INBRX-106: A NOVEL HEXAVALENT ANTI-OX40 AGONIST FOR THE TREATMENT OF SOLID TUMORS

Emily Rowell*, Heather Kinkead, Elisabeth Torretti, Bryan Becklund, Florian Sulzmaier, William Crago, Kyle Jones, John Timmer, Quinn Deveraux, Brendan Eckelman, Analeah Heidt. *Inhibrx, Inc., La Jolla, CA, USA*

Background OX40 is a co-stimulatory receptor enriched on immune cells in the tumor microenvironment. OX40 agonism promotes anti-tumor responses, both singly and in combination with checkpoint inhibitors. The cognate OX40 ligand, OX40L, is a trimeric protein that activates robust signaling through clustering. INBRX-106 is a novel hexavalent OX40 agonist that has been rationally designed to optimize target clustering and provide superior agonism to previously explored bivalent entities, leading to more potent anti-tumor activity.

Methods INBRX-106 is a homodimer, each half comprising three identical humanized, camelid single-domain antibody binding domains targeting OX40 linked end-to-end, and fused to an effector-enabled human IgG1 constant domain (Fc). Due to lack of rodent cross-reactivity, a valency, affinity and activity-matched murine surrogate, Hex-C04, was generated for the purpose of preclinical modeling. Hex-C04 contains an mIgG2a effector enabled Fc, the mouse isotype most analogous to the activity of human IgG1. The activity and potency of INBRX-106 and Hex-C04 were evaluated in functional in vitro T-cell assays, and the anti-tumor efficacy of Hex-C04 was evaluated alone or in combination with PD-1 blockade across a number of syngeneic tumor models.

Results INBRX-106 binds specifically to OX40 with a sub nanomolar apparent affinity, without blocking the binding of its ligand OX40L. In vitro, cross-linking by INBRX-106 rapidly induces loss of OX40 surface expression in addition to driving receptor signaling. In primary T-cell assays, INBRX-106 is more potent than a bivalent comparator antibody, inducing greater upregulation of activation markers, cytokine production and proliferation. This costimulatory activity exhibits a bell-shaped dose-response curve, with maximal activity occurring at receptor occupancies of 30–100%. In vivo, tumor growth control by Hex-C04 also follows a bell-shaped dose response curve. Rapid loss of OX40 is observed in vivo as well, with both the degree and duration of OX40 loss dependent on Cmax and exposure. Hex-C04 demonstrated strong single-agent activity across a variety of preclinical tumor models including models that do not respond to a PD-1/PD-L1 checkpoint inhibitor, and this activity was improved in combination with a PD-1 blocking antibody.

Conclusions Preclinically, INBRX-106 significantly outperforms bivalent antibodies in co-stimulatory capacity and anti-tumor activity. On the weight of this data, Inhibrx Inc. has initiated a first-in-human Phase 1 trial of INBRX-106 as a single agent or in combination with Keytruda® (pembrolizumab). The complex relationship between dose, OX40 target modulation and activity indicate the importance of integrating preclinical data sets with emerging clinical data to make informed decisions regarding INBRX-106 dose and schedule.

Trial Registration NCT04198766

Ethics Approval The care and use of all animals were reviewed and approved by the IACUC committees of Explora BioLabs and Molecular Diagnostic Services and conducted in accordance with AAALAC regulations.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.856>