CLINICAL STUDY PROTOCOL

A Phase 1 (First-In-Human [FIH]), Multi-Site, Dose Escalation and Expansion Study of WTX-330 in Adult Patients with Advanced or Metastatic Solid Tumors or Lymphoma

Investigational Product: WTX-330
Protocol Number: WTX-330x2101

Sponsor:
Werewolf Therapeutics, Inc.
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Version Number: 02
Date: 06 April 2023

SIGNATURE PAGE

STUDY TITLE: A Phase 1 (First-In-Human [FIH]), Multi-Site, Dose Escalation and Expansion Study of WTX-330 in Adult Patients with Advanced or Metastatic Solid Tumors or Lymphoma

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
DocuSigned by: Randi Isaacs Signer Name: Randi Isaacs Signing Reason: I approve this document Signing Time: 06-Apr-2023 | 9:37:33 AM EDT ID: 05BCE7B477CA67A8254CF147069	06-Apr-2023
Randi Isaacs Chief Medical Officer Werewolf Therapeutics	

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Werewolf to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Werewolf and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Werewolf, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with United States (US) Food and Drug Administration (FDA) Regulations, Institutional Review Board (IRB)/Ethics Committee (EC) Regulations and International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP).

_____ _____

Investigator Signature Date

_____

Investigator Printed Name

SYNOPSIS

TITLE: A Phase 1 (First-In-Human [FIH]), Multi-Site, Dose Escalation and Expansion Study of WTX-330 in Adult Patients with Advanced or Metastatic Solid Tumors or Lymphoma

BRIEF TITLE: A first-in-human study of WTX-330 to assess safety and determine the recommended dose in adult patients with advanced or metastatic solid tumors and lymphoma

SPONSOR: Werewolf Therapeutics, Inc.

CLINICAL PHASE: 1

INVESTIGATION TYPE: Oncology

STUDY TYPE: Dose escalation and expansion study

PROTOCOL NUMBER: WTX-330x2101

INVESTIGATIONAL PRODUCT: WTX-330

STUDY PURPOSE AND RATIONALE:

The recent development of immuno-oncology agents that enhance antitumor immunity is rapidly changing the treatment of cancer. However, these agents are not effective in all tumor types or in all patients with a certain tumor type. This gap represents an unmet medical need for novel immunotherapy approaches.

Interleukin-12 (IL-12) is a potent, pleiotropic cytokine known to enhance immune-mediated killing of cancer cells. The mechanism of action of IL-12 includes stimulation of both innate and adaptive immune cells. Antigen-presenting cells (APCs) such as dendritic cells and macrophages produce IL-12 upon activation. Binding of IL-12 to its receptor expressed on multiple immune cell types activates the Janus kinase-signal transducer and activator of transcription (JAK/STAT) signaling pathway to induce changes in gene expression. IL-12 signaling activity induces interferon gamma (IFNγ) and together, these two cytokines produce a broad range of immunological activities including induction of T helper type 1 (Th1) cell differentiation; activation of cytotoxic natural killer (NK) and T cells; and inhibition or reprograming of immunosuppressive cells such as tumor-associated macrophages (TAM) and myeloid-derived suppressor cells (MDSCs). IL-12 also enhances antigen presentation by APCs, which is necessary to stimulate immune responses in tumors that have not naturally generated antitumor immunity.

Numerous studies demonstrate that IL-12 has robust antitumor activity in a range of preclinical models and induces immune memory. These observations have generated significant interest in developing recombinant human IL-12 (rhIL-12) as a therapeutic agent for cancer. In early clinical studies, systemically administered rhIL-12 demonstrated clinical activity in several tumor types including renal cell carcinoma (RCC), melanoma, and non-Hodgkin lymphoma (NHL). However, systemic administration of rhIL-12 was shown to be toxic, resulting in death of 2 patients in a Phase 2 clinical study and multiple hospitalizations. Additional clinical studies using more

tolerable doses and schedules yielded only modest clinical activity, possibly due to a lack of sufficient exposure of rhIL-12 in the tumor microenvironment (TME).

WTX-330 is a conditionally activated IL-12 prodrug that was designed to address the multiple shortcomings of rhIL-12. [redacted]

This Phase 1 FIH dose escalation and dose expansion study will investigate WTX-330 as a monotherapy for patients with relapsed/refractory (r/r) advanced or metastatic solid tumors and lymphomas. The patients enrolled in this study will include those demonstrating primary or secondary resistance to immune checkpoint inhibitor (CPI) therapy as well as patients with tumor types for which CPIs are not approved. The FIH study will characterize the clinical safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary antitumor efficacy of WTX-330.

KEY STUDY OBJECTIVES:

The primary objectives of the Dose Escalation part of this study are the following:

- To evaluate the safety and tolerability of WTX-330
- To determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of WTX-330

The primary objectives of the Dose Expansion part of this study are the following:

- To further characterize the safety and tolerability of WTX-330
- To evaluate the antitumor activity of WTX-330 as measured by overall response rate (ORR; complete response [CR] + partial response [PR]) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, immune ORR (immune-ORR [iORR]; immune CR [iCR] + immune PR [iPR]) by immune RECIST (iRECIST), or Lugano classification (Cheson et al., 2014) for lymphomas

The secondary objectives of this study are the following:

- To characterize the PK profile of WTX-330 (i.e., both parent compound and free IL-12)
- [redacted]
- To evaluate the immunogenicity of WTX-330 (i.e., the potential to generate an anti-drug antibody [ADA] response)
- [redacted]

STUDY DESIGN:

This is a Phase 1, FIH, multi-site study starting with dose escalation of WTX-330 (Part 1) followed by dose expansion of WTX-330 (Part 2) in two arms (A and B).

Dose Escalation (Part 1)

The dose escalation part of the study will be conducted in patients with relapsed/refractory (r/r) advanced and/or metastatic solid tumors. Patients with primary CNS malignancies are ineligible. Patients with castrate-resistant prostate cancer (CRPC) and non-Hodgkin lymphoma (NHL) will be eligible for Dose Expansion (see Arm B below) but are not eligible for Dose Escalation. During dose escalation, WTX-330 will be administered as a single agent on Days 1 and 15 (i.e., every 2 weeks, Q2W) of 28-day treatment cycle.

The starting dose of WTX-330 is 0.016 mg/kg. Selection of the starting dose in this FIH clinical study was informed by safety and PK data from non-Good Laboratory Practice (GLP) and GLP toxicological studies in cynomolgus monkeys, pharmacology studies in tumor-bearing mice, and the prior clinical experience with rhIL-12. A total of eight provisional dose levels are defined for the dose escalation. A dose level with a 50% lower dose than the starting dose is also included if the first dose level is not tolerated.

To minimize the number of patients treated at potentially subtherapeutic dose levels, cohorts will enroll a minimum of 3 patients and up to 6 patients. In each dose cohort, a minimum of 3 patients are required to have completed the dose-limiting toxicity (DLT) observation period before initiating enrollment of the subsequent cohort.

To help ensure patient safety, dosing of the first 2 patients at each dose level will be staggered by at least 7 days and dosing of the second and all following patients will be staggered by at least 2 days. The DLT assessment period for a dose cohort must be completed and the data reviewed by the Dose Escalation Committee (DEC) prior to the recruitment of patients into the next dose cohort. The DEC is comprised of the study Investigators, the Sponsor's medical representative(s) and independent functional experts as required.

Patients may receive WTX-330 for as long as they continue to show clinical benefit, as assessed by the Investigator, or until disease progression or other treatment discontinuation criteria are met. No intrapatient dose escalation is allowed.

A Bayesian Logistic Regression Model (BLRM) incorporating escalation with overdose control (EWOC) will be used to guide the dose escalation (Appendix F). Data from patients satisfying the requirements for inclusion in the dose-determining set (DDS) will be included in the model. After completion of a dose cohort, or at any time the BLRM is updated, a decision to escalate and the actual dose and schedule selected will be determined by the DEC based on a review of all available clinical, PK and laboratory data and on the recommendation of the BLRM regarding the highest admissible dose according to the EWOC principle.

Dose escalation will continue until determination of the MTD and/or RDE. Once the MTD/RDE is identified, the Dose Expansion part of the study (Part 2) will open. Determination of the RDE and selection of an optimal dosage will be informed not only by clinical PK, PD, antitumor activity and safety data, but also by nonclinical pharmacology and toxicology data.

Dose Expansion (Part 2)

Patients in Dose Expansion will have a confirmed diagnosis of a r/r locally advanced or metastatic solid tumor or lymphoma for which the patient has progressed or is intolerant of standard therapy, or for whom no standard therapy with proven benefit exists. Dose Expansion (Part 2) will be conducted in 2 arms that will enroll the following patient populations:

- Arm A: Patients with indications for which a CPI is indicated/approved (e.g., cutaneous malignant melanoma, RCC, non-small cell lung cancer [NSCLC], head and neck squamous cell carcinoma [HNSCC], urothelial carcinoma, etc.) who have been treated with a CPI regimen and who demonstrate primary or secondary resistance to CPI therapy. Primary resistance is defined as disease progression or stable disease (SD) < 6 months as the best response after at least 6 weeks of exposure to inhibitors of PD-(L)1. Secondary resistance is defined as disease progression ≥ 6 months after initiation of PD-(L)1 inhibitors in patients who have received clinical benefit (i.e., CR or PR or SD > 6 months). Patients who discontinue CPI therapy for toxicity or other reasons and who don't demonstrate primary or secondary resistance to CPIs as defined here are not eligible. Patients with Hodgkin lymphoma are also ineligible.
- Arm B: Patients with tumor types for which CPI therapy is not indicated/approved (e.g., pancreatic cancer, microsatellite-stable [MSS] colorectal carcinoma, castrate-resistant prostate cancer [CRPC], NHL) and who are CPI naïve. Patients with NHL should have either follicular lymphoma or diffuse large B-cell lymphoma (DLBCL), though other subtypes of NHL including T-cell lymphomas may be considered after a discussion with the Sponsor. All patients with NHL must have received at least 2 prior systemic therapies. Patients with primary CNS malignancies are not eligible.

Additional arms may be added in the Dose Expansion for specific indications of interest.

Patients will remain on study treatment until they experience unacceptable toxicity, progressive disease per RECIST (Appendix D; Eisenhauer et al., 2009) or iRECIST (Appendix E) for solid tumors, or confirmed progressive disease for NHL (dose expansion part) according to Lugano classification (Cheson et al., 2014), and/or treatment discontinued at discretion of the Investigator, or the patient withdraws consent.

The study consists of a screening period, a treatment period with either Dose Escalation (Part 1) or Dose Expansion (Part 2), an End-of-Treatment (EOT) visit, and a safety follow-up period. The Safety Follow-Up Visit should occur either 30 days after the last dose of study drug or prior to the start of a new cancer regimen, whichever comes first. Overall survival status will be evaluated every 12 weeks (+/- 2 weeks) for patients who are on Dose Expansion (Part 2). Patients will be contacted via telephone to evaluate overall survival until initiation of a new therapy or death, whichever comes first.

The end of the study is defined as when 80% of patients have either discontinued the study or have completed follow-up. Throughout the study, patients will be assessed for efficacy, PK, PD and safety of WTX-330.

POPULATION:

Inclusion Criteria

Each patient must meet all the following criteria to participate in the study:

1. Age ≥ 18 years, able to understand and voluntarily sign a written informed consent form (ICF) and willing and able to comply with protocol requirements
2. For all patients in Dose Escalation (Part 1): A confirmed diagnosis of a r/r locally advanced or metastatic solid tumor for which the patient has progressed on or is intolerant of standard therapy, or for whom no standard therapy with proven benefit exists. Patients with castrate-resistant prostate cancer (CRPC) and non-Hodgkin lymphoma (NHL) will not be enrolled in dose escalation.
3. For all patients in Dose Expansion (Part 2): A confirmed diagnosis of r/r locally advanced or metastatic solid tumors and lymphomas for which the patient has progressed on or is intolerant of standard therapy, or for whom no standard therapy with proven benefit exists. Dose Expansion (Part 2) consists of two arms, Arm A and Arm B. The following additional criteria must be met for patients to be eligible for Arm A or Arm B:

   Arm A: Patients with indications for which a CPI is indicated/approved, (e.g., cutaneous malignant melanoma, RCC, NSCLC, HNSCC, urothelial carcinoma, etc.) who demonstrate primary or secondary resistance to CPI therapy, as defined above in Study Design. [redacted]

   Arm B: Patients with tumor types for which CPI therapy is not indicated/approved (e.g., pancreatic cancer, MSS colorectal carcinoma, CRPC, NHL, etc.) and who are CPI naïve. Patients with NHL should have either follicular lymphoma or DLBCL. [redacted]
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
5. At least one measurable lesion per RECIST 1.1 (Appendix D; Eisenhauer et al., 2009) or evaluable lesion per Lugano classification (Cheson et al., 2014). CRPC patients (i.e., in Arm B) may not have bone-only disease.
6. Agrees to undergo a pre-treatment and on-treatment biopsy of a primary or metastatic solid tumor or lymphoma lesion.
7. Human immunodeficiency virus (HIV) infected patients must be on antiretroviral therapy (ART). Patients on ART must have well-controlled HIV infection/disease [redacted]

[redacted]

8. Has adequate organ and bone marrow function [redacted]

[redacted]

9. Willingness of men and women of reproductive potential to agree to highly effective birth control for the duration of treatment and for 4 months following the last dose of study drug.

[redacted]

[redacted]

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participating in the study:

1. A history of another active malignancy (a second cancer) within the previous 2 years, except for localized cancers that are not related to the current cancer being treated, is considered cured, and, in the opinion of the Investigator, presents a low risk of recurrence. These exceptions include, but are not limited to, basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
2. Received prior treatment with IL-12 (including by intratumoral injection).
3. Patients with primary CNS malignancies are excluded from all parts of the trial. Patients with CRPC and NHL are excluded from Dose Escalation.
4. Presence of symptomatic CNS metastases or CNS metastases that require local CNS directed therapy (such as XRT or surgery) or increasing doses of corticosteroids within 2 weeks prior to the first dose of study drug. Patients with treated brain metastases should be neurologically stable and receiving ≤ 10 mg per day of prednisone or equivalent prior to study entry. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment, have recovered from the acute effects of radiation therapy or surgery prior to enrollment, have fulfilled the steroid requirement for these metastases, and are neurologically stable and asymptomatic.
5. Significant cardiovascular disease, [redacted]
6. Significant electrocardiogram (ECG) abnormalities at Screening, [redacted]

7. Active autoimmune disease requiring systemic treatment in the past 2 years (i.e., with use of disease-modifying antirheumatic agents or immunosuppressive drugs).

[redacted]

8. Diagnosis of immunodeficiency, on immunosuppressive therapy, or receiving chronic systemic or enteric steroid therapy (dose > 10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

[redacted]

9. In patients with NHL, prior receipt of an allogeneic stem cell transplant or prior allogeneic CAR-T cell therapy [redacted]

10. Major surgery (excluding placement of vascular access) within 2 weeks prior to the first dose of study drug.

11. Investigational agent or anticancer therapy (including chemotherapy, biologic therapy, immunotherapy, anticancer Chinese medicine, or other anticancer herbal remedy) within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug. In addition, no concurrent investigational anticancer therapy is permitted during the study.

12. Radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities and not require corticosteroids. [redacted]

13. Any unresolved toxicities from prior therapy greater than National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 Grade 1 at the time of starting study drug with the exception of alopecia and Grade 2 platinum therapy-related neuropathy.

14. Use of sensitive substrates of major CYP450 isozymes.

    Note: A list of substrates which are sensitive to these enzymes is provided in Appendix B. If a sensitive substrate cannot be stopped and replaced with another medication, the patient's inclusion in the study should be discussed with the Sponsor.

15. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with a patient's ability to sign the ICF, adversely affect the patient's ability to cooperate and participate in the study, or compromise the interpretation of study results.

16. Received a live vaccine within 30 days of the first dose of study drug.

17. Active, uncontrolled systemic bacterial, viral, or fungal infection.

18. HIV-infected participants with a history of Kaposi sarcoma and/or Multicentric Castleman Disease.

19. Active infection as determined by hepatitis B surface antigen and hepatitis B core antibody, or hepatitis B virus deoxyribonucleic acid (DNA) by quantitative polymerase chain reaction (qPCR) testing.
20. Active infection as determined by hepatitis C virus (HCV) antibody or HCV RNA by qPCR testing.
21. Pregnant or lactating.
22. History of hypersensitivity to any of the study drug components.

KEY EFFICACY, PHARMACOKINETIC AND PHARMACODYNAMIC/BIOMARKER ASSESSMENTS:

Efficacy Assessments

Solid tumor responses will be evaluated based on RECIST 1.1 (Appendix D; Eisenhauer et al., 2009) and iRECIST (Appendix E), whereas NHL responses will be assessed by Lugano classification (Cheson et al., 2014) at the times indicated in the Schedule of Assessments (SoA) (Appendix A). For solid tumors, disease assessments will include radiographic measurements of tumors in the chest, abdomen, pelvis, and at any other known sites of disease using computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT. NHL will be evaluated with PET/CT. Intravenous (IV) and oral contrast should be used unless there is a clear contraindication such as decreased renal function or an allergy that cannot be addressed with standard prophylactic treatments. Baseline tumor assessments will be performed at Screening (i.e., within 28 days of Cycle 1 Day 1). Patients with CNS metastases must have brain imaging (MRI preferred; CT with contrast is acceptable if MRI imaging contraindicated) performed during Screening. On-study scans should be performed every 8 weeks (±7 days) from Cycle 1 Day 1 for the first 6 cycles and every 12 weeks (±7 days) thereafter, and include imaging of the chest, abdomen, pelvis, and any additional areas of disease identified at baseline, using the same modality as used for baseline imaging until progressive disease per RECIST 1.1 and iRECIST for solid tumors, or Lugano classification for NHL, withdrawal of consent, or initiation of a new anticancer therapy.

Pharmacokinetic Assessments

Plasma samples for WTX-330 PK assessments of the parent compound and free IL-12 will be obtained. Concentrations of WTX-330 and free IL-12 will be determined with a validated bioanalytical method. PK parameters such as AUC, maximum observed plasma concentration (C_{max}) minimum observed plasma concentration (C_{min}), time to maximum observed plasma concentration (T_{max}), terminal-elimination half-life ($t_{½}$), clearance, volume of distribution (V_d), and volume of distribution at steady state (V_{ss}) will be determined.

[redacted]

SAFETY ASSESSMENTS

The safety and tolerability profile of WTX-330 will be assessed by monitoring adverse events (AEs; including DLTs, serious AEs [SAEs], and AEs of special interest [AESIs]), physical examination findings (including ECOG performance status), clinical laboratory evaluations, vital sign measurements, and ECGs. AEs will be graded according to the NCI-CTCAE version 5.0. Cytokine release syndrome (CRS) will be graded by ASTCT consensus grading criteria.

STATISTICAL ANALYSES:

Primary (Dose Escalation) Analysis

An adaptive 2-parameter BLRM incorporating EWOC will be used to guide the dose escalation (Appendix F). This model uses all the information currently available about the dose-DLT relationship of WTX-330 and is summarized in a prior distribution. For this study, nonclinical data informing the starting dose and the prior clinical experience with recombinant human IL-12 are used to compute the prior distribution. This prior distribution is then updated after each cohort of patients is treated and incorporates all the DLT data available in the DDS. The posterior targeted toxicity to define the MTD will be between 16% and 33%. In addition, and according to the EWOC principle, any dose of WTX-330 that has a $\geq$ 25% chance of being in the excessive toxicity category is not considered for the next dose group. Dose escalation decisions will be made by the DEC based on the recommendations from the BLRM and all available clinical, safety, PK and PD data.

Primary (Dose Expansion) Analysis

For primary analysis of the Dose Expansion (Part 2) cohorts, a probability of success design for the ORR based on the best overall response (BOR) will be used. To model the primary analysis of the dose expansion cohorts, 2 independent Bayesian beta binomial designs with beta (0.05, 0.95) prior distributions will be used. The response criteria for success are defined as follows: the study is considered successful in an extension arm if the posterior probability that the true response rate exceeds 10% is at least 90%. The final analysis will take place after the completion of the dose expansion cohorts when the last patient has had the final end-of-study visit.

Safety Analyses

Safety analyses will generally be descriptive and presented in tabular format with the appropriate summary statistics for the safety set (i.e., all patients who received at least 1 dose of WTX-330 and had at least 1 post-baseline safety assessment). The safety set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship.

Efficacy Analyses

All efficacy analyses will be performed for investigator-assessed response criteria (per RECIST (Appendix D; Eisenhauer et al., 2009) and iRECIST (Appendix E) for solid tumors, or per Lugano classification (Cheson et al., 2014) for NHL [Dose Expansion part]). For NHL, the response will be analyzed for radiological response, metabolic response (PET/CT) and overall response:

- ORR defined by achieving confirmed CR and/or PR will be presented by percentage rates and 95% confidence intervals (CIs). For changes in tumor size, waterfall plots will be presented. For all response assessments, swimmer plots will be presented.

- Disease Control Rate (DCR) at months 3, 6 and 9, as defined by achieving CR and/or PR and/or SD, will be presented by percentage rates and 95% CIs.
- DOR defined as time from first assessment of PR or CR to follow-on first assessment of progressive disease will be summarized by descriptive statistics including median DOR and respective 95% CIs. The DOR will also be listed.
- Time from first treatment received until progressive disease (PFS) or death (OS), whichever comes first, will be summarized by Kaplan-Meier estimates, median PFS/OS and respective 95% CIs. Patients with no event will be censored at the last available tumor assessment or death for PFS and at the last timepoint known alive for OS.

Pharmacokinetic Analyses

Non-compartmental analysis will be performed on time and concentration profiles of WTX-330 in the PK set (all patients who have received at least 1 dose of study drug and have at least 1 post-dose PK measurement). Summary statistics of PK parameters such as AUC, C_{max}, C_{min}, T_{max}, $t_{½}$, clearance, V_d, and V_{ss} will be reported by dose group. In addition, assessment of dose-proportionality and steady state attainment will be conducted.

[redacted]

SAMPLE SIZE DETERMINATION:

The overall sample size for this study is approximately 75 patients between Dose Escalation (Part 1) and Dose Expansion (Part 2) and will depend on the observed DLT profiles of WTX-330.

These sample sizes are selected based on practical consideration to confirm safety of WTX-330 for each indication and without formal power calculation.

SITES: Up to 12 sites in the USA

SPONSOR:

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