Figure 1: Mechanism of action of KN026

![Mechanism of action of KN026](image1.png)

**ABSTRACT**

KN026 is a bispacific antibody simultaneously targeting the extracellular domains II and IV of the human HER2 (Figure 1). It blocks both ligand-dependent and ligand-independent HER2 signaling pathway. The IgG1 Fc fragment of KN026 binds FcRγIIa mediates potent ADCC and inhibits tumor cell proliferation. Clinical translation of efficacious dosing regimens in patients were then decided based on bispacific antibody could be challenging due to altered target engagement and difference between preclinical and clinical tumors. Here we present a joint translational and population PK and exposure-response (ER) modeling framework incorporating preclinical and clinical data from a bispacific antibody to predict recommended Phase 2 doses (RP2Ds). Recommended on the target concentrations from the translational model and population PK analysis in patients and further validated by preliminary human efficacy data.

**OBJECTIVES**

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 model based on tumor growth and sparse concentration data from mouse followed by a human population PK analysis.

**METHODS**

A saturable tumor growth component and an E_{max} drug effect model \(^{(1)}\) was fitted to data from NCI-N87 and Calu-3 xenograft models:

\[
\frac{dTV(t)}{dt} = KG \times \left(1 - \frac{TV(t)}{TV_{50} + TV(t)}\right) \times TV(t) - KD \times \frac{Conc}{KC50 + Conc} \times TV(t)
\]

A literature-documented tumor growth equation \(^{(2)}\) more relevant to the observed tumor growth dynamics in breast cancer patients was used to replace the tumor growth component in the developed tumor growth inhibition model for mice:

\[
\frac{dTV(t)}{dt} = \lambda_0 \times \left(1 - \frac{TV(t)}{V_m}\right) \times TV(t) - KD \times \frac{Conc}{RC_{50} + Conc} \times TV(t)
\]

Population pharmacokinetics and PK-tumor growth model (Figure 2) was fitted to human data to validate the finding from preclinical analysis.

**RESULTS**

Figure 2: PK-tumor growth model fitted for human data

![PK-tumor growth model fitted for human data](image2.png)

Simulations were next conducted to predict tumor size dynamics in humans under various KN026 regimens to inform dose selection.

Figure 3: Goodness of fit for NCI-N87 and Calu-3 xenograft model

![Goodness of fit for NCI-N87 and Calu-3 xenograft model](image3.png)

Figure 4: Goodness of fit for population pharmacokinetic analysis in humans

![Goodness of fit for population pharmacokinetic analysis in humans](image4.png)

**CONCLUSIONS**

The current analyses suggested that RP2Ds of KN026 in HER2-positive breast cancer patients were 20 mg/kg Q2W and 30 mg/kg Q3W. Loading doses were assessed to have the advantage of maximizing initial tumor killing.

1. Drug Metab. Dispos. 2013; 41: 727-734

Printed by CalleePosters. The poster may not be published, posted online, or used in commercial presentation without permission from Alphamab Oncology