UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 3, 2023

WEREWOLF THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-40366**	**82-3523180**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

200 Talcott Ave, 2nd Floor **Watertown, Massachusetts**	**02472**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's telephone number, including area code: (617) 952-0555

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, $0.0001 par value per share	HOWL	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 7.01. Regulation FD Disclosure

On November 3, 2023, Werewolf Therapeutics, Inc. (the "Company") issued a press release announcing preliminary first-in-human clinical data from initial monotherapy dose-escalation cohorts in the Company's Phase 1/1b clinical trial of WTX-124. A copy of the press release is furnished as Exhibit 99.1 hereto and is incorporated herein by reference.

The information furnished under this Item 7.01, including Exhibit 99.1, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01. Other Events.

Investor Presentation

On November 3, 2023, the Company made available a presentation to be used with investors to discuss the preliminary first-in-human clinical data from the Company's Phase 1/1b clinical trial of WTX-124. A copy of the presentation is filed as Exhibit 99.2 hereto and is incorporated herein by reference.

Preliminary Data from Phase 1/1b Clinical Trial of WTX-124

On November 3, 2023, the Company announced preliminary first-in-human clinical data from initial monotherapy dose-escalation cohorts in the Company's lead clinical program, WTX-124x2101. This clinical program is an ongoing, multi-center Phase 1/1b clinical trial of WTX-124, the Company's interleukin 2 (IL-2) INDUKINE molecule, in patients with advanced or metastatic solid tumors.

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 and 12 mg). The preliminary data established proof of mechanism for WTX-124 and proof of concept for Werewolf's INDUKINE design.

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.
- 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, 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.

Dose escalation is ongoing in the monotherapy and combination therapy arms of the trial, with cohort 5 (18 mg) fully enrolled. Additional data from monotherapy dose-escalation cohorts will inform declaration of recommended dose for expansion and opening of the monotherapy expansion arms expected in the first half of 2024.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release, dated November 3, 2023.
99.2	Investor Presentation, dated November 3, 2023.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

Cautionary Note Regarding Forward-Looking Statements

Any statements in this Current Report on Form 8-K about the Company's future expectations, plans and prospects, as well as any other statements regarding matters that are not historical facts, may constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements are subject to risks and uncertainties and actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, the Company'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 and other statements containing 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. 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 Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") and in subsequent filings the Company may make with the SEC. All forward-looking statements contained in this Current Report on Form 8-K speak only as of the date hereof, and the Company specifically disclaims any obligation to update any forward-looking statement, whether because of new information, future events or otherwise, except as required by law.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

WEREWOLF THERAPEUTICS, INC.

Date: November 3, 2023

By: /s/ Timothy W. Trost
Timothy W. Trost
Chief Financial Officer and Treasurer

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

- 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 -

WATERTOWN, Mass., November 3, 2023 (GLOBE NEWSWIRE) — Werewolf Therapeutics, Inc. (the "Company" or "Werewolf") (Nasdaq: HOWL), an innovative biopharmaceutical company pioneering the development of conditionally activated therapeutics engineered to stimulate the body's immune system for the treatment of cancer, today announced preliminary first-in-human clinical data from initial monotherapy dose-escalation cohorts in the Company's lead clinical program, WTX-124x2101. This clinical program is an ongoing, multi-center Phase 1/1b clinical trial of WTX-124, Werewolf's interleukin 2 (IL-2) INDUKINE molecule, in patients with advanced or metastatic solid tumors. The preliminary data will be presented today at the Society for Immunotherapy of Cancer's (SITC) 38th Annual Meeting in San Diego, California.

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 12mg 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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Exhibit 99.2

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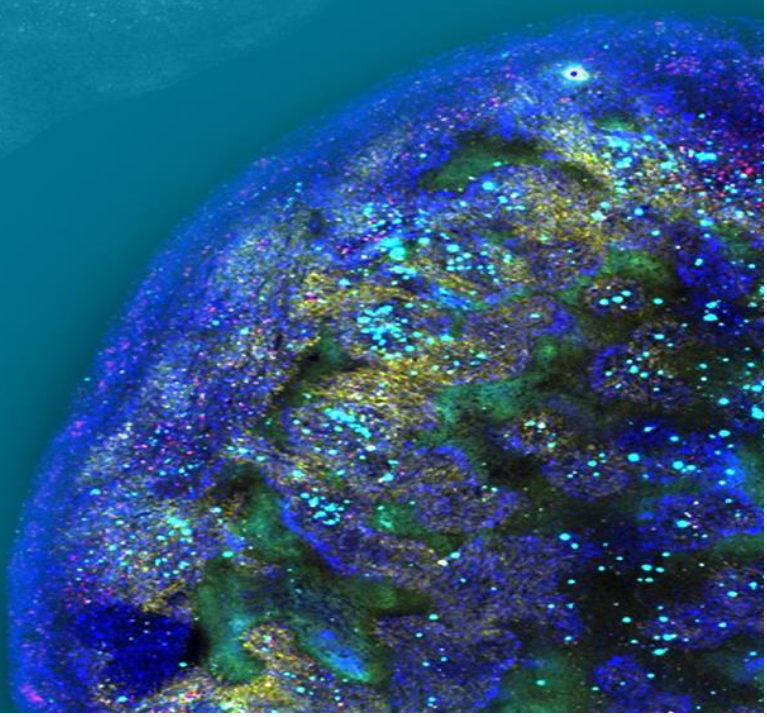
Shifting the Balance in Cytokine Therapeutics



SITC 2023

WTX-124 Phase 1/1b Clinical Trial
Preliminary Data Overview
Investor Webcast
November 3, 2023

Cautionary Note Regarding Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding Werewolf Therapeutics, Inc.'s (the "Company") strategy, future operations, prospects, plans, objectives of management, the expected timeline regarding preclinical and clinical development for product candidates, including the announcement of data, the potential activity and efficacy of product candidates in future preclinical studies and clinical trials, and the Company's expected cash runway, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. The words "aim," "anticipate," "approach," "believe," "contemplate," "continue," "could," "design," "designed to," "engineered," "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 presentation represent the Company's views as of the date of this presentation. 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 presentation.

Key Value-drivers

WTX-124

Preliminary clinical data* establish proof of mechanism for WTX-124 and proof of concept for INDUKINE™ design

Dose-escalation ongoing in both monotherapy and pembrolizumab combination

Recommended dose for expansion (RDE) and opening of expansion arms expected in 1H 2024

WTX-330

Ongoing enrollment in monotherapy dose escalation

JZP898

IND application clearance received for Phase 1 clinical development

WTX-712

Selection of IL-21 development candidate

On-going Value Creation

PREDATOR™ Platform

Capability to expand the pipeline with new INDUKINE molecules for a broad range of mechanisms and indications

Business Development

Broad portfolio of clinical and preclinical stage assets for potential partnering

*Preliminary clinical data includes data collected as of October 18, 2023, from 16 patients in an ongoing, open label Phase 1/1b clinical trial.

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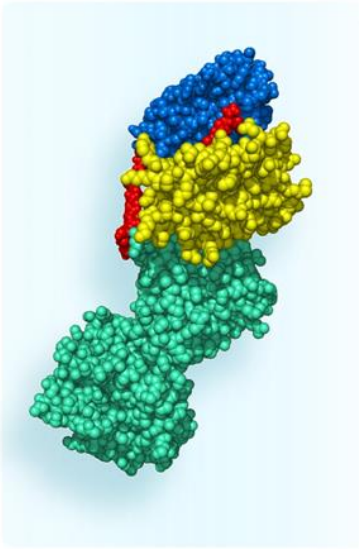
WTX-124 Phase 1/1b
Preliminary Data

Preliminary clinical data collected as of October 18, 2023,
from an ongoing Phase I/1b study

WTX-124: Expanding the Utility of IL-2 Therapy



The Challenge

Deliver the benefits of IL-2 therapy with less toxicity to a broader range of patients

Potential WTX-124 Advantages and Opportunity

- Delivery of IL-2 selectively to the TME to improve the therapeutic index
- Potential for activity beyond approved indications for rhIL-2
- IL-2 therapy with an improved therapeutic index could address an immediate unmet medical need for patients whose disease has progressed despite treatment with checkpoint therapy
- Strong rationale for combination with checkpoint inhibitors in earlier lines of therapy

Status

- Enrolling patients in Phase 1/1b clinical trial both as a single agent and in combination with pembrolizumab
- Wholly owned

Abbreviation: TME-tumor microenvironment

First-In-Human Study of WTX-124 Monotherapy and in Combination with Pembrolizumab

Phase 1/1b clinical trial (WTX-124x2101)

Monotherapy Dose Escalation

Patients with IO sensitive tumor types who have exhausted all SOC options or for whom SOC is not indicated

Determination of *monotherapy* MTD/RDE

Combination Dose Escalation with Pembrolizumab

Patients with IO sensitive tumor types who have exhausted all SOC options or for whom SOC is not indicated

Determination of *combination therapy* MTD/RDE

Monotherapy/Combination Dose Expansion

- Advanced or metastatic renal cell carcinoma
- Advanced or metastatic cutaneous malignant melanoma
- Other advanced or metastatic IO sensitive tumor types TBD

Trial Details

- Monotherapy and combination therapy dose escalations to enroll in parallel with staggered start for combination
- mTPI (Modified Toxicity Probability Interval) design
- Enrolling ~150 patients total
- Assessment of safety, pharmacokinetics, MTD/RDE, biomarkers, ADA and efficacy
- Concurrent biomarker analysis on blood and tumor tissue to evaluate POM and confirm differential activity based on conditional activation

SITC November 3, 2023: Announced initial safety, tolerability, pharmacokinetics and biomarker data

Abbreviations: MTD-maximum tolerated dose; RDE-recommended dose for expansion; ADA-anti drug antibody; IO-immuno-oncology; SOC-standard of care; POM-proof of mechanism

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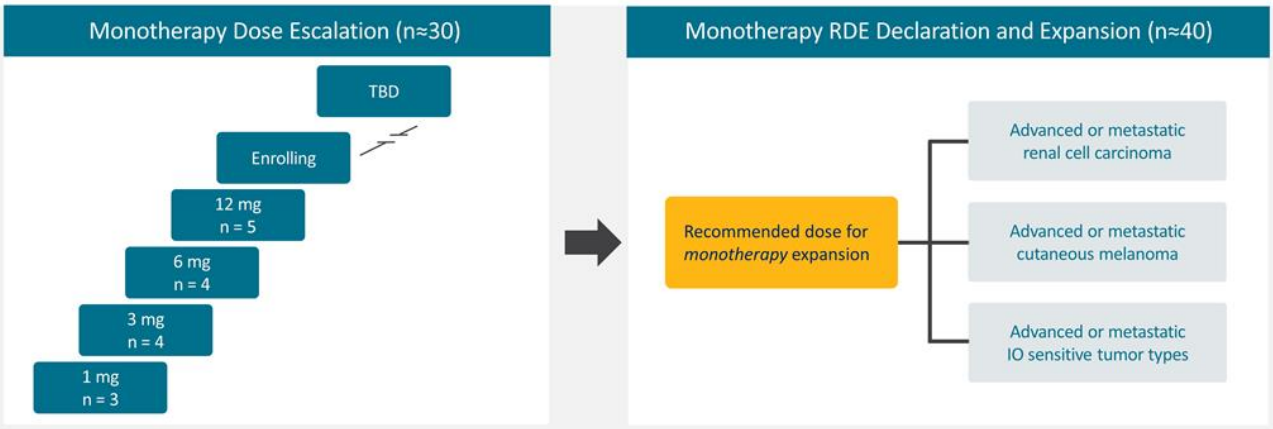
Study Schema for Monotherapy Dose Escalation Portion of WTX-124x2101



- Patients with IO sensitive tumor types who have exhausted all SOC options or for whom SOC is not indicated
- mTPI (Modified Toxicity Probability Interval) design, ability to add enrichment cohorts at meaningful dose levels
- Assessment of safety, pharmacokinetics, MTD/RDE, biomarkers, ADA and efficacy
- Concurrent biomarker analysis on blood and tumor tissue to evaluate POM and confirm differential activity based on conditional activation

1H 2024: Anticipated additional monotherapy dose escalation data, RDE declaration and opening of expansion arms

Abbreviations: RDE-recommended dose for expansion; POM-proof of mechanism; SOC-standard of care; MTD-maximum tolerated dose; ADA-antidrug antibody

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Patient Demographics from Early Monotherapy Dose Escalation Cohorts

Enrollment of heavily pretreated patients with tumor types for which immunotherapy, including Proleukin, is indicated

Characteristic		1 mg (N=3)	3 mg (N=4)	6 mg (N=4)	12 mg (N=5)	Total (N=16)
Age (years)	Mean (SD)	70.7 (12.42)	69.5 (7.33)	57.8 (9.36)	69.8 (11.32)	66.9 (10.62)
	Median	64.0	67.5	61.0	73.0	66.0
Sex, n (%)	Female	2 (66.7%)	2 (50.0%)	3 (75.0%)	1 (20.0%)	8 (50.0%)
	Male	1 (33.3%)	2 (50.0%)	1 (25.0%)	4 (80.0%)	8 (50.0%)
Race, n (%)	Black/African-American	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (6.2%)
	White	2 (66.7%)	3 (75.0%)	3 (75.0%)	5 (100.0%)	13 (81.2%)
	Unknown	1 (33.3%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	2 (12.5%)
	Melanoma*	1 (33.3%)	2 (50.0%)	2 (50.0%)	3 (60.0%)	8 (50.0%)
Tumor type, n (%)	NSCLC	1 (33.3%)	2 (50.0%)	1 (25.0%)	1 (20.0%)	5 (31.3%)
	Renal Cell Carcinoma	1 (33.3%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	2 (12.5%)
	Cutaneous SCC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (6.3%)
Prior lines of systemic therapy (including immunotherapy), n (%)	1	0 (0.0%)	0 (0.0%)	1 (25.0%)	1 (20.0%)	2 (12.5%)
	2	0 (0.0%)	2 (50.0%)	0 (0.0%)	2 (40.0%)	4 (25.0%)
	3	2 (66.7%)	1 (25.0%)	2 (50.0%)	0 (0.0%)	5 (31.2%)
	≥4	1 (33.3%)	1 (25.0%)	1 (25.0%)	2 (40.0%)	5 (31.2%)

*Includes patients with cutaneous, uveal and mucosal melanoma; all patients enrolled in Cohorts 1-4 previously progressed on standard-of-care immunotherapy regimens; 9/16 (56.3%) previously developed immune-related adverse events while receiving immunotherapy

**Preliminary clinical data includes data collected as of October 18, 2023, from 16 patients in an ongoing Phase 1/1b clinical trial.

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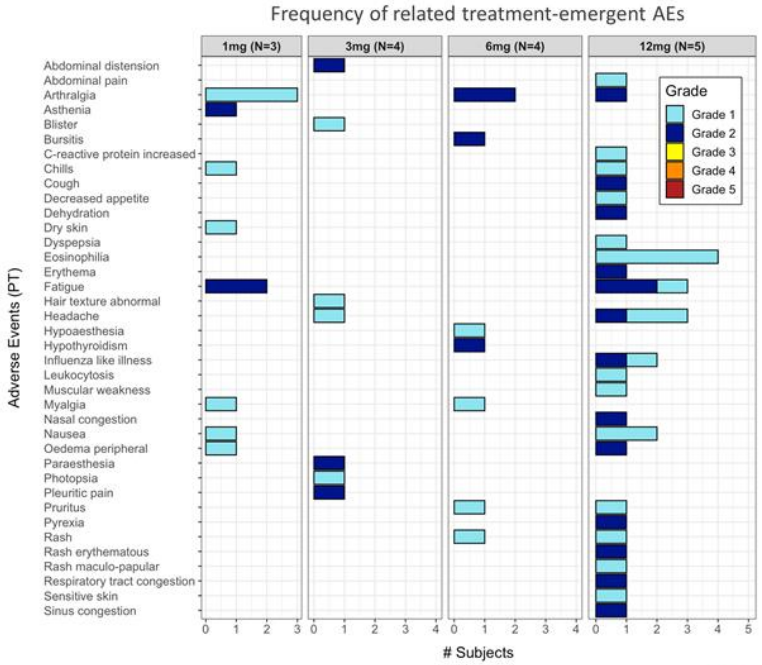
WTX-124 was Generally Well-Tolerated in the Outpatient Setting at Relevant Doses

Sixteen patients in four dose escalation cohorts (1-12 mg IV Q2W) were evaluable for safety

Key safety findings to date:

- All study drug related treatment-emergent adverse events (TEAEs) were mild to moderate in severity
- Arthralgias and fatigue were the most common related TEAEs
- No patient developed vascular leak syndrome of any grade (adverse event common to HD IL-2)
- No evidence of cytokine release syndrome
- No patient developed a dose-limiting toxicity or a treatment-related serious AE
- No patient discontinued study drug due to a treatment-related AE

Abbreviation: HD-high dose



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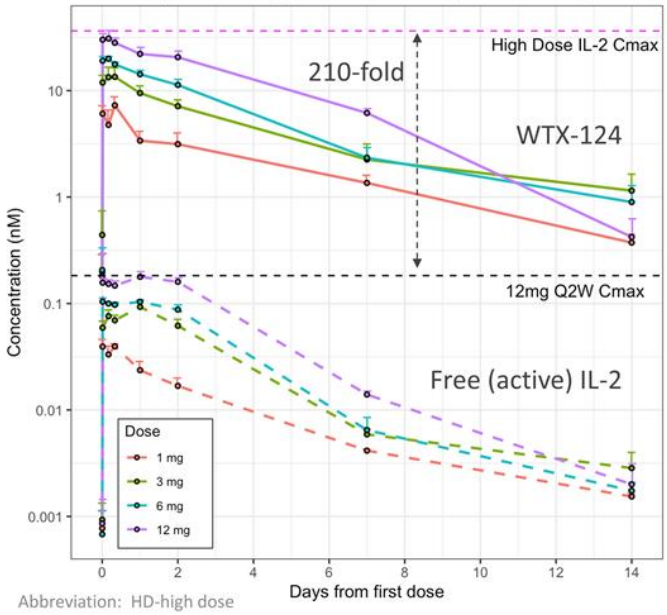
Plasma PK Data Show an Extended WTX-124 Half-Life with Low Free (Active) IL-2 Exposure

Preliminary PK data validate INDUKINE design and support improved therapeutic index and safety profile of WTX-124

Cycle 1 PK profiles for WTX-124 and free (active) IL-2 compared to high-dose IL-2 C_{max} (mean ± SEM)



Abbreviation: HD-high dose

Key findings include:

- Dose-dependent increase in WTX-124 plasma exposure
- Low free (active) IL-2 levels (<1.6% of prodrug) during the dosing phase
- WTX-124 prodrug Cmax at 12 mg IV Q2W is comparable to HD IL-2
- Free (active) IL-2 at 12 mg IV Q2W was **~210-fold lower** than HD IL-2
- Preliminary WTX-124 half-life ranged from 1.86-5.79 days
- Preliminary ADA data: 5/15 patients exhibited non-dose dependent, treatment-emergent ADA (4/5 are low titer) with no impact on repeat dose exposure
- Data suggest wide therapeutic index consistent with INDUKINE hypothesis, continued dose escalation is supported

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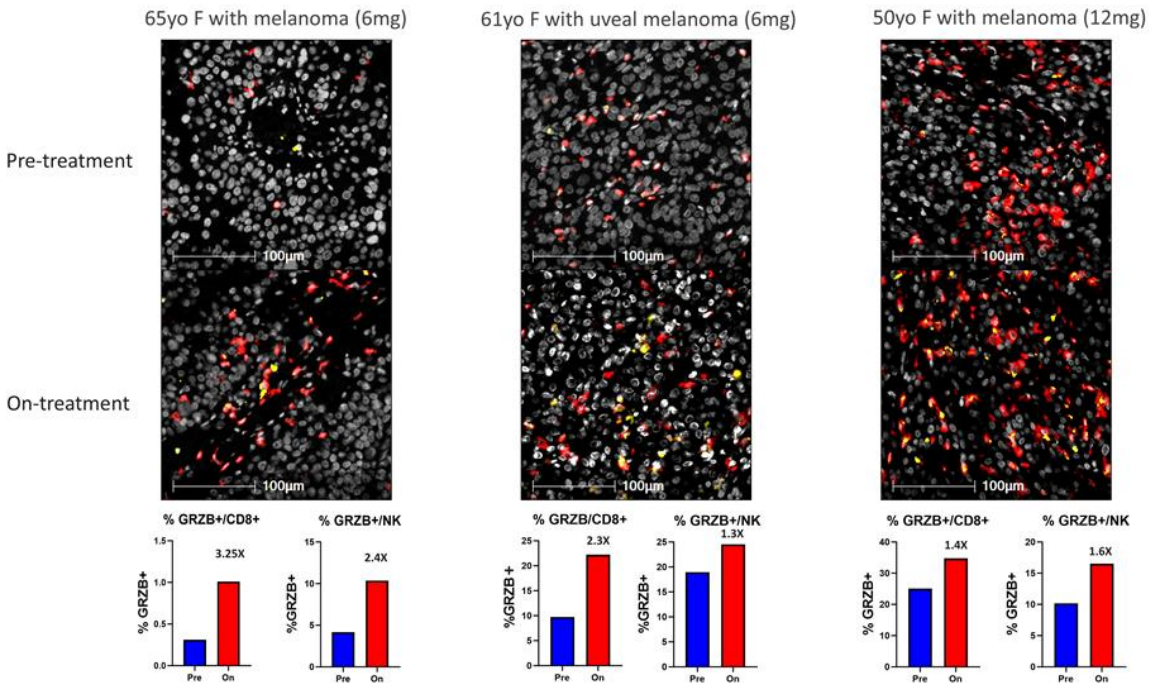
Immunofluorescence Staining of Tumor Biopsies from Patients Treated with WTX-124

Tumor-specific expansion and activation of CD8 T cells and NK cells differentiate WTX-124 among next-gen IL-2 molecules



DAPI
CD8
GRZB

Granzyme B (GRZB) is one of the primary markers of activated T cells

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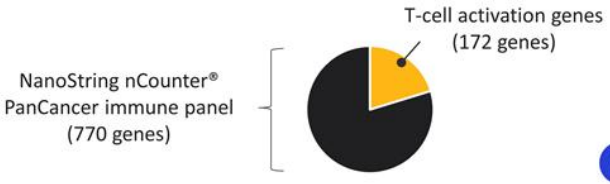
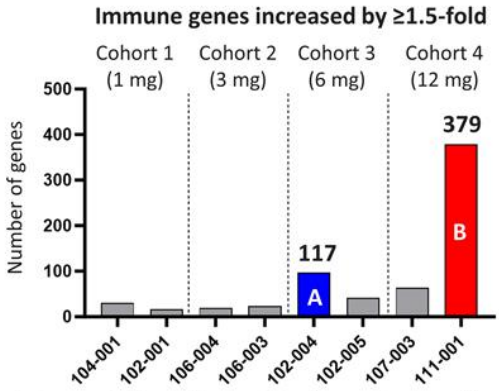
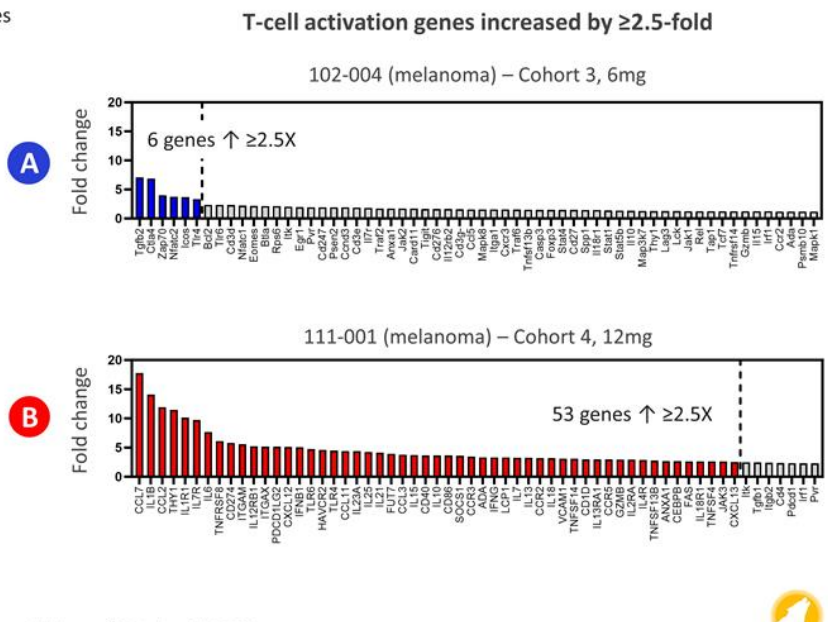
WTX-124 Induced Dose-Dependent Changes in Immune Gene Expression Consistent with IL-2 Activity in the Tumor Microenvironment







*Data presented for eight patients for whom on-treatment biopsies were available as of October 18, 2023

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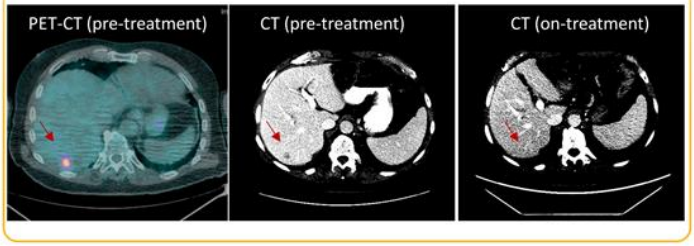
WTX-124 Demonstrated Monotherapy Antitumor Activity in Patients Refractory to ICI Therapy

At 12 mg IV Q2W, WTX-124 shrank treatment-refractory tumor metastatic deposits (3/5 patients); all 12 mg responders remain on study drug

Objective response observed at 12 mg dose

- 78-year-old man with melanoma who progressed on nivolumab/relatlimab (Opdualag™)
- Achieved a RECIST 1.1 partial response (PR; unconfirmed) at the first restaging scan (8 weeks) after two cycles of WTX-124
- Imaging studies (*see below*) show complete resolution of a 1.4 cm target lesion in the liver
- Stable non-target bone lesion in the T11 vertebral body



Additional evidence of antitumor activity

Cohort 4 (12 mg):

- 72-year-old man with cutaneous SCC with shrinkage of a premaxillary subcutaneous nodule on ultrasound; at the first restaging scan (8 weeks), investigator interpretation was consistent with a partial response**
- 76-year-old man with refractory NSCLC with rapid necrosis of a large, visible scalp lesion after the first dose of study drug; mixed response, remains on study drug

Cohort 3 (6 mg):

- 65-year-old woman with progressive melanoma at baseline with stable disease (SD) for 4 months

Cohort 1 (1 mg):

- 63-year-old man with refractory NSCLC with SD for 6 months

Abbreviation: ICI-immune checkpoint inhibitor

*Preliminary clinical data includes data collected as of October 18, 2023, from 16 patients in an ongoing Phase 1/1b clinical trial.

**Staging scan data as of November 1, 2023.

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Proof of Mechanism for WTX-124 and Proof of Concept for INDUKINE Design

Preliminary monotherapy dose escalation data from ongoing Phase 1/1b study establish biologic and clinical activity for WTX-124

- **WTX-124 administered as a monotherapy IV Q2W has been well tolerated and reached exposures associated with intratumoral IL-2 pharmacodynamic activity and clinical responses despite enrollment of a heterogeneous patient population and small patient numbers**
- WTX-124 up to 12 mg IV Q2W was generally well tolerated with no cases of vascular leak syndrome of any grade, no DLTs, no related SAEs, and no treatment discontinuations due to related AEs
- PK data showed extended prodrug exposure in plasma with substantially lower levels of free (active) IL-2 than HD IL-2 therapy (Proleukin®), accounting for the improved therapeutic index and opportunity for continued dose escalation
- WTX-124 6-12 mg IV Q2W achieved biologically relevant IL-2 exposures in the tumor microenvironment as demonstrated by antitumor activity (uPR, SD by RECIST 1.1) and CD8+ T cell and NK cell expansion and activation
- Data support potential of WTX-124 to elicit monotherapy activity from the delivery of a fully potent, wild-type IL-2 to the TME in patients with refractory solid tumors
- Expecting to report additional interim data from monotherapy arm, informing RDE declaration and opening of expansion arms in 1H 2024

Abbreviations: AE-adverse event; SAE-serious adverse event; DLT-dose limiting toxicity; HD-high dose; TME-tumor microenvironment; RDE-recommended dose for expansion; uPR-unconfirmed partial response; SD-stable disease

*Preliminary clinical data includes data collected as of October 18, 2023, from 16 patients in an ongoing, open label Phase 1/1b clinical trial.

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Thank You!