Background

Anti-CTLA-4 agents have demonstrated clinical benefit in a range of tumors; however, the safety risks arising from systemic immune activation limit the dose and their use in certain settings [Hamid 2011, Lebbe 2019, Wolchok 2013, Wolchok 2010]. Patients with high affinity FcR polymorphisms have shown improved clinical responses to ipilimumab [Arce-Vargas 2018, Quezada 2019] suggesting that enhanced effector function could improve response to anti-CTLA-4 therapies.

Ipiteimumab data provide compelling rationale for an improved anti-CTLA4 therapy.

XTX101 is more potent than ipilimumab analog

XTX101 Nonclincial Potency and Activity

Wide publication of XTX101 across human tumors in ex vivo assay

Cancer type Sample size % that activate XTX101

colon 11 91
breast 4 75
melanoma 7 71
bladder 5 80
NSCLC 9 67
liver 5 60
ovarian 11 64
RCC 30 57

Fresh tumor biopsies were obtained from human cancer patients and assessed for cleavage of XTX101 and restoration of binding to CTLA-4 by ELISA assay. XTX101 was cleaved by all tumor types assessed. Overall, 67% of tumors cleaved XTX101.

Study Overview

XTX101-01/02-001 (NCT04896697) is a first-in-human, Phase 1/2, multicenter, open-label study designed to evaluate the safety and tolerability of XTX101 as monotherapy and XTX101 and pembrolizumab combination therapy in patients with advanced solid tumors.

Part 1A will examine XTX101 monotherapy in a modified accelerated and standard 3+3 dose escalation design and is currently enrolling subjects with locally advanced or metastatic disease who have failed standard therapy, or for whom standard therapy is not curative or available.

Based on the results of Part 1A, patients with selected advanced solid tumors will be enrolled in Part 1B, which will evaluate XTX101 monotherapy in relation to specific pharmacodynamic biomarkers.

Part 1C will examine XTX101 in combination with pembrolizumab in a standard 3+3 dose escalation design with doses of XTX101 selected based on the data from Part 1A and pembrolizumab administered at 200 mg every 3 weeks (Q3W) intravenously.

After completion of Part 1C, the study will initiate Part 2, examining the RP2D of XTX101 and pembrolizumab combination therapy in patients with unresectable or metastatic melanoma.

References