ORIGINAL ARTICLE

Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma

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ABSTRACT

BACKGROUND

The standard treatment for patients with multiple myeloma who are not candidates for high-dose therapy is melphalan and prednisone. This phase 3 study compared the use of melphalan and prednisone with or without bortezomib in previously untreated patients with multiple myeloma who were ineligible for high-dose therapy.

METHODS

We randomly assigned 682 patients to receive nine 6-week cycles of melphalan (at a dose of 9 mg per square meter of body-surface area) and prednisone (at a dose of 60 mg per square meter) on days 1 to 4, either alone or with bortezomib (at a dose of 1.3 mg per square meter) on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9. The primary end point was the time to disease progression.

RESULTS

The time to progression among patients receiving bortezomib plus melphalan–prednisone (bortezomib group) was 24.0 months, as compared with 16.6 months among those receiving melphalan–prednisone alone (control group) (hazard ratio for the bortezomib group, 0.48; P<0.001). The proportions of patients with a partial response or better were 71% in the bortezomib group and 35% in the control group; complete-response rates were 30% and 4%, respectively (P<0.001). The median duration of the response was 19.9 months in the bortezomib group and 13.1 months in the control group. The hazard ratio for overall survival was 0.61 for the bortezomib group (P=0.008). Adverse events were consistent with established profiles of toxic events associated with bortezomib and melphalan–prednisone. Grade 3 events occurred in a higher proportion of patients in the bortezomib group than in the control group (53% vs. 44%, P=0.02), but there were no significant differences in grade 4 events (28% and 27%, respectively) or treatment-related deaths (1% and 2%).

CONCLUSIONS

Bortezomib plus melphalan–prednisone was superior to melphalan–prednisone alone in patients with newly diagnosed myeloma who were ineligible for high-dose therapy. (ClinicalTrials.gov number, NCT00111319.)

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Therapy with melphalan plus prednisone, which has been the standard of care for patients with newly diagnosed multiple myeloma for more than 40 years,[1,2] is associated with a median survival of 29 to 37 months.[3-6] During the past decade, high-dose therapy with hematopoietic stem-cell transplantation has become the preferred treatment for patients under the age of 65 years,[7-9] but older patients and patients with clinically significant coexisting illnesses usually do not tolerate this treatment. Since the median age at diagnosis of myeloma is approximately 70 years,[10] more than half the patients with newly diagnosed myeloma may not be eligible for high-dose therapy. For these patients, improved treatment is needed. The proteasome inhibitor bortezomib is active in relapsed or refractory myeloma.[11] On the basis of results of a phase 3 trial,[12,13] bortezomib was approved for the treatment of myeloma in patients who had received at least one previous therapy.

In preclinical studies, bortezomib sensitized melphalan-sensitive and melphalan-resistant myeloma cell lines to melphalan and down-regulated cellular responses to genotoxic stress.[14,15] In combined phase 1 and 2 trials, bortezomib plus melphalan had encouraging activity in patients with relapsed or refractory myeloma.[16] These findings led to a combined phase 1 and 2 trial of bortezomib–melphalan and prednisone in patients with newly diagnosed multiple myeloma who were 65 years of age or older.[17,18] The complete-response rate of 32%, the median time to progression of 27 months, and the estimated 38-month survival rate of 85% were improvements over the results in historical control subjects who received only melphalan–prednisone.[17,18] Our phase 3 trial compared bortezomib plus melphalan–prednisone with melphalan–prednisone alone in patients with newly diagnosed myeloma who were ineligible for high-dose therapy.

METHODS

PATIENTS

Patients with newly diagnosed, untreated, symptomatic, measurable myeloma who were not candidates for high-dose therapy plus stem-cell transplantation because of age (≥65 years) or coexisting conditions were eligible. Measurable disease was defined as the presence of quantifiable M protein in serum or urine or measurable soft-tissue or organ plasmacytomas. Review boards at all participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice. All patients provided written informed consent.

STUDY DESIGN AND TREATMENT

This randomized (1:1), open-label, phase 3 study was conducted at 151 centers in 22 countries in Europe, North and South America, and Asia. Patients were recruited from December 2004 to September 2006. They received nine 6-week cycles of melphalan (at a dose of 9 mg per square meter of body-surface area) and prednisone (at a dose of 60 mg per square meter) on days 1 to 4, alone or in combination with bortezomib (at a dose of 1.3 mg per square meter), by intravenous bolus on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9. The planned 54-week treatment corresponded to the standard duration of melphalan–prednisone therapy. Randomization was stratified according to baseline levels of β_2-microglobulin (<2.5, 2.5 to 5.5, or >5.5 mg per liter [<212, 212 to 466, or >466 nmol per liter]), serum albumin (<3.5 or ≥3.5 g per deciliter), and region (North America, Europe, or other region). Treatment was discontinued on withdrawal of the patient's consent, disease progression, or the occurrence of unacceptable toxic effects. The dose of melphalan or bortezomib was reduced if there was any prespecified hematologic toxic effect or grade 3 or 4 nonhematologic toxic effect; bortezomib-associated neuropathic pain and peripheral sensory neuropathy were managed with the use of established dose-modification guidelines.[19] Patients with myeloma-associated bone disease received bisphosphonates, unless such therapy was contraindicated.[20]

The primary end point was the time to disease progression. Prespecified secondary end points included the rate of complete response, the duration of response, the time to subsequent myeloma therapy, and overall survival. (Additional prespecified secondary end points are described in the Supplementary Appendix, available with the full text of this article at www.nejm.org.) The trial was designed by the senior academic authors, in collaboration with Johnson & Johnson Pharmaceutical Research & Development and

Millennium Pharmaceuticals. Data were collected by the sponsors and analyzed in collaboration with the senior academic authors, who vouch for the completeness and accuracy of the data and the analyses. The first draft of the manuscript was developed by the senior academic investigators with editorial assistance from representatives of Johnson & Johnson Pharmaceutical Research & Development. Additional writing assistance was provided by both sponsors.

ASSESSMENTS

We assessed the response to treatment using criteria of the European Group for Blood and Marrow Transplantation (EBMT)[21] and a prespecified computer algorithm that was validated in a previous trial.[13] In a post hoc analysis, we assessed the response by applying an algorithm to implement the International Uniform Response Criteria for Multiple Myeloma.[22] Disease progression was determined by EBMT criteria. These criteria included relapse from complete response, which was defined as the reappearance of M protein on immunofixation. Investigators assessed progression on the basis of analyses of M protein in serum and urine that were performed by a central laboratory and other factors described below. Investigators provided the sponsors with documentation supporting the diagnosis of progressive disease, which was reviewed in real time for consistency with EBMT criteria.[21] The sponsors also determined progression with the use of a computer algorithm that applied EBMT criteria. Data presented here include assessments performed both by the investigators and by algorithmic analysis.

Blood and 24-hour urine samples were collected every 3 weeks during the 54-week treatment phase and then every 8 weeks until disease progression. Other efficacy assessments included bone marrow examination and skeletal survey as required by EBMT criteria[21] or in cases in which such assessment was clinically required or indicated on the basis of measurement of extramedullary plasmacytomas or analysis of corrected serum calcium levels.

Patients were followed for survival and subsequent myeloma therapy at least every 12 weeks after disease progression. Safety was evaluated throughout the study and until 30 days after the administration of the last dose of a study drug. Adverse events were graded with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. Serious adverse events were monitored monthly by the independent data and safety monitoring committee.

STATISTICAL ANALYSIS

We analyzed the time to progression, the time to subsequent myeloma therapy, and overall survival from randomization and compared the differences between groups using stratified log-rank tests in the intention-to-treat population (all randomized patients). Distributions were estimated with use of the Kaplan–Meier method. For time-to-progression analyses, data from patients in whom there was no disease progression were censored at the last assessment or at the start of subsequent therapy. Hazard ratios were estimated with the use of the stratified Cox proportional-hazards model for the intention-to-treat population, as well as within subgroups that were defined according to baseline characteristics in order to assess the consistency of treatment effects (seven prespecified analyses according to age, sex, race, baseline β_2-microglobulin level, baseline albumin level, region, and disease stage and one post hoc analysis according to creatinine clearance).

Response rates were analyzed in the population of patients who could be evaluated for a response and were compared between groups on the basis of a stratified Cochran–Mantel–Haenszel chi-square test. The efficacy of bortezomib plus melphalan–prednisone was assessed post hoc within subgroups that were defined as having a poor prognosis on the basis of age (≥75 years), an impaired creatinine clearance (<60 ml per minute), or a high-risk cytogenetic profile — the presence of a t(4;14),t(14;16) translocation or a 17p deletion — on the basis of fluorescence in situ hybridization performed at local study sites. Safety was analyzed in all patients who underwent randomization and received at least one dose of a study drug.

Treatment differences were tested at a two-sided alpha level of 0.05. We determined that a sample size of 340 patients per group would provide a power of 80% to detect a 33% improvement in the time to progression in patients receiving bortezomib plus melphalan–prednisone, as compared with those receiving melphalan–prednisone alone. We planned three interim analyses using the O'Brien–Fleming method.[23] On the basis of the third analysis (with a data cutoff of June 15, 2007), the data and safety

monitoring committee recommended that the study be stopped, since the prespecified statistical boundary (an alpha level of 0.0108) for the primary end point of time to progression had been crossed (hazard ratio in the bortezomib group, 0.54; P<0.001). Data from the third analysis are presented.

RESULTS

PATIENTS AND TREATMENT

From a total of 682 patients who were enrolled, we randomly assigned 344 patients to receive bortezomib plus melphalan–prednisone (bortezomib group) and 338 to receive only melphalan–prednisone (control group) (Fig. 1 in the Supplementary Appendix). Baseline demographic and disease characteristics were well balanced between the two groups (Table 1). Among the study patients, 30% were 75 years of age or older, 33% had a β_2-microglobulin level of more than 5.5 mg per liter (>466 nmol per liter), and 10% reported having grade 1 peripheral sensory neuropathy before treatment. At the data cutoff point, 47 patients (14%) in the bortezomib group and 33 patients (10%) in the control group were still receiving the assigned protocol therapy.

EFFICACY

The median time to progression on the basis of data from the central laboratory, as assessed by the investigators, was 24.0 months in the bortezomib group and 16.6 months in the control group (hazard ratio in the bortezomib group, 0.48; P<0.001) (Fig. 1A). The time-to-progression benefit in the bortezomib group was independent of age, sex, race, baseline β_2-microglobulin level, baseline albumin level, geographic region, clinical stage (on the basis of the International Staging System[24]), or creatinine clearance (Fig. 2).

The response could be evaluated in 337 patients in the bortezomib group and 331 in the control group. The rates of partial response or better (according to EBMT criteria) were 71% in the bortezomib group as compared with 35% in the control group (P<0.001), and the complete-response rates were 30% and 4%, respectively (P<0.001) (Table 2). In the post hoc analysis of response according to the International Uniform Response Criteria, the rates of complete response were 33% and 4% in the bortezomib group and the control group, respectively (Table 2). Of the 79 patients in the bortezomib group who were considered to have stable disease on the basis of the International Uniform Response Criteria, 4 had negative results on immunofixation, and 19 had a reduction in the M protein level in serum or urine of 50% or more. However, these patients were not recorded as having had a complete or partial response, since they did not fulfill some aspects of the International Uniform Response Criteria, mainly because the confirmatory test results were missing. An additional 38 patients had a reduction in M protein of 25 to 49% or met the requirements for a minimal response, according to EBMT criteria for nonsecretory disease.

The median duration of a response (according to EBMT criteria) was 19.9 months in the bortezomib group and 13.1 months in the control group; the median duration of response among patients who had a complete response was 24.0 months in the bortezomib group and 12.8 months in the control group. The median time to subsequent therapy and the associated treatment-free interval were significantly longer in the bortezomib group than in the control group, with 35% and 57% of patients, respectively, starting second-line treatment within 2 years (Table 2, and Fig. 2B in the Supplementary Appendix). Of 121 patients in the control group who received subsequent therapy, 54 (45%) received therapy that included bortezomib.

After a median follow-up of 16.3 months, 45 patients (13%) in the bortezomib group and 76 patients (22%) in the control group had died (hazard ratio in the bortezomib group, 0.61, P=0.008); median survival was not reached in either group (Fig. 1B).

We also assessed the efficacy of bortezomib therapy in three subgroups of patients who had a poor prognosis. In 107 patients who were 75 years of age or older, as compared with 237 younger patients, the median time to progression was identical, the rate of complete response (according to EBMT criteria) was slightly lower (26% vs. 32%, P=0.29), and median overall survival was slightly shorter (P=0.17). The 185 patients with impaired renal function (creatinine clearance, <60 ml per minute) did not differ significantly from the 159 patients with normal renal function (creatinine clearance, ≥60 ml per minute) with respect to the complete-response rate (28% and 32%, respectively), the time to progression (P=0.09),

or the overall rate of survival (P=0.99). The 26 patients with high-risk cytogenetic profiles — including the presence of a t(4;14),t(14;16) translocation or a 17p deletion — and the 142 patients with standard cytogenetic profiles had the same rate of complete response (28%), with similar times to progression (P=0.55) and overall survival (P=0.99). The results remained similar with the inclusion of 75 patients with a 13q deletion in the high-risk group (data not shown). Time-to-progression and survival curves for these subgroups are shown in Figure 3 in the Supplementary Appendix.

ADVERSE EVENTS

The median number of treatment cycles administered was 8 (46 weeks) in the bortezomib group and 7 (39 weeks) in the control group. The median dose intensities for melphalan and prednisone were the same in the two groups (99% or more of those expected). The bortezomib group and the control group did not differ significantly with respect to rates of death during treatment (5% and 4%, respectively) or treatment-related death (1% and 2%).

Table 3 lists the most common adverse events

Table 1. Baseline Characteristics of the Patients.*

Variable	Bortezomib Group (N=344)	Control Group (N=338)
Age		
Median — yr	71	71
Range — yr	57–90	48–91
Subgroup — no. (%)		
<65 yr	14 (4)	9 (3)
≥75 yr	107 (31)	101 (30)
Male sex — no. (%)	175 (51)	166 (49)
Race — no. (%)†		
White	304 (88)	295 (87)
Asian	33 (10)	36 (11)
Black	5 (1)	7 (2)
Other	2 (1)	0
Region — %‡		
Europe	79	78
North America	9	9
Other	11	13
Karnofsky performance status ≤70 — no. (%)	122 (35)	111 (33)
Type of myeloma — %		
IgG	64	62
IgA	24	26
IgD	1	1
IgM	1	1
Light chain	8	8
Biclonal	2	2
Lytic bone lesions — no./total no. (%)	224/343 (65)	222/336 (66)
Median plasma cells on bone marrow biopsy — %	40	41
International Staging System stage — %		
I	19	19
II	47	47
III	35	34

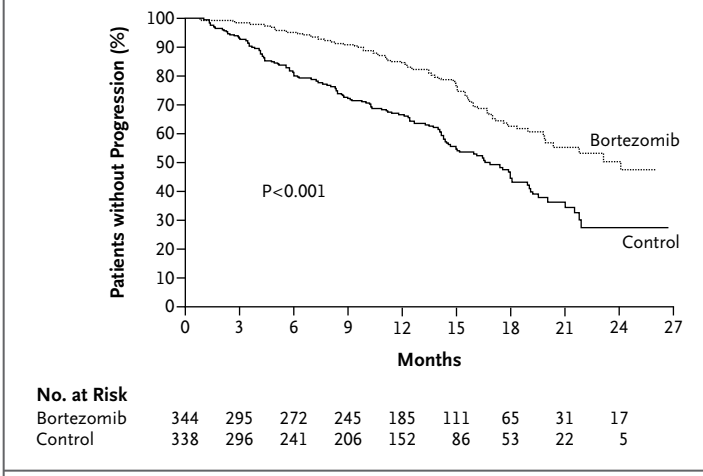
Table 1. (Continued.)

Variable	Bortezomib Group (N=344)	Control Group (N=338)
Serum β_2-microglobulin level		
Median — mg/liter	4.2	4.3
Range — mg/liter	1.7–21.6	0.6–60.9
Subgroup — %‡		
<2.5 mg/liter	12	12
2.5–5.5 mg/liter	55	55
>5.5 mg/liter	33	33
Albumin level		
Median — g/dl	3.3	3.3
Range — g/dl	1.3–4.7	1.4–5.0
Subgroup — %‡		
<3.5 g/dl	58	62
≥3.5 g/dl	42	38
Hemoglobin — g/liter		
Median	104.00	106.00
Range	64.0–159.0	73.0–165.0
Platelet count/mm^3		
Median	221,500	221,500
Range	68,000–515,000	33,000–587,000
Creatinine clearance (calculated) — %		
<30 ml/min	6	5
30–60 ml/min	48	50
>60 ml/min	46	46
History of cardiac condition — no. (%)	121 (35)	105 (31)

* Percentages may not total 100 because of rounding. To convert the values for serum β_2-microglobulin to nanomoles per liter, multiply by 84.75.
† Race was self-reported.
‡ Patients were stratified on the basis of this subgroup at randomization.

overall and grade 3 or 4 events; also listed are adverse events that had specific clinical relevance. Hematologic toxic effects were similar in the two groups. Peripheral sensory neuropathy was reported more frequently in the bortezomib group, including grade 1 neuropathy in 49 patients (14%), grade 2 in 58 patients (17%), grade 3 in 43 patients (13%), and grade 4 in 1 patient (<1%). At the time of data cutoff, 74% of peripheral-neuropathy events had either resolved (56%) or decreased by at least one toxicity grade (18%) within a median of 2 months. All grade 3 or 4 gastrointestinal symptoms were more frequent in the bortezomib group than in the control group (19% vs. 5%), as was any grade of herpes zoster (13% vs. 4%); the incidence of herpes zoster was reduced to 3% in patients in the bortezomib group who were receiving antiviral prophylaxis. Incidences of grade 3 or 4 pneumonia and deep-vein thrombosis were low and similar in the two groups (Table 3).

The rate of serious adverse events in the bortezomib group was higher than that in the control group (46% vs. 36%). Fifty patients (15%) in the bortezomib group and 47 patients (14%) in the control group discontinued treatment because of adverse events, including 37 patients (11%) and 35 patients (10%), respectively, who had treatment-related events. Bortezomib alone was discontinued in an additional 63 patients (19%).



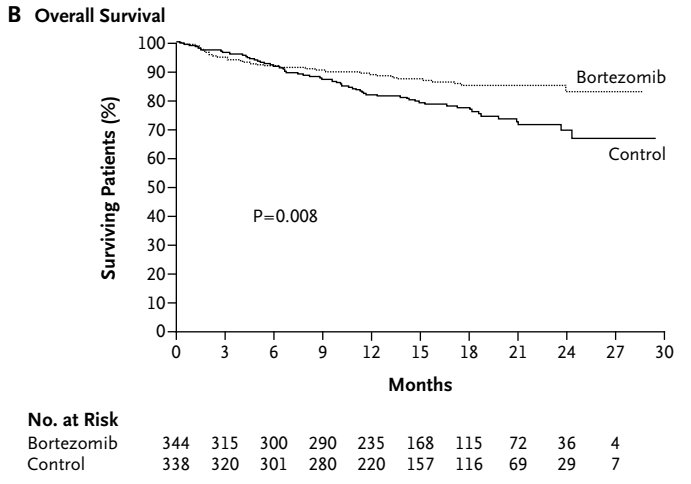


Figure 1. Kaplan–Meier Curves for the Time to Disease Progression and Overall Survival (Intention-to-Treat Population).

Panel A shows the time to disease progression on the basis of assessment by the investigators; the median time to progression was 24.0 months in the bortezomib group and 16.6 months in the control group (hazard ratio in the bortezomib group, 0.48). According to algorithmic analysis, the median time to progression was 20.7 months in the bortezomib group and 15.0 months in the control group (hazard ratio in the bortezomib group, 0.54; P<0.001). Panel B shows overall survival after a median follow-up of 16.3 months. Median survival was not reached in either group. During that time, 45 patients (13%) in the bortezomib group and 76 patients (22%) in the control group died (hazard ratio in the bortezomib group, 0.61).

DISCUSSION

This phase 3 study showed that the addition of bortezomib to melphalan–prednisone was associated with significant improvement in outcomes in patients with newly diagnosed myeloma who were ineligible for high-dose therapy. The median time to progression (the primary end point) was 7.4 months longer in the bortezomib group than in the control group (hazard ratio, 0.48; P<0.001). This benefit was seen across all subgroups of patients, as defined according to baseline demographic and disease characteristics.

There were significant improvements associated with bortezomib therapy for all prespecified secondary end points, including the rate of complete response (according to EBMT criteria), the time to subsequent myeloma therapy, and overall survival. The response was more rapid and durable in the bortezomib group than in the control group. In the bortezomib group, the median time to a complete response was longer than the median time to the first response (Table 2), suggesting that prolonged treatment might improve the quality of the response, as was reported for patients with relapsed myeloma who were receiving bortezomib alone.[12] The complete-response rate of 30% (according to EBMT criteria) that was associated with bortezomib was substantial in phase 3 trials involving patients with myeloma who were 65 years of age or older.[25-27] Among patients in the bortezomib group who had a complete response, the median duration of the response was 24 months. In the bortezomib group, the longer time to subsequent therapy was associated with a prolonged treatment-free interval, which may represent an added value for patients. At a median follow-up of 16.3 months, 45 patients in the bortezomib group and 76 in the control group had died (hazard ratio in the bortezomib group, 0.61; P=0.008), indicating a survival benefit associated with bortezomib, despite the finding that 45% of patients in the control group received subsequent therapy that included bortezomib after disease progression.

Superior efficacy in the treatment of myeloma has now been shown with bortezomib or thalidomide[25-27] in combination with melphalan and prednisone. Therefore, melphalan and prednisone alone can no longer be considered the standard of care in patients who are 65 years of age or older. Data from a combined phase 1 and 2 trial have also suggested that lenalidomide plus melphalan–prednisone has clear antimyeloma activity.[28] It would not be appropriate to compare the results of our trial with phase 3 studies of thalidomide because of confounding differences in study populations (e.g., age), the duration of therapy, the use of maintenance therapy, and especially the methodology and criteria used for defini-

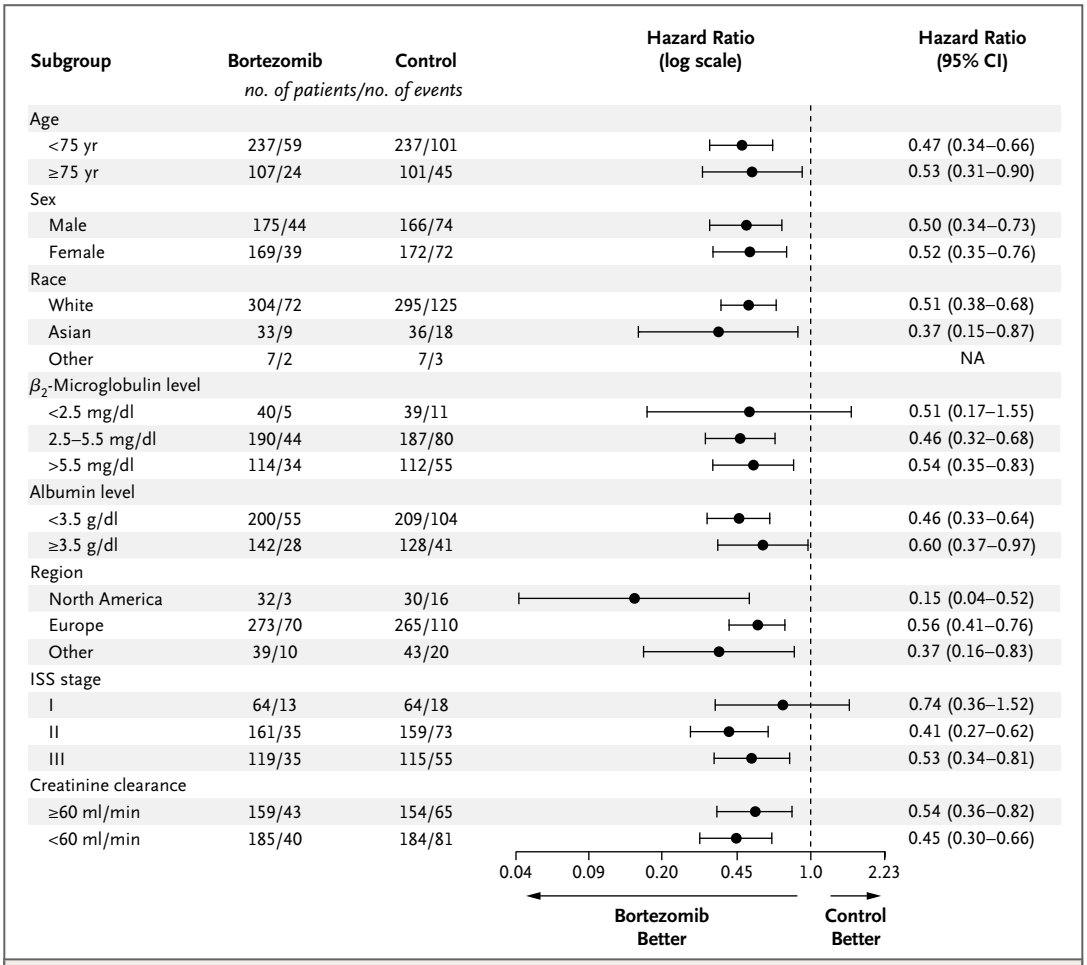


Figure 2. Subgroup Analyses of Time to Disease Progression as Assessed by the Investigators.

The prespecified and post hoc analyses of the time to disease progression among subgroups of patients, as defined according to baseline demographic and disease characteristics, showed hazard ratios that were lower than 1 (indicating a lower risk of progression) in the bortezomib group, as compared with the control group, for each subgroup. The I bars represent 95% confidence intervals. ISS denotes International Staging System. To convert the values for serum β_2-microglobulin to nanomoles per liter, multiply by 84.75.

tions of response and progression.[29,30] Our study included assessment every 3 weeks, measurement of the time to events starting at randomization, and the use of EBMT criteria. The effect of methodologic differences is apparent within the bortezomib group: the median time to progression as assessed by investigators (24.0 months) was 3 months longer than that as assessed by algorithmic analysis and was not reached at 27 months in a post hoc analysis on the basis of a previously described modification of the International Uniform Response Criteria.[25]

The adverse events reported in the bortezomib group were consistent with established toxicity profiles for both bortezomib[11,13,31] and melphalan–prednisone.[4,6] The rate of death during treatment was low in both groups, as compared with historical data on early mortality among elderly patients.[32,33] The rate of peripheral sensory neuropathy in the bortezomib group was consistent with the rate reported in previous studies, taking into account the duration of therapy and the cumulative dose of bortezomib.[17,34] After only 16.3 months of follow-up, peripheral neuropathy improved or resolved in most patients, confirming that prompt modification of the bortezomib dose according to established guidelines[19] is important to avoid severe neurotoxicity and ensure revers-

Table 2. Best Response to Treatment and Time-to-Event Data.*

Response and Time to Event	Bortezomib Group (N=337)	Control Group (N=331)	P Value†
Best response			
EBMT criteria — no. (%)			
Complete or partial response	238 (71)	115 (35)	<0.001
Complete response	102 (30)	12 (4)	<0.001
Partial response	136 (40)	103 (31)	ND
Minimal response	32 (9)	72 (22)	ND
Stable disease	60 (18)	133 (40)	ND
Progressive disease	3 (1)	7 (2)	ND
International Uniform Response Criteria — no (%)‡			
Complete, very good partial, or partial response	251 (74)	128 (39)	<0.001
Complete response	111 (33)	13 (4)	<0.001
Very good partial response	28 (8)	13 (4)	ND
Partial response	112 (33)	102 (31)	ND
Stable disease	79 (23)	192 (58)	ND
Progressive disease	3 (1)	7 (2)	ND
Time to event			
Median time to response — mo§			
First response	1.4	4.2	<0.001
Complete response	4.2	5.3	<0.001
Median duration of response — mo§			
Complete or partial response	19.9	13.1	ND
Complete response	24.0	12.8	ND
Time to subsequent myeloma therapy — mo¶	Not reached	20.8	<0.001
Treatment-free interval — mo¶	Not reached	9.4	ND

* A total of 14 patients, 7 in each study group, could not be evaluated for a response: 5 did not receive a study drug, and 9 had no measurable disease at baseline on the basis of an assessment by a central laboratory, even though these patients met the eligibility criterion of measurable disease according to evaluation by a local laboratory. Among the patients who could be evaluated, responses were not determined for 4 patients in the bortezomib group and 4 in the control group. Percentages may not total 100 because of rounding. EBMT denotes European Group for Blood and Marrow Transplantation, and ND not determined.

† P values were calculated by stratified Cochran–Mantel–Haenszel chi-square tests for comparisons of response rates and by stratified log-rank tests for comparisons of time-to-event data. P values for comparisons of time to response are based on the total study population.

‡ Of the 79 patients in the bortezomib group who were considered to have stable disease on the basis of International Uniform Response Criteria and who could be evaluated, 4 patients (1%) had negative results on immunofixation (complete response) and 19 (6%) had a reduction of at least 50% in the M protein level (partial response); these patients were not recorded as having a complete or partial response, primarily because the confirmatory test results were missing. With the inclusion of these patients, the response rate would be 81% and the complete-response rate would be 34%. Patients could not be assessed for the category of stringent complete response because immunohistochemical, immunofluorescence, and free light-chain assays were not performed. The response definitions are the same as for the EBMT criteria, except the International Uniform Response Criteria do not require that the changes in M protein be confirmed a minimum of 6 weeks after the initial assessment.

§ Data were determined by computer algorithm, applying EBMT criteria.

¶ Data were based on 344 patients in the bortezomib group and 338 in the control group.

Table 3. Adverse Events (Safety Population).*

Events	Bortezomib Group (N=340)			Control Group (N=337)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)					
Any event	338 (99)	181 (53)	96 (28)	326 (97)	148 (44)	92 (27)
Hematologic events†						
Thrombocytopenia	178 (52)	68 (20)	58 (17)	159 (47)	55 (16)	47 (14)
Neutropenia	165 (49)	102 (30)	34 (10)	155 (46)	79 (23)	49 (15)
Anemia	147 (43)	53 (16)	9 (3)	187 (55)	66 (20)	26 (8)
Leukopenia	113 (33)	67 (20)	10 (3)	100 (30)	55 (16)	13 (4)
Lymphopenia	83 (24)	49 (14)	18 (5)	58 (17)	30 (9)	7 (2)
Gastrointestinal events						
Nausea	164 (48)	14 (4)	0	94 (28)	1 (<1)	0
Diarrhea	157 (46)	23 (7)	2 (1)	58 (17)	2 (1)	0
Constipation	125 (37)	2 (1)	0	54 (16)	0	0
Vomiting	112 (33)	14 (4)	0	55 (16)	2 (1)	0
Infections						
Pneumonia	56 (16)	16 (5)	6 (2)	36 (11)	13 (4)	4 (1)
Herpes zoster	45 (13)	11 (3)	0	14 (4)	6 (2)	0
Nervous system disorders						
Peripheral sensory neuropathy	151 (44)	43 (13)	1 (<1)	16 (5)	0	0
Neuralgia	121 (36)	28 (8)	2 (1)	5 (1)	1 (<1)	0
Dizziness	56 (16)	7 (2)	0	37 (11)	1 (<1)	0
Other conditions						
Pyrexia	99 (29)	8 (2)	2 (1)	64 (19)	6 (2)	2 (1)
Fatigue	98 (29)	23 (7)	2 (1)	86 (26)	7 (2)	0
Anorexia	77 (23)	9 (3)	1 (<1)	34 (10)	4 (1)	0
Asthenia	73 (21)	20 (6)	1 (<1)	60 (18)	9 (3)	0
Cough	71 (21)	0	0	45 (13)	2 (1)	0
Insomnia	69 (20)	1 (<1)	0	43 (13)	0	0
Peripheral edema	68 (20)	2 (1)	0	34 (10)	0	0
Rash	66 (19)	2 (1)	0	24 (7)	1 (<1)	0
Back pain	58 (17)	9 (3)	1 (<1)	62 (18)	11 (3)	1 (<1)
Dyspnea	50 (15)	11 (3)	2 (1)	44 (13)	5 (1)	3 (1)
Hypokalemia	44 (13)	19 (6)	3 (1)	25 (7)	8 (2)	2 (1)
Arthralgia	36 (11)	4 (1)	0	50 (15)	2 (1)	1 (<1)
Deep-vein thrombosis	4 (1)	3 (1)	0	6 (2)	2 (1)	0

* Listed adverse events were reported in at least 15% of patients, and grade 3 or 4 events were reported in at least 5% of patients. Other adverse events of particular clinical relevance are also listed. Patients could have more than one adverse event. Included are all patients who received at least one dose of a study drug.

† Rates of red-cell transfusions were 26% in the bortezomib group and 35% in the control group; rates of use of erythropoiesis-stimulating agents for treatment-related anemia were 30% and 39%, respectively.

ibility. Hematologic toxic effects were similar in the two groups, and the incidence of deep-vein thrombosis was very low in both groups, even though the protocol did not require prophylaxis.

In conclusion, this study showed that bortezomib plus melphalan–prednisone was superior to melphalan–prednisone alone for the treatment of patients with newly diagnosed myeloma who were ineligible for high-dose therapy, although bortezomib was associated with a slightly higher rate of adverse events. Our findings suggest that bortezomib plus melphalan–prednisone is a valuable front-line treatment for patients with myeloma who are 65 years of age or older and cannot receive more aggressive treatment.[35]

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