1074 PK/RO MODELING OF WTX-124, A TUMOR-ACTIVATED IL-2 PRODRUG, HIGHLIGHTS THE POTENTIAL FOR A SUBSTANTIALLY IMPROVED THERAPEUTIC INDEX COMPARED TO OTHER IL-2 MOLECULES

Kulandayan K Subramanian*, Sameer Chopra, Kristin Morris, Christopher J Nirschl, Celesztina Domonkos, Kyriakos Economides, Andres Salmeron, Cynthia Seidel-Dugan, Randi Isaacs, Daniel J Hicklin. *Werewolf Therapeutics, Watertown, MA, USA*

Background Though high dose recombinant human IL-2 (rhIL-2) is an effective immunotherapy for certain patients with metastatic melanoma and renal cell carcinoma, the clinical benefits are counterbalanced by life-threatening toxicities. To address this challenge, many novel IL-2 molecules that do not bind to the alpha subunit of the high-affinity IL-2 receptor ('non-alpha' IL-2s) have entered the clinic. However, minimal monotherapy antitumor activity has been observed at doses tolerated by patients. Conditional activation is a novel engineering strategy for toxic drug molecules that could provide an alternative approach to improve the tolerability of rhIL-2 without compromising its activity. Here we used PK/RO modeling to investigate the potential for conditional activation to further improve the therapeutic index of IL-2.

Methods We developed a pharmacokinetic (PK) model to directly compare peripheral and tumor lymphocyte IL-2 receptor occupancy (RO) for rhIL-2, non-alpha IL-2, and IL-2 prodrugs that are selectively activated in the tumor microenvironment. Conditional activation was simulated for both wild-type and non-alpha IL-2. The PK model was trained on prodrug and free IL-2 PK data in plasma and tumor from tumor-bearing mice dosed with WTX-124, a novel tumor-activated wild-type IL-2 prodrug. The same PK dataset was used to model both non-alpha IL-2 and tumor-activated non-alpha IL-2. The PK models were then used to simulate RO on peripheral lymphocytes and on tumor-infiltrating CD8+ T cells (TILs), based on published models and known affinities for IL-2 receptors.

Results The model predicts that both tumor-activated IL-2 molecules produce markedly lower RO on peripheral lymphocytes than rhIL-2 and non-alpha IL-2. Conversely, a tumor-activated wild-type IL-2 molecule produces high RO on TILs. Comparable RO on TILs can be produced with a tumor-activated non-alpha IL-2, but only at substantially higher doses. Both rhIL-2 and non-alpha IL-2 can also achieve high RO on TILs but only when peripheral lymphocyte RO is high, consistent with the observed toxicity in patients.

Conclusions PK/RO modeling reveals that tumor-activated IL-2 molecules are far more likely than non-alpha molecules to improve the therapeutic index for rhIL-2 by maximizing RO on TILs and minimizing RO on peripheral lymphocytes. A tumor-activated wild-type IL-2 molecule (WTX-124) is predicted to achieve higher RO on TILs than comparable doses of a tumor-activated non-alpha IL-2 molecule. The models also show that substantially higher doses of the tumor-activated non-alpha IL-2 molecule are required to attain the same RO on TILs as WTX-124. A first-in-human clinical trial of WTX-124 is presently underway (NCT05479812).

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1074