ORIGINAL ARTICLE

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

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ABSTRACT

BACKGROUND

Lenalidomide plus dexamethasone is a reference treatment for relapsed multiple myeloma. The combination of the proteasome inhibitor carfilzomib with lenalidomide and dexamethasone has shown efficacy in a phase 1 and 2 study in relapsed multiple myeloma.

METHODS

We randomly assigned 792 patients with relapsed multiple myeloma to carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group). The primary end point was progression-free survival.

RESULTS

Progression-free survival was significantly improved with carfilzomib (median, 26.3 months, vs. 17.6 months in the control group; hazard ratio for progression or death, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P=0.0001). The median overall survival was not reached in either group at the interim analysis. The Kaplan–Meier 24-month overall survival rates were 73.3% and 65.0% in the carfilzomib and control groups, respectively (hazard ratio for death, 0.79; 95% CI, 0.63 to 0.99; P=0.04). The rates of overall response (partial response or better) were 87.1% and 66.7% in the carfilzomib and control groups, respectively (P<0.001; 31.8% and 9.3% of patients in the respective groups had a complete response or better; 14.1% and 4.3% had a stringent complete response). Adverse events of grade 3 or higher were reported in 83.7% and 80.7% of patients in the carfilzomib and control groups, respectively; 15.3% and 17.7% of patients discontinued treatment owing to adverse events. Patients in the carfilzomib group reported superior health-related quality of life.

CONCLUSIONS

In patients with relapsed multiple myeloma, the addition of carfilzomib to lenalidomide and dexamethasone resulted in significantly improved progression-free survival at the interim analysis and had a favorable risk–benefit profile. (Funded by Onyx Pharmaceuticals; ClinicalTrials.gov number, NCT01080391.)

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Survival rates have improved for patients with multiple myeloma, yet relapse remains common,[1] indicating an ongoing need for new therapeutic approaches. The immunomodulatory agent lenalidomide in combination with high-dose dexamethasone is approved for use in relapsed multiple myeloma on the basis of phase 3 trials showing superiority to dexamethasone alone, with a median progression-free survival of 11.1 months and an overall response rate of 60%.[2-4] In previously untreated patients, lower weekly doses of dexamethasone proved less toxic and more effective than high-dose dexamethasone.[5] Indeed, in a recent phase 3 study, lenalidomide with weekly dexamethasone, administered until disease progression, was associated with significantly improved progression-free survival in patients with newly diagnosed multiple myeloma.[6] The combination of lenalidomide and weekly dexamethasone is therefore considered a reference regimen for both newly diagnosed and relapsed multiple myeloma.

Carfilzomib is an epoxyketone proteasome inhibitor that binds selectively and irreversibly to the constitutive proteasome and immunoproteasome. In phase 1 studies, a maximum tolerated dose was not established for carfilzomib monotherapy. However, on the basis of the overall observed side-effect profile, an initial dose of 20 mg per square meter of body-surface area with subsequent escalation to 27 mg per square meter was selected for further study.[7,8] This regimen of carfilzomib monotherapy was subsequently approved in the United States for use in patients with relapsed and refractory multiple myeloma on the basis of a phase 2 study that showed a 23.7% overall response rate in this population.[7] In a phase 1 and 2 study, carfilzomib, lenalidomide, and weekly dexamethasone showed activity in patients with relapsed disease; adverse events were consistent with the known toxicity profiles of the three agents.[9,10] In the randomized, open-label, multicenter, phase 3 study described here, we evaluated the safety and efficacy of carfilzomib with lenalidomide and weekly dexamethasone as compared with lenalidomide and weekly dexamethasone alone in patients with relapsed multiple myeloma.

Methods

Patients

Adults with relapsed multiple myeloma and measurable disease who had received one to three prior treatments were eligible. Patients previously treated with bortezomib were eligible provided that they did not have disease progression during treatment. Patients previously treated with lenalidomide and dexamethasone were eligible so long as they did not discontinue therapy because of adverse effects, have disease progression during the first 3 months of treatment, or have progression at any time during treatment if lenalidomide plus dexamethasone was their most recent treatment. All patients had adequate hepatic, hematologic, and renal function (creatinine clearance, ≥50 ml per minute) at screening. Patients were excluded if they had grade 3 or 4 peripheral neuropathy (or grade 2 with pain) within 14 days before randomization or New York Heart Association class III or IV heart failure.

The study protocol, which is available with the full text of this article at NEJM.org, was approved by the institutional review boards of all participating institutions. All patients provided written informed consent.

Study Design

Patients were randomly assigned, in a 1:1 ratio, to receive carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group) in 28-day cycles until withdrawal of consent, disease progression, or the occurrence of unacceptable toxic effects. Randomization was stratified according to the β_2-microglobulin level (<2.5 mg per liter vs. ≥2.5 mg per liter), previous therapy with bortezomib (no vs. yes), and previous therapy with lenalidomide (no vs. yes). Carfilzomib was administered as a 10-minute infusion on days 1, 2, 8, 9, 15, and 16 (starting dose, 20 mg per square meter on days 1 and 2 of cycle 1; target dose, 27 mg per square meter thereafter) during cycles 1 through 12 and on days 1, 2, 15, and 16 during cycles 13 through 18, after which carfilzomib was discontinued. Lenalidomide (25 mg) was given on days 1 through 21. Dexamethasone (40 mg) was administered on days 1, 8, 15, and 22. Pretreatment and post-treatment intravenous hydration (250 to 500 ml) was required during cycle 1. Pretreatment hydration could be continued in subsequent cycles at the investigator's discretion. Patients in both groups received only lenalidomide and dexamethasone beyond cycle 18 until disease progression. Patients also received antiviral and antithrombotic prophylaxis.

The primary end point was progression-free

survival in the intention-to-treat population. Secondary end points included overall survival, the rate of overall response (partial response or better), duration of response, health-related quality of life, and safety. The rate of clinical benefit (minimal response or better) was an exploratory end point.

The trial was designed by the first, second, next-to-last, and last authors and the sponsor, Onyx Pharmaceuticals. Data were collected and analyzed by the sponsor; all the authors had access to the data. The first author prepared an initial draft of the manuscript in collaboration with the sponsor and a medical writer paid by the sponsor. All authors contributed to subsequent drafts, made the decision to submit the manuscript for publication, and vouch for the accuracy and integrity of the data and analyses and for the fidelity of the study to the protocol.

ASSESSMENTS

Treatment responses and disease progression were assessed centrally in a blinded manner by an independent review committee. Disease assessments were made with the use of the International Myeloma Working Group Uniform Response Criteria,[11] with minimal response defined according to European Society for Blood and Marrow Transplantation criteria.[12,13]

Disease assessments were performed on day 1 of each cycle. After treatment discontinuation, patients were followed for disease status (if they did not already have disease progression during treatment) and survival every 3 months for up to 1 year and for survival every 6 months thereafter. Health-related quality of life was assessed with the use of the European Organization for Research and Treatment of Cancer Quality of Life Core Module (QLQ-C30) questionnaire.[14]

Data on adverse events were collected until 30 days after administration of the last dose of study treatment, and events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. An independent data and safety monitoring committee periodically reviewed unblinded safety data.

STATISTICAL ANALYSIS

The primary end point was evaluated with the use of a group sequential design with one planned interim analysis. In total, 526 events (disease progression or death) were required to provide 90% power to detect a 25% reduction in the risk of disease progression or death (hazard ratio of 0.75) at a one-sided significance level of 0.025. An interim analysis was to be performed after approximately 420 events had occurred (80% of the planned total). An O'Brien–Fleming stopping boundary for efficacy was calculated with the use of a Lan–DeMets alpha-spending function on the basis of the number of events observed at the data-cutoff date.[15,16] All reported P values are two-sided.

If there was a significant between-group difference in progression-free survival at the interim analysis, secondary end points were to be sequentially tested in the order of overall survival, overall response rate, and health-related quality of life, each at a one-sided significance level of 0.025. Efficacy evaluations were based on the intention-to-treat population (all randomly assigned patients). The safety analysis included all patients who received at least one dose of study treatment.

Progression-free survival and overall survival were compared between treatment groups with the use of a log-rank test stratified according to the factors used for randomization. Hazard ratios were estimated by means of a stratified Cox proportional-hazards model. Distributions were summarized with the use of the Kaplan–Meier method.

The overall response rate was compared between groups with the use of a stratified Cochran–Mantel–Haenszel chi-square test. The odds ratio and corresponding 95% confidence interval were estimated with the use of the Mantel–Haenszel method. Duration of response was summarized by means of the Kaplan–Meier method. Scores for health-related quality of life were compared between groups with the use of a repeated-measures mixed-effects model. All analyses were predefined in the statistical analysis plan.

RESULTS

PATIENTS AND TREATMENT

Between July 2010 and March 2012, a total of 792 patients in North America, Europe, and the Middle East underwent randomization (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Baseline characteristics were well balanced between treatment groups (Table 1, and Table S1 in the Supplementary Appendix).

EFFICACY

The cutoff date for the interim analysis was June 16, 2014. A total of 118 patients in the carfilzo-

Table 1. Baseline Characteristics of the Intention-to-Treat Population.*

Characteristic	Carfilzomib Group (N=396)	Control Group (N=396)	Total (N=792)
Age			
Median — yr	64.0	65.0	64.0
Range — yr	38.0–87.0	31.0–91.0	31.0–91.0
Distribution — no. of patients (%)			
18–64 yr	211 (53.3)	188 (47.5)	399 (50.4)
≥65 yr	185 (46.7)	208 (52.5)	393 (49.6)
ECOG performance status — no. of patients (%)†			
0 or 1	356 (89.9)	361 (91.2)	717 (90.5)
2	40 (10.1)	35 (8.8)	75 (9.5)
Cytogenetic risk at study entry — no. of patients (%)‡			
High risk	48 (12.1)	52 (13.1)	100 (12.6)
Standard risk	147 (37.1)	170 (42.9)	317 (40.0)
Unknown	201 (50.8)	174 (43.9)	375 (47.3)
Creatinine clearance§			
Mean — ml/min	85.0±28.9	85.9±30.2	85.4±29.6
Distribution — no. of patients (%)			
30 to <50 ml/min	25 (6.3)	31 (7.8)	56 (7.1)
≥50 ml/min	370 (93.4)	358 (90.4)	728 (91.9)
Unknown or other value	1 (0.3)	7 (1.8)	8 (1.0)
Serum β_2-microglobulin — no. of patients (%)			
<2.5 mg/liter	77 (19.4)	77 (19.4)	154 (19.4)
≥2.5 mg/liter	319 (80.6)	319 (80.6)	638 (80.6)
Previous regimens¶			
Median — no.	2.0	2.0	2.0
Range — no.	1–3	1–3	1–3
Distribution — no. of patients (%)			
1 regimen	184 (46.5)	157 (39.6)	341 (43.1)
2 or 3 regimens	211 (53.3)	238 (60.1)	449 (56.7)
Previous therapies — no. of patients (%)			
Bortezomib	261 (65.9)	260 (65.7)	521 (65.8)
Lenalidomide	79 (19.9)	78 (19.7)	157 (19.8)

* Plus–minus values are means ±SD.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.
‡ The high-risk group consisted of patients with the genetic subtype t(4;14) or t(14;16) or with deletion 17p in 60% or more of plasma cells, according to central review of bone marrow samples obtained at study entry. The standard-risk group consisted of patients without t(4;14) or t(14;16) and with deletion 17p in less than 60% of plasma cells. The cutoff value of 60% for the proportion of plasma cells with deletion 17p was used on the basis of recommendations from the International Myeloma Workshop Consensus Panel 2.[17]
§ Per eligibility criteria, patients were required to have a creatinine clearance of at least 50 ml per minute at screening. One patient in the control group had a creatine clearance of less than 30 ml per minute at baseline.
¶ One patient (0.3%) in each group received four previous regimens.

mib group (29.8%) and 86 patients in the control group (21.7%) were still receiving study treatment.

At the time of the prespecified interim analysis, 431 progression-free survival events had been documented. The study met its primary objective of showing that carfilzomib improves progression-free survival when administered with lenalidomide and dexamethasone. The median progression-free survival was 26.3 months (95% confidence interval [CI], 23.3 to 30.5) in the carfilzomib group as compared with 17.6 months (95% CI, 15.0 to 20.6) in the control group (hazard ratio

for progression or death, 0.69; 95% CI, 0.57 to 0.83; P=0.0001, which crossed the prespecified stopping boundary) (Fig. 1A). The benefit with respect to progression-free survival in the carfilzomib group was observed across all predefined subgroups (Fig. 1B).

Because the primary objective was met, an interim analysis of overall survival was conducted. As of June 16, 2014, a total of 305 deaths had occurred (60% of the prespecified 510 events required for final analysis) (Fig. 2). The median follow-up was 32.3 months in the carfilzomib group and 31.5 months in the control group. The Kaplan–Meier 24-month overall survival rates were 73.3% (95% CI, 68.6 to 77.5) in the carfilzomib group and 65.0% (95% CI, 59.9 to 69.5) in the control group. The median overall survival was not reached in either group, with a trend in favor of the carfilzomib group (hazard ratio for death, 0.79; 95% CI, 0.63 to 0.99; P=0.04). However, these results did not cross the prespecified stopping boundary for overall survival at the interim analysis.

Overall response rates were 87.1% (95% CI, 83.4 to 90.3) in the carfilzomib group and 66.7% (95% CI, 61.8 to 71.3) in the control group (P<0.001) (Table 2), including a complete response or better in 31.8% and 9.3% of patients in the two groups, respectively (P<0.001). The mean time to a response was 1.6 months in the carfilzomib group and 2.3 months in the control group; the median duration of response was 28.6 months and 21.2 months, respectively. Health-related quality of life improved in the carfilzomib group as compared with the control group during 18 cycles of treatment (P<0.001) (Table S2 and Fig. S2 in the Supplementary Appendix). The minimal clinically important difference for between-group differences on the QLQ-C30 Global Health Status and Quality of Life scale is 5.0 points,[18] which was met at cycle 12 (5.6 points) and approached at cycle 18 (4.8 points).

Figure 1 (facing page). Progression-free Survival.

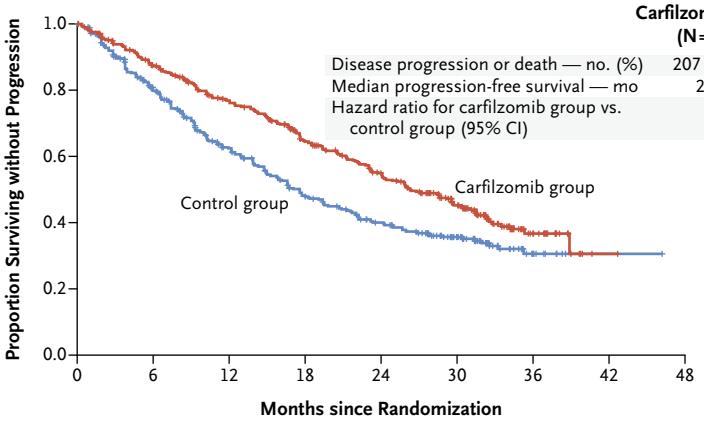
Disease progression was assessed by the independent review committee. Panel A shows Kaplan–Meier estimates in the intention-to-treat population, with stratification according to the β_2-microglobulin level (<2.5 mg vs. ≥2.5 mg per liter), previous therapy with bortezomib (no vs. yes), and previous therapy with lenalidomide (no vs. yes). The median progression-free survival was 8.7 months longer in the carfilzomib group than in the control group. Panel B shows hazard ratios and 95% confidence intervals for progression-free survival in prespecified subgroups according to baseline characteristics. Disease nonresponsive to bortezomib indicates that patients had a less-than-minimal response to any bortezomib-containing regimen, had disease progression during any bortezomib-containing regimen, or had disease progression within 60 days after the completion of any bortezomib-containing regimen. If patients had disease progression during any bortezomib-containing regimen, they were eligible for study enrollment if the date of progression occurred after the discontinuation of bortezomib.

SAFETY

A total of 392 patients in the carfilzomib group and 389 patients in the control group received at least one dose of study treatment. The median duration of treatment was 88.0 weeks (range, 1.0 to 185.0) in the carfilzomib group and 57.0 weeks (range, 1.0 to 201.0) in the control group; 69.9% and 77.9% of patients in the two groups, respectively, discontinued treatment, most commonly owing to disease progression (39.8% and 50.1%) or adverse events (15.3% and 17.7%) (Table S3 in the Supplementary Appendix). In the carfilzomib group, adverse events resulted in a reduction of the carfilzomib dose in 11.0% of patients and a reduction of the lenalidomide dose in 43.4% of patients. In the control group, the lenalidomide dose was reduced in 39.1% of patients.

Adverse events of any grade that occurred more frequently in the carfilzomib group than in the control group by at least 5 percentage points included hypokalemia, cough, upper respiratory tract infection, diarrhea, pyrexia, hypertension, thrombocytopenia, nasopharyngitis, and muscle spasms (Table 3, and Table S4 in the Supplementary Appendix); rates of discontinuation due to these events were less than 1% in both groups. There was no meaningful difference between groups in the incidence of peripheral neuropathy (17.1% in the carfilzomib group and 17.0% in the control group). Adverse events of grade 3 or higher were reported in 83.7% of patients in the carfilzomib group and 80.7% of patients in the control group, and serious adverse events were reported in 59.7% and 53.7% of patients, respectively. Adverse events of specific interest (grade 3 or higher) included dyspnea (2.8% in the carfilzomib group and 1.8% in the control group), cardiac failure (grouped term; 3.8% and 1.8%), ischemic heart disease (grouped term; 3.3% and 2.1%), hypertension (4.3% and 1.8%), and acute renal failure (grouped term; 3.3% and 3.1%).

A



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	

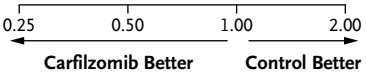
P=0.0001

No. at Risk

Carfilzomib group	396	332	279	222	179	112	24	1
Control group	396	287	206	151	117	72	18	1

B

Subgroup	Carfilzomib	Control	Hazard Ratio (95% CI)
	no.		
All patients	396	396	0.69 (0.57–0.83)
Sex			
Female	181	164	0.68 (0.51–0.92)
Male	215	232	0.74 (0.58–0.95)
Age			
18–64 yr	211	188	0.60 (0.46–0.79)
≥65 yr	185	208	0.85 (0.65–1.11)
Cytogenetic risk at study entry			
High risk	48	52	0.70 (0.43–1.16)
Standard risk	147	170	0.66 (0.48–0.90)
β_2-microglobulin			
<2.5 mg/liter	68	71	0.60 (0.36–1.02)
≥2.5 mg/liter	324	319	0.71 (0.58–0.87)
Geographic region			
Europe	302	288	0.70 (0.56–0.86)
North America	84	87	0.88 (0.57–1.37)
Peripheral neuropathy at baseline			
No	252	259	0.61 (0.48–0.77)
Yes	144	137	0.95 (0.69–1.30)
Previous treatment with bortezomib			
No	135	136	0.73 (0.52–1.02)
Yes	261	260	0.70 (0.56–0.88)
Previous treatment with lenalidomide			
No	317	318	0.69 (0.55–0.85)
Yes	79	78	0.80 (0.52–1.22)
Disease nonresponsive to bortezomib in any previous regimen			
No	336	338	0.70 (0.57–0.86)
Yes	60	58	0.80 (0.49–1.30)
Disease refractory to immunomodulatory agent in any previous regimen			
No	311	308	0.72 (0.58–0.90)
Yes	85	88	0.64 (0.44–0.91)
Disease nonresponsive to bortezomib and refractory to immunomodulatory agent in any previous regimen			
No	372	369	0.70 (0.57–0.85)
Yes	24	27	0.89 (0.45–1.77)



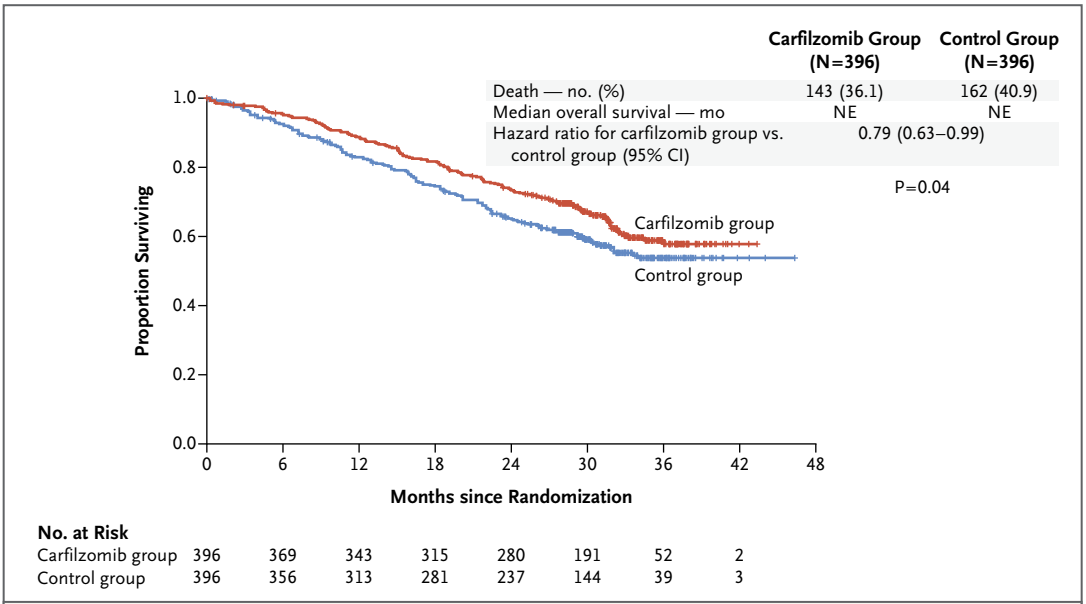


Figure 2. Overall Survival.

Kaplan–Meier estimates of overall survival in the intention-to-treat population are shown. The interim analysis of overall survival was performed after 305 deaths had occurred (60% of the prespecified 510 deaths for the final analysis). The interim analysis of overall survival did not cross the prespecified stopping boundary. NE denotes not estimable.

Table 2. Treatment Responses in the Intention-to-Treat Population.*

Variable	Carfilzomib Group (N=396)	Control Group (N=396)	P Value
Best response — no. (%)†			
Complete response or better	126 (31.8)	37 (9.3)	<0.001
Stringent complete response	56 (14.1)	17 (4.3)	
Complete response	70 (17.7)	20 (5.1)	
Very good partial response or better	277 (69.9)	160 (40.4)	<0.001
Stable or progressive disease	14 (3.5)	59 (14.9)	
Overall response rate — % (95% CI)‡	87.1 (83.4–90.3)	66.7 (61.8–71.3)	<0.001
Clinical benefit rate — % (95% CI)§	90.9 (87.6–93.6)	76.3 (71.8–80.4)	<0.001
Time to response — mo			
Mean	1.6±1.4	2.3±2.4	
Median	1.0	1.0	
Duration of response — mo			
Median	28.6	21.2	
95% CI	24.9–31.3	16.7–25.8	

* Treatment responses were assessed by an independent review committee. Plus–minus values are means ±SD. CI denotes confidence interval.

† A stringent complete response was defined by a negative immunofixation test for myeloma protein in serum or urine and the disappearance of any soft-tissue plasmacytomas, with less than 5% plasma cells in the bone marrow, a normal serum free light-chain ratio, and an absence of clonal cells in the bone marrow.[11] See Table S6 in the Supplementary Appendix for definitions of complete response, very good partial response, stable disease, and progressive disease.

‡ Overall response was defined as a partial response or better. See Table S6 in the Supplementary Appendix for the definition of a partial response.

§ Clinical benefit was defined as a minimal response or better. See Table S7 in the Supplementary Appendix for the definition of a minimal response.

Table 3. Adverse Events in the Safety Population.*

Event	Carfilzomib Group (N=392)		Control Group (N=389)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
	number of patients (percent)			
Most common nonhematologic adverse events				
Diarrhea	166 (42.3)	15 (3.8)	131 (33.7)	16 (4.1)
Fatigue	129 (32.9)	30 (7.7)	119 (30.6)	25 (6.4)
Cough	113 (28.8)	1 (0.3)	67 (17.2)	0
Pyrexia	112 (28.6)	7 (1.8)	81 (20.8)	2 (0.5)
Upper respiratory tract infection	112 (28.6)	7 (1.8)	75 (19.3)	4 (1.0)
Hypokalemia	108 (27.6)	37 (9.4)	52 (13.4)	19 (4.9)
Muscle spasms	104 (26.5)	4 (1.0)	82 (21.1)	3 (0.8)
Other adverse events of interest				
Dyspnea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure†	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Cardiac failure‡	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Ischemic heart disease§	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)

* Adverse events reported in at least 25% of patients in either treatment group are listed. Other adverse events of particular clinical relevance are also listed. The safety population included all patients who received at least one dose of a study drug.

† The category of acute renal failure included (in descending order of frequency) acute renal failure, renal failure, renal impairment, azotemia, oliguria, anuria, toxic nephropathy, and prerenal failure.

‡ The category of cardiac failure included (in descending order of frequency) cardiac failure, congestive cardiac failure, pulmonary edema, hepatic congestion, cardiopulmonary failure, acute pulmonary edema, acute cardiac failure, and right ventricular failure.

§ The category of ischemic heart disease included (in descending order of frequency) angina pectoris, myocardial infarction, acute myocardial infarction, an increased serum creatine kinase level, coronary artery disease, myocardial ischemia, coronary artery occlusion, an increased troponin level, an increased level of troponin T, an acute coronary syndrome, abnormal results on a cardiac stress test, cardiomyopathy stress, unstable angina, coronary-artery stenosis, an abnormal ST-T segment on electrocardiography, and an abnormal T wave on electrocardiography.

A total of 7.7% of patients in the carfilzomib group and 8.5% of patients in the control group died during treatment or within 30 days after receiving the last dose of study treatment. In each treatment group, 6.9% of patients died owing to adverse events. Overall, 14 deaths were reported as treatment-related: 6 in the carfilzomib group and 8 in the control group. Adverse events leading to more than 2 deaths in either group were myocardial infarction (3 in the carfilzomib group and 1 in the control group), cardiac failure (1 and 3, respectively), and sepsis (3 and 2).

DISCUSSION

The addition of carfilzomib to lenalidomide and dexamethasone led to significantly improved outcomes in patients with relapsed multiple myeloma, with a clinically relevant 31% decrease in the risk of disease progression or death and an increase of 8.7 months in the median progression-free survival (26.3 months in the carfilzomib group vs. 17.6 months in the control group). No other regimens have been associated with an equivalent duration of median progression-free survival in the absence of transplantation.[4,19-22]

A three-drug regimen consisting of a proteasome inhibitor (bortezomib), an immunomodulatory agent (thalidomide), and high-dose dexamethasone was previously investigated in a phase 3 study; it showed improved efficacy as compared with thalidomide and dexamethasone alone in patients with multiple myeloma that had relapsed after autologous transplantation (median progression-free survival, 19.5 months vs. 13.8 months). However, the group of patients

assigned to the three-drug regimen had a high rate of discontinuation due to adverse events (28%).[19] A second regimen of bortezomib, lenalidomide, and dexamethasone was investigated in patients with relapsed (including drug-refractory) multiple myeloma, and results showed an overall response rate of 64% and a median progression-free survival of 9.5 months.[22] Our findings regarding the use of carfilzomib in combination with lenalidomide and dexamethasone reinforce and extend the evidence in support of using a three-drug regimen composed of a proteasome inhibitor, an immunomodulatory agent, and dexamethasone in patients with relapsed multiple myeloma. In further support of this three-drug regimen, preliminary results have shown that carfilzomib, lenalidomide, and dexamethasone can also be highly effective in patients with newly diagnosed multiple myeloma.[23,24]

The benefit with respect to progression-free survival in the carfilzomib group was observed across all prespecified subgroups, including patients previously exposed to bortezomib or lenalidomide and those with a high cytogenetic risk. Patients in the carfilzomib group also had a higher overall response rate than those in the control group, with a longer median duration of response. The finding that the rate of complete response or better in the carfilzomib group was more than 3 times the rate in the control group is particularly encouraging, because studies have shown an association between more robust responses and improved survival in patients with multiple myeloma.[25] Overall survival favored the carfilzomib group, with a hazard ratio for death of 0.79; however, the result did not cross the stopping boundary at the interim analysis of overall survival.

A number of common adverse events were reported at a higher rate in the carfilzomib group than in the control group, including diarrhea, cough, fever, and hypertension. Although the duration of treatment was longer in the carfilzomib group than in the control group (median, 88 weeks vs. 57 weeks), serious adverse events, including cardiac events, were reported more frequently during the first 18 cycles of treatment than in later cycles (Table S5 in the Supplementary Appendix). A particular point of interest is that cardiac and renal events have been reported previously with carfilzomib monotherapy.[26,27] Such events were also observed in this trial but at rates consistent with those in prior carfilzomib studies. The frequency of deaths that were considered to be related to adverse events was identical in the two groups despite the prolonged treatment exposure in the carfilzomib group. Patients in the carfilzomib group remained in remission longer and reported superior health-related quality of life (according to the score on the QLQ-C30 Global Health Status and Quality of Life scale) than those in the control group during 18 cycles of treatment.

The median progression-free survival in the control group was considerably longer than anticipated (17.6 months). Previous studies of lenalidomide plus high-dose dexamethasone have shown a median progression-free survival of 9 to 11 months in similar patient populations.[4,28] This improvement could be due to the reduced toxicity of lower doses of dexamethasone. Studies examining continuous versus fixed-duration lenalidomide therapy have shown that continuous treatment leads to improved progression-free survival.[6,29-32] In our study, carfilzomib treatment was discontinued according to the study protocol after 18 cycles, because data on the long-term safety of carfilzomib were not yet available when the study was initiated. Results in patients with newly diagnosed multiple myeloma show that continuous treatment with carfilzomib, lenalidomide, and dexamethasone can lead to more robust responses,[23,24,33] but additional studies are needed to test this hypothesis. Other ongoing studies are exploring different carfilzomib doses and schedules as a means of improving efficacy and convenience for patients.[23,24,34]

In conclusion, carfilzomib combined with lenalidomide and dexamethasone led to a significant improvement in progression-free survival, as compared with lenalidomide and dexamethasone alone, in patients with relapsed multiple myeloma. These findings were bolstered by higher response rates, more robust responses, a favorable risk–benefit profile, improved health-related quality of life, and a trend toward improved overall survival with the three-drug regimen.

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APPENDIX

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