



**Werewolf**  
THERAPEUTICS

# Conditionally Activated Immunotherapies for Patients with Cancer

CORPORATE PRESENTATION | February 2026



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# Clinically Validated Technology to Solve the Limitations of Potent Cancer Immunotherapies



## Werewolf Therapeutics

*A novel class of tumor-activated immunotherapies for patients with cancer*

### WTX-124 (IL-2 INDUKINE molecule)

Potential **best-in-class efficacy and tolerability profile** observed in current Phase 1/1b clinical trial as a monotherapy and in combination with ICI in outpatient setting, including **30% ORR in a defined subset of monotherapy melanoma patients** based on preliminary data. Seeking strategic partner for further development.

### WTX-330 (IL-12 INDUKINE molecule)

Potential **first-in-class profile** with first systemically administered IL-12 therapy to demonstrate **clinical monotherapy activity and tolerability**; improved therapeutic index and efficacy further established based on interim data from ongoing Phase 1b/2 clinical trial. Seeking strategic partner for further development.

### INDUCER T cell engagers

Werewolf has developed a cutting-edge T-cell engager platform designed to address critical limitations in one of the fastest-growing areas of cancer therapeutics.

INDUCER molecules demonstrated complete silencing and efficient tumor activation in preclinical studies.

**WTX-1011 (STEAP1)** and **WTX-2022 (CDH6)** demonstrated differentiated masking and lack of CRS in NHPs.

# Overcoming Off-Target Toxicity has been a Key Challenge for Cytokine and T Cell Engager Therapies

## THE CHALLENGE

Off-Tumor Toxicity Limits Therapeutic Index

*Suboptimal Pharmaceutical Properties*



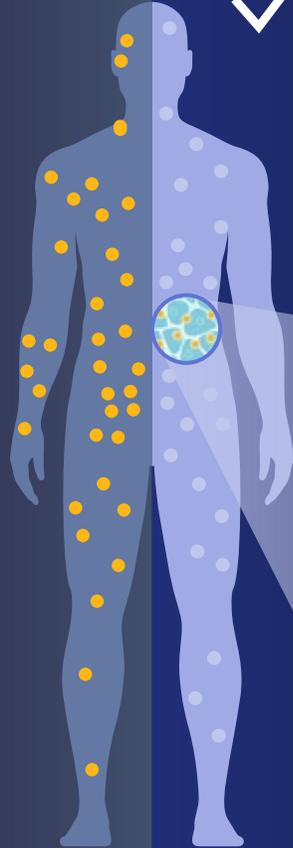
Toxicity with Poor Clinical Outcomes



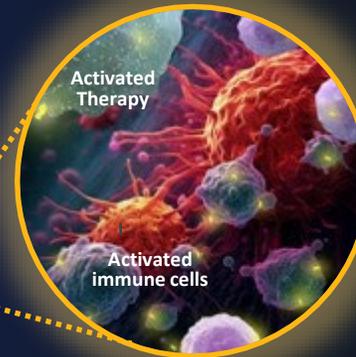
## OUR SOLUTION

Conditionally Activated Immunotherapy

*With Optimized Therapeutic Index*



Targeted Delivery to the Tumor Microenvironment



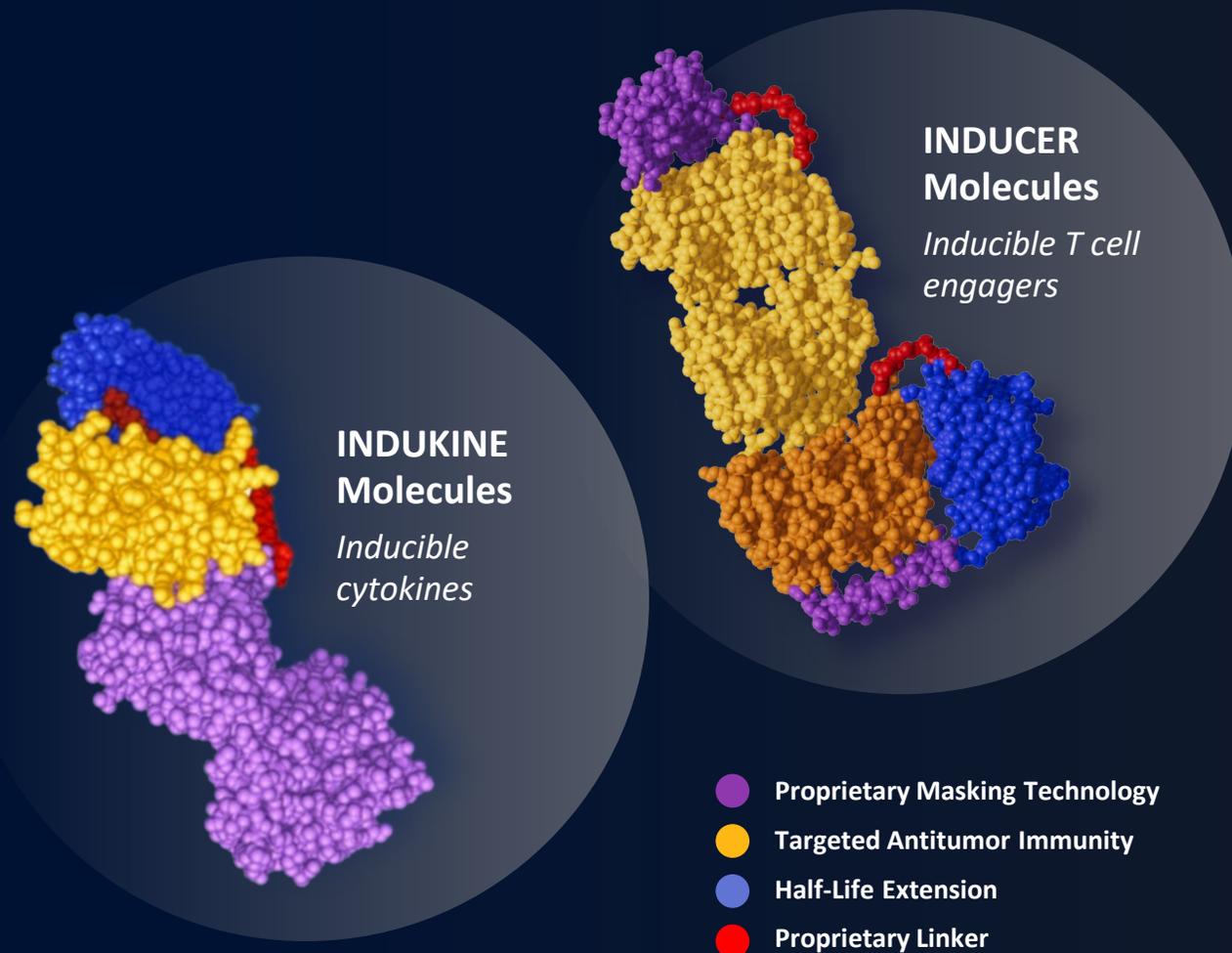
On-Target Immune Activation



**Werewolf** is pioneering the development of therapeutic modalities that stimulate the immune system where needed, remaining inactive in peripheral tissues until selectively activating within the tumor microenvironment, to overcome limitations of current proinflammatory immune therapies.

# Unique and Customizable Molecules with Tissue-Targeted Properties Across Multiple Indications

*INDUKINE and INDUCER molecules are enabled by differentiated masking and protease linker technology*



## Platform Technology Validated by WTX-124 Clinical Data

- ✓ Preferential exposure of active molecule in the TME<sup>1</sup>
- ✓ On-target immune activation in TME<sup>1,3</sup>
- ✓ Reduction of systemic toxicity and off-tumor effects<sup>2,4</sup>
- ✓ Confirmed, durable responses in multiple solid tumors<sup>4</sup>
- ✓ Wide therapeutic index compatible with outpatient administration<sup>5</sup>

Abbreviation: TME-tumor microenvironment

<sup>1</sup>Nirschi CJ et al., Cancer Immunology Research 2022 10(5):581-596

<sup>2</sup>Nirschi CJ et al., SITC 2023 Poster: Optimal Antitumor Immunity is Triggered by WTX-124, a Clinical Stage Conditionally Activated INDUKINE™ Molecule

<sup>3</sup>Based on patient data for whom treatment biopsies were available as of February 7, 2025.

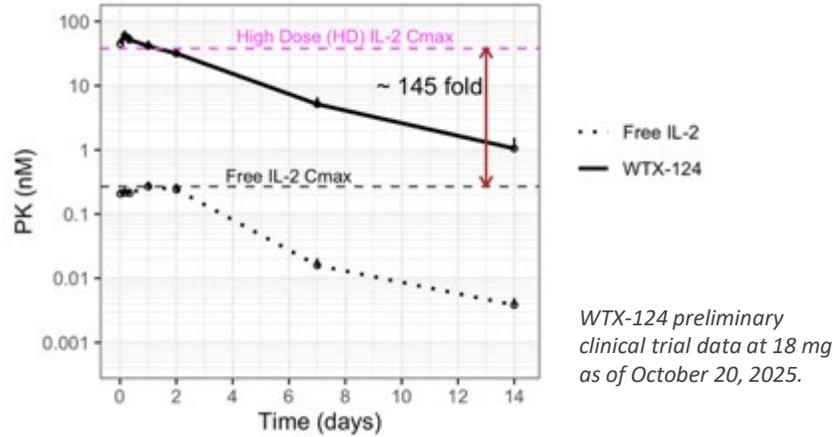
<sup>4</sup>Preliminary clinical data as of May 1, 2024, for an ongoing, open label Phase 1/1b clinical trial.

<sup>5</sup>Preliminary clinical data as of March 26, 2025, for an ongoing, open label Phase 1/1b clinical trial.

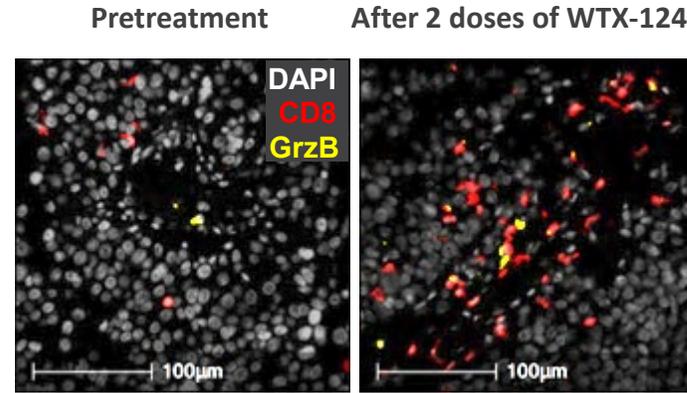
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# PREDATOR Masking and Linker Technology Validated by WTX-124 Clinical Data

## Optimized therapeutic index observed in patients

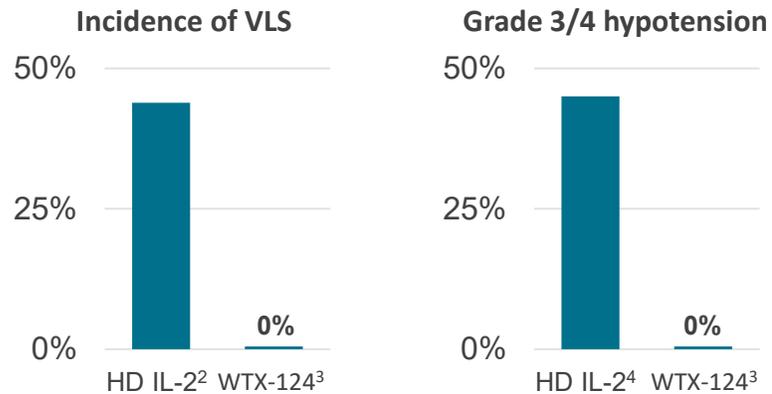


## On-target immune activation in tumors



Increased CD8 T cell infiltration/activation in the tumor of a 65-year-old woman with cutaneous melanoma

## Highly favorable tolerability profile<sup>1</sup>



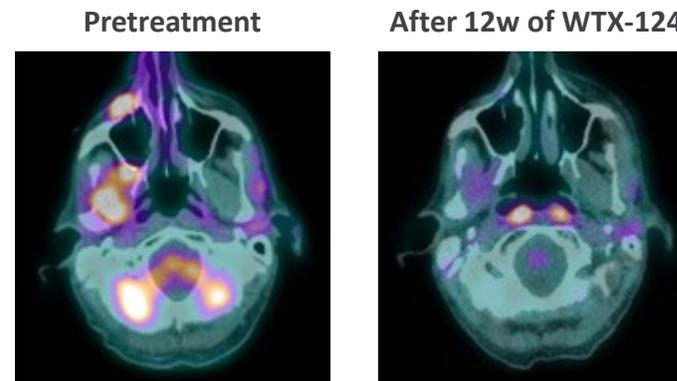
<sup>1</sup>Data presented is not from head-to-head study

<sup>2</sup>Jeong et al., J Clin Med, 2019 – incidence of VLS by meta-analysis

<sup>3</sup>Preliminary clinical trial data as of October 20, 2025

<sup>4</sup>Atkins et al., J Clin Oncol, 1999

## Durable clinical responses (including CRs)



Complete response in an ICI-refractory CSCC patient, now off all anticancer therapy >1.5 years

# Pipeline of Conditionally Activated Biologics

	PROGRAM (Target)	INDICATIONS	DISCOVERY	IND-ENABLING	PHASE 1	PHASE 1b
INDUKINE	WTX-124 IL-2	Advanced/Metastatic Cancers	[Progress bar]			
	WTX-330 IL-12	Advanced/Metastatic Cancers	[Progress bar]			
	WTX-712 IL-21	Cancer	[Progress bar]			
	WTX-518 IL-18	Cancer	[Progress bar]			
	WTX-921 IL-10	Inflammatory Diseases including IBD	[Progress bar]			
INDUCER	WTX-1011 STEAP1	STEAP1+ Cancers	[Progress bar]			
	WTX-2022 CDH6	CDH6+ Cancers	[Progress bar]			
	Undisclosed Multiple	Cancer	[Progress bar]			
Partnered Program	JZP898 IFN $\alpha$	Cancer	Globally licensed to Jazz Pharmaceuticals			

Abbreviations: IND-investigational new drug application; IBD-irritable bowel disease



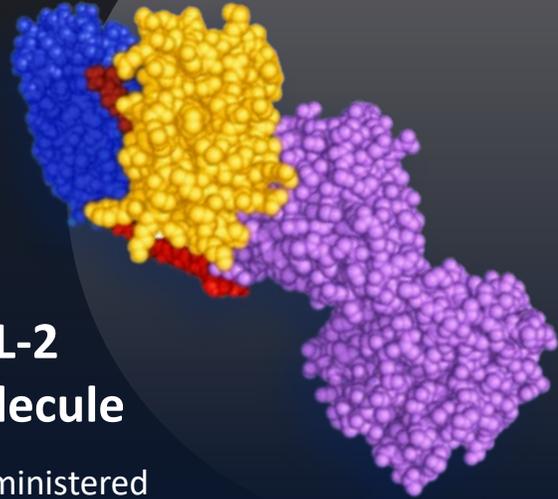


***INDUKINE Molecule***  
**WTX-124**

# WTX-124: Potential Best-in-Class Molecule Serves as Foundational IL-2 Therapy

## WTX-124, an IL-2 INDUKINE Molecule

- ✓ Systemically administered
- ✓ Fully potent, alpha-binding IL-2
- ✓ Selectively activated in the tumor microenvironment via proprietary linker technology
- ✓ Designed to deliver a tolerable, full potency IL-2 mechanism as monotherapy or in combination



## Clinical Proof of Concept Established

- Safely administered in **outpatient setting** with no patient restrictions (no VLS) as a monotherapy or in combination with SOC CPI
- Objective responses, some durable, observed as a **monotherapy** in melanoma, CSCC and GEJ, and in **combination** with CPI in melanoma, NSCLC and RCC
- Observed monotherapy activity in a subset of heavily pretreated melanoma patients (**30% ORR**), improved over historical high-dose IL-2 activity

## Potential Registration-Enabling Path

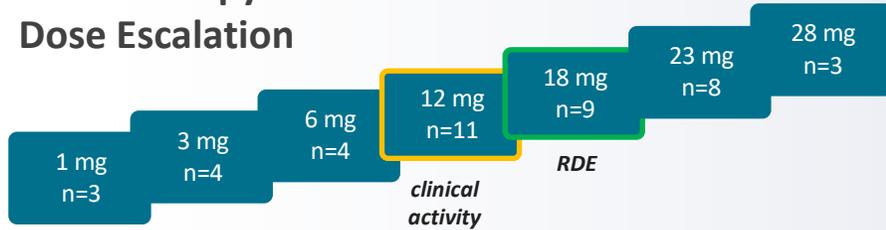
- **FDA Fast Track** designation granted for WTX-124 monotherapy in **advanced cutaneous melanoma**
- **Positive FDA EOP1 meeting** provided guidance for registration path in melanoma – **18 mg accepted** as recommended dose
- Seeking strategic partner for further development

Abbreviations: VLS-vascular leak syndrome; SOC-standard of care; CSCC-cutaneous squamous cell carcinoma; GEJ-gastro-esophageal junction; CPI-checkpoint inhibitor; RCC-renal cell cancer; NSCLC-non-small cell lung cancer; ORR-overall response rate; FDA-Food and Drug Administration; EOP1-end of phase 1

# WTX-124 Program Status

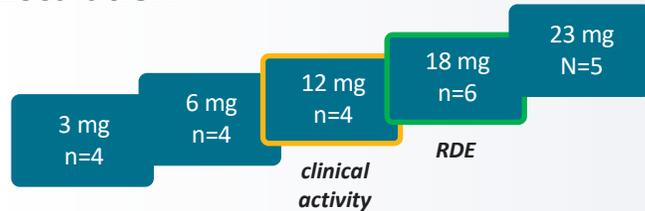
145 patients have received at least one dose of WTX-124 as of October 31, 2025 (65 escalation, 80 expansion)

## Monotherapy Dose Escalation



**18mg IV Q2W** selected as WTX-124 monotherapy RDE (MTD not established)

## Combination Therapy Dose Escalation



**18mg IV Q2W** selected as WTX-124 RDE in combination with pembrolizumab 400mg IV Q6W (MTD not established)

## MONOTHERAPY/COMBINATION THERAPY DOSE EXPANSION

- 1 **Renal cell carcinoma**
  - Monotherapy: n=20
  - Combination therapy: n=20
- 2 **Cutaneous melanoma**
  - Monotherapy: n=20
  - Combination therapy: n=20
- 3 **Cutaneous SCC**
  - Monotherapy: n=10
- 4 **NSCLC, PD-L1+**
  - Combination therapy: n=20



### Trial Details

mTPI-2 (Modified Toxicity Probability Interval 2) study design; enrolling ~175 patients with IO-sensitive tumors

Monotherapy and combination therapy dose escalations enrolled in parallel with staggered start for combination

Assessment of safety, efficacy, pharmacokinetics, biomarkers, and ADA

Tumor biopsies obtained on treatment to evaluate PD biomarkers supporting proof of mechanism

Abbreviations: RDE-recommended dose for expansion; IV-intravenous; Q2W-once every two weeks; Q6W-once every six weeks MTD-maximum tolerated dose; ADA-antidrug antibody; SOC-standard of care;

PD-pharmacodynamic; IO-immunotherapy

Note: Dose escalation completed February 4, 2025.

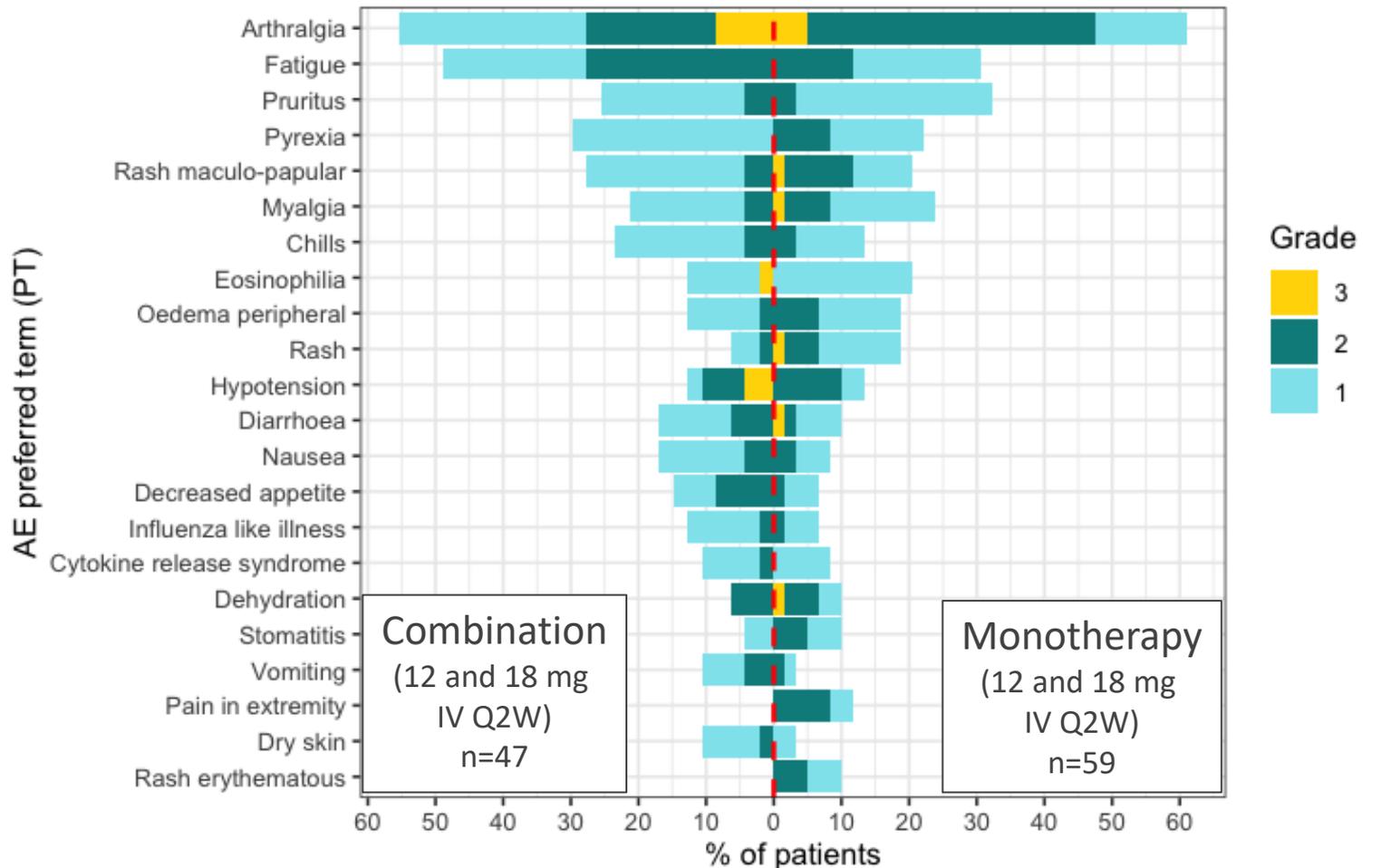
# WTX-124: Safely Administered in Outpatient Setting Without Restriction

*Safety profile supports combinability of WTX-124 with ICI or other SOC in earlier lines of therapy*

## Key safety findings at active dose levels (12, 18mg):

- No evidence of vascular leak syndrome (of any grade) or recurrence of prior immune-related adverse events
- Grade 3 and 4 related TEAEs seen in 25.5% (27/106) and 1.9% (2/106) of patients, respectively, and were all manageable and reversible
- Most frequent related TEAEs included arthralgias, fatigue, pruritis, pyrexia
- No excess toxicity or new safety signals seen when WTX-124 was combined with pembrolizumab

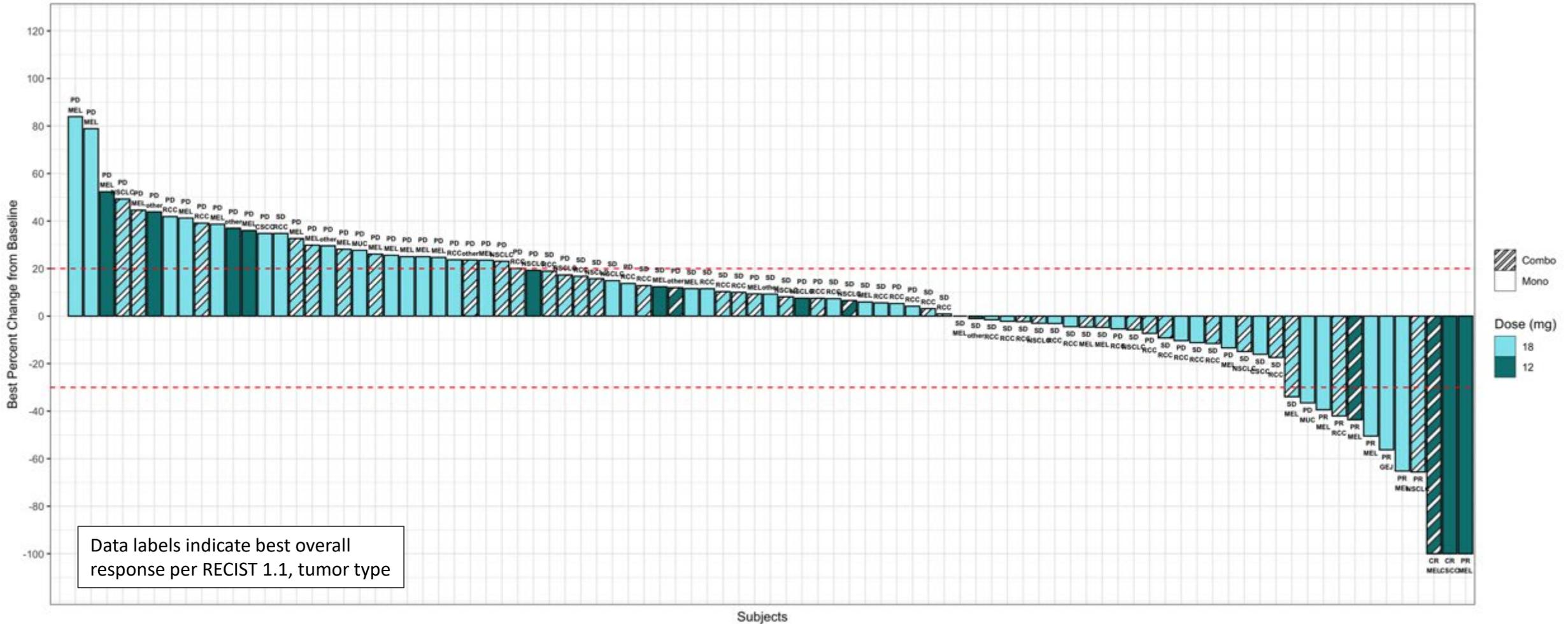
## Treatment-Emergent Adverse Events (TEAEs) in > 10% of patients



Abbreviations: ICI-immune checkpoint inhibitor; SOC-standard of care; AE-adverse event; IV-intravenous; Q2W-every two weeks

Notes: Preliminary clinical data as of October 20, 2025. Each related TEAE is counted once per patient based on the highest grade.

# WTX-124: Regression of SOC Refractory Solid Tumors Observed in One-Third of Patients

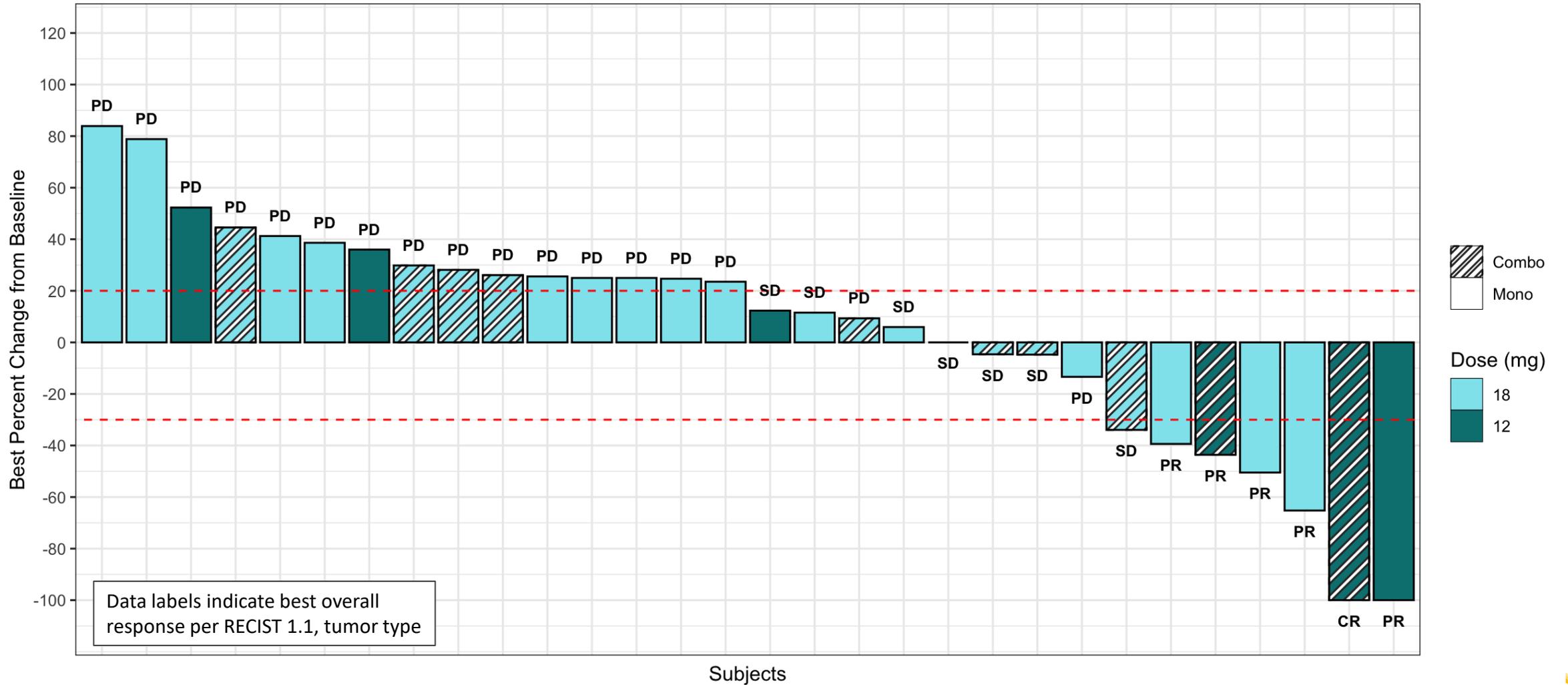


Abbreviations: SOC—standard of care; IO—immuno-oncology (immunotherapy); PD—progressive disease; SD—stable disease; PR—partial response; CR—complete response; MEL—melanoma; BCC—basal cell carcinoma; UV—uveal melanoma; URO—urothelial cancer; MUC—mucosal melanoma; MSI-H—microsatellite instability high (small bowel adenocarcinoma); NSCLC—non-small cell lung cancer; CHOL—cholangiocarcinoma; H&N—head and neck cancer (paranasal sinus adenocarcinoma); RCC—renal cell cancer; HCC—hepatocellular carcinoma; GEJ—gastroesophageal junction tumor; CSCC—cutaneous squamous cell carcinoma

Note: Preliminary clinical data as of October 30, 2025.

# WTX-124: Complete Regression of IO-Resistant Melanoma Metastases Observed

*Resolution of metastatic deposits observed at challenging sites of disease including in the liver*



Abbreviations: IO-immunotherapy; PD-progressive disease; SD-stable disease; PR-partial response; CR-complete response  
 Note: Preliminary clinical data as of October 30, 2025.

# WTX-124 Demonstrates Objective Response Rate of 30% as Monotherapy in Defined Subset of Cutaneous Melanoma

	Monotherapy			Combination		
	Escalation	Expansion	All	Escalation	Expansion	All
Efficacy evaluable	6	14	20	5	6	11
Efficacy evaluable (not IO primary resistant)	4	10	14	5	2	7
PR/CR	1 <sup>#</sup>	3	4	2	0	2
SD	2	2	4	0	3	3
PD	3	9	12	3	3	6
<b>ORR*/ORR**</b>	<b>17%/25%</b>	<b>21%/30%</b>	<b>20%/28.6%</b>	<b>40%/40%</b>	<b>0%</b>	<b>18%/28.6%</b>
DOR, mean days (STD)	53	112 (48.9)	97.3 (49.6)	393.5 (78.5)	n/a	393.5 (78.5)

<sup>#</sup>Unconfirmed, PD on confirmatory scan

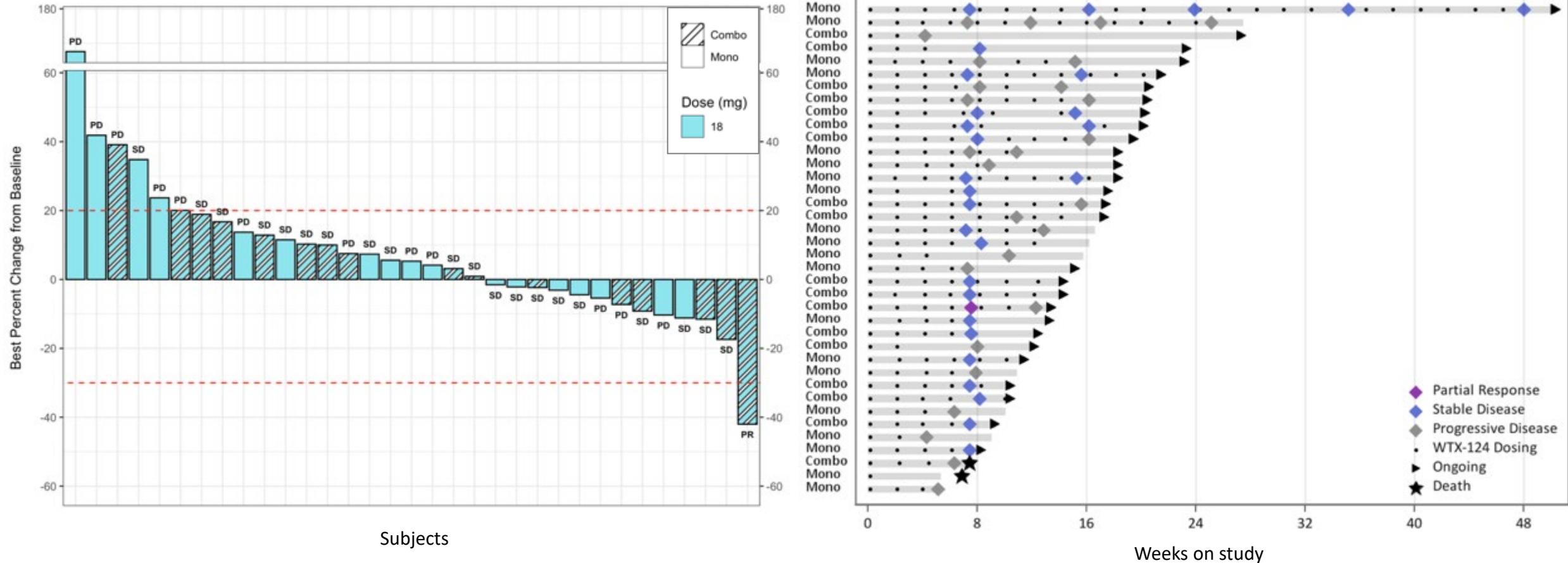
\*PR/CR divided by number of efficacy evaluable patients treated with active doses of WTX-124 (12 or 18 mg)

\*\*PR/CR divided by number of efficacy evaluable patients who were not primary IO resistant, defined as no response to any prior IO regimen

Abbreviations: PR-partial response; CR-complete response; SD-stable disease; PD-progressive disease ORR-overall response rate; DOR-duration of response; IO-immunotherapy; STD-standard deviation

Note: Preliminary clinical data as of October 30, 2025.

# WTX-124: Tumor Regression and Prolonged Disease Control Observed in RCC

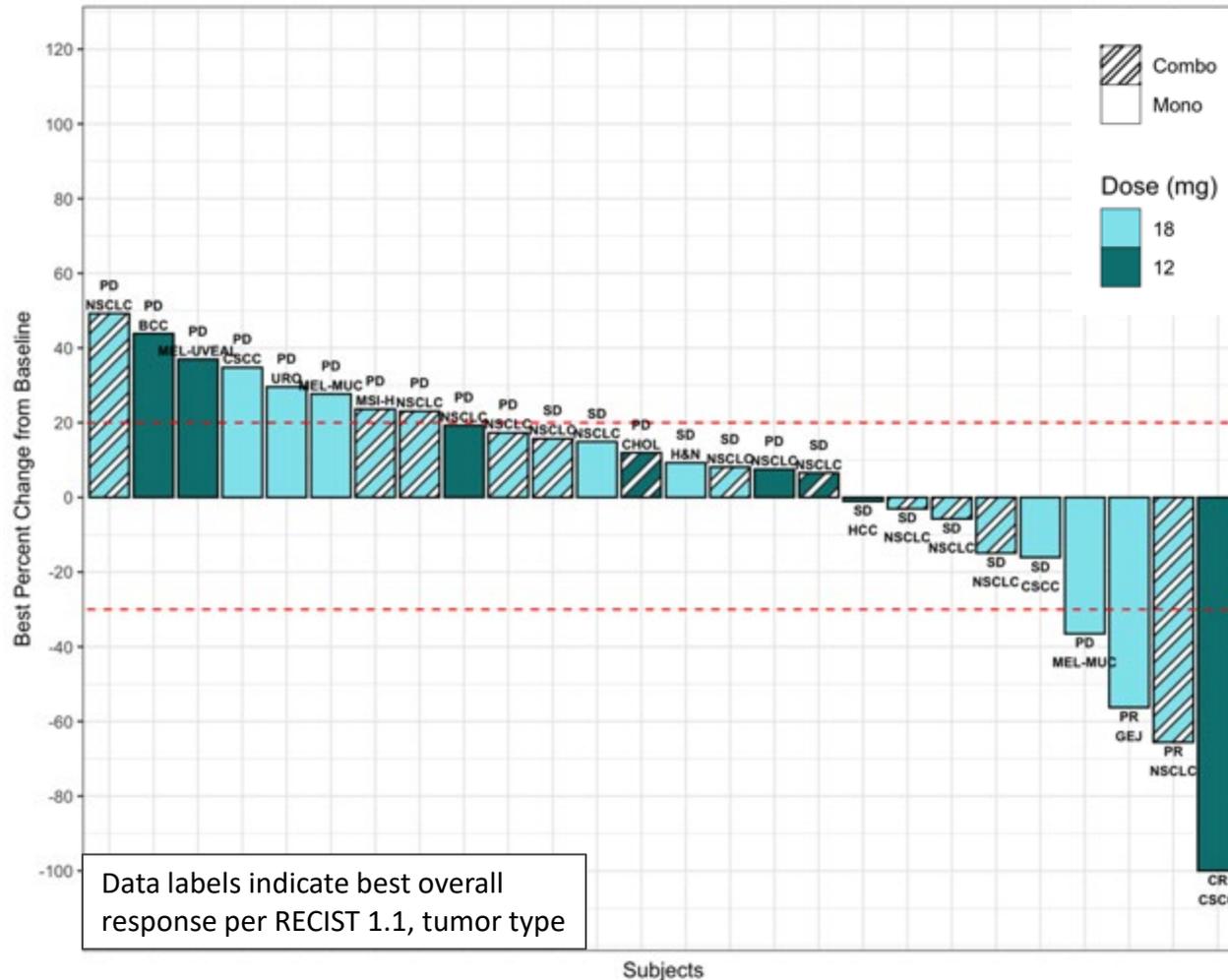


- RCC expansion arms fully enrolled (n=40); updated data will be available in 1H26
- Heavily pretreated patient population; most received 3-4 prior lines, including VEGF inhibitors, or are primary IO resistant
- Analyzing data to understand drivers of response
- Results support further consideration of WTX-124 in an earlier line of therapy

Abbreviations: RCC-renal cell carcinoma; PD-progressive disease; SD-stable disease; PR-partial response; VEGF-Vascular Endothelial Growth Factor  
 Note: Preliminary clinical data as of October 30, 2025.

# WTX-124: Encouraging Antitumor Activity Observed in Additional Solid Tumor Indications

*Development opportunities to be informed by additional data from ongoing Ph1/1b study (final data expected in 1H26)*



# Confirmed PR in NSCLC patient treated with WTX-124/pembrolizumab

- 67-year-old woman with PD-L1+ NSCLC s/p three prior lines of systemic therapy:
  1. Carboplatin/pemetrexed/bevacizumab
  2. Docetaxel/selinexor
  3. Atezolizumab (BOR SD)
- At study entry, patient had metastases to the adrenal gland, bone and multiple lymph nodes

## Timeline of response to WTX-124/pembrolizumab:

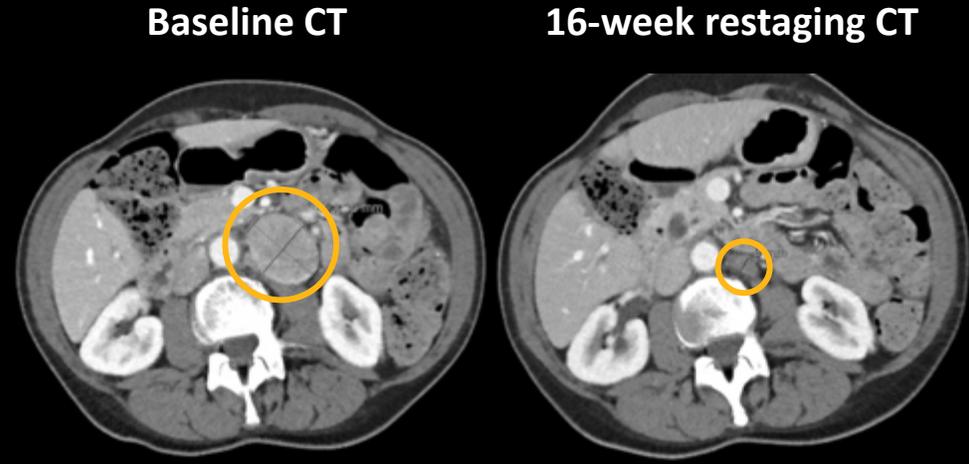


Patient soon to start Cycle 5 of combination therapy

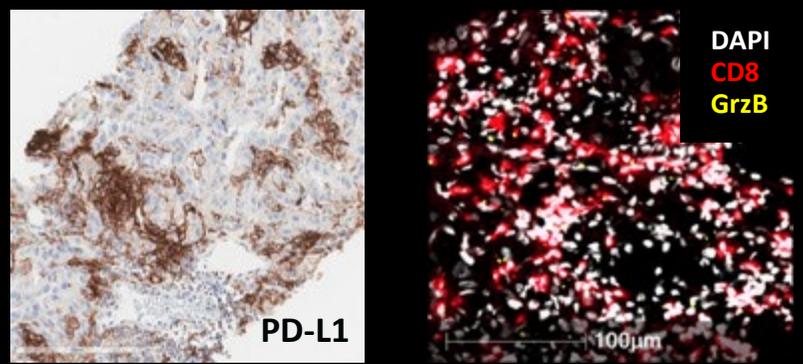
Related AEs include rash, arthralgia and myalgia (all manageable in outpatient setting)

Abbreviations: PR-partial response; NSCLC-non-small cell lung cancer; s/p-status post; TL-target lesion; BOR-best overall response; SD-stable disease; AE-adverse event; IHC-immunohistochemistry; IF-immunofluorescence; TME-tumor microenvironment; CT-computed tomography; SOD-sum of diameters

Note: Preliminary clinical data as of October 30, 2025.



CT images showed marked regression of a large paraaortic lymph node target lesion



Baseline biomarkers were notable for high PD-L1 (IHC) and a T-cell-inflamed TME (multiplexed IF)

# Complete response ongoing at 24 months in a patient with ICI-refractory cutaneous SCC

- 72-year-old man with metastatic cutaneous SCC who progressed on RT/cetuximab and had no response to four doses of cemiplimab – *panel a*
- Initiated treatment with **12 mg WTX-124 IV Q2W** three months after discontinuing cemiplimab
- Baseline CT showed a 2.6 cm premaxillary target lesion (T) and a non-target lesion (NT) extending into the pterygopalatine fossa – *panel b*

## WTX-124 Treatment Response

### 3 weeks:

On-treatment biopsy of target lesion showed no tumor

### 8 weeks:

Partial response (PR) with **62% decrease** of target lesion, no increase of non-target lesion – *panel c*

### 12 weeks:

Complete metabolic response of T/NT lesions – *panel d*

Patient tolerated therapy well with only Grade 2 arthralgias, Grade 2 rash

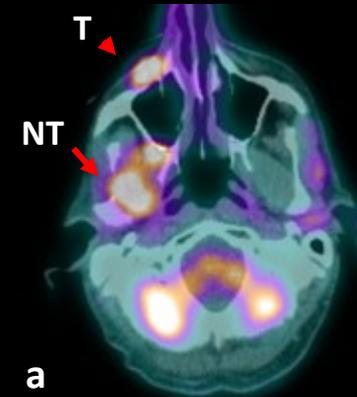
WTX-124 treatment stopped at 21 weeks in setting of confirmed complete response

**Response ongoing at >1.5 year off drug with no additional therapy**

Abbreviations: SCC-squamous cell carcinoma; CT-computed tomography scan; IV-intravenous; Q2W-every two weeks; PET-positron emission tomography; ICI-immune checkpoint inhibitor; CR-complete response

Note: Preliminary clinical data as of October 30, 2025.

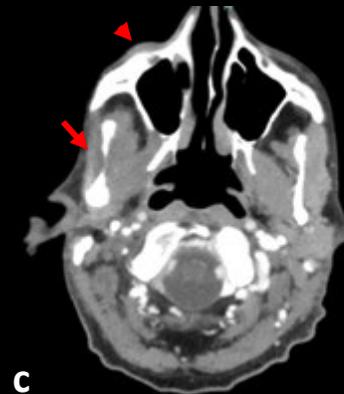
June 2023:  
PET-CT at time of  
progression on cemiplimab



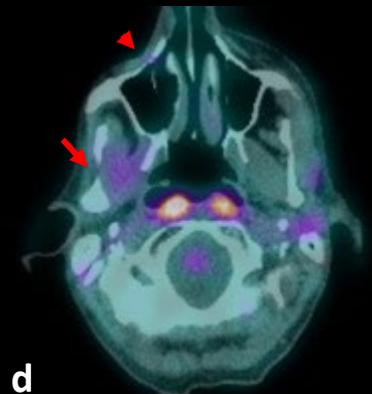
September 2023:  
Baseline CT performed  
at study entry



November 1, 2023:  
First restaging CT  
at 8 weeks



November 30, 2023:  
Confirmatory PET-CT  
at 12 weeks



# WTX-124: Next Generation IL-2 Molecule Has Validated PREDATOR Platform

## Key Takeaways

- ✓ WTX-124 has successfully met internally established tolerability and efficacy benchmarks
- ✓ Monotherapy WTX-124 has demonstrated overall activity in relapsed/refractory cutaneous melanoma comparable to high dose IL-2 but with a favorable tolerability profile
- ✓ Fast Track designation validated early WTX-124 melanoma monotherapy data
- ✓ Positive End of Phase 1 meeting with the U.S. Food and Drug Administration provided guidance on dose and design of randomized controlled trial
- ✓ Seeking strategic partner for further development

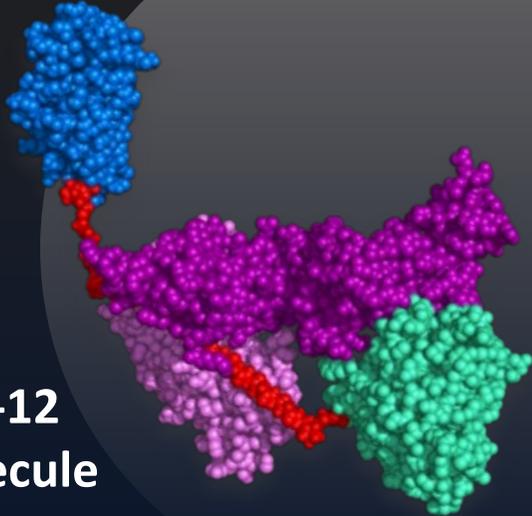


***INDUKINE Molecule***  
**WTX-330**

# WTX-330: Potential First-in-Class Molecule to Address Immunotherapy Resistant Cancers

## WTX-330, an IL-12 INDUKINE Molecule

- ✓ Systemically administered
- ✓ Validated masking and linker technology
- ✓ Fully potent, non-half-life extended IL-12 released in tumor microenvironment
- ✓ Designed to deliver a tolerable, full potency IL-12 mechanism as monotherapy or in combination to stimulate antitumor activity in poorly immunogenic cancer indications



## Key Clinical Data

- **First systemically administered IL-12** therapy demonstrating **monotherapy activity and tolerability** upon administration in the outpatient setting in FIH study
- Second INDUKINE molecule to **clinically validate Predator platform** and demonstrate POC through improved therapeutic index
- Twelve patients treated to date in **Phase 1b/2 trial** with **highly favorable tolerability** profile and **additional evidence of antitumor activity**, building upon data from FIH study

## Next Steps

- Preclinical proof of concept established for unique sequential **combination administration of WTX-330 and WTX-124**, which may provide a novel development path in poorly immunogenic tumors
- Seeking strategic partner for further development

Abbreviations: FIH-first in human; POC-proof of concept

Note: Preliminary clinical data as of October 31, 2025, in ongoing clinical trial.

# WTX-330: Phase 1b/2 Dose- and Regimen-Optimization Study WTX-330x2102

## Part A: Dose and Regimen Finding (ongoing)

WTX-330 IV Q2W 28-day cycle

### FIXED DOSE FINDING

Patients with r/r advanced/metastatic solid tumors

### STEP-UP DOSE FINDING

Patients with r/r advanced/metastatic solid tumors

## Part B: Expansion (potential)

**Population:** Relapsed/refractory metastatic GI malignancies including microsatellite stable (MSS) colorectal cancer, GEJ, gastric, gallbladder

**Arm A (n~20):** Monotherapy WTX-330

**Arm B (n~20):** Monotherapy WTX-330 followed by monotherapy WTX-124



## Trial Details

Part A to find optimal dose and regimen

Seeking strategic partner to initiate Part B evaluating WTX-330/124 combination in selected indications (relapsed/refractory GI malignancies)

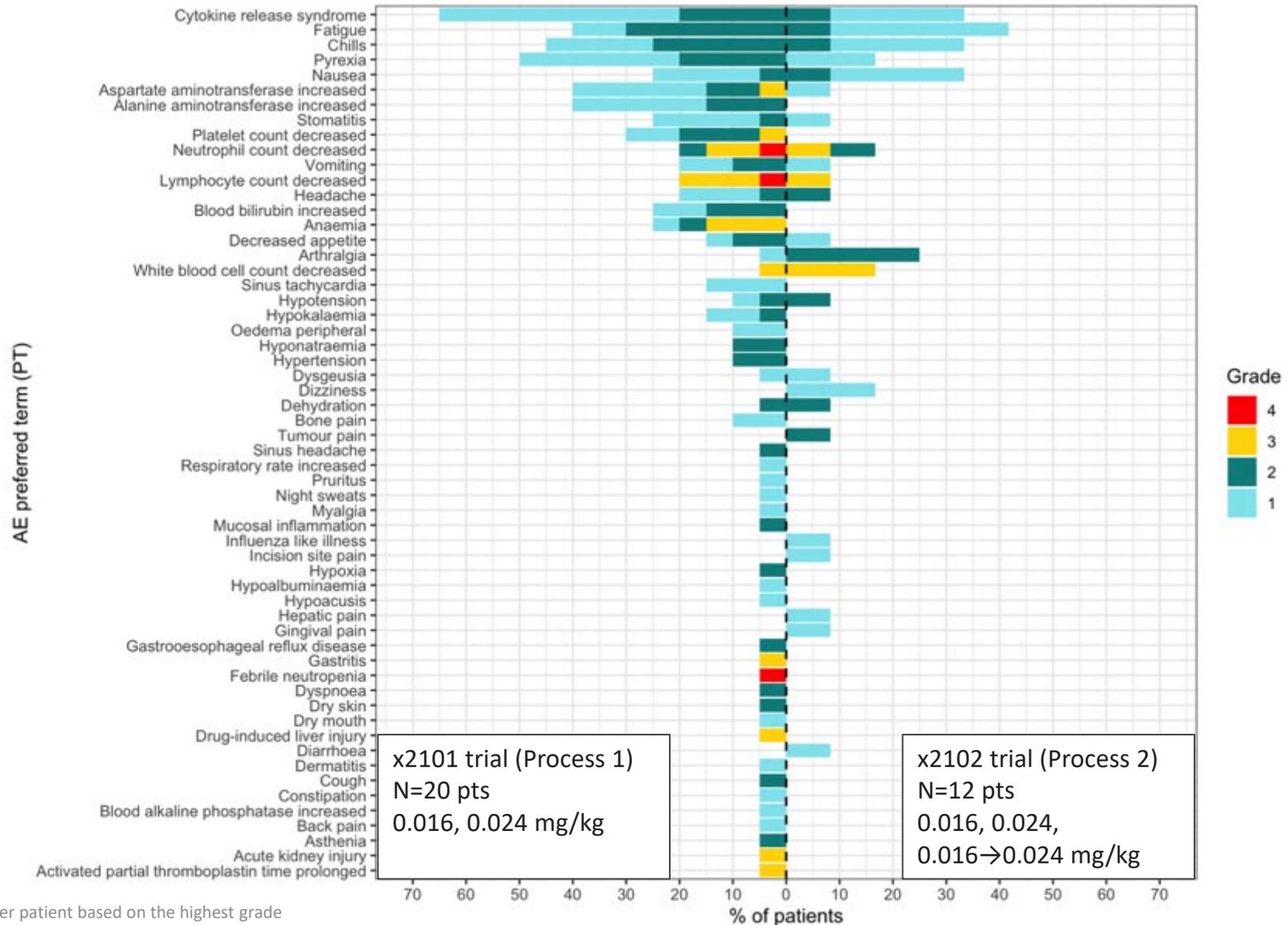
Goals for selection of a specific regimen include:

- Maximize WTX-330 exposure delivered
- Reduce frequency of related toxicities and peripheral IFN $\gamma$  levels
- Enhance IL-12 pharmacodynamic activity observed
- Maximize antitumor activity

Abbreviations: FIH-first in human; IV-intravenous; Q2W-once every two weeks; r/r-relapsed/refractory; ICI-immune checkpoint inhibitor; GI-gastrointestinal; GEJ-gastroesophageal junction; IFN $\gamma$  – interferon gamma

Note: Study ongoing – 12 patients dosed in 3 cohorts, 0.016 mg/kg fixed dose, 0.024 mg/kg fixed dose, 0.016/0.024 step-up dose, as of October 30, 2025.

# WTX-330: Dramatic Improvement in Safety Profile Due to Optimized Manufacturing Process



Each adverse event is counted once per patient based on the highest grade

Abbreviation: AE-adverse event

Note: Preliminary clinical data as of October 31, 2025, in ongoing clinical trial.

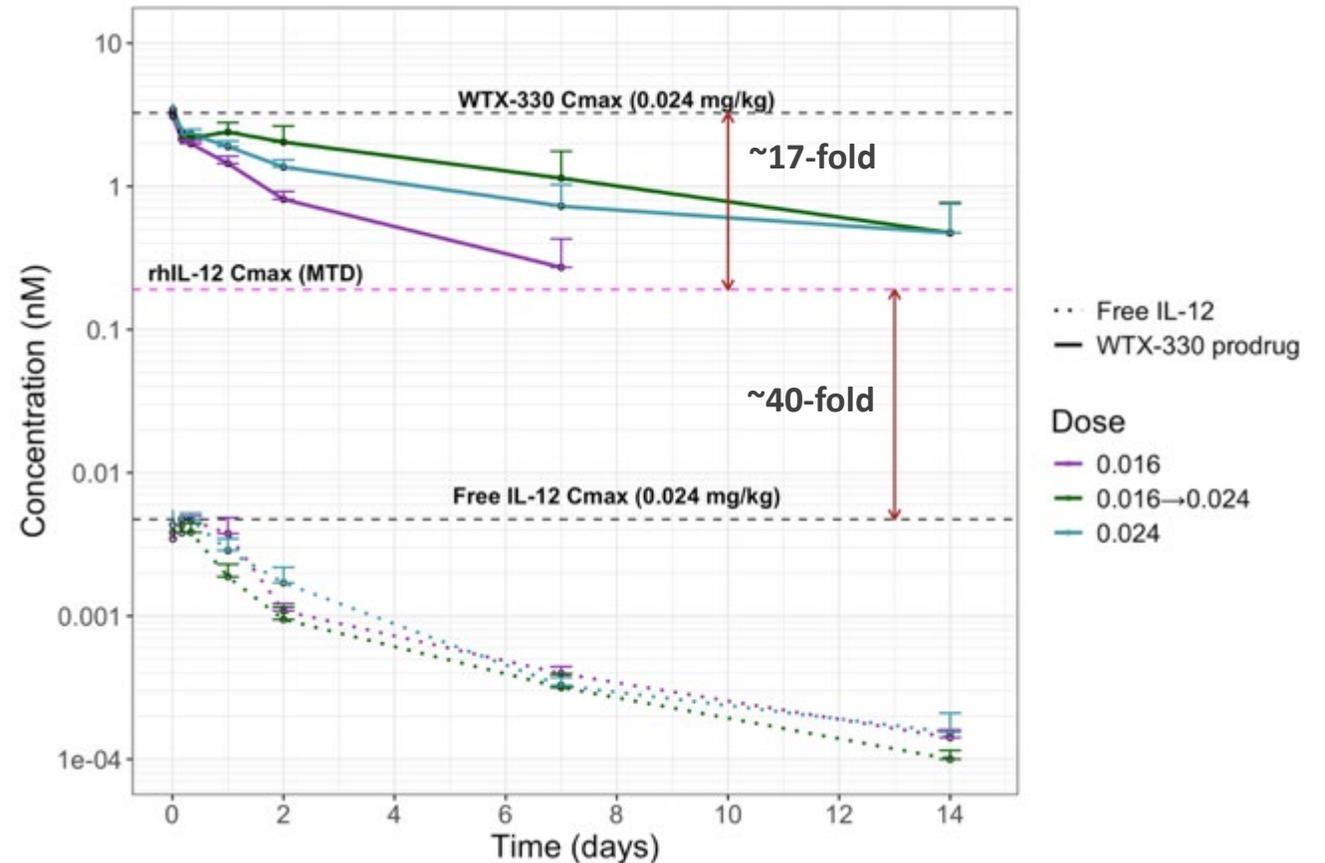
# WTX-330: 17-Fold Greater IL-12 Compared to Recombinant Human IL-12 Therapy at its MTD

PK data account for the improved therapeutic index of WTX-330 compared to rhIL-12

## Preliminary PK findings:

- WTX-330 dosed at 0.024 mg/kg IV Q2W has a ~17-fold higher C<sub>max</sub> than rhIL-12 at its MTD (500 ng/kg; Atkins MB et al. 1997)
- Peak free IL-12 exposure after 0.024 mg/kg WTX-330 is ~40-fold lower than rhIL-12 at its MTD
- Across all dose levels, free IL-12 levels are very low (0.12%\* of prodrug exposure)
- PK exposure generally preserved upon repeat dosing

First-dose PK profiles for WTX-330 and free IL-12 compared to rhIL-12 C<sub>max</sub> at its MTD (mean ± SEM)

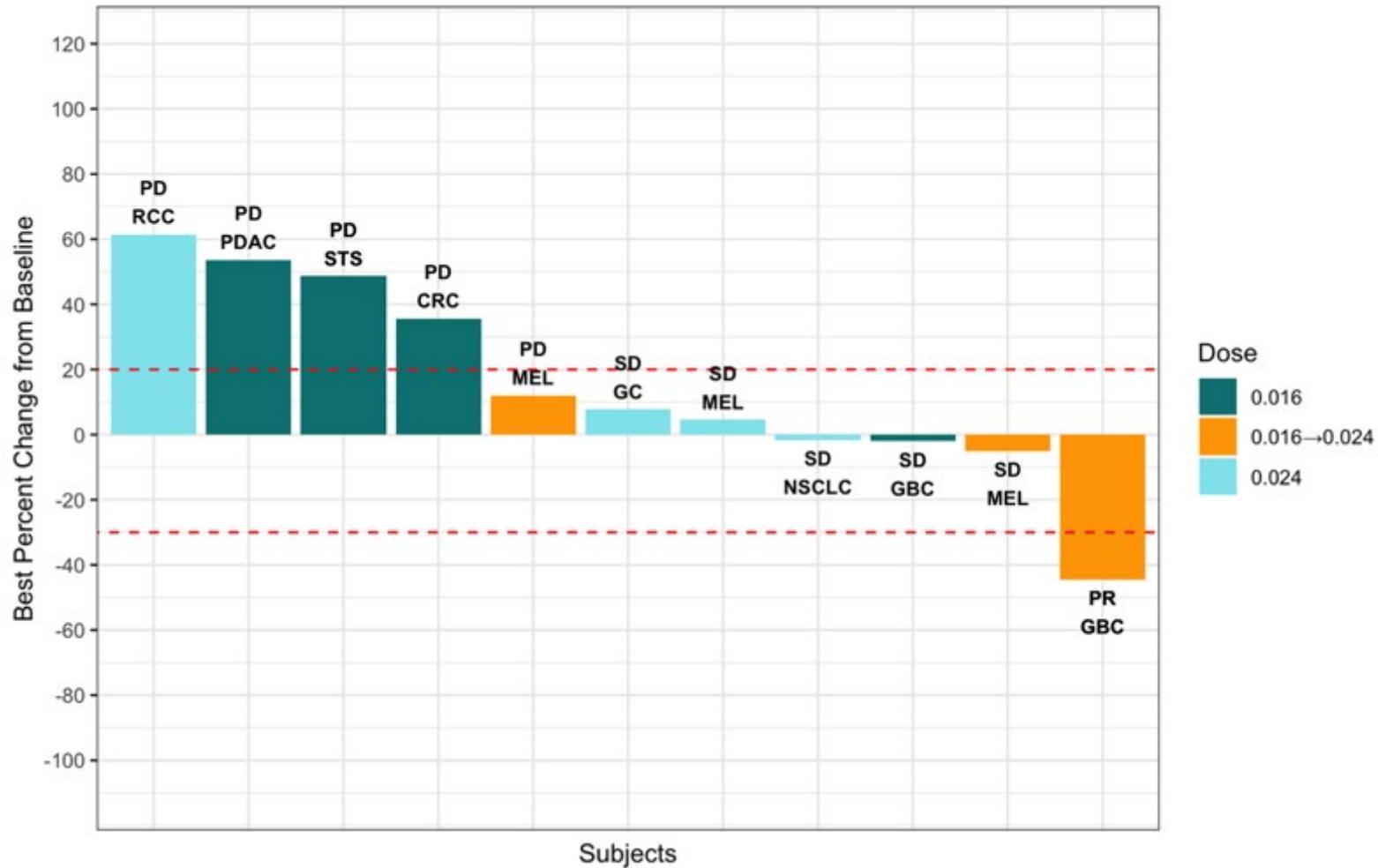


\*Mean C<sub>max</sub> ratio (free IL-12/WTX-330 prodrug) in Cycle 1 expressed as percentage.

Abbreviations: PK-pharmacokinetic, IV-intravenous, MTD-Maximum tolerated dose; Q2W-once every two weeks

Note: Preliminary clinical data as of October 31, 2025.

# WTX-330: Preliminary Efficacy Data from Phase 1b/2 Initial Cohorts Showed Further Evidence of Antitumor Activity in Challenging Tumor Types



Abbreviations: PDAC-pancreatic ductal adenocarcinoma; STS-soft tissue sarcoma; CRC-colorectal cancer; MEL-melanoma; GC-gastric cancer; NSCLC-non-small cell lung cancer; GBC-gallbladder cancer  
Note: Preliminary clinical data as of December 2, 2025, in ongoing clinical trial.

# Objective response in a patient with refractory gallbladder cancer

- 57-year-old woman with MSS, TMB-low gallbladder cancer whose BOR was PD to each of two prior lines of SOC therapy:
  1. Cisplatin/gemcitabine/durvalumab
  2. 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX)
- At study entry, the patient had metastases to the liver as well as hilar and retroperitoneal lymph nodes
- Treated with step-up regimen (0.016→0.024 mg/kg)

## Restaging scans demonstrated:

8 weeks:

**30%**

↓ in TL SOD  
(Unconfirmed PR)

14 weeks:

**45%**

↓ in TL SOD  
(Confirmed PR)

14 weeks:

Normalization of  
CA19-9 and CEA  
biomarkers

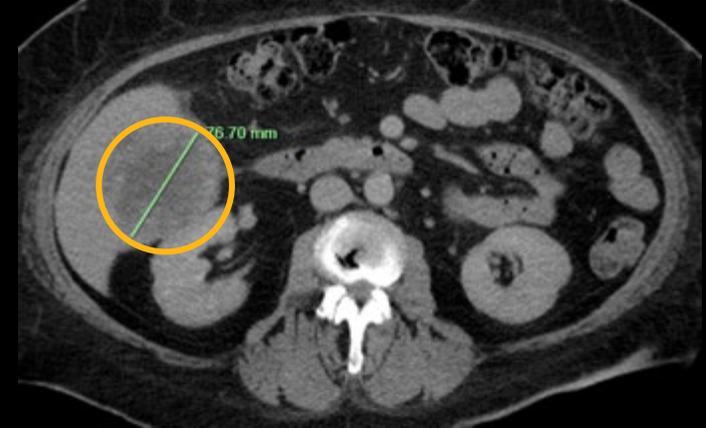
Patient ongoing in Cycle 4 of therapy

Only related AEs were headache and intermittent arthralgias

Abbreviations: PR-partial response; NSCLC-non-small cell lung cancer; s/p-status post; TL-target lesion; BOR-best overall response; SD-stable disease; AE-adverse event; IHC-immunohistochemistry; IF-immunofluorescence; TME-tumor microenvironment; CT-computed tomography; SOD-sum of diameters

Note: Preliminary clinical data as of October 30, 2025.

Baseline CT



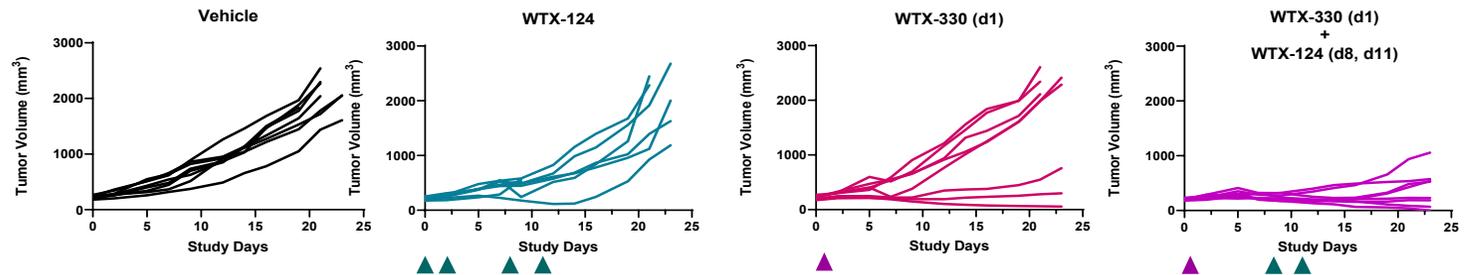
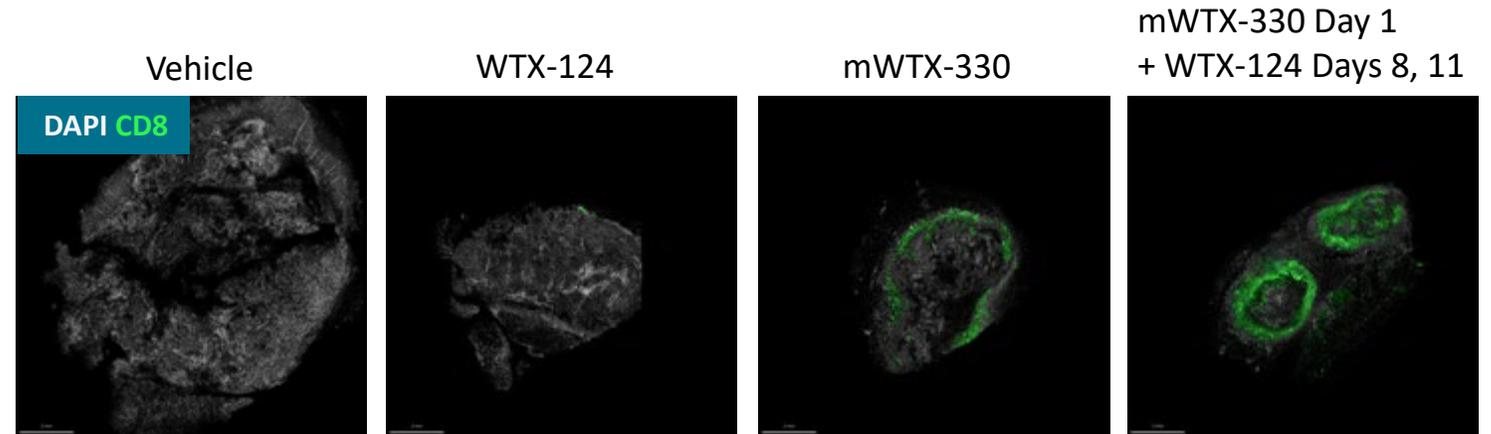
8-week restaging CT



# Addressing IO Resistance with Novel WTX-330 & WTX-124 Combination Therapy

*In preclinical study, mWTX-330 pretreatment sensitized EMT-6 tumors to WTX-124*

Hypothesis: WTX-330 enhances adaptive antitumor immune recognition and activation in immunotherapy resistant cancers that is then amplified by WTX-124 (“induction → amplification” strategy)



% TGI	0	0	20	80
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Clinical translation: A potential development path with a strategic partner could evaluate sequenced combination of WTX-330 and WTX-124 in ICI-resistant GI cancers

LePrevost, J., Morris, K., et al. J Immunother Cancer 2025;13(Suppl 2):A1–A1534  
 Abbreviations: TGI-tumor growth inhibition; ICI-immune checkpoint inhibitor; GI-gastrointestinal

# WTX-330: Potential First-in-Class Systemic IL-12 Therapy

## Key Takeaways

- ✓ First systemically delivered IL-12 therapy to demonstrate monotherapy activity and tolerable administration in the outpatient setting
- ✓ Anti-tumor and biomarker activity in less immunogenic tumor types, consistent with mechanism of action, addresses multiple unmet medical needs
- ✓ Preclinical data support a combination strategy of sequential WTX-330 followed by WTX-124 to enhance anti-tumor activity in poorly immunogenic tumors, especially relapsed/refractory GI malignancies and tumors resistant to SOC immunotherapies
- ✓ Twelve patients treated to date with excellent tolerability profile and evidence of anti-tumor activity; seeking strategic partner for further development



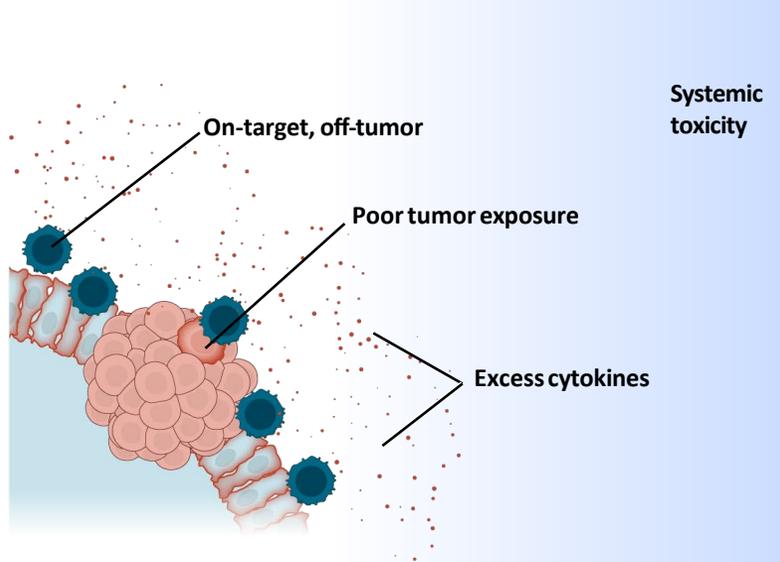
***INDUCER Molecules***  
*Inducible T Cell Engagers*

# INDUCER Molecules Utilize Werewolf's PREDATOR Platform for Optimal TCE Design

*INDUCER: Inducible T Cell EngageR*

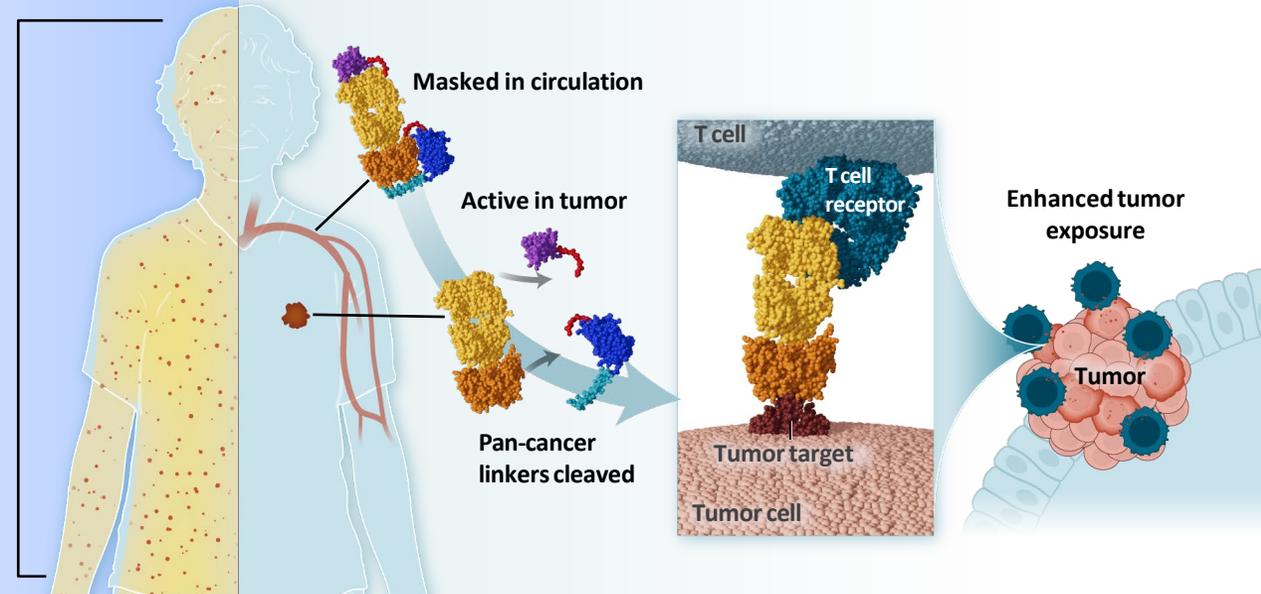
## TCE Challenges

- On-target, off-tumor adverse effects and toxicity including dose-limiting Cytokine Release Syndrome (CRS)
- Poor tumor exposure leading to sub-optimal therapeutic effect



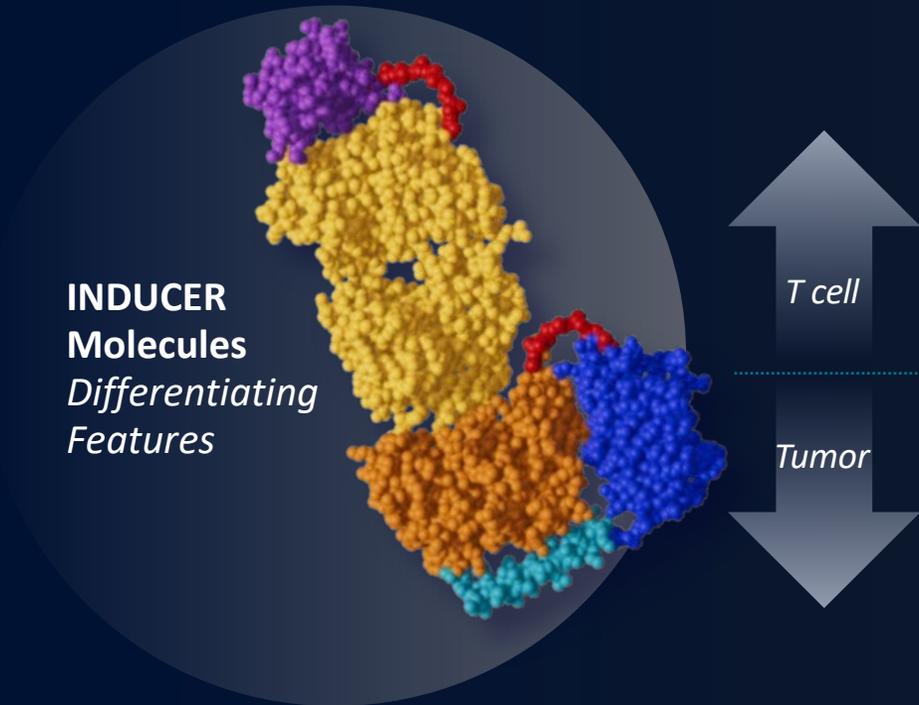
## Werewolf's Solution

- Optimized CD3 masking strategy to reduce CRS
- Novel, proprietary, tumor protease sensitive linkers to increase the therapeutic Index
- Improved exposure of active INDUCER molecule in tumors



# INDUCER Molecules: Next Generation Conditionally Activated T Cell Engagers

*Proprietary masking technology and clinically validated pan-cancer linker to improve therapeutic index*

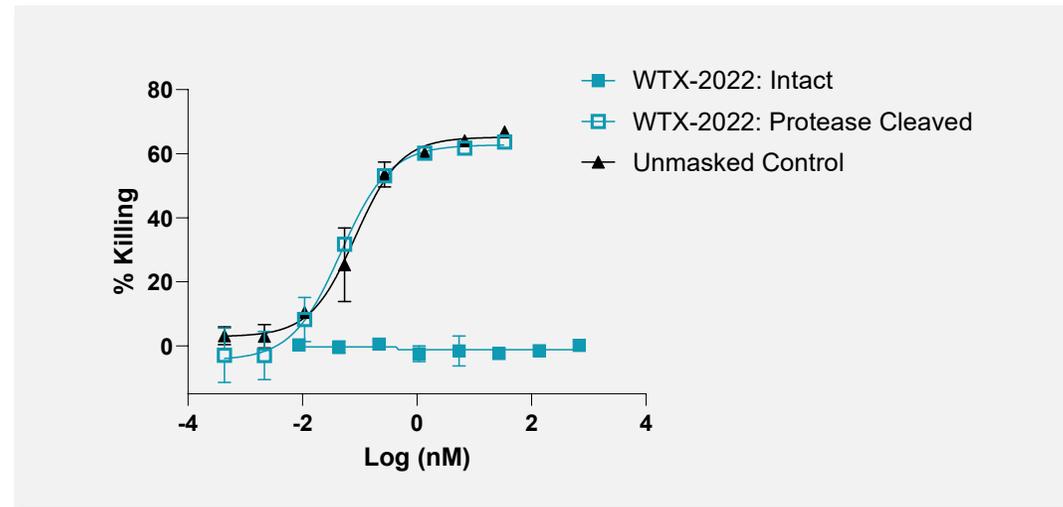
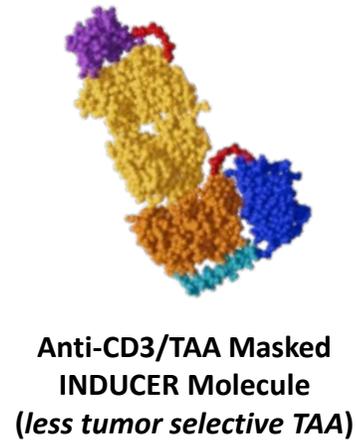
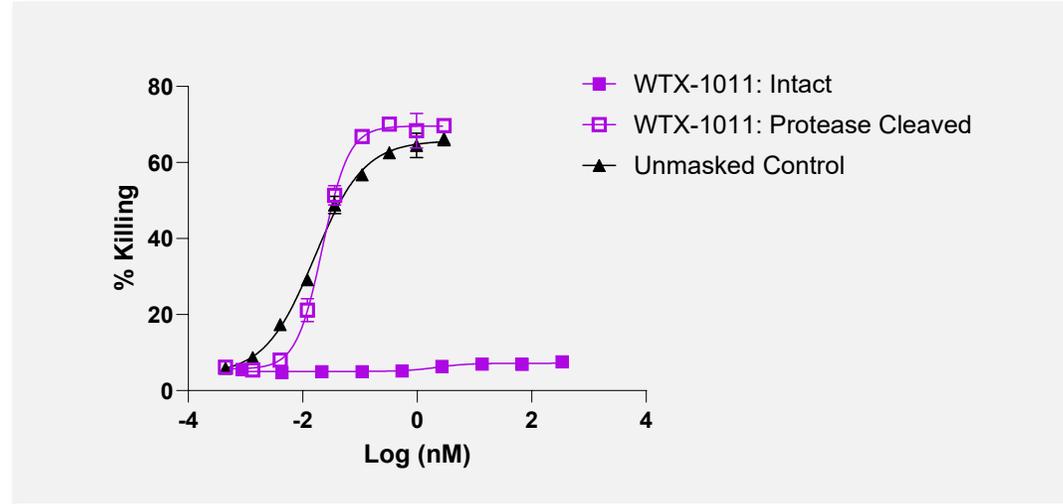
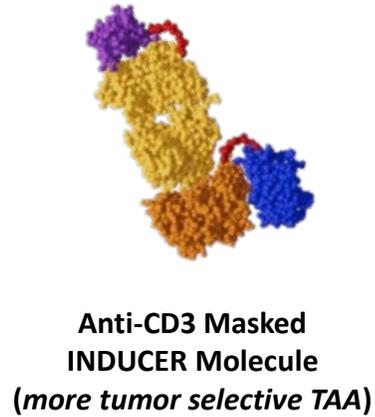


- ✓ *Tumor protease cleavable linkers*  
**Novel pan-cancer linker** acts as tumor-specific switch, enabling precise unmasking in the TME
- ✓ *Anti-CD3 mask*  
**Proprietary and optimized anti-CD3 masking technology** to reduce off-tumor toxicity
- ✓ *Anti-CD3*  
**Novel anti-CD3 Antibody** optimized for developability

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- ✓ *Anti-HSA for half-life extension*  
Proprietary **anti-HSA** for half-life extension and increased tumor exposure
- ✓ *Tumor antigen binding domain*  
Tumor-associated **antigen binding domain** selected for optimal immune cell engagement
- ✓ *Tumor targeting mask*  
**Proprietary and optimized targeting mask** utilized for tumor targets with extensive expression in normal tissues: improved exposure

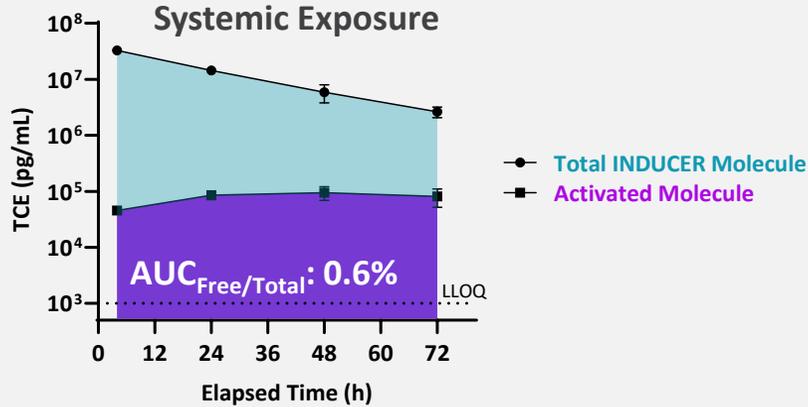
# INDUCER Designs with Robust, Reversible Masking that Address a Large Universe of Tumor Selective Targets



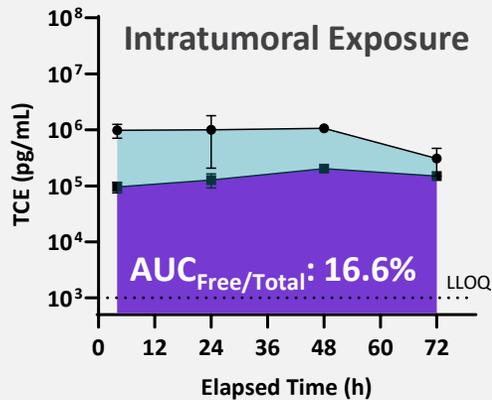
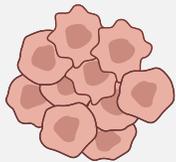
Abbreviation: TAA-tumor associated antigen

# INDUCER Molecules Selectively Target Active TCE Exposure to the Tumor Microenvironment

## INDUCER PK: Selective Unmasking in Tumor

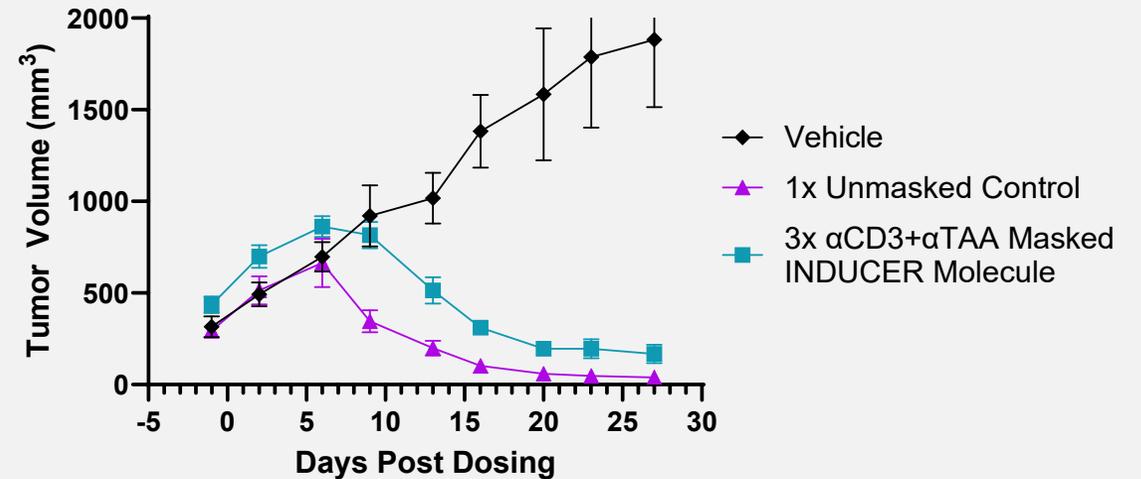


$AUC_{Tumor/Plasma}: 7.5\%$



Systemic and tumor exposure of total and activated INDUCER molecules in HT1376 NSG tumor model after a single IV infusion

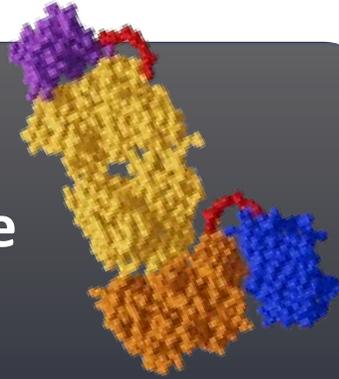
## Antitumor Efficacy of $\alpha$ CD3+ $\alpha$ TAA Masked INDUCER Molecule in a Humanized CDX Model



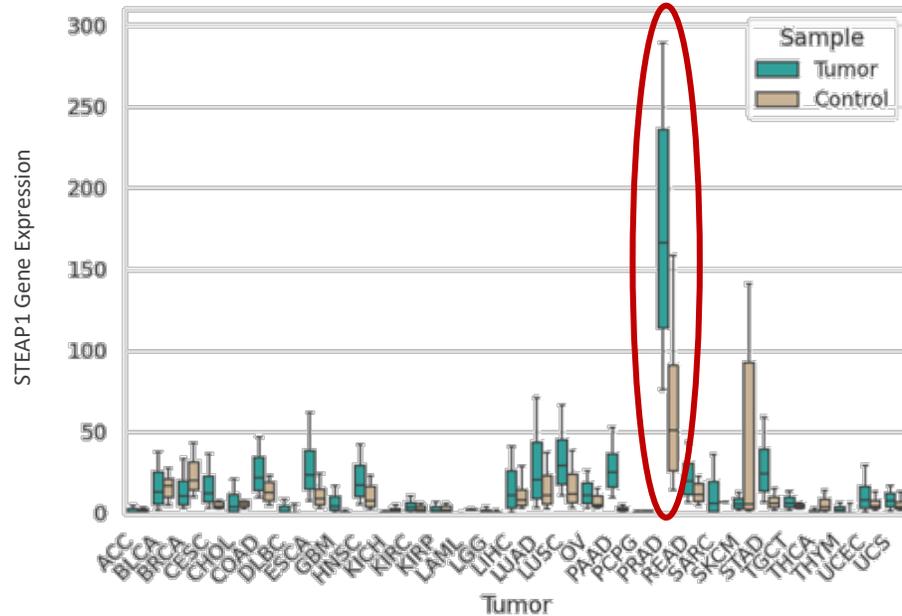
Efficacy of unmasked control and anti-CD3+anti-TAA masked INDUCER molecule in the human T cell engrafted NSG mice OVCAR-3 CDX tumor model

Abbreviations: AUC-area under the curve; NSG-NOD scid gamma; IV-intravenous; CDX-cell line-derived xenograft; TCE-T cell engager

# WTX-1011: STEAP1 INDUCER Molecule for Prostate Cancer



STEAP1 is Overexpressed in Prostate Cancer



## Background and Rationale

- STEAP1 is overexpressed in prostate tumors with limited expression in normal tissues
- Clinically validated prostate cancer target with potential in other indications

## The Opportunity

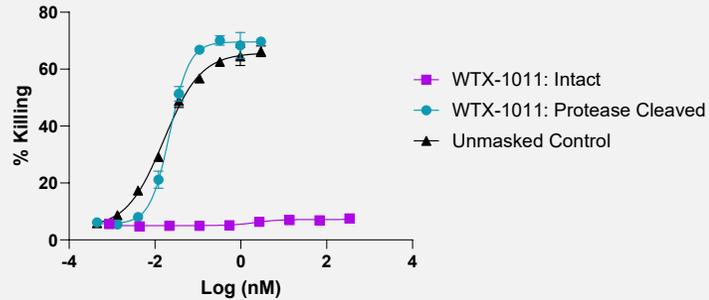
- INDUCER design offers potential to achieve increased tumor exposure and antitumor activity with an improved safety profile
- Development program anticipated in advanced, relapsed/refractory STEAP1-expressing cancers including CRPC

## Program Status

- Cell line development initiated and IND-enabling studies ongoing

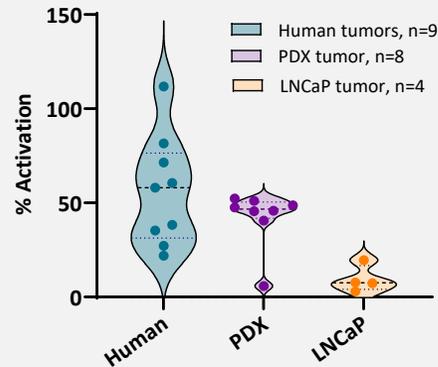
# WTX-1011: Unmasked by Human Prostate Tumors and Demonstrated Antitumor Activity in Preclinical Studies

## In Vitro Cell Killing Assay



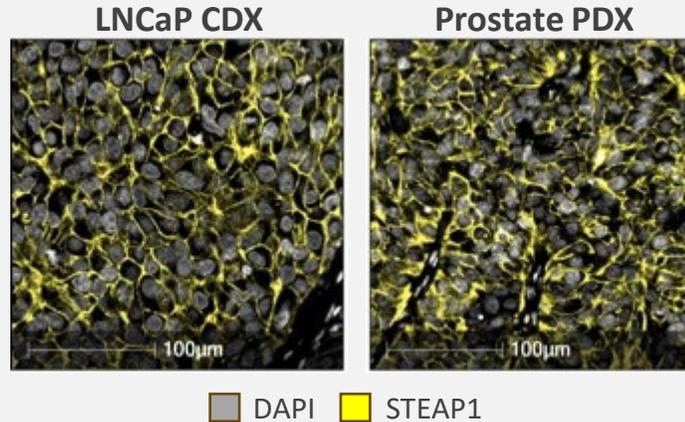
T cell-dependent cellular cytotoxicity with STEAP1-HEK293 cells

## In Vitro Activation of WTX-1011 by Dissociated Tumors



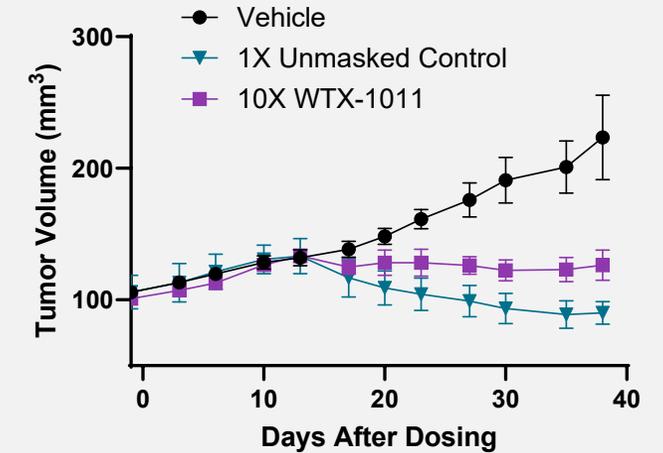
WTX-1011 activation by dissociated human prostate tumors, patient derived xenograft (PDX) prostate tumors, and LNCaP cell-line derived xenograft (CDX) tumors

## Expression of STEAP1 on Prostate CDX and PDX Tumors



A FFPE PDX prostate tumor or LNCaP CDX tumors were stained with an anti-human STEAP1 antibody and imaged using the Lunaphore COMET IF Imaging system

## In Vivo Efficacy of WTX-1011 in LNCaP CDX Tumor Model

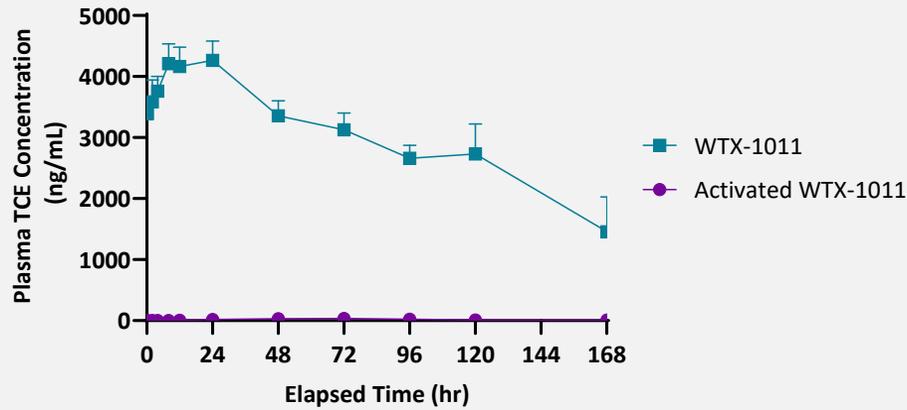


Efficacy of unmasked control and WTX-1011 in the human T cell engrafted NSG mice LNCaP CDX tumor model

- Anti-CD3 mask provided complete and reversible silencing
- WTX-1011 was broadly unmasked by human prostate tumor specimens and prostate PDX and CDX tumors
- WTX-1011 controlled tumor growth in the LNCaP CDX tumor model

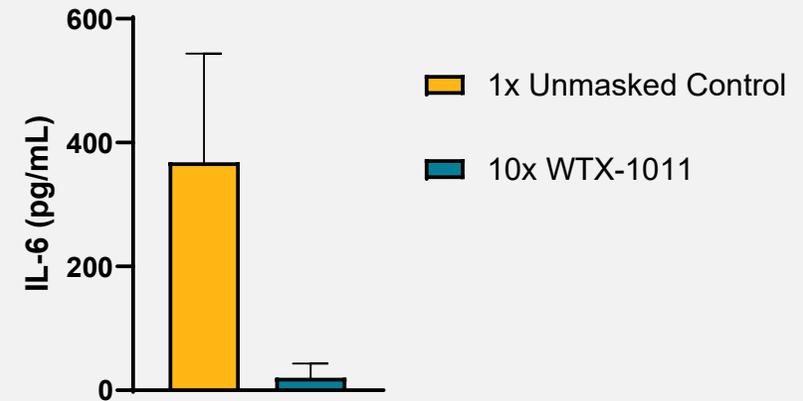
# WTX-1011: Favorable PK, Limited Peripheral Activation, and Negligible Cytokine Release in NHP

## PK of WTX-1011 in NHP



Plasma levels of WTX-1011 and activated INDUCER molecule after IV administration of WTX-1011 in NHP

## Cytokine Release in NHP



Plasma IL-6 levels 4 hours after IV administration of non-masked STEAP1 INDUCER molecule or 10x greater dose of WTX-1011

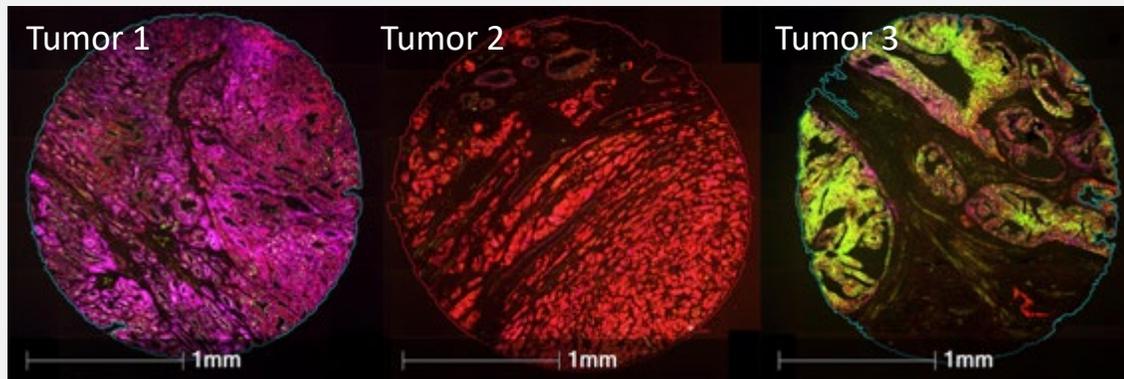
- WTX-1011 showed beneficial exposure in cynomolgus monkeys with a half-life close to 100 hours
- WTX-1011 was stable in the periphery, with less than 0.7% of active INDUCER detected
- Low levels of WTX-1011 cytokine production compared to a 10-fold lower dose of unmasked STEAP1 targeted TCE

# Trispecific INDUCER Molecules for Prostate Cancer

## Background and Rationale

- Targeting multiple tumor antigens may overcome intra- and interpatient TAA heterogeneity to provide improved efficacy
- STEAP1, PSMA, and KLK2 are selectively overexpressed and exhibit heterogeneous expression in prostate cancer
- INDUCER designs demonstrated efficient, reversible masking and tumor cell cytotoxicity on antigen-expressing cell lines

### Intra- and Interpatient Heterogeneity of Prostate Cancer TAA Expression

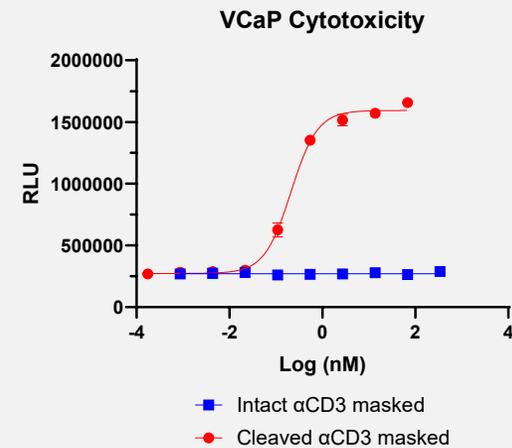


	PSMA+	STEAP1+	KLK2+	STEAP1+ and/or PSMA+	STEAP1+ and/or KLK2+	PSMA+ and/or KLK2+
% Positive Tumors*	53%	59%	71%	76%	94%	100%

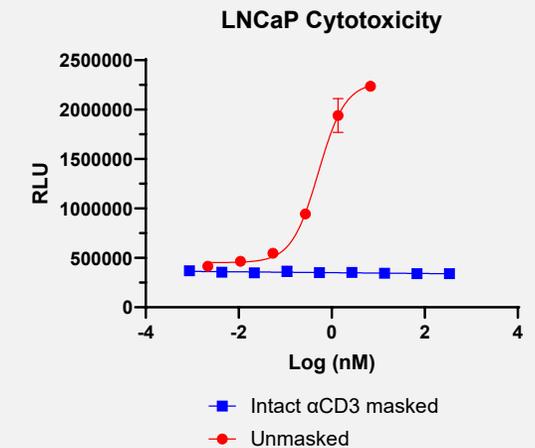
\*Positive = >50% of cells express TAA(s), normalized by cells that express any TAA, N = 17 tumors

Abbreviations: TAA-tumor associated antigen; RLU-relative luminescence units

### STEAP1 x KLK2 x CD3



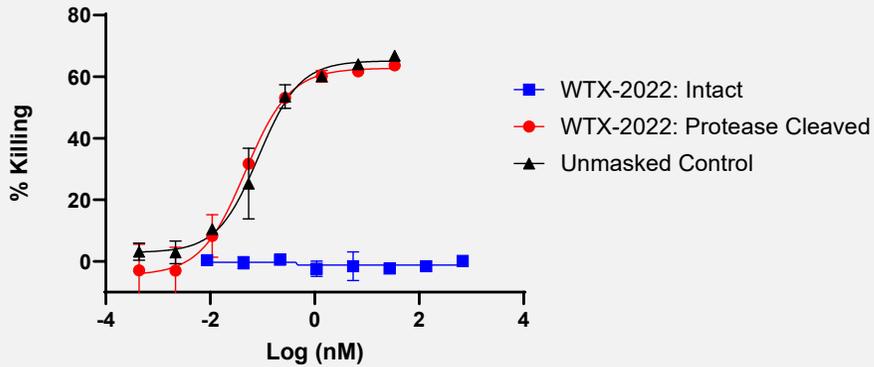
### STEAP1 x PSMA x CD3





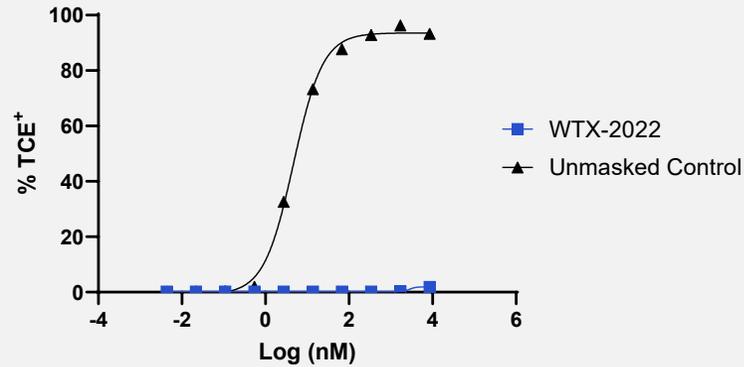
# WTX-2022: Masking $\alpha$ CD3 and $\alpha$ CDH6 for Optimal Tumor Exposure

## Highly Effective, Reversible anti-CD3/CDH6 Masking



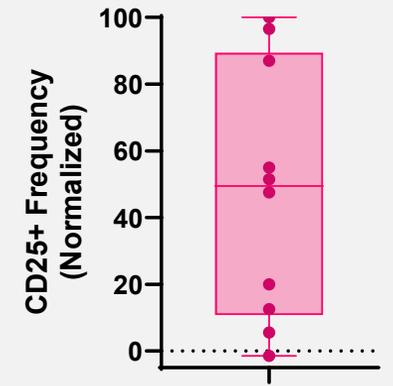
T cell-dependent cellular cytotoxicity with CDH6-HEK293 cells

## Anti-CDH6 Mask Prevented Binding to CDH6+ Cells



Binding of INDUCER molecules to OVCAR-3 cells

## WTX-2022 Was Unmasked by Human Ovarian Tumors

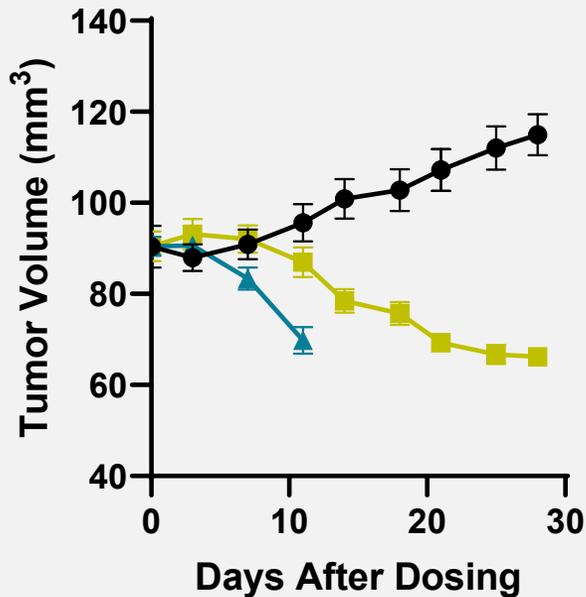


Functional readout of INDUCER molecule activation by dissociated human ovarian tumors

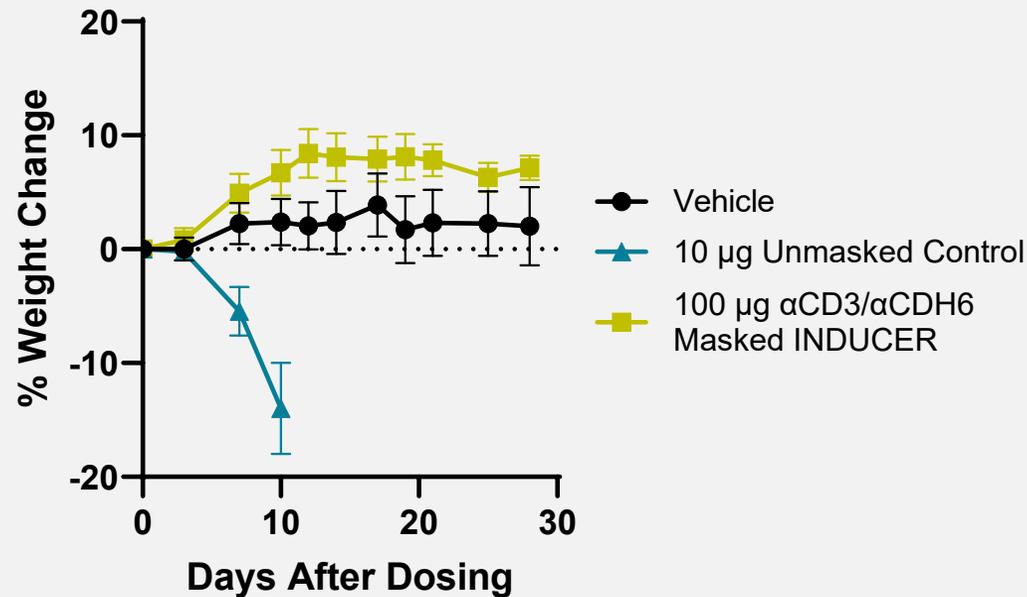
- $\alpha$ CD3 INDUCER masking alone prevented activity but  $\alpha$ CDH6 mask added to mitigate anticipated target mediated drug disposition (TMDD) in healthy tissues
- Masking is reversible, and WTX-2022 is activated by human ovarian tumors

# CDH6 INDUCER Molecules Demonstrated Tolerable Antitumor Efficacy

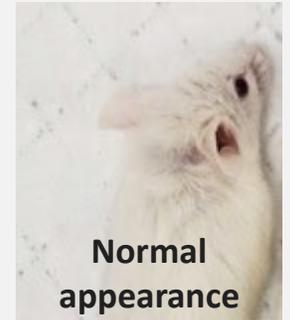
### In Vivo Efficacy of CDH6 INDUCER in OVCAR-3 Tumor Model



### CDH6 INDUCER Masking Prevents Off-tumor Toxicity



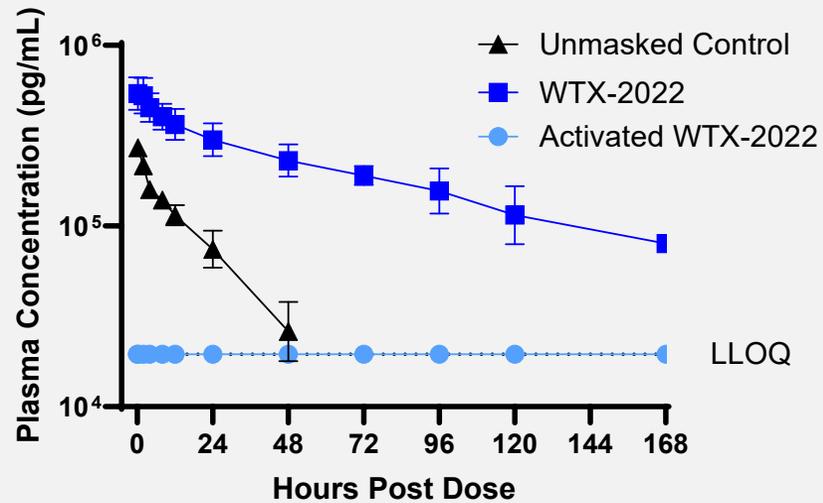
### Unmasked Control CDH6 INDUCER



- Anti-CD3/CDH6 masked INDUCER demonstrated potent antitumor activity
- Unmasked CDH6-targeted TCE is toxic, and masked INDUCER completely prevented toxicity

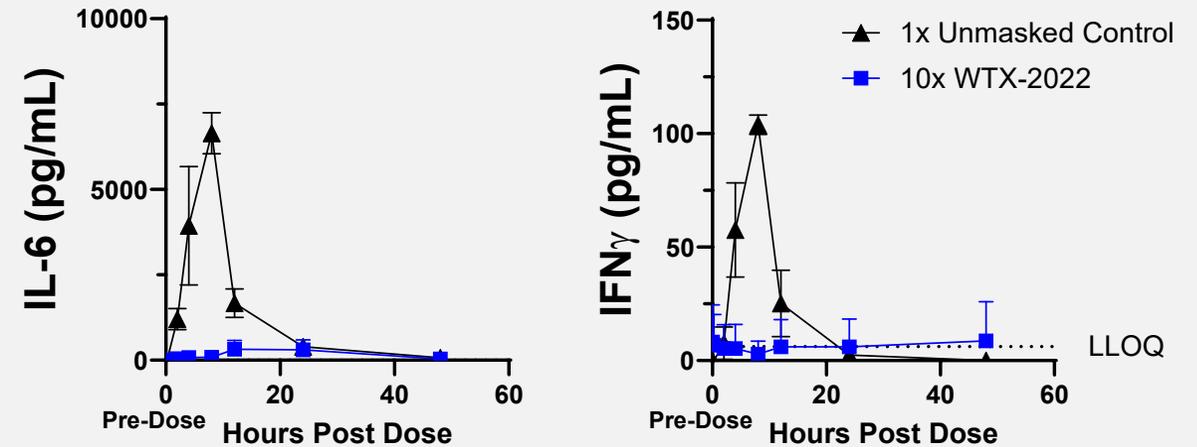
# WTX-2022: Masking Prevented Cytokine Release and Improved Exposure in Cynomolgus Monkeys

## Differentiated Exposure of Masked INDUCER Molecule vs Unmasked Control



Unmasked CDH6 control TCE (with half-life extension) and WTX-2022 INDUCER plasma levels after IV administration. WTX-2022 dosed 10x higher than unmasked control. Activated INDUCER exposure was below LLOQ.

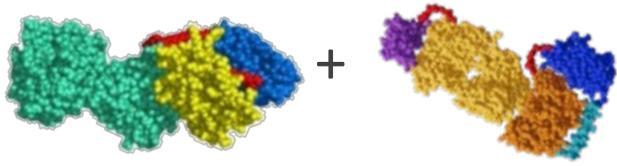
## Cytokine Release in NHP



Plasma cytokine levels of IL-6 and IFN $\gamma$  after IV administration of unmasked CDH6 TCE control molecule or 10x greater dose of WTX-2022.

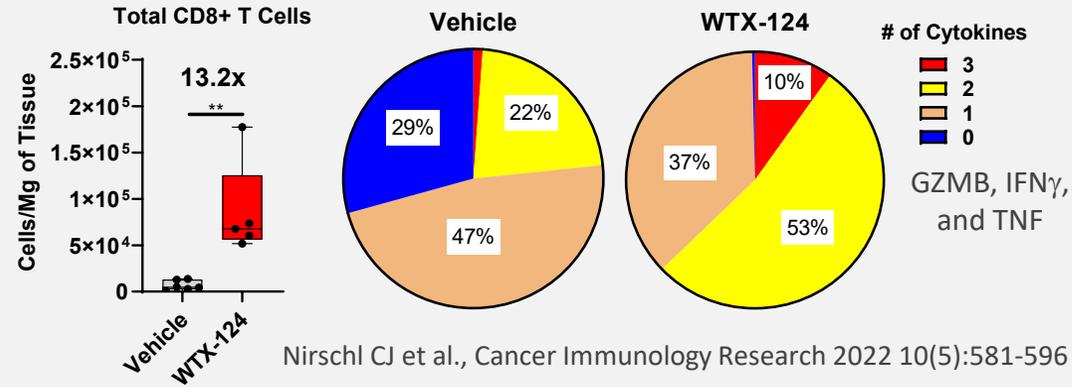
WTX-2022 showed sustained plasma exposure in cynomolgus monkeys ( $T_{1/2}$  ~50 hours), reduced TMDD, no detectable activated INDUCER molecule, and no cytokine release even when dosed 10X higher than unmasked TCE molecule

# Opportunity to Combine INDUCER T Cell Engager Therapy with INDUKINE Molecules

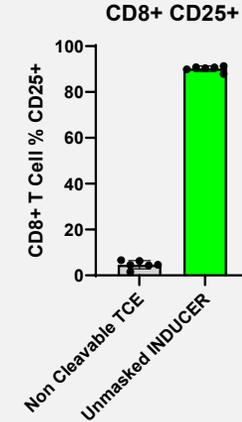


- IL-2 (WTX-124) expands the population of intratumoral effector T cells and primes them to be more effective killers
- TCEs upregulate CD25 on CD8+ T cells, providing a feed forward loop for IL-2
- Combination with IL-2 INDUKINE molecule enhances the activity of a T cell engager in a mouse model
- Other INDUKINE molecules (e.g., IL-21, IL-18 and IL-12) are also interesting opportunities for combination

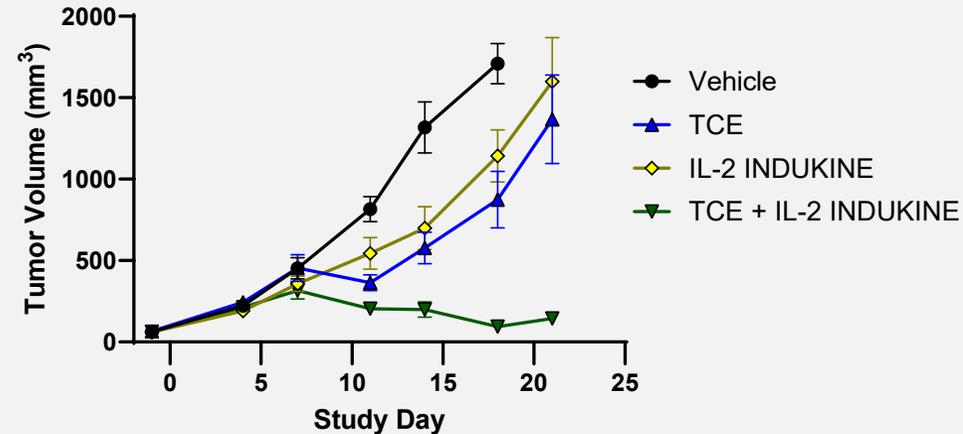
## IL-2 Expands CD8 Effector T Cells and Promotes Effector Molecule Expression



## TCEs Upregulate CD25 in Cell Killing Assay



## IL-2 INDUKINE Molecule Improves the Activity of a T Cell Engager in the A431 CDX Model



# INDUCER Molecules: Raising the Bar for T Cell Engagers

## Key Takeaways

- ✓ **Addressing Key Challenges:** engineered to overcome the limitations of current T-cell engager therapies, including on-target/off-tumor toxicity and dose-limiting Cytokine Release Syndrome (CRS)
- ✓ **Breakthrough Masking Technology:** innovative, reversible masking strategy designed to ensure precise control of INDUCER molecules to minimize adverse effects
- ✓ **De-risked Development for INDUCER molecules:** incorporates clinically validated linker
- ✓ **Preclinical Success:** demonstrated efficient tumor activation with complete absence of CRS
- ✓ **Scalable and Versatile:** broadly applicable platform supports targets with broad normal tissue expression as well as trispecific targeting
- ✓ **Advancing Pipeline:**
  - Robust pipeline of INDUCER molecules that address a range of malignancies with high unmet medical need
  - Strong rationale to combine INDUCER molecules with WTX-124



**Werewolf**  
THERAPEUTICS

Thank you!