Total
No. of patients	322	324	646
Total no. patients who received subsequent therapy	256 (80)	252 (78)	508 (79)
Dexamethasone	164 (51)	153 (47)	317 (49)
Prednisone	50 (16)	57 (18)	107 (17)
Prednisolone	20 (6)	24 (7)	44 (7)
Cyclophosphamide	99 (31)	85 (26)	184 (29)
Melphalan	70 (22)	78 (24)	148 (23)
Bortezomib	58 (18)	74 (23)	132 (20)
Doxorubicin	34 (11)	18 (6)	52 (8)
Vincristine	31 (10)	19 (6)	50 (8)
Thalidomide	101 (31)	99 (31)	200 (31)
Lenalidomide	66 (21)	75 (23)	141 (22)
Radiotherapy	19 (6)	21 (7)	40 (6)

Abbreviation: PLD, pegylated liposomal doxorubicin.

inhibitors, and other classes of targeted inhibitors.<sup>14-16</sup> If promising results are confirmed with longer follow-up, then these combinations can bring about a shift in the treatment paradigm, maximizing their synergism while minimizing toxicities.

In summary, the current results demonstrate that, despite the superior TTP observed and the early trend in favor of OS with the combination therapy, long-term follow-up revealed that treatment with the bortezomib-PLD combination did not improve OS compared with bortezomib monotherapy in patients with relapsed or refractory MM. The inability to sustain the observed early survival advantage may have been caused by the effects of subsequent lines of therapy, and underscores the need for long-term follow-up of phase 3 trials while recognizing the challenge of having adequate power to detect differences in long-term OS.

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## CONFLICT OF INTEREST DISCLOSURES

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## AUTHOR CONTRIBUTIONS

**Robert Z. Orlowski, Trilok Parekh, Liang Xiu,** and **Andrew Cakana** were responsible for the design, conduct, and data analysis and interpretation for the study. **Trilok Parekh** was also responsible for the collection and assembly of data and additional administrative support. **Robert Z. Orlowski, Arnon Nagler, Pieter Sonneveld, Joan Bladé, Roman Hajek, Andrew Spencer, Jesús F. San-Miguel, Tadeusz Robak, Anna Dmoszynska, Noemi Horvath, Ivan Spicka, Heather J. Sutherland,** and **Alexander N. Suvorov** were responsible for the provision of study materials or patient enrollment. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors meet International Committee of Medical Journal Editors criteria, and all those who fulfilled those criteria are listed as authors. All authors provided direction and comments on the article, made the final decision about where to publish these data, and approved submission to the journal.

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