A First-in-Human, Multicenter, Phase 1/2, Open-Label Study of XTX202, a Tumor-Selective Interleukin-2 (IL-2), in Patients with Advanced Solid Tumors

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Background

High-dose interleukin-2 (IL-2) has been approved in metastatic renal cell carcinoma (RCC) and metastatic melanoma and can result in durable complete responses and cures. However, clinical use of high dose IL-2 has been limited by life-threatening treatment-related toxicities, consisting mainly of vascular leak syndrome.

XTX202 is a masked, tumor-selective IL-2 that is designed to be pharmacologically inactive in non-tumor tissue when circulating systemically and is unmasked/activated by matrix metalloproteases (MMPs) found preferentially in the tumor microenvironment (TME). XTX202 is designed to improve the therapeutic index with the goal of overcoming the known tolerability challenges of existing IL-2 therapies and achieving enhanced anti-tumor activity.

XTX202, a Geographically Precise Solutions enabled cytokine

XTX202 is designed to improve therapeutic index through tumor-selective activation

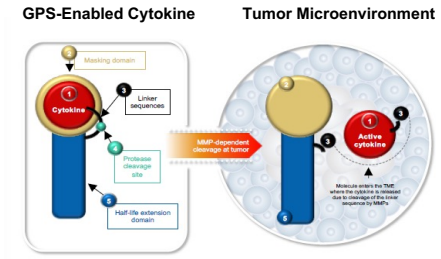

Figure 1: As a Geographically Precise Solutions (GPS)-enabled cytokine, XTX202 is engineered with a masking domain designed to pharmacologically inactivate IL-2 until it is activated by MMPs in the TME. XTX202 is designed with an extended half-life domain to overcome the limitation of short circulating half-life of the native cytokine. It is also designed to enhance potency of IL-2 by reduced binding to high affinity IL-2 receptor complex expressed on regulatory T-cells (Tregs) and limiting activation of Tregs that inhibit an immune response - while maintaining activation of effector T cells that promote anti-tumor immunity by binding to the intermediate-affinity IL-2 receptors.

Preclinical Rationale

XTX202 provided protease-dependent control of IL-2 activity *in vitro*

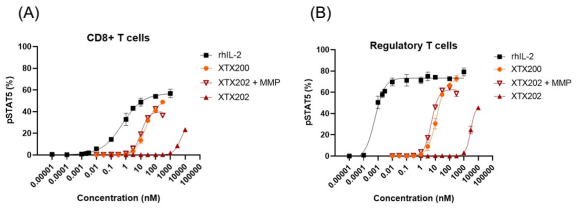

Figure 2: Primary human peripheral blood mononuclear cells were incubated with varying doses of recombinant human IL-2 (rhIL-2) and test articles for 24 hours and evaluated for STAT5 phosphorylation by flow cytometry. XTX202 resulted in attenuated STAT5 phosphorylation compared to rhIL-2 and XTX200 (unmasked molecule). Upon MMP activation, XTX202 resulted in a similar STAT5 phosphorylation as unmasked XTX200 in CD8 T cells (A) and Treg cells. (B) In contrast to rhIL-2 that was more active against Treg cells, XTX200 and proteolytically cleaved XTX202 demonstrated similar activity in primary human CD8+ T cells and Treg cells.

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XTX202 elicited tumor growth inhibition at well-tolerated doses in syngeneic bladder cancer MB49 mouse model

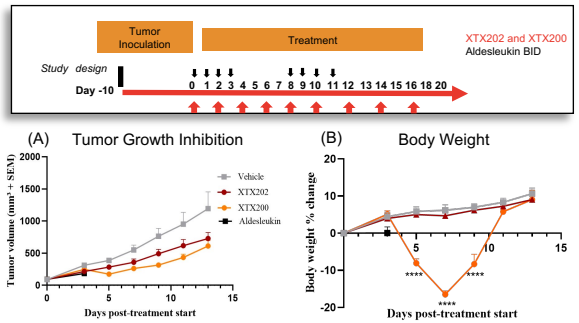


Figure 3. Anti-tumor activity of XTX200 (unmasked molecule), XTX202 and aldesleukin was evaluated in hFcRn Tg32 transgenic mice bearing the murine MB49 bladder carcinoma model. Compared with vehicle, XTX202 administered at 2mg/kg every 2 days significantly inhibited tumor growth, achieving 44% tumor growth inhibition on Day 13. XTX200 at 0.36 mg/kg every 2 days and aldesleukin at 3 mg/kg twice a day (BID) for five days were not well-tolerated. One out of 8 of the animals treated with aldesleukin was found dead on day 5. XTX200 resulted in significant body weight loss at days 5, 7 and 9. All animals recovered body weight at day 11.

O'Neil et al. ASCO 2021

Study Overview

XTX202-01/02-001 (NCT05052268) is a first-in-human, Phase 1/2, multicenter, open-label study of XTX202.

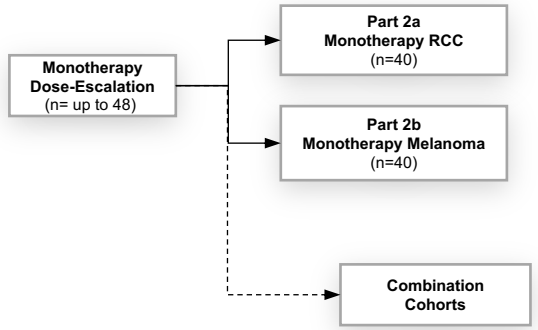
Phase 1: Patients with advanced solid tumors are eligible for Phase 1 and will receive XTX202 monotherapy administered every 21 days in an accelerated and standard 3+3 dose escalation design to determine a recommended Phase 2 dose (RP2D) of XTX202.

Phase 2: Consists of 2 parts to determine the efficacy of XTX202 monotherapy in patient specific populations

- **Part 2a** will enroll patients with metastatic RCC who have received prior tyrosine kinase inhibitor therapy and have been treated and progressed on anti-PD-1 therapy
- **Part 2b** will enroll patients with unresectable or metastatic melanoma who have received immune-checkpoint therapy with anti-PD-1 therapy and anti-CTLA-4 therapy

Additional cohorts may examine XTX202 in combination with other therapies in the future.

Phase 1/2 Clinical Trial in Patients with Solid Tumors



Study Design

Phase 1 dose escalation

Initial 100% Escalation			
DL	Dose (mg/kg)	Freq.	Escalation
1	0.27	Q3W	Accelerated
2	0.53	Q3W	Accelerated
3	1.0	Q3W	Accelerated
4	2.0	Q3W	Accelerated
5	4.0	Q3W	Accelerated
6	8.0	Q3W	3+3
7	11	Q3W	3+3
8	15	Q3W	3+3
9	21	Q3W	3+3

If a Grade ≥ 2 AE or DLT is observed, escalation transitions to Alternative Escalation

Alternative 40% Escalation			
DL	Dose (mg/kg)	Freq.	Escalation
1	0.27	Q3W	Accelerated
2	0.38	Q3W	3+3
3	0.53	Q3W	3+3
4	0.74	Q3W	3+3
5	1.0	Q3W	3+3
6	1.4	Q3W	3+3
7	2.0	Q3W	3+3
8	2.8	Q3W	3+3
9	4.0	Q3W	3+3
10	5.6	Q3W	3+3
11	8.0	Q3W	3+3
12	11	Q3W	3+3
13	15	Q3W	3+3
14	21	Q3W	3+3

Abbreviations: AE = adverse event; DL = dose level; DLT = dose limiting toxicity; Q3W = every 3 weeks; SRC = safety review committee.

Note: Additional dosing schedules may be explored at any DL based on recommendation of the SRC and confirmation from the Sponsor. Intermediate DLs may be explored during dose escalation if approved by the SRC; lower DLs may be explored as additional DLs based on results of escalation and if approved by the SRC and Sponsor.

Study Primary Objectives

Phase 1:

- To evaluate the safety and tolerability of XTX202 monotherapy in patients with advanced solid tumors
- To determine the RP2D and schedule of XTX202 monotherapy

Phase 2:

- To evaluate the efficacy of XTX202 monotherapy in patients with metastatic RCC and patients with unresectable or metastatic melanoma

References

O'Neil et al. ASCO (2021)
Malkova et al. Next-gen Cytokines Therapeutics Summit (2021)
ClinicalTrials.gov Identifier: NCT05052268