Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma

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Abstract

BACKGROUND—Lenalidomide plus dexamethasone is a standard treatment for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation. We sought to determine whether the addition of daratumumab would significantly reduce the risk of disease progression or death in this population.

METHODS—We randomly assigned 737 patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation to receive daratumumab plus lenalidomide and dexamethasone (daratumumab group) or lenalidomide and dexamethasone alone (control group). Treatment was to continue until the occurrence of disease progression or unacceptable side effects. The primary end point was progression-free survival.

RESULTS—At a median follow-up of 28.0 months, disease progression or death had occurred in 240 patients (97 of 368 patients [26.4%] in the daratumumab group and 143 of 369 patients [38.8%] in the control group). The estimated percentage of patients who were alive without disease progression at 30 months was 70.6% (95% confidence interval [CI], 65.0 to 75.4) in the daratumumab group and 55.6% (95% CI, 49.5 to 61.3) in the control group (hazard ratio for

disease progression or death, 0.56; 95% CI, 0.43 to 0.73; P<0.001). The percentage of patients with a complete response or better was 47.6% in the daratumumab group and 24.9% in the control group (P<0.001). A total of 24.2% of the patients in the daratumumab group, as compared with 7.3% of the patients in the control group, had results below the threshold for minimal residual disease (1 tumor cell per 10^5 white cells) (P<0.001). The most common adverse events of grade 3 or 4 were neutropenia (50.0% in the daratumumab group vs. 35.3% in the control group), anemia (11.8% vs. 19.7%), lymphopenia (15.1% vs. 10.7%), and pneumonia (13.7% vs. 7.9%).

CONCLUSIONS—Among patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation, the risk of disease progression or death was significantly lower among those who received daratumumab plus lenalidomide and dexamethasone than among those who received lenalidomide and dexamethasone alone. A higher incidence of neutropenia and pneumonia was observed in the daratumumab group. (Funded by Janssen Research and Development; MAIA ClinicalTrials.gov number, NCT02252172.)

Multiple myeloma is a hematologic cancer in which clonal plasma-cell proliferation leads to complications and death.[1] Initial treatment for newly diagnosed multiple myeloma depends on whether a patient may have unacceptable toxic effects from high-dose chemotherapy and may be unable to undergo autologous stem-cell transplantation.[1] Younger patients without substantial coexisting conditions usually receive an induction regimen followed by high-dose chemotherapy and autologous stem-cell transplantation.[2] For patients who are ineligible for stem-cell transplantation, multiagent regimens, including alkylating agents, glucocorticoids, immunomodulatory drugs, proteasome inhibitors, and new agents, are the standard of care.[2–5]

Daratumumab, a human IgGκ monoclonal antibody that targets CD38, has direct antitumor and immunomodulatory activity.[6–10] Initial approval of daratumumab as monotherapy for patients with heavily pretreated myeloma was based on the phase 1/2 GEN501 and SIRIUS trials.[11,12] Subsequently, daratumumab in combination with standard-of-care therapy showed clinical benefit across phase 3 trials involving patients with newly diagnosed myeloma (the ALCYONE trial) and patients with relapsed or refractory myeloma (the CASTOR and POLLUX trials).[13–15] In the POLLUX trial, treatment with daratumumab plus lenalidomide and dexamethasone resulted in a risk of disease progression or death that was 63% lower than the risk with lenalidomide and dexamethasone alone.[15] After a median follow-up of 44.3 months, the median progression-free survival was 44.5 months in the daratumumab group, as compared with 17.5 months in the control group, with no new safety concerns observed.[16]

In the phase 3 Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide (FIRST) trial[5,17] involving patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation, treatment with lenalidomide and dexamethasone administered until disease progression resulted in significantly longer overall survival than treatment with melphalan, prednisone, and thalidomide; these findings established the regimen of lenalidomide and dexamethasone as standard of care. Here, we report the results of a prespecified interim analysis of a phase 3 trial (MAIA) in which we assessed the efficacy and safety of daratumumab plus lenalidomide and dexamethasone as

compared with lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma who were ineligible for autologous stem-cell transplantation.

Methods

Trial Design and Oversight

In this randomized, open-label, phase 3 trial, patients were enrolled from March 2015 through January 2017 at 176 sites in 14 countries across North America, Europe, the Middle East, and the Asia–Pacific region. The independent ethics committee or institutional review board 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. The trial was designed by the authors in collaboration with the sponsor, Janssen Research and Development. The sponsor compiled and maintained the data and funded professional medical writers to prepare the manuscript for submission. The authors reviewed and approved the manuscript. The sponsor and the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Eligible patients had documented newly diagnosed multiple myeloma,[18] had an Eastern Cooperative Oncology Group performance status score of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability), and were ineligible for high-dose chemotherapy with stem-cell transplantation owing to age (65 years) or to the presence of coexisting conditions that were likely to result in the development of unacceptable side effects associated with high-dose chemotherapy with stem-cell transplantation. Other inclusion criteria were a hemoglobin level of 7.5 g or more per deciliter, an absolute neutrophil count of 1000 or more per cubic millimeter, a platelet count of 70,000 or more per cubic millimeter (>50,000 per cubic millimeter if 50% of nucleated bone marrow cells were plasma cells), aspartate aminotransferase and alanine aminotransferase levels no more than 2.5 times the upper limit of the normal range, a total bilirubin level no more than 2.0 times the upper limit of the normal range, creatinine clearance of 30 ml or more per minute, and a corrected serum calcium level of 14 mg or less per deciliter (3.5 mmol or less per liter). Additional eligibility criteria are listed in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND TREATMENT

Using an interactive Web-response system, we randomly assigned patients, in a 1:1 ratio, to receive daratumumab plus lenalidomide and dexamethasone (daratumumab group) or lenalidomide and dexamethasone alone (control group) (Fig. S1 in the Supplementary Appendix). Randomization was stratified according to International Staging System disease stage (I vs. II vs. III, with higher stages indicating more severe disease) (see Table S1 in the Supplementary Appendix for details on the staging criteria), geographic region (North America vs. other), and age (<75 vs. 75 years).

During each 28-day cycle, all the patients received oral lenalidomide (25 mg on days 1 through 21) and oral dexamethasone (40 mg on days 1, 8, 15, and 22) until disease progression or unacceptable toxic effects. For patients who had a creatinine clearance between 30 and 50 ml per minute, a reduced dose of lenalidomide (10 mg) was recommended. Adjustment of the dose of lenalidomide was recommended in the case of neutropenia and thrombocytopenia (Table S2 in the Supplementary Appendix). Patients who were older than 75 years of age or who had a body-mass index (the weight in kilograms divided by the square of the height in meters) of less than 18.5 received dexamethasone at a dose of 20 mg once weekly. Patients in the daratumumab group received intravenous daratumumab at a dose of 16 mg per kilogram of body weight once weekly during cycles 1 and 2, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter; preinfusion medications were administered approximately 1 hour before each daratumumab dose (details are provided in the Supplementary Appendix).

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, which was defined as the time from randomization to either disease progression or death. Secondary efficacy end points included the time to progression; the percentage of patients with a complete response (undetectable M-protein level on two consecutive serum and urine immunofixation tests and <5% plasma cells in bone marrow), a stringent complete response (complete response plus a normal free light-chain ratio and absence of clonal plasma cells, as assessed by immunofluorescence or immunohistochemical analysis or by two-color to four-color flow cytometry), negative status for minimal residual disease (at a threshold of 1 tumor cell per 10^5 white cells), overall response (including partial response, very good partial response, complete response, and stringent complete response), and a very good partial response (defined by a 90% reduction in serum M protein plus a urinary M-protein level of <100 mg per 24 hours) or better; overall survival; the time to response; the duration of response; efficacy in the subgroup of patients with a high-risk cytogenic profile (defined by a del17p, t[14;16], or t[4;14] abnormality [or a combination of these] on fluorescence in situ hybridization or karyotype analysis); and safety. Progressive disease was defined according to International Myeloma Working Group criteria (Table S3 in the Supplementary Appendix).[19,20] Complete definitions of these end points are provided in the Supplementary Appendix.

Serum samples and 24-hour urine samples were obtained for efficacy assessment every 28 days for 2 years and then every 8 weeks thereafter until disease progression; all samples were evaluated at a central laboratory. In the case of patients who had positive serum immunofixation and daratumumab interference, complete responses were confirmed with the use of reflex assays.[21] Minimal residual disease was evaluated by means of the Adaptive Biotechnologies clonoSEQ next-generation sequencing assay (version 2.0) with the use of bone marrow aspirate obtained at baseline, at the time of suspected complete or stringent complete response, and at 12, 18, 24, and 30 months after the first dose in patients who had a complete response or better. Safety assessments included the evaluation of adverse events, which were graded according to version 4 of the National Cancer Institute Common Terminology Criteria for Adverse Events[22]; electrocardiography; clinical laboratory testing; physical examinations; and vital signs.

STATISTICAL ANALYSIS

The primary analysis was performed in 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 the trial treatment. The primary end point of progression-free survival was compared between the treatment groups with the use of a stratified log-rank test, and the treatment effect (hazard ratio) and corresponding 95% confidence interval were estimated with the use of a stratified Cox regression model, with treatment as the sole explanatory variable. Other time-to-event efficacy end points were analyzed similarly. Response to trial treatment and progressive disease were evaluated with the use of a validated computer algorithm.[14,15] Continuous variables were summarized with the use of descriptive statistics, and categorical variables were summarized as numbers and percentages. Time-to-event variables were summarized with the use of the Kaplan–Meier method. We analyzed binary end points using a stratified Cochran–Mantel–Haenszel test. If the risk of the primary end point was found to be significantly lower in the daratumumab group than in the control group, the following secondary end points, as ordered here, were to be tested sequentially: complete response or better, very good partial response or better, negative status for minimal residual disease, overall response, and overall survival. The significance level was determined according to the alpha-spending function specific to each end point (see the Supplementary Appendix). For the evaluation of overall survival, a modified linear alpha-spending function was used to determine the alpha level at the time of each of three analyses (the second interim analysis, the primary progression-free survival analysis, and the final overall survival analysis). The alpha level was 0.0001 at the time of this first analysis.

Of two planned interim analyses, the first evaluated only safety after 100 patients had received at least 8 weeks of treatment or had discontinued treatment. The second, reported here, assessed safety and efficacy after 240 events of disease progression or death had occurred (i.e., 62% of the 390 planned events for the primary analysis). The final overall survival analysis is planned to be performed after 330 deaths have been reported. We estimated that a sample of 730 patients would provide the trial with 80% power to detect a risk of disease progression or death that was 25% lower with daratumumab plus lenalidomide and dexamethasone than with lenalidomide and dexamethasone alone, using a log-rank test at a two-sided alpha level of 0.05.

Results

PATIENTS AND TREATMENT

A total of 737 patients were randomly assigned — 368 to the daratumumab group and 369 to the control group. Demographic and clinical characteristics of the two groups were well balanced at baseline (Table 1). The median age was 73 years (range, 45 to 90), and 14.3% of patients had a high-risk cytogenetic profile. The median time since the diagnosis of multiple myeloma was 0.9 months (range, 0 to 14.5).

Among the patients who underwent randomization, 729 patients (364 in the daratumumab group and 365 in the control group) received at least one dose of the trial treatment (Fig.

S2 in the Supplementary Appendix). At the time of the clinical data cutoff for the primary analysis (September 24, 2018), a total of 118 patients (32.4%) in the daratumumab group and 207 patients (56.7%) in the control group had discontinued treatment, most commonly because of progressive disease (14.6% in the daratumumab group and 23.8% in the control group) and adverse events (7.4% and 16.2%, respectively). Patients who discontinued treatment for reasons other than disease progression and remained in the trial were followed for the primary end point.

The median duration of treatment was 25.3 months (range, 0.1 to 40.4) in the daratumumab group and 21.3 months (range, 0.03 to 40.6) in the control group, and the median number of treatment cycles was 27 (range, 1 to 44) in the daratumumab group and 22 (range, 1 to 43) in the control group (Table S4 in the Supplementary Appendix). The median relative dose intensity (see the Supplementary Appendix for definitions) for daratumumab was 98.4%. The median relative dose intensity for lenalidomide was 76.2% in the daratumumab group and 91.4% in the control group; 112 patients (30.8%) in the daratumumab group and 83 patients (22.7%) in the control group received 10 mg or less of the starting dose of lenalidomide. In addition, a higher percentage of patients in the daratumumab group than in the control group had dose modifications of lenalidomide owing to adverse events that occurred after the start of treatment, including lenalidomide discontinuations (20.9% and 17.0%, respectively) or dose delays, reductions, reescalations, or skipping (combined, 77.5% and 64.7%, respectively). The median relative dose intensity for dexamethasone was 84.2% in the daratumumab group and 90.7% in the control group.

A total of 35 patients in the daratumumab group discontinued treatment with lenalidomide and dexamethasone completely but continued to receive daratumumab monotherapy. The median duration of single-agent daratumumab treatment was 7.3 months (range, 0.03 to 31.2) among these patients.

EFFICACY

At a median follow-up of 28.0 months (range, 0 to 41.4), disease progression or death had occurred in 240 patients (97 of 368 patients [26.4%] in the daratumumab group and 143 of 369 patients [38.8%] in the control group). The Kaplan–Meier estimate of the percentage of patients who were alive without disease progression at 30 months was 70.6% (95% confidence interval [CI], 65.0 to 75.4) in the daratumumab group and 55.6% (95% CI, 49.5 to 61.3) in the control group. The median progression-free survival was not reached in the daratumumab group and was 31.9 months (95% CI, 28.9 to not reached) in the control group. The hazard ratio for disease progression or death in the daratumumab group as compared with the control group was 0.56 (95% CI, 0.43 to 0.73; P<0.001) (Fig. 1).

Prespecified subgroup analyses of progression-free survival confirmed the superiority of the daratumumab regimen over the control regimen across all subgroups, except in the subgroup of patients who had hepatic impairment at baseline (Fig. 2). The progression-free survival benefit was maintained among patients 75 years of age or older (hazard ratio, 0.63; 95% CI, 0.44 to 0.92).

In the intention-to-treat population, the percentage of patients with a complete response or better was significantly higher in the daratumumab group than in the control group (47.6% vs. 24.9%), as was the percentage with very good partial response or better (79.3% vs. 53.1%) (P<0.001 for both comparisons) (Table 2). The percentage of patients with an overall response was 92.9% in the daratumumab group and 81.3% in the control group (P<0.001).

The percentage of patients who were negative 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 (24.2% vs. 7.3%, P<0.001) (Table 2). Negative status for minimal residual disease was associated with longer progression-free survival than positive status, regardless of the trial treatment (Fig. S3 in the Supplementary Appendix). All the patients who were negative for minimal residual disease had a complete response or better.

At a median follow-up of 28.0 months, 138 patients had died — 62 (16.8%) in the daratumumab group and 76 (20.6%) in the control group (Fig. S4 in the Supplementary Appendix). The median overall survival was not reached in either group, and follow-up for long-term survival is ongoing.

Among the patients who had a response (partial response or better), 80.3% (95% CI, 75.1 to 84.5) in the daratumumab group and 65.7% (95% CI, 58.6 to 71.8) in the control group sustained the response for 30 months. The median time to the first response was 1.05 months in both groups, and the median time to a complete response or better was 10.4 months in the daratumumab group and 11.2 months in the control group. The percentage of patients who were negative for minimal residual disease increased over time at a higher rate in the daratumumab group than in the control group (Fig. S5 in the Supplementary Appendix).

SAFETY

Table 3 summarizes the most common adverse events of any grade (in >30% of patients in either group) and the most common adverse events of grade 3 or 4 (in >10% of patients in either group) during treatment in the safety population. The most common adverse events of grade 3 or 4 were neutropenia (50.0% in the daratumumab group and 35.3% in the control group), anemia (11.8% and 19.7%), lymphopenia (15.1% and 10.7%), pneumonia (13.7% and 7.9%), and leukopenia (11.0% and 4.9%). The incidence of infections of any grade was 86.3% in the daratumumab group and 73.4% in the control group; the incidence of grade 3 or 4 infections was 32.1% in the daratumumab group and 23.3% in the control group.

Serious adverse events were reported in 62.9% of the patients in the daratumumab group and in 62.7% of the patients in the control group. Pneumonia was the most common serious adverse event, occurring in 13.2% of the patients in the daratumumab group and in 7.4% of the patients in the control group. The percentage of patients who had adverse events that led to discontinuation of the trial treatment was 7.1% in the daratumumab group and 15.9% in the control group. Discontinuation of the trial treatment owing to an infection occurred in 0.5% of the patients in the daratumumab group and in 1.4% of the patients in the control group; no patients in the daratumumab group, as compared with 1 patient (0.3%) in the control group, discontinued treatment because of neutropenia.

Adverse events that resulted in death were observed in 25 patients (6.9%) in the daratumumab group and in 23 patients (6.3%) in the control group; the most common such event was pneumonia, which resulted in death in 0.5% and 0.8% of the patients, respectively. Invasive second primary cancers occurred in 12 patients (3.3%) in the daratumumab group (solid tumors in 2.7% and hematologic cancers in 0.5%) and in 13 patients (3.6%) in the control group (solid tumors in 3.0% and hematologic cancers in 0.5%).

Infusion-related reactions associated with daratumumab were reported in 40.9% of the patients in the daratumumab group; 2.7% of the patients had events of grade 3 or 4, including one patient who had grade 4 hypertension, and no grade 5 events were reported (Table S5 in the Supplementary Appendix). Infusion-related reactions usually occurred during administration of the first dose (in 98.0% of the patients who had such reactions), and only one patient (the patient who had grade 4 hypertension) discontinued daratumumab treatment after an infusion-related reaction.

Discussion

The results of this phase 3 trial showed that among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation, treatment with daratumumab plus lenalidomide and dexamethasone resulted in significantly longer progression-free survival than lenalidomide and dexamethasone alone; the risk of disease progression or death was 44% lower in the daratumumab group than in the control group. These findings can be added to those from a growing list of trials that support the use of daratumumab-based regimens across patient populations with multiple myeloma.[13–16,24,25] In our trial, the percentage of patients with a complete response or better was nearly twice as high and the percentage of patients who were negative for minimal residual disease was more than 3 times as high in the daratumumab group as in the control group; these findings are consistent with those of previous trials. We anticipate that responses in individual patients, including negative status for minimal residual disease, will deepen over time, as has been observed with other daratumumab-containing regimens.[26,27]

The results of this interim analysis showed that the benefit of daratumumab with respect to progression-free survival was not as high in the subgroup of patients who had a high-risk cytogenetic profile as it was in the subgroup of patients who had a standard-risk cytogenetic profile. However, in the CASTOR and POLLUX trials, among patients with relapsed or refractory multiple myeloma who had a high-risk cytogenetic profile, substantial benefits with respect to progression-free survival and minimal residual disease with daratumumab plus standard-of-care regimens were observed after a longer follow-up period.[16,25]

Cross-trial comparisons are limited by differences in patient populations and trial designs but are important to contextualize our findings. The phase 3 Southwest Oncology Group (SWOG) S0777 trial of lenalidomide plus dexamethasone with or without bortezomib in patients with newly diagnosed myeloma for whom immediate autologous stem-cell transplantation was not indicated showed that the triplet combination resulted in longer progression-free survival (median, 41 months vs. 29 months; hazard ratio, 0.74), including among patients who were 65 years of age or older (43% of the trial population; median, 34

months vs. 24 months) and among patients who were older than 75 years of age (median, 34 months vs. 17 months).[4,28] Our trial population was notably older; 99% of the patients were 65 years of age or older, and 44% were 75 years of age or older. The median progression-free survival benefit in the daratumumab group in our trial was maintained for patients 75 years of age or older (hazard ratio, 0.63); the hazard ratio observed in the FIRST trial — in which lenalidomide and dexamethasone administered until disease progression was compared with melphalan, prednisone, and thalidomide — was 0.78 in the subgroup of patients older than 75 years of age.[17] Progression-free survival was longer in the control group of our trial than in the similarly treated group in the FIRST trial, a finding that may be attributed to the longer median duration of treatment observed in the control group in our trial (21.3 months in our trial vs. 18.4 months in the FIRST trial).[5]

The median duration of treatment was longer in the daratumumab group than in the control group (25.3 months vs. 21.3 months). Although patients in the daratumumab group received treatment for a longer period of time, they received less lenalidomide than the control group, possibly owing to a higher incidence of adverse events that led to dose discontinuations or dose modifications in this group. Nevertheless, the efficacy of the daratumumab-based regimen was not affected by the lower dose of lenalidomide, as shown by the consistent progression-free survival benefit in the subgroup of patients who had a baseline creatinine clearance level of 60 ml or less per minute.

The daratumumab group had a higher incidence of neutropenia and infections (including pneumonia) than the control group. However, the incidence of grade 3 or 4 infections was 29% with lenalidomide and dexamethasone in the primary analysis of the FIRST trial,[5] which was consistent with the incidence in our trial (32.1% in the daratumumab group and 23.3% in the control group). The percentage of patients who discontinued treatment because of these adverse events was low in our trial and was consistent with the safety profile observed in the POLLUX and ALCYONE trials, the latter of which represents a similar population of patients with newly diagnosed myeloma who were ineligible for stem-cell transplantation.

In this trial involving patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation, the addition of daratumumab to lenalidomide and dexamethasone resulted in significantly longer progression-free survival, a higher response rate, an increased depth of response, and a longer duration of response than lenalidomide and dexamethasone alone. Daratumumab plus lenalidomide and dexamethasone was associated with a higher incidence of neutropenia and infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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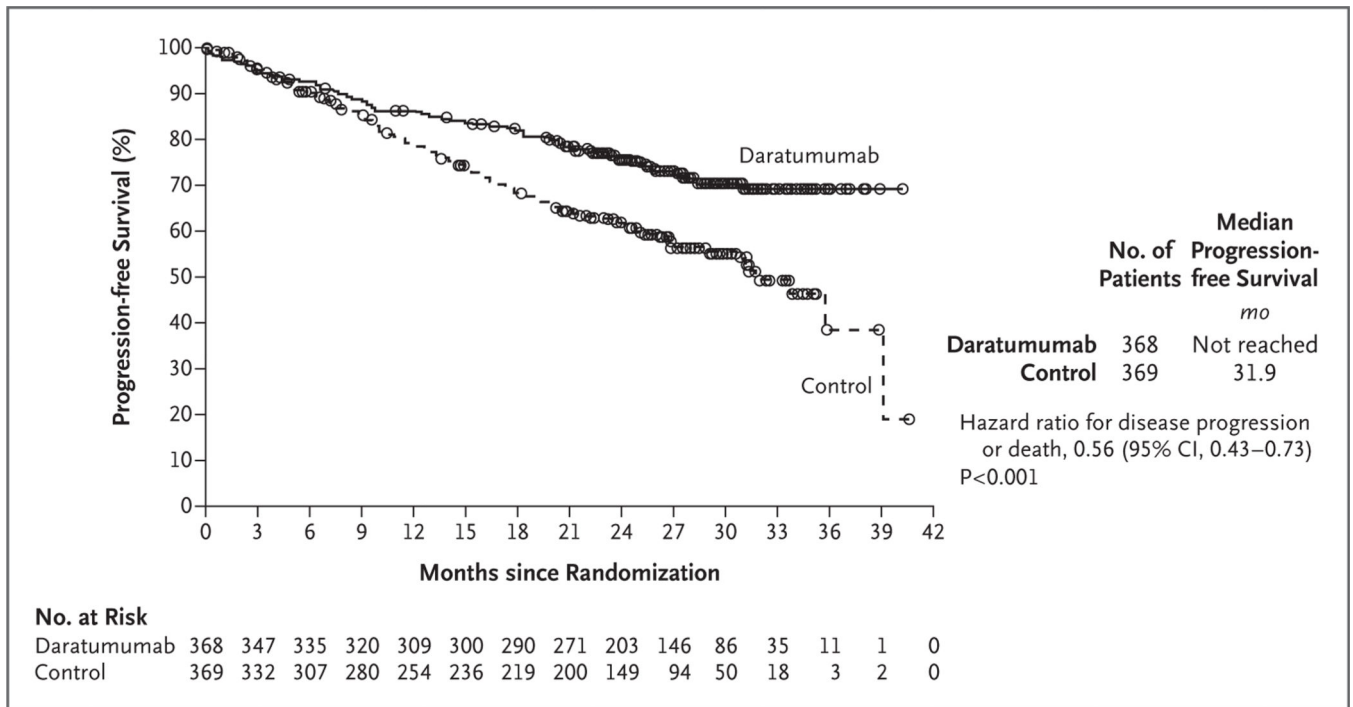
Figure 1. Progression-free Survival.

Shown are the results of the Kaplan–Meier estimates of progression-free survival among patients in the intention-to-treat population. The daratumumab group received treatment with daratumumab, lenalidomide, and dexamethasone; the control group received treatment with lenalidomide and dexamethasone. The interim analysis of progression-free survival was performed after 240 events of disease progression or death had occurred (62% of the planned 390 events for the final analysis).

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	56/189	72/195	NE	35.8		0.65 (0.46–0.93)
Female	41/179	71/174	NE	31.4		0.47 (0.32–0.69)
Age						
<75 yr	48/208	78/208	NE	33.7		0.50 (0.35–0.71)
≥75 yr	49/160	65/161	NE	31.9		0.63 (0.44–0.92)
Race						
White	86/336	128/339	NE	33.7		0.55 (0.42–0.72)
Other	11/32	15/30	NE	31.2		0.68 (0.31–1.49)
Geographic region						
North America	32/101	40/102	NE	31.4		0.65 (0.41–1.04)
Other	65/267	103/267	NE	31.9		0.52 (0.38–0.71)
ISS disease stage						
I	16/98	25/103	NE	35.8		0.59 (0.31–1.11)
II	40/163	69/156	NE	28.9		0.43 (0.29–0.64)
III	41/107	49/110	NE	24.9		0.72 (0.48–1.09)
Baseline creatinine clearance						
>60 ml/min	48/206	84/227	NE	33.7		0.52 (0.36–0.74)
≤60 ml/min	49/162	59/142	NE	31.2		0.60 (0.41–0.87)
Type of multiple myeloma						
IgG	63/225	77/231	NE	35.8		0.74 (0.53–1.03)
Non-IgG	19/74	42/76	NE	23.5		0.32 (0.18–0.55)
Cytogenetic profile						
High risk	18/48	17/44	NE	NE		0.85 (0.44–1.65)
Standard risk	67/271	111/279	NE	31.2		0.49 (0.36–0.67)
Baseline hepatic function						
Normal	83/335	132/340	NE	31.9		0.51 (0.39–0.68)
Impaired	14/31	11/29	NE	NE		1.08 (0.49–2.38)
ECOG score						
0	24/127	41/123	NE	35.8		0.49 (0.29–0.81)
1	53/178	69/187	NE	NE		0.63 (0.44–0.90)
≥2	20/63	33/59	NE	23.5		0.51 (0.29–0.89)

0.1 — 1.0 — 10.0

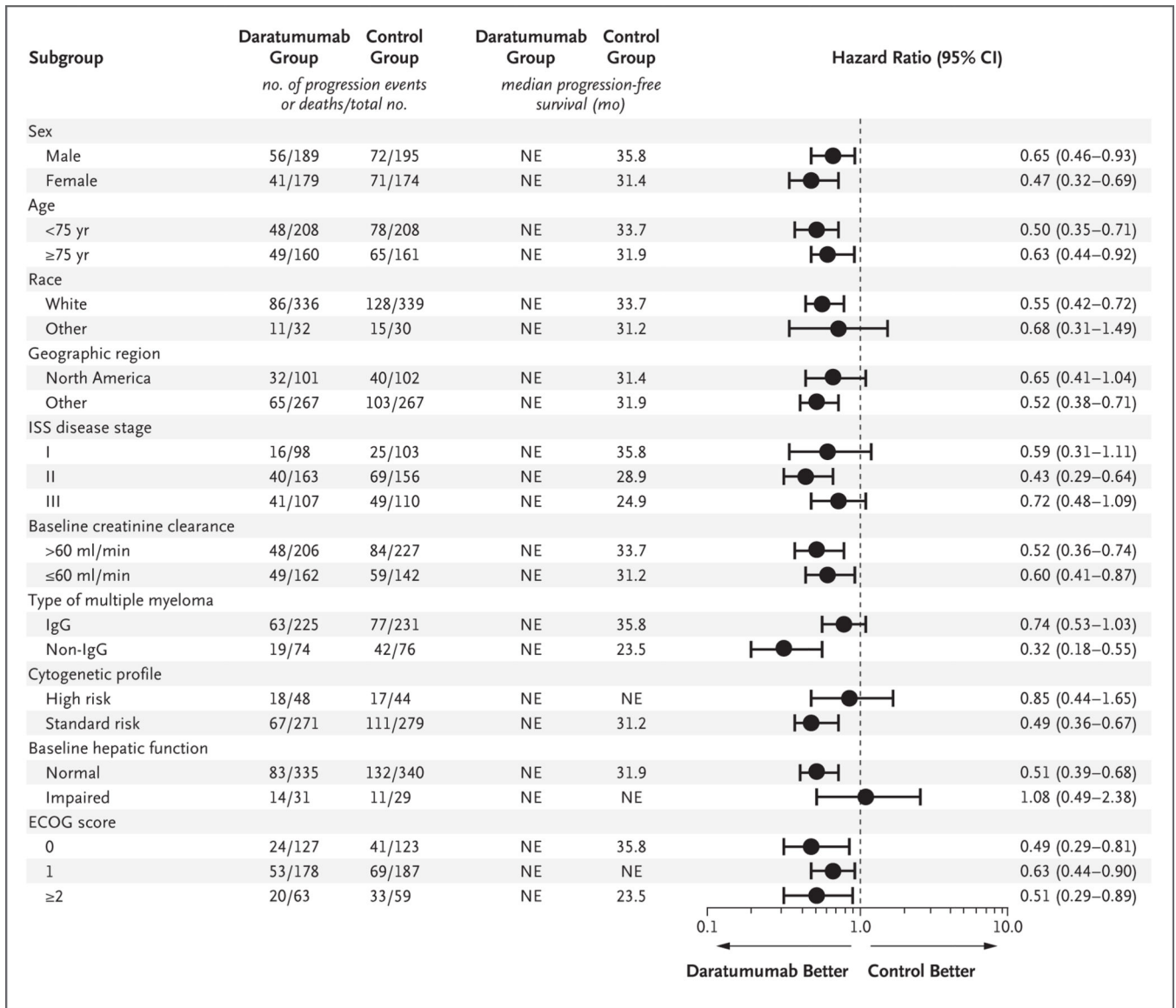← Daratumumab Better   Control Better →

Figure 2. Prespecified Subgroup Analysis of Progression-free Survival.
Shown are the results of an analysis of progression-free survival in prespecified subgroups in the intention-to-treat population. The daratumumab group received treatment with daratumumab, lenalidomide, and dexamethasone; the control group received treatment with lenalidomide and dexamethasone. The International Staging System (ISS) disease stage, which is derived on the basis of the combination of serum β_2-microglobulin and albumin levels, consists of three stages, with higher stages indicating more advanced disease. The subgroup analysis for the type of myeloma was performed on data from patients who had measurable disease in serum. A high-risk cytogenetic profile was defined by the detection of a del17p, t(14;16), or t(4;14) cytogenetic abnormality (or a combination of these) on fluorescence in situ hybridization or karyotype analysis. Impaired baseline hepatic function includes mild impairment (total bilirubin level less than or equal to the upper limit of the normal range [ULN] and aspartate aminotransferase level higher than the ULN, or total

bilirubin level higher than 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). 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.

Table 1.

Demographic and Baseline Disease Characteristics in the Intention-to-Treat Population.[*]

Characteristic	Daratumumab Group (N = 368)	Control Group (N = 369)
Median age (range) — yr	73.0 (50–90)	74.0 (45–89)
Age category — no. (%)		
<65 yr	4 (1.1)	4 (11)
65 to <70 yr	74 (20.1)	73 (19.8)
70 to <75 yr	130 (35.3)	131 (35.5)
75 yr	160 (43.5)	161 (43.6)
ECOG performance status — no. (%)[†]		
0	127 (34.5)	123 (33.3)
1	178 (48.4)	187 (50.7)
2[‡]	63 (17.1)	59 (16.0)
ISS disease stage — no. (%)[§]		
I	98 (26.6)	103 (27.9)
II	163 (44.3)	156 (42.3)
III	107 (29.1)	110 (29.8)
Type of measurable disease — no. (%)		
IgG	225 (61.1)	231 (62.6)
IgA	65 (17.7)	66 (17.9)
Other[¶]	9 (2.4)	10 (2.7)
Detected in urine only	40 (10.9)	34 (9.2)
Detected as serum free light-chain only	29 (7.9)	28 (7.6)
Cytogenetic profile — no./total no. (%)[‖]		
Standard risk	271/319 (85.0)	279/323 (86.4)
High risk	48/319 (15.0)	44/323 (13.6)
Median time since initial diagnosis of multiple myeloma (range) — mo	0.95 (0.1–13.3)	0.89 (0–14.5)

[*] The intention-to-treat population included all patients who underwent randomization. Post hoc analyses showed no significant differences between the two groups in the characteristics evaluated at baseline.

[†] 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.

[‡] Two patients had a score of greater than 2 (one patient had a score of 3, and another patient had a score of 4).

[§] The International Staging System (ISS) disease stage, which is derived on the basis of the combination of serum β_2-microglobulin and albumin levels, consists of three stages. Higher stages indicate more severe disease.

[¶] This category includes IgD, IgE, IgM, and biclonal.

[‖] Cytogenetic risk was based on fluorescence in situ hybridization or karyotype analysis; patients who had a high-risk cytogenetic profile had at least one high-risk abnormality (del17p, t[14;16], or t[4;14]).

Table 2.

Summary of Response Rates and Minimal Residual Disease Status in the Intention-to-Treat Population.[*]

Variable	Daratumumab Group (N = 368)	Control Group (N = 369)	P Value
Overall response — no. (% [95% CI])	342 (92.9 [89.8–95.3])	300 (81.3 [76.9–85.1])	<0.001[†]
Best overall response — no. (%)			
Complete response or better	175 (47.6)	92 (24.9)	<0.001[†]
Stringent complete response[‡]	112 (30.4)	46 (12.5)	—
Complete response	63 (17.1)	46 (12.5)	—
Very good partial response or better	292 (79.3)	196 (53.1)	<0.001[†]
Very good partial response	117 (31.8)	104 (28.2)	—
Partial response	50 (13.6)	104 (28.2)	—
Stable disease	11 (3.0)	56 (15.2)	—
Progressive disease	1 (03)	0	—
Response could not be evaluated	14 (3.8)	13 (3.5)	—
Negative status for minimal residual disease — no. (%)[§]	89 (24.2)	27 (7.3)	<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 protocol). The following secondary end points were tested sequentially, each with an overall two-sided alpha level of 0.05, with the use of a hierarchical testing approach: complete response or better, very good partial response or better, negative status for minimal residual disease, and overall response.

[†] The P value was 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 immunofluorescence or immunohistochemical 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 a postrandomization assessment performed 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.[23]

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

Table 3.

Most Common Adverse Events and Second Primary Cancers Reported during Treatment in the Safety Population.[*]

Event	Daratumumab Group (N = 364)		Control Group (N = 365)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Hematologic adverse events				
Neutropenia	207 (56.9)	182 (50.0)	154 (42.2)	129 (35.3)
Anemia	126 (34.6)	43 (11.8)	138 (37.8)	72 (19.7)
Leukopenia	68 (18.7)	40 (11.0)	34 (9.3)	18 (4.9)
Lymphopenia	66 (18.1)	55 (15.1)	45 (12.3)	39 (10.7)
Nonhematologic adverse events				
Infections	314 (86.3)	117 (32.1)	268 (73.4)	85 (23.3)
Pneumonia	82 (22.5)	50 (13.7)	46 (12.6)	29 (7.9)
Diarrhea	207 (56.9)	24 (6.6)	168 (46.0)	15 (4.1)
Constipation	149 (40.9)	6 (1.6)	130 (35.6)	1 (03)
Fatigue	147 (40.4)	29 (8.0)	104 (28.5)	14 (3.8)
Peripheral edema	140 (38.5)	7 (19)	107 (29.3)	2 (0.5)
Back pain	123 (33.8)	11 (3.0)	96 (26.3)	11 (3.0)
Asthenia	117 (32.1)	16 (4.4)	90 (24.7)	13 (3.6)
Nausea	115 (31.6)	5 (14)	84 (23.0)	2 (0.5)
Second primary cancer[†]	32 (8.8)	NA	26 (7.1)	NA
Invasive second primary cancer	12 (3.3)	NA	13 (3.6)	NA
Any infusion-related reaction	149 (40.9)	10 (2.7)	NA	NA

[*]
The safety population included all patients who received at least one dose of the trial treatment. Adverse events of any grade that were reported in more than 30% of patients in either treatment group and grade 3 or 4 adverse events that were reported in more than 10% of 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.