Supplementary Material

Population Pharmacokinetics of Blinatumomab in Pediatric and Adult Patients Having Hematological Malignancies

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RUNNING TITLE

Pediatric/Adult PopPK of Blinatumomab in Hematological Malignancies

KEYWORDS

Blinatumomab, BLINCYTO®, BiTE®, population pharmacokinetic analysis, relapsed/refractory acute lymphoblastic leukemia

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1. SUPPLEMENTARY MATERIAL

1.1. SUPPLEMENTARY METHODS

Pharmacostatistical Modeling

To assess similarities in blinatumomab PK between adult populations studied in five clinical studies (MT103-104, MT103-202, MT103-205, MT103-206, and MT103-211) and adult and pediatric patients included in this analysis from three additional studies (MT103-203, 20120216, and 00103311), external validation was conducted using a previously published model (Table 1) [1].

Based on previous analyses, IIV in the PK model parameters was assumed to follow a log-normal distribution and, consequently, an exponential random effects model was used. The correlations between random effects were explored and incorporated into the model if deemed necessary. Residual variability (σ) was evaluated using an additive error model after natural logarithmic transformation of the measured blinatumomab concentrations and model predictions (the “transformation at both sides” approach). The magnitude of IIV and σ was expressed approximately as the percent coefficient of variation (%CV).

For each potential model, the improvement in fit obtained was assessed by examination of several diagnostics. The change in the minimum value of the objective function (MVOF), a statistic that was approximately proportional to minus twice the log-likelihood of the data, was examined. For a single comparison, a change in the MVOF (ΔMVOF) of ≥10.8 was required to reach statistical significance (α=0.001) for the addition of one fixed effect. This *p*-value was selected to account for multiple comparisons and to avoid the inclusion of borderline effects.

The goodness-of-fit of NONMEM analyses was also assessed by examination of scatterplots of observed concentrations versus population-predicted concentrations and versus individual-predicted concentrations, and scatterplots of conditional weighted residuals (CWRES) and normalized prediction distribution error (NPDE) versus population-predicted concentrations and versus time since last dose.

In addition, the estimated shrinkage of random effects was also assessed as previously described [2]. The covariance step was examined, and the asymptotic standard errors of fixed and random effects produced by NONMEM were used to calculate the relative standard errors (RSEs). In addition, correlations between population parameters and the condition number were evaluated whether the model was ill-conditioned.

Covariate Analysis

The covariates included in the analysis were demographic factors (age, BSA, and sex), renal function test (CrCL), liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin, and total bilirubin), disease status (lactate dehydrogenase [LDH] and hemoglobin), dose level, and treatment cycle. The estimate of CrCL was calculated according to the Schwartz formula [3, 4] for pediatric patients or the Cockcroft-Gault formula [5] for adults (all other studies). There were only 9 patients that had greater than 2 cycles of treatment in the analysis dataset and so for the purposes of covariate exploration those cycles were grouped into cycle 2. Race was not tested as a covariate because whites/Caucasians represented greater than 90% of the patients represented in these datasets. T-cell and B-cell baseline values were not available in all studies, and therefore, could not be tested as a covariate. In general, independent categories of categorical covariates were tested independently only if they represented at least 10% of the patients, and the sample size was greater than 30 patients. Missing values for the quantitative covariates were imputed using the median value in each variable set, and missing values for categorical covariates were analyzed as an independent category.

Empirical Bayes estimates (EBEs) of the individual model parameters were used to identify potential correlations provided the shrinkage was lower than 0.3 [6] by graphical exploration and Pearson correlation coefficient. Covariates that showed statistical significance (p<0.01) and a significant correlation (r^2>0.1) were retained for a formal evaluation using a forward inclusion (χ^2=7.88, df: 1, p<0.005), followed by a backward elimination (χ^2=10.83, df: 1, p<0.001) approach [7]. The effects of continuous covariates were modeled multiplicatively using normalized power models, and the effects of categorical covariates were modeled multiplicatively using a similar notation:

$$TVP = \theta_n \cdot \prod_{m=1}^{M} \left(\frac{cov_m}{ref_m} \right)^{\theta_{(n+m)}} \cdot \prod_{p=1}^{P} \theta_{(n+M+p)}^{cov_{M+p}} \qquad (1),$$

where the typical value of a model parameter (TVP) was described as a function of M individual continuous covariates (cov_m, m=1,..,M) and P individual categorical (0 or 1) covariates (cov_{M+p}, p=1,..,P). θ_n is the estimated typical model parameter value with covariates equal to the reference covariate values (cov_m=ref_m, cov_{M+p}=0). $\theta_{(n+m)}$ and $\theta_{(n+M+p)}$ are estimated parameters that describe the magnitude of the covariate-parameter relationships.

After the univariate analysis in the context of the mixed effects modeling, the covariates with statistically significant effects on PK parameters were incorporated into the population model, all at one time, to establish the intermediate population model. At this stage, the exploratory analyses described above using the individual parameter estimates, computed from intermediate population models, were repeated. If there was any additional significant covariate, it was included in the population model using the same procedure described above. A full model was determined when no additional improvement seemed possible. Then, the relative contribution of each covariate to the goodness-of-fit was re-evaluated using the backward elimination method, by deleting it from the full model. If the exclusion of a fixed effect resulted in an increase in MVOF less than 10.8 (p<0.001, χ^2, 1 df), the covariate was removed from the model. With this methodology, only covariates showing significant contributions were conserved in the model. In addition, if, within the range of covariate values evaluated, the difference in the typical parameter was less than 20%, the covariate was then considered not clinically relevant and, if deemed appropriate, might be excluded from the model. In addition, the improvement in fit after incorporating the covariates was assessed by the reduction in the IIV and residual variability, the reduction of the standard errors, and the examination of diagnostic plots.

Supplementary References

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1.2. SUPPLEMENTARY TABLES

Supplementary Table 1 Descriptive statistics for continuous demographics for patients in the blinatumomab population pharmacokinetics dataset

All data	**Study**					
	MT103-104		**MT103-202**		**MT103-203**	
	N	**Median (min, max)**	**N**	**Median (min, max)**	**N**	**Median (min, max)**
Age (years)	67	62.00 (20.00, 80.00)	20	44.50 (20.00, 77.00)	32	42.50 (18.00, 73.00)
Body weight (kg)	67	77.00 (52.00, 110.50)	20	73.75 (53.00, 124.70)	32	75.85 (54.40, 104.00)
Body surface area (m^2)	67	1.93 (1.56, 2.32)	20	1.84 (1.56, 2.45)	32	1.89 (1.59, 2.31)
AST (U/L)	67	27.00 (12.00, 58.00)	20	23.70 (13.00, 56.80)	32	22.50 (7.00, 66.00)
ALT (U/L)	67	23.00 (6.00, 92.00)	20	23.85 (11.00, 98.60)	32	34.60 (11.00, 95.00)
Total bilirubin (µmol/L)	67	6.80 (2.00, 20.50)	20	6.90 (2.00, 10.30)	32	6.80 (3.00, 22.30)
Lactate dehydrogenase (U/L)	67	254.0 (156.0, 1313.0)	20	187.5 (151.0, 345.0)	32	183.5 (91.0, 333.0)
Serum albumin (g/L)	67	40.90 (26.00, 51.00)	20	40.05 (33.70, 53.00)	31	42.00 (32.00, 48.00)
Hemoglobin (g/dL)	67	11.70 (6.90, 15.50)	20	11.45 (8.80, 14.30)	32	11.95 (8.60, 16.10)
Creatinine clearance (mL/min)	67	87.15 (38.92, 150.00)	20	114.39 (51.04, 150.00)	32	123.91 (64.00, 150.00)

All data	Study					
	MT103-205		MT103-206		MT103-211	
	N	Median (min, max)	N	Median (min, max)	N	Median (min, max)
Age (years)	46	5.00 (0.62, 16.00)	36	31.50 (18.00, 77.00)	213	39.00 (18.00, 79.00)
Body weight (kg)	46	21.20 (7.50, 68.90)	36	69.05 (50.00, 107.20)	213	73.70 (44.00, 148.70)
Body surface area (m^2)	46	0.83 (0.37, 1.77)	36	1.80 (1.50, 2.30)	213	1.88 (1.39, 2.70)
AST (U/L)	46	37.00 (14.00, 553.00)	36	31.00 (13.00, 105.00)	213	31.00 (11.00, 336.00)
ALT (U/L)	46	67.50 (12.00, 807.00)	36	50.10 (10.00, 346.00)	213	46.00 (6.00, 384.00)
Total bilirubin (µmol/L)	46	6.80 (1.70, 34.20)	36	8.60 (3.40, 30.80)	212	8.60 (1.70, 41.10)
Lactate dehydrogenase (U/L)	46	359.0 (114.0, 5270.0)	36	215.0 (128.0, 1708.0)	213	445.0 (98.0, 23,772.0)
Serum albumin (g/L)	45	39.00 (30.00, 48.00)	35	40.00 (27.00, 44.00)	212	35.00 (15.00, 49.00)
Hemoglobin (g/dL)	46	9.65 (7.10, 15.00)	36	10.60 (7.50, 13.70)	213	10.00 (7.00, 14.30)
Creatinine clearance (mL/min)	46	150.00 (53.90, 150.00)	36	112.85 (43.70, 150.00)	213	127.99 (38.52, 150.00)

All Data	Study				All	
	20120216		00103311			
	N	Median (min, max)	N	Median (min, max)	N	Median (min, max)
Age (years)	37	55.00 (23.00, 77.00)	223	39.00 (18.00, 80.00)	674	41.0 (0.6, 80.0)
Body weight (kg)	37	73.80 (42.00, 110.00)	220	68.00 (39.00, 139.80)	671	70.7 (7.5, 148.7)
Body surface area (m^2)	37	1.81 (1.32, 2.42)	218	1.80 (1.31, 2.63)	669	1.8 (0.4, 2.7)
AST (U/L)	37	23.00 (10.00, 83.00)	222	28.00 (6.00, 146.00)	673	28.2 (6.0, 553.0)
ALT (U/L)	37	37.00 (9.00, 245.00)	222	43.00 (7.00, 414.00)	673	41.0 (6.0, 807.0)
Total bilirubin (µmol/L)	37	7.70 (2.60, 18.80)	222	8.60 (1.00, 44.50)	672	8.2 (1.0, 44.5)
Lactate dehydrogenase (U/L)	37	275.0 (147.0, 2364.0)	223	312.0 (76.0, 13,922.0)	674	296.5 (76.0, 23,772.0)
Serum albumin (g/L)	37	35.00 (23.00, 48.00)	219	37.00 (21.00, 50.00)	666	37.1 (15.0, 53.0)
Hemoglobin (g/dL)	37	9.60 (6.30, 14.10)	223	9.60 (4.80, 16.70)	674	10.1 (4.8, 16.7)
Creatinine clearance (mL/min)	37	105.40 (36.04, 150.00)	220	122.79 (40.51, 150.00)	671	120.9 (36.0, 150.0)

ALT: alanine aminotransferase; AST: aspartate aminotransferase

Supplementary Table 2 Descriptive statistics for categorical demographics for patients in the blinatumomab population PK dataset

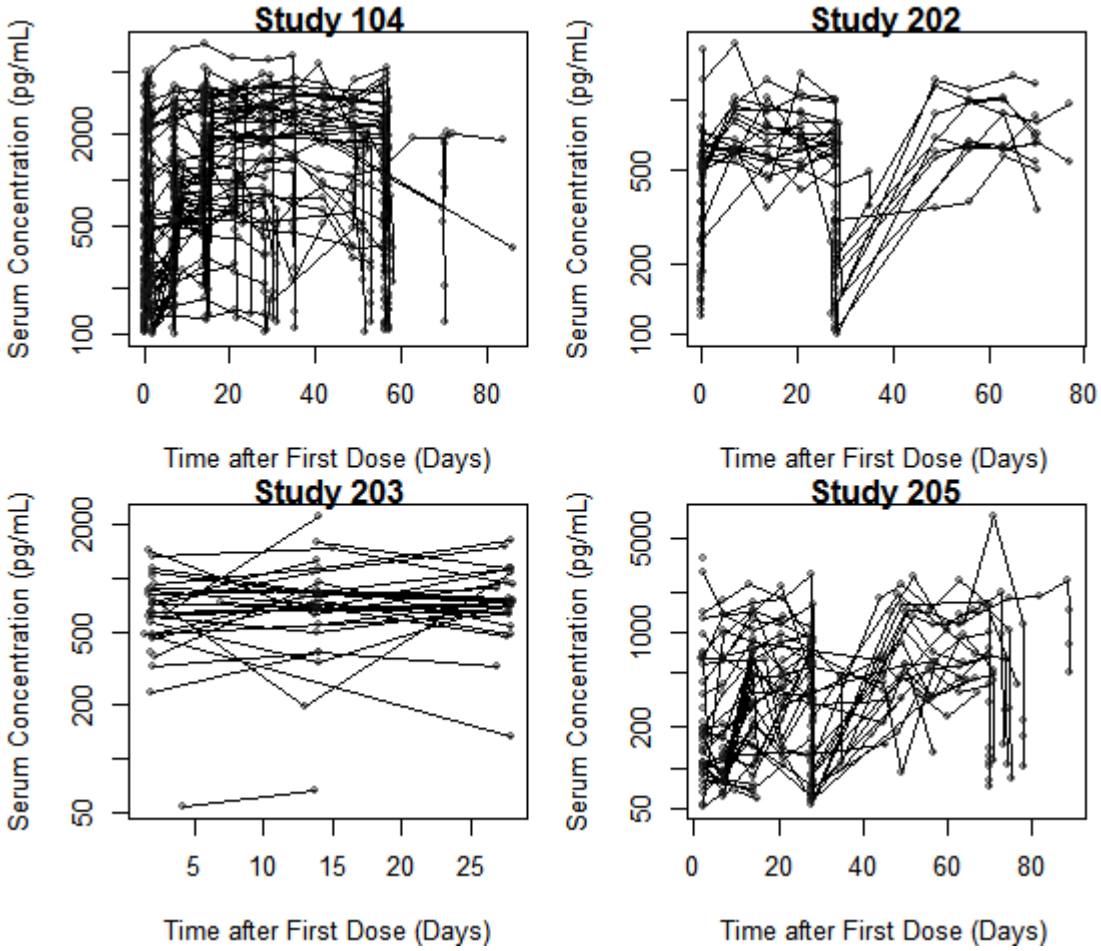
	All																**All**	
	Study																	
	MT103-104		**MT103-202**		**MT103-203**		**MT103-205**		**MT103-206**		**MT103-211**		**20120216**		**00103311**			
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age group	67	100	20	100	32	100	.	.	36	100	213	100	37	100	223	100	628	93.1
18 years and older																		
Adolescents [a]	.	.	.	.	.	.	3	6.5	.	.	.	.	.	.	.	.	3	0.4
Children [a]	.	.	.	.	.	.	33	71.7	.	.	.	.	.	.	.	.	33	4.8
Infants [a]	.	.	.	.	.	.	10	21.7	.	.	.	.	.	.	.	.	10	1.4
Sex	17	25.3	11	55.0	11	34.3	21	45.6	14	38.8	83	38.9	17	45.9	94	42.1	268	39.7
Female																		
Male	50	74.6	9	45.0	21	65.6	25	54.3	22	61.1	130	61.0	20	54.0	129	57.8	406	60.2
Race	.	.	.	.	.	.	.	.	.	.	1	0.4	.	.	3	1.3	4	0.5
American Indian or Alaskan Native																		
Asian	.	.	.	.	.	.	.	.	.	.	6	2.8	1	2.7	15	6.7	22	3.2
Black or African American	.	.	.	.	.	.	.	.	1	2.7	6	2.8	2	5.4	5	2.2	14	2.0

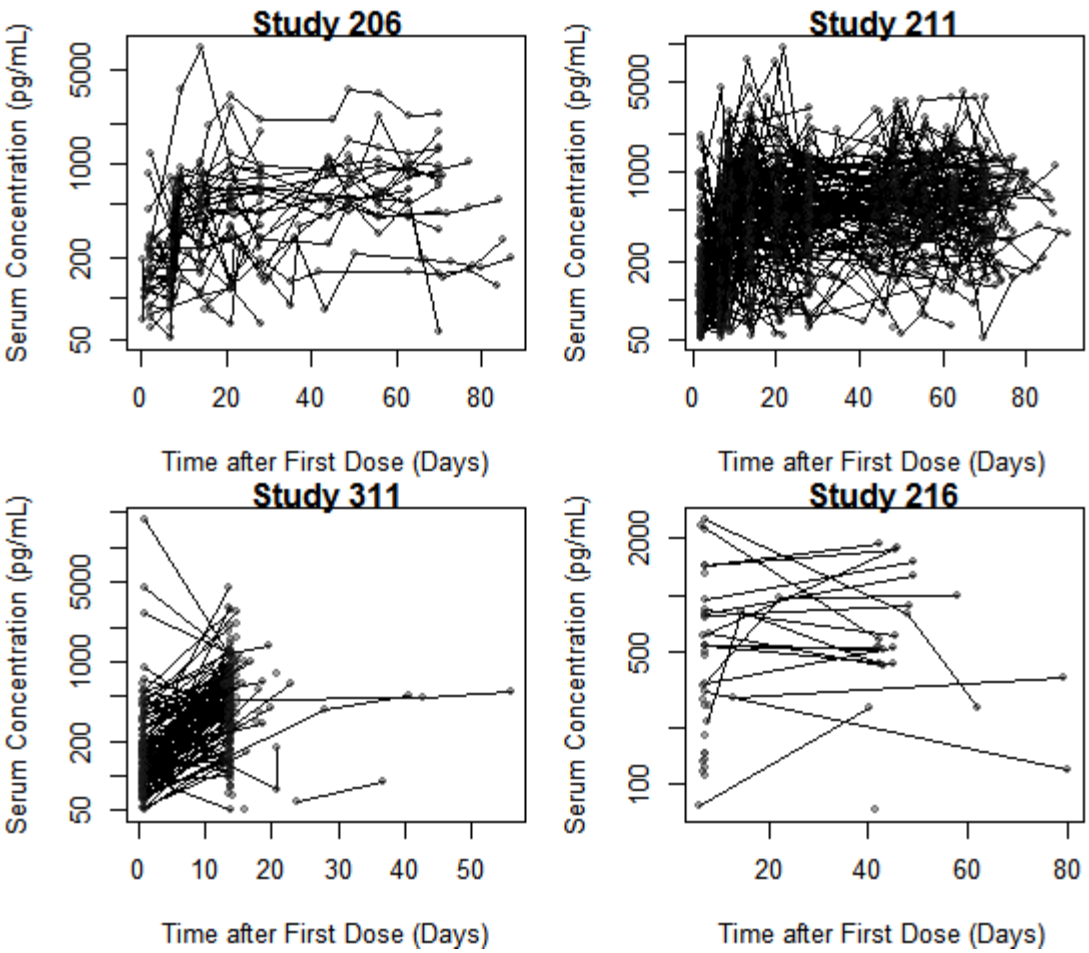
	All Study																All	
	MT103-104		MT103-202		MT103-203		MT103-205		MT103-206		MT103-211		20120216		00103311			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Native Hawaiian or Other Pacific Islander	.	.	.	.	.	.	.	.	.	.	1	0.4	.	.	1	0.4	2	0.2
Other	.	.	.	.	.	.	4	8.6	.	.	37	17.3	1	2.7	11	4.9	53	7.8
White	67	100	20	100	32	100	42	91.3	35	97.2	162	76.0	33	89.1	188	84.3	579	85.9

[a]Definitions of pediatric populations from the 1994 rule on “Specific Requirements on Content and Format of Labeling for Human Prescription Drugs”; Revision of “Pediatric Use” Subsection in the Labeling, 59 FR 64240, 64241-42 (December 13, 1994)

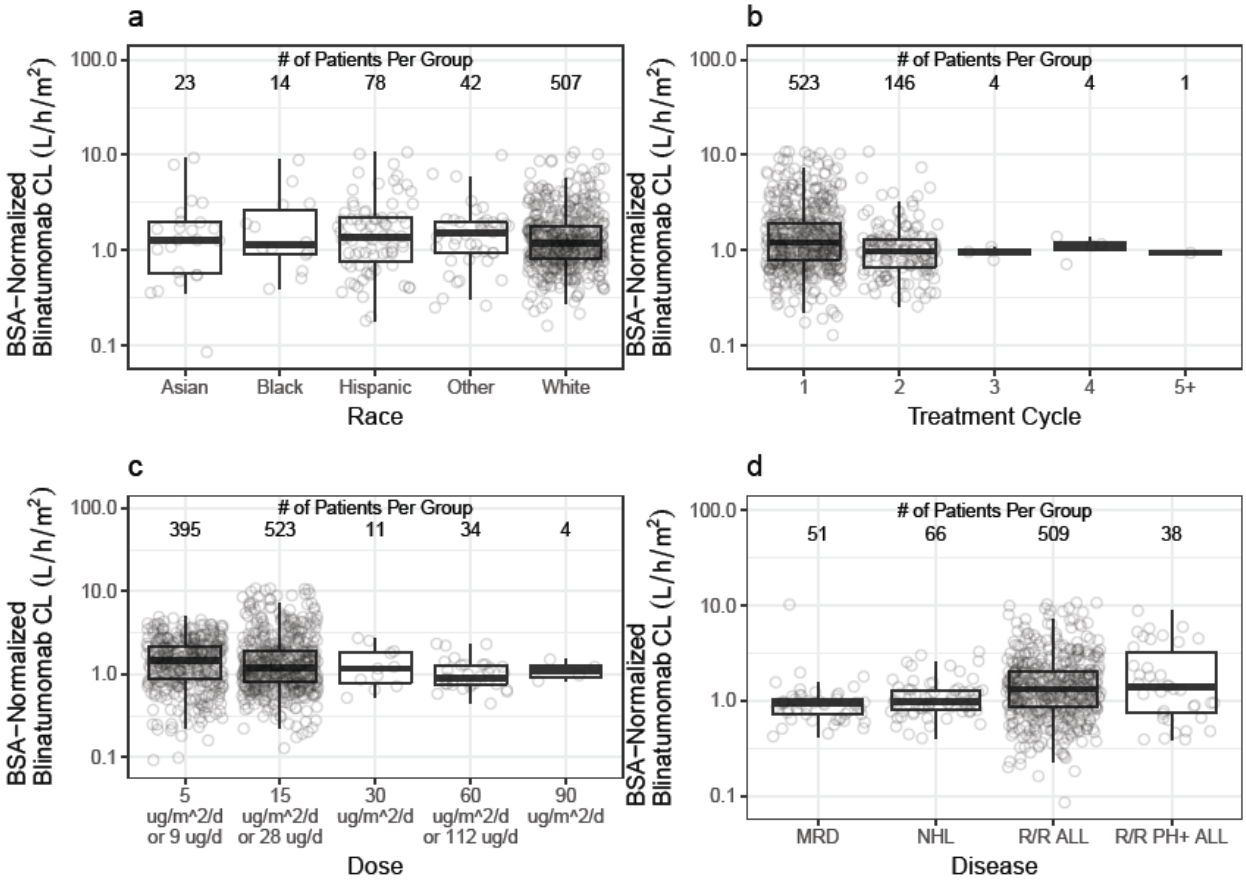
1.3. SUPPLEMENTARY FIGURES

Supplementary Fig. 1 Individual concentration versus time profiles by study. Studies 104, 202, 203, 205, 206, 211, 216, and 311 refer to Studies MT103-104, MT103-202, MT103-203, MT103-205, MT103-206, MT103-211, 20120216, and 00103311, respectively

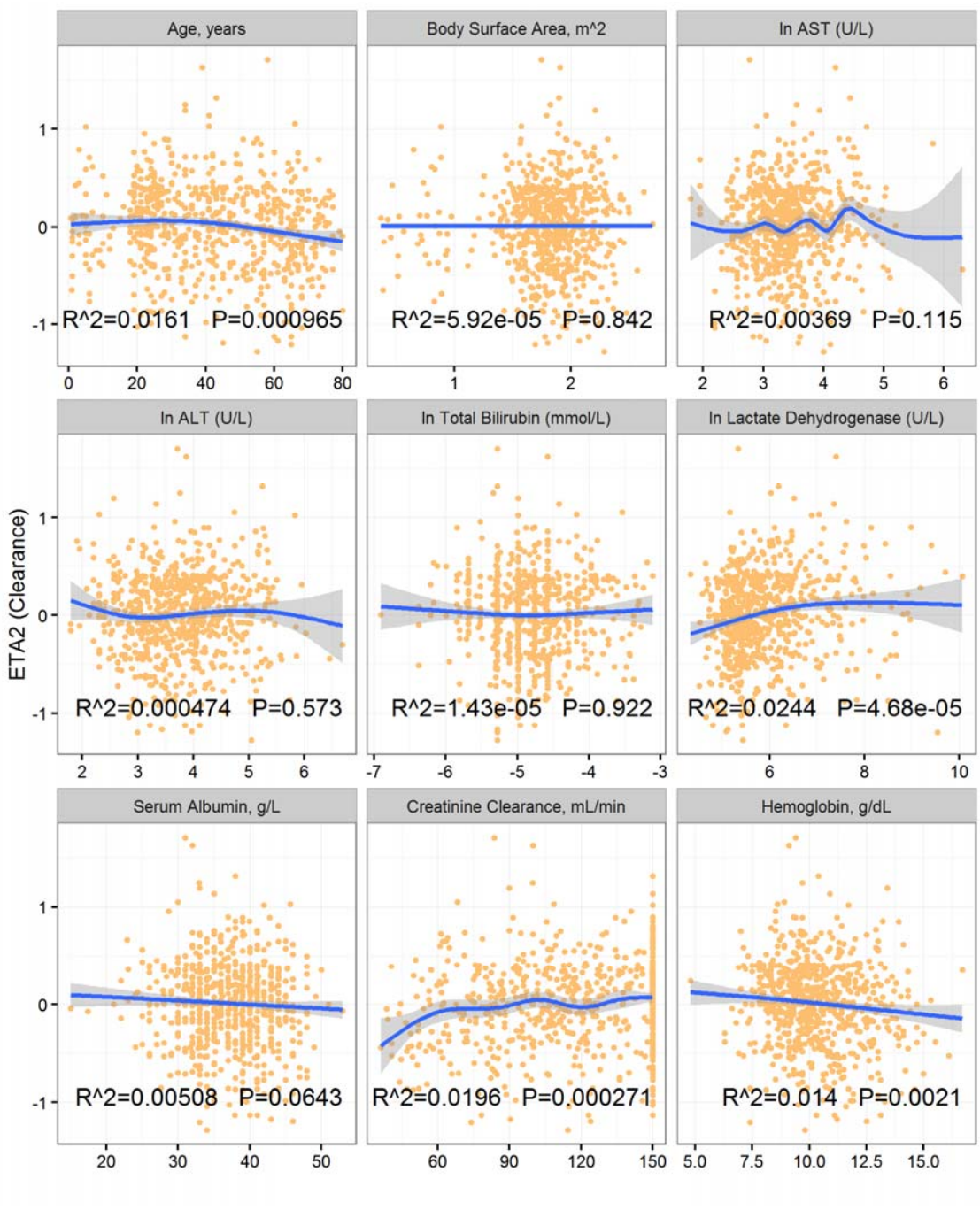



Study 206
Serum Concentration (pg/mL)
50
200
1000
5000
0
20
40
60
80
Time after First Dose (Days)
Study 211
Serum Concentration (pg/mL)
50
200
1000
5000
0
20
40
60
80
Time after First Dose (Days)
Study 311
Serum Concentration (pg/mL)
50
200
1000
5000
0
10
20
30
40
50
Time after First Dose (Days)
Study 216
Serum Concentration (pg/mL)
100
500
2000
20
40
60
80
Time after First Dose (Days)

Supplementary Fig. 2 Relationships between BSA-normalized blinatumomab clearances and demographic, treatment, and disease-related factors. ALL: acute lymphoblastic leukemia; BSA: body surface area; CL: clearance; MRD: minimal residual disease; NHL: non-Hodgkin's lymphoma; PH: Philadelphia chromosome; R/R: relapsed or refractory. **a** Clearance by race. **b** Clearance by treatment cycle after dose administration of 5 μg/m^2/day or 9 μg/day in adults. **c** Clearance by dose after cycle 1 dose administration in adults. **d** Clearance by disease. The top, middle, and bottom of the boxes are the third quartile, median, and first quartile, respectively. The whiskers are drawn to the nearest value not beyond a 1.5*(upper hinge – lower hinge). In figures a and d individual blinatumomab CL values were calculated as R_0/C_{ss} where C_{ss} is the average C_{ss}. In figures b and c individual blinatumomab CL values were calculated as R_0/C_{ss} where C_{ss} is the individual C_{ss}. Height or weight data was not collected for 4 subjects in the clinical dataset



Supplementary Fig. 3 Relationship between the interindividual random effects for clearance and covariates for the final model. Blue lines are smoothers plus 95% shading intervals. Orange dots are observed data and the in-graph statistics (coefficient of determination and p-value) are for a linear regression. ALT: alanine aminotransferase; AST: aspartate aminotransferase



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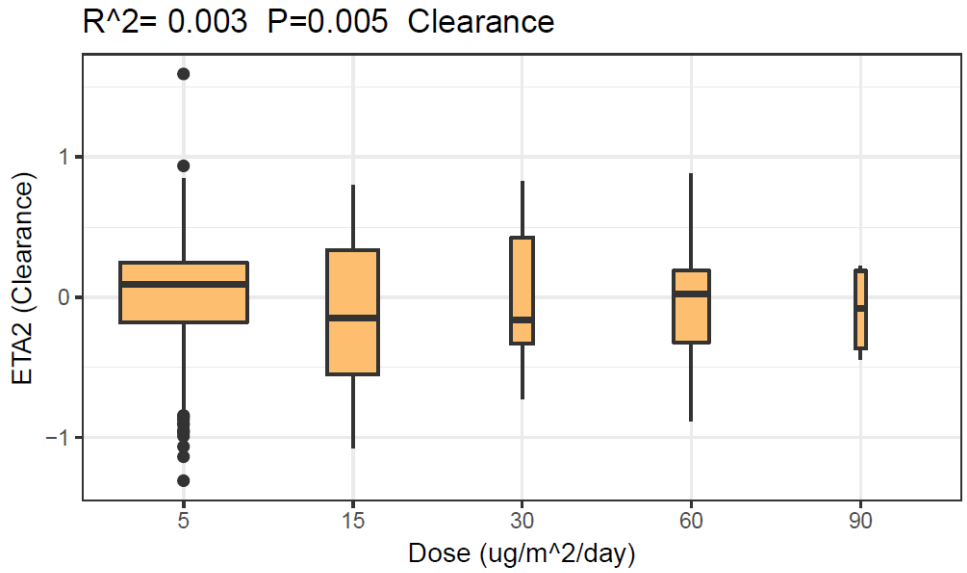

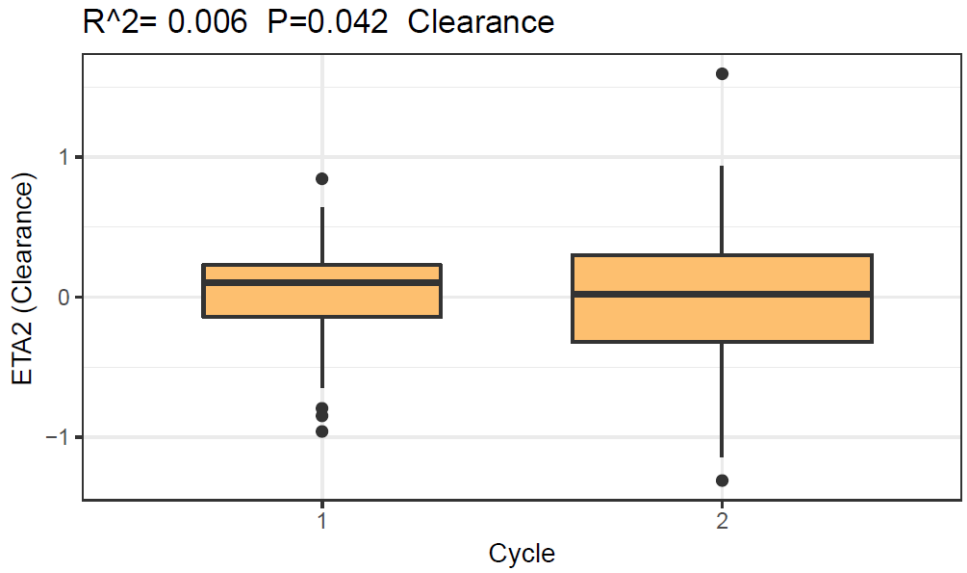

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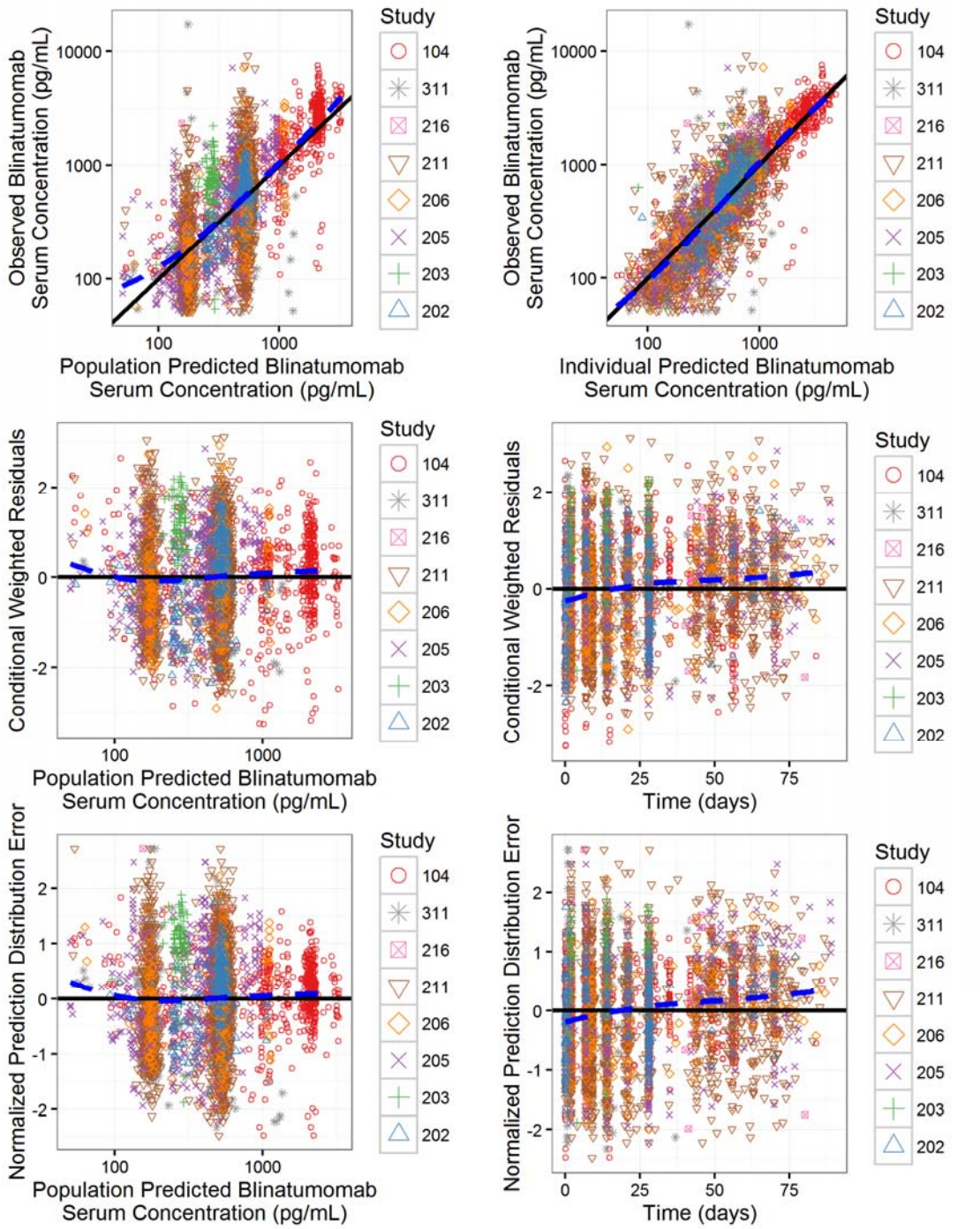

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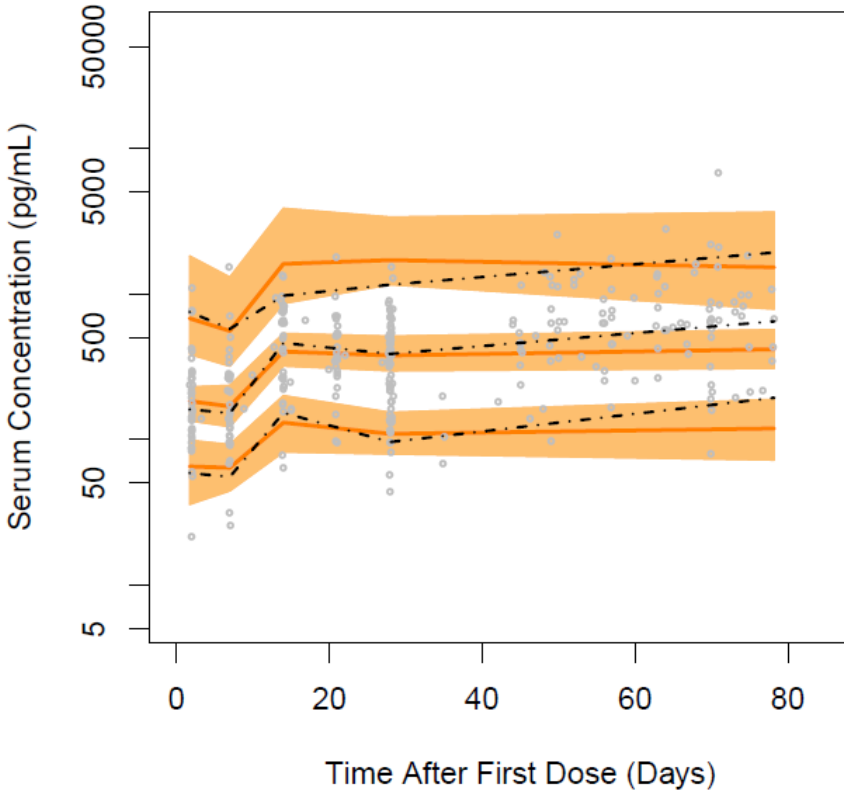

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