**INCAGN1949, an Anti-OX40 Antibody With an Optimal Agonistic Profile and the Ability to Selectively Deplete Intratumor Regulatory T Cells**

**Abstract**

INCAGN1949 is a T cell costimulatory agonist that can mimic the immunostimulatory and durability of T cell immune responses. INCAGN1949 agonist antibodies have shown significant target antigenic activity in preclinical models, and can contribute to the activation of tumor-infiltrating lymphocytes (TILs) in patients with advanced solid tumors. Preclinical evaluations demonstrated that INCAGN1949 mediates potent immunomodulatory activity in vitro and in vivo, supporting the potential for selective depletion of intratumor regulatory T cells (Treg cell), which mediate the selective depletion of OX40high intratumor regulatory T cells. Immunohistochemistry and flow cytometry analyses demonstrated that INCAGN1949 was shown to maintain a sigmoidal dose response curve across a broad range of antibody concentrations. This suggests a selective depletion mechanism in a range of tumors.

**Mechanism 1: OX40 Forward Signaling in Activated T Cells**

**INCAGN1949 Demonstrates Increased Activation of Primary T Cells**

**INCAGN1949 Mediates Effective OX40 Xing Clustering**

**INCAGN1949 Enhances Primary T Cell Function Across a Broad Range of Concentrations**

**Mechanism 2: Intratumoral Depletion of T Cells**

**INCAGN1949 Is Well Tolerated In Vivo and Demonstrates Immunomodulatory Activity in Cynomolgus Monkeys**

**Summary**

INCAGN1949 is an effective agonist of the OX40 pathway and has confirmed immunomodulatory activity in vivo. INCAGN1949 is well tolerated in vivo and demonstrates immunomodulatory activity in cynomolgus monkeys.

**Materials and Methods**

**Results**

**Conclusions**

**References**

5. IFNγ secretion by human primary T cells in the presence of superantigen and INCAGN1949 as compared to other anti-OX40 antibody variants (Ab1-Ab10) or isotype control. Bottom: The effect of INCAGN1949 on IL-2 secretion by human primary T cells in the presence of superantigen and INCAGN1949 as compared to other anti-OX40 antibody variants (Ab1-Ab10) or isotype control.

**Figure Legends**

A. Anti-OX40 antibody variants: A. Anti-OX40 antibody variants (Ab1-Ab10) or isotype control as assessed by IFNγ secretion by human primary T cells in the presence of superantigen. Bottom: The effect of INCAGN1949 on IL-2 secretion by human primary T cells in the presence of superantigen and INCAGN1949 as compared to other anti-OX40 antibody variants (Ab1-Ab10) or isotype control.

B. OX40 Xing clustering: OX40 Xing clustering in human CD8+ T cells co-cultured with OX40+ tumor cells in the presence of superantigen and INCAGN1949. Bottom: The effect of INCAGN1949 on OX40 Xing clustering in human CD8+ T cells co-cultured with OX40+ tumor cells in the presence of superantigen.

C. Intratumoral depletion: Intratumoral depletion of tumor-infiltrating lymphocytes (TILs) in a murine tumor model.

D. Intratumoral depletion: Intratumoral depletion of tumor-infiltrating lymphocytes (TILs) in a murine tumor model.

E. Serum cytokines: Serum cytokines in cynomolgus monkeys treated with INCAGN1949.


G. Time-dependent antibody response: Time-dependent antibody response in cynomolgus monkeys.

H. Cytokine levels: Cytokine levels in cynomolgus monkeys treated with INCAGN1949.