A FIRST-IN-HUMAN, MULTICENTER, PHASE 1/2, OPEN-LABEL STUDY OF XTX101 IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Anti-CTLA-4 agents have demonstrated clinical benefit in a range of tumors; however, the safety risks limit the dose and their use in certain settings.¹⁻⁴ XTX101 is a fully humanized mAb with an engineered Fc region for enhanced FcγR binding and with covalently linked peptides that mask each CTLA-4 antigen-binding region of the antibody. The masking peptides are designed to be selectively cleaved and released by proteases that are more active in the tumor microenvironment compared to healthy tissue. XTX101 is intended to have minimal peripheral CTLA-4 binding and inhibition. Upon proteolytic cleavage of the masking peptides within the tumor microenvironment, the cleaved and active form of XTX101 is intended to bind to CTLA-4, inhibit its function, and induce antibody-dependent cellular cytotoxicity (ADCC). Here we describe the first-in-human study that is currently enrolling subjects with locally advanced or metastatic disease who have failed standard therapy, or standard therapy is not curative or available.

Methods The objectives of this study are to determine a dose or doses of XTX101 administered every 21 days that are well-tolerated, biologically active, and suitable for advancing into further studies. The initial portion of the study consists of three parts. Part 1A will evaluate ascending fixed doses of XTX101 monotherapy using an accelerated, single-subject, dose-level design for the first three dose cohorts followed by a standard 3+3 design. Part 1B will examine XTX101 monotherapy in patients with any histologically or cytologically confirmed solid tumor malignancy for which anti-PD-1 or anti-PD-L1 treatment is approved and has progressed on or after prior anti-PD-1 or anti-PD-L1 therapy. Currently approved tumor types for anti-PD-1 or anti-PD-L1 treatment include melanoma, squamous cell skin cancer, non-small cell lung cancer, head and neck carcinoma, esophageal carcinoma, renal cell cancer, urothelial carcinoma, or microsatellite instability-high/mismatch deficient colorectal cancer. Part 1B will require mandatory fresh tumor biopsies pre-dose and post-dose to fully characterize the pharmacodynamic profile of XTX101. Part 1C will examine escalating doses of XTX101 in combination with pembrolizumab. Subjects may receive XTX101 for up to 24 months in the absence of disease progression, toxicity, a complete response, or termination of the study. Disease responses will be determined by iRECIST methods every third treatment cycle for the first year and then every four treatment cycles thereafter until progressive disease.

Trial Registration NCT04896697

REFERENCES

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Ethics Approval This study was approved by an Institutional Review Board for each participating site.

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