KN-052, a Novel PDL1/OX40 Bispecific Antibody, Exhibits Potent Antitumor Efficacy

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Abstract

KN052 is a recombinant PDL1/OX40 bispecific antibody which can block PDL1 and PD1/CD80 pathway and activate OX40 signal pathway at the same time. The In vivo anti-tumor activity of KN052 was further evaluated with MC38 and MCA205 syngeneic model in hPDL1/hOX40 humanized mouse. Dose-dependent tumor inhibition was observed in both models. KN052 showed good tolerance in cynomolgus monkeys under GLP condition. The HNSTD (highest non-severely toxic dose) of KN052 was determined as 30mg/kg in cynomolgus monkeys. DMPK of KN052 were also studied in mouse and monkey. These preclinical data demonstrated favorable PK and safety profile of KN052. Currently KN052 is in FIH phase I investigation and the initial read out is expected Q3 in 2023.

Introduction

Mechanism of KN052

KN052 is a recombinant PDL1/OX40 bispecific antibody which can block PDL1 and PD1/CD80 pathway and activate OX40 signal pathway at the same time. PDL1 inhibition can restore tumor immune surveillance. Meanwhile activation of OX40 may induce T-cell activation and amplification. On the other hand, activated Tregs tends to overexpress OX40 as well, thus KN052 may also induce ADCC dependent Treg depletion that in turn further boost immune activation.

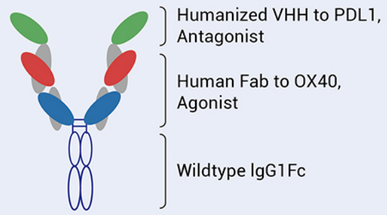

Figure 1 Structure of KN052

In vitro pharmacology

KN052 can bind to Human PDL1 -Chis and KD is 2.38E-09M (Fortebio BLI)
KN052 can bind to Human OX40-Chis and KD is 1.19E-08M (Fortebio BLI)

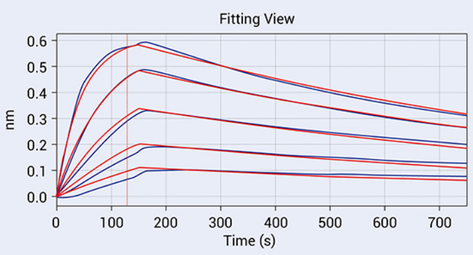

Figure 2 KN052 Binds to PDL1-Chis

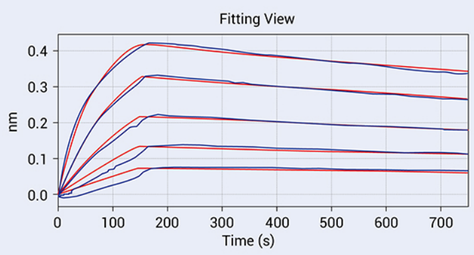

Figure 3 KN052 Binds to OX40

The binding EC50 of KN052 PDL1 (CHO) and OX 40(HEK 293) cell were 0.492nM and 9.158nM, respectively. KN052 displayed high affinity to both PDL1 and OX40.

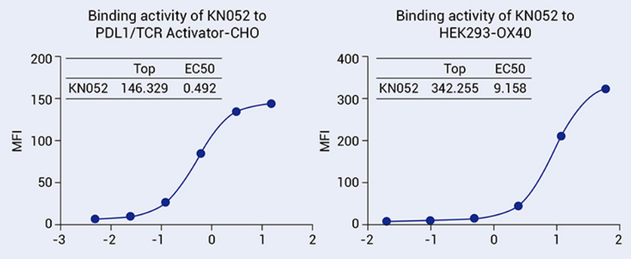

Figure 4 Binding activity of KN052 to PDL1 and OX40 in CHO and HEK 293 Cells

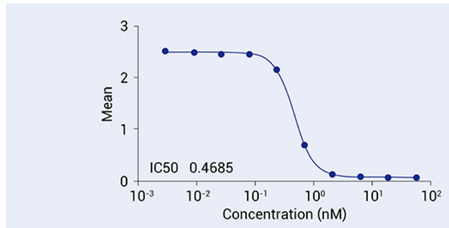

Figure 5 Binding inhibition of PD1 and PDL1 by KN052

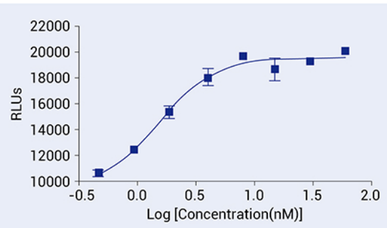

Figure 5 Activation of OX40 single pathway by KN052 on HEK293-OX40-NFκB-RE

The IC_{50} of KN052 was 0.4685 nM and KN052 showed high inhibitory.
The EC_{50} of KN052 was 1.598 nM and KN052 showed higher activation on OX40 single pathway.

In vivo Pharmacology

Tumor inhibition rate of KN052 at 3 mg/kg, and 15 mg/kg was 78.81%~98.58% and 64.19%~97.96%, respectively. The tumor volume of 5/6 mice was shrinked almost completely at 15 mg/kg group on day 21 and transplanted $3x10^5$ MC38 tumor cells to same mouse on the other side and the tumor did not grow until 23 days, which indicates that KN052 has long term antitumor efficacy.

Figure 6 Anti-tumor Efficacy of KN052 in MC38 animal model

Figure 7 Anti-tumor Efficacy of KN052 in MCA205 animal model

Safety Pharmacology

In a 6-week repeat-dose toxicity study in monkeys at 3 mg/kg、10 mg/kg and 30 mg/kg/dose. Compared to the control group or the pre-dose data, KN052 showed good safety profile at any dose levels except one monkey died, maybe caused by ADA induced hypersensitivity, not related KN052 at 10 mg/kg group.

Pharmacokinetics

Cynomolgus monkeys from three groups were administrated iv. with a single dose of 3.0 mg/kg, 10.0 mg/kg, 30.0 mg/kg of KN052 respectively. The first dose pharmacokinetics (GLP tox study) indicated that KN052 have general linear dynamic characteristics, and pharmacokinetics parameters showed no significant differences between males and females in the range 3-30 mg/kg.

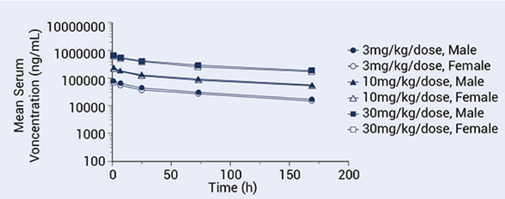

Figure 8 Concentration-Time Curve of KN052 in Cynomolgus Monkeys

Summary

1. KN052 displayed high affinity binding to human PDL1 and OX40 with KD of 2.38E-09M and 1.19E-08M.
2. The single dose pharmacokinetics study indicated that KN052 have general linear dynamic characteristics, and pharmacokinetics parameters shows no significant differences between males and females in the range 3-30 mg/kg.
3. The HNSTD of KN052 was determined at 30mg/kg in cynomolgus monkeys.
4. FIH clinical trial is undergoing in China and initial readout was expected within this year.