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ORIGINAL RESEARCH

Daratumumab Monotherapy for Relapsed or Refractory Multiple Myeloma: Results of an Early Access Treatment Protocol in Europe and Russia

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ABSTRACT

Introduction: Daratumumab is a human IgGκ monoclonal antibody targeting CD38. Despite the demonstrated benefit of daratumumab in multiple myeloma, not all patients have access to commercially available daratumumab. Here we report a pooled analysis of patients from the UK, Spain, Italy, and Russia enrolled in an open-label, early access treatment protocol (EAP) that provided daratumumab (16 mg/kg) monotherapy to patients with heavily pre-treated relapsed or refractory multiple myeloma (RRMM).

Methods: Intravenous daratumumab 16 mg/kg was administered to patients who had received ≥ 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory drug

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(IMiD), or who were double refractory to both a PI and an IMiD. Safety and patient-reported outcomes data were collected.
Results: A total of 293 patients received ≥ 1 dose of daratumumab. The median duration of daratumumab exposure was 4.2 (range 0.03–24.1) months, with a median number of 13 (range 1–37) infusions. The overall response rate was 33.1%, and the median progression-free survival was 4.63 months. Grade 3/4 treatment-emergent adverse events occurred in 60.1% of patients, of which the most common were thrombocytopenia (18.8%), anemia (11.9%), and neutropenia (11.6%). The most common serious adverse events were pneumonia (4.4%) and pyrexia (4.1%). Infusion-related reactions occurred in 45.1% of patients. The median change from baseline in all domains of patient-reported outcome instruments (European Quality of Life Five Dimensions Questionnaire [EQ-5D–5L], European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ-C30], and EORTC Multiple Myeloma Module [QLQ-MY20]) was generally 0 or close to 0.
Conclusion: These EAP results are consistent with those from previous trials of daratumumab monotherapy and confirm its safety in patients from Europe and Russia with heavily pre-treated RRMM.
Trial Registration: ClinicalTrials.gov identifier, NCT02477891.

Keywords: Daratumumab; Early access protocol; Europe; Monoclonal antibody; Multiple myeloma; Russia

Key Summary Points
Why carry out this study?
Daratumumab monotherapy is approved in patients with heavily pre-treated relapsed or refractory multiple myeloma (RRMM) in many countries; however, not all patients have access to commercially available daratumumab.
The objective of this study was to provide early access to daratumumab monotherapy and collect additional safety and patient-reported outcomes data for patients with heavily pre-treated RRMM.
What was learned from the study?
No new safety concerns were identified, and health-related quality of life was maintained during daratumumab treatment.
The results from this study confirm the favorable safety profile of daratumumab monotherapy in patients from Europe and Russia with heavily pre-treated RRMM.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13482702.

INTRODUCTION

Multiple myeloma (MM) is a malignant disease characterized by proliferation of plasma cells in the bone marrow that results in bone, renal, and hematologic complications [1, 2]. Similar annual incidences of MM are seen across Europe and the USA, with estimates of 4.7 and 3.8 per 100,000 persons per year, respectively [3, 4]. For patients with relapsed or refractory MM

(RRMM), standard-of-care therapy includes regimens consisting of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) [5, 6]. Although these agents have improved clinical outcomes, patients with RRMM continue to have poor prognosis, and additional treatment may lead to further complications [1, 7]. Thus, there is a need for novel, safe, and effective therapies for patients with RRMM.

Daratumumab is a human IgGκ monoclonal antibody that targets CD38 with a direct on-tumor [8–11] and immunomodulatory [12–14] mechanism of action. In a pooled analysis of the phase 1/2 GEN501 and phase 2 SIRIUS studies, daratumumab monotherapy in patients with heavily pre-treated RRMM resulted in an overall response rate (ORR) of 31.1% and a median overall survival of 20.1 months [15]. Based on these results, daratumumab 16 mg/kg intravenous (IV) was approved in Europe and the USA as monotherapy in patients with heavily pre-treated RRMM [16, 17]. Subsequently, phase 3 studies provided support for the approval of daratumumab in combination with standard-of-care regimens in patients with RRMM who received ≥ 1 prior line of therapy (the CASTOR and POLLUX studies [18, 19]) and in patients with newly diagnosed MM (NDMM; the ALCYONE, MAIA, and CASSIOPEIA studies [20–22]). Despite these approvals, not all patients have access to commercially available daratumumab or are eligible for inclusion in ongoing daratumumab clinical trials.

MMY3010 is a multicenter, open-label, early access treatment protocol (EAP) designed to provide early access to daratumumab monotherapy and collect additional safety and patient-reported outcomes (PROs) data for patients with heavily pre-treated RRMM. Results from U.S. and Spanish cohorts of MMY3010 were consistent with those from previously reported clinical trials of daratumumab monotherapy and confirmed the safety profile of daratumumab in patients with heavily pre-treated RRMM [23, 24]. Here, we present results from a pooled analysis of patients with RRMM enrolled in MMY3010 from the UK, Spain, Italy, and Russia.

METHODS

Study Design and Patients

The EAP (ClinicalTrials.gov identifier, NCT02477891) enrolled patients from the UK (15 sites), Spain (15 sites), Italy (15 sites), and Russia (6 sites). The protocol and amendments for this study were reviewed by an independent ethics committee and institutional review board in each country (Electronic Supplementary Material). This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable regulatory requirements. All patients provided written informed consent.

Eligible patients were ≥ 18 years of age with documented MM and evidence of disease progression on or after the most recent prior treatment regimen, as defined by International Myeloma Working Group (IMWG) criteria [25, 26], had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2, and had received ≥ 3 prior lines of therapy that included a PI and an IMiD or were double refractory to a PI and an IMiD. Patients resided in areas where daratumumab was not yet commercially available through local healthcare providers, had not been enrolled in another daratumumab study, and were not eligible for or did not have access to enrollment in another ongoing clinical study of daratumumab. Patients were excluded from the study if they had prior exposure to any anti-CD38 monoclonal antibody; known chronic obstructive pulmonary disease with a forced expiratory volume in 1 s < 50% of predicted normal; known moderate or severe persistent asthma within the past 2 years or current uncontrolled asthma; clinically significant cardiac disease, cardiac arrhythmia, or clinically significant electrocardiogram abnormalities; known allergies, hypersensitivities, or intolerance to monoclonal antibodies or human proteins or known sensitivities to mammalian-derived products; or plasma cell leukemia, Waldenström's macroglobulinemia, POEMS syndrome (polyneuro-

pathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or amyloidosis. Additionally, patients were excluded if they had any of the following laboratory test results: absolute neutrophil count $\leq 0.5 \times 10^9$/L, hemoglobin level ≤ 7 g/dL (≤ 4 mmol/L), platelet count $< 50 \times 10^9$/L, alanine aminotransferase level $\geq 2.5 \times$ upper limit of normal (ULN), total bilirubin level $\geq 2 \times$ ULN, creatinine clearance ≤ 20 mL/min/1.73 m^2, potassium level < 3.0 mEq/L, or corrected serum calcium level > 14.0 mg/dL (> 3.5 mmol/L).

Dosing

Daratumumab (16 mg/kg) was administered IV every week during cycles 1 and 2, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter until disease progression, unacceptable toxicity, lack of clinical benefit, or study conclusion. Each cycle was 28 days. To reduce the occurrence of infusion-related reactions (IRRs), pre-infusion medications, including methylprednisolone, an antihistamine, and acetaminophen, were administered approximately 1 h before daratumumab infusion; a corticosteroid was administered on the 2 days following daratumumab infusion for the prevention of delayed IRRs. For patients with a higher risk of respiratory complications, additional post-infusion medications were considered, including an antihistamine, a short-acting β2 adrenergic receptor agonist, and control medications for lung disease (including inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for patients with asthma, and long-acting bronchodilators, such as tiotropium or salbumatol, ± inhaled corticosteroids for patients with chronic obstructive pulmonary disease). Use of antibiotic prophylaxis was dependent on local practice.

Assessments

Safety evaluations included monitoring of treatment-emergent adverse events (TEAEs), physical examinations, vital sign measurements, ECOG performance status score, and clinical laboratory parameters. Only treatment-emergent serious adverse events (SAEs), grade ≥ 3 TEAEs, and TEAEs of special interest (IRRs, bronchospasm, or any unscheduled laboratory abnormalities associated with these events) were collected. The date of onset, severity, and outcome of TEAEs, as well as the relationship of TEAEs to the study drug and any action taken in response to TEAEs were reported. Adverse events (AEs) were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events (version 4.03; https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03).

Efficacy was not formally evaluated in this study. Investigator-assessed disease response (e.g., disease progression or lack of clinical benefit) was used to determine whether continued treatment with daratumumab was warranted, and investigator-assessed best disease response according to IMWG criteria was reported [27]. Assessments were conducted according to local standard of care as clinically indicated from the start of daratumumab treatment until discontinuation of study treatment or switch to commercial daratumumab, at which time patients were withdrawn from the study and no follow-up continued.

PROs included health-related quality of life (HRQoL) measures, which were evaluated using the European Quality of Life Five Dimensions Questionnaire (EQ-5D–5L), the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), and the EORTC Multiple Myeloma Module (QLQ-MY20). Assessments were electronically collected at baseline; pre-dose day 1 during cycles 1, 2, 3, 6, and every other cycle thereafter; and at the end-of-treatment visit. Compliance was defined as the number of forms received as a percentage of the number of forms expected; forms were expected from all patients who were on study treatment at each visit.

Statistical Analyses

The analysis population included all patients who received ≥ 1 dose of daratumumab. SAS software version 9.4 was used for data analysis (SAS Institute, Cary, NC, USA). No sample size calculations were performed. Globally, the plan was to provide daratumumab to up to 2000

Table 1 Patient demographics and baseline characteristics

Characteristic	Daratumumab (*N* = 293)
Age, years	
Category, *n* (%)	
18 to < 65	150 (51.2)
65 to < 75	103 (35.2)
≥ 75	40 (13.7)
Median (range)	64 (32–85)
Mean (SD)	63.5 (9.4)
Sex, *n* (%)	
Male	166 (56.7)
Female	127 (43.3)
Race, *n* (%)	
White	274 (93.5)
Other	19 (6.5)
ECOG PS score, *n* (%)	
0	112 (38.2)
1	148 (50.5)
2	33 (11.3)
Number of previous lines of therapy, *n* (%)	
≥ 3	293 (100)
Creatinine clearance, mL/min[a]	(*n* = 292)
Category, *n* (%)	
≥ 90	81 (27.7)
60 to < 90	108 (37.0)
30 to < 60	89 (30.5)
15 to < 30	14 (4.8)
< 15	0
Median (range)	70.8 (18.2–242.3)
Mean (SD)	76.1 (34.6)
Hemoglobin, g/L	
Category, *n* (%)	
< 80	18 (6.1)
80–100	105 (35.8)
> 100	170 (58.0)
Median (range)	105.0 (71.0–156.0)
Mean (SD)	106.1 (17.2)
Platelet count, 10^9/L	
Category, *n* (%)	
< 75	42 (14.3)
≥ 75	251 (85.7)
Median (range)	150.0 (17.0–483.0)
Mean (SD)	154.1 (72.7)

Note: percentages may not add to 100% due to rounding
ECOG PS Eastern Cooperative Oncology Group performance status, *SD* standard deviation
[a] Creatinine clearance was estimated using the Cockcroft and Gault formula based on laboratory tests

patients, and the final number was determined by medical need and local health authority approvals. Unless otherwise specified, continuous endpoints were summarized using descriptive statistics. All categorical endpoints were summarized using frequencies and percentages. The Kaplan–Meier method was used to analyze progression-free survival (PFS), defined as the time between the first dose of study treatment and disease progression or death, whichever occurred first. The mean and median changes from baseline for all PRO assessment scores were determined for each patient who completed the assessments at baseline and each respective time point. No inferential statistical analysis was performed.

RESULTS

Patient Demographics and Disposition

Between 10 February 2016 and 2 August 2018, of the 325 patients screened, 294 patients were enrolled in the study and 293 patients received ≥ 1 dose of daratumumab, including 98 (33.4%) from the UK, 73 (24.9%) from Spain, 72 (24.6%) from Italy, and 50 (17.1%) from Russia. Patient demographics and baseline characteristics are shown in Table 1. The median age of patients was 64 (range 32–85) years, with 13.7% of patients aged ≥ 75 years, and 56.7% of patients were male. The majority of patients were white (93.5%) and had a baseline ECOG performance status score of 0 or 1 (88.7%). Patients had a history of vascular disorders (38.9%); surgical and medical procedures (31.1%); musculoskeletal and connective tissue disorders (22.9%); metabolism and nutrition disorders (20.8%); and benign, malignant, and unspecified (including cysts and polyps) neoplasms (15.0%). Common comorbidities (> 5% of patients) included hypertension (31.4%), peripheral neuropathy and anemia (6.8% each), hypercholesterolemia (5.8%), deep vein thrombosis and back pain (5.5% each), and pulmonary embolism (5.1%).

At a median follow-up of 6.3 months, 244 (83.3%) patients had discontinued treatment. As planned, the remaining 49 (16.7%) patients who did not discontinue treatment stopped receiving study treatment through the EAP once market authorization/reimbursement occurred and transitioned to commercially available daratumumab without follow-up. The most common (> 10% of patients) primary reasons for treatment discontinuation included progressive disease, disease relapse, or lack of efficacy (66.6%) and AEs (11.3%). Other primary reasons for treatment discontinuation included death (2.7%), patient withdrawal (1.4%), physician decision (0.7%), loss to follow-up (0.3%), and other (0.3%).

Treatment Exposure

The extent of exposure to daratumumab reported only refers to the EAP study supply and follow-up. After patients transitioned to commercial stock, data collection stopped. Patients received a median of 5 treatment cycles (range 1–27 cycles; Table 2), and 46.1% of patients received ≥ 6 cycles of treatment. The median duration of daratumumab exposure was 4.2 (range 0.03–24.1) months, with a median of 13 (range 1–37) infusions. The median duration of infusion decreased from the first (7.1 h) to second (4.3 h) and all subsequent infusions (3.5 h).

Safety

A total of 176 (60.1%) patients reported a grade 3/4 TEAE (Table 3). The most common (> 10% of patients) grade 3/4 TEAEs reported were thrombocytopenia (18.8%), anemia (11.9%), and neutropenia (11.6%; Table 3). A total of 61 (20.8%) patients discontinued therapy due to TEAEs, among whom 11 (3.8%) patients discontinued therapy due to TEAEs that were deemed to be daratumumab related. The most frequently reported TEAEs leading to treatment discontinuation were thrombocytopenia (2.7%), general physical health deterioration (2.4%), and hypercalcemia (1.4%). TEAEs considered to be related to daratumumab that led to modifications and delays in infusions were reported in 120 (41.0%) and 13 (4.4%) patients, respectively. None of the 40 (13.7%) TEAEs leading to death were considered to be related to daratumumab. SAEs were reported in 140 (47.8%) patients, with grade 3/4 SAEs reported in 113 (38.6%) patients; 35 patients were deemed as having an SAE with a causal relationship to daratumumab. The most common (> 3% of patients) SAEs reported were pneumonia (4.4%), pyrexia (4.1%), lower respiratory tract infection (3.8%), general physical health deterioration (3.8%), hypercalcemia (3.8%), and thrombocytopenia (3.4%). The most common grade 3/4 SAEs were pneumonia, lower respiratory tract infection, thrombocytopenia, and hypercalcemia (10 [3.4%] patients each) and pyrexia (9 [3.1%] patients).

TEAEs of infections or infestations were reported in 91 (31.1%) patients, with the most common (≥ 2% of patients) being lower respiratory tract infection (6.5%; with the first onset

Table 2 Treatment exposure[a] and infusion time

	Daratumumab (N = 293)
Duration of treatment, months	
Median (range)	4.2 (0.0–24.1)
Mean (SD)	5.8 (5.5)
Number of treatment cycles	
Median (range)	5.0 (1–27)
Mean (SD)	7.0 (6.0)
Total number of daratumumab infusions	
Median (range)	13.0 (1–37)
Mean (SD)	14.0 (8.5)
Relative dose intensity, %	
Median (range)	100.0 (85.7–110.0)
Mean (SD)	100.2 (2.3)
Duration of infusion,[b] h	
First infusion	(n = 284)
Median (range)	7.1 (1.0–25.9)
Mean (SD)	8.2 (3.4)
Second infusion	(n = 265)
Median (range)	4.3 (3.3–22.3)
Mean (SD)	5.1 (2.1)
All subsequent infusions	(n = 3353)
Median (range)	3.5 (0.9–20.8)
Mean (SD)	3.6 (0.6)

[a] A patient was considered as treated in a cycle if any nonzero dose of daratumumab was received in that cycle
[b] Duration of infusion includes both actual infusion time and interruption time, if any

within ≤ 8 weeks from first dose of study treatment in 8 of 19 patients), pneumonia (4.8%), respiratory tract infection (3.8%), nasopharyngitis (2.7%), and rhinitis and upper respiratory tract infection (2.0% each).

IRRs were reported in 132 (45.1%) patients and were primarily grade 1 or 2 (Table 4). A majority of IRRs occurred during the first

Table 3 Most common (> 3% of patients) grade 3/4 treatment-emergent adverse events

	Daratumumab (N = 293)
Patients with grade 3/4 TEAE, n (%)	176 (60.1)
Hematologic, n (%)	
Thrombocytopenia	55 (18.8)
Anemia	35 (11.9)
Neutropenia	34 (11.6)
Lymphopenia	23 (7.8)
Leukopenia	16 (5.5)
Nonhematologic, n (%)	
Lower respiratory tract infection	13 (4.4)
Pneumonia	11 (3.8)
Pyrexia	10 (3.4)
Hypercalcemia	10 (3.4)
Back pain	9 (3.1)

Table 4 Most common (> 3% of patients) infusion-related reactions

	Daratumumab (N = 293)	
	Any grade	Grade 3/4
Patients with IRR, n (%)	132 (45.1)	10 (3.4)
Dyspnea	26 (8.9)	3 (1.0)
Nasal congestion	26 (8.9)	0
Cough	15 (5.1)	0
Chills	13 (4.4)	0
Nausea	13 (4.4)	0
Hypertension	12 (4.1)	2 (0.7)
Bronchospasm	11 (3.8)	1 (0.3)
Pyrexia	11 (3.8)	1 (0.3)
Throat irritation	10 (3.4)	0
Lacrimation increased	10 (3.4)	0

Table 5 Summary of EQ-5D–5L change from baseline, by visit

		Change from baseline			
	Baseline	**Cycle 2, day 1**	**Cycle 3, day 1**	**Cycle 6, day 1**	**Cycle 8, day 1**
Utility score[a]					
N[b]	279	202	170	109	85
Mean	0.66	0.00	0.00	0.01	0.03
SD	0.27	0.20	0.20	0.23	0.20
Median	0.70	0.00	0.00	0.00	0.02
Visual analog score[c]					
N[b]	279	202	170	109	84
Mean	57.59	0.19	1.87	2.43	3.74
SD	19.41	16.78	16.00	18.21	20.65
Median	59.00	0.00	1.00	3.00	3.00

EQ-5D–5L European Quality of Life Five Dimensions Questionnaire
[a] The EQ-5D–5L utility score ranges from 0 to 1 and represents the general, self-evaluated health status of each patient. A higher score indicates a high level of utility. All scores were collected electronically at baseline and on day 1 of each cycle
[b] The number of patients shown are those who completed the assessment at both baseline and each respective time point
[c] The EQ-5D–5L visual analog score ranges from 0 to 100, with a high score indicating a high level of self-evaluated health status. All scores were collected electronically at baseline and on day 1 of each cycle

infusion, with 130 (44.4%), 5 (1.8%), and 4 (1.5%) patients experiencing an IRR during the first, second, and subsequent infusions, respectively. The most common (> 5% of patients) IRRs were dyspnea (8.9%), nasal congestion (8.9%), and cough (5.1%). Grade 3/4 IRRs occurred in ten (3.4%) patients and included dyspnea (1.0%), hypertension (0.7%), and bronchospasm, laryngospasm, pyrexia, chest discomfort, decreased oxygen saturation, hypersensitivity, anaphylactic reaction, and nonspecified IRR (0.3% each); all grade 3/4 IRRs occurred during the first infusion.

Efficacy and Survival

The investigator-assessed ORR (stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 33.1%. The best disease responses achieved were sCR in one (0.3%) patient, CR in seven (2.4%) patients, VGPR in 28 (9.6%) patients, and PR in 61 (20.8%) patients. Additionally, best disease response of minimal response was achieved in 20 (6.8%) patients, of stable disease was achieved in 79 (27.0%) patients, and of progressive disease was observed in 44 (15.0%) patients. Clinical benefit was achieved in 196 (66.9%) patients. Twenty-seven (9.2%) patients were not evaluable for disease response. The investigator-assessed median PFS was 4.63 months (95% confidence interval [CI] 3.75–5.75), and the 6-month estimated PFS rate was 42.9% (95% CI 37.1–48.7).

Patient-reported Outcomes

A total of 279 (95.2%) patients completed the EQ-5D–5L assessment at baseline, with 208 patients completing the assessment at cycle 2, day 1. The compliance rate was 84.4% at cycle 6, day 1, with 114 patients completing the assessment out of the expected 135 patients. The EQ-5D–5L utility score had a mean and median change from baseline of 0 or close to 0, and the EQ-5D–5L visual analog scale had minimal mean and median changes from

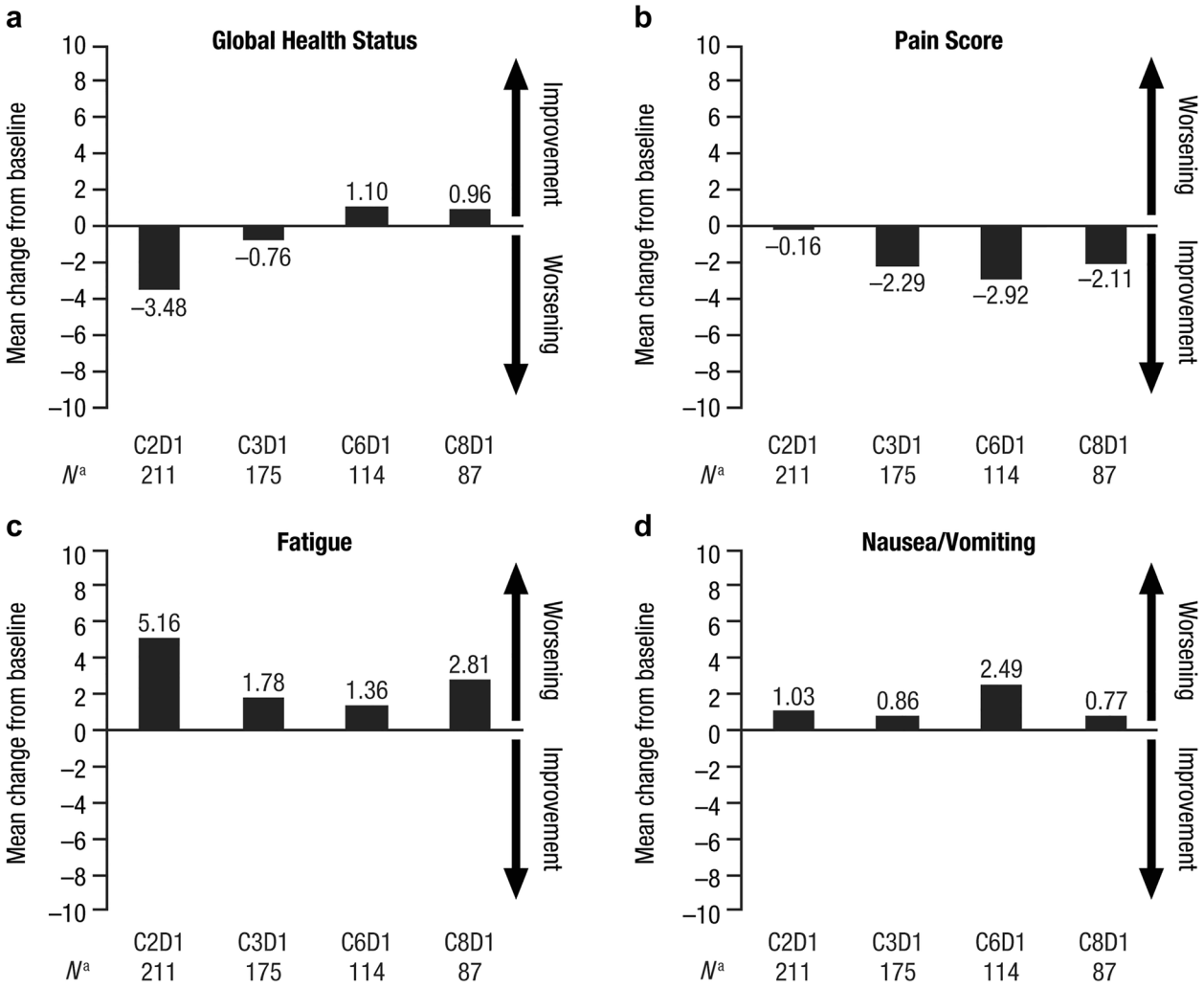

Fig. 1 Mean change from baseline in EORTC QLQ-C30 global health status (**a**) and symptom scores of pain (**b**), fatigue (**c**), and nausea/vomiting (**d**). *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, *C* cycle, *D* day [a]The number of patients shown are those who completed the assessment at both baseline and each respective time point

baseline throughout daratumumab treatment (Table 5).

A total of 282 patients completed the EORTC QLQ-C30 and EORTC QLQ-MY20 assessments at baseline, with 216 and 212 patients completing the assessment at cycle 2 day 1, respectively. The compliance rates with EORTC QLQ-C30 and EORTC QLQ-MY20 assessments at cycle 6, day 1 were 85.9 and 85.2%, respectively. The EORTC QLQ-C30 and EORTC QLQ-MY20 assessments demonstrated that patient global health status, functional ability, and symptoms remained relatively constant throughout daratumumab treatment, with an observed median change from baseline of generally 0 in most domains. Mean patient-reported global health status (Fig. 1a), pain symptom scores (Fig. 1b), fatigue symptom scores (Fig. 1c), and nausea/vomiting symptom scores (Fig. 1d) of EORTC QLQ-C30 changed minimally from baseline. Similarly, no major changes in PROs were seen in patients achieving PR or better.

DISCUSSION

In this cohort of the MMY3010 EAP, 293 patients with heavily pre-treated RRMM from the UK, Spain, Italy, and Russia were given early access to daratumumab monotherapy. Pooled analysis confirmed the tolerable safety profile and efficacy of daratumumab monotherapy in patients with heavily pre-treated RRMM. No new safety concerns were identified, and HRQoL was maintained. Of note, results from patients in the Spanish cohort included in this pooled analysis were previously published in a separate report [24]. The data collected from this European and Russian cohort expand on and complement the previously reported results from the U.S. ($N = 348$) and Spanish ($N = 73$) cohorts of this EAP [23, 24].

The rate of grade 3/4 TEAEs (60.1%) was higher in this study than in the GEN501 study and the U.S. EAP cohort [23, 28]. The rate of any-grade SAEs (47.8%) was higher in this study than in previous clinical trials of daratumumab monotherapy (the GEN501 and SIRIUS studies) and in the U.S. EAP cohort [23, 28, 29]. However, comparisons between the current study and other clinical studies are limited by differences in eligibility criteria and study design. In the previously reported Spanish cohort of this EAP, rates of grade 3/4 TEAEs and any-grade SAEs were similarly higher than in the U.S. cohort; however, patients from the European and Russian cohort had a longer exposure to daratumumab and an increased number of daratumumab infusions compared to U.S. patients [23, 24]. The most common grade 3/4 TEAEs reported by patients were hematologic, a finding consistent with results reported in previous clinical trials and in the U.S. and Spanish cohorts of this EAP [15, 23, 24, 29]. IRRs were reported in 45.1% of patients and mostly occurred during the first infusion; the most common IRRs were respiratory, also similar to findings reported previously [15, 23, 24, 29].

Although efficacy was not a formal endpoint of this study, an investigator-assessed ORR of 33.1% was observed, similar to the ORR of 29.2% reported in the SIRIUS study and the ORRs of 23.3 and 24.7% reported in the U.S. and Spanish cohorts of this EAP study, respectively [23, 24, 29]. The rates of CR or better and VGPR or better were also similar to those reported in the SIRIUS study [29]. Additionally, the observed median PFS of 4.6 months was similar to the median PFS of 3.7 months reported in the SIRIUS study and the 4.0 months reported in the combined analysis of SIRIUS and GEN501 [15, 29]. The responses observed in this population of heavily pre-treated RRMM patients with ≥ 3 prior lines of therapy, including PIs and IMiDs, provide further confirmation of the efficacy of daratumumab monotherapy.

In phase 3 studies (CASTOR, POLLUX, ALCYONE, MAIA, and CASSIOPEIA), daratumumab combined with standard-of-care regimens reduced the risk of disease progression or death by $\geq 44\%$ and improved the depth of response, including minimal residual disease negativity, versus standard of care alone in RRMM or NDMM [20–22, 30, 31]. Based on the positive outcomes in clinical trials of daratumumab as monotherapy and in combination with standard-of-care regimens across lines of therapy, daratumumab is approved in many countries for the treatment of MM. Despite advances in the treatment of MM over the last decade, however, there is a paucity of real-world, evidence-based data on the impact of these new therapies on quality of life and symptom burden in patients with RRMM. The added value of PROs in the interpretation of clinical trial outcomes is gaining importance. In this context, one of the objectives of this EAP was to assess HRQoL.

Although no substantial improvements in PROs were noted, maintenance of patient-reported HRQoL quantified by the EQ-5D–5L, EORTC QLQ-C30, and EORTC QLQ-MY20 questionnaires was observed. The minimal changes from baseline to last assessment in the EQ-5D–5L utility score and visual analog scale and in EORTC QLQ-C30 and EORTC QLQ-MY20 domain scores suggest that overall health status is maintained with daratumumab treatment. These results are consistent with findings from U.S. and Spanish cohorts of this EAP [23, 24]. Overall, the minimal change from

baseline observed for these assessments in this study indicates that HRQoL was maintained during a median of 4.2 months of daratumumab therapy.

Limitations to the current study include the short median duration of follow-up, low median number of treatment cycles, and investigator-based assessment of disease response and progression, limiting interpretation of the efficacy results from the study. Additionally, data on refractoriness to prior treatments were not collected.

CONCLUSIONS

In conclusion, the safety profile of daratumumab monotherapy was confirmed by the large cohort of European and Russian patients enrolled in the MMY3010 EAP; the safety profile was consistent with that reported in earlier clinical trials of daratumumab in patients with heavily pre-treated RRMM. No new safety concerns were identified, and there was a low incidence of treatment discontinuations due to TEAEs. PRO results indicate that HRQoL was maintained during daratumumab treatment. Collectively, this EAP provides additional evidence of the favorable safety profile of daratumumab in patients with heavily pre-treated RRMM and the associated maintenance of patient-reported HRQoL.

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Data Availability. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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