Werewolf THERAPEUTICS

Shifting the Balance In Cytokine Therapeutics

SITC 2023

A phase 1/1b study of the tumor-activated IL-2 prodrug WTX-124 alone or in combination with pembrolizumab in patients with immunotherapy-sensitive locally advanced or metastatic solid tumors

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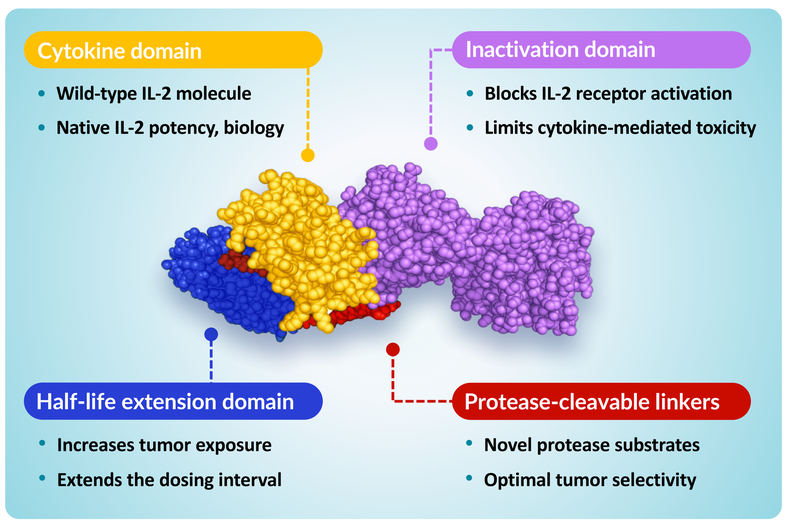
INTRODUCTION

WTX-124 is an engineered IL-2 prodrug for solid tumor indications



IL-2 is an approved immunotherapy that produces durable remissions in patients with melanoma and renal cell carcinoma but is hampered by severe toxicities. There have been no next generation IL-2 molecules that have reported improved tolerability with comparable antitumor activity. To address this challenge, we engineered an IL-2 INDUKINE™ molecule (WTX-124) to be administered systemically but activated selectively in the tumor microenvironment. Distinct from other IL-2 molecules, WTX-124 is designed to release a fully potent, wild-type cytokine in tumors. In the first-in-human trial (WTX-124x2101), WTX-124 is being investigated both as a monotherapy and in combination with pembrolizumab in patients with refractory solid tumors. Here we present interim data from the first four dose levels in the ongoing monotherapy dose escalation portion of the Phase 1/1b clinical trial of WTX-124.

WTX-124x2101 FIRST-IN-HUMAN STUDY DESIGN

Monotherapy and combination therapy with pembrolizumab

Dose Escalation (N~70 patients)

- Modified toxicity probability interval 2 (mTPI-2) study design
- WTX-124 administered as a flat dose in cohorts of 3-6 patients

Monotherapy (N~35)

- WTX-124 IV Q2W in 28-day cycles
- DLT period = 28 days

Combo gated to demonstrating safety in the first three monotherapy cohorts

Combination Therapy (N~35)

- WTX-124 IV Q2W + pembrolizumab 400mg IV Q6W (42-day cycles)
- DLT period = 28 days (identical to monotherapy escalation)

MTD/ RDE

Dose Expansion (N=80 patients)

- Expansion arms for monotherapy and combination therapy may open and start enrollment in parallel

Monotherapy (N=40)

- Arm A: Renal cell carcinoma
- Arm B: Cutaneous melanoma

Opportunities exist to open expansion arms in additional indications

Combination therapy (N~40)

- Arm C: Renal cell carcinoma
- Arm D: Cutaneous melanoma

MTD/ RDE

PATIENT POPULATIONS

DOSE ESCALATION

Any solid tumor for which an immune checkpoint inhibitor (ICI) is approved

1. MONOTHERAPY (WTX-124)

- Relapsed/refractory to SOC
- No more than 4 prior lines
- Prior ICI is mandatory

1b. COMBINATION (WTX-124/pembrolizumab)

- Relapsed/refractory to SOC
- No more than 4 prior lines
- Prior ICI is mandatory
- No discontinuation of prior anti-PD-(L)1 due to toxicity (i.e., irAE)

PATIENT DEMOGRAPHICS BY COHORT

Cohorts 1-4 of WTX-124 monotherapy dose escalation

Characteristic, n (%)		1mg (N=3)	3mg (N=4)	6mg (N=4)	12mg (N=5)	Total (N=16)
Age	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	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	Black/African-American	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (6.3%)
	White	2 (66.7%)	3 (75.0%)	3 (75.0%)	5 (100.0%)	13 (81.3%)
	Unknown	1 (33.3%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	2 (12.5%)
ECOG PS	0	0 (0.0%)	2 (50.0%)	1 (25.0%)	2 (40.0%)	5 (31.3%)
	1	3 (100.0%)	2 (50.0%)	3 (75.0%)	3 (60.0%)	11 (68.8%)
Tumor type	Melanoma*	1 (33.3%)	2 (50.0%)	2 (50.0%)	3 (60.0%)	8 (50.0%)
	NSCLC	1 (33.3%)	2 (50.0%)	1 (25.0%)	1 (20.0%)	5 (31.3%)
	RCC	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%)
Mutational burden	TMB-H	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	2 (12.5%)
	TMB-L	1 (33.3%)	3 (75.0%)	2 (50.0%)	0 (0.0%)	6 (37.5%)
	Not determined	1 (33.3%)	1 (25.0%)	2 (50.0%)	4 (80.0%)	8 (50.0%)
Prior lines of systemic therapy#	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 (31.3%)
	≥4	1 (33.3%)	1 (25.0%)	1 (25.0%)	2 (40.0%)	5 (31.3%)

*Includes patients with cutaneous (n=5), uveal (n=2), and mucosal (n=1) 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.

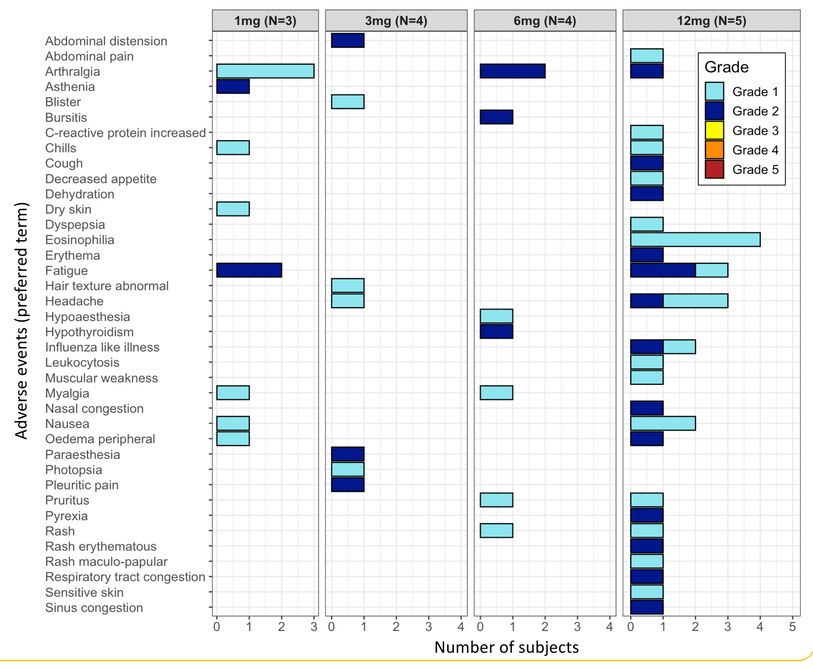
Abbreviations: SD: standard deviation; NR: not reported; ECOG: Eastern Cooperative Oncology Group; PS: performance status; TMB: tumor mutational burden; TMB-H: high TMB (≥10 mutations/megabase); TMB-L: low TMB (≤10 mutations/megabase); NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; SCC: squamous cell carcinoma.

FREQUENCY OF RELATED TREATMENT-EMERGENT ADVERSE EVENTS

No evidence of vascular leak syndrome following dosing of WTX-124 in the outpatient setting

Shown at right is the frequency of treatment-emergent adverse events (TEAEs) that are at least possibly related to WTX-124. Key findings to date include:

- All TEAEs related to WTX-124 were low grade (i.e., CTCAE grades 1 and 2)
- Arthralgias and fatigue were the most common TEAEs related to therapy
- No patient developed vascular leak syndrome or cytokine release syndrome of any grade
- No patient developed a dose-limiting toxicity or treatment-related serious adverse event
- No patient discontinued therapy due to a treatment-related adverse event

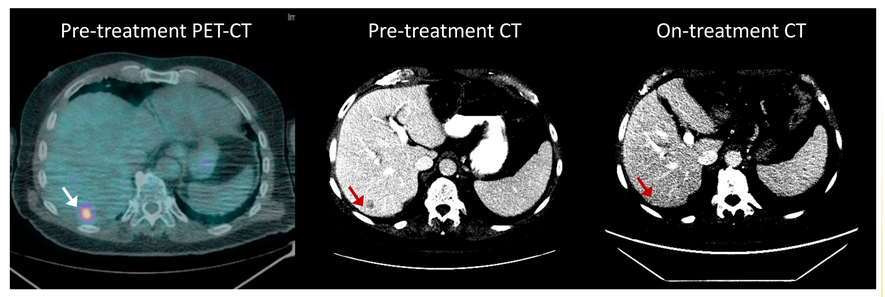


CLINCAL RESPONSES TO WTX-124 MONOTHERAPY

Antitumor activity is demonstrated during the ongoing dose escalation

Objective response observed at 12mg dose:

- A 78-year-old man with *BRAF* wild-type metastatic melanoma refractory to standard-of-care therapies achieved an unconfirmed partial response (PR) per RECIST 1.1 on the first restaging CT scan at 8 weeks.
- The patient was diagnosed in June 2018 with stage III melanoma and treated surgically and with adjuvant nivolumab for 10 months prior to discontinuing therapy due to toxicity.
- For relapsed disease, the patient was treated with combined nivolumab and relatlimab (Opdualag™) in December 2022, achieving a best overall response of PR by RECIST 1.1 before progressing in July 2023.
- The patient then enrolled in the WTX-124 first-in-human study, with the first dose of study drug administered in August 2023.
- After 2 cycles of therapy with 12mg WTX-124 IV Q2W, restaging imaging studies showed complete resolution of a 1.4cm target lesion in the liver (*top right*). The patient also had a stable non-target lesion in the T11 vertebral body (*not shown*).



Additional evidence of antitumor activity in WTX-124 monotherapy dose escalation:

Cohort 4 (12mg):

- A 76-year-old man with refractory non-small cell lung cancer (NSCLC) had rapid necrosis of metastatic deposits in the scalp after the first dose of study drug
- A 72-year-old man with cutaneous squamous cell carcinoma had shrinkage of a premaxillary subcutaneous nodule on ultrasound at the time of the on-treatment biopsy

Cohort 3 (6mg):

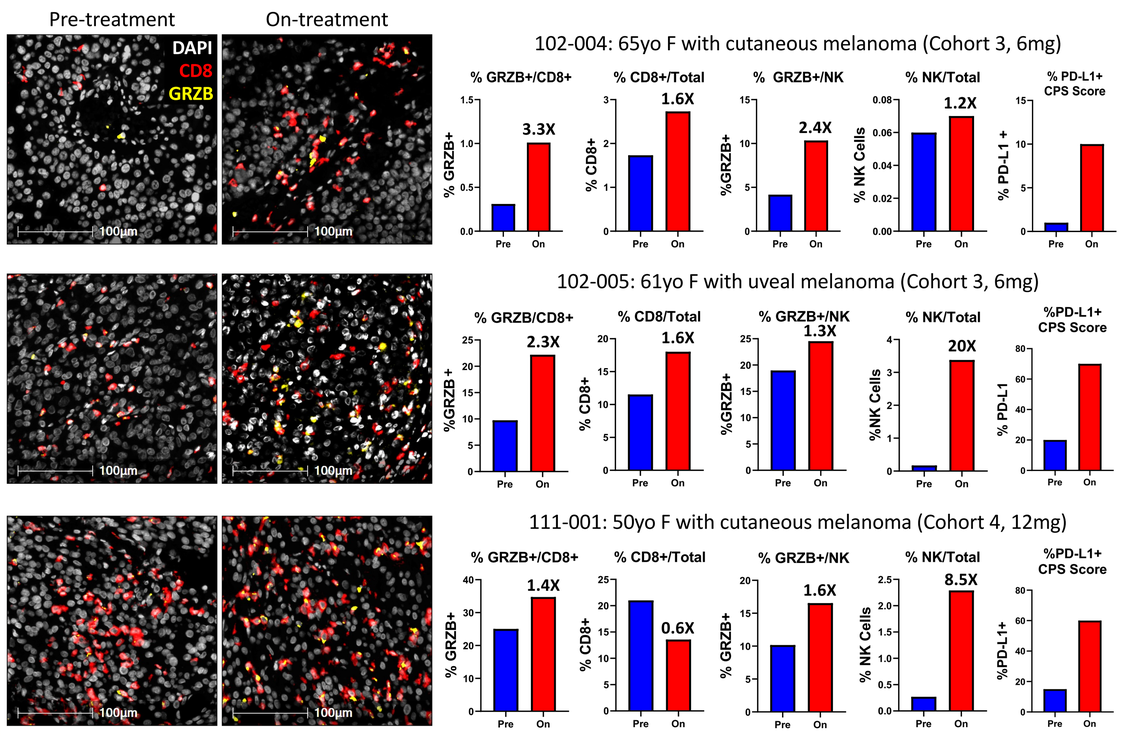
- A 65-year-old woman with progressive melanoma had stable disease (SD) per RECIST 1.1 for ~4 months (*see bottom left for tumor biomarker data from this patient 102-004*)

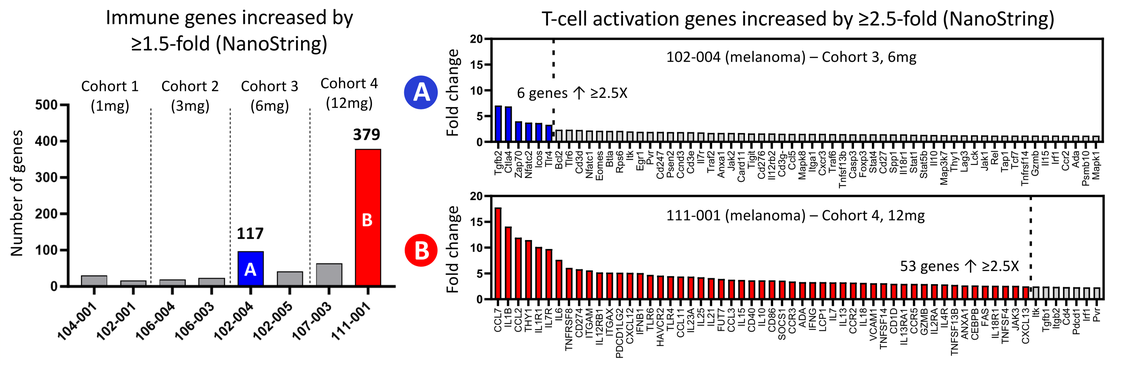
Cohort 1 (1mg):

- A 63-year-old man with refractory NSCLC had SD per RECIST 1.1 for ~6 months

TRANSLATIONAL BIOMARKERS

On-treatment tumor biopsies show evidence of CD8+ T and NK cell expansion and activation





Paired tumor biopsies from patients treated with 6 or 12mg WTX-124 IV Q2W show evidence of IL-2 pharmacodynamic activity in the tumor microenvironment. Pre-treatment samples were fresh biopsies or archival tumor less than one year old; on-treatment tumor biopsies were collected between cycle 1 day 22 and day 28 (i.e., after the first two doses of WTX-124). Biomarker assays include multiplexed immunofluorescence (IF) microscopy with whole-slide quantification (*images and bar graphs, top*) and NanoString nCounter® PanCancer Immune Profiling (*bar graphs*, *bottom*). The PD-L1 combined positive score (CPS) was calculated by whole-slide quantification of PD-L1 expression by immunohistochemistry (*images not shown*). By NanoString, the on-treatment tumor biopsy from **Patient A (102-004; 6mg)** showed 117/770 immune genes increase by ≥1.5-fold from baseline, including 6/172 T-cell activation genes that increased by ≥2.5-fold. In the 12mg cohort, the on-treatment tumor biopsy from **Patient B (111-001)** showed 379/770 immune genes increase by ≥1.5-fold from baseline, including 53/172 T-cell activation genes that increased by ≥2.5-fold.

PRELIMINARY PHARMACOKINETIC PROFILE

Plasma PK data show an extended WTX-124 half-life with very low free (active) IL-2 exposure

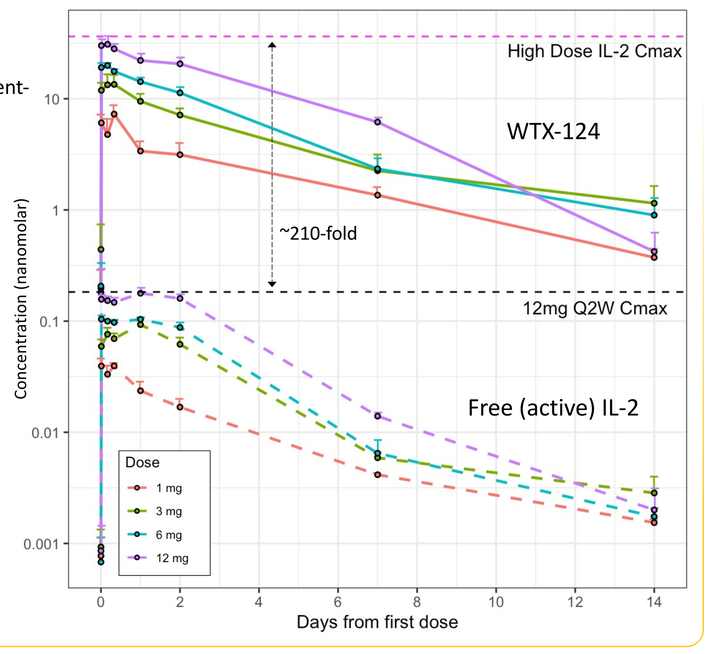
- Dose-dependent increase in WTX-124 plasma exposure
- Low free (active) IL-2 levels (<1.6% of prodrug) during the dosing phase
- WTX-124 prodrug Cmax at 12mg IV Q2W is comparable to HD IL-2
- Free (active) IL-2 at 12mg IV Q2W is ~**210-fold lower** than HD IL-2
- Preliminary WTX-124 half-life ranges from 1.86-5.79 days
- Preliminary ADA: 5/15 patients exhibit non-dose dependent, treatment-emergent ADA (low titer in 4/5); no impact on repeat dose exposure

Cycle 1 PK parameters

	Parameter Mean (CV%)	1mg (N=3)	3mg (N=4)	6mg (N=3#)	12mg (N=4Δ)
WTX-124 PK	Cmax (µg/mL)	0.51 (54%)	1.23 (40%)	1.66 (10%)	2.63 (32%)
	Tmax (hrs)	1.6 (130%)	2.22 (92%)	2.6 (77%)	3.12 (117%)
	AUC(0-14d)*	2.05 (37%)	4.54 (36%)	6.29 (17%)	11.41 (17%)
	Tlast (hrs)	345 (4%)	347 (7%)	248 (70%)	333 (41%)
	$t_{1/2}$ (days)	4.39 (27%)	3.66 (41%)	3.02 (11%)	2.69 (43%)
Free IL-2 PK	Cmax (pg/mL)	721 (47%)	1601 (25%)	1907 (12%)	2962 (20%)
	Tmax (hrs)	0.4 (31%)	19 (53%)	8.2 (167%)	23.3 (78%)
	AUC(0-14d)&	1999 (27%)	5347@ (7%)	7285@ (1.8%)	15635^(14%)
	Tlast (hrs)	345 (4%)	347 (7%)	248 (70%)	333 (41%)
	$t_{1/2}$ (days)	3.46 (13%)	2.41@ (5%)	2.25@ (7%)	2.75^ (67%)

(#) outlier patient removed from non-compartmental PK analysis; (Δ) samples from the 5th patient in this cohort were not received in time for analysis; (*)units=µg*d/mL; (&) units=pg*d/mL; (@) extrapolation not feasible for n=1 patient PK profile; (^) extrapolation not feasible with n=2 PK profiles.

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



SUMMARY and CONCLUSIONS

- **WTX-124 administered as a monotherapy IV Q2W reached exposures associated with intratumoral IL-2 pharmacodynamic activity and clinical responses with limited toxicities**
- WTX-124 dosed up to 12mg IV Q2W in the outpatient setting 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 adverse events
- PK data showed extended WTX-124 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 permissive of continued dose escalation
- WTX-124 6-12mg IV Q2W achieved biologically meaningful IL-2 exposure in the tumor microenvironment as evidenced by antitumor activity (unconfirmed PR, SD by RECIST 1.1) and CD8+ T cell and NK cell expansion and activation
- The data demonstrate that WTX-124 has the potential to deliver a fully potent, wild-type IL-2 molecule to the TME in patients with refractory solid tumors with limited toxicities
- WTX-124 monotherapy dose escalation is ongoing with expectation of RDE declaration and opening of expansion arms in 1H 2024

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