Phase 1/2 Study of XTX202, a Tumor-Activated IL-2βγ in Advanced Solid Tumors

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Jad Chahoud, MD[1], Yousef Zakharia, MD[2], Meredith McKean, MD[3], Sanjay Goel, MD[4], Bartosz Chmielowski, MD, PhD[5], Diana L. Hanna, MD[6], Gregory A. Daniels, MD, PhD[7], Richard Wu, MD, PhD[8], Suthee Rapisuwon, MD[10], Randolph Hurley, MD[11], Anurag Gupta, PhD[11], Meghan Duncan[11], Aika Siu[11], Ekta Patel, PhD[11], Damiano Fantini[11], PhD, David Crowe[11], Sattanathan Paramasivan, PhD[11], Katarina Luptakova, MD[11], Howard L. Kaufman, MD[12], and Diwakar Davar, MD[5]

(1) Moffitt Cancer Center and Research Institute, Tampa, FL; (2) University of Iowa Hospitals and Clinics, Iowa City, IA; (3) Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN; (4) Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; (5) University of California Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; (6) USC Norris Comprehensive Cancer Center, Los Angeles, CA; (7) UC San Diego Moores Cancer Center, La Jolla, CA; (8) The Ohio State University Wexner Medical Center James Cancer Hospital and Solove Research Institute, Columbus, OH; (9) MedStar Georgetown University Hospital, Washington, DC; (10) HealthPartners Cancer Center at Regions Hospital, Saint Paul, MN; (11) Xilio Therapeutics, Inc., Waltham, MA; (12) Massachusetts General Hospital, Boston, MA (13) UPMC Hillman Cancer Center, Pittsburgh, PA

Background

- Aldesleukin has demonstrated responses in ~15% of RCC and melanoma patients, who were predominantly treatment-naïve (97% of RCC and 54% of melanoma patients).
- However, clinical use of aldesleukin has been confined to specialized centers able to provide intensive support, as patients experienced severe and potentially life-threatening adverse events related to systemic exposure to high dose IL-2, including vascular leak syndrome.
- Low dose rhIL-2 is generally tolerated but predominantly targets α-receptor and thus activates regulatory T cells, leading to immunosuppression.
- The critical challenge in the development of IL-2 therapies is to improve patient tolerability.

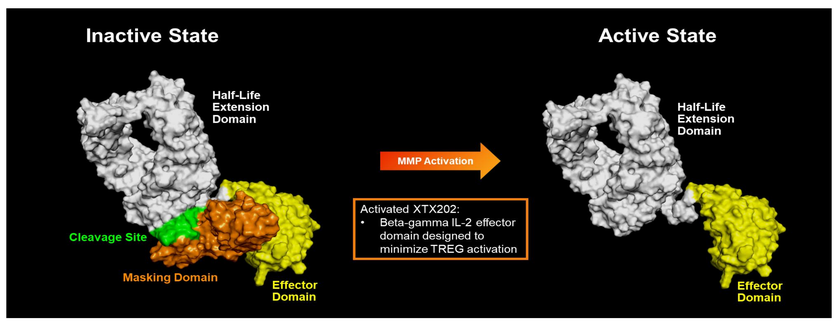
Patient population in pivotal aldesleukin studies were primarily younger patients (median age 42-53) naïve to systemic therapy:

- only 3% (RCC) and 46% (melanoma) of patients had prior systemic therapy. [1-2]

Of the multiple prognostic factors analyzed,[1,2] only ECOG PS and prior systemic therapy were associated with response:

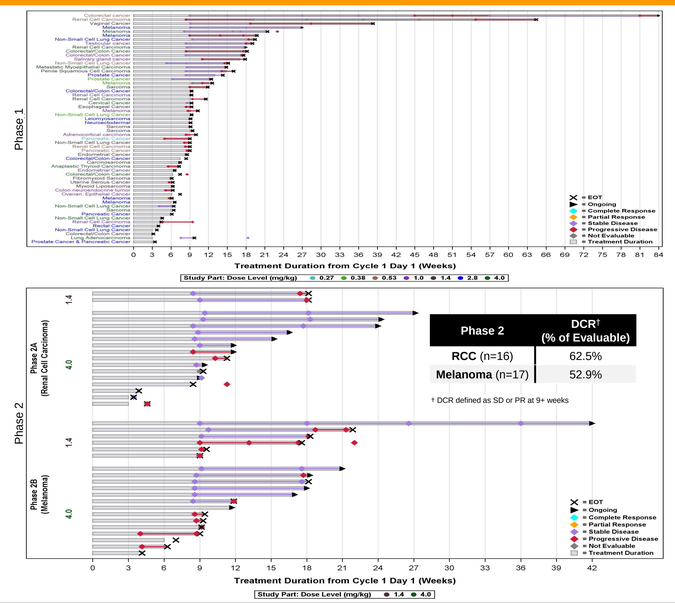
- ORR was only 9% in both RCC and melanoma with ECOG PS of 1.
- In melanoma, ORR was 10% among patient who received prior systemic therapy.

XTX202, a Masked Tumor-Activated IL-2βγ Designed to Overcome the Limitations of Systemically Active Molecules



- XTX202 is an investigational tumor-activated IL-2βγ designed to be inactive in the periphery and activated by matrix metalloproteases (MMP) in the tumor microenvironment.
- XTX202 is designed to retain Fc post-activation enabling high, sustained tumor exposure, cross-presentation and receptor binding.
- XTX202 was evaluated in a Phase 1/2 first-in human clinical trial in advanced solid tumors (NCT05052268). Preliminary data demonstrated a tolerable safety profile in patients with advanced solid tumors, dose-proportional PK, tumor-specific activation and tumor-specific PD changes.[3] While the MTD has not been reached in Phase 1 dose escalation, 2 doses were recommended for evaluation in Phase 2 based on the totality of data: 1.4 mg/kg and 4 mg/kg Q3W [Hanna et al., SITC 2023]

XTX202 Anti-tumor activity: > 50% Disease Control Rate in Phase 2

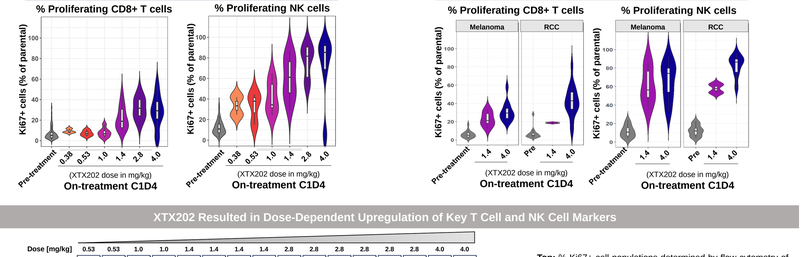


Dose Level* (number of response-evaluable patients across Phase 1 and Phase 2)	DCR† (% of response-evaluable patients)
<1.4 mg/kg (n=14)	14.3%
1.4 mg/kg (n=21)	38.1%
2.8 mg/kg (n=7)	42.9%
4.0 mg/kg (n=38)	52.6%
Total (n=80)	**41.3%**

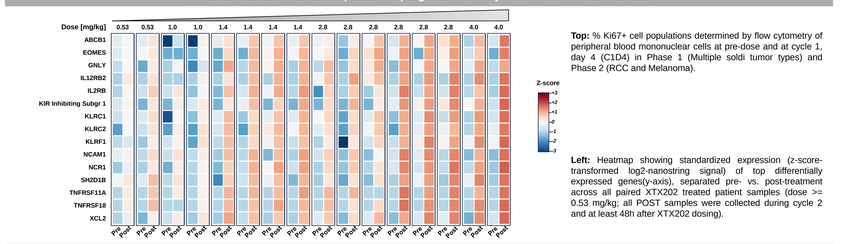
* Highest administered dose is used
† DCR defined as SD or PR at 9+ weeks

XTX202 Demonstrated Dose-Dependent Pharmacology in CD8+ T Cells and NK Cells Consistent with IL-2 Biology in the Absence of DLTs in Patients

XTX202 Induced CD8+ T and NK Cell Proliferation in a Dose-Dependent Manner in Melanoma and RCC Patients



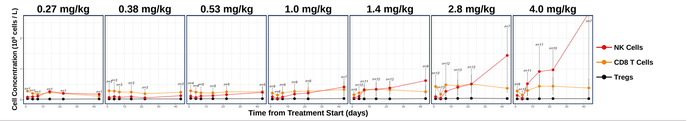
XTX202 Resulted in Dose-Dependent Upregulation of Key T Cell and NK Cell Markers



Top: % Ki67+ cell populations determined by flow cytometry of peripheral blood mononuclear cells at pre-dose and at cycle 1, day 4 (C1D4) in Phase 1 (Multiple soldi tumor types) and Phase 2 (RCC and Melanoma).

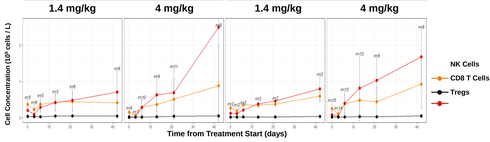
Left: Heatmap showing standardized expression (z-score-transformed log2-nanostring signal) of top differentially expressed genes(y-axis), separated pre- vs. post-treatment across all paired XTX202 treated patient samples (dose >= 0.53 mg/kg; all POST samples were collected during cycle 2 and at least 48h after XTX202 dosing).

Minimal Peripheral TREG Stimulation Observed at Any Dose Level Consistent with βγ-Biased Design Intent



Pharmacodynamic Effect of XTX202 was Confirmed in Melanoma and RCC Patients (Phase 2)

Melanoma		RCC	
1.4 mg/kg	4 mg/kg	1.4 mg/kg	4 mg/kg



Absolute Lymphocytes Count. Spaghetti graph showing the average concentration of different cell types in the periphery (y-axis, concentration expressed in 10^9 cells/L) at different time points (x-axis) for each treatment dose group (columns). Colors indicate cell types. Points and error bars indicate average +/- sd. The sample size is annotated for each group and timepoint.

XTX202 Study Design

Phase 1	Phase 2	
Phase 1A Monotherapy Dose Escalation Advanced Solid Tumors	Phase 2, Cohort A Monotherapy Expansion RCC Cohort	*Dose level 1: 1.4 mg/kg Q3W*
Phase 1B Monotherapy PD Cohort Defined tumor types*	Phase 2, Cohort B Monotherapy Expansion Melanoma Cohort	*Dose level 2: 4.0 mg/kg Q3W*

XTX202 was administered in outpatient setting with a Q3W schedule

*Tumor types eligible for Phase 1B included: RCC of clear cell histology, melanoma, squamous cell skin carcinoma, ovarian cancer, NSCLC

Results

Phase 1: Patients with a Wide Range of Advanced Solid Tumors

Patient Characteristics	Total (N=58)
Demographics	
Age, median (range)	68 (25, 82)
Female	22 (38%)
ECOG PS 0	20 (35%)
ECOG PS 1	37 (64%)
ECOG PS 2	1 (2%)
Prior Lines of Anti-Cancer Treatment	**Median 4 (1-13)**
1	5 (8.6%)
2	9 (15.5%)
3	11 (19%)
4	14 (24.1%)
5	8 (13.8%)
≥6	11 (19%)
Prior Treatment with IO	
≥1	41 (71%)
Time since initial diagnosis (months)	**Median 29 (4-146.6)**

Tumor Types	Total (N=58)*
Colorectal	8
Melanoma	7
NSCLC	7
RCC	6
Sarcoma	6
Pancreatic	4
Prostate cancer	3
Endometrial cancer	2
Cervical	1
Esophageal	1
Other	13

Disposition	Total (N=58)
Continuing on Treatment	**3**
Discontinued Treatment	**55**
Progressive Disease	39
Adverse Events	2
Withdrawal of Consent	3
Death (due to progressive disease)	5
Other	6

- *One patient at 2.8 mg/kg dose in Part 1A had 2 primary cancer diagnoses of pancreatic cancer and prostate cancer and is therefore included in both tumor types in the table.*

Phase 1
- Advanced and IO-treatment refractory solid tumors
- 76% of patients had 3 or more prior lines of treatment
- 71% of patients had prior IO treatment

Phase 2: Patients with Advanced RCC and Melanoma

Patient Characteristics	Total (N=37)
Demographics	
Age, median (range)	62 (33, 80)
Female	17 (45.9%)
ECOG PS 0	18 (48.6%)
ECOG PS 1	19 (51.4%)
ECOG PS 2	0 (0%)
Prior Lines of Anti-Cancer Treatment	**Median 3 (1-12)**
1	11 (29.7%)
2	6 (16.2%)
3	5 (13.5%)
4	6 (16.2%)
5	3 (8.1%)
≥6	6 (16.2%)
Prior Treatment with IO	
≥1	37 (100%)
Time since initial diagnosis (months)	**Median 39.75 (10.2-198)**

Tumor Types	Total (N=37)
Melanoma	20
RCC	17

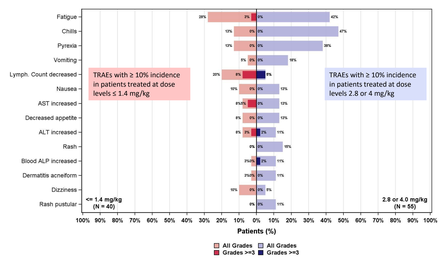
Disposition	Total (N=37)
Continuing on Treatment	**15**
Discontinued Treatment	**22**
Progressive Disease	16
Adverse event	0
Withdrawal of Consent	1
Death	0
Other	5

Phase 2
- 100% of patients had prior IO treatment
- 15 patients still ongoing

XTX202 Safety: TRAEs Primarily Grade 1-2

- Grade 4 TRAEs were limited to asymptomatic laboratory abnormalities*
- No Grade 5 TRAEs
- Only 2 out of 95 (2%) patients with treatment discontinuation due to TRAEs †
- Events of clinical interests on the study included capillary leak syndrome, not reported on the study, and cytokine release syndrome, reported in 4 patients (4%); 1 patient with Grade 3 and 3 patients with Grade 1-2

AE Category / Term *TRAEs with ≥10% incidence (any Grade)*	All Patients *(n=95)*	
	Any Grade	Grade ≥3
Fatigue	36% (n=34)	1% (n=1)
Chills	33% (n=31)	0
Pyrexia	27% (n=26)	0
Vomiting	13% (n=12)	0
Nausea	12% (n=11)	0
Lymphocyte count decreased	12% (n=11)	6% (n=6)
Aspartate aminotransferase increased	11% (n=10)	2% (n=2)
Decreased appetite	11% (n=10)	0
Dose reduction	11% (n=10)	
Treatment discontinuation due to TRAE	2% (n=2)	



Grade 3 TRAEs not included above:
Lymphocyte count decreased (n=6); neutrophil count decreased (n=3), n=2 each: transaminases increased; ALT increased; diarrhea, hypoxia, and n=1 each: colitis; myalgia; lymphopenia; hyperbilirubinemia; blood ALP increased; CRS; IRR; acute kidney injury; adverse drug reaction; abdominal pain; chronic inflammatory demyelinating polyradiculoneuropathy; peripheral motor neuropathy; pleural effusion; hypertension; autoimmune hepatitis.

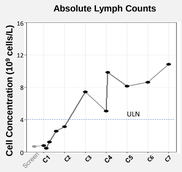
* Grade 4 TRAEs included 2 patients with Grade 4 lymphocyte count decreased/lymphopenia, and patient with Grade 4 neutrophil count decreased
† autoimmune hepatitis and hyperbilirubinemia, 1 each

Individual Patients Experienced Sustained NK Cell Expansion That Was Not Associated with Signs of Toxicity

53 year old female with RCC:

Received XTX202 at 4 mg/kg dose through 7 cycles. Stable disease at cycle 4 and 7, patient ongoing on treatment as of data cutoff date.

Noted to have increasing absolute lymphocytes count:



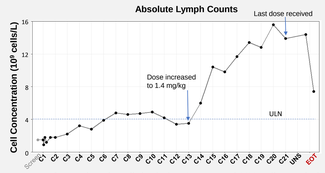
Flow cytometry performed at the clinical site: expanded population of NK cells that are CD8 positive.

Only Grade 1-2 TRAE

64 year old male with RCC:

Started XTX202 at 0.53 mg/kg dose, received 12 cycles and escalated to 1.4 mg/kg with C13, received 8 additional cycles at 1.4 mg/kg until disease progression.

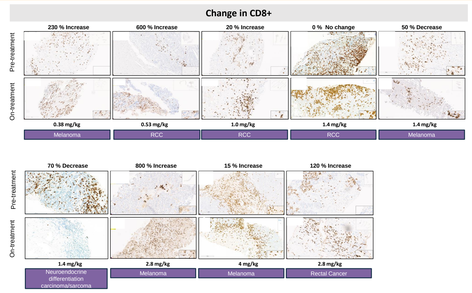
Noted to have increasing absolute lymphocytes count following dose escalation:

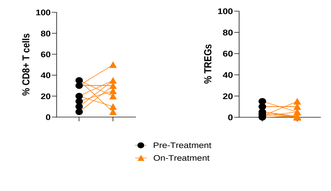


Flow cytometry performed at the clinical site: Increased NK cell population comprising 72% of the total lymphocytes. NK cells expressed CD2, CD7, CD16, CD45, CD56 and CD8; negative for CD4 expression. The NK cells show a normal immunophenotype.

Only limited Grade 1-2 TRAEs

Increases in CD8+ Effector T Cells Observed in Most Tumor Samples from Patients Treated With XTX202, Without Evidence of TREG Increase





Immunohistochemistry for CD8 was performed on available pre- and on-treatment (cycle 2 day 2-21) tumor biopsies. The percentage of tumor-infiltrating immune cells was scored by a certified pathologist by assessing the percent positivity in the intra-tumoral stroma as a fraction of all immune cells in the intra-tumoral stroma. Change in CD8+ cells in tumor takes into account changes in intra-tumoral immune cells as assessed by H&E stain and CD8+ IHC.

Conclusions

- **The patient population enrolled in the Phase 2 trial for XTX202 comprised older, heavily pre-treated patients with a lower performance status in contrast to the younger predominantly treatment-naïve RCC and melanoma patient population with good performance status that was included in pivotal aldesleukin trials**
- **XTX202 was administered at doses up to 4 mg/kg Q3W as an outpatient regimen and was generally well-tolerated with TRAEs primarily Grade 1-2, supporting effective masking of XTX202:**
  - **No Grade 5 TRAEs**
  - **Higher Grade TRAEs were generally asymptomatic laboratory abnormalities**
  - **Well-tolerated with repeated administration (up to 20 months)**
- **Evidence of tumor-selective XTX202 activation and PD**
- **Consistent with IL-2βγ biology, a dose-dependent increase in CD8+ T and NK cells with no accompanying high-grade toxicity was observed in response to XTX202 treatment**
- **The totality of data supports a favorable profile for combination therapy**

Data cutoff date: April 22, 2024

Abbreviations: AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; CRS: cytokine release syndrome; DCR: disease control rate; DLT: dose limiting toxicity; ECOG PS: ECOG Performance Status; IHC: immunohistochemistry; IO: immuno-oncology; IRR: infusion-related reaction; MMP: matrix metalloprotease; MSS CRC: microsatellite stable colorectal cancer; MTD: maximum tolerated dose; NK: natural killer; NSCLC: non-small cell lung cancer; ORR: objective response rate; PK: pharmacokinetic; PD: pharmacodynamic; PR: partial response; Q3W: every 3 weeks; RCC: renal cell carcinoma; rhIL-2: recombinant human interleukin 2; SD: stable disease; TRAE: treatment related adverse event; TREG: regulatory T cells; ULN: upper limit of normal.

References:
1. Journal of Clinical Oncology, Vol 13, No 3 (March), 1995: pp 688-696;
2. Journal of Clinical Oncology, Vol 17, No 7 (July), 1999: pp 2105-2116;
3. Hanna et al., SITC 2023

Contact information: medicalaffairs@xiliotx.com