Population Pharmacokinetics Modeling of Monalizumab in Cancer Patients with Longitudinal Patient/Disease Characteristics

Nan Zhang[1], Chunling Fan[1],Mike Cheng[1], Patrick Mitchell[2], Carine Paturel[4], Pascale Andre[4], Kourtesis Panagiotis[1], Mayukh Das[1], Nassim Morsli[3], Megan Gibbs1, Xuyang Song[1]

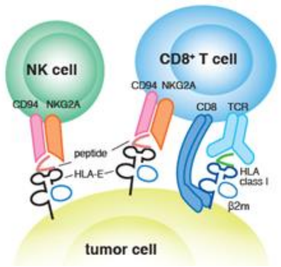
[1]AstraZeneca, Gaithersburg, MD, USA; [2]AstraZeneca, Waltham, MA, USA; [3]AstraZeneca, Cambridge, UK; [4]Innate Pharma, 117 Avenue de Luminy, 13009 Marseille, France.

9711

Background

- Monalizumab is a potentially first-in-class humanized immunoglobulin 4 monoclonal antibody that targets Natural Killer Group 2A (NKG2A). The binding of NKG2A/CD94 to its receptor HLA-E results in an inhibitory signaling by tumors on NK cells, tumor-infiltrating CD8+ T cells and γ^5 T cell (**Figure 1**).
- Monalizumab blocks binding of NKG2A/CD94 to HLA-E, reducing inhibitory signaling and thereby enhancing NK and T cell effector responses. HLA-E is overexpressed in several solid tumors, including CRC, NSCLC, ovarian and endometrial cancer.

Figure 1. Mechanism of action of monalizumab



Objectives

- This analysis was to develop a population pharmacokinetics (PK) model of monalizumab, and identify and quantify the influence of baseline and longitudinal patient and disease characteristics on PK.

Study design and methods

- Data were pooled from two clinical studies (**Figure 2**):
  - D419NC00001 (Study 001): Phase 1/2; monalizumab (flat dose) + durvalumab in patients with advanced solid tumor
  - IPH2201-203 (Study 203): Phase 1b/2; monalizumab (weight-based dose) + cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)
- Monalizumab PK data with 74 subjects following 0.4−10 mg/kg or 750 mg every 2 weeks (Q2W) and 1500 mg every 4 weeks (Q4W), and 369 subjects following 22.5−750 mg Q2W, or 750 mg Q4W.
- Population PK modeling was performed using a nonlinear mixed effects modeling approach in NONMEM software (v. 7.3).
- Stepwise covariate modeling approach was used to explore the impact of clinical and disease characteristics including longitudinal biomarkers on PK.
- Final model was selected based on goodness-of-fit plots and validated using visual predictive check.
- Five hundred simulations were conducted to evaluate the impact of body weight on PK exposure of monalizumab in a population of 500 subjects with a constant albumin level (the median level in the original dataset). Baseline body weights were resampled for the 500 subjects using the distribution in the original dataset.
- Data used for population PK modeling and simulations are shown in **Table 1.**

Figure 2. Study design

Study 001 (D419NC00001) n=369

Part 1: Dose escalation

Monalizumab at 5 increasing doses IV 7.5, 22.5, 75, 225, 750 mg Q2W or 750 mg Q4W + durvalumab 1500 mg IV Q4W

Part 2: Dose expansion

Monalizumab 750 mg Q2W + durvalumab 1500 mg Q4W

Part 3: Dose exploration

Cohort A: Monalizumab 750 mg Q2W + durvalumab 1500 mg Q4W + mFOLFOX6 + bevacizumab (A1) or + mFLOFOX6 + cetuximab (A2) or + mFOLFOX6 (A3)
Cohort C1A/C2A: Monalizumab 750 mg Q2W + durvalumab 1500 mg Q4W
Cohort C1B/C2B: Monalizumab 750 mg Q2W + cetuxiamb 500 mg Q2W

Study 203 (IPH2201-203) n=74

Phase 1b

Monalizumab at 5 increasing doses IV 0.4, 1, 2, 4, or 10 mg/kg Q2W + cetuximab

Phase II

Cohort 1: Monalizumab 10 mg/kg Q2W + cetuximab (A2)
Cohort 2: Monalizumab 750 mg Q2W + cetuximab
Cohort 3: Monalizumab 1500 mg Q4W + cetuximab

QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 1. Data used for population PK modeling and simulations

Continuous covariates	Median (Range)	Categorical covariates	N
Age (yr)	59 (23-82)	Sex	
Baseline body weight (kg)	70.45 (41.2-153.9)	Male	220
ALB (U/L)	3.8 (1.98-4.7)	Female	223
ALP (U/L)	93 (34-1625)	Baseline ADA	
ALT (U/L)	19 (4-183)	0 (negative)	313
AST (U/L)	23 (9-169)	1 (positive)	24
TBILI (mg/dL)	0.45 (0.1-3.9)	Missing	106
Creatinine (mg/dL)	0.77 (0.33-2.113)	Post baseline ADA	
CRCL	97.13 (31.46-307.59)	0 (all negative)	313
LDH (U/L)	225 (84-3332)	1 (at least 1 post-first dose positive)	24
Baseline tumor size	67 (10,307)	Missing	

Categorical covariates	N	Categorical covariates	N
Tumor type		Smoking status I	
Colorectal carcinoma	244	0	313
Ovarian cancer	43	1	24
Endometrical cancer	43	Missing	106
NSCLC	20	Smoking status II	
Cervical cancer	16	0	230
Castration-resistant prostate cancer	3	1	205
SCCHN	74	Missing	8
Race		ECOG performance status	
White	307	0	193
Black/African American	22	1	249
Asian	53	Missing	1
Other	11		
Missing	50		

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRCL, creatinine clearance; TBILI, bilirubin; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase

- PK data were available for 443 patients
- 2326 serum samples were evaluable

Population PK modeling

- A two-compartment linear model described the PK data well following all dosing regimens (**Figures 3–4**).
- Typically, monalizumab clearance was 0.263 L/day; V_1 was 3.9 L, V_2 was 2.49 L with moderate between-patient variability of ~35% for clearance and ~24% for volume of distribution (**Table 2**).
- Baseline body weight and time-varying albumin were identified as statistically significant covariates for clearance and V_1 and tumor type was identified as a statistically significant covariate for V_1.

Figure 3. Final model structure

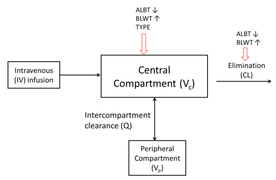


Table 2. Final model equations and parameter estimation

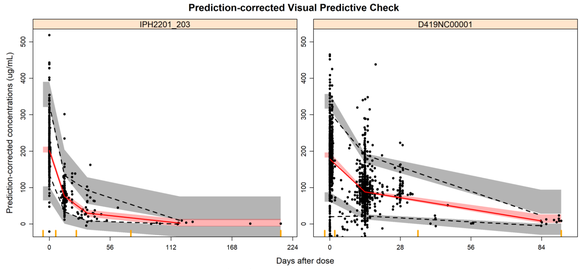
Final model equations:

- $Clearance\ (L/day) = 0.263 \times \left(\frac{WT}{70}\right)^{0.008} \times \frac{ALB^{-0.4}}{3.8}$
- $V_1\ (L) = 3.9 \times \left(\frac{WT}{70}\right)^{0.007} \times \frac{ALB^{-0.086}}{3.8} \times (1 + 0.376 \times NSCLC)$
- $V_2\ (L) = 2.49$
- $Q\ (L/day) = 0.453$

Parameter (unit)	Typical Value	% RSE	Between-patient variability, CV%	% RSE
CL (L/day)	0.263	(3)	34.5	(7)
V_1 (L)	3.9	(2)	24.4	(9)
V_2 (L)	2.49	(9)		
Q (L/day)	0.453	(26)	Correlation between CL and V_1	
Exponent: CL on WT	0.0083	(13)	74%	
Exponent: V1 on WT	0.007	(13)		
Exponent: CL on ALB	-0.399	(12)		
Exponent: V1 on ALB	-0.086	(34)		
NSCLC on V1	0.376	(20)		
Residual Additive Error	13.4	(22)		
Residual Proportional Error (CV%)	0.301	(4)		

CV, coefficient of variation; NSCLS, non small cell lung cancer; RSE, residual standard error; WT, body weight

Figure 4. Prediction-corrected visual predictive check of final model



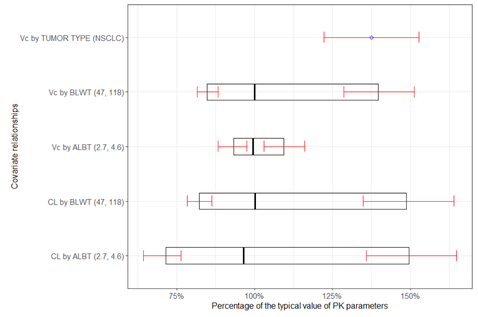
Black dashed lines and red solid line are the 5th, 95th, and 50th percentiles of the observed data. The shaded areas are the corresponding 95% confidence interval based on simulated data

- The Visual Predictive Model suggests good predictive performance and an adequate description of the entire pool of patients by the final model.

Impact of Constant and Time-varying Covariates (Figure 5)

- Clearance and volume of distribution both increased with increasing body weight
- Clearance and volume of distribution decreased as the individual longitudinal albumin level increased and vice versa. This finding of monalizumab PK is consistent with other checkpoint inhibitor drugs, e.g. durvalumab and ipilimumab.
- Volume of distribution increased when patient tumor type is non small cell lung cancer

Figure 5. Forest plot of covariate effects on popPK parameters



Red error bar indicates the 2.5th and 97.5th percentile of the bootstrapping result.

Figure 6. Comparison of $C_{max,ss}$ and cumulative AUC of monalizumab at 750 mg Q2W (12 cycles) and 1500 mg Q4W (6 cycles)

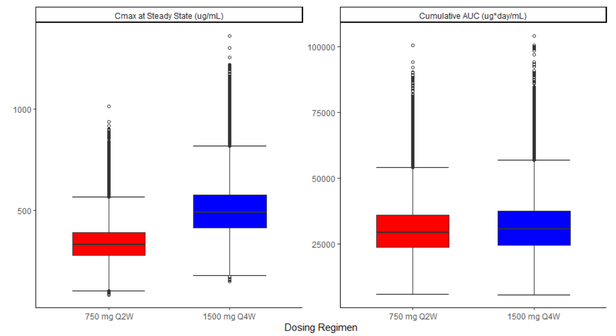
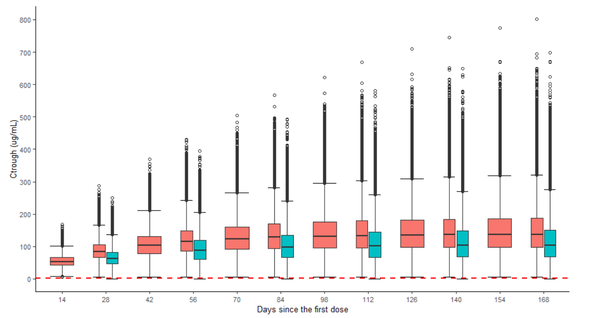


Figure 7. Comparison of trough concentration of monalizumab between 750 mg Q2W (red) and 1500 mg Q4W (blue) over time



- Body weight and time-varying albumin were identified as statistically significant covariate for clearance and V1, NSCLC was identified as a significant covariate on V1; however, it was not clinically relevant since the changes in key PK parameters were ~25% **(Figure 5)**.
- PK simulations showed the C_{max} of 750 mg Q2W at cycle 12 is lower than that of 1500 mg Q4W at cycle 6, while the cumulative AUC from day 0 to 168 are comparable (**Figure 6**). Predicted results suggested that the two regimens would maintain a trough concentration above target concentration (2 µg/mL) in >95% patients, where nonlinear clearance is expected to be fully saturated (**Figure 7**).

Conclusions

- A two-compartment population PK model with linear clearance adequately described the data.
- This quantitative approach supports the hypothesis that increase in body weight and albumin over time is associated with increase and decrease in monalizumab CL, consistent with other checkpoint inhibitor drugs. No dose adjustments were needed to account for the impact of covariate baseline body weight.
- The population PK model supports previous dose selection of 750 mg Q2W or equivalent dose in future Phase 2/3 clinical studies.

Acknowledgments
Study 001 was sponsored by AstraZeneca and Study 203 was sponsored by Innate Pharma.
COI disclosure
Xuyang Song is an employee of and stockholder in AstraZeneca, Gaithersburg, MD, USA

Contact Email: Xuyang.Song@AstraZeneca.com

Presented at the 29th Annual Meeting of the Population Approach Group Europe (PAGE), 2021