ORIGINAL ARTICLE

Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma

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ABSTRACT

BACKGROUND

Multiple myeloma cells uniformly overexpress CD38. We studied daratumumab, a CD38-targeting, human IgG1κ monoclonal antibody, in a phase 1–2 trial involving patients with relapsed myeloma or relapsed myeloma that was refractory to two or more prior lines of therapy.

METHODS

In part 1, the dose-escalation phase, we administered daratumumab at doses of 0.005 to 24 mg per kilogram of body weight. In part 2, the dose-expansion phase, 30 patients received 8 mg per kilogram of daratumumab and 42 received 16 mg per kilogram, administered once weekly (8 doses), twice monthly (8 doses), and monthly for up to 24 months. End points included safety, efficacy, and pharmacokinetics.

RESULTS

No maximum tolerated dose was identified in part 1. In part 2, the median time since diagnosis was 5.7 years. Patients had received a median of four prior treatments; 79% of the patients had disease that was refractory to the last therapy received (64% had disease refractory to proteasome inhibitors and immunomodulatory drugs and 64% had disease refractory to bortezomib and lenalidomide), and 76% had received autologous stem-cell transplants. Infusion-related reactions in part 2 were mild (71% of patients had an event of any grade, and 1% had an event of grade 3), with no dose-dependent adverse events. The most common adverse events of grade 3 or 4 (in ≥5% of patients) were pneumonia and thrombocytopenia. The overall response rate was 36% in the cohort that received 16 mg per kilogram (15 patients had a partial response or better, including 2 with a complete response and 2 with a very good partial response) and 10% in the cohort that received 8 mg per kilogram (3 had a partial response). In the cohort that received 16 mg per kilogram, the median progression-free survival was 5.6 months (95% confidence interval [CI], 4.2 to 8.1), and 65% (95% CI, 28 to 86) of the patients who had a response did not have progression at 12 months.

CONCLUSIONS

Daratumumab monotherapy had a favorable safety profile and encouraging efficacy in patients with heavily pretreated and refractory myeloma. (Funded by Janssen Research and Development and Genmab; ClinicalTrials.gov number, NCT00574288.)

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Current therapies, including proteasome inhibitors and immunomodulatory agents, have improved outcomes substantially in patients with multiple myeloma.[1] Unfortunately, the majority of these patients have a relapse and have limited treatment options after exposure to these classes of agents.[2,3] Patients with disease that is refractory to both proteasome inhibitors and immunomodulatory drugs have poor prognoses; the estimated median overall survival is 9 months, and the estimated event-free survival is 5 months at best.[2,3]

CD38 is a 45-kD, type II transmembrane glycoprotein that associates with cell-surface receptors in lipid rafts, regulates cytoplasmic Ca^{2+} flux, and mediates signal transduction in lymphoid and myeloid cells.[4,5] CD38 is highly and uniformly expressed on myeloma cells[6,7] and is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of nonhematopoietic origin, which makes it a potential target in the treatment of myeloma.[5]

Daratumumab (HuMax-CD38, Genmab), a human IgG1κ monoclonal antibody, binds to a unique CD38 epitope.[8] Preclinical studies showed that daratumumab induced target-cell killing of CD38-expressing tumor cells by means of multiple mechanisms, including complement-mediated and antibody-dependent cell-mediated cytotoxic effects, antibody-dependent cellular phagocytosis, apoptosis,[8,9] and to a lesser extent, inhibition of the enzymatic activity of CD38.[10] The antimyeloma activity of daratumumab in preclinical studies prompted the initiation of this phase 1–2 study involving patients with relapsed myeloma or relapsed and refractory myeloma.

Methods

Patients

Eligible patients had myeloma requiring systemic therapy and had had a relapse after, or had disease that was refractory to, two or more different prior therapies, including immunomodulatory agents, proteasome inhibitors, chemotherapy, and autologous stem-cell transplantation. Patients were 18 years of age or older, had a life expectancy of at least 3 months, an Eastern Cooperative Oncology Group performance-status score of 2 or less (on a scale from 0 to 5, with 0 indicating no symptoms and higher numbers indicating increasing disability), and a measurable level of M protein or free light chains (or both) according to the International Myeloma Working Group (IMWG) guidelines.[11] Exclusion criteria were an absolute neutrophil count of less than 1000 per cubic millimeter, a platelet count of less than 75×10^9 per liter, a serum creatinine level greater than 2 times the upper limit of the normal range, alanine aminotransferase and alkaline phosphatase levels greater than 3.5 times the upper limit of the normal range, a bilirubin level greater than 2.5 times the upper limit of the normal range, a hemoglobin level of less than 7.5 g per deciliter, other malignant conditions, uncontrolled infections, clinically significant cardiovascular and respiratory conditions, and meningeal involvement of myeloma.

Study Design

The study was a two-part, phase 1–2, open-label, multicenter trial. Part 1 was a dose-escalation study, and part 2 was a dose-expansion study (Fig. 1). The ethics committee or institutional review board at each study site approved the study protocol and the statistical analysis plan (both of which are available with the full text of this article at NEJM.org). The study 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.

Study Treatments

In part 1, the dose-escalation study, patients in 10 cohorts received doses of 0.005 to 24 mg of daratumumab per kilogram of body weight. The study had a 1+3 design in the 2 lowest-dose cohorts and a 3+3 design in each of the remaining 8 cohorts (Fig. 1A). If a dose-limiting toxic event occurred in one patient in the first 2 cohorts that included one patient, or in one of three patients in the subsequent 8 cohorts, an additional three patients were treated at the same dose.

All the patients in part 1 received a predose (10% of the full dose but not more than 10 mg in total) before the first full dose; after the first full dose, there was a 3-week washout period for assessment of safety and pharmacokinetics. A second predose was then administered, followed by six full infusions administered weekly, making the total treatment period 8 weeks long (Fig. 1A).

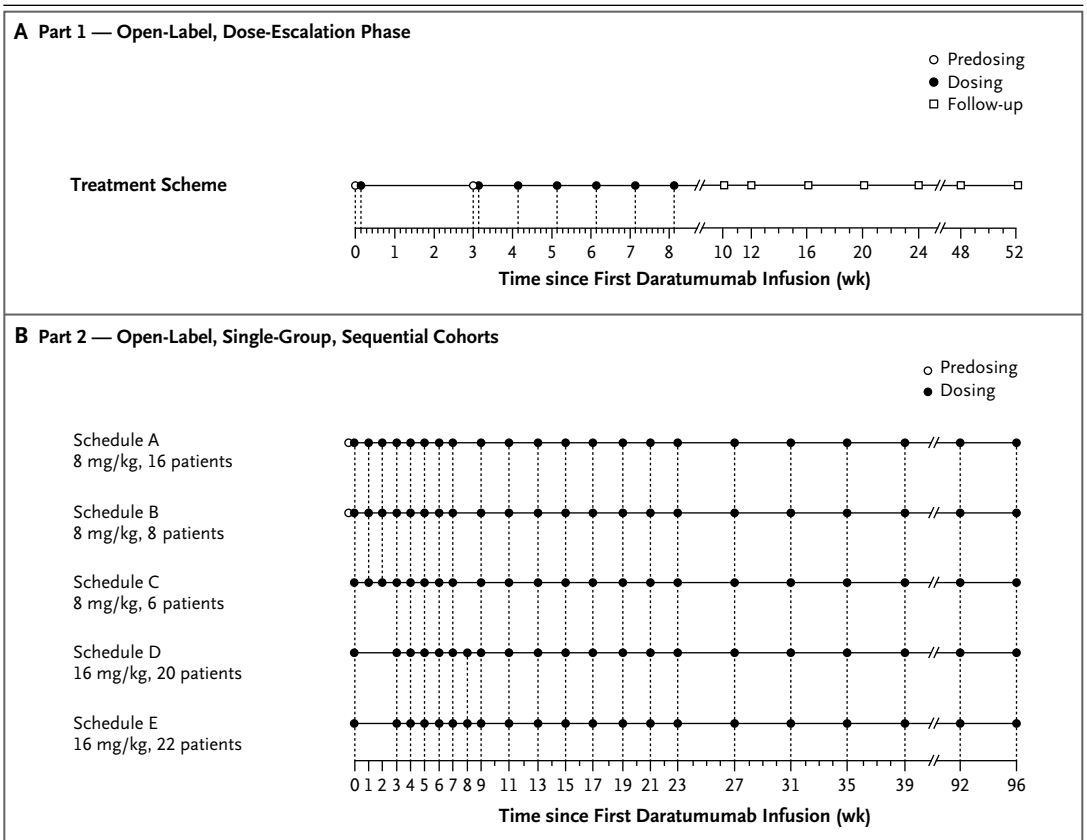


Figure 1. Trial Design.

Part 1, a dose-escalation phase, included 10 dose cohorts (0.005, 0.05, 0.1, 0.5, 1, 2, 4, 8, 16, and 24 mg per kilogram) (Panel A). The two lowest-dose cohorts (0.005 and 0.05 mg per kilogram) had a 1+3 design, and the other eight cohorts (0.1, 0.5, 1, 2, 4, 8, 16, and 24 mg per kilogram) had a 3+3 design. Part 2, a dose-expansion phase, included five dosing schedules (Panel B). Patients who received the schedule A, B, or C regimen received 8 mg per kilogram, and those who received the schedule D or E regimen received 16 mg per kilogram. The first full infusion of 500 ml (diluted in sterile, pyrogen-free 0.9% sodium chloride) had a 4-hour duration in schedule A and a 6-hour duration in schedule B. In schedules C, D, and E, the first full infusion was 1000 ml over a period of 6 hours. In the absence of infusion-related reactions during the first 3 hours of the first infusion, the second dose was administered in 500 ml over a period of 3.25 to 4 hours (schedules A, B, and C) or 1000 ml over a period of 6 hours (schedules D and E). All subsequent infusions were 500 ml over a period of 3.25 to 4 hours. Schedule E evaluated a phase 3 drug product (commercial product) that is produced with a larger-scale manufacturing process. All other schedules used the phase 2 drug product. Patients who received the schedule A or B regimen received predosing that was 10% of the full dose but not more than 10 mg in total. Schedules A through E were conducted consecutively.

Predosing on the day before the first two full infusions was intended to minimize the risk of infusion-related reactions. Premedication included antihistamines, acetaminophen, and glucocorticoids. The protocol-specified premedications and dosing schedules are described in the Supplementary Appendix, available at NEJM.org.

In part 2, doses of daratumumab of 8 mg per kilogram and 16 mg per kilogram were administered with different schedules (Fig. 1B, and the Methods section in the Supplementary Appendix). In schedules A, B, and C, patients were treated with daratumumab at a dose of 8 mg per kilogram in eight once-weekly infusions and then in twice-monthly infusions for 16 weeks. In schedules D and E, patients were treated with daratumumab at a dose of 16 mg per kilogram, and after the first infusion they had a 3-week washout period to allow for the collection of pharmacokinetic data. They were then treated weekly for 7 weeks and then twice monthly for 14 weeks. All the patients in part 2 then received monthly

infusions. Patients received the therapy until disease progression or until an unmanageable level of toxic events occurred. In part 2, patients received a single predose of daratumumab (10 mg) before the first full infusion only in schedules A and B. A predose was optional in schedule D but was not used.

Infusion rates and volumes also differed between the schedules. Four different infusion protocols were assessed. The first full infusion of 500 ml (diluted in sterile, pyrogen-free 0.9% sodium chloride) had a 4-hour duration in schedule A and a 6-hour duration in schedule B. In schedules C, D, and E, first full infusion was 1000 ml over a period of 6 hours. In the absence of infusion-related reactions during the first 3 hours of the first infusion, the second dose was administered in 500 ml over a period of 3.25 to 4 hours (schedules A, B, and C) or 1000 ml over a period of 6 hours (schedules D and E). All subsequent infusions were 500 ml over a period of 3.25 to 4 hours. Schedule E evaluated a phase 3 drug product (commercial product) that is produced with a larger-scale manufacturing process. All other schedules used the phase 2 drug product. This report presents data from patients enrolled between March 27, 2008, and the clinical cutoff date of January 9, 2015.

END POINTS AND ASSESSMENTS

The primary end point was safety, which was determined according to the frequencies and severities of adverse events and was assessed at each treatment visit. An independent data monitoring committee evaluated all serious adverse events, nonserious adverse events of grade 3 or higher, and events that caused a patient's withdrawal from treatment. The National Cancer Institute Common Terminology Criteria for Adverse Events were used for safety assessments (see the Supplementary Appendix).[12]

Secondary end points were pharmacokinetics, objective response according to the IMWG uniform response criteria for myeloma[11] (Table S1 in the Supplementary Appendix), relative reductions in levels of M protein and free light chains, time to disease progression, duration of response, progression-free survival, and overall survival. In the high-dose cohort, in cases in which comigration of daratumumab and M protein interfered with the assessment of efficacy, a new assay was used to confirm the presence of complete responses.[13]

STUDY OVERSIGHT

This study was sponsored by Janssen Research and Development and Genmab. The investigators and sponsors were responsible for the study design and statistical analysis plan. The investigators and their research teams collected the data. Janssen Research and Development and Genmab compiled the data for summation and analysis and confirmed the accuracy of the data. All the investigators had full access to the data and analyses and were not restricted by confidentiality agreements. The first and last authors wrote the first draft of the manuscript; all the authors reviewed and revised the manuscript, approved the final version, and made the decision to submit the manuscript for publication. Writing assistance was provided by MedErgy and was funded by Janssen Research and Development. All the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol.

STATISTICAL ANALYSIS

Responses were evaluated in accordance with the IMWG response criteria with the use of a computerized algorithm. Time-to-event end points, progression-free survival, and duration of response were analyzed with the use of the Kaplan–Meier method. Data regarding progression-free survival and duration of response were censored at the last disease assessment on or before the onset of new anticancer therapy, at the last disease assessment for patients who had not had an event at the time of data cutoff, or at the last disease assessment before patients were lost to follow-up. Formal statistical hypotheses were not formulated or tested, and no power calculations were performed. Prespecified subgroup analyses were performed to identify baseline characteristics that were associated with response; the results should be interpreted with caution owing to small sample sizes. Pharmacokinetic variables were estimated by means of a noncompartmental analysis.

RESULTS

PATIENTS AND TREATMENT

In part 1, we enrolled 32 patients; single dose-limiting toxic events were observed at doses of 0.1 mg per kilogram and 1 mg per kilogram. In part 2 of the study, 72 patients were enrolled (Fig. 1). The results from part 1 are reported in the Supplementary Appendix. The baseline char-

acteristics of the patients who were enrolled in parts 1 and 2 are described in Table S2 in the Supplementary Appendix and in Table 1, respectively. Patients in part 2 had been heavily pretreated, with a median of 4 (range, 3 to 10) prior therapies in the cohort that received 8 mg per kilogram and 4 (range, 2 to 12) prior therapies in the cohort that received 16 mg per kilogram. The median times since diagnosis were 66.2 months and 68.1 months, respectively. A total of 76% of the patients had undergone autologous stem-cell transplantation.

A total of 21 patients (70%) in the cohort that received 8 mg per kilogram and 30 (71%) in the cohort that received 16 mg per kilogram had disease that was refractory to bortezomib; 26 (87%) and 31 (74%) in the two cohorts, respectively, had disease refractory to lenalidomide; 2 (7%) and 7 (17%), respectively, had disease refractory to carfilzomib; 2 (7%) and 15 (36%), respectively, had disease refractory to pomalidomide; and 19 (63%) and 27 (64%), respectively, had disease refractory to both bortezomib and lenalidomide.

In part 2, the median duration of follow-up was 16.9 months (range, 0.4 to 24.9) in the cohort that received 8 mg per kilogram and 10.2 months (range, 1.2 to 16.0) in the cohort that received 16 mg per kilogram. At the clinical cutoff date of January 9, 2015, a total of 14 patients (19%) were still receiving treatment and 58 (81%) had discontinued treatment. All 30 patients in the cohort that received 8 mg per kilogram discontinued owing to progressive disease. Of the 28 patients in the cohort that received 16 mg per kilogram who discontinued treatment, 23 discontinued owing to progressive disease, 4 owing to physician decision, and 1 owing to an adverse event. The adverse event was classified as grade 5 pneumonia, and the investigator did not think that it was related to the study drug. The patient was placed in hospice care because of advanced myeloma and ongoing complications and subsequently died owing to the advent of pneumonia.

Patients received a median of 10.5 full infusions (range, 1 to 26) in the cohort that received 8 mg per kilogram and 13.5 full infusions (range, 1 to 24) in the cohort that received 16 mg per kilogram (Table 1). The median durations of the first, second, and subsequent full infusions were 6.6 hours, 4.2 hours, and 3.3 hours, respectively, in the cohort that received 8 mg per kilogram and 7.7 hours, 6.7 hours, and 3.3 hours, respectively, in the cohort that received 16 mg per kilogram.

SAFETY

The adverse events that occurred in part 1 of the study are summarized in Tables S3, S4, and S5 in the Supplementary Appendix. No maximum tolerated dose was found, and dose-limiting toxic events were observed at doses of 0.1 mg per kilogram (grade 3 anemia in one patient) and 1 mg per kilogram (grade 3 elevation of the aspartate aminotransferase level in one patient). After treating three additional patients at these dose levels with no further dose-limiting toxic events, the dose level was safely escalated to 24 mg per kilogram.

In part 2, infusion-related reactions occurred in 71% of the patients and were of grade 1 or 2, except in one patient receiving the schedule E regimen who had grade 3 reactions (Table S6 in the Supplementary Appendix). No patient discontinued treatment because of an infusion-related reaction. The majority of the infusion-related reactions occurred during the first infusion, with reactions occurring during that infusion in 67% of the patients in the cohort that received 8 mg per kilogram and in 71% in the cohort that received 16 mg per kilogram; 9% of the patients in the cohort that received 8 mg per kilogram and 7% in the cohort that received 16 mg per kilogram had reactions that were associated with more than one infusion.

The frequency of infusion-related reactions was lower among the patients who received the schedule C first-infusion regimen (8 mg per kilogram in 1000 ml for 6 hours) than among those who received the schedule A or B regimen (8 mg per kilogram in 500 ml for 4 to 6 hours) or the schedule D or E regimen (16 mg per kilogram in 1000 ml for 6 hours). This finding suggests that the infusion rate may be important for the management of infusion-related reactions (see the Methods section and Table S6 in the Supplementary Appendix).

In part 2, most of the adverse events observed with daratumumab were of grade 1 or 2 (Table 2). The most common adverse events, defined as events that occurred in at least 25% of the patients in either treatment group, were fatigue, allergic rhinitis, and pyrexia. Other adverse events of interest in part 2 were nasopharyngitis (in 24% of the patients) and cough (in 21%) (data not shown). No clinically relevant changes were observed in the QT interval corrected for heart rate (Fridericia's correction formula), and most adverse events resolved without a delay in treat-

Table 1. Demographic Characteristics of the Patients, Clinical Characteristics at Baseline, and Number and Duration of Infusions of Daratumumab in the Dose-Expansion Study.*

Characteristic	8-mg/kg Cohort				16-mg/kg Cohort		
	Schedule A (N=16)	Schedule B (N=8)	Schedule C (N=6)	All Schedules (N=30)	Schedule D (N=20)	Schedule E (N=22)	Both Schedules (N=42)
Age — yr							
Median	60	56	60	59	62	67	64
Range	41–76	38–74	44–72	38–76	50–75	44–76	44–76
Sex — no. (%)							
Female	4 (25)	3 (38)	2 (33)	9 (30)	5 (25)	10 (45)	15 (36)
Male	12 (75)	5 (62)	4 (67)	21 (70)	15 (75)	12 (55)	27 (64)
ECOG performance-status score — no. (%)†							
0	1 (6)	1 (12)	4 (67)	6 (20)	6 (30)	6 (27)	12 (29)
1	14 (88)	7 (88)	2 (33)	23 (77)	14 (70)	14 (64)	28 (67)
2	1 (6)	0	0	1 (3)	0	2 (9)	2 (5)
No. of prior lines of therapy							
Median	4.0	4.5	4.5	4.0	4.0	5.0	4.0
Range	3–7	3–10	3–10	3–10	2–12	2–10	2–12
Prior therapy to which disease was refractory — no. (%)							
Bortezomib	12 (75)	4 (50)	5 (83)	21 (70)	12 (60)	18 (82)	30 (71)
Carfilzomib	0	1 (12)	1 (17)	2 (7)	3 (15)	4 (18)	7 (17)
Lenalidomide	14 (88)	6 (75)	6 (100)	26 (87)	11 (55)	20 (91)	31 (74)
Pomalidomide	0	0	2 (33)	2 (7)	5 (25)	10 (45)	15 (36)
Thalidomide	6 (38)	1 (12)	3 (50)	10 (33)	7 (35)	5 (23)	12 (29)
Alkylating agent	13 (81)	3 (38)	5 (83)	21 (70)	11 (55)	14 (64)	25 (60)
Proteasome inhibitor and immunomodulatory drug	10 (62)	4 (50)	5 (83)	19 (63)	10 (50)	17 (77)	27 (64)
Bortezomib and lenalidomide	10 (62)	4 (50)	5 (83)	19 (63)	9 (45)	18 (82)	27 (64)
Predose	Yes	Yes	No	Yes and no‡	No	No	No
No. of full infusions							
Median	10.0	10.5	11.5	10.5	13.0	15.5	13.5
Range	1–20	1–26	3–18	1–26	1–24	2–19	1–24
Duration of full infusion — hr							

First infusion							
Median	6.5	7.6	6.5	6.6	7.4	7.8	7.7
Range	3.9–9.4	6.1–9.2	6.5–8.4	3.9–9.4	6.3–9.3	6.3–11.3	6.3–11.3
Second infusion							
Median	4.2	5.9	4.0	4.2	6.7	6.6	6.7
Range	3.3–5.7	4.0–6.0	3.7–4.2	3.3–6.0	6.0–7.0	5.4–8.2	5.4–8.2
Subsequent infusions							
Median	3.5	3.3	3.3	3.3	3.4	3.3	3.3
Range	3.0–4.4	3.1–4.2	3.2–3.5	3.0–4.4	3.0–6.8	3.2–7.2	3.0–7.2

* There were no clinically meaningful differences between the cohort that received 8 mg per kilogram and the cohort that received 16 mg per kilogram. Four different infusion protocols were assessed. The first full infusion of 500 ml (diluted in sterile, pyrogen-free 0.9% sodium chloride) had a 4-hour duration in schedule A and a 6-hour duration in schedule B. In schedules C, D, and E, the first full infusion was 1000 ml over a period of 6 hours. In the absence of infusion-related reactions during the first 3 hours of the first infusion, the second dose was administered in 500 ml over a period of 3.25 to 4 hours (schedules A, B, and C) or 1000 ml over a period of 6 hours (schedules D and E). All subsequent infusions were 500 ml over a period of 3.25 to 4 hours. Schedule E evaluated a phase 3 drug product (commercial product) that is produced with a larger-scale manufacturing process. All other schedules used the phase 2 drug product.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
‡ Patients who received the schedule A or B regimen received predosing of daratumumab and those who received the schedule C regimen did not. Predosing was defined as 10% of the full dose but not more than 10 mg in total.

ment. The most frequent hematologic adverse event was neutropenia, which occurred in 5 patients (12%) in the cohort that received 16 mg per kilogram.

Grade 3 or 4 adverse events were reported in 53% of the patients in the cohort that received 8 mg per kilogram and in 26% in the cohort that received 16 mg per kilogram. Adverse events of grade 3 or 4 that were reported in two or more patients were pneumonia (in five patients), thrombocytopenia (in four), and neutropenia, leukopenia, anemia, and hyperglycemia (in two each). Serious adverse events occurred in 40% of the patients in the cohort that received 8 mg per kilogram and in 33% in the cohort that received 16 mg per kilogram; the most frequent serious adverse events in both of these cohorts were infection-related events, which occurred in 17% of the patients in the cohort that received 8 mg per kilogram and in 10% in the cohort that received 16 mg per kilogram.

EFFICACY

In part 1 of the study, 4 of 12 patients (33%) had a partial response when they received doses in the range of 4 to 24 mg per kilogram, which was the range in which consistent clinical responses were observed (Table S7 in the Supplementary Appendix). In part 2, the overall response rate was 36% in the cohort that received 16 mg per kilogram (with 2 patients having a complete response, 2 having a very good partial response, and 11 having a partial response) and 10% in the cohort that received 8 mg per kilogram (with 3 patients having a partial response) (Fig. 2A, and Table S8 in the Supplementary Appendix).

The complete responses in the two patients in the cohort that received 16 mg per kilogram were confirmed with the use of a daratumumab interference reflex assay (Fig. S1 in the Supplementary Appendix).[13] This assay addresses the issue of interference caused by monoclonal antibodies overlapping with the migration of endogenous immunoglobulin proteins in serum protein and immunofixation electrophoresis tests[14] and can be used to determine whether additional testing is warranted to assess the presence of a complete response or a stringent complete response.

A waterfall plot (Fig. 2B) shows that the qualities of the responses were higher in the cohort that received 16 mg per kilogram than in

Table 2. Most Common Adverse Events in the Dose-Expansion Study.*

Event	8-mg/kg Cohort (N=30)		16-mg/kg Cohort (N=42)		Total (N=72)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	number (percent)					
Fatigue	13 (43)	1 (3)	17 (40)	0	30 (42)	1 (1)
Allergic rhinitis	12 (40)	0	10 (24)	0	22 (31)	0
Pyrexia	13 (43)	0	7 (17)	1 (2)	20 (28)	1 (1)
Diarrhea	9 (30)	0	6 (14)	0	15 (21)	0
Upper respiratory tract infection	8 (27)	0	7 (17)	0	15 (21)	0
Dyspnea	8 (27)	0	6 (14)	0	14 (19)	0

* The most common adverse events were defined as those that occurred in at least 25% of the patients in either dose cohort.

the cohort that received 8 mg per kilogram. A reduction of at least 50% in the level of M protein or free light chains was observed in 19 of 41 patients (46%) in the cohort that received 16 mg per kilogram, as compared with 4 of 27 (15%) in the cohort that received 8 mg per kilogram.

Exploratory subgroup analyses of the response rate among patients in the cohort that received 16 mg per kilogram are shown in Figure 2C. Exploratory subgroup analyses in the cohort that received 8 mg per kilogram are shown in Table S9 in the Supplementary Appendix. The response rates among patients who had disease that was refractory to both bortezomib and lenalidomide were similar to those in the total population. The overall response rate was higher among patients who had had two or three prior lines of therapy than among more heavily pretreated patients (56% vs. 23%).

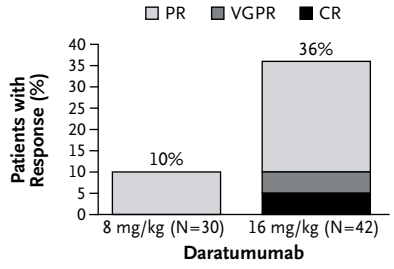
Bone marrow plasma-cell levels in the 3 patients with a response in the cohort that received 8 mg per kilogram were below 5% at baseline and at the first postbaseline measurement. A total of 13 of the 15 patients with a response in the cohort that received 16 mg per kilogram had data that could be evaluated, and these patients either had a decrease in the bone marrow plasma-cell level (8 patients) or had a level that remained stable below 5% (5 patients) (Fig. S2 in the Supplementary Appendix).

In patients who had a response to treatment and received 16 mg per kilogram, the estimated median time to the first response was 0.9 months (range, 0.5 to 3.2), and the estimated median time to the best response was 1.8 months (range, 0.5 to 9.0). The estimated median duration of response was 6.9 months (95% confidence interval [CI], 6.2 to 10.6) in the cohort

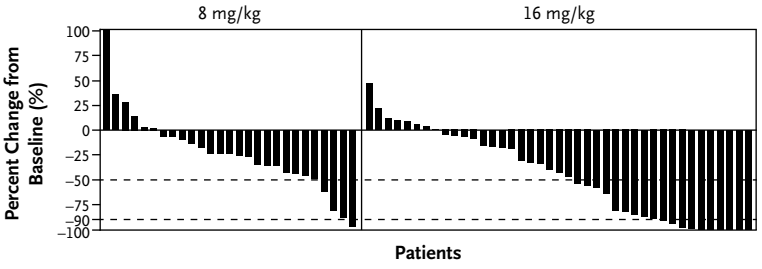
Figure 2 (facing page). Overall Response Rates after Daratumumab Monotherapy among Patients with Relapsed Multiple Myeloma or Relapsed and Refractory Multiple Myeloma.

Panel A shows the overall response rate in the two dose cohorts. The complete responses (CRs) were initially evaluated as very good partial responses (VGPRs) by the response algorithm that was based on the International Myeloma Working Group (IMWG) guidelines, owing to interference by daratumumab that comigrated with M protein. They were confirmed as complete responses with the use of a daratumumab interference reflex assay (Fig. S1 in the Supplementary Appendix). PR denotes partial response. Panel B shows a waterfall plot of the maximum change from baseline in the level of M protein or free light chains after daratumumab monotherapy, evaluated according to the IMWG guidelines. Data were available for 28 of 30 patients in the cohort that received 8 mg per kilogram and for 41 of 42 in the cohort that received 16 mg per kilogram. The dashed lines at –50% and –90% indicate reductions that correspond to a partial response or a very good partial response, respectively, depending on the type of measurable paraprotein (i.e., serum or urine M protein and free light chain). Panel C shows the results of a subgroup analysis of the overall best response in the 42 patients treated with daratumumab at a dose of 16 mg per kilogram. The vertical line indicates 36%, which was the overall response rate in the cohort that received 16 mg per kilogram. Race was determined by the investigator, and race data were missing for 8 patients.

A Overall Response Rate

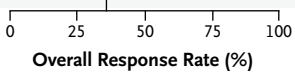


B Relative Change from Baseline in Paraprotein Level



C Subgroup Analyses

Subgroup	No. of Patients	Overall Response Rate *% of patients (95% CI)*
All patients	42	36 (22–52)
Age		
18–64 yr	22	27 (11–50)
65–74 yr	16	56 (30–80)
≥75 yr	4	0 (0–60)
Sex		
Male	27	44 (26–65)
Female	15	20 (4–48)
Race		
White	32	31 (16–50)
Other	2	0 (0–84)
Lines of therapy		
≤3 lines	16	56 (30–80)
>3 lines	26	23 (9–44)
Prior therapy to which disease was refractory		
Proteasome inhibitor (PI)	30	37 (20–56)
Immunomodulatory drug (IMiD)	31	36 (19–55)
PI+IMiD	27	33 (17–54)
PI+IMiD+alkylating agent	21	33 (15–57)
Last line	32	34 (19–53)
Bortezomib (BORT)	30	37 (20–56)
Carfilzomib (CARF)	7	29 (4–71)
Lenalidomide (LEN)	31	36 (19–55)
Pomalidomide (POM)	15	33 (12–62)
Thalidomide (THAL)	12	33 (10–65)
Alkylating agent	25	28 (12–49)
BORT+LEN	27	33 (17–54)
CARF+POM	5	40 (5–85)
BORT+LEN+CARF	7	29 (4–71)
BORT+LEN+POM	13	31 (9–61)
BORT+LEN+CARF+POM	5	40 (5–85)
BORT+LEN+CARF+POM+THAL	3	33 (1–91)
Type of myeloma		
IgG	24	29 (13–51)
Non-IgG	18	44 (22–69)
Baseline creatinine clearance		
≥60 ml/min	29	38 (21–58)
≥30 to <60 ml/min	12	33 (10–65)
<30 ml/min	1	0 (0–98)
Percent of bone marrow plasma cells at baseline		
≤30%	37	35 (20–53)
>30 to ≤60%	5	40 (5–85)
>60%	0	—



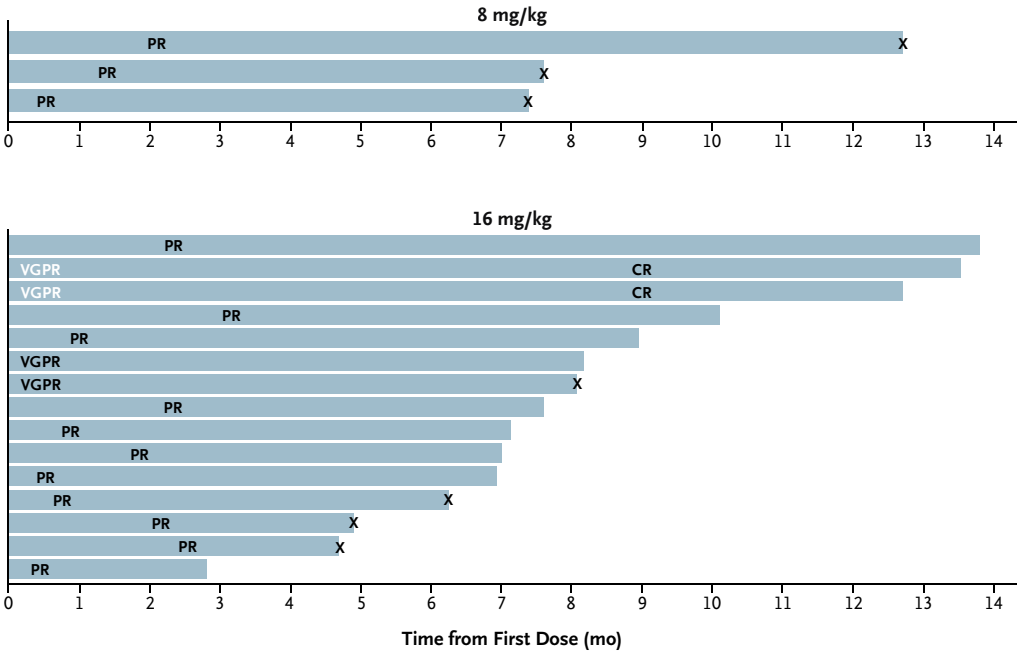


Figure 3. Swim-Lane Plot of Data from Patients with a Response.

Responses in white font indicate the first response, and those in black font the best response. X indicates disease progression. Owing to daratumumab interference, the complete responses were originally designated as very good partial responses on the basis of the IMWG-based algorithm.

that received 8 mg per kilogram and was not reached in the cohort that received 16 mg per kilogram, with 65% (95% CI, 28 to 86) of the patients who had a response in this cohort remaining progression-free at 12 months. The timing and depth (partial, complete, etc.) of the response in each patient who had a partial response or better in the two dose cohorts are shown in Figure 3.

The estimated median progression-free survival was 2.4 months (95% CI, 1.4 to 3.5) in the cohort that received 8 mg per kilogram and 5.6 months (95% CI, 4.2 to 8.1) in the cohort that received 16 mg per kilogram (Fig. S3 in the Supplementary Appendix). The overall survival rate at 12 months was 77% (95% CI, 52 to 90) in the cohort that received 8 mg per kilogram and 77% (95% CI, 58 to 88) in the cohort that received 16 mg per kilogram.

PHARMACOKINETICS

The elimination of daratumumab was nonlinear; clearance decreased with increasing dose and with multiple doses. After the first full infusion, the mean clearance decreased with increasing dose level from 1.064 ml per hour per kilogram in the group that received 2 mg per kilogram to 0.287 ml per hour per kilogram in the group that received 24 mg per kilogram; after the last full infusion, the mean clearance was also decreased with increasing dose level, from 0.586 ml per hour per kilogram in the group that received 2 mg per kilogram to 0.162 ml per hour per kilogram in the group that received 24 mg per kilogram.

The maximum concentration increased in approximate proportion to dose after the first infusion and in greater than a dose-proportional manner after the last dose. In patients who received 1 to 24 mg per kilogram, the mean half-life after the first infusion ranged from 28 to 155 hours (i.e., 1.2 to 6.5 days) and the mean half-life after the last infusion ranged from 36 to 587 hours (i.e., 1.5 to 24.5 days). In part 2, the mean (±SD) half-life was 9.0±4.3 days after the first dose of 16 mg per kilogram and 10.6±9.0 days after varying numbers of repeat doses (median, 13.5 full infusions; range, 1 to 24). Parallel receptor-saturation studies were not performed.

Preliminary pharmacokinetic analyses to inform the decisions regarding dose in part 2 of the study included a comparison of the daratumumab trough concentrations in individual patients with predicted trough concentrations that were consistent with inhibition of 90% of the target-mediated clearance. After the repeated administration of doses of 8 mg per kilogram, the observed trough concentrations were generally lower than the predicted concentrations, which indicated that clearance was faster than would be expected with saturation of target-mediated clearance and that the target was not fully saturated throughout the dosing interval. Conversely, patients in the cohort that received 16 mg per kilogram had trough concentrations that were generally similar to those predicted after the inhibition of target-mediated clearance. Therefore, 16 mg per kilogram was the lowest tested dose with pharmacokinetics that were consistent with target saturation throughout the dosing interval, and an increase in the dose was not expected to have a clinically meaningful effect.

DISCUSSION

Daratumumab, an anti-CD38 human antibody, showed encouraging efficacy in patients with myeloma who had had a median of four prior lines of therapy, including 64% of patients who had disease that was refractory to lenalidomide and bortezomib. Moreover, daratumumab monotherapy (at a dose of 16 mg per kilogram) induced durable responses that deepened over time, including complete and very good partial responses, with 65% of the patients who had a response remaining progression-free at 12 months. In patients with a partial response or better, the level of bone marrow plasma cells was generally markedly reduced.

The responses compare favorably with those observed with other investigational agents in patients with relapsed myeloma or relapsed and refractory myeloma. In a phase 2 study of carfilzomib in patients with relapsed and refractory myeloma (80% of whom had disease that was refractory to both bortezomib and lenalidomide), the patients treated with carfilzomib had a response rate of 24% and a median duration of response of 7.8 months.[15] A pivotal phase 2 study involving patients with relapsed and refractory myeloma who had been treated with pomalidomide, with or without dexamethasone, showed response rates of 33% with pomalidomide plus dexamethasone and 18% with pomalidomide alone and median durations of response of 8.3 months and 10.7 months, respectively.[16]

Monoclonal antibodies are likely to change myeloma treatment, and daratumumab is one of several in clinical development (as monotherapy or as part of a combination therapy).[3] Preclinical studies indicate that the addition of lenalidomide to daratumumab enhances the killing of lenalidomide-resistant or bortezomib-resistant myeloma cells in vitro and reduces tumor growth in an in vivo xenograft model.[17] An ongoing phase 1–2 study of daratumumab in combination with lenalidomide and dexamethasone in patients with relapsed myeloma or relapsed and refractory myeloma has shown high response rates and responses that improved over time.[18] SAR650984, a humanized IgG1 monoclonal antibody, also targets CD38,[19] and clinical responses have been reported in patients with relapsed myeloma or relapsed and refractory myeloma who received the drug as monotherapy[20] or in combination with lenalidomide and dexamethasone, findings that further validate this approach.[21] Elotuzumab, a humanized IgG1 monoclonal antibody that targets the signaling lymphocytic activation molecule F7 (SLAMF7),[22] was associated with stable disease as the best response when it was used as a single agent[23] but has shown clinically relevant activity in combination with lenalidomide and dexamethasone in two studies.[22,24]

Daratumumab binds to an important target, has multiple mechanisms of action, and may represent an effective single-agent treatment option for patients with relapsed and refractory myeloma, especially those with disease that is otherwise resistant to other treatments or those who have unacceptable side effects from other treatments. Daratumumab had an acceptable safety profile, with infusion-related reactions of grade 1 and 2 across the two dose cohorts in part 2 (except for one patient with infusion-related reactions of grade 3), including mild and transient bronchospasm, headache, dyspnea, and fever. Most events occurred during the first infusion, and no patient discontinued treatment because of an infusion-related reaction. The median infusion times were reduced to 3.3 hours by the third infusion.

In conclusion, daratumumab showed single-agent antitumor activity in a population of pa-

tients with highly difficult-to-treat myeloma who had very few effective treatment options. Its target and mechanisms of action differentiate it from existing therapies.

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APPENDIX

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