ORIGINAL ARTICLE

Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma

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ABSTRACT

BACKGROUND

The combination of bortezomib, melphalan, and prednisone is a standard treatment for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation. Daratumumab has shown efficacy in combination with standard-of-care regimens in patients with relapsed or refractory multiple myeloma.

METHODS

In this phase 3 trial, we randomly assigned 706 patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation to receive nine cycles of bortezomib, melphalan, and prednisone either alone (control group) or with daratumumab (daratumumab group) until disease progression. The primary end point was progression-free survival.

RESULTS

At a median follow-up of 16.5 months in a prespecified interim analysis, the 18-month progression-free survival rate was 71.6% (95% confidence interval [CI], 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The overall response rate was 90.9% in the daratumumab group, as compared with 73.9% in the control group (P<0.001), and the rate of complete response or better (including stringent complete response) was 42.6%, versus 24.4% (P<0.001). In the daratumumab group, 22.3% of the patients were negative for minimal residual disease (at a threshold of 1 tumor cell per 10^5 white cells), as compared with 6.2% of those in the control group (P<0.001). The most common adverse events of grade 3 or 4 were hematologic: neutropenia (in 39.9% of the patients in the daratumumab group and in 38.7% of those in the control group), thrombocytopenia (in 34.4% and 37.6%, respectively), and anemia (in 15.9% and 19.8%, respectively). The rate of grade 3 or 4 infections was 23.1% in the daratumumab group and 14.7% in the control group; the rate of treatment discontinuation due to infections was 0.9% and 1.4%, respectively. Daratumumab-associated infusion-related reactions occurred in 27.7% of the patients.

CONCLUSIONS

Among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation, daratumumab combined with bortezomib, melphalan, and prednisone resulted in a lower risk of disease progression or death than the same regimen without daratumumab. The daratumumab-containing regimen was associated with more grade 3 or 4 infections. (Funded by Janssen Research and Development; ALCYONE ClinicalTrials.gov number, NCT02195479.)

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*A complete list of investigators in the ALCYONE trial is provided in the Supplementary Appendix, available at NEJM.org.

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The risk of multiple myeloma increases with age,[1-3] and despite progress in the development of effective treatment, the disease remains incurable.[4-7] The most widely approved regimens for elderly patients are lenalidomide plus dexamethasone[8] and — outside the United States — melphalan, prednisone, and thalidomide[9] and melphalan, prednisone, and bortezomib.[10] These regimens are associated with a progression-free survival of 18 months to 2 years and an overall survival of 4 to 5 years.[10-12]

Daratumumab is a human IgGκ monoclonal antibody that targets CD38. Its multifaceted mechanisms of action include direct antitumor effects[13-15] and an immunomodulatory component that results in depletion of immunosuppressive cells and clonal expansion of cytotoxic T cells.[16]

In patients with at least one previous line of therapy, daratumumab plus standard-of-care regimens (bortezomib–dexamethasone [CASTOR trial][17] and lenalidomide–dexamethasone [POLLUX trial][18]) significantly prolonged progression-free survival and induced higher response rates. These daratumumab-based combinations reduced the risk of disease progression or death by more than 60%.[17,18]

The VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone) trial established fixed-duration treatment with bortezomib, melphalan, and prednisone as an effective therapy for patients with newly diagnosed multiple myeloma who are ineligible for stem-cell transplantation.[10] The GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto)[9] and PETHEMA (Programa Español de Tratamientos en Hematología)[19] trials improved dosing by reducing toxicity without sacrificing efficacy. Treatment with daratumumab plus bortezomib, melphalan, and prednisone was evaluated in a phase 1 safety trial.[20] In this article, we report a prespecified interim analysis of this randomized, phase 3 trial (ALCYONE) of bortezomib, melphalan, and prednisone with or without daratumumab in patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation.

METHODS

TRIAL DESIGN AND OVERSIGHT

This multicenter, randomized, open-label, active-controlled phase 3 trial enrolled patients between February 9, 2015, and July 14, 2016, at 162 sites in 25 countries across North and South America, Europe, and the Asia–Pacific region. Independent ethics committees or institutional review boards at each site approved the protocol (available with the full text of this article at NEJM.org). The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice guidelines. All the patients provided written informed consent. Janssen Research and Development sponsored this trial and designed it in collaboration with the academic authors. Data were compiled and maintained by the sponsor. Authors were given access to the data and were not restricted by confidentiality agreements. Professional medical writers who were funded by the sponsor prepared the manuscript. All the authors reviewed and revised the manuscript and approved it for submission. The sponsor and authors vouch for the accuracy and completeness of the data from the prespecified interim analysis and for the adherence of the trial to the protocol.

A Quick Take is available at NEJM.org

PATIENTS

We recruited patients with newly diagnosed, documented multiple myeloma[21] who were not eligible for high-dose chemotherapy with stem-cell transplantation owing to coexisting conditions or an age of 65 years or older. These patients had a hemoglobin level of 7.5 g or more per deciliter, an absolute neutrophil count of 1.0×10^9 or more per liter, aspartate aminotransferase and alanine aminotransferase levels of 2.5 or fewer times the upper limit of the normal range, a total bilirubin level of 1.5 or fewer times the upper limit of the normal range, a creatinine clearance of 40 ml or more per minute, a corrected serum calcium level of 14 mg or less per deciliter (≤3.5 mmol per liter), a platelet count of 70×10^9 or more per liter (if <50% of bone marrow nucleated cells were plasma cells; otherwise, platelet count of $>50\times10^9$ per liter), and an Eastern Cooperative Oncology Group performance status of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability).

We excluded patients with primary amyloidosis, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, Waldenström's macroglobulinemia (or other conditions in which IgM paraprotein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions), previous systemic therapy

or stem-cell transplantation, cancer within 3 years before randomization (exceptions were squamous-cell and basal-cell carcinomas of the skin, carcinoma in situ of the cervix, and any cancer that was considered to be cured with minimal risk of recurrence within 3 years), peripheral neuropathy, or grade 2 or higher neuropathic pain (as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], version 4).

TRIAL TREATMENTS

Patients were randomly assigned by means of an interactive Web-response system in a 1:1 ratio to daratumumab in combination with bortezomib, melphalan, and prednisone (daratumumab group) or bortezomib, melphalan, and prednisone alone (control group) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Randomization was stratified according to International Staging System (ISS) disease stage (I, II, or III, with higher stages indicating a poorer prognosis; stages are determined on the basis of albumin and β_2-microglobulin levels), geographic region (Europe vs. other), and age (<75 years vs. ≥75 years). Treatment assignments were not blinded.

All the patients received up to nine (42-day) cycles of subcutaneous bortezomib (1.3 mg per square meter of body-surface area, twice weekly on weeks 1, 2, 4, and 5 of cycle 1 and once weekly on weeks 1, 2, 4, and 5 of cycles 2 through 9), oral melphalan (9 mg per square meter, once daily on days 1 through 4 of each cycle), and oral prednisone (60 mg per square meter, once daily on days 1 through 4 of each cycle). In the experimental group, intravenous daratumumab at a dose of 16 mg per kilogram of body weight was administered with oral or intravenous dexamethasone (to manage infusion reactions; see the Supplementary Appendix) at a dose of 20 mg once weekly in cycle 1, every 3 weeks in cycles 2 through 9, and every 4 weeks thereafter until disease progression or unacceptable toxic effects. Dexamethasone at a dose of 20 mg was substituted for prednisone on day 1 of each cycle.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, defined as the time from randomization to either disease progression or death. Key efficacy secondary end points were the overall response rate and the rates of very good partial response or better (comprising very good partial, complete, and stringent complete responses) (Table S1 in the Supplementary Appendix), complete response or better (comprising complete and stringent complete responses), negative status for minimal residual disease (at a threshold of 1 tumor cell per 10^5 white cells),[22] and overall survival. Other end points were safety, side-effect profile, time to response, and duration of response. Progressive disease was defined according to International Myeloma Working Group criteria.[23,24] Definitions of these end points are provided in the Supplementary Appendix.

Efficacy assessments, based on biochemical variables that included serum and urine monoclonal proteins and serum free light chains, were performed at a central laboratory. Samples were collected every 3 weeks during the first year after randomization, every 4 weeks during the second year, and every 8 weeks thereafter until disease progression. If daratumumab interference with serum paraprotein assessment was suspected (i.e., IgGκ-positive samples), immunofixation reflex assays were performed to confirm complete responses.[25] Minimal residual disease was assessed by means of an Adaptive Biotechnologies clonoSEQ next-generation sequencing assay (version 2.0) with the use of bone marrow aspirate collected at screening, at the time of confirmation of complete response or stringent complete response, and at 12, 18, 24, and 30 months after the first dose in patients having a complete response or stringent complete response (see the Supplementary Appendix). Safety assessments included evaluation of adverse events graded in accordance with the NCI CTCAE (version 4), clinical laboratory testing, electrocardiograms, measurement of vital signs, and physical examinations.[26]

STATISTICAL ANALYSIS

The primary analysis population was the intention-to-treat population of all the patients who underwent randomization. The safety population comprised patients who received any dose of trial treatment. Continuous variables were summarized with descriptive statistics, and categorical variables were summarized in frequency tables. Time-to-event variables were evaluated with the Kaplan–Meier method. Response to trial treatment was determined with the use of a validated

computer algorithm, as described previously.[17,18] Binary end points, such as response rate, were assessed with a stratified Cochran–Mantel–Haenszel test, and an odds ratio and two-sided 95% confidence interval were calculated. If the between-group difference in the primary end point was significant at the time of the second interim analysis, the efficacy secondary end points of overall response rate and rates of very good partial response or better, complete response or better, and negative status for minimal residual disease, as ordered here, were sequentially tested, each with an overall two-sided alpha level of 0.05.

Of two planned interim analyses, the first evaluated only safety after 100 patients had received at least two treatment cycles or had discontinued treatment. The second, reported here, assessed safety and efficacy when 231 events of disease progression or death had occurred (i.e., 64% of the planned 360 events for the final analysis; an alpha of 0.0103 was spent). The final overall survival analysis will occur after 330 deaths.

A sample size of 350 patients per group (under the assumption of an annual dropout rate of 5%) was estimated to provide 85% power to detect a 27.6% lower risk of disease progression or death in the daratumumab group than in the control group, with the use of a log-rank test with a two-sided alpha level of 0.05. The primary efficacy end point was estimated with the Kaplan–Meier method, and the treatment effect (hazard ratio) and its two-sided 95% confidence interval were estimated with a stratified Cox regression model. Statistical significance was evaluated with a stratified log-rank test based on the predetermined alpha level at the clinical cutoff date. Additional statistical methods are described in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT

Of 706 patients, 350 were assigned to the daratumumab group and 356 to the control group. Demographic and clinical characteristics were generally well balanced between the two groups (Table 1, and Table S2 in the Supplementary Appendix). The median age at baseline was 71.0 years (range, 40 to 93), and the median time since diagnosis was 0.8 months (range, 0.1 to 25.3).

A total of 700 patients (346 in the daratumumab group and 354 in the control group) received the assigned intervention. At the clinical cutoff date (June 12, 2017), a total of 276 patients (79.8%) in the daratumumab group and 220 patients (62.1%) in the control group had completed all nine cycles of bortezomib, melphalan, and prednisone; 17 patients in each group were still receiving treatment with bortezomib, melphalan, and prednisone. Per protocol, all the patients in the control group discontinued treatment after nine cycles and all the patients in the daratumumab group continued daratumumab as monotherapy. During the first nine cycles, 19.4% of the patients in the daratumumab group and 33.1% of the patients in the control group discontinued treatment; a lower percentage of patients in the daratumumab group than in the control group discontinued treatment owing to disease progression (6.6% vs. 13.3%) and adverse events (4.9% vs. 9.3%), and a similar percentage discontinued treatment owing to death (3.2% and 2.3%, respectively). Beyond cycle 9, the most common reasons for discontinuation during daratumumab treatment were progressive disease (8.7%) and death (0.6%) (Fig. S2 in the Supplementary Appendix).

The median duration of treatment was 14.7 months (63.9 weeks) in the daratumumab group and 12.0 months (52.1 weeks) in the control group. The median relative dose intensity (the sum of all doses received in all cycles divided by the number of treatment cycles) of bortezomib and melphalan was the same in both treatment groups (bortezomib, 5.5 mg per square meter per cycle [of a maximum potential dose of 10.4 mg per square meter in cycle 1 and 5.2 mg per square meter per cycle in cycles 2 through 9]; melphalan, 35.0 mg per square meter per cycle [of a maximum potential dose of 36 mg per square meter per cycle]). In the daratumumab group, prednisone equivalents were calculated because other glucocorticoids were also used. The median equivalent dose intensity of prednisone in the daratumumab group was 251.8 mg per square meter per cycle, and the actual dose intensity in the control group was 237.3 mg per square meter per cycle (of a maximum potential prednisone dose of 240 mg per square meter per cycle). The median relative dose intensity of daratumumab was 30.9 mg per kilogram per cycle (95.7 mg per kilogram in cycle 1, 32.0 mg per

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

Characteristic	Daratumumab Group (N=350)	Control Group (N=356)
Age		
Median (range) — yr	71.0 (40–93)	71.0 (50–91)
Distribution — no. (%)		
<65 yr	36 (10.3)	24 (6.7)
65–74 yr	210 (60.0)	225 (63.2)
≥75 yr	104 (29.7)	107 (30.1)
ECOG performance status — no. (%)†		
0	78 (22.3)	99 (27.8)
1	182 (52.0)	173 (48.6)
2	90 (25.7)	84 (23.6)
ISS disease stage — no. (%)‡		
I	69 (19.7)	67 (18.8)
II	139 (39.7)	160 (44.9)
III	142 (40.6)	129 (36.2)
Cytogenetic profile — no./total no. (%)§		
Standard risk	261/314 (83.1)	257/302 (85.1)
High risk¶	53/314 (16.9)	45/302 (14.9)
Median time since initial diagnosis of multiple myeloma (range) — mo	0.8 (0.1–11.4)	0.8 (0.1–25.3)‖

* The intention-to-treat population was defined as all the patients who had undergone randomization. Post hoc analyses showed no significant differences between the two groups in the characteristics evaluated at baseline. Percentages may not sum to 100 because of rounding.

† Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.

‡ The International Staging System (ISS) disease stage is derived on the basis of the combination of serum β_2-microglobulin and albumin levels. Higher stages indicate more severe disease.

§ Cytogenetic risk was based on fluorescence in situ hybridization or karyotype testing. Cytogenetic data assessed by means of next-generation sequencing for the total intention-to-treat population were not available at the data cutoff date, and analysis is ongoing.

¶ These patients had at least one high-risk abnormality: del17p, t(4;14), or t(14;16).

‖ At the time of initial diagnosis, the patient with a time since initial diagnosis of multiple myeloma of 25.3 months did meet International Myeloma Working Group diagnostic criteria for multiple myeloma with a hemoglobin level of less than 10 g per deciliter and at least 10% plasma cells on examination of the bone marrow. A decision was made by the physician not to initiate treatment at the time of diagnosis. The patient's disease was stable and actively monitored until treatment was begun at a later date.

kilogram per cycle in cycles 2 through 9, and 16.0 mg per kilogram per cycle in cycles 10 or more). The median cumulative dose of bortezomib was 46.9 mg per square meter in the daratumumab group and 42.2 mg per square meter in the control group.

EFFICACY

The primary efficacy end point was progression-free survival. At the clinical cutoff date, an event of disease progression or death had occurred in 88 patients (25.1%) in the daratumumab group versus 143 patients (40.2%) in the control group. The hazard ratio for disease progression or death in the daratumumab group versus the control group was 0.50 (95% confidence interval [CI], 0.38 to 0.65; P<0.001) (Fig. 1). The Kaplan–Meier estimate of the 12-month rate of progression-free survival was 86.7% (95% CI, 82.6 to 89.9) in the daratumumab group and 76.0% (95% CI, 71.0 to 80.2) in the control group; the 18-month rate of progression-free survival was 71.6% (95% CI, 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group.

The median progression-free survival was not reached (95% CI, could not be estimated) in the daratumumab group versus 18.1 months (95% CI, 16.5 to 19.9) in the control group (P<0.001).

Prespecified subgroup analyses of progression-free survival showed that the superiority of daratumumab in combination with bortezomib, melphalan, and prednisone over bortezomib, melphalan, and prednisone alone was consistent across all subgroups, including patients 75 years of age or older and those with a poor prognosis (ISS disease stage III, renal impairment, or high-risk cytogenetic profile) (Fig. 2). Although the hazard ratio for disease progression or death in the daratumumab group was higher among patients with a high-risk cytogenetic profile (0.78) than among those with a standard-risk cytogenetic profile (0.39), the results still favored the daratumumab group over the control group; interpretation of the results in patients with a high-risk cytogenetic profile is limited because of the small number of patients.

Post hoc analyses of progression-free survival according to disease stage as defined by revised ISS criteria[27] showed results in patients with disease stage III (hazard ratio for disease progression or death, 0.75) (Table S3 in the Supplementary Appendix) that were similar to those in patients with a high-risk cytogenetic profile.

Prespecified key efficacy secondary end points were sequentially tested with the use of a hierarchical approach. The overall response rate was 90.9% in the daratumumab group and 73.9% in the control group (P<0.001) (Table 2). The rate of very good partial response or better was significantly higher in the daratumumab group than in the control group (71.1% vs. 49.7%, P<0.001), as was the rate of complete response or better (42.6% vs. 24.4%, P<0.001). Consistent with the higher rates of complete or stringent complete response, the rate of negative status for minimal residual disease (at a threshold of 1 tumor cell per 10^5 white cells) was more than 3 times as high in the daratumumab group as in the control group (22.3% vs. 6.2%, P<0.001). Negative status for minimal residual disease was associated with longer progression-free survival than positive status, irrespective of trial treatment. In patients with persistent minimal residual disease, progression-free survival was longer in the daratumumab group than in the control group (Fig. S3 in the Supplementary Appendix).

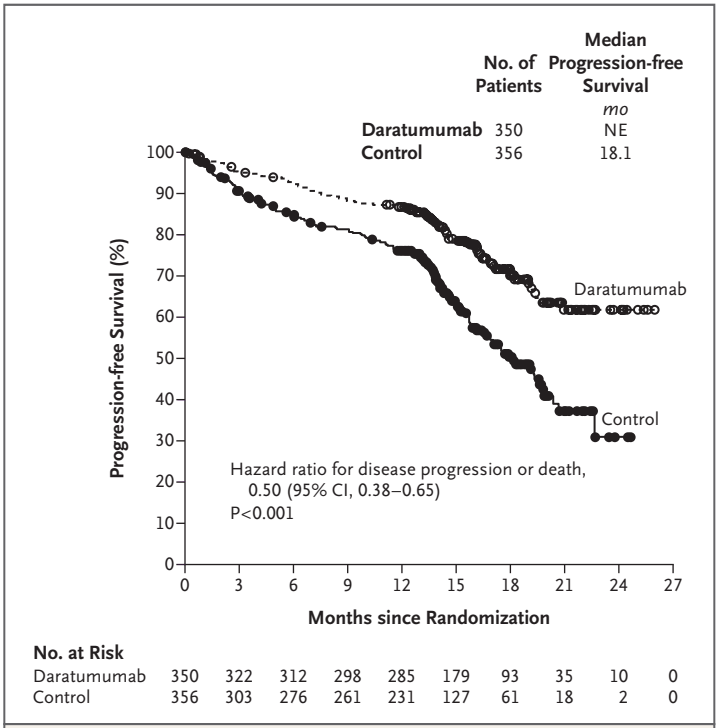

Figure 1. Progression-free Survival.

Shown are the results of the Kaplan–Meier estimates of progression-free survival among patients in the intention-to-treat population, which included all the patients who underwent randomization. The daratumumab group received treatment with daratumumab, bortezomib, melphalan, and prednisone; the control group received treatment with bortezomib, melphalan, and prednisone alone. The interim analysis of median progression-free survival was performed after 231 events of disease progression or death had occurred (64% of the planned 360 events for the final analysis); the results of the analysis crossed the prespecified stopping boundary. NE denotes could not be estimated.

The median time to response was 0.79 months in the daratumumab group and 0.82 months in the control group, and the median time to best response was 4.9 months and 4.1 months, respectively. The median duration of response was not reached (95% CI, could not be estimated) in the daratumumab group and 21.3 months (95% CI, 18.4 to could not be estimated) in the control group. The estimated percentage of patients who continued to have a response after 18 months was 77.2% in the daratumumab group and 60.4% in the control group.

At a median follow-up of 16.5 months, death had occurred in 45 patients in the daratumumab group and 48 patients in the control group (Fig. S4 in the Supplementary Appendix). The median overall survival was not reached in either group. Follow-up for long-term survival is ongoing.

Subgroup	Daratumumab Group	Control Group	Daratumumab Group	Control Group	Hazard Ratio (95% CI)
	no. of progression events or deaths/total no.		*median progression-free survival (mo)*		
Sex					
Male	50/160	68/167	NE	18.1	0.60 (0.42–0.87)
Female	38/190	75/189	NE	17.9	0.41 (0.28–0.61)
Age					
<75 yr	60/246	101/249	NE	17.9	0.49 (0.36–0.68)
≥75 yr	28/104	42/107	NE	20.4	0.53 (0.32–0.85)
Race					
White	79/297	121/304	NE	18.1	0.56 (0.42–0.74)
Other	9/53	22/52	NE	16.8	0.26 (0.12–0.57)
Geographic region					
Europe	80/289	121/295	NE	18.1	0.57 (0.43–0.76)
Other	8/61	22/61	NE	17.5	0.22 (0.10–0.50)
Baseline creatinine clearance					
≤60 ml/min	32/150	63/145	NE	16.9	0.36 (0.24–0.56)
>60 ml/min	56/200	80/211	NE	18.3	0.63 (0.45–0.88)
Baseline hepatic function					
Normal	73/301	115/303	NE	19.1	0.53 (0.40–0.71)
Impaired	15/46	28/52	NE	13.5	0.42 (0.22–0.80)
ISS disease stage					
I	12/69	18/67	NE	19.4	0.50 (0.24–1.05)
II	35/139	70/160	NE	17.5	0.49 (0.32–0.73)
III	41/142	55/129	NE	16.8	0.53 (0.35–0.79)
Type of multiple myeloma					
IgG	51/207	93/218	NE	17.4	0.45 (0.32–0.64)
Non-IgG	26/82	29/83	NE	NE	0.81 (0.48–1.37)
Cytogenetic profile at trial entry					
High risk	24/53	19/45	18.0	18.1	0.78 (0.43–1.43)
Standard risk	54/261	108/257	NE	17.4	0.39 (0.28–0.55)
ECOG performance status					
0	14/78	35/99	NE	19.4	0.40 (0.21–0.74)
1 or 2	74/272	108/257	NE	17.6	0.52 (0.39–0.70)

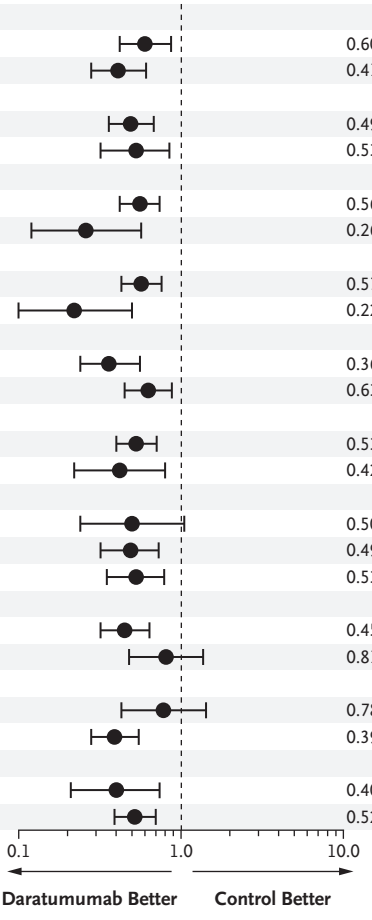

Figure 2. Prespecified Subgroup Analysis of Progression-free Survival.

Shown are the results of an analysis of progression-free survival in prespecified subgroups of the intention-to-treat population that were defined according to baseline characteristics. The daratumumab group received treatment with daratumumab, bortezomib, melphalan, and prednisone; the control group received treatment with bortezomib, melphalan, and prednisone alone. Race was determined by the investigator. Impaired baseline hepatic function includes mild impairment (total bilirubin level ≤ the upper limit of the normal range [ULN] and aspartate aminotransferase level > the ULN, or total bilirubin level > the ULN and ≤1.5 times the ULN), moderate impairment (total bilirubin level >1.5 times and ≤3 times the ULN), and severe impairment (total bilirubin level >3 times the ULN). The International Staging System (ISS) consists of three stages, with higher stages indicating more severe disease: stage I, serum β_2-microglobulin level less than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g or more per deciliter; stage II, neither stage I nor III; and stage III, serum β_2-microglobulin level 5.5 mg or more per liter (≥470 nmol per liter). The subgroup analysis for the type of multiple myeloma was performed on data from patients who had measurable disease in serum. A high-risk cytogenetic profile was defined by a finding of t(4;14), t(14;16), or del17p on fluorescence in situ hybridization testing or a finding of t(4;14) or del17p on karyotype testing. Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. NE denotes could not be estimated.

SAFETY

The secondary objective of safety was evaluated with the use of adverse-event reporting. The most common adverse events of any grade (in ≥20% of the patients in either group) were neutropenia (in 49.7% of the patients in the daratumumab group and 52.5% of those in the control group), thrombocytopenia (in 48.8% and 53.7%, respectively), peripheral sensory neuropathy (in 28.3% and 34.2%, respectively), anemia (in 28.0% and 37.6%, respectively), upper respiratory tract infection (in 26.3% and 13.8%, respectively),

Table 2. Summary of Responses and Status Regarding Minimal Residual Disease.*

Variable	Daratumumab Group (N=350)	Control Group (N=356)	P Value
Overall response			
No. with response	318	263	—
Rate — % (95% CI)	90.9 (87.3–93.7)	73.9 (69.0–78.4)	<0.001†
Best overall response — no. (%)			
Complete response or better	149 (42.6)	87 (24.4)	<0.001†
Stringent complete response‡	63 (18.0)	25 (7.0)	—
Complete response	86 (24.6)	62 (17.4)	—
Very good partial response or better	249 (71.1)	177 (49.7)	<0.001†
Very good partial response	100 (28.6)	90 (25.3)	—
Partial response	69 (19.7)	86 (24.2)	—
Stable disease	20 (5.7)	76 (21.3)	—
Progressive disease	0	2 (0.6)	—
Response could not be evaluated	12 (3.4)	15 (4.2)	—
Negative status for minimal residual disease — no. (%)§	78 (22.3)	22 (6.2)	<0.001¶

* Response was assessed on the basis of International Myeloma Working Group recommendations (details on the criteria for disease responses are provided in the trial protocol). This analysis included patients who could be evaluated for response and 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. The following secondary end points were sequentially tested, each with an overall two-sided alpha level of 0.05, with the use of a hierarchical testing approach: overall response rate, rate of very good partial response or better, rate of complete response or better, and rate of negative status for minimal residual disease.

† The P value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test.

‡ Criteria for a stringent complete response included 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.

§ The threshold for minimal residual disease was defined as 1 tumor cell per 10^5 white cells. Status regarding minimal residual disease is based on postrandomization assessment conducted on bone marrow samples with the use of a validated next-generation sequencing assay (clonoSEQ Assay, version 2.0; Adaptive Biotechnologies) in accordance with International Myeloma Working Group guidelines on assessment of minimal residual disease.[22]

¶ The P value was calculated with the use of Fisher's exact test.

diarrhea (in 23.7% and 24.6%, respectively), pyrexia (in 23.1% and 20.9%, respectively), and nausea (in 20.8% and 21.5%, respectively) (Table 3, and Table S4 in the Supplementary Appendix). The most frequently reported adverse events of grade 3 or 4 (in ≥10% of patients in either group) were hematologic, including neutropenia (in 39.9% of the patients in the daratumumab group and 38.7% of those in the control group), thrombocytopenia (in 34.4% and 37.6%, respectively), and anemia (in 15.9% and 19.8%, respectively) (Table 3). The rate of grade 3 or 4 infections was higher in the daratumumab group than in the control group (23.1% vs. 14.7%); the most common grade 3 or 4 infection was pneumonia, with a higher rate in the daratumumab group than in the control group (11.3% vs. 4.0%) (Table 3). Most infections, including pneumonia, resolved (in 87.9% of the patients in the daratumumab group and 86.5% of those in the control group), and rates of discontinuation of trial treatment owing to infections did not differ substantially between the two groups (0.9% and 1.4%, respectively). One patient in each group (0.3%) discontinued trial treatment owing to pneumonia of any grade. Death due to infection occurred in five patients (1.4%) in the daratumumab group (two patients died from pneumonia, and one patient each died from peritonitis, septic shock, and upper respiratory tract infection) and in four patients (1.1%) in the control group (one patient each died from septic shock, candida-related sepsis, bacterial pneumonia, and sepsis).

Serious adverse events occurred in 41.6% of the patients in the daratumumab group and 32.5% of those in the control group. Pneumonia

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

Event	Daratumumab Group (N=346)		Control Group (N=354)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Hematologic adverse events				
Neutropenia	172 (49.7)	138 (39.9)	186 (52.5)	137 (38.7)
Thrombocytopenia	169 (48.8)	119 (34.4)	190 (53.7)	133 (37.6)
Anemia	97 (28.0)	55 (15.9)	133 (37.6)	70 (19.8)
Nonhematologic adverse events				
Peripheral sensory neuropathy	98 (28.3)	5 (1.4)	121 (34.2)	14 (4.0)
Diarrhea	82 (23.7)	9 (2.6)	87 (24.6)	11 (3.1)
Pyrexia	80 (23.1)	2 (0.6)	74 (20.9)	2 (0.6)
Nausea	72 (20.8)	3 (0.9)	76 (21.5)	4 (1.1)
Infections	231 (66.8)	80 (23.1)	170 (48.0)	52 (14.7)
Upper respiratory tract infection	91 (26.3)	7 (2.0)	49 (13.8)	5 (1.4)
Pneumonia	53 (15.3)	39 (11.3)	17 (4.8)	14 (4.0)
Second primary cancer†	8 (2.3)	NA	9 (2.5)	NA
Any infusion-related reaction	96 (27.7)	17 (4.9)	NA	NA

* The safety population included all the patients who received at least one dose of trial treatment. Adverse events of any grade that were reported in at least 20% of the patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 10% of the patients in either treatment group are listed. NA denotes not applicable.
† The presence of a second primary cancer was prespecified in the statistical analysis plan as an adverse event of clinical interest.

(in 10.1% and 3.1%, respectively) was the most common. The rate of discontinuation of trial treatment due to adverse events was lower in the daratumumab group (4.9%) than in the control group (9.0%).

Adverse events within 30 days after the last trial treatment leading to death occurred in 14 patients (4.0%) in the daratumumab group and 16 patients (4.5%) in the control group. Daratumumab-related infusion reactions (mostly of grade 1 or 2) occurred in 27.7% of the patients, with the majority during the first infusion (Table S5 in the Supplementary Appendix). Grade 3 infusion-related reactions occurred in 4.3% of the patients, and grade 4 reactions occurred in 0.6%. The number of patients with a second primary cancer was similar in the two groups: 8 patients (2.3%) in the daratumumab group and 9 patients (2.5%) in the control group. Tumor lysis syndrome was reported in 2 patients (0.6%) in each group.

DISCUSSION

In this phase 3 trial, daratumumab combined with bortezomib, melphalan, and prednisone resulted in significantly longer progression-free survival than bortezomib, melphalan, and prednisone alone and was associated with a 50% lower risk of disease progression or death among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation. Hierarchical testing of the key efficacy secondary end points supported the primary analysis, with significant differences in the depth of response. For example, the sum of the rates of complete response and of stringent complete response was nearly twice as high in the daratumumab group as in the control group, and the rate of negative status for minimal residual disease was more than three times as high.

Cross-trial comparisons have limitations, especially when inclusion criteria may vary on the

basis of the toxicity of the treatments given. However, the magnitude of benefit in the daratumumab group, as measured by the hazard ratio for disease progression or death (0.50), compares favorably with that in other randomized trials involving patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation — specifically, the VISTA trial (hazard ratio, 0.61)[28] and the FIRST (Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide) trial of lenalidomide and dexamethasone (hazard ratio, 0.72).[8] In addition, median progression-free survival in the control group (18.1 months) was consistent with that in the group receiving bortezomib, melphalan, and prednisone in the VISTA trial (18.3 months).[10,28]

Of the patients receiving daratumumab, 42.6% had a complete response or better and 18.0% had a stringent complete response. Furthermore, 22.3% of the patients were negative for minimal residual disease. In this trial, negative status for minimal residual disease was associated with longer progression-free survival than positive status, irrespective of trial treatment. These results are consistent with those of the CASTOR[29] and POLLUX trials[18] and of the IFM (Intergroupe Francophone du Myélome) 2009 Study[30] of lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation.

Although patients with a high-risk cytogenetic profile benefited from daratumumab treatment, those with a standard-risk cytogenetic profile had a lower hazard ratio for disease progression or death. It should be noted that cytogenetic data were assessed at each site per local practice.

Combining daratumumab with bortezomib, melphalan, and prednisone did not increase overall toxicity. Except for infection, adverse events were balanced between the daratumumab and control groups, with a lower rate of peripheral sensory neuropathy in the daratumumab group.

Our trial shows that the combination of daratumumab with bortezomib, melphalan, and prednisone resulted in significant clinical benefits as compared with bortezomib, melphalan, and prednisone alone in patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation. Overall, daratumumab in combination with this standard-of-care regimen was associated with infusion-related reactions and more infections, including a higher rate of pneumonia (which did not result in higher rates of discontinuation or death); the usual chemotherapy-related toxic effects were not increased by the addition of daratumumab.

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APPENDIX

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