Werewolf THERAPEUTICS

Creating Powerful Proinflammatory Cancer Therapies

Trial in Progress

A multicenter phase 1/1b dose escalation study of WTX-124 as a monotherapy and in combination with pembrolizumab in patients with selected advanced or metastatic solid tumors

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This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

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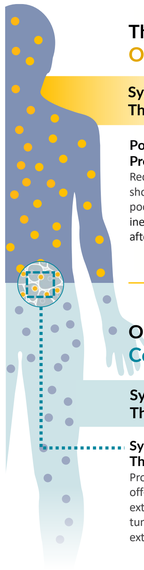
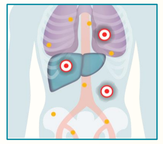
OUR APPROACH: CONDITIONALLY ACTIVATED IMMUNOTHERAPY



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



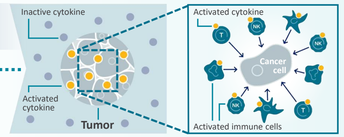
High Toxicity
High systemic cytokine exposure causes serious toxicities

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-2 prodrug for cancer immunotherapy

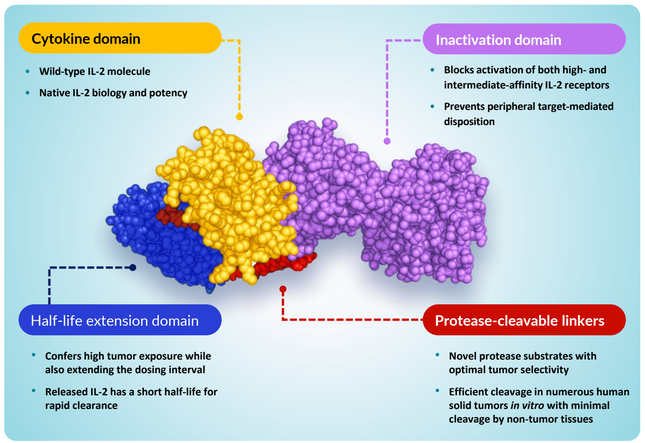
- An unmet medical need exists for patients with advanced cancer who are non-responsive to immunotherapy and/or who progress on SOC checkpoint inhibitor regimens
- IL-2 could help to address this need through its established immune-stimulatory activities. IL-2 promotes differentiation, expansion, and activation of effector and memory T cells as well as enhances T and NK cell functional activity. In mice with chronic LCMV infection, IL-2 has synergistic activity with PD-1 blockade by acting on PD-1^{+}TCF1^{+} stem-like CD8^{+} T cells
- High dose (HD) recombinant human IL-2 (rhIL-2; Proleukin™) is FDA approved for patients with advanced or metastatic cutaneous melanoma and renal cell carcinoma

Unfortunately, use of HD rhIL-2 is limited by:

1. Life-threatening toxicities (i.e., FDA black-box warning for capillary leak syndrome)
2. A requirement for inpatient administration with accessible ICU-level care
3. Preferential treatment of patients with optimal performance status and few comorbidities
4. An inconvenient dosing schedule (every 8 hours for 5 days)
5. Low overall response rate at the approved dose

A reliable strategy to systemically deliver IL-2 with tumor-restricted activity would represent a major advance in the field of cytokine therapy and could address a major unmet medical need

WTX-124
An IL-2 INDUKINE™ molecule to address the limitations of recombinant human IL-2



WTX-124x2101 FIRST-IN-HUMAN STUDY DESIGN
Monotherapy and combination therapy with pembrolizumab

Dose Escalation (N~70 patients)
- Modified toxicity probability interval 2 design
- WTX-124 administered as a flat dose in cohorts of 3-6 patients

Dose Expansion (N~80 patients)
- Expansion arms for monotherapy and combination therapy can open and start enrollment in parallel

Monotherapy (N~35)
- WTX-124 IV Q2W (28-day cycle)
- DLT period = 28 days

Safety must be established in the first three monotherapy cohorts

MTD/RDE

Monotherapy (N~40)
- Arm A: Renal cell carcinoma
- Arm B: Cutaneous melanoma

Opportunities may exist to open additional expansion arms

Combination Therapy (N~35)
- WTX-124 IV Q2W + pembrolizumab 400mg IV Q6W (42-day cycle)
- WTX-124 dose starts one level below highest safe dose as monotherapy
- DLT period = 28 days

MTD/RDE

Combination therapy (N~40)
- Arm C: Renal cell carcinoma
- Arm D: Cutaneous melanoma

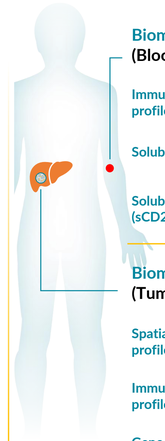
STUDY OBJECTIVES and ENDPOINTS

	OBJECTIVES	ENDPOINTS
PRIMARY	• Evaluate safety and tolerability • Determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) • Evaluate antitumor activity	• Incidence of treatment emergent adverse events (TEAEs) • Incidence of dose-limiting toxicities (DLTs) • Changes in clinical laboratory parameters • ORR and DOR (RECIST 1.1) and iORR (iRECIST)
SECONDARY	• Characterize pharmacokinetic profile • Evaluate antitumor activity • Evaluate changes in immunological biomarkers (blood, tumor) • Assess immunogenicity • Evaluate overall survival (expansion only)	• Plasma [WTX-124] and [free IL-2]; calculated PK parameters • PFS (RECIST 1.1) and iPFS (iRECIST) • Frequency of immune cell subsets (blood) • Lymphocyte density and/or activation state (tumor) • Antidrug antibody (ADA) occurrence • 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 lymphocytes, eosinophils • Intratumoral immune cell frequency • Tumor microenvironment gene expression profile • Prodrug activation in tumor biopsy *in vitro*

PATIENT POPULATIONS

	1. MONOTHERAPY (WTX-124)	1b. COMBINATION (WTX-124/pembrolizumab)
DOSE ESCALATION **Any solid tumor for which an immune checkpoint inhibitor (ICI) is approved**	• Relapsed/refractory to SOC • No more than 4 prior lines • Prior ICI is mandatory	• Relapsed/refractory to SOC • No more than 4 prior lines • Prior ICI is mandatory • No d/c of anti-PD-(L)1 due to irAE(s)
DOSE EXPANSION	**Arm A (RCC) and Arm B (Melanoma)** *All received prior ICI*	**Arm C (RCC) and Arm D (Melanoma)** *Prior ICI not required for melanoma*
Renal Cell Carcinoma	• No more than 3 prior lines • Prior VEGFi, ICI are mandatory • Only 1 prior line with ICI	• No more than 2 prior lines • Prior VEGFi, ICI are mandatory • Only 1 prior line with ICI • No d/c of anti-PD-(L)1 due to irAE(s)
Melanoma (*BRAF* wild type)	• No more than 1 prior line • Prior ICI is mandatory • Adjuvant is a prior line if pt. relapses within 6 months of completion	• 0-1 prior lines (i.e., can be ICI naïve) • Adjuvant is a prior line if pt. relapses within 6 months of completion • No d/c of anti-PD-(L)1 due to irAE(s)
Melanoma (*BRAF* mutant)	• No more than 2 prior lines • Prior ICI is mandatory, but not BRAFi/MEKi • Adjuvant is a prior line if pt. relapses w/in 6 months of completion	• 0-2 prior lines (i.e., can be ICI and BRAFi/MEKi naïve) • Adjuvant is a prior line if pt. relapses within 6 months of completion • No d/c of anti-PD-(L)1 due to irAE(s)

TRANSLATIONAL BIOMARKER STRATEGY
Interrogating antitumor immune activation in patients



Biomarker (Blood)	Key question addressed	Method
Immune cell profile	Does WTX-124 affect immune cell frequency and/or immunophenotype?	Flow cytometry, CBC
Soluble cytokines	Does WTX-124 modulate cytokine levels?	MSD panel
Soluble IL-2Rα (sCD25)	Does WTX-124 increase sCD25?	MSD assay

Biomarker (Tumor)	Key question addressed	Method
Spatial immune profile	Does WTX-124 affect TIL activation, density and/or localization? PD-L1 expression?	IHC/IF
Immune cell profile	Does WTX-124 affect immune cell frequency and/or immunophenotype?	Flow cytometry
Gene expression profile	How does WTX-124 globally impact the tumor immune microenvironment?	NanoString
WTX-124 cleavage	To what extent does the patient's tumor proteolytically activate WTX-124 to release free IL-2?	Novel *in vitro* assay

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

SUMMARY and CONCLUSIONS

- Recombinant human IL-2 is an approved treatment for advanced melanoma and renal cell carcinoma, but its use is limited by a narrow therapeutic index
- WTX-124 is a novel INDUKINE™ molecule rationally engineered to optimize the therapeutic index for IL-2 therapy
- WTX-124 incorporates a wild type cytokine anticipated to leverage the full biology and potency of IL-2 to stimulate antitumor immune responses
- Enrollment in monotherapy dose escalation of the WTX-124x2101 first-in-human study is presently ongoing
- Guiding towards data package in 4Q 2023

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CLINICAL TRIAL PAGE:

https://clinicaltrials.gov/ct2/show/NCT05479812