Optimal dose estimation using an integrated approach from Phase I data of givastomig, a novel Claudin18.2×4-1BB bispecific antibody

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BACKGROUND

- Givastomig/ABL111 (Giva) is a first-in-class, bispecific antibody that targets Claudin (CLDN) 18.2 and is engineered to conditionally induce 4-1BB signaling for T-cell activation specifically at tumor sites, thereby avoiding systemic toxicities.
- A phase 1 study was designed to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of Giva. The objective of this analysis was to identify the optimal dose range for givastomig in patients with advanced gastroesophageal adenocarcinoma (GEC).

METHODS

- Modeling was conducted utilizing an integrated approach, including target exposure estimation, PK/PD characterization, population analysis, and modeling and simulation methodologies. The data in the analysis were collected from nonclinical studies, and clinical phase 1 (TJ033721STM101) dose escalation and expansion study [0.1 to 15 mg/kg intravenously (IV) Q2W].
- A target threshold was derived from the clinical PKPD relationship, and the data from the preclinical cytokine release and the mouse tumor model.
- A population PK (PopPK) model simulation was used to evaluate givastomig exposure and the probability of achieving the target threshold.

RESULTS

Pharmacokinetics

- Figure 1 demonstrates that givastomig exposure, as measured by both Cmax and AUC increased in an approximately dose-proportional manner.
- Table 1 presents the mean PK parameters following the initial dose of givastomig. The observed apparent effective half-life within a Q2W interval after the first dose was 5.3-7.3 days, when givastomig was administrated at doses equal or greater than 5 mg/kg.

Figure 1. Mean Serum Concentration of Givastomig

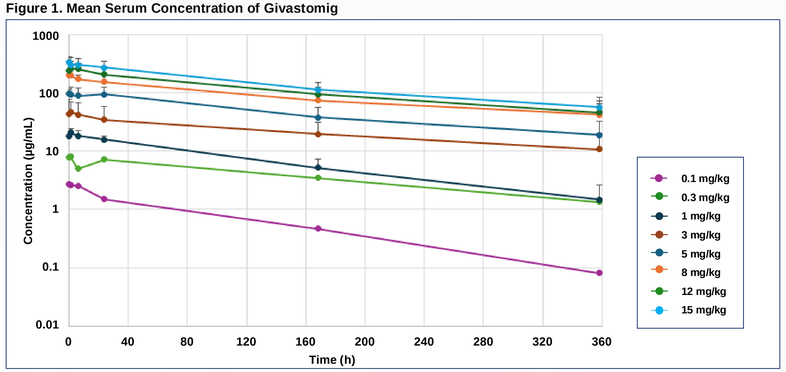


Table 1. Summary of PK Parameters (Mean±SD) Following the Initial Dose of Givastomig

Parameters	0.1 mg/kg (N=1)	0.3 mg/kg (N=1)	1 mg/kg (N=4)	3 mg/kg (N=3)	5 mg/kg (N=10)	8 mg/kg (N=6)	12 mg/kg (N=16)	15 mg/kg (N=9)
C_{max} (µg/mL)	2.68	8.05	21.0 ± 3.90	60.1 ± 16.2	112 ± 28.1	228 ± 74.3	275 ± 74.9	363 ± 79.9
$AUC_{0\text{-}358h}$ (mg*day/mL)	0.22	1.31	2.24 ± 0.78	5.53 ± 4.25	14.5 ± 8.45	33.0 ± 17.7	40.2 ± 14.5	51.1 ± 12.0
$T_{1/2}$ (h)	79.1	138	88.1 ± 23.4	144 ± 55.6	126 ± 66.7	175 ± 54.3	152 ± 57.5	150 ± 36.0

AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; PK = pharmacokinetic; SD = standard deviation; $T_{1/2}$ = terminal phase elimination half-life. Excluded subjects with potential ADA-impact.

RESULTS

PopPK Model

- The population PK modeling was conducted based on the PK data as of January 15, 2024 after administering givastomig at 0.1-15 mg/kg Q2W (N=63). Data from low-dose cohorts were excluded due to potential ADA impact caused by non-linearity. One compartment model with linear elimination characterized by clearance [CL] and central compartment volume [V]) described the PK of givastomig across all Q2W doses, with inter-individual variability <40% in major PK parameters. Except for body weight, no other clinically significant covariates, such as age, sex, weight, CLDN18.2 status, race, country, tumor type, and ethnics, were identified. The parameters of the population PK model in humans are summarized in Table 2.

Table 2. Parameter Estimates of the Population PK Model

Parameters	Description, Unit	Estimate	%RSE, est	IIV variance (%)	%RSE, iiv
CL	Clearance, L/h	0.016	5.11	39	9.8
V	Volume of central compartment, L	3.62	2.69	18	12.3
δ, WT to V	Covariate, WT to V	0.42	25.7	-	-
Residual error, proportional		0.31	3.12	-	-

RSE: relative standard error; IIV: inter-individual variability; CL: linear clearance from central compartment; V: volume of the central compartment; WT: body weight.

PK/PD Modeling for the Estimation of the Target Threshold

- PK/PD modeling using the Emax model was performed with in vivo soluble 4-1BB levels in patients treated with givastomig, in vitro cytokine release assays (IL-2 and IFN-γ), and in vivo tumor growth inhibition (TGI) studies in mouse models (Figure 2).
- The concentration for maximal (≥ 90%) cytokine release stimulation with “no hook effect” was 0.6 – 6.6 µg/mL.
- Single dose PK/PD study in MC38 mouse model demonstrated plateaued TGI% and modulation of immune profiles at 2 – 10 mg/kg (data not shown) and the corresponding blood concentration was 0.4 – 1.5 µg/mL.
- Assuming a 5% tumor penetration rate, based on in vitro cytokine release and the mouse tumor model, the target concentration threshold was determined to be at 12 µg/mL, consistent with the clinical PK/PD relationship.
- Dose-dependent increase in soluble 4-1BB after givastomig treatment was observed (Figure 3). Induction in s4-1BB approached a plateau at ≥8 mg/kg.

Figure 2. Preliminary PK/PD Correlations of In Vivo Maximal Soluble 4-1BB Induction vs Givastomig Dose (left), In Vitro Cytokine Release Assays (middle), and In Vivo PK/PD Mouse Model (right)

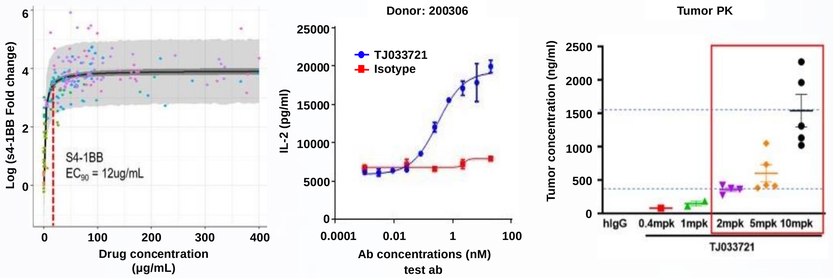
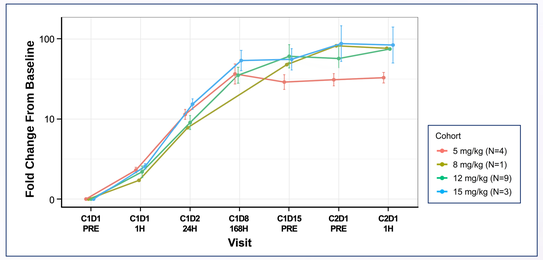


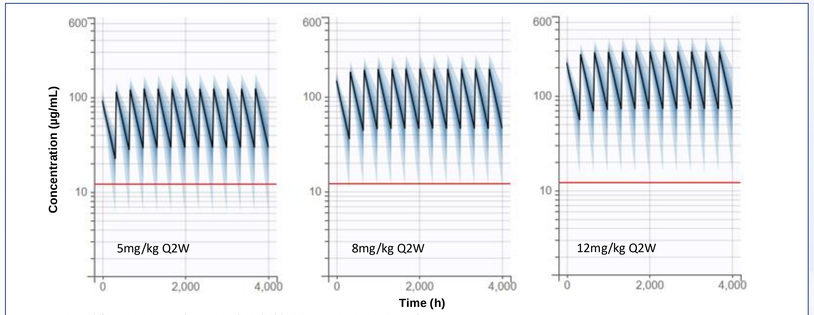
Figure 3. PD Effect on Peripheral Soluble 4-1BB in CLDN18.2+ GEC Patients (n=21)



Model Application

- Simulations of givastomig profiles in human serum were performed based on the established PopPK model against the target threshold (12 µg/mL).
- Figure 4 presents the model simulated PK profiles of givastomig at the dose levels of 5, 8 and 12 mg/kg Q2W. The results suggest that a dose level of at least 8 mg/kg is needed for the majority of patients to achieve and maintain the target threshold. At 12mg/kg, the target threshold would be achieved in all patients throughout the treatment.

Figure 4. Simulations of Givastomig Concentration Profiles in Human Serum at 5, 8 and 12 mg/kg Q2W Based on the Established PopPK Model



Note: red line represents the target threshold; Q2W: once every 2 weeks;
shadow area covers 5-95% simulated populations according to the estimated IIV from the PopPK model.

CONCLUSION

- This evaluation of the optimal givastomig dose was performed using clinical data from patients with solid tumors treated with givastomig, including patients with CLDN18.2-positive advanced GEC.
- Based on clinical safety and efficacy, the PKPD relationship and model evaluation, a dose range between 8-12 mg/kg Q2W was identified as the preferred dose range for heavily pre-treated GEC patients.
- A study investigating givastomig in combination with standard of care treatment in first-line metastatic GEC is ongoing.

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Reference:
Gao J, et al. *Journal for ImmunoTherapy of Cancer* 2023;11:e006704.