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A phase 1/1b trial of the IL-2 prodrug WTX-124 in patients with locally advanced or metastatic solid tumors after checkpoint inhibitor therapy: Updated results of the monotherapy dose escalation and initial results of the combination therapy dose escalation with pembrolizumab

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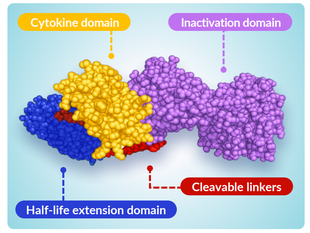
INTRODUCTION

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 advanced cancer but is hampered by severe toxicities. To improve the therapeutic index for IL-2, Werewolf has engineered an INDUKINE™ molecule (WTX-124) to be systemically administered but preferentially activated in the tumor microenvironment. Distinct from all other next generation IL-2 molecules, WTX-124 is designed to release a fully potent, wild type cytokine in tumors. In the ongoing first-in-human trial (WTX-124x2101), WTX-124 is administered as a monotherapy or in combination with pembrolizumab to patients with solid tumors refractory to all standard of care therapies including immune checkpoint inhibitors (ICIs). Here we update the monotherapy dose escalation data and present initial results for the combination therapy dose escalation with pembrolizumab.

- **Cytokine domain –** wild type IL-2 molecule with native potency and established biology
- **Half-life extension domain –** designed to maximize tumor prodrug exposure
- **Inactivation domain –** blocks IL-2 receptor activation in the periphery to limit toxicity
- **Cleavable linkers –** novel protease substrates optimized for tumor selectivity

WTX-124x2101 FIRST-IN-HUMAN TRIAL

Monotherapy and combination therapy with pembrolizumab

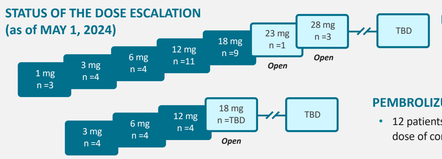
Dose escalation (*mono and combo ongoing*)

- Modified toxicity probability interval 2 (mTPI-2) study design
- Patients must have a solid tumor for which immunotherapy is indicated and have progressed on all available SOC
- WTX-124 is administered as a flat dose IV Q2W alone or with pembrolizumab 400mg IV Q6W in 28- (monotherapy) or 42-day cycles (combination)
- DLT period = 28 days for both monotherapy, combination

Expansion arms (*enrolling Arms A-C*)

- **Arm A, monotherapy**: Renal cell carcinoma (n=20)
- **Arm B, monotherapy**: Melanoma (n=20)
- **Arm C, monotherapy**: Cutaneous squamous cell carcinoma (n=10)
- **Arm D, combination**: Renal cell carcinoma (n=20)
- **Arm E, combination**: Melanoma (n=20)
- *Additional expansion arms under consideration*

STATUS OF THE DOSE ESCALATION (as of MAY 1, 2024)



MONOTHERAPY

- 35 patients treated with at least one dose of WTX-124

PEMBROLIZUMAB COMBINATION

- 12 patients treated with at least one dose of combination therapy

PATIENT DEMOGRAPHICS, MONOTHERAPY AND COMBINATION THERAPY

All patients progressed on SOC immunotherapy regimens and many were ineligible for HD IL-2

Characteristic, n (%)		Monotherapy (n=35)	Combination (n=12)	Total (N=47)
Age (years)	Mean (SD)	66.1 (9.21)	57.7 (13.15)	63.9 (10.86)
	Median	67.0	59.0	65.0
Sex	Female	14 (40.0%)	6 (50.0%)	20 (42.6%)
	Male	21 (60.0%)	6 (50.0%)	27 (57.4%)
Race	Asian	1 (2.9%)	1 (8.3%)	2 (4.3%)
	Black/African-American	2 (5.7%)	0 (0.0%)	2 (4.3%)
	White	28 (80.0%)	11 (91.7%)	39 (83.0%)
	Other	1 (2.9%)	0 (0.0%)	1 (2.1%)
	Unknown	3 (8.6%)	0 (0.0%)	3 (6.4%)
ECOG PS	0	12 (34.3%)	9 (75.0%)	21 (44.7%)
	1	23 (65.7%)	3 (25.0%)	26 (55.3%)
Tumor type	Melanoma*	18 (51.4%)	6 (50.0%)	24 (51.1%)
	NSCLC	6 (17.1%)	2 (16.7%)	8 (17.0%)
	RCC	3 (8.6%)	1 (8.3%)	4 (8.5%)
	Cutaneous SCC	2 (5.7%)	0 (0.0%)	2 (4.3%)
	Gastroesophageal junction	1 (2.9%)	0 (0.0%)	1 (2.1%)
	Other	5 (14.3%)	3 (25.0%)	8 (17.0%)
Prior lines of systemic therapy	1	5 (14.3%)	5 (41.7%)	10 (21.3%)
	2	8 (22.9%)	3 (25.0%)	11 (23.4%)
	3	13 (37.1%)	2 (16.7%)	15 (31.9%)
	≥4	9 (25.7%)	2 (16.7%)	11 (23.4%)
Prior lines of immunotherapy#	1	14 (40.0%)	6 (50.0%)	20 (42.6%)
	2	11 (31.4%)	4 (33.3%)	15 (31.9%)
	3	7 (20.0%)	2 (16.7%)	9 (19.1%)
	≥4	3 (8.6%)	0 (0.0%)	3 (6.4%)

Dataset includes all patients treated with at least one dose of WTX-124 or WTX-124/pembrolizumab by the data cutoff date of May 1, 2024 (N=47)

*Melanoma includes patients with cutaneous melanoma (n=11 monotherapy, n=6 combination therapy), uveal melanoma (n=3 monotherapy, n=0 combination therapy), and mucosal melanoma (n=4 monotherapy, n=0 combination therapy)

*Lines of immunotherapy include IO agents used alone or in combination with each other or chemotherapy, targeted therapy, etc.

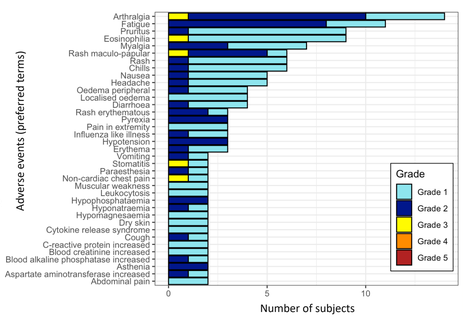
Abbreviations:
SD: standard deviation; **ECOG:** Eastern Cooperative Oncology Group; **PS:** performance status; **NSCLC:** non-small cell lung cancer; **RCC**: renal cell carcinoma; **SCC:** squamous cell carcinoma

FREQUENCY OF RELATED TREATMENT-EMERGENT ADVERSE EVENTS (TEAEs)

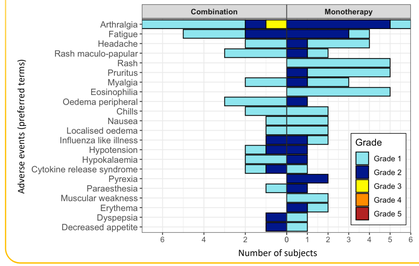
Related TEAEs were primarily mild to moderate, including at clinically active doses (≥12 mg IV Q2W)

RIGHT: Shown are TEAEs at least possibly related to WTX-124 and occurring in more than one patient (N=35). Key findings:

- Majority were mild to moderate (Gr1, Gr2); none were Gr4, Gr5
- Gr3 related TEAEs occurred at ≥18 mg IV Q2W and were manageable, reversible
- No evidence of VLS, ≥Gr2 CRS, or infusion-related reactions in any patient
- No recurrence of irAEs that previously occurred on checkpoint inhibitors



No new safety signals were observed when WTX-124 was combined with pembrolizumab



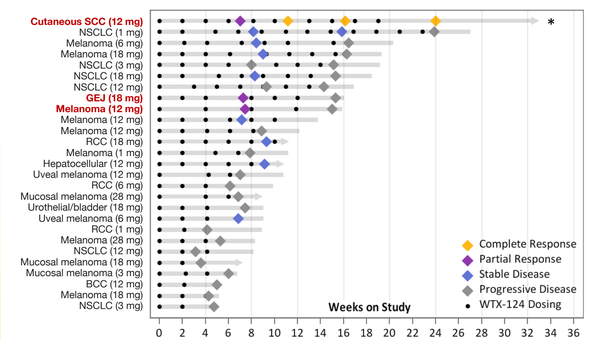
LEFT: Shown are related TEAEs occurring in more than one patient treated with 3-12 mg WTX-124 IV Q2W as a monotherapy (n=19) or in combination with pembrolizumab (n=12). Key findings include:

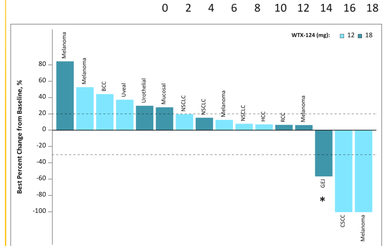
- The majority of related TEAEs for combination therapy were mild to moderate, as for monotherapy
- No substantial increase was observed in the frequency and/or severity of related TEAEs in patients treated with combination therapy vs. monotherapy*

*Note that 11 patients received the active dose of 12 mg WTX-124 monotherapy whereas only four patients received this dose in combination with pembrolizumab

CLINCAL RESPONSES TO WTX-124 MONOTHERAPY

Antitumor activity demonstrated at doses ≥12 mg IV Q2W during the ongoing dose escalation



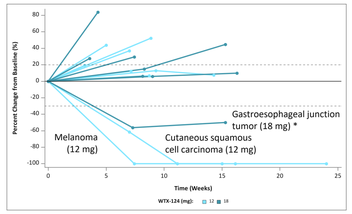


ABOVE: Swimmer's plot shows three patients with objective responses to WTX-124 (12 mg, 18 mg IV Q2W) and eight patients with stable disease. Arrow indicates ongoing. *Patient with cutaneous SCC has a durable CR ongoing at 8+ months and is being followed off drug

LEFT: Waterfall plot for patients treated at clinically active dose levels (12, 18 mg) considered for the RDE shows complete regression of target lesions in the three responding patients. Seven additional patients had stable target lesions. *Metastatic lymph node target lesion normalized in size (<1 cm)

Abbreviations: **SCC:** squamous cell cancer; **NSCLC:** non-small cell lung cancer; **GEJ:** gastroesophageal junction adenocarcinoma; **RCC:** renal cell carcinoma; **HCC:** hepatocellular carcinoma; **BCC:** basal cell carcinoma

Target lesion responses to WTX-124 monotherapy occurred rapidly and were durable



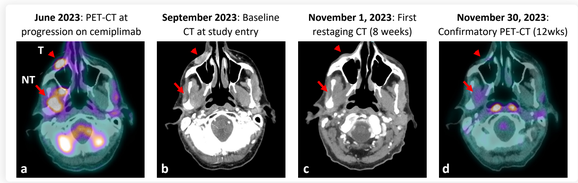
LEFT: Spider plot for patients treated at clinically active dose levels (12, 18 mg) considered for the RDE shows complete, durable regression of target lesions in the three responding patients. Asterisk (*) indicates that the metastatic lymph node target lesion normalized in size (<1 cm)

Note that all three objective responses to WTX-124 monotherapy had occurred within the first two cycles of therapy (i.e., documented on the first restaging CT scan at ~8 weeks)

PATIENT VIGNETTE 1: CUTANEOUS SQUAMOUS CELL CARCINOMA

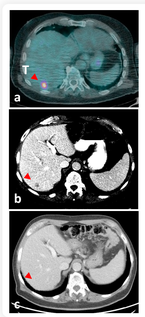
Ongoing confirmed complete response (CR) to monotherapy in a 72yo man with ICI-refractory cutaneous SCC

- Patient had progressed on RT/cetuximab and had no response to four doses (12 weeks) of cemiplimab (Libtayo®; anti-PD-1) **–panel a**
- Baseline CT showed a 2.6 cm premaxillary target lesion (T, arrowhead) and a non-target lesion (NT, arrow) extending into the pterygopalatine fossa **–panel b**
- Initiated treatment with **12 mg WTX-124 IV Q2W**
- At 3 weeks, on-treatment biopsy of the target lesion showed no tumor (multiple FFPE sections reviewed)
- At 8 weeks, the first restaging CT showed a PR with a 62% decrease in T and no increase in NT **–panel c**
- At 12 weeks, a PET-CT showed a complete metabolic response of T and NT, consistent with a CR **–panel d**
- Patient tolerated therapy well (G2 rash, G2 arthralgias)
- WTX-124 treatment stopped at 21 weeks in the setting of a confirmed CR, now ongoing at 8+ months



PATIENT VIGNETTE 2: CUTANEOUS MELANOMA (*BRAF* wild type)

Partial response (PR) to WTX-124 monotherapy in a 78-year-old man with secondary ICI resistance

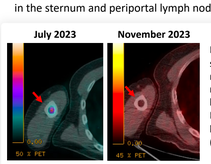


July 2023: Baseline PET-CT showed progression on nivolumab/relatlimab (Opdualag™; anti-PD-1/anti-LAG3) as first line therapy for metastatic disease (BOR PR) **–panels a, b**

July 2023: Baseline CT at study entry demonstrated a 1.4 cm target liver lesion (T, arrowhead)

September 2023: First restaging CT at 8 weeks showed 100% reduction of the target lesion, which was durable even after patient progressed at new lesions

- Patient discontinued adjuvant nivolumab due to toxicity and then progressed on nivolumab/relatlimab (Opdualag™; anti-PD-1/anti-LAG3) as first line therapy for metastatic disease (BOR PR) **–panels a, b**
- Initiated treatment with **12 mg WTX-124 IV Q2W**
- At 5 weeks, a target liver lesion (T) biopsied at baseline could not be reidentified. At 8 weeks, CT showed a complete response at T (**panel c**) and no increase of a T11 non-target lesion (NT). At 16 weeks, T remained absent, but NT increased; new lesions were identified in the sternum and periportal lymph nodes



PET-CT images show complete resolution of a metastatic lesion in the R upper humerus (arrow)

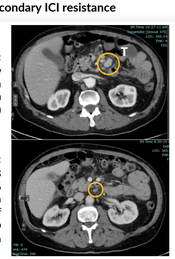
PATIENT VIGNETTE 3: GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

Partial response (PR) to WTX-124 monotherapy in a 63-year-old man with secondary ICI resistance

- Patient previously progressed on FOLFOX/nivolumab and nivolumab/BMS986253 (anti-IL-8). BOR for each prior line was SD
- Baseline CT showed a mesenteric lymph node target lesion (T) and four lymph node non-target lesions (NT)
- Initiated treatment with **18 mg WTX-124 IV Q2W**
- At 3 weeks, a L axillary lymph node biopsied at baseline could not be reidentified
- At 8 weeks, the first restaging CT showed a 56% reduction of the target lesion (with normalization to <1 cm) and no increase of NTs, consistent with a PR
- At 16 weeks, the target lesion response was ongoing but progression was observed at one of the four NTs. Patient discontinued WTX-124 but has neither progressed nor needed additional therapy for 3 mos

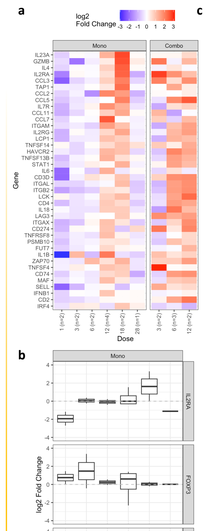
October 2023: Baseline CT at study entry showed a 1.6 cm mesenteric lymph node target lesion (T)

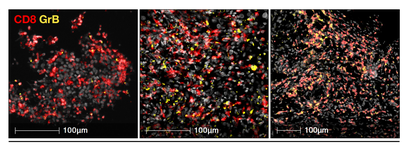
January 2024: First restaging CT at 8 weeks showed a 56% reduction of T, with normalization of lymph node size to <1 cm



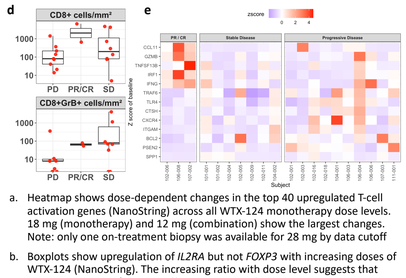
ANALYSIS OF TUMOR BIOMARKERS

Dose dependent increase in intratumoral T-cell activation; baseline TIL infiltration associates with response





	Patient 102-006	Patient 107-002	Patient 101-001
Tumor:	Cutaneous SCC	Melanoma	RCC
Prior IO:	Cemiplimab (1° resistance)	Nivolumab/relatlimab (2° resistance)	Pembrolizumab/axitinib (2° resistance)
Dose:	12 mg mono	12 mg mono	18 mg mono
Response:	CR (confirmed)	PR (non-confirmed)	SD (awaiting confirmation)



a. Heatmap shows dose-dependent changes in the top 40 upregulated T-cell activation genes (NanoString) across all WTX-124 monotherapy dose levels. 18 mg (monotherapy) and 12 mg (combination) show the largest changes. Note: only one on-treatment biopsy was available for 28 mg by data cutoff

b. Boxplots show upregulation of *IL2RA* but not *FOXP3* with increasing doses of WTX-124 (NanoString). The increasing ratio with dose level suggests that WTX-124 activates/expands effector T cells preferentially over Tregs

c. Multiplexed immunofluorescence analysis of baseline tumor biopsies show substantial infiltration of activated effector T cells in patients with ICI resistance who had CR/PR/SD to WTX-124 monotherapy. GrB –granzyme B

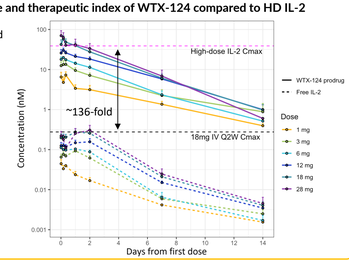
d. Quantification of CD8⁺ and CD8⁺GrB⁺ T cells/mm² in all baseline biopsies

e. A baseline signature in responders identified by DESeq2 (NanoString data)

PRELIMINARY PHARMACOKINETIC PROFILE

PK data account for the improved safety profile and therapeutic index of WTX-124 compared to HD IL-2

- WTX-124 dosed at 18 mg IV Q2W has a ~1.5-fold higher C_{max} than HD IL-2
- Peak free IL-2 exposure after 18 mg WTX-124 is ~136-fold lower than HD IL-2
- Across all dose levels, free IL-2 levels are very low (<1.6% of prodrug exposure)
- WTX-124 PK is approximately dose-proportional up to 18 mg IV Q2W
- Repeat dosing does not cause accumulation of WTX-124 or free IL-2
- ADA are transient, primarily low titer, and have no impact on repeat dose exposure
- Pembrolizumab does not affect WTX-124 PK



SUMMARY and CONCLUSIONS

- **WTX-124 18 mg IV Q2W was selected as the monotherapy RDE based on clinical activity and acceptable safety in the outpatient setting (expansion arms open)**
- WTX-124 as a monotherapy produced objective clinical responses including a durable confirmed complete response (CR) and two partial responses (PRs) in patients relapsed/refractory to all SOC therapies including ICIs
- Responding patients had rapid, complete and durable regression of target lesions detected within the first two cycles of therapy
- Related TEAEs were primarily mild to moderate in severity, manageable and reversible; no new safety signals were identified when WTX-124 was combined with pembrolizumab
- Analysis of paired tumor biopsies by NanoString suggests that WTX-124 robustly activates/expands effector T cells preferentially over Tregs
- Increased T cell activation signature for the combination suggests a potential for improved efficacy by combining WTX-124 with pembrolizumab
- **WTX-124 is clinically active and well tolerated in patients who would not all be eligible for HD IL-2 based on age, indication or other factors**

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This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA