

Population Pharmacokinetics and Exposure–Response Analyses of Daratumumab in Combination With Pomalidomide and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma

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BACKGROUND AND OBJECTIVES

Daratumumab, a human IgG monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action, has been approved to treat patients with multiple myeloma (MM).

We aimed to develop a population pharmacokinetic (PPK) model to characterize the pharmacokinetics (PK) of intravenously (IV) and subcutaneously (SC) administered daratumumab in combination with dexamethasone and pomalidomide (Pd) in patients with relapsed or refractory multiple myeloma (RRMM), and also conduct an exposure-response (E-R) analysis to explore E-R relationships for efficacy and selected treatment-emergent adverse events (TEAEs).

METHODS

Data

The PPK analysis included serum concentrations of daratumumab from APOLLO [1] and EQUULEUS D-Pd cohort [2]. The E-R analysis for efficacy and safety was based on data from APOLLO only. Key study design elements and PK sampling are provided in **Table 1**.

Table 1. Overview of Studies Included in the PPK and E-R Analysis.

Study	Study design	PK and efficacy/safety data
APOLLO	A randomized, open-label, phase 3 study comparing Pd with or without daratumumab in patients with relapsed or refractory MM who have received at least 1 prior line of therapy with both lenalidomide and a PI	299 randomized patients; D-Pd: 149, Pd: 150 PK evaluable patients (n=140) Patients on daratumumab SC only: n=133 Sampling: C1D1+4, C3D1+4, C5-7-12D1
	Daratumumab (D-Pd patients): 1,800 mg SC or 16 mg/kg IV, QW for C1 and 2, then Q2W for C3 to 6, and then Q4W thereafter.	Patients switched from daratumumab IV to SC: n=4 Sampling: SC pre-dose first 3 cycles (starting with C3 or later)+2 FU(each cycle D1 after C3)
	Pomalidomide (all patients): 4 mg PO on D1-21 of each cycle	Patients on daratumumab IV only: n=3 Sampling: C1D1 pre-dose, C1D1 EOI, C3D1, C7D1, 4 and 8 weeks after last dose
EQUULEUS (D-Pd cohort)	Dexamethasone (all patients): 40 mg (20 mg for patients aged ≥75 years) PO, once daily on D1, 8, 15, and 22 of each cycle. Split IV/PO when together with daratumumab	Efficacy: Primary endpoint: Progression free survival Safety: Safety is a secondary endpoint. Monitoring for TEAEs takes place continuously throughout the study
	An open-label, multicenter, phase 1b study of daratumumab in combination with backbone regimens for the treatment of patients with MM	103 patients receiving D-Pd PK evaluable patients (n=99) Sampling: C1-4D1, C1D22 predose + EOI + 2 FU (Week 3 & 9)
	Daratumumab: 16 mg/kg IV, QW for C1 and 2, then Q2W for C3 to 6, and then Q4W thereafter.	Efficacy: Secondary endpoints include overall response rate

Abbreviations: C=cycle; D=day; EOI=end of infusion; EOT=end of treatment; FU=follow up; D-Pd=daratumumab with pomalidomide and dexamethasone; Pd=pomalidomide and dexamethasone; PI=protease inhibitor; PO=oral; QW=every week; Q2W=every 2 weeks; Q4W=every 4 weeks.
Note: each cycle is 4 weeks.

Population Pharmacokinetic Modeling

The PPK analysis was performed using nonlinear mixed-effects modeling (NONMEM 7.4.1). Exploratory analysis, diagnostic graphics, and post-processing of NONMEM analysis results were carried out using R. A previously developed PPK structural and covariate model for daratumumab IV/SC monotherapy was used to fit the PK data of daratumumab in patients with RRMM who received D-Pd combination therapy [3]. Covariates were evaluated in the PPK model. Model-based simulated trough concentrations at Cycle 3 Day 1 ($C_{trough,C3D1}$) were also compared between covariate subgroups. Model evaluation was based on objective function value, acceptable parameter precision, goodness-of-fit and visual predictive checks.

PK Simulations

Simulations were performed using post-hoc PK parameters or typical PK parameters (for the clearances versus time plot) from the final PK model to graphically compare: 1) D-Pd combination therapy versus previous monotherapy; 2) daratumumab SC 1,800 mg versus daratumumab IV 16 mg/kg through daratumumab concentrations, target saturation, and clearance over time under the recommended dose schedules.

PK exposure metrics were generated by simulations using post-hoc PK parameters following the actual dose regimen for APOLLO patients receiving daratumumab. Exposure metrics included predicted peak concentration after first dose ($C_{peak,first}$), predicted trough concentration after first dose ($C_{trough,first}$), predicted maximum peak concentration ($C_{peak,max}$), $C_{trough,C3D1}$, and predicted maximum trough concentration ($C_{trough,max}$).

Exposure-response Assessment

The efficacy analysis was performed by plotting Kaplan-Meier curves of progression-free survival among PK exposure quartiles (i.e., first peak concentration, first trough concentration, maximum trough concentration) compared to control group. The rates of selected TEAEs among PK exposure quartiles were numerically compared to those of the control group.

RESULTS & DISCUSSION

The PPK analysis was based on 1,146 daratumumab PK samples from 239 patients. Observed PK data of daratumumab were well described by a 2-compartment PPK model with first-order absorption and parallel nonspecific linear clearance (CL) and Michaelis-Menten elimination (**Figure 1**). The decrease of total target receptors (CD38) over time was empirically characterized by an exponential reduction of maximum capacity V_{max} over time. The parameter estimates of the final model are provided in **Table 2**.

Figure 1. Michaelis-Menten PK Model for Daratumumab IV/SC.

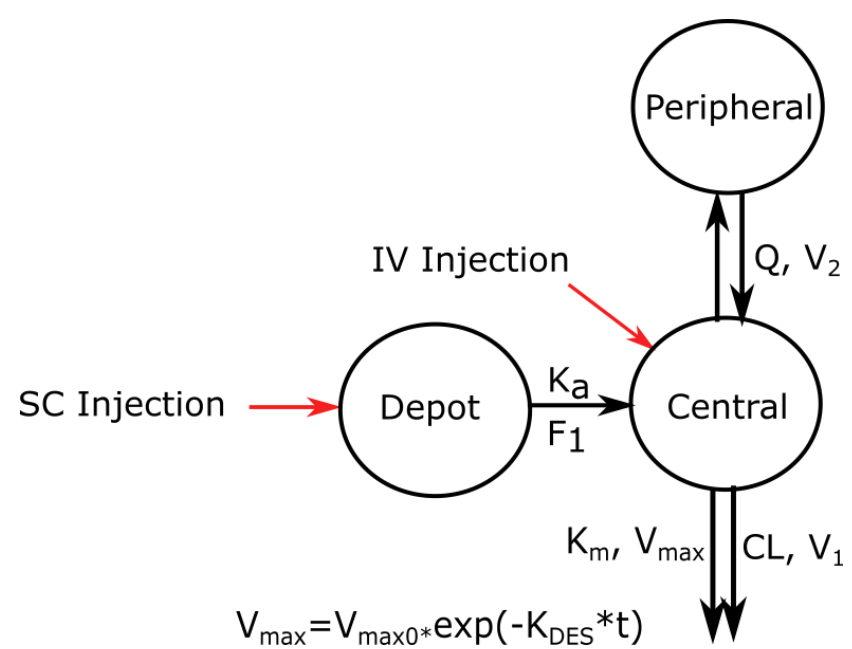
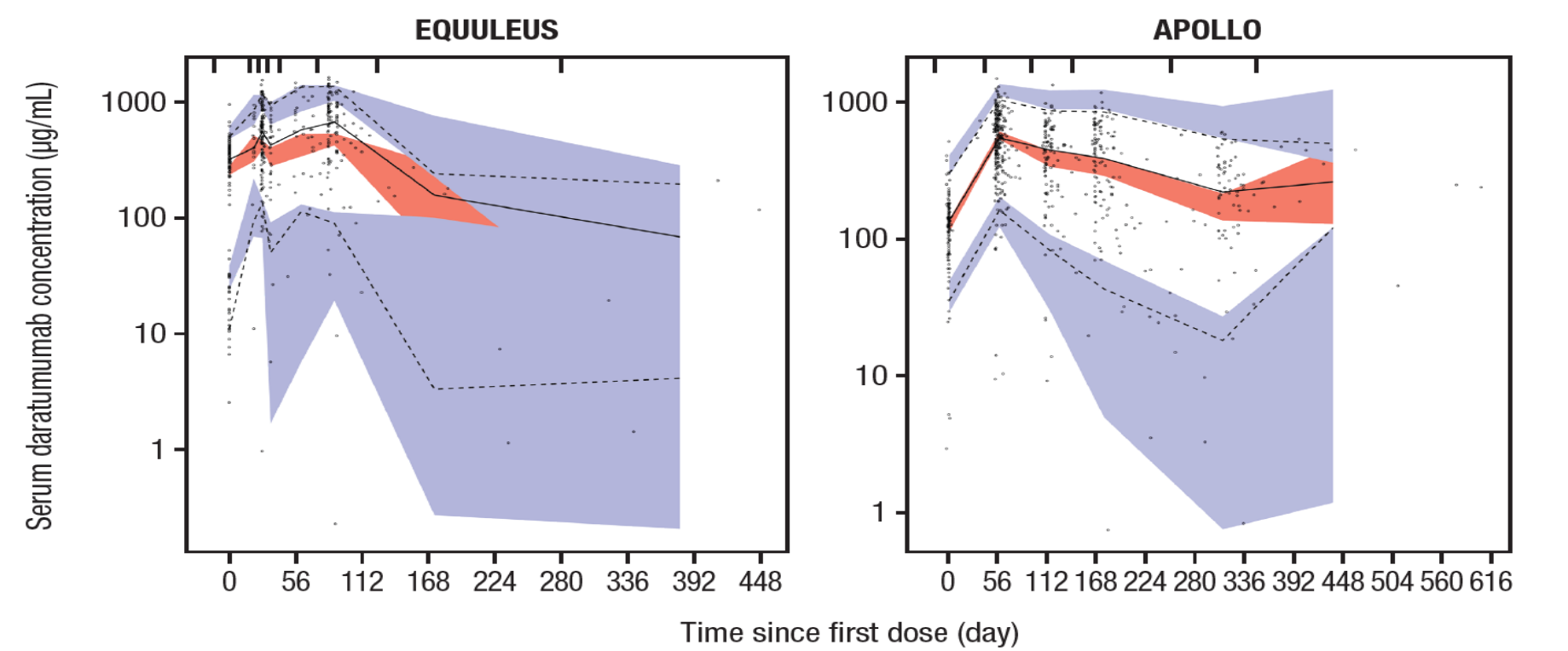


Table 2. Parameter Estimates of the Daratumumab PPK Model

Parameter, unit	Description	Estimate	RSE (%)	95% CI	IIV (%CV)	RSE on IIV (%)
CL (L/h)	Linear clearance	0.00432	9.51	(0.00351, 0.00513)	43.5	8.65
ALB on CL ^a	Effect of serum albumin concentration on CL	-0.665	35.8	(-1.13, -0.199)	-	-
WT on CL ^a	Effect of body weight on CL	0.832	21.4	(0.483, 1.18)	-	-
TPMC on CL ^a	Effect of type of myeloma (IgG vs non-IgG) on CL	0.833	19.3	(0.517, 1.15)	-	-
V ₁ (L)	Central volume of distribution	4.36	5.87	(3.86, 4.86)	28.0	10.8
WT on V ₁ ^b	Effect of body weight on V ₁	0.562	28.3	(0.25, 0.874)	-	-
SEX on V ₁ ^b	Effect of sex on V ₁	-0.168	33.9	(-0.28, -0.0563)	-	-
V ₂ (L)	Peripheral volume of distribution	2.80	14.6	(2.00, 3.60)	-	-
Q (L/h)	Intercompartmental clearance	0.00814	20.8	(0.00483, 0.0115)	-	-
V _{max} (mg/h)	Maximum velocity of the saturable clearance	1.47	13.1	(1.09, 1.85)	59.6	13.4
K _{DES} (1/h)	First-order rate for decrease of V _{max}	0.000282	23.2	(0.000154, 0.000410)	75.3	20.2
K _m (μg/mL)	Michaelis-Menten constant	3.81	34.9	(1.20, 6.42)	-	-
K _a (1/h)	First-order absorption rate	0.0120	9.9	(0.00967, 0.0143)	55.4	12.2
F ₁	Bioavailability	0.689 (FIX)	-	-	-	-
ADD ERR (%CV)	Additive error term on the log-scale	27.7	1.8	(26.7, 28.7)	-	-

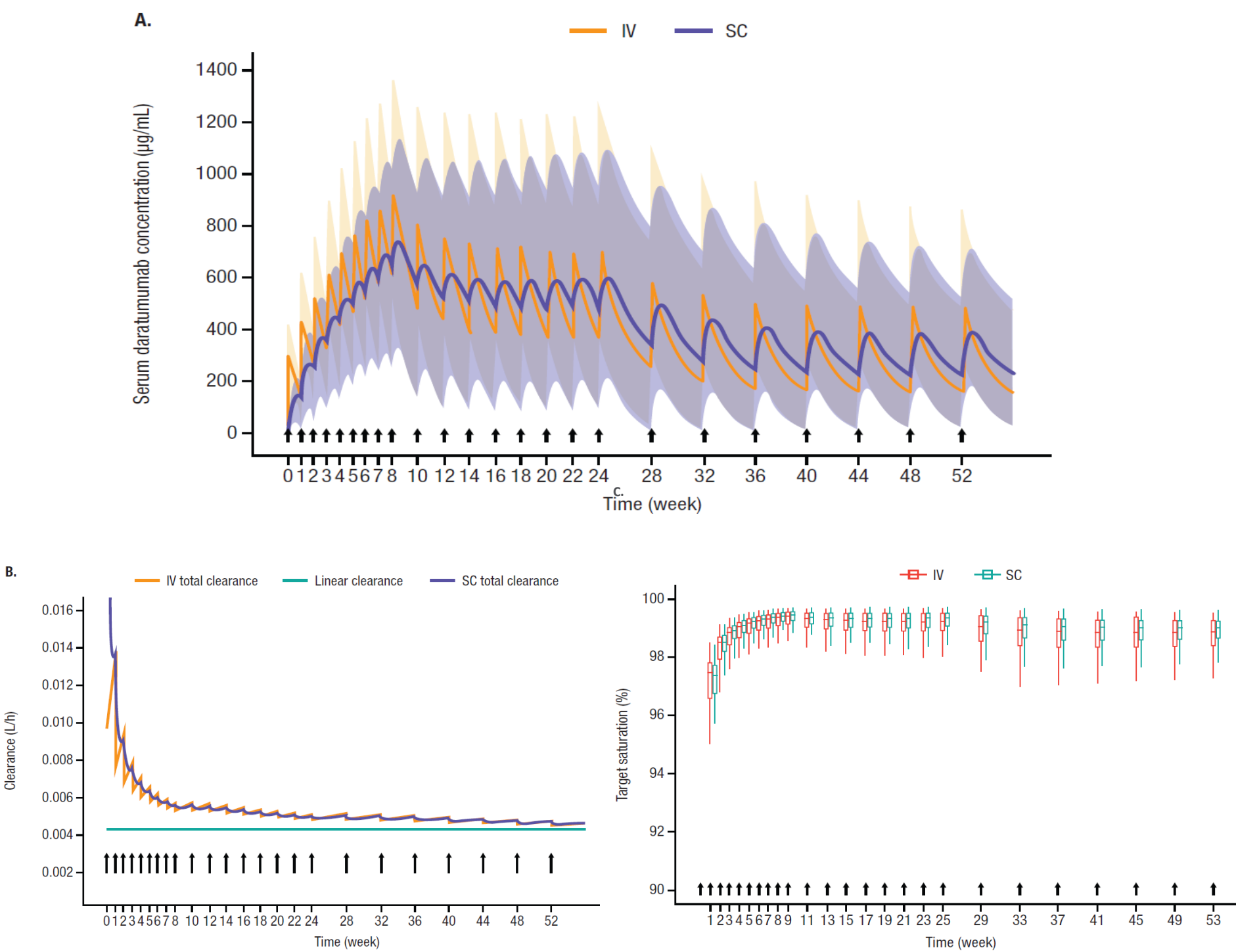
^aTVCL=0.00432*($\frac{WT}{70}$)^{0.832}*($\frac{ALB}{38}$)^{-0.665}*TPMCL, where TPMCL is a shift factor of 1 for non-IgG and 1+0.833 for IgG.
^bTVV1=4.36*($\frac{WT}{76}$)^{0.562}*SEX_{V1}, where SEX_{V1} is a shift factor of 1 for male and 1-0.168 for female.

Figure 2. Visual Predictive Check for the Final PPK Model Stratified by Study.



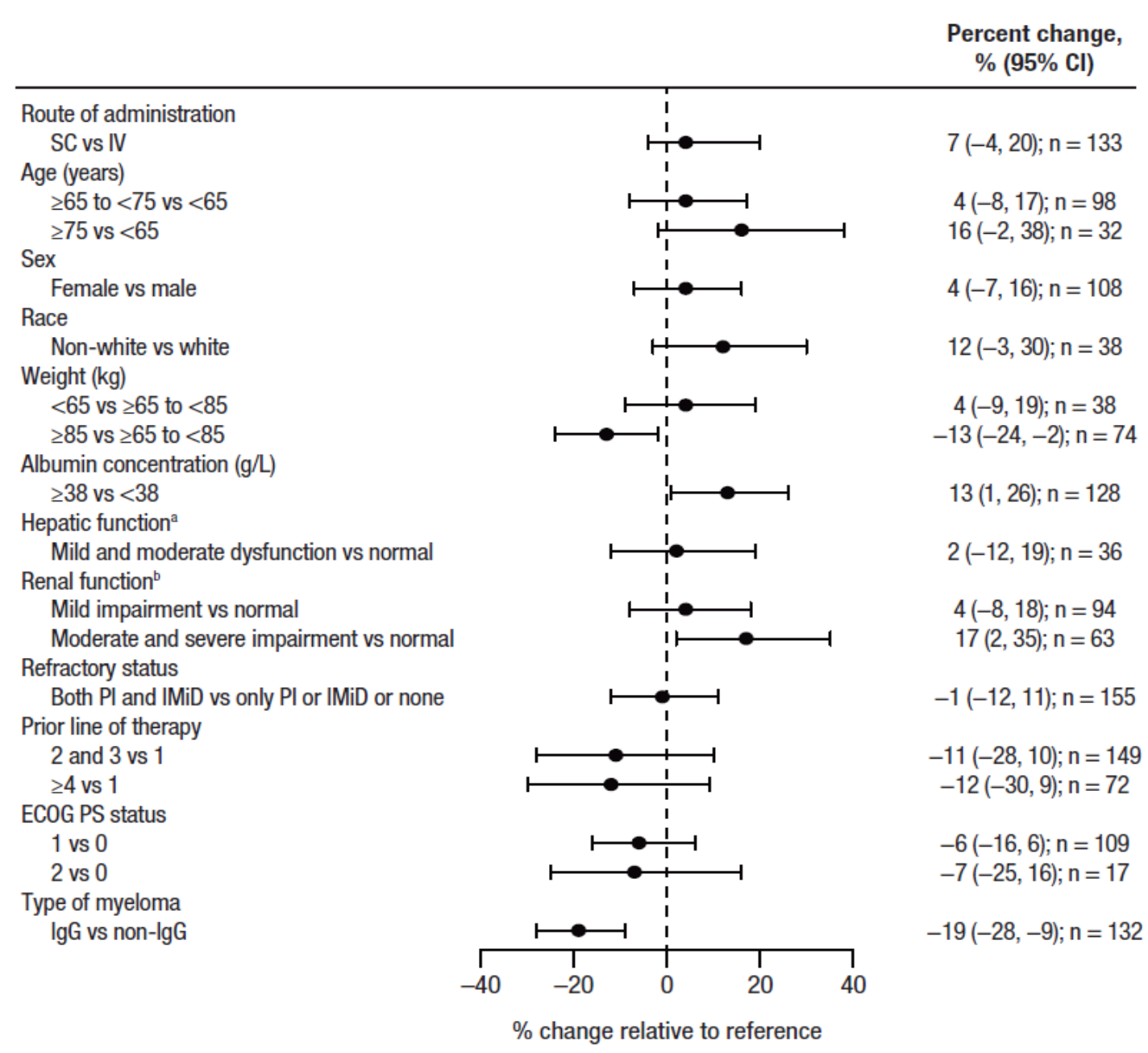
Goodness of fit plots (not shown here) and visual predictive checks in **Figure 2** showed that the final PPK model provided a good description of the data.

Figure 3. A) Simulated Median PK Profile and 90% Prediction Interval of Daratumumab, B) Simulated Typical Total and Linear Clearance, C) Simulated Target Saturation Over Time, After Daratumumab SC 1,800 mg or Daratumumab IV 16 mg/kg Administration per the Recommended Dose Schedule for D-Pd Combination Therapy



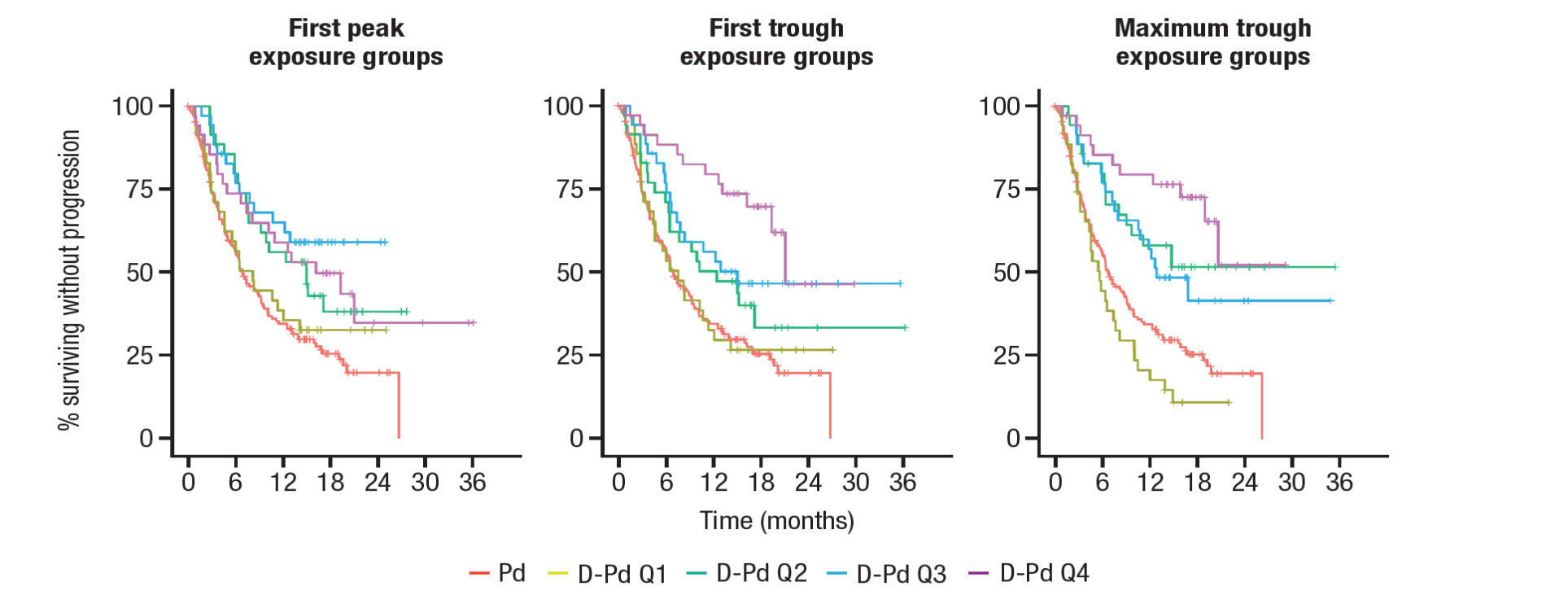
The daratumumab SC 1,800 mg dose resulted in smaller peak-to-trough fluctuations, lower C_{max} , and higher C_{trough} throughout the recommended dose schedule compared with daratumumab IV 16 mg/kg (**Figure 3A**). The dynamics of the simulated typical clearance profiles showed that the total clearance decreased over time and approached the linear, non-specific CL after about 16 weeks (**Figure 3B**). Target saturation, calculated based on the simulated concentrations and the estimated K_m , was maintained above 95% during all phases (**Figure 3C**).

Figure 4. Forest Plot of Subgroup Analyses on Percent Change and 95% CI Relative to Reference Value for Simulated $C_{trough,C3D1}$ per the Recommended Dose Schedule for D-Pd Combination Therapy.



The current PPK analysis confirmed the previously identified statistically significant effects of body weight, albumin concentration and type of myeloma on linear clearance, as well as of body weight and sex on central volume of distribution. No other covariates were identified. The statistically significant covariates were not clinically relevant, with a difference of <20% on $C_{trough,C3D1}$ (**Figure 4**) and $C_{max,C3D1}$ (not shown) between covariate subgroups. Therefore, no dose adjustment is recommended based on any of these factors.

Figure 5. Kaplan-Meier Curves of Progression-free Survival by Daratumumab Exposure Subgroups in Combination With Pd in APOLLO.



The E-R dataset contained data from 290 patients from APOLLO (D-Pd, n=140; Pd, n=150). The E-R analysis showed statistically significant improvements in PFS for patients in D-Pd groups compared with control group. PFS improvements were consistent across PK exposure metrics (**Figure 5**) and clinically important subgroups.

Table 3. Comparison of TEAE Rates Across Predicted Daratumumab Exposure Subgroups for D-Pd Combination Therapy in APOLLO.

	Pd % (95% CI)	D-Pd Exposure Quartiles, % (95% CI)			
TEAE	n=150	Q1 n=35	Q2 n=35	Q3 n=35	Q4 n=35
Neutropenia					
Any grade	53.3 (45.3, 61.2)	82.9 (68.3, 92.8)	77.1 (61.6, 88.8)	71.4 (55.3, 84.5)	71.4 (55.3, 84.5)
Grade ≥3	50.7 (42.7, 58.6)	74.3 (58.4, 86.7)	74.3 (58.4, 86.7)	71.4 (55.3, 84.5)	71.4 (55.3, 84.5)
Infections					
Any grade	55.3 (47.3, 63.1)	74.3 (58.4, 86.7)	74.3 (58.4, 86.7)	71.4 (55.3, 84.5)	71.4 (55.3, 84.5)
Grade ≥3	23.3 (17.1, 30.5)	42.9 (27.4, 59.3)	31.4 (17.7, 47.7)	25.7 (13.3, 41.6)	20.0 (9.1, 35.1)
Anemia					
Any grade	44.7 (36.9, 52.7)	48.6 (32.6, 64.8)	42.9 (27.4, 59.3)	28.6 (15.5, 44.7)	25.7 (13.3, 41.6)
Grade ≥3	21.3 (15.3, 28.3)	34.3 (20.1, 50.7)	17.1 (7.2, 31.7)	5.7 (1.0, 16.6)	8.6 (2.2, 20.7)
Thrombocytopenia					
Any grade	33.3 (26.1, 41.1)	42.9 (27.4, 59.3)	37.1 (22.5, 53.6)	22.9 (11.2, 38.4)	20.0 (9.1, 35.1)
Grade ≥3	18.0 (12.4, 24.7)	31.4 (17.7, 47.7)	25.7 (13.3, 41.6)	5.7 (1.0, 16.6)	8.6 (2.2, 20.7)
IRRs ^b					
Any grade	0	8.6 (2.2, 20.7)	5.7 (1.0, 16.6)	2.9 (0.2, 12.0)	5.7 (1.0, 16.6)
Grade ≥3	0	0	0	0	0

There was no apparent increase in TEAE rates with increasing daratumumab PK exposures for IRRs, thrombocytopenia, anemia, neutropenia, and infections (all grades and grades ≥3) (**Table 3**).

CONCLUSION

The PPK and E-R analyses support the daratumumab SC 1,800 mg dose regimen in combination with Pd for the treatment of patients with RRMM. No body weight-based dose adjustment is recommended for efficacy or safety reasons.

REFERENCES

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