722 INBRX-121 IS AN NKP46-TARGETED DETUNED IL-2 WITH ANTITUMOR ACTIVITY AS A MONOTHERAPY OR IN COMBINATION WITH MULTIPLE CANCER IMMUNOTHERAPY MODALITIES

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Background Natural Killer (NK) cells play a pivotal role in cancer immunosurveillance due to their potent cytolytic activity and NK cell-centric therapies have emerged as safer alternatives to targeting T cells.[1 2] Interleukin 2 (IL-2) drives NK cell expansion and activity, but its therapeutic utility is limited by rapid clearance, expansion of immunosuppressive regulatory T cells, and by severe dose-limiting toxicities.[3] INBRX-121 overcomes these liabilities through specific targeting of an affinity-detuned IL-2 variant to cells expressing NKp46.

Methods An IL-2 variant was engineered to eliminate binding to CD25 and to have attenuated affinity for CD122. This detuned cytokine was fused to a high-affinity single-domain antibody targeting NKp46 to generate INBRX-121. The ability of INBRX-121 to target IL-2-like signaling specifically to NKp46-expressing cells was evaluated in vitro using human lymphocytes by measuring STAT5 signaling and cytotoxic activity in tumor cell co-cultures. Characterization of the pharmacokinetic/pharmacodynamic relationship of INBRX-121 was completed in non-human primates across escalating dose levels, while anti-tumor activity as a monotherapy and in combination with Rituximab or PD-1 checkpoint blockade was tested in Raji xenografts and syngeneic CT-26 mouse models, respectively.

Results INBRX-121 induces a STAT5 signal equal to that of wild-type IL-2 in human lymphocytes but shows an NK cell-centric activity profile. Cells targeted by INBRX-121 have increased proliferative capacity and improved cytotoxicity in antibody-dependent and -independent tumor cell killing assays. INBRX-121 shows prolonged pharmacokinetic exposure in vivo and is well-tolerated in mice and cynomolgus monkeys. The NKp46-specific IL-2 stimulus in these models results in a robust, dose-dependent NK cell expansion. As predicted by its in vitro activity, INBRX-121 also enhances the cytotoxic capacity of NK cells in vivo measured via elevated intracellular levels of Granzyme B. In a Raji xenograft model, INBRX-121 slows tumor growth as a single agent and synergizes with Rituximab to induce complete tumor regression. Similarly, co-treatment with INBRX-121 improves the incomplete suppression of CT-26 tumor growth by a PD-1 blocking antibody to yield complete responses that show immunological memory upon re-challenge.

Conclusions INBRX-121 offers a unique approach to overcoming the limitations of current IL-2 therapeutics. NKp46-targeting of a detuned IL-2 variant helps to avoid IL-2-mediated toxicity while enhancing the antitumor activities of NK cells. Through its novel therapeutic concept INBRX-121 provides a promising treatment option for multiple cancer indications both as a monotherapy and in combination with a variety of frontline agents.

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Ethics Approval All animal studies were conducted in accordance with AAALAC regulations and were approved by the IACUC for Explora BioLabs (#SP17-010-013) and BTS Research (20-015 Enrollment 05).

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