WTX-613, A CONDITIONALLY ACTIVATED IFNα INDUKINE™ MOLECULE, INDUCES ANTI-TUMOR IMMUNE RESPONSES RESULTING IN STRONG TUMOR GROWTH CONTROL IN SYNGENEIC MOUSE TUMOR MODELS

Ethika Tyagi*, Heather Brodkin, Josue Canales, Dan Hicklin, Nesreen Ismail, Kristin Morris, Christopher Nirschl, Andres Salmeron, Cindy Sidel-Dugan, Philipp Steiner, Zoe Steuert, Jenna Sullivan, William Winston. Werewolf Therapeutics, Cambridge, MA, United States

Background Interferon α (IFNα) was the first cytokine clinically tested as a cancer therapy. IFNα is a member of the type-I IFN family and activates immune responses either directly by engaging IFNα receptors (IFNAR) ubiquitously expressed on immune cells or indirectly by inducing chemokines that attract myeloid and lymphoid cells to the tumor site. High dose IFNα therapy was approved for melanoma, lymphoma, and leukemia but its use is limited by systemic toxicity and modest efficacy.

Methods WTX-613 is a novel systemically delivered IFNα2b pro-drug identified using the Predator™ discovery platform. The inducible WTX-613 INDUKINE™ molecule is designed to deliver wild-type IFNα2b in the tumor microenvironment to reduce systemic toxicity. WTX-613 has two identical half-life extension (HLE) domains tethered to IFNα2b via a tumor protease-sensitive linker. The HLE domain supports less frequent systemic administration but importantly also prevents binding of WTX-613 to IFNAR due to steric hindrance until removal of the HLE domains by tumor proteases.

Results WTX-613 was selected as a lead molecule due to its improved in vitro profile. Since human IFNα is not functional in the mouse, a surrogate WTX-613 molecule was created consisting of mouse IFNα1 to explore anti-tumor responses in mouse syngeneic tumor models. Intraperitoneal (i.p.) administration of the WTX-613 surrogate resulted in anti-tumor responses in the more immunogenic MC38 colon model which was well tolerated by the mice. Furthermore, less immunogenic tumor models such as B16F10 melanoma and EMT6 breast carcinoma, which are generally less responsive to I/O therapy, also responded with similar anti-tumor activity. Importantly, wild-type mouse IFNα1 was only active in mouse models during the dosing period, and tumors grew back once treatment was stopped. However, the WTX-613 surrogate INDUKINE™ molecule had long lasting anti-tumor activity when dosed at equimolar amounts compared to the native IFNα during the dosing period. The WTX-613 surrogate strongly activated NK and CD8+ cell responses and induced APC and effector cell markers in MC38 tumors. Specifically, the WTX-613 surrogate was better than native IFNα1 in inducing CD8+, NK, and DC cells.

Conclusions Preclinical data obtained so far support the continued development of this innovative and differentiated engineered IFNα therapy and progression into clinical trials.

Ethics Approval All mouse in vivo work was performed in accordance with current regulations and standards of the U.S. Department of Agriculture and the NIH at Charles River Laboratories (Morrisville, NC and Worcester, MA).

http://dx.doi.org/10.1136/jitc-2021-SITC2021.723