611 XTX202–01/02–001, PHASE 1/2 FIRST-IN HUMAN STUDY OF XTX202, A MASKED, TUMOR-ACTIVATED IL-2βγ, IN PATIENTS WITH ADVANCED SOLID TUMORS: RESULTS FROM PHASE 1

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Background Aldesleukin requires high systemic doses (8.4 million IU/kg equaling 0.518 mg/kg per weekly cycle) to achieve therapeutic benefit; however, such doses typically result in life-threatening toxicities. 'Non-α' interleukin-2 (IL-2) agents demonstrated modest efficacy; however observed toxicities limited dose escalation.

To overcome systemic toxicity of IL-2, we employed protein engineering to generate XTX202, an investigational tumor-activated, half-life extended IL-2βγ that is designed to be inert until activated by proteases enriched in the tumor microenvironment (TME).[1]

Methods XTX202–01/02–001 is evaluating safety and tolerability of XTX202 in advanced solid tumors patients (Phase 1); and efficacy in metastatic renal cell carcinoma (RCC) and melanoma (Phase 2). XTX202 is administered outpatient intravenously every 3 weeks.

Results As of June 15, 2023, 37 patients (22 males), median age 65 years (36–82), median 4 prior lines of therapy (1–14), were treated with XTX202 in Phase 1 across 6 dose levels (DL, 0.27–2.8 mg/kg), most common histologies: colorectal (n=5), RCC (n=4), and non-small cell lung cancer (n=4).

All grade treatment-related adverse events (TRAE, ≥10% incidence): fatigue (19%), lymphocyte count decreased (16%); pyrexia (11%); and dizziness (11%). Grade 3 TRAEs: lymphocyte count decreased (8%), AST increased (3%), ALT increased (3%), blood bilirubin increased (3%), and myalgia (3%). No grade 4 or 5 TRAEs and no signs of vascular leak syndrome or hemodynamic compromise were observed. There was 1 dose limiting toxicity: reversible grade 3 elevation of AST and ALT at DL4 (1 mg/kg). All 6 DLs including 2.8 mg/kg have been cleared. With a plan to evaluate 2 dose levels in Phase 2, initial recommended phase 2 dose of 1.4 mg/kg was established, while dose escalation to 4 mg/kg is ongoing in Phase 1.

Pharmacokinetic (PK) analysis demonstrated dose-proportional exposure. Calculated fraction of activated XTX202 in peripheral blood was negligible (0–3%). Along with PK evidence of minimal peripheral XTX202 activation, no increases in peripheral CD8 or Tregs were observed in samples available through 2 cycles of therapy (figure 1). In contrast, average 3.4-fold increase in CD8 cells was observed in 4 available on-treatment tumor samples (figure 2).

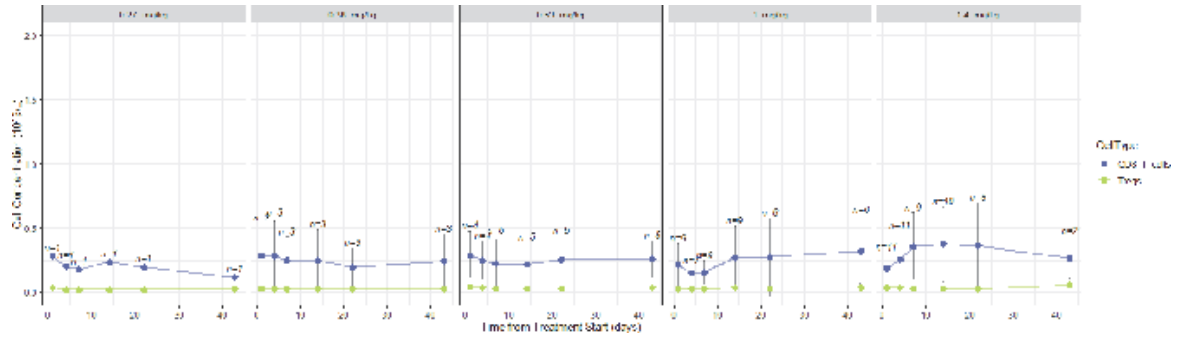
Conclusions CD8 increases in tumor biopsies consistent with IL-2 biology, contrasted against minimal peripheral pharmacodynamic (PD) changes, suggest that XTX202 is selectively activated in TME. This is supported by confirmatory PK and the ability to escalate above 2.8 mg/kg with toxicity manageable in the outpatient setting. Updated clinical data, PK and comprehensive PD data (peripheral blood and available tumor biopsies) will be presented.

Trial Registration NCT05052268

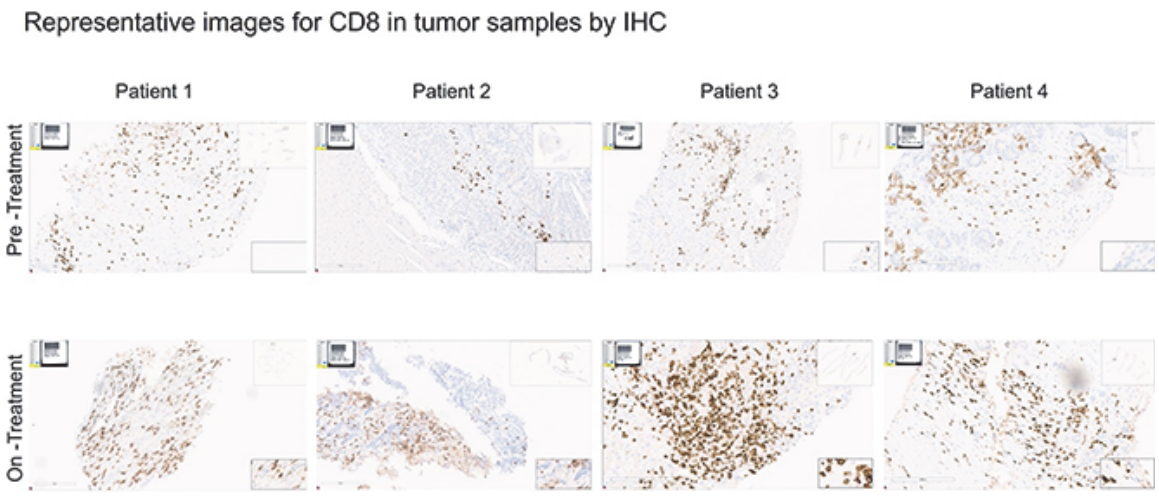
REFERENCE

1. O'Neil J *et al*. XTX202, a protein-engineered IL-2, exhibits tumor-selective activity in mice without peripheral toxicities in non-human primates. ASCO 2021

Ethics Approval This study obtained ethics approval though a central IRB (Advara IRB: Pro00057609).



Abstract 611 Figure 1



Abstract 611 Figure 2 Representative images for CD8 in tumor samples by IHC

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