



ORIGINAL RESEARCH

Pharmacokinetics and Exposure–Response Analyses of Daratumumab in Combination Therapy Regimens for Patients with Multiple Myeloma

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ABSTRACT

Introduction: Daratumumab, a human IgG monoclonal antibody targeting CD38, has demonstrated activity as monotherapy and in combination with standard-of-care regimens in multiple myeloma. Population pharmacokinetic analyses were conducted to determine the pharmacokinetics of intravenous daratumumab in combination therapy versus monotherapy, evaluate the effect of patient- and disease-

related covariates on drug disposition, and examine the relationships between daratumumab exposure and efficacy/safety outcomes. **Methods:** Four clinical studies of daratumumab in combination with lenalidomide/dexamethasone (POLLUX and GEN503); bortezomib/dexamethasone (CASTOR); pomalidomide/dexamethasone, bortezomib/thalidomide/dexamethasone, and bortezomib/melphalan/prednisone (EQUULEUS) were included in the analysis. Using various dosing schedules, the majority of patients (684/694) received daratumumab at a dose of 16 mg/kg. In GEN503, daratumumab was administered at a dose of 2 mg/kg ($n = 3$), 4 mg/kg ($n = 3$), 8 mg/kg ($n = 4$), and 16 mg/kg ($n = 34$). A total of 650 patients in EQUULEUS ($n = 128$), POLLUX ($n = 282$), and CASTOR ($n = 240$) received daratumumab 16 mg/kg. The exposure–efficacy

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and exposure–safety relationships examined progression-free survival (PFS) and selected adverse events (infusion-related reactions; thrombocytopenia, anemia, neutropenia, lymphopenia, and infections), respectively.

Results: Pharmacokinetic profiles of daratumumab were similar between monotherapy and combination therapy. Covariate analysis identified no clinically important effects on daratumumab exposure, and no dose adjustments were recommended on the basis of these factors. Maximal clinical benefit on PFS was achieved for the majority of patients (approximately 75%) at the 16 mg/kg dose. No apparent relationship was observed between daratumumab exposure and selected adverse events.

Conclusion: These data support the recommended 16 mg/kg dose of daratumumab and the respective dosing schedules in the POLLUX and CASTOR pivotal studies.

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Keywords: CD38; Daratumumab; Pharmacokinetics; Multiple myeloma; Oncology

INTRODUCTION

Despite recent advancements in treatment strategies for multiple myeloma (MM), outcomes remain poor and treatment options are limited for patients who relapse following therapy with a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or those who are refractory to these agents [1, 2]. Daratumumab is a human monoclonal antibody that targets CD38 and induces anti-myeloma activity through on-tumor and immunomodulatory

mechanisms of action [3–8]. Clinical studies of daratumumab monotherapy (GEN501 and SIR-IUS) demonstrated deep and durable responses in patients with heavily treated relapsed or relapsed and refractory MM [9, 10]. Clinical and pharmacokinetics (PK) data from these studies led to the approval of daratumumab monotherapy in many countries worldwide [11] and established the recommended dose (16 mg/kg actual body weight) and dosing schedule (once weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter) for treatment [10, 12–14]. In a pooled analysis of GEN501 and SIRIUS, daratumumab monotherapy (16 mg/kg) was well tolerated, and patients with heavily treated MM achieved an overall response rate (ORR) of 31.1% [10, 15].

Recent studies have indicated that there is a significant benefit to patient outcomes when daratumumab is combined with various background therapy regimens. The combination of daratumumab with lenalidomide and dexamethasone (D-Rd) resulted in an ORR of 81% in the single-arm phase 1/2 GEN503 study of the combination in heavily treated patients with refractory or relapsed and refractory MM [16]. In the phase 3 POLLUX study, D-Rd elicited a significant 63% reduction in disease progression or death compared with lenalidomide and dexamethasone (Rd) alone [17]. Similarly, in the phase 3 CASTOR study, daratumumab plus bortezomib and dexamethasone (D-Vd) significantly reduced the risk of progression or death by 61% compared to bortezomib and dexamethasone (Vd) alone in patients with relapsed and refractory disease treated with a median of two lines of therapy [18]. On the basis of these pivotal studies, daratumumab in combination with Rd or Vd was first approved in the USA and Europe [19], and subsequently many other countries, for the treatment of patients with MM who have received one or more prior lines of therapy. A recent phase 1 study (EQUULEUS) of daratumumab in combination with pomalidomide and dexamethasone (D-Pd) yielded promising results, with an ORR of 60%, and 29% of patients who achieved a complete response or better reached minimal residual disease negative status at a sensitivity threshold of 10^{-5} [20]. On the basis of these findings, D-Pd

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was approved in the USA for patients with MM who have received at least two prior lines of therapy including lenalidomide and a proteasome inhibitor. Recently, daratumumab added to the standard of care regimen of bortezomib, melphalan, and prednisone (D-VMP) was shown to reduce the risk of progression or death by 50% in transplant-ineligible newly diagnosed MM patients [21].

PK data from the monotherapy studies (GEN501 and SIRIUS) indicate that daratumumab exhibits nonlinear PK consistent with target-mediated drug disposition [13]. Population PK modeling showed that efficacious concentrations of daratumumab were achieved rapidly in patients receiving daratumumab 16 mg/kg via the standard dosing schedule and were maintained as the frequency of dosing was reduced [12, 14]. Given the promising efficacy of daratumumab when combined with other treatments across all lines of treatment, it is necessary to understand the PK of daratumumab when administered as part of a combination regimen and the relationship of daratumumab exposure with efficacy and safety.

The purpose of this investigation was to determine the PK of daratumumab in combination therapy. Population PK analyses were performed using data from four clinical studies of daratumumab combination therapy including POLLUX, GEN503, CASTOR, and EQUULEUS. We compared PK of combination therapies versus daratumumab monotherapy, evaluated the effect of patient- and disease-related covariates on drug disposition, and examined the relationships between daratumumab exposure and safety and efficacy outcomes.

METHODS

Patients and Study Designs

Population PK analyses were performed on combined datasets from four clinical studies: CASTOR (MMY3004; ClinicalTrials.gov identifier, NCT02136134), POLLUX (MMY3003; NCT02076009), GEN503 (NCT01615029), and EQUULEUS (MMY1001; NCT01998971), all of

which have been described in detail elsewhere [16–18, 20]. Key eligibility criteria for each study are shown in Supplemental Table 1. CASTOR was a randomized, active-controlled, multicenter, phase 3 study comparing D-Vd to Vd alone in patients with relapsed or relapsed and refractory MM [18]. In CASTOR, patients received daratumumab 16 mg/kg once weekly for 9 weeks (cycles 1–3), every 3 weeks for 15 weeks (cycles 4–8), and every 4 weeks thereafter (Supplemental Table 2). POLLUX was a randomized, active-controlled, multicenter, phase 3 study comparing D-Rd to Rd alone in patients with relapsed or refractory MM [17]. In POLLUX, daratumumab 16 mg/kg was administered once weekly for 8 weeks (cycles 1–2), then every 2 weeks for 16 weeks (cycles 3–6), and then every 4 weeks thereafter. GEN503 was a phase 1/2, open-label, dose-escalation (part 1) and dose-expansion (part 2) study of D-Rd in patients with refractory or relapsed and refractory MM [16]. In part 2 of GEN503, patients received daratumumab 16 mg/kg on the same dosing schedule as the POLLUX study. EQUULEUS was a multi-arm, phase 1/2, open-label study of daratumumab in combination with a variety of backbone regimens in newly diagnosed and relapsed or refractory MM [20]. Dosing schedules were once weekly for 6 weeks [cycles 1–2 for Vd and bortezomib, thalidomide, and dexamethasone (VTd); cycle 1 for bortezomib, melphalan, and prednisone (VMP)], then every 3 weeks thereafter, or were consistent with the dosing schedule in POLLUX (Rd), depending on the combination partners.

In the combined analysis, daratumumab was administered intravenously to a total of 694 patients using various dosing schedules. A total of 650 patients in EQUULEUS ($n = 128$), POLLUX ($n = 282$), and CASTOR ($n = 240$) received daratumumab 16 mg/kg. In GEN503, a total of 34 patients received daratumumab 16 mg/kg, while the remaining patients received daratumumab at doses of 2 mg/kg ($n = 3$), 4 mg/kg ($n = 3$), and 8 mg/kg ($n = 4$). Thus, the population PK dataset included 694 patients, 684 of whom received daratumumab 16 mg/kg. Patients who received less than 16 mg/kg of daratumumab were not included in the efficacy and safety analysis.

Compliance with Ethics Guidelines

All studies were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and all patients provided written informed consent.

Population PK and Exposure–Response Analysis

Analyses were performed on pooled datasets from CASTOR, POLLUX, GEN503, and EQUULEUS. In CASTOR, samples were collected within 2 h prior to and immediately following daratumumab infusions on day 1 of cycles 1, 3, 6, 9, and 12 (cycles 1–8: 21 days; cycles 9+: 28 days). In POLLUX, samples were collected within 2 h prior to and immediately following daratumumab infusions on day 1 of cycles 1, 3, and 12 (28-day cycles). In both CASTOR and POLLUX, samples were collected at the end of treatment and during the follow-up visit. In GEN503, part 1, samples were collected prior to and at the end of infusion on all daratumumab infusion days, at each follow-up visit, and at the end of treatment visit. In part 2 of GEN503, the sampling schedule was reduced to day 1 of cycles 1, 3, 6, and 12, and at weeks 4 and 8 after the last treatment dose. In EQUULEUS, samples from the D-VMP and D-Pd regimens were collected within 2 h prior to and at the end of infusion on days 1 and 22 of cycle 1, day 1 of cycles 2–4, and weeks 3 and 9 of the follow-up phase (D-VMP: 42-day cycles; D-Pd: 28-day cycles). In the D-VTd and D-Vd arms of EQUULEUS, samples were collected within 2 h prior to and at the end of infusion on day 1 of cycles 1–4 and at weeks 3 and 9 of the follow-up phase (D-VTd and D-Vd: 21-day cycles). Serum daratumumab concentrations were evaluated using a validated enzyme-linked immunosorbent assay [lower limit of quantitation (LLOQ) = 0.2 µg/mL; BioAnalytical Research Corporation Global Central Laboratory, Ghent, Belgium; Janssen Research & Development, LLC, Spring House, PA, USA]. Immunogenicity was analyzed by determining the presence of anti-daratumumab antibodies. A population PK model, previously developed

using data from daratumumab monotherapy studies [14], was used to fit concentration–time data from the four combination studies. No direct impact of the background therapies on the PK of daratumumab was expected given the lack of overlapping clearance mechanisms for daratumumab and the co-administered small-molecule therapies [22–24]. NONMEM® 7.2 software (ICON, Dublin, Ireland) was used for population PK modeling. Software package R (version 3.1.2) was used for data management, post-processing, and all other analyses of NONMEM runs. PK simulations were run using the dosing schedules for CASTOR and for POLLUX.

Subgroup analyses were performed to evaluate the relationship between daratumumab exposure and patient- and disease-related characteristics, including age, race, sex, body weight, hepatic or renal impairment, type of myeloma (immunoglobulin [Ig] G versus non-IgG), baseline Eastern Cooperative Oncology Group status, number of prior therapies, and refractory status. The relationship between daratumumab exposure [maximal pre-infusion (trough) concentration ($C_{\text{pre-infusion,max}}$)] and progression-free survival (PFS) was examined for the POLLUX and CASTOR studies in which PFS was the primary endpoint. The relationship between $C_{\text{pre-infusion,max}}$ and adverse events (AEs) of interest, selected because of their frequency in anti-myeloma treatment (i.e., incidence of thrombocytopenia, anemia, neutropenia, lymphopenia, and infections), was examined by treatment regimen [i.e., D-Rd (combined data from POLLUX and GEN503), D-Vd (CASTOR), and D-Pd (EQUULEUS)]. To evaluate the relationship between the incidence of infusion-related reactions (IRRs) and daratumumab exposure, the predicted end-of-infusion concentration after the first infusion ($C_{\text{max,1st}}$) was used because the majority of IRRs occurred during the first infusion.

Cox proportional hazard regression models, implemented in the “survival” package in the software program R, were used to explore the relationship between $C_{\text{pre-infusion,max}}$ and PFS for CASTOR and POLLUX using P-splines. The respective control groups were used as a reference level for calculating relative hazard. The exposure–safety relationship was explored on the

basis of exposure quantiles of $C_{\text{post-infusion,max}}$ and their corresponding 95% confidence interval for the selected AEs and $C_{\text{max,1st}}$ for IRRs.

RESULTS

Patient and Disease Characteristics

The population PK dataset included 4426 measurable samples from 694 patients (POLLUX, $n = 282$; GEN503, $n = 44$; EQUULEUS, $n = 128$; CASTOR, $n = 240$), 684 of whom received daratumumab 16 mg/kg. A small proportion (2.5%) of the samples were below the LLOQ of 0.2 $\mu\text{g/mL}$ for daratumumab and excluded from the population PK analysis. Descriptive statistics of baseline continuous and categorical patient and disease covariates are summarized in Supplemental Table 3 and Supplemental Table 4, respectively.

Comparison of PK of Daratumumab Following Monotherapy and Combination Therapy Regimens

Regardless of the background regimen in the treatment combination, daratumumab concentrations were similar to those in the

monotherapy studies (Supplemental Fig. 1). The similar PK of daratumumab between the monotherapy and combination therapy studies suggested that the small-molecule combinations would not impact daratumumab PK. As in the monotherapy studies, concentration–time data for daratumumab in combination regimens were adequately described by a two-compartment population PK model with parallel linear and non-linear Michaelis–Menten eliminations. The parameter estimates of the final covariate model are presented in Supplemental Table 5. Exposure to daratumumab was similar between monotherapy and combination therapies. The average predicted $C_{\text{pre-infusion,max}}$ was 632.8 $\mu\text{g/mL}$ following combination therapy with daratumumab using the POLLUX dosing schedule (after 8 weekly infusions) and 667.0 $\mu\text{g/mL}$ for the CASTOR schedule (after 9 weekly infusions) versus 530.7 $\mu\text{g/mL}$ following daratumumab monotherapy (after 8 weekly infusions). The model-derived mean [\pm standard deviation (SD)] half-life associated with linear elimination was 23.3 ± 11.8 days in the combination studies, assuming the standard (POLLUX-like) dosing schedule, compared with 18.0 ± 9.0 days in the monotherapy studies. Consistent with the monotherapy studies, steady state levels of daratumumab were

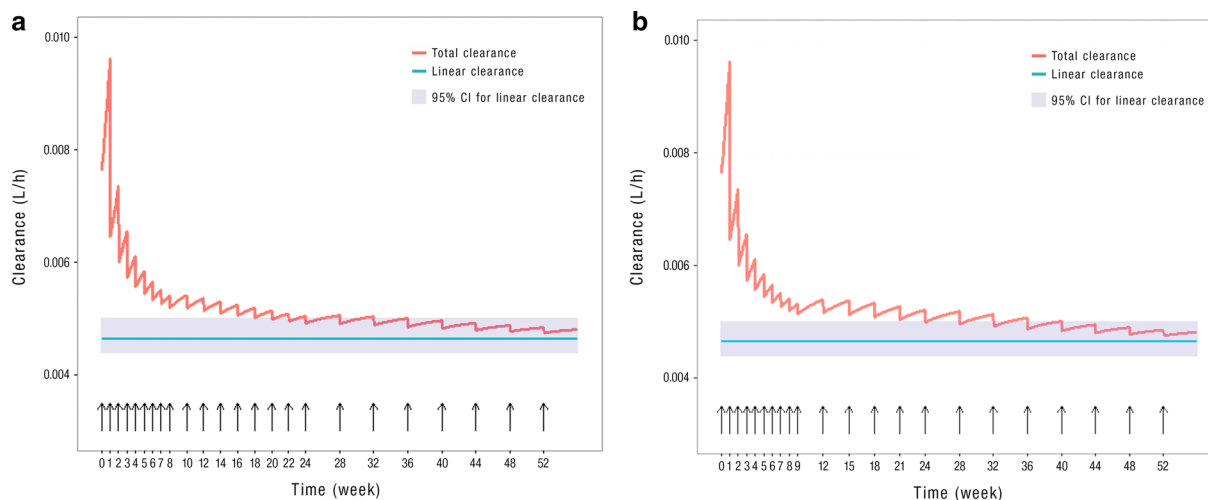


Fig. 1 Model-based simulation of daratumumab clearance versus time using POLLUX (a) and CASTOR (b) dosing schedules. The red line represents total clearance, and the blue line represents linear clearance. The blue shaded region delineates the 95% CI for linear clearance. Arrows represent dosing events. *CI* confidence interval

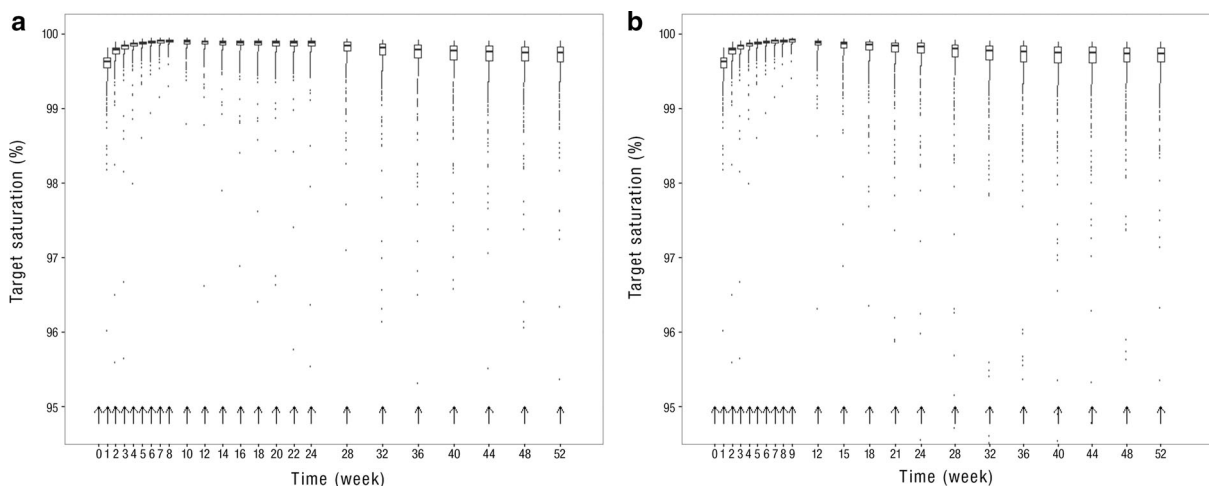


Fig. 2 Target saturation profile of daratumumab at pre-infusion time points for the POLLUX (a) and CASTOR (b) dosing schedules. For the POLLUX dosing schedule (a), the simulations were performed assuming the dosing schedule of QW for 8 weeks, Q2W for 16 weeks, and then Q4W thereafter. For the CASTOR dosing schedule (b), the simulations were performed assuming the dosing schedule of QW for 9 weeks, Q3W for 15 weeks, and then Q4W for 32 weeks thereafter. The predicted target saturation was calculated as $100 \times C/(K_M + C)$, where C represents the pre-infusion (trough) concentration at each time point. Arrows represent dosing events. *QW* weekly, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q3W* every 3 weeks

reached at approximately 5 months into the every-4-week (Q4W) dosing period. The total clearance of daratumumab decreased over time and approached the non-specific linear clearance after approximately 8 weeks under the standard dosing schedule (Fig. 1a) as well as the different dosing schedule used in the CASTOR study (Fig. 1b). Total clearance continued to stay close to linear clearance during the Q4W dosing period, suggesting that target saturation was maintained. During the Q4W dosing period, concentrations consistent with 99% target saturation were maintained at trough concentrations in more than 90% of patients treated with the recommended dosing schedule (Fig. 2a) and the CASTOR dosing schedule (Fig. 2b).

Effects of Patient and Disease Characteristics on Daratumumab Exposure

The effects of patient and disease characteristics on the estimated $C_{\text{pre-infusion,max}}$ were similar to or smaller than those estimated using the model based on the monotherapy studies [14] (Table 1)

and were similar regardless of dosing schedule (data not shown). Consistent with the results from the monotherapy studies, all of the investigated covariate effects were within 25% of the reference value. Clearance and volume of distribution of daratumumab increased with increasing body weight; however, daratumumab exposure differed by less than 20% across patients with varied body weights when daratumumab was administered on a milligram per kilogram basis. Daratumumab exposure was approximately 23% lower in patients with IgG-type MM compared with those who had non-IgG MM. No dose adjustments are recommended on the basis of the presence of the IgG myeloma subtype [14].

Relationship Between Daratumumab Exposure and Efficacy

An exposure–response analysis on PFS for POLLUX and CASTOR was done with their control groups (Rd and Vd, respectively) as the reference level to calculate the relative hazard (Fig. 3a, b). The relative hazard for PFS and

Table 1 Effect of covariates on daratumumab exposure: comparison of change relative to reference value of the $C_{\text{pre-infusion,max}}$ between monotherapy and combination therapies (POLLUX dosing schedule)

Covariate	Monotherapy	Combination therapies
Renal function		
Mild vs. normal	1.15 (0.86–1.54)	0.99 (0.91–1.07)
Moderate vs. normal	0.96 (0.71–1.30)	0.97 (0.89–1.06)
Severe vs. normal	1.00 (0.47–2.12)	1.02 (0.78–1.32)
Hepatic function		
Mild vs. normal	0.71 (0.51–0.98)	1.01 (0.91–1.12)
Moderate/severe vs. normal	NE	0.95 (0.63–1.41)
Age, years		
≥ 65 vs. < 65	1.07 (0.84–1.35)	1.06 (0.99–1.13)
≥ 75 vs. < 75	1.09 (0.71–1.69)	1.01 (0.90–1.13)
Sex		
Male vs. female	0.86 (0.68–1.09)	0.96 (0.90–1.03)
Race		
White vs. non-white	0.88 (0.61–1.27)	1.10 (1.01–1.19)
Body weight ^a , kg		
Q3 vs. Q4	1.06 (0.76–1.47)	0.98 (0.90–1.08)
Q2 vs. Q4	0.90 (0.65–1.25)	0.89 (0.81–0.98)
Q1 vs. Q4	0.76 (0.54–1.06)	0.81 (0.74–0.90)
Albumin, g/L		
< 35 vs. ≥ 35 (normal)	0.72 (0.57–0.92)	0.79 (0.74–0.86)
Prior line of therapy		
2 vs. 1	NA	0.98 (0.90–1.06)
3 vs. 1	NA	0.97 (0.88–1.07)
> 3 vs. 1	NA	0.84 (0.75–0.93)
> 3 vs. ≤ 3	0.83 (0.63–1.11)	NA
Refractory status		
PI only vs. none	NA	0.93 (0.82–1.06)
IMiD only vs. none	NA	0.95 (0.84–1.08)
Double vs. none	NA	0.92 (0.81–1.05)
Double vs. other	1.08 (0.80–1.46)	NA
ECOG status		
1 vs. 0	0.88 (0.68–1.15)	0.99 (0.92–1.06)

Table 1 continued

Covariate	Monotherapy	Combination therapies
2 vs. 0	0.85 (0.51–1.43)	0.95 (0.82–1.11)
Type of myeloma		
IgG vs. non-IgG	0.50 (0.40–0.62)	0.77 (0.73–0.83)

The $C_{\text{pre-infusion,max}}$ for the monotherapy and combination therapies were 530.65 $\mu\text{g/mL}$ (494.6–566.7) and 632.8 $\mu\text{g/mL}$ (620.0–645.6), respectively

NE not evaluable, *Q* quantile, *NA* not applicable because of different grouping for monotherapy and combination therapy analyses, *PI* proteasome inhibitor, *IMiD* immunomodulatory drug, *ECOG* Eastern Cooperative Oncology Group, *Ig* immunoglobulin

^a The quantiles of body weight for combination studies were Q1 < 64.6 kg, Q2 > 64.6 to \leq 75.9 kg, Q3 > 75.9 to \leq 88.0 kg, and Q4 > 88.0 kg. The quantiles of body weight for monotherapy studies were Q1 < 63.9 kg, Q2 > 63.9 to \leq 78.6 kg, Q3 > 78.6 to \leq 88.1 kg, and Q4 > 88.1 kg

depth of response decreased rapidly with increasing daratumumab exposure based on the data from POLLUX and CASTOR (data not shown). When the maximum trough concentration was approximately 250 $\mu\text{g/mL}$, the risk compared to the control group was substantially reduced (by approximately 25% for POLLUX and CASTOR). When $C_{\text{pre-infusion,max}}$ was

greater than 250 $\mu\text{g/mL}$, the decline in relative hazards appeared to slow down, suggesting limited additional benefit at higher pre-infusion daratumumab concentrations. The majority of patients (approximately 75%) approached maximum effect, indicating that the maximum clinical benefit on PFS was achieved at the recommended 16 mg/kg dose and dosing schedule.

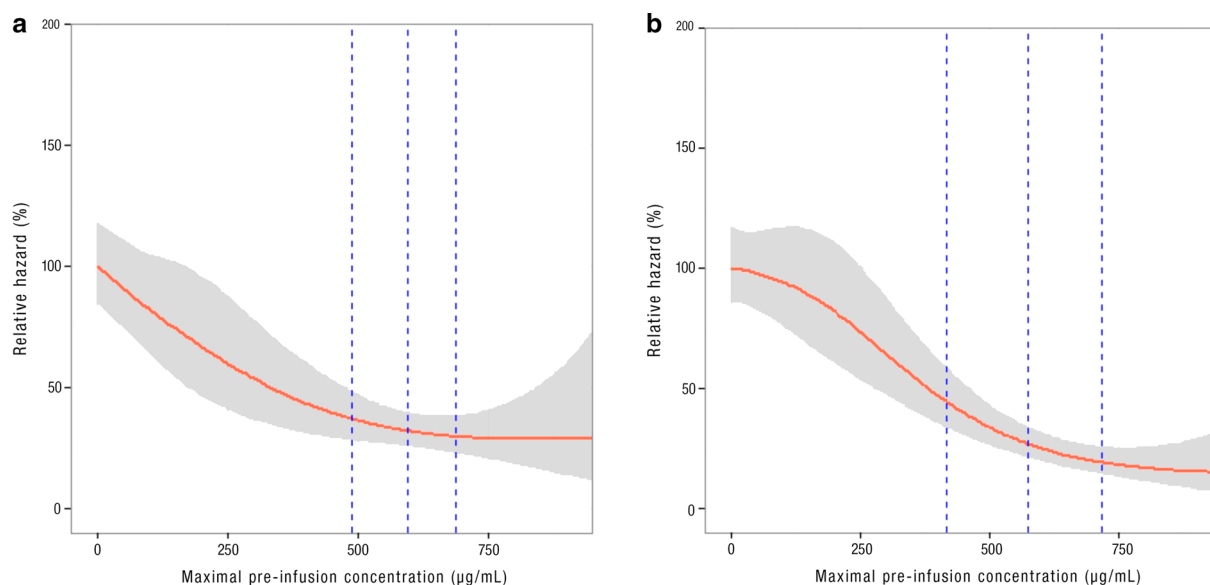


Fig. 3 Relative hazard of PFS at different predicted maximal trough concentrations for POLLUX (a) and CASTOR (b). The solid red line is the point estimate, and the gray shaded areas represent the 95% CI. The blue vertical dotted lines separate the quartiles of $C_{\text{pre-infusion,max}}$. The control group of each study (*Rd* in POLLUX and *Vd* in CASTOR) was used as the reference (i.e., $C_{\text{pre-infusion,max}} = 0$). $C_{\text{pre-infusion,max}}$ up to the 8th QW dose for POLLUX and CASTOR. Stratified Cox regression models based on risk stratification of the patients were used to estimate the relative hazard. *PFS* progression-free survival, *CI* confidence interval, *Rd* lenalidomide and dexamethasone, *Vd* bortezomib and dexamethasone, *QW* weekly

Table 2 Comparison of treatment-emergent adverse event rates between predicted daratumumab exposure quartiles

TEAE	Control				Exposure quartiles, % (95% CI)			
	% (95% CI)	1st	2nd	3rd	4th			
Combined POLLUX and GEN503	Rd, N = 281	D-Rd, N = 82	D-Rd, N = 81	D-Rd, N = 81	D-Rd, N = 82			
IRRs ^a	NA	69.5 (59.1–78.8)	45.7 (35.1–56.5)	38.3 (28.2–49.1)	39.0 (28.9–49.8)			
Grade ≥ 3	NA	9.8 (4.6–17.4)	1.2 (0.1–5.3)	7.4 (3–14.4)	1.2 (0.1–5.3)			
Thrombocytopenia	27.4 (22.4–32.8)	31.7 (22.3–42.2)	28.4 (19.4–38.8)	25.9 (17.2–36.1)	25.6 (17.0–35.7)			
Grade ≥ 3	13.5 (9.9–17.8)	15.9 (9.1–24.8)	13.6 (7.3–22.1)	12.3 (6.4–20.6)	9.8 (4.6–17.4)			
Neutropenia	43.1 (37.4–48.9)	70.7 (60.3–79.8)	65.4 (54.7–75.2)	54.3 (43.5–64.9)	59.8 (49.0–69.9)			
Grade ≥ 3	37.0 (31.5–42.8)	63.4 (52.7–73.3)	59.3 (48.4–69.5)	46.9 (36.3–57.8)	51.2 (40.5–61.9)			
Anemia	34.9 (29.5–40.6)	31.7 (22.3–42.2)	30.9 (21.5–41.4)	29.6 (20.4–40.1)	28.0 (19.1–38.3)			
Grade ≥ 3	19.6 (15.2–24.5)	19.5 (11.9–29.0)	14.8 (8.2–23.6)	4.9 (1.6–11.1)	8.5 (3.8–15.9)			
Lymphopenia	5.3 (3.1–8.4)	4.9 (1.5–11.0)	6.2 (2.3–12.8)	4.9 (1.6–11.1)	9.8 (4.6–17.4)			
Grade ≥ 3	3.6 (1.8–6.2)	4.9 (1.5–11.0)	6.2 (2.3–12.8)	3.7 (0.9–9.3)	8.5 (3.8–15.9)			
Infections	72.6 (67.2–77.6)	81.7 (72.4–89.0)	84.0 (75.0–90.8)	85.2 (76.4–91.8)	85.4 (76.7–91.9)			
Grade ≥ 3	22.8 (18.1–27.9)	31.7 (22.3–42.2)	27.2 (18.3–37.5)	29.6 (20.4–40.1)	23.2 (15.0–33.0)			
CASTOR	Vd, N = 237	D-Vd, N = 60	D-Vd, N = 60	D-Vd, N = 60	D-Vd, N = 60			
IRRs ^a	NA	75.0 (63.1–84.8)	38.3 (26.7–50.9)	40.0 (28.2–52.6)	28.3 (18.0–40.5)			
Grade ≥ 3	NA	16.7 (8.7–27.4)	5.0 (1.3–12.5)	8.3 (3.1–17.1)	5.0 (1.3–12.5)			
Thrombocytopenia	43.9 (37.7–50.2)	61.7 (49.1–73.3)	61.7 (49.1–73.3)	53.3 (40.8–65.6)	58.3 (45.7–70.3)			
Grade ≥ 3	32.9 (27.1–39.1)	55.0 (42.4–67.2)	50.0 (37.5–62.5)	36.7 (25.2–49.2)	40.0 (28.2–52.6)			
Neutropenia	9.3 (6.0–13.4)	23.3 (13.9–35.0)	13.3 (6.3–23.4)	15.0 (7.5–25.4)	20.0 (11.3–31.3)			
Grade ≥ 3	4.2 (2.1–7.3)	16.7 (8.7–27.4)	10.0 (4.1–19.2)	10.0 (4.1–19.2)	15.0 (7.5–25.4)			
Anemia	31.2 (25.5–37.3)	38.3 (26.7–50.9)	21.7 (12.6–33.1)	21.7 (12.6–33.1)	21.7 (12.6–33.1)			
Grade ≥ 3	16.0 (11.7–21.1)	25.0 (15.2–36.9)	16.7 (8.7–27.4)	8.3 (3.1–17.1)	5.0 (1.3–12.5)			

Table 2 continued

CASTOR	Vd, N = 237	D-Vd, N = 60	D-Vd, N = 60	D-Vd, N = 60
Lymphopenia	3.8 (1.8–6.7)	10.0 (4.1–19.2)	10.0 (4.1–19.2)	16.7 (8.7–27.4)
Grade ≥ 3	2.5 (1.0–5.1)	10.0 (4.1–19.2)	5.0 (1.3–12.5)	11.7 (5.2–21.3)
Infections	53.2 (46.8–59.5)	63.3 (50.8–74.8)	63.3 (50.8–74.8)	68.3 (56.0–79.2)
Grade ≥ 3	19.4 (14.7–24.8)	33.3 (22.3–45.8)	20.0 (11.3–31.3)	11.7 (5.2–21.3)
EQUULEUS	D-Pd, N = 25	D-Pd, N = 24	D-Pd, N = 25	D-Pd, N = 25
IRRs ^a	NE	41.7 (23.5–61.5)	48.0 (29.3–67.1)	36.0 (19.2–55.5)
Grade ≥ 3	NE	0 (NE–NE)	0 (NE–NE)	8.0 (1.4–22.7)
Thrombocytopenia	NE	41.7 (23.5–61.5)	44.0 (25.8–63.3)	16.0 (5.3–33.3)
Grade ≥ 3	NE	16.7 (5.5–34.6)	20.0 (7.7–38.2)	4.0 (0.2–16.5)
Neutropenia	NE	72.0 (52.8–86.9)	87.5 (70.7–96.7)	76.0 (57.2–89.7)
Grade ≥ 3	NE	68.0 (48.6–83.9)	83.3 (65.4–94.5)	76.0 (57.2–89.7)
Anemia	NE	68.0 (48.6–83.9)	58.3 (38.5–76.5)	36.0 (19.2–55.5)
Grade ≥ 3	NE	44.0 (25.8–63.3)	45.8 (27.1–65.4)	4.0 (0.2–16.5)
Lymphopenia	NE	16.0 (5.3–33.3)	25.0 (10.8–44.3)	20.0 (7.7–38.2)
Grade ≥ 3	NE	12.0 (3.1–28.2)	12.5 (3.3–29.3)	16.0 (5.3–33.3)
Infections	NE	48.0 (29.3–67.1)	62.5 (42.6–79.9)	100.0 (NE–NE)
Grade ≥ 3	NE	32.0 (16.1–51.4)	25.0 (10.8–44.3)	32.0 (16.1–51.4)

For POLLUX and GEN503, quartiles (Q) for $C_{\max,1st}$ were Q1 (≤ 247 µg/mL), Q2 (247–303 µg/mL), Q3 (303–347 µg/mL), and Q4 (347–464 µg/mL); and quartiles for $C_{\text{post-infusion,max}}$ were Q1 (≤ 740 µg/mL), Q2 (740–870 µg/mL), Q3 (870–1008 µg/mL), and Q4 (1008–1470 µg/mL). For CASTOR, quartiles for $C_{\max,1st}$ were Q1 (≤ 240 µg/mL), Q2 (240–291 µg/mL), Q3 (291–341 µg/mL), and Q4 (341–735 µg/mL); and quartiles for $C_{\text{post-infusion,max}}$ were Q1 (≤ 769 µg/mL), Q2 (769–932 µg/mL), Q3 (932–1111 µg/mL), and Q4 (1111–1708 µg/mL). For EQUULEUS, quartiles for $C_{\max,1st}$ were Q1 (≤ 266 µg/mL), Q2 (266–319 µg/mL), Q3 (319–372 µg/mL), and Q4 (372–907 µg/mL); and quartiles for $C_{\text{post-infusion,max}}$ were Q1 (≤ 574 µg/mL), Q2 (574–836 µg/mL), Q3 (836–1036 µg/mL), and Q4 (1036–1844 µg/mL).

TEAE treatment-emergent adverse event, CI confidence interval, Rd lenalidomide and dexamethasone, D-Rd daratumumab plus lenalidomide and dexamethasone, IRR infusion-related reaction, NA not applicable, Vd bortezomib and dexamethasone, D-Vd daratumumab plus bortezomib and dexamethasone, D-Pd daratumumab plus pomalidomide and dexamethasone, NE not evaluable

^a End-of-infusion concentration after $C_{\max,1st}$ was used as the exposure measure for analyses of IRRs. $C_{\text{post-infusion,max}}$ was used as the exposure measure for analyses of other AEs

Relationship Between Daratumumab Exposure and Safety

There was no apparent relationship between $C_{\text{pre-infusion,max}}$ and any of the examined AEs of interest including thrombocytopenia, anemia, neutropenia, and lymphopenia based on data from the four combination therapy studies (Table 2). Although the rate of infections of any grade appeared to increase numerically with daratumumab exposure, this trend was not observed for grade 3 or higher infections. Similarly, no association between increasing $C_{\text{max,1st}}$ and the incidence of IRRs was identified. Across all of the studies, two patients were identified as being positive for anti-daratumumab antibodies, one from POLLUX and one from EQUULEUS; no differences between the PK of these patients and those without anti-daratumumab antibodies were discernable.

DISCUSSION

The benefits of adding daratumumab to combination regimens in the treatment of relapsed or relapsed and refractory MM necessitate an understanding of the PK profile of the drug in these regimens. This population PK analysis included data from a large number of subjects in early and late phase, multinational, clinical trials evaluating the use of daratumumab in combination therapy for patients with MM. These data allowed evaluation of important patient-related covariates across various patient populations and daratumumab dosing schedules as well as confirmation of the findings in monotherapy studies that had relatively smaller sample sizes [25].

The PK of daratumumab in combination with other treatment regimens were consistent with the PK of daratumumab administered as monotherapy [12–14].

Daratumumab exposure was similar when administered with various combination therapies and as monotherapy. The predicted $C_{\text{pre-infusion,max}}$ (632.8 $\mu\text{g/mL}$ vs 530.65 $\mu\text{g/mL}$, respectively) and mean half-life (23 vs 18 days, respectively) for daratumumab combination therapy versus monotherapy at the recommended dose and dosing schedule in POLLUX

were similar. Achievement of steady state was consistently reached at approximately 5 months into the Q4W dosing period of the standard daratumumab dosing schedule. Moreover, daratumumab in combination with small-molecule therapies achieved greater than 99% target saturation at trough concentrations in more than 90% of patients following the Q4W dosing regimen. When the $C_{\text{pre-infusion,max}}$ was above the $\text{EC}_{90}^{\text{ORR}}$ identified at 274 $\mu\text{g/mL}$ from the monotherapy studies [12], the ORR was markedly higher compared to those patients with $C_{\text{pre-infusion,max}}$ below 274 $\mu\text{g/mL}$ (data not shown).

As observed in the monotherapy studies [14], no demographic or clinical characteristics were identified as having a clinically relevant effect on daratumumab PK. The covariate effects were all within 25%, and thus, no dose adjustment is recommended on the basis of these covariates. Increasing body weight was associated with increased daratumumab clearance and volume of distribution; however, daratumumab exposures were consistent across patients' weight range, indicating that a body weight-based dose is reasonable and effective for administration of daratumumab in combination therapies. Elevated levels of IgG M-protein can lead to increased clearance of IgG-based monoclonal antibodies as a result of competition for the neonatal Fc receptor, which protects IgG from degradation [26]. Similar to findings observed in the daratumumab monotherapy studies [14], the IgG MM patients had lower concentrations of daratumumab than the non-IgG MM patients. However, the difference was only 23%, approximately half of the magnitude of the difference observed in monotherapy studies [25], and was not considered clinically important.

Although most monoclonal antibodies have a biphasic PK profile with rapid distribution and slower elimination, individual PK properties of monoclonal antibodies are unique based on the biology of their target antigen [27]. The specific clearance of monoclonal antibodies is affected by binding to the target antigen, internalization, and subsequent intracellular protein catabolism. Fc-mediated effector functions not only contribute to the mechanism of action of monoclonal antibodies but also can impact their clearance. These factors highlight the need

for PK evaluations of each therapeutic monoclonal antibody used for treatment of MM.

The exposure–efficacy analyses suggest that maximum clinical benefit on PFS has been attained for the majority of the subjects (approximately 75%) with an acceptable safety profile at the recommended dose, 16 mg/kg. Target saturation was maintained throughout dosing, even during Q4W dosing. At the recommended dose of 16 mg/kg, the safety profile was acceptable, and there was no apparent relationship within the studied concentration range between drug exposure and IRRs, thrombocytopenia, anemia, neutropenia, and lymphopenia. The overall event rate of infection (any grade) appeared to increase with drug exposure, but this trend was not observed for grade 3 or higher infections.

There are some limitations to this study that are intrinsic to population PK analyses. Although a substantial number of MM patients from multiple clinical trials were utilized for analyses of PK over time, these analyses were limited by the schedule of PK sampling that varied slightly in each study protocol. In addition, data from clinical trials that utilized different daratumumab combination therapies were pooled for the analysis, with differences in sample size, phase of drug testing, and inclusion criteria between studies. Nevertheless, the PK data from this study are consistent with previous findings from daratumumab monotherapy studies and support the recommended 16 mg/kg dose of daratumumab in combination therapy.

CONCLUSION

These data support the recommended daratumumab 16 mg/kg dose in combination treatment regimens for patients with MM.

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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 Yale Open Data Access (YODA) Project site at <http://yoda.yale.edu>.

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REFERENCES

1. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter International Myeloma Working Group study. *Leukemia*. 2012;26(1):149–57.
2. Usmani S, Ahmadi T, Ng Y, et al. Analysis of real-world data on overall survival in multiple myeloma patients with ≥ 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or double refractory to a PI and an IMiD. *Oncologist*. 2016;21:1355–61.
3. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol*. 2011;186(3):1840–8.
4. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38⁺ immune-regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood*. 2016;128(3):384–94.
5. Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al. Direct in vitro comparison of daratumumab with surrogate analogs of CD38 antibodies MOR03087, SAR650984 and Ab79. *Blood*. 2014;124(21):3474.
6. Overdijk MB, Jansen JH, Nederend M, et al. The therapeutic CD38 monoclonal antibody daratumumab induces programmed cell death via Fc γ receptor-mediated cross-linking. *J Immunol*. 2016;197(3):807–13.
7. Overdijk MB, Verploegen S, Bogels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs*. 2015;7(2):311–21.
8. van de Donk NWCJ, Janmaat ML, Mutis T, et al. Monoclonal antibodies targeting CD38 in hematological malignancies and beyond. *Immunol Rev*. 2016;270(1):95–112.
9. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med*. 2015;373(13):1207–19.
10. Lonial S, Weiss BM, Usmani S, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet*. 2016;387(10027):1551–60.
11. McKeage K. Daratumumab: first global approval. *Drugs*. 2016;76(2):275–81.
12. Xu XS, Yan X, Puchalski T, et al. Clinical implications of complex pharmacokinetics for daratumumab dose regimen in patients with relapsed/refractory multiple myeloma. *Clin Pharmacol Ther*. 2016;101(6):721–4.

13. Clemens PL, Yan X, Lokhorst HM, et al. Pharmacokinetics of daratumumab following intravenous infusion in relapsed or refractory multiple myeloma after prior proteasome inhibitor and immunomodulatory drug treatment. *Clin Pharmacokinet*. 2016;56(8):915–24.
14. Yan X, Clemens PL, Puchalski T, et al. Target-mediated drug disposition of daratumumab following intravenous infusion in relapsed or refractory multiple myeloma after prior proteasome inhibitors and immunomodulatory drugs: a population pharmacokinetic analysis. *Blood*. 2015;126(23):4222.
15. Usmani S, Weiss B, Bahlis NJ, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. *Blood*. 2015;128(1):37–44.
16. Plesner T, Arkenau HT, Gimsing P, et al. Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma. *Blood*. 2016;128:1821–8.
17. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(14):1319–31.
18. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(8):754–66.
19. Bhatnagar V, Gormley NJ, Luo L, et al. FDA approval summary: daratumumab for treatment of multiple myeloma after one prior therapy. *Oncologist*. 2017;22(11):1347–53.
20. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood*. 2017;130(8):974–81.
21. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med*. 2018;378(6):518–28.
22. Guglieri-Lopez B, Perez-Pitarch A, Moes DJ, et al. Population pharmacokinetics of lenalidomide in multiple myeloma patients. *Cancer Chemother Pharmacol*. 2017;79(1):189–200.
23. Li Y, Xu Y, Liu L, Wang X, Palmisano M, Zhou S. Population pharmacokinetics of pomalidomide. *J Clin Pharmacol*. 2015;55(5):563–72.
24. LoRusso PM, Venkatakrishnan K, Ramanathan RK, et al. Pharmacokinetics and safety of bortezomib in patients with advanced malignancies and varying degrees of liver dysfunction: phase I NCI Organ Dysfunction Working Group Study NCI-6432. *Clin Cancer Res*. 2012;18(10):2954–63.
25. Yan X, Clemens PL, Puchalski T, et al. Influence of disease and patient characteristics on daratumumab exposure and clinical outcomes in relapsed or refractory multiple myeloma. *Clin Pharmacokinet*. 2018;57(4):529–38.
26. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol*. 2007;7(9):715–25.
27. Kamath AV. Translational pharmacokinetics and pharmacodynamics of monoclonal antibodies. *Drug Discov Today Technol*. 2016;21–22:75–83.