Werewolf Therapeutics Presents Preliminary Monotherapy Data from Phase 1/1b Clinical Trial
Establishing Proof of Mechanism for WTX-124 at the Society for Immunotherapy of Cancer’s (SITC) 38th Annual Meeting

November 3, 2023

- Preliminary data on WTX-124 provide compelling early evidence of dose-dependent biomarker and antitumor activity in patients with advanced or metastatic solid tumors relapsed or refractory to standard of care therapy, including two patients with ongoing unconfirmed partial responses (uPR) in the highest dose tested to date, cohort 4 (12 mg) -

- Safety data indicate WTX-124 is generally well-tolerated through cohort 4 with no dose limiting toxicities and no indication of vascular leak syndrome (VLS) or other typically severe IL-2-mediated toxicities -

- Preliminary data support the potential of WTX-124 to be a differentiated next-generation IL-2 compound by showing immune cell activation in the tumor microenvironment (TME) and monotherapy clinical activity in an outpatient setting -

- Wide therapeutic index supportive of continued dose escalation with cohort 5 (18 mg) fully enrolled and with additional interim data from monotherapy dose escalation arm and recommended dose for expansion arm expected in the first half of 2024 -

- Five additional posters showcasing preclinical data from Werewolf pipeline, including WTX-330, WTX-712 and novel adoptive cell therapy approaches, will also be available in the poster sessions -

- Company to host webcast today at 8:30 AM ET -

Study WTX-124x2101 is evaluating WTX-124 as a monotherapy and in combination with pembrolizumab in patients with immunotherapy sensitive advanced or metastatic solid tumors who have failed standard of care treatment, including checkpoint inhibitor therapy. The preliminary data include data collected as of October 18, 2023, from 16 heavily pretreated patients from the first four monotherapy dose escalation cohorts (1, 3, 6, 12 mg). The preliminary data established proof of mechanism for WTX-124 and proof of concept for Werewolf's INDUKINE design.

"We are encouraged by these preliminary data demonstrating that WTX-124 was generally well tolerated while delivering a wild-type IL-2 to the tumor microenvironment and eliciting monotherapy biomarker and clinical activity, including two patients with ongoing unconfirmed partial responses in the 12 mg cohort," said Daniel J. Hicklin, Ph.D., President and Chief Executive Officer of Werewolf. "We look forward to sharing additional data to inform our recommended dose to proceed into monotherapy expansion arms in the first half of 2024."

The preliminary data include assessments of safety and tolerability, pharmacokinetics, relevant biomarkers and preliminary antitumor activity. Data as of the October 18, 2023, cutoff date are summarized as follows:

**WTX-124 was generally well-tolerated at all doses tested up to and including 12 mg in the outpatient setting.**

- All treatment-emergent adverse events (TEAEs) were Grade 1 or Grade 2, and arthralgias and fatigue were the most common TEAEs. Vascular leak syndrome was not observed, and there were no dose limiting toxicities, treatment-related serious adverse events (SAEs) or treatment-related study discontinuations.
- WTX-124 was delivered intravenously once every two weeks (Q2W).

**WTX-124 showed expected pharmacokinetics with evidence of wide therapeutic index allowing for continued dose escalation.**

**WTX-124 demonstrated both translational biomarker activity and early evidence of monotherapy antitumor activity at 6 mg and 12 mg doses.**

- CD8+ T and NK cell proliferation and activation in the tumor microenvironment and immune cell gene expression changes
were seen at 6 mg and 12 mg dose levels.

- Among five patients treated at 12 mg, one patient achieved an unconfirmed partial response (uPR), one patient had a restaging scan that was consistent with a partial response as of November 1, 2023, and one other showed evidence of anti-tumor activity.

“IL-2 is a well-validated cytokine, but the challenges associated with administering high-dose IL-2 have limited its use. Next-generation approaches have not been successful to date in demonstrating monotherapy activity at well-tolerated doses,” said Randi Isaacs, M.D., Chief Medical Officer of Werewolf. “Although still early in the trial, today’s presentation at SITC of preliminary data from monotherapy dose escalation highlights WTX-124’s potential to deliver this important mechanism with limited toxicity and to provide another therapeutic option to cancer patients.”

Dose escalation is ongoing in the monotherapy and combination therapy arms of the trial with additional data from monotherapy dose-escalation cohorts informing declaration of recommended dose for expansion (RDE) and opening of the monotherapy expansion arms expected in the first half of 2024.

In addition, five preclinical posters further supporting the INDUKINE hypothesis, WTX-124 properties, and other INDUKINE molecules are being presented at the meeting, including:

Title: 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 (Abstract #1074)

- Plasma and tumor data from mice were used to perform pharmacodynamic and receptor occupancy modeling to predict IL-2 receptor occupancy on peripheral lymphocytes and tumor infiltrating lymphocytes (TILs) suggesting WTX-124 has a substantially improved, best-in-class therapeutic index as compared to other IL-2 molecules investigated, including a half-life extended non-alpha IL-2 and a non-alpha IL-2 tumor-activated prodrug.

Title: Optimal Antitumor Immunity Triggered by WTX-124, a Clinical Stage Conditionally Activated INDUKINE™ Molecule that Releases Fully Potent IL-2 in the Tumor Microenvironment (Abstract #1058)

- WTX-124 generated robust anti-tumor activity in a MC38 tumor bearing mouse model and promoted the expansion and activation of tumor specific CD8+ T cells as compared to a variant Non-Alpha IL-2 containing INDUKINE molecule which failed to generate anti-tumor activity, to drive tumor specific CD8+ T cell expansion, or to activate tumor infiltrating immune cells even when dosed up to 28 times higher than the active dose of WTX-124. In addition, while both molecules protected tumor infiltrating CD8+ T cells from exhaustion, only treatment with WTX-124 was able to induce an effector phenotype in tumor specific CD8+ T cells and drive clustering of CD8+ T cells with CD103+ cross presenting dendritic cells within the tumor.

Title: Spatial Analysis of Tumor Infiltrating Lymphocyte Populations in Syngeneic Mouse Tumor Models After Treatment with IL-12 (mWTX-330) and IL-2 (WTX-124) INDUKINE™ Molecules (Abstract #1059)

- Combination treatment with WTX-124 and alpha PD-1 generated robust anti-tumor activity in a CT26 model resulting in widespread tumor infiltration by CD8+ T cells driving immune activation in the tumor microenvironment. In addition, detection of structured and unstructured lymphoid aggregates, including the clustering of various adaptive and innate immune cells within the tumor microenvironment suggests a zone of cytotoxic cell education within the tumor microenvironment.

Title: The Combination of ACT and INDUKINE™ Therapy Leads to Improved Antitumor Immunity in Solid Tumors (Abstract # 252)

- Systemic WTX-124 was shown to preferentially expand CD4 CAR T cells while WTX-330 expanded CD8 CAR T cells, demonstrating that the administration of INDUKINE proteins with adoptive cell therapy could reinvigorate donor cell function leading to improved immunity, engraftment and long-term responses in solid tumors.

Title: Development of WTX-712, a Conditionally Activated IL-21 INDUKINE™ Molecule for the Treatment of Cancer (Abstract # 1075)

- WTX-712 was shown to be peripherally inactive in preclinical studies, releasing IL-21 selectively within the tumor microenvironment while driving CD8+ T cell polyfunctionality and promoting immune cell interactions. In addition, WTX-712 demonstrated enhanced activity when combined with immune checkpoint inhibitors, blocking PD-1/PD-L1 or CTLA-4 pathways, indicating further evaluation of WTX-712 is warranted.

The posters will be available on the ‘Scientific Resources’ section of Werewolf Therapeutics website at https://investors.werewolftx.com/news-and-events/scientific-resources.

Conference Call Information:
Management will host a call to review the preliminary data today, November 3, at 8:30 AM ET. Details for the call can be found here and at https://investors.werewolftx.com/news-and-events/events.

About Werewolf Therapeutics:
Werewolf Therapeutics, Inc. is an innovative clinical-stage biopharmaceutical company pioneering the development of therapeutics engineered to
stimulate the body’s immune system for the treatment of cancer. We are leveraging our proprietary PREDATOR™ platform to design conditionally activated molecules that stimulate both adaptive and innate immunity with the goal of addressing the limitations of conventional proinflammatory immune therapies. Our INDUKINE™ molecules are intended to remain inactive in peripheral tissue yet activate selectively in the tumor microenvironment. Our most advanced product candidates, WTX-124 and WTX-330, are systemically delivered, conditionally activated Interleukin-2 (IL-2), and Interleukin-12 (IL-12) INDUKINE molecules for the treatment of solid tumors. WTX-124 is in development as a monotherapy and in combination with KEYTRUDA® (pembrolizumab) in multiple solid tumor types. WTX-330 is in development as a single agent in refractory and/or immunotherapy unresponsive or resistant advanced or metastatic solid tumors and non-Hodgkin lymphoma.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements that involve substantial risk and uncertainties. All statements, other than statements of historical facts, contained in this press release, including statements regarding Werewolf’s future operations, prospects, plans, objectives of management, the expected timeline for the clinical development of product candidates and availability of data from such clinical development, and the potential activity and efficacy of product candidates in preclinical studies and clinical trials constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. The words “aim,” “anticipate,” “believe,” “contemplate,” “continue,” “could,” “design,” “designed to,” “estimate,” “expect,” “goal,” “intend,” “may,” “might,” “objective,” “ongoing,” “plan,” “potential,” “predict,” “project,” “promise,” “should,” “target,” “will,” or “would,” or the negative of these terms, or other comparable terminology are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. The Company may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including: uncertainties inherent in the development of product candidates, including the conduct of research activities, the initiation and completion of preclinical studies and clinical trials; uncertainties as to the availability and timing of results from preclinical studies and clinical trials; the timing of and the Company’s ability to submit and obtain regulatory approval for investigational new drug applications; whether results from preclinical studies will be predictive of the results of later preclinical studies and clinical trials; whether preliminary data from a clinical trial will be predictive of the results of the trial and future clinical trials; the Company’s ability to obtain sufficient cash resources to fund the Company’s foreseeable and unforeseeable operating expenses and capital expenditure requirements; as well as the risks and uncertainties identified in the “Risk Factors” section of the Company’s most recent Form 10-Q filed with the Securities and Exchange Commission (“SEC”), and in subsequent filings the Company may make with the SEC. In addition, the forward-looking statements included in this press release represent the Company’s views as of the date of this press release. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company’s views as of any date subsequent to the date of this press release.

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