

A PHASE 1/1B STUDY OF THE TUMOR-ACTIVATED IL-2 PRODRUG WTX-124 ALONE OR IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH IMMUNOTHERAPY-SENSITIVE LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

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Background High-dose IL-2 is an FDA-approved immunotherapy that produces durable remissions in patients with melanoma and renal cell carcinoma (RCC) but is hampered by toxicities arising from peripheral immune activation. To address this challenge, we engineered an IL-2 INDUKINE™ molecule (WTX-124) to be administered systemically but selectively activated in the tumor microenvironment (TME) by dysregulated proteases. Distinct from other next-generation IL-2 molecules, WTX-124 is designed to release a fully potent, wild-type cytokine in tumors. In preclinical models, the released IL-2 causes expansion and activation of tumor-infiltrating CD8+ T cells and generates substantial antitumor activity.¹

Methods This first-in-human trial is investigating the safety, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and antitumor activity of WTX-124 administered as a monotherapy or in combination with pembrolizumab (anti-PD-1) to adult patients with relapsed/refractory solid tumors for which checkpoint inhibitors are standard of care. Dose escalation utilizes a mTPI-2 study design to help identify the recommended dose of WTX-124 administered intravenously (IV) every two weeks (Q2W) as a monotherapy or in combination with pembrolizumab 400 mg IV every six weeks. In dose expansion, patients with advanced or metastatic cutaneous melanoma or RCC will receive either WTX-124 monotherapy or combination therapy in one of four arms (n=20 patients/arm). Pre- and on-treatment tumor biopsies and blood samples are being used to investigate PK and multiple immune parameters.

Results As of June 22, 2023, 11 patients have been treated with WTX-124 in three monotherapy dose escalation cohorts (1, 3, and 6 mg). The most common tumor types include non-small cell lung cancer (n=4), cutaneous melanoma (n=3), and RCC (n=2). No DLTs have been reported. Of 19 treatment-related AEs (TRAEs) occurring in 5 patients, 26% were Grade 2 and the remainder Grade 1. The most common TRAEs were fatigue and arthralgias, each occurring in three patients. No patient developed capillary leak syndrome of any grade. WTX-124 exhibits approximately dose-proportional PK with very low levels of active IL-2 (<1% of prodrug). Tumor biopsies are being analyzed for changes in the frequency and functionality of tumor-infiltrating lymphocytes, PD-L1 expression, and immune cell gene expression. Updated data on safety, PK, biomarkers, and preliminary antitumor activity will be presented.

Conclusions The novel INDUKINE™ molecule WTX-124 is well-tolerated at doses ≤6 mg IV Q2W. PK data show sustained prodrug exposure in plasma with low levels of active IL-2. The data demonstrate the potential of WTX-124 to

safely deliver a fully potent, wild-type IL-2 to the TME in patients with solid tumors.

Trial Registration NCT05479812

REFERENCE

1. Nirschl CJ, Brodtkin HR, Hicklin DJ, *et al.* Discovery of a conditionally activated IL-2 that promotes antitumor immunity and induces tumor regression. *Cancer Immunol Res.* 2022 May 3;10(5):581–596.

Ethics Approval The study protocol was approved by the institutional review (ethics) board at each participating clinical site. These include: HonorHealth (WIRB, #IRB-22-0043); Emory (WIRB, #STUDY00004612); NEXT Oncology (Salus IRB, #NXSAT21.151); Indiana University (IRB, #15531); and Providence Cancer Institute (PSJH IRB, #STUDY2022000507). All patients provided written informed consent prior to taking part in the study.

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