LB268

# Assessment of Flat Dosing Strategy for INCMGA00012 in Patients With Advanced Tumors

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## Abstract

**Background:** INCMGA00012, a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes human PD-1, is being developed for the treatment of multiple solid tumor types, both as monotherapy and in combination with other potentially immunoactive agents. Flat dosing may provide advantages over weight-based dosing in various ways, including convenience of preparation and administration, reduced errors in preparation calculation, and minimization of drug waste. A modeling and simulation approach was employed to support flat doses for later phase studies.

**Patients and Methods:** INCMGA00012 has been administered to approximately 200 participants in a phase 1 study (Study INCMGA 0012-101) at weight-based doses ranging from 1 to 10 mg/kg Q2W or Q4W and at flat doses of 500 mg Q4W and 750 mg Q4W. PK data from weight-based doses were used for population PK model development and data from flat doses were used for model validation. Simulations were performed to support the selection of RP2 flat dose.

**Results:** The concentrations of INCMGA00012 were adequately described by a 2-compartment model with first-order elimination. Higher clearance was estimated for 1 mg/kg (23.5 mL/h) than the other dose groups (13.5 mL/h). Body weight dependence of clearance and volume of distribution for central compartment were characterized by power relationships with exponents of 0.911 and 0.493, respectively. The model was validated using PK data from participants who received INCMGA00012 500 mg Q4W and 750 mg Q4W, respectively, in the cohort expansion phase. Median steady-state trough concentrations of 500 mg Q4W and 750 mg Q4W exceeded the target value.

**Conclusion:** Modeling and simulation provide justification for 500 mg Q4W for further clinical development of INCMGA00012 based upon favorable safety, PK characteristics, and presumed flat exposure-response relationships for efficacy.

## Introduction

- INCMGA00012, a humanized, hinge-stabilized, immunoglobulin gamma 4 kappa (IgG4κ) monoclonal antibody that recognizes human programmed cell death (PD)-1, is being developed for the treatment of multiple solid tumor types, both as monotherapy and in combination with other potentially immunoactive agents
- Flat dosing may provide advantages over weight-based dosing in various ways, including convenience of preparation and administration, reduced errors in preparation calculation, and minimization of drug waste. Body size–based doses and fixed doses of monoclonal antibodies have been evaluated, and the 2 approaches perform similarly in terms of efficacy and safety[1,2]
- Dose proportionality in maximum plasma drug concentration ($C_{max}$) and supra-dose proportionality in area under the curve (AUC) were observed over the dose from 1 mg/kg to 10 mg/kg for the first dose. The elimination half-life ($t_{1/2}$) of ~409 hours of INCMGA00012 suggests that the drug is expected to attain steady-state conditions within 85 days, and predicted accumulations of the every 2 week (Q2W) and every 4 week (Q4W) regimens are expected to be approximately 2 and 1.5, respectively
- The objectives of this population pharmacokinetic (PK) analysis and simulation were to characterize PK of INCMGA00012, investigate the effect of body weight on PK parameters, simulate PK profiles for different dosing regimens to compare weight-based and fixed-dose regimens, and assess percentage of patients with trough plasma concentration ($C_{trough}$) ≥ target concentration (pembrolizumab $C_{trough}$ = 21 μg/mL)[3]

## Methods

### *Study Design and Bioanalytic Methods*

- INCMGA 00012-101 is a phase 1, dose-escalation and dose-expansion study. INCMGA00012 has been administered to approximately 200 participants in this study at weight-based doses ranging from 1 mg/kg to 10 mg/kg Q2W or Q4W and at flat doses of 375 mg every 3 weeks (Q3W), 500 mg Q4W, and 750 mg Q4W. PK data from weight-based doses were used for population PK model development, and data from flat doses were used for model validation. Simulations were performed to support the selection of the recommended phase 2 flat dose (RP2D)
- Blood samples for INCMGA00012 were collected at predose, end of infusion (EOI), 6 hours after EOI on cycle 1 day 1, predose, EOI on cycle 1 day 15, on days 1 and 15 of cycle 2 and beyond, no specific time points on days 2, 4, and 8 of cycle 1 for Q2W; at predose, EOI, 6 hours after EOI on cycle 1 day 1; predose, EOI on day 1 of cycle 2 and beyond, no specific time points on days 2, 4, 8, 15 of cycle 1, day 15 of cycle 2 and beyond for Q4W; at predose, EOI, 6 hours after EOI on cycle 1 day 1, predose, EOI on day 1 of cycle 2 and beyond, no specific time points on days 2, 4, 8, 15 of cycle 1, days 8 and 15 of cycle 2 for Q3W
- INCMGA00012 serum concentrations were determined using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) method

### *Population Pharmacokinetic Analysis*

- Data exploration and graphical analysis were performed with SAS version 9.4, SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC)
- Population PK was conducted with NONMEM (Version 7.4.1, Icon Development Solutions, Ellicott City, MD) and the GFortran Compiler 4.6 NONMEM runs were executed using PDX-pop for NONMEM (Version 5.2.1, Icon Development Solutions)
- Models were evaluated based on the following:
  - Objective functions
  - Diagnostic plots (eg, plots of observed vs predicted data, residual and weighted residual plots)
  - Precision of the parameter estimates as measured by the percent standard error of the mean (SEM)
  - External validation using data from flat-dose groups
- Time-invariant covariate, body weight, was explored as a potential factor that may impact INCMGA00012 pharmacokinetics

### *Simulation Methods*

- A simulation was generated based on the results of the final population PK model using similar distribution of weight, sex, and age from the modeling dataset. Two hundred fifty patients were simulated for each selected weight-based dose and flat dose. The simulation was repeated 500 times
- The observed mean and SEM of external data were plotted along with the median and 90% prediction interval of the simulated data to evaluate the accuracy and robustness of the final population model
- The median and 90% prediction interval of the simulated steady-state data for each dose were plotted along with the target concentration as reference line
- The median and 90% prediction interval of the simulated trough concentrations for each dose were plotted along with the target concentration as reference line to show accumulation and when to reach steady state. The proportion of patients with $C_{trough}$ ≥ target concentration was calculated for each dose group

## Results

- The final population PK dataset contained 327 PK samples from 36 participants
- Doses ranged from 1 mg/kg to 10 mg/kg, Q2W and Q4W for the modeling dataset
- The median body weight was 79.35 kg, with a range of 47.3 kg to 133.5 kg; 64% of participants were female
- The concentrations of INCMGA00012 were adequately described by a 2-compartment model with first-order elimination. Higher clearance was estimated for 1 mg/kg (0.0235 L/h) than the other dose groups (0.0135 L/h). **Table 1** presents the model parameters

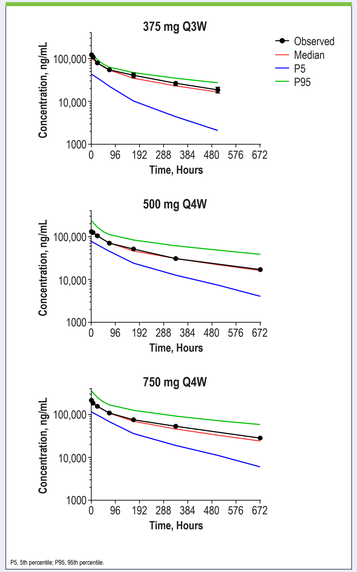
**Table 1. Final Model Parameters**

| Fixed Effects | Value | RSE, % | Standard Deviation of the Random Effects | Value | RSE, % |
|---|---|---|---|---|---|
| CL for 1 mg/kg, L/h | 0.0235 | 17.5 | omega_CL | 0.146 | 37.7 |
| CL for >1 mg/kg, L/h | 0.0135 | 16.5 | | | |
| V1, L | 3.65 | 4.93 | omega_V1 | 0.0754 | 40.8 |
| Q, L/h | 0.0282 | 9.01 | — | — | — |
| V2, L | 2.62 | 18.3 | omega_V2 | 0.537 | 33.3 |
| WT on CL | 0.911 | 25.6 | — | — | — |
| WT on V1 | 0.493 | 37.7 | — | — | — |
| Residual error model | | | | | |
| Proportional | 0.0242 | 34.0 | — | — | — |

CL, clearance; Q, intercompartmental clearance; RSE, relative standard error; V1, central volume of distribution; V2, peripheral volume of distribution; WT, weight.

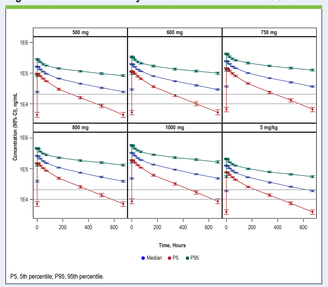
- Body weight dependence of clearance and volume of distribution for central compartment were characterized by power relationships with exponents of 0.911 and 0.493, respectively
- The central tendency aligned very well between the observed and the predicted concentrations for 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W. The mean and SEM of observed concentrations for 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W fell within the 90% confidence band of the predicted concentrations (**Figure 1**). Hence, the model was validated using PK data from participants who received INCMGA00012 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W, respectively
- Median steady-state trough concentrations of 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W exceeded the target value (**Table 2**)
- The median steady-state concentration at 500 mg Q4W was 24.8 μg/mL, and 58% of participants had trough concentrations greater than the target concentration by simulation, which justified the clinical exploration in an expansion cohort of the study (**Figures 2** and **3**)
- The median steady-state concentration at 375 mg Q3W was 29.6 μg/mL, and 62% of participants had trough concentrations greater than the target concentration (**Figures 4** and **5**)

**Figure 1. Mean (SEM) Observed Concentrations vs Simulated Concentrations (Median, P5, and P95) for the First Dose**




P5, 5th percentile; P95, 95th percentile.

**Figure 2. Simulated Steady-State Concentrations for Q4W**




P5, 5th percentile; P95, 95th percentile.

**Figure 3. Simulated Trough Concentrations for Q4W**

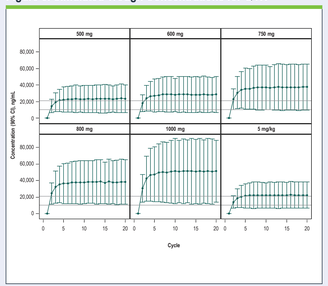
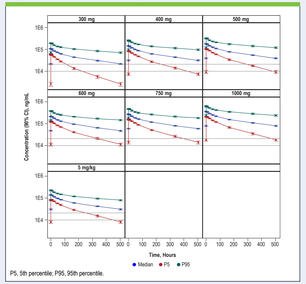



**Figure 4. Simulated Steady-State Concentrations for Q3W**




P5, 5th percentile; P95, 95th percentile.

**Figure 5. Simulated Trough Concentrations for Q3W**

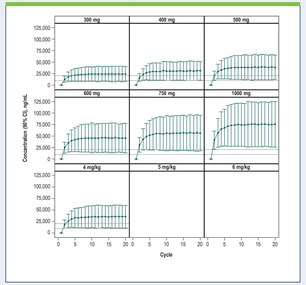



**Table 2. Proportion of Patients With $C_{trough}$ ≥ Target Concentration for Body Weight–Based Dosing (mg/kg) and Flat Dosing (mg)**

| Dose | Q3W | Q4W |
|---|---|---|
| 5 mg/kg | 71% | 45% |
| 375 mg | 62% | — |
| 500 mg | 78% | 58% |
| 750 mg | 89% | 74% |

Target concentration: pembrolizumab $C_{trough}$ = 21 μg/mL.

## Discussion and Conclusions

- **INCMGA00012 is well tolerated over a wide range of doses with encouraging clinical activity[4]**
- **Fixed-dose regimens will provide comparable benefit-risk profile to weight-based regimens**
- **Overall, the 500-mg Q4W dose had very similar PK properties to the 3-mg/kg Q2W dose and has approximately a 58% probability for steady-state trough serum concentration ≥21 μg/mL, which is associated with maximum target engagement and greatest probability of efficacy, based on pembrolizumab data.[5] From these observations, 500 mg Q4W was selected as the RP2D for further monotherapy development**
- **The 375-mg Q3W dose was selected in order to maintain steady-state trough serum concentration ≥21 μg/mL in clinical trials, and to provide additional flexibility in monotherapy or combinations (eg, chemotherapy) while maintaining this schedule**

### Disclosures

**Xuejun Chen, Phil Wang, Swamy Yeleswaram:** Employment and stock ownership – *Incyte Corporation*. **Sanjeev Kaul:** Employment – *Bio-ClinPharm Consulting LLC*. **Bradley Sumrow:** Employment and stock ownership – *MacroGenics, Inc.*

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