

Mélanie Wilbaux¹, Zhengqi Tan¹, Joseph Grossman², Gerald Fetterly², Dhan Chand², Amit Roy¹

¹Pumas-AI, inc., USA; ²Agenus, USA

Poster IV-090 - Abstr. 177

BACKGROUND

- Optimizing dosing regimens for therapeutic antibodies through population pharmacokinetic (popPK) modeling is critical for maximizing clinical benefit while maintaining practical administration schedules.
- Balstilimab (BAL)**: an IgG4 anti-PD-1 antibody and complete blocker of PD-1/PD-L1/2 interactions, is being developed in combination with botensilimab (BOT), a novel multifunctional Fc-enhanced IgG1 anti-CTLA-4 antibody designed to optimize FcγR co-engagement and enhance anti-tumor immunity against 'cold' tumors¹.
- Intravenous BOT + BAL combination therapy** has demonstrated **clinical activity** across multiple refractory solid tumors, including advanced microsatellite stable metastatic colorectal cancer².
- While the current regimen for BAL is **3 mg/kg every two weeks (Q2W)**, various dosing strategies, including weight-based and fixed-dose regimens, have been evaluated, requiring comprehensive PK analysis to optimize BAL dosing.
- Objectives:**
 - To evaluate **BAL exposure comparability** between **fixed and weight-based dosing**, as well as **alternative dosing regimens (Q3W)**, using **popPK modeling & simulation** of BAL concentrations when administered alone or with BOT.

Abbreviations: CTLA-4, cytotoxic T-lymphocyte associated protein 4; Fc, fragment crystallizable; FcγR, fragment crystallizable gamma receptor; IgG4, immunoglobulin G4; PD-1, programmed cell death protein 1; PD-L1/2, programmed death ligand 1 and 2.

DATA

- A total of 6,339 BAL concentrations from **721 patients** across 5 clinical studies (2 Phase I and 3 Phase II) in patients with advanced solid tumors, who received BAL intravenously as monotherapy or with BOT:

Treatment	N patients (%)
Treatment combination	
BAL monotherapy	229 (31.8%)
BAL + BOT combination	492 (68.2%)
Weight-based doses	
1 mg/kg Q2W	10 (1.4%)
3 mg/kg Q2W	499 (69.2%)
10 mg/kg Q2W	10 (1.4%)
6 mg/kg Q3W	10 (1.4%)
10 mg/kg Q3W	10 (1.4%)
Fixed doses	
240 mg Q2W	116 (16.1%)
300 mg Q3W	18 (2.5%)
450 mg Q3W	48 (6.7%)

Table 1. Treatment Summary in the Analysis Population

- Clinical trials IDs: NCT03104699, NCT03894215, NCT0386072, NCT05608044, NCT05529316

Abbreviations: ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate.

Characteristics	Median (range) or N patients (%)
Baseline body weight [kg]	70.47 (35.80, 163.00)
Baseline age [years]	59.00 (20.00, 91.00)
Sex	
Male	219 (30.4%)
Female	502 (69.6%)
Subject type	
Colorectal cancer (CRC)	251 (34.8%)
Other tumor types	470 (65.2%)
Baseline albumin [g/dL]	4.00 (1.79, 5.20)
Baseline eGFR [mL/min/1.73m²]	91.33 (29.12, 198.05)
Baseline hepatic impairment	
Normal	633 (87.8%)
Mild	85 (11.8%)
Moderate	2 (0.3%)
Missing	1 (0.1%)
Baseline ECOG status	
ECOG 0	333 (46.2%)
ECOG 1+	385 (53.4%)
Missing	3 (0.4%)
Antidrug Antibodies (ADA)	
Not detected or not confirmed	707 (98.1%)
Detected and confirmed	14 (1.9%)

Table 2. Key Patients' Baseline Characteristics
Missing individual-level covariates were imputed in the modeling using the median (continuous) or mode (categorical).

RESULTS

- BAL PK was best described by a **linear 2-compartment model with time-varying clearance (CL)**, characterized by a sigmoid-Emax function
- IIV was included on CL, volumes of distribution (Vc and Vp) and maximal change in CL (Emax), with correlation between CL, Vc and Vp.
- RUV was modeled with a combination of additive and proportional effects.
- The base model included **body weight** effect on both CL and Vc.
- After backward elimination, the **final popPK model** included **baseline albumin and age** as factors affecting CL.
- Notable non-significant covariates included BOT co-administration, tumor type, anti-drug antibodies, sex, ECOG status, eGFR, and hepatic impairment.
- Minimal effects of intrinsic and extrinsic factors** on dose-normalized BAL Cavg:

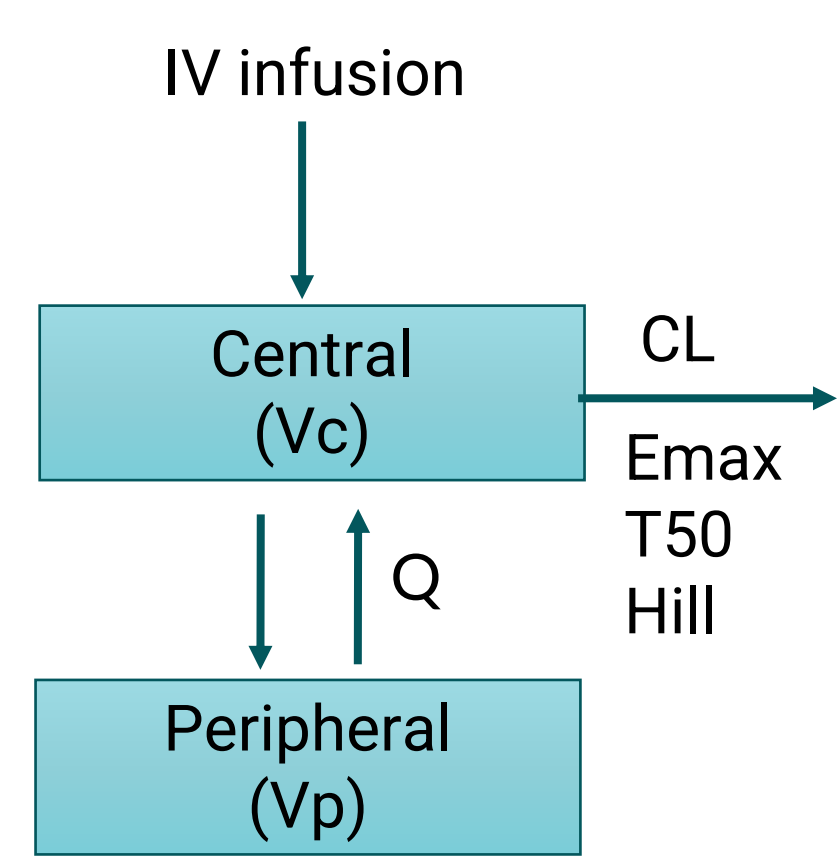


Figure 3. Structural BAL PK Model

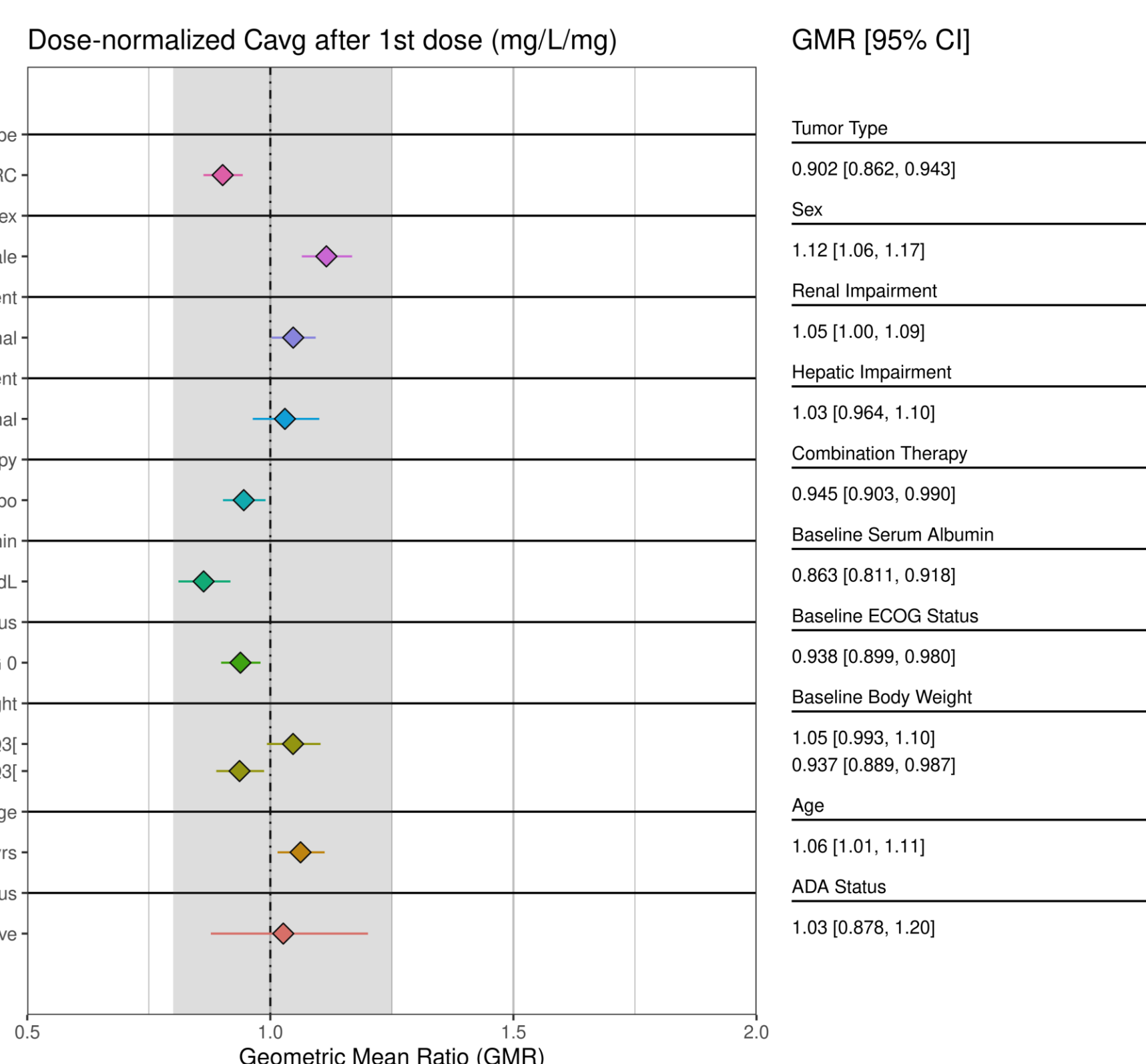


Figure 5. Relationships Between Intrinsic and Extrinsic Factors and BAL Exposure

Abbreviations: GMR, geometric mean ratio.

References

- Chand D. et al., Botensilimab, an Fc-Enhanced Anti-CTLA-4 Antibody, is Effective against Tumors Poorly Responsive to Conventional Immunotherapy. *Cancer Discov.* 2024 Dec 2;14(12):2407-2429.
- Bullock A. et al., Botensilimab plus Balstilimab in Relapsed/Refractory Microsatellite Stable Metastatic Colorectal Cancer: a Phase 1 Trial. *Nat Med.* 2024 Sep;30(9):2558-2567.
- Rackauckas C. et al., Accelerated Predictive Healthcare Analytics with Pumas, a High Performance Pharmaceutical Modeling and Simulation Platform. *BioRxiv.* 2020;11:28-402297.
- Bajaj G. et al., Model-Based Population Pharmacokinetic Analysis of Nivolumab in Patients With Solid Tumors: Model-Based Population Pharmacokinetic Analysis of Nivolumab. *CPT Pharmacometrics Syst Pharmacol.* 2017 Jan;6(1):58-66.
- U.S. Food and Drug Administration, Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer: Guidance for Industry. 2022 Dec.

Acknowledgments

Agenus Inc. funded and is the sponsor of the studies.

MAIN FINDINGS

In patients with advanced solid tumors, model-based simulation of BAL PK validates:

- Equivalent exposure between fixed and weight-based dosing:**
 - BAL 240 mg Q2W showed a 14% higher geometric mean exposure (steady-state C_{max}, C_{trough} and Cavg) compared to 3 mg/kg Q2W, falling within the 0.80-1.25 equivalence range.
 - Body weight equivalency also demonstrated between 450 mg Q3W and 6 mg/kg Q3W.
- Q3W dosing frequency as an effective alternative to Q2W:**
 - Extended interval dosing at 450 mg Q3W provided comparable Cavg and C_{trough} to 240 mg Q2W, with geometric mean within 20%.
 - While all evaluated regimens showed higher C_{max} than the reference 3 mg/kg Q2W, values remained below those observed at 10 mg/kg Q2W, suggesting acceptable safety profiles.

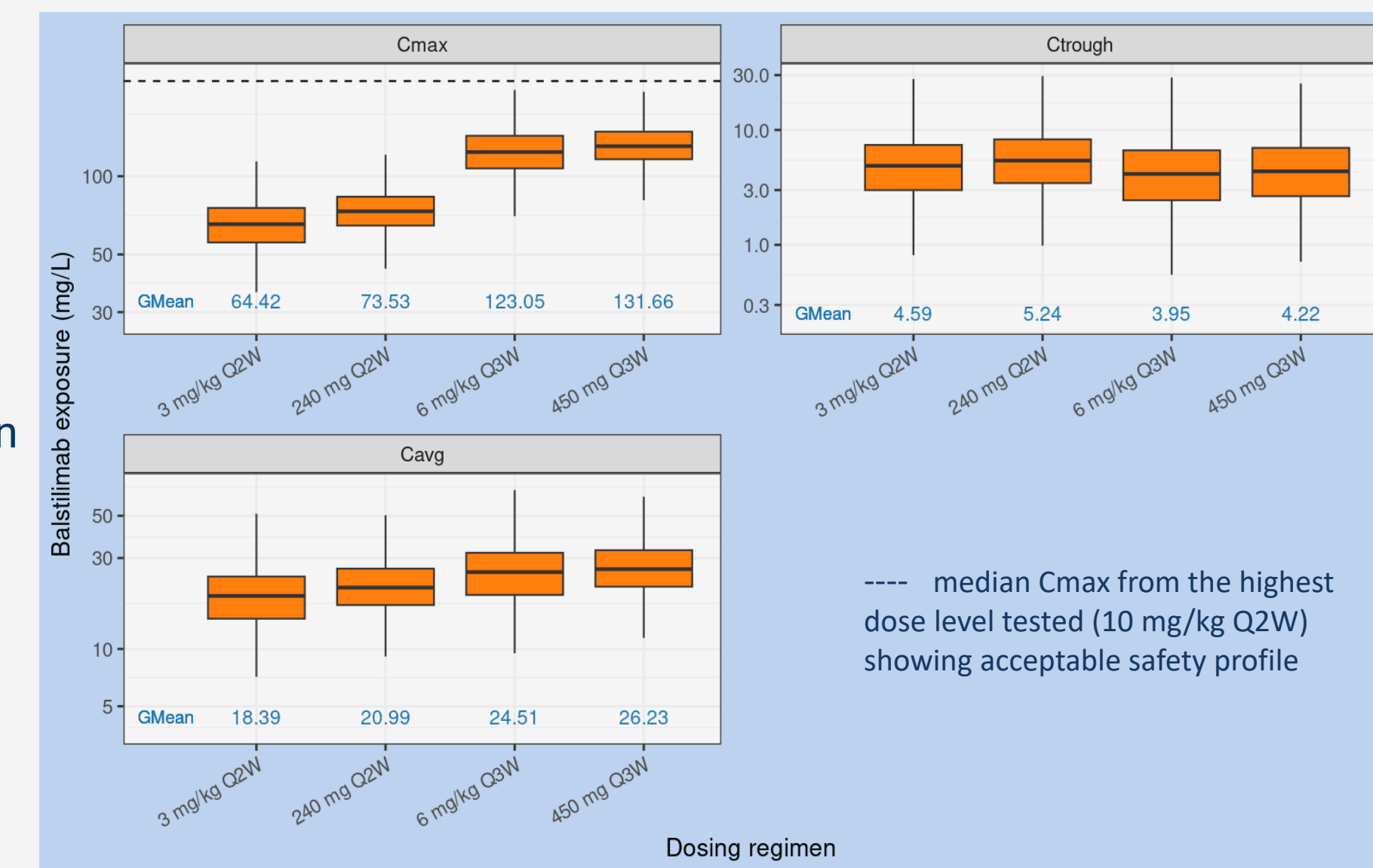


Figure 1. Comparison of BAL Exposure Metrics at Steady-State for Various Dosing Regimens

Abbreviations: Cavg, average concentration; C_{max}, maximum concentration; C_{trough}, trough concentration; GMean, geometric mean.

METHODS

- Model development followed a stepwise approach (Figure 2).
- Model selection criteria included Bayesian Information Criterion (BIC), condition number, parameter precision, shrinkage values, and diagnostic plots including prediction-corrected visual predictive checks (pcVPC).
- Analyses were performed using Pumas v2.5.1 on the JuliaHub platform³.

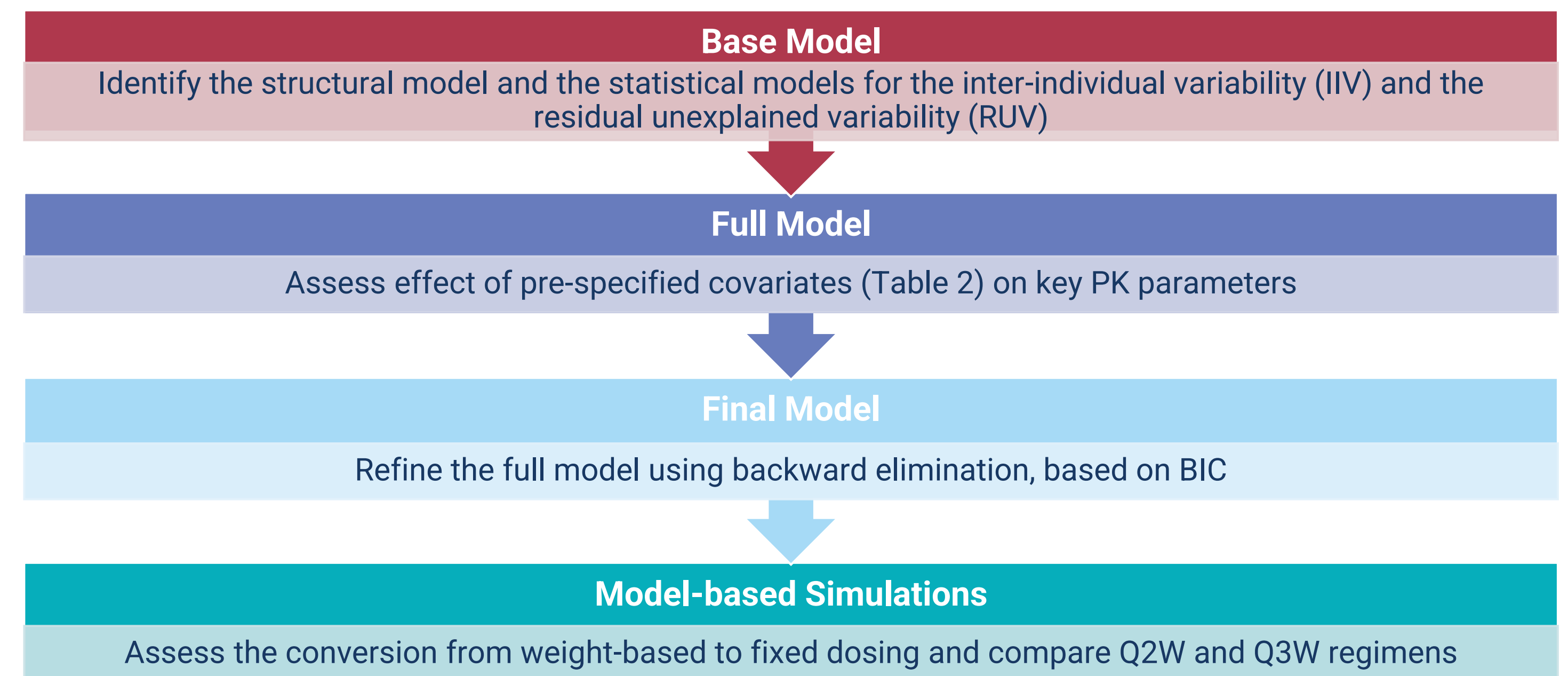


Figure 2. PopPK Modeling & Simulation Strategy

Parameter	Value	RSE (%)	95% CI
Condition Number	84.87	/	/
Population Parameters			
Clearance (CL; L/h)	0.037	2.7	(0.036, 0.039)
Central volume of distribution (V _c ; L)	3.625	1.1	(3.547, 3.703)
Inter-compartmental clearance (Q; L/h)	0.012	8.3	(0.011, 0.014)
Peripheral volume of distribution (V _p ; L)	2.14	3.1	(2.007, 2.272)
Maximal change in CL (Emax)	-0.103	27.2	(-0.158, -0.049)
Sigmoidicity of the CL relationship with time (Hill)	1.441	31.2	(0.561, 2.321)
Time at which the change in CL is 50% of Emax (T50; h)	1571	31.6	(597.9, 2544)
CL ~ Baseline body weight	0.175	33.7	(0.059, 0.29)
CL ~ Age	-0.238	21	(-0.337, -0.14)
CL ~ Baseline albumin	-0.375	29.3	(-0.59, -0.161)
V _c ~ Baseline body weight	0.373	11.3	(0.291, 0.456)
Inter-Individual Variability			
ω ² CL (%CV)	0.114 (34.7%)	7	(0.098, 0.13)
ω ² V _c (%CV)	0.04 (20.2%)	12.5	(0.031, 0.049)
ω ² V _p (%CV)	0.113 (34.6%)	12.4	(0.084, 0.141)
ω ² Emax (%CV)	0.095 (31.6%)	47.4	(0.007, 0.183)
Covariance			
Covariance_CL-V _c (%Corr)	0.043 (63.9%)	11.6	(0.034, 0.052)
Covariance_CL-V _p (%Corr)	0.021 (18.5%)	42.9	(0.003, 0.039)
Covariance_V _c -V _p (%Corr)	0.029 (42.9%)	24.1	(0.016, 0.042)
Random Unexplained Variability			
σ _{prop} (%CV)	0.247 (25.1%)	2.4	(0.234, 0.259)
σ _{add}	0.011	18.2	(0.006, 0.016)

Table 3. Parameter Estimates from the Final BAL PopPK Model

- Population mean estimates for CL and V_c were 0.89 L/day and 3.62 L, respectively.
- Geometric mean terminal half-life estimate was 7.84 days.
- Good agreement between median (5th/95th percentiles) of observed and simulated concentration-time profile:

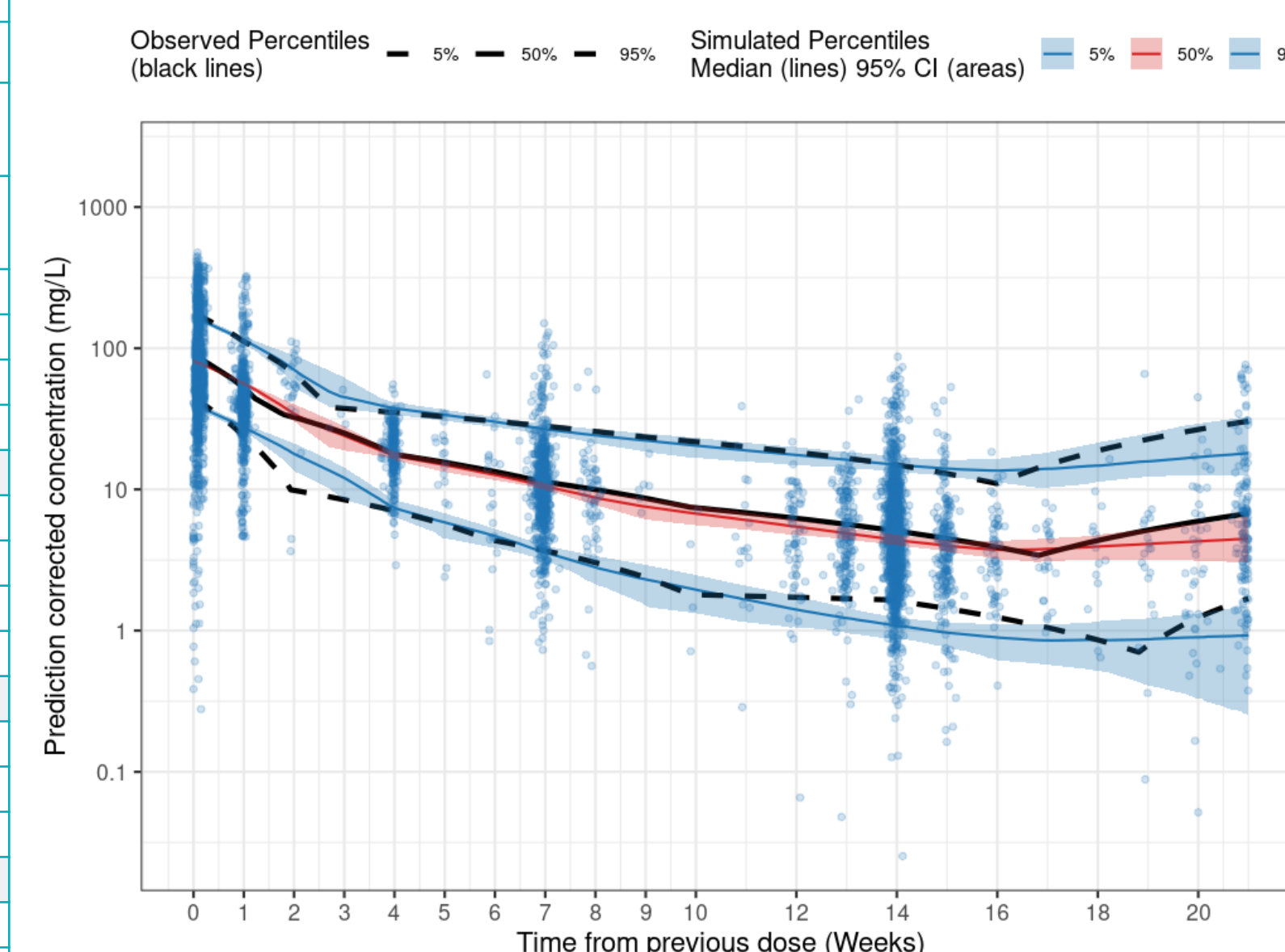


Figure 4. pcVPC from the Final BAL PopPK Model

CONCLUSIONS

- The popPK model characterized BAL disposition with **time-varying clearance**, consistent with observations for other anti-cancer monoclonal antibodies⁴.
- The **minimal impact of intrinsic and extrinsic factors**, including BOT co-administration, supports a simplified dosing approach without need for adjustments.
- Model-based simulations demonstrated **comparable BAL exposure between weight-based and fixed dosing regimens**, supporting conversion to more convenient fixed dosing of 240 mg Q2W or an alternative extended-interval regimen of 450 mg Q3W, according to the FDA guidance on pharmacokinetic-based criteria for supporting alternative dosing regimens of PD-1/PD-L1 blocking antibodies⁵.

