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 at a metallocryptotase (MMP) site. 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**

**Background**

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

**Preclinical Rationale**

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

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

**Figure 1. As a Geographically Precise Solutions (GPS) enabled cytokine, XTX202 is engineered with a masking domain designed to pharmacologically inactive 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, and 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 immune response, while maintaining activation of effector T cells that promote anti-tumor immunity by binding to the intermediate-affinity IL-2 receptors.**

**Figure 2. Primary human peripheral blood mononuclear cells were incubated with various doses of recombinant human IL-2 (rhIL-2) and tested for 24 hours and evaluated for STAT5 phosphorylation by flow cytometry. XTX202 resulted in attenuated STAT5 phosphorylation compared to rhIL-2 and XTX200 (unmasked molecules). Upon MMP activation, XTX202 resulted in similar STAT5 phosphorylation as unmasked XTX200 in C6 Tumor Cells (A) and Treg Cells (B) as compared to rhIL-2 that was active against Treg cells. XTX202 and proteolytically cleaved XTX202 demonstrated similar activity in primary human C6 T Cells and Treg Cells.**

Malkova et al. Next-Gen Cytokine Therapeutics Summit 2021

**Figure 3. Anti-tumor activity of XTX200 (unmasked molecule), XTX202 and aldesleukin was evaluated in HfLhFr2-Tg transgenic mice bearing the murine MB49 bladder carcinoma model. Compared with vehicle, XTX202 administered at 2mg/kg every 3 days significantly reduced tumor growth, achieving 44% tumor growth inhibition on Day 13. XTX200 at 0.38 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 eight 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-CTLA4 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**

**Table 1.**

<table>
<thead>
<tr>
<th>Initial Dose Escalation</th>
<th>Alternative Dose Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg/kg Day 1 (BID)</td>
<td>2 mg/kg Day 1 (BID)</td>
</tr>
<tr>
<td>2 mg/kg Day 1 (BID)</td>
<td>4 mg/kg Day 1 (BID)</td>
</tr>
<tr>
<td>4 mg/kg Day 1 (BID)</td>
<td>10 mg/kg Day 1 (BID)</td>
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</tbody>
</table>

**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**

Malkova et al. Next-Gen Cytokine Therapeutics Summit 2021

O’Neil et al. ASCO (2021)