153

Presented at the

2024 American College of Clinical Pharmacology® (ACCP) Annual Meeting

Bethesda, MD, USA • September 8-10, 2024

Population Pharmacokinetics/Pharmacodynamics Modeling of INCAGN02385 in Patients With Select Advanced Malignancies

Yunlan Fang, Breann Barker, Zhiwan Dong, Xiang Liu, Jennifer Sheng, Xuejun Chen, Yan-ou Yang

Incyte Research Institute, Wilmington, DE, USA

Introduction

- INCAGN02385 is a humanized Fc-engineered immunoglobulin G1κ (IgG1κ) monoclonal antibody that selectively binds to the inhibitory receptor lymphocyte activation gene 3 protein (LAG-3), leading to enhanced T-cell receptor signaling and potentially eliciting antitumor immunity
- INCAGN02385 is being studied for the treatment of select advanced malignancies in combination with other agents
- The study objective was to develop a population pharmacokinetics (PK)/pharmacodynamics (PD) model to characterize INCAGN02385 exposure, peripheral LAG-3 receptor occupancy (RO), and interparticipant variability in patients with advanced malignancies, when administered intravenously as monotherapy

Methods

Data Source

- Population PK/PD model development used PK and RO data from the first-in-human study of INCAGN02385 (NCT03538028)
  - Patients received intravenous INCAGN02385 doses ranging from 25 mg to 750 mg every 2 weeks (q2w)
  - The final analysis dataset included 202 PK samples and 98 RO samples from 22 patients with select advanced malignancies

Model Development

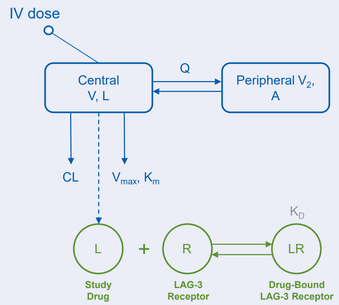
- A nonlinear mixed-effects model was developed and implemented using Monolix® (version 2021R2)
- Patient demographic and baseline characteristics, including but not limited to weight, age, sex, and baseline albumin and alkaline phosphatase levels, were evaluated for covariate search using a stepwise covariate building approach
- Model selection was based on the corrected Bayesian information criterion (cBIC), precision and plausibility of parameter estimates, and goodness-of-fit diagnostic plots

Results

- A schematic representation and equations of the PK/PD model are shown in **Figure 1**
  - A 2-compartment PK model with parallel linear and Michaelis-Menten elimination was used to describe nonspecific clearance and target-specific clearance pathways, respectively
  - A sigmoid maximum effect model with baseline was used to describe LAG-3 target engagement, which was driven by the INCAGN02385 serum concentration
- Parameter estimates of the final population PK/PD model are presented in **Table 1**
  - All parameters and their variabilities were estimated within an acceptable degree of precision and were physiologically plausible for an antibody
  - Baseline albumin and alkaline phosphatase were identified as significant covariates of central volume of distribution (V). V was lower in patients with higher baseline albumin and/or alkaline phosphatase
  - Baseline albumin was also found to impact the maximal velocity of the nonlinear elimination (V_{max}). Target-specific clearance occurred more rapidly in patients with lower baseline albumin
- Goodness-of-fit diagnostic plots are presented in **Figures 2–4**
  - Population and individual predictions for PK and RO aligned well with observations **(Figure 2)**
  - Weighted residuals across time and population/individual predictions for PK and RO distributed evenly around y=0 (**Figure 3** and **Figure 4**, respectively)
- Visual predictive check plots showed simulations from the final population PK/PD model can adequately capture the central trend and variability in observed PK and RO data **(Figure 5)**

Schematic Diagram and Parameter Estimates of Final Model

Figure 1. Schematic Representation and Equations for the PK/PD Model



Structural Model

$$\frac{dD}{dt} = \frac{In(t)}{V} - \frac{CL}{V} \times D - \frac{V_{max} D}{K_m + D} - \frac{Q}{V} \times D + \frac{Q}{V_2} \times \frac{A}{V}$$

$$\frac{dA}{dt} = Q \times D - \frac{Q}{V_2} \times A$$

$$E = E_0 + \frac{E_{max} \times D^{\gamma}}{EC_{50} + D^{\gamma}}$$

Individual Model*

$$V_i = V \times \left(\frac{ALB_i}{ALB_{median}}\right)^{\beta_{V\_ALB}} \times \left(\frac{ALP_i}{ALP_{median}}\right)^{\beta_{V\_ALP}} \times e^{\eta_{V,i}}$$

$$V_{max,i} = V_{max} \times \left(\frac{ALB_i}{ALB_{median}}\right)^{\beta_{V_{max}\_ALB}}$$

$$CL_i = CL \times e^{\eta_{CL,i}} \qquad EC_{50,i} = EC_{50} \times e^{\eta_{EC_{50},i}}$$

*Individual parameters that are not listed in the equations are equal to corresponding population parameters.

β_{V_ALB}, effect of baseline albumin on volume of distribution central compartment; β_{V_ALP}, effect of baseline alkaline phosphatase on volume of distribution central compartment; $\beta_{V_{max}\_ALB}$, effect of baseline albumin on maximal velocity of the nonlinear elimination; γ, shape parameter; η, random effect; A, amount of investigational drug; ALB_i, individual baseline albumin; ALB, baseline albumin; ALP, baseline alkaline phosphatase; ALP_i, individual baseline alkaline phosphatase; CL, clearance; D, drug concentration; E, effect; E_0, baseline effect; EC_{50}, concentration in serum that achieves 50% of predicted maximum effect; E_{max}, maximum effect; In(t), infusion rate; IV, intravenous; K_D, dissociation constant; K_m, Michaelis-Menten constant; L, investigational drug; LAG-3, lymphocyte activation gene 3; LR, drug-bound lymphocyte activation gene 3 protein receptor; PD, pharmacodynamics; PK, pharmacokinetics; Q, intercompartmental clearance; R, free lymphocyte activation gene 3 protein receptor; V, volume of distribution central compartment; V_2, volume of distribution peripheral compartment; V_i, individual volume of distribution central compartment; V_{max}, maximal velocity of the nonlinear elimination.

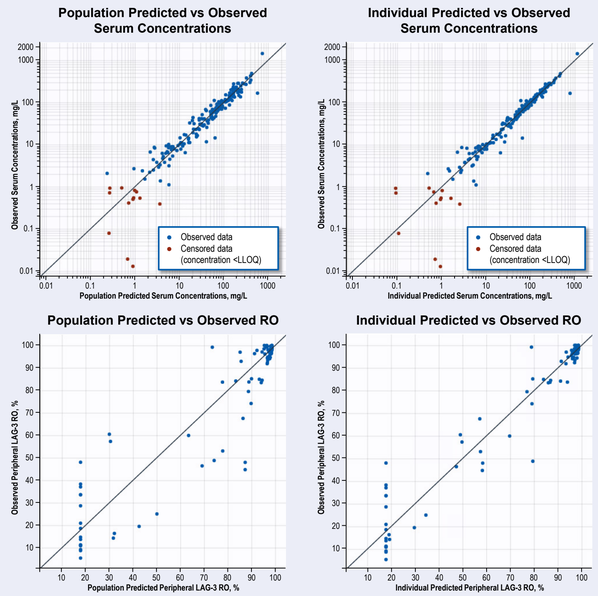
Table 1. Parameter Estimates of the Final Population PK/PD Model

Parameters	Estimate	RSE, %	ω (RSE/Shrinkage), %
Fixed and random effects			
CL, L/h	0.0092	6.39	0.15 (28.3/54.4)
V, L	3.28	7.75	0.31 (21.6/17.9)
V_2, L	2.94	10.9	
Q, L/h	0.056	16.0	
V_{max}, nM/h	0.015	30.3	
K_m, nM	0.81	2.84	
β_{V_ALB}	−1.54	35.1	
β_{V_ALP}	−1.21	18.3	
$\beta_{V_{max}\_ALB}$	−2.82	30.5	
E_0, %	17.9	11.3	
E_{max}, %	80.9	2.52	
EC_{50}, nM	1.04	51.2	0.85 (34.7/59.1)
γ	1.14	19.3	
Error model parameters			
Additive error (PK)	1.19	18.9	6.65
Proportional error (PK)	0.19	8.43	6.65
Additive error (RO)	0.57	7.71	4.59

β_{V_ALB}, effect of baseline albumin on volume of distribution central compartment; β_{V_ALP}, effect of baseline alkaline phosphatase on volume of distribution central compartment; $\beta_{V_{max}\_ALB}$, effect of baseline albumin on maximal velocity of the nonlinear elimination; CL, clearance; E_0, baseline effect; EC_{50}, concentration in serum that achieves 50% of predicted maximum effect; E_{max}, maximum effect; K_m, Michaelis-Menten constant; PD, pharmacodynamics; PK, pharmacokinetics; Q, intercompartmental clearance; RO, receptor occupancy; RSE, relative standard error; V, volume of distribution central compartment; V_2, volume of distribution peripheral compartment; V_{max}, maximal velocity of the nonlinear elimination.

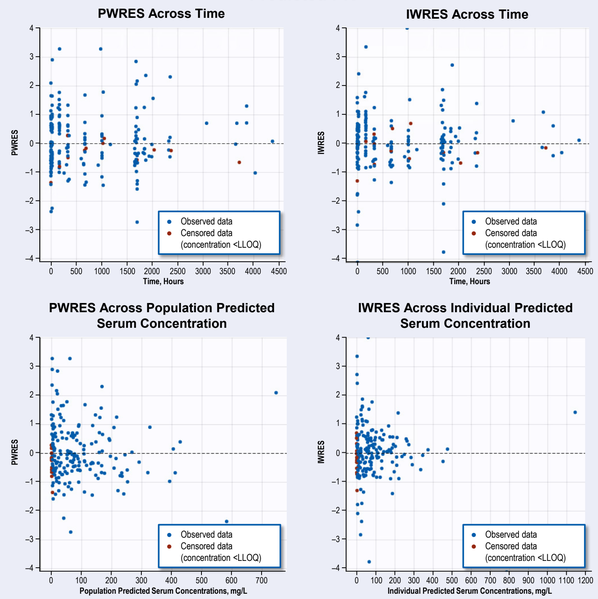
Goodness-of-Fit Diagnostic Plots

Figure 2. Observations vs Predictions of the Final Population PK/PD Model



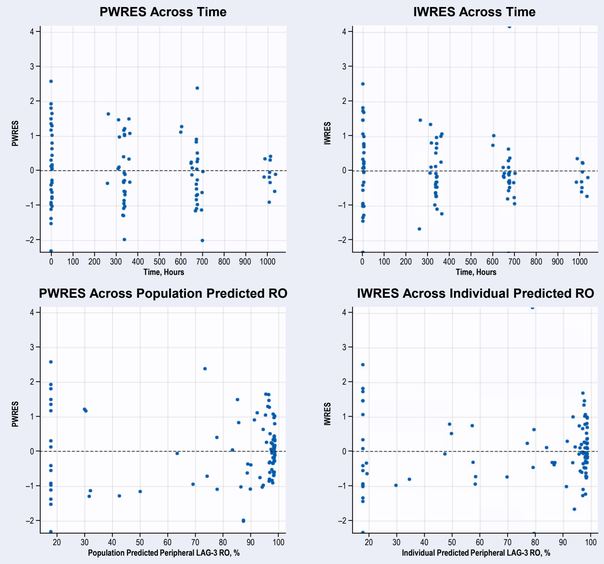
LAG-3, lymphocyte activation gene 3; LLOQ, lower limit of quantification; PD, pharmacodynamics; PK, pharmacokinetics; RO, receptor occupancy.

Figure 3. Scatter Plots of Weighted Residuals Across Time and Predicted PK



IWRES, individual-weighted residuals; LLOQ, lower limit of quantification; PK, pharmacokinetics; PWRES, population-weighted residuals.

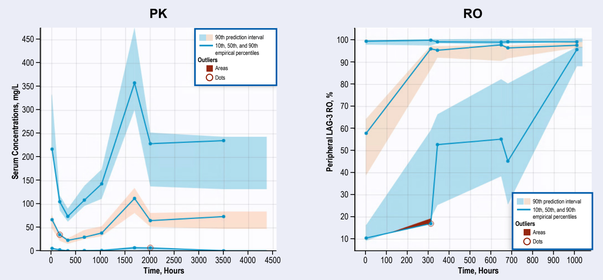
Figure 4. Scatter Plots of Weighted Residuals Across Time and Predicted RO



IWRES, individual-weighted residuals; LAG-3, lymphocyte activation gene 3; PWRES, population-weighted residuals; RO, receptor occupancy.

Visual Predictive Check Plots

Figure 5. Visual Predictive Check of the Final Population PK/PD Model



LAG-3, lymphocyte activation gene 3; PD, pharmacodynamics; PK, pharmacokinetics; RO, receptor occupancy.

Conclusions

- **We developed a population PK/PD model that can adequately describe the relationship between INCAGN02385 exposure and peripheral blood LAG-3 target engagement, as well as characterize the interparticipant variability in patients with advanced malignancies**
- **This population PK/PD model can be leveraged as a valuable prediction tool to support future dose selection for clinical development**

Disclosures

Fang, Barker, Dong, Liu, Sheng, Chen, Yang: Employment and stock ownership – *Incyte Corporation*.

Acknowledgments

Editorial and graphics support was provided by Envision Pharma Group (Fairfield, CT, USA) and funded by Incyte Corporation.

To download a copy of this poster, scan code