Population Pharmacokinetics of Zimberelimab (AB122) and Dose Justification by Model Informed Drug Development (MIDD) Approach

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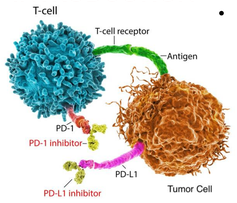
INTRODUCTION



- Immune checkpoint proteins, such as programmed cell death protein-1 (PD-1), play a key role in providing a major resistance mechanism by which tumor cells can escape immune surveillance. Immune checkpoint inhibitors aim to block immune checkpoint proteins from binding, allowing immune cells to kill cancer cells.
- Zimberelimab (AB122) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that selectively binds to the PD-1 membrane receptors, blocking interactions between PD-1 and PD-L1.
- AB122 is being developed for the treatment of various cancers.

OBJECTIVES

- Develop a population pharmacokinetic (PopPK) model to characterize the AB122 concentration-time profile in patients with various cancers;
- Investigate the effects of selected covariates, which may explain variability in AB122 PK parameters;
- Inform dose selection for Phase 2/3 studies using clinical trial simulations.

METHODS

Study	Summary of Design	No. of Patients	No. of Samples
AB122CSP0001	A Phase 1 dose-escalation study in patients with advanced solid tumors	39	319
AB154CSP0001	A Phase 1 dose-escalation study in patients with advanced solid tumors	33	275
ARC-4	A Phase 1/1b dose-escalation and dose-expansion study in patients with NSCLC	12	98
ARC-5	A Phase 1 dose-escalation and dose-expansion study in patients with advanced malignancies	41	398
ARC-6	A Phase 1b/2 study in patients with mCRPC	28	182
ARC-7	A Phase 2 study in patients with metastatic (Stage IV) squamous or non-squamous NSCLC	11	90
ARC-8	A Phase 1 dose-escalation and dose-expansion study in patients with advanced GI malignancies	17	140

Data

- AB122 was administered intravenously (IV) (80 to 720 mg) every 2-4 weeks (Q2W, Q3W, or Q4W) either as a monotherapy or in combination with other immune/chemo-therapies (See supplementary materials).
- The PopPK analysis included AB122 concentration-time data from 7 clinical studies (See table above).
- The analysis included a total of 181 cancer patients (28 with non-small cell lung cancer [NSCLC], 13 with colorectal cancer, 5 with ovarian cancer, 57 with metastatic castrate resistant prostate cancer [mCRPC], and 78 patients with other advanced malignancies) with 1502 PK samples.

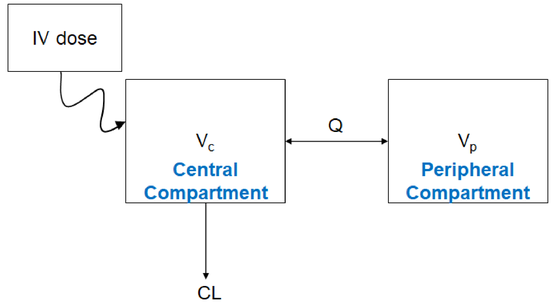
Modeling & Simulations

- Nonlinear mixed effects modeling methodology was implemented using NONMEM (version 7.5, ICON). The first-order conditional estimation method with interaction (FOCE-I) was used.
- Model development was based on successful minimization, assessment of standard goodness-of-fit (GOF) plots, and reductions in objective function value and residual variability.
- Covariates such as body weight, age, sex, albumin, type/stage of cancer, baseline tumor burden, and markers of renal and hepatic function were evaluated using a forward selection and backward elimination procedure (See supplementary materials).
- Clinical simulations were conducted with various dosing scenarios to select candidate regimens for Phase 2/3 studies.

The PK of zimberelimab was adequately described by a two-compartment model with direct IV administration in the central compartment and first-order elimination.

PK

PK Model Structure



CL: clearance; IV: intravenous; Q: inter-compartmental clearance; Vc: central volume of distribution; Vp: peripheral volume of distribution

PK Parameter Estimates

Parameter	Parameter Estimate	RSE (%)
CL (L/day)	0.33	3.8
V_c (L)	3.87	2.2
Q (L/day)	0.53	15
V_p (L)	2.87	9.5
WEIGHT on Vc (Ref: 76.4 kg)	0.55	16
WEIGHT on CL (Ref: 76.4 kg)	0.59	25
SEX on Vc	0.85	4.8
Interindividual Variability (%CV)		
η_{CL}	36.6	6.7
η_{Vc}	19.4	10
$p(\eta_{CL},\eta_{Vc})$	0.37	16
Residual Error		
Proportional Error (%CV)	20.7	4.6

Parameter values are presented as point estimates with relative standard error (RSE); Interindividual variability values are presented as %CV; CL = clearance, Q = inter-compartmental clearance, Vc = central volume of distribution, Vp= peripheral volume of distribution, ηCL = interindividual variability of CL, ηVc = interindividual variability of Vc, p(ηCL,ηVc) = correlation between CL and Vc

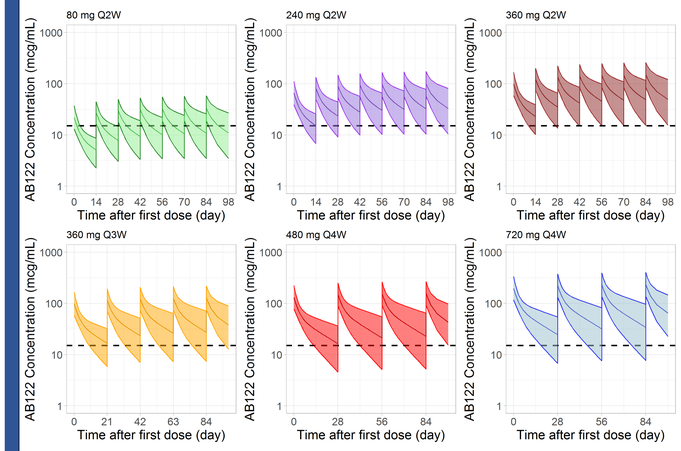
Model equations: $\mathrm{CL} = 0.33\left(\frac{\mathrm{WEIGHT}}{76.4}\right)^{0.59}$; $\mathrm{V_C} = 3.87(0.85)^{\mathrm{female}}\left(\frac{\mathrm{WEIGHT}}{76.4}\right)^{0.55}$

Statistically-significant covariates in the PK model included sex and body weight on central volume of distribution; and body weight on clearance.

A preliminary population PK model of zimberelimab was developed. Clinical simulations identified suitable zimberelimab doses for current and future clinical trials at different dosing frequencies.

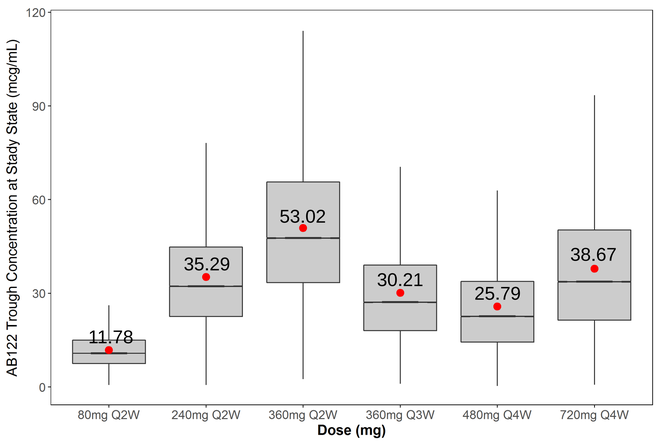
Clinical Simulation

Simulated PK Profiles of AB122



Solid lines (top to bottom) represent 95th, mean, and 5th percentile of predicted AB122 concentration in dose range from 80-720 mg every 2-4 weeks; shaded areas represent 90% prediction interval; dashed lines represent a reference line of 15 µg/mL.

AB122 Trough Concentration at Steady State (Day 84)



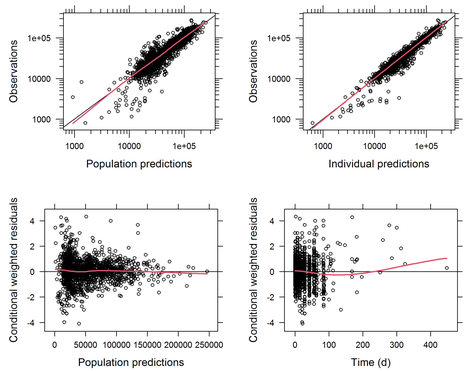
The bottom and the top of each vertical line represents minimum and maximum AB122 concentration, respectively. The horizontal lines of the boxes (from bottom to top) represent the first quartile, median, and the third quartile of AB122 concentration, respectively. Red dots and numeric text represent the mean concentration within each dose level.

Scan QR code for supplementary materials

CONCLUSIONS

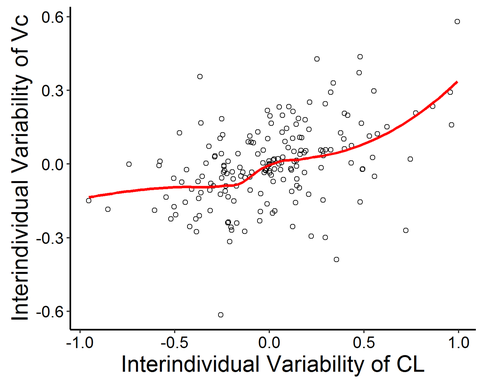
- The PK of AB122 was adequately described by a 2-compartment model with first-order elimination.
  - The terminal half-life of AB122 was 16.2 days
  - Statistically-significant covariates in the PK model included sex and body weight on Vc; and body weight on CL.
- Trough concentrations following IV administration of 240mg Q2W, 360mg Q3W, 480mg Q4W, and 720mg Q4W achieved a pre-set effective concentration threshold of 15 µg/mL, that would result in >99% peripheral receptor occupancy of PD-1 receptors, a level of target occupancy that is widely believed to result in maximal efficacy for checkpoint inhibitors.
- The current population PK model based simulations were used for Phase 2/3 dose selection.

Diagnostic plots for the final population PK model



Open symbols are data points from all 7 studies. Red lines are regression lines in observations vs. population predictions (PRED)/ individual predictions (IPRED) plots. Red lines are smooth lines in conditional weighted residuals (CWRES) vs. PRED/Time plots.

Correlation between Clearance and Central Volume of Distribution



Open symbols are interindividual variability estimates of clearance (CL) and central volume of distribution (Vc). Red line is the loess line.

REFERENCES

- Okazaki et al, 2001
- Bennett et al, 2003

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