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).

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 63 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 NCT03052268

REFERENCE

Ethics Approval This study obtained ethics approval though a central IRB (Advara IRB: Pro00057609).
Abstract 611 Figure 2  Representative images for CD8 in tumor samples by IHC

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