715 WTX-330 IS AN IL-12 PRO-DRUG THAT IS CONDITIONALLY ACTIVATED WITHIN THE TUMOR MICROENVIRONMENT AND INDUCES REGRESSIONS IN MOUSE TUMOR MODELS

[1]Kristin Morris*, [1]Heather Brodkin, [1]Daniel Hicklin, [1]Nesreen Ismail, [1]Christopher Nirschl, [1]Andres Salmeron, [1]Philipp Steiner, [1]Zoe Steuert, [2]Jenna Sullivan, [1]William Winston. *[1]Werewolf Therapeutics, Cambridge, MA, United States; [2]Werewolftx.com, Cambridge, MA, United States*

Background Systemic administration of proinflammatory cytokines is a promising approach to treat cancer. However, poor pharmacokinetic properties and dose-limiting toxicities after systemic administration of cytokines such as interleukin 12 (IL-12) renders this strategy impractical. WTX-330 is a novel therapy identified using the Predator™ discovery platform that is designed to selectively deliver active wild-type IL-12 to the tumor microenvironment.

Methods WTX-330 is an inducible polypeptide (INDUKINE™ molecule) that consists of wild-type IL-12 tethered to a high affinity antibody blockade domain and a half-life extension (HLE) domain via tumor protease-sensitive linkers.

Results WTX-330 shows favorable inducible activity in vitro. WTX-330 incubated ex vivo with various primary human tumors led to the release of active IL-12, while WTX-330 was stable in human serum and normal tissues. Intraperitoneal (i.p.) administration of mouse WTX-330 led to complete tumor regression in multiple syngeneic tumor models. Importantly, equimolar amounts of wild-type IL-12, while active, was not tolerated by the mice compared to the IL-12 INDUKINE™ molecule. Mouse surrogate WTX-330 led to increased activation and frequencies of cross-presenting dendritic cells, NK cells and tumor specific CD8 T cells in B16F10 tumors. Moreover, mouse WTX-330, but not wild type IL-12, led to increased T cell activation specifically within B16F10 tumors as compared to the periphery. WTX-330 was well tolerated in non-human primates at different dose levels and schedules with exposure levels which exceeded the levels needed for anti-tumor activity in mice. In addition, there was low systemic exposure of IL-12 in the plasma after dosing with WTX-330 as compared to levels observed after treatment with wild-type IL-12.

Conclusions Pharmacological and translational data obtained so far clearly support continued preclinical development with the goal of moving this innovative and differentiated engineered IL-12 therapy into human clinical testing.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.715