Werewolf THERAPEUTICS

Creating Powerful Proinflammatory Cancer Therapies

Trial in Progress

A first-in-human, phase 1, multicenter dose escalation and dose expansion study of WTX-330 in adult patients with advanced or metastatic solid tumors or non-Hodgkin lymphoma

Ildefonso Ismael Rodriguez-Rivera[1], Justin C. Moser[2], Mateusz Opyrchal[3], Aparna R. Parikh[4], Saero Park[5], Marissa Bruno[5], Paul Windt[5], Kulandayan K. Subramanian[5], Sameer S. Chopra[5], Randi Isaacs[5]. NEXT Oncology, San Antonio, TX[1], HonorHealth Research and Innovation Institute, Scottsdale, AZ[2], Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN[3], Massachusetts General Hospital Cancer Center, Boston, MA[4], Werewolf Therapeutics Inc., Watertown, MA[5]

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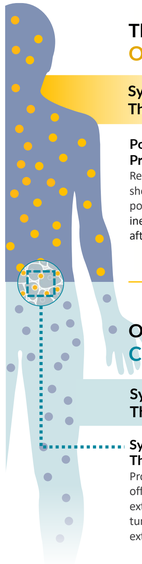
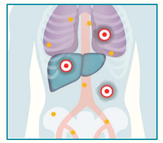
OUR APPROACH: CONDITIONALLY ACTIVATED IMMUNOTHERAPY



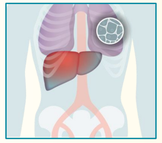
The Challenge:
Off-Tumor Cytokine Toxicity Limits Therapeutic Index

Systemic Cytokine Therapy

Poor Pharmaceutical Properties
Recombinant cytokines have short half-lives, resulting in poor tumor exposure and inefficient immune activation after IV dosing



High Toxicity
High systemic cytokine exposure causes serious toxicities

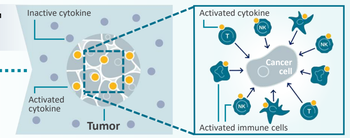


Limited Efficacy
Low tumor exposure inefficiently activates antitumor immunity

Our Solution:
Conditionally Activated Immunotherapy

Systemic INDUKINE™ Therapy

Systemically Delivered Therapy
Prodrug design reduces off-tumor effects; half-life extension confers high tumor exposure while also extending the dosing interval



Targeted Intratumoral Delivery
Biologically relevant exposure in the tumor microenvironment

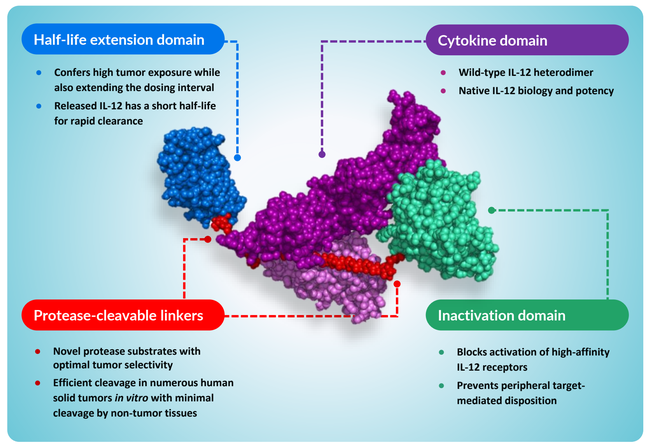
On-Target Immune Activation
Wild type cytokines elicit complete biology with optimal potency

BACKGROUND
Development of an IL-12 prodrug for cancer immunotherapy

- An unmet medical need exists for:
  - Patients who are non-responsive to or who progress on SOC immune checkpoint inhibitors (ICIs)
  - Patients with tumor types for which ICIs provide no clinical benefit
- IL-12 could help to address this need by promoting increased:
  - Proliferation and cytotoxic activity of effector T cells and NK cells
  - T helper type 1 (Th1) responses
  - Antigen-presenting cell (APC) activity
  - IFNγ release (which leverages many additional antitumor mechanisms)
- In numerous immunocompetent mouse models, IL-12 has robust T-cell dependent antitumor activity and induces immune memory formation
- Unfortunately, recombinant human IL-12 caused significant toxicities and deaths when previously investigated as a systemic anticancer therapy in patients

A reliable strategy to systemically deliver IL-12 with tumor-restricted activity would represent a major advance in the field of cytokine therapy and could address a major unmet medical need

WTX-330
An IL-12 INDUKINE™ molecule to address the limitations of recombinant IL-12



WTX-330x2101 FIRST-IN-HUMAN STUDY DESIGN
Investigating WTX-330 as a monotherapy

Dose Escalation (~35 patients)

- BLRM study design with overdose control
- Dosing based on body weight (mg/kg)
- Administered IV Q2W (28-day cycle)
- DLT period = 28 days
- Starting dose determined based on an integrative analysis of GLP toxicity data, preclinical efficacy data, and published literature on rhIL-12 (IV, SC)

MTD/RDE

Dose Expansion (N~40 patients)

- Two basket expansion arms (A, B) to open and enroll patients in parallel
- Arms span multiple solid tumor indications and NHL
- Evaluation of activity in patients with intrinsic and/or acquired resistance to immune checkpoint inhibitors
- Results may guide additional expansion arm(s) in specific indications

STUDY OBJECTIVES and ENDPOINTS

	OBJECTIVES	ENDPOINTS
PRIMARY	• Evaluate safety and tolerability • Determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) • Evaluate antitumor activity (escalation and expansion cohorts)	• Incidence of treatment emergent adverse events (TEAEs) • Incidence of dose-limiting toxicities (DLTs) • Changes in clinical safety laboratory parameters • ORR and DOR (RECIST 1.1) and iORR (iRECIST) • Response by Lugano criteria (NHL only)
SECONDARY	• Characterize PK profile • Evaluate changes in immunological biomarkers (blood, tumor) • Assess immunogenicity • Evaluate antitumor activity and overall survival (expansion cohorts)	• Plasma [WTX-330] and [free IL-12]; calculated PK parameters • Changes in immune cell subsets (blood); lymphocyte density and/or activation state (tumor) • Antidrug antibody (ADA) occurrence • ORR, DOR, DCR, and PFS (by RECIST 1.1, iRECIST, and Lugano criteria for NHL); overall survival
EXPLORATORY	• Evaluate pharmacodynamics • Investigate immunological biomarkers (blood, tumor) that may correlate with treatment outcome • Assess tumor biopsies for potential biomarkers of target engagement and immune activation	• Cytokine levels • Peripheral lymphocyte subsets • Intratumoral immune cell frequency • Tumor microenvironment gene expression profile • Prodrug activation in tumor biopsy *in vitro*

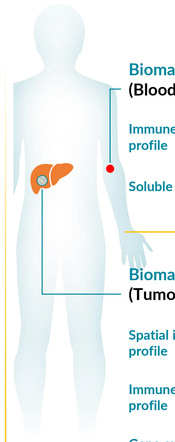
PATIENT POPULATIONS

	PATIENT POPULATION	EXAMPLES	KEY EXCEPTIONS
DOSE ESCALATION	• Relapsed/refractory (r/r) advanced or metastatic solid tumors	• Many	• Primary CNS malignancies • Castrate-resistant prostate cancer (CRPC) • *Non-Hodgkin lymphoma (NHL)*
DOSE EXPANSION ARM A	• r/r solid tumors for which ICIs are approved • Primary* or secondary resistance# to ICI-containing regimen	• Cutaneous melanoma • NSCLC • HNSCC • MSI-H tumors	• Patients who d/c anti-PD-(L)1 therapy due to toxicity or for other reasons besides progression
DOSE EXPANSION ARM B	• r/r solid tumors for which ICIs are **NOT** approved • Non-Hodgkin Lymphoma (NHL)	• MSS colorectal • CRPC • NHL: DLBCL, follicular	• Primary CNS malignancies • Patients who received anti-PD-(L)1 in a clinical trial or off-label

*Primary ICI resistance: Disease progression or SD < 6 months as the best response after ≥ 6 weeks of treatment with a SOC PD-(L)1 inhibitor regimen.

#Secondary ICI resistance: Disease progression ≥ 6 months after initiation of a SOC PD-(L)1 inhibitor regimen in patients who received clinical benefit (e.g., CR, PR, or SD > 6 months).

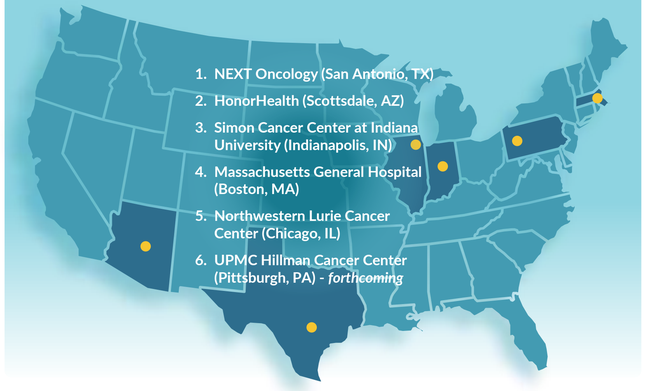
TRANSLATIONAL BIOMARKER STRATEGY
Interrogating antitumor immune activation in patients



Biomarker (Blood)	Key question addressed	Method
Immune cell profile	Does WTX-330 affect immune cell frequency and/or immunophenotype?	Flow cytometry, CBC
Soluble cytokines	Does WTX-330 modulate cytokine levels?	MSD panel

Biomarker (Tumor)	Key question addressed	Method
Spatial immune profile	Does WTX-330 affect TIL activation, density and/or localization? PD-L1 expression?	IHC/IF
Immune cell profile	Does WTX-330 affect immune cell frequency and/or immunophenotype?	Flow Cytometry
Gene expression profile	How does WTX-330 globally impact the tumor immune microenvironment?	NanoString
WTX-330 cleavage	To what extent does the patient's tumor proteolytically activate WTX-330 to release free IL-12?	Novel *in vitro* assay

ACTIVE STUDY SITES
Assembling a world-class team of clinical investigators



SUMMARY and CONCLUSIONS

- An unmet medical need exists for patients with cancer who demonstrate primary or secondary resistance to standard of care ICI regimens, and for patients with tumor types for which ICIs are not approved
- WTX-330 is an IL-12 INDUKINE™ molecule that uses a prodrug strategy to leverage the favorable proinflammatory activities of this potent and pleiotropic cytokine to safely stimulate antitumor immune responses
- Enrollment in the dose escalation part of the WTX-330x2101 first-in-human study is presently ongoing

Werewolf Therapeutics
200 Talcott Avenue
Watertown, MA 02472

media@werewolftx.com
info@werewolftx.com
https://werewolftx.com/

CLINICAL TRIAL PAGE:

https://clinicaltrials.gov/ct2/show/NCT05678998