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Title: Using translational tumor growth inhibition modeling approach and population PK analysis to predict efficacious doses for KN026, a HER2 bispecific antibody

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Background: KN026 is a bispecific antibody simultaneously targeting the extracellular domains II and IV of the human HER2. It blocks both ligand-dependent and ligand-independent HER2 signaling pathway. The IgG1 Fc fragment of KN026 binds FcRγIIIa mediates potent ADCC and inhibits tumor cell proliferation. Preclinical results indicate that KN026 induces strong HER2 receptor internalization leading to better anti-tumor activity than trastuzumab and similar or better anti-tumor response than trastuzumab and pertuzumab in combination.

Aim: The goal of the present work is to predict efficacious doses for KN026 for the treatment of HER2-positive solid tumors using a translational tumor growth inhibition modeling approach based on tumor growth and KN026 exposure data from mouse, followed by a population PK analysis based on KN026 concentration data from patients in a first-in-human (FIH) clinical trial.

Methods: A tumor growth inhibition model was first developed to fit observed tumor volume time course data from NCI-N87 and Calu-3 xenografts following multiple doses of KN026. A translational tumor growth inhibition model was next developed by adjusting the tumor growth component to more realistically reflect tumor growth dynamics as reported in HER2-positive breast cancer patients. Model parameters intrinsic to KN026 efficacy (E_{max}, EC_{50}) were assumed constant across species. To determine the target concentration, simulations were performed for different initial tumor volumes and tumor doubling time in humans under different KN026 exposures. Next, intensively sampled pharmacokinetics data from 20 patients in a FIH trial of KN026 were used to develop the human population PK model. KN026 concentration-time profiles in humans were then simulated across a variety of candidate dosing regimens and compared with the projected target concentration from translational tumor growth inhibition modeling. Recommended efficacious doses and dosing schedules were predicted if steady state trough concentration from more than 90% simulated subjects achieve the target concentration.

Results: A tumor growth inhibition model (formula 1) adequately described the data from xenograft models. To build the translational tumor growth inhibition model (formula 2), a literature-documented tumor growth equation more relevant to the observed tumor growth dynamics in breast cancer patients was used to replace the growth component in formula 1 originally fitted to mouse data. Simulation results from the translational tumor growth inhibition model show that tumor stasis can be achieved at the KN026 trough concentration lower than 20 μg/mL. More aggressive tumors will take longer time to achieve tumor stasis under the same given concentration. A two-compartment PK model incorporating body weight as a covariate on both volume of distribution and clearance describes human PK data well. Efficacious steady state dose levels were predicted to be 20 mg/kg Q2W and 30 mg/kg Q3W. Loading doses with a higher frequency were predicted to have the advantage of maximizing initial tumor killing.

$$\frac{dTV(t)}{dt} = KG * \left(1 - \frac{TV(t)}{TG50 + TV(t)}\right) * TV(t) - KD * \frac{Conc}{KC50 + Conc} * TV(t) \quad (1)$$

$$\frac{dTV(t)}{dt} = \frac{\lambda_0 * (1 - \frac{TV(t)}{V_{max}})}{(1 + (\frac{\lambda_0}{\lambda_1} * TV(t))^{\psi})^{\frac{1}{\psi}}} * TV(t) - KD * \frac{Conc}{KC50 + Conc} * TV(t) \quad (2)$$

Conclusions: The use of the modeling and simulation approach to aid decision in drug development has become a popular tool. Here we present a translational PK-PD modeling framework incorporating preclinical tumor growth data and clinical PK data to inform dose selection strategy for KN026 in patients with HER2-positive solid tumors. Furthermore, simulation results suggest that loading doses with higher dosing frequency will likely be beneficial. These model predictions will be further validated by emerging PK and efficacy data from ongoing clinical trials of KN026.

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