ORIGINAL ARTICLE

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

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ABSTRACT

BACKGROUND

Daratumumab, a human IgGκ monoclonal antibody that targets CD38, induces direct and indirect antimyeloma activity and has shown substantial efficacy as monotherapy in heavily pretreated patients with multiple myeloma, as well as in combination with bortezomib in patients with newly diagnosed multiple myeloma.

METHODS

In this phase 3 trial, we randomly assigned 498 patients with relapsed or relapsed and refractory multiple myeloma to receive bortezomib (1.3 mg per square meter of body-surface area) and dexamethasone (20 mg) alone (control group) or in combination with daratumumab (16 mg per kilogram of body weight) (daratumumab group). The primary end point was progression-free survival.

RESULTS

A prespecified interim analysis showed that the rate of progression-free survival was significantly higher in the daratumumab group than in the control group; the 12-month rate of progression-free survival was 60.7% in the daratumumab group versus 26.9% in the control group. After a median follow-up period of 7.4 months, the median progression-free survival was not reached in the daratumumab group and was 7.2 months in the control group (hazard ratio for progression or death with daratumumab vs. control, 0.39; 95% confidence interval, 0.28 to 0.53; P<0.001). The rate of overall response was higher in the daratumumab group than in the control group (82.9% vs. 63.2%, P<0.001), as were the rates of very good partial response or better (59.2% vs. 29.1%, P<0.001) and complete response or better (19.2% vs. 9.0%, P=0.001). Three of the most common grade 3 or 4 adverse events reported in the daratumumab group and the control group were thrombocytopenia (45.3% and 32.9%, respectively), anemia (14.4% and 16.0%, respectively), and neutropenia (12.8% and 4.2%, respectively). Infusion-related reactions that were associated with daratumumab treatment were reported in 45.3% of the patients in the daratumumab group; these reactions were mostly grade 1 or 2 (grade 3 in 8.6% of the patients), and in 98.2% of these patients, they occurred during the first infusion.

CONCLUSIONS

Among patients with relapsed or relapsed and refractory multiple myeloma, daratumumab in combination with bortezomib and dexamethasone resulted in significantly longer progression-free survival than bortezomib and dexamethasone alone and was associated with infusion-related reactions and higher rates of thrombocytopenia and neutropenia than bortezomib and dexamethasone alone. (Funded by Janssen Research and Development; ClinicalTrials.gov number, NCT02136134.)

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Multiple myeloma is associated with organ dysfunction, including bone lesions, anemia, renal insufficiency, and hypercalcemia.[1,2] Proteasome inhibitors (e.g., bortezomib) in combination with glucocorticoids are standard regimens for relapsed or relapsed and refractory multiple myeloma[3] (definitions of these terms are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org) and have contributed considerably to patient survival.[4] Nevertheless, almost all patients will have a relapse.

Daratumumab is a human IgGκ monoclonal antibody that targets CD38, which is highly expressed on myeloma cells and other hematopoietic cell types.[5,6] Daratumumab has direct and indirect antitumor activity and diverse mechanisms of action, including induction of apoptosis; immune-mediated actions, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis; and immunomodulatory functions that target and deplete CD38-positive regulator immune suppressor cells, which leads to T-cell expansion and activation in patients who have a response.[7-11]

In heavily pretreated patients with relapsed or relapsed and refractory multiple myeloma, single-agent daratumumab was associated with an overall response rate of 31% and a median overall survival of 20.1 months.[12] On the basis of these findings, daratumumab monotherapy at a dose of 16 mg per kilogram of body weight was approved by the Food and Drug Administration for the treatment of multiple myeloma in patients who have previously received at least three therapies, including a proteasome inhibitor and an immunomodulatory agent, or in patients whose disease is refractory to treatment in both these drug classes.[13]

Treatment with daratumumab in combination with proteasome inhibitors and immunomodulatory agents has resulted in high response rates and acceptable safety profiles in early-phase clinical trials.[14,15] Specifically, in a phase 1 trial involving patients with newly diagnosed multiple myeloma, daratumumab in combination with bortezomib-based regimens, including bortezomib plus dexamethasone, induced responses in all patients.[14] We report the results of a prespecified interim analysis of a randomized phase 3 trial of daratumumab in combination with bortezomib and dexamethasone as compared with bortezomib and dexamethasone alone in patients with relapsed or relapsed and refractory multiple myeloma.

METHODS

TRIAL DESIGN AND OVERSIGHT

This was a multicenter, randomized, open-label, active-controlled, phase 3 trial. The trial protocol, which is available at NEJM.org, was approved by the independent ethics committee or institutional review board at each trial center. All the patients provided written informed consent, and the trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Janssen Research and Development sponsored the trial. The sponsor and investigators were jointly responsible for the trial design and the statistical analysis plan (available with the protocol). The investigators and associated research teams collected the data, which were compiled and maintained by the sponsor. One of the authors who was an employee of the sponsor was the physician responsible for the trial. Professional medical writers were funded by the sponsor to prepare the manuscript for submission. All the authors reviewed, revised, and approved the manuscript for submission. The sponsor and investigators vouch for the accuracy and completeness of the data from the prespecified interim analysis and for the fidelity of the trial to the protocol.

PATIENTS

Patients were eligible for enrollment in the trial if they had received at least one previous line of therapy for multiple myeloma, had at least a partial response to one or more of their previous therapies, and had documented progressive disease, according to International Myeloma Working Group (IMWG) criteria (a list of these criteria is provided in the Supplementary Appendix),[16,17] during or after the completion of their last regimen. At screening, all patients were required to have measurable disease on the basis of assessments of the serum, urine, or both or to have measurable disease as assessed by the serum free light-chain assay, in accordance with the criteria specified by the IMWG.

Key exclusion criteria were a neutrophil count of 1000 or less per cubic millimeter, a hemoglo-

bin level of 7.5 g or less per deciliter, a platelet count of less than 75,000 per cubic millimeter, a creatinine clearance of 20 ml or less per minute per 1.73 m^2 of body-surface area, an alanine aminotransferase or aspartate aminotransferase level of 2.5 or more times the upper limit of the normal range, and a bilirubin level of 1.5 or more times the upper limit of the normal range; in addition, patients were excluded if they had disease that was refractory to bortezomib or if they had unacceptable side effects from bortezomib, if they had disease that was refractory to another proteasome inhibitor, or if they had grade 2 or higher peripheral neuropathy or neuropathic pain.

TRIAL TREATMENTS

Patients were randomly assigned in a 1:1 ratio to receive either daratumumab in combination with bortezomib and dexamethasone (daratumumab group) or bortezomib and dexamethasone alone (control group). Randomization was stratified according to International Staging System (ISS) disease stage at the time of screening (stage I, II, or III, with higher stages indicating more severe disease; definitions are provided in the Supplementary Appendix), the number of previous lines of therapy (1 vs. 2 or 3 vs. >3), and previous treatment with bortezomib (no vs. yes).

All patients received up to 8 cycles (21 days per cycle) of bortezomib (on the basis of the dosing schedule of the pivotal SUMMIT trial[18]) and dexamethasone. For patients assigned to the daratumumab group, daratumumab at a dose of 16 mg per kilogram was administered intravenously once per week (days 1, 8, and 15) during cycles 1 to 3, once every 3 weeks (on day 1) during cycles 4 to 8, and once every 4 weeks thereafter until the patient withdrew consent, the disease progressed, or unacceptable toxic effects developed (Fig. S1 in the Supplementary Appendix). Patients in the daratumumab group received medications before or after their infusions of daratumumab as needed to manage infusion-related reactions (Table S3 in the Supplementary Appendix). Bortezomib was administered subcutaneously at a dose of 1.3 mg per square meter on days 1, 4, 8, and 11 of cycles 1 to 8, and dexamethasone was administered orally or intravenously at a dose of 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12, for a total dose of 160 mg per cycle. The dose of dexamethasone could be reduced to 20 mg once weekly for patients who were older than 75 years of age, for patients who had a body-mass index (the weight in kilograms divided by the square of the height in meters) of less than 18.5, or for patients who had previous unacceptable side effects associated with glucocorticoid therapy.

END POINTS AND ASSESSMENTS

The primary end point of the trial was progression-free survival, which was defined as the time from the date of randomization to the date of disease progression or death, whichever occurred first. We assessed response to treatment and disease progression using a computerized algorithm (details are provided in the Supplementary Appendix) that combined all pertinent laboratory results and the results of imaging, as assessed by the investigator, for each patient and derived the outcome in accordance with IMWG criteria.[16,17] Results from a previous phase 2 trial in which the same algorithm was used showed very strong concordance with the findings of an independent review committee from the trial.[19] Secondary efficacy end points included the time to disease progression, the overall response rate, the proportion of patients who achieved very good partial response or better, the duration of response, the time to response, and overall survival. The time to subsequent antimyeloma treatment was an exploratory efficacy end point. Definitions of these efficacy end points are provided in the Supplementary Appendix. Serum and urine monoclonal proteins and serum free light-chains were measured at a central laboratory. Serum tests and 24-hour urine tests were performed on day 1 of each cycle for the first 18 months and every other month thereafter until the onset of disease progression. All responses, including progressive disease, were confirmed by a second, consecutive assessment. In cases in which a patient had a possible complete response but the investigator suspected that the patient's dose of daratumumab had interfered with the quantitation of serum M-protein as determined by either the electrophoresis assay or the immunofixation assay, additional reflex testing with the use of an antiidiotype antibody was used to confirm the complete response.[20,21] Definitions of all response categories are provided in the protocol. Serum samples were assessed for the development of antibodies to daratumumab.

Safety assessments included the evaluation of

adverse events (which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03), electrocardiography, vital signs, and clinical laboratory testing, which was performed at a local laboratory. An independent data and safety monitoring committee periodically reviewed the safety data.

STATISTICAL ANALYSIS

In this trial, we used a group sequential design with one prespecified interim analysis to evaluate the primary end point. We estimated that a sample size of approximately 480 patients would result in a total of 295 events of disease progression or death, which would give the trial 85% power to detect a risk of disease progression or death that was lower by 30% (hazard ratio, 0.70) with daratumumab in combination with bortezomib and dexamethasone than with bortezomib and dexamethasone alone, using a log-rank test at an overall two-sided alpha level of 0.05. The interim analysis was to be performed after approximately 177 events had been observed (i.e., 60% of the planned events for the final analysis). The O'Brien–Fleming stopping boundary at the time of the interim analysis for the primary end point 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.[22,23]

If the results of the primary end point were found to be significant at the interim analysis, the major secondary end points were to be tested sequentially in the order of time to disease progression, rate of very good partial response, overall response rate, and overall survival, each at an overall two-sided alpha level of 0.05. Efficacy analyses were based on the intention-to-treat population, which included all patients who underwent randomization. The safety population included all patients who received at least one dose of trial treatment. The population of patients who could be evaluated for response included patients who had measurable disease at the baseline or screening visit and who received at least one dose of trial treatment and had at least one assessment of disease after the baseline visit.

The end points of progression-free survival, which included disease status and deaths, and time to disease progression, which included disease status only, were compared between the daratumumab group and the control group with the use of a stratified log-rank test. Hazard ratios and corresponding 95% confidence intervals were estimated with the use of a stratified Cox regression model, with treatment as the sole explanatory variable. The Kaplan–Meier method was used to estimate the distributions. A stratified Cochran–Mantel–Haenszel chi-square test was used to test between-group differences in the overall response rate, the rate of very good partial response or better (i.e., very good partial response, complete response, or stringent complete response), and the rate of complete response or better (i.e., complete response or stringent complete response). The duration of response was summarized by means of the Kaplan–Meier method.

RESULTS

PATIENTS AND TREATMENT

From September 4, 2014, to September 24, 2015, patients were recruited at 115 centers in 16 countries across Europe, North America, South America, and the Asia-Pacific region. A total of 498 patients were enrolled; 251 were randomly assigned to the daratumumab group and 247 to the control group. The demographic, disease, and clinical characteristics of the two groups were well balanced at baseline (Table 1). Across the two treatment groups, the median age of the patients was 64 years (range, 30 to 88). The median time since the initial diagnosis of multiple myeloma was 3.8 years. Patients had received a median of 2 (range, 1 to 10) previous lines of therapy; 23.9% of the patients had received at least 3 previous lines of therapy. Across the two treatment groups, 61.2% of the patients had undergone autologous stem-cell transplantation, 65.5% had received previous treatment with bortezomib, 75.7% had received immunomodulatory drugs, 48.4% had received both proteasome inhibitors and immunomodulatory drugs, 32.3% had disease that was refractory to their last line of therapy, and 32.9% had disease that was refractory to immunomodulatory drugs.

At the time of the data-cutoff date of January 11, 2016, among the patients who had received at least one dose of trial treatment (safety population: 243 patients in the daratumumab group and 237 in the control group), 74 patients (30.5%)

Table 1. Demographic, Baseline Disease, and Clinical Characteristics in the Intention-to-Treat Population.*

Characteristic	Daratumumab Group (N=251)	Control Group (N=247)
Age		
Median (range) — yr	64 (30–88)	64 (33–85)
Distribution — no. (%)		
<65 yr	132 (52.6)	125 (50.6)
65–74 yr	96 (38.2)	87 (35.2)
≥75 yr	23 (9.2)	35 (14.2)
Type of measurable disease — no. (%)		
IgG	125 (49.8)	138 (55.9)
IgA	56 (22.3)	54 (21.9)
Other	5 (2.0)	4 (1.6)
Detected in urine only	40 (15.9)	36 (14.6)
Detected in serum free light-chains only	25 (10.0)	14 (5.7)
Not evaluated	0	1 (0.4)
ISS disease staging — no. (%)†		
I	98 (39.0)	96 (38.9)
II	94 (37.5)	100 (40.5)
III	59 (23.5)	51 (20.6)
Cytogenetic profile — no. (%)‡		
Standard-risk cytogenetic abnormality	140/181 (77.3)	137/174 (78.7)
High-risk cytogenetic abnormality	41/181 (22.7)	37/174 (21.3)
Del17p	28/181 (15.5)	21/174 (12.1)
t(4;14)	14/181 (7.7)	15/174 (8.6)
t(14;16)	4/181 (2.2)	5/174 (2.9)
Median time since initial diagnosis of multiple myeloma (range) — yr	3.87 (0.7–20.7)	3.72 (0.6–18.6)
Number of previous lines of therapy — no. (%)		
1	122 (48.6)	113 (45.7)
2	70 (27.9)	74 (30.0)
3	37 (14.7)	32 (13.0)
>3	22 (8.8)	28 (11.3)
Median no. of previous lines of therapy (range)	2 (1–9)	2 (1–10)
Previous autologous stem-cell transplantation — no. (%)	156 (62.2)	149 (60.3)
Previous alkylating agent therapy — no. (%)	240 (95.6)	224 (90.7)
Previous proteasome inhibitor therapy — no. (%)	169 (67.3)	172 (69.6)
Previous immunomodulatory drug therapy — no. (%)	179 (71.3)	198 (80.2)
Previous proteasome inhibitor + immunomodulatory drug therapy — no. (%)	112 (44.6)	129 (52.2)
Disease refractory to last line of therapy — no. (%)	76 (30.3)	85 (34.4)

* There were no significant between-group differences in the characteristics evaluated at baseline, with the exception of previous immunomodulatory drug therapy (P=0.02). The intention-to-treat population was defined as all patients who underwent randomization.

† International Staging System (ISS) disease staging was derived on the basis of the combination of serum β_2-microglobulin and albumin. The ISS consists of three stages: stage I, serum β_2-microglobulin level lower than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g per deciliter or higher; stage II, neither stage I nor III; and stage III, serum β_2-microglobulin 5.5 mg per liter or higher (470 nmol per liter). Higher stages indicate more severe disease.

‡ Complete cytogenetic data were not available at the data-cutoff date. High-risk patients could be counted in more than one subcategory.

in the daratumumab group and 104 (43.9%) in the control group had discontinued treatment, primarily because of progressive disease (19.3% and 25.3%, respectively) and adverse events (7.8% and 9.7%, respectively) (Fig. S2 in the Supplementary Appendix). A total of 79.8% of the patients in the daratumumab group and 57.4% in the control group had received the maximum of eight cycles of bortezomib treatment. The median relative dose intensity (the proportion of administered doses relative to planned doses) for bortezomib and dexamethasone was similar in the two treatment groups (86.5% and 93.5% for bortezomib in the daratumumab group and the control group, respectively, and 98.2% and 100% for dexamethasone in the two groups, respectively). The median relative dose intensity for daratumumab was 99.2%.

EFFICACY

After a median follow-up period of 7.4 months, a total of 189 events of disease progression or death had occurred (64% of the 295 planned events for the final analysis): 67 in the daratumumab group and 122 in the control group. The 12-month rate of progression-free survival (i.e., the absence of disease progression or death), which was estimated with the use of the Kaplan–Meier method, was 60.7% (95% confidence interval [CI], 51.2 to 69.0) in the daratumumab group as compared with 26.9% (95% CI, 17.1 to 37.5) in the control group. The median progression-free survival was not reached (95% CI, 12.3 to not estimable) in the daratumumab group and was 7.2 months (95% CI, 6.2 to 7.9) in the control group (hazard ratio for disease progression or death with daratumumab vs. control, 0.39; 95% CI, 0.28 to 0.53; P<0.001, which crossed the prespecified stopping boundary), which represented a 61.4% lower risk of progression or death in the daratumumab group than in the control group (Fig. 1A). In the time-to-event analysis of disease progression, the percentage of patients who were free from disease progression after 12 months was 65.4% (95% CI, 56.1 to 74.8) in the daratumumab group as compared with 28.8% (95% CI, 17.8 to 39.8) in the control group (hazard ratio for disease progression, 0.30; 95% CI, 0.21 to 0.43; P<0.001) (Fig. 1B).

The overall response rate was 82.9% in the daratumumab group and 63.2% in the control group (P<0.001) (Table 2). Rates were also higher in the daratumumab group than in the control group with respect to very good partial response or better (59.2% vs. 29.1%, P<0.001) and complete response or better (19.2% vs. 9.0%, P=0.001). Similar results were observed in the intention-to-treat population (Table S1 in the Supplementary Appendix). No very good partial responses with positive serum immunofixation of IgGκ were reclassified as either complete responses or stringent complete responses as a result of additional immunofixation electrophoresis reflex testing to account for daratumumab. Deeper responses (i.e., very good partial responses or better) translated into a greater benefit in progression-free survival in the daratumumab group than in the control group (Fig. S3 in the Supplementary Appendix). The median time to the first response was 0.9 months in the daratumumab group and 1.6 months in the control group, and the median duration of response was longer in the daratumumab group than in the control group (not reached [95% CI, 11.5 months to not estimable] vs. 7.9 months [95% CI, 6.7 to 11.3]) (Fig. S4 in the Supplementary Appendix).

Prespecified subgroup analyses of progression-free survival confirmed the superiority of daratumumab in combination with bortezomib and dexamethasone over bortezomib and dexamethasone alone in all subgroups, including the subgroup of patients who had previously received bortezomib (Fig. 2). In addition, median progression-free survival was significantly longer in the daratumumab group than in the control group among patients with ISS stage I disease (hazard ratio for progression or death with daratumumab vs. control, 0.25). The rate of progression-free survival was higher among patients in the daratumumab group than among patients in the control group in the subgroup of patients who had received one previous line of therapy; the 12-month progression-free survival rate was 77.5% (95% CI, 65.2 to 86.0) in the daratumumab group as compared with 29.4% (95% CI, 12.5 to 48.7) in the control group (hazard ratio for progression or death, 0.31; 95% CI, 0.18 to 0.52; P<0.001) (Fig. S5 in the Supplementary Appendix). Among patients who had received two or three previous lines of therapy, median progression-free survival was 9.3 months (95% CI, 7.6 to not estimable) in the daratumumab group as compared with 6.5 months (95% CI, 5.7 to 8.1) in the control group (hazard ratio for progression or death, 0.52; 95% CI, 0.33 to 0.81; P=0.004) (Fig. S6 in the Supplementary Appendix).

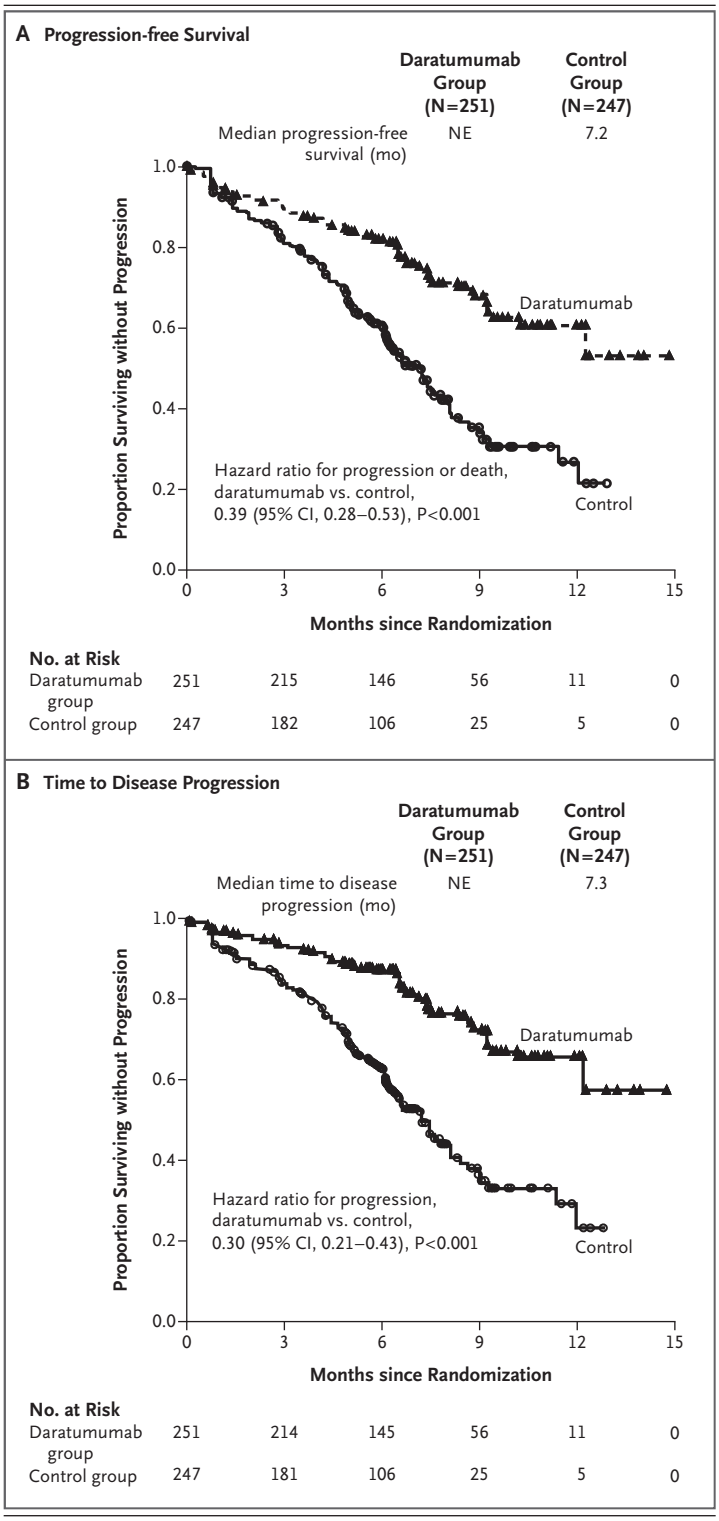

Figure 1. Median Progression-free Survival and Median Time to Disease Progression.

Panel A shows Kaplan–Meier estimates of progression-free survival among patients in the intention-to-treat population, which included all patients who underwent randomization. Panel B shows Kaplan–Meier estimates of disease progression in a time-to-event analysis of data from patients in the intention-to-treat population. The daratumumab group received treatment with daratumumab, bortezomib, and dexamethasone; the control group received treatment with bortezomib and dexamethasone alone. The interim analysis of median progression-free survival was performed after 189 events of disease progression or death had occurred (64% of the planned 295 events for the final analysis); the results of the analysis crossed the prespecified stopping boundary. NE denotes not estimable.

On the basis of the results of the interim analysis, the independent data and safety monitoring committee recommended that the trial be unblinded early (and that daratumumab monotherapy be offered to patients in the control group who had disease progression) because the prespecified statistical boundary (an alpha level of 0.0102) for the primary end point of progression-free survival had been crossed. An additional analysis of progression-free survival was performed, which included data from the time of randomization to progression or death while patients were receiving the next line of therapy (progression-free survival 2 analysis). Because of the short follow-up period, median progression-free survival while patients were receiving the next line of therapy (progression-free survival 2) as well as overall survival were not reached in either treatment group; 80 events of progression or death while patients were receiving the next line of therapy (31 in the daratumumab group vs. 49 in the control group; hazard ratio, 0.57; 95% CI, 0.37 to 0.90) and a total of 65 deaths during the course of the study (29 in the daratumumab group vs. 36 in the control group; hazard ratio, 0.77; 95% CI, 0.47 to 1.26) were reported (Fig. S7 and Table S2 in the Supplementary Appendix). Long-term follow-up is continuing to better characterize the effect of daratumumab on these longer-term clinical end points.

SAFETY

Most patients in the daratumumab group and the control group had at least one adverse event after the start of treatment (98.8% and 95.4%, respectively). The most common adverse events of any grade (occurring in at least 15% of patients in either treatment group) and the most common adverse events of grade 3 or 4 (occur-

Table 2. Summary of Responses among Patients Who Could Be Evaluated for Response.*

Response Category	Daratumumab Group (N=240)	Control Group (N=234)	P Value†
Overall response			
No. with response	199	148	
Rate — % (95% CI)	82.9 (77.5–87.5)	63.2 (56.7–69.4)	<0.001
Best overall response — no. (%)			
Complete response or better	46 (19.2)	21 (9.0)	0.001
Complete response	35 (14.6)	16 (6.8)	
Stringent complete response‡	11 (4.6)	5 (2.1)	
Very good partial response or better	142 (59.2)	68 (29.1)	<0.001
Very good partial response	96 (40.0)	47 (20.1)	
Partial response	57 (23.8)	80 (34.2)	
Minimal response	10 (4.2)	20 (8.5)	
Stable disease	24 (10.0)	47 (20.1)	
Progressive disease	5 (2.1)	16 (6.8)	
Response could not be evaluated	2 (0.8)	3 (1.3)	

* Response was assessed on the basis of International Uniform Criteria Consensus recommendations (details on the criteria for disease responses are provided in the protocol). The population of patients who could be evaluated for response included patients who had a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening. In addition, patients must have received at least one dose of trial treatment and must have had at least one disease assessment after the baseline visit.

† P values were calculated with the use of the Cochran–Mantel–Haenszel chi-square test.

‡ Criteria for a stringent complete response include the criteria for a complete response plus a normal free light-chain ratio and absence of clonal plasma cells as assessed by immunohistochemical or immunofluorescence analysis or by two-color-to-four-color flow cytometry.

ring in at least 5% of patients in either treatment group) in the safety population are summarized in Table 3. Higher rates of grade 3 or 4 adverse events were observed in the daratumumab group than in the control group (76.1% vs. 62.4%). Three of the most common grade 3 or 4 adverse events reported in the daratumumab group and the control group were thrombocytopenia (45.3% and 32.9%, respectively), anemia (14.4% and 16.0%, respectively), and neutropenia (12.8% and 4.2%, respectively).

With respect to hematologic adverse events, we observed higher rates in the daratumumab group than in the control group of any grade of thrombocytopenia (58.8% vs. 43.9%), neutropenia (17.7% vs. 9.3%), and lymphopenia (13.2% vs. 3.8%), and this trend was also observed for grade 3 or 4 thrombocytopenia, neutropenia, and lymphopenia (Table 3). With respect to nonhematologic adverse events, the rate of any grade of peripheral sensory neuropathy was higher in the daratumumab group than in the control group (47.3% vs. 37.6%), although the rate of grade 3 or 4 peripheral sensory neuropathy was similar in the two groups (4.5% and 6.8%, respectively). The rates of grade 3 or 4 infections and infestations were similar in the two groups (21.4% and 19.0%, respectively), and the rates of bleeding events of any grade were 7.0% in the daratumumab group and 3.8% in the control group. The rates of secondary primary cancers were 2.5% and 0.4%, respectively; a majority of these cancers had developed within 6 months after the initiation of trial treatment and occurred in patients who had previous exposure to immunomodulatory drugs and alkylating agents (details are provided in the Supplementary Appendix).

The percentage of patients who discontinued treatment because of at least one adverse event was similar in the daratumumab group and the control group (7.4% and 9.3%, respectively). The most common adverse events (occurring in at least 1% of patients in either group) that led to

Subgroup	Control Group	Daratumumab Group	Control Group	Daratumumab Group	Hazard Ratio (95% CI)
	no. of progression or death events/total no.		*median progression-free survival (mo)*		
Age					
<65 yr	59/125	39/132	7.3	10.3	0.44 (0.28–0.68)
≥65 yr	63/122	28/119	6.7	NE	0.35 (0.22–0.57)
Sex					
Male	80/147	38/137	6.3	NE	0.41 (0.27–0.61)
Female	42/100	29/114	7.6	NE	0.38 (0.22–0.64)
ISS disease staging					
I	36/96	15/98	8.4	NE	0.25 (0.13–0.48)
II	55/100	26/94	6.2	NE	0.37 (0.23–0.61)
III	31/51	26/59	5.3	8.6	0.55 (0.31–0.98)
No. of previous lines of therapy					
1	51/113	20/122	7.5	NE	0.31 (0.18–0.52)
2	37/74	22/70	6.5	10.3	0.50 (0.28–0.89)
3	17/32	16/37	6.6	8.8	0.66 (0.31–1.41)
>3	17/28	9/22	5.4	8.4	0.48 (0.20–1.16)
Previous autologous stem-cell transplantation					
Yes	74/149	42/156	6.7	NE	0.38 (0.26–0.57)
No	48/98	25/95	7.2	NE	0.34 (0.19–0.59)
Previous bortezomib therapy					
Yes	81/164	52/162	6.7	12.3	0.46 (0.32–0.66)
No	41/83	15/89	7.5	NE	0.25 (0.13–0.47)
Previous therapy with immunomodulatory agent					
Yes	101/198	51/179	6.6	12.3	0.38 (0.27–0.55)
No	21/49	16/72	9.1	NE	0.50 (0.24–1.04)
Disease refractory to previous therapy with immunomodulatory agent					
Yes	58/97	34/83	5.4	9.2	0.50 (0.31–0.80)
No	43/101	17/96	7.4	12.3	0.32 (0.18–0.59)
Disease refractory to last line of previous therapy					
Yes	51/85	30/76	5.0	9.3	0.42 (0.25–0.70)
No	71/162	37/175	7.9	12.3	0.38 (0.25–0.58)
Type of multiple myeloma					
IgG	70/138	39/125	6.6	12.3	0.38 (0.25–0.59)
Non-IgG	28/58	12/61	7.3	NE	0.33 (0.16–0.70)
Baseline creatinine clearance					
>60 ml/min	82/163	45/186	7.2	NE	0.30 (0.20–0.44)
≤60 ml/min	40/70	19/57	6.5	NE	0.55 (0.30–1.02)

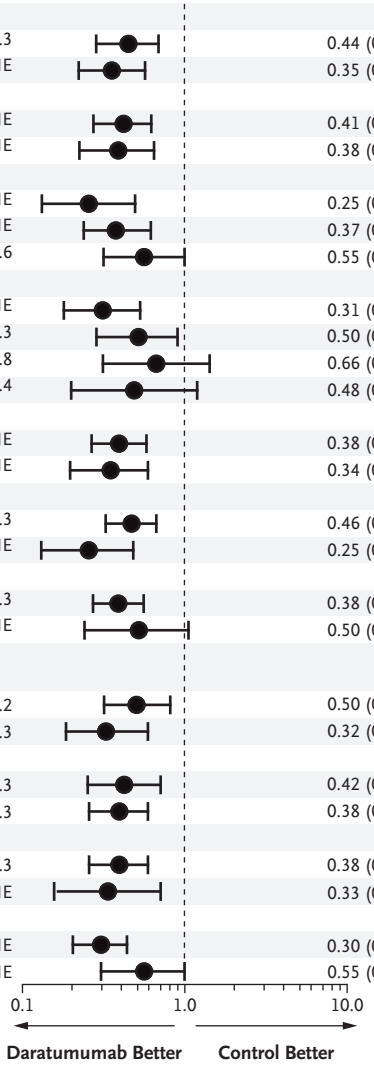

Figure 2. Prespecified Subgroup Analysis of Progression-free Survival.

Results are shown of an analysis of progression-free survival in prespecified subgroups of the intention-to-treat population that were defined according to baseline characteristics. No significant interaction was observed between the treatment groups with regard to any of the subgroups. The International Staging System (ISS) consists of three stages, with higher stages indicating more severe disease: stage I, serum β_2-microglobulin level lower than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g per deciliter or higher; stage II, neither stage I nor III; and stage III, serum β_2-microglobulin 5.5 mg per liter or higher (470 nmol per liter). The subgroup analysis of disease that was refractory to immunomodulatory agents was performed on data from patients who had previously received an immunomodulatory agent. The subgroup analysis of the type of multiple myeloma was performed on data from patients who had measurable disease in serum. Baseline creatinine clearance was used to assess renal function. To convert the values for creatinine clearance to milliliters per second, multiply by 0.01667.

treatment discontinuation were peripheral sensory neuropathy (0.4% and 2.5%, respectively) and pneumonia (1.2% and 0.4%, respectively). Adverse events that led to death were reported in 13 patients (5.3%) in the daratumumab group and in 14 patients (5.9%) in the control group;

Table 3. Most Common Adverse Events in the Safety Population.*

Event	Daratumumab Group (N=243)		Control Group (N=237)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Common hematologic adverse event				
Thrombocytopenia	143 (58.8)	110 (45.3)	104 (43.9)	78 (32.9)
Anemia	64 (26.3)	35 (14.4)	74 (31.2)	38 (16.0)
Neutropenia	43 (17.7)	31 (12.8)	22 (9.3)	10 (4.2)
Lymphopenia	32 (13.2)	23 (9.5)	9 (3.8)	6 (2.5)
Common nonhematologic adverse events				
Peripheral sensory neuropathy	115 (47.3)	11 (4.5)	89 (37.6)	16 (6.8)
Diarrhea	77 (31.7)	9 (3.7)	53 (22.4)	3 (1.3)
Upper respiratory tract infection	60 (24.7)	4 (1.6)	43 (18.1)	2 (0.8)
Fatigue	52 (21.4)	11 (4.5)	58 (24.5)	8 (3.4)
Cough	58 (23.9)	0	30 (12.7)	0
Constipation	48 (19.8)	0	37 (15.6)	2 (0.8)
Dyspnea	45 (18.5)	9 (3.7)	21 (8.9)	2 (0.8)
Insomnia	41 (16.9)	0	35 (14.8)	3 (1.3)
Peripheral edema	40 (16.5)	1 (0.4)	19 (8.0)	0
Asthenia	21 (8.6)	2 (0.8)	37 (15.6)	5 (2.1)
Pyrexia	38 (15.6)	3 (1.2)	27 (11.4)	3 (1.3)
Pneumonia	29 (11.9)	20 (8.2)	28 (11.8)	23 (9.7)
Hypertension	21 (8.6)	16 (6.6)	8 (3.4)	2 (0.8)
Secondary primary cancer†	6 (2.5)	NA	1 (0.4)	NA

* The safety population included all patients who received at least one dose of trial treatment. Adverse events of any grade that were reported in at least 15% of patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 5% of patients in either treatment group are listed. NA denotes not applicable.

† The presence of a secondary primary cancer was prespecified in the statistical analysis plan as an adverse event of clinical interest. The other adverse events of clinical interest included infusion-related reactions, infections or infestations, peripheral neuropathies, and cardiac disorders.

these events were mainly a result of the general deterioration of the patients' physical health (0.4% and 1.3%, respectively). Other adverse events leading to death that were reported in 2 or more patients in either treatment group were pneumonia (1 patient in the daratumumab group and 2 in the control group), ischemic stroke (2 patients and no patients, respectively), and respiratory failure (2 patients and no patients, respectively). No cases of immunogenicity were reported in the daratumumab group, and no cases of hemolysis were reported in either treatment group.

Infusion-related reactions of any grade that were associated with daratumumab were reported in 45.3% of the patients; for 98.2% of these patients, the events occurred during the first infusion. Infusion-related reactions were mostly limited to grade 1 or 2 events; at least one grade 3 event was reported in 21 patients (8.6%), and no grade 4 events were reported. The most common adverse event terms that were documented by the investigator as infusion-related reactions were dyspnea (10.7%), bronchospasm (9.1%), and cough (7.0%) (Table S3 in the Supplementary Appendix). Two patients discontinued treatment because of infusion-related reactions: bronchospasm in 1 patient and bronchospasm, laryngeal edema, and rash in the other patient.

DISCUSSION

Among patients with relapsed or relapsed and refractory multiple myeloma, the combination of daratumumab, bortezomib, and dexamethasone resulted in significantly longer progression-free survival than bortezomib and dexamethasone alone, with a risk of disease progression or death that was 61.4% lower in the daratumumab group than in the control group. The benefit was maintained across all subgroups, including the subgroups of patients with ISS stage III disease, those who had received two or three previous lines of therapy, those who had previously received immunomodulatory drugs, and those who had previously received bortezomib. In the daratumumab group, deep, rapid, and durable responses were reported, with the rates of very good partial response or better and complete response or better approximately double those in the control group. The median duration of response and time to subsequent antimyeloma therapy were shorter in the control group than in the daratumumab group, which suggests that patients who received daratumumab were also able to maintain longer periods of remission. Overall, these findings are consistent with observations from phase 1 and phase 1/2 trials that showed an additive benefit of daratumumab in combination with proteasome inhibitors or immunomodulatory drugs (pomalidomide or lenalidomide) and dexamethasone[14,15,24] and highlight the advantages of combination therapy.[25]

The benefit of combining antibodies that target CD38 with proteasome inhibition may be explained in part by enhanced direct cytotoxicity on myeloma cells, an effect that was shown in vitro in preclinical studies.[26,27] The direct and indirect mechanisms of action of daratumumab in combination with bortezomib and dexamethasone, as well as the recently identified role of daratumumab in the inhibition of regulatory T cells,[11] may have multiplicative effects.

Cross-trial comparisons are often confounded by differences in design, methods, and patient population. However, our trial, in which the hazard ratio for progression or death with daratumumab versus control was 0.39, shows the benefit of the triplet regimen with daratumumab over other proteasome-inhibitor–based combination therapies without immunomodulatory drugs in this patient population,[28] including carfilzomib plus dexamethasone (median progression-free survival of 18.7 months, vs. 9.4 months in the control group, with a hazard ratio of 0.53 and an objective response rate of 77%)[29] and panobinostat in combination with bortezomib and dexamethasone, which resulted in a hazard ratio of 0.63 (median progression-free survival of 12.0 months, vs. 8.1 months in the control group, with an overall response rate of 61%).[30] Recently, a phase 2 trial of elotuzumab in combination with bortezomib and dexamethasone versus bortezomib and dexamethasone alone showed a median progression-free survival of 9.7 months versus 6.9 months (hazard ratio for progression or death, 0.72).[31]

The addition of daratumumab to bortezomib and dexamethasone was associated with a higher incidence of adverse events, primarily thrombocytopenia and infusion-related reactions. Grade 3 or 4 hematologic adverse events were more common in the daratumumab group than in the control group; however, the rates of grade 3 or 4 infections as well as the rates of adverse events that led to treatment discontinuation were similar in the two groups. The rate of infusion-related reactions was expected and was consistent with findings from previous trials of daratumumab administered either as monotherapy[19,32] or as combination therapy.[15,24]

In this prespecified interim analysis, no analyses according to baseline cytogenetic features were possible because the evaluation of these data is ongoing. In addition, because of the relatively short follow-up period, we could not assess whether the addition of daratumumab to bortezomib and dexamethasone confers an overall survival benefit. The final analysis of overall survival will be confounded by the treatment effects of daratumumab in the control group because patients in the control group were allowed to receive daratumumab after the interim analysis was completed.

In summary, among patients with relapsed or relapsed and refractory multiple myeloma, daratumumab in combination with bortezomib and dexamethasone resulted in significantly longer progression-free survival than bortezomib and dexamethasone alone. The addition of daratumumab was associated with infusion-related reactions and higher rates of thrombocytopenia

and neutropenia. The infusion-related reactions occurred primarily during the first infusion.

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APPENDIX

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