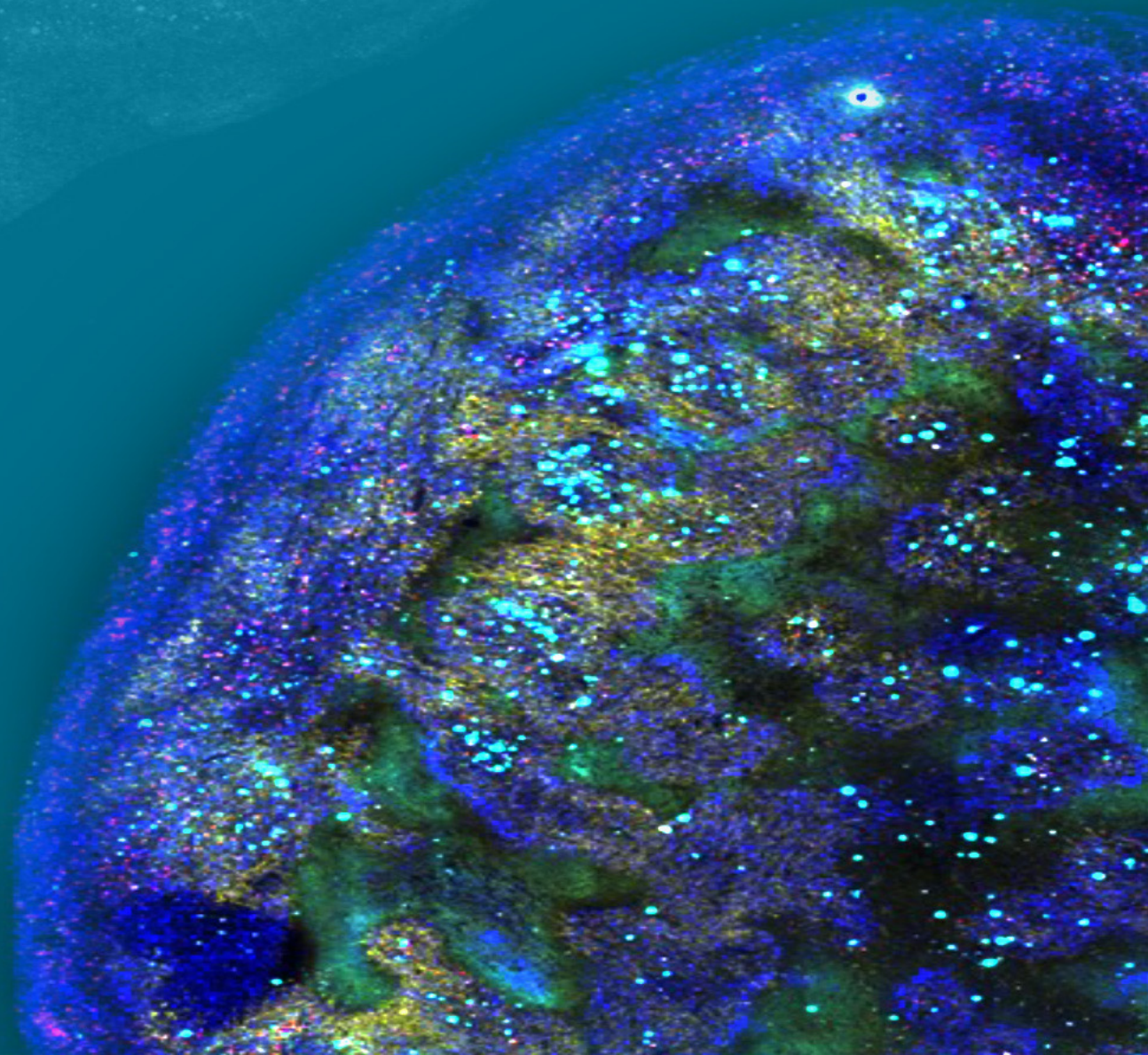




Shifting the Balance in Cytokine Therapeutics

Corporate Overview | May 2, 2024



Cautionary 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 projection of the cash runway, the expected timeline for the preclinical and clinical development of product candidates and the availability of data from such preclinical and clinical development, the potential activity and efficacy of product candidates in future preclinical studies and clinical trials, and the anticipated safety profile of product candidates, 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 manage cash resources and obtain additional 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.

Who we are

Our mission is to unlock the promise of cytokines as more effective immunotherapies

We are a clinical-stage biopharmaceutical company developing next generation, conditionally activated cytokine therapies for the treatment of cancer and other serious diseases

We have two investigational drugs in Phase 1 clinical trials

Our headquarters and research facilities are located in Watertown, Massachusetts



Clinical-Stage Company with Compelling Portfolio of Innovative Cytokine Therapeutics

Designed on a platform capable of addressing broad therapeutic applications in oncology and beyond



Clinical Programs

WTX-124

Ongoing enrollment in the dose escalation stage of a Phase 1/1b trial as a monotherapy and in combination with pembrolizumab

WTX-330

Ongoing enrollment in the dose escalation stage of a Phase 1 trial as a monotherapy



Key Catalysts

WTX-124

Initial clinical data demonstrated WTX-124 monotherapy clinical activity and PoC for INDUKINE™ design

Anticipating additional monotherapy dose escalation data to inform RDE and opening of expansion arms in 1H24



Robust Pipeline

JZP898

IFN α INDUKINE licensed to Jazz Pharmaceuticals; Enrolling in Phase 1 trial

WTX-712

IL-21 INDUKINE development candidate

WTX-518

IL-18 INDUKINE development candidate



Scalable Platform

PREDATOR™ Platform

Capability for pipeline expansion for a broad range of mechanisms and indications

Business Development

Broad portfolio of clinical and preclinical stage assets available for partnering



Financial Stability

Cash and cash equivalents of \$139.2M (as of March 31, 2024), together with cash impacts of loan refinancing, provides runway through at least 1Q 2026

Overcoming Off-Target Toxicity has been a Key Challenge for Cytokine Therapy

The Challenge:
Off-Tumor Cytokine Toxicity Limits
Therapeutic Index

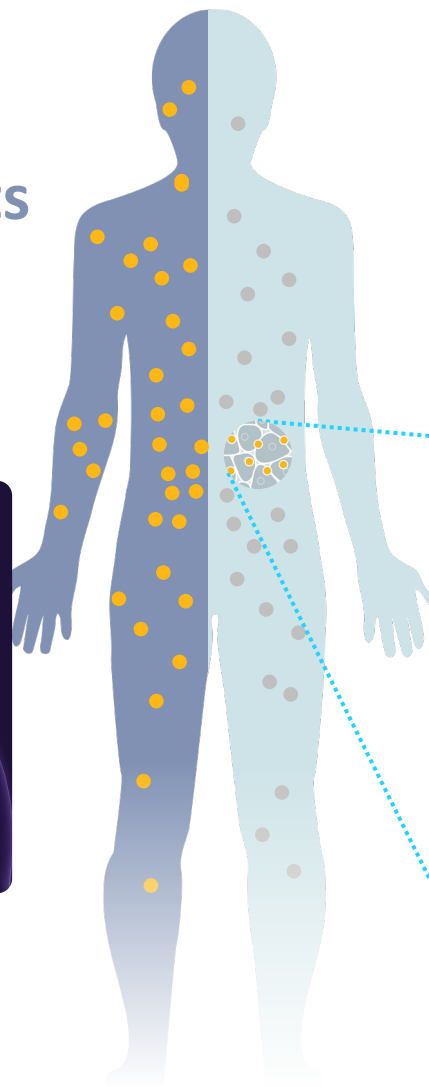
Suboptimal Pharmaceutical Properties



Toxicity

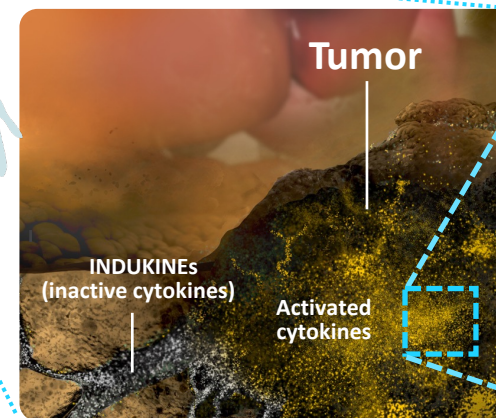


Poor Clinical Outcomes

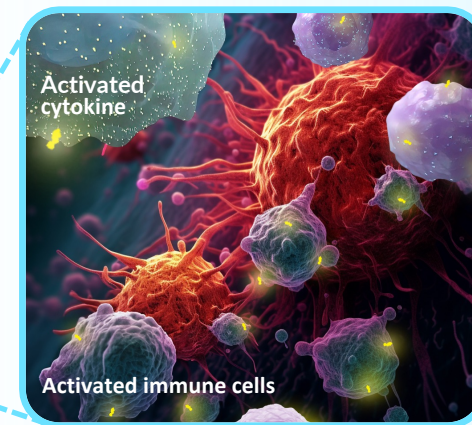


Our Solution:
Conditionally Activated
Immunotherapy

With Optimized Therapeutic Index



Targeted Delivery to the
Tumor Microenvironment



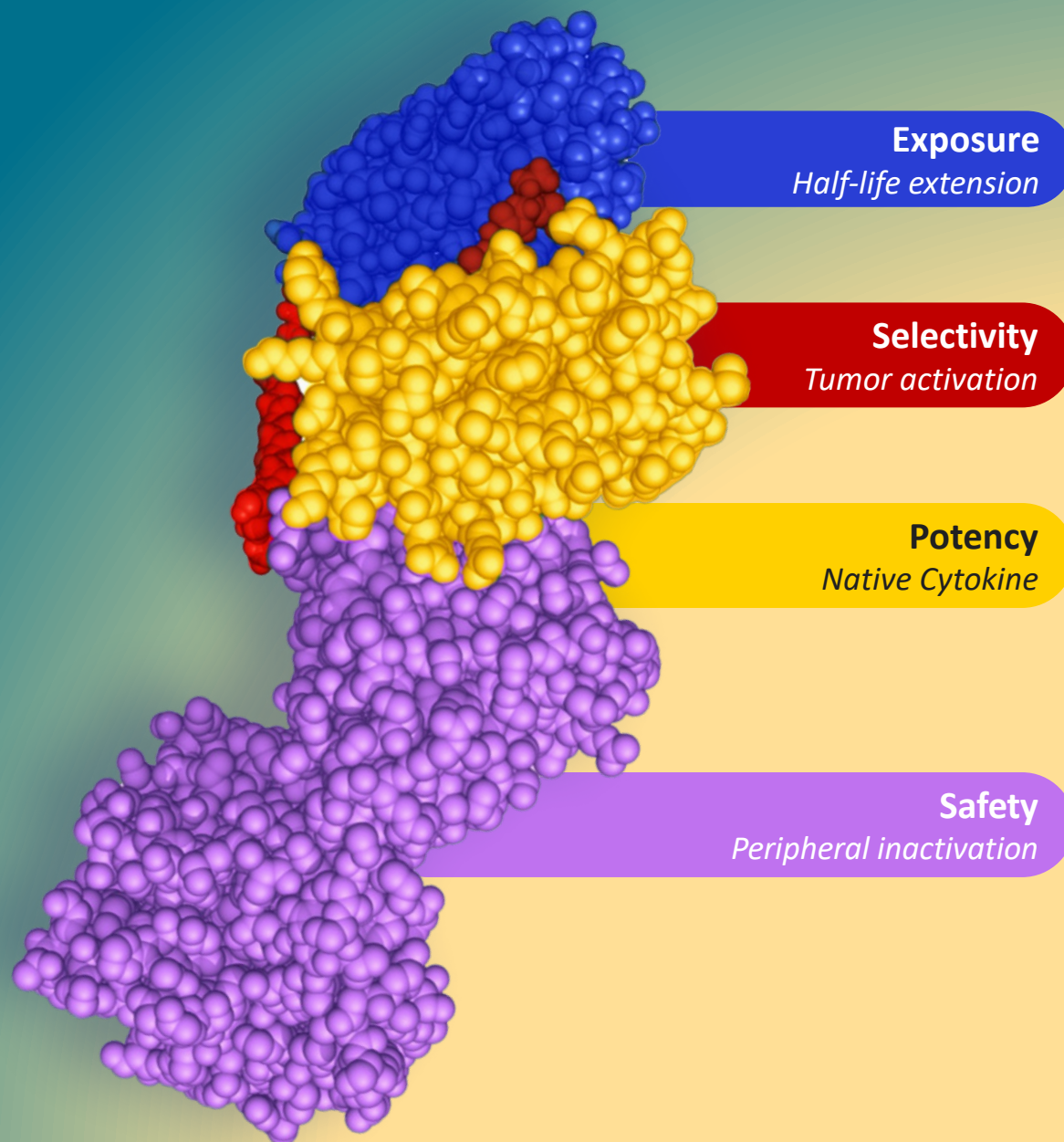
On-Target Immune
Activation



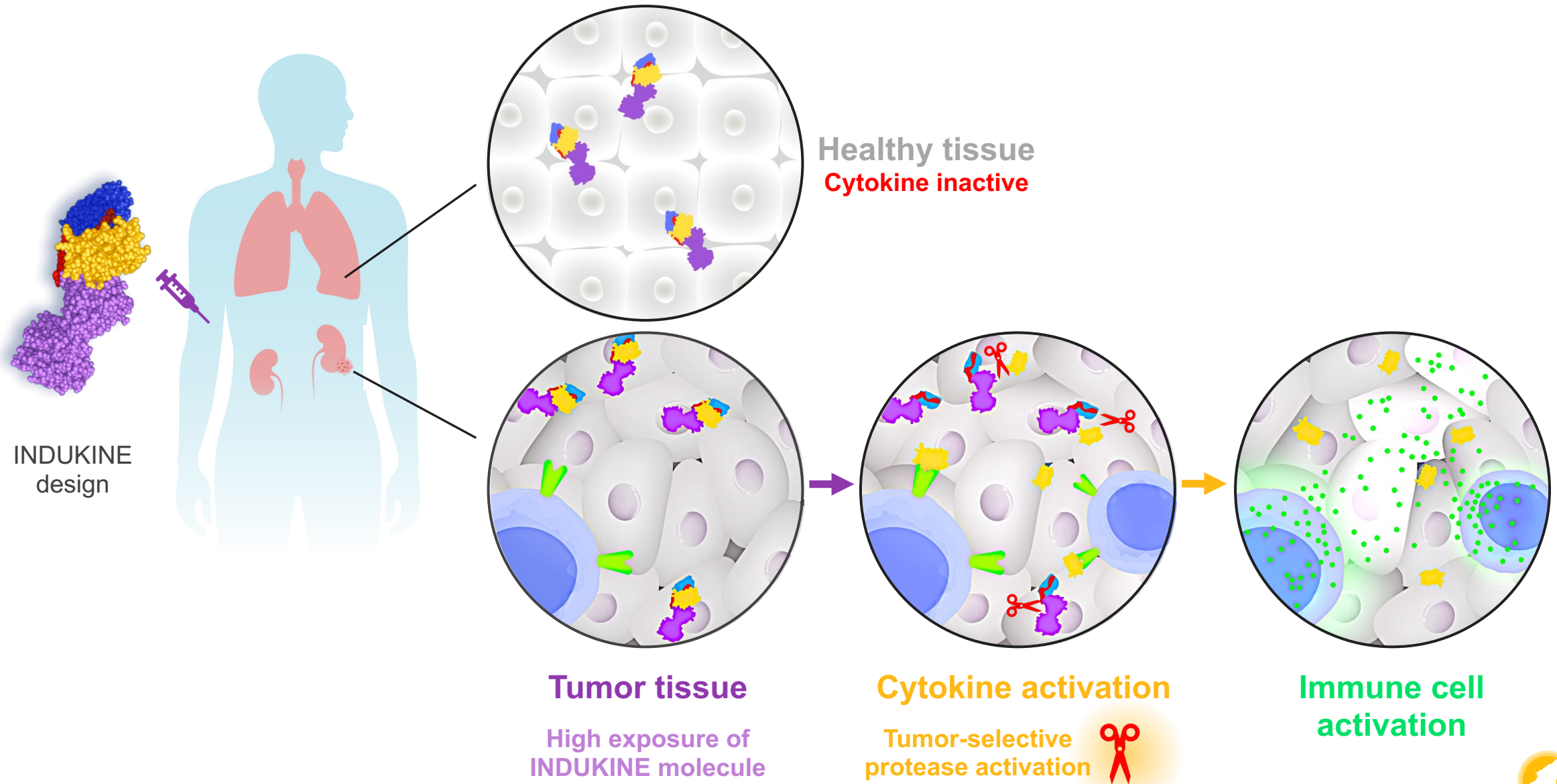
PREDATOR Platform

Tunable, Tissue-targeted Therapeutics for Cancer and other Diseases

INDUKINE molecules contain multiple domains, each with a unique function that can be 'tuned' for specific mechanisms and pharmaceutical properties necessary to treat disease

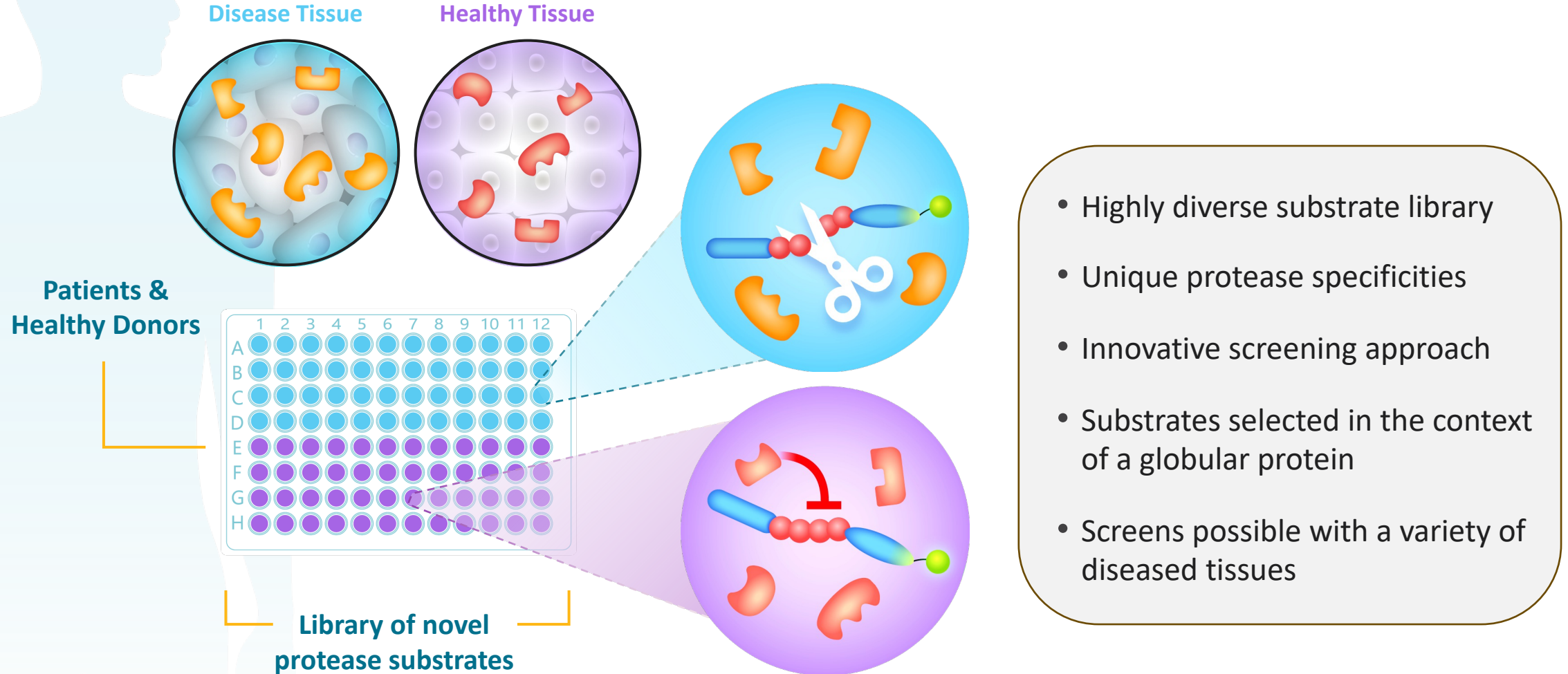


INDUKINE Molecules: Targeting Cytokine Activity to Diseased Tissue









PREDATOR Platform: Disease Selective Protease (DSP) Substrate Screen

Innovative Linker Discovery Approach to Address Protease Heterogeneity Across Diseases and Patients

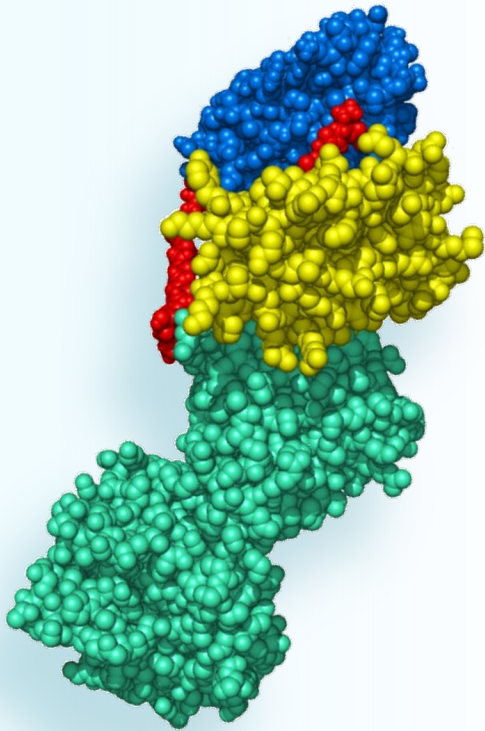


A Balanced Portfolio of Clinical and Preclinical Drug Candidates

PROGRAM	INDICATIONS	DISCOVERY	IND-ENABLING	PHASE 1	PHASE 2	RIGHTS
WTX-124 IL-2 INDUKINE Molecule	Advanced or Metastatic Solid Tumors Monotherapy and in combination with Pembrolizumab					
WTX-330 IL-12 INDUKINE Molecule	Advanced or Metastatic Solid Tumors and Lymphoma Monotherapy					
JZP898 IFN α INDUKINE Molecule	Cancer Indications Exclusive Global Rights Licensed to Jazz					
WTX-712 IL-21 INDUKINE Molecule	Cancer Indications					
WTX-518 IL-18 INDUKINE Molecule	Cancer Indications					
Novel INDUKINE Molecules	Immuno-oncology Inflammatory Diseases					

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

Delivering IL-2 to the Tumor Microenvironment with Improved Safety and Therapeutic Index



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 rhIL2
- IL-2 therapy with an improved therapeutic index could address an immediate unmet medical need for patients who have progressed on checkpoint therapy
- Strong rationale for combination with checkpoint inhibitors in earlier lines of therapy

Status

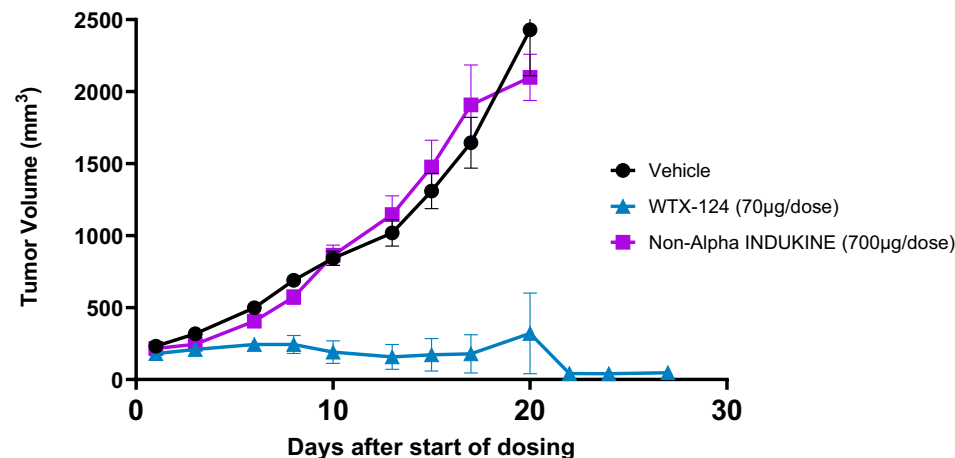
- Enrolling patients in Phase 1 clinical trial both as a single agent and in combination with Pembrolizumab
- Released preliminary clinical data at 2023 Society for Immunotherapy of Cancer Annual Meeting
- Company to present an update at 2024 American Society for Clinical Oncology annual meeting
- On track for RDE declaration and opening of expansion arms anticipated 1H 2024

Abbreviations: TME-tumor microenvironment; RDE-recommended dose for expansion

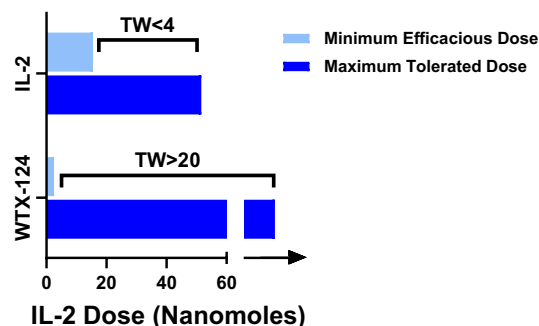
WTX-124 has an Improved Therapeutic Index Compared to Native IL-2

Full potency IL-2 is required for complete tumor regression in preclinical models; WTX-124 generates immune memory

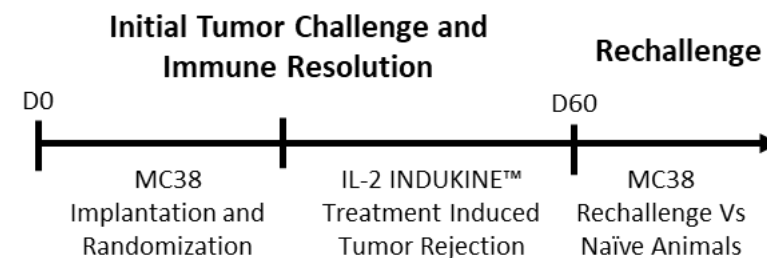
WTX-124 antitumor activity is substantially more potent than non-alpha IL-2 INDUKINE in MC38 tumor model



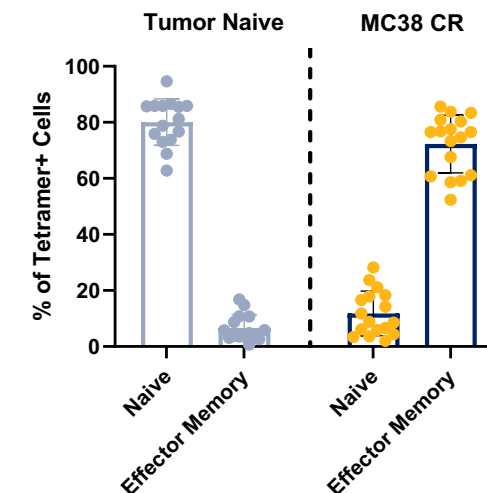
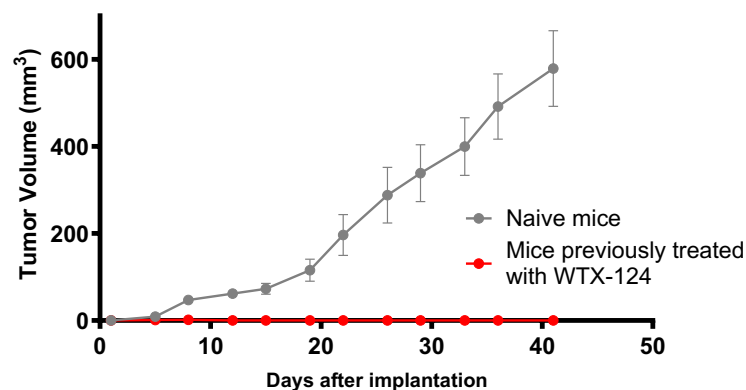
Improved therapeutic window compared to IL-2 cytokine



WTX-124 activates long-term antitumor immune memory



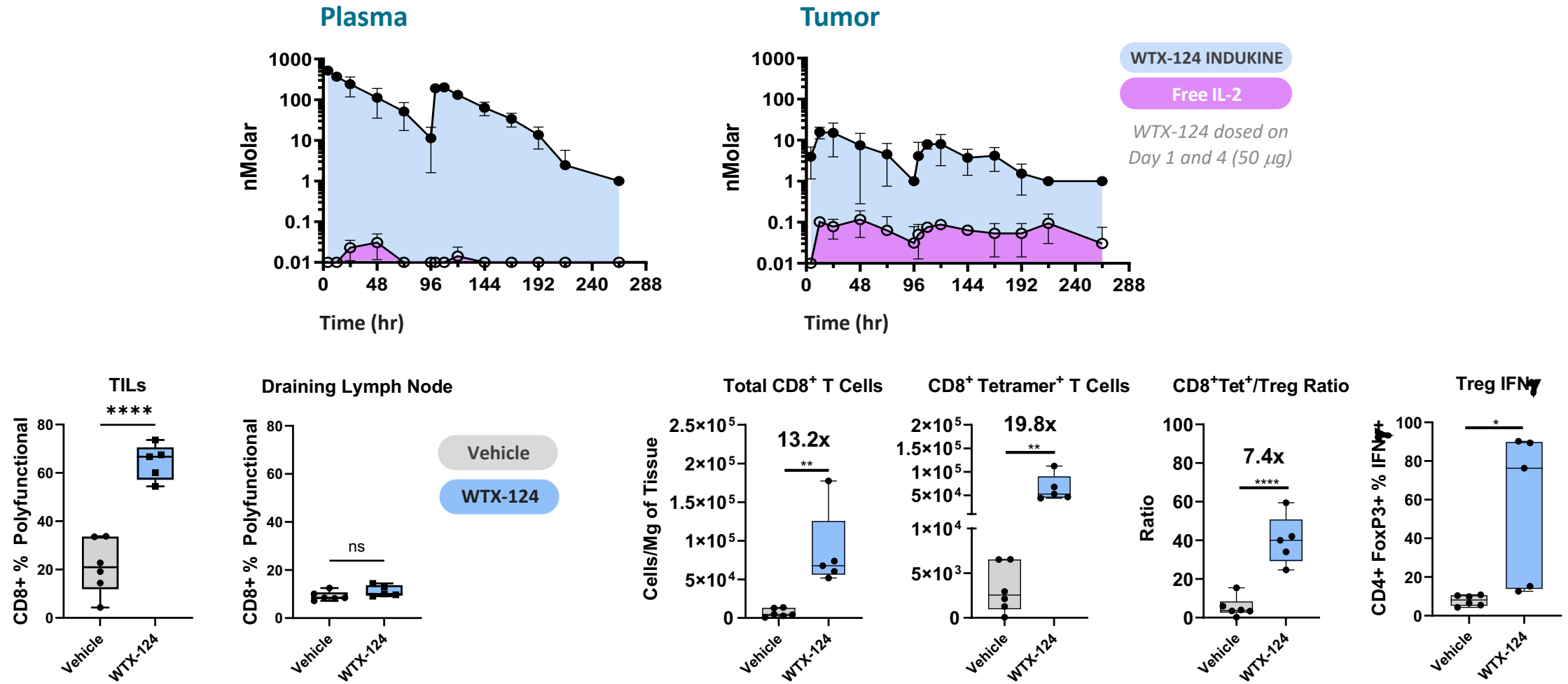
MC38 Tumor Model Rechallenge



Nirschl CJ et al., SITC 2023 Poster: Optimal Antitumor Immunity is Triggered by WTX-124, a Clinical Stage Conditionally Activated INDUKINE™ Molecule

WTX-124 Delivers IL-2 Selectively to Tumor Tissue in Preclinical Models

Robust expansion and activation of antitumor CD8⁺ T effector cells in the TME

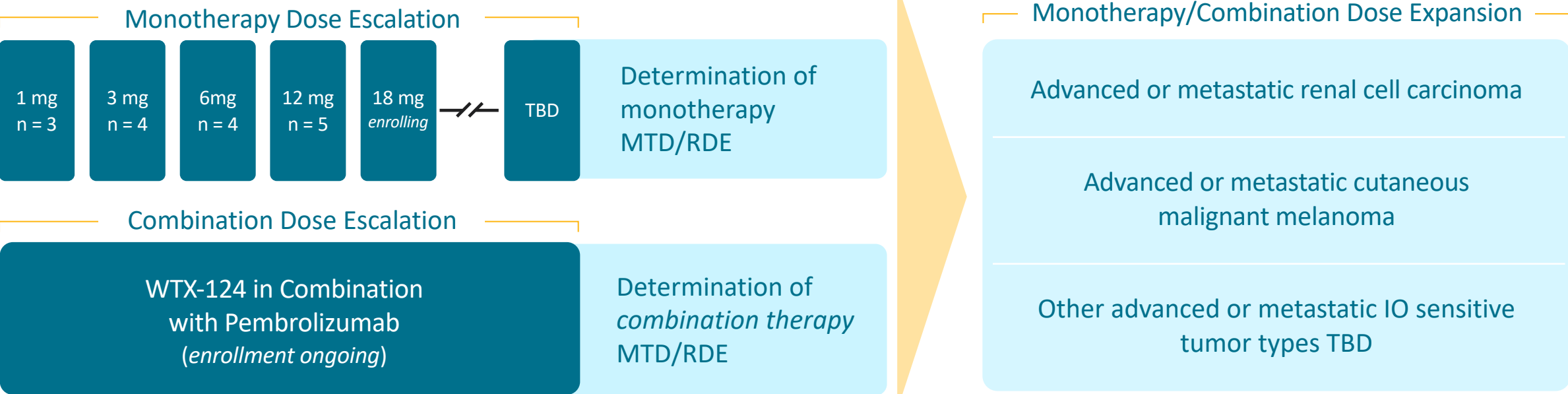



Nirschl CJ et al., Cancer Immunology Research 2022 10(5):581-596

Abbreviations: TIL-tumor infiltrating lymphocytes; TME-tumor microenvironment

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

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



 Trial Details	Monotherapy and combination therapy dose escalations enrolled 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 to evaluate proof of mechanism and tumor-selective conditional activation
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1H 2024: Additional monotherapy dose escalation data, RDE declaration and opening of expansion arms anticipated

Patient Demographics from Early Monotherapy Dose Escalation Cohorts (n=16)

Demographics

AGE (years)	Mean (SD)	66.9 (10.62)
	Median	66.0
SEX, n (%)	Female	8 (50.0%)
	Male	8 (50.0%)
RACE, n (%)	Black/African-American	1 (6.2%)
	White	13 (81.2%)
	Unknown	2 (12.5%)

Prior lines of systemic therapy, (including immunotherapy)

	<u>n (%)</u>
1	2 (12.5%)
2	4 (25.0%)
3	5 (31.2%)
≥4	5 (31.2%)

Tumor type

	<u>n (%)</u>
Melanoma*	8 (50.0%)
NSCLC	5 (31.3%)
Renal Cell Carcinoma	2 (12.5%)
Cutaneous SCC	1 (6.3%)

- *Enrollment of heavily pretreated patients with tumor types for which immunotherapy, including Proleukin, is indicated*
- *All patients received prior immunotherapy and progressed*
- *Nine patients (56.3%) developed immune-related adverse events while receiving prior immunotherapy*

*Includes patients with cutaneous, uveal and mucosal melanoma; all patients enrolled in Cohorts 1-4 previously progressed on standard-of-care immunotherapy regimens

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

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

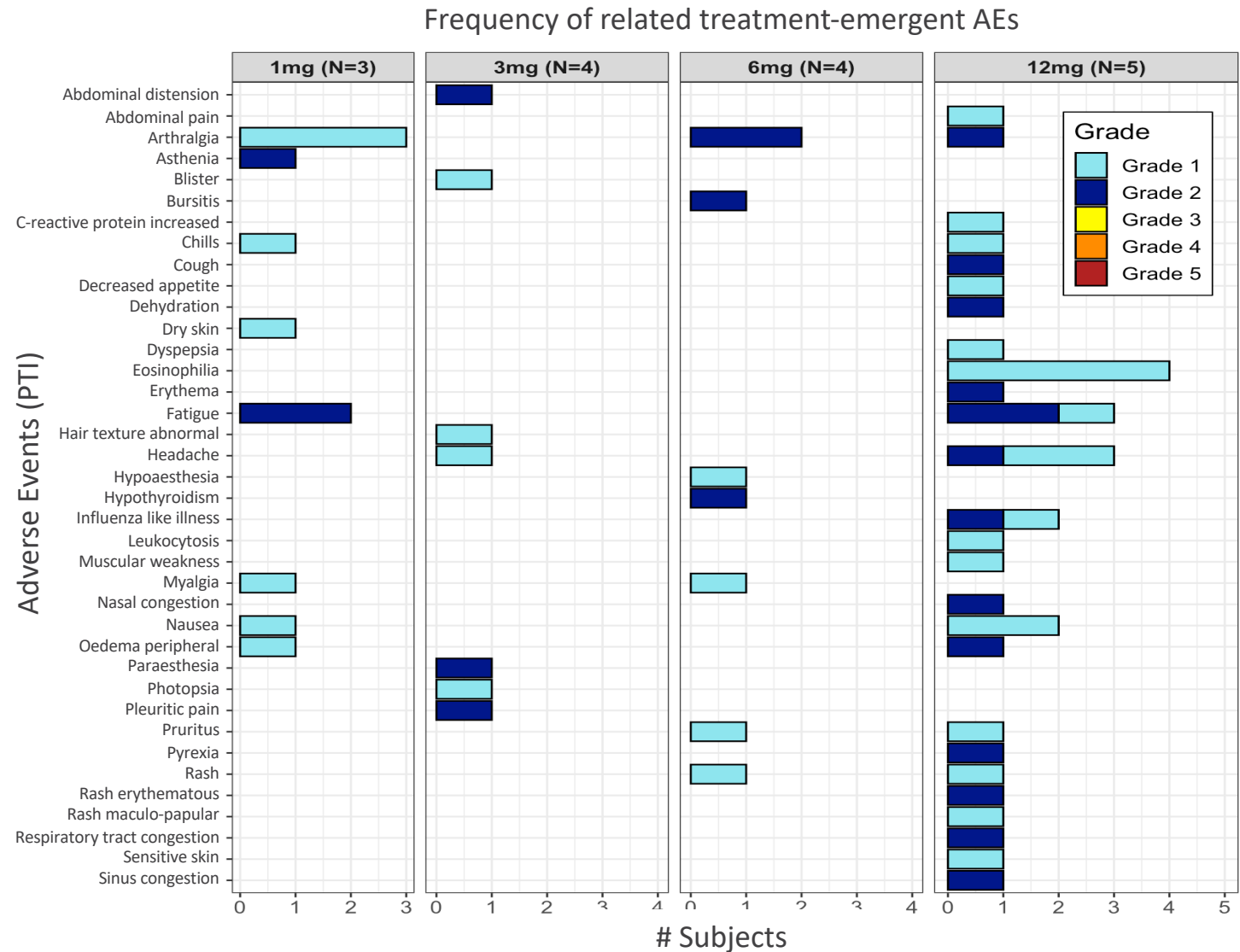
Sixteen patients in four dose escalation cohorts (1-12 mg IV Q2W) were evaluable for safety

Key safety findings to date:

- Drug related TEAEs: no Grade 3 or higher
- Arthralgias and fatigue were the most common related TEAEs
- No vascular leak syndrome of any grade (adverse event common to HD IL-2)
- No evidence of cytokine release syndrome
- No patient developed dose-limiting toxicity or treatment-related serious AE
- No patient discontinued study drug due to treatment-related AE

Abbreviations: TEAEs-treatment-emergent adverse events; HD-high dose; Q2W-once every two weeks

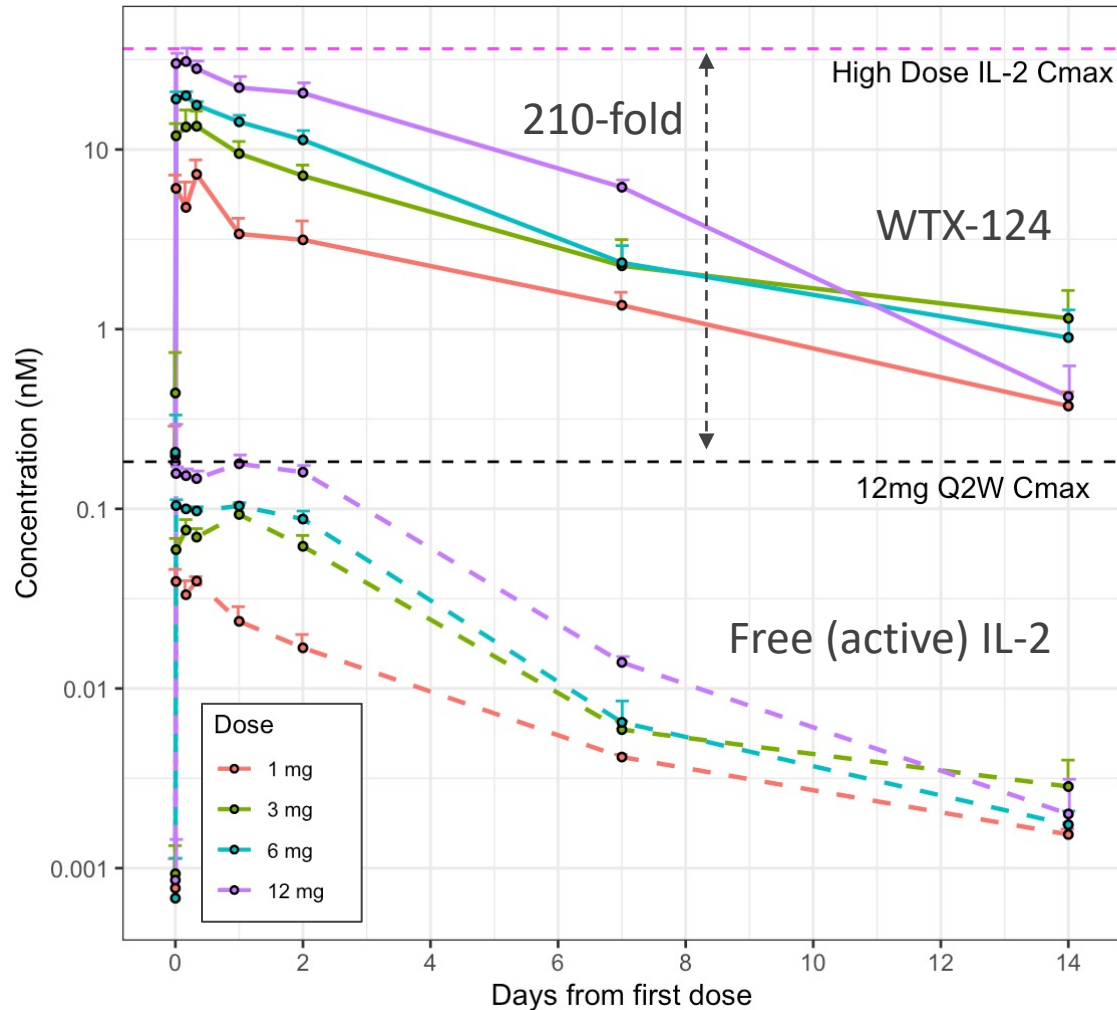
Note: Preliminary clinical data as of October 18, 2023, from 16 patients in an ongoing, open label Phase 1/1b clinical trial.



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)



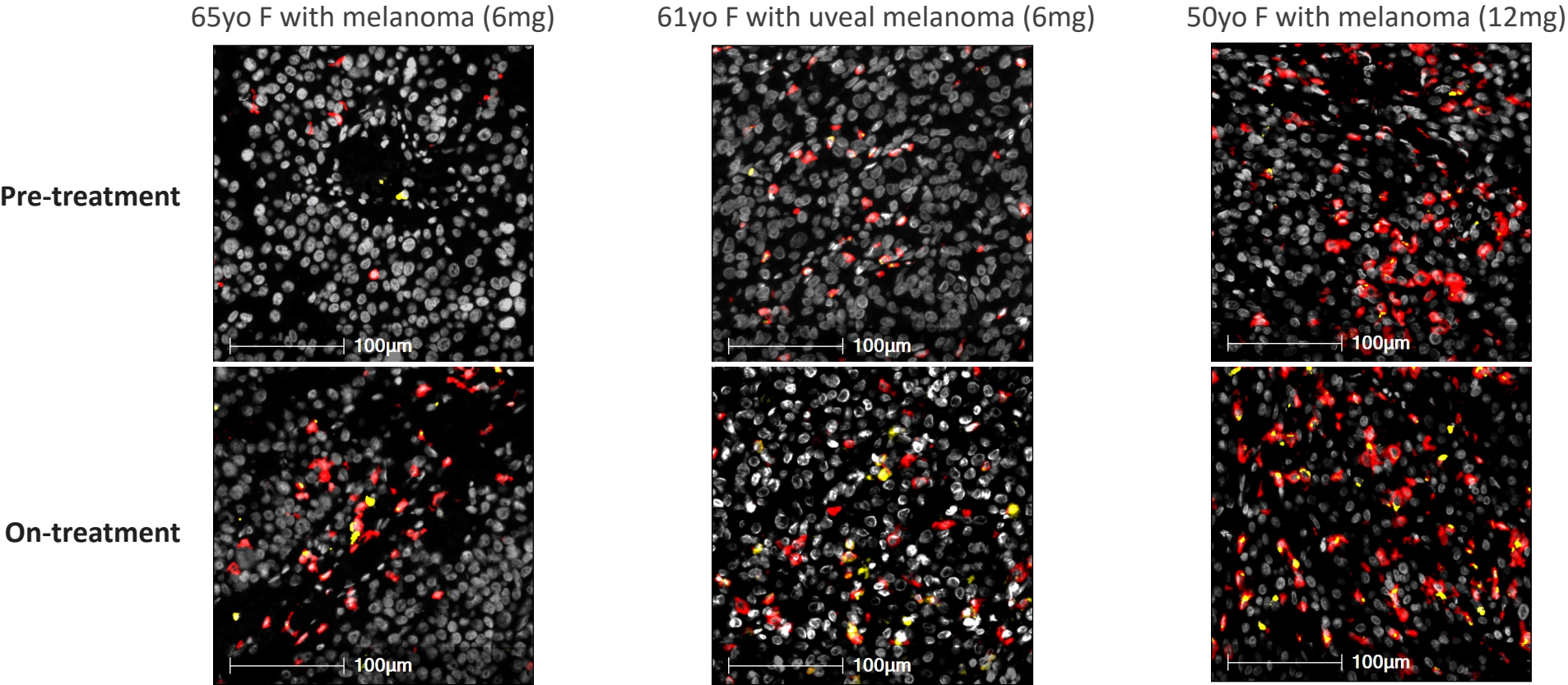
Key findings to date:

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

Abbreviations: HD-high dose; Q2W-once every two weeks

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

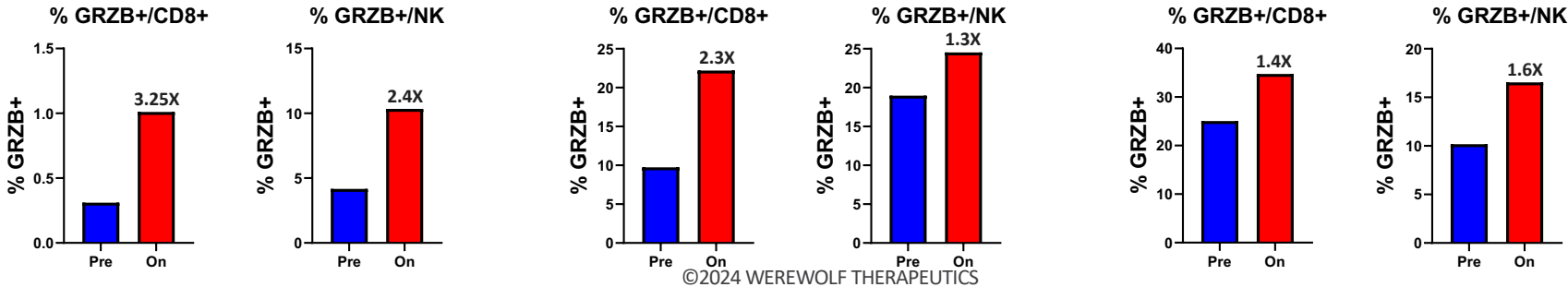


DAPI

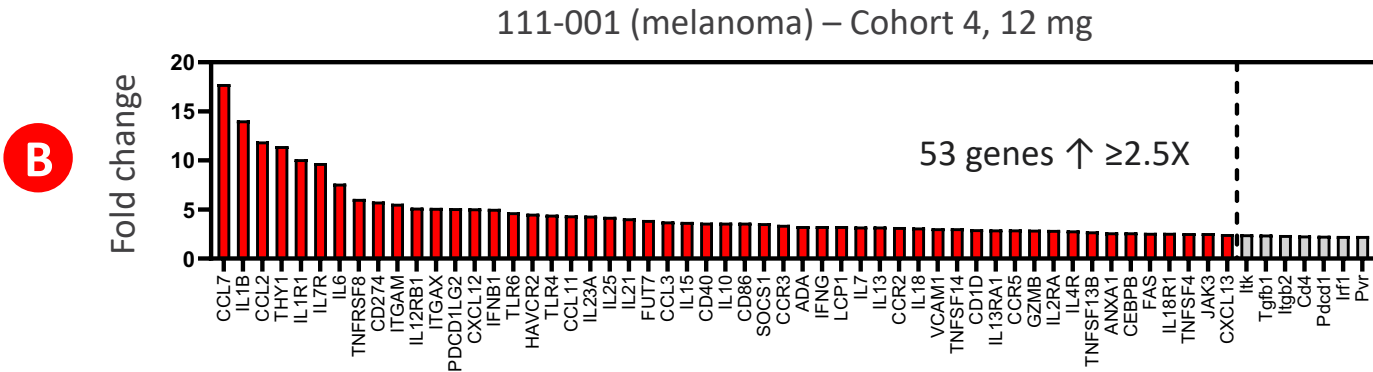
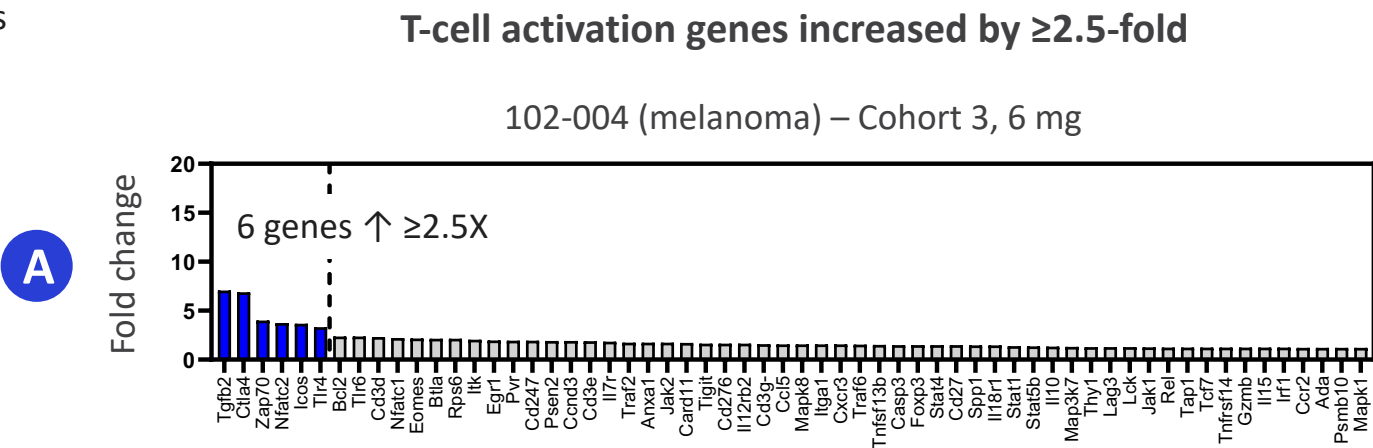
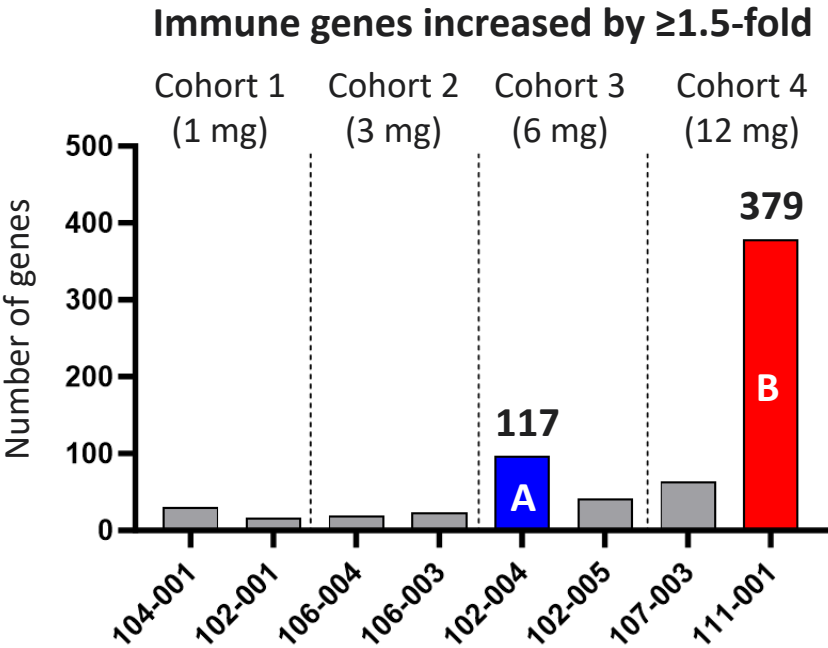
CD8

GRZB

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



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



Note: Data presented for eight patients for whom on-treatment biopsies were available as of October 11, 2023
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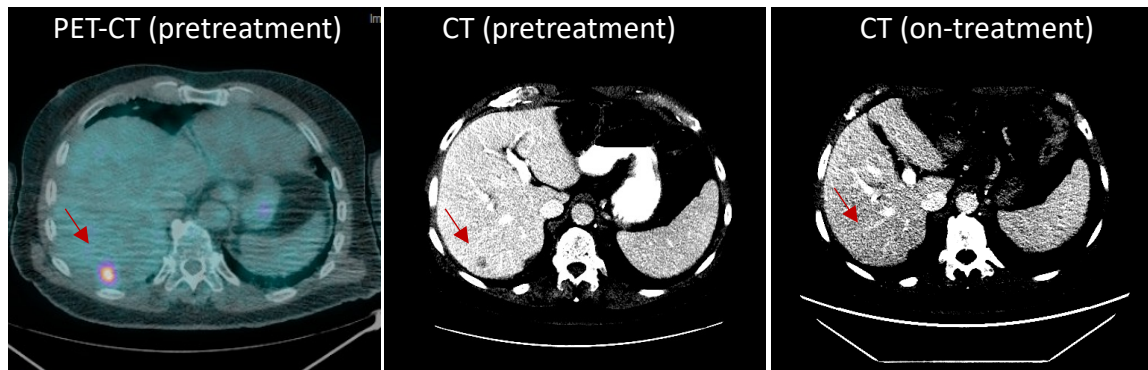


WTX-124 Demonstrated Monotherapy Antitumor Activity in Patients Refractory to ICI Therapy

At 12 mg dose level, WTX-124 shrank treatment-refractory tumor metastatic deposits (3/5 patients)

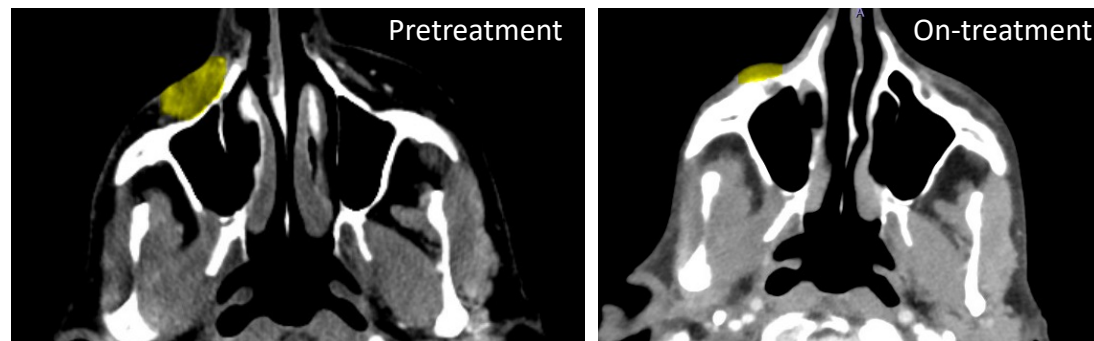
1. Patient 107-002: unconfirmed PR (RECIST 1.1)

- 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 (*below*) show complete resolution of a 1.4 cm target lesion in the liver
- Stable non-target bone lesion in the T11 vertebral body



2. Patient 102-006: unconfirmed PR (RECIST 1.1)

- 72-year-old man with cutaneous SCC who progressed on cemiplimab (Libtayo®); initial 8-week restaging CT scan showed uPR (>60% reduction in premaxillary target lesion)



3. Patient 106-006

- 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, remained on study drug for 14 weeks

Abbreviation: ICI-immune checkpoint inhibitors; PR-partial response; SCC-squamous cell carcinoma; NSCLC-Non-small cell lung cancer

Note: Preliminary clinical data as of November 1, 2023, from 16 patients in an ongoing, open label Phase 1/1b clinical trial.

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

Monotherapy WTX-124 administered in an outpatient setting has been well tolerated and has reached exposures associated with clinical responses in dose escalation

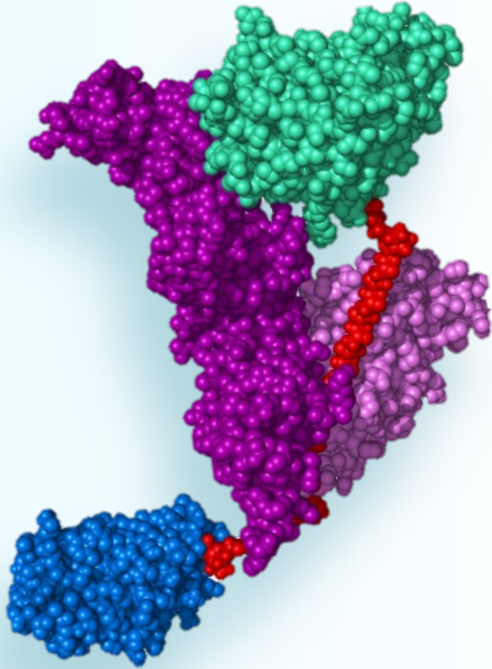
- Majority of patients treated would not have been eligible to receive HD IL-2 due to age, indication, or underlying organ function
- Among 16 patients treated with WTX-124 at doses up to 12 mg IV Q2W, there were no cases of vascular leak syndrome and no DLTs
- PK data showed extended prodrug exposure and low levels of free (active) IL-2 resulting in improved therapeutic index and opportunity for continued dose escalation
- WTX-124 administered at doses of 6-12 mg IV Q2W demonstrated CD8+ T cell and NK cell activation and antitumor activity (including 2 uPR at 12 mg) in multiple tumor types

Additional interim data from monotherapy dose escalation and data informing RDE declaration expected to be reported 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; Q2W-once every two weeks

Note: Based on preliminary clinical data as of November 1, 2023, from 16 patients in an ongoing, open label Phase 1/1b clinical trial.

WTX-330: Leveraging the Potential of IL-12 Therapy



The Challenge

Develop a tolerable IL-12 therapy to stimulate innate and adaptive antitumor immune responses

Potential WTX-330 Advantages and Opportunity

- Delivery of IL-12 mechanism selectively to the TME with an improved therapeutic index
- Potent preclinical antitumor activity in poorly immunogenic, anti-PD-1 therapy refractory tumors
- Leverage IL-12 biology in the clinic to address mechanisms of checkpoint inhibitor resistance
- Potential for multiple combination strategies to enhance anti-tumor activity

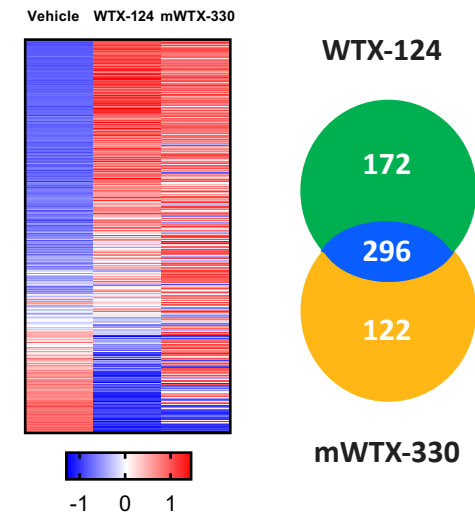
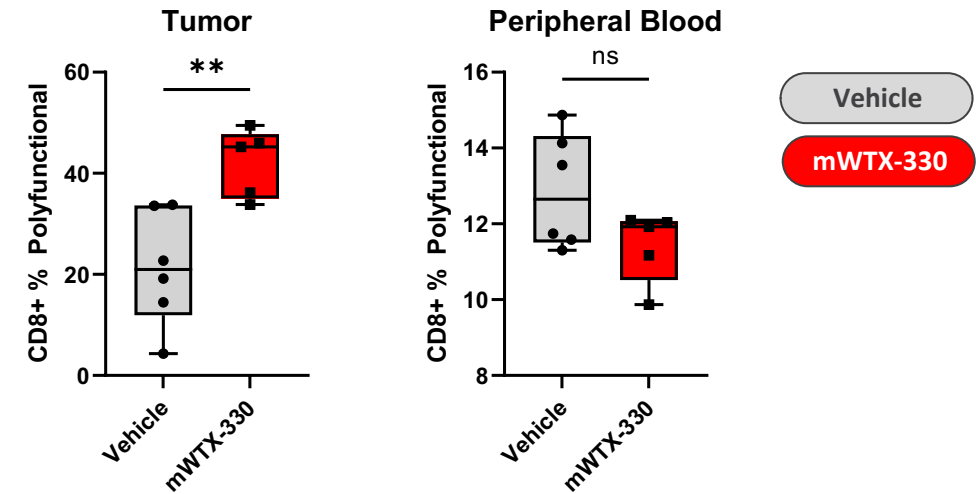
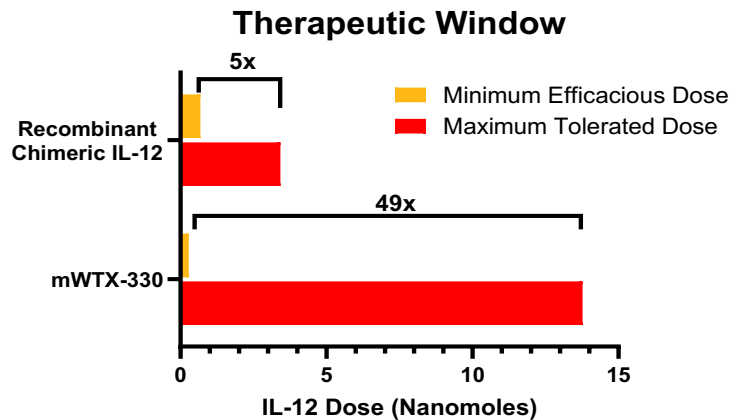
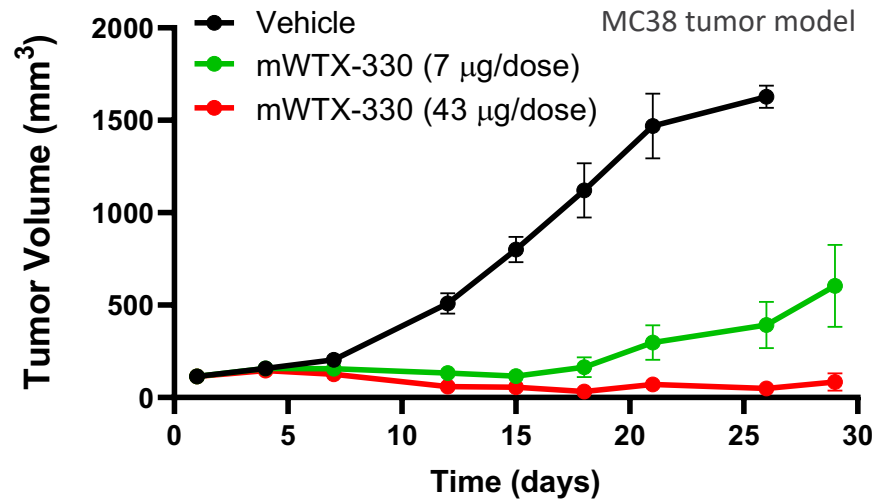
Status

- Phase 1 clinical trial actively enrolling
- Release of initial data from Phase 1 clinical trial anticipated in 2Q 2024

Abbreviation: TME-tumor microenvironment

IL-12 INDUKINE Delivers IL-12 Selectively to Tumor Tissue with an Improved Therapeutic Index

Robust activation of antitumor CD8+ T effector cells and pleiotropic immune activation in the TME in preclinical models



Differential Gene Signatures

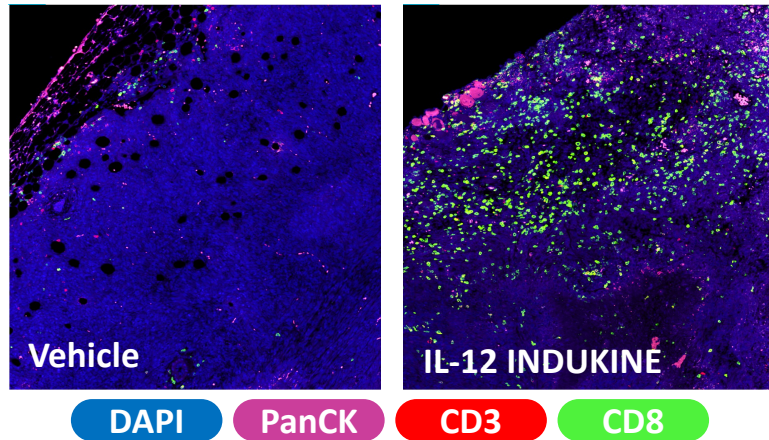
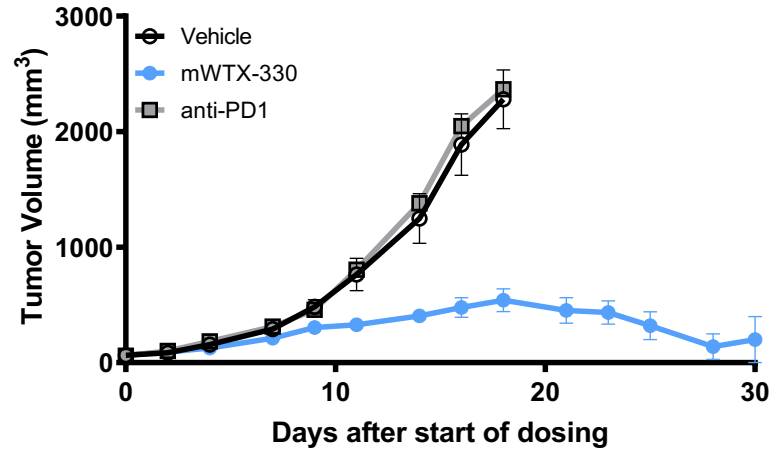
- ✓ Intratumoral IL-12 pathway activation
- ✓ Activation of multiple antigen presentation mechanisms
- ✓ Th1 lineage skewing
- ✓ Treg instability
- ✓ Increased chemokine expression

Nirschl CJ et al., Cancer Immunology Research, 1 July 2023; 11 (7): 962–977
Abbreviation: TME-tumor microenvironment

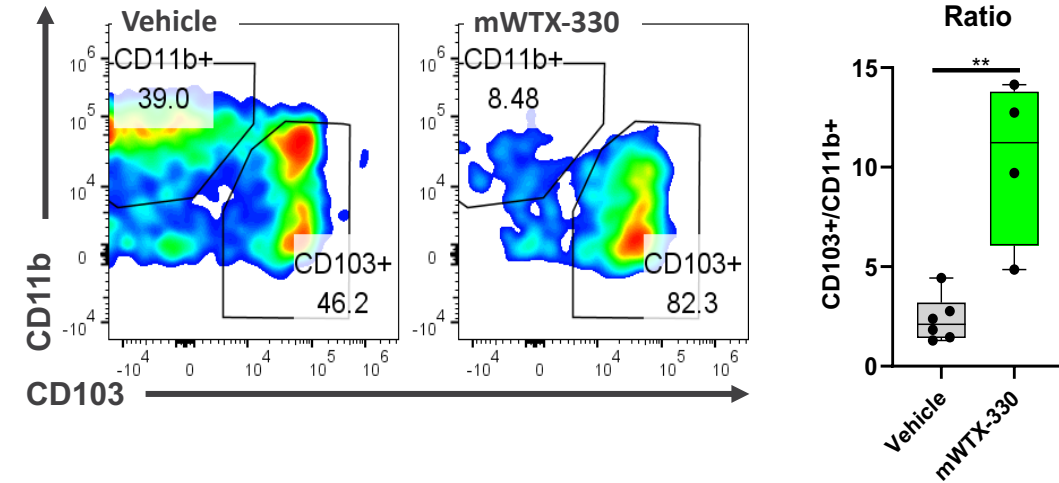
IL-12 INDUKINE Inhibits Growth of Poorly Immunogenic EMT-6 Mouse Tumors

Increased Clonality of Tumor Infiltrating CD8+ T Cells in preclinical models

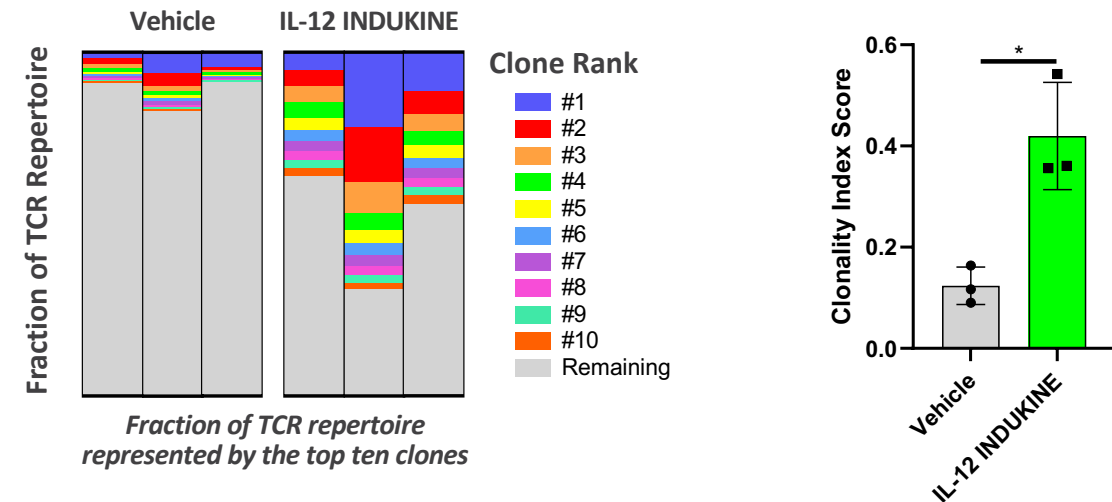
Efficacy in anti-PD-1 refractory EMT-6 tumors



Increase of cross-presenting DCs in tumors



Increased TCR clonality of tumor infiltrating T cells



Nirschl CJ et al., Cancer Immunology Research, 1 July 2023; 11 (7): 962–977

First-In-Human Study of WTX-330 Evaluating Safety, Tolerability and Clinical Activity

Monotherapy Dose Escalation



Relapsed/refractory advanced or metastatic solid tumors failing SOC, including immune checkpoint inhibitors

Monotherapy expansion arms to open after determination of MTD/RDE

Monotherapy Dose Expansion

CPI-naïve relapsed or refractory advanced tumor indications (tumor types for which CPIs are not approved, including NHL and mCRPC)

CPI primary or secondary resistant relapsed or refractory advanced tumor indications



Trial Details

CPI-unapproved and CPI-resistant indications supported by IL-12 biology and preclinical data

Bayesian study design, n~75

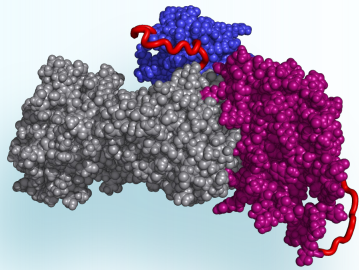
Assessment of safety, MTD/RDE, pharmacokinetics, biomarkers, ADA and efficacy

Concurrent biomarker analysis on blood and tumor tissue to evaluate proof of mechanism and confirm differential activity based on conditional activation

STATUS: Actively enrolling patients – preliminary data anticipated in 2Q 2024

Abbreviations: MTD-maximum tolerated dose; RDE-recommended dose for expansion; ADA-anti drug antibody; NHL-Non-Hodgkin lymphoma; mCRPC-metastatic castration-resistant prostate cancer; CPI-checkpoint inhibitor

WTX-712: Expanding the Utility of IL-21 Therapy



Potential WTX-712 Advantages and Opportunity

- IL-21 distinctively leads to an effective anti-tumor response driven by activation and differentiation of multiple anti-tumor cell types including Tfh cells, B cells, and cytotoxic effector cells (CD8+ T cells, NK, and NKT cells) as well as inhibiting Tregs and promoting M1 macrophage function
- IL-21 supports the generation and maintenance of lymphoid structures including TLS, which are increasingly recognized as critical for antitumor immunity
- IL-21 cytokine therapy showed signs of clinical activity but has been limited by toxicity, suggesting an opportunity for approaches with an improved therapeutic index
- Our preclinical data demonstrate a positive combination effect of WTX-712 with CPI
- WTX-712 provides a differentiated anti-tumor immunity approach to common gamma-chain-cytokines, complementing our IL-2 INDUKINE WTX-124

Status

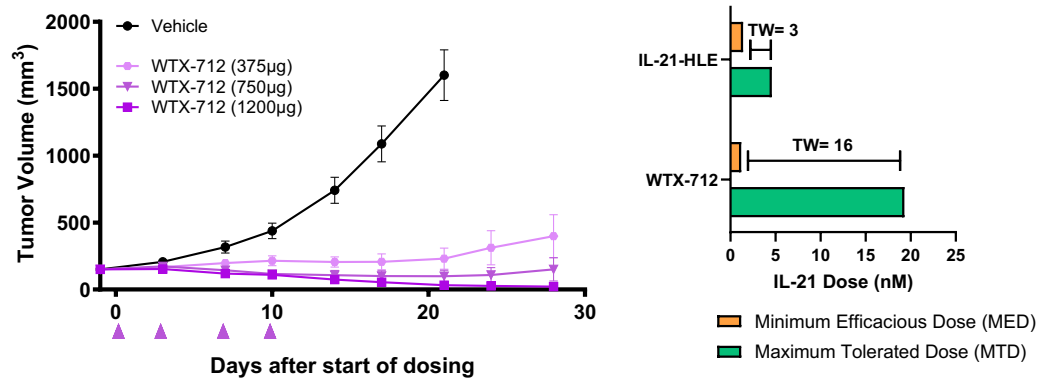
- IND-enabling studies

Abbreviations: TLS-tertiary lymphoid structure; CPI-checkpoint inhibitor

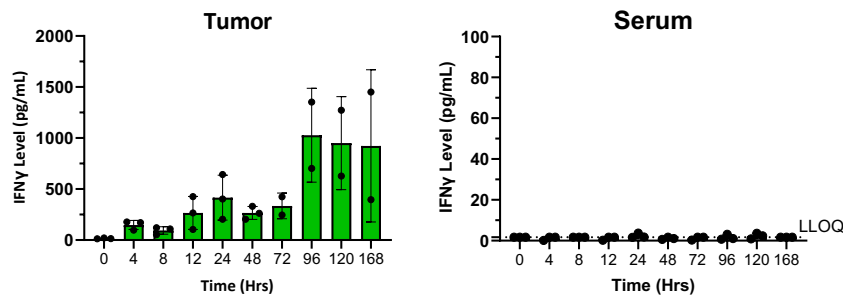
WTX-712 has an Improved Therapeutic Index Compared to Native IL-21

Tumor selective activity results in robust anti-tumor immune activation in preclinical studies

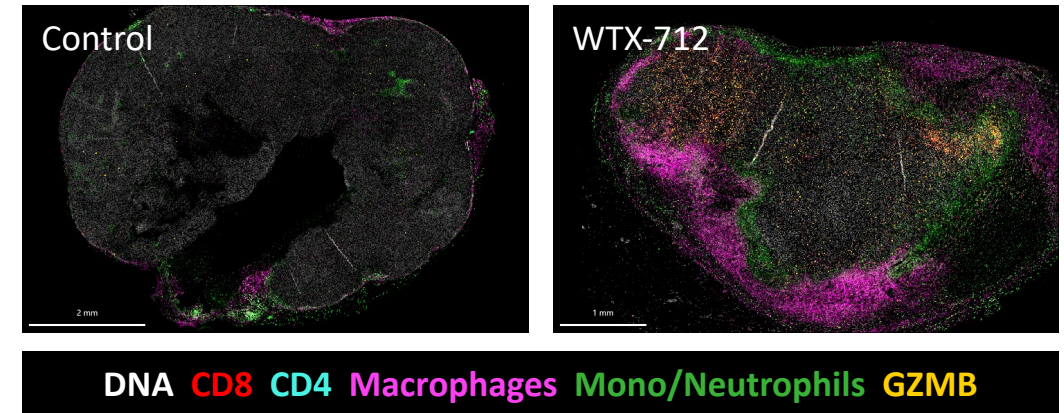
WTX-712 antitumor activity in MC38 tumor model with an improved therapeutic window compared to IL-21 cytokine



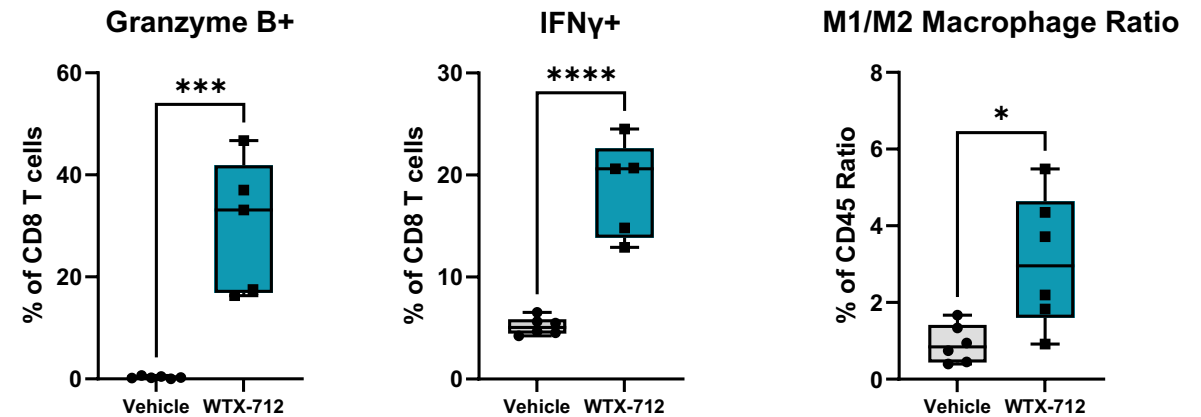
WTX-712 specifically induces IFN γ in the tumor



WTX-712 treatment transforms the tumor microenvironment



CD8 T Cells Expressing Effector Molecules



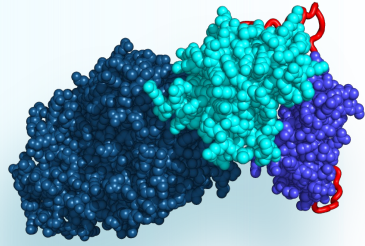
Sullivan JM et al., AACR 2023 Poster: Generation of IL-21 INDUKINE™ Molecules for the Treatment of Cancer

Sullivan JM et al., SITC 2023 Poster: Development of WTX-712, a Conditionally Active IL-21 INDUKINE™ Molecule for the Treatment of Cancer

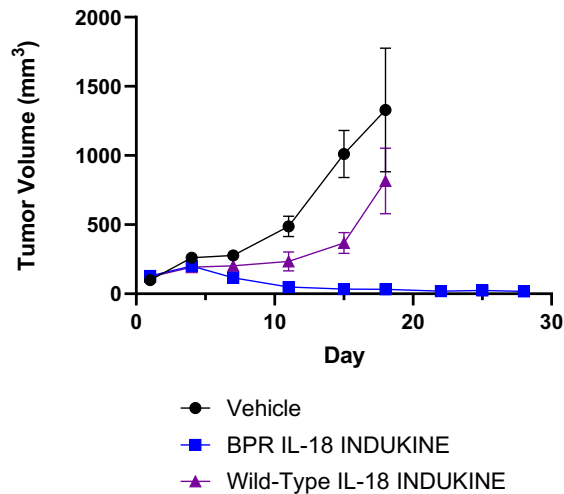
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WTX-518: Overcoming the Limitations of IL-18 Therapy

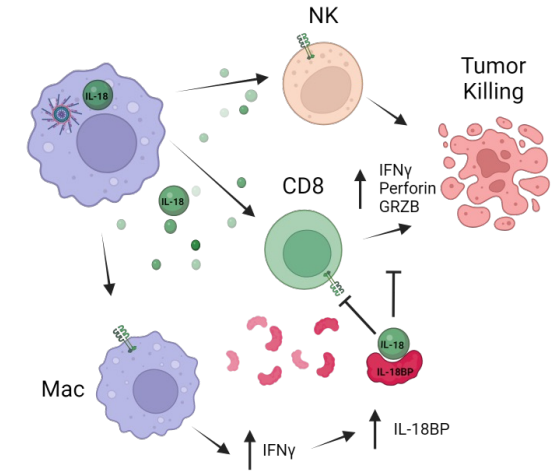


Improved antitumor activity of BPR IL-18
INDUKINE in MC38 tumor model



Potential WTX-518 Advantages and Opportunity

- IL-18 activates innate (strong NK activator) and adaptive immune cells promoting production of IFN- γ from antigen experienced T cells and favoring Th1 differentiation of naïve T cells
- IL-18 activity is heavily regulated by the decoy protein IL-18BP, which when overcome, can promote effective antitumor immunity but with an increased risk of IL-18 mediated toxicity
- The design of WTX-518 uniquely eliminates the ability of IL-18BP to inhibit IL-18 and systemically delivers IL-18 prodrug for conditional activation within the TME, providing optimal antitumor immunity with an improved therapeutic window
- IL-18 and IL-12 synergize to drive T cell activation and release of IFN- γ . WTX-518 complements our current portfolio already containing WTX-330 (IL-12 INDUKINE).



Status

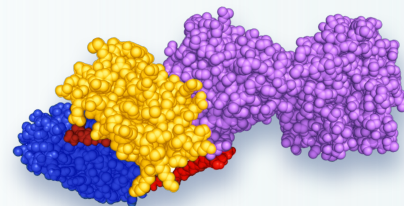
- IND-enabling studies

Abbreviations: TME-tumor microenvironment; BPR-binding protein resistant



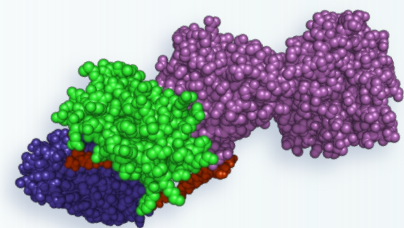
PREDATOR Platform

Werewolf's innovative PREDATOR Platform offers value creation through pipeline expansion and partnering opportunities



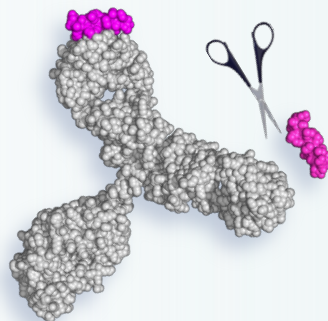
Oncology-focused INDUKINE Therapeutics

- Additional proinflammatory mechanisms
- Cell-based therapies
- mRNA therapies



Non-Oncology INDUKINE Therapeutics

- Inflammation
- Other diseases



Expanding Conditional-Activation Technology to New Modalities

- Targeted antibodies, T cell engagers, ADCs
- Cell-based therapies
- Disease-specific linkers

Shifting the Balance in Cytokine Therapeutics

- Two lead programs in Phase 1 development are wholly owned by Werewolf
- Collaboration is central to our growth strategy with Jazz global partnership on JZP898

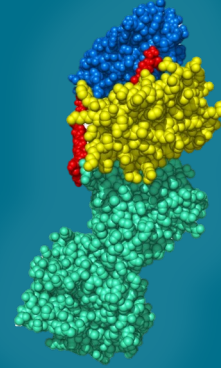
PREDATOR Platform: Value Creation Engine

Our protein engineering technology optimizes the design of conditionally activated cytokine therapeutics (INDUKINE molecules) to diseased tissues.

Opportunity to pursue non-cancer indications such as inflammatory diseases.

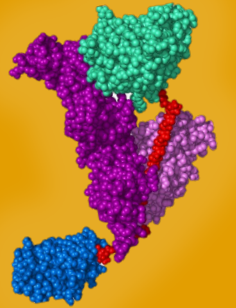
WTX-124

Phase 1/1b Clinical Trial in Advanced and Metastatic Solid Tumors



WTX-330

Phase 1 Clinical Trial in Advanced and Metastatic Solid Tumors and Lymphoma



Deep Pipeline

JZP898, an IFN α INDUKINE molecule, in clinical development by Jazz Pharmaceuticals

WTX-712, an IL-21 INDUKINE molecule, in preclinical development for the treatment of cancer

WTX-518, an IL-18 INDUKINE molecule, in preclinical development for the treatment of cancer

Strong Cash Position

Approximately \$139.2M in cash and cash equivalents (as of March 31, 2024)

Financial runway through at least 1Q 2026 with opportunity for multiple value-enhancing catalysts in the near term

Approximately 43.5M shares outstanding (as of April 29, 2024)

Experienced Leadership



Daniel J. Hicklin, PhD
President and CEO



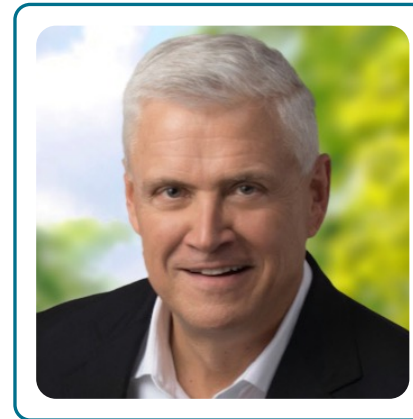
Randi E. Isaacs, MD
Chief Medical Officer



Chulani Karunatilake, PhD
Chief Technology Officer



Ellen Lubman, MBA
Chief Business Officer



Tim Trost, CPA
Chief Financial Officer



Thank You!