Supplementary material

Population Pharmacokinetics for Belantamab Mafodotin Monotherapy and Combination Therapies in Patients With Relapsed/Refractory Multiple Myeloma

Clinical Pharmacokinetics

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Bioanalysis of Pharmacokinetic Samples

ADC (containing ≥1 molecule of mcMMAF) concentrations were determined using enzyme-linked immunosorbent assay (ELISA). Human plasma samples were minimally diluted 50-fold with assay buffer prior to analysis. The assay used an anti-mcMMAF capture antibody and a biotinylated anti-idiotypic minibody detection reagent specific for the antibody backbone portion of belantamab mafodotin with streptavidin conjugated to horseradish peroxidase to detect the ADC. The SuperSignal ELISA Femto substrate was used to generate a chemiluminescent endpoint.

Cys-mcMMAF concentrations were determined by extracting cys-mcMMAF from human plasma by acidic protein precipitation using 1% formic acid in acetonitrile, followed by cyclization of the linear isomer of cys-mcMMAF to the cyclized isomer using 70/30 (volume per volume) methanol/water with 10% ammonium hydroxide. [$^{15}N^{13}C_3D_3$]-cys-mcMMAF was used as an internal standard. Extracts were analyzed by ultra-high performance liquid-chromatography tandem mass spectrometry using an electrospray interface and multiple reaction monitoring.

Pharmacogenomic Methods

Genetic research was optional. Venous blood was collected from patients who provided written informed consent for genetic research in the DREAMM-2, DREAMM-3, DREAMM-6, and DREAMM-7 trials.

Genomic DNA was extracted from peripheral blood using the following: the FlexiGene® DNA kit on the FlexStar Platform (Qiagen, Valencia, CA) by Covance/LabCorp (Indianapolis, USA, and Geneva, Switzerland) for DREAMM-2 and DREAMM-6 and by Q^2 Solution (Valencia, CA, USA, and Edinburgh, Scotland, UK) for DREAMM-7; the Tecan Freedom EVO®-HSM by Promega Automated Genomic DNA Isolation kits (Promega, Madison, WI) by Q^2 Solution (Valencia, USA and Scotland, UK) for DREAMM-3.

Genotyping was performed using either Sanger sequencing (all studies) or TaqMan quantitative polymerase chain reaction assays (DREAMM-2 and DREAMM-3 only) for the *FCGR3A* polymorphism (rs396991), and the Axiom™ Precision Medicine Research Array for genetic variants in the transporters of interest by Sampled (Piscataway, NJ) (all studies). Genotypes for rs1045642 in *ABCB1* and rs4793665 in *ABCC3* were imputed. All genotype calling and quality control measures were performed in accordance with the manufacturer's protocol.

Germline genetic variants in *ABCB1* (P-gP), *SLCO1B1* (OATP1B1), *SLCO1B3* (OATP1B3), *ABCC2* (multidrug resistance-associated protein [MRP] 2), *ABCC3* (MRP3), *ABCB11* (BSEP), and *FCGR3A* (FcgRIIIa) were included in this exploratory evaluation.

Covariate Analysis

Covariate model building was performed starting with backwards elimination of the covariate effects that were in the legacy model 2023. A covariate effect was retained in the model if, upon removal, the increase in the objective function value (OFV) corresponded to a significance level of 0.001 (increase ≥10.83 points for one degree of freedom). The models with the covariates retained following the initial stepwise backward elimination procedure were used as a starting point for the covariate stepwise forward addition procedure. The covariate that was considered to have the most significance according to the likelihood ratio test was included in the model first. This new model then served as a starting model for the next iteration. The test of significance and adding-on steps were repeated until all significant covariates were included and the full model was defined. Statistical significance was defined as a reduction in the OFV corresponding to a significance level of 0.01 (OFV reduction ≥6.64 for one degree of freedom).

The significance of each covariate was then tested in a second backward elimination procedure. Covariates were removed individually from the full model, and were retained in the model if, upon removal, the OFV increase corresponded to a significance level of 0.001 (increase ≥10.83 points for one degree of freedom). The least significant covariate that did not meet the statistical significance criterion was excluded from the model. The elimination steps were repeated until all nonsignificant covariates were identified.

Supplementary Results: Patient Population

The PopPK dataset had a total of 8880 measurable ADC concentration values, obtained from 977 patients that were analyzed using a PopPK approach. After exclusion of pre-first dose samples, the PopPK dataset contained 9440 concentrations (**Table S2**); 445 (4.7%) were not reportable (e.g., below the limit of quantification). Additionally, 57 (0.6%) were duplicate samples, 8 were missing clinical information, and 2 were collected at the same time as the first dose that had measurable concentrations, representing <1% of the initial dataset, and were excluded from the PopPK dataset. Forty-eight samples were excluded from the PopPK dataset due to a |CWRES| >6 when fitting the prior final model.

The PopPK dataset had a total of 6354 cys-mcMMAF concentration values, obtained from 937 patients, that were analyzed using the PopPK approach. The PopPK dataset contained 9383 concentrations; 2956 (31.5%) were not reportable (e.g., below the limit of quantification). Additionally, 60 (0.6%) were duplicate samples, and 2 samples collected at the same time as the first dose that had measurable concentrations, representing <1% of the initial dataset, were excluded from the PopPK dataset. Three samples were excluded from the PopPK dataset due to a |CWRES| >6 when fitting the prior final model.

Table S1 Summary of clinical studies included in the PopPK analysis and DREAMM-8 external validation

Study	Study description	Dose and administration	Number of actual patients	PK sampling[a]
DREAMM-2 [1] PK sample cutoff: 15 January 2022 Data cutoff: 31 March 2022	Phase II, open-label, 2-arm, randomized, multicenter study to evaluate the efficacy and safety of belantamab mafodotin monotherapy in patients with RRMM who received ≥3 prior therapies	*Belantamab mafodotin dose:* 2.5 mg/kg or 3.4 mg/kg *Administration:* Infusion over 30 min, Q3W	N=196[b] on frozen liquid at 2.5 mg/kg and 3.4 mg/kg N=25[c] on lyophile at 3.4 mg/kg	*Initial protocol:* C1D1: Predose, EOI, 1 hours after EOI, and 3 hours after EOI C2D1, C6D1, C9D1, and C12D1: Predose and EOI Every 6 cycles starting C18: Predose *Following Protocol Amendment 2:* C1D1 and C3D1: Predose, EOI, 2 hours after SOI, 24 hours after SOI (Day 2), Day 4, and 1 sample on Days 8 to 15 C2D1, C6D1, C9D1, and C12D1: Predose and EOI Every 6 cycles starting C18: Predose
DREAMM-3 [2] PK sample cutoff: 6 May 2022 Data cutoff: 12 September 2022	Phase III, open-label, 2-arm, randomized, multicenter study to evaluate the efficacy and safety of belantamab mafodotin monotherapy compared with pomalidomide/dexamethasone in patients with RRMM who received ≥2 prior therapies	*Belantamab mafodotin dose:* 2.5 mg/kg *Administration:* Infusion over at least 30 min, Q3W	N=approximately 320 randomized 2:1 to either Arm 1 (belantamab mafodotin) or Arm 2 (standard of care)	*Enhanced PK sampling (first 25% of patients enrolled and all patients from Northeast Asian countries):* C1D1 and C3D1: Predose, EOI, 2 hours after SOI, 24 hours after SOI (Day 2), Day 4, 1 sample on Days 8 to 15, and Day 22 C2D1, C4D1, and C6D1: Predose and EOI C9D1 and C12D1: Predose Every 6 cycles starting C18: Predose *Standard PK sampling:* C1D1 and C3D1: Predose, EOI, and 24 hours after SOI (Day 2) C2D1: Predose and EOI C4D1 and C6D: Predose and EOI C9D1 and C12D1: Predose Every 6 cycles starting C18: Predose
DREAMM-6 [3]	Phase I/II, open-label, dose-escalation and dose-expansion study to evaluate the safety,	*Arm A belantamab mafodotin dose:*	N=151, of which: N=44 in Arm A N=107 in Arm B	*Arm A: Single and stretch dosing:*

Study	Study description	Dose and administration	Number of actual patients	PK sampling[a]
PK sample cutoff: 25 October 2022 Data cutoff: 28 February 2023	tolerability, and clinical activity of belantamab mafodotin in combination with lenalidomide plus dexamethasone (Arm A), or bortezomib plus dexamethasone (Arm B) in patients with RRMM who received ≥1 prior therapy	1.9 and 2.5 mg/kg Q4W (single) 2.5 mg/kg Q4W (split, 50% and 50% dose on Days 1 and 8 of any 28-day cycle) 1.9 mg/kg Q8W (stretch) *Arm B belantamab mafodotin dose:* 1.9, 2.5, and 3.4 mg/kg Q3W (single) 2.5 and 3.4 mg/kg Q3W (split, 50% and 50% dose on Days 1 and 8 of any 21-day cycle) 1.9 and 2.5 mg/kg Q6W (stretch) 2.5 mg/kg Q6W (S/D stretch), 2.5 mg/kg C1D1 followed by 1.9 mg/kg starting on Day 1 of alternate 21-day cycles (C3, C5, C7, and so on) *Administration:* Infusion over 30–60 minutes *Presentation:* Frozen liquid		Dose 1: Predose, EOI, 2 hours after SOI, 24 hours after SOI (Day 2), Day 4, Days 8 to 15, and Day 29 (Stretch or if Single Dose 2 is delayed) Dose 2, 3, and 6: Predose and EOI Dose 9 and 12: Predose Every 6 doses starting Dose 18: Predose *Arm A: Split dosing:* Dose 1: Predose, EOI, 2 hours after SOI, 24 hours after SOI at Days 1 and 8, Day 4, Day 11, Days 15 to 21, and Day 29 (if Dose 2 is delayed) Dose 2: Predose, EOI at Days 1 and 8 Dose 3 and 6: Predose at Days 1 and 8 Dose 9 and 12: Predose at Day 1 Every 6 doses starting Dose 18: Predose at Day 1 *Arm B: Single and split dosing:* Dose 1: Predose, EOI, 2 hours after SOI, 24 hours after SOI (Day 2) and Day 8 (if split), Day 4, Day 11, and Day 22 (if Dose 2 is delayed) Dose 2: Predose, EOI Dose 3: Predose, EOI at Days 1 and 8 (if split), Day 4, and Day 11 Dose 6: Predose, EOI Dose 9 and 12: Predose Every 6 doses starting Dose 18: Predose *Arm B: Stretch and S/D stretch dosing:* Dose 1: Predose, EOI, 2 hours after SOI, 24 hours after SOI (Day 2), Day 4, Day 11, Day 22, and Day 43 (if Dose 2 is delayed) Dose 2: Predose, EOI, Day 4, and Day 11 Dose 3: Predose, EOI, and Day 22 Dose 4: Predose and EOI Dose 5: Predose Dose 6: Predose, EOI, and Day 22

Study	Study description	Dose and administration	Number of actual patients	PK sampling[a]
				Dose 9 and every 3 doses onward: Predose
DREAMM-7 [4] PK sample cutoff 31 December 2022 Data cutoff: 02 October 2023	Phase III study of belantamab mafodotin, bortezomib, and dexamethasone (B-Vd) versus daratumumab, bortezomib, and dexamethasone (D-Vd) in patients with RRMM who received ≥1 prior therapy	*Belantamab mafodotin dose:* 2.5 mg/kg *Administration:* Infusion over at least 30 min, Q3W *Presentation:* Lyophile	N approximately 478 patients randomized 1:1 to either Arm A (B-Vd) or Arm B (D-Vd)	*Enhanced PK sampling (first 20% of patients enrolled and all patients from Northeast Asian countries):* Dose 1: Predose, EOI, 2 hours after SOI, 24 hours after SOI (Day 2), Day 4, 1 sample Days 8 to 15, and Day 22 (if Dose 2 is delayed) Dose 2, 4, and 6: Predose and EOI Dose 9 and 12: Predose Every 6 doses starting Dose 18: Predose *Standard PK sampling:* Dose 1: Predose, EOI, 24 hours after SOI (Day 2), and Day 22 (if Dose 2 is delayed) Dose 2, 4, and 6: Predose and EOI Dose 9 and 12: Predose Every 6 doses starting Dose 18: Predose
DREAMM-12 [5] PK sample cutoff: 22 June 2022 Data cutoff: part 1 interim analysis 15 September 2022	Phase I study to evaluate the PK and safety of belantamab mafodotin monotherapy in patients with RRMM who received ≥3 prior therapies (or ≥2 if ineligible for autologous SCT), and who have normal or varying degrees of impaired renal function	*Belantamab mafodotin dose:* 2.5 mg/kg *Administration:* Infusion over at least 30 min, Q3W	Part 1 N approximately 23[d] patients were assigned to either Group 1 (normal/mildly impaired renal function) or Group 2 (severely impaired renal function)	Cycle 1: Predose, EOI, 2 hours after SOI, 4 hours after SOI, 8 hours after SOI, 24 hours after SOI (Day 2), Day 4, 1 sample Days 8 to 15, and Day 22 (if Dose 2 is delayed) Cycle 2: Predose, EOI, and 24 hours after SOI (Day 2) Cycle 3: Predose, EOI, 2 hours after SOI, 4 hours after SOI, 8 hours after SOI, 24 hours after SOI (Day 2), Day 4, 1 sample Days 8 to 15, and Day 22 (if Dose 4 is delayed) Cycles 4, 6, 9, and 12: Predose and EOI Following Cycle 12 Q6 cycle (C18, C24, etc): Predose
DREAMM-14 [6] PK sample cutoff: 9 February 2023	Phase II, randomized, parallel, open-label study to investigate the safety, efficacy, and PK of various dosing regimens of single-agent belantamab mafodotin in patients with	*Belantamab mafodotin dose:* Arm A: 2.5 mg/kg Q3W Arm B: 1.9 mg/kg Q3W Arm C: 2.5 mg/kg Q6W Arm D: 1.9 mg/kg Q6W	N=138,[d] of which: Arm A: N=34 Arm B: N=34 Arm C: N=33 Arm D: N=31 Arm E: N=6	Dose 1: Predose, EOI, 2h after SOI, 24h after SOI (Day2), Day 4, Days 8 to 15, Day 22 (if next dose is delayed), and Day 43 Dose 2: Predose and EOI Dose 3: Predose and EOI Dose 4: Predose

Study	Study description	Dose and administration	Number of actual patients	PK sampling[a]
Data cutoff: interim analysis 24 February 2023	RRMM who received ≥3 prior therapies	Arm E: 2.5 mg/kg Q3W with dose modifications based on ocular symptoms and visual acuity *Administration:* infusion over at least 30 min		Dose 6: Predose Dose 9: Predose Dose 12: Predose
External Validation				
DREAMM-8 [7] PK sample cutoff: 31 August 2023 Data cutoff: 29 January 2024	Phase III study of belantamab mafodotin, pomalidomide, and dexamethasone (B-Pd) versus pomalidomide plus bortezomib and dexamethasone (PVd) in patients with RRMM who received ≥1 prior therapy including lenalidomide	*Belantamab mafodotin dose:* 2.5 mg/kg on Day 1 of Cycle 1 and 1.9 mg/kg in Cycle 2 and beyond (2+) of every 28-day cycle (Q4W) *Administration:* Infusion over at least 30 minutes, Q4W *Presentation:* Lyophile	N=302 patients randomized 1:1 to either Arm A (B-Pd) or Arm B (PVd)	*Enhanced PK sampling (20% of patients enrolled and all patients from Japan and Korea):* Dose 1: Predose, EOI, 2 hours after SOI, 24 hours after SOI (Day 2), Day 4, 1 sample on Days 8 to 15, and Day 29 (if Dose 2 is delayed) Dose 2, Dose 4, and Dose 6: Predose, EOI Dose 9 and Dose 12: Predose Every 6 doses starting Dose 18: Predose *Standard PK sampling:* Dose 1: Predose, EOI, 24 hours after SOI (Day 2), and Day 29 (if Dose 2 is delayed) Dose 2, Dose 4, and Dose 6: Predose, EOI Dose 9 and Dose 12: Predose Every 6 doses starting Dose 18: Predose

[a]For monotherapy clinical studies, cycle number was used to describe planned PK sampling time as a new cycle started with each additional belantamab mafodotin dosing. For combination clinical studies, the number of belantamab mafodotin doses given on Day 1 of a cycle was used to describe the planned PK sampling time.

[b]Number of randomized patients=196; the number of patients who received belantamab mafodotin as frozen-liquid presentation=194.

[c]Number of randomized patients=25; the number of patients who received belantamab mafodotin as lyophilized presentation=24.

[d]Number of randomized patients as expected at the time of analysis (ie, not the total planned number of patients)

C Cycle, D Day, EOI end of infusion, N number of patients, PK pharmacokinetics, PopPK population PK, QXW every X weeks, RRMM relapsed/refractory multiple myeloma, S/D step-down, SCT stem cell transplant, SOI start of infusion

Table S2 Summary of PopPK sample size

Population	Number (%) of patients	Number (%) of samples	
		ADC	Cys-mcMMAF
Pre-first dose samples		895	937
Total in the dataset, excluding pre-first dose samples	977 (100)	9440 (100)	9383 (100)
Measurable concentrations used in PopPK		8880 (94.1)	6354 (67.7)
DREAMM-2	218 (22.3)	1965	1421
DREAMM-3	217 (22.2)	2098	1448
DREAMM-6	152 (15.6)	1708	1289
DREAMM-7	242 (24.8)	1840	1227
DREAMM-12	23 (2.4)	340	276
DREAMM-14	125 (12.8)	929	693
Non-reportable concentrations (i.e., BLQ)		445 (4.7)	2956 (31.5)
DREAMM-2	–	115	665
DREAMM-3	–	63	640
DREAMM-6	–	126	509
DREAMM-7	–	125	802
DREAMM-12	–	7	80
DREAMM-14	–	9	260
Duplicate samples		57 (0.6)	60 (0.6)
DREAMM-2	–	1	5
DREAMM-3	–	8	7
DREAMM-6	–	43	43
DREAMM-7	–	1	1
DREAMM-12	–	0	1
DREAMM-14	–	4	3
Missing clinical information	–	8 (0.1)	8 (0.1)
DREAMM-2	–	0	0
DREAMM-3	–	0	0
DREAMM-6	–	0	0

DREAMM-7	–	8	8
DREAMM-12	–	0	0
DREAMM-14	–	0	0
|CWRES| >6	–	48 (0.5)	3 (0.0)
DREAMM-2	–	6	0
DREAMM-3	–	14	0
DREAMM-6	–	6	0
DREAMM-7	–	15	2
DREAMM-12	–	0	0
DREAMM-14	–	7	1
Sample with measurable concentration at time zero (excluded from analysis)	–	2 (0.0)	2 (0.0)
DREAMM-2	–	0	0
DREAMM-3	–	2	2
DREAMM-6	–	0	0
DREAMM-7	–	0	0
DREAMM-12	–	0	0
DREAMM-14	–	0	0
DREAMM-8 external validation			
Pre-first dose samples	–	143	141
Total in the dataset, excluding pre-first dose samples	150 (100)	1396 (100)	1365 (100)
Measurable concentrations used in PopPK	–	1221 (87.5)	829 (60.7)
Non-reportable concentrations (i.e., BLQ)	–	161 (11.5)	532 (39.0)
Duplicate samples	–	2 (0.1)	2 (0.1)
Missing clinical information	–	0 (0)	0 (0)
|CWRES| >6	–	12 (0.9)	2 (0.1)
Sample with measurable concentration at time 0 (excluded	–	0 (0)	0 (0)

ADC antibody-drug conjugate, BLQ below the lower limit of quantification, CWRES conditional weighted residuals, cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, PopPK population pharmacokinetic

Table S3 PK parameter estimates for the ADC legacy model 2023

	ADC Legacy Model 2023			
Parameter	**Estimate**	**RSE%**	**95% CI[b]**	**Shrinkage (%)**
Typical values				
CL (L/day)	0.904	1.45	0.878, 0.930	-
ADC Vc (L)	4.18	0.871	4.11, 4.25	-
Q (L/day)	0.715	3.62	0.664, 0.766	-
ADC Vp (L)	6.38	2.46	6.07, 6.69	-
Imax	-0.471	4.54	-0.512, -0.429	-
TI50 (days)	65.5	6.03	57.8, 73.3	-
Gamma	2.77	4.73	2.52, 3.03	-
Covariate effects				
Weight on ADC Vc and ADC Vp (θ_{V_WTBL})	0.942	4.95	0.850, 1.03	-
Weight on CL and Q (θ_{CL_WTBL})	0.556	8.64	0.462, 0.650	-
Albumin on CL (θ_{CL_ALBBL})	-0.718	10.1	-0.860, -0.576	-
Albumin on ADC Vc ($\theta_{ADC\ Vc\_ALBBL}$)	-0.342	15.7	-0.447, -0.237	-
sBCMA on CL ($\theta_{CL\_SBCMABL}$)	0.103	7.84	0.0873, 0.119	-
IgG on CL (θ_{CL_IGGBL})	0.144	6.66	0.125, 0.163	-
BMI on ADC Vc ($\theta_{ADC\ Vc\_IBMIBL}$)	-0.476	12.4	-0.591, -0.360	-
IgG on ADC Vc ($\theta_{ADC\ Vc\_IGGBL}$)	-0.0179	37.4	-0.0310, -0.00477	-
sBCMA on ADC Vc ($\theta_{ADC\ Vc\_SBCMABL}$)	0.0382	15.4	0.0267, 0.0498	-
Inter-patient variability CV%				
On CL	26.7	3.95	24.6, 28.7	14.7%
ADC Vc-CL covariance[a]	0.0336	8.67	0.0279, 0.0393	-
On ADC Vc	19.9	3.64	18.4, 21.2	15.7%

On Q	21.9	28.1	NA, 31.9	65.8%
On ADC Vp	31.4	7.85	26.2, 36.0	50.0%
On Imax	33.6	9.03	27.1, 39.2	37.3%
On TI50	65.4	8.62	53.9, 76.1	55.5%
Residual error				
Additive error variance on log scale, $(\log(ng/mL))^2$	0.0631	6.24	0.0554, 0.0708	12.9%

PK parameter estimation

$CLi=\theta_{CL}\bullet\exp(CL,Time)\bullet(ALBBL/40)^{\theta CL\_ALBBL}\bullet(SBCMABL/50)^{\theta CL\_SBCMABL}\bullet(IGGBL/15)^{\theta CL\_IGGBL}(WTBL/75)^{\theta CL\_WTBL}\bullet\exp(\eta CL)$

$ADC\ Vci=\theta_{ADC\ Vc}\bullet(WTBL/75)^{\theta V\_WTBL}\bullet(ALBBL/40)^{\theta ADC\ Vc\_ALBBL}\bullet(IBMIBL/27)^{\theta ADC\ Vc\_IBMIBL}\bullet(IGGBL/15)^{\theta ADC\ Vc\_IGGBL}\bullet(SBCMABL/50)^{\theta ADC\ Vc\_SBCMABL}\bullet\exp(\eta ADC\ Vc)$

$Qi=\theta_{Q}\bullet(WTBL/75)^{\theta CL\_WTBL}\bullet\exp(\eta Q)$

$ADC\ Vpi=\theta_{ADC\ Vp}\bullet(WTBL/75)^{\theta V\_WTBL}\bullet\exp(\eta ADC\ Vp)$

$IMAXi=\theta_{IMAX}+(\eta IMAX)$ and $TI50i=\theta_{TI50}\bullet\exp(\eta TI50)$

CL,Time=[(IMAXi•Time^Gamma)/(TI50i^Gamma+Time^Gamma)]

Inter-patient variability

Log-normal distribution CV%=SQRT(exp (Ω)–1)•100 and normal distribution CV%=(SQRT(Ω)/θ)•100

Residual error

$Y=\ln(IPRED)+\varepsilon$

[a]Correlation coefficient of 0.651; [b]the 95% CI was calculated using standard errors from the estimation. εresidual error, η individual deviation from the population value, θ fixed effect parameter (typical value), Ω inter-patient variability variance, ADC antibody-drug conjugate, ADC Vc antibody-drug conjugate central volume of distribution, ADC Vp antibody-drug conjugate peripheral volume of distribution, ALBBL baseline albumin, BMI body mass index, CI confidence interval, CL clearance, CV% percent coefficient of variation, i individual patient index, IBMIBL baseline body mass index, IgG immunoglobulin G, IGGBL baseline immunoglobulin G, IMAX natural log of the maximum fold-change from baseline in clearance, IPRED individual prediction, NA not applicable, PK pharmacokinetic, Q intercompartmental clearance, RSE% percent relative standard error, sBCMA soluble B-cell maturation antigen, SBCMABL baseline SBCMA, SQRT square root, TI50 time from first dose to half-maximal fold-change in clearance on the natural log scale, V volume of distribution, WTBL baseline body weight

Table S4 Key steps leading to the final ADC and cys-mcMMAF PopPK models

ADC				
Run No.	**Description**	**OFV**	**Condition #[a]**	**Comments**
Run1101	Legacy model 2023	-11060.9	19.79	Two-compartment model with time-varying CL with ETA Imax and TI50 ETA on CL, ADC Vc, ADC Vp, Q, Imax, and TI50 Covariance between ETA on CL and ADC Vc Exponential residual error (additive on log scale) **Covariates on CL:** Baseline albumin, sBCMA, IgG, and body weight **Covariates on ADC Vc:** Baseline albumin, body weight, BMI, IgG, and sBCMA **Covariates on Q:** Baseline body weight **Covariates on ADC Vp:** Baseline body weight
Final_backward	Backward screen	-11053.9	NA	Baseline IgG effect on ADC Vc removed from legacy model 2023 **Covariates on CL:** Baseline albumin, sBCMA, IgG, and body weight **Covariates on ADC Vc:** Baseline albumin, body weight, BMI, and sBCMA **Covariates on Q:** Baseline body weight **Covariates on ADC Vp:** Baseline body weight
Final_forward – covariate search	Full model	-11201.9	NA	New covariates added are italicized. **Covariates on CL:** Baseline albumin, sBCMA, IgG, body weight, and *race* **Covariates on ADC Vc:** Baseline albumin, body weight, BMI, *IgG*, and sBCMA **Covariates on Q:** Baseline body weight **Covariates on ADC Vp:** Baseline body weight, *IgG*, and *albumin* **Covariates on Imax:** Baseline sBCMA, IgG, LDH, and combination therapy
Final_backward – covariate search	Final covariate search model	-11185.6	NA	IgG on ADC Vc and ADC Vp were removed during the backward elimination. **Covariates on CL:** Baseline albumin, sBCMA, IgG, body weight, and race **Covariates on ADC Vc:** Baseline albumin, body weight, BMI, and sBCMA **Covariates on Q:** Baseline body weight **Covariates on ADC Vp:** Baseline body weight and albumin **Covariates on Imax:** Baseline sBCMA, IgG, LDH, and combination therapy
Run1208	Final model	-11173.9	90.93	LDH removed from Imax **Covariates on CL:** Baseline albumin, sBCMA, IgG, body weight, and race **Covariates on ADC Vc:** Baseline albumin, body weight, BMI, IgG, and sBCMA **Covariates on Q:** Baseline body weight **Covariates on ADC Vp:** Baseline body weight and albumin

				Covariates on Imax: Baseline sBCMA, IgG, and combination therapy
Cys-mcMMAF				
Run No.	**Description**	**OFV**		**Comments**
run7003	Legacy model 2023	-14110.512	888400	Two-compartment model with first-order elimination parameterized using rate constants to link the central and peripheral compartments. Parameters estimated with ADVAN6 ETA on CL_{MMAF}, cys-mcMMAF Vc, and K43 Additive plus proportional residual error **Covariates on CL_{MMAF}:** sBCMA, baseline body weight **Covariates on cys-mcMMAF Vc:** sBCMA, baseline IgG**,** baseline body weight, baseline albumin
run7500	Final model	-14146.546	778.5	Parameters estimated with ADVAN5 **Covariates on CL_{MMAF}:** sBCMA, baseline body weight **Covariates on cys-mcMMAF Vc:** sBCMA, baseline IgG**,** baseline body weight, baseline albumin, race, BMI

[a]The condition number cannot be reported for runs in which the covariance step was not performed.

ADC antibody-drug conjugate, ADC Vc antibody-drug conjugate central volume of distribution, ADC Vp antibody-drug conjugate peripheral volume of distribution, BMI body mass index, CL clearance, CL_{MMAF} clearance of cys-mcMMAF, cys-mcMMAF Vc cys-mcMMAF central volume of distribution, cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, ETA individual deviation from the population value, IgG immunoglobulin G, Imax natural log of the maximum fold-change from baseline in clearance, K43 distribution rate constant from the peripheral to the central compartment, LDH lactate dehydrogenase, NA not applicable, OFV objective function value, PK pharmacokinetic, PopPK population PK, Q intercompartmental clearance, sBCMA soluble B-cell maturation antigen, TI50 time from first dose to half-maximal fold-change in clearance on the natural log scale

Table S5 PK parameter estimates for the alternate B2M ADC model

	ADC Alternate B2M Model			
Parameter	**Estimate**	**RSE%**	**95% CI[b]**	**Shrinkage (%)**
Typical values				
CL (L/day)	0.929	1.55	0.900, 0.957	-
ADC Vc (L)	4.23	0.810	4.16, 4.29	-
Q (L/day)	0.713	3.63	0.663, 0.764	-
ADC Vp (L)	6.65	2.56	6.32, 6.98	-
Imax	-0.396	7.84	-0.457, -0.335	-
TI50 (days)	65.2	9.23	53.4, 77.0	-
Gamma	2.87	12.9	2.15, 3.60	-
Covariate effects				
Weight on ADC Vc and ADC Vp (θ_{V_WTBL})	0.925	5.88	0.818, 1.03	-
Weight on CL and Q (θ_{CL_WTBL})	0.529	12.3	0.401, 0.657	-
Albumin on CL (θ_{CL_ALBBL})	-0.632	13.0	-0.793, -0.471	-
Albumin on ADC Vc ($\theta_{ADC\ Vc\_ALBBL}$)	-0.236	25.4	-0.353, -0.118	-
B2M on CL (θ_{CL_B2MBL})	0.264	10.2	0.211, 0.316	-
IgG on CL (θ_{CL_IGGBL})	0.170	5.61	0.151, 0.189	-
BMI on ADC Vc ($\theta_{ADC\ Vc\_IBMIBL}$)	-0.459	13.7	-0.582, -0.335	-
B2M on ADC Vc ($\theta_{ADC\ Vc\_B2MBL}$)	0.119	14.3	0.0858, 0.153	-
Asian race on CL (θ_{CL_RACEA})	0.931	2.85	0.879, 0.983	-
AA race on CL (θ_{CL_RACEB})	0.903	3.48	0.841, 0.964	-
Combination therapy on Imax (θ_{IMAX_COMBO})	1.48	7.81	1.26, 1.71	-
IgG on Imax (θ_{IMAX_IGGBL})	0.201	19.4	0.124, 0.277	-
B2M on Imax (θ_{IMAX_B2MBL})	0.329	26.4	0.159, 0.499	-
Albumin on ADC Vp ($\theta_{ADC\ Vp\_ALBBL}$)	0.593	25.0	0.302, 0.884	-
Inter-patient variability CV%				

On CL	26.9	3.77	24.9, 28.9	14.5%
ADC Vc-CL covariance[a]	0.0333	8.59	0.0277, 0.0389	-
On ADC Vc	19.8	3.67	18.3, 21.2	15.9%
On Q	18.2	38.5	NA, 29.0	70.5%
On ADC Vp	30.6	8.26	25.3, 35.3	50.0%
On Imax	29.4	11.1	22.2, 35.3	40.4%
On TI50	69.3	10.1	54.9, 82.7	54.0%
Residual error				
Additive error variance on log scale, $(\log(ng/mL))^2$	0.0634	6.20	0.0557, 0.0711	12.7%

PK parameter estimation

$CLi=\theta_{CL}\bullet\exp(CL,Time)\bullet(ALBBL/40)^{\theta CL\_ALBBL}\bullet(B2MBL/300)^{\theta CL\_B2MBL}\bullet(IGGBL/15)^{\theta CL\_IGGBL}$ $(WTBL/75)^{\theta CL\_WTBL}\bullet(\theta_{CL\_RACEA})$[if Asian] $\bullet(\theta_{CL\_RACEB})$[if AA]$\bullet\exp(\eta_{CL})$

$ADC\ Vci=\theta_{ADC\ Vc}\bullet(WTBL/75)^{\theta V\_WTBL}\bullet(ALBBL/40)^{\theta ADC\ Vc\_ALBBL}\bullet(IBMIBL/27)^{\theta ADC\ Vc\_IBMIBL}\bullet(B2MBL/300)^{\theta ADC\ Vc\_SBCMABL}\bullet\exp(\eta ADC\ Vc)$

$Qi=\theta_{Q}\bullet(WTBL/75)^{\theta CL\_WTB}\bullet\exp(\eta Q)$

$ADC\ Vpi=\theta_{ADC\ Vp}\bullet(WTBL/75)^{\theta V\_WTBL}\bullet(ALBBL/40)^{\theta ADC\ Vp\_ALBBL}\bullet\exp(\eta ADC\ Vp)$

$IMAXi=\theta_{IMAX}\bullet(\theta_{IMAX\_COMBO})$[if not monotherapy]$\bullet(IGGBL/15)^{\theta IMAX\_IGGBL}\bullet(B2MBL/300)^{\theta IMAX\_SBCMABL}+(\eta IMAX)$ and $TI50i=\theta_{TI50}\bullet(IGGBL/15)^{\theta TI50\_IGGBL}\bullet\exp(\eta TI50)$

CL,Time=[(IMAXi•Time^Gamma)/(TI50i^Gamma+Time^Gamma)]

Inter-patient variability

Log-normal distribution CV%=SQRT(exp(Ω)–1)•100 and normal distribution CV%=(SQRT(Ω)/θ)•100

Residual error

Y=ln(IPRED)+ε

[a]Correlation coefficient of 0.641; [b]the 95% CI was calculated using standard errors from the estimation.

ε residual error, η individual deviation from the population value, θ fixed effect parameter (typical value), Ω inter-patient variability variance, AA African American, ADC antibody-drug conjugate, ADC Vc antibody-drug conjugate central volume of distribution, ADC Vp antibody-drug conjugate peripheral volume of distribution, ALBBL baseline albumin, B2M β2 microglobulin, B2MBL baseline B2M, BMI body mass index, CI confidence interval, CL clearance, CV% percent coefficient of variation, i individual patient index, IBMIBL baseline body mass index, IgG immunoglobulin G, IGGBL baseline immunoglobulin G, IMAX natural log of the maximum fold-change from baseline in clearance, IPRED individual prediction, NA not applicable, PK pharmacokinetic, Q intercompartmental clearance, RSE% percent relative standard error, sBCMA soluble B-cell maturation antigen, SQRT square root, TI50 time from first dose to half-maximal fold-change in clearance on the natural log scale, V volume of distribution, WTBL baseline body weight

Table S6 PK parameter estimates for the cys-mcMMAF legacy model 2023

	Cys-mcMMAF Legacy Model 2023			
Parameter	**Estimate**	**RSE%**	**95% CI[c]**	**Shrinkage (%)**
Typical values				
CL_{MMAF} (L/day)	651	2.45	619, 682	-
cys-mcMMAF Vc (L)	8.37	27.6	3.84, 12.9	-
K34 (1/day)	265	29.3	113, 417	-
K43 (1/day)	6.41	4.55	5.84, 6.98	-
RATE-DAR (1/day)	0.0368	3.99	0.034, 0.0397	-
Covariate effects				
sBCMABL on CL_{MMAF} ($\theta_{CL\_SBCMABL}$)	-0.0485	31.1	-0.0781, -0.0189	-
Weight on CL_{MMAF} (θ_{CL_WTBL})	0.695	12.6	0.523, 0.866	-
Albumin on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_\ ALBBL}$)	-0.554	27.7	-0.855, -0.254	-
IgG on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_IGGBL}$)	0.169	11.1	0.132, 0.206	-
sBCMABL on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_SBCMABL}$)	0.108	15.9	0.0742, 0.141	-
Weight on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_WTBL}$)	0.733	12.5	0.553, 0.912	-
Inter-patient and inter-occasion variability, CV%				
On CL_{MMAF}	28.8	11.2	21.4, 34.8	34.6
CL_{MMAF}-cys-mcMMAF Vc covariance[a]	0.0871	12.9	0.065, 0.109	-
On cys-mcMMAF Vc	68.2	3.77	62.0, 74.2	16.6
cys-mcMMAF Vc-K43 covariance[b]	0.380	12.0	0.291, 0.47	-
On K43	135	4.33	117, 154	31.1
On IOV CL_{MMAF}	57.2	2.91	53.3, 60.8	41.8
On IOV cys-mcMMAF Vc	45.3	2.61	42.8, 47.8	37.3
Residual error				

Proportional error CV%	26.2	1.04	25.7, 26.8	26.9
Additive error SD (nmol/L)	1×10^{-6} FIXED	-	-	-

PK parameter estimation

$CLi=\theta_{CLMMAF}\bullet (SBCMABL/50)^{\theta CL\_SBCMABL}\bullet(WTBL/75)^{\theta CL\_WTBL}\bullet\exp(\eta_{CLMMAF}+\kappa_{CLMMAF,\,j})$

$\text{cys-mcMMAF } Vci=\theta_{\text{cys-mcMMAF Vc}}\bullet(SBCMABL/50)^{\theta\text{cys-mcMMAF Vc\_SBCMABL}}\bullet(IGGBL/15)^{\theta\text{cys-mcMMAF Vc\_IGGBL}}\bullet(ALBBL/40)^{\theta\text{cys-mcMMAF Vc\_ALBBL}}\bullet(WTBL/75)^{\theta\text{cys-mcMMAF Vc\_WTBL}}\bullet\exp(\eta_{\text{cys-mcMMAF Vc}}+\kappa_{\text{cys-mcMMAF Vc, j}})$

$K43=\theta_{K43}\bullet EXP(\eta_{K43})$

Inter-patient variability:

Log-normal distribution CV%=SQRT(exp (Ω)–1) •100

Residual error

Y=IPRED+IPRED•ε1+ε2

[a]Correlation coefficient of 0.499; [b]Correlation coefficient of 0.603; [c]the 95% CI was calculated using standard errors from the estimation.

ε1 proportional residual error, ε2 additive residual error, η individual deviation from the population value, θ fixed effect parameter (typical value), Ω inter-patient variability variance, ALBBL baseline albumin, CI confidence interval, CL clearance, CL_{MMAF} cys-mcMMAF clearance, CV% percent coefficient of variation, cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, cys-mcMMAF Vc cys-mcMMAF central volume of distribution, i individual patient index, IgG immunoglobulin G, IGGBL baseline immunoglobulin G, IOV inter-occasion variability, IPRED individual prediction, K34 distribution rate constant from the central to the peripheral compartment, K43 distribution rate constant from the peripheral to the central compartment, KAPPA ($\kappa_{,\,j}$) inter-occasion variability at j-occasion, PK pharmacokinetic, RATE-DAR rate change in drug-antibody ratio over time since most recent dose, RSE% percent relative standard error, sBCMABL baseline soluble B-cell maturation antigen, SD standard deviation, SQRT square root, WTBL baseline body weight

Table S7 PK parameter estimates for the alternate B2M cys-mcMMAF model

	Cys-mcMMAF Alternate B2M Model			
Parameter	**Estimate**	**RSE%**	**95% CI[c]**	**Shrinkage (%)**
Typical values				
CL_{MMAF} (L/day)	639	2.7	605, 673	-
cys-mcMMAF Vc (L)	10.7	9.1	8.82, 12.6	-
K34 (1/day)	215	9.87	173, 256	-
K43 (1/day)	5.86	4.99	5.29, 6.43	-
RATE-DAR (1/day)	0.0381	3.96	0.0351, 0.041	-
Covariate effects				
B2MBL on CL_{MMAF} (θ_{CL_B2MBL})	-0.0966	40.6	-0.173, -0.0197	-
Weight on CL_{MMAF} (θ_{CL_WTBL})	0.718	12.0	0.549, 0.887	-
Albumin on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_\ ALBBL}$)	-0.406	39.6	-0.721, -0.0911	-
IgG on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_IGGBL}$)	0.186	9.86	0.15, 0.222	-
B2MBL on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_B2MBL}$)	0.261	17.1	0.173, 0.349	-
Weight on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_WTBL}$)	1.26	13.4	0.927, 1.59	-
Asian race on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_\_RACEA}$)	0.851	5.82	0.754, 0.948	-
AA race on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_\_RACEB}$)	0.82	9.47	0.668, 0.972	-
BMI on cys-mcMMAF Vc ($\theta_{cys\text{-}mcMMAF\ Vc\_BMI}$)	-0.889	23.0	-1.29, -0.489	-
Inter-patient variability CV%				
On CL_{MMAF}	28.5	10.8	21.5, 34.3	35.3
CL_{MMAF}-cys-mcMMAF Vc covariance[a]	0.0807	13.4	0.0595, 0.102	-
On cys-mcMMAF Vc	65.8	3.63	60.1, 71.2	17.4
cys-mcMMAF Vc-K43 covariance[b]	0.384	10.9	0.302, 0.467	-

On K43	135	4.13	118, 153	29.6
On IOV CL_{MMAF}	56.9	2.81	53.2, 60.4	42.3
On IOV cys-mcMMAF Vc	45.7	2.43	43.3, 48.0	36.1
Residual error				
Proportional error CV%	26.3	1.04	25.8, 26.8	26.9
Additive error SD (nmol/L)	1×10^{-6} FIXED	-	-	-

PK parameter estimation

$CLi=\theta_{CLMMAF}\bullet(B2MBL/300)^{\theta CL\_B2MBL}\bullet(WTBL/75)^{\theta CL\_WTBL}\bullet\exp(\eta_{CLMMAF}+\kappa_{CLMMAF,\,j})$

$\text{cys-mcMMAF Vci}=\theta_{\text{cys-mcMMAF Vc}}\bullet(B2MBL/300)^{\theta\text{cys-mcMMAF Vc\_B2MBL}}(IGGBL/15)^{\theta\text{cys-mcMMAF Vc\_IGGBL}}\bullet(ALBBL/40)^{\theta\text{cys-mcMMAF Vc\_ALBBL}}\bullet(WTBL/75)^{\theta\text{cys-mcMMAF Vc\_WTBL}}\bullet(IBMIBL/27)^{\theta\text{cys-mcMMAF Vc\_IBMIBL}}\bullet(\theta_{CLMMAF\_RACEA})\text{[if Asian]}\bullet(\theta_{CLMMAF\_RACEB})\text{[if AA]}\bullet\exp(\eta_{\text{cys-mcMMAF Vc}}+\kappa_{\text{cys-mcMMAF Vc},\,j})$

$K43=\theta_{K43}\bullet\exp(\eta_{K43})$

Inter-patient variability:

Log-normal distribution CV%=SQRT(exp(Ω)–1)•100

Residual error

Y=IPRED+IPRED•ε1+ε2

[a]Correlation coefficient of 0.482; [b]Correlation coefficient of 0.630; [c]the 95% CI was calculated using standard errors from the estimation.

ε1 proportional residual error, ε2 additive residual error, η individual deviation from the population value, θ fixed effect parameter (typical value), Ω inter-patient variability variance, AA African American, ALBBL baseline albumin, B2M β2 microglobulin, B2MBL baseline B2M, BMI body mass index, CI confidence interval, CL clearance, C_{LMMAF} cys-mcMMAF clearance, cys-mcMMAF Vc cys-mcMMAF central volume of distribution, CV% percent coefficient of variation, cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, i individual patient index, IBMIBL baseline body mass index, IgG immunoglobulin G, IGGBL baseline immunoglobulin G, IOV inter-occasion variability, IPRED individual prediction, K34 distribution rate constant from the central to the peripheral compartment, K43 distribution rate constant from the peripheral to the central compartment, KAPPA ($\kappa_{,\,j}$) inter-occasion variability at j-occasion, PK pharmacokinetic, RATE-DAR rate change in drug-antibody ratio over time since most recent dose, RSE% percent relative standard error, SD standard deviation, SQRT square root, WTBL baseline body weight

Table S8 Comparison of PopPK estimates of the legacy 2023 final model for cys-mcMMAF when estimated with the current dataset and using ADVAN6 and ADVAN5

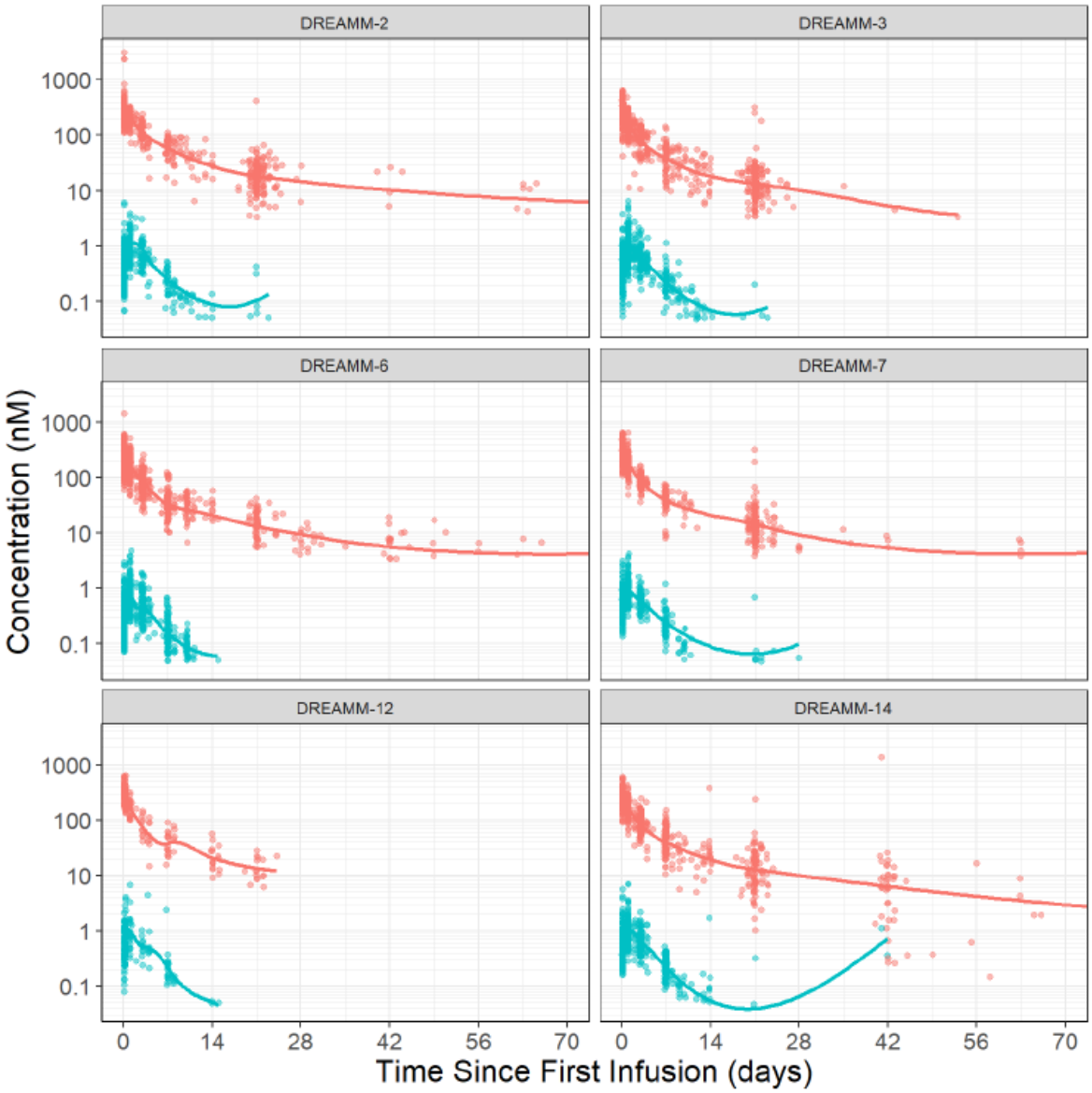
Parameter	**Estimate (%RSE) –ADVAN6 runnpde802**	**Estimate (%RSE) – ADVAN5 run802A5.mod**
Typical values		
CL_{MMAF} (L/day)	692 (3.47)	692 (2.47)
Cys-mcMMAF Vc (L)	24.2 (12.3)	24.2 (0.97)
K34 (1/day)	90.6 (15.1)	90.5 (2.72)
K43 (1/day)	5.58 (9.00)	5.58 (3.72)
RATE-DAR (1/day)	0.0424 (11.6)	0.0424 (10.2)
Covariate effects		
sBCMA on CL_{MMAF} ($\theta_{CL\_SBCMABL}$)	-0.0932 (22.8)	-0.0933 (22.6)
Weight on CL_{MMAF} (θ_{CL_WTBL})	0.572 (20.2)	0.571 (9.56)
Albumin on cys-mcMMAF Vc (θ_{Vc_ALBBL})	-0.967 (21.6)	-0.967 (2.98)
IgG on cys-mcMMAF Vc (θ_{Vc_IGGBL})	0.164 (14.4)	0.165 (5.88)
SBCMABL on cys-mcMMAF Vc ($\theta_{Vc\_SBCMABL}$)	0.0887 (31.1)	0.0887 (26.9)
Weight on cys-mcMMAF Vc (θ_{Vc_WTBL})	0.559 (25.0)	0.559 (7.13)
Inter-patient and inter-occasion variability CV%		
On CL_{MMAF}	31.0 (16.7)	31 (22.7)
CL_{MMAF}- cys-mcMMAF Vc covariance[a]	0.0894 (18.9)	0.0894 (19.3)
On cys-mcMMAF Vc	55.2 (7.05)	55.2 (7.1)
Cys-mcMMAF Vc -K43 covariance[b]	0.207 (31.6)	0.207 (33.3)
On K43	114 (10.1)	114 (10.3)
On IOV, CL_{MMAF}	40.8 (11.7)	40.7 (13)
On IOV, cys-mcMMAF Vc	45.1 (6.18)	45.1 (6.12)
Residual error		
Proportional error CV%	25.7 (3.47)	25.7 (2.8)

Parameter	Estimate (%RSE) –ADVAN6 runnpde802	Estimate (%RSE) – ADVAN5 run802A5.mod
Additive error SD (nmol/L)	1×10^{-6} FIXED	1×10^{-6} FIXED
PK parameter equations		
$CLi=q_{CLMMAF}\cdot (SBCMABL/100)^{qCL\_SBCMABL}\cdot(WTBL/75)^{qCL\_WTBL}\cdot\exp(h_{CLMMAF}+k_{CLMMAF,\,j})$		
$V3i=q_{Vc}\cdot(SBCMABL/SBCMAREF)^{qVc\_SBCMABL}\cdot(BIGG/10)^{qVc\_BIGG}\cdot(ALLBL/10)^{qVc\_ALBBL}\cdot(WTBL/75)^{qVc\_WTBL}\cdot \exp(h_{Vc}+k_{Vc},\, j)$		
$K43=q_{K43}\cdot\exp(h_{K43})$		
SBCMAREF=50; if from China, SBCMAREF=102		
Inter-patient variability		
Lognormal distribution CV%=SQRT(EXP(Ω)–1)·100		
Residual error		
$Y=IPRED+IPRED\cdot \varepsilon1+ \varepsilon2$		

[a]Correlation coefficient of 0.573 for both runs; [b]Correlation coefficient of 0.442 for both runs.

ε1 proportional residual error, ε2 additive residual error, h individual deviation from the population value, Ω inter-patient variability variance, q fixed effect parameter (typical value), ALBBL baseline albumin, BIGG baseline IgG, cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, CL_{MMAF} cys-mcMMAF clearance, CV% percent coefficient of variation, EXP exponentiate, i individual patient index, IgG immunoglobulin G, IGGBL baseline immunoglobulin G, IOV inter-occasion variability, IPRED individual prediction, K34 distribution rate constant from the central to the peripheral compartment, K43 distribution rate constant from the peripheral to the central compartment, KAPPA (κ, j) inter-occasion variability at j-occasion, PK pharmacokinetic, RATE-DAR rate change in drug-antibody ratio over time since most recent dose, %RSE percent relative standard error, sBCMA soluble B-cell maturation antigen SBCMABL baseline sBCMA, SBCMAREF reference sBCMA, SD standard deviation, SQRT square root, Vc cys-mcMMAF central volume of distribution, WTBL baseline weight

Fig. S1 Concentration-time profile for ADC and cys-mcMMAF by clinical study for Cycle 1



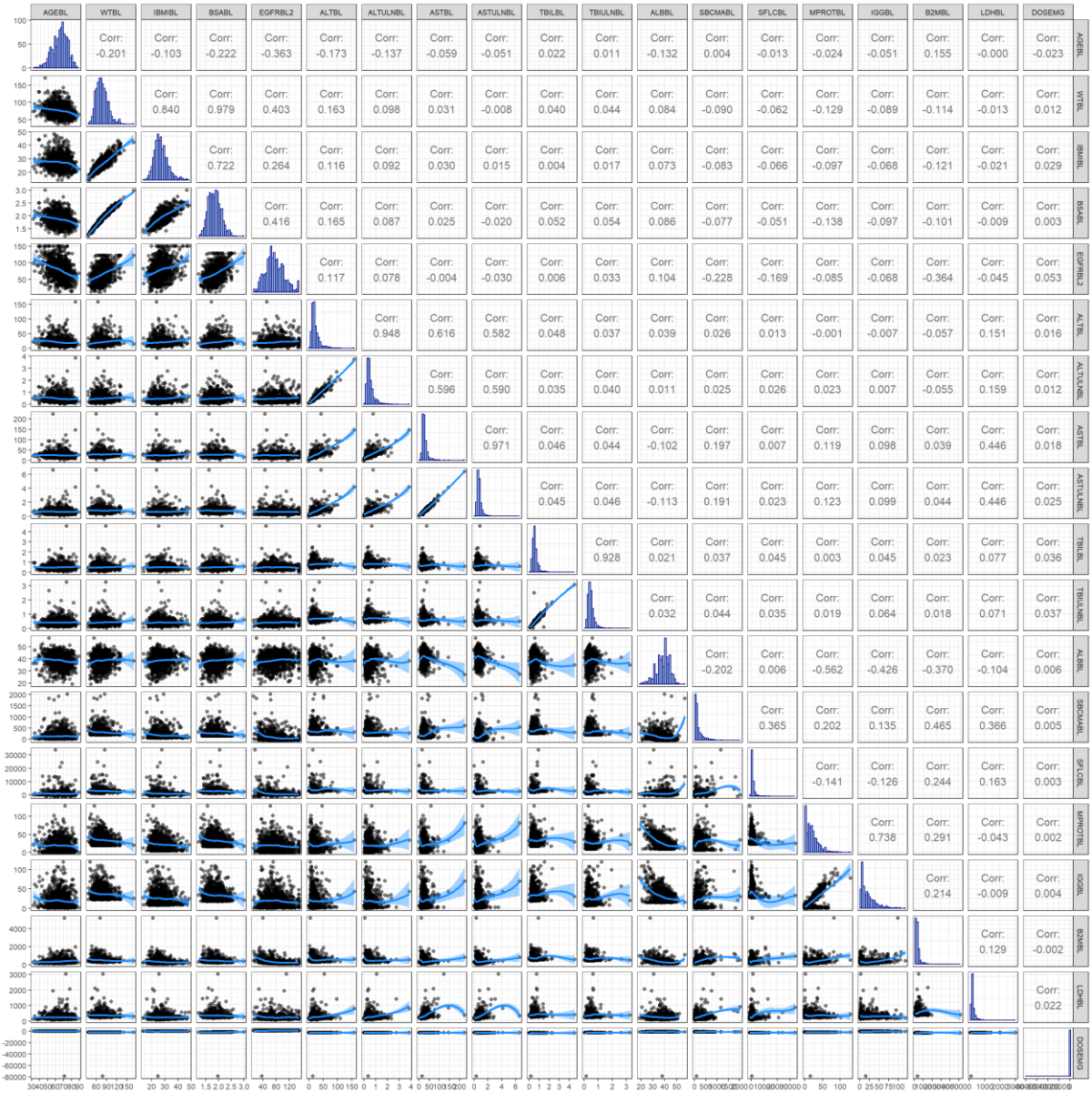
Cycle 1 concentrations were excluded for seven patients due to an error in Cycle 1 dosing.

Red circles represent ADC concentrations and blue circles represent cys-mcMMAF concentrations.

Colored lines are locally weighted smooth regression lines for each analyte.

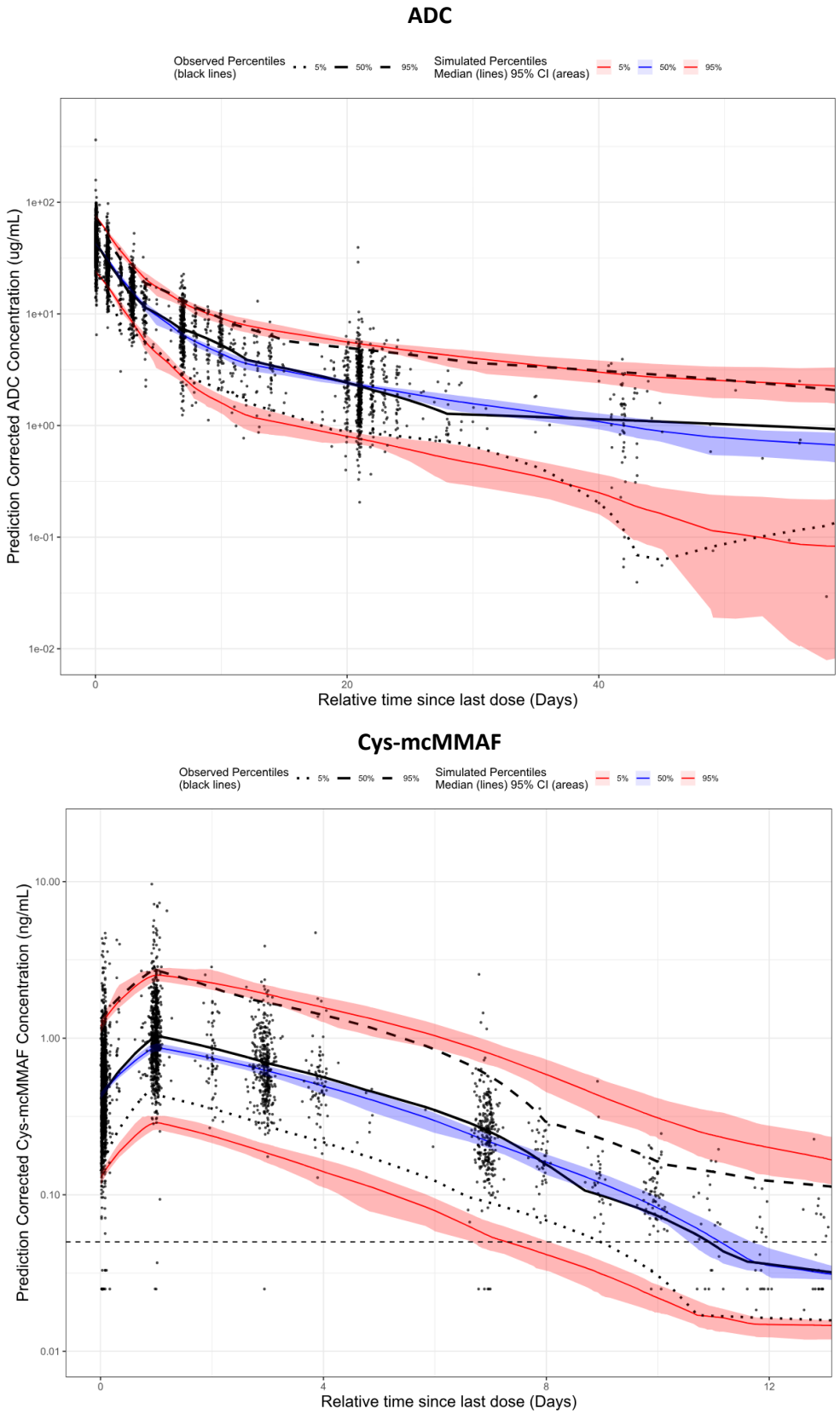
ADC antibody-drug conjugate, cyc-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, nM nanomolar

Fig. S2 Correlations between continuous covariates



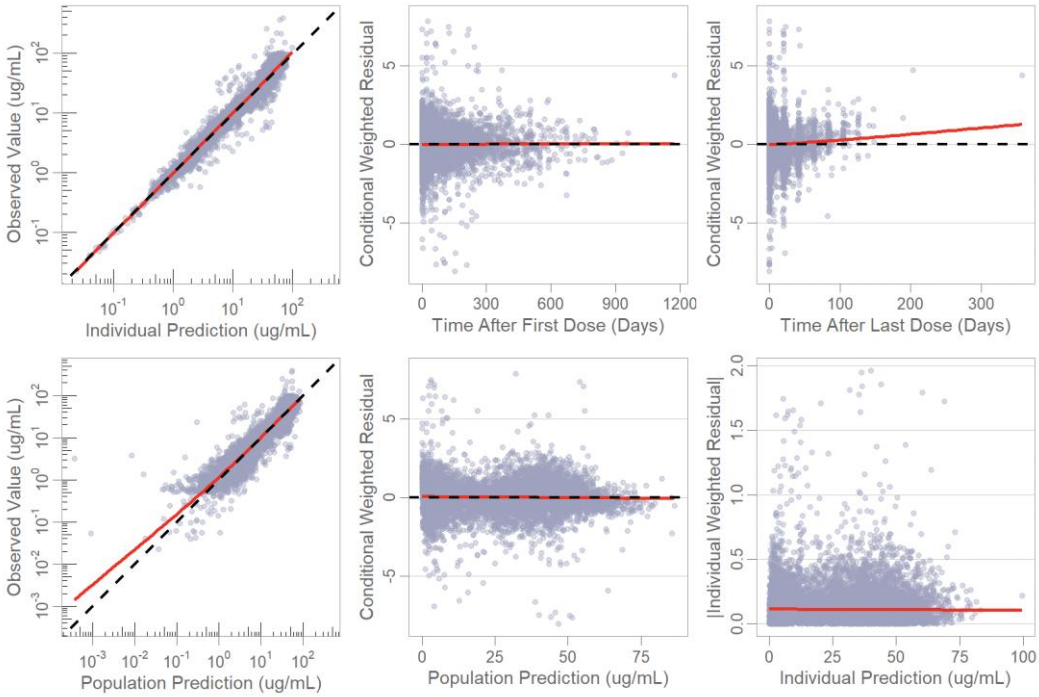
AGEBL baseline age, ALBBL imputed baseline albumin, ALTBL baseline alanine aminotransferase, ALTULNBL baseline alanine aminotransferase divided by upper limit of normal, ASTBL baseline aspartate aminotransferase, ASTULNBL baseline aspartate aminotransferase divided by upper limit of normal, B2MBL baseline β2 microglobulin, BSABL baseline body surface area, Corr correlation, DOSEMG dose in milligrams, EGFRBL2 estimated glomerular filtration rate capped to 150 mL/min, IBMIBL baseline body mass index, IGGBL baseline immunoglobulin G, LDHBL baseline lactate dehydrogenase, MPROTBL baseline M-protein, SBCMABL baseline soluble B-cell maturation antigen, SFLCBL baseline serum free light chain, TBILBL baseline total bilirubin, TBIULNBL baseline total bilirubin divided by upper limit of normal, WTBL baseline body weight

Fig. S3 Prediction corrected visual predictive check for dose 1 using the final ADC and cys-mcMMAF PopPK models



Black dots are prediction corrected data points. The black solid line is the prediction corrected median, and the black dashed lines are the prediction corrected 5th and 95th percentiles. The blue solid line is the prediction corrected predicted median, and the red solid lines are the prediction corrected predicted 5th and 95th percentiles. The blue area is the 95% CI of the prediction corrected simulated median, and the red areas are the prediction corrected 95% CI of the simulated 5th and 95th percentiles. Observed and simulated concentrations below LLOQ are set to 1/2 LLOQ for visual predictive check analysis. The thin horizontal black dashed lines represent the LLOQ (0.05 ng/mL). All concentrations have been dose-normalized to a belantamab mafodotin 2.5 mg/kg dose.
ADC antibody-drug conjugate, CI confidence interval, cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, LLOQ lower limit of quantification, PK pharmacokinetic, PopPK population PK

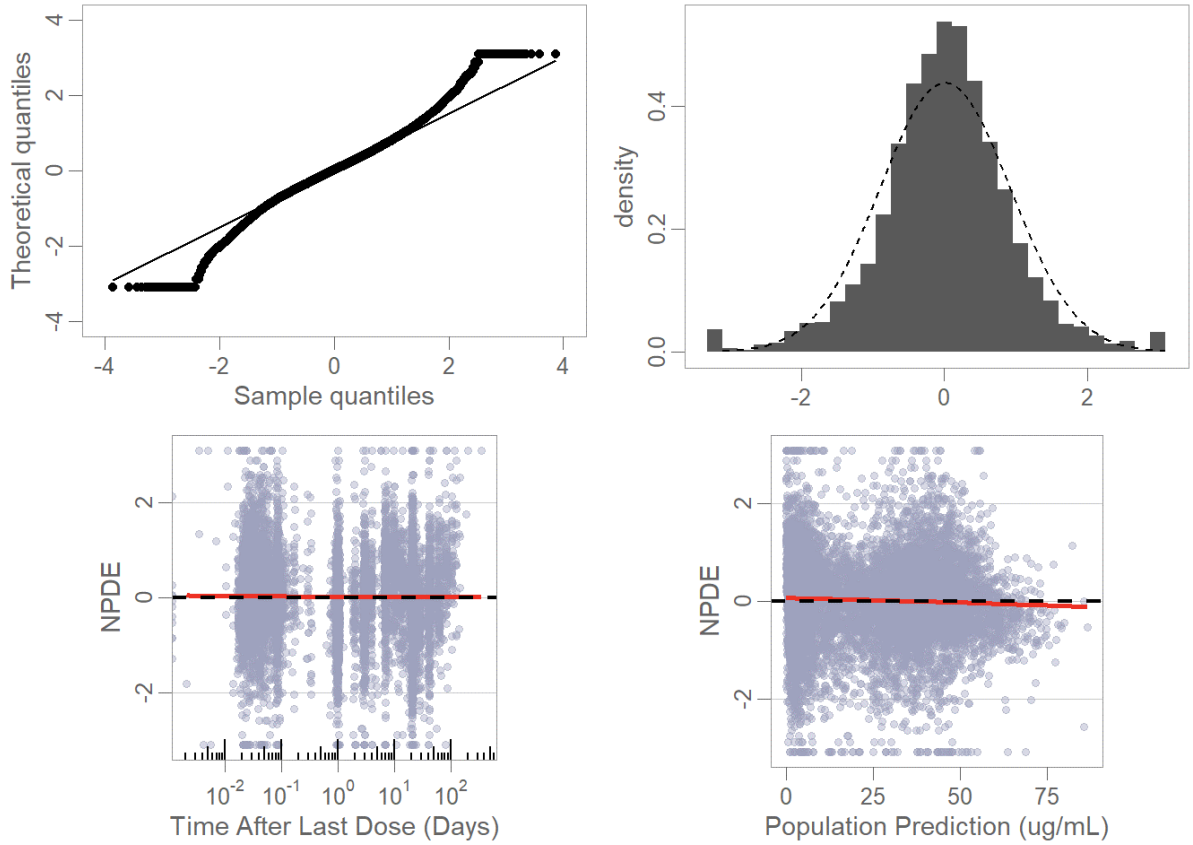
Fig. S4 Goodness of fit with the final ADC PopPK model



The dots are individual data points, and the solid lines are LOESS lines. In the 2 plots in the first column, the dashed lines are lines of identity, and in the 2 plots in the second column and the top plot in the third column, the dashed lines are at y=0.

ADC antibody-drug conjugate, LOESS locally weighted scatterplot smoothing, PopPK population pharmacokinetic

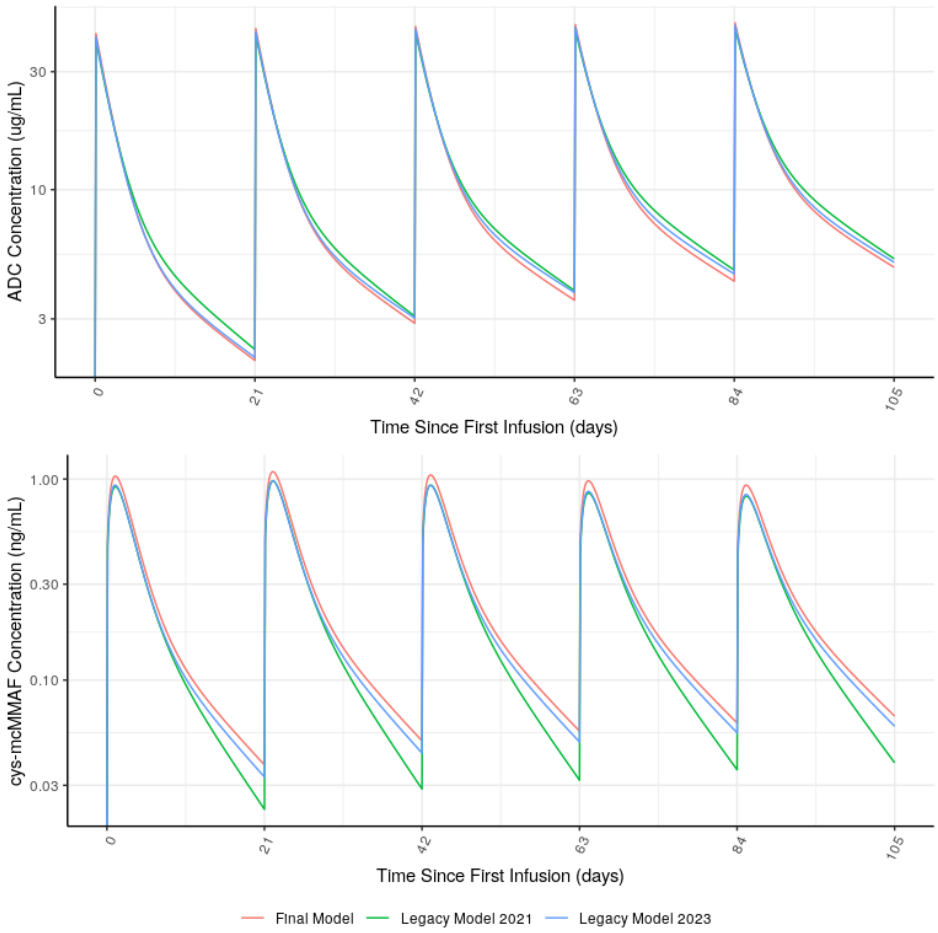
Fig. S5 Normal prediction distribution error with the final ADC PopPK model



The dots are individual data points, the solid black line in upper left plot is the quantile-quantile line, the dashed black curves in the upper right plot represent equivalent normal distributions, the dashed black lines represent y=0, and the solid red lines are LOESS lines.

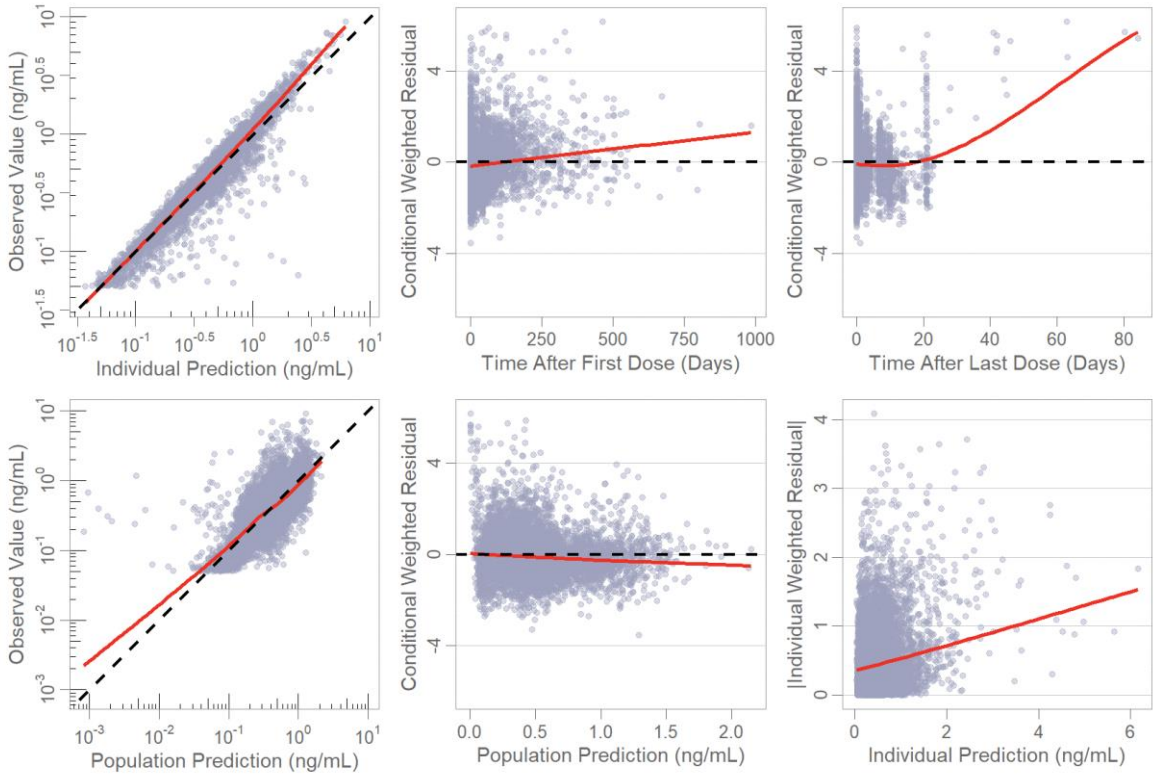
ADC antibody-drug conjugate, LOESS locally weighted scatterplot smoothing, NPDE normalized prediction distribution error, PopPK population pharmacokinetic

Fig. S6 Concentration-time profile for a typical patient receiving 2.5 mg/kg Q3W monotherapy: first 5 cycles



ADC antibody-drug conjugate, cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, Q3W every 3 weeks

Fig. S7 Goodness of fit with the final cys-mcMMAF PopPK model

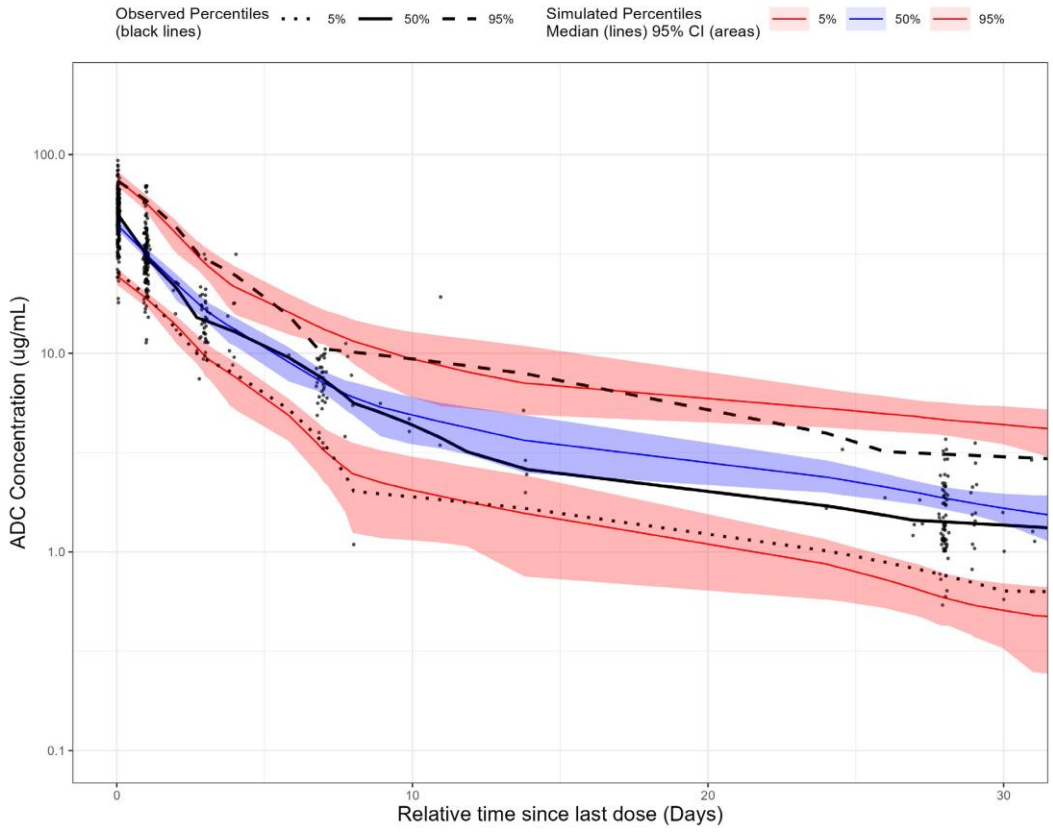


The dots are individual data points, and the solid lines are LOESS lines. In the 2 plots in the first column, the dashed lines are lines of identity, and in the 2 plots in the second column and the top plot in the third column, the dashed lines are at y=0.

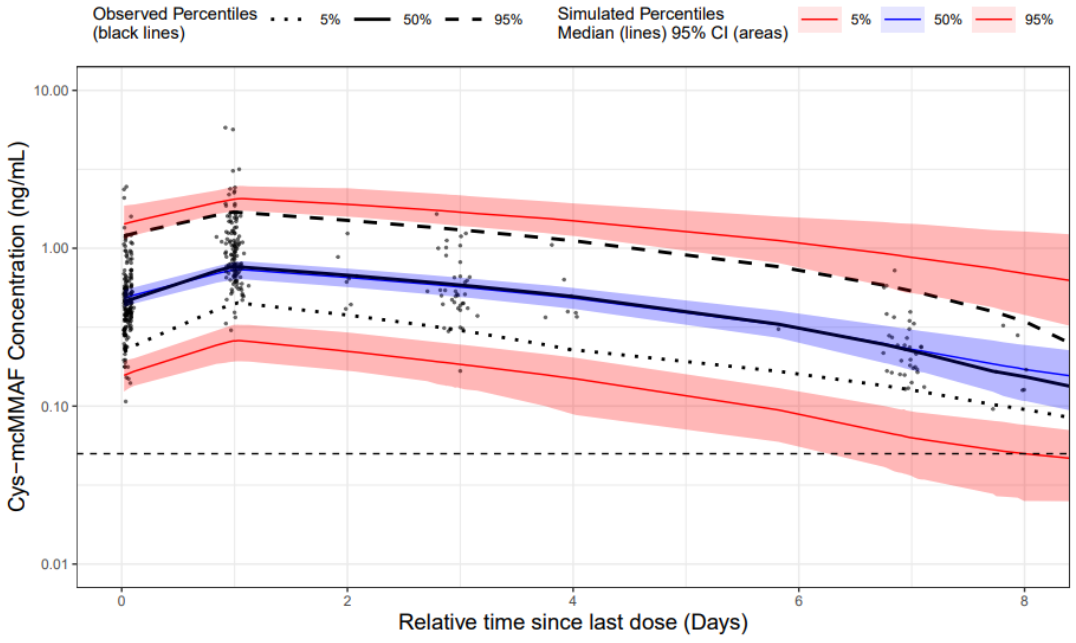
Cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, LOESS locally weighted scatterplot smoothing, PopPK population pharmacokinetic

Fig. S8 DREAMM-8 external validation: visual predictive check for dose 1 using the final ADC and cys-mcMMAF PopPK models

ADC



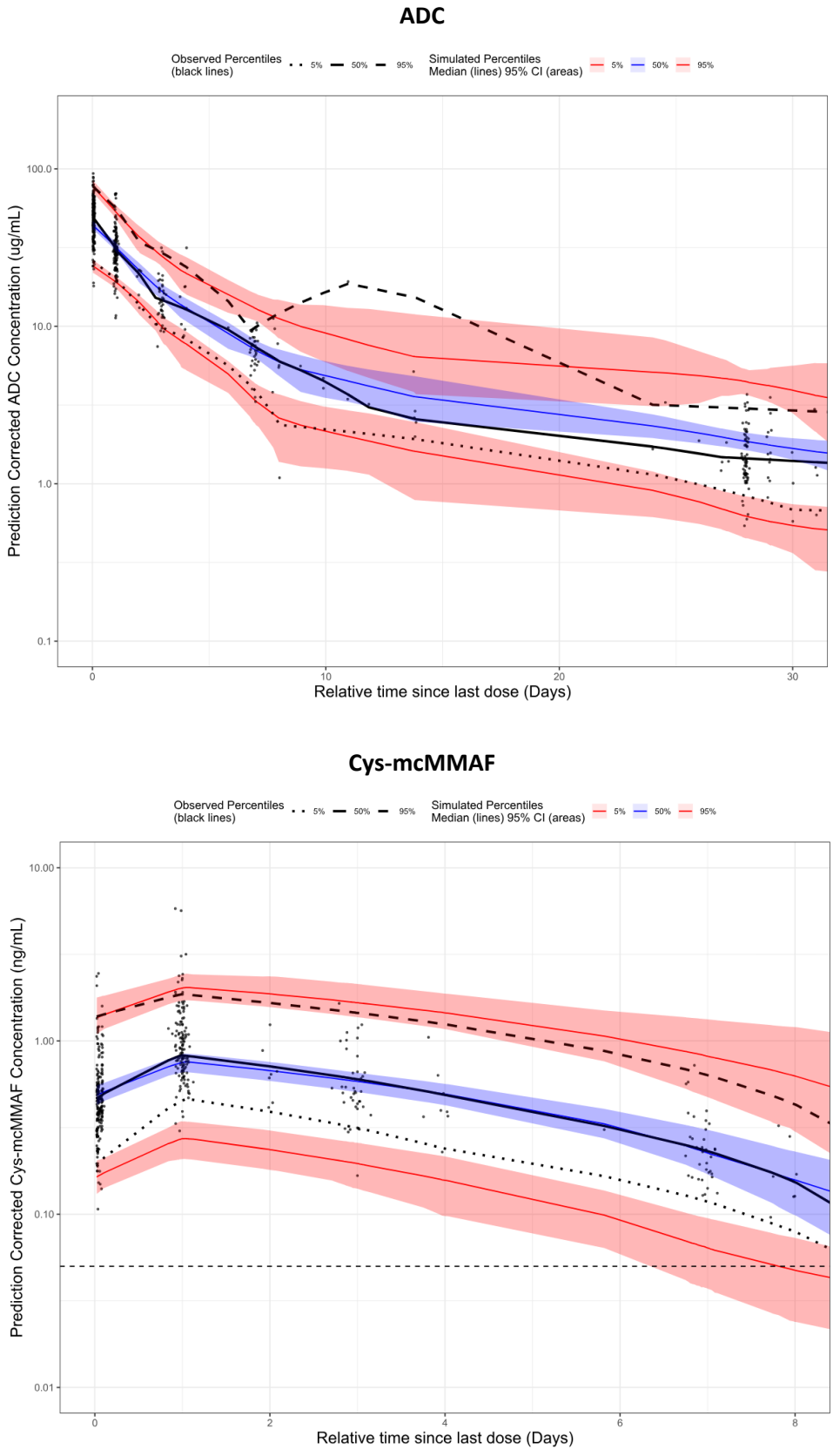
Cys-mcMMAF



The black dots are observed data points, the black solid line is the observed median, and the black dashed lines are the observed 5th and 95th percentiles. The blue solid line is the predicted median, and the red solid lines are the predicted 5th and 95th percentiles. The blue area is the 95% CI of the simulated median, and the red areas are the 95% CI of the simulated 5th and 95th percentiles. Observed and simulated concentrations below LLOQ are set to 1/2 LLOQ for visual predictive check analysis. The thin horizontal black dashed lines represent the LLOQ (0.05 ng/mL). All concentrations have been dose-normalized to a belantamab mafodotin 2.5 mg/kg dose.

ADC antibody-drug conjugate, CI confidence interval, cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, LLOQ lower limit of quantification, PopPK population pharmacokinetic

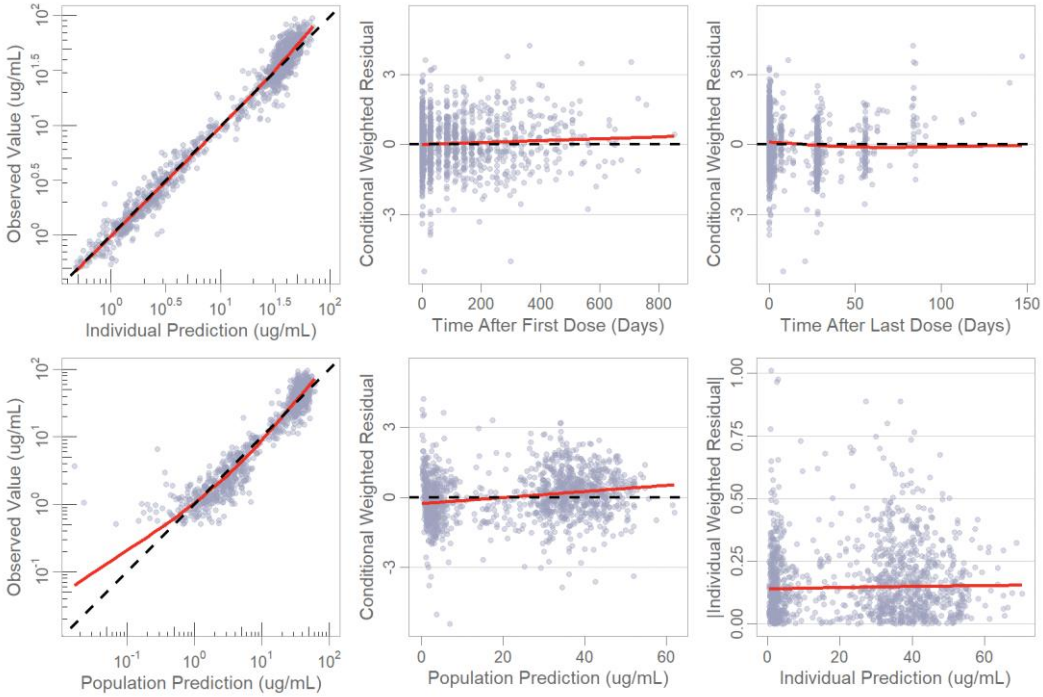
Fig. S9 DREAMM-8 external validation: prediction corrected visual predictive check for dose 1 using the final ADC and cys-mcMMAF PopPK models



Black dots are prediction corrected data points. The black solid line is the prediction corrected median, and the black dashed lines are the prediction corrected 5th and 95th percentiles. The blue solid line is the prediction corrected predicted median, and the red solid lines are the prediction corrected predicted 5th and 95th percentiles. The blue area is the 95% CI of the prediction corrected simulated median, and the red areas are the prediction corrected 95% CI of the simulated 5th and 95th percentiles. Observed and simulated concentrations below LLOQ are set to 1/2 LLOQ for visual predictive check analysis. The thin horizontal black dashed lines represent the LLOQ (0.05 ng/mL). All concentrations have been dose-normalized to a belantamab mafodotin 2.5 mg/kg dose.

ADC antibody-drug conjugate, CI confidence interval, cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, LLOQ lower limit of quantification, PK pharmacokinetic, PopPK population PK

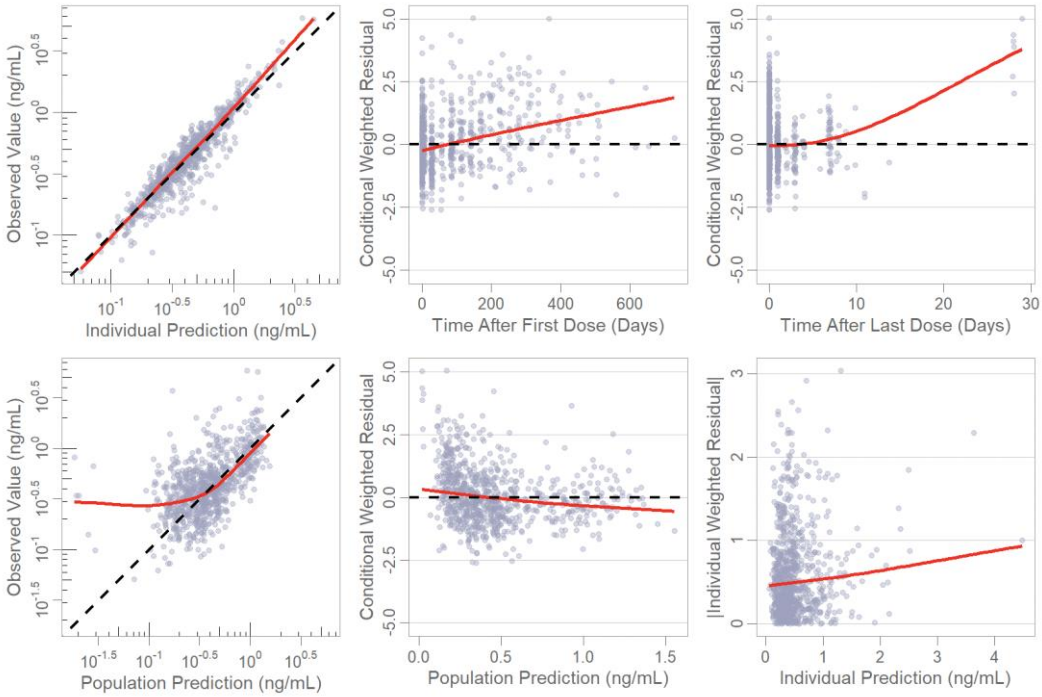
Fig. S10 DREAMM-8 external validation: goodness of fit with the final ADC PopPK model



The dots are individual data points, and the solid lines are LOESS lines. In the 2 plots in the first column, the dashed lines are lines of identity, and in the 2 plots in the second column and the top plot in the third column, the dashed lines are at y=0.

ADC antibody-drug conjugate, LOESS locally weighted scatterplot smoothing, PopPK, population pharmacokinetic

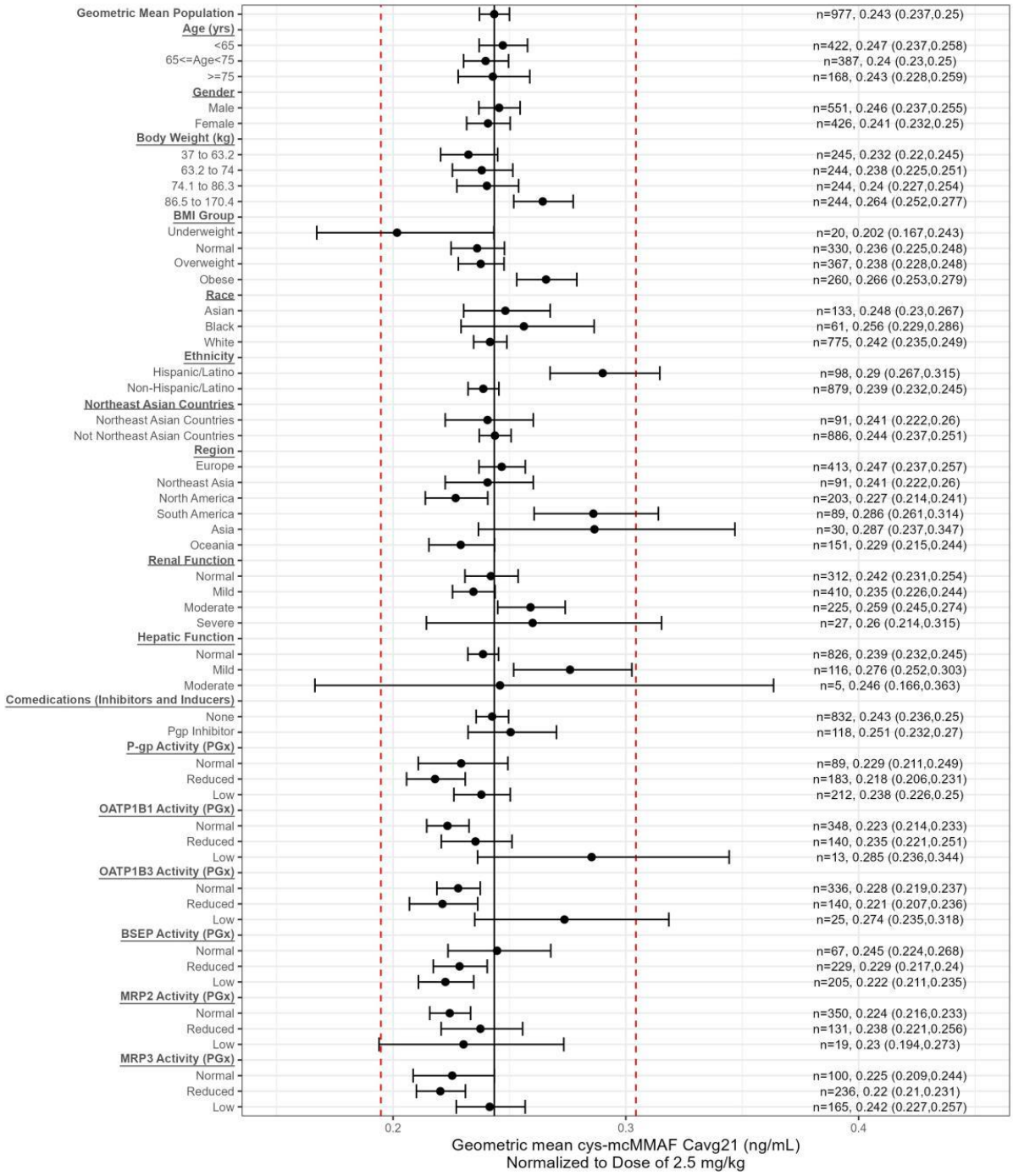
Fig. S11 DREAMM-8 external validation: goodness of fit with the final cys-mcMMAF PopPK model

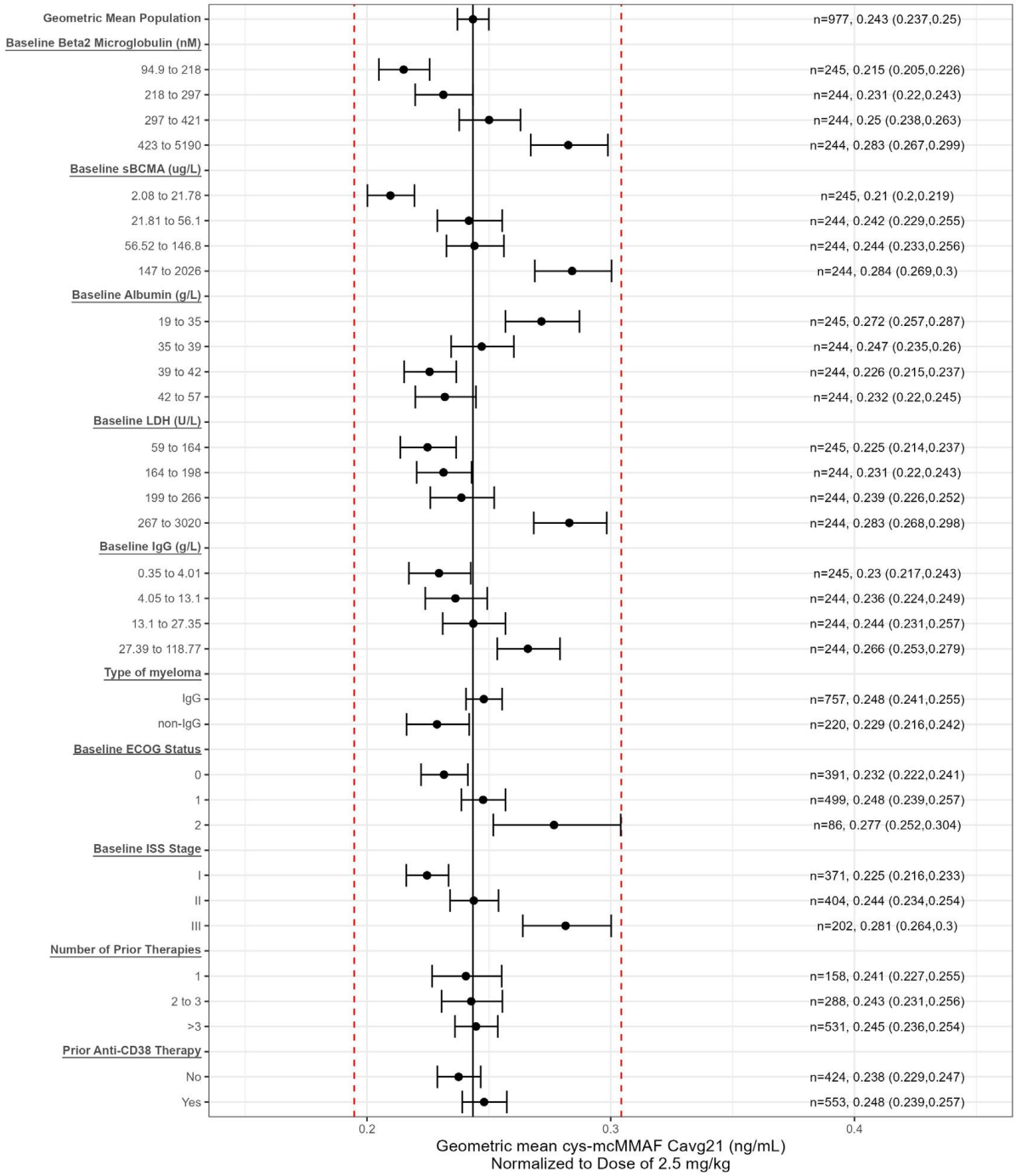


The dots are individual data points, and the solid lines are LOESS lines. In the 2 plots in the first column, the dashed lines are lines of identity, and in the 2 plots in the second column and the top plot in the third column, the dashed lines are at y=0. Plot observations were truncated at time after the last dose <30 days. This excluded 2 observations.

Cys-mcMMAF cysteine maleimidocaproyl monomethyl auristatin F, LOESS locally weighted scatterplot smoothing, PopPK population pharmacokinetic

Fig. S12 Cycle 1 cys-mcMMAF C_{avg21} by subgroup





The solid black circle represents geometric mean, and the error bar represents the 95% CI. The solid black line represents the geometric mean value of all patients. Dashed red lines represent an interval of 0.8 to 1.25 times the geometric mean of all patients. All the patient exposures were normalized to a belantamab mafodotin 2.5 mg/kg dose. Subgroups with <5 patients were omitted from the plot. Missing data were imputed at the median value for the population except for pharmacogenomic activity, where unknowns were left uncategorized. BMI groupings: underweight <18.5, normal 18.5 to 24.9, overweight 25 to 29.9, and obese 30+ kg/m^2.

BMI body mass index, BSEP bile salt export pump, C_{avg21} average concentration over a dosing interval of 21 days, CD38 cluster of differentiation 38, CI confidence interval, cys-mcMMAF cysteine maleimidocaproyl

monomethyl auristatin F, ECOG Eastern Cooperative Oncology Group, IgG immunoglobulin G, ISS International Staging System, LDH lactate dehydrogenase, MRP multidrug resistance-associated protein, OATP organic anion transporting polypeptide, P-gp P-glycoprotein, PGx pharmacogenomic, sBCMA soluble B-cell maturation antigen

1. Nooka AK, Cohen AD, Lee HC, Badros A, Suvannasankha A, Callander N, et al. Single-agent belantamab mafodotin in patients with relapsed/refractory multiple myeloma: Final analysis of the DREAMM-2 trial. Cancer. 2023;129(23):3746-60. https://doi.org/10.1002/cncr.34987.
2. Dimopoulos MA, Hungria VTM, Radinoff A, Delimpasi S, Mikala G, Masszi T, et al. Efficacy and safety of single-agent belantamab mafodotin versus pomalidomide plus low-dose dexamethasone in patients with relapsed or refractory multiple myeloma (DREAMM-3): a phase 3, open-label, randomised study. Lancet Haematol. 2023;10(10):e801-e12. https://doi.org/10.1016/S2352-3026(23)00243-0.
3. Popat R, Nooka A, Stockerl-Goldstein K, Abonour R, Ramaekers R, Khot A, et al. DREAMM-6: Safety, Tolerability and Clinical Activity of Belantamab Mafodotin (Belamaf) in Combination with Bortezomib/Dexamethasone (BorDex) in Relapsed/Refractory Multiple Myeloma (RRMM). Blood. 2020;136(Supplement 1):19-20. https://doi.org/10.1182/blood-2020-139332.
4. Hungria V, Robak P, Hus M, Zherebtsova V, Ward C, Ho PJ, et al. Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024. https://doi.org/10.1056/NEJMoa2405090.
5. A Study of Belantamab Mafodotin Monotherapy in Multiple Myeloma Participants With Normal and Varying Degree of Impaired Renal Function (DREAMM12) [internet]. ClinicalTrials.gov identifier: NCT04398745. [cited 2024 July 8]. Available from: https://clinicaltrials.gov/study/NCT04398745. Accessed 12 Aug 2024.
6. Hultcrantz M, Kleinman D, Ghataorhe P, McKeown A, He W, Ling T, et al. Exploring alternative dosing regimens of single-agent belantamab mafodotin on safety and efficacy in patients with relapsed or refractory multiple myeloma: DREAMM-14. Journal of Clinical Oncology. 2022;40(16_suppl):TPS8073-TPS. https://doi.org/10.1200/JCO.2022.40.16_suppl.TPS8073.
7. Dimopoulos MA, Beksac M, Pour L, Delimpasi S, Vorobyev V, Quach H, et al. Belantamab Mafodotin, Pomalidomide, and Dexamethasone in Multiple Myeloma. N Engl J Med. 2024. https://doi.org/10.1056/NEJMoa2403407.