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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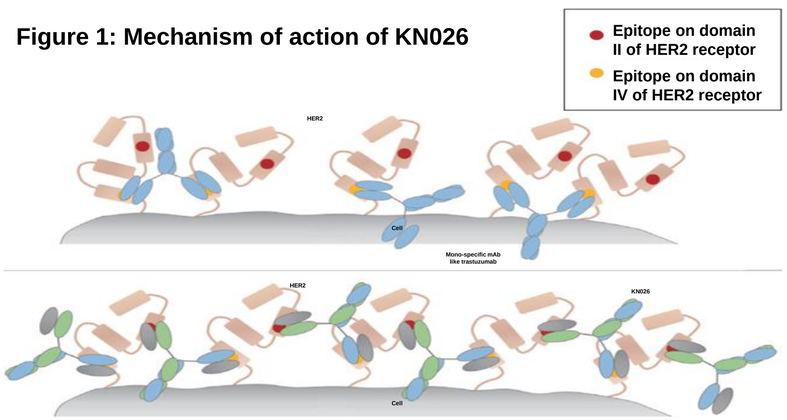
ABSTRACT

KN026 is a bispecific 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 FcRgIIIa mediates potent ADCC and inhibits tumor cell proliferation. Clinical translation of efficacious dosing regimens in patients were then decided basedbispecific 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 bispecific 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.

Figure 1: Mechanism of action of KN026



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

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

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

$$\frac{dTV(t)}{dt} = \frac{\lambda_0 \times \left(1 - \frac{TV(t)}{V_{max}}\right)}{\left(1 + \left(\frac{\lambda_0}{\lambda_1} \times TV(t)\right)^{\psi}\right)^{\frac{1}{\psi}}} \times TV(t) - KD \times \frac{Conc}{KC_{50} + Conc} \times TV(t)$$

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

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

$$\frac{d(tumor\ size)}{dt} = \underbrace{KL \cdot tumor\ size(t)}_{\text{Tumor growth}} - \underbrace{\{KD \cdot Exposure^{\gamma} \cdot Resistance(t)\} \cdot tumor\ size(t)}_{\text{Drug-induced tumor decay with resistance}}$$

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

RESULTS

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

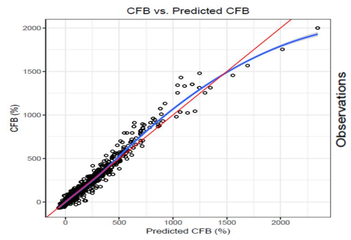
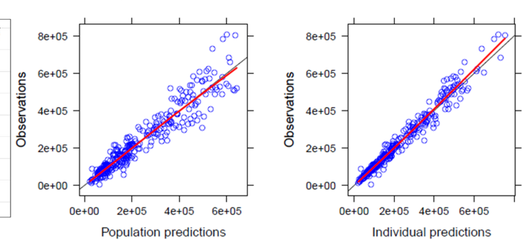


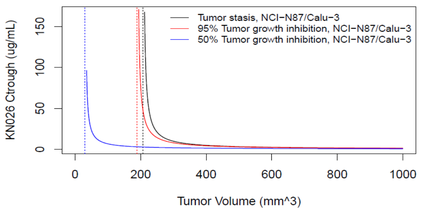
Figure 4: Goodness of fit for population pharmacokinetic analysis in humans



RESULTS

Figure 5: Target KN026 concentration depended on tumor volume

The analysis from translational model indicates that KN026 trough concentration of 20 μg/mL is needed for tumor stasis while 78.1 μg/mL is needed to achieve 95% tumor growth inhibition for lower tumor volume or fast growing tumors



Simulations for population PK and tumor dynamics in humans indicates that KN026 doses of 20 mg/kg Q2W or 30 mg/kg Q3W will be needed to achieve target concentration in more than 90% of simulated population and 30% tumor shrinkage in more than half of the simulated individuals. Loading doses will have the advantage of maximizing initial tumor killing

Figure 6: Concentration-time profile in candidate regimens (upper: 20 mg/kg Q2W; lower: 30 mg/kg Q3W)

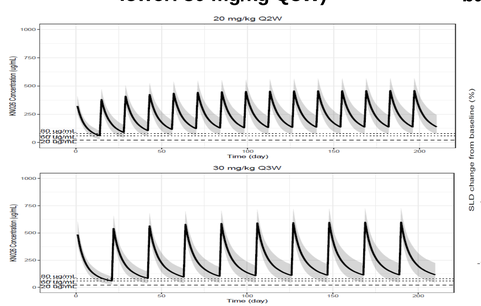
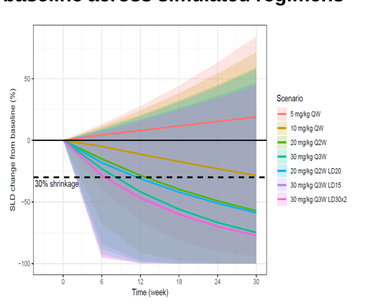


Figure 7: Comparison of predicted sum of longitudinal diameter change from baseline across simulated regimens



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

REFERENCES

1. Drug Metab. Dispos. 2013; 41: 727-734
2. JournalAAPS J. 2017; 19 (4): 1054-1070