A First-in-Human, Multicenter, Phase 1/2, Open-Label Study of XTX101 in Patients with Advanced Solid Tumors[4]

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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 FcγR 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.

Ipilimumab data provide compelling rationale for an improved anti-CTLA4 therapy

Ipilimumab Melanoma Randomized Phase 3 Study

	Dose	Median OS	Adverse Events: gr 3/4 irAEs/discont.
Standard Approved Dose	3 mg/kg	11.5 mo	14% / 19%
	10 mg/kg	15.7 mo	30% / 31%

Conclusion: Treatment with higher dose resulted in increased overall survival (OS) but also increased AEs and discontinuations. [Ascierto 2017]

XTX101

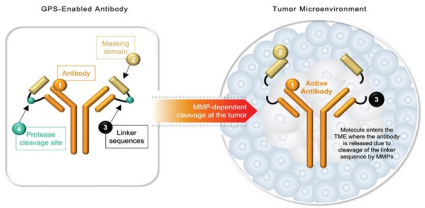
XTX101 is a tumor-selective anti-CTLA-4 mAb that is designed to improve upon the therapeutic index of existing anti-CTLA-4 therapies by overcoming potency and tolerability limitations.

XTX101 is designed for improved potency:

- Higher affinity binding to the target CTLA-4
- Enhanced Fc effector function and Treg depletion

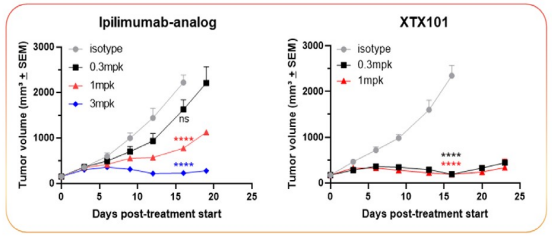
XTX101 is designed to have reduced peripheral immune activity

- Complementarity-defining region (CDR) sequences are masked while in circulation
- Activated by protease-dependent release of the masks
- Selectively active in the tumor microenvironment and avoids toxicity associated with systemic immune activation



XTX101 Nonclinical Potency and Activity

XTX101 is more potent than ipilimumab analog



MB49 cells were inoculated subcutaneously into C57BL/6-huCTLA-4 mice. Mice were dosed with a single-dose i.v. A two-way ANOVA with Bonferonni's multiple comparisons post-test was performed to determine the statistical significance of treatment vs. isotype on Day 16 (ns not significant,;*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001).

A dose of 3 mg/kg of the ipilimumab analog is required to achieve similar efficacy and CR rate as XTX101 at 0.3 mg/kg, suggesting XTX101 has 10x higher potency than the analog.

Broad activation 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 select 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.

Primary Objectives

Objectives (Part 1A, Part 1B, and Part 1C):

Primary:

- Evaluate safety and tolerability of XTX101 monotherapy and in combination with pembrolizumab in patients with advanced solid tumors
- Determine the recommended Phase 2 dose (RP2D) and schedule of XTX101 as monotherapy and XTX101 in combination with pembrolizumab

Objectives (Part 2):

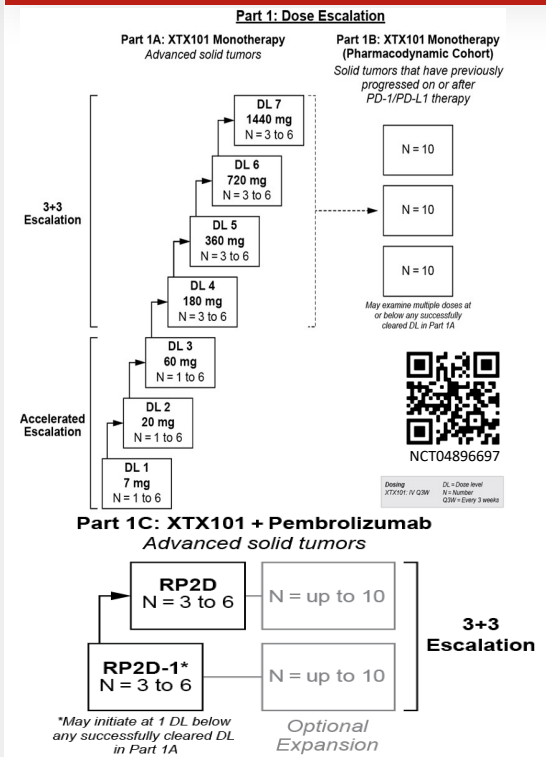
Primary:

- Evaluate antitumor activity of XTX101 and pembrolizumab combination therapy in patients with unresectable or metastatic melanoma

Secondary:

- Evaluate safety and tolerability of XTX101 and pembrolizumab combination
- Evaluate the RP2D of XTX101 and pembrolizumab combination
- Characterize PK of XTX101 and pembrolizumab combination

Study Design



Part 2: XTX101 + Pembrolizumab

Screen (28 days) → XTX101 + Pembrolizumab **(N=40)** Measurable, unresectable, metastatic melanoma not previously treated with PD-1/L-1

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