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ORIGINAL REPORT

# Randomized Phase III Study of Pegylated Liposomal Doxorubicin Plus Bortezomib Compared With Bortezomib Alone in Relapsed or Refractory Multiple Myeloma: Combination Therapy Improves Time to Progression

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## ABSTRACT

### Purpose
This phase III international study compared the efficacy and safety of a combination of pegylated liposomal doxorubicin (PLD) plus bortezomib with bortezomib monotherapy in patients with relapsed or refractory multiple myeloma.

### Patients and Methods
Six hundred forty-six patients were randomly assigned to receive either intravenous bortezomib 1.3 mg/m$^2$ on days 1, 4, 8, and 11 of an every 21-days cycle, or the same bortezomib regimen with PLD 30 mg/m$^2$ on day 4.

### Results
Median time to progression was increased from 6.5 months for bortezomib to 9.3 months with the PLD + bortezomib combination ($P$ = .000004; hazard ratio, 1.82 [monotherapy *v* combination therapy]; 95% CI, 1.41 to 2.35). The 15-month survival rate for PLD + bortezomib was 76% compared with 65% for bortezomib alone ($P$ = .03). The complete plus partial response rate was 41% for bortezomib and 44% for PLD + bortezomib, a difference that was not statistically significant. Median duration of response was increased from 7.0 to 10.2 months ($P$ = .0008) with PLD + bortezomib. Grade 3/4 adverse events were more frequent in the combination group (80% *v* 64%), with safety profiles consistent with the known toxicities of the two agents. An increased incidence in the combination group was seen of grade 3/4 neutropenia, thrombocytopenia, asthenia, fatigue, diarrhea, and hand-foot syndrome.

### Conclusion
PLD with bortezomib is superior to bortezomib monotherapy for the treatment of patients with relapsed or refractory multiple myeloma. The combination therapy is associated with a higher incidence of grade 3/4 myelosuppression, constitutional symptoms, and GI and dermatologic toxicities.

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## INTRODUCTION

Targeting the ubiquitin-proteasome pathway, which is responsible for most intracellular proteolysis, is a rational approach to cancer therapy. Preclinical studies showed that proteasome inhibitors were active against hematologic malignancies, including non-Hodgkin's lymphoma[1] and multiple myeloma (MM).[2,3] Bortezomib, the first clinically relevant proteasome inhibitor,[4,5] was recently compared with dexamethasone in patients with relapsed/refractory MM. Treatment with bortezomib resulted in a superior time to progression (TTP) of 6.22 versus 3.49 months and a superior overall survival (OS).[6] As a result, bortezomib is one standard of care for relapsed/refractory myeloma patients who have received one or more prior therapies.

Proteasome inhibition is also a rational approach to chemosensitization and overcoming chemoresistance. Several mechanisms by which malignant cells avoid the impact of chemotherapeutics are suppressed by proteasome inhibitors, including bcl-2, nuclear factor kappa B, and P-glycoprotein (reviewed in Voorhees et al[7] and Rajkumar et al[8]). In preclinical studies, bortezomib enhanced the activity of a number of antimyeloma agents, including doxorubicin,[9-11] and bortezomib suppressed repair pathways[12] that could sensitize cells to DNA



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damaging agents such as anthracyclines. Proteasome inhibitors themselves are pleiotropic, and activate prosurvival mechanisms that limit their effectiveness, including the heat shock response pathways.[13] Interestingly, doxorubicin and pegylated liposomal doxorubicin (PLD) suppressed bortezomib-mediated induction of some heat shock/stress response proteins, possibly explaining the synergy between these agents.[11,14]

On the basis of this preclinical rationale, PLD + bortezomib was evaluated in a phase I trial.[15] A schedule of bortezomib 1.3 mg/m$^2$ on days 1, 4, 8, and 11 every 21 days, with PLD 30 mg/m$^2$ on day 4, was safe and tolerable, and anti-MM activity was seen. A complete response (CR) rate of 36%, and an overall response rate of 73% was observed in a small cohort of myeloma patients, and longer-term follow-up demonstrated a 9.3-month TTP and a median OS of more than 3 years.[16]

To test the possibility that PLD + bortezomib prolongs TTP compared with bortezomib alone in patients with relapsed/refractory MM, a randomized controlled study was undertaken. The findings of a planned interim analysis (IA), reported herein, support the hypothesis that this combination regimen is superior to single-agent bortezomib.

## PATIENTS AND METHODS

### *Patients*

Patients with confirmed MM and measurable disease were eligible, and must have progressed after a response to one or more lines of therapy, or have been refractory to initial treatment. They had 0 to 1 Eastern Cooperative Oncology Group (ECOG) performance status, platelets at or higher than 75,000/mm$^3$, hemoglobin at or higher than 8.0 g/dL, absolute neutrophils at or higher than 1,000/mm$^3$, and creatinine clearance at or higher than 30 mL/min. Patients were bortezomib naïve, and were excluded if they had previous progression while receiving anthracycline-containing therapy. Additional exclusion criteria included prior doxorubicin exposure more than 240 mg/m$^2$, clinically significant cardiac disease, a left ventricular ejection fraction (LVEF) less than institutional normal limits, or grade 2 or higher peripheral neuropathy. Review boards at participating institutions approved the study, which was conducted according to the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice, and all patients provided written informed consent.

### *Study Design and Treatment*

This international randomized, controlled, open-label study enrolled 646 patients from 123 centers and randomly assigned them to bortezomib or PLD + bortezomib (Fig 1). Patients were stratified according to serum $\beta_2$-microglobulin levels ($\leq 2.5$, $> 2.5$ and $\leq 5.5$, or $>5.5$ mg/L) at screening, and

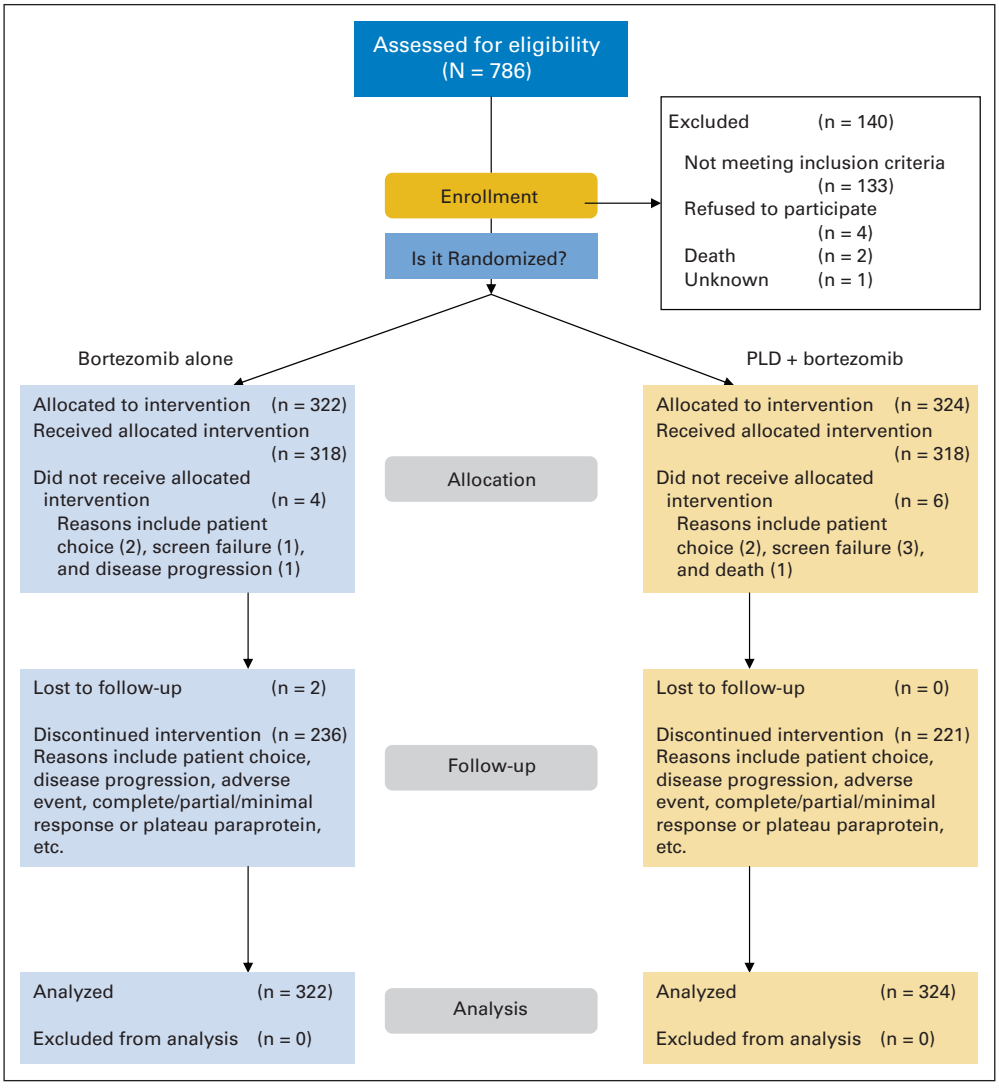


**Fig 1.** CONSORT diagram. PLD, pegylated liposomal doxorubicin.



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**Table 1.** Baseline Characteristics of Multiple Myeloma Patients According to Treatment Group

| Characteristic | Bortezomib (n = 322) | | PLD + Bortezomib (n = 324) | | Total (N = 646) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Age, years | | | | | | |
| Median | 62.0 | | 61.0 | | 61.0 | |
| Range | 34-88 | | 28-85 | | 28-88 | |
| Sex | | | | | | |
| Male | 174 | 54 | 189 | 58 | 363 | 56 |
| Female | 148 | 46 | 135 | 42 | 283 | 44 |
| Type of myeloma | | | | | | |
| No. of patients | 322 | | 324 | | 646 | |
| IgG | 200 | 62 | 184 | 57 | | 59 |
| IgA | 78 | 24 | 89 | 27 | | 26 |
| IgD | 2 | 1 | 4 | 1 | | 1 |
| IgM | 2 | 1 | 2 | 1 | | 1 |
| Light-chain | 37 | 11 | 40 | 12 | 77 | 12 |
| Nonsecretory | 0 | 0 | 1 | < 1 | 1 | < 1 |
| Unspecified | 3 | 1 | 4 | 1 | 7 | 1 |
| Time since initial diagnosis, months | | | | | | |
| Number of patients | 318 | | 321 | | 639 | |
| Mean | 46.0 | | 44.9 | | 45.5 | |
| SD | 36.01 | | 32.75 | | 34.39 | |
| Median | 37.5 | | 35.2 | | 36.7 | |
| Range | 3-244 | | 2-185 | | 2-244 | |
| Baseline ECOG status | | | | | | |
| No. of patients | 321 | | 323 | | 644 | |
| 0 | 145 | 45 | 139 | 43 | 284 | 44 |
| 1 | 176 | 55 | 184 | 57 | 360 | 56 |
| Serum $\beta_2$-microglobulin | | | | | | |
| No. of patients | 322 | | 324 | | 646 | |
| Category, mg/L | | | | | | |
| ≤ 2.5 | 45 | 14 | 45 | 14 | 90 | 14 |
| > 2.5 and ≤ 5.5 | 178 | 55 | 181 | 56 | 359 | 56 |
| > 5.5 | 99 | 31 | 98 | 30 | 197 | 30 |
| Response to prior treatment | | | | | | |
| No. of patients | 322 | | 324 | | 646 | |
| Responded to initial therapy, progressed | 295 | 92 | 295 | 91 | 590 | 91 |
| Progressed during initial treatment | 27 | 8 | 29 | 9 | 56 | 9 |
| Cytogenetic abnormality | | | | | | |
| No. of patients | 322 | | 324 | | 646 | |
| Not performed | 186 | 58 | 188 | 58 | 374 | 58 |
| Yes | 61 | 19 | 56 | 17 | 117 | 18 |
| No | 66 | 20 | 75 | 23 | 141 | 22 |
| Not assessable | 9 | 3 | 5 | 2 | 14 | 2 |
| Hemoglobin, g/L | | | | | | |
| No. of patients | 317 | | 318 | | 635 | |
| Mean | 111.3 | | 111.7 | | 111.5 | |
| SD | 17.60 | | 17.50 | | 17.54 | |
| Median | 111.0 | | 111.1 | | 111.0 | |
| Range | 76-160 | | 66-154 | | 66-160 | |
| Platelets count, giga/L | | | | | | |
| No. of patients | 317 | | 317 | | 634 | |
| Mean | 200.9 | | 202.1 | | 201.5 | |
| SD | 68.98 | | 78.33 | | 73.74 | |
| Median | 196.0 | | 202.0 | | 197.5 | |
| Range | 43-450 | | 56-550 | | 43-550 | |
| Serum creatinine, $\mu$mol/L | | | | | | |
| No. of patients | 321 | | 323 | | 644 | |
| Mean | 97.5 | | 98.7 | | 98.1 | |
| SD | 40.55 | | 34.39 | | 37.56 | |
| Median | 88.4 | | 91.0 | | 90.0 | |
| Range | 50-554 | | 25-327 | | 25-554 | |

(continued on following page)



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**Table 1.** Baseline Characteristics of Multiple Myeloma Patients According to Treatment Group (continued)

| Characteristic | Bortezomib (n = 322) | | PLD + Bortezomib (n = 324) | | Total (N = 646) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| No. of previous therapies | | | | | | |
| No. of patients | 322 | | 324 | | 646 | |
| 1 | 110 | 34 | 109 | 34 | 219 | 34 |
| ≥ 2 | 212 | 66 | 215 | 66 | 427 | 66 |
| Type of previous therapy | | | | | | |
| Corticosteroid | 321 | > 99 | 322 | 99 | 643 | > 99 |
| Alkylating agent | 291 | 90 | 299 | 92 | 590 | 91 |
| Anthracycline | 216 | 67 | 220 | 68 | 436 | 67 |
| Thalidomide/lenalidomide | 138 | 43 | 130 | 40 | 268 | 41 |
| Stem-cell transplantation | 173 | 54 | 186 | 57 | 359 | 56 |

Abbreviations: PLD, pegylated liposomal doxorubicin; Ig, immunoglobulin; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

response to prior treatment (response followed by progression, or primary refractory). All patients received bortezomib 1.3 mg/m$^2$ as an intravenous bolus on days 1, 4, 8, and 11 of every 21-days-cycle. Patients assigned to the combination arm received PLD 30 mg/m$^2$ as a 1-hour or longer intravenous infusion on day 4 of each cycle after bortezomib. Transfusion support and neutrophil and erythropoietic growth factors were allowed, and bisphosphonates were used according to established guidelines.[17] Study treatment continued until disease progression, unacceptable treatment-related toxicity, or for eight cycles, although patients who were still responding after eight cycles could continue, provided that treatment was tolerated. Patients in the combination group who discontinued PLD because of PLD-specific toxicity, such as hand-foot syndrome (HFS), could continue receiving bortezomib. The study did not provide for crossover to the combination arm from single-agent bortezomib.

The primary end point was TTP, defined as the interval from random assignment to disease progression, or death resulting from disease progression, and was performed on the intent-to-treat (ITT) population. Secondary end points included OS, defined as the interval from random assignment to death from any cause, progression-free survival (PFS), defined as time from random assignment to progression or death from any cause, overall response rate (CR + partial response [PR]), and safety profiles.

### Assessments

TTP and response rates were determined by a computer algorithm according to the stringent European Blood and Marrow Transplant Group criteria without reference to investigator TTP or response reports.[6,18] The sole exception was in the definition of near-CR (nCR), a PR subcategory meeting all CR criteria except for a positive immunofixation. All patients, including those who discontinued treatment, were followed for progression with assessments every 3 weeks for 42 weeks, and every 6 weeks thereafter.

Safety, assessed for all patients who received one or more drug doses until 30 days after the last dose, was graded according to the National Cancer Institute Common Toxicity Criteria (version 3). The original terms used in the case report forms to identify adverse events (AEs) were coded using the MedDRA (version 9.1) dictionary.

### Statistical Analysis

The study was designed to provide 80% power to detect a hazard ratio (HR) of 1.3 (monotherapy *v* combination) for TTP at a two-sided overall significance level of .05. Approximately 460 events were needed for the final analysis, and an IA was planned when approximately 230 events were observed. On the basis of the O'Brien-Fleming group sequential procedures, the IA nominal significance level was .003.[19] TTP distributions were estimated using the Kaplan-Meier method, and compared using the stratified log-rank test. A stratified Cox proportional-hazards model was used to estimate the HR and its 95% CI. Similar analyses were performed for OS and PFS. Response rates were compared with the Cochran-Mantel-Haenszel test, controlling for randomization strata. All secondary end points were tested at the two-sided nominal significance level of .05. The IA was performed after 249 events on the basis of a data cutoff of April 28, 2006, at which the median follow-up from random assignment was 7.2 months. The IA showed that patients undergoing treatment with PLD + bortezomib had a significant TTP prolongation, which crossed the prespecified IA boundary. As a result, the Independent Data Monitoring Committee recommended that these findings should be reported.

## RESULTS

### Patients and Treatment

From December 2004 to March 2006, 322 and 324 patients were randomly assigned to bortezomib and PLD + bortezomib, respectively. At the IA, 236 patients (73%) in the bortezomib group and 221 patients (68%) in the PLD + bortezomib group had discontinued treatment. Baseline demographic data and other characteristics were well balanced (Table 1), and the groups were similar in the number and type of prior therapies.

### Efficacy

For the ITT population, the median TTP was 6.5 months with bortezomib and 9.3 months with PLD + bortezomib. The risk of developing disease progression was reduced by 45% with PLD + bortezomib ($P$ = .000004; HR, 1.82; 95% CI, 1.41 to 2.35; Fig 2A). Median PFS for patients treated with bortezomib was 6.5 months, whereas on the PLD + bortezomib arm this was 9.0 months ($P$ = .000026; HR, 1.69; 95% CI, 1.32 to 2.16; Fig 2B). As of the cutoff date for the IA, there were 39 deaths (12%) in the bortezomib group and 28 (9%) in the PLD + bortezomib group ($P$ = .113; HR, 1.48; 95% CI, 0.91 to 2.41). Per US Food and Drug Administration request, an updated survival analysis was performed on the basis of a data cutoff of November 28, 2006. On the basis of death in 22% of the patients enrolled (25% in the bortezomib and 18% in the combination group), a survival advantage was observed for the PLD + bortezomib group ($P$ = .0476; HR, 1.41; 95% CI, 1.002 to 1.97; Fig 2C). The 15-month survival rate for PLD + bortezomib was 76% (95% CI, 70% to 83%) compared with 65% (95% CI, 58% to 73%) for bortezomib alone ($P$ = .03).

The overall response rate (CR + PR) in the ITT population was 41% with bortezomib and 44% with PLD + bortezomib ($P$ = .43;



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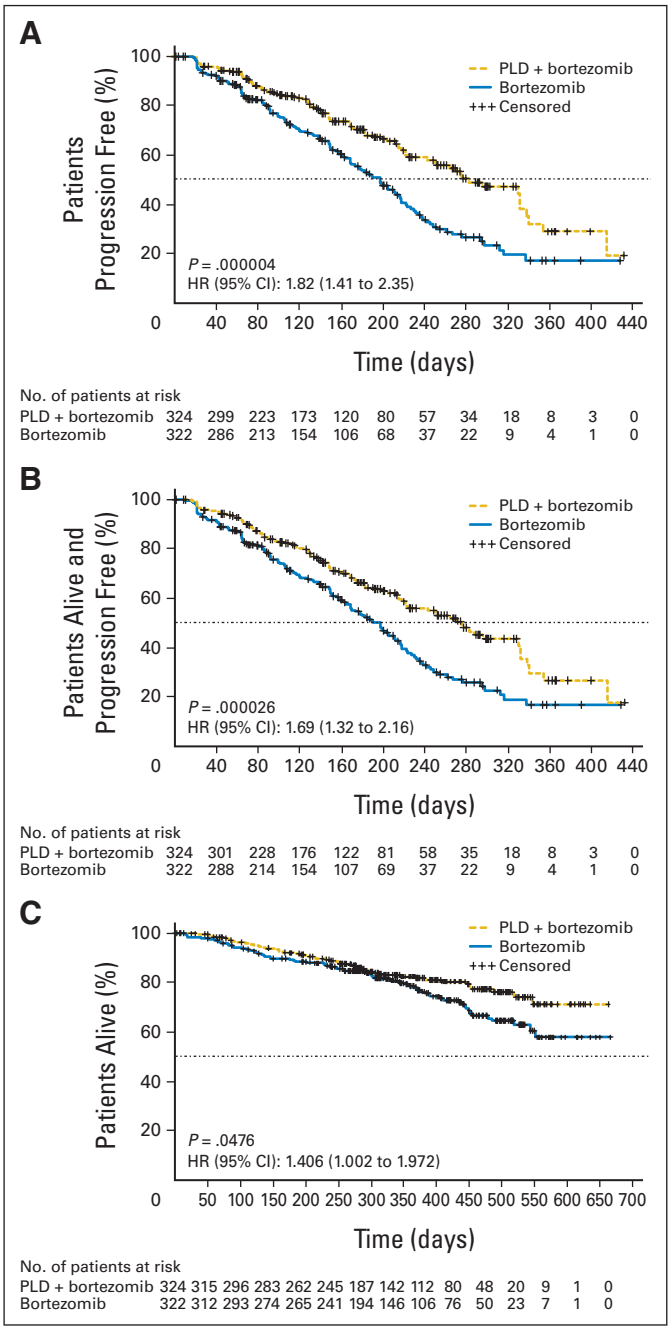


**Fig 2.** Kaplan-Meier plots are shown of (A) time to disease progression, (B) progression-free survival, and (C) overall survival in the pegylated liposomal doxorubicin (PLD) and bortezomib or bortezomib groups. HR, hazard ratio.

Table 2). The median duration of response (DOR) was 7.0 months for bortezomib and 10.2 months for PLD + bortezomib ($P = .0008$; Table 3). To further explore the differences in the depth of response in the two groups, we evaluated the very good partial response (VGPR) rate as defined by the new MM international uniform response criteria.[20] In the ITT population, the CR + VGPR rate was 19% for bortezomib and 27% for PLD + bortezomib ($P = .0157$).

### *Subgroup Analysis*

Subgroup analysis showed that the TTP HR in nearly all subpopulations favored PLD + bortezomib (Fig 3).

**Table 2.** Response Rate: CR or PR

| Response | Bortezomib (n = 322) No. | Bortezomib (n = 322) % | PLD + Bortezomib (n = 324) No. | PLD + Bortezomib (n = 324) % | P* |
|---|---|---|---|---|---|
| Total (CR + PR) | 133 | 41 | 144 | 44 | .43 |
| CR | 8 | 2 | 14 | 4 | |
| PR | 125 | 39 | 130 | 40 | |
| nCR | 25 | 8 | 28 | 9 | |
| CR + VGPR† | 63 | 19 | 90 | 27 | .0157 |

Abbreviations: CR, complete response; PR, partial response; PLD, pegylated liposomal doxorubicin; nCR, near CR; VGPR, very good partial response.
*Cochran-Mantel-Haenszel test controlling for $\beta_2$-microglobulin and response to initial treatment.
†VGPR as defined by the multiple myeloma international uniform response criteria.[20]

### *Drug Exposure, Patient Disposition, and Safety*

A total of 636 patients received at least one study drug dose and were included in the safety population, with 318 in each group. In both, a median of five cycles was administered, and median treatment duration was approximately 105 days. Mean and median cycle lengths were similar, and consistent with the protocol-planned 21 days. Monotherapy patients received a 24.4 mg/m$^2$ mean cumulative bortezomib dose compared with 23.2 mg/m$^2$ in the combination group. The median of the mean dose per patient of bortezomib per administration was approximately 1.28 mg/m$^2$/d for both groups. Similarly, the median of the mean PLD dose per patient was 29.83 mg/m$^2$/d, consistent with the protocol-specified initial dose.

Grade 3 or 4 AEs were more frequent in the combination group (64% *v* 80%; Table 4), with an increase in hematologic and GI events (Table 5). The most common AEs across both groups were nausea, diarrhea, constipation, fatigue, thrombocytopenia, and neutropenia (Table 5). The most common grade 3 AEs were neutropenia and thrombocytopenia. Grade 4 AEs were rare except for myelosuppression, with grade 3/4 neutropenia reported in 14% and 30% in the monotherapy and PLD + bortezomib groups, respectively (Table 5). The incidence of febrile neutropenia was low and similar for the two groups, whereas grade 3 and 4 thrombocytopenia was reported in 15% and 22%, respectively (Table 5). Grade 3 or higher

**Table 3.** Time to Response and Duration of Response for Patients With Complete or Partial Response

| Response Criteria | Bortezomib (n = 133) | PLD + Bortezomib n = 144 |
|---|---|---|
| Time to first response, days | | |
| Mean | 44.3 | 43.0 |
| SD | 25.89 | 24.04 |
| Median | 43.0 | 43.0 |
| Range | 15-197 | 21-156 |
| Duration of overall response, days | | |
| Median* | 213.0 | 311.0 |
| 95% CI | 180.0 to 254.0 | 309.0 to 394.0 |
| Log-rank *P* | .0008 | |

Abbreviations: PLD, pegylated liposomal doxorubicin; SD, standard deviation.
*Based on Kaplan-Meier product-limit estimates.



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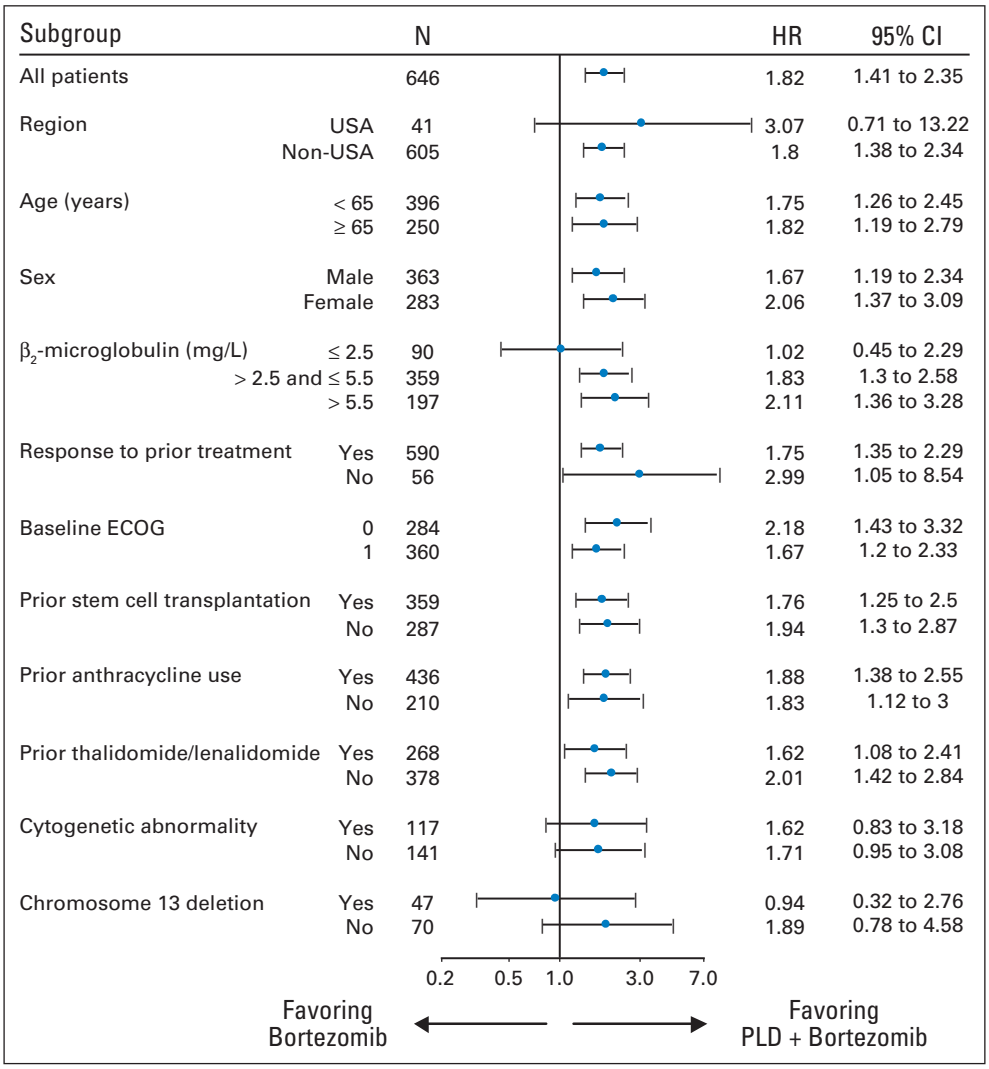


**Fig 3.** Hazard ratio (HR) estimates for time to disease progression (bortezomib *v* pegylated liposomal doxorubicin [PLD] + bortezomib) for all randomly assigned patients and various subgroups. ECOG, Eastern Cooperative Oncology Group.

bleeding events were reported in four (1%) and 13 (4%) patients, respectively (Table 6).

HFS occurred only in patients in the combination group (Table 5). The overall incidence was 16%, of which grade 3 was 5%, and led to PLD discontinuation in 5%, with no grade 4 events. Stomatitis was reported more frequently with PLD + bortezomib, with most events of grade 2 or lower severity.

The incidence and severity of neuropathy did not increase with the addition of PLD to bortezomib (Table 6). Three patients (1%) in both groups had deep vein thrombosis, pulmonary embolism, or both (Table 6).

The incidence of all cardiac AEs was similar between the groups (Table 6). Congestive heart failure (CHF) was observed in 3% in both (Table 7). A total of 52 patients, including 22 (7%) receiving bortezomib, and 30 (9%) receiving PLD + bortezomib, experienced an LVEF decrease, defined as a 15% or greater absolute decrease, or a decrease to less than institutional lower normal limit and an absolute decrease of 5% or greater. Among these, five patients (2%) receiving bortezomib and eight patients (3%) receiving PLD + bortezomib had an LVEF less than 45%. Among those, three (1%) in each group suffered CHF (Table 7). In the bortezomib group, all three had grade 2 ventricular dysfunction, whereas in the PLD + bortezomib group, two had ventricular dysfunction, grades 2 and 3, respectively, and one had grade 3 chronic heart failure (data not shown).

Deaths within 30 days after the last study medication occurred in 4% of patients in the monotherapy group and 3% in the combination group. Drug-related deaths, as determined by the investigator, were similar in the two groups, including three patients receiving monotherapy and four receiving the combination.

## DISCUSSION

This randomized, controlled study demonstrates that patients treated with PLD + bortezomib had a significantly prolonged TTP ($P = .000004$) and PFS ($P = .000026$), and a longer DOR ($P = .0008$), compared with bortezomib monotherapy. There was a 45% reduction in the risk of developing disease progression. Median TTP was improved from 6.5 months for bortezomib to 9.3 months for PLD + bortezomib. Importantly, this study's bortezomib monotherapy control arm reproduced the efficacy data seen in a prior pivotal trial studying a comparable population.[6] The improved efficacy of the



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**Table 4.** Overview of Treatment-Emergent AEs

| AE Characteristic | Bortezomib (n = 318) | | PLD + Bortezomib (n = 318) | | |
|---|---|---|---|---|---|
| | No. | % | No. | % | *P* |
| Any AEs | 307 | 97 | 312 | 98 | .326 |
| Drug-related AEs | 273 | 86 | 299 | 94 | < .001 |
| Serious AE | 98 | 31 | 115 | 36 | .179 |
| Drug-related serious AEs | 47 | 15 | 69 | 22 | .031 |
| Grade 3 or 4 AEs | 204 | 64 | 253 | 80 | < .001 |
| Drug-related grade 3 or 4 AEs | 165 | 52 | 217 | 68 | < .001 |
| AE leading to bortezomib discontinuation | 76 | 24 | 96 | 30 | .090 |
| AE leading to PLD discontinuation | 0 | 0 | 115 | 36 | NA |
| AE with outcome death | 11 | 3 | 13* | 4 | .8364 |
| Drug-related AE with outcome death | 5 | 2 | 5 | 2 | .99 |

NOTE. Incidence is based on the number of patients, not the number of events. AEs reported any time during treatment or within 30 days of end of treatment are included. Drug-related means possible, probable, or very likely.
Abbreviations: AE, adverse event; PLD, pegylated liposomal doxorubicin; NA, not applicable.
*This total includes one patient who was alive at the clinical cutoff date and who had an adverse event for weight loss that was erroneously reported to have a fatal outcome.

combination was consistent across a variety of clinically relevant subgroups, many of which were at high risk for disease progression (Fig 3). These included patients 65 years of age or older, an elevated $\beta_2$-microglobulin, and primary refractory disease. Patients treated with prior immunomodulatory drugs, anthracycline-based therapies, and stem-cell transplantation benefited from the combination. Also, patients with cytogenetic abnormalities benefited from PLD + bortezomib, with the exception of those with chromosome 13 deletions, suggesting that bortezomib was responsible for activity among this one subpopulation.

The OS data were not mature, and were not statistically significantly different between the two groups at the IA. Notably, an updated survival analysis demonstrated that there was a survival advantage for those receiving PLD + bortezomib ($P = .0476$). Follow-up survival data are being collected, and a final analysis will be conducted when 80% of patients have died.

Addition of PLD to bortezomib resulted in a modest improvement in the CR + PR rate in this phase III study, which was lower than that seen in phase I. It is possible that the response rate in the PLD + bortezomib group in this trial was adversely affected by clinical factors, such as the greater frequency of drug discontinuations. Patients receiving the combination were more likely to suffer an AE (30%) leading to discontinuation, compared with bortezomib alone (24%). These discontinuation rates were higher than in phase I. Also, the median number of PLD + bortezomib cycles delivered in phase I was higher[16] than in this study. Thus, the ability to deliver more cycles of

**Table 5.** Adverse Events During Treatment Reported by at Least 15% of Patients Receiving PLD and Bortezomib or Bortezomib, Including Grade 3 and Grade 4 Events

| Event | Bortezomib (n = 318) | | | | | | PLD + Bortezomib (n = 318) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Grade 3 | | Grade 4 | | Total | | Grade 3 | | Grade 4 | | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | *P* |
| Total patients with adverse event | 307 | 97 | | | | | 312 | 98 | | | | | |
| Nausea | 117 | 37 | 1 | < 1 | 0 | 0 | 146 | 46 | 7 | 2 | 0 | 0 | .0241 |
| Diarrhea | 109 | 34 | 14 | 4 | 0 | 0 | 136 | 43 | 22 | 7 | 0 | 0 | .034 |
| Constipation | 89 | 28 | 2 | 1 | 0 | 0 | 90 | 28 | 3 | 1 | 0 | 0 | 1.000 |
| Vomiting | 62 | 19 | 3 | 1 | 0 | 0 | 100 | 31 | 13 | 4 | 0 | 0 | < .001 |
| Thrombocytopenia | 81 | 25 | 25 | 8 | 24 | 8 | 95 | 30 | 34 | 11 | 37 | 12 | .249 |
| Anemia | 65 | 20 | 23 | 7 | 5 | 2 | 72 | 23 | 23 | 7 | 6 | 2 | .563 |
| Neutropenia | 64 | 20 | 34 | 11 | 12 | 4 | 110 | 35 | 65 | 20 | 29 | 9 | < .001 |
| Fatigue | 83 | 26 | 7 | 2 | 0 | 0 | 100 | 31 | 15 | 5 | 2 | 1 | .161 |
| Pyrexia | 69 | 22 | 4 | 1 | 0 | 0 | 93 | 29 | 4 | 1 | 0 | 0 | .0361 |
| Asthenia | 51 | 16 | 9 | 3 | 0 | 0 | 62 | 19 | 18 | 6 | 0 | 0 | .300 |
| Anorexia | 36 | 11 | 0 | | 0 | 0 | 57 | 18 | 5 | 2 | 0 | 0 | .024 |
| Neuralgia | 51 | 16 | 12 | 4 | 2 | 1 | 44 | 14 | 9 | 3 | 0 | 0 | .505 |
| Headache | 50 | 16 | 0 | 0 | 0 | 0 | 58 | 18 | 2 | 1 | 1 | < 1 | .460 |
| Cough | 36 | 11 | 0 | 0 | 0 | 0 | 52 | 16 | 0 | 0 | 0 | 0 | .085 |
| Stomatitis | 10 | 3 | 1 | < 1 | 0 | 0 | 58 | 18 | 7 | 2 | 0 | 0 | < .001 |
| Hand-foot syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 50 | 16 | 15 | 5 | 0 | 0 | < .001 |

Abbreviation: PLD, pegylated liposomal doxorubicin.



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**Table 6.** Selected Adverse Events of Clinical Interest in Patients Receiving PLD and Bortezomib or Bortezomib

| | % | | | |
|---|---|---|---|---|
| | Bortezomib (n = 318) | | PLD + Bortezomib (n = 318) | |
| Adverse Event | Total | Grade 3/4 | Total | Grade 3/4 |
| Peripheral neuropathy* | 39 | 9 | 35 | 4 |
| Febrile neutropenia | 2 | 2 | 3 | 3 |
| Bleeding/hemorrhage | 9 | 1 | 14 | 4 |
| Thromboembolic events | 1 | 1 | 1 | 1 |
| Cardiac events | 7 | 3 | 10 | 2 |
| Alopecia | 1 | NA† | 2 | NA† |

Abbreviations: PLD, pegylated liposomal doxorubicin; NA, not applicable.
*Includes dictionary-derived terms: neuropathy, peripheral neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy.
†Alopecia is reported as grade 1 (partial) or grade 2 (complete).

therapy, and of the complete regimen, may have led to the higher response rate in phase I, although it is of note that the TTP was identical between the two studies.

Although PLD + bortezomib increased only the overall response rate slightly over bortezomib alone, this translated into a dramatic TTP improvement. One explanation may be that the responses with PLD + bortezomib were more durable, and is supported by the improved median DOR. This suggests that the benefits of PLD may be in enhancing the sensitivity of patients with bortezomib-responsive disease, possibly by improving the depth of a PR or CR. VGPR analysis confirmed the latter possibility; the CR + VGPR rate was 19% for bortezomib, and 27% for PLD + bortezomib ($P = .0157$). These data support the hypothesis that PLD enhances the clinical benefits of bortezomib by improving the depth of a PR or CR.

The median numbers of cycles delivered was the same for bortezomib monotherapy and PLD + bortezomib, mean cumulative bortezomib doses were similar, and the addition of PLD did not increase treatment-emergent neuropathy, a dose-limiting bortezomib toxicity. These findings indicate that PLD did not compromise the ability to deliver bortezomib therapy. Importantly, in a population among whom almost 70% had received prior anthracyclines, addition of PLD did not increase cardiac toxicity. CHF was reported in 3% of both groups, which was not significantly higher than the 2% seen in a similar population treated with high-dose dexamethasone.[16]

There was, however, an increase in grade 3 or 4 AEs in the combination group, mostly caused by an increase in myelosuppression, including neutropenia and thrombocytopenia, and GI events, including diarrhea and nausea. These events were predictable, often manageable by dose modifications and supportive therapy, and did not increase febrile neutropenia. As expected, HFS was reported only in the combination group, its incidence was low, and most episodes were of grade 1 to 2 severity.

Relapsed or refractory MM is an incurable disease for which, until recently, there were few treatment options. For more than 30 years, high-dose dexamethasone was one such standard, but bortezomib was recently found to be clinically superior.[6] In the current study, addition of PLD provided a further 45% reduction in the risk of developing progression, prolonged TTP by 3 months, and an early benefit in OS was seen. Although anthracyclines have been widely used for many years in combination regimens for MM, their benefit has never been proven, leading some to question their utility.[21] The current study conclusively demonstrates that a pegylated liposomal anthracycline can play a key role in improving the efficacy of combination therapy in the relapsed/refractory setting. Studies evaluating the efficacy of PLD in the up-front setting are also underway, and will further define the optimal use of anthracyclines in MM.

Bortezomib is being studied in combination with a variety of agents, including inhibitors of heat shock protein 90, protein kinase B, and interleukin-6. Clinical data have already suggested that addition of dexamethasone to bortezomib improves the response rate and quality in the up-front[22] and relapsed/refractory[23] settings. In the latter study, dexamethasone addition did not alter the type or number of AEs, possibly suggesting that bortezomib + dexamethasone could be a better-tolerated regimen than that with PLD. However, larger randomized studies would be needed to test that hypothesis in the relapsed/refractory population, and to provide measures of response durability, which are currently lacking. Moreover, it is likely that an

**Table 7.** Symptomatic Cardiac Adverse Events

| | Bortezomib (n = 318) | | | | PLD + Bortezomib (n = 318) | | | | Total (N = 636) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Related* | | Total | | Related* | | Total | | Related* | |
| Cardiac Adverse Event | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Total patients with adverse event | 17 | 5 | | | 23 | 7 | | | 40 | 6 | | |
| Congestive heart failure† | 10 | 3 | 3 | 1 | 9 | 3 | 5 | 2 | 19 | 3 | 8 | 1 |
| Symptomatic arrhythmia‡ | 4 | 1 | 2 | 1 | 9 | 3 | 5 | 2 | 13 | 2 | 7 | 1 |
| Coronary ischemia disease§ | 4 | 1 | 0 | 0 | 3 | 1 | 2 | 1 | 7 | 1 | 2 | < 1 |
| Other‖ | 3 | 1 | 2 | 1 | 7 | 2 | 6 | 2 | 10 | 2 | 8 | 1 |

NOTE. Symptomatic cardiac adverse event is defined as cardiac event ≥ grade 2.
Abbreviation: PLD, pegylated liposomal doxorubicin.
*Rated by the investigator as at least possibly related to treatment.
†Includes the following MedRA-derived terms: ventricular dysfunction, cardiac failure, right ventricular failure, congestive cardiac failure, chronic cardiac failure, acute pulmonary edema, and pulmonary edema.
‡Includes the following MedRA-derived terms: arrhythmia, nodal arrhythmia, palpitation, bradycardia, tachycardia, tachyarrhythmia, sinus bradycardia, sinus tachycardia, atrioventricular block, supraventricular tachycardia, atrial fibrillation, atrial flutter, left bundle branch block, QRS axis abnormal, extrasystoles
§Includes the following MedRA-derived terms: angina pectoris, myocardial ischemia, and myocardial infraction.
‖Others include cardiac adverse events other than congestive heart failure, symptomatic arrhythmia, and coronary ischemia disease: cardiomegaly, pericardial effusion, cardio-respiratory arrest, troponin increase, ejection fraction decrease, restrictive cardiomyopathy, cardiac arrest.



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even more efficacious approach would be to add dexamethasone to PLD + bortezomib. We did not pursue this approach here because our goal was to evaluate the benefits of adding PLD only, but preliminary studies have suggested this regimen is well-tolerated, and active.[24]

Another class of agents with significant anti-MM activity are the immunomodulatory drugs thalidomide and lenalidomide, which are often prescribed with high-dose dexamethasone.[25,26] Lenalidomide + dexamethasone in particular have shown a superior response rate, TTP, and OS to dexamethasone alone, but use of these regimens was complicated by steroid-mediated toxicities, and by thromboembolic events that led to recommendations for prophylactic anticoagulation. Among patients in the PLD + bortezomib group, the rate of thromboembolic events was low in the absence of prophylactic anticoagulation. Thus, this regimen may be especially helpful in steroid-intolerant patients, or in those who have a high risk for thromboembolism and/or anticoagulation. Additional studies will be necessary to identify patient subgroups that benefit most from one of these options. In this regard, plasma cells were purified from patients on this study, and gene expression profiles are being evaluated to determine whether there is a profile predictive of response. Another option may be to use PLD + bortezomib as a scaffold onto which other agents can be added to further enhance activity, and studies are ongoing to test the impact of adding dexamethasone, lenalidomide, melphalan, or thalidomide.

In conclusion, this study demonstrates that PLD + bortezomib is superior to bortezomib for the treatment of MM patients who have received at least one prior therapy. PLD and bortezomib represent an additional new standard of care for this patient population.

## 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.*

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## *Appendix*

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



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