A First-in-Human Study of XTX301, a Masked, Tumor-Activated Interleukin-12 (IL-12), in Patients with Advanced Solid Tumors (TPS2672)

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Study Design

Primary objectives
- Safety and tolerability of XTX301 monotherapy in patients with advanced solid tumors
- Recommended Phase 2 Dose and schedule of XTX301 monotherapy

Secondary objectives
- Pharmacokinetic profile of XTX301 monotherapy in patients with advanced solid tumors
- Immunogenicity of XTX301 monotherapy in patients with advanced solid tumors
- Preliminary antitumor activity of XTX301 monotherapy in patients with advanced solid tumors

Exploratory objectives
Pharmacodynamic (PD) biomarkers in peripheral blood and in tumor specimens to characterize the biological effects of XTX301:
- functional and phenotypic characterization of peripheral blood and serum cytokines, chemokines, and proteins
- PD markers in tumors, including changes in immune-related gene expression and phenotypic characterization of tumor-infiltrating immune cells after treatment with XTX301
- XTX301 concentration in tumor

Preclinical data support potential for broad therapeutic index

mXTX301 elicited tumor growth inhibition in both hot and cold syngeneic mouse tumor models

"Cold Tumors" Backfill Cohort

Part 1B+ Monotherapy PD Cohort

N= up to 40
"Hot Tumors"

Part 1A

Monotherapy Dose-Escalation 3+3 study design

Advanced Solid Tumors

Cold Tumor
- Lack of CD8+ T cells and NK cells within tumor
- Presence of immune suppressive cells (TREGs, MDSCs)
- Poor response to checkpoint inhibitors

Hot Tumor
- CD8+ T cells and NK cells are abundant in tumor
- Pro-inflammatory microenvironment
- Improved prognosis and effective killing of tumor cells with immunotherapy treatment

Inactive State
Active State

Preclinical data support potential for broad therapeutic index

mXTX301 elicited tumor growth inhibition in both hot and cold syngeneic mouse tumor models

(A) mXTX301-elicted tumor growth inhibition in both hot and cold syngeneic mouse tumor models

Figure 1: mXTX301 is a murine surrogate for XTX301, mXTX301 was used for in vivo studies since human IL-12 does not bind to mouse IL-12 receptors. mXTX301 demonstrates anti-tumor activity in MC38 and B16F10 syngeneic tumor models. (A) C57BL/6 mice were implanted subcutaneously with MC38 tumor cells and received a single intravenous injection of mXTX301, unmasked control, or vehicle at indicated dose levels (N=12). Data represent mean ± SEM (Standard error of the mean).****P<0.0001 (A) Animals were implanted subcutaneously with B16F10 tumor cells and received a single intravenous injection of mXTX301. Tumor growth data are presented as mean for tumor volume ± SEM. Two-way ANOVA followed by Bonferroni post hoc test (**P<0.005; ****P<0.0001). TGI: tumor growth inhibition

XTX301 is designed to produce a localized anti-tumor immune response while limiting exposure of the active form of XTX301 in non-tumor tissue, and thereby improving the therapeutic index of IL-12. [Malkova et al. AOCR 2023]

Figure 2: A large exposure difference in the group mean AUC0-24h between HNSTD in non-human primates and dose with anti-tumor activity in mice supports the potential for a broad therapeutic index for XTX301.