

SUPPLEMENTARY INFORMATION

Supplementary Tables

TABLE S1 Baseline categorical covariates [*N* (%)] in the PopPK model development dataset

	BGB-A317-001 (<i>n</i> = 450)	BGB-A317-102 (<i>n</i> = 300)	BGB-A317-203 (<i>n</i> = 70)	BGB-A317-204 (<i>n</i> = 112)	BGB-A317-205 (<i>n</i> = 30)	BGB-A317-206 (<i>n</i> = 54)	BGB-A317-208 (<i>n</i> = 248)	BGB-A317-209 (<i>n</i> = 76)	BGB-A317-302 (<i>n</i> = 264)	BGB-A317-303 (<i>n</i> = 532)	BGB-A317-304 (<i>n</i> = 222)	BGB-A317-307 (<i>n</i> = 238)	Total (<i>N</i> = 2596)
Sex													
Male	246 (54.7 %)	207 (69.0 %)	40 (57.1 %)	83 (74.1 %)	25 (83.3 %)	40 (74.1 %)	216 (87.1 %)	40 (52.6 %)	224 (84.8 %)	414 (77.8 %)	167 (75.2 %)	218 (91.6 %)	1920 (74.0 %)
Female	204 (45.3 %)	93 (31.0 %)	30 (42.9 %)	29 (25.9 %)	5 (16.7 %)	14 (25.9 %)	32 (12.9 %)	36 (47.4 %)	40 (15.2 %)	118 (22.2 %)	55 (24.8 %)	20 (8.4%)	676 (26.0 %)
Race													
White	289 (64.2 %)	–	–	–	–	–	96 (38.7 %)	–	51 (19.3 %)	92 (17.3 %)	–	–	528 (20.3 %)
Asian	130 (28.9 %)	300 (100%)	70 (100%)	112 (100%)	30 (100%)	54 (100%)	125 (50.4 %)	76 (100%)	211 (79.9 %)	423 (79.5 %)	222 (100%)	238 (100%)	1991 (76.7 %)
Black/ African Americ an	5 (1.1%)	–	–	–	–	–	4 (1.6%)	–	–	1 (0.2%)	–	–	10 (0.4%)
Other	26 (5.8%)	–	–	–	–	–	2 (0.8%)	–	–	16 (3.0%)	–	–	44 (1.7%)
Missing	–	–	–	–	–	–	21	–	2	–	–	–	23

[illegible]

0	88 (19.6 %)	–	–	–	–	–	–	–	–	–	–	–	88 (3.4%)
1	152 (33.8 %)	–	–	–	30 (100%)	54 (100%)	–	39 (51.3 %)	–	–	222 (100%)	238 (100%)	735 (28.3 %)
2	99 (22.0 %)	–	28 (40.0 %)	–	–	–	138 (55.6 %)	25 (32.9 %)	254 (96.2 %)	532 (100%)	–	–	1076 (41.4 %)
3	61 (13.6 %)	–	15 (21.4 %)	–	–	–	102 (41.1 %)	7 (9.2%)	–	–	–	–	185 (7.1%)
≥4	50 (11.1 %)	–	27 (38.6 %)	–	–	–	8 (3.2%)	4 (5.3%)	–	–	–	–	49 (1.9%)
Missing	–	300 (100%)	–	112 (100%)	–	–	–	1 (1.3%)	10 (3.8%)	–	–	–	423 (16.3 %)

Abbreviations: ADA, anti-drug antibodies; cHL, classical Hodgkin lymphoma; CRC, colorectal cancer; EC, esophageal carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status, GC, gastric cancer; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PopPK, population pharmacokinetic; TUMTP, tumor type; UC, urothelial bladder cancer.

TABLE S2 Baseline continuous covariates (median [min, max]) in the PopPK model development dataset

	001 (n = 450)	102 (n = 300)	203 (n = 70)	204 (n = 112)	205 (n = 30)	206 (n = 54)	208 (n = 248)	209 (n = 76)	302 (n = 264)	303 (n = 532)	304 (n = 222)	307 (n = 238)	Total (N = 2596)
Age (years)	61.0 [18.0, 81.0]	56.5 [18.0, 82.0]	32.5 [18.0, 69.0]	62.5 [36.0, 81.0]	60.5 [42.0, 74.0]	61.0 [36.0, 75.0]	62.0 [28.0, 90.0]	53.5 [19.0, 81.0]	62.0 [29.0, 83.0]	61.0 [28.0, 88.0]	60.0 [27.0, 75.0]	62.0 [38.0, 74.0]	60.0 [18.0, 90.0]
Weight (kg)	69.1 [31.9, 129]	62.0 [40.0, 105]	66.0 [40.0, 93.0]	65.5 [36.0, 94.5]	55.0 [38.0, 88.0]	65.3 [36.0, 109]	69.0 [40.0, 113]	63.3 [35.0, 85.0]	58.2 [35.1, 130]	66.4 [35.0, 130]	64.0 [41.0, 100]	62.0 [45.0, 113]	65.0 [31.9, 130]
Albumin (g/L)	37.0 [17.0, 50.0]	41.8 [26.2, 53.0]	43.0 [26.7, 53.2]	42.6 [23.0, 51.4]	40.6 [25.4, 48.6]	41.9 [30.5, 48.2]	41.9 [28.0, 52.0]	42.4 [33.0, 53.3]	41.6 [26.0, 54.4]	42.5 [27.0, 56.9]	42.0 [26.8, 61.3]	40.8 [28.2, 54.1]	41.0 [17.0, 61.3]
ALT (U/L)	18.0 [4.00, 340]	18.0 [3.00, 103]	15.0 [2.50, 80.0]	15.0 [6.00, 79.0]	14.0 [4.00, 129]	16.8 [4.30, 137]	30.0 [6.00, 158]	13.6 [4.00, 80.0]	15.0 [4.00, 225]	17.0 [3.00, 157]	18.0 [7.00, 99.0]	18.0 [2.70, 88.0]	18.0 [2.50, 340]
AST (U/L)	24.0 [5.00, 338]	25.0 [8.00, 134]	19.1 [9.00, 91.4]	19.0 [6.10, 86.0]	18.0 [10.0, 137]	19.0 [11.0, 68.9]	38.0 [13.0, 195]	21.0 [6.00, 130]	19.0 [7.00, 98.0]	20.0 [6.00, 104]	20.0 [9.00, 71.6]	19.0 [8.70, 113]	22.0 [5.00, 338]
Bilirubin (μmol/L)	8.00 [2.00, 96.0]	10.8 [4.20, 29.9]	9.65 [4.20, 75.9]	8.80 [0.513 , 21.1]	12.0 [5.20, 21.8]	10.4 [5.00, 20.9]	12.0 [2.00, 35.2]	9.95 [3.30, 25.0]	8.55 [2.90, 33.0]	8.53 [2.05, 30.8]	10.3 [3.00, 29.8]	10.2 [3.50, 29.4]	9.30 [0.513 , 96.0]
eGFR (mL/min/1.73 m²)	89.8 [30.7, 146]	94.8 [42.9, 147]	119 [62.5, 162]	67.2 [30.0, 112]	98.3 [61.4, 119]	96.6 [76.0, 124]	96.8 [31.0, 143]	103 [52.8, 151]	97.0 [36.0, 134]	93.9 [35.7, 138]	97.6 [47.4, 135]	96.9 [57.4, 128]	94.9 [30.0, 162]
Creatinine (μmol/L)	71.8 [29.2, 186]	70.5 [34.0, 136]	56.9 [21.5, 116]	93.4 [44.9, 194]	69.5 [44.0, 113]	68.0 [32.8, 96.0]	69.2 [39.0, 165]	60.0 [30.0, 113]	69.0 [32.6, 168]	70.9 [31.4, 177]	66.0 [43.6, 136]	68.4 [39.0, 112]	70.0 [21.5, 194]
LDH (U/L)	236 [87.0, 6010]	224 [111,2 564]	213 [126,8 42]	204 [102,1 452]	184 [114,1 123]	223 [132,8 92]	203 [123,1 713]	217 [127,2 820]	183 [107,2 401]	204 [93.0, 1311]	211 [102,1 228]	208 [116,1 409]	207 [87.0, 6010]

	001 (n = 450)	102 (n = 300)	203 (n = 70)	204 (n = 112)	205 (n = 30)	206 (n = 54)	208 (n = 248)	209 (n = 76)	302 (n = 264)	303 (n = 532)	304 (n = 222)	307 (n = 238)	Total (N = 2596)
TUMSZ (mm)/ SUMPPD (mm²)	71.0 [10.0, 310]	61.5 [10.0, 355]	1775 [136,1 1266]	69.4 [15.0, 239]	44.3 [15.0, 151]	82.0 [12.0, 194]	75.3 [10.0, 408]	59.5 [11.0, 204]	42.0 [10.0, 261]	58.0 [10.0, 380]	67.3 [10.0, 230]	79.3 [15.0, 207]	63.3 [10, 408]

Note: All study numbers are preceded with 'BGB-A317-'.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; PopPK, population pharmacokinetic; TUMSZ, tumor size.

TABLE S3 Key PK parameters and covariate effects for representative patients

PK parameters and baseline covariates		Estimate	% change from typical values
Typical CL (L/day, 65 kg, ALB=41 g/L, TUMSZ=63 mm, ADA negative, tumors except cHL and GC)		0.153	—
Weight (kg)	10th percentile (50 kg)	0.132	-13.8
	90th percentile (83 kg)	0.176	+14.8
Albumin (g/L)	10th percentile (34 g/L)	0.167	+8.92
	90th percentile (47 g/L)	0.144	-6.04
Tumor size (mm)	10th percentile (23 mm)	0.142	-7.14
	90th percentile (136 mm)	0.162	+5.82
ADA	Treatment-emergent ADA positive	0.171	+11.7
Tumor type	GC	0.164	+7.15
	cHL	0.123	-19.4
Typical V_c (L, male, 65 kg, 60 years)		3.05	—
Weight (kg)	10th percentile (50 kg)	2.75	-9.88
	90th percentile (83 kg)	3.36	+10.2
Sex	Female	2.71	-11.0
Age (year)	10th percentile (45 years)	2.96	-2.74
	90th percentile (71 years)	3.10	+1.64
Typical Q_2 (L/day)		0.74	—
Typical V_2 (L)		1.27	—
Typical Q_3 (L/day)		0.092	—
Typical V_3 (L)		2.10	—
Proportional residual error (%)		12.6	—
Additive residual error ($\mu\text{g/mL}$)		2.09	—

Abbreviations: ADA, anti-drug antibodies; ALB, albumin; cHL, classical Hodgkin lymphoma; CL, clearance; GC, gastric cancer; PK, pharmacokinetic; Q_2 and Q_3 , CL of distribution from the central to the peripheral compartments; TUMSZ, tumor size; V_c , volume of distribution in central compartment; V_2 and V_3 , volume of the peripheral compartment.

TABLE S4 Geometric mean (% CV) simulated steady-state exposure of tislelizumab by tumor type following 200 mg Q3W dosing

Characteristics		Tumor type									
		NSCLC	EC	HCC	UC	GC	CRC	cHL	OC	NPC	Other
No. of subjects (%)		1151 (44.3)	373 (14.4)	316 (12.2)	151 (5.82)	102 (3.93)	81 (3.12)	70 (2.7)	52 (2)	21 (0.809)	279 (10.7)
AUC _{ss} (µg*day/mL)	Geometric mean (% CV)	1297 (26.0)	1302 (29.2)	1202 (29.2)	1319 (29.7)	1150 (28.9)	1227 (27.0)	1626 (29.8)	1259 (35.7)	1407 (20.3)	1263 (30.3)
	% difference ^a	1.11	1.48	-6.35	2.77	-10.3	-4.41	26.7	-1.86	9.68	-1.55
C _{max,ss} (µg/mL)	Geometric mean (% CV)	111 (20.6)	110 (22.2)	103 (24.6)	116 (21.3)	102 (23.0)	107 (21.5)	131 (24.4)	116 (23.6)	125 (16.0)	111 (23.6)
	% difference ^a	0.443	-0.238	-6.5	5.12	-7.49	-2.81	19.1	5.13	13.6	0.803
C _{min,ss} (µg/mL)	Geometric mean (% CV)	41.8 (33.3)	42.1 (37.3)	38.1 (36.4)	41.6 (34.5)	35.4 (37.7)	39 (35.6)	55.3 (37.0)	37.1 (48.3)	44.8 (25.9)	39.5 (38.1)
	% difference ^a	1.98	2.72	-7.08	1.48	-13.6	-4.94	34.8	-9.40	9.37	-3.61
Body weight (kg) [min; median; max]		[35; 65; 130]	[35.1; 59; 130]	[40; 67.5; 113]	[36; 67; 105]	[31.9; 59.2; 120]	[35; 66; 102]	[40; 66; 93]	[43; 69.5; 103]	[45; 58; 71]	[35; 68.9; 129]
Albumin (g/L) [min; median; max]		[20; 41.9; 380]	[24; 41; 54.4]	[20; 41.8; 52]	[23; 41.9; 435]	[22; 38.6; 50]	[24; 41; 51.5]	[26.7; 43; 53.2]	[21; 38; 47]	[29.4; 42.7; 50]	[17; 39; 53.3]
Age (year) [min; median; max]		[26; 61; 88]	[29; 62; 83]	[22; 61; 90]	[36; 63; 81]	[22; 61.5; 81]	[19; 56; 79]	[18; 32.5; 69]	[19; 61; 80]	[35; 48; 61]	[18; 58; 82]
Tumor size (mm)/SUMPPD (mm ²) [min; median; max]		[10; 65; 380]	[10; 45; 261]	[10; 75.8; 408]	[15; 63.8; 239]	[10; 62; 252]	[11; 68; 207]	[136; 1780; 11300]	[10; 64; 284]	[16; 42.6; 162]	[11; 70; 355]
Sex [M/F, n (%)]		906 (78.7)/245 (21.3)	302 (81)/71 (19)	272 (86.1)/44 (13.9)	113 (74.8)/38 (25.2)	64 (62.7)/38 (37.3)	54 (66.7)/27 (33.3)	40 (57.1)/30 (42.9)	0 (0)/52 (100)	17 (81)/4 (19)	152 (54.5)/127 (45.5)

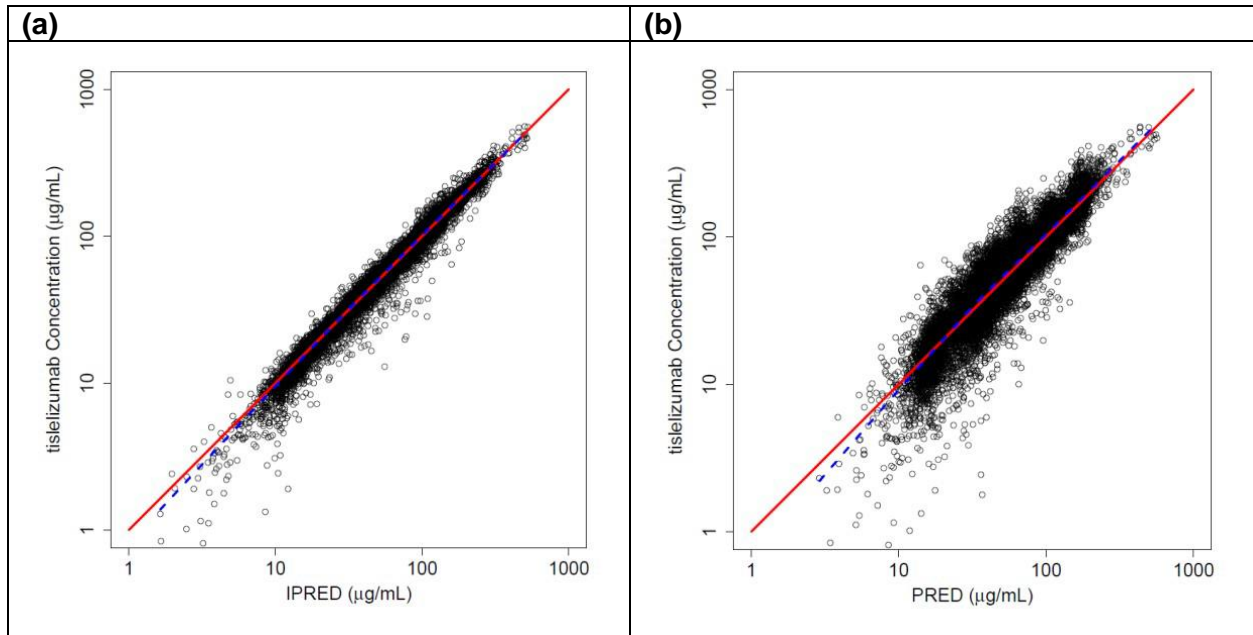
ADA [negative/positive, <i>n</i> (%)]	934 (81.1)/2 17 (18.9)	314 (86.5)/4 9 (13.5)	241 (80.6)/5 8 (19.4)	127 (84.7)/2 3 (15.3)	92 (90.2)/1 0 (9.8)	70 (86.4)/1 1 (13.6)	64 (91.4)/6 (8.57)	40 (76.9)/1 2 (23.1)	19 (90.5)/2 (9.52)	235 (84.2)/4 4 (15.8)
--	---------------------------------	-----------------------------	-----------------------------	-----------------------------	---------------------------	----------------------------	--------------------------	----------------------------	--------------------------	-----------------------------

Abbreviations: ADA, anti-drug antibodies; AUC_{ss}, area under the curve at steady state; cHL, classical Hodgkin lymphoma; CRC, colorectal cancer; CV, coefficient of variation; EC, esophageal cancer; F, female; GC, gastric cancer; HCC, hepatocellular carcinoma; M, male; NPC, nasopharyngeal cancer; NSCLC, non-small cell lung cancer; OC, ovarian cancer; Q3W, every three weeks; UC, urothelial bladder cancer.

^a% difference from the geometric mean simulated exposures of the overall population.

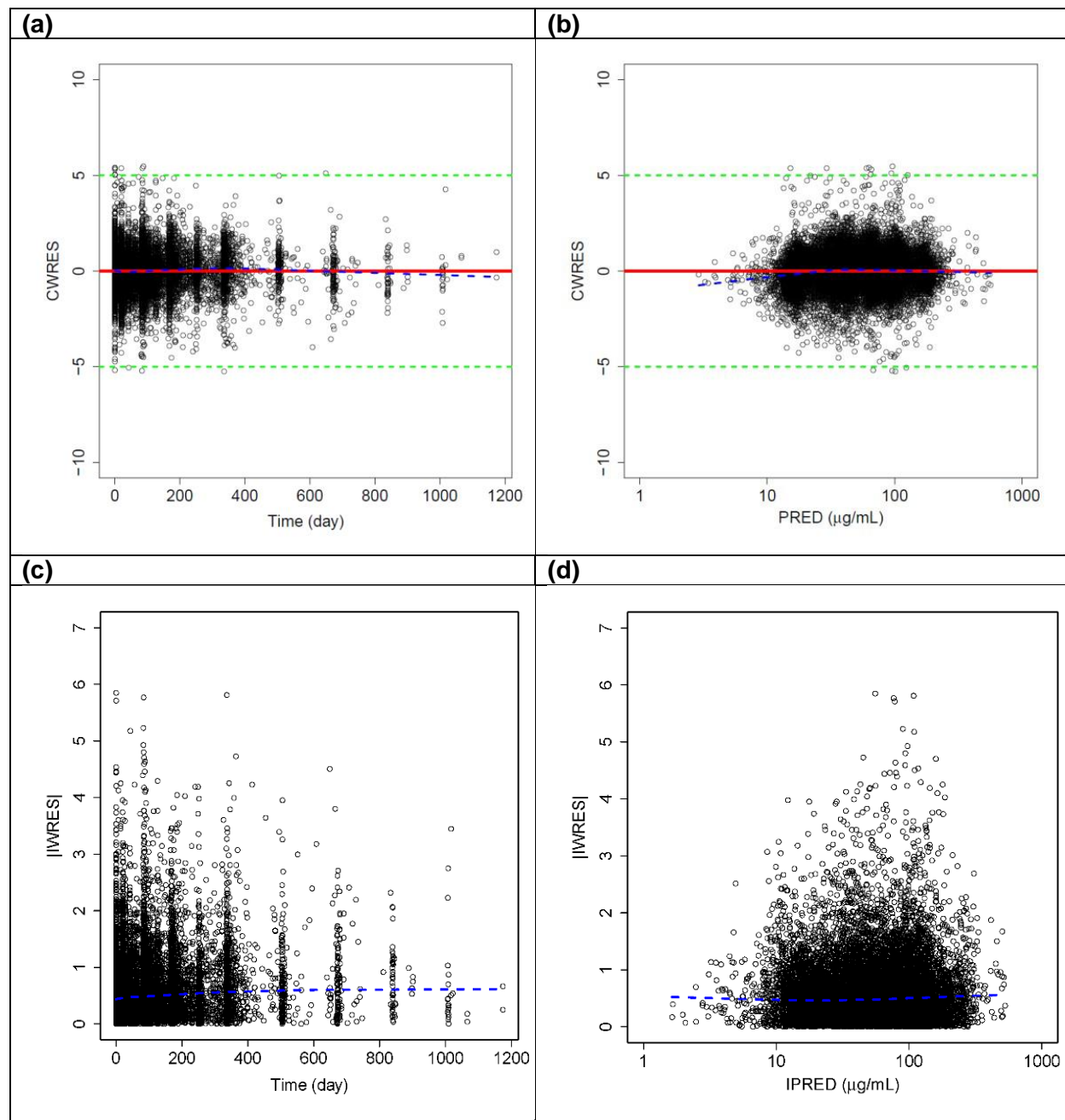
Supplementary Figures

FIGURE S1 Predicted versus observed concentration for the final PopPK model dataset. (a) Observed versus IPRED and (b) observed versus population PRED.



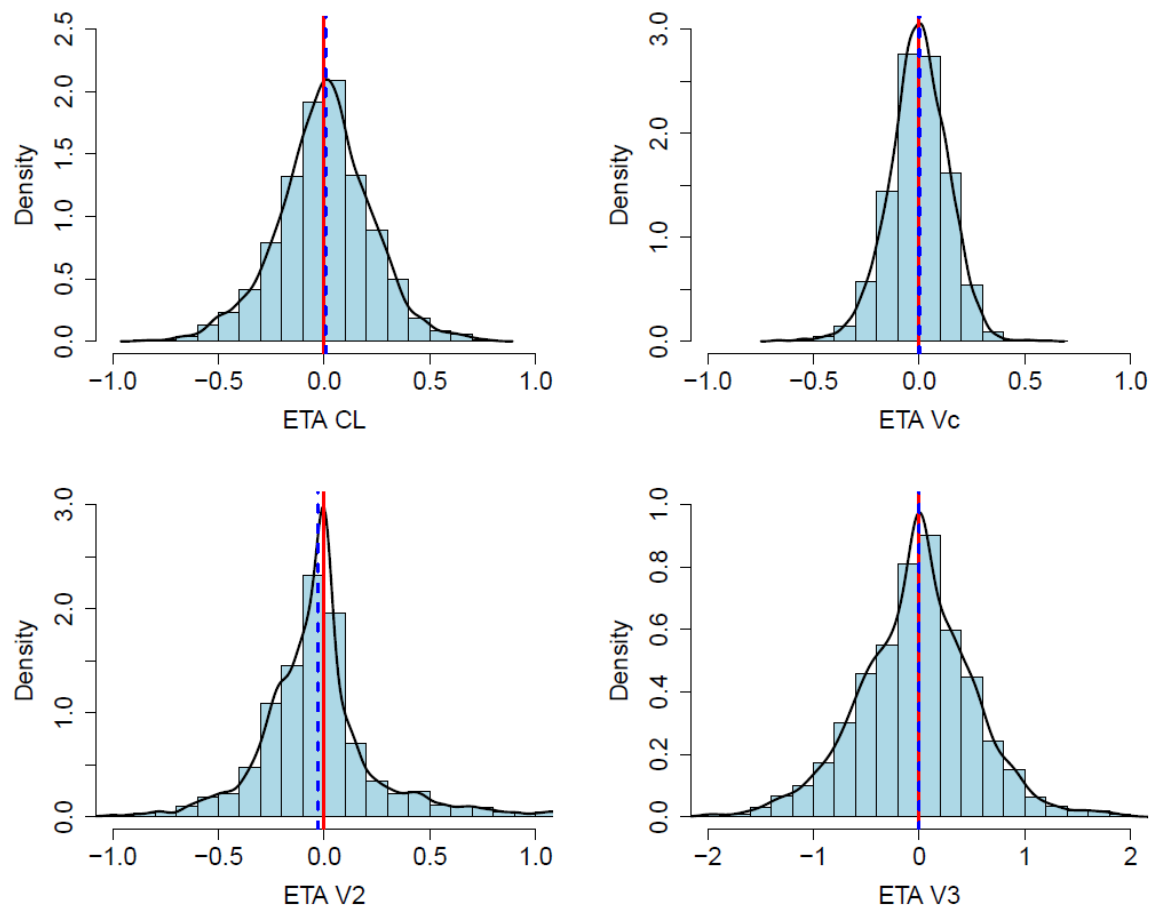
Points are individual data and red lines represent the unit diagonal. The blue dashed lines are smooth curves (lowess) showing the relationship between two variables. IPRED, individual predicted concentrations; PopPK, population pharmacokinetic; PRED, predicted concentrations.

FIGURE S2 Residual diagnostic plots for the final PopPK model. (a) CWRES versus time and (b) population PRED. (c) |IWRES| versus time and (d) IPRED.



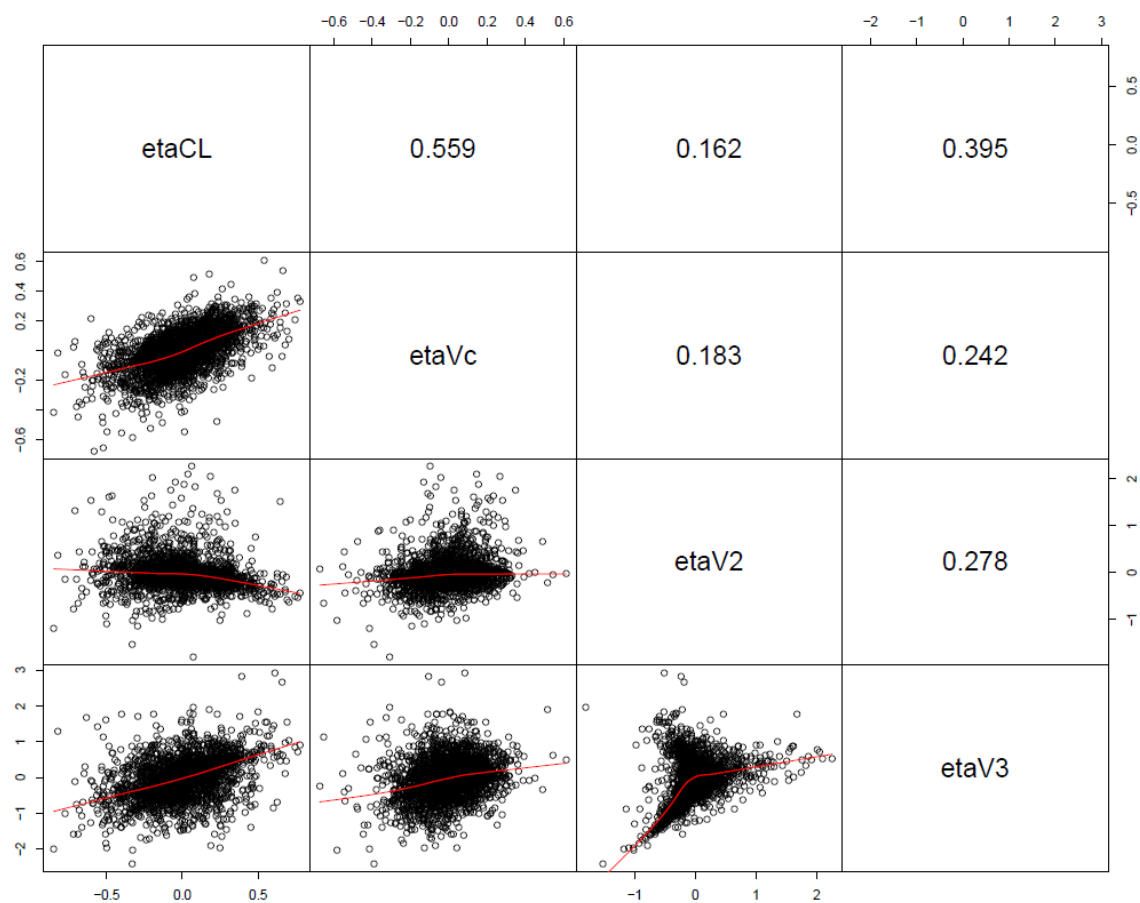
Points are individual data. Red solid lines represent the unit line at zero. Green dotted lines represent |CWRES| of 5. The blue dashed lines are smooth curves (lowess) showing the relationship between two variables. |IWRES|, absolute individual weighted residuals; CWRES, conditional weighted residuals; IPRED, individual predicted concentrations; IWRES, individual weighted residuals; PopPK, population pharmacokinetic; PRED, predicted concentrations.

FIGURE S3 Interindividual random effect histograms for the final PopPK model.



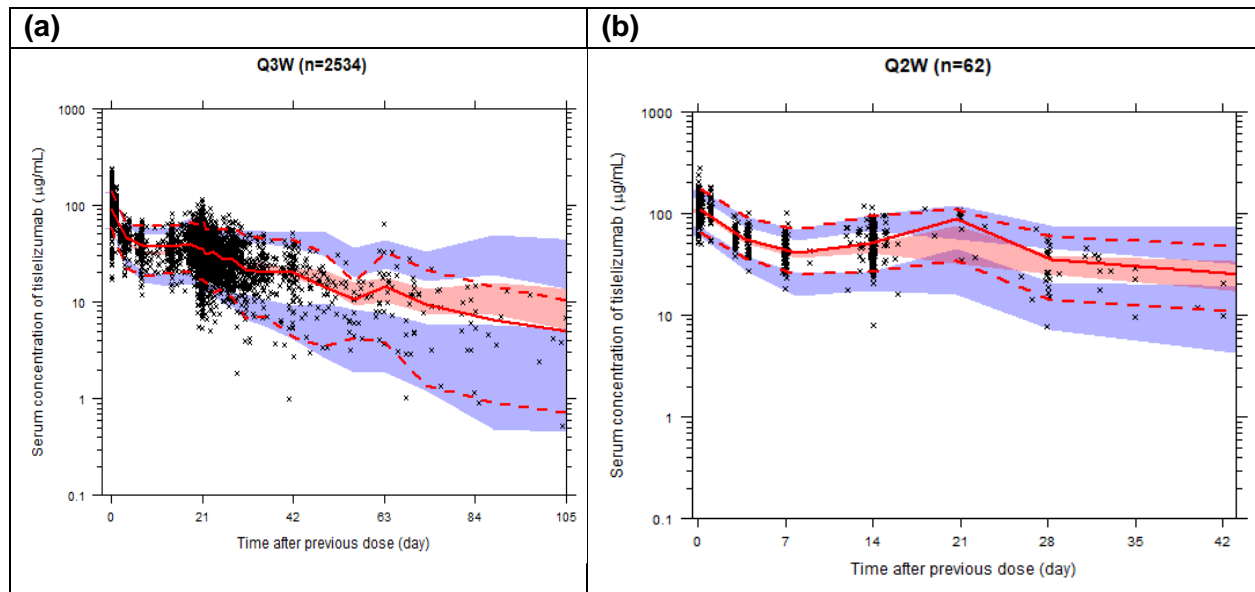
Red solid lines represent the unit line at zero. Blue dashed lines represent the median value of ETAs. CL, clearance; ETA, random effect; ETA CL, individual ETA for CL; ETA V_c, individual ETA for V_c; ETA V₂, individual ETA for V₂; ETA V₃, individual ETA for V₃; PopPK, population pharmacokinetic; V_c, volume of distribution in central compartment; V₂ and V₃, volume of the peripheral compartment.

FIGURE S4 Correlation of interindividual random effect estimates from the final PopPK model.



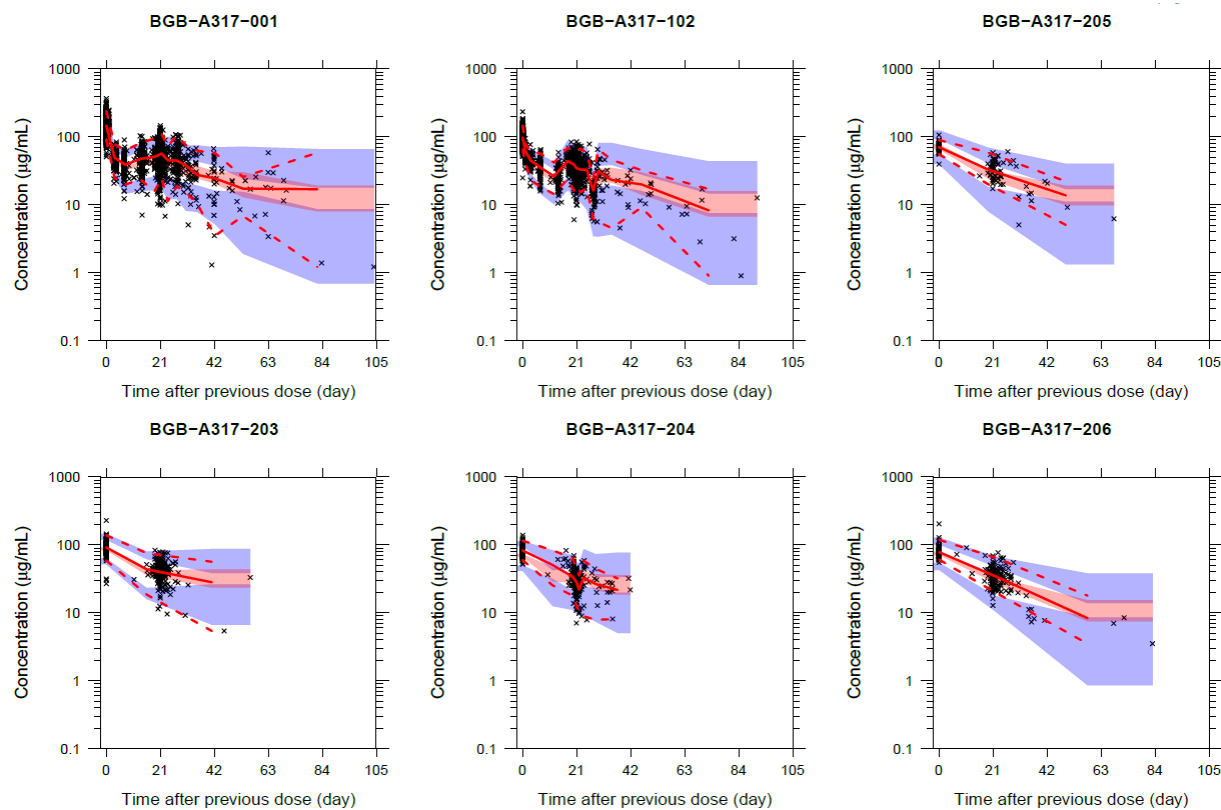
Points are the post hoc estimates from NONMEM following intravenous administration. Red lines are smooth curves (lowess) showing the relationship between two variables. Values are Spearman's correlation coefficients between two variables. CL, clearance; ETA, random effect; PopPK, population pharmacokinetic; V_c , volume of distribution in central compartment; V_2 and V_3 , volume of the peripheral compartment.

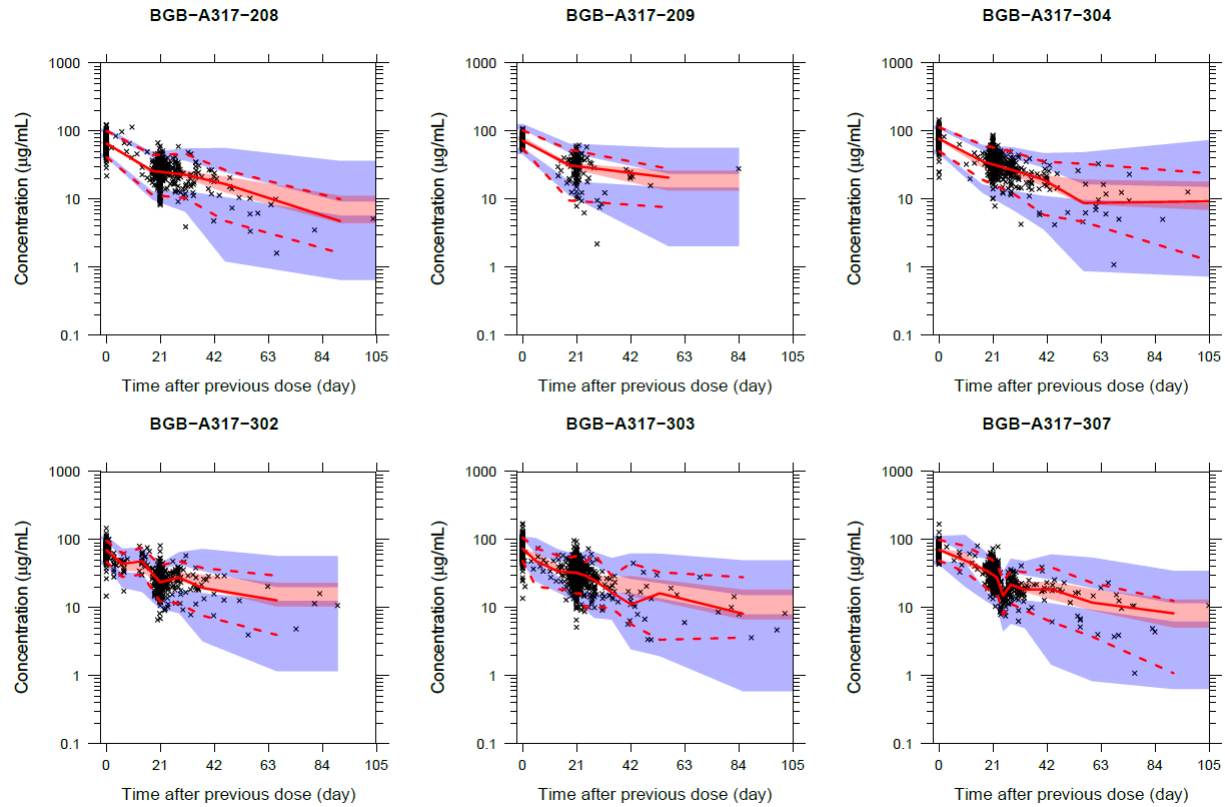
FIGURE S5 Prediction-corrected visual predictive check of tislelizumab serum concentration-time profiles stratified by tislelizumab regimen (a) Q3W and (b) Q2W.



Black cross symbols are individual observed concentrations, solid red lines represent the median observed concentrations, and dashed red lines represent 2.5th and 97.5th percentiles of the observed concentrations over time. Red shaded areas represent the 95% CI of the predicted median concentrations, and blue/purple shaded areas represent the 95% CI of the predicted 2.5th and 97.5th percentiles of the concentrations over time. CI, confidence interval; Q2W, every 2 weeks; Q3W, every 3 weeks.

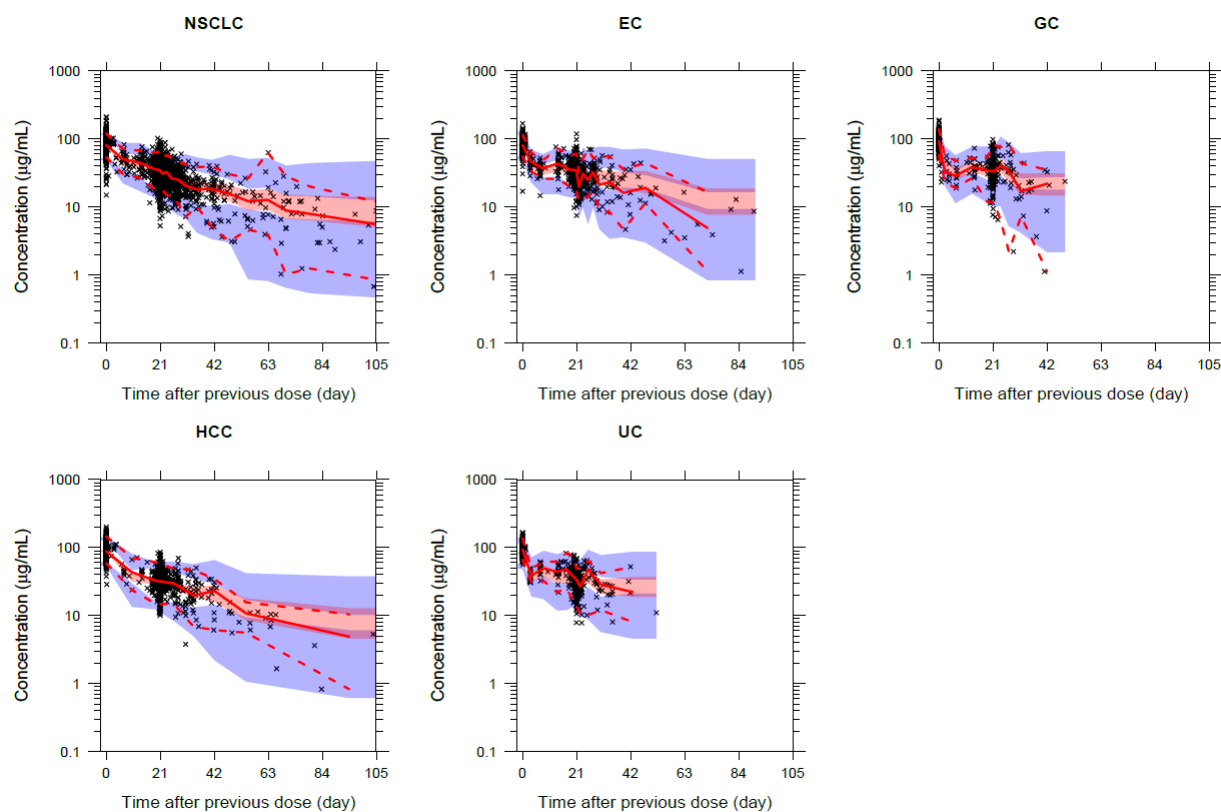
FIGURE S6 Prediction-corrected visual predictive check of tislelizumab serum concentration-time profiles stratified by study.

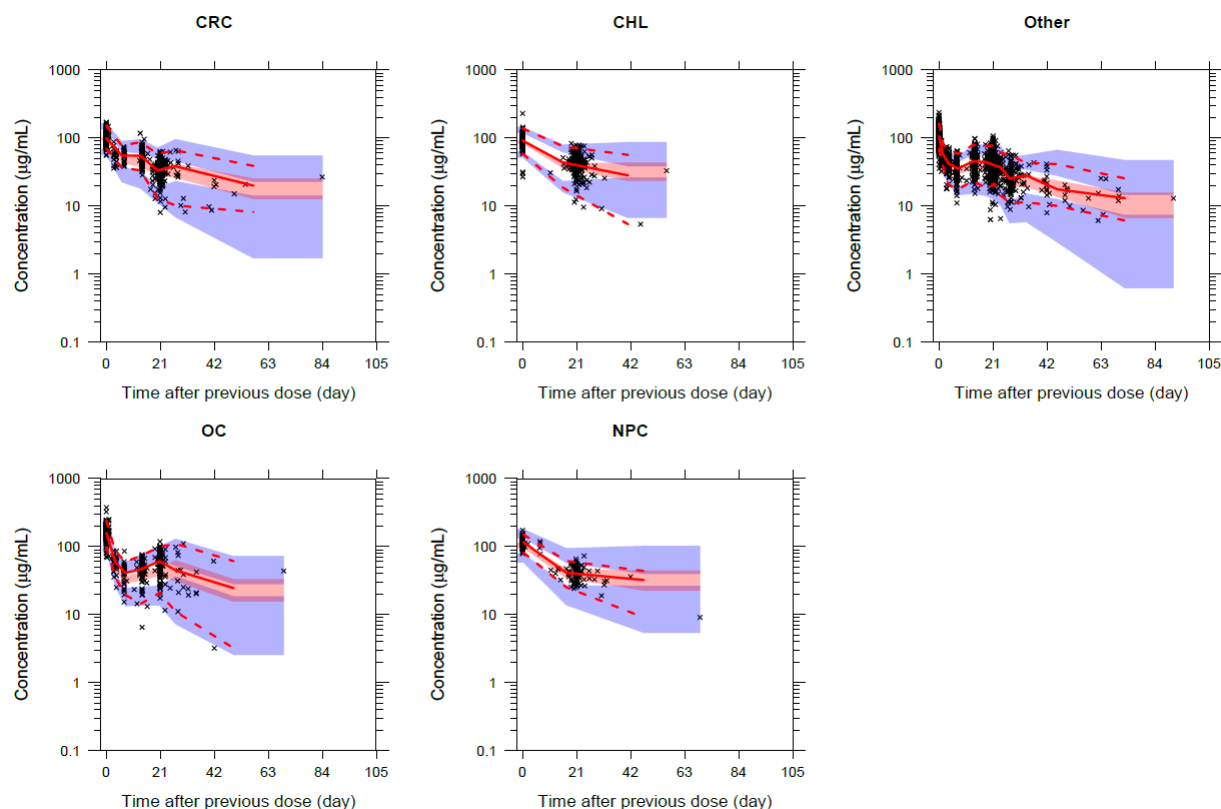




Black cross symbols are individual observed concentrations, solid red lines represent the median observed concentrations, and dashed red lines represent 2.5th and 97.5th percentiles of the observed concentrations over time. Red shaded areas represent the 95% CI of the predicted median concentrations, and blue/purple shaded areas represent the 95% CI of the predicted 2.5th and 97.5th percentiles of the concentrations over time. CI, confidence interval.

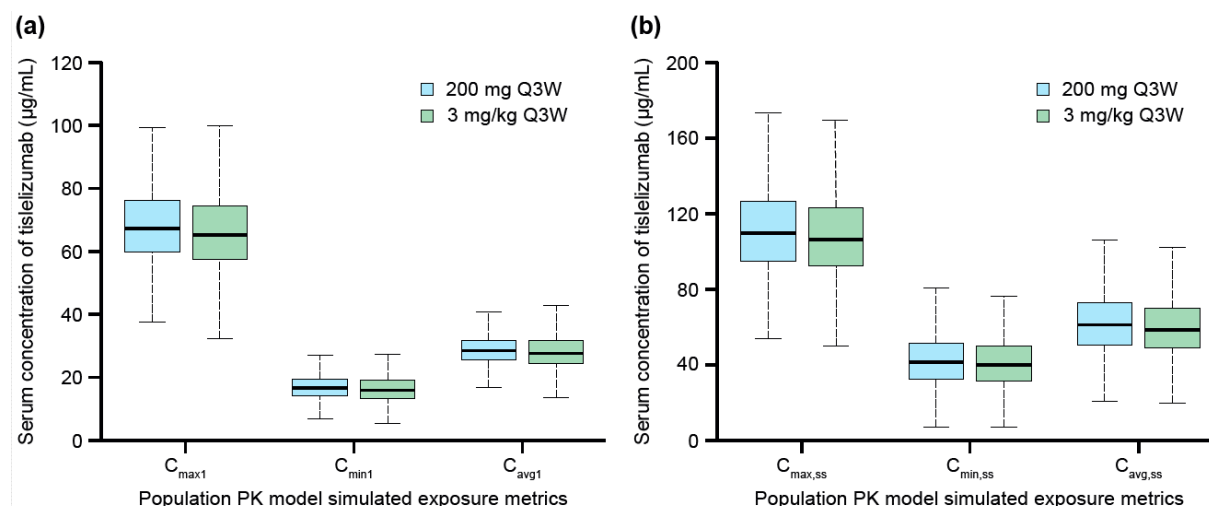
FIGURE S7 Prediction-corrected visual predictive check of tislelizumab serum concentration-time profiles stratified by tumor type.





Black cross symbols are individual observed concentrations, solid red lines represent the median observed concentrations, and dashed red lines represent 2.5th and 97.5th percentiles of the observed concentrations over time. Red shaded areas represent the 95% CI of the predicted median concentrations, and blue/purple shaded areas represent the 95% CI of the predicted 2.5th and 97.5th percentiles of the concentrations over time. cHL, classical Hodgkin lymphoma; CI, confidence interval; CRC, colorectal cancer; EC, esophageal carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer, OC, ovarian cancer; UC, urothelial bladder carcinoma.

FIGURE S8 Comparison of predicted tislelizumab exposure metrics after first dose and steady state by treatment regimen.



The median is represented by the horizontal line in the middle of each box. The top and bottom ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extending from the ends of the box to the outermost data represent 1.5 × (the upper or lower interquartile range). C_{avg1}, average concentration after the first dose; C_{avg,ss}, average concentration at steady state; C_{max1}, maximum concentration after the first dose; C_{max,ss}, maximum concentration at steady state; C_{min1}, trough concentration after the first dose; C_{min,ss}, trough concentration at steady state; PK, pharmacokinetic; Q3W, every three weeks.

NONMEM control stream

```
$PROBLEM      Population PK Analysis for BGB-A317
$INPUT        EXCLFL ROW STUDYID ID USUBJID=DROP TRT=DROP DOSE DOSESCH
              PHASE DAY TIME CYCLE NTIME TFDS DV LDV AMT RATE DUR EVID
              MDV BLQ AGE WT SEX RACE REGON=DROP EGFR CREAT BIL AST ALT
              ALB ECOG LDH ADA TUMSZ TUMSZIRC TUMTP=DROP ADATIT THERAPY
              LINTHER ADAONSET ADADUR MSIH ESCC ASIA TUMTPN
;TIME=hr DV=mg/L AMT=mg RATE=mg/hr
$DATA         pkinput.csv IGNORE=@ IGNORE(EXCLFL.GT.0)
$SUBROUTINE   ADVAN11 TRANS4
$PK
  IF (AMT.GT.0) TDOS=TIME
  TAD=TIME-TDOS

  WTT=65
  IF (WT.GT.0) WTT=WT
  WTCL=THETA(7)*LOG(WTT/65)
  WTV=THETA(8)*LOG(WTT/65)

  SEXV=THETA(9)*SEX

  ALBT=41
  IF (ALB.GT.0) ALBT=ALB
  ALBCL=THETA(10)*LOG(ALBT/41)
```

```

TUMSZ0=63
IF (STUDYID.NE.203.AND.TUMSZ.GT.0) TUMSZ0=TUMSZ
TUMSZCL=THETA (11) *LOG (TUMSZ0/63)

AGEV=THETA (12) *LOG (AGE/60)

ADA1=0
IF (ADA.EQ.1) ADA1=1
ADACL=THETA (13) *ADA1

;0=NSCLC,1=EC,2=HCC,3=UC,4=GC,5=CRC,6=CHL,7=OC,8=NPC,9=Other
TUMTP4=0
TUMTP6=0
IF (TUMTPN.EQ.4) TUMTP4=1
IF (TUMTPN.EQ.6) TUMTP6=1

TUMTPCL=THETA (14) *TUMTP4+THETA (15) *TUMTP6

CL=EXP (THETA (1) +WTCL+ALBCL+TUMSZCL+ADACL+TUMTPCL+ETA (1) )
V1=EXP (THETA (2) +WTV+SEXV+AGEV+ETA (2) )
Q2=EXP (THETA (3) )
V2=EXP (THETA (4) +ETA (3) )      Q3=EXP (THETA (5) )
V3=EXP (THETA (6) +ETA (4) )

K10=CL/V1
K12=Q2/V1
K21=Q2/V2
K13=Q3/V1
K31=Q3/V3
S1=V1

$ERROR
  IPRED=F
  Y=F* (1+EPS (1) )+EPS (2)
  W=SQRT (SIGMA (1) *F*F + SIGMA (2) )
  IWRES= (DV-IPRED) /W

$THETA  (-10,-5.05,10) ; TH1 CL (L/hr)
(-10,1.11,10) ; TH2 V1 (L)
(-10,-3.47,10) ; TH3 Q (L/hr)  (-10,.219,10) ; TH4
V2 (L)
(-10,-5.54,10) ; TH5 Q3 (L/hr)
(-10,.708,10) ; TH6 V3 (L)
(0,.559,3) ; TH7 WT ON CL
(0,.396,10) ; TH8 WT ON V1
0 FIX ; (-10,-.117,10) ; TH9 SEX ON V1
(-10,-.433,10) ; TH10 ALB ON CL
(-10,.0747,10) ; TH11 TUMSZ ON CL
(-10,.0958,10) ; TH12 AGE ON V1
(-10,.11,10) ; TH13 ADA ON CL
(-10,.0783,10) ; TH14 GC ON CL
(-10,-.216,10) ; TH15 CHL ON CL
$OMEGA  BLOCK (2)
.1
.01 .1
$OMEGA  .553
.858
$SIGMA  .0158
4.32
$ESTIMATION MAX=9999 PRINT=5 METHOD=1 INTER NOABORT CTYPE=4
          NOTHETABOUNDTEST NOOMEGABOUNDTEST NOSIGMABOUNDTEST NSIG=3
          SIGL=9

```