Original Research

Daratumumab Split First Versus Single Dosing Schedule Among Patients With Multiple Myeloma Treated in a US Community Oncology Setting: A Retrospective Observational Study

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ABSTRACT

Purpose: Daratumumab was initially approved by the US Food and Drug Administration to be given intravenously over the course of several hours during each administration. Because the duration of the first dose can exceed 7 h, the US Oncology Network developed a split first dose schedule to administer the first administration (dose) over 2 consecutive days.

Methods: This trial was a retrospective cohort study of adult multiple myeloma (MM) patients who initiated daratumumab within the US Oncology Network between November 1, 2015, and June 30, 2017. Descriptive analyses were conducted to compare split dose versus single-dose groups, and a multivariable linear regression model was developed to identify factors associated with total administration time.

Findings: In total, 622 patients were included in the analysis (364 split first dose patients and 258 single-dose patients). Infusion reactions to the first administration were documented for 47.8% of split first dose patients and 48.3% of single-dose patients. Among the total study population, the most common reactions were lower respiratory tract–related reactions (26.1%), upper respiratory tract–related reactions (17.2%), and gastrointestinal adverse events (12.5%), with no statistically significant differences between groups. The median infusion duration was 4.5 h for day 1 of the split first dose and 6.5 h for the single dose ($P < 0.0001$); the total median infusion time was 8.7 h for the split first dose. In multivariable regression, the only factor associated with infusion time was dosing schedule.

Implications: These results provide real-world evidence regarding the safety and infusion time of the first infusion of daratumumab. Although the total administration time was longer among patients receiving a split first dose, the shorter day 1 infusion for this dosing schedule without increased infusion reactions may be an option for community oncology clinics. (*Clin Ther*. 2019;41:866–881)

Key Words: community oncology, electronic healthcare records, monoclonal antibody, myeloma and other plasma cell dyscrasias, retrospective observational research.

INTRODUCTION

Multiple myeloma (MM) is a cancer of bone marrow plasma cells that disrupts normal cell production and causes bone destruction, bone marrow failure, and complications such as infection, kidney failure, anemia, and bone loss.[1] There are an estimated 30,000 new cases and 13,000 deaths annually due to

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MM in the United States, and the incidence is increasing by ~0.8% annually.[2,3] Although MM responds to a variety of treatments, it is considered incurable.[4] Several new classes of treatments that have become available in recent years have been associated with substantially improved survival[4,5]; mortality rates declined at an average of 0.8% annually between 2004 and 2013.[3] However, the vast majority of patients who respond to treatment will ultimately relapse and require further therapy.[4]

Daratumumab, a human immunoglobulin G kappa monoclonal antibody targeting CD38, has a direct on-tumor and immunomodulatory mechanism of action and has received multiple US Food and Drug Administration (FDA) approvals for the treatment of MM.[6–12] Daratumumab at a dose of 16 mg/kg, either as monotherapy or in combination with standard-of-care therapies, has shown efficacy in several clinical trials of patients with relapsed/refractory MM who had received previous therapy and of newly diagnosed patients ineligible for autologous stem cell transplantation.[11,13–27]

Among relapsed/refractory patients in the SIRIUS (Daratumumab Monotherapy in Patients With Treatment-Refractory Multiple Myeloma) Phase II trial, daratumumab monotherapy was associated with an overall response rate of 29.2%.[15] The median duration of response was 7.4 months, progression-free survival (PFS) was 3.7 months, 12-month overall survival was 64.8%, and the median overall survival was 17.5 months. In the CASTOR (Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma) Phase III trial, patients with MM and at least 1 previous line of therapy received bortezomib and dexamethasone with or without daratumumab.[14] After a median follow-up of 31.3 months, PFS was significantly longer among patients who received daratumumab compared with control subjects (median, 16.7 vs 7.1 months; hazard ratio [HR], 0.32; 95% CI, 0.25–0.40; $P < 0.0001$).[26] In the POLLUX (Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma) Phase III trial, patients with at least 1 previous line of therapy received lenalidomide and dexamethasone with or without daratumumab.[16] After a median follow-up of 38.5 months, the daratumumab group had a higher 36-month PFS (55% vs 28%) and a significantly longer median PFS (not reached vs 17.5 months; HR, 0.44; 95% CI, 0.35–0.55; $P < 0.0001$).[25]

Patients with newly diagnosed MM in the ALCYONE (Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma) trial were treated with bortezomib, melphalan, and prednisone with or without daratumumab.[13] The group treated with daratumumab had an overall response rate of 90.9% compared with 73.9%, which included a 42.6% versus 24.4% ($P < 0.001$) complete response or better. There was a 50% reduction in the risk of disease progression or death in the daratumumab group compared with the control group (HR, 0.50; 95% CI, 0.38–0.65; $P < 0.001$).

In clinical trials, 46% of daratumumab-treated patients experienced an infusion reaction during the initial infusion, although fewer events were observed during subsequent infusions.[11] Nearly all daratumumab-related reactions occurred during the infusion or the 4 h after completion (median, 1.4 h to onset).[11,28] Common infusion reactions include respiratory symptoms such as nasal congestion, cough, throat irritation, chills, vomiting, and nausea. Severe infusion reactions include hypertension, bronchospasm, hypoxia, dyspnea, laryngeal edema, and pulmonary edema.

At the time of the current study, the FDA-approved dose of daratumumab was 16 mg/kg administered intravenously over the course of a single day.[3] Infusion reactions to the first administration are common. To mitigate the risk, in addition to pre/post medications, the first infusion is administered more slowly than subsequent infusions. For the first infusion, the dilution volume is 1000 mL at a rate of 50 mL/h for the first hour.[11] In the absence of infusion reactions, the infusion rate can be increased 50 mL every hour to a maximum of 200 mL/h. In clinical trials, the median infusion duration was >7 h for the first administration.[11] Subsequent infusions are often shorter due to fewer infusion reactions.

To manage the first infusion duration, the US Oncology Network (USON) developed a split first dose daratumumab administration schedule. The aim of the current study was to provide real-world insight into the MM patient population receiving daratumumab in the community oncology setting and compare the infusion time and safety associated with split first dose versus those of single-dose daratumumab.

Patients and Methods

The goal of this retrospective observational cohort trial was to examine demographic and clinical

characteristics among patients with MM who initiated daratumumab within USON practices. USON comprises >1400 affiliated physicians and >450 cancer treatment center locations across the United States, with >995,000 patients treated annually.[29] iKnowMed (iKM)is an integrated Web-based database and oncology-specific electronic health care record (EHR) system that captures outpatient practice encounter histories from patients treated within the USON.

The single-dose schedule was defined as the FDA-approved prescribed dose of 16 mg/kg on day 1 with a gap of ≥5 days before the next administration. Daratumumab is diluted with normal saline to a total volume of 1000 mL (see Supplemental Table I in the online version at https://doi.org/10.1016/j.clinthera.2019.03.013). The administration is started at a rate of 50 mL/h, which can be increased in 50 mL/h increments in the absence of infusion reactions to a total rate of 200 mL/h.

The split first-dose daratumumab administration schedule was developed by USON physicians and was incorporated into iKM in December 2016 and is available to all USON practices. This schedule recommends that two 8 mg/kg daratumumab dosages be administered over the course of 2 consecutive days, instead of a single 16 mg/kg infusion in a single day. On each day, daratumumab is administered at 50 mL/h for 1 h (see Supplemental Table I in the online version at https://doi.org/10.1016/j.clinthera.2019.03.013). If no infusion reactions occur, the infusion rate can be increased in 50 mL/h increments every hour to a maximum of 200 mL/h on each day. Pre/post medications are also included to manage infusion reactions for both dosing schedules (see Supplemental Table II in the online version at https://doi.org/10.1016/j.clinthera.2019.03.013). Examples of these medications include montelukast sodium, diphenhydramine, acetaminophen, and dexamethasone.

The study observation period lasted from November 1, 2015, through August 31, 2017, or date of last record, whichever occurred first. The index date was the date of the first daratumumab infusion between November 1, 2015, and June 30, 2017. Patients were followed up until their second administration of daratumumab (ie, the second infusion for the single-dose group and the third infusion for the split first-dose group). No minimum or maximum follow-up time was

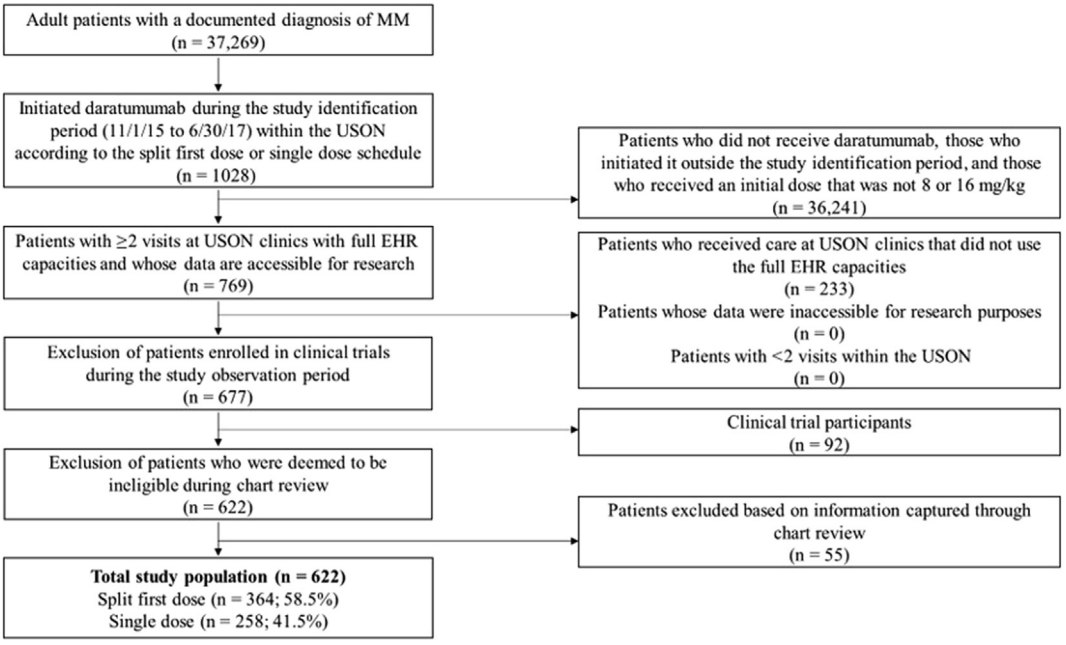

Figure 1. Study attrition. EHR = electronic health record; MM = multiple myeloma; USON = US Oncology Network.

required for the analyses. The Fig. 1 presents the study attrition based on the inclusion and exclusion criteria.

Data were collected via programmatic queries of the iKM EHR system and chart review. Structured data from the iKM database were used to address most research questions, whereas a subset of the study population underwent a targeted chart review to provide supplemental information captured from unstructured (eg, free-text) fields. In total, 359 patients were selected for chart review based on a random 1:1 sampling technique; of these patients, 2 charts were inaccessible for research purposes. The final count was 357 patients: 180 screened as split first dose and 177 screened as single dose.

Descriptive analyses were conducted to evaluate the demographic, clinical, and treatment characteristics of the study population, as well as occurrence of infusion reactions. Continuous variables were described by using means, SD, median, and range (minimum−maximum). Categorical variables were defined by using patient counts and percentages. In case of missing observations, the number and percentage of missing were reported.

To assess associations between categorical variables when all cell size counts were ≥ 5, χ^2 testing was used. When distribution could not be assumed to be χ^2 the Fisher exact test was used. Depending on normality, analysis of variance/*t* tests or Kruskal−Wallis tests were used for continuous variables. A *P* value <0.05 was considered statistically significant.

To identify factors associated with total infusion time, a multivariable linear regression model was developed. This analysis was limited to study-eligible patients who had been selected for chart review, as their dosing administration schedule and eligibility had been verified through chart review. The dependent variable was the total administration time of the first dose (defined as the first 2 infusions for the split first dose group and one infusion for the single-dose group).

To identify covariates to include in the model, the parameter estimates for the treatment covariates in a univariate model were compared with the parameter estimates in a bivariate model with a selected number of relevant covariates (ie, age, sex, race, ethnicity, body mass index category, body surface area, smoking status, practice region, stage at diagnosis, MM subtype, MM isotype, performance status, comorbidities, daratumumab initiation date, use of pre/post medications, combination and monotherapy use, line of therapy, formula dosage, duration between administrations, occurrence of infusion reactions). Any covariate that changed the univariate parameter estimates by >10% and those with clinical significance were included in the multivariable model. Although the covariates included may not have been statistically significant themselves, they could have affected the results of the treatment covariate. Pearson and scatterplot correlation testing were performed for some variables in the model. Analyses were conducted by using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina). An exemption, waiver of informed consent and authorization for research were granted by the US Oncology Institutional Review Board.

RESULTS

Patient Characteristics

In total, 677 patients met the eligibility criteria for the study based on the structured EHR data. Of these, chart review was performed for 357 (52.7% of the study population) (Fig. 1). During chart review, information was discovered in the charts of 55 patients that disqualified them for the study because they did not initiate treatment with daratumumab during the study identification period within the USON. For example, a progress note indicated that the patient's first daratumumab administration occurred at a hospital that was outside of the USON. After the chart review, therefore, the final study population comprised 622 patients, with 364 split first dose and 258 single-dose patients.

Table I presents the baseline demographic and clinical characteristics. In the overall population at initiation of daratumumab infusion, the median age was 63.6 years (range, 31.8−90 + years), and the majority were male and white. At diagnosis, approximately one quarter each were diagnosed with International Staging System Stage I and II disease. Before initiation of daratumumab, approximately three quarters of the study population had a Karnofsky performance status score >80.

Overall, the demographic profiles of the split first dose and single-dose patients were well balanced at baseline (Table I). The baseline clinical and disease characteristics were also similar between the groups, except for Karnofsky performance status. A

Table I. Characteristics of the study population, presented for each administration schedule. Values are given as number (%) unless otherwise indicated.

Characteristic	Overall (N = 622)	Split First Dose (n = 364)	Single Dose (n = 258)	*P*
Median (range) age at index date, y	63.6 (31.8–90+)	63.6 (31.8–90+)	63.4 (33.5–87.7)	0.4854
Male	337 (54.2)	195 (53.6)	142 (55.0)	0.7175
Race				0.2161
Black or African American	66 (10.6)	42 (11.5)	24 (9.3)	
White	487 (78.3)	275 (75.5)	212 (82.2)	
Other*	12 (1.9)	9 (2.5)	3 (1.2)	
No information	57 (9.2)	38 (10.4)	19 (7.4)	—
BMI				0.9226
Normal weight (18.5–24.9 kg/m^2)	196 (31.5)	116 (31.9)	80 (31.0)	
Obese (25.0–29.9 kg/m^2)	185 (29.7)	112 (30.8)	73 (28.3)	
Overweight (≥30.0 kg/m^2)	215 (34.6)	123 (33.8)	92 (35.7)	
Underweight (<18.5 kg/m^2)	14 (2.3)	8 (2.2)	6 (2.3)	
No information	12 (1.9)	5 (1.4)	7 (2.7)	—
ISS stage at diagnosis				0.4673
I	162 (26.0)	103 (28.3)	59 (22.9)	
II	168 (27.0)	102 (28.0)	66 (25.6)	
III	223 (35.9)	128 (35.2)	95 (36.8)	
No information	69 (11.1)	31 (8.5)	38 (14.7)	—
Karnofsky performance status				0.0213
100	50 (8.0)	38 (10.4)	12 (4.7)	
80, 90	407 (65.4)	234 (64.3)	173 (67.1)	
60, 70	125 (20.1)	77 (21.2)	48 (18.6)	
40, 50	7 (1.1)	2 (0.5)	5 (1.9)	
No information	33 (5.3)	13 (3.6)	20 (7.8)	—
Practice region				<0.0001
Midwest	57 (9.2)	42 (11.5)	15 (5.8)	
Northeast	34 (5.5)	32 (8.8)	2 (0.8)	
South	365 (58.7)	198 (54.4)	167 (64.7)	
West	166 (26.7)	92 (25.3)	74 (28.7)	
Monotherapy use	197 (31.7)	101 (27.8)	96 (37.2)	0.0124
Median (IQR) daratumumab formula dose, first infusion, mg/kg	8.1 (8.05)	8.0 (0.32)	16.0 (0.55)	<0.0001
Median (IQR) daratumumab formula dose, total administration, mg/kg	16.0 (0.51)	16.0 (0.47)	16.0 (0.55)	0.6675
Median (IQR) daratumumab formula dose, second infusion, mg/kg†	8.3 (7.94)	8.0 (0.30)	16.0 (0.54)	<0.0001
Median (range) duration between first and second daratumumab infusion, d	0.0 (0.0–13.0)	0.0 (0.0–4.0)	6.0 (0.0–13.0)	<0.0001
Premedication use at index date				
Dexamethasone	472 (75.9)	315 (86.5)	157 (60.9)	<0.0001
Granisetron	105 (16.9)	72 (19.8)	33 (12.8)	0.0219
Ondansetron	142 (22.8)	84 (23.1)	58 (22.5)	0.8614

Table I. (*Continued*)

Characteristic	Overall (N = 622)	Split First Dose (n = 364)	Single Dose (n = 258)	*P*
Metoclopramide	3 (0.5)	0	3 (1.2)	0.0709
Methylprednisolone	451 (72.5)	240 (65.9)	211 (81.8)	<0.0001
Ranitidine	148 (23.8)	74 (20.3)	74 (28.7)	0.0159
Diphenhydramine	617 (99.2)	362 (99.5)	255 (98.8)	0.6538
Hydrocortisone	153 (24.6)	81 (22.3)	72 (27.9)	0.1067
Acetaminophen	611 (98.2)	359 (98.6)	252 (97.7)	0.3748
Lorazepam	41 (6.6)	17 (4.7)	24 (9.3)	0.0218
Postmedication use at index date				
Dexamethasone	477 (76.7)	320 (87.9)	157 (60.9)	<0.0001
Granisetron	108 (17.4)	75 (20.6)	33 (12.8)	0.0113
Ondansetron	155 (24.9)	95 (26.1)	60 (23.3)	0.4193
Metoclopramide	4 (0.6)	1 (0.3)	3 (1.2)	0.3124
Methylprednisolone	451 (72.5)	240 (65.9)	211 (81.8)	<0.0001
Ranitidine	153 (24.6)	79 (21.7)	74 (28.7)	0.0465
Montelukast	5 (0.8)	3 (0.8)	2 (0.8)	1.0000
Diphenhydramine	617 (99.2)	362 (99.5)	255 (98.8)	0.6538
Hydrocortisone	156 (25.1)	84 (23.1)	72 (27.9)	0.1710
Acetaminophen	612 (98.4)	360 (98.9)	252 (97.7)	0.3327
Lorazepam	45 (7.2)	21 (5.8)	24 (9.3)	0.0938
Premedication use 4 wk before index date				
Dexamethasone	556 (89.4)	345 (94.8)	211 (81.8)	<0.0001
Granisetron	124 (19.9)	83 (22.8)	41 (15.9)	0.0335
Ondansetron	242 (38.9)	144 (39.6)	98 (38.0)	0.6912
Metoclopramide	9 (1.4)	5 (1.4)	4 (1.6)	1.0000
Methylprednisolone	456 (73.3)	244 (67.0)	212 (82.2)	<0.0001
Ranitidine	162 (26.0)	81 (22.3)	81 (31.4)	0.0105
Montelukast	5 (0.8)	3 (0.8)	2 (0.8)	1.0000
Diphenhydramine	617 (99.2)	362 (99.5)	255 (98.8)	0.6538
Hydrocortisone	167 (26.8)	87 (23.9)	80 (31.0)	0.0488
Acetaminophen	612 (98.4)	360 (98.9)	252 (97.7)	0.3327
Lorazepam	45 (7.2)	19 (5.2)	26 (10.1)	0.0212

BMI = body mass index; IQR = interquartile range; ISS = International Staging Systems.
† These values represent the second half of the split first dose administration and the second full dosage of daratumumab for patients who receive the single dose on day 1.
* Due to privacy concerns related to small counts of patients not classified as black/African American or white, patients with other racial classifications were included in this category (eg, Asian or Native American).

statistically significant difference was found in the scores between the 2 groups ($P = 0.0213$): a higher proportion of split first dose patients had a score >80 at the index date (74.7% vs 71.8%, respectively), although performance status scores were missing for a higher proportion of the single-dose patients (7.8% vs 3.6%).

Most patients in this study received care from clinics in the southern or western regions of the United States. This trend reflects the geographic dispersion of clinics

within the USON. However, significantly fewer patients on the split first dose schedule received care in southern or western clinics compared with those on the single-dose schedule (79.7% vs 93.4%; $P < 0.0001$).

Daratumumab Treatment Patterns

More than two thirds of the patients received daratumumab as part of a combination regimen, both in the overall population and in the dose schedule groups (Table I). Daratumumab monotherapy was significantly less common among split first dose patients compared with single-dose patients (27.8% vs 37.2%; $P = 0.0124$).

Across this USON-based study cohort, daratumumab utilization increased over time, with 81 patients initiating treatment in the first quarter (Q1) of 2016 and 156 initiating in Q1 of 2017 (see the Supplemental Figure in the online version at https://doi.org/10.1016/j.clinthera.2019.03.013). At the beginning of the study observation period (November 2015), a higher proportion of patients were on the single-dose administration schedule. By the second quarter (Q2) of 2016, this trend shifted, and an increasing proportion of patients were on the split first dose administration schedule ($P < 0.0001$). In Q2 of 2017, a total of 98 patients initiated the split first dose administration schedule compared with 30 patients who initiated the single-dose administration schedule.

The use of premedication increased over time. More patients in the single-dose group used premedication in Q1 of 2016, and more patients in the split first dose group in Q1 and Q2 of 2017 used premedication ($P < 0.0001$ for trend). A similar pattern of use was observed for postmedication use at the index date ($P < 0.0001$ for trend). In the overall population, nearly all patients used diphenhydramine and acetaminophen, followed by dexamethasone and methylprednisolone in approximately three quarters of the population. The most common postmedications observed were similar in types and proportions to the most common premedication.

Compared with split first dose patients, those who underwent the single-dose schedule had significantly lower premedication use of dexamethasone ($P < 0.0001$) and granisetron ($P = 0.0219$), and significantly higher use of methylprednisolone ($P < 0.0001$), ranitidine ($P = 0.0159$), and lorazepam ($P = 0.0218$). Likewise, split first dose patients had significantly higher postmedication use of dexamethasone ($P < 0.0001$) and granisetron ($P = 0.0113$) and significantly lower use of methylprednisolone ($P < 0.0001$).

Clinical Outcomes

Table II presents data on the daratumumab infusion durations that were collected from the entire study population (N = 622). The median infusion duration was 4.5 h for day 1 of the split first dose group and 6.5 h for the single-dose group ($P < 0.0001$). The total median infusion time was 8.7 h for the split first dose. The median total administration time for the split first dose group (n = 364) was 8.7 h (range, 1.5−14.8 h; mean, 8.9 [1.7] hours) compared with 6.5 h (range, 0.7−9.9; mean, 5.8 [2.1] hours) for the single-dose group (n = 258; $P < 0.0001$). The median infusion time was 4.5 h (range, 0.1−8.1 h; mean, 4.6 [1.4] hours) for day 1 of the split first dose administration and 4.2 h (range, 0.5−7.6 h; mean, 5.8 [2.1] hours) for day 2.

Occurrence of infusion reactions for the subset of patients selected for chart review (n = 302) is presented in Table III (see Supplemental Table III for additional details in the online version at https://doi.org/10.1016/j.clinthera.2019.03.013). In total, 48.0% experienced at least 1 infusion reaction: 47.8% of split first dose patients and 48.3% of single-dose patients experienced at least 1 infusion reaction to the first dose of daratumumab (ie, day 1 infusion). Among split first dose patients, 3.8% experienced an infusion reaction during the second daratumumab administration. No statistically significant differences were observed in the occurrence of specific infusion reactions between groups.

The most common infusion reactions during the first administration included lower respiratory tract−related reactions (26.1%), upper respiratory tract−related reactions (17.2%), and gastrointestinal adverse events (12.5%). The most common specific infusion-related reactions during the first administration included chest discomfort/difficulty breathing (11.1%), cough (9.5%), vomiting/nausea (7.9%), nasal congestion (7.6%), and dyspnea (7.4%). The proportions of patients experiencing each reaction to the first administration were similar when comparing the split first dose schedule with the single-dose schedule. For the split first dose patients, 14 (3.8%) experienced a reaction to the second

Table II. Daratumumab administration times, presented for each administration schedule.

Variable	Overall (N = 622)	Split First Dose (n = 364)	Single Dose (n = 258)	*P*
Daratumumab infusion time, first infusion, h				<0.0001
Patients with available data	608	360	248	
Mean (SD)	5.1 (1.8)	4.6 (1.4)	5.8 (2.1)	
Median (range)	4.8 (0.1–9.9)	4.5 (0.1–8.1)	6.5 (0.7–9.9)	
Daratumumab infusion time, second infusion, h				—
Patients with available data		339		
Mean (SD)		4.3 (0.8)		
Median (range)		4.2 (0.5–7.6)		
Total daratumumab administration time, h				<0.0001
Patients with available data		341	248	
Mean (SD)		8.9 (1.7)	5.8 (2.1)	
Median (range)		8.7 (1.5–14.8)	6.5 (0.7–9.9)	

infusion. Among them, 4 (1.1%) experienced lower respiratory tract–related events, 3 (0.8%) gastrointestinal events, and 2 (0.5%) musculoskeletal pain.

The univariate analysis (Table IV and Supplemental Table IV [in the online version at https://doi.org/10.1016/j.clinthera.2019.03.013]) and the multivariate linear regression analysis (Table V) were limited to patients whose eligibility was confirmed through chart review (n = 302). The only factor in these analyses associated with total administration time was dosing schedule (split first dose or single-dose administration).

DISCUSSION

This study of patients with MM receiving daratumumab in the USON provided the opportunity to retrospectively assess occurrence of infusion reactions and administration time associated with 2 dosing schedules. The use of real-world data is advantageous because it reflects community oncology practice trends, as opposed to tightly controlled clinical trials. In addition, this study used both structured data obtained by querying the EHRs and unstructured data obtained through a targeted chart review of the EHRs. By supplementing the structured data analysis with a targeted chart review, we could capture more comprehensive data that were unavailable in structured fields. Leveraging these sources provided key insights into treatment patterns among patients with MM receiving daratumumab and factors associated with the use of daratumumab.

Of the 622 eligible patients with MM in the overall study population, 364 (58.5%) received the split first dose administration of daratumumab and 258 (41.5%) received the single-dose administration. The lower utilization of daratumumab monotherapy among split first dose patients compared with single-dose patients (27.8% vs 37.2%; $P = 0.0124$) may reflect the FDA-approval history of daratumumab and the rate of adoption of split-dose infusion. Specifically, daratumumab was initially approved by the FDA as a monotherapy in November 2015, before the adoption of the split dose protocol within the USON.[30,31] The FDA subsequently approved daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone in November 2016.[30] In June 2017, daratumumab was approved in combination with pomalidomide and dexamethasone.[31]

At initiation of daratumumab, baseline characteristics were well balanced between the patients who received the split first dose and the single-dose administrations. Karnofsky performance

Table III. Infusion reactions, presented for each administration schedule. Values are given as number (%).

Variable	Overall (N = 302)	Split First Dose (n = 184)	Single Dose (n = 118)	*P*
Count of infusion-related reactions (total, first administration)				
0	157 (52.0)	96 (52.2)	61 (51.7)	0.9152
1	49 (16.2)	27 (14.7)	22 (18.6)	
2	34 (11.3)	23 (12.5)	11 (9.3)	
3	25 (8.3)	15 (8.2)	10 (8.5)	
4	12 (4.0)	8 (4.3)	4 (3.4)	
≥5	25 (8.3)	15 (8.2)	10 (8.5)	
Infusion-related reactions (first administration)*				
Chills (eg, chills or rigors)	27 (8.9)	14 (7.5)	13 (11.1)	0.3793
Flushing (eg, flushing, hot flashes)	20 (6.6)	14 (7.5)	6 (5.1)	
Gastrointestinal (eg, abdominal discomfort, diarrhea, vomiting, nausea)	38 (12.5)	24 (12.9)	14 (12.0)	
Itching	13 (4.3)	8 (4.3)	5 (4.3)	
Lower respiratory tract related (eg, bronchospasm, chest discomfort, difficulty breathing, cough, dyspnea, hypoxia)	79 (26.1)	45 (24.2)	34 (29.1)	
Upper respiratory tract related (eg, congestion, epistaxis, nasal congestion, throat discomfort)	52 (17.2)	30 (16.1)	22 (18.8)	
Count of infusion-related reactions (total, second infusion)				
0		350 (96.2)		—
1		12 (3.3)		
2		2 (0.5)		
Infusion-related reactions (total, second infusion)				
Cardiovascular (eg, tachycardia, hypotension, hypertension)		1 (0.3)		—
Chills (eg, chills or rigors)		1 (0.3)		
Fatigue		1 (0.3)		
Gastrointestinal (eg, abdominal discomfort, diarrhea, vomiting, nausea)		3 (0.8)		
Lower respiratory tract related (eg, bronchospasm, chest discomfort, difficulty breathing, cough, dyspnea, hypoxia)		4 (1.1)		
		2 (0.5)		

Table III. (*Continued*)

Variable	Overall (N = 302)	Split First Dose (n = 184)	Single Dose (n = 118)	*P*
Musculoskeletal pain (eg, back pain)				
Other/not specified		1 (0.3)		
Sleep difficulties		1 (0.3)		
Upper respiratory tract related (eg, congestion, epistaxis, nasal congestion, throat discomfort)		1 (0.3)		

* Infusion reactions experienced by at least 10 patients in the chart review study population are presented. Additional details on these infusion reactions are presented in Supplemental Table III (in the online version at https://doi.org/10.1016/j.clinthera.2019.03.013).

status scores, however, tended to be higher among patients who received the split first dose schedule ($P = 0.0213$ for trend). The clinical relevance of this difference has uncertain clinical meaning, as it may reflect a higher proportion of missing performance status records among the single-dose patients as well as the FDA approval history of daratumumab. With split first dose utilization increasing over time and with the FDA approval of daratumumab as combination therapy in earlier lines of therapy, the split dose may have been more likely to be administered to patients with higher performance status. Likewise, the proportion of split first dose patients who received treatment in the Midwest and northwest regions of the United States was higher, which may reflect differences in clinic prescribing practices.

For the first infusion of daratumumab (day 1), the median infusion time was 2 h shorter for the first half of the split first dose compared with that of the single dose (4.5 vs 6.5 h, respectively; $P < 0.0001$). The total median administration time for both halves of the split first dose was 8.7 h (range, 1.5−14.8 h; mean, 8.9 [1.7] hours), which was significantly longer than that of the single dose ($P < 0.0001$). The split first dose administration may span ~2 h longer overall because, on both days, the infusion rate is initiated at 50 mL/h and is incrementally increased by 50 mL/h if tolerated.[11] In contrast, the single-dose administration may be shorter overall because it can proceed at 200 mL/h after the same incremental increase. For community oncology practices, which may not have the means to complete an infusion lasting >7 h, the decrease in the median time of the first daratumumab infusion to 4.5 h may be more important than the longer total infusion time of 8.7 h over 2 days. Furthermore, the shorter infusion duration may provide more patient scheduling flexibility and a buffer if the infusion duration is a longer time than expected.

The infusion durations observed in the current study are consistent with other published evidence. However, results from clinical trials on this topic are limited. Lokhorst et al[32] performed a dose-escalation trial of daratumumab. Among the patients who received daratumumab 16 mg/kg (n = 42), the median durations of the first, second, and third infusions were 6.6, 4.2, and 3.3 h, respectively. Among the patients who received daratumumab 8 mg/kg (n = 30), the median durations of the first, second, and third infusions were 7.7, 6.7, and 3.3 h.

In a Phase Ib study, Usmani et al[33] evaluated patients with MM who received daratumumab- and carfilzomib-based regimens. Among the 32 who received a split first dose of daratumumab, the median infusion time of the first split dose infusion (day 1) was 4.2 h (range, 4.0−10.3 h). The duration of the second infusion (day 2), the total administration time, and the results for the single-dose patients were not reported in the conference abstract.

Table IV. Univariate linear regression for significant factors* associated with total administration time among patients selected for chart review (n = 184 split first dose; n = 118 single dose).

Analysis Variable	Parameter Estimate	SE	*P*
Race			
White (reference)	—	—	—
Black or African American	0.15463	0.44517	0.7286
Other	2.39838	0.79797	0.0029
No information	0.4718	0.46822	0.3145
Ethnicity			
Latino/Hispanic (reference)	—	—	—
Not Latino/Hispanic	–1.10924	0.52007	0.0338
No information	–0.9372	0.68982	0.1754
Practice region			
South (reference)	—	—	—
Northeast	0.33716	0.48961	0.4916
Midwest	0.35244	0.48961	0.4722
West	0.76527	0.31415	0.0155
Comorbidities			
Anemia	0.41839	0.69097	0.5453
Cardiovascular disease	0.28336	1.5947	0.8591
Renal disease	2.55622	1.29538	0.0495
Daratumumab initiation over time			
2015 Q4 (reference)	—	—	—
2016 Q1	1.2654	0.68303	0.0650
2016 Q2	1.66611	0.6999	0.0180
2016 Q3	1.93778	0.69613	0.0058
2016 Q4	1.90444	0.69257	0.0064
2017 Q1	2.09285	0.63053	0.0010
2017 Q2	1.91598	0.63399	0.0028
Daratumumab premedications over time			
2015 Q4 (reference)	—	—	—
2016 Q1	1.2654	0.68303	0.0650
2016 Q2	1.66611	0.6999	0.0180
2016 Q3	1.93778	0.69613	0.0058
2016 Q4	1.90444	0.69257	0.0064
2017 Q1	2.09285	0.63053	0.0010
2017 Q2	1.91598	0.63399	0.0028
Daratumumab postmedications over time			
2015Q4 (reference)	—	—	—
2016Q1	1.2654	0.68303	0.0650
2016Q2	1.66611	0.6999	0.0180
2016Q3	1.93778	0.69613	0.0058
2016Q4	1.90444	0.69257	0.0064
2017Q1	2.09285	0.63053	0.0010
2017Q2	1.91598	0.63399	0.0028
Daratumumab postmedications			

Table IV. (*Continued*)

Analysis Variable	Parameter Estimate	SE	*P*
Acetaminophen	0.24725	1.13172	0.8272
Dexamethasone	0.78587	0.32237	0.0154
Granisetron	0.51003	0.34701	0.1428
Hydrocortisone	0.08911	0.30382	0.7695
Lorazepam	−1.03501	0.54421	0.0582
Methylprednisolone	−0.02763	0.29792	0.9262
Metoclopramide	−1.43219	2.24963	0.5249
Ondansetron	0.49864	0.32444	0.1255
Ranitidine	−0.55319	0.33018	0.0950
Montelukast	−1.05127	1.59353	0.5100
Actual daratumumab formula dose, first infusion	−2.14434	0.24285	<0.0001
Daratumumab administration schedule			
Single dose (reference)	—	—	—
Split first dose	2.63252	0.22859	<0.0001
Planned daratumumab formula dose, first infusion	−0.26804	0.03036	<0.0001
Planned daratumumab formula dose, second infusion	−0.25015	0.031	<0.0001
Actual daratumumab formula dose, first infusion	−0.24836	0.02986	<0.0001
Actual daratumumab formula dose, second infusion	−0.27087	0.03114	<0.0001
Total daratumumab formula dose	0.28759	0.06785	<0.0001
Duration between first and second daratumumab infusion	−0.34899	0.03553	<0.0001
Infusion-related reactions (total)			
Cough	0.31453	0.44062	0.4759
Chills	−0.52372	0.61556	0.3956
Hypoxia	−0.75143	0.7602	0.3238
Nasal congestion	1.11087	0.44289	0.0127
Hypertension	−2.1849	2.24743	0.3318
Throat irritation	1.18915	0.54306	0.0294
Bronchospasm	3.7532	2.23989	0.0949
Vomiting and/or nausea	−0.5641	0.45396	0.2151
Other	0.36243	0.27745	0.1925
Infusion-related reactions, first infusion			
Hypertension	−2.1849	2.24743	0.3318
Hypoxia	−0.08724	0.92751	0.9251
Nasal congestion	2.01323	0.56589	0.0004
Throat irritation	2.39097	0.70931	0.0009
Vomiting and/or nausea	1.09488	0.63501	0.0858
Other	1.66963	0.30989	<0.0001
Dyspnea	1.19328	0.55795	0.0333
Chills	1.41758	0.92358	0.1260
Cough	2.75197	0.67122	<0.0001
Count of infusion-related reactions: first administration			
0 (reference)	—	—	—
1	−2.17728	0.47994	<0.0001

(*continued on next page*)

Table IV. (*Continued*)

Analysis Variable	Parameter Estimate	SE	*P*
2	−1.73144	0.66475	0.0097
3	−4.07793	0.69921	<0.0001
4	−1.34644	1.03755	0.1955
≥5	−0.44459	0.69921	0.5254

Q = quarter.
* All covariates considered are presented in Supplemental Table IV (in the online version at https://doi.org/10.1016/j.clinthera.2019.03.013).

For the Phase II LYRA (A Phase 2 Study of Daratumumab [Dara] Plus Cyclophosphamide, Bortezomib, and Dexamethasone [Cybord] in Newly Diagnosed and Relapsed Patients [Pts] with Multiple Myeloma [MM]) study, 48 newly diagnosed and relapsed/refractory patients with MM received a split first dose of daratumumab plus cyclophosphamide, bortezomib, and dexamethasone.[34] The median infusion times of the first and second daratumumab doses (days 1 and 2) were 4.3 and 3.5 h, respectively.

The types of infusion reactions in this study resemble those reported in clinical trials. Usmani et al[33] found that 28% of their study participants experienced an infusion-related reaction. The most common reactions were cough, throat irritation, nausea, and headache. In SIRIUS, the most common (≥5%) daratumumab-related infusion reactions included nasal congestion (12%), throat irritation (7%), and cough, dyspnea, chills, and vomiting (6% each).[15] Likewise, in CASTOR, they were dyspnea (10.7%), bronchospasm (9.1%), and cough (7.0%).[14] Similarly, in POLLUX, the most common were cough (8.5%), dyspnea (8.5%), and vomiting (5.7%).[16] Last, in ALCYONE, the most common reactions were dyspnea (7.2%), chills (6.4%), and hypertension (4.6%).[13]

Table V. Multivariate linear regression for factors associated with total administration time among patients selected for chart review (n = 184 split first dose; n = 118 single dose).

Variable	Parameter Estimate	SE	*P*
Intercept	5.92799	0.69498	<0.0001
Daratumumab administration schedule			
Single dose (reference)	—	—	—
Split first dose	2.65186	0.2471	<0.0001

Our study also found that the most frequently occurring infusion reactions were upper and lower respiratory tract related, with the top specific reactions being chest discomfort/difficulty breathing, cough, vomiting and/or nausea, nasal congestion, and dyspnea. Although a higher proportion of patients in the current study (48.0% overall; 47.3% of split first dose and 48.3% of single dose) experienced infusion reactions, the relatively small number of patients who received the split first dose schedule (n = 32) in the study by Usmani et al[33] may have contributed to this difference.

The daratumumab package insert reports that 46% of patients in clinical trials (n = 820) experienced infusion reactions to their first daratumumab dose, with 3% experiencing a reaction to the second administration.[11] The LYRA study reported that 44% of patients experienced an infusion-related reaction, 38% to their first daratumumab dose and 4% to their second.[34] In the current study, most split first dose patients experienced a reaction to their first daratumumab dose, with 3.8% of patients experiencing a reaction to the second infusion (14 had a reaction to the second infusion; among these patients, 10 also had a reaction on day 1).

In general, there were large proportions of patients in both dosing schedule groups with missing data or observed low utilization of some pre/post

medications. Notably, documentation of montelukast premedication use at the index date was infrequently captured by structured EHR fields considered for this study. In contrast, nearly all patients were documented as treated with diphenhydramine and acetaminophen. The inconsistent documentation of pre/post medications in the structured EHR fields used for this analysis limits any conclusions about utilization of these treatments. Future research can consider alternative methods for capturing pre/post medication use to better understand their influence on infusion reactions, particularly the association between montelukast and respiratory events. For example, a targeted chart review could provide more detailed insight about patients' medication histories by augmenting the structured data with information captured in progress notes and other unstructured records.

Other limitations of the current study should be noted. This trial was an observational, retrospective study that used EHR data. Accordingly, study data were populated by providers during routine care and not collected for research purposes. As such, the unique recording practices of the providers limited standardization of data capture. Other data may have been underrepresented in the data sources used for this analysis. In particular, pre/post medication data were sourced exclusively from structured fields of the EHRs for this study. Some of these medications, especially montelukast, did not seem to have been comprehensively documented in the structured EHR fields used for analysis as providers may have recorded these prescriptions in nonstructured fields, such as progress notes.

Results cannot be generalized to the US population or to all community oncology practices without further evaluation, as not all community oncology practices are included in the iKM dataset and not all the USON practices utilize the full capabilities of the iKM EHR. Therefore, practices that participate in the USON and use the full capacities of iKM may differ from other community oncology practices in terms of the patient population that is seen or the prescribing practices of the physicians.

Despite these limitations, EHR-based research such as the current one may better represent real-world care practice standards than what is observed in clinical trials or at academic medical centers, which include a more select patient population. Real-world studies such as this one may be increasingly used to compare outcomes in the clinical trial and community oncology settings, as well as explore factors that contribute to observed differences.[35] As evidence of this trend, several recently published studies have leveraged EHR data to investigate MM treatment patterns and outcomes in the community oncology setting.[36–38]

CONCLUSIONS

The results of this study suggest that the split first dose was commonly used in a large US network of community oncology practices, was associated with a shorter day 1 infusion than the single-dose administration schedule for daratumumab, and did not increase the infusion reaction rate compared with the single-dose day 1 schedule. Although the total administration time of the split dose schedule was longer, in the community oncology setting, the split first dose schedule may be advantageous given clinics' normal operating hours. Future research can augment this study to explore additional clinical outcomes and factors associated with providers' choice of the daratumumab dosing schedule.

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CONFLICTS OF INTEREST

Dr. Rifkin, Ms. Aguilar and Dr. Baidoo received research funding and provided research consulting services to Janssen Scientific Affairs, LLC. Drs. Maiese and Singer were employed by Janssen Scientific Affairs, LLC during the conduct of the

study. The study sponsor, Janssen Scientific Affairs, LLC was involved in the study design, interpretation of data, writing of the manuscript and decision to submit the manuscript for publication.

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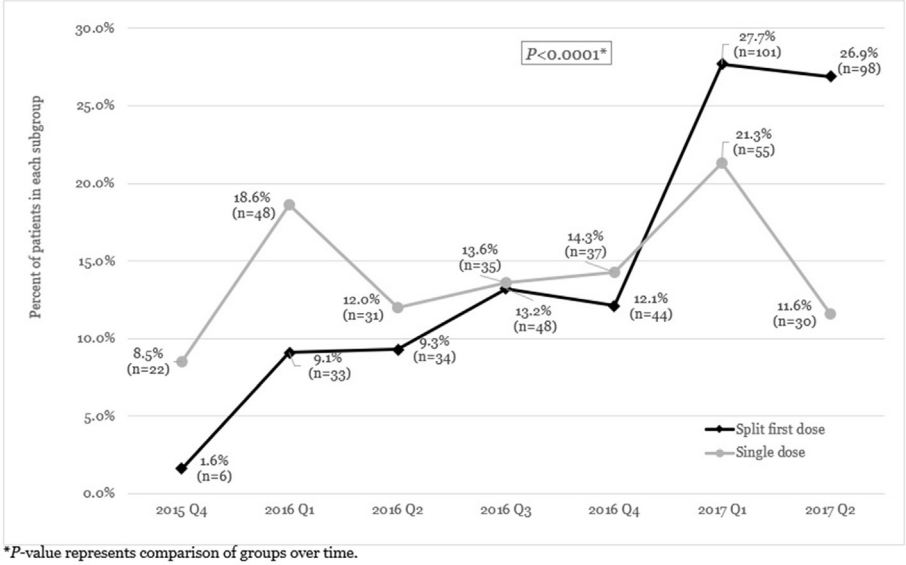
APPENDIX A. SUPPLEMENTARY DATA

The following are the Supplementary data to this article:



*P-value represents comparison of groups over time.

Supplemental Table 1. Infusion rates for administration.

	Dilution Volume	Initiation Rate	Rate Increment*	Maximum Rate
Standard (single) dose	1000 mL	50 mL/h	50 mL/h every hour	200 mL/h
Split First Dose	500 mL on each day	50 mL/h	50 mL/h every hour	200 mL/h

*On each day, in the absence of infusion reactions.

Supplemental Table 2. Pre-/Post-medications.

Medication	Frequency
Acetaminophen	Prior to each daratumumab infusion (cycle days 1 and 2 for split first dose patients)
Albuterol sulfate	During or after each daratumumab infusion (cycle days 1 and 2 for split first dose patients)
Acyclovir	Twice daily
Diphenhydramine (injection or oral)	Prior to each daratumumab infusion (cycle days 1 and 2 for split first dose patients)
Granisetron (injection)	On days of each daratumumab infusion (cycle days 1 and 2 for split first dose patients)
Granisetron (oral)	Daily as needed
Hydrocortisone	On days of each daratumumab infusion (cycle days 1 and 2 for split first dose patients)
Lorazepam	On days of each daratumumab infusion (cycle days 1 and 2 for split first dose patients)
Methylprednisolone	On days of each daratumumab infusion (cycle days 1 and 2 for split first dose patients)
Metoclopramide	Every 4 h as needed
Montelukast sodium	1 day prior to infusion, daily for 3 days then as needed after cycle 1
Ondansetron	On days of each daratumumab infusion (cycle days 1 and 2 for split first dose patients)
Prochlorperazine maleate (injection)	On days of each daratumumab infusion (cycle days 1 and 2 for split first dose patients)
Prochlorperazine maleate (oral)	Every 6 h as needed
Ranitidine	1 h prior to each daratumumab infusion (cycle days 1 and 2 for split first dose patients)

Supplemental Table 3. Occurrence of specific infusion-related reactions.

	Overall (n = 302)	Split first dose (n = 184)	Single dose (n = 118)	*P* value
Infusion-related reactions (total, first administration), n (%)				
Abdominal discomfort (e.g., epigastric pain, stomach cramps)	6 (1.6)	5 (2.1)	1 (0.7)	0.2502
Bronchospasm	2 (0.5)	2 (0.9)	0 (0.00)	
Cardiovascular (e.g., tachycardia, hypotension)	7 (1.8)	5 (2.1)	2 (1.4)	
Chest discomfort/difficulty breathing	42 (11.1)	26 (11.1)	16 (11.0)	
Chills	16 (4.2)	7 (3.0)	9 (6.2)	
Congestion (e.g., runny nose, sneezing)	15 (3.9)	8 (3.4)	7 (4.8)	

(*continued on next page*)

Supplemental Table 3. (*Continued*)

	Overall (n = 302)	Split first dose (n = 184)	Single dose (n = 118)	*P* value
Cough	36 (9.5)	17 (7.3)	19 (13.0)	
Diarrhea	6 (1.6)	4 (1.7)	2 (1.4)	
Dizziness	5 (1.3)	3 (1.3)	2 (1.4)	
Dyspnea	28 (7.4)	23 (9.8)	5 (3.4)	
Epistaxis	2 (0.5)	1 (0.4)	1 (0.7)	
Eye discomfort (e.g., watery and red eyes)	8 (2.1)	4 (1.7)	4 (2.7)	
Fatigue	2 (0.5)	2 (0.9)	0 (0.00)	
Fever	3 (0.8)	2 (0.9)	1 (0.7)	
Flushing	16 (4.2)	10 (4.3)	6 (4.1)	
Headache	7 (1.8)	2 (0.9)	5 (3.4)	
Hot flashes	7 (1.8)	5 (2.1)	2 (1.4)	
Hypertension	1 (0.3)	1 (0.4)	0 (0.00)	
Hypoxia	15 (3.9)	10 (4.3)	5 (3.4)	
Itching	13 (3.4)	8 (3.4)	5 (3.4)	
Mental status (e.g., confusion, agitated)	9 (2.4)	9 (3.8)	0 (0.00)	
Multiple	6 (1.6)	4 (1.7)	2 (1.4)	
Musculoskeletal pain (e.g., back pain)	8 (2.1)	6 (2.6)	2 (1.4)	
Nasal congestion	29 (7.6)	17 (7.3)	12 (8.2)	
Other/not specified	15 (3.9)	11 (4.7)	4 (2.7)	
Rigors/chills	15 (3.9)	10 (4.3)	5 (3.4)	
Sleep difficulties	3 (0.8)	2 (0.9)	1 (0.7)	
Throat discomfort (e.g., sore throat, throat tightness)	8 (2.1)	2 (0.9)	6 (4.1)	
Throat irritation	20 (5.3)	12 (5.1)	8 (5.5)	
Vomiting and/or nausea	30 (7.9)	16 (6.8)	14 (9.6)	
Infusion-related reactions (total, second infusion), n (%)				
Abdominal discomfort (e.g., epigastric pain, stomach cramps)		2 (0.5)		—
Cardiovascular (e.g., tachycardia, hypotension)		1 (0.3)		
Chest discomfort/difficulty breathing		3 (0.8)		
Cough		1 (0.3)		
Dyspnea		1 (0.3)		
Fatigue		1 (6.3)		
Musculoskeletal pain (e.g., back pain)		2 (0.5)		
Nasal congestion		1 (0.3)		
Other/not specified		1 (0.3)		
Rigors/chills		1 (0.3)		
Sleep difficulties		1 (0.3)		
Vomiting and/or nausea		1 (0.3)		

Supplemental Table 4. Univariate linear regression for factors associated with total administration time among patients selected for chart review (n = 184 split first dose/ n = 118 single dose).

Analysis variable	Parameter estimate	Standard error	*P* value
Age (years)			
< 65 (reference)	—	—	—
65-75	–0.11119	0.30197	0.7130
>75	0.55972	0.39874	0.1615
Gender	–0.34171	0.27171	0.2096
Female (reference)	—	—	—
Male	–0.34171	0.27171	0.2096
Race			
Caucasian (reference)	—	—	—
Black or African American	0.15463	0.44517	0.7286
Other	2.39838	0.79797	0.0029
No information	0.4718	0.46822	0.3145
Ethnicity			
Latino/Hispanic (reference)	—	—	—
Not Latino/Hispanic	–1.10924	0.52007	0.0338
No information	–0.9372	0.68982	0.1754
BMI category			
Normal (reference)	—	—	—
Obese	0.03644	0.34377	0.9156
Overweight	–0.15715	0.32753	0.6317
Underweight	–0.69685	1.03606	0.5018
No information	0.28315	2.26843	0.9008
BSA			
25-50th percentile (reference)	—	—	—
<25th percentile	0.64083	0.33142	0.0542
>75th percentile	0.181	0.32976	0.5835
Smoking status			
Never (reference)	—	—	—
Current	–0.6805	0.55601	0.2220
Former	–0.48873	0.29436	0.0980
No information	–0.21893	1.13372	0.8470
Practice region			
South (reference)	—	—	—
Northeast	0.33716	0.48961	0.4916
Midwest	0.35244	0.48961	0.4722
West	0.76527	0.31415	0.0155
International Staging Systems stage at diagnosis			
Stage I (reference)	—	—	—
Stage II	0.46019	0.36445	0.2078
Stage III	0.48492	0.3562	0.1745
No information	0.19557	0.47924	0.6835

(*continued on next page*)

Supplemental Table 4. (*Continued*)

Analysis variable	Parameter estimate	Standard error	*P* value
MM subtype			
IgG (reference)	—	—	—
IgA	0.7046	0.36341	0.0535
No information	0.45507	0.30084	0.1315
MM subtype isotype			
Kappa light chain (reference)	—	—	—
Lambda light chain	–0.12086	0.34582	0.7270
No information	0.10015	0.31431	0.7503
Karnofsky performance status			
< 40 (reference)	—	—	—
40, 50	–0.35083	1.66443	0.8332
60, 70	–0.91721	0.58197	0.1162
80, 90	–0.9881	0.5287	0.0627
No information	–0.70806	0.76658	0.3565
Comorbidities			
Anemia	0.41839	0.69097	0.5453
Cardiovascular disease	0.28336	1.5947	0.8591
Renal disease	2.55622	1.29538	0.0495
Daratumumab initiation over time			
2015Q4 (reference)	—	—	—
2016Q1	1.2654	0.68303	0.0650
2016Q2	1.66611	0.6999	0.0180
2016Q3	1.93778	0.69613	0.0058
2016Q4	1.90444	0.69257	0.0064
2017Q1	2.09285	0.63053	0.0010
2017Q2	1.91598	0.63399	0.0028
Daratumumab pre-medications over time			
2015Q4 (reference)	—	—	—
2016Q1	1.2654	0.68303	0.0650
2016Q2	1.66611	0.6999	0.0180
2016Q3	1.93778	0.69613	0.0058
2016Q4	1.90444	0.69257	0.0064
2017Q1	2.09285	0.63053	0.0010
2017Q2	1.91598	0.63399	0.0028
Daratumumab post-medications over time			
2015Q4 (reference)	—	—	—
2016Q1	1.2654	0.68303	0.0650
2016Q2	1.66611	0.6999	0.0180
2016Q3	1.93778	0.69613	0.0058
2016Q4	1.90444	0.69257	0.0064
2017Q1	2.09285	0.63053	0.0010
2017Q2	1.91598	0.63399	0.0028
Daratumumab post-medications			
Acetaminophen	0.24725	1.13172	0.8272
Dexamethasone	0.78587	0.32237	0.0154

Supplemental Table 4. (*Continued*)

Analysis variable	Parameter estimate	Standard error	*P* value
Granisetron	0.51003	0.34701	0.1428
Hydrocortisone	0.08911	0.30382	0.7695
Lorazepam	−1.03501	0.54421	0.0582
Methylprednisolone	−0.02763	0.29792	0.9262
Metoclopramide	−1.43219	2.24963	0.5249
Ondansetron	0.49864	0.32444	0.1255
Ranitidine	−0.55319	0.33018	0.0950
Montelukast	−1.05127	1.59353	0.5100
Daratumumab pre-medications			
Acetaminophen	0.24725	1.13172	0.8272
Dexamethasone	0.58667	0.45386	0.1972
Diphenhydramine	1.87388	1.59079	0.2398
Granisetron	0.08868	0.33181	0.7895
Hydrocortisone	−0.03154	0.29792	0.9158
Lorazepam	−0.98345	0.55943	0.0799
Methylprednisolone	0.04058	0.30019	0.8926
Metoclopramide	−0.38815	1.59462	0.8079
Ondansetron	−0.02357	0.27831	0.9326
Ranitidine	−0.59345	0.32196	0.0664
Daratumumab regimen	0.56394	0.28801	0.0512
Monotherapy (reference)	—	—	—
Combination therapy	0.56394	0.28801	0.0512
Line of therapy			
LOT1 (reference)	—	—	—
LOT2	−0.02299	0.6436	0.9715
LOT3	−0.25853	0.62154	0.6778
LOT4+	0.1414	0.43278	0.7441
No information	−1.62876	1.60116	0.3099
Actual daratumumab formula dose - first infusion	−2.14434	0.24285	<0.0001
Daratumumab administration schedule			
Single dose (reference)	—	—	—
Split first dose	2.63252	0.22859	<0.0001
Planned daratumumab formula dose - first infusion	−0.26804	0.03036	<0.0001
Planned daratumumab formula dose — second infusion	−0.25015	0.031	<0.0001
Actual daratumumab formula dose — first infusion	−0.24836	0.02986	<0.0001
Actual daratumumab formula dose — second infusion	−0.27087	0.03114	<0.0001
Total daratumumab formula dose	0.28759	0.06785	<0.0001
Duration between first and second daratumumab infusion	−0.34899	0.03553	<0.0001
Discontinuation prior to second administration	1.4692	1.12834	0.1940
Infusion-related reactions (total)			
Cough	0.31453	0.44062	0.4759
Chills	−0.52372	0.61556	0.3956
Hypoxia	−0.75143	0.7602	0.3238
Nasal congestion	1.11087	0.44289	0.0127

(*continued on next page*)

Supplemental Table 4. (*Continued*)

Analysis variable	Parameter estimate	Standard error	*P* value
Hypertension	−2.1849	2.24743	0.3318
Throat irritation	1.18915	0.54306	0.0294
Bronchospasm	3.7532	2.23989	0.0949
Vomiting and/or nausea	−0.5641	0.45396	0.2151
Other	0.36243	0.27745	0.1925
Infusion-related reactions - first infusion			
Hypertension	−2.1849	2.24743	0.3318
Hypoxia	−0.08724	0.92751	0.9251
Nasal congestion	2.01323	0.56589	0.0004
Throat irritation	2.39097	0.70931	0.0009
Vomiting and/or nausea	1.09488	0.63501	0.0858
Other	1.66963	0.30989	<0.0001
Dyspnea	1.19328	0.55795	0.0333
Chills	1.41758	0.92358	0.1260
Cough	2.75197	0.67122	<0.0001
Count of infusion-related reactions: first administration			
0 (reference)	—	—	—
1	−2.17728	0.47994	<0.0001
2	−1.73144	0.66475	0.0097
3	−4.07793	0.69921	<0.0001
4	−1.34644	1.03755	0.1955
≥5	−0.44459	0.69921	0.5254
Count of infusion-related reactions: first infusion			
0 (reference)	—	—	—
≥5	1.32412	0.7194	0.0668