Preclinical evaluation of KD033, a human anti-PD-L1/IL-15 bispecific protein, in human PD-1/PD-L1 transgenic C57/B16 mice with PD-L1 positive and negative tumors

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Background

• KD033 is a clinical-stage bispecific fusion molecule consisting of a high-affinity anti-human-PD-L1 antibody and human IL-15.
• Previous preclinical studies with mouse anti-PD-L1/IL-15 (KD033 surrogate) have demonstrated that targeting IL-15 with anti-PD-L1 antibody resulted in increased efficacy, safety and maximal tolerated dose compared to administrations of free IL-15, with reduction of tumor growth in both PD-L1 positive and negative tumor models (1).
• The goal of the current study is to evaluate the efficacy of KD033, the human anti-PD-L1/IL-15, in a human PD-1/PD-L1 transgenic mouse model with human-PD-L1 positive and negative tumor cells.

Methods

KD033

antihuman PD-1 antibody
lgG1 LALA
IL15R-alpha
IL15

Human-PD-1/PD-L1 transgenic C57/Bl6 mice were infected with human-PD-L1 positive MC38 tumors. Tumors were reduced to <15 mm³ in 2 out of 6 hPDL1- MC38-bearing mice, tumors were reduced to <15 mm³ after treatment with KD033 and did not grow after re-inoculation with the same tumor without additional treatments.

In the peripheral blood: No significant difference in IFNγ/granzyme accumulations and cytotoxic cell levels between hPDL1+ and hPDL1- MC38-bearing mice after treatment with KD033

PBMC immunophenotyping by flow cytometry:

In tumors: Significant increase in CD8 T and NK cells infiltration into hPDL1- MC38 tumors (IHC)

Conclusions

• The efficacy of anti-PD-L1/IL-15 fusion protein KD033 was not limited to PD-L1 tumor expression
• Increases in CD8 and Th1 cells infiltration correlated with tumor growth inhibition in KD033 treated hPDL1+ MC38 tumors
• Increases in Th1, NK cells, macrophages and neutrophils in addition to CD8 and cytotoxic cells in KD033 treated hPDL1+ MC38 tumors correlated with increased tumor growth inhibition

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