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Development of a Pharmacokinetic-Tumor Target Engagement Model Using Nonclinical Data to Inform Phase 1 Dosing Scheme for a Novel Bispecific CD40-EpCAM Antibody, KK2269

Ragini Vuppugalla[1], Krina Mehta[1], Andrzej Kierzek[2], Birses Debir[2], Hidenori Takada[3], Maiko Adachi[3], Hiroyuki Ishida[3], Munetoshi Ando[3], Douglas Marsteller[1], Matthew Hruska[1]

[1] Kyowa Kirin, Inc., Princeton, NJ, USA; [2] Certara, Sheffield, UK; [3] Kyowa Kirin Co., Ltd., Tokyo, Japan

Background

- Several systemic CD40 agonists have been investigated as potential cancer immunotherapies. However, systemic toxicities may limit these antibodies from exerting their full activity.[1]
- KK2269 is a recombinant fully human immunoglobulin G subclass 4 bispecific antibody targeting EpCAM and CD40 receptors
- Nonclinical studies demonstrated that KK2269 exerts CD40 agonistic signals on dendritic cells (DCs) only when the antibody is cross-linked to EpCAM-expressing tumor cells. This approach potentially enables KK2269 to exert activity locally while avoiding systemic toxicities mediated by activation of CD40.

Objectives

- To develop a pharmacokinetic-tumor CD40 target engagement model (PK-TE) model using in vitro and in vivo nonclinical pharmacology and literature-based data of KK2269 in mice
- To predict the time profile of tumor CD40 TE and understand the relationship between the predicted tumor TE for CD40 and observed antitumor activity in the investigated dose range in mice
- To translate the PK-TE model to solid tumor patients and perform simulations to inform the monotherapy and combination therapy dosing scheme and regimen for the first-in-human (FIH) study

Methods

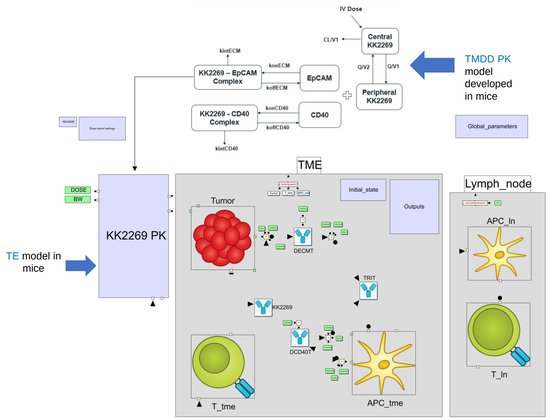
PK-TE Model Development in Tumor-Bearing Mice

- Serum PK of KK2269 from dose-ranging PK studies in mouse-EpCAM–expressing B16F10 tumor- and non-tumor–bearing humanized CD40 (hCD40) mice, antitumor efficacy of KK2269 in mouse-EpCAM–expressing B16F10 tumor-bearing hCD40 mice, in vitro Biacore binding affinities, and EpCAM and CD40 expression levels on relevant cells were used for model development
- The PK-TE model development comprises two components (**Figure 1**)
  - First, a two-compartment target-mediated drug disposition (TMDD) model was developed to characterize the serum PK in mouse-EpCAM–expressing B16F10 tumor- and non-tumor–bearing hCD40 mice after administration of a single IV dose of KK2269
  - Second, mice PK and antitumor activity data were modeled using a mechanistic KK2269 PK-TE model to understand the quantitative relationship among serum concentrations, tumor trimer concentrations, and TE for CD40 on DCs in tumors
  - The relationship between the predicted tumor TE for CD40 and observed antitumor activity in mice was used to inform dosing in humans
- Model development was performed using the naïve pooled approach with the first-order conditional estimation and interaction (FOCE-I) algorithm in NONMEM
- Model evaluation was conducted based on objective function values, goodness-of-fit plots, and visual predictive checks

PK-TE Model Translation to Humans

- The PK model developed in mice was used for recalibrating the primary PK parameters (CL, V1, Q, and V2) in the cynomolgus monkey (monkey). Species-specific binding-related parameters (kon and koff) were used for both CD40 and EpCAM.
- Then, the human primary PK parameters were projected from monkey PK by using allometric exponents of 0.85 and 1 for the CL and volume terms, respectively
- The structural PK model and all mechanistic parameters were kept the same as the mice model in monkeys and humans.
- A reduced version of the tumor growth and TE model was developed in humans by (1) removal of the lymph node compartment and T-cell components and (2) assumption of constant DC density in the tumor microenvironment (TME) in cancer patients based on data from the Immune Landscape of Cancer
- The model was translated to humans by incorporating literature-based longitudinal tumor size data from patients with NSCLC to calibrate tumor growth parameters in solid tumor patients. Three representative tumors, small, medium, and large at baseline, with different growth rates were selected for simulations.
- EpCAM expression on human tumors of interest was obtained from the literature

Figure 1. PK-TE Model in Tumor-Bearing Mice



APC, antigen-presenting cell; TE, target engagement; TMDD, target-mediated drug disposition.

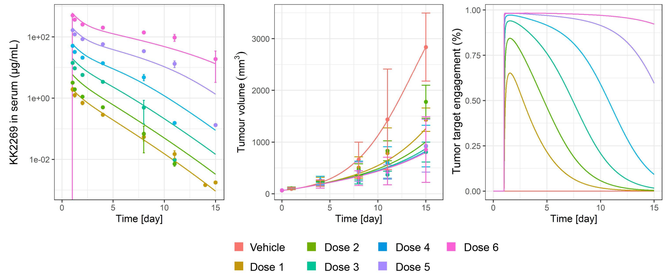
- KK2269 distribution in the TME was predicted using the tumor-disposition Krogh cylinder model[2]
- KK2269 is distributed to the TME and binds to either EpCAM or CD40 to form dimers that can subsequently bind to form trimers, which were used to estimate TE
  - TE = Trimer/total CD40
- TE leads to activation and migration of antigen-presenting cells (APCs) from TME to lymph node
- APCs in lymph recruit antigen-specific cytotoxic T-cells (CTL). CTLs migrate to TME and kill tumor
- Tumor death leads to release of antigens, which enhance killing in a positive feedback of the cancer immunity cycle
- Mice tumor growth parameters were estimated using the untreated tumor volume data
- Parameters for the dynamics of APCs and CTLs were obtained either from the literature or by fitting to in vitro experimental data

Results

PK-TE Model Development in Mice

- A two-compartment PK model with two full TMDD (CD40 and EpCAM) components well described the PK data in mice
- A reasonable agreement was observed between the observed serum PK and tumor growth data in mice and the corresponding data predicted by the PK-TE model (**Figure 2**)
  - The model predicted ~65% CD40 TE at tumor time to maximum concentration (T_{max}) at a dose that yielded modest antitumor activity in mice
  - Additionally, the model predicted a dose-dependent increase followed by saturation of the CD40 TE (~98% at tumor T_{max}) at higher doses
  - The model also predicted a bell-shaped dose response with a decrease in antitumor activity at >100 mg/kg doses in mice (not included in the figure)

Figure 2. PK and Antitumor Efficacy Data Were Described Well by the PK-TE Model in Mice



Points and error bars represent the observed mean and SD, respectively. Lines represent predictions. The TE (%) predicted by the PK-TE model at various doses in mice is shown in the third panel.
TE, target engagement.

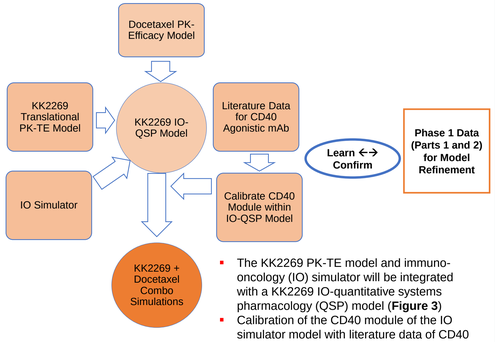
Translation of PK-TE Model to Humans

- This model was translated to solid tumor subjects to inform the Phase 1 doses of KK2269 for monotherapy and combination studies with docetaxel (NCT06266299)
  - The projected human PK were consistent with the PK of typical monoclonal antibodies (mAbs)
  - The human starting dose was projected to target 50% CD40 TE at tumor T_{max}
  - The efficacious dose was projected to target near maximal predicted TE (~97%) at tumor T_{max}, and TE was maintained above 50% for 75% of the dosing interval
    - Similar to the efficacious dose in mice
  - The dosing schemes for monotherapy and combination studies with docetaxel were selected based on the above projected starting and efficacious human doses
  - These doses sufficiently bracket the projected efficacious dose range in humans and ensure, thorough characterization of the dose response for safety, PK, and pharmacodynamic (PD) biomarkers of KK2269, that the dose selection in subsequent studies will be better informed

Future Directions

- Integration of the PK-TE model with an IO QSP model and use of Phase 1 data to inform Phase 2 dosing decisions

Figure 3. Integration of the KK2269 PK-TE and IO Simulator with KK2269-IO QSP Model



IO, immuno-oncology; mAb, monoclonal antibody; QSP, quantitative systems pharmacology; TE, target engagement.

- The KK2269 PK-TE model and immuno-oncology (IO) simulator will be integrated with a KK2269 IO-quantitative systems pharmacology (QSP) model (**Figure 3**)
- Calibration of the CD40 module of the IO simulator model with literature data of CD40 agonistic mAbs
- Docetaxel PK-efficacy model integration into the KK2269 IO-QSP model is ongoing
- Integration of the KK2269 IO-QSP model will be refined/updated with the Phase 1 data and used to inform KK2269 and docetaxel combination simulations to enable Phase 2 dosing decisions

Conclusions

- A mechanistic KK2269 PK-TE model has been developed using available in-house preclinical data and information from the literature
- A two-compartment PK model with separate TMDD components for EpCAM and CD40 well described the serum PK in mice and monkeys
- Human PK were projected from monkey PK (TMDD model) using allometric scaling
- The final KK2269 PK-TE model well described the PK and antitumor efficacy data in mice
- The PK-TE model was used to inform the dosing scheme and dosing regimen selection for a Phase 1 study in patients with solid tumors
- This selected dose range in humans allows a thorough evaluation of the safety and tolerability of KK2269
- An integrated KK2269 PK-TE–IO-QSP model is being developed and validated to inform Phase 2 doses/dosing regimen of KK2269 in combination with docetaxel
- QSP modeling and simulation-based approaches play a crucial role during early development of IO bispecific antibodies

References

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Disclosures

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