12 KEY PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS THAT CORRELATE WITH THE ANTI-TUMOR ACTIVITY OF A BISPECIFIC PD-L1 CONDITIONAL 4–1BB AGONIST

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Background 4-1BB is a costimulatory molecule that is predominantly expressed on activated CD8+ T cells and is induced upon T cell receptor mediated activation.[1] Within the tumor microenvironment, 4-1BB-expressing T cells are enriched for anti-tumor reactivity [2]; thus, 4-1BB agonism provides an opportunity for selective activation of anti-cancer immune effector cells. Early efforts to develop 4-1BB targeted agonists were limited by poor tolerability (Urelumab) or insufficient efficacy (Utomilumab). INBRX-105 is a bispecific antibody that aims to overcome these prior limitations through induction of 4-1BB agonism specifically at sites of PD-L1 expression. Preclinical models have defined pharmacokinetic (PK) and pharmacodynamic (PD) parameters that are correlated with maximal INBRX-105-specific immune responses and anti-tumor activity.

Methods INBRX-105 was generated by linking 2 humanized single-domain antibody binding domains targeting human PD-L1 and 4-1BB, fused to an effector-silenced human IgG1 constant domain (Fc). A bispecific, anti-mouse PD-L1x4-1BB surrogate molecule, INBRX-105-a, was engineered to match the function and target affinities of INBRX-105. This surrogate was tested for in vivo activity in non-tumor-bearing and MC-38 tumor-bearing animals, including measurements of serum exposure, PD-L1 receptor occupancy, immunophenotyping of peripheral blood and intra-tumoral immune cell populations.

Results INBRX-105-a was shown to be an appropriate anti-mouse surrogate for INBRX-105 in a variety of in vitro assays. Comparable potencies of activity were demonstrated in a PD-L1 dependent 4-1BB reporter assay, as well as in cytokine induction through co-stimulation of primary T cells. In vivo, INBRX-105-a showed robust induction of mouse CD8+ T effector memory populations (CD8+ TEM) at dose levels that achieved $\geq$ 96 hours of PD-L1 receptor occupancy. A serum concentration of 800 ng/mL at 96 hours, achieved by a dose of 2 mg/kg in mice, was sufficient to provide the requisite occupancy for maximal pharmacodynamics. CD8+ TEM responses were dependent on 4-1BB agonism and were more efficiently induced by PD-L1 localization, as opposed to 4-1BB multivalent clustering alone. Optimal tumor responses, including complete responses and demonstration of immunological memory, were observed when maximal 4-1BB driven pharmacodynamics were paired with extended PD-1/PD-L1 pathway blockade, provided either by an orthogonal molecule or increased exposure of INBRX-105.

Conclusions Preclinical receptor occupancy and pharmacokinetic determinations have defined a dose of INBRX-105-like activity that induces maximal pharmacodynamics. Additional PD-1 checkpoint inhibition does not change the pharmacodynamic profile of INBRX-105-a, but does allow for optimal efficacy. INBRX-105 is currently being evaluated in patients with advanced solid tumors in a first-in-human trial (NCT03809624).

Trial Registration INBRX-105 is currently being evaluated in patients with advanced solid tumors in a first-in-human trial (NCT03809624).

REFERENCES

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Ethics Approval The care and use of all animals were reviewed and approved by Explora BioLabs' IACUC # SP17-010-013 and conducted in accordance with AAALAC regulations.

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